Phyllostictine A Ring Assembly via Ring Closing Metathesis

by

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Contents

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Declaration

Except where clearly indicated, the work reported in this thesis is an account of my own independent research at the University of Warwick, carried out between October 2010 and September 2014.

The research reported in this thesis has not been submitted, either wholly or in part, for a degree at another institution.

Abstract

This thesis describes work focused on the chemical synthesis and herbicidal activity of the natural product phyllostictine A, a molecule of unique structure and unknown mode of action.

Chapter 1 serves to introduce the natural product and describe the known activity of the natural product. Furthermore, it discusses literature methods for the construction of α-methylene-β-lactams, a key component of phyllostictine A.

Chapter 2 describes work towards the construction of the macrocyclic rings found in phyllostictine A. As a result α-methylene-β-lactams have been shown, for the first time, to participate in RCM reactions. Formation of 11- and 12-membered trisubstituted membered rings was possible, however, the nature of the nitrogen substituent has a large impact. For example, 12-membered rings **124, 130** were formed in 37% yield when a para-methoxyphenyl group was utilised, while simple ethyl substitution could only achieve yields of 20%. Boc protected lactam **169** produced only linear dimer **170**. The synthesis of tetrasubstituted alkenes via RCM was attempted with lactam **145**, however, resulted in an unexpected rearrangement product. Not only was the RCM sensitive to the nitrogen substituent but also the size of ring being formed. For example, 11-membered rings produced significant amounts of the 22-membered dimers **89** and **87**. Throughout the RCM reactions performed in this thesis held a preference for the *Z*-alkene. The trend was confirmed both by NMR shift analysis and X-ray crystallography.

Chapter 3 describes work towards the synthesis of 4,4-disubstituted α-methylene-β-lactam subunit of phyllostictine A. Three methods: epoxide rearrangement, carbonylation of methyleneaziridines and carbonylation of 2-bromo-allyl-propenes were explored.

Chapter 4 describes the herbicidal activity of phyllostictine A against the single celled algae *C. reinhardtii*. ED_{50} data was obtained for phyllostictine A against *C. reinhardtii* for the first time. Furthermore, it was shown to be comparable to the commercial herbicide glyphosate. Six novel α-methylene-β-lactams synthesised in Chapter 2 were tested for herbicidal activity against *C. reinhardtii* which has enabled us to develop preliminary structure-activity relationships.

Abbreviations

Ac	Acetyl
Bn	Benzyl
Boc	tert-Butoxycarbonyl
CAN	Ceric ammonium nitrate
COSY	Correlation spectroscopy
CSA	Camphorsulfonic acid
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBN	1,5-Diazabicyclo[4.3.0]non-5-ene
DBU	1,8-Diazabicycloundec-7-ene
DCC	N,N'-Dicyclohexylcarbodiimide
δ	Chemical shift
DFT	Density functional theory
DIBAL	Diisobutylaluminium hydride
DMAc	Dimethylacetamide
DMAP	4-Dimethylaminopyridine
DMF	N,N'-Dimethylformamide
DMSO	Dimethyl sulfoxide
dppp	1,3-Bis(diphenylphosphino)propane
ED_{50}	Effective dose needed to kill 50% of the population
EDC	N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide
ee	Enantiomeric excess
EI	Electron Impact
ESI	Electrospray Ionisation
Et	Ethyl
FT-IR	Fourier Transform-Infrared
h	Hours
HMBC	Heteronuclear Multiple Bond Connectivity
HMPA	Hexamethylphosphoramide

HMQC	Heteronuclear Multiple Quantum Coherence
HOBt	1-Hydroxybenzotriazole
HPLC	High-Performance Liquid Chromatography
HRMS	High-Resolution Mass Spectroscopy
LDA	Lithium diisopropylamide
m/z	mass to charge ratio
mCPBA	meta-Chloroperoxybenzoic acid
Me	Methyl
Ms	Methanesulfonyl
NBS	*N*-Bromosuccinimide
NMM	4-Methylmorpholine
NMR	Nuclear Magnetic Resonance
nOe	Nuclear Overhauser Effect
NOESY	Nuclear Overhauser Effect Spectroscopy
OD_{750}	Optical density at 750 nm
PCC	Pyridinium chlorochromate
PMB	p-methoxybenzyl
PMP	p-methoxyphenyl
ppm	Parts per million
TBAI	Tetra-*N*-butylammonium iodide
TBCHD	2,4,4,6-Tetrabromo-2,5-cyclohexadienone
TMEDA	Tetramethylethylenediamine
TMS	Trimethylsilyl
Ts	para-Toluenesulfonyl
Xantphos®	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
Xphos®	2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl

Chapter 1

Introduction

This thesis is focused on the synthesis and herbicidal activity of compounds related to the natural product phyllostictine A, isolated from the pathogenic fungus *Phyllosticta cirsii*. Phyllostictine A is an exciting, structurally unique, new herbicide isolated in 2008 by Evidente and co-workers with an unknown mode of action.[1]

The world's population is estimated to reach 8-11 billion by 2050, a 100% increase on 1998 levels.[2] Therefore, securing food for the growing population will continue to be an important issue. The primary problem facing growers, is that, they start from a position of food shortage[3] and the higher yields traditionally gained from successful hybrid farming are not increasing fast enough to ensure enough food in the years ahead.[4] The birth of industrial agriculture in the 19th century created its own set of problems including; soil erosion, nutrient deficiencies, soil disease and an increase in pests.

Of the problems faced by growers, weeds have the biggest impact on crop yields. Not only do herbicides increase the obtainable yield, they also reduce the overall losses.[5] Many methods of crop protection have been used throughout history. Hand weeding is the most effective, however, this is very labour intensive and gradually its use has declined. By the 1970's only 5% of weeds were controlled by hand, with methods such as chemical crop protection taking over (Table 1.1). There are now over 300 registered active compounds used in crop protection spanning 25 modes of action. However, due to misuse of these compounds weeds are now resistant to 148 herbicides and 84% of the known modes of action, and reports of herbicide resistance increase year on year. Further compounding the problem, no new herbicidal modes of action have been discovered in the last 20 years.[6]

In the search for new effective herbicides with new modes of action, natural products are an attractive area of study since they are are often structurally novel, selective, require lower dosing and degrade to become environmentally benign.[7]

Table 1.1

Year	% Control of weeds by year in USA			
	Human Energy	**Animal Energy**	**Mechanical Energy**	**Chemical Energy**
1920	40	60	–	–
1947	20	10	70	–
1975	5	trace	40	55
1990	<1	trace	24	75

1.1 Natural Products in Crop Protection

A Lithica poem from c. 400 B.C. announces "All the pest that out of earth arise, the earth itself the antidote supplies."[8] Early reports such as this highlight the long history natural products have had in crop protection. For example, Pliny the elder $(23-79$ A.D.) describes in a document on agricultural practices the use of oils for controlling pests.[8] After the agricultural revolution, powdered *Chrysanthemum* heads were used to control insects. The active natural product was later found to be pyrethrum, which has been commercialised today as the insecticide Raid (Figure 1.1). The sheer diversity of structures that natural products provide has allowed several of them to be commercialised either directly or as derivatives with improved activity, stability and physicochemical properties. For example, the fungus derived strobilurin A had the acrylate portion of its structure optimised to the commercial fungicide Amistar by Syngenta (Figure 1.1).[9] Furthermore, the oil of the Myrtaceae shrub leptospermone has been optimised and commercialised into the broad spectrum herbicide Callisto by Syngenta (Figure 1.1).[10]

1.2 Pathogenic fungas *Phyllosticta*

Phyllosticta is a genus of phytopathogens that cause leaf spot symptoms and fruit diseases to an range of hosts, including some economically important crops like citrus,[11] banana, apple and grapes.[12] The *Phyllosticta* species cause necrotic lesions generally, circular, small and 1-2 mm in diameter. After infection, the leaf becomes dry in the centre of the lesion, ultimately, the infected portion falls out and creates a hole.
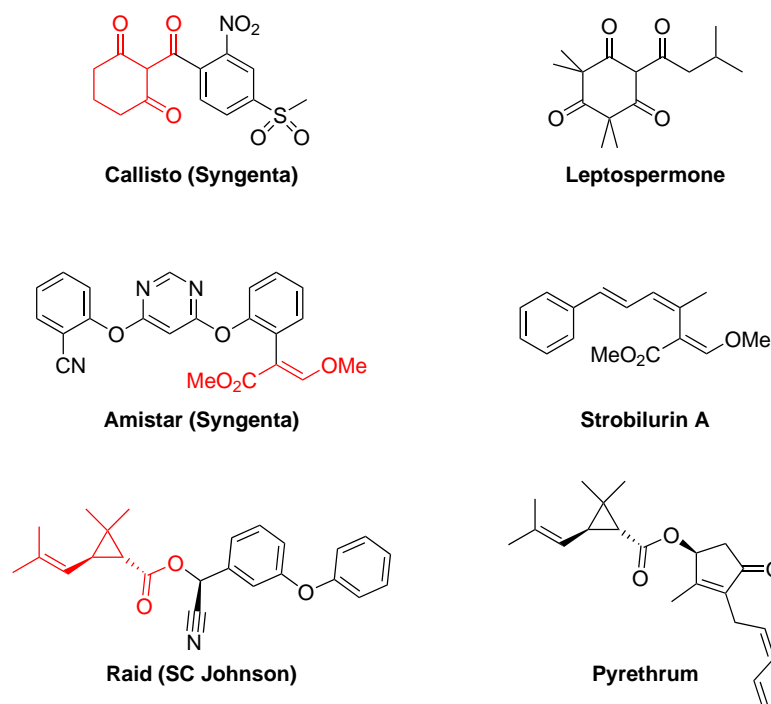
Callisto (Syngenta)

Leptospermone

Amistar (Syngenta)

Strobilurin A

Raid (SC Johnson)

Pyrethrum

Figure 1.1

Whilst these effects are caused by herbicidal metabolites, other biologically active metabolites have been isolated from various *Phyllosticta* species. For example, taxol (entry 8, Table 1.2) a potent anti-cancer drug, and brefeldin (entry 1, Table 1.2) a well studied antibiotic.

Table 1.2

Entry	Compound	Properties	Taxa	Ref.
1	Brefeldin	Bioactive metabolite	*P. medicaginis*	13
2	Phyllosinol	Bioactive metabolite	*Phyllosticta. sp., P. maydis*	14
3	Phyllostictine	Mycoherbicide, anti-cancer	*P. cirsii*	1,15
4	Phyllostin	Anti-microbial	*P. cirsii*	16
5	Phyllostoxin	Mycoherbicide	*P. cirsii*	16
6	PM-toxin	Mycoherbicide	*P. maydis*	17
7	Tauranine	Anti-cancer activity	*P. spinarum*	18
8	Taxol	Anti-cancer activity	*P. tabernaemontanae*	19
9	Phyllospinarone	Inhibition of cell proliferation	*P. spinarum*	18

1.2.1 *Phyllosticta cirsii*

The genus of *Phyllosticta* has not been thoroughly studied, however, *Phyllosticta cirsii* has yielded a variety of useful compounds, resulting from initial investigations into the use of *P. cirsii* as a biocontrol for Canada thistle.[20] It was this initial discovery as a potential biocontrol, that lead to the eventual isolation of the active metabolites phyllostin, phyllostoxin and the phyllostictines (Figure 1.2).
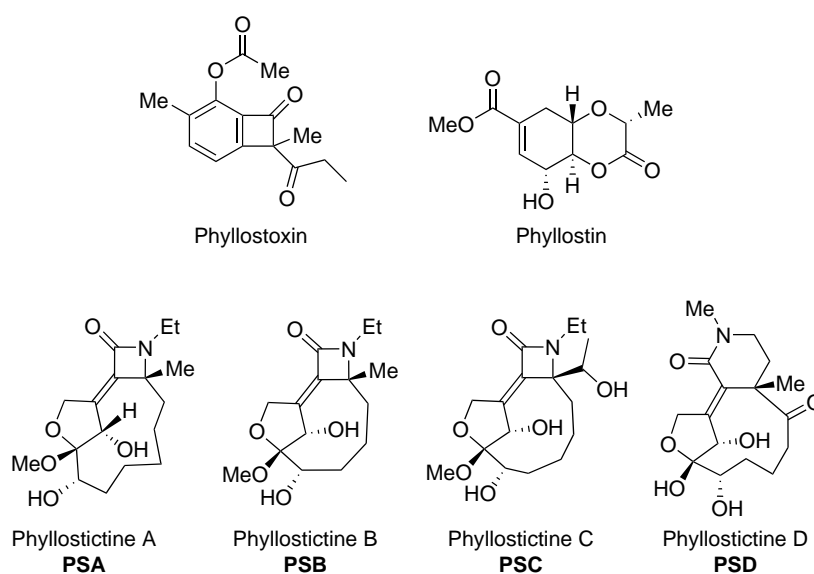

Phyllostoxin

Phyllostin

Phyllostictine A
PSA

Phyllostictine B
PSB

Phyllostictine C
PSC

Phyllostictine D
PSD

Figure 1.2

1.3 Phyllostictines

The phyllostictines are a family of four natural products isolated in 2008 by Evidente and co-workers (Figure 1.2). They were isolated from the filtrate cultures of *Cirsium arvense* (L.) infected with *P. cirsii*. Also known as Canada thistle, *C. arvense* is a potent weed native to the Mediterranean, that has colonised most of the world, and can reduce wheat yields by up to 45%.[21]

1.3.1 Isolation and Structural Identification

The organic extract of the liquid culture (7.7 L) of *P. cirsii* had high phytotoxicity. Extensive purification using a combination of column chromatography and thin layer

chromatography provided four metabolites, phyllostictines A-D, containing an oxaza-tricycloalkenone ring system (Figure 1.2). Their unique structures were characterised primarily by a combination of ^1H and ^{13}C-NMR spectroscopy.

Phyllostictine A was found to have an initial molecular formula of $C_{17}H_{27}NO_5$, consistent with five double bond equivalents. The lactam carbonyl and tetrasubstituted alkene were identified by NMR and IR spectroscopy. The IR also identified hydroxyl groups, with the UV spectrum offering evidence of an α,β-unsaturated lactam. The Et group on the nitrogen of the lactam was easily identified by a triplet at 0.83 ppm which was coupled to a methylene at 1.30 ppm.
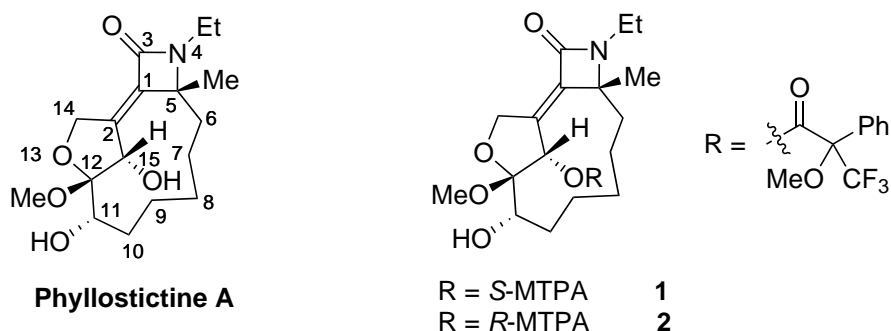

Phyllostictine A

R = *S*-MTPA   **1**
R = *R*-MTPA   **2**

Figure 1.3

The absolute stereochemistry at C-15 was determined by the Mosher's method (Figure 1.3). Reaction of phyllostictine A with *R*-(−)-α-methoxy-α-trifluoromethylphenylacetyl (MTPA) and *S*-(+)-MTPA chlorides yielded the di-astereomeric *S*-MTPA and *R*-MTPA esters respectively. The comparison of these esters with phyllostictine A gave the following differences in ppm [Δδ(**1**−**2**): H-11 +0.07; H$_2$-10 + 0.17; H-9 + 0.24; H-9' + 0.13]. This allowed assignment of the *S*-configuration at C-15. NOESY spectroscopy was used to identify the geometry of the double bond. H-15 enhanced H-11, OMe and Me-C(5) indicating the depicted *E*-configuration of the tetrasubstituted double bond. This NOESY data was used to assign the relative configuration at C-5, C-11 and C-12 as *R*, *S*, and *S* respectively, to give the final structure seen in Figure 1.3. Although Evidente and co-workers reported phyllostictine

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A as a clear oil, it would clearly be desirable to derivatise it as a crystalline solid, to unambiguously confirm the proposed structure by X-ray crystallography.

1.3.2 Biological Activity

The four phyllostictines were tested in a leaf puncture assay, with isolated leaves of Canada thistle. All were tested at a concentration of approximately 6 mM. The leaves were kept moist for 3 days, at which time necrosis was seen. Phyllostictine A was found to have the greatest activity (entry 1, Table 1.3) having necrosis of >5 mm. Phyllostictines B and D had necrosis between 3-5 mm (entries 2 and 4, Table 1.3). Phyllostictine C showed no activity (entry 3, Table 1.3) at this concentration. From these results, Evidente and co-workers proposed a structure-activity relationship based on conformational freedom, and activity. They suggested that the lactam, and its nitrogen substituent is not the origin of the activity.

Table 1.3

Entry	Phyllostictine	Toxicity[a] (20 μL 6 mM)
1	A	++++
2	B	+++
3	C	−
4	D	+++

[a]scale: −, non toxic, +++, necrosis 3-5 mm, ++++, necrosis >5 mm

Additional biological screens were undertaken. Phyllostictines A and B were tested for anti-fungal activity against *Geotrichum candidum*, however, even at concentrations as high as 100 μg/disk, they were completely inactive. Anti-bacterial activity was also investigated. Against *Lactobacillus* (Gram+) bacteria, phyllostictine A was active at 5 μg/disk, whilst even when tested at 100 μg/disk, it was inactive against *Escherichia coli* (Gram−). Finally, phyllostictine A caused total mortality of *Artemia salina* (brine shrimp) at 10^{-3} M whilst phyllostictine B produced negligible activity.

Since phyllostictine A was the most active member of the family it was taken forward for further investigation. A report by Zonno disclosed optimised phyllostictine

A production of 28 mg/L.[22] Phyllostictine A, furasic acid (a well known fungal toxin), and the broad spectrum herbicide glyphosate were tested against isolated protoplasts of *C. arvense* and tobacco leaf. Phyllostictine A at 10^{-3} M was shown to be faster acting than glyphosate at 4.2^{-3} M in both assays, causing 100% inhibition (relative to the control) after 6 h.[22]

The activity appears to be time dependent, for example, after 1 h in the thistle protoplast assay, phyllostictine A at 5 x 10^{-4} M inhibits 50% of the control but after 6 h this had increased to 100%. The other herbicides tested did not show such a time dependency, with furasic acid and glyphosate inhibiting around 60% and 40% respectively, for the 6 h duration. These assays revealed that phyllostictine A could have a foliar application, and that compared to furasic acid, a potent fungal toxin, it was significantly more effective at similar concentrations (Figure 1.4).

In 2009, Vurro reported additional herbicidal activities of phyllostictine A. Phyllostictine A was shown to inhibit the germination of *Orobanche ramosa* seeds, by 5% at 10 μM, and 28% at 100 μM as a percentage of the control.[7]

In 2011, Kiss and co-workers reported phyllostictine A also has anti-cancer activity. Although it did not discriminate between proliferating cancer and normal cells,[15] it was shown to possess *in vitro* anti-cancer activity against a variety of human cancer cell lines (U373 GBM, A549 NSCLC, Hs683 and SKMEL-28). Potency at the μM level was observed. Furthermore, using mass spectrometry, some evidence for conjugate addition of the thiol of cystine to C-2 of phyllostictine A was presented.

1.3.3   Known β-Lactam Herbicides

The phyllostictines all contain lactams, with A-C containing a β-lactam. β-Lactams are well known for their antibiotic activity, providing the active functionality of the penicillins. However, as far as we are aware, there is only one report of β-lactams inducing
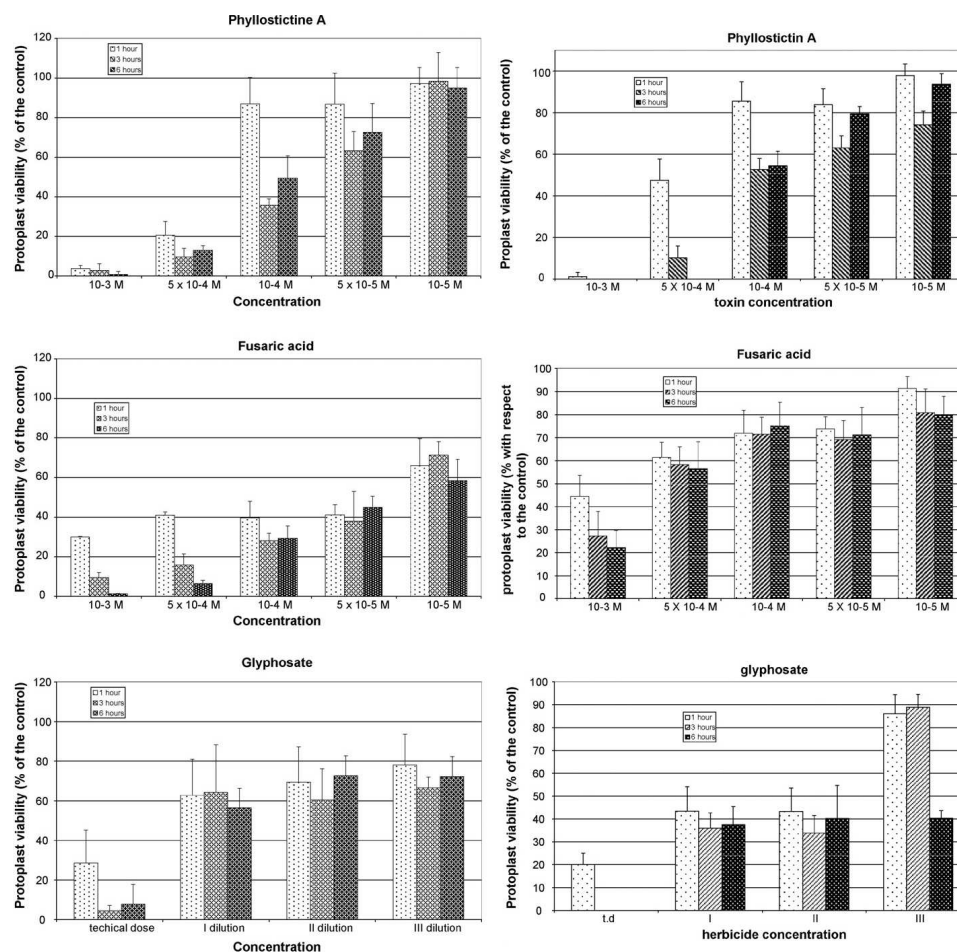
Figure 1.4 – Reproduced from *Plant Sci.*, **2008**, *175*, 818-825.[22]

herbicidal activity. Tabtoxin (**3**) a monobactam metabolite of *Pseudomonas syringae pv. tabaci*, which causes wildfire disease in tobacco. Like the phyllostictines, it has diverse biological activity, being highly toxic to bacteria, algae, higher plants and animals. It has been well studied, with Baldwin reporting the stereospecific total synthesis in 1984[23,24] and Crop Genetics International, patenting its use as a growth regulator and herbicide.[25]
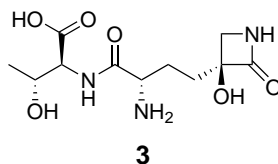

3

Figure 1.5

1.4 Synthesis of α-Methylene-β-Lactams

Methods for the synthesis of α-methylene-β-lactams are quite limited, and those available are reviewed herein being pertinent to the context of this thesis. This section focusses on the major advances in the formation of α-methylene-β-lactams over the last 50 years or so, with isolated examples of α-methylene-β-lactam formation[26–33] not discussed in detail.

The earliest report of their synthesis was by Moriconi and Kelly in 1966 from CSI addition to allenes.[34,35] Use of only a few allenes was surveyed (Scheme 1.1).
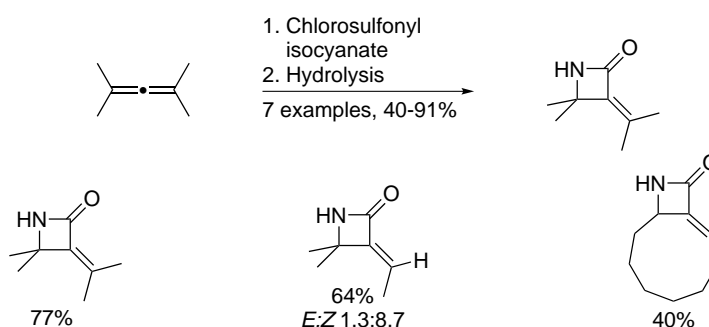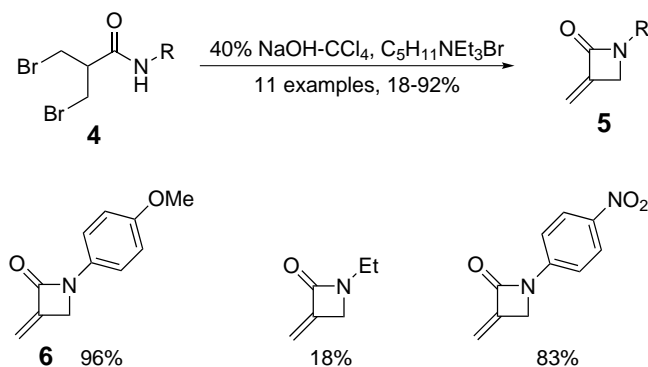

Scheme 1.1

In 1978, three new methods[36–38] for the formation of α-methylene-β-lactams were reported, inspired by detailed reports of the biological activity of α-methylene-β-lactones.[39]

Of these three methods, the most widely explored, was reported by Fletcher and Kay of ICI Plant Protection. In a one-pot process, dibromo amide **4** was converted to **5** under phase transfer conditions (Scheme 1.2).

Some variation in the nitrogen substituents was possible, although yields were lower with N-alkyl derivatives. No examples were reported with substituents at the alkene terminus, or at the saturated ring carbon. The authors reported that lactam **6** rapidly forms adducts with dimethylamine and ethanethiol at room temperature.
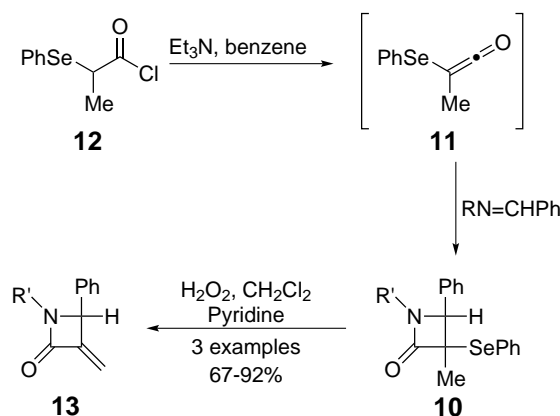
Scheme 1.2

In 1978, Shibuya reported a new synthesis from a preformed β-lactam **7**. The synthesis begins with enolate formation and subsequent capture with TMS-Cl to give silane **8**. Further treatment with LDA followed by addition of a ketone, gives the 3-trimethylsilylcarbinol that undergoes elimination to give lactam **9** (Scheme 1.3). This method enables substitution of the alkene terminus. Ohno would later use this method-ology in the first total synthesis of the α-methylene-β-lactam containing antibiotic asparenomycin C.[27]
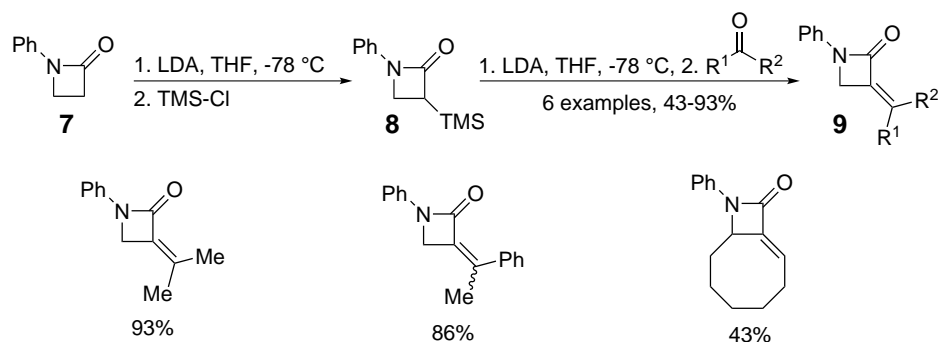
Scheme 1.3

Agawa has reported an alternative method to introduce the exocyclic double bond.[37,40,41] The essential feature of this method is elimination of a sulphoxide or selenoxide, to generate the methylene group. The authors were able to improve upon the initial report which required temperatures >200 °C at reduced pressure with sulphoxides,[37] to milder elimination conditions of refluxing CH_2Cl_2 using the phenylselenoxide. The precursor lactams **10** were derived from a Staudinger reaction of a selenium containing ketene **11**, generated *in situ* from 2-phenylselenopropanoyl chloride (**12**), and subsequent reaction with various imines. Whilst different imines would give the potential for variation at C-4, they only reported phenyl substitution at this position (Scheme 1.4).

Scheme 1.4

After several reports of antibiotics containing α-methylene-β-lactams,[27,42,43] Buynak disclosed several papers on the chemistry of α-methylene-β-lactams.[44–46] His synthesis exploited the silver catalysed rearrangement of propargylic acetates to allenyl acetates. He was able to show through crystallography that the methylene group is conjugated to the amide, due to the coplanarity seen in the structure (Figure 1.6). Furthermore, he explored some of the chemistry related to lactam **14**. For example, the oxidation of **15** with selenium dioxide to form aldehyde **16**, hydrogenation of **14** with PtO_2 forming the *cis* product **17** exclusively, and finally the alkylation of the nitrogen with simple alkyl electrophiles (Scheme 1.5).

The next major breakthrough came with Mori's carbonylation of 2-bromopropenylamine **23**. Looking for a route to rapidly access analogues of monobactams, he discovered the
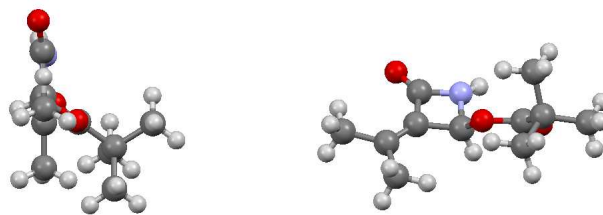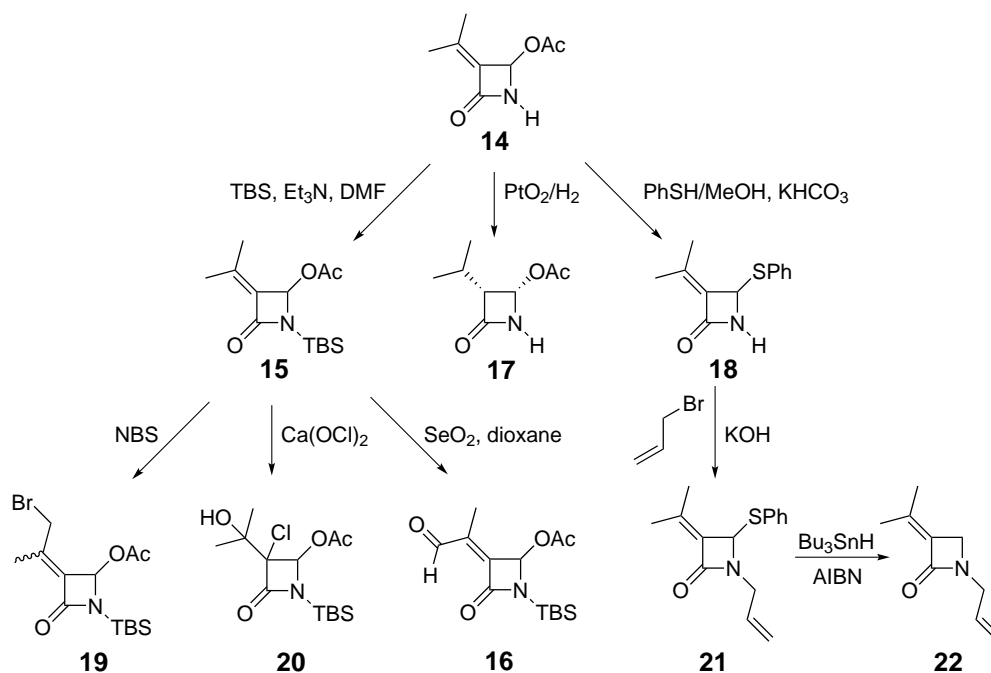
Figure 1.6

Scheme 1.5

palladium catalysed carbonylation of **23** was an efficient route to these molecules. It showed good tolerance for different N-substitutions, and could be extended to include derivatives substituted at either the alkene or C-4. The disadvantage of this method was the need to use highly toxic HMPA. Furthermore, lengthy precursor syntheses and variable yields were observed for lactams substituted at C-4. However, it marked the first instance of α-methylene-β-lactams being formed by transition metal catalysis (Scheme 1.6).

Tanaka showed that allyl stannanes **25** can be converted to the corresponding bromide **26** which can be further ring closed to α-methylene-β-lactams **27**. Yields were consistently good and this method is applicable to chiral substrates. The main limitation of the
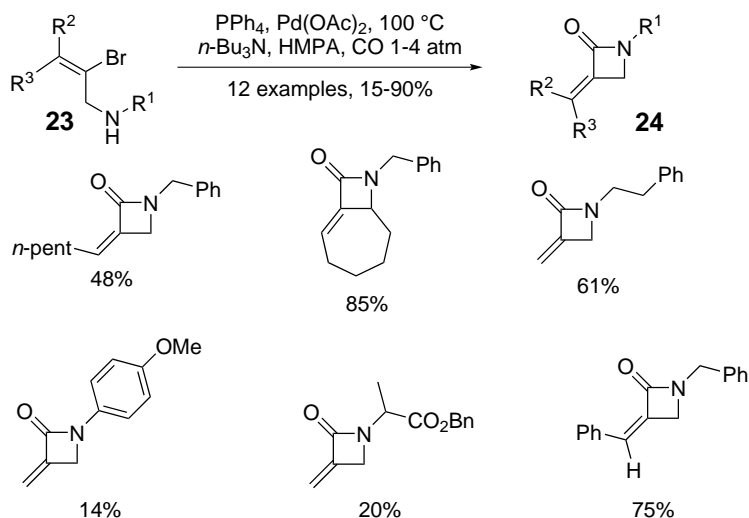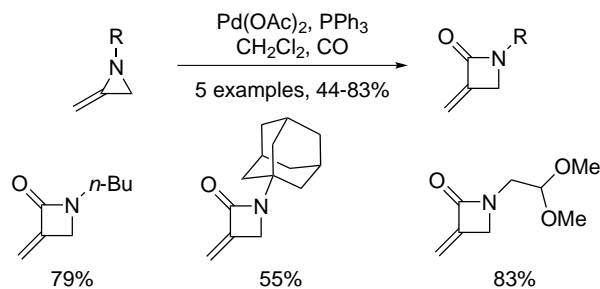
Scheme 1.6

method lies in the synthesis of the allyl stannane precursors (Scheme 1.7).[47]
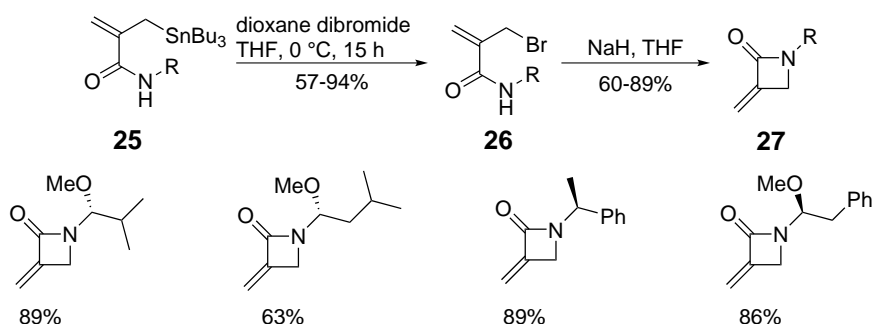
Scheme 1.7

In 1987, Alpa reported the metal catalysed synthesis of α-methylene-β-lactams from methyleneaziridines.[48] Using a palladium catalyst and triphenylphosphine, carbon monoxide inserts regioselectively into the N−C sp^2 bond. Only five examples were reported, and all involved *N*-alkyl methyleneaziridines (Scheme 1.8).

Tanaka[49] in a variation of his previous method, disclosed new methodology for the synthesis of α-methylene-β-lactams. The dianion derived from **28** was added to an aldehyde. After formation of mesylate **29**, the diastereomers were separted by chromatography. Exposure of **29** to TBAF produced lactam **30** as a side product. When **29** was exposed to NaH, **31** was formed in 55-61% yield. Only the phenyl substituted nitrogen is reported, but the potential variation in the initial carbonyl addition should not be
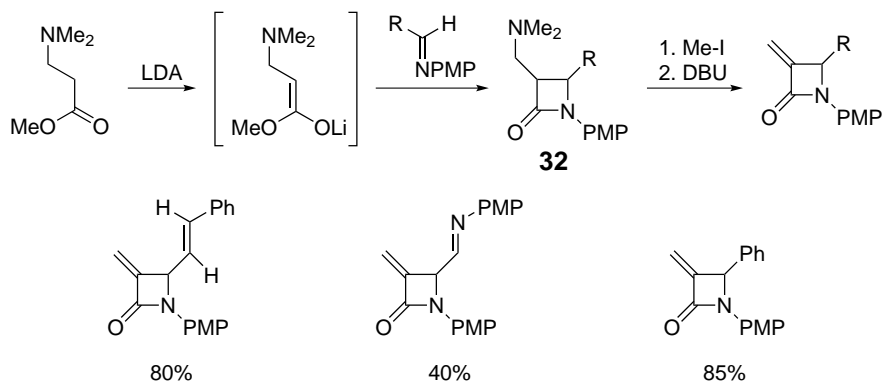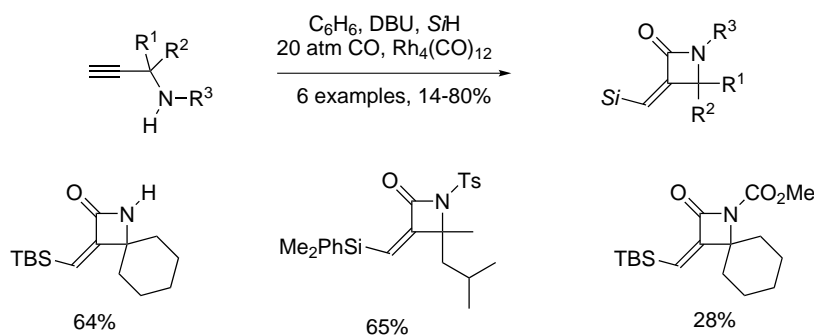
Scheme 1.8

underplayed (Scheme 1.9).
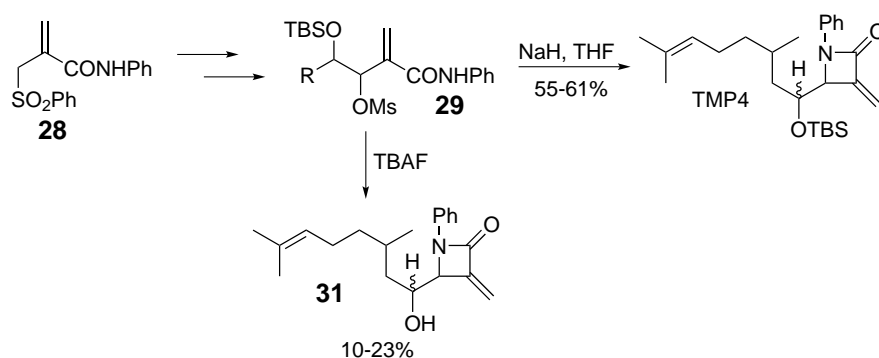
Scheme 1.9

In 1990, Alcaide reported a novel approach to α-methylene-β-lactams based on Staudinger lactam formation.[50,51] The lactam was formed exclusively as the *trans* diastereomer. Amine **32** is converted to the α-methylene-β-lactam by quaternization of the amine with excess methyl iodide, followed by elimination with DBU. The route allows for mono-substitution at C-4 through the imine partner and a few varied examples are illustrated (Scheme 1.10). In 1991, Matsuda[52] and co-workers reported the synthesis of α-silylmethylene-β-lactams by rhodium catalysed carbonylation. Most notably, examples were produced in which C-4 was fully substituted (Scheme 1.11).

