Investigating Rhodium-Catalysed Hydroacylation and Carbon-Carbon Bond Activation

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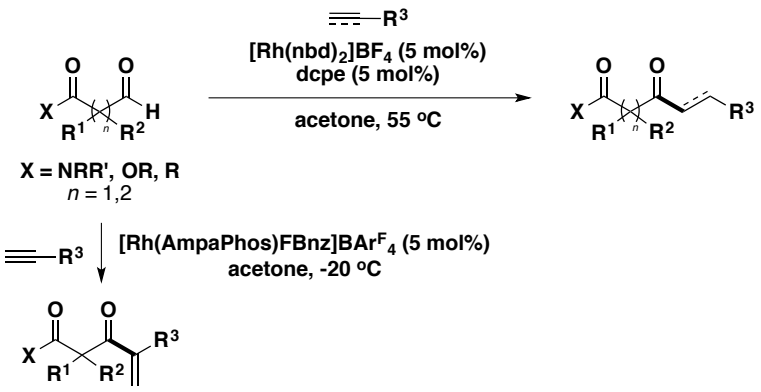
Abstract

The work described in this thesis documents the development of new rhodium(I)-catalysed methodologies within two areas of research. The first examines the use of carbonyls as chelating groups in hydroacylation to produce synthetically valuable ketones and enones. The second area explores new carbon-carbon bond activation methodologies.

Chapter 1 presents a literature review of the historical development of rhodium-catalysed hydroacylation, with a focus on chelating groups that can currently be used to suppress decarbonylation. A brief review of methodologies that avoid the requirement for a tether is also included.

Chapter 2 describes the development of a novel hydroacylation methodology employing carbonyl-based functional groups as tethers on aldehyde substrates.

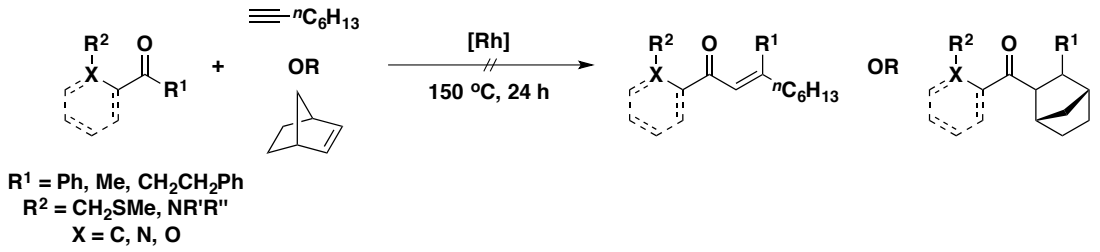


The chapter begins with the optimisation studies for the hydroacylation of *β*-formyl amides with terminal and internal alkynes, allenes and terminal alkenes, and subsequently explores the substrate scope for each case. The chapter then outlines the investigations undertaken

with 1,4-dicarbonyl and 1,5-dicarbonyl systems, *N*-formyl amides, *β*-formyl esters and finally *β*-formyl ketones. A detailed description of the routes undertaken to synthesise each starting material is also presented.

Chapter 3 presents a short review surveying the key milestones in the development of carbon-carbon activation methodologies. The chapter begins with a theoretical comparison to carbon-hydrogen activation and a discussion of the unique challenges that are faced. An overview of the major strategies employed to enact these processes is subsequently presented for both strained and unstrained substrates.

Chapter 4 outlines the attempts undertaken to develop a novel carbon-carbon bond activation methodology. The work evaluates sulfur-, nitrogen- and alkene-based chelating groups, known to be successful in hydroacylation, in analogous ketone substrates.



Chapter 5 discusses the conclusions from this work and the potential for further work.

Chapter 6 presents the experimental procedures and data.

Declaration

The work described in this thesis is entirely the work of the author except where specifically indicated. This thesis has not been previously submitted for a degree, diploma or any other qualification at the University of Oxford or elsewhere.

Thomas Coxon

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Secondly, to Willis group members, past and present. You've been a mad bunch over the years, but I will always remember fondly our various antics together, both in and out of lab. Some of you deserve a special mention: *To Sang*, for being one of the best fumehood buddies you could ask for, and conveniently looking like a certain galactic space pilot. We've shared many happy times together and I can only hope there will be more to come. *To Maitane*, my favourite Spanish queen, for finishing off the carbonyl project, and having more balls than all the boys put together. *To Vincent*, for being happy ALL the time. *To Jimmy*, for the constant abuse and 'banter'. *To Alyn the Shark*, for reliably providing entertainment on nights out, e.g. by sleeping in a corridor in Poland. *To Tim*, for our deep chats, and for having a great girlfriend. *To all of the above plus Ming, Rob, Phil and Thomas*, for proofreading. You know far more chemistry than I ever could. *To Manjeet*, for being the best desk buddy, for the good times and gossip, and for being there for me from the very beginning. You've been a rock. *To Anais, Nate, Yiding, Michael F. and James L.,* for all the laughs and generally making everything far more enjoyable.

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Finally, I wish to dedicate this thesis to my family: Mum, Dad and Sarah, for providing the support and love when needed. You've sacrificed a lot for me in my life, and I can only hope that one day I'll be able to repay the favour.

Table of Contents

Abbreviations

Ac	acetate
acac	acetylacetone
app.	apparent
aq.	aqueous
Ar	aryl
atm	atmospheres
b	branched
BAr^F_4	tetrakis[3,5-bis(trifluoro-methyl)phenyl]borate
bmim	1-butyl-3-methylimidazolium
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
br	broad
Bt	benzotriazole
Bu	butyl
Bz	benzoate
c.	concentrated
°C	degrees Celsius
cat.	catalyst or catalytic
Cbz	carboxybenzyl
CI	chemical ionisation
cm^{-1}	wavenumber
CM	complex mixture
cod	1,5-cyclooctadiene
coe	*cis*-cyclooctene
conc.	concentration
conv.	conversion
COSY	correlation spectroscopy
Cp*	pentamethylcyclopentadienyl

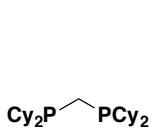
Cy	cyclohexyl
d	doublet
DCE	1,2-dichloroethane
DCM	dichloromethane
DEPT	distortionless enhancement by polarisation transfer
DFT	density functional theory
DIBAL-H	diisobutylaluminium hydride
DMAP	4-dimethylaminopyridine
DMB	dimethoxylbenzyl
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
E	Entgegen
ee	enantiomeric excess
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
EI	electron impact
equiv.	equivalents
ESI	electrospray ionisation
Et	ethyl
EtOAc	ethyl acetate
EWG	electron withdrawing group
FBnz	fluorobenzene
FI	field ionisation
g	gram(s)
h	hour(s)
hr	hour(s)
$[H^+]$	acid
Het	heterocycle
Hex	hexyl
HDMS	bis(trimethylsilyl)amine
HPLC	high performance liquid chromatography

HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum correlation spectroscopy
Hz	Hertz
i	iso
IR	infrared
J	coupling constant
l	linear
L	litre(s) or ligand
LDA	lithium diisopropylamine
lit.	literature
LRMS	low resolution mass spectrometry
m	multiplet
m	*meta*
M	molar
[M]	metal
m-CPBA	*m*-chloroperoxybenzoic acid
Me	methyl
mg	milligram(s)
min	minute(s)
mmol	millimoles
mol	moles
mol%	mole percentage
mol. sieves	molecular sieves
mp	melting point
MTM	methyl thiomethyl
m/z	mass to charge ratio
n	normal (unless otherwise stated)
N	normal
n/a	not applicable
nbd	norbornadiene
NHC	*N*-heterocyclic carbene

nm	nanometres
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
Nuc	nucleophile
o	*ortho*
p	*para*
P	phosphine ligand
PC	propylene carbonate
Pent	pentyl
PG	protecting group
pin	pinacol
Ph	phenyl
ppm	parts per million
Pr	propyl
psi	pounds per square inch
p-TSA	*para*-toluenesulfonic acid
pyr	pyridine
q	quartet
quant.	quantitative
R	generic group/substituent
RT	room temperature
s	singlet
s	secondary
S	coordinating solvent
sat.	saturated
sec	second(s)
sec	secondary
SM	starting material
t	triplet
t	tertiary
TBAI	tetrabutylammonium iodide

TBS	*tert*-butyldimethyl silyl
temp.	temperature
tert	tertiary
Tf	trifluoromethylsulfonyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TM	transition metal
TMS	trimethylsilyl
Tol	tolyl
Ts	tosyl
UV	ultraviolet
X	heteroatom (unless otherwise stated)
$[\alpha]_D$	specific rotation
δ	chemical shift
η	hapticity
μ	micro
ν_{max}	frequency
Z	Zusammen

Ligand Structures



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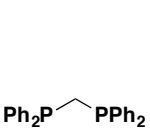

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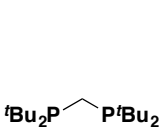

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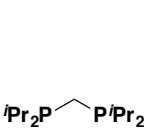

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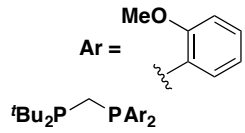

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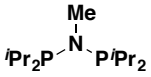

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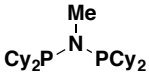

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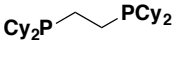

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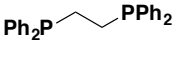

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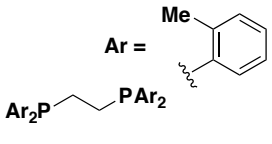

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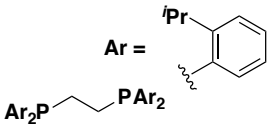

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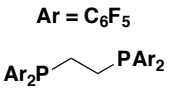

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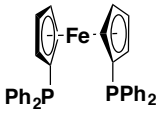

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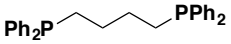

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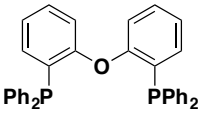

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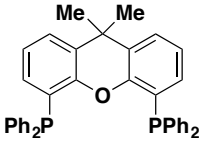

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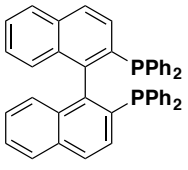

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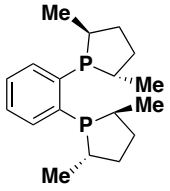

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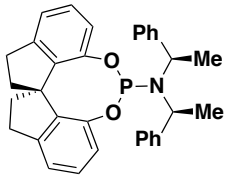

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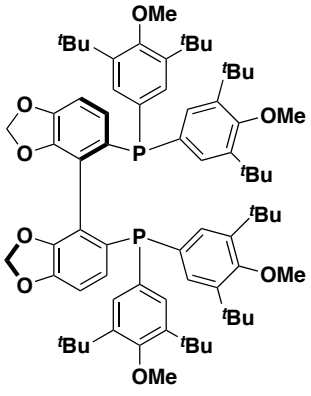


DTBM-Segphos

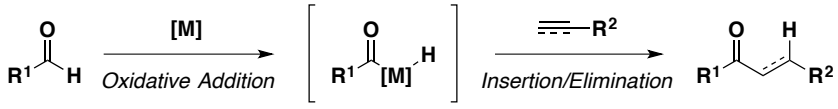
Chapter 1

Rhodium-Catalysed Hydroacylation

1.1 Introduction

The catalytic activation and subsequent functionalisation of C–H bonds has enjoyed a wealth of attention over the last few decades.[1,2] By employing low catalyst loadings and mild reaction conditions, a vast array of new bonds can be formed *via* C–H activation, making it an attractive tool for synthetic chemists.[3-14]

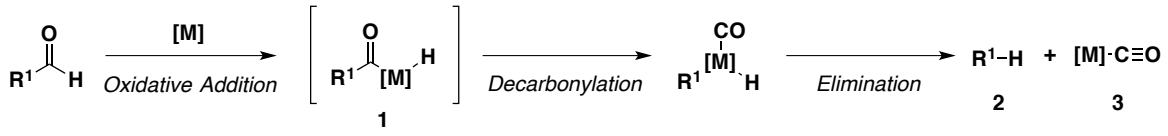
One such process is hydroacylation, which formally involves the addition of an acyl moiety and a hydrogen atom across a C–C π bond.[15-18] Typically arising from the catalytic activation of aldehyde C–H bonds using transition metals, this transformation provides efficient and atom-economic access to ketones and enones (**Scheme 1.1**).



Scheme 1.1: General outline of the hydroacylation process.

Despite the synthetic benefits it offers, hydroacylation has not enjoyed the widespread utility of other C–H activation processes due to the limited set of substrates that can currently be employed. This restriction arises principally from the deleterious side reactions that can take

place, the most prevalent of these being metal-mediated reductive decarbonylation (**Scheme 1.2**).[15-17] Resulting from the instability of the acyl-metal hydride intermediate **1**, this damaging process is irreversible, forming alkanes **2** (which are lost) and metal-carbonyl complexes **3** which are either inactive or, at the very best, extremely poor catalysts for hydroacylation. As such, any development of a hydroacylation methodology must take this reductive decarbonylation into account and attempt to suppress it.

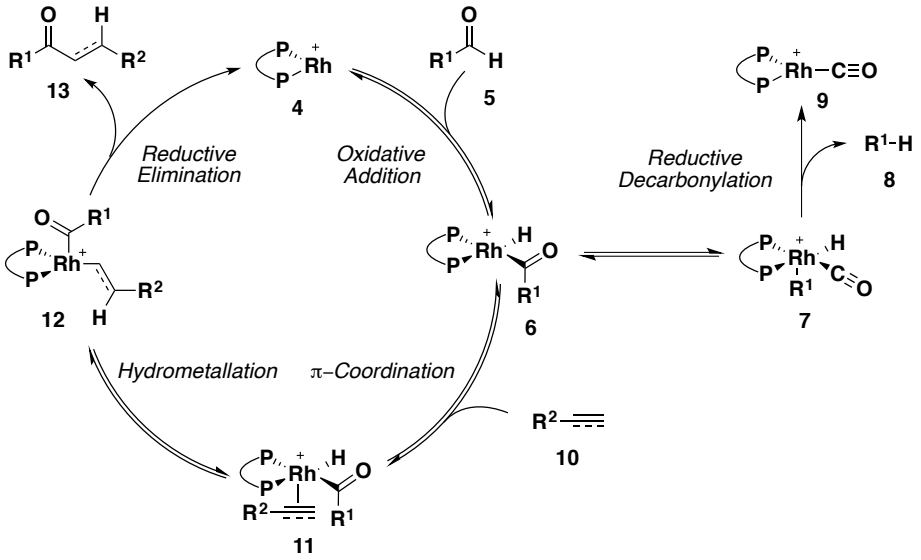


Scheme 1.2: The deleterious reductive decarbonylation side reaction.

A wide range of catalysts have been reported to facilitate hydroacylation, and whilst there are several known examples of non-transition metal processes,[19-26] the majority are based on late transition metal complexes such as rhodium, ruthenium,[27-31] nickel,[32-35] cobalt[36-39] and iridium.[40,41] However, rhodium is currently the most prevalent of these and relevant to this thesis, and therefore only rhodium-catalysed hydroacylation methodologies will be discussed from now on.

Mechanistically, an absolute understanding of the hydroacylation process remains elusive, although the catalytic cycle in **Scheme 1.3** is generally accepted as a result of several mechanistic studies. One of the earliest of these reports by Bosnich on the intramolecular hydroacylation of 4-pentenal used deuterium-labelling studies to propose the existence of an acyl-rhodium hydride intermediate, although no intermediates were definitively isolated.[42] Further computational calculations by Morehead and Sargent supported this work, identifying the final reductive elimination step to be rate limiting and suggesting why certain

solvent and substrate concentrations could affect the propensity for decarbonylation.[43] Studies from Brookhart,[44] Willis and Weller[45-48] have advanced this work by isolating and spectroscopically determining the structures of intermediates within the suggested catalytic cycle, including an acyl-hydride complex following oxidative addition and the various vinyl intermediates preceding reductive elimination. Combining this information with the findings various other studies,[49,50] a generalised catalytic cycle is shown in **Scheme 1.3**.



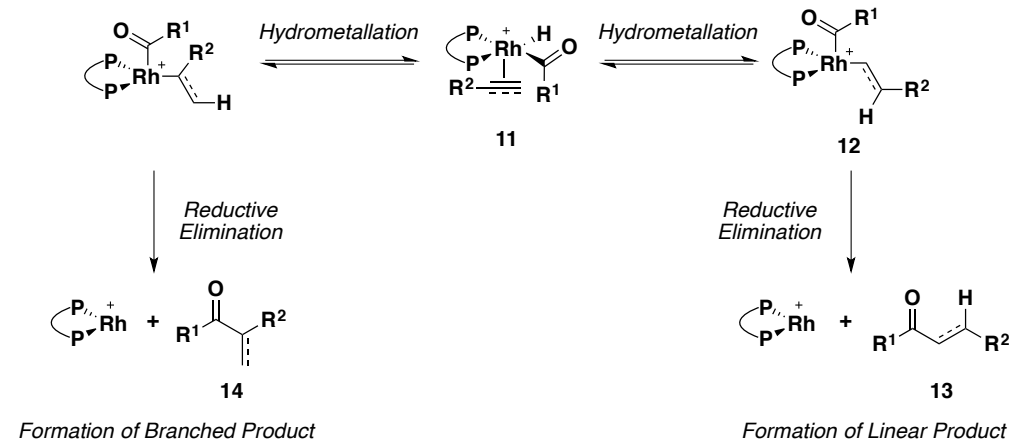
Scheme 1.3: Proposed mechanism for the hydroacylation of aldehydes using a Rh(I) catalyst.

This cycle outlines the hydroacylation of aldehyde **5** with the unsaturated coupling component **10** to give the linear product **13**, although a similar cycle has been considered for the formation of the equivalent branched isomer. Employing a generic $[Rh(diphosphine)]^+$ catalyst **4**, the Rh(I) initially undergoes reversible oxidative addition of the aldehyde C–H bond, forming a Rh(III) acyl hydride intermediate **6**. With two vacant coordination sites around the metal centre, this intermediate has two possible routes to take. The desirable hydroacylation pathway involves π-coordination of the unsaturated alkyne or alkene **10** to the Rh(III) centre, giving **11**. Hydrometallation can then take place to generate the Rh(III)

species **12**. Irreversible reductive elimination of the product occurs as the rate limiting process, creating the ketone or enone product **13** and reforming the Rh(I) catalyst. The second and usually undesirable pathway of the rhodium acyl hydride intermediate **6**, uses the *cis* vacant coordination site to enact a decarbonylation step as discussed previously, in which the acyl C–C bond is broken to give a rhodium-carbonyl complex **7**. This can then reductively eliminate to give an alkane **8**, leaving behind the now deactivated metal complex **9**, which cannot participate further in the hydroacylation cycle.

As mentioned, during the hydrometallation step, the acyl group can migrate to either end of the unsaturated bond in coordination molecule **11**, forming either linear **13** or branched **14** products (**Scheme 1.4**). This can give rise to regioselectivity issues when developing a methodology, and conditions must be chosen in which the desired isomer is favoured. Willis and Weller reported that, using their *β*-sulfur aldehyde motifs, hydrometallation to form the linear isomer is usually the energetically preferred process, due to a lower energy barrier and faster reductive elimination of the product.[48] Other systems have shown a reversibility in the branched hydrometallation step, compared to full irreversibility for the equivalent linear process.[51] However, catalysts and conditions have frequently been established to selectively promote formation of the branched isomer when desired.[52]

The following sections of this chapter outline the historical development of hydroacylation and the various strategies employed, beginning with intramolecular methodologies before progressing onto intermolecular variants.



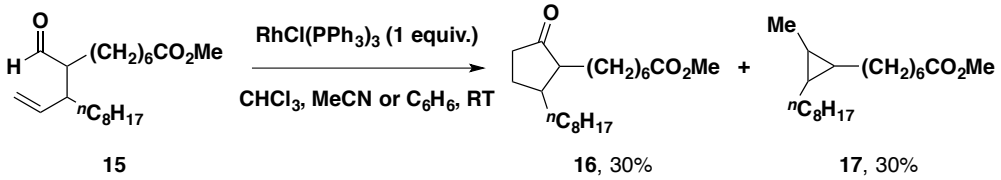
Scheme 1.4: Comparison of hydrometallation and reductive elimination steps for the formation of linear and branched isomers.

1.2 Rhodium-Catalysed Intramolecular Hydroacylation

Early developments in the field of hydroacylation centered around the use of intramolecular systems and stoichiometric rhodium catalyst to generate cyclopentanone products. The intramolecular systems chosen presented two major benefits in promoting a facile transformation. The first relates to the relative stability of the metallacyclic intermediates formed to destructive pathways such as decarbonylation, ensuring a catalytic cycle can proceed.[15] The second concerns the ability of the π-bond to pre-coordinate to the rhodium metal and act as a directing group, bringing the aldehyde C–H bond in closer proximity to the metal centre and thereby lowering the kinetic barrier. Since the earliest reports, significant advances have been made, with intramolecular alkene hydroacylation being performed under very mild conditions and low catalyst loadings. Alongside the ability to synthesise a variety of ring sizes, applications to asymmetric catalysis have allowed the formation of enantioselective products and as such, has proved extremely useful in a number of target syntheses.[53-58] Several of these developed methodologies will now be discussed.

1.2.1 Cyclopentanone Synthesis

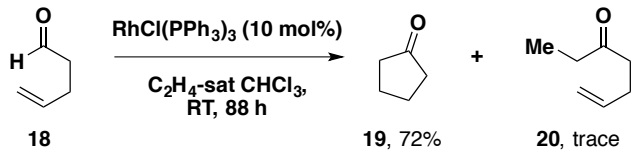
The first reported example of a rhodium-mediated hydroacylation reaction by Sakai in 1972 used stoichiometric amounts of Wilkinson's complex[59] at room temperature with a 4-enal **15** to give cyclopentanone **16** in a 30% yield (**Scheme 1.5**).[60] Unfortunately, the cyclopropane **17**, originating from the decarbonylative pathway, was produced in a similar amount, indicating the challenges to be faced with regards to suppression of this second possible route.[61-63]



15 **16**, 30% **17**, 30%

Scheme 1.5: The Sakai group's serendipitous discovery of the first reported hydroacylation.

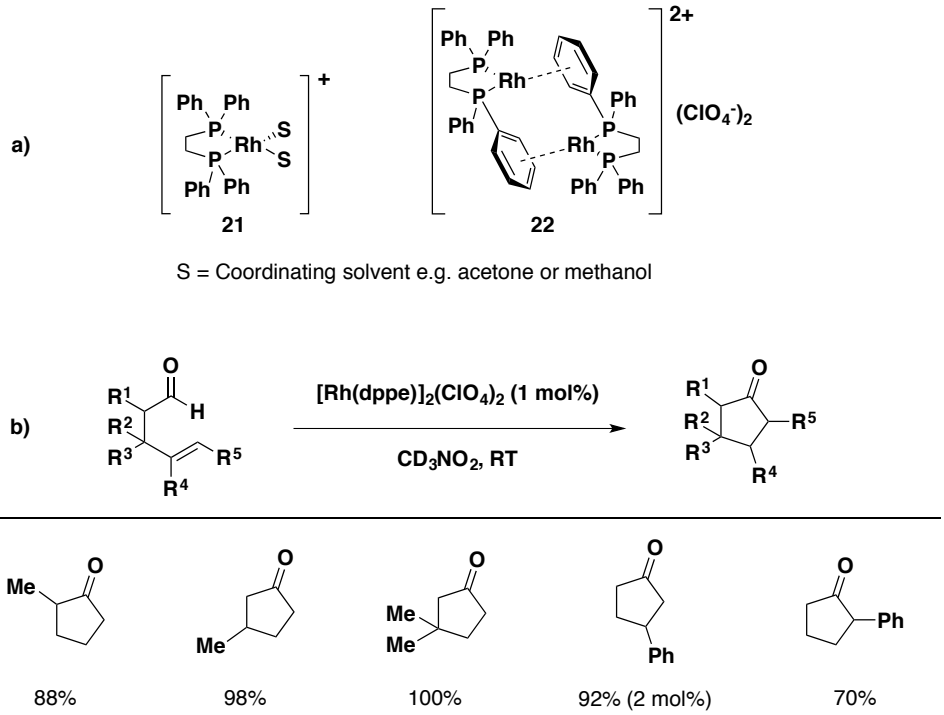
Subsequently, Miller and co-workers reported in 1976 that only catalytic amounts of rhodium complexes were required when the reaction solvents were saturated with ethylene gas.[64] By reversibly binding the rhodium metal, ethylene molecules could block the vacant coordination sites required for decarbonylation to ensue. With 4-pentenal **18**, a cyclisation successfully provided cyclopentanone **19** in 72% yield using 10 mol% of Wilkinson's catalyst (**Scheme 1.6**). However, the presence of ethylene led to the formation of small quantities of **20**, resulting from an intermolecular hydroacylation process involving ethylene and 4-pentenal **18**.



18 **19**, 72% **20**, trace

Scheme 1.6: The Miller group's reported catalytic cyclisation of 4-pentenal.

Optimisations of this reaction were continued by Larock for the synthesis of a broader range of cyclopentanones, however, several major limitations were still present. Catalyst loadings of up to 50 mol% were required, and applications to larger ring sizes proved unsuccessful.[65] A major breakthrough occurred in 1988 with the arrival of Bosnich's highly electrophilic rhodium complexes.[42] Using bidentate phosphine ligands coordinated to a cationic rhodium metal centre (of which $[Rh(dppe)]ClO_4$ was determined to be the best for his reported methodology, generated *in situ* as **21** or isolated as the arene-bridged dimer **22**), an effective intramolecular hydroacylation of 4-pentenal derivatives was reported. These conditions could furnish various substituted cyclopentanones in good yields with loadings of just 1 mol% catalyst and no significant presence of the decarbonylation products. Since then, cationic rhodium complexes remained extremely popular in reports of hydroacylation, predominantly due to their high activity and thus utility under milder conditions.[66,67]

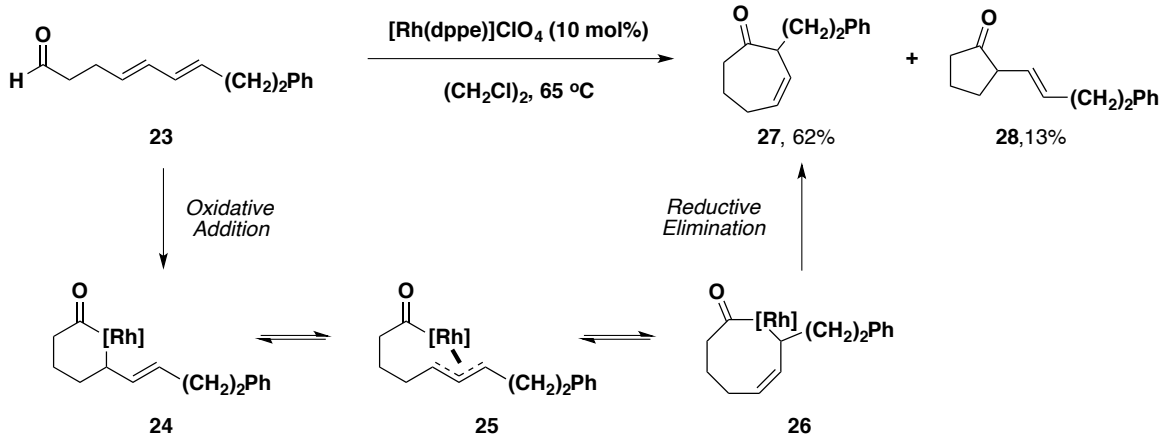


Scheme 1.7: a) Catalytic species used by Bosnich; b) Reported hydroacylation of 4-pentenals to cyclopentenones.

1.2.2 Larger Ring Synthesis

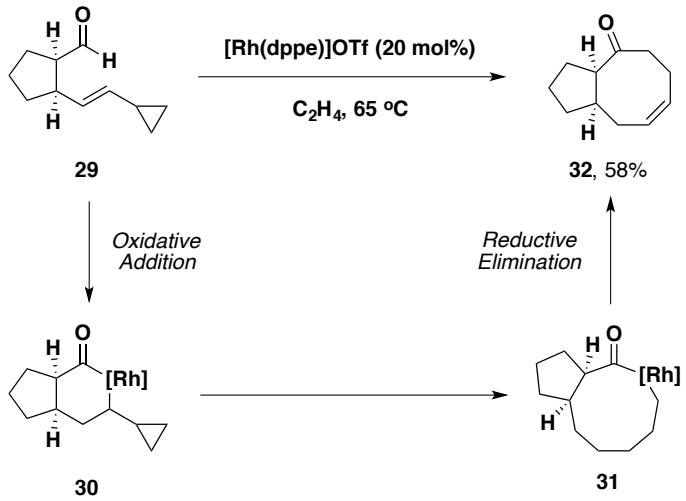
Formation of ring sizes larger than cyclopentanones presents a challenge. Usually, if a five-membered closure is possible, then this is the pathway the reaction will take due its kinetic favorability. Rings closures of larger sizes can often be slower, and therefore risk a greater chance of decarbonylation. As such, methods to prepare six-membered rings and above tend to require substrates that incorporate additional functionality which promotes the desired transformation.[64]

One such example by Mori utilises an adjacent alkenyl group to expand the rhodium metallacycle and access cycloheptanone products (**Scheme 1.8**).[68,69] Following the formation of expected metallacycle **24**, an isomerisation to **26** can occur by way of π-allylrhodium species **25**. It was found that the alkene geometry had a profound impact of the favorability of this isomerisation, with (*E*)-alkenes in the 6-position preferring this route. This is exemplified by diene **23**, which gave the cycloheptanone **27** as the major product in a 62% yield and cyclopentanone **28** as the minor product in 13% yield (**Scheme 1.8**).



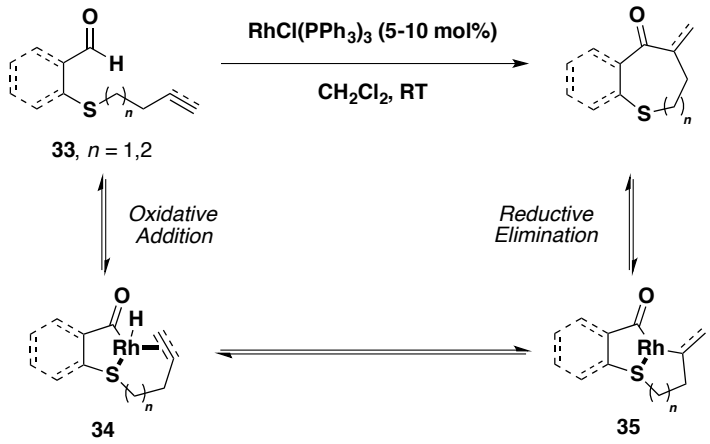
Scheme 1.8: The Mori group's route to cycloheptanones.

Shair and co-workers demonstrated a similar approach to this by employing the use of an adjacent strained cyclopropane moiety, an example of which is shown in **Scheme 1.9**.[70] Following oxidative addition of aldehyde **29**, the six membered rhodacycle **30** can 'expand' by breaking the adjacent C–C bond of the cyclopropane group, forming **31**. Reductive elimination affords the cyclooctanone **32**.



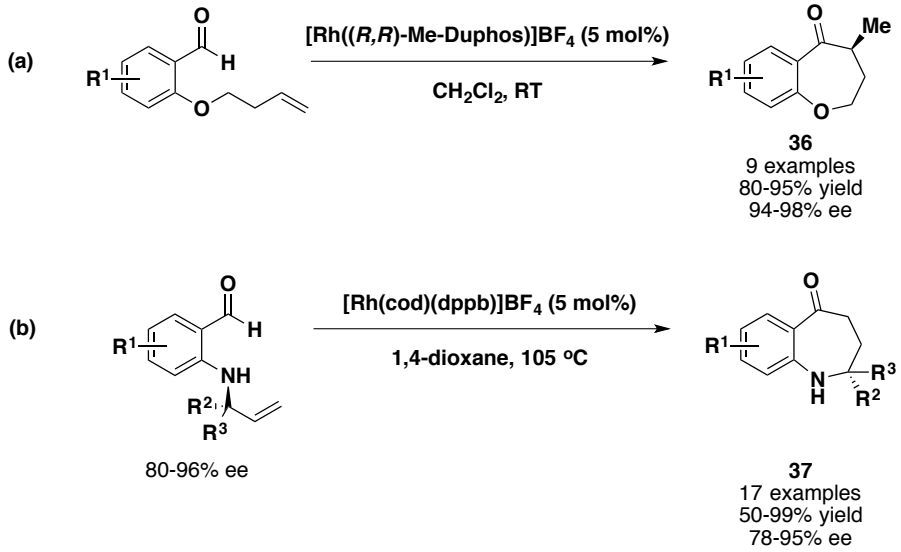
Scheme 1.9: Shair and co-workers' employment of cyclopropane groups to form cyclooctanones.

An alternative strategy exploiting the chelating ability of heteroatoms was demonstrated initially by Bendorf (**Scheme 1.10**).[71] By installing a sulfur atom into a long chain enal **33**, reductive decarbonylation could be inhibited due to the formation of a stable five-membered rhodacycle **34**, allowing access to the large ring intermediate **35**. Both alkenes and alkynes could be used here, achieving good yields in the synthesis of seven- and eight-membered rings.



Scheme 1.10: The Bendorf group's use of sulfur to facilitate cycloheptanone formation.

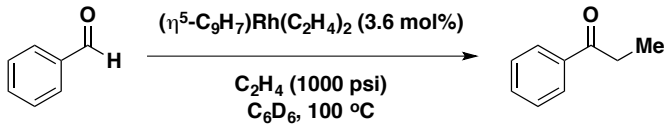
This strategy has been extended to include other heteroatoms, first by Dong *et al.*, in which ether linkages and chiral cationic catalysts are employed to generate enantioselective cycloheptanones **36** (**Scheme 1.11 (a)**).[72] Unfortunately, the substrate scope here was limited to substitutions on the aryl ring only. Nguyen and co-workers then used *N*-chelation to synthesise a greatly improved scope of seven-membered cyclic aza-ketones **37** in excellent yields and enantiopurity (**Scheme 1.11 (b)**).[73]



Scheme 1.11: a) The Dong group's enantioselective hydroacylation using ether linkages; b) Nguyen and co-workers' use of nitrogen chelating atoms in hydroacylation.

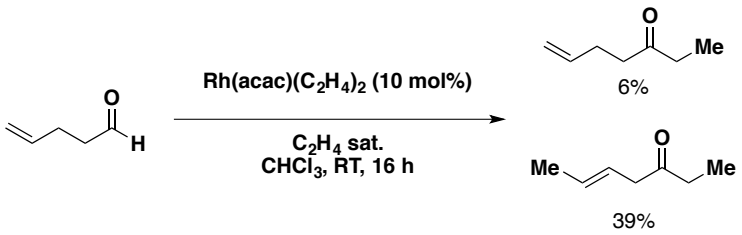
1.3 Rhodium-Catalysed Intermolecular Hydroacylation

Extending these hydroacylation conditions to intermolecular processes has continued to remain a challenge, predominantly due to the favorability of the decarbonylation pathway in such cases. One of the earliest intermolecular hydroacylation methodologies developed used simple aromatic aldehydes under extremely high pressures of ethylene atmosphere (1000 psi at 25 °C) to generate ethyl ketones. The need for this high pressure of ethylene implied that saturation of the rhodium complex by alkene coordination was a prerequisite for reactivity (an example of which is shown in **Scheme 1.12**).[74]



Scheme 1.12: The Marder and Millstein group's early attempts at intermolecular hydroacylation.

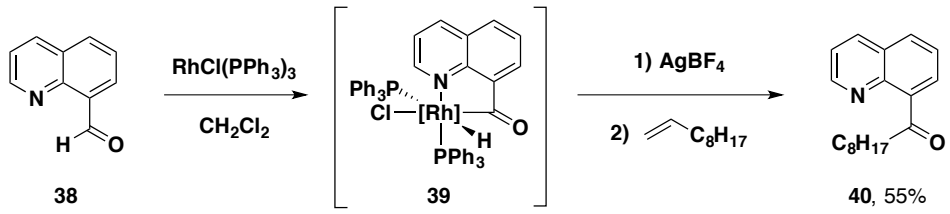
Building upon this understanding, Miller employed enals as the aldehyde component in intermolecular hydroacylation systems, and it was postulated that coordination of the alkene group aided catalyst stability, acting as a 'chelating group' in preventing the decarbonylation pathway (**Scheme 1.13**).[75,76] Since then, the use of heteroatom chelating groups has emerged as the predominant strategy for intermolecular hydroacylation, with the location of this group demonstrated on either the aldehyde or unsaturated components. Several of these examples will now be discussed, with nitrogen, oxygen and sulfur being the most prevalent heteroatoms used for chelating groups.



Scheme 1.13: An example of the Miller group's enal systems for intermolecular hydroacylation.

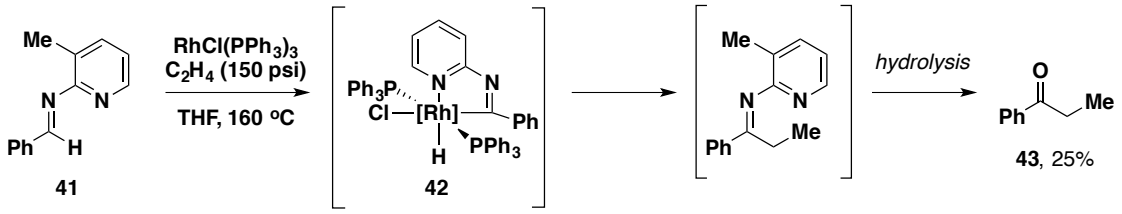
1.3.1 Nitrogen-Based Chelating Groups

The Suggs group's investigations into complex **39,** which had been isolated from oxidative addition of quinoline **38** with stoichiometric Wilkson's catalyst, identified that treatment with $AgBF_4$ and 1-octene could generate the hydroacylation adduct **40** (**Scheme 1.14**).[77,78]



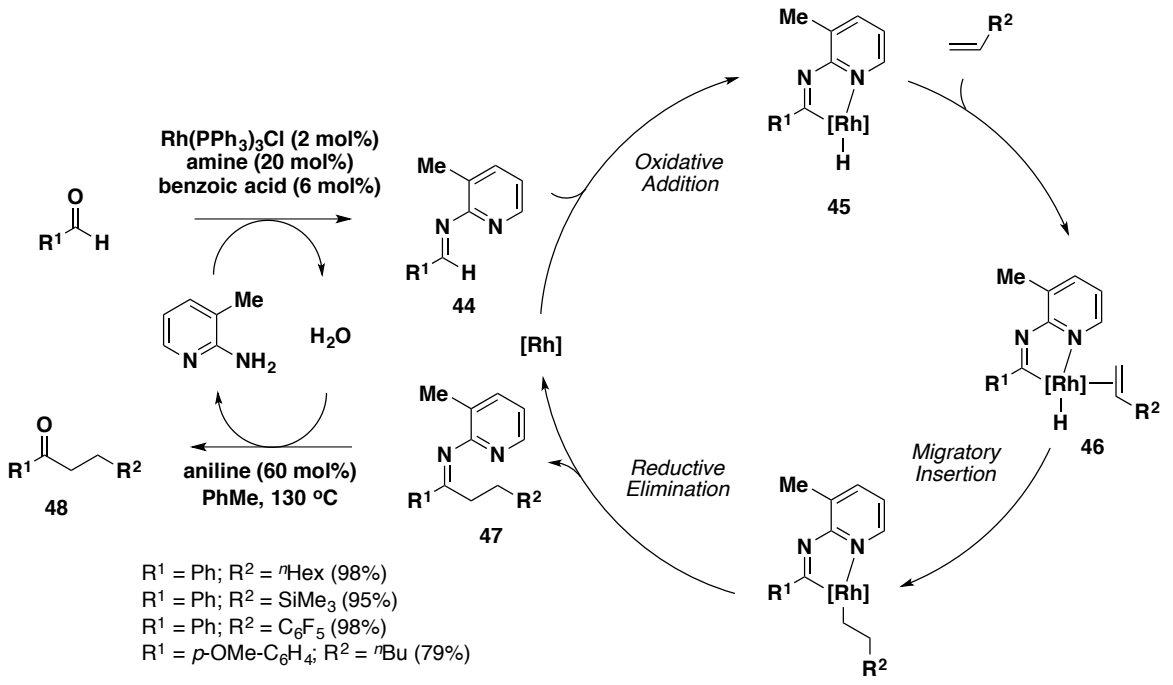
Scheme 1.14: Use of quinolines as a chelating group by Suggs.

Attempts to translate this into a catalytic process unfortunately led to reduced yields and limited substrate scope. An additional downside of these systems was the necessary incorporation of large quinoline groups in the products. A potential solution to these problems were brought forward when the Suggs group discovered that picolyl imines such as **41** could behave as equivalents to chelating aldehydes.[79] Having isolated stable rhodium-iminoacyl complexes such as **42**, they were treated with Wilkinson's catalyst (5 mol%) and ethylene to deliver, after hydrolysis, the hydroacylation adducts such as **43** (**Scheme 1.15**).



Scheme 1.15: Suggs and co-workers' initial attempts at using picolyl imines in hydroacylation.

In the 1990s, the Jun group built upon these results by developing a way to generate and hydrolyse the imines *in situ* from the corresponding aldehydes and amines, using catalytic benzoic acid (6 mol%) and aniline (60 mol%) for each process, respectively.[80] Thus, a simple route incorporating various alkenes with aldehydes could be achieved in good to excellent yields, without incorporation of the directing groups in the final products (**Scheme 1.16**). Mechanistically, the imine **44** is generated *in situ* using benzoic acid as a catalyst, which then undergoes oxidative addition with the rhodium complex to form **45**. The alkene coordinates, and complex **46** undergoes migratory insertion followed by reductive elimination to give imine **47**. This is then hydrolysed, catalysed by aniline to give the ketone adduct **48**.

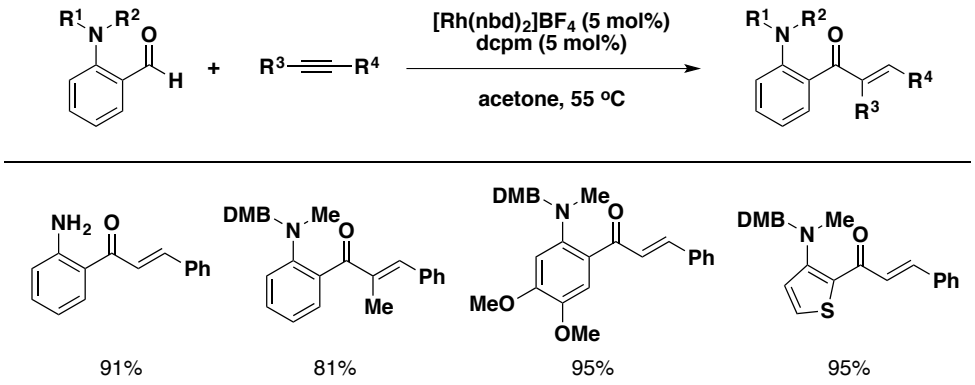


Scheme 1.16: Mechanism and scope of the Jun group's traceless chelation-controlled hydroacylation.

Applications to alkyne hydroacylation were also possible, although in most cases the branched isomer was the predominant regioisomer formed.[81-85] This has been attributed to the reasonably small size of the triphenylphosphine ligands. Bosnich's cationic complexes also proved inferior as, in this particular instance, oxidative addition with cationic rhodium is thermodynamically less favoured than that with a neutral rhodium complex.

In recent years, Willis and co-workers have demonstrated the versatility of 2-aminobenzaldehyde derivatives as aldehyde coupling partners in intermolecular alkyne hydroacylation.[86] Using a small bite-angle ligand dcpm, a variety of hydroacylation adducts could be synthesised from both terminal and internal unactivated alkynes in good to excellent yields and impressive regiocontrol (**Scheme 1.17**). Catalyst loadings could be lowered to as little as 2 mol% by the addition of 10 mol% acetonitrile, believed to stabilise the

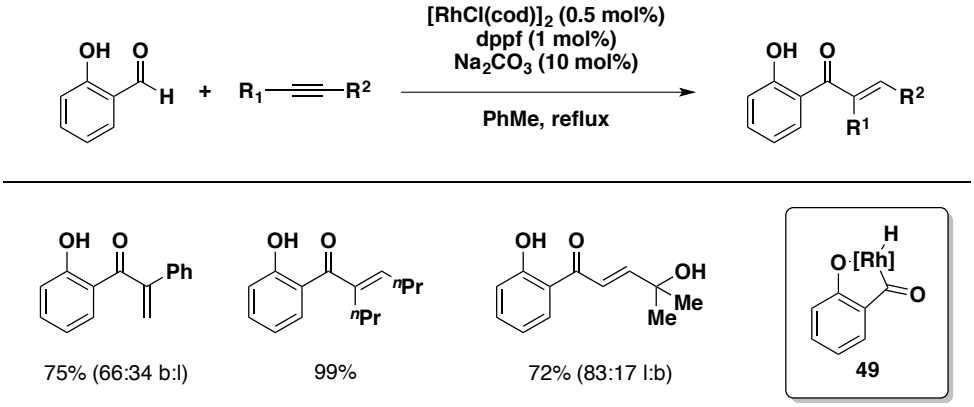
intermediates in the catalytic cycle.



Scheme 1.17: The Willis group's intermolecular alkyne hydroacylation with 2-aminobenzaldehyde derivatives.

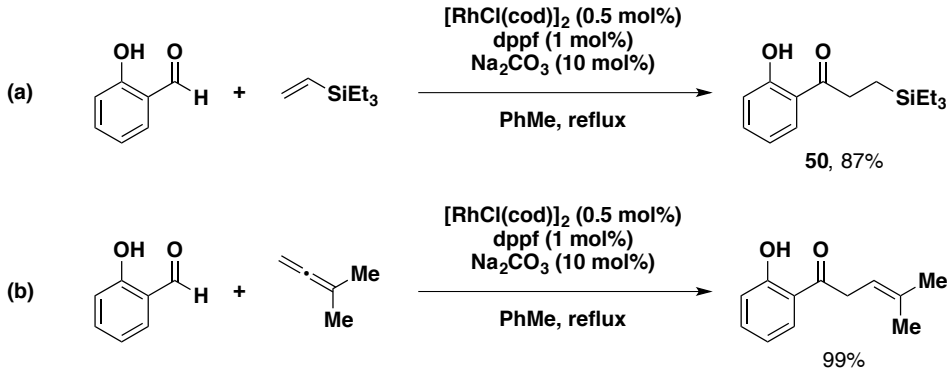
1.3.2 Oxygen-Based Chelating Groups

Development of oxygen-based chelating systems for hydroacylation began in 1997, when Miura demonstrated the utility of simple salicylaldehyde derivatives as *O*-chelated coupling partners (**Scheme 1.18**).[87,88] Such substrates present a synthetic attractiveness due to their ready availability and preinstalled chelating group. By using a low catalyst loading of neutral rhodium complex $[RhCl(cod)]_2$ with the ferrocene-based ligand dppf and catalytic base, reasonable activity could be seen with alkynes. It was proposed that the base was necessary to deprotonate the phenol group on the aldehyde, making it more nucleophilic and promoting its chelating ability in the catalytic intermediates (an example of which is **49**, **Scheme 1.18**). However, several limitations presented themselves under Miura's conditions, the most concerning of these being the poor linear:branched regioselectivity with alkynes, despite the good to excellent yields observed. Branched enones were usually only slightly more favoured, with linear selectivity only observed for propargylic alcohols. Using symmetrical internal alkynes avoided this problem, and this method continues to be used for the synthesis of such products.



Scheme 1.18: Miura's alkyne hydroacylation using salicylaldehydes.

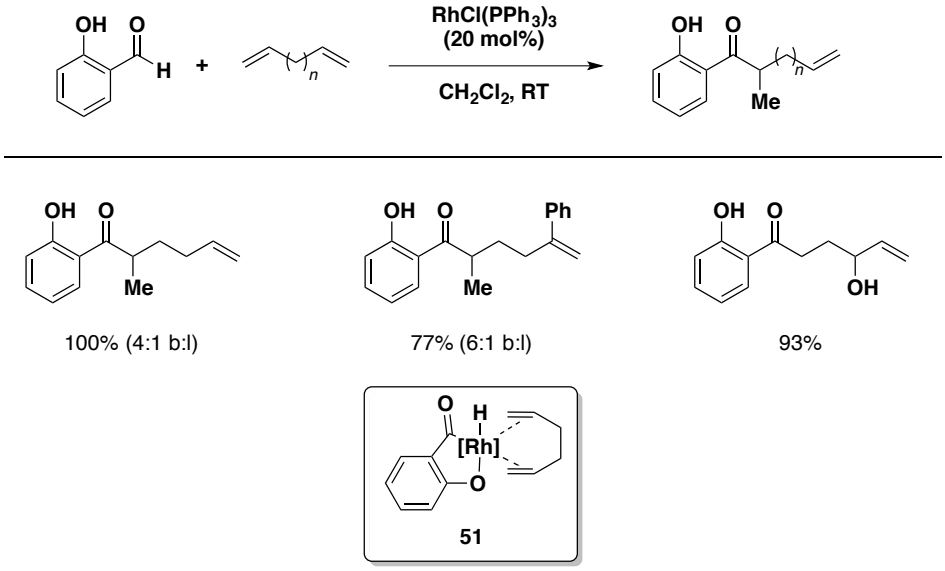
Disappointingly, reactions of these aldehydes with most alkenes delivered poor reactivity, for example norbornene only yielded 6% of the desired product. An exception was vinyltriethylsilane, which, using the established conditions, gave the hydroacylation adduct **50** in good yield (**Scheme 1.19 (a)**). However, simple allenes proved to be acceptable coupling partners to deliver *β*-*γ*-enones, as illustrated in **Scheme 1.19 (b)**.



Scheme 1.19: (a) Miura and co-workers' singular example of successful alkene hydroacylation. (b) Example of allene hydroacylation.

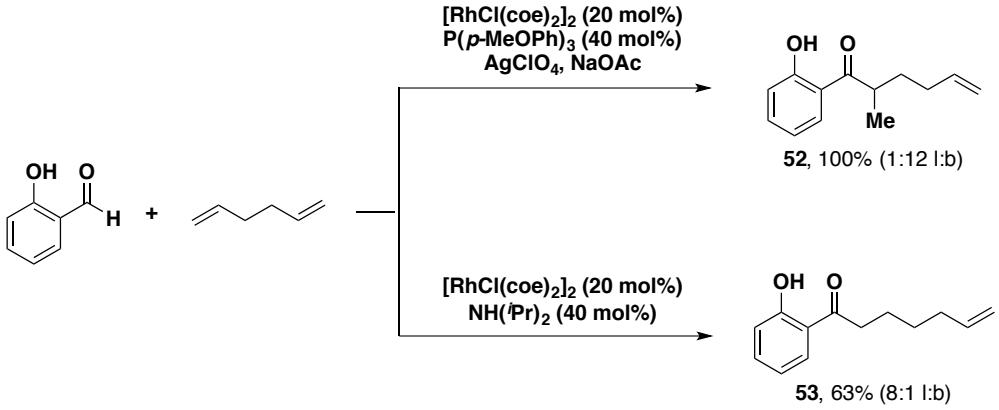
Work with these *O*-tethered aldehydes was continued by Suemune, who investigated the use of such substrates with dienes.[89,90] Using mild conditions and Wilkinson's complex (20 mol%), excellent yields could be achieved for the addition of salicylaldehydes to various 1,4- and 1,5-dienes, but low yields for 1,6-dienes. Once again, however, poor regiocontrol

was observed for successfully coupled substrates. Deuterium labelling studies suggested that, mechanistically, double chelation involving two-point interactions not only with the aldehyde but with the diene also (**51**, **Scheme 1.20**), and an irreversible reductive elimination accounted for the high levels of reactivity.



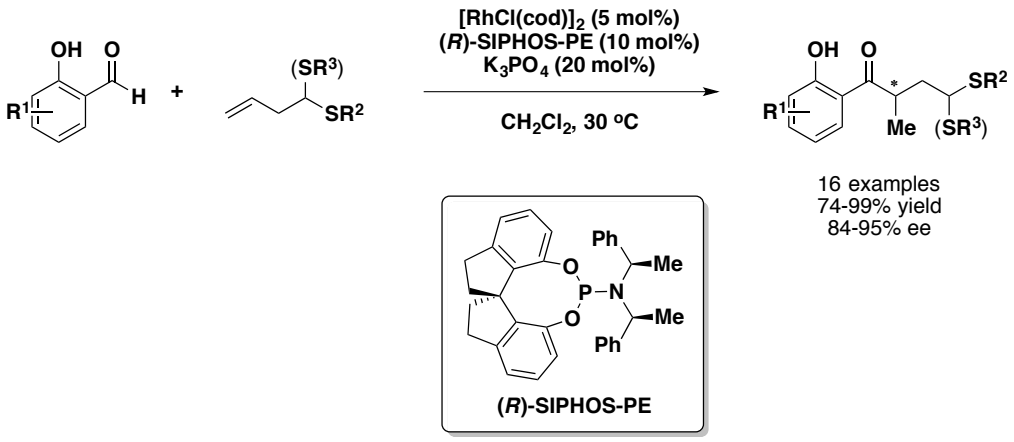
Scheme 1.20: Suemune's reported hydroacylation of salicylaldehydes with dienes.

To improve upon these regioselectivities, Suemune undertook an extensive screening of catalysts and reaction conditions. Eventually, it was determined that each regioisomer could be accessed selectively by using the catalyst $[RhCl(coe)_2]_2$, together with the additives P(*o*-MePh)$_3$, $AgClO_4$ and NaOAc to access the linear isomer **52**, and the base NH(^{i}Pr)$_2$ added to deliver the branched isomer **53** (**Scheme 1.21**).[90]



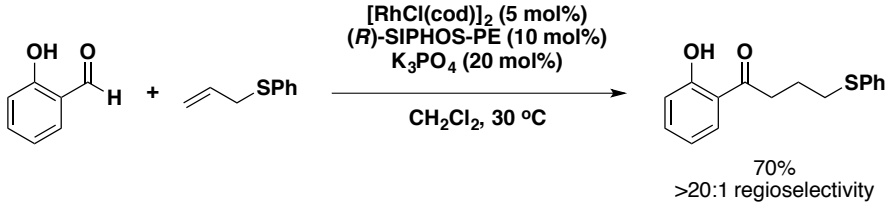
Scheme 1.21: Optimised conditions for accessing each isomer selectively.

Continuing with this concept of double chelation of both aldehyde and alkene components, Dong proposed that replacing the second unsaturated π-bond on the alkene with a more strongly coordinating sulfur atom would improve the levels of regioselectivity. As this transformation created an *α*-stereocentre, by using a chiral phosphoramidite ligand, the Dong group was able to develop this into an enantioselective process with good levels of enantiocontrol, albeit only with terminal alkenes (and thus only a methyl group generated in the *α*-position).[91]



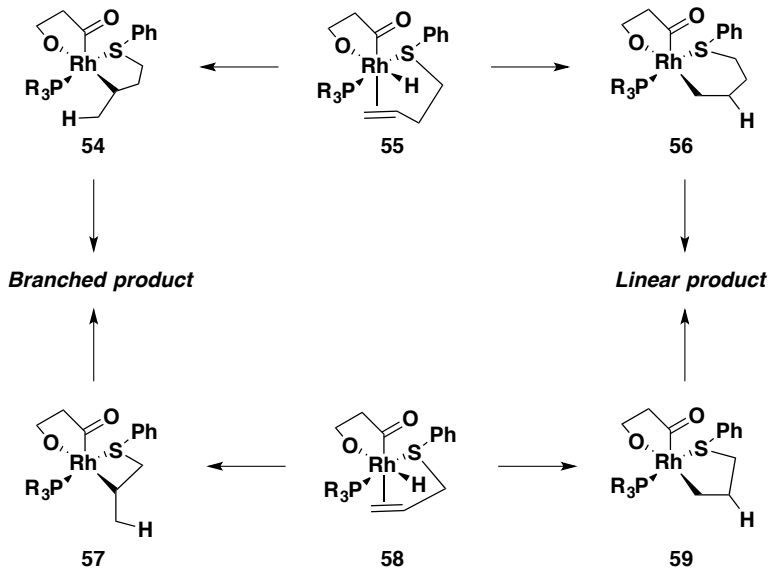
Scheme 1.22: The Dong group's enantioselective hydroacylation of salicylaldehydes.

Interestingly, when allylic sulfides were employed instead, near complete linear selectivity was observed (**Scheme 1.23**).



Scheme 1.23: Use of allyl sulfides to deliver linear selectivity.

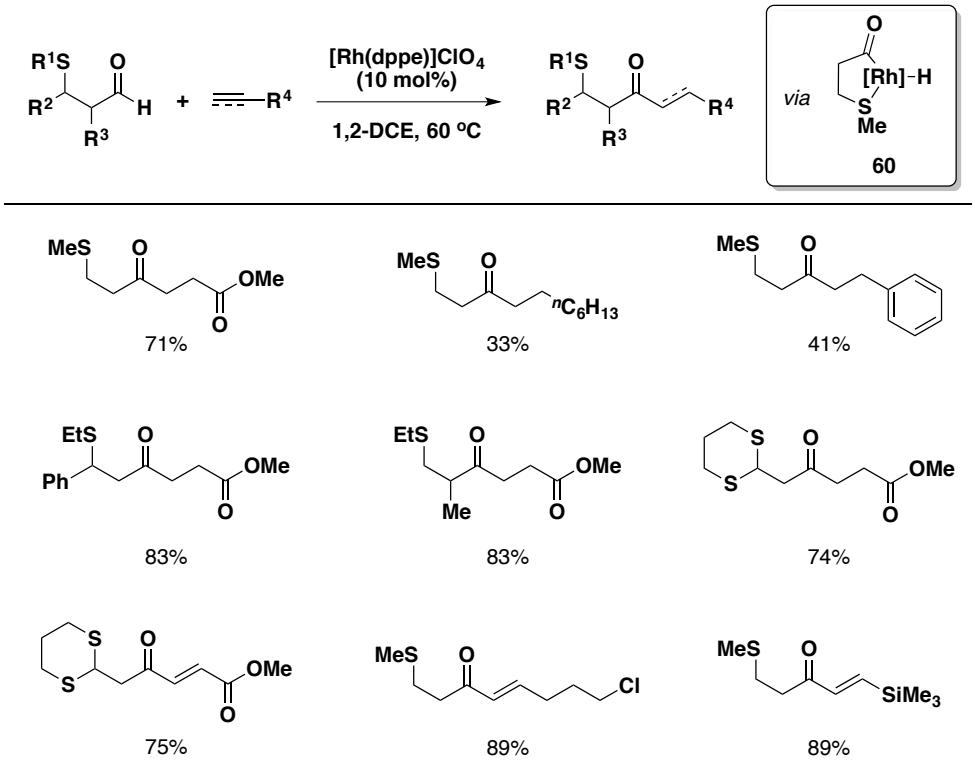
These differences in regioselectivities were rationalised by the relative favorabilities in ring formation upon migratory insertion. For the homoallylic sulfides, 'double chelation' following oxidative addition gives complex **55** (**Scheme 1.24**). Hydrometallation can then form either a five-membered **54** or six-membered **56** chelate, with the five membered rhodacycle being the preferential one here, leading to the branched isomer. Alternatively, the options for allylic sulfides from the initial complex **58** are either a four-membered **57** or five-membered **59** systems, thus leading to a more favourable formation of the linear product. As such, the Dong group were able to utilise the understanding behind this theory to effectively use allylic alcohols as unsaturated coupling partners.[92]



Scheme 1.24: Mechanistic rationale for differences in selectivities.

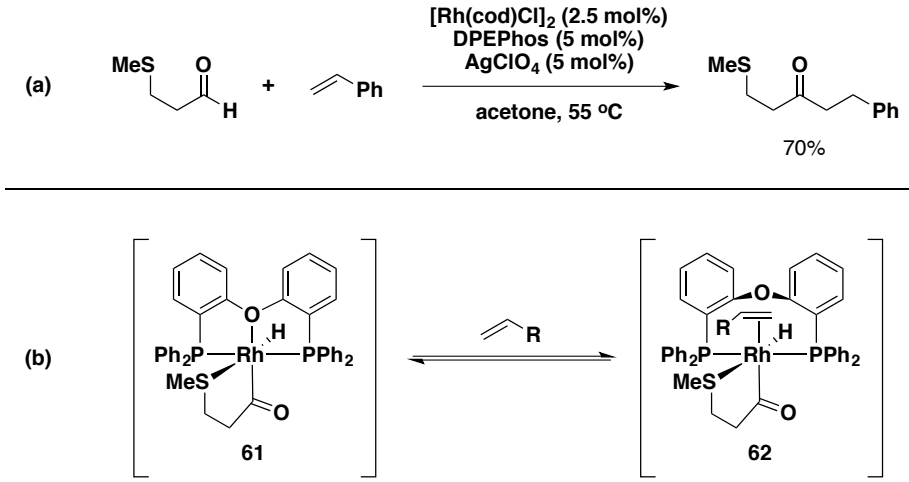
1.3.3 Sulfur-Based Chelating Groups

The benefits of using sulfur atoms in chelation control have been discussed previously in Bendorf's preparation of cyclic ketones (**Scheme 1.10**).[71] Since then, the use of sulfur-based chelating groups in intermolecular hydroacylation has been pioneered by Willis and Weller, using Bosnich-type cationic rhodium complexes with an ever-increasing array of bisphosphine ligands. In their seminal report in 2004, it was determined that locating the sulfur atom β- to the aldehyde was crucial for any reactivity to be observed.[93] The reason for this was attributed to the five-membered chelate in intermediate **60**, which was believed to possess some stability towards decarbonylation. By reacting various β-sulfur containing aldehydes with a range of electron deficient alkenes and terminal alkynes, the desired products could be achieved in good to excellent yields and regioselectivity (**Scheme 1.25**).[94,95] Unactivated alkenes, however, gave reduced yields.



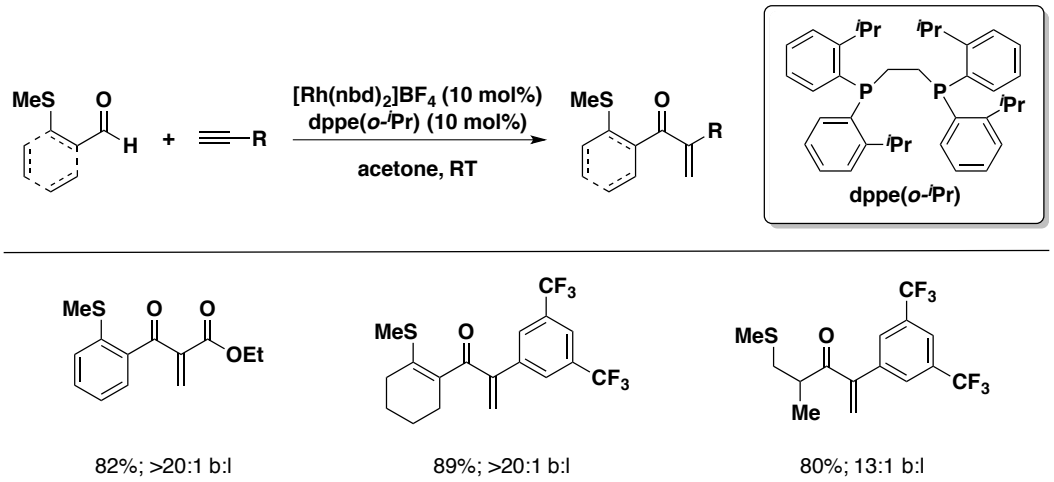
Scheme 1.25: The Willis group's sulfur-tethered hydroacylation of alkenes and alkynes.

To improve these results, Willis and Weller commenced designing new catalysts to allow for more efficient reactivity. In 2006, they reported a so-called 'second generation' catalyst, the hemilabile DPEPhos ligand. This catalyst, generated *in situ* from bench-stable precursors, could now enact the hydroacylation of *β*-sulfur aldehydes with unactivated alkenes in improved yields, using a reduced catalyst loading (**Scheme 1.26 (a)**).[46] The enhanced reactivity was thought to arise through the additional stabilisation provided by the ether linkage in this ligand, which can reversibly coordinate to the rhodium metal and thereby prevent decarbonylation, whilst allowing for the binding of the alkene or alkyne component. This was confirmed by X-ray crystallography, amongst other techniques, when the stabilised acyl-hydride complex **61** was isolated alongside the intermediate **62** arising from the π-coordination of the alkene (**Scheme 1.26 (b)**).[45]



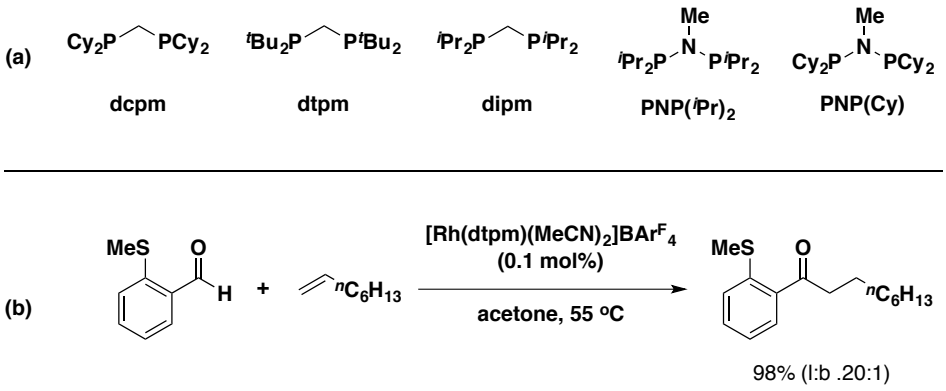
Scheme 1.26: (a) Demonstrated improvement of reactivity with second generation catalyst; (b) Hemilabile activity of the ether linkage in DPEPhos.

Despite this marked improvement, in 2012, Willis and Weller set about designing a new 'third generation' of ligands. The initial rationale for pursuing this new class was the belief that accelerating the rate limiting step (i.e. reductive elimination) in the catalytic cycle would limit the propensity for any intermediates to undergo decarbonylation. Whilst, traditionally, larger bite-angle and sterically bulky bisphosphines are known to expedite reductive elimination, interestingly these ligands actually led to only moderate levels of reactivity and much reduced regioselectivity.[96] Willis and co-workers were able to take advantage of this and optimise a catalyst system to favour branched selectivity in alkyne hydroacylation (**Scheme 1.27**).[52]



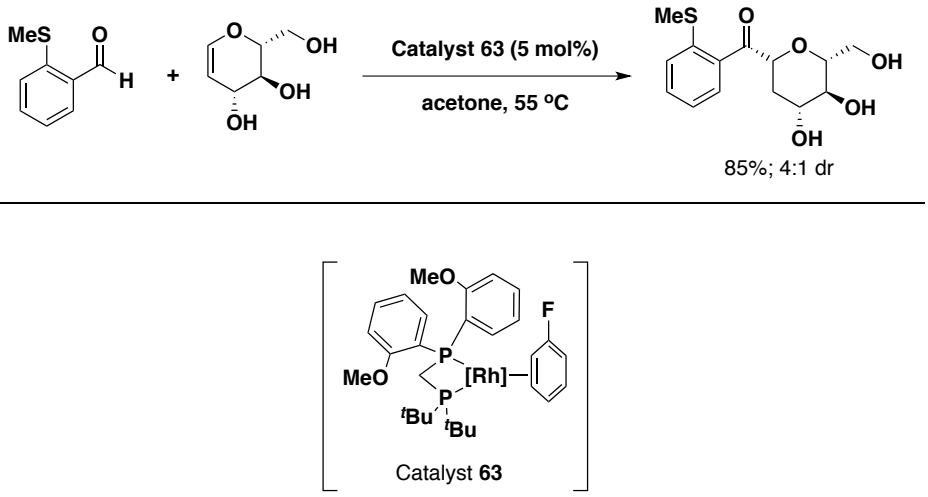
Scheme 1.27: Optimisation of branched selective hydroacylation.

Turning their attention to small bite-angle ligands, it was observed that employing such properties did indeed promote superior levels of reactivity and selectivity for the linear regioisomer. These ligands (examples of which can be seen in **Scheme 1.28 (a)**) could achieve turnovers of 300 h^{-1} at just 0.1 mol% catalyst loading,[48] and delivered much improved yields in olefin hydroacylation (example **Scheme 1.28 (b)**).[97] The causes of these effects were studied by Werner in the carbonylation of π-allyl rhodium-complexes, proposing that reductive elimination was promoted by small bite-angles.[98]



Scheme 1.28: (a) Examples of small bite-angle ligands used in this study; (b) Improved reactivity in olefin hydroacylation with third generation ligands.

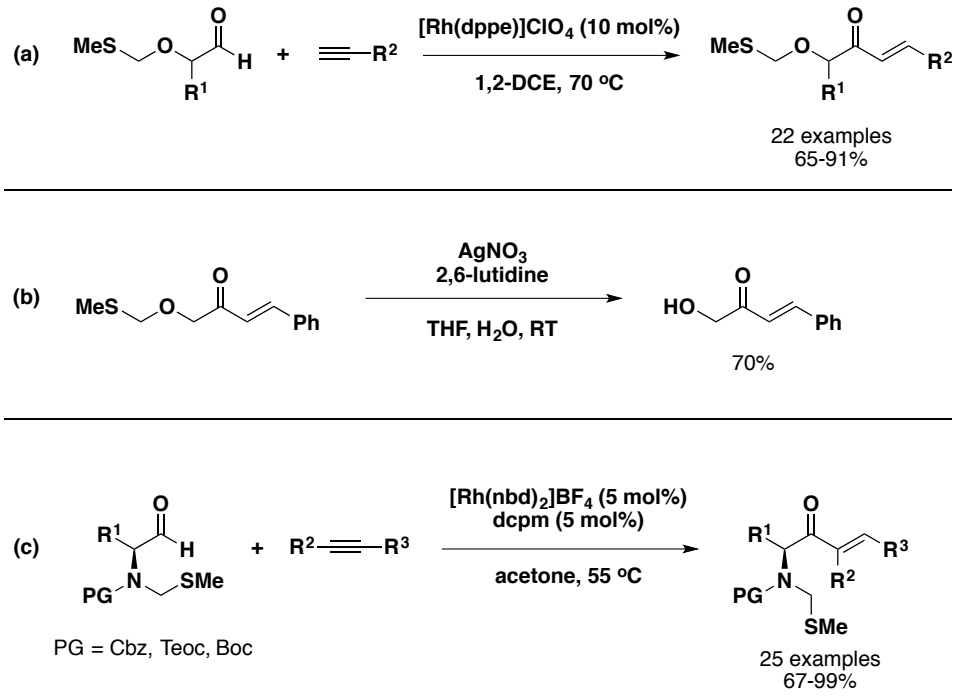
Modification and fine-tuning of the electronic or steric properties of these ligands is relatively accessible, allowing for individual optimisations for the hydroacylation transformation required. For example, adjustment of the common small bite-angle ligands outlined previously led to the design and synthesis of catalyst **63**. Containing potentially chelating *o*-methoxy groups on the phenyl substituents of one phosphorus atom, this catalyst has been shown to execute the hydroacylation of internal alkenes with *β*-sulfur containing aldehydes (**Scheme 1.29**).[99] Until this point, hydroacylation of these unsaturated substrates had proved most challenging.



Scheme 1.29: Hydroacylation of internal alkenes using catalyst **63**.

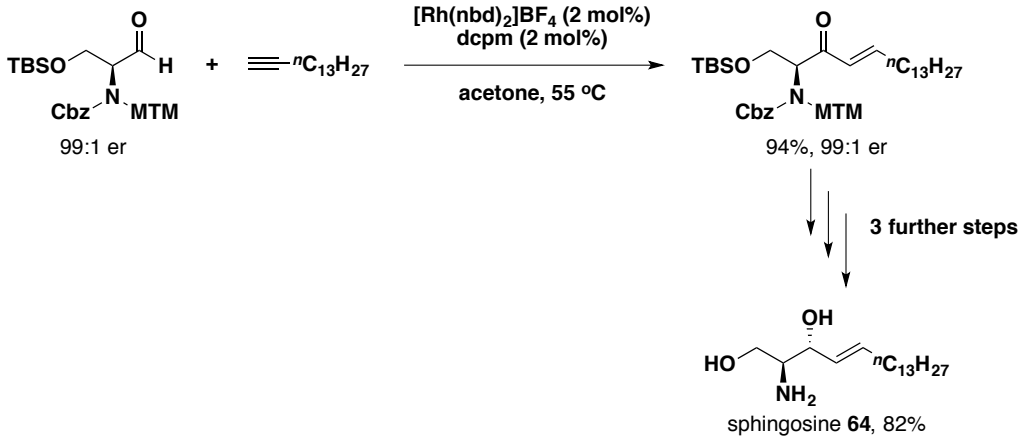
The robustness of these small bite-angle ligands has allowed their application to aldehyde substrates containing a methylthiomethyl (MTM) group as the chelating moiety. Previously, reactivity with MTM containing substrates had been demonstrated using the 'first generation' ligand dppe in terminal alkyne hydroacylation (**Scheme 1.30 (a)**), although this reactivity was lower in comparison to the equivalent *β*-sulfur aldehydes.[100] Attempts to combine these aldehydes with alkenes and internal alkynes also failed. However, facile removal of the MTM post-transformation had been proven, establishing the potential and

versatility of this directing group (**Scheme 1.30 (b)**). Using the small bite-angle ligand dcpm, the utility of the MTM chelating group was vastly improved. Hydroacylation of MTM-protected α-amino aldehydes could be achieved in high yields with retention of stereochemistry (**Scheme 1.30 (c)**).[101] Internal alkynes could also be coupled successfully.



Scheme 1.30: (a) The MTM group as a tether with 'first generation' catalysts; (b) Removal of the MTM group post-hydroacylation; (c) The MTM group with α-amino aldehydes with 'third generation' catalysts.

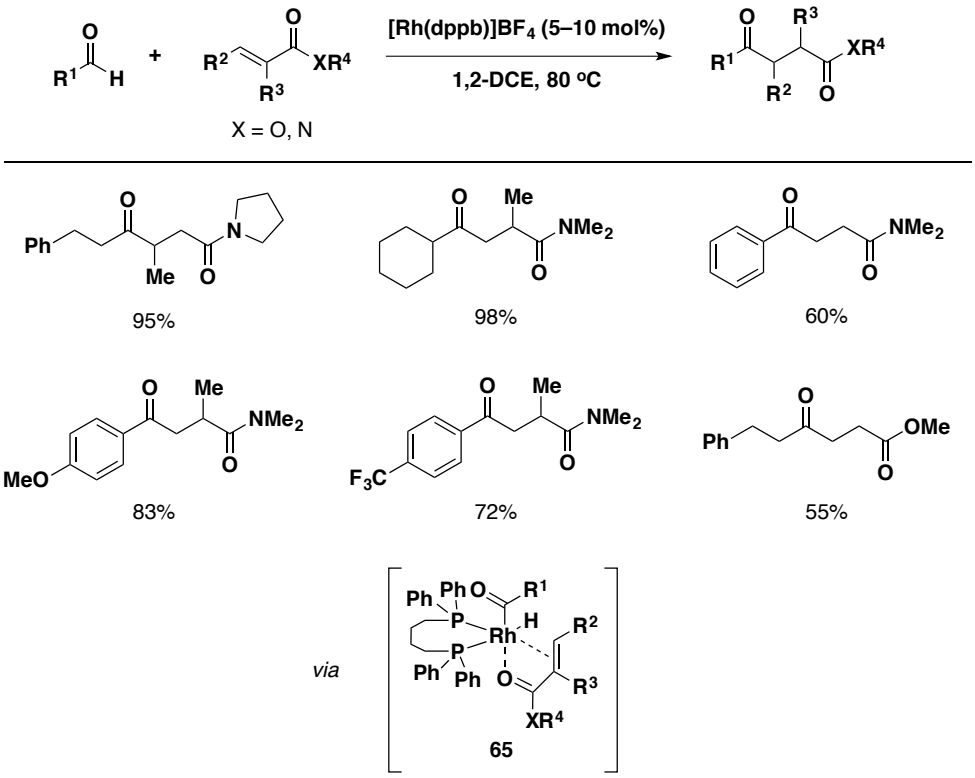
The Willis group was able to apply this new and improved methodology with MTM-protected α-amino aldehydes to the synthesis of sphingosine **64** in an efficient and economic manner. The hydroacylation process represented one of the crucial C–C bond-forming steps in the product synthesis (**Scheme 1.30**).[101]



Scheme 1.30: Application of MTM-protected aldehydes to the synthesis of sphingosine.

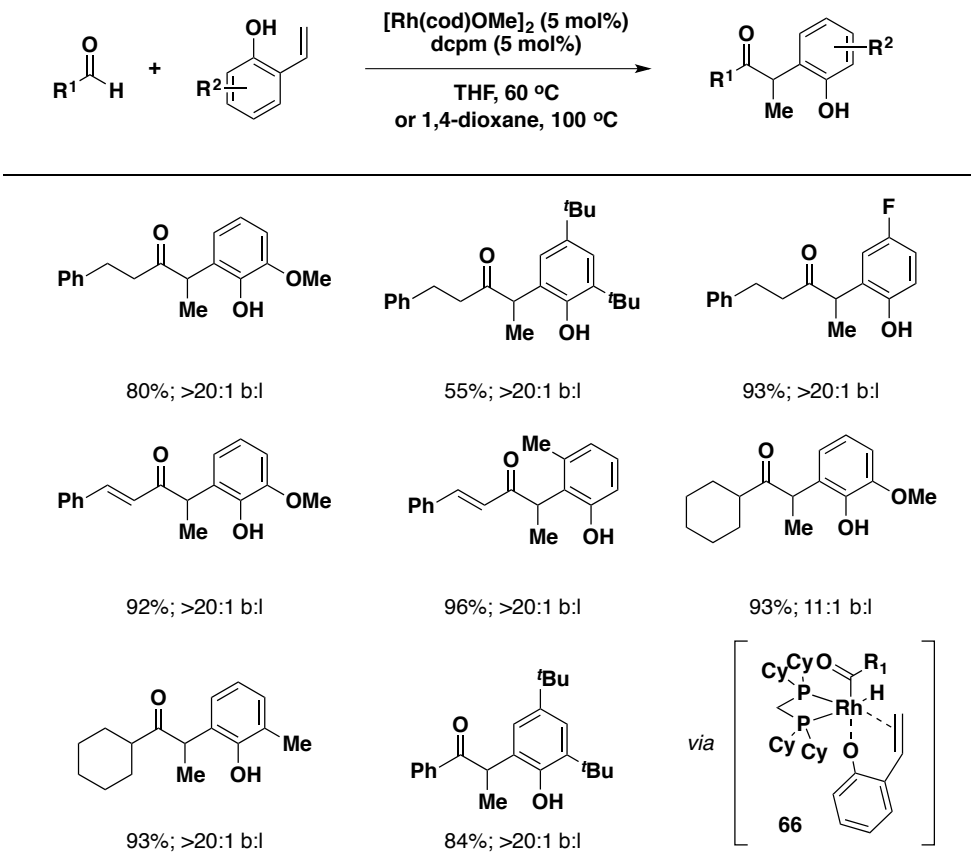
1.3.4 Non-Chelating Aldehydes

As the field of hydroacylation continues to evolve, researchers seek to ever increase the substrate scope possible in intermolecular processes. As such, methodologies have now been reported in which the chelating group is not located on the aldehyde component, but on the unsaturated coupling partner instead. The first case of this to appear was disclosed by Tanaka and co-workers in 2007, in which the cationic species [Rh(dppb)]BF_4 promoted the generation of the adduct formed from non-chelating aldehydes and acrylamides or acrylates (**Scheme 1.32**).[102] Stabilisation of the rhodium-acyl hydride intermediate **65** to reductive decarbonylation was thought to be due to the additional coordination of the carbonyl group on the olefin unit. Further investigations led Tanaka to develop an asymmetric process using methyl acrylamides.[103]



Scheme 1.32: Tanaka's use of amide and ester carbonyls as tethers on the unsaturated component.

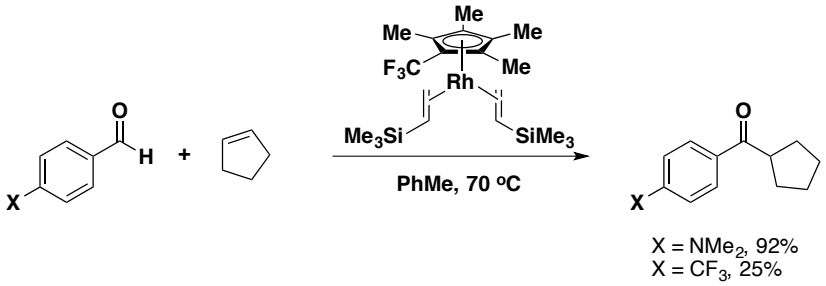
More recently, the Dong group advanced their investigations of oxygen-chelating groups by successfully combining *ortho*-vinyl phenols with a variety of non-chelating aldehydes in hydroacylation. By using small bite-angle ligands with the rhodium complex $[Rh(cod)(OMe)]_2$, excellent yields could be achieved with impressive selectivities for the branched regioisomer.[104] It is believed that the utilisation of an electron-rich catalyst lowers the barrier for the rate limiting, non-directed oxidative addition of the aldehyde C–H bond.[105] Subsequently, the reaction is thought to proceed *via* the stabilised intermediate **66**, where the oxygen heteroatom of the olefin coordinates to the metal centre, thereby limiting the favorability for the decarbonylation pathway (**Scheme 1.33**).



Scheme 1.33: Selected examples from Dong's hydroacylation with vinyl phenols.

1.3.5 Towards Tetherless Hydroacylation

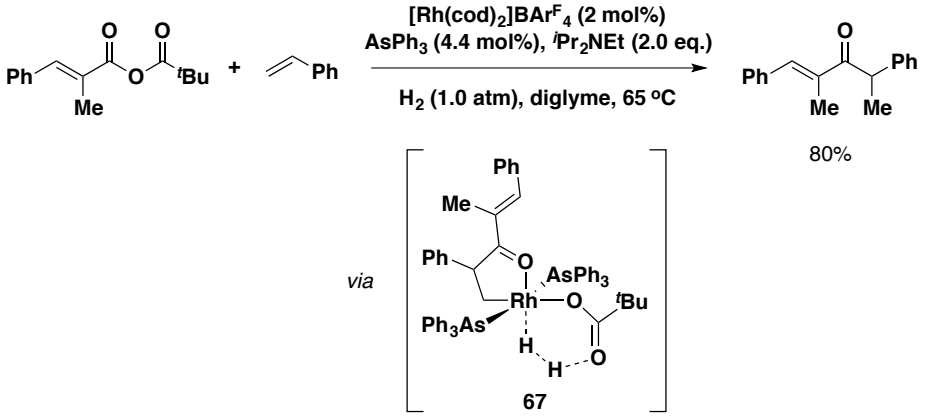
Whilst the success of various heteroatom tethers in hydroacylation processes has been demonstrated throughout this chapter, the presence of these now redundant chelating groups in the products continue to remain a disadvantage. The pursuit of a completely tetherless procedure has gained significant momentum in recent years, with one of the seminal reports outlined by Brookhart in 2007.[106] By using an electron-poor cyclopentadienyl-based catalyst with non-chelating aldehydes containing an especially strong C–C bond adjacent to the carbonyl (such as electron rich benzaldehydes), a reasonable yield for the hydroacylation adduct could be achieved (**Scheme 1.34**). Those with weaker C–C bonds, such as alkyl aldehydes, underwent decarbonylation.



Scheme 1.34: Brookhart's example of a tetherless hydroacylation process.

Further tetherless hydroacylation processes have been reported using metals such as Ir,[107-109] Ru,[110-116] Co,[117-121] Ni,[122-128] Au[129,130] or *N*-heterocyclic carbene (NHC)[131-148] catalysts, thus broadening the array of possible transformations that can be achieved. However, in all of these methodologies significant limitations are present, predominantly concerning the substrate scope. As such, a general tetherless hydroacylation procedure currently remains elusive.

Moving beyond the realms of simple aldehyde C–H activation, Krische has proposed a conceptually unique method for synthesising formal hydroacylation products (**Scheme 1.35**). Starting from acid anhydride materials and alkenes, and utilising unusual triphenylarsine ligands and a base with a Bosnich-type cationic rhodium complex, the procedure initially begins with oxidative addition and olefin insertion of the anhydride.[149,150] In a hydrogen gas atmosphere, hydrogenolysis of the acylrhodium(III) carboxylate can then take place, to give the alkyl rhodium hydride. This can reductively eliminate, delivering the hydroacylation product and a carboxylic acid byproduct. Computational studies have supported the theory that hydrogenolysis takes place *via* a six-membered transition state **67**, highlighting a potential reason for the poor reactivity observed with equivalent acyl chlorides or fluorides.[151-153]



Scheme 1.35: Krische's novel procedure to synthesise hydroacylation type products.

1.4 Summary

The historical development of hydroacylation has often centred around preventing the formation of side products, usually those of the reductive decarbonylation pathway which renders the catalyst inactive. Intramolecular processes have advanced to a mature degree, with a wide range of synthetic methodologies now available to access five-membered rings and above. The evolution of intermolecular hydroacylation has been slower and required more conceptual creativity, namely through employment of heteroatom chelates on either coupling component to suppress the alternative decarbonylation route. However, the power of these transformations and synthetic utility they represent are becoming increasingly apparent, as substrate scope slowly expands to include a variety of new linkages and even non-chelating systems. Nevertheless, the challenges remain in place with regards to designing the optimal system to allow for mild reaction conditions, broad scope and regiospecificity.

Despite the increasing importance and generality of rhodium-catalysed hydroacylation, it is often noted that the presence of the chelating group in the products is a major drawback in

its utility and synthetic appeal. Whilst it would be of interest to explore methods to efficiently remove or transform these chelating groups, there has been a need to expand the range of chelating groups to include those suitable enough to enact the coupling process, but which may also be desirable themselves in the products.

It is therefore our aim in Chapter 2 to explore new chelating groups in rhodium-catalysed intermolecular hydroacylation, which themselves pose synthetic appeal in the generated products.

Chapter 2

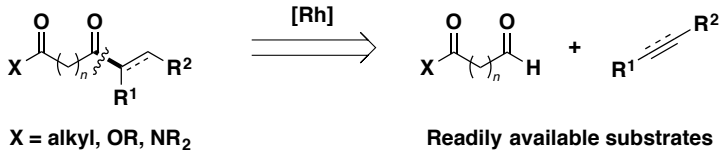
Investigating Carbonyl Tethers for Rhodium-Catalysed Hydroacylation

2.1 Introduction

Although a small number of non-chelation controlled hydroacylation methodologies exist, the vast majority rely on chelating systems to promote the selective activation of aldehyde C–H bonds (see **Section 1.3**).[53-105] By installing an appropriate directing group on either coupling partner, the efficient functionalisation of an otherwise unreactive aldehyde C–H bond can be made possible, providing a powerful and widely applicable retrosynthetic disconnection. However, the installation and removal of these chelating groups are often considered to be a practical drawback. Whilst commonly used chelates such as *β*-sulfur tethers[71,93-101] deliver efficient reactivity in hydroacylation, subsequent steps are required to remove the directing group if such a moiety is undesirable in the product.

To overcome the limitation of this approach, there are three possible solutions. Firstly, one can simplify the chelating group to allow its removal to become easier, for example, by using a straightforward protecting group. Secondly, the tether can be attached *via* a transient covalent bond as discussed in **Section 1.3.1**, rendering the chelating group as catalytic.

Thirdly, one can employ the use of common functional groups desirable in the end product, circumnavigating the need for any further steps at all. It was our aim to explore this last concept, namely by investigating the use of the carbonyl group in amides, esters and ketones to enact an efficient and selective hydroacylation procedure (**Scheme 2.1**). With carbonyls being some of the most abundant and synthetically useful functional groups in organic chemistry, such a methodology could generate a broad range of highly sought after dicarbonyl products.



Scheme 2.1: Proposed hydroacylation methodology using amides, esters and ketones.

2.2 Intermolecular Hydroacylation of *β*-Amido Aldehydes

The ubiquity and importance of amide functional groups cannot be overstated, with their motifs present in the majority of organic natural products. It is no surprise, therefore, that their involvement in transition-metal catalysed processes, particularly C–H bond activations, continues to evolve.[16,102,103] However, to our knowledge, their ability to act as a chelating group in intermolecular aldehyde hydroacylation has yet to be fully explored.

Therefore, our initial investigations focused on using substrates containing an amide tether, specifically *β*-amido aldehydes of the type seen in **Figure 2.1**. Assuming any chelation would operate through the carbonyl group, this 1,3-dicarbonyl arrangement maps itself comparably onto motifs known to be successful in similar rhodium-catalysed processes, such as the sulfur, nitrogen and oxygen-chelating aldehydes discussed in **Section 1.3** (**Figure 2.1**).

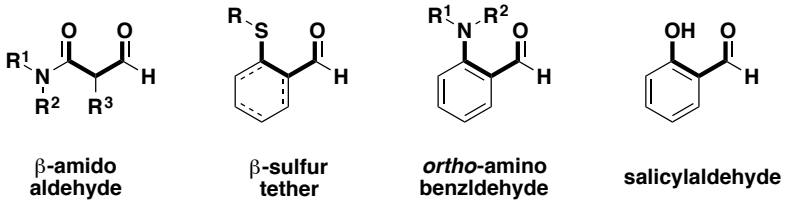


Figure 2.1: Comparison of *β*-amido aldehyde motif with known hydroacylation systems.

Our hypothesis was that the amide chelate could behave in an analogous manner to its counterparts, providing a five-membered chelate stable to decarbonylation upon initial oxidative addition (see **Section 1.1**). Importantly, the 1,3-dicarbonyl products formed would be of particular relevance to the synthesis of many bioactive natural products, such as those outlined in **Figure 2.2**.[154-156]

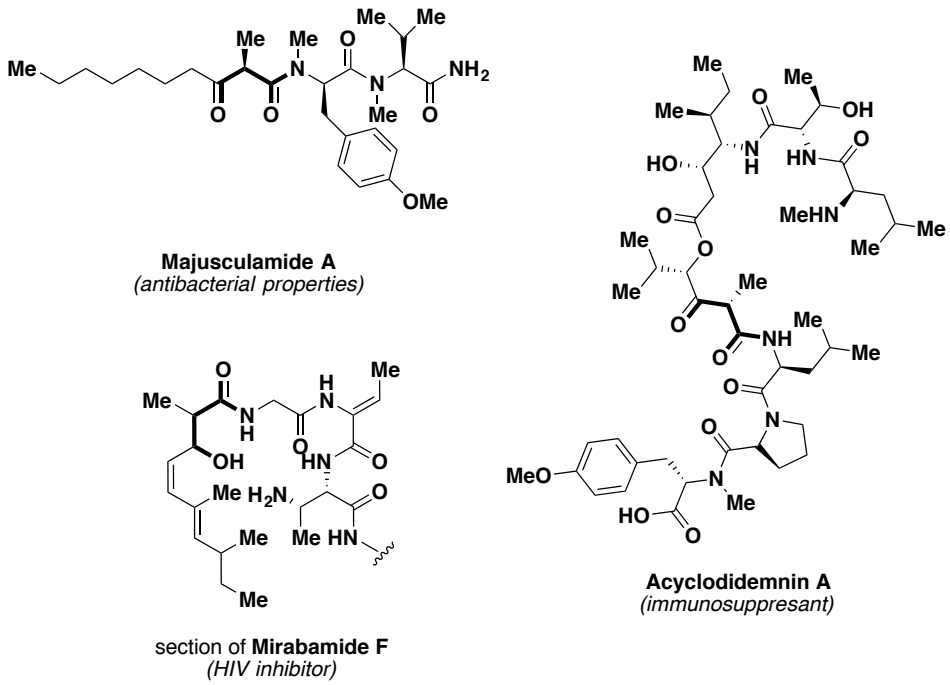


Figure 2.2: Selected examples of potential applications to bioactive molecule synthesis. The highlighted section of 'Mirabamide F' could be acquired following a selective reduction of the enone carbonyl subsequent to the alkyne hydroacylation step.

This arrangement also presents opportunities for a traceless hydroacylation process, potentially achieved by hydrolysis of the amide product and subsequent decarboxylation (**Figure 2.3**).

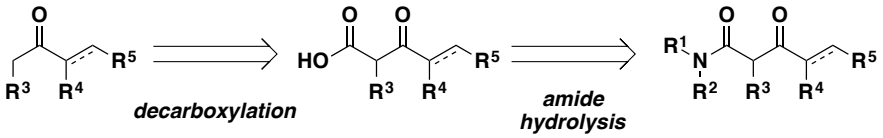


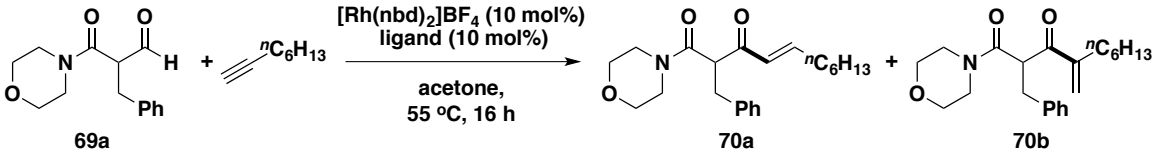
Figure 2.3: Theoretical removal of amide chelate post-hydroacylation

Our attention therefore turned to the design of an appropriate catalyst system. Aldehyde **69a** was selected for initial optimisation work with 1-octyne, employing the standard practical method used in the Willis group (for the hydroacylation of *β*-sulfur containing aldehydes) as a starting point. This requires the use of bench stable rhodium precatalyst $[Rh(nbd)_2]BF_4$ and generates the active catalyst *in situ via* hydrogenation with a selected bisphosphine ligand in dry acetone. As such, a range of bisphosphine ligands were initially screened using a high catalyst loading of 10 mol% to promote the likelihood of reactivity (**Table 2.1**). However, we were surprised to observe that most ligands utilised delivered full conversion to the products, with only a limited number (**Table 2.1**, entries **8**, **9**, **11** and **13**) returning some aldehyde starting material.

The main variation observed between catalyst systems was the regioselective preference for the linear isomer **70a** over the branched **70b**. Typically, the small bite angle ligands of dcpm, dppm and PNP(Cy) tend to deliver the greatest linear regioselectivity for *β*-sulfur systems.[97] However, for our substrates, only moderate selectivity for those ligands was observed. Curiously, (*o*-^{i}Pr)dppe, a branched selective ligand for *β*-sulfur systems,[52] gave modest linear selectivity with this amido aldehyde (**Table 2.1**, entry **8**), whereas dtpm and AmpaPhos

delivered the only instances where a preference for the branched isomer **70b** was observed (**Table 2.1**, entries **15** and **16**). These latter results will be explored further later in the chapter (**Section 2.7**).

Table 2.1: Ligand screening for hydroacylation of amide **69a** at 10 mol% catalyst loading.

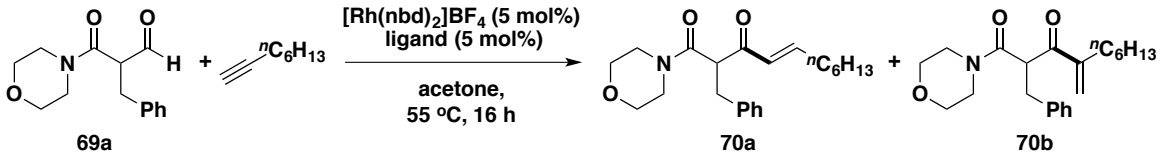


Entry	Ligand	Conversion[a] (%)	a:b ratio[a]
1	dcpm	100	10:1
2	dppm	100	4:1
3	dcpe	100	>20:1
4	dppe	100	7:1
5	dppb	100	11:1
6	dppf	100	4:1
7	(*o*-Me)dppe	100	7:1
8	(*o*-^{i}Pr)dppe	87	5:1
9	pentafluoro-dppe	91	5:1
10	PNP(Cy)	100	7:1
11	BINAP	98	4:1
12	DPEPhos	100	6:1
13	XantPhos	55	-
14	DTBM-SegPhos	100	9:1
15	dtpm[b]	100	1:3
16	AmpaPhos[b]	100	1:5

Conditions: **69a** (0.15 mmol, 1.0 equiv.), 1-octyne (0.18 mmol, 1.2 equiv.), $[Rh(nbd)_2]BF_4$ (10 mol%), ligand (10 mol%), acetone (1.0 M with respect to the aldehyde), 55 °C, 16 h. [a]Determined by ^{1}H NMR spectroscopy of crude reaction mixtures. [b]dtpm and AmpPhos were used as the pre-formed $[Rh(dtpm)(C_6H_5F)][BAr^F{}_4]$ and $[Rh(AmpaPhos)(C_6H_5F)][BAr^F{}_4]$ complexes, respectively.

Considering the high catalyst loading of 10 mol% in these experiments, five ligands delivering the highest linear selectivities were tested again at the lower catalyst loading of 5 mol% (**Table 2.2**).

Table 2.2: Ligand screening for hydroacylation of aldehyde **69a** at 5 mol% catalyst loading



Entry	Ligand	Conversion[a] (%)	a:b ratio[a]
1	dcpm	100 (88)	10:1
2	dcpe	100 (90)	>20:1
3	dppe	100 (94)	8:1
4	dppb	100 (93)	14:1
5	DPEPhos	100 (86)	6:1

Conditions: **69a** (0.30 mmol, 1.0 equiv.), 1-octyne (0.36 mmol, 1.2 equiv.), $[Rh(nbd)_2]BF_4$ (5 mol%), ligand (5 mol%), acetone (1.0 M with respect to the aldehyde), 55 °C, 1 h. [a] Determined by ^1H NMR spectroscopy of crude reaction mixtures. Value in parenthesis is the isolated yield of combined linear and branched products.

In these experiments, full conversions and excellent yields could be obtained within one hour. However, as dcpe was the only ligand to deliver near complete linear selectivity, it was selected as the optimal ligand for this aldehyde system (**Table 2.2**, entry **2**).

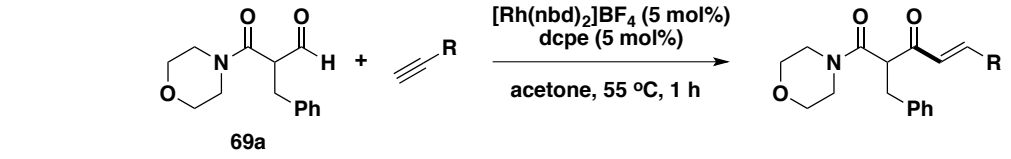
2.3 Reactivity of Alkynes in Hydroacylation

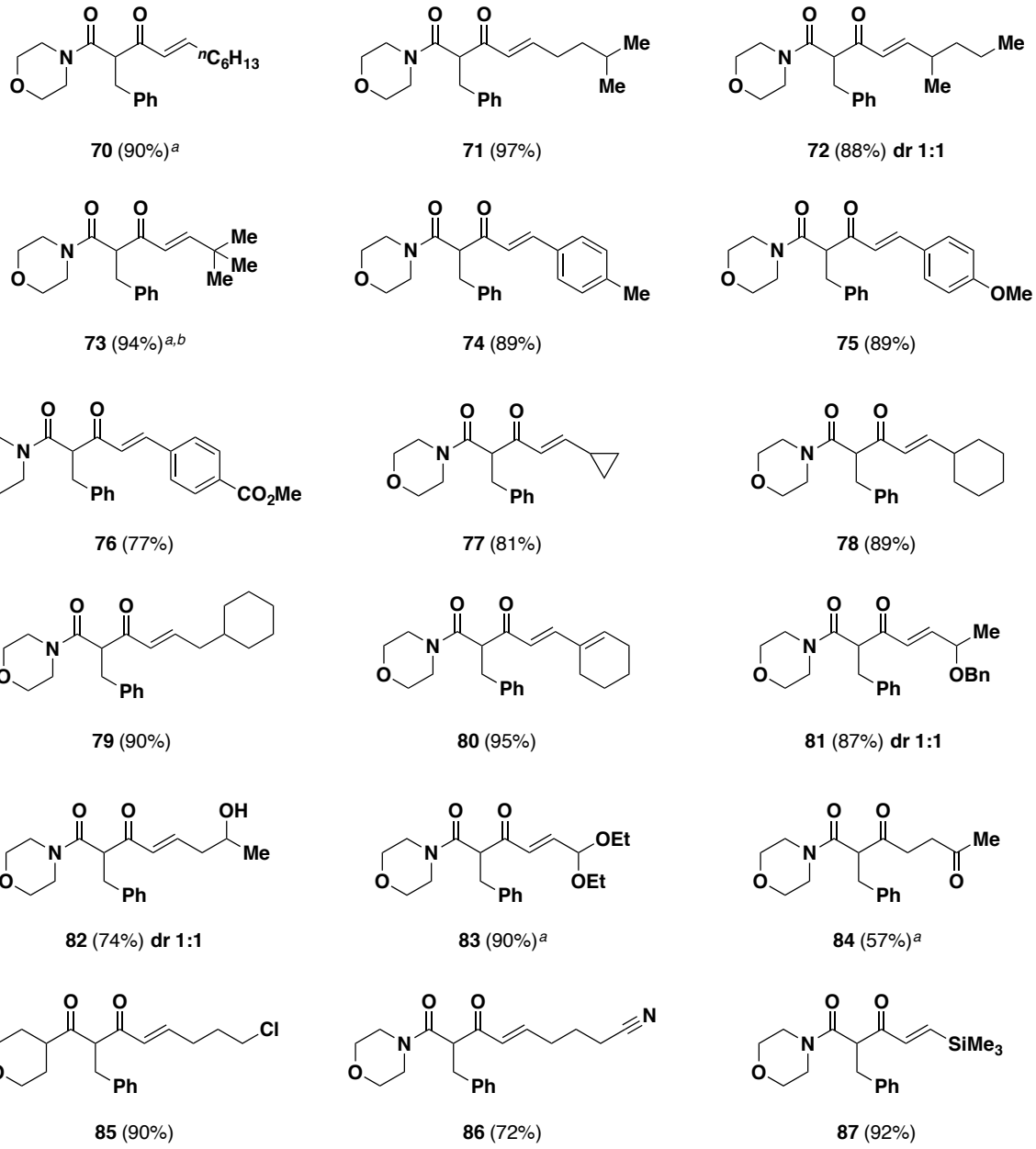
With the optimised conditions in hand for the hydroacylation of *β*-amido aldehyde **69a** with 1-octyne, the scope and functional group tolerance of this methodology was examined with other alkynes.

2.3.1 Scope of Terminal Alkynes

The isolated yields were consistently high when aldehyde **69a** was combined with a range of terminal alkynes (**Scheme 2.4**), with all reactions proceeding to full conversion within one hour. To our satisfaction, a broad range of alkyl substitution patterns, both in branching (**Scheme 2.4**, entries **71**, **72** and **73**) and ring size (**Scheme 2.4**, entries **77**, **78** and **79**) could be incorporated, as well as aryl rings with both electron-donating (**Scheme 2.4**, entries **74** and **75**) and an electron-withdrawing group (**Scheme 2.4**, entry **76**). The same can be said for a variety of heteroatom groups, most notably the acetal (**Scheme 2.4**, entry **83**) and halide moieties (**Scheme 2.4**, entry **85**), which provide useful handles for further functionalisation. Interestingly, upon reacting aldehyde **69a** with 3-butyn-2-ol, a migration of the alkene bond occurred, resulting in a diketone product (**Scheme 2.4**, entry **84**). This, however, did not occur with the use of 4-pentyn-2-ol, in which the free hydroxyl group is retained (**Scheme 2.4**, entry **82**). Analogous behaviour had been observed previously in the attempted formation of furans *via* hydroacylation by Willis *et al*, and its occurrence has been shown to be highly ligand dependent.[157]

A large scale preparation of enone **73** was subsequently achieved at a much lower catalyst loading of 1 mol%, delivering 1.5 g of the product in the same yield of 94%. This result clearly demonstrates the robustness and synthetic utility of this methodology.





Conditions: Aldehyde (0.25 mmol, 1.0 equiv.), terminal alkyne (0.30 mmol, 1.2 equiv.), $[Rh(nbd)_2]BF_4$ (5 mol%), dcpe (5 mol%), acetone (1.0 M with respect to the aldehyde), 55 °C, 1 h. [a] Performed on 0.30 mmol of aldehyde scale. [b] Additionally performed on a 1.5 g scale, using 1 mol% catalyst loading, to give a 94% yield.

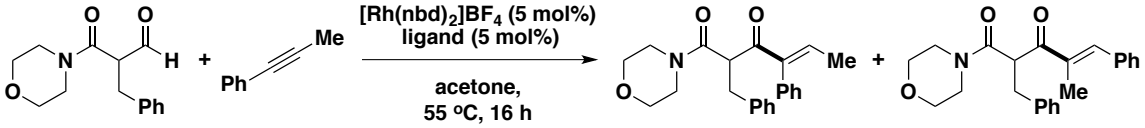
Scheme 2.4: Scope of terminal alkynes in hydroacylation of *β*-amido aldehyde **69a**.

2.3.2 Re-optimisation and Scope for Internal Alkynes

Substitution of 1-octyne for the internal alkyne 1-phenyl-1-propyne **88** under the previously optimised conditions delivered less than satisfactory regiocontrol (**Table 2.3**, entry **1**). Although hydroacylation occurred with complete aldehyde conversion, the regioselectivity became 2:1 in favour of the enone **89a**. Therefore, a selection of ligands was investigated to determine if this number could be improved (**Table 2.3**). Pleasingly, whilst the majority of ligands showed poor regioselectivity despite complete consumption of the starting material, the use of DPEPhos allowed for adequate levels of regiocontrol (**Table 2.3**, entry **5**).

Based on reports of hydroacylation processes using sulfur tethers with DPEPhos, the regioisomer **89b** would be expected as the major product, presumably due to steric factors.[46] It is currently unclear as to why, with *β*-amido aldehydes, the opposite selectivity is observed.

Table 2.3: Ligand screening for hydroacylation of *β*-amido aldehyde **69a** with alkyne **88**.

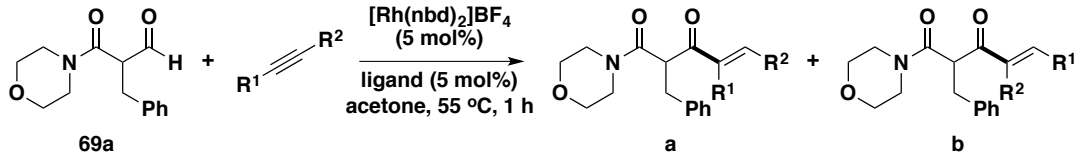


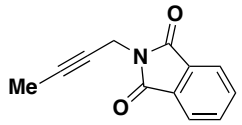
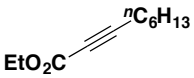
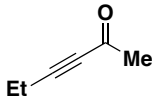
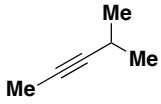
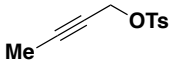
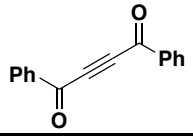
Entry	Ligand	Conversion[a] (%)	a:b ratio[a]
1	dcpe	100	2:1
2	dcpm	100	1:1
3	dppe	100	3:1
4	dppm	100	2:1
5	DPEPhos	100 (73)	7:1

Conditions: **69a** (0.30 mmol, 1.0 equiv.), 1-phenyl-1-propyne **88** (0.36 mmol, 1.2 equiv.), $[Rh(nbd)_2]BF_4$ (5 mol%), ligand (5 mol%), acetone (1.0 M with respect to the aldehyde), 55 °C, 1 h. [a]Determined by ^1H NMR spectroscopy of crude reaction mixtures. Value in parenthesis is the isolated yield of predominant isomer.

In order to conclude if the hemilabile ligand DPEPhos demonstrated similar regioselectivity for other unsymmetrical internal alkynes, a number of these alkynes were screened across a range of different ligands (**Table 2.4**). Conveniently, DPEPhos proved to be the optimal ligand in most cases for both conversion and selectivity. Unfortunately, no reactivity was ever observed with alkynes **94** and **95**. Interestingly, when alkyne **91** was used, the selectivity could be completely switched by substituting DPEPhos for dcpe to form the alternative isomer **97b** (**Scheme 2.5**). More importantly, the ability of alkynes possessing ester, ketone and branched alkyl groups adjacent to the triple bond to undergo complete reactivity in this manner is unprecedented with many other aldehyde substrates, and represents a broadening of scope in hydroacylation methodologies.[94-101]

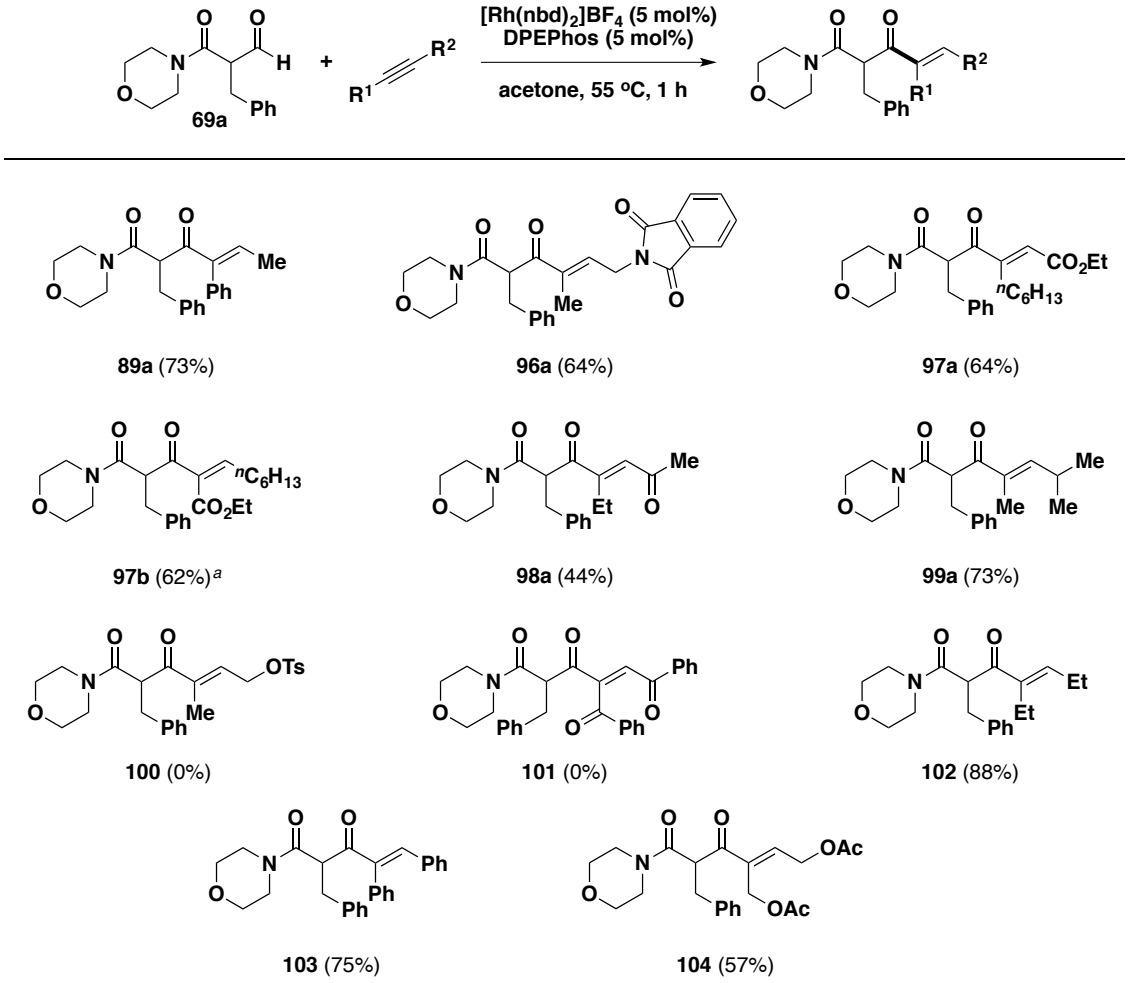
Table 2.4: Ligand screening for hydroacylation of *β*-amido aldehyde **69a** with internal alkynes.



Entry	R^1—≡—R^2	Ligand	Conversion[a] (%)	a:b ratio[a]
1a		dcpm	100	2:1
1b		dppm	100	2:1
1c	**90** 	dcpe	100	2:1
1d		dppe	100	3:1
1e		DPEPhos	100 (64)	4:1
2a	**91** 	dcpe	100 (62)	20:1
2b		DPEPhos	100 (64)	1:5
3a		dcpm	100	1:1
3b		dppm	100	1:1
3c	**92** 	dcpe	-[b]	-
3d		dppe	100	1:1
3e		DPEPhos	100 (44)	4:1
4a		dppm	29	-[c]
4b	**93** 	dcpe	45	-[c]
4c		DPEPhos	100 (73)	>20:1
5a	**94** 	dcpe	0	-
5b		DPEPhos	0	-
6a		dcpe	0	-
6b	**95** 	DPEPhos	0	-

Conditions: **69a** (0.30 mmol, 1.0 equiv.), alkyne (0.36 mmol, 1.2 equiv.), $[Rh(nbd)_2]BF_4$ (5 mol%), ligand (5 mol%), acetone (1.0 M with respect to the aldehyde), 55 °C, 1 h. [a]Determined by ^1H NMR spectroscopy of crude reaction mixtures. Value in parenthesis is the isolated yield of major isomer. [b]Decomposition of starting material occurred. [c]Results not obtained.

For completeness, three symmetrical alkynes were also tested using DPEPhos. We were pleased to observe good to excellent yields, especially concerning enone **103**, as the hydroacylation of diphenylacetylene has proved challenging for other tethered aldehyde classes.[97-101] **Scheme 2.5** summarises the results seen using the revised optimal conditions for internal alkynes.



Conditions: Aldehyde (0.30 mmol, 1.0 equiv.), internal alkyne (0.36 mmol, 1.2 equiv.), $[Rh(nbd)_2]BF_4$ (5 mol%), DPEPhos (5 mol%), acetone (1.0 M with respect to the aldehyde), 55 °C, 16 h. [a] Synthesised using dcpe as the ligand.

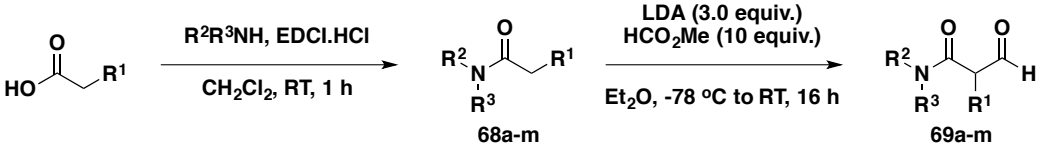
Scheme 2.5: Summary of scope of internal alkynes in the hydroacylation of *β*-amido aldehyde **69a**.

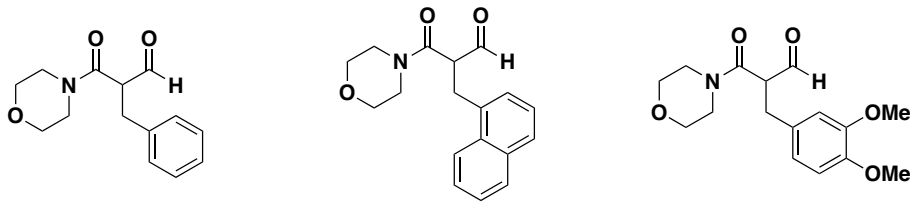
2.4 Synthetic Routes to *β*-Amido Aldehydes

In order to assess the reaction scope with respect to the aldehyde component, it was necessary to first develop approaches to synthesise a broad range of *β*-amido aldehydes. These could be separated into three classes: those with one substituent on the *α*-carbon atom (*α*-monosubstituted), those with two (*α*-disubstituted), and those with none (*α*-unsubstituted).

2.4.1 Synthesis of *α*-Monosubstituted *β*-Amido Aldehydes

One of the attractive of features of using of *α*-monosubstituted *β*-amido aldehydes is their relative convenience of synthesis. The original aldehyde **69a** used in preliminary investigations had been synthesised using a procedure formalised by Johnson,[158] in which the *α*-carbon atom of the corresponding amide **68a** is deprotonated with freshly prepared lithium diisopropylamide and subsequently formylated by methyl formate. Due to its simplicity, this process was applied to other amides, themselves synthesised *via* an amine coupling with the corresponding carboxylic acid, ultimately generating a range of *β*-amido aldehydes seen in **Scheme 2.6**. In accordance with observations by Johnson,[158] yields were moderate in many cases due to difficulty in purification. The generality of this reaction, however, was observed in its tolerance towards alterations in the *α*-carbon substituent and groups on the amide nitrogen atom, including bulky groups such as isopropyl (**Scheme 2.6**, entry **69e**) and cyclohexyl (**Scheme 2.6**, entry **69f**) substituents.

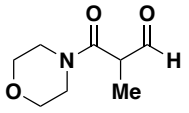




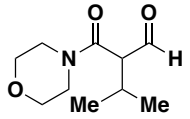
68a (92%)
69a (71%)

68b (87%)
69b (49%)

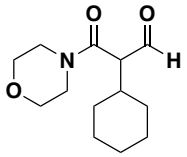
68c (91%)
69c (22%)



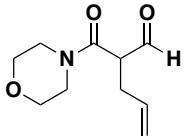
68d (41%)[a]
69d (49%)



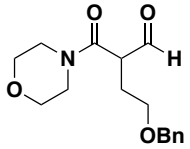
68e (62%)
69e (68%)



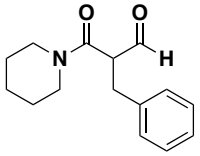
68f (91%)
69f (36%)



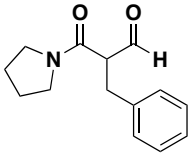
68g (82%)
69g (72%)



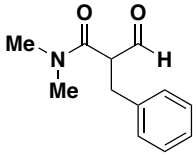
68h (58%)[b]
69h (79%)



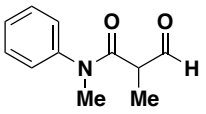
68i (88%)
69i (62%)



68j (73%)
69j (71%)



68k (79%)
69k (65%)



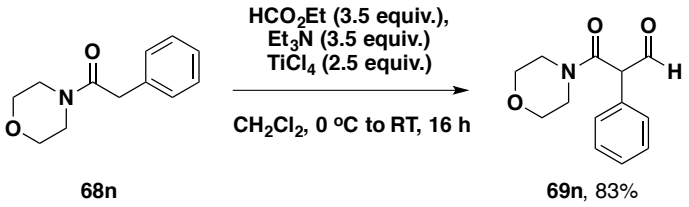
68m (83%)[a]
69m (51%)

Conditions: Step 1: Carboxylic acid (30 mmol), amine (33 mmol), EDCI.HCl (33 mmol), CH_2Cl_2 (0.2 M with respect to acid), RT, 1 h; Step 2: Freshly prepared lithium diisiopropylamide (30 mmol, 0.7 M in Et_2O), amide (10 mmol), methyl formate (100 mmol), Et_2O (0.3 M with respect to amide), -78 °C to RT, 16 h. [a]Prepared using propionyl anhydride (60 mmol), amine (50 mmol) and pyridine (250 mmol), RT, 2 h. [b]Prepared from γ-butyrolactone (25 mmol), morpholine (25 mmol), Ag_2O (50 mmol), and TBAI (2.5 mmol) in CH_2Cl_2 (100 mL), then benzyl bromide (50 mmol), RT, 48 h.

Scheme 2.6: Range of *β*-amido aldehydes synthesised using Johnson's procedure.[158]

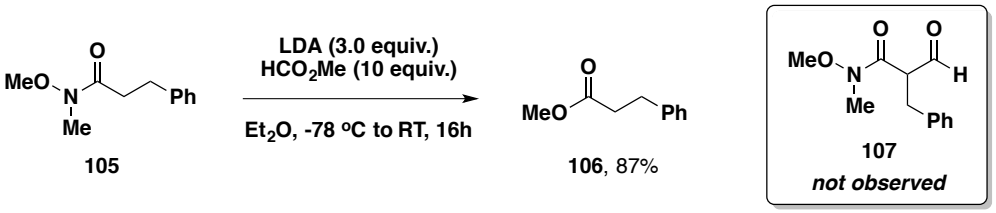
There were, however, some limitations in the scope of this reaction. Due to the decreased pK_a of the *α*-proton in amide **68n**, an alternative synthesis for generating the aldehyde **69n**

using titanium tetrachloride and triethylamine was employed, as recommended by Johnson[158] (**Scheme 2.7**).



Scheme 2.7: Johnson's synthesis of aldehyde **69n**.[158]

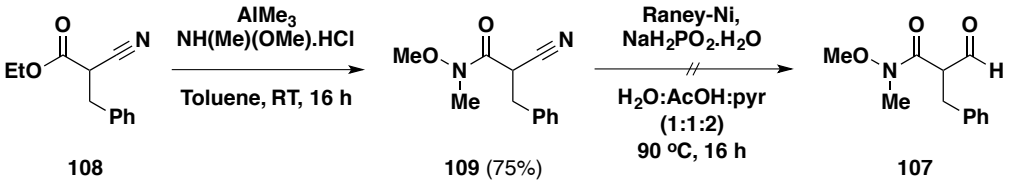
Surprisingly, attempts to make aldehyde **107** *via* the original formylation method resulted in complete conversion to the methyl ester **106** (**Scheme 2.8**). Presumably, this could arise from a decomposition of the methyl formate enacted by the excess LDA to generate the methoxide counterion, which may attack the Weinreb amide **105**. There is literature precedent for a similar a process being employed for synthetic purposes.[159] An attempt to hinder any potential involvement of the lithium counterion in accelerating this process by addition of DMPU also failed to deliver the desired aldehyde.



Scheme 2.8: Unexpected synthesis of ester **106** instead of aldehyde **107**.

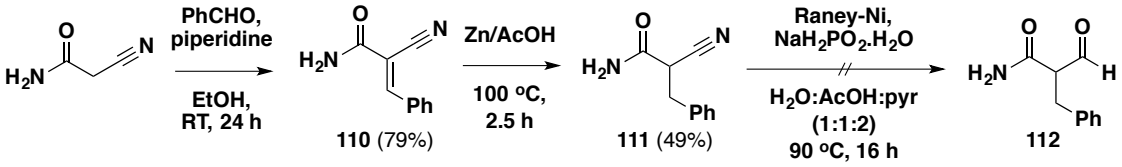
An alternative approach was devised in which the aldehyde could be installed *via* the reduction of a nitrile group using Raney® nickel. The benefits of such a final step would be the extreme selectivity of the Raney® nickel for the reduction of the nitrile group to the imine before hydrolysis.[160] Therefore, a synthetic approach was proposed as outlined in **Scheme 2.9**. Whilst installation of the Weinreb amide in **109** proved straightforward, to our disappointment the final reduction step resulted in inseparable mixture of products, none of

which were the desired aldehyde **107**. As such, attempts to synthesise this particular substrate were abandoned.



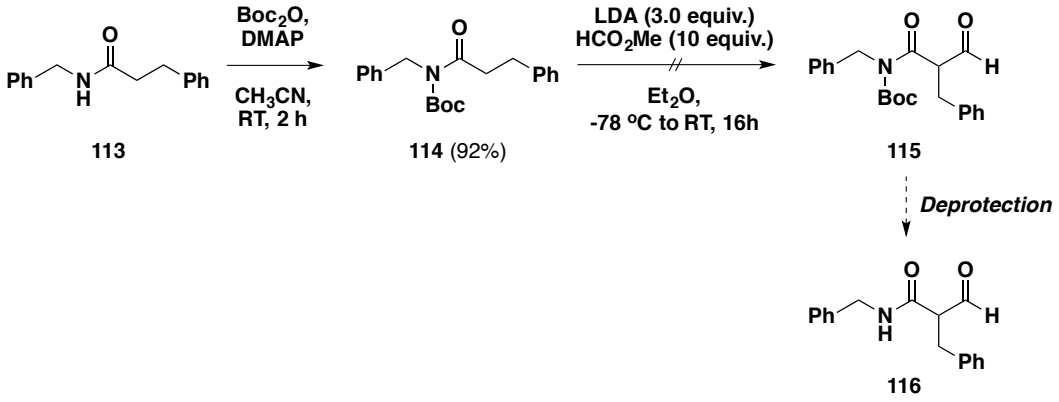
Scheme 2.9: Attempt to synthesise aldehyde **107** *via* nitrile reduction of **109**.

Given the synthetic importance and utility of amides containing free N−H bonds, we decided to synthesise aldehyde **112** for investigation. Due to the likelihood of deleterious side reactions using Johnson's method,[158] a different route was outlined once again employing the use of nitrile reduction by Raney® nickel. However, this step once again failed to generate the required aldehyde **112**, in spite the ease of synthesising nitriles **110** and **111** (**Scheme 2.10**).



Scheme 2.10: Attempted synthesis of NH_2 containing aldehyde **112**.

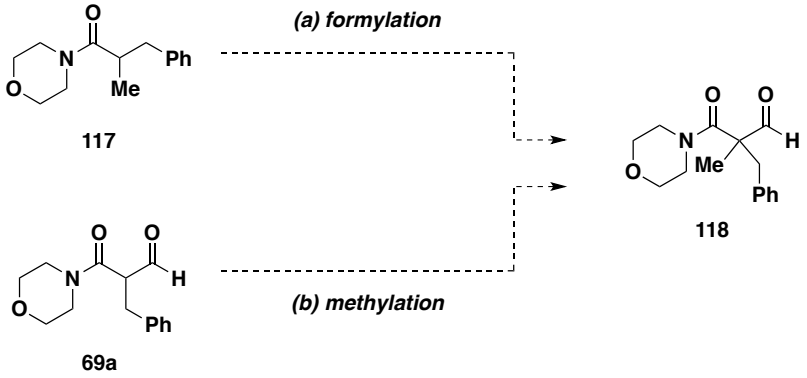
In a second attempt, efforts were made to first Boc-protect the free amide prior to a traditional LDA/methyl formate formylation reaction, which could then be deprotected under mild conditions. Unfortunately, attempted formylation of this Boc-protected amide **114** did not proceed, returning only starting material (**Scheme 2.11**). As synthesis of monosubstituted *β*-amido aldehydes containing free N−H bonds proved to be challenging, attempts were thus suspended due to time constraints.



Scheme 2.11: Attempted synthesis of N-H containing aldehyde **116** *via* Boc protection.

2.4.2 Synthesis of *α*-Disubstituted *β*-Amido Aldehydes

In order to broaden the potential aldehyde scope within this methodology, efforts were undertaken to synthesise a selection of *β*-amido aldehydes with both positions substituted at the *α*-carbon atom such as aldehyde **118**. Before experimental work began, two of the more straightforward routes outlined in **Scheme 2.12** were disregarded.

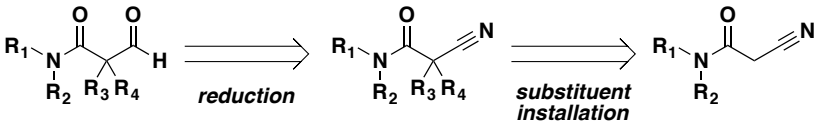


Scheme 2.12: Disregarded routes for synthesising disubstituted aldehyde **118**.

Firstly, a simple formylation of a *α*-disubstituted amide **117** using LDA**,** similar to that used for *α*-monosubstituted amides**,** was discounted as such reactivity has no precedence in the literature. Secondly, methylation of the *α*-monosubstituted *β*-amido aldehyde **69a** was most likely to lead to direct methylation of the enolate oxygen generated upon deprotonation,[161]

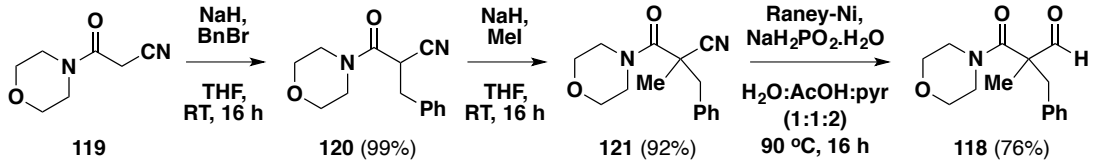
and would require synthesis of the α-monosubstituted β-amido aldehyde in the first place, some of which proved difficult to achieve (see **Section 2.4.1**).

As such, a more general synthetic route was proposed, in which a variety of substituents could be incorporated into the resulting aldehyde. By first of all installing the required substituent groups on an cyanoacetamide, one can then reduce the nitrile to an aldehyde using Raney® nickel under hydrolysing conditions, leaving all other groups untouched (**Scheme 2.13**).



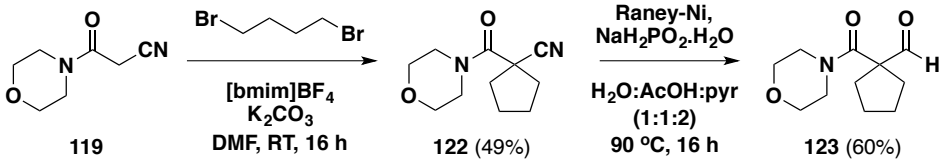
Scheme 2.13: Retrosynthetic approach to disubstituted β-amido aldehydes.

This approach was effectively applied to synthesis of aldehyde **118**, in which a benzyl and methyl group were successively installed in high yields before the nitrile reduction (**Scheme 2.14**).



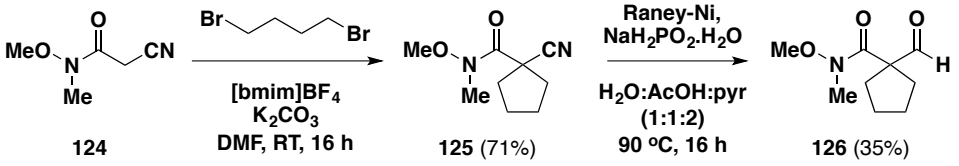
Scheme 2.14: Synthesis of disubstituted aldehyde **118**.

Similarly, a cyclopentyl group could be successfully incorporated onto the α-carbon atom, albeit in moderate yield, ultimately leading to aldehyde **123** (**Scheme 2.15**).



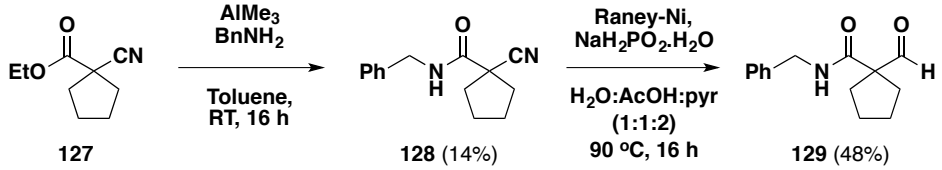
Scheme 2.15: Synthesis of disubstituted aldehyde **123**.

As the Raney® nickel nitrile reduction proved to be far more successful for α-disubstituted amides over α-monosubstituted ones (see **Section 2.4.1**), we decided to return to the amide groups that so far proved challenging to synthesis. Beginning with the Weinreb amide group, a synthetic route similar to that as the synthesis of **123** was employed by first installing a cyclopentyl ring system, this time delivering the desired aldehyde **126** (**Scheme 2.16**).



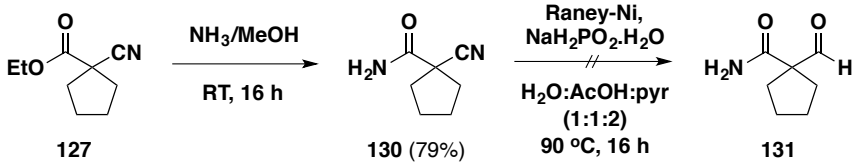
Scheme 2.16: Synthesis of Weinreb amide containing aldehyde **126**.

Since this approach proved promising in its generality and scope, it was applied to the synthesis of aldehyde **129**, which contained a coveted N−H bond in the amide group. For this substrate, the route began with ester **127** with the cyclopentyl group pre-installed. After converting **127** to the desired amide **128**, the subsequent reduction proceeded as planned, generating aldehyde **129** (**Scheme 2.17**).



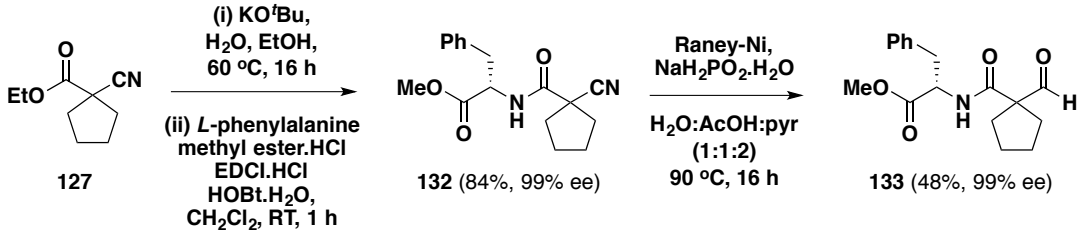
Scheme 2.17: Synthesis of aldehyde **129**.

However, when such a route was used to generate aldehyde **131** with two N−H bonds, the final reduction step failed to deliver the desired product, with various polymerisation products being observed instead (**Scheme 2.18**). It was therefore deemed unlikely that such an aldehyde **131** could be isolated.



Scheme 2.18: Attempted synthesis of aldehyde **131**.

Despite this, the success of synthesising aldehyde **129** presented us with an opportunity to incorporate an amino acid functionality *via* a peptide bond, and demonstrate its applicability with such substrates. Thus, aldehyde **133** was formed using *L*-phenylalanine. We were also pleased to observe that under the amide coupling and Raney® nickel reduction/hydrolysis conditions the enantiopurity was preserved (**Scheme 2.19**).



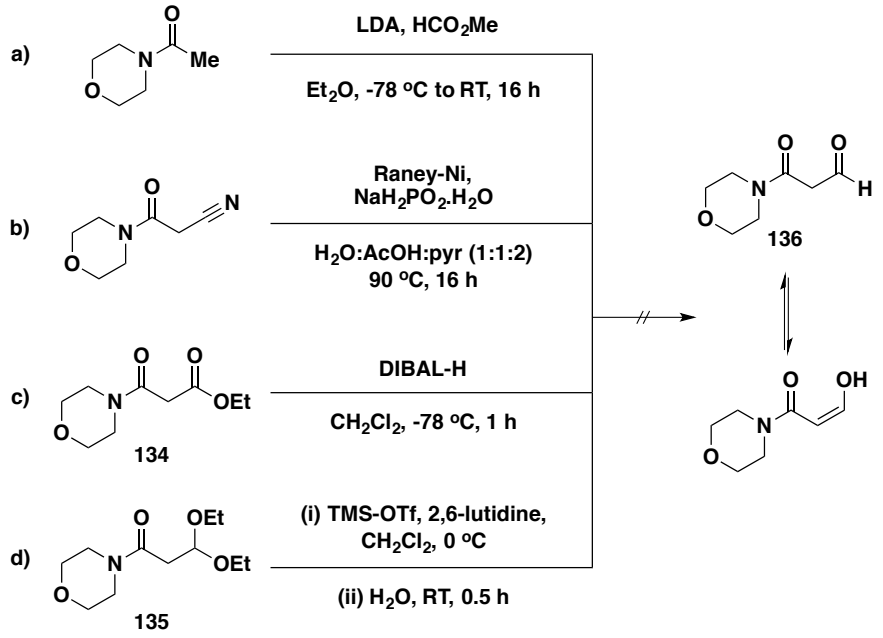
Scheme 2.19: Synthesis of amino-acid derived aldehyde **133**.

2.4.3 Synthesis of *α*-Unsubstituted *β*-Amido Aldehydes

α-Unsubstituted *β*-amido aldehydes of the type seen in **Scheme 2.20** are inherently difficult to synthesise, mainly due to their facile tautomerisation and thus propensity for further reactivity. It is therefore no surprise that few examples exist in the literature.

In spite of this, several endeavours to synthesise substrate **136** were tried, to no avail. Both Johnson's formylation[158] (**Scheme 2.20**, route **(a)**) and the Raney® nickel nitrile group reduction (**Scheme 2.20**, route **(b)**) failed to give any of the desired aldehyde. Likewise, a DIBAL-H mono-reduction of the ester group in **134** (**Scheme 2.20**, route **(c)**) and hydrolysis of acetal **135** using trimethylsilyl triflate and 2,6-lutidine as a nucleophilic catalyst

(**Scheme 2.20**, route **(d)**) also did not succeed. Further attempts to generate aldehyde **136** were therefore suspended.

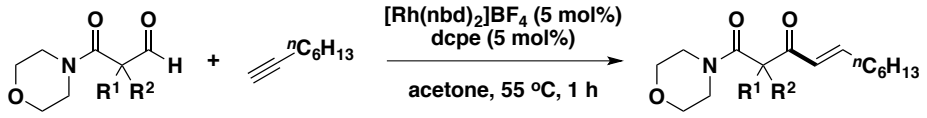


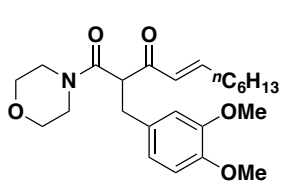
Scheme 2.20: Attempted syntheses of α-unsubstituted β-amido aldehyde **136**.

2.5 Reactivity of β-Amido Aldehydes in Hydroacylation

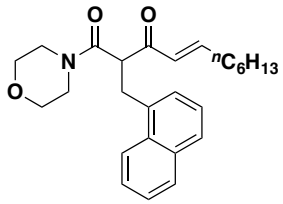
Until this point, only β-amido aldehyde **69a** had been investigated for reactivity in hydroacylation, with the substrate demonstrating excellent reliability and selectivity during the scope carried out. The substrate scope was therefore examined using the β-amido aldehydes synthesised in **Section 2.4** (**Scheme 2.21**).

Pleasingly, a range of substituents could be introduced at the α-carbon position including substituted aryl (**Scheme 2.21**, entry **137**), bulky alkyl (**Scheme 2.21**, entries **141** and **142**) and alkenyl (**Scheme 2.21**, entry **144**) groups, all with complete conversions and linear selectivity within one hour. The methodology also permits disubstitution next to the carbonyl, generating the products in excellent yields (**Scheme 2.21**, entries **145** and **146**).

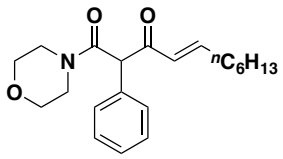




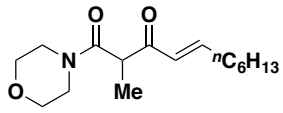
137 (81%)



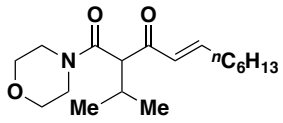
138 (83%)



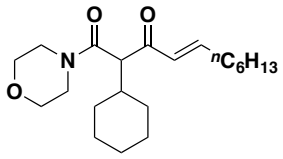
139 (89%)



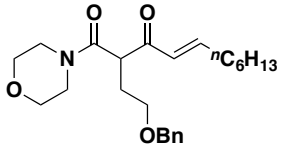
140 (77%)



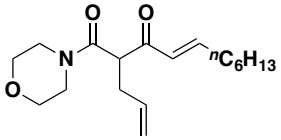
141 (92%)



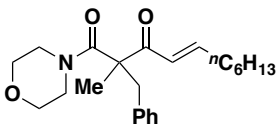
142 (87%)



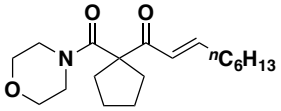
143 (91%)



144 (67%)



145 (92%)

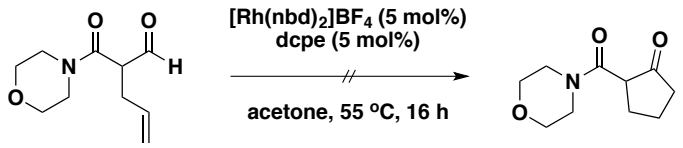


146 (95%)

Conditions: Aldehyde (0.30 mmol, 1.0 equiv.), 1-octyne (0.36 mmol, 1.2 equiv.), $[Rh(nbd)_2]BF_4$ (5 mol%), dcpe (5 mol%), acetone (1.0 M with respect to the aldehyde), 55 °C, 1 h.

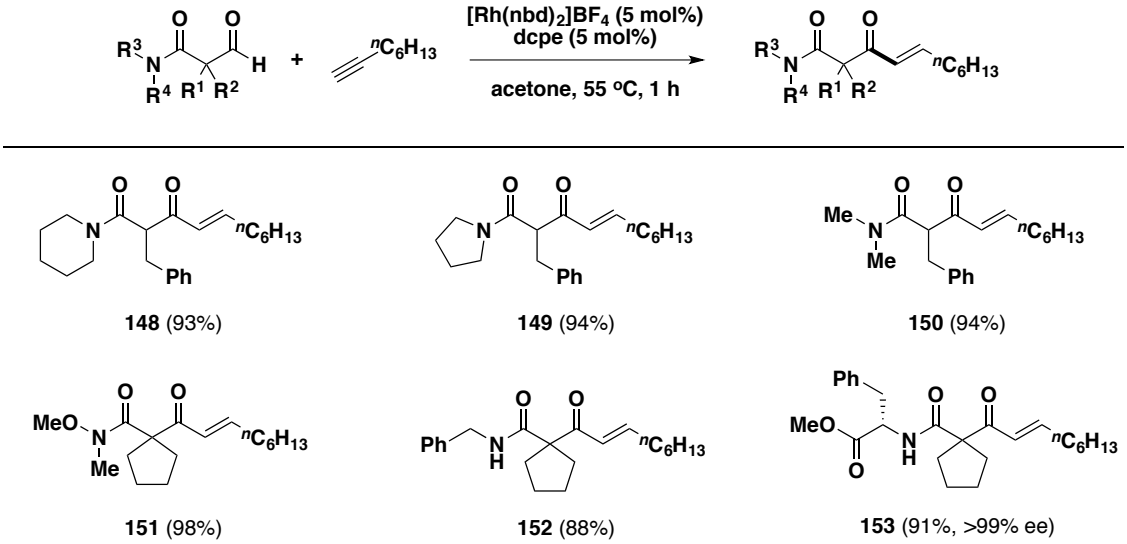
Scheme 2.21: Scope of *β*-amido aldehydes with 1-octyne when the *α*-substituents are changed.

In the case of the alkenyl substrate **69g**, we were curious to investigate if there may be an intramolecular alkene hydroacylation process competing with the expected intermolecular alkyne hydroacylation (**Scheme 2.22**). In order to test this, another experiment was conducted with substrate **69g** in which the 1-octyne component was omitted. Interestingly, however, no cyclopentanone product **147** was observed.



Scheme 2.22: Potential competing intramolecular hydroacylation process with aldehyde **69g**.

This methodology also tolerates a change in substituent on the amide nitrogen atom (**Scheme 2.23**), including various rings (**Scheme 2.23**, entries **148** and **149**) and alkyl groups (**Scheme 2.23**, entry **150**). More importantly, the presence of a synthetically valuable Weinreb amide (**Scheme 2.23**, entry **151**) and free N−H bond (**Scheme 2.23**, entries **152** and **153**) did not negatively affect the reactivity, thus providing useful handles for further functionalisation. A particularly noteworthy example is the amino-acid derived product **153**. Not only are the various functional groups on the amino acid handle carried through the reaction without affect, but, crucially, the enantiopurity of the starting material is retained in the enone product. This exciting result has the potential to open up a wide range of further applications for this methodology regarding asymmetric substrates, although such investigations are out of the scope of this thesis.



Conditions: Aldehyde (0.30 mmol, 1.0 equiv.), 1-octyne (0.36 mmol, 1.2 equiv.), $[Rh(nbd)_2]BF_4$ (5 mol%), dcpe (5 mol%), acetone (1.0 M with respect to the aldehyde), 55 °C, 1 h.

Scheme 2.23: Scope of *β*-amido aldehydes with 1-octyne when the amide group is changed.

2.6 Ring-Based *β*-Amido Aldehyde Systems in Hydroacylation

A substrate class of particular interest that had so far not been investigated were *β*-amido aldehydes in which the amide group is part of a larger alicyclic ring system (**Figure 2.4**). Such motifs have been subject to much investigation in recent years due to their abundance as motifs in natural products. Specifically, derivatives of 2-pyrrolidinone and 2-piperidone can show significant biological and pharmacological activities and are present in many well-known pharmaceuticals. Many of these examples possess additional carbonyl groups *β*- to the amide carbonyl, thus making them directly relevant to the methodology developed in this thesis. Such precedents include Pseurotin A and (+)-Epolactaene, two pyrrolidinone based fungal isolates which have shown potential for bioactivity with regards to nerve cells,[162,163] and piperidine-based **154** isolated from an Indonesian Streptomyces, which has demonstrated promising antibacterial properties (**Figure 2.4**).[164]

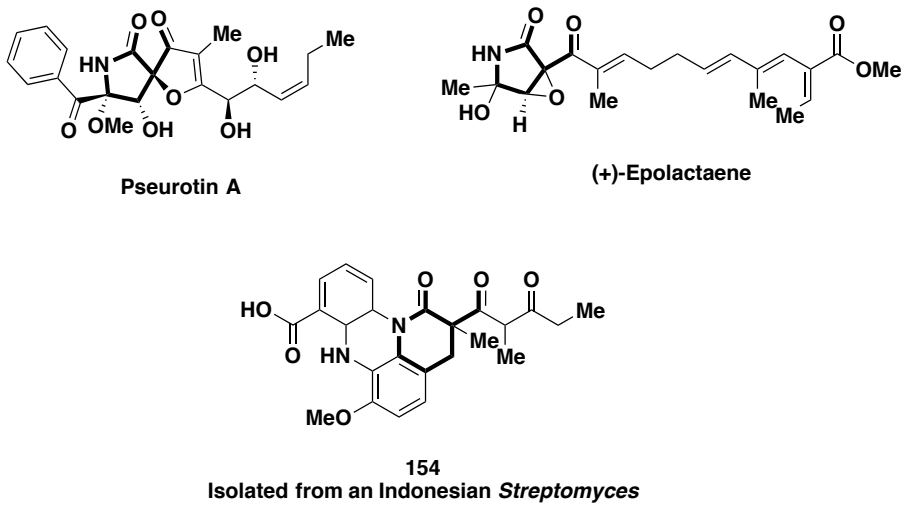
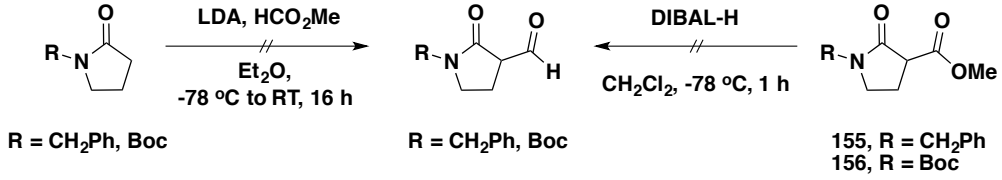


Figure 2.4: Selected examples of ring-based *β*-amido carbonyl systems showing bioactivity.

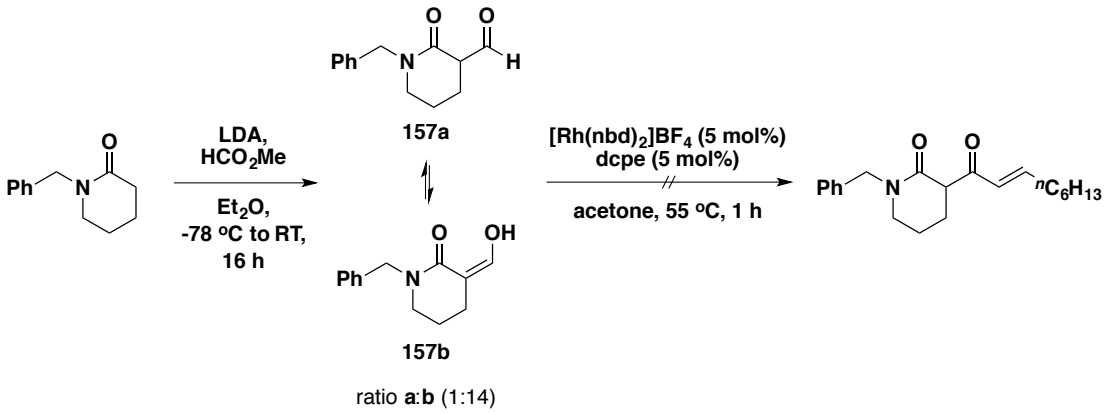
With this in mind, efforts began with the prospect of synthesising a 2-pyrrolidinone-based aldehyde system. Both formylation and ester reduction strategies were attempted, nonetheless in both cases and inseparable array of compounds were created. The benzyl protecting group on the amide nitrogen was subsequently switched for a Boc-group in the hope that this may alter the outcome of either reaction, but unfortunately this was not observed (**Scheme 2.24**).



Scheme 2.24: Attempts to synthesise 2-pyrrolidinone-based *β*-amido aldehydes.

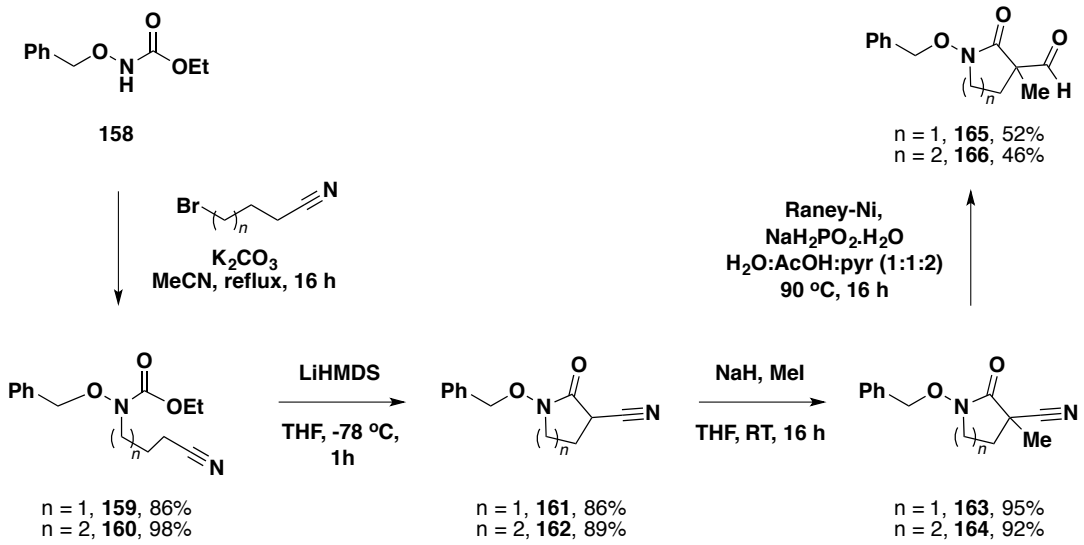
However, potential rationalisation for the challenges occurring here became apparent when benzyl protected 2-piperidone was formylated under the standard conditions. Instead of isolating the expected aldehyde **157a**, the product existed predominantly in the enol form

157b. This substrate therefore failed to couple with 1-octyne in hydroacylation, possibly as so little aldehyde was present in the starting material (**Scheme 2.25**).



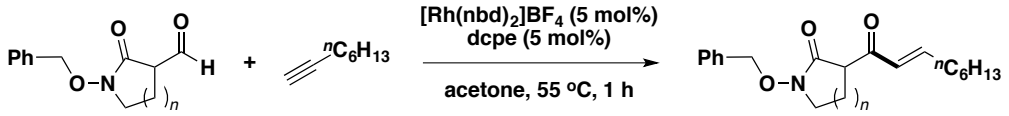
Scheme 2.25: Synthesis and subsequent failed hydroacylation of substrate **157**.

As such, it was believed that preventing the tautomerisation of aldehyde **157** by methylating the α-carbon atom (and thus making it a quaternary centre) would allow it to react effectively in hydroacylation. Despite its potential simplicity, methylation of enol **157** was not attempted due to most likely methylation of the enol oxygen atom (see **Section 2.4.2**), and thus a new synthetic route was devised (**Scheme 2.26**). In this route, which can be applied to both five- and six-membered ring synthesis, a ring closing of a nitrile-containing carbamate was conducted,[165] followed by the proposed methylation of the α-carbon atom. The nitrile group could then be reduced using Raney® nickel under hydrolysing conditions to give β-amido aldehydes **165** and **166**. Attempts to conduct this synthesis using a benzyl group as the amide nitrogen atom protecting group, instead of the oxybenzyl group, failed to deliver the cyclisation products.



Scheme 2.26: Successful synthesis ring-based substrates **165** and **166**.

With the desired ring-based *β*-amido aldehydes in hand, they were consequently subjected to the hydroacylation conditions with 1-octyne (**Scheme 2.27**). Curiously, whilst the 2-piperidone-based **166** generated the predicted linear enone **168** within the usual time of 1 h, the hydroacylation of 2-pyrrolidinone-based **165** only achieved a 32% yield of enone **167**, even after prolonged heating. One explanation for this difference in reactivity could be due to the greater angle of interaction between the amide carbonyl group and aldehyde C−H bond around the rhodium metal centre, making the carbonyl's chelating ability less effective. However, further studies are being undertaken to explore this concept.

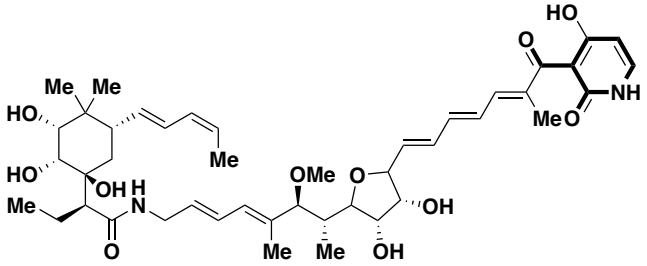


167 (32%)[a] **168** (98%)

Conditions: Aldehyde (0.30 mmol, 1.0 equiv.), 1-octyne (0.36 mmol, 1.2 equiv.), $[Rh(nbd)_2]BF_4$ (5 mol%), dcpe (5 mol%), acetone (1.0 M with respect to the aldehyde), 55 °C, 1 h. [a] 16 h reaction time.

Scheme 2.27: Reactivity of ring-based *β*-amido aldehydes **165** and **166**.

A natural extension of this investigation was to examine the effects of containing the amide group in an aromatic ring-based system instead of the alicylic rings looked at so far. Such motifs are themselves synthetically valuable, being present in the antibiotic Kirromycin, an inhibitor of a bacterial elongation factor EF-TU (**Figure 2.5**).[166]

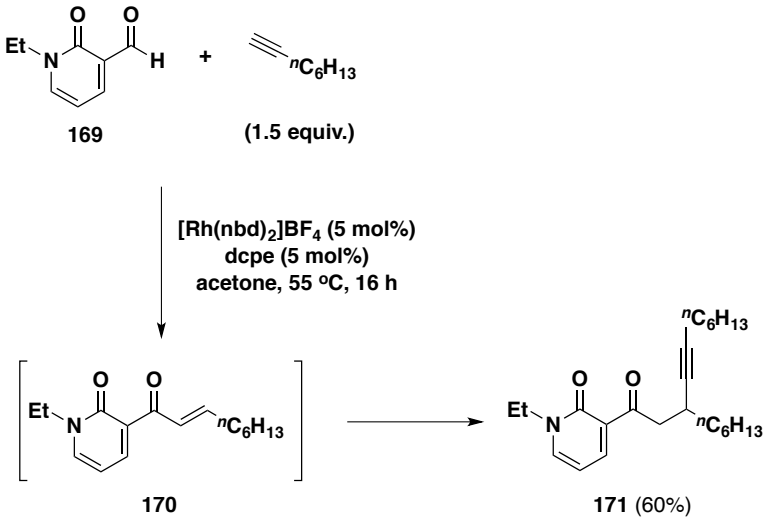


Kirromycin

Figure 2.5: Example of a biologically active 2-pyridone based system.

Accordingly, the 2-pyridone-based aldehyde **169** was subjected to the hydroacylation conditions. However, instead of obtaining the expected product, the enone **170** generated from the original hydroacylation catalytic cycle was never observed and appeared to have undergone a rhodium-catalysed conjugate addition with the remaining alkyne in the solution, giving ketone **171** (**Scheme 2.28**). Considering the incomplete conversion of aldehyde

starting material, it appears that this conjugate addition reaction is more favourable than hydroacylation of the remaining aldehyde. This peculiar result has been postulated to arise primarily from the fact that the 2-pyridone represents the most electron-withdrawing amide group tested, and thus is more likely to favour subsequent conjugate addition.



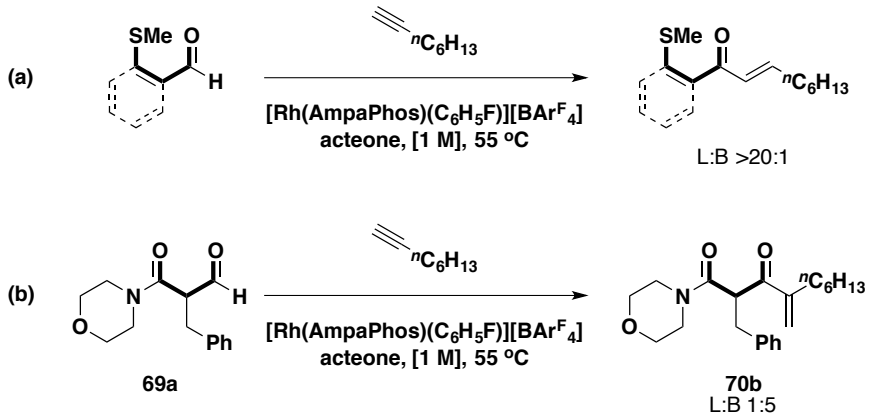
Scheme 2.28: Unexpected hydroacylation/conjugate addition of aldehyde **171**.

2.7 Branched-Selective Alkyne Hydroacylation

The investigations outlined previously in this chapter clearly evidenced a powerful hydroacylation methodology for the access of linear enones from *β*-amido aldehydes. Nonetheless, a curious result observed during initial optimisations, in which use of the ligand AmpaPhos led to a branched selectivity ratio of 5:1, remained intriguing (**Table 2.1,** entry **16**, **Section 2.2.1**). As this was the only ligand tested which displayed a preference for the branched isomer over the linear, it was decided that this result would be explored further to identify a possible branched-selective methodology.

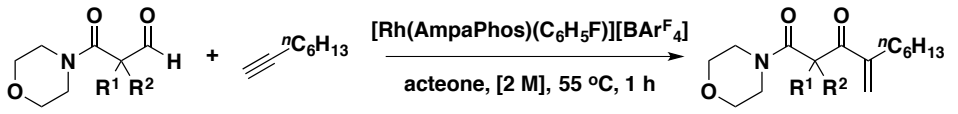
Previous work in the Willis had shown us that, in the hydroacylation of *β*-sulfur tethered substrates with 1-octyne, using the ligand AmpaPhos delivers the linear enone product in

near complete regioselectivity (**Scheme 2.29 (a)**).[167] Therefore, to rationalise our result (**Scheme 2.29 (b)**), it was postulated that the steric bulk of the α-carbon substituents could being playing a role in determining the regioselectivity outcome.



Scheme 2.29: Comparative behaviour of β-amide and β-sulfur tethers in alkyne hydroacylation using the ligand AmpaPhos.

We therefore set out to investigate if a pattern existed between the size and number of substituents on the α-carbon atom and branched regioselectivity. From the results gathered in **Scheme 2.30**, a tentative trend can be seen in which the smaller α-substituents (in this case a methyl group in **140b**) actually affords a much greater branched selectivity than the bulkier methyl-benzyl arrangement in **145**, which actually favours the linear regioisomer slightly.



140b (66%)[a]
B:L (9:1)[b]

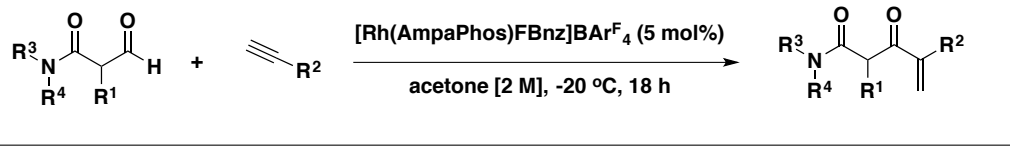
70b (90%)[a]
B:L (5:1)[b]

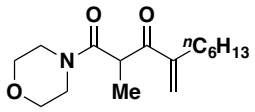
145b (90%)[a]
B:L (1:2)[b]

Conditions: Aldehyde (0.30 mmol, 1.0 equiv.), 1-octyne (0.36 mmol, 1.2 equiv.), [Rh(AmpaPhos)(C_6H_5F)][BAr^F_4] (5 mol%), acetone (2.0 M with respect to the aldehyde), 55 °C, 1 h. [a]Isolated yield of combined linear and branched products. [b]Determined by ^{1}H NMR spectroscopy.

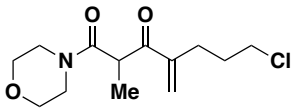
Scheme 2.30: Influence of steric bulk in the α-carbon position on branched regioselectivity.

Further optimisation work undertaken by other members of the group indicated that the branched regioselectivity of a range of terminal alkynes with aldehyde **69d** could be improved even further by lowering the temperature to –20 °C (**Scheme 2.31**). Extension of these conditions to the slightly bulkier aldehyde **69a**, also afforded excellent selectivity with 1-octyne (**Scheme 2.31**, entry **70b**), however, this ratio dropped upon application to other terminal alkynes (**Scheme 2.31**, entry **75b**).

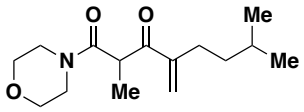




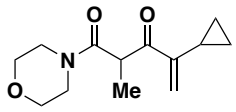
140b (69%)[a]
B:L = 17:1[b]



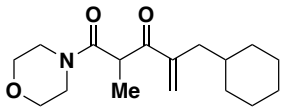
(69%)[a]
B:L = 15:1[b]



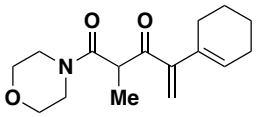
(77%)[a]
B:L = 17:1[b]



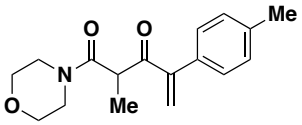
(76%)[a]
B:L = >20:1[b]



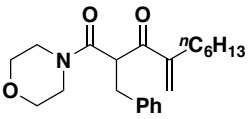
(84%)[a]
B:L = 17:1[b]



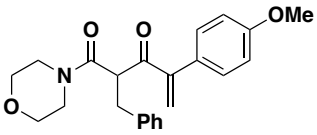
(40%)[a]
B:L = 2:1[b]



(64%)[a]
B:L = 7:1[b]



70b (83%)[a]
B:L = 17:1[b]



75b (98%)[a]
B:L = 5:1[b]

Conditions: Aldehyde (0.30 mmol, 1.0 equiv.), 1-octyne (0.36 mmol, 1.2 equiv.), [Rh(AmpaPhos)(C_6H_5F)][BAr^F_4] (5 mol%), acetone (2.0 M with respect to the aldehyde), -20 °C, 18 h. [a]Isolated yield of combined linear and branched products. Reactions conducted by Dr Maitane Fernandez-Chento. [b]Determined by ^{1}H NMR spectroscopy.

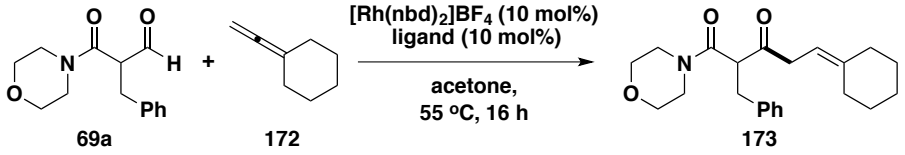
Scheme 2.31: Scope of branched-selective alkyne hydroacylation. Experiments undertaken by Dr Maitane Fernández-Chento.

2.8 Reactivity of Allenes in Hydroacylation

Allenes have proved themselves to be useful C=C bond components for a variety of transition metal-catalysed processes.[168] Despite this, their use in hydroacylation remains limited to coupling with salicylaldehyde substrates[169] and aldehydes containing *β*-sulfur tethers.[170]

Our investigations into the hydroacylation of *β*-amido aldehydes with allenes began first by conducting experiments to determine the effects of ligand variation on reactivity. Five of the more readily available bisphosphine ligands, which had performed well in alkyne hydroacylation, were used in attempts to couple vinylidenecyclohexane **172** with aldehyde **69a** (**Table 2.5**). A high catalyst loading of 10 mol% was used, together with an extended reaction time of 16 hours, in accordance with reports that more forcing conditions are often required to ensure complete conversion of aldehyde starting material when using allenes.[44]

Table 2.5: Ligand screening for hydroacylation of aldehyde **69a** with allene **172**.



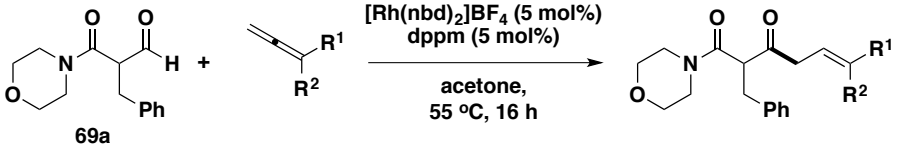
Entry	Ligand	Conversion[a] (%)	Yield (%)
1	dcpm	100	53
2	dcpe	100	45
3	dppm	100	70
4	dppe	100	60
5	DPEPhos	100	47

Conditions: **69a** (0.15 mmol, 1.0 equiv.), vinylidenecyclohexane **172** (0.18 mmol, 1.2 equiv.), $[Rh(nbd)_2]BF_4$ (10 mol%), ligand (10 mol%), acetone (2.0 M with respect to the aldehyde), 55 °C, 16 h. [a]Determined by ^1H NMR spectroscopy of crude reaction mixtures.

To our delight, all five ligands ensured full consumption of the aldehyde, however, yields of *β*-*γ*-unsaturated ketone **173** were varied. The optimal result obtained with dppm was repeated at a more reasonable catalyst loading of 5 mol%, delivering a satisfying yield of 70% within 5 hours (**Table 2.5**, entry **3**).

Unfortunately, application of these optimal conditions failed with all other allenes tested, including allenes containing electron-donating (**Table 2.6**, entry **3**) and electron-withdrawing groups (**Table 2.6**, entries **4** and **5**). This included the reaction with 3-methyl-1,2-butadiene (**Table 2.6**, entry **1**), which failed despite the structural and electronic similarities to the successful allene vinylidenecyclohexane **172**. This nonperformance may have arisen due to the reaction being conducted at a lower temperature of 30 °C, as the allene boiling point is lower than the optimised temperature of 55 °C. Given this limited success of allene hydroacylation, experiments were suspended.

Table 2.6: Attempted scope of allene hydroacylation conditions with aldehyde **69a**.



Entry	Allene	Conversion[a]
1[b]	R^1 = Me; R^2 = Me	0
2	R^1 = Cy; R^2 = H	0
3	R^1 = OMe; R^2 = H	0
4	R^1 = CO_2Et; R^2 = H	0
5	R^1 = CO_2Et; R^2 = Me	0

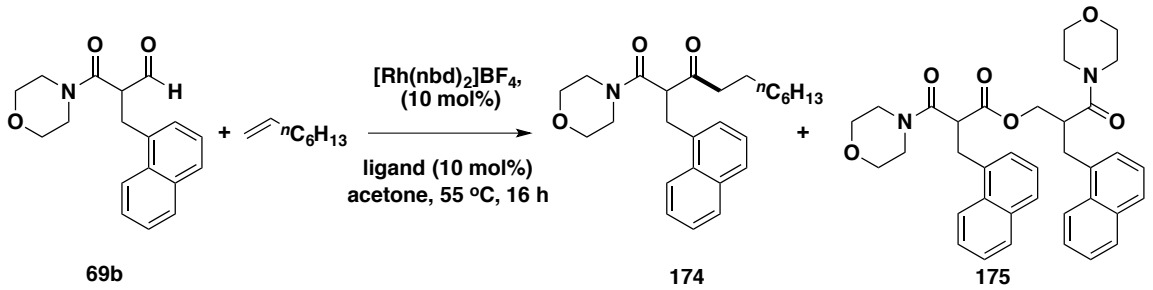
Conditions: **69a** (0.30 mmol, 1.0 equiv.), allene (0.36 mmol, 1.2 equiv.), $[Rh(nbd)_2]BF_4$ (5 mol%), dppm (5 mol%), acetone (2.0 M with respect to the aldehyde), 55 °C, 16 h. [a]Determined by ^{1}H NMR spectroscopy of crude reaction mixtures. [b]Conducted at 30 °C, instead of 55 °C, as the boiling point of the allene used is 40-41 °C.

2.9 Reactivity of Alkenes in Hydroacylation

Methodologies involving rhodium-catalysed hydroacylation of alkenes typically differ from their alkyne counterparts, as they often require a combination of either higher catalyst loadings,[44] activated substrates[46] or specific ligand requirements.[99] In developing our own system, it seemed prudent therefore to re-optimise conditions for the hydroacylation of *β*-amido aldehyde **69b** with the unactivated alkene, 1-octene.

Beginning with ligand screening, the reactivity using each ligand varied considerably compared to the initial investigations seen with alkynes and allenes (**Table 2.7**). Interestingly, however, was the presence of a new side product, in addition to the expected ketone **174**, that had not yet been observed in any other experiments. It was later determined to be the ester **175**, a result of a Tishchenko-style dimerisation of the aldehyde starting material. This potentially indicated that, whilst the initial C–H oxidative addition may be rapid, the migratory insertion is relatively slower, allowing for competition between the alkene molecule and the remaining aldehyde. Whilst this side product was not seen for the bisphosphine ligands dcpm (**Table 2.7**, entry **1**) or dcpe (**Table 2.7**, entry **3**), their overall conversion of starting material was poor, and thus the ligand dppm was selected to proceed in further optimisation experiments, with a focus on limiting the formation of ester **175** and increasing the isolated yield. Notably, the ligands dtpm and AmpaPhos (used in the forms [Rh(dtpm)(C_6H_5F)][BAr^F_4] and [Rh(AmpaPhos)(C_6H_5F)][BAr^F_4], respectively), failed to generate any product, despite their previous success with challenging substrates such as internal alkenes in the alkene hydroacylation of *β*-sulfur-tethered aldehydes.[99]

Table 2.7: Ligand screening for hydroacylation of aldehyde **69b** with 1-octene.



69b 174 175

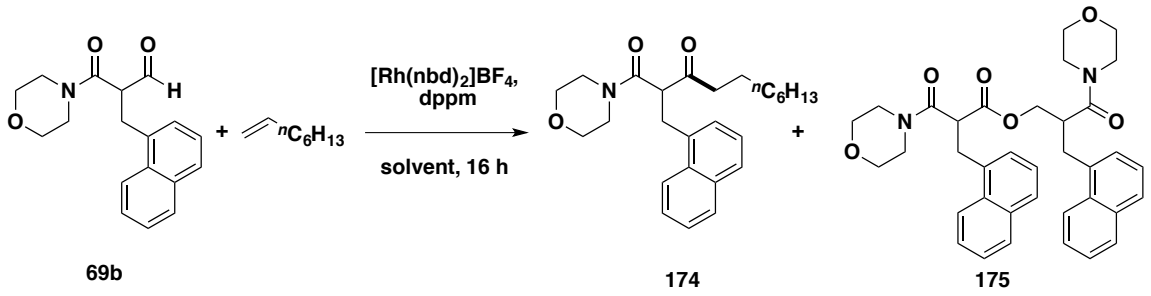
Entry	Ligand	Conversion[a] (%)	174:175 ratio[a]
1	dcpm	20	1:0
2	dppm	100 (14)[b]	4:1
3	dcpe	11	1:0
4	dppe	66	1:1
5	PNP(Cy)	71	4:1
6	dtpm[c]	0	-
7	AmpaPhos[d]	0	-

Conditions: **69b** (0.15 mmol, 1.0 equiv.), 1-octene (0.45 mmol, 3.0 equiv.), $[Rh(nbd)_2]BF_4$ (10 mol%), ligand (10 mol%), acetone (1.0 M with respect to the aldehyde), 55 °C, 16 h. [a]Determined by ^{1}H NMR spectroscopy of crude reaction mixtures. [b]Value in parentheses indicates isolated yield of pure ketone product **174**. [c]dtpm was used as the pre-formed $[Rh(dtpm)(C_6H_5F)][BAr^F_4]$ complex. [d]AmpaPhos was used as the pre-formed $[Rh(AmpaPhos)(C_6H_5F)][BAr^F_4]$ complex.

Using dppm as the ligand of choice, four conditions were subsequently varied in order to improve the yield of ketone **174**: catalyst loading, temperature, concentration and solvent (**Table 2.8**). Reducing the temperature to room temperature (25 °C) drastically diminished the aldehyde conversion, albeit only to the ketone product (**Table 2.8**, entry **2**). A similar observation occurred when the catalyst loading was halved to 5 mol%, however, the presence of Tishchenko product **175** was still observed (**Table 2.8**, entry **3**). Reducing the concentration to 1.0 M with respect to the aldehyde seemed to have a small positive effect

with regards to the ketone:ester ratio, although the isolated yield still remained poor (**Table 2.8**, entry **4**). Switching the solvent to 1,2-DCE or 2-butanone, both of which have been used successfully in other rhodium-catalysed hydroacylation reactions,[171] also gave no apparent overall benefit (**Table 2.8**, entry **5** and **6**).

Table 2.8: Ligand screening for hydroacylation of aldehyde **69b** with 1-octene.



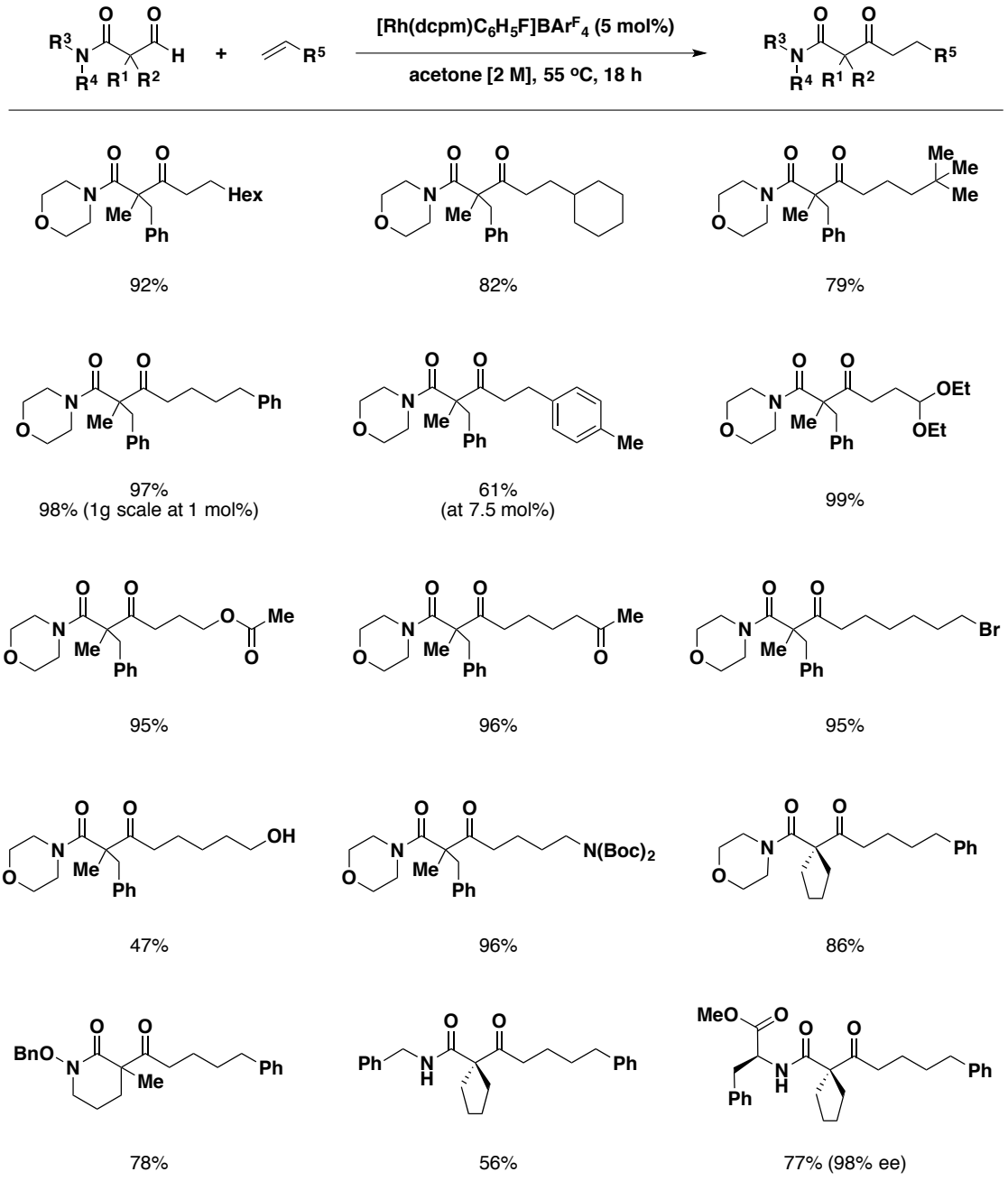
69b **174** **175**

Entry	Catalyst Loading	Temp. (°C)	Conc. (M)	Solvent	Conversion[a] (%)	174:175 ratio[a]
1	10 mol%	55	2.0	Acetone	100 (14)	2:1
2	10 mol%	25	2.0	Acetone	33	1:0
3	5 mol%	55	2.0	Acetone	33	4:1
4	10 mol%	55	1.0	Acetone	100 (18)	3:1
5	10 mol%	55	2.0	1,2-DCE	55	4:1
6	10 mol%	55	2.0	2-butanone	80	1:1

Conditions: **69b** (0.15 mmol, 1 equiv.), 1-octene (0.18 mmol, 1.2 equiv.), $[Rh(nbd)_2]BF_4$:ligand 1:1 ratio, solvent, 16 h. [a]Determined by ^1H NMR spectroscopy of crude reaction mixtures. Value in parentheses indicates isolated yield of pure ketone product **174**.

Further optimisation work on this reaction was continued by other members of the group. It was subsequently determined that, whilst the alkene hydroacylation of monosubstituted *β*-amido aldehydes continued to be poor, a suitable set of conditions could be obtained for disubstituted aldehydes. Using the preformed catalyst $[Rh(dcpm)(C_6H_5F)][BAr^F{}_4]$ at 5 mol%, disubstituted aldehydes could couple with a range of unactivated terminal alkenes

in good to excellent yields (**Scheme 2.32**). Application of these conditions to internal alkenes proved unsuccessful, and this system currently remains undeveloped.

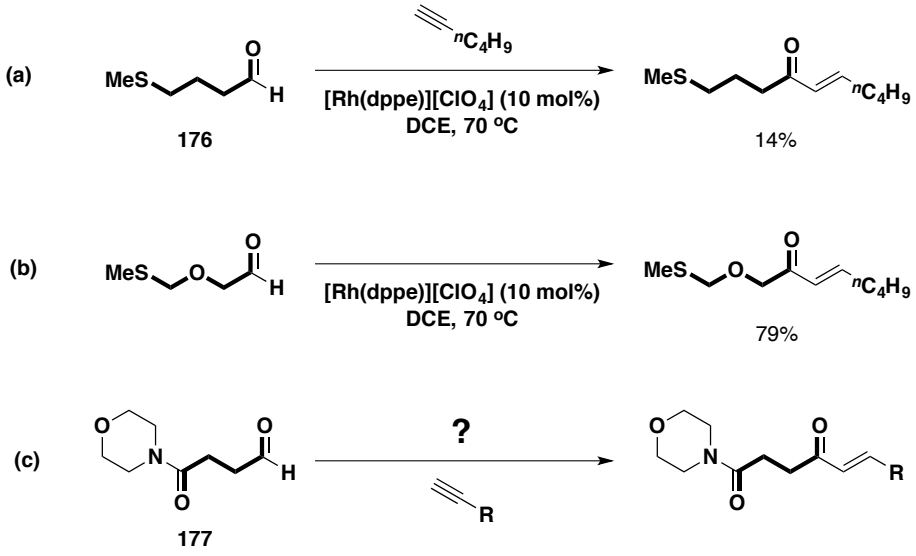


Conditions: Aldehyde (0.30 mmol, 1.0 equiv.), alkene (0.45 mmol, 3.0 equiv.), [Rh(dcpm)(C_6H_5F)][BAr^F_4] (5 mol%), acetone (2.0 M with respect to the aldehyde), 55 °C, 18 h. Reactions conducted by Dr Maitane Fernandez-Chento.

Scheme 2.32: Scope of alkene hydroacylation. Experiments undertaken by Dr Maitane Fernández-Chento.

2.10 Intermolecular Hydroacylation of 1,4-Dicarbonyl Systems

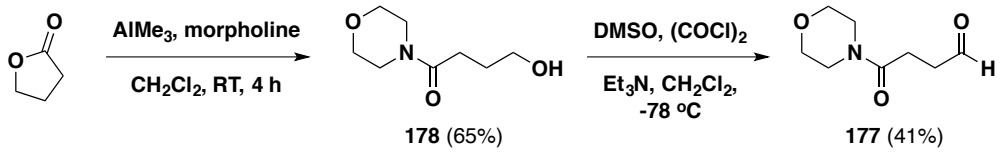
Looking to extend the scope of utility of the amide tether further, it was decided that γ-amido aldehydes such as **177** were to be examined in hydroacylation (**Scheme 2.33, (c)**). Our hopes had been raised following a report by Willis *et al*. in which the analogous γ-sulfur tethered substrate **176** had undergone a successful hydroacylation, albeit in a low yield (**Scheme 2.33 (a)**).[100] The use a methylthiomethyl ether moiety gave a much greater yield, an example of which is shown in **Scheme 2.33 (b)**.[100] However, the overall reduced activity of these γ-tethered systems compared to β-substituted equivalents was rationalised by the involvement of a kinetically less favourable six-membered chelate following oxidative addition, as opposed to the much preferred five-membered chelate seen with β-substituted systems (see **Section 2.2**). It was therefore expected that any reactivity of the γ-amido aldehydes would be harder to achieve than their β-amido aldehyde counterparts.



Scheme 2.33: (a) and (b): Known hydroacylation reactions using γ-tethered aldehydes; (c): Proposed application to γ-amido aldehydes.

To begin our investigations, γ-amido aldehyde **177** was synthesised in two steps from γ-

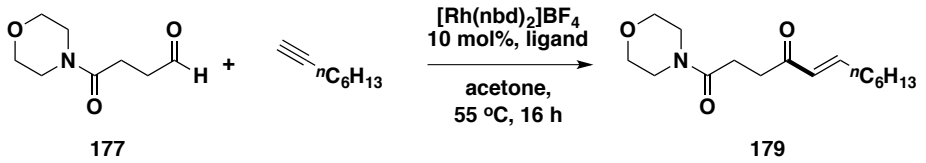
butyrolactone. An initial ring opening with morpholine using the Lewis acid trimethylaluminium followed by a Swern oxidation of the resultant alcohol **178** gave the aldehyde **177** (**Scheme 2.34**).



Scheme 2.34: Synthesis of aldehyde **177**.

Despite utilising a catalyst loading of 10 mol%, examination of this substrate in our usual ligand screening process delivered disappointing conversions to the linear enone **179** (the branched isomer not being observed). Therefore, no accurate yields could be obtained from such low conversions (**Table 2.9**).

Table 2.9: Ligand screening for hydroacylation of aldehyde **177** with 1-octyne.

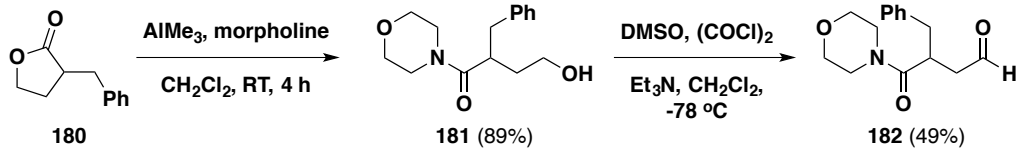


Entry	Ligand	Conversion[a] (%)
1	dcpm	7
2	dcpe	0
3	dppm	36
4	dppe	19

Conditions: **177** (0.15 mmol, 1.0 equiv.), 1-octyne (0.18 mmol, 1.2 equiv.), $[Rh(nbd)_2]BF_4$ (10 mol%), ligand (10 mol%), acetone (2.0 M with respect to the aldehyde), 55 °C, 16 h. [a]Determined by ^1H NMR spectroscopy of crude reaction mixtures.