Adam and co-workers have reported the synthesis of chiral α-methylene-β-lactams.[53] Racemic **33** was subjected to kinetic resolution using Chirazyme® lipase L-2 (*Candida antarctica*). This precursor **34** was produced in four steps using a simple ring closure strategy (Scheme 1.12). Alternatively, kinetic resolution of **35** with allyl acetate and Chirazyme L-1® (*Burkholderia sp.*) provided resolved acetate **36** which could be hydrol-
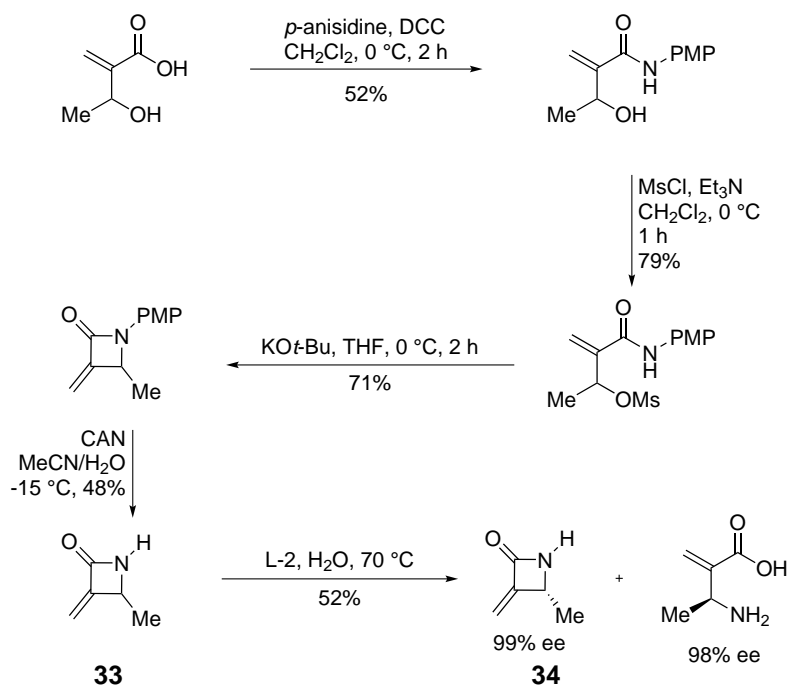
Scheme 1.10

Scheme 1.11

ysed and transformed using Scheme 1.12 to yield enantiomerically pure α-methylene-β-lactam **37** (Scheme 1.13).

Ma[54] reported a general method for the synthesis of α-methylene-β-lactams via Pd[II] catalysed carbonylation of propargylic amines. The product contains a vinyl chloride handle, that could be useful in subsequent transformations. The reported route offers little variation in the *N*-substituent (R''' = H, Bn or Ts), however, many examples are provided of mono-substitution at C-4 (Scheme 1.14). Chiral amines were carbonylated to give the corresponding α-methylene-β-lactam with high levels of enantiomeric excess.

Kambe and co-workers,[55,56] have reported α-methylene-β-lactam synthesis from substituted carbamoyls, either by radical 4-*exo*-dig cyclisation of radicals or Pd catalysed intramolecular addition. This novel radical cyclisation provided modest yields and no clear route to removing the β-tellurium atom (Scheme 1.15).

Most recently You, Lei and co-workers reported a mild carbonylation of allylamines

Scheme 1.12

using palladium(II) in combination with copper(II) as a reoxidant to form α-methylene-β-lactams under 1 bar of CO. They reported that it tolerates many *N*-substituents with yields ranging from 27-98%. The chemistry allowed introduction of C-4 substituents with enantiocontrol (Scheme 1.16).

In conclusion, there are many useful methods for the synthesis of α-methylene-β-lactams, however, the synthesis of 4,4-disubstituted derivatives remains challenging. In the context of any total synthesis of phyllostictine A, methods for their formation in an
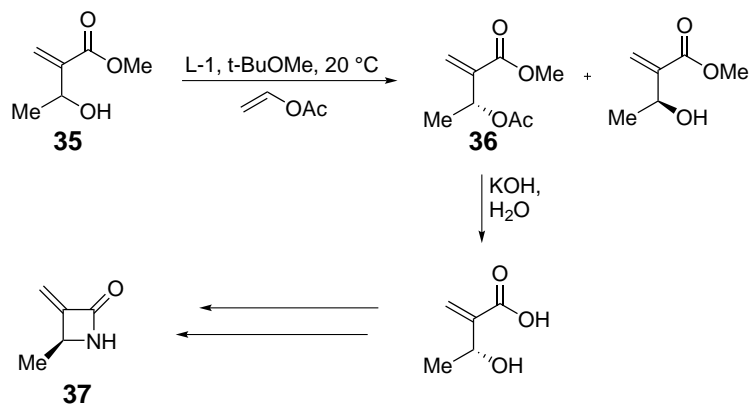
Scheme 1.13
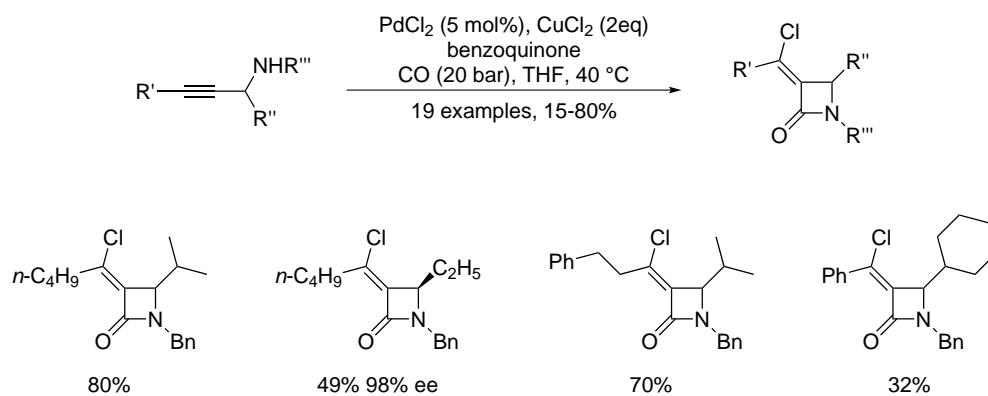
Scheme 1.14

Scheme 1.15

enantiocontrolled manner will need to be developed.

Scheme 1.16

1.5   Synthetic Analysis of Phyllostictine A

The phyllostictines are a structurally challenging class of molecule, with interesting biology. To date, no synthetic studies directed towards the phyllostictines have been disclosed. Our group is interested in developing routes to these molecules, in-particular, achieving the first total synthesis of ph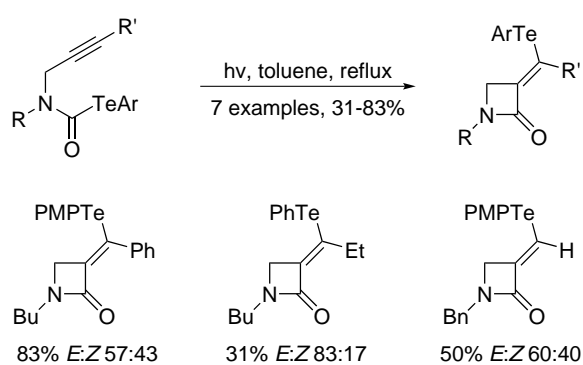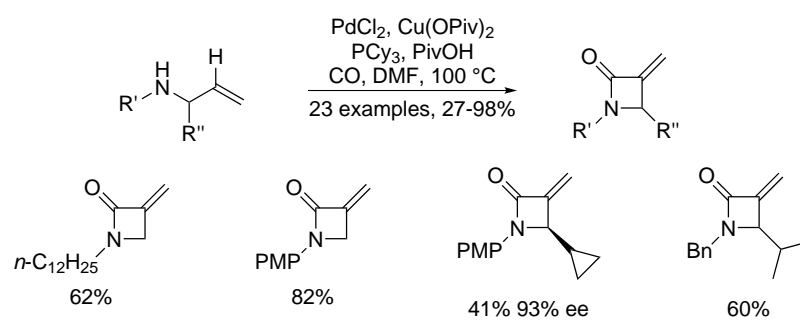yllostictine A. Along the way, we hope to develop a deeper understanding of the herbicidal mode of action of these natural products. The synthesis of simpler analogues, will be an important tool in determining their mode of action, as well as potentially improving their potency and suitability as commercial herbicides.

Our planned strategy to phyllostictine A is based upon an audacious ring closing metathesis reaction to produce the tetrasubstituted double bond by closure of diene **38**. Demostrating the feasibility of undertaking RCM reactions of α-methylene-β-lactams forms the basis of the work described in Chapter 2. The diene necessary to complete the final step is anticipated to come from the cross coupling of THF **39** and α-methylene-β-lactam **40**, followed by functional group interconversions. Dr. Geden in our group has already synthesised THF **39**. Efforts are now focused on its asymmetric synthesis.

The α-methylene-β-lactam contained in phyllostictine A presents a significant synthetic challenge, due to the fact it is both chiral and 4,4-disubstituted. As we have seen, there are relatively few methods of forming α-methylene-β-lactams. In the first instance it will be important to establish methods for synthesising racemic 4,4-disubstituted α-methylene-β-lactams. This topic is the basis of the work presented in Chapter 3.
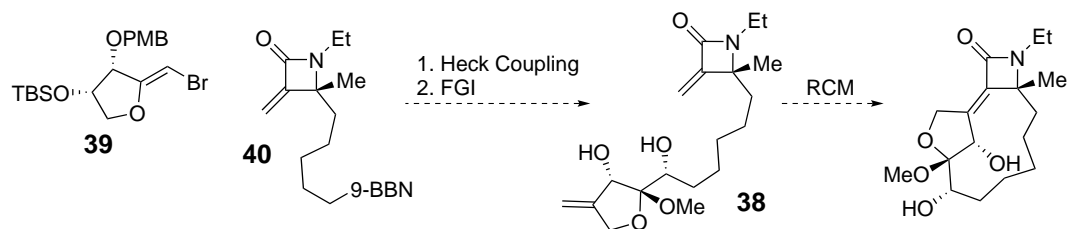
Scheme 1.17

1.6   Conclusions

Growing global populations and the misuse of herbicides has lead to the situation where some weeds are now resistant to all the current classes of herbicide action. No new modes of action have been identified for over 20 years. Recently, phyllostictine A, a new potent mycoherbicide, faster acting than glyphosate and more potent than furasic acid, has been isolated which represents an exciting new avenue for research in this area. It contains a unique structure that was identified by a combination of MS and NMR techniques. The Mosher's method was used to assign the absolute and relative stereochemistry in combination with NOESY measurements.

A key challenge in any total synthesis of these natural products will involve control of the stereochemistry at the fully substituted C-5 carbon, and formation of the tetrasubstituted double bond of the α-methylene-β-lactam. Current knowledge of their herbicidal mode of action is very limited. Three key ideas are explored in this thesis: (*i*) the development of methods for the synthesis of the 11- and 12-membered macrocyclic rings of phyllostictine A via RCM, (*ii*) an exploration of approaches to the 4,4-disubstituted α-methylene-β-lactam unit, and (*iii*) further development of biological assays and structure-activity relationships related to this compound class.

Chapter 2

Simplified Phyllostictine A Analogues via Metathesis

2.1 Synthetic Strategy to Phyllostictine A

Chapter 1 highlighted phyllostictine A as a fascinating natural product displaying varied biological activity via unknown mechanisms of action. Due to the difficulties in isolating large quantities of it from natural sources, we wish to complete the first total synthesis of this natural product. In doing so, we also had in mind that we wished to: (*i*) establish a flexible synthetic route - allowing other members of the phyllostictine family to be made; (*ii*) explore the biological activity of various synthetic intermediates, to probe the mechanism of action; and (*iii*) use this to develop structure-activity relationships and hence create simpler synthetic herbicides. Completion of the total synthesis would also confirm the structure and absolute configuration.

The key steps in the strategy are described in section 1.5 and employ attractive transition metal catalysed reactions (Scheme 1.17). It is hoped that the new knowledge and chemistry developed will find application beyond phyllostictine A. This chapter details work using model systems to ascertain whether the macrocyclic ring of phyllostictine A can be made by ring closing metathesis (RCM). To date, α-methylene-β-lactams have not been used as substrates in RCM. These investigations were expected to identify: (*i*) the most effective catalyst systems; (*ii*) methods for controlling the stereochemistry about the tetrasubstituted double bond; (*iii*) the optimal *N*-substitution pattern for the sensitive β-lactam; and (*iv*) what ring sizes can be made, thus determining which phyllostictines can be made by this approach.

We selected two simple substrates **41** and **42** for initial investigation. Upon RCM, diene **41** might produce macrocycle **43**, which overlays the 12-membered ring of phyllostictine A. Alternatively diene **42** would yield **44**, mapping the smaller 11-membered ring (Scheme 2.1). Thus, our first objective was to establish suitable routes to dienes **41** and **42** and examine their RCM chemistry.
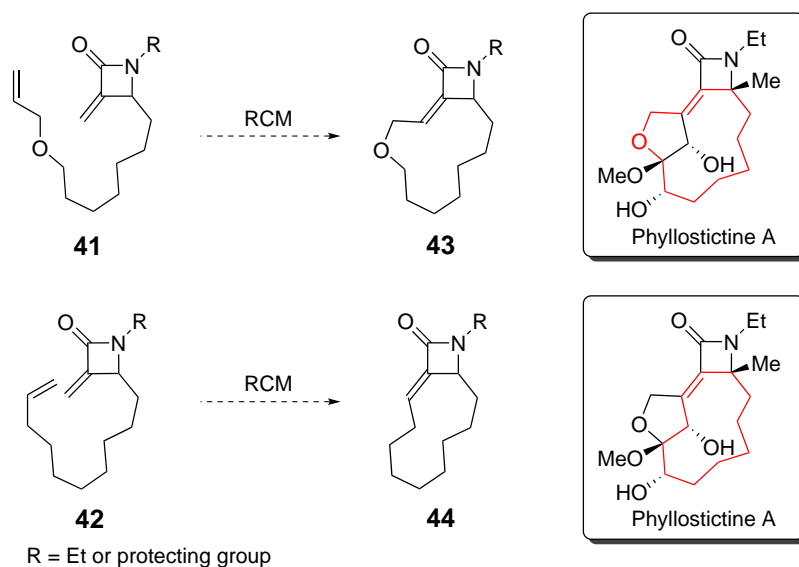
Scheme 2.1

From the methods of forming α-methylene-β-lactams surveyed in section 1.4, we chose to use the method reported by Adam and co-workers to construct these lactams (Scheme 2.2).[53] This method uses the ring closure of an activated alcohol **45**, to make the α-methylene-β-lactam **46** (Scheme 2.2). The acrylic acid **47** can be readily accessed via the Bayliss-Hillman reaction and subsequent hydrolysis of the acrylate ester.

This is an attractive route because it provides easy substitution at two key positions. Firstly, the amide substituent can be varied by changing the amine partner in the coupling reaction to form **48**. Specifically it has been shown that protecting groups such as PMP can be removed under mild conditions[53] and replaced with other useful groups such as Boc[57] and secondly, the alkyl group ultimately attached to C-4 of the lactam ring can be readily changed by varying the aldehyde utilised in the Bayliss-Hillman reaction.
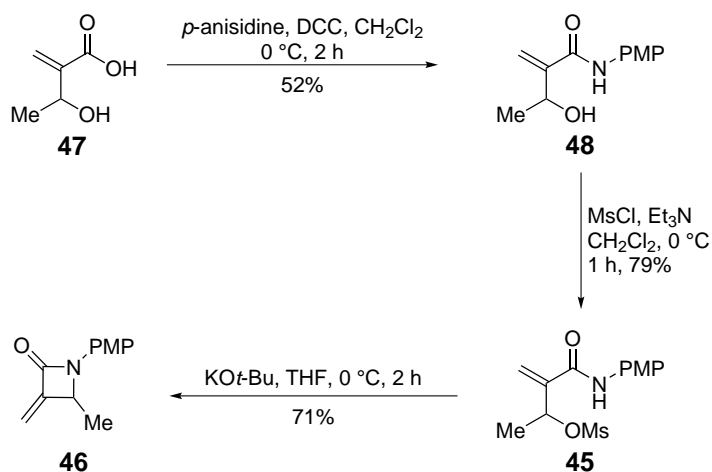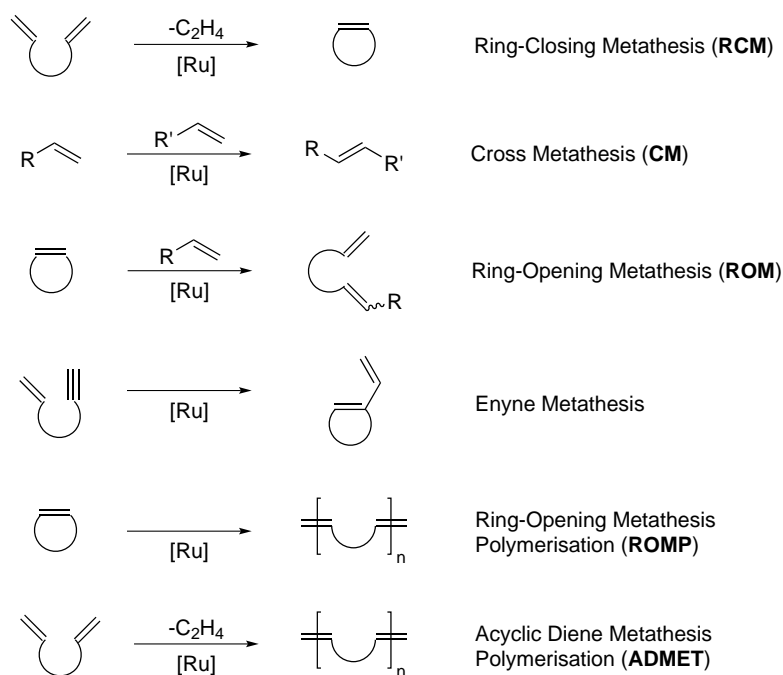
Scheme 2.2

2.2 Introduction to Alkene Metathesis

Metathesis reactions derive their names from the Greek meta - "change" and thesis - "places". They have had a huge impact on the chemical community since their discovery. For example, ring closing metathesis (RCM), cross metathesis (CM), ring opening metathesis (ROM), enyne metathesis, ring opening metathesis polymerisation (ROMP), and acyclic diene metathesis (ADMET) all have found widespread application (Scheme 2.3).

$Ph_2C=W(CO)_5$ was the first well defined catalyst reported to show metathesis activity.[58] Until then only weak metathesis activity had been reported with transition metal salts that were combined with main group alkylating agents, for example, $WOCl_4/EtAlCl_2$. Owing to this, the technique did not become popular with synthetic chemists until 1990, when, Schrock introduced the molybdenum catalyst **SH** (Figure 2.1).[59] This catalyst showed excellent activity with a variety of alkenes, and although it requires the total exclusion of oxygen and moisture, it still remains an important catalyst for sterically hindered substrates or those possessing basic substituents such as amines.

The development of Ru based catalysts in the late 1980s came from the observation that performing ROMP reactions in water with $RuCl_3$(hydrate) reduced the

Scheme 2.3

initiation time from 20 h in organic solvents to 30 min.[60] Over the next two decades,

several important Ru catalysts were subsequently reported. Today, three routinely used

commercially available catalysts* are: **G1**,[62] **G2**,[63] and **HG2**[64,65] (Figure 2.1). The

introduction of these catalysts has changed the landscape of organic synthesis. They

are extremely powerful reagents, for reasons not limited to their high activity, ability to

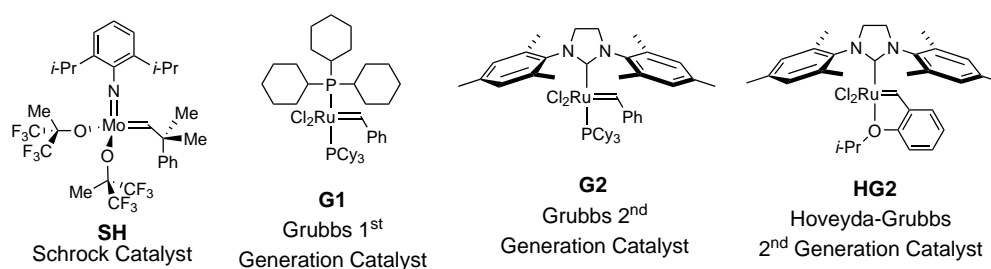simultaneously make and break C−C bonds, and their high functional group tolerance.

Figure 2.1

2.2.1 Mechanism

The mechanism for olefin metathesis was originally proposed by Chauvin in 1971[66] (later supported with studies from Grubbs)[67] and involves a series of alternating [2+2] cycloadditions and cycloreversions via a metallacyclobutane intermediate (Scheme 2.4). The individual steps are reversible, and therefore, the product distribution is generally under thermodynamic control. The irreversible loss of ethylene frequently provides the driving force for the forward reaction.
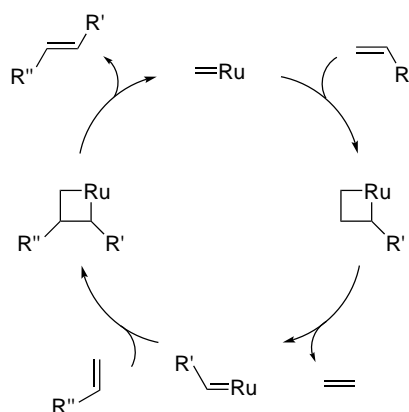
Scheme 2.4

2.2.2 Use in Natural Product Synthesis

The first successful use of ring closing metathesis in natural product synthesis was reported by Hoveyda and provided the late stage intermediate **49** in the synthesis of the anti-fungal agent Sch 38516 alglycone **50** (Scheme 2.5).[68] Other notable examples include; Nicolaou's synthesis of the epothilones, which are potent anti-cancer compounds,[69] and Wood's total synthesis of ingenol[70] (**51**), a molecule with a diverse range of biological activities (Scheme 2.6).
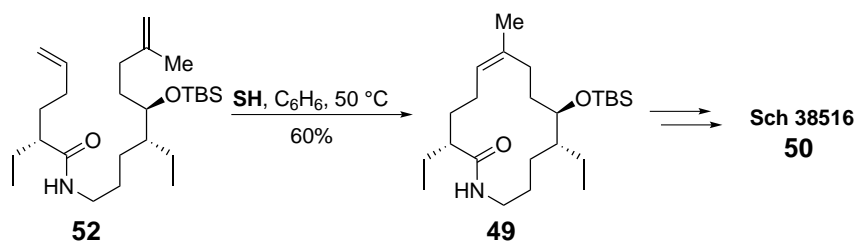
Scheme 2.5
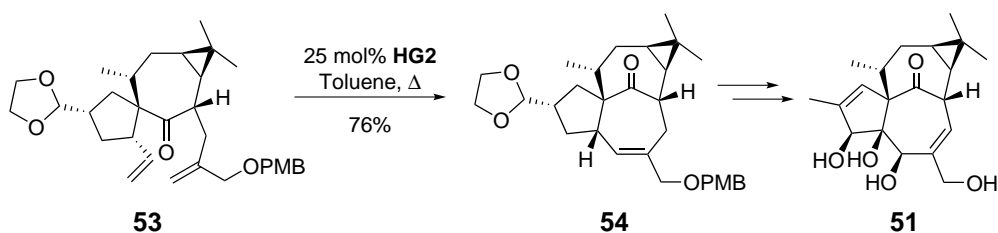
Scheme 2.6

2.2.3 Metathesis Reactions of α-Methylene-β-Lactams

In 2006, Howell and co-workers reported the cross metathesis (CM) of 3-alkylideneoxetan-2-one **55** with a variety of alkenes using both **G2** and **HG2** to yield trisubstituted alkenes **56** in 55-94% yield and *Z:E* selectivities of >20:1 in some instances (Scheme 2.7).[71]
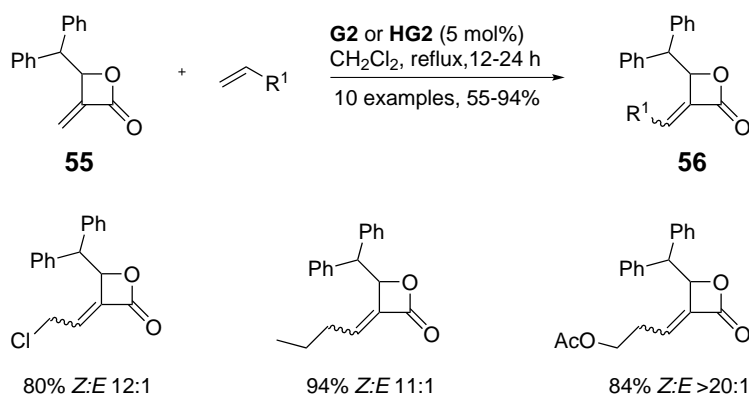
Scheme 2.7

Next they examined use of the corresponding α-methylene-β-lactams. These substrates undergo CM with a variety of partners and nitrogen substituents. Interestingly they

showed that for the first time, tetrasubstituted alkenes could be formed via CM.[57]

The reaction is clearly sensitive to the nature of the *N*-substituent. For instance, comparing the results of three different *N*-substituents: Boc, H, PMP in the reaction with 1-pentene, they discovered that although the yields and *E:Z* selectivities were broadly similar, Boc protection required just one aliquot of the catalyst to be added, whilst the free amide required three, and the PMP protected lactam five (Scheme 2.8).

57

R¹ = H
R¹ = Boc
R¹ = PMP

58

R¹ = H, 89% 2:1
R¹ = Boc, 84% 2.5:1
R¹ = PMP, 80% 2.5:1
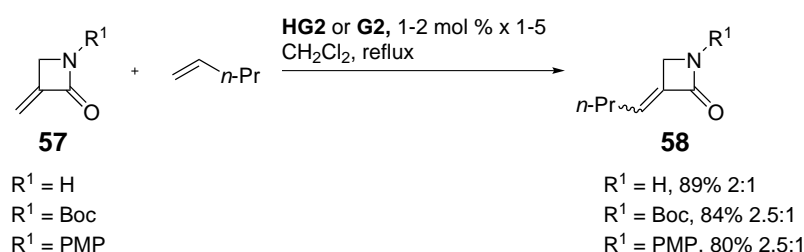
Scheme 2.8

Furthermore, Boc substituted lactam **59** was the only one effective for tetrasubstituted double bond formation. Similar yields were observed in the formation of tetrasubstituted lactam **60** and trisubstituted lactam **61**. However, the *E:Z* selectivity was affected, with poorer selectivity seen in the formation of **60** (Scheme 2.9). With the α-methylene-β-lactam of phyllostictine A being tetrasubstituted, it is encouraging that tetrasubstituted alkenes can be formed via metathesis processes.
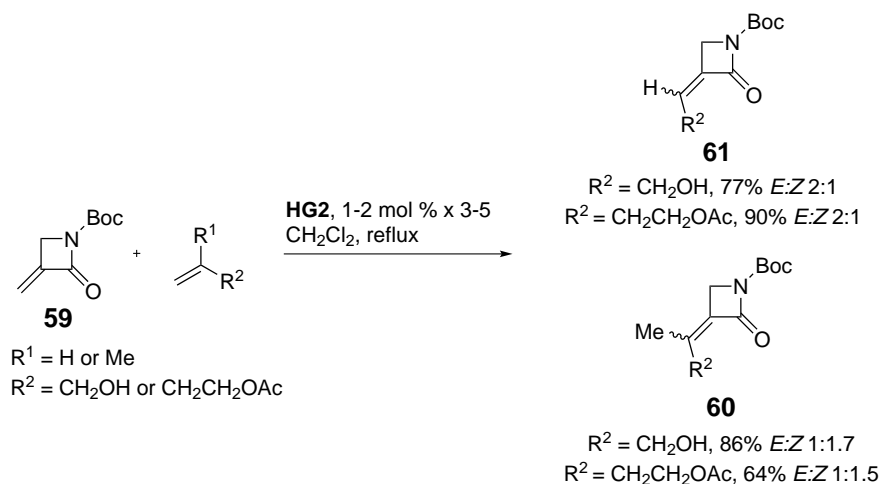
Scheme 2.9

By extending this methodology to RCM, this offers a potential route to the phyllostictines. Forming tetrasubstituted double bonds by RCM, although uncommon, is a known process. Grubbs and co-workers have developed catalysts specifically for this task,[72,73] whilst novel methods involving relay ring closing metathesis have also been reported.[74] However, the use of RCM to form tetra-substituted double bonds in natural product total synthesis is rare. Reiser reported the formation of tetra-substituted double bonds whilst investigating the total synthesis of the guaianolide ixerin Y, using **G2** and microwave irradiation.[75] However, it is Stoltz's report of the total synthesis of elatol **62** that is the first total synthesis employing novel catalysts to form tetrasubstituted double bonds via RCM (Scheme 2.10).[76]
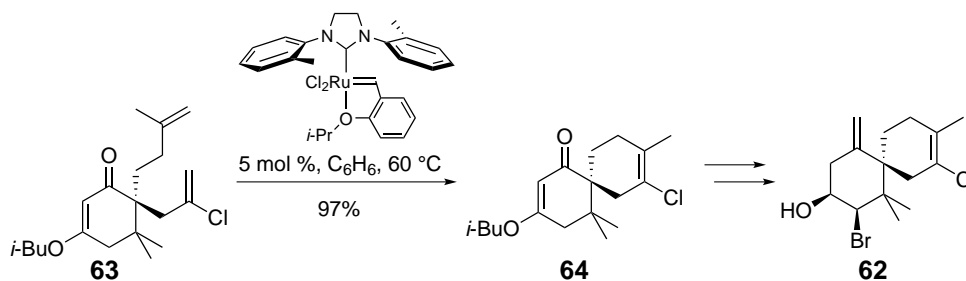
Scheme 2.10

2.3   Ring Closing Metathesis of *N*-Ethyl Lactams

2.3.1   Initial Studies Towards 11-Membered Rings

The simplest model system we could conceive was **65**, bearing an *N*-ethyl substituent analogous to the natural product itself. The synthesis of this molecule being explored by RCM of diene **66** (Scheme 2.11).
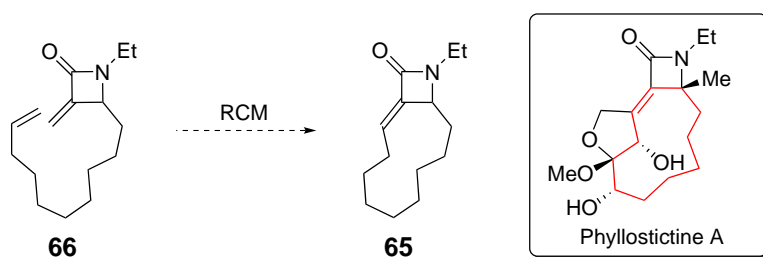
Scheme 2.11

The synthesis of diene **66** began from the commercially available aldehyde **67**, which was subjected to a Baylis-Hillman reaction, yielding ester **68**, in 55% yield after 7 days.[†] Smooth transformation to carboxylic acid **69** with lithium hydroxide and subsequent coupling with EtNH$_2$ in THF gave amide **70** in 95% yield. EDC gave better results than initial attempts with DCC, whose reactions were poor yielding with products less easy to purify. Subsequent mesylation yielded mesylate **71** in 68% yield. Finally, ring closure with KO*t*-Bu at −15 °C yielded α-methylene-β-lactam **66**, in an acceptable 23% yield over the 5 steps (Scheme 2.12). The structure of lactam **66** was positively identified by the distinctive C=O IR stretch at 1747 cm^{-1} indicative of the β-lactam ring, the α-methylene functionality also has distinctive singlets in the ^{1}H-NMR at 5.57 and 5.01 ppm, respectively. Before commencing any ring closing metathesis reactions, some preliminary cross metathesis reactions were carried out to gain some confidence with the technique.

[†]Yields of the Baylis-Hillman reactions with long chain aldehydes such as **67** could be improved to 80%, however, extended reaction times in excess of 30 days were required.
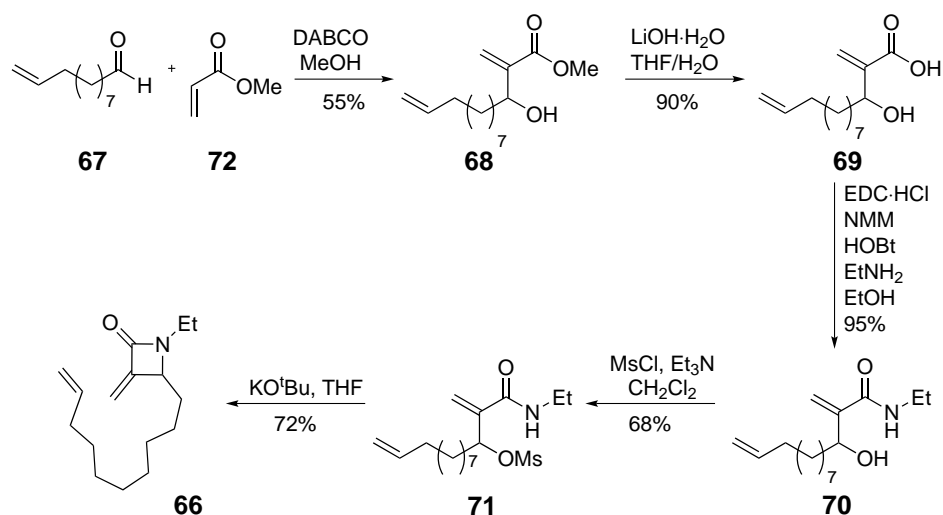
Scheme 2.12

2.3.2   Establishing *E,Z* Chemical Shifts of α-Methylene-β-lactams

Although Howell reported many examples of CM with α-methylene-β-lactams, we wished to repeat some of this work to have authentic NMR data to compare our RCM products to and also synthesise some novel cross partners which were not investigated by Howell. Knowing that the PMP group can be removed under oxidation with CAN, and with reports that PMB could be removed in the same way,[77] we synthesised lactam **73** and lactam **74**. Lactam **73** was made via the Adam's method, beginning from para formaldehyde in 5 steps (Scheme 2.13).
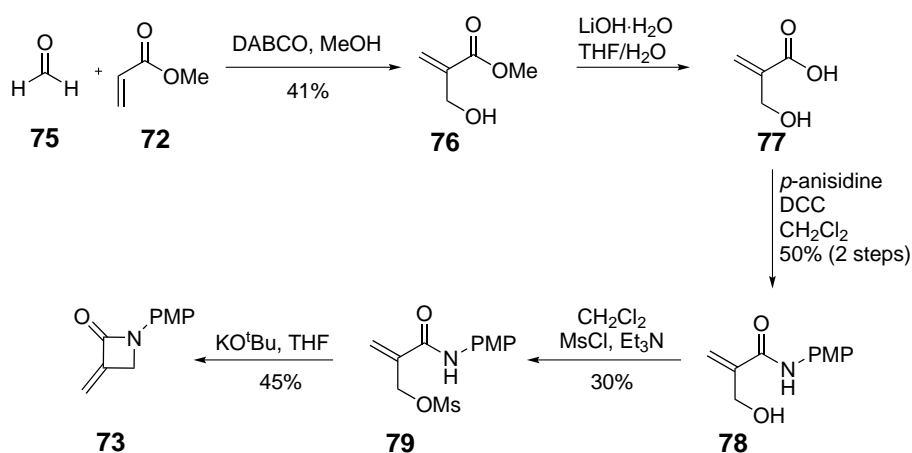
Scheme 2.13

Lactam **74**, was synthesised via carbonylation of bromide **80**, which in turn, was synthe-

sised in 90% yield from 2,3-dibromopropene and p-methoxybenzylamine. The carbony-lation conditions involved use of Pd(PPh$_3$)$_4$, nBu$_3$N, CO and DMAc. The reaction gave the desired product **74** in 30% yield (Scheme 2.14) . Wanting to improve upon this, a brief exploration of the ligand was undertaken. Throughout the optimisation Pd(OAc)$_2$ was used as the Pd source Table 2.1 summarises our findings.
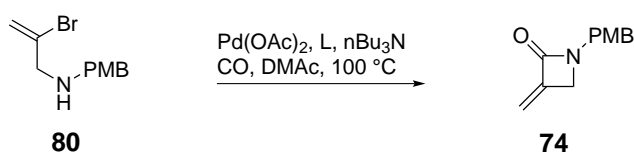
Scheme 2.14

Table 2.1

Ligand (L)	Yield
PPh$_3$	30%
xphos®	28%
xantphos®	60%
dppp	30%

The use of the bulky monodentate ligand Xphos® produced a comparable result to the monodentate ligand PPh$_3$. Next we trialled a bidentate ligand Xantphos® which is extremely bulky and produced an improvement in yield. The less bulky bidentate ligand, would have we used the 1,3-bis(diphenylphosphino)propane (dppp), proved less useful.

With lactams **73** and **74** in hand, several relevant cross partners were reacted separately with both **73** and **74** under the general general conditions shown in Scheme 2.15. The most successful cross partner was 1-octene (**81**) (entry 1, Table 2.2) with good yields seen with **73** and **74**. Allyl acetate (**82**) gave lower yields with both **73** and **74** (entry 2, Table 2.2). The other oxygen containing compounds only produced trace

amounts of material with **74** and none with **73** (entry 3 and 4, Table 2.2). Finally, the branched alkene **83** did not react with either starting material under these conditions (entry 5, Table 2.2).
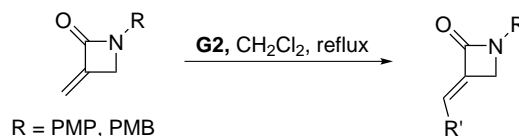
Scheme 2.15

Table 2.2

Entry	Cross Partner	Conditions	Yield with PMB	Yield with PMP
1	**81**	2% **G2**	54% *E:Z* 4:1	89% *E:Z* 1.6:1
2	OAc **82**	2% **G2**	25% *E* only	10% *E:Z* 10:1
3	OEt **84**	2% **G2**	12% *E* only	0%
4	OH **83**	2% **G2**	trace *E:Z* 1:1.3	0%
5	**85**	2% **G2**	0%	0%

The cross coupling reaction of 1-octene with **74** produced both the *E* and *Z* isomer. This allowed us to establish the relative chemical shifts for *E* and *Z* isomers of α-methylene-β-lactams. The isomers were readily separated by simple chromatography and we were able to correlate the chemical shifts with reported alkene shifts.[57] A full table of the *E* and *Z* shifts recorded for α-methylene-β-lactams synthesised in this thesis can be found in Appendix II.

Using **66**, a RCM reaction was carried out with Grubbs 2nd generation catalyst (**G2**) at 2 mM concentration for 24 h in refluxing CH$_2$Cl$_2$. Disappointingly, after work up and chromatography, no 11-membered ring products could be isolated. Semi-preparative HPLC of the alkene containing fractions, allowed two products to be isolated; the linear dimer **86** (32%), and the 22-membered dimer **87** (2%),

(Scheme 2.16). In the ^{1}H-NMR spectra of lactam **87**, the distinctive singlets of the α-methylene group and terminal double bond pattern of **66**, had been replaced by a double triplet at 5.44 ppm, resulting from the one remaining alkene environment in the molecule. Furthermore the *m/z* 465 [M + Na]$^+$ of **87** was supportive of a cyclic dimer. With regards to the alkene stereochemistry, from the experiments carried out in section 2.3.2 and the chemical shifts reported by Howell, the double bond **87** was assigned as the *Z*-isomer. X-ray structures of related dimeric α-methylene-β-lactams **88**, **89** and **90** reported later in this chapter which were also *Z*-configured, further supporting this assignment.

Lactam **86** was identified by the distinctive singlets at 5.54 ppm and 5.02 ppm and lack of terminal double bond pattern, which was replaced by single triplet at 5.31 ppm. In both cases the indicative carbonyl stretch of approx 1740 cm^{-1} was seen in the IR spectrum, confirming the presence of β-lactam rings. Furthermore, a molecular ion *m/z* 493 [M + Na] consistent with **86** was seen by mass spectrometry.
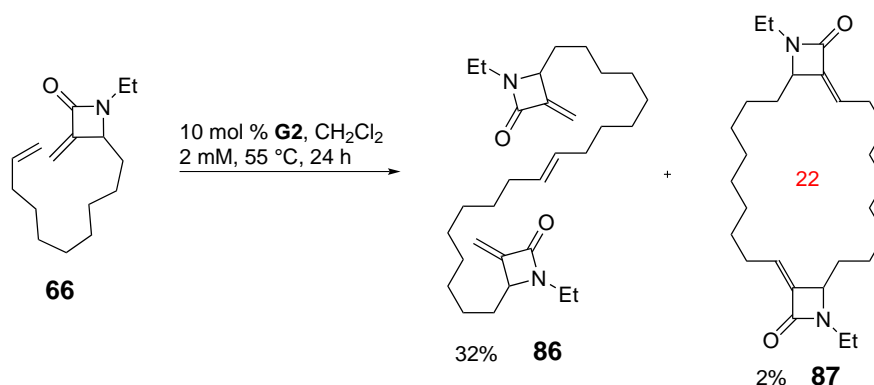
Scheme 2.16

The formation of 11-membered rings by RCM does have precedent, however, they are rarely efficient.[78] For example, in Harmata's synthesis of buddledone A, the conformational freedom and angle strain of diene **91** lead to the formation of linear dimer **92** as the thermodynamic product.[79] Other products isolated were the styrene coupled prod-

uct and the starting material. A solution to the problem was eventually found by taking advantage of the geminal disubstitution effect, imparted by TMS-protected cyanohydrin **93**. This substitution released the conformational strain and allowed the formation of buddledone A **94** in 31% over seven steps (Scheme 2.17).
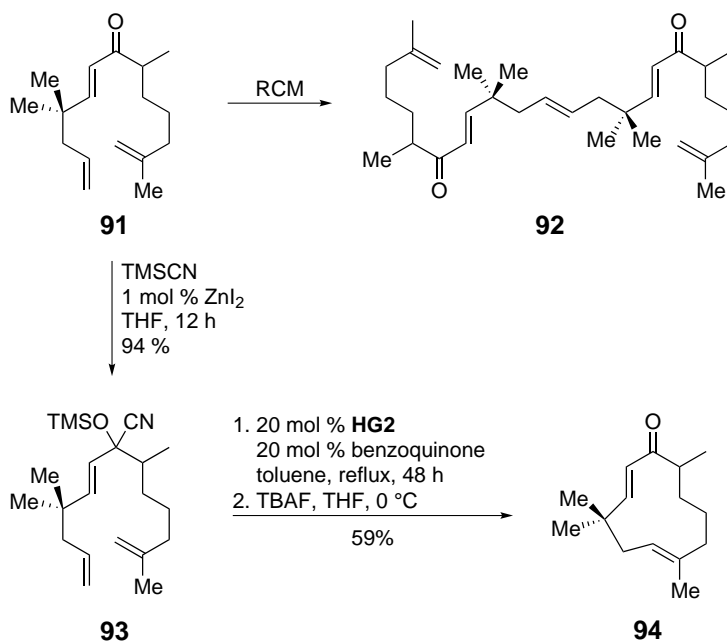
Scheme 2.17

Hoveyda has also made useful observations, during the synthesis of clavirolide C (**95**). Whilst RCM to form clavirolide C intermediate **96** was facile with allylic silyl ether **97**, it was noted that the corresponding α, β-unsaturated ketone (not depicted) lead to significant (30-35%) formation of the 22-membered homodimer. These two examples highlight the sensitivity of these 11-membered ring forming reactions to subtleties in substrate design (Scheme 2.18).
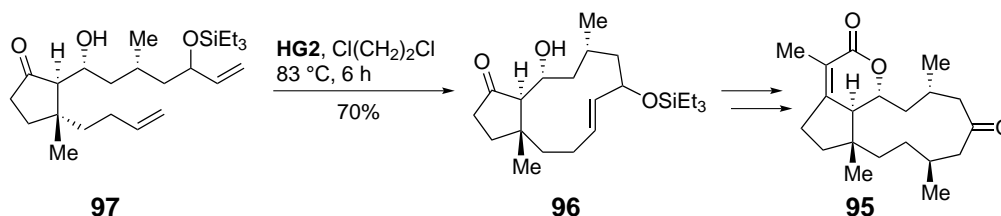
Scheme 2.18

The isolation of **86** and **87** indicates that the formation of the 11-membered ring is not

favored with α-methylene-β-lactams. Linear dimers often occur with unsymmetrical dienes, and there formation is via "acyclic diene metathesis" (ADMET). It is usually thought that metathesis steps are all reversible. However, in cases where the rate of the reverse reaction with ethylene is slower than the dimer formation due to ethylene's poor solubility in CH_2Cl_2 results in a situation where the formation of the ADMET dimer can be thought of as *irreversible*.[80] This essentially shuts down the simple RCM model for macrocycle synthesis. If monomer formation is to proceed it must go via a cyclo-depolymerisation reaction. Fogg and co-workers provide evidence for this mechanistic pathway by observing by GC and MALDI-MS, the formation of ADMET dimers that subsequently, and quantitatively formed the RCM product. This has given significant support for the idea that ADMET dimers are intermediates in RCM.[80]

An explanation for the observed products is presented in Scheme 2.19. Formation of **86** from **66** is irreversible by loss of ethylene. The formation of **98** is maybe slow due to steric effects of the lactam, or electronic interactions with the amide. The catalyst at this point may become deactivated by decomposition ending the reaction with **86** as product.

However, if formed, **98** does not appear to undergo cyclo-depolymerisation to form the desired 11-membered **65**. Instead **98** proceeds with another ADMET addition with the presumably the most reactive alkene of **66**, presumed to be the terminal alkene. The trimer **99** may now undergo cyclo-depolymerisation to form the low strain 22-membered ring **87**, and **100**. Simple RCM of **100** however, is not observed and it must either decompose becoming inactive or return to the ADMET cycle (Scheme 2.19).

It should be noted that due to the poor mass balance in this reaction, small quantities of the 11-membered ring may have been formed but not isolated. Rather than attempt to improve this reaction through variation in catalyst or reaction conditions, we decided to explore the synthesis of the larger 12-membered ring.
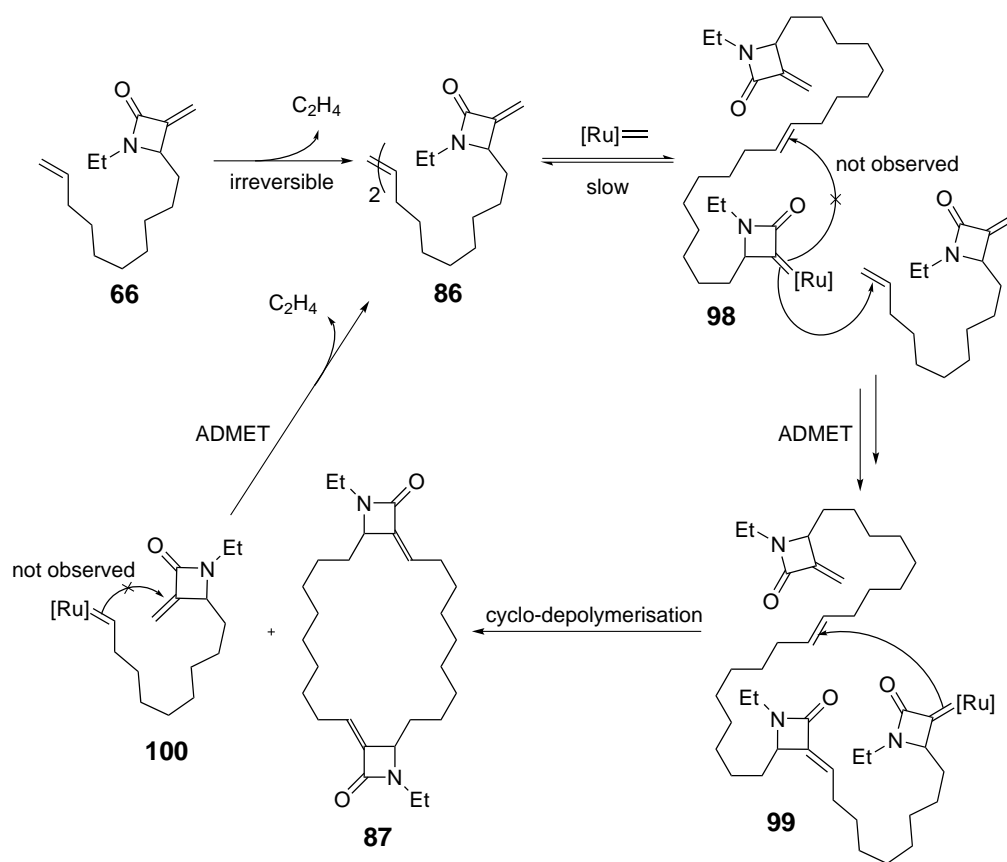
Scheme 2.19

2.3.3 Towards 12-Membered Ring Systems

Since the synthesis of the 11-membered ring was not successful with an *N*-Et substituent, we decided to explore construction of ether **101** via RCM (Scheme 2.20).
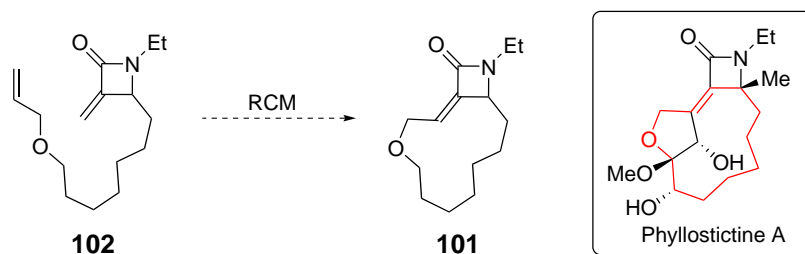
Scheme 2.20

The synthesis of α-methylene-β-lactam **102** employed the same methodology used in Scheme 2.12, however, starting from the commercially available 1,8-octadiol (**103**). This versatile diol would prove to be invaluable in subsequent experiments. Using literature methods,[81] **103** underwent ether synthesis with NaH and 1.1 equivalents of allyl bromide, purification to remove the di-allylated material yielded **104** in a 40% yield. Subsequent oxidation with PCC yielded the corresponding aldehyde **105**, in 22% yield over the two steps (Scheme 2.21). This methodology enabled us to make **105** in multi-gram quantities.
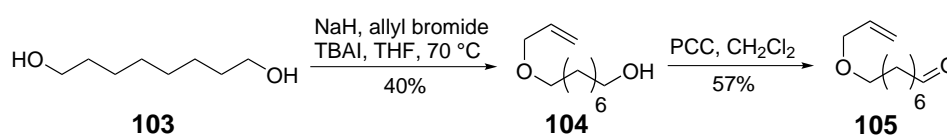
Scheme 2.21

In a further 5 steps, we were able to produce the required α-methylene-β-lactam **102**, using the same methodology described previously (Scheme 2.22). No attempts to optimise the relativity low yielding cyclisation to **102** were made as adequate quantities of materials could be obtained.

RCM was attempted with **102**, under a variety of conditions. For example, using **G2** (10 mol%) at 2 mM concentration; **HG2** catalyst at 2 mM; **G1** catalyst at 2 mM. However,
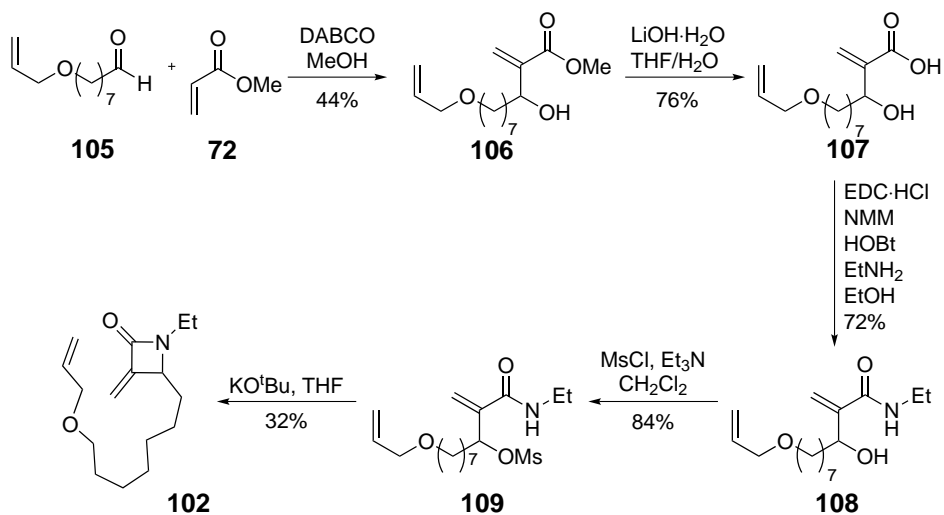
Scheme 2.22

none were seemingly successful. Products with the correct m/z $[M + Na]^+$ 260 corresponding to the 12-membered ring were observed by ESI-MS, but when chromatography was used to purify these compounds, no clean products could be obtained. Other products were also observed by ESI-MS including what we believe to be the linear dimer m/z $[M + Na]^+$ 525 and the styrene coupled product $[M + Na]^+$ 364. Attempts to isolate these free of impurities were also unsuccessful. No further attempts were made to optimise the use of **102**, and an alternative method was sort for the formation of **101**.

2.3.4   Use of the Crotyl Group

We looked for ways to improve the synthesis of **101** from diene **102**. Some initial attempts involved using Lewis acidic additives (CuCl,[65] TiO*i*-Pr[82]), as we speculated that the amide nitrogen may have been interacting with the catalyst. However, these reactions were unsuccessful. Evidence of the linear dimer being formed in both these reactions by ESI-MS and ^{1}H-NMR provided some support for an ADMET mechanism. One of the key features of the ADMET mechanism is loss of ethylene contributing to the stagnation of the forward reactions. Propene is less volatile and has a higher solubility than ethylene in organic solvents,[83,84] therefore we imagined that use of the crotyl group could impart some reversibility to the initial step.

This approach is somewhat analogues to relay ring closing metathesis. This strategy involves the fast formation of cyclopentene to form Ru= in otherwise hindered or deactivated positions. For example, Porco Jr's total synthesis of oximidine III intermediateiate (**110**) utilities relay RCM in a key step.[85] Finding that **111** could not convert to **110** with either the **G2** or **HG2** catalysts, they installed, via CM a readily available terminal alkene **112**. When **112** was exposed to **HG**, facile loss of cyclopentene generated active Ru species **113** that subsequently formed **110** in 71% yield.
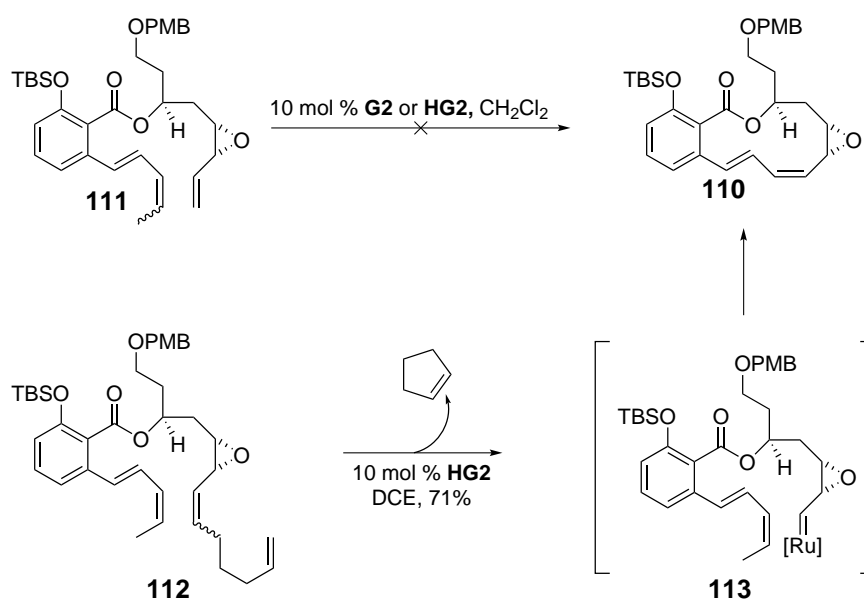
Scheme 2.23

Whilst this is an elegant approach, due to the readily available nature of crotyl bromide we looked to explore if generation of propene in the initiation would facilitate the formation of the 12-membered ring. In 7 steps, we were able to prepare the crotyl derived lactam **114** using the Adam's approach (Scheme 2.24).

When the RCM was attempted with lactam **114**, for the first time the desired 12-membered ring was formed. After initial column chromatography, and further purification by semi-preparative HPLC, two products were isolated. They had distinct ^{1}H-NMR spectra and were identified as the 24-membered dimer **120** (29%), and the required 12-membered ring **101** (20%) (Scheme 2.25). However, **101** was not stable,
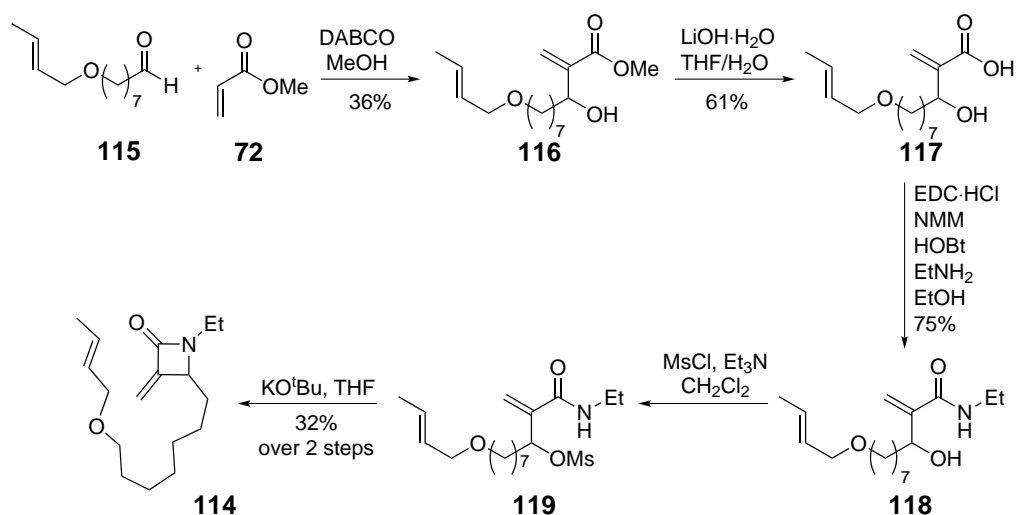
Scheme 2.24

and decomposed in CDCl$_3$ while full spectroscopic data was being acquired. Initial ^{1}H-NMR data pointed towards the *Z*-stereochemistry, with the alkene having a similar chemical shift to other *Z*-lactams (Appendix II). The dimeric product was evidenced by its molecular ion *m/z* 497 [M + Na]$^+$.

Insufficient material was available to repeat this result, and since other strategies being undertaken in parallel proved more fruitful, the 7-step sequence to reproduce this chemistry was not undertaken. The structure of **101** was later confirmed by comparison with material made via an alternative route (Scheme 2.45).
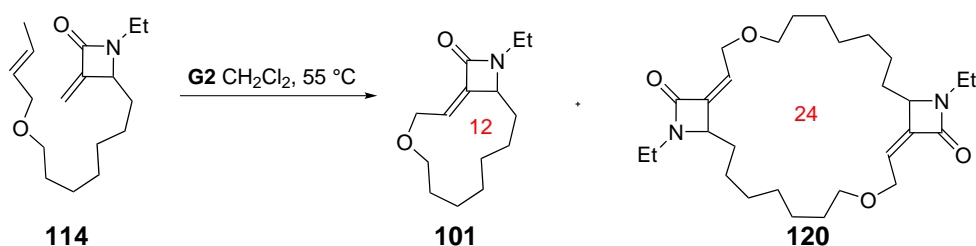
Scheme 2.25

Whilst the yield of the product was rather modest, these represents the first examples of RCM reactions of α-methylene-β-lactams. Furthermore, it was encouraging to see that the 12-membered ring was formed in the "correct" *Z*-geometry relative to the natural

product.

2.4 Ring Closing Metathesis Systems containing *N-Para-methoxyphenyl* Lactams

Finding that the N-Et systems gave low yields at best in the RCM chemistry, and knowing that the CM metathesis of α-methylene-β-lactams is sensitive to the *N*-substituent, we decided to examine the use of other *N*-protecting groups. To this end, we were drawn to the use of the *N-para*-methoxyphenyl (*N*-PMP) group, which can be successfully removed from α-methylene-β-lactams by use of ceric ammonium nitrate (CAN) deprotection.[53] Moreover, alkylation of the resulting N-H compounds is reported to be facile with simple electrophiles.[46] Thus we set out to explore the synthesis and RCM reactions of lactams **121** and **122** (Scheme 2.26).
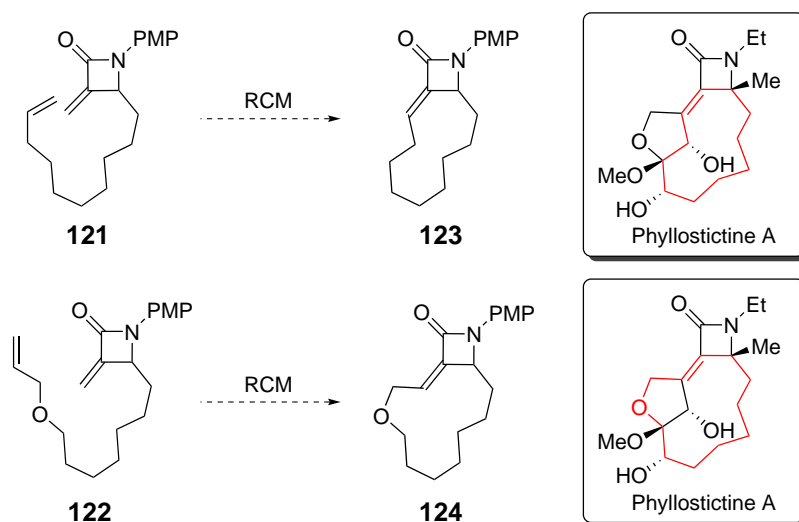
Scheme 2.26

2.4.1 Towards 11-Membered Rings

The requisite 11-membered ring precursor **121** was readily synthesised in 3 steps from acylic acid **125**. (Scheme 2.27).

When diene **121** was exposed to **G2**, at a substrate concentration of 2 mM, the results were encouraging. The crude ^{1}H-NMR spectrum did not show any of the linear
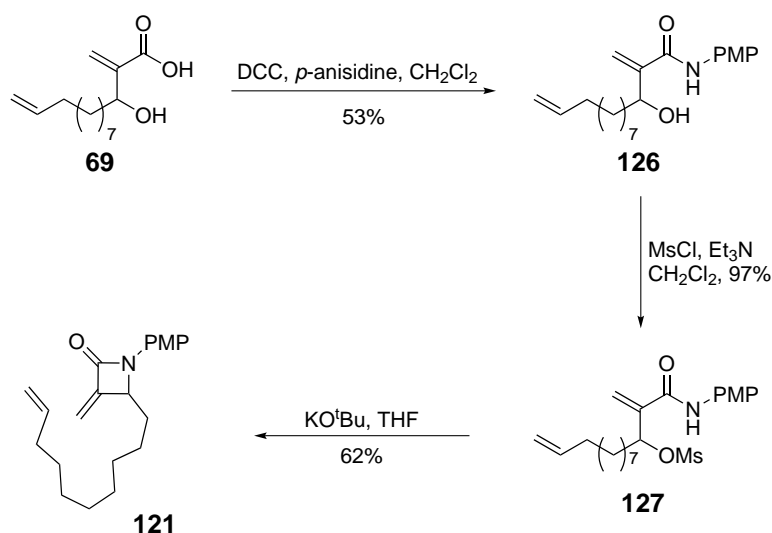
Scheme 2.27

dimer seen in Scheme 2.16. However, the mass balance was poor, and, there were a lot of decomposition products. After chromatography, both **123** and **89** could be isolated (Scheme 2.28). The 11- and 22-membered rings respectively had distinct NMR spectra. Interestingly, both were isolated as single geometric isomers, with no evidence for the alternative isomer by NMR. Dimer **89** appeared to be produced as a mixture of diastereomers (as judged by ^{13}C-NMR) however, only one of which was crystalline and helped to confirm the structure of the dimer.
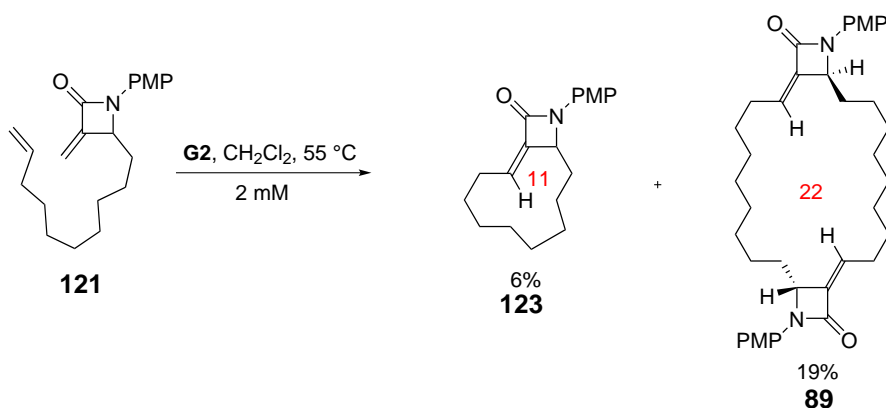
Scheme 2.28

Whilst we were reasonably confident of our assignment of *Z*-stereochemistry based on NMR shifts, crystals suitable for X-ray diffraction were obtained for the 11-membered **123**. The crystal structure confirmed this assignment. (Figure 2.2). Crystals seemingly

44

suitable for diffraction were also obtained for the 22-membered ring **89**, and it was also shown to be *Z*-configured. However, due to the poor quality of the large crystals, this structure could not be fully refined to publishable limits.
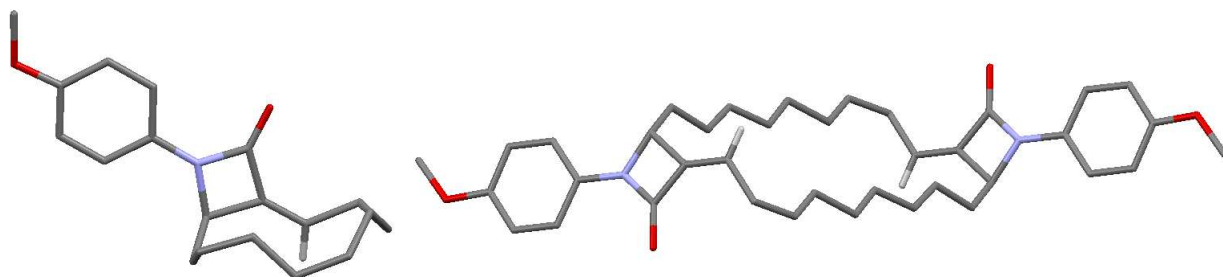
Figure 2.2

The formation of **123** was encouraging as it was the first time we had been able to produce this ring size and properly isolate an RCM product. The preference for the *Z*-isomer might be explained by considering *trans*-annular strain. The alternative geometric isomer, *E*-**128** appears to suffer from significant steric clashing of CH_2 groups, encouraging the less strained *Z*-isomer to be formed (Figure 2.3). Further evidence is provided by molecular mechanics calculations (MMFF94 force field). Calculations of zero point energy for the indivdual isomers places *E*-**128** at 227.23 kJ/mol and *Z*-**123** at 223.55 kJ/mol. Of course, this analysis assumes that the reaction is under thermodynamic control (*vide infra*).
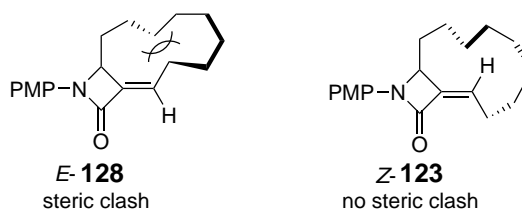
Figure 2.3

2.4.2 Towards 12-Membered Rings

As PMP protection had led to improvements in the RCM to 11-membered rings, this modification was also explored for the formation of the larger ring size. The now well established method for making the dienes was applied to the synthesis of α-methylene-β-lactam **122**, in 38% yield over 3 steps, from **107** (Scheme 2.29).
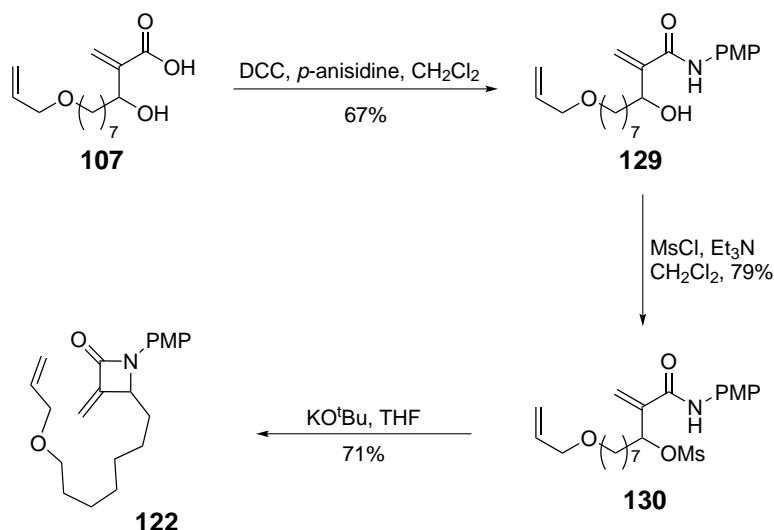
Scheme 2.29

α-Methylene-β-lactam **122** was treated with the **G2** catalyst at 2 mM substrate concentration for 24 h. After work up and chromatography, three products were isolated. The 24-membered product **88**, and a chromatographically inseparable 1:1.6 *E*:*Z* ratio of the 12-membered products **131** and **124** (Scheme 2.30). Trace amounts of the linear dimer (identified by ESI-MS) was also detected. Although the dimer was isolated as 2 diasteromers (as judged by ^{13}C-NMR) only one was crystalline and X-ray crystallography was used to prove its structure.

The better yields with both N-Et and N-PMP derivatives indicate that, the 12-membered macrocycles are more readily formed than 11-membered macrocycles. It is not clear whether it is a reduction in ring strain that results in the improved yields, or if the ether oxygen is having a positive effect on the cyclisation.

Crystals suitable for X-ray diffraction were obtained from both the dimeric material, and also the major *Z*-isomer **124**. Both were shown to possess the *Z*-alkene stereochemistry (Figure 2.4).
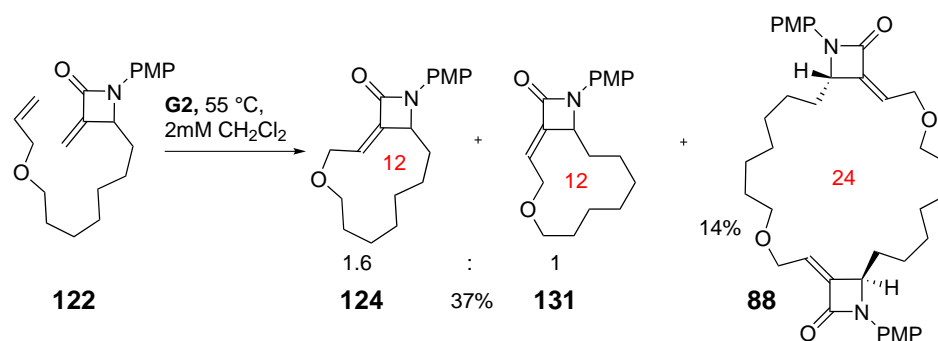
Scheme 2.30
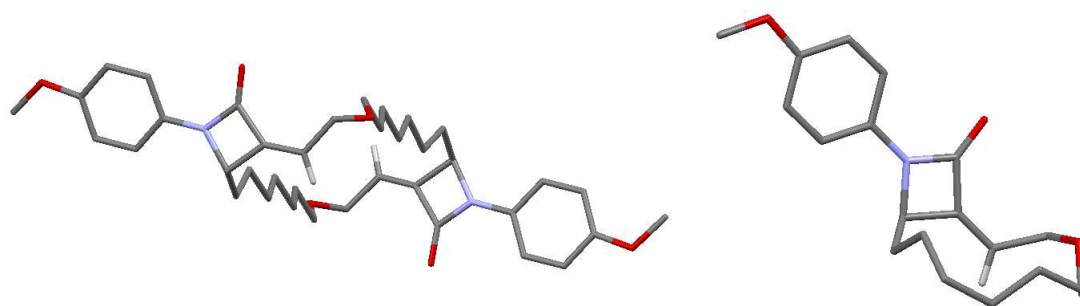
Figure 2.4

Encouraged by this initial result, we tested other common metathesis catalysts. The **G1** catalyst returned starting material exclusively, whilst the **HG2** catalyst produced linear dimer **132** in 65% yield (Scheme 2.31).
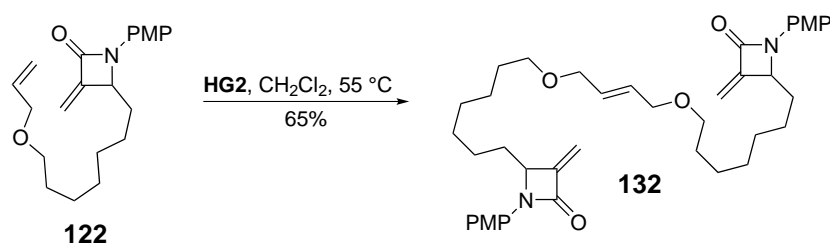
Scheme 2.31

Use of the a crotyl substituted diene in section 2.3.4 led to some improvements previously, hence we elected to make crotyl substituted lactam **133**. The requisite lactam was made in 3 steps from **117**.
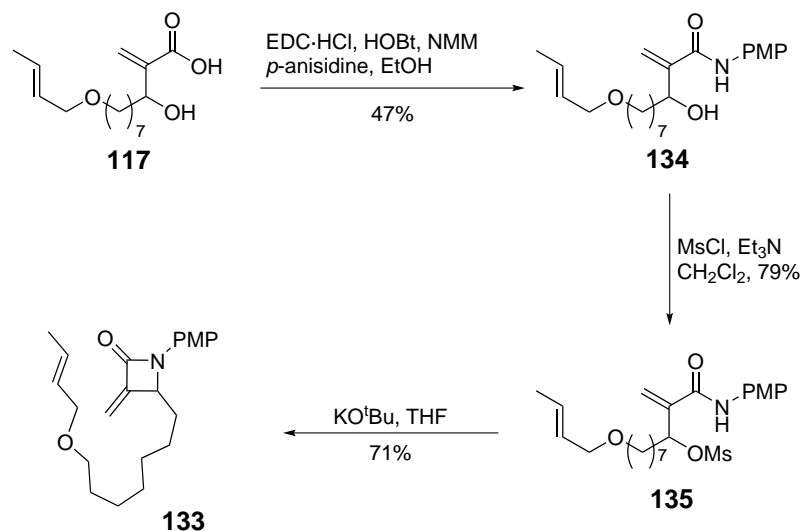
Scheme 2.32

When lactam **136** was exposed to the **G2** catalyst at 2 mM concentration, the results were disappointing. The combined yields **124**/**131** were lower at 20%, **88** was produced in larger amounts (Scheme 2.33). Although the stereoselectivity of the 12-membered rings was slightly improved to 1:3, no further experiments were carried out with this system, due to the unfavourable results.
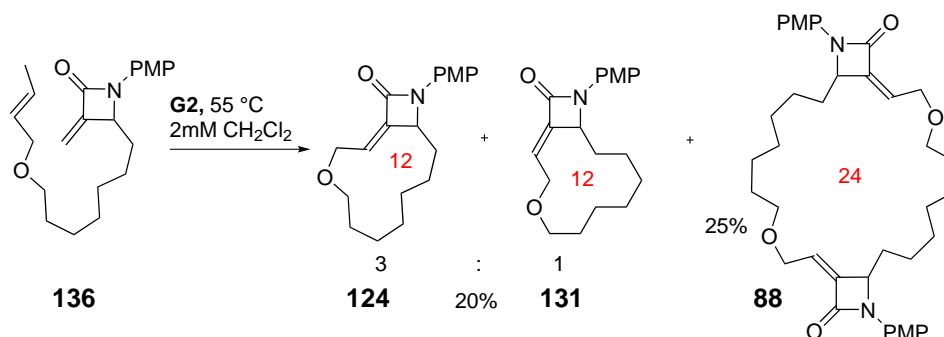
Scheme 2.33

With the most common catalysts trialed and no improvement found, a series of dilution

Table 2.3

Entry	[mmol]^a	% Yield	*E*-131 : *Z*-124
1	2	37	1:1.6
2	1	33	1:2.3
3	0.5	44	1:3.9
4	0.25	44	1:8.4

^{a}Concentration of CH_2Cl_2 related to the substrate **122** with 10 mol% **G2**

experiments were carried out. The aim was to suppress dimer formation. Surprisingly, this did not occur. The yield of the dimer **88** remained more or less constant. However, the *E*:*Z* ratio did markedly change. At 0.25 mmol concentration (entry 4, Table 2.3) >8:1 selectivity in favor of the *Z*-isomer was observed. One explanation is that over time the *Z*-isomer, was being preferentially transformed into the dimer, eroding the *E*:*Z* selectivity. To test this, **124** was purified by semi-preparative HPLC. Attempts were also made to isolate **131** by semi-preparative HPLC, however, this was not successful.