In an attempt to improve these results, aldehyde **182** was proposed for investigation as it was believed that the benzyl group *α*- to the amide carbonyl would make the substrate sterically

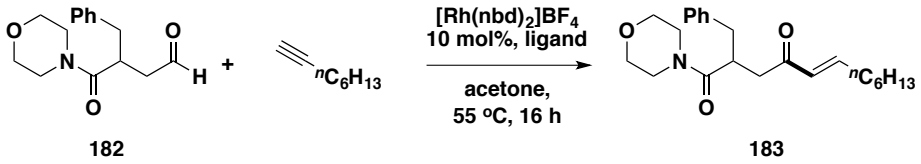
more comparable to *β*-amido aldehyde **69a**. Aldehyde **182** could be synthesised in a similar manner to the unsubstituted substrate **177**, using 3-benzyldihydrofuran-2(3*H*)-one **180**, which itself was derived from *γ*-butyrolactone (**Scheme 2.35**).



Scheme 2.35: Synthesis of aldehyde **182**.

This time, more pleasing conversions were observed in ligand screening (**Table 2.10**). Out of the bisphosphines tested, dppm and dppe gave the greatest conversions, with dppe triumphing at 84% conversion. Unfortunately, this high conversion translated poorly to an isolated yield of 20% for the linear enone **183**. Upon dropping the catalyst loading to a more practical amount of 5 mol%, the conversions fell to almost negligible quantities (**Table 2.10**, entry **8** and **9**). Changing the solvent from acetone to 1,2-DCE also had a negative effect on conversions (**Table 2.10**, entry **10** and **11**). Therefore, the current optimal conditions (**Table 2.10**, entry **4**) still require further optimisation in order to successfully employ a more reasonable catalyst loading. It also remains unclear as to why the presence of the benzyl group in **182** enables a great level of conversion under certain conditions, compared to when it is absent in aldehyde **177**. One possible explanation could be that the benzyl group promotes more reactive conformations within the substrate. Further work is currently being undertaken to explore this phenomenon.

Table 2.10: Ligand screening for hydroacylation of amide **182** with 1-octyne.



182 **183**

Entry	Ligand	Catalyst Loading	Solvent	Conversion[a] (%)
1	dcpm	10 mol%	Acetone	31
2	dcpe	10 mol%	Acetone	0
3	dppm	10 mol%	Acetone	60
4	dppe	10 mol%	Acetone	84 (20)
5	dppp	10 mol%	Acetone	5
6	dppf	10 mol%	Acetone	0
7	DPEPhos	10 mol%	Acetone	0
8	dppm	5 mol%	Acetone	0
9	dppe	5 mol%	Acetone	9
10	dppm	10 mol%	1,2-DCE	12
11	dppe	10 mol%	1,2-DCE	48

Conditions: **182** (0.30 mmol, 1.0 equiv.), 1-octyne (0.36 mmol, 1.2 equiv.), [Rh(nbd)$_2$]BF$_4$, ligand, solvent (2.0 M with respect to the aldehyde), 55 °C, 16 h. [a]Determined by ^{1}H NMR spectroscopy of crude reaction mixtures. Value in parenthesis is the isolated yield of the pure product.

As noted in **Scheme 2.33 (b)**, the presence of a heteroatom instead of the *β*-carbon atom in *γ*-sulfur tethered aldehydes dramatically improved their reactivity in alkyne hydroacylation, potentially due to the heteroatom creating an electronic bias for a gauche conformation and thus making the 6-membered chelate more favourable. Applying this structural design to our *γ*-amido aldehydes would result in substrates of the form **185**, where the carbonyls remain in a 1,4-dicarbonyl arrangement, but the amide group is seemingly 'flipped' around so the amide nitrogen atom behaves as an *α*-substituent to the aldehyde group (**Figure 2.6**). It was

hoped, therefore, that these 1,4-dicarbonyl systems would see enhanced reactivity under milder conditions.

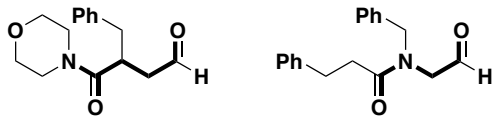
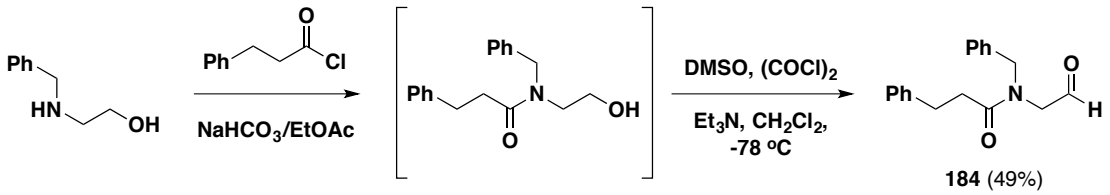


Figure 2.6: Comparison of the two 1,4-dicarbonyl systems tested.

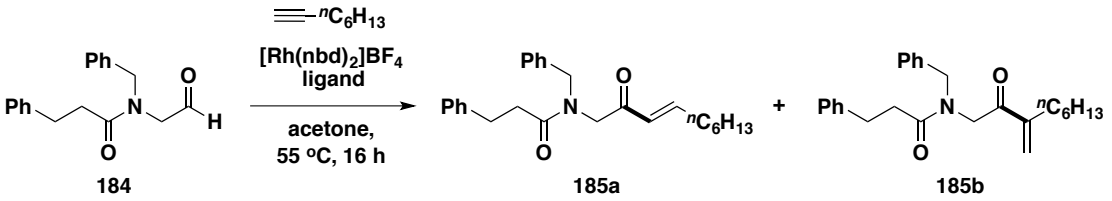
The synthesis of these substrates required a different approach to those used previously, first by coupling an amino-alcohol with an acyl chloride, followed by oxidation of the alcohol group to an aldehyde (**Scheme 2.36**).



Scheme 2.36: Synthesis of aldehyde **184**.

Application of this substrate to a range of selected catalysts and conditions gave us better conversions, particularly at the preferred catalyst loading of 5 mol% (**Table 2.11**). Using dppe, a conversion of 83% could be achieved, giving a moderate yield of 51% for the linear product **185a** (**Table 2.11**, entry **6**). While further experiments need to be undertaken to determine if this amide arrangement is universally beneficial in terms of reactivity compared to *γ*-amido aldehyde **182**, it is clear in this particular case that there is an advantage in overall conversion. However, it is also apparent that the regioselectivity has greatly diminished. Whereas *γ*-amido aldehyde **182** gave us complete selectivity for the linear enone product, for the 1,4-dicarbonyl system **184** we now observe a 4:1 mixture in favour of the linear isomer **185a**. It currently remains unknown as to why this is the case.

Table 2.11: Ligand screening for hydroacylation of aldehyde **184** with 1-octyne.

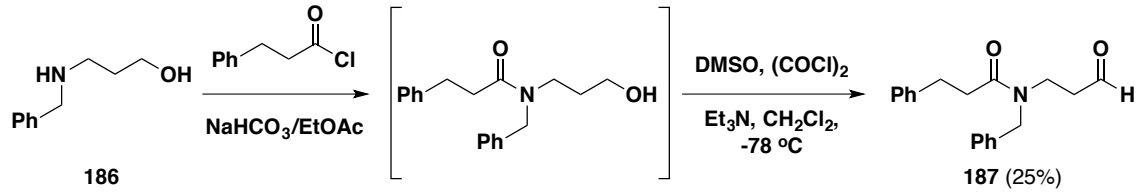


Entry	Ligand	Catalyst Loading	Conversion[a] (%)	185a:b ratio
1	dcpm	10 mol%	41	-
2	dcpe	10 mol%	0	-
3	dppm	10 mol%	43	-
4	dppe	10 mol%	97	4:1
5	dppm	5 mol%	12	-
6	dppe	5 mol%	83 (51)[b]	4:1

Conditions: **184** (0.30 mmol, 1.0 equiv.), 1-octyne (0.36 mmol, 1.2 equiv.), $[Rh(nbd)_2]BF_4$, ligand, acetone (2.0 M with respect to the aldehyde), 55 °C, 16 h. [a]Determined by ^1H NMR spectroscopy of crude reaction mixtures. [b]Value in parentheses indicates isolated yield of linear product **185a.**

2.11 Intermolecular Hydroacylation of 1,5-Dicarbonyl Systems

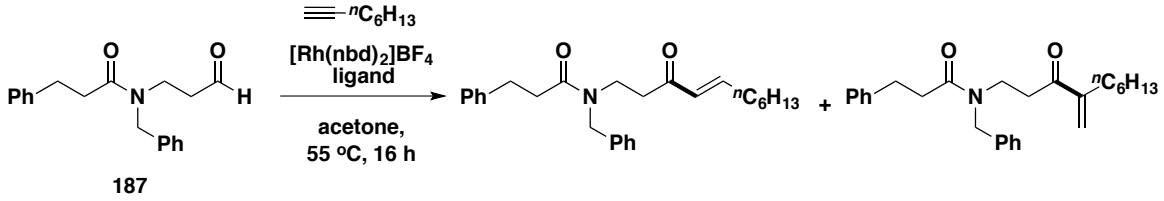
Given the relative success of the 1,4-dicarbonyl system **184**, it was decided to examine if this could be taken one step further by increasing the linkage by an additional carbon atom to give a 1,5 dicarbonyl system. Such an aldehyde **187** could be synthesised in a similar manner as previously used, employing a longer chain amino-alcohol **186** (**Scheme 2.37**).



Scheme 2.37: Synthesis of aldehyde **187**.

Unfortunately, all attempts to conduct a hydroacylation of **187** with 1-ocytne failed (**Table 2.12**). It is believed that in order for this substrate to react successfully, a kinetically unfavourable 7-membered chelate would be required and thus any product formation would be highly unlikely. In light of this hypothesis, all further attempts were suspended.

Table 2.12: Ligand screening for hydroacylation of aldehyde **187** with 1-octyne.



187

Entry	Ligand	Conversion[a] (%)
1	dcpm	0
2	dcpe	0
3	dppm	0
4	dppe	0

Conditions: **187** (0.15 mmol, 1.0 equiv.), 1-octyne (0.18 mmol, 1.2 equiv.), $[Rh(nbd)_2]BF_4$ (10 mol%), ligand (10 mol%), acetone (2.0 M with respect to the aldehyde), 55 °C, 16 h. [a]Determined by ^{1}H NMR spectroscopy of crude reaction mixtures.

2.12 Intermolecular Hydroacylation of *N*-Formyl Amides

A final structural variation of the amide-aldehyde group combination to be tested in this methodology was *N*-formyl amides of the form **188** and **189** (**Figure 2.7**). Whilst the carbonyls in *N*-formyl amides remain in a 1,3 arrangement as in our successful *β*-amido aldehyde system, the amide is seemingly 'flipped' around so that the aldehyde group is directly bonded to the amide nitrogen atom. The electronics of the aldehyde are therefore significantly modified, raising a potential issue in terms of reactivity and C–H bond activation. Whilst such activation by a transition metal catalyst has been explored with

formamides using nickel catalysis,[172-175] analogous reactivity for *N*-formyl amides is currently unprecedented in the literature.

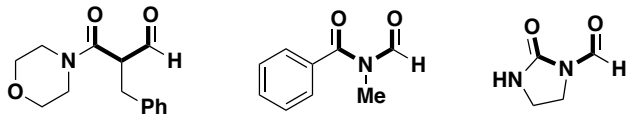
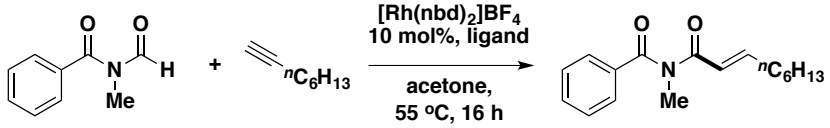


Figure 2.7: Structural comparison of *β*-amido aldehyde **69a** and *N*-formyl amides **188** and **189**.

Neither substrate delivered any conversion to the enone product at the high catalyst loading of 10 mol% (**Tables 2.13** and **2.14**). Whilst there may be additional factors involved, such as the electron withdrawing effect of the phenyl group in **188**, and the carbonyl geometry in the ring system **189**, it is believed that these may be secondary to the electronic influence of the nitrogen atom. Therefore, work on this substrate class was not continued.

Table 2.13: Ligand screening for hydroacylation of aldehyde **188** with 1-octyne.

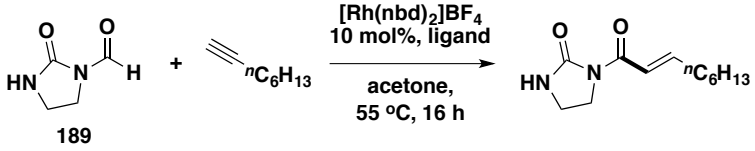


188

Entry	Ligand	Conversion[a] (%)
1	dcpm	0
2	dcpe	0
3	dppm	0
4	dppe	0

Conditions: **188** (0.15 mmol, 1.0 equiv.), 1-octyne (0.18 mmol, 1.2 equiv.), $[Rh(nbd)_2]BF_4$ (10 mol%), ligand (10 mol%), acetone (2.0 M with respect to the aldehyde), 55 °C, 16 h. [a]Determined by ^1H NMR spectroscopy of crude reaction mixtures.

Table 2.14: Ligand screening for hydroacylation of aldehyde **189** with 1-octyne.



189

Entry	Ligand	Conversion[a] (%)
1	dcpm	0
2	dcpe	0
3	dppm	0
4	dppe	0

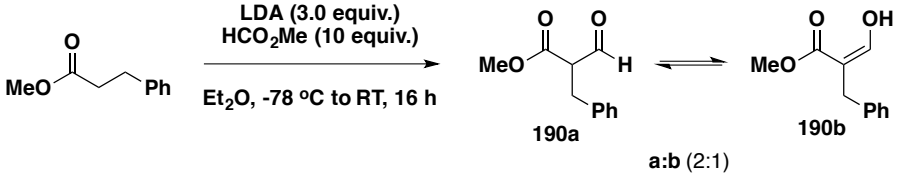
Conditions: **189** (0.15 mmol, 1.0 equiv.), 1-octyne (0.18 mmol, 1.2 equiv.), $[Rh(nbd)_2]BF_4$ (10 mol%), ligand (10 mol%), acetone (2.0 M with respect to the aldehyde), 55 °C, 16 h. [a]Determined by ^{1}H NMR spectroscopy of crude reaction mixtures.

2.13 Intermolecular Hydroacylation of *β*-Formyl Esters

Sections **2.1** to **2.12** outlined our investigations into using the amide carbonyl group as an effective tether to enable hydroacylation processes of various efficiencies. In taking this concept forward, we believed that the carbonyl group in the corresponding ester moieties could facilitate a similar mode of reactivity. With esters being on a par with amides in terms of ubiquity and synthetic importance, the potential synthetic applications of such a methodology would be very broad indeed.

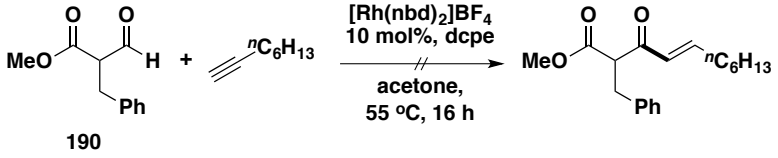
As such, we initially sought to synthesise the methyl ester counterpart **190** of our standard *β*-formyl amide **69a**, once again using Johnson's formylation method with LDA and methyl formate.[158] However, an important differentiation occurred. Instead of existing entirely in the aldehyde form, as observed with all *β*-formyl amides synthesised, the substrate methyl

2-benzyl-3-oxopropanoate **190** rapidly enolised under neutral conditions to generate a keto:enol equilibrium of ratio 2:1 in $CDCl_3$ (**Scheme 2.37**).



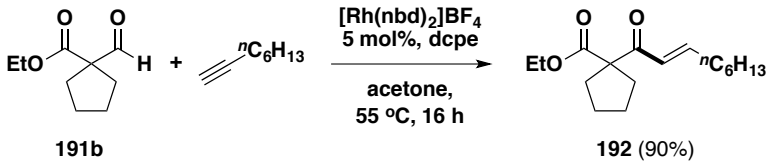
Scheme 2.37: Synthesis and subsequent enolisation of aldehyde **190**.

When **190** was used in our optimised hydroacylation conditions, no reactivity occurred, even at 10 mol% catalyst loading (**Scheme 2.38**). A potential rationale was proposed in which the existence of the enol form somehow prevented the rhodium catalyst from facilitating C–H activation, perhaps by coordinating to the rhodium metal as a bidentate ligand.



Scheme 2.38: Failed hydroacylation attempt with aldehyde **190**.

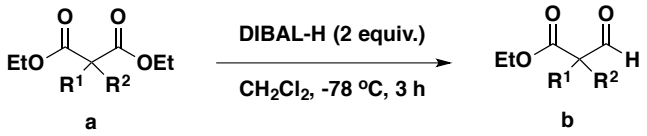
A method of examining the validity of this theory, whilst also finding a way around this problem, was to design a *β*-formyl ester in which enolisation could be prevented. This could be achieved by synthesising an aldehyde of the form **191b**, where the *α*-carbon atom contains two substituent groups, in this case two bonds of a 5-membered ring. Much to our delight, this substrate engaged successfully with our optimised hydroacylation conditions and, at 5 mol% loading, gave the linear product **192** with complete regioselectivity and 90% yield (**Scheme 2.39**).



191b **192** (90%)

Scheme 2.39: Successful hydroacylation of α-disubstituted aldehyde **191b**.

Seeking to expand the scope of this reaction, and to explore any influence the α-substituent groups may have on reactivity, a synthetic route to disubstituted β-formyl esters was developed. Using the equivalent diethyl esters as starting points (due to the ease of manipulation of their substituent groups), the ester-aldehyde combination could be achieved by a one-step monoreduction using DIBAL-H under strict low temperature conditions. Such a method allowed access to a handful of ethyl ester containing aldehydes (**Scheme 2.40**).



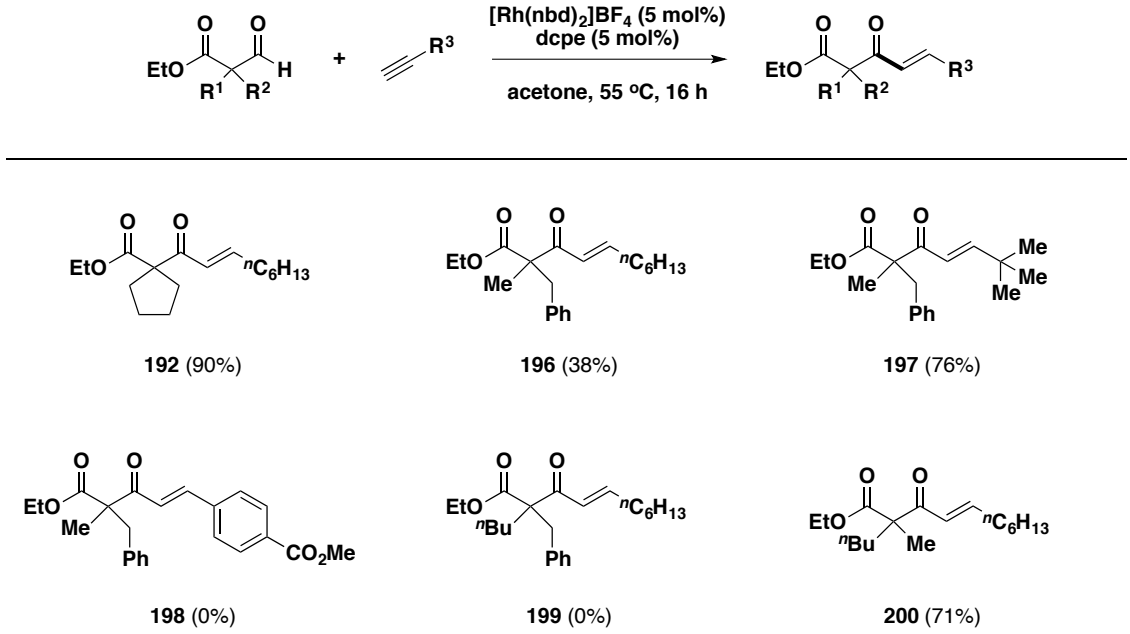
191b (38%) **193b** (46%) **194b** (95%) **195b** (63%)

Conditions: Diester (5.0 mmol), DIBAL-H (1.0 M in CH_2Cl_2, 10.0 mmol), CH_2Cl_2 (0.5 M with respect to ester), -78 °C, 3 h.

Scheme 2.40: Range of α-disubstituted β-formyl esters synthesised.

Interestingly, the activity of these substrates in hydroacylation showed a high degree of variation compared to what had been observed previously with β-formyl amides (**Scheme 2.41**). Changing the cyclopentyl group on the α-carbon atom to a methyl-benzyl arrangement led to a sharp drop in conversion with 1-octyne (**Scheme 2.41**, entry **196**), and none at all with the electron deficient methyl-4-ethynylbenzoate (**Scheme 2.41**, entry **198**).

The conversion was increased with the use of the bulkier 3,3-dimethyl-1-butyne (**Scheme 2.41**, entry **197**), although it remains unclear as to why this is the case. Increasing the steric bulk of the *α*-carbon substituents to a *n*-butyl-benzyl arrangement seemed to prevent any C–H activation from occurring at all (**Scheme 2.41**, entry **199**), although reducing this slightly to *n*-butyl-methyl apparently allowed for reasonable conversion to take place (**Scheme 2.41**, entry **200**).



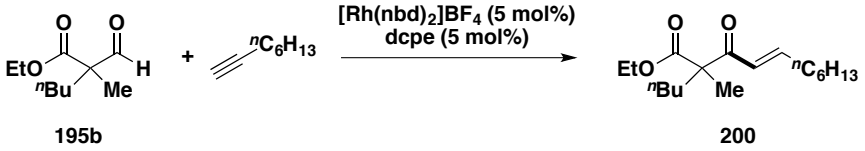
Conditions: Aldehyde (0.30 mmol, 1.0 equiv.), terminal alkyne (0.36 mmol, 1.2 equiv.), $[Rh(nbd)_2]BF_4$ (5 mol%), dcpe (5 mol%), acetone (1.0 M with respect to the aldehyde), 55 °C, 16 h.

Scheme 2.41: Scope of *β*-formyl ester hydroacylation using conditions optimised for amides.

In most cases in the above scheme (**Scheme 2.41**), the disappointing yields arose from relatively low conversions. In an attempt to see if tweaking the reaction conditions could have any effect on these numbers, aldehyde **195b** was selected for further optimisation investigations (**Table 2.15**). Ligand, temperature, concentration and solvent were briefly screened in each case, to determine if any one of them could have a major impact on yield. Altering the concentration in both directions (**Table 2.15**, entries **4** and **5**) and lowering the

temperature (**Table 2.15**, entry **2**) appeared to have a negative effect, along with using 2-butanone as the solvent (**Table 2.15**, entries **7** and **8**). Insubstantial increases were seen with using dcpm as the ligand (**Table 2.15**, entry **3**) and 1,2-DCE as the solvent (**Table 2.15**, entry **6**). Whilst, overall, slight variations in conversion occurred, no combination of the above conditions gave complete conversion, suggesting that the issues may lie elsewhere.

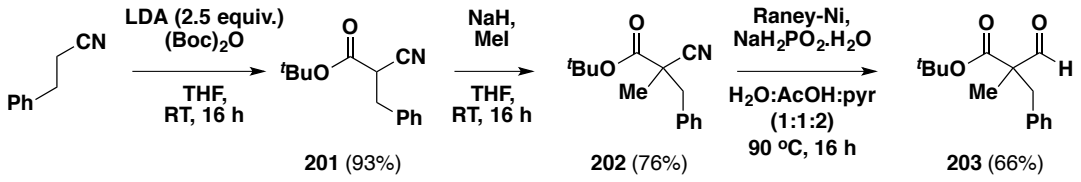
Table 2.15: Conditions screening for hydroacylation of ester **195b** with 1-octyne.



Entry	Ligand	Temp. (°C)	Conc. (M)	Solvent	Conversion[a] (%)
1	dcpe	55	1.0	Acetone	79 (71)
2	dcpe	25	1.0	Acetone	60
3	dcpm	55	1.0	Acetone	86
4	dcpe	55	0.5	Acetone	43
5	dcpe	55	4.0	Acetone	67
6	dcpe	55	1.0	1,2-DCE	85
7	dcpe	80	1.0	2-butanone	65
8	dcpe	80	4.0	2-butanone	49

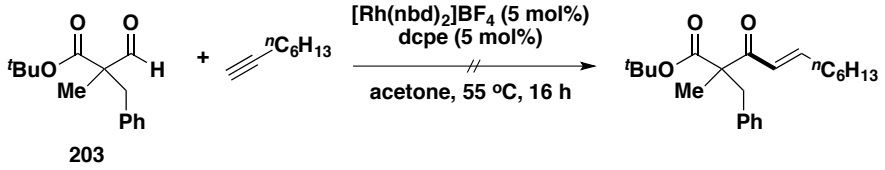
Conditions: **195b** (0.30 mmol, 1.0 equiv.), 1-octyne (0.36 mmol, 1.2 equiv.), $[Rh(nbd)_2]BF_4$ (5 mol%), ligand (5 mol%), solvent, 16 h. [a]Determined by ^1H NMR spectroscopy of crude reaction mixtures. Value in parentheses indicates isolated yield of pure enone product.

Therefore, it was proposed that the type of ester group substituent may be affecting the reaction here. As such, a *t*-butyl ester **203**, containing the methyl-benzyl arrangement in the *α*-position, was synthesised. An inability to use the methodology laid out in **Scheme 2.40** required us to develop an alternative synthetic route to aldehyde **203**, using a nitrile group in the intermediate (**Scheme 2.42**).



Scheme 2.42: Synthesis of aldehyde **203**.

However, despite observing some product when the equivalent ethyl ester was used (**Scheme 2.41**, entry **196**), with *t*-butyl ester **203**, no enone was observed (**Scheme 2.43**). One potential explanation may be due to the steric bulk of the ester group somehow weakening any coordination to the metal centre.



Scheme 2.43: Failed hydroacylation attempt of aldehyde **203**.

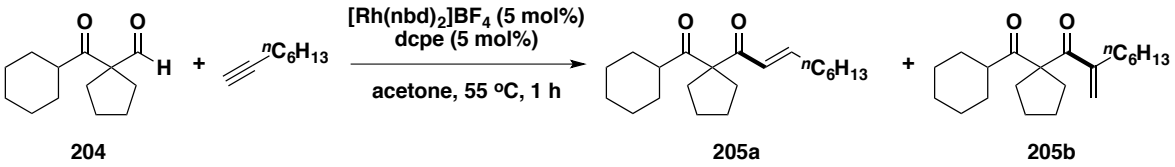
Whilst many more studies need to be carried with *β*-formyl esters to determine the reasons for their unreliable reactivity, investigations were temporarily halted in order to pursue other substrate classes.

2.14 Intermolecular Hydroacylation of *β*-Formyl Ketones

As a natural extension of what had been completed so far, ketones were the final class of carbonyl tethers that remained to be investigated in our hydroacylation methodology. As *α*-monosubstituted *β*-formyl ketones are known to exist in a keto:enol equilibrium and would therefore be unlikely candidates for hydroacylation (similar to the equivalent ester, which failed in our test reactions), *α*-disubstituted aldehyde **204** was chosen for initial screening (**Table 2.16**). An initial ligand evaluation showed near complete conversions across the board at 5 mol% catalyst loading and dcpm (**Table 2.16**, entry **1**) and dcpe

(**Table 2.16**, entry **2**) offering complete linear regioselectivity. In keeping with the ligand preferred for *β*-formyl amides and esters, dcpe was therefore selected as optimal, giving an impressive isolated yield of 95%.

Table 2.16: Ligand screening for hydroacylation of aldehyde **204** at 5 mol % catalyst loading.



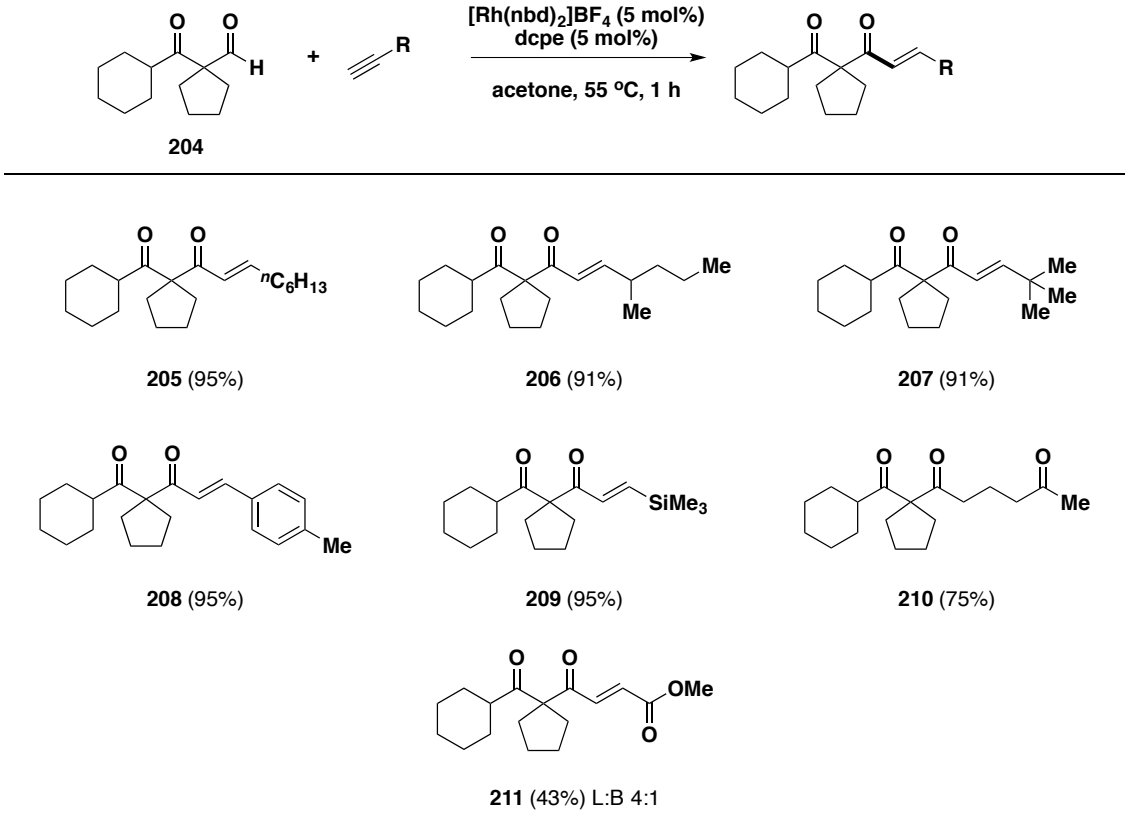
204 **205a** **205b**

Entry	Ligand	Conversion[a] (%)	205a:b ratio[a]
1	dcpm	100	>20:1
2	dcpe	100 (95)	>20:1
3	dppm	98	3:1
4	dppe	100	5:1

Conditions: **204** (0.30 mmol, 1.0 equiv.), 1-octyne (0.36 mmol, 1.2 equiv.), $[Rh(nbd)_2]BF_4$ (5 mol%), ligand (5 mol%), acetone (1.0 M with respect to the aldehyde), 55 °C, 1 h. [a]Determined by ^1H NMR spectroscopy of crude reaction mixtures. Value in parenthesis is the isolated yield of linear product **205a**.

With such a positive result with 1-ocytne, we sought to examine the efficacy across a range of alkynes (**Scheme 2.44**). Pleasingly, the handful of alkynes tested delivered good to excellent yields, demonstrating a versatility with ketone tethers similar to that observed with amides. Interestingly, the use of 4-pentyn-2-ol as the alkyne component resulted in a migration of the enone C=C double to generate a third ketone group, similar to that observed in Section 2.3.1 (**Scheme 2.44**, entry **210**). Curiously, this particular phenomenon was not observed with *β*-formyl amide **69a** and 4-pentyn-2-ol, and only partially when 3-butyn-2-ol was employed. Likewise, the vigorous reaction observed with methyl propiolate

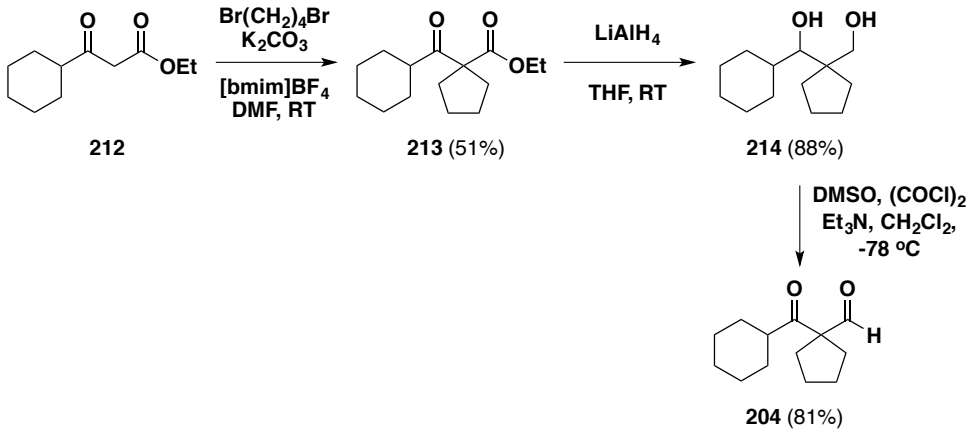
(**Scheme 2.44**, entry **211**) was surprising due to the relative electron deficiency of the alkyne bond. Sadly, however, the yield and regiocontrol were reduced relative to other alkynes.



Conditions: Aldehyde (0.30 mmol, 1.0 equiv.), alkyne (0.36 mmol, 1.2 equiv.), $[Rh(nbd)_2]BF_4$ (5 mol%), dcpe (5 mol%), acetone (1.0 M with respect to the aldehyde), 55 °C, 1 h.

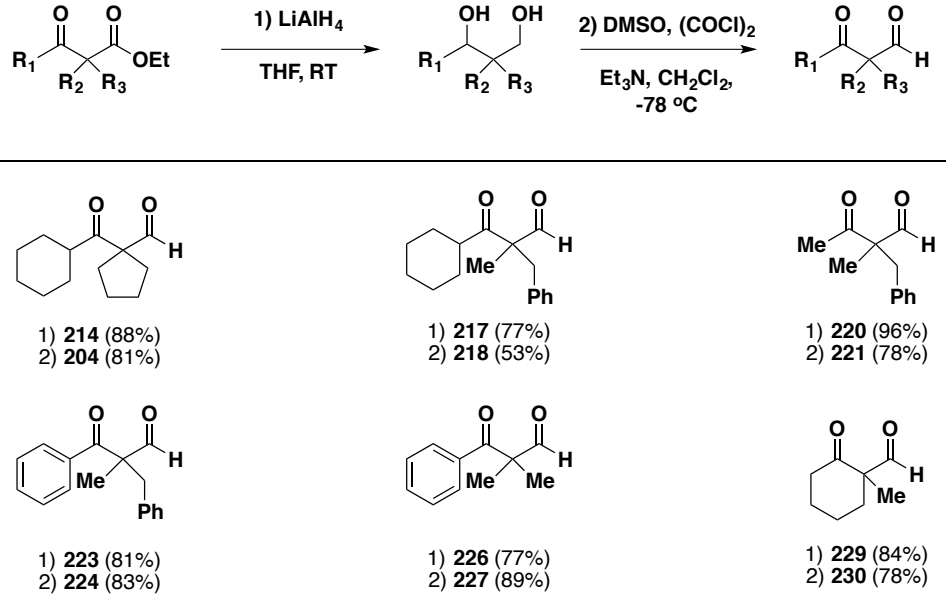
Scheme 2.44: Hydroacylation scope of *β*-formyl ketone **204** with a range of alkynes.

With a set of optimised conditions at hand, we were keen to assess the scope of the aldehyde component, and thus needed to synthesise a variety of *β*-formyl ketones. Substrate **204** had been made using a route which initially involved manipulation of the substituent groups on *β*-keto ester **212**, followed by reduction of the ester to an alcohol (unavoidably reducing the ketone in the process) and finally a double Swern oxidation back to the ketone and forming an aldehyde group at the terminus (**Scheme 2.45**).



Scheme 2.45: Synthesis of *β*-formyl ketone **204**.

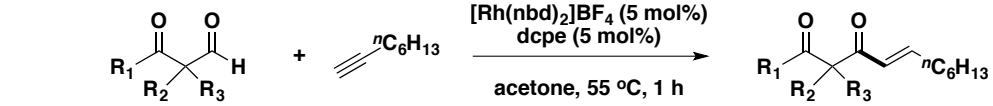
Despite requiring multiple steps to synthesise, this route provided access to a selection of *β*-formyl ketones with various *α*-substituent combinations and keto-groups in good yields (**Scheme 2.46**), in addition to one example where the ketone group is contained within a six membered ring (**Scheme 2.46**, entry **230**). This substrate also required methylation at the *α*-position to prevent enolisation.

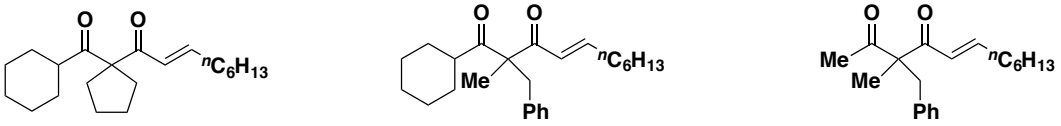


Conditions: Step 1: Keto-ester (1.0 equiv.), $LiAlH_4$ (2.5 equiv.), THF (0.1 M), RT, 0 °C to 16 h; Step 2: Diol (1 equiv.), DMSO (4.2 equiv.), $(COCl)_2$ (2.1 equiv.), Et_3N (7.2 equiv.), CH_2Cl_2 (1.0 M), -78 °C, 30 min.

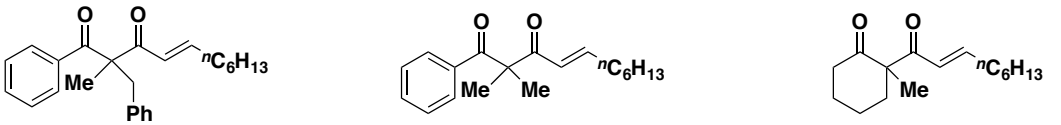
Scheme 2.46: Synthesis of *β*-formyl ketones.

Upon applying these substrates to the optimised hydroacylation conditions, we were delighted to observe excellent yields in most cases (**Scheme 2.47**). Entry **262** indicated that even a simple acetyl group can be used in chelation assistance, whilst entry **265** showed that incorporating the carbonyl tether in a 6-membered ring seems to have no negative impact. Most notably, the methyl-benzyl arrangement that had caused some disappointment with the *β*-formyl esters showed no problems here, in a similar manner to the equivalent *β*-formyl amide (**Scheme 2.47**, entry **231**). However, in combination with a phenyl ketone, this arrangement once again limited reactivity, this time completely (**Scheme 2.47**, entry **233**), although this was redeemed upon altering the *α*-substituents to two methyl groups (**Scheme 2.47**, entry **234**). It is currently not understood as to why this patterns occurs specifically for the phenyl ketone.





205 (95%) **231** (93%) **232** (65%)



233 (0%) **234** (87%) **235** (92%)

Conditions: Aldehyde (0.30 mmol, 1.0 equiv.), 1-octyne (0.36 mmol, 1.2 equiv.), $[Rh(nbd)_2]BF_4$ (5 mol%), dcpe (5 mol%), acetone (1.0 M with respect to the aldehyde), 55 °C, 1 h.

Scheme 2.47: Hydroacylation scope of *β*-formyl ketones with 1-octyne.

2.15 Summary

In conclusion, a novel synthetic route to *β*-amido enones has been developed *via* the hydroacylation of *β*-amido aldehydes with terminal alkynes, in which the amide carbonyl acts as a tether to allow the catalytic process to take place. The methodology utilises a relatively simple rhodium(I) catalyst under mild conditions, with selective access to both linear and branched regioisomers when desired. A slight alteration in catalyst design provides efficient reactivity with internal alkynes, many of which have otherwise proved challenging substrates in analogous hydroacylation processes, and with terminal alkenes. Extending the carbon chain length to 1,4-dicarbonyl systems has provided us with some promising initial results, which could be developed further to broaden the scope. Despite this, the hydroacylation of 1,5-dicarbonyl systems and *N*-formyl amides proved elusive.

Extending these optimised conditions to *β*-formyl esters gave mixed results and a requirement for the *α*-carbon atom to contain two substituents to prevent enolisation, limiting the scope. However, with *β*-formyl ketones, the yields observed were far more satisfactory, demonstrating a powerful methodology when using ketones as tethers. Overall, this chapter proves that carbonyl based amides, esters and ketones can act as efficient chelating systems in rhodium catalysed intermolecular hydroacylation.

Chapter 3

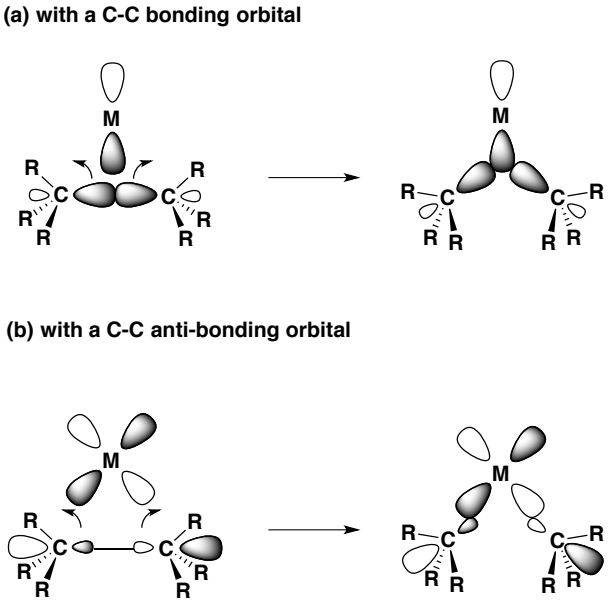
Rhodium-Catalysed C–C Bond Activation

3.1 C–C *vs.* C–H Bond Activation

The cleavage of C–C bonds is ubiquitous in the refining of crude oil, with these vital industrial processes being conducted on colossal scales.[176] In contrast, the catalytic activation and subsequent reorganization of C–C bonds in fine chemicals is much rarer.[176] The prevalence of reported methods targeting C–C bonds[176-183] still lags behind the more advanced field of C–H bond activation,[184-190] despite having made significant progress over the last thirty years. It is perhaps unsurprising to see why: C–C bond activation is seen as a *destructive* pathway of reactivity contrary to the traditional focus on methodologies which *construct* C–C bonds. However, a selective approach to the direct functionalisation of specific C–C bonds using transition metals can create unique opportunities to streamline synthetic routes.

In comparison to C–H activation, the strategies required for C–C activations differ considerably. In C–C activation, whilst the role of thermodynamics is often less important (in fact, C–C oxidative addition can sometimes be exothermic),[182] the key challenge is kinetic

in nature. C–C bonds are typically sterically hindered compared to their more abundant C–H counterparts, thus restricting access to the bond targeted for activation. In addition, the highly directed nature of σ-C–C bond orbitals result in less favourable orbital directionality for interaction with transition metal catalysts than σ-C–H bonds, and thus significant distortion is required (**Scheme 3.1**).[182] Methods for cleaving C–C bonds must therefore incorporate strategies to overcome these kinetic barriers, the most crucial of these being strain-release, chelation-assistance and decarbonylation.[176] Whilst many of these strategies employ other transition metal catalysts, rhodium-based systems are the most versatile and relevant to this work, hence only these methodologies will be discussed in this chapter.



Scheme 3.1: C–C orbital interactions with metal catalyst during oxidative addition.

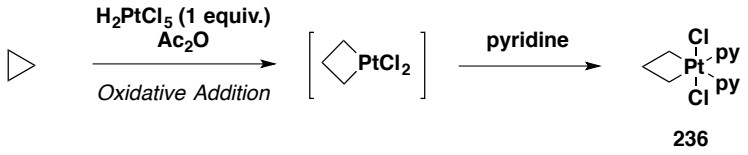
3.2 Strain-Driven C–C Bond Activations

Small ring systems, particularly three- and four-membered rings, offer important routes to C–C bond activation. The relief of ring strain following oxidation addition results in a more

stable expanded ring-metallocycle, providing a powerful thermodynamic driving force.[191] In addition, the HOMO of both cyclopropane and cyclobutane are largely p-orbital in character, thus allowing greater accessibility by the catalyst and helping to overcome the kinetic barrier.[192] Whilst methodologies exploiting these concepts continue to evolve,[193-197] several key examples will now be discussed.

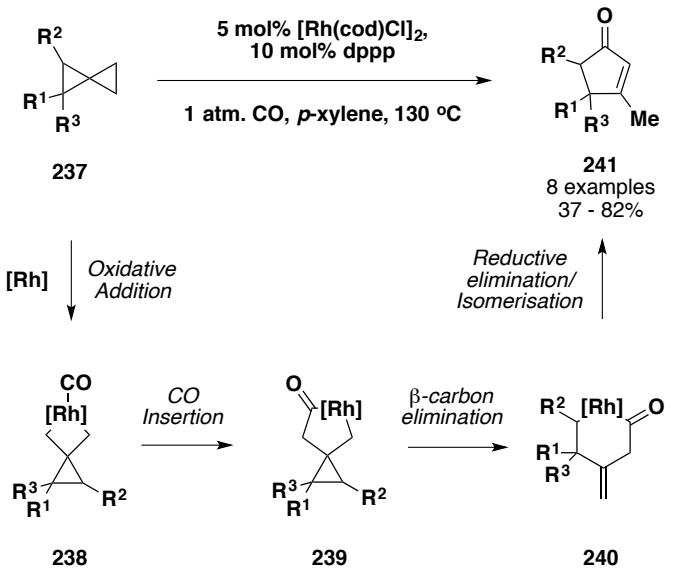
3.2.1 C–C Activation of Three-Membered Rings

Since three-membered rings exhibit the greatest ring strain, simple cyclopropanes have been of particular interest in the development of transition metal-mediated C–C bond cleavages. In general, the strain-driven oxidative addition of a C–C bond in cyclopropanes leads to a metallacyclobutane such as **236**, which was first isolated by Tipper in 1955 using hexachloroplatinic acid in acetic anhydride (**Scheme 3.2**).[198]



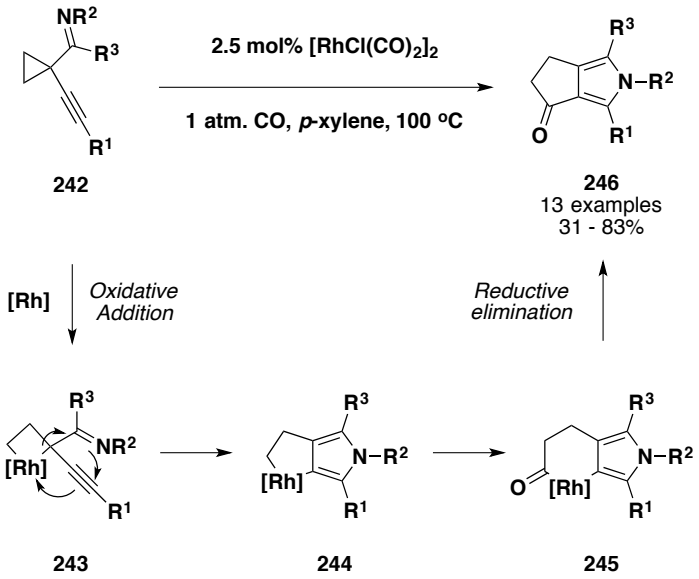
Scheme 3.2: Discovery of the first metallacyclobutane by Tipper.

When using a rhodium catalyst for this purpose, these intermediates can go on to react in a variety of manners. For example, in Murakami's reported rhodium-catalysed C–C bond activation of spiropentanes **237**, the substrates react in the presence of carbon monoxide to provide access to a variety of cyclopentenones (**Scheme 3.3**).[199] In the proposed mechanism, the more distal C–C bond undergoes oxidative addition (due to its greater accessibility) to generate metallacyclobutane **238**. Carbon monoxide insertion generates rhodacyclopentanone **239**, which, following β-carbon elimination, reductive elimination and subsequent isomerisation of **240**, affords the cyclopentenones **241**.



Scheme 3.3: Murakami's C–C activation of spiropentanes.

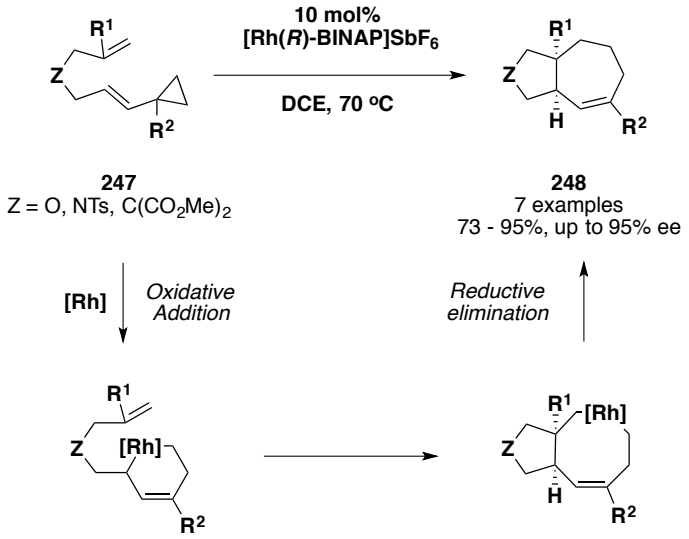
α-Cyclopropyl ketones and imines have been shown to exhibit rhodium-catalysed C–C bond cleaving, with the carbonyl/imine group acting as an effective tether in directing the catalyst to the proximal C–C bond. These tethers also facilitate the reaction kinetically leading to faster processes. For instance, Tang and Shi reported an intramolecular carbonylative synthesis of pyrrole products **246** from 3-alkynyl cyclopropyl imines such as **242** (**Scheme 3.4**).[200] The cyclopropyl imine initially undergoes oxidative addition by the rhodium(I) catalyst to the proposed intermediate **243**, and, following co-ordination of the alkyne component in the presence of carbon monoxide, undergoes a migratory insertion to afford the rhodacycle **245**. Reductive elimination delivers 3-azabicylco[3.2.0]hepta-1,4-diene **246**, regenerating the catalyst.



Scheme 3.4: Using imines as directing groups in C–C bond activation.

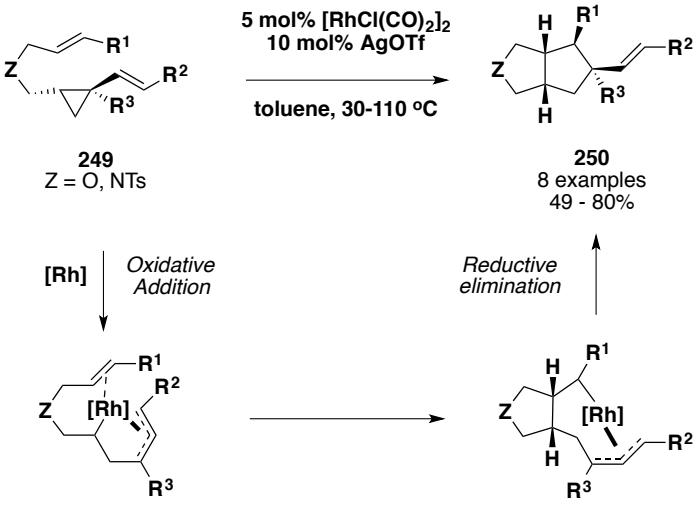
A widely used substrate class in C–C bond activations is vinylcyclopropanes. The presence of the unsaturated group once again assists in directing the transition metal towards the proximal C–C bond. More importantly, the energetically favourable ring strain release leads to the formation of a particularly versatile allyl-metal bond, which can be reacted further to produce a variety of useful compounds.[201] Depending upon whether the vinyl substituent participates in a subsequent formal cycloaddition reaction following initial oxidative addition, vinylcyclopropanes can behave as a five-carbon synthon (by participating) or a three-carbon synthon (by not participating). Wender has extensively studied vinylcyclopropanes as five-carbon synthons in intramolecular rhodium(I)-catalysed formal [5 + 2]-cycloadditions with alkynes,[202-204] alkenes[205,206] and allenes.[207-209] Most notably, in 2006 Wender reported an enantioselective version using [Rh(BINAP)SbF_6].[210] The reaction proceeds *via* directed oxidative addition to the proximal C–C bond of the vinylcyclopropane **247**, followed by migratory insertion of the six-membered rhodacycle to generate a variety

of fused cycloheptenes **248** after final reductive elimination of the catalyst (**Scheme 3.5**).



Scheme 3.5: Enantioselective [5 + 2] cycloaddition after C–C activation of a vinylcyclopropane.

An example of three-carbon synthon reactivity can be seen in Yu's 2008 report,[211] where use of a $[Rh(CO)_2]^+$ cationic catalyst generated *in situ* with vinylcyclopropanes **249** undergoes a [3 + 2] cycloaddition when *trans*-alkenes are pendant in the substrate (*cis*-alkenes are forced to undergo [5 + 2] cycloadditions). Ultimately, this delivers 5,5-*cis*-fused products **250** as single diastereoisomers in moderate to good yields (**Scheme 3.6**).

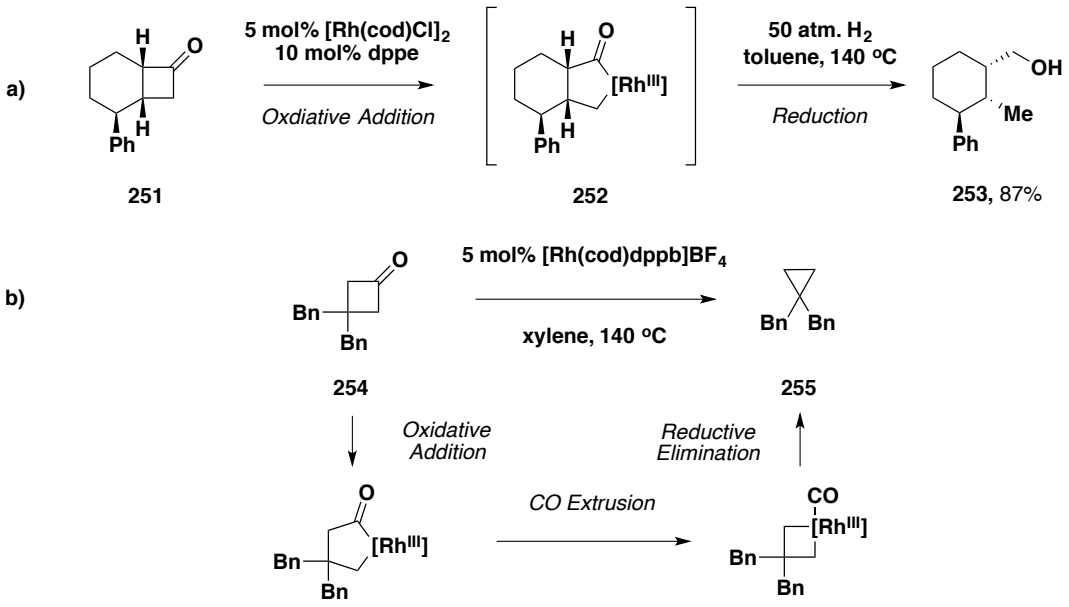


Scheme 3.6: [3 + 2] Cycloaddition following C–C activation of vinylcyclopropanes.

3.2.2 C–C Activation of Four-Membered Rings

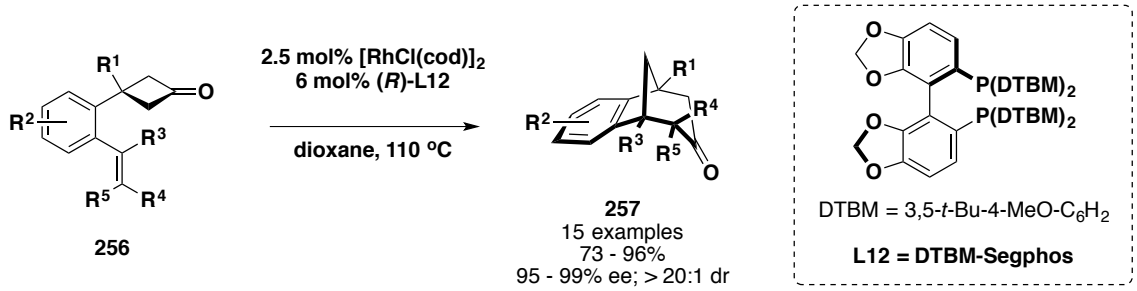
Cyclobutanes exhibit similar ring strain to cyclopropanes, also allowing them to participate in C–C σ-bond activation. Usually, the strain-driven oxidative addition step leads to a metallacyclopentane intermediate, which proceeds to react in a variety of different pathways to close the catalytic cycle. Whilst there is a wealth of literature exploring the use of highly strained biphenylenes with Ni,[212-216] Ir[217,218] and Pd[219,220] catalysts, four membered rings bearing a ketone moiety such as cyclobutanones and cyclobutenones have been shown to be particularly versatile with Rh catalysts in C–C activations.[221] Following the initial C–C cleavage, the resulting acyl-metal bond is stronger than an alkyl-metal bond from a simple cyclobutane, and the carbonyl helps to pre-coordinate the metal catalyst with the substrate, thus promoting the desired reactivity.

This pioneering work was first developed by Ito and Murakami in 1994 with the use of cyclobutanones **251** together with the rhodium(I) catalyst $[Rh(cod)Cl)_2]$ (**Scheme 3.7 (a)**).[222] Initial insertion into the least hindered acyl-carbon bond gives the rhoda-cyclopentanone **252**, which can undergo reductive ring cleavage under a H_2 atmosphere to give the alcohol **253** in 87% yield. The report also describes another reaction with a different cyclobutanone substrate **254**, which, if used with a stoichiometric amount of Wilkinson's catalyst, leads to decarbonylation and subsequent ring contraction to give **255**. This was later shown to be catalytic with $[Rh(cod)dppb]BF_4$, delivering the product in quantitative yield (**Scheme 3.7 (b)**).[223]



Scheme 3.7: (a) Ito and Murakami's C–C activation of cyclobutanone **251**; (b) Catalytic activation of cyclobutanone **254**.

In 2002, the concepts behind this work were extended to include the intramolecular interception of the rhodium(III) cyclopentanone by a tethered C=C bond, giving a benzobicycloheptanone product. In 2014, Cramer was subsequently able to develop an enantioselective version by employing the use of DTBM-Segphos as a steering ligand. The authors rationalised that high levels of enantioselectivity arose from coordination of the rhodium metal to both the olefin and carbonyl, providing a rigid environment for the enantiodetermining step to take place (**Scheme 3.8**).[224]



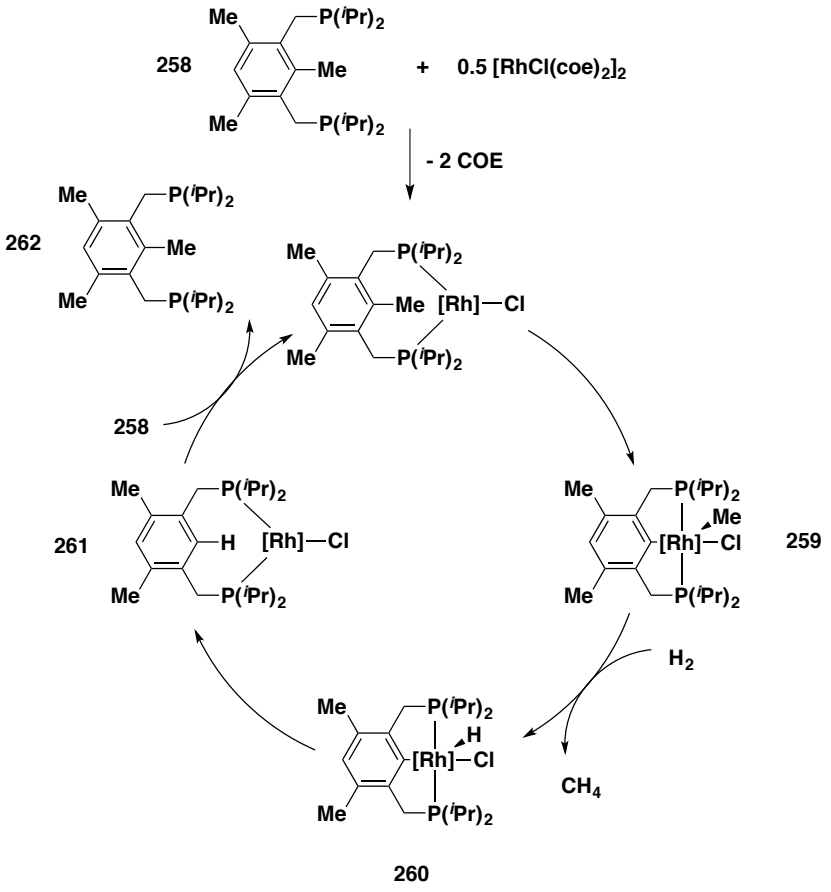
Scheme 3.8: Cramer's enantioselective C–C activation of cyclobutanone **256**.

3.3 C–C Bond Activations of Unstrained Substrates

For unstrained substrates, alternative strategies have been devised to promote catalytic C–C bond activations. Primarily, a chelation assisted approach is used *via* the incorporation of suitable directing groups, which bring the metal catalyst in close proximity to the target C–C bond.[225,226] However, additional driving forces such as decarbonylation can be employed to facilitate the C-C cleaving process.

3.3.1 Chelation-Assisted Strategies

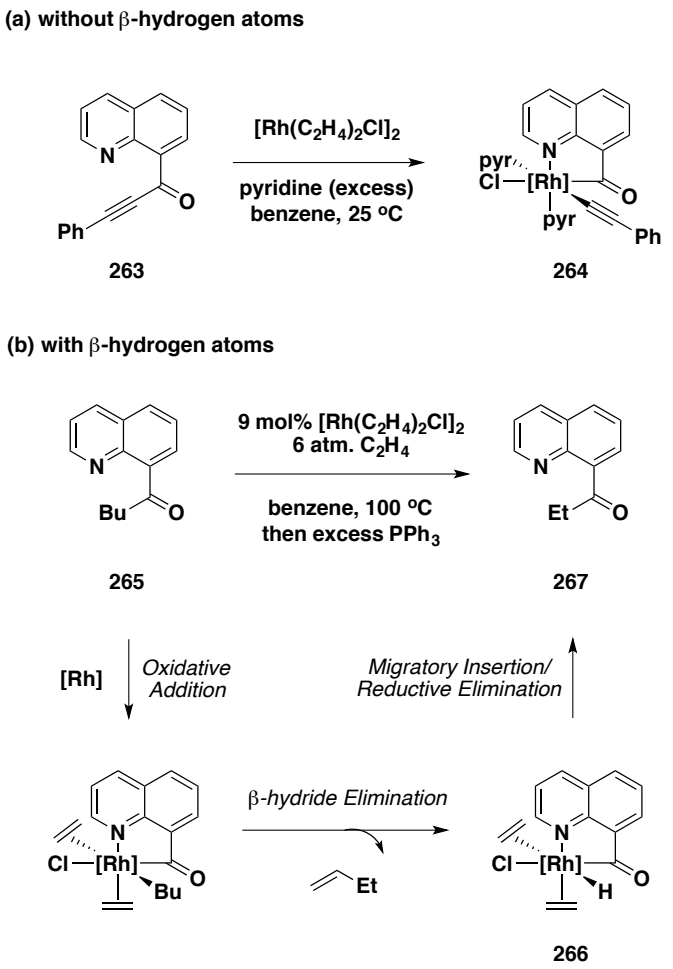
Whilst the development of stoichiometric unstrained C–C bond activations had been taking place since 1965,[176] a pioneering catalytic methodology was described by Milstein and co-workers in 1998.[227] By using biphosphine pincer complexes **258** to bring the rhodium metal centre close to the adjacent C–C bond (whilst leaving the other methyl groups untouched), the large kinetic barrier could be overcome to generate intermediate **259**. It is worth noting that the C–C activation is thermodynamically favourable here, making this irreversible and the preferred pathway over a possible C–H activation. By applying a H_2 atmosphere, the Rh-methyl bond can undergo hydrogenolysis to produce methane and complex **260**. Reductive elimination returns a C–H bond to product **262** and allows the catalyst to re-enter the cycle (**Scheme 3.9**).



Scheme 3.9: Milstein's catalytic C–C activation using pincer biphosphine chelates.

The use of quinolones as a chelating group in catalytic C–C activation was first reported by Suggs and Jun in 1981.[228] The authors describe two transformations of 8-quinolinlyl ketones using the rhodium(I) complex $[Rh(C_2H_4)_2Cl]_2$, in which the nitrogen atom of the quinolone directs oxidative addition of the metal toward the α-keto C–C bond, forming a 5-membered rhodacyclic intermediate. If the ketone group bears no β-hydrogen atoms such as **263**, this rhodacycle appears stable and can be trapped with pyridine to give isolable **264** (**Scheme 3.10, (a)**). For those with β-hydrogen atoms, as in the case of substrate **265**, β-hydride elimination occurs to give 1-butene and the complex **266**. In an ethylene atmosphere, migratory insertion of an ethylene molecule takes place, followed by reductive elimination

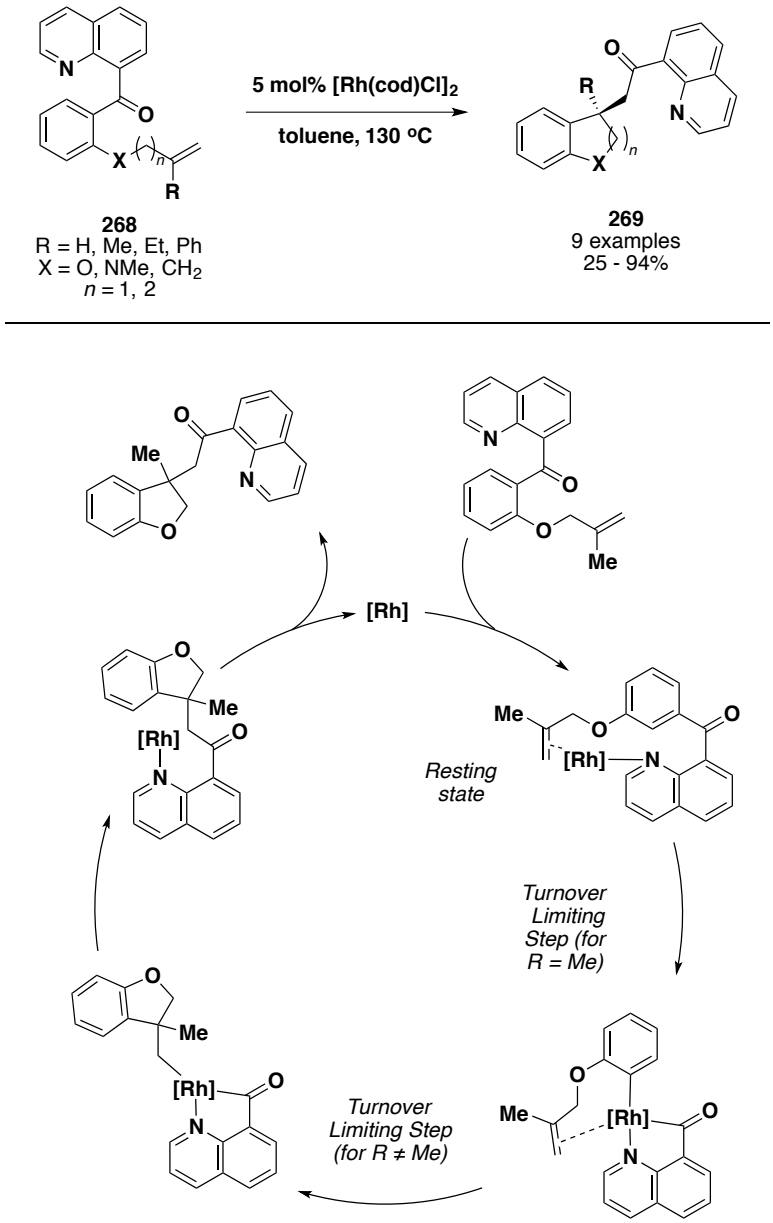
to afford 8-quinolyl ethyl ketone **267** (**Scheme 3.10**, **(b)**).



Scheme 3.10: Initial use of quinolones in chelation assisted C–C bond activation.

Since this exchange reaction was limited to ethylene, it was another 20 years before this procedure was investigated again. In 2009, Douglas published an extension of this work using 8-acylquinolines **268** with tethered olefins, which upon the expected C–C bond cleavage, led to dihydrobenzofurans **269** in moderate yields.[229] Mechanistic studies into this work by Johnson[230,231] observed a kinetic isotope effect with substrates containing minimal substitution of the alkene (R = Me), suggesting C–C bond activation was the rate determining step in this case. Interestingly, with more sterically substituted alkenes (R ≠ Me), the alkene

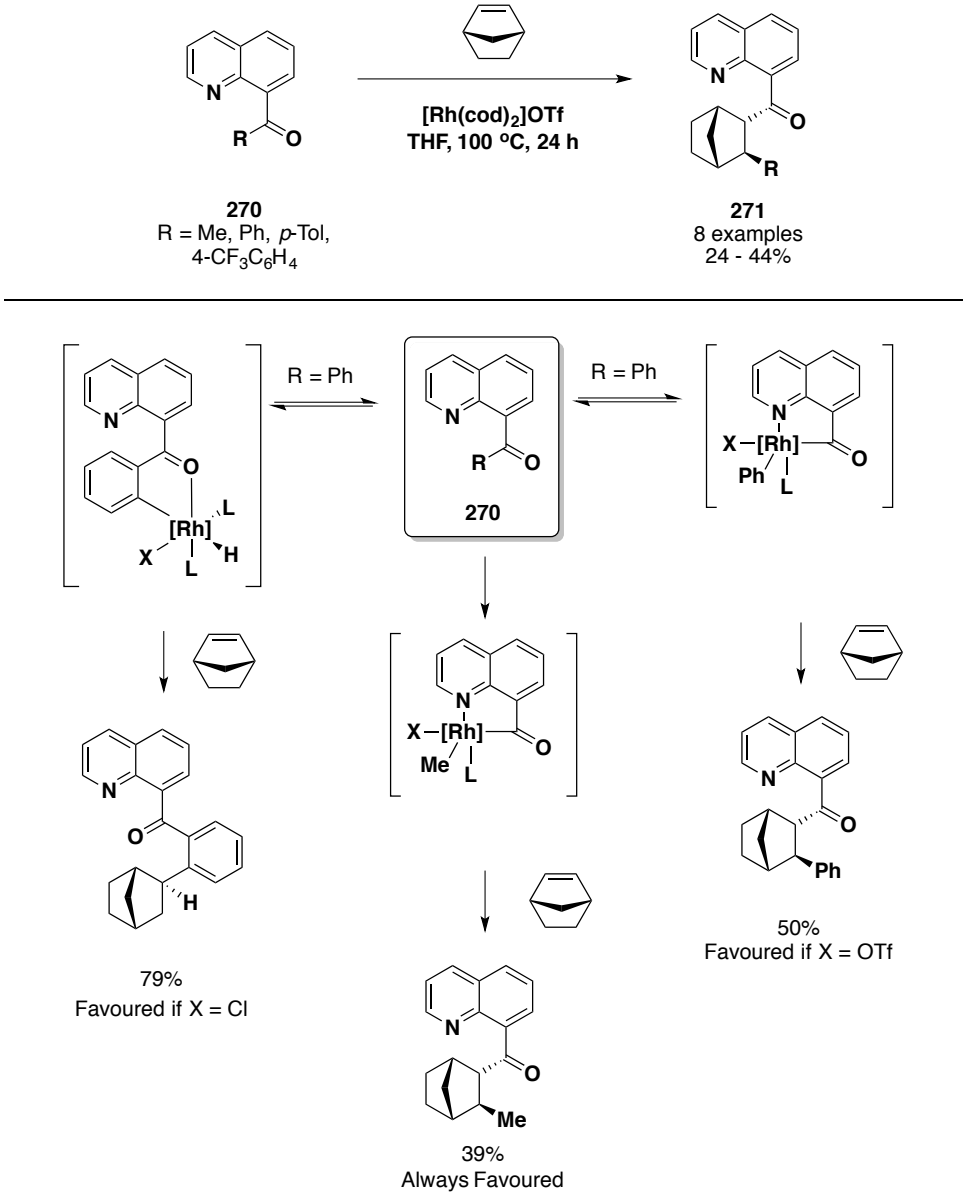
insertion become the rate determining step (**Scheme 3.11**).



Scheme 3.11: Synthesis of dihydrobenzofurans and proposed mechanism.

Importantly, Douglas was also able to report an intermolecular version of this reaction, using 8-acylquinoline **270** and norbornene (due its inability to undergo *β*-hydride elimination).[232] In this case, a competing C–H activation could occur if R = Ph. However, by using a cationic rhodium(I) catalyst with a triflate counterion and high temperatures of 100 °C, the C–C

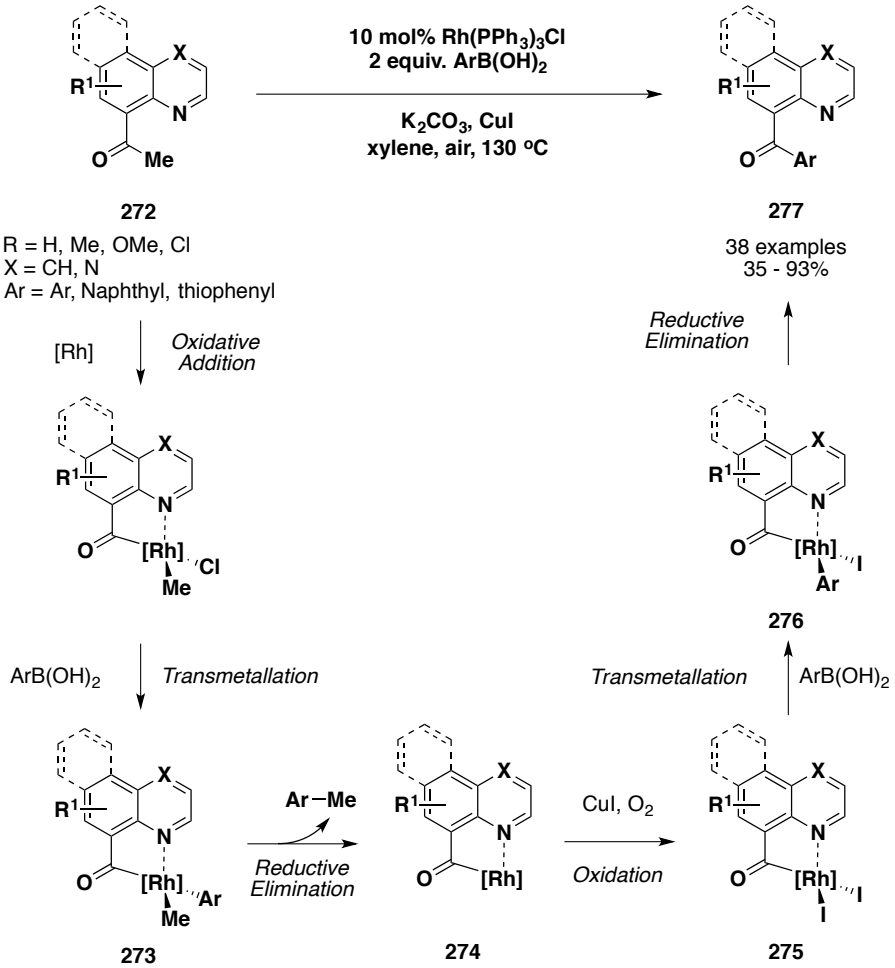
activation products **271** could be generated in moderate yields (**Scheme 3.12**).



Scheme 3.12: Intermolecular carboacylation with acylquinolines and norbornene.

In 2012, Wang demonstrated that such chelation-assisted C–C activation strategies could be coupled with a C–C bond forming cross-coupling reaction.[233] By heating the substrate with Wilkinson's catalyst, stoichiometric copper(I) iodide and potassium carbonate under air, 8-acylquinolines **272** could react with aryl boronic acids to give the aryl ketone cross-coupling products **277** in reasonable to high yields (**Scheme 3.13**). Whilst the scope of electron-

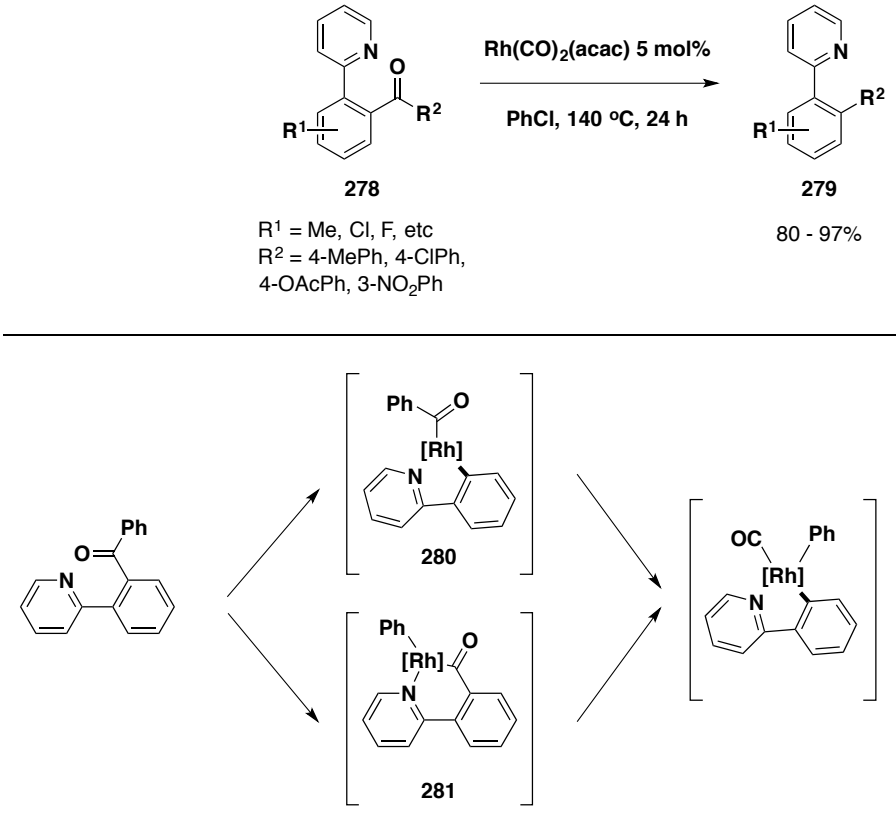
donating and electron-withdrawing substituents on the quinolines was relatively broad for this methodology, substitutions at the *ortho* position could not be tolerated. The authors proposed a mechanism in which, following oxidative addition a transmetallation takes place with the boronic acid to give intermediate **273**. This reductively eliminates the methyl group from the metal centre to give the Rh(I) complex **274**, which is subsequently reoxidised to give a Rh(III) complex **275** (hence the need for an aerobic atmosphere). This complex undergoes transmetallation again to give **276**, which reductively eliminates the products **277** and the catalytic cycle continues.



Scheme 3.13: Combining C–C bond activation with a cross-coupling reaction.

In the same year, Shi and co-workers reported that pyridines could be used to direct C–C

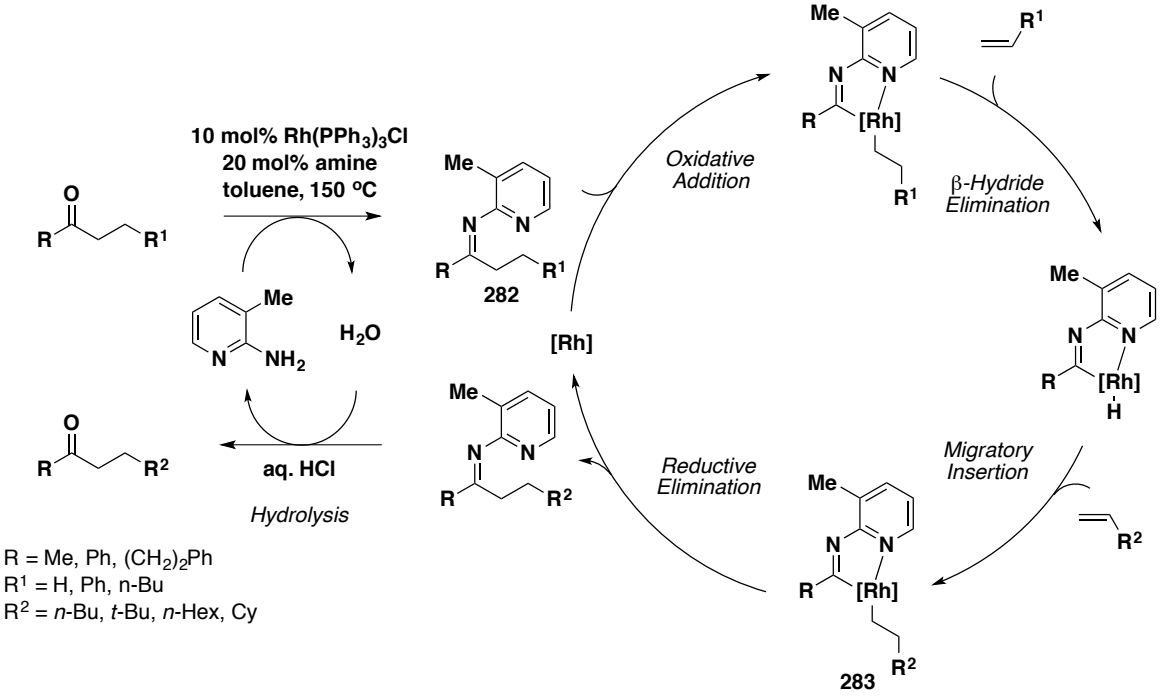
bond activations in the decarbonylation of biaryl ketone and alkyl/alkenyl aryl ketones **278**.[234] By using 5 mol% $Rh(CO)_2(acac)$ and refluxing in chlorobenzene, a variety of decarbonylated products **279** could be made in 80-97% yield. When other nitrogen-based directing groups were also tried (e.g. pyrazolyl and oxazolyl), the yields fell much lower (to 52% and 44% respectively). Mechanistically, the pathway is thought to proceed *via* a 5-membered rhodacycle **280** rather than the intermediate **281**, although the latter cannot be ruled out (**Scheme 3.14**).



Scheme 3.14: Decarbonylation of biaryl ketones using pyridine chelation-assistance.

Naturally, one of the major limitations of chelation-assisted C–C bond activation is the requirement for specific substrates with attached directing groups. To avoid this restriction, Suggs investigated the use of an 'organic cofactor' which could be used as a temporary

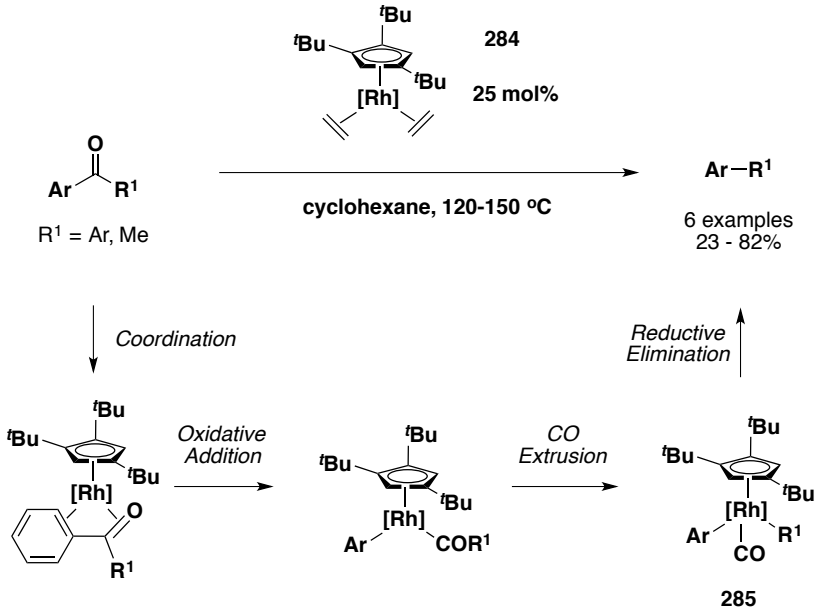
directing group, offering a greater scope to substrates without the need for post or pre-functionalisation. In his investigations into aldehyde C–H activation,[235,236] the author determined the 2-aminopicolyl group could indeed complete the transformation effectively, whilst being easily installed and removed *via* condensation of carbonyl groups. As the active imine species was generated *in situ*, only catalytic amounts of the cofactor was required.[237] He later applied this same to C–C activation to ketones in a formal σ-bond metathesis reaction using Wilkinson's catalyst (**Scheme 3.15**).[238] Following condensation of the ketone with 2-amino-picoline, the subsequent imine **282** undergoes C–C bond cleavage following coordination of the rhodium(I) metal. *β*-Hydride elimination and displacement of the resulting alkene by the reagent olefin leads to a migratory insertion to give complex **283**. Reductive elimination and C–C bond formation closes the cycle, delivering the ketone product. Jun also demonstrated that such an approach could work with *sec*-alcohols to deliver similar products.[239]



Scheme 3.15: Mechanism of alkyl-exchange *via* C–C bond activation using an organic cofactor.

3.3.2 Decarbonylation Without Chelation Assistance

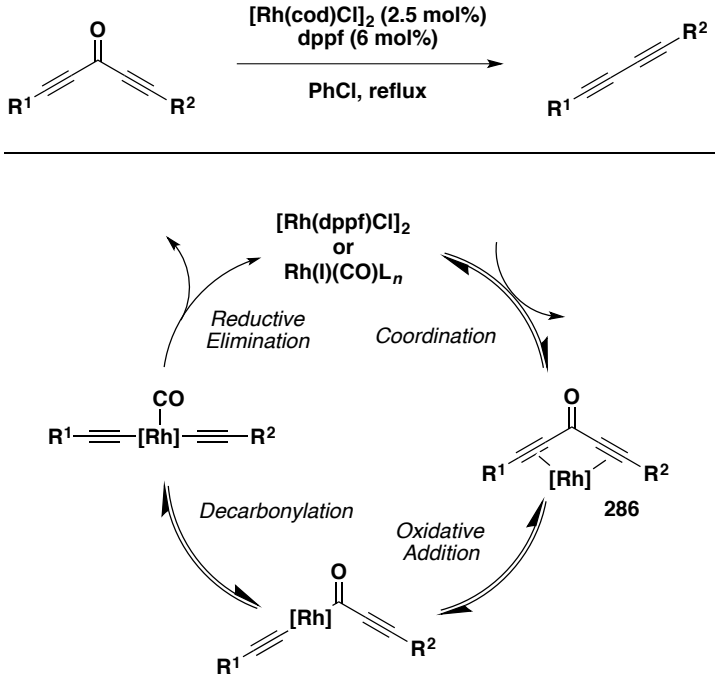
In comparison to strained substrates, literature examples utilising decarbonylation as the main driving force for catalytic C–C bond cleavage are much more scarce. The first undirected example of this process was reported by Brookhart in 2004,[240] in which he used a highly active rhodium(I) catalyst **284** with an extremely bulky Cp ligand (**Scheme 3.16**). η^4-Coordination of the ketone to the metal centre allows subsequent oxidative addition and CO extrusion. Reductive elimination of the resulting complex **285** gives the aryl products, and the reaction proceeds catalytically, albeit with a high loading of 25 mol%.



Scheme 3.16: Brookhart's decarbonylative C–C cleavage of benzo- and acetophenone derivatives.

In 2013, Dong and co-workers demonstrated that the C–C single bond in unstrained diynones could be catalytically cleaved to deliver conjugated diynes following decarbonylation (**Scheme 3.17**).[241] From DFT calculations,[242] the mechanism proposed initially involves η^4-coordination of the substrate to the metal, bringing it into proximity for oxidative addition to occur. The resulting Rh^{III} complex **286** undergoes decarbonylation and subsequent reductive

elimination to generate the products. It is worth noting that the first three steps are all reversible, with the final elimination step driving the catalytic cycle forward. The use of a biphosphine ligand here is also crucial to assist in the elimination of CO from the rhodium metal centre and regenerate the catalyst. For unsymmetrical diynones, only diynes are obtained, suggesting that no acetylene units are exchanged in the process. Dong also extended this methodology to conjugated monoynones,[242] however the substrate scope here is predominantly limited to aryl substituents.



Scheme 3.17: Dong's rhodium-catalysed decarbonylation of diynones.

3.4 Summary

Over the last three decades, significant progress has been made in the field of selective C–C bond activation by transition metal catalysts, particularly rhodium-based ones. As the field has progressed away from stoichiometric transformations towards catalytic ones, the synthetic utility of these approaches has become more apparent. Yet further progress remains

a challenge, due to the thermodynamic and kinetic hurdles in place arising from the relative stability of C–C bonds and their weak orbital interactions with catalysts. The use of strained ring systems to overcome these challenges continues to be explored in great depth, with numerous examples of C–C activations of three- and four- membered ring systems being reported.[193-197] These ring openings can lead to a variety of different reaction pathways and therefore present attractive methodologies for complex molecule synthesis. Disappointingly, extending such methodologies to unstrained substrates has proved to be much more difficult, as each step in the catalytic cycle presents its own difficulties. Those methodologies that have been developed concentrate mainly on chelation-assisted strategies from either permanent or temporary directing groups, often generating products in only reasonable yields. Hence there is much room for improvement. With only a handful of directing groups that can operate in C–C bond activations, the methodologies presented in this introduction are quite specific toward certain substrate classes. Ideally, development of this field would involve moving away from these specifics and creating more general C–C activation methods. It is the aim of this project to investigate the potential for such methods and explore new areas in chelation-assisted C–C bond activation of more common substrates.

Chapter 4

Chelation-Assisted Strategies for Rhodium-Catalysed C–C Bond Activation

4.1 Introduction and Project Aims

The activation of C–C bonds by homogenous transition metal catalysis has been one of the most prominent challenges in recent decades. As discussed in **Chapter 3**, several methods have been devised to cleave C–C bonds with varying degrees of success. Whilst the majority of these methods employ strain-driven strategies (**Section 3.2**),[199-224] methodologies involving unstrained molecules present a far greater challenge, but offer a broader synthetic utility.[225-242] Only a handful of catalytic methodologies exist for such unstrained substrates, with chelate-assisted strategies proving by far to be the most successful (**Section 3.3**). In a similar manner to C–H bond activation, the presence of a chelating group lowers the kinetic barrier by directing an incoming metal complex towards the C–C bond to be cleaved (usually adjacent to a carbonyl or imine).[225,226] However, only three types of directing group have so far been shown to deliver any form of reactivity, and these are limited to pyridine-based heterocycles, as outlined in **Figure 4.1**.

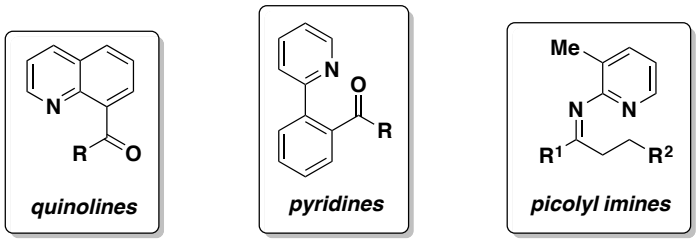
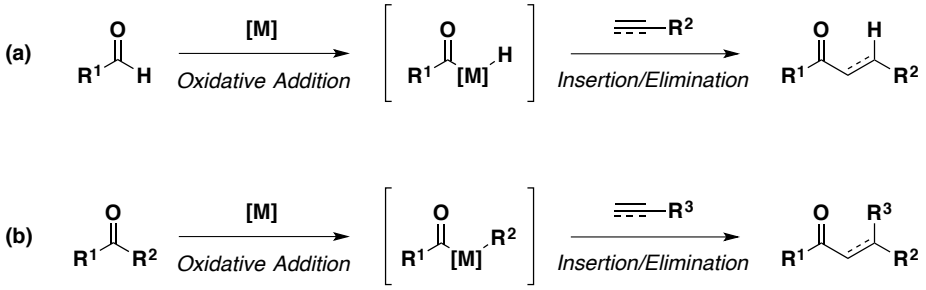


Figure 4.1: Chelating groups and substrate types known to be successful in C–C bond activation methodologies. For a discussion on their applications and mechanisms, see **Section 3.3.1.**

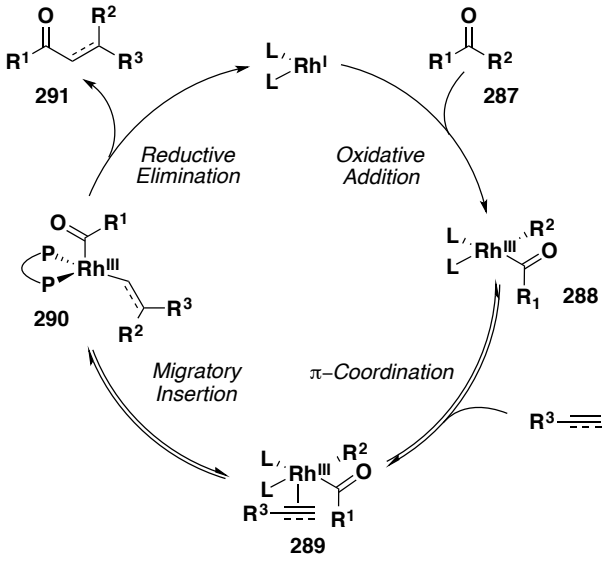
Such constraints on the substrate scope prevent the general utility of C–C activation and thus any wider synthetic application. As such, it was the aim of this project to broaden the array of chelating groups that can enact rhodium-catalysed C–C activation processes. Utilising our understanding of chelation-controlled C–H activation in the field of hydroacylation, a conceptually similar 'carboacylation' was envisaged involving the catalytic cleavage of a C–C bond adjacent to a carbonyl, as directed by a chelating group. The subsequent insertion of an unsaturated component could then lead to either a different ketone product or an enone, depending on the unsaturated bond incorporated (**Scheme 4.1**).



Scheme 4.1: Comparison of transition-metal catalysed hydroacylation (part (a)) with the proposed C–C activation methodology to be investigated in this work (part (b)).

Mechanistically, by comparing the proposed mechanisms of known rhodium-catalysed C–C activation reactions (**Section 3.3**) with those determined for conceptually similar C–H activation reactions (**Scheme 1.3**), it could be postulated that any successful reaction could proceed *via* the mechanism outlined in **Scheme 4.2**. Employing a Rh(I)-based catalyst,

ketone **287** could undergo irreversible oxidative addition of a C–C bond as guided by an incorporated directing group, forming a Rh(III) acyl alkyl intermediate **288**. In most known C–C cleaving transformations, this is believed to be the rate-limiting step.[182] Subsequent π-coordination of the unsaturated alkyne or alkene to the Rh(III) centre gives intermediate **289**, after which migratory insertion of the acyl group could occur, generating an alkyl or alkenyl species **290**. Finally, irreversible reductive elimination of the product would deliver the ketone or enone product **291**, reforming the Rh(I) catalyst.



Scheme 4.2: Potential mechanism for our proposed C–C activation strategy.

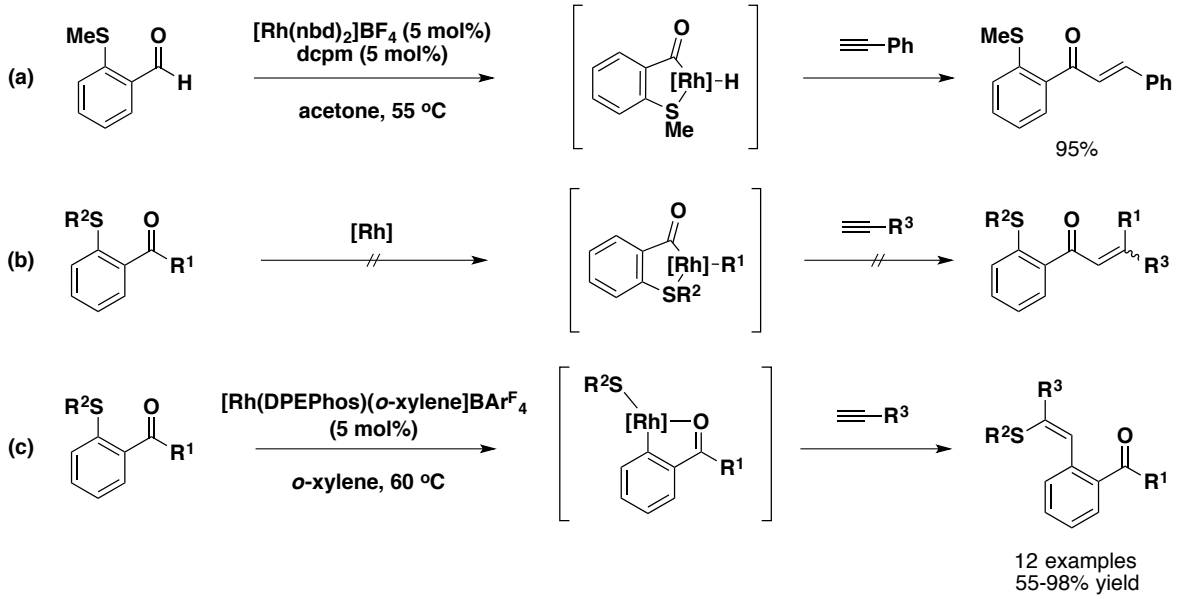
The key challenge within this proposed catalytic cycle would be the initial C–C oxidative addition, and the application of an appropriate chelating group in order to enact this step. Considering the success of various chelating groups in C–H activations, it was decided that our investigations would therefore cover three main classes: sulfur-based, nitrogen-based and alkene directing groups, with the hope of establishing a set of conditions which could allow the desired transformations to take place. The remainder of this chapter discusses the results of these studies.

4.2 Investigating Sulfur-Based Chelating Groups

The precedent for *β*-sulfur chelating group in the C–H activation of aldehydes have been firmly established, as pioneered by Willis and Weller[45,46,48,52,71,93-101] (**Section 1.3.3**). Whilst the predominant purpose of these chelating groups in such hydroacylation reactions is to suppress decarbonylation, it was believed that their directing group ability could be exploited *via* a similar mechanism in our C–C activation methodology.

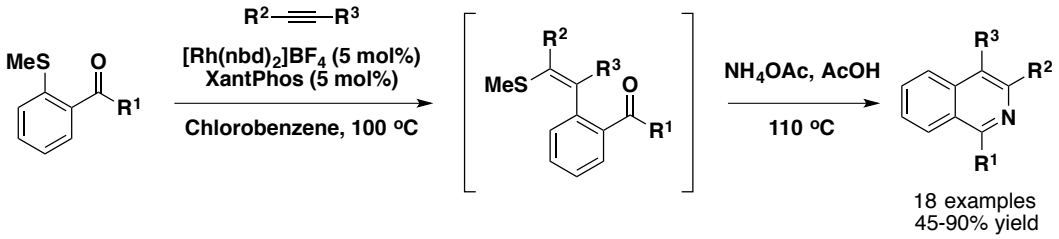
4.2.1 Previous Work

Prior to the commencement of this work, attempts in the Willis group to cleave the C–C bond in *β*-sulfur aryl ketones and insert an alkyne were unsuccessful. Instead of obtaining the desired enone product (**Scheme 4.3 (b)**), activation of the C–S bond occurred instead to deliver carbothiolation products (**Scheme 4.3 (c)**).[243]



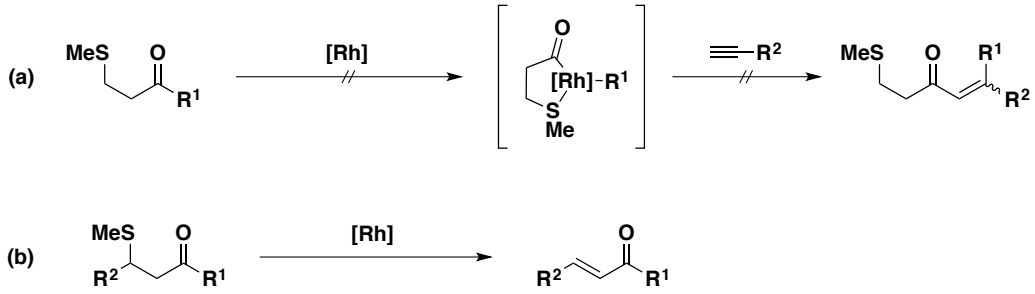
Scheme 4.3: (a) C–H activation of *β*-sulfur aldehydes using rhodium to give an enone product; (b) conceptually similar carboacylation of *β*-sulfur ketones desired but not observed; (c) C–S activation observed under Rh(I) catalysis with *β*-sulfur ketones.

The formation of this product was consistently favourable and successfully applied to a wide range of alkynes and ketones. Subsequent mechanistic investigations determined that the carbonyl group in the aryl ketones acted itself as a chelating group to enable the C–S activation to take place. This methodology was later extended to provide an efficient route to substituted isoquinolines (**Scheme 4.4**), using a source of ammonia under acidic conditions, NH_4OAc, and XantPhos as the ligand to provide a more rigid environment.[244]



Scheme 4.4: Extension of carbothiolation result to the synthesis of isoquinolines.

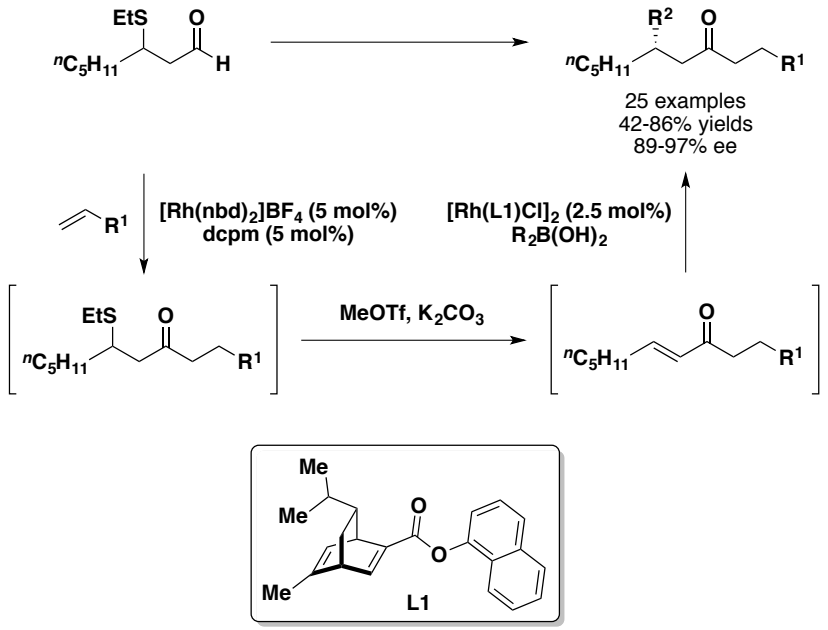
When similar attempts were made to cleave the C–C bonds in *β*-sulfur alkyl ketones, once again the desired C–C activated product was not observed (**Scheme 4.5 (a)**). Instead, apparent *β*-elimination of the sulfide group occurred, leaving an enone product instead (**Scheme 4.5 (b)**).[245]



Scheme 4.5: (a) Expected C–C activation of *β*-sulfur alkyl ketones; (b) elimination of sulfur group observed with *β*-sulfur alkyl ketones.

In due course, these results led to the development of an overall traceless hydroacylation of alkyl aldehydes, where the sulfide group is eliminated following the initial rhodium-catalysed hydroacylation (**Scheme 4.6**).[246] In optimisation studies, the presence of methyl

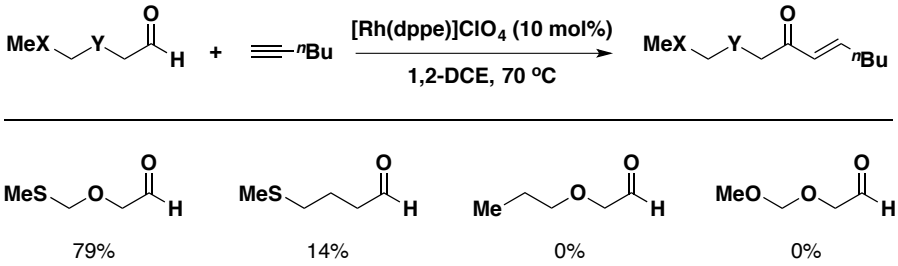
triflate and potassium carbonate were required to drive the elimination step to completion. This work ultimately led to the enantioselective synthesis of *β*-aryl ketones *via* further reaction of the enone product in an asymmetric conjugate addition of boronic acids (**Scheme 4.6**)



Scheme 4.6: Elimination of sulfide group observed with *β*-sulfur alkyl ketones applied to traceless hydroacylation procedure and subsequent asymmetric conjugate addition.

4.2.2 Methylthiomethyl (MTM) Tethers

In **Section 1.3.3**, the efficient use of the methylthiomethyl (MTM) moiety as a directing group in hydroacylation was discussed. MTM-substituted *α*-hydroxy and *α*-amino aldehydes have proven to be excellent substrates in rhodium-catalysed C–H activation, with the ease of subsequent MTM group removal affirming the benefits of its use.[100] A series of control experiments also determined that both the sulfur and oxygen/nitrogen atoms were required for the transformations to take place, with a hypothesis that the *α*-heteroatom facilitates a reactive *gauche* conformation (**Scheme 4.7**). Unfortunately, attempts to verify this mode of coordination, through ^{1}H or ^{31}P NMR spectroscopy, or X-ray crystallography, all failed.[100,101]



Scheme 4.7: Importance of both *S*- and *O*- involvement in MTM chelation.

Following the success of this approach in C–H activation, it was envisaged that the use of the MTM group in substituted α-amino and α-hydroxy ketones of type seen in **Figure 4.2** would promote a rhodium-catalysed activation of C–C bonds.

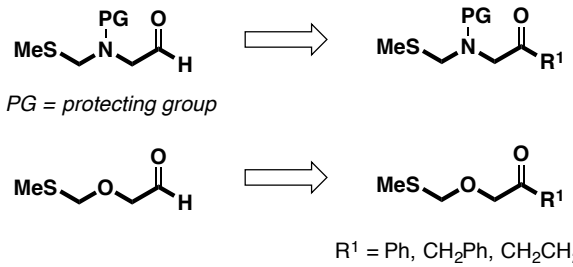
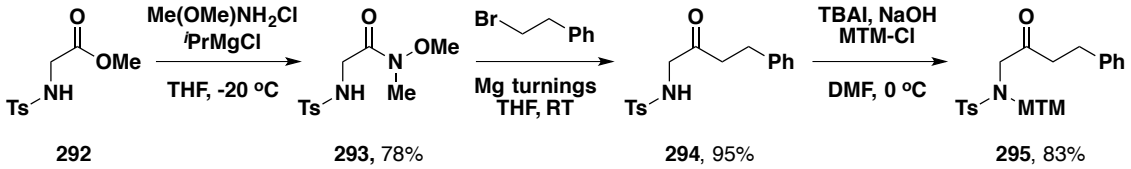


Figure 4.2: General structure of α-amino and α-hydroxy ketones to be investigated.

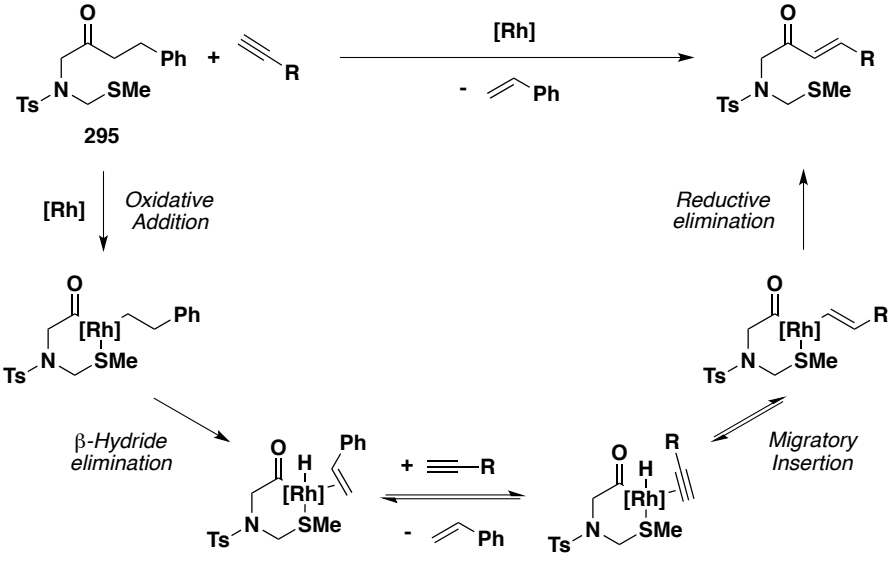
This project therefore began with the substrate **295** being chosen for initial investigation, containing a tosyl/MTM-protected amino group in the α-position with respect to the carbonyl. Synthesis took place *via* the introduction of the phenethyl group, as the Grignard reagent, to Weinreb amide **293**, followed by MTM-protection of the sulfonamide N–H bond in intermediate **294** (**Scheme 4.8**). It should be noted that previous synthetic attempts concluded that MTM-protection could not take place prior to Grignard attack of the Weinreb amide, as such conditions would destroy the MTM group.



292 **293,** 78% **294**, 95% **295**, 83%

Scheme 4.8: Synthesis of MTM-protected α-amino ketone **295**.

Potential reactivity of this substrate in C–C activation was rationalised by a possible directing group effect of the MTM substituent, facilitating cleavage of the α-C–C bond by a rhodium catalyst. A subsequent β-hydride elimination could occur, similar to that seen with Jun's picolyl imine substrates (**Scheme 3.15**),[238] releasing phenylethene and allowing coordination of an alkyne, which could then be subject to a potentially reversible migratory insertion and reductive elimination of an enone product (**Scheme 4.9**).

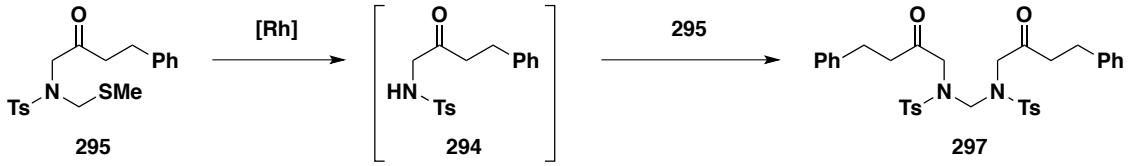


Scheme 4.9: Possible mode of reactivity for substrate **295** in C–C activation.

With substrate **295** in hand, our attention turned to designing an appropriate catalyst system which might lead to a coupling reaction with the 1-octyne. For all optimisation experiments, a high catalyst loading of 10 mol% was employed to increase the likelihood of any reactivity being observable. Investigations began with the screening of three rhodium(I) catalysts containing olefin-based ligands ($[Rh(cod)_2]OTf$, $[RhCl(C_2H_4)_2]_2$, $[Rh(nbd)_2]BF_4$) over five different solvents (toluene, chlorobenzene, propylene carbonate,[171] 1,2-dichlorethane and 2-butanone). These catalysts and solvents were chosen due to their demonstrated utility in existing chelation-controlled C–C activation processes (see **Section 3.3**). For all

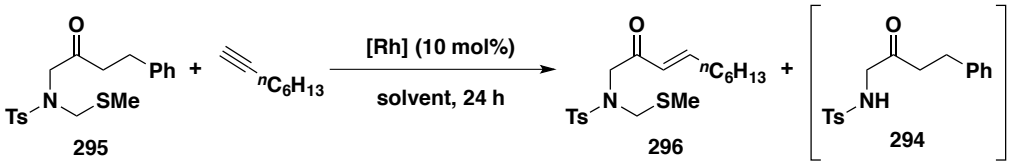
experiments, reactions were heated in a sealed pressure tube, allowing temperatures to be reached in some cases well above the boiling points of the solvents. It was believed that temperatures of over 100 °C would be required to observe any desired reactivity, due to the high energy barrier for the initial C–C oxidative addition as the rate-determining step. As such, temperatures of 110, 130 and 150 °C were tested depending on the solvent used.

The results from each of the conditions employed are shown in **Table 4.1**, and overall gave disappointing results. The desired enone product **296** was not observed, and in most cases starting material was recovered, alongside by-product **294**, which results from cleavage of the substrate MTM group. Thus, in most cases the rhodium catalyst was behaving only as a Lewis acid, abstracting the sulfur group from the nitrogen atom. Such behaviour of Lewis acids towards the MTM-group is known and has been employed by the Willis group in MTM-deprotection, after hydroacylation.[100,101] When no rhodium catalyst was utilised, yet the reaction was still heated to a high temperature, no by-product **294** was observed (**Table 4.1**, entry **16**). Interestingly, in two cases (**Table 4.1**, entry **9** and **14**), another amine side product **297** was observed, resulting from a reaction between amine **294** with an imine formed from another molecule of starting material **295** (**Scheme 4.10**). It is unknown why this product is formed under these conditions.



Scheme 4.10: Formation of side product **297**.

Table 4.1: Screening of conditions for C–C activation of ketone **295** by variation of solvent and temperature.



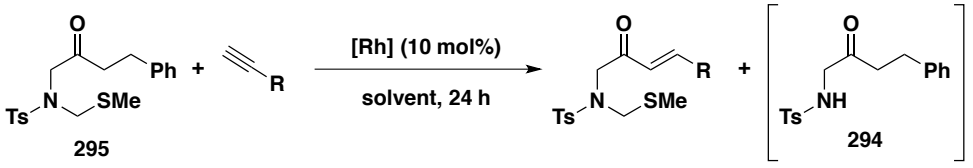
Entry	Catalyst	Solvent[a]	Temperature (°C)	Products (Yield %)[b]
1	$[Rh(cod)_2]OTf$	PhMe	110	SM + **294**
2	$[Rh(cod)_2]OTf$	PhCl	130	SM + **294**
3	$[Rh(cod)_2]OTf$	PC	150	**294**
4	$[Rh(cod)_2]OTf$	1,2-DCE	150	SM + **294**
5	$[Rh(cod)_2]OTf$	2-butanone	150	SM + **294**
6	$[RhCl(C_2H_4)_2]_2$	PhMe	110	SM
7	$[RhCl(C_2H_4)_2]_2$	PhCl	130	SM + **294**
8	$[RhCl(C_2H_4)_2]_2$	PC	150	SM
9	$[RhCl(C_2H_4)_2]_2$	1,2-DCE	150	SM + **297** (23)
10	$[RhCl(C_2H_4)_2]_2$	2-butanone	150	SM + **294**
11	$[Rh(nbd)_2]BF_4$	PhMe	110	CM + **294**
12	$[Rh(nbd)_2]BF_4$	PhCl	130	CM + **294**
13	$[Rh(nbd)_2]BF_4$	PC	150	**294**
14	$[Rh(nbd)_2]BF_4$	1,2-DCE	150	**294** + **297** (20)
15	$[Rh(nbd)_2]BF_4$	2-butanone	150	**294**
16	-	PC	150	SM

Conditions: **295** (0.15 mmol, 1.0 equiv.), 1-octyne (0.18 mmol, 1.2 equiv.), Rh catalyst (10 mol%), solvent (0.5 M with respect to the ketone), 24 h. [a]PC = propylene carbonate. [b]Determined by ^1H NMR spectroscopy of crude reaction mixtures. Value in parentheses indicates any isolated yield of product. SM = starting material, CM = complex mixture.

As no products were observed which contained any signs of 1-octyne incorporation, two other terminal alkynes (phenylacetylene and 1-pentadecyne) were tested to determine if there was an alkyne-dependent effect. 1-Pentadecyne's extremely high boiling point (291 °C)

would also take in account any effects of heating reaction mixtures to temperatures above that of 1-octyne's or phenylacetylene's boiling points (127 °C and 143 °C, respectively). However, screening across a selection of rhodium catalysts and solvents gave very similar results to those observed with 1-octyne (**Table 4.2**).

Table 4.2: Screening of conditions for C–C activation of ketone **295** by variation of alkyne and solvent.

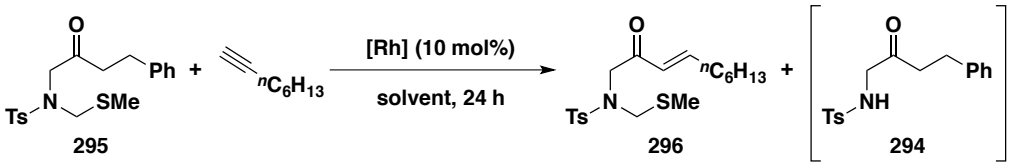


Entry	Catalyst	Solvent	Temperature (°C)	R	Products
1	$[Rh(cod)_2]OTf$	PhMe	110	Ph	SM + **294**
2	$[Rh(cod)_2]OTf$	2-butanone	150	$^{n}C_{13}H_{27}$	SM + **294**
3	$[RhCl(C_2H_4)_2]_2$	PhMe	110	Ph	SM
4	$[RhCl(C_2H_4)_2]_2$	2-butanone	150	$^{n}C_{13}H_{27}$	SM + **294**
5	$[Rh(nbd)_2]BF_4$	PhMe	110	Ph	CM + **294**
6	$[Rh(nbd)_2]BF_4$	2-butanone	150	$^{n}C_{13}H_{27}$	**294**

Conditions: **295** (0.15 mmol, 1.0 equiv.), alkyne (0.18 mmol, 1.2 equiv.), Rh catalyst (10 mol%), solvent (0.5 M with respect to the ketone), 24 h. [a]Determined by ^{1}H NMR spectroscopy of crude reaction mixtures. SM = starting material, CM = complex mixture.

Due to the predominance of the MTM-deprotected by-product **294** in most reactions, it was believed that using phosphorus-based ligands would attenuate the rhodium metal's Lewis acidity, allowing it to engage in more constructive C–C bond activation. As such, Wilkinson's catalyst ($Rh(PPh_3)_3Cl$) and $[Rh(nbd)_2]BF_4$ with either bisphosphine ligands dcpm or dppe were investigated as potential C–C activation catalysts, and a variety of solvents and temperatures screened (**Table 4.3**).

Table 4.3: Screening of conditions for C–C activation of ketone **295** by variation of rhodium catalyst precursor and ligand.

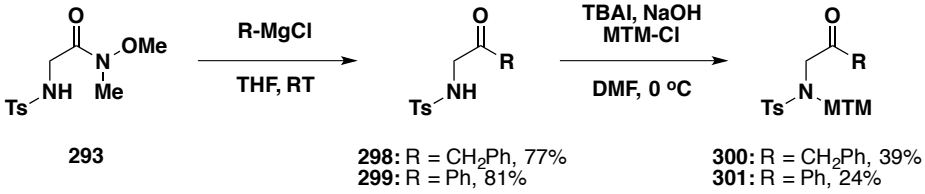


Entry	Catalyst	Ligand Added	Solvent[a]	Temperature (°C)	Products[b]
1	$Rh(PPh_3)_3Cl$	-	PhMe	100	SM
2	$Rh(PPh_3)_3Cl$	-	PhMe	125	SM
3	$Rh(PPh_3)_3Cl$	-	PC	130	SM + **294**
4	$Rh(PPh_3)_3Cl$	-	PC	150	SM + **294**
5	$[Rh(nbd)_2]BF_4$	dppe	Pinacolone	120	SM + **294**
6	$[Rh(nbd)_2]BF_4$	dppe	2-butanone	120	SM + **294**
7	$[Rh(nbd)_2]BF_4$	dppe	PC	120	SM + **294**
8	$[Rh(nbd)_2]BF_4$	dppe	Acetone	70	SM
9	$[Rh(nbd)_2]BF_4$	dppe	Acetone	85	SM + **294**
10	$[Rh(nbd)_2]BF_4$	dppe	Acetone	100	SM + **294**
11	$[Rh(nbd)_2]BF_4$	dppe	Acetone	110	SM + **294**
12	$[Rh(nbd)_2]BF_4$	dppe	Acetone	125	SM + **294**
13	$[Rh(nbd)_2]BF_4$	dcpm	1,2-DCE	125	SM
14	$[Rh(nbd)_2]BF_4$	dcpm	1,2-DCE	150	SM
15	$[Rh(nbd)_2]BF_4$	dcpm	2-butanone	125	SM
16	$[Rh(nbd)_2]BF_4$	dcpm	2-butanone	150	SM
17	$[Rh(nbd)_2]BF_4$	dcpm	PC	150	SM + **294**
18	$[Rh(nbd)_2]BF_4$	dcpm	Acetone	110	SM
19	$[Rh(nbd)_2]BF_4$	dcpm	Acetone	125	SM
20	$[Rh(cod)OMe]_2$	dcpm	PC	150	SM

Conditions: **295** (0.15 mmol, 1.0 equiv.), 1-octyne (0.18 mmol, 1.2 equiv.), Rh catalyst (10 mol%), ligand added (10 mol%), solvent (0.5 M with respect to the ketone), 24 h. [a]PC = propylene carbonate. [b]Determined by ^1H NMR spectroscopy of crude reaction mixtures. SM = starting material.

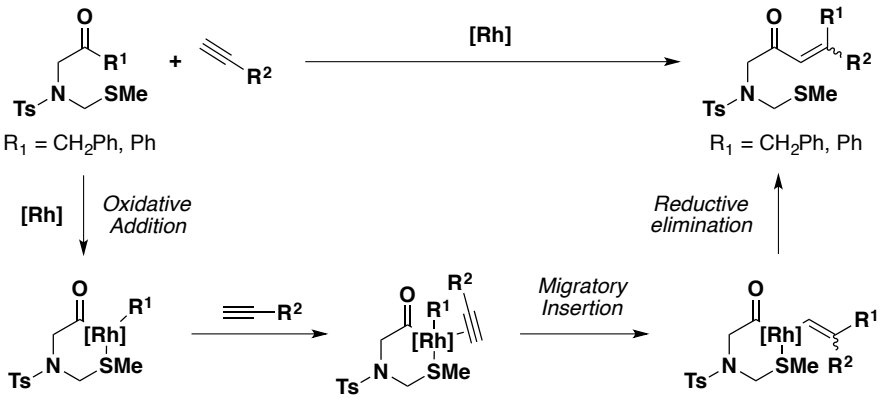
Once again, no desired enone product **296** was observed, although it did become clear that MTM-deprotection was less apparent with the use of these catalysts. Use of the catalyst precursor $[Rh(cod)OMe]_2$ with dcpm was successful in preventing the formation of this by-product, however it did not lead to formation of the desired product (**Table 4.3**, entry **20**). In all other cases, there was no clear trend observed with solvent or temperature, and thus no firm conclusions could be drawn for moving forward with this substrate.

Therefore, it was decided that investigations would continue on two new α-amino ketones containing different C–C bonds for activation (**Scheme 4.11**). Structurally similar to **295** and synthesised *via* the same method, **300** contains a benzyl substituent and **301** a phenyl substituent.



Scheme 4.11: Synthesis of MTM-protected α-amino ketones **300** and **301**.

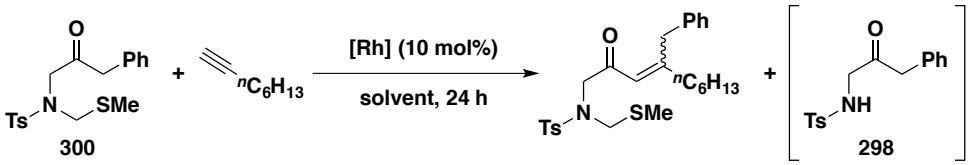
Potential reactivity of these substrates would differ to that of **295**, in that β-hydride elimination could not occur and thus any alkyne would be seemingly 'inserted' between the C–C bond, retaining the phenyl or benzyl group (**Scheme 4.12**).



Scheme 4.12: Possible mode of reactivity for substrates **300** and **301** in C–C activation.

Unfortunately, reaction trials for each of these substrates gave similar results to as previously observed, namely the presence of the MTM-deprotected by-products **298** and **299** without the occurrence of any C–C activation (**Table 4.4** and **4.5**). With no desired product obtained, investigations on these MTM-protected α-amino ketones were abandoned.

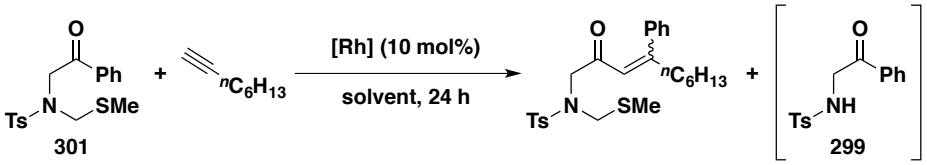
Table 4.4: Screening of conditions for C–C activation of ketone **300**.



Entry	Catalyst	Ligand Added	Solvent[a]	Temperature (°C)	Products[b]
1	$[Rh(cod)_2]OTf$	-	PC	150	SM + **298**
2	$[Rh(cod)_2]OTf$	-	1,2-DCE	125	SM + **298**
3	$[RhCl(C_2H_4)_2]_2$	-	PC	150	SM
4	$[RhCl(C_2H_4)_2]_2$	-	1,2-DCE	125	SM + **298**
5	$[Rh(nbd)_2]BF_4$	-	PC	150	**298**
6	$[Rh(nbd)_2]BF_4$	-	1,2-DCE	125	SM + **298**
7	$Rh(PPh_3)_3Cl$	-	PhMe	110	SM
8	$Rh(PPh_3)_3Cl$	-	PC	150	SM + **298**
9	$[Rh(nbd)_2]BF_4$	dppe	acetone	110	SM
10	$[Rh(nbd)_2]BF_4$	dppe	2-butanone	150	SM + **298**
11	$[Rh(nbd)_2]BF_4$	dcpm	acetone	110	SM
12	$[Rh(nbd)_2]BF_4$	dcpm	2-butanone	150	SM + **298**

Conditions: **300** (0.15 mmol, 1.0 equiv.), 1-octyne (0.18 mmol, 1.2 equiv.), Rh catalyst (10 mol%), ligand added (10 mol%), solvent (0.5 M with respect to the ketone), 24 h. [a]PC = propylene carbonate. [b]Determined by ^{1}H NMR spectroscopy of crude reaction mixtures. SM = starting material.

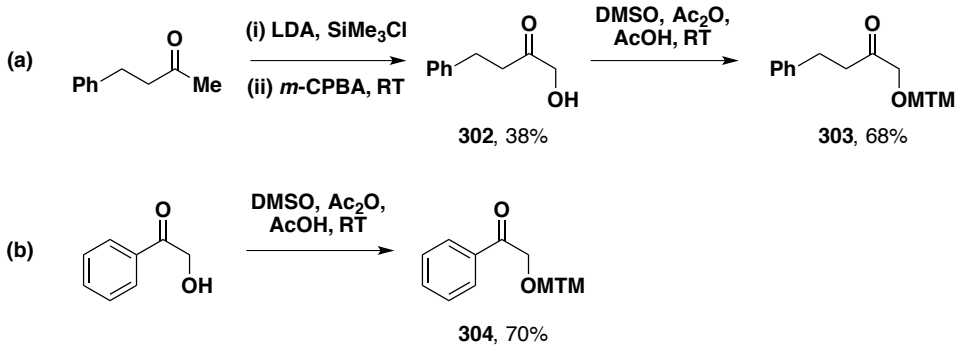
Table 4.5: Screening of conditions for C–C activation of ketone **301**.



Entry	Catalyst	Ligand Added	Solvent[a]	Temperature (°C)	Products[b]
1	$[Rh(cod)_2]OTf$	-	PC	150	SM + **299**
2	$[Rh(cod)_2]OTf$	-	1,2-DCE	125	SM + **299**
3	$[RhCl(C_2H_4)_2]_2$	-	PC	150	SM
4	$[RhCl(C_2H_4)_2]_2$	-	1,2-DCE	125	SM + **299**
5	$[Rh(nbd)_2]BF_4$	-	2-butanone	150	**299**
6	$[Rh(nbd)_2]BF_4$	-	1,2-DCE	125	SM + **299**
7	$Rh(PPh_3)_3Cl$	-	PhMe	110	SM
8	$Rh(PPh_3)_3Cl$	-	PC	150	SM + **299**
9	$[Rh(nbd)_2]BF_4$	dppe	acetone	110	SM
10	$[Rh(nbd)_2]BF_4$	dppe	2-butanone	150	SM + **299**
11	$[Rh(nbd)_2]BF_4$	dcpm	acetone	110	SM
12	$[Rh(nbd)_2]BF_4$	dcpm	2-butanone	150	SM

Conditions: **301** (0.15 mmol, 1.0 equiv.), 1-octyne (0.18 mmol, 1.2 equiv.), Rh catalyst (10 mol%), ligand added (10 mol%), solvent (0.5 M with respect to the ketone), 24 h. [a]PC = propylene carbonate. [b]Determined by ^{1}H NMR spectroscopy of crude reaction mixtures. SM = starting material.

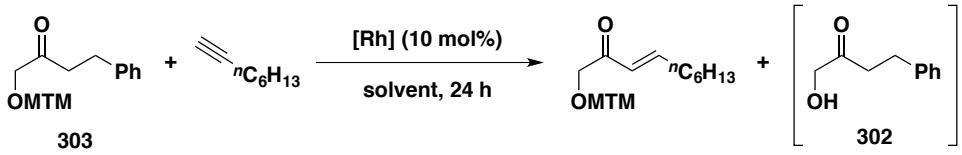
With MTM-protected α-amino ketones proving unsuccessful, our attention then turned to α-hydroxy ketones, should these behave any differently. Two substrates **303** and **304**, which are structurally analogous to the amino examples **295** and **301** were synthesised as starting materials, this time using a Pummerer rearrangement to MTM-protect the hydroxyl groups (**Scheme 4.13**).[247]



Scheme 4.13: Synthesis of MTM-protected *α*-hydroxy ketones **303** and **304**.

Disappointingly, when these substrates were subjected to a more focussed selection of conditions, no product resulting from the desired C–C bond cleavage could be identified. In fact, these *α*-hydroxy ketones seemed more prone to decomposition under the reactions conditions chosen, with complex mixtures containing alcohol **302** often observed, and little to no starting material remaining (**Tables 4.6** and **4.7**).

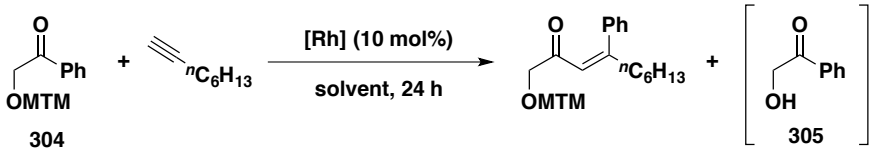
Table 4.6: Screening of conditions for C–C activation of ketone **303**.



Entry	Catalyst	Ligand Added	Solvent	Temperature (°C)	Products[a]
1	$[Rh(cod)_2]OTf$	-	2-butanone	150	CM + **302**
2	$[RhCl(C_2H_4)_2]_2$	-	2-butanone	150	CM
3	$[Rh(nbd)_2]BF_4$	-	2-butanone	150	CM + **302**
4	$[Rh(nbd)_2]BF_4$	dcpm	2-butanone	125	CM
5	$[Rh(nbd)_2]BF_4$	dcpm	1,2-DCE	150	CM + **302**
6	$[Rh(cod)OMe]_2$	dcpm	1,4-dioxane	150	SM

Conditions: **303** (0.15 mmol, 1.0 equiv.), 1-octyne (0.18 mmol, 1.2 equiv.), Rh catalyst (10 mol%), ligand added (10 mol%), solvent (0.5 M with respect to the ketone), 24 h. [a]Determined by ^1H NMR spectroscopy of crude reaction mixtures. SM = starting material, CM = complex mixture.

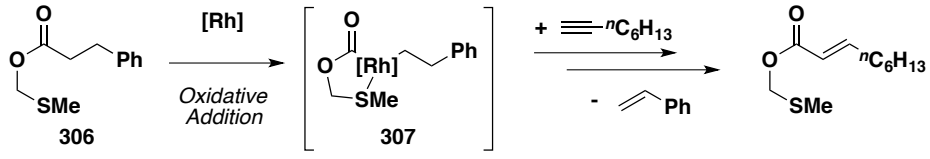
Table 4.7: Screening of conditions for C–C activation of ketone **304**.



Entry	Catalyst	Ligand Added	Solvent	Temperature (°C)	Products[a]
1	$[Rh(cod)_2]OTf$	-	2-butanone	150	CM
2	$[RhCl(C_2H_4)_2]_2$	-	2-butanone	150	CM
3	$[Rh(nbd)_2]BF_4$	-	2-butanone	150	CM
4	$[Rh(nbd)_2]BF_4$	dcpm	2-butanone	125	CM + **305**
5	$[Rh(nbd)_2]BF_4$	dcpm	1,2-DCE	150	CM + **305**
6	$[Rh(cod)OMe]_2$	dcpm	1,4-dioxane	150	SM

Conditions: **304** (0.15 mmol, 1.0 equiv.), 1-octyne (0.18 mmol, 1.2 equiv.), Rh catalyst (10 mol%), ligand added (10 mol%), solvent (0.5 M with respect to the ketone), 24 h. [a]Determined by ^{1}H NMR spectroscopy of crude reaction mixtures. SM = starting material, CM = complex mixture.

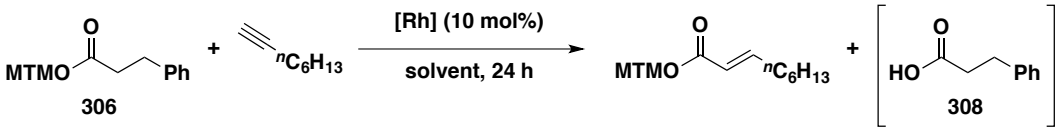
With all results prior to this point indicating an incompatibility of the MTM group in α-heteroatom systems in providing the sufficient chelating ability to enact C–C activation, a final set of attempts was made with MTM-protected carboxylate **306** (**Scheme 4.14**). The idea behind this substrate would be that any C–C activation provided by the MTM group here would proceed *via* a much more favourable five-membered chelate **307**, rather than the six-membered chelates theorised for the α-heteroatom ketones.[100] Of course, changing the nature of the carbonyl adjacent to the activated C–C bond from a ketone to an ester could have an effect on any electronic factors, and this was important to consider.



Scheme 4.14: Potential reactivity of MTM-protected carboxylate **306**.

With these collected results in mind, it was perhaps unsurprising to observe that in most cases, only starting material was returned, even at the very high temperatures and catalyst loadings (**Table 4.8**). Only with the highly Lewis acidic catalyst $[Rh(cod)_2]OTf$ did any activity occur, however, the product of this was mostly the MTM-deprotected carboxylic acid **308**. It was decided that investigations into the use of the MTM-group for C–C activation would be discontinued in order to pursue the next class of chelating groups.

Table 4.8: Screening of conditions for C–C activation of carboxylate **306**.



Entry	Catalyst	Ligand Added	Solvent	Temperature (°C)	Products[a]
1	$[Rh(cod)_2]OTf$	-	1,2-DCE	150	CM + **308**
2	$[Rh(cod)_2]OTf$	-	2-butanone	150	CM + **308**
3	$[Rh(cod)_2]OTf$	-	PhMe	150	CM + **308**
4	$[RhCl(C_2H_4)_2]_2$	-	1,2-DCE	150	SM
5	$[RhCl(C_2H_4)_2]_2$	-	2-butanone	150	SM
6	$[RhCl(C_2H_4)_2]_2$	-	PhMe	150	SM
7	$Rh(PPh_3)_3Cl$	-	1,2-DCE	150	SM
8	$Rh(PPh_3)_3Cl$	-	2-butanone	150	SM
9	$Rh(PPh_3)_3Cl$	-	PhMe	150	SM
10	$[Rh(nbd)_2]BF_4$	dcpm	2-butanone	120	SM
11	$[Rh(nbd)_2]BF_4$	dcpm	2-butanone	150	SM

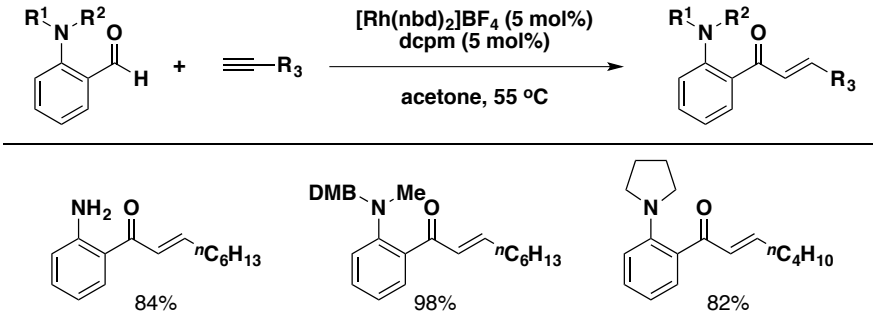
Conditions: **306** (0.15 mmol, 1.0 equiv.), 1-octyne (0.18 mmol, 1.2 equiv.), Rh catalyst (10 mol%), ligand added (10 mol%), solvent (0.5 M with respect to the ketone), 24 h. [a]Determined by ^{1}H NMR spectroscopy of crude reaction mixtures. SM = starting material, CM = complex mixture.

4.3 Investigating Nitrogen-Based Chelating Groups

As discussed in the introduction of this chapter (**Section 4.1**), the three most successful chelating groups employed in C–C activation are all based around nitrogen atom-containing heterocycles (**Figure 4.1**). It was therefore hoped that our experiments using alternative nitrogen-based chelates would prove successful.

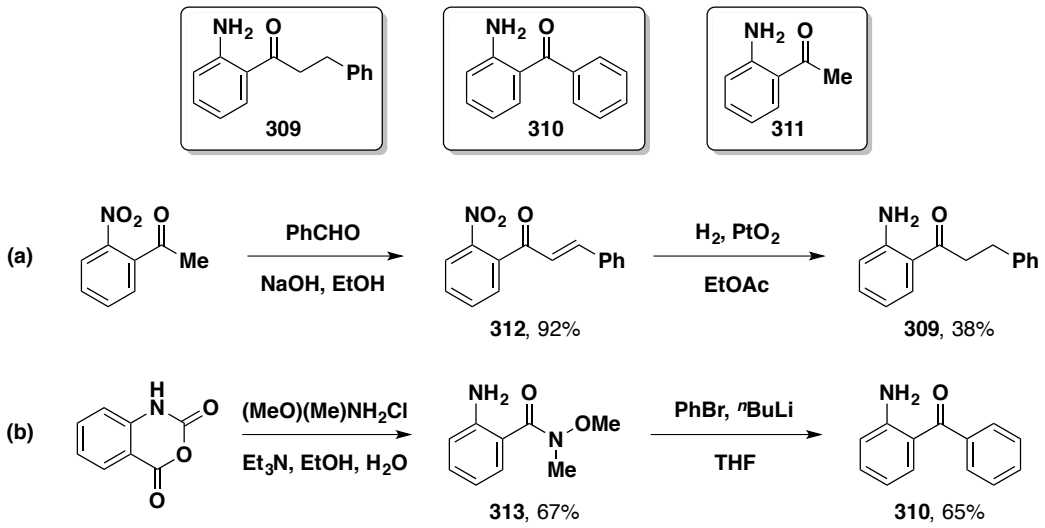
4.3.1 Aniline-Based Substrates

By exploiting our understanding of rhodium-catalysed hydroacylation to determine a starting point for investigations, it was proposed that aniline based derivatives could behave as effective directing groups in C–C activation. This hypothesis was based on the hydroacylation results reported by Willis and co-workers, in which such tethers enabled efficient conversions to the desired enone products *via* C–H activation (**Scheme 4.15**).[86]



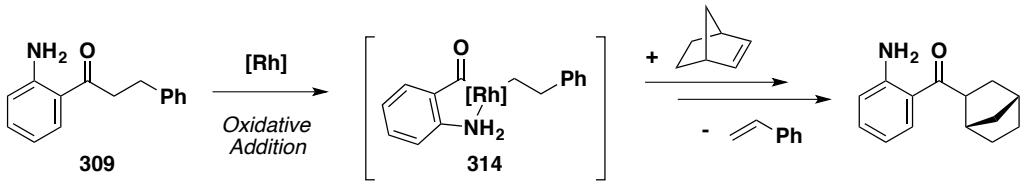
Scheme 4.15: Successful use of aniline based substrates in C–H activation.

Consequently, three NH_2-based anilines were selected for investigation to begin with, containing ketone substituents that could potentially be activated (that is, the phenethyl, phenyl and methyl groups, **Scheme 4.16**). With methyl ketone **311** being commercially available, phenethyl ketone **309** (**Scheme 4.16 (a)**) and phenyl ketone **310** (**Scheme 4.16 (b)**) were synthesised straightforwardly *via* independent routes.[248,249]



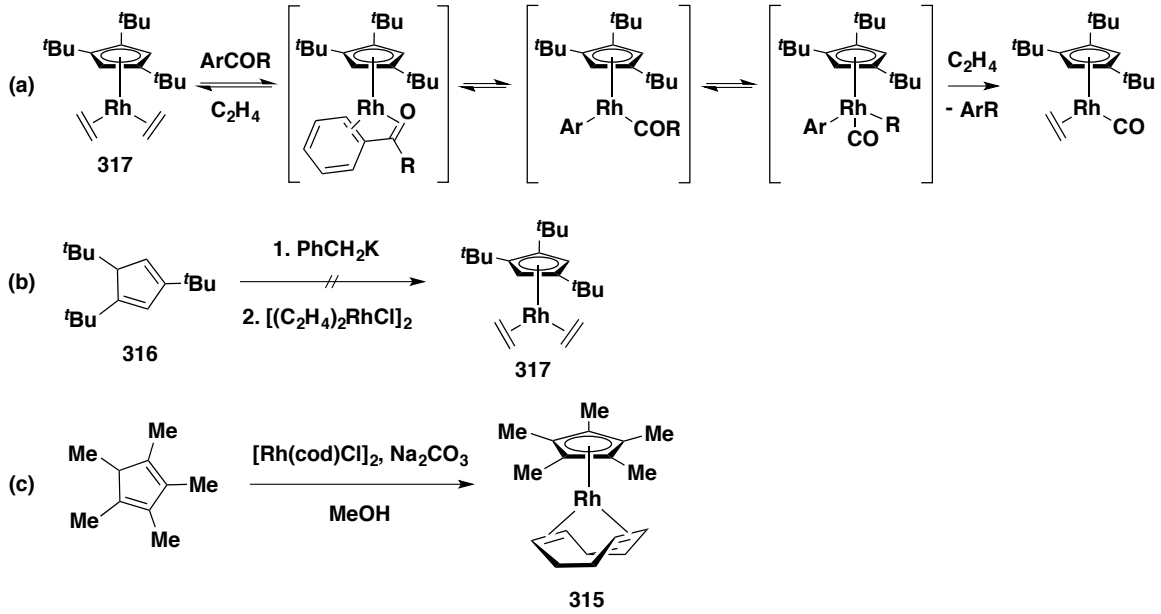
Scheme 4.16: Substrates for initial investigation and synthesis of anilines **309** and **310**.

As such, various attempts to enact a C–C activation process with these substrates and experiments were undertaken using either 1-octyne (as with the MTM-protected substrates) or norbornene as the unsaturated coupling component. Norbornene was chosen as the most suitable alkene due to the inability of its hydrometallated form to undergo *β*-hydride elimination with a metal catalyst,[232] and thus its prevention of any reversibility within the catalytic cycle once hydrometallation had occurred. It should also be noted that, for all experiments conducted, the unsaturated component was added to excess (using three equivalents compared to the ketone), so that it could coordinate competitively with any phenylethene produced from *β*-hydride elimination of the phenethyl rhodium complex **314** following C–C oxidative addition (**Scheme 4.17**).



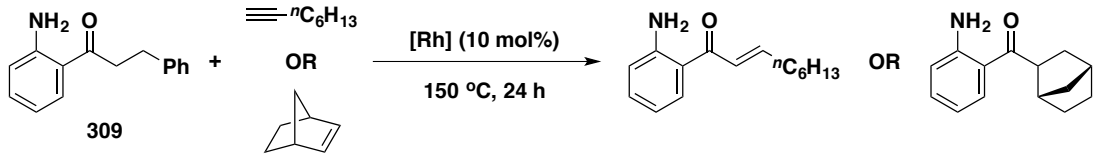
Scheme 4.17: Potential route of reactivity for substrate **309**.

Attention was initially turned towards substrate **309** for investigation, and a selection of screening conditions were applied in attempts to enact the desired C–C bond cleavage seen in **Table 4.9**. Throughout all reactions, a high catalyst loading of 10 mol% and an extremely high temperature of 150 °C was maintained for the same reasons as those outlined in **Section 4.2.2**. As before, catalysts and solvents were used that had shown to be successful in known C–C activation methodologies (see **Section 3.3**). However, an exception to this was the rhodium catalyst Cp*Rh(cod) **315**, a bulky cyclopentadienylrhodium complex. Reports by Brookhart indicated that this type of complex could mediate the decarbonylation of non-chelating aryl ketones *via* C–C activation, with catalyst **317** demonstrating particular activity with cyclohexane as the solvent (**Scheme 4.18 (a)**).[250] Unfortunately, attempts to synthesise catalyst **317** failed under the conditions available to us (**Scheme 4.18 (b)**), and thus the more bench stable catalyst Cp*Rh(cod) **315** was synthesised (**Scheme 4.18 (c)**), which still possessed the crucial feature of an electron-rich, bulky cyclopentadienyl ligand, and hence was used in our C–C activation screening studies.[251]



Scheme 4.18: (a) Brookhart's report of catalyst **317** facilitating decarbonylation of aryl ketones; (b) failed synthesis of catalyst **317**; (c) successful synthesis of conceptually similar catalyst **315**.

Table 4.9: Screening of conditions for C–C activation of ketone **309**.

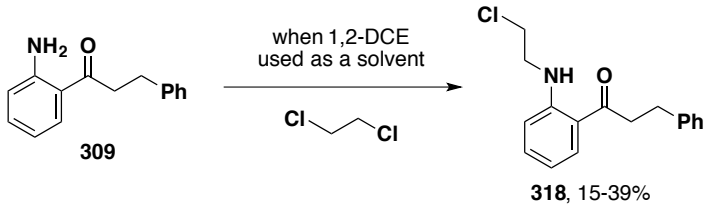


Entry	Catalyst	Unsaturated Component	Solvent	Products[a]
1	$[Rh(cod)_2]OTf$	norbornene	1,2-DCE	SM + **319**(29)
2	$[Rh(cod)_2]OTf$	1-octyne	1,2-DCE	SM + CM
3	$[Rh(cod)_2]OTf$	norbornene	PhMe	SM
4	$[Rh(cod)_2]OTf$	1-octyne	PhMe	SM
5	$[RhCl(C_2H_4)_2]_2$	norbornene	1,4-dioxane	SM
6	$[RhCl(C_2H_4)_2]_2$	1-octyne	1,4-dioxane	SM
7	$Rh(PPh_3)_3Cl$	norbornene	1,2-DCE	SM + **318**(39)
8	$Rh(PPh_3)_3Cl$	1-octyne	1,2-DCE	SM + **318**(35)
9	$[Rh(nbd)_2]BF_4$/dcpm	norbornene	PhMe	SM
10	$[Rh(nbd)_2]BF_4$/dcpm	1-octyne	1,2-DCE	SM + **318**(15)
11	Cp*Rh(cod) **315**	norbornene	Cyclohexane	SM
12	Cp*Rh(cod) **315**	1-octyne	Cyclohexane	SM

Conditions: **309** (0.15 mmol, 1.0 equiv.), unsaturated component (0.45 mmol, 3.0 equiv.), Rh catalyst (10 mol%), ligand added (10 mol%), solvent (0.5 M with respect to the ketone), 150 °C, 24 h. [a]Determined by ^{1}H NMR spectroscopy of crude reaction mixtures. Value in parentheses indicates any isolated yield of product. SM = starting material, CM = complex mixture.

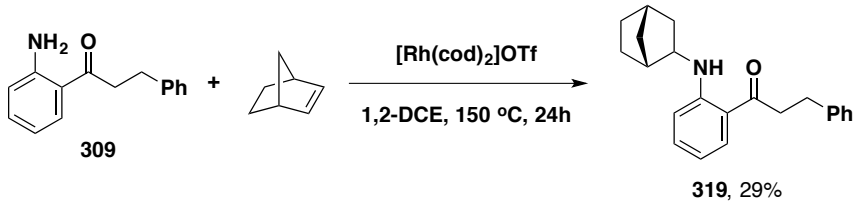
Results of optimisation experiments were disappointing (**Table 4.9**), with most instances returning starting material, including those with catalyst **315** (**Table 4.9**, entries **11** and **12**). However, two by-products were observed under certain conditions. In presence of the solvent 1,2-dichloroethane, traces of by-product **318** were discovered (**Table 4.9**, entries **7**, **8** and **10**), formed from the amine group reacting with the solvent itself (**Scheme 4.19**). Whilst its presence is likely a consequence of the extremely high temperatures used, it remains unclear

if the rhodium catalyst has any involvement in this substitution process.



Scheme 4.19: Formation of by-product **318** in the presence of 1,2-DCE.

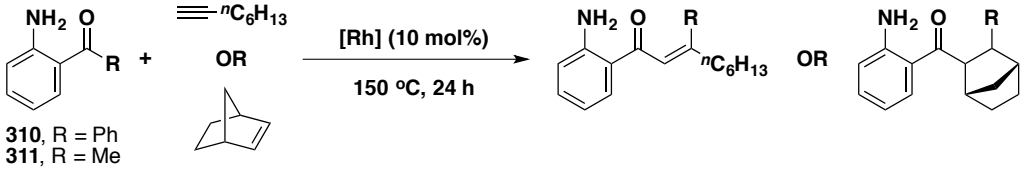
The second by-product to be observed resulted from the hydroamination of norbornene with substrate **309**, forming a secondary amine **319** (**Scheme 4.20**). This only occurred on one occasion when the highly Lewis acidic catalyst $[Rh(cod)_2]OTf$ was used in the more polar solvent 1,2-DCE (**Table 4.9**, entry **1**). As more effective methodologies for this process currently exist in the literature,[252] any pursuit of developing this reaction further was discounted.



Scheme 4.20: Formation of by-product **319.**

With the observation of any C–C activation product with substrate **309** proving elusive, experiments were continued using the phenyl and methyl ketones **310** and **311**, in attempts to enact the transformation as seen in **Table 4.10**. To limit any side reactions, the use of 1,2-DCE was replaced with another polar solvent, propylene carbonate, which has proved useful in C–H activations.[171] Despite this suppression, and increasing the reaction concentration to 1.0 M, once again no desired C–C activation product was observed with starting material was returned in most cases (**Table 4.10**).

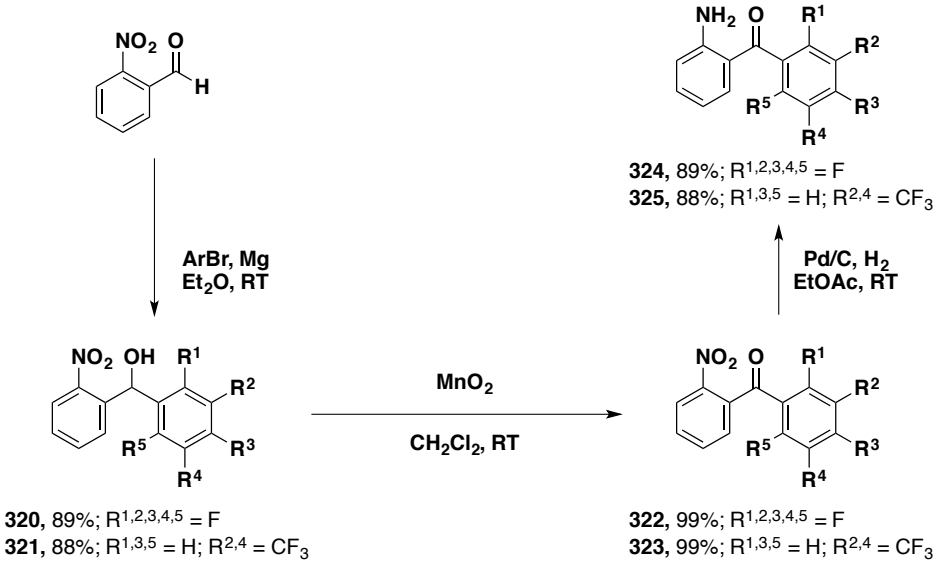
Table 4.10: Screening of conditions for C–C activation of ketones **310** and **311**.



Entry	R	Catalyst	Unsaturated Component	Solvent[a]	Products[b]
1	Ph	$[Rh(cod)_2]OTf$	1-octyne	PhMe	SM
2	Ph	$[Rh(cod)_2]OTf$	1-octyne	PC	SM + CM
3	Ph	$[Rh(cod)_2]OTf$	norbornene	PhMe	SM
4	Ph	$[RhCl(C_2H_4)_2]_2$	1-octyne	PhMe	SM
5	Ph	$[RhCl(C_2H_4)_2]_2$	1-octyne	PC	SM
6	Ph	$[RhCl(C_2H_4)_2]_2$	norbornene	PhMe	SM
7	Ph	$Rh(PPh_3)_3Cl$	1-octyne	PhMe	SM
8	Ph	$Rh(PPh_3)_3Cl$	norbornene	PhMe	SM
9	Ph	Cp*Rh(cod) **315**	1-octyne	Cyclohexane	SM
10	Ph	Cp*Rh(cod) **315**	norbornene	Cyclohexane	SM
11	Me	$[Rh(cod)_2]OTf$	1-octyne	PhMe	SM
12	Me	$[Rh(cod)_2]OTf$	1-octyne	PC	SM + CM
13	Me	$[Rh(cod)_2]OTf$	norbornene	PhMe	SM
14	Me	$[RhCl(C_2H_4)_2]_2$	1-octyne	PhMe	SM
15	Me	$[RhCl(C_2H_4)_2]_2$	1-octyne	PC	SM
16	Me	$[RhCl(C_2H_4)_2]_2$	norbornene	PhMe	SM
17	Me	$Rh(PPh_3)_3Cl$	1-octyne	PhMe	SM
18	Me	$Rh(PPh_3)_3Cl$	norbornene	PhMe	SM
19	Me	Cp*Rh(cod) **315**	1-octyne	Cyclohexane	SM
20	Me	Cp*Rh(cod) **315**	norbornene	Cyclohexane	SM

Conditions: Ketone (0.15 mmol, 1.0 equiv.), unsaturated component (0.45 mmol, 3.0 equiv.), Rh catalyst (10 mol%), ligand added (10 mol%), solvent (1.0 M with respect to the ketone), 150 °C, 24 h. [a]PC = propylene carbonate. [b]Determined by ^{1}H NMR spectroscopy of crude reaction mixtures. SM = starting material, CM = complex mixture.

To improve the likelihood of reactivity, derivatives of the phenyl ketone **310** containing electron withdrawing groups on the phenyl substituent were investigated. It was believed that the electronic influence from these groups might weaken the ketone C–C bond, thus lowering the kinetic barrier to activation. Ketones **324** and **324**, possessing five fluorine substituents or two trifluoromethyl groups, respectively, were made from 2-nitrobenzaldehyde *via* the synthetic routes outlined in **Scheme 4.21**.[253]



320, 89%; $R^{1,2,3,4,5}$ = F
321, 88%; $R^{1,3,5}$ = H; $R^{2,4}$ = CF_3

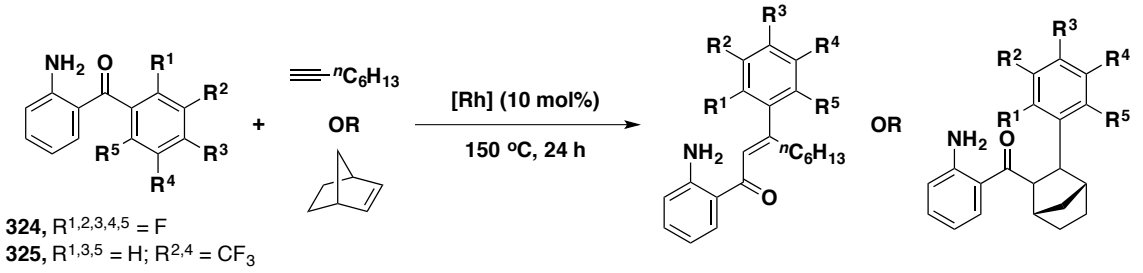
322, 99%; $R^{1,2,3,4,5}$ = F
323, 99%; $R^{1,3,5}$ = H; $R^{2,4}$ = CF_3

324, 89%; $R^{1,2,3,4,5}$ = F
325, 88%; $R^{1,3,5}$ = H; $R^{2,4}$ = CF_3

Scheme 4.21: Synthesis of ketones **324** and **325** from 2-nitrobenzaldehyde.

The results from their application to various C–C activation conditions, however, remained disappointing (**Table 4.11**). Similar to the unsubstituted phenyl ketone **310**, most experiments returned starting material, and two by-products could be observed overall under certain conditions. Under similar conditions (**Table 4.11**, entry **2**) as observed with the formation of secondary amine **319** (see **Scheme 4.20**), the product **326** was also observed with pentafluorophenyl-ketone **324** in the presence of norbornene (**Scheme 4.22**).

Table 4.11: Screening of conditions for C–C activation of ketones **324** and **325**.



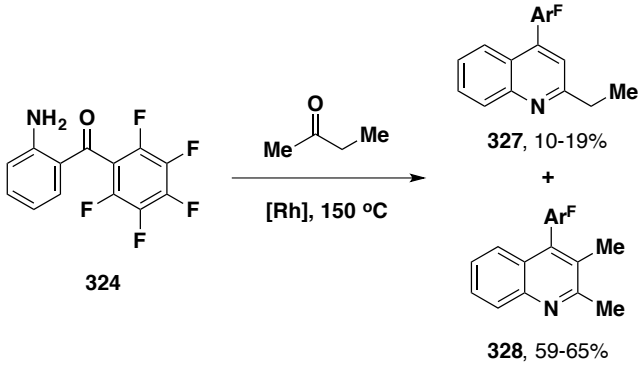
324, $R^{1,2,3,4,5}$ = F
325, $R^{1,3,5}$ = H; $R^{2,4}$ = CF_3

Entry	Substrate	Catalyst	Unsaturated Component	Solvent[a]	Products[b]
1	**324**	$[Rh(cod)_2]OTf$	1-octyne	1,2-DCE	SM
2	**324**	$[Rh(cod)_2]OTf$	norbornene	1,2-DCE	SM + **326**(27)
3	**324**	$[Rh(cod)_2]OTf$	1-octyne	PhMe	SM
4	**324**	$[Rh(cod)_2]OTf$	norbornene	PC	CM
5	**324**	$[Rh(cod)_2Cl]_2$	1-octyne	2-butanone	**327**(13) + **328**(65)
6	**324**	$[Rh(cod)_2Cl]_2$	norbornene	2-butanone	**327**(10) + **328**(61)
7	**324**	$[Rh(cod)_2Cl]_2$	1-octyne	1,4-dioxane	SM
8	**324**	$[Rh(cod)_2Cl]_2$	norbornene	1,4-dioxane	SM
9	**324**	$Rh(PPh_3)_3Cl$	1-octyne	2-butanone	**327**(14) + **328**(60)
10	**324**	$Rh(PPh_3)_3Cl$	norbornene	2-butanone	**327**(19) + **328**(59)
11	**324**	$Rh(PPh_3)_3Cl$	norbornene	PhMe	SM
12	**324**	$[Rh(nbd)_2]BF_4$/dcpm	1-octyne	1,2-DCE	SM
13	**324**	$[Rh(nbd)_2]BF_4$/dcpm	norbornene	1,2-DCE	SM
14	**324**	$[RhCl(C_2H_4)_2]_2$	norbornene	PhMe	SM
15	**324**	Cp*Rh(cod) **315**	norbornene	Cyclohexane	SM
16	**325**	$[Rh(cod)_2]OTf$	norbornene	PhMe	SM
17	**325**	$Rh(PPh_3)_3Cl$	norbornene	PhMe	SM
18	**325**	$[Rh(nbd)_2]BF_4$/dcpm	norbornene	PhMe	SM
19	**325**	Cp*Rh(cod) **315**	norbornene	Cyclohexane	SM

Conditions: Ketone (0.15 mmol, 1.0 equiv.), unsaturated component (0.45 mmol, 3.0 equiv.), Rh catalyst (10 mol%), ligand added (10 mol%), solvent (1.0 M with respect to ketone), 150 °C, 24 h. [a]PC = propylene carbonate. [b]Determined by ^{1}H NMR spectroscopy of crude mixtures. Value in parentheses indicates any isolated yield of product. SM = starting material, CM = complex mixture.

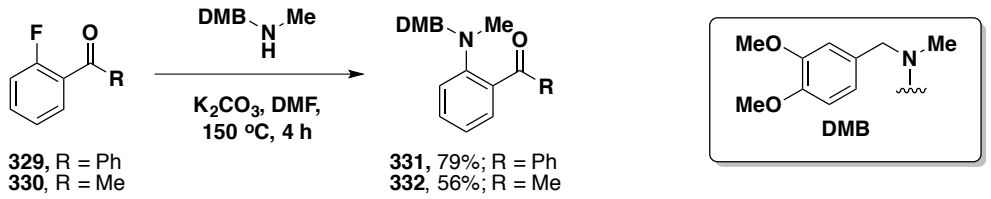
Scheme 4.22: Formation of side product **326**.

In all cases when the solvent 2-butanone was employed (**Table 4.11**, entries **5**, **6**, **9** and **10**), complete conversion to the quinoline by-products **327** and **328** was observed (**Scheme 4.23**). These were presumably formed *via* a Friedländer reaction, which are typically catalysed by a Lewis acid such as a rhodium(I) cation.[254] Further use of 2-butanone as a solvent was therefore avoided with free anilines.



Scheme 4.23: Formation of quinoline by-products **327** and **328** when 2-butanone was used as the solvent.

Considering the propensity of the free aniline substrates employed to undergo deleterious side reactions, it was decided to protect these amines with the 3,4-dimethoxybenzyl ('DMB') and methyl groups, similar to the arrangement used in Willis' aldehyde substrates for hydroacylation (**Scheme 4.15**).[86] It was also hoped that the electron donating nature of these groups would increase the availability of the nitrogen lone pair and increase its coordinating ability. Ketones **331** and **332** were therefore synthesised *via* the route shown in **Scheme 4.24**.



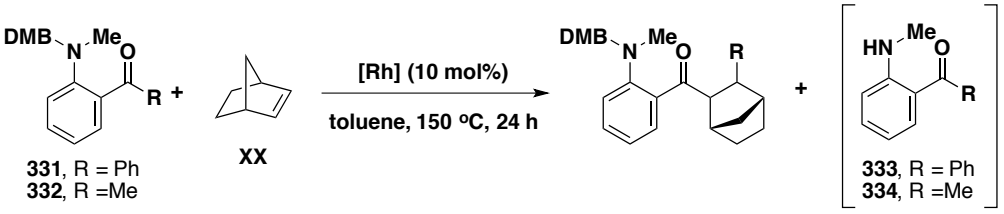
329, R = Ph
330, R = Me

331, 79%; R = Ph
332, 56%; R = Me

Scheme 4.24: Synthesis of protected aniline ketones **331** and **332**.

Disappointingly, the DMB group proved to be relatively labile under all the reaction conditions screened, leaving only a mixture of starting material and secondary amine **333** or **334** (**Table 4.12**).

Table 4.12: Screening of conditions for C–C activation of ketones **331** and **332**.



331, R = Ph
332, R =Me

XX

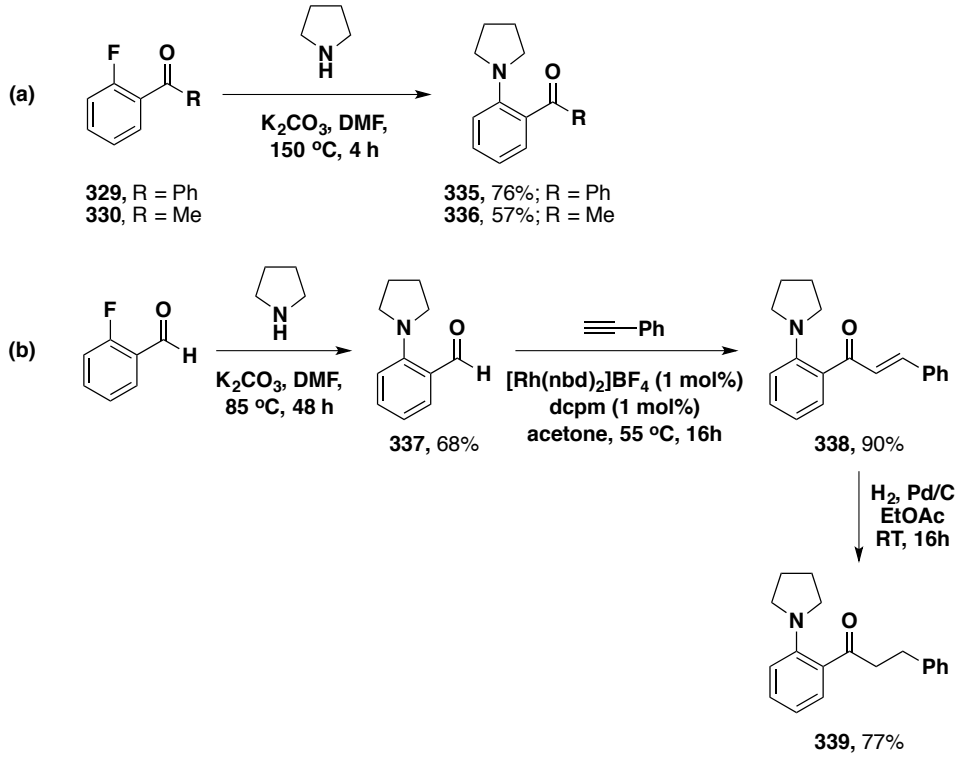
333, R = Ph
334, R =Me

Entry	R	Catalyst	Products[a]
1	Ph	$[Rh(cod)_2]OTf$	SM + **333**(89)
2	Ph	$[RhCl(C_2H_4)_2]_2$	SM + **333**(54)
3	Ph	$Rh(PPh_3)_3Cl$	SM + **333**(62)
4	Me	$[Rh(cod)_2]OTf$	SM + **334**(70)
5	Me	$[RhCl(C_2H_4)_2]_2$	SM + **334**(39)
6	Me	$Rh(PPh_3)_3Cl$	SM + **334**(55)

Conditions: Ketone (0.15 mmol, 1.0 equiv.), norbornene (0.45 mmol, 3.0 equiv.), Rh catalyst (10 mol%), toluene (1.0 M with respect to the ketone), 150 °C, 24 h. [a]Determined by ^{1}H NMR spectroscopy of crude reaction mixtures. Value in parentheses indicates any isolated yield of product. SM = starting material.

To avoid this issue, investigations turned to substrates in which the aniline nitrogen atom was incorporated into a pyrrolidine ring. Such substrates were made as in **Scheme 4.25**, with phenethyl-containing **339** being synthesised *via* hydroacylation of aldehyde **337**,[86] facilitated

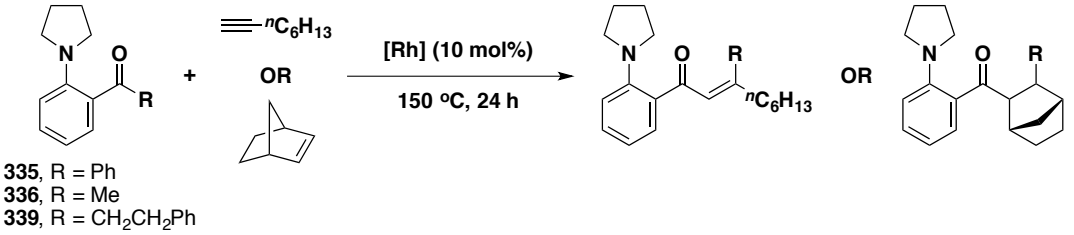
by coordination of the pyrrolidine nitrogen, and subsequent hydrogenation of the enone **338**.



Scheme 4.25: Synthetic routes to protected aniline-based ketones **335**, **336** and **339**.

Analysing these substrates with regards to C–C activation under the conditions outlined in **Table 4.13** saw only starting material returned, however it was duly noted that side reactions had successfully been prevented using this class of substrates. Attempts to attenuate the electronics of the rhodium catalyst by including bisphosphine ligands, which are used regularly in rhodium-catalysed C–H activation, also failed to demonstrate any potential (**Table 4.14**), despite ligands of differing bite angles and substituents being employed.

Table 4.13: Screening of conditions for C–C activation of ketones **335**, **336** and **339**.

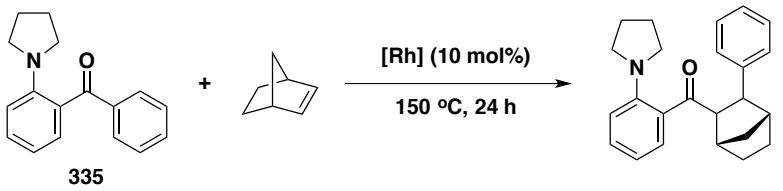


335, R = Ph
336, R = Me
339, R = CH_2CH_2Ph

Entry	R	Catalyst	Unsaturated Component	Solvent	Products[a]
1	Ph	$[Rh(cod)_2]OTf$	1-octyne	1,2-DCE	SM
2	Ph	$[Rh(cod)_2]OTf$	norbornene	1,2-DCE	SM
3	Ph	$[Rh(cod)_2]OTf$	1-octyne	1,4-dixoane	SM
4	Ph	$[Rh(cod)_2]OTf$	norbornene	1,4-dixoane	SM
5	Ph	$[RhCl(C_2H_4)_2]_2$	1-octyne	2-butanone	SM
6	Ph	$[RhCl(C_2H_4)_2]_2$	norbornene	2-butanone	SM
7	Ph	$Rh(PPh_3)_3Cl$	1-octyne	2-butanone	SM
8	Ph	$Rh(PPh_3)_3Cl$	norbornene	2-butanone	SM
9	Ph	$Rh(PPh_3)_3Cl$	norbornene	PhMe	SM
10	Ph	Cp*Rh(cod) **315**	1-octyne	Cyclohexane	SM
11	Ph	Cp*Rh(cod) **315**	norbornene	Cyclohexane	SM
11	Me	$[Rh(cod)_2]OTf$	norbornene	PhMe	SM
12	Me	$[RhCl(C_2H_4)_2]_2$	norbornene	PhMe	SM
13	Me	$Rh(PPh_3)_3Cl$	norbornene	PhMe	SM
14	Me	$[Rh(nbd)_2]BF_4$	norbornene	PhMe	SM
15	CH_2CH_2Ph	$[Rh(cod)_2]OTf$	norbornene	PhMe	SM
16	CH_2CH_2Ph	$[RhCl(C_2H_4)_2]_2$	norbornene	PhMe	SM
17	CH_2CH_2Ph	$Rh(PPh_3)_3Cl$	norbornene	PhMe	SM
18	CH_2CH_2Ph	$[Rh(nbd)_2]BF_4$	norbornene	PhMe	SM
19	CH_2CH_2Ph	Cp*Rh(cod) **315**	norbornene	Cyclohexane	SM

Conditions: Ketone (0.15 mmol, 1.0 equiv.), unsaturated component (0.45 mmol, 3.0 equiv.), Rh catalyst (10 mol%), solvent (1.0 M with respect to the ketone), 150 °C, 24 h. [a]Determined by ^1H NMR spectroscopy of crude reaction mixtures. SM = starting material.

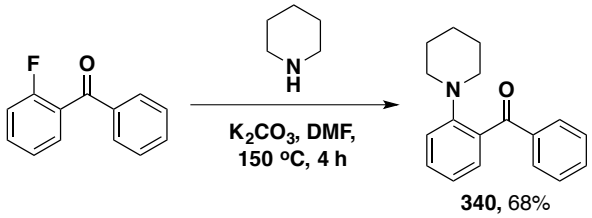
Table 4.14: Screening of conditions for C–C activation of ketone **335**.



Entry	Catalyst	Ligand Added	Solvent[a]	Products[b]
1	$[Rh(nbd)_2]BF_4$	-	PhMe	SM
2	$[Rh(nbd)_2]BF_4$	-	PC	SM
3	$[Rh(nbd)_2]BF_4$	dcpm	1,2-DCE	SM
4	$[Rh(nbd)_2]BF_4$	dcpm	PC	SM
5	$[Rh(cod)Cl]_2$	-	PhMe	SM
6	$[Rh(cod)Cl]_2$	dcpm	PhMe	SM
7	$[Rh(cod)Cl]_2$	dcpm	1,2-DCE	SM
8	$[Rh(cod)Cl]_2$	dppe	PhMe	SM
9	$[Rh(cod)Cl]_2$	dppe	1,2-DCE	SM
10	$[Rh(cod)Cl]_2$	dppf	PhMe	SM
11	$[Rh(cod)OMe]_2$	-	1,4-dioxane	SM
12	$[Rh(cod)OMe]_2$	dcpm	1,4-dioxane	SM
13	$[Rh(cod)OMe]_2$	dcpm	1,4-dioxane	SM
14	$[Rh(cod)OMe]_2$	dppe	2-butanone	SM
15	$[Rh(cod)OMe]_2$	dppe	2-butanone	SM

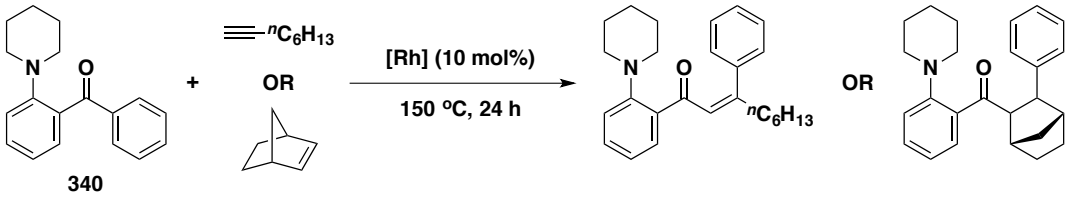
Conditions: **335** (0.15 mmol, 1.0 equiv.), norbornene (0.45 mmol, 3.0 equiv.), Rh catalyst (10 mol%), ligand added (10 mol%), solvent (0.5 M with respect to the ketone), 24 h. [a]PC = propylene carbonate. [b]Determined by ^{1}H NMR spectroscopy of crude reaction mixtures. SM = starting material.

To observe if any reactivity could be observed by increasing the ring size in which the nitrogen atom was incorporated, substrate **340** was synthesised using piperidine according to **Scheme 4.26**. However, changing this feature of the substrate appeared to have no effect in terms of carboacylation reactivity (**Table 4.15**).



Scheme 4.26: Synthesis of ketone **340**.

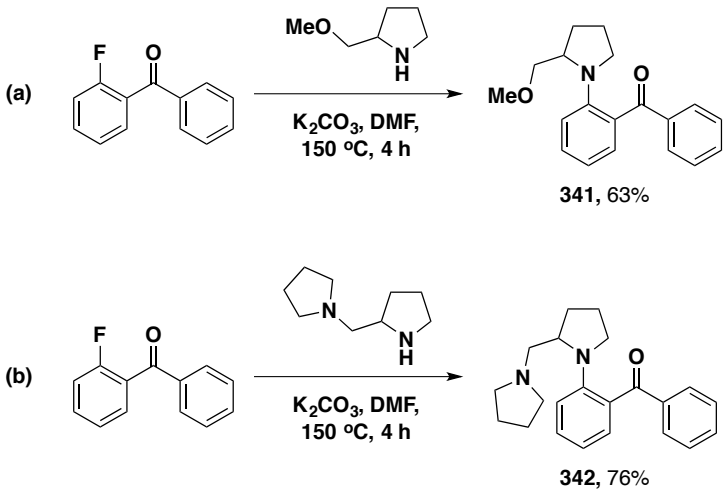
Table 4.15: Screening of conditions for C–C Activation of Ketone **340**.



Entry	Catalyst	Unsaturated Component	Solvent	Products[a]
1	$[Rh(cod)_2]OTf$	norbornene	1,2-DCE	SM
2	$[Rh(cod)_2]OTf$	1-octyne	1,2-DCE	SM
3	$[Rh(cod)_2]OTf$	norbornene	PhMe	SM
4	$[Rh(cod)_2]OTf$	1-octyne	PhMe	SM
5	$[RhCl(C_2H_4)_2]_2$	norbornene	2-butanone	SM
6	$[RhCl(C_2H_4)_2]_2$	1-octyne	2-butanone	SM
7	$Rh(PPh_3)_3Cl$	norbornene	2-butanone	SM
8	$Rh(PPh_3)_3Cl$	1-octyne	2-butanone	SM
9	$[Rh(nbd)_2]BF_4$/dcpm	norbornene	PhMe	SM
10	$[Rh(nbd)_2]BF_4$/dcpm	1-octyne	1,2-DCE	SM
11	$[Rh(nbd)_2]BF_4$/dppe	norbornene	PhMe	SM
12	$[Rh(nbd)_2]BF_4$/dppe	1-octyne	1,2-DCE	SM
13	Cp*Rh(cod) **315**	norbornene	Cyclohexane	SM
14	Cp*Rh(cod) **315**	1-octyne	Cyclohexane	SM

Conditions: **340** (0.15 mmol, 1.0 equiv.), unsaturated component (0.45 mmol, 3.0 equiv.), Rh catalyst (10 mol%), solvent (1.0 M with respect to the ketone), 150 °C, 24 h. [a]Determined by ^{1}H NMR spectroscopy of crude reaction mixtures. SM = starting material.

In an attempt to increase the coordination ability of the chelating group and provide a more powerful handle for facilitating C–C activation, substrates **341** and **342** were synthesised, containing either a methoxy or second pyrrolidine group tethered to the pyrrolidine group at the 2- position (**Scheme 4.27**).

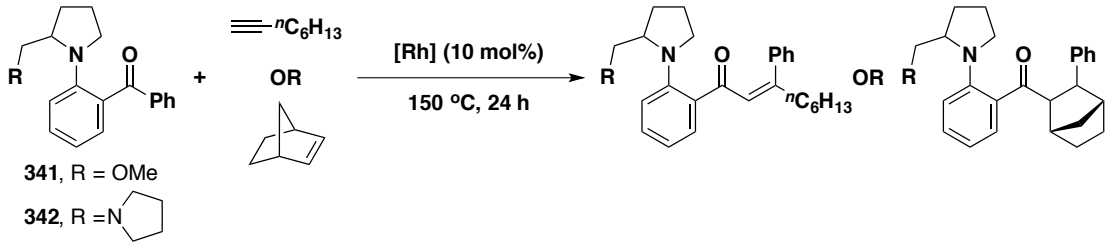


Scheme 4.27: Synthetic routes to ketones **341** and **342**.

It was proposed that both heteroatoms on the chelating group would coordinate simultaneously to the rhodium centre, providing more of a rigid environment in which the ketone C–C bond could be brought sufficiently close enough to the metal for activation. Disappointingly, the results in **Table 4.16** did not validate this theory.

With no C–C activation observed with any of the aniline-based ketone substrates investigated throughout this section, experiments were consequently suspended on this substrate class due to time constraints.

Table 4.16: Screening of conditions for C–C Activation of Ketones **341** and **342**.

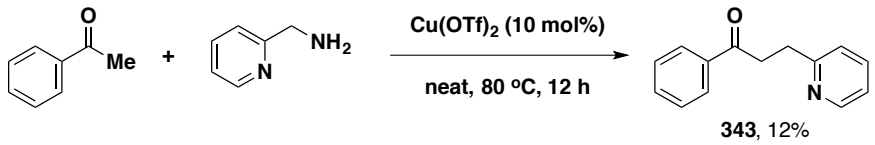


Entry	Substrate	Catalyst	Unsaturated Component	Solvent	Products[a]
1	**341**	$[Rh(cod)_2]OTf$	1-octyne	1,2-DCE	SM
2	**341**	$[Rh(cod)_2]OTf$	norbornene	1,2-DCE	SM
3	**341**	$[Rh(cod)_2]OTf$	1-octyne	PhMe	SM
4	**341**	$[Rh(cod)_2]OTf$	norbornene	PhMe	SM
5	**341**	$[RhCl(C_2H_4)_2]_2$	1-octyne	2-butanone	SM
6	**341**	$[RhCl(C_2H_4)_2]_2$	norbornene	2-butanone	SM
7	**341**	$Rh(PPh_3)_3Cl$	1-octyne	2-butanone	SM
8	**341**	$Rh(PPh_3)_3Cl$	norbornene	2-butanone	SM
9	**341**	$[Rh(nbd)_2]BF_4$/dcpm	norbornene	PhMe	SM
10	**341**	$[Rh(nbd)_2]BF_4$/dcpm	norbornene	1,2-DCE	SM
11	**341**	Cp*Rh(cod) **315**	norbornene	Cyclohexane	SM
12	**342**	$[Rh(cod)_2]OTf$	norbornene	1,2-DCE	SM
13	**342**	$[Rh(cod)_2]OTf$	norbornene	PhMe	SM
14	**342**	$[RhCl(C_2H_4)_2]_2$	1-octyne	2-butanone	SM
15	**342**	$[RhCl(C_2H_4)_2]_2$	norbornene	2-butanone	SM
16	**342**	$Rh(PPh_3)_3Cl$	1-octyne	2-butanone	SM
17	**342**	$Rh(PPh_3)_3Cl$	norbornene	2-butanone	SM
18	**342**	$[Rh(nbd)_2]BF_4$/dppe	norbornene	PhMe	SM
19	**342**	$[Rh(nbd)_2]BF_4$/dppe	norbornene	1,2-DCE	SM
20	**342**	Cp*Rh(cod) **315**	norbornene	Cyclohexane	SM

Conditions: Ketone (0.15 mmol, 1.0 equiv.), unsaturated component (0.45 mmol, 3.0 equiv.), Rh catalyst (10 mol%), solvent (1.0 M with respect to the ketone), 150 °C, 24 h. [a]Determined by ^{1}H NMR spectroscopy of crude reaction mixtures. SM = starting material.

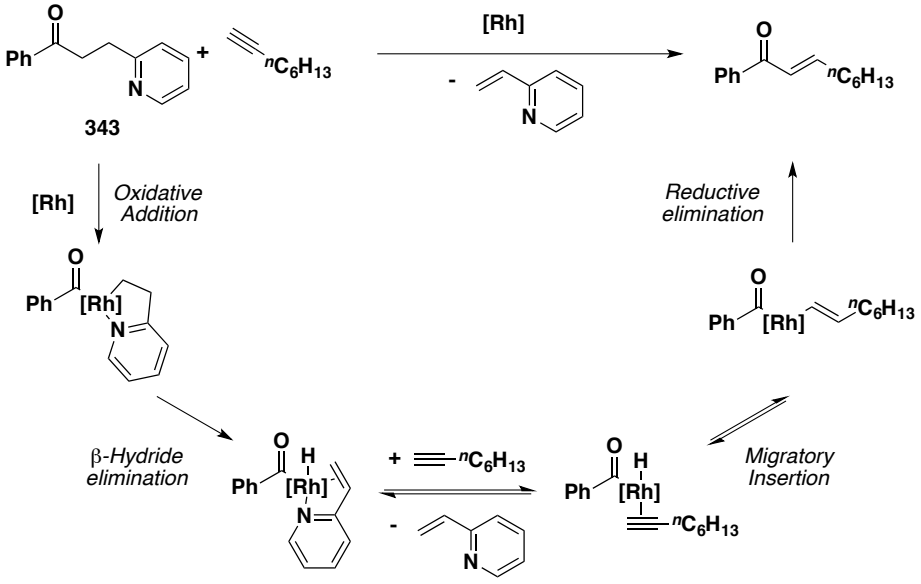
4.3.2 Pyridine-Based Substrates

Given the relative success of the pyridine group in reported C–C activation methodologies (see **Section 3.3.1**), it was decided to explore their effectiveness further. In particular, we set out to determine if the pyridine group could be removed from the substrate concurrently with the desired C–C activation process, considering the presence of pyridine groups in the final products can sometimes be undesirable. Therefore, substrate **343**, containing the chelating group on the leaving fragment, was chosen for investigation and synthesised according to **Scheme 4.28**.[255]



Scheme 4.28: Synthesis of ketone **343**.

The reason for this substrate choice centred around the fact that, hypothetically, once initial oxidative addition had taken place as guided by the nitrogen lone pair, a *β*-hydride elimination could take place to generate a coordinated 2-vinylpyridine (**Scheme 4.29**).

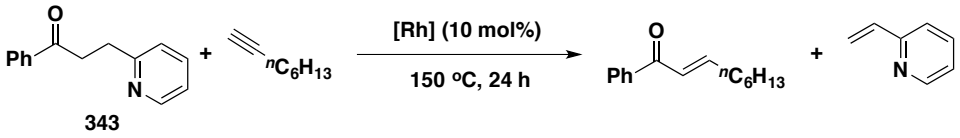


Scheme 4.29: Potential C–C activation of substrate **343** with a rhodium catalyst.

Displacement of 2-vinylpyridine might be possible in the presence of an excess (3.0 equivalents) of alkyne, and subsequent migratory insertion and reductive elimination could then occur to give the enone product (**Scheme 4.29**).

When substrate **343** was subjected to various conditions in attempts to enact this process (**Table 4.17**), unfortunately mainly starting material was returned, with signs of very small amounts of decomposition with Wilkinson's catalyst (**Table 4.17**, entries **5** and **6**). This may be due to inability of 1-octyne to displace 2-vinylpyridine from the metal centre (**Scheme 4.29**). Considering these results, no more investigations were conducted on this particular substrate.

Table 4.17: Screening of conditions for C–C Activation of Ketone **343**.

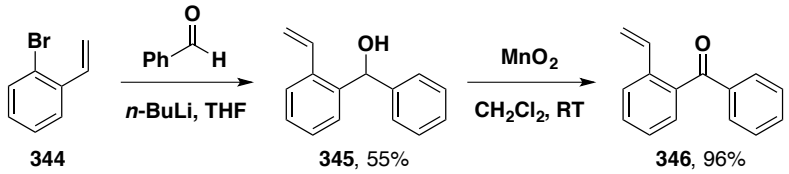


Entry	Catalyst	Solvent	Products[a]
1	$[Rh(cod)_2]OTf$	PhMe	SM
2	$[Rh(cod)_2]OTf$	1,2-DCE	SM
3	$[RhCl(C_2H_4)_2]_2$	PhMe	SM
4	$[RhCl(C_2H_4)_2]_2$	1,2-DCE	SM
5	$Rh(PPh_3)_3Cl$	PhMe	SM + CM
6	$Rh(PPh_3)_3Cl$	1,2-DCE	SM + CM

Conditions: **343** (0.15 mmol, 1.0 equiv.), 1-octyne (0.45 mmol, 3.0 equiv.), Rh catalyst (10 mol%), solvent (1.0 M with respect to the ketone), 24 h. [a]Determined by ^{1}H NMR spectroscopy of crude reaction mixtures. SM = starting material, CM = complex mixture.

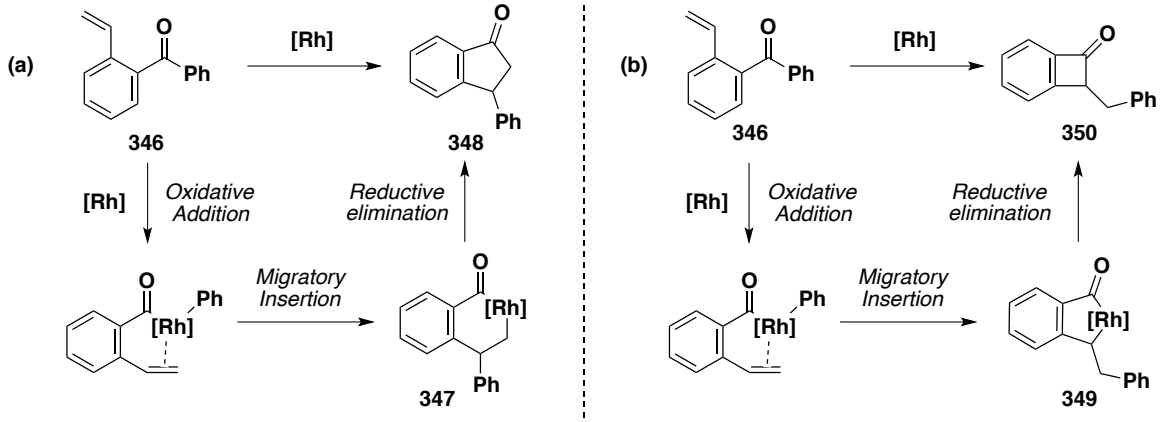
4.4 Investigating Alkene Chelating Groups

Alkenes have themselves proved to be an important class of chelating groups in C–H activation, whilst often additionally providing the unsaturated component across which the C–H bond is seemingly added.[16] In an attempt to assess the validity of terminal alkene bonds as chelating groups in C–C activation, substrate **346** was synthesised from 1-bromo-2-vinylbenzene **344** and benzaldehyde *via* oxidation of the allylic alcohol intermediate **345** (**Scheme 4.30**).



Scheme 4.30: Synthesis of ketone **346**.

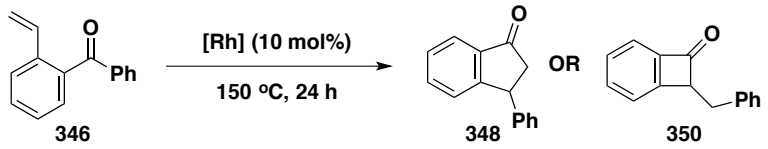
Should the desired C–C activation occur with this substrate, two possible regioisomers could be formed. Following the initial oxidative addition step, the migratory insertion could take place to give either a six-membered intermediate **347**, reductively eliminating cyclopentanone **348** (**Scheme 4.31 (a)**), or a five-membered rhodacycle **349** and subsequent reductive elimination to give more strained cyclobutanone **350** (**Scheme 4.31 (b)**).



Scheme 4.31: (a) and (b): Two possible routes of C–C activation for ketone **346**.

Unfortunately, exposing this substrate to the selection of conditions in **Table 4.18** did not lead to any observation of either product **348** or **350**. In most cases, starting material was returned, however under certain conditions some observable decomposition occurred (**Table 4.18**, entries **2**, **3** and **4**). Attempts to increase the reactivity of catalyst Cp*Rh(cod) **315**, by hydrogenating the catalyst solution to remove the cyclooctadiene group prior to addition of the ketone, also failed (**Table 4.18**, entry **10**). Due to time constraints, investigations of other alkenes and substrate arrangements did not take place.

Table 4.18: Screening of conditions for C–C Activation of Ketone **346**.



Entry	Catalyst	Solvent	Products[b]
1	$[Rh(cod)_2]OTf$	PhMe	SM
2	$[Rh(cod)_2]OTf$	1,2-DCE	CM
3	$[RhCl(C_2H_4)_2]_2$	PhMe	SM + CM
4	$[RhCl(C_2H_4)_2]_2$	1,2-DCE	SM + CM
5	$Rh(PPh_3)_3Cl$	PhMe	SM
6	$Rh(PPh_3)_3Cl$	1,2-DCE	SM
7	$[Rh(nbd)_2]BF_4$/dcpm	PhMe	SM
8	$[Rh(nbd)_2]BF_4$/dcpm	1,2-DCE	SM
9	Cp*Rh(cod) **315**	Cyclohexane	SM
10	Cp*Rh(cod) **315**/H_2[a]	Cyclohexane	SM

Conditions: **346** (0.15 mmol, 1.0 equiv.), Rh catalyst (10 mol%), solvent (1.0 M with respect to the ketone), 24 h. [a]The catalyst was hydrogenated in solution for 1 h, in an attempt to remove the 'cod' group. [b]Determined by ^{1}H NMR spectroscopy of crude reaction mixtures. SM = starting material, CM = complex mixture.

4.5 Summary

In this chapter, a variety of attempts have been made to increase the substrate scope of rhodium-catalysed C–C activation achieved *via* chelation control. This has been investigated by using existing knowledge of rhodium-catalysed C–H activation to broaden the array of chelating groups that can be used. The first class examined was sulfur-based, and in particular the methylthiomethyl (MTM) group which proved to be relatively labile under the conditions tested, failing to generate any desired product. The second class employed nitrogen atoms from either an aniline moiety or a pyridine group, however, once again no success was found here, despite the various substrate alterations made in efforts to lower the kinetic barrier to activation. Finally, alkene tethers were briefly examined in an attempted intramolecular process, yet unfortunately the conditions screened did not lead to an appropriate transformation.

The problems encountered throughout these investigations clearly highlight the issues faced in the field of C–C activation as a whole. Despite the failure of the experiments conducted here, such attempts merely constitute a minor subsection of an otherwise vast array of possibilities that are yet to be explored. Considering the synthetic potential of this field, continuation of its development will undoubtedly prove to be a most rewarding venture.

Chapter 5

Conclusions and Future Work

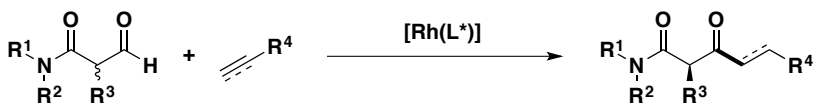
The work presented in this thesis has disclosed the plausibility of several new concepts regarding chelation-control in rhodium(I)-catalysed C–H and C–C bond activations. These concepts were analysed in order to improve the synthetic utility and generality of such bond activations, with the aim of creating novel routes to biologically relevant motifs. From the investigations conducted, the following can be concluded:

a) Amides and ketones as aldehyde tethers in rhodium(I)-catalysed hydroacylation

An efficient methodology involving the use of *β*-amido aldehydes as substrates in rhodium(I)-catalysed hydroacylation has been developed. These aldehydes can be coupled with a variety of alkynes, achieving excellent yields and regioselectivities with terminal alkynes using the ligands dcpe or AmpaPhos for the linear or branched isomers, respectively, and DPEPhos with internal alkynes. Traditionally challenging coupling partners such as terminal alkenes have also been demonstrated to react efficiently with *α*-disubstituted *β*-amido aldehydes using a preformed rhodium(I) catalyst containing dcpm. Preliminary investigations using 1,4-dicarbonyl systems with amides have exhibited promising levels of reactivity, further expanding the substrate scope of chelation-controlled hydroacylation. The

use of *β*-formyl ketones has also led to a highly efficient coupling reaction with terminal alkynes, with the current limitation in place for *α*-disubstituted substrates to prevent enolisation of the aldehyde group. Investigations using 1,5-dicarbonyl systems and *N*-formyl amides did not lead to any observed reactivity.

Given the potential for stereochemistry retention within these reactions, as demonstrated by the synthesis of enone **153** (**Scheme 2.23**), future work should explore the possibility of developing an asymmetric approach involving these substrates. One such approach might include a dynamic kinetic resolution of racemic *β*-amido aldehydes with a chiral catalyst to generate enantiopure enones (**Scheme 5.1**). The utility of such a procedure could be highly attractive in the synthesis of natural products.



Scheme 5.1: Possible dynamic kinetic resolution of racemic β-amido aldehydes with a chiral rhodium catalyst.

b) Esters as aldehyde tethers in rhodium(I)-catalysed hydroacylation

The use of esters as chelating groups in hydroacylation proved to be much less efficient in our preliminary investigations. As with ketones, reactivity is only observed using *α*-disubstituted substrates, however, this reactivity is often poor with limited conversions even under relatively forcing conditions. Whilst future work should include attempts to improve upon these results, *β*-formyl carboxylic acids or carboxylates (**Figure 5.1**) could be investigated as substitutes. The potentially facile removal of the tether *via* decarboxylation following hydroacylation could result in a traceless-tethered process, thus broadening its

synthetic utility even further.

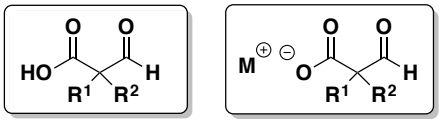


Figure 5.1: *β*-Formyl carboxylic acids and carboxylates to be investigated as potential hydroacylation substrates.

c) New tethers in rhodium(I)-catalysed C–C bond activation

The use of the methylthiomethyl (MTM)- group, alkenes, or anilines as tethers failed to facilitate any carboacylation or analogous C–C bond activation processes in the substrates tested, despite their relative successes as tethers in hydroacylation. These results highlight the kinetic and thermodynamic challenges involved in developing such a methodology and will require more advanced investigations. Given the establishment of amides and ketones as effective chelating groups in hydroacylation in this thesis, future work should explore using such tethers in a carboacylation process, paying careful attention to substrate design and the conditions tested.

Overall, this thesis exemplifies the powerful transformations that can be undertaken involving C–H and C–C bond activation, whilst accentuating the theoretical and practical challenges for each. The continuing development of these fields should prove to be highly stimulating.

Chapter 6

Experimental Data and Procedures

6.1 General Considerations

Reactions were conducted under an inert atmosphere of nitrogen gas, which was passed through a Drierite® and silica filled drying tube before use. Unless otherwise stated, all reactions used dry solvents collected fresh from an in-house solvent purification system, which involved passing the solvent through anhydrous alumina columns using an Innovative Technology Inc. PS-400-7 solvent purification system. Glassware was oven-dried (>100 °C), and allowed to cool to room temperature before use using a positive nitrogen pressure. 'Petrol' refers to the fraction of light petroleum ether, boiling in the range of 40-60 °C. Acetone, for use in rhodium reactions, was purchased from Sigma-Aldrich (HPLC grade), distilled over Drierite® and degassed prior to use. 1,2-DCE was distilled over CaH_2 and degassed prior to use. Reagents were purchased from Sigma-Aldrich Chemical Co. Ltd., Acros Organics Ltd., Alfa Aesar, Strem Chemicals Inc., or Fluorochem Ltd., and used as supplied.

Reactions were monitored by thin layer chromatography (TLC) using pre-coated aluminium backed silica plates (Merck Kieselgel 60 F254). Plates were visualised under ultraviolet light

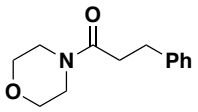
(254 nm) followed by staining with potassium permanganate. Flash column chromatography was carried out using Apollo scientific silica gel 60 (particle size 0.040- 0.063 nm) with the indicated eluents.

^{1}H, ^{13}C, and ^{19}F NMR spectra were obtained on a Bruker AVIIIHD 400 NanoBay (400 MHz) spectrometer, using the residual solvent as an internal standard, and at an ambient temperature unless otherwise stated. Assignments were made on the basis of chemical shifts, coupling constants, COSY, HSQC, and DEPT data and comparison with spectra of related compounds. Chemical shifts (δ) are reported in parts per million (ppm) with the multiplicities of the spectra reported as following: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; app, apparent. Coupling constants (*J*) are given in Hertz (Hz) and reported to the nearest 0.5 Hz.

Low-resolution ESI mass spectra were recorded on a Waters LCT Premier spectrometer. High-resolution ESI mass spectrometry measurements were recorded on a Bruker Daltronics microTOF (ESI^{+}) spectrometer or Micromass LCT under the conditions of chemical ionisation (CI) by the internal service at the Department of Organic Chemistry, University of Oxford. Values quoted are a ratio of mass to charge in Daltons and relative intensities of peaks observed are quoted as a percentage. Infra-red spectra were recorded as thin films on a Bruker Tensor 27 FTIR spectrometer. Melting points were determined using a Stuart Scientific Melting Point Apparatus SMP1.

6.2 Chapter 2 Experimental

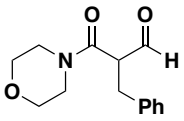
General procedure A for the preparation of amides from carboxylic acids, as exemplified by the synthesis of 1-morpholino-3-phenylpropan-1-one, 68a



To a round bottomed flask containing hydrocinnamic acid (4.50 g, 30.0 mmol) in CH_2Cl_2 (150 mL) was added morpholine (2.90 mL, 33.0 mmol) and EDCI.HCl (6.30 g, 33.0 mmol). The reaction mixture was left to stir for 1 h, followed by quenching with sat. aq. $NaHCO_3$ solution (100 mL). The layers were separated and the organic layer was washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica (eluent 30% Et_2O/petrol) to give the amide **68a** (6.05 g, 92%) as a colourless oil.

δ_H ($CDCl_3$, 400 MHz) 7.31–7.25 (2H, m, 2 × Ar*H*), 7.23–7.17 (3H, m, 3 × Ar*H*), 3.60 (4H, br. s, 2 × OC*H*$_2$CH$_2$N), 3.52–3.45 (2H, m, OCH$_2$C*H*$_2$N), 3.36–3.30 (2H, m, OCH$_2$C*H*$_2$N), 2.97 (2H, t, *J* 7.0. C(O)C*H*$_2$CH$_2$Ph), 2.60 (2H, t, *J* 7.0. C(O)CH$_2$C*H*$_2$Ph); δ_C ($CDCl_3$, 101 MHz) 170.8, 141.1, 128.5(2), 128.4(6), 126.3, 66.8, 66.4, 45.9, 41.9, 34.8, 31.5; *m/z* (ESI$^+$) 242 ([M + Na]$^+$, 100%). Data is consistent with the literature.[256]

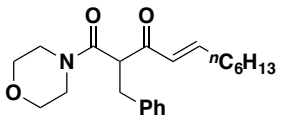
General procedure B for the preparation of *β*-formyl amides, as exemplified by the synthesis of 2-benzyl-3-morpholino-3-oxopropanal, 69a



Following the procedure by Johnson *et al*.,[4-65] a round bottomed flask containing distilled diisopropylamine (4.2 mL, 30 mmol) in Et_2O (30 mL) was cooled to –78 °C. *n*-BuLi (2.5 M, 12 mL, 30 mmol) was then added dropwise and the mixture was left to stir for 5 minutes. 1-Morpholino-3-phenylpropan-1-one **68a** (2.2 g, 10 mmol) was subsequently added dropwise and the reaction mixture was warmed up to 0 °C and stirred for 1 h. The mixture was then cooled to –78 °C followed by dropwise addition of methyl formate (6.17 mL, 100 mmol). The solution was warmed to room temperature and left to stir for 16 h, followed by careful quenching with 1 N HCl (20 mL) and dilution with CH_2Cl_2 (30 mL). The layers were separated and the aqueous layer was further extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica (eluent 30% acetone/petrol) to give the aldehyde **69a** (1.75 g, 71%) as a pale yellow oil.

δ_H ($CDCl_3$, 400 MHz) 9.72 (1H, d, *J* 2.5, C*H*O), 7.34–7.29 (2H, m, 2 × Ar*H*), 7.28–7.24 (1H, m, 1 × Ar*H*), 7.24–7.19 (2H, m, 2 × Ar*H*), 3.79–3.58 (3H, m, C*H*CH_2Ph, OC$H_A$$H_B$$CH_2N, OCH_2CH_A$$H_B$N), 3.53–3.38 (3H, m, OC$H_2$$CH_2$N, $OCH_2CH_A$$H_B$N), 3.32–3.20 (3H, m, OCH_2C$H_A$$H_BN, CHCH_2$Ph), 2.99 (1H, m, $OCH_2CH_A$$H_B$N), 2.94–2.88 (1H, m, $OCH_A$$H_B$$CH_2$N); δ_C ($CDCl_3$, 101 MHz) 198.3, 167.1, 137.4, 129.1, 128.9, 127.1, 66.6, 66.1, 56.6, 46.2, 42.2, 34.5; *m/z* (ESI^+) 302 ([M + Na + MeOH]$^+$, 50%), 581 ([2M + Na + MeOH]$^+$, 100%). Data is consistent with the literature.[158]

General procedure C for the hydroacylation of aldehydes using an *in-situ* generated catalyst, as exemplified by the synthesis of (*E*)-2-benzyl-1-morpholinoundec-4-ene-1,3-dione, 70a

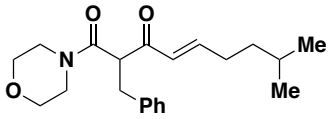


$Rh(nbd)_2BF_4$ (5.6 mg, 15 μmol) and dcpe (6.3 mg, 15 μmol) were dissolved in acetone (0.3 mL) under a N_2 atmosphere. H_2 was bubbled through the red solution for 2 min at room temperature, until a light orange colour was observed. Following this, the solution was purged with N_2 until the solvent was evaporated. The resulting catalyst solution was dissolved again in acetone (0.3 mL) and transferred to a flask containing 2-benzyl-3-morpholino-3-oxopropanal **69a** (74 mg, 0.30 mmol) and 1-octyne (54 μL, 0.36 mmol) under N_2. The reaction mixture was then heated to 55 °C for 1 hour and then allowed to cool to room temperature. The reaction was then filtered through a plug of silica and concentrated *in vacuo* to obtain the crude product. The crude product was purified by flash chromatography on silica (eluent 50% EtOAc/petrol) to give the *enone* **70a** (96 mg, 90%) as a pale yellow oil.

δ_H ($CDCl_3$, 400 MHz) 7.23–7.16 (2H, m, 2 × Ar*H*), 7.16–7.08 (3H, m, 3 × Ar*H*), 6.85 (1H, dt, *J* 15.5, 7.0, C(O)CH=C*H*CH_2), 6.19 (1H, dt, *J* 15.5, 1.5, C(O)C*H*=CHCH_2), 3.88 (1H, dd, *J* 8.5, 6.0, C*H*CH_2Ph), 3.55–3.40 (4H, m, OC*H*$_2$$CH_2N, OCH_2$C*H*$_2$N), 3.39–3.20 (2H, m, OC*H*$_A$H$_B$$CH_2N, OCH_2$C*H*$_AH_B$N), 3.25 (1H, dd, *J* 11.0, 8.5, CHC*H*$_A$H$_B$Ph), 3.17–3.04 (3H, m, OCH$_A$*H*$_B$$CH_2N, OCH_2CH_A$*H*$_B$N, CHCH$_A$*H*$_B$Ph), 2.17–2.08 (2H, m, CHC*H*$_2$$CH_2$($CH_2$)$_3$$CH_3$), 1.42–1.30 (2H, m, CHCH$_2$C*H*$_2$(CH_2)$_3$$CH_3$), 1.28–1.13 (6H, m, CH($CH_2$)$_2$(C*H*$_2$)$_3$$CH_3$), 0.81 (3H, t, *J* 7.5, CH_2C*H*$_3$); δ_C ($CDCl_3$, 101 MHz) 194.5, 167.4,

150.0, 138.6, 129.0, 128.6, 126.7, 126.6, 66.7, 66.3, 57.4, 46.3, 42.6, 35.1, 32.6, 31.6, 28.9, 28.0, 22.6, 14.1; ν_{max} (neat)/cm^{-1} 2958, 2926, 2855, 1682, 1627, 1432, 1230, 1114, 700; *m/z* (ESI$^+$) 358 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{22}H_{32}O_3N^+$ ([M + H]$^+$) requires 358.23767, found 358.23107.

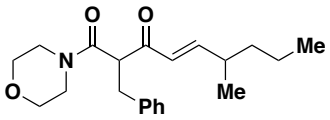
(*E*)-2-Benzyl-8-methyl-1-morpholinonon-4-ene-1,3-dione, 71



Synthesised according to the general procedure **C**, using 2-benzyl-3-morpholino-3-oxopropanal **69a** (62 mg, 0.25 mmol), 5-methyl-1-hexyne (40 μL, 0.30 mmol), [Rh(nbd)$_2$]BF$_4$ (4.7 mg, 5 mol%) and dcpe (5.3 mg, 5 mol%) in acetone (0.25 mL, 1.0 M). The crude product was purified by flash chromatography on silica (eluent 50% EtOAc/petrol) to give the *enone* **71** (83 mg, 97%) as a colourless oil.

δ_H ($CDCl_3$, 400 MHz) 7.23–7.16 (2H, m, 2 × Ar*H*), 7.16–7.08 (3H, m, 3 × Ar*H*), 6.86 (1H, dt, *J* 15.5, 7.0, C(O)CH=C*H*CH$_2$), 6.20 (1H, dt, *J* 15.5, 1.5, C(O)C*H*=CHCH$_2$), 3.87 (1H, dd, *J* 8.5, 6.0, C*H*CH$_2$Ph), 3.56–3.41 (4H, m, OC*H*$_2$CH$_2$N, OCH$_2$C*H*$_2$N), 3.38–3.21 (3H, m, OC*H*$_A$H$_B$CH$_2$N, OCH$_2$C*H*$_A$H$_B$N, CHC*H*$_A$H$_B$Ph), 3.17–3.04 (3H, m, OCH$_A$*H*$_B$CH$_2$N, OCH$_2$CH$_A$*H*$_B$N, CHCH$_A$*H*$_B$Ph), 2.19–2.08 (2H, m, CHC*H*$_2$CH$_2$CH(CH$_3$)$_2$), 1.47 (1H, m, CHCH$_2$CH$_2$C*H*(CH$_3$)$_2$), 1.31–1.19 (2H, m, CHCH$_2$C*H*$_2$CH(CH$_3$)$_2$), 0.82 (6H, d, *J* 6.5, CHCH$_2$CH$_2$CH(C*H*$_3$)$_2$); δ_C ($CDCl_3$, 101 MHz) 194.4, 167.4, 150.1, 138.6, 129.0, 128.6, 126.7, 126.4, 66.7, 66.3, 57.4, 46.3, 42.6, 37.0, 35.1, 30.5, 27.6, 22.4; ν_{max} (neat)/cm^{-1} 2957, 2865, 1682, 1628, 1432, 1230, 730, 700; *m/z* (ESI$^+$) 344 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{21}H_{30}O_3N^+$ ([M + H]$^+$) requires 344.22202, found 344.22209.

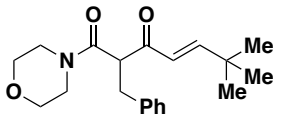
(*E*)-2-Benzyl-6-methyl-1-morpholinonon-4-ene-1,3-dione, 72



Synthesised according to the general procedure **C**, using 2-benzyl-3-morpholino-3-oxopropanal **69a** (62 mg, 0.25 mmol), 3-methylhex-1-yne (40 μL, 0.30 mmol), $[Rh(nbd)_2]BF_4$ (4.7 mg, 5 mol%) and dcpe (5.3 mg, 5 mol%) in acetone (0.25 mL, 1.0 M). The crude product was purified by flash chromatography on silica (eluent 50% EtOAc/petrol) to give the *enone* **72** (76 mg, 88%) as a colourless oil. **72** exists as an inseparable 1:1 mixture of diastereomers.

δ_H ($CDCl_3$, 400 MHz) 7.23–7.17 (2H, m, 2 × Ar*H*), 7.17–7.09 (3H, m, 3 × Ar*H*), 6.73 (1H, dd, *J* 15.0, 8.0, C(O)CH=C*H*), 6.69* (1H, dd, *J* 15.0, 8.0, C(O)C*H*=CH), 6.16 (1H, dd, *J* 15.0, 1.5, C(O)CH=C*H*), 6.12* (1H, dd, *J* 15.0, 1.5, C(O)CH=C*H*), 3.90 (1H, dd, *J* 8.0, 6.0, C*H*CH_2Ph), 3.89* (1H, dd, *J* 8.0, 6.0, C*H*CH_2Ph), 3.55–3.41 (4H, m, OCH_2CH_2N, OCH_2CH_2N), 3.39–3.23 (3H, m, OC$H_AH_BCH_2$N, $OCH_2CH_AH_B$N, CHCH_AH_BPh), 3.18–3.04 (3H, m, $OCH_AH_BCH_2$N, $OCH_2CH_AH_B$N, $CHCH_AH_B$Ph), 2.29–2.18 (1H, m, C*H*$(CH_3)(CH_2)_2CH_3$), 1.31–1.13 (4H, m, $CH(CH_3)(CH_2)_2CH_3$), 0.95 (3H, d, *J* 6.5, $CH(CH_3)(CH_2)_2CH_3$), 0.94* (3H, d, *J* 6.5, $CH(CH_3)(CH_2)_2CH_3$), 0.86–0.77 (3H, m, $CH(CH_3)(CH_2)_2CH_3$); δ_C ($CDCl_3$, 101 MHz) (* denotes second diastereomer) 194.8, 167.4(3), 167.4(0)*, 155.0, 138.6(0), 138.5(6)*, 129.0, 128.6, 126.7, 125.0, 124.9*, 66.7, 66.3, 57.4, 57.3*, 46.2, 42.6, 38.1(8), 38.1(6)*, 36.6(5), 36.6(1)*, 35.1, 20.4, 20.3*, 19.4(1), 19.3(5)*, 14.0; ν_{max} (neat)/cm^{-1} 2959, 2859, 1652, 1627, 1454, 1183, 701; *m/z* (ESI^+) 344 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{21}H_{30}O_3N^+$ ($[M + H]^+$) requires 344.22202, found 344.22210.

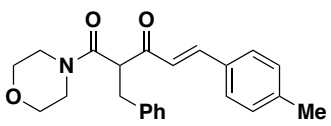
(*E*)-2-Benzyl-6,6-dimethyl-1-morpholinohept-4-ene-1,3-dione, 73



Synthesised according to the general procedure **C**, using 2-benzyl-3-morpholino-3-oxopropanal **69a** (74 mg, 0.30 mmol), 3,3-dimethyl-1-butyne (44 μL, 0.36 mmol), $[Rh(nbd)_2]BF_4$ (5.6 mg, 5 mol%) and dcpe (6.3 mg, 5 mol%) in acetone (0.3 mL, 1.0 M). The crude product was purified by flash chromatography on silica (eluent 50% EtOAc/petrol) to give the *enone* **73** (78 mg, 94%) as a colourless oil.

δ_H ($CDCl_3$, 400 MHz) 7.23–7.17 (2H, m, 2 × Ar*H*), 7.17–7.09 (3H, m, 3 × Ar*H*), 6.80 (1H, d, *J* 16.0, C(O)CH=C*H*), 6.07 (1H, d, *J* 16.0, C(O)C*H*=CH), 3.91 (1H, dd, *J* 8.5, 6.0, C*H*CH_2Ph), 3.55–3.42 (4H, m, OC*H*$_2$$CH_2N, OCH_2C*H*_2$N), 3.40–3.21 (3H, m, OC*H*$_A$$H_B$$CH_2N, OCH_2C*H*_A$$H_B$N, CHC*H*$_A$$H_B$Ph), 3.16–3.04 (3H, m, OCH_A*H*$_B$$CH_2N, OCH_2CH_A*H*_B$N, $CHCH_A$*H*$_B$Ph), 0.99 (9H, s, C(C*H*$_3$)$_3$); δ_C ($CDCl_3$, 101 MHz) 195.1, 167.5, 159.1, 138.6, 129.1, 128.6, 126.7, 122.0, 66.7, 66.3, 57.3, 46.3, 42.6, 35.1, 34.0, 28.6; ν_{max} (neat)/cm^{-1} 2956, 2860, 1682, 1627, 1432, 1114, 701; *m/z* (ESI^+) 330 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{20}H_{28}O_3N^+$ ($[M + H]^+$) requires 330.20637, found 330.20584.

(*E*)-2-Benzyl-1-morpholino-5-(*p*-tolyl)pent-4-ene-1,3-dione, 74

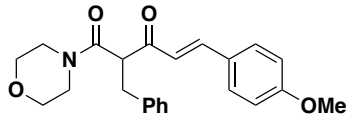


Synthesised according to the general procedure **C**, using 2-benzyl-3-morpholino-3-oxopropanal **69a** (62 mg, 0.25 mmol), 4-ethynyltoluene (38 μL, 0.30 mmol), $[Rh(nbd)_2]BF_4$ (4.7 mg, 5 mol%) and dcpe (5.3 mg, 5 mol%) in acetone (0.25 mL, 1.0 M). The crude product

was purified by flash chromatography on silica (eluent 50% EtOAc/petrol) to give the *enone* **74** (81 mg, 89%) as an off white crystalline solid.

δ_H ($CDCl_3$, 400 MHz) 7.55 (1H, d, *J* 15.5, C(O)CH=C*H*Ar), 7.36 (2H, d, *J* 8.0, 2 × Ar*H*), 7.24–7.04 (7H, m, 7 × Ar*H*), 6.80 (1H, d, *J* 15.5, C(O)C*H*=CHAr), 3.95 (1H, dd, *J* 8.5, 6.0, C*H*CH_2Ph), 3.60–3.43 (4H, m, OC*H*$_2$$CH_2N, OCH_2C*H*_2$N), 3.41–3.29 (3H, m, OC*H*$_A$$H_B$$CH_2N, OCH_2C*H*_A$$H_B$N, CHC*H*$_A$$H_B$Ph), 3.25–3.10 (3H, m, OCH_A*H*$_B$$CH_2N, OCH_2CH_A*H*_B$N, $CHCH_A$*H*$_B$Ph), 2.29 (3H, s, ArC*H*$_3$); δ_C ($CDCl_3$, 101 MHz) 194.6, 167.4, 144.7, 141.6, 138.6, 131.4, 129.7, 129.1, 128.7, 128.6, 126.8, 121.2, 66.8, 66.4, 58.3, 46.3, 42.7, 35.3, 21.6; mp: 137–139 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 2979, 2919, 2857, 1630, 1599, 1432, 1112, 751, 729; *m/z* (ESI^+) 358 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{23}H_{26}O_3N^+$ ($[M + H]^+$) requires 364.19072, found 364.19073.

(*E*)-2-Benzyl-5-(4-methoxyphenyl)-1-morpholinopent-4-ene-1,3-dione, 75

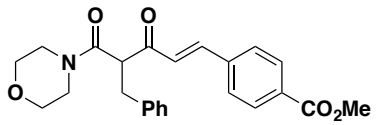


Synthesised according to the general procedure **C**, using 2-benzyl-3-morpholino-3-oxopropanal **69a** (62 mg, 0.25 mmol), 4-ethynylanisole (39 μL, 0.30 mmol), $[Rh(nbd)_2]BF_4$ (4.7 mg, 5 mol%) and dcpe (5.3 mg, 5 mol%) in acetone (0.25 mL, 1.0 M). The crude product was purified by flash chromatography on silica (eluent 50% EtOAc/petrol) to give the *enone* **75** (83 mg, 89%) as a yellow oil.

δ_H ($CDCl_3$, 400 MHz) 7.55 (1H, d, *J* 15.5, C(O)CH=C*H*Ar), 7.47–7.39 (2H, m, 2 × Ar*H*), 7.22–7.10 (5H, m, 5 × Ar*H*), 6.85–6.79 (2H, m, 2 × Ar*H*), 6.72 (1H, d, *J* 15.5, C(O)C*H*=CHAr), 3.94 (1H, dd, *J* 8.5, 6.0, C*H*CH_2Ph), 3.75 (3H, s, ArOC*H*$_3$), 3.59–3.43

(4H, m, OCH_2CH$_2$N, OCH$_2$CH_2N), 3.42–3.30 (3H, m, OCH_AH$_B$CH$_2$N, OCH$_2$CH_AH$_B$N, CHCH_AH$_B$Ph), 3.24–3.09 (3H, m, OCH$_A$$H_BCH_2N, OCH_2CH_A$$H_B$N, CHCH$_A$$H_B$Ph); δ_C ($CDCl_3$, 101 MHz) 194.6, 167.4, 144.7, 141.6, 138.6, 131.4, 129.7, 129.1, 128.8, 128.6, 126.8, 121.2, 66.8, 66.4, 58.3, 46.3, 42.7, 35.3, 21.6; ν_{max} (neat)/cm^{-1} 2979, 2859, 1633, 1593, 1571, 1288, 1112, 730; *m/z* (ESI$^+$) 380 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{23}H_{26}O_4N^+$ ([M + H]$^+$) requires 380.18563, found 380.18544.

Methyl (*E*)-4-(4-benzyl-5-morpholino-3,5-dioxopent-1-en-1-yl)benzoate, 76

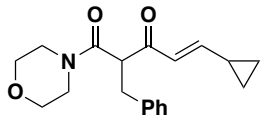


Synthesised according to the general procedure **C**, using 2-benzyl-3-morpholino-3-oxopropanal **69a** (62 mg, 0.25 mmol), methyl-4-ethynylbenzoate (480 mg, 0.30 mmol), [Rh(nbd)$_2$]BF$_4$ (4.7 mg, 5 mol%) and dcpe (5.3 mg, 5 mol%) in acetone (0.25 mL, 1.0 M). The crude product was purified by flash chromatography on silica (eluent 50% EtOAc/petrol) to give the *enone* **76** (79 mg, 77%) as an off-white crystalline solid.

δ_H ($CDCl_3$, 400 MHz) 8.00–7.94 (2H, m, 2 × Ar*H*), 7.57 (1H d, *J* 16.0, C(O)CH=C*H*Ar), 7.52 (2H, d, *J* 8.5, 2 × Ar*H*), 7.23–7.18 (2H, m, 2 × Ar*H*), 7.17–7.11 (3H, m, 3 × Ar*H*), 6.92 (1H, d, *J* 16.0, C(O)C*H*=CHAr), 3.99 (1H, dd, *J* 8.5, 6.0, C*H*CH$_2$Ph), 3.84 (3H, s, ArCO$_2$CH_3), 3.56–3.42 (4H, m, OCH_2CH$_2$N, OCH$_2$CH_2N), 3.41–3.28 (3H, m, OCH_AH$_B$CH$_2$N, OCH$_2$CH_AH$_B$N, CHCH_AH$_B$Ph), 3.24–3.09 (3H, m, OCH$_A$$H_BCH_2N, OCH_2CH_A$$H_B$N, CHCH$_A$$H_B$Ph); δ_C ($CDCl_3$, 101 MHz) 194.3, 167.2, 166.3, 142.9, 138.3, 138.2, 131.8, 130.1, 129.0, 128.7, 128.5, 126.9, 124.2, 66.7, 66.3, 58.2, 52.3, 46.4, 42.7, 35.2; mp: 144–146 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 2919, 2855, 1718, 1678, 1434, 1276, 1110,

733; *m/z* (ESI$^+$) 408 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{24}H_{26}O_5N^+$ ([M + H]$^+$) requires 408.18055, found 408.18036.

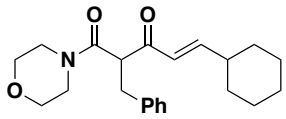
(*E*)-2-Benzyl-5-cyclopropyl-1-morpholinopent-4-ene-1,3-dione, 77



Synthesised according to the general procedure **C**, using 2-benzyl-3-morpholino-3-oxopropanal **69a** (62 mg, 0.25 mmol), cyclopropylacetylene (25 μL, 0.30 mmol), $[Rh(nbd)_2]BF_4$ (4.7 mg, 5 mol%) and dcpe (5.3 mg, 5 mol%) in acetone (0.25 mL, 1.0 M). The crude product was purified by flash chromatography on silica (eluent 50% EtOAc/petrol) to give the *enone* **77** (63 mg, 81%) as a colourless oil.

δ_H ($CDCl_3$, 400 MHz) 7.23–7.16 (2H, m, 2 × Ar*H*), 7.16–7.09 (3H, m, 3 × Ar*H*), 6.37–6.31 (2H, m, C(O)CH=C*H*CH, C(O)C*H*=CHCH), 3.81 (1H, dd, *J* 8.5, 6.0, C*H*CH_2Ph), 3.57–3.41 (4H, m, OC$H_2$$CH_2$N, OCH_2CH_2N), 3.40–3.23 (3H, m, OC$H_A$$H_B$$CH_2N, OCH_2CH_A$$H_BN, CHCH_A$$H_B$Ph), 3.20–3.02 (3H, m, $OCH_A$$H_B$$CH_2$N, $OCH_2CH_A$$H_B$N, $CHCH_A$$H_B$Ph), 1.58–1.46 (1H, m, C*H*$(CH_2)_2$), 0.98–0.89 (2H, m, CH(CH_2)$_A$$(CH_2)_B$), 0.64–0.56 (2H, m, CH$(CH_2)_A$(C$H_2$)$_B$); δ_C ($CDCl_3$, 101 MHz) 193.6, 167.5, 155.5, 138.7, 129.0, 128.6, 126.7, 123.2, 66.7, 66.3, 57.8, 46.3, 42.6, 35.1, 15.3, 9.5; ν_{max} (neat)/cm^{-1} 2921, 2857, 1632, 1453, 1270, 1173, 752; *m/z* (ESI$^+$) 314 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{19}H_{24}O_3N^+$ ([M + H]$^+$) requires 314.17507, found 314.17490.

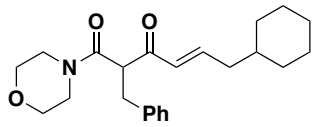
(*E*)-2-Benzyl-5-cyclohexyl-1-morpholinopent-4-ene-1,3-dione, 78



Synthesised according to the general procedure **C**, using 2-benzyl-3-morpholino-3-oxopropanal **69a** (62 mg, 0.25 mmol), cyclohexylacetylene (39 μL, 0.30 mmol), $[Rh(nbd)_2]BF_4$ (4.7 mg, 5 mol%) and dcpe (5.3 mg, 5 mol%) in acetone (0.25 mL, 1.0 M). The crude product was purified by flash chromatography on silica (eluent 50% EtOAc/petrol) to give the *enone* **78** (79 mg, 89%) as a colourless oil.

δ_H ($CDCl_3$, 400 MHz) 7.24– 7.16 (2H, m, 2 × Ar*H*), 7.16–7.08 (3H, m, 3 × Ar*H*), 6.77 (1H, dt, *J* 15.5, 7.0, C(O)CH=C*H*CH), 6.14 (1H, dt, *J* 15.5, 1.5, C(O)C*H*=CHCH), 3.89 (1H, dd, *J* 8.5, 6.0, C*H*CH_2Ph), 3.55–3.41 (4H, m, OCH_2CH_2N, OCH_2CH_2N), 3.39–3.21 (3H, m, O$CH_AH_BCH_2$N, $OCH_2CH_AH_BN$, $CHCH_AH_B$Ph), 3.16–3.03 (3H, m, $OCH_AH_BCH_2$N, $OCH_2CH_AH_BN$, $CHCH_AH_B$Ph), 2.13–2.01 (1H, m, C*H*$(CH_2)_5$), 1.72–1.56 (5H, m, 2.5 × CH_2), 1.28– 1.01 (5H, m, 2.5 × CH_2); δ_C ($CDCl_3$, 101 MHz) 194.9, 167.5, 154.5, 138.6, 129.0, 128.6, 126.7, 124.3, 66.7, 66.3, 57.3, 46.3, 42.6, 40.7, 35.1, 31.7, 25.8, 25.6; ν_{max} (neat)/cm^{-1} 2924, 2852, 1681, 1628, 1445, 1274, 1114, 752; *m/z* (ESI^+) 356 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{22}H_{30}O_3N^+$ ($[M + H]^+$) requires 356.22202, found 356.22205.

(*E*)-2-Benzyl-6-cyclohexyl-1-morpholinohex-4-ene-1,3-dione, 79

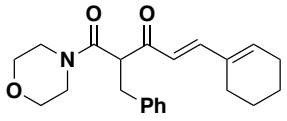


Synthesised according to the general procedure **C**, using 2-benzyl-3-morpholino-3-oxopropanal **69a** (62 mg, 0.25 mmol), 3-cyclohexyl-1-propyne (44 μL, 0.30 mmol),

$[Rh(nbd)_2]BF_4$ (4.7 mg, 5 mol%) and dcpe (5.3 mg, 5 mol%) in acetone (0.25 mL, 1.0 M). The crude product was purified by flash chromatography on silica (eluent 50% EtOAc/petrol) to give the *enone* **79** (83 mg, 90%) as a colourless oil.

δ_H ($CDCl_3$, 400 MHz) 7.23–7.17 (2H, m, 2 × Ar*H*), 7.16–7.08 (3H, m, 3 × Ar*H*), 6.83 (1H, dt, *J* 15.5, 7.5, C(O)CH=C*H*CH_2), 6.17 (1H, dt, *J* 15.5, 1.5, C(O)C*H*=CHCH_2), 3.88 (1H, dd, *J* 8.5, 6.0, C*H*CH_2Ph), 3.54–3.41 (4H, m, OC$H_2$$CH_2$N, OCH_2CH_2N), 3.39–3.20 (3H, m, OC$H_A$$H_B$$CH_2N, OCH_2CH_A$$H_BN, CHCH_A$$H_B$Ph), 3.17–3.03 (3H, m, $OCH_A$$H_B$$CH_2$N, $OCH_2CH_A$$H_B$N, $CHCH_A$$H_B$Ph), 2.02 (2H, app. t, *J* 7.0, C$H_2$$CH(CH_2)_5$), 1.68–1.52 (5H, m, 2.5 × CH_2), 1.40–1.28 (1H, m, CH_2C*H*$(CH_2)_5$), 1.23–1.02 (3H, m, 1.5 × CH_2), 0.92–0.78 (2H, m, CH_2); δ_C ($CDCl_3$, 101 MHz) 194.3, 167.4, 148.7, 138.6, 129.0, 128.6, 127.7, 126.7, 66.7, 66.3, 57.3, 46.3, 42.6, 40.5, 37.4, 35.1, 33.1, 26.3, 26.2; ν_{max} (neat)/cm^{-1} 2921, 2857, 1681, 1627, 1454, 1114, 731, 701; *m/z* (ESI^+) 370 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{23}H_{32}O_3N^+$ ($[M + H]^+$) requires 370.23767, found 370.23747.

(*E*)-2-Benzyl-5-(cyclohex-1-en-1-yl)-1-morpholinopent-4-ene-1,3-dione, 80

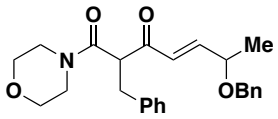


Synthesised according to the general procedure **C**, using 2-benzyl-3-morpholino-3-oxopropanal **69a** (62 mg, 0.25 mmol), 1-ethynylcyclohexene (35 μL, 0.30 mmol), $[Rh(nbd)_2]BF_4$ (4.7 mg, 5 mol%) and dcpe (5.3 mg, 5 mol%) in acetone (0.25 mL, 1.0 M). The crude product was purified by flash chromatography on silica (eluent 50% EtOAc/petrol) to give the *enone* **80** (84 mg, 95%) as a pale yellow oil.

δ_H ($CDCl_3$, 400 MHz) δ 7.23–7.08 (6H, m, 5 × Ar*H,* C(O)C*H*=CHC=CH), 6.22–6.09 (2H,

m, C(O)CH=C*H*C=CH, C(O)CH=CHC=C*H*), 3.90 (1H, dd, *J* 8.5, 6.0, C*H*CH_2Ph), 3.58–3.42 (4H, m, OC$H_2$$CH_2N, OCH_2CH_2$N), 3.41–3.24 (3H, m, OC$H_A$$H_B$$CH_2N, OCH_2CH_A$$H_BN, CHCH_A$$H_B$Ph), 3.22–3.12 (2H, m, OCH$_A$$H_B$$CH_2N, OCH_2CH_A$$H_B$N,), 3.07 (1H, dd, *J* 14.0, 6.0, CHCH$_A$$H_B$Ph), 2.19–2.10 (2H, m, CHCH_2), 2.09–2.02 (2H, m, CHCH_2), 1.67–1.49 (4H, m, 2 × CH_2); δ_C ($CDCl_3$, 101 MHz) 194.9, 167.5, 148.0, 141.8, 138.8, 135.3, 129.0, 128.6, 126.6, 119.2, 66.7, 66.3, 57.9, 46.2, 42.6, 35.2, 26.8, 24.2, 21.9 (2C); ν_{max} (neat)/cm^{-1} 2927, 2858, 1627, 1589, 1433, 1113, 731, 701; *m/z* (ESI$^+$) 354 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{22}H_{28}O_3N^+$ ([M + H]$^+$) requires 354.20637, found 354.20603.

(*E*)-2-Benzyl-6-(benzyloxy)-1-morpholinohept-4-ene-1,3-dione, 81

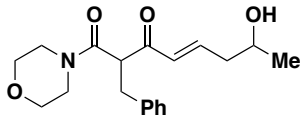


Synthesised according to the general procedure **C**, using 2-benzyl-3-morpholino-3-oxopropanal **69a** (62 mg, 0.25 mmol), [(but-3-yn-2-yloxy)methyl]benzene (48 mg, 0.30 mmol), $[Rh(nbd)_2]BF_4$ (4.7 mg, 5 mol%) and dcpe (5.3 mg, 5 mol%) in acetone (0.25 mL, 1.0 M). The crude product was purified by flash chromatography on silica (eluent 50% EtOAc/petrol) to give the *enone* **81** (88 mg, 87%) as a colourless oil. **81** exists as an inseparable 1:1 mixture of diastereomers.

δ_H ($CDCl_3$, 400 MHz) (* denotes second diastereomer) 7.30–7.16 (7H, m, 7 × Ar*H*), 7.16–7.08 (3H, m, 3 × Ar*H*), 6.75 (1H, dd, *J* 16.0, 8.0, C(O)CH=C*H*CH), 6.71* (1H, dd, *J* 16.0, 8.0, C(O)CH=C*H*CH), 6.36 (1H, dd, *J* 16.0, 1.5, C(O)C*H*=CHCH), 6.33* (1H, dd, *J* 16.0, 1.5, C(O)C*H*=CHCH), 4.42 (1H, app. d, *J* 12.0, OC$H_A$$H_B$Ph), 4.34 (1H, d, *J* 12.0, OCH$_A$$H_B$Ph), 4.33* (1H, d, *J* 12.0, OCH$_A$$H_B$Ph), 4.08–4.00 (1H, m, C*H*(CH_3)(OBn)), 3.92

(1H, dd, *J* 9.0, 6.0, C*H*CH_2Ph), 3.55–3.19 (7H, m, OC$H_2$$CH_2N, OCH_2CH_2N, OCH_A$$H_B$$CH_2N, OCH_2CH_A$$H_BN, CHCH_A$$H_B$Ph), 3.15–2.95 (3H, m, OC$H_A$$H_B$$CH_2N, OCH_2CH_A$$H_BN, CHCH_A$$H_B$Ph), 1.23 (3H, d, *J* 6.5, CH(CH_3)(OBn)), 1.22* (3H, d, *J* 6.5, CH(CH_3)(OBn)); δ_C ($CDCl_3$, 101 MHz) (* denotes second diastereomer) 194.4, 194.2*, 167.5, 167.3*, 149.0, 148.9*, 138.4, 138.0*, 129.1, 128.7, 128.5, 127.8, 127.7*, 127.5, 126.8, 126.0, 125.9, 74.0(5), 73.9(8)*, 70.9, 70.8*, 66.7, 66.2, 57.2, 57.0*, 46.4, 46.3*, 42.6, 42.5*, 35.1, 35.0*, 20.6(0), 20.5(6)*; ν_{max} (neat)/cm^{-1} 2972, 2858, 1687, 1630, 1453, 1113, 699; *m/z* (ESI^+) 408 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{25}H_{30}O_4N^+$ ($[M + H]^+$) requires 408.21693, found 408.21691.

(*E*)-2-Benzyl-7-hydroxy-1-morpholinooct-4-ene-1,3-dione, 82

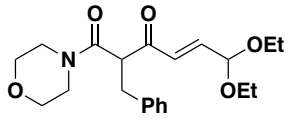


Synthesised according to the general procedure **C**, using 2-benzyl-3-morpholino-3-oxopropanal **69a** (62 mg, 0.25 mmol), 4-pentyn-2-ol (28 μL, 0.30 mmol), $[Rh(nbd)_2]BF_4$ (4.7 mg, 5 mol%) and dcpe (5.3 mg, 5 mol%) in acetone (0.25 mL, 1.0 M). The crude product was purified by flash chromatography on silica (eluent 50% EtOAc/petrol) to give the *enone* **82** (61.5 mg, 74%) as a colourless oil. **82** exists as an inseparable 1:1 mixture of diastereomers.

δ_H ($CDCl_3$, 400 MHz) (* denotes second diastereomer) 7.24–7.17 (2H, m, 2 × Ar*H*), 7.17–7.08 (3H, m, 3 × Ar*H*), 6.85 (1H, dt, *J* 15.5, 7.0, C(O)CH=C*H*CH_2), 6.23 (1H, d, *J* 15.5, C(O)C*H*=CHCH_2), 3.93 (1H, dd, *J* 9.0, 6.0, C*H*CH_2Ph), 3.86 (1H, app. sext, *J* 6.0, CH_2C*H*(OH)CH_3), 3.58–3.29 (6H, m, OC$H_2$$CH_2N, OCH_2CH_2N, OCH_A$$H_B$$CH_2$N,

$OCH_2CH_AH_BN$), 3.20 (1H, dd, *J* 14.0, 9.0, $CHCH_AH_BPh$), 3.14–2.96 (3H, m, $OCH_AH_BCH_2N$, $OCH_2CH_AH_BN$, $CHCH_AH_BPh$), 2.33–2.24 (3H, m, $CH_2CH(OH)CH_3$, $CH_2CH(OH)CH_3$), 1.14 (3H, d, *J* 6.0, $CH_2CH(OH)CH_3$), 1.13* (3H, d, *J* 6.0, $CH_2CH(OH)CH_3$); δ_C ($CDCl_3$, 101 MHz) (* denotes second diastereomer) 194.2, 167.6, 145.5, 138.4, 129.1, 128.6, 126.8, 66.6(2), 66.5(8)*, 66.5, 66.2, 56.8, 46.3, 42.5, 42.1, 42.0*, 35.0, 23.4, 15.3; ν_{max} (neat)/cm^{-1} 3430, 2969, 2861, 1679, 1621, 1441, 1113, 702; *m/z* (ESI^+) 332 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{19}H_{26}O_4N^+$ ($[M + H]^+$) requires 332.18503, found 332.18602.

(*E*)-2-Benzyl-6,6-diethoxy-1-morpholinohex-4-ene-1,3-dione, 83

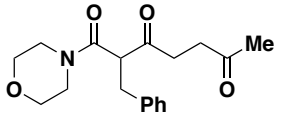


Synthesised according to the general procedure **C**, using 2-benzyl-3-morpholino-3-oxopropanal **69a** (74 mg, 0.30 mmol), 3,3-diethoxyprop-1-yne (46 mg, 0.30 mmol), $[Rh(nbd)_2]BF_4$ (5.6 mg, 5 mol%) and dcpe (6.3 mg, 5 mol%) in acetone (0.3 mL, 1.0 M). The crude product was purified by flash chromatography on silica (eluent 50% EtOAc/petrol) to give the *enone* **83** (84 mg, 90%) as a pale yellow oil.

δ_H ($CDCl_3$, 400 MHz) 7.24–7.07 (5H, m, 5 × Ar*H*), 6.62 (1H, dd, *J* 16.0, 4.0, C(O)CH=C*H*), 6.43 (1H, dd, *J* 16.0, 1.0, C(O)C*H*=CH), 4.95 (1H, dd, *J* 4.0, 1.0, $CH(OCH_2CH_3)_2$), 3.96 (1H, dd, *J* 9.0, 6.0, $CHCH_2Ph$), 3.60–3.32 (9H, m, OCH_2CH_2N, OCH_2CH_2N, $OCH_ACH_BCH_2N$, $CH(OCH_2CH_3)_2$), 3.32–3.18 (2H, m, $OCH_2CH_AH_BN$, $CHCH_AH_BPh$), 3.15–2.99 (3H, m, $OCH_AH_BCH_2N$, $OCH_2CH_AH_BN$, $CHCH_AH_BPh$), 1.14 (3H, t, *J* 7.0, OCH_2CH_3), 1.13 (3H, t, *J* 7.0, OCH_2CH_3); δ_C ($CDCl_3$, 101 MHz) 194.2, 167.2, 142.8, 138.3, 129.0, 128.6, 128.5,

126.8, 99.3, 66.6, 66.2, 61.5, 56.9, 46.3, 42.5, 34.8, 15.2; ν_{max} (neat)/cm^{-1} 2979, 2888, 1650, 1630, 1440, 1114, 1054, 701; *m/z* (ESI$^+$) 398 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{21}H_{29}O_5NNa^+$ ([M + Na]$^+$) requires 398.19379, found 398.19337.

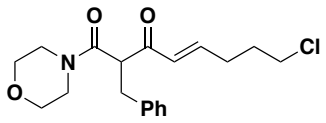
2-Benzyl-1-morpholinoheptane-1,3,6-trione, 84



Synthesised according to the general procedure **C**, using 2-benzyl-3-morpholino-3-oxopropanal **69a** (74 mg, 0.30 mmol), 3-butyn-2-ol (28 μL, 0.36 mmol), $[Rh(nbd)_2]BF_4$ (5.6 mg, 5 mol%) and dcpe (6.3 mg, 5 mol%) in acetone (0.3 mL, 1.0 M). The crude product was purified by flash chromatography on silica (eluent 50% acetone/petrol) to give the *diketone* **84** (55 mg, 57%) as a colourless oil.

δ_H ($CDCl_3$, 400 MHz) 7.25–7.18 (2H, m, 2 × Ar*H*), 7.18–7.09 (3H, m, 3 × Ar*H*), 3.90 (1H, dd, *J* 8.5, 6.5, C*H*CH_2Ph), 3.63–3.52 (2H, m, OC$H_A$$H_B$$CH_2N, OCH_2CH_A$$H_B$N), 3.49–3.42 (1H, m, $OCH_2CH_A$$H_B$N), 3.42–3.27 (3H, m, OC$H_2$$CH_2N, OCH_2CH_A$$H_B$N), 3.19–3.13 (2H, m, CHCH_2Ph), 3.05 (1H, ddd, *J* 13.0, 6.0, 3.0, $OCH_A$$H_B$$CH_2$N), 2.91 (1H, ddd, *J* 10.0, 7.0, 3.0, $OCH_2CH_A$$H_B$N), 2.83–2.74 (1H, m, C(O)C$H_A$$H_B$$CH_2$), 2.71–2.52 (3H, m, 1H, m, C(O)$CH_A$$H_B$$CH_2$, C(O)$CH_2CH_2$), 2.10 (3H, s, C(O)C$H_3$); δ_C ($CDCl_3$, 101 MHz) 207.1, 204.2, 167.7, 138.4, 129.0, 128.7, 126.8, 66.6, 66.2, 57.9, 46.5, 42.5, 37.3, 34.9, 33.9, 29.8; ν_{max} (neat)/cm^{-1} 2965, 2921, 2858, 1710, 1630, 1437, 1112, 701; *m/z* (ESI$^+$) 340 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{18}H_{24}O_4N^+$ ([M + H]$^+$) requires 318.16998, found 318.16993.

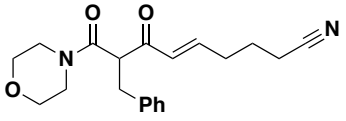
(*E*)-2-Benzyl-8-chloro-1-morpholinooct-4-ene-1,3-dione, 85



Synthesised according to the general procedure **C**, using 2-benzyl-3-morpholino-3-oxopropanal **69a** (62 mg, 0.25 mmol), 5-chloro-1-pentyne (32 μL, 0.30 mmol), $[Rh(nbd)_2]BF_4$ (4.7 mg, 5 mol%) and dcpe (5.3 mg, 5 mol%) in acetone (0.25 mL, 1.0 M). The crude product was purified by flash chromatography on silica (eluent 50% EtOAc/petrol) to give the *enone* **85** (79 mg, 90%) as a colourless oil.

δ_H ($CDCl_3$, 400 MHz) 7.25–7.08 (5H, m, 5 × Ar*H*), 6.81 (1H, dt, *J* 15.5, 7.0, C(O)CH=C*H*CH_2), 6.25 (1H, dt, *J* 15.5, 1.5, C(O)C*H*=CHCH_2), 3.89 (1H, dd, *J* 8.5, 6.0, C*H*CH_2Ph), 3.54–3.19 (9H, m, OC*H*$_2$$CH_2N, OCH_2$C*H*$_2$N, OC*H*$_AH_B$$CH_2N, OCH_2$C*H*$_AH_B$N, CHC*H*$_AH_BPh, CH_2CH_2C*H*_2$Cl), 3.16–3.04 (3H, m, OCH$_A$*H*$_B$$CH_2N, OCH_2CH_A$*H*$_B$N, CHCH$_A$*H*$_B$Ph), 2.38–2.24 (2H, m, C*H*$_2$$CH_2$$CH_2$Cl), 1.84 (2H, app. p, *J* 6.5, CH_2C*H*$_2$$CH_2$Cl); δ_C ($CDCl_3$, 101 MHz) 194.1, 167.4, 147.2, 138.4, 129.0, 128.6, 127.5, 126.8, 66.7, 66.3, 57.4, 46.3, 44.0, 42.6, 35.0, 30.6, 29.5; ν_{max} (neat)/cm^{-1} 2969, 2851, 1682, 1626, 1433, 1113, 701; *m/z* (ESI$^+$) 350 ([M (^{35}Cl) + H]$^+$, 100%); 352 ([M (^{37}Cl) + H]$^+$, 30%); HRMS (ESI$^+$) $C_{19}H_{25}O_3N^{35}Cl^+$ ([M (^{35}Cl) + H]$^+$) requires 350.15175, found 350.15177; $C_{19}H_{25}O_3N^{37}Cl^+$ ([M (^{37}Cl) + H]$^+$) requires 352.14880, found 352.14855.

(*E*)-8-Benzyl-9-morpholino-7,9-dioxonon-5-enenitrile, 86

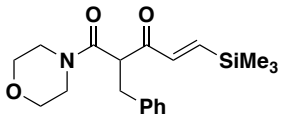


Synthesised according to the general procedure **C**, using 2-benzyl-3-morpholino-3-

oxopropanal **69a** (62 mg, 0.25 mmol), 5-hexynenitrile (32 μL, 0.30 mmol), $[Rh(nbd)_2]BF_4$ (4.7 mg, 5 mol%) and dcpe (5.3 mg, 5 mol%) in acetone (0.25 mL, 1.0 M). The crude product was purified by flash chromatography on silica (eluent 50% EtOAc/petrol) to give the *enone* **86** (61 mg, 72%) as a colourless oil.

δ_H ($CDCl_3$, 400 MHz) 7.26–7.08 (5H, m, 5 × Ar*H*), 6.77 (1H, dt, *J* 15.5, 7.0, C(O)CH=C*H*CH_2), 6.27 (1H, dt, *J* 15.5, 1.5, C(O)C*H*=$CHCH_2$), 3.89 (1H, dd, *J* 8.5, 6.0, C*H*CH_2Ph), 3.62–3.17 (7H, m, OC*H*$_2CH_2N$, OCH_2CH_2N, OC*H*$_A$H$_B$$CH_2N$, $OCH_2CH_AH_BN$, CHC*H*$_A$H$_B$Ph), 3.16–2.99 (3H, m, $OCH_AH_BCH_2N$, $OCH_2CH_AH_BN$, $CHCH_AH_BPh$), 2.44–2.21 (4H, m, C*H*$_2CH_2CH_2CN$, $CH_2CH_2CH_2CN$), 1.75 (2H, app. p, *J* 7.0, $CH_2CH_2CH_2CN$); δ_C ($CDCl_3$, 101 MHz) 194.0, 167.3, 145.8, 138.3, 129.0, 128.7, 128.0, 126.9, 118.9, 66.7, 66.3, 57.3, 46.4, 42.6, 35.0, 31.0, 23.7, 16.6; ν_{max} (neat)/cm^{-1} 2924, 2857, 2246, 1626, 1432, 1113, 728, 701; *m/z* (ESI^+) 363 ($[M + Na]^+$, 100%); HRMS (ESI^+) $C_{20}H_{24}O_3N_2Na^+$ ($[M + Na]^+$) requires 363.16791, found 363.16770.

(*E*)-2-Benzyl-1-morpholino-5-(trimethylsilyl)pent-4-ene-1,3-dione, 87

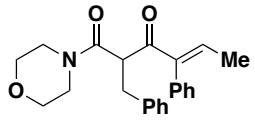


Synthesised according to the general procedure **C**, using 2-benzyl-3-morpholino-3-oxopropanal **69a** (62 mg, 0.25 mmol), ethynyltrimethylsilane (43 μL, 0.30 mmol), $[Rh(nbd)_2]BF_4$ (4.7 mg, 5 mol%) and dcpe (5.3 mg, 5 mol%) in acetone (0.25 mL, 1.0 M). The crude product was purified by flash chromatography on silica (eluent 50% EtOAc/petrol) to give the *enone* **87** (79 mg, 92%) as a colourless oil.

δ_H ($CDCl_3$, 400 MHz) 7.19–7.04 (5H, m, 5 × Ar*H*), 6.98 (1H, d, *J* 19.0, C(O)CH=C*H*Si),

6.45 (1H, d, *J* 19.0, C(O)C*H*=CHSi), 3.96 (1H, dd, *J* 9.0, 6.0, C*H*CH_2Ph), 3.50–3.26 (5H, m, OC*H*$_2$$CH_2N, OCH_2$C*H*$_2$N, OC*H*$_AH_B$$CH_2$N), 3.25–3.15 (2H, m, OCH$_2$C*H*$_A$H$_B$N, CHC*H*$_A$H$_B$Ph), 3.09–2.97 (3H, m, OCH$_A$*H*$_B$$CH_2N, OCH_2CH_A$*H*$_B$N, CHCH$_A$*H*$_B$Ph), 0.00 (9H, s, Si(C*H*$_3$)$_3$); δ_C ($CDCl_3$, 101 MHz) 195.9, 169.4, 150.9, 140.9, 140.4, 130.9, 130.5, 128.6, 68.5, 68.1, 57.9, 48.2, 44.4, 36.9, 0.0; ν_{max} (neat)/cm^{-1} 2958, 2856, 1686, 1631, 1360, 1114, 841, 700; *m/z* (ESI$^+$) 346 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{19}H_{28}O_3NSi^+$ ([M + H]$^+$) requires 346.18330, found 346.18324.

(*E*)-2-Benzyl-1-morpholino-4-phenylhex-4-ene-1,3-dione, 89a

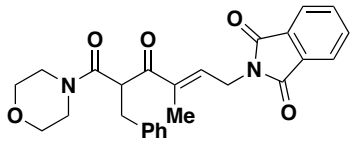


Synthesised according to the general procedure **C**, using 2-benzyl-3-morpholino-3-oxopropanal **69a** (74 mg, 0.30 mmol), 1-phenyl-1-propyne **88** (23 μL, 0.18 mmol), [Rh(nbd)$_2$]BF_4 (5.6 mg, 5 mol%) and DPEPhos (8.1 mg, 5 mol%) in acetone (0.3 mL, 1.0 M). The crude product was purified by flash chromatography on silica (eluent 50% EtOAc/petrol) to give the *enone* **89a** (80 mg, 73%) as a pale yellow crystalline solid.

δ_H ($CDCl_3$, 400 MHz) 7.36–7.28 (2H, m, 2 × Ar*H*), 7.28–7.18 (6H, m, 5 × Ar*H*, C=C*H*(CH$_3$)), 7.18–7.11 (3H, m, 3 × Ar*H*), 4.45 (1H, dd, *J* 9.0, 5.5, C*H*CH_2Ph), 3.63–3.47 (2H, m, OCH$_2$C*H*$_A$H$_B$N, OC*H*$_A$H$_B$$CH_2$N), 3.44–3.31 (3H, m, OC*H*$_2$$CH_2N, OCH_2CH_A$*H*$_B$N), 3.29–3.10 (3H, m, CHC*H*$_2$Ph, OCH$_2$C*H*$_A$H$_B$N), 3.03–2.82 (2H, m, OCH$_A$*H*$_B$$CH_2N, OCH_2CH_A$*H*$_B$N), 1.99 (3H, *d*, *J* 1.0, C=CH(C*H*$_3$)); δ_C ($CDCl_3$, 101 MHz) 196.8, 168.5, 139.0, 138.6, 136.9, 135.3, 129.7, 129.3, 128.9, 128.7, 128.6, 126.9, 66.6, 66.0, 65.9, 52.5, 46.2, 42.3, 35.9, 15.3, 13.7; mp: 117–119 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 2980, 2890, 1673, 1628,

1432, 1113, 699; *m/z* (ESI$^+$) 386 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{23}H_{26}O_3N^+$ ([M + H]$^+$) requires 364.19072, found 364.19037.

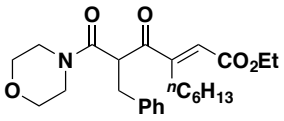
(*E*)-2-(5-Benzyl-3-methyl-6-morpholino-4,6-dioxohex-2-en-1-yl)isoindoline-1,3-dione, 96a



Synthesised according to the general procedure **C**, using 2-benzyl-3-morpholino-3-oxopropanal **69a** (74 mg, 0.30 mmol), *N*-(2-butynyl)-phthalimide **90** (72 mg, 0.36 mmol), $[Rh(nbd)_2]BF_4$ (5.6 mg, 5 mol%) and DPEPhos (8.1 mg, 5 mol%) in acetone (0.3 mL, 1.0 M). The crude product was purified by flash chromatography on silica (eluent 50% EtOAc/petrol) to give the *enone* **96a** (85 mg, 64%) as a pale yellow crystalline solid.

δ_H ($CDCl_3$, 400 MHz) 7.78 (2H, dd, *J* 5.5, 3.0, 2 × Ar*H*), 7.67 (2H, dd, *J* 5.5, 3.0, 2 × Ar*H*), 7.17–7.10 (2H, m, 2 × Ar*H*), 7.09–7.00 (3H, m, 3 × Ar*H*), 6.27–6.15 (1H, m, C=C*H*CH_2), 4.42–4.28 (2H, m, CHCH_2N), 4.24 (1H, dd, *J* 8.5, 6.0, C*H*CH_2Ph), 3.58–3.43 (2H, m, $OCH_2CH_AH_BN$, $OCH_AH_BCH_2N$), 3.36–3.21 (3H, m, OCH_2CH_2N, $OCH_2CH_AH_BN$), 3.17–3.06 (3H, m, CHCH_2Ph, $OCH_2CH_AH_BN$), 2.83–2.75 (1H, m, $OCH_2CH_AH_BN$), 2.75–2.67 (1H, m, $OCH_AH_BCH_2N$), 1.89 (3H, s, CH_3); δ_C ($CDCl_3$, 101 MHz) 195.7, 168.3, 167.6, 139.3, 138.6, 134.4, 133.6, 131.9, 129.2, 128.6, 126.8, 123.5, 66.4, 65.8, 51.8, 46.1, 42.1, 36.0, 35.6, 12.2; mp: 74–76 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 2924, 2857, 1771, 1711, 1630, 1428, 1112, 726; *m/z* (ESI$^+$) 469 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{26}H_{27}O_5N_2^+$ ([M + H]$^+$) requires 447.19145, found 447.19102.

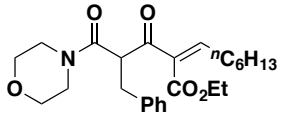
Ethyl (*E*)-3-(2-benzyl-3-morpholino-3-oxopropanoyl)non-2-enoate, 97a



Synthesised according to the general procedure **C**, using 2-benzyl-3-morpholino-3-oxopropanal **69a** (74 mg, 0.30 mmol), ethyl 2-nonynoate **91** (72 μL, 0.36 mmol), $[Rh(nbd)_2]BF_4$ (5.6 mg, 5 mol%) and DPEPhos (8.1 mg, 5 mol%) in acetone (0.3 mL, 1.0 M). The crude product was purified by flash chromatography on silica (eluent 50% EtOAc/petrol) to give the *enone* **97a** (82 mg, 64%) as a pale yellow oil.

δ_H ($CDCl_3$, 400 MHz) 7.26–7.15 (3H, m, 3 × Ar*H*), 7.13–7.09 (2H, m, 2 × Ar*H*), 6.17 (1H, s, C=C*H*CO_2Et), 4.26 (1H, dd, *J* 9.5, 5.5, C*H*CH_2Ph), 4.14 (2H, q, *J* 7.0, $CO_2CH_2CH_3$), 3.53–3.34 (5H, m, OCH_2CH_2N, OCH_2CH_2N, $OCH_AH_BCH_2N$), 3.23–3.08 (3H, m, $OCH_2CH_AH_BN$, $CHCH_2Ph$), 2.94–2.84 (1H, m, $OCH_AH_BCH_2N$), 2.80–2.60 (3H, m, $OCH_2CH_AH_BN$, $CH_2(CH_2)_4CH_3$), 1.35–1.17 (11H, m, $CO_2CH_2CH_3$, $CH_2(CH_2)_4CH_3$), 0.84–0.77 (3H, m, CH_2CH_3); δ_C ($CDCl_3$, 101 MHz) 196.3, 167.8, 165.3, 155.2, 138.3, 129.2, 128.7, 127.0, 124.4, 66.5, 65.8, 60.9, 52.7, 46.3, 42.2, 35.2, 31.5, 29.5, 29.0, 27.6, 22.6, 14.2, 14.1; ν_{max} (neat)/cm^{-1} 2956, 2927, 2857, 1723, 1697, 1633, 1441, 1180, 1113, 1030, 701; *m/z* (ESI$^+$) 452 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{25}H_{36}O_5N^+$ ([M + H]$^+$) requires 430.25880, found 430.25853.

Ethyl (*Z*)-2-(2-benzyl-3-morpholino-3-oxopropanoyl)non-2-enoate, 97b

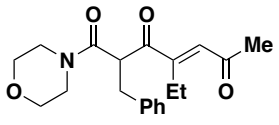


Synthesised according to the general procedure **C**, using 2-benzyl-3-morpholino-3-

oxopropanal **69a** (74 mg, 0.30 mmol), ethyl 2-nonynoate **91** (72 μL, 0.36 mmol), $[Rh(nbd)_2]BF_4$ (5.6 mg, 5 mol%) and dcpe (6.3 mg, 5 mol%) in acetone (0.3 mL, 1.0 M). The crude product was purified by flash chromatography on silica (eluent 50% EtOAc/petrol) to give the *enone* **97b** (80 mg, 62%) as a pale yellow oil.

δ_H ($CDCl_3$, 400 MHz) 7.26–7.08 (5H, m, 5 × Ar*H*), 7.00 (1H, t, *J* 7.5, C=C*H*), 4.55 (1H, dd, *J* 10.5, 4.5, C*H*CH_2Ph), 4.26–4.03 (2H, m, $CO_2CH_2CH_3$), 3.58–3.42 (2H, m, $OCH_AH_BCH_2N$, $OCH_2CH_AH_BN$), 3.41–3.27 (3H, m, OCH_2CH_2N, $OCH_2CH_AH_BN$), 3.23–3.02 (3H, m, $OCH_2CH_AH_BN$, $CHCH_2Ph$), 2.95–2.83 (1H, m, $OCH_2CH_AH_BN$), 2.80–2.71 (1H, m, $OCH_AH_BCH_2N$), 2.40–2.18 (2H, m, $CH_2(CH_2)_4CH_3$), 1.45–1.34 (2H, m, $CH_2CH_2(CH_2)_3CH_3$), 1.32–1.14 (9H, m, $CO_2CH_2CH_3$, $(CH_2)_2(CH_2)_3CH_3$), 0.86–0.76 (3H, m, CH_2CH_3); δ_C ($CDCl_3$, 101 MHz) 196.9, 167.9, 154.2, 138.7, 132.6, 129.3, 129.1, 128.6, 126.7, 66.6, 66.2, 61.2, 56.0, 46.5, 42.2, 34.6, 31.6, 30.0, 29.1, 28.6, 22.5, 14.2, 14.1; ν_{max} (neat)/cm^{-1} 2927, 2857, 1702, 1637, 1459, 1237, 1114, 1029, 701; *m/z* (ESI^+) 452 ($[M + Na]^+$, 100%); HRMS (ESI^+) $C_{25}H_{36}O_5N^+$ ($[M + H]^+$) requires 430.25880, found 430.25850.

(*E*)-2-Benzyl-4-ethyl-1-morpholinohept-4-ene-1,3,6-trione, 98a

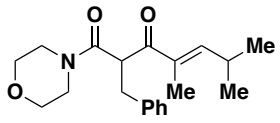


Synthesised according to the general procedure **C**, using 2-benzyl-3-morpholino-3-oxopropanal **69a** (74 mg, 0.30 mmol), 3-hexyn-2-one **92** (39 μL, 0.36 mmol), $[Rh(nbd)_2]BF_4$ (5.6 mg, 5 mol%) and DPEPhos (8.1 mg, 5 mol%) in acetone (0.3 mL, 1.0 M). The crude product was purified by flash chromatography on silica (eluent 50% EtOAc/petrol) to give

the *enone* **98a** (45 mg, 44%) as a pale yellow oil.

δ_H ($CDCl_3$, 400 MHz) 7.50–7.02 (5H, m, 5 × Ar*H*), 6.45 (1H, s, C=C*H*), 4.25 (1H, dd, *J* 8.5, 6.0, C*H*CH_2Ph), 3.65–3.43 (2H, m, OC*H*$_A$H$_B$$CH_2N, OCH_2C*H*_AH_B$N), 3.46–3.32 (3H, m, OC*H*$_2$$CH_2N, OCH_2CH_A$*H*$_B$N), 3.26–3.08 (3H, m, CHC*H*$_2$Ph, OCH_2C*H*$_A$H$_B$N), 3.00–2.80 (2H, m, OCH$_A$*H*$_B$$CH_2N, OCH_2CH_A$*H*$_B$N), 2.71–2.44 (2H, m, C*H*$_2$$CH_3$), 2.19 (3H, s, C(O)C*H*$_3$), 0.93 (3H, t, *J* 7.5, CH_2C*H*$_3$); δ_C ($CDCl_3$, 101 MHz) 198.7, 197.2, 167.7, 152.9, 138.3, 130.4, 129.2, 128.8, 127.0, 66.5, 65.9, 53.2, 46.3, 42.3, 35.4, 32.0, 21.1, 13.5; ν_{max} (neat)/cm^{-1} 2924, 2857, 1693, 1632, 1454, 1114, 702; *m/z* (ESI^+) 366 ($[M + Na]^+$, 100%); HRMS (ESI^+) $C_{20}H_{26}O_4N^+$ ($[M + H]^+$) requires 344.18563, found 344.18580.

(*E*)-2-Benzyl-4,6-dimethyl-1-morpholinohept-4-ene-1,3-dione, 99a

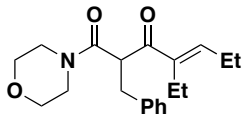


Synthesised according to the general procedure **C**, using 2-benzyl-3-morpholino-3-oxopropanal **69a** (74 mg, 0.30 mmol), 4-methyl-2-pentyne **93** (42 μL, 0.36 mmol), $[Rh(nbd)_2]BF_4$ (5.6 mg, 5 mol%) and DPEPhos (8.1 mg, 5 mol%) in acetone (0.3 mL, 1.0 M). The crude product was purified by flash chromatography on silica (eluent 40% EtOAc/petrol) to give the *enone* **99a** (73 mg, 73%) as a pale yellow oil.

δ_H ($CDCl_3$, 400 MHz) 7.24–7.18 (2H, m, 2 × Ar*H*), 7.18–7.09 (3H, m, 3 × Ar*H*), 6.05 (1H, app. dd, *J* 9.5, 1.0, C=C*H*($CH(CH_3)_2$)), 4.29 (1H, dd, *J* 9.5, 5.5, C*H*CH_2Ph), 3.65–3.57 (1H, m, OCH_2C*H*$_A$H$_B$N), 3.56–3.46 (1H, m, OC*H*$_A$H$_B$$CH_2$N), 3.44–3.25 (3H, m, OC*H*$_2$$CH_2N, OCH_2CH_A$*H*$_B$N), 3.21–3.03 (3H, m, OCH_2C*H*$_A$H$_B$N, CHC*H*$_2$Ph), 2.95–2.85 (1H, m, OCH_2CH$_A$*H*$_B$N), 2.85–2.75 (1H, m, OCH$_A$*H*$_B$$CH_2$N), 2.66–2.55 (1H, m, C*H*$(CH_3)_2$), 1.73

(3H, d, *J* 1.5, C(O)C(C*H*$_3$)), 0.91 (6H, t, *J* 6.5, CH(C*H*$_3$)$_2$); δ_C ($CDCl_3$, 101 MHz) 196.6, 168.7, 148.8, 139.0, 134.6, 129.3, 128.6, 126.7, 66.5, 65.9, 51.9, 46.2, 42.2, 35.7, 28.1, 22.2, 21.9, 11.9; ν_{max} (neat)/cm^{-1} 2943, 2877, 1670, 1459, 995, 751, 699; *m/z* (ESI$^+$) 352 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{20}H_{28}O_3N^+$ ([M + H]$^+$) requires 330.20637, found 330.20634.

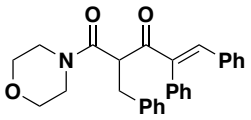
(*E*)-2-Benzyl-4-ethyl-1-morpholinohept-4-ene-1,3-dione, 102



Synthesised according to the general procedure **C**, using 2-benzyl-3-morpholino-3-oxopropanal **69a** (74 mg, 0.30 mmol), 3-hexyne (41 μL, 0.36 mmol), $[Rh(nbd)_2]BF_4$ (5.6 mg, 5 mol%) and DPEPhos (8.1 mg, 5 mol%) in acetone (0.3 mL, 1.0 M). The crude product was purified by flash chromatography on silica (eluent 40% EtOAc/petrol) to give the *enone* **102** (87 mg, 88%) as a pale yellow oil.

δ_H ($CDCl_3$, 400 MHz) 7.24–7.17 (2H, m, 2 × Ar*H*), 7.17–7.08 (3H, m, 3 × Ar*H*), 6.23 (1H, t, *J* 7.0, C=C*H*(CH$_2$CH$_3$)), 4.29 (1H, dd, *J* 9.0, 5.5, C*H*CH$_2$Ph), 3.62–3.47 (2H, m, OC*H*$_A$H$_B$CH$_2$N, OCH$_2$C*H*$_A$H$_B$N), 3.47–3.29 (3H, m, OC*H*$_2$CH$_2$N, OCH$_2$CH$_A$*H*$_B$N), 3.26–3.12 (2H, m, OCH$_2$C*H*$_A$H$_B$N, CHC*H*$_A$H$_B$Ph), 3.06 (1H, dd, *J* 13.5, 5.5, CHCH$_A$*H*$_B$Ph), 2.99–2.86 (2H, m, OCH$_A$*H*$_B$CH$_2$N, OCH$_2$CH$_A$*H*$_B$N), 2.40–2.03 (4H, m, 2 × C*H*$_2$CH$_3$), 0.95 (3H, t, *J* 7.5, CH$_2$C*H*$_3$), 0.86 (3H, t, *J* 7.5, CH$_2$C*H*$_3$); δ_C ($CDCl_3$, 101 MHz) 195.9, 168.6, 143.9, 142.3, 139.1, 129.2, 128.6, 126.7, 66.6, 66.0, 52.1, 46.1, 42.2, 35.8, 22.0, 19.4, 13.6, 13.5; ν_{max} (neat)/cm^{-1} 2964, 2932, 1675, 1386, 1232, 1114, 701; *m/z* (ESI$^+$) 352 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{20}H_{28}O_3N^+$ ([M + H]$^+$) requires 330.20637, found 330.20611.

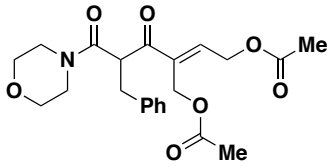
(*E*)-2-Benzyl-1-morpholino-4,5-diphenylpent-4-ene-1,3-dione, 103



Synthesised according to the general procedure **C**, using 2-benzyl-3-morpholino-3-oxopropanal **69a** (74 mg, 0.30 mmol), diphenylacetylene (64 mg, 0.36 mmol), $[Rh(nbd)_2]BF_4$ (5.6 mg, 5 mol%) and DPEPhos (8.1 mg, 5 mol%) in acetone (0.3 mL, 1.0 M). The crude product was purified by flash chromatography on silica (eluent 50% EtOAc/petrol) to give the *enone* **103** (96 mg, 75%) as a pale yellow crystalline solid.

δ_H ($CDCl_3$, 400 MHz) 7.65 (1H, s, C=C*H*Ph), 7.40–7.28 (3H, m, 3 × Ar*H*), 7.22–6.97 (10H, m, 10 × Ar*H*), 6.84 (2H, d, *J* 7.5, 2 × Ar*H*), 4.04 (1H, dd, *J* 9.5, 5.5, C*H*CH_2Ph), 3.73–3.57 (1H, m, $OCH_2CH_AH_BN$), 3.51–3.34 (1H, m, $OCH_AH_BCH_2N$), 3.24 (1H, dd, *J* 13.5, 5.0, $CHCH_AH_BPh$), 3.15–2.99 (2H, m, $CHCH_AH_BPh$, $OCH_AH_BCH_2N$), 2.97–2.86 (1H, m, $OCH_AH_BCH_2N$), 2.78 (1H, ddd, *J* 12.5, 9.0, 3.0, $OCH_2CH_AH_BN$), 2.36–2.25 (1H, m, $OCH_2CH_AH_BN$), 2.26–2.15 (1H, m, $OCH_AH_BCH_2N$), 2.10–1.98 (1H, m, $OCH_2CH_AH_BN$); δ_C ($CDCl_3$, 101 MHz) 195.2, 167.9, 139.7, 138.7, 138.7, 136.6, 134.4, 131.0, 130.3, 129.3 (3C), 128.6, 128.4, 128.2, 126.8, 66.1, 65.3, 53.6, 45.5, 41.7, 35.5; mp: 67–69 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 2961, 2925, 1681, 1627, 1571, 1112, 702; *m/z* (ESI^+) 448 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{28}H_{28}O_3N^+$ ($[M + H]^+$) requires 426.20637, found 426.20601.

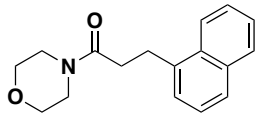
(*E*)-2-(2-Benzyl-3-morpholino-3-oxopropanoyl)but-2-ene-1,4-diyl diacetate, 104



Synthesised according to the general procedure **C**, using 2-benzyl-3-morpholino-3-oxopropanal **69a** (74 mg, 0.30 mmol), 1,4-diacetoxy-2-butyne (54 μL, 0.36 mmol), $[Rh(nbd)_2]BF_4$ (5.6 mg, 5 mol%) and DPEPhos (8.1 mg, 5 mol%) in acetone (0.3 mL, 1.0 M). The crude product was purified by flash chromatography on silica (eluent 50% EtOAc/petrol) to give the *enone* **104** (71 mg, 57%) as a pale yellow oil.

δ_H ($CDCl_3$, 400 MHz) 7.26–7.14 (3H, m, 3 × Ar*H*), 7.15–7.07 (2H, m, 2 × Ar*H*), 6.51 (1H, t, *J* 6.0, C=C*H*($CH_2OC(O)CH_3$)), 4.82 (2H, d, *J* 5.5, CH_2OC(O)CH_3), 4.77 (1H, d, *J* 12.5, C$H_A$$H_B$OC(O)$CH_3$), 4.73 (1H, d, *J* 12.5, $CH_A$$H_B$OC(O)$CH_3$), 4.26 (1H, dd, *J* 8.0, 6.5, C*H*CH_2Ph), 3.61–3.48 (2H, m, OC$H_A$$H_B$$CH_2N, OCH_2CH_A$$H_B$N), 3.45–3.31 (3H, m, OC$H_2$$CH_2$N, $OCH_2CH_A$$H_B$N), 3.23–3.09 (3H, m, OCH_2C$H_A$$H_BN, CHCH_2$Ph), 3.00–2.77 (2H, m, $OCH_A$$H_B$$CH_2$N, $OCH_2CH_A$$H_B$N), 2.02 (3H, s, C(O)C$H_3$), 1.97 (3H, s, C(O)C$H_3$); δ_C ($CDCl_3$, 101 MHz) 193.8, 170.5, 170.4, 167.8, 140.0, 138.4, 136.4, 129.2, 128.7, 127.0, 66.5, 65.8, 60.8, 57.7, 52.7, 46.2, 42.3, 35.2, 20.8, 20.7; ν_{max} (neat)/cm^{-1} 2980, 1739, 1689, 1633, 1227, 1114, 1030, 703; *m/z* (ESI^+) 440 ($[M + Na]^+$, 100%); HRMS (ESI^+) $C_{22}H_{28}O_7N^+$ ($[M + H]^+$) requires 418.18603, found 418.18619.

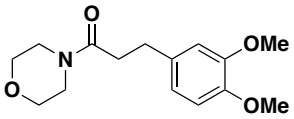
1-Morpholino-3-(naphthalen-1-yl)propan-1-one, 68b



Synthesised according to the general procedure **A**, using 3-(naphthalen-1-yl)propanoic acid (6.4 g, 32 mmol), morpholine (3.08 mL, 35.2 mmol) and EDCI.HCl (6.75 g, 35.2 mmol) in CH_2Cl_2 (150 mL). The crude product was purified by flash chromatography on silica (eluent 50% EtOAc/petrol) to give the *amide* **68b** (7.49 g, 87%) as a colourless oil.

δ_H ($CDCl_3$, 400 MHz) 8.06 (1H, d, *J* 8.5, Ar*H*), 8.00–7.81 (1H, m, Ar*H*), 7.76 (1H, d, *J* 8.0, Ar*H*), 7.62–7.49 (2H, m, 2 × Ar*H*), 7.48–7.34 (2H, m, 2 × Ar*H*), 3.68–3.56 (4H, m, OC*H*$_2$CH$_2$N, OCH$_2$C*H*$_2$N), 3.55–3.45 (2H, m, C(O)CH$_2$C*H*$_2$Ar), 3.40–3.30 (2H, m, OC*H*$_2$CH$_2$N), 3.26–3.15 (2H, m, OCH$_2$C*H*$_2$N), 2.76 (2H, t, *J* 8.4, C(O)C*H*$_2$CH$_2$Ar); δ_C ($CDCl_3$, 101 MHz) 171.0, 137.1, 133.9, 131.7, 128.9, 127.1, 126.4, 126.2, 125.6(7), 125.6(6), 123.5, 66.8, 66.3, 45.9, 41.9, 34.0, 28.7; ν_{max} (neat)/cm^{-1} 2967, 2855, 1637, 1457, 1113, 777; HRMS (CI$^+$) $C_{17}H_{20}O_2N^+$ ([M + H]$^+$) requires 270.1494, found 270.1494.

3-(3,4-Dimethoxyphenyl)-1-morpholinopropan-1-one, 68c

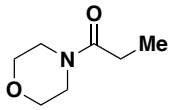


Synthesised according to the general procedure **A**, using 3-(3,4-dimethoxyphenyl)propanoic acid (6.3 g, 30 mmol), morpholine (2.9 mL, 33 mmol) and EDCI.HCl (6.3 g, 33 mmol) in CH_2Cl_2 (150 mL) to give the *amide* **68c** (5.75 g, 91%) as a colourless oil.

δ_H ($CDCl_3$, 400 MHz) 6.75–6.64 (3H, m 3 × Ar*H*), 3.79 (3H, s, OC*H*$_3$), 3.78 (3H, s, OC*H*$_3$), 3.59–3.52 (4H, m, 2 × OC*H*$_2$CH$_2$N), 3.50–3.45 (2H, m, OCH$_2$C*H*$_2$N), 3.33–3.28 (2H, m,

OCH_2CH_2N), 2.85 (2H, t, J 6.5, $C(O)CH_2CH_2Ar$), 2.52 (2H, t, *J* 6.5, $C(O)CH_2CH_2Ar$); δ_C ($CDCl_3$, 101 MHz) 170.9, 148.9, 147.4, 133.7, 120.2, 111.8, 111.3, 66.9, 66.5, 55.9, 55.9, 46.0, 41.9, 35.1, 31.1; ν_{max} (neat)/cm^{-1} 2933, 2857, 1634, 1514, 1235, 1114, 1025, 727; *m/z* (ESI^+) 581 ($[2M + Na]^+$, 100%); HRMS (ESI^+) $C_{15}H_{21}O_4NNa^+$ ($[M + Na]^+$) requires 302.13628, found 302.13650.

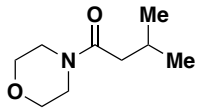
1-Morpholinopropan-1-one, 68d



To a round bottomed flask containing CH_2Cl_2 (100 mL) was added pyridine (20 mL, 250 mmol) under a N_2 atmosphere. The flask was cooled to 0 °C, and propionyl anhydride (7.8 mL, 60 mmol) was added slowly, followed by morpholine (4.3 mL, 50 mmol). The reaction mixture was warmed to room temperature and left to stir for 2 h. The mixture was subsequently washed with 1 N HCl (100 mL), 1 N NaOH solution (100 ml) and water (100 mL). The aqueous layers were back-extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica (eluent 50% EtOAc/petrol) to give the amide **68d** (3.48 g, 41%) as a colourless oil.

δ_H ($CDCl_3$, 400 MHz) 3.39 (4H, m, 2 × OCH_2CH_2N), 3.36–3.29 (2H, m, OCH_2CH_2N), 3.25–3.18 (2H, m, OCH_2CH_2N), 2.08 (2H, q, *J* 7.5, $C(O)CH_2CH_3$), 0.87 (3H, t, *J* 7.5, $C(O)CH_2CH_3$); δ_C ($CDCl_3$, 101 MHz) 172.1, 66.6, 66.4, 45.6, 41.6, 25.9, 9.1; *m/z* (ESI^+) 309 ($[2M + Na]^+$, 100%). Data is consistent with the literature.[257]

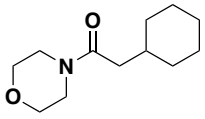
3-Methyl-1-morpholinobutan-1-one, 68e



Synthesised according to the general procedure **A**, using 3-methylbutanoic acid (3.3 mL, 30 mmol), morpholine (2.9 mL, 33 mmol) and EDCI.HCl (6.3 g, 33 mmol) in CH_2Cl_2 (150 mL) to give the amide **68e** (3.18 g, 62%) as a colourless oil.

δ_H ($CDCl_3$, 400 MHz) 3.56–3.51 (4H, m, 2 × OC*H*$_2$CH$_2$N), 3.51–3.47 (2H, m, OCH$_2$C*H*$_2$N), 3.40–3.33 (2H, m, OCH$_2$C*H*$_2$N), 2.08 (2H, d, *J* 7.0, C(O)C*H*$_2$), 2.05–1.93 (1H, m, CH$_2$C*H*(CH$_3$)$_2$), 0.85 (6H, d, *J* 6.5, CH$_2$CH(C*H*$_3$)$_2$); δ_C ($CDCl_3$, 101 MHz) 171.0, 66.8, 66.6, 46.1, 41.7, 41.7, 25.6, 22.6; *m/z* (ESI$^+$) 194 ([M + Na]$^+$, 100%). Data is consistent with the literature.[258]

2-Cyclohexyl-1-morpholinoethan-1-one, 68f

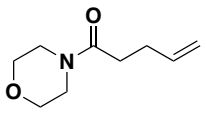


Synthesised according to the general procedure **A**, using cyclohexaneacetic acid (4.2 mL, 30 mmol), morpholine (2.9 mL, 33 mmol) and EDCI.HCl (6.3 g, 33 mmol) in CH_2Cl_2 (150 mL) to give the *amide* **68f** (5.79 g, 91%) as a white crystalline solid.

δ_H ($CDCl_3$, 400 MHz) 3.62–3.49 (6H, m, 2 × OC*H*$_2$CH$_2$N, OCH$_2$C*H*$_2$N), 3.44–3.36 (2H, m, OCH$_2$C*H*$_2$N), 2.11 (2H, d, *J* 7.0, C(O)C*H*$_2$Cy), 1.80–1.51 (6H, m, C(O)CH$_2$C*H*, 2 × CH$_2$, C*H*$_A$H$_B$), 1.21–1.17 (2H, m, CH$_2$), 1.13–0.98 (1H, m, CH$_A$*H*$_B$), 0.95–0.81 (2H, m, CH$_2$); δ_C ($CDCl_3$, 101 MHz) 171.0, 66.9, 66.7, 46.3, 41.8, 40.4, 35.0, 33.3, 26.2, 26.1; mp: 74–76 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 2921, 2851, 1632, 1362, 1233, 1114, 1033, 728;

HRMS (CI^+) $C_{12}H_{21}O_2N^+$ ($[M]^+$) requires 211.1557, found 211.1557.

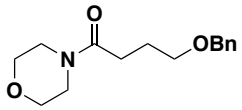
1-Morpholinopent-4-en-1-one, 68g



Synthesised according to the general procedure **A**, using 4-pentenoic acid (3.1 mL, 30 mmol), morpholine (2.9 mL, 33 mmol) and EDCI.HCl (6.3 g, 33 mmol) in CH_2Cl_2 (150 mL) to give the amide **68g** (4.17 g, 82%) as a colourless oil.

δ_H ($CDCl_3$, 400 MHz) 5.83–5.64 (1H, m, CH_2CH=CH_2), 4.95–4.83 (2H, m, CH_2CH=CH_2), 3.55– 3.49 (4H, m, 2 × OCH_2CH_2N), 3.49–3.44 (2H, m, OCH_2CH_2N), 3.36–3.31 (2H, m, OCH_2CH_2N), 2.32–2.21 (4H, m, $C(O)CH_2CH_2CH$=CH_2, $C(O)CH_2CH_2CH$=CH_2); δ_C ($CDCl_3$, 101 MHz) 170.7, 137.2, 115.2, 66.8, 66.5, 45.8, 41.8, 32.1, 29.0; *m/z* (ESI^+) 192 ($[M + Na]^+$, 100%). Data is consistent with the literature.[259]

4-(Benzyloxy)-1-morpholinobutan-1-one, 68h

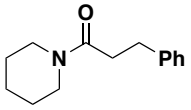


Using the procedure according to Landais *et al*,[260] γ-butyrolactone (1.9 mL, 25 mmol) and morpholine (2.2 mL, 25 mmol) were mixed together in a round bottomed flask and stirred for 8 h at 110 °C. The resulting pale yellow mixture was then added to a solution of Ag_2O (11.5 g, 49.6 mmol) and tetrabutylammonium iodide (910 mg, 2.5 mmol) in CH_2Cl_2 (100 mL). Benzyl bromide (6.0 mL, 51 mmol) was then added and the mixture was stirred for 48 h at room temperature shielded from the light. The crude mixture was then filtered

through Celite®, washed with CH_2Cl_2 and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica (eluent 50% EtOAc/petrol) to give the amide **68h** (3.77 g, 58% over two steps) as a colourless oil.

δ_H ($CDCl_3$, 400 MHz) 7.41–7.26 (5H, m, 5 × Ar*H*), 4.51 (2H, s, CH_2Ph), 3.63 (6H, m, 2 × OCH_2CH_2N, OCH$_2$CH_2N), 3.55 (2H, t, *J* 6.0, C(O)CH_2CH_2CH_2O), 3.48–3.43 (2H, m, OCH$_2$CH_2N), 2.53–2.38 (2H, m, C(O)CH$_2$CH$_2$CH_2O), 1.97 (2H, m, C(O)CH$_2$CH_2CH$_2$O); δ_C ($CDCl_3$, 101 MHz) 171.4, 138.4, 128.4, 127.6 (2C), 72.9, 69.4, 66.9, 66.7, 45.9, 41.9, 29.6, 25.3; *m/z* (ESI$^+$) 286 ([M + Na]$^+$, 100%). Data is consistent with the literature.[260]

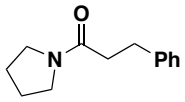
3-Phenyl-1-(piperidin-1-yl)propan-1-one, 68i



Synthesised according to the general procedure **A**, using hydrocinnamic acid (4.5 g, 30 mmol), piperidine (3.3 mL, 33 mmol) and EDCI.HCl (6.3 g, 33 mmol) in CH_2Cl_2 (150 mL) to give the amide **68i** (5.74 g, 88%) as a colourless oil.

δ_H ($CDCl_3$, 400 MHz) 7.36–7.15 (5H, m, 5 × Ar*H*), 3.61–3.51 (2H, m, NCH_2), 3.39–3.26 (2H, m, NCH_2), 2.97 (2H, t, *J* 8.0, C(O)CH_2CH$_2$Ph), 2.62 (2H, t, *J* 8.0, C(O)CH$_2$CH_2Ph), 1.68–1.56 (2H, m, CH_2), 1.56–1.40 (4H, m, 2 × CH_2); δ_C ($CDCl_3$, 101 MHz) 170.3, 141.4, 128.5, 128.4, 126.1, 46.6, 42.7, 35.2, 31.6, 26.4, 25.6, 24.5; *m/z* (ESI$^+$) 240 ([M + Na]$^+$, 100%). Data is consistent with the literature.[261]

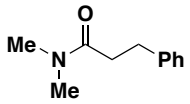
3-Phenyl-1-(pyrrolidin-1-yl)propan-1-one, 68j



Synthesised according to the general procedure **A**, using hydrocinnamic acid (4.5 g, 30 mmol), pyrrolidine (2.8 mL, 33 mmol) and EDCI.HCl (6.3 g, 33 mmol) in CH_2Cl_2 (150 mL) to give the amide **68j** (4.47 g, 73%) as a colourless oil.

δ_H ($CDCl_3$, 400 MHz) 7.34–7.17 (5H, m, 5 × Ar*H*), 3.47 (2H, t, *J* 7.0, NCH_2), 3.29 (2H, t, *J* 7.0, NCH_2), 3.00 (2H, t, *J* 8.0, C(O)CH_2CH$_2$Ph), 2.57 (2H, t, *J* 8.0, C(O)CH$_2$CH_2Ph), 1.95–1.77 (4H, m, 2 × CH_2); δ_C ($CDCl_3$, 101 MHz) 170.7, 141.5, 128.4 (2C), 126.1, 46.6, 45.67, 36.8, 31.2, 26.8, 24.4; *m/z* (ESI^+) 226 ($[M + Na]^+$, 100%). Data is consistent with the literature.[262]

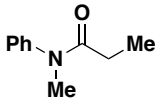
***N*,*N*-Dimethyl-3-phenylpropanamide, 68k**



Synthesised according to the general procedure **A**, using hydrocinnamic acid (4.5 g, 30 mmol), dimethylamine hydrochloride (2.7 g, 33 mmol), triethylamine (4.6 mL, 33 mmol) and EDCI.HCl (6.3 g, 33 mmol) in CH_2Cl_2 (150 mL) to give the amide **68k** (4.20 g, 79%) as a colourless oil.

δ_H ($CDCl_3$, 400 MHz) 7.34–7.18 (5H, m, 5 × Ar*H*), 3.00 (2H, t, *J* 8.0, C(O)CH_2CH$_2$Ph), 2.96 (3H, s, N(CH_3)$_A$(CH$_3$)$_B$), 2.94 (3H, s, N(CH$_3$)$_A$(CH_3)$_B$), 2.63 (2H, t, *J* 8.0, C(O)CH$_2$CH_2Ph); δ_C ($CDCl_3$, 101 MHz) 172.2, 141.5, 128.5, 128.4, 126.1, 37.2, 35.4, 35.3, 31.4; *m/z* (ESI^+) 200 ($[M + Na]^+$, 100%). Data is consistent with the literature.[263]

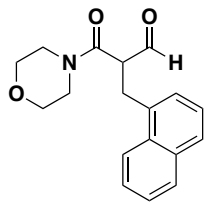
_N_-Methyl-_N_-phenylpropionamide, 68m



To a round bottomed flask containing CH_2Cl_2 (120 mL) was added pyridine (20 mmol, 250 mmol) under a N_2 atmosphere. The flask was cooled to 0 °C, and propionyl anhydride (7.7 mL, 60 mmol) was added slowly, followed by *N*-methylaniline (5.4 mL, 50 mmol). The reaction mixture was warmed up to room temperature and left to stir for 2 h. The mixture was subsequently washed with 1 N HCl (100 mL), 1 N NaOH solution (100 ml) and water (100 mL). The aqueous layers were back-extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica (eluent 80% EtOAc/petrol) to give the amide **68m** (6.78 g, 83%) as a pale brown solid.

δ_H ($CDCl_3$, 400 MHz) 7.31 (2H, t, *J* 7.5, 2 × Ar*H*), 7.23 (1H, t, *J* 7.5, Ar*H*), 7.09 (2H, d, *J* 7.5, 2 × Ar*H*), 3.16 (3H, s, NC*H*$_3$), 1.98 (2H, q, *J* 7.5, C(O)C*H*$_2$CH$_3$), 0.94 (3H, t, *J* 7.5, C(O)CH$_2$C*H*$_3$); δ_C ($CDCl_3$, 101 MHz) 173.8, 144.1, 129.6, 127.6, 127.2, 37.2, 27.4, 9.6; mp 54–56 °C (CH_2Cl_2); *m/z* (ESI$^+$) 186 ([M + Na]$^+$, 100%). Data is consistent with the literature.[264]

3-Morpholino-2-(naphthalen-1-ylmethyl)-3-oxopropanal, 69b

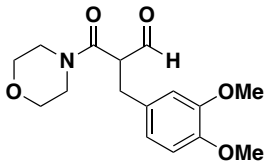


Synthesised according to the general procedure **B**, using 1-morpholino-3-(naphthalen-1-

yl)propan-1-one **68b** (2.20 g, 10.0 mmol), diisopropylamine (4.2 mL, 30 mmol), *n*-BuLi (2.5 M, 12 mL, 30 mmol) and methyl formate (6.17 mL, 100 mmol) in Et_2O (30 mL). The crude product was purified by flash chromatography on silica (eluent 40% EtOAc/petrol) to give the *aldehyde* **69b** (1.33 g, 49%) as a pale yellow solid.

δ_H ($CDCl_3$, 400 MHz) 9.86 (1H, d, *J* 2.5, C*H*O), 8.03 (1H, d, *J* 8.5, Ar*H*), 7.95–7.87 (1H, m, Ar*H*), 7.81 (1H, d, *J* 8.0, Ar*H*), 7.66–7.50 (2H, m, 2 × Ar*H*), 7.48–7.37 (2H, m, 2 × Ar*H*), 3.99–3.88 (1H, m, C*H*CH_2Ar), 3.80 (1H, dd, *J* 14.0, 5.0, CHCH_AH_BPh), 3.72–3.58 (2H, m, $CHCH_AH_B$Ar, $OCH_2CH_AH_BN$), 3.57–3.46 (1H, m, $OCH_AH_BCH_2N$), 3.41–3.21 (1H, m, $OCH_2CH_AH_BN$), 3.15–3.02 (2H, m, OCH_2CH_2N), 3.00–2.85 (1H, m, $OCH_2CH_AH_BN$), 2.64–2.39 (1H, m, $OCH_2CH_AH_BN$), 2.26–2.04 (1H, m, $OCH_AH_BCH_2N$); δ_C ($CDCl_3$, 101 MHz) 198.6, 167.7, 133.9, 133.3, 131.6, 129.2, 128.1, 127.7, 126.7, 126.0, 125.6, 122.9, 66.4, 65.6, 55.0, 46.1, 42.0, 32.0; mp: 51–53 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 2963, 2857, 1741, 1619, 1113, 801; *m/z* (ESI^+) 298 ($[M + Na]^+$, 100%); HRMS (ESI^+) $C_{18}H_{20}O_3N^+$ ($[M + H]^+$) requires 298.14377, found 298.14369.

2-(3,4-Dimethoxybenzyl)-3-morpholino-3-oxopropanal, 69c

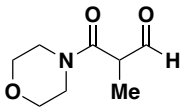


Synthesised according to the general procedure **B**, using 3-(3,4-dimethoxyphenyl)-1-morpholinopropan-1-one **68c** (2.79 g, 10.0 mmol), diisopropylamine (4.2 mL, 30 mmol), *n*-BuLi (2.5 M, 12 mL, 30 mmol) and methyl formate (6.17 mL, 100 mmol) in Et_2O (30 mL). The crude product was purified by flash chromatography on silica (eluent

40% acetone/petrol) to give the *aldehyde* **69c** (0.67 g, 22%) as a thick brown oil.

δ_H ($CDCl_3$, 400 MHz) 9.63 (1H, d, *J* 2.5, C*H*O), 6.73 (1H, d, *J* 8.0, Ar*H*), 6.69–6.62 (2H, m, 2 × Ar*H*), 3.79(0) (3H, s, OCH_3), 3.78(5) (3H, s, OCH_3), 3.64 (1H, td, *J* 7.5, 2.5,C*H*CH_2Ar), 3.57–3.51 (3H, m, OCH_2CH_2N, $OCH_AH_BCH_2N$), 3.47–3.36 (2H, m, OCH_2CH_2N), 3.25 (1H, ddd, *J* 13.0, 6.5, 3.0, $OCH_2CH_AH_BN$), 3.11 (2H, d, *J* 7.5, $CHCH_2Ar$), 3.04 (1H, ddd, *J* 11.5, 6.5, 3.0, $OCH_AH_BCH_2N$), 2.96 (1H, ddd, *J* 13.0, 6.5, 3.0, $OCH_2CH_AH_BN$); δ_C ($CDCl_3$, 101 MHz) 198.5, 167.2, 149.1, 148.1, 129.8, 121.0, 112.2, 111.4, 66.6, 66.3, 56.9, 56.0 (2C), 46.2, 42.3, 34.1; ν_{max} (neat)/cm^{-1} 2969, 2858, 1723, 1626, 1515, 1267, 1236, 1113, 1025; *m/z* (ESI^+) 362 ($[M + Na + MeOH]^+$, 100%); HRMS (ESI^+) $C_{16}H_{21}O_5NNa^+$ ($[M + Na]^+$) requires 330.13119, found 330.13107.

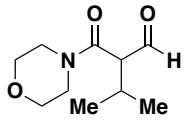
2-Methyl-3-morpholino-3-oxopropanal, 69d



Synthesised according to the general procedure **B**, using 1-morpholinopropan-1-one **68d** (1.43 g, 10.0 mmol), diisopropylamine (4.2 mL, 30 mmol), *n*-BuLi (2.5 M, 12 mL, 30 mmol) and methyl formate (6.17 mL, 100 mmol) in Et_2O (30 mL). The crude product was purified by flash chromatography on silica (eluent 30% acetone/petrol) to give the aldehyde **69d** (0.84 g, 49%) as a pale yellow oil.

δ_H ($CDCl_3$, 400 MHz) 9.57 (1H, d, *J* 2.0, C*H*O), 3.69–3.58 (5H, m, 2 × OCH_2CH_2N, $OCH_2CH_AH_BN$), 3.56–3.38 (4H, m, C(O)C*H*CH_3, OCH_2CH_2N, $OCH_2CH_AH_BN$), 1.34 (3H, d, *J* 7.0, C(O)CHCH_3); δ_C ($CDCl_3$, 101 MHz) 198.5, 168.2, 66.8, 66.6, 49.2, 46.2, 42.3, 11.8; *m/z* (ESI^+) 194 ($[M + Na]^+$, 100%). Data is consistent with the literature.[158]

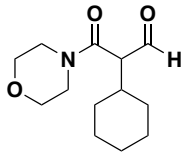
3-Methyl-2-(morpholine-4-carbonyl)butanal, 69e



Synthesised according to the general procedure **B**, using 3-methyl-1-morpholinobutan-1-one **68e** (1.71 g, 10.0 mmol), diisopropylamine (4.2 mL, 30 mmol), *n*-BuLi (2.5 M, 12 mL, 30 mmol) and methyl formate (6.17 mL, 100 mmol) in Et_2O (30 mL). The crude product was purified by flash chromatography on silica (eluent 30% acetone/petrol) to give the aldehyde **69e** (1.36 g, 68%) as a colourless oil.

δ_H ($CDCl_3$, 400 MHz) 9.60 (1H, d, *J* 4.5, C*H*O), 3.75–3.44 (8H, m, 2 × OCH_2CH_2N, 2 × OCH_2CH_2N), 3.13 (1H, dd, *J* 9.5, 4.5, C(O)C*H*CH$(CH_3)_2$), 2.56 (1H, dsep, *J* 9.5, 1.0, C(O)CHC*H*$(CH_3)_2$), 0.99 (3H, d, *J* 1.0, CH((CH_3)$_A$$(CH_3)_B$), 0.97 (3H, d, *J* 1.0, CH((CH_3)$_A$(CH_3)$_B$); δ_C ($CDCl_3$, 101 MHz) 200.3, 166.8, 66.9, 66.7, 62.5, 46.3, 42.3, 28.6, 20.8, 20.0; *m/z* (ESI^+) 222 ($[M + Na]^+$, 100%). Data is consistent with the literature.[158]

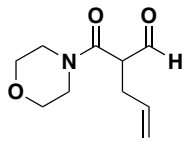
2-Cyclohexyl–3-morpholino-3-oxopropanal, 69f



Synthesised according to the general procedure **B**, using 2-cyclohexyl-1-morpholinoethan-1-one **68f** (2.11 g, 10.0 mmol), diisopropylamine (4.2 mL, 30 mmol), *n*-BuLi (2.5 M, 12 mL, 30 mmol) and methyl formate (6.17 mL, 100 mmol) in Et_2O (30 mL). The crude product was purified by flash chromatography on silica (eluent 30% acetone/petrol) to give the aldehyde **69f** (0.84 g, 36%) as a colourless oil.

δ_H ($CDCl_3$, 400 MHz) 9.58 (1H, d, *J* 4.5, C*H*O), 3.74–3.40 (8H, m, 2 × OC*H*$_2$CH$_2$N, 2 × OCH$_2$C*H*$_2$N), 3.18 (1H, dd, *J* 9.5, 4.5, C*H*CHO), 2.35–2.21 (1H, m, C(O)CHC*H*$(CH_2)_5$), 1.84–1.57 (6H, m, 3 × C*H*$_2$), 1.31–1.10 (2H, m, C*H*$_2$), 0.95 (2H, dddd, *J* 28.0, 25.0, 12.5, 3.5, C*H*$_2$); δ_C ($CDCl_3$, 101 MHz) 200.5, 166.8, 66.9, 66.7, 61.6, 46.3, 42.3, 37.8, 31.0, 30.6, 26.0 (2C), 25.8; *m/z* (ESI^+) 240 ($[M + H]^+$, 100%). Data is consistent with the literature.[158]

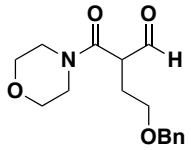
2-(Morpholine-4-carbonyl)pent-4-enal, 69g



Synthesised according to the general procedure **B**, using 1-morpholinopent-4-en-1-one **68g** (1.69 g, 10.0 mmol), diisopropylamine (4.2 mL, 30 mmol), *n*-BuLi (2.5 M, 12 mL, 30 mmol) and methyl formate (6.17 mL, 100 mmol) in Et_2O (30 mL). The crude product was purified by flash chromatography on silica (eluent 30% acetone/petrol) to give the aldehyde **69g** (1.41 g, 72%) as a colourless oil.

δ_H ($CDCl_3$, 400 MHz) 9.57 (1H, d, *J* 2.5, C*H*O), 5.75 (1H, ddt, *J* 17.0, 10.0, 7.0, C(O)CHCH$_2$C*H*=CH$_2$), 5.18–5.04 (2H, m, C(O)CHCH$_2$CH=C*H*$_2$), 3.76–3.41 (9H, m, C(O)C*H*CH$_2$CH=CH$_2$, 2 × OC*H*$_2$CH$_2$N, 2 × OCH$_2$C*H*$_2$N), 2.67 (2H, t, *J* 7.0, C(O)CHC*H*$_2$CH=CH$_2$); δ_C ($CDCl_3$, 101 MHz) 198.3, 166.6, 133.6, 118.1, 66.8, 66.7, 54.5, 46.3, 42.4, 31.6; *m/z* (ESI^+) 250 ($[M + Na + MeOH]^+$, 100%). Data is consistent with the literature.[158]

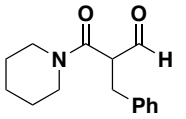
4-(Benzyloxy)-2-(morpholine-4-carbonyl)butanal, 69h



Synthesised according to the general procedure **B**, using 4-(benzyloxy)-1-morpholinobutan-1-one **68h** (2.63 g, 10.0 mmol), diisopropylamine (4.2 mL, 30 mmol), *n*-BuLi (2.5 M, 12 mL, 30 mmol) and methyl formate (6.17 mL, 100 mmol) in Et_2O (30 mL). The crude product was purified by flash chromatography on silica (eluent 30% acetone/petrol) to give the aldehyde **69h** (2.30 g, 79%) as a colourless oil.

δ_H ($CDCl_3$, 400 MHz) 9.63 (1H, d, *J* 2.5, C*H*O), 7.40–7.26 (5H, m, 5 × Ar*H*), 4.50 (1H, d, *J* 12.0, OC*H*$_A$H$_B$Ph), 4.46 (1H, d, *J* 12.0, OCH$_A$*H*$_B$Ph), 3.76 (1H, td, *J* 7.0, 2.5, C*H*CHO), 3.69–3.45 (10H, m, 2 × OC*H*$_2$CH$_2$N, 2 × OCH$_2$C*H*$_2$N, CHC*H*$_2$CH$_2$OBn), 2.31 (1H, dtd, *J* 14.5, 7.0, 4.0, CH$_2$C*H*$_A$H$_B$OBn), 2.17 (1H, dtd, *J* 14.5, 7.0, 4.0, CH$_2$CH$_A$*H*$_B$OBn); δ_C ($CDCl_3$, 101 MHz) 198.4, 167.2, 137.9, 128.4, 127.8, 127.6, 73.1, 67.2, 66.8, 66.7, 52.3, 46.2, 42.3, 27.9; *m/z* (ESI$^+$) 314 ([M + Na]$^+$, 100%). Data is consistent with the literature.[158]

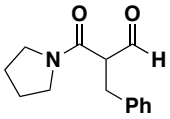
2-Benzyl-3-oxo-3-(piperidin-1-yl)propanal, 69i



Synthesised according to the general procedure **B**, using 3-phenyl-1-(piperidin-1-yl)propan-1-one **68i** (2.17 g, 10.0 mmol), diisopropylamine (4.2 mL, 30 mmol), *n*-BuLi (2.5 M, 12 mL, 30 mmol) and methyl formate (6.17 mL, 100 mmol) in Et_2O (30 mL). The crude product was purified by flash chromatography on silica (eluent 30% acetone/petrol) to give the aldehyde **69i** (1.53 g, 62%) as a colourless oil.

δ_H ($CDCl_3$, 400 MHz) 9.70 (1H, d, *J* 2.5, C*H*O), 7.33–7.27 (2H, m, 2 × Ar*H*), 7.26–7.18 (3H, m, 3 × Ar*H*), 3.80 (1H, td, *J* 7.5, 2.5, C(O)C*H*CHO), 3.68–3.58 (1H, m, NCH_AH_B), 3.49–3.40 (1H, m, NCH_AH_B), 3.23 (2H, d, *J* 7.5, CHCH_2Ph), 3.23–3.17 (1H, m, NC$H_{A'}H_{B'}$), 3.08 (1H, ddd, *J* 13.5, 7.0, 3.5, NC$H_{A'}H_{B'}$), 1.58–1.46 (3H, m, 1.5 × CH_2), 1.45–1.31 (2H, m, CH_2), 1.03–0.91 (1H, m, 0.5 × CH_2); δ_C ($CDCl_3$, 101 MHz) 198.7, 166.6, 137.7, 129.1, 128.7, 126.9, 56.9, 47.0, 43.1, 34.3, 26.0, 25.5, 24.2; *m/z* (ESI^+) 268 ($[M + Na]^+$, 100%). Data is consistent with the literature.[158]

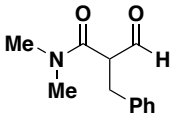
2-Benzyl-3-oxo-3-(pyrrolidin-1-yl)propanal, 69j



Synthesised according to the general procedure **B**, using 3-phenyl-1-(pyrrolidin-1-yl)propan-1-one **68j** (2.03 g, 10.0 mmol), diisopropylamine (4.2 mL, 30 mmol), *n*-BuLi (2.5 M, 12 mL, 30 mmol) and methyl formate (6.17 mL, 100 mmol) in Et_2O (30 mL). The crude product was purified by flash chromatography on silica (eluent 30% acetone/petrol) to give the aldehyde **69j** (1.64 g, 71%) as a colourless oil.

δ_H ($CDCl_3$, 400 MHz) 9.74 (1H, d, *J* 3.0, C*H*O), 7.33–7.26 (2H, m, 2 × Ar*H*), 7.26–7.19 (3H, m, 3 × Ar*H*), 3.60 (1H, ddd, *J* 9.0, 6.0, 3.0, C(O)C*H*CHO), 3.50–3.37 (2H, m, NCH_2), 3.36–3.27 (1H, m, NCH_AH_B), 3.23 (2H, dd, *J* 9.0, 6.0, CHCH_2Ph) 2.84–2.69 (1H, m, NCH_AH_B), 1.88–1.59 (4H, m, 2 × NCH_2CH_2); δ_C ($CDCl_3$, 101 MHz) 198.9, 166.8, 137.7, 129.0, 128.6, 126.9, 59.9, 46.6, 45.9, 34.3, 25.8, 24.2; *m/z* (ESI^+) 254 ($[M + Na]^+$, 100%). Data is consistent with the literature.[158]

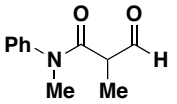
2-Benzyl-*N*,*N*-dimethyl-3-oxopropanamide, 69k



Synthesised according to the general procedure **B**, using *N*,*N*-dimethyl-3-phenylpropanamide **68k** (1.77 g, 10.0 mmol), diisopropylamine (4.2 mL, 30 mmol), *n*-BuLi (2.5 M, 12 mL, 30 mmol) and methyl formate (6.17 mL, 100 mmol) in Et_2O (30 mL). The crude product was purified by flash chromatography on silica (eluent 30% acetone/petrol) to give the aldehyde **69k** (1.34 g, 65%) as a pale yellow oil.

δ_H ($CDCl_3$, 400 MHz) 9.69 (1H, d, *J* 2.5, C*H*O), 7.35–7.17 (5H, m, 5 × Ar*H*), 3.79 (1H, td, *J* 7.5, 2.5, C*H*CH_2Ph), 3.22 (2H, d, *J* 7.5, CHC*H*$_2$Ph), 2.91 (3H, s, N(C*H*$_3$)$_A$(CH_3)$_B$), 2.69 (3H, s, N(CH_3)$_A$(C*H*$_3$)$_B$); δ_C ($CDCl_3$, 101 MHz) 198.5, 168.4, 137.7, 128.9, 128.7, 126.9, 57.4, 37.2, 35.6, 34.2; *m/z* (ESI^+) 228 ($[M + Na]^+$, 100%). Data is consistent with the literature.[158]

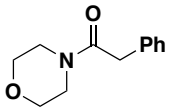
***N*,2-Dimethyl-3-oxo-*N*-phenylpropanamide, 69m**



Synthesised according to the general procedure **B**, using *N*-methyl-*N*-phenylpropionamide **68m** (1.63 g, 10.0 mmol), diisopropylamine (4.2 mL, 30 mmol), *n*-BuLi (2.5 M, 12 mL, 30 mmol) and methyl formate (6.17 mL, 100 mmol) in Et_2O (30 mL). The crude product was purified by flash chromatography on silica (eluent 30% acetone/petrol) to give the *aldehyde* **69m** (0.97 g, 51%) as a colourless oil. The product exists in an unknown mixture of diastereomers and tautomers. Data for the major compound below:

δ_H ($CDCl_3$, 400 MHz) 9.50 (1H, d, *J* 1.5, C*H*O), 7.51–7.24 (3H, m, 3 × Ar*H*), 7.24–7.05 (2H, m, 2 × Ar*H*), 4.19–4.01 (1H, m, C(O)C*H*CH_3), 3.24 (3H, s, NC*H*$_3$), 1.21 (3H, dd, *J* 7.0, 1.5, C(O)CHC*H*$_3$); δ_C ($CDCl_3$, 101 MHz) 198.8, 169.9, 143.1, 130.1, 128.4, 127.4, 50.3, 37.5, 12.5; ν_{max} (neat)/cm^{-1} 2979, 2937, 1727, 1642, 1594, 1498, 774, 701; *m/z* (ESI^+) 214 ($[M + Na]^+$, 100%); HRMS (ESI^+) $C_{11}H_{14}O_2N^+$ ($[M + H]^+$) requires 192.10191, found 192.10206.

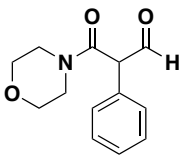
1-Morpholino-2-phenylethan-1-one, 68n



Synthesised according to the general procedure **A**, using phenylacetic acid (4.1 g, 30 mmol), morpholine (2.9 mL, 33 mmol) and EDCI.HCl (6.3 g, 33 mmol) in CH_2Cl_2 (150 mL) to give the amide **68n** (5.48 g, 89%) as a white crystalline solid.

δ_H ($CDCl_3$, 400 MHz) 7.35 (2H, td, *J* 7.0, 1.5, 2 × Ar*H*), 7.30–7.23 (3H, m, 3 × Ar*H*), 3.75 (2H, s, C(O)C*H*$_2$Ph), 3.66 (4H, br. s, 2 × OC*H*$_2$CH_2N), 3.53–3.42 (4H, m, 2 × OCH_2C*H*$_2$N); δ_C ($CDCl_3$, 101 MHz) 169.6, 134.8, 128.8, 128.5, 126.9, 66.8, 66.5, 46.5, 42.1, 40.9; mp 60–62 °C (CH_2Cl_2); *m/z* (ESI^+) 433 ($[2M + Na]^+$, 100%). Data is consistent with the literature.[265]

3-Morpholino-3-oxo-2-phenylpropanal, 69n

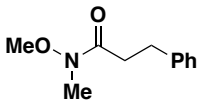


A flask containing 1-morpholino-2-phenylethan-1-one **68n** (2.05 g, 10.0 mmol) and ethyl formate (2.8 mL, 35 mmol) in CH_2Cl_2 (3 mL) was cooled to 0 °C. To this was added a

solution of $TiCl_4$ (2.75 mL, 25.0 mmol) in CH_2Cl_2 (3 mL) *via* syringe pump over 30 min, followed by syringe pump addition of Et_3N (4.9 mL, 35 mmol) over another 30 min. The reaction mixture was slowly warmed to room temperature and stirred for 16 h, followed by quenching with 1 N HCl (10 mL) and diluted with water (50 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The organic extracts were combined, dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica (eluent 30% acetone/petrol) to give the aldehyde **69n** (1.93 g, 83%) as pale yellow oil.

δ_H ($CDCl_3$, 400 MHz) 9.85 (1H, d, *J* 3.5, C*H*O), 7.49–7.31 (4H, m, 4 × Ar*H*), 7.22–7.17 (1H, m, Ar*H*), 4.50 (1H, d, *J* 3.5, C(O)C*H*Ph), 3.83–3.67 (2H, m, $OCH_AH_BCH_2N$, $OCH_2CH_AH_BN$), 3.64–3.49 (3H, m, OCH_2CH_2N, $OCH_2CH_AH_BN$), 3.45–3.29 (1H, m, $OCH_2CH_AH_BN$), 3.28–3.17 (2H, m, $OCH_AH_BCH_2N$, $OCH_2CH_AH_BN$); δ_C ($CDCl_3$, 101 MHz) 196.3, 167.5, 131.3, 129.7, 128.6, 128.4, 66.6, 66.1, 61.2, 45.9, 41.9; *m/z* (ESI^+) 234 ($[M + H]^+$, 100%). Data is consistent with the literature.[158]

_N_-Methoxy-_N_-methyl-3-phenylpropanamide, 105

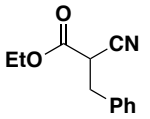


Synthesised according to the general procedure **A**, using hydrocinnamic acid (4.5 g, 30 mmol), *N*,*O*-dimethylhydroxylamine hydrochloride (3.2 g, 33 mmol), triethylamine (4.6 mL, 33 mmol) and EDCI.HCl (6.3 g, 33 mmol) in CH_2Cl_2 (150 mL) to give the amide **105** (4.93 g, 85%) as a colourless oil.

δ_H ($CDCl_3$, 400 MHz) 7.39–7.16 (5H, m, 5 × Ar*H*), 3.62 (3H, s, $N(CH_3)OCH_3$), 3.20 (3H, s,

N(C*H*$_3$)OCH$_3$), 2.99 (2H, t, *J* 8.0, C(O)C*H*$_2$CH$_2$Ph), 2.77 (2H, t, *J* 8.0, C(O)CH$_2$C*H*$_2$Ph); δ_C ($CDCl_3$, 101 MHz) 173.8, 141.4, 128.5, 128.5, 126.1, 61.2, 33.8, 32.2, 30.7; *m/z* (ESI^+) 216 ($[M + Na]^+$, 100%). Data is consistent with the literature.[262]

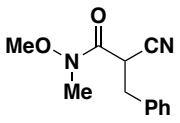
Ethyl 2-cyano-3-phenylpropanoate, 108



To a round bottomed flask containing EtOH (200 mL) was added benzaldehyde (20.4 mL, 200 mmol), ethyl cyanoacetate (10.6 mL, 100 mmol) and *o*-phenylenediamine (10.8 g, 100 mmol). Proline (2.3 g, 20 mmol) was then added and the reaction stirred at room temperature for 16 h. The solvent was removed *in vacuo* and the crude residue was purified by flash chromatography on silica (eluent 50% EtOAc/petrol) to give the ester **108** (17.77 g, 87%) as a yellow oil.

δ_H ($CDCl_3$, 400 MHz) 7.39–7.25 (5H, m, 5 × Ar*H*), 4.23 (2H, q, *J* 7.0, $CO_2C\mathit{H}_2CH_3$), 3.75 (1H, dd, *J* 8.5, 6.0, C(O)C*H*CN), 3.28 (1H, dd, *J* 13.5, 6.0, CH_AH$_B$Ph), 3.20 (1H, dd, *J* 13.5, 8.5, CH_AH$_B$Ph), 1.27 (3H, t, *J* 7.0, $CO_2CH_2C\mathit{H}_3$); δ_C ($CDCl_3$, 101 MHz) 165.5, 135.4, 129.1, 128.8, 127.7, 116.2, 62.9, 39.6, 35.7, 13.9; *m/z* (ESI^+) 204 ($[M + H]^+$, 100%). Data is consistent with the literature.[266]

2-Cyano-*N*-methoxy-*N*-methyl-3-phenylpropanamide, 109

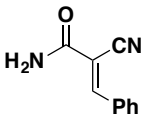


A solution of trimethylaluminium (2 M in PhCl, 25 mL, 50 mmol) was added dropwise to a

suspension of *N,O*-dimethylhydroxylamine hydrochloride (4.88 g, 50.0 mmol) in toluene (25 mL) at 0 °C for 30 min. The mixture was stirred at room temperature for 1 h. This solution was then added dropwise to a solution of ethyl 2-cyano-3-phenylpropanoate, **108**, (5.08 g, 25.0 mmol) in THF (25 mL) at 0 °C for 20 min. After stirring at room temperature for 16 h, the mixture was diluted carefully with 1 N HCl (25 mL) and extracted with EtOAc (50 mL). The organic phase was washed with brine (50 mL), dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica (eluent 25% EtOAc/petrol) to give the *amide* **109** (4.09 g, 75%) as a thick yellow oil.

δ_H ($CDCl_3$, 400 MHz) 7.40–7.33 (2H, m, 2 × Ar*H*), 7.32–7.24 (3H, m, 3 × Ar*H*), 4.07 (1H, dd, *J* 8.5, 7.0, C(O)C*H*CN), 3.69 (3H, s, OCH_3), 3.28 (1H, dd, *J* 13.5, 6.5, CH_AH$_B$Ph), 3.22 (3H, s, NCH_3), 3.18 (1H, dd, *J* 13.5, 8.5, CH$_A$$H_B$Ph); δ_C ($CDCl_3$, 101 MHz) 165.3, 136.3, 129.1, 128.8, 127.5, 117.1, 61.6, 36.5, 35.3, 32.6; ν_{max} (neat)/cm^{-1} 2941, 2824, 1669, 1455, 975, 700; HRMS (CI^+) $C_{12}H_{28}O_2N_3^+$ ($[M + NH_4]^+$) requires 236.1399, found 236.1399.

(*E*)-2-Cyano-3-phenylacrylamide, 110

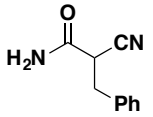


Benzaldehyde (2.0 mL, 20 mmol) and cyanoacetamide (1.68 g, 20.0 mmol) were dissolved in EtOH (50 mL), to which 6 drops of piperidine were added and the solution was stirred for 24 h at room temperature. The solvent was evaporated under reduced pressure to give a solid crude product which was recrystallised from EtOH, to give the amide **110** (2.71 g, 79%) as a pale yellow crystalline solid.

δ_H (DMSO-d^6, 400 MHz) 8.20 (1H, s, C=C*H*(Ph)), 8.05–7.92 (3H, m, 2 × Ar*H*,

C(O)NH_AH$_B$), 7.81 (1H, br. s, C(O)NH$_A$$H_B$), 7.68–7.36 (3H, m, 3 × Ar*H*); δ_C (DMSO-*d*^{6}, 101 MHz) 163.2, 151.1, 132.8, 132.4, 130.5, 129.7, 116.9, 107.1; mp 120–121 °C (EtOH); *m/z* (ESI$^+$) 173 ([M + H]$^+$, 100%). Data is consistent with the literature.[266]

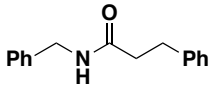
2-Cyano-3-phenylpropanamide, 111



(*E*)-2-Cyano-3-phenylacrylamide **110** (2.41 g, 14 mmol) and zinc powder (14.65 g, 224 mmol) were dissolved in glacial acetic acid (60 mL) and the solution was stirred for 3 h at 100 °C. The reaction mixture was then cooled to room temperature, filtered through a Celite® pad and washed with EtOAc (100 mL). The filtrate was neutralised with saturated aqueous $NaHCO_3$ solution and the organic layer was separated, washed with brine (50 mL), dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude solid product was recrystallised from EtOH to give the amide **110** (1.19 g, 49%) as a white crystalline solid.

δ_H (DMSO-*d*^{6}, 400 MHz) 7.80 (1H, s, C(O)NH_AH$_B$), 7.51 (1H, s, C(O)NH$_A$$H_B$), 7.46–7.20 (5H, m, 5 × Ar*H*), 3.95 (1H, dd, *J* 9.0, 6.5, C(O)C*H*CN), 3.17 (1H, dd, *J* 13.5, 6.5, CH_AH$_B$Ph), 3.05 (1H, dd, *J* 13.5, 9.0, CH$_A$$H_B$Ph); δ_C (DMSO-*d*^{6}, 101 MHz) 166.8, 137.3, 129.4, 128.9, 127.5, 118.9, 40.0, 35.7; mp 129–130 °C (EtOH); *m/z* (ESI$^+$) 175 ([M + H]$^+$, 100%). Data is consistent with the literature.[266]

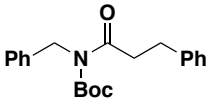
_N_-Benzyl-3-phenylpropanamide, 113



Synthesised according to the general procedure **A**, using hydrocinnamic acid (4.5 g, 30 mmol), benzylamine (3.6 mL, 33 mmol) and EDCI.HCl (6.3 g, 33 mmol) in CH_2Cl_2 (150 mL) to give the amide **113** (6.58 g, 92%) as a white crystalline solid.

δ_H ($CDCl_3$, 400 MHz) 7.34–7.26 (5H, m, 5 × Ar*H*), 7.26–7.18 (3H, m, 3 × Ar*H*), 7.18–7.12 (2H, m, 2 × Ar*H*), 6.36 (1H, br. s., N*H*), 4.37 (2H, d, *J* 6.0, NHCH_2Ph), 2.98 (2H, t, *J* 8.0, C(O)CH_2CH$_2$Ph), 2.52 (2H, t, *J* 9.0, C(O)CH$_2$CH_2Ph); δ_C ($CDCl_3$, 101 MHz) 172.2, 140.9, 138.3, 128.6(1), 128.5(5), 128.4, 127.7, 127.3, 126.2, 43.4, 38.3, 31.8; mp 80–82 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 3285, 3061, 3028, 2928, 1638, 1537, 1453, 1221, 695. Data is consistent with the literature.[263]

***tert*-Butyl benzyl(3-phenylpropanoyl)carbamate, 114**

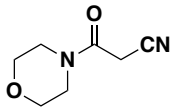


To a round-bottomed flask was added *N*-benzyl-3-phenylpropanamide **113** (3.6 g, 15 mmol), di-*tert*-butyl dicarbonate (6.55 g, 30.0 mmol), DMAP (0.73 g, 6.0 mmol) in CH_3CN (15 mL). The reaction mixture was stirred for 2 h under an N_2 atmosphere. The resulting mixture was concentrated *in vacuo* to give a thick oil, which was purified by flash chromatography on silica (eluent EtOAc:Et$_3$N:petrol in a 16:3:81 ratio) to give the *amide* **114** (4.68 g, 92%) as a white crystalline solid.

δ_H ($CDCl_3$, 400 MHz) 7.42–7.16 (10H, m, 10 × Ar*H*), 4.94 (2H, s, NHCH_2Ph), 3.31 (2H, dd,

J 8.5, 7.0, C(O)C*H*$_2$CH$_2$Ph), 3.06 (2H, dd, *J* 8.5, 7.0, C(O)CH$_2$C*H*$_2$Ph), 1.44 (9H s, C(C*H*$_3$)$_3$); δ_C ($CDCl_3$, 101 MHz) 175.4, 153.1, 141.2, 138.3, 128.6, 128.4, 128.3, 127.5, 127.1, 126.0, 83.2, 47.4, 40.0, 31.3, 27.9; mp: 64–66 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 2979, 1731, 1693, 1367, 1143, 995, 697; HRMS (CI^+) $C_{21}H_{26}O_3N^+$ ($[M + H]^+$) requires 340.1917, found 340.1917.

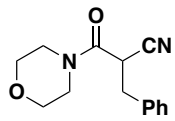
3-Morpholino-3-oxopropanenitrile, 119



In a round bottomed flask, morpholine (5.3mL, 60 mmol) was added to methyl cyanoacetate (5.3 mL, 60 mmol) and the mixture was stirred at room temperature for 16 h. A yellow solid started to precipitate from the reaction mixture, which was filtered and washed with Et_2O leading to the amide **119** (8.81 g, 95%) as brown crystalline solid.

δ_H ($CDCl_3$, 400 MHz) 3.73–3.65 (4H, m, 2 × OC*H*$_2$CH$_2$N), 3.62–3.57 (2H, m, OCH$_2$C*H*$_2$N), 3.55 (2H, s, C*H*$_2$CN), 3.47–3.39 (2H, m, OCH$_2$C*H*$_2$N); δ_C ($CDCl_3$, 101 MHz) 160.9, 114.5, 66.7, 66.4, 46.8, 42.9, 25.2; mp 82–84 °C (EtOH); *m/z* (ESI^+) 177 ($[M + Na]^+$, 100%). Data is consistent with the literature.[267]

2-Benzyl-3-morpholino-3-oxopropanenitrile, 120

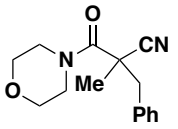


To a round bottomed flask containing sodium hydride (60% in mineral oil, 1.2 g, 30 mmol) in THF (45 mL) at 0 °C was added a solution of 3-morpholino-3-oxopropanenitrile **119** (5.2 g, 40 mmol) and the resulting mixture stirred at this temperature for 30 min. Benzyl

bromide (3.8 mL, 32 mmol) was then slowly added, and the reaction was stirred at room temperature for 16 h. The mixture was then carefully quenched with water (50 mL) and then extracted with Et_2O (2 × 50 mL). The organic phase was washed with water (2 × 50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica (eluent 50% EtOAc/petrol) to give the amide **120** (7.49 g, 99%) as a thick colourless oil.

δ_H ($CDCl_3$, 400 MHz) 7.41–7.22 (5H, m, 5 × Ar*H*), 3.87 (1H, t, *J* 7.5, C*H*CH_2Ph), 3.70–3.51 (5H, m, OC*H*$_2$$CH_2N, OCH_2C*H*_2$N, OC*H*$_A$$H_B$$CH_2$N), 3.49–3.38 (1H, m, OCH_2C*H*$_A$$H_B$N), 3.35–3.08 (4H, m, CHC*H*$_2$Ph, OCH_2CH_A*H*$_B$N, OCH_A*H*$_B$$CH_2$N); δ_C ($CDCl_3$, 101 MHz) 163.0, 136.0, 129.2, 128.9, 127.7, 117.2, 66.4, 66.0, 46.5, 42.9, 36.5, 36.1; *m/z* (ESI^+) 267 ($[M + Na]^+$, 100%). Data is consistent with the literature.[268]

General procedure D for the methylation of *α*-carbonyl groups, as exemplified by the synthesis of 2-benzyl-2-methyl-3-morpholino-3-oxopropanenitrile, 121

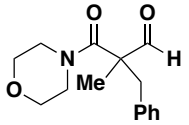


To a round bottomed flask containing sodium hydride (60% in mineral oil, 1.44 g, 36.0 mmol) in THF (45 mL) at 0 °C was added 2-benzyl-3-morpholino-3-oxopropanenitrile **120** (7.3 g, 30 mmol), and the resulting mixture stirred at this temperature for 30 min. Iodomethane (5.6 mL, 90 mmol) was then slowly added, and the reaction was stirred at room temperature for 2 h. The mixture was then carefully quenched with water (5 mL) and, once the evolution of gas had ceased, it was partitioned between CH_2Cl_2 (100 mL) and water (100 mL). The organic phase was washed with water (2 × 50 mL), dried over $MgSO_4$, filtered

and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica (eluent 50% EtOAc/petrol) to give the *amide* **121** (7.13 g, 92%) as a white crystalline solid.

δ_H ($CDCl_3$, 400 MHz) 7.49–7.13 (5H, m, 5 × Ar*H*), 3.72–3.49 (8H, m, 2 × OC*H*$_2$CH$_2$N, 2 × OCH$_2$C*H*$_2$N), 3.20 (1H, d, *J* 13.5, C*H*$_A$H$_B$Ph), 2.96 (1H, d, *J* 13.5, CH$_A$*H*$_B$Ph), 1.52 (3H, s, C*H*$_3$); δ_C ($CDCl_3$, 101 MHz) 165.9, 134.4, 130.5, 128.6, 127.9, 121.0, 66.2 (2C), 47.6, 44.1, 43.6, 41.9, 24.1; mp: 60–62 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 2922, 2857, 1650, 1454, 1116, 1028, 702; HRMS (CI$^+$) $C_{15}H_{19}O_2N_2^+$ ([M + H]$^+$) requires 259.1448, found 259.1448.

General procedure E for the reduction of nitrile groups to aldehydes, as exemplified by the synthesis of 2-benzyl-2-methyl-3-morpholino-3-oxopropanal, 118

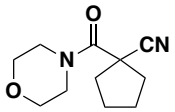


To a solution of 2-benzyl-2-methyl-3-morpholino-3-oxopropanenitrile **121** (2.07 g, 8.0 mmol, 1.0 equiv.) in a mixture of 1:1:2 water:acetic acid:pyridine (60 mL) was added at 0 ºC Raney®-Nickel (50% in water, 11.3 g, 96.0 mmol, 12.0 equiv.) and sodium hypophosphite monohydrate (10.2 g, 96.0 mmol, 12.0 equiv.). The reaction was stirred at 90 ºC for 16 h before being filtered through Celite®. The filtrate was extracted with CH_2Cl_2 (2 × 60 mL). The combined organic phases were washed with 1 N HCl (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica (eluent 50% EtOAc/petrol) to give the *aldehyde* **118** (1.58 g, 76%) as an off-white solid.

δ_H ($CDCl_3$, 400 MHz) 9.70 (1H, s, C*H*O), 7.42–7.20 (3H, m, 3 × Ar*H*), 7.20–7.05 (2H, m,

2 × Ar*H*), 3.87–3.33 (8H, m, 2 × OC*H*$_2$CH$_2$N, 2 × OCH$_2$C*H*$_2$N), 3.22 (2H, s, C*H*$_2$Ph), 1.34 (3H, s, C*H*$_3$); δ_C ($CDCl_3$, 101 MHz) 200.0, 169.1, 135.6, 130.5, 128.4, 127.1, 66.6, 58.5, 43.6, 39.9, 18.9; mp: 94–96 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 2979, 2857, 1720, 1637, 1115, 1029, 702; HRMS (CI$^+$) $C_{15}H_{20}O_3N^+$ ([M + H]$^+$) requires 262.1442, found 262.1442.

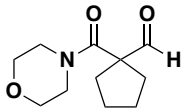
General Procedure F for the cycloalkylation of active methylene compounds, as exemplified by the synthesis of 1-(morpholine-4-carbonyl)cyclopentane-1-carbonitrile, 122



Following the procedure by Gnanaprakasam,[269] to a round bottomed flask containing 3-morpholino-3-oxopropanenitrile **119** (4.62 g, 30.0 mmol, 1.0 equiv.) and powdered K_2CO_3 (10.4 g, 75.0 mmol, 2.5 equiv.) in DMF (60 mL) was added 1,4-dibromobutane (3.9 mL, 33 mmol, 1.1 equiv.) and a catalytic amount of [bmim]BF_4 (0.56 mL, 3.0 mmol, 0.1 equiv.). The reaction mixture was left to stir for 16 h, filtered and washed with Et_2O. The filtrate was diluted with water (200 mL) and extracted with Et_2O (4 × 75 mL). The organic layers were combined and washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica (eluent 40% EtOAc/petrol) to give the *amide* **122** (3.06 g, 49%) as a colourless oil.

δ_H ($CDCl_3$, 400 MHz) 3.87–2.99 (8H, m, 2 × OC*H*$_2$CH$_2$N, 2 × OCH$_2$C*H*$_2$N), 2.20–2.01 (2H, m, (C)C*H*$_2$CH$_2$), 2.01–1.83 (2H, m, (C)C*H*$_2$CH$_2$), 1.63–1.22 (4H, m, 2 × (C)CH$_2$C*H*$_2$); δ_C ($CDCl_3$, 101 MHz) 165.2, 121.8, 66.3, 65.7, 47.1, 44.6, 43.5, 37.1, 25.0; mp: 62–64 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 2961, 2859, 1649, 1425, 1237, 1114, 730; HRMS (EI$^+$) $C_{11}H_{16}O_2N_2^+$ ([M]$^+$) requires 208.1205, found 208.1212.

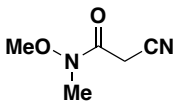
1-(Morpholine-4-carbonyl)cyclopentane-1-carbaldehyde, 123



Synthesised according to the general procedure **E**, using 1-(morpholine-4-carbonyl)cyclopentane-1-carbonitrile **122** (1.25 g, 6.0 mmol), Raney®-Ni (50% in water, 8.45 g, 72.0 mmol), sodium hypophosphite monohydrate (3.82 g, 36.0 mmol) in a 1:1:2 mixture of water:acetic acid:pyridine (60 mL). The crude product was purified by flash chromatography on silica (eluent 50% EtOAc/petrol) to give the *aldehyde* **123** (1.01 g, 60%) as an off-white solid.

δ_H ($CDCl_3$, 400 MHz) 9.44 (1H, s, C*H*O), 3.97–3.42 (6H, m, 2 × O$CH_2$$CH_2N, OCH_2CH_2$N), 3.35–3.01 (2H, m, OC$H_2CH_2$N), 2.21–2.11 (2H, m, (C)CH_2CH_2), 2.11–2.01 (2H, m, (C)CH_2CH_2), 1.70–1.61 (2H, m, (C)CH_2CH_2), 1.60–1.50 (2H, m, (C)CH_2CH_2); δ_C ($CDCl_3$, 101 MHz) 197.8, 169.1, 66.8, 66.4, 65.4, 46.5, 43.3, 37.4, 31.5, 25.9, 25.2; mp: 88–90 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 2958, 2861, 1716, 1636, 1424, 1235, 1114; HRMS (CI^+) $C_{11}H_{18}O_3N^+$ ($[M + H]^+$) requires 212.1288, found 212.1288.

2-Cyano-*N*-methoxy-*N*-methylacetamide, 124

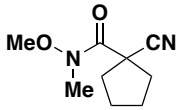


Synthesised according to the general procedure **A**, using cyanoacetic acid (4.25 g, 50.0 mmol), *N,O*-dimethylhydroxylamine hydrochloride (5.37 g, 55.0 mmol), triethylamine (7.7 mL, 55 mmol) and EDCI.HCl (10.5 g, 55 mmol) in CH_2Cl_2 (200 mL). The crude product was purified by flash chromatography on silica (eluent 50% EtOAc/petrol) to give amide

124 (4.80 g, 75%) as a dark yellow solid.

δ_H ($CDCl_3$, 400 MHz) 3.78 (3H, s, OC*H*$_3$), 3.60 (2H, s, C(O)C*H*$_2$CN), 3.23 (3H, s, NC*H*$_3$); δ_C ($CDCl_3$, 101 MHz) 163.0, 114.0, 61.7, 32.5, 24.0; mp 50–52 °C (EtOH); *m/z* (ESI^+) 151 ($[M + Na]^+$, 100%). Data is consistent with the literature.[270]

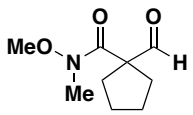
1-Cyano-*N*-methoxy-*N*-methylcyclopentane-1-carboxamide, 125



Synthesised according to the general procedure **F**, using 2-cyano-*N*-methoxy-*N*-methylacetamide **124** (4.10 g, 32.0 mmol), Cs_2CO_3 (26.1 g, 80.0 mmol), 1,4-dibromobutane (3.8 mL, 32 mmol) and [bmim]BF_4 (0.60 mL, 3.2 mmol) in DMF (50 mL). The crude product was purified by flash chromatography on silica (eluent 40% EtOAc/petrol) to give the amide **125** (4.11 g, 71%) as a colourless oil.

δ_H ($CDCl_3$, 400 MHz) 3.81 (3H, s, OC*H*$_3$), 3.20 (3H, s, NC*H*$_3$), 2.33–2.15 (4H, m, 2 × (C)C*H*$_2$CH$_2$), 1.96–1.61 (4H, m, 2 × (C)CH$_2$C*H*$_2$); δ_C ($CDCl_3$, 101 MHz) 168.6, 122.2, 60.8, 45.5, 36.7, 33.3, 25.0; *m/z* (ESI^+) 205 ($[M + Na]^+$, 100%). Data is consistent with the literature.[270]

1-Formyl-*N*-methoxy-*N*-methylcyclopentane-1-carboxamide, 126

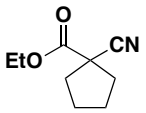


Synthesised according to the general procedure **E**, using 1-cyano-*N*-methoxy-*N*-methylcyclopentane-1-carboxamide **125** (1.09 g, 6.0 mmol), Raney®-Ni (50% in water,

11.3 g, 96 mmol), sodium hypophosphite monohydrate (10.2 g, 96.0 mmol) in a 1:1:2 mixture of water:acetic acid:pyridine (60 mL). The crude product was purified by flash chromatography on silica (eluent 50% EtOAc/petrol) to give the *aldehyde* **126** (0.39 g, 35%) as a yellow oil.

δ_H ($CDCl_3$, 400 MHz) 9.45 (1H, s, C*H*O), 3.55 (3H, s, OCH_3), 3.20 (3H, s, NCH_3), 2.15–1.98 (4H, m, 2 × (C)CH_2CH_2), 1.75–1.64 (2H, m, (C)CH_2CH_2), 1.64–1.54 (2H, m, (C)CH_2CH_2); δ_C ($CDCl_3$, 101 MHz) 196.4, 173.5, 63.7, 60.8, 33.0, 31.6, 25.9; ν_{max} (neat)/cm^{-1} 2944, 2811, 1719, 1659, 1365, 988; HRMS (CI^+) $C_9H_{16}O_3N^+$ ($[M + H]^+$) requires 186.1130, found 186.1130.

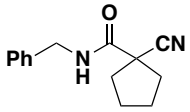
Ethyl 1-cyanocyclopentane-1-carboxylate, 127



Synthesised according to the general procedure **F**, using ethyl cyanoacetate (10.6 mL, 100 mmol), K_2CO_3 (34.6 g, 250 mmol), 1,4-dibromobutane (13.1 mL, 110 mmol) and [bmim]BF_4 (1.87 mL, 10.0 mmol) in DMF (150 mL). The crude product was purified by flash chromatography on silica (eluent 20% EtOAc/petrol) to give the ester **127** (15.69 g, 94%) as a colourless oil.

δ_H ($CDCl_3$, 400 MHz) 4.22 (2H, q, *J* 7.0, $CO_2CH_2CH_3$), 2.35–2.10 (4H, m, 2 × (C)CH_2CH_2), 1.96–1.71 (4H, m, 2 × (C)CH_2CH_2), 1.28 (3H, t, *J* 7.0, $CO_2CH_2CH_3$); δ_C ($CDCl_3$, 101 MHz) 169.5, 121.0, 62.6, 47.5, 37.6, 25.1, 13.9; *m/z* (ESI^+) 190 ($[M + Na]^+$, 100%). Data is consistent with the literature.[269]

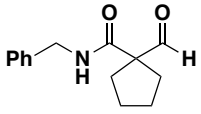
_N_-Benzyl-1-cyanocyclopentane-1-carboxamide, 128



A solution of trimethylaluminium (2 M in PhCl, 25 mL, 50 mmol) was added dropwise to a suspension of benzylamine (5.46 mL, 50.0 mmol) in toluene (25 mL) at 0 °C for 30 min. The mixture was stirred at room temperature for 1 h. This solution was then added dropwise to a solution of ethyl 1-cyanocyclopentane-1-carboxylate **127**, (4.18 g, 25.0 mmol) in THF (25 mL) at 0 °C for 20 min. After stirring at room temperature for 16 h, the mixture was diluted carefully with 1 N HCl (25 mL) and extracted with EtOAc (50 mL). The organic phase was washed with brine (50 mL), dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica (eluent 25% EtOAc/petrol) to give the *amide* **128** (4.09 g, 75%) as a thick yellow oil.

δ_H ($CDCl_3$, 400 MHz) 7.62–6.84 (5H, m, 5 × Ar*H*), 6.60 (1H, br. s, N*H*), 4.40 (2H, d, *J* 5.5, NC*H*$_2$Ph), 2.33 2.19 (2H, m, (C)C*H*$_2$CH$_2$), 2.18–2.07 (2H, m, (C)C*H*$_2$CH$_2$), 1.90–1.71 (4H, m, 2 × (C)CH$_2$C*H*$_2$); δ_C ($CDCl_3$, 101 MHz) 168.3, 137.2, 128.9, 127.8, 127.7, 122.8, 48.1, 44.4, 38.0, 25.5; ν_{max} (neat)/cm^{-1} 3336, 2950, 2874, 1664, 1524, 1269, 698; *m/z* (ESI$^+$) 251 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{14}H_{17}ON_2^+$ ([M + H]$^+$) requires 229.13354, found 229.13368.

_N_-Benzyl-1-formylcyclopentane-1-carboxamide, 129

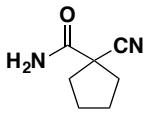


Synthesised according to the general procedure **E**, using *N*-benzyl-1-cyanocyclopentane-1-

carboxamide **128** (1.14 g, 5.0 mmol), Raney®-Ni (50% in water, 11.3 g, 96 mmol), sodium hypophosphite monohydrate (10.2 g, 96.0 mmol) in a 1:1:2 mixture of water:acetic acid:pyridine (60 mL). The crude product was purified by flash chromatography on silica (eluent 20% EtOAc/petrol) to give the *aldehyde* **129** (0.55 g, 48%) as yellow oil.

δ_H ($CDCl_3$, 400 MHz) 9.49 (1H, s, C*H*O), 7.31–7.24 (2H, m, 2 × Ar*H*), 7.24–7.14 (3H, m, 3 × Ar*H*), 6.44 (1H, br. s, N*H*), 4.37 (2H, d, *J* 5.5, CH_2Ph), 2.49–1.94 (4H, m, 2 × (C)CH_2CH_2), 1.83–1.68 (2H, m, (C)CH_2CH_2), 1.61–1.53 (2H, m, (C)CH_2CH_2); δ_C ($CDCl_3$, 101 MHz) 201.7, 170.6, 138.0, 128.8, 127.6, 127.6, 65.1, 43.8, 32.6, 26.0; ν_{max} (neat)/cm^{-1} 3327, 2957, 2871, 1724, 1624, 1527, 698; HRMS (CI^+) $C_{14}H_{17}O_2N^+$ ($[M + H]^+$) requires 232.1338, found 232.1338.

1-Cyanocyclopentane-1-carboxamide, 130

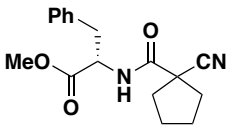


Ethyl 1-cyanocyclopentane-1-carboxylate **127** (2.51 g, 15.0 mmol) was added to a solution of ammonia (32 mL, 7 N in MeOH, 225 mmol) and the mixture was left to stir at room temperature for 16 h. The solvent was then evaporated to give a solid crude product which was recrystallised from EtOH, giving the *amide* **130** (1.65 g, 79%) as a white crystalline solid.

δ_H ($CDCl_3$, 400 MHz) 6.62 (1H, br. s, N*H*), 6.51 (1H, br. s, N*H*), 2.46–2.11 (4H, m, 2 × (C)CH_2CH_2), 2.05–1.58 (4H, m, 2 × (C)CH_2CH_2); δ_C ($CDCl_3$, 101 MHz) 171.2, 122.7, 47.6, 37.8, 25.4; mp: 126–128 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 3407, 3148, 2963, 2880, 2238, 1696, 1376, 825, 721; HRMS (CI^+) $C_7H_{11}ON_2^+$ ($[M + H]^+$) requires 139.0870, found

139.0870.

Methyl (1-cyanocyclopentane-1-carbonyl)-*L*-phenylalaninate, 132

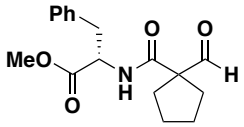


To a stirring solution of ethyl 1-cyanocyclopentane-1-carboxylate **127** (3.02 g, 30.0 mmol) in water (31.6 mL) and ethanol (60 mL) at 60 °C was added a solution of potassium *tert*-butoxide (3.36 g, 30 mmol) in ethanol (30 mL) dropwise over 30 min. The reaction mixture was stirred for 16 h at this temperature, after which the solvent was removed under reduced pressure. To the remaining residue was added Et_2O (30 mL) and was stirred vigorously with a glass rod until a precipitate forms. The precipitate was filtered and washed with 1:1 Et_2O:EtOH (2 × 3 mL), Et_2O (3 × 15 mL), then dried to form the intermediate potassium 1-cyanocyclopentane-1-carboxylate. To a solution of potassium 1-cyanocyclopentane-1-carboxylate (3.54 g, 20.0 mmol) in CH_2Cl_2 (120 mL) was added *L*-phenylalanine methyl ester hydrochloride (4.74 g, 22.0 mmol), EDCI.HCl (4.22 g, 22.0 mmol) and HOBt.H_2O (4.05 g, 30.0 mmol). The reaction mixture was left to stir for 1 h, followed by quenching with sat. aq. $NaHCO_3$ solution (100 mL). The layers were separated and the organic layer was washed with brine (100 mL). The organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica (eluent 20% EtOAc/petrol) to give the *amide* **132** (5.07 g, 84%) as a thick colourless oil.

δ_H ($CDCl_3$, 400 MHz) 7.36–7.24 (3H, m, 3 × Ar*H*), 7.22–7.11 (2H, m, 2 × Ar*H*), 6.72 (1H, d, *J* 7.5, N*H*), 5.14–4.61 (1H, m, C*H*CO_2CH_3), 3.76 (3H, s, $CHCO_2CH_3$), 3.22 (1H, dd,

J 14.0, 5.5, C*H*$_A$H$_B$Ph), 3.09 (1H, dd, *J* 14.0, 7.0, CH$_A$*H*$_B$Ph), 2.35–1.97 (4H, m, 2 × (C)C*H*$_2$CH$_2$), 1.97–1.67 (4H, m, 2 × (C)CH$_2$C*H*$_2$); δ_C ($CDCl_3$, 101 MHz) 171.2, 168.0, 135.4, 129.2, 128.7, 127.4, 122.2, 53.8, 52.6, 47.9, 37.7, 37.7, 37.6, 25.4, 25.4; ν_{max} (neat)/cm^{-1} 3349, 2954, 2875, 2235, 1745, 1681, 1578, 1215, 700; HRMS (CI$^+$) $C_{17}H_{21}O_3N_2^+$ ([M + H]$^+$) requires 301.1557, found 301.1557; $[\alpha]_D^{25}$: +19.1 (*c* = 1.0, $CHCl_3$).

Methyl (1-formylcyclopentane-1-carbonyl)-*L*-phenylalaninate, 133

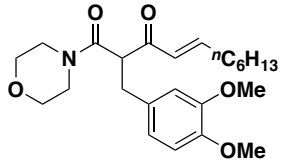


Synthesised according to the general procedure **E**, using methyl (1-cyanocyclopentane-1-carbonyl)-*L*-phenylalaninate **132** (2.41 g, 8.0 mmol), Raney®-Ni (50% in water, 15.0 g, 128 mmol), sodium hypophosphite monohydrate (13.57 g, 128 mmol) in a 1:1:2 mixture of water:acetic acid:pyridine (60 mL). The crude product was purified by flash chromatography on silica (eluent 30% EtOAc/petrol) to give the *aldehyde* **133** (1.08 g, 48%) as yellow crystalline solid.

δ_H ($CDCl_3$, 400 MHz) 9.41 (1H, s, C*H*O), 7.42–7.12 (3H, m, 3 × Ar*H*), 7.10–6.90 (2H, m, 2 × Ar*H*)), 6.44 (1H, d, *J* 7.5, N*H*), 4.78 (1H, ddd, *J* 7.5, 7.0, 5.5, C*H*CO$_2$CH$_3$), 3.66 (3H, s, CHCO$_2$C*H*$_3$), 3.10 (1H, dd, *J* 14.0, 5.5, C*H*$_A$H$_B$Ph), 2.98 (1H, dd, *J* 14.0, 7.0, CH$_A$*H*$_B$Ph), 2.17–1.85 (4H, m, 2 × (C)C*H*$_2$CH$_2$), 1.69–1.60 (2H, m, (C)CH$_2$C*H*$_2$), 1.58–1.49 (2H, m, (C)CH$_2$C*H*$_2$); δ_C ($CDCl_3$, 101 MHz) 200.7, 171.8, 170.5, 135.7, 129.2, 128.6, 127.2, 65.0, 53.3, 52.4, 37.8, 32.3 (2C), 25.8(3), 25.8(1); mp: 61–63 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 3340, 2952, 2871, 1726, 1655, 1520, 1215, 701; *m/z* (ESI$^+$) 326 ([M + Na]$^+$, 100%); HRMS (ESI$^+$)

$C_{20}H_{28}O_3N^+$ ([M + H]$^+$) requires 304.15433, found 304.15434; $[\alpha]_D^{25}$: +35.1 (*c* = 1.0, $CHCl_3$).

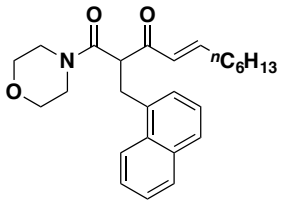
(*E*)-2-(3,4-Dimethoxybenzyl)-1-morpholinoundec-4-ene-1,3-dione, 137



Synthesised according to the general procedure **C**, using 2-(3,4-dimethoxybenzyl)-3-morpholino-3-oxopropanal **69c** (92 mg, 0.30 mmol), 1-octyne (54 μL, 0.36 mmol), $[Rh(nbd)_2]BF_4$ (5.6 mg, 5 mol%) and dcpe (6.3 mg, 5 mol%) in acetone (0.3 mL, 1.0 M). The crude product was purified by flash chromatography on silica (eluent 50% EtOAc/petrol) to give the *enone* **137** (101 mg, 81%) as a thick orange oil.

δ_H ($CDCl_3$, 400 MHz) 6.77 (1H, dt, *J* 15.5, 7.0, C(O)CH=C*H*CH_2), 6.64–6.48 (3H, m, 3 × Ar*H*), 6.12 (1H, dt, *J* 15.5, 1.5, C(O)C*H*=$CHCH_2$), 3.74 (1H, dd, *J* 8.5, 6.0, C*H*CH_2Ar), 3.67(5) (3H, s, OCH_3), 3.66(5) (3H, s, OCH_3), 3.52–3.45 (1H, m, $OCH_2CH_AH_BN$), 3.43–3.32 (3H, m, OCH_2CH_2N, $OCH_2CH_AH_BN$), 3.32–3.20 (2H, m, $OCH_AH_BCH_2N$, $OCH_2CH_AH_BN$), 3.19–3.03 (3H, m, $OCH_AH_BCH_2N$, $OCH_2CH_AH_BN$, $CHCH_AH_BAr$), 2.91 (1H, dd, *J* 14.0, 6.0, $CHCH_AH_BAr$), 2.10–1.93 (2H, m, $CHCH_2CH_2(CH_2)_3CH_3$), 1.31–1.20 (2H, m, $CHCH_2CH_2(CH_2)_3CH_3$), 1.17–1.06 (6H, m, $CH(CH_2)_2(CH_2)_3CH_3$), 0.77–0.64 (3H, t, *J* 7.5, CH_2CH_3); δ_C ($CDCl_3$, 101 MHz) 194.6, 167.4, 150.1, 148.9, 147.8, 131.1, 126.4, 120.9, 112.3, 111.2, 66.7, 66.4, 58.0, 55.9 (2C), 46.2, 42.6, 34.7, 32.6, 31.5, 28.9, 28.0, 22.5, 14.1; ν_{max} (neat)/cm^{-1} 2927, 2855, 1684, 1627, 1575, 1254, 1190, 1114, 1027, 729; *m/z* (ESI$^+$) 440 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{24}H_{36}O_5N^+$ ([M + H]$^+$) requires 418.25880, found 418.25852.

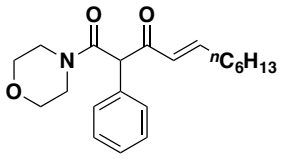
(*E*)-1-Morpholino-2-(naphthalen-1-ylmethyl)undec-4-ene-1,3-dione, 138



Synthesised according to the general procedure **C**, using 3-morpholino-2-(naphthalen-1-ylmethyl)-3-oxopropanal **69b** (89 mg, 0.30 mmol), 1-octyne (54 μL, 0.36 mmol), $[Rh(nbd)_2]BF_4$ (5.6 mg, 5 mol%) and dcpe (6.3 mg, 5 mol%) in acetone (0.3 mL, 1.0 M). The crude product was purified by flash chromatography on silica (eluent 50% EtOAc/petrol) to give the *enone* **138** (102 mg, 83%) as a pale yellow oil.

δ_H ($CDCl_3$, 400 MHz) 7.90 (1H, d, *J* 8.0, Ar*H*), 7.78 (1H, d, *J* 8.0, Ar*H*), 7.66 (1H, dd, *J* 7.0, 2.0, Ar*H*), 7.50–7.37 (2H, m, 2 × Ar*H*), 7.33–7.24 (2H, m, 2 × Ar*H*), 6.80 (1H, dt, *J* 15.5, 7.0, C(O)CH=C*H*CH_2), 6.15 (1H, d, *J* 15.5, C(O)C*H*=$CHCH_2$), 4.08 (1H, dd, *J* 9.0, 5.5, C*H*CH_2Ar), 3.75–3.56 (2H, m, CHC*H*$_2$Ar), 3.56–3.48 (1H, m, $OCH_2CH_AH_BN$), 3.47–3.40 (1H, m, $OCH_AH_BCH_2N$), 3.40–3.31 (1H, m, $OCH_2CH_AH_BN$), 3.23–3.15 (1H, m, $OCH_AH_BCH_2N$), 3.13–2.99 (2H, m, $OCH_2CH_AH_BN$, $OCH_AH_BCH_2N$), 2.80–2.66 (1H, m, $OCH_2CH_AH_BN$), 2.56–2.46 (1H, m, $OCH_AH_BCH_2N$), 2.15–2.05 (2H, m, CHC*H*$_2$$CH_2(CH_2)_3CH_3$), 1.38–1.27 (2H, m, $CHCH_2CH_2(CH_2)_3CH_3$), 1.26–1.15 (6H, m, $CH(CH_2)_2(CH_2)_3CH_3$), 0.80 (3H, t, *J* 7.0, CH_2CH_3); δ_C ($CDCl_3$, 101 MHz) 194.4, 167.9, 149.7, 134.5, 133.9, 131.7, 129.1, 127.6(3), 127.5(9), 126.9, 126.4, 125.7, 125.6, 123.2, 66.5, 65.9, 55.3, 46.2, 42.4, 32.6, 32.1, 31.6, 28.9, 28.0, 22.6, 14.1; ν_{max} (neat)/cm^{-1} 2970, 2855, 1683, 1629, 1456, 1228, 1113, 778; *m/z* (ESI^+) 430 ($[M + Na]^+$, 100%); HRMS (ESI^+) $C_{26}H_{34}O_3N^+$ ($[M + H]^+$) requires 408.25332, found 408.25302.

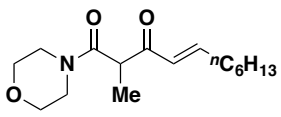
(*E*)-2-Phenyl-1-morpholinoundec-4-ene-1,3-dione, 139



Synthesised according to the general procedure **C**, using 2-phenyl-3-morpholino-3-oxopropanal **69n** (70 mg, 0.30 mmol), 1-octyne (54 μL, 0.36 mmol), $[Rh(nbd)_2]BF_4$ (5.6 mg, 5 mol%) and dcpe (6.3 mg, 5 mol%) in acetone (0.3 mL, 1.0 M). The crude product was purified by flash chromatography on silica (eluent 50% EtOAc/petrol) to give the *enone* **139** (92mg, 89%) as a pale yellow oil.

δ_H ($CDCl_3$, 400 MHz) 7.40–7.13 (5H, m, 5 × Ar*H*), 6.85 (1H, dt, *J* 15.5, 7.0, C(O)CH=C*H*CH_2), 6.14 (1H, dt, *J* 15.5, 1.5, C(O)C*H*=CHCH_2), 4.88 (1H, s, C*H*Ph), 3.70–3.60 (2H, m, OC$H_A$$H_B$$CH_2N, OCH_2CH_A$$H_B$N), 3.59–3.43 (3H, m, $OCH_2CH_A$$H_BN, OCH_2$$CH_2$N), 3.35–3.19 (3H, m, $OCH_A$$H_B$$CH_2$N, OCH_2CH_2N), 2.21–2.02 (2H, m, CHC$H_2$$CH_2$$(CH_2)_3CH_3$), 1.40–1.26 (2H, m, $CHCH_2$C$H_2$$(CH_2)_3CH_3$), 1.27–1.07 (6H, m, $CH(CH_2)_2$$(CH_2)_3CH_3$), 0.78 (3H, t, *J* 7.0, CH_2CH_3); δ_C ($CDCl_3$, 101 MHz) 193.3, 167.4, 148.9, 133.5, 129.2, 129.0, 128.0, 127.7, 66.7, 66.3, 61.6, 46.4, 42.4, 32.5, 31.5, 28.8, 27.9, 22.5, 14.1; ν_{max} (neat)/cm^{-1} 2960, 2927, 1722, 1681, 1447, 1214, 1114, 980, 721; *m/z* (ESI^+) 344 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{21}H_{30}O_3N^+$ ($[M + H]^+$) requires 344.22202, found 344.22197.

(*E*)-2-Methyl-1-morpholinoundec-4-ene-1,3-dione, 140

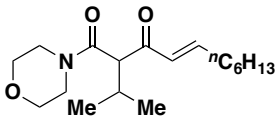


Synthesised according to the general procedure **C**, using 2-methyl-3-morpholino-3-

oxopropanal **69d** (51 mg, 0.30 mmol), 1-octyne (54 μL, 0.36 mmol), $[Rh(nbd)_2]BF_4$ (5.6 mg, 5 mol%) and dcpe (6.3 mg, 5 mol%) in acetone (0.3 mL, 1.0 M). The crude product was purified by flash chromatography on silica (eluent 50% EtOAc/petrol) to give the *enone* **140** (65 mg, 77%) as a pale yellow oil.

δ_H ($CDCl_3$, 400 MHz) 6.93 (1H, dt, *J* 15.5, 7.0, C(O)CH=C*H*CH_2), 6.18 (1H, dt, *J* 15.5, 1.5, C(O)C*H*=$CHCH_2$), 3.67 (2H, app. q, *J* 7.0, C*H*CH_3, $OCH_2CH_AH_BN$), 3.62–3.52 (3H, m, OCH_2CH_2N, $OCH_AH_BCH_2N$), 3.52–3.45 (2H, m, $OCH_AH_BCH_2N$, $OCH_2CH_AH_BN$), 3.42–3.33 (2H, m, OCH_2CH_2N), 2.23–2.11 (2H, m, $CHCH_2CH_2(CH_2)_3CH_3$), 1.44–1.36 (2H, m, $CHCH_2CH_2(CH_2)_3CH_3$), 1.33 (3H, d, *J* 7.0, $CHCH_3$), 1.28–1.16 (6H, m, $CH(CH_2)_2(CH_2)_3CH_3$), 0.80 (3H, t, *J* 7.5, CH_2CH_3); δ_C ($CDCl_3$, 101 MHz) 196.3, 168.6, 150.1, 126.0, 66.8, 66.5, 50.5, 46.1, 42.5, 32.5, 31.5, 28.8, 27.9, 22.5, 14.0, 13.8; ν_{max} (neat)/cm^{-1} 2927, 2855, 18686, 1431, 1115, 1029; *m/z* (ESI^+) 282 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{16}H_{28}O_3N^+$ ($[M + H]^+$) requires 282.20637, found 282.20619.

(*E*)-2-Isopropyl-1-morpholinoundec-4-ene-1,3-dione, 141

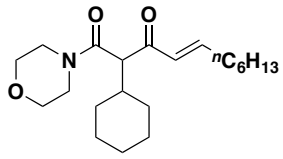


Synthesised according to the general procedure **C**, using 3-methyl-2-(morpholine-4-carbonyl)butanal **69e** (60 mg, 0.30 mmol), 1-octyne (54 μL, 0.36 mmol), $[Rh(nbd)_2]BF_4$ (5.6 mg, 5 mol%) and dcpe (6.3 mg, 5 mol%) in acetone (0.3 mL, 1.0 M). The crude product was purified by flash chromatography on silica (eluent 40% EtOAc/petrol) to give the *enone* **141** (93 mg, 92%) as a colourless oil.

δ_H ($CDCl_3$, 400 MHz) 6.94 (1H, dt, *J* 15.5, 7.0, C(O)CH=C*H*CH_2), 6.37 (1H, dt, *J* 15.5, 1.5,

C(O)C*H*=CHCH$_2$), 3.72 (1H, ddd, *J* 13.0, 5.5, 2.5, OCH$_2$C*H*$_A$H$_B$N), 3.64–3.34 (7H, m, 2 × OC*H*$_2$CH$_2$N, OCH$_2$CH$_A$*H*$_B$N), 3.18 (1H, d, *J* 10.5, C(O)C*H*CH(CH$_3$)$_2$), 2.59–2.48 (1H, m, C*H*(CH$_3$)$_2$), 2.19–2.08 (2H, m, CHC*H*$_2$CH$_2$(CH$_2$)$_3$CH$_3$), 1.42–1.32 (2H, m, CHCH$_2$C*H*$_2$(CH$_2$)$_3$CH$_3$), 1.28–1.17 (6H, m, CH(CH$_2$)$_2$(C*H*$_2$)$_3$CH$_3$), 0.90 (3H, d, *J* 6.5, CH(C*H*$_3$)$_A$(CH$_3$)$_B$), 0.84–0.77 (6H, m, CH(CH$_3$)$_A$(C*H*$_3$)$_B$, CH$_2$C*H*$_3$); δ_C (CDCl$_3$, 101 MHz) 195.6, 166.8, 150.0, 125.5, 66.9, 66.7, 65.5, 46.2, 42.7, 32.5, 31.5, 28.8, 28.5, 27.9, 22.5, 21.6, 20.0, 14.0; ν_{max} (neat)/cm^{-1} 2979, 2856, 1642, 1621, 1430, 1115, 1069; *m/z* (ESI$^+$) 332 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{18}H_{32}O_3N^+$ ([M + H]$^+$) requires 310.23167, found 310.23743.

(*E*)-2-Cyclohexyl-1-morpholinoundec-4-ene-1,3-dione, 142

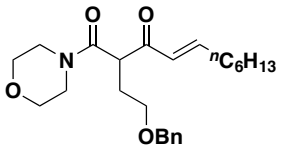


Synthesised according to the general procedure **C**, using 2-cyclohexyl–3-morpholino-3-oxopropanal **69f** (72 mg, 0.30 mmol), 1-octyne (54 μL, 0.36 mmol), [Rh(nbd)$_2$]BF$_4$ (5.6 mg, 5 mol%) and dcpe (6.3 mg, 5 mol%) in acetone (0.3 mL, 1.0 M). The crude product was purified by flash chromatography on silica (eluent 50% EtOAc/petrol) to give the *enone* **142** (90 mg, 87%) as a pale yellow oil.

δ_H (CDCl$_3$, 400 MHz) 6.92 (1H, dt, *J* 15.5, 7.0, C(O)CH=C*H*CH$_2$), 6.38 (1H, dt, *J* 15.5, 1.5, C(O)C*H*=CHCH$_2$), 3.70 (1H, ddd, *J* 13.0, 5.5, 2.5, OCH$_2$C*H*$_A$CH$_B$N), 3.64–3.37 (7H, m, 2 × OCH$_2$C*H*$_2$N, OC*H*$_2$CH$_2$N, OCH$_A$*H*$_B$CH$_2$N), 3.27 (1H, d, *J* 10.5, C*H*Cy), 2.30–2.19 (1H, m, C(O)CHC*H*(CH$_2$)$_5$), 2.18–2.07 (2H, m, CHC*H*$_2$CH$_2$(CH$_2$)$_3$CH$_3$), 1.74 (1H, app. d, *J* 12.5, 0.5 × C*H*$_2$), 1.68–1.54 (3H, m, 1.5 × C*H*$_2$), 1.47 (1H, app. d, *J* 12.5, 0.5 × C*H*$_2$), 1.42–1.33

(2H, m, CH_2), 1.28–1.16 (8H, m, 4 × CH_2), 1.13–1.02 (1H, m, 0.5 × CH_2), 0.90–0.74 (5H, m, CH_2, CH_2CH_3); δ_C ($CDCl_3$, 101 MHz) 195.6, 166.7, 149.8, 125.7, 66.9, 66.7, 64.3, 46.2, 42.7, 37.6, 32.5, 31.8, 31.5, 30.5, 28.8, 28.0, 26.2, 25.9(3), 25.9(0), 22.5, 14.0; ν_{max} (neat)/cm^{-1} 2924, 2852, 1643, 1620, 1114, 1032, 730; *m/z* (ESI^+) 372 ($[M + Na]^+$, 100%); HRMS (ESI^+) $C_{21}H_{36}O_3N^+$ ($[M + H]^+$) requires 350.26897, found 350.26845.

(*E*)-2-(2-(Benzyloxy)ethyl)-1-morpholinoundec-4-ene-1,3-dione, 143

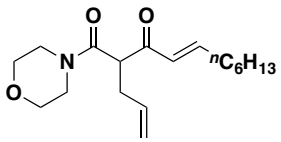


Synthesised according to the general procedure **C**, using 4-(benzyloxy)-2-(morpholine-4-carbonyl)butanal **69h** (91 mg, 0.30 mmol), 1-octyne (54 μL, 0.36 mmol), $[Rh(nbd)_2]BF_4$ (5.6 mg, 5 mol%) and dcpe (6.3 mg, 5 mol%) in acetone (0.3 mL, 1.0 M). The crude product was purified by flash chromatography on silica (eluent 50% EtOAc/petrol) to give the *enone* **143** (110 mg, 91%) as a pale yellow oil.

δ_H ($CDCl_3$, 400 MHz) 7.30–7.16 (5H, m, 5 × Ar*H*), 6.90 (1H, dt, *J* 15.5, 7.0, C(O)CH=C*H*CH_2), 6.16 (1H, dt, *J* 15.5, 1.5, C(O)C*H*=$CHCH_2$), 4.41 (1H, d, *J* 12.0, OCH_AH_BPh), 4.36 (1H, d, *J* 12.0, OCH_AH_BPh), 3.89 (1H, td, *J* 7.0, 1.5, C*H*CHO), 3.65–3.58 (1H, m, $OCH_2CH_ACH_BN$), 3.56–3.49 (3H, m, OCH_2CH_2N, $OCH_ACH_BCH_2N$), 3.48–3.38 (6H, m, OCH_2CH_2N, $OCH_2CH_AH_BN$, $OCH_AH_BCH_2N$, $CHCH_2CH_2OBn$), 2.25–2.03 (4H, m, $CHCH_2CH_2OBn$, $CHCH_2CH_2(CH_2)_3CH_3$), 1.41–1.30 (2H, m, $CHCH_2CH_2(CH_2)_3CH_3$), 1.27–1.15 (6H, m, $CH(CH_2)_2(CH_2)_3CH_3$), 0.80 (3H, t, *J* 7.5, CH_2CH_3); δ_C ($CDCl_3$, 101 MHz) 195.3, 167.8, 149.9, 138.2, 128.4, 127.6(4), 127.6(0), 126.6, 72.9, 67.7, 66.8, 66.5, 52.2, 46.2, 42.6, 32.6, 31.5, 29.1, 28.9, 28.0, 22.5, 14.1; ν_{max} (neat)/cm^{-1} 2957, 2856, 1687, 1635,

1433, 1114, 732; *m/z* (ESI$^+$) 402 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{24}H_{36}O_4N^+$ ([M + H]$^+$) requires 402.26389, found 402.26277.

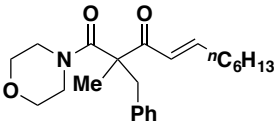
(*E*)-2-Allyl-1-morpholinoundec-4-ene-1,3-dione, 144



Synthesised according to the general procedure **C**, using 2-(morpholine-4-carbonyl)pent-4-enal **69g** (59 mg, 0.30 mmol), 1-octyne (54 μL, 0.36 mmol), $[Rh(nbd)_2]BF_4$ (5.6 mg, 5 mol%) and dcpe (6.3 mg, 5 mol%) in acetone (0.3 mL, 1.0 M). The crude product was purified by flash chromatography on silica (eluent 50% EtOAc/petrol) to give the *enone* **144** (62 mg, 67%) as a colourless oil.

δ_H ($CDCl_3$, 400 MHz) 6.93 (1H, dt, *J* 15.5, 7.0, C(O)CH=C*H*CH_2), 6.22 (1H, dt, *J* 15.5, 1.5, C(O)C*H*=CHCH_2), 5.68 (1H, ddt, *J* 17.0, 10.0, 7.0, CH_2CH=CH_2), 5.05–4.99 (1H, m, CH_2CH=CH_AH_B), 4.98–4.95 (1H, m, CH_2CH=CH_AH_B), 3.69–3.53 (5H, m, C(O)C*H*, OCH_2CH_2N, OC$H_2CH_A$$H_BN, OCH_A$$H_B$$CH_2$N), 3.53–3.37 (4H, m, OC$H_2CH_2N, OCH_2CH_A$$H_BN, OCH_A$$H_B$$CH_2$N), 2.67 (1H, dt, *J* 14.0, 7.0, CHC$H_A$$H_B$CH=$CH_2$), 2.53 (1H, dt, *J* 14.0, 7.0, CHC$H_A$$H_B$CH=$CH_2$), 2.22–2.08 (2H, m, CHC$H_2CH_2$$(CH_2)_3CH_3$), 1.44–1.33 (2H, m, $CHCH_2CH_2(CH_2)_3CH_3$), 1.30–1.17 (6H, m, $CH(CH_2)_2(CH_2)_3CH_3$), 0.81 (3H, t, *J* 7.0, CH_2CH_3); δ_C ($CDCl_3$, 101 MHz) 194.9, 167.1, 150.4, 134.7, 125.9, 117.3, 66.8, 66.5, 56.4, 46.1, 42.6, 33.1, 32.6, 31.5, 28.8, 27.9, 22.5, 14.0; ν_{max} (neat)/cm^{-1} 2979, 2856, 1642, 1621, 1430, 1115, 1069; *m/z* (ESI$^+$) 330 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{18}H_{30}O_3N^+$ ([M + H]$^+$) requires 308.22202, found 308.22175.

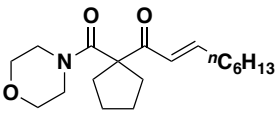
(*E*)-2-Benzyl-2-methyl-1-morpholinoundec-4-ene-1,3-dione, 145



Synthesised according to the general procedure **C**, using 2-benzyl-2-methyl-3-morpholino-3-oxopropanal **118** (78 mg, 0.30 mmol), 1-octyne (54 μL, 0.36 mmol), $[Rh(nbd)_2]BF_4$ (5.6 mg, 5 mol%) and dcpe (6.3 mg, 5 mol%) in acetone (0.3 mL, 1.0 M). The crude product was purified by flash chromatography on silica (eluent 50% EtOAc/petrol) to give the *enone* **145** (102 mg, 92%) as a colourless oil.