Lactams **124** and **88** were then separately exposed to the initial metathesis reaction conditions: 2 mM, **G2**, refluxing CH_2Cl_2 for 24 h. After work-up, both were analysed by analytical HPLC. In the case of **124**, redistribution of products was seen, with both **131** and **88** observed, in a ratio of **124**:**131**:**88** 1.3:1.2:1 (by HPLC), and approximately similar ratio was seen by ^{1}H-NMR (Appendix III).

Using **88**, although **131** could not be detected, a peak corresponding to **124** was observed after resubjection to the metathesis conditions, in a ratio of **124**:**88** 1:5.6. None of the linear dimer was seen in either experiment.

These results indicate that the products are in equilibrium, and that dimer **88** is not the thermodynamic product since if it was **88** would have remained unaffected by the reaction conditions. Other reports in the literature support this supposition. For example, Clark reports the formation of **137**, as an inseparable mixture as well as a dimeric product **138**, during the synthesis of marine polycyclic ether sub-units (Scheme 2.34).[86]

In this case, the dimeric product **138** was shown to be the thermodynamic product, by re-subjecting it to the reactions conditions and returning only starting material **138** (Scheme 2.35).
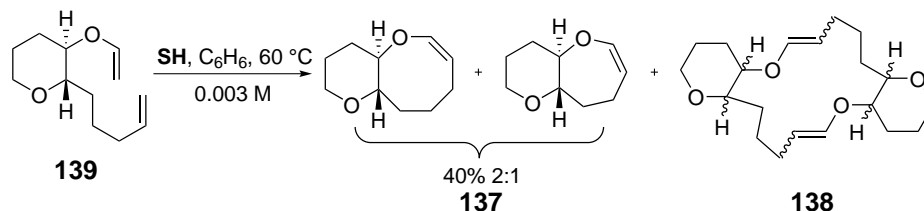
Scheme 2.34
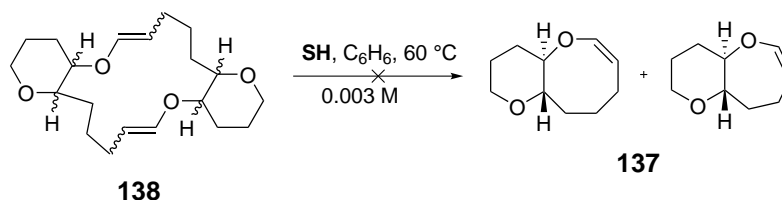
Scheme 2.35

Whilst the HPLC experiments show that the reaction is under equilibrium, the exact mechanism for isomerisation of the monomeric products is not clear. Stereoisomers **131** and **124** could interconvert by reformation of the Ru carbene intermediates, or by simple isomerisation of the alkene. For example, the catalyst could degrade to $RuCl_2(PR_3)_3$ in situ, catalysts which are known to isomerise alkenes.[87] Further investigation would be required to more fully understand this complex process.

To explore structure-activity relationships (*vide infra*) of phyllostictine A, we wanted to determine if the α-methylene group was important for herbicidal activity. To this end, **141** was prepared by the hydrogenation of a mixture of **131** and **124** with PtO_2 under an atmosphere of H_2. After chromatography, the hydrogenated analogue **141** was isolated in an unoptimised 48% yield as a single stereoisomer (Scheme 2.37). This material was tentatively assigned as *syn-* as a result of addition of hydrogen to the least hindered face of **124**. The addition of H_2 to other lactams has been shown to occur in a *syn*-fashion.[45] For example, Buynak took **142** and removed the double bond with

PtO$_2$ to form **143** exclusively (Scheme 2.36).
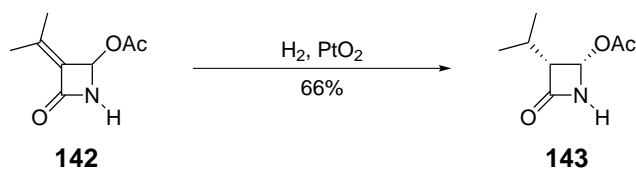
Scheme 2.36
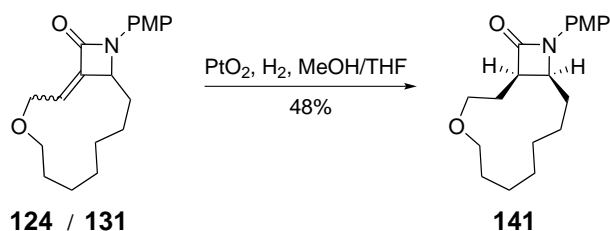
Scheme 2.37

2.4.3   Towards Tetrasubstituted Alkenes

Having established for the first time that α-methylene-β-lactams undergo RCM to form trisubstituted double bonds, we next wanted to ascertain if this could be extended to the preparation of tetrasubstituted alkenes, more closely related to phyllostictine A.
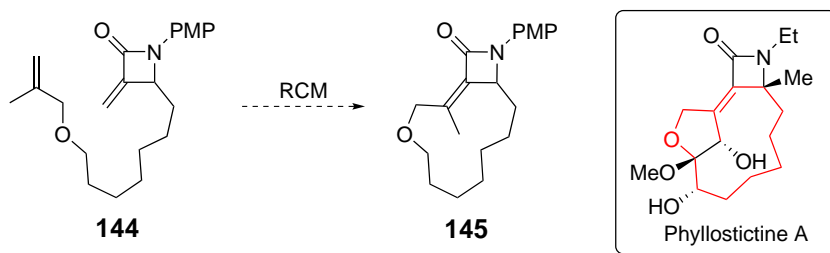
Scheme 2.38

Tetrasubstituted alkenes are difficult to form via RCM, and often require non-standard catalysts.[72] For example, Grubbs reported several catalysts derived from the **HG2** catalyst. These new catalysts were obtained through optimisation of the substitution pattern on the NHC aromatic rings.
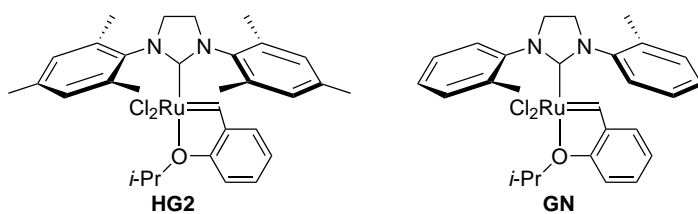
Figure 2.5

Using this modified catalyst **GN**, they were able to reduce the reaction times from: 24 h to 1 h in general. In some cases (entry 1, Table 2.4) **GN** improved the yield from 30% to >95%. Although **GN** is highly efficient with symmetric dienes (entry 1, Table 2.4), it was not able to catalyse the formation of the 6-membered lactone **146** (entry 3, Table 2.4).[72] Examples such as this, highlight the challenges faced when using a RCM strategy to form phyllostictine A.

Table 2.4

Entry	Substrate	Conversion %		Product
		HG2	**GN**	
1	**147**	30, 24 h	>95, <1 h	**150**
2	**148**	43, 24 h	88, 11 h	**151**
3	**149**	0	0	**146**

To explore this further, we set about the synthesis of diene **144** with a view to forming **145** (Scheme 2.38). Lactam **144** was synthesised using the versatile approach outlined previously. 1,8-Octanediol (**103**) was alkylated with 3-bromo-2-methylpropene using NaH and tetrabutylammonium iodide. Subsequent oxidation with PCC yielded the aldehyde **152** in 23% yield over the 2 steps.

The Bayliss-Hillman reaction of **152** with methyl acrylate **72** proceeded in 60% yield. Hydrolysis of ester **154** produced acid **155** in 74% yield. Subsequent amide coupling
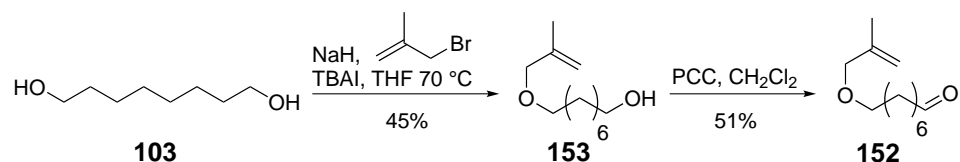
Scheme 2.39

yielded **156**, however, it could not be readily purified and co-eluted with excess *p*-anisidine. As a result, this amide was subjected to mesylation and ring closure without purification. The final lactam **144** was isolated free from *p*-anisidine in 32% yield over these 3 steps (Scheme 2.40).
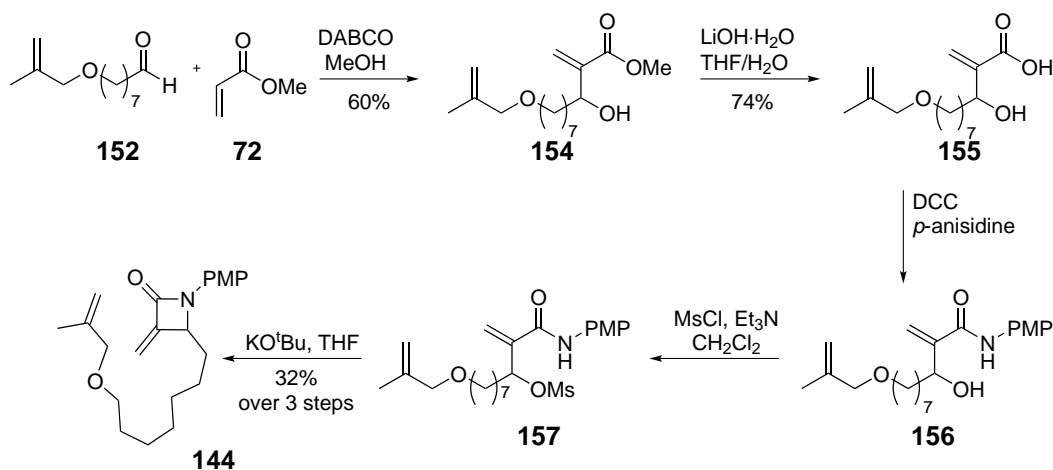
Scheme 2.40

Howell reported that the **HG2** catalyst was effective for promoting CM to form tetra-substituted α-methylene-β-lactams. Therefore, **144** was exposed to this catalyst using the standard conditions of 2 mM, at reflux for 24 h. Upon work up, no reaction was seen and the starting material was returned. α-Methylene-β-lactam **144**, was then subjected to RCM with the **G2** catalyst. Upon work up, chromatography and semi-preparative HPLC two products were isolated. The styrene coupled product **158** in 66% yield (relative to the styrene available from the catalyst) and lactam **159** (10%), where a methyl group had been added to the α-methylene-β-lactam (Scheme 2.41). Lactam **159** was finally assigned using a combination of mass spectrometry and ^{1}H-NMR.

Initially we were intrigued by the ^{1}H-NMR because where we were expecting no alkene signal, there were three each integrating to one hydrogen. Furthermore, a new doublet integrating to three hydrogens at 2.01 ppm (J = 7 Hz) was also seen. The distinctive α-methylene signals had been replaced with a quartet at 5.65 ppm, indicating that substitution had taken place. It was assigned as the *Z*-stereoisomer on the basis of the chemical shift. This quartet coupled strongly in the COSY spectrum with the new doublet at 2.01 ppm. Further evidence for this molecule was given by the mass spectrum. The observed mass of *m/z* 394 [M + Na]$^+$ was fully consistant with **159**.
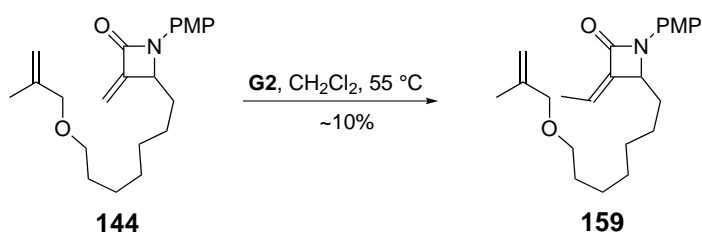
Scheme 2.41

Products such as this can arise from the isomerisation of the initial alkenes, promoted by thermal catalyst decomposition products.[88,89] In the case of **159**, it is proposed that a substrate induced decomposition occurs. Steynberg has used DFT to model substrate induced catalyst decomposition in both **G1** and **G2** catalysts (Scheme 2.42).[90] This DFT modelling proposed that, upon coordination of the substrate with the active Ru= species **160**, β-hydride transfer of the metallacyclobutane occurs forming **161** with an energy barrier of 24.3 kcal/mol for **G2**. The energy barrier for processes such as **160** to **162** is calculated to be 12 kcal/mol.[91]

The resulting Ru-allyl intermediate **161** now proceeds to form propene **163**, via hydride transfer to the terminal allyl carbon, with an energetic cost of -2.3 kcal/mol.[90] The resulting Ru^{II} species is inactive in metathesis, being coordinatively unsaturated.

Further evidence for this decomposition pathway was given when ethene saturated C_6D_6
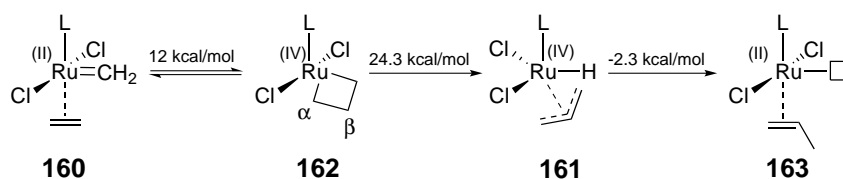
Scheme 2.42

solution was exposed to the **G1** catalyst. Following the reaction by ^{1}H-NMR, Steynberg and co-workers found that after 16 h a mixture of propene, 1-butene, 2-butene, cyclopropane, and isobutene could be observed, in a 60:21:10:7:2 ratio, determined by GC (Scheme 2.43).
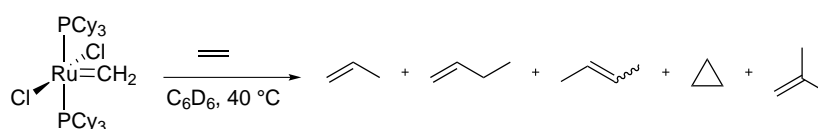
Scheme 2.43

Guided by these results, we propose the following mechanism to account for the formation of the methyl substituted product **159**. In lactam **144**, both alkenes are hindered and disubstituted, therefore, coordination with Ru to either alkene is slow and disfavored. Coordination with the α-methylene group could occur leading to β-hydride transfer, ultimately making the catalyst inactive (Scheme 2.44). A possible reason why this is not seen in the trisubstituted systems is that the terminal alkene is more reactive. Additional support for this comes from the observation that the linear dimers formed are derived from the terminal alkene and not from the α-methylene group.
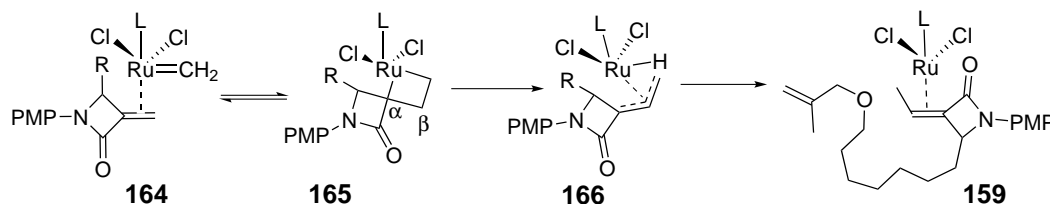
Scheme 2.44

2.4.4 *N*-Et lactam formation

As seen in Scheme 2.25, formation of lactam **101** was low yielding. One solution would be to interchange the PMP for an ethyl group after the RCM. Deprotection with ceric ammonium nitrate in MeCN/H_2O after 1 h, produced the unprotected lactam. This was immediately subjected to alkylation using KOH with Et-I as solvent. After semi-preparative HPLC, lactam **101** was isolated in 21% yield, over the two steps and as a single isomer (Scheme 2.45). The resulting product was identical by ^{1}H-NMR to that formed directly from lactam **114** (Scheme 2.24). On this occasion, full characterisation was obtained successfully.
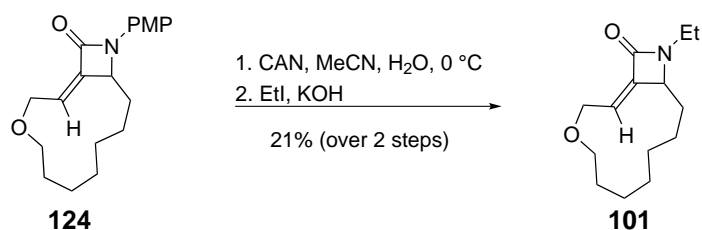
Scheme 2.45

It is appropriate to note that the quality of the CAN used in the deprotection was critical to success. Using old stocks, no reaction was seen even with under very forcing conditions (refluxing MeCN/H_2O, 24 h). However, newly purchased CAN, gave complete deprotection in 1 h.

2.5   *N*-Boc Protected 12-Membered Ring System

In Howell's paper on the cross metathesis of α-methylene-β-lactams, the best yields were achieved with Boc protected lactams.[57] With the *N*-Et lactams being low yielding and optimisation with PMP somewhat exhausted, we looked to use Boc protection to improve the yields of the RCM reactions. Importantly, *N*-Boc can be removed under mild conditions in the presence of β-lactams.[92]

The most convenient route to *N*-Boc derivative **167** was via the PMP protected lactam **122**. Subjection of **122** to CAN deprotection followed by immediate protection, with Boc$_2$O[57] yielded the Boc protected lactam **167**, in 35% yield over 2 steps (Scheme 2.46). No further efforts were made to optimise this reaction.
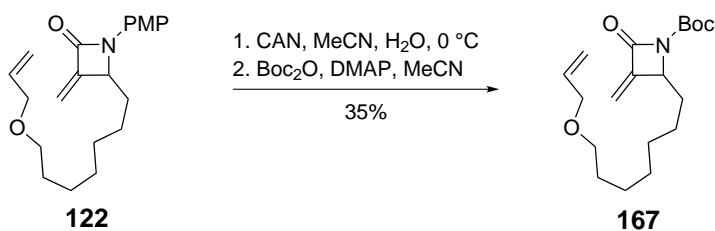
Scheme 2.46

Disappointingly, reaction of **167** with the **G2** catalyst, did not yield the 12-membered ring, but linear dimer **168** in 83% yield (Scheme 2.47).
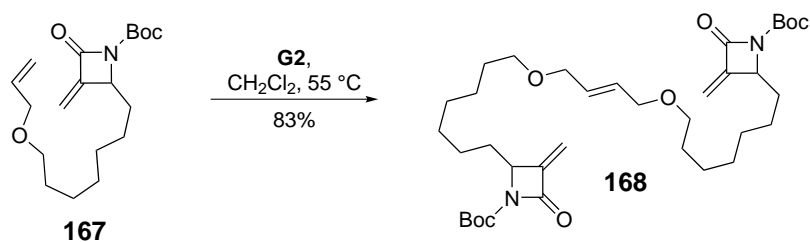
Scheme 2.47

Although Howell reported that Boc protected α-methylene-β-lactams are effective in CM, a small increase in the steric bulk of the lactam prevented reaction (Scheme 2.48). Since **167** is somewhat analogous to the structure of **169**, this may account for the disappointing results we obtained.

169 R = Boc, R^1 = Me		**171** R = Boc, R^1 = Me, 0%
170 R = Bn, R^1 = H		**172** R = Bn, R^1 = H, 74%
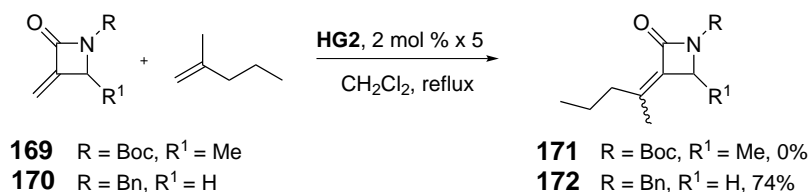
Scheme 2.48

Linear dimers are not unusual in RCM reactions that involve highly asymmetric dienes. For example, Blechert reported that acrylate **173** preferentially forms dimer **174**, rather than 5-membered ring **175** (Scheme 2.49).[64]

With no hint of the desired product being formed, no further attempts were made to optimise these reactions and instead we changed out focus to other members of the phyllostictine family.
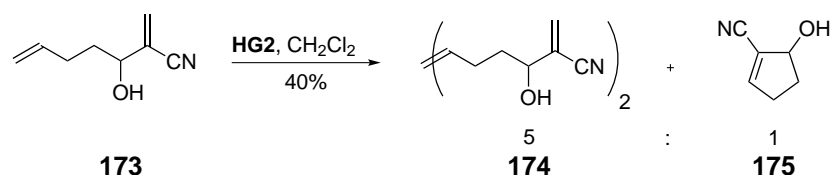
Scheme 2.49

2.6 Ring Closing Metathesis Studies Towards Phyllostictine C

Phyllostictine C contains a smaller 10-membered carbocyclic ring. In parallel with the other studies, we sought to examine if this smaller ring size could be made by the same RCM strategy. We were especially interested to ascertain if the smaller ring might result in the formation of the *E*-stereochemistry, since up to this point we had seen selectivity for the *Z*-stereoisomer.

We selected the PMP protecting group, as this had led to the best yields in RCM reactions so far. Thus we targeted the preparation of diene **176**, with a view to making **177** (Scheme 2.50).
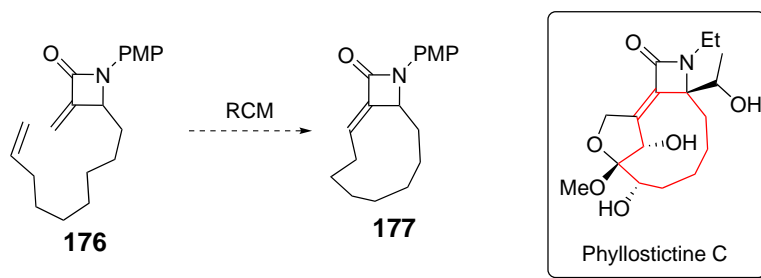
Scheme 2.50

The required diene **176**, was synthesised from the commercial available aldehyde **178**, according to the scheme laid out in Scheme 2.51. After successful reaction with methyl acrylate in a Bayliss-Hillman reaction, **179** was isolated in 39% yield. Subsequent hydrolysis with lithium hydroxide to **180** allowed amide coupling with *p*-anisidine, mediated by DCC to be achieved, forming amide **181** in 43% yield. Mesylate **182** was successfully formed in 61% yield. Finally, ring closure with KO*t*-Bu yielded **176** in a

modest 40% yield.
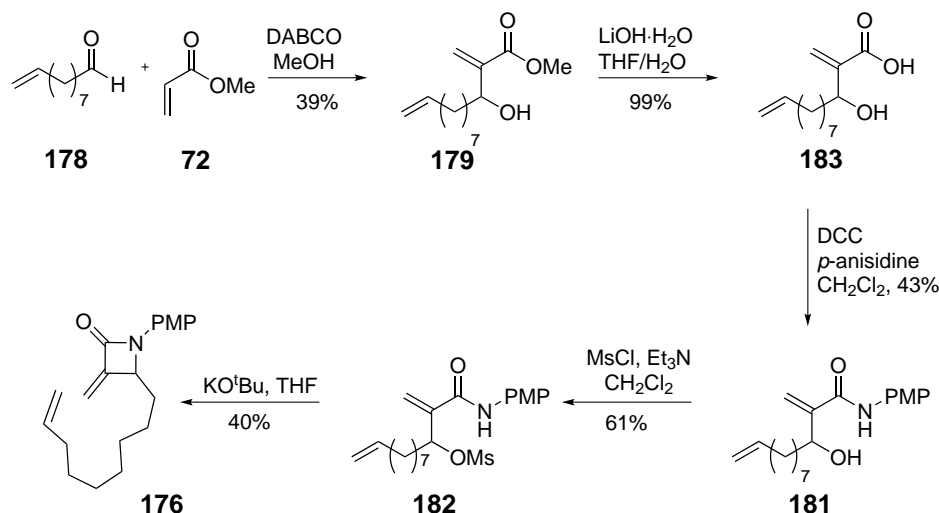
Scheme 2.51

Diene **176** was exposed to the **G2** catalyst at 2 mM in refluxing CH_2Cl_2. After 4 hours, no change was seen by TLC, and the reaction was worked up. After chromatography, the 20-membered dimer **90**, was isolated in 37% along with a trace of starting material (Scheme 2.52). Lactam **90** was identified by its distinctive m/z $[M + Na]^+$ 570, with none of the desired product m/z $[M + Na]^+$ 308 being seen. Linear dimer was also detected having m/z $[M + Na]^+$ 621 in the mass spectrum of some alkene containing fractions. However, we were unable to separate it from the impurities. The stereochemistry was assigned initially as Z on the basis of the alkene proton in the ^{1}H-NMR $\delta = 5.70\text{-}5.57$. It was consistent with those of the 22- and 24- membered rings which have $\delta = 5.52$ and 5.86-5.80 respectively. The stereochemistry was later confirmed by X-ray crystallography (Figure 2.6). Generally, 10-membered rings have the largest ring strain of the medium ring cycloalkanes[93] and therefore, it is perhaps not surprising that this reaction failed to yield **177**.

Undeterred, we reasoned that it might be possible to form the 10-membered ring from the more flexible lactam precursor **181**. Therefore, **181** was exposed to the same RCM
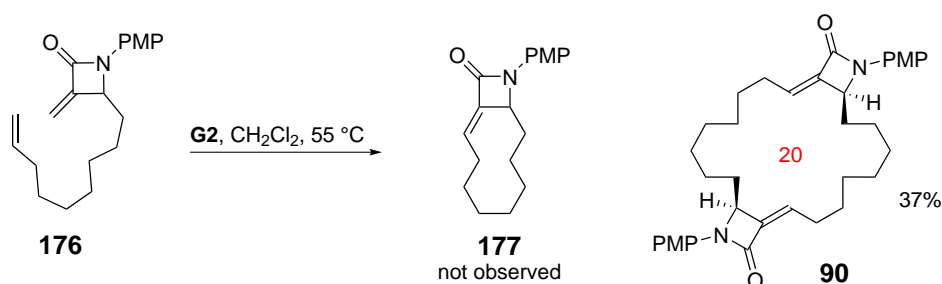
Scheme 2.52
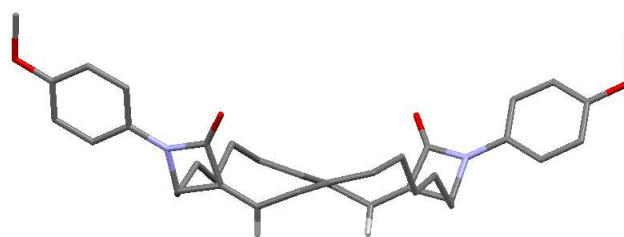
Figure 2.6

conditions as **176**. None of the desired compound was obtained after chromatography. The only isolated product was the linear dimer m/z [M + Na]$^+$ 657 in trace amounts, which contained the distinctive α-methylene singlets but no terminal double bond (Scheme 2.53). There is scope to potentially isolate the 10-membered ring by subjecting **184** to a more reactive catalyst, for example, the **SH** catalyst,[94] although these ideas were not pursued at this juncture.
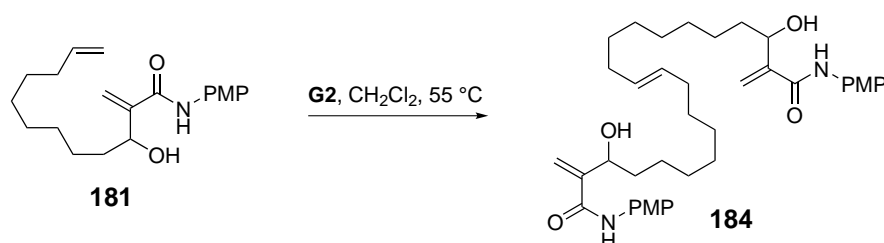
Scheme 2.53

Such behaviour has been seen with other Bayliss-Hillman derived substrates.[95] Kim reported that, exposure of **186** to **G2** in toluene, produced **187** rather than lactone **188**. The only other compound isolated was **189** resulting from initiation of the catalyst (Scheme 2.54).
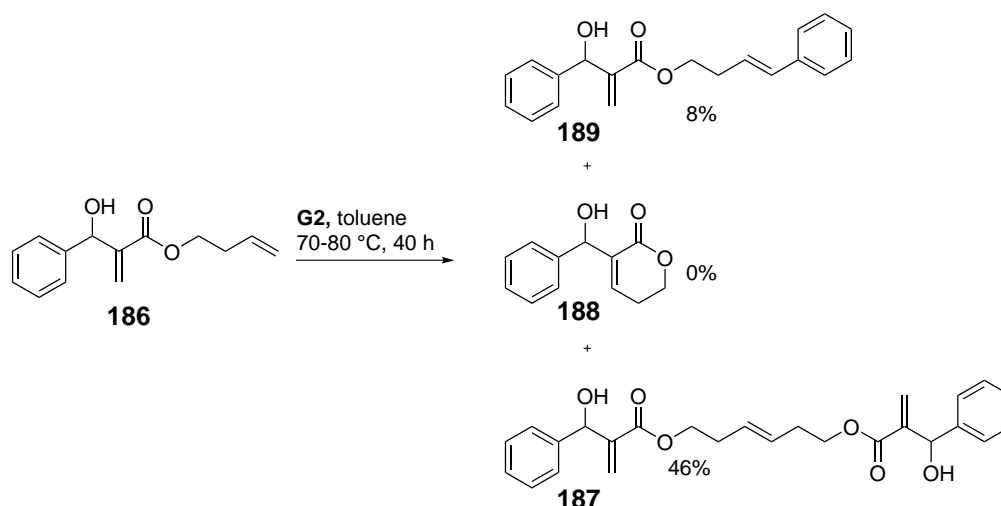
Scheme 2.54

Moreover, Song has shown that simple Bayliss-Hillman substrates **190**, will not form the desired 8- or 9-membered rings but instead the dimers **191** as the thermodynamic products (Scheme 2.55). [96,97]
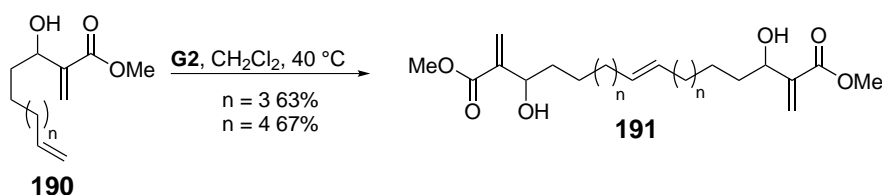
Scheme 2.55

2.7   Conclusions

α-Methylene-β-lactams have been shown to undergo RCM for the first time and the resulting methodology used to produce a simple analogue of phyllostictine A. Mechanistic studies have thus far been rather inconclusive. There is some evidence that the macrocyclic products maybe formed via an ADMET mediated mechanism, however, the reversibility of the reaction was demonstrated through re-subjection of products to the reaction conditions.

In general, reactions involving N-Et substituted β-lactams were poor yielding, for

reasons that are unclear. The desired 11-membered ring **65** could not be isolated, only the 22-membered dimer **192**. With the larger 12-membered precursor **102**, it was possible to produce 12-membered ring **101** in poor yields by the use of the crotyl group in the starting diene (Scheme 2.24). Side products were the 24-membered cyclic dimer **193** and the linear dimer **194**. Interestingly, selectivity for the *Z*-stereochemistry was observed.

A great improvement was made in the RCM of α-methylene-β-lactams by changing to the PMP protecting group. It is clear that 12-membered rings were more easily produced than 11-membered rings, as the reactions produced less dimeric products. Under optimised conditions of: **G2** catalyst, 0.25 mM substrate concentration, it was possible to produce **124** from **122** in 38% yield as a >8:1 *Z*:*E* isomers (Scheme 2.30). HPLC studies have shown that, dimer **88** is not the thermodynamic product and that 12-membered **124** is an equilibrium with it, under the ring closing metathesis conditions.[98]

Tetrasubstituted analogues such as **145** could not be produced using this methodology, however, non standard catalysts such as **GH** may yet prove fruitful in the future. An unusual methyl addition product **159** was seen when this was attempted (Scheme 2.41).

Although the Boc protected α-methylene-β-lactam **167** was active in RCM, it did not improve upon the results obtained with PMP protected lactam **122**. Clearly, the amide substituent is a very important factor in the outcome of these reactions.

Finally, we attempted to produce phyllostictine C analogues using this methodology. However, no trace of **177** was seen and the dimeric product **90** was obtained. More reactive catalysts may allows access to such 10-membered rings, although this is yet to be tested.

Chapter 3

Towards the α-methylene-β-lactam

core of phyllostictine A

3.1   New Routes to Form 4,4-Disubstituted α-Methylene-β-Lactams

In Chapter 2, the feasibility of using RCM to make the 12-membered ring of phyllostictine A was demonstrated. The synthesis of the RCM precursors being achieved via a lengthy but reliable route.[53]

Phyllostictine A contains not only a tetrasubstituted double bond but also a fully substituted chiral carbon at C-5 (Figure 1.4). From the survey of methods to form α-methylene-β-lactams carried out in Chapter 1, it is clear that no asymmetric methods for the synthesis of 4,4-disubstituted α-methylene-β-lactams currently exist. In light of this, we imagined that we would need to develop new methodology in this regard to complete the total synthesis.

Of the methods surveyed, three stood out in terms of their potential to form asymmetric α-methylene-β-lactams (Scheme 3.1). Firstly, the Staudinger synthesis of β-lactams could provide access to simple chiral analogues, however, for this to be effective, the methylene functionality would need to be installed after lactam formation. We proposed that this could potentially be achieved via epoxide rearrangement.

Secondly, by ring expansion of a methyleneaziridine. The advantage of this method would be that methyleneaziridines can be alkylated asymmetrically[99] allowing for effective formation of substituted α-methylene-β-lactams. Finally, carbonylative ring closure was appealing because it was imagined that both simple and complex substrates could be accessed readily under mild conditions, via the Overman rearrangement, for which asymmetric variants exist.[100]

Clearly, many questions remain regarding the use of these methods. For example, no general methods exist for rearranging epoxides to form α-methylene-β-lactams. Methyleneaziridines substituted at C-3 have not been shown to undergo carbonylation,

and the carbonylation of 2-bromoallyl amines does not currently extend to making 4,4-disubstituted α-methylene-β-lactams.
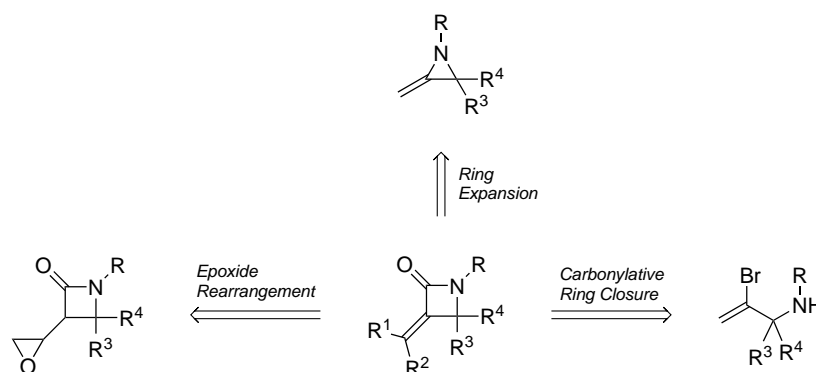
Scheme 3.1

This chapter details studies directed towards 4,4-disubstituted α-methylene-β-lactams by exploration of these different routes. It was imagined these studies might identify the most efficient routes to 4,4-disubstituted α-methylene-β-lactams relevant to the synthesis of the natural product.

3.2 Epoxide Rearrangement

The only report of α-methylene-β-lactams being formed directly from the rearrangement of epoxides, is as an undesired side product during the synthesis of (-)-SCH 57939, a potential cholesterol absorption inhibitor. Epoxide **195** was exposed to *p*-FC$_6$H$_4$ONa with the aim of forming lactam **196**. However, the rearrangement product **197** was isolated in 20% yield alongside **196**.[101]
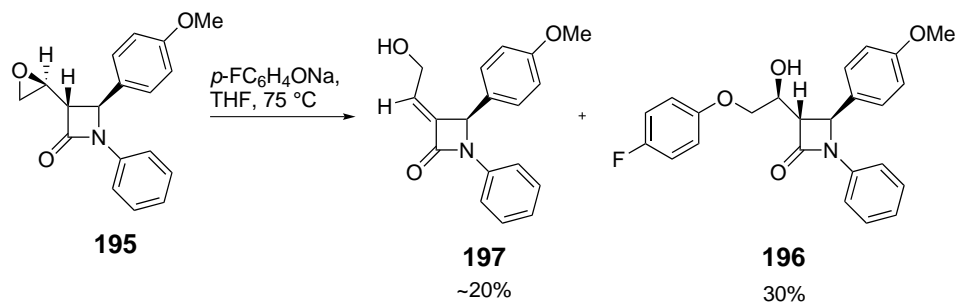
Scheme 3.2

Related methods based on cyclic carbonate rearrangements via loss of CO_2, have also been reported. For example, Meegan and co-workers used triphosgene to form cyclic carbonate **198**, which was subsequently eliminated with DBU to form α-methylene-β-lactam **199** in 72% (Scheme 3.3).[102] These examples gave us some encouragement to explore this strategy in the context of the total synthesis of phyllostictine A.
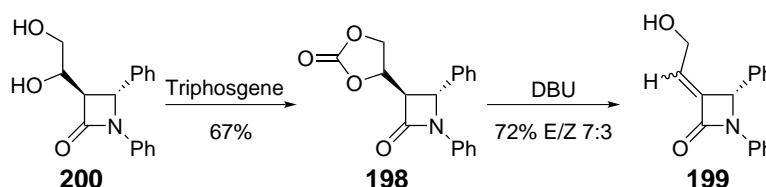
Scheme 3.3

To test the strategy of epoxide rearrangement to form α-methylene-β-lactams, we targeted the formation of **201**, by way of epoxide **202** (Scheme 3.4). This methodology has the potential to concurrently introduce the C-15 hydroxyl group.
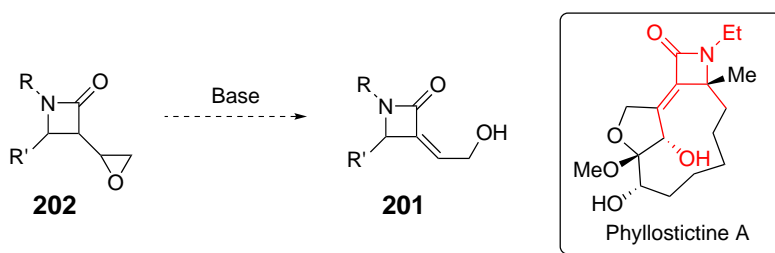
Scheme 3.4

To rapidly access lactams with which to test epoxide rearrangement, we used the Staudinger synthesis to form allylic lactam **203** (Scheme 3.5). The Staudinger synthesis uses the reactivity of an acid chloride to generate a ketene, that is then subject to nucleophilic attack by an imine forming a zwitterionic intermediate. This intermediate undergoes a conrotatory electrocyclic ring-closure to form the β-lactam as product.[103] Using this procedure is attractive because methods for controlling the enantioselectivity of the two stereocenters formed in the reaction are well established.[104] Hence, it could provide a route to phyllostictine A, if epoxide opening to form the corresponding α-methylene-β-lactams could be achieved.

Crotonyl chloride (**204**) and the preformed imine **205**, derived from aniline and benzaldehyde, were combined with Et$_3$N to form lactam **203** as a single diastereomer in 46% yield after chromatography (Scheme 3.5). The data were consistent with literature values. [105] Lactam **203** was then exposed to mCPBA, providing **206** as a 1:2.5 ratio of inseparable diastereomers, in 70% yield (Scheme 3.5). The relative stereochemistry of the two diastereomers was not determined, and the mixture was used in subsequent studies.
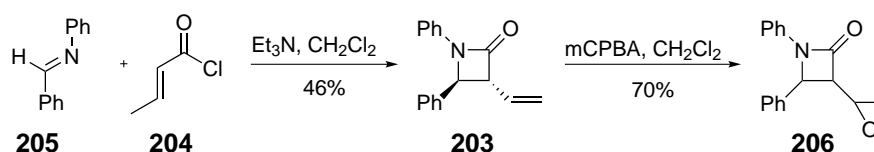
Scheme 3.5

With **206** in hand, a variety of non-nucleophilic bases were explored to try and open epoxide **206** (Table 3.1). DBN and DBU were initially trialled since they are bulky non-nucleophilic bases, and are often used in E1cB processes. However, reaction with **206** returned the starting material exclusively when stirred at room temperature (entries 1-2, Table 3.1). Similar results were obtained at 55 °C. KO^{t}Bu resulted in consumption of the starting material but lactam **207** was not observed (entry 5, Table 3.1).

Strong lithium bases were also investigated. After reaction at −78 °C with LDA, the crude ^{1}H-NMR appeared to have a small alkene peak at δ = 5.82 as a double, doublet. However, after column chromatography, **207** was not recovered (entry 6, Table 3.1).

LiNEt$_2$ was also reacted with **206**. In this case, two double doublets were seen at 5.80 ppm and 6.14 ppm potentially, derived from the two diastereomers of **207**. Again, after column chromatography, these products could not be isolated.

An acid promoted rearrangement was also attempted with CSA, in MeCN/DMSO

(1:1). However, this returned starting material even when heated to 80 °C (entry 6, Table 3.1). With no immediate success being achieved with this method, and the relativity harsh conditions that would likely be needed to effect introduction of the double bond, this strategy was abandoned.
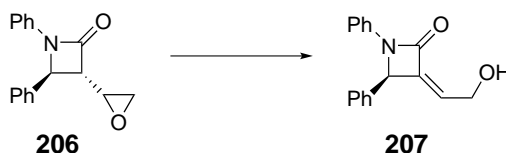
Scheme 3.6

Table 3.1

Entry	Reagent	Solvent	Temp. °C	Yield %
1	DBN	Toluene	rt	0
2	DBU	Toluene	rt	0
3	DBN	Toluene	55	0
4	DBU	Toluene	55	0
5	KO^{t}Bu	HO^{t}Bu	rt	0
6	LDA	THF	-78	trace
7	LiNEt$_2$	THF	rt	trace
8	CSA	MeCN/DMSO	80	0

3.3   Ring Expansion of Methyleneaziridines

The ring expansion of methyleneazirdines is a potentially powerful way to access the α-methylene-β-lactam of phyllostictine A. This is because substituents can be readily introduced at C-3 of the ring.[106] Furthermore, stereoselectivity can be achieved in this alkyation by use of a homochiral *N*-substituent. For example, Shipman and co-workers have shown that useful levels of diastereocontrol can be realised using the use of simple (*S*)-*N*-(1-phenylethyl) substituent (Scheme 3.7).[99,107]
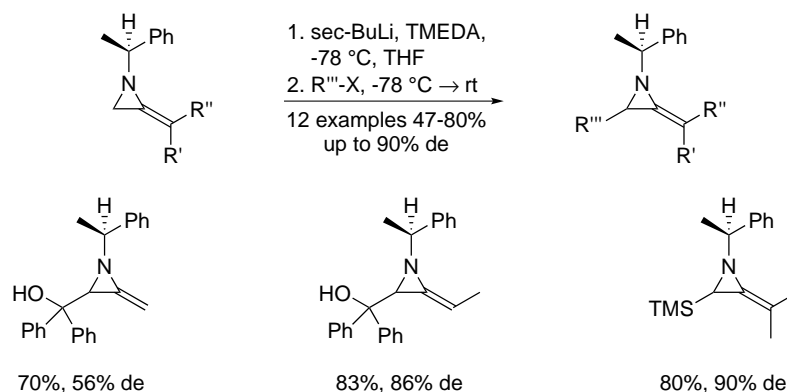
Scheme 3.7

Combining the known alkylation and ring expansion chemistries of methyleneaziridines, with the ring forming potential via RCM of α-methylene-β-lactams, one can conceive a strategy to phyllostictine A. For example, model systems could be constructed from methyleneaziridine **208** by double alkylation to give **209**, before undergoing carbonylation to form **210** and finally RCM to form α-methylene-β-lactam **211** (Scheme 3.8).
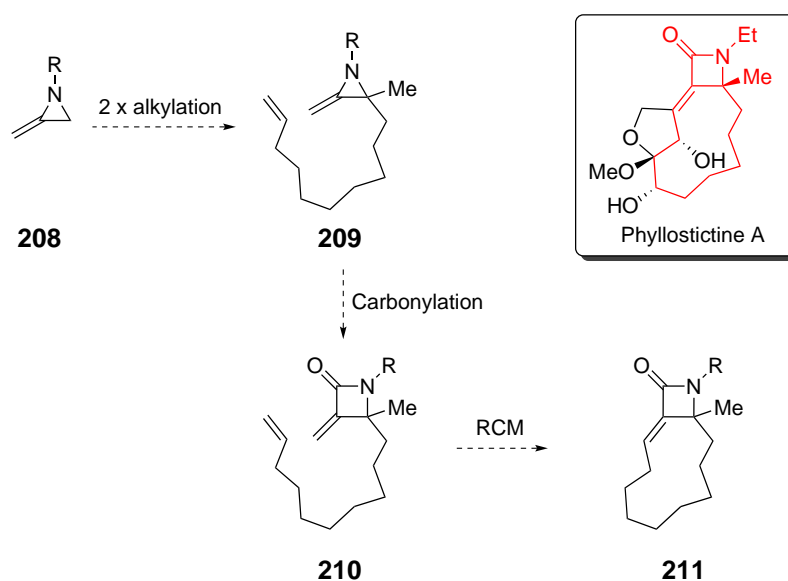
Scheme 3.8

3.3.1   Use of (*S*)-*N*-(1-Phenylethyl)-2-methyleneaziridine

Whilst *N*-ethyl methyleneaziridine would yield the closest analogues of phyllostictine A, it is very volatile, and difficult to isolate.[108] As an alternative, the versatile

methyleneaziridine **212** was used in initial studies. This methyleneaziridine **212** was prepared and isolated after distillation in 73% yield according to literature methods (Scheme 3.9).[109]
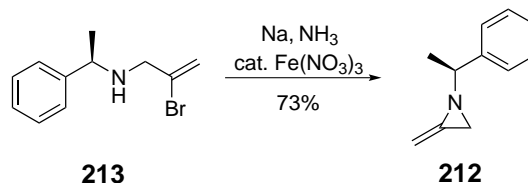
Scheme 3.9

Initial attempts to apply the carbonylation conditions reported by Alper to **212** were unsuccessful, returning only the starting material (Scheme 3.10).
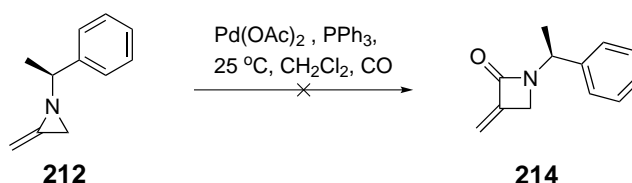
Scheme 3.10

It is not only methyleneaziridines that can undergo carbonylation to form α-methylene-β-lactams. Mori and co-workers developed carbonylation chemistry of 2-bromo-allyl-amines (Scheme 1.6).[110] However, the reported reaction uses HMPA as a solvent which is extremely toxic. Undeterred, we decided to explore this chemistry further. In our studies, HMPA was replaced with DMAc, since it is also a high boiling polar solvent but has lower toxicity. These new reaction conditions were applied to **213**. After column chromatography, lactam **214** was isolated in an encouraging 10% yield (Scheme 3.11). This known compound had data which matched that in the literature.[47]
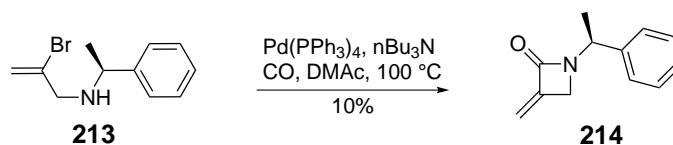
Scheme 3.11

These more forcing conditions where then applied to **212**. Upon work up, the crude ^{1}H-NMR, showed a large amount of Bu$_3$N, along with methylene peaks at δ = 5.73, 5.16. An acid wash (0.1 M HCl) was used to remove the Bu$_3$N. Unfortunately, the alkene signals were then lost, suggesting that the compond is sensitive to acid. The reaction was repeated without the Bu$_3$N and after work up and chromatography, α-methylene-β-lactam **214** was isolated in 3% yield (Scheme 3.12).
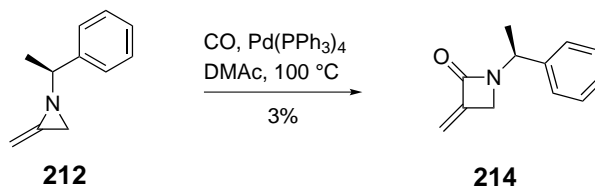
Scheme 3.12

With a method for carbonylating methyleneaziridines at least demonstrated, we wished to test the carbonylation potential of substituted methyleneaziridines. To achieve this, iodide **215** was first synthesised from alcohol **216**. Tosylation of alcohol **216** with tosyl chloride and subsequent displacement with excess NaI gave the required iodide in good yield (Scheme 3.13).
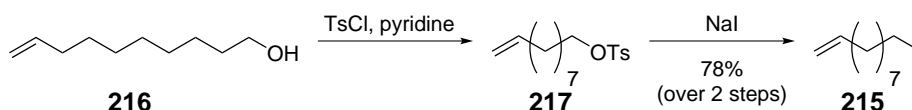
Scheme 3.13

Iodide **215** has not previously been used in the alkylation of methyleneaziridines. The alkylation chemistry was initially conducted, using 1.3 equivalents of the methyleneaziridine. After forming the methyleneaziridine anion over 5 h at −78 °C, iodide **215** was added. After work up, **218** was observed in the ^{1}H-NMR as a 40:60 mixture of diastereomers, along with unreacted **215** (Scheme 3.14). Several attempts were made to purify this mixture via distillation, since methyleneaziridines are not stable to chromatography. However, it did not prove possible to separate **218** from **215**.
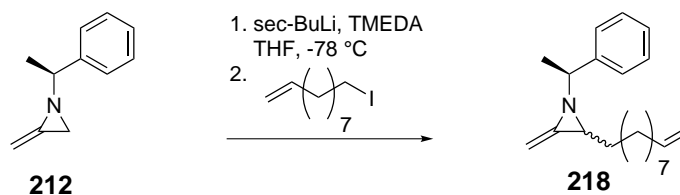
Scheme 3.14

Having established that electrophile **215** is useful in methyleneaziridine alkylation chemistry, we looked to apply it to the N-Et derivative **219**, as any unreacted starting methyleneaziridine could be removed due to its increased volatility.

3.3.2   Use of *N*-Ethyl Methyleneaziridine

Formation of bromide **220** was achieved by reaction of 2,3-dibromopropene (**221**), with EtNH$_2$ in H$_2$O in quantitative yield (Scheme 3.15).
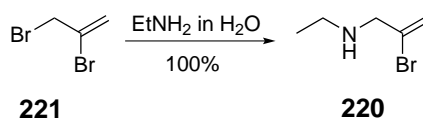
Scheme 3.15

Cyclisation of **219** was successful with Na in liquid ammonia, but isolation proved troublesome (Scheme 3.16). After work up and distillation, the residue contained Et$_2$O **222**, the alkyne side product **223**, alongside methyleneaziridine **219**, in a 30:12:58 ratio (Scheme 3.16). This mixture was used to perform preliminary carbonylations and alkylation reactions.
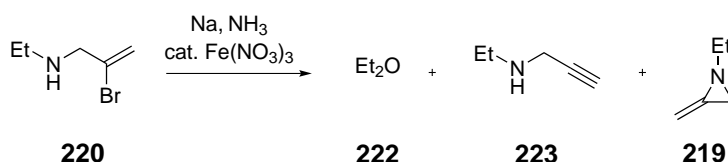
Scheme 3.16

Firstly, carbonylation of methyleneaziridine **219** was attempted. Applying the conditions

used with (S)-*N*-(1-phenylethyl)-2-methyleneaziridine (**212**), none of the desired lactam **224** was isolated (Scheme 3.17).

Pd(OAc)$_2$, PPh$_3$
100 °C, DMAc, CO

219   **224**
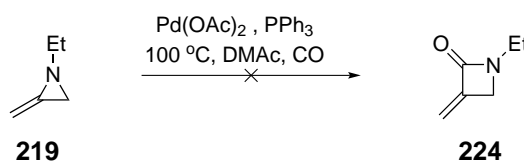
Scheme 3.17

Concerned that the impurities within **219** could be poisoning the catalyst, **219** was alkylated in the hope that the resulting product could be purified. *sec*-BuLi was used to generate the anion of methyleneaziridine **219**, then iodide **215** was added. After work up, methyleneaziridine **225** was observed with 73% conversion calculated by analysing the ratio between excess **215** and **225** and correlating that with the isolated weight. 0.1 eq of **215** remained in the reaction mixture (Scheme 3.18).

1. sec-BuLi, TMEDA
   THF, -78 °C
2.
215

73% conversion

219   **225**
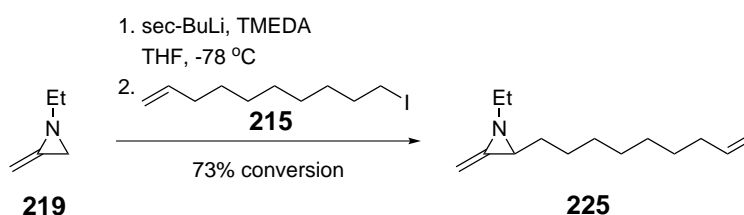
Scheme 3.18

Carbonylation of **225** to form the corresponding lactam **226** was attempted. The conditions used were based on the best conditions employed in section 2.3.2 using Xantphos®, palladium acetate, DMAc and 100 °C. Disappointingly only starting material was recovered (Scheme 3.19).

Pd(OAc)$_2$, Xantphos
nBu$_3$N, CO
DMAc, 100 °C

225   **226**
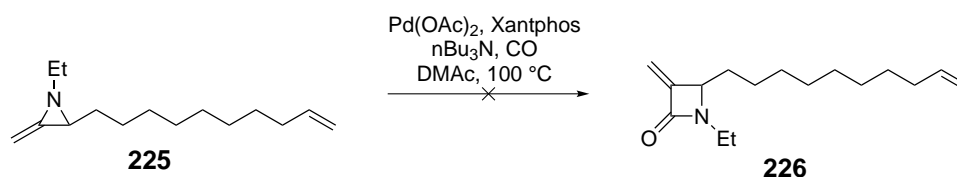
Scheme 3.19

The major problems encountered making the methyleneaziridine substrates in a high state of purity and the very low if any conversion to product, led us to abandon this approach.

3.4   Towards Quaternary α-Methylene-β-Lactams

The Overman rearrangement is a variant of the Claisen rearrangement, a carbon-carbon bond forming reaction. An allyl vinyl ether forms a γ,δ-unsaturated carbonyl via a [3,3]-sigmatropic rearrangement.[111] In the Overman rearrangement, an imine provides one of the required π bonds, and after rearrangement, furnishes allylic amines. Crucially, β,β-disubstituted amines can be formed. For example, Nakajima produced amide **227** in 90% yield from imidate **228** (Scheme 3.20).[112] Asymmetric Overman[113] and aza-Claisen[114] rearrangements have been used to form β-monosubstituted amines (Scheme 3.21).
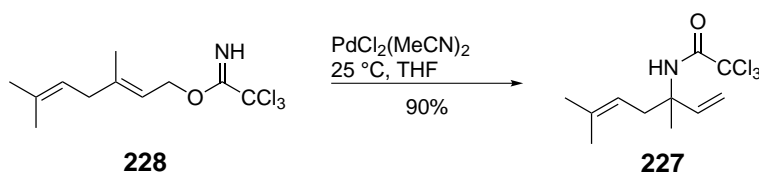
Scheme 3.20
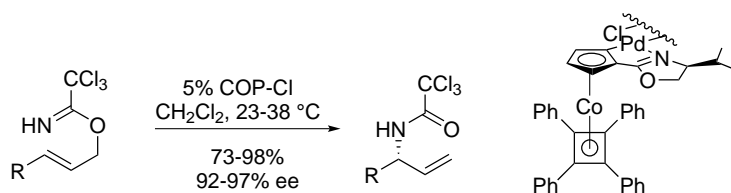
Scheme 3.21

From the methods surveyed in Chapter 1, it was clear there are currently no methods for creating chiral 4,4-disubstituted α-methylene-β-lactams. However, we imagined that Mori's[110] synthesis involving the carbonylation of 2-bromo-allyl amines could provide a route to 4,4-disubstituted α-methylene-β-lactams, since the Overman rearrangement might allow access to the requisite precursors as single enantiomers. We targeted lactam **229** as a suitable model substrate, potentially accessible via carbonylation of amine **230**

(Scheme 3.22).
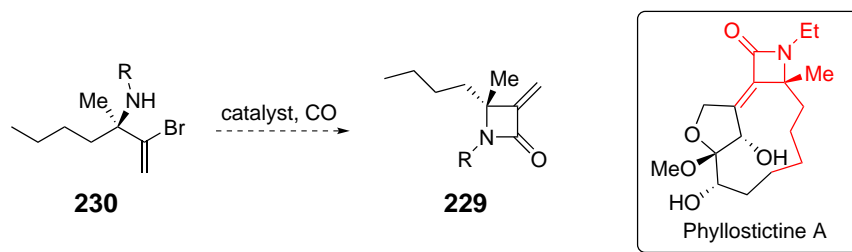
Scheme 3.22

Thus, we set about the synthesis of amine **230**, which could be used to make racemic **229** with a variety of *N*-substituents by reductive amination. Alkene **231** was synthesised in 2 steps by cuprate addition to ethyl butynoate (**232**) and subsequent reduced with DIBAL (Scheme 3.23).

Formation of trichloroacetimidate **233** was straightforward from **231** throught the use of trichloroacetonitrile and DBU. This was used without purification and immediately exposed to the rearrangement conditions. Either thermal rearrangement in toluene with K_2CO_3 or a Pd^{II} catalyst can be used to promote the rearrangement, and both methods were explored. Thermally promoted rearrangement to **233** produced significant decomposition and low yields (5%). Yields of **233** with $Pd[(Cl)_2(MeCN)_2]$ were slightly improved (18%), although this reaction clearly needs further optimisation.

Formation of vinyl bromide **234**, crucial for the carbonylation, was achieved in the following manner. Addition of PhSeBr across the double bond gave **235**. Oxidation with ozone at -78 °C yielded selenoxide **236** which was added drop wise to refluxing toluene for 30 min, to yield **234** in 12% yield over three steps (Scheme 3.23).[115] mCPBA and peracetic acid were explored as alternative oxidants to O_3, however, neither improved the yield.
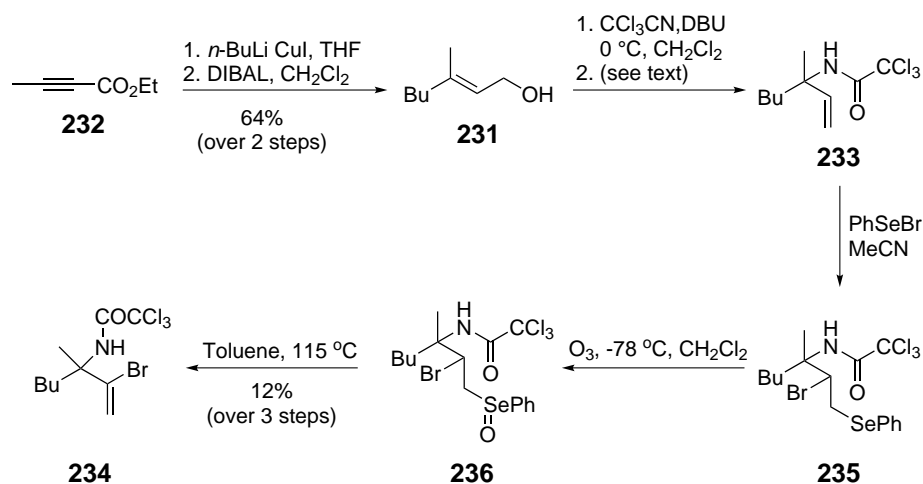
Scheme 3.23

To overcome the very low yield for the conversion of **233** to **234**, bromine installation might be possible from the outset (Scheme 3.25). Overman rearrangements of vinyl bromides are known as illustrated in Scheme 3.24.[116] To make the requisite vinyl bromide, we explored quenching of cuprate **237** with a variety of electrophilic bromine sources (NBS, Br_2, TBCHD). Unfortunately, no evidence for the formation of **238** was seen.
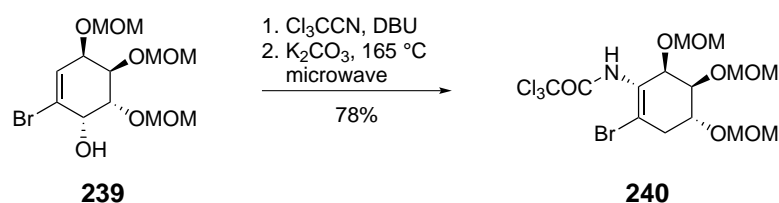
Scheme 3.24
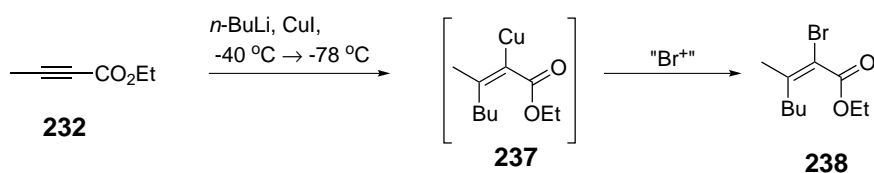
Scheme 3.25

The very low yields and time consuming nature of this chemistry, prevented us from moving forward in the synthesis. Recently, work published by Li[117] in early 2014 and

highlighted in Chapter 1, provides new methodology for the synthesis of α-methylene-β-lactams from allyl amines via a C-H activation process. Dr. Marca via the Overman rearrangement and Dr. Geden via the aza-Claisen rearrangement are continuing to investigate this chemistry within the Shipman group, with the aim of applying it to the total synthesis of phyllostictine A.

3.5   Conclusions

Three strategies for the synthesis of α-methylene-β-lactams have been explored. The Staudinger method provided rapid access to allyl lactams, that allowed us to test the epoxide rearrangement step, however, from this model study it was clear that such β-lactams do not readily undergo epoxide rearrangement and overly harsh conditions needed would be unlikely to be applicable to the total synthesis of phyllostictine A.

The strategy that used carbonylation of methyleneaziridines, might still prove useful. However, at this time, the chemistry does not appear practical and is very experimentally demanding (Scheme 3.12).

The Overman rearrangement may provide a useful way to build carbonylation substrates. Unfortunately, difficulties associated with adding the requisite bromine atom proved insurmountable in the time available, although new chemistry that negates this need[117] might ultimately allow us to overcome these difficulties.

Clearly, the synthesis of chiral 4,4-disubstituted α-methylene-β-lactams remains a significant challenge that has yet to be solved in our laboratory.

Chapter 4

Herbicidal Activity

4.1 Establishment of Herbicdial Activity of Phyllostictine A

Chapter 1 described the known activity of phyllostictine A. To be able to test new analogues and begin to understand structure-activity relationships, it was necessary to establish an ED_{50} value for the natural product. We selected *Chlamydomonas reinhardtii* (P. A. Dangeard) as a model organism to probe the herbicidal activity of our analogues. This chapter details work to develop two different assays of herbicidal activity based on the growth rates of *C. reinhardtii*. We aimed to: (*i*) establish if phyllostictine A is active against *C. reinhardtii*; (*ii*) determine the ED_{50} for phyllostictine A and compare its activity to known commerical herbicides; and (*iii*) evaluate a series of our synthetic phyllostictine A analogues to develop initial structure-activity relationships.

We were generously donated a 10 mg sample of phyllostictine A by Evidente to undertake aspects of the work. The integrity of the sample was verified by NMR spectroscopy (Appendix I). Due to the small quantities of phyllostictine A available to us, the assays were first optimised and developed with two commercial herbicides (glyphosate and s-metolachlor).

4.2 *Chlamydomonas reinhardtii*

C. reinhardtii is a model organism that was one of the first green algae to have its genome studied and sequenced.[118] It is a photosynthetic biflagellate unicell, with a life cycle of 7-10 h under ideal laboratory conditions.[119] This short life cycle coupled with its sensitivity to a wide range of herbicide families[120] makes it a good model for screening herbicidal activity. Furthermore, as higher plants evolved from green algae it has the advantage of sharing many biochemical and metabolic pathways with higher plants.[121] *C. reinhardtii* has already been used as a model organism to explore adaptation in the presence of a number of environmental stresses, as well as exploring many of the basic physiological processes in plants.[118]

Reboud and co-workers have already established that many commercial herbicides inhibit the growth of *C. reinhardtii*.[122] These values will allows us to compare any novel analogues with established commercial herbicides. Furthermore, Neve and co-workers have used *C. reinhardtii* for studying herbicide cycling and how it relates to resistance.[123]

There are relatively few reports of *C. reinhardtii* being used to screen potential herbicides,[124] despite it being commented[120,122,125] that it has much potential in this regard. *C. reinhardtii* has been reported in screening assays that monitor residual herbicide levels in food[120] and as an initial screen of photosystem II inhibitors in water run off, prior to further analysis.[126]

4.3   Herbicidal Activity of Phyllostictine A

4.3.1   Algal-Lawn

The first assay investigated was an "algal-lawn" type assay. In this assay, *C. reinhardtii* in a 0.5% agar solution is applied to a Petri dish containing a 1.5% agar solution of Bold's Medium. Herbicides were then applied to the agar in the form of filter paper disks. The *C. reinhardtii* was then allowed to grow. If the herbicide was active, rings of inhibition were seen. The results are visual and qualitative in nature. Li and co-workers have used this lawn style assay to semi-quantitatively identify, the relative activity of 11 herbicide families.[125] *C. reinhardtii* was shown to be sensitive to herbicide families that affect its susceptible modes of action. However, some herbicides, such as the cellulose cell wall synthesis inhibitor isoxaben were inactive presumably because *C. reinhardtii* has glycoprotein based cell walls.[125] Other algae have also been reported as active in algal-lawn type assays,[120] although these were not explored herein.

Taking inspiration from Evidente's original paper describing phyllostictine A activity in leaf puncture assays,[1] and modifying the method as described in section 5.2, three concentrations of phyllostictine A were selected (Table 4.1). s-Metolachlor was used as a standard herbicide control (the activity against *C. reinhardtii* of which had been established by the Neve group) and Bold's media used as a control. Figure 4.1 shows clearly that at 10^{-3} M, phyllostictine A shows strong inhibition in the growth of *C. reinhardtii*. In contrast, s-metolachlor does not show a clear zone of inhibition but rather a general reduction in growth at 14.1 nM and 1.41 nM (s-Metolachlor is an very potent herbicide reflected in the low concentrations required to inhibit growth). Phyllostictine A shows similar visual activity to the synthetic auxins tested by Li, showing distinct but small zones of inhibition. Mitosis inhibitors such as chloropropham showed similar results to s-metolachlor (also a mitosis inhibitor) with larger clearing zones (Figure 4.2).[125]
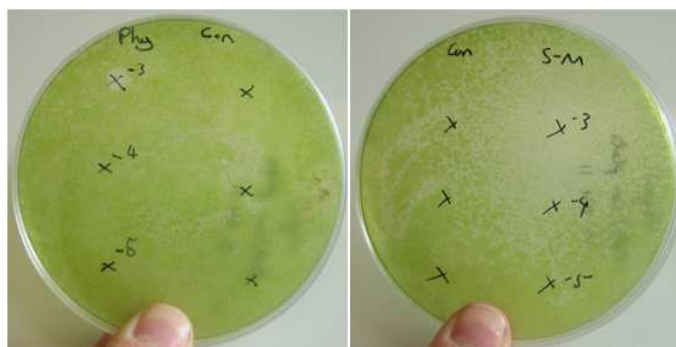
Figure 4.1

Table 4.1

s-metolachlor	Result[a]	Phyllostictine A	Result
14.1 nM	+	10^{-3} M	+
1.41 nM	+	10^{-4} M	-
0.141 nM	-	10^{-5} M	-

[a]+ = inhibition, - = no inhibition
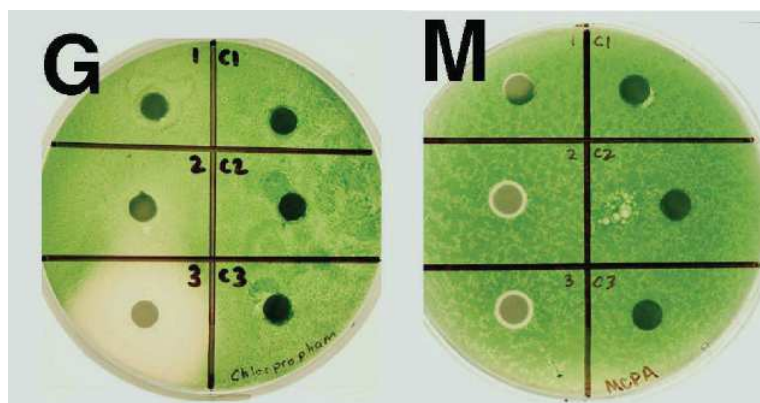
Figure 4.2 – Li's results where G = chloropropham and M = 2-methyl-4-chlorophenoxyacetic acid.[125]

4.3.2 Quantitative assays using *C. reinhardtii*

The second assay that was explored was a "liquid culture" assay. The liquid culture assay is a quantitative assay that enables the measurement of absorbance values, which can be correlated with an estimate of population.[122] In previous studies, Lagator established a correlation between number of cell divisions and optical density at 750 nm (OD_{750}).[127] Once analysed with a dose-response model (section 5.2.4), ED_{50} values can be calculated allowing for quantitative assessment of the potency of different herbicides.

This technique employing *C. reinhardtii* has already been used by the Neve group.[123,128] Specifically, it was used to model the evolution of herbicide resistance. However, the 20 mL scale of the reported assay was found to be unsuitable for us as only limited quantities of the natural product and novel analogues were available. As a result we decided to use 96-well plates which have a total volume of 200 µL, leading to a 100-fold reduction in scale.

Before committing to using our limited supply of phyllostictine A this miniaturized micro-well plate assay was first developed using the commercial herbicide glyphosate. Glyphosate was tested at a range of concentrations above and below the minimum inhibitory concentration of 0.39 mM,[127] to ensure a proper dose-response was observed. The assay was repeated over several weeks to ensure its reproducibility.

Although some variability was observed between experiments, glyphosate in this assay was found to have a mean ED_{50} of 0.3 mM which is comparable to published value of 0.2 mM[120] in other liquid culture assays.

Glyphosate Dose Response
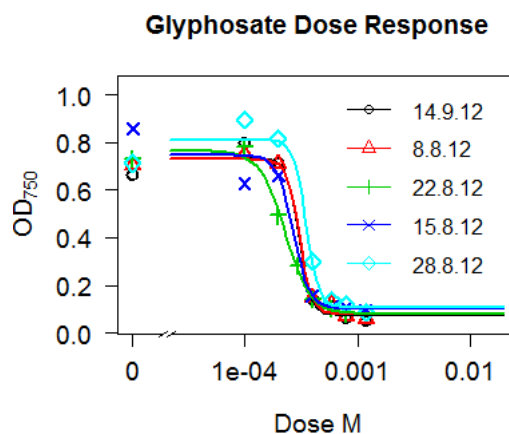
Figure 4.3

Table 4.2

Experiment	ED_{50} (mM)	std. error (mM)
1	0.301	0.0355
2	0.303	0.0355
3	0.227	0.0146
4	0.267	0.0409
5	0.348	0.0657

Having optimised the assay with a commercial herbicide, we next explored the activity of phyllostictine A. Phyllostictine A was dissolved in EtOH and a stock solution of 0.2 M was made up with Bold's medium. The concentrations studied varied between 10^{-2} and 10^{-4} M since activity was not seen below 10^{-4} M during the algal-lawn studies (Figure 4.1). The assay was repeated just twice using phyllostictine A because of the limited amounts available.

Table 4.3

Experiment	ED_{50} (mM)	std. error (mM)
1	0.821	0.0989
2	0.361	0.0448

The stability of the phyllostictine A compound in solution may account for the discrepancy in determined ED_{50}, although other explanations could account for the variability. From this data, we conclude that phyllostictine A has an ED_{50} in the sub-mM range, consistent with the what was seen in the algal-lawn assay. It has similar potency to glyphosate against *C. reinhardtii*.
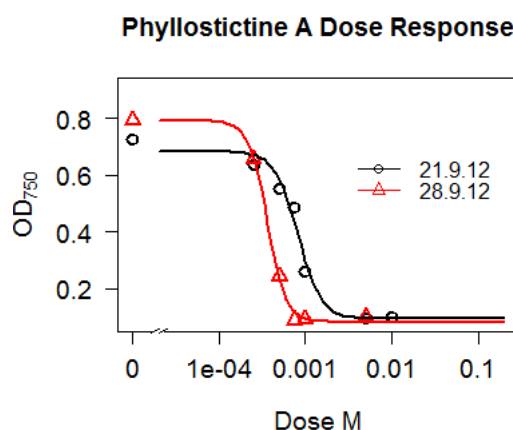
Figure 4.4

4.4 Activity of Analogues

Additionally, we have explored the activity of a small number of synthetic analogues made in Chapter 2.

Lactam **73** was tested in three separate experiments in the 96-well plate assay, with some variability in ED_{50} again observed (Table 4.4). However, it is clear that this simple lactam has mM activity against *C. reinhardtii*. Lactam **73** had a mean ED_{50} of 4 mM whilst phyllostictine A was about an order of magnitude more potent (ED_{50} = 0.6

mM).
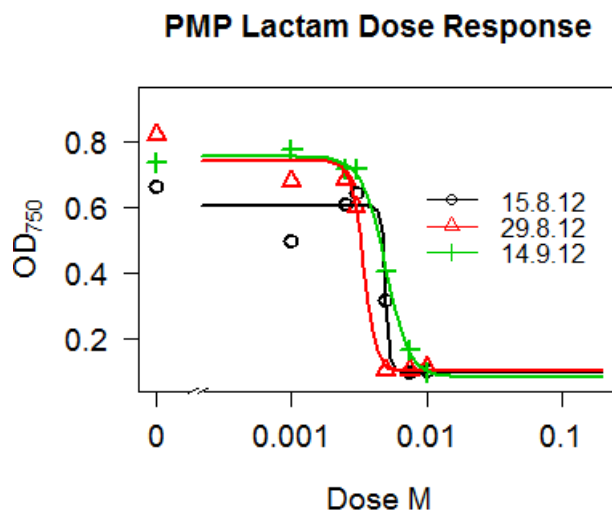
Figure 4.5

Table 4.4

Experiment	ED$_{50}$ (mM)	std. error (mM)
1	4.95	0.407
2	4.95	1.081
3	3.41	0.201

Due to a laboratory move and the unavailability of the incubator room, a new assay was designed and subsequently run by Nicole Pereira. The new assay was based on the 20 mL culture tube assay [127] and miniaturised to a 5 mL volume. In other words, larger volumes than the 96-well plate. This volume allows for ideal growth conditions (continuous light and rotary shaking) ultimately leading to improved reproducibility.

The analogues tested using this method are show in Figure 4.6. The majority of the compounds did not have good solubility in water or in 0.5% DMSO in H$_2$O. As a result, only a very narrow range of concentrations could be used.

Analogue **74** was the most active at 0.05 mM, totally inhibiting the growth of *C.*
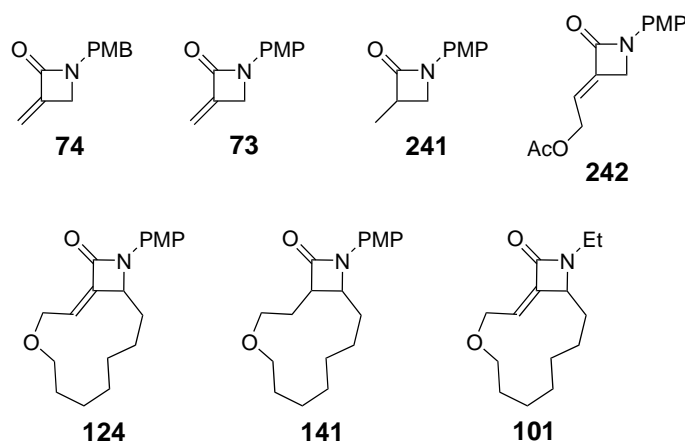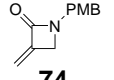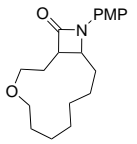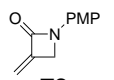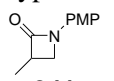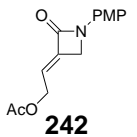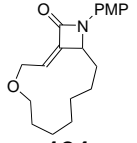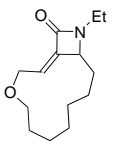
Figure 4.6

reinhardtii at this concentration. Furthermore it was more active than glyphosate at this dose. The next most active compound was the saturated lactam **141**. This is interesting because it implies that the unsaturation is not important, and may imply that this functional group is not important in phyllostictine A. Bicyclic lactam **124** did not show an expected dose response being more active at lower concentrations. This finding was reproducible. For example, at 0.01 mM, **124** inhibited the growth of *C. reinhardtii* to 44% of the control, however, at 0.05 mM 65% of the control was recorded. A possible explanation is **124** has poor solubility in the Bold's media and the constant agitation of the incubator caused the compound to precipitate during the seven days of the assay. This trend was not seen with related compounds **73** and **241**. Lactam **141** was not more active than **73** at any of the concentrations tested. It is therefore not clear as to whether the unsaturation has an affect on the activity or not.

Most disappointingly, lactam **101** did not show good activity at 0.05 mM. It is most closely related to the structure of the natural products containing both the 12-membered ether ring, and the N-Et substituted β-lactam.

Lactam **242** shows very poor activity as well as poor solubility. This was disappointing to us because we believed that the addition of a hydrophilic acetate group would improve solubility. An interesting experiment would be to hydrolyse the acetate

Table 4.5

Concentration	0.001 mM		0.01 mM		0.025 mM		0.05 mM		0.1 mM		0.25	
	% Control	sterr.	% Control	sterr.	% Control	sterr.	% Control	sterr.	% Control	sterr	% Control	sterr
74	-	-	60	33	-	-	0	0.3	-	-	2	0.3
141	-	-	25	13	-	-	2	0.3	-	-	-	-
73	82	11	29	5	-	-	5	0.0	4	2	-1	0.1
Glyphosate	101	7	102	2	-	-	28	15	-1	1	0	1
241	-	-			-	-	37	7	22	2	19	1
242	-	-	122	19	-	-	42	21	-	-	-	-
124	-	-	45	10	52	15	66	10	-	-	-	-
101	91	9	83	10	-	-	81	6	-	-	-	-

group to form the allylic alcohol, however, hydrolysing an acetate selectively in the presence of the sensitive β-lactam would be very challenging.