δ_H ($CDCl_3$, 400 MHz) 7.20–7.11 (3H, m, 3 × Ar*H*), 7.04 (1H, dt, *J* 15.1, 7.0, C(O)CHC*H*CH_2), 7.00–6.92 (2H, m, 2 × Ar*H*), 6.23 (1H, dt, *J* 15.5, 1.5, C(O)C*H*$CHCH_2$), 3.72–3.33 (6H, m, 2 × OCH_2CH_2N, OCH_2CH_2N), 3.26–3.09 (4H, m, OCH_2CH_2N, CH_2Ph), 2.27–2.07 (2H, m, $CHCH_2CH_2(CH_2)_3CH_3$), 1.45–1.33 (2H, m, $CHCH_2CH_2(CH_2)_3CH_3$), 1.29–1.16 (9H, m, $CH(CH_2)_2(CH_2)_3CH_3$, (C)CH_3), 0.81 (3H, t, *J* 7.5, CH_2CH_3); δ_C ($CDCl_3$, 101 MHz) 198.1, 170.4, 150.2, 136.3, 130.4, 128.1, 126.8, 125.9, 66.9, 65.9, 59.0, 46.5, 43.2, 40.8, 32.5, 31.5, 28.9, 28.1, 22.6, 20.6, 14.1; ν_{max} (neat)/cm^{-1} 2926, 2855, 1639, 1622, 1417, 1220, 1116, 1065, 701; *m/z* (ESI^+) 394 ($[M + Na]^+$, 100%); HRMS (ESI^+) $C_{23}H_{34}O_3N^+$ ($[M + H]^+$) requires 372.25332, found 372.25307.

(*E*)-1-(1-(Morpholine-4-carbonyl)cyclopentyl)non-2-en-1-one, 146

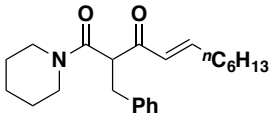


Synthesised according to the general procedure **C**, using 1-(morpholine-4-carbonyl)cyclopentane-1-carbaldehyde **123** (63 mg, 0.30 mmol), 1-octyne (54 μL,

0.36 mmol), $[Rh(nbd)_2]BF_4$ (5.6 mg, 5 mol%) and dcpe (6.3 mg, 5 mol%) in acetone (0.3 mL, 1.0 M). The crude product was purified by flash chromatography on silica (eluent 50% EtOAc/petrol) to give the *enone* **146** (92 mg, 95%) as a colourless oil.

δ_H ($CDCl_3$, 400 MHz) 7.01 (1H, dt, *J* 15.5, 7.0, C(O)CH=C*H*CH_2), 6.16 (1H, dt, *J* 15.5, 1.5, C(O)C*H*=CHCH_2), 3.65–3.55 (4H, m, OC*H*$_2$$CH_2N, OCH_2C*H*_2$N), 3.51–3.43 (2H, m, OCH_2C*H*$_2$N), 3.22–3.16 (2H, m, OCH_2C*H*$_2$N), 2.24–2.05 (6H, m, 2 × (C)C*H*$_2$$CH_2$, CHC*H*$_2$$CH_2$$(CH_2)_3CH_3$), 1.67–1.52 (4H, m, 2 × (C)CH_2C*H*$_2$), 1.47–1.34 (2H, m, $CHCH_2$C*H*$_2$$(CH_2)_3CH_3$), 1.32–1.20 (6H, m, $CH(CH_2)_2$(C*H*$_2$$)_3CH_3$), 0.85 (3H, t, *J* 7.5, CH_2C*H*$_3$); δ_C ($CDCl_3$, 101 MHz) 196.9, 171.2, 150.0, 125.6, 66.8, 66.1, 65.5, 46.1, 43.2, 33.5, 32.4, 31.5, 28.8, 28.1, 26.2, 22.5, 14.0; ν_{max} (neat)/cm^{-1} 2926, 2855, 1640, 1624, 1421, 1180, 1116; HRMS (CI^+) $C_{19}H_{31}O_3N^+$ ($[M]^+$) requires 321.2291, found 321.2291.

(*E*)-2-Benzyl-1-(piperidin-1-yl)undec-4-ene-1,3-dione, 148

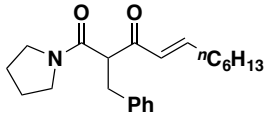


Synthesised according to the general procedure **C**, using 2-benzyl-3-oxo-3-(piperidin-1-yl)propanal **69i** (87 mg, 0.30 mmol), 1-octyne (54 μL, 0.36 mmol), $[Rh(nbd)_2]BF_4$ (5.6 mg, 5 mol%) and dcpe (6.3 mg, 5 mol%) in acetone (0.3 mL, 1.0 M). The crude product was purified by flash chromatography on silica (eluent 50% EtOAc/petrol) to give the *enone* **148** (99 mg, 93%) as a pale yellow oil.

δ_H ($CDCl_3$, 400 MHz) 7.23–7.14 (2H, m, 2 × Ar*H*), 7.14–7.07 (3H, m, 3 × Ar*H*), 6.84 (1H, dt, *J* 15.5, 7.0, C(O)CH=C*H*CH_2), 6.20 (1H, dt, *J* 15.5, 1.5, C(O)C*H*=CHCH_2), 3.91 (1H, dd, *J* 8.0, 6.5, C*H*CH_2Ph), 3.51–3.39 (2H, m, NC*H*$_2$), 3.28–3.19 (2H, m, NC*H*$_A$$CH_B$,

CHCH_AH_BPh), 3.17–3.03 (2H, m, NCH$_A$CH_B, CHCH$_A$$H_B$Ph), 2.15–2.06 (2H, m, CHCH_2CH$_2$(CH$_2$)$_3$CH$_3$), 1.50–1.41 (2H, m, CH_2), 1.40–1.32 (4H, m, 2 × CH_2), 1.30–1.16 (7H, m, 3.5 × CH_2), 1.14–1.04 (1H, m, 0.5 × CH_2), 0.81 (3H, t, *J* 7.5, CH$_2$CH_3); δ_C ($CDCl_3$, 101 MHz) 194.9, 167.0, 149.5, 139.0, 129.0, 128.4, 126.8, 126.5, 57.6, 46.9, 43.4, 35.1, 32.5, 31.6, 28.8, 28.0, 26.1, 25.5, 24.4, 22.5, 14.1; ν_{max} (neat)/cm^{-1} 2928, 2855, 1685, 1625, 1441, 1026, 700; *m/z* (ESI$^+$) 378 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{23}H_{34}O_2N^+$ ([M + H]$^+$) requires 356.25841, found 356.25834.

(*E*)-2-Benzyl-1-(pyrrolidin-1-yl)undec-4-ene-1,3-dione, 149

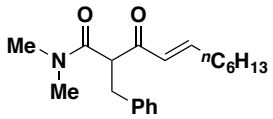


Synthesised according to the general procedure **C**, using 2-benzyl-3-oxo-3-(pyrrolidin-1-yl)propanal **69j** (69 mg, 0.30 mmol), 1-octyne (54 μL, 0.36 mmol), [Rh(nbd)$_2$]BF_4 (5.6 mg, 5 mol%) and dcpe (6.3 mg, 5 mol%) in acetone (0.3 mL, 1.0 M). The crude product was purified by flash chromatography on silica (eluent 50% EtOAc/petrol) to give the *enone* **149** (96 mg, 94%) as a pale yellow oil.

δ_H ($CDCl_3$, 400 MHz) 7.24–7.02 (5H, m, 5 × Ar*H*), 6.83 (1H, dt, *J* 15.5, 7.0, C(O)CH=C*H*CH$_2$), 6.24 (1H, dt, *J* 15.5, 1.5, C(O)C*H*=CHCH$_2$), 3.76 (1H, dd, *J* 8.5, 6.0, C*H*CH$_2$Ph), 3.35 (2H, t, *J* 6.0, NCH_2), 3.28–3.19 (2H, m, NCH_ACH$_B$, CHCH_AH$_B$Ph), 3.04 (1H, dd, *J* 14.0, 6.0, CHCH$_A$$H_B$Ph), 2.92 (1H, dt, *J* 10.0, 6.0, NCH$_A$CH_B), 2.19–2.05 (2H, m, CHCH_2CH$_2$(CH$_2$)$_3$CH$_3$), 1.78–1.58 (2H, m, CHCH$_2$CH_2(CH$_2$)$_3$CH$_3$), 1.41–1.29 (4H, m, 2 × NCH$_2$CH_2), 1.27–1.15 (6H, m, CH(CH$_2$)$_2$(CH_2)$_3$CH$_3$), 0.80 (3H, t, *J* 7.5, CH$_2$CH_3); δ_C ($CDCl_3$, 101 MHz) 194.7, 167.2, 149.3, 138.9, 129.0, 128.4, 127.0, 126.5, 59.8, 46.7,

46.1, 35.1, 32.5, 31.6, 28.8, 28.0, 25.9, 24.2, 22.5, 14.1; ν_{max} (neat)/cm^{-1} 2927, 2856, 1684, 1627, 1421, 700; *m/z* (ESI$^+$) 364 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{22}H_{32}O_2N^+$ ([M + H]$^+$) requires 342.24276, found 342.24247.

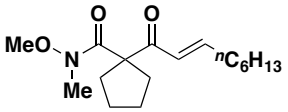
(*E*)-2-Benzyl-*N*,*N*-dimethyl-3-oxoundec-4-enamide, 150



Synthesised according to the general procedure **C**, using 2-benzyl-*N*,*N*-dimethyl-3-oxopropanamide **69k** (62 mg, 0.30 mmol), 1-octyne (54 μL, 0.36 mmol), [Rh(nbd)$_2$]BF$_4$ (5.6 mg, 5 mol%) and dcpe (6.3 mg, 5 mol%) in acetone (0.3 mL, 1.0 M). The crude product was purified by flash chromatography on silica (eluent 50% EtOAc/petrol) to give the *enone* **150** (89 mg, 94%) as a pale yellow oil.

δ_H ($CDCl_3$, 400 MHz) 7.22–7.15 (2H, m, 2 × Ar*H*), 7.14–7.08 (3H, m, 3 × Ar*H*) 6.84 (1H, dt, *J* 15.5, 7.0, C(O)CH=C*H*CH$_2$), 6.21 (1H, dt, *J* 15.5, 1.5, C(O)C*H*=CHCH$_2$), 3.91 (1H, dd, *J* 8.5, 6.0, C*H*CH$_2$Ph), 3.23 (1H, dd, *J* 14.0, 8.5, CHCH_AH$_B$Ph), 3.05 (1H, dd, *J* 14.0, 6.0, CHCH$_A$$H_B$Ph), 2.84 (3H, s, N(C$H_3$)$_A$(CH$_3$)$_B$), 2.73 (3H, s, N(CH$_3$)$_A$(C$H_3$)$_B$), 2.18–2.06 (2H, m, CHC$H_2CH_2$(CH$_2$)$_3CH_3$), 1.41–1.30 (2H, m, CHCH$_2$CH_2(CH$_2$)$_3$CH$_3$), 1.25–1.15 (6H, m, CH(CH$_2$)$_2$(CH_2)$_3$CH$_3$), 0.80 (3H, t, *J* 7.5, CH$_2$CH_3); δ_C ($CDCl_3$, 101 MHz) 194.7, 168.8, 149.6, 138.9, 129.0, 128.5, 126.7, 126.5, 58.0, 37.3, 35.9, 35.2, 32.6, 31.6, 28.8, 28.0, 22.5, 14.1; ν_{max} (neat)/cm^{-1} 2928, 2857, 1685, 1634, 1394, 1134, 700; *m/z* (ESI$^+$) 338 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{20}H_{30}O_2N^+$ ([M + H]$^+$) requires 316.22711, found 316.22688.

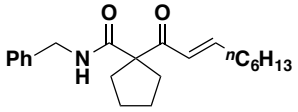
(*E*)-*N*-Methoxy-*N*-methyl-1-(non-2-enoyl)cyclopentane-1-carboxamide, 151



Synthesised according to the general procedure **C**, using 1-formyl-*N*-methoxy-*N*-methylcyclopentane-1-carboxamide **126** (55 mg, 0.30 mmol), 1-octyne (54 μL, 0.36 mmol), $[Rh(nbd)_2]BF_4$ (5.6 mg, 5 mol%) and dcpe (6.3 mg, 5 mol%) in acetone (0.3 mL, 1.0 M). The crude product was purified by flash chromatography on silica (eluent 10% EtOAc/petrol) to give the *enone* **151** (88 mg, 98%) as a colourless oil. **151** exists as two rotamers, in a ratio of approximately 1:1.

δ_H ($CDCl_3$, 400 MHz) (* denotes second rotamer) 6.83 (1H, dt, *J* 15.5, 7.0, C(O)CH=C*H*CH_2), 5.96 (1H, dt, *J* 15.5, 1.5, C(O)C*H*=$CHCH_2$), 3.51* (3H, s, OCH_3), 3.46 (3H, s, OCH_3), 3.12* (3H, s, NCH_3), 3.10 (3H, s, NCH_3), 2.14–1.98 (6H, m, 2 × (C)C$H_2$$CH_2$, $CHCH_2CH_2(CH_2)_3CH_3$), 1.63–1.47 (4H, m, 2 × (C)CH_2CH_2), 1.40–1.31 (2H, m, $CHCH_2CH_2(CH_2)_3CH_3$), 1.25–1.16 (6H, m, $CH(CH_2)_2(CH_2)_3CH_3$), 0.85–0.73 (3H, m, CH_2CH_3); δ_C ($CDCl_3$, 101 MHz) (* denotes second rotamer) 205.3, 194.8, 148.0, 126.4, 64.5, 60.7*, 60.5, 33.4, 33.2, 32.4, 31.5, 28.8, 28.1, 26.2*, 26.1, 22.5, 14.0; ν_{max} (neat)/cm^{-1} 2929, 2820, 1656, 1630, 1356, 977; HRMS (CI^+) $C_{17}H_{30}O_3N^+$ ($[M + H]^+$) requires 296.2231, found 296.2231.

(*E*)-*N*-Benzyl-1-(non-2-enoyl)cyclopentane-1-carboxamide, 152

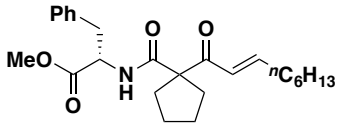


Synthesised according to the general procedure **C**, using *N*-benzyl-1-formylcyclopentane-1-

carboxamide **129** (69 mg, 0.30 mmol), 1-octyne (54 μL, 0.36 mmol), $[Rh(nbd)_2]BF_4$ (5.6 mg, 5 mol%) and dcpe (6.3 mg, 5 mol%) in acetone (0.3 mL, 1.0 M). The crude product was purified by flash chromatography on silica (eluent 20% EtOAc/petrol) to give the *enone* **152** (90 mg, 88%) as a colourless oil.

δ_H ($CDCl_3$, 400 MHz) 7.41–7.01 (5H, m, 5 × Ar*H*), 6.85 (1H, dt, *J* 15.5, 7.0, C(O)CH=C*H*CH_2), 6.34–6.12 (1H, dt, *J* 15.5, 1.5, C(O)C*H*=CHCH_2), 5.93 (1H, t, *J* 5.5, N*H*), 4.33 (2H, d, *J* 5.5, NC*H*$_2$Ph), 2.27–1.94 (6H, m, 2 × (C)C*H*$_2$$CH_2$, CHC*H*$_2$$CH_2$$(CH_2)_3CH_3$), 1.62–1.53 (2H, m, (C)$CH_2$C*H*$_2$), 1.53–1.43 (2H, m, (C)$CH_2$C*H*$_2$), 1.39–1.28 (2H, m, CH$CH_2$C*H*$_2$$(CH_2)_3CH_3$), 1.24–1.06 (6H, m, CH$(CH_2)_2$(C*H*$_2$$)_3CH_3$), 0.80 (3H, t, *J* 7.5, CH_2C*H*$_3$); δ_C ($CDCl_3$, 101 MHz) 197.6, 171.7, 149.7, 138.2, 128.6, 127.5, 127.4, 125.7, 66.9, 43.9, 32.7, 32.5, 31.6, 28.9, 28.0, 25.7, 22.6, 14.1; ν_{max} (neat)/cm^{-1} 3340, 2927, 1857, 1652, 1625, 1523, 1268, 697; *m/z* (ESI^+) 364 ($[M + Na]^+$, 100%); HRMS (ESI^+) $C_{22}H_{32}O_2N^+$ ($[M + H]^+$) requires 342.24276, found 342.24257.

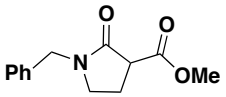
Methyl (*E*)-(1-(non-2-enoyl)cyclopentane-1-carbonyl)-*L*-phenylalaninate, 153



Synthesised according to the general procedure **C**, using methyl (1-formylcyclopentane-1-carbonyl)-*L*-phenylalaninate **133** (91 mg, 0.30 mmol), 1-octyne (54 μL, 0.36 mmol), $[Rh(nbd)_2]BF_4$ (5.6 mg, 5 mol%) and dcpe (6.3 mg, 5 mol%) in acetone (0.3 mL, 1.0 M). The crude product was purified by flash chromatography on silica (eluent 10% EtOAc/petrol) to give **153** (114 mg, 92%) as a colourless oil.

δ_H ($CDCl_3$, 400 MHz) 7.26–7.11 (3H, m, 3 × Ar*H*), 6.98 (2H, dd, *J* 7.5, 1.5, 2 × Ar*H*), 6.88 (1H, dt, *J* 15.5, 7.0, C(O)CH=C*H*CH_2), 6.10 (1H, dt, *J* 15.5, 1.5, C(O)C*H*=$CHCH_2$), 5.78 (1H, d, *J* 8.0, N*H*), 4.91–4.62 (1H, m, NC*H*), 3.62 (3H, s, OCH_3), 3.03 (1H, dd, *J* 14.0, 5.5, $CHCH_AH_BPh$), 2.92 (1H, dd, *J* 14.0, 7.0, $CHCH_AH_BPh$), 2.30–1.85 (6H, m, 3 × CH_2), 1.62–1.40 (4H, m, 2 × CH_2), 1.40–1.28 (2H, m, CH_2), 1.26–1.12 (6H, m, 3 × CH_2), 0.82 (3H, t, *J* 7.5, CH_2CH_3); δ_C ($CDCl_3$, 101 MHz) 197.0, 171.6, 171.6, 149.6, 135.7, 129.1, 128.6, 127.1, 125.5, 66.8, 53.4, 52.3, 37.8, 32.6, 32.6, 31.6, 28.9, 28.0, 25.6, 22.5, 14.1; ν_{max} (neat)/cm^{-1} 3344, 2953, 2851, 1745, 1658, 1624, 1522, 1213, 699; *m/z* (ESI^+) 436 ($[M + Na]^+$, 100%); HRMS (ESI^+) $C_{25}H_{36}O_4N^+$ ($[M + H]^+$) requires 414.26389, found 414.20342; $[\alpha]_D^{25}$: +7.4 (*c* = 1.0, $CHCl_3$).

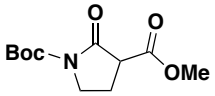
Methyl 1-benzyl-2-oxopyrrolidine-3-carboxylate, 155



To a stirred solution of LHMDS (21 mL, 1 M in cyclohexane, 21 mmol) in dry THF (6 mL) at –78 °C was added 1-benzylpyrrolidin-2-one (1.75 g, 10.0 mmol) dropwise as a solution in THF (6 mL). Subsequently, methylchloroformate (1.0 mL, 10 mmol) as a solution in THF (6 mL) was also added dropwise. The resulting solution was stirred for 5 min and then quenched with 1M HCl (20 mL) and warmed to room temperature. The mixture was extracted with EtOAc (3 × 20 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica (eluent 50% EtOAc/petrol) to give the ester **155** (1.72 g, 74%) as a colourless oil.

δ_H ($CDCl_3$, 400 MHz) 7.37–7.22 (5H, m, 5 × Ar*H*), 4.48 (2H, s, CH_2Ph), 3.80 (3H, s, OCH_3), 3.57–3.46 (1H, m, C*H*CO_2CH_3), 3.39 (1H, td, *J* 9.5, 5.0, NCH_AH_B), 3.24 (1H, ddd, *J* 9.5, 8.5, 6.0, NCH_AH_B), 2.45–2.32 (1H, m, $NCH_2CH_AH_B$), 2.30–2.18 (1H, m, $NCH_2CH_AH_B$); δ_C ($CDCl_3$, 101 MHz) 170.8, 169.7, 135.9, 128.7, 128.1, 127.7, 52.7, 48.4, 47.0, 45.1, 22.2; HRMS (CI^+) $C_{13}H_{16}O_3N^+$ ($[M + H]^+$) requires 234.1131, found 234.1131. Data is consistent with the literature.[271]

1-(*tert*-Butyl) 3-methyl 2-oxopyrrolidine-1,3-dicarboxylate, 156

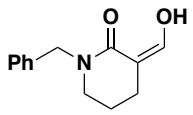


To a stirred solution of LHMDS (57 mL, 1 M in cyclohexane, 57 mmol) in dry THF (20 mL) at –78 °C was added *tert*-butyl 2-oxopyrrolidine-1-carboxylate (4.6 mL, 27 mmol) dropwise as a solution in THF (20 mL). Subsequently, methylchloroformate (2.1 mL, 27 mmol) as a solution in THF (20 mL) was also added dropwise. The resulting solution was stirred for 5 min and then quenched with 1M HCl (70 mL) and warmed to room temperature. The mixture was extracted with EtOAc (3 × 50 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica (eluent 50% EtOAc/petrol) to give the ester **156** (5.67 g, 86%) as a pale yellow solid.

δ_H ($CDCl_3$, 400 MHz) 3.88–3.82 (1H, m, NC$H_ACH_BCH_2$), 3.74 (3H, s, OCH_3), 3.72–3.64 (1H, m, $NCH_ACH_BCH_2$), 3.53 (1H, dd, *J* 9.0, 7.5, C(O)C*H*), 2.40–2.31 (1H, m, $NCH_2CH_ACH_B$), 2.28–2.16 (1H, m, $NCH_2CH_ACH_B$), 1.49 (9H, s, C(CH_3)$_3$); δ_C ($CDCl_3$, 101 MHz) 169.1, 168.7, 149.8, 83.4, 52.8, 50.1, 44.9, 27.9, 21.4; mp 65–67 °C (CH_2Cl_2);

HRMS (CI^+) $C_{11}H_{18}O_5N^+$ ($[M + H]^+$) requires 244.1177, found 244.1177. Data is consistent with the literature.[272]

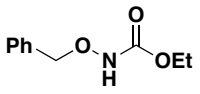
1-Benzyl-3-(hydroxymethylene)piperidin-2-one, 157



Synthesised according to the general procedure **B**, using 1-benzyl-2-piperidone (1.8 mL, 10 mmol), diisopropylamine (4.2 mL, 30 mmol), *n*-BuLi (2.5 M, 12 mL, 30 mmol) and methyl formate (6.17 mL, 100 mmol) in Et_2O (30 mL). The crude product was purified by flash chromatography on silica (eluent 50% EtOAc/petrol) to give the *amide* **157** (1.60 g, 25%) as a pale yellow oil. **157** is in keto-enol equilibrium (keto:enol 1:13.8).

δ_H ($CDCl_3$, 400 MHz) (*enol form*) 13.44 (1H, d, *J* 11.0, C=CH(O*H*)), 7.55–6.68 (5H, m, 5 × Ar*H*), 6.98 (1H, dt, *J* 11.0, 1.5, C=C*H*(OH)), 4.64 (2H, s, NCH_2Ph), 3.23 (2H, t, *J* 5.5, NC$H_2$$CH_2CH_2$), 2.33 (2H, td, *J* 5.5, 1.5, $NCH_2CH_2CH_2$), 2.07–1.48 (2H, m, $NCH_2CH_2CH_2$); δ_C ($CDCl_3$, 101 MHz) 199.8, 169.6, 165.8, 158.0, 136.9, 136.6, 128.7, 128.7, 128.1, 127.9, 127.6, 127.5, 100.9, 55.1, 50.3, 49.5, 47.2, 46.9, 24.5, 22.9, 21.2, 21.0; ν_{max} (neat)/cm^{-1} 3030, 2932, 2857, 1641, 1493, 1191, 701; *m/z* (ESI^+) 272 ($[M + Na + MeOH]^+$, 100%); HRMS (ESI^+) $C_{13}H_{16}O_2N^+$ ($[M + H]^+$) requires 218.11756, found 218.11775.

***N*-Benzyloxycarbamic acid ethyl ester, 158**

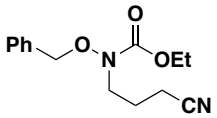


A mixture of *O*-benzylhydroxylamine hydrochloride (16.0 g, 100 mmol) and pyridine

(50 mL) was stirred under N_2 for 2 h. The mixture was then cooled to 0 °C, and ethyl chloroformate (9.56 mL, 100 mmol) was added and the mixture was stirred at room temperature for 16 h. The reaction mixture was diluted with EtOAc (200 mL), washed with 1 N HCl (3 × 100 mL) and saturated aqueous $NaHCO_3$ solution (3 × 100 mL). The organic layer was then dried over $MgSO_4$, filtered and concentrated *in vacuo*. The carbamate **158** (16.11 g, 83%) was obtained as a colourless oil which was used in the next step without further purification.

δ_H ($CDCl_3$, 400 MHz) 7.63 (1H, s, $PhCH_2ONH$), 7.38 (5H, m, 5 × Ar*H*), 4.87 (2H, s, $PhCH_2O$), 4.21 (2H, q, *J* 7.0, OCH_2CH_3), 1.28 (3H, t, *J* 7.0, OCH_2CH_3); δ_C ($CDCl_3$, 101 MHz) 157.7, 135.6, 129.2, 128.6, 128.5, 78.6, 61.9, 14.5; *m/z* (ESI^+) 218 ($[M + Na]^+$, 100%). Data is consistent with the literature.[165]

Ethyl (benzyloxy)(3-cyanopropyl)carbamate, 159

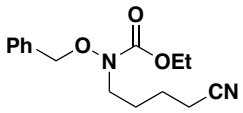


Potassium carbonate (20.7 g, 150 mmol) was added to a solution of *N*-benzyloxycarbamic acid ethyl ester **158** (5.86 g, 30.0 mmol) and 4-bromovaleronitrile (3.6 mL, 36 mmol) in MeCN (200 mL) and the mixture was stirred at reflux for 16 h. The mixture was poured into water (100 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with brine (75 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica (eluent 40% EtOAc/petrol) to give the carbamate **159** (6.80 g, 86%) as a pale yellow oil.

δ_H ($CDCl_3$, 400 MHz) 7.44–7.30 (5H, m, 5 × Ar*H*), 4.84 (2H, s, $PhCH_2O$), 4.21 (2H, q, *J* 7.0,

OC*H*$_2$CH$_3$), 3.53 (2H, t, *J* 6.5, NC*H*$_2$CH$_2$CH$_2$CN), 2.29 (2H, t, *J* 7.0, NCH$_2$CH$_2$C*H*$_2$CN), 1.84 (2H, p, *J* 7.0, NCH$_2$C*H*$_2$CH$_2$CN), 1.31 (3H, t, *J* 7.0, OCH$_2$C*H*$_3$); δ_C ($CDCl_3$, 101 MHz) 157.2, 135.2, 129.5, 128.8, 128.5, 119.2, 77.1, 62.4, 48.1, 23.4, 14.8, 14.5; *m/z* (ESI^+) 285 ($[M + Na]^+$, 100%). Data is consistent with the literature.[165]

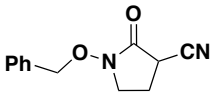
(4-Cyanobutyl)-*N*-benzyloxy-carbamic acid ethyl ester, 160



Potassium carbonate (20.7 g, 150 mmol) was added to a solution of *N*-benzyloxycarbamic acid ethyl ester **158** (5.86 g, 30.0 mmol) and 5-bromovaleronitrile (4.2 mL, 36 mmol) in MeCN (200 mL) and the mixture was stirred at reflux for 16 h. The mixture was poured into water (100 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with brine (75 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica (eluent 40% EtOAc/petrol) to give the carbamate **160** (8.10 g, 98%) as a pale yellow oil.

δ_H ($CDCl_3$, 400 MHz) 7.47–7.33 (5H, m, 5 × Ar*H*), 4.86 (2H, s, PhC*H*$_2$O), 4.24 (2H, q, *J* 7.0, OC*H*$_2$CH$_3$), 3.48 (2H, t, *J* 6.5, NC*H*$_2$(CH$_2$)$_2$CH$_2$CN), 2.33 (2H, t, *J* 7.0, NCH$_2$(CH$_2$)$_2$C*H*$_2$CN), 1.79–1.60 (4H, m, NCH$_2$(C*H*$_2$)$_2$CH$_2$CN), 1.33 (3H, t, *J* 7.0, OCH$_2$C*H*$_3$); δ_C ($CDCl_3$, 101 MHz) 157.4, 135.3, 129.4, 128.7, 128.5, 119.4, 77.2, 62.3, 48.5, 26.1, 22.6, 16.8, 14.6; *m/z* (ESI^+) 299 ($[M + Na]^+$, 100%). Data is consistent with the literature.[165]

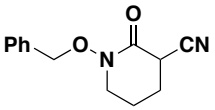
1-(Benzyloxy)-2-oxopyrrolidine-3-carbonitrile, 161



A solution of lithium bis(trimethylsilyl) amide (41 mL, 1 M in THF, 41 mmol) was added to a solution of ethyl (benzyloxy)(3-cyanopropyl)carbamate **159** (5.24 g, 20.0 mmol) in THF (200 mL) under N_2 at –78 °C and the mixture was stirred at –78 °C for 1 h. The reaction was quenched at –78 °C with 10% AcOH aqueous solution (100 mL) and the solvent removed *in vacuo*. The residue was dissolved in EtOAc (100 mL), washed with brine (3 × 100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica (eluent 30% EtOAc/petrol) to give the amide **161** (3.73 g, 86%) as a colourless oil.

δ_H ($CDCl_3$, 400 MHz) 7.47–7.18 (5H, m, 5 × Ar*H*), 4.93 (2H, m, PhCH_2O), 3.46 (1H, t, *J* 9.0, NCH_2CH_2CHCN), 3.3–3.18 (2H, m, NCH_2CH_2CHCN), 2.43–2.24 (1H, m, $NCH_2CH_ACH_BCHCN$), 2.20–2.01 (1H, m, $NCH_2CH_ACH_BCHCN$); δ_C ($CDCl_3$, 101 MHz) 162.5, 134.5, 129.5, 129.2, 128.7, 117.0, 77.0, 44.9, 30.7, 21.1; *m/z* (ESI^+) 239 ($[M + Na]^+$, 100%). Data is consistent with the literature.[165]

1-(Benzyloxy)-2-oxopiperidine-3-carbonitrile, 162

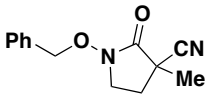


A solution of lithium bis(trimethylsilyl) amide (41 mL, 1 M in THF, 41 mmol) was added to a solution of (4-cyanobutyl)-*N*-benzyloxy-carbamic acid ethyl ester **158** (5.5 g, 20 mmol) in THF (200 mL) under N_2 at –78 °C and the mixture was stirred at this temperature for 1 h.

The reaction was quenched at –78 °C with 10% AcOH aqueous solution (100 mL) and the solvent removed *in vacuo*. The residue was dissolved in EtOAc (100 mL), washed with brine (3 × 100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica (eluent 30% EtOAc/petrol) to give the amide **162** (4.10 g, 89%) as a colourless oil.

δ_H ($CDCl_3$, 400 MHz) 7.49–7.34 (5H, m, 5 × Ar*H*), 5.05–4.94 (2H, m, PhCH_2O), 3.62 (1H, dd, *J* 7.5, 5.5, $NCH_2(CH_2)_2CHCN$), 3.43-3.31 (2H, m, $NCH_2(CH_2)_2CHCN$), 2.17–1.74 (4H, m, $NCH_2(CH_2)_2CHCN$); δ_C ($CDCl_3$, 101 MHz) 159.4, 134.6, 129.8, 129.1, 128.6, 117.1, 76.1, 50.7, 36.0, 25.6, 21.5; *m/z* (ESI^+) 253 ($[M + Na]^+$, 100%). Data is consistent with the literature.[165]

1-(Benzyloxy)-3-methyl-2-oxopyrrolidine-3-carbonitrile, 163

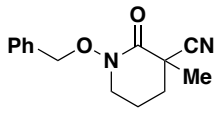


Synthesised according to the general procedure **D**, using 1-(benzyloxy)-2-oxopyrrolidine-3-carbonitrile **161** (3.50 g, 15.7 mmol), sodium hydride (60% in mineral oil, 0.76 g, 18.9 mmol) and iodomethane (2.93 mL, 47.1 mmol) in THF (30 mL). The crude product was purified by flash chromatography on silica (eluent 50% EtOAc/petrol) to give the *amide* **163** (3.43 g, 95%) as a white crystalline solid.

δ_H ($CDCl_3$, 400 MHz) 7.68–7.33 (5H, m, 5 × Ar*H*), 5.03 (2H, s, CH_2Ph), 3.50–3.08 (2H, m, NCH_2CH$_2$), 2.63–2.30 (1H, m, $NCH_2CH_AH_B$), 2.10–1.86 (1H, m, $NCH_2CH_AH_B$), 1.56 (3H, s, CH_3); δ_C ($CDCl_3$, 101 MHz) 164.9, 134.4, 129.7, 129.3, 128.8, 119.6, 77.0, 44.1, 37.3, 29.9, 21.8; mp: 59–61 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 2980, 2887, 1719, 1005, 700; *m/z* (ESI^+)

253 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{13}H_{15}O_2N_2^+$ ([M + H]$^+$) requires 231.11280, found 231.11292.

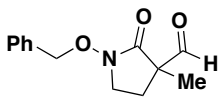
1-(Benzyloxy)-3-methyl-2-oxopiperidine-3-carbonitrile, 164



Synthesised according to the general procedure **D**, using 1-(benzyloxy)-2-oxopiperidine-3-carbonitrile **162** (2.76 g, 12.0 mmol), sodium hydride (60% in mineral oil, 0.58 g, 14.4 mmol) and iodomethane (2.24 mL, 36.0 mmol) in THF (25 mL). The crude product was purified by flash chromatography on silica (eluent 50% EtOAc/petrol) to give the *amide* **164** (2.69 g, 92%) as a pale yellow crystalline solid.

δ_H ($CDCl_3$, 400 MHz) 7.44–7.40 (2H, m, 2 × Ar*H*), 7.39–7.35 (3H, m, 3 × Ar*H*), 4.95 (2H, s, CH_2Ph), 3.48–3.26 (2H, m, NCH_2(CH_2)$_2$), 2.21–2.11 (1H, m, N(CH_2)$_2$C$H_A$$H_B$), 2.11–1.93 (1H, m, NC$H_2$(C$H_A$$H_B$)C$H_2$), 1.92–1.81 (1H, m, NC$H_2$(C$H_A$$H_B$)C$H_2$), 1.81–1.69 (1H, m, N($CH_2$)$_2CH_A$$H_B$), 1.63 (3H, s, C$H_3$); δ_C ($CDCl_3$, 101 MHz) 162.9, 134.6, 129.9, 129.0, 128.6, 120.8, 75.8, 51.1, 41.0, 33.4, 23.2, 20.2; mp: 55–57 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 2943, 2877, 1670, 1459, 995, 751, 699; *m/z* (ESI$^+$) 267 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{14}H_{17}O_2N_2^+$ ([M + H]$^+$) requires 245.12815, found 245.12856.

1-(Benzyloxy)-3-methyl-2-oxopyrrolidine-3-carbaldehyde, 165

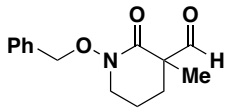


Synthesised according to the general procedure **E**, using 1-(benzyloxy)-3-methyl-2-

oxopyrrolidine-3-carbonitrile **163** (1.84 g, 8.0 mmol), Raney®-Ni (50% in water, 15.0 g, 128 mmol), sodium hypophosphite monohydrate (13.6 g, 128 mmol) in a 1:1:2 mixture of water:acetic acid:pyridine (60 mL). The crude product was purified by flash chromatography on silica (eluent 50% EtOAc/petrol) to give the *aldehyde* **165** (0.97 g, 52%) as a pale yellow crystalline solid.

δ_H ($CDCl_3$, 400 MHz) 9.55 (1H, s, C*H*O), 7.55–7.25 (5H, m, 5 × Ar*H*), 4.99 (1H, d, *J* 10.5, C$H_A$$H_B$Ph), 4.97 (1H, d, *J* 10.5, CH$_A$$H_B$Ph), 3.30–3.14 (2H, m, NCH_2CH$_2$), 2.59–2.39 (1H, m, NCH$_2$CH_AH$_B$), 1.72–1.58 (1H, m, NCH$_2$CH$_A$$H_B$), 1.38 (s, 3H); δ_C ($CDCl_3$, 101 MHz) 198.5, 168.3, 134.8, 129.5, 129.1, 128.6, 76.9, 53.6, 44.3, 23.8, 18.5; mp: 82–84 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 2979, 2885, 1731, 1698, 1403, 1004, 700; *m/z* (ESI$^+$) 288 ([M + MeOH + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{13}H_{16}O_3N^+$ ([M + H]$^+$) requires 234.11247, found 234.11262.

1-(Benzyloxy)-3-methyl-2-oxopiperidine-3-carbaldehyde, 166

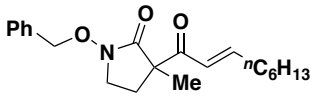


Synthesised according to the general procedure **E**, using 1-(benzyloxy)-3-methyl-2-oxopiperidine-3-carbonitrile **164** (1.36 g, 5.5 mmol), Raney®-Ni (50% in water, 15.0 g, 128 mmol), sodium hypophosphite monohydrate (13.6 g,128 mmol) in a 1:1:2 mixture of water:acetic acid:pyridine (60 mL). The crude product was purified by flash chromatography on silica (eluent 50% EtOAc/petrol) to give the *aldehyde* **166** (0.62 g, 46%) as a pale yellow crystalline solid.

δ_H ($CDCl_3$, 400 MHz) 9.64 (1H, s, C*H*O), 7.46–7.41 (2H, m, 2 × Ar*H*), 7.39–7.35 (3H, m, 3 × Ar*H*), 4.99 (1H, d, *J* 10.5, CH_AH$_B$Ph), 4.95 (1H, d, *J* 10.5, CH$_A$$H_B$Ph), 3.43–3.24 (2H,

m, NCH_2(CH$_2$)$_2$), 2.25–2.07 (1H, m, N(CH$_2$)$_2$CH_AH$_B$), 1.87–1.67 (2H, m, NCH$_2$CH_2CH$_2$), 1.56–1.43 (1H, m, N(CH$_2$)$_2$CH$_A$$H_B$), 1.41 (3H, s, C$H_3$); δ_C (CDCl$_3$, 101 MHz) 200.0, 167.0, 135.0, 129.8, 128.9, 128.5, 75.9, 55.7, 51.0, 28.2, 20.6, 20.1; mp: 79–81 °C (CH$_2$Cl$_2$); ν_{max} (neat)/cm^{-1} 2947, 2874, 1727, 1653, 1485, 1347, 1008, 700; *m/z* (ESI$^+$) 270 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{14}H_{18}O_3N^+$ ([M + H]$^+$) requires 248.12812, found 248.12817.

(*E*)-1-(Benzyloxy)-3-methyl-3-(non-2-enoyl)pyrrolidin-2-one, 167

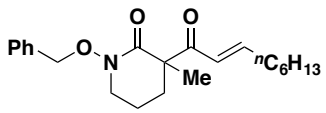


Synthesised according to the general procedure **C**, using 1-(benzyloxy)-3-methyl-2-oxopyrrolidine-3-carbaldehyde **165** (70 mg, 0.30 mmol), 1-octyne (54 μL, 0.36 mmol), [Rh(nbd)$_2$]BF$_4$ (5.6 mg, 5 mol%) and dcpe (6.3 mg, 5 mol%) in acetone (0.3 mL, 1.0 M). The crude product was purified by flash chromatography on silica (eluent 20% EtOAc/petrol) to give the *enone* **167** (33 mg, 32%) as a colourless oil.

δ_H (CDCl$_3$, 400 MHz) 7.38–7.32 (2H, m, 2 × Ar*H*), 7.32–7.26 (3H, m, 3 × Ar*H*), 6.94 (1H, dt, *J* 15.0, 7.0, C(O)CHC*H*CH$_2$), 6.59 (1H, dt, *J* 15.0, 1.5, C(O)C*H*CHCH$_2$), 4.93 (1H, d, *J* 10.5, CH_AH$_B$Ph), 4.89 (1H, d, *J* 10.5, CH$_A$$H_B$Ph), 3.24–3.07 (2H, m, NCH_2CH$_2$), 2.73–2.48 (1H, m, NCH$_2$CH_AH$_B$), 2.27–2.11 (2H, m, CHCH_2CH$_2$(CH$_2$)$_3$CH$_3$), 1.60–1.51 (1H, m, NCH$_2$CH$_A$$H_B$), 1.44–1.35 (2H, m, CHCH$_2$CH_2(CH$_2$)$_3$CH$_3$), 1.33 (3H, s, C(O)C(CH_3)), 1.31–1.14 (6H, m, CH(CH$_2$)$_2$(CH_2)$_3$CH), 0.80 (3H, t, *J* 7.5, CH$_2$CH_3); δ_C (CDCl$_3$, 101 MHz) 195.4, 169.9, 150.1, 135.0, 129.5, 129.0, 128.5, 124.5, 76.7, 53.7, 44.6, 32.7, 31.6, 28.9, 28.1, 26.8, 22.6, 20.9, 14.1; ν_{max} (neat)/cm^{-1} 2928, 2857, 1710, 1659, 1623, 1455, 974, 699; *m/z* (ESI$^+$) 366 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{21}H_{30}O_3N^+$ ([M + H]$^+$) requires 344.22202, found

344.22200.

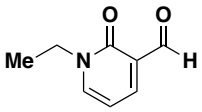
(*E*)-1-(Benzyloxy)-3-methyl-3-(non-2-enoyl)piperidin-2-one, 168



Synthesised according to the general procedure **C**, using 1-(benzyloxy)-3-methyl-2-oxopiperidine-3-carbaldehyde **166** (74 mg, 0.30 mmol), 1-octyne (54 μL, 0.36 mmol), $[Rh(nbd)_2]BF_4$ (5.6 mg, 5 mol%) and dcpe (6.3 mg, 5 mol%) in acetone (0.3 mL, 1.0 M). The crude product was purified by flash chromatography on silica (eluent 20% EtOAc/petrol) to give the *enone* **168** (106 mg, 98%) as a colourless oil.

δ_H ($CDCl_3$, 400 MHz) 7.39–7.33 (2H, m, 2 × Ar*H*), 7.30–7.23 (3H, m, 3 × Ar*H*), 6.96 (1H, dt, *J* 15.0, 7.0, C(O)CH=C*H*CH_2), 6.53 (1H, dt, *J* 15.5, 1.5, C(O)C*H*=CHCH_2), 4.91 (1H, d, *J* 10.5, CH_AH_BPh), 4.82 (1H, d, *J* 10.5, CH_AH_BPh), 3.41–3.20 (2H, m, NC$H_2(CH_2)_2$), 2.27–2.19 (1H, m, $N(CH_2)_2CH_AH_B$), 2.18–2.10 (2H, m, CHC$H_2CH_2(CH_2)_3CH_3$), 1.76–1.62 (2H, m, $NCH_2CH_2CH_2$), 1.49–1.32 (6H, m, $N(CH_2)_2CH_AH_B$, $CHCH_2CH_2(CH_2)_3CH_3$, C(O)C(CH_3)), 1.29–1.15 (6H, m, $CH(CH_2)_2(CH_2)_3CH_3$), 0.78 (3H, t, *J* 7.5, CH_2CH_3); δ_C ($CDCl_3$, 101 MHz) 196.7, 169.1, 150.0, 135.2, 129.6, 128.7, 128.4, 124.4, 75.7, 56.3, 51.4, 32.6, 31.6, 31.0, 28.9, 28.1, 22.5, 22.4, 20.2, 14.1; ν_{max} (neat)/cm^{-1} 2928, 2857, 1658, 1621, 1484, 993, 748, 698; HRMS (CI^+) $C_{22}H_{32}NO_3^+$ ($[M + H]^+$) requires 358.2373, found 358.2373.

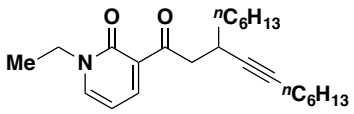
1-Ethyl-2-oxo-1,2-dihydropyridine-3-carbaldehyde, 169



Iodotrimethylsilane (2.85 mL, 20.0 mmol) was added to a solution of 2-methoxy-3-pyridinecarboxyaldehyde (2.46 mL, 20.8 mmol) in dry $CHCl_3$ (20 mL). The solution was heated at 60° C for 1 h and then quenched with dry MeOH (3.0 mL). After concentration, the solid residue was recrystallised with EtOH. The resulting white solid was dissolved in dry DME (40 mL) and potassium carbonate (2.46 g, 10.0 mmol) was added. Ethyl iodide (0.80 mL, 10.0 mmol) was added dropwise over 10 min and the reaction was heated to reflux. After 16 h, the reaction mixture was cooled to room temperature, filtered and the solvent removed under reduced pressure. The crude product was purified by flash chromatography on silica (eluent 100% EtOAc) to give the *aldehyde* **169** (1.21 g, 40% over two steps) as a yellow solid.

δ_H ($CDCl_3$, 400 MHz) 10.37 (1H, s, C*H*O), 8.03 (1H, dd, *J* 7.0, 2.0, Ar*H*), 7.64 (1H, dd, *J* 6.5, 2.0, Ar*H*), 6.48–6.15 (1H, m, Ar*H*), 4.09 (2H, q, *J* 7.0, NCH_2CH_3), 1.43 (3H, t, *J* 7.0, NCH_2CH_3); δ_C ($CDCl_3$, 101 MHz) 189.9, 162.2, 143.7, 141.1, 125.1, 105.8, 45.2, 14.7; mp: 80–82 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 2974, 2880, 1687, 1543, 1260, 895, 769; *m/z* (ESI^+) 174 ($[M + Na]^+$, 100%); HRMS (ESI^+) $C_8H_{10}O_2N^+$ ($[M + H]^+$) requires 152.07115, found 152.07111.

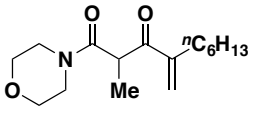
1-Ethyl-3-(3-hexylundec-4-ynoyl)pyridin-2(1*H*)-one, 171



Synthesised according to the general procedure **C**, using 1-ethyl-2-oxo-1,2-dihydropyridine-3-carbaldehyde **169** (45 mg, 0.30 mmol), 1-octyne (66 μL, 0.45 mmol) $[Rh(nbd)_2]BF_4$ (5.6 mg, 5 mol%) and dcpe (6.3 mg, 5 mol%) in acetone (0.3 mL, 1.0 M). The crude product was purified by flash chromatography on silica (eluent 30% EtOAc/petrol) to give the *alkyne* **171** (70 mg, 60%) as a pale yellow oil.

δ_H ($CDCl_3$, 400 MHz) 8.03 (1H, dd, *J* 7.0, 2.5, Ar*H*), 7.49 (1H, dd, *J* 6.5, 2.5, Ar*H*), 6.22 (1H, dd, *J* 7.0, 6.5, Ar*H*), 3.99 (2H, q, *J* 7.0, NC*H*$_2$CH$_3$), 3.22 (1H, dd, *J* 7.0, 2.5, C(O)C*H*$_2$CH), 2.95–2.82 (1H, m, C(O)CH$_2$C*H*), 2.02 (2H, td, *J* 7.0, 2.0, C≡CC*H*$_2$CH$_2$(CH$_2$)$_3$CH$_3$), 1.45-1.31 (9H, m, 3 × C*H*$_2$, NCH$_2$C*H*$_3$), 1.27–1.16 (12H, m, 6 × C*H*$_2$), 0.87–0.77 (6H, m, 2 × CH$_2$C*H*$_3$); δ_C ($CDCl_3$, 101 MHz) 198.5, 160.6, 143.1, 141.9, 128.1, 105.6, 82.9, 81.0, 49.0, 45.5, 35.4, 31.8, 31.4, 29.1, 29.1, 28.4, 27.3, 27.1, 22.6, 22.6, 18.7, 14.7, 14.1, 14.0; ν_{max} (neat)/cm^{-1} 2980, 2974, 1690, 1648, 1583, 1249, 760; *m/z* (ESI$^+$) 372 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{24}H_{38}O_2N^+$ ([M + H]$^+$) requires 372.28971, found 372.28925.

2-Methyl-4-methylene-1-morpholinodecane-1,3-dione, 140b

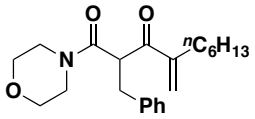


Synthesised according to the general procedure **C**, using 2-methyl-3-morpholino-3-oxopropanal **69d** (51 mg, 0.30 mmol), 1-octyne (54 μL, 0.36 mmol),

[Rh(AmpaPhos)(C_6H_5F)][BAr^F_4] (22.0 mg, 0.015 mmol, 5 mol%) in acetone (0.30 mL, 1.0 M). The crude product was purified by flash chromatography on silica (eluent 50% EtOAc/petrol) to give the *enone* **140b** (56 mg, 66%; B:L ratio 9:1) as a pale yellow oil.

δ_H ($CDCl_3$, 400 MHz) 5.92 (1H, s, C=CH_AH$_B$), 5.73 (1H, app. t, *J* 1.5, C=CH$_A$$H_B$), 4.14 (1H, q, *J* 7.0, C*H*CH$_3$), 3.74–3.47 (6H, 2 × OCH_2CH$_2$N, OCH$_2$CH_2N), 3.42–3.22 (2H, m, OCH$_2$CH_2N), 2.27–2.12 (2H, m, CHCH$_2$CH_2(CH$_2$)$_3$CH$_3$), 1.38–1.28 (5H, m, CHCH$_2$CH_2(CH$_2$)$_3$CH$_3$, CHCH_3), 1.27–1.17 (6H, m, CH(CH$_2$)$_2$(CH_2)$_3$CH$_3$), 0.85–0.73 (3H, m, CH$_2$CH_3); δ_C ($CDCl_3$, 101 MHz) 198.2, 169.5, 147.9, 124.1, 66.8, 66.4, 46.1, 46.0, 42.4, 31.6, 31.2, 29.0, 28.2, 22.6, 14.5, 14.1; ν_{max} (neat)/cm^{-1} 1674, 1637, 1432, 1277, 1226, 1115, 1029; *m/z* (ESI$^+$) 304 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{16}H_{28}O_3N^+$ ([M + H]$^+$) requires 282.20637, found 282.20587.

2-Benzyl-4-methylene-1-morpholinodecane-1,3-dione, 70b

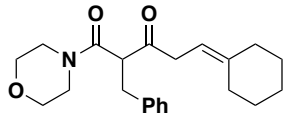


Synthesised according to the general procedure **C**, using 2-benzyl-3-morpholino-3-oxopropanal **69a** (74 mg, 0.30 mmol), 1-octyne (54 μL, 0.36 mmol), [Rh(AmpaPhos)(C_6H_5F)][BAr^F_4] (22.0 mg, 0.015 mmol, 5 mol%) in acetone (0.30 mL, 1.0 M). The crude product was purified by flash chromatography on silica (eluent 50% EtOAc/petrol) to give the *enone* **70b** (97 mg, 90%; B:L ratio 5:1) as a pale yellow oil.

δ_H ($CDCl_3$, 400 MHz) 7.41–6.95 (5H, m, 5 × Ar*H*), 5.70 (1H, s, C=CH_AH$_B$), 5.63 (1H, s, C=CH$_A$$H_B$), 4.31 (1H, dd, *J* 9.0, 5.5, C*H*CH$_2$Ph), 3.64–3.44 (2H, m, OCH$_2$CH_AH$_B$N, OCH_AH$_B$CH$_2$N), 3.43–3.26 (3H, m, OCH$_A$$H_BCH_2N, OCH_2CH_2$N), 3.25–3.00 (3H, m,

CHC*H*$_2$Ph, OCH$_2$C*H*$_A$H$_B$N), 2.98–2.89 (1H, m, OCH$_2$CH$_A$*H*$_B$N), 2.90–2.79 (1H, m, OCH$_A$*H*$_B$CH$_2$N), 2.22–2.15 (2H, m, CHC*H*$_2$CH$_2$(CH$_2$)$_3$CH$_3$), 1.40–1.27 (2H, m, CHCH$_2$C*H*$_2$(CH$_2$)$_3$CH$_3$), 1.28–1.07 (6H, m, CH(CH$_2$)$_2$(C*H*$_2$)$_3$CH$_3$), 0.91–0.70 (3H, m, CH$_2$C*H*$_3$); δ_C (CDCl$_3$, 101 MHz) 196.2, 168.2, 148.7, 138.8, 129.2, 129.0, 128.6, 128.6, 126.8, 123.1, 66.5, 65.9, 52.6, 46.2, 42.2, 35.4, 31.6, 31.4, 29.0, 28.0, 22.6, 14.1; ν_{max} (neat)/cm^{-1} 1686, 1628, 1454, 1432, 1271, 1228, 1114, 1033; *m/z* (ESI$^+$) 380 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{22}H_{32}O_3N^+$ ([M + H]$^+$) requires 358.23767, found 358.23721.

2-Benzyl-5-cyclohexylidene-1-morpholinopentane-1,3-dione, 173

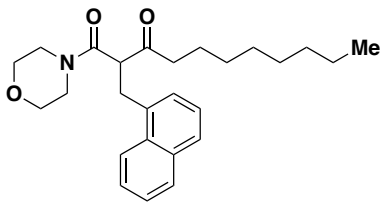


Synthesised according to the general procedure **C**, using 2-benzyl-3-morpholino-3-oxopropanal **69a** (74 mg, 0.30 mmol), vinylidenecyclohexane **172** (48 μL, 0.36 mmol), [Rh(nbd)$_2$]BF$_4$ (5.6 mg, 5 mol%) and dppm (5.8 mg, 5 mol%) in acetone (0.3 mL, 1.0 M). The crude product was purified by flash chromatography on silica (eluent 20% EtOAc/petrol) to give the *alkene* **173** (75 mg, 70%) as a colourless oil.

δ_H (CDCl$_3$, 400 MHz) 7.47–6.90 (5H, m, 5 × Ar*H*), 5.09 (1H, t, *J* 7.0, CH$_2$C*H*=C), 3.83 (1H, t, *J* 8.0, C*H*CH$_2$Ph), 3.65–3.56 (1H, m, OCH$_2$C*H*$_A$CH$_B$N), 3.55–3.48 (1H, m, OC*H*$_A$CH$_B$CH$_2$N), 3.44–3.31 (3H, m, OC*H*$_2$CH$_2$N, OCH$_2$CH$_A$C*H*$_B$N), 3.29–3.20 (1H, m, OCH$_2$C*H*$_A$CH$_B$N), 3.18–3.08 (4H, m, C(O)C*H*$_2$CH, CHC*H*$_2$Ph), 3.05–2.97 (1H, m, OCH$_2$CH$_A$C*H*$_B$N), 2.94–2.82 (1H, m, OCH$_A$C*H*$_B$CH$_2$N), 2.09–1.93 (4H, m, 2 × C*H*$_2$), 1.54–1.33 (6H, m, 3 × C*H*$_2$); δ_C (CDCl$_3$, 101 MHz) 204.0, 167.5, 144.4, 138.5, 129.0, 128.6, 126.8, 111.9, 66.6, 66.1, 57.2, 46.4, 42.4, 39.4, 37.1, 34.9, 29.0, 28.4, 27.5, 26.6; ν_{max} (neat)/cm^{-1}

2926, 2854, 1716, 1631, 1441, 1113, 701; *m/z* (ESI^+) 378 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{22}H_{30}O_3N^+$ ($[M + H]^+$) requires 356.22202, found 356.22198.

1-Morpholino-2-(naphthalen-1-ylmethyl)undecane-1,3-dione, 174

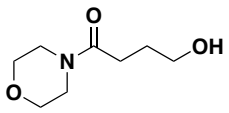


Synthesised according to the general procedure **C**, using 3-morpholino-2-(naphthalen-1-ylmethyl)-3-oxopropanal **69b** (89 mg, 0.30 mmol), 1-octene (0.14 mL, 0.90 mmol), $[Rh(nbd)_2]BF_4$ (11.2 mg, 10 mol%) and dppm (11.6 mg, 10 mol%) in acetone (0.15 mL, 2.0 M). The crude product was purified by flash chromatography on silica (eluent 40% EtOAc/petrol) to give the *ketone* **174** (17 mg, 14%) as a pale yellow oil.

δ_H ($CDCl_3$, 400 MHz) 7.89 (1H, d, *J* 8.5, Ar*H*), 7.79 (1H, dd, *J* 8.0, 1.0, Ar*H*), 7.68 (1H, d, *J* 8.0, Ar*H*), 7.44 (2H, dddd, *J* 16.0, 8.0, 7.0, 1.5, 2 × Ar*H*), 7.36–7.23 (2H, m, 2 × Ar*H*), 3.97 (1H, dd, *J* 10.5, 4.5, C*H*CH_2Ar), 3.68 (1H, dd, *J* 14.0, 4.5, CHC$H_A$$H_B$Ar), 3.55 (2H, app. dd, *J* 14.0, 10.5, $CHCH_AH_B$Ar, $OCH_2CH_AH_BN$), 3.43 (1H, ddd, *J* 11.5, 5.0, 3.0, $OCH_AH_BCH_2N$), 3.24 (1H, ddd, *J* 13.5, 8.0, 3.0, $OCH_2CH_AH_BN$), 3.11–2.90 (3H, m, OCH_2CH_2N, $OCH_2CH_AH_BN$), 2.57 (1H, dd, *J* 12.5, 4.5, $OCH_2CH_AH_BN$), 2.48 (1H, dt, *J* 17.5, 7.5, $C(O)CH_AH_BCH_2$), 2.37 (1H, dt, *J* 17.5, 7.5, $C(O)CH_AH_BCH_2$), 2.28–2.18 (1H, m, $OCH_AH_BCH_2N$), 1.60–1.46 (2H, m, CH_2), 1.26–1.13 (10H, m, 5 × CH_2), 0.81 (3H, t, *J* 7.0, CH_2CH_3); δ_C ($CDCl_3$, 101 MHz) 205.4, 168.1, 134.5, 133.9, 131.6, 129.1, 127.6, 127.5, 126.4, 125.8, 125.6, 123.1, 100.0, 66.5, 65.8, 56.2, 46.4, 42.3, 40.5, 32.0, 31.8, 29.4, 29.1, 23.6, 22.7, 14.1; ν_{max} (neat)/cm^{-1} 2970, 2856, 1720, 1634, 1434, 1229, 1115, 778; *m/z* (ESI^+)

432 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{26}H_{36}O_3N^+$ ([M + H]$^+$) requires 410.26897, found 410.26864.

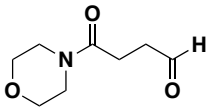
4-Hydroxy-1-morpholinobutan-1-one, 178



Trimethylaluminium (23 mL, 2 M in PhCl, 46 mmol) was added over 1 h to a solution of morpholine (4.2 mL, 48 mmol) in CH_2Cl_2 (20 mL) at –78 °C. The solution was warmed to room temperature and stirred for 4 h. The solution was then cooled to 0 °C and γ-butyrolactone (1.5 mL, 20 mmol) was added dropwise and the resulting mixture stirred for another 2 h. The solution was then quenched with sat. aq. potassium sodium L-tartrate tetrahydrate solution (20 mL) and stirred overnight. The resulting precipitate was filtered through Celite® and washed with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the alcohol **178** (2.23 g, 65%) as a colourless oil. The crude product required no additional purification.

δ_H ($CDCl_3$, 400 MHz) 3.68–3.60 (6H, m, 2 × OC*H*$_2$CH$_2$N, C*H*$_2$OH), 3.60–3.55 (2H, m, OCH$_2$C*H*$_2$N), 3.46 (2H, t, *J* 4.5, OCH$_2$C*H*$_2$N), 2.84 (1H, br. s, CH$_2$O*H*), 2.44 (2H, t, *J* 7.0, C(O)C*H*$_2$), 1.86 (2H, p, *J* 7.0, C(O)CH$_2$C*H*$_2$); δ_C ($CDCl_3$, 101 MHz) 172.1, 66.8, 66.6, 62.0, 46.0, 42.0, 30.1, 27.7; *m/z* (ESI$^+$) 174 ([M + H]$^+$, 100%). Data is consistent with the literature.[273]

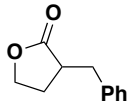
4-Morpholino-4-oxobutanal, 177



To a flame dried reaction flask containing DMSO (1.1 mL, 15 mmol) in CH_2Cl_2 (3.5 mL) was slowly added oxalyl chloride (0.63 mL, 7.5 mmol) at –78 °C over 30 min. The reaction mixture was stirred at this temperature for 15 min before addition of 4-hydroxy-1-morpholinobutan-1-one **178** (1.2 g, 7.0 mmol) in CH_2Cl_2 (2.5 mL). The reaction was stirred for 30 min before addition of triethylamine (4.8 mL, 34 mmol). The reaction mixture was then slowly warmed to room temperature and water (50 mL) was then added and the product extracted with CH_2Cl_2 (50 mL). The combined organic layers were washed with brine, then dried over $MgSO_4$ and the solvent removed *in vacuo.* The crude product was purified by flash chromatography on silica (eluent 40% acetone/petrol) to give the *aldehyde* **177** (0.49 g, 41%) as a colourless oil.

δ_H ($CDCl_3$, 400 MHz) 9.83 (1H, s, C*H*O), 3.71–3.61 (4H, m, 2 × O$CH_2$$CH_2$N), 3.61–3.55 (2H, m, O$CH_2CH_2$N), 3.51–3.46 (2H, m, O$CH_2CH_2$N), 2.81 (2H, t, *J* 6.5, CH_2CH_2CHO), 2.61 (2H, t, *J* 6.5, C$H_2$$CH_2$CHO); δ_C ($CDCl_3$, 101 MHz) 201.0, 169.7, 66.8, 66.5, 45.7, 42.1, 38.5, 25.5; ν_{max} (neat)/cm^{-1} 2911, 2858, 1714, 1624, 1440, 1112, 1032, 848; HRMS (CI^+) $C_8H_{14}O_3N^+$ ($[M + H]^+$) requires 172.0973, found 172.0973.

3-Benzyldihydrofuran-2(3*H*)-one, 180

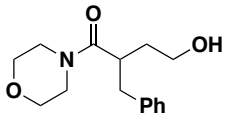


To a round bottomed flask containing diisopropylamine (15.4 mL, 110 mmol) in THF

(100 mL) at –78 °C was added *n*-BuLi (44 mL, 2.5 M in hexanes, 110 mmol) dropwise over 10 min. To this solution was added γ-butyrolactone (7.7 mL, 100 mL) and the mixture was stirred for 20 minutes. Benzyl bromide (14.3 mL, 120 mmol) was then added carefully and the mixture was stirred at –78 °C for 1 h. The reaction was then quenched with sat aq. ammonium chloride solution (100 mL) and the product was extracted with Et_2O (100 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica (eluent 30% Et_2O/petrol) to give the ester **180** (11.4 g, 65%) as a colourless oil.

δ_H ($CDCl_3$, 400 MHz) 7.38–7.30 (2H, m, 2 × Ar*H*), 7.31–7.22 (3H, m, 3 × Ar*H*), 4.22 (1H, td, *J* 9.0, 3.0, C*H*$_A$H$_B$Ph), 4.14 (1H, td, *J* 9.0, 6.5, CH$_A$*H*$_B$Ph), 3.25 (1H, dd, *J* 13.5, 4.0, OC*H*$_A$H$_B$), 2.91–2.80 (1H, m, C(O)C*H*CH$_2$), 2.76 (1H, dd, *J* 13.5, 9.5, OCH$_A$*H*$_B$), 2.24 (1H, dddd, *J* 12.5, 8.5, 6.5, 3.0, C(O)CHCH$_A$*H*$_B$), 1.99 (1H, dq, *J* 12.5, 9.5, C(O)CHC*H*$_A$H$_B$); δ_C ($CDCl_3$, 101 MHz) 178.8, 138.5, 128.9, 128.7, 126.7, 66.6, 41.1, 36.1, 28.0; *m/z* (ESI$^+$) 199 ([M + Na]$^+$, 100%). Data is consistent with the literature.[274]

2-Benzyl-4-hydroxy-1-morpholinobutan-1-one, 181

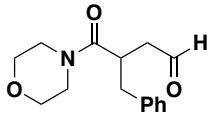


Trimethylaluminium (23 mL, 2 M in PhCl, 46 mmol) was added over 1 h to a solution of morpholine (4.2 mL, 48 mmol) in CH_2Cl_2 (20 mL) at –78 °C. The solution was warmed to room temperature and stirred for 4 h. The solution was then cooled to 0 °C and 3-benzyldihydrofuran-2(3*H*)-one **180** (3.52 g, 20 mmol) was added dropwise and the resulting mixture stirred for another 2 h. The solution was then quenched with sat. aq.

potassium sodium L-tartrate tetrahydrate solution (20 mL) and stirred overnight. The resulting precipitate was filtered through Celite® and washed with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the *alcohol* **181** (4.70 g, 89%) as a colourless oil. The crude product required no additional purification.

δ_H ($CDCl_3$, 400 MHz) 7.43–6.95 (5H, m, 5 × Ar*H*), 3.71–3.63 (2H, m, $OCH_2CH_AH_BN$, CH_AH_BOH), 3.63–3.52 (2H, m, CH_AH_BOH, $OCH_AH_BCH_2N$), 3.44–3.19 (5H, m, OCH_2CH_2N, OCH_2CH_2N, $CHCH_2Ph$), 3.08 (1H, ddd, *J* 13.5, 5.5, 3.0, $OCH_2CH_AH_BN$), 2.93 (1H, dd, *J* 13.0, 10.0, $CHCH_AH_BPh$), 2.83–2.74 (2H, m, $CHCH_AH_BPh$, $OCH_AH_BCH_2N$), 2.68 (1H, s, O*H*), 2.10–1.97 (1H, m, $CH_AH_BCH_2OH$), 1.86–1.74 (1H, m, $CH_AH_BCH_2OH$); δ_C ($CDCl_3$, 101 MHz) 174.0, 139.5, 129.0, 128.5, 126.5, 66.7, 66.3, 60.2, 46.2, 42.2, 39.8, 39.6, 35.6; ν_{max} (neat)/cm^{-1} 3406, 2921, 2858, 1766, 1615, 1453, 1113, 1027; HRMS (CI^+) $C_{15}H_{22}O_3N^+$ ($[M + H]^+$) requires 264.1599, found 264.1599.

3-Benzyl-4-morpholino-4-oxobutanal, 182

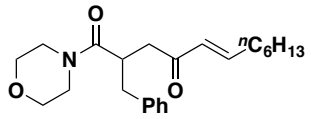


To a flame dried reaction flask containing DMSO (1.67 mL, 23.8 mmol) in CH_2Cl_2 (30 mL) was slowly added oxalyl chloride (1.04 mL, 11.9 mmol) at –78 °C over 15 min. The reaction mixture was stirred at this temperature for 10 min before addition of 2-benzyl-4-hydroxy-1-morpholinobutan-1-one **181** (2.6 g, 9.9 mmol) in CH_2Cl_2 (15 mL). The reaction was stirred for 45 min before addition of triethylamine (4.14 mL, 29.7 mmol). The reaction mixture was then slowly warmed to room temperature and water (50 mL) was then added and the product extracted with CH_2Cl_2 (50 mL). The combined organic layers were washed with brine, then

dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica (eluent 30% acetone/petrol) to give the *aldehyde* **182** (1.27 g, 49%) as a colourless oil.

δ_H ($CDCl_3$, 400 MHz) 9.75 (1H, s, C*H*O), 7.37–7.23 (3H, m, 3 × Ar*H*), 7.21–7.11 (2H, m, 2 × Ar*H*), 3.66–3.58 (2H, m, CHCH_AH$_B$Ph, OCH_AH$_B$CH$_2$N), 3.54 (1H, ddd, *J* 11.5, 6.0, 3.0, OCH$_A$$H_BCH_2$N), 3.48–3.38 (4H, m, C*H*CH$_2$Ph, CHCH$_A$$H_BPh, OCH_2CH_AH_BN, OCH_A$$H_BCH_2$N), 3.23 (1H, dd, *J* 19.0, 9.5, OCH$_2$CH_AH$_B$N), 3.09 (1H, ddd, *J* 13.5, 6.0, 3.0, OCH$_2$CH$_A$$H_B$N), 2.98–2.84 (2H, m, C$H_AH_BCHO, OCH_A$$H_BCH_2$N), 2.74 (1H, dd, *J* 13.0, 6.0, CH$_A$$H_B$CHO), 2.64 (1H, dd, *J* 19.0, 3.5, OCH$_2$CH$_A$$H_B$N); δ_C ($CDCl_3$, 101 MHz) 200.6, 172.5, 138.5, 129.0, 128.6, 126.9, 66.6, 66.2, 47.2, 46.2, 42.2, 39.2, 36.6; ν_{max} (neat)/cm^{-1} 2978, 2858, 1717, 1625, 1444, 1113, 702; HRMS (CI$^+$) $C_{15}H_{20}O_3N^+$ ([M + H]$^+$) requires 262.1443, found 262.1443.

(*E*)-2-Benzyl-1-morpholinododec-5-ene-1,4-dione, 183

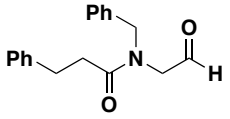


Synthesised according to the general procedure **C**, using 3-benzyl-4-morpholino-4-oxobutanal **182** (78 mg, 0.30 mmol), 1-octyne (54 μL, 0.36 mmol), $[Rh(nbd)_2]BF_4$ (11.2 mg, 10 mol%) and dppe (12.0 mg, 5 mol%) in acetone (0.3 mL, 1.0 M). The crude product was purified by flash chromatography on silica (eluent 40% EtOAc/petrol) to give the *enone* **183** (22 mg, 20%) as a pale yellow oil.

δ_H ($CDCl_3$, 400 MHz) 7.27–7.15 (3H, m, 3 × Ar*H*), 7.14–7.02 (2H, m, 2 × Ar*H)*, 6.78 (1H, dt, *J* 16.0, 7.0, C(O)CH=C*H*CH$_2$), 5.98 (1H, dt, *J* 16.0, 1.5, C(O)C*H*=CHCH$_2$), 3.62–3.15

(8H, m, OC*H*$_2$CH$_2$N, OCH$_2$C*H*$_2$N, OC*H*$_A$H$_B$CH$_2$N, OCH$_2$C*H*$_A$H$_B$N, C*H*CH$_2$Ph, C(O)C*H*$_A$H$_B$), 3.01 (1H, ddd, *J* 13.5, 5.5, 3.0, C(O)CH$_A$*H*$_B$), 2.83–2.75 (2H, m, CHC*H*$_A$H$_B$Ph, OCH$_A$*H*$_B$CH$_2$N), 2.72–2.52 (2H, m, CHCH$_A$*H*$_B$Ph, OCH$_2$CH$_A$*H*$_B$N), 2.20–2.07 (2H, m, CHC*H*$_2$CH$_2$(CH$_2$)$_3$CH$_3$), 1.44–1.31 (2H, m, CHCH$_2$C*H*$_2$(CH$_2$)$_3$CH$_3$), 1.30–1.17 (6H, m, CH(CH$_2$)$_2$(C*H*$_2$)$_3$CH$_3$), 0.81 (3H, t, *J* 7.5, CH$_2$C*H*$_3$); δ_C (CDCl$_3$, 101 MHz) 199.0, 173.2, 148.4, 139.0, 130.1, 129.1, 128.5, 126.7, 66.6, 66.3, 46.2, 43.1, 42.1, 39.4, 37.8, 32.5, 31.6, 28.9, 28.0, 22.6, 14.1; ν_{max} (neat)/cm^{-1} 2980, 2855, 1680, 1624, 1440, 1113, 699; *m/z* (ESI$^+$) 394 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{23}H_{33}O_3NNa^+$ ([M + Na]$^+$) requires 394.23527, found 394.23543.

_N_-Benzyl-_N_-(2-oxoethyl)-3-phenylpropanamide, 184

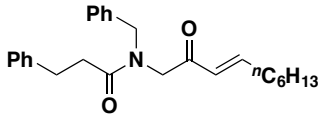


To a vigorously stirring biphasic mixture of *N*-benzylethanolamine (3.45 mL, 24.3 mmol) in EtOAc (40 mL) and sat. aq. NaHCO$_3$ solution (20 mL) at 0 °C was added 3-phenylpropanoyl chloride (5.05 mL, 34.0 mmol) dropwise. After stirring for 20 min, the reaction was diluted with water and extracted EtOAc (2 × 30 mL). The combined organic extracts were washed with 1 N HCl (30 mL), dried over MgSO$_4$ and the solvent removed *in vacuo* to give the intermediate (6.40 g), which was used in the next step without purification. Next, to a flame dried reaction flask containing oxalyl chloride (1.04 mL, 11.9 mmol) in CH$_2$Cl$_2$ (30 mL) was slowly added DMSO (1.67 mL, 23.8 mmol) at –78 °C over 15 min. The reaction mixture was stirred at this temperature for 10 min before addition of intermediate (2.81 g, 9.9 mmol) in CH$_2$Cl$_2$ (15 mL). The reaction was stirred for 15 min before addition of triethylamine

(4.14 mL, 29.7 mmol). The reaction mixture was then slowly warmed to room temperature over 45 min, then sat. aq. ammonium chloride solution (50 mL) was added and the product extracted with CH_2Cl_2 (50 mL). The combined organic layers were washed with brine, then dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica (eluent 50% EtOAc/petrol) to give the *aldehyde* **184** (1.38 g, 49%) as a colourless oil. **184** exists as two rotamers, in a ratio of 4:1.

δ_H ($CDCl_3$, 400 MHz) (* denotes minor rotamer) 9.51 (1H, s, C*H*O), 9.38* (1H, s, C*H*O), 7.41–7.27 (5H, m, 5 × Ar*H*), 7.27–7.20 (3H, m, 3 × Ar*H*), 7.14–7.07 (2H, m, 2 × Ar*H*), 4.68* (2H, s, CH_2), 4.57 (2H, s, CH_2Ph), 4.09 (2H, s, CH_2), 3.99* (2H, s, CH_2), 3.07 (2H, t, *J* 8.0, CH_2), 2.83 (2H, t, *J* 8.0, CH_2), 2.54* (2H, t, *J* 8.0, CH_2); δ_C ($CDCl_3$, 101 MHz) (* denotes minor rotamer) 197.4, 197.1*, 173.2*, 172.4, 140.9, 136.5*, 135.7, 129.1, 128.8*, 128.6, 128.5, 128.1, 127.9*, 126.7, 126.3, 57.0*, 55.9, 52.5, 50.2*, 35.2*, 34.7, 31.4*, 31.3; ν_{max} (neat)/cm^{-1} 2923, 2824, 1731, 1639, 1451, 1210, 698; *m/z* (ESI^+) 304 ($[M + Na]^+$, 100%); HRMS (ESI^+) $C_{18}H_{20}O_2N^+$ ($[M + H]^+$) requires 282.14886, found 282.14877.

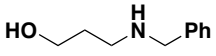
(*E*)-2-Benzyl-1-morpholino-4,5-diphenylpent-4-ene-1,3-dione, 185a



Synthesised according to the general procedure **C**, using *N*-benzyl-*N*-(2-oxoethyl)-3-phenylpropanamide **184** (84 mg, 0.30 mmol), 1-octyne (54 μL, 0.36 mmol), $[Rh(nbd)_2]BF_4$ (5.6 mg, 5 mol%) and dppe (6.0 mg, 5 mol%) in acetone (0.3 mL, 1.0 M). The crude product was purified by flash chromatography on silica (eluent 20% EtOAc/petrol) to give the *enone* **185a** (60 mg, 51%) as a pale yellow oil. **185a** exists as two rotamers, in a ratio of 3:1.

δ_H ($CDCl_3$, 400 MHz) (* denotes minor rotamer) 7.28–7.15 (5H, m, 5 × Ar*H*), 7.14–7.06 (3H, m, 3 × Ar*H)*, 7.01 (2H, d, *J* 6.5, 2 × Ar*H*), 6.87–6.72 (1H, m, C(O)CH=C*H*), 6.12–5.91 (1H, m, C(O)C*H*=CH), 4.54* (2H, s, CH_2Ph), 4.48 (2H, s, CH_2Ph), 4.23 (2H, s, C(O)CH_2N), 3.96* (2H, s, C(O)CH_2N), 2.94 (2H, t, *J* 7.5, CH_2CH_2Ph), 2.74–2.62 (2H, m, CH_2CH_2Ph), 2.44–2.32* (2H, m, CH_2CH_2Ph), 2.17–2.02 (2H, m, $CHCH_2CH_2(CH_2)_3CH_3$), 1.42–1.29 (2H, m, $CHCH_2CH_2(CH_2)_3CH_3$), 1.27–1.13 (6H, m, $CH(CH_2)_2(CH_2)_3CH_3$), 0.80 (3H, t, *J* 7.0, CH_2CH_3); δ_C ($CDCl_3$, 101 MHz) (* denotes minor rotamer) 194.4, 193.9*, 172.9*, 172.9, 150.0*, 149.0, 141.3*, 141.2, 137.1*, 136.3, 128.9, 128.6, 128.4(9), 128.4(8), 128.4*, 127.7, 127.6, 127.5*, 126.6, 126.1, 54.2*, 52.7, 52.0, 49.9*, 35.1*, 34.8, 32.7, 31.6*, 31.6*, 31.4*, 31.3, 28.9, 27.9, 27.8*, 22.6, 14.1; ν_{max} (neat)/cm^{-1} 2979, 2928, 1686, 1648, 1452, 1334, 953, 733, 699; *m/z* (ESI^+) 414 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{26}H_{34}O_2N^+$ ($[M + H]^+$) requires 392.25841, found 392.25650.

3-(Benzylamino)propan-1-ol, 186

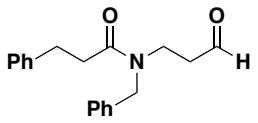


To a stirred solution of 3-amino-1-propanol (3.8 mL, 50 mmol) in MeOH (100 mL) was added benzaldehyde (6.6 mL, 65 mmol) and the mixture was allowed to stir for 10 min at room temperature. Then reaction was cooled to 0 °C and $NaBH_4$ (2.46 g, 65 mmol) was added portionwise, and the mixture was stirred for 30 min at 0 °C followed by 2 h at room temperature. The reaction was then cooled to 0 °C again, and 6 N HCl (25 mL) was added dropwise and the MeOH was removed under reduced pressure. The residue was diluted in water (50 mL) and Et_2O (25 mL) and the phases separated, with the aqueous layer washed with Et_2O (2 × 20 mL). To the aqueous phase was added KOH (7.0 g, 125 mmol) whilst

stirring, whereby an oil separated. This oil was extracted with Et_2O (3 × 40 mL) and the combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the amino-alcohol **186** (3.04 g, 59%) as a pale yellow oil.

δ_H ($CDCl_3$, 400 MHz) 7.38–7.25 (5H, m, 5 × Ar*H*), 3.83–3.77 (4H, m, CH_2Ph, CH_2OH), 3.11 (2H, br. s, O*H*, N*H*), 2.88 (2H, t, *J* 6.0, NCH_2CH$_2$CH$_2$OH), 1.74 (2H, app. p, *J* 6.0, NCH$_2$CH_2CH$_2$OH); δ_C ($CDCl_3$, 101 MHz) 139.5, 128.5, 128.2, 127.2, 63.8, 54.0, 49.0, 30.9.; ν_{max} (neat)/cm^{-1} 3288, 3062, 3027, 2979, 1453, 1070, 740, 698. Data is consistent with the literature.[275]

_N_-Benzyl-_N_-(3-oxopropyl)-3-phenylpropanamide, 187

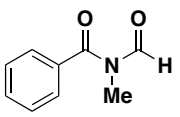


To a vigorously stirring biphasic mixture of 3-(benzylamino)propan-1-ol **186** (2.50 g, 24.3 mmol) in EtOAc (40 mL) and sat. aq. $NaHCO_3$ solution (20 mL) at 0 °C was added 3-phenylpropanoyl chloride (5.05 mL, 34.0 mmol) dropwise. After stirring for 20 min, the reaction was diluted with water and extracted EtOAc (2 × 30 mL). The combined organic extracts were washed with 1 N HCl (30 mL), dried over $MgSO_4$ and the solvent removed *in vacuo* to give the intermediate (6.50 g), which was used in the next step without purification. Next, to a flame dried reaction flask containing oxalyl chloride (1.04 mL, 11.9 mmol) in CH_2Cl_2 (30 mL) was slowly added DMSO (1.67 mL, 23.8 mmol) at –78 °C over 15 min. The reaction mixture was stirred at this temperature for 10 min before addition of intermediate (2.94 g, 9.9 mmol) in CH_2Cl_2 (15 mL). The reaction was stirred for 15 min before addition of triethylamine (4.14 mL, 29.7 mmol). The reaction mixture was

then slowly warmed to room temperature over 45 min, then sat. aq. ammonium chloride solution (50 mL) was added and the product extracted with CH_2Cl_2 (50 mL). The combined organic layers were washed with brine, then dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica (eluent 50% EtOAc/petrol) to give the *aldehyde* **187** (0.74 g, 25%) as a colourless oil. **187** exists as two rotamers, in a ratio of 3:1.

δ_H ($CDCl_3$, 400 MHz) (* denotes minor rotamer) 9.77 (1H, t, *J* 1.5, C*H*O), 9.65* (1H, s, C*H*O), 7.41–7.26 (5H, m, 5 × Ar*H*), 7.24–7.16 (3H, m, 3 × Ar*H*), 7.10 (2H, dd, *J* 6.5, 1.5, 2 × Ar*H*), 4.62* (2H, s, CH_2Ph), 4.52 (2H, s, CH_2Ph), 3.66 (2H, t, *J* 6.5, CH_2), 3.57–3.46* (2H, m, CH_2), 3.08* (2H, t, *J* 7.5, CH_2), 3.06–2.95 (2H, m, CH_2), 2.79–2.72 (2H, m, CH_2), 2.72–2.62 (2H, m, CH_2), 2.55* (2H, t, *J* 7.5); δ_C ($CDCl_3$, 101 MHz) (* denotes minor rotamer) 200.8, 199.3*, 172.9, 172.2*, 141.2*, 141.0, 137.4*, 136.6, 129.0, 128.7*, 128.6, 128.5, 128.5, 128.0*, 127.7, 127.5*, 126.3, 126.2*, 52.0, 48.8*, 43.0*, 42.7, 40.8, 40.3*, 35.1, 35.0*, 31.6*, 31.4; ν_{max} (neat)/cm^{-1} 2927, 1720, 1637, 1472, 1208, 734, 699; *m/z* (ESI^+) 350 ($[M + MeOH + Na]^+$, 100%); HRMS (ESI^+) $C_{19}H_{22}O_2N^+$ ($[M + H]^+$) requires 296.16451, found 296.16437.

_N_-Formyl-_N_-methylbenzamide, 188

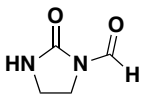


To a stirred solution of *N*-methylbenzamide (1.35 g, 10.0 mmol) and methyl formate (1.85 mL, 30.0 mmol) in dry CH_2Cl_2 (20 mL) at 0 °C was successively added $TiCl_4$ (2.2 mL, 20 mmol) and triethylamine (3.35 mL, 24.0 mmol) dropwise under a N_2 atmosphere. The

mixture was subsequently stirred at this temperature for 1 h and then warmed to room temperature for 1 h. Water was added to the mixture, which was extracted with EtOAc (2 × 30 mL). The combined organic extracts were washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica (eluent 15% acetone/petrol) to give the aldehyde **188** (1.14 g, 70%) as a yellow oil.

δ_H ($CDCl_3$, 400 MHz) 8.91 (1H, s, C*H*O), 7.53–7.38 (5H, m, 5 × Ar*H*), 3.20 (3H, s, NCH_3); δ_C ($CDCl_3$, 101 MHz) 172.5, 164.4, 133.4, 132.2, 128.9, 128.8, 27.5; HRMS (CI^+) $C_9H_{10}NO_2^+$ ($[M + H]^+$) requires 164.0712, found 164.0712. Data is consistent with the literature.[276]

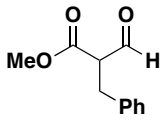
2-Oxoimidazolidine-1-carbaldehyde, 189



A solution of benzoyl chloride (3.5 mL, 30 mmol) in DMF (3 mL) was added to a stirred solution obtained by heating suspension of 2-imidazolidone (2.58 g, 30.0 mmol) in DMF (15 mL) at 80 °C. The reaction mixture was allowed to stand at room temperature for 15 min before the complete precipitation of a white solid. The resulting suspension was collected by filtration and washed with CH_2Cl_2 (10 mL) to furnish a white crystalline solid. This solid was dissolved in H_2O (0.5 mL) and the resulting solution was heated at 80 °C for 5 min and then allowed to stand at room temperature for 5 h. A new solid precipitated, which was collected by filtration, washed with cold brine (10 mL) and Et_2O (10 mL) to give the aldehyde **189** (1.42 g, 41%) as a white crystalline solid.

δ_H (DMSO-d^6, 400 MHz) 8.75 (1H, s, C*H*O), 7.90 (1H, br. s, N*H*), 3.69 (2H, d, *J* 8.5, CH_2NCHO), 3.41 (2H, d, *J* 8.5, CH_2NH); δ_C (DMSO-d^6, 101 MHz) 160.2, 156.6, 39.2, 37.4; mp 161–163 °C (EtOH); *m/z* (ESI$^+$) 137 ([M + Na]$^+$, 100%). Data is consistent with the literature.[277]

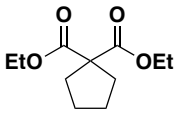
Methyl 2-benzyl-3-oxopropanoate, 190



Synthesised according to the general procedure **B**, using methyl 3-phenylpropanoate (1.64 g, 10.0 mmol), diisopropylamine (4.2 mL, 30 mmol), *n*-BuLi (12 mL, 2.5 M, 30 mmol) and methyl formate (6.17 mL, 100 mmol) in Et_2O (30 mL). The crude product was purified by flash chromatography on silica (eluent 40% EtOAc/petrol) to give the ester **190** (1.02 g, 53%) as a pale yellow oil. **190** is in keto-enol equilibrium (keto:enol 2:1).

δ_H ($CDCl_3$, 400 MHz) (*keto form*) 9.79 (1H, d, *J* 2.0, C*H*O), 7.37–7.31 (2H, m, 2 × Ar*H*), 7.30–7.21 (3H, m, 3 × Ar*H*), 3.77 (3H, s, OCH_3), 3.65 (1H, ddd, *J 8.0*, 6.5, 2.0, C*H*CHO), 3.34–3.19 (2H, m, CH_2Ph); (*enol form*) 11.55 (1H, d, *J* 12.5, C=CH(O*H*)), 7.37–7.31 (2H, m, 2 × Ar*H*), 7.10 (1H, dt, *J* 12.5, 1.0, C=C*H*(OH)), 3.77 (3H, s, OCH_3), 3.47 (2H, br. s, CH_2Ph); δ_C ($CDCl_3$, 101 MHz) 196.3, 172.5, 169.1, 161.9, 140.0, 137.5, 128.9, 128.7, 128.4, 128.3, 126.9, 126.2, 104.4, 60.3, 52.5, 51.6, 33.1, 32.2; *m/z* (ESI$^+$) 247 ([M + Na + MeOH]$^+$, 100%). Data is consistent with the literature.[278]

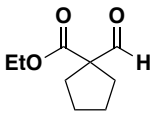
Diethyl cyclopentane-1,1-dicarboxylate, 191a



Synthesised according to the general procedure **F**, using diethyl malonate (3.0 mL, 20 mmol), K_2CO_3 (6.91 g, 25 mmol), 1,4-dibromobutane (2.6 mL, 22 mmol) and [bmim]BF_4 (0.4 mL, 2.0 mmol) in DMF (50 mL). The crude product was purified by flash chromatography on silica (eluent 10% EtOAc/petrol) to give the diester **191a** (3.70 g, 86%) as a colourless oil.

δ_H ($CDCl_3$, 400 MHz) 4.19 (4H, q, *J* 7.0, 2 × $CO_2CH_2CH_3$), 2.31–2.11 (4H, m, 2 × CH_2), 1.86–1.67 (4H, m, 2 × CH_2), 1.25 (6H, t, *J* 7.0, 2 × $CO_2CH_2CH_3$); δ_C ($CDCl_3$, 101 MHz) 172.7, 61.2, 60.3, 34.4, 25.5, 14.0; ν_{max} (neat)/cm^{-1} 2980, 2875, 1727, 1256, 1173. Data is consistent with the literature.[269]

General procedure G for the *mono*-reduction of diesters to *β*-formyl esters, as exemplified by ethyl 1-formylcyclopentane-1-carboxylate, 191b

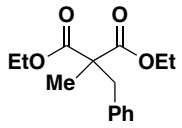


Diethyl cyclopentane-1,1-dicarboxylate **191a** (1.1 g, 5.0 mmol) was dissolved in anhydrous CH_2Cl_2 (10 mL) and cooled to –78 ºC while stirring under a N_2 atmosphere. To this solution, diisobutylaluminum hydride (1 M in CH_2Cl_2, 10 mL, 10 mmol) was added dropwise so that the temperature did not go above –65 ºC. After stirring for 1 h at –78 ºC, water (2 mL) and saturated aqueous ammonium chloride (4 mL) were added again at such a rate that the temperature did not go above –65 ºC. A saturated aqueous solution of potassium sodium L-tartrate tetrahydrate (10 mL) was added, and the mixture was allowed to warm to room

temperature for 16 h while stirring vigorously. The solution was then filtered and the solid washed with CH_2Cl_2. The filtrate was diluted with water (50 mL) and extracted with CH_2Cl_2 (2 × 30 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica (eluent 10% EtOAc/petrol) to give the aldehyde **191b** (0.32 g, 38%) as a colourless oil.

δ_H ($CDCl_3$, 400 MHz) 9.59 (1H, s, C*H*O), 4.14 (2H, q, *J* 7.0, $CO_2CH_2CH_3$), 2.13–1.95 (4H, m, 2 × CH_2), 1.73–1.60 (2H, m, CH_2), 1.60–1.48 (2H, m, CH_2), 1.21 (3H, t, *J* 7.0, $CO_2CH_2CH_3$); δ_C ($CDCl_3$, 101 MHz) 197.8, 172.8, 64.7, 61.5, 31.5, 25.7, 14.1; ν_{max} (neat)/cm^{-1} 2979, 2884, 1774, 1385, 1243, 1163, 954. Data is consistent with the literature.[279]

Diethyl 2-benzyl-2-methylmalonate, 193a

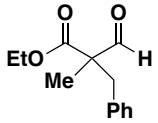


To a solution of diethyl benzylmalonate (23.4 mL, 100 mmol) and iodomethane (7.5 mL, 120 mmol) in DMF (75 mL) was added powdered KOH (6.73 g, 120 mmol) at 0 ºC during 20 min and the reaction mixture stirred at room temperature for 3 h. After the addition of toluene (100 mL) and water (50 mL), the organic layer was separated and washed with water (3 × 50 mL) and brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica (eluent 5% EtOAc/petrol) to give the ester **193a** (25.37 g, 96%) as a colourless oil.

δ_H ($CDCl_3$, 400 MHz) 7.32–7.24 (3H, m, 3 × Ar*H*), 7.18–7.12 (2H, m, 2 × Ar*H*), 4.23 (4H, q, *J* 7.0, 2 × $CO_2CH_2CH_3$), 3.26 (2H, s, CH_2Ph), 1.37 (3H, s, CH_3), 1.28 (6H, t, *J* 7.0,

2 × $CO_2CH_2CH_3$); δ_C ($CDCl_3$, 101 MHz) 172.0, 136.2, 130.2, 128.2, 126.9, 61.3, 54.8, 41.1, 19.7, 14.1; ν_{max} (neat)/cm^{-1} 2985, 2939, 1729, 1098, 701. Data is consistent with the literature.[280]

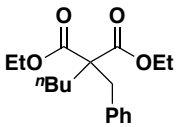
Ethyl 2-benzyl-2-methyl-3-oxopropanoate, 193b



Synthesised according to the general procedure **G**, using diethyl 2-benzyl-2-methylmalonate **193a** (2.64 g, 10.0 mmol) and diisobutylaluminum hydride (1 M in CH_2Cl_2, 20 mL, 20 mmol) in CH_2Cl_2 (20 mL). The crude product was purified by flash chromatography on silica (eluent 5% EtOAc/petrol) to give the aldehyde **193b** (1.01 g, 46%) as a colourless oil.

δ_H ($CDCl_3$, 400 MHz) 9.80 (1H, s, C*H*O), 7.32–7.22 (3H, m, 3 × Ar*H*), 7.18–7.09 (2H, m, 2 × Ar*H*), 4.21 (2H, q, *J* 7.0, $CO_2CH_2CH_3$), 3.25 (1H, d, *J* 13.5, CH_AH_BPh), 3.11 (1H, d, *J* 13.5, CH_AH_BPh), 1.30 (3H, s, CH_3), 1.26 (3H, t, *J* 7.0, $CO_2CH_2CH_3$); δ_C ($CDCl_3$, 101 MHz) 199.6, 171.7, 135.5, 130.1, 128.4, 127.1, 61.6, 58.7, 40.3, 17.1, 14.1; *m/z* (ESI^+) 463 ($[2M + Na]^+$, 100%). Data is consistent with the literature.[281]

Diethyl 2-benzyl-2-butylmalonate, 194a

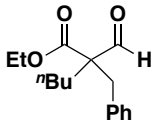


To a round bottomed flask containing sodium hydride (60% in mineral oil, 5.50 g, 138 mmol) in THF (50 mL) at 0 °C was added a solution of diethyl benzylmalonate (12.9 mL,

55.0 mmol) and the resulting mixture stirred at this temperature for 30 min. 1-Iodobutane (6.4 mL, 56 mmol) was then slowly added, and the reaction was stirred under reflux for 16 h. The mixture was then carefully quenched with water (5 mL) and, once the evolution of gas had ceased, it was partitioned between CH_2Cl_2 (100 mL) and water (100 mL). The organic phase was washed with water (2 × 50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica (eluent 5% EtOAc/petrol) to give the diester **194a** (5.87 g, 35%) as a colourless oil.

δ_H ($CDCl_3$, 400 MHz) 7.32–7.22 (3H, m, 3 × Ar*H*), 7.11 (2H, dd, *J* 8.0, 1.5, 2 × Ar*H*), 4.21 (4H, q, *J* 7.0, 2 × $CO_2CH_2CH_3$), 3.27 (2H, s, CH_2Ph), 1.90–1.71 (2H, m, (C)CH_2), 1.39–1.30 (4H, m, $CH_2(CH_2)_2CH_3$), 1.28 (6H, t, *J* 7.0, 2 × $CO_2CH_2CH_3$), 0.94 (3H, t, *J* 7.0, $(CH_2)_3CH_3$); δ_C ($CDCl_3$, 101 MHz) 171.4, 136.4, 129.9, 128.2, 126.8, 61.1, 58.8, 37.9, 31.4, 26.3, 22.9, 14.1, 13.9; ν_{max} (neat)/cm^{-1} 2935, 2872, 1730, 1202, 1179, 1033, 700. Data is consistent with the literature.[282]

Ethyl 2-benzyl-2-formylhexanoate, 194b

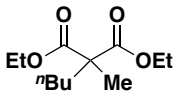


Synthesised according to the general procedure **G**, using diethyl 2-benzyl-2-butylmalonate **194a** (2.45g, 8.0 mmol) and diisobutylaluminum hydride (1 M in CH_2Cl_2, 16 mL, 16 mmol) in CH_2Cl_2 (16 mL). The crude product was purified by flash chromatography on silica (eluent 5% EtOAc/petrol) to give the *aldehyde* **194b** (2.00 g, 95%) as a colourless oil.

δ_H ($CDCl_3$, 400 MHz) 9.77 (1H, s, C*H*O), 7.21–7.09 (3H, m, 3 × Ar*H*), 7.05–6.96 (2H, m,

2 × Ar*H*), 4.10 (2H, q, *J* 7.0, $CO_2C\mathit{H}_2CH_3$), 3.09 (1H, d, *J* 13.5, $C\mathit{H}_AH_BPh$), 3.02 (1H, d, *J* 13.5, $CH_A\mathit{H}_BPh$), 2.03–1.59 (2H, m, (C)CH_2), 1.31–1.00 (7H, m, (C)$CH_2(C\mathit{H}_2)_2CH_3$, $CO_2CH_2C\mathit{H}_3$), 0.81 (3H, t, *J* 7.0, (C)$(CH_2)_3C\mathit{H}_3$); δ_C ($CDCl_3$, 101 MHz) 201.6, 171.8, 135.8, 130.0, 128.3, 126.9, 62.0, 61.2, 39.7, 33.6, 26.6, 23.1, 14.1, 13.8; ν_{max} (neat)/cm^{-1} 2957, 2867, 1718, 1200, 701; HRMS (CI^+) $C_{16}H_{23}O_3^+$ ($[M + H]^+$) requires 263.1646, found 263.1646.

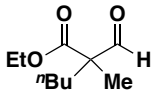
Diethyl 2-butyl-2-methylmalonate, 195a



To a solution of diethyl butylmalonate (13.2 mL, 60.0 mmol) and iodomethane (5.4 mL, 72 mmol) in DMF (45 mL) was added powdered KOH (4.04 g, 72.0 mmol) at 0 ºC and the reaction mixture stirred at room temperature for 16 h. After the addition of toluene (100 mL) and water (50 mL), the organic layer was separated and washed with water (3 × 50 mL) and brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica (eluent 5% EtOAc/petrol) to give the diester **195a** (13.6 g, 98%) as a colourless oil.

δ_H ($CDCl_3$, 400 MHz) 4.13 (4H, q, *J* 7.0, 2 × $CO_2C\mathit{H}_2CH_3$), 1.93–1.73 (2H, m, (C)C$\mathit{H}_2(CH_2)_2CH_3$), 1.35 (3H, s, (C)CH_3), 1.28 (2H, p, *J* 7.0, $CH_2C\mathit{H}_2CH_2CH_3$), 1.24–1.11 (8H, m, $CH_2CH_2C\mathit{H}_2CH_3$, 2 × $CO_2CH_2C\mathit{H}_3$), 0.86 (3H, t, *J* 7.0, $(CH_2)_3C\mathit{H}_3$); δ_C ($CDCl_3$, 101 MHz) 172.4, 60.9, 53.5, 35.1, 26.4, 22.9, 19.7, 14.0, 13.8; ν_{max} (neat)/cm^{-1} 2958, 2873,1729, 1233, 1125, 1021, 861. Data is consistent with the literature.[283]

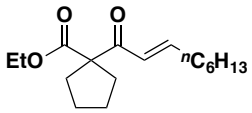
Ethyl 2-formyl-2-methylhexanoate, 195b



Synthesised according to the general procedure **G**, using diethyl 2-butyl-2-methylmalonate **195a** (2.30g, 10.0 mmol) and diisobutylaluminum hydride (1 M in CH_2Cl_2, 20 mL, 20 mmol) in CH_2Cl_2 (20 mL). The crude product was purified by flash chromatography on silica (eluent 5% EtOAc/petrol) to give the aldehyde **195b** (1.18 g, 63%) as a colourless oil.

δ_H ($CDCl_3$, 400 MHz) 9.70 (1H, s, C*H*O), 4.20 (2H, q, *J* 7.0, $CO_2CH_2CH_3$), 1.93–1.80 (1H, m, (C)CH_AH_B), 1.76–1.63 (1H, m, (C)CH_AH_B), 1.35–1.16 (10H, m, (C)$CH_2(CH_2)_2CH_3$, $CO_2CH_2CH_3$, (C)CH_3), 0.88 (3H, t, *J* 7.0, (C)$(CH_2)_3CH_3$); δ_C ($CDCl_3$, 101 MHz) 199.9, 172.3, 61.3, 57.5, 34.1, 26.3, 23.0, 16.6, 14.1, 13.8; ν_{max} (neat)/cm^{-1} 2936, 2803, 1718, 1462, 1226, 1145, 1021. Data is consistent with the literature.[284]

Ethyl (*E*)-1-(non-2-enoyl)cyclopentane-1-carboxylate, 192

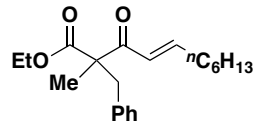


Synthesised according to the general procedure **C**, using ethyl 1-formylcyclopentane-1-carboxylate **191** (51 mg, 0.30 mmol), 1-octyne (54 μL, 0.36 mmol), $[Rh(nbd)_2]BF_4$ (5.6 mg, 5 mol%) and dcpe (6.3 mg, 5 mol%) in acetone (0.3 mL, 1.0 M). The crude product was purified by flash chromatography on silica (eluent 20% Et_2O /petrol) to give the *enone* **192** (76 mg, 90%) as a colourless oil.

δ_H ($CDCl_3$, 400 MHz) 6.88 (1H, dt, *J* 15.5, 7.0, C(O)CH=C*H*CH_2), 6.06 (1H, d, *J* 15.5,

C(O)C*H*=CHCH$_2$), 4.09 (2H, q, *J* 6.5, CO$_2$C*H*$_2$CH$_3$), 2.16–1.99 (6H, m, CHC*H*$_2$CH$_2$(CH$_2$)$_3$CH$_3$, 2 × C*H*$_2$), 1.93–1.86 (1H, m, 0.5 × C*H*$_2$), 1.66–1.49 (4H, m, 2 × C*H*$_2$), 1.41–1.32 (2H, m, C*H*$_2$), 1.28–1.11 (8H, m, 2.5 × C*H*$_2$, CO$_2$CH$_2$C*H*$_3$), 0.81 (3H, t, *J* 6.5, CH$_2$C*H*$_3$); δ_C (CDCl$_3$, 101 MHz) 195.0, 173.8, 148.7, 125.9, 65.4, 61.2, 33.0, 32.5, 31.5, 28.8, 28.0, 25.8, 25.6, 22.5, 14.0; ν_{max} (neat)/cm^{-1} 2956, 2928, 2853, 1735, 1698, 1630, 1234, 1173, 1113; HRMS (CI$^+$) $C_{17}H_{28}O_3^+$ ([M + H]$^+$) requires 281.2105, found 281.2105.

Ethyl (*E*)-2-benzyl-2-methyl-3-oxoundec-4-enoate, 196

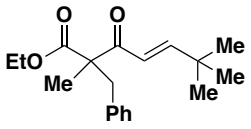


Synthesised according to the general procedure **C**, using ethyl 2-benzyl-2-methyl-3-oxopropanoate **193b** (62 μL, 0.30 mmol), 1-octyne (54 μL, 0.36 mmol), [Rh(nbd)$_2$]BF$_4$ (5.6 mg, 5 mol%) and dcpe (6.3 mg, 5 mol%) in acetone (0.3 mL, 1.0 M). The crude product was purified by flash chromatography on silica (eluent 5% EtOAc/petrol) to give the *enone* **196** (38 mg, 38%) as a colourless oil.

δ_H (CDCl$_3$, 400 MHz) 7.20–7.12 (3H, m, 3 × Ar*H*), 7.01 (2H, dd, *J* 8.0, 1.5, 2 × Ar*H*), 6.95 (1H, dt, *J* 15.5, 7.0, C(O)CH=C*H*CH$_2$), 6.17 (1H, dt, *J* 15.5, 1.5, C(O)C*H*=CHCH$_2$), 4.14–4.06 (2H, m, CO$_2$C*H*$_2$CH$_3$), 3.23 (1H, d, *J* 14.0, C*H*$_A$H$_B$Ph), 3.03 (1H, d, *J* 14.0, CH$_A$*H*$_B$Ph), 2.19–2.08 (2H, m, CHC*H*$_2$CH$_2$(CH$_2$)$_3$CH$_3$), 1.44–1.32 (2H, m, CHCH$_2$C*H*$_2$(CH$_2$)$_3$CH$_3$), 1.26–1.18 (9H, m, CH(CH$_2$)$_2$(C*H*$_2$)$_3$CH$_3$, (C)C*H*$_3$), 1.15 (3H, t, *J* 7.0, CO$_2$CH$_2$C*H*$_3$), 0.80 (3H, t, *J* 7.5, CH$_2$C*H*$_3$); δ_C (CDCl$_3$, 101 MHz) 195.7, 172.8, 149.3, 136.6, 130.2, 128.1, 126.7, 125.1, 61.3, 59.5, 40.3, 32.5, 31.6, 28.9, 28.0, 22.6, 18.9, 14.1, 14.0; ν_{max} (neat)/cm^{-1} 2928, 2856, 1737, 1697, 1627, 1454, 1184, 701; HRMS (CI$^+$) $C_{21}H_{31}O_3^+$ ([M + H]$^+$) requires

330.2193, found 330.2193.

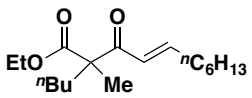
Ethyl (*E*)-2-benzyl-2,6,6-trimethyl-3-oxohept-4-enoate, 197



Synthesised according to the general procedure **C**, using ethyl 2-benzyl-2-methyl-3-oxopropanoate **193b** (62 μL, 0.30 mmol), 3,3-dimethyl-1-butyne (44 μL, 0.36 mmol), $[Rh(nbd)_2]BF_4$ (5.6 mg, 5 mol%) and dcpe (6.3 mg, 5 mol%) in acetone (0.3 mL, 1.0 M). The crude product was purified by flash chromatography on silica (eluent 5% EtOAc/petrol) to give the *enone* **197** (69 mg, 76%) as a colourless oil.

δ_H ($CDCl_3$, 400 MHz) 7.19–7.09 (3H, m, 3 × Ar*H*), 7.05–6.99 (2H, m, 2 × Ar*H*), 6.94 (1H, d, *J* 15.5, C(O)CH=C*H*), 6.04 (1H, d, *J* 15.5, C(O)C*H*=CH), 4.11 (2H, q, *J* 7.0, $CO_2CH_2CH_3$), 3.21 (1H, d, *J* 13.5, CH_AH_BPh), 3.04 (1H, d, *J* 13.5, CH_AH_BPh), 1.21 (3H, s, CH_3), 1.15 (3H, t, *J* 7.0, $CO_2CH_2CH_3$), 0.99 (9H, s, $C(CH_3)_3$); δ_C ($CDCl_3$, 101 MHz) 196.3, 172.8, 158.5, 136.6, 130.2, 128.1, 126.7, 120.3, 61.2, 59.7, 40.4, 34.0, 28.7, 19.1, 14.1; ν_{max} (neat)/cm^{-1} 2960, 2868, 1736, 1696, 1623, 1107, 1050, 701; HRMS (CI^+) $C_{19}H_{26}O_3^+$ ($[M + H]^+$) requires 303.1957, found 303.1957.

Ethyl (*E*)-2-butyl-2-methyl-3-oxoundec-4-enoate, 200

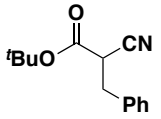


Synthesised according to the general procedure **C**, using ethyl 2-benzyl-2-methyl-3-oxopropanoate **195b** (62 μL, 0.30 mmol), 1-octyne (54 μL, 0.36 mmol), $[Rh(nbd)_2]BF_4$

(5.6 mg, 5 mol%) and dcpe (6.3 mg, 5 mol%) in acetone (0.3 mL, 1.0 M). The crude product was purified by flash chromatography on silica (eluent 50% EtOAc/petrol) to give the *enone* **200** (63 mg, 71%) as a pale yellow oil.

δ_H ($CDCl_3$, 400 MHz) 7.06–6.76 (1H, dt, *J* 15.0, 7.0, C(O)CH=C*H*CH_2), 6.15 (1H, dt, *J* 15.0, 1.5, C(O)C*H*=CHCH_2), 4.10 (2H, q, *J* 7.0, $CO_2CH_2CH_3$), 2.21–1.98 (2H, m, $CHCH_2CH_2(CH_2)_3CH_3$), 1.85–1.77 (1H, m, (C)CH_AH_B), 1.71–1.62 (1H, m, (C)CH_AH_B), 1.41–1.31 (2H, m, $CHCH_2CH_2(CH_2)_3CH_3$), 1.29–1.11 (14H, m, 4 × CH_2, CH_3, $CO_2CH_2CH_3$), 1.12–1.01 (2H, m, CH_2), 0.91–0.67 (6H, m, 2 × CH_2CH_3); δ_C ($CDCl_3$, 101 MHz) 196.4, 173.5, 148.8, 125.0, 61.1, 58.3, 32.5, 31.6, 28.8, 28.0, 26.2, 23.1, 22.6, 18.7, 16.6, 14.1, 13.9, 13.8; ν_{max} (neat)/cm^{-1} 2957, 2930, 1736, 1698, 1629, 1146, 727; HRMS (CI^+) $C_{18}H_{33}O_3^+$ ($[M + H]^+$) requires 297.2423, found 297.2423.

tert-Butyl 2-cyano-3-phenylpropanoate, 201

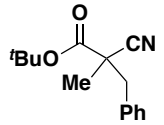


To a round bottomed flask containing freshly prepared lithium diisopropylamide (1 M in THF, 100 mmol) in THF (100 mL) at –78 °C was added a solution of 3-phenylpropionitrile (5.2 mL, 40 mmol) in THF (50 mL) and the resulting mixture stirred at this temperature for 30 min, and then room temperature for 30 min. The reaction was cooled back to –78 °C, and a solution of di-*tert*-butyl-dicarbonate (9.7 mL, 42 mmol) in THF (50 mL) was then slowly added, and the reaction was stirred at –78 °C for 3 h. The mixture was then carefully quenched with saturated aqueous ammonium chloride (50 mL) and then extracted with Et_2O (2 × 100 mL). The organic phase was washed with 10% HCl (2 × 50 mL), dried over $MgSO_4$,

filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica (eluent 10% Et_2O/petrol) to give the amide **201** (8.64 g, 93%) as a colourless oil.

δ_H ($CDCl_3$, 400 MHz) 7.42–7.27 (5H, m, 5 × Ar*H*), 3.66 (1H, dd, *J* 8.0, 6.0, C(O)C*H*CN), 3.38–2.94 (2H, m, CH_2Ph), 1.46 (9H, s, C(CH_3)$_3$); δ_C ($CDCl_3$, 101 MHz) 164.4, 135.5, 129.1, 128.8, 127.7, 116.6, 84.2, 40.5, 35.8, 27.7; *m/z* (ESI^+) 254 ($[M + Na]^+$, 100%). Data is consistent with the literature.[285]

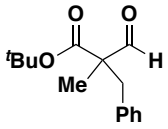
tert-Butyl 2-cyano-2-methyl-3-phenylpropanoate, 202



Synthesised according to the general procedure **D**, using *tert*-butyl 2-cyano-3-phenylpropanoate **201** (3.0 g, 13 mmol), sodium hydride (60% in mineral oil, 0.63 g, 15.6 mmol) and iodomethane (2.5 mL, 39 mmol) in THF (25 mL). The crude product was purified by flash chromatography on silica (eluent 50% EtOAc/petrol) to give the ester **202** (3.73 g, 76%) as a thick colourless oil.

δ_H ($CDCl_3$, 400 MHz) 7.37–7.24 (5H, m, 5 × Ar*H*), 3.17 (1H, d, *J* 13.5, CH_AH$_B$Ph), 2.98 (1H, d, *J* 13.5, CH$_A$$H_B$Ph), 1.55 (3H, s, C$H_3$), 1.41 (9H, s, C(C$H_3$)$_3$); δ_C ($CDCl_3$, 101 MHz) 167.8, 134.5, 130.1, 128.4, 127.7, 120.0, 83.8, 45.9, 43.4, 27.6, 23.3; ν_{max} (neat)/cm^{-1} 2980, 2855, 1150, 840, 733, 700. Data is consistent with the literature.[286]

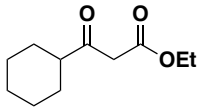
tert-Butyl 2-benzyl-2-methyl-3-oxopropanoate, 203



Synthesised according to the general procedure **E**, using *tert*-butyl 2-cyano-2-methyl-3-phenylpropanoate **202** (1.96 g, 8.0 mmol), Raney®-Ni (50% in water, 11.3 g, 96.0 mmol), sodium hypophosphite monohydrate (10.2 g, 96.0 mmol) in a 1:1:2 mixture of water:acetic acid:pyridine (60 mL). The crude product was purified by flash chromatography on silica (eluent 50% EtOAc/petrol) to give the *aldehyde* **203** (1.32 g, 66%) as a colourless oil.

δ_H ($CDCl_3$, 400 MHz) 9.75 (1H, s, C*H*O), 7.32–7.21 (3H, m, 3 × Ar*H*), 7.21–7.10 (2H, m, 2 × Ar*H*), 3.19 (1H, d, *J* 13.5, C$H_A$$H_B$Ph), 3.09 (1H, d, *J* 13.5, C$H_A$$H_B$Ph), 1.44 (9H, s, C(C$H_3$)$_3$), 1.25 (3H, s, C$H_3$); δ_C ($CDCl_3$, 101 MHz) 199.9, 170.8, 135.7, 130.2, 128.3, 126.9, 82.5, 59.0, 40.1, 28.0, 17.3; ν_{max} (neat)/cm^{-1} 2979, 2934, 1716, 1369, 1150, 1118, 843, 701; HRMS (CI^+) $C_{15}H_{21}O_3^+$ ($[M + H]^+$) requires 249.1491, found 249.1491.

Ethyl 3-cyclohexyl-3-oxopropanoate, 212

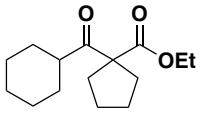


Cyclohexanecarbonyl chloride (8.0 mL, 60 mmol) was added to a stirred solution of ethyl acetate (9.4 mL, 96 mmol) and 1-methylimidazole (5.7 mL, 72 mmol) in toluene (150 mL) at –45 ºC under a N_2 atmosphere, followed by being stirred at the same temperature for 15 min. $TiCl_4$ (22 mL, 198 mmol) and *N,N*-diisopropylethylamine (37.6 mL, 216 mmol)

were successively added to the mixture, which was stirred at the same temperature for 30 min. The mixture was quenched with water (100 mL) and extracted with Et_2O (2 × 100 mL). The combined organic phase was washed with water (50 mL), brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica (eluent 5% EtOAc/petrol) to give the ester **212** (7.60 g, 64%, keto:enol 10:1) as a colourless oil.

δ_H ($CDCl_3$, 400 MHz) (* denotes enol tautomer) 12.14* (1H, s, CH=C(O*H*)), 4.96* (1H, s, C*H*=C(OH)), 4.18 (2H, q *J* 7.0, $CO_2CH_2CH_3$), 3.45 (2H, s, C(O)CH_2), 2.48–2.37 (1H, m, C(O)C*H*$(CH_2)_5$), 1.91–1.59 (5H, m, 2.5 × CH_2), 1.39–1.11 (8H, m, 2.5 × CH_2, $CO_2CH_2CH_3$); δ_C ($CDCl_3$, 101 MHz) 205.8, 182.7, 173.1, 167.4, 86.9, 61.2, 59.8, 50.8, 47.3, 43.5, 29.9, 28.1, 25.8, 25.7, 25.4, 14.1; *m/z* (ESI^+) 221 ($[M + Na]^+$, 100%). Data is consistent with the literature.[287]

Ethyl 1-(cyclohexanecarbonyl)cyclopentane-1-carboxylate, 213

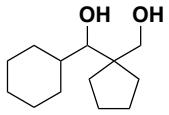


Synthesised according to the general procedure **F**, using ethyl 3-cyclohexyl-3-oxopropanoate **212** (5.95 g, 30.0 mmol), K_2CO_3 (10.4 g, 75.0 mmol), 1,4-dibromobutane (3.9 mL, 33 mmol) and [bmim]BF_4 (0.56 mL, 3.0 mmol) in DMF (60 mL). The crude product was purified by flash chromatography on silica (eluent 5% EtOAc/petrol) to give the *ester* **213** (3.88 g, 51%) as a colourless oil.

δ_H ($CDCl_3$, 400 MHz) 4.16 (2H, q, *J* 7.0, $CO_2CH_2CH_3$), 2.53 (1H, tt, *J* 11.5, 3.0, C(O)C*H*$(CH_2)_5$), 2.19–1.99 (4H, m, 2 × CH_2), 1.79–1.52 (9H, m, 4.5 × CH_2), 1.49–1.34 (2H,

m, C*H*$_2$), 1.29–1.15 (6H, m, $CO_2CH_2CH_3$, 1.5 × C*H*$_2$); δ_C ($CDCl_3$, 101 MHz) 209.6, 173.5, 67.2, 61.2, 48.4, 32.7, 30.4, 25.6, 25.6, 25.4, 14.1; ν_{max} (neat)/cm^{-1} 2932, 2855, 1736, 1705, 1429, 732; HRMS (CI$^+$) $C_{15}H_{25}O_3^+$ ([M + H]$^+$) requires 253.1804, found 253.1804.

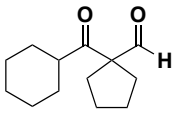
General procedure H for the reduction of dicarbonyl compounds using $LiAlH_4$, as exemplified by cyclohexyl(1-(hydroxymethyl)cyclopentyl)methanol, 214



To a suspension of $LiAlH_4$ (1.14 g, 30.0 mmol, 2.5 equiv.) in THF (80 mL) was added ethyl 1-(cyclohexanecarbonyl)cyclopentane-1-carboxylate **213** (3.0 g, 12 mmol, 1.0 equiv.) in THF (40 mL) over 30 min at 0 °C. After stirring for 16 h at room temperature, the reaction was quenched with successive addition of water (1.1 mL), NaOH solution (1 M in water, 1.1 mL), and water (3.4 mL) at 0 °C. The suspension was filtered through Celite® and the filtrate concentrated under reduced pressure. The crude product was purified by flash chromatography on silica (eluent 40% EtOAc/petrol) to give the *diol* **214** (2.25 g, 88%) as a thick colourless oil.

δ_H ($CDCl_3$, 400 MHz) 3.78 (1H, d, *J* 10.5, C*H*$_A$H$_B$OH), 3.43 (1H, d, *J* 10.5, CH$_A$*H*$_B$OH), 3.26 (1H, d, *J* 3.0, C*H*OH), 2.77 (2H, s, 2 × O*H*), 1.99–1.83 (2H, m, C*H*$_2$), 1.84–1.72 (2H, m, C*H*$_2$), 1.72–1.54 (8H, m, 4 × C*H*$_2$), 1.47–1.35 (1H, m, 0.5 × C*H*$_2$), 1.35–1.12 (6H, m, 3 × C*H*$_2$); δ_C ($CDCl_3$, 101 MHz) 84.8, 68.3, 51.5, 40.9, 33.9, 33.1, 32.4, 28.5, 26.9, 26.4 (2C), 25.3, 24.8; ν_{max} (neat)/cm^{-1} 3338, 2927, 2852, 907, 730; HRMS (CI$^+$) $C_{13}H_{28}O_4N^+$ ([M + NH_4]$^+$) requires 230.2120, found 230.2113.

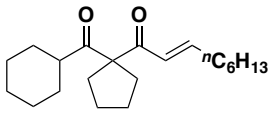
General procedure J for double Swern oxidation of diol compounds, as exemplified by 1-(cyclohexanecarbonyl)cyclopentane-1-carbaldehyde, 204



To a flame dried reaction flask containing oxalyl chloride (1.81 mL, 21.4 mmol, 2.1 equiv.) in CH_2Cl_2 (10 mL) was slowly added DMSO (3.05 mL, 43.0 mmol, 4.2 equiv.) at –78 °C to avoid exotherm. Immediately, Cyclohexyl(1-(hydroxymethyl)cyclopentyl)methanol **214** (1.84 g, 10.2 mmol, 1.0 equiv.) in CH_2Cl_2 (10 mL) was added dropwise to the solution. The reaction was stirred for 30 min at –78 °C before addition of triethylamine (10.2 mL, 73.4 mmol, 7.2 equiv.). The reaction mixture was then slowly warmed to room temperature and water (50 mL) was then added and the product extracted with Et_2O (75 mL). The combined organic layers were washed with saturated aqueous $CuSO_4$ (2 × 50 mL), saturated aqueous NH_4 (50 mL) then dried over $MgSO_4$ and the solvent removed *in vacuo.* The crude product was purified by flash chromatography on silica (eluent 10% EtOAc/petrol) to give the *aldehyde* **204** (1.73 g, 81%) as a colourless oil.

δ_H ($CDCl_3$, 400 MHz) 9.57 (1H, s, C*H*O), 2.57 (1H, tt, *J* 11.5, 3.5, C(O)C*H*), 2.23–2.10 (2H, m, CH_2), 2.10–2.00 (2H, m, CH_2), 1.83–1.72 (2H, m, CH_2), 1.73–1.54 (7H, m, 3.5 × CH_2), 1.45–1.30 (2H, m, CH_2), 1.30–1.16 (3H, m, 1.5 × CH_2); δ_C ($CDCl_3$, 101 MHz) 210.7, 199.5, 73.2, 48.3, 29.9, 29.3, 25.6, 25.6, 25.5; ν_{max} (neat)/cm^{-1} 2930, 2855, 1725, 1695, 1449, 981; *m/z* (ESI^+) 263 ([M + MeOH + Na]$^+$, 100%); HRMS (ESI^+) $C_{13}H_{21}O_2^+$ ([M + H]$^+$) requires 209.15361, found 209.15387.

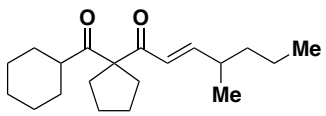
(*E*)-1-(1-(Cyclohexanecarbonyl)cyclopentyl)non-2-en-1-one, 205



Synthesised according to the general procedure **C**, using 1-(cyclohexanecarbonyl)cyclopentane-1-carbaldehyde **204** (60 μL, 0.30 mmol), 1-octyne (54 μL, 0.36 mmol), $[Rh(nbd)_2]BF_4$ (5.6 mg, 5 mol%) and dcpe (6.3 mg, 5 mol%) in acetone (0.3 mL, 1.0 M). The crude product was purified by flash chromatography on silica (eluent 5% Et_2O/petrol) to give the *enone* **205** (91 mg, 95%) as a colourless oil.

δ_H ($CDCl_3$, 400 MHz) 6.87 (1H, dt, *J* 15.5, 7.0, C(O)CH=C*H*CH_2), 6.02 (1H, dt, *J* 15.5, 1.5, C(O)C*H*=CHCH_2), 2.45 (1H, tt, *J* 11.5, 3.5, C(O)C*H*), 2.19–2.01 (6H, m, 3 × CH_2), 1.68–1.59 (2H, m, CH_2), 1.58–1.52 (2H, m, CH_2), 1.51–1.44 (4H, m, 2 × CH_2), 1.39–1.25 (4H, m, 2 × CH_2), 1.25–1.15 (7H, m, 3.5 × CH_2), 1.15–1.07 (3H, m, 1.5 × CH_2), 0.79 (3H, t, *J* 7.5, CH_2CH_3); δ_C ($CDCl_3$, 101 MHz) 211.2, 195.9, 149.2, 126.6, 74.6, 48.0, 32.4, 31.5, 30.9, 30.2, 28.8, 27.9, 25.6, 25.5, 25.4, 22.5, 14.0; ν_{max} (neat)/cm^{-1} 2927, 2855, 1709, 1625, 1429, 1143; *m/z* (ESI^+) 341 ($[M + Na]^+$, 100%); HRMS (ESI^+) $C_{21}H_{35}O_2^+$ ($[M + H]^+$) requires 319.26316, found 319.26337.

(*E*)-1-(1-(Cyclohexanecarbonyl)cyclopentyl)-4-methylhept-2-en-1-one, 206

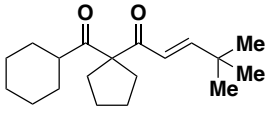


Synthesised according to the general procedure **C**, using 1-(cyclohexanecarbonyl)cyclopentane-1-carbaldehyde **205** (60 μL, 0.30 mmol),

3-methylhex-1-yne (49 μL, 0.36 mmol), $[Rh(nbd)_2]BF_4$ (5.6 mg, 5 mol%) and dcpe (6.3 mg, 5 mol%) in acetone (0.3 mL, 1.0 M). The crude product was purified by flash chromatography on silica (eluent 5% Et_2O/petrol) to give the *enone* **206** (83 mg, 91%) as a colourless oil.

δ_H ($CDCl_3$, 400 MHz) 6.76 (1H, dd, *J* 15.5, 8.0, C(O)CH=C*H*), 5.97 (1H, dd, *J* 15.5, 1.0, C(O)C*H*=CH), 2.45 (1H, tt, *J* 11.5, 3.5, C(O)C*H*), 2.30–2.15 (1H, m, C*H*$(CH_3)(CH_2)_2CH_3$), 2.14–1.99 (4H, m, 2 × CH_2), 1.69–1.43 (8H, m, 4 × CH_2), 1.37–1.03 (10H, m, $CH(CH_3)(CH_2)_2CH_3$, 3 × CH_2), 0.93 (3H, d, *J* 6.5, $CH(CH_3)(CH_2)_2CH_3$), 0.79 (3H, t, *J* 7.0, $CH(CH_3)(CH_2)_2CH_3$); δ_C ($CDCl_3$, 101 MHz) 211.2, 196.1, 154.4, 124.9, 74.6, 48.1, 38.2, 36.6, 31.0, 30.9, 30.2, 25.6, 25.4, 20.4, 19.4, 14.0; ν_{max} (neat)/cm^{-1} 2929, 2856, 1708, 1660, 1450, 1144; *m/z* (ESI^+) 327 ($[M + Na]^+$, 100%); HRMS (ESI^+) $C_{20}H_{33}O_2^+$ ($[M + H]^+$) requires 305.24751, found 305.24756.

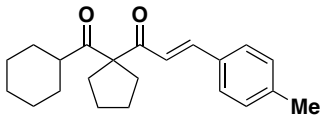
(*E*)-1-(1-(Cyclohexanecarbonyl)cyclopentyl)-4,4-dimethylpent-2-en-1-one, 207



Synthesised according to the general procedure **C**, using 1-(cyclohexanecarbonyl)cyclopentane-1-carbaldehyde **204** (60 μL, 0.30 mmol), 3,3-dimethyl-1-butyne (44 μL, 0.36 mmol), $[Rh(nbd)_2]BF_4$ (5.6 mg, 5 mol%) and dcpe (6.3 mg, 5 mol%) in acetone (0.3 mL, 1.0 M). The crude product was purified by flash chromatography on silica (eluent 5% Et_2O/petrol) to give the *enone* **207** (79 mg, 91%) as a colourless oil.

δ_H ($CDCl_3$, 400 MHz) 6.87 (1H, d, *J* 15.5, C(O)CH=C*H*), 5.91 (1H, d, *J* 15.5, C(O)C*H*=CH), 2.44 (1H, tt, *J* 11.5, 3.5, C(O)C*H*), 2.12–2.03 (4H, m, 2 × CH_2), 1.66–1.59 (2H, m, CH_2), 1.57–1.52 (2H, m, CH_2), 1.52 –1.46 (5H, m, 2.5 × CH_2), 1.35–1.24 (2H, m, CH_2), 1.17–1.08 (3H, m, 1.5 × CH_2), 0.97 (9H, s, C(CH_3)$_3$); δ_C ($CDCl_3$, 101 MHz) 211.2, 196.5, 158.6, 121.8, 74.7, 48.1, 33.9, 31.0, 30.3, 28.5, 25.5 (2C), 25.4; ν_{max} (neat)/cm^{-1} 2931, 2857, 1684, 1621, 1449, 1144; *m/z* (ESI$^+$) 313 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{19}H_{31}O_2^+$ ([M + H]$^+$) requires 291.23186, found 291.23175.

(*E*)-1-(1-(Cyclohexanecarbonyl)cyclopentyl)-3-(*p*-tolyl)prop-2-en-1-one, 208

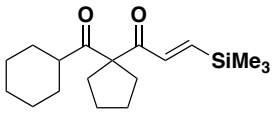


Synthesised according to the general procedure **C**, using 1-(cyclohexanecarbonyl)cyclopentane-1-carbaldehyde **204** (60 μL, 0.30 mmol), 4-ethynyltoluene (46 μL, 0.36 mmol), $[Rh(nbd)_2]BF_4$ (5.6 mg, 5 mol%) and dcpe (6.3 mg, 5 mol%) in acetone (0.3 mL, 1.0 M). The crude product was purified by flash chromatography on silica (eluent 5% EtOAc/petrol) to give the *enone* **208** (92 mg, 95%) as a colourless oil.

δ_H ($CDCl_3$, 400 MHz) 7.57 (1H, d, *J* 15.5, C(O)CH=C*H*), 7.35 (2H, d, *J* 8.0, 2 × Ar*H*), 7.10 (2H, d, *J* 8.0, 2 × Ar*H*), 6.58 (1H, d, *J* 15.5, C(O)C*H*=CH), 2.50 (1H, tt, *J* 11.5, 3.0, C(O)C*H*), 2.28 (3H, s, ArCH_3), 2.20–2.08 (4H, m, 2 × CH_2), 1.65–1.45 (9H, m, 4.5 × CH_2), 1.38–1.22 (2H, m, CH_2), 1.15–1.01 (3H, m, 1.5 × CH_2); δ_C ($CDCl_3$, 101 MHz) 211.3, 195.8, 143.8, 141.3, 131.6, 129.7, 128.6, 121.6, 75.1, 48.1, 31.0, 30.2, 25.6, 25.6, 25.5, 21.5; ν_{max} (neat)/cm^{-1} 2930, 2855, 1677, 1601, 1323, 755; *m/z* (ESI$^+$) 347 ([M + Na]$^+$, 100%);

HRMS (ESI$^+$) $C_{22}H_{29}O_2^+$ ([M + H]$^+$) requires 325.21621, found 325.21600.

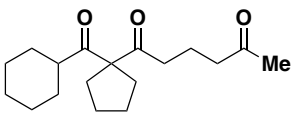
(*E*)-1-(1-(Cyclohexanecarbonyl)cyclopentyl)-3-(trimethylsilyl)prop-2-en-1-one, 209



Synthesised according to the general procedure **C**, using 1-(cyclohexanecarbonyl)cyclopentane-1-carbaldehyde **204** (60 μL, 0.30 mmol), ethynyltrimethylsilane (51 μL, 0.36 mmol), $[Rh(nbd)_2]BF_4$ (5.6 mg, 5 mol%) and dcpe (6.3 mg, 5 mol%) in acetone (0.3 mL, 1.0 M). The crude product was purified by flash chromatography on silica (eluent 5% Et_2O/petrol) to give the *enone* **209** (87 mg, 95%) as a colourless oil.

δ_H ($CDCl_3$, 400 MHz) 7.09 (1H, d, *J* 18.5, C(O)CH=C*H*), 6.36 (1H, d, *J* 18.5, C(O)C*H*=CH), 2.38 (1H, tt, *J* 11.5, 3.5, C(O)C*H*), 2.10–1.90 (4H, m, 2 × CH_2), 1.64–1.55 (2H, m, CH_2), 1.55–1.40 (7H, m, 4.5 × CH_2), 1.35–1.19 (2H, m, CH_2), 1.17–0.99 (3H, m, 1.5 × CH_2), 0.00 (9H, s, Si(CH_3)$_3$); δ_C ($CDCl_3$, 101 MHz) 213.0, 197.2, 150.9, 140.5, 76.2, 50.1, 33.0, 32.1, 27.5, 27.4, 27.3, 0.0; ν_{max} (neat)/cm^{-1} 2932, 2856, 1684, 1217, 840; *m/z* (ESI$^+$) 329 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{18}H_{31}O_2Si^+$ ([M + H]$^+$) requires 307.20878, found 307.20892.

1-(1-(Cyclohexanecarbonyl)cyclopentyl)hexane-1,5-dione, 210

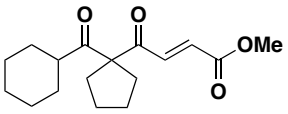


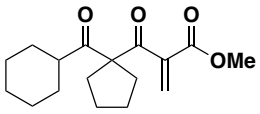
Synthesised according to the general procedure **C**, using

1-(cyclohexanecarbonyl)cyclopentane-1-carbaldehyde **204** (60 μL, 0.30 mmol), 4-pentyn-2-ol (34 μL, 0.36 mmol), $[Rh(nbd)_2]BF_4$ (5.6 mg, 5 mol%) and dcpe (6.3 mg, 5 mol%) in acetone (0.3 mL, 1.0 M). The crude product was purified by flash chromatography on silica (eluent 5% Et_2O/petrol) to give the *triketone* **210** (66 mg, 75%) as a colourless oil.

δ_H ($CDCl_3$, 400 MHz) 2.49 (1H, tt, *J* 11.5, 3.5, C(O)C*H*), 2.39 (2H, t, *J* 7.0, C(O)CH_2), 2.32 (2H, t, *J* 7.0, C(O)CH_2), 2.13–1.98 (7H, m, C(O)CH_3, 2 × CH_2), 1.75 (2H, p, *J* 7.0, C(O)CH_2CH_2), 1.70–1.63 (2H, m, CH_2), 1.61–1.45 (7H, m, 4.5 × CH_2), 1.40–1.25 (2H, m, CH_2), 1.21–1.06 (3H, m, 1.5 × CH_2); δ_C ($CDCl_3$, 101 MHz) 211.6, 208.1, 207.5, 75.4, 47.4, 42.3, 38.0, 31.3, 30.1, 29.8, 25.6, 25.5, 25.2, 18.0; ν_{max} (neat)/cm^{-1} 2931, 2856, 1713, 1689, 1365, 1145; HRMS (CI^+) $C_{18}H_{29}O_3^+$ ($[M + H]^+$) requires 293.2116, found 293.2116.

Methyl (*E*)-4-(1-(cyclohexanecarbonyl)cyclopentyl)-4-oxobut-2-enoate and Methyl 2-(1-(cyclohexanecarbonyl)cyclopentane-1-carbonyl)acrylate, 211

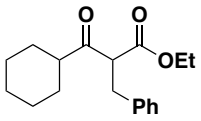




Synthesised according to the general procedure **C**, using 1-(cyclohexanecarbonyl)cyclopentane-1-carbaldehyde **204** (60 μL, 0.30 mmol), methyl propiolate (80 μL, 0.90 mmol), $[Rh(nbd)_2]BF_4$ (5.6 mg, 5 mol%) and dcpe (6.3 mg, 5 mol%) in acetone (0.3 mL, 1.0 M). The crude product was purified by flash chromatography on silica (eluent 5% Et_2O/petrol) to give an *enone* **211** (32 mg, 43%, L:B 4:1) as a colourless oil.

δ_H ($CDCl_3$, 400 MHz) (* denotes the minor branched product) 7.01 (1H, d, *J* 15.5, C(O)CH=C*H*CO_2CH_3), 6.71 (1H, d, *J* 15.5, C(O)C*H*=CHCO_2CH_3), 6.40* (1H, s, C(O)C=CH_AH_B), 6.16* (1H, s, C(O)C=CH_AH_B), 3.73 (3H, s, CO_2CH_3), 3.70* (3H, s, CO_2CH_3), 2.59* (1H, tt, *J* 11.5, 3.5, C(O)C*H*), 2.46 (1H, tt, *J* 11.5, 3.5, C(O)C*H*), 2.19–2.00 (4H, m, 2 × CH_2), 1.77–1.40 (9H, m, 4.5 × CH_2), 1.40–1.23 (2H, m, CH_2), 1.21–1.02 (3H, m, 1.5 × CH_2); δ_C ($CDCl_3$, 101 MHz) (* denotes the minor branched product) 210.3, 209.7*, 198.3*, 195.7, 165.6, 165.0*, 141.0*, 136.7, 133.3*, 131.5, 74.8, 74.0*, 52.3(4), 52.2(7)*, 47.9, 47.5*, 33.2*, 30.9, 30.2*, 30.0, 25.7*, 25.6, 25.5(5)*, 25.4(9), 25.4; ν_{max} (neat)/cm^{-1} 2933, 2857, 1731, 1686, 1448; HRMS (CI^+) $C_{17}H_{25}O_4^+$ ($[M + H]^+$) requires 293.1757, found 240.1757.

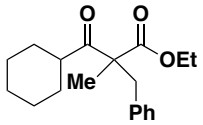
Ethyl 2-benzyl-3-cyclohexyl-3-oxopropanoate, 215



To a round bottomed flask containing sodium hydride (60% in mineral oil, 1.2 g, 30 mmol) in THF (45 mL) at 0 °C was added a solution of ethyl 3-cyclohexyl-3-oxopropanoate **212** (5.98 g, 30 mmol) and the resulting mixture stirred at this temperature for 30 min. Benzyl bromide (3.6 mL, 30 mmol) was then slowly added, and the reaction was stirred at room temperature for 16 h. The mixture was then carefully quenched with water (50 mL) and then extracted with EtOAc (2 × 50 mL). The organic phase was washed with water (2 × 50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica (eluent 5% EtOAc/petrol) to give the ester **215** (4.75 g, 55%) as a colourless oil.

δ_H ($CDCl_3$, 400 MHz) 7.31–7.24 (2H, m, 2 × Ar*H*), 7.24–7.14 (3H, m, 3 × Ar*H*), 4.16 (2H, q, *J* 7.0, $CO_2CH_2CH_3$), 3.94 (1H, t, *J* 7.5, C(O)C*H*CH_2Ph), 3.16 (2H, dd, *J* 7.5, 2.0, C(O)CHCH_2Ph), 2.38 (1H, tt, *J* 11.0, 3.0, C(O)C*H*$(CH_2)_5$), 1.85–1.55 (5H, m, 2.5 × CH_2), 1.44–1.26 (1H, m, 0.5 × CH_2), 1.27–1.00 (7H, m, 2 × CH_2, $CO_2CH_2CH_3$); δ_C ($CDCl_3$, 101 MHz) 207.7, 169.1, 138.5, 128.9, 128.5, 126.6, 61.3, 58.8, 51.1, 34.3, 28.0, 25.7, 25.4, 14.1; ν_{max} (neat)/cm^{-1} 2930, 2854, 1740, 1709, 1450, 1152, 750, 699. Data is consistent with the literature.[288]

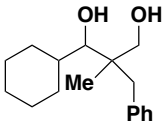
Ethyl 2-benzyl-3-cyclohexyl-2-methyl-3-oxopropanoate, 216



Synthesised according to the general procedure **D**, using ethyl 2-benzyl-3-cyclohexyl-3-oxopropanoate **215** (4.1 g, 14 mmol), sodium hydride (60% in mineral oil, 0.64 g, 16.0 mmol) and iodomethane (2.6 mL, 42 mmol) in THF (30 mL). The crude product was purified by flash chromatography on silica (eluent 50% EtOAc/petrol) to give the *ketone* **216** (3.94 g, 93%) as a colourless oil.

δ_H ($CDCl_3$, 400 MHz) 7.31–7.19 (3H, m, 3 × Ar*H*), 7.10 (2H, dd, *J* 7.5, 1.5, 2 × Ar*H*), 4.18 (2H, tq, *J* 7.0, 3.5, $CO_2CH_2CH_3$), 3.34 (1H, d, *J* 13.5, CH_AH_BPh), 2.98 (1H, d, *J* 13.5, CH_AH_BPh), 2.61 (1H, tt, *J* 11.0, 3.0, C(O)C*H*$(CH_2)_5$), 1.83–1.64 (5H, m, 2.5 × CH_2), 1.56–1.38 (2H, m, CH_2), 1.30 (3H, s, CH_3), 1.29–1.17 (6H, m, $CO_2CH_2CH_3$, 1.5 × CH_2); δ_C ($CDCl_3$, 101 MHz) 210.8, 172.3, 136.8, 130.2, 128.1, 126.7, 61.3, 61.2, 47.9, 40.2, 30.6, 30.1, 25.7, 25.6, 25.6, 18.7, 14.1; ν_{max} (neat)/cm^{-1} 2932, 2855, 1737, 1706, 1450, 1180, 990, 744, 701; HRMS (CI^+) $C_{19}H_{27}O_3^+$ ($[M + H]^+$) requires 303.1960, found 303.1960.

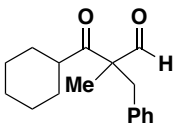
2-Benzyl-1-cyclohexyl-2-methylpropane-1,3-diol, 217



Synthesised according to the general procedure **H**, using ethyl 2-benzyl-3-cyclohexyl-2-methyl-3-oxopropanoate **216** (3.33 g, 11.0 mmol), and $LiAlH_4$ (1.04 g, 27.5 mmol) in THF (100 mL). The crude product was purified by flash chromatography on silica (eluent 40% EtOAc/petrol) to give the *diol* **217** (2.22 g, 77%) as a white crystalline solid.

δ_H ($CDCl_3$, 400 MHz) (* denotes second diastereomer) 7.55–7.05 (5H, m, 5 × Ar*H*), 3.74 (1H, d, *J* 10.5, C*H*$_A$H$_B$OH), 3.57–3.45 (1H, m, C*H*$_A$H$_B$OH*, C*H*OH), 3.42–3.31 (2H, m, CH$_A$*H*$_B$OH, CH$_A$*H*$_B$OH*, C(O)C*H*$(CH_2)_5$), 3.18 (1H, s, O*H*), 3.05 (1H, d, *J* 13.0, C*H*$_A$H$_B$Ph), 3.01 (1H, s, O*H*), 2.95* (1H, d, *J* 13.0, C*H*$_A$H$_B$Ph), 2.79* (1H, d, *J* 13.0, CH$_A$*H*$_B$Ph), 2.55 (1H, d, *J* 13.0, CH$_A$*H*$_B$Ph), 2.00–1.48 (6H, m, 3 × C*H*$_2$), 1.47–1.27 (3H, m, 1.5 × C*H*$_2$), 1.26–1.13 (1H, m, 0.5 × C*H*$_2$), 0.82 (3H, s, C*H*$_3$), 0.75* (3H, s, C*H*$_3$); δ_C ($CDCl_3$, 101 MHz) 138.1, 130.9, 130.8, 127.9, 126.1, 126.0, 84.4, 82.7, 70.1, 68.5, 43.0, 42.7, 41.8, 39.4, 39.1, 37.4, 34.0, 33.8, 27.7, 27.5, 27.0, 26.5, 26.3, 19.4, 18.2; mp: 84–88 °C (EtOH); ν_{max} (neat)/cm^{-1} 3327, 2922, 2859, 1449, 1031, 701; HRMS (CI$^+$) $C_{17}H_{30}O_2N^+$ ([M + NH_4]$^+$) requires 280.2273, found 280.2273.

2-Benzyl-3-cyclohexyl-2-methyl-3-oxopropanal, 218

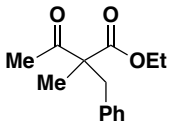


Synthesised according to the general procedure **J**, using 2-benzyl-1-cyclohexyl-2-methylpropane-1,3-diol **217** (1.84 g, 7.0 mmol), DMSO (2.10 mL, 29.4 mmol), oxalyl

chloride (1.25 mL, 14.7 mmol) and triethylamine (7.03 mL, 50.4 mmol) in CH_2Cl_2 (24 mL). The crude product was purified by flash chromatography on silica (eluent 10% Et_2O/petrol) to give the *aldehyde* **218** (0.97 g, 53%) as a colourless oil.

δ_H ($CDCl_3$, 400 MHz) 9.66 (1H, s, C*H*O), 7.30–7.09 (3H, m, 3 × Ar*H*), 7.07–6.84 (2H, m, 2 × Ar*H*), 3.15 (1H, d, *J* 13.5, CH_AH$_B$Ph), 3.05 (1H, d, *J* 13.5, CH$_A$$H_B$Ph), 2.50 (1H, tt, *J* 11.5, 3.5, C(O)C*H*), 1.72–1.62 (2H, m, CH_2), 1.61–1.52 (2H, m, CH_2), 1.51–1.44 (1H, m, 0.5 × CH_2), 1.32–1.18 (5H, m, CH_3, 1.5 × CH_2), 1.17–1.07 (3H, m, 1.5 × CH_2); δ_C ($CDCl_3$, 101 MHz) 211.4, 201.2, 135.7, 130.2, 128.4, 126.9, 65.9, 47.7, 39.5, 28.9, 28.9, 25.6, 25.4, 25.4, 16.1; ν_{max} (neat)/cm^{-1} 2930, 2855, 1727, 1698, 1457, 987, 701; HRMS (CI$^+$) $C_{17}H_{23}O_2^+$ ([M + H]$^+$) requires 259.1701, found 259.1701.

Ethyl 2-benzyl-2-methyl-3-oxobutanoate, 219

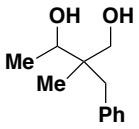


Synthesised according to the general procedure **D**, using ethyl 2-benzylacetoacetate (10.7 mL, 50.5 mmol), sodium hydride (60% in mineral oil, 2.06 g, 51.5 mmol) and iodomethane (3.1 mL, 50 mmol) in THF (75 mL). The crude product was purified by flash chromatography on silica (eluent 50% EtOAc/petrol) to give the ester **219** (10.11 g, 86%) as a colourless oil.

δ_H ($CDCl_3$, 400 MHz) 7.25–7.21 (3H, m, 3 × Ar*H*), 7.10–7.08 (2H, m, 2 × Ar*H*), 4.23–4.13 (2H, m, $CO_2CH_2CH_3$), 3.27 (1H, d, *J* 13.5, CH_AH$_B$Ph), 3.05 (1H, d, *J* 13.5, CH$_A$$H_B$Ph), 2.17 (3H, s, C(O)C$H_3$), 1.29–1.23 (6H, m, (C)CH_3, $CO_2CH_2CH_3$); δ_C ($CDCl_3$, 101 MHz) 205.3, 172.4, 136.4, 130.1, 128.1, 126.8, 61.3, 60.8, 40.4, 26.4, 19.0, 13.9; *m/z* (ESI$^+$) 257

([M + Na]$^+$, 100%). Data is consistent with the literature.[289]

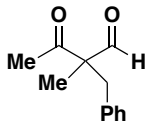
2-Benzyl-2-methylbutane-1,3-diol, 220



Synthesised according to the general procedure **H**, using ethyl 2-benzyl-2-methyl-3-oxobutanoate **219** (4.68 g, 22.0 mmol), and $LiAlH_4$ (1.90 g, 50.0 mmol) in THF (150 mL). The crude product was purified by flash chromatography on silica (eluent 40% EtOAc/petrol) to give the *diol* **220** (3.74 g, 96%) as a thick colourless oil. **220** exists in a mixture of two diastereomers (1:1.7).

δ_H ($CDCl_3$, 400 MHz) (* denotes second diastereomer) 7.43–7.10 (5H, m, 5 × Ar*H*), 3.93 (1H, q, *J* 6.5, C*H*OH), 3.79* (1H, q, *J* 6.5, C*H*OH), 3.73 (1H, d, *J* 11.0, CH_AH$_B$OH), 3.68 (2H, s, 2 × O*H*), 3.51* (1H, d, *J* 10.5, CH_AH$_B$OH), 3.42 (1H, d, *J* 11.0, CH$_A$$H_B$OH), 3.38* (1H, d, *J* 10.5, CH$_A$$H_B$OH), 3.05 (1H, d, *J* 13.0, CH$_A$$H_B$Ph), 2.86 *(1H, d, *J* 13.0, CH$_A$$H_B$Ph), 2.80* (1H, d, *J* 13.0, CH_AH$_B$Ph), 2.49 (1H, d, *J* 13.0, CH_AH$_B$Ph), 1.29 (3H, d, *J* 6.5, CHCH_3), 1.28(6)* (3H, d, *J* 6.5, CHCH_3), 0.72 (3H, s, (C)CH_3), 0.71* (3H, s, (C)CH_3); δ_C ($CDCl_3$, 101 MHz) 138.2, 138.0, 130.8(4), 130.8(1), 127.9, 126.1, 126.0, 76.1, 74.0, 69.5, 67.7, 65.9, 41.7, 41.6, 41.1, 35.6, 19.0, 18.3, 18.1, 17.5, 15.3; ν_{max} (neat)/cm^{-1} 3330, 2931, 2877, 1452, 1031, 701; HRMS (CI$^+$) $C_{12}H_{19}O_2^+$ ([M + H]$^+$) requires 195.1385, found 195.1385.

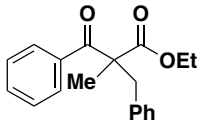
2-Benzyl-2-methyl-3-oxobutanal, 221



Synthesised according to the general procedure **J**, using 2-benzyl-2-methylbutane-1,3-diol **220** (1.98 g, 10.2 mmol), DMSO (3.05 mL, 43.0 mmol), oxalyl chloride (1.81 mL, 21.4 mmol) and triethylamine (10.3 mL, 73.4 mmol) in CH_2Cl_2 (30 mL). The crude product was purified by flash chromatography on silica (eluent 10% Et_2O/petrol) to give the *aldehyde* **221** (1.51 g, 78%) as a colourless oil.

δ_H ($CDCl_3$, 400 MHz) 9.75 (1H, s, C*H*O), 7.34–7.20 (3H, m, 3 × Ar*H*), 7.15–7.05 (2H, m, 2 × Ar*H*), 3.20 (1H, d, *J* 13.5, CH_AH$_B$Ph), 3.15 (1H, d, *J* 13.5, CH$_A$$H_B$Ph), 2.12 (3H, s, C(O)C$H_3$), 1.30 (3H, s, (C)C$H_3$); δ_C ($CDCl_3$, 101 MHz) 207.1, 201.2, 135.4, 130.1, 128.5, 127.1, 65.1, 39.9, 28.0, 16.4; ν_{max} (neat)/cm^{-1} 2980, 1727, 1699, 1357, 756, 702; HRMS (CI$^+$) $C_{12}H_{15}O_2^+$ ([M + H]$^+$) requires 191.1067, found 191.1067.

Ethyl 2-benzyl-2-methyl-3-oxo-3-phenylpropanoate, 222

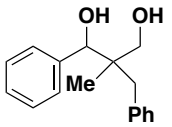


Synthesised according to the general procedure **D**, using 2-benzyl-3-oxo-3-phenylpropanoate (8.47g, 30.0 mmol), sodium hydride (60% in mineral oil, 0.86 g, 36.0 mmol) and iodomethane (5.6 mL, 90 mmol) in THF (50 mL). The crude product was purified by flash chromatography on silica (eluent 50% EtOAc/petrol) to give the ester **222** (6.02 g, 68%) as a colourless oil.

δ_H ($CDCl_3$, 400 MHz) 8.01–7.86 (2H, m, 2 × Ar*H*), 7.63–7.53 (1H, m, Ar*H*), 7.51–7.41 (2H,

m, 2 × Ar*H*), 7.32–7.20 (3H, m, 3 × Ar*H*), 7.13–7.04 (2H, m, 2 × Ar*H*), 4.21–4.04 (2H, m, $CO_2CH_2CH_3$), 3.47 (1H, d, *J* 13.5, CH_AH_BPh), 3.38 (1H, d, *J* 13.5, CH_AH_BPh), 1.52 (3H, s, (C)CH_3), 1.05 (3H, t, *J* 7.0, $CO_2CH_2CH_3$); δ_C ($CDCl_3$, 101 MHz) 197.3, 173.6, 136.2, 135.8, 132.7, 130.4, 128.6, 128.6, 128.1, 126.9, 61.4, 58.3, 42.2, 21.1, 13.7; ν_{max} (neat)/cm^{-1} 2986, 2937, 1733, 1681, 1237, 1182, 972, 699; HRMS (CI^+) $C_{19}H_{21}O_3^+$ ($[M + H]^+$) requires 297.1497, found 297.1497.

2-Benzyl-2-methyl-1-phenylpropane-1,3-diol, 223

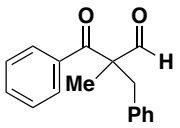


Synthesised according to the general procedure **H**, using ethyl 2-benzyl-2-methyl-3-oxo-3-phenylpropanoate **222** (4.85 g, 16.4 mmol), and $LiAlH_4$ (1.56 g, 41.0 mmol) in THF (120 mL). The crude product was purified by flash chromatography on silica (eluent 40% EtOAc/petrol) to give the *diol* **223** (3.42 g, 81%) as a thick colourless oil. **223** exists in a mixture of two diastereomers (1:1.23).

δ_H ($CDCl_3$, 400 MHz) (* denotes second diastereomer) 7.69–7.07 (10H, m, 10 × Ar*H*), 4.80 (1H, s, C*H*OH), 4.61* (1H, s, C*H*OH), 4.18 (1H, br. s, O*H*), 3.94 (1H, br. s, O*H*), 3.63 (1H, d, *J* 11.0, CH_AH_BOH), 3.45* (1H, d, *J* 11.0, CH_AH_BOH), 3.41* (1H, d, *J* 11.0, CH_AH_BOH), 3.27 (1H, d, *J* 11.0, CH_AH_BOH), 3.21 (1H, d, *J* 13.0, CH_AH_BPh), 3.02* (1H, d, *J* 13.0, CH_AH_BPh), 2.91* (1H, d, *J* 13.0, CH_AH_BPh), 2.38 (1H, d, *J* 13.0, CH_AH_BPh), 0.69 (3H, s, (C)CH_3), 0.56* (3H, s, (C)CH_3); δ_C ($CDCl_3$, 101 MHz) 141.3, 141.1, 138.0, 131.0, 131.0, 128.0, 128.0, 127.9, 127.9, 127.7, 127.6, 126.2, 126.0, 82.9, 81.3, 69.0, 67.2, 42.4, 42.1, 41.0, 35.9, 19.1, 18.2; ν_{max} (neat)/cm^{-1} 3320, 2930, 2877, 1452, 1025, 701; HRMS (CI^+)

$C_{17}H_{24}O_2N^+$ ($[M + NH_4]^+$) requires 274.1802, found 274.1802.

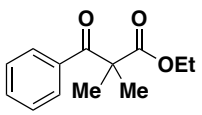
2-Benzyl-2-methyl-3-oxo-3-phenylpropanal, 224



Synthesised according to the general procedure **J**, using 2-benzyl-2-methyl-1-phenylpropane-1,3-diol **223** (3.42 g, 13.3 mmol), DMSO (4.0 mL, 56 mmol), oxalyl chloride (2.37 mL, 28.0 mmol) and triethylamine (13.0 mL, 96.1 mmol) in CH_2Cl_2 (45 mL). The crude product was purified by flash chromatography on silica (eluent 20% EtOAc/petrol) to give the *aldehyde* **224** (1.77 g, 53%) as a white crystalline solid.

δ_H ($CDCl_3$, 400 MHz) 9.75 (1H, s, C*H*O), 7.66–7.57 (2H, m, 2 × Ar*H*), 7.49–7.41 (1H, m, Ar*H*), 7.38–7.30 (2H, m, 2 × Ar*H*), 7.16–7.08 (3H, m, 3 × Ar*H*), 6.99–6.91 (2H, m, 2 × Ar*H*), 3.32 (2H, s, CH_2Ph), 1.33 (3H, s, CH_3); δ_C ($CDCl_3$, 101 MHz) 200.9, 199.1, 136.6, 135.5, 132.9, 130.4, 128.9, 128.8, 128.3, 127.0, 64.1, 40.3, 18.4; mp: 66–68 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 2933, 2819, 1723, 1674, 1452, 700; HRMS (CI^+) $C_{17}H_{17}O_2^+$ ($[M + H]^+$) requires 253.1230, found 253.1230.

Ethyl 2,2-dimethyl-3-oxo-3-phenylpropanoate, 225

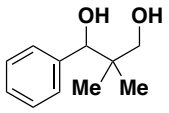


To a suspension of NaH (2.10g, 52.5 mmol, 60% wt. dispersion in oil) and ethyl benzoylacetate (9.0 mL, 52 mmol) in THF (125 mL) and DMF (1.5 mL) was added methyl iodide (3.92 mL, 63.0 mmol) dropwise at 0 °C, and the mixture was stirred for 2 h under

reflux. After cooling to 0 °C, NaH (2.10 g, 52.5 mmol) followed by methyl iodide (3.92 mL, 63.0 mmol) was added carefully. The reaction mixture was refluxed again for 16 h and then quenched with water (100 mL). The organic product was extracted with diethyl ether, washed with water and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The ester **225** (5.9 g, 52%) was obtained as a colourless oil which was used in the next step without further purification.

δ_H ($CDCl_3$, 400 MHz) 7.83 (2H, dt, *J* 8.5, 2 × Ar*H*), 7.53–7.47 (1H, m, Ar*H*), 7.43–7.36 (2H, m, 2 × Ar*H*), 4.10 (2H, q, *J* 7.0, OCH_2CH_3), 1.53 (6H, s, 2 × CH_3), 1.02 (3H, t, *J* 7.0, OCH_2CH_3); δ_C ($CDCl_3$, 101 MHz) 197.7, 174.9, 135.2, 132.6, 128.6, 128.4, 61.3, 53.2, 23.9, 13.7; ν_{max} (neat)/cm^{-1} 2983, 2983, 1734, 1682, 1266, 1137, 981, 690. Data is consistent with the literature.[290]

2,2-Dimethyl-1-phenylpropane-1,3-diol, 226

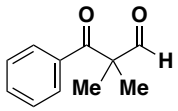


Synthesised according to the general procedure **H**, using ethyl 2,2-dimethyl-3-oxo-3-phenylpropanoate **225** (2.20 g, 10.0 mmol), and $LiAlH_4$ (25 mL, 1 M in THF, 25 mmol) in THF (100 mL). The crude product was purified by flash chromatography on silica (eluent 30% EtOAc/petrol) to give the diol **226** (3.42 g, 81%) as a white crystalline solid.

δ_H ($CDCl_3$, 400 MHz) 7.40–7.21 (5H, m, 5 × Ar*H*), 4.66 (1H, s, C*H*OH), 3.59 (1H, d, *J* 11.0, CH_AH_BOH), 3.51 (1H, d, *J* 11.0, CH_AH_BOH), 3.13 (2H, br. s, 2 × O*H*), 0.89 (3H, s, (C)(CH_A)(CH_B)), 0.86 (3H, s, (C)(CH_A)(CH_B)); δ_C ($CDCl_3$, 101 MHz) 141.4, 127.8, 127.6, 127.5, 82.2, 72.1, 39.1, 22.8, 19.0; mp 76–78 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 3323, 2933, 2872,

1475, 1041, 736, 702. Data is consistent with the literature.[291]

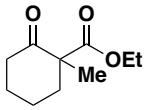
2,2-Dimethyl-3-oxo-3-phenylpropanal, 227



Synthesised according to the general procedure **J**, using 2,2-dimethyl-1-phenylpropane-1,3-diol **226** (0.90 g, 5.0 mmol), DMSO (1.5 mL, 21 mmol), oxalyl chloride (0.89 mL, 10.5 mmol) and triethylamine (5.0 mL, 36 mmol) in CH_2Cl_2 (15 mL). The crude product was purified by flash chromatography on silica (eluent 15% EtOAc/petrol) to give the aldehyde **227** (0.52 g, 59%) as a colourless oil.

δ_H ($CDCl_3$, 400 MHz) 9.78 (1H, s, C*H*O), 7.82–7.75 (2H, m, 2 × Ar*H*), 7.59–7.52 (1H, m, Ar*H*), 7.50–7.38 (2H, m, 2 × Ar*H*), 1.50 (6H, s, 2 × CH_3); δ_C ($CDCl_3$, 101 MHz) 200.5, 199.3, 135.8, 133.0, 129.0, 128.7, 59.5, 20.6; ν_{max} (neat)/cm^{-1} 2980, 2935, 1719, 1673, 1257, 948, 704. Data is consistent with the literature.[292]

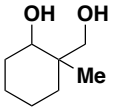
Ethyl 1-methyl-2-oxocyclohexane-1-carboxylate, 228



Synthesised according to the general procedure **D**, using ethyl 2-oxocyclohexanecarboxylate (8.0 mL, 50 mmol), sodium hydride (60% in mineral oil, 2.4 g, 60 mmol) and iodomethane (6.2 mL, 100 mmol) in THF (50 mL). The crude product was purified by flash chromatography on silica (eluent 50% EtOAc/petrol) to give the ester **228** (8.55 g, 93%) as a colourless oil.

δ_H ($CDCl_3$, 400 MHz) 4.13 (2H, q, *J* 7.0, $CO_2CH_2CH_3$), 2.56–2.23 (3H, m, $(CO)CH_2$, $(C)(CH_3)CH_AH_B$), 2.01–1.89 (1H, m, $(C)(CH_3)CH_2CH_AH_B$), 1.73–1.54 (3H, m, $C(O)CH_2CH_2$, $(C)(CH_3)CH_2CH_AH_B$), 1.47–1.34 (1H, m, $(C)(CH_3)CH_AH_B$), 1.21 (3H, s, $(C)CH_3$), 1.18 (3H, t, *J* 7.0, $CO_2CH_2CH_3$); δ_C ($CDCl_3$, 101 MHz) 208.2, 173.0, 61.2, 57.0, 40.6, 38.2, 27.5, 22.6, 21.2, 14.0; *m/z* (ESI^+) 207 ($[M + Na]^+$, 100%). Data is consistent with the literature.[293]

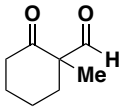
2-(Hydroxymethyl)-2-methylcyclohexan-1-ol, 229



Synthesised according to the general procedure **H**, using ethyl 1-methyl-2-oxocyclohexane-1-carboxylate **228** (3.68 g, 20.0 mmol), and $LiAlH_4$ (1.90 g, 50.0 mmol) in THF (150 mL). The crude product was purified by flash chromatography on silica (eluent 50% EtOAc/petrol) to give the diol **229** (2.43 g, 73%) as a 50:50 mixture of *cis* and *trans* isomers, in the form of a white crystalline solid.

δ_H ($CDCl_3$, 400 MHz) (* denotes second diastereomer) 3.95–3.67 (3H, m, 2 × OH, CH_AH_BOH), 3.61 (1H, dd, *J* 11.5, 4.5, $CHOH$), 3.53–3.31 (1H, m, CH_AH_BOH) , 1.81–1.53 (3H, m, 1.5 × CH_2), 1.51–1.30 (3H, m, 1.5 × CH_2), 1.27–1.14 (1H, m, 0.5 × CH_2), 1.13–1.03 (1H, m, 0.5 × CH_2), 1.00 (3H, s, $(C)CH_3$), 0.98* (3H, s, $(C)CH_3$); δ_C ($CDCl_3$, 101 MHz) (* denotes second diastereomer) 77.0(1), 76.9(8)*, 74.7*, 69.8, 39.1*, 38.1, 33.3*, 32.2, 30.5, 30.2*, 24.5*, 22.5, 22.4, 21.1, 20.4*, 13.4*; mp 87–89 °C (EtOH); *m/z* (ESI^+) 167 ($[M + Na]^+$, 100%). Data is consistent with the literature.[294]

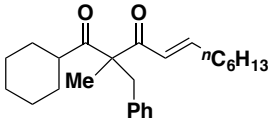
1-Methyl-2-oxocyclohexane-1-carbaldehyde, 230



Synthesised according to the general procedure **J**, using 2-(hydroxymethyl)-2-methylcyclohexan-1-ol **229** (1.47 g, 10.2 mmol), DMSO (3.05 mL, 43.0 mmol), oxalyl chloride (1.81 mL, 21.4 mmol) and triethylamine (10.2 mL, 73.4 mmol) in CH_2Cl_2 (30 mL). The crude product was purified by flash chromatography on silica (eluent 10% EtOAc/petrol) to give the aldehyde **230** (1.12 g, 78%) as a colourless oil.

δ_H ($CDCl_3$, 400 MHz) 9.45 (1H, s, C*H*O), 2.48–2.38 (1H, m, C(O)CH_AH_B), 2.38–2.29 (1H, m, C(O)CH_AH_B), 2.28–2.21 (1H, m, (C)(CH_3)CH_AH_B), 1.95–1.84 (1H, m, C(O)CH_2CH_AH_B), 1.80–1.69 (2H, m, C(O)$CH_2CH_AH_B$, C(O)$(CH_2)_2$CH_AH_B), 1.69–1.60 (1H, m, C(O)$(CH_2)_2CH_AH_B$), 1.60–1.50 (1H, m, (C)(CH_3)CH_AH_B), 1.18 (3H, s, CH_3); δ_C ($CDCl_3$, 101 MHz) 209.6, 201.1, 61.2, 40.6, 34.6, 26.7, 21.6, 17.7; *m/z* (ESI^+) 163 ($[M + Na]^+$, 100%). Data is consistent with the literature.[295]

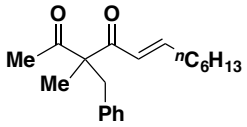
(*E*)-2-Benzyl-1-cyclohexyl-2-methylundec-4-ene-1,3-dione, 231



Synthesised according to the general procedure **C**, using 2-benzyl-3-cyclohexyl-2-methyl-3-oxopropanal **218** (78 mg, 0.30 mmol), 1-octyne (54 µL, 0.36 mmol), $[Rh(nbd)_2]BF_4$ (5.6 mg, 5 mol%) and dcpe (6.3 mg, 5 mol%) in acetone (0.3 mL, 1.0 M). The crude product was purified by flash chromatography on silica (eluent 5% Et_2O/petrol) to give **231** (103 mg, 93%) as a colourless oil.

δ_H ($CDCl_3$, 400 MHz) 7.17–7.05 (3H, m, 3 × Ar*H*), 7.00–6.92 (3H, m, 2 × Ar*H*, C(O)CH=C*H*CH_2), 6.25 (1H, dt, *J* 15.0, 1.5, C(O)C*H*=CHCH_2), 3.22 (1H, d, *J* 14.0, CC*H*$_A$H$_B$Ph), 3.04 (1H, d, *J* 14.0, CCH$_A$*H*$_B$Ph), 2.47 (1H, ddd, *J* 11.5, 8.5, 3.0, C(O)C*H*), 2.15 (2H, app. q, *J* 7.0, CHC*H*$_2$(CH_2)$_4$$CH_3$), 1.69–1.61 (2H, m, C*H*$_2$), 1.58–1.52 (2H, m, C*H*$_2$), 1.41–1.33 (3H, m, 1.5 × C*H*$_2$), 1.24–1.09 (14H, m, 5.5 × C*H*$_2$, C*H*$_3$), 0.85–0.75 (3H, m, CH_2C*H*$_3$); δ_C ($CDCl_3$, 101 MHz) 212.8, 196.5, 149.6, 136.8, 130.2, 128.1, 126.6, 125.8, 66.8, 47.8, 39.4, 32.5, 31.6, 30.5, 30.0, 28.9, 28.0, 25.6, 25.5, 25.4, 22.6, 17.4, 14.1; ν_{max} (neat)/cm^{-1} 2928, 2855, 1703, 1683, 1623, 1450, 987, 700; *m/z* (ESI^+) 391 ($[M + Na]^+$, 100%); HRMS (ESI^+) $C_{25}H_{37}O_2^+$ ($[M + H]^+$) requires 369.27881, found 369.27881.

(*E*)-3-Benzyl-3-methyldodec-5-ene-2,4-dione, 232

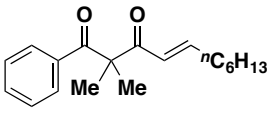


Synthesised according to the general procedure **C**, using 2-benzyl-2-methyl-3-oxobutanal **221** (57 mg, 0.30 mmol), 1-octyne (54 μL, 0.36 mmol), $[Rh(nbd)_2]BF_4$ (5.6 mg, 5 mol%) and dcpe (6.3 mg, 5 mol%) in acetone (0.3 mL, 1.0 M). The crude product was purified by flash chromatography on silica (eluent 10% EtOAc/petrol) to give the *enone* **232** (58 mg, 65%) as a colourless oil.

δ_H ($CDCl_3$, 400 MHz) 7.22–7.06 (3H, m, 3 × Ar*H*), 7.02–6.91 (3H, m, 2 × Ar*H*, C(O)CH=C*H*CH_2), 6.18 (1H, dt, *J* 15.5, 1.5, C(O)C*H*=CHCH_2), 3.15 (1H, d, *J* 14.0, C*H*$_A$H$_B$Ph), 3.10 (1H, d, *J* 14.0, CH$_A$*H*$_B$Ph), 2.20–2.08 (2H, m, CHC*H*$_2$$CH_2$($CH_2$)$_3$$CH_3$), 2.03 (3H, s, C(O)C*H*$_3$), 1.42–1.32 (2H, m, $CHCH_2$C*H*$_2$(CH_2)$_3$$CH_3$), 1.26–1.18 (6H, m, CH($CH_2$)$_2$(C*H*$_2$)$_3$$CH_3$), 1.16 (3H, s, (C)C*H*$_3$), 0.80 (3H, t, *J* 7.5, CH_2C*H*$_3$); δ_C ($CDCl_3$,

101 MHz) 207.3, 196.9, 150.2, 136.5, 130.1, 128.2, 126.7, 125.2, 66.3, 39.6, 32.6, 31.6, 28.9, 28.0, 27.3, 22.6, 17.9, 14.1; ν_{max} (neat)/cm^{-1} 2928, 2856, 1714, 1686, 1623, 1454, 701; HRMS (CI^+) $C_{20}H_{29}O_2^+$ ([M + H]$^+$) requires 301.2168, found 301.2168.

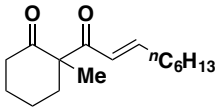
(*E*)-2,2-Dimethyl-1-phenylundec-4-ene-1,3-dione, 234



Synthesised according to the general procedure **C**, using 2,2-dimethyl-3-oxo-3-phenylpropanal **227** (53 mg, 0.30 mmol), 1-octyne (54 μL, 0.36 mmol), $[Rh(nbd)_2]BF_4$ (5.6 mg, 5 mol%) and dcpe (6.3 mg, 5 mol%) in acetone (0.3 mL, 1.0 M). The crude product was purified by flash chromatography on silica (eluent 10% EtOAc/petrol) to give the *enone* **234** (102 mg, 83%) as a pale yellow oil.

δ_H ($CDCl_3$, 400 MHz) 7.75–7.62 (2H, m, 2 × Ar*H*), 7.48–7.38 (1H, m, Ar*H*), 7.40–7.18 (2H, m, 2 × Ar*H*), 6.93 (1H, dt, *J* 15.5, 7.0, C(O)CH=C*H*CH_2), 5.99 (1H, dt, *J* 15.0, 1.5, C(O)C*H*=$CHCH_2$), 2.25–1.71 (2H, m, $CHCH_2CH_2(CH_2)_3CH_3$), 1.40 (6H, s, 2 × CH_3), 1.32–1.18 (2H, m, $CHCH_2CH_2(CH_2)_3CH_3$), 1.16–0.97 (6H, m, $CH(CH_2)_2(CH_2)_3CH_3$), 0.74 (3H, t, *J* 7.0, CH_2CH_3); δ_C ($CDCl_3$, 101 MHz) 199.9, 198.8, 150.0, 135.7, 132.9, 129.1, 128.5, 125.8, 59.8, 32.4, 31.4, 28.6, 27.8, 23.1, 22.4, 14.0; ν_{max} (neat)/cm^{-1} 2973, 2849, 1727, 1629, 1249, 701; *m/z* (ESI$^+$) 309 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{19}H_{27}O_2^+$ ([M + H]$^+$) requires 287.20111, found 287.20102.

(*E*)-2-Methyl-2-(non-2-enoyl)cyclohexan-1-one, 235

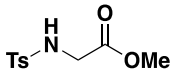


Synthesised according to the general procedure **C**, using 1-methyl-2-oxocyclohexane-1-carbaldehyde **230** (40 μL, 0.30 mmol), 1-octyne (54 μL, 0.36 mmol), $[Rh(nbd)_2]BF_4$ (5.6 mg, 5 mol%) and dcpe (6.3 mg, 5 mol%) in acetone (0.3 mL, 1.0 M). The crude product was purified by flash chromatography on silica (eluent 10% EtOAc/petrol) to give the *enone* **235** (69 mg, 92%) as a colourless oil.

δ_H ($CDCl_3$, 400 MHz) 6.95 (1H, dt, *J* 15.0, 7.0, C(O)CH=C*H*CH_2), 6.10 (1H, dt, *J* 15.0, 1.5, C(O)C*H*=CHCH_2), 2.55–2.46 (1H, m, (C)(CH_3)CH_AH_B), 2.43–2.34 (1H, m, C(O)CH_AH_B), 2.27–2.16 (1H, m, C(O)CH_AH_B), 2.15–2.07 (2H, m, CHCH_2CH_2(CH_2)$_3$$CH_3$), 2.00–1.89 (1H, m, C(O)(CH_2)$_2$CH_AH_B), 1.68–1.54 (3H, m, C(O)CH_2CH_2, C(O)(CH_2)$_2$CH_AH_B), 1.43–1.32 (3H, m, CHCH_2CH_2(CH_2)$_3$$CH_3$, (C)($CH_3$)C$H_AH_B$), 1.29–1.17 (6H, m, CH($CH_2$)$_2$(C$H_2$)$_3$$CH_3$), 1.15 (3H, s, (C)C$H_3$), 0.80 (3H, t, *J* 7.5, CH_2CH_3); δ_C ($CDCl_3$, 101 MHz) 211.1, 197.2, 150.2, 124.3, 62.7, 41.9, 36.8, 32.5, 31.5, 28.8, 27.9, 27.8, 22.5, 22.3, 20.9, 14.0; ν_{max} (neat)/cm^{-1} 2928, 2858, 1717, 1685, 1672, 1457, 984; *m/z* (ESI^+) 273 ($[M + Na]^+$, 100%); HRMS (ESI^+) $C_{16}H_{27}O_2^+$ ($[M + H]^+$) requires 251.20056, found 251.20082.

6.3 Chapter 4 Experimental

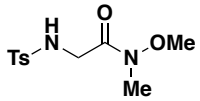
Methyl tosylglycinate, 292



To a solution of glycine methyl ester hydrochloride (7.53 g, 60.0 mmol) in CH_2Cl_2 (120 mL) was added triethylamine (17.6 mL, 126 mmol). *p*-Toluenesulfonyl chloride (12.6 g, 60.0 mmol) was added portionwise at 0 °C, and the reaction mixture was stirred at room temperature for 16 h. The mixture was diluted with water (100 mL) and extracted with diethyl ether (3 × 100 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by recrystallisation (CH_2Cl_2) to give the ester **292** (13.4 g, 92%) as an off-white crystalline solid.

δ_H ($CDCl_3$, 400 MHz) 7.73 (2H, d, *J* 8.5, 2 × Ar*H*), 7.28 (2H, d, *J* 8.5, 2 × Ar*H*), 5.59 (1H, t, *J* 6.0, CH_2NH), 3.76 (2H, d, *J* 6.0, CH_2NH), 3.60 (3H, s, $COOCH_3$), 2.39 (3H, s, $ArCH_3$); δ_C ($CDCl_3$, 101 MHz) 169.4, 143.7, 136.2, 129.7, 127.1, 52.5, 44.0, 21.4; mp: 44–47 °C (CH_2Cl_2); *m/z* (ESI^+) 509 ($[2M + Na]^+$, 100%). Data in accordance with the literature.[296]

***N*-Methoxy-*N*-methyl-2-[(4-methylphenyl)sulfonamido]acetamide, 293**

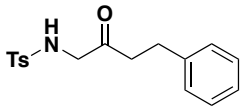


To a solution of methyl tosylglycinate **292** (14.6 g, 60.0 mmol) and *N*, *O*-dimethylhydroxylamine hydrochloride (12.9 g, 132 mmol) in THF (150 mL) at –20 °C was added dropwise isopropylmagnesium chloride (135 mL, 2 M in THF, 270 mmol). The reaction mixture was then stirred at –20 °C for 15 min and then warmed up to room

temperature for 30 min. Saturated aq. ammonium chloride (150 mL) was added and the organic layer was extracted with EtOAc (100 mL). The organic layer was washed with 1 N HCl (100 mL), saturated aq. $NaHCO_3$ (100 mL), brine (100 mL), dried over $MgSO_4$ and filtered. The solvent was evaporated *in vacuo* and the crude product was purified by flash chromatography (eluent 40% Et_2O/petrol) to give the amide **293** (12.8 g, 78%) as a white crystalline solid.

δ_H ($CDCl_3$, 400 MHz) 7.77 (2H, d, *J* 8.5, 2 × Ar*H*), 7.32 (2H, d, *J* 8.5, 2 × Ar*H*), 5.62 (1H, s, CH_2NH), 3.91 (2H, app. s, CH_2NH), 3.65 (1H, s, OCH_3), 3.13 (1H, s, NCH_3); δ_C ($CDCl_3$, 101 MHz) 168.3, 143.6, 136.1, 129.7, 127.2, 61.6, 43.2, 32.4, 21.5; mp: 76–78 °C (CH_2Cl_2); *m/z* (ESI^+) 567 ($[2M + Na]^+$, 100%). Data in accordance with the literature.[297]

4-Methyl-*N*-(2-oxo-4-phenylbutyl)benzenesulfonamide, 294

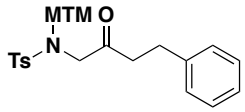


Magnesium turnings were activated by grinding in a mortar, and then the metal (2.5 g, 100 mmol) was suspended in THF (150 mL), and a few drops of iodine in MTBE were added. 2-Phenylethylbromide (9.8 ml, 72 mmol) was added portionwise at 0 °C, and the reactivity was confirmed by disappearance of the yellow iodine colour. After stirring for 10 min at room temperature, this solution was transferred to another solution containing *N*-methoxy-*N*-methyl-2-((4-methylphenyl)sulfonamido)acetamide **293** (3.3 g, 12 mmol) stirring in THF (100 mL) at 0 °C. The mixture was stirred at this temperature for 10 min and then warmed to room temperature for 2 h. It was then cooled down again to 0 °C, and 1 N HCl (50 mL) was added carefully at such a rate that the temperature did not rise above 20 °C. The organic

layer was extracted with EtOAc (2 × 60 mL) and washed with 1 N HCl (80 mL), saturated aq. $NaHCO_3$ (80 mL), brine (80 mL), dried over $MgSO_4$ and filtered. The solvent was evaporated *in vacuo* and the crude product was purified by flash chromatography (eluent 50% Et_2O/petrol) to give the ketone **294** (3.6 g, 95%) as a brown crystalline solid.

δ_H ($CDCl_3$, 400 MHz) 7.67–7.60 (2H, m, 2 × Ar*H*), 7.25–7.09 (5H, m, 5 × Ar*H*), 7.05–6.98 (2H, m, 2 × Ar*H*), 5.23 (1H, t, *J* 4.5, N*H*CH_2), 3.71 (2H, d, *J* 4.5, NHC*H*$_2$), 2.77 (2H, t, *J* 7.5, C(O)C*H*$_2$$CH_2$Ph), 2.59 (2H, t, *J* 7.5, C(O)CH_2C*H*$_2$Ph), 2.35 (3H, s, ArC*H*$_3$); δ_C ($CDCl_3$, 101 MHz) 202.9, 143.8, 139.9, 136.1, 129.8, 128.6, 128.2, 127.2, 126.5, 51.7, 41.6, 29.5, 21.6; mp: 118–120 °C (CH_2Cl_2); *m/z* (ESI^+) 340 ($[M + Na]^+$, 100%). Data in accordance with the literature.[298]

4-Methyl-*N*-[(methylthio)methyl]-*N*-(2-oxo-4-phenylbutyl)benzenesulfonamide, 295

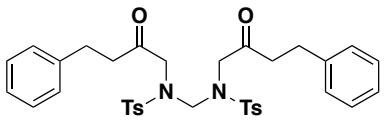


4-Methyl-*N*-(2-oxo-4-phenylbutyl)benzenesulfonamide **294** (3.45 g, 10.9 mmol) and tetrabutylammonium iodide (2.0 g, 5.4 mmol) were dissolved in DMF (60 mL) under a nitrogen atmosphere. The reaction was cooled to 0 °C and then sodium hydroxide powder (0.65 g, 16.3 mmol) was then added portionwise and stirred for 5 min. Methylthiomethyl chloride (1.37 mL, 16.3 mmol) and the mixture was allowed to stir for a further 2 h at 0 °C. Then reaction was then partitioned between EtOAc (60 mL) and water (60 mL) and the organic layer was separated and washed with water (2 × 50 mL) and brine (50 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give the crude product. Column chromatography (eluent 2% EtOAc/toluene) yielded the

amide **295** (3.4 g, 83%) as brown solid.

δ_H ($CDCl_3$, 400 MHz) 7.62–7.55 (2H, m, 2 × Ar*H*), 7.25–7.11 (5H, m, 5 × Ar*H*), 7.11–7.05 (2H, m, 2 × Ar*H*), 4.29 (2H, s, NCH_2C(O)), 4.09 (2H, s, NCH_2SCH_3), 2.83–2.76 (2H, m, C(O)C$H_2$$CH_2$Ph), 2.73–2.66 (2H, m, C(O)CH_2CH_2Ph), 2.36 (3H, s, ArCH_3), 2.00 (3H, s, NCH_2SCH_3); δ_C ($CDCl_3$, 101 MHz) 204.5, 143.9, 140.5, 136.5, 129.8, 128.7, 128.4, 127.5, 126.4, 53.6, 53.1, 41.2, 29.6, 21.7, 14.4; mp: 82–84 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 2981, 1728, 1344, 1158, 1088, 1012, 747, 677, 634; *m/z* (ESI^+) 400 ($[M + Na]^+$, 100%); HRMS (ESI^+) $C_{19}H_{23}O_3NS_2Na^+$ ($[M + Na]^+$) requires 400.10116, found 400.10103.

_N_,_N_'-Methylenebis[4-methyl-_N_-(2-oxo-4-phenylbutyl)benzenesulfonamide], 297

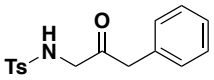


$[Rh(C_2H_4)_2Cl]_2$ (4.3 mg, 0.011 mmol) and 4-methyl-*N*-[(methylthio)methyl]-*N*-(2-oxo-4-phenylbutyl)benzenesulfonamide **295** (41 mg, 0.11 mmol) were dissolved in 2-butanone (0.2 mL) in a sealed pressure vial under a N_2 atmosphere. The reaction was then heated to 120 °C for 16 hours and allowed to cool to room temperature. The resulting solution was filtered through a plug of silica and concentrated *in vacuo* to obtain the crude product. Purification by flash chromatography on silica (eluent 50% Et_2O/petrol) gave the *diketone* **297** (16 mg, 23%) as a dark yellow oil.

δ_H ($CDCl_3$, 400 MHz) 7.44 (4H, d, *J* 7.5, 4 × Ar*H*), 7.25–7.07 (14H, m, 14 × Ar*H*), 4.61 (2H, s, NCH_2N), 4.31 (4H, s, 2 × C(O)CH_2N), 2.82 (4H, t, *J* 7.5, 2 × C(O)C$H_2$$CH_2$Ph), 2.65 (4H, t, *J* 7.5, 2 × C(O)CH_2CH_2Ph), 2.33 (6H, s, 2 × ArCH_3); δ_C ($CDCl_3$, 101 MHz) 203.8, 143.8,

140.5, 136.9, 129.7, 128.5, 128.3, 127.1, 126.2, 59.9, 53.3, 40.8, 29.2, 21.6; ν_{max} (neat)/cm^{-1} 2927, 1730, 1338, 1155, 1088, 929, 748, 699, 661; *m/z* (ESI$^+$) 669 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{35}H_{38}O_6N_2S_2Na^+$ ([M + Na]$^+$) requires 669.20635, found 669.20611.

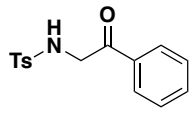
4-Methyl-*N*-(2-oxo-3-phenylpropyl)benzenesulfonamide, 298



To a stirred solution of *N*-methoxy-*N*-methyl-2-[(4-methylphenyl)sulfonamido]acetamide **293** (3.3 g, 12 mmol) in THF (45 mL) at 0 °C was added benzylmagnesium chloride (36 mL, 2M in THF, 72 mmol) carefully. The reaction was stirred at this temperature for 10 min and then warmed to room temperature for 2 h. The brown mixture was then cooled again to 0 °C, and 1 M HCl (50 mL) was added carefully at such a rate that the temperature did not rise above 20 °C. The organic layer was extracted with EtOAc (2 × 60 mL) and washed with 1 N HCl (80 mL), saturated aq. $NaHCO_3$ (80 mL), brine (80 mL), dried over $MgSO_4$ and filtered. The solvent was evaporated *in vacuo* and the crude product was purified by flash chromatography (eluent 50% Et_2O/petrol) to give the *ketone* **298** (2.8 g, 77%) as a brown crystalline solid.

δ_H ($CDCl_3$, 400 MHz) 7.57 (2H, d, *J* 8.5, 2 × Ar*H*), 7.25–7.13 (5H, m, 5 × Ar*H*), 6.99 (2H, dd, *J* 7.5, 2.0, 2 × Ar*H*), 5.26 (1H, t, *J* 5.0, N*H*CH_2), 3.80 (2H, d, *J* 5.0, NHCH_2), 3.55 (2H, s, C(O)CH_2Ph), 2.33 (3H, s, ArCH_3); δ_C ($CDCl_3$, 101 MHz) 201.6, 143.8, 136.0, 132.5, 129.9, 129.3, 129.1, 127.7, 127.2, 50.9, 47.3, 21.7; mp: 108–110 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 3267, 1723, 1412, 1353, 1159, 1051, 813, 680, 661; *m/z* (ESI$^+$) 629 ([2M + Na]$^+$, 100%).