Since it was demonstrated that phyllostictine A is active against *C. reinhardtii*, we must conclude that other functionality in the natural product are essential for bioactivity. Why **73** and **74** are active is consequently difficult to understand, although their potency may arise from the aromatic nucleus.

4.5   Conclusions

For the first time phyllostictine A has been shown to have activity against *C. reinhardtii*. It was shown to be active in two different assays. In the qualitative algal-lawn assay, it produced zones of growth inhibition between 10^{-3} and 10^{-4} M. In a quantitative 96 well plate assay, a mean ED_{50} value 0.58 mM was determined. This level of potency was similar to that of glyphosate (0.3 mM). Reproducability appears to be an issue on scaling the assay down to the format.

A new culture tube assay was developed by Pereira which has proved to be more reproducible. It was used to test 7 synthetic compounds produced in this thesis, and these were ranked in terms of their potency at 0.05 mM. Solubility appears to be a critical factor, with the less soluble compounds producing some odd data.

The most active compound **74** identified has little in common with phyllostictine A, where as **101** most closely related to it had poor activity. From this initial structure activity relationship study it appears as though the alkene contained within phyllostictine A is not responsible for the observed herbicidal activity since its removal in simple bi-cyclic analogues increases potency. This trend is not observed in mono-cyclic analogues indicating they potentially work via different modes of action. Clearly further analogues and alternative assays will need to be used to develop a clear picture of the

structure-activity relationship in this compound class.

Chapter 5

Experimental

5.1 General Information

All reactions were performed under an atmosphere of dry nitrogen in flame- or oven-dried glassware unless otherwise stated. Anhydrous solvents were purchased from Sigma-Aldrich or Fisher Scientific in Sure-Seal bottles for use as reaction solvents. All other solvents were reagent grade and used as received.

Commercially available starting materials were used without further purification unless otherwise stated. Thin layer chromatography was performed on pre-coated aluminium-backed plates (Merck Silicagel 60 F254), visualised by UV 254 nm then stained with potassium permanganate or ceric ammonium molybdate solution. Flash chromatography was performed using Fluorochem LC60A 40-63 micron silica. HPLC was performed using an Agilent 1100 series, with an Agilent Prep C-18 scaler column. Melting points were recorded on a Gallenkamp MPD350 apparatus and are reported as observed. Single crystal X-ray diffraction data were obtained using an Oxford Diffraction Gemini XRD system. Infrared spectra were recorded on a Perkin Elmer Spectrum 100 FT-IR spectrometer or a Bruker Alpha Platinum ATR spectrometer with internal calibration.

Low resolution mass spectra were recorded on an Esquire 2000 platform with electrospray ionisation, high resolution mass spectra were obtained using a Bruker MicroTOF spectrometer. Nuclear magnetic resonance spectra were recorded on Bruker DPX (300, 400, 500 or 600 MHz) or AV (400 or 700 MHz) spectrometers. Chemical shifts are reported in parts per million relative to the standard tetramethylsilane. The peak multiplicities were specified as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint). Coupling constants (J) are reported in Hertz.

Biological manipulations were performed in a flow hood, using autoclaved equipment.

5.2 Materials and Methods

5.2.1 Culture Conditions

The stock populations used were maintained in disposable 25x150 mm borosilicate glass tubes containing 20 mL of modified Bold's Medium[129] in an orbital shaker incubator. The cultures in the incubator were maintained at 28 °C, 180 rpm and under continuous light exposure provided by six florescent tubes mounted in the incubator lid (Osram L30 W/21-840, cool white, light intensity measured at the tube location was 161 $\mu molm^{-2}s^{-1}$).

5.2.2 Algal-lawn Assay

All manipulations were carried out in a flow hood with autoclaved Petri dishes and pipette tips. Agar (20 mL 1.5 % in H_2O) was added to a Petri-dish to form a flat even layer, which was allowed to set with the Petri dish lid off. *C. reinhardtii* (1 mL from stock population described in section 5.2.1) was added to hand hot agar (9 mL 0.5 % in Bold's medium) and mixed by inverting in a falcon tube. The mixture was then poured carefully on top of the previous layer and allowed to set with the Petri dish lid off. The back of the Petri dish were then marked up to indicate where herbicides should be applied for example Figure 5.1. The lid was replaced and the plates stored in the dark until needed.
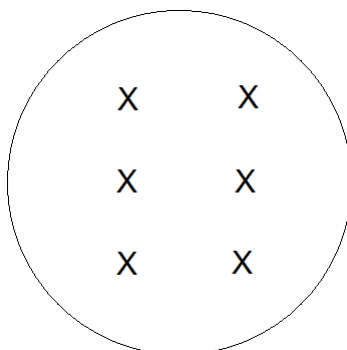
Figure 5.1 – Permanent marker Layout of a Petri dish used in the algal-lawn assay.

Herbicides of the desired concentration in Bold's medium with minimum MeOH to aid

solvation were now applied to the "lawn" on the marked areas with 10 μL spots. Control spots were also applied consisting of Bold's media with the maximum MeOH % used. The plates were run in triplicate. The plates were kept in a 28 °C room under fluorescent lights for 7 days. The results were recorded photographically.

5.2.3 96-well Plate Assay

To ensure that approx 5000 cells of *C.reinhardtii* were initially added to the wells, an estimate of the stock population was made by measuring the OD_{750}, using a Jenway 6315 bench-top spectrophotometer with a 24-25.5 mm test tube holder fitted to allow the 25x150 mm glass tubes to be measured. It was tested and found to have a sensitivity to OD_{750} of 0.001.[127]

Once the OD was measured, equation (5.1), derived from studies by Lagator, was used to estimate the population per mL.[127]

$$Cells/mL = 1119400(OD_{750})^2 + 1086300(OD_{750}) \qquad (5.1)$$

The remaining volumes of herbicide (X) and Bold's media (B) were calculated as per equation (5.2) still allowing for a total volume of 200 μL. The plates were then incubated for 7 days. The concentrations used are shown in Table 5.1.

$$X \ (\mu L) + B \ (\mu L) + (5000 \ cells) = 200 \ \mu L \ (5.2)$$

5.2.4 Dose Response Analysis

ED_{50} were derived from dose-response curves. Response was determined by recording OD_{750} as an independent variable.[130] The analysis of this optical density data was carried out in R (R version 3.1.0:2014-04-10)[131] and modelled using the drc package version 2.3-96.[132] The dose response model used to fit the optical density data was the

Table 5.1 – Concentrations used in the 96 well plate assay

Concentration mM		
Glyphosate	**Phyllostictine A**	**Lactam 73**
0	0	0
0.10	0.25	1.0
0.20	0.50	2.5
0.39	0.75	3.0
0.59	1.00	5.0
0.79	5.00	7.5
1.18	10.00	10.0

standard four parameter log-logistic model (Equation 5.2). The four parameters are slope (b), lower limit (c), upper limit (d) and point of inflection which in this case is the ED_{50} (e). For a visual account of the dose response see Figure 5.2.

$$y = f(x) = c + \frac{d - c}{1 + \exp(b(\log(x) - \log(e)))} \tag{5.2}$$
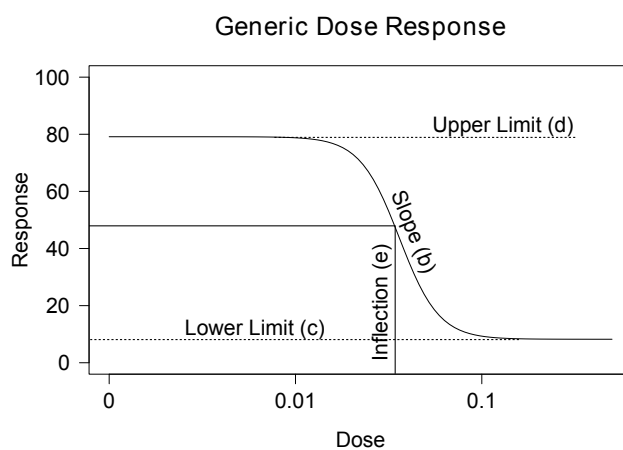
Figure 5.2

5.3   Chemical Synthesis

Methyl 3-hydroxy-2-methylenetridec-12-enoate (68)
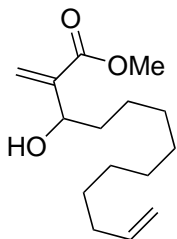
10-Undecen-al (3.00 g, 17.9 mmol) was dissolved in methyl acrylate (1.29 mL, 14.3 mmol). MeOH (450 μL) and DABCO (280 mg, 2.5 mmol) were added and the solution stirred for 7 days. The volatiles were removed and the crude product was purified via column chromatography (20% EtOAc in 40-60 °C petroleum ether) to give the *title compound* as an oil (1.91 g, 52%). ^{1}H-NMR (CDCl$_3$, 400 MHz, δ): 6.22 (s, 1H, -CC*H*H), 5.85-5.75 (m, 2 x 1H, -C*H*CH$_2$; -CC*H*H), 4.98 (d, J = 17.1 Hz, 1H, -CHC*H*H), 4.92 (dd, J = 10.3, 0.9 Hz, 1H, -CHCH*H*), 4.39 (t, J = 6.4 Hz, 1H, -C*H*OH), 3.78 (s, 3H, -COOC*H*$_3$), 2.86 (br s, 1H, -CHO*H*), 2.03 (q, J = 7.0 Hz, 2H, -C*H*$_2$CH=CH$_2$), 1.71-1.53 (m, 2H, -C*H*$_2$CHOH-), 1.50-1.22 (m, 12H, 6 x -C*H*$_2$); ^{13}C-NMR (CDCl$_3$, 100 MHz, δ): 167.0 (C=O), 142.7 (C), 139.1 (CH), 124.8 (CH$_2$), 114.1 (CH$_2$), 71.4 (CH), 51.8 (CH$_3$), 36.3 (CH$_2$), 33.8 (CH$_2$), 29.5 (CH$_2$), 29.4 (CH$_2$), 29.2 (CH$_2$), 29.0 (CH$_2$), 28.9 (CH$_2$), 25.8 (CH$_2$); IR (cm^{-1}): 3430 (-OH), 2926 (-OOH), 2854 (-CH$_2$), 1719 (-CO$_2$H), 1627 (-C=C); MS-ESI 277 [M + Na]$^+$; HRMS ES$^+$ [M + Na]$^+$ calcd for C$_{15}$H$_{26}$NaO$_3$, 277.1774; found, 277.1772; R$_f$ = 0.3 (20% EtOAc in 40-60 °C petroleum ether).

3-Hydroxy-2-methylenetridec-12-enoic acid (69)
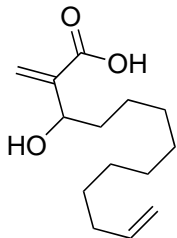
Methyl 3-hydroxy-2-methylenetridec-12-enoate (**68**) (1.91 g, 7.52 mmol) was dissolved in THF (20 mL). LiOH·H$_2$O (1.5 g, 37.6 mmol) in H$_2$O (20 mL) was added and the solution stirred for 18 h. The layers were allowed to separate and the aqueous layer acidified to pH 1 with 2N HCl, and extracted with EtOAc (3 x 20 mL). The combined organics were dried (MgSO$_4$), filtered and the solvent removed, to give the *title compound* as a clear oil, which was used without further purification (1.8 g, 99%). ^{1}H-NMR (CDCl$_3$, 400 MHz, δ): 6.80 (br s, 1H, -COO*H*), 6.30 (s, 1H, -CC*H*$_2$),

6.30 (s, 1H, -CCH_2), 5.83 (s, 1H, -CCH$_2$), 5.73 (ddt, J = 16.9 Hz, 10.3 Hz, 6.6 Hz, 1H, -CHCH$_2$), 4.91 (ddt, J = 17.1 Hz, 5.1 Hz, 1.9 Hz, 1H, -CHCHH), 4.85 (ddt, J = 11.2 Hz, 8.2 Hz, 1.0 Hz, 1H, -CHCHH), 4.36 (t, J = 6.4 Hz, 1H, -CHOH), 1.96 (q, J = 5.3 Hz, 2H, -CH_2CH=CH$_2$), 1.66-1.53 (m, 2H, -CH_2CHOH-), 1.39-1.15 (m, 12H, 6 x -CH_2); ^{13}C-NMR (CDCl$_3$, 100 MHz, δ): 171.2 (C=O), 141.9 (C), 139.2 (CH), 127.4 (CH$_2$), 114.1 (CH$_2$), 71.5 (CH), 36.1 (CH$_2$), 33.8 (CH$_2$), 29.5 (CH$_2$), 29.4 (CH$_2$), 29.39 (CH$_2$), 29.1 (CH$_2$), 28.9 (CH$_2$), 25.8 (CH$_2$); IR (cm^{-1}): 3500 (-OH), 2924 (-OOH), 2854 (-CH$_2$), 1693 ($-$CO$_2$H), 1627 (-C=C); MS-ESI 263 [M + Na]$^+$; HRMS ES$^+$ [M + Na]$^+$ calcd for C$_{14}$H$_{24}$NaO$_3$, 263.1623; found, 263.1623.

3-Hydroxy-N-(4-methoxyphenyl)-2-methylenetridec-12-enamide (126)
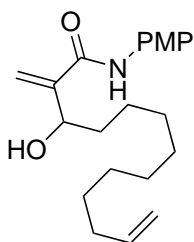
3-Hydroxy-2-methylenetridec-12-enoic acid (**69**) (900 mg, 3.75 mmol) and *p*-anisidine (461 mg, 3.75 mmol) were dissolved in CH$_2$Cl$_2$ (20 mL) and cooled to 0 °C. DCC (772 mg, 3.75 mmol) in CH$_2$Cl$_2$ (50 mL) was added slowly and the solution allowed to warm to room temperature over 18 h. The resulting suspension was filtered through Celite, washed with a small amount of CH$_2$Cl$_2$ and the solvent removed. Column chromatography (30% EtOAc in 40-60 °C petroleum ether) yielded the *title compound* as a white solid (688 mg, 53%). ^{1}H-NMR (CDCl$_3$, 300 MHz, δ): 8.54 (br s, 1H, -CONH-), 7.50-7.43 (m, 2H, -ArH), 6.89-6.81 (m, 2H, -ArH), 5.99 (s, 1H, -CCHH), 5.78 (ddt, J = 16.8 Hz, 10.3 Hz, 6.6 Hz, 1H, -CHCH$_2$), 5.50 (s, 1H, -CCHH), 5.02-4.86 (m, 2H, -CHCH_2), 4.43 (q, J = 6.4 Hz, 1H, -CHOH), 3.78 (s, 3H, -ArOCH_3), 2.72 (d, J = 4.7 Hz, 1H, -OH), 1.96 (q, J = 6.6 Hz, 2H, -CH$_2$CH=CH$_2$), 1.85-1.60 (m, 2H, -CH_2CHOH-), 1.50-1.16 (m, 12H, 6 x -CH_2); ^{13}C-NMR (CDCl$_3$, 75 MHz, δ): 164.5 (C=O), 156.2 (C), 138.6 (CH), 130.1 (C), 121.3 (2 x CH), 120.8 (CH), 113.8 (2 x CH), 113.7 (CH$_2$), 73.7 (CH), 54.9 (CH$_3$), 35.1 (CH$_2$), 33.2 (CH$_2$), 28.84 (CH$_2$), 28.76 (CH$_2$), 28.5 (CH$_2$), 28.3 (CH$_2$), 25.8 (CH$_2$); IR (cm^{-1}): 3283 (-OH), 2925; 2853 (-CH$_2$), 1511 (-CONR$_2$), 1246 (-CO-CH$_3$), 828 (para disub -ArH); MS-ESI: 346 [M + H], 368 [M + Na]; HRMS ES$^+$: [M + Na]$^+$ calcd for C$_{21}$H$_{31}$NNaO$_3$, 368.2196,

found, 368.2198; R_f = 0.3 (20% EtOAc in 40-60 °C petroleum ether).

2-(4-Methoxyphenylcarbamoyl)trideca-1,12-dien-3-yl methanesulfonate (127)
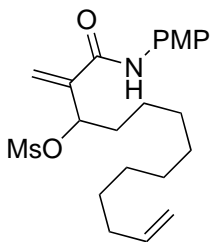
3-Hydroxy-N-(4-methoxyphenyl)-2-methylenetridec-12-enamide (**126**) (688 mg, 1.99 mmol) was dissolved in CH_2Cl_2 (10 mL) and cooled to -78 °C. Et_3N (550 μL, 3.99 mmol) was added followed by MsCl (300 μL, 3.99 mmol) dropwise. After 2 h the reaction was quenched with H_2O (10 mL) and warmed to room temperature. The organics were separated and dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Column chromatography (30% EtOAc in 40-60 °C petroleum ether) yielded the *title compound* as an oil (816 mg, 97%). ^{1}H-NMR ($CDCl_3$, 300 MHz, δ): 7.70 (br s, 1H, -CON*H*-), 7.49-7.41 (m, 2H, -Ar*H*), 6.90-6.83 (m, 2H, -Ar*H*), 5.94 (s, 1H, -CC*H*H), 5.87-5.71 (m, 2H, 1 x -C*H*CH$_2$ 1 x -CC*H*H), 5.41 (t, *J* = 6.6 Hz, 1H, -C*H*OSOOCH$_3$), 5.03-4.88 (m, 2H, -CHC*H*$_2$), 3.79 (s, 3H, -ArOC*H*$_3$), 3.02 (s, 3H, -OSOOC*H*$_3$), 2.05-1.97 (m, 2H, -C*H*$_2$CH=CH$_2$), 1.91 (q, *J* = 7.5 Hz, 2H, -C*H*$_2$CHOH-), 1.48-1.22 (m, 12H, 6 x -C*H*$_2$); ^{13}C-NMR ($CDCl_3$, 75 MHz, δ): 164.5 (C=O), 157.0 (C), 144.2 (C), 139.3 (CH), 130.6 (C), 122.1 (2 x CH), 121.4 (CH), 114.4 (2 x CH), 114.3 (CH$_2$), 81.5 (CH), 55.6 (CH$_3$), 38.7 (CH$_3$), 35.1 (CH$_2$), 33.9 (CH$_2$), 29.5 (CH$_2$), 29.2 (CH$_2$), 29.0 (CH$_2$), 25.5 (CH$_2$); IR (cm^{-1}): 3358 (-NH), 2926; 2854 (-CH$_2$), 1663 (-C=C), 1511 (-CONR$_2$), 1351 (-S=O), 1245 (-CO-CH$_3$), 1173 (-S=O), 827 (para disub -ArH); MS-ESI: 424 [M + H]$^+$, 446 [M + Na]; HRMS: ES$^+$ [M + H]$^+$ calcd for $C_{22}H_{33}NNaO_5S$, 446.1972; found, 446.1967; R$_f$ = 0.3 (30% EtOAc in 40-60 °C petroleum ether).

4-(Dec-9-enyl)-1-(4-methoxyphenyl)-3-methyleneazetidin-2-one (121)
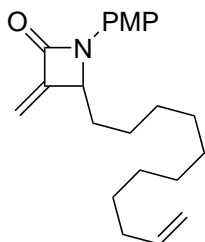
2-(4-Methoxyphenylcarbamoyl)trideca-1,12-dien-3-yl methanesulfonate (**127**) (230 mg, 0.54 mmol) was dissolved in THF (10 mL) and cooled to -15 °C. KO^{t}Bu (60 mg, 0.60 mmol) was added in one portion and stirred for 2 h at -15 °C. The reaction was quenched with sat. NH$_4$Cl (10 mL) the organics separated, dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The crude product

was purified via column chromatography (5% EtOAc in 40-60 °C petroleum ether) to give the *title compound* (111 mg, 62%). ^{1}H-NMR (CDCl$_3$, 400 MHz, δ): 7.39 (app d, J = 9.0 Hz, 2H, ArH), 6.93 (app d, J = 9.0 Hz, 2H, ArH), 5.88-5.78 (m, 2 x 1H, -CCH_2; -CHCH$_2$), 5.28 (s, 1H, -CCH_2), 5.01 (dd, J = 17.1 Hz, 1.7 Hz, 1H, -CHCH$_2$), 4.95 (d, J = 11.1 Hz, 1H, -CHCHH), 4.58-4.53 (m, 1H, -CHCNAr), 3.83 (s, 3H, -ArOCH_3), 2.10-1.99 (m, 2H, 1H -CH_2CH=CH$_2$; -CHHCHCNAr), 1.86-1.76 (m, 1H, -CHHCHCNAr), 1.48-1.23 (m, 12H, 6 x -CH$_2$); ^{13}C-NMR (CDCl$_3$, 75 MHz, δ): 164.5 (C=O), 155.6 (C), 147.9 (C), 138.6 (CH), 130.6 (C), 118.1 (CH), 117.8 (CH), 113.9 (CH), 113.8 (CH), 113.6 (CH$_2$), 108.8 (CH), 59.9 (CH), 54.9 (CH$_3$), 33.2 (CH$_2$), 30.1 (CH$_2$), 28.9 (CH$_2$), 28.7 (CH$_2$), 28.4 (CH$_2$), 28.2 (CH$_2$), 23.7 (CH$_2$); IR (cm^{-1}): 2925; 2853 (-CH$_2$) 1727 (-CONR$_2$), 1509 (-C=C), 1245 (-CO-CH$_3$), 827 (para disub -ArH); ESI+-MS: 328 [M + H]$^+$, 350 [M + Na]$^+$; HRMS: ES$^+$ [M + H]$^+$ calcd for C$_{21}$H$_{30}$NO$_2$, 328.2271; found, 328.2277; R$_f$ = 0.3 (5% EtOAc in 40-60 °C petroleum ether).

RCM reaction of 4-(Dec-9-enyl)-1-(4-methoxyphenyl)-3-methyleneazetidin-2-one (121)

4-(Dec-9-enyl)-1-(4-methoxyphenyl)-3-methyleneazetidin-2-one (**121**) (62 mg, 0.19 mmol) was dissolved in CH$_2$Cl$_2$ (95 mL). Grubbs 2nd generation catalyst (15 mg, 0.018 mmol) was added in one portion and the solution heated at reflux for 24 h. The solution was allowed to cool and the solvent removed under reduced pressure. Column chromatography (10-20% EtOAc in 40-60 °C petroleum ether) yielded two compounds. The 22-membered dimer (1*Z*,14*Z*)-12,25-bis(4-methoxyphenyl)-12,25-diazatricyclo[22.2.0.0^{11,14}]hexacosa-1,14-diene-13,26-dione) (**89**) (11 mg, 20%) and 11-membered ring (*Z*)-12-(4-methoxyphenyl)-12-azabicyclo[9.2.0]tridec-1-en-13-one (**123**) (3 mg, 6%).

(*Z*)-12-(4-methoxyphenyl)-12-azabicyclo[9.2.0]tridec-1-en-13-one (123)
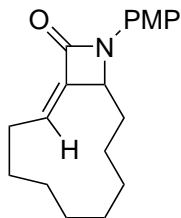
^{1}H-NMR (CDCl$_3$, 600 MHz, δ): 7.42-7.39 (m, 2H, -ArH), 6.91-6.88 (m, 2H, -ArH), 5.71 (dd, *J* = 12.1 Hz, 4.5 Hz, 1H, -CC*H*CH$_2$-), 4.52 (d, *J* = 5.5 Hz, 1H, -C*H*CNAr), 3.79 (s, 3H, -ArOCH*3*), 2.87-2.76 (m, 1H, -CCHC*H*H), 2.29-2.15 (m, 2 x 1H, -NArC*H*CHH-; -CCHC*H*H), 1.93-1.83 (m, 1H -NArCHC*H*H-) 1.62-1.36 (m, 12H, 6 x -C*H*$_2$); ^{13}C-NMR (CDCl$_3$, 150 MHz, δ): 161.7 (C=O), 156.0 (C), 139.5 (C), 132.8 (C) 132.0 (CH), 117.7 (2 x CH), 114.7 (2 x CH), 59.0 (CH), 55.7 (CH$_3$), 29.6 (CH$_2$), 27.6 (CH$_2$), 27.2 (CH$_2$), 25.8 (CH$_2$), 25.1 (CH$_2$), 22.4 (CH$_2$), 20.8 (CH$_2$); ESI$^+$-MS: 300 [M + H]$^+$, 322 [M + Na]$^+$; HRMS: ES$^+$ [M + H]$^+$ calcd for C$_{19}$H$_{26}$NO$_2$, 300.1958; found, 300.1958; IR (cm^{-1}): 2925; 2853 (-CH$_2$) 1731 (-CONR$_2$), 1511 (-C=C), 1246 (-CO-CH$_3$), 829 (para disub -ArH); mp 155-160 °C (from CH$_2$Cl$_2$), R$_f$ = 0.3 (20% EtOAc in 40-60 °C petroleum ether).

(1*Z*,14*Z*)-12,25-bis(4-methoxyphenyl)-12,25-diazatricyclo[22.2.0.0^{11,14}]hexacosa-1,14-diene-13,26-dione) (89)
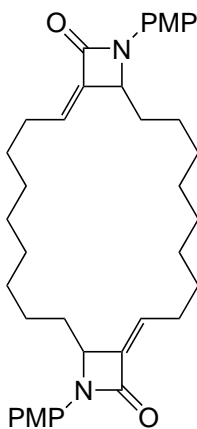
^{1}H-NMR (CDCl$_3$, 400 MHz, δ): 7.31-7.23 (m, 4H, -ArH), 6.84-6.77 (m, 4H, -ArH), 5.52 (dt, *J* = 11.0 Hz, 4.5 Hz, 2H, -CCHCH$_2$-), 4.44-4.39 (m, 2H, -CHCNAr), 3.72 (s, 6H, -ArOCH$_3$), 2.95-2.81 (m, 2H, -CCHCHH), 2.17-2.07 (m, 2H, CCHCHH), 1.94-1.81 (m, 2H -NArCHCHH-), 1.80-1.67 (m, 2H -NArCHCHH-), 1.38-1.02 (m, 24H, 12 x -CH$_2$); ^{13}C-NMR (CDCl$_3$, 100 MHz, δ): 161.6 (C=O), 161.0 (C=O), 156.0 (2 x C), 139.6 (C), 139.4 (C), 131.9 (C), 131.8 (C), 131.0 (CH), 130.7, 118.1 (2 x CH), 118.0 (2 x CH), 114.6 (4 x CH), 59.42 (CH), 59.36 (CH), 55.6 (2 x CH$_3$), 30.3 (CH$_2$), 30.14 (CH$_2$), 30.08 (CH$_2$), 29.9 (CH$_2$), 29.8 (CH$_2$), 29.5 (CH$_2$), 29.4 (CH$_2$), 29.30 (CH$_2$),

29.27 (CH_2), 29.1 (CH_2), 29.0 (CH_2), 28.54 (CH_2), 28.48 (CH_2), 23.1 (CH_2), 22.8 (CH_2); ESI$^+$-MS: 599 [M + H]$^+$, 621 [M + Na]$^+$; HRMS: ES$^+$ [M + H]$^+$ calcd for $C_{38}H_{51}N_2O_4$, 599.3843; found, 599.3850; IR (cm^{-1}): 2920; 2849 (-CH_2) 1712 (-CONR$_2$), 1509 (-C=C), 1246 (-CO-CH_3), 826 (para disub -ArH); mp 149-155 °C (from CH_2Cl_2); R$_f$ = 0.2 (20% EtOAc in 40-60 °C petroleum ether).

8-(Allyloxy)octan-1-ol (104)
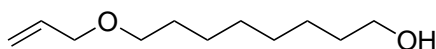
1,8 Octadiol (3.5 g, 23.3 mmol) was dissolved in THF (25 mL) and added to NaH (60% in mineral oil, 1.1 g, 28.0 mmol) via cannula. The slurry was stirred for 1 h at room temperature. Allyl bromide (1.9 mL, 22.0 mmol) and TBAI (25 mg) were dissolved in THF (25 mL) and added to the NaH solution via cannula. This was heated to reflux for 7 h. Once cool sat. NH_4Cl (50 mL) was added and the aqueous layer extracted with EtOAc (3 x 20 mL). The combined organics were dried (Na_2SO_4) and the volatiles removed under reduced pressure. Column chromatography (2% MeOH in CH_2Cl_2) yielded the *title compound* as an oil (1.77 g, 40%). Data is consistent with that reported.[81] ^{1}H-NMR (CDCl$_3$, 400 MHz, δ): 5.91 (ddt, J = 17.1, 1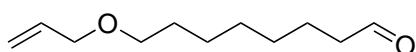0.4, 5.7 Hz, 1H, -C*H*CH$_2$), 5.27 (dd, J = 17.2, 1.6 Hz, 1H, -CHC*H*H), 5.17 (dd, J = 10.4, 1.0 Hz, 1H, -CHCH*H*), 3.96 (d, J = 5.6 Hz, 2H, -C*H*$_2$CH=CH$_2$), 3.63 (t, J = 6.6 Hz, 2H, -OC*H*$_2$-), 2.42 (t, J = 6.7 Hz, 2H, OHCC*H*$_2$-), 1.64-1.3 (m, 12H, 6 x C*H*$_2$); R$_f$ = 0.4 (2% MeOH in CH_2Cl_2).

8-(Allylocy)octanal (105)

8-(Allyloxy)octan-1-ol (1.77 g, 9.52 mmol) was dissolved in CH_2Cl_2 (30 mL) and NaOAc (376 mg, 4.57 mmol) added. PCC (2.5 g, 11.4 mmol) was added in one portion and the solution stirred for 2 h. The mixture was diluted with Et$_2$O (50 mL) then filtered through a short pad of SiO_2. The pad was washed exhaustively with Et$_2$O. The volatiles were removed under reduced pressure. Column chromatography (10% EtOAc in 40-60 °C petroleum ether) yielded the *title compound* as a clear oil (1.00 g, 57%). Data is consistent with that reported.[81] ^{1}H-NMR (CDCl$_3$, 400 MHz, δ): 9.76 (s, 1H, C*H*O), 5.91 (ddt, J = 17.2, 10.6, 5.5 Hz, 1H, -C*H*CH$_2$), 5.27 (dd, J = 17.2, 1.8 Hz, 1H, -CHC*H*H), 5.17 (dd, J = 10.4, 1.8 Hz, 1H, -CHCH*H*), 3.96 (dt, J = 5.6, 1.4 Hz, 2H, -C*H*$_2$CH=CH$_2$), 3.42 (t, J = 6.6 Hz, 2H, -OC*H*$_2$-), 2.42 (dt, J = 7.4, 1.8 Hz, 2H, CHOC*H*$_2$-), 1.72-1.3 (m, 12H, 6 x C*H*$_2$); R$_f$ = 0.3 (10% EtOAc in 40-60 °C petroleum

ether).

Methyl 10-(allyloxy)-3-hydroxy-2-methylenedecanoate (106)
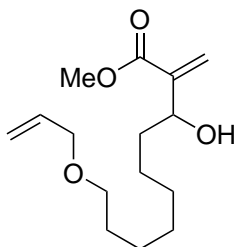
8-(Allylocy)octanal (2.30 g, 12.5 mmol) was dissolved in methyl acrylate (0.95 mL, 10.5 mmol). MeOH (300 μL) and DABCO (294 mg, 2.6 mmol) were added and the solution stirred for 7 days. The volatiles were removed and the crude product was purified via column chromatography (20% EtOAc in 40-60 °C petroleum ether) to give the *title compound* as a clear oil (1.24 g, 44% yield). ^{1}H-NMR (CDCl$_3$, 250 MHz, δ): 6.21 (d, J = 1.1 Hz, 1H, -CC*H*H), 5.92 (ddt, J = 17.2, 10.4, 5.6 Hz, 1H, -C*H*CH$_2$), 5.79 (t, J = 1.1 Hz, 1H, -CC*H*H), 5.26 (dq, J = 17.2, 1.7 Hz, 1H, -CHC*H*H), 5.17 (dq, J = 10.3, 1.8 Hz, 1H, -CHCH*H*), 4.38 (t, J = 6.3 Hz, 1H, -C*H*OH), 3.96 (dt, J = 5.6, 1.4 Hz, 2H, -C*H*$_2$CH=CH$_2$), 3.78 (s, 3H, -COOC*H*$_3$), 3.42 (t, J = 6.6 Hz, 2H, -OC*H*$_2$-), 1.72-1.13 (m, 12H, 6 x C*H*$_2$); ^{13}C-NMR (CDCl$_3$, 100 MHz, δ): 178.4 (C=O), 142.4 (C), 135.1 (CH), 125.0 (CH$_2$), 116.7 (CH$_2$), 71.9 (CH$_2$), 71.8 (CH), 70.5 (CH$_2$), 51.9 (CH$_3$), 36.2 (CH$_2$), 33.8 (CH$_2$), 29.4 (CH$_2$), 26.1 (CH$_2$), 24.5 (CH$_2$); IR (cm^{-1}): 3430 (-OH), 2931 (-OOH), 2857 (-CH$_2$), 1717 (-CO$_2$H); MS-ESI: 293 [M + Na]; HRMS ES$^+$: [M + Na]$^+$ calcd for C$_{15}$H$_{26}$NaO$_4$, 293.1723, found 293.1721; R$_f$ = 0.3 (20% EtOAc in 40-60 °C petroleum ether).

10-(Allyloxy)-3-hydroxy-2-methylenedecanoic acid (107)
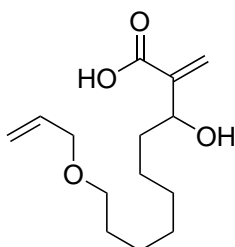
Methyl 10-(allyloxy)-3-hydroxy-2-methylenedecanoate (**106**) (1.24 g, 4.59 mmol) was dissolved in THF (20 mL). LiOH·H$_2$O (940 mg, 23.0 mmol) in H$_2$O (20 mL) was added and the solution stirred for 18 h. The layers were allowed to separate and the aqueous layer acidified to pH 1 with 2N HCl, and extracted with EtOAc (3 x 20 mL). The combined organics were dried (MgSO$_4$), filtered and the solvent removed under reduced pressure to yield the *title compound* as a clear oil which was used without further purification (900 mg, 76%). ^{1}H-NMR (CDCl$_3$,

400 MHz, δ): 6.37 (s, 1H, -CCH_2), 5.97-5.87 (m, 2H, -CHCH_2 -CCH_2), 5.27 (dq, J = 17.2 Hz, 1.5 Hz, 1H, -CHCHH), 5.17 (d, J = 10.3 Hz, 1H, -CHCHH), 4.43 (t, J = 6.0 Hz, 1H, -CHOH), 3.97 (d, J = 4.6 Hz, 2H, -CH_2CH=CH$_2$), 3.43 (t, J = 6.7 Hz, 2H, -OCH_2-), 1.71-1.24 (m, 10H, 5 x CH_2); ^{13}C-NMR (CDCl$_3$, 100 MHz, δ): 170.6 (C=O), 141.9 (C), 135.0 (CH), 127.2 (CH$_2$), 116.9 (CH$_2$), 71.8 (CH$_2$), 71.6 (CH), 70.5 (CH$_2$), 36.2 (CH$_2$), 29.7 (CH$_2$), 29.4 (CH$_2$), 29.3 (CH$_2$), 26.1 (CH$_2$), 25.7 (CH$_2$); IR (cm^{-1}): 3358 (-COOH), 2932; 2856 (-CH$_2$), 1695 (-COOH), 1627 (-C=C), 1245 (-CO-CH$_3$); MS-ESI: 279 [M + Na]; HRMS ES$^+$: [M + Na]$^+$ calcd for C$_{14}$H$_{24}$NaO$_4$, 279.1567, found, 279.1566.

10-(Allyloxy)-3-hydroxy-N-(4-methoxyphenyl)-2-methylenedecanamide (129)
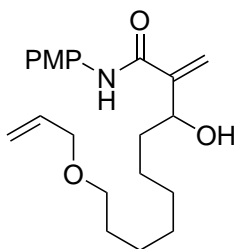
10-(Allyloxy)-3-hydroxy-2-methylenedecanoic acid (**107**) (900 mg, 3.52 mmol) and *p*-anisidine (432 mg, 3.52 mmol) were dissolved in CH$_2$Cl$_2$ (50 mL) and cooled to 0 °C. DCC (724 mg, 3.52 mmol) in CH$_2$Cl$_2$ (80 mL) was added slowly and the solution allowed to warm to room temperature over 18 h. The resulting suspension was filtered through Celite, washed with a small amount of CH$_2$Cl$_2$ and the solvent removed under reduced pressure. Column chromatography (25% EtOAc, 1% Et$_3$N in 40-60 °C petroleum ether) yielded the *title compound* as a white solid (798 mg, 67% yield). ^{1}H-NMR (CDCl$_3$, 400 MHz, δ): 8.83 (s, 1H, NH), 7.49-7.46 (m, ArH), 6.88-6.84 (m, ArH), 6.00 (s, 1H, -CCH_2), 5.71 (ddt, J = 17.2 Hz, 10.6 Hz, 5.6 Hz, 1H, -CHCH$_2$), 5.47 (s, 1H, -CCH_2), 5.26 (dq, J = 17.2 Hz, 1.7 Hz, 1H, -CHCHH), 5.16 (dq, J = 10.4 Hz, 1.6 Hz, -CHCHH), 4.41 (t, J = 6.6 Hz, 1H, -CHOH), 3.95 (dt, J = 5.6 Hz, 1.4 Hz, 2H, -CH_2CH=CH$_2$), 3.79 (s, 3H, -ArOCH_3), 3.42-3.35 (m, 3H, 1 x -OCH_2-; 1 x -CHOH), 1.94-1.24 (m, 10H, 5 x CH_2); ^{13}C-NMR (CDCl$_3$, 100 MHz, δ): 165.3 (C=O), 156.5 (C), 145.4 (C), 135.0 (CH), 130.9 (C), 121.9 (CH), 121.7 (2 x CH$_2$), 116.8 (CH$_2$), 114.16 (2 x CH), 74.2 (CH), 71.8 (CH$_2$), 70.5 (CH$_2$), 55.5 (CH$_3$), 35.7 (CH$_2$), 29.7 (CH$_2$), 29.4 (CH$_2$), 29.3 (CH$_2$), 26.1 (CH$_2$), 25.9 (CH$_2$); IR (cm^{-1}): 3293 (-OH), 2925; 2853 (-CH$_2$) 1511 (-CONR$_2$), 1509 (-C=C), 1245 (-CO-

CH_3), 827 (para disub -ArH); MS-ESI: 384 [M + Na]; HRMS ES$^+$: [M + Na]$^+$ calcd for $C_{21}H_{31}NNaO_4$, 384.2145, found, 384.249; mp: 74-76 °C (from CHCl$_3$); R_f = 0.3 (25% EtOAc, 1% Et$_3$N in 40-60 °C petroleum ether).