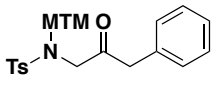
4-Methyl-*N*-(2-oxo-2-phenylethyl)benzenesulfonamide, 299



To a stirred solution of *N*-methoxy-*N*-methyl-2-[(4-methylphenyl)sulfonamido]acetamide, **293** (3.3 g, 12 mmol) in THF (45 mL) at 0 °C was added phenylmagnesium chloride (60 mL, 1 M in THF, 60 mmol) carefully. The reaction was stirred at this temperature for 10 min and then warmed to room temperature for 2 h. The brown mixture was then cooled down again to 0 °C, and 1 M HCl (50 mL) was added carefully at such a rate that the temperature did not rise above 20 °C. The organic layer was extracted with EtOAc (2 × 60 mL) and washed with 1 N HCl (80 mL), saturated aq. $NaHCO_3$ (80 mL), brine (80 mL), dried over $MgSO_4$ and filtered. The solvent was evaporated *in vacuo* and the crude product was purified by flash chromatography (eluent 50% Et_2O/petrol) to give the ketone **299** (2.8 g, 81%) as a brown crystalline solid.

δ_H ($CDCl_3$, 400 MHz) 7.85 (2H, dd, *J* 8.0, 1.1, 2 × Ar*H*), 7.80 (2H, d, *J* 8.0, 2 × Ar*H*), 7.59 (1H, t, *J* 7.5, Ar*H*), 7.46 (2H, app. t, *J* 8.0, 2 × Ar*H*), 7.29 (2H, d, *J* 8.0, 2 × Ar*H*), 5.84 (1H, s, N*H*CH_2CO), 4.48 (2H, d, *J* 4.5, NHC*H*$_2$CO), 2.39 (3H, s, ArC*H*$_3$); δ_C ($CDCl_3$, 101 MHz) 192.7, 143.8, 134.4, 133.8, 129.8, 129.0, 127.9, 127.2, 126.1, 48.8, 21.5; mp: 110–112 °C (CH_2Cl_2); *m/z* (ESI^+) 601 ($[2M + Na]^+$, 100%). Data in accordance with the literature.[299]

4-Methyl-*N*-[(methylthio)methyl]-*N*-(2-oxo-3-phenylpropyl)benzenesulfonamide, 300

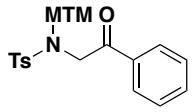


4-Methyl-*N*-(2-oxo-3-phenylpropyl)benzenesulfonamide **298** (0.75 g, 2.5 mmol) and

tetrabutylammonium iodide (0.46 g, 1.2 mmol) were dissolved in DMF (10 mL) under a nitrogen atmosphere. The reaction was cooled to 0 °C and then sodium bis(trimethylsilyl)amide (1.4 mL, 2 M in THF, 2.8 mmol) was then added dropwise and stirred for 30 min at room temperature. Methylthiomethyl chloride (0.3 mL, 3.7 mmol) and the mixture was allowed to stir for a further 2 h. Then reaction was then partitioned between EtOAc (30 mL) and water (30 mL) and the organic layer was separated and washed with water (2 × 30 mL) and brine (30 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give the crude product. Column chromatography (eluent 2% EtOAc/toluene) yielded the *amide* **300** (0.9 g, 39%) as pale brown solid.

δ_H ($CDCl_3$, 400 MHz) 7.53 (2H, d, *J* 8.5, 2 × Ar*H*), 7.30–7.15 (5H, m, 5 × Ar*H*), 7.11–7.06 (2H, m, 2 × Ar*H*), 4.32 (2H, s, NCH_2C(O)), 4.20 (2H, s, NCH_2SCH_3), 3.63 (2H, s, C(O)CH_2Ph), 2.34 (3H, s, ArCH_3), 2.00 (3H, s, NCH_2SCH_3); δ_C ($CDCl_3$, 101 MHz) 202.5, 143.9, 136.4, 133.1, 129.8, 129.5, 128.9, 129.0, 127.5, 127.4, 52.9, 52.5, 21.7, 14.4; mp: 72–74 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 2920, 1728, 1338, 1155, 1089, 1048, 939, 814, 743, 699, 657; *m/z* (ESI^+) 386 ([M + Na]$^+$, 100%); HRMS (ESI^+) $C_{18}H_{21}O_3NS_2Na^+$ ([M + Na]$^+$) requires 386.08551, found 386.08539.

4-Methyl-*N*-[(methylthio)methyl]-*N*-(2-oxo-2-phenylethyl)benzenesulfonamide, 301

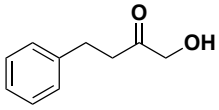


4-Methyl-*N*-(2-oxo-2-phenylethyl)benzenesulfonamide **299** (2.7 g, 9.8 mmol) and tetrabutylammonium iodide (1.8 g, 4.9 mmol) were dissolved in DMF (50 mL) under a

nitrogen atmosphere. The reaction was cooled to 0 °C and then sodium hydroxide powder (0.59 g, 14.6 mmol) was added portionwise and stirred for 5 min. Methylthiomethyl chloride (1.22 mL, 14.6 mmol) and the mixture was allowed to stir for a further 2 h at 0 °C. Then reaction was then partitioned between EtOAc (50 mL) and water (50 mL) and the organic layer was separated and washed with water (2 × 50 mL) and brine (50 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give the crude product. Column chromatography (eluent 5% EtOAc/toluene) yielded the *amide* **301** (0.8 g, 24%) as a pale brown solid.

δ_H ($CDCl_3$, 400 MHz) 7.82 (2H, dd, *J* 8.0, 1.0, 2 × Ar*H*), 7.68–7.61 (2H, m, 2 × Ar*H*), 7.52 (1H, d, *J* 7.5, Ar*H*), 7.44–7.37 (2H, m, 2 × Ar*H*), 7.22 (2H, d, *J* 8.0, 2 × Ar*H*), 4.90 (2H, s, NCH_2C(O)), 4.49(2H, s, NCH_2SCH_3), 2.35 (3H, s, ArCH_3), 2.04 (3H, s, NCH_2SCH_3); δ_C ($CDCl_3$, 101 MHz) 193.6, 143.8, 137.1, 135.0, 133.9, 129.7, 129.0, 128.1, 127.5, 52.6, 50.0, 21.7, 14.3; mp: 86–88 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 2921, 2361, 2342, 1698, 1597, 1340, 1157, 1090, 748, 669; *m/z* (ESI^+) 372 ($[M + Na]^+$, 100%); HRMS (ESI^+) $C_{17}H_{19}O_3NS_2Na^+$ ($[M + Na]^+$) requires 372.06986, found 372.06974.

1-Hydroxy-4-phenylbutan-2-one, 302

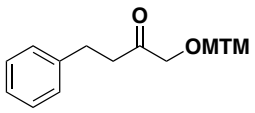


To a solution of trimethyl[(4-phenylbut-1-en-2-yl)oxy]silane (8.54 g, 38.8 mmol) in CH_2Cl_2 (300 mL) at 0 °C was added *m*-chloroperbenzoic acid (70% in H_2O, 10.4 g, 42.0 mmol) portionwise. The reaction mixture was then warmed to room temperature and stirred for 4 h. Et_2O (200 mL) and 1.5 N HCl (130 mL) were added, and the resulting two-phase mixture

was stirred vigorously for 5 h. The organic phase was washed with saturated aqueous $NaHCO_3$ (2 × 130 mL) and brine (130 mL), dried with $MgSO_4$ and concentrated *in vacuo*. The residue was then purified by column chromatography (eluent 10% EtOAc/petrol) to give the title alcohol **302** (2.47 g, 38%) as an amorphous yellow solid.

δ_H ($CDCl_3$, 400 MHz) 7.37–7.19 (5H, m, 5 × Ar*H*), 4.21 (2H, s, C(O)CH_2OH), 3.45 (1H, br. s, C(O)CH$_2$O*H*), 2.99 (2H, t, *J* 7.5, PhCH$_2$CH_2C(O)), 2.75 (2H, t, *J* 7.5, PhCH_2CH$_2$C(O)); δ_C ($CDCl_3$, 101 MHz); 209.0, 140.2, 128.6, 128.2, 126.4, 68.3, 39.8, 29.5; ν_{max} (neat)/cm^{-1} 2361, 1717, 1496, 1453, 1062, 749, 699. Data in accordance with the literature.[300]

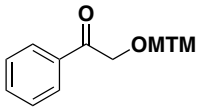
1-[(Methylthio)methoxy]-4-phenylbutan-2-one, 303



To a solution of 1-hydroxy-4-phenylbutan-2-one **302** (1.45 g, 8.85 mmol) in DMSO (40 mL) at 0 °C was added glacial acetic acid (30 mL) and acetic anhydride (50 mL). The ice bath was removed and the reaction mixture was stirred at room temperature for 16 h. The reaction mixture was then cooled to 0 °C and treated with 250 mL of a saturated aqueous $NaHCO_3$ solution and 15 g solid $NaHCO_3$. The contents of the flask were subsequently allowed to stir for 90 min. The reaction mixture was diluted with EtOAc (60 mL), the layers were separated and the aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (50 mL) and brine (50 mL), dried over $MgSO_4$ and filtered. The solvent was evaporated *in vacuo* and the crude product was purified by flash chromatography on silica (eluent 20% EtOAc/hexane) to give the *ketone* **303** (1.35 g, 68%) as a yellow oil.

δ_H ($CDCl_3$, 400 MHz) 7.38–7.18 (5H, m, 5 × Ar*H*), 4.71 (2H, s, CH_2SCH_3), 4.17 (2H, s, C(O)CH_2O), 2.96 (2H, t, *J* 7.5, PhCH_2CH_2C(O)), 2.81 (2H, t, *J* 7.5, PhCH_2CH_2C(O)), 2.16 (3H, s, CH_2SCH_3); δ_C ($CDCl_3$, 101 MHz) 207.0, 140.7, 128.6, 128.3, 126.2, 75.7, 72.4, 40.7, 29.4, 14.0; ν_{max} (neat)/cm^{-1} 2922, 1722, 1453, 1082, 750, 699; *m/z* (ESI^+) 247 ($[M + Na]^+$, 100%); HRMS (ESI^+) $C_{12}H_{16}O_2SNa^+$ ($[M + Na]^+$) requires 247.07632, found 247.07642.

2-[(Methylthio)methoxy]-1-phenylethan-1-one, 304

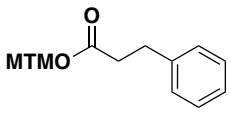


To a solution of 2-hydroxyacetophenone (2.50 g, 18.4 mmol) in DMSO (80 mL) at 0 °C was added glacial acetic acid (60 mL) and acetic anhydride (100 mL). The ice bath was removed and the reaction mixture was stirred at room temperature for 16 h. The reaction mixture was then cooled to 0 °C and treated with saturated aqueous $NaHCO_3$ solution (250 mL) and solid $NaHCO_3$ (30 g). The contents of the flask were subsequently allowed to stir for 90 min. The reaction mixture was diluted with EtOAc (100 mL), the layers were separated and the aqueous layer was extracted with EtOAc (2 × 75 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (75 mL) and brine (75 mL), dried over $MgSO_4$ and filtered. The solvent was evaporated *in vacuo* and the crude product was purified by flash chromatography on silica (eluent 30% Et_2O/hexane) to give the *ketone* **304** (2.52 g, 70%) as a colourless oil.

δ_H ($CDCl_3$, 400 MHz) 7.94 (2H, dt, *J* 8.5, 1.5, 2 × Ar*H*), 7.62–7.55 (1H, m, Ar*H*), 7.51–7.44 (2H, m, 2 × Ar*H*), 4.90 (2H, s, CH_2SCH_3), 4.83 (2H, s, C(O)CH_2O), 2.16 (3H, s, CH_2SCH_3); δ_C ($CDCl_3$, 101 MHz) 195.6, 133.6, 128.7, 127.8, 75.7, 69.7, 14.0; ν_{max} (neat)/cm^{-1} 2921,

1699, 1449, 1226, 1107, 1002, 732, 606; *m/z* (ESI^+) 415 ($[2M + Na]^+$, 100%); HRMS (ESI^+) $C_{10}H_{12}O_2SNa^+$ ($[M + Na]^+$) requires 219.04502, found 219.04508.

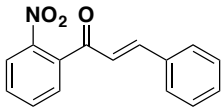
3-[(Methylthio)methoxy]-1-phenylpropan-1-one, 306



DMSO (7.80 mL, 110 mmol) in CH_2Cl_2 (50 mL) was added dropwise to a stirred solution of oxalyl chloride (4.7 mL, 55 mmol) in CH_2Cl_2 (75 mL) at –60 °C to –65 °C under an inert atmosphere. After 5 min, hydrocinnamic acid (7.5 g, 50 mmol) was added to the reaction mixture and stirring was continued for 15 min. Triethylamine (35.0 mL, 250 mmol) was added dropwise and after 5 min, the reaction was warmed to room temperature and then diluted with CH_2Cl_2 (50 mL). Water (60 mL) was added to the reaction mixture and the aqueous layer was extracted with CH_2Cl_2 (50 mL). The combined organic extract was washed with water (50 mL), then brine (50 mL) and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by flash chromatography on silica (eluent 20% Et_2O/petrol) to give the ketone **306** (6.3 g, 60%) as a colourless oil.

δ_H ($CDCl_3$, 400 MHz) 7.38–7.30 (2H, m, 2 × Ar*H*), 7.30–7.22 (3H, m, 3 × Ar*H*), 5.17 (2H, s, CH_2SCH$_3$), 3.02 (2H, t, *J* 7.5, C(O)CH_2CH$_2$Ph), 2.72 (2H, t, *J* 7.5, C(O)CH$_2$CH_2Ph), 2.21 (3H, s, CH$_2$SCH_3); δ_C ($CDCl_3$, 101 MHz) 172.5, 140.3, 128.6, 128.4, 126.4, 68.2, 35.9, 30.9, 15.4; *m/z* (ESI^+) 233 ($2M + Na]^+$, 100%). Data in accordance with the literature.[301]

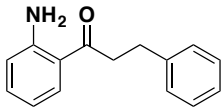
(*E*)-1-(2-Nitrophenyl)-3-phenylprop-2-en-1-one, 312



To a solution of 2-nitroacetophenone (8.0 mL, 60 mmol) in EtOH (150 mL) at 0 °C was added NaOH powder (2.9 g, 72 mmol) portionwise and allowed to dissolve. To this mixture was slowly added benzaldehyde (6.4 mL, 63 mL) and the reaction was stirred for 3 h at 0 °C during which time the product crystallised out from the mixture. The product was filtered, and the crystals were washed thoroughly with ice-cold EtOH to give enone **312** (14.0 g, 92%) as a light brown solid.

δ_H ($CDCl_3$, 400 MHz) 8.18 (1H, dd, *J* 8.0, 1.0, Ar*H*), 7.78 (1H, td, *J* 7.5, 1.0, Ar*H*), 7.63–7.70 (1H, m, Ar*H*), 7.48–7.55 (3H, m, 3 × Ar*H*), 7.37-7.42 (3H, m, 3 × Ar*H*), 7.27 (1H, d, *J* 16.5, C(O)C*H*CHPh), 7.03 (1H, d, *J* 16.5, C(O)CHC*H*Ph); δ_C ($CDCl_3$, 101 MHz) 193.0, 146.8, 146.4, 136.3, 134.1, 133.9, 131.1, 130.7, 129.0, 128.8, 128.6, 126.3, 124.6; mp: 124–126 °C (CH_2Cl_2); *m/z* (ESI^+) 276 ($[M + Na]^+$, 100%). Data in accordance with literature.[302]

1-(2-Aminophenyl)-3-phenylpropan-1-one, 309

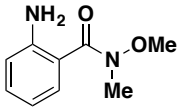


(*E*)-1-(2-Nitrophenyl)-3-phenylprop-2-en-1-one **312** (2.79 g, 11.0 mmol) and PtO_2 (Adam's catalyst) (0.25 g, 1.10 mmol) were dissolved in EtOAc (50 mL). H_2 gas was bubbled through the solution for 1 h and then the solution was stirred in a H_2 atmosphere at room temperature for 16 h. The mixture was then filtered through Celite® and the solution was concentrated *in vacuo*. The crude material was purified by flash chromatography (eluent 50% Et_2O/petrol)

to give the amine **309** (0.95 g, 38%) as an off-white solid.

δ_H ($CDCl_3$, 400 MHz) 7.58 (1H, dd, *J* 8.0, 1.5, Ar*H*), 7.21–7.04 (6H, m, 6 × Ar*H*), 6.52–6.45 (2H, m, 2 × Ar*H*), 6.16 (2H, br. s, ArNH_2), 3.12 (2H, t, *J* 8.0, C(O)CH_2CH_2Ph), 2.91 (2H, t, *J* 8.0, C(O)CH_2CH_2Ph); δ_C ($CDCl_3$, 101 MHz) 201.5, 150.5, 141.6, 134.3, 131.1, 128.6, 128.5, 126.1, 117.9, 117.4, 115.8, 41.0, 30.7; mp: 74–76 °C (CH_2Cl_2); *m/z* (ESI^+) 248 ($[M + Na]^+$, 100%). Data in accordance with the literature.[248]

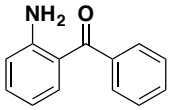
2-Amino-*N*-methoxy-*N*-methylbenzamide, 313



To a round-bottomed flask, *N*,*O*-dimethylhydroxylamine (14.6 g, 0.15 mol) and triethylamine (21.0 mL, 0.15 mol) in EtOH:H_2O (9:1, 40 mL) was stirred for 10 min. Isatoic anhydride (16.3 g, 0.10 mol) was then added slowly. The reaction mixture was heated to reflux for 2 h. Upon completion, the mixture was poured onto an ice/saturated $NaHCO_3$ mixture. The ethanol was removed *in vacuo* and the mixture was extracted with EtOAc (50 mL). The organic extracts were washed with brine (3 × 40 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product. Column chromatography (eluent 30–80% EtOAc/petrol) yielded amine **313** (12.0 g, 67%) as thick brown oil.

δ_H ($CDCl_3$, 400 MHz) 7.35 (1H, dd, *J* 7.5, 1.4, Ar*H*), 7.17 (1H, ddd, *J* 8.0, 7.5, 1.5, Ar*H*), 6.65–6.72 (2H, m, 2 × Ar*H*), 4.76 (2H, s, ArNH_2), 3.59 (3H, s, OCH_3), 3.33 (3H, s, NCH_3); δ_C ($CDCl_3$, 101 MHz) 169.8, 146.7, 131/1, 128.9, 116.9, 116.4(0), 116.3(8), 60.8, 34.1; *m/z* (ESI^+) 383 ($[2M + Na]^+$, 100%). Data is consistent with the literature.[303]

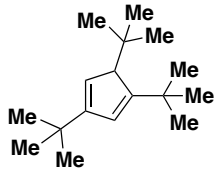
2-Aminobenzophenone, 310



To a mixture of 2-amino-*N*-methoxy-*N*-methylbenzamide **313** (2.16 g, 12.0 mmol) and bromobenzene (1.3 mL, 12.0 mmol) in THF (70 mL) at –78 °C under nitrogen was added *n*-BuLi (9.6 mL, 2.5 M in hexanes, 24 mmol) slowly. After 20 min, 1 N HCl (20 mL) was added and the mixture was extracted with EtOAc (50 mL). The organic layer was washed with water (50 mL) and brine (50 mL), dried over $MgSO_4$ and filtered. The solvent was evaporated *in vacuo* and the crude product was purified by recrystallisation (CH_2Cl_2) to give the amine **310** (1.5 g, 65%) as a yellow solid.

δ_H ($CDCl_3$, 400 MHz) 7.50 (2H, dt, *J* 7.0, 1.3, 2 × Ar*H*), 7.27–7.40 (4H, m, 4 × Ar*H*), 7.12 (1H, ddd, *J* 8.5, 7.0, 1.5, Ar*H*), 6.57 (1H, dd, *J* 8.0, 1.0, Ar*H*), 6.44 (1H, td, *J* 8.0, 1.0, Ar*H*), 6.02 (2H, br. s, ArNH_2); δ_C ($CDCl_3$, 101 MHz) 199.0, 150.1, 140.1, 134.5, 134.2, 131.0, 129.1, 128.0, 118.0, 117.0, 115.4; mp: 109–111 °C (CH_2Cl_2); *m/z* (ESI^+) 198 ($[M + H]^+$, 100%). Data in accordance with the literature.[249]

1,3,5-Tri-*tert*-butylcyclopenta-1,3-diene, 316

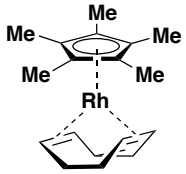


Prepared according to the procedure by Casserly *et al*.[304] Sodium hydride (60% dispersion in mineral oil, 15.2 g, 380 mmol), dibenzo-18-crown-6 (1.8 g, 5.0 mmol) and *t*-butyl bromide (54.5 mL, 485 mmol) were dissolved in THF (25 mL) under a N_2 atmosphere. Then a solution

of cyclopentadiene (4.2 mL, 50 mmol) in THF (10 mL) was added dropwise to the reaction mixture. Once the gas evolution had decayed, the mixture was heated to 60 °C for 48 h using a reflux condenser. The reaction was then cooled to room temperature and diluted with petroleum ether, after which the precipitated solid was filtered off and washed several times with petroleum ether. The organic phases were combined and the solvent removed *in vacuo* to give the crude product, which was purified by vacuum distillation (130 °C at 35 mbar) to give **316** (5.27 g, 45%).

δ_H ($CDCl_3$, 400 MHz) 6.20 (1H, s, $[C(CCH_3)_3]CH[C(CCH_3)_3]$), 5.74 (1H d, *J* 1.6, $[C(CCH_3)_3]CHCH(CCH_3)_3$), 2.84 (1H, br. s, $[C(CCH_3)_3]CHCH(CCH_3)_3$), 1.17 (9H, s, $C(CCH_3)_3$), 1.05 ((9H, s, $C(CCH_3)_3$), 0.97 ((9H, s, $C(CCH_3)_3$); δ_C ($CDCl_3$, 101 MHz) 159.8, 153.7, 129.2, 126.2, 63.0, 34.2, 33.9, 32.1, 32.0, 30.3, 29.6; *m/z* (ESI^+) 235 ($[M + H]^+$, 100%). Data in accordance with the literature.[304]

(1,5-Cyclooctadiene)(η-pentamethylcyclopentadienyl)rhodium(I), 315

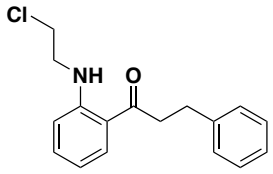


Prepared according to the procedure by Amouri *et al*.[251] To a 100 mL Schlenk tube equipped with a magnetic stirring bar was added $[Rh(cod)Cl]_2$ (250 mg, 0.5 mmol) in methanol (0.15 mL), pentamethylcyclopentadiene (0.25 mL, 0.93 mmol) and anhydrous Na_2CO_3 (264 mg, 2 mmol). The mixture was refluxed while stirring under N_2 atmosphere. After 30 min, the colour of the reaction mixture is changed to light yellow. The reaction was stopped after a further 2 h and the solution was filtered to remove excess Na_2CO_3. The

reaction mixture was allowed to stand in an ice-bath for 30 min, during which time yellow crystals of **315** (320 mg, 92%) were formed.

δ_H (CD_2Cl_2, 400 MHz) 2.83 (4H, app. br. s, 2 × C*H*=C*H*), 2.02–2.09 (4H, m, 2 × C$H_2$$CH_2$), 1.78–1.86 (4H, m, 2 × CH_2CH_2), 1.69 (15H, s, $C_5(CH_3)_5$); δ_C (CD_2Cl_2, 101 MHz) 70.7, 70.5, 33.2, 9.7. Data in accordance with the literature.[251]

1-(2-[(2-Chloroethyl)amino)phenyl]-3-phenylpropan-1-one, 318

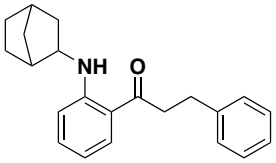


1-(2-Aminophenyl)-3-phenylpropan-1-one **309** (34 mg, 0.15 mmol), $Rh(PPh_3)_3Cl$ (139 mg, 0.015 mmol) and bicyclo[2.2.1]hept-2-ene (28 mg, 0.30 mmol) were dissolved in 1,2-dichloroethane (0.15 mL) in a sealed pressure vial under a N_2 atmosphere. The reaction was then heated to 150 °C for 24 hours and allowed to cool to room temperature. The resulting solution was filtered through a plug of silica and concentrated *in vacuo* to obtain the crude product. Purification by flash chromatography on silica (eluent 20% Et_2O/petrol) gave the *ketone* **318** (16.8 mg, 39%) as a bright yellow oil.

δ_H ($CDCl_3$, 400 MHz) 9.11 (1H, br. s, ArN*H*), 7.72 (1H, dd, *J* 8.0, 1.5, Ar*H*), 7.26–7.33 (6H, m, 6 × Ar*H*), 6.62–6.68 (1H, m, Ar*H*), 6.55 (1H, ddd, *J* 8.0, 7.0, 1.5, Ar*H*), 3.63 (2H, td, *J* 6.0, 1.0, NHC$H_2$$CH_2$Cl), 3.54 (2H, t, *J* 6.0, $NHCH_2$CH_2Cl), 3.21 (2H, t, *J* 6.5, C(O)C$H_2$$CH_2$Ph), 2.96 (2H, t, *J* 6.5, C(O)CH_2CH_2Ph); δ_C ($CDCl_3$, 101 MHz) 202.0, 150.5, 141.6, 135.2, 132.0, 128.6, 128.5, 126.2, 117.8, 115.0, 111.5, 44.4, 42.4, 41.2, 30.8; ν_{max} (neat)/cm^{-1} 3302, 2957, 2926, 1639, 1574, 1578, 1496, 1251, 1029, 747, 699; *m/z* (ESI^+)

288 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{17}H_{19}ClNO^+$ ([M + H]$^+$) requires 288.11497, found 288.11499.

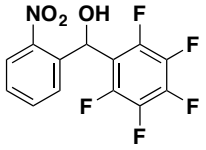
1-[2-(Bicyclo[2.2.1]heptan-2-ylamino)phenyl]-3-phenylpropan-1-one, 319



1-(2-Aminophenyl)-3-phenylpropan-1-one **309** (34 mg, 0.15 mmol), Rh(cod)$_2$OTf (70 mg, 0.015 mmol) and bicyclo[2.2.1]hept-2-ene (28 mg, 0.30 mmol) were dissolved in 1,2-dichloroethane (0.15 mL) in a sealed pressure vial under a N_2 atmosphere. The reaction was then heated to 150 °C for 24 hours and allowed to cool to room temperature. The resulting solution was filtered through a plug of silica and concentrated *in vacuo* to obtain the crude product. Purification by flash chromatography on silica (eluent 20% Et_2O/petrol) gave the *ketone* **319** (12.9 mg, 27%) as a yellow oil.

δ_H ($CDCl_3$, 400 MHz) 8.82 (1H, d, *J* 5.5, N*H*), 7.68 (1H, dd, *J* 8.0, 1.5, Ar*H*), 7.37–7.02 (6H, m, 6 × Ar*H*), 6.61 (1H, d, *J* 8.5, Ar*H*), 6.46 (1H, ddd, *J* 8.0, 7.0, 1.0, Ar*H*), 3.30–3.22 (1H, m, NC*H*CH_2), 3.19 (2H, t, *J* 6.5, C(O)C*H*$_2$$CH_2$Ph), 2.95 (2H, t, *J* 6.5, C(O)CH_2C*H*$_2$Ph), 2.29–2.20 (2H, m, 2 × C*H*$(CH_2)_2$), 1.77 (1H, ddd, *J* 13.0, 7.5, 2.5, C*H*$_A$$CH_B$), 1.53–1.41 (3H, m, 3 × C*H*$_A$$CH_B$), 1.38–1.26 (1H, m, CH_AC*H*$_B$), 1.22–1.01 (3H, m, 3 × CH_AC*H*$_B$); δ_C ($CDCl_3$, 101 MHz) 201.5, 150.3, 141.6, 134.8, 131.8, 128.5, 128.4, 126.1, 116.9, 113.7, 112.8, 55.7, 41.5, 41.0 (2C), 35.7(2), 35.6(6), 30.8, 28.6, 26.4; ν_{max} (neat)/cm^{-1} 3304, 2954, 2869, 1637, 1572, 1540, 1156, 745, 699; *m/z* (ESI$^+$) 320 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{22}H_{26}NO^+$ ([M + H]$^+$) requires 320.20089, found 320.20081.

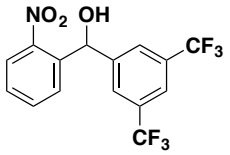
(2-Nitrophenyl)(perfluorophenyl)methanol, 320



Magnesium turnings were activated by grinding in a mortar, and then the metal (0.66 g, 27.1 mmol) was suspended in Et_2O (60 mL), and a few drops of iodine in MTBE were added. 1,2-Bromopentafluorobenzene (32.82 ml, 22.6 mmol) was added dropwise at 0 °C, and the reactivity was confirmed by disappearance of the yellow iodine colour. After stirring for 10 min at room temperature, this solution was transferred to another solution containing *o*-nitrobenzaldehyde (3.42 g, 22.6 mmol) stirring in Et_2O (40 mL) at 0 °C. The mixture was stirred at room temperature for 16 h. It was then cooled down again to 0 °C, and 4 N HCl (10 mL) was added carefully at such a rate that the temperature did not rise above 20 °C. The organic layer was extracted with Et_2O (2 × 60 mL) and washed brine (80 mL), dried over $MgSO_4$ and filtered. The solvent was evaporated *in vacuo* and the crude product was purified by flash chromatography (eluent 40% Et_2O/petrol) to give the alcohol **320** (6.45 g, 89%) as a thick brown oil.

δ_H ($CDCl_3$, 400 MHz) 8.12 (1H, d, *J* 8.0, Ar*H*), 8.07 (1H, dd, *J* 8.0, 1.0, Ar*H*), 7.76 (1H, td, *J* 7.5, 1.0, Ar*H*), 7.55 (1H, td, *J* 7.0, 1.0, Ar*H*), 6.81 (1H, s, C*H*OH), 3.61 (1H, s, CHO*H*); δ_C ($CDCl_3$, 101 MHz) 146.6, 135.9, 133.8, 129.1, 128.8, 125.1, 146.5–114.6 (m), 63.4; δ_F ($CDCl_3$, 377 MHz, ^1H decoupled) –141.5 to –141.8 (2F, m), –153.7 (1F, td, *J* 21.0, 2.0), –161.5 to –161.7 (2F, m); *m/z* (ESI^+) 342 ($[M + Na]^+$, 100%). Data in accordance with the literature.[253]

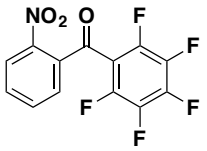
[3,5-Bis(trifluoromethyl)phenyl](2-nitrophenyl)methanol, 321



Magnesium turnings were activated by grinding in a mortar, and then the metal (0.66 g, 27.1 mmol) was suspended in Et_2O (60 mL), and a few drops of iodine in MTBE were added. 1,2-Bis(trifluoromethyl)-5-bromobenzene (3.90 ml, 22.6 mmol) was added dropwise at 0 °C, and the reactivity was confirmed by disappearance of the yellow iodine colour. After stirring for 10 min at room temperature, this solution was transferred to another solution containing *o*-nitrobenzaldehyde (3.42 g, 22.6 mmol) stirring in Et_2O (40 mL) at 0 °C. The mixture was stirred at room temperature for 16 h. It was then cooled down again to 0 °C, and 4 N HCl (10 mL) was added carefully at such a rate that the temperature did not rise above 20 °C. The organic layer was extracted with Et_2O (2 × 60 mL) and washed brine (80 mL), dried over $MgSO_4$ and filtered. The solvent was evaporated *in vacuo* and the crude product was purified by flash chromatography (eluent 40% Et_2O/petrol) to give the *alcohol* **321** (7.28 g, 88%) as a thick brown oil.

δ_H ($CDCl_3$, 400 MHz) 7.94 (1H, dd, *J* 8.0, 1.0, Ar*H*), 7.78 (2H, s, 2 × Ar*H*), 7.74 (1H, s, Ar*H*), 7.61 (1H, td, *J* 8.0, 1.0, Ar*H*), 7.51 (1H, dd, *J* 8.0, 1.0, Ar*H*, 7.49–7.41 (1H, m, Ar*H*), 6.42 (1H, app. s, C*H*OH), 3.22 (1H, s, CHO*H*); δ_C ($CDCl_3$, 101 MHz) 148.2, 144.0, 137.1, 134.2, 131.8 (q, $^2J_{CF}$ 33.5), 129.7, 129.5, 127.10, 125.1, 123.2 (q, $^1J_{CF}$ 272.5), 121.9 (q, $^3J_{CF}$ 7.5), 70.3; δ_F ($CDCl_3$, 377 MHz, ^{1}H decoupled) –62.9; ν_{max} (neat)/cm^{-1} 3382, 2980, 1526, 1275, 1126, 856; HRMS (FI$^+$) $C_{15}H_9O_3F_6^+$ ([M]$^+$) requires 365.0487, found 365.0496.

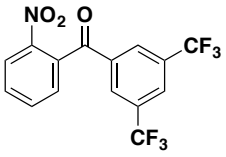
(2-Nitrophenyl)(perfluorophenyl)methanone, 322



To a solution of (2-nitrophenyl)(perfluorophenyl)methanol **320** (6.45 g, 20.2 mmol) in CH_2Cl_2 (100 mL) was added MnO_2 (15.0 g, 172 mmol). The solution was stirred at room temperature for 24 h. The reaction mixture was filtered through Celite®, and the solvent was removed under reduced pressure to give ketone **322** (6.44 g, 99%) as a thick brown oil.

δ_H ($CDCl_3$, 400 MHz) 8.19 (1H, dd, *J* 8.0, 1.0, Ar*H*), 7.85 (1H, td, *J* 7.5, 1.0, Ar*H*), 7.76 (1H, td, *J* 7.5, 1.5, Ar*H*), 7.62 (1H, dd, *J* 7.5, 1.5, Ar*H*); δ_C ($CDCl_3$, 101 MHz) 184.0, 146.1, 136.2, 134.6, 132.1, 129.0, 124.6, 147.4–112.5 (m); δ_F ($CDCl_3$, 377 MHz, ^{1}H decoupled) –139.2 (2F, dt, *J* 20.0, 6.0), –146.3 to –146.5 (1F, m), –159.9 to –160.1 (2F, m); *m/z* (ESI^+) 340 ($[M + Na]^+$, 100%). Data in accordance with the literature.[253]

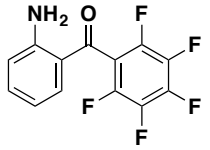
[3,5-Bis(trifluoromethyl)phenyl](2-nitrophenyl)methanone, 323



To a solution of [3,5-bis(trifluoromethyl)phenyl](2-nitrophenyl)methanol **321** (7.28 g, 20.0 mmol) in CH_2Cl_2 (100 mL) was added MnO_2 (15.0 g, 172 mmol). The solution was stirred at room temperature for 24 h. The reaction mixture was filtered through Celite®, and the solvent was removed under reduced pressure to give the *ketone* **323** (7.23g, 99%) as a thick brown oil.

δ_H ($CDCl_3$, 400 MHz) 8.21 (1H, dd, *J* 8.0, 1.0, Ar*H*), 8.07 (2H, s, 2 × Ar*H*), 8.00 (1H, s, Ar*H*), 7.79 (1H, td, *J* 7.5, 1.0, Ar*H*), 7.70 (1H, ddd, *J* 8.0, 7.5, 1.5, Ar*H*), 7.42 (1H, dd, *J* 7.5, 1.5, Ar*H*); δ_C ($CDCl_3$, 101 MHz) 190.7, 146.4, 137.8, 134.8, 134.3, 132.6 (q, $^2J_{CF}$ 34.0), 131.6, 128.8, 128.6, 126.9 (q, $^3J_{CF}$ 7.5), 125.0, 122.7 (q, $^1J_{CF}$ 273.0); δ_F ($CDCl_3$, 377 MHz, ^{1}H decoupled) –62.9; ν_{max} (neat)/cm^{-1} 2980, 1690, 1529, 1275, 1176, 680; *m/z* (ESI$^+$) 386 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{15}H_7O_3NF_6Na^+$ ([M + Na]$^+$) requires 386.02223, found 386.02208.

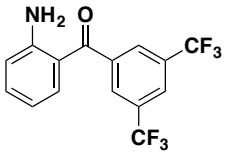
(2-Nitrophenyl)(perfluorophenyl)methanone, 324



(2-Nitrophenyl)(perfluorophenyl)methanone **322** (4.56 g, 14.4 mmol) and palladium on carbon (5% wt. loading, 0.9 g) were dissolved in EtOAc (70 mL). H_2 gas was bubbled through the solution for 1 h and then the solution was stirred in a H_2 atmosphere at room temperature for 16 h. The mixture was then filtered through Celite® and the solution was concentrated *in vacuo*. The crude material was purified by flash chromatography (eluent 30% Et_2O/petrol) to give the ketone **324** (3.68 g, 89%) as a yellow crystalline solid.

δ_H ($CDCl_3$, 400 MHz) 7.38 (1H, ddd, *J* 8.5, 7.0, 1.5, Ar*H*), 7.22 (1H, dd, *J* 8.0, 1.5, Ar*H*), 6.82–6.69 (1H, m, Ar*H*), 6.64 (1H, ddd, *J* 8.0, 7.0, 1.0, Ar*H*), 6.51 (2H, s, NH_2); δ_C ($CDCl_3$, 101 MHz) 186.0, 151.7, 136.4, 133.4, 117.3, 117.2, 116.4, 145.1–114.0 (m); δ_F ($CDCl_3$, 377 MHz, ^{1}H decoupled) –140.6 to –140.9 (2F, m), –152.1 (1F, t, *J* 21.0), –159.96 to –160.4 (2F, m); mp: 90–92 °C (CH_2Cl_2); *m/z* (ESI$^+$) 288 ([M + H]$^+$, 100%). Data in accordance with the literature.[253]

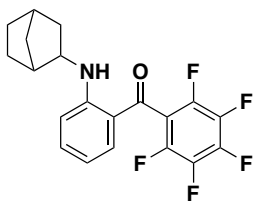
(2-Aminophenyl)[3,5-bis(trifluoromethyl)phenyl]methanone, 325



[3,5-Bis(trifluoromethyl)phenyl](2-nitrophenyl)methanone **323** (5.97 g, 16.4 mmol) and palladium on carbon (5% wt. loading, 0.9 g) were dissolved in EtOAc (70 mL). H_2 gas was bubbled though the solution for 1 h and then the solution was stirred in a H_2 atmosphere at room temperature for 16 h. The mixture was then filtered through Celite® and the solution was concentrated *in vacuo*. The crude material was purified by flash chromatography (eluent 30% Et_2O/petrol) to give the *ketone* **325** (4.80 g, 88%) as a yellow crystalline solid.

δ_H ($CDCl_3$, 400 MHz) 7.95 (2H, s, 2 × Ar*H*), 7.91 (1H, s, Ar*H*), 7.31–7.05 (2H, m, 2 × Ar*H*), 6.73–6.54 (1H, m, Ar*H*), 6.50 (1H, ddd, *J* 8.0, 7.0, 1.0, Ar*H*), 6.16 (2H, s, NH_2); δ_C ($CDCl_3$, 101 MHz) 195.4, 151.6, 142.0, 135.4, 133.8, 131.7 (q, $^2J_{CF}$ 33.5), 124.3 (q, $^3J_{CF}$ 7.0) 129.0, 120.3 (q, $^1J_{CF}$ 273.0) 117.4, 116.5, 115.9; δ_F ($CDCl_3$, 377 MHz, ^{1}H decoupled) –62.9; mp: 45–47 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 3472, 3357, 2980, 1636, 1615, 1321, 1029, 845; *m/z* (ESI$^+$) 334 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{15}H_{10}ONF_6Na^+$ ([M + H]$^+$) requires 334.06611, found 334.06603.

[2-(Bicyclo[2.2.1]heptan-2-ylamino)phenyl](perfluorophenyl)methanone, 326

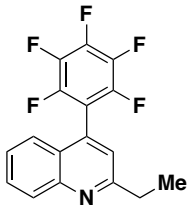


$Rh(cod)_2OTf$ (7.0 mg, 0.015 mmol), 2-(bicyclo[2.2.1]hept-2-ene (17 mg, 0.18 mmol) and (2-nitrophenyl)(perfluorophenyl)methanone **324** (43 mg, 0.15 mmol) were dissolved in 2-

butanone (0.15 mL) in a sealed pressure vial under a N_2 atmosphere. The reaction was then heated to 150 °C for 24 h and allowed to cool to room temperature. The resulting solution was filtered through a plug of silica and concentrated *in vacuo* to obtain the crude product. Purification by flash chromatography on silica (eluent 50% Et_2O/petrol) gave the *ketone* **326** (15 mg, 27%) as a yellow oil.

δ_H ($CDCl_3$, 400 MHz) 8.78 (1H, d, *J* 5.5, N*H*), 7.51–7.24 (1H, m, Ar*H*), 7.21–7.01 (1H, m, Ar*H*), 6.68 (1H, d, *J* 8.5, Ar*H*), 6.57–6.29 (1H, m, Ar*H*), 3.34 (1H, app. q, *J* 7.5, 7.0, C*H*NH), 2.49–2.16 (2H, m, 2 × C*H*), 1.82 (1H, ddd, *J* 12.5, 7.5, 2.0, 0.5 × CH_2), 1.60–1.41 (3H, m, 1.5 × CH_2), 1.42–1.32 (1H, m, 0.5 × CH_2), 1.28–1.08 (3H, m, 1.5 × CH_2); δ_C ($CDCl_3$, 101 MHz) 185.3, 151.4, 136.7, 134.3, 116.6, 114.5, 112.9, 146.8–111.1 (m), 55.9, 41.6, 41.0, 35.8, 35.7, 28.5, 26.4; δ_F ($CDCl_3$, 377 MHz, ^{1}H decoupled) –140.6 to –141.0 (2F, m), –152.6 (1F, t, *J* 21.0), –160.1 to –160.7 (2F, m); ν_{max} (neat)/cm^{-1} 3656, 3318, 2957, 1621, 1576, 1493, 1245, 989, 746, 667; *m/z* (ESI$^+$) 382 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{20}H_{17}NOF_5^+$ ([M + H]$^+$) requires 382.12248, found 382.12224.

2-Ethyl-4-(perfluorophenyl)quinoline, 327

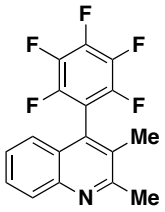


$Rh(PPh_3)_3Cl$ (13.9 mg, 0.015 mmol) and (2-nitrophenyl)(perfluorophenyl)methanone **324** (43 mg, 0.15 mmol) were dissolved in 2-butanone (0.15 mL) in a sealed pressure vial under a N_2 atmosphere. The reaction was then heated to 150 °C for 24 h and allowed to cool to room temperature. The resulting solution was filtered through a plug of silica and

concentrated *in vacuo* to obtain the crude product. Purification by flash chromatography on silica (eluent 50% Et_2O/petrol) gave the *quinoline* **327** (6.1 mg, 13%) as a yellow oil.

δ_H ($CDCl_3$, 400 MHz) 8.07 (1H, d, *J* 8.5, Ar*H*), 7.67 (1H, ddd, *J* 8.5, 6.5, 1.5, Ar*H*), 7.34–7.46 (2H, m, 2 × Ar*H*), 7.21 (1H, s, Ar*H*), 2.99 (2H, q, *J* 7.5, ArCH_2CH_3), 1.36 (3H, t, *J* 7.5, ArCH_2CH_3); δ_C ($CDCl_3$, 101 MHz) 163.4, 148.2, 133.1, 129.9, 129.6, 126.7, 124.8, 124.2, 123.1, 146.8–110.4 (m), 32.2, 13.8; δ_F ($CDCl_3$, 377 MHz, ^{1}H decoupled) –138.7 to –139.2 (2F, m), –152.8 (1F, t, *J* 21.0), –160.5 to –161.3 (2F, m); ν_{max} (neat)/cm^{-1} 2979, 1493, 1439, 1006, 755; *m/z* (ESI^+) 324 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{17}H_{11}NF_5^+$ ($[M + H]^+$) requires 324.08062, found 324.08053.

2,3-Dimethyl-4-(perfluorophenyl)quinoline, 328

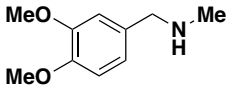


$Rh(PPh_3)_3Cl$ (13.9 mg, 0.015 mmol) and (2-nitrophenyl)(perfluorophenyl)methanone **324** (43 mg, 0.15 mmol) were dissolved in 2-butanone (0.15 mL) in a sealed pressure vial under a N_2 atmosphere. The reaction was then heated to 150 °C for 24 h and allowed to cool to room temperature. The resulting solution was filtered through a plug of silica and concentrated *in vacuo* to obtain the crude product. Purification by flash chromatography on silica (eluent 50% Et_2O/petrol) gave the *quinoline* **328** (32 mg, 65%) as a yellow oil.

δ_H ($CDCl_3$, 400 MHz) 8.09–7.92 (1H, m, Ar*H*), 7.56 (1H, ddd, *J* 8.5, 7.0, 1.5, Ar*H*), 7.33 (1H, ddd, *J* 8.0, 7.0, 1.0, Ar*H*), 7.23–7.05 (1H, m, Ar*H*), 2.69 (3H, s, ArCH_3), 2.14 (3H, s,

ArCH_3); δ_C ($CDCl_3$, 101 MHz) 158.9, 146.2, 130.7, 130.0, 129.1, 128.9, 126.7, 125.6, 124.0, 145.8–110.8 (m), 24.5, 17.0; δ_F ($CDCl_3$, 377 MHz, ^{1}H decoupled) –136.6 to –140.3 (2F, m), –152.8 (1F, t, *J* 17.5), –160.5 to –161.0 (2F, m); ν_{max} (neat)/cm^{-1} 2980, 1521, 1493, 1118, 986, 935, 728, 672; *m/z* (ESI$^+$) 324 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{17}H_{11}NF_5^+$ ([M + H]$^+$) requires 324.08062, found 324.07994.

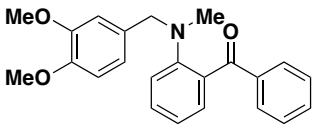
1-(3,4-Dimethoxyphenyl)-*N*-methylmethanamine



To a stirring solution of veratraldehyde (20.0 g, 120 mmol) in methanol (200 mL) was added methyl amine (40% aq, 11.7 mL, 150 mmol) in one portion. The reaction mixture was then stirred at room temperature for 15 min, after which it was cooled down to 0 °C and $NaBH_4$ (2.27 g, 60.0 mmol) was added portionwise. The resulting solution was left to stir at room temperature for 1 h. The reaction was then quenched by careful addition of water (100 mL) and the methanol was removed under reduced pressure. The organic product was then extracted with CH_2Cl_2 (3 × 100 mL), and the combined organic layers were dried over $MgSO_4$. The solvent was removed *in vacuo* to afford the amine (20.0 g, 92%) as a colourless oil, which was used in the next step without further purification.

δ_H ($CDCl_3$, 400 MHz) 6.80 (1H, s, Ar*H*), 6.76-6.71 (2H, m, 2 × Ar*H*), 3.79 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 3.59 (2H, s, NCH_2Ar), 2.36 (3H, s, NCH_3), 1.37 (1H, br. s, N*H*); δ_C ($CDCl_3$, 101 MHz) 148.6, 147.6, 132.5, 119.9, 111.0, 110.6, 55.6, 55.5, 55.4, 35.7; *m/z* (ESI$^+$) 182 ([M + H]$^+$, 100%). Data in accordance with the literature.[86]

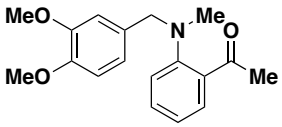
General procedure K for the preparation of anilines, as exemplified by the synthesis of {2-[(3,4-Dimethoxybenzyl)(methyl)amino]phenyl}(phenyl)methanone, 331



Potassium carbonate (1.91 g, 13.8 mmol) and 1-(3,4-dimethoxyphenyl)-*N*-methylmethanamine (2.06 g, 13.8 mmol) were added to a solution of (2-fluorophenyl)(phenyl)methanone (2.0 mL, 12 mmol) in DMF (10 mL) in a sealed pressure tube. The solution was heated to 150 °C under N_2 for 4 h. The reaction was cooled down to room temperature and poured into flask of water (50 mL). The product was extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with 1 N HCl (2 × 50 mL), brine (50 mL), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo*, and purification by flash chromatography (eluent 30% Et_2O/petrol) afforded the *ketone* **331** (3.12 g, 79%) as a yellow oil.

δ_H ($CDCl_3$, 400 MHz) 7.90–7.83 (2H, m, 2 × Ar*H*), 7.58 (1H, td, *J* 7.5, 1.5, Ar*H*), 7.49–7.41 (3H, m, 3 × Ar*H*), 7.36 (1H, dd, *J* 7.5, 1.5, Ar*H*), 7.14 (1H, d, *J* 7.5, Ar*H*), 7.06 (1H, td, *J* 7.5, 1.0, Ar*H*), 6.71 (1H, d, *J* 7.0, Ar*H*), 6.54 (2H, m, 2 × Ar*H*), 4.08 (2H, s, NCH_2Ar), 3.85 (3H, s, OCH_3), 3.67 (3H, s, OCH_3), 2.57 (3H, s, NCH_3); δ_C ($CDCl_3$, 101 MHz) 198.3, 151.5, 148.9, 148.0, 137.7, 132.9, 132.2, 131.2, 130.5, 130.0, 129.8, 128.3, 121.0, 120.2, 119.0, 111.0, 110.6, 60.2, 55.8(4), 55.7(5), 40.8; ν_{max} (neat)/cm^{-1} 2834, 1656, 1594, 1574, 1259, 1027, 711; HRMS (FI^+) $C_{23}H_{23}O_3N^+$ ($[M]^+$) requires 361.1678, found 361.1678.

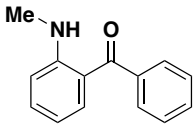
1-{2-[(3,4-Dimethoxybenzyl)(methyl)amino]phenyl}ethan-1-one, 332



Prepared according to general procedure **K** using potassium carbonate (1.91 g, 13.8 mmol), 1-(3,4-dimethoxyphenyl)-*N*-methylmethanamine (2.06 g, 13.8 mmol), 2-fluoroacetophenone (1.5 mL, 12 mmol) in DMF (10 mL). The solution was heated to 150 °C under N_2 for 4 h and purified by flash chromatography (eluent 30% Et_2O/petrol) afforded the *ketone* **332** (1.75 g, 56%) as a yellow oil.

δ_H ($CDCl_3$, 400 MHz) 7.47 (1H, dd, *J* 7.5, 1.5, Ar*H*), 7.36 (1H, ddd, *J* 8.5, 7.5, 1.5, Ar*H*), 7.00 (2H, t, *J* 7.5, 2 × Ar*H*), 6.83–6.74 (2H, m, 2 × Ar*H*), 6.69 (1H, d, *J* 2.0, Ar*H*), 4.15 (2H, s, NCH_2Ar), 3.87 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 2.69 (3H, s, NCH_3), 2.67 (3H, s, C(O)CH_3); δ_C ($CDCl_3$, 101 MHz) 203.8, 151.3, 148.9, 148.2, 134.0, 131.7, 129.8, 129.4, 121.2, 120.7, 119.3, 111.4, 110.8, 60.7, 55.8, 55.7, 41.5, 29.3; ν_{max} (neat)/cm^{-1} 2935, 1675, 1592, 1514, 1260, 1237, 1027, 763; HRMS (FI^+) $C_{18}H_{21}O_3N^+$ ($[M]^+$) requires 299.1521, found 299.1531.

[2-(Methylamino)phenyl](phenyl)methanone, 333

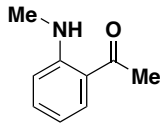


{2-[(3,4-Dimethoxybenzyl)(methyl)amino]phenyl}(phenyl)methanone **331** (49 mg, 0.15 mmol), $Rh(PPh_3)_3Cl$ (13.9 mg, 0.015 mmol) and 1-octene (28 μL, 0.18 mmol) were dissolved in toluene (0.15 mL) in a sealed pressure vial under a N_2 atmosphere. The reaction was then heated to 150 °C for 24 h and allowed to cool to room temperature. The resulting

solution was filtered through a plug of silica and concentrated *in vacuo* to obtain the crude product. Purification by flash chromatography on silica (eluent 40% Et_2O/petrol) gave the ketone **333** (19.6 mg, 62%) as a bright yellow oil.

δ_H ($CDCl_3$, 400 MHz) 8.47 (1H, br. s, N*H*), 7.56–7.49 (2H, m, 2 × Ar*H*), 7.47–7.30 (5H, m, 5 × Ar*H*), 6.69 (1H, d, *J* 8.5, Ar*H*), 6.46 (1H, ddd, *J* 8.0, 7.0, 1.0, Ar*H*), 2.89 (3H, d, *J* 5.0, NCH_3); δ_C ($CDCl_3$, 101 MHz) 199.4, 152.7, 140.6, 135.5, 135.1, 130.7, 129.0, 128.0, 117.2, 113.6, 111.1, 29.5; *m/z* (ESI^+) 212 ($[M + H]^+$, 100%). Data in accordance with literature.[305]

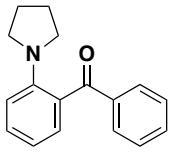
1-[2-(Methylamino)phenyl]ethan-1-one, 334



1-{2-[(3,4-Dimethoxybenzyl)(methyl)amino]phenyl}ethan-1-one **332** (40 mg, 0.15 mmol), $Rh(PPh_3)_3Cl$ (139 mg, 0.015 mmol) and 1-octene (28 μL, 0.18 mmol) were dissolved in toluene (0.15 mL) in a sealed pressure vial under a N_2 atmosphere. The reaction was then heated to 150 °C for 24 h and allowed to cool to room temperature. The resulting solution was filtered through a plug of silica and concentrated *in vacuo* to obtain the crude product. Purification by flash chromatography on silica (eluent 30% Et_2O/petrol) gave the ketone **334** (12.3 mg, 55%) as a bright yellow oil.

δ_H ($CDCl_3$, 400 MHz) 8.71 (1H, br. s, N*H*), 7.67 (1H, dd, *J* 8.0, 1.5, Ar*H*), 7.31 (1H, ddd, *J* 8.5, 7.0, 1.5, Ar*H*), 6.76–6.58 (1H, m, Ar*H*), 6.52 (1H, ddd, *J* 8.0, 7.0, 1.0, Ar*H*), 2.84 (3H, d, *J* 5.0, NCH_3), 2.51 (3H, s, C(O)CH_3); δ_C ($CDCl_3$, 101 MHz) 200.8, 151.9, 135.1, 132.7, 117.5, 113.8, 111.2, 29.3, 27.9; *m/z* (ESI^+) 150 ($[M + H]^+$, 100%). Data in accordance with the literature.[306]

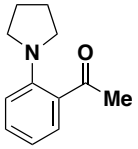
Phenyl[2-(pyrrolidin-1-yl)phenyl]methanone, 335



Prepared according to general procedure **K** using potassium carbonate (1.91 g, 13.8 mmol), 2-fluorobenzophenone (2.0 mL, 12 mmol), pyrrolidine (1.15 mL, 13.8 mmol) in DMF (10 mL). The solution was heated to 85 °C under N_2 for 4 h and purified by flash chromatography (eluent 20% Et_2O/petrol) afforded the ketone **335** (2.29 g, 76%) as a yellow oil.

δ_H ($CDCl_3$, 400 MHz) 8.03–7.97 (2H, m, 2 × Ar*H*), 7.62–7.53 (1H, m, Ar*H*), 7.53–7.42 (2H, m, 2 × Ar*H*), 7.42–7.34 (1H, m, Ar*H*), 7.30 (1H, dd, *J* 7.5, 1.5, Ar*H*), 6.90–6.86 (1H, m, Ar*H*), 6.76–6.69 (1H, m, Ar*H*), 3.17 (4H, t, *J* 6.5, 2 × NC$H_2$$CH_2$), 1.91 (4H, t, *J* 6.5, 2 × NC$H_2$$CH_2$); δ_C ($CDCl_3$, 101 MHz) 196.7, 148.0, 138.5, 132.7, 131.5, 130.5, 128.3, 128.2, 124.1, 114.7, 114.0, 51.3, 25.9; ν_{max} (neat)/cm^{-1} 2867, 1648, 1595, 1479, 1444, 1236, 913, 700. Data in accordance with the literature.[307]

1-[2-(Pyrrolidin-1-yl)phenyl]ethan-1-one, 336

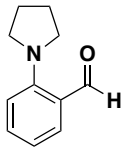


Prepared according to general procedure **K** using potassium carbonate (1.91 g, 13.8 mmol), 2-fluoroacetophenone (1.5 mL, 12 mmol), pyrrolidine (1.15 mL, 13.8 mmol) in DMF (10 mL). The solution was heated to 150 °C under N_2 for 4 h and purified by flash chromatography (eluent 30% Et_2O/petrol) afforded the ketone **336** (1.30 g, 57%) as a yellow

oil.

δ_H ($CDCl_3$, 400 MHz) 7.52 (1H, dd, *J* 7.5, 1.5, Ar*H*), 7.33 (1H, ddd, *J* 8.5, 7.0, 1.5, Ar*H*), 6.87–6.81 (1H, m, Ar*H*), 6.79–6.71 (1H, m, Ar*H*), 3.14 (4H, dd, *J* 6.5, 4.0, 2 × NC$H_2$$CH_2$), 2.61 (3H, s, C(O)C$H_3$), 1.96 (4H, dd, *J* 6.5, 4.0, 2 × NC$H_2$$CH_2$); δ_C ($CDCl_3$, 101 MHz) 201.1, 147.5, 131.8, 129.5, 126.8, 115.6, 114.3, 51.7, 29.2, 25.9; *m/z* (ESI^+) 190 ($[M + H]^+$, 100%). Data in accordance with the literature.[308]

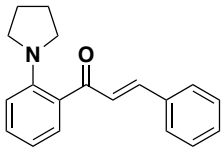
2-(Pyrrolidin-1-yl)benzaldehyde, 337



Prepared according to general procedure **K** using potassium carbonate (2.8 g, 20 mmol), 2-fluorobenzaldehyde (1.4 mL, 16 mmol), pyrrolidine (1.7 mL, 20 mmol) in DMF (12 mL). The solution was heated to 85 °C under N_2 for 48 h and purified by flash chromatography (eluent 10% Et_2O/petrol) afforded the aldehyde **337** (1.93 g, 68%) as an orange oil.

δ_H ($CDCl_3$, 400 MHz) 9.95 (1H, s, C*H*O), 7.57 (1H, dd, *J* 8.0, 2.0, Ar*H*), 7.24 (1H, ddd, *J* 8.5, 7.0, 2.0, Ar*H*), 6.74–6.62 (2H, m, 2 × Ar*H*), 3.21 (4H, t, *J* 6.5, 2 × NC$H_2$$CH_2$), 1.84 (4H, t, *J* 6.5, 2 × $NCH_2C$$H_2$); δ_C ($CDCl_3$, 101 MHz) 189.3, 149.8, 134.0, 132.8, 122.8, 116.2, 114.4, 52.5, 25.8; ν_{max} (neat)/cm^{-1} 2970, 2571, 1676, 1599, 1478; *m/z* (ESI^+) 176 ($[M + H]^+$, 100%). Data in accordance with the literature.[86]

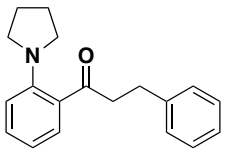
(*E*)-3-Phenyl-1-[2-(pyrrolidin-1-yl)phenyl]prop-2-en-1-one, 338



$Rh(nbd)_2BF_4$ (0.12 g, 0.33 mmol) and dcpm (0.13 g, 0.33 mmol) were dissolved in acetone (20 mL). H_2 was bubbled through the red solution for 5 min at room temperature, until a pale yellow colour was observed. Following this, the solution was purged with N_2 for 2 min. The resulting catalyst solution was added to a flask containing 2-(pyrrolidin-1-yl)benzaldehyde **337** (2.87 g, 16.3 mmol) and phenylacetylene (2.2 mL, 20 mmol) under nitrogen. The reaction was then heated to 55 °C for 16 hours and allowed to cool to room temperature. The resulting solution was filtered through a plug of silica and concentrated *in vacuo* to obtain the crude product. Purification by flash chromatography on silica chromatography (eluent 30% Et_2O/petrol) gave the enone **338** (4.07 g, 90%) as a dark orange oil.

δ_H ($CDCl_3$, 400 MHz) 7.55 (1H, d, *J* 16.0, C(O)CHC*H*Ph), 7.49 (2H, dd, *J* 6.5, 3.0, 2 × Ar*H*), 7.40 (1H, dd, *J* 7.5, 1.5, Ar*H*), 7.35–7.23 (4H, m, 4 × Ar*H*), 7.13 (1H, d, *J* 16.0, C(O)C*H*CHPh), 6.76 (1H, dd, *J* 8.5, 0.9, Ar*H*), 6.68 (1H, td, *J* 7.5, 1.0, Ar*H*), 3.10 (4H, t, *J* 6.5, 2 × NCH_2CH_2), 1.83 (4H, t, *J* 6.5, 2 × NCH_2CH_2); δ_C ($CDCl_3$, 101 MHz) 194.9, 147.9, 144.2, 135.0, 131.7, 130.4, 130.3, 129.0, 128.4, 127.1, 126.0, 115.7, 114.2, 51.6, 26.0; ν_{max} (neat)/cm^{-1} 2969, 2869, 1656, 1445, 740; *m/z* (ESI^+) 278 ($[M + H]^+$, 100%); Data in accordance with the literature.[86]

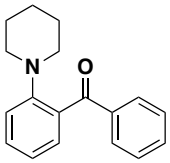
3-Phenyl-1-[2-(pyrrolidin-1-yl)phenyl]propan-1-one, 339



(*E*)-3-Phenyl-1-(2-(pyrrolidin-1-yl)phenyl)prop-2-en-1-one **338** (4.06 g, 14.7 mmol) and palladium on carbon (5% wt. loading, 0.4 g) were dissolved in EtOAc (70 mL). H_2 gas was bubbled through the solution for 1 h and then the solution was stirred in a H_2 atmosphere at room temperature for 16 h. The mixture was then filtered through Celite® and the solution was concentrated *in vacuo*. The crude material was purified by flash chromatography (eluent 30% Et_2O/petrol) to give the *ketone* **339** (3.18 g, 77%) as an off-white solid.

δ_H ($CDCl_3$, 400 MHz) 7.47 (1H, dd, *J* 8.0, 1.5, Ar*H*), 7.29–7.39 (5H, m, 5 × Ar*H*), 7.25 (1H, td, *J* 6.0, 2.5, Ar*H*), 6.85 (1H, d, *J* 8.5, Ar*H*), 6.73–6.81 (1H, t, *J* 8.5, Ar*H*), 3.34 (2H, t, *J* 7.5, C(O)CH_2CH$_2$Ph), 3.13 (2H, t, *J* 7.5, C(O)CH$_2$CH_2Ph), 3.06 (4H, t, *J* 6.5, 2 × NCH_2CH$_2$), 1.93 (4H, t, *J* 6.5, 2 × NCH$_2$CH_2); δ_C ($CDCl_3$, 101 MHz) 202.7, 147.4, 141.4, 131.7, 129.2, 128.6, 128.5, 126.7, 126.1, 115.7, 114.4, 51.7, 43.1, 31.1, 25.9; mp: 58–60 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 3025, 2868, 1665, 1358, 1166, 972, 742, 698; *m/z* (ESI$^+$) 280 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{19}H_{22}ON^+$ ([M + H]$^+$) requires 280.16959, found 280.16948.

Phenyl[2-(piperidin-1-yl)phenyl]methanone, 340

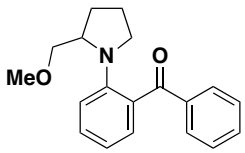


Prepared according to general procedure **K** using potassium carbonate (1.91 g, 13.8 mmol),

2-fluorobenzophenone (2.0 mL, 12 mmol), piperidine (1.36 mL, 13.8 mmol) in DMF (10 mL). The solution was heated to 150 °C under N_2 for 4 h and purified by flash chromatography (eluent 20% Et_2O/petrol) afforded the ketone **340** (2.15 g, 68%) as a pale yellow crystalline solid.

δ_H ($CDCl_3$, 400 MHz) 7.68 (2H, dd, *J* 7.0, 1.5, 2 × Ar*H*), 7.41–7.47 (1H, m, Ar*H*), 7.27–7.39 (4H, m, 4 × Ar*H*), 6.94–7.02 (2H, m, 2 × Ar*H*), 2.75 (4H, t, *J* 5.5, 2 × NC*H*$_2$CH$_2$(CH$_2$)), 1.15–1.24 (2H, m, NCH$_2$CH$_2$(C*H*$_2$)), 1.06 (4H, app. p, *J* 5.5, 2 × NCH$_2$C*H*$_2$(CH$_2$)); δ_C ($CDCl_3$, 101 MHz) 199.1, 152.6, 137.6, 133.3, 132.6, 131.7, 130.3, 123.0, 127.9, 121.9, 118.8, 53.6, 25.7, 23.9; mp: 93–95 °C (CH_2Cl_2); *m/z* (ESI$^+$) 266 ([M + H]$^+$, 100%). Data in accordance with the literature.[309]

{2-[2-(Methoxymethyl)pyrrolidin-1-yl]phenyl}(phenyl)methanone, 341

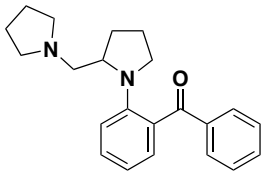


Prepared according to general procedure **K** using potassium carbonate (1.2 g, 8.5 mmol), 2-fluorobenzophenone (1.5 mL, 8.9 mmol), 2-(methoxymethyl)pyrrolidine (1.0 mL, 8.1 mmol) in DMF (7 mL). The solution was heated to 85 °C under N_2 for 16 h and purified by flash chromatography (eluent 20% Et_2O/petrol) afforded the *ketone* **341** (1.51 g, 63%) as a yellow oil.

δ_H ($CDCl_3$, 400 MHz) 7.93–7.86 (2H, m, 2 × Ar*H*), 7.60–7.53 (1H, m, Ar*H*), 7.49–7.42 (2H, m, 2 × Ar*H*), 7.39 (1H, ddd, *J* 8.5, 7.0, 1.5, Ar*H*), 7.33 (1H, dd, *J* 7.5, 1.5, Ar*H*), 7.05 (1H, d, *J* 8.5, Ar*H*), 6.85–6.79 (1H, m, Ar*H*), 4.00 (1H, app. tq, *J* 7.0, 3.5, NC*H*CH$_2$), 3.61 (1H,

dd, *J* 9.5, 3.5, NCHCH_ACH$_B$OCH$_3$), 3.35 (3H, s, OCH_3), 3.23–3.13 (2H, m, NCHCH_ACH$_B$OCH$_3$, NCH_ACH$_B$), 2.87 (1H, dd, *J* 10.5, 5.5, NCH$_A$CH_B), 2.18–2.08 (1H, m, NCHRCH$_2$CH_ACH$_B$), 1.83–1.58 (3H, m, NCHRCH_2CH$_2$, NCHRCH$_2$CH$_A$CH_B); δ_C ($CDCl_3$, 101 MHz) 197.7, 147.5, 138.0, 132.7, 131.3, 131.2, 130.1, 128.2, 126.8, 116.8, 114.8, 74.1, 59.2, 58.1, 54.0, 30.1, 24.8; ν_{max} (neat)/cm^{-1} 3059, 2980, 2869, 1650, 1579, 1482, 1356, 1240, 957, 748, 699; *m/z* (ESI$^+$) 296 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{19}H_{22}O_2N^+$ ([M + H]$^+$) requires 296.16451, found 296.16490.

Phenyl{2-[2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]phenyl}methanone, 342

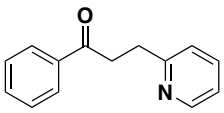


Prepared according to general procedure **K** using potassium carbonate (0.55 g, 4.0 mmol), 2-fluorobenzophenone (0.68 mL, 4.0 mmol), 1-(2-pyrrolidinylmethyl)pyrrolidine (0.6 mL, 3.7 mmol) in DMF (5 mL). The solution was heated to 85 °C under N_2 for 16 h and purified by flash chromatography (eluent 20% Et_2O/petrol) afforded the *ketone* **342** (0.93 g, 76%) as a yellow oil.

δ_H ($CDCl_3$, 400 MHz) 7.92–7.86 (2H, m, 2 × Ar*H*), 7.59–7.52 (1H, m, Ar*H*), 7.48–7.41 (2H, m, 2 × Ar*H*), 7.38 (1H, ddd, *J* 8.5, 7.0, 1.5, Ar*H*), 7.33 (1H, dd, *J* 7.5, 1.5, Ar*H*), 7.01 (1H, d, *J* 8.5, Ar*H*), 6.82–6.74 (1H, m, Ar*H*), 3.96 (1H, dtd, *J* 9.5, 6.5, 3.0, NC*H*CH$_2$), 3.16 (1H, td, *J* 9.5, 6.0, NCH_ACH$_B$CH$_2$), 2.88–2.79 (2H, m, NCH$_A$CH_BCH$_2$, NCHCH_ACH$_B$N), 2.61–2.53 (4H, m, 2 × NCH_2CH$_2$), 2.33 (1H, dd, *J* 12.0, 9.5, NCHCH_ACH$_B$N), 2.26–2.15 (1H, m, NCHRCH$_2$CH_ACH$_B$), 1.85–1.59 (7H, m, 2 × NCH$_2$CH_2, NCHRCH_2CH$_2$,

NCHRCH$_2$CH$_A$C*H*$_B$); δ_C ($CDCl_3$, 101 MHz) 197.5, 147.5, 138.1, 132.6, 131.4, 131.3, 130.1, 128.2, 126.6, 116.3, 114.7, 59.2, 58.4, 54.8, 54.0, 31.7, 25.0, 23.5; ν_{max} (neat)/cm^{-1} 2980, 2957, 2871, 1650, 1594, 1481, 1445, 1264, 967, 733; *m/z* (ESI$^+$) 335 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{22}H_{27}ON_2^+$ ([M + H]$^+$) requires 335.21179, found 335.21144.

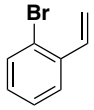
1-Phenyl-3-(pyridin-2-yl)propan-1-one, 343



To a flask containing a stirrer bar was added acetophenone (2.3 mL, 20 mmol) and 2-picolylamine (2.5 mL, 24 mmol) and $Cu(OTf)_2$ (0.72 g, 2.0 mmol) and reaction was stirred neat at 80 °C for 12 h. The reaction mixture was loaded directly onto a silica column and purified by column chromatography (eluent 20% Et_2O/petrol) yielded ketone **343** (0.50 g, 12%) as brown solid.

δ_H ($CDCl_3$, 400 MHz) 8.41–8.33 (1H, m, Ar*H*), 7.85 (2H, dt, *J* 8.5, 1.5, 2 × Ar*H*), 7.47–7.35 (2H, m 2 × Ar*H*), 7.33–7.24 (2H, m, 2 × Ar*H*), 7.10 (1H, d, *J* 7.5, Ar*H*), 6.94 (1H, ddd, *J* 7.5, 5.0, 1.0, Ar*H*), 3.37 (2H, t, *J* 7.5, C(O)C*H*$_2$CH$_2$Ar), 3.10 (2H, t, *J* 7.5, C(O)CH$_2$C*H*$_2$Ar); δ_C ($CDCl_3$, 101 MHz) 199.1, 160.6, 149.2, 136.8, 136.3, 133.0, 128.5, 128.0, 123.3, 121.2, 37.7, 32.0; mp: 120–122 °C (CH_2Cl_2); *m/z* (ESI$^+$) 212 ([M + Na]$^+$, 100%). Data in accordance with the literature.[255]

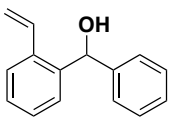
1-Bromo-2-vinylbenzene, 344



To a stirred solution of methyltriphenylphosphonium bromide (11.0 g, 30.0 mmol) in THF (100 mL) was added *n*-BuLi (2.5 M in hexanes, 12 mL, 30 mmol) dropwise at –78 °C, and the mixture was stirred at room temperature for 1 h. It was then cooled down to –78 °C again, and 2-bromobenzaldehyde (2.9 mL, 25 mmol) was added slowly. After 3 h stirring at room temperature, the reaction was quenched with careful addition of water (75 mL). The organic layer was then extracted with petrol (3 × 75 mL) and the combined organic phases were washed with brine (75 mL), dried over $MgSO_4$ and filtered to give the alkene **344** (4.55 g, 98%) as a colourless oil. This was used in the next step without further purification.

δ_H ($CDCl_3$, 400 MHz) 7.42 (2H, dd, *J* 8.5,1.5, 2 × Ar*H*), 7.14 (1H, td, *J* 7.0, 1.5, Ar*H*), 6.90–7.00 (2H, m, Ar*H*, ArC*H*=CH_2), 5.57 (1H, dd, *J* 17.5, 1.0, ArCH=C$H_A$$H_B$ (*E*)), 5.23 (1H, dd, *J* 11.0, 1.0, ArCH=C$H_A$$H_B$ (*Z*)); δ_C ($CDCl_3$, 101 MHz) 137.5, 135.9, 132.9, 129.2, 127.6, 126.9, 123.7, 116.8; ν_{max} (neat)/cm^{-1} 3059, 1626, 1466, 1414, 1026, 915, 760, 694. Data in accordance with the literature.[310]

Phenyl(2-vinylphenyl)methanol, 345

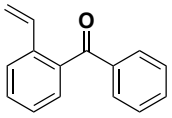


To a solution of 1-bromo-2-vinylbenzene (4.57 g, 24.8 mmol) in THF (50 mL) at –78 °C was added *n*-BuLi (2.50 M, 9.90 mL, 24.8 mmol) dropwise, and the mixture was stirred for 2 h at the same temperature. Benzaldehyde (2.53 mL, 24.8 mmol) in THF (25 mL) was added

to the reaction mixture and the reaction was warmed to room temperature and stirred for 1 h. The reaction was then quenched carefully with water (50 mL) and allowed to stir until all the solid was dissolved completely. The organic layer was separated and washed with Et_2O (3 × 50 mL) and the combined organic phases were dried over $MgSO_4$, filtered, and the solvent removed *in vacuo*. The crude product was purified by flash chromatography (eluent 15% Et_2O/petrol) afforded the alkene **344** (2.86 g, 55%) as a colourless oil.

δ_H ($CDCl_3$, 400 MHz) 7.58 (1H, dd, *J* 5.5, 3.5, Ar*H*), 7.51 (1H, dd, *J* 5.5, 3.5, Ar*H*), 7.32–7.42 (7H, m, 7 × Ar*H*), 7.06 (1H, dd, *J* 17.5, 11.0, ArC*H*=CH_2), 6.11 (1H, d, *J* 4.0, ArC*H*(OH)Ph), 5.69 (1H, dd, *J* 17.5, 1.5, ArCH=CH_AH_B (*E*)), 5.35 (1H, dd, *J* 11.0, 1.5, ArCH=CH_AH_B (*Z*)), 2.78 (1H, d, *J* 4.0, ArCH(O*H*)Ph); δ_C ($CDCl_3$, 101 MHz); 143.1, 140.5, 136.3, 134.4, 128.5, 128.1, 127.9, 127.5, 126.9(9), 126.9(6), 126.4, 116.7, 72.9; *m/z* (ESI^+) 233 ($[M + Na]^+$, 100%). Data in accordance with the literature.[311]

Phenyl(2-vinylphenyl)methanone, 346



To a solution of phenyl(2-vinylphenyl)methanol **345** (2.58 g, 12.3 mmol) in CH_2Cl_2 (100 mL) was added MnO_2 (15.0 g, 172 mmol). The solution was stirred at room temperature for 24 h. The reaction mixture was filtered through Celite®, and the solvent was removed under reduced pressure to give ketone **346** (2.45 g, 96%) as a thick brown oil.

δ_H ($CDCl_3$, 400 MHz) 7.85 (2H, dt, *J* 8.5, 1.5, 2 × Ar*H*), 7.71 (1H, d, *J* 8.0, Ar*H*), 7.57–7.63 (1H, m, Ar*H*), 7.44–7.53 (3H, m, 3 × Ar*H*), 7.33–7.39 (2H, m, 2 × Ar*H*), 6.82 (1H, dd, *J* 17.5,

11.0, ArC*H*=CH_2), 5.74 (1H, dd, *J* 17.5, 1.0, ArCH=CH_AH_B (*E*)), 5.26 (1H, dd, *J* 11.0, 1.0, ArCH=CH_AH_B (*Z*)); δ_C ($CDCl_3$, 101 MHz); 198.2, 137.9, 137.6, 136.7, 134.3, 133.4, 130.4, 130.3, 128.6, 128.5, 127.2, 126.0, 116.6; *m/z* (ESI^+) 209 ($[M + H]^+$, 100%). Data in accordance with the literature.[311]

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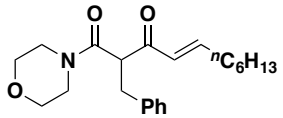
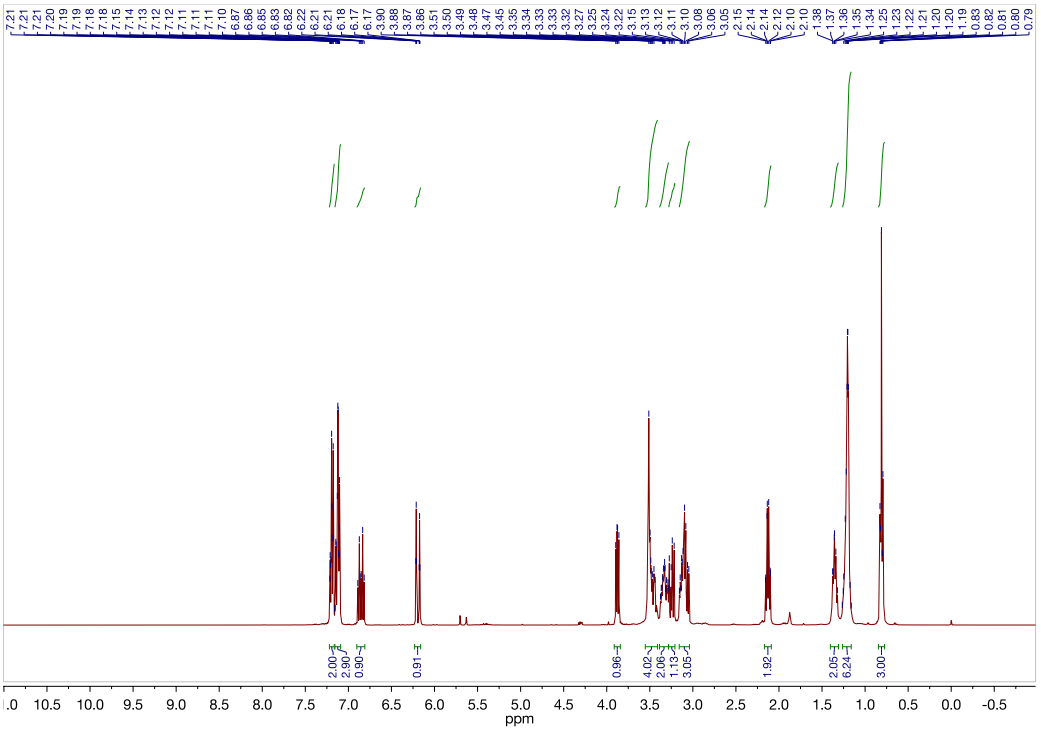
Appendix: Spectra

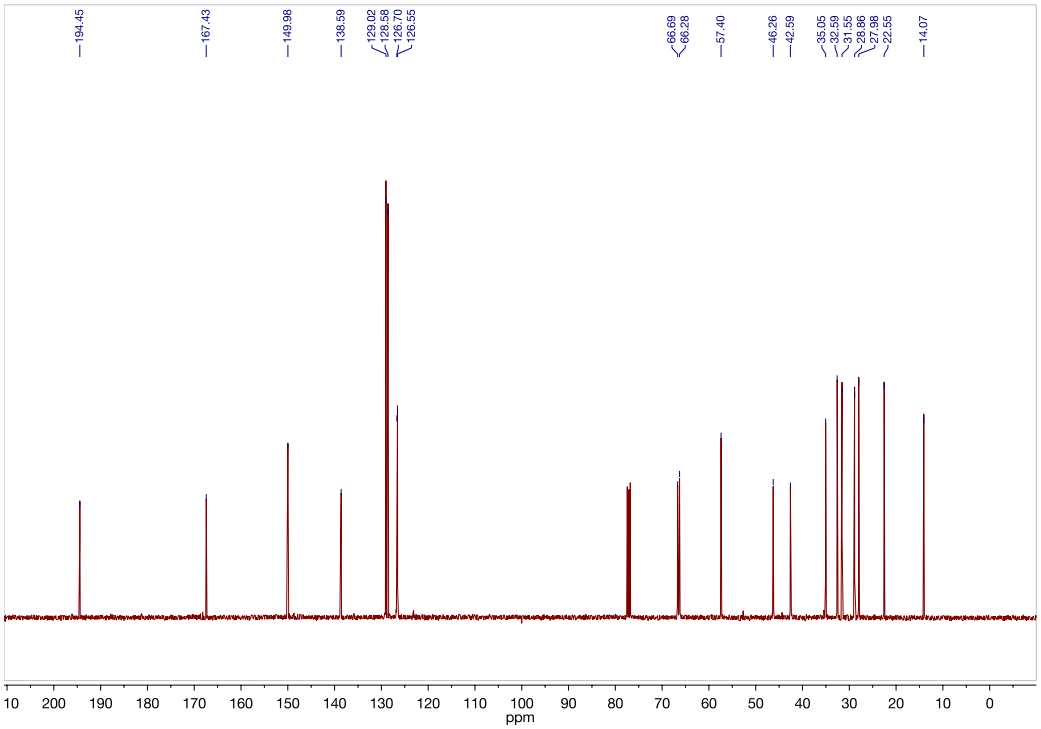
^{1}H and ^{13}C spectra of all novel compounds synthesised in Chapters 2 and 4.

HPLC traces are also shown for chiral products and their racemates.

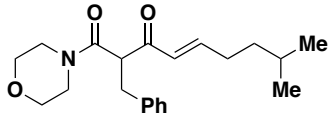
(*E*)-2-Benzyl-1-morpholinoundec-4-ene-1,3-dione, 70a

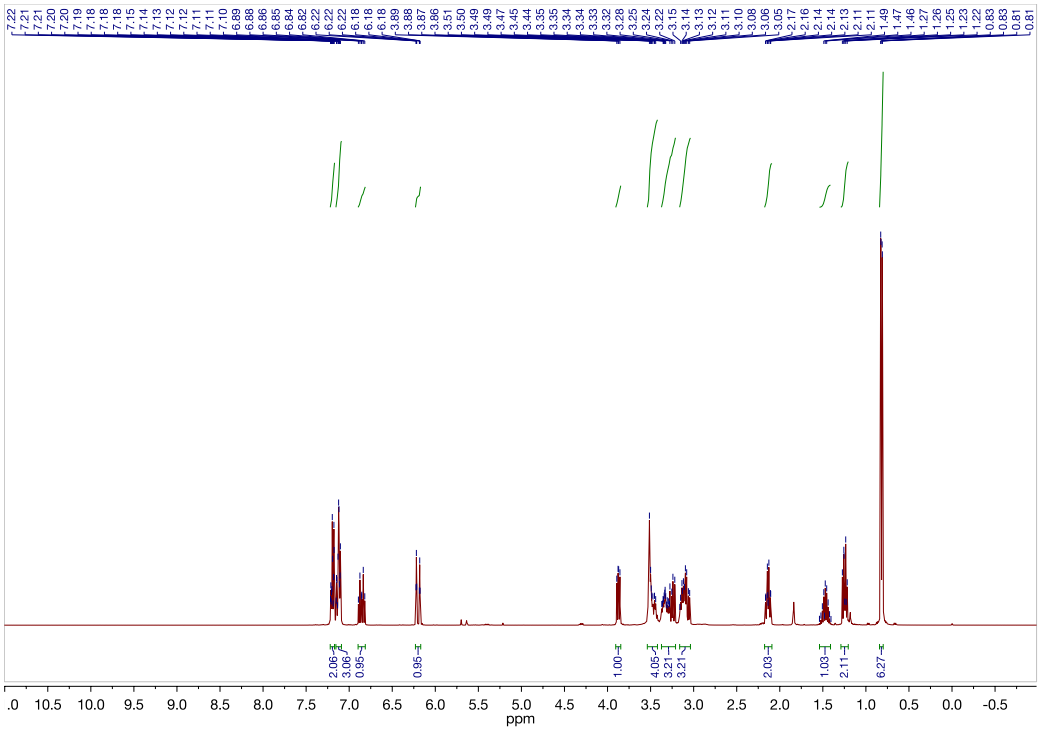


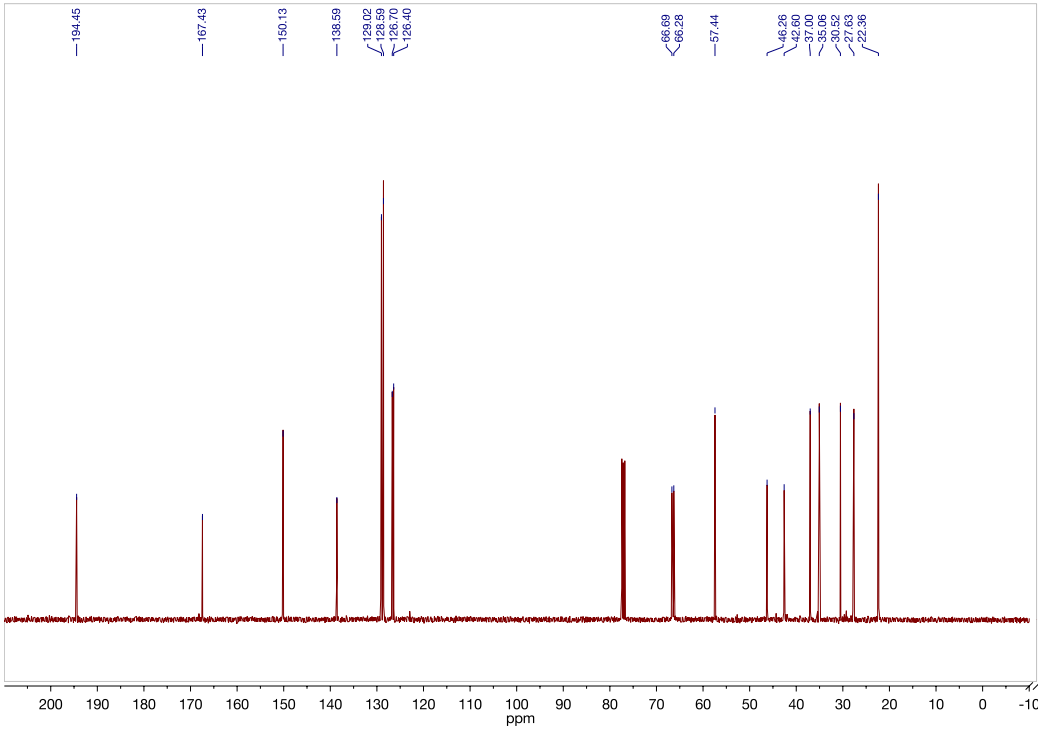




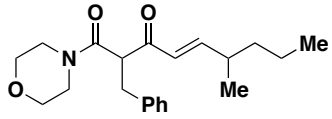
(*E*)-2-Benzyl-8-methyl-1-morpholinonon-4-ene-1,3-dione, 71

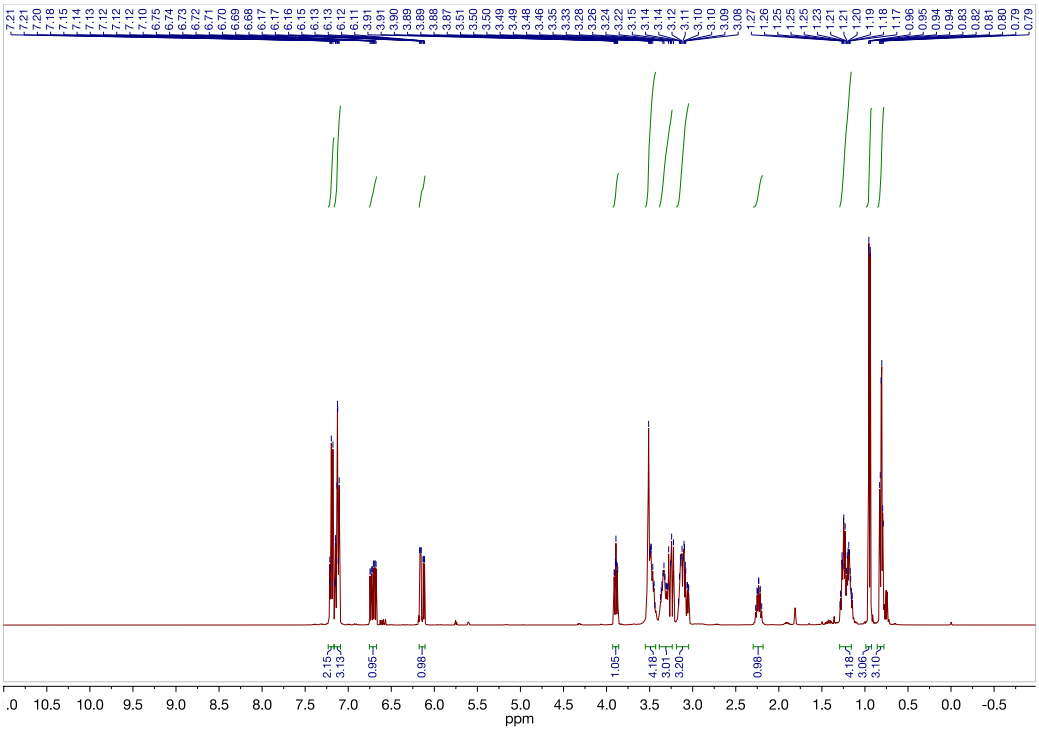


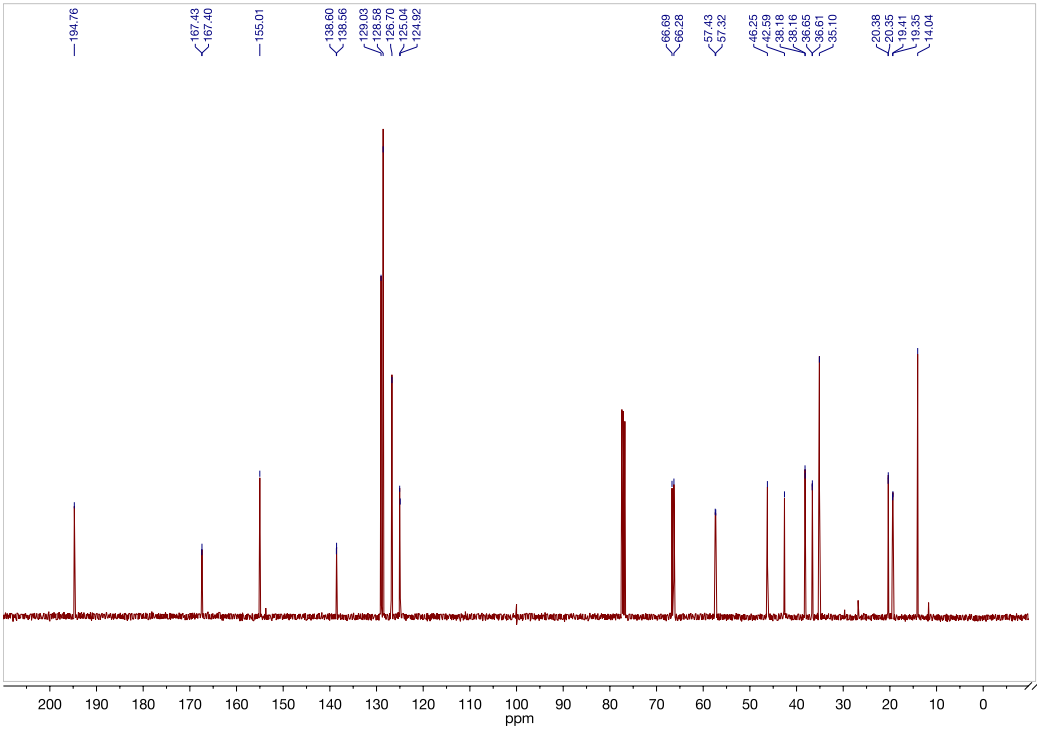




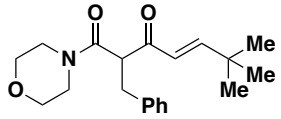
(*E*)-2-Benzyl-6-methyl-1-morpholinonon-4-ene-1,3-dione, 72

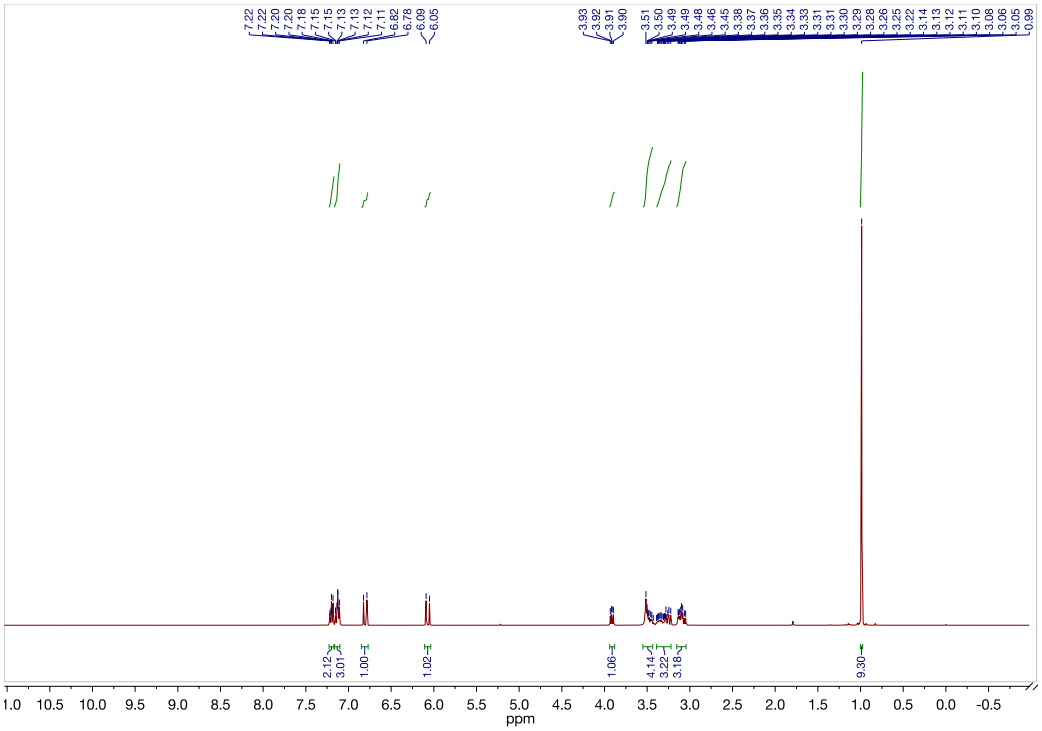


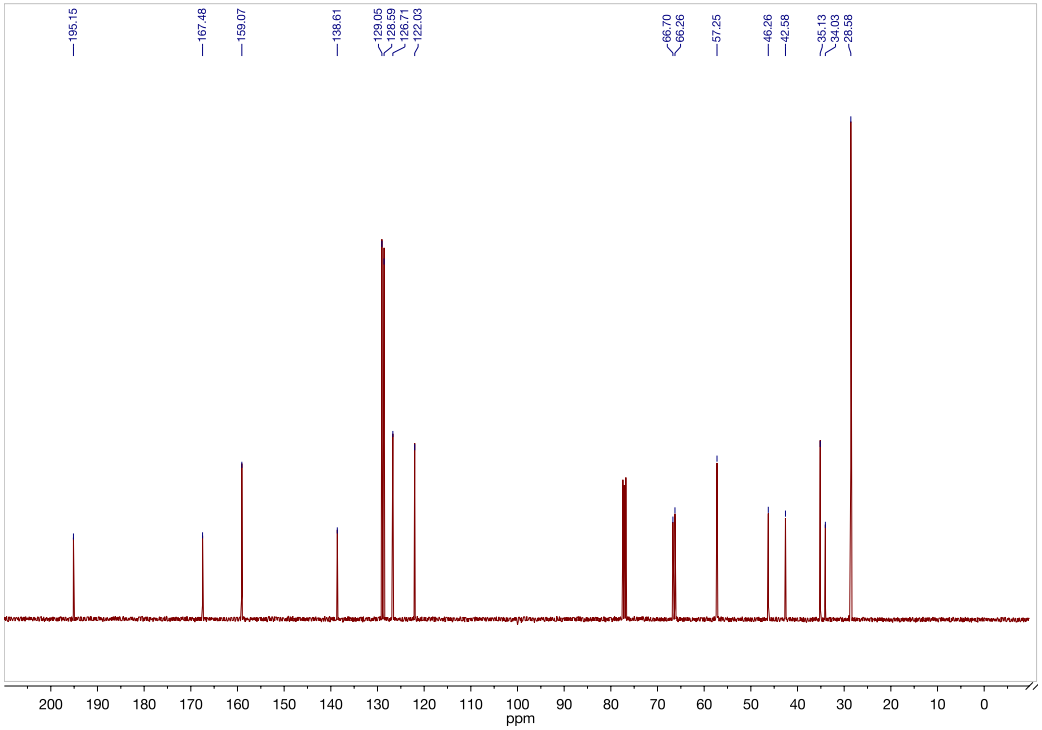




(*E*)-2-Benzyl-6,6-dimethyl-1-morpholinohept-4-ene-1,3-dione, 73







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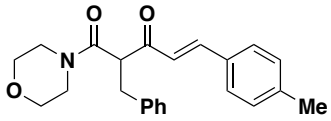

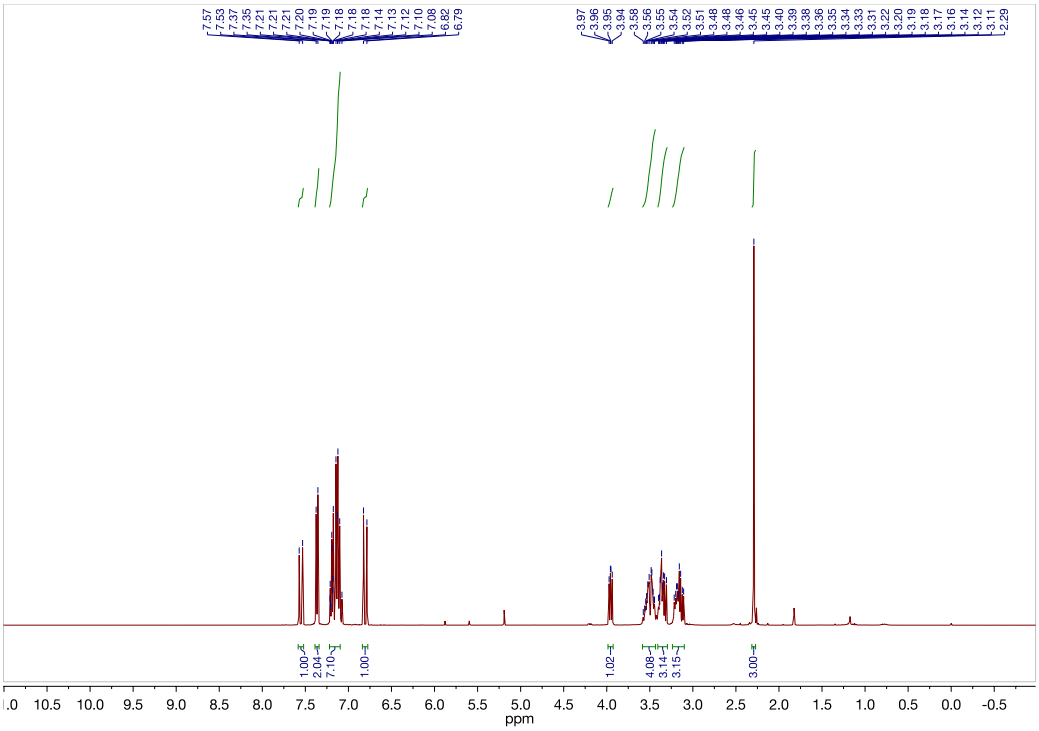

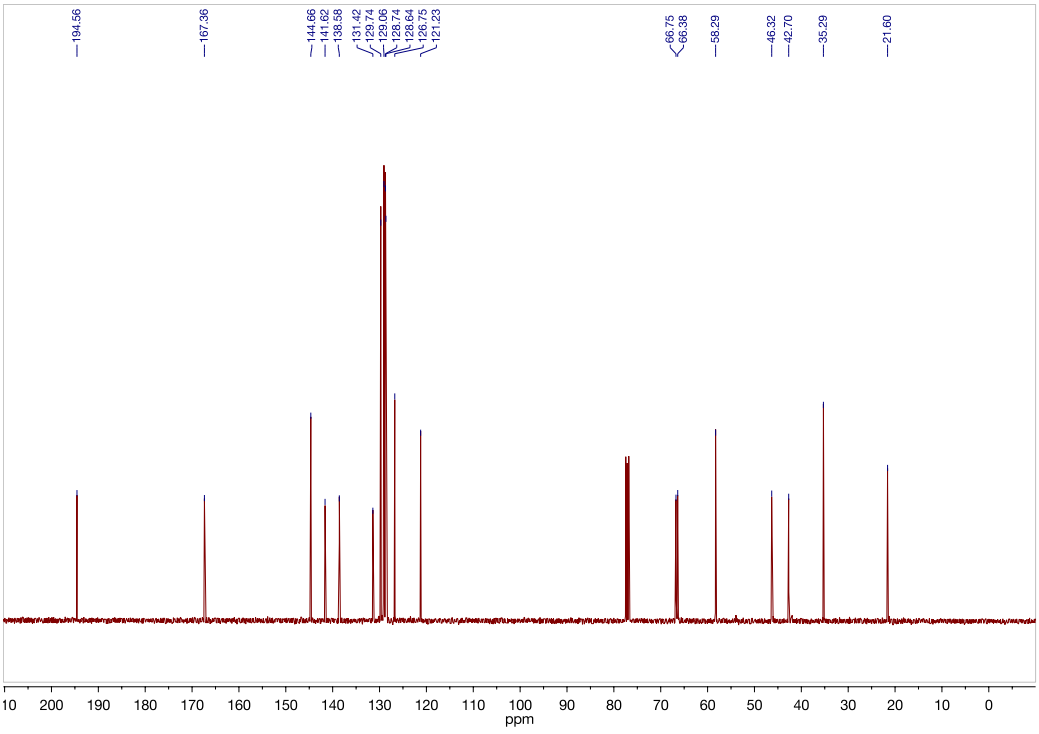

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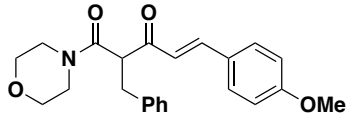
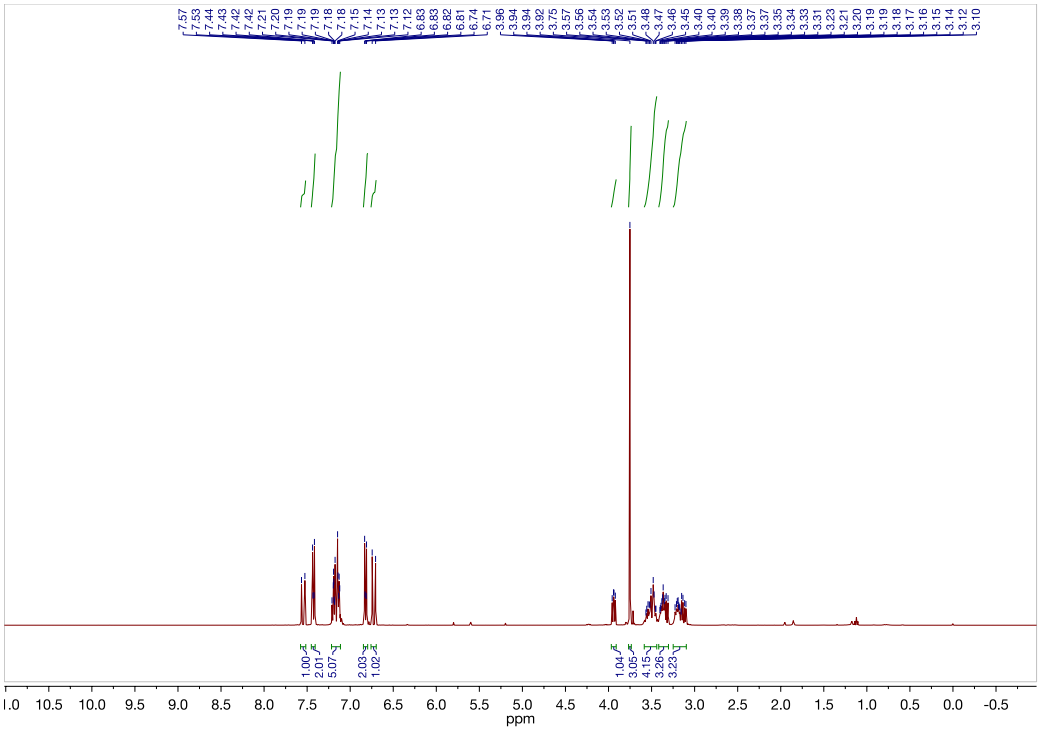
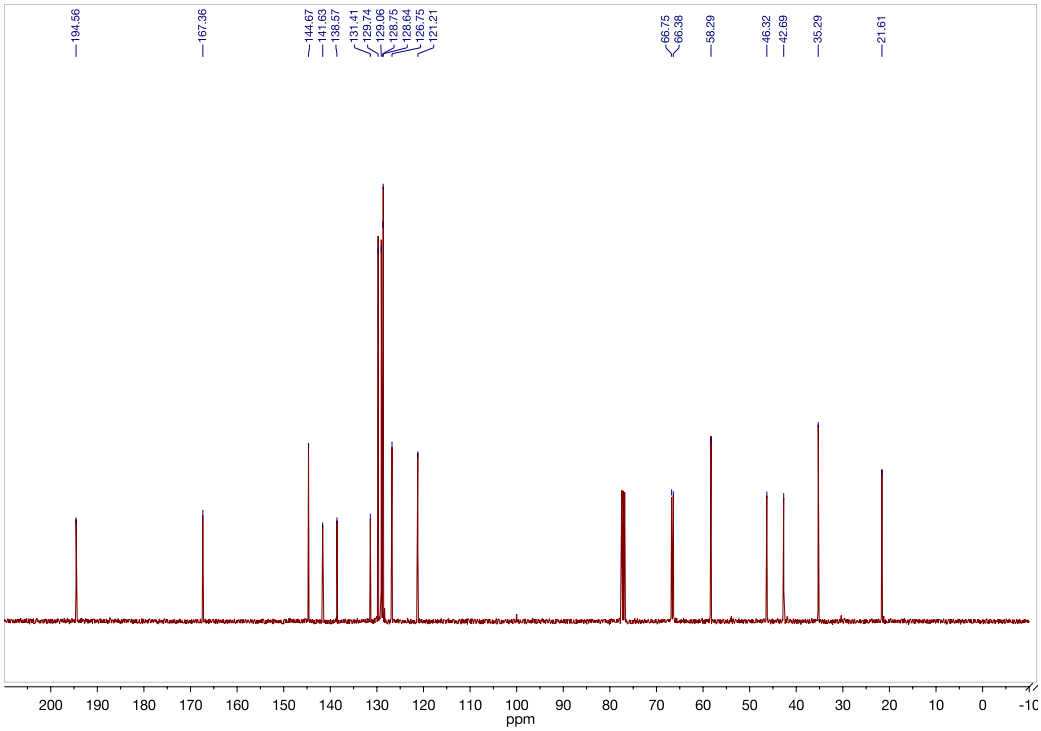
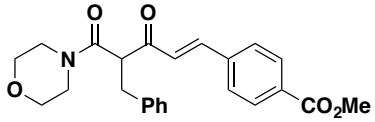
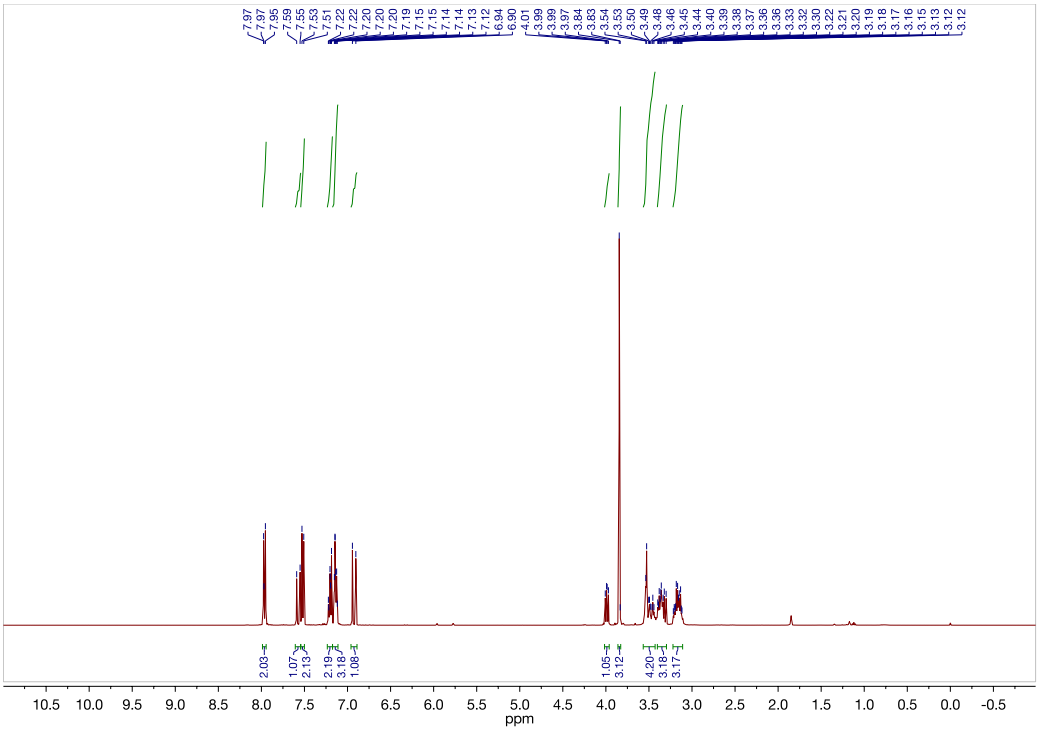


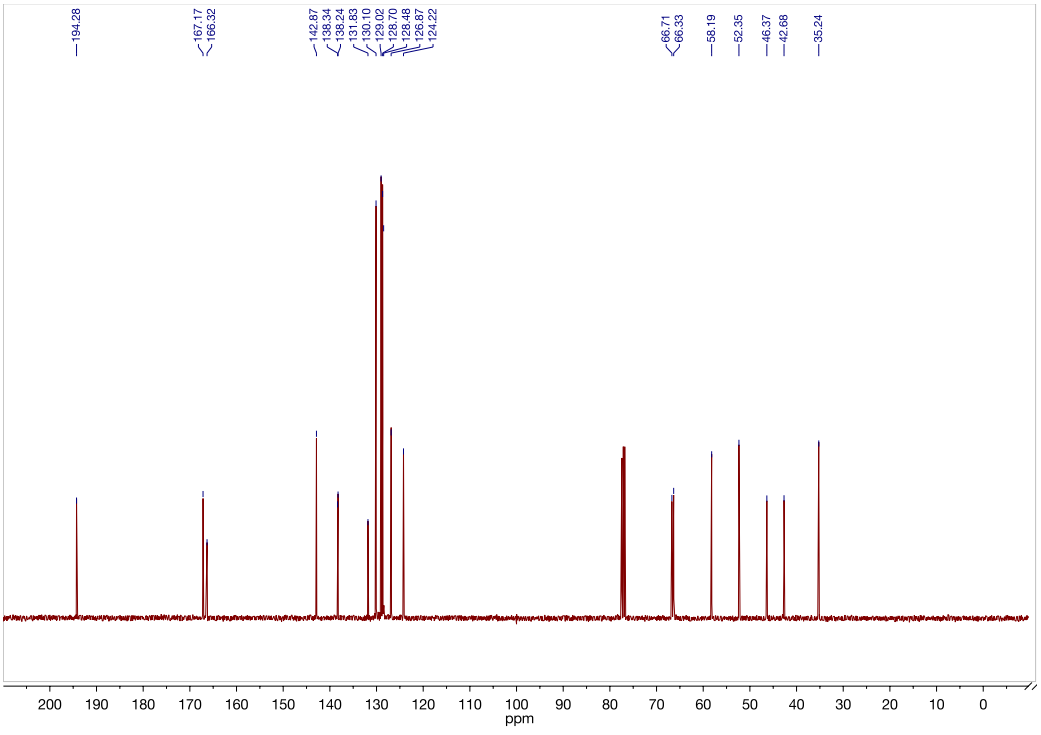




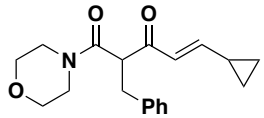
Methyl (*E*)-4-(4-benzyl-5-morpholino-3,5-dioxopent-1-en-1-yl)benzoate, 76

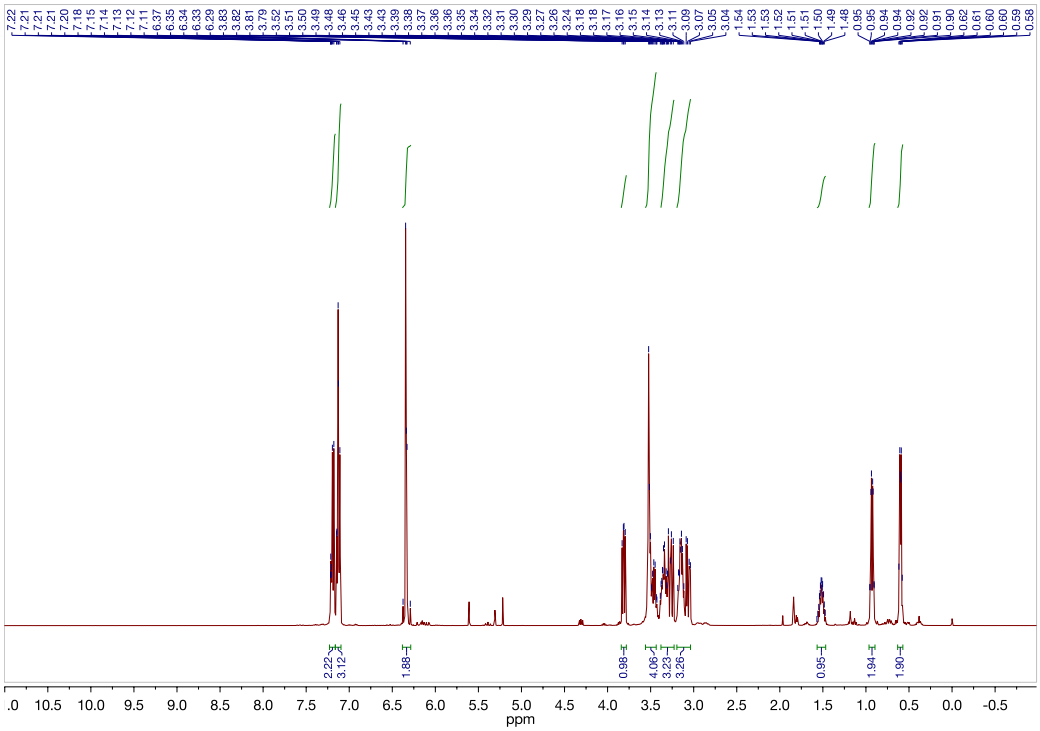


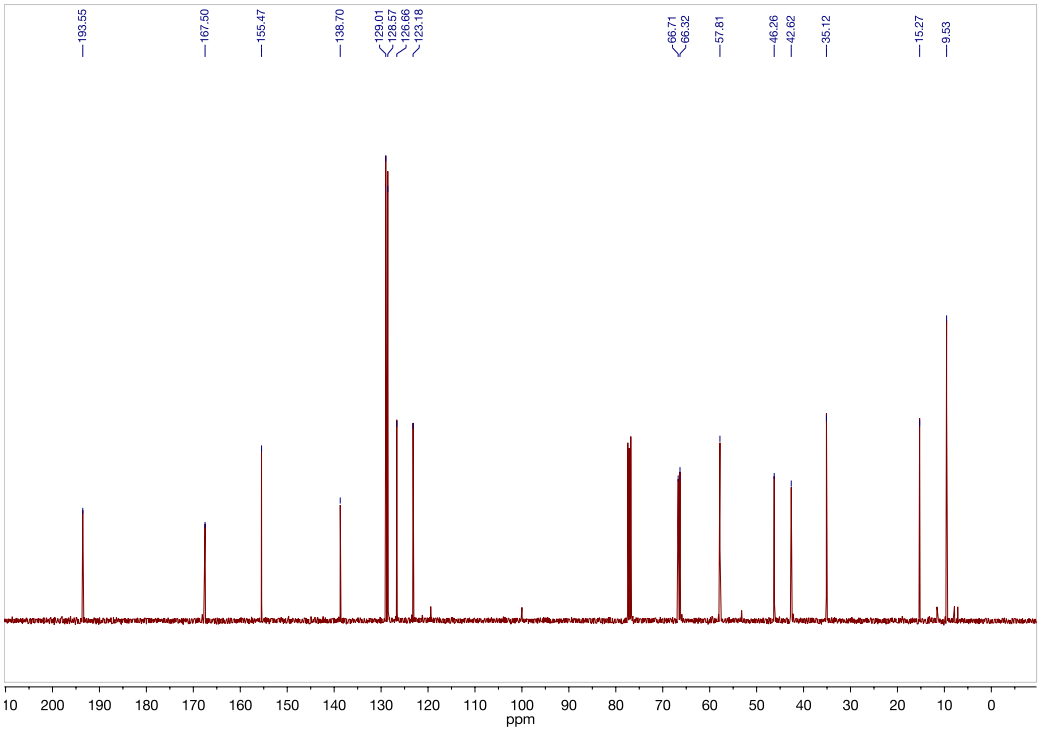




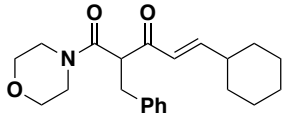
(*E*)-2-Benzyl-5-cyclopropyl-1-morpholinopent-4-ene-1,3-dione, 77

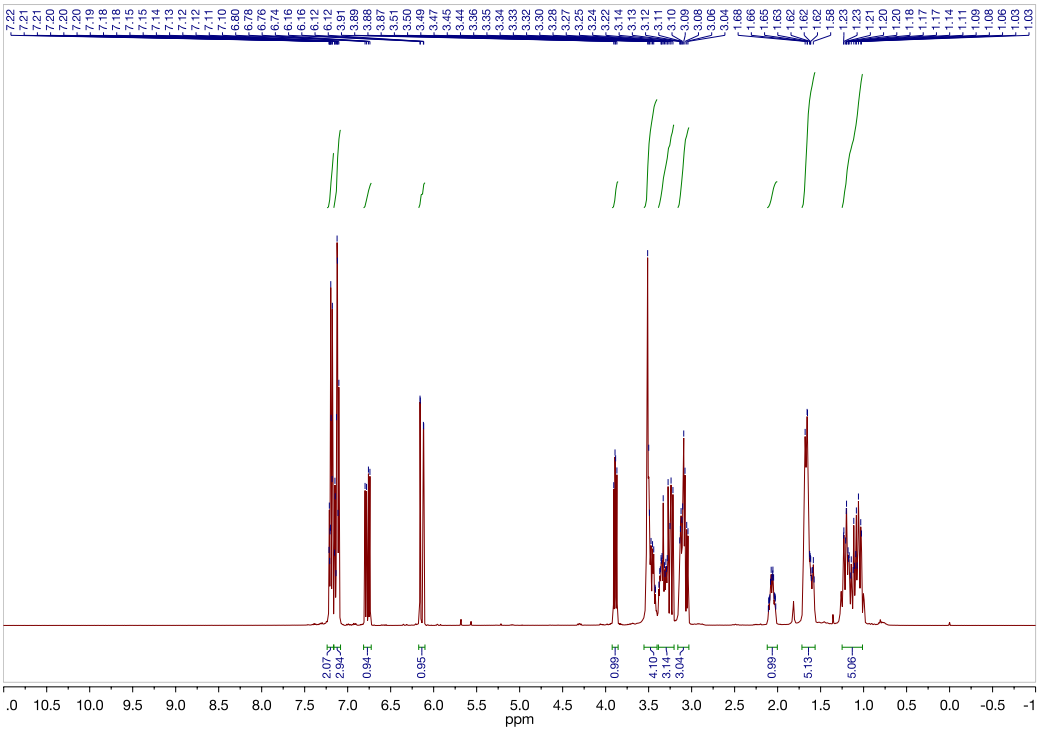


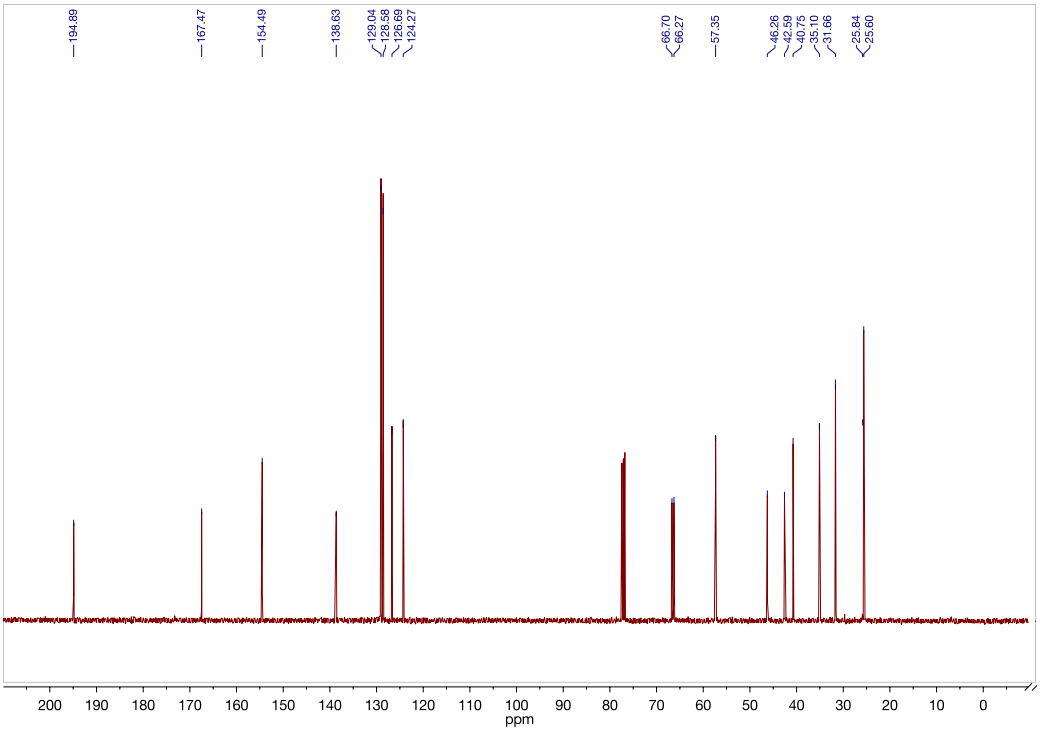




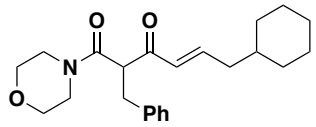
(*E*)-2-Benzyl-5-cyclohexyl-1-morpholinopent-4-ene-1,3-dione, 78

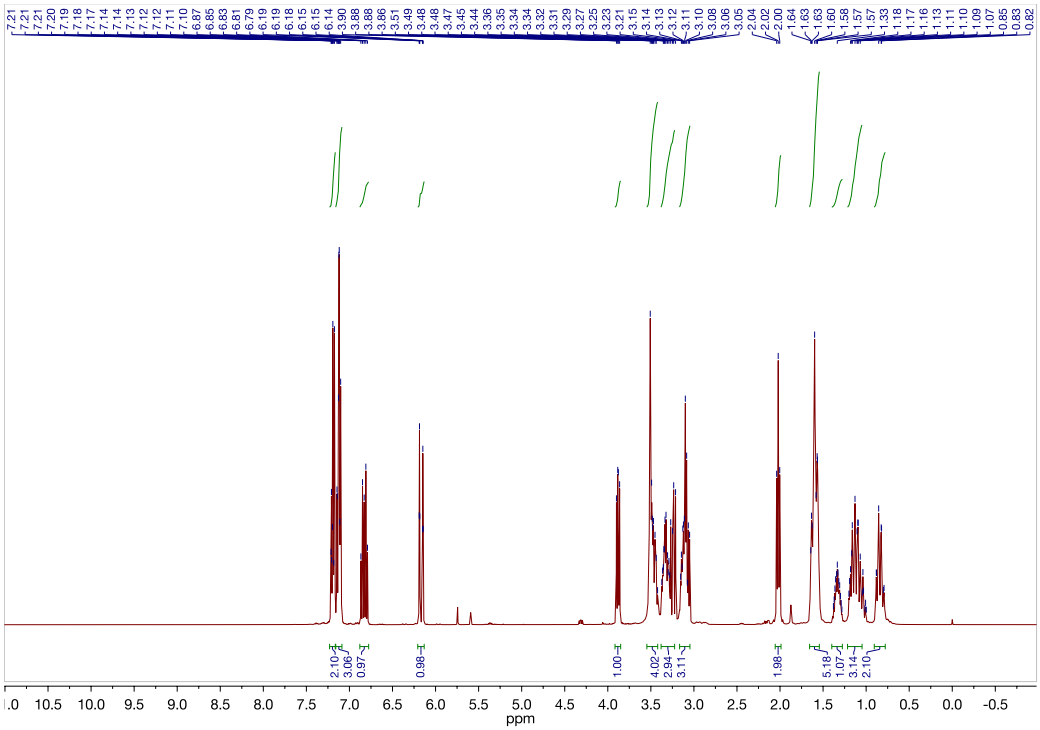


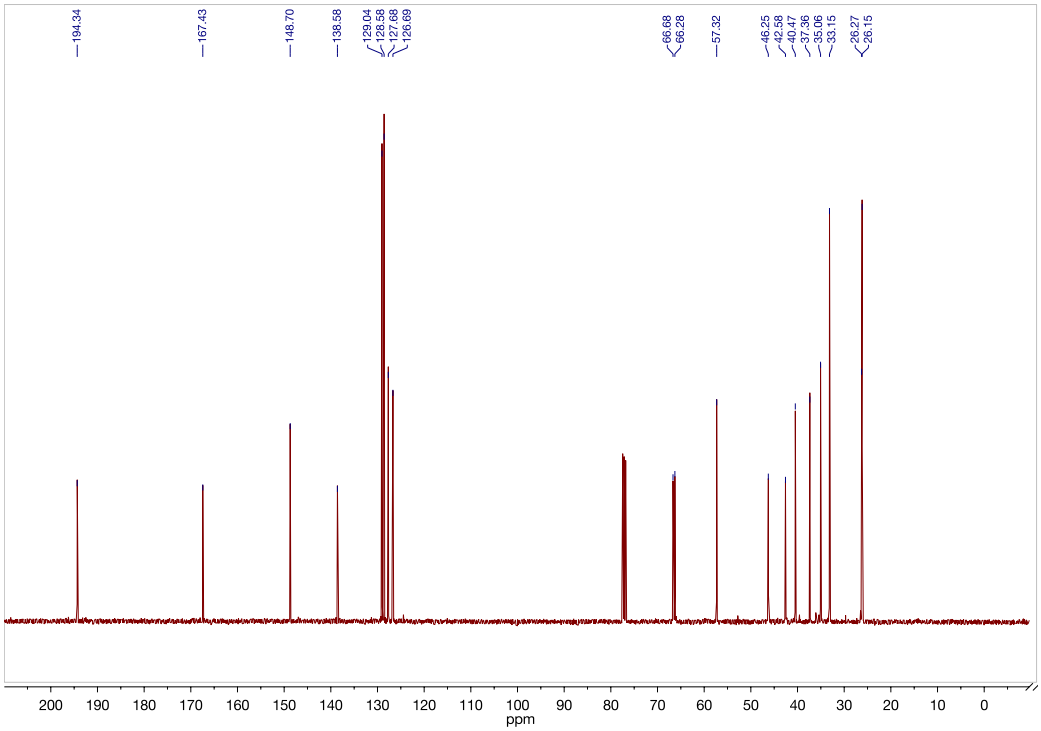




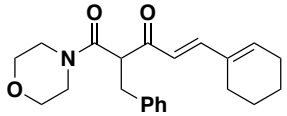
(*E*)-2-Benzyl-6-cyclohexyl-1-morpholinohex-4-ene-1,3-dione, 79

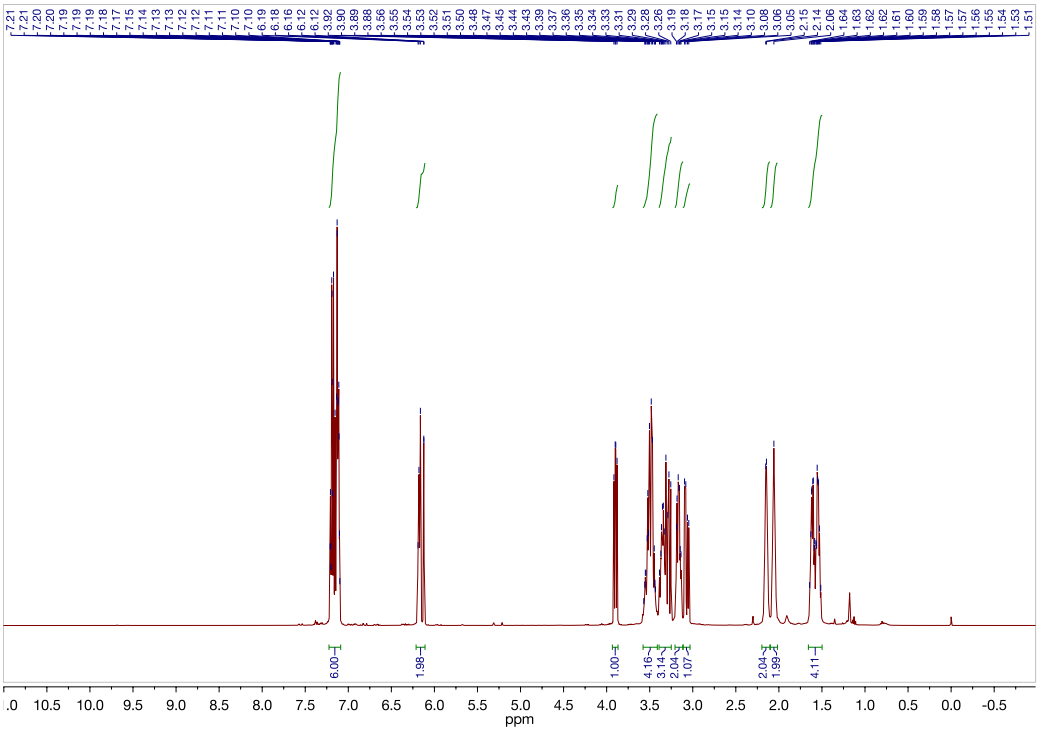


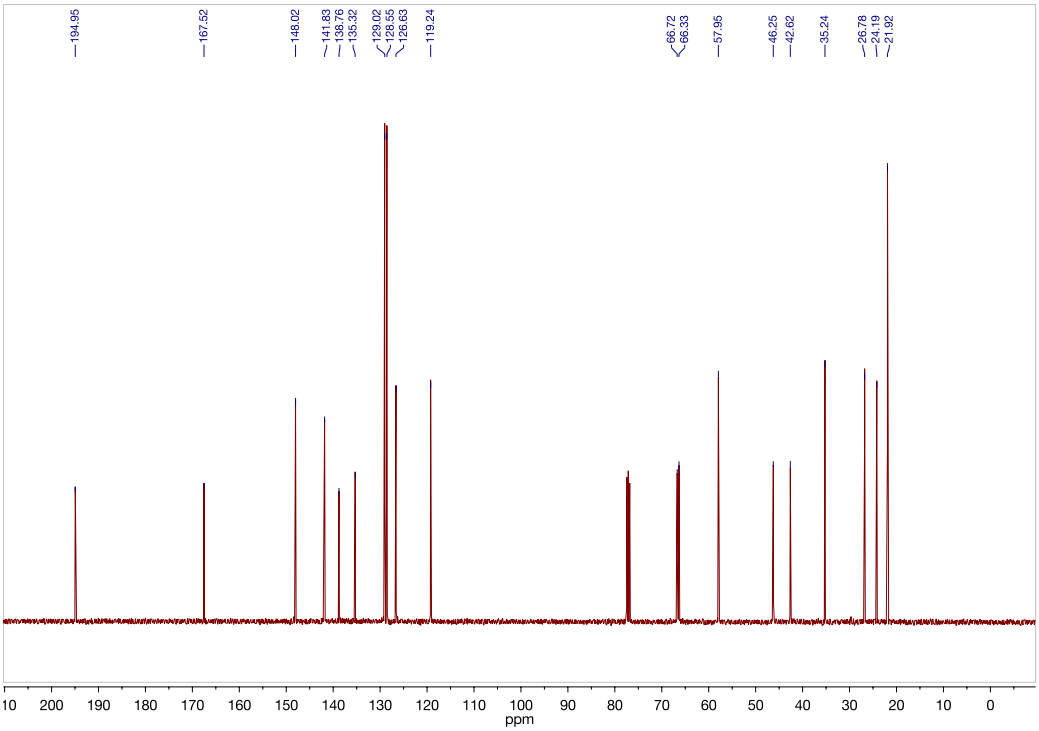




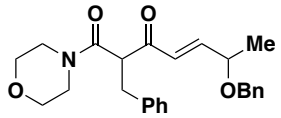
(*E*)-2-Benzyl-5-(cyclohex-1-en-1-yl)-1-morpholinopent-4-ene-1,3-dione, 80

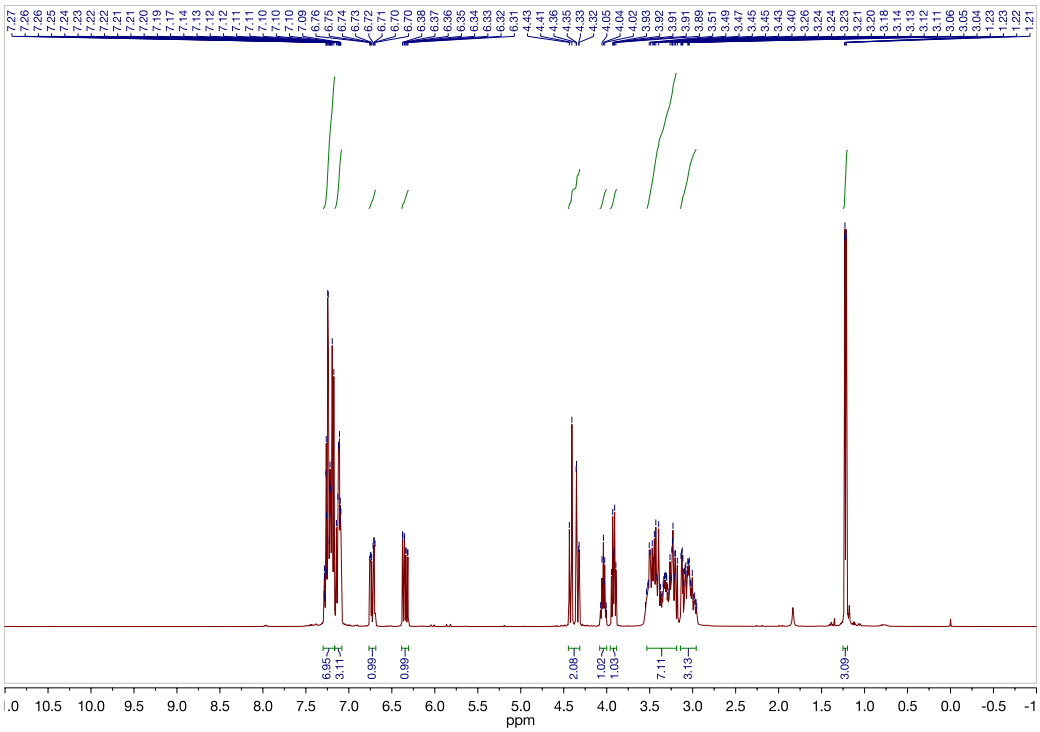


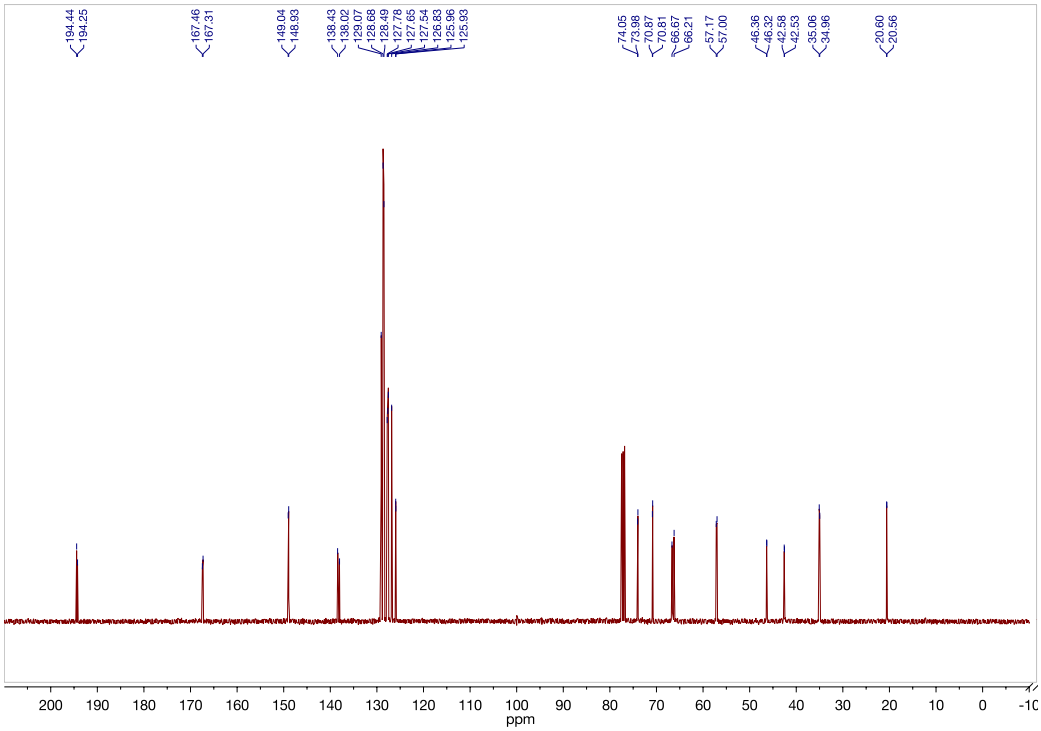




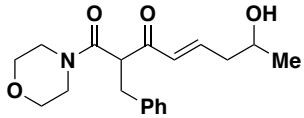
(*E*)-2-Benzyl-6-(benzyloxy)-1-morpholinohept-4-ene-1,3-dione, 81

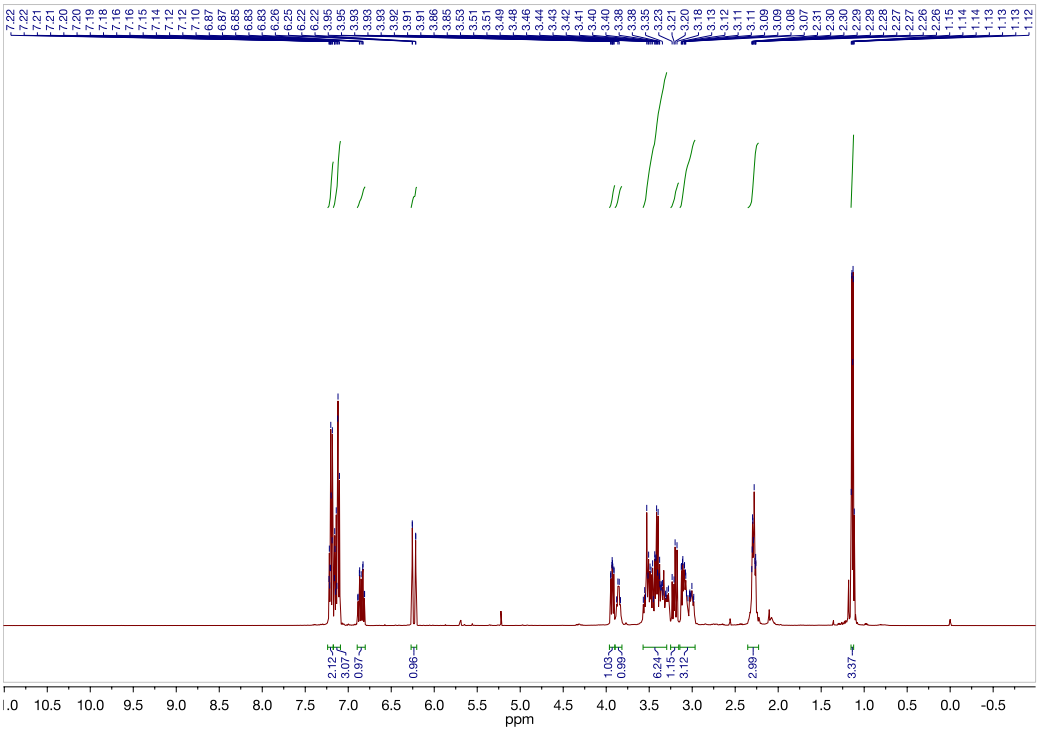


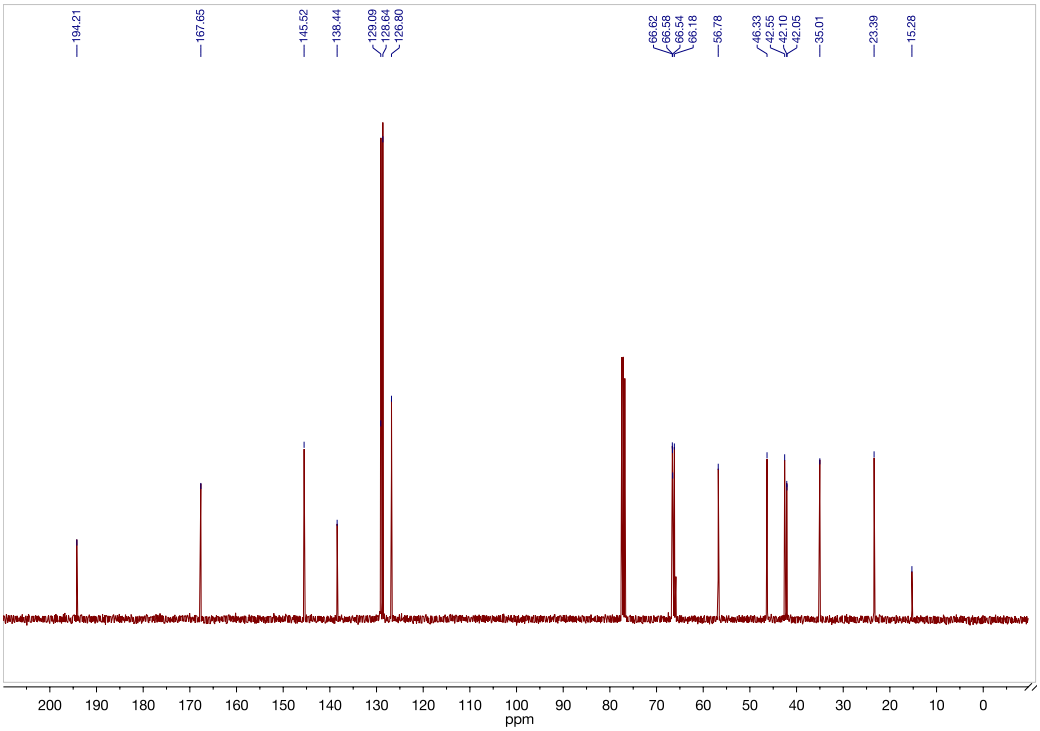




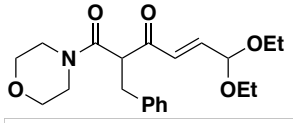
(*E*)-2-Benzyl-7-hydroxy-1-morpholinooct-4-ene-1,3-dione, 82

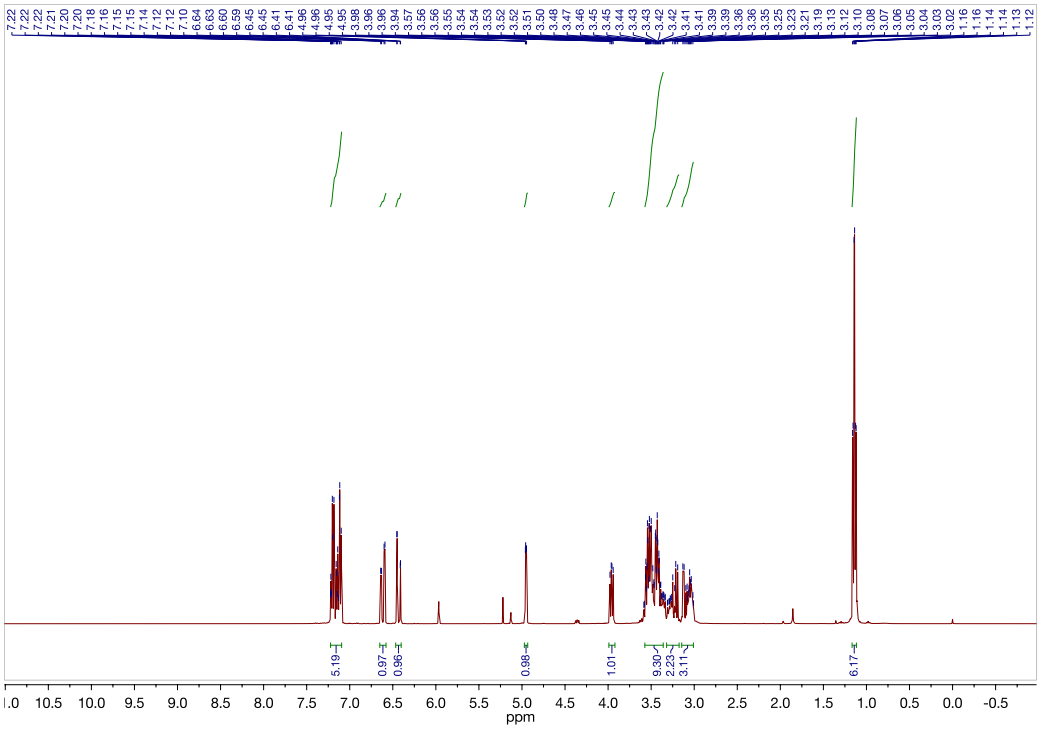


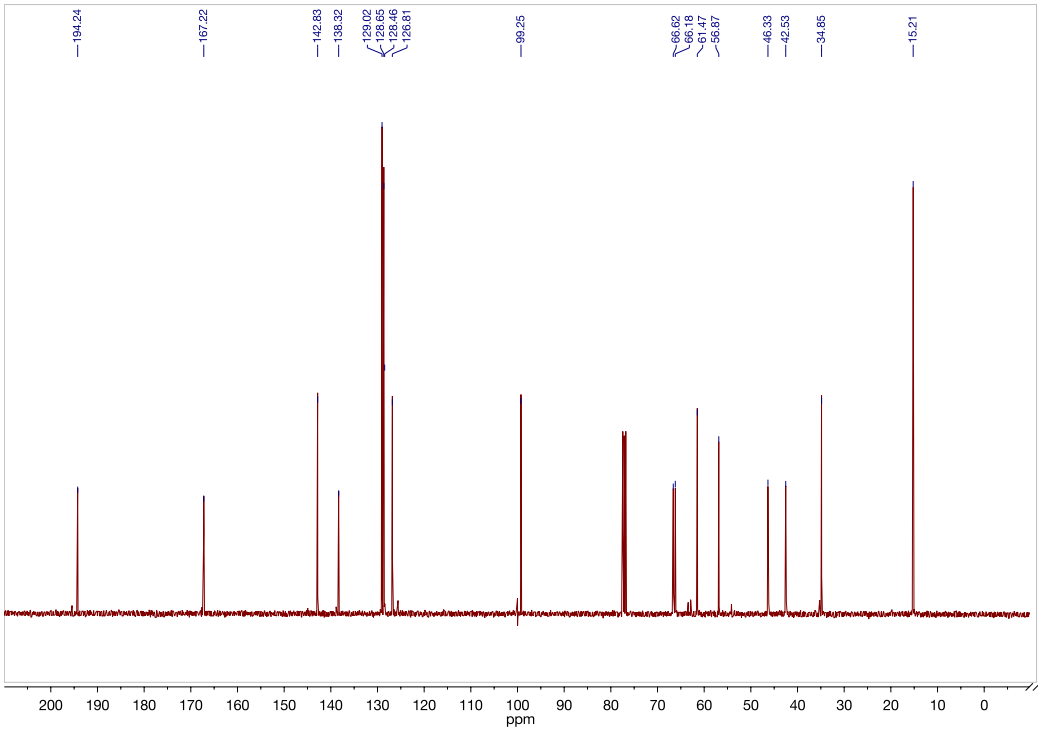




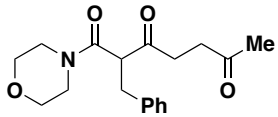
(*E*)-2-Benzyl-6,6-diethoxy-1-morpholinohex-4-ene-1,3-dione, 83

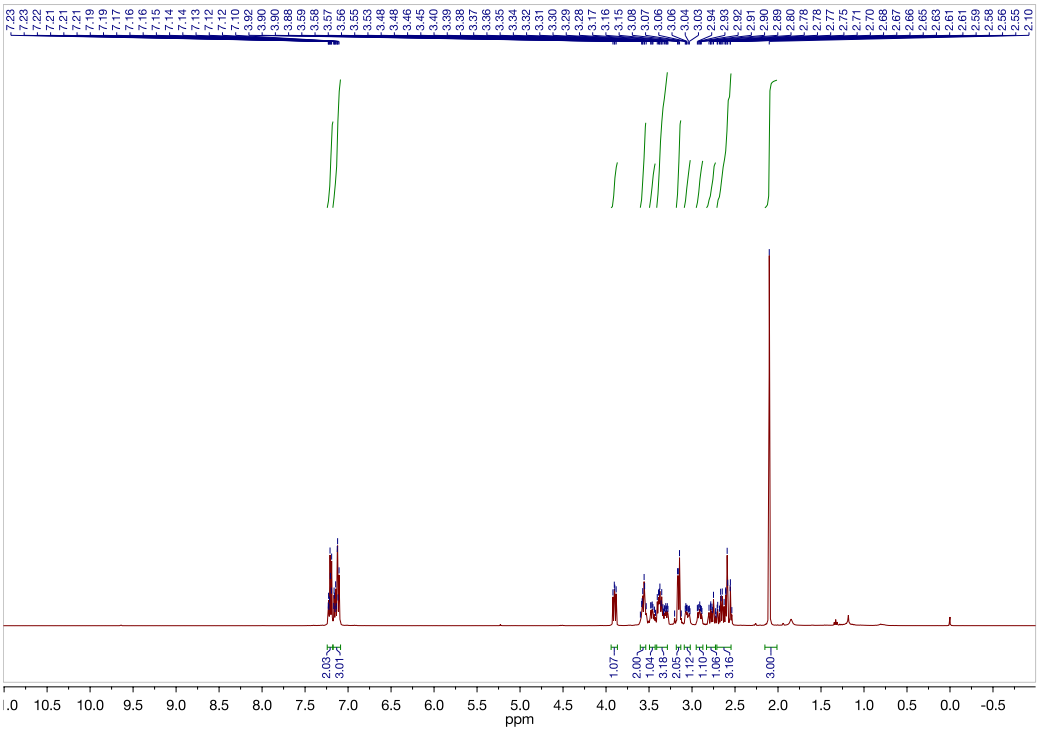


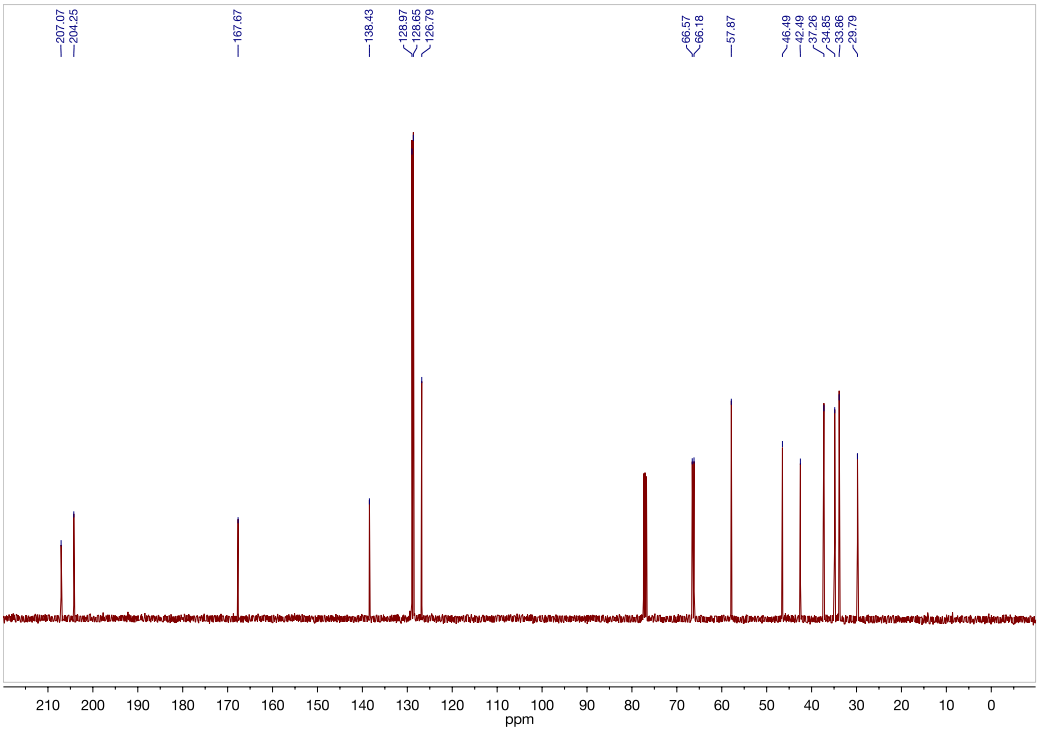




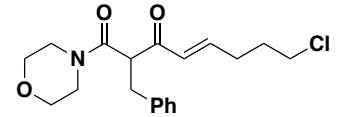
2-Benzyl-1-morpholinoheptane-1,3,6-trione, 84

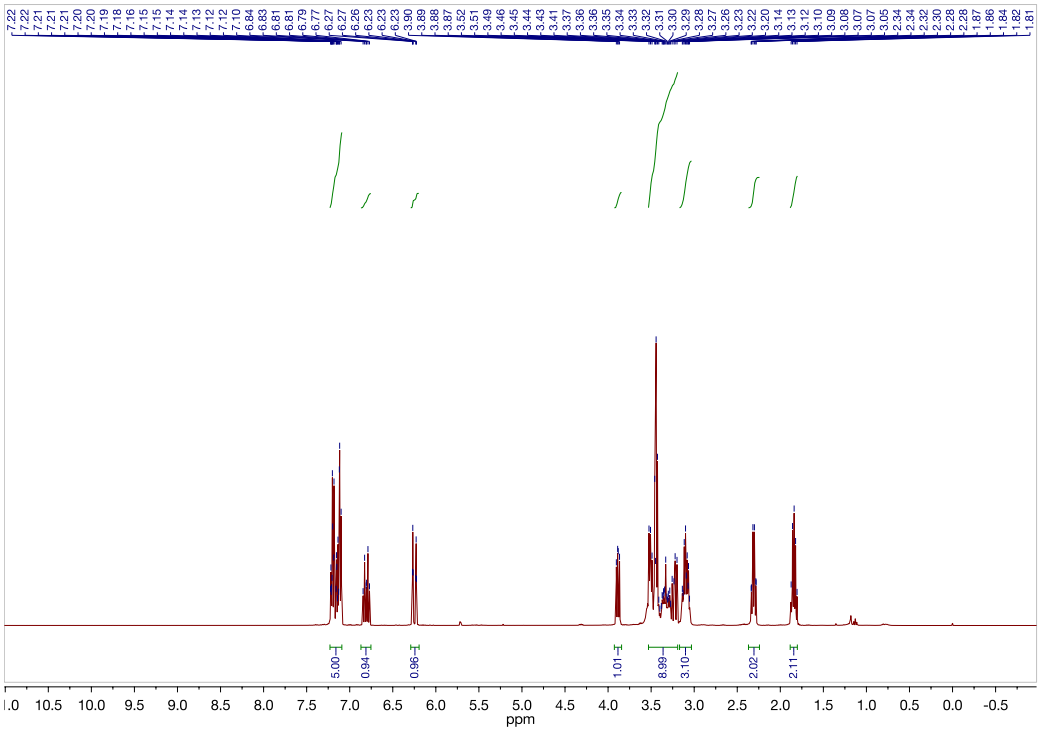


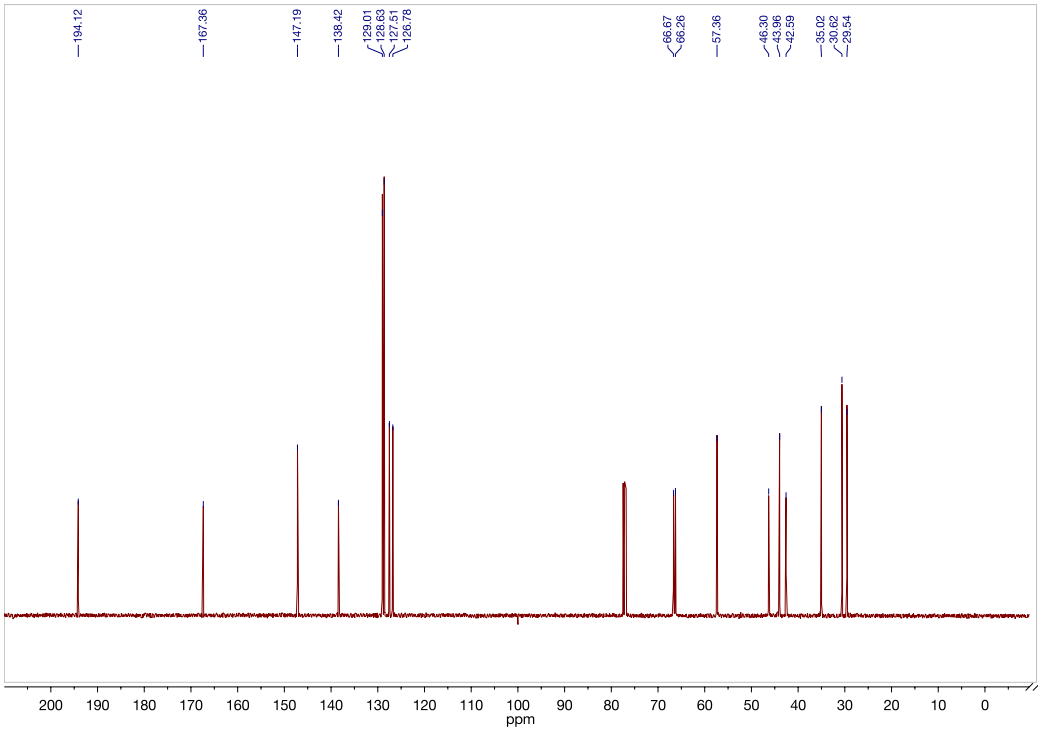




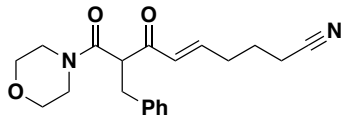
(*E*)-2-Benzyl-8-chloro-1-morpholinooct-4-ene-1,3-dione, 85

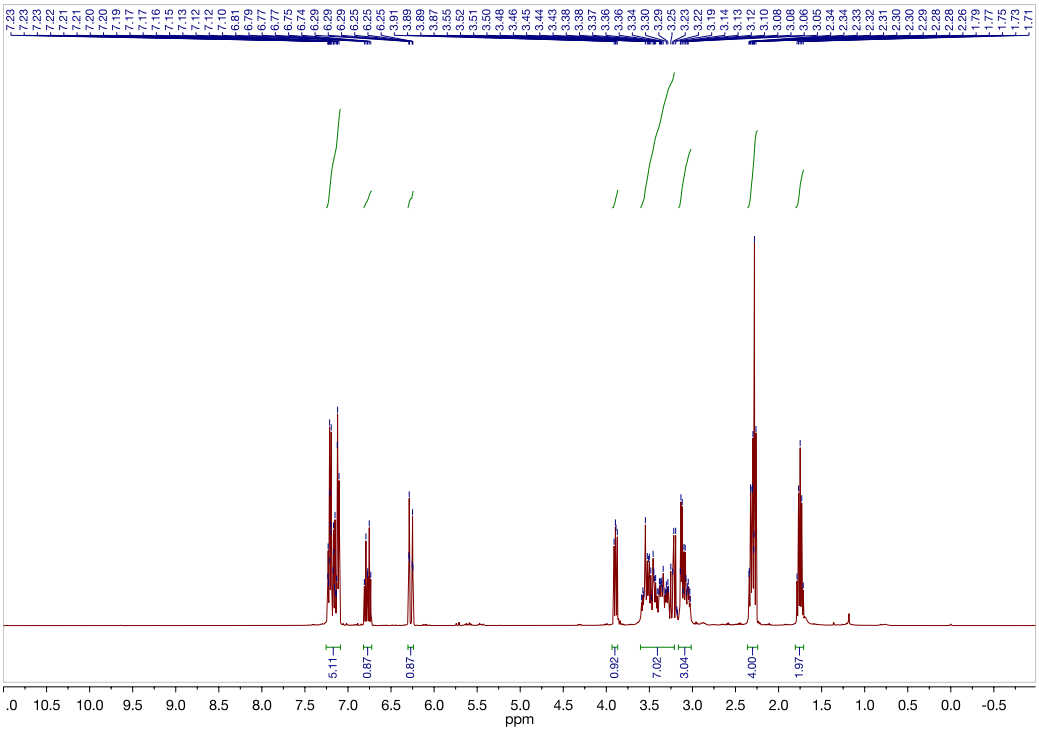


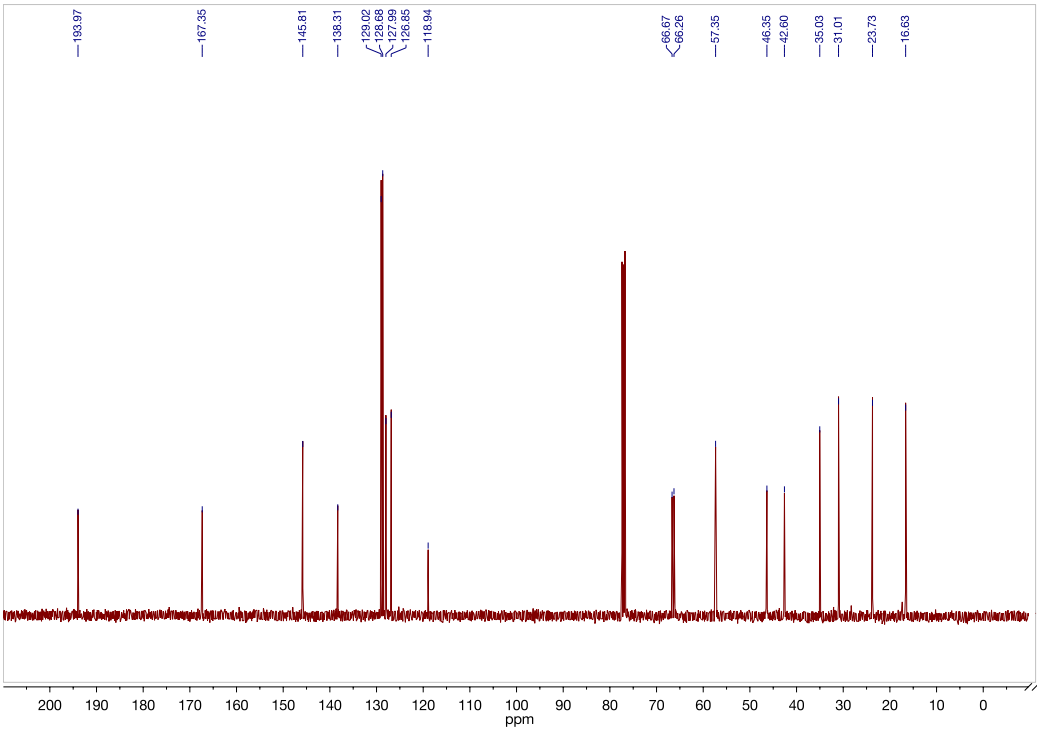




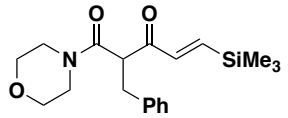
(*E*)-8-Benzyl-9-morpholino-7,9-dioxonon-5-enenitrile, 86

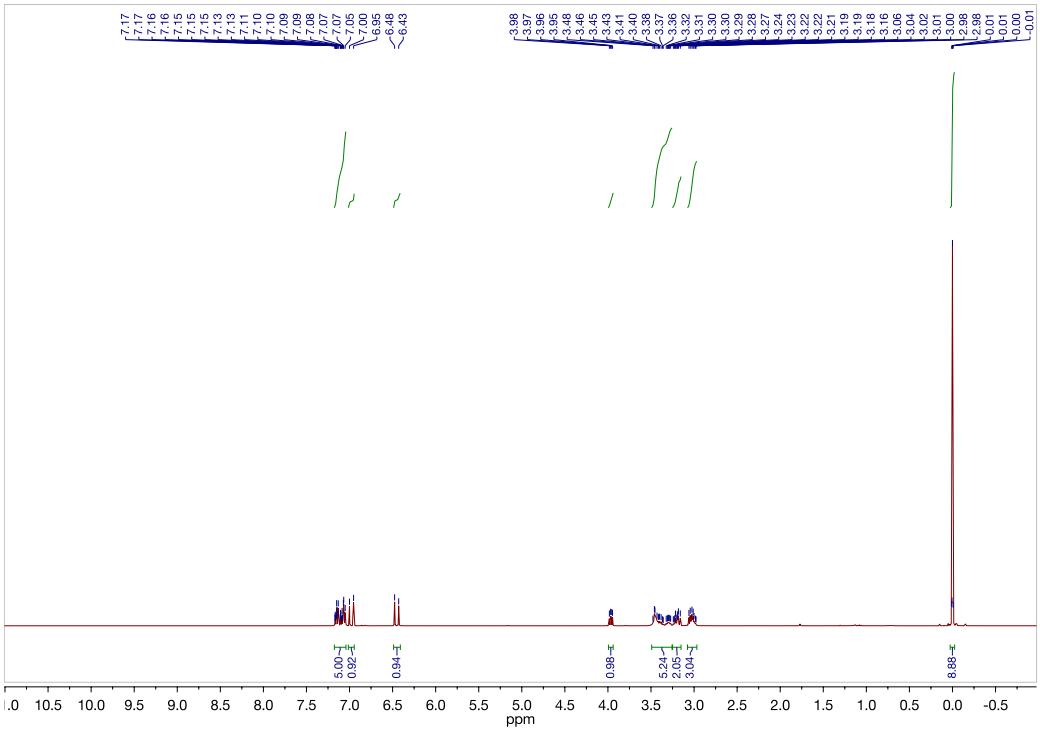


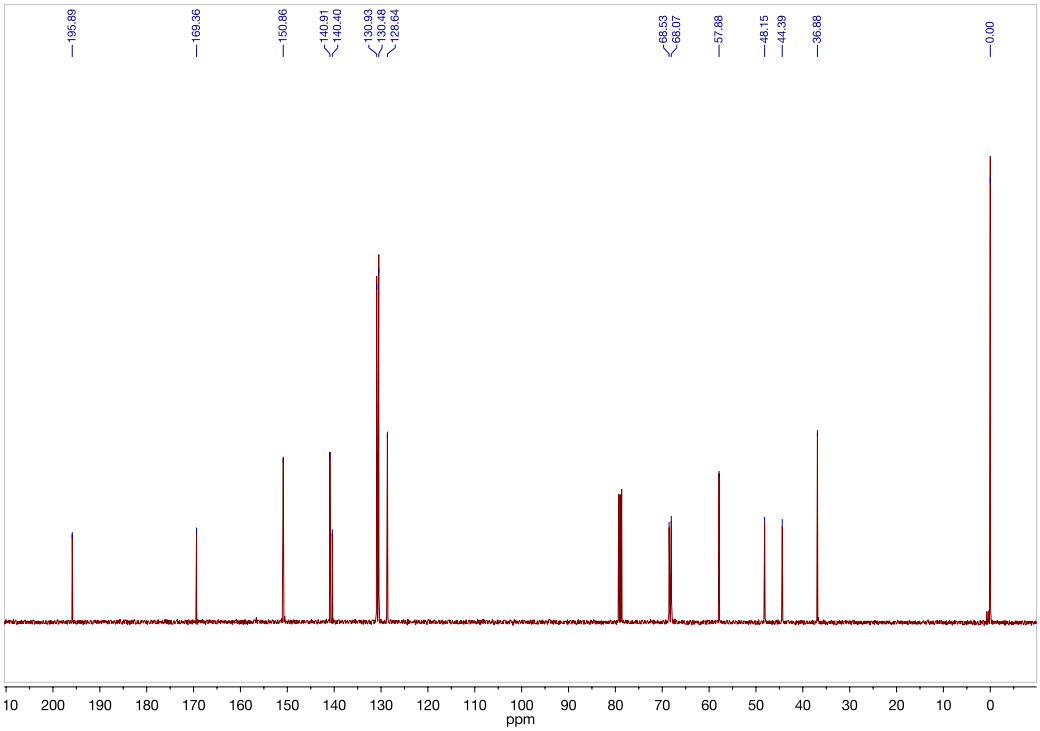




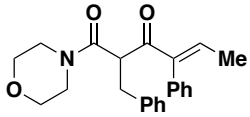
(*E*)-2-Benzyl-1-morpholino-5-(trimethylsilyl)pent-4-ene-1,3-dione, 87

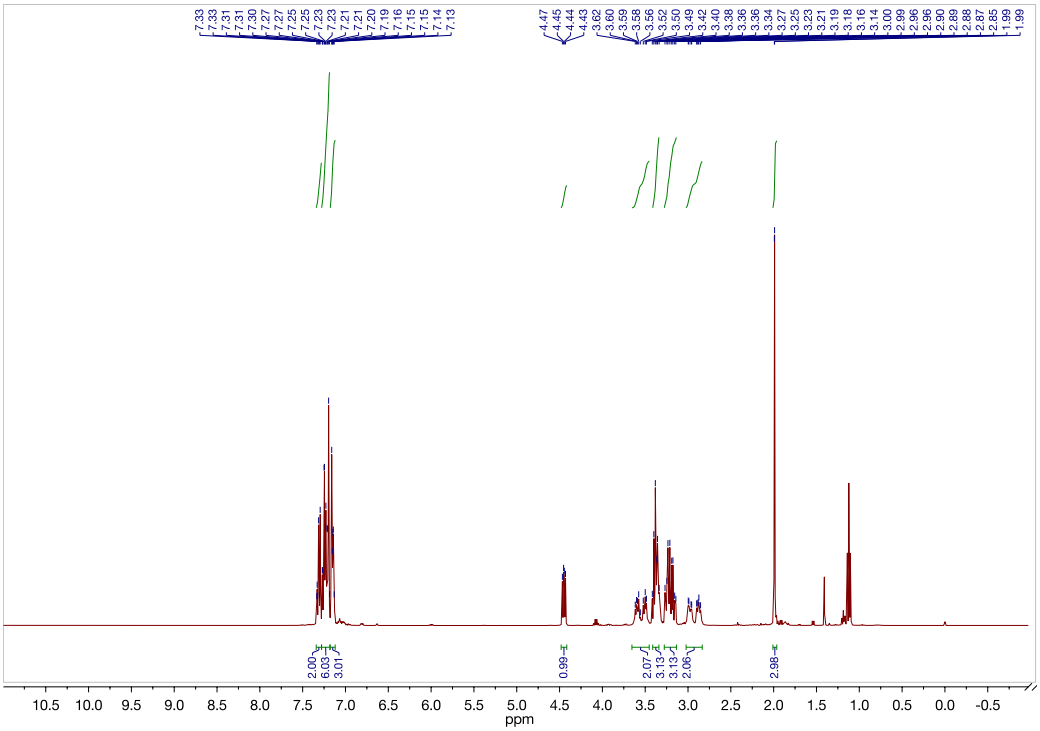


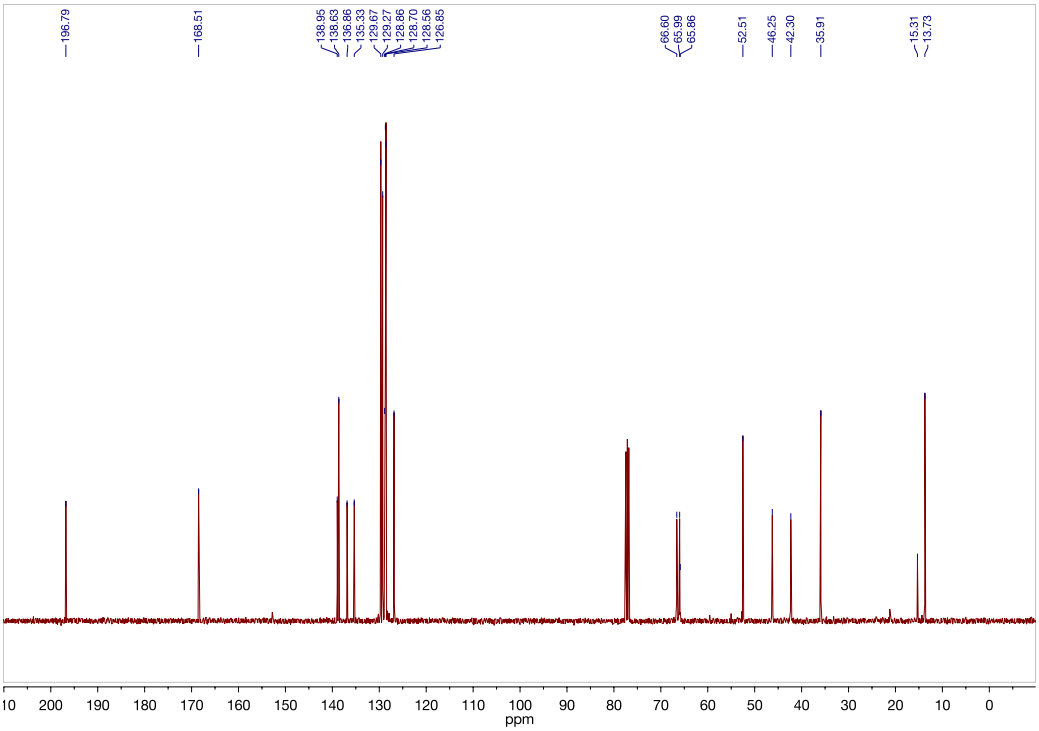




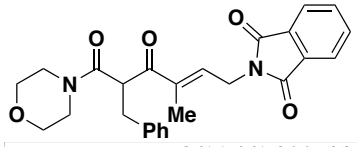
(*E*)-2-Benzyl-1-morpholino-4-phenylhex-4-ene-1,3-dione, 89a

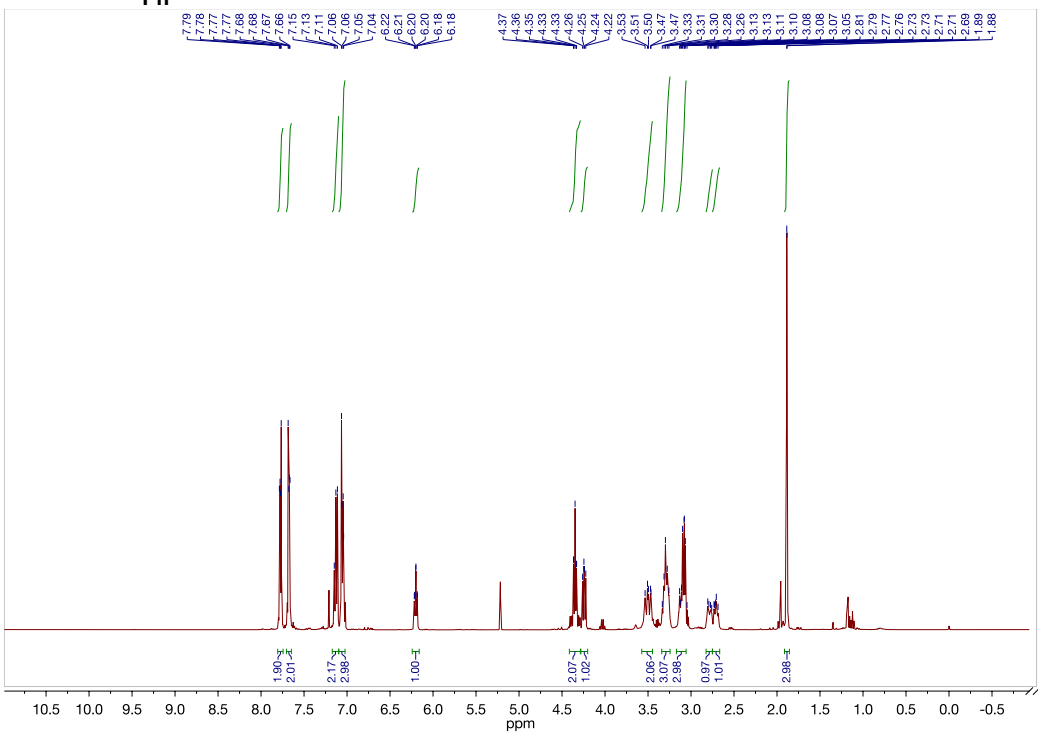


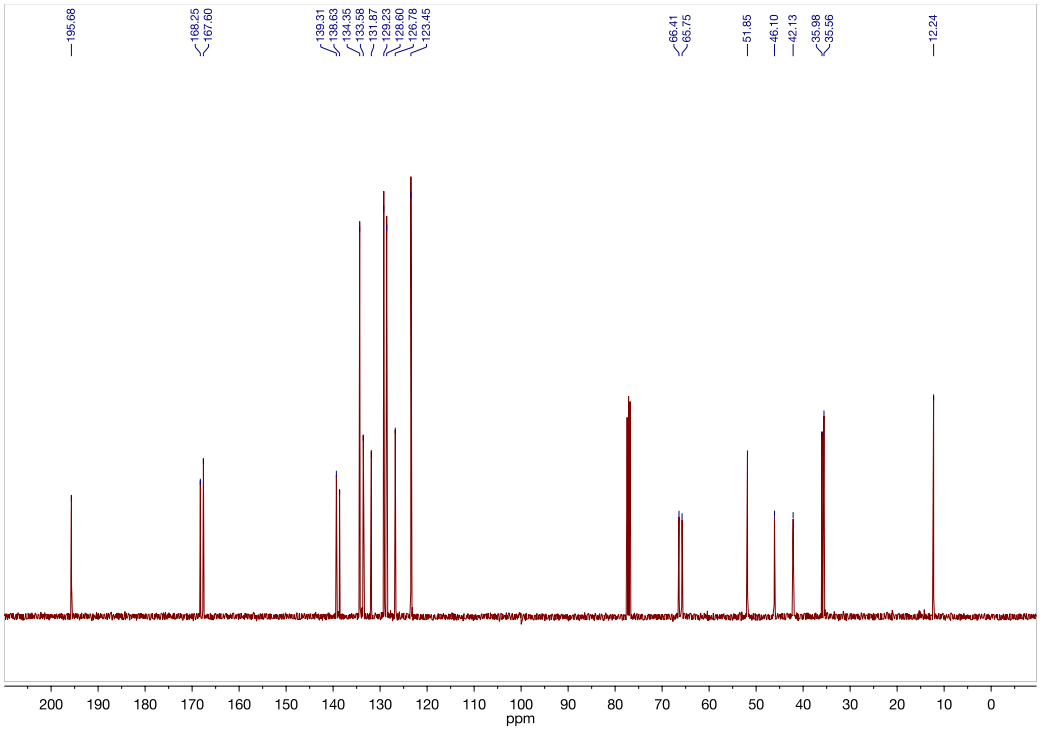




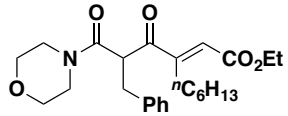
(*E*)-2-(5-Benzyl-3-methyl-6-morpholino-4,6-dioxohex-2-en-1-yl)isoindoline-1,3-dione, 96a

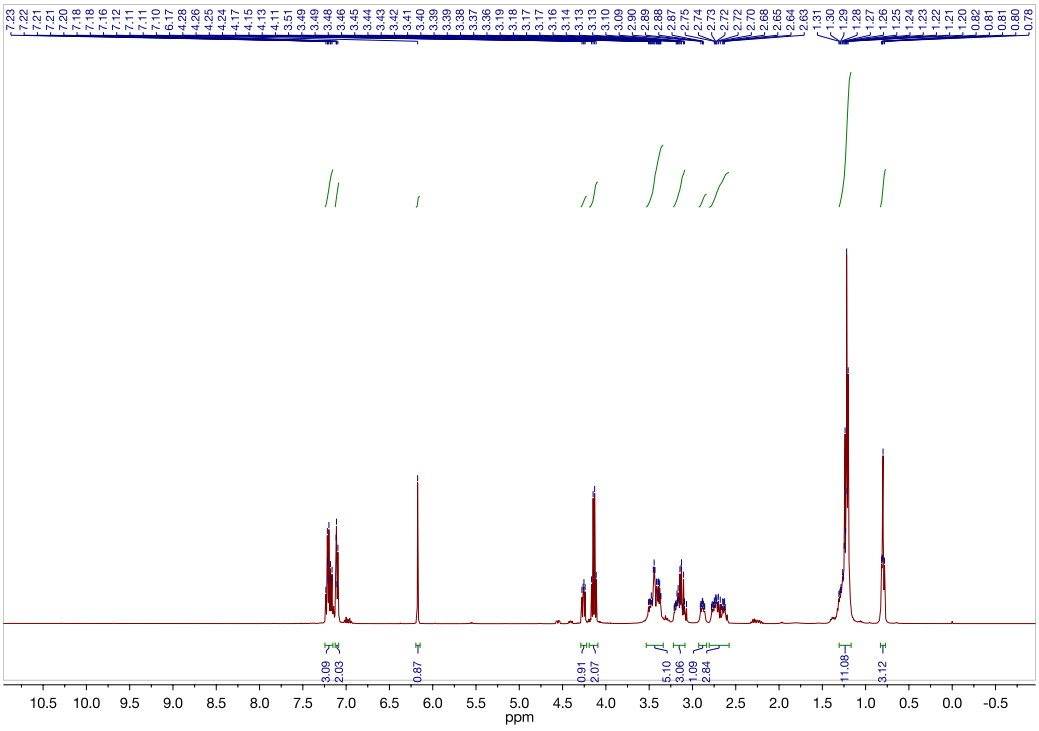


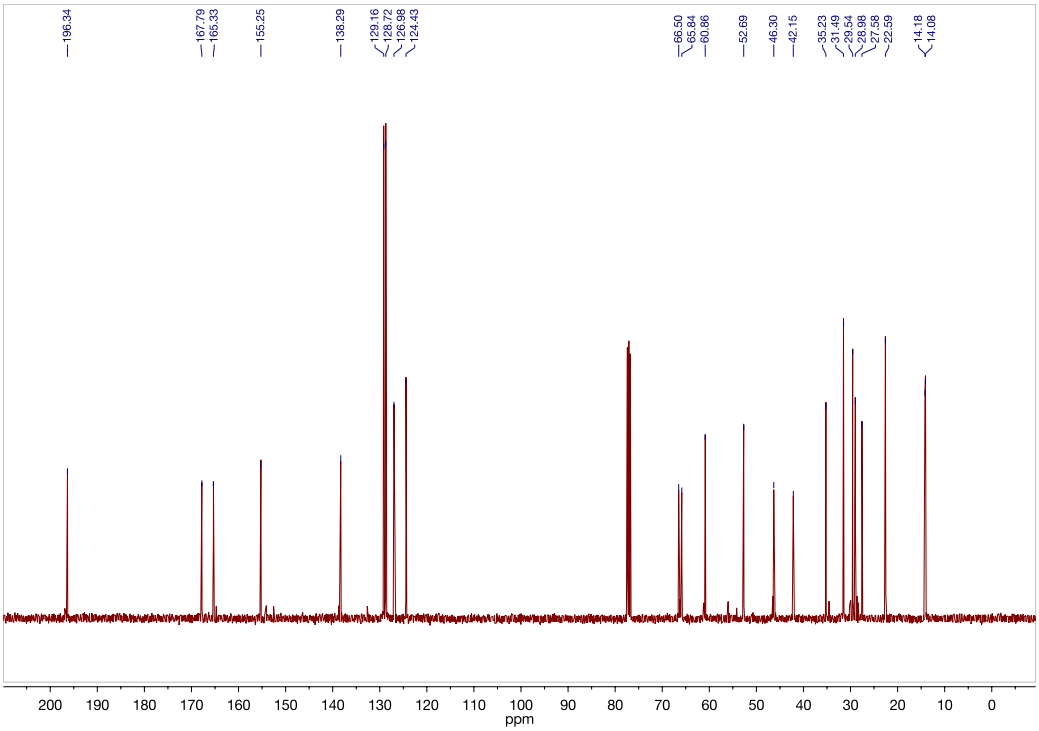




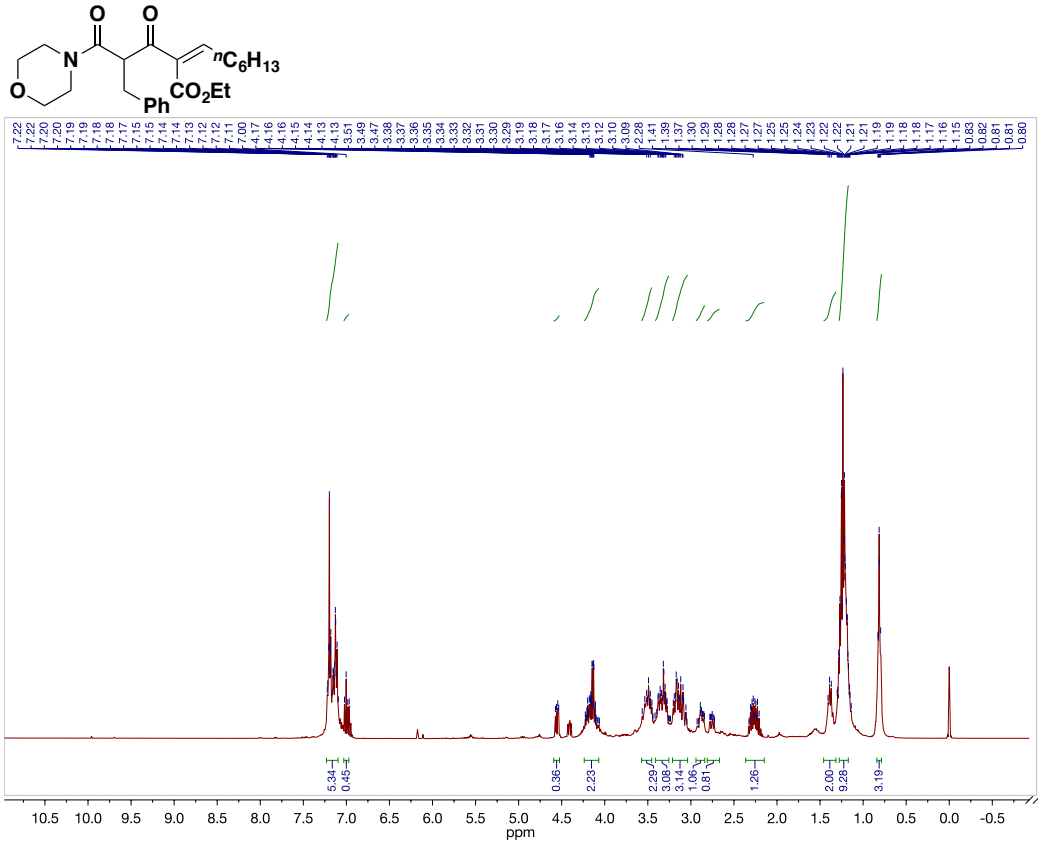
Ethyl (*E*)-3-(2-benzyl-3-morpholino-3-oxopropanoyl)non-2-enoate, 97a

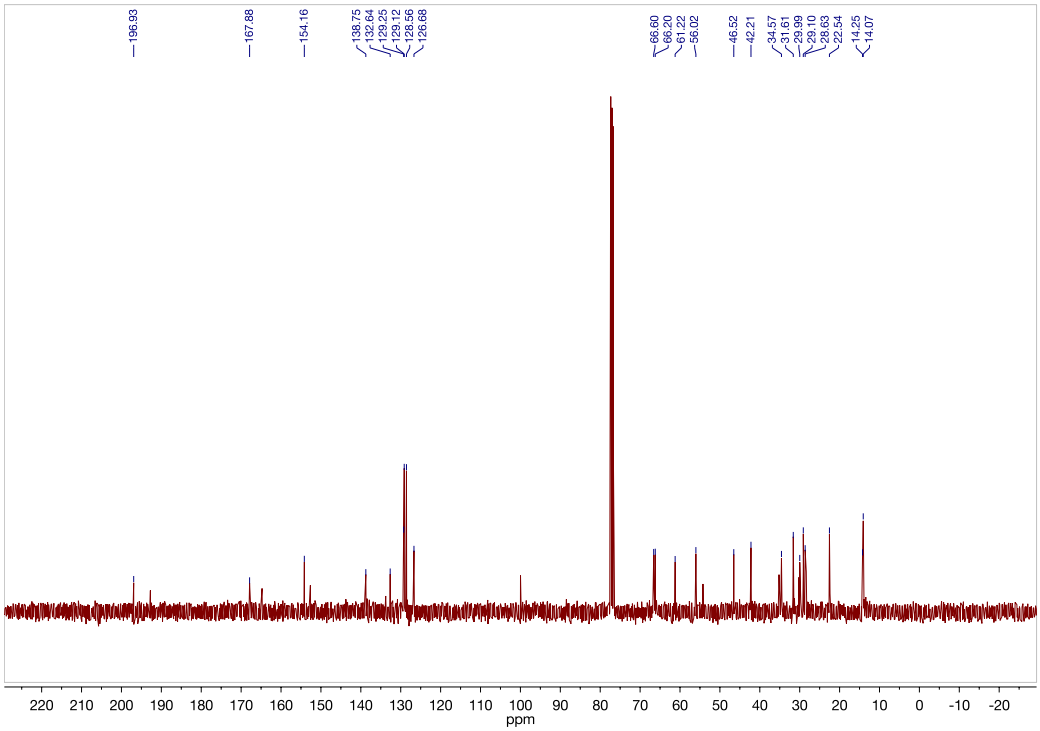




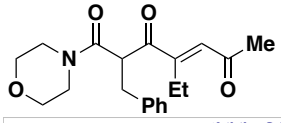


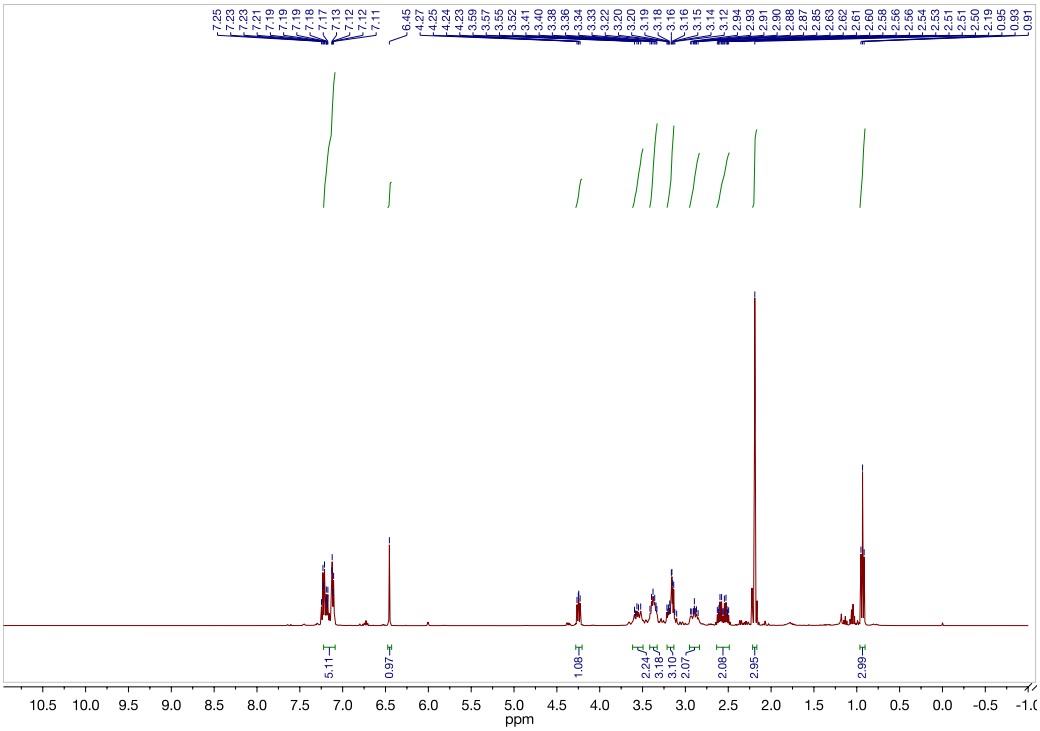
Ethyl (*Z*)-2-(2-benzyl-3-morpholino-3-oxopropanoyl)non-2-enoate, 97b

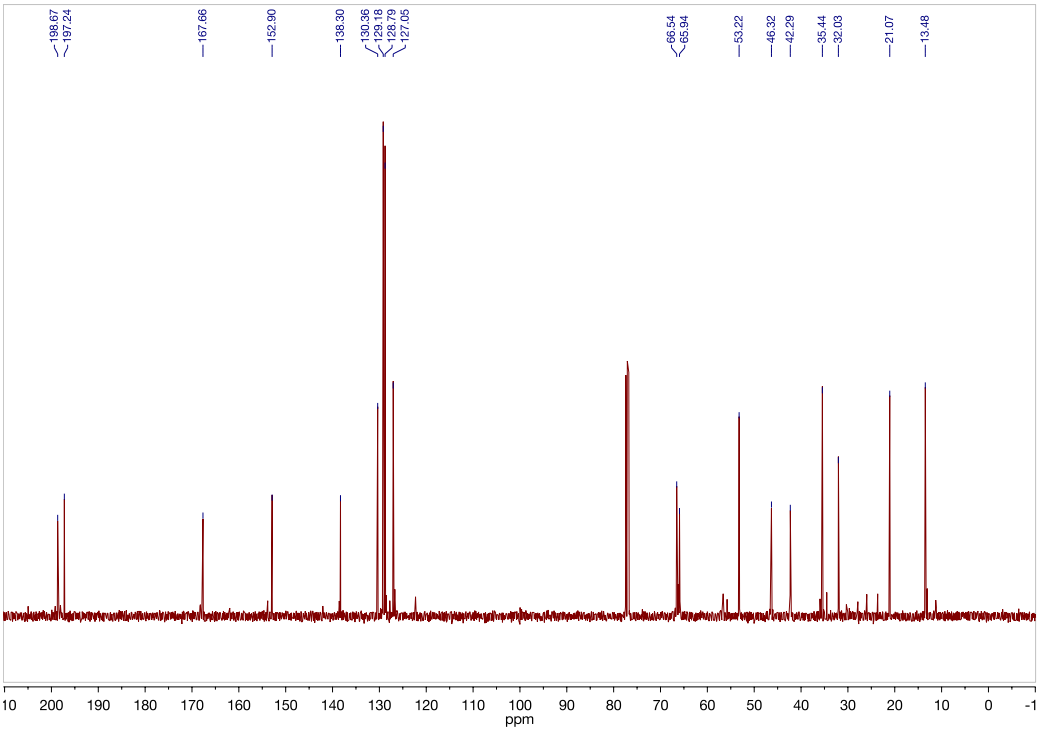




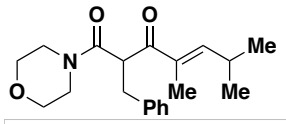
(*E*)-2-Benzyl-4-ethyl-1-morpholinohept-4-ene-1,3,6-trione, 98a

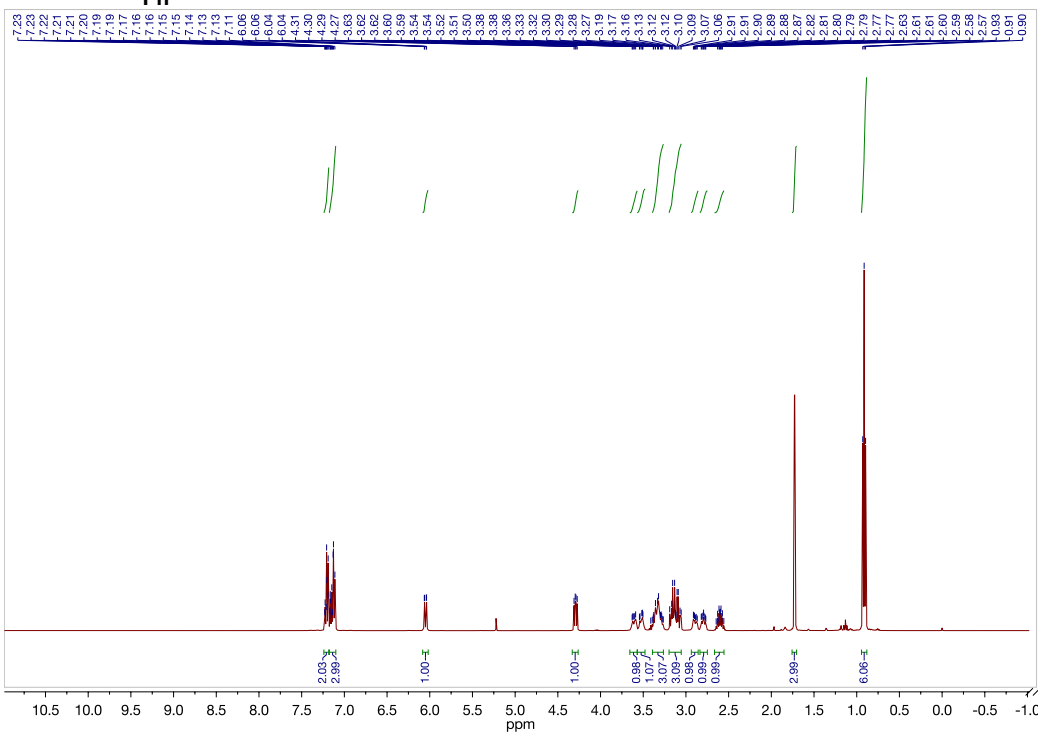


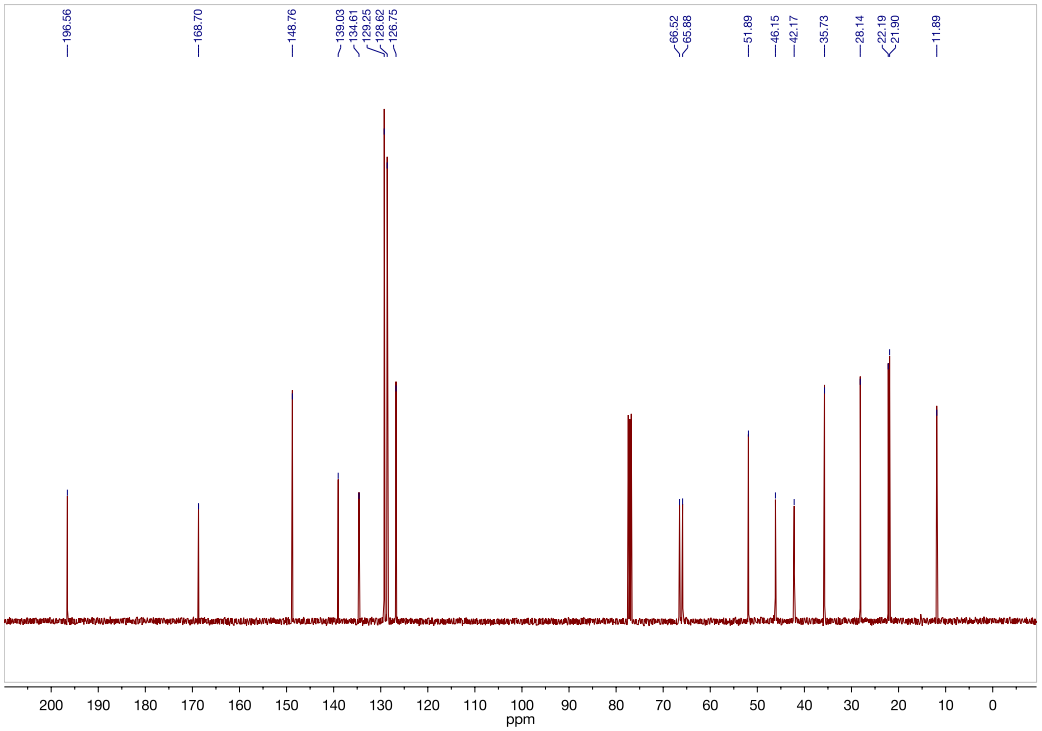




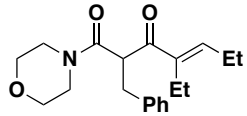
(*E*)-2-Benzyl-4,6-dimethyl-1-morpholinohept-4-ene-1,3-dione, 99a

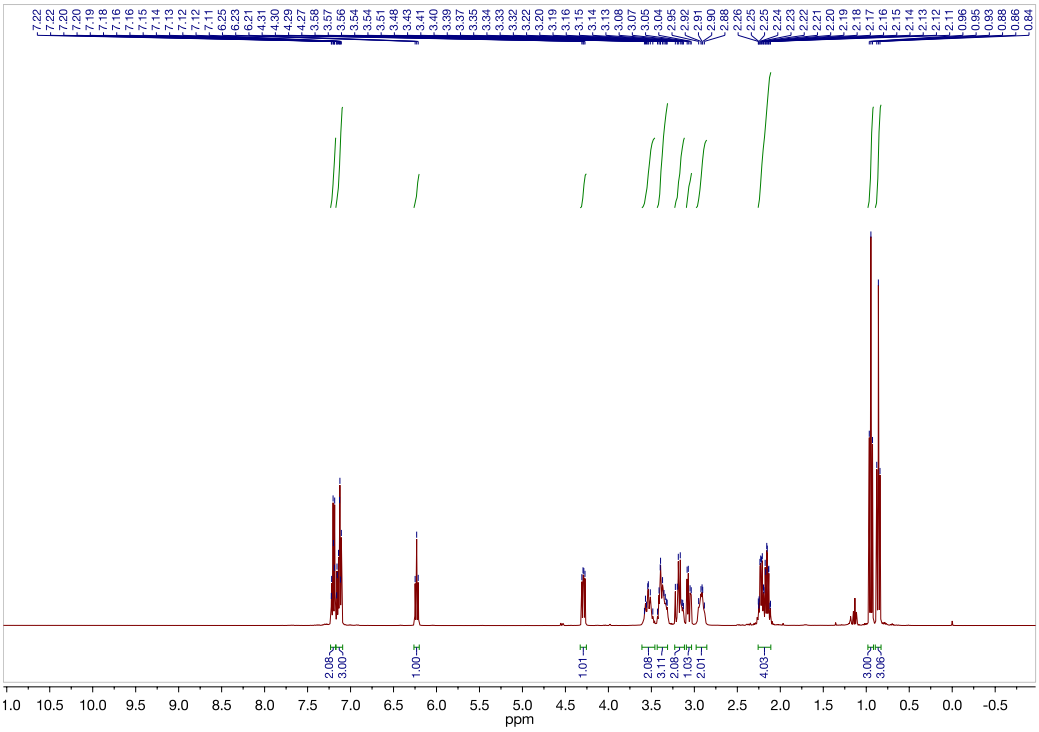


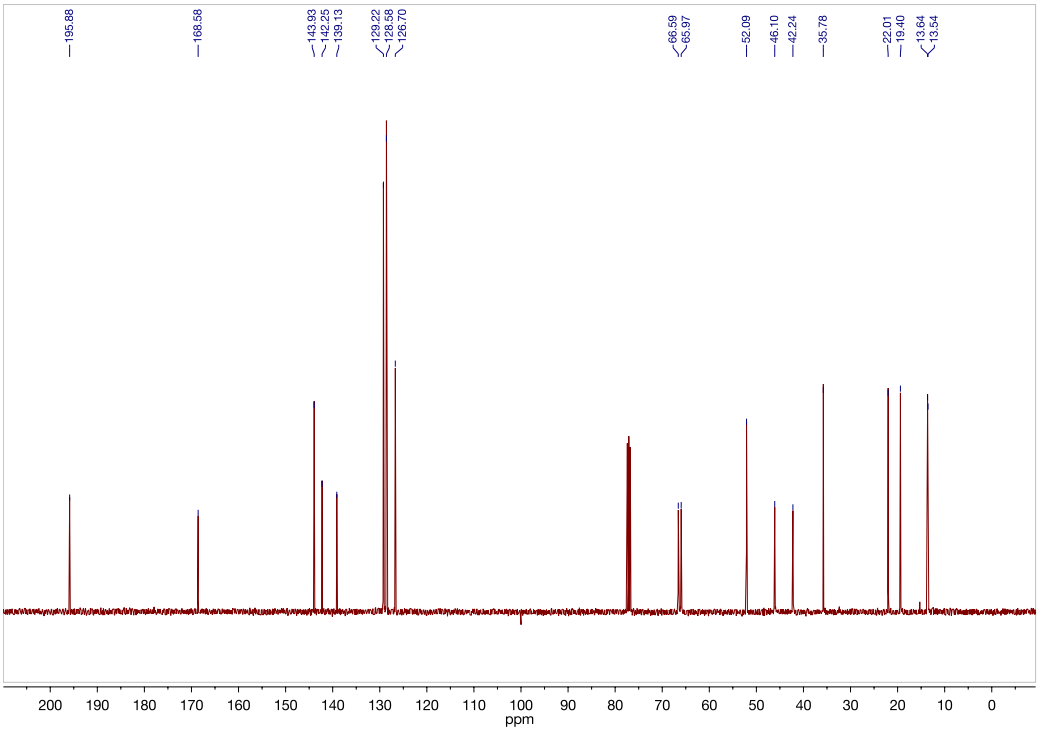




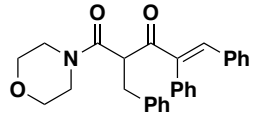
(*E*)-2-Benzyl-4-ethyl-1-morpholinohept-4-ene-1,3-dione, 102

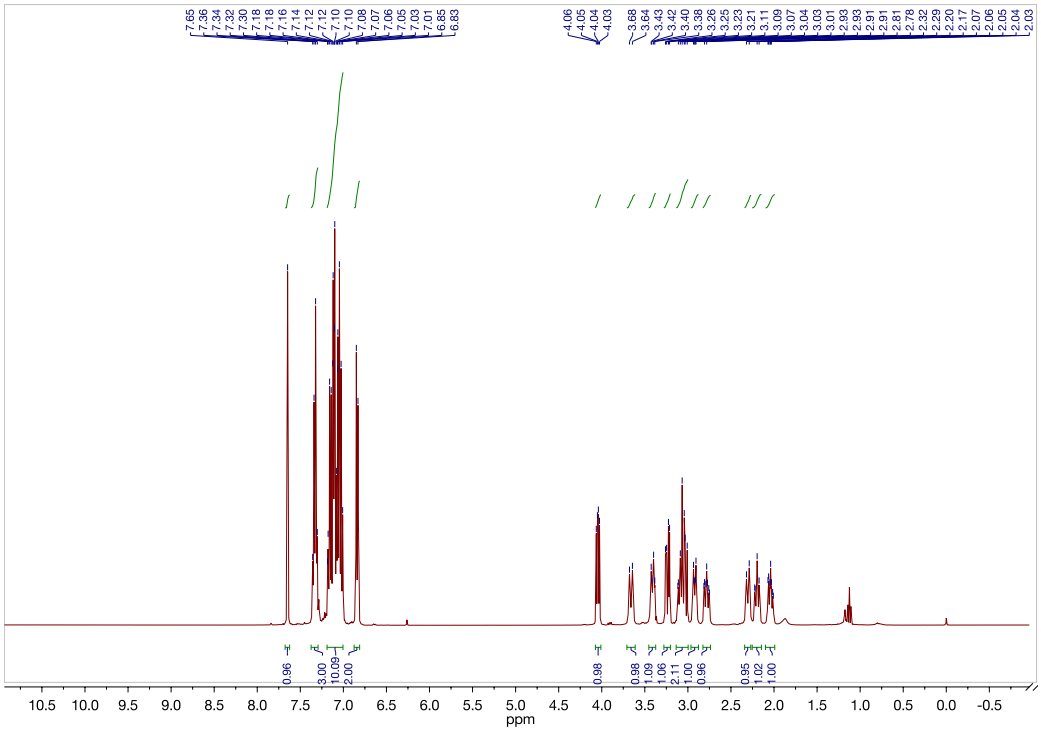


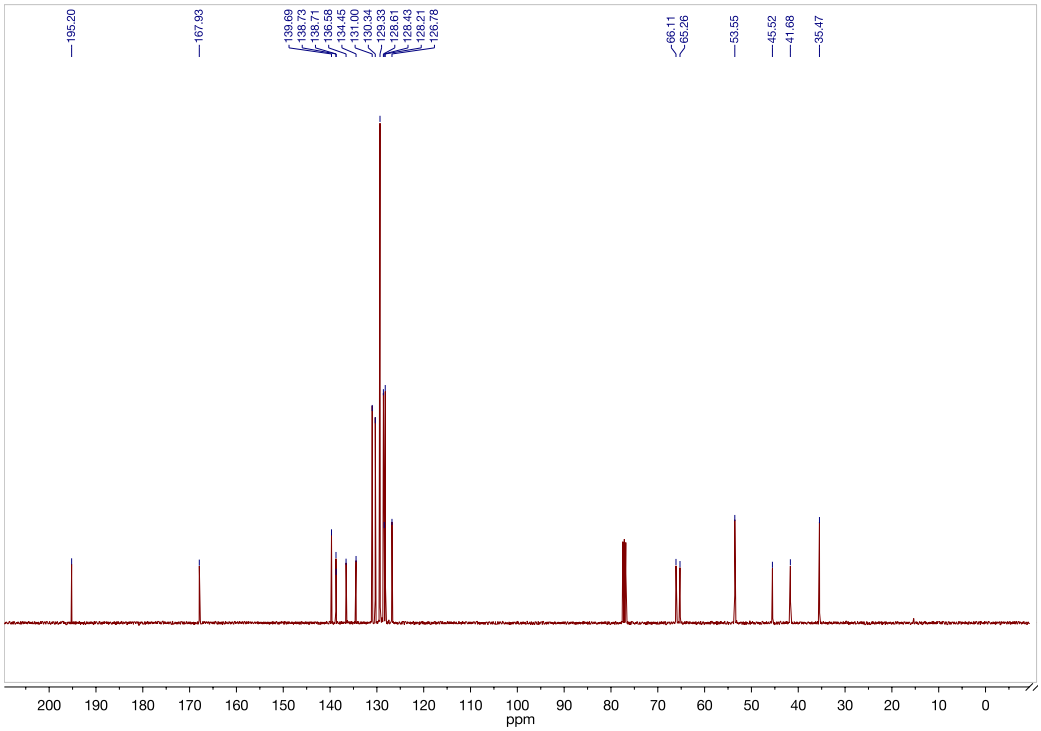




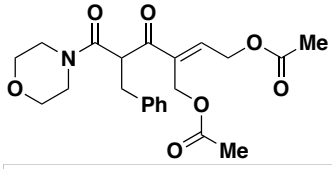
(*E*)-2-Benzyl-1-morpholino-4,5-diphenylpent-4-ene-1,3-dione, 103

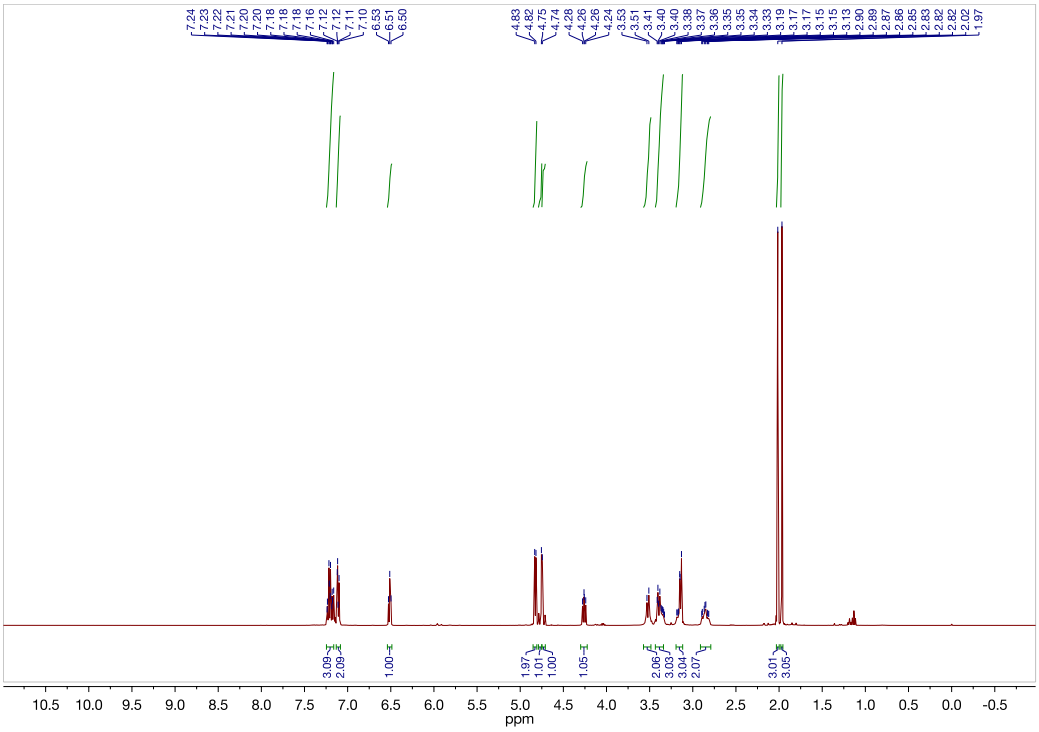


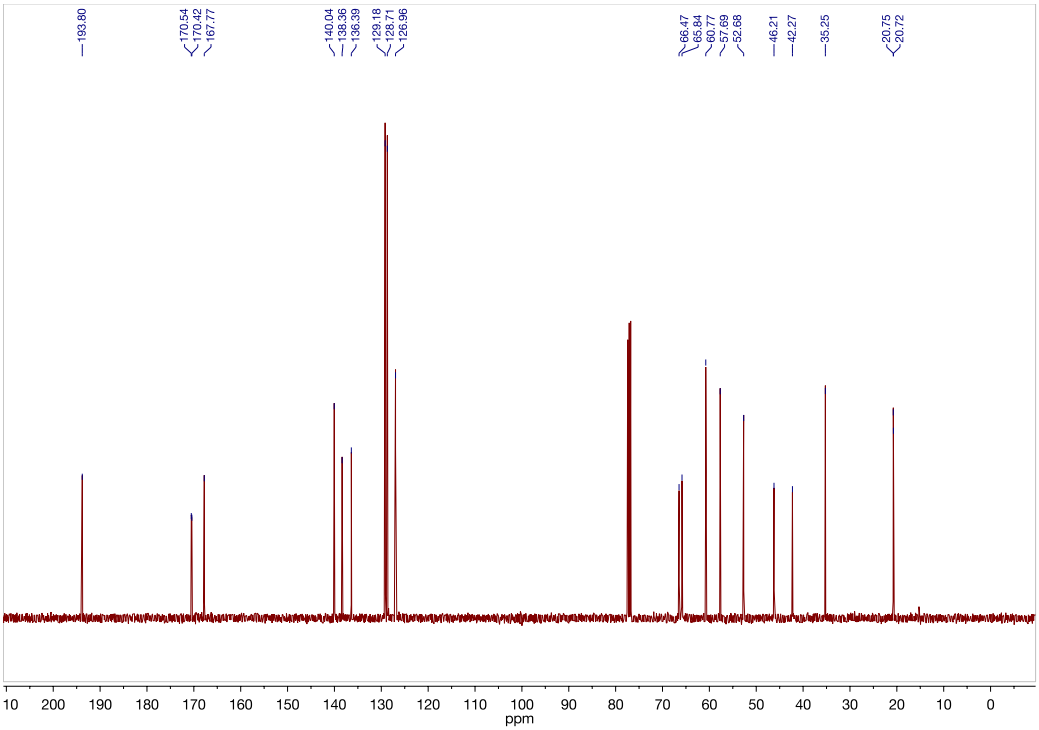




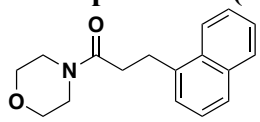
(*E*)-2-(2-Benzyl-3-morpholino-3-oxopropanoyl)but-2-ene-1,4-diyl diacetate, 104

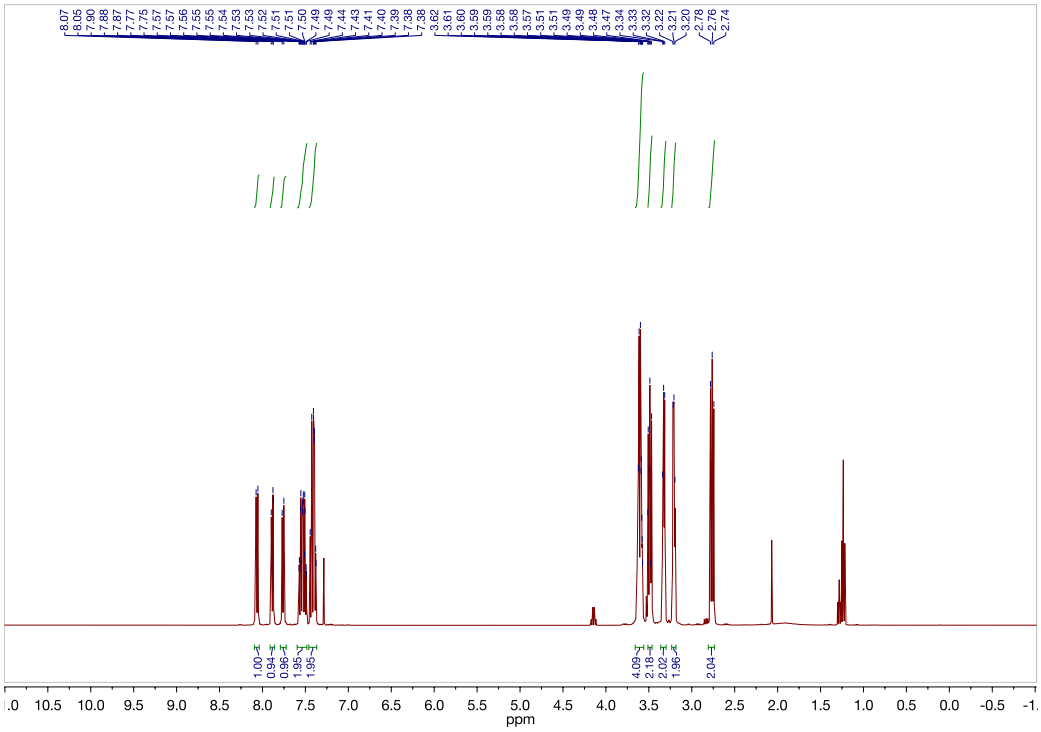


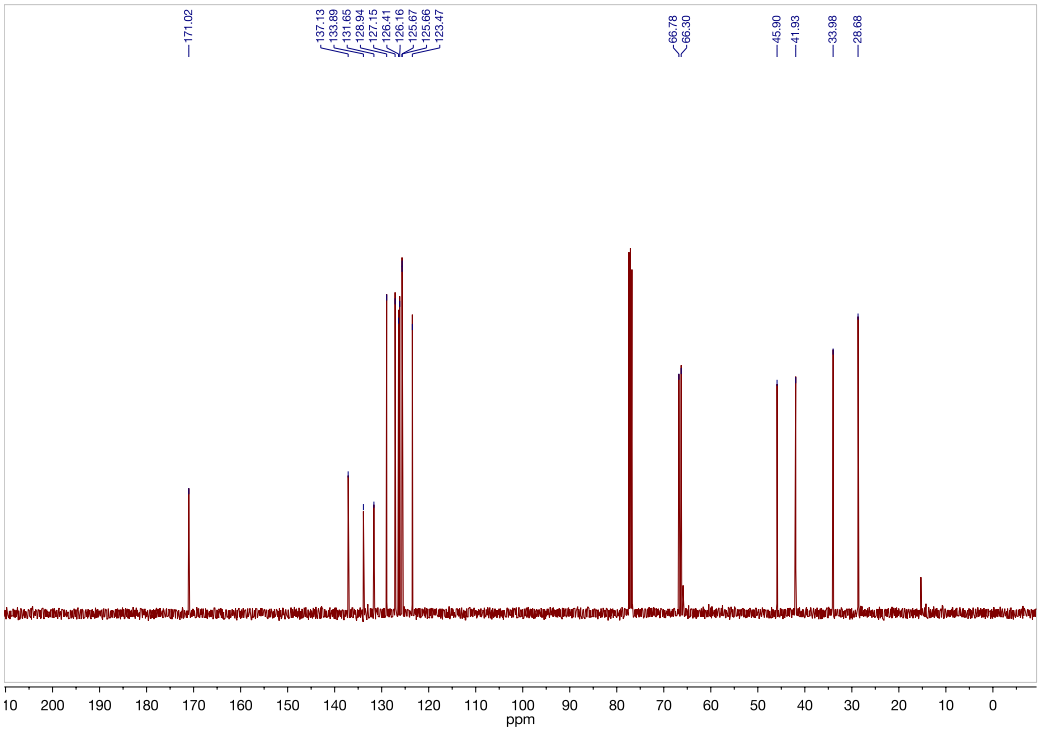




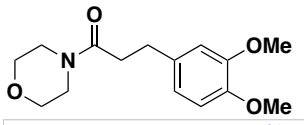
1-Morpholino-3-(naphthalen-1-yl)propan-1-one, 68b

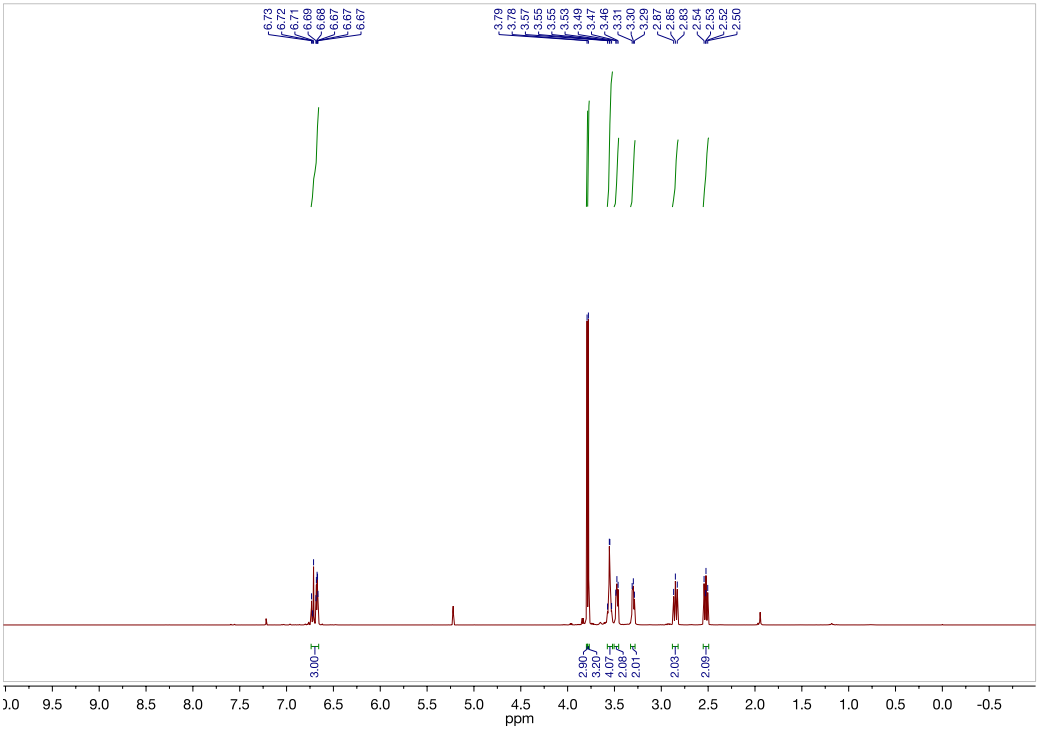


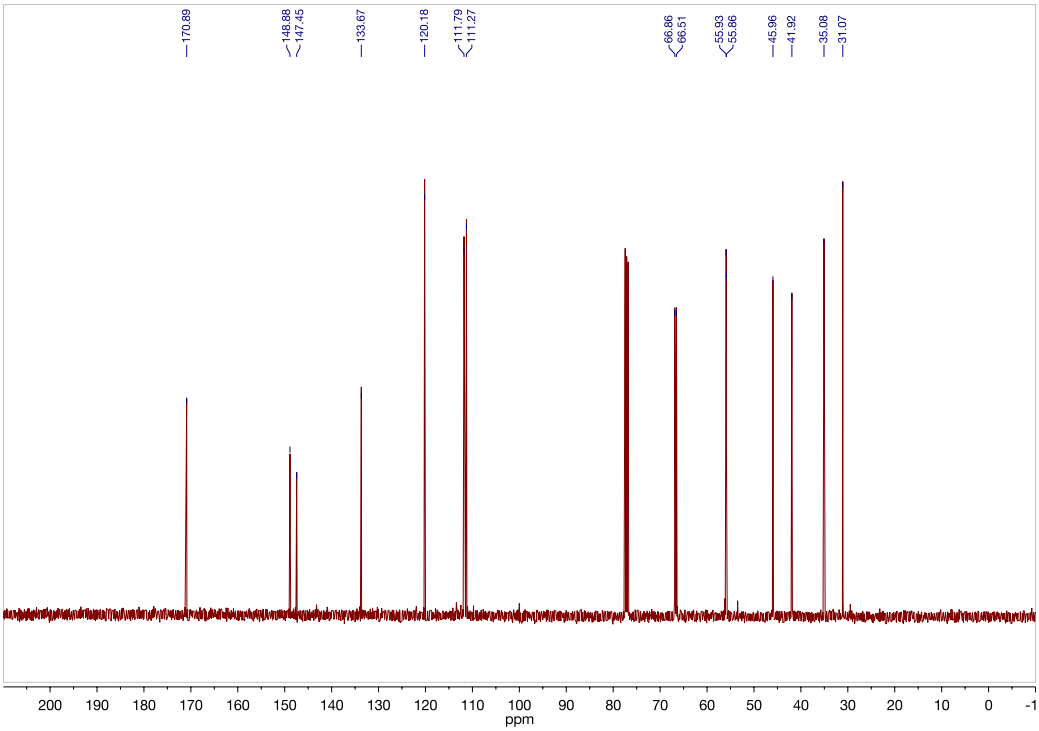




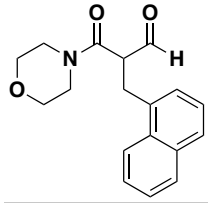
3-(3,4-Dimethoxyphenyl)-1-morpholinopropan-1-one, 68c

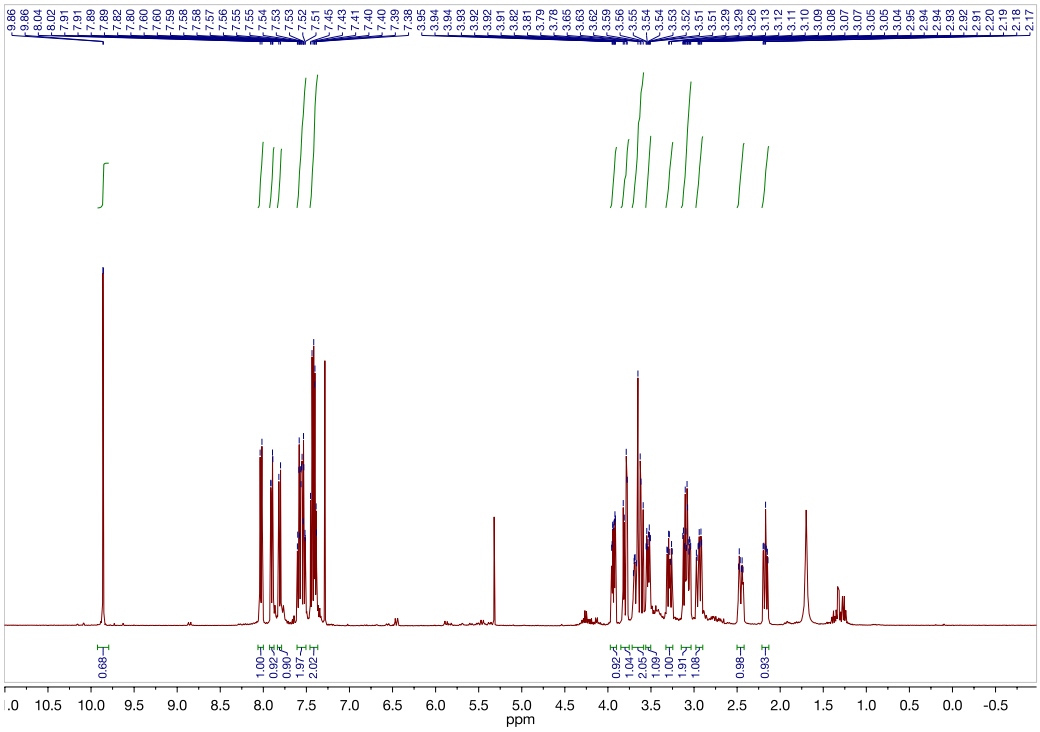


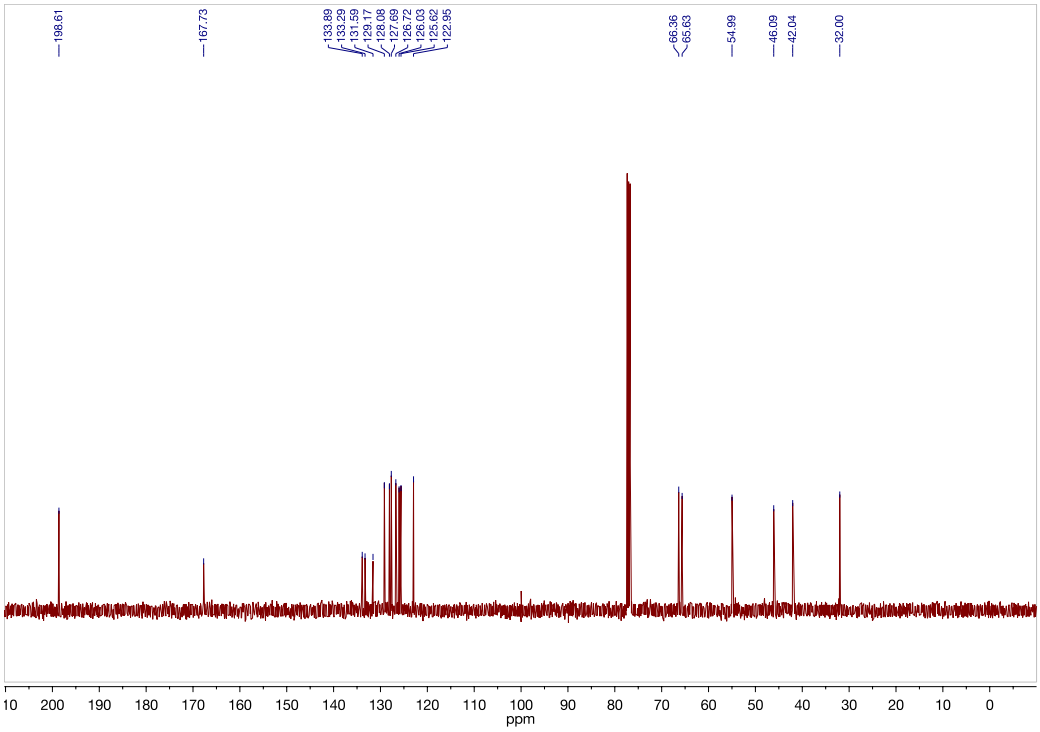




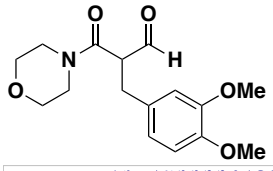
3-Morpholino-2-(naphthalen-1-ylmethyl)-3-oxopropanal, 69b

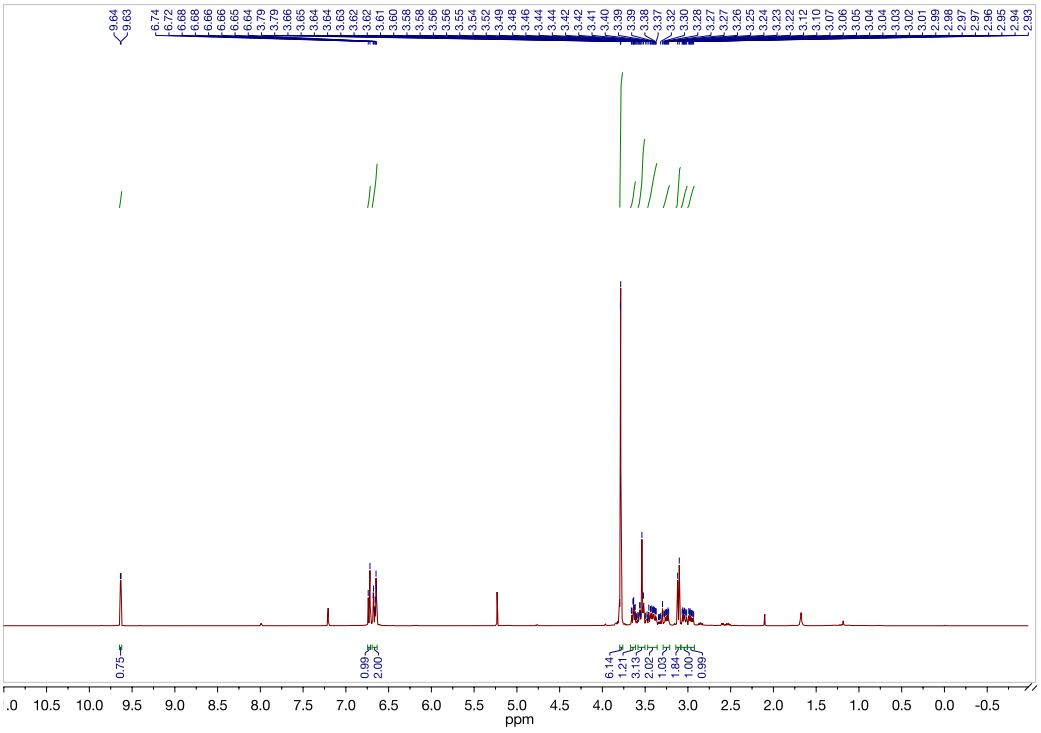


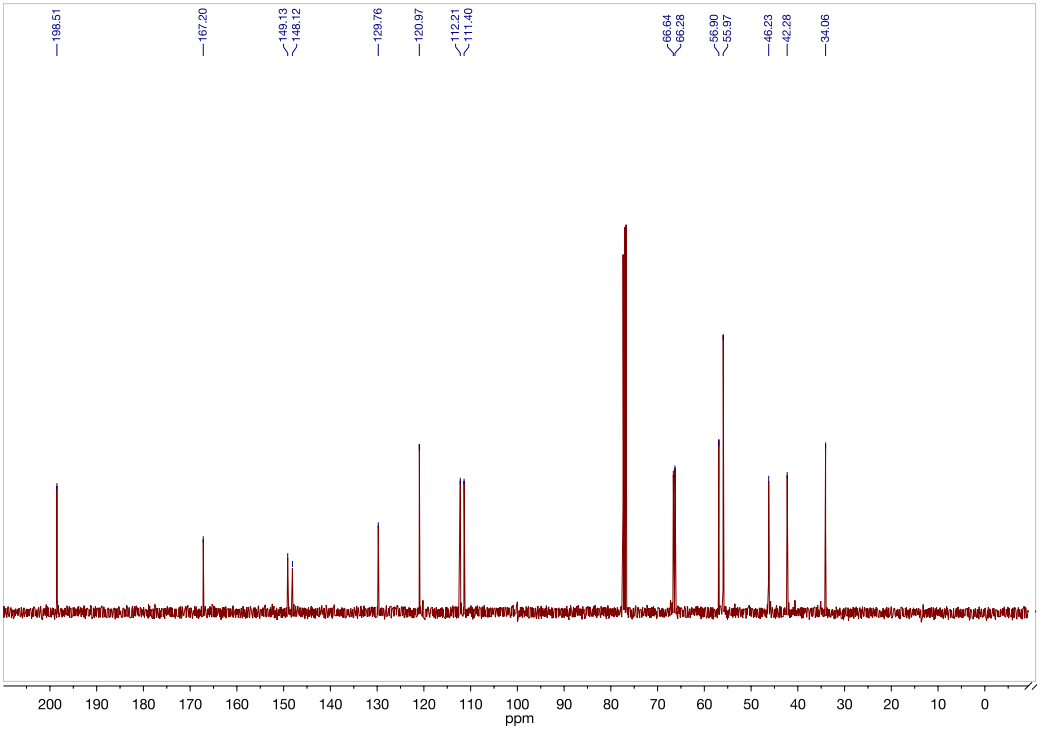




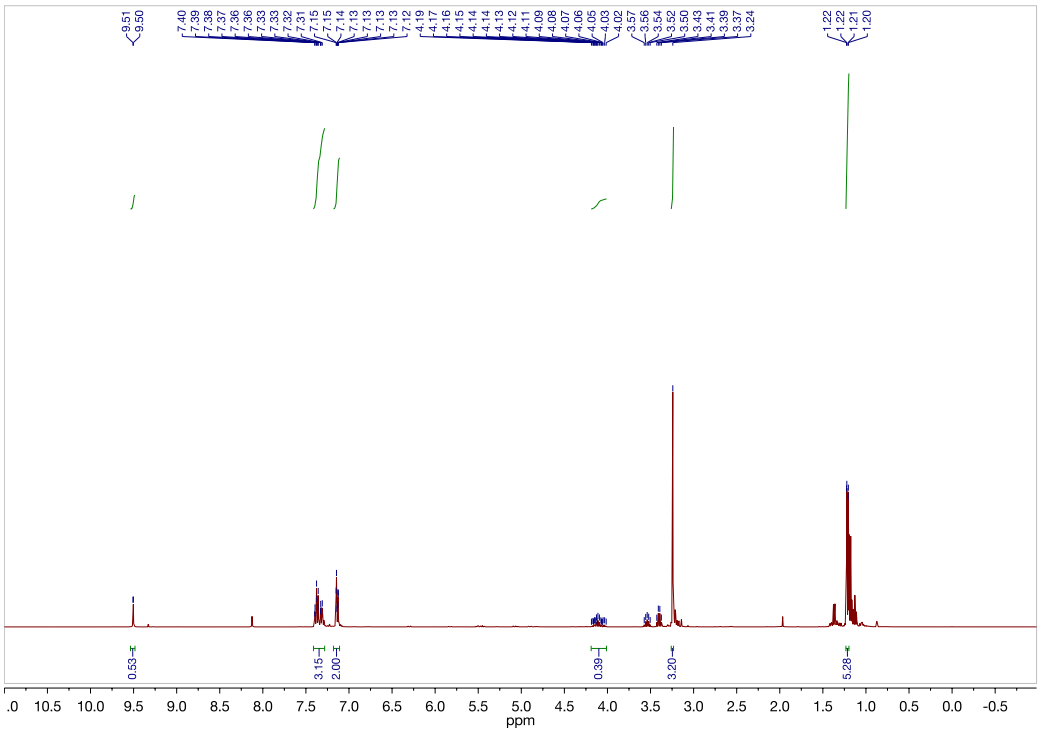
2-(3,4-Dimethoxybenzyl)-3-morpholino-3-oxopropanal, 69c

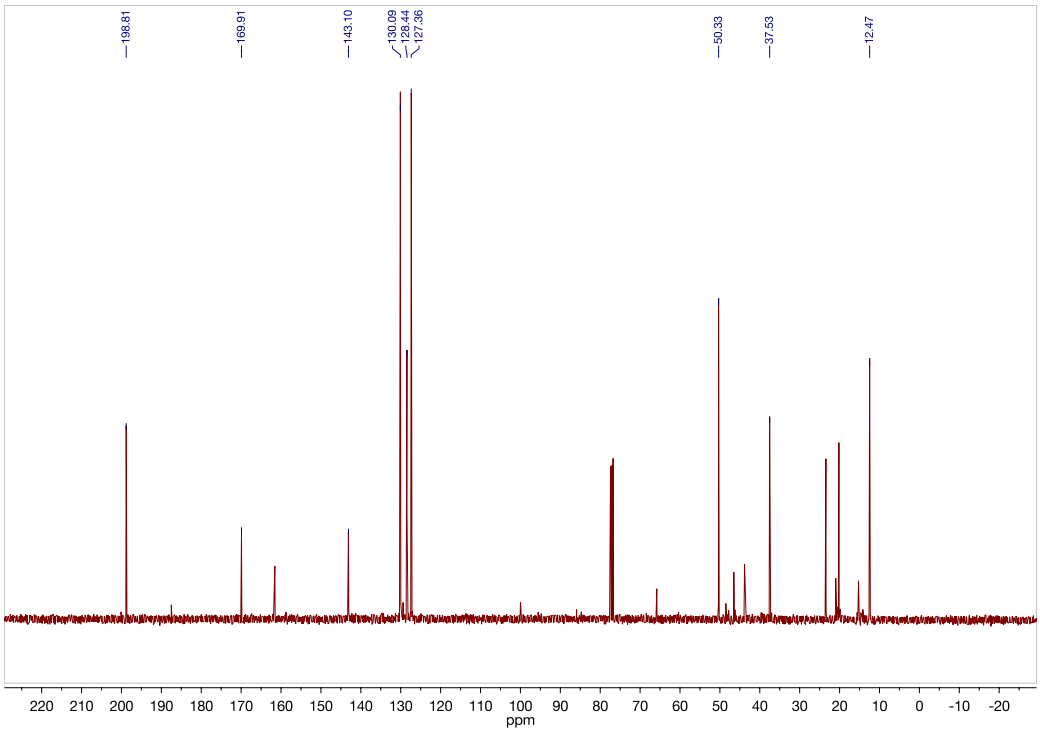




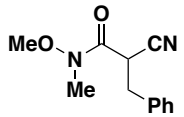


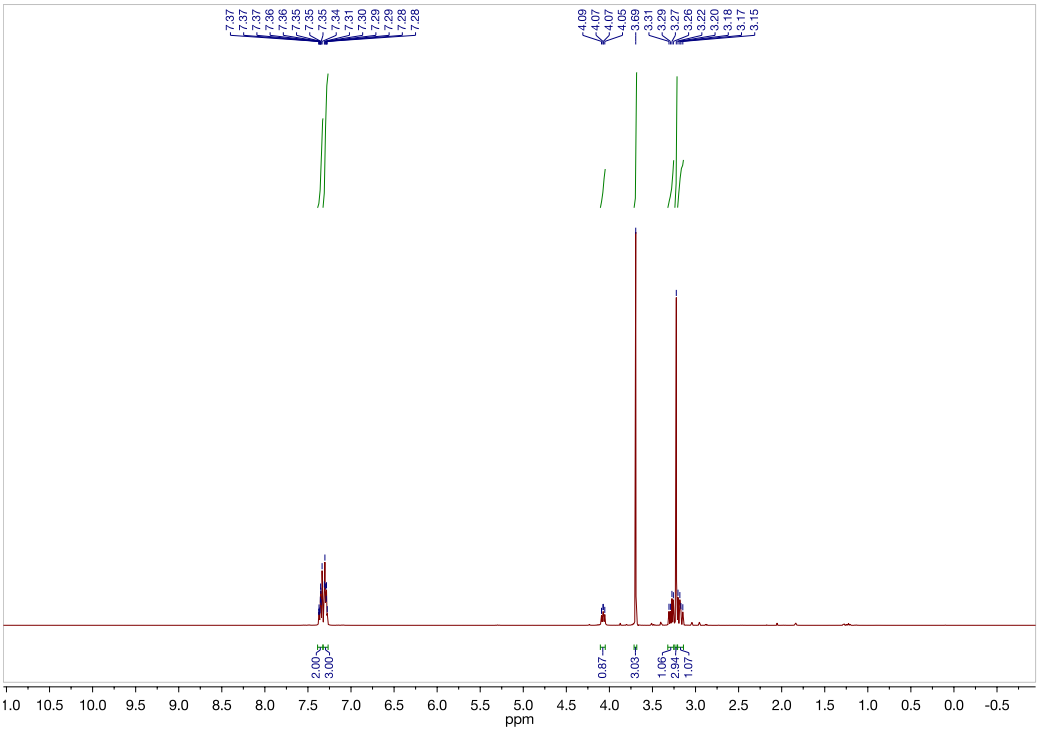
N,2-Dimethyl-3-oxo-*N*-phenylpropanamide, 69m

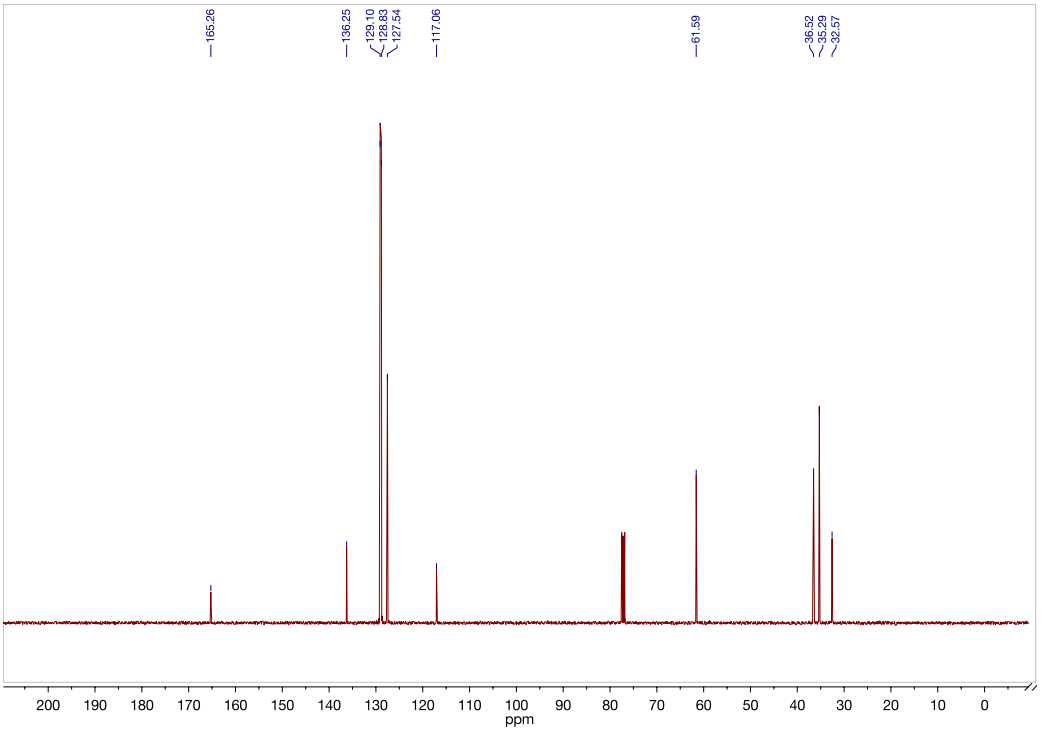




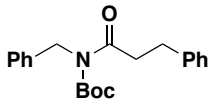
2-Cyano-*N*-methoxy-*N*-methyl-3-phenylpropanamide, 109

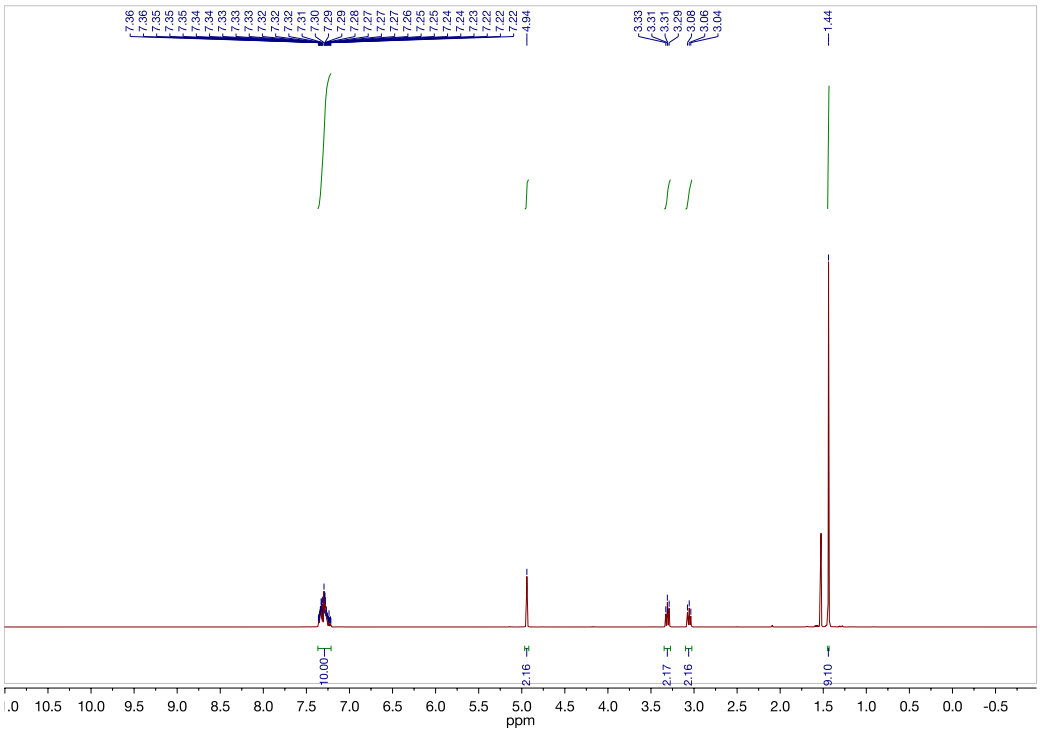


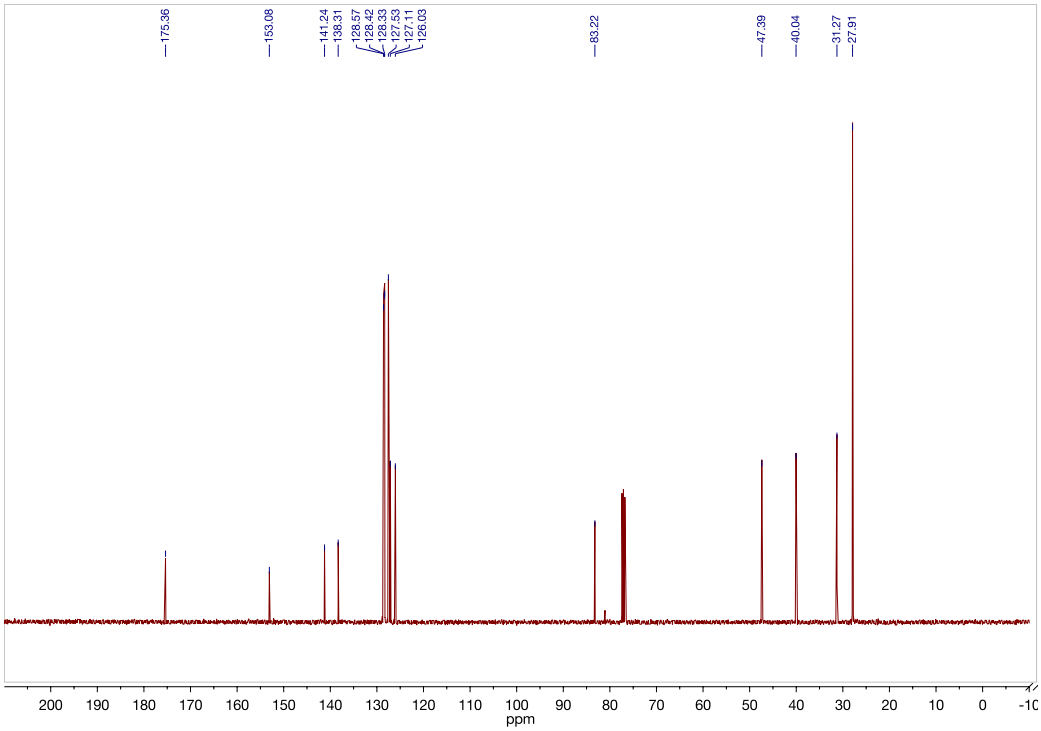




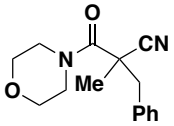
tert-Butyl benzyl(3-phenylpropanoyl)carbamate, 114

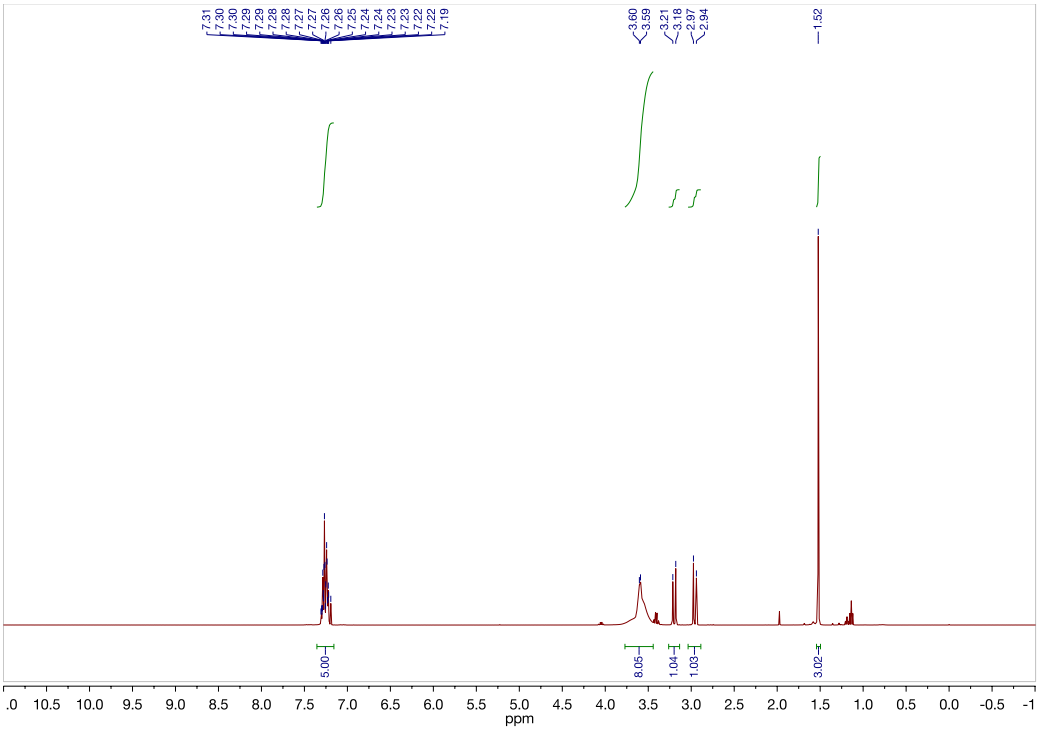


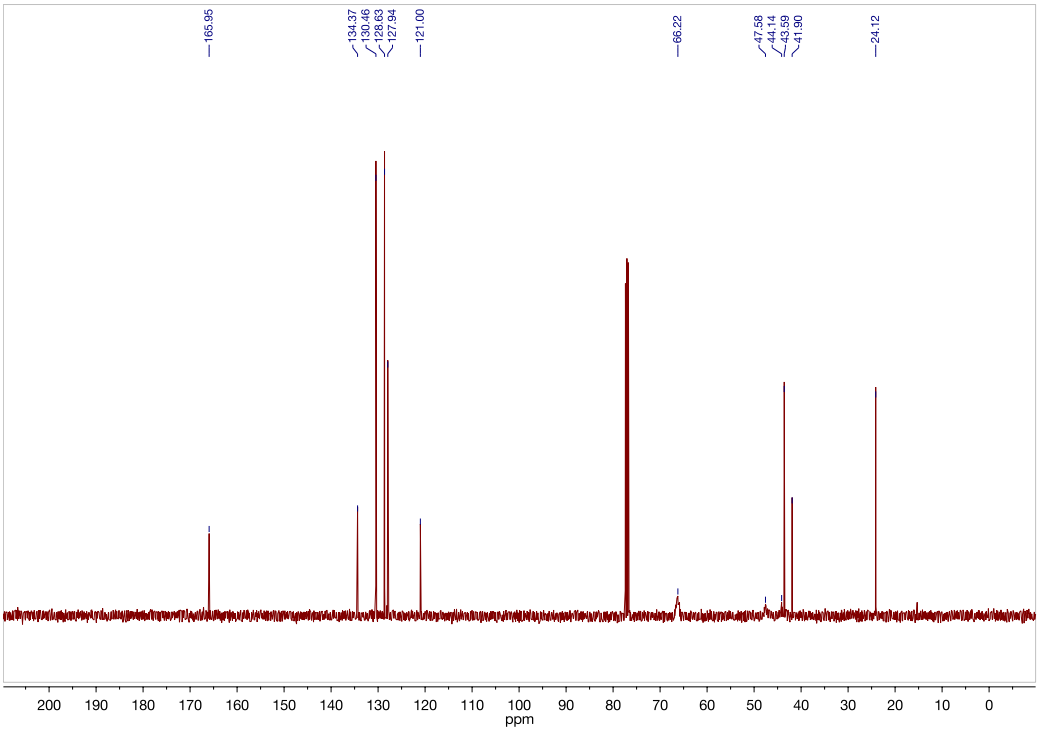




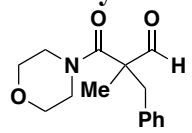
2-Benzyl-2-methyl-3-morpholino-3-oxopropanenitrile, 121

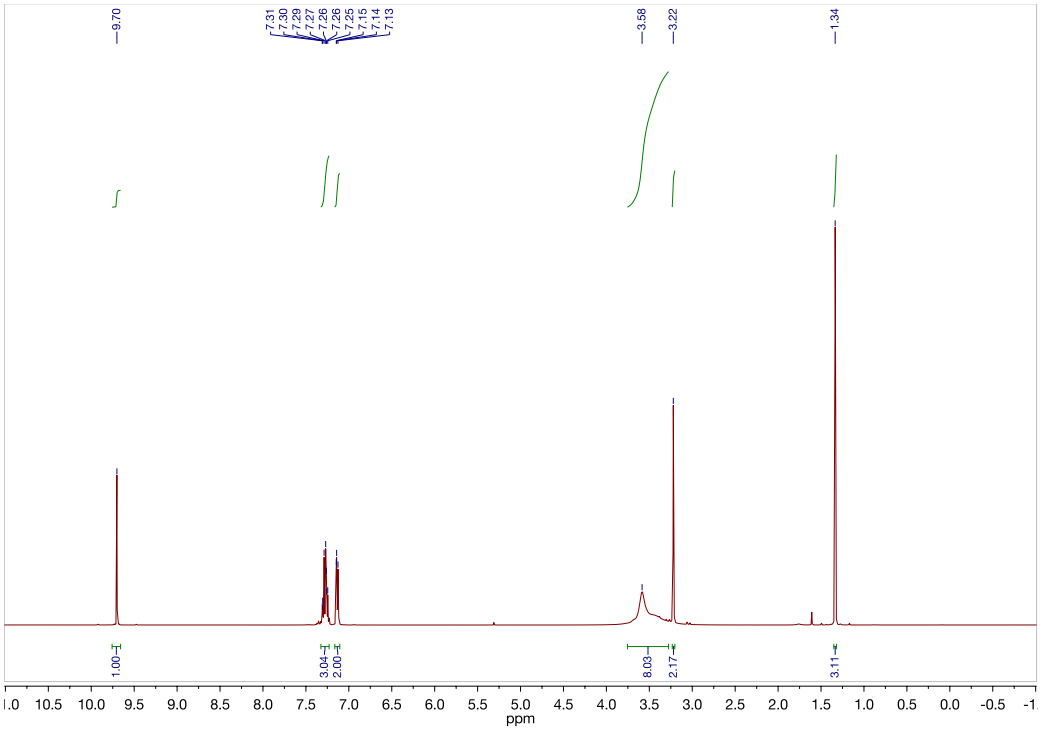


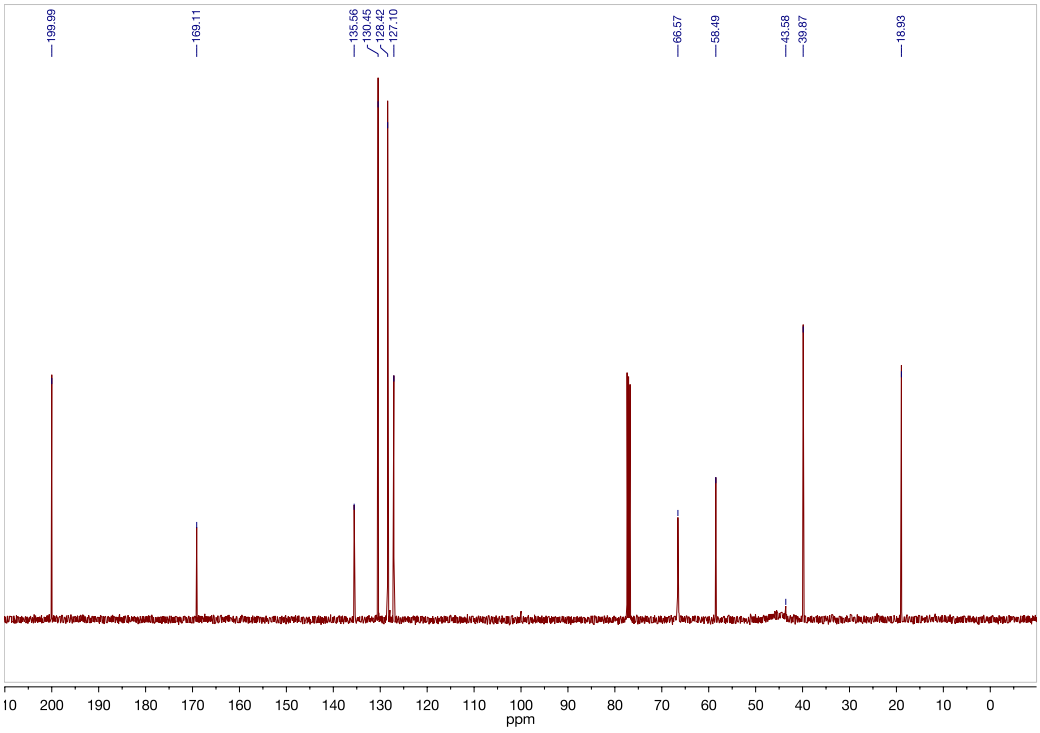




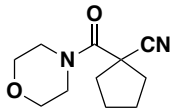
2-Benzyl-2-methyl-3-morpholino-3-oxopropanal, 122

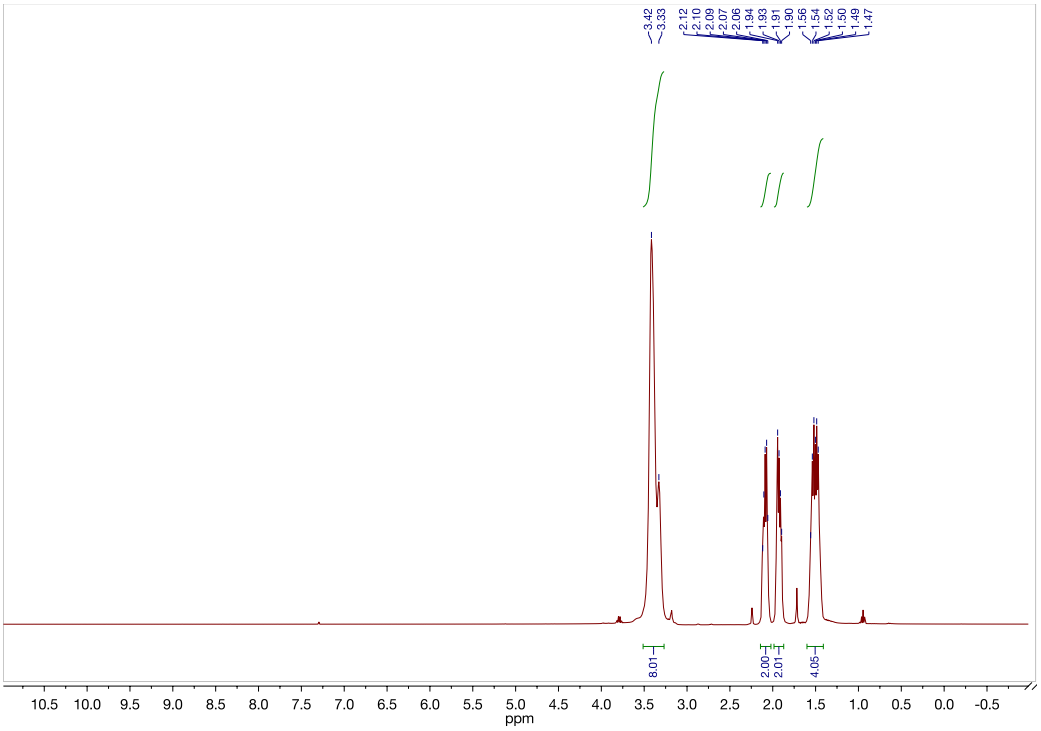


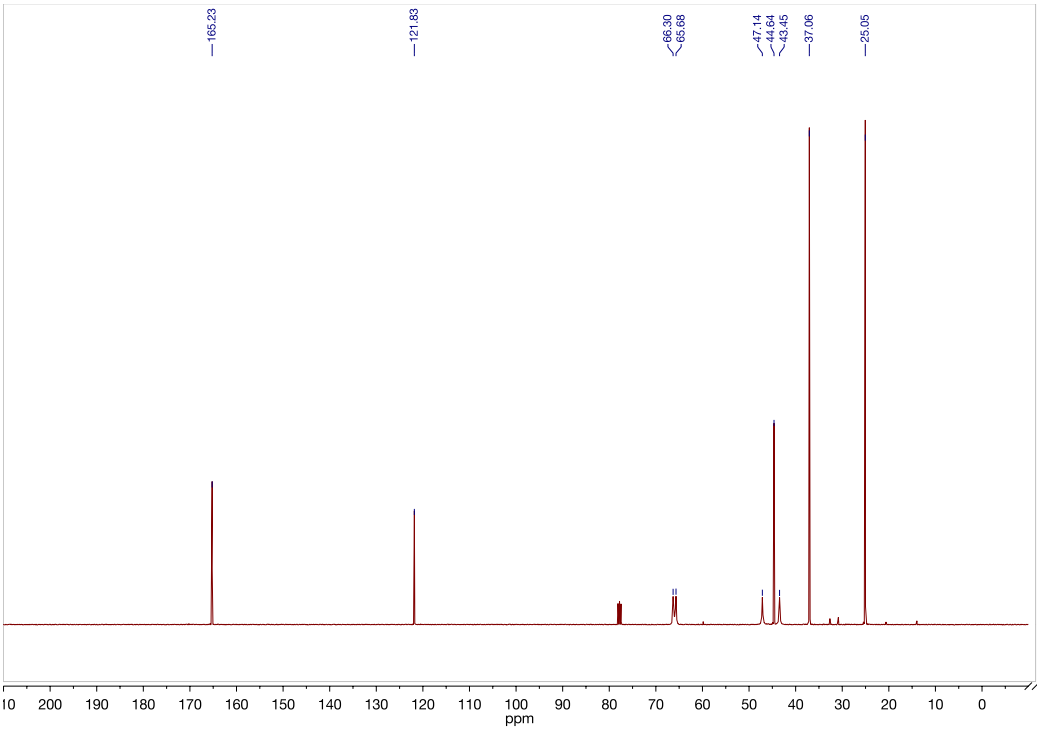




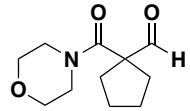
1-(Morpholine-4-carbonyl)cyclopentane-1-carbonitrile, 122

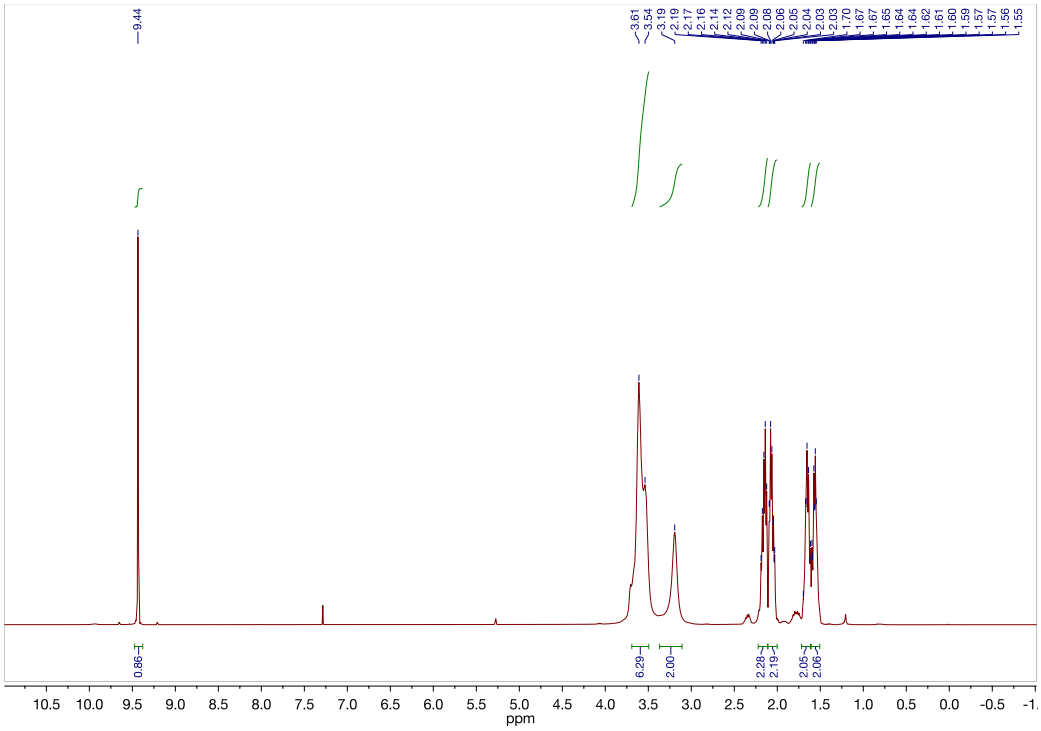


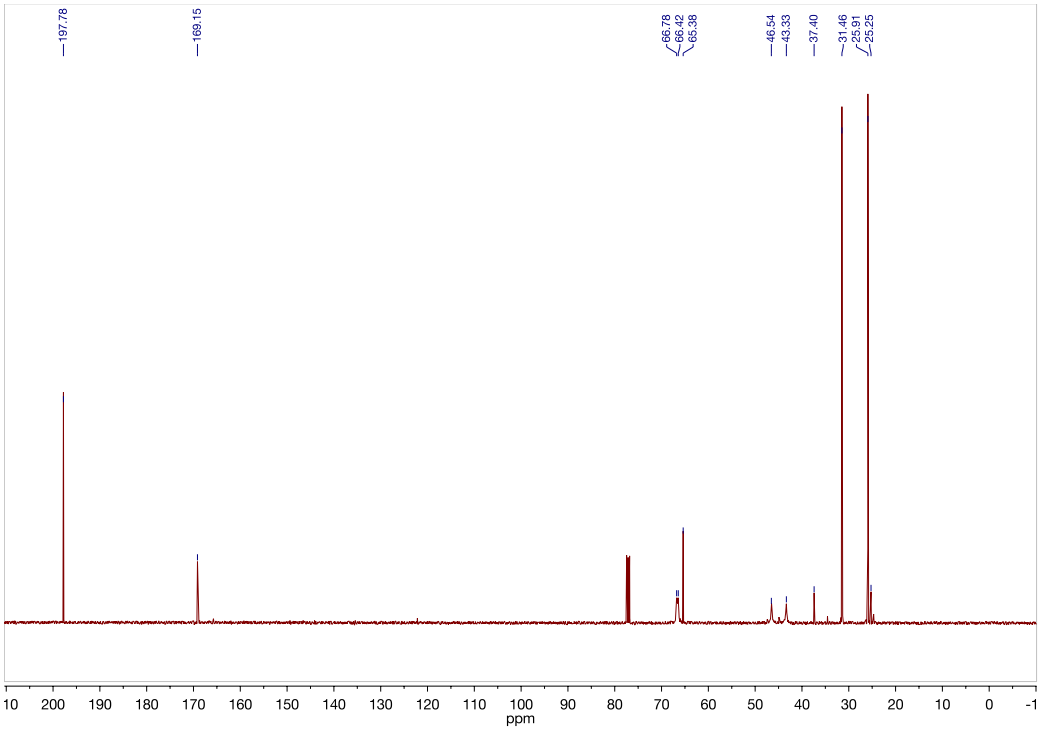




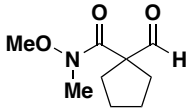
1-(Morpholine-4-carbonyl)cyclopentane-1-carbaldehyde, 123

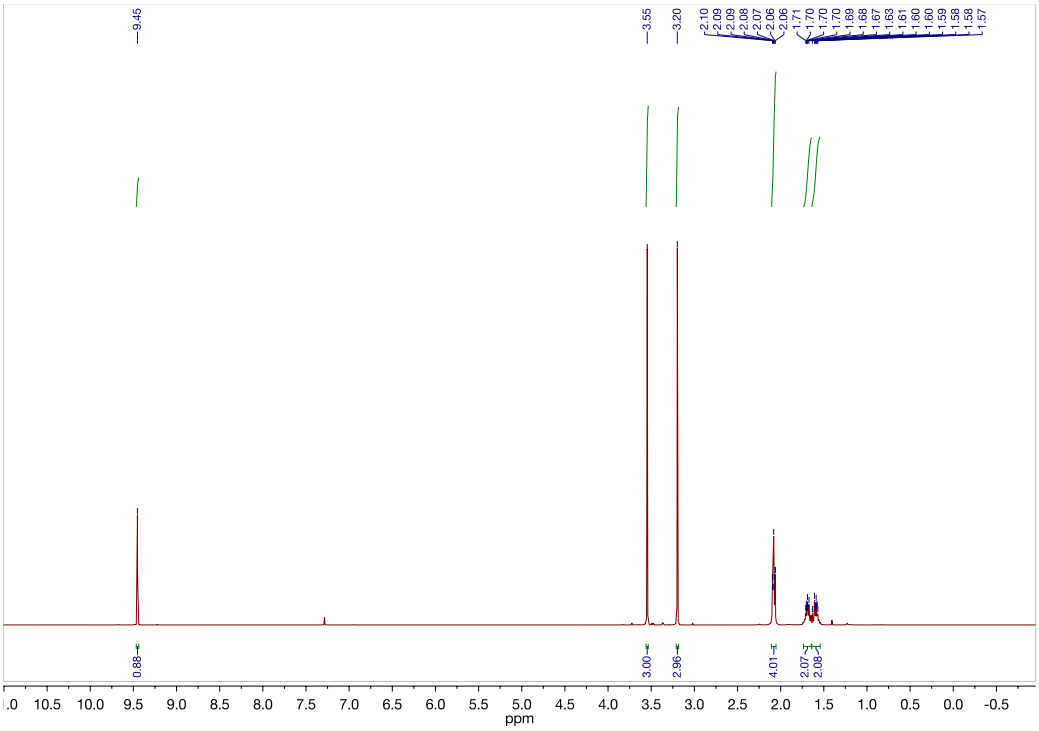


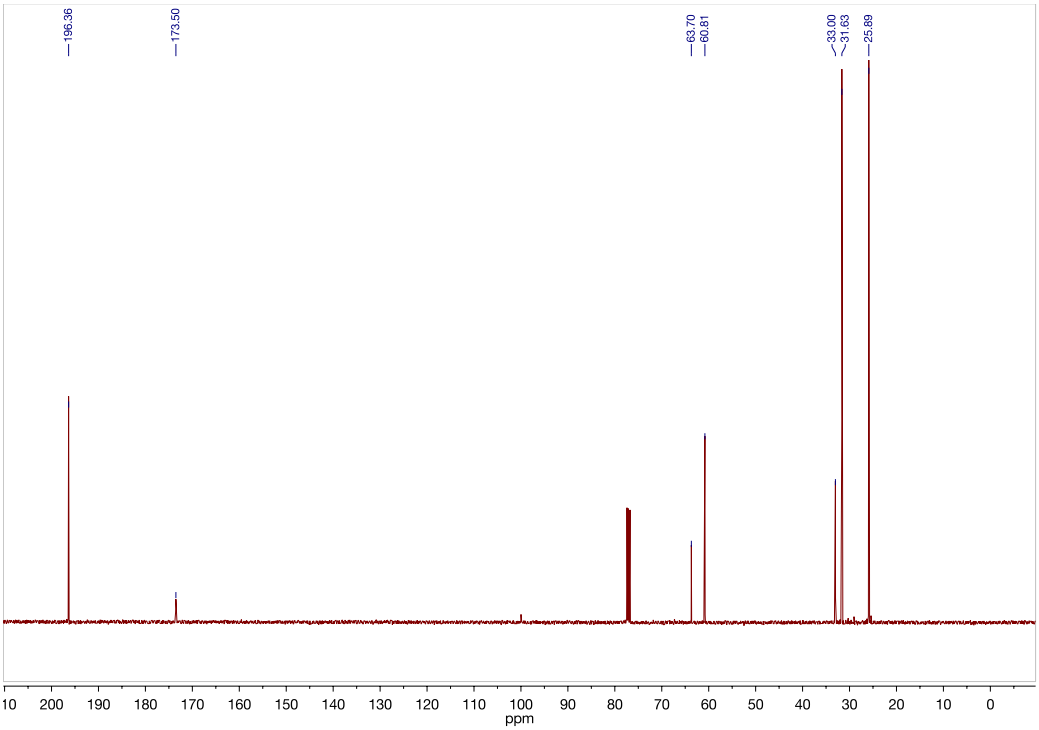




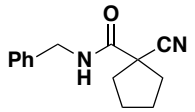
1-Formyl-*N*-methoxy-*N*-methylcyclopentane-1-carboxamide, 126

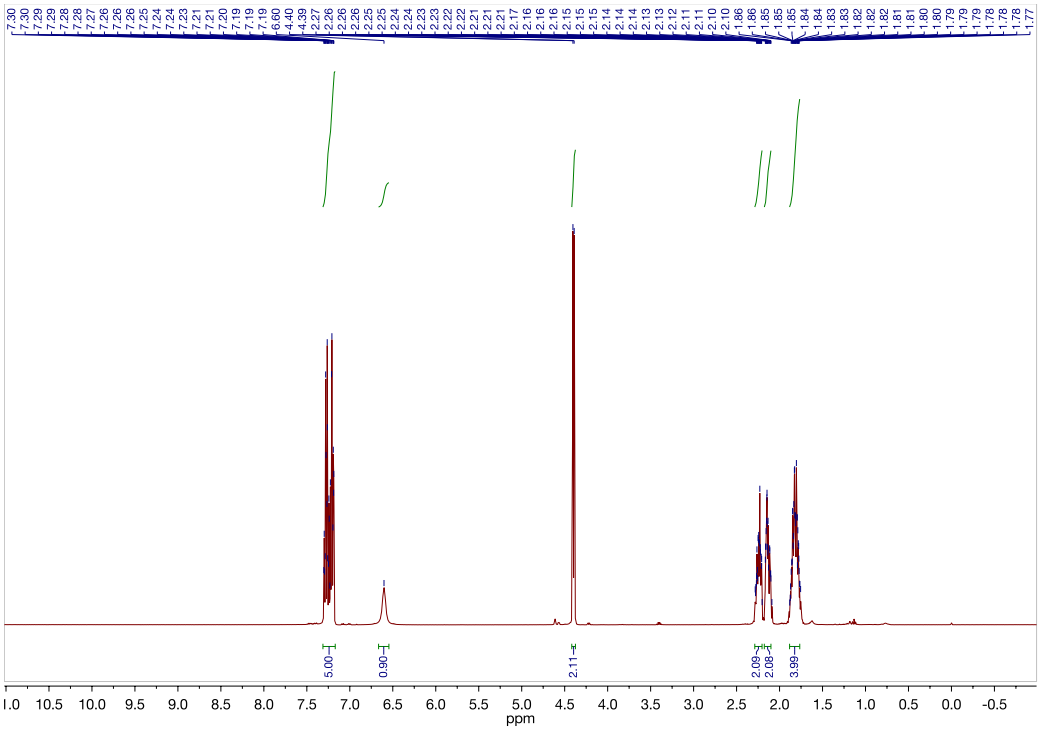


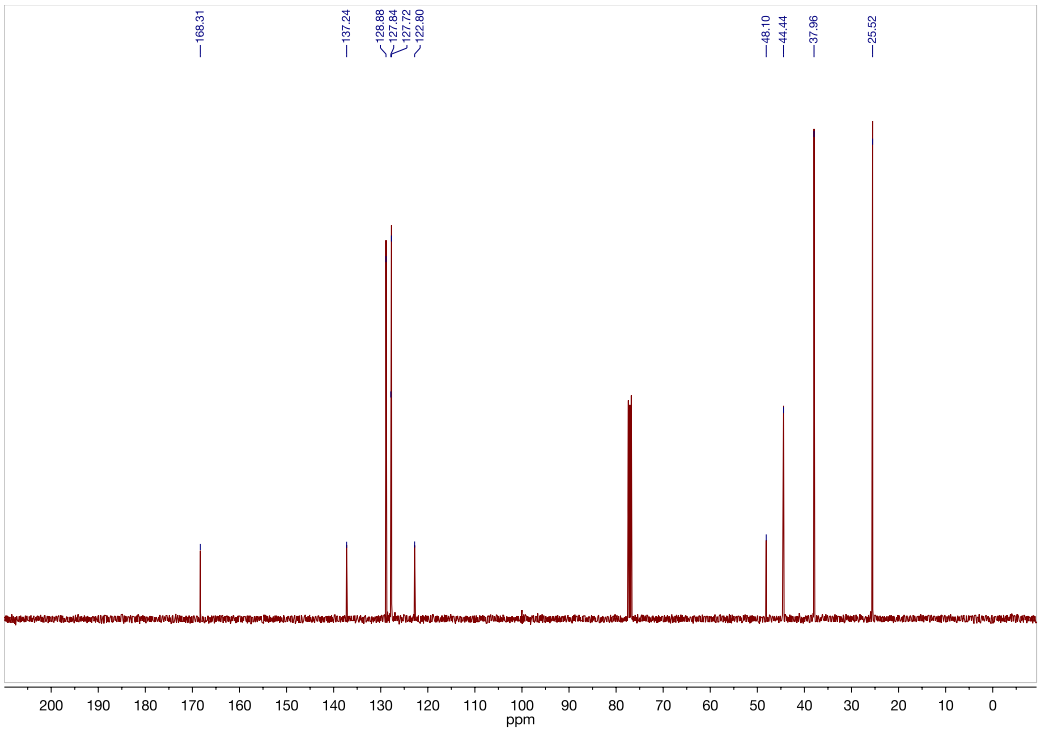




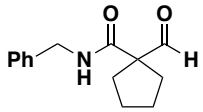
N-Benzyl-1-cyanocyclopentane-1-carboxamide, 128

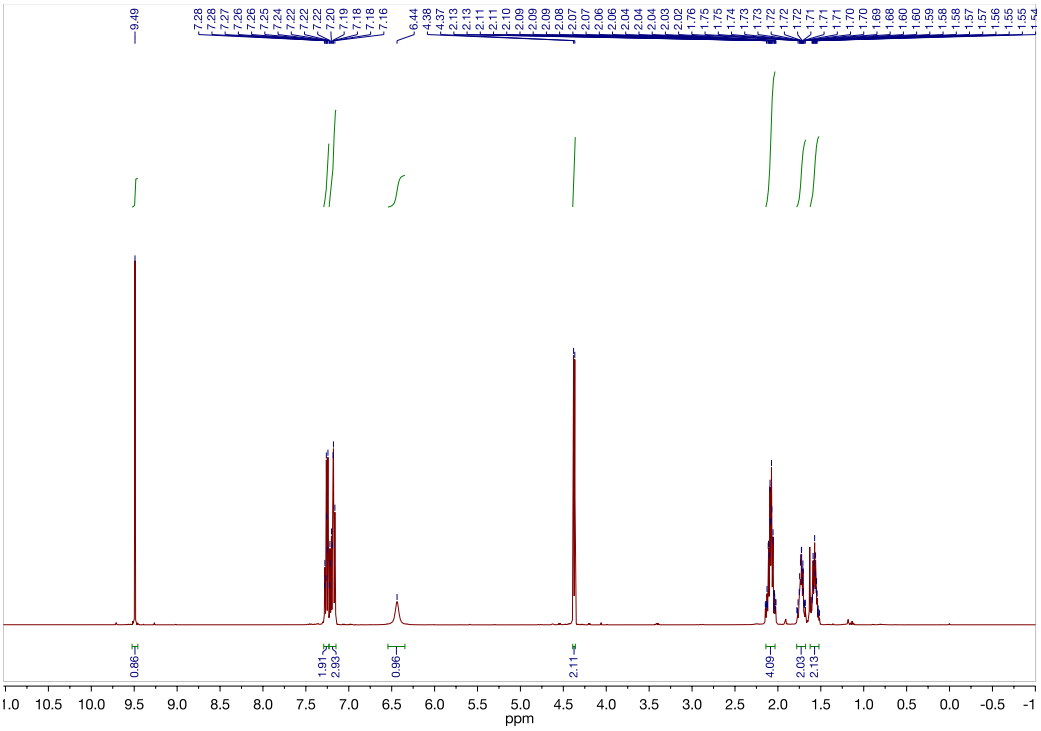


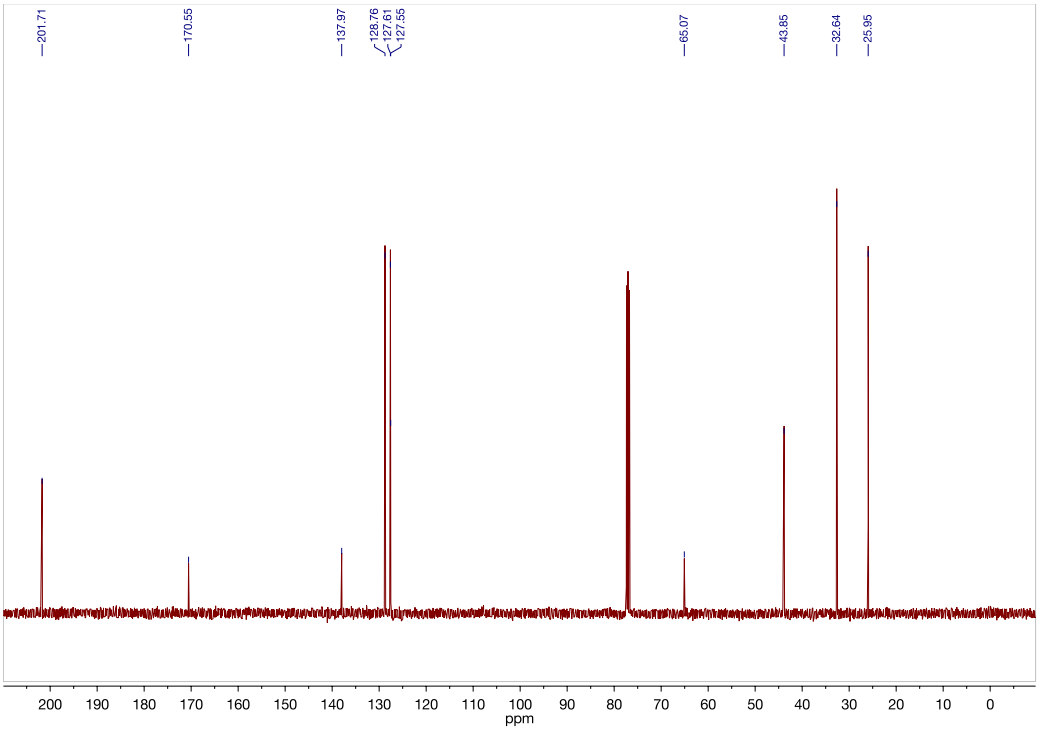




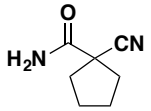
N-Benzyl-1-formylcyclopentane-1-carboxamide, 129

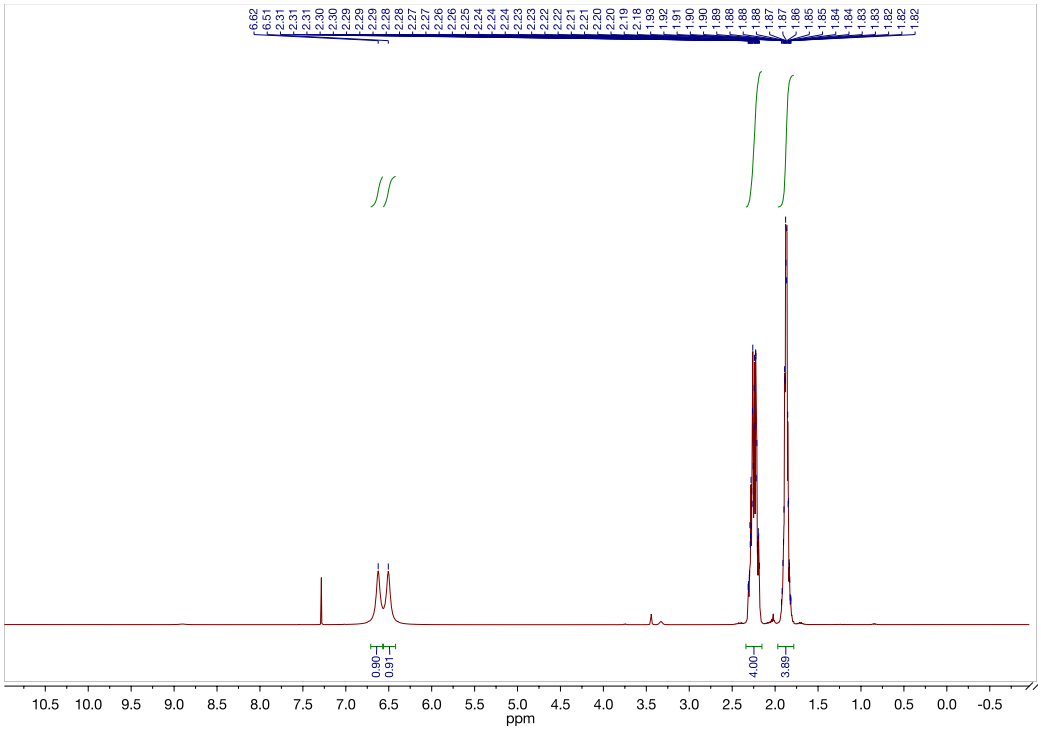


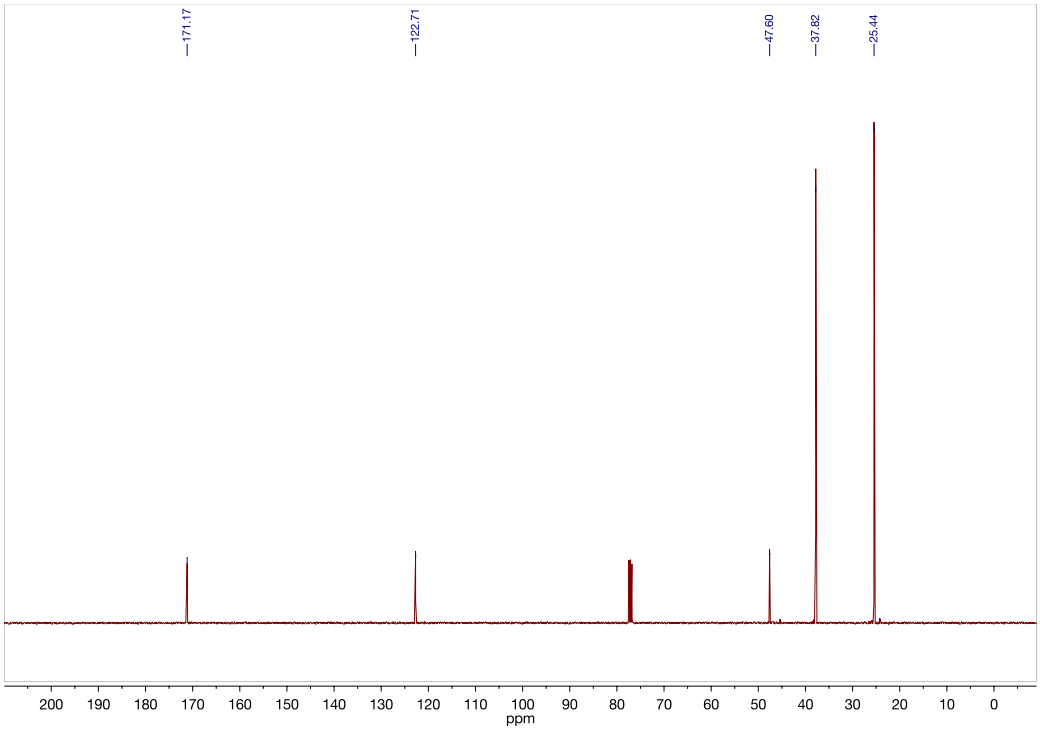




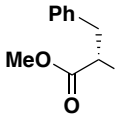
1-Cyanocyclopentane-1-carboxamide, 130

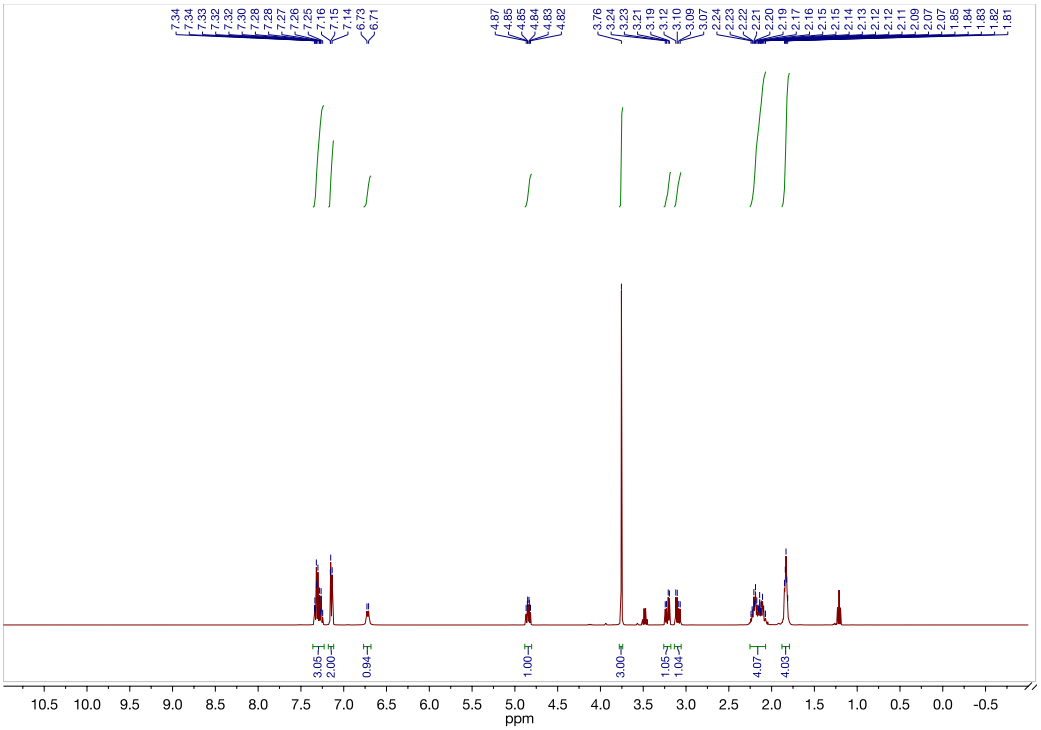


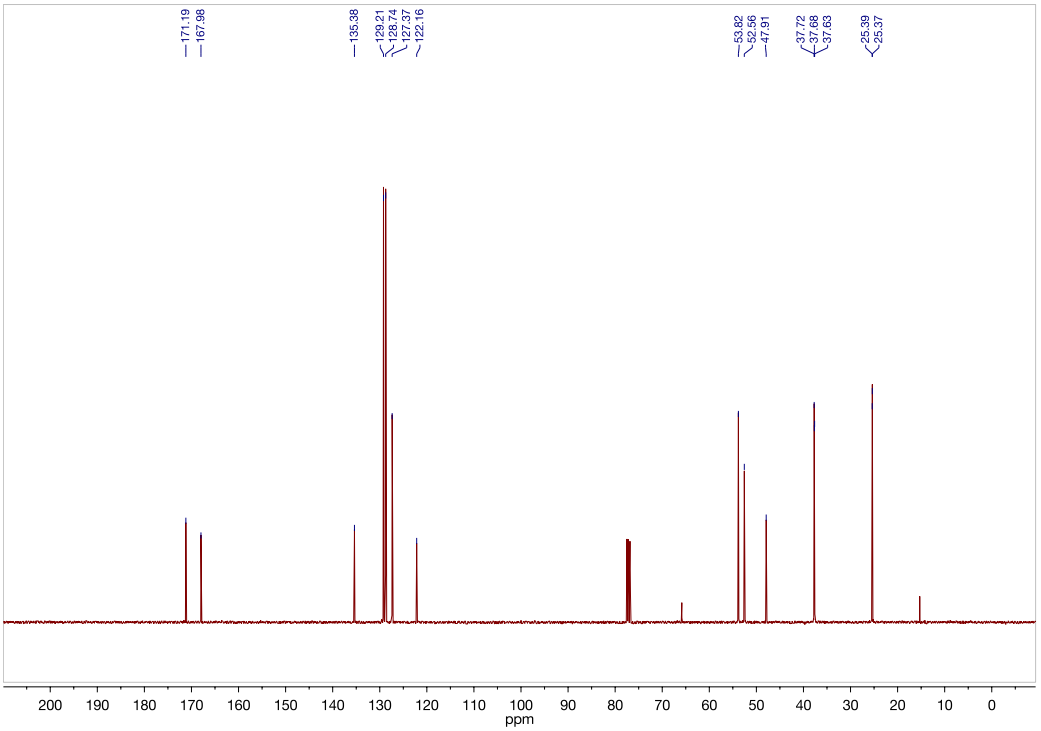




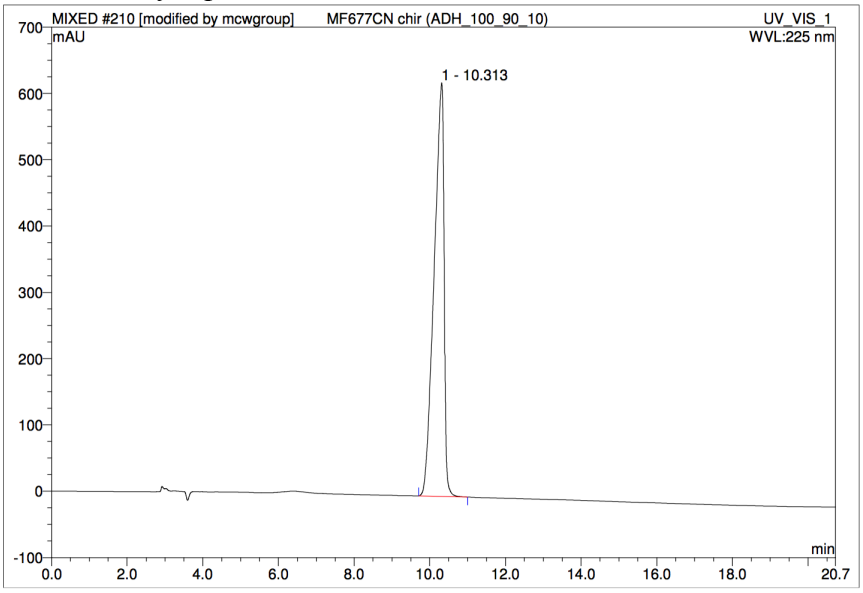
Methyl (1-cyanocyclopentane-1-carbonyl)-*L*-phenylalaninate, 132





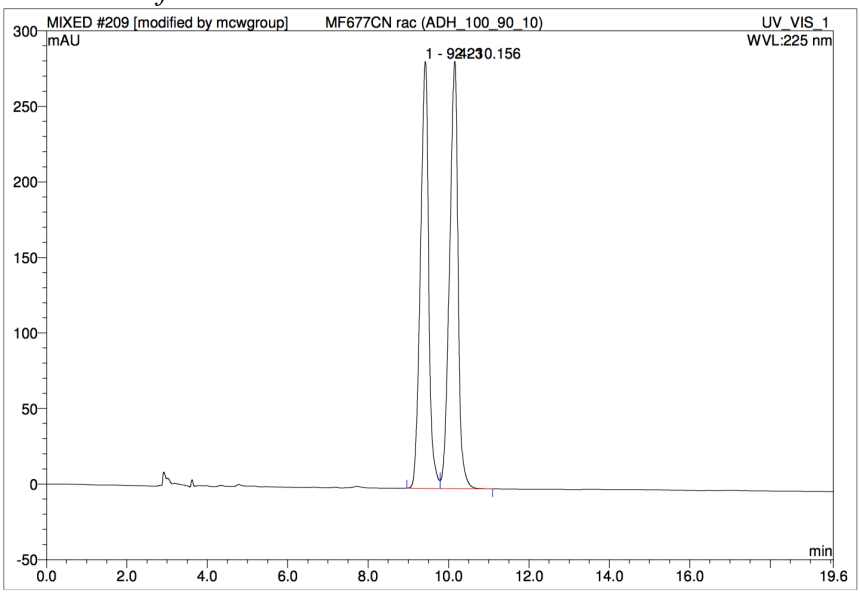


HPLC trace for product:



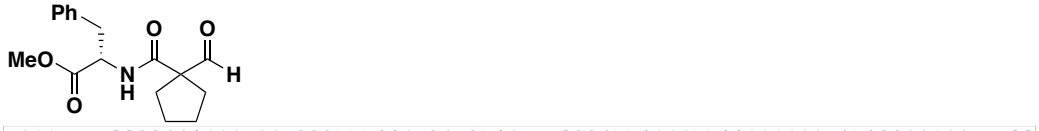
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	10.31	n.a.	623.716	188.889	100.00	n.a.	BMB*
Total:			623.716	188.889	100.00	0.000	

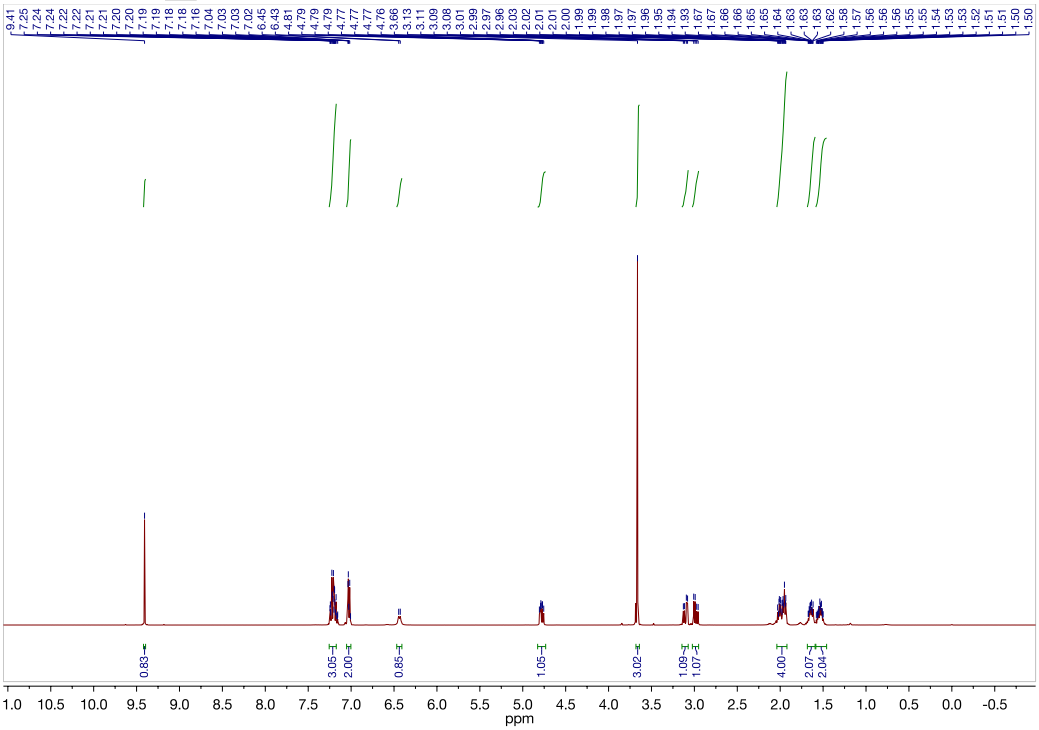
HPLC trace for racemate:

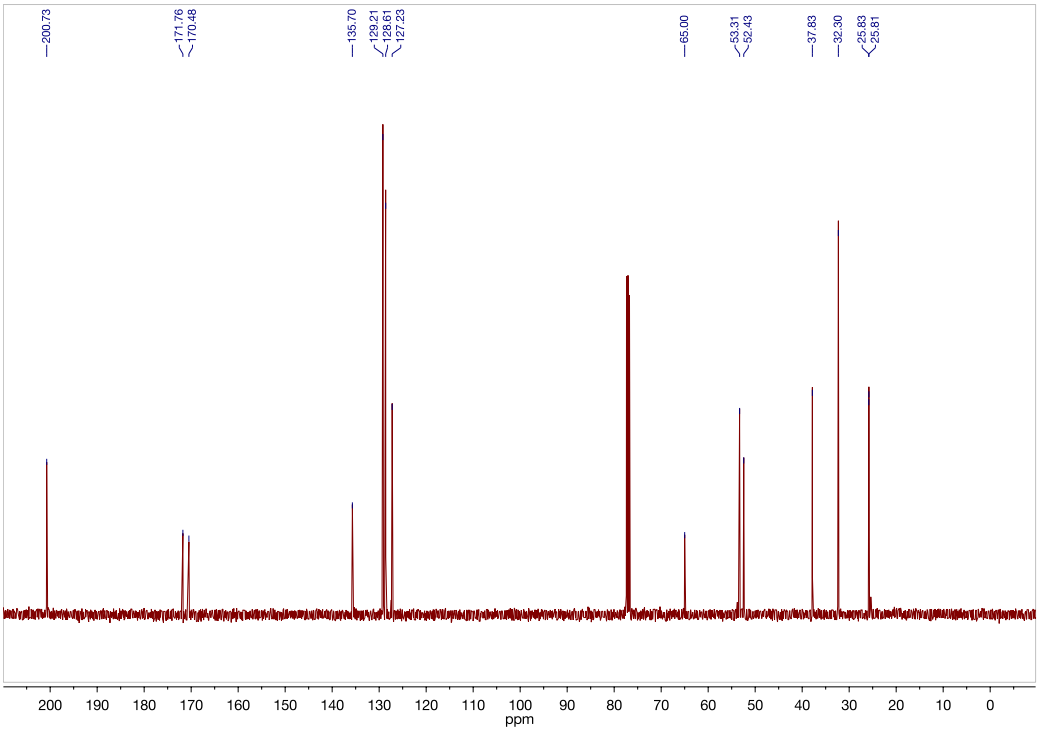


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	9.42	n.a.	282.568	67.408	49.15	n.a.	BM *
2	10.16	n.a.	282.817	69.749	50.85	n.a.	MB*
Total:			565.385	137.157	100.00	0.000	

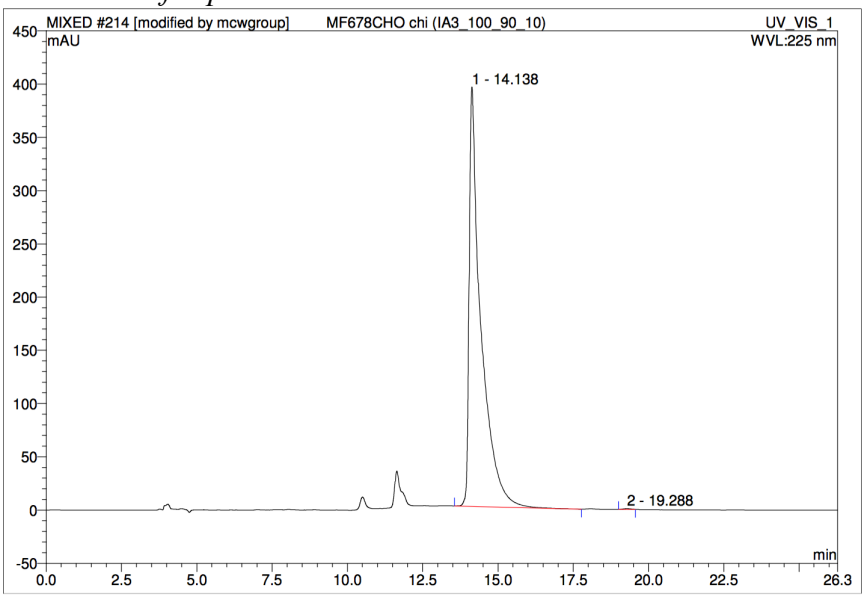
Methyl (1-formylcyclopentane-1-carbonyl)-*L*-phenylalaninate, 133





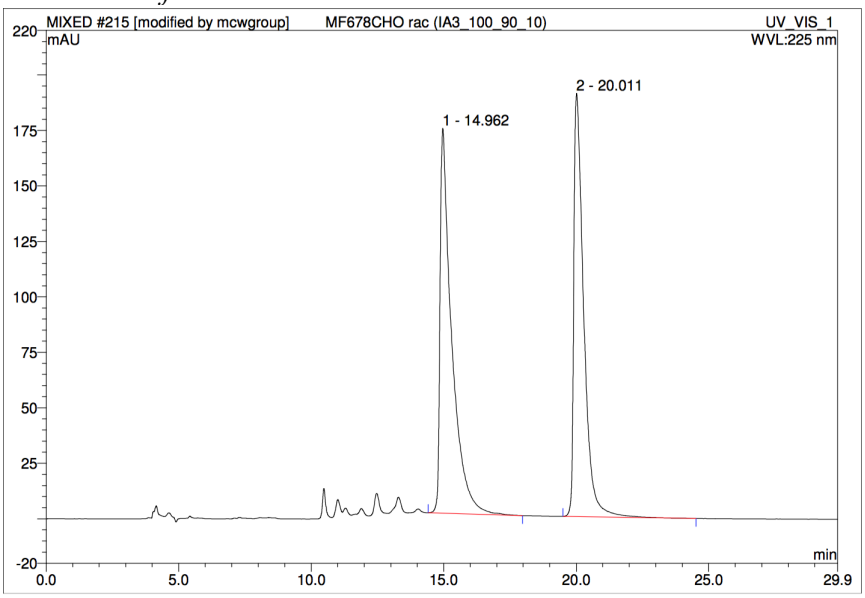


HPLC trace for product:



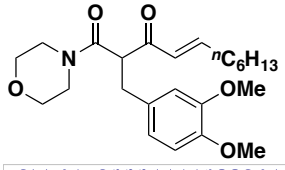
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	14.14	n.a.	393.724	177.796	99.87	n.a.	BMB*
2	19.29	n.a.	0.815	0.225	0.13	n.a.	BMB*
Total:			394.538	178.021	100.00	0.000	

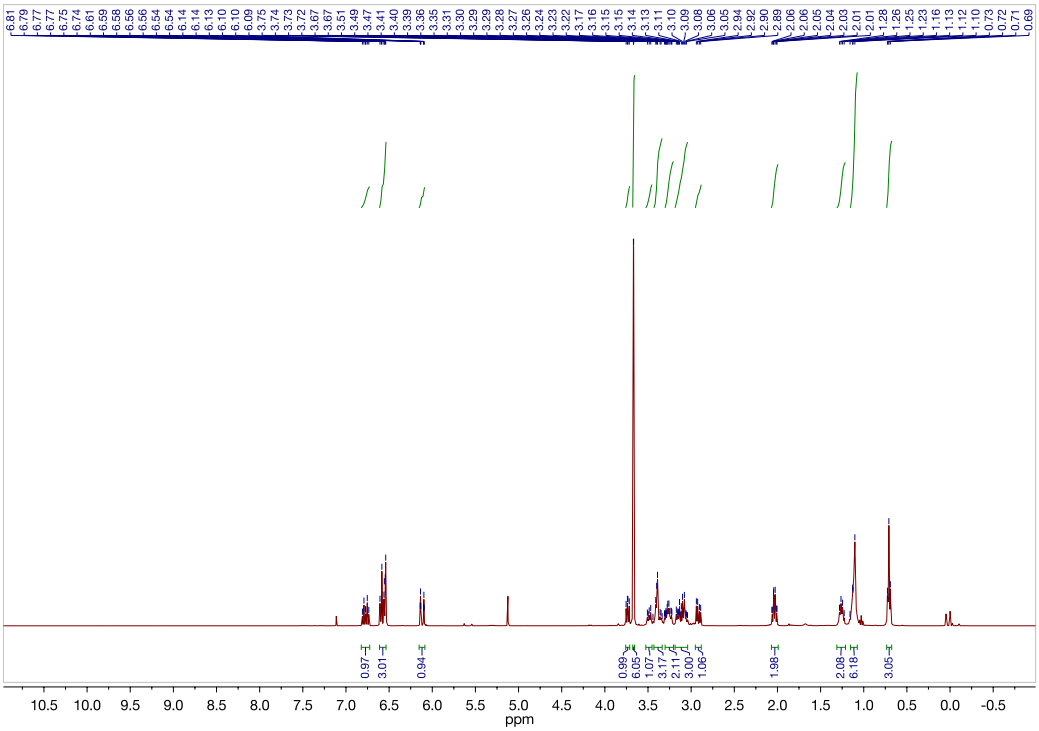
HPLC trace for racemate:

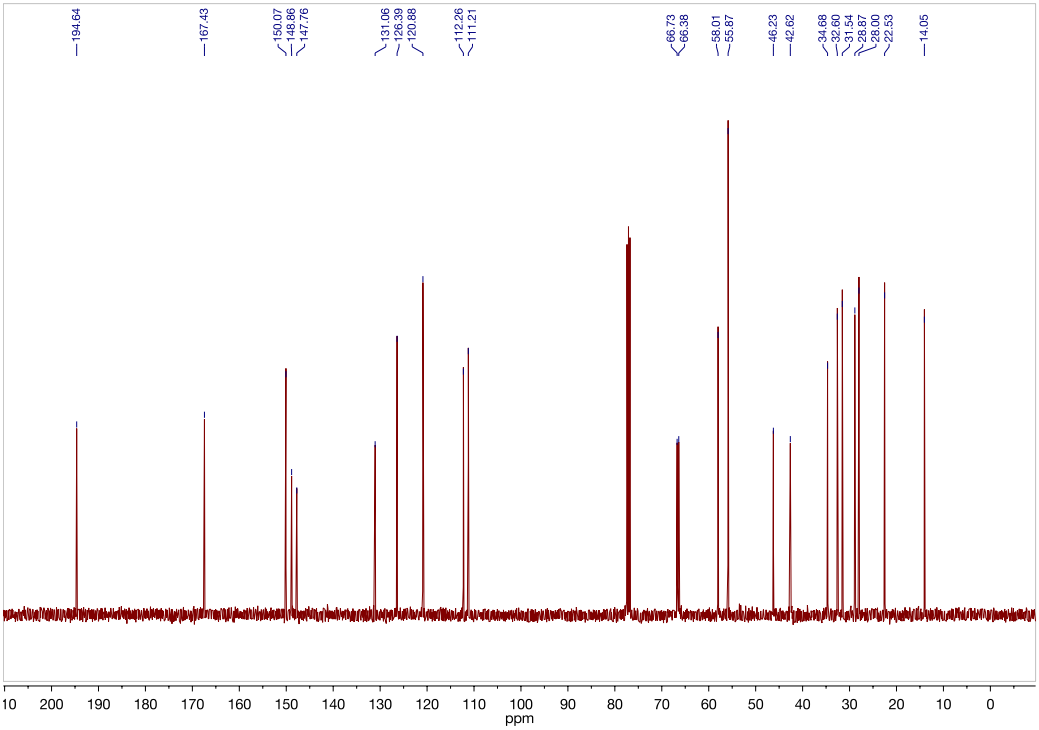


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	14.96	n.a.	173.404	88.132	51.68	n.a.	BMB*
2	20.01	n.a.	190.754	82.404	48.32	n.a.	BMB*
Total:			364.158	170.536	100.00	0.000	

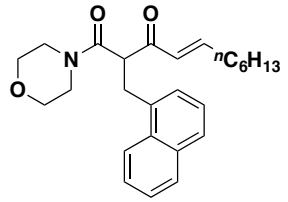
(*E*)-2-(3,4-Dimethoxybenzyl)-1-morpholinoundec-4-ene-1,3-dione, 137

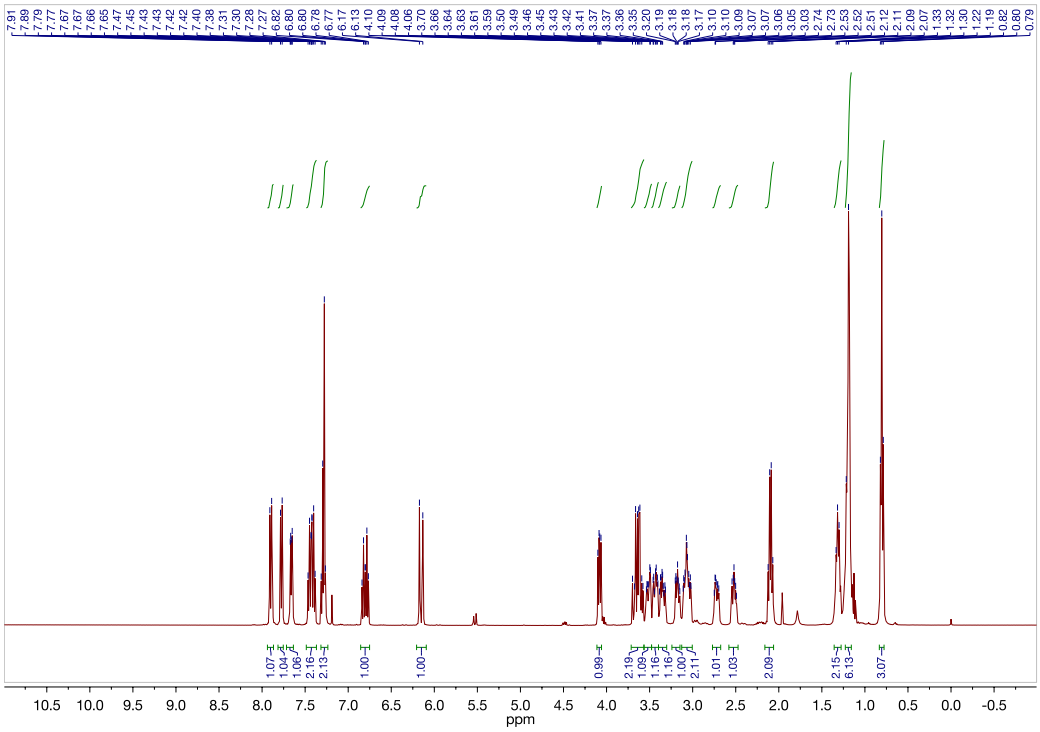


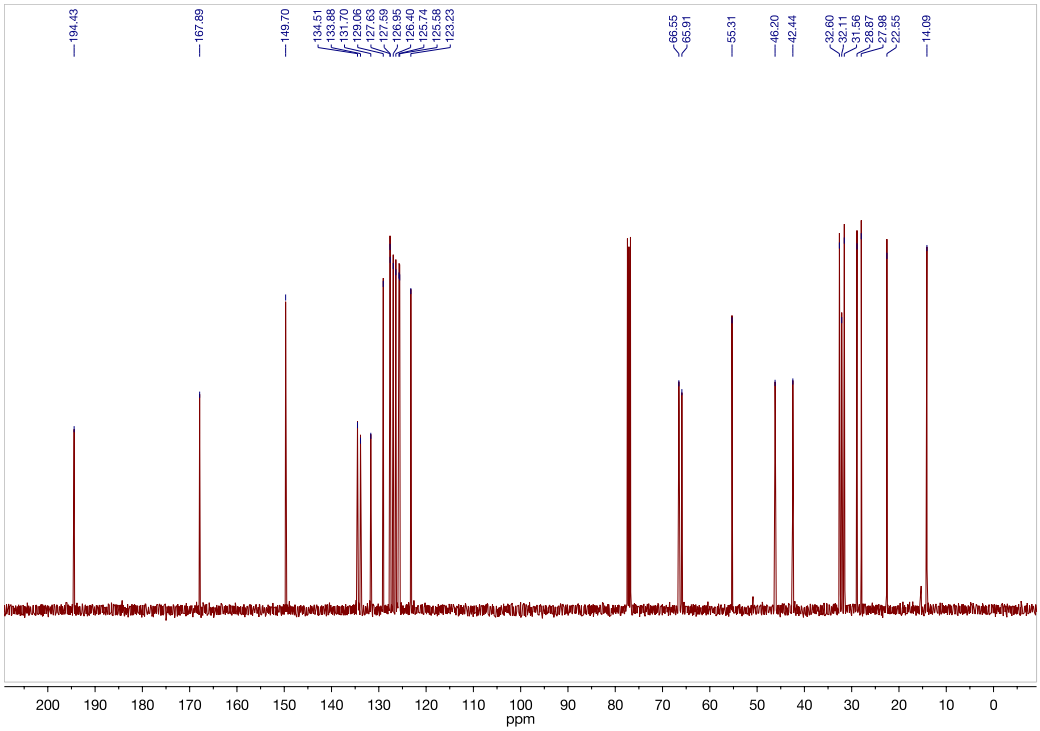




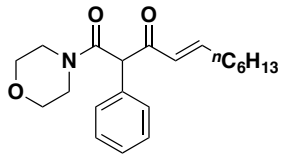
(*E*)-1-Morpholino-2-(naphthalen-1-ylmethyl)undec-4-ene-1,3-dione, 138

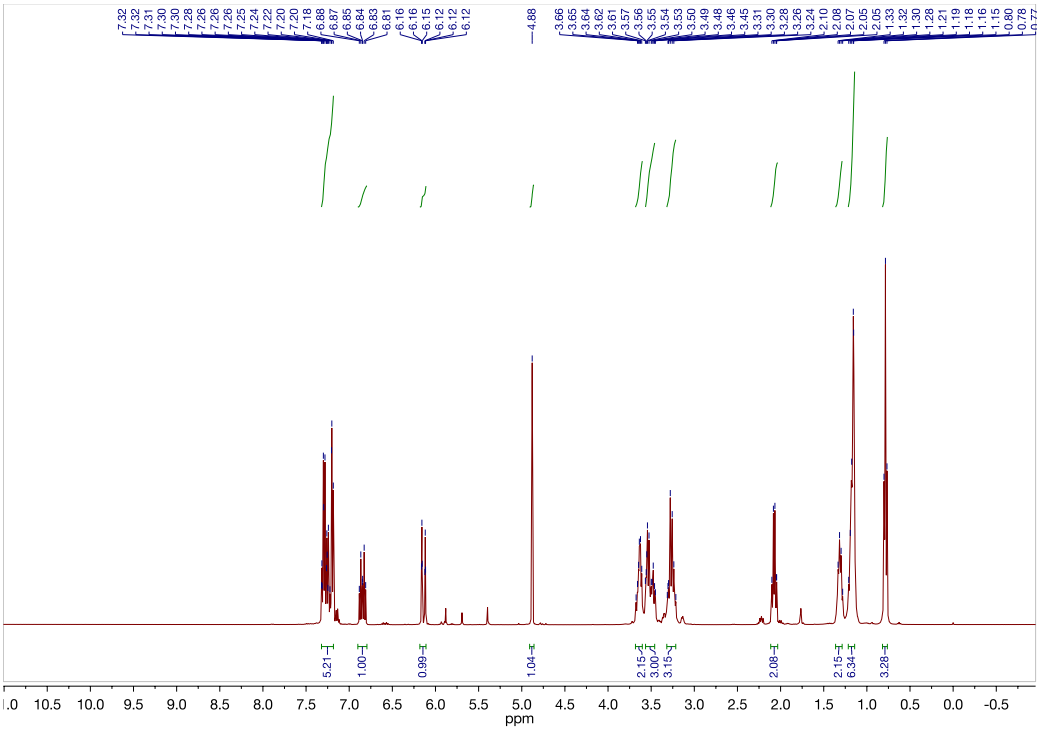


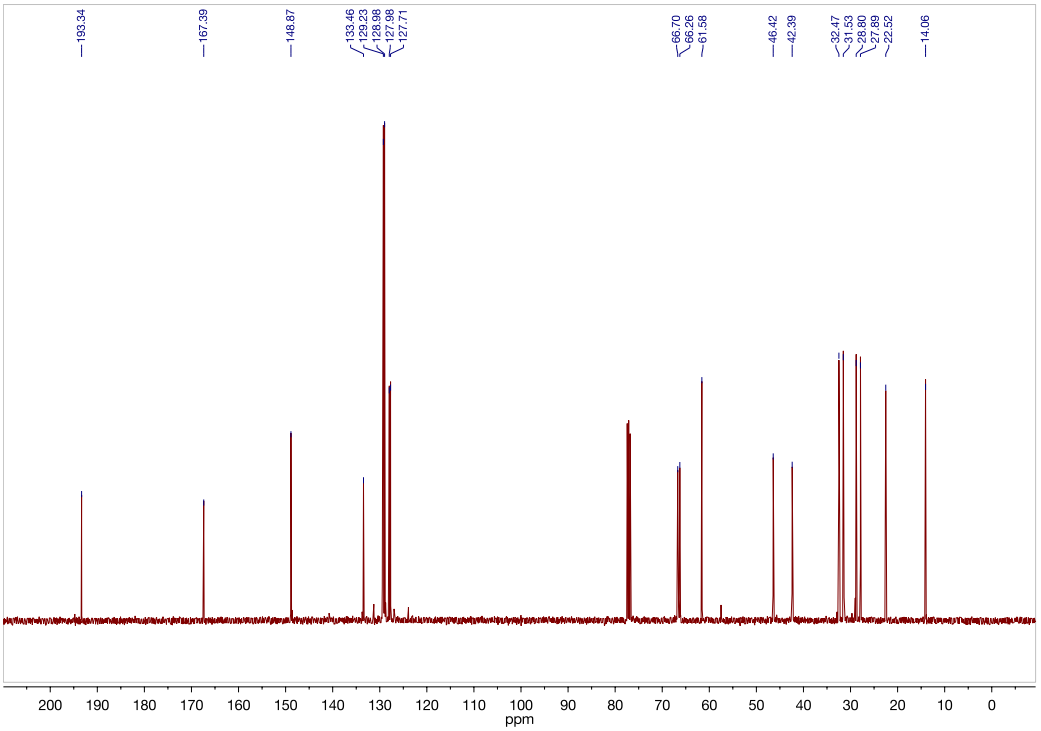




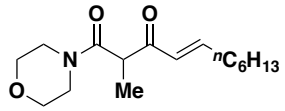
(*E*)-2-Phenyl-1-morpholinoundec-4-ene-1,3-dione, 139

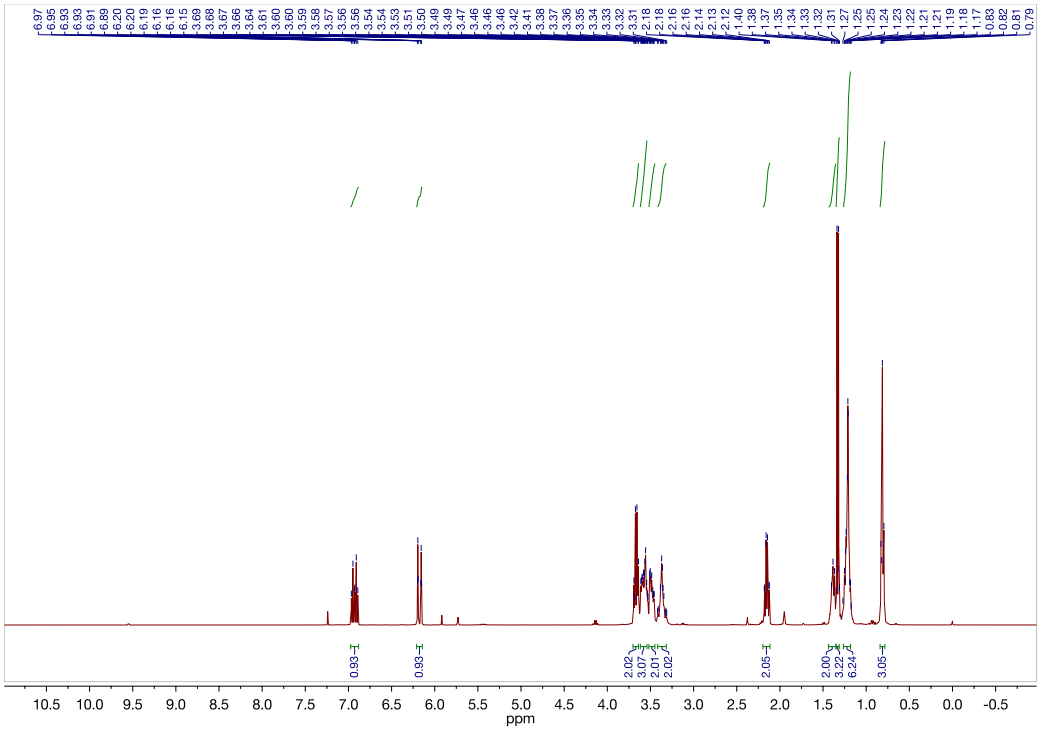


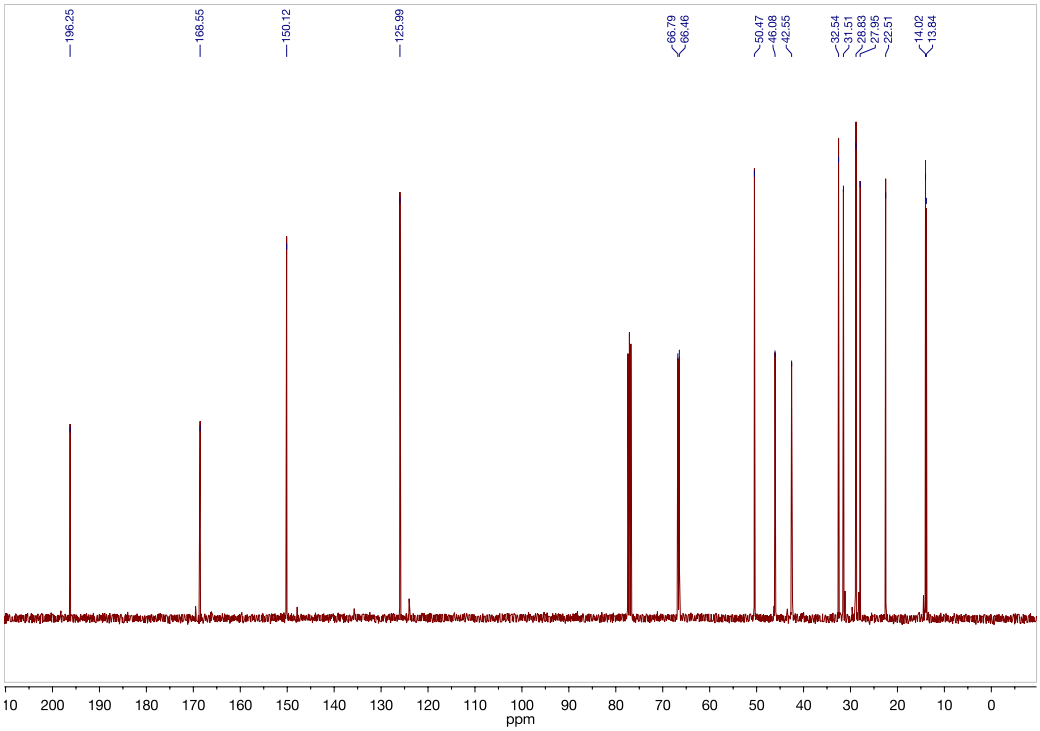




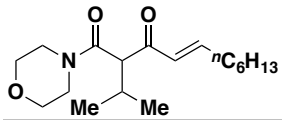
(*E*)-2-Methyl-1-morpholinoundec-4-ene-1,3-dione, 140

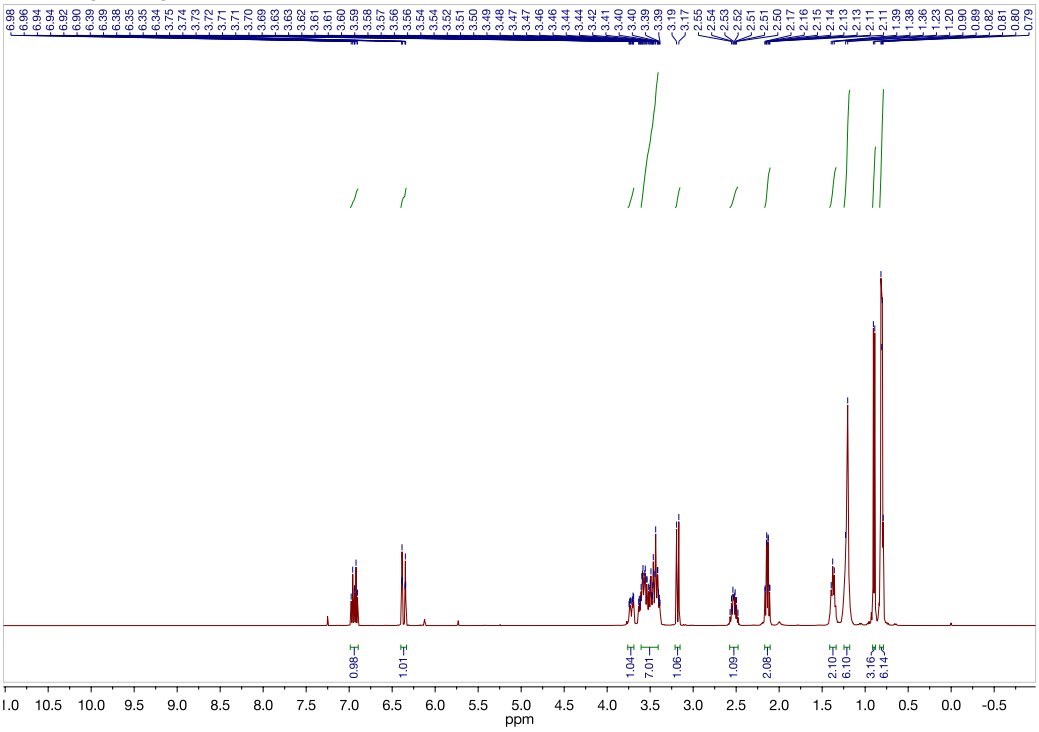


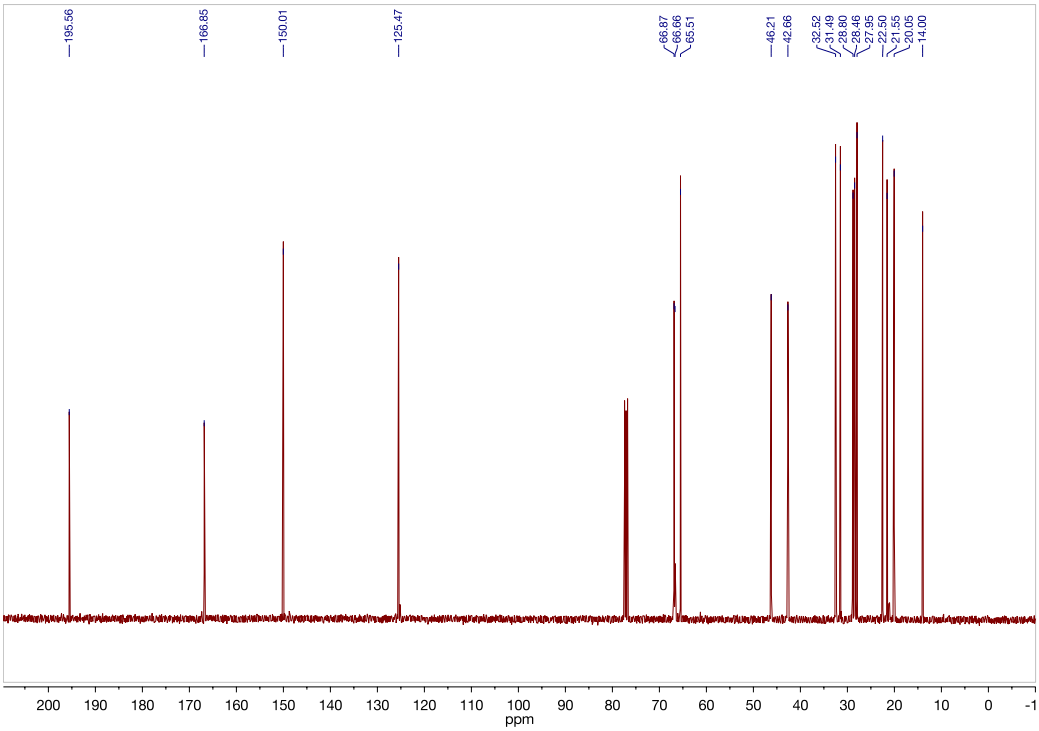




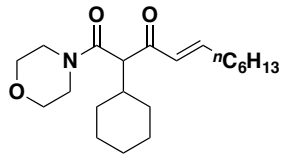
(*E*)-2-Isopropyl-1-morpholinoundec-4-ene-1,3-dione, 141

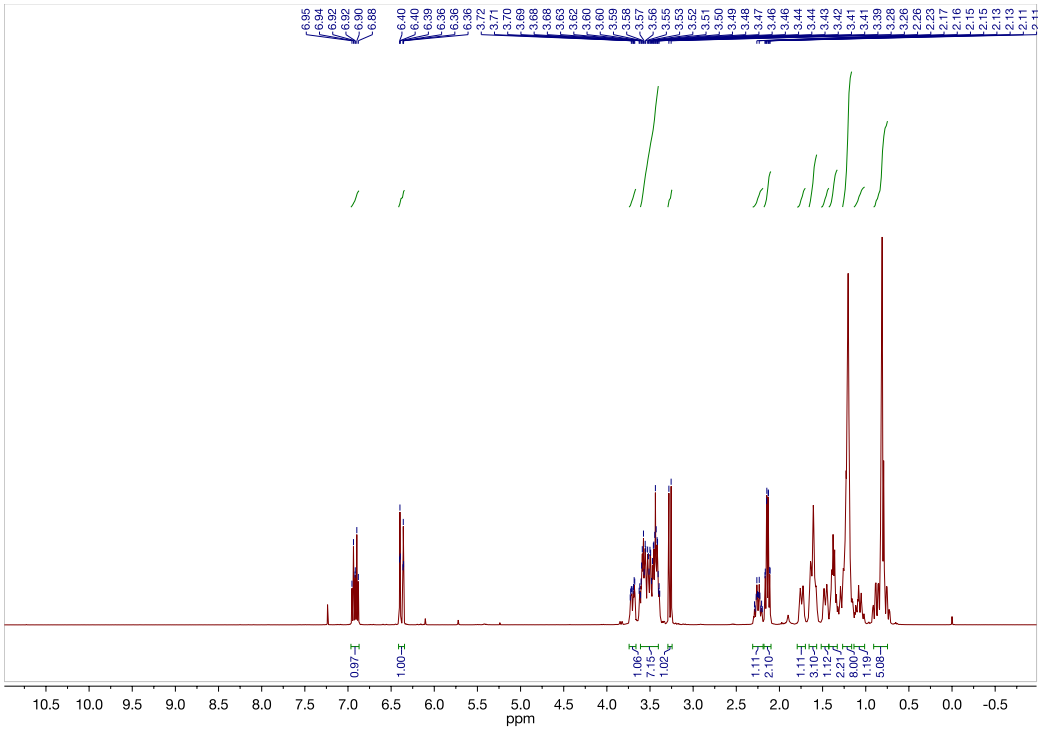


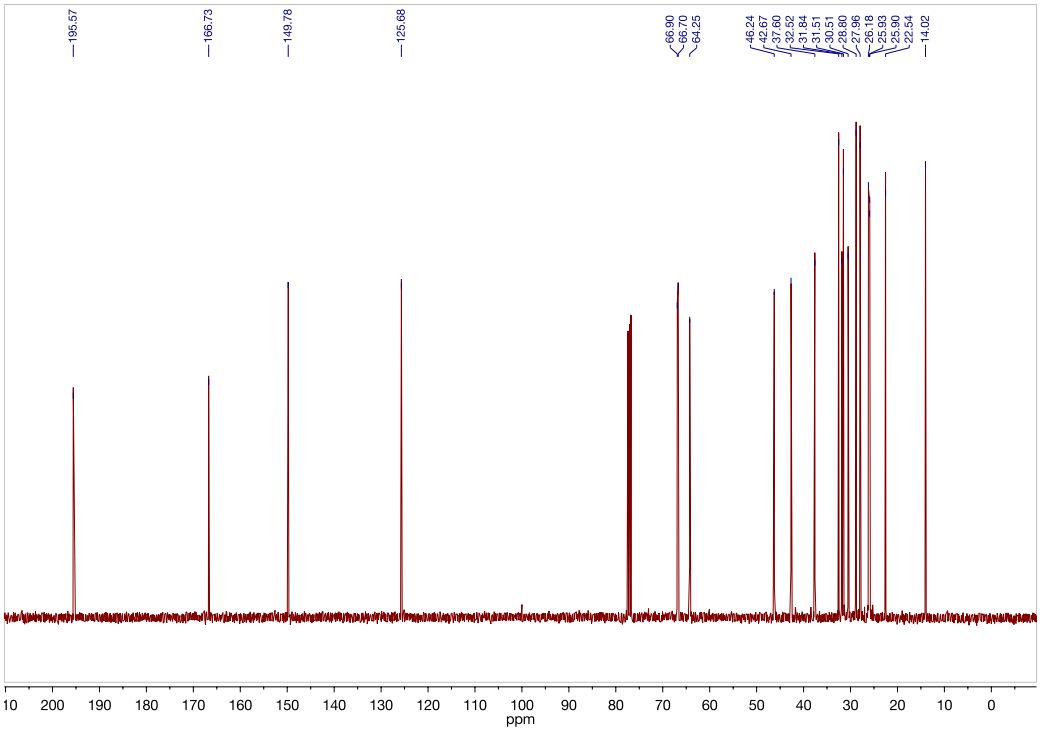




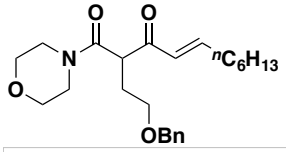
(*E*)-2-Cyclohexyl-1-morpholinoundec-4-ene-1,3-dione, 142

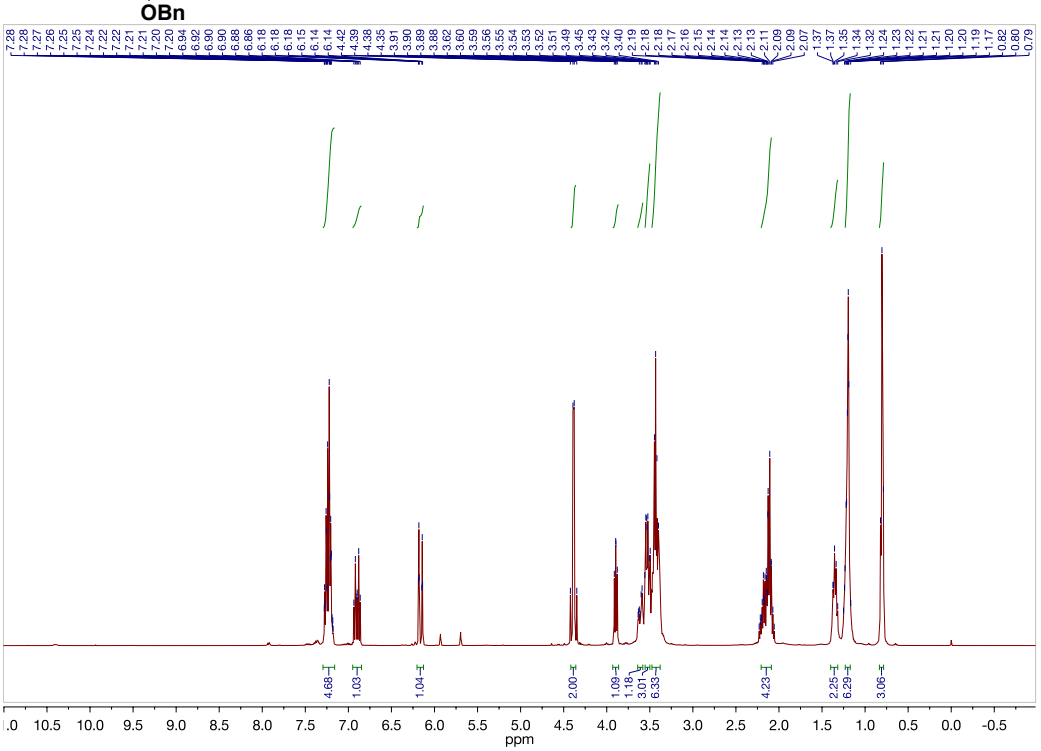


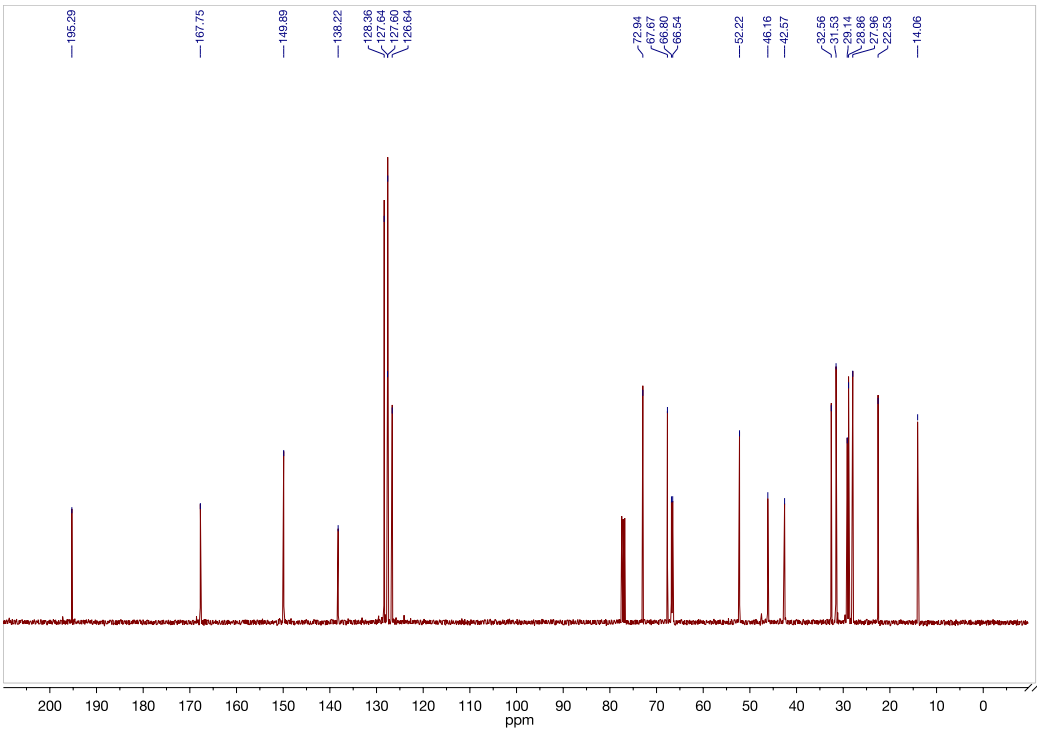




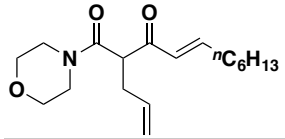
(*E*)-2-(2-(Benzyloxy)ethyl)-1-morpholinoundec-4-ene-1,3-dione, 143

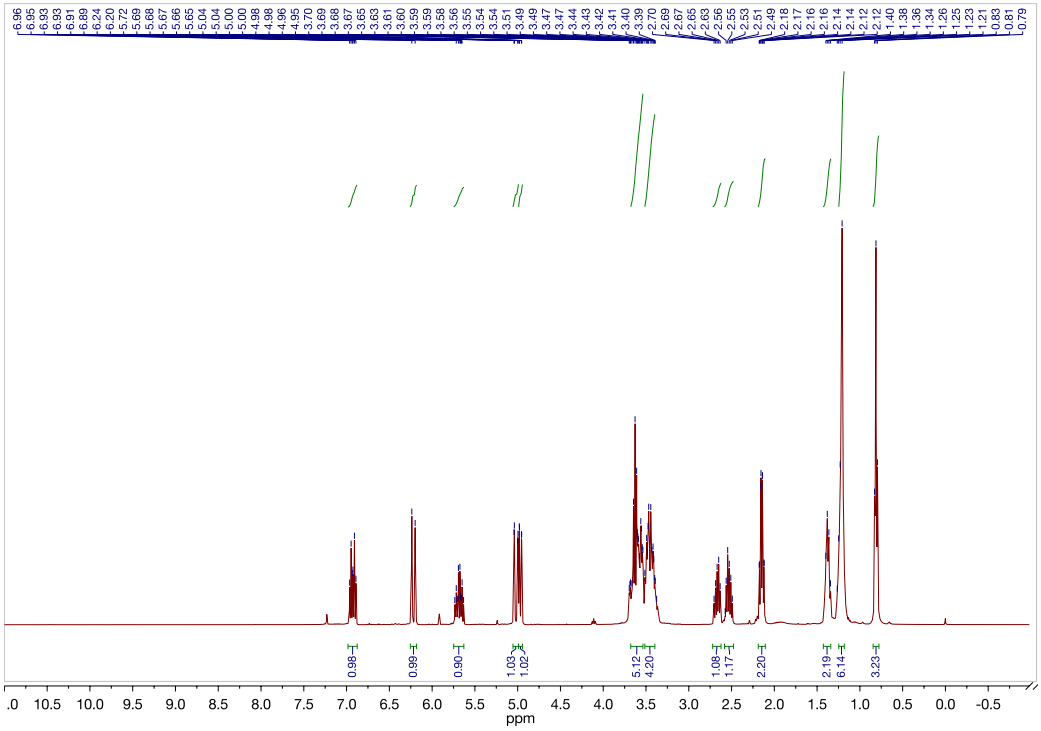


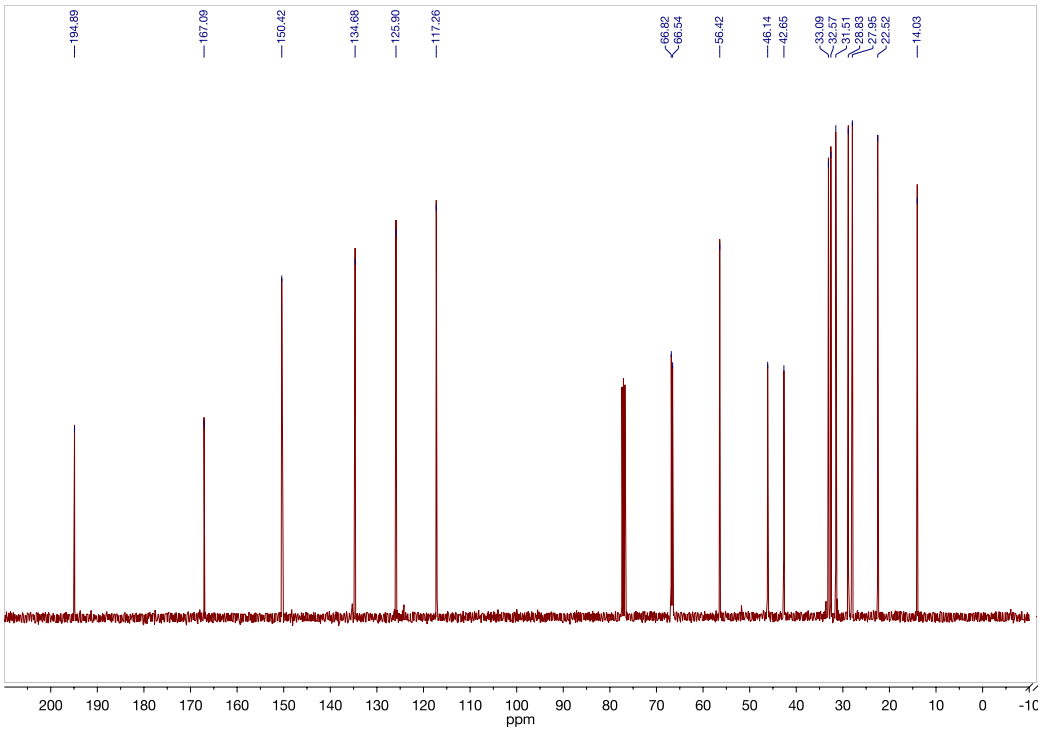




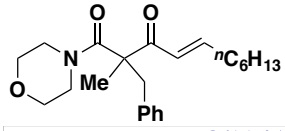
(*E*)-2-Allyl-1-morpholinoundec-4-ene-1,3-dione, 144

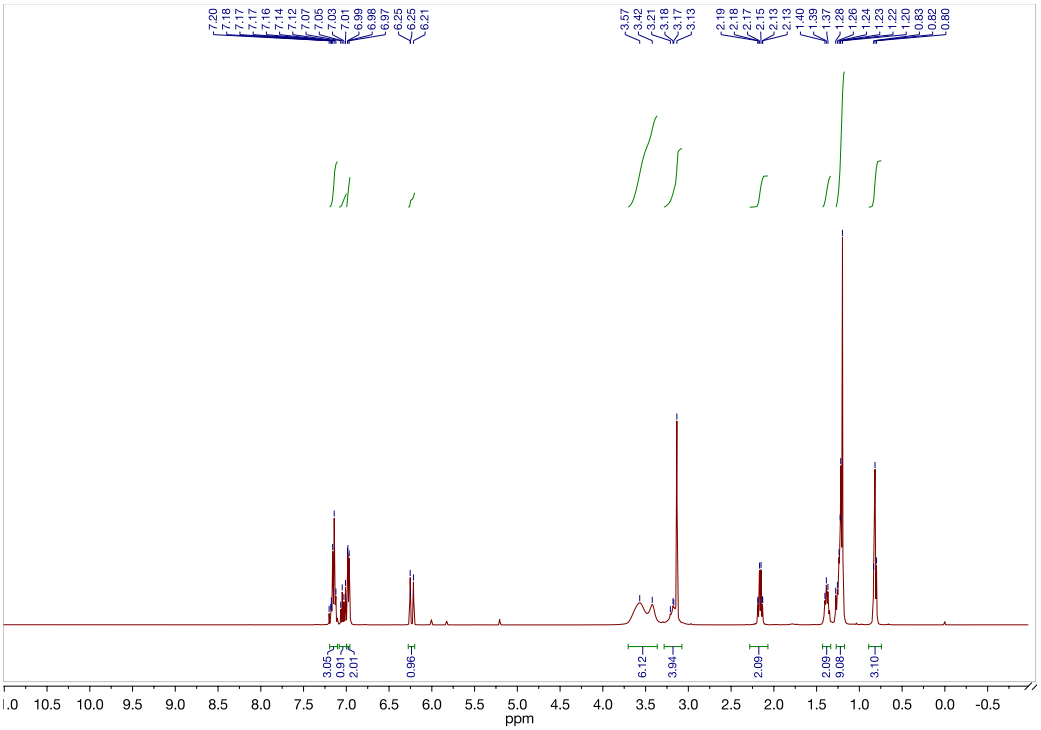


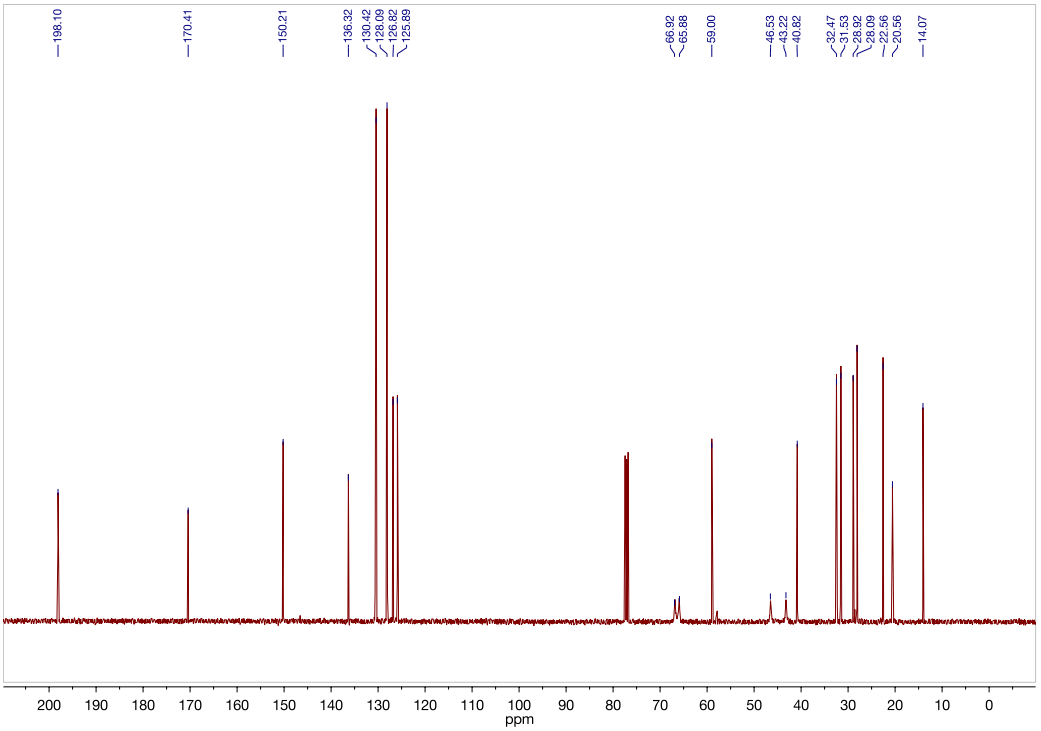




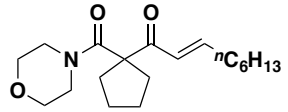
(*E*)-2-Benzyl-2-methyl-1-morpholinoundec-4-ene-1,3-dione, 145

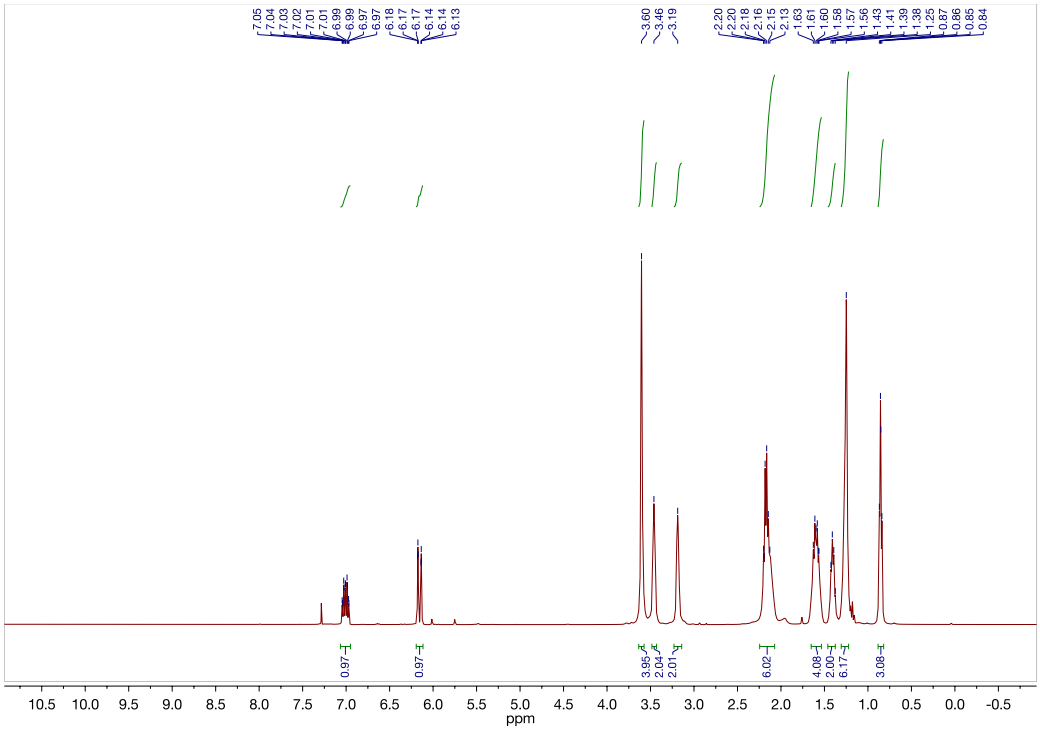


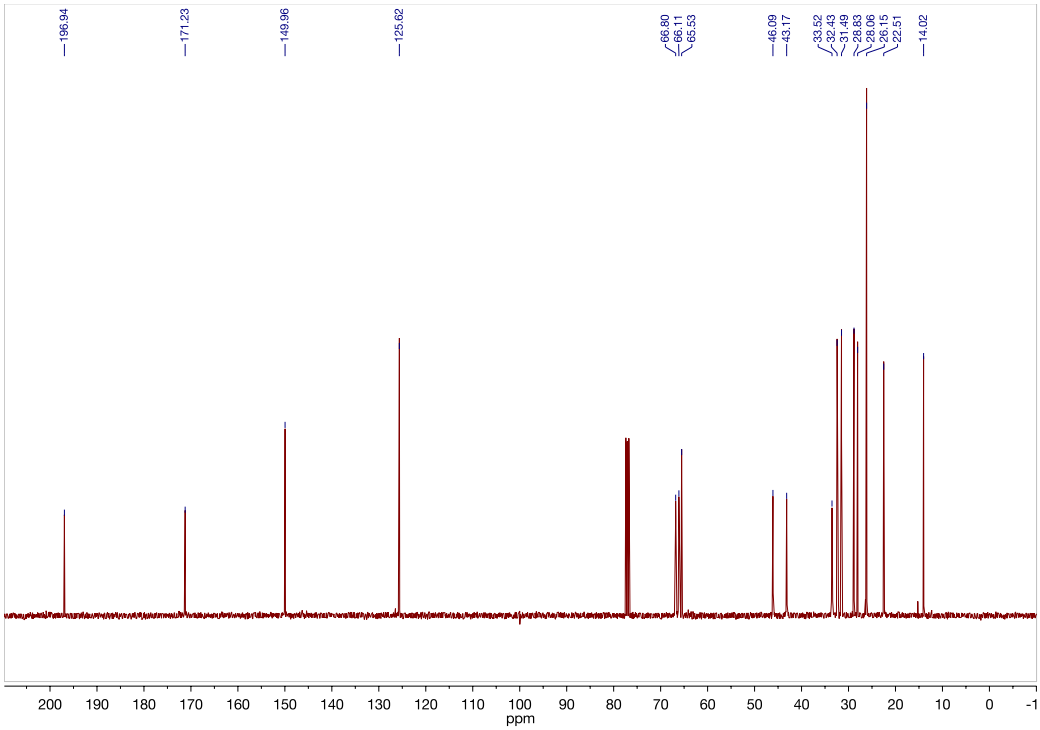




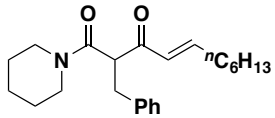
(*E*)-1-(1-(Morpholine-4-carbonyl)cyclopentyl)non-2-en-1-one, 146

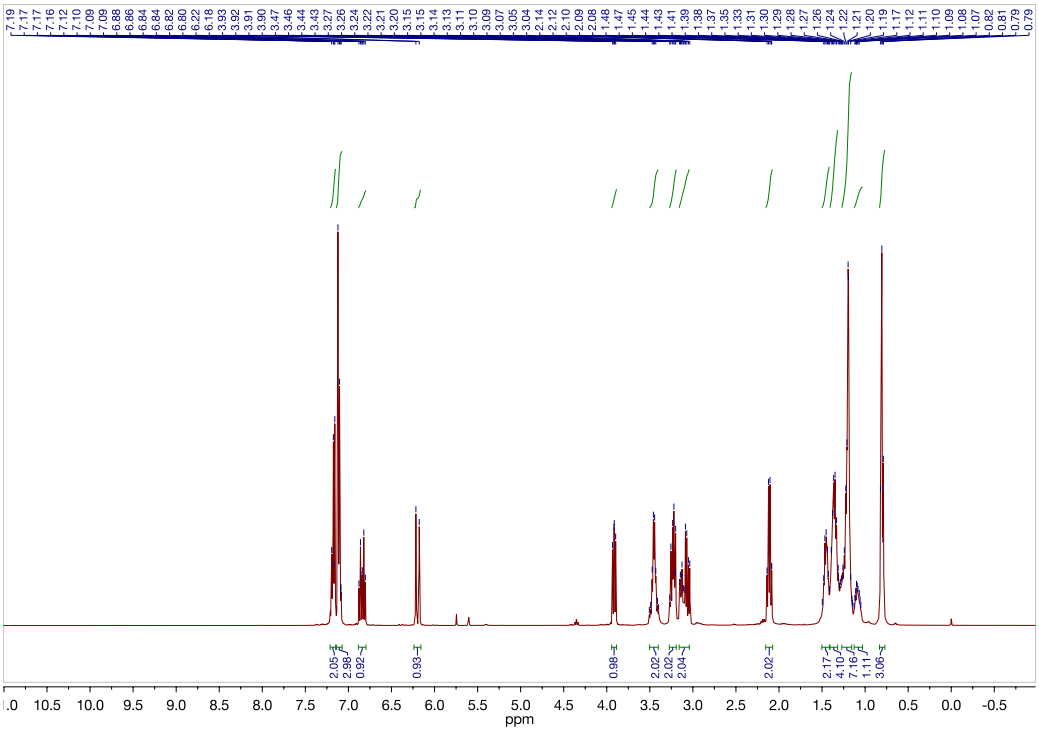


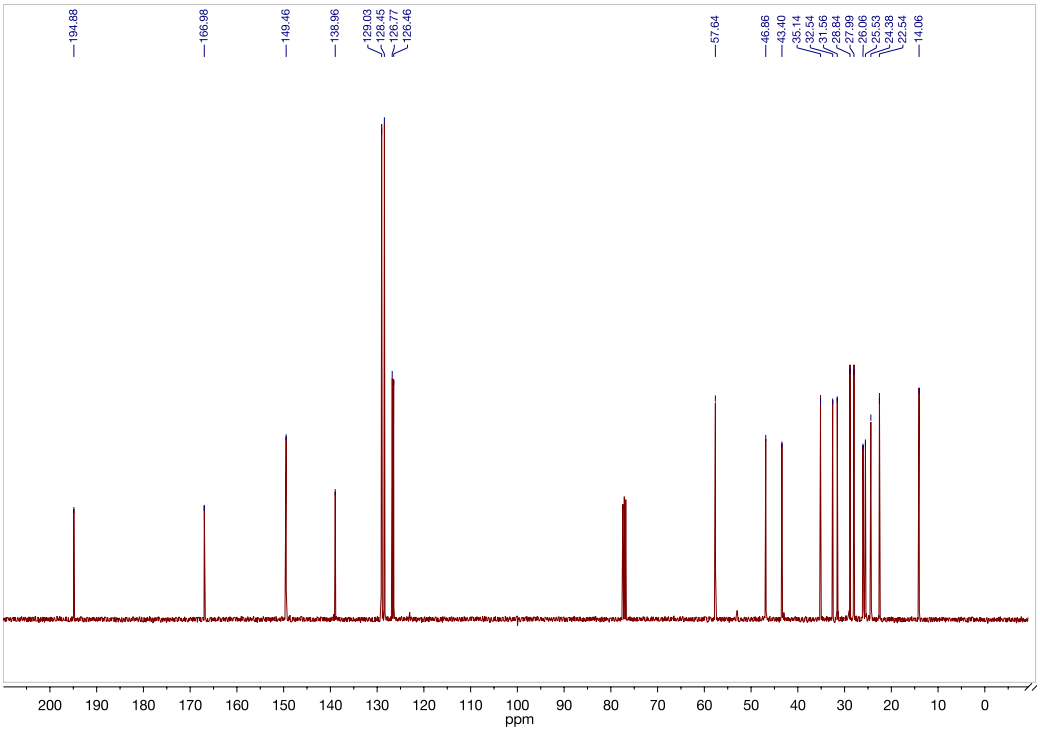




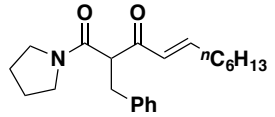
(*E*)-2-Benzyl-1-(piperidin-1-yl)undec-4-ene-1,3-dione, 148