2-(4-Methoxyphenylcarbamoyl)-10-(allyloxy)dec-1-en-3-yl methanesulfonate (130)
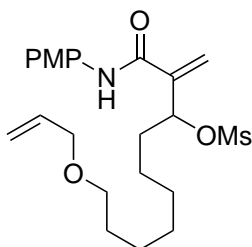
10-(Allyloxy)-3-hydroxy-N-(4-methoxyphenyl)-2-methylenedecanamide (**129**) (580 mg, 1.49 mmol) was dissolved in CH$_2$Cl$_2$ (20 mL) and cooled to -78 °C. Et$_3$N (410 μL, 2.99 mmol) was added, followed by MsCl (230 μL, 2.99 mmol) dropwise. After 4 h at -78 °C the reaction was quenched with H$_2$O (20 mL) and warmed to room temperature. The organics were separated and dried (MgSO$_4$), filtered and the solvent was removed. Column chromatography (30% EtOAc in 40-60 °C petroleum ether) yielded the *title compound* as a clear oil (562 mg, 79% yield). ^{1}H-NMR (CDCl$_3$, 400 MHz, δ): 7.77 (s, 1H, N*H*), 7.48-7.42 (m, 2H, ArH), 6.90-6.85 (m, 2H, ArH), 5.97-5.86 (m, 2H, 1 x C*H*, 1 x C*H*), 5.77 (s, 1H, -CC*H*$_2$), 5.42 (t, *J* = 6.6 Hz, 1H, -C*H*OMs), 5.26 (dq, *J* = 17.2 Hz, 1.7 Hz, 1H, -CHC*H*H), 5.16 (dq, *J* = 10.4 Hz, 1.6 Hz, 1H, -CHC*H*H), 3.95 (dt, *J* = 5.6 Hz, 1.4 Hz, 2H, -C*H*$_2$CH=CH$_2$), 3.79 (s, 3H, -ArOC*H*$_3$), 3.41 (t, *J* = 6.6 Hz, 2H, -OC*H*$_2$-), 3.02 (s, 3H, -OSOOC*H*$_3$) 1.91 (q, *J* = 7.2 Hz, 2H, -C*H*$_2$CHOMs-), 1.60-1.53 (m, 2H, -OC*H*$_2$CH2-), 1.48-1.29 (m, 8H, 4 x C*H*$_2$); ^{13}C-NMR (CDCl$_3$, 100 MHz, δ): 164.4 (C=O), 156.8 (C), 144.0 (C), 135.1 (CH), 130.5 (C), 122.0 (2 x CH), 121.0 (CH$_2$), 116.8 (CH$_2$), 114.24 (2 x CH), 81.3 (CH), 71.8 (CH$_2$), 70.4 (CH$_2$), 55.5 (CH$_3$), 38.6 (CH$_3$), 35.0 (CH$_2$), 29.7 (CH$_2$), 29.2 (CH$_2$), 29.0 (CH$_2$), 26.1 (CH$_2$), 25.3 (CH$_2$); IR (cm^{-1}): 3358 (-NH), 2933; 2856 (-CH$_2$), 1666 (-C=C), 1510 (-CONR$_2$), 1509 (-C=C), 1349 (-S=O), 1245 (-CO-CH$_3$), 1170 (-S=O), 827 (para disub -ArH); MS-ESI: 440 [M + H]$^+$, 462 [M + Na]$^+$; HRMS ES$^+$: [M + Na]$^+$ calcd for $C_{22}H_{33}NNaO_6S$ 462.1921; found, 462.1937; R_f = 0.3 (30% EtOAc in 40-60 °C petroleum ether).

4-(7-(Allyloxy)heptyl)-1-(4-methoxyphenyl)-3-methyleneazetidin-2-one (122)
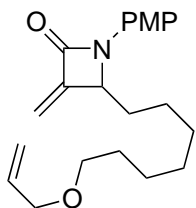
2-(4-Methoxyphenylcarbamoyl)-10-(allyloxy)dec-1-en-3-yl methanesulfonate (**130**) (562 mg, 1.28 mmol) was dissolved in THF (20 mL) and cooled to -15 °C. KO^{t}Bu (158 mg, 1.41 mmol) was added in one portion and the solution stirred for 4 h at -15 °C. The reaction was quenched with sat. NH$_4$Cl (20 mL) the organics separated, dried (MgSO$_4$), filtered and the solvent removed under reduced pressure. Column chromatography (30% EtOAc in 40-60 °C petroleum ether) yielded the *title compound* as a clear oil. (311 mg, 71% yield). ^{1}H-NMR (CDCl$_3$, 400 MHz, δ): 7.40-7.33 (m, 2H, ArH), 6.92-6.87 (m, 2H, ArH), 5.91 (ddt, *J* = 17.2 Hz, 10.5 Hz, 5.6 Hz, 1H, -C*H*CH$_2$), 5.77 (t, *J* = 1.6 Hz, 1H, -CC*H*H), 5.29-5.23 (m, 2H, 1 x -CC*H*H, 1 x -CHC*H*H), 5.16 (ddt, *J* = 10.4 Hz, 4.3 Hz, 1.6 Hz, 1H, -CHC*H*H), 4.54-4.50 (m, 1H, -C*H*CNAr), 3.95 (dt, *J* = 5.6 Hz, 1.4 Hz, 2H, -C*H*$_2$CH=CH$_2$), 3.78 (s, 3H, -ArOC*H*$_3$), 3.40 (t, *J* = 6.6 Hz, 2H, -OC*H*$_2$-), 2.05-1.96 (m, 1H, -C*H*HCHCNAr), 1.83-1.73 (m, 1H, -C*H*HCHCNAr), 1.60-1.51 (m, 2H, -OCH$_2$C*H*$_2$-), 1.45-1.26 (m, 8H, 4 x CH$_2$); ^{13}C-NMR (CDCl$_3$, 100 MHz, δ): 160.1 (C=O), 156.2 (C), 148.5 (C), 135.1 (CH), 131.1 (C), 118.4 (2 x CH), 116.7 (CH$_2$), 114.6 (2 x CH), 109.4 (CH$_2$), 71.8 (CH$_2$), 70.4 (CH$_2$), 60.4 (CH), 55.5 (CH$_3$), 30.8 (CH$_2$), 29.8 (CH$_2$), 29.5 (CH$_2$), 29.3 (CH$_2$), 26.1 (CH$_2$), 24.3 (CH$_2$); IR (cm^{-1}): 2931; 2856 (-CH$_2$), 1739 (-CONR$_2$), 1510 (-C=C), 1246 (-CO-CH$_3$), 827 (para disub -ArH); MS-ESI: 344 [M + H]$^+$, 366 [M + Na]$^+$; HRMS ES$^+$: [M $^+$ Na]$^+$ calcd for C$_{21}$H$_{29}$NNaO$_3$, 366.2040; found, 366.2036; R$_f$ = 0.3 (30% EtOAc in 40-60 °C petroleum ether).

Tert-butyl 2-(7-(allyloxy)heptyl)-3,4-dimethleneazetidine-1-carboxylate (167)
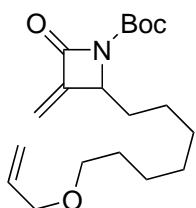
4-(7-(Allyloxy)heptyl)-1-(4-methoxyphenyl)-3-methyleneazetidin-2-one (**122**) (100 mg, 0.29 mmol) was dissolved in MeCN (10 mL) and cooled to 0 °C. CAN (480 mg, 0.88 mmol) was dissolved in H$_2$O (10 mL) and added dropwise and the solution was stirred for 2 h at 0 °C. It was then diluted with Et$_2$O (15 mL) and sat. NaHCO$_3$

(10 mL) added. The solution was separated and the aqueous layer extracted with Et_2O (3 x 10 mL), the combined organics were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The oil was immediately dissolved in MeCN (10 mL), DMAP added (4 mg, 0.29 mmol) and the solution cooled to 0 °C. Boc_2 (130 mg, 5.9 mmol) was added in one portion and the reaction stirred for 2 h at 0 °C. The reaction was diluted with CH_2Cl_2 (10 mL) then washed with 1 M $NaHSO_4$ (15 mL), sat. $NaHCO_3$ (20 mL) and brine (20 mL). The organics were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Column chromatography (10% EtOAc in 40-60 °C petroleum ether) yielded the *title compound* a clear oil (36 mg, 35% over 2 steps). ^{1}H-NMR (CDCl$_3$, 400 MHz, δ): 5.94-5.83 (m, 2H, 1 x -C*H*CH$_2$, 1 x -CC*H*H), 5.36 (s, 1H, -CC*H*H), 5.23 (d, *J* = 17.3 Hz, 1H, -CHC*H*H), 5.14 (d, *J* = 10.3 Hz, 1H, -CHC*H*H), 4.39 (s, 1H, -C*H*CN-), 3.93 (d, *J* = 5.6 Hz, 2H, -C*H*$_2$O-), 3.39 (t, *J* = 6.6 Hz, 2H, -OC*H*$_2$-), 2.01-1.89 (m, 1H, -C*H*HCHCN-), 1.80-1.71 (m, 1H, -C*H*HCHCN-), 1.60-1.53 (m, 2H, -OCH$_2$C*H*$_2$-), 1.50 (s, 9H, -C(C*H*$_3$)$_3$), 1.42-1.20 (m, 8H, 4 x C*H*$_2$); ^{13}C-NMR (CDCl$_3$, 100 MHz, δ): 160.0 (C=O), 148.8 (C), 147.9 (C), 135.2 (CH), 116.9 (CH$_2$), 114.5 (CH$_2$), 83.2 (C), 71.9 (CH$_2$), 70.6 (CH$_2$), 60.6 (CH), 31.7 (CH$_2$), 29.8 (CH$_2$), 29.6 (CH$_2$), 29.4 (CH$_2$), 28.2 (CH$_3$), 26.2 (CH$_2$), 24.7 (CH$_2$); IR (cm^{-1}): MS-ESI: 344 [M + Na]$^+$; R_f = 0.3 (10% EtOAc in 40-60 °C petroleum ether).

RCM of 4-(7-(Allyloxy)heptyl)-1-(4-methoxyphenyl)-3-methyleneazetidin-2-one (122)

4-(7-(Allyloxy)heptyl)-1-(4-methoxyphenyl)-3-methyleneazetidin-2-one (**122**) (50 mg, 0.14 mmol) was dissolved in CH_2Cl_2 (70 mL) and Grubbs 2nd generation catalyst (9 mg, 0.014 mmol) added in one portion and the solution was refluxed for 24 h. The solution was allowed to cool to room temperature and the solvent removed under reduced pressure. Column chromatography (20-30% EtOAc in 40-60 °C petroleum ether) yielded the *title compound*s (dimer 14%, monomer 37% E:Z 1:1.6).

(Z)-14-(4-Methoxyphenyl)-9-oxa-14-aza-bicyclo[10.2.0]tetradec-11-en-13-one
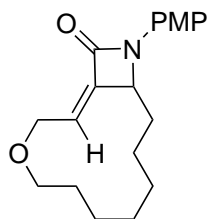
^{1}H-NMR (CDCl$_3$, 400 MHz, δ): 7.31-7.28 (m, 2H, ArH), 6.83-6.81 (m, 2H, ArH), 5.88 (dd, J = 10.8 Hz, 4.1 Hz, 1H, -CHCH$_2$O-), 4.60 (dd, J = 12.8 Hz, 10.9 Hz, 1H, CHCHHO-), 4.48 (dd, J = 6.6 Hz, 3.6 Hz, 1H, -CHCH$_2$CH2-), 4.09 (dd, J = 12.8, 4.1 Hz, 1H, -CHCHHO-), 3.73 (s, 3H, ArOCH$_3$), 3.62 (ddd, J = 10.7 Hz, 4.2 Hz, 2.3 Hz, 1H, -OCHHCH$_2$-), 3.42 (ddt, J = 11.2, 10.8, 3.1 Hz, 1H, -OCHHCH$_2$-), 2.03-1.92 (m, 1H, -CHCHHCH$_2$-), 1.92-1.88 (m, 1H, -CHCHHCH$_2$-), 1.62-1.13 (m, 10H, 5 x CH$_2$); ^{13}C-NMR (CDCl$_3$, 125 MHz, δ): 160.0 (C=O), 156.2 (C), 142.8 (C), 131.2 (C), 126.8 (CH), 126.7 (CH), 118.3 (CH), 114.6 (CH), 68.0 (CH$_2$), 65.0 (CH$_2$), 59.2 (CH), 55.5 (CH$_3$), 28.5 (CH$_2$), 28.2 (CH$_2$), 27.2 (CH$_2$), 24.3 (CH$_2$), 22.0 (CH$_2$), 20.2 (CH$_2$); IR (cm^{-1}): 2918; 2852 (-CH$_2$), 1728 (-CONR$_2$), 1512 (-C=C), 1246 (-CO-CH$_3$), 830 (para disub -ArH); ESI$^+$-MS: 316 [M + H]$^+$, 338 [M + Na]$^+$; HRMS: ES$^+$ [M + H]$^+$ calcd for C$_{19}$H$_{26}$NO$_3$, 316.1907; found, 316.1911 [M + Na]$^+$ calcd for C$_{19}$H$_{25}$NNaO$_3$, 338.1727; found, 338.1728; R$_f$ = 0.3 (30% EtOAc in 40-60 °C petroleum ether).

(E)-14-(4-Methoxyphenyl)-9-oxa-14-aza-bicyclo[10.2.0]tetradec-11-en-13-one
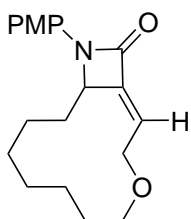
^{1}H-NMR (CDCl$_3$, 400 MHz, δ): 7.31-7.28 (m, 2H, ArH), 6.83-6.81 (m, 2H, ArH), 6.25 (ddd, J = 6.4 Hz, 3.5 Hz, 1.5 Hz, 1H, -CHCH$_2$O-), 4.81 (t, J = 4.2 Hz, 1H, -CHCH$_2$CH2-), 4.22 (dd, J = 3.5, 0.6 Hz, 0.5H, -CHCHHO-), 4.19-4.17 (m, 0.5H, -CHCHHO-), 4.00 (dd, J = 14.6, 6.4 Hz, 1H, -CHCHHO-), 3.73 (s, 3H, ArOCH$_3$), 3.60-3.54 (m, 1H, -OCHHCH$_2$-), 3.53-3.46 (m, 1H, -OCHHCH$_2$-), 2.03-1.92 (m, 1H, -CHCHHCH$_2$-), 1.92-1.88 (m, 1H, -CHCHHCH$_2$-), 1.62-1.13 (m, 10H, 5 x CH$_2$); R$_f$ = 0.3 (30% EtOAc in 40-60 °C petroleum ether).

(1Z,14Z)-12,25-bis(4-methoxyphenyl)-12,25-diazatricyclo[22.2.0.0^{11,14}]hexacosa-1,14-diene-13,26-dione)
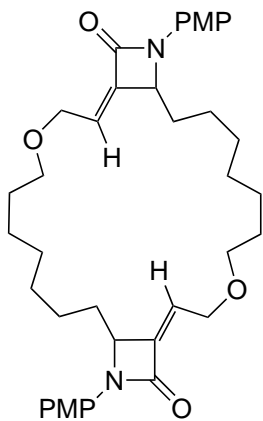
^{1}H-NMR (CDCl$_3$, 400 MHz, δ): 7.37-7.31 (m, 4H, ArH), 6.91-6.87 (m, 4H, ArH), 5.86-5.80 (m, 2H, 2 x -CC*H*CH$_2$-), 4.57 (ddd, *J* = 24.1, 12.8, 6.0 Hz, 2H, 2 x -CHC*H*H), 4.46 (t, *J* = 6.5 Hz, 2H, 2 x -NArC*H*CH$_2$), 4.36 (ddd, *J* = 24.1, 12.8, 6.0 Hz, 2H, 2 x -CHC*H*H), 3.80 (s, 6H, 2 x -ArOC*H*$_3$), 3.55-3.44 (m, 4H, 2 x -CH$_2$OC*H*$_2$CH$_2$-), 2.08-1.96 (m, 2H, 2 x -NCHC*H*H-), 1.84-1.69 (m, 2H, 2 x -NCHC*H*H-), 1.68-1.49 (m, 4H, 2 x -CH$_2$OC*H*$_2$CH$_2$-), 1.46-1.20 (m, 12H, 6 x -CH$_2$); ^{13}C-NMR (CDCl$_3$, 100 MHz, δ): 159.9 (C=O), 156.3 (C), 142.0 (C), 131.3 (C), 126.8 (CH), 126.7 (CH), 118.3 (CH), 114.7 (CH), 70.55 (CH$_2$), 70.46 (CH$_2$), 66.62 (CH$_2$), 66.56 (CH$_2$), 59.5 (CH), 55.7 (CH$_3$), 31.0 (CH$_2$), 30.9 (CH$_2$), 30.1 (CH$_2$), 30.0 (CH$_2$), 29.8 (CH$_2$), 29.4 (CH$_2$), 26.1 (CH$_2$), 24.3 (CH$_2$), 24.0 (CH$_2$); IR (cm^{-1}): 2931; 2856 (-CH$_2$), 1733 (-CONR$_2$), 1509 (-C=C), 1298 (-CO-CH$_3$), 829 (para disub -ArH); ESI$^+$-MS: 631 [M + H]$^+$, 653 [M + Na]$^+$; HRMS: ES$^+$ [M + H]$^+$ calcd for C$_{38}$H$_{51}$N$_2$O$_6$, 631.3742; found, 631.3750, [M + Na]$^+$ calcd for C$_{38}$H$_{51}$N$_2$NaO$_6$, 653.3561; found, 653.3567; R$_f$ = 0.2 (30% EtOAc in 40-60 °C petroleum ether).

4,4'((But-2-ene-1,4-diylbis(oxy))bis(heptane-7,1-diyl))bis(1-(4-methoxyphenyl)-3-methyleneazetidin-2-one (132)
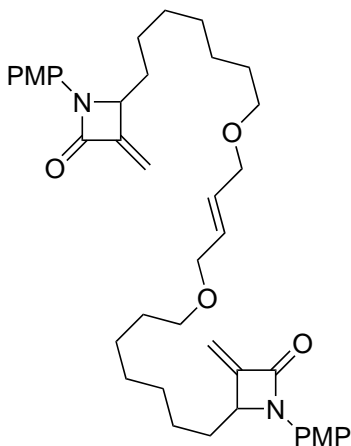
4-(7-(Allyloxy)heptyl)-1-(4-methoxyphenyl)-3-methyleneazetidin-2-one (**122**) (50 mg, 0.14 mmol) was dissolved in CH_2Cl_2 (70 mL) and Hoveyda-Grubbs 2nd generation catalyst (9 mg, 0.014 mmol) added in one portion. The solution was refluxed for 24 h at which point it was cooled to room temperature and the solvent removed. Column chromatography (15% EtOAc, 1% Et_3N in 40-60 °C petroleum ether) yielded the *title compound* as an oil (30 mg, 65% yield). ^{1}H-NMR (CDCl$_3$, 400 MHz, δ): 7.37-7.33 (m, 4H, ArH), 6.92-6.87 (m, 4H, ArH), 5.80-5.77 (m, 4H, -OCH$_2$C*H*CH*C*H$_2$O-, -CC*H*H), 5.24 (s, 2H, 2 x -CC*H*H), 4.51 (d, *J* = 7.1 Hz, 2H, 2 x -NC*H*CCH$_2$), 3.94 (d, *J* = 2.5 Hz, 4H, 2 x -CHC*H*$_2$O-), 3.78 (s, 6H, 2 x -ArOC*H*$_3$), 3.38 (t, *J* = 6.6 Hz, 4H, 2 x -CH$_2$OC*H*$_2$CH$_2$-), 2.03-1.94 (m, 2H, 2 x -NCHCC*H*H-), 1.81-1.72 (m, 2H, 2 x -NCHCC*H*H-), 1.57-1.49 (m, 4H, 2 x -CH$_2$OCH$_2$C*H*$_2$-), 1.43-1.24 (m, 16H, 8 x -CH$_2$); ^{13}C-NMR (CDCl$_3$, 100 MHz, δ): 160.1 (C=O), 156.2 (C), 148.5 (C), 131.1 (C), 129.5 (CH), 118.4 (CH), 114.6 (CH), 109.4 (CH$_2$), 70.8 (CH$_2$), 70.5 (CH$_2$), 60.5 (CH), 55.5 (CH$_3$), 30.7 (CH$_2$), 29.7 (CH$_2$), 29.5 (CH$_2$), 29.3 (CH$_2$), 26.1 (CH$_2$), 24.3 (CH$_2$); IR (cm^{-1}): 2931; 2856 (-CH$_2$), 1733 (-CONR$_2$), 1509 (-C=C), 1298 (-CO-CH$_3$), 829 (para disub -ArH); ESI$^+$-MS: 659 [M + H]$^+$; HRMS: ES$^+$ [M + H]$^+$ calcd for C$_{40}$H$_{55}$N$_2$O$_6$, 659.4055; found, 659.4068; R$_f$ = 0.3 (15% EtOAc, 1% Et$_3$N in 40-60 °C petroleum ether).

13-(4-Methoxyphenyl)-4-oxa-13-azabicyclo[10.2.0]tetradecan-14-one (141)
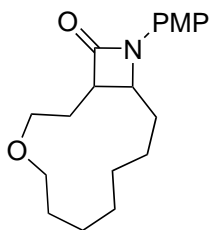
(E/Z)-14-(4-Methoxyphenyl)-9-oxa-14-aza-bicyclo[10.2.0]tetradec-11-en-13-one (27 mg, 0.086 mmol) and PtO_2 (2 mg, 0.0089 mmol) were added to a flask and the atmosphere replaced with H_2. A mixture of EtOH/THF (2 mL:4 mL) was added and the suspension was stirred vigorously for 18 h at room temperature. The solvent was removed and the crude material immediately purified via column chromatography (20% EtOAc in 40-60 °C petroleum ether), to give the *title compound* as an oil (13 mg, 48%). ^{1}H-NMR (CDCl$_3$, 400 MHz, δ): 7.32-7.25 (m, 2H, ArH), 6.90-6.85 (m, 2H, ArH), 4.13-4.08 (m, 1H, -NArC*H*-), 3.78 (s, 3H, -OCH$_3$), 3.63-3.57 (m, 1H, -CHCH$_2$C*H*HO-), 3.45-3.41 (m, 2H, -OCH$_2$CH2CH$_2$-), 3.40-3.32 (m, 2H, -CCHCH$_2$C*H*HO-; -CC*H*CH$_2$-), 2.19-1.91 (m, 3H, -CCHC*H$_2$*CH$_2$O-; -NArCHC*H*H-) 1.76-1.59 (m, 3H, -NArCHCH*H*-; -OCH$_2$C*H$_2$*CH$_2$-), 1.58-0.81 (m, 8H, 4 x -CH$_2$); ^{13}C-NMR (CDCl$_3$, 100 MHz, δ): 167.5 (C=O), 155.9 (C), 130.8 (C), 119.3 (2 x CH), 114.4 (2 x CH), 72.5 (CH$_2$), 71.1 (CH$_2$), 57.1 (CH), 55.7 (CH$_3$), 53.0 (CH), 26.8 (CH$_2$), 26.1 (CH$_2$), 25.9 (CH$_2$), 24.9 (CH$_2$), 24.4 (CH$_2$), 24.3 (CH$_2$); IR (cm^{-1}): 2932; 2853 (-CH$_2$), 1738 (-CONR$_2$), 1510 (-C=C), 1244 (-CO-CH$_3$), 830 (para disub -ArH); ESI$^+$-MS: 318 [M + H]$^+$, 340 [M + Na]$^+$; HRMS: ES$^+$ [M + H]$^+$ calcd for C$_{19}$H$_{26}$NO$_3$, 340.1883; found, 340.1883; R$_f$ = 0.3 (20% EtOAc in 40-60 °C petroleum ether).

(Z)-4-oxa-13-azabicyclo[10.2.0]tetradec-1-en-14one
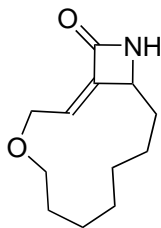
(Z/E)-14-(4-Methoxyphenyl)-9-oxa-14-aza-bicyclo[10.2.0]tetradec-11-en-13-one (5 mg, 0.06 mmol) was dissolved in MeCN (2 mL) and cooled to 0 °C. CAN (99 mg, 0.18 mmol) in H_2O (2 mL) was added dropwise and the reaction stirred for 1 h at 0 °C, after which time it was poured into Et$_2$O (5 mL) and sat. NaHCO$_3$ (5 mL). The aqueous was extracted with Et$_2$O (3 x 5 mL), the combined organics were dried, and the solvent removed under reduced pressure. Semi-preparative HPLC (40% H_2O

in MeCN) yielded the *title compound* (1 mg, 30%), which was unstable in CDCl$_3$. ^{1}H-NMR (CDCl$_3$, 300 MHz, δ): 6.12 (br s, 1H, N*H*), 5.87 (dd, *J* = 10.8 Hz, 3.0 Hz, 1H, -C*H*CH$_2$O-), 4.60 (dd, *J* = 12.8 Hz, 10.8 Hz, 1H, CHC*H*HO-), 4.16-4.09 (m, 2H, -C*H*CH$_2$CH2-; -CHC*H*HO-), 3.72-3.65 (m, 1H, -OC*H*HCH$_2$-), 3.44-3.37 (m, 1H, -OC*H*HCH$_2$-), 1.72-1.12 (m, 12H, 6 x C*H*$_2$); ESI$^+$-MS: 232 [M + Na]$^+$ 441 [2M + Na]$^+$; HRMS: ES$^+$ [M + Na]$^+$ calcd for C$_{12}$H$_{19}$NNaO$_2$, 232.1308; found, 232.1313.

(Z)-13-Ethyl-4-oxa-13-azabicyclo[10.2.0]tetradec-1-en-14-one (101)
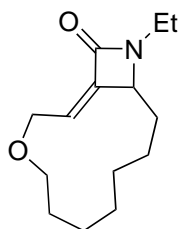
(Z)-14-(4-Methoxyphenyl)-9-oxa-14-aza-bicyclo[10.2.0]tetradec-11-en-13-one (19 mg, 0.06 mmol) was dissolved in MeCN (2 mL) then cooled to 0 °C. CAN (99 mg, 0.18 mmol) in H$_2$O (2 mL) was added dropwise and the reaction stirred for 1 h at 0 °C, after which time it was poured into Et$_2$O (5 mL) and sat. NaHCO$_3$ (5 mL). The aqueous was extracted with Et$_2$O (3 x 5 mL), the combined organics were dried, and the solvent removed under reduced pressure. Column chromatography (50% EtOAc in 40-60 °C petroleum ether) yielded the *title compound*, which used immediately dissolved in Et-I (5 mL). KOH (5 mg, 0.096) was added and the solution stirred for 18 h at room temperature. The solution was then poured into H$_2$O (5 mL). The layers were separated and the aqueous extracted with Et$_2$O (2 x 5 mL). The combined organics were dried (MgSO$_4$), filtered and the volatiles removed under reduced pressure. Semi-preparative HPLC (40% H$_2$O in MeCN, flow rate 1 mL/min) yielded the *title compound* as a solid (3 mg, 21% over two steps). ^{1}H-NMR (CDCl$_3$, 700 MHz, δ): 5.78 (dd, *J* = 10.8, 3.7 Hz, 1H, -CH$_2$C*H*C-, 4.56 (dd, *J* = 12.8, 10.9 Hz, 1H, -OC*H*HCHC-), 4.12-4.11 (m, 2H, -OC*H*HCHC-; -CH$_2$C*H*(C)N-), 3.69 (dt, *J* = 11.1 , 4.9 Hz, -OC*H*HCH$_2$-), 3.54-3.49 (m, 1H, -NC*H*HCH$_3$), 3.44 (dt, *J* = 11.1 , 4.9 Hz, -OC*H*HCH$_2$-), 3.16-3.11 (m, 1H, -NC*H*HCH$_3$), 1.87-1.82 (m, 1H, -CHC*H*HCH$_2$-), 1.69-1.65 (m, 1H, -CHC*H*HCH$_2$-), 1.53-1.49 (m, 2H, -OCH$_2$C*H*$_2$-), 1.47-1.22 (m, 10H, 5 x C*H*$_2$), 1.19 (t, *J* = 7.2 Hz, -NCH$_2$C*H*$_3$); ^{13}C-NMR (CDCl$_3$, 175 MHz, δ): 163.2 (C=O), 143.7 (C), 125.2 (CH), 67.3 (CH$_2$), 65.3 (CH$_2$), 558.1 (CH), 34.8 (CH$_2$), 29.7

(CH_2), 28.7 (CH_2), 28.6 (CH_2), 27.4 (CH_2), 24.7 (CH_2), 21.9 (CH_2), 20.4 (CH_2), 13.4 (CH_3); IR (cm^{-1}): 2928; 2856 (-CH_2), 1738 (-$CONR_2$), 1395 (-C=C), 1220 (-CO-CH_2); ESI^+-MS: 260 [M + Na]$^+$; HRMS: ES$^+$ [M + Na]$^+$ calcd for $C_{14}H_{23}NNaO_2$, 260.1621; found, 260.1617.

8-(But-2-en-1-yloxy)octan-1-ol (243)
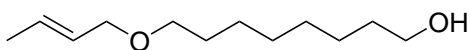
1,8 Octadiol (7.1 g, 48.6 mmol) was dissolved in THF (50 mL) and added to NaH (60% in mineral oil, 2.2 g, 55.0 mmol) via cannula. The slurry was stirred for 1 h at room temperature. Crotonyl bromide (5.75 mL, 56.2 mmol) and TBAI (35 mg) were dissolved in THF (50 mL) and added to the NaH solution via cannula. This was heated to reflux for 16 h. Once cool sat. NH_4Cl (50 mL) was added and the aqueous layer extracted with EtOAc (3 x 50 mL). The combined organics were dried ($MgSO_4$ and the volatiles removed under reduced pressure. Column chromatography (20% EtOAc in 40-60 °C petroleum ether) yielded the *title compound* as an oil (5 g, 51%). There are two products due to the isomers of crotyl bromide used, only the major product was well resolved and so is recorded below. The ratio is approximately 1:4.5.
^{1}H-NMR (CDCl$_3$, 400 MHz, δ): 5.76-5.64 (m, 1H, -CH_3C*H*CH-), 5.63-5.53 (m, 1H, -CH_3CHC*H*-), 3.88 (d, J = 6.2 Hz, 2H, -OC*H$_2$*CH-), 3.63 (t, J = 6.6 Hz, 1H, -CH_2OC*H$_2$*-), 3.39 (t, J = 6.7 Hz, 2H, -C*H$_2$*CHO-), 1.71 (d, J = 6.3 Hz, 3H, C*H$_3$*CHCH-), 1.63-1.28 (m, 10H, 5 x -C*H$_2$*-); ^{13}C-NMR (CDCl$_3$, 100 MHz, δ): 129.2 (CH), 127.8 (CH), 71.5 (CH_2), 70.3 (CH_2), 63.1 (CH_2), 32.8 (CH_2), 29.8 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 26.2 (CH_2), 25.7 (CH_2), 17.8 (CH_3); IR (cm^{-1}): 3353 (-OH), 2929, 2856 (CH_2); MS-ESI: 223 [M + Na]$^+$; HRMS ES$^+$: [M + Na]$^+$ calcd for $C_{12}H_{24}NaO_2$ 223.1699; found, 223.1666; R_f = 0.3 (20% EtOAc in 40-60 °C petroleum ether).

8-(But-2-en-1-yloxy)octanal (115)
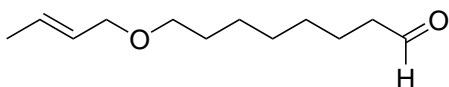
8-(But-2-en-1-yloxy)octan-1-ol (5 g, 25.0 mmol) was dissolved in CH_2Cl_2 (50 mL) and SiO_2 was added to make a slurry. PCC (6.5 g, 30.0 mmol) was added in one portion and the solution stirred for 16 h. The mixture was diluted with Et_2O (50 mL) then filtered through a short pad of SiO_2. The pad was washed exhaustively with Et_2O. The volatiles were removed under reduced pressure. Column chromatography (10% EtOAc in 40-60 °C petroleum ether) yielded the *title compound* as a clear oil (1.4 g, 28%). ^{1}H-NMR (CDCl$_3$, 400 MHz, δ): 9.74 (apparent d, $J = 1.7$ Hz, 1H, -C*H*O), 5.76-5.64 (m, 1H, -CH$_3$C*H*CH-), 5.63-5.53 (m, 1H, -CH$_3$CHC*H*-), 3.88 (d, $J = 6.1$ Hz, 2H, -OC*H$_2$*CH-), 3.38 (t, $J = 6.7$ Hz, 1H, -C*H$_2$*OC*H$_2$*-), 2.42 (t, $J = 7.4$ Hz, 2H, -C*H$_2$*CHO-), 1.71 (d, $J = 6.3$ Hz, 3H, C*H$_3$*CHCH-), 1.68-1.27 (m, 10H, 5 x -C*H$_2$*-); ^{13}C-NMR (CDCl$_3$, 100 MHz, δ): 202.9 (C=O), 129.2 (CH), 127.8 (CH), 71.5 (CH$_2$), 70.2 (CH$_2$), 43.9 (CH$_2$), 29.7 (CH$_2$), 29.2 (CH$_2$), 29.1 (CH$_2$), 26.0 (CH$_2$), 22.0 (CH$_2$), 17.7 (CH$_3$); MS-ESI 221 [M + Na]$^+$; HRMS: ES$^+$ [M + Na]$^+$ calcd for C$_{12}$H$_{22}$NNaO$_2$, 221.1512; found, 221.1517; R$_f$ = 0.3 (10% EtOAc in 40-60 °C petroleum ether).

Methyl 10-(but-2-en-1-yloxy)-3-hydroxy-2-methylenedecanoate (116)
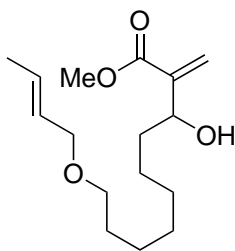
8-(But-2-en-1-yloxy)octanal (4 g, 20.2 mmol) was dissolved in methyl acrylate (2 mL, 22.1 mmol), MeOH (1 mL) and DABCO (640 mg, 5.71 mmol) were added and the solution stirred for 9 days. The volatiles were removed and the crude product was purified via column chromatography (20% EtOAc in 40-60 °C petroleum ether) to give the *title compound* as a clear oil (1.686 g, 29%). ^{1}H-NMR (CDCl$_3$, 400 MHz, δ): 6.22 (d, *J* = 1.0 Hz, 1H, C*H*HC-), 5.79 (t, *J* = 1.0 Hz, 1H, C*H*HC-), 5.76-5.65 (m, 1H, -CH$_3$C*H*CH-), 5.64-5.53 (m, 1H, -CH$_3$CHC*H*-), 4.38 (q, *J* = 5.6 Hz, 1H, -CH$_2$C(C)*H*OH), 3.88 (dt, *J* = 6.1, 1.0 Hz, 2H, -OC*H*$_2$CH-), 3.78 (s, 3H, -COOC*H*$_3$), 3.38 (t, *J* = 6.7 Hz, 1H, -CH$_2$OC*H*$_2$-), 2.55 (d, *J* = 6.0 Hz, 1H, -O*H*), 1.71 (dd, *J* = 6.3, 1.2 Hz, 3H, C*H*$_3$CHCH-), 1.68-1.25 (m, 10H, 5 x -C*H*$_2$-); ^{13}C-NMR (CDCl$_3$, 100 MHz, δ): 167.1 (C=O), 142.5 (C), 129.2 (CH), 127.8 (CH), 125.0 (CH$_2$), 71.8 (CH), 71.5 (CH$_2$), 70.3 (CH$_2$), 51.9 (CH$_3$), 36.2 (CH$_2$), 29.8 (CH$_2$), 29.4 (CH$_2$), 26.1 (CH$_2$), 25.8 (CH$_2$), 17.8 (CH$_3$); IR (cm^{-1}): 3430 (-OH), 2929, 2855 (-CH$_2$), 1725 (-CO$_2$H); MS-ESI: 307 [M + Na]$^+$; HRMS ES$^+$: [M + Na]$^+$ calcd for C$_{22}$H$_{33}$NNaO$_6$S 462.1921; found, 462.1937; R$_f$ = 0.3 (20% EtOAc in 40-60 °C petroleum ether).

10-(But-2-en-1-yloxy)-3-hydroxy-2-methylenedecanoic acid (117)
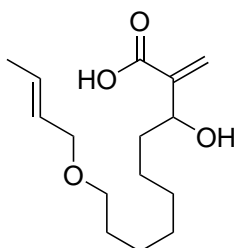
Methyl 10-(but-2-en-1-yloxy)-3-hydroxy-2-methylenedecanoate (1.686 g, 5.94 mmol) was dissolved in THF (50 mL). LiOH·H$_2$O (1.2 g, 29.3 mmol) in H$_2$O (50 mL) was added and the solution stirred for 16 h. The layers were allowed to separate and the aqueous layer acidified to pH 1 with 2N HCl. This was extracted with EtOAc (3 x 20 mL). The combined organics were dried (MgSO$_4$), filtered and the solvent removed under reduced pressure to give the *title compound* as a clear oil, which was used without further purification (1.600 g, 99%). ^{1}H-NMR (CDCl$_3$, 400 MHz, δ): 6.38 (s, 1H, C*H*HC-), 5.90 (s, 1H, C*H*HC-), 5.76-5.66 (m, 1H, -CH$_3$C*H*CH-), 5.65-5.53 (m, 1H, -CH$_3$CHC*H*-), 4.41 (t, *J* = 7.0 Hz, 1H,

-CH$_2$C(C)HOH), 3.88 (dt, J = 6.2, 1.0 Hz, 2H, -OCH_2CH-), 3.40 (t, J = 6.7 Hz, 1H, -CH$_2$OCH_2-), 1.71 (dd, J = 6.3, 1.0 Hz, 3H, CH_3CHCH-), 1.68-1.25 (m, 12H, 6 x -CH_2-); ^{13}C-NMR (CDCl$_3$, 100 MHz, δ): 170.8 (C=O), 142.5 (C), 129.4 (CH), 127.7 (CH), 127.4 (CH$_2$), 71.59 (CH), 71.56 (CH$_2$), 70.3 (CH$_2$), 36.2 (CH$_2$), 29.7 (CH$_2$), 29.4 (CH$_2$), 29.3 (CH$_2$), 26.1 (CH$_2$), 25.7 (CH$_2$), 17.8 (CH$_3$); IR (cm^{-1}): 3358 (-COOH), 2928; 2855 (-CH$_2$), 1707 (-COOH), 1053 (-CO-CH$_3$); MS-ESI: 293 [M + Na]$^+$; HRMS ES$^+$: [M + Na]$^+$ calcd for C$_{15}$H$_{26}$NaO$_4$ 293.1723; found, 293.1722.