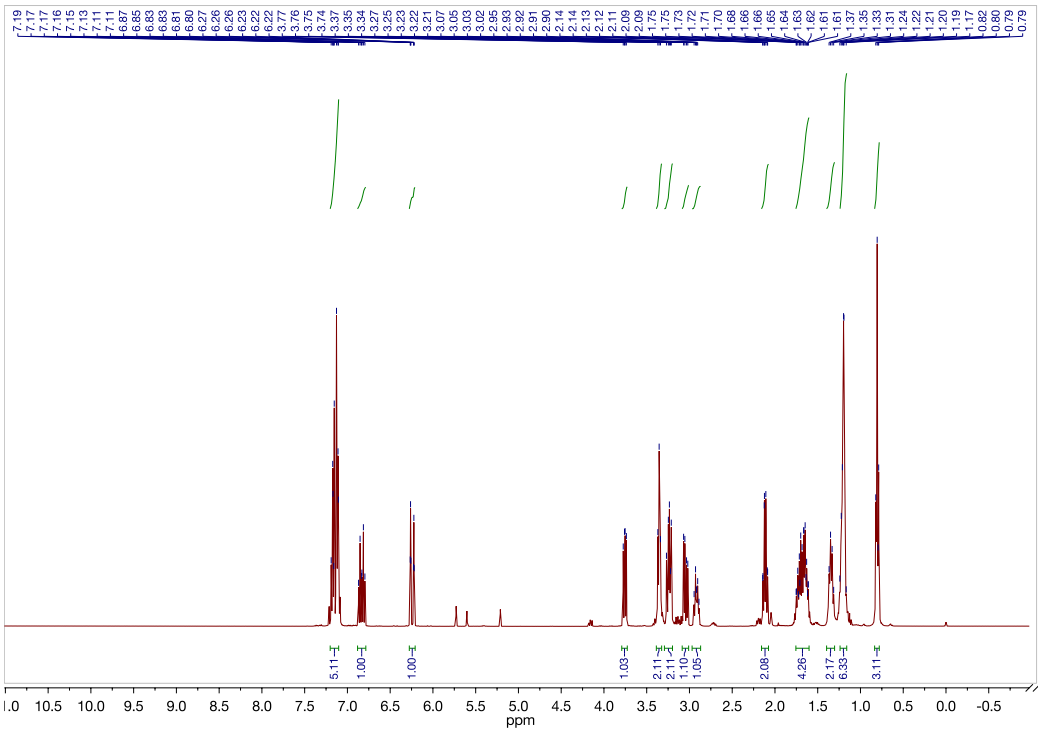


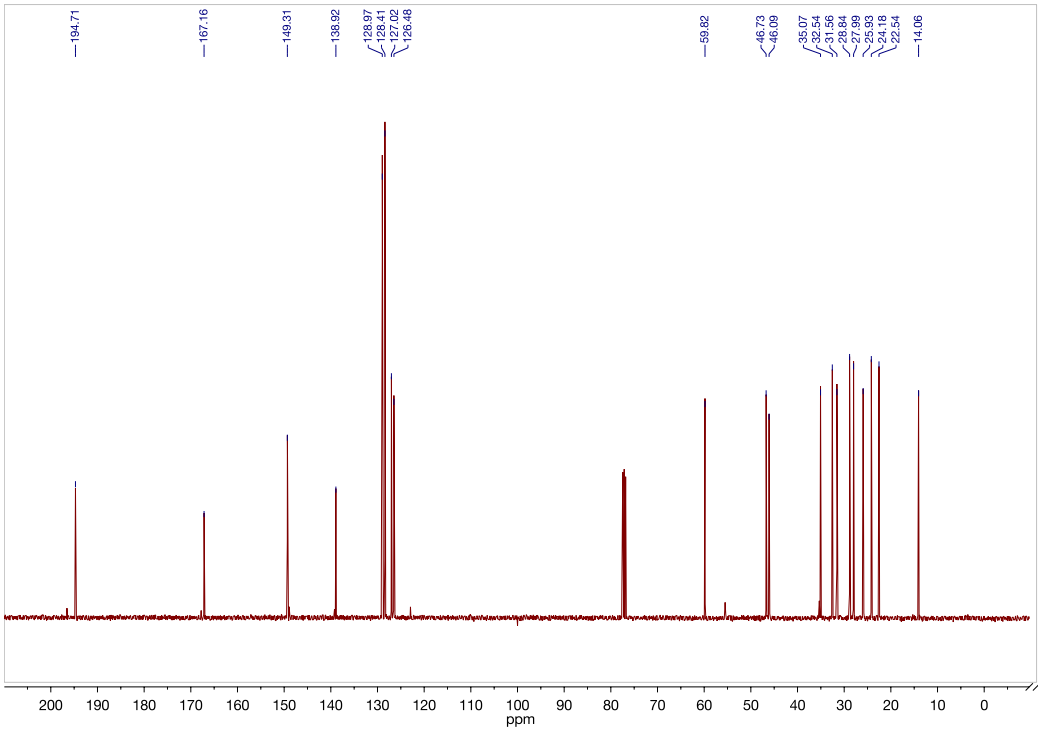




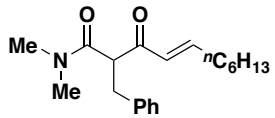
(*E*)-2-Benzyl-1-(pyrrolidin-1-yl)undec-4-ene-1,3-dione, 149

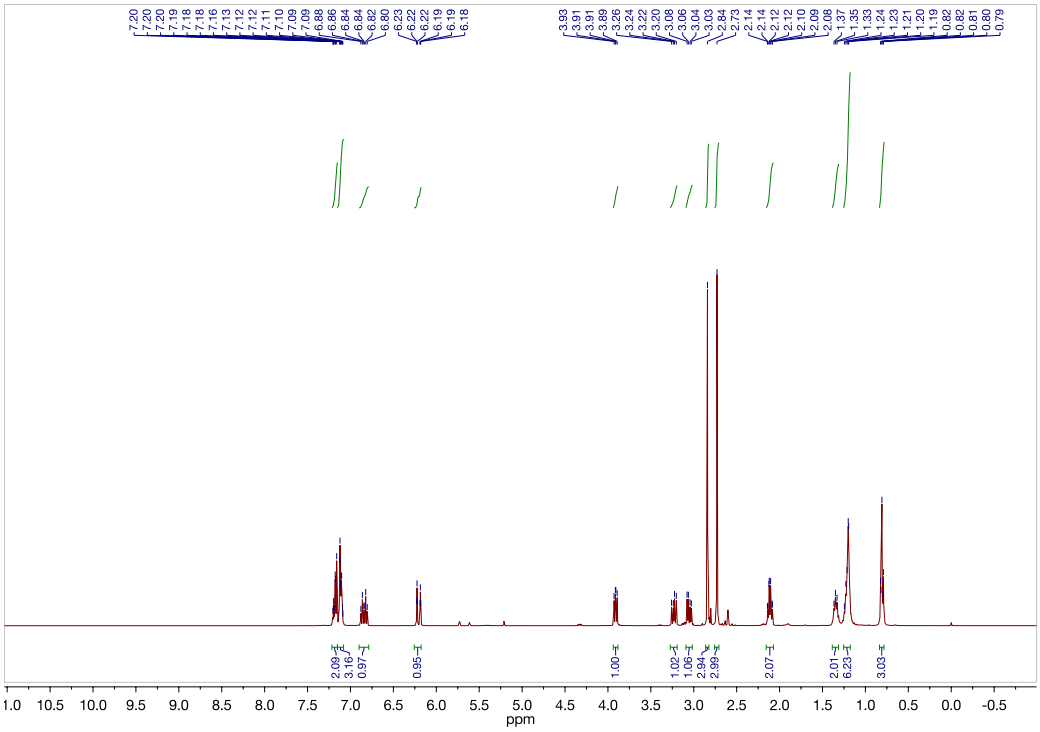


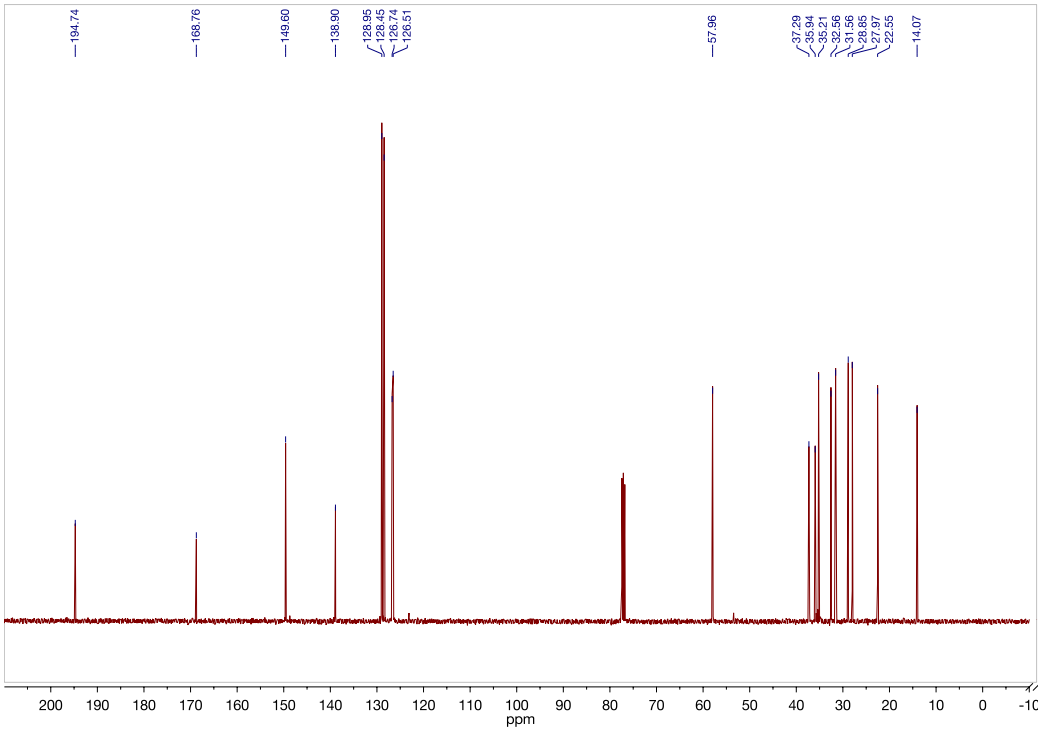




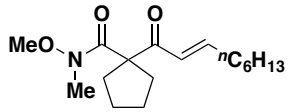
(*E*)-2-Benzyl-*N*,*N*-dimethyl-3-oxoundec-4-enamide, 150

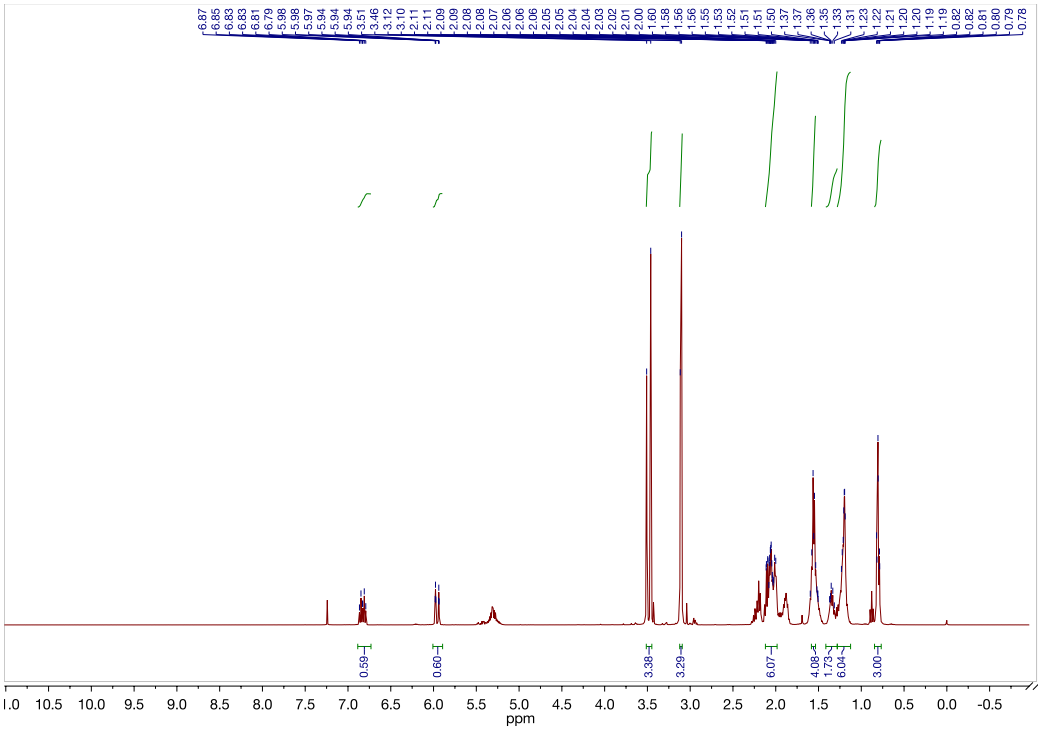


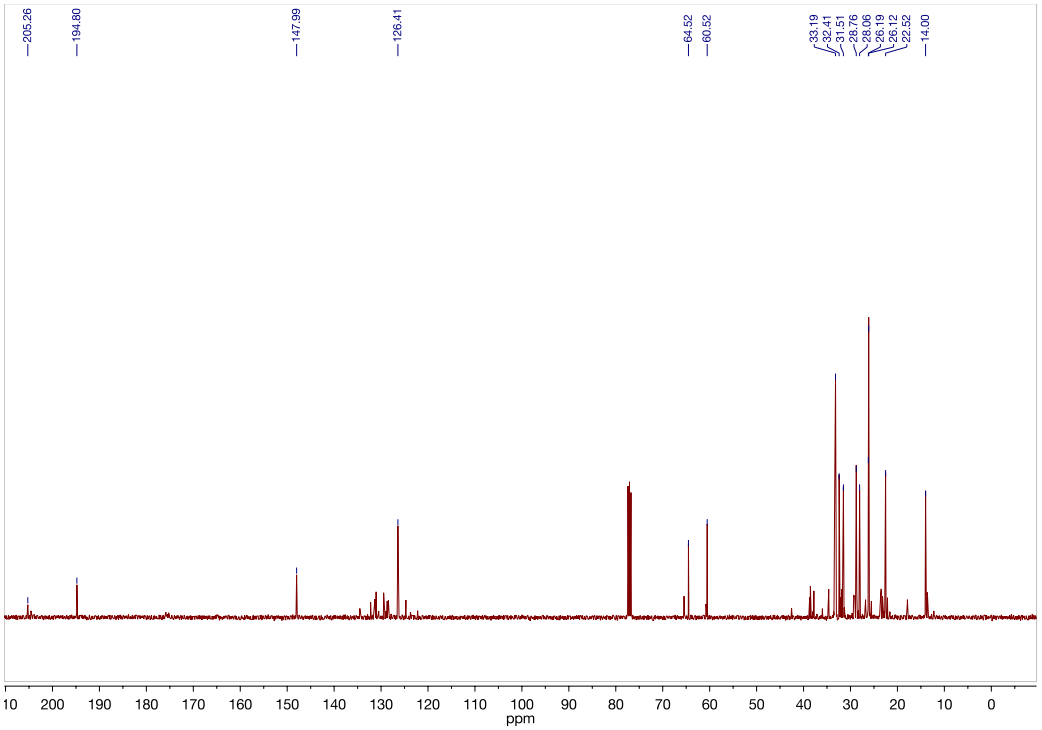




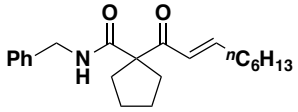
(*E*)-*N*-Methoxy-*N*-methyl-1-(non-2-enoyl)cyclopentane-1-carboxamide, 151

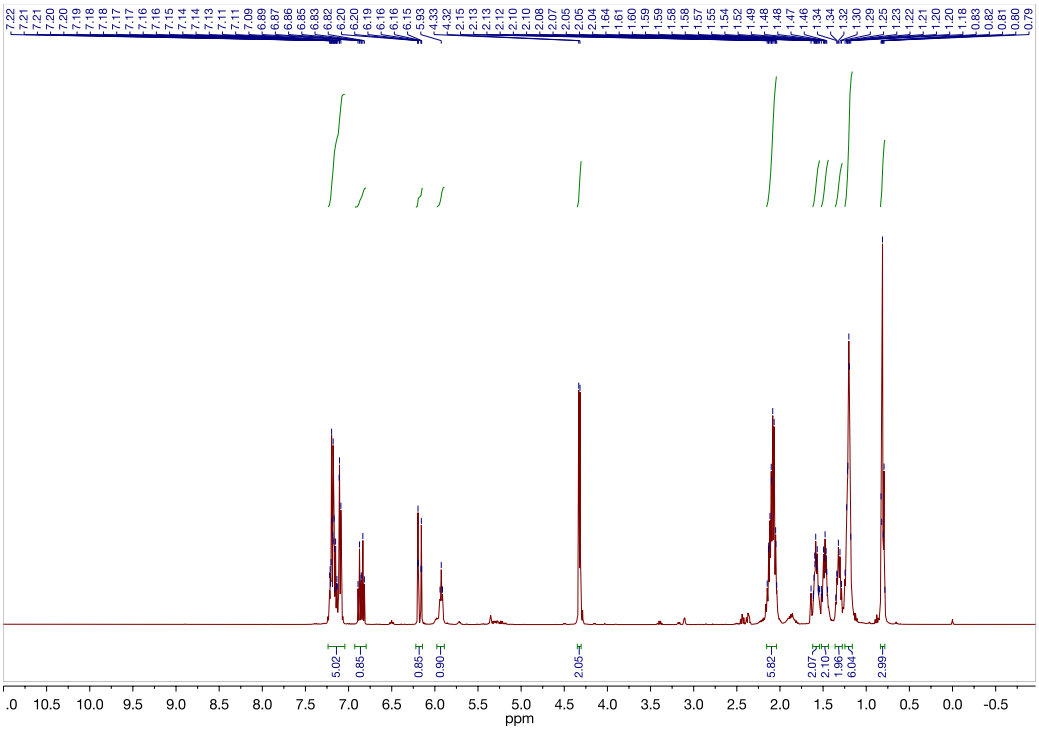


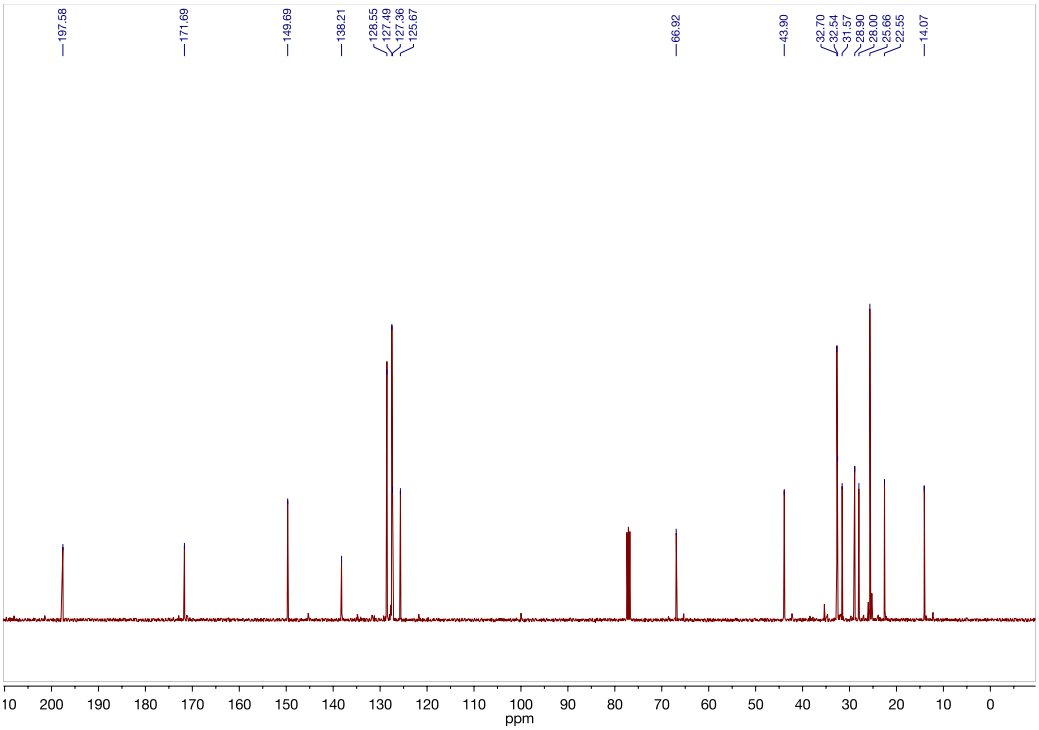




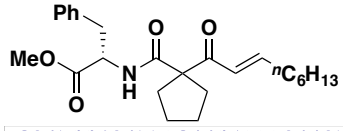
(*E*)-*N*-Benzyl-1-(non-2-enoyl)cyclopentane-1-carboxamide, 152

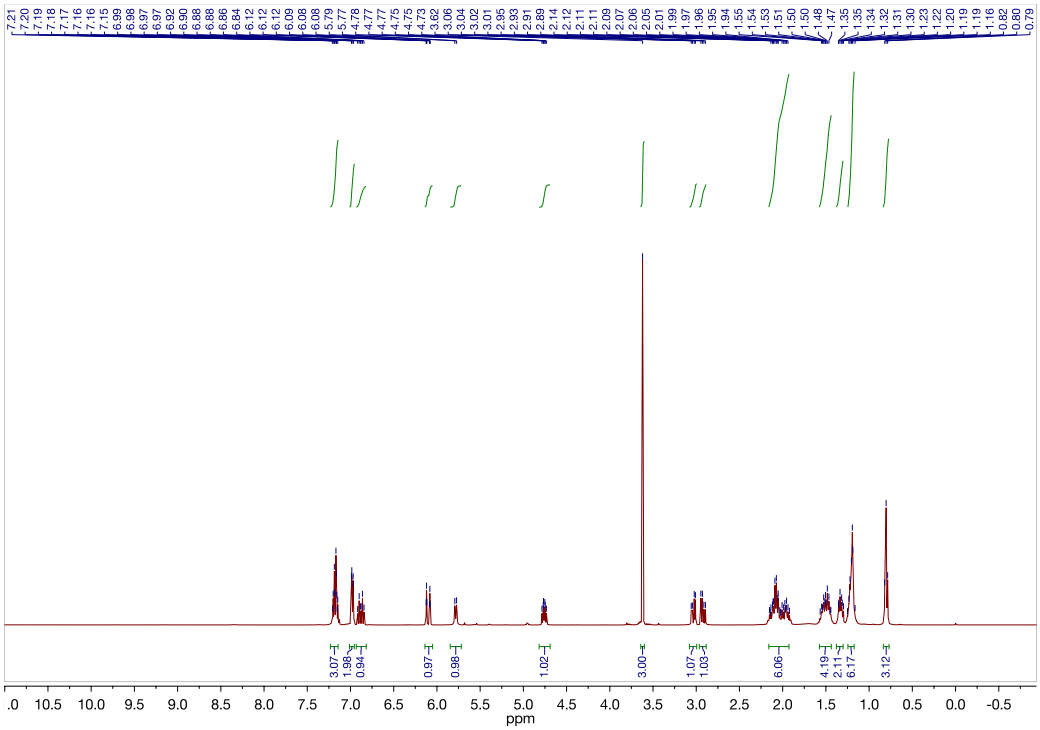


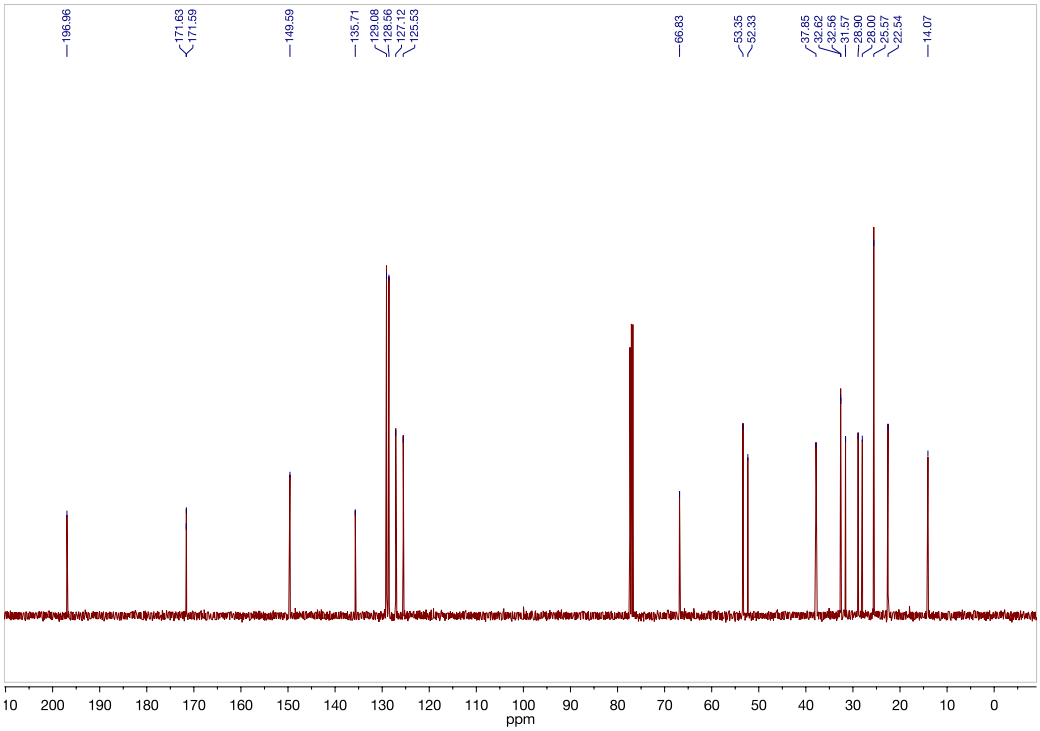




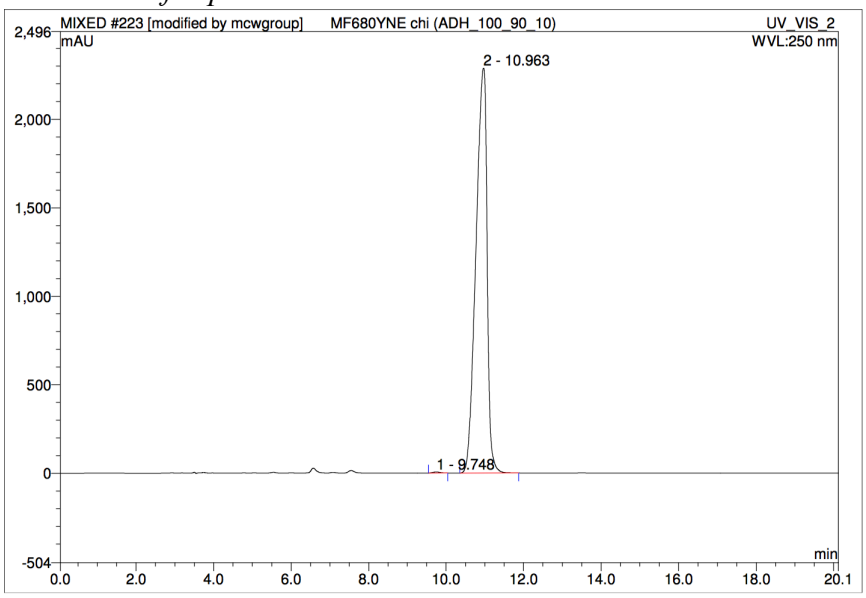
Methyl (*E*)-(1-(non-2-enoyl)cyclopentane-1-carbonyl)-*L*-phenylalaninate, 153





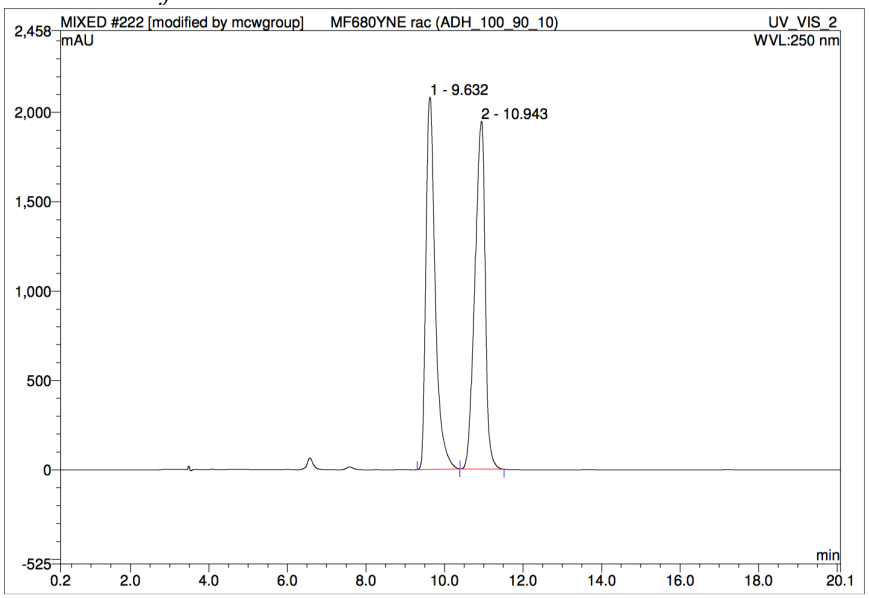


HPLC trace for product:



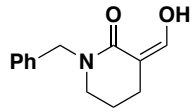
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	9.75	n.a.	6.087	1.356	0.18	n.a.	BMB*
2	10.96	n.a.	2286.645	761.987	99.82	n.a.	BMB*
Total:			2292.732	763.342	100.00	0.000	

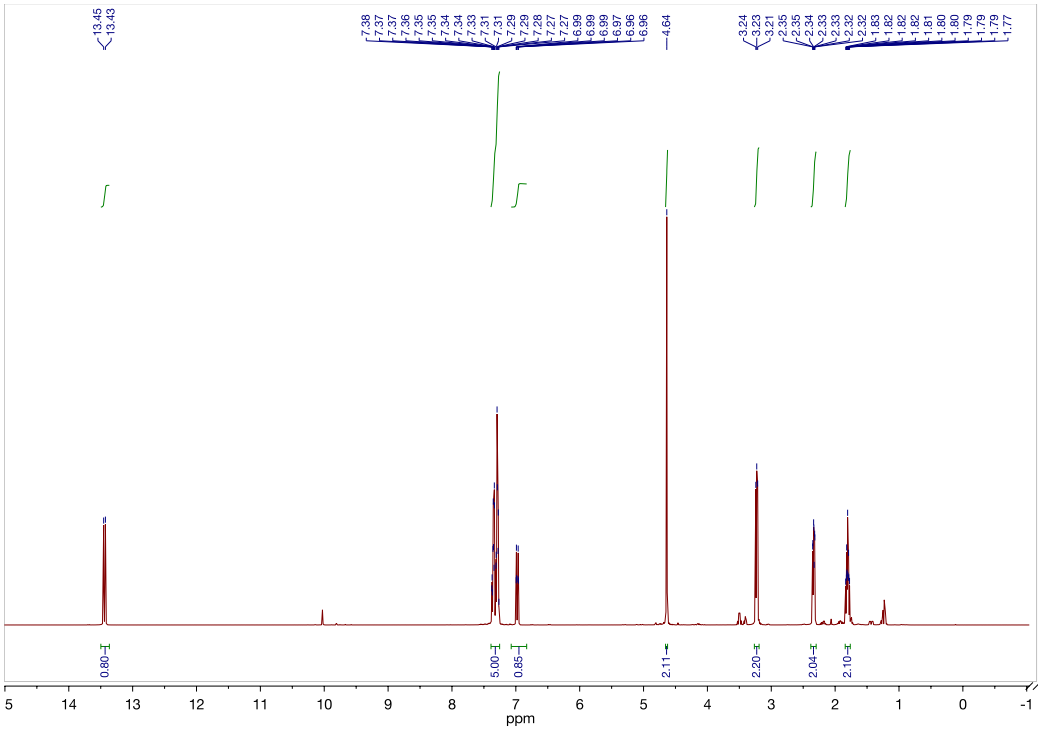
HPLC trace for racemate:

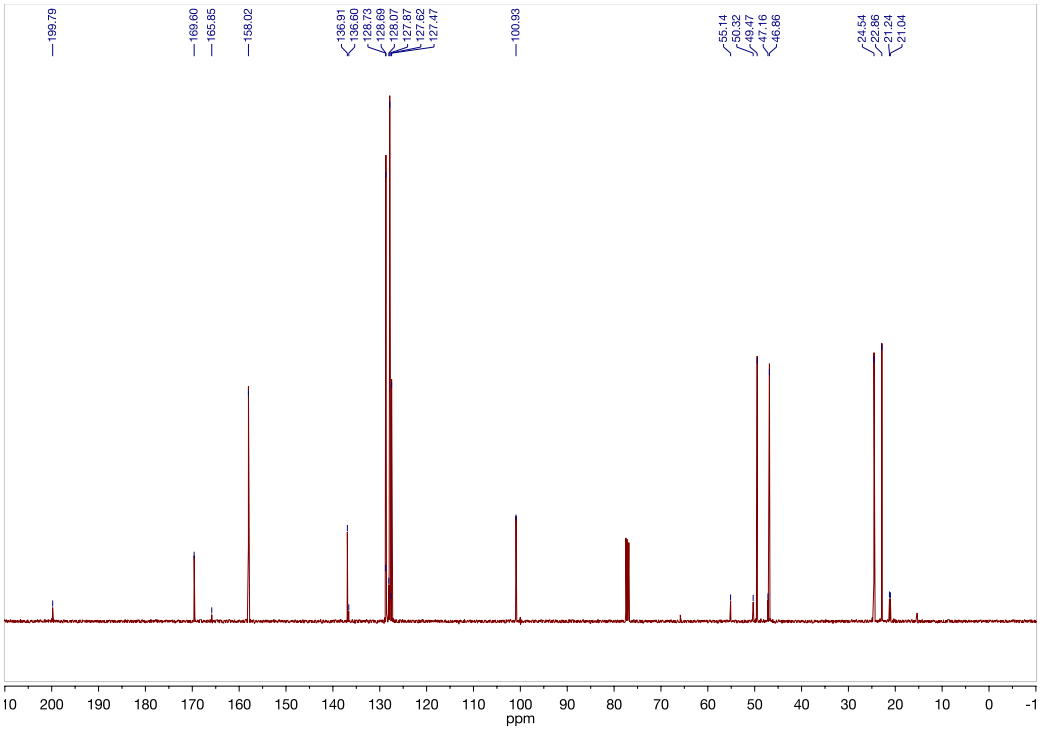


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	9.63	n.a.	2083.243	576.327	49.24	n.a.	BMB*
2	10.94	n.a.	1946.367	594.082	50.76	n.a.	BMB*
Total:			4029.610	1170.409	100.00	0.000	

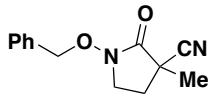
1-Benzyl-3-(hydroxymethylene)piperidin-2-one, 157

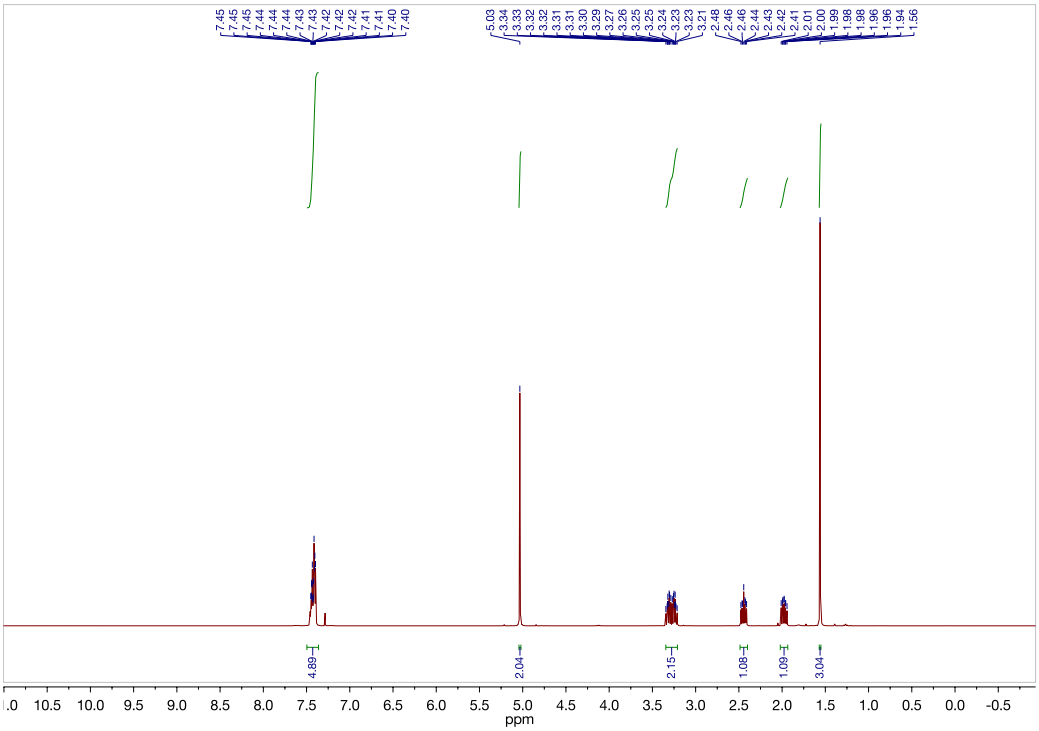


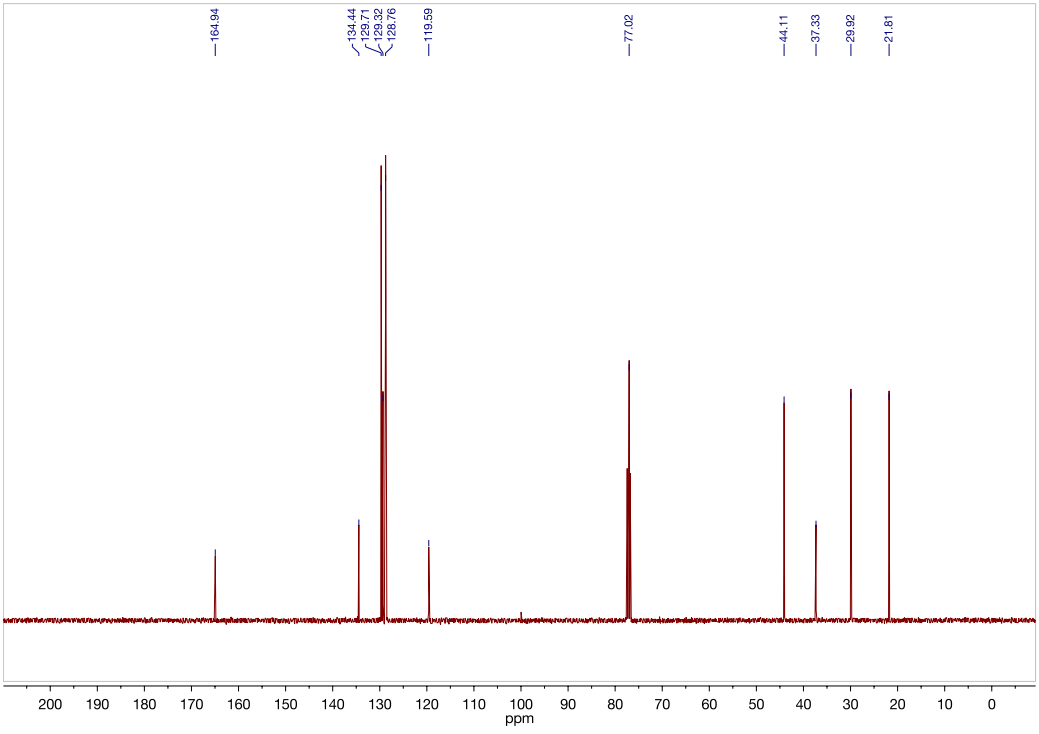




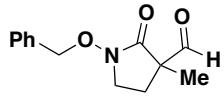
1-(Benzyloxy)-3-methyl-2-oxopyrrolidine-3-carbonitrile, 163

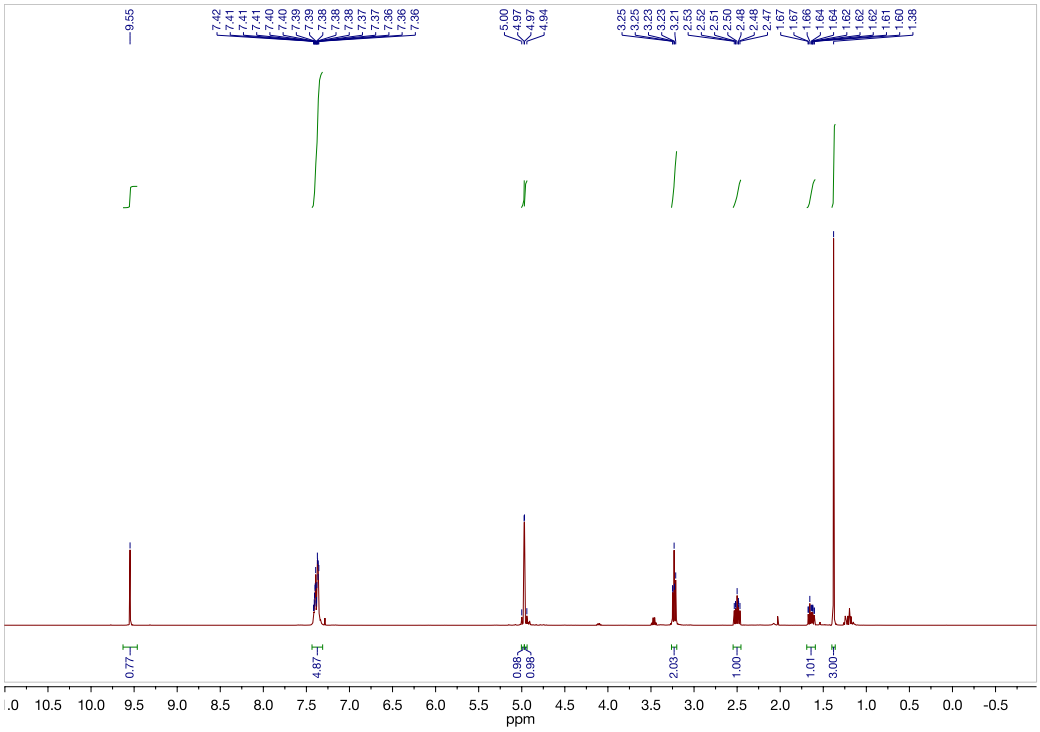


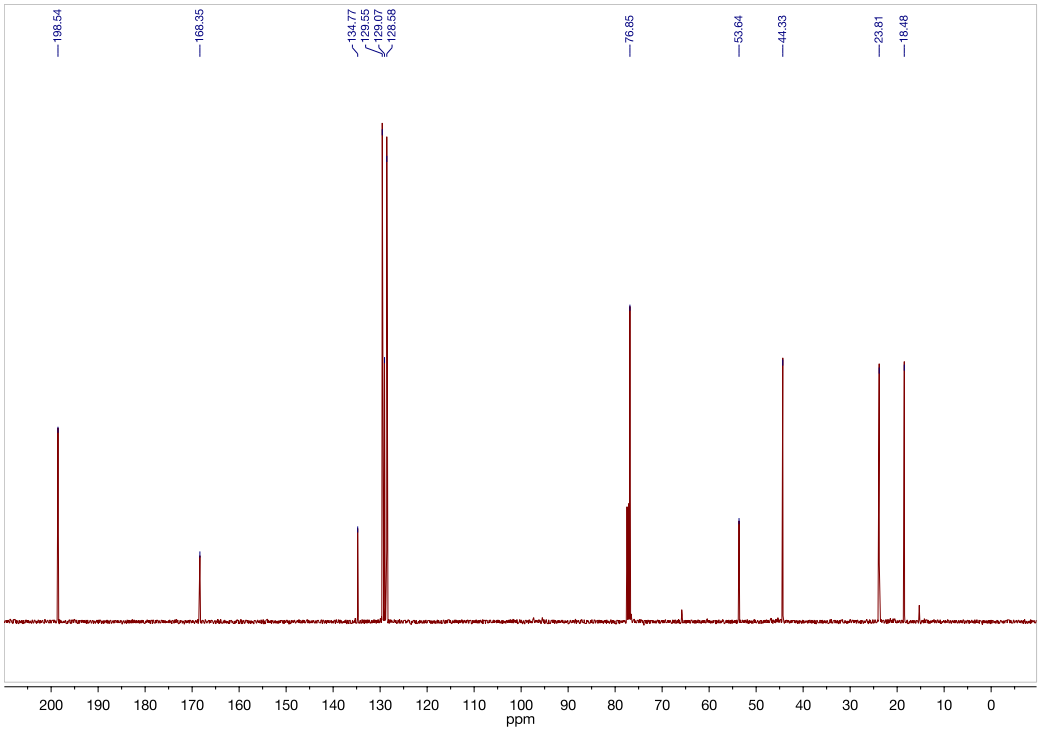




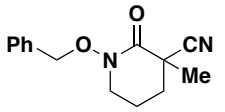
1-(Benzyloxy)-3-methyl-2-oxopyrrolidine-3-carbaldehyde, 165

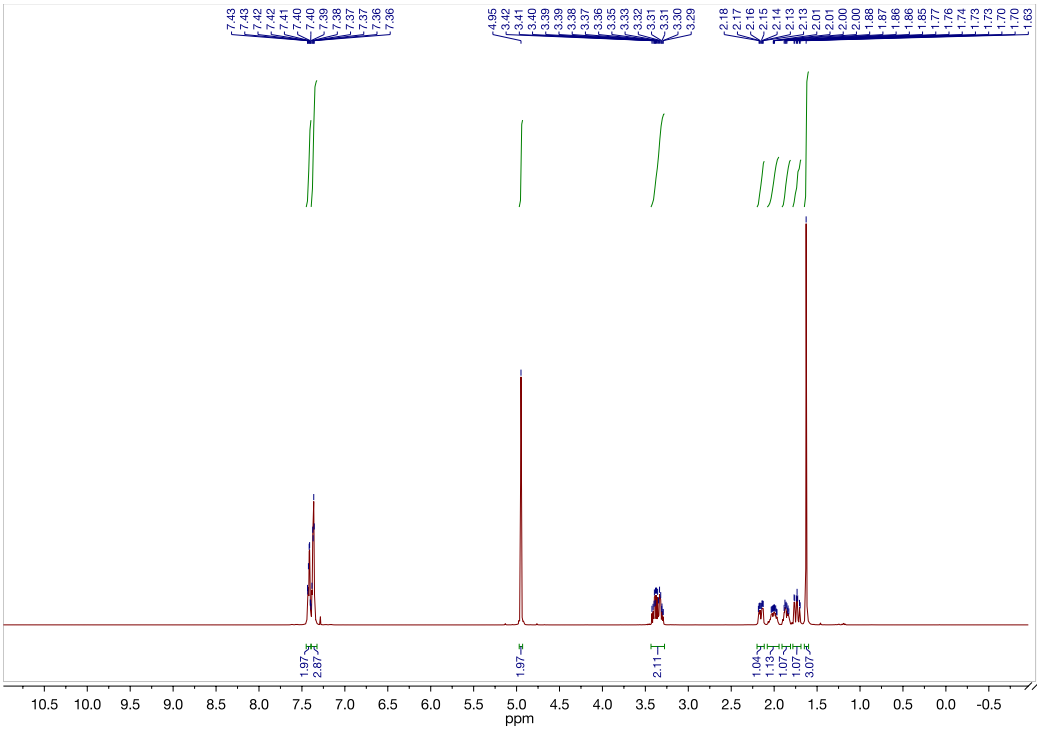


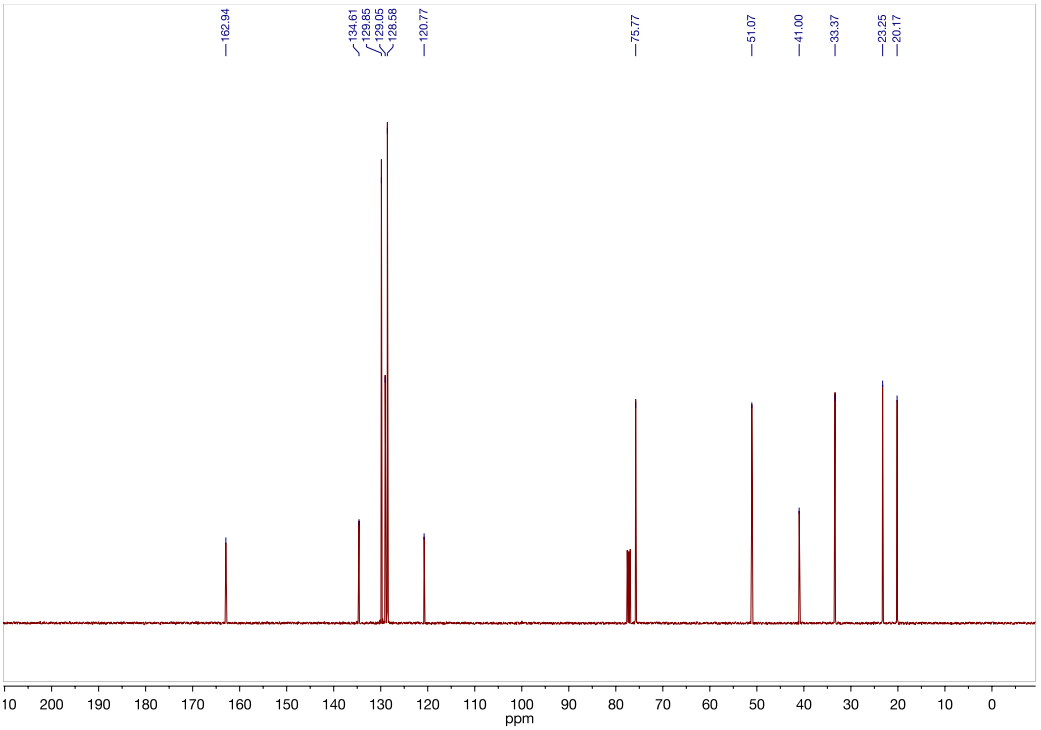




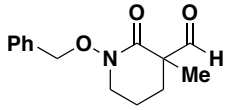
1-(Benzyloxy)-3-methyl-2-oxopiperidine-3-carbonitrile, 164

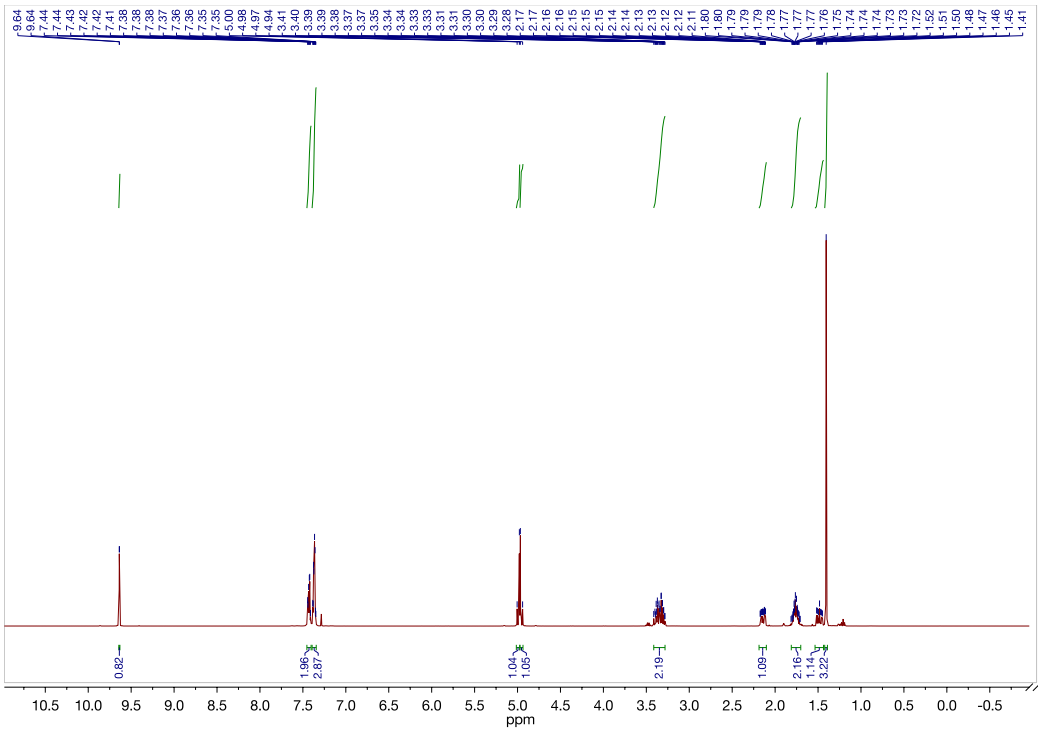


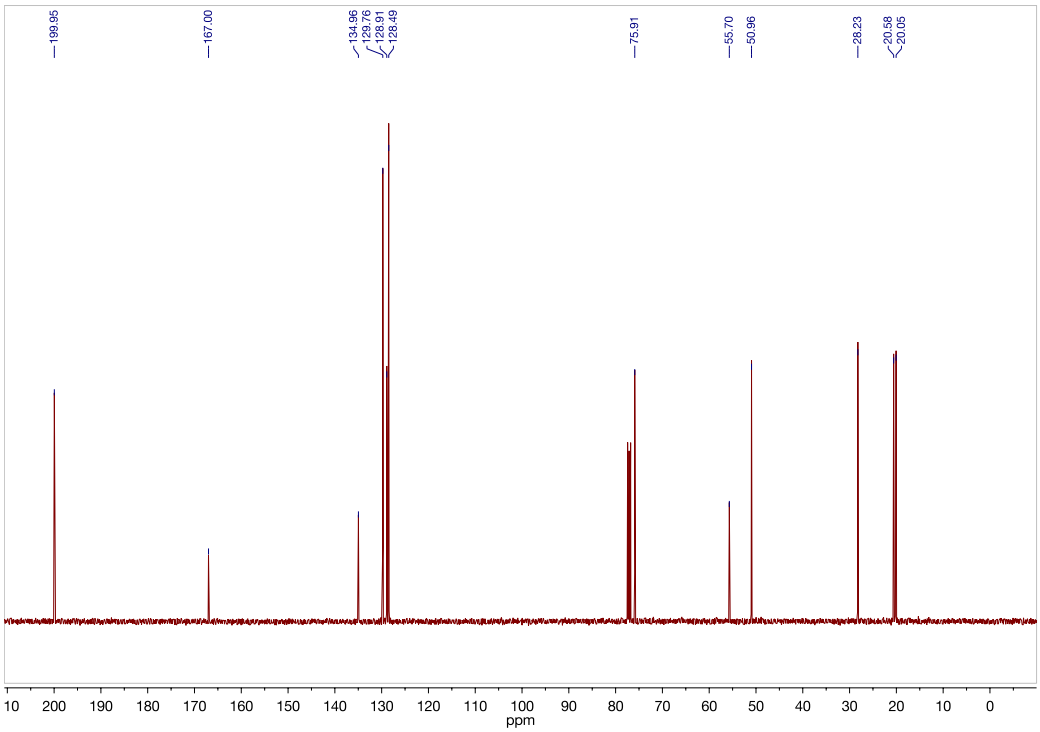




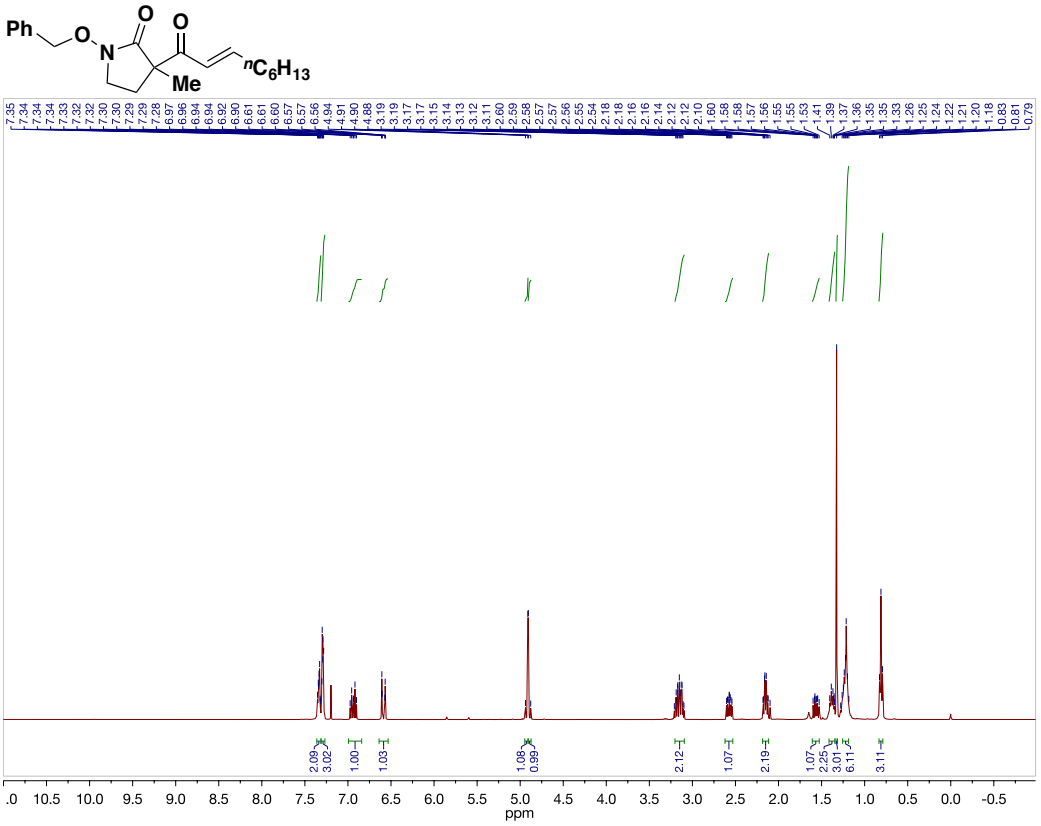
1-(Benzyloxy)-3-methyl-2-oxopiperidine-3-carbaldehyde, 166

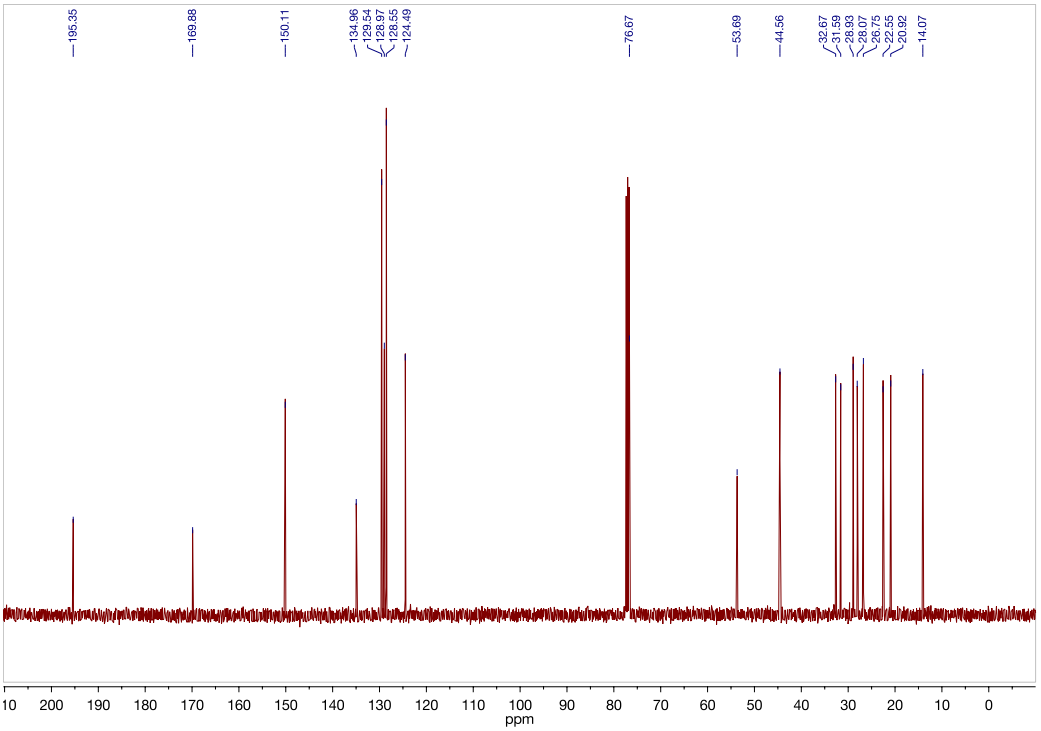




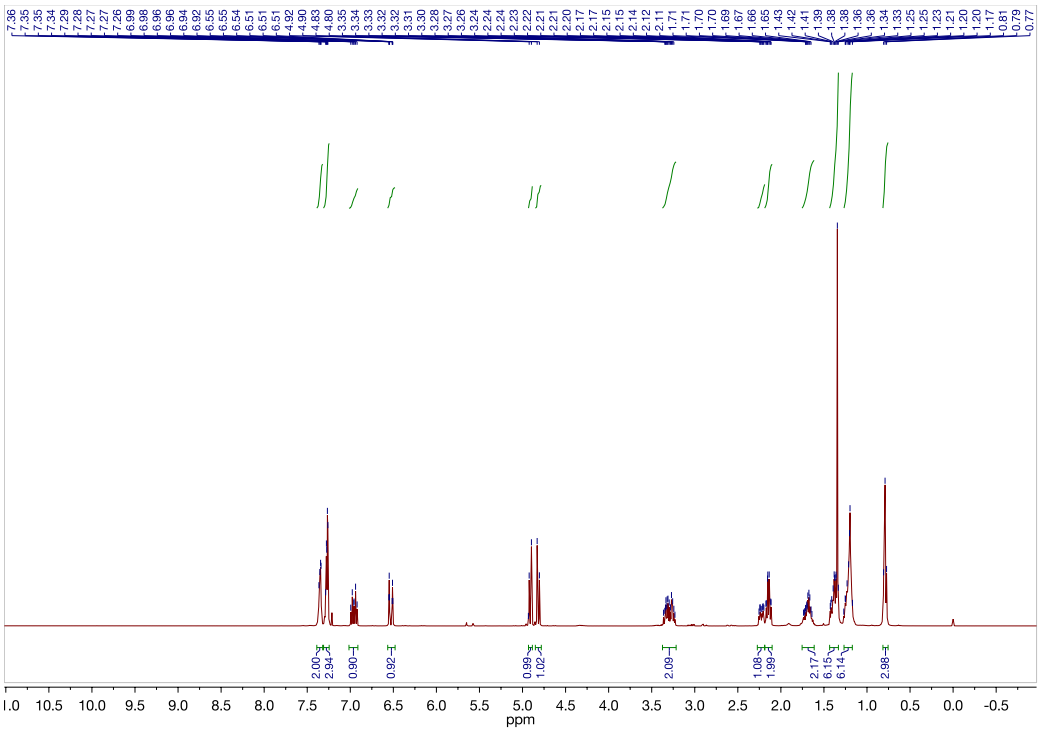


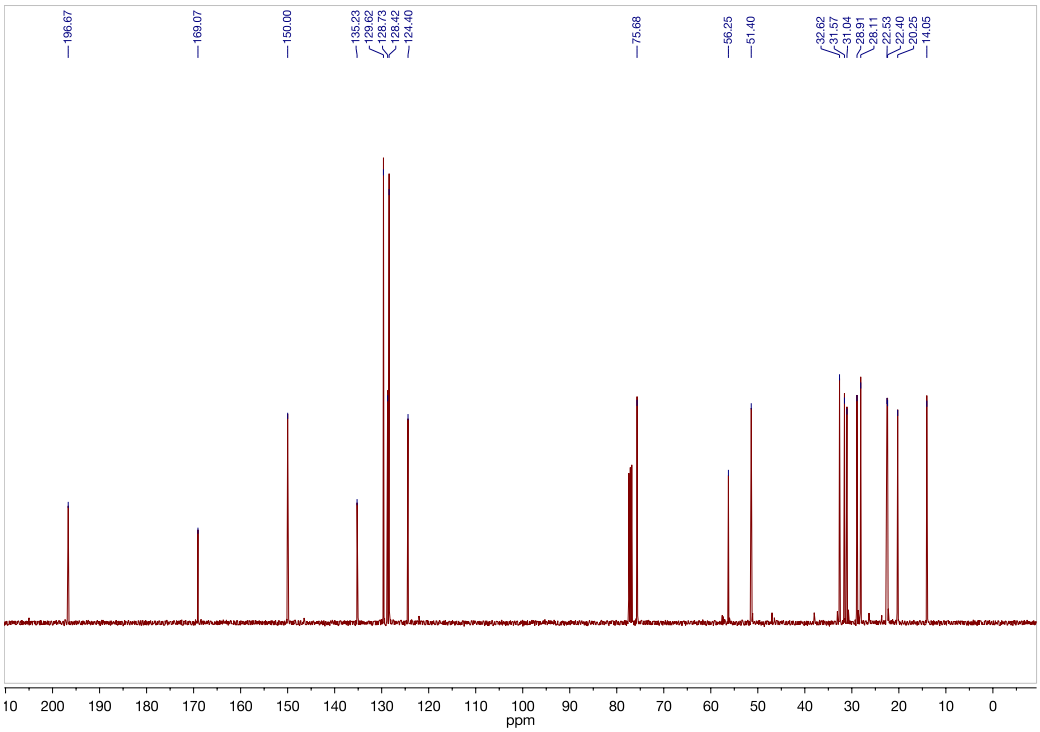
(*E*)-1-(Benzyloxy)-3-methyl-3-(non-2-enoyl)pyrrolidin-2-one, 167



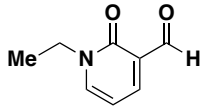


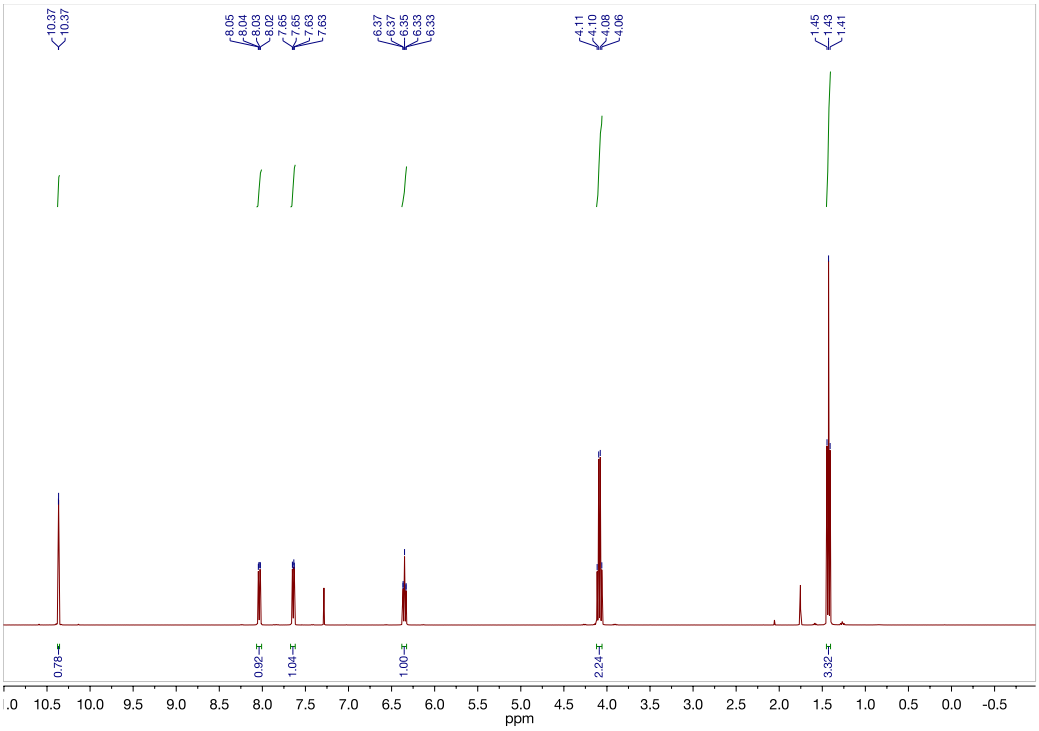
(*E*)-1-(Benzyloxy)-3-methyl-3-(non-2-enoyl)piperidin-2-one, 168

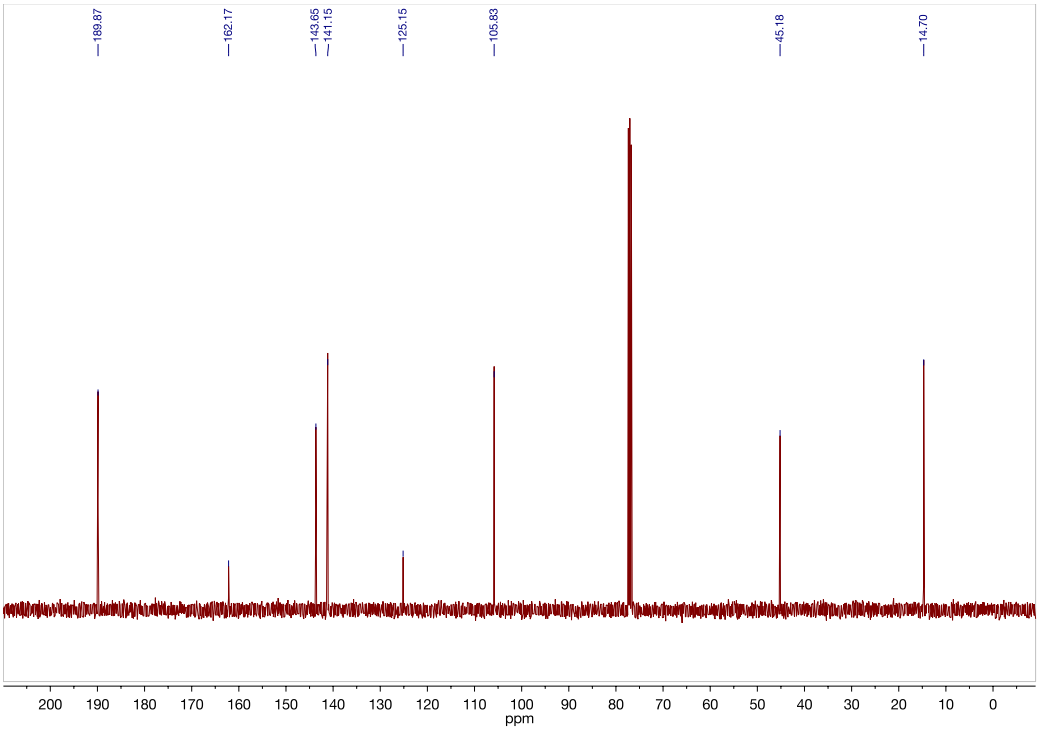




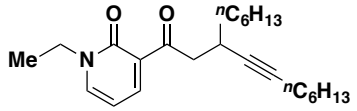
1-Ethyl-2-oxo-1,2-dihydropyridine-3-carbaldehyde, 169

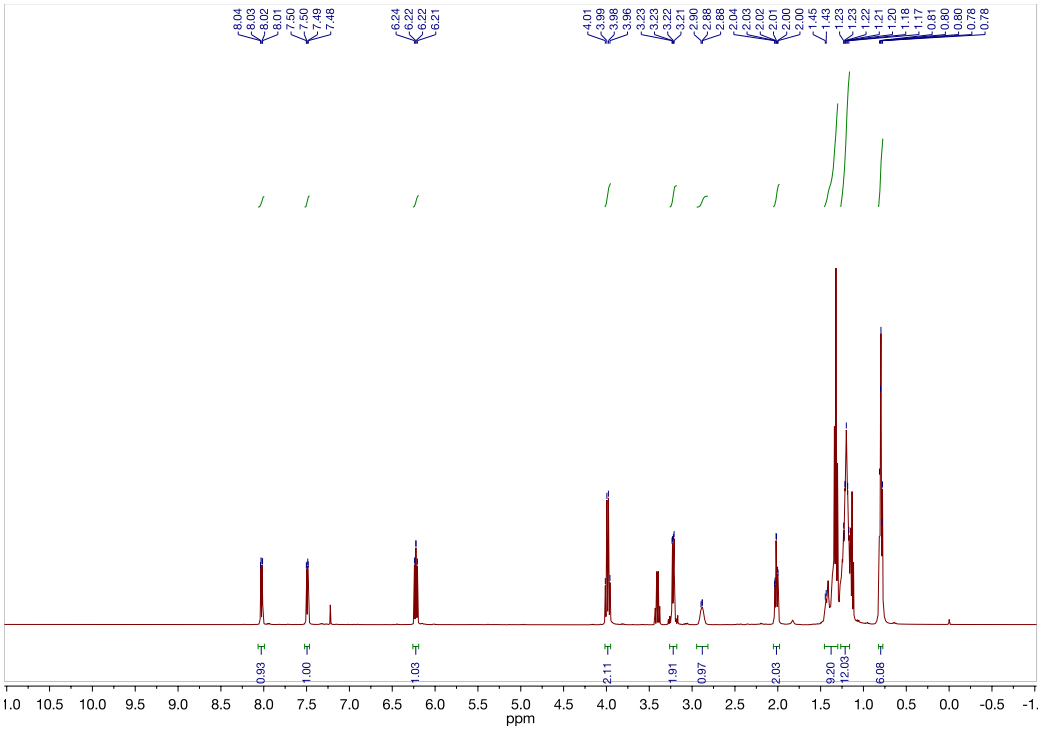


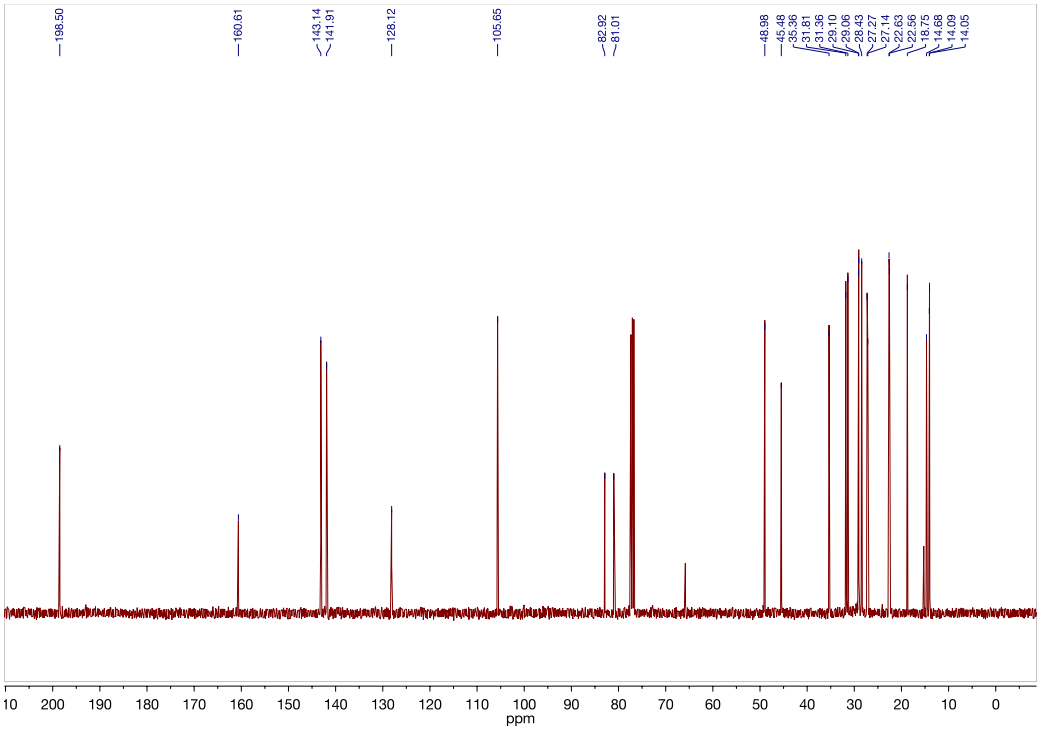




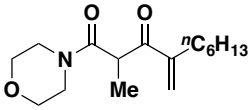
1-Ethyl-3-(3-hexylundec-4-ynoyl)pyridin-2(1*H*)-one, 171

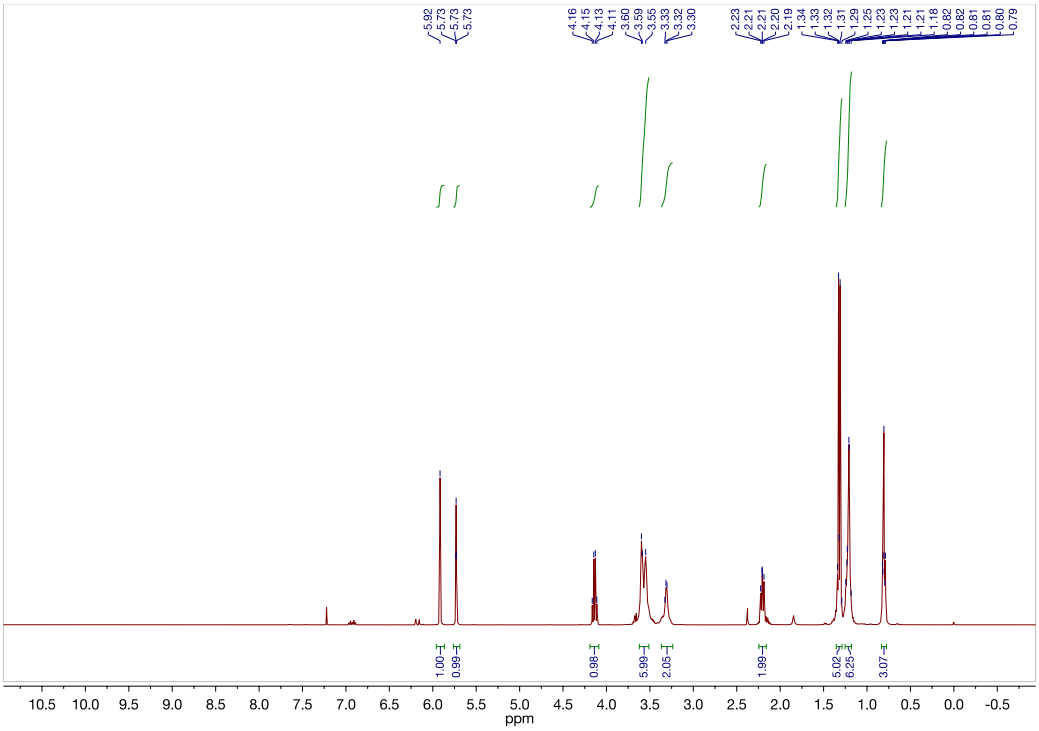


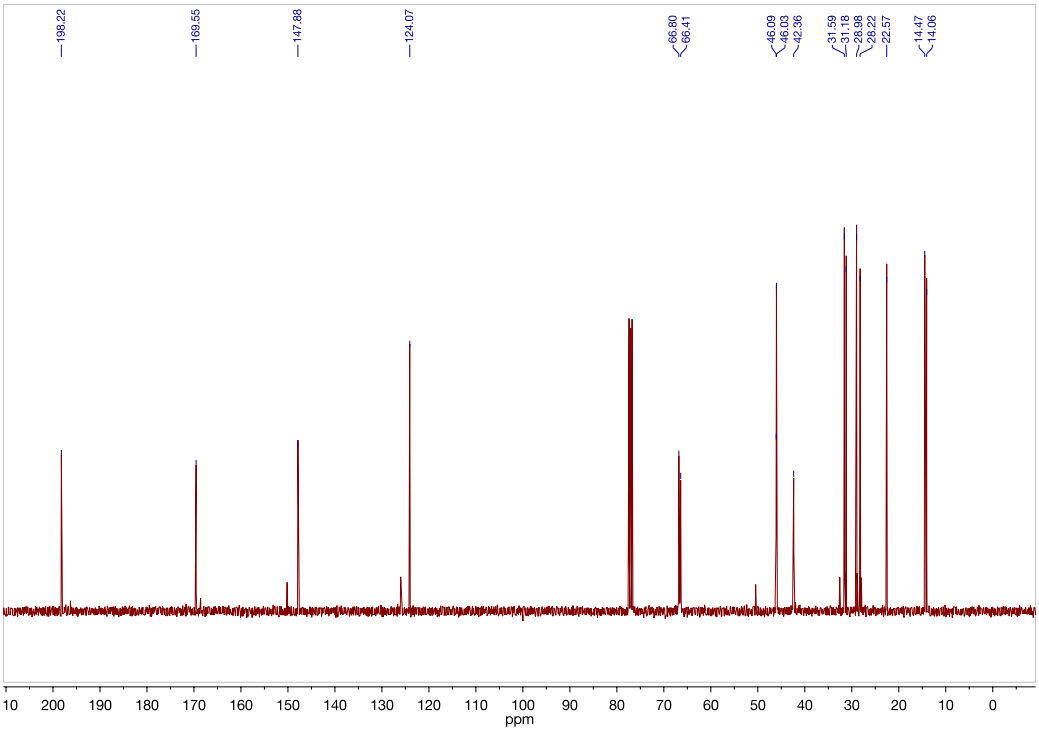




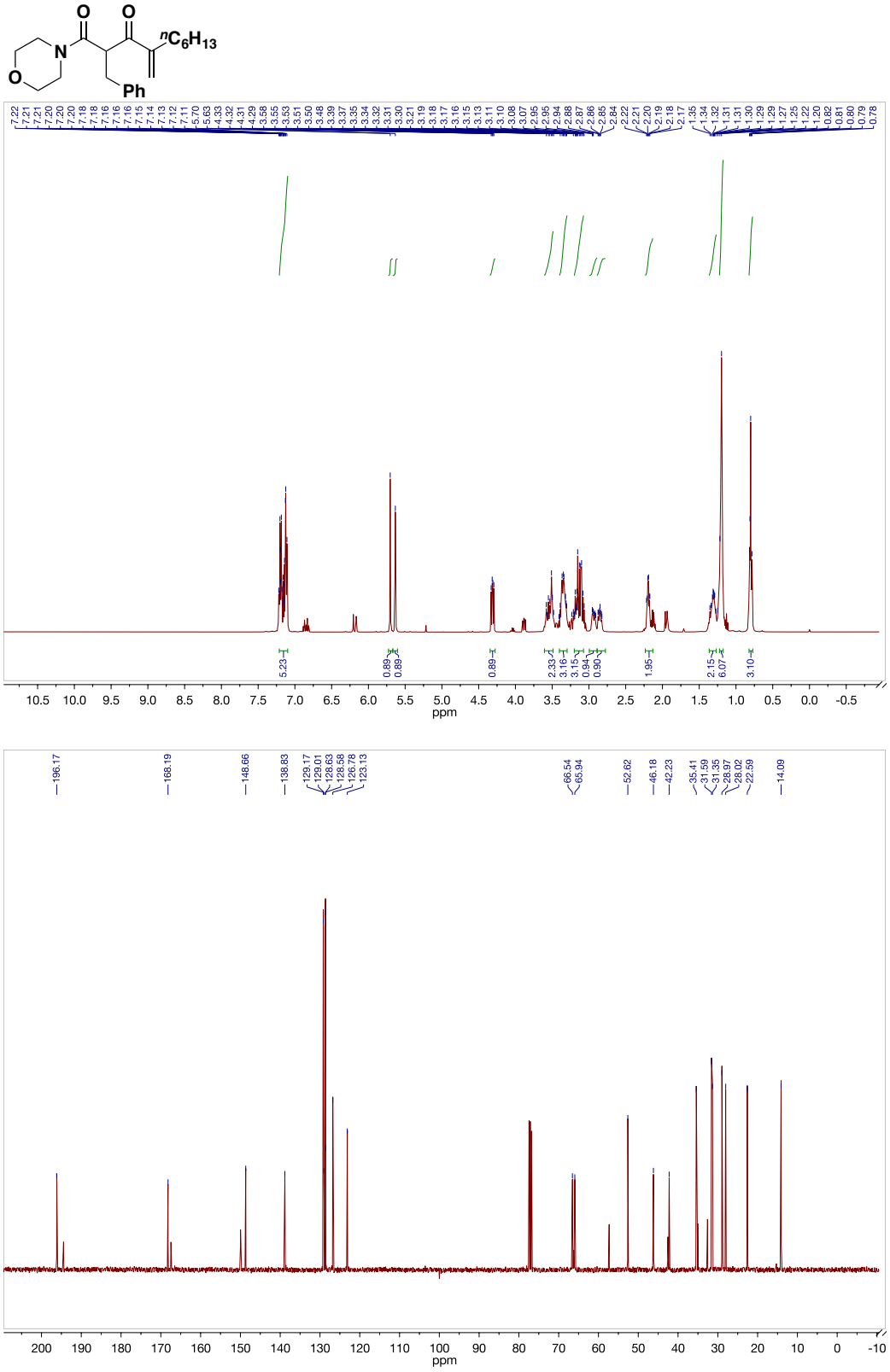
2-Methyl-4-methylene-1-morpholinodecane-1,3-dione, 140b



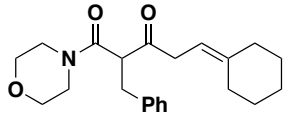


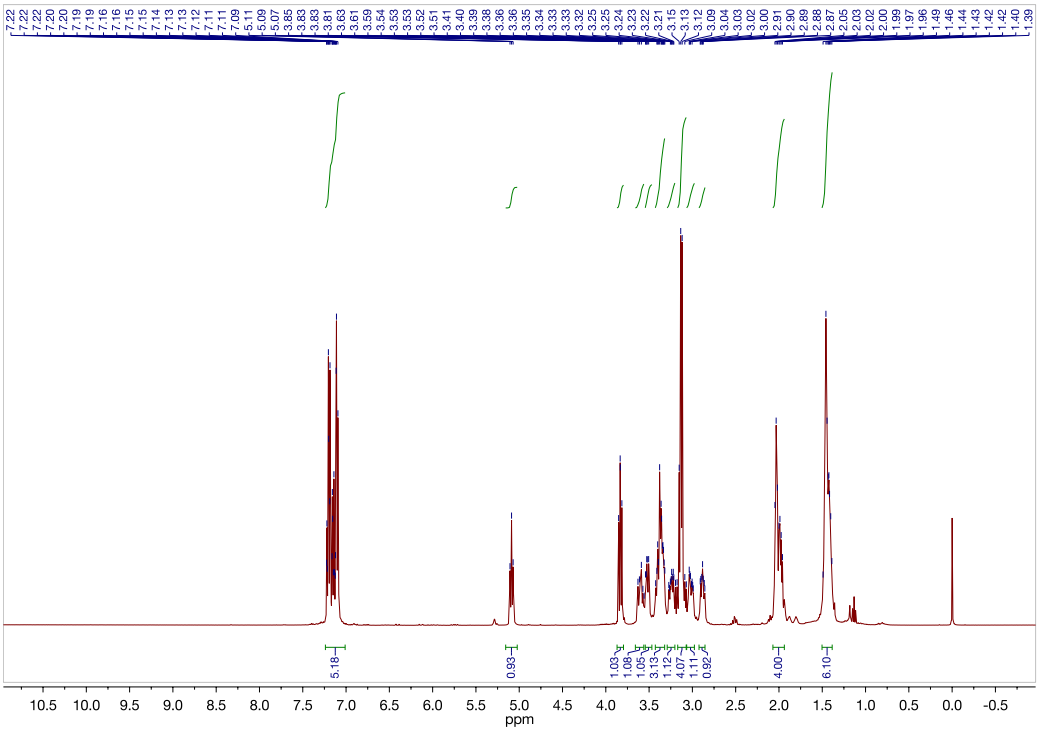


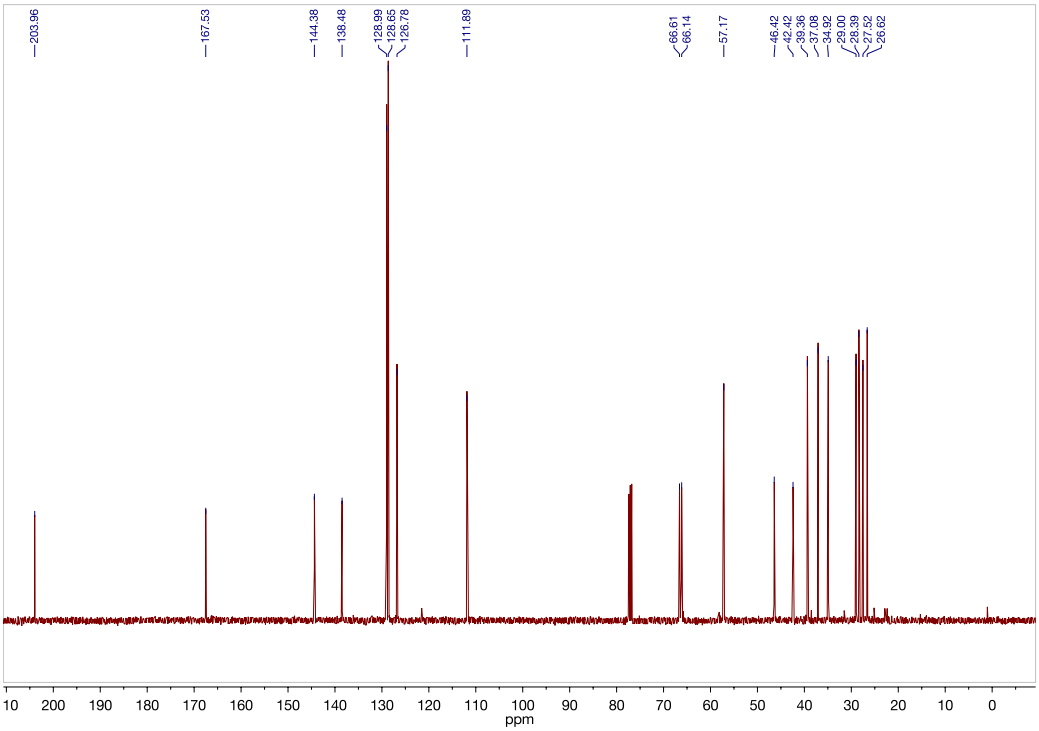
2-Benzyl-4-methylene-1-morpholinodecane-1,3-dione, 70b



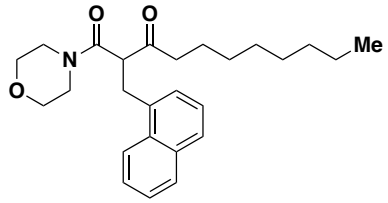
2-Benzyl-5-cyclohexylidene-1-morpholinopentane-1,3-dione, 173

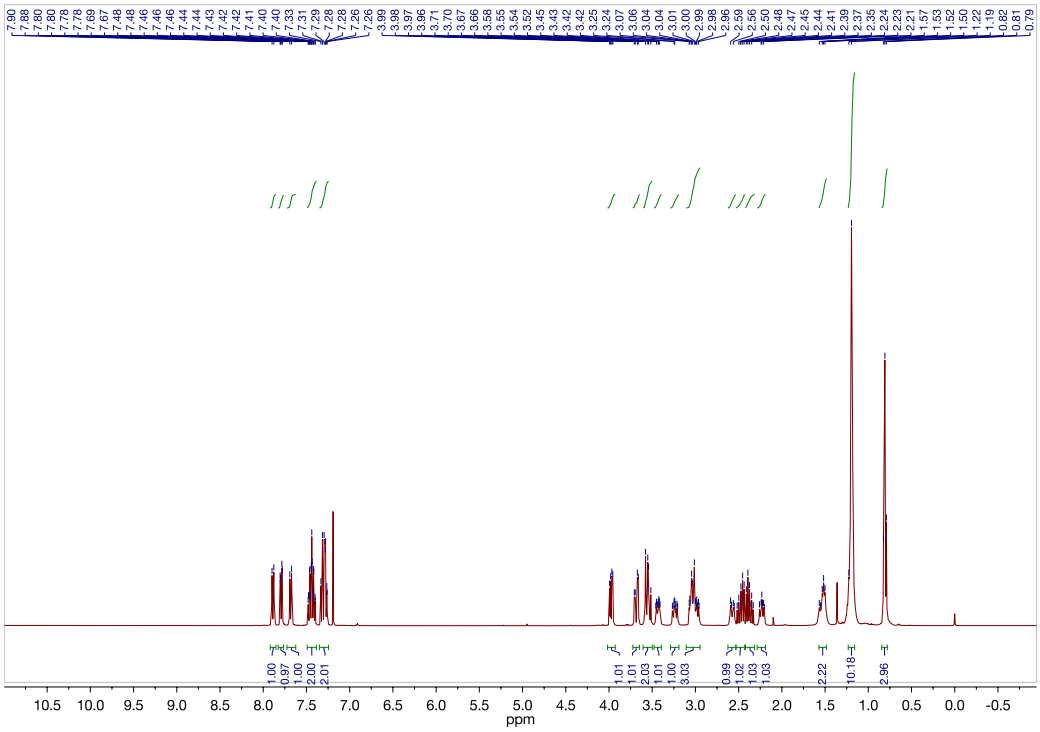


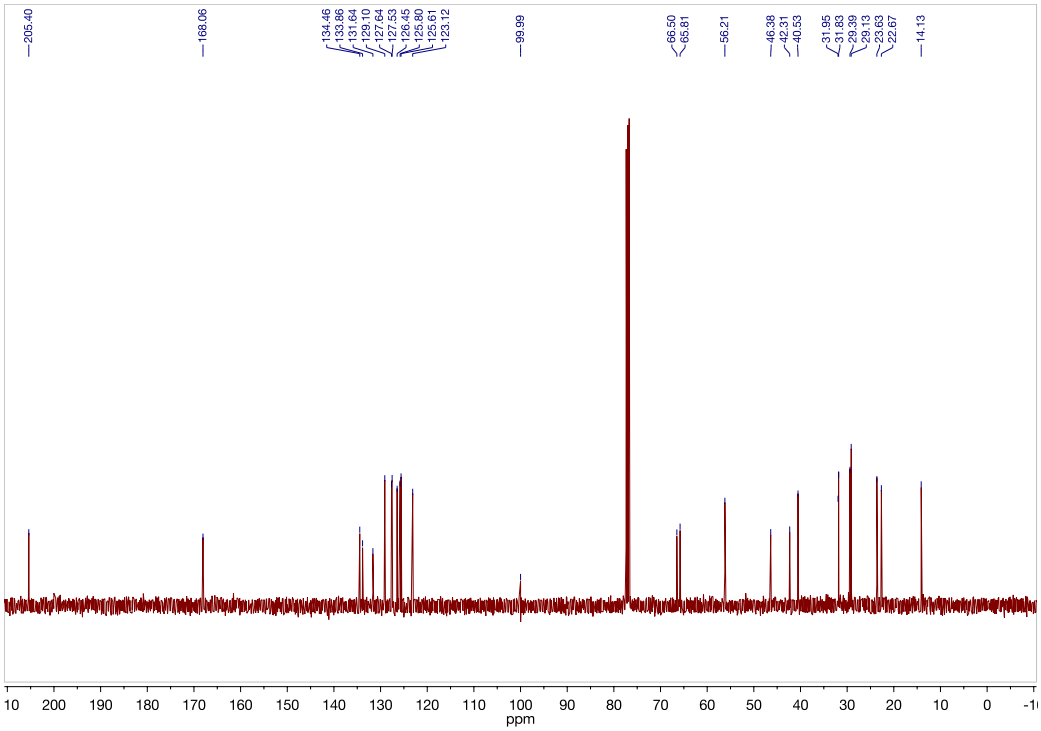




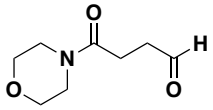
1-Morpholino-2-(naphthalen-1-ylmethyl)undecane-1,3-dione, 174

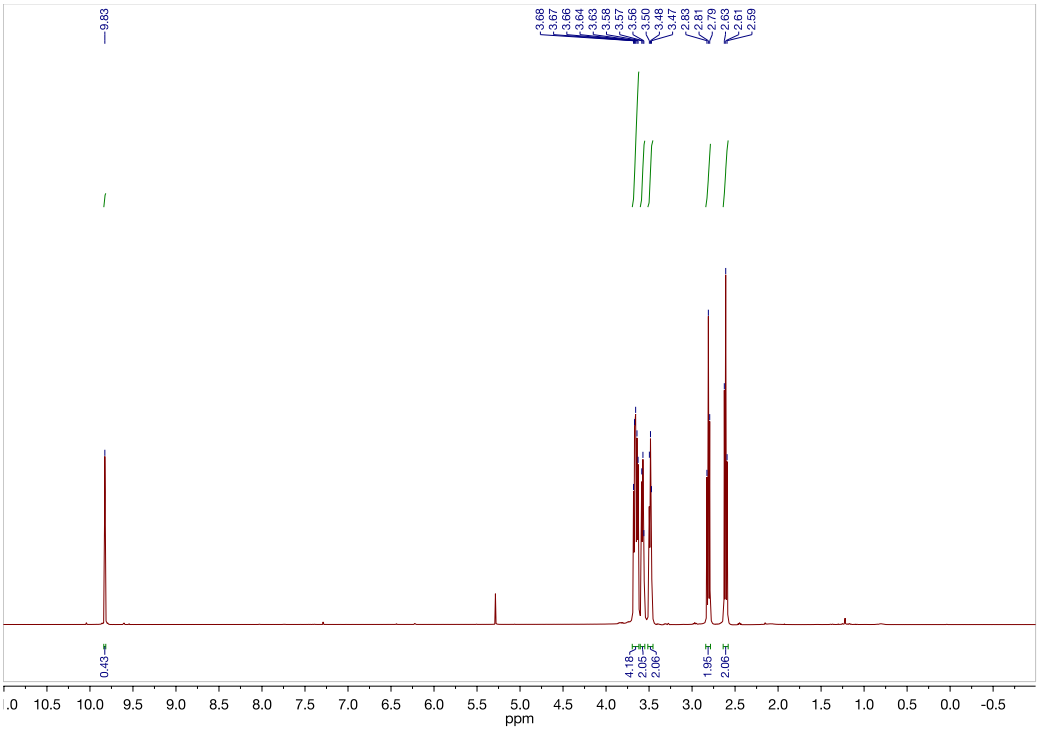


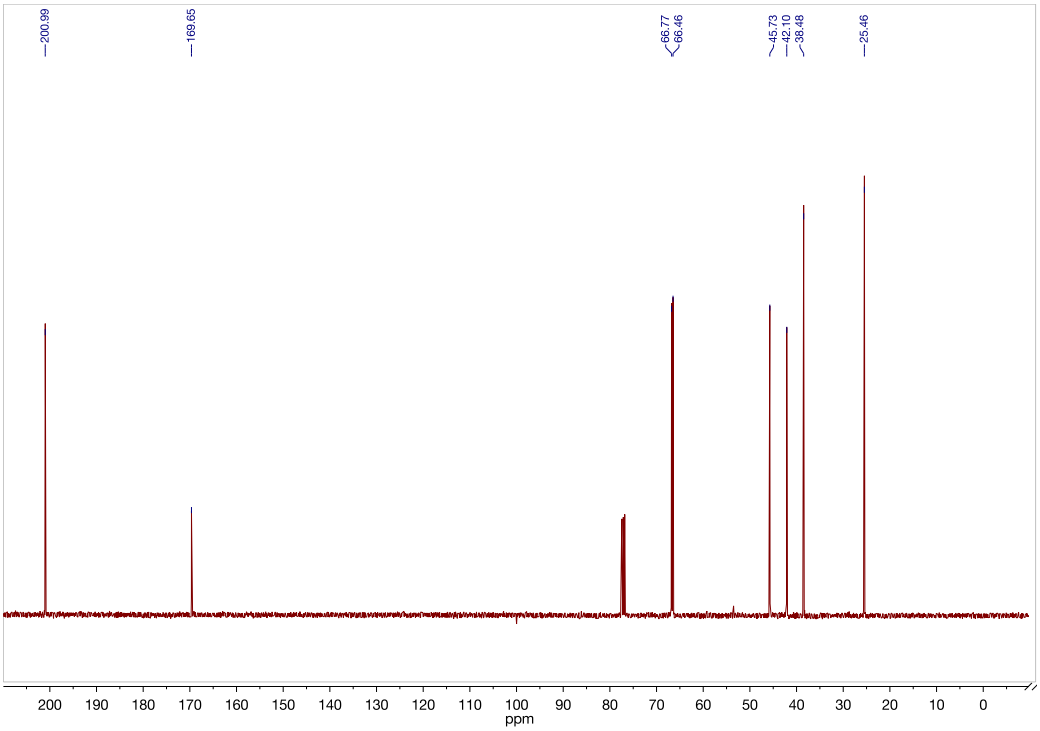




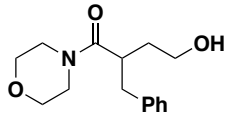
4-Morpholino-4-oxobutanal, 177

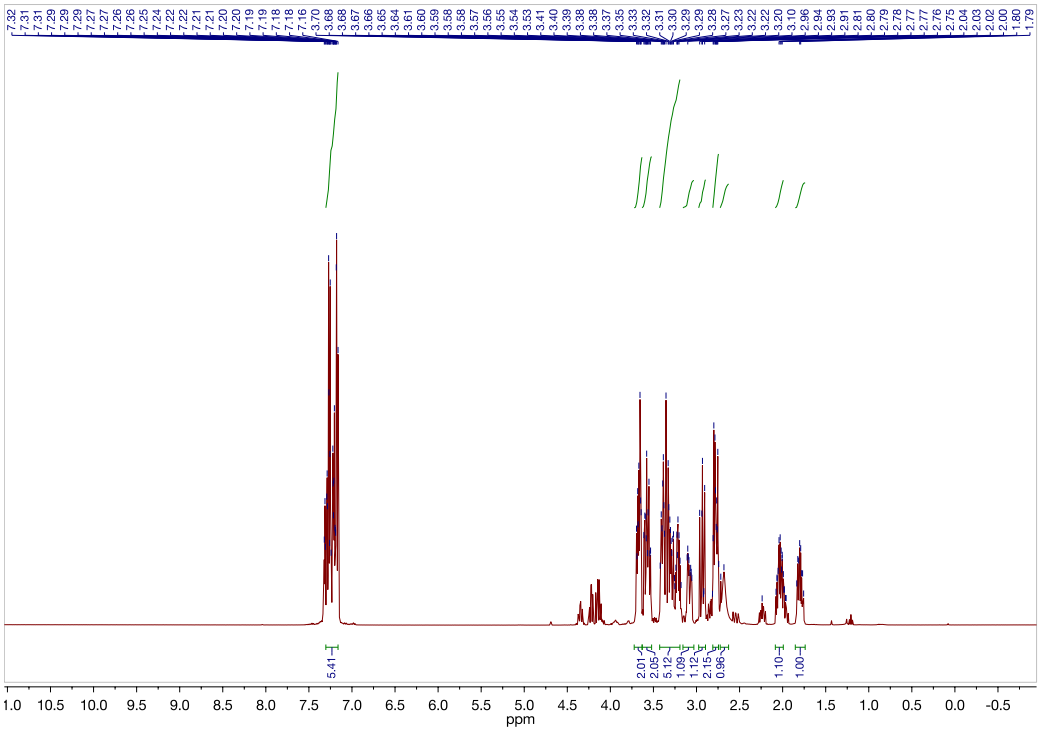


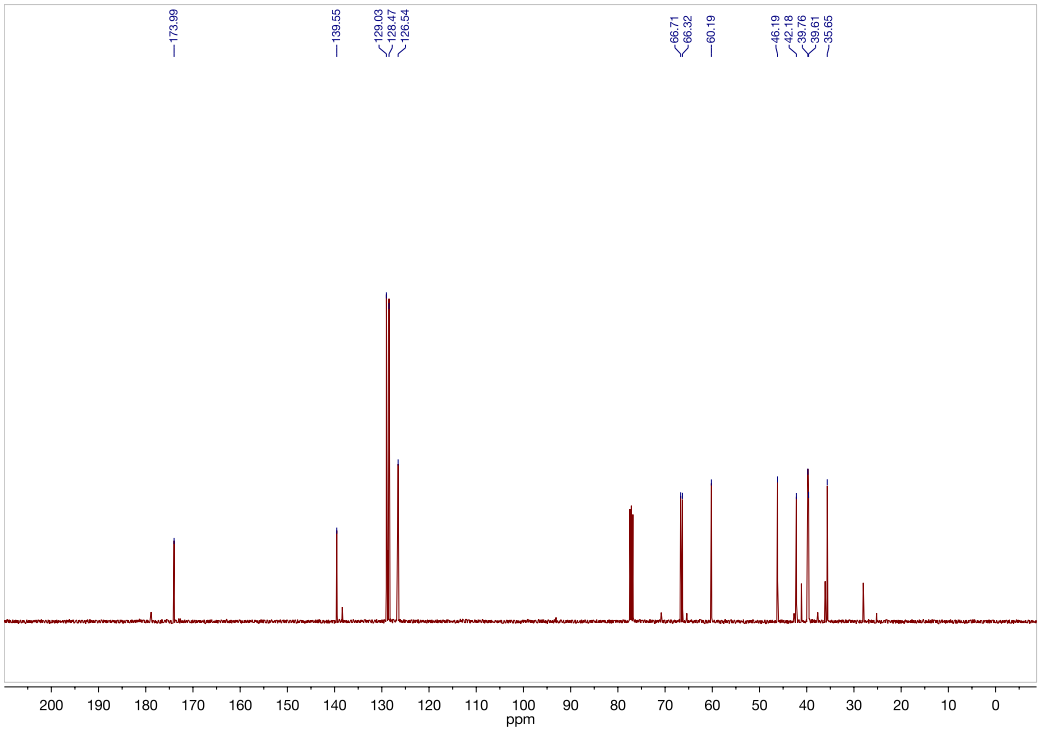




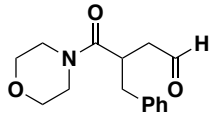
2-Benzyl-4-hydroxy-1-morpholinobutan-1-one, 181

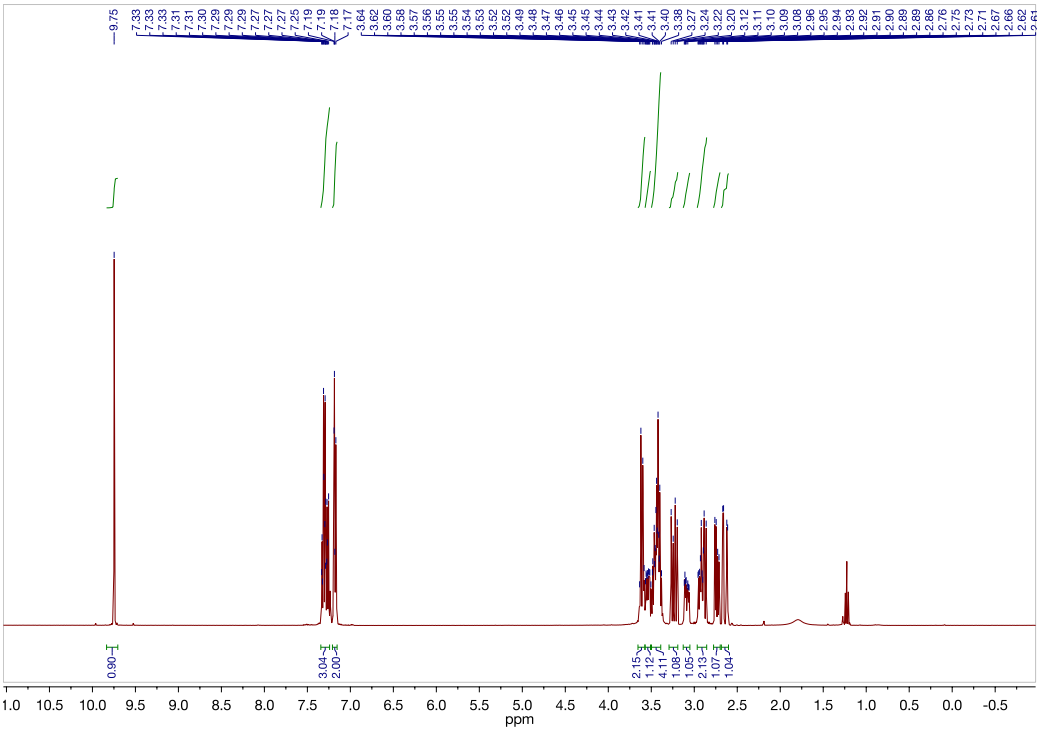


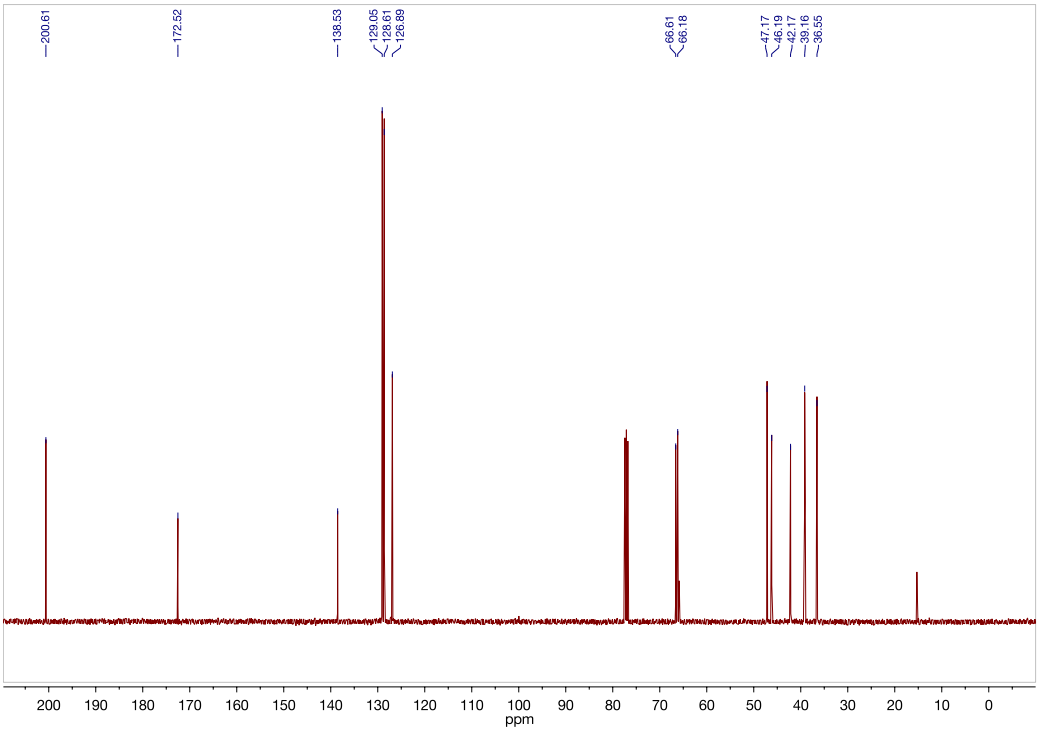




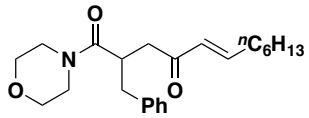
3-Benzyl-4-morpholino-4-oxobutanal, 182

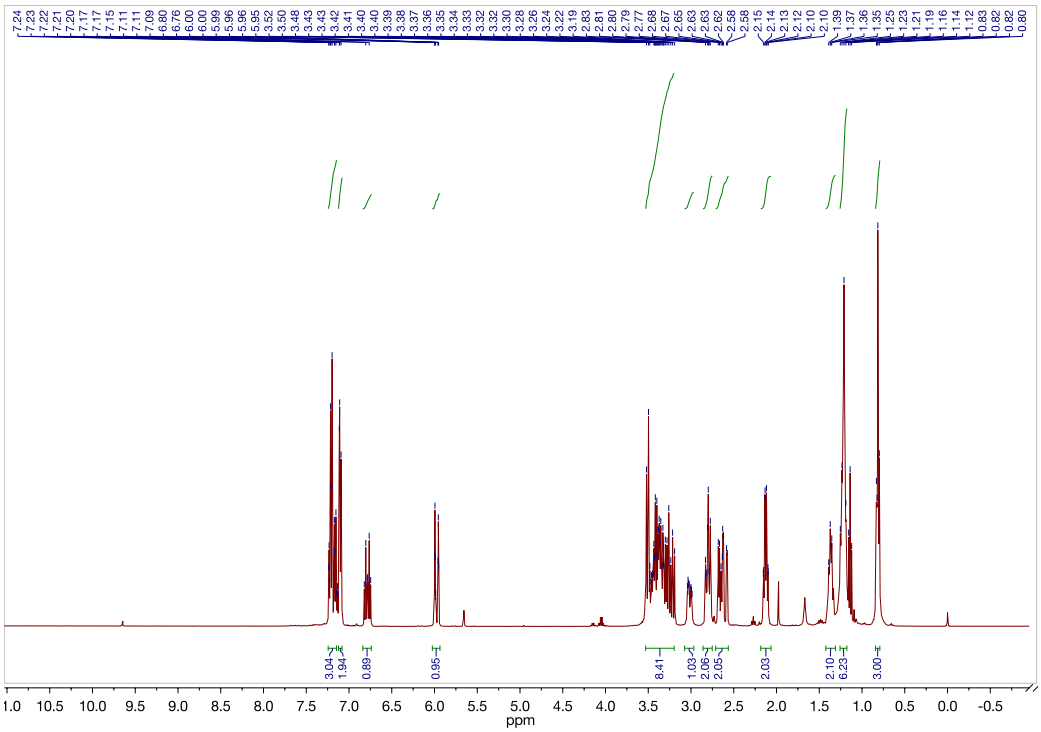


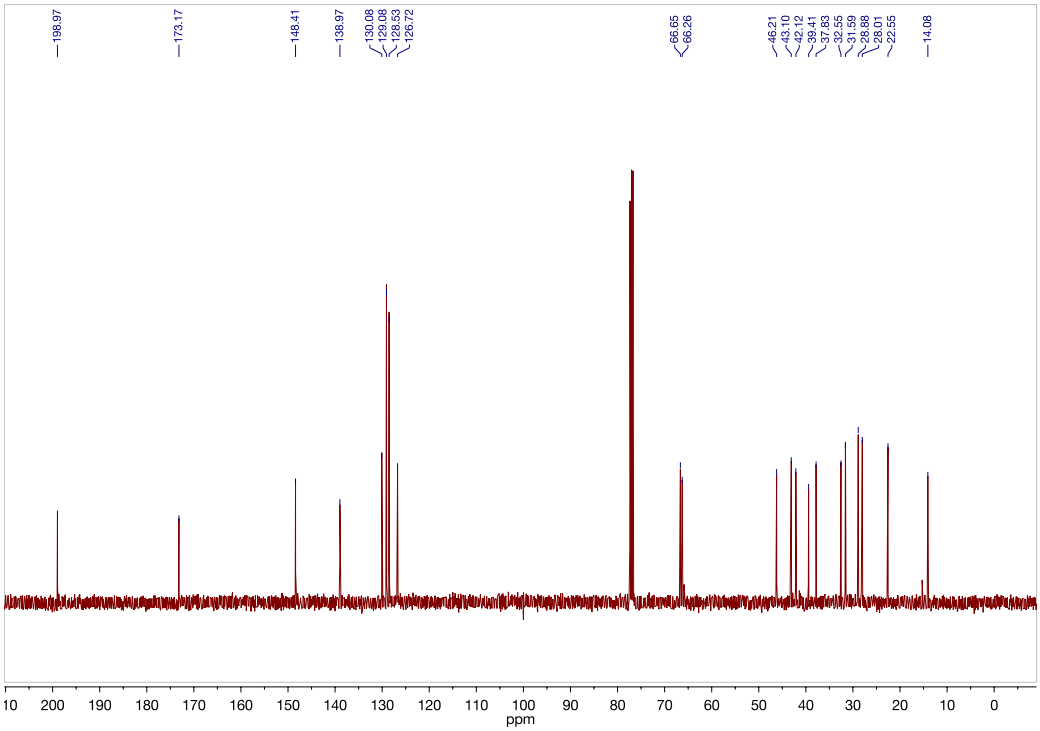




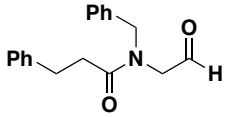
(*E*)-2-Benzyl-1-morpholinododec-5-ene-1,4-dione, 183

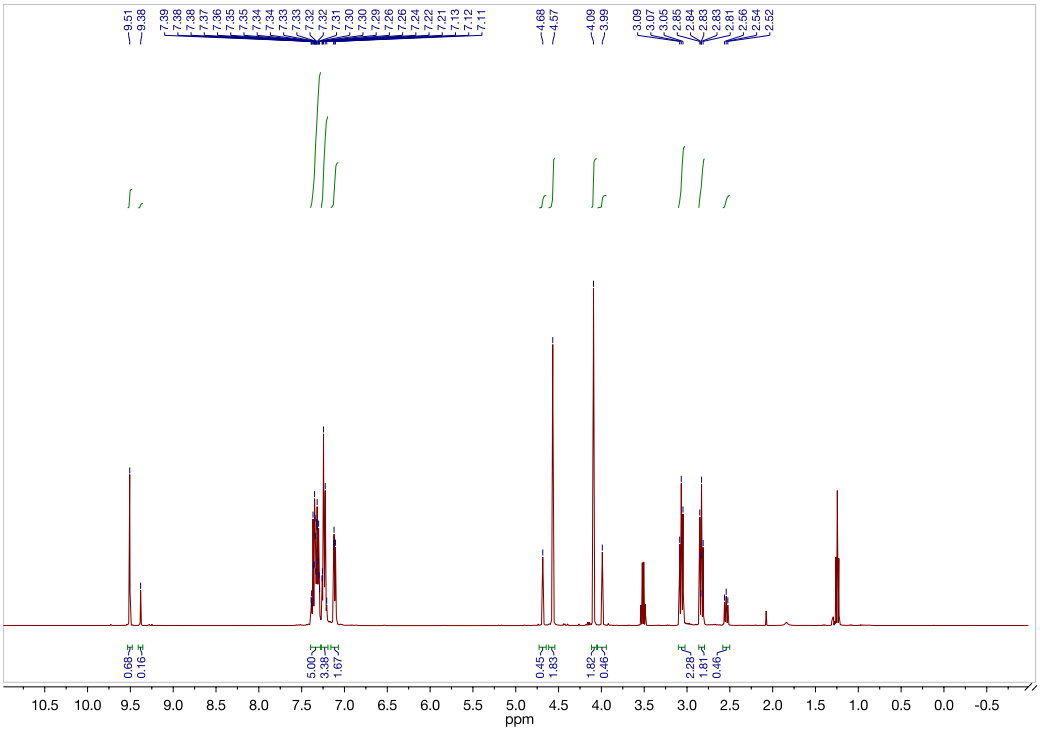


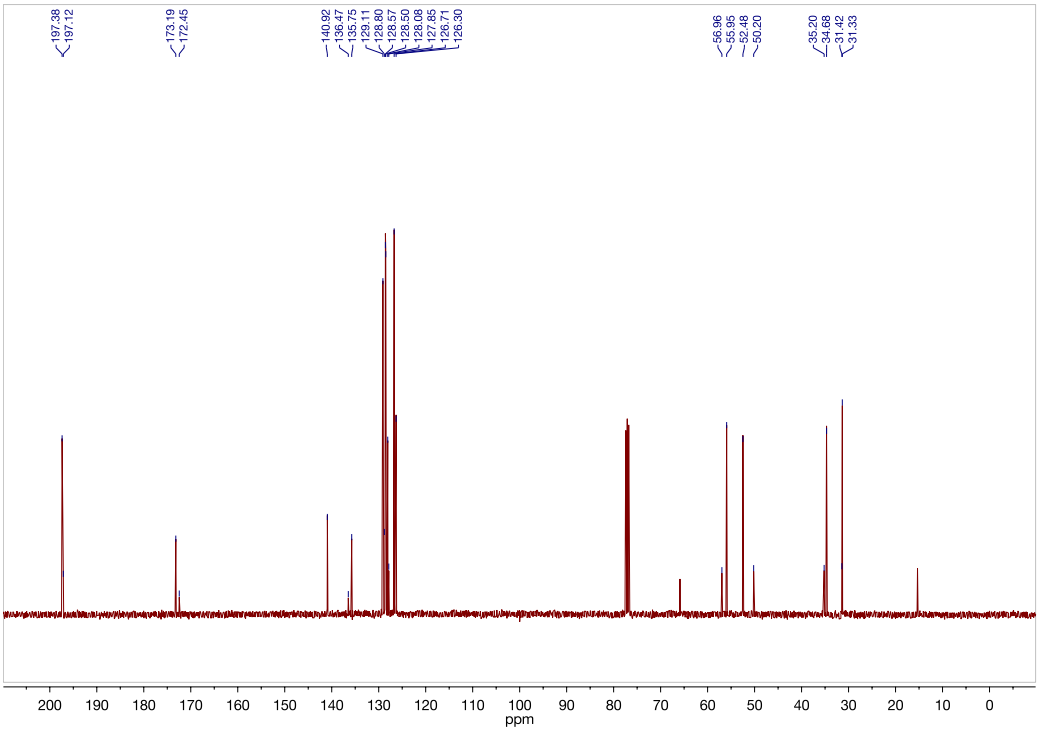




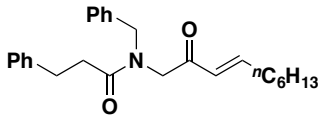
N-Benzyl-*N*-(2-oxoethyl)-3-phenylpropanamide, 184

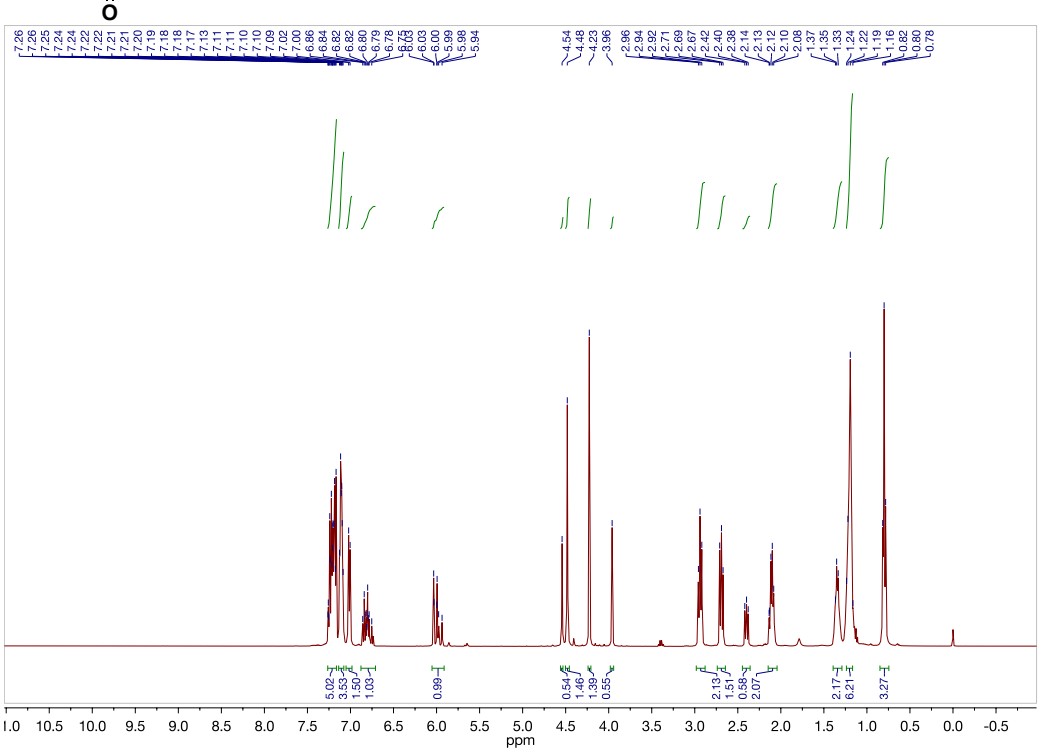


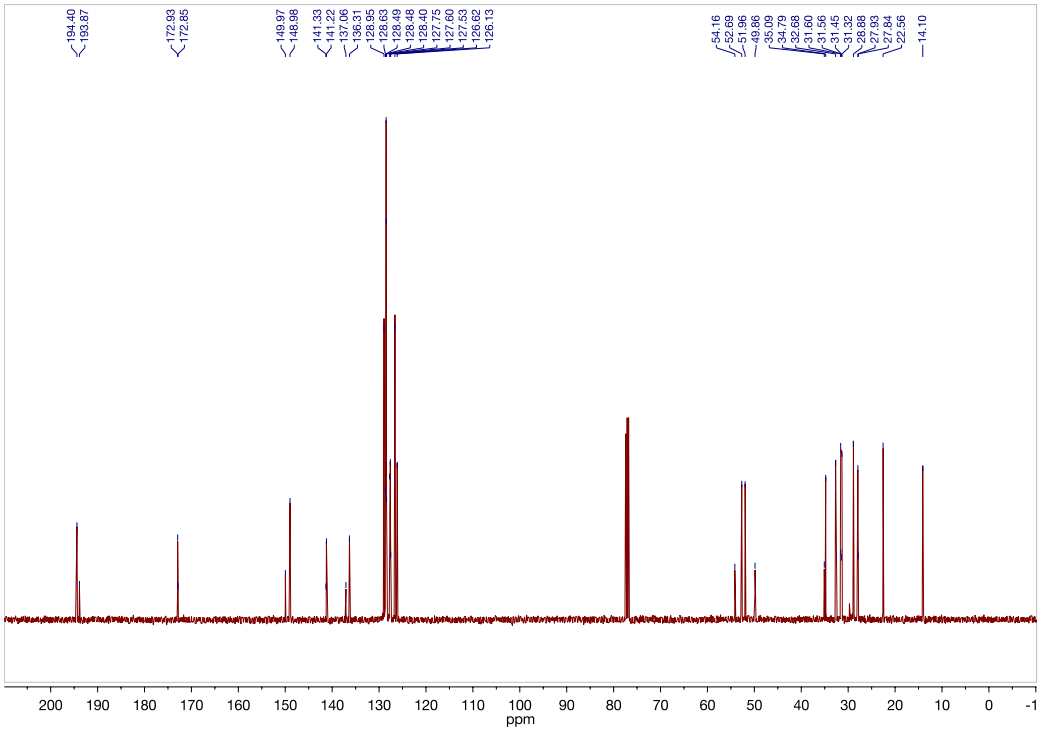




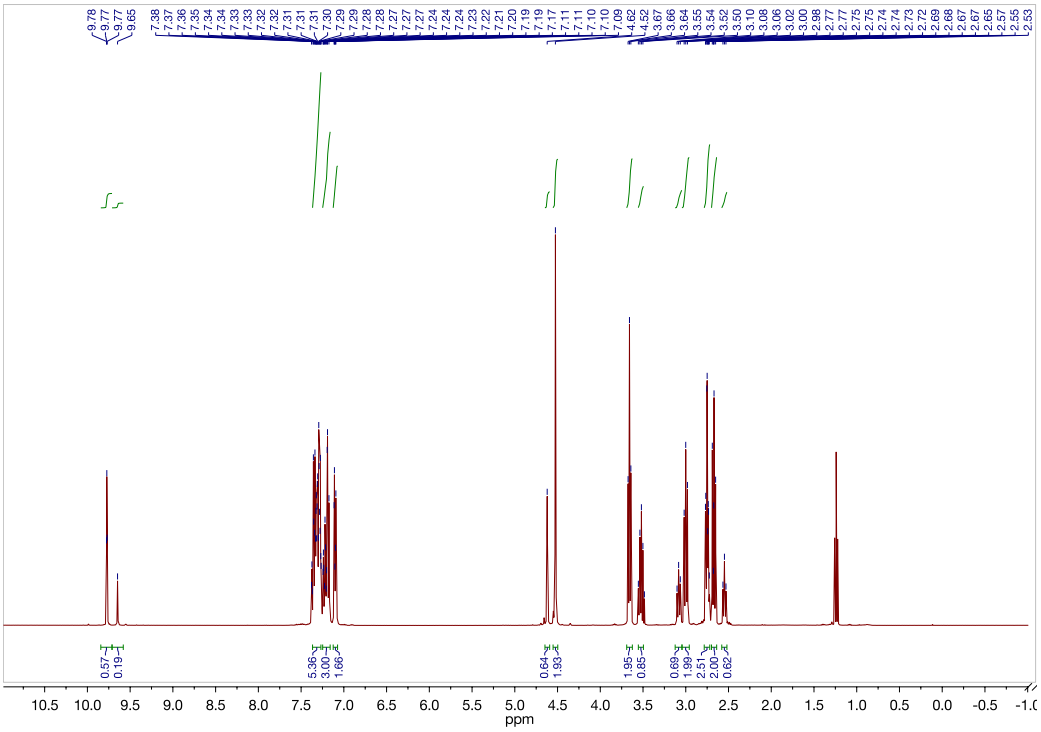
(*E*)-2-Benzyl-1-morpholino-4,5-diphenylpent-4-ene-1,3-dione, 185a

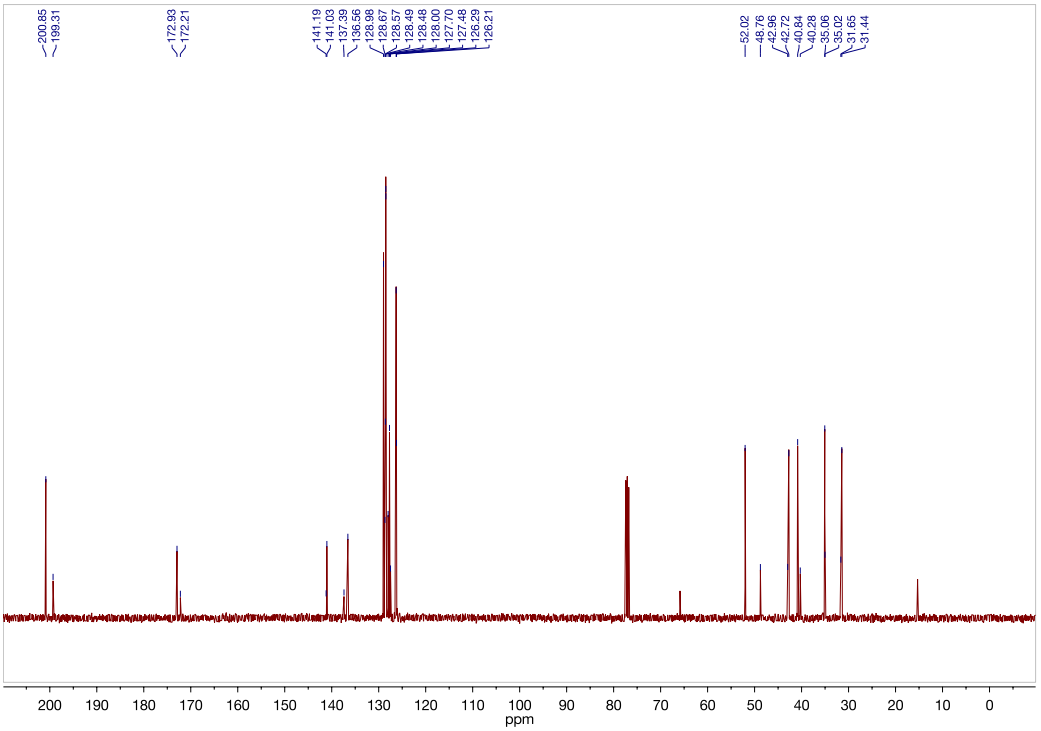




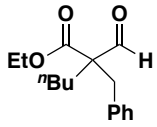


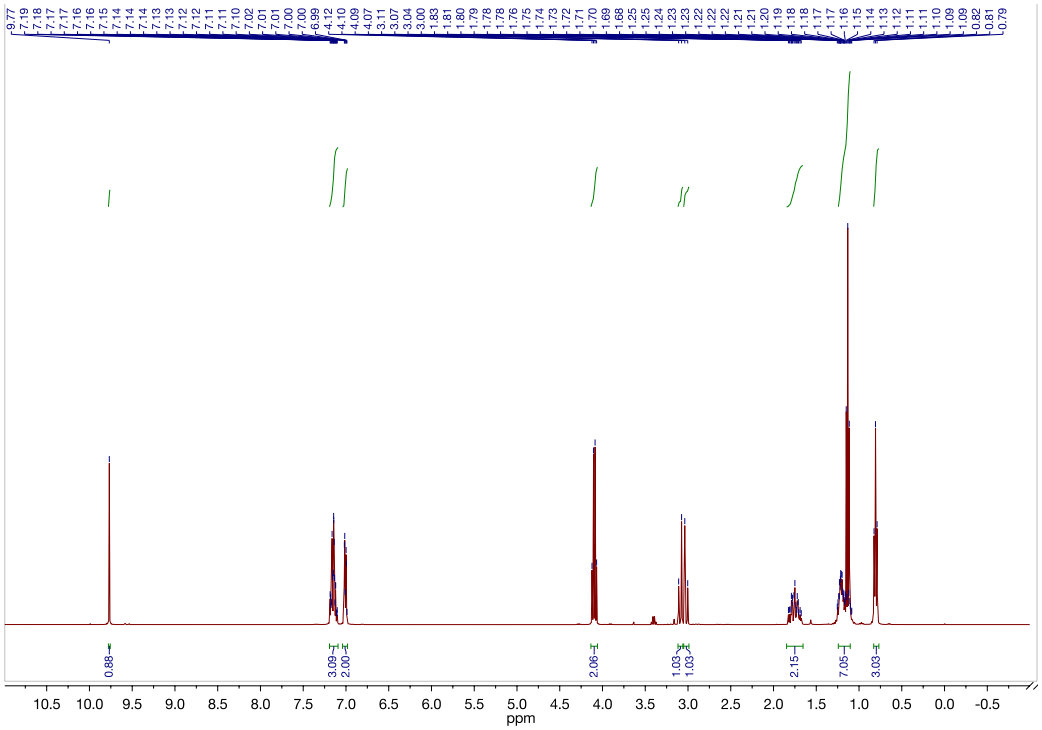
N-Benzyl-*N*-(3-oxopropyl)-3-phenylpropanamide, 187

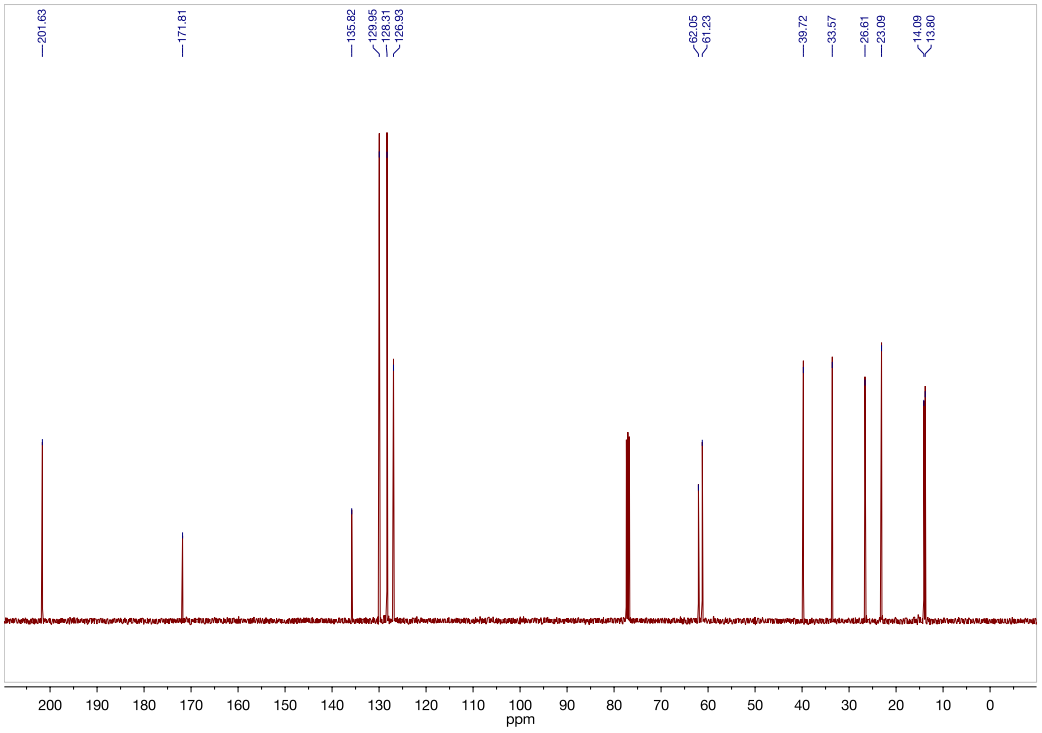




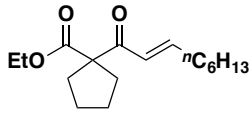
Ethyl 2-benzyl-2-formylhexanoate, 194b

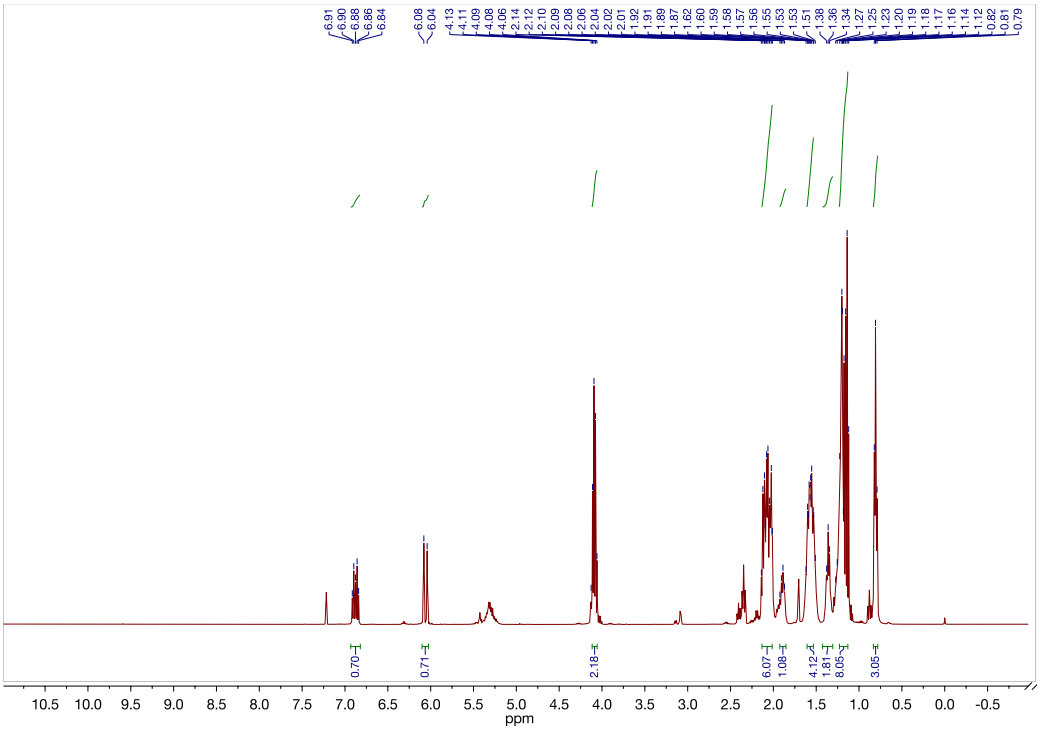


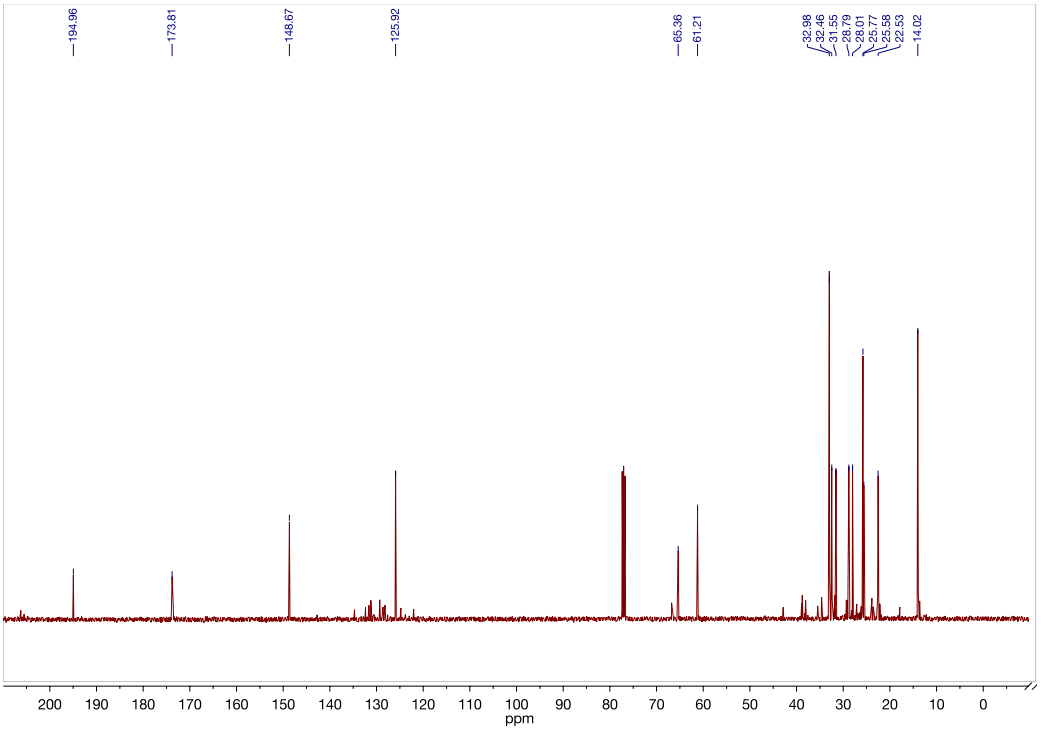




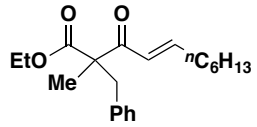
Ethyl (*E*)-1-(non-2-enoyl)cyclopentane-1-carboxylate, 192

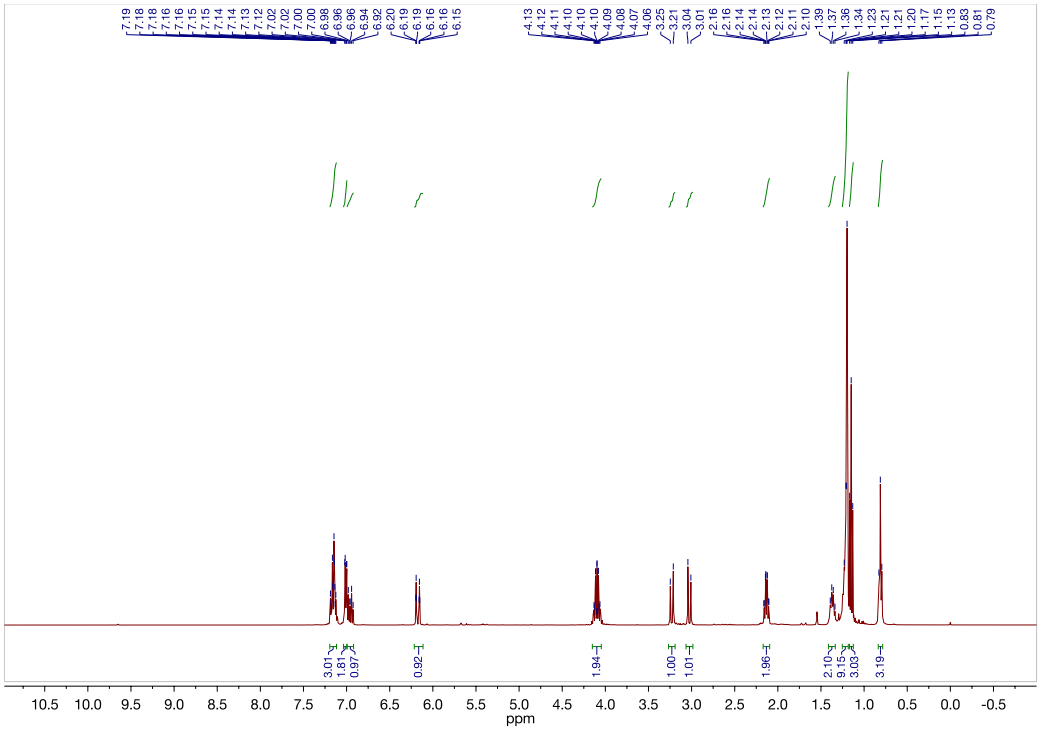


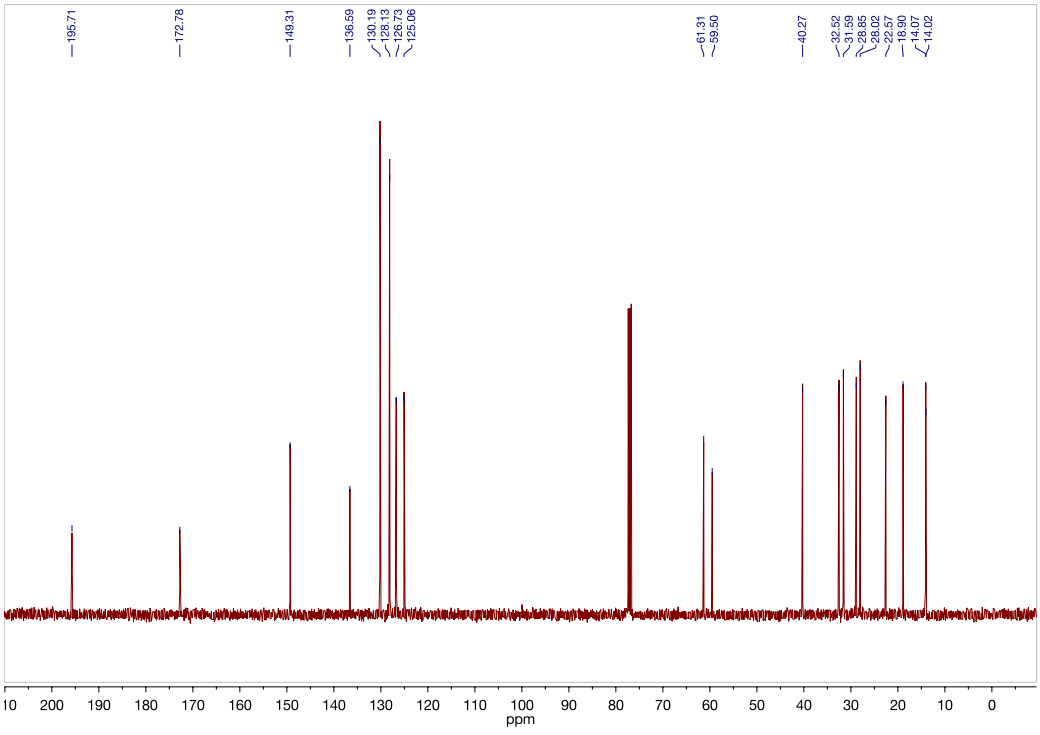




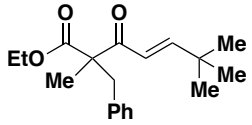
Ethyl (*E*)-2-benzyl-2-methyl-3-oxoundec-4-enoate, 5-104 a)

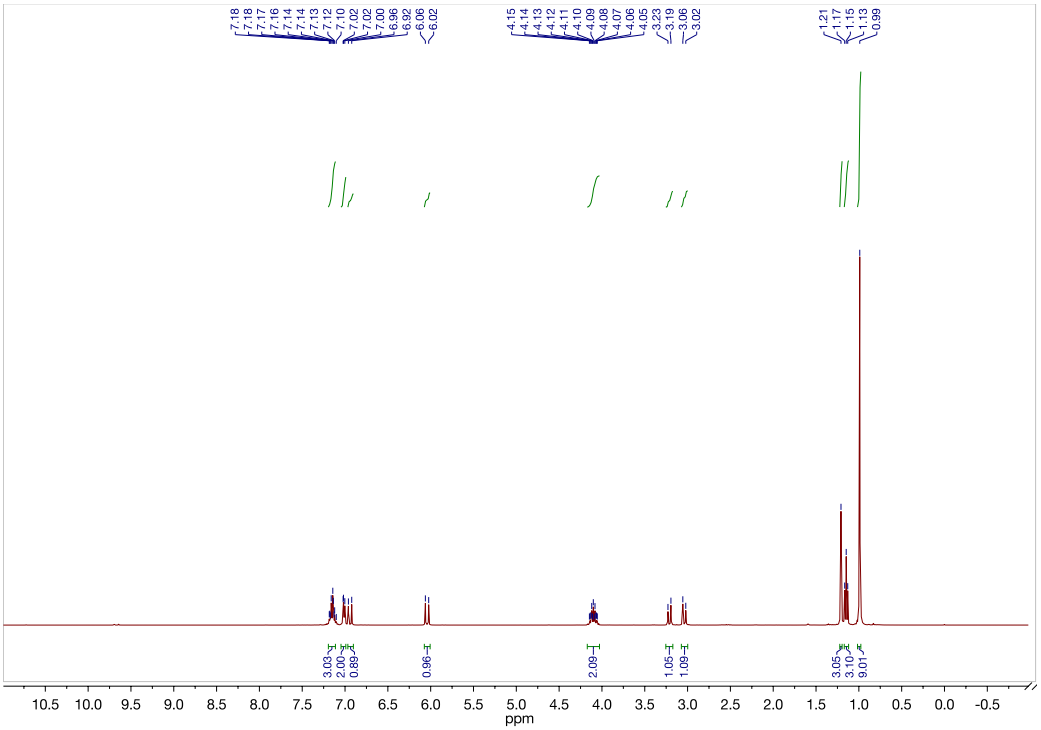


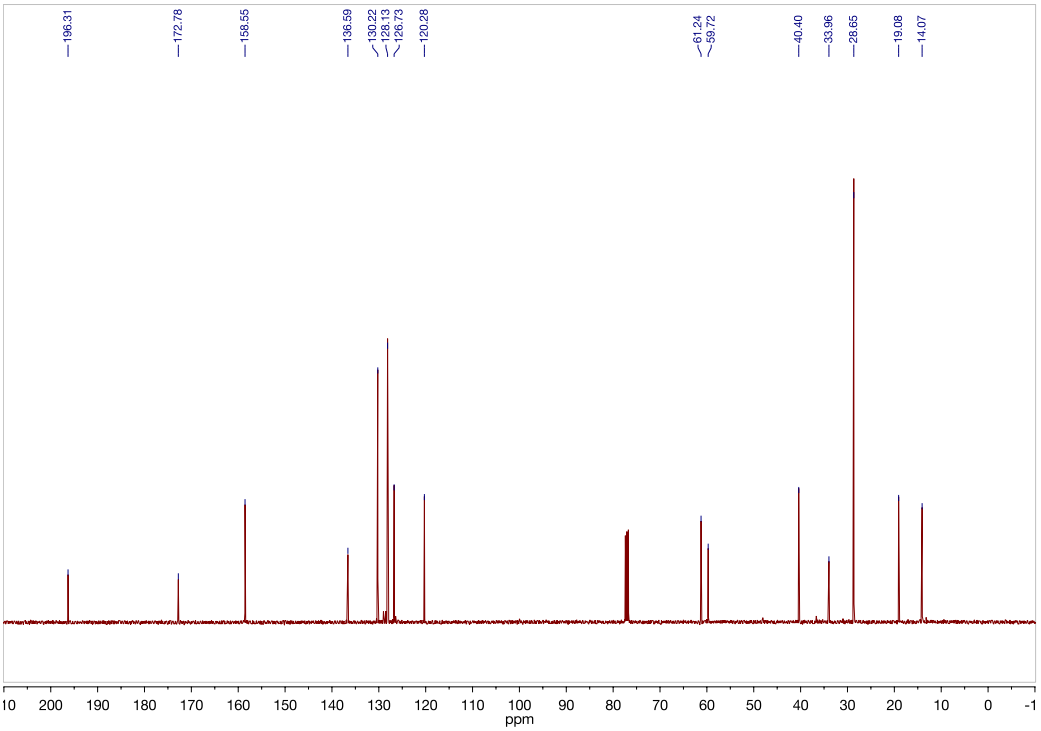




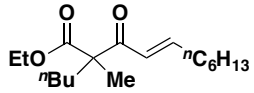
Ethyl (*E*)-2-benzyl-2,6,6-trimethyl-3-oxohept-4-enoate, 5-104 c)

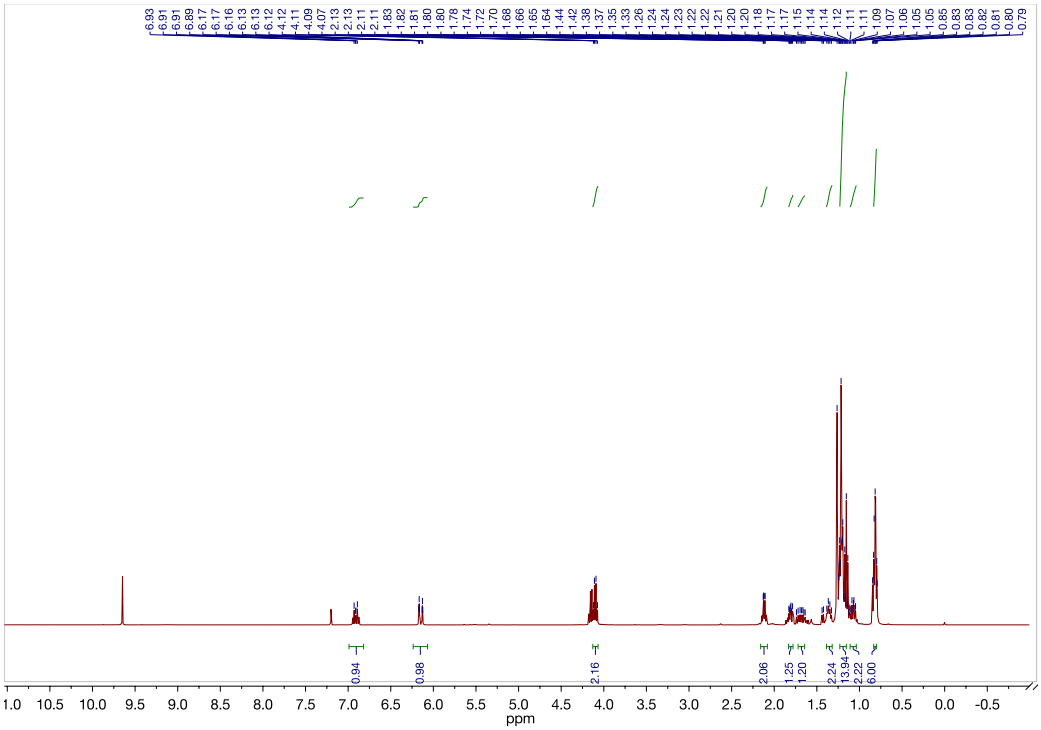


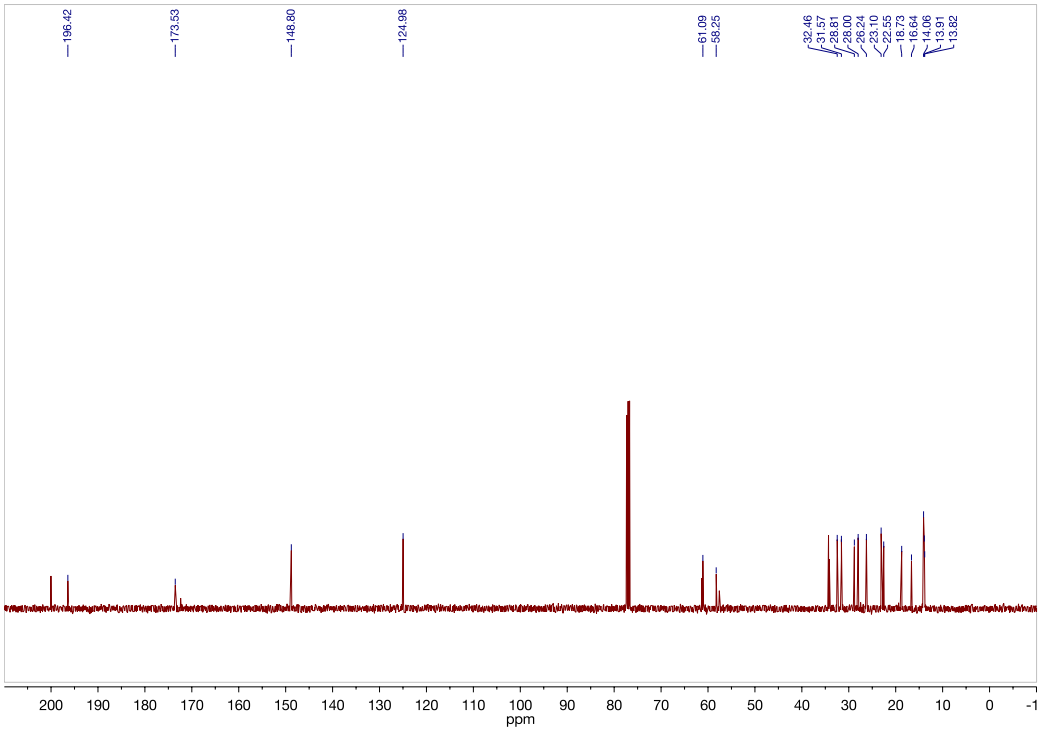




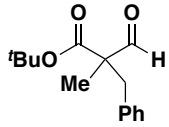
Ethyl (*E*)-2-butyl-2-methyl-3-oxoundec-4-enoate, 200

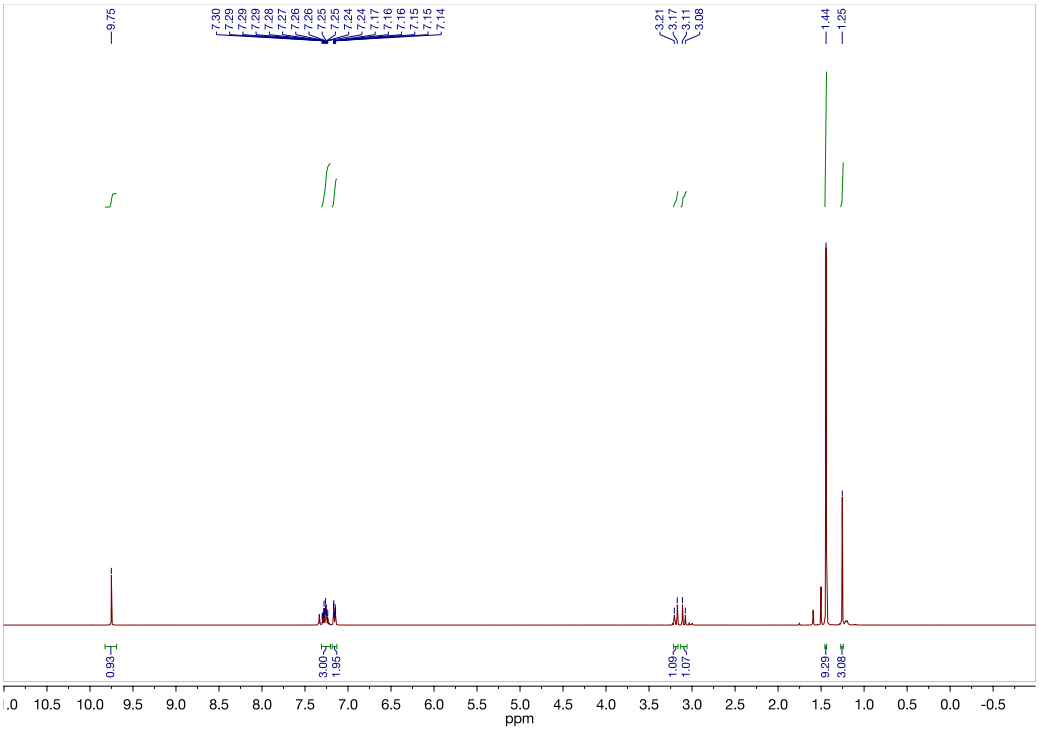


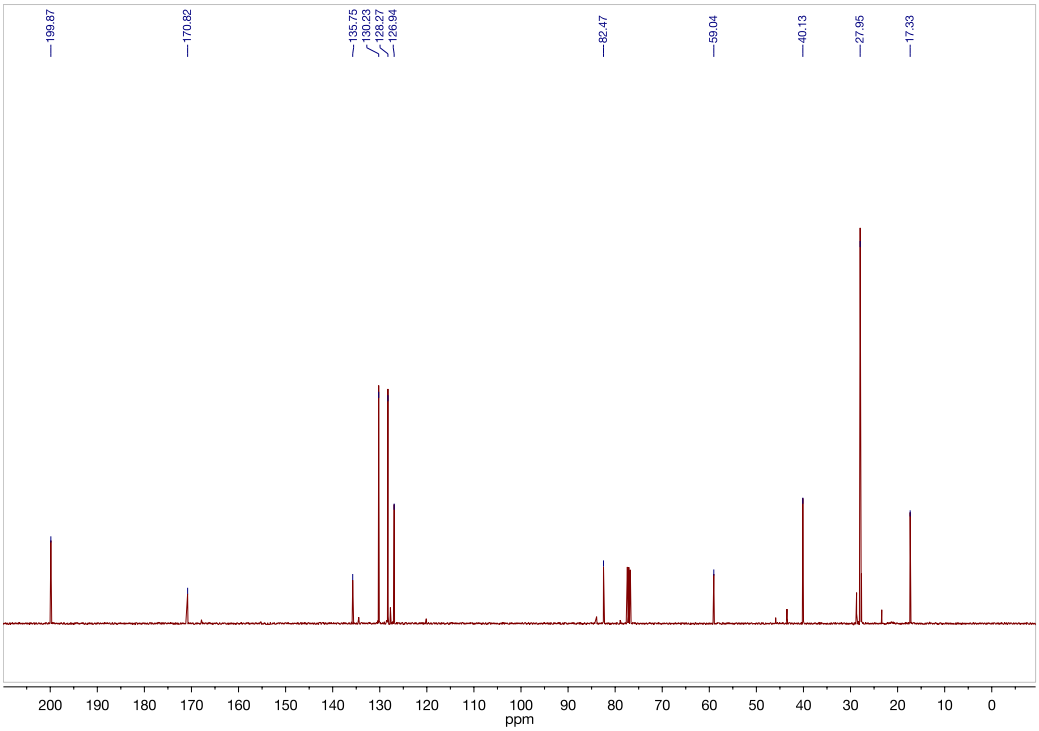




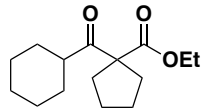
tert-Butyl 2-benzyl-2-methyl-3-oxopropanoate, 203

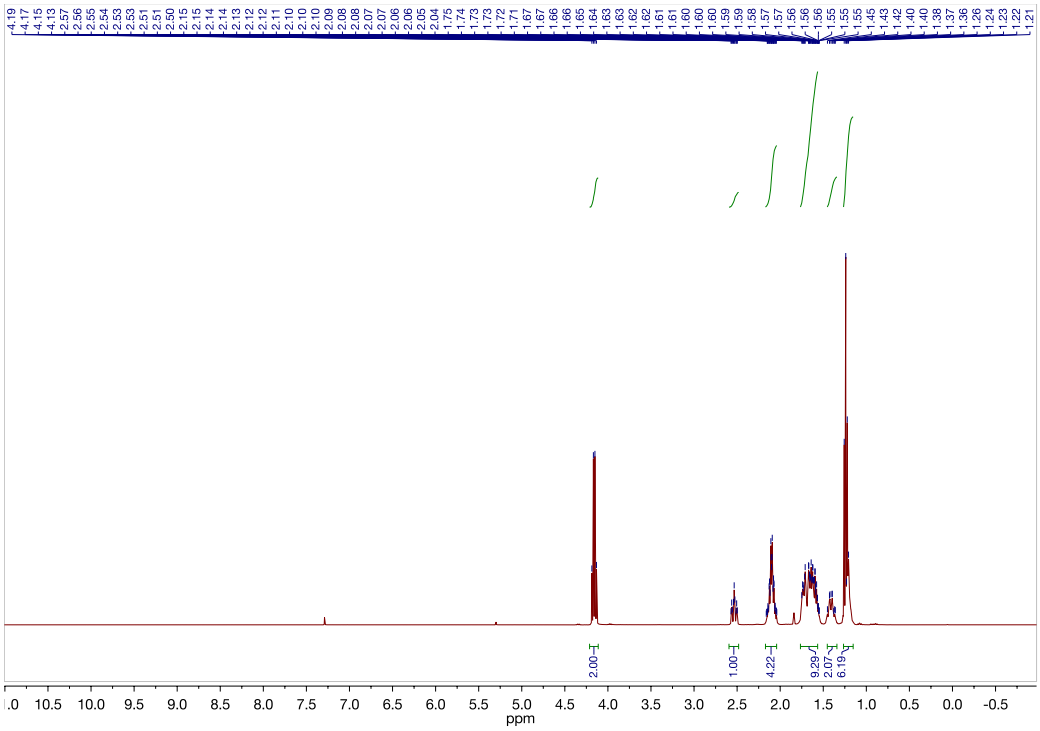


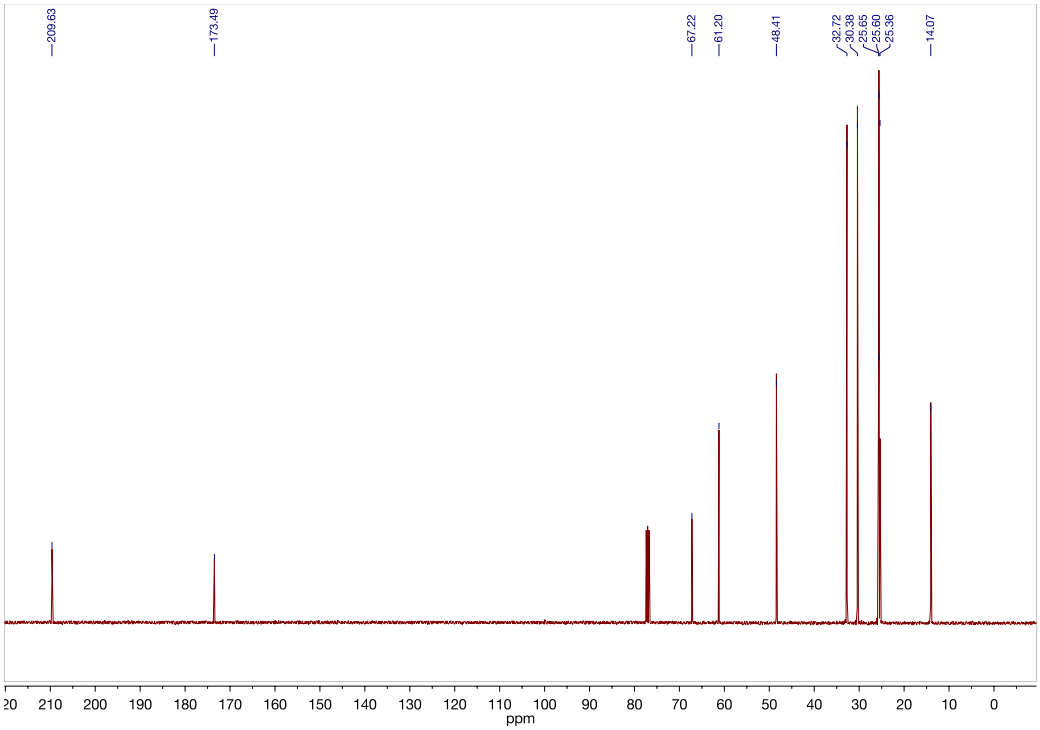




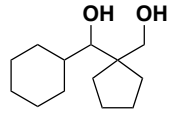
Ethyl 1-(cyclohexanecarbonyl)cyclopentane-1-carboxylate, 213

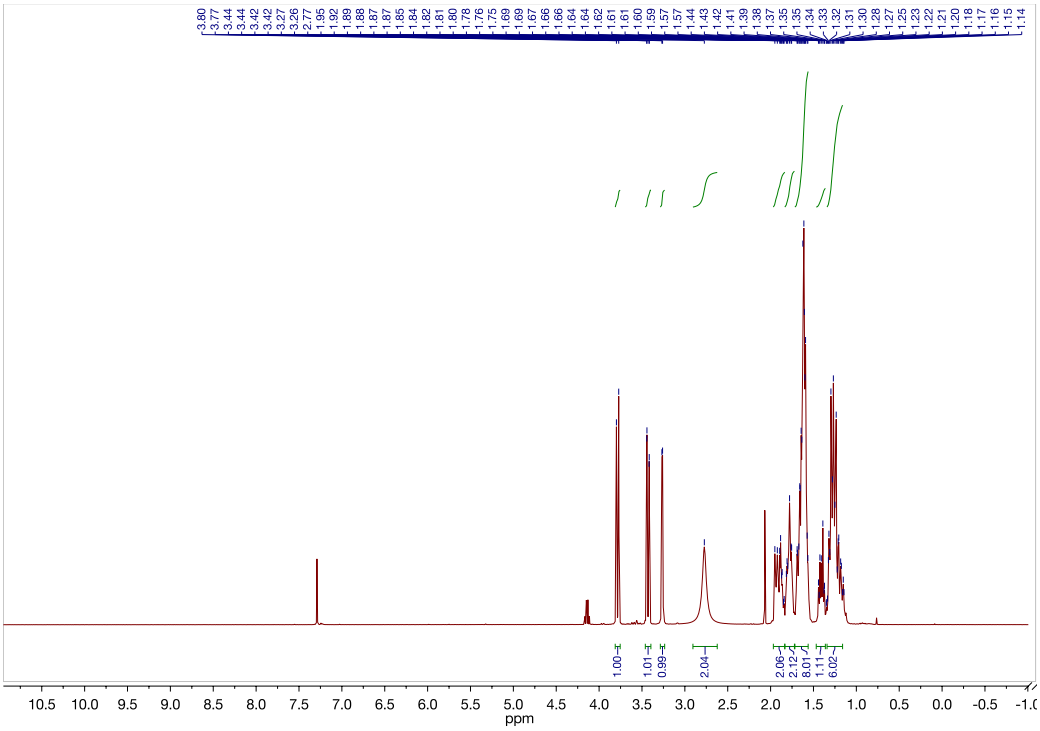


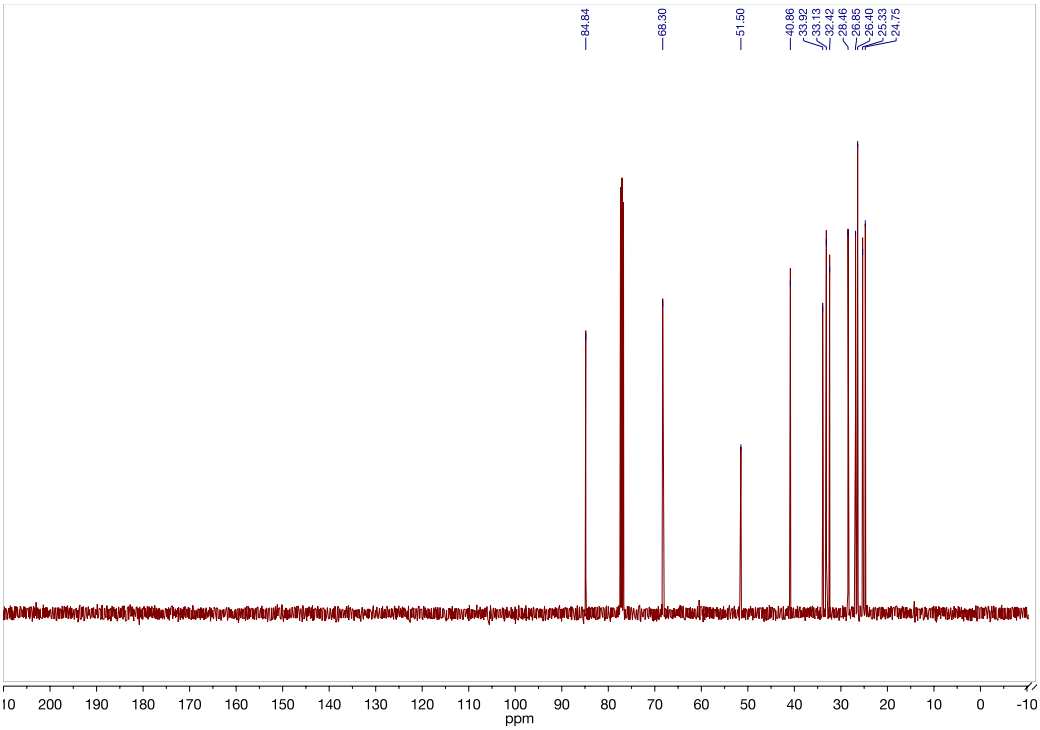




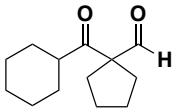
Cyclohexyl(1-(hydroxymethyl)cyclopentyl)methanol, 214

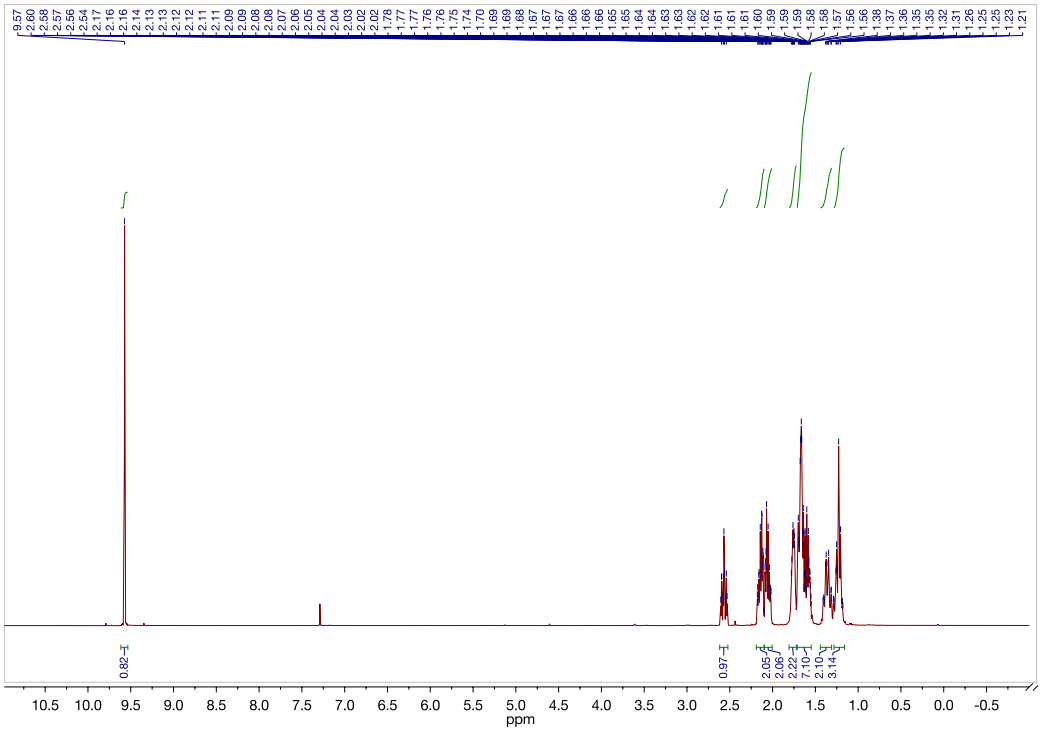


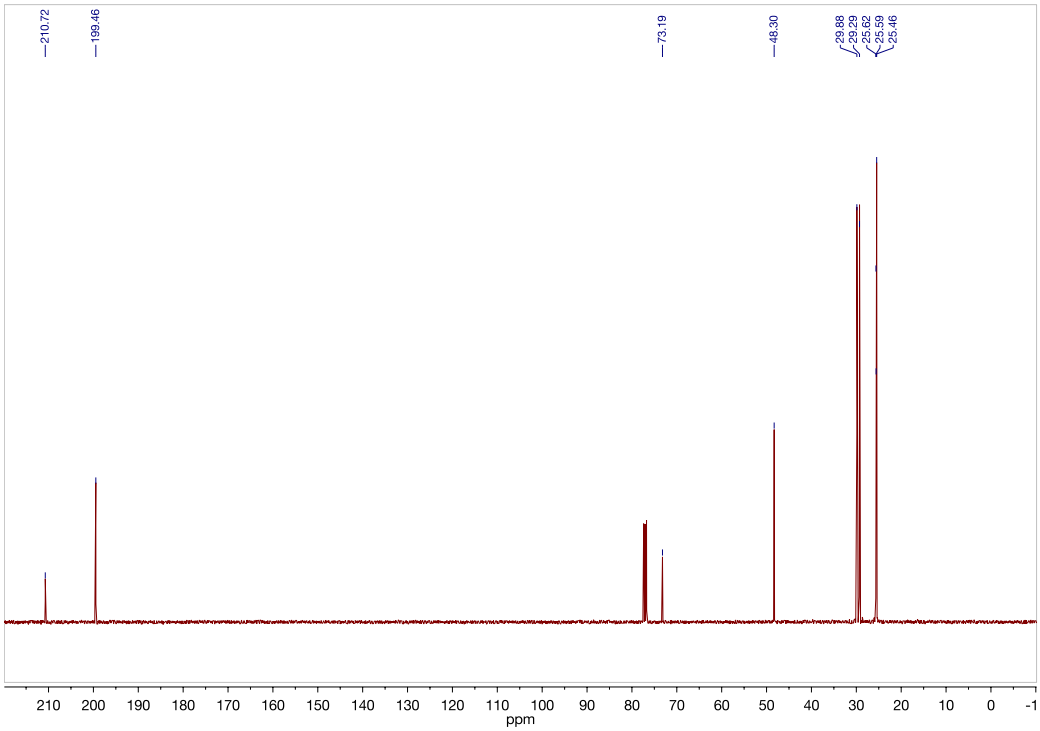




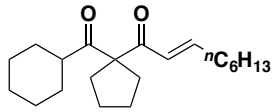
1-(Cyclohexanecarbonyl)cyclopentane-1-carbaldehyde, 204

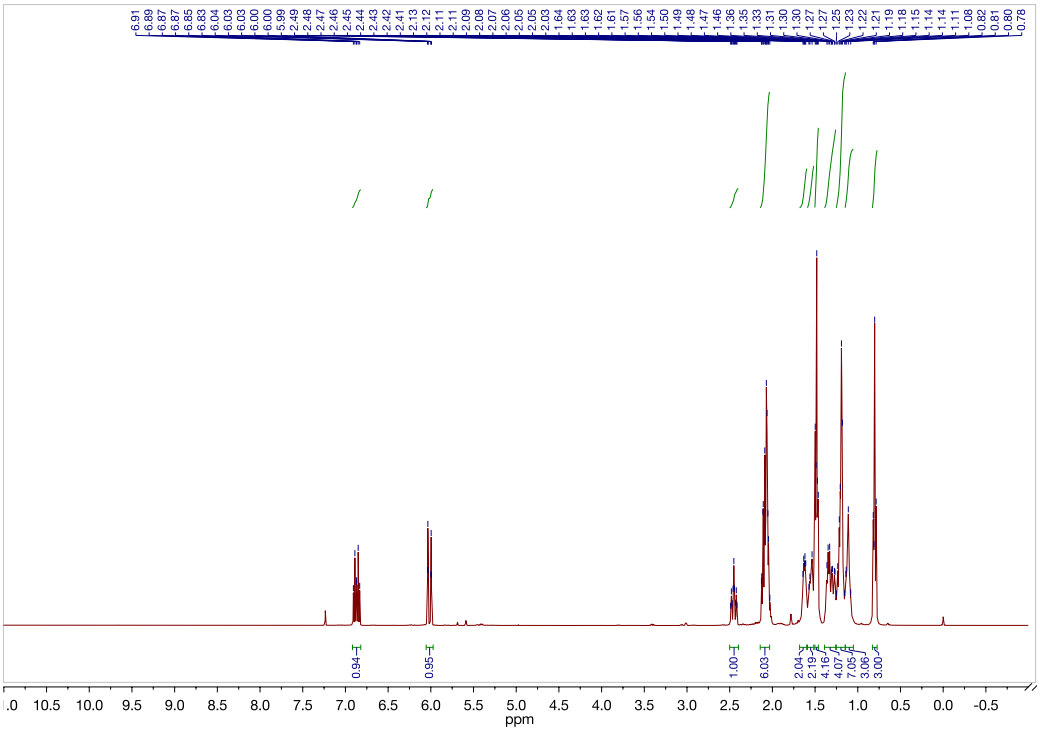


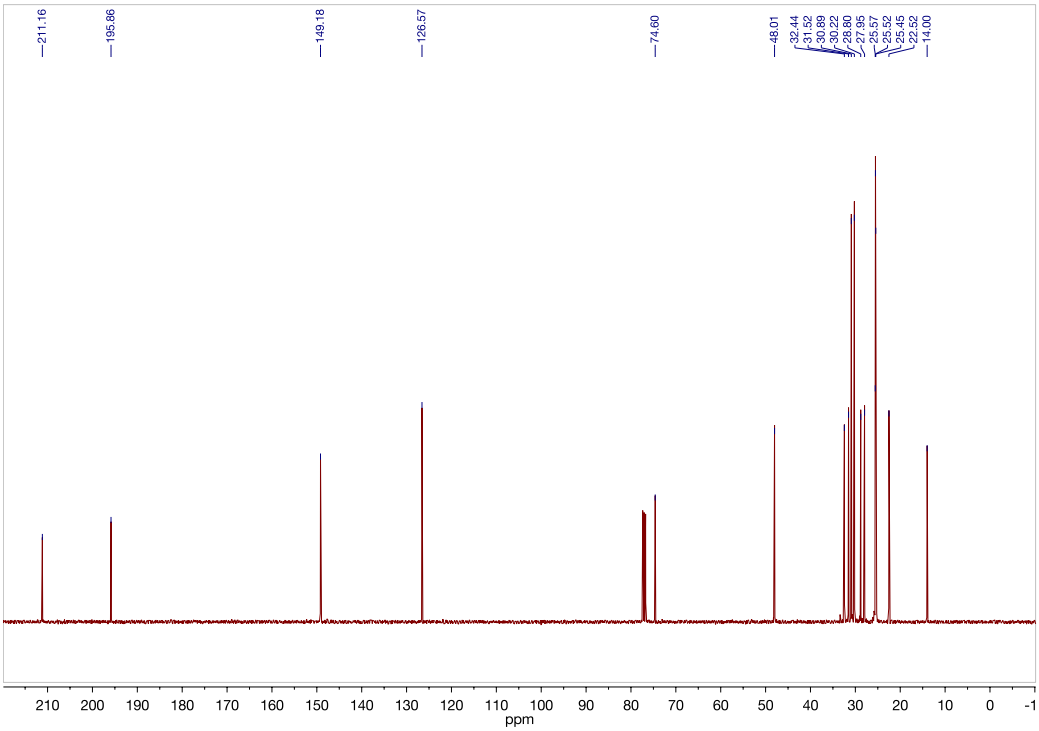




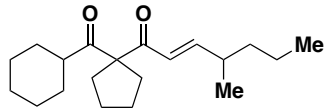
(*E*)-1-(1-(Cyclohexanecarbonyl)cyclopentyl)non-2-en-1-one, 205

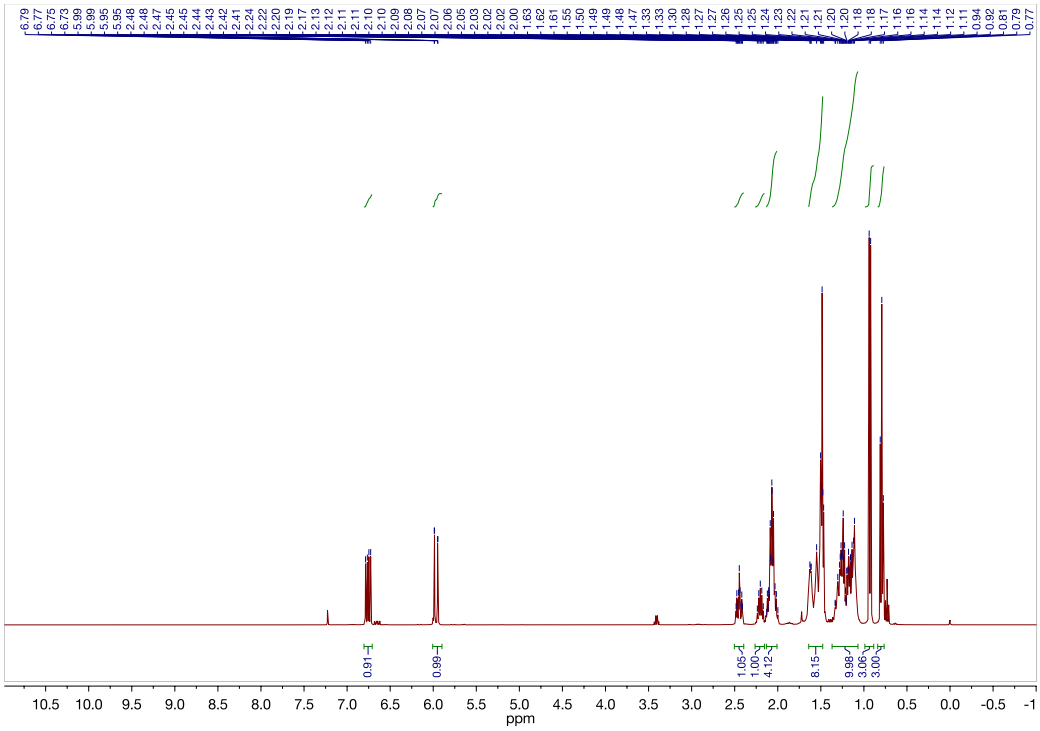


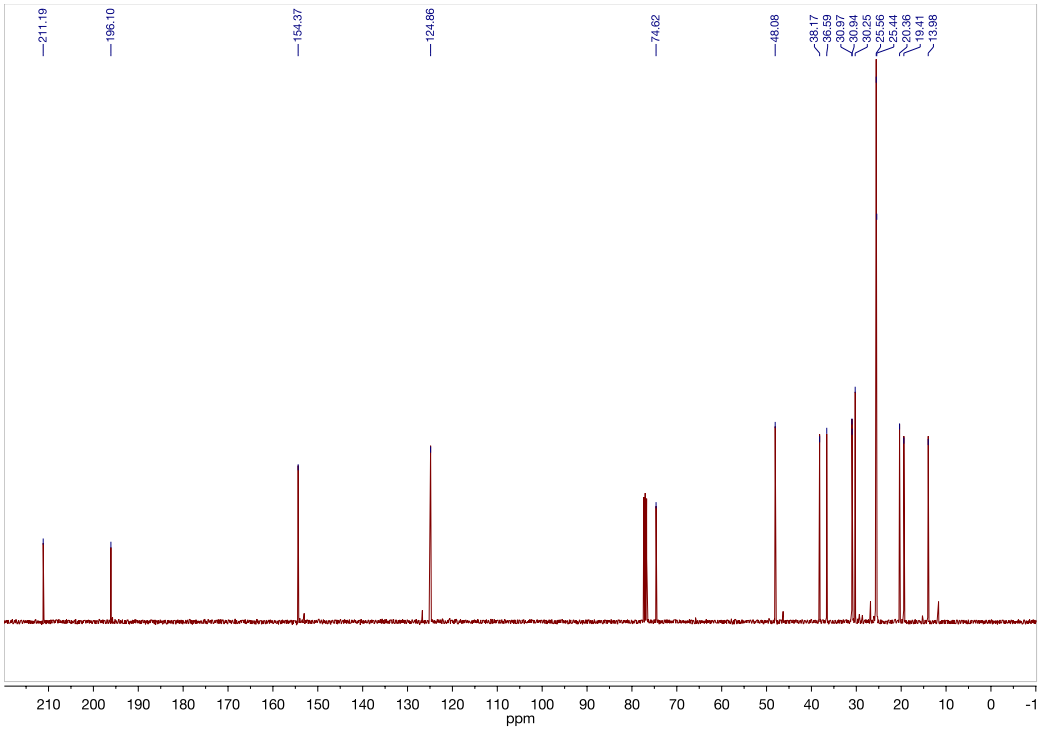




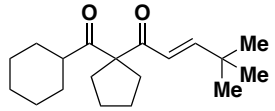
(*E*)-1-(1-(Cyclohexanecarbonyl)cyclopentyl)-4-methylhept-2-en-1-one, 206

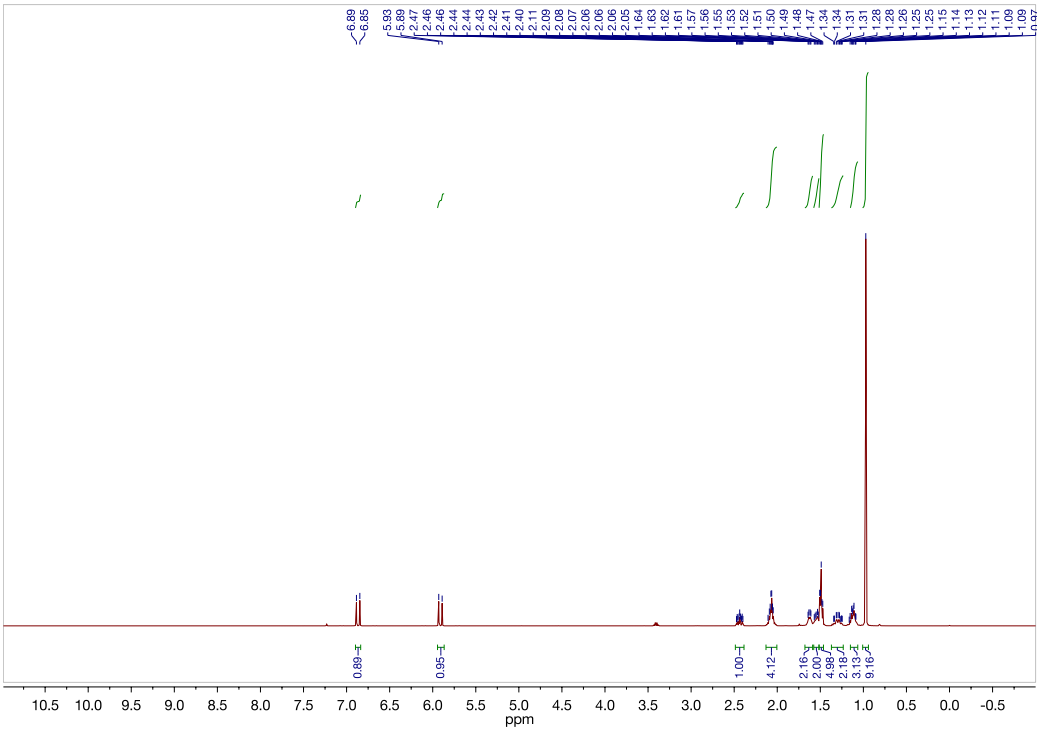


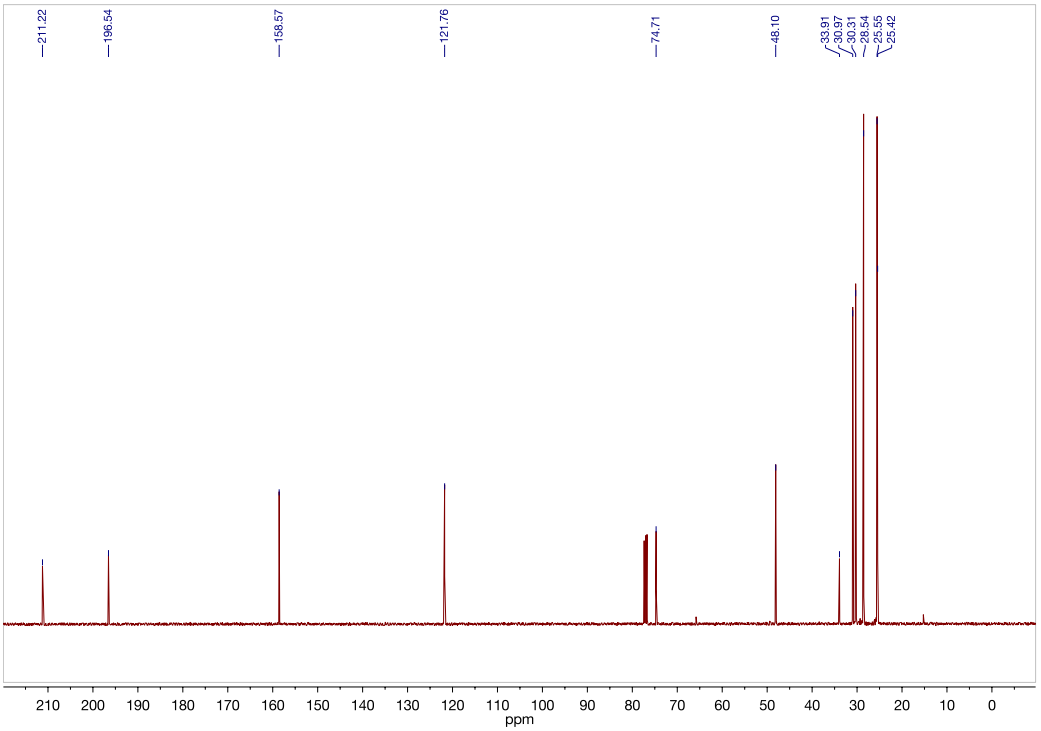




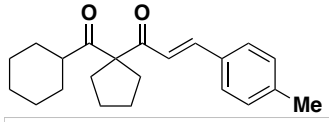
(*E*)-1-(1-(Cyclohexanecarbonyl)cyclopentyl)-4,4-dimethylpent-2-en-1-one, 207

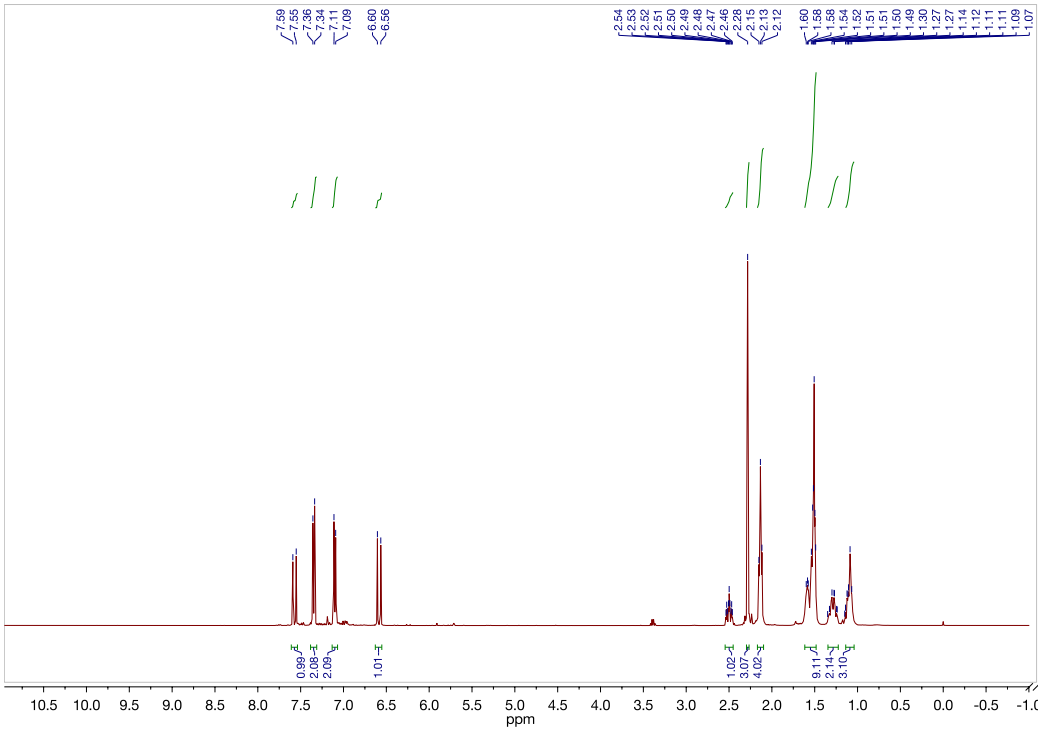


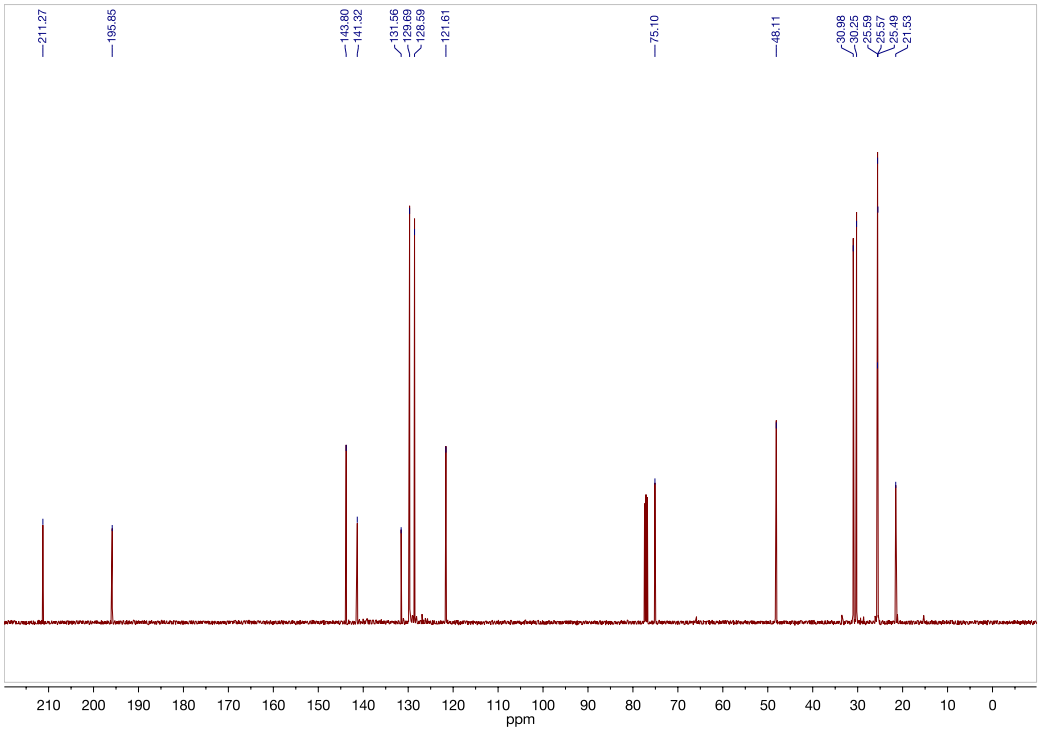




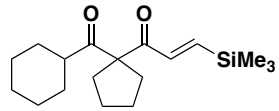
(*E*)-1-(1-(Cyclohexanecarbonyl)cyclopentyl)-3-(*p*-tolyl)prop-2-en-1-one, 208

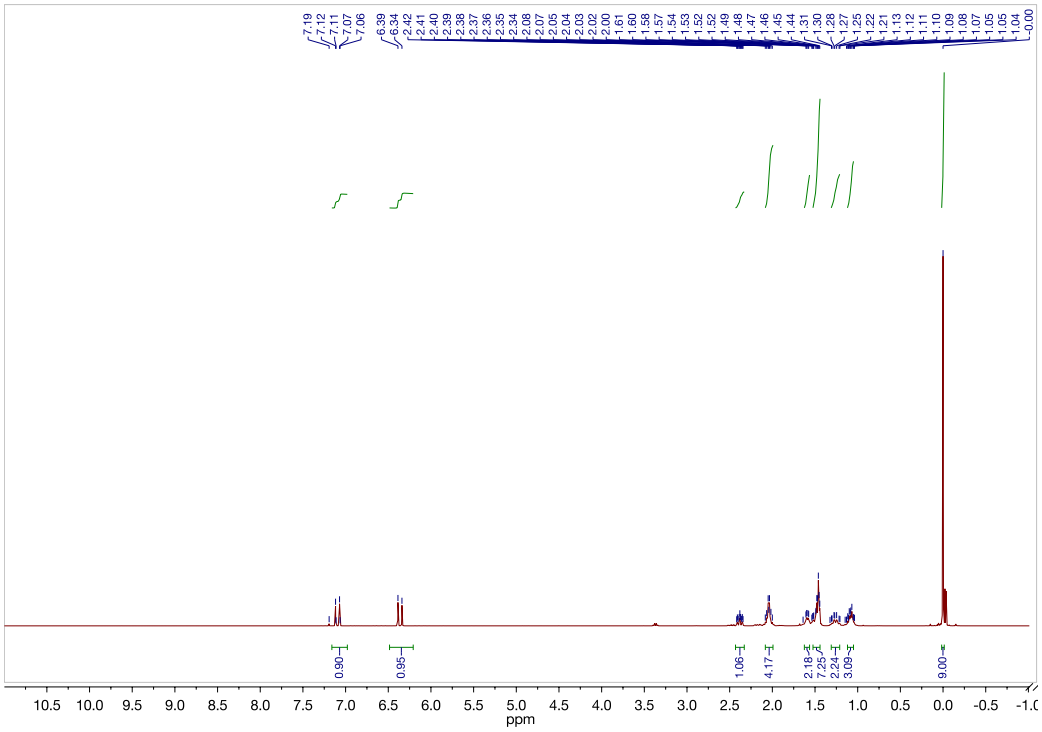


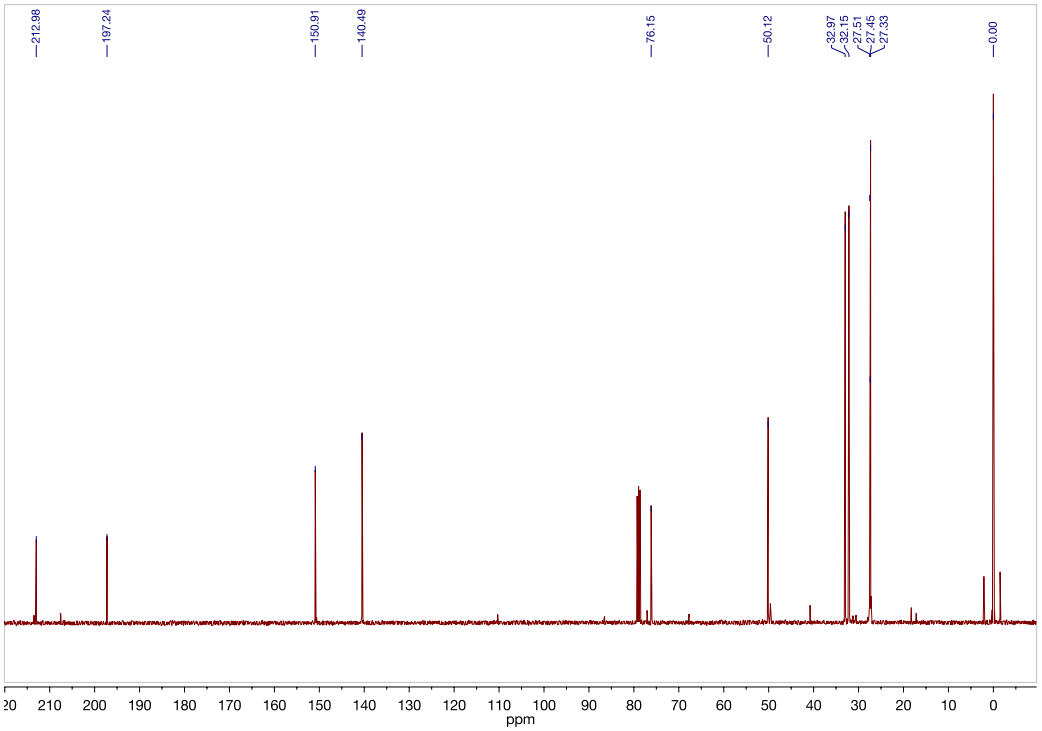




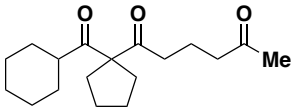
(*E*)-1-(1-(Cyclohexanecarbonyl)cyclopentyl)-3-(trimethylsilyl)prop-2-en-1-one, 209

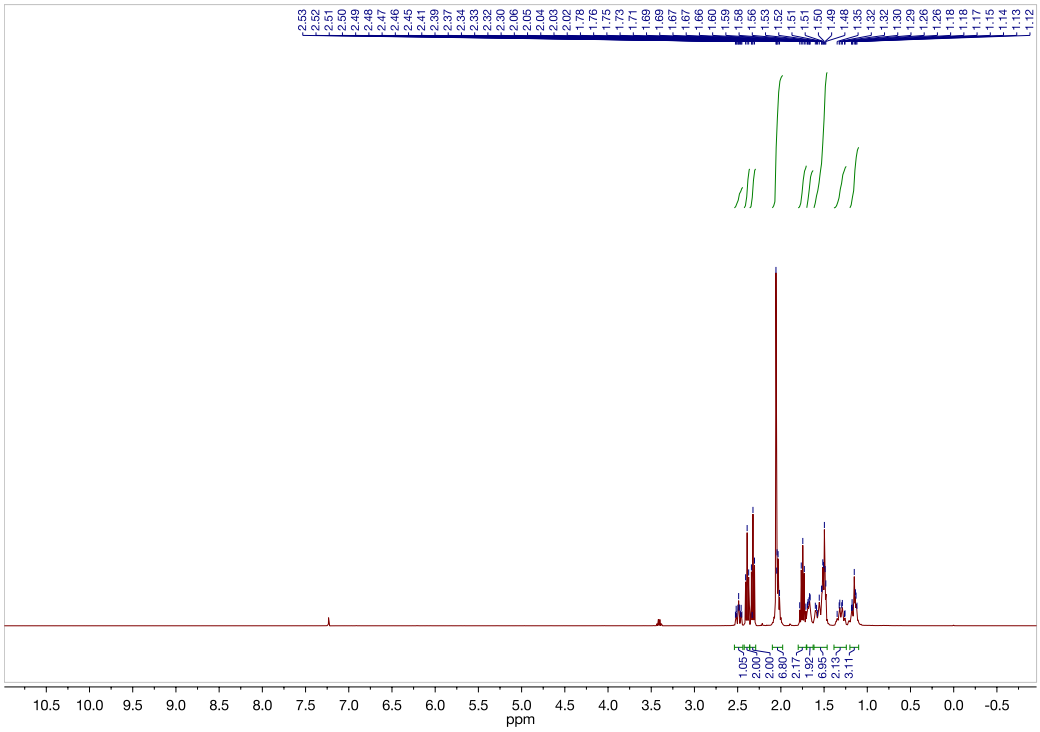


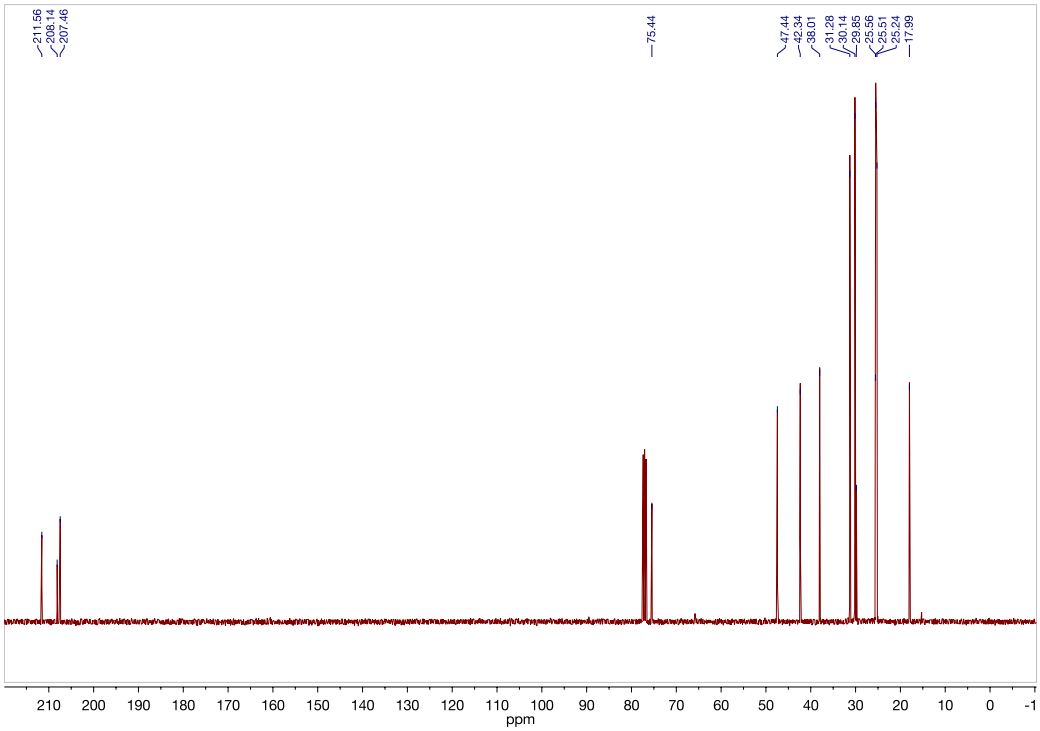




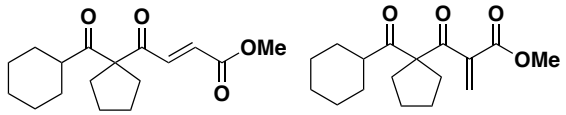
1-(1-(Cyclohexanecarbonyl)cyclopentyl)hexane-1,5-dione, 210

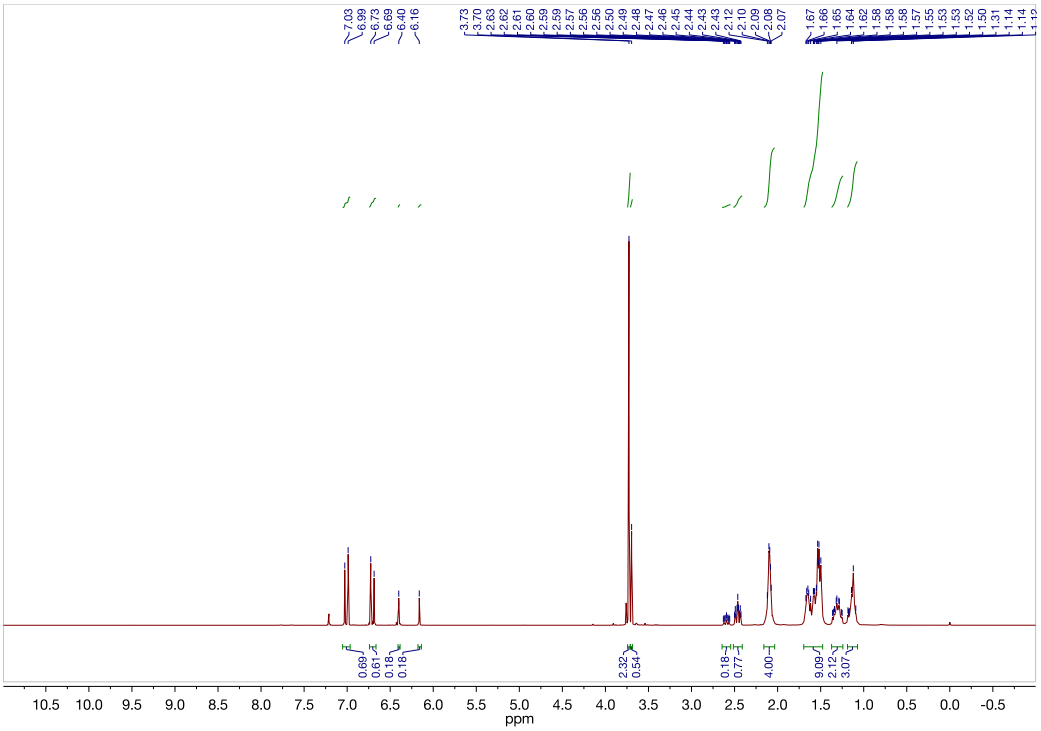


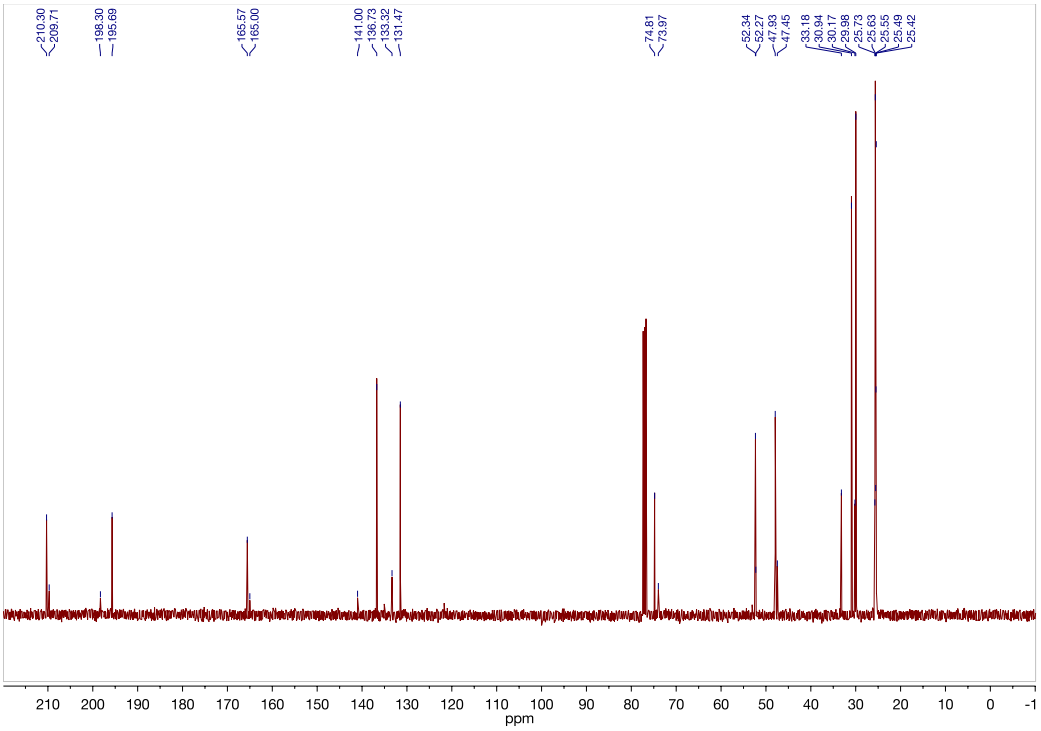




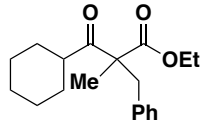
Methyl (*E*)-4-(1-(cyclohexanecarbonyl)cyclopentyl)-4-oxobut-2-enoate and Methyl 2-(1-(cyclohexanecarbonyl)cyclopentane-1-carbonyl)acrylate, 211

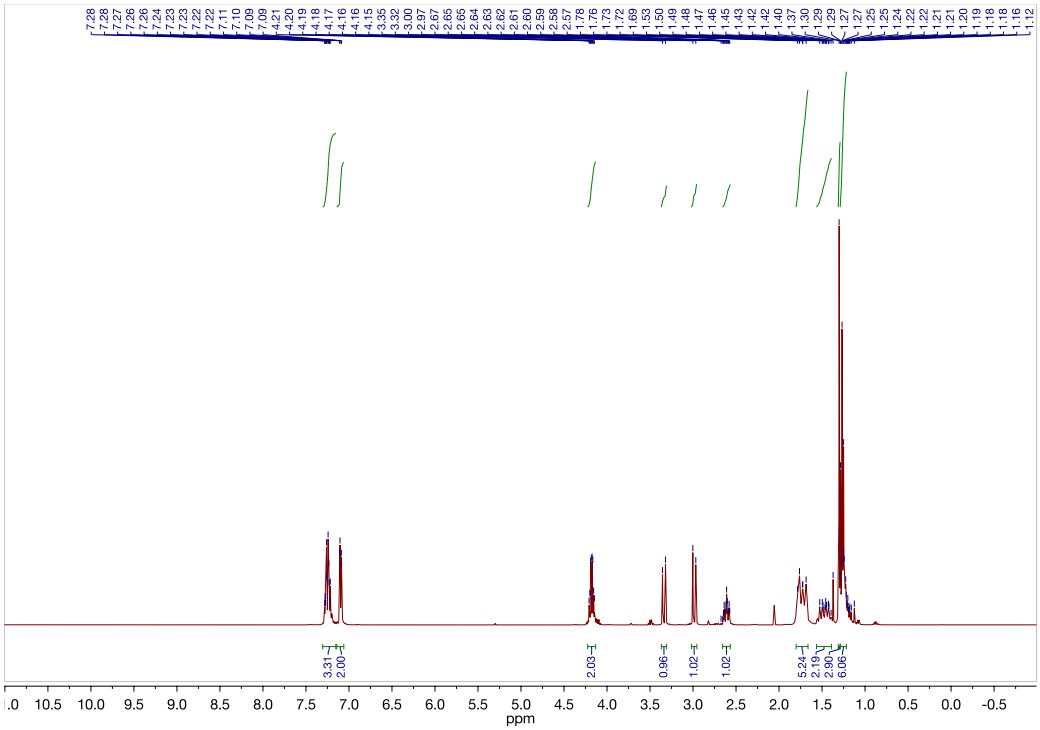


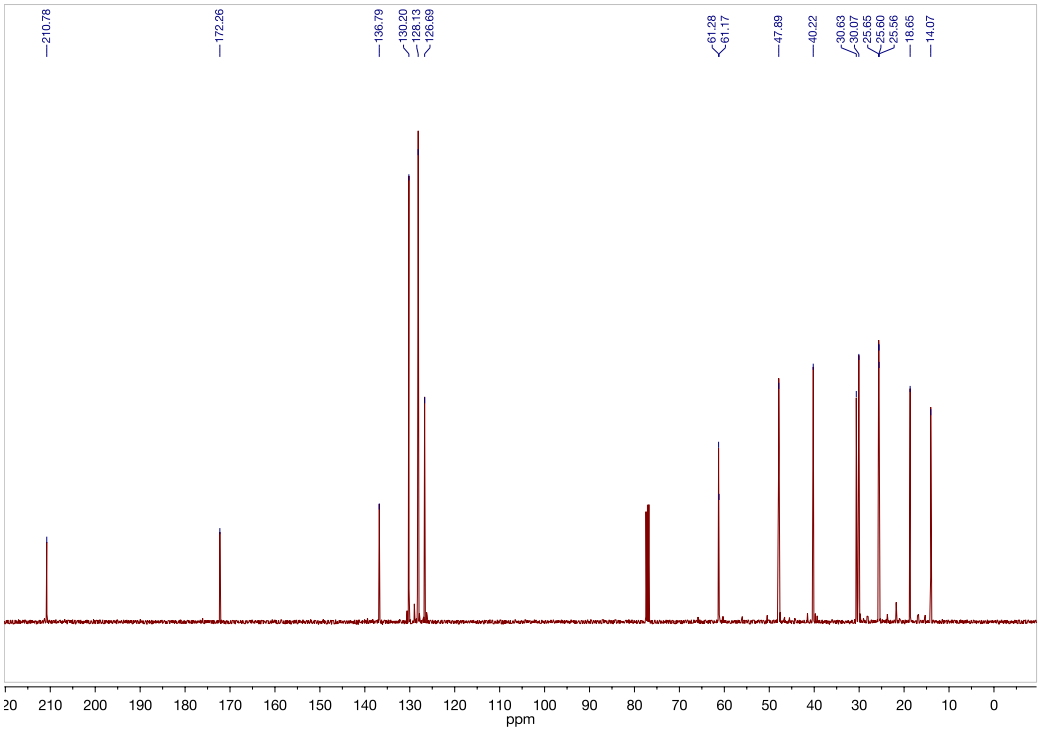




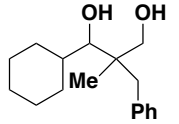
Ethyl 2-benzyl-3-cyclohexyl-2-methyl-3-oxopropanoate, 216

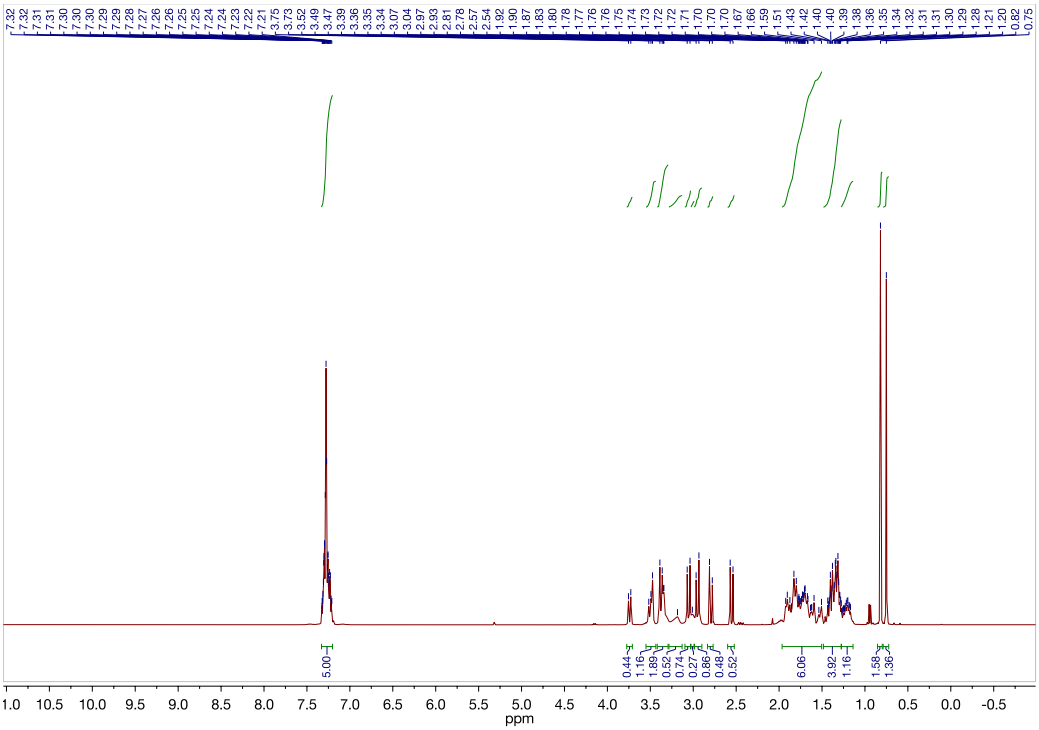


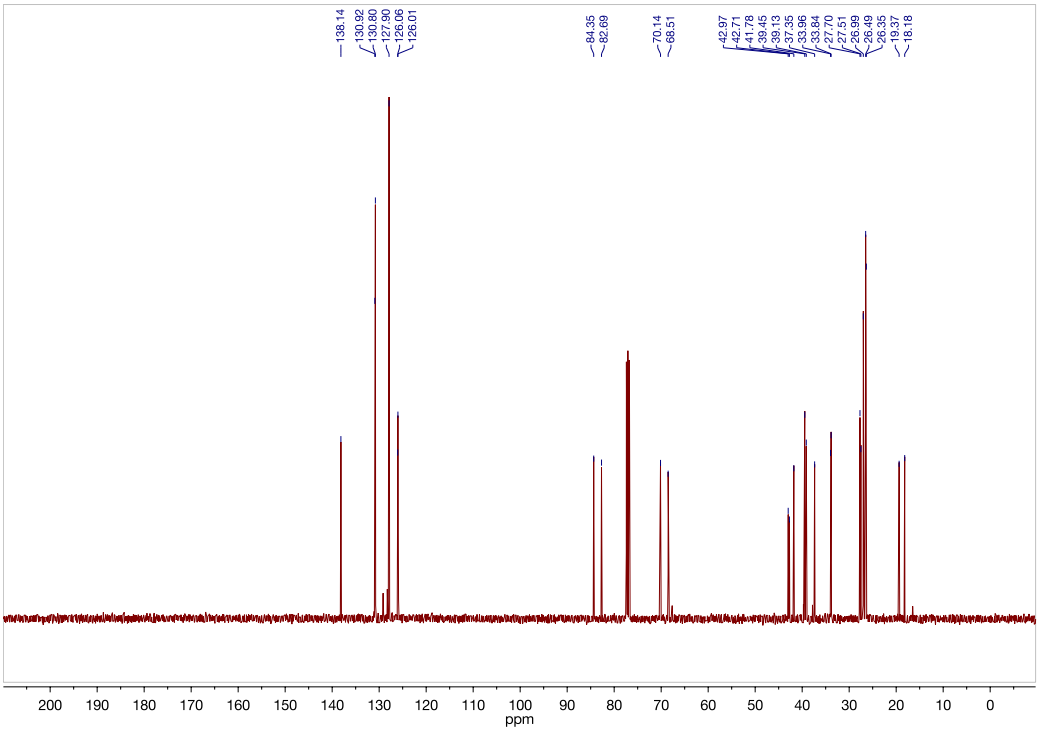




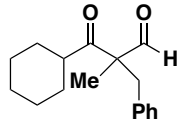
2-Benzyl-1-cyclohexyl-2-methylpropane-1,3-diol, 217

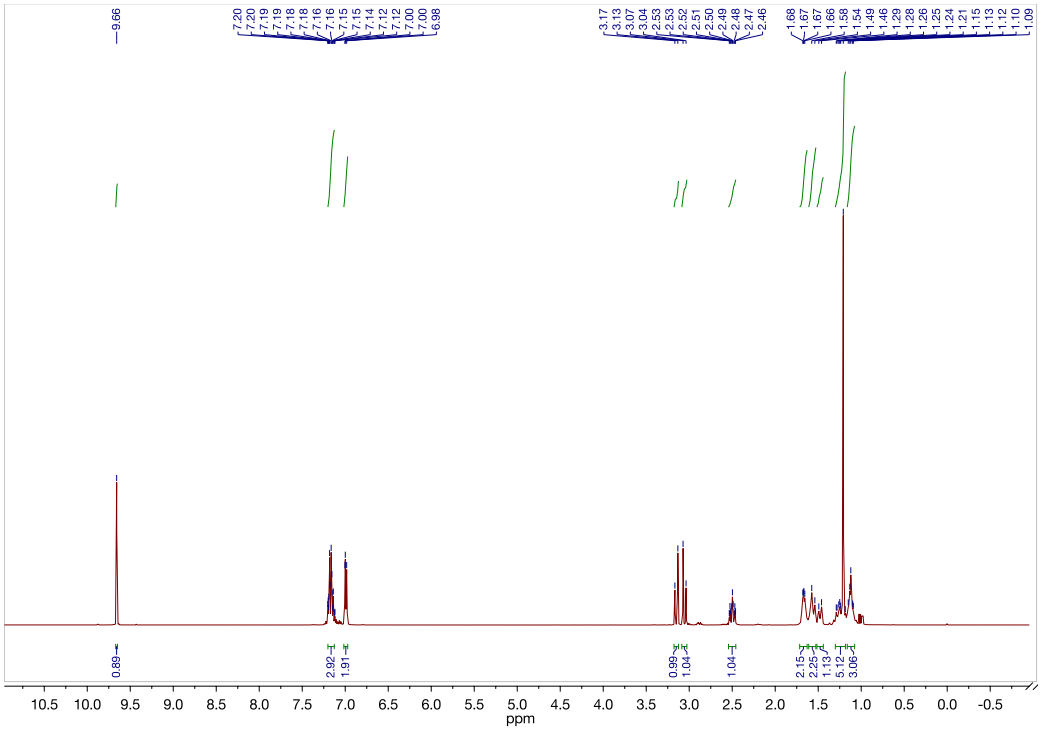


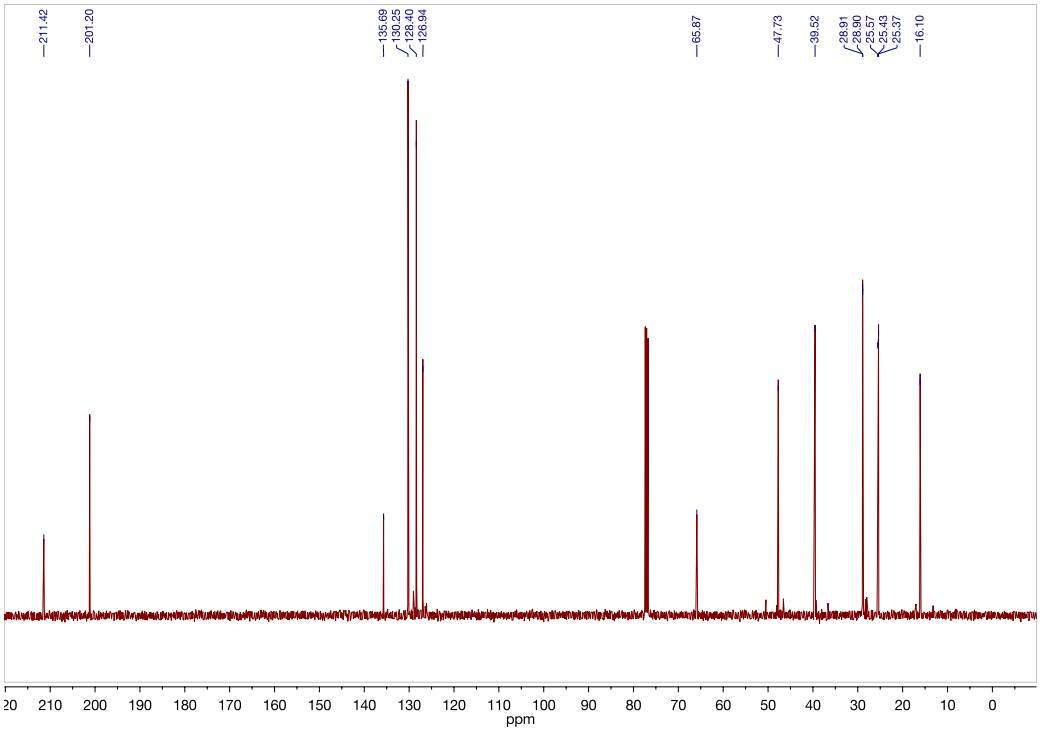




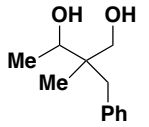
2-Benzyl-3-cyclohexyl-2-methyl-3-oxopropanal, 218

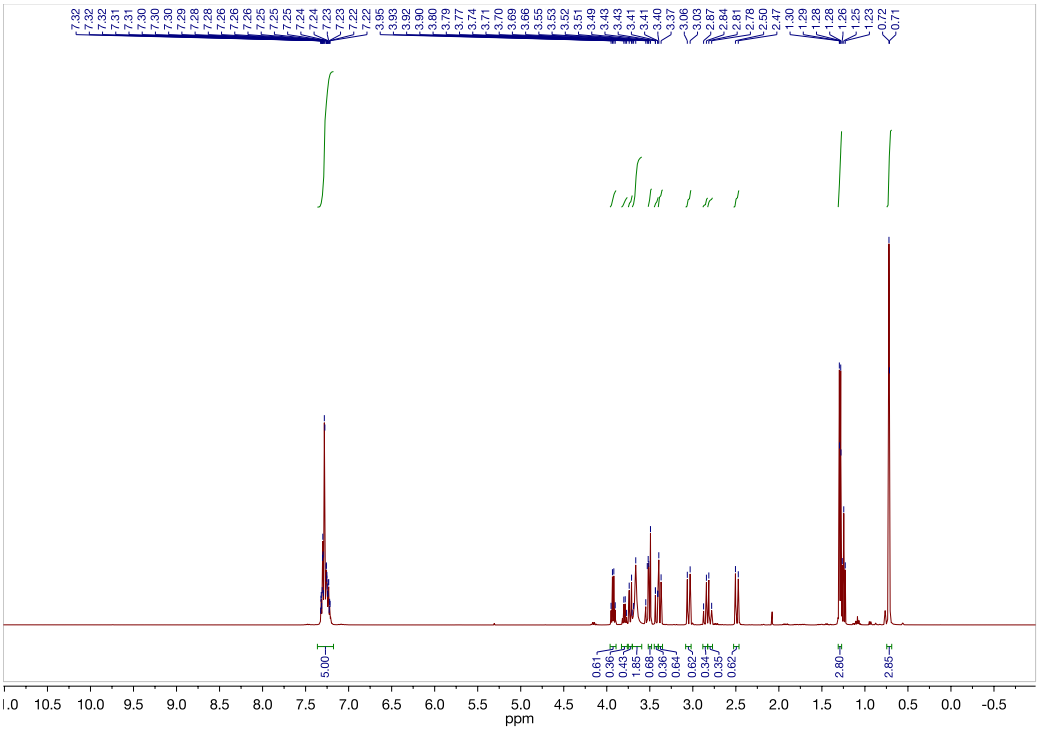


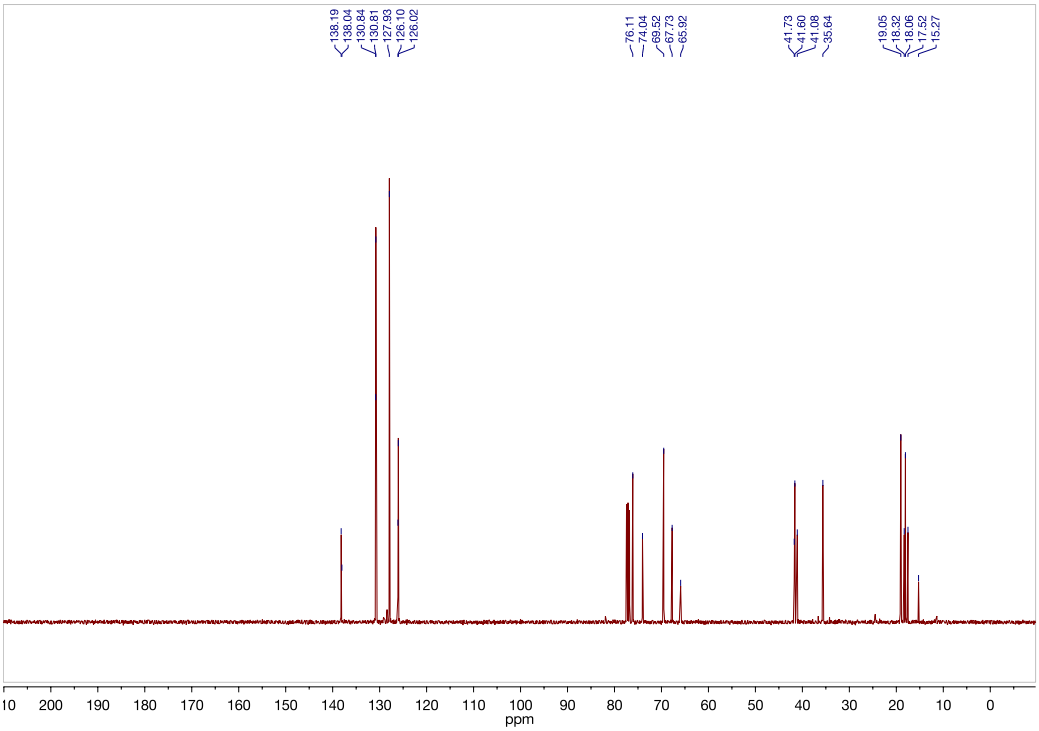




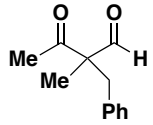
2-Benzyl-2-methylbutane-1,3-diol, 220

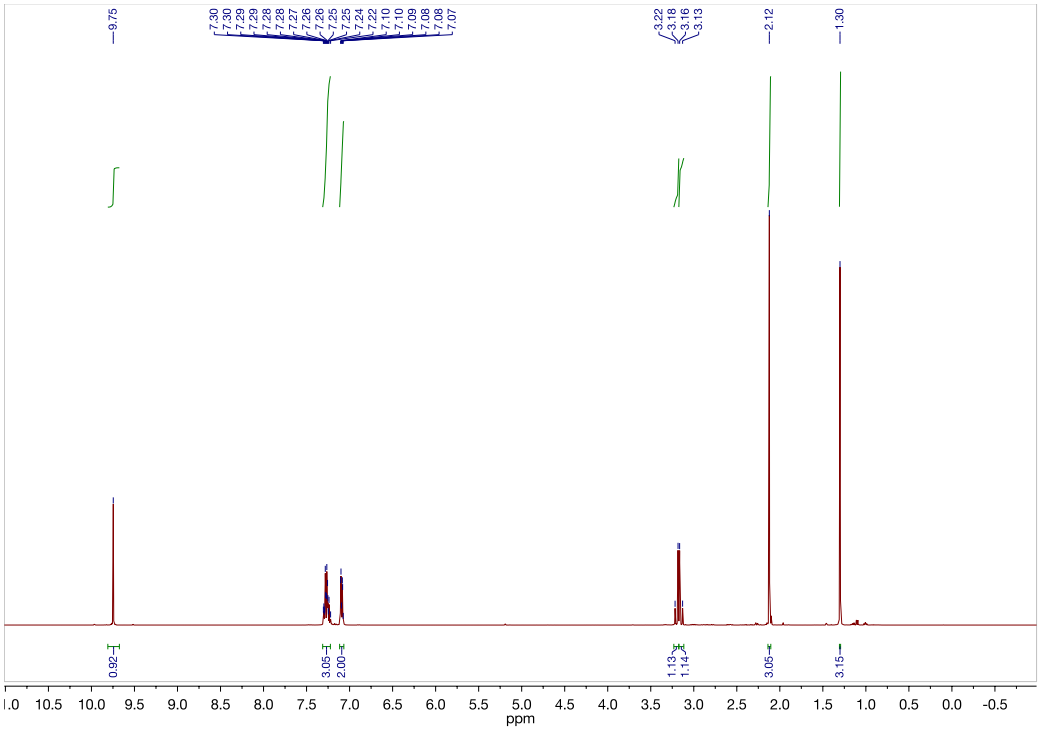


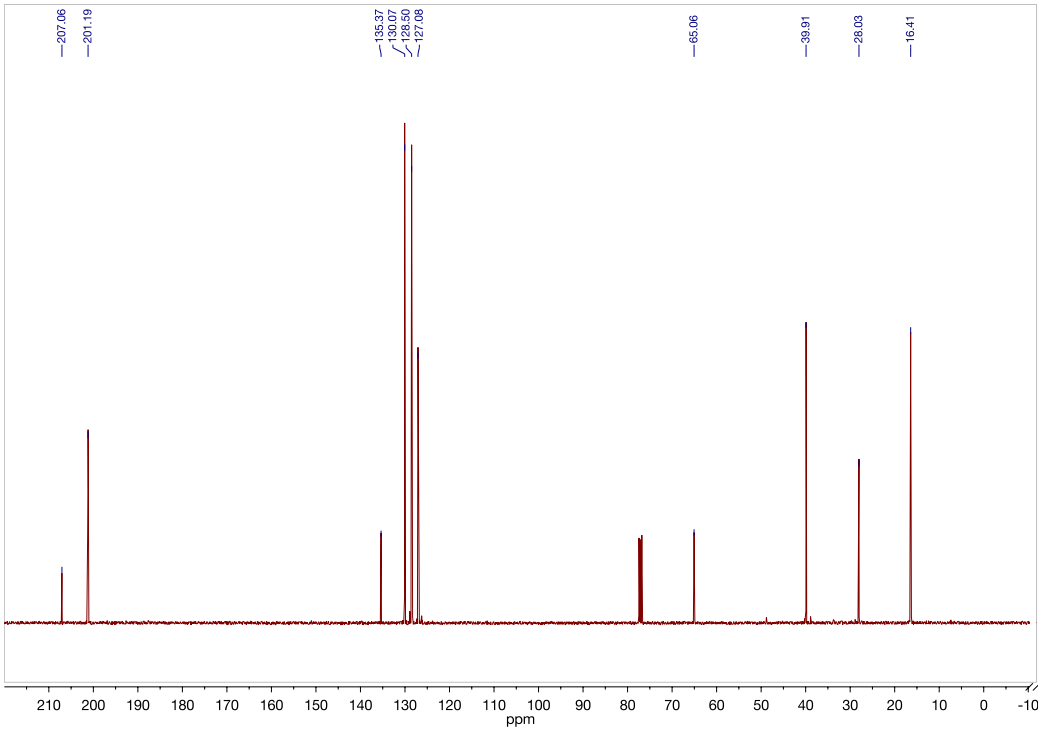




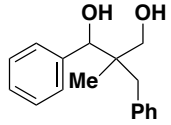
2-Benzyl-2-methyl-3-oxobutanal, 221

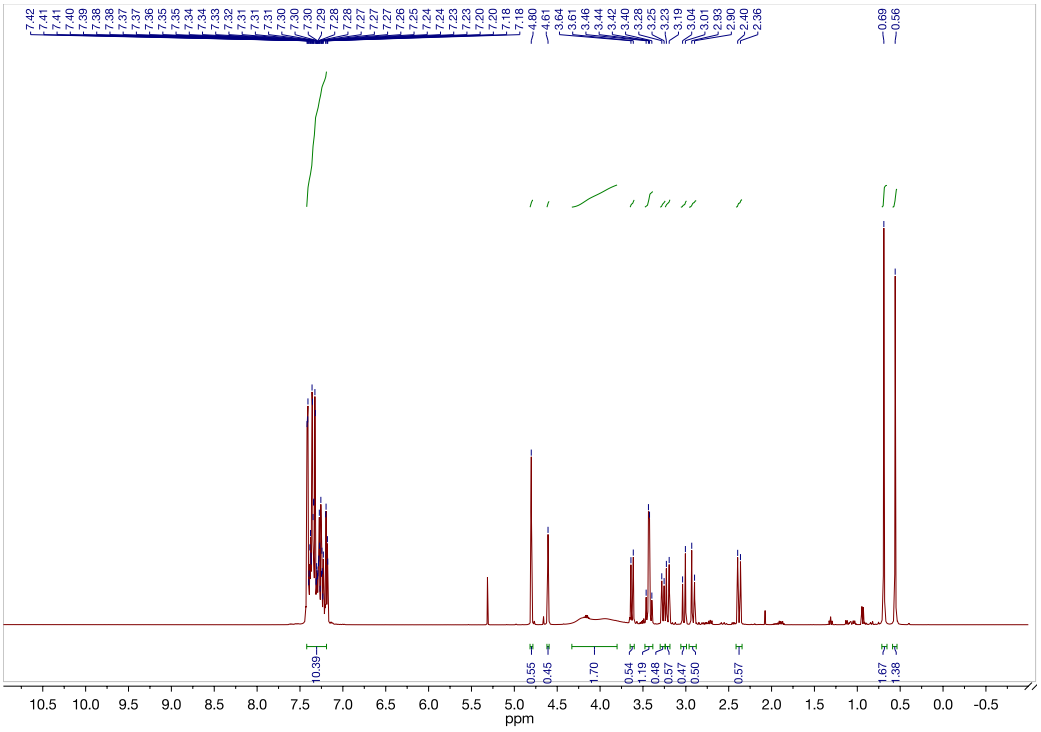


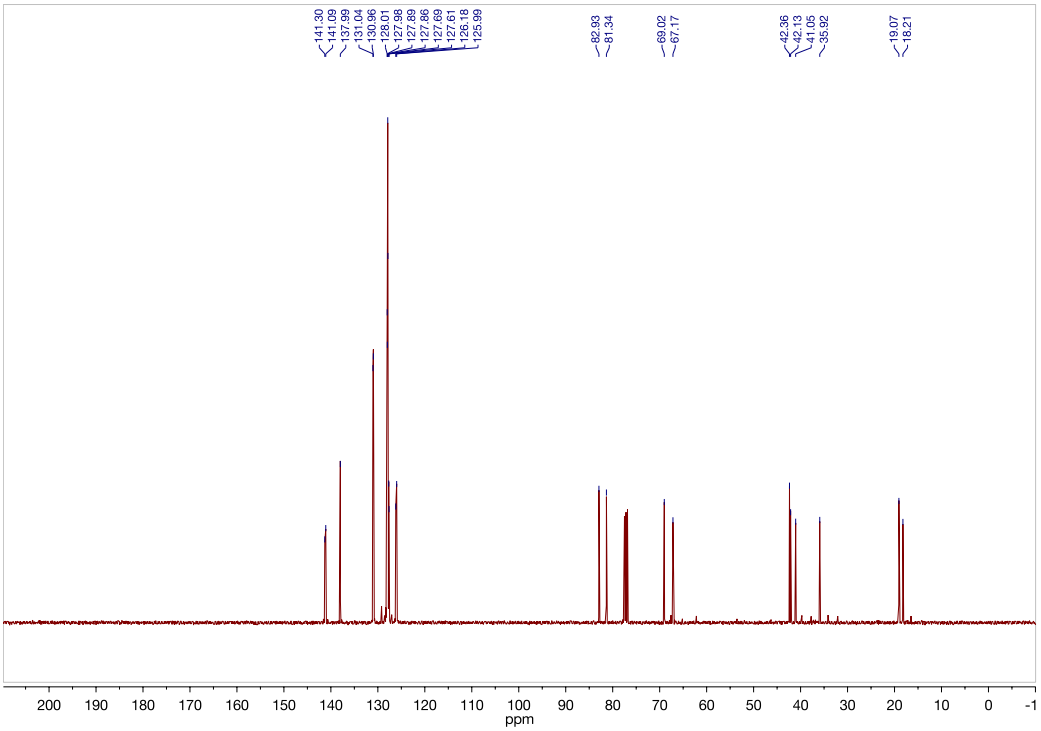




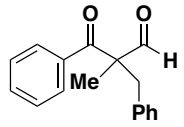
2-Benzyl-2-methyl-1-phenylpropane-1,3-diol, 223

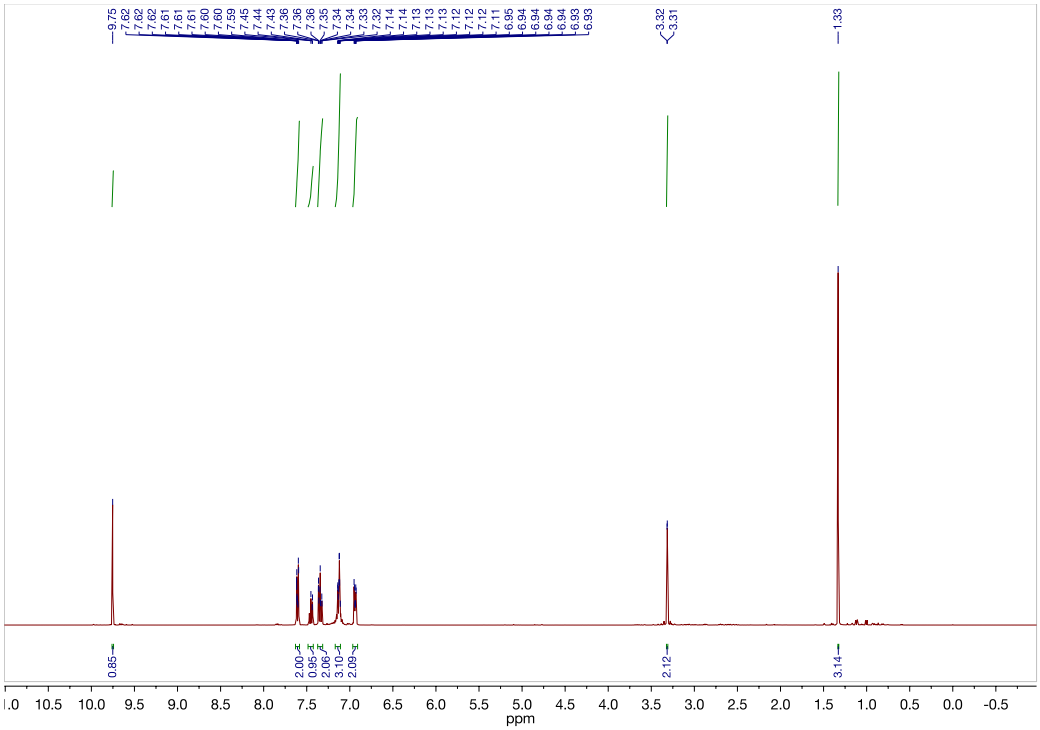


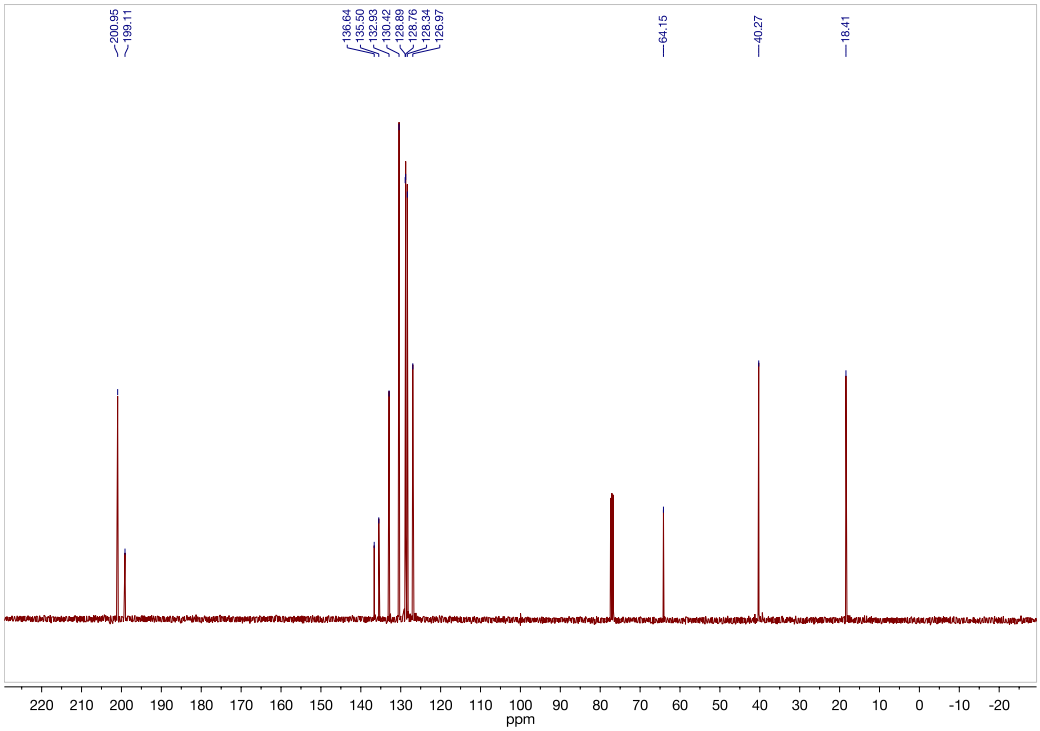




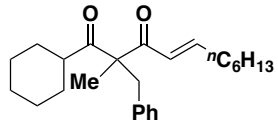
2-Benzyl-2-methyl-3-oxo-3-phenylpropanal, 224

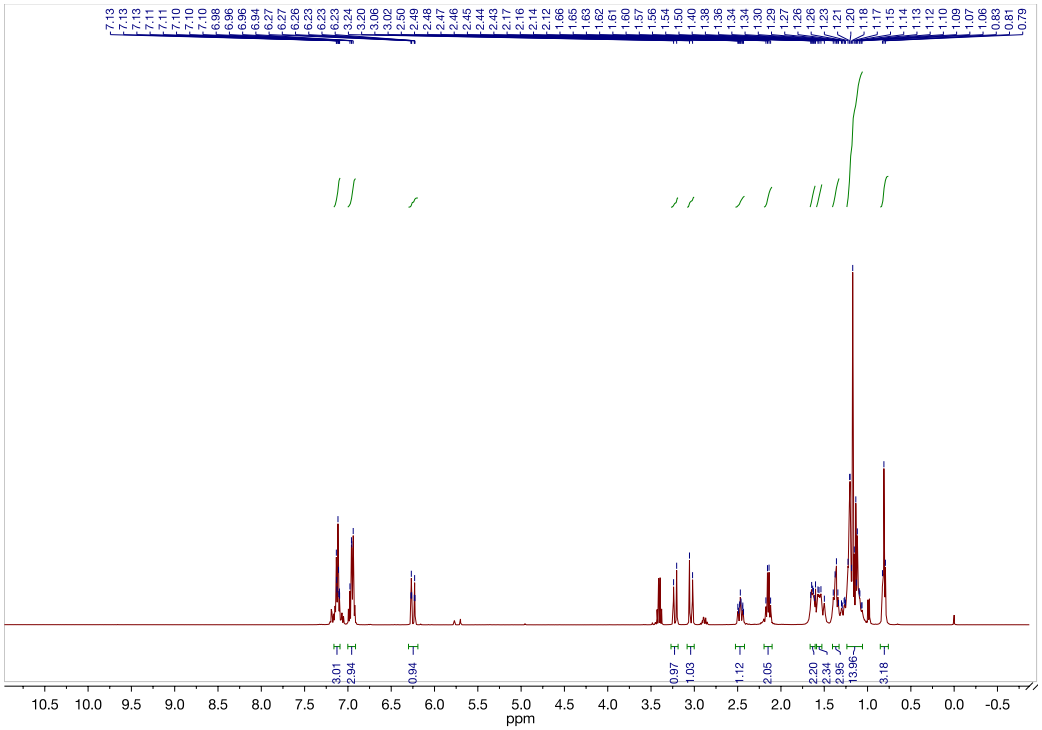


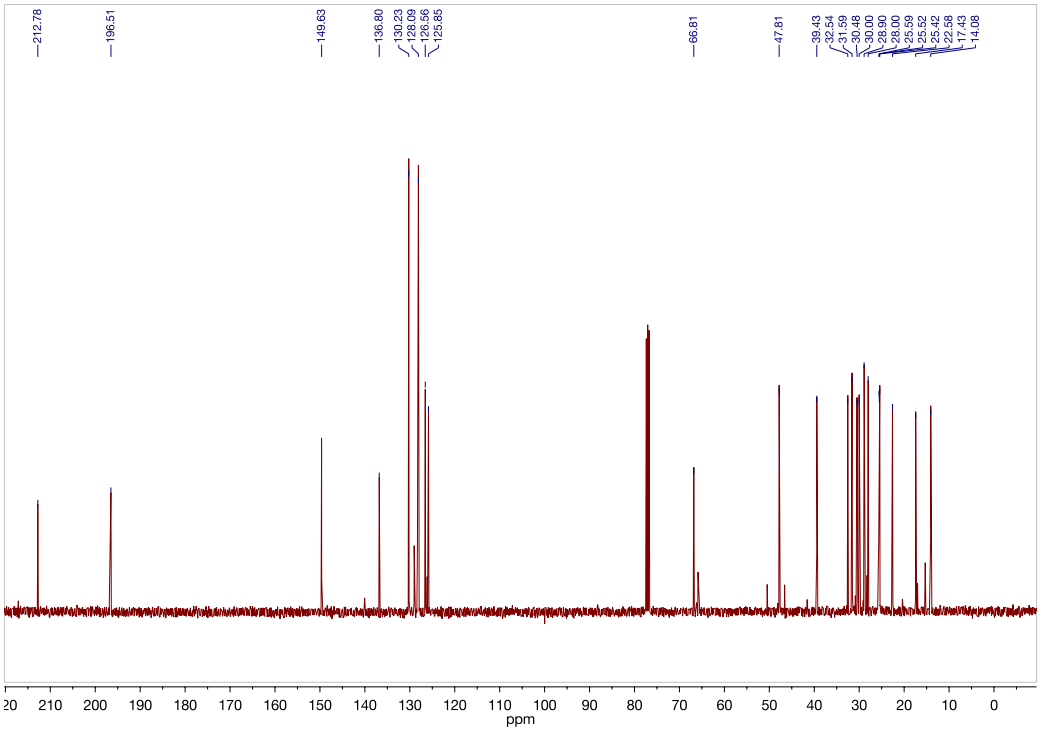




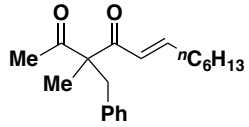
(*E*)-2-Benzyl-1-cyclohexyl-2-methylundec-4-ene-1,3-dione, 231

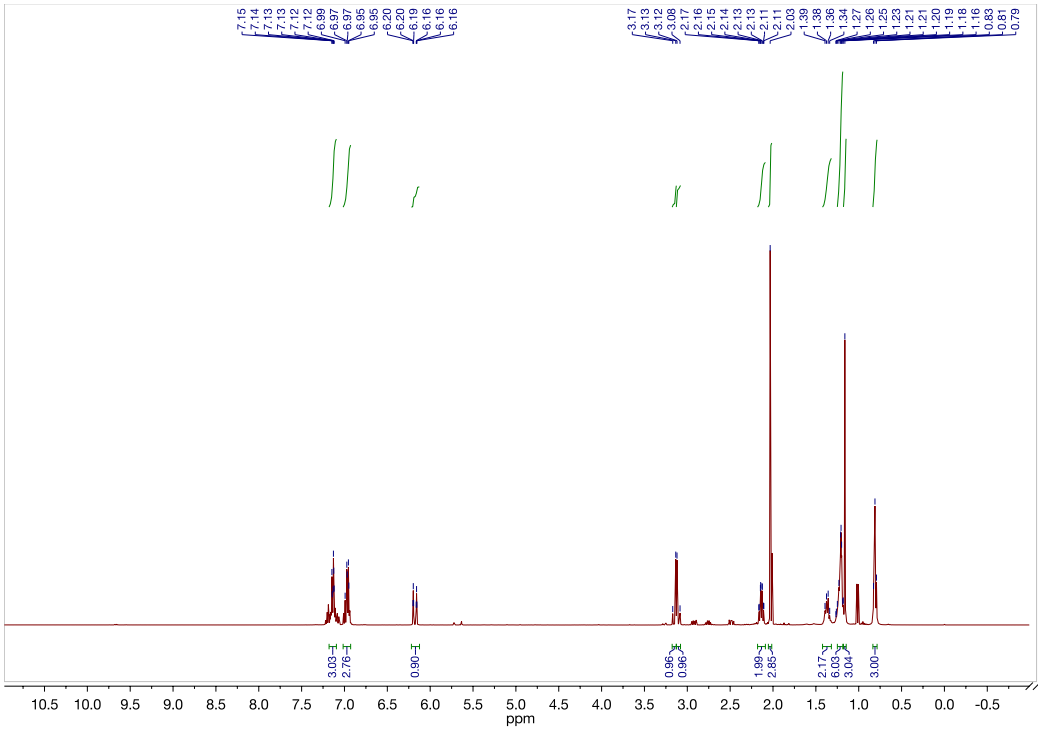


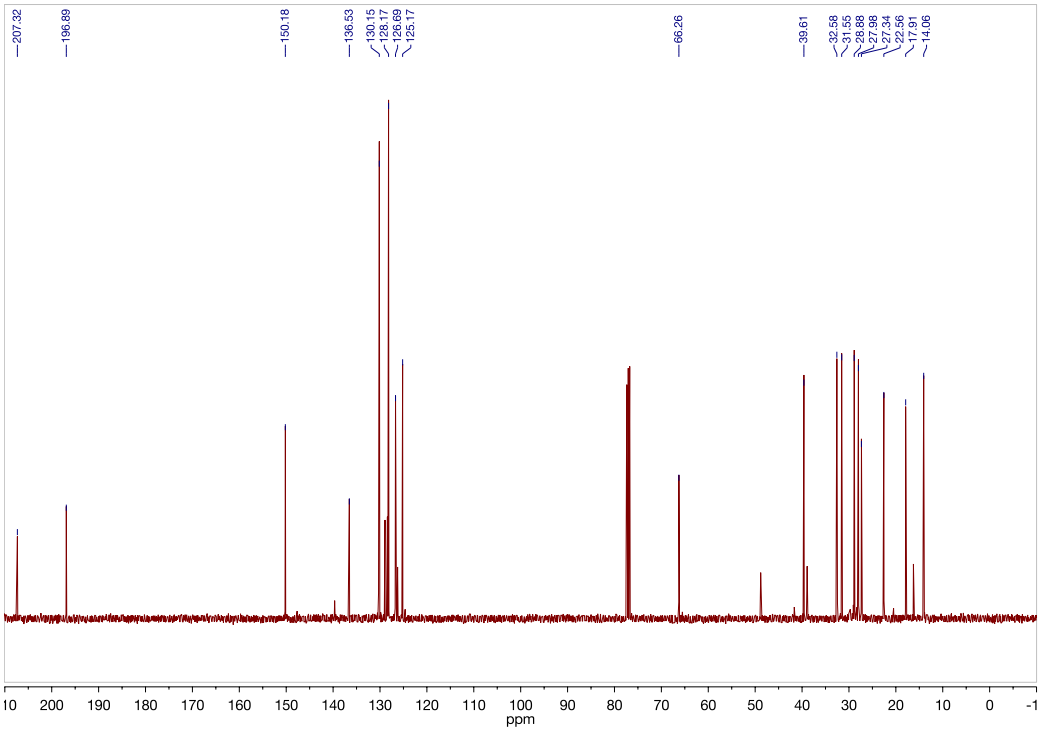




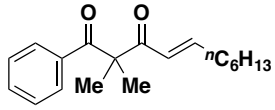
(*E*)-3-Benzyl-3-methyldodec-5-ene-2,4-dione, 232

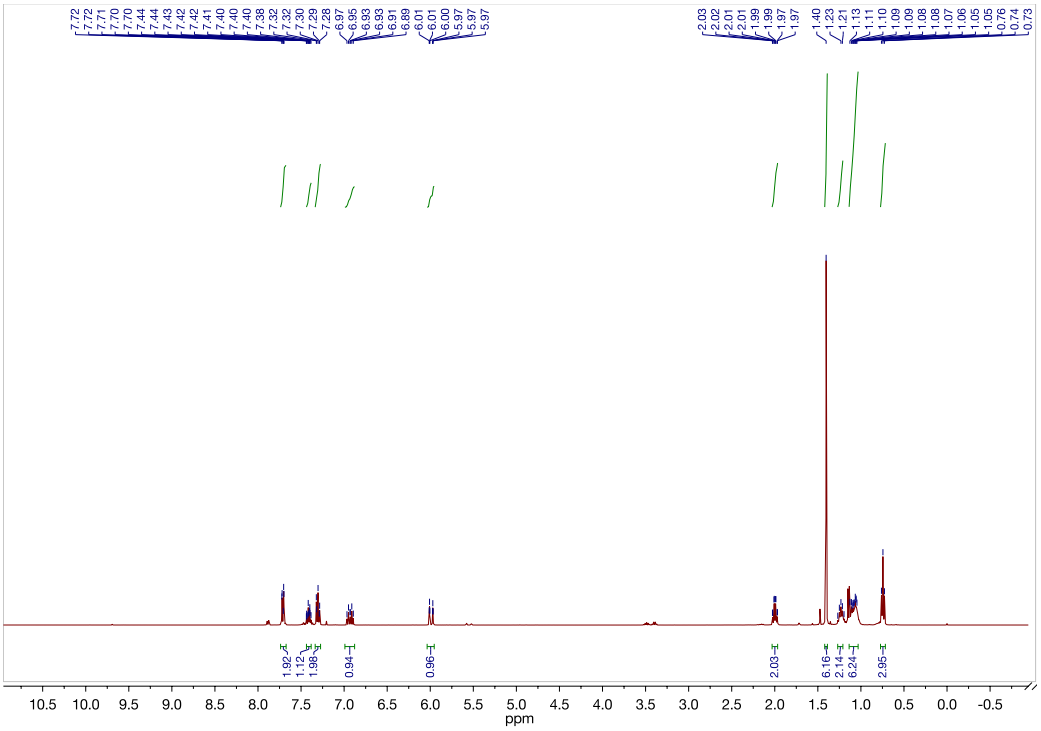


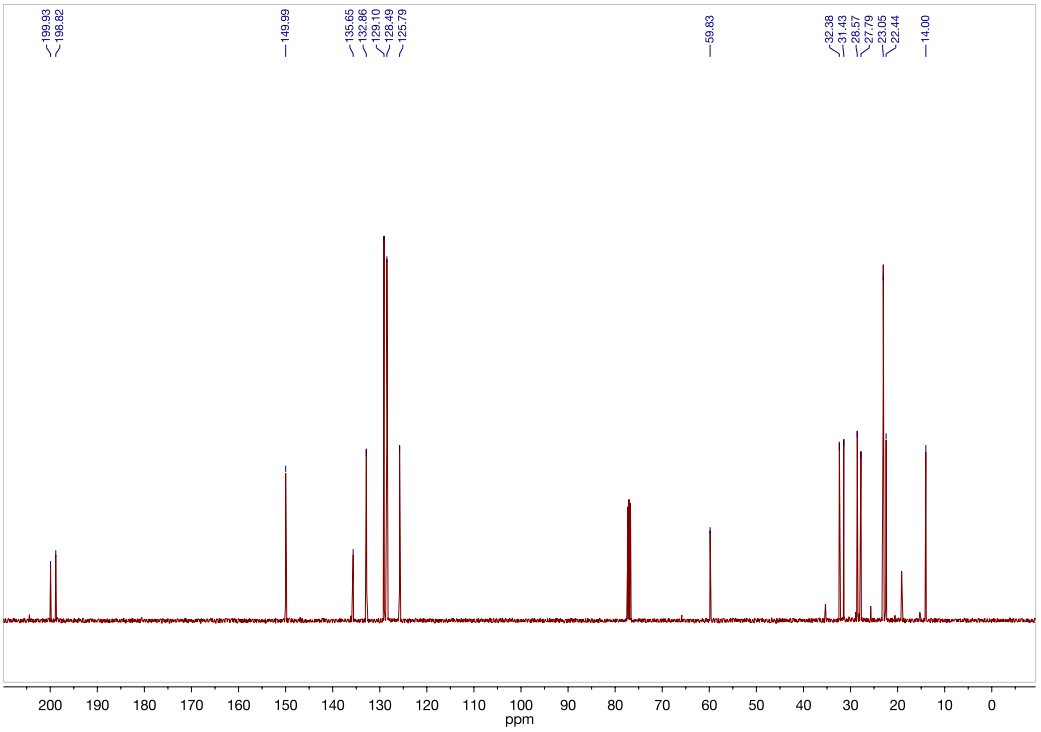




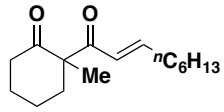
(*E*)-2,2-Dimethyl-1-phenylundec-4-ene-1,3-dione, 234

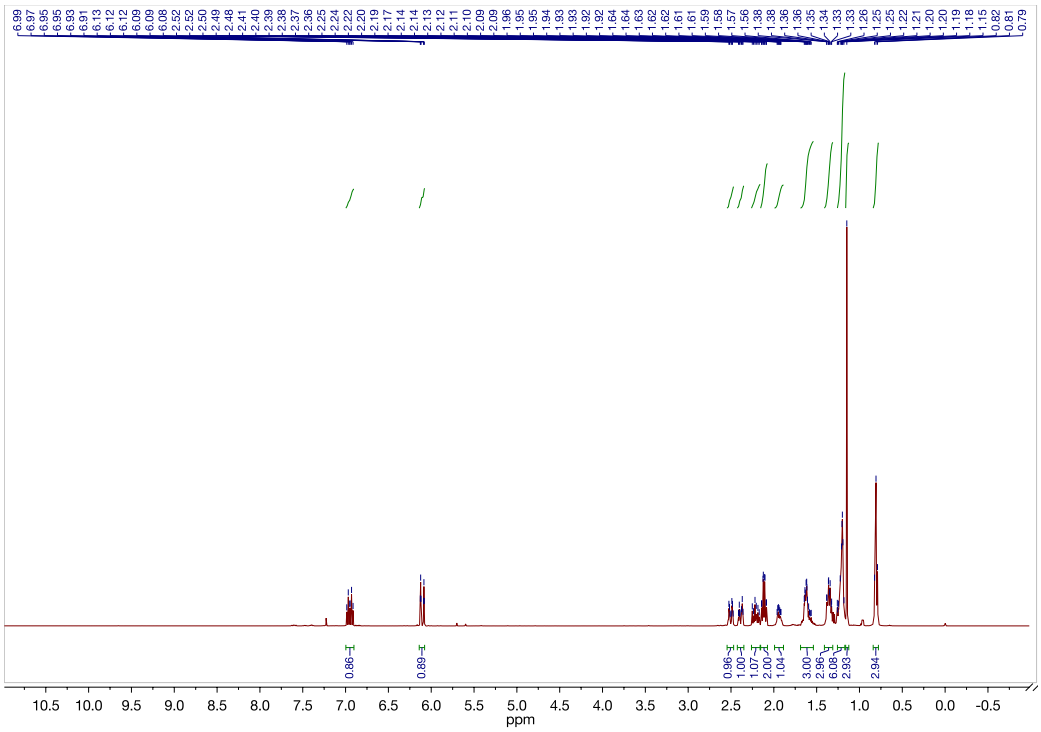


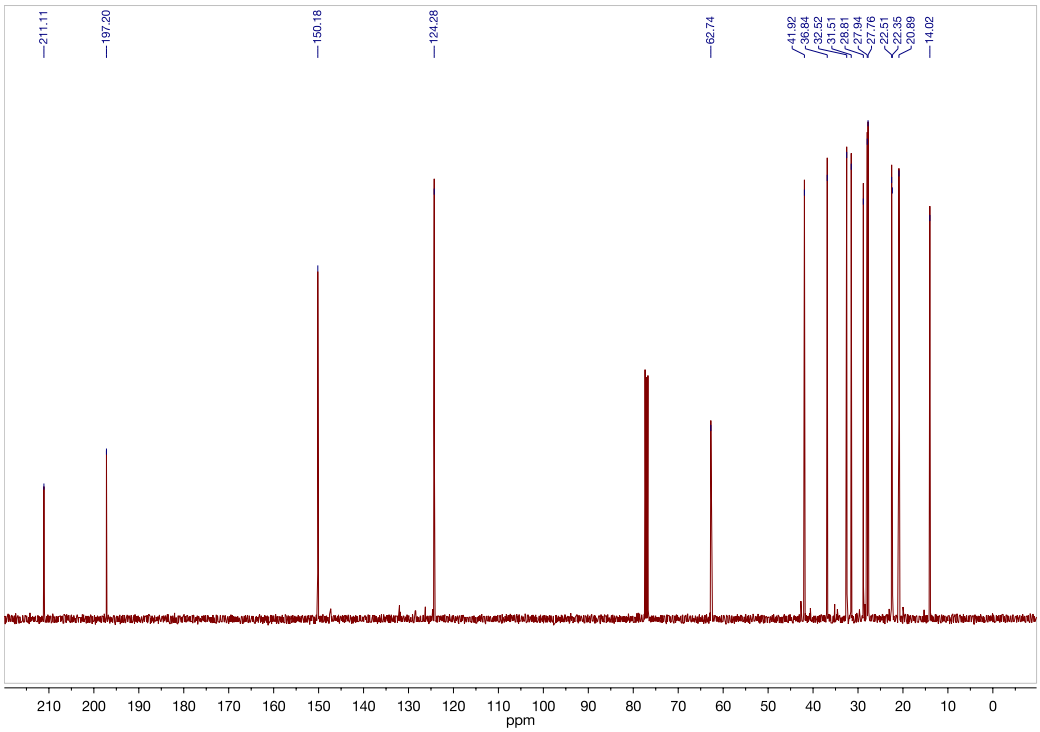




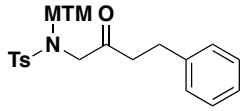
(*E*)-2-Methyl-2-(non-2-enoyl)cyclohexan-1-one, 235

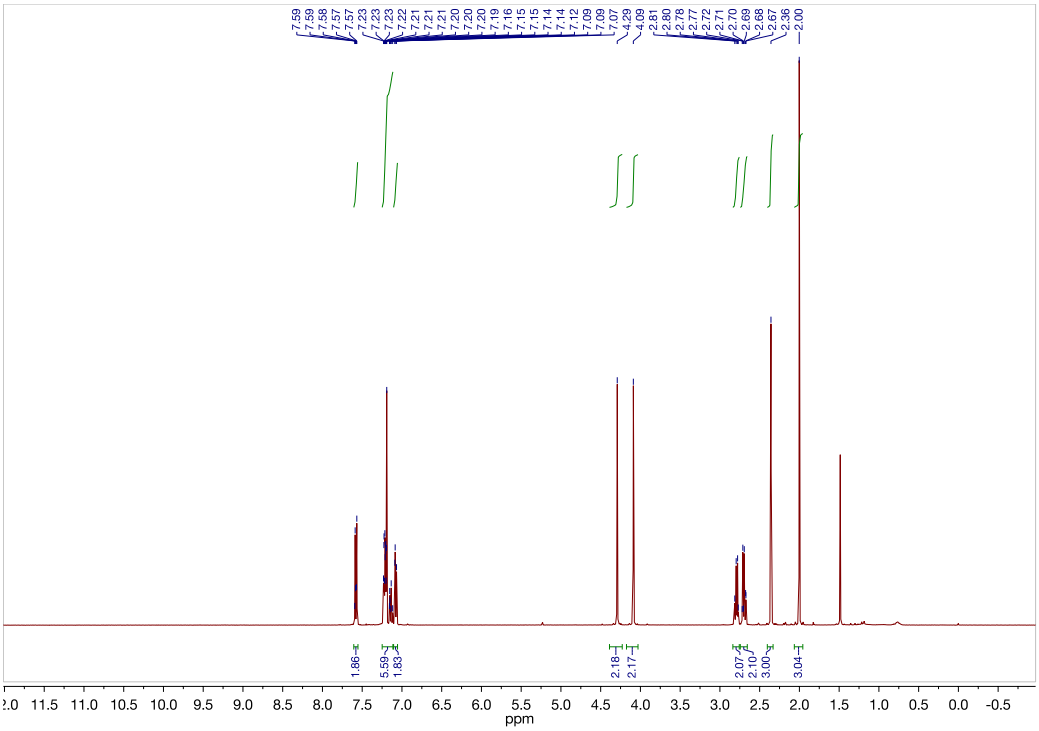


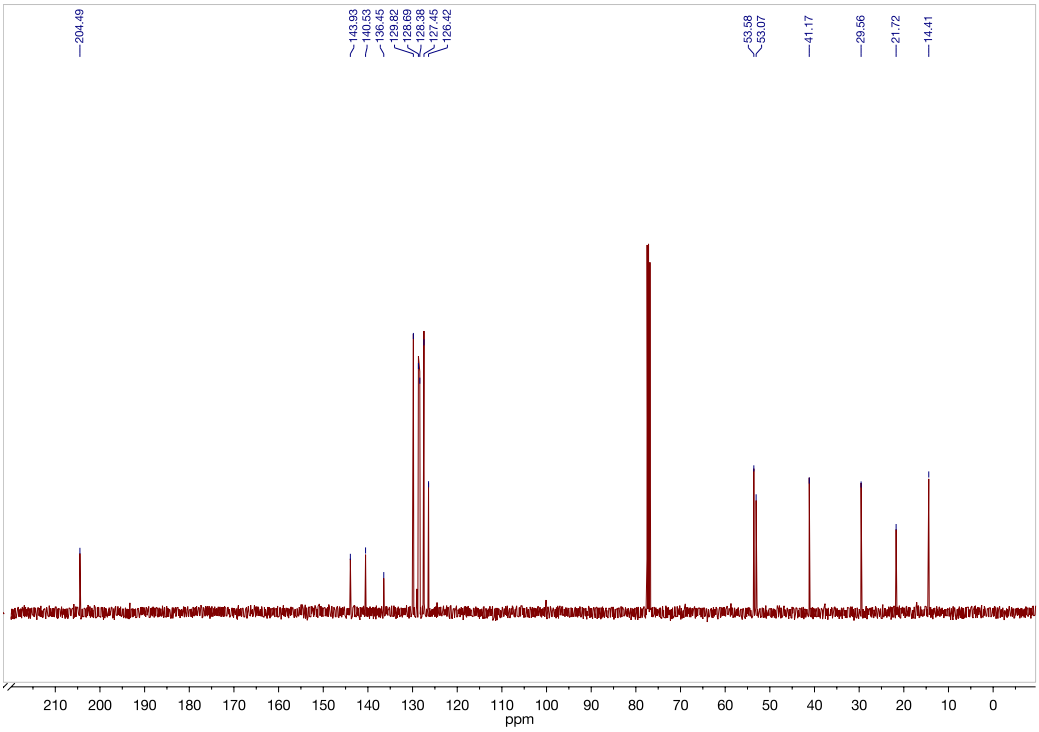




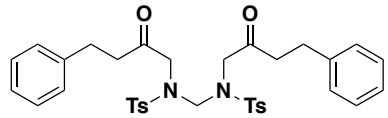
4-Methyl-*N*-[(methylthio)methyl]-*N*-(2-oxo-4-phenylbutyl)benzenesulfonamide, 295

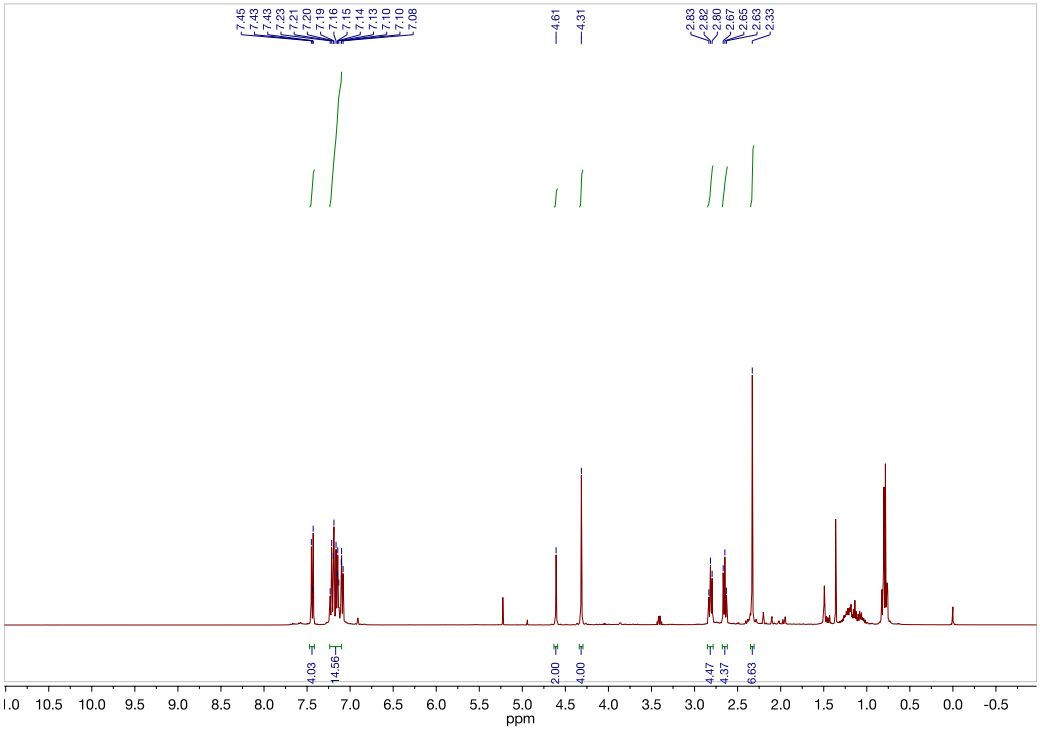


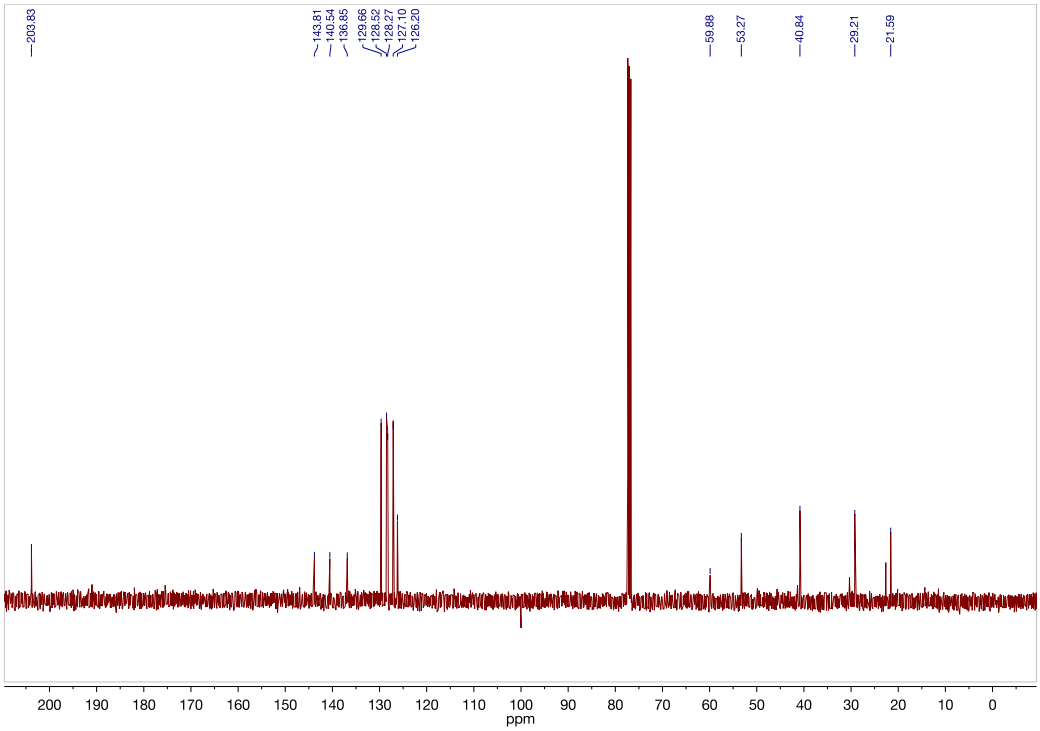




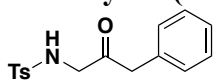
_N_,_N_'-Methylenebis[4-methyl-_N_-(2-oxo-4-phenylbutyl)benzenesulfonamide], 297

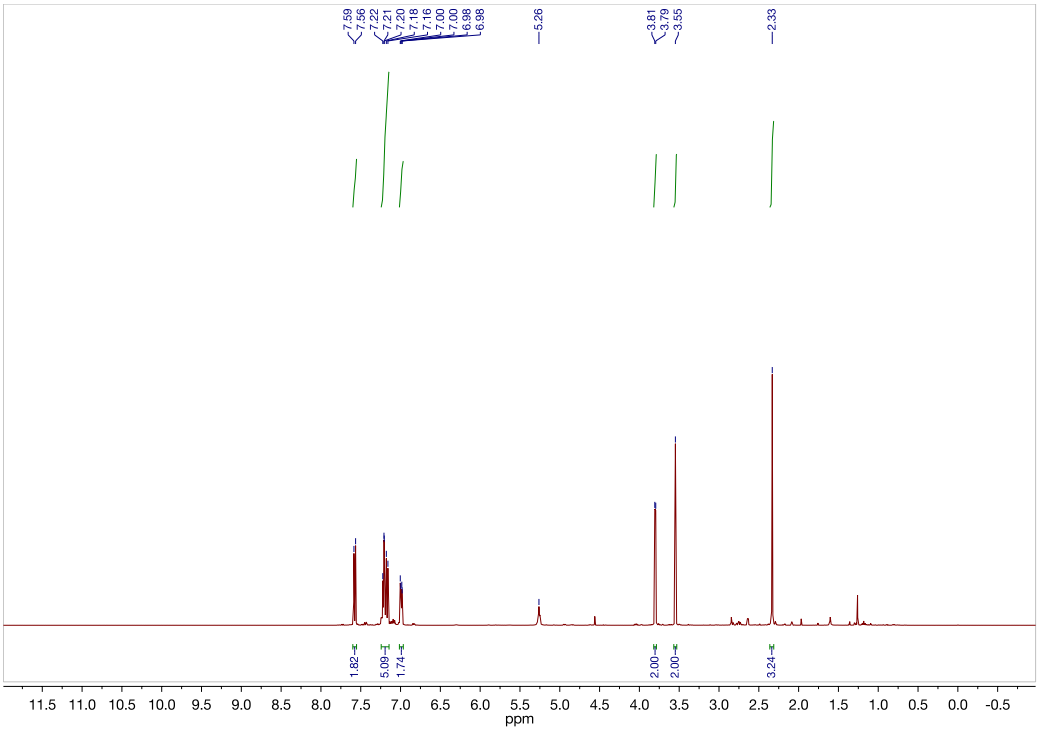


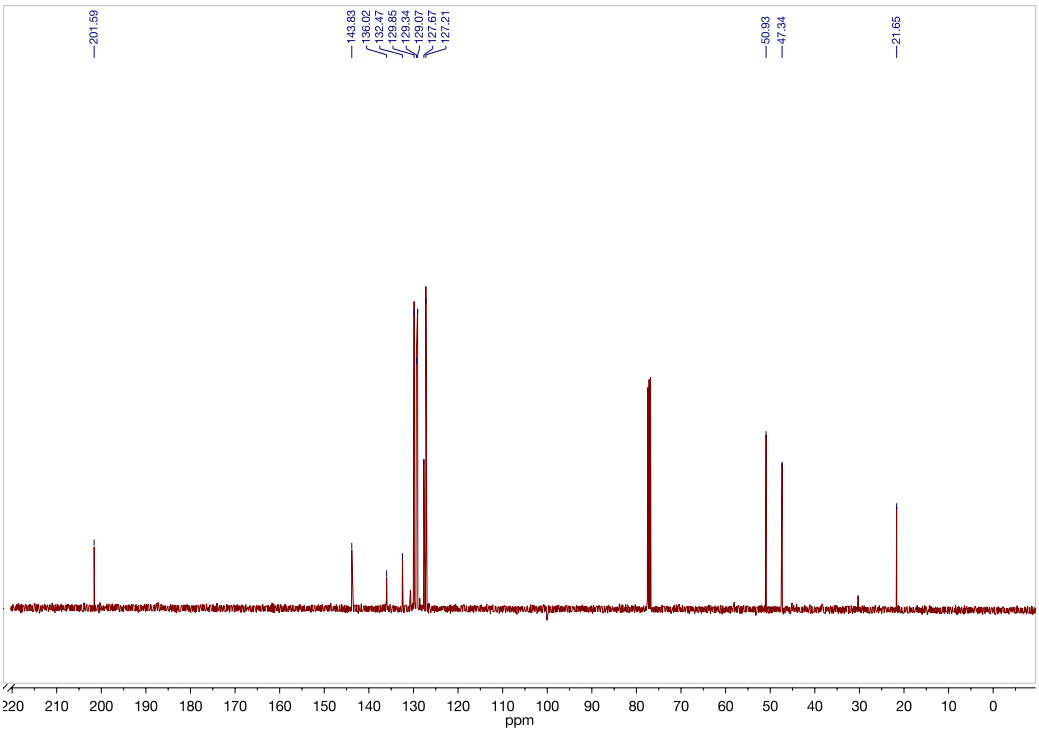




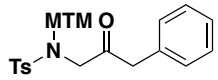
4-Methyl-*N*-(2-oxo-3-phenylpropyl)benzenesulfonamide, 298

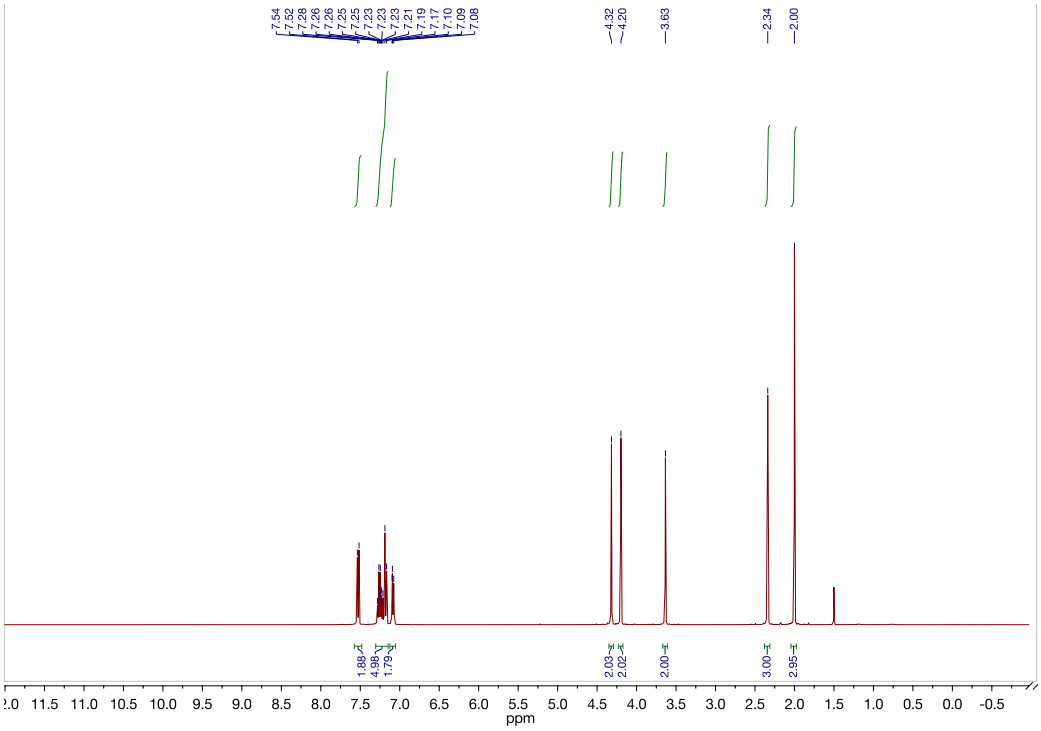


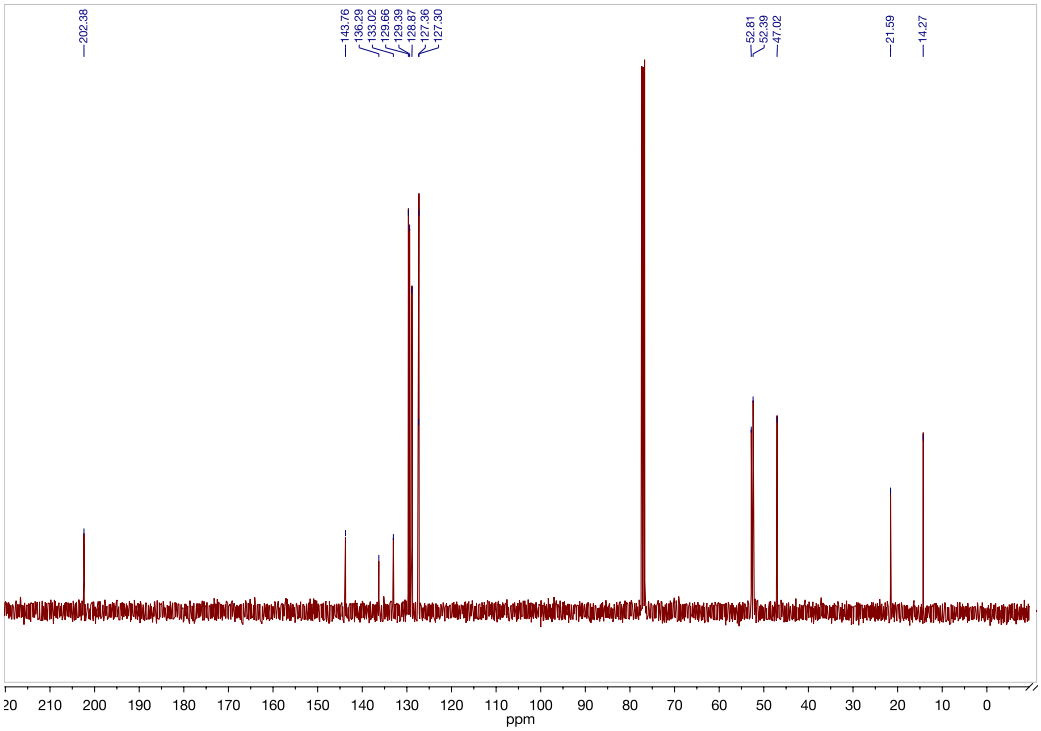




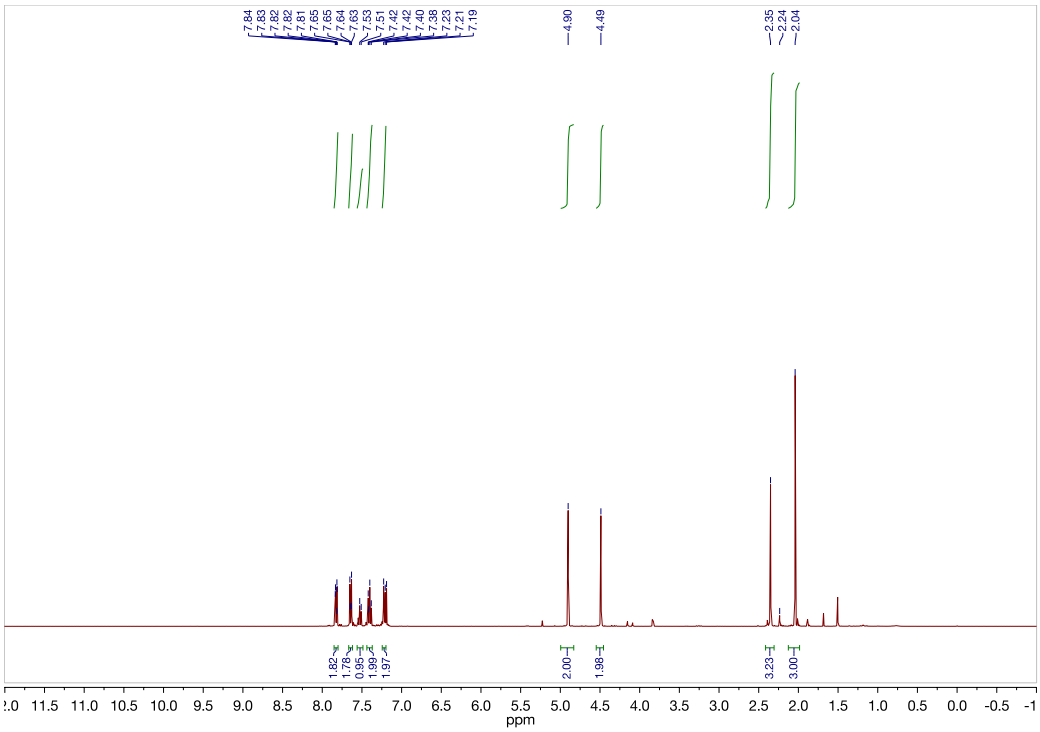
4-Methyl-*N*-[(methylthio)methyl]-*N*-(2-oxo-3-phenylpropyl)benzenesulfonamide, 300

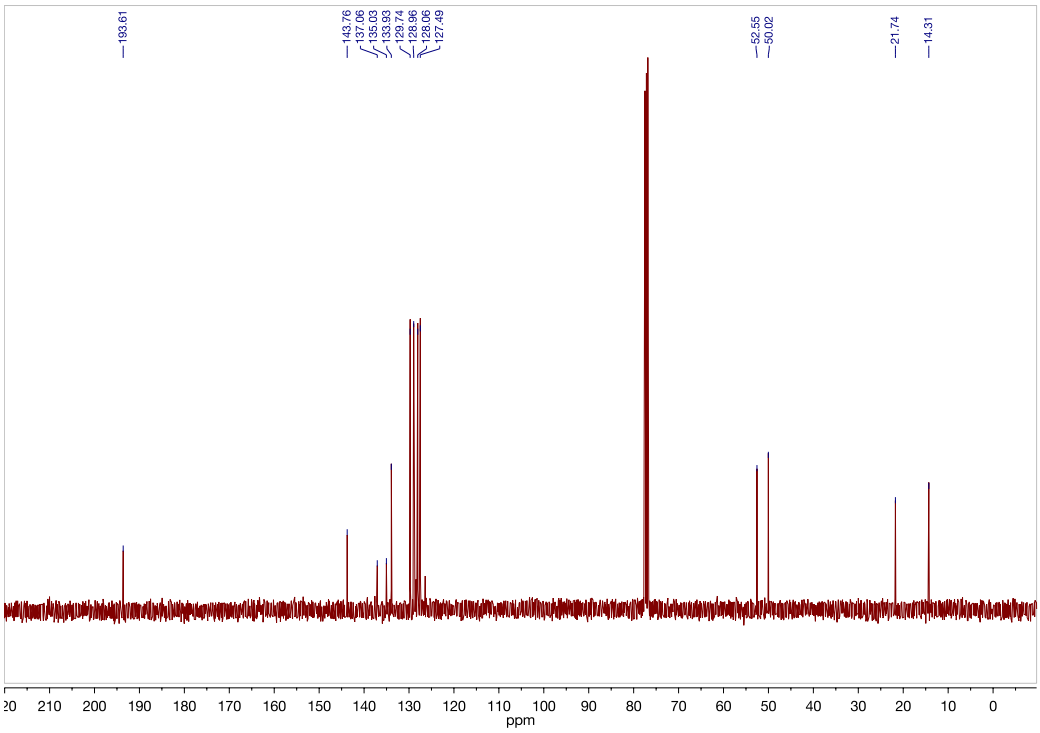




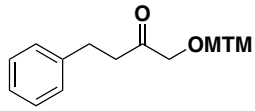


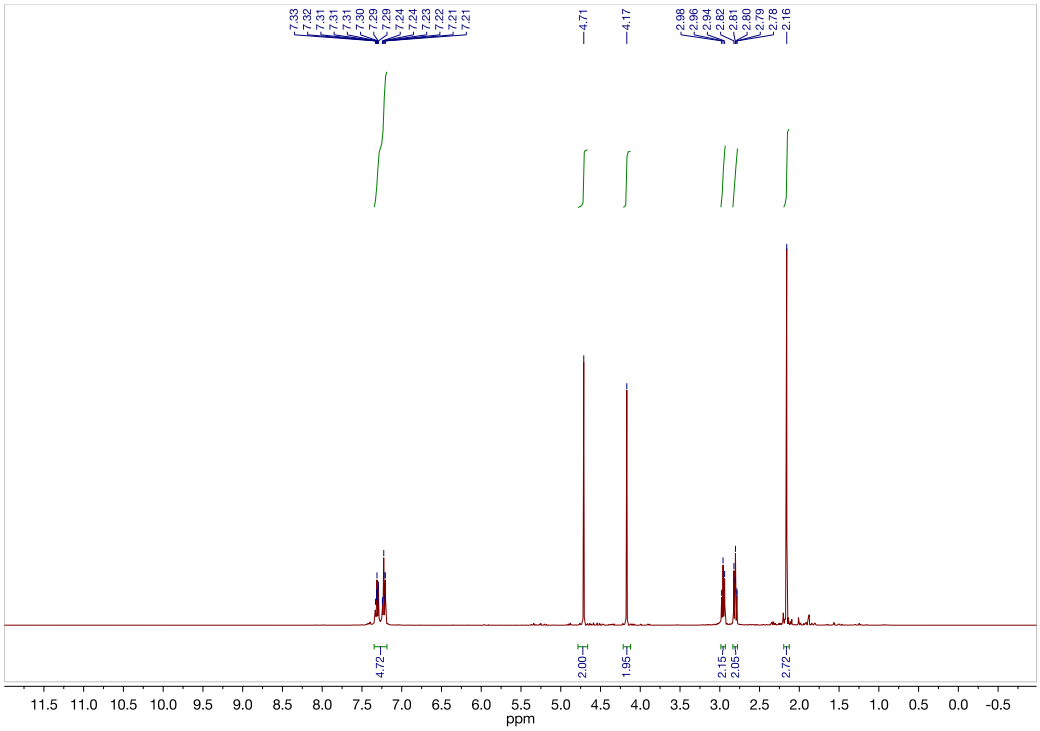
4-Methyl-*N*-[(methylthio)methyl]-*N*-(2-oxo-2-phenylethyl)benzenesulfonamide, 301

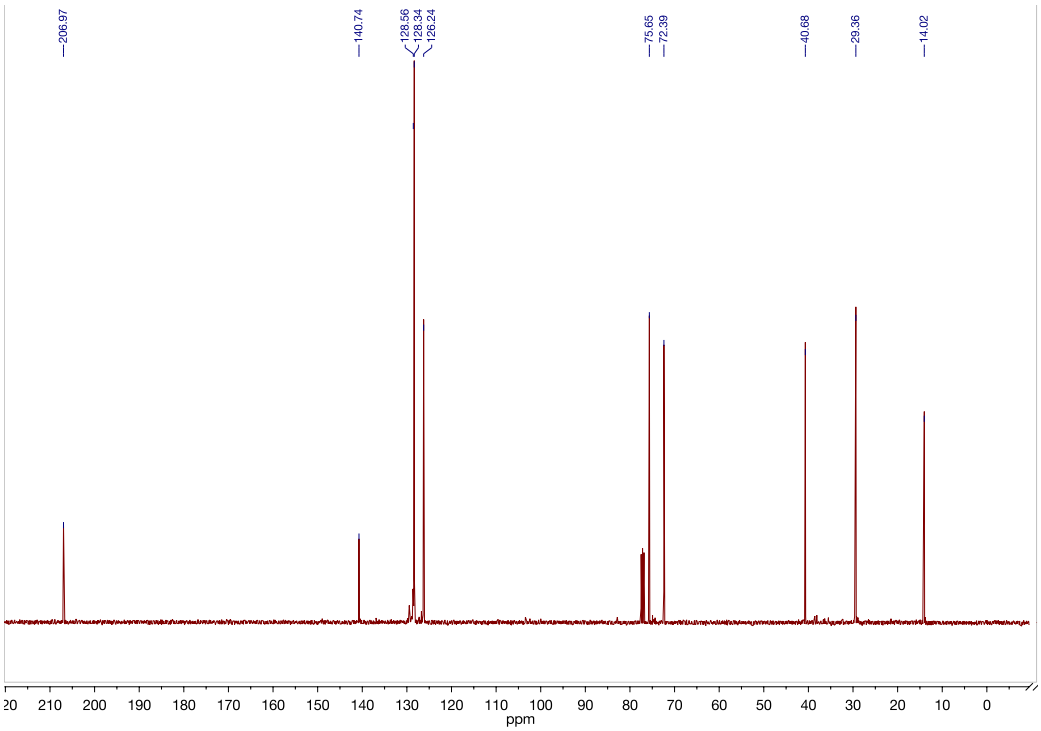




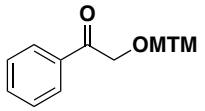
1-[(Methylthio)methoxy]-4-phenylbutan-2-one, 303

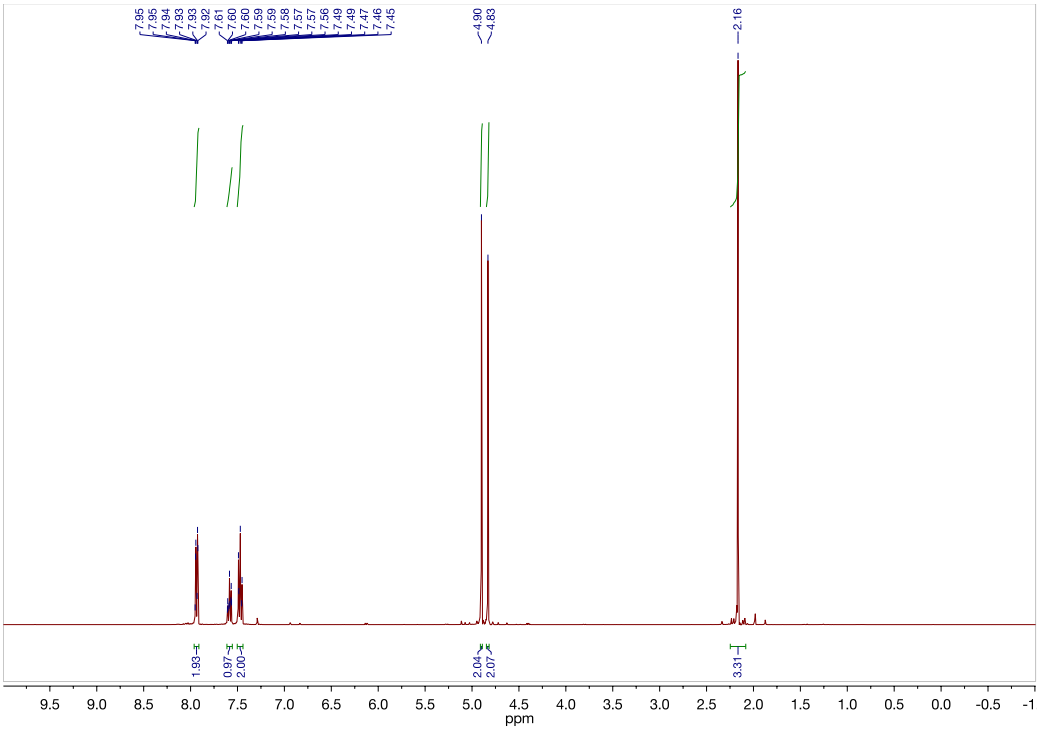


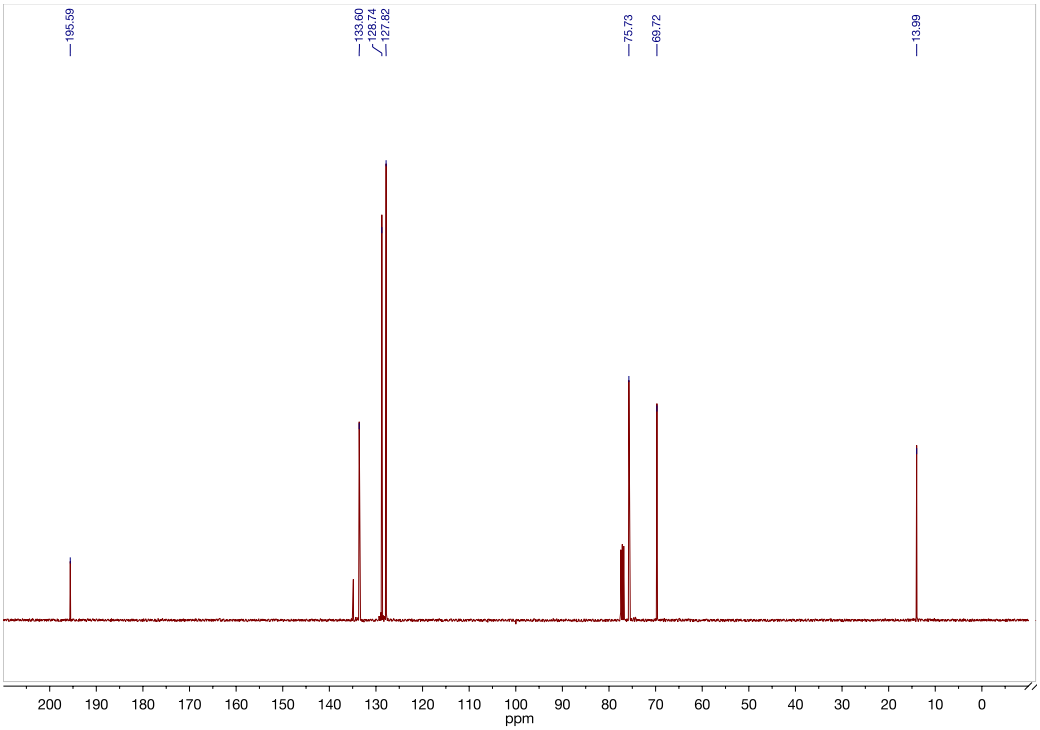




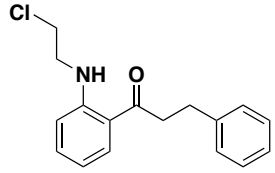
2-[(Methylthio)methoxy]-1-phenylethan-1-one, 304

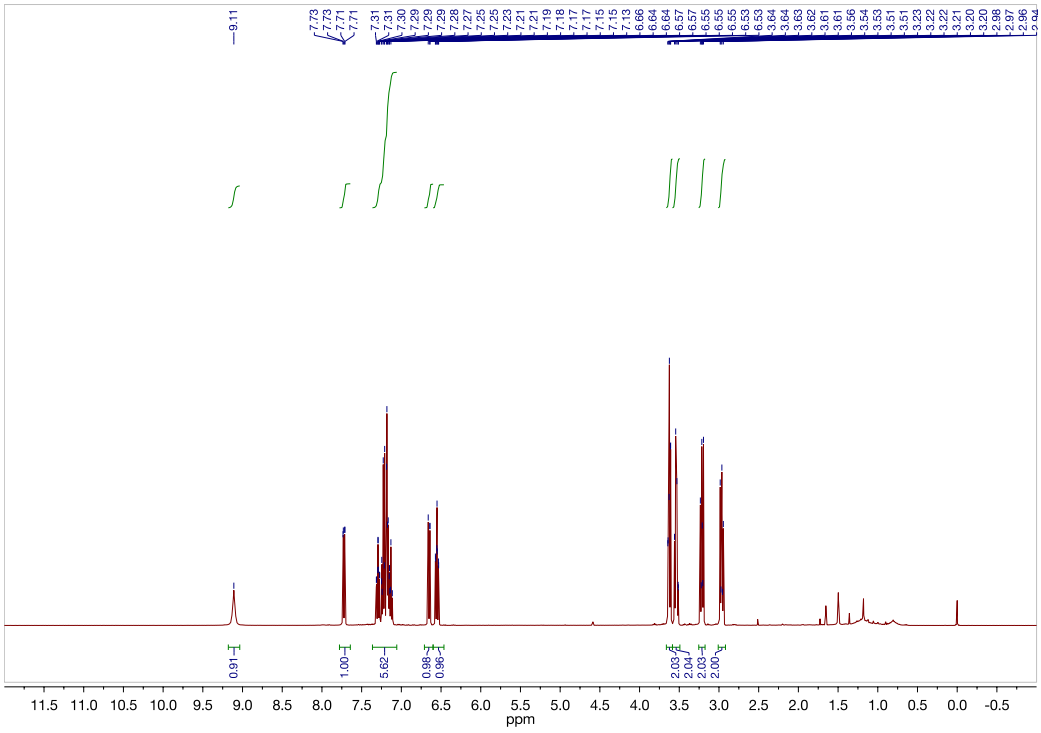


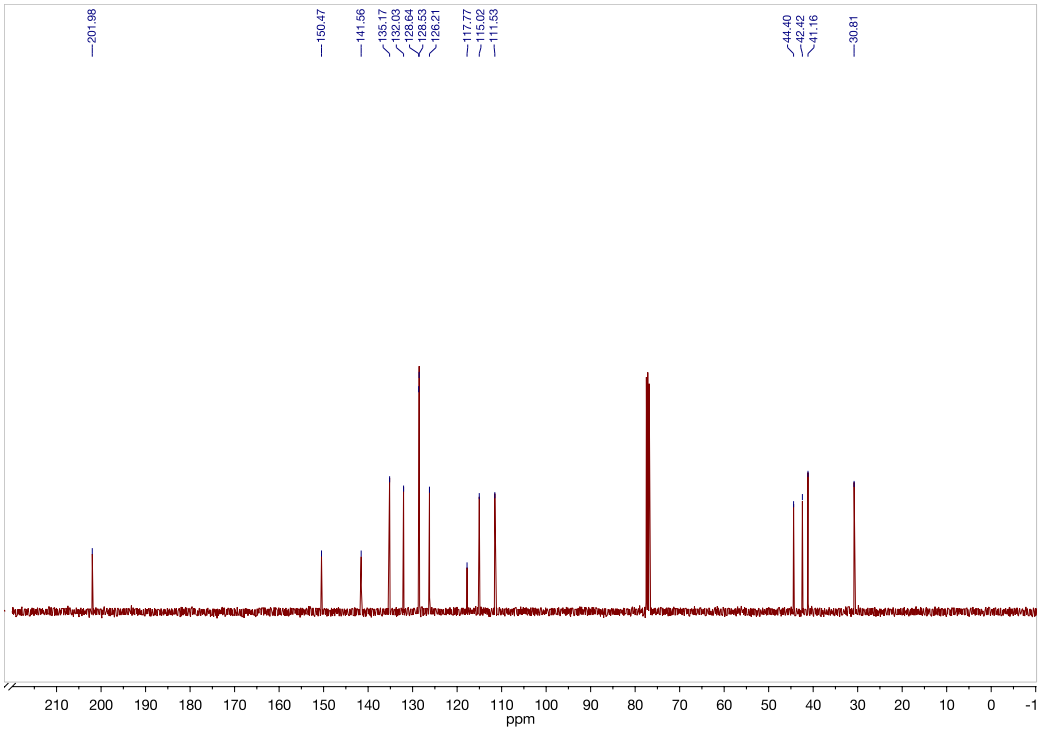




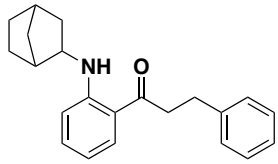
1-(2-[(2-Chloroethyl)amino)phenyl]-3-phenylpropan-1-one, 318

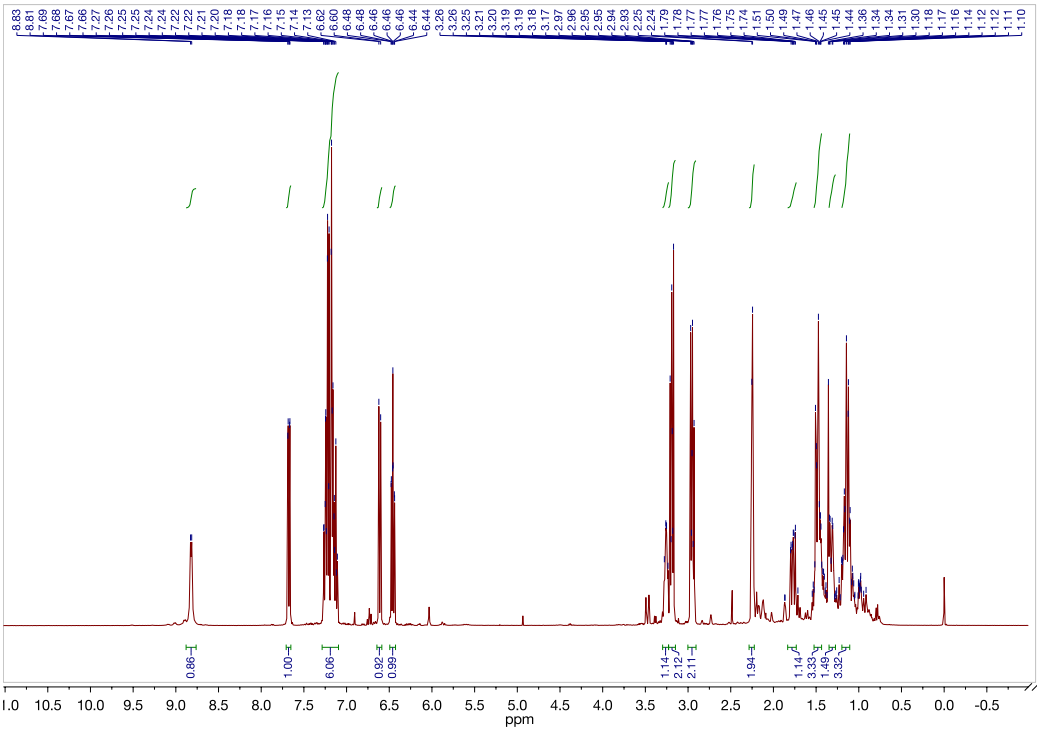


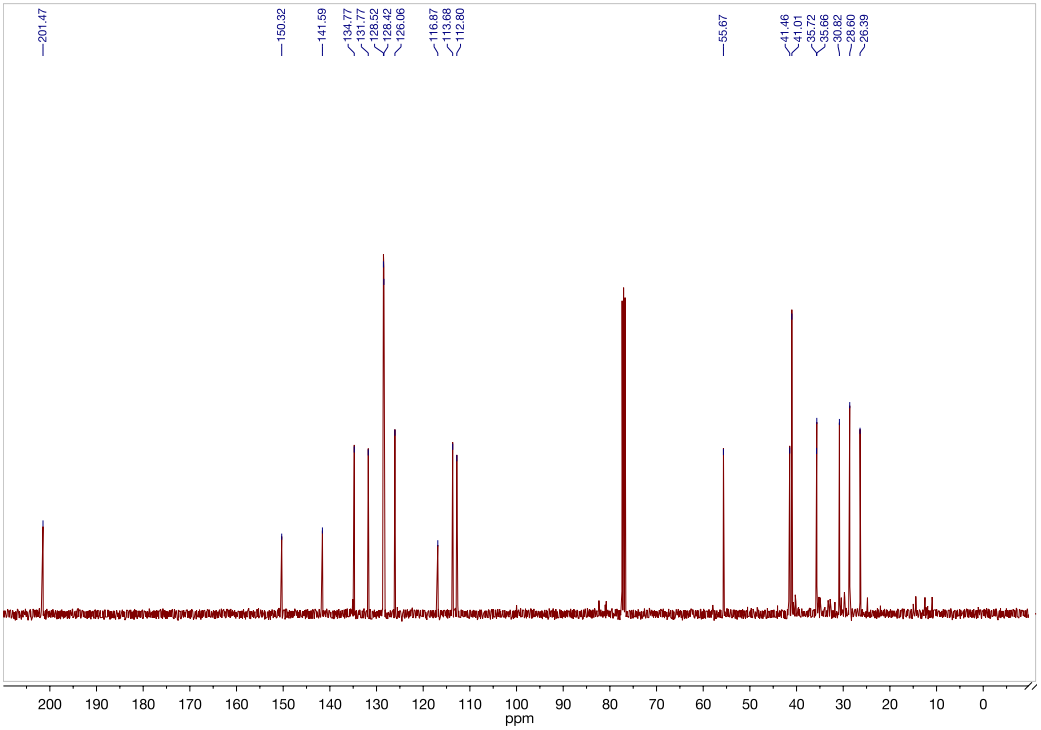




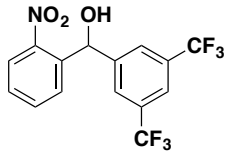
1-[2-(Bicyclo[2.2.1]heptan-2-ylamino)phenyl]-3-phenylpropan-1-one, 319

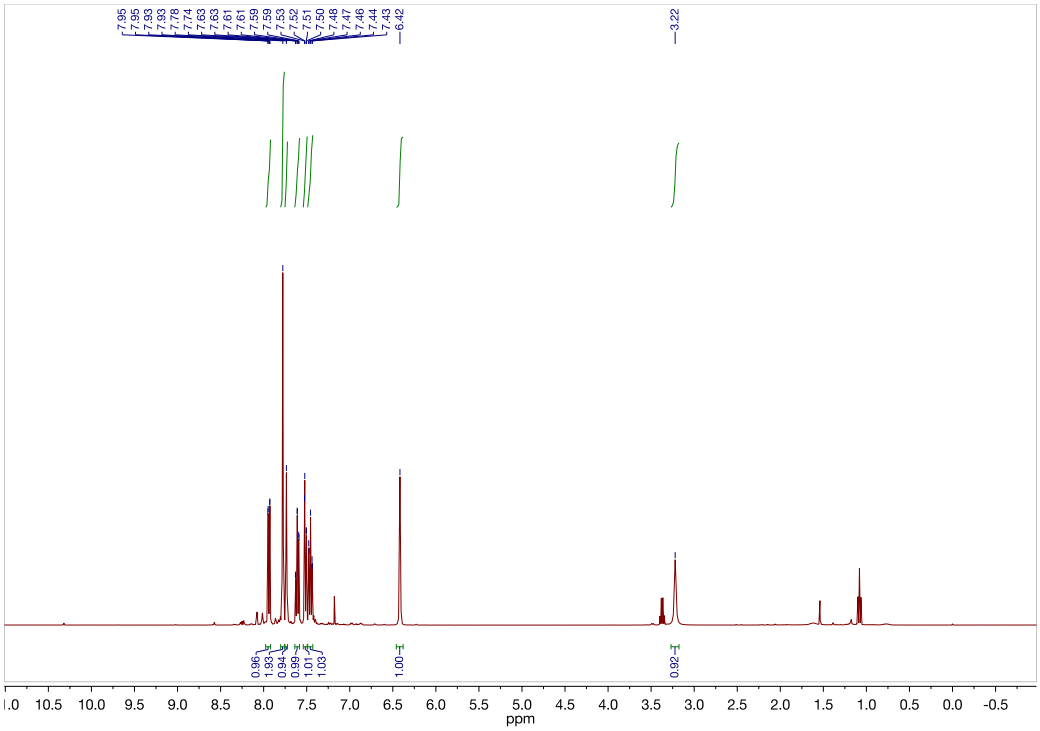


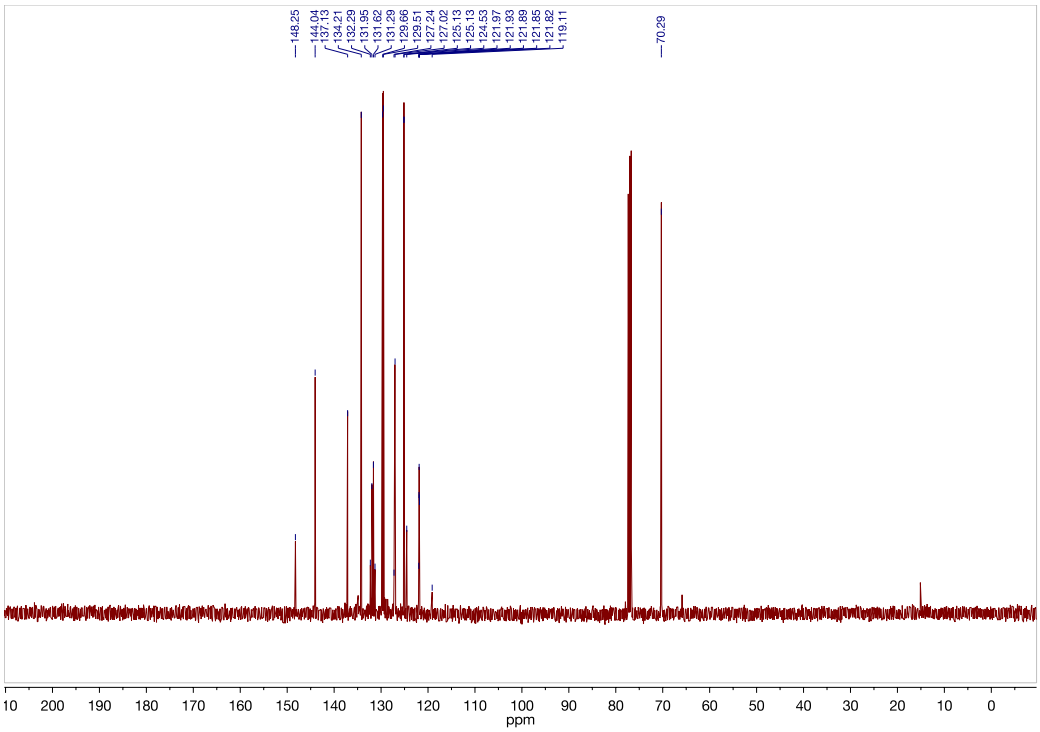




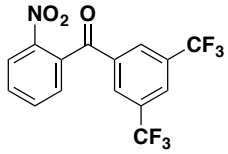
[3,5-Bis(trifluoromethyl)phenyl](2-nitrophenyl)methanol, 321

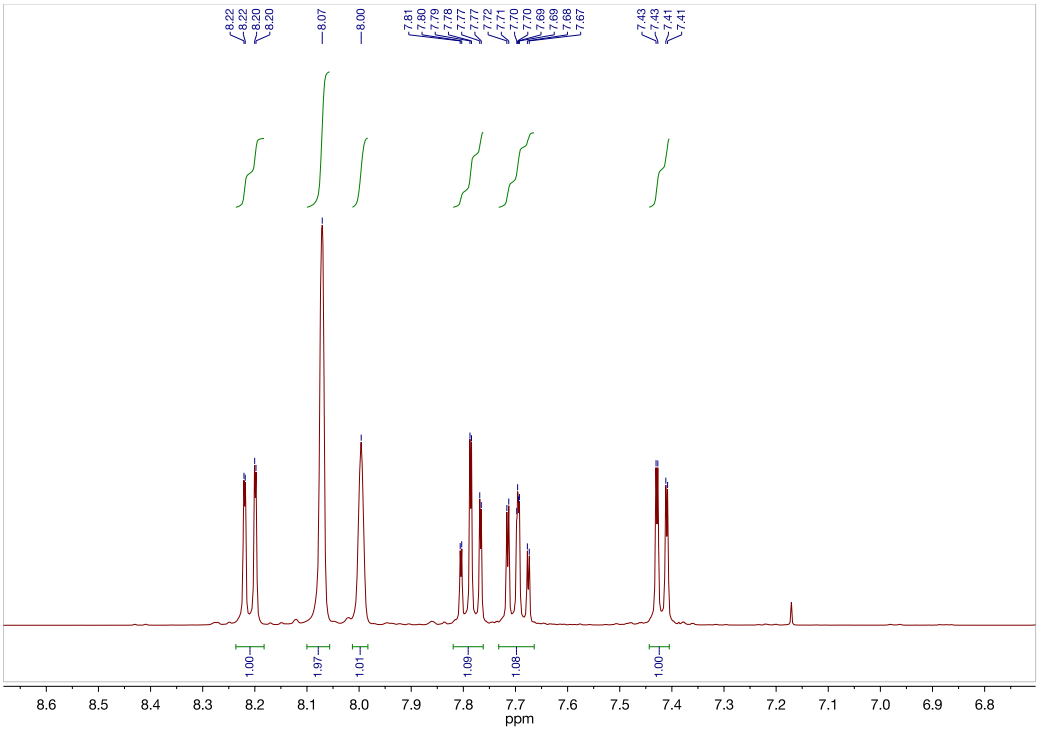


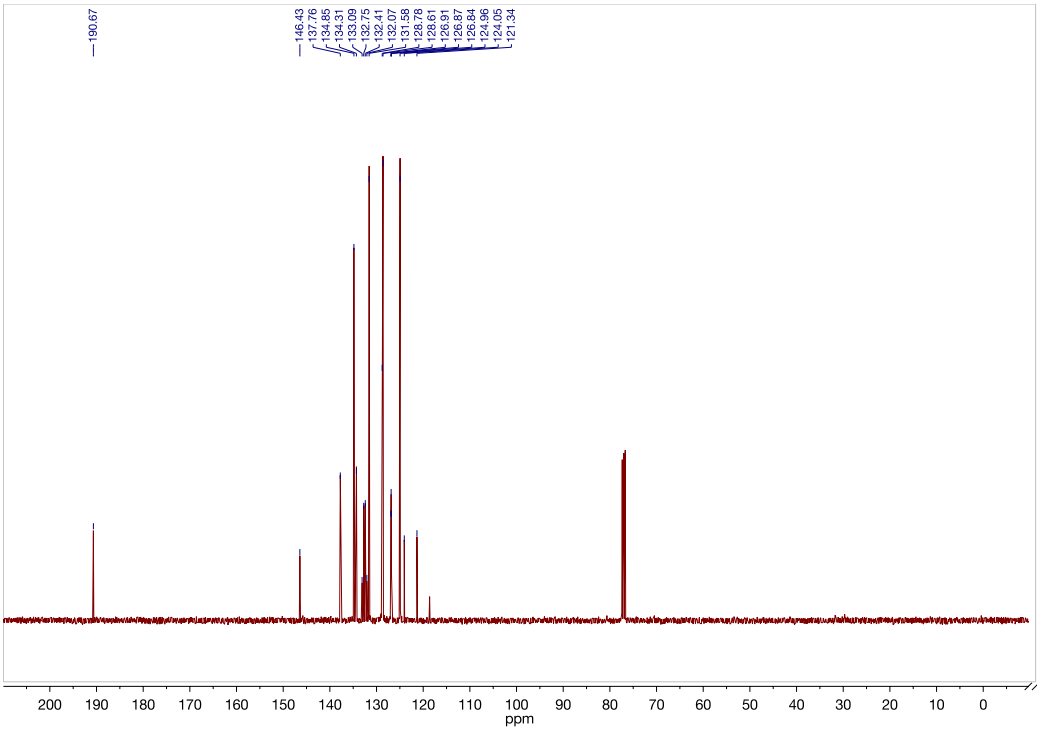




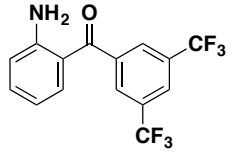
[3,5-Bis(trifluoromethyl)phenyl](2-nitrophenyl)methanone, 323

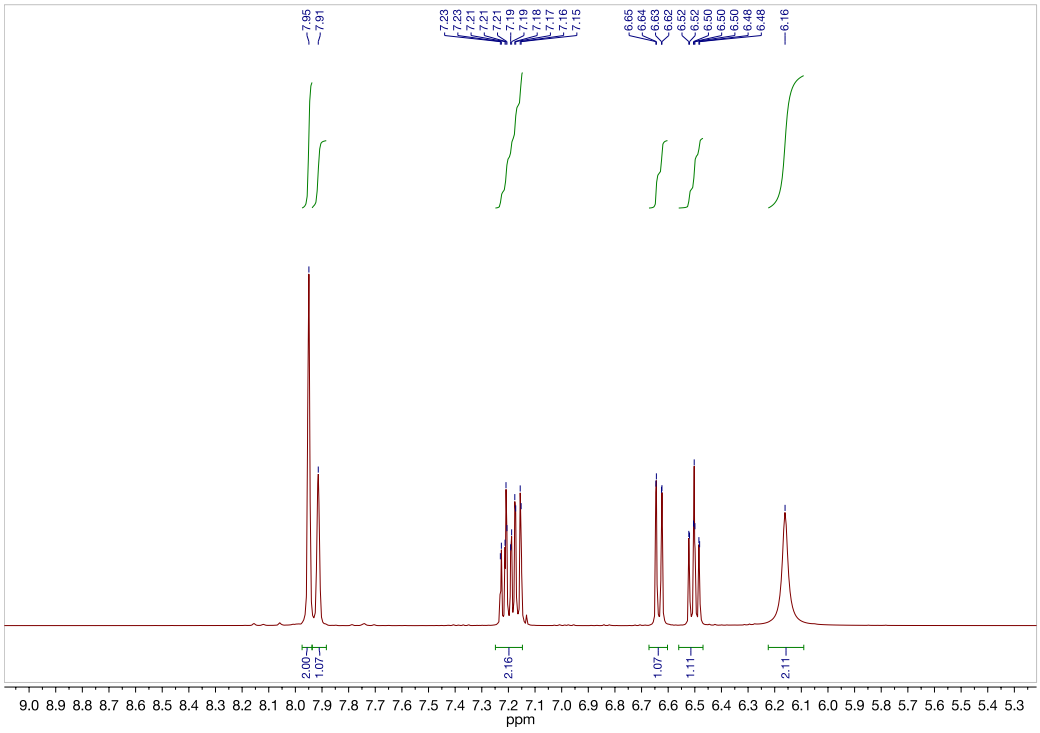


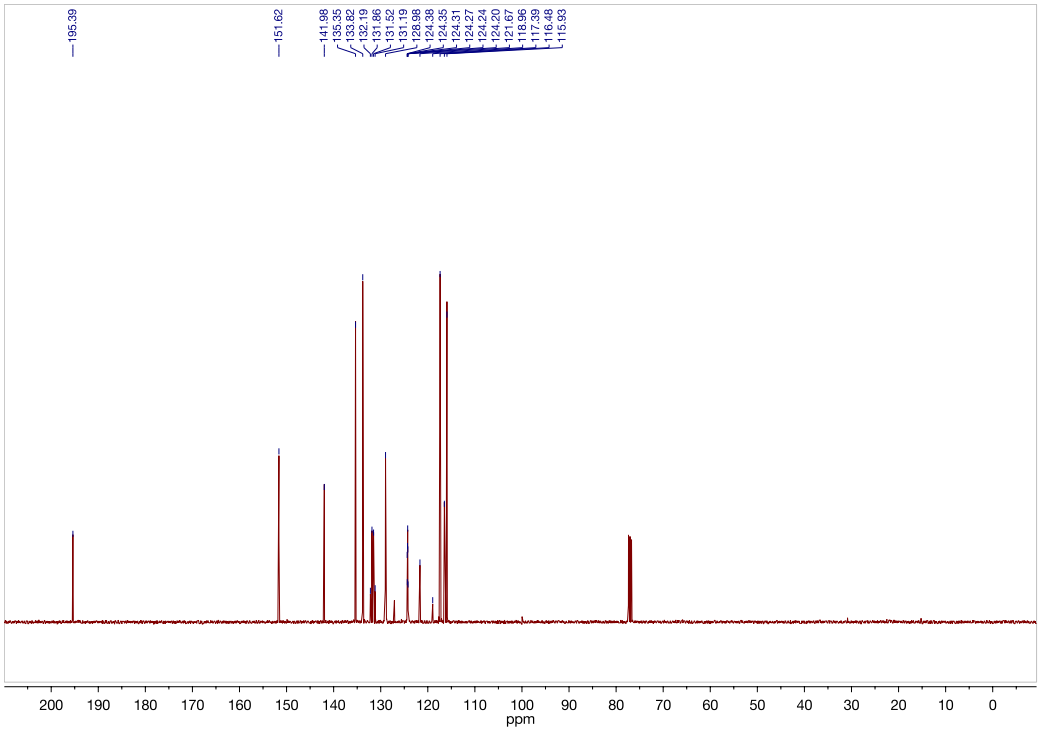




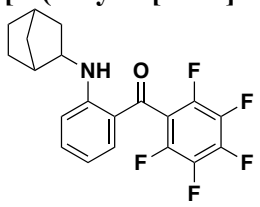
(2-Aminophenyl)[3,5-bis(trifluoromethyl)phenyl]methanone, 325

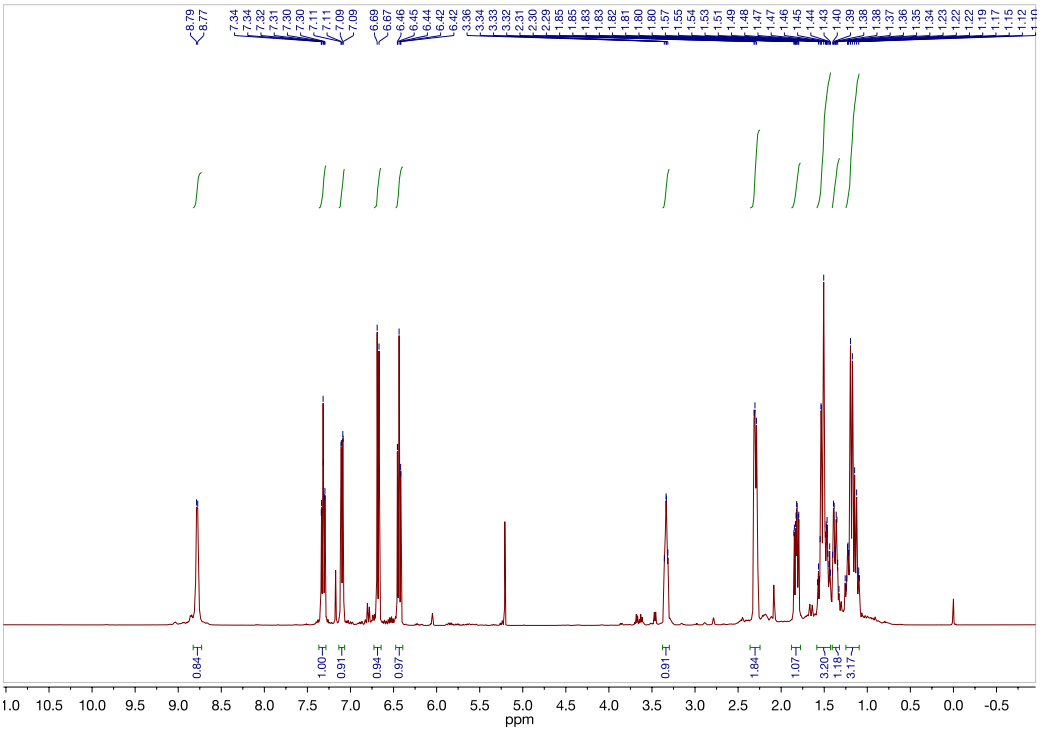


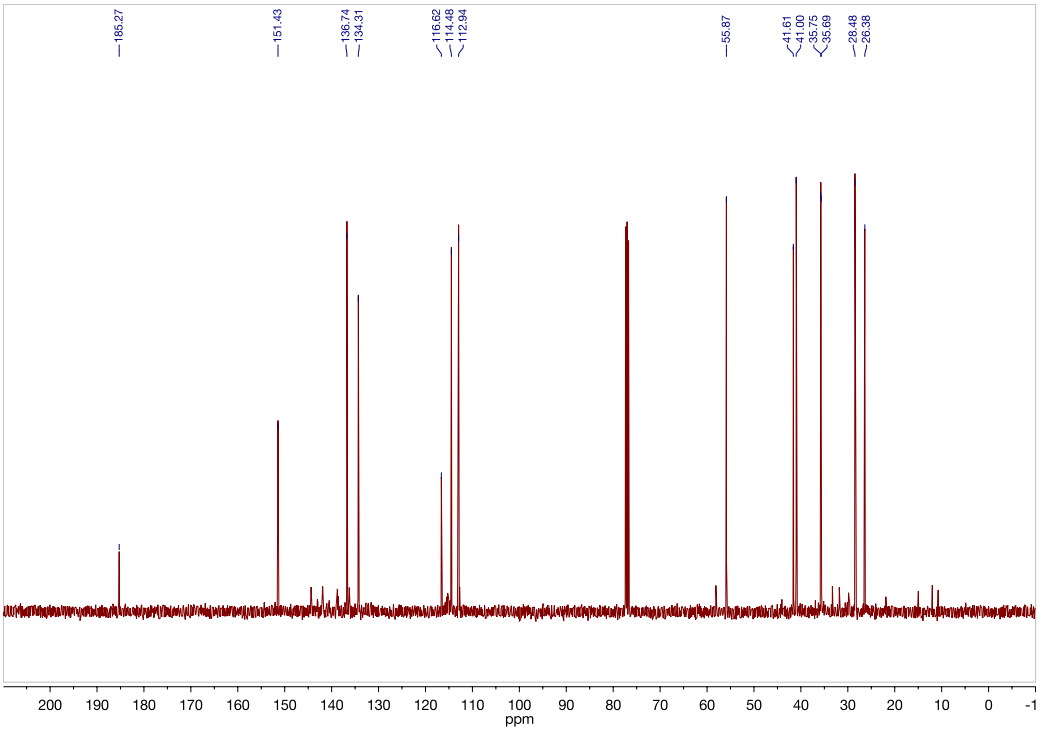




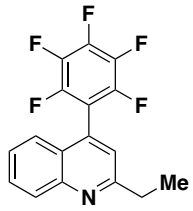
[2-(Bicyclo[2.2.1]heptan-2-ylamino)phenyl](perfluorophenyl)methanone, 326

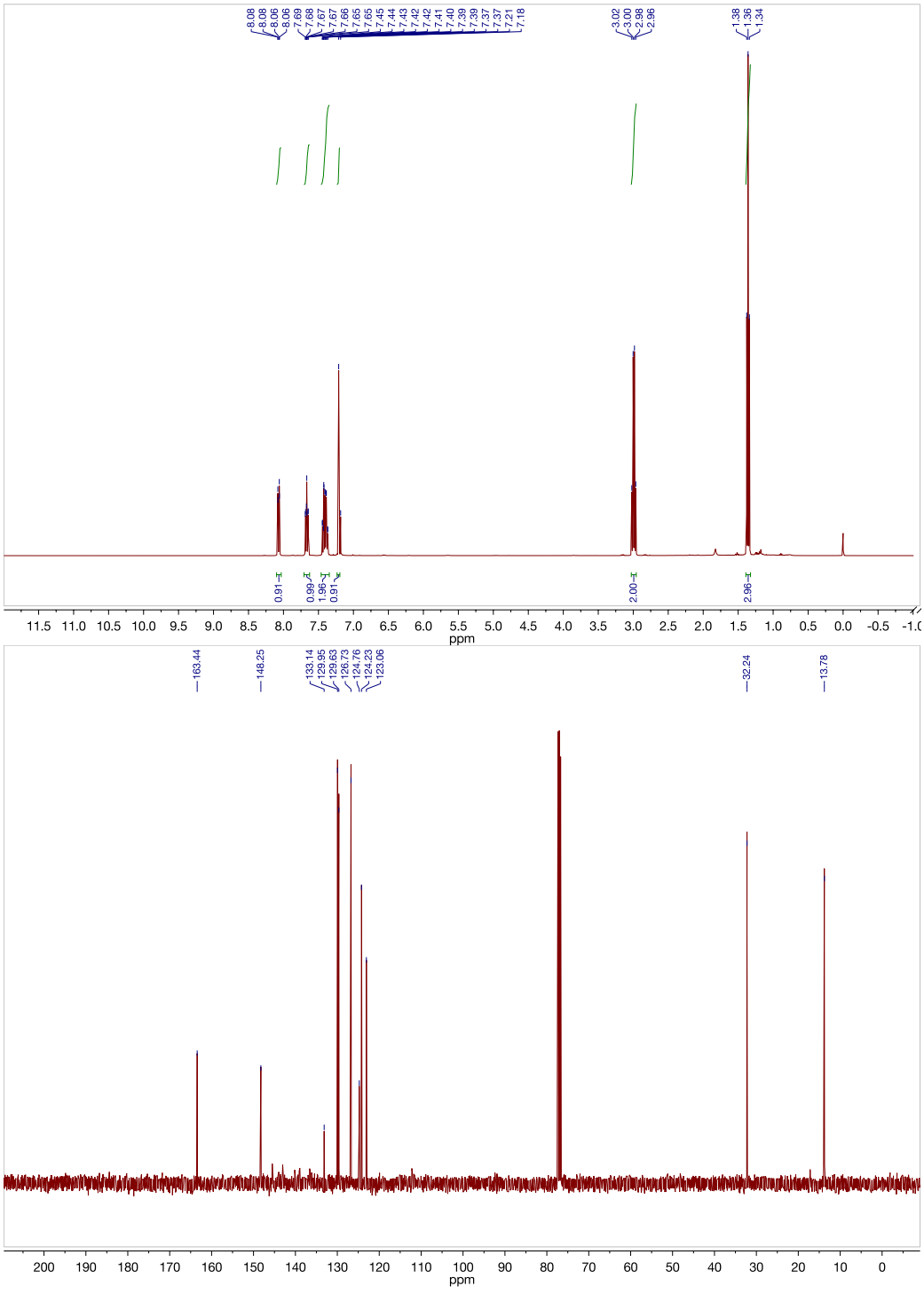




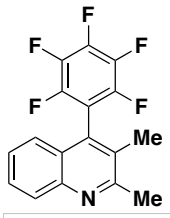


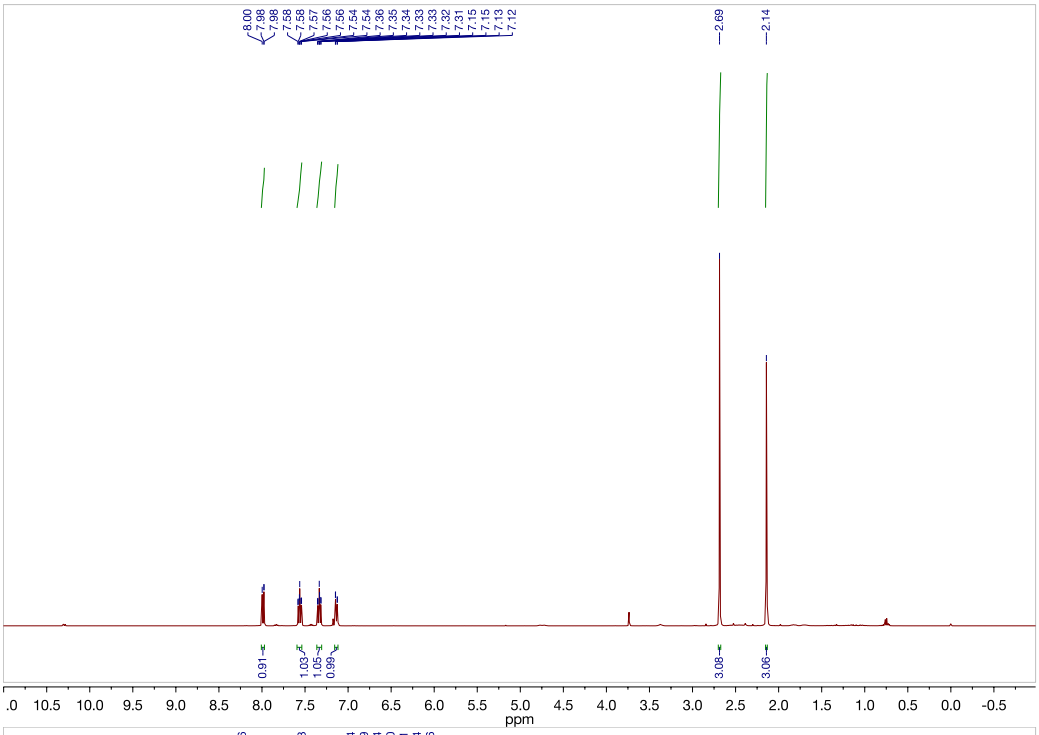
2-Ethyl-4-(perfluorophenyl)quinoline, 327

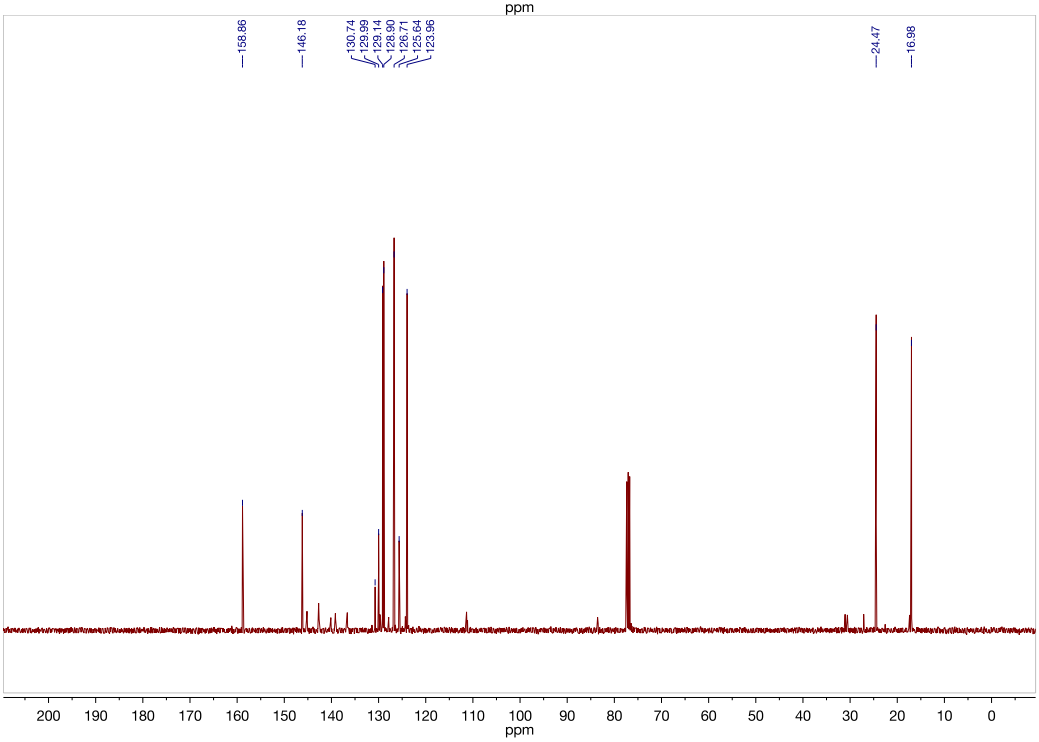




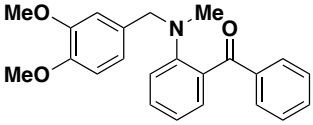
2,3-Dimethyl-4-(perfluorophenyl)quinoline, 328

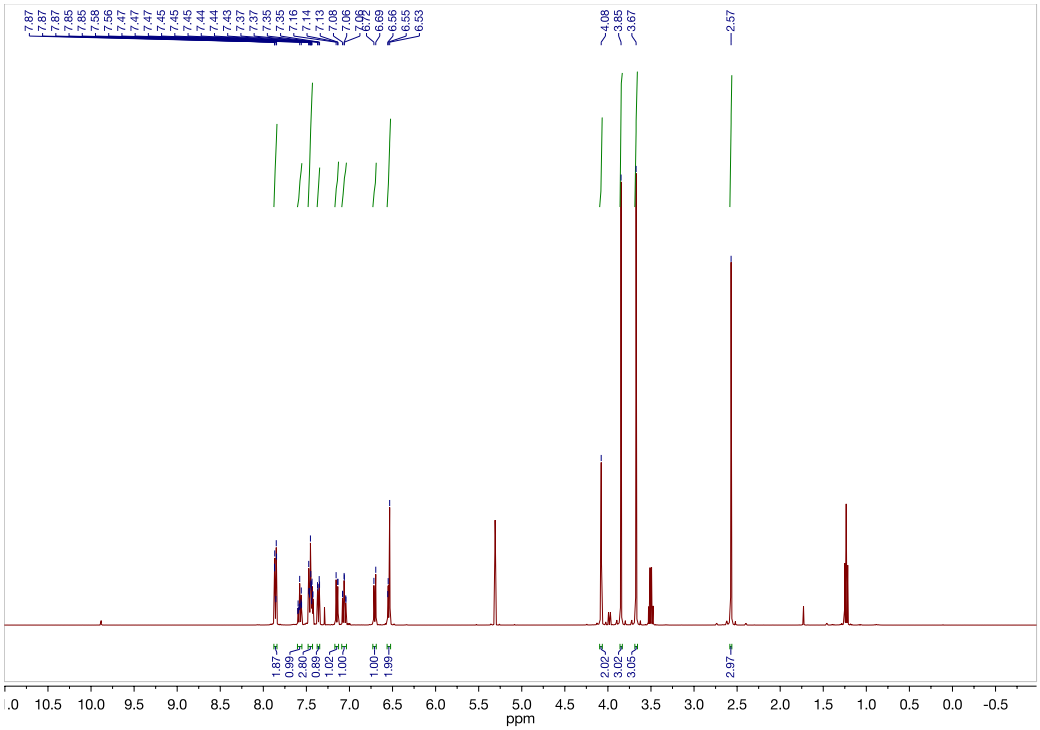


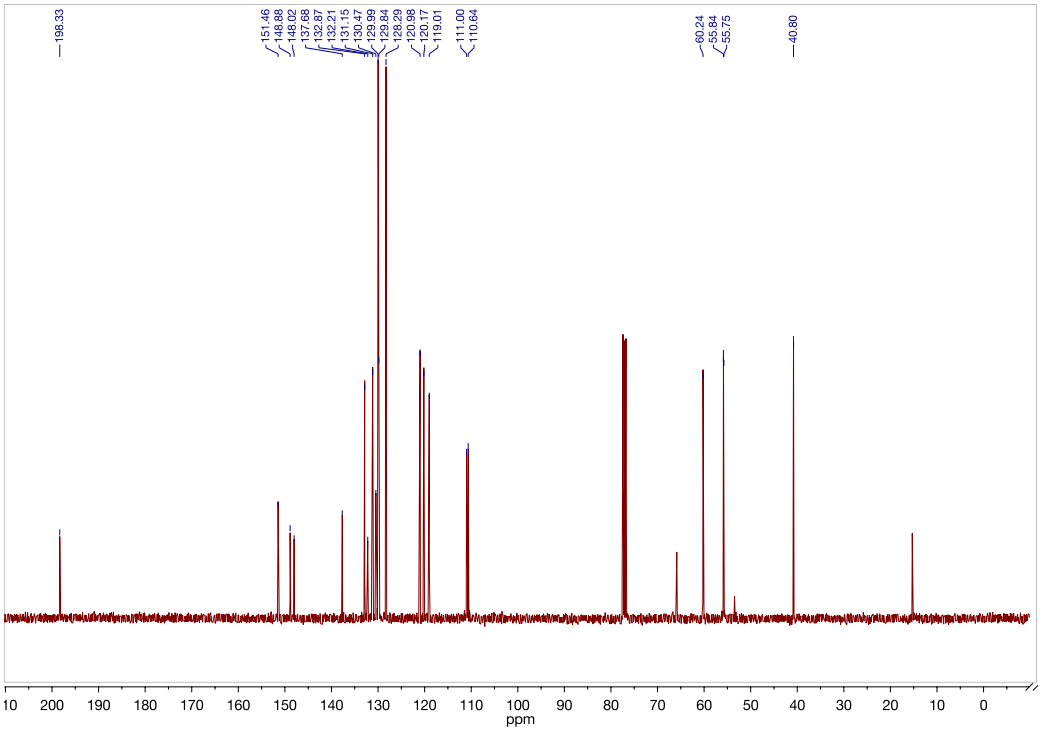




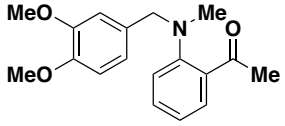
{2-[(3,4-Dimethoxybenzyl)(methyl)amino]phenyl}(phenyl)methanone, 331

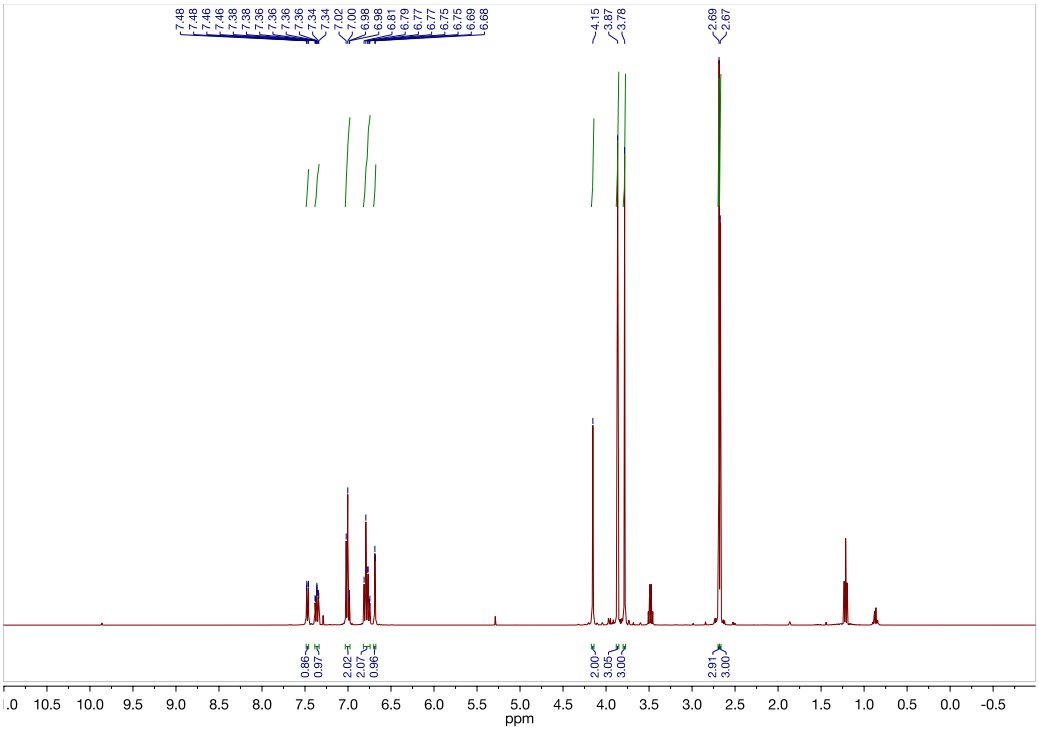


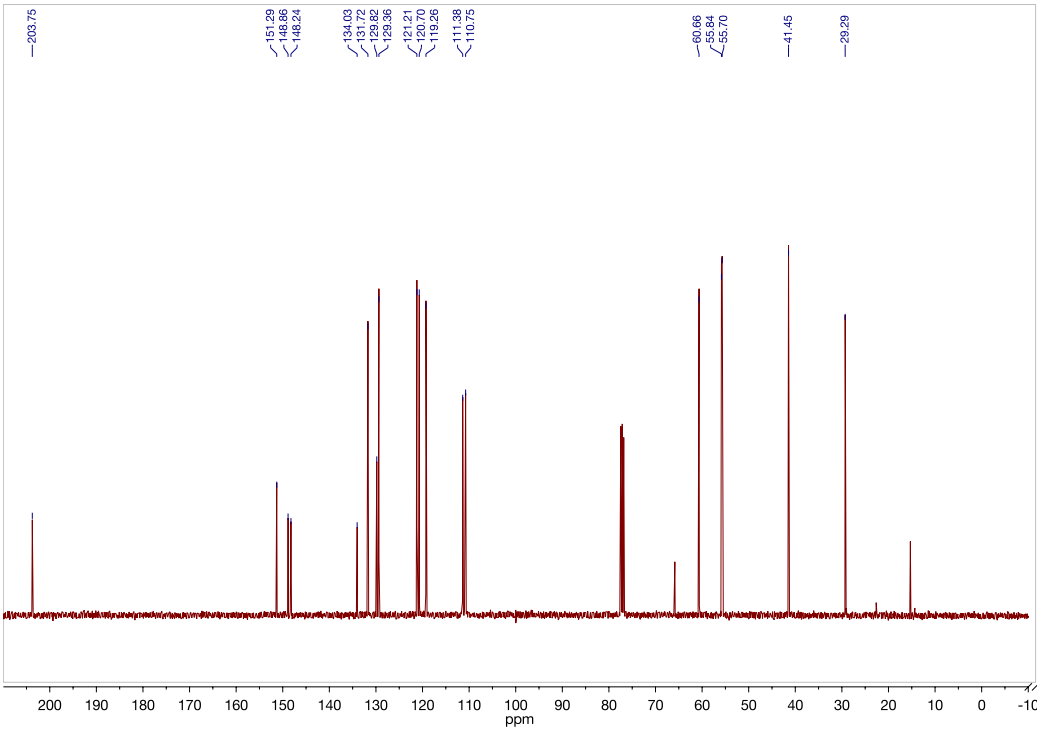




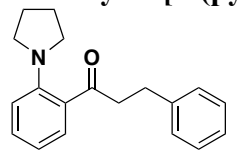
1-{2-[(3,4-Dimethoxybenzyl)(methyl)amino]phenyl}ethan-1-one, 332

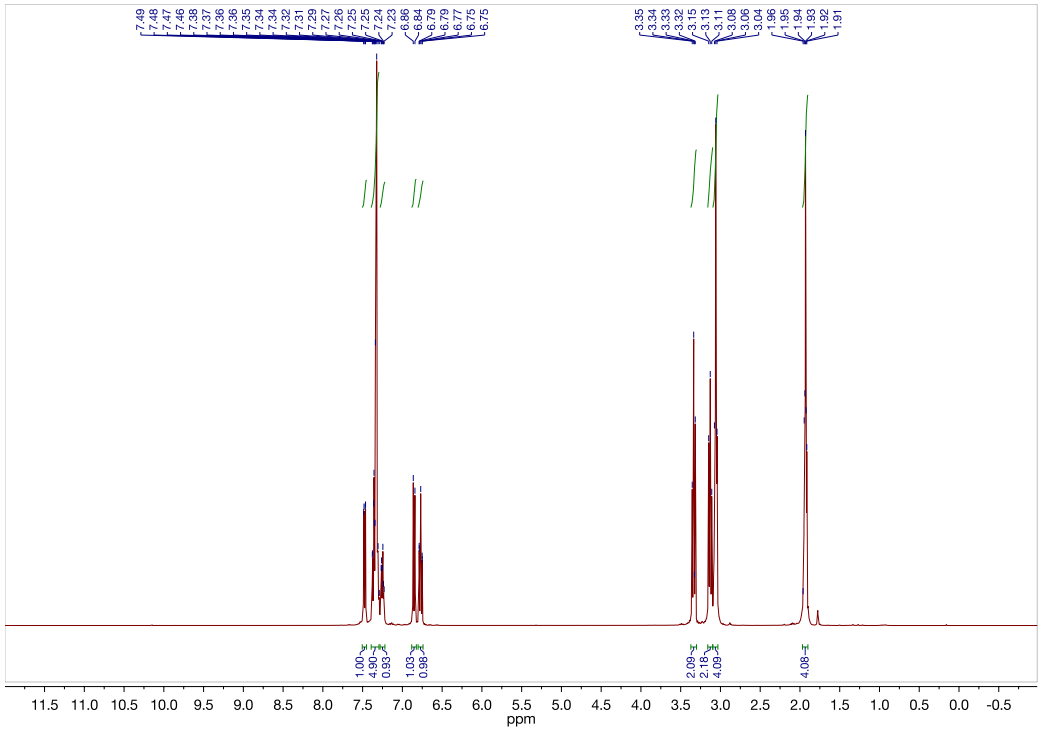


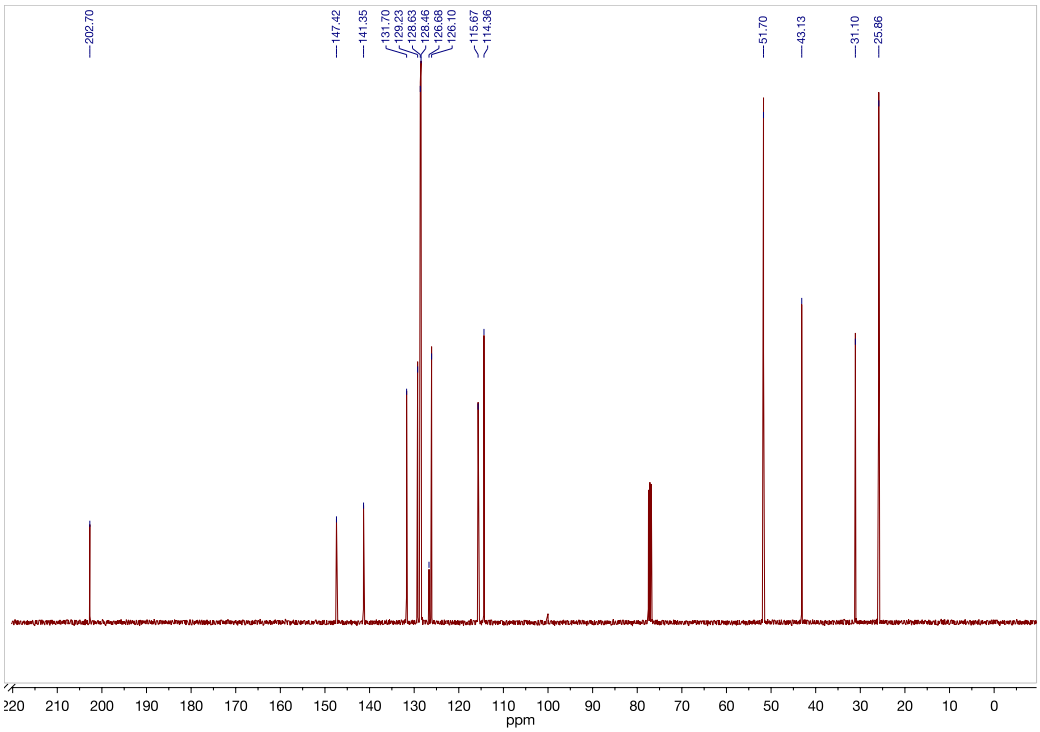




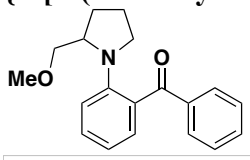
3-Phenyl-1-[2-(pyrrolidin-1-yl)phenyl]propan-1-one, 339

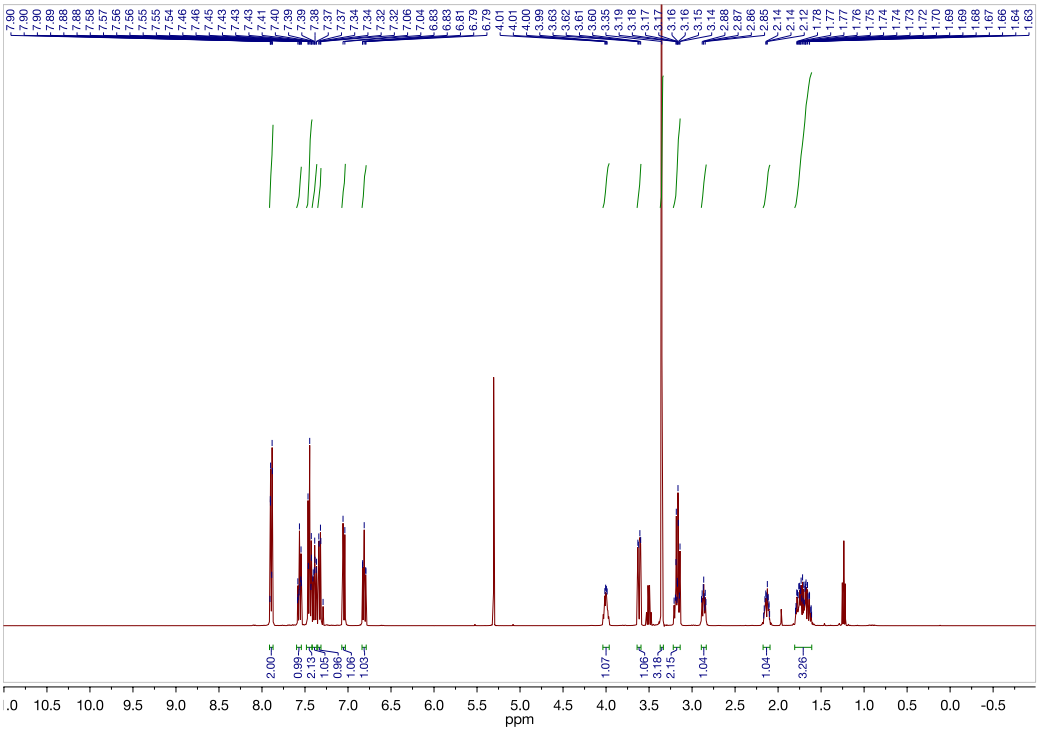


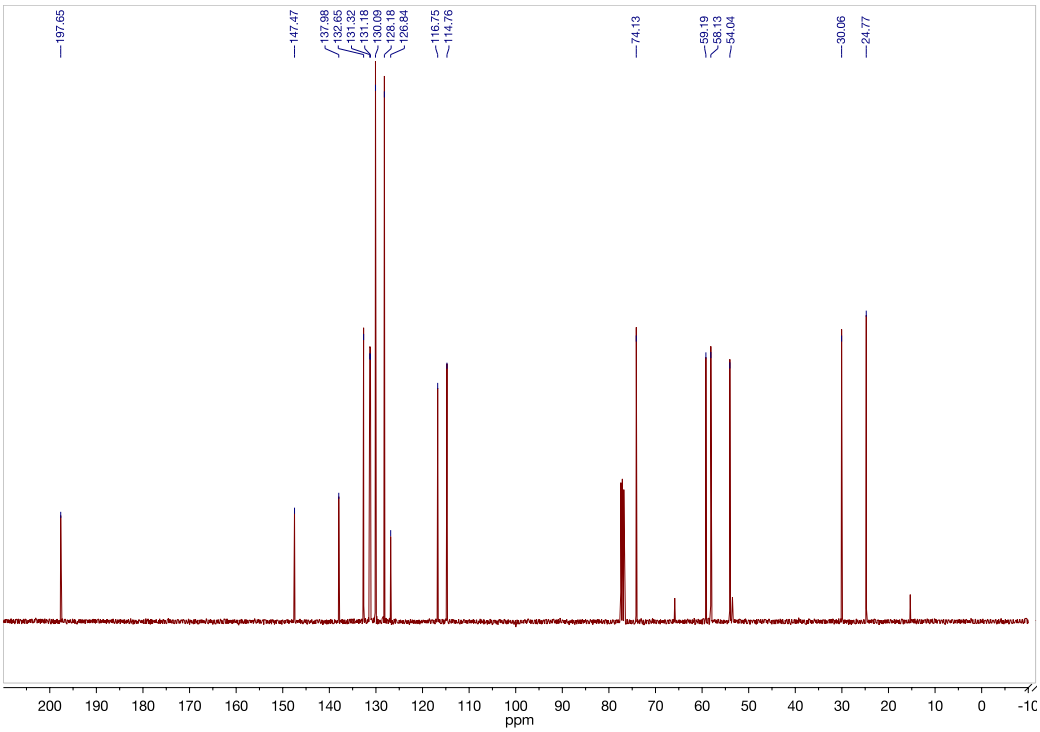




{2-[2-(Methoxymethyl)pyrrolidin-1-yl]phenyl}(phenyl)methanone, 341







Phenyl{2-[2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]phenyl}methanone, 342