10-(But-2-en-1-yloxy)-3-hydroxy-N-(4-methoxyphenyl)-2-methylenedecanamide (134)
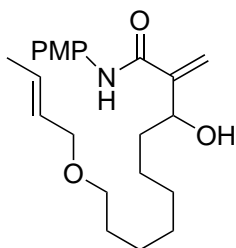
10-(But-2-en-1-yloxy)-3-hydroxy-2-methylenedecanoic acid (193 mg, 0.71 mmol) and *p*-anisidine (87 mg, 0.71 mmol) were dissolved in EtOH (7 mL) and cooled to 0 °C. HOBt (88%, 20 mg, 0.11 mmol) and NMM (200 μL, 1.57 mmol) were added followed by EDC · HCl, the solution was allowed to warm to room temperature over 18 h. It was then diluted with EtOAc (10 mL) and washed with H$_2$O (10 mL). The organics were separated, dried (MgSO$_4$), filtered and the solvent removed under reduced pressure. Column chromatography (40% EtOAc in 40-60 °C petroleum ether) yielded the *title compound* (125 mg, 47%). ^{1}H-NMR (CDCl$_3$, 400 MHz, δ): 9.26 (s, 1H, -NH), 7.47-7.44 (m, 2H, ArH), 6.83-6.81 (m, 2H, ArH), 5.99 (s, 1H, CHHC-), 5.73-5.63 (m, 1H, -CH$_3$CHCH-), 5.61-5.23 (m, 1H, -CH$_3$CHCH-), 5.40 (s, 1H, CHHC-), 4.36 (t, J = 6.9 Hz, 1H, -CH$_2$C(C)HOH), 4.29 (br s, 1H, -OH), 3.87 (d, J = 6.0 Hz, 2H, -OCH_2CH-), 3.75 (s, 3H, -OCH_3), 3.37 (t, J = 6.7 Hz, 1H, -CH$_2$OCH_2-), 1.69 (d, J = 6.3 Hz, 3H, CH_3CHCH-), 1.66-1.21 (m, 12H, 6 x -CH_2-); ^{13}C-NMR (CDCl$_3$, 100 MHz, δ): 165.4 (C=O), 156.4 (C), 145.1 (C), 131.0 (C), 129.3 (CH), 127.7 (CH), 121.9 (CH), 122.0 (CH$_2$), 114.1 (CH), 73.9 (CH), 71.5 (CH$_2$), 70.2 (CH$_2$), 55.4 (CH$_3$), 35.8 (CH$_2$), 29.7 (CH$_2$), 29.4 (CH$_2$), 29.4 (CH$_2$), 26.1 (CH$_2$), 26.0 (CH$_2$), 17.8 (CH$_3$); IR (cm^{-1}): 3301 (-OH), 2933; 2856 (-CH$_2$) 1510 (-CONR$_2$), 1244 (-CO-CH$_3$), 830 (para disub -ArH); MS-ESI: 398 [M + Na]$^+$; HRMS

ES$^+$: [M + Na]$^+$ calcd for C$_{22}$H$_{33}$NNaO$_4$ 398.2302; found, 398.2323; R$_f$ = 0.3 (40% EtOAc in 40-60 °C petroleum ether).

4-(7-(But-2-en-1-yloxy)heptyl)-1-(4-methoxyphenyl)-3-methyleneazetidine-2-one (133)
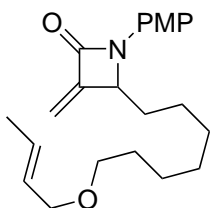
10-(But-2-en-1-yloxy)-3-hydroxy-N-(4-methoxyphenyl)-2-methylenedecanamide (852 g, 2.27 mmol) was dissolved in CH$_2$Cl$_2$ (10 mL) and cooled to -78 °C. Et$_3$N (600 µL, 4.63 mmol) was added, followed by MsCl (350 µL, 4.54 mmol) dropwise. The reaction was stirred for 5 h at -78 °C, after which time the reaction was quenched with H$_2$O (20 mL). The organics were separated, dried (MgSO$_4$), filtered and the solvent was removed under reduced pressure. The crude 10-(but-2-en-1-yloxy)-2-((4-methoxyphenyl)carbamoyl)dec-1-en-3-yl methanesulfonate (539 mg, 1.19 mmol) was dissolved in THF (10 mL) and cooled to -15 °C. KO^{t}Bu (146 mg, 1.30 mmol) was added in one portion and stirred at -15 °C for 2 h. The reaction was quenched with sat. NH$_4$Cl (10 mL), the organics were separated, dried (MgSO$_4$), filtered and the solvent removed under reduced pressure. Column chromatography (20% EtOAc in 40-60 °C petroleum ether) yielded the *title compound* as a clear oil (240 mg, 30% over 2 steps). ^{1}H-NMR (CDCl$_3$, 400 MHz, δ): 7.37-7.34 (m, 2H, Ar*H*), 6.90-6.88 (m, 2H, Ar*H*), 5.77 (t, *J* = 1.5 Hz, 1H, C*H*HC-), 5.77-5.66 (m, 1H, -CH$_3$C*H*CH-), 5.62-5.53 (m, 1H, -CH$_3$CHC*H*-), 5.24 (s, 1H, C*H*HC-), 4.52 (apparent d, *J* = 9.2 Hz, 1H, -CH$_2$C(C)*H*-), 3.87 (d, *J* = 6.2 Hz, 2H, -OC*H*$_2$CH-), 3.80 (s, 3H, -OC*H*$_3$), 3.37 (t, *J* = 6.7 Hz, 1H, -CH$_2$OC*H*$_2$-), 2.06-1.95 (m, 1H, -C*H*HCHN-), 1.83-1.74 (m, 1H, -C*H*HCHN-), 1.70 (ddd, *J* = 6.3, 1.1 Hz, 3H, C*H*$_3$CHCH-), 1.60-1.50 (m, 2H, -OCH$_2$C*H*$_2$-), 1.47-1.24 (m, 8H, 4 x -C*H*$_2$-); ^{13}C-NMR (CDCl$_3$, 100 MHz, δ): 160.1 (C=O), 156.2 (C), 148.5 (C), 131.1 (C), 129.2 (CH), 127.8 (CH), 118.4 (CH), 114.5 (CH), 109.4 (CH$_2$), 71.6 (CH$_2$), 70.2 (CH$_2$), 60.4 (CH), 55.5 (CH$_3$), 30.8 (CH$_2$), 29.7 (CH$_2$), 29.5 (CH$_2$), 29.3 (CH$_2$), 26.1 (CH$_2$), 24.3 (CH$_2$), 17.8 (CH$_3$); IR (cm^{-1}): 2930; 2855 (-CH$_2$), 1735 (-CONR$_2$), 1455 (-C=C), 1174 (-CO-CH$_3$), 728 (para disub -ArH); MS-ESI: 380 [M + Na]$^+$;

HRMS ES$^+$: [M + Na]$^+$ calcd for $C_{22}H_{31}NNaO_3$ 380.2196; found, 380.2198; R$_f$ = 0.3 (20% EtOAc in 40-60 °C petroleum ether).
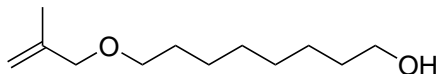
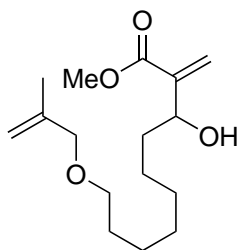### 8-((2-Methylallyl)oxy)octan-1-ol (153)

1,8 Octadiol (7.1 g, 48.6 mmol) was dissolved in THF (50 mL) and added to NaH (60% in mineral oil, 2.2 g, 55.0 mmol) via cannula. The slurry was stirred for 1 h at room temperature. 3-Bromo-2-methylpropene (4.4 mL, 43.3 mmol) and TBAI (50 mg) were dissolved in THF (50 mL) and added to the NaH solution via cannula. This was heated to reflux for 16 h. Once cool sat. NH_4Cl (50 mL) was added and the aqueous layer extracted with EtOAc (3 x 50 mL). The combined organics were dried ($MgSO_4$ and the volatiles removed under reduced pressure. Column chromatography (10% EtOAc in 40-60 °C petroleum ether) yielded the *title compound* as an oil (4.4 g, 45%). ^{1}H-NMR (CDCl$_3$, 400 MHz, δ): 4.95 (s, 1H, -CCH$_3$C*H*H), 4.87 (s, 1H, -CCH$_3$C*H*H), 3.85 (s, 2H, -OC*H*$_2$CCH$_3$-), 3.63 (t, *J* = 6.6 Hz, 2H, -C*H*$_2$OH), 3.37 (t, *J* = 6.6 Hz, 2H, -OC*H*$_2$-), 1.72 (s, 3H, CH$_2$CC*H*$_3$CH$_2$-), 1.62-1.23 (m, 12H, 6 x -C*H*$_2$-); ^{13}C-NMR (CDCl$_3$, 100 MHz, δ): 142.7 (C), 111.9 (CH$_2$), 74.9 (CH$_2$), 70.4 (CH$_2$), 63.2 (CH$_2$), 33.0 (CH$_2$), 29.9 (CH$_2$), 29.6 (CH$_2$), 29.5 (CH$_2$), 26.3 (CH$_2$), 25.8 (CH$_2$), 19.6 (CH$_3$); R$_f$ = 0.3 (10% EtOAc in 40-60 °C petroleum ether).

8-((2-Methylallyl)oxy)octanal (152)
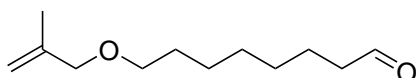
8-((2-Methylallyl)oxy)octan-1-ol (**153**) (4.4 g, 22.0 mmol) was dissolved in CH_2Cl_2 (50 mL) and SiO_2 was added to make a slurry. PCC (5.6 g, 26.4 mmol) was added in one portion and the solution stirred for 5 h. The mixture was diluted with Et$_2$O (50 mL) then filtered through a short pad of SiO_2. The pad was washed exhaustively with Et$_2$O. The volatiles were removed under reduced pressure. Column chromatography (15% EtOAc in 40-60 °C petroleum ether) yields the *title compound* as a clear oil (2.5 g, 51%). ^{1}H-NMR (CDCl$_3$, 400 MHz, δ): 9.74 (s, 1H, -C*H*O), 4.93

(s, 1H, -CCH$_3$CHH), 4.86 (s, 1H, -CCH$_3$CHH), 3.84 (s, 2H, -OCH_2CCH$_3$-), 2.40 (td, J = 7.4 Hz, 1.8 Hz, 2H, -OCH_2-), 1.72 (s, 3H, CH$_2$CCH_3CH$_2$-), 1.66-1.28 (m, 12H, 6 x -CH_2-); ^{13}C-NMR (CDCl$_3$, 100 MHz, δ): 203.0 (C=O), 142.7 (C), 111.9 (CH$_2$), 74.9 (CH$_2$), 70.2 (CH$_2$), 44.0 (CH$_2$), 29.9 (CH$_2$), 29.4 (CH$_2$), 29.3 (CH$_2$), 26.2 (CH$_2$), 22.2 (CH$_2$), 19.6 (CH$_3$); MS-ESI: 221 [M + Na]$^+$; HRMS ES$^+$: [M + Na]$^+$ calcd for C$_{12}$H$_{22}$NaO$_2$ 221.1512; found, 221.1517; R$_f$ = 0.3 (15% EtOAc in 40-60 °C petroleum ether).

Methyl 3-hydroxy-10-((2-methylally)oxy)-2-methylenedecanoate (154)

8-((2-Methylallyl)oxy)octanal (**152**) (2.5 g, 12.6 mmol) was dissolved in methyl acrylate (1.5 mL, 18.9 mmol). and DABCO (1.4 g, 12.6 mmol) were added and the solution stirred for 7 days. The volatiles were removed and the crude product was purified via column chromatography (15% EtOAc in 40-60 °C petroleum ether) to give the *title compound* as a clear oil (1.954 g, 60%). $^1$H-NMR (CDCl$_3$, 400 MHz, δ): 6.20 (s, 1H, -CC*H*H), 5.77 (s, 1H, -CC*H*H), 4.93 (s, 1H, -CCH$_3$C*H*H), 4.89 (s, 1H, -CCH$_3$C*H*H), 4.38 (q, J = 6.4 Hz, 1H, -C*H*OHC-), 3.84 (s, 2H, -OC*H*$_2$CCH$_3$-), 3.76 (s, 3H, COOC*H*$_3$), 3.36 (t, J = 6.6 Hz, 2H, -C*H*$_2$OH), 2.57 (br s, 1H, -O*H*), 1.71 (s, 3H, CH$_2$CC*H*$_3$CH$_2$-), 1.61-1.22 (m, 12H, 6 x -C*H*$_2$-); ^{13}C-NMR (CDCl$_3$, 100 MHz, δ) 167.2 (C=O), 142.74 (C), 142.68 (C), 125.1 (CH$_2$), 111.9 (CH$_2$), 74.9 (CH$_2$), 71.9 (CH), 70.3 (CH$_2$), 52.0 (CH$_3$), 36.4 (CH$_2$), 29.9 (CH$_2$), 29.5 (CH$_2$), 26.3 (CH$_2$), 25.9 (CH$_2$), 19.6 (CH$_3$); MS-ESI: 307 [M + Na]$^+$;HRMS ES$^+$: [M + Na]$^+$ calcd for C$_{16}$H$_{28}$NaO$_4$ 307.1880; found, 307.1884; R$_f$ = 0.3 (15% EtOAc in 40-60 °C petroleum ether).

3-Hydroxy-10-((2-methylally)oxy)-2-methylenedecanoic acid (155)
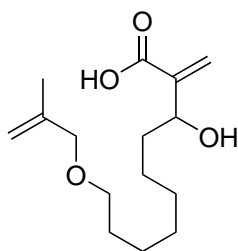
Methyl 3-hydroxy-10-((2-methylally)oxy)-2-methylenedecanoate (**154**) (1.954 g, 4.59 mmol) was dissolved in THF (20 mL). LiOH · H$_2$O (1.4 mg, 34.0 mmol) in H$_2$O (20 mL) was added and the solution stirred overnight. The layers were allowed to separate and the aqueous layer acidified to pH 1 with 2N HCl. This was extracted with EtOAc (3 x 20 mL). The combined organics were dried (MgSO$_4$), filtered and the solvent removed under reduced pressure yielded the *title compound* as a clear oil, which was used without further purification (1.369 g, 74%). ^{1}H-NMR (CDCl$_3$, 400 MHz, δ): 7.37 (br s, 1H, -COO*H*), 6.36 (s, 1H, -CC*H*H), 5.88 (s, 1H, -CC*H*H), 4.93 (s, 1H, -CCH$_3$C*H*H), 4.86 (s, 1H, -CCH$_3$C*H*H), 4.40 (t, J = 6.6 Hz, 1H, -C*H*OH-), 3.86 (s, 2H, -OC*H*$_2$CCH$_3$-), 3.38 (t, J

= 6.6 Hz, 2H, -C*H*OH), 1.71 (s, 3H, CH$_2$CC*H$_3$*CH$_2$-), 1.69-1.60 (m, 2H, -C*H$_2$*CHOH-), 1.60-1.51 (m, 2H, -OCH$_2$C*H$_2$*-), 1.46-1.18 (m, 8H, 4 x -C*H$_2$*-); ^{13}C-NMR (CDCl$_3$, 100 MHz, δ) 171.1 (C=O), 142.6 (C), 142.1 (C), 127.3 (CH$_2$), 112.1 (CH$_2$), 74.9 (CH$_2$), 71.6 (CH), 70.3 (CH$_2$), 36.3 (CH$_2$), 29.8 (CH$_2$), 29.52 (CH$_2$), 29.45 (CH$_2$), 26.3 (CH$_2$), 25.9 (CH$_2$), 19.6 (CH$_3$); IR (cm^{-1}): 3434 (-COOH), 2929; 2855 (-CH$_2$), 1715 (-COOH), 1630 (-C=C), 1262 (-CO-CH$_3$).

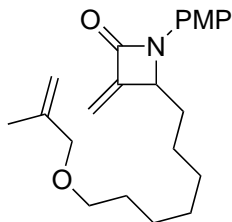## 3-Hydroxy-N-(4-methoxyphenyl)-10-((2-methylally)oxy)-2-methylenedecanamide (156)
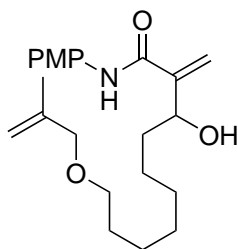
3-Hydroxy-10-((2-methylally)oxy)-2-methylenedecanoic acid (**155**) (1.369 g, 5.07 mmol) and *p*-anisidine (623 mg, 5.07 mmol) were dissolved in CH$_2$Cl$_2$ (20 mL) and cooled to 0 °C. DCC (1.04 mg, 5.07 mmol) in CH$_2$Cl$_2$ (50 mL) was added slowly and the solution allowed to warm to room temperature over 18 h. The resulting suspension was filtered through Celite, washed with a small amount of CH$_2$Cl$_2$ and the solvent removed under reduced pressure. Column chromatography (30% EtOAc in 40-60 °C petroleum ether) yielded the *title compound* contaminated with *p*-anisidine as a white solid (1.29 g). ^{1}H-NMR (CDCl$_3$, 400 MHz, δ): 8.65 (br s, 1H, N*H*) 7.47-7.45 (m, 2H, ArH), 6.86-6.84 (m, 2H, ArH), 5.98 (s, 1H, -CC*H*H), 5.48 (s, 1H, -CCH*H*), 4.92 (s, 1H, -CCH$_3$C*H*H), 4.85 (s, 1H, -CCH$_3$CH*H*), 4.42 (t, *J* = 7.5 Hz, 1H, -C*H*OHC-), 3.84 (s, 2H, -OC*H$_2$*CCH$_3$-), 3.78 (s, 3H, -ArOC*H$_3$*), 3.35 (t, *J* = 6.5 Hz, 2H, -C*H$_2$*OH), 3.02 (br s, 1H, -O*H*), 1.83-1.18 (m, 15H, 1 x C*H$_3$*, 6 x -C*H$_2$*-); ^{13}C-NMR (CDCl$_3$, 100 MHz, δ): 165.4 (C=O), 156.9 (C), 145.8 (C), 142.5 (C), 131.1 (C), 122.1 (CH), 121.7 (CH$_2$), 114.3 (CH), 111.9 (CH$_2$), 74.9 (CH$_2$), 74.4 (CH), 70.3 (CH$_2$), 55.7 (CH$_3$), 35.8 (CH$_2$), 29.9 (CH$_2$), 29.5 (CH$_2$), 29.4 (CH$_2$), 26.2 (CH$_2$), 26.1 (CH$_2$), 19.6 (CH$_3$); IR (cm^{-1}): 3300 (-OH), 2928; 2855 (-CH$_2$) 1628 (-CONR$_2$), 1245 (-CO-CH$_3$), 899 (para disub -ArH); MS-ESI: 376 [M + H]$^+$, 398 [M + Na]$^+$; HRMS ES$^+$: [M + Na]$^+$ calcd for C$_{22}$H$_{33}$NaO$_4$ 398.2302; found, 398.2304; R$_f$ = 0.3 (30% EtOAc in 40-60 °C petroleum ether).

1-(4-Methoxyphenyl)-4-(7-((2-methylallyl)oxy)heptyl)-3-methyleneazetidin-2-one (144)

3-Hydroxy-N-(4-methoxyphenyl)-10-((2-methylally)oxy)-2-methylenedecanamide (**156**) (1.2 g, 3.46 mmol) was dissolved in CH_2Cl_2 (10 mL) and cooled to -78 °C. Et_3N (950 μL, 6.92 mmol) was added, followed by MsCl (530 μL, 6.92 mmol) dropwise. The reaction was allowed to warm to room temperature over 18 h, after which time the reaction was quenched with H_2O (20 mL). The organics were separated, dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. The crude 2-((4-methoxyphenyl)carbamoyl)-10-((2-methylallyl)oxy)dec-1-en-3-yl methanesulfonate was dissolved in THF (20 mL) and cooled to 0 °C. KO^{t}Bu (474 mg, 5.08 mmol) was added in one portion and solution was allowed to warm to room temperature over 18 h. The reaction was quenched with sat. NH_4Cl (15 mL), the organics were separated, dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Column chromatography (20% EtOAc in 40-60 °C petroleum ether) yielded the *title compound* as a clear oil (583 mg, 32% over 2 steps). ^{1}H-NMR (CDCl$_3$, 400 MHz, δ): 7.37-7.32 (m, 2H, Ar*H*), 6.91-6.86 (m, 2H, Ar*H*), 5.76 (s, 1H, -CC*H*H), 5.24 (s, 1H, -CC*H*H), 4.93 (s, 1H, -CCH$_3$C*H*H), 4.86 (s, 1H, -CCH$_3$C*H*H), 4.52 (d, *J* = 6.6 Hz, 1H, -C*H*CNAr), 3.85 (s, 2H, -OC*H*$_2$CCH$_3$-), 3.79 (s, 3H, -ArOC*H*$_3$), 3.36 (t, *J* = 6.6 Hz, 2H, -OC*H*$_2$-), 2.05-1.94 (m, 1H, -C*H*HCHCNAr), 1.83-1.74 (m, 1H, -CH*H*CHCNAr), 1.72 (s, 3H, CH$_2$CC*H*$_3$CH$_2$-), 1.61-1.49 (m, 2H, -OCH$_2$C*H*$_2$-), 1.45-1.26 (m, 8H, 4 x C*H*$_2$); ^{13}C-NMR (CDCl$_3$, 100 MHz, δ): 160.3 (C=O), 156.4 (C), 148.7 (C), 142.7 (C), 131.3 (C), 118.9 (2 x CH), 114.7 (2 x CH), 111.9 (CH$_2$), 109.5 (CH$_2$), 74.9 (CH$_2$), 70.3 (CH$_2$), 60.6 (CH), 55.7 (CH$_3$), 30.9 (CH$_2$), 29.9 (CH$_2$), 29.7 (CH$_2$), 29.4 (CH$_2$), 26.3 (CH$_2$), 24.4 (CH$_2$), 19.6 (CH$_3$); IR (cm^{-1}): 2930; 2855 (-CH$_2$), 1736 (-CONR$_2$), 1509 (-C=C), 1244 (-CO-CH$_3$), 827 (para disub -ArH); MS-ESI: 380 [M + Na]$^+$; HRMS ES$^+$: [M + Na]$^+$ calcd for C$_{22}$H$_{31}$NNaO$_3$ 380.2196; found, 380.2193; R$_f$ = 0.3 (20% EtOAc in 40-60 °C petroleum ether).

RCM reactions of 1-(4-methoxyphenyl)-4-(7-((2-methylallyl)oxy)heptyl)-3-methyleneazetidin-2-one (144)

1-(4-methoxyphenyl)-4-(7-((2-methylallyl)oxy)heptyl)-3-methyleneazetidin-2-one (**144**) (50 mg, 0.14 mmol) was dissolved in CH_2Cl_2 (70 mL). Grubbs 2nd generation catalyst (11 mg, 0.014 mmol) was added and the reaction refluxed for 24 h. The solution was cooled and the solvent removed under reduced pressure. Column chromatography (10% EtOAc) yielded the styrene coupled product, and the methyl substituted product. This was further purified by semi-preparative HPLC (10% H_2O in MeCN, 1 mL/min) to yield the styrene coupled product (1-(4-methoxyphenyl)4-4(7-((2-methyl-3-phenylallyl)oxy)heptyl)-3-methyleneazetidin-2-one) (4 mg, 66%), and the elmination product ((E)-3-ethylidene-1-(4-methoxyphenyl)-4-(7-((2-methylallyl)oxy)heptyl)azetidin-2-one) (7 mg, 13%).

((Z)-3-ethylidene-1-(4-methoxyphenyl)-4-(7-((2-methylallyl)oxy)heptyl)azetidin-2-one) (144)
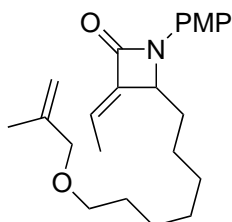
^{1}H-NMR (CDCl$_3$, 400 MHz, δ): 7.35-7.33 (m, 2H, ArH), 6.89-6.87 (m, 2H, ArH), 5.74 (q, *J* = 7.1 Hz, 1H, -CC*H*CH$_3$), 4.94 (s, 1H, -CCH$_3$C*H*H), 4.87 (s, 1H, -CCH$_3$C*H*H), 4.40 (dd, *J* = 7.4, 2.2 Hz, 1H, -C*H*CNAr), 3.85 (s, 2H, -OC*H$_2$*CCH$_3$-), 3.79 (s, 3H, -ArOC*H$_3$*), 3.37 (t, *J* = 6.6 Hz, 2H, -OC*H$_2$*-), 2.10 (d, *J* = 7.1 Hz, 3H, -CCHC*H$_3$*), 2.01-1.89 (m, 1H, -C*H*HCHCNAr), 1.78-1.66 (m, 1H, -CH*H*CHCNAr), 1.73 (s, 3H, CH$_2$CC*H$_3$*CH$_2$-), 1.66-1.62 (m, 2H, -OCH$_2$C*H$_2$*-), 1.48-1.24 (m, 8H, 4 x C*H$_2$*); ^{13}C-NMR (CDCl$_3$, 100 MHz, δ): 161.1 (C=O), 142.6 (C), 140.3 (C), (C), 131.5 (C), 125.3 (CH), 118.1 (CH), 114.9 (CH), 111.8 (CH$_2$), 74.8 (CH$_2$), 70.1 (CH$_2$), 59.5 (CH), 55.5 (CH$_3$), 31.1 (CH$_2$), 29.7 (CH$_2$), 29.6 (CH$_2$), 29.3 (CH$_2$), 26.1 (CH$_2$), 24.3 (CH$_2$), 19.5 (CH$_3$), 14.7 (CH$_3$); IR (cm^{-1}): 2935; 2850 (-CH$_2$), 1722 (-CONR$_2$), 1510 (-C=C), 1247 (-CO-CH$_3$), 827 (para disub -ArH); MS-ESI: 394 [M + Na]$^+$; HRMS ES$^+$: [M + Na]$^+$ calcd for C$_{23}$H$_{33}$NNaO$_3$ 394.2358;

found, 394.2361.

(1-(4-methoxyphenyl)4-4(7-((2-methyl-3-phenylallyl)oxy)heptyl)-3-methyleneazetidin-2-one)
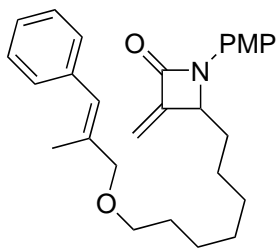
^{1}H-NMR (CDCl$_3$, 400 MHz, δ): 8.01-8.04 (m, 2H, ArH), 7.43-7.33 (m, 4H, ArH), 6.93-6.91 (m, 2H, ArH), 6.44 (s, 1H, -CCH$_3$C*H*Ph), 4.93 (s, 1H, -CCH$_3$C*H*H), 4.86 (s, 1H, -CCH$_3$CH*H*), 4.55 (d, *J* = 3.8 Hz, 1H, -C*H*CNAr), 3.84 (s, 2H, -OC*H*$_2$CCH$_3$-), 3.81 (s, 3H, -ArOC*H*$_3$), 3.35 (t, *J* = 6.6 Hz, 2H, -OC*H*$_2$-), 2.11-1.90 (m, 1H, -C*H*HCHCNAr), 1.78-1.66

(m, 1H, -CH*H*CHCNAr), 1.71 (s, 3H, CH$_2$CC*H*$_3$CH$_2$-), 1.54-1.39 (m, 2H, -OCH$_2$C*H*$_2$-), 1.39-1.19 (m, 8H, 4 x C*H*$_2$); ^{13}C-NMR (CDCl$_3$, 100 MHz, δ): 130.0 (CH), 128.7 (CH), 118.4 (CH), 114.6 (CH), 111.8 (CH$_2$), 74.8 (CH$_2$), 70.0 (CH$_2$), 58.7 (CH), 55.5 (CH$_3$), 31.1 (CH$_2$), 29.7 (CH$_2$), 29.6 (CH$_2$), 29.5 (CH$_2$), 26.1 (CH$_2$), 24.3 (CH$_2$), 19.5 (CH$_3$); IR (cm^{-1}): 2930; 2855 (-CH$_2$), 1730 (-CONR$_2$), 1509 (-C=C), 1269 (-CO-CH$_3$), 827 (para disub -ArH); MS-ESI: 470 [M + Na]$^+$; HRMS ES$^+$: [M + Na]$^+$ calcd for C$_{29}$H$_{37}$NNaO$_3$ 470.2671; found, 470.2674.

Methyl 3-hydroxy-2-methylenedodec-11-enoate (179)
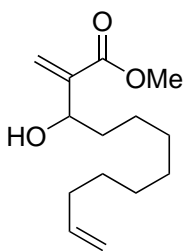
Dec-9-enal (1.00 g, 6.49 mmol) was dissolved in methyl acrylate (0.5 mL, 5.36 mmol). DABCO (150 mg, 1.34 mmol) and MeOH (150 μL) were added and the solution stirred for 24 h. The volatiles were removed under reduced pressure. Column chromatography (10% EtOAc in 40-60 °C petroleum ether) yielded the *title compound* as an oil (120 g, 8%). ^{1}H-NMR (CDCl$_3$, 400 MHz, δ): 6.22 (s, 1H, -CC*H*H), 5.86-5.76 (m, 2 x 1H, -C*H*CH$_2$; -CC*H*H), 4.99 (dd, *J* = 17.1, 1.5 Hz, 1H, -CHC*H*H), 4.92 (dd, *J* = 10.2, 1.0 Hz, 1H, -CHCH*H*), 4.38 (q, *J* = 6.6 Hz, 1H, -C*H*OH), 3.78 (s, 3H, -COOC*H*$_3$), 2.53 (br s, 1H, -CHO*H*), 2.03 (q, *J* = 7.0 Hz, 2H, -C*H*$_2$CH=CH$_2$), 1.69-1.61 (m, 2H, -C*H*$_2$CHOH-), 1.47-1.25 (m, 10H, 5 x -C*H*$_2$); ^{13}C-NMR (CDCl$_3$, 100 MHz, δ):

167.1 (C=O), 142.5 (C), 139.2 (CH), 125.0 (CH_2), 114.1 (CH_2), 71.9 (CH), 51.9 (CH_3), 36.2 (CH_2), 33.8 (CH_2), 29.40 (CH_2), 29.38 (CH_2), 29.1 (CH_2), 28.9 (CH_2), 25.8 (CH_2); IR (cm^{-1}):3432 (-OH), 2925 (-OOH), 2855 (-CH_2), 1717 ($-CO_2Me$), 1639 (-C=C); MS-ESI: 263 [M + Na]$^+$; HRMS ES$^+$: [M + Na]$^+$ calcd for $C_{14}H_{24}NaO_3$ 263.1618; found, 263.1615; R_f = 0.3 (10% EtOAc in 40-60 °C petroleum ether).

3-Hydroxy-2-methylenedodec-11-enoic acid (183)
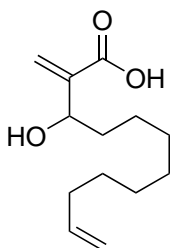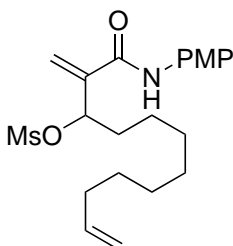
Methyl 3-hydroxy-2-methylenedodec-11-enoate (**179**) (120 mg, 0.50 mmol) was dissolved in THF (2.5 mL). LiOH $\cdot$ H_2O (100 mg, 2.50 mmol) in H_2O (2.5 mL) was added and the solution stirred for 18 h. The layers were allowed to separate and the aqueous layer acidified to pH 1 with 2N HCl, and extracted with EtOAc (3 x 10 mL). The combined organics were dried ($MgSO_4$), filtered and the solvent removed to give the *title compound* as a clear oil, which was used without further purification (110 mg, 97%). ^{1}H-NMR (CDCl$_3$, 400 MHz, δ): 6.39 (s, 1H, -CC*H*H), 5.92 (s, 1H, -CC*H*H), 5.81 (ddt, J = 17.0 Hz, 10.2 Hz, 6.7 Hz, 1H, -C*H*CH$_2$), 4.91 (dq, J = 17.1 Hz, 1.8 Hz, 1H, -CHC*H*H), 4.85 (dq, J = 10.2 Hz, 1.0 Hz, 1H, -CHC*H*H), 4.43 (dd, J = 7.4, 5.6 Hz, 1H, -C*H*OH), 2.03 (q, J = 6.5 Hz, 2H, -C*H*$_2$CHCH$_2$), 1.73-1.59 (m, 2H, -C*H*$_2$CHOH-), 1.48-1.24 (m, 10H, 5 x -C*H*$_2$); ^{13}C-NMR (CDCl$_3$, 100 MHz, δ): 171.2 (C=O), 141.8 (C), 139.2 (CH), 127.5 (CH_2), 114.2 (CH_2), 71.5 (CH), 36.2 (CH_2), 33.8 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.1 (CH_2), 28.9 (CH_2), 25.8 (CH_2); IR (cm^{-1}): 3550 (-OH), 2925 (-OOH), 2854 (-CH_2), 1693 ($-CO_2H$), 1627 (-C=C); MS-ESI: 249 [M + Na]$^+$; HRMS ES$^+$: [M + Na]$^+$ calcd for $C_{13}H_{22}NaO_3$ 249.1461; found, 249.1459.

## 3-Hydroxy-N-(4-methoxyphenyl)-2-methylenedodec-11-enamide (181)
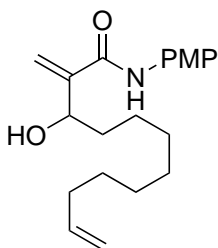
3-Hydroxy-2-methylenedodec-11-enoic acid (**183**) (110 mg, 0.49 mmol) and *p*-anisidine (60 mg, 0.49 mmol) were dissolved in CH_2Cl_2 (3 mL) and cooled to 0 °C. DCC (100 mg, 0.49 mmol) in CH_2Cl_2 (10 mL) was added slowly and the solution was allowed to warm to room temperature over 18 h. The resulting suspension was filtered through Celite, washed with a small amount of CH_2Cl_2 and the solvent removed. Column chromatography (30% EtOAc in 40-60 °C petroleum ether) yielded the *title compound* as a white solid (64 mg, 40%). ^{1}H-NMR (CDCl$_3$, 400 MHz, δ): 8.49 (br s, 1H, -CON*H*-), 7.42-7.40 (m, 2H, -Ar*H*), 6.82-6.79 (m, 2H, -Ar*H*), 5.93 (s, 1H, -CCH*H*), 5.72 (ddt, *J* = 16.9 Hz, 10.3 Hz, 6.7 Hz, 1H, -C*H*CH$_2$), 5.45 (s, 1H, -CC*H*H), 4.91 (dq, *J* = 17.1 Hz, 1.7 Hz, 1H, -CHC*H*H), 4.85 (dq, *J* = 10.2 Hz, 1.2 Hz, 1H, -CHC*H*H), 4.38 (q, *J* = 6.3 Hz, 1H, -C*H*OH), 3.73 (s, 3H, -ArOC*H*$_3$), 2.70 (d, *J* = 5.2 Hz, 1H, -O*H*), 1.96 (q, *J* = 7.7 Hz, 2H, -C*H*$_2$CHCH$_2$), 1.74-1.58 (m, 2H, -C*H*$_2$CHOH-), 1.41-1.16 (m, 10H, 5 x -C*H*$_2$); ^{13}C-NMR (CDCl$_3$, 100 MHz, δ): 164.9 (C=O), 156.8 (C), 145.5 (C), 139.2 (CH), 130.1 (C), 121.9 (CH), 121.5 (CH$_2$), 114.2 (CH), 74.3 (CH), 55.5 (CH$_3$), 35.7 (CH$_2$), 33.8 (CH$_2$), 29.4 (CH$_2$), 29.3 (CH$_2$), 29.0 (CH$_2$), 28.9 (CH$_2$), 25.8 (CH$_2$); IR (cm^{-1}): ; MS-ESI: 332 [M + H]$^+$, 354 [M + Na]$^+$; HRMS ES$^+$: [M + H]$^+$ calcd for $C_{20}H_{30}NO_3$ 332.2220; found, 332.221; R$_f$ = 0.3 (30% EtOAc in 40-60 °C petroleum ether).

2-((4-Methoxyphenyl)carbamoyl)dodeca-1,11-dien-3-yl methanesulfonate (182)

3-Hydroxy-N-(4-methoxyphenyl)-2-methylenedodec-11-enamide (**181**) (400 mg, 1.21 mmol) was dissolved in CH_2Cl_2 (12 mL) and cooled to 0 °C. Et$_3$N (310 μL, 2.42 mmol) was added followed by MsCl (200 μL, 2.42 mmol) dropwise. After 2 h the reaction was quenched with H_2O (10 mL) and warmed to room temperature. The organics were separated and dried (MgSO$_4$), filtered and the solvent removed under reduced pressure. Column chromatography

(30% EtOAc in 40-60 °C petroleum ether) yields the *title compound* as an oil (291 mg, 61%). ^{1}H-NMR (CDCl$_3$, 400 MHz, δ): 7.78 (br s, 1H, -CON*H*-), 7.39-7.36 (m, 2H, -Ar*H*), 6.80-6.78 (m, 2H, -Ar*H*), 5.87 (s, 1H, -CC*H*H), 5.77-5.67 (m, 2H, 1 x -C*H*CH$_2$ 1 x -CC*H*H), 5.35 (t, *J* = 6.6 Hz, 1H, -C*H*OSOOCH$_3$), 4.91 (dq, *J* = 17.1, 1.7 Hz, 1H, -CHC*H*$_2$), 4.85 (m, 1H, -CHC*H*$_2$), 3.71 (s, 3H, -ArOC*H*$_3$), 2.94 (s, 3H, -OSOOC*H*$_3$), 1.95 (q, *J* = 7.4 Hz, 2H, -C*H*$_2$CHCH$_2$), 1.83 (q, *J* = 7.1 Hz, 2H, -C*H*$_2$CHOH-), 1.42-1.17 (m, 10H, 5 x -C*H*$_2$); ^{13}C-NMR (CDCl$_3$, 100 MHz, δ): 164.5 (C=O), 156.8 (C), 143.9 (C), 139.1 (CH), 130.5 (C), 122.0 (2 x CH), 121.0 (CH), 114.2 (2 x CH), 114.2 (CH$_2$), 81.3 (CH), 55.5 (CH$_3$), 38.6 (CH$_3$), 35.1 (CH$_2$), 33.7 (CH$_2$), 29.2 (CH$_2$), 29.02 (CH$_2$), 28.98 (CH$_2$), 28.8 (CH$_2$), 25.4 (CH$_2$); R$_f$ = 0.3 (30% EtOAc in 40-60 °C petroleum ether).
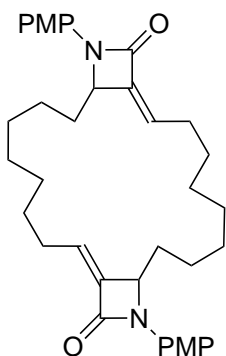
1-(4-Methoxyphenyl)-3-methylene-4-(non-8-en-1-yl)azetidin-2-one (176)
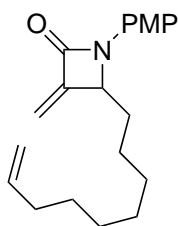
2-((4-Methoxyphenyl)carbamoyl)dodeca-1,11-dien-3-yl methanesulfonate (**182**) (291 mg, 0.74 mmol) was dissolved in THF (10 mL) and cooled to -15 °C. KO^{t}Bu (90 mg, 0.81 mmol) was added in one portion and stirred for 2 h at -15 °C. The reaction was quenched with sat. NH$_4$Cl (10 mL) the organics separated, dried (MgSO$_4$), filtered and the solvent removed under reduced pressure. The crude product was purified via column chromatography (10% EtOAc in 40-60 °C petroleum ether) to give the *title compound* (154 mg, 67%). ^{1}H-NMR (CDCl$_3$, 400 MHz, δ): 7.37-7.35 (m, 2H, Ar*H*), 6.90-6.89 (m, 2H, Ar*H*), 5.84-5.74 (m, 2 x 1H, -CC*H*H; -C*H*CH$_2$), 5.25 (t, *J* = 1.2 Hz, 1H, -CC*H*H), 4.98 (dq, *J* = 17.1 Hz, 1.7 Hz, 1H, -CHC*H*$_2$), 4.92 (dq, *J* = 10.1, 1.1 Hz, 1H, -CHC*H*H), 4.54-4.51 (m, 1H, -C*H*CNAr), 3.80 (s, 3H, -ArOC*H*$_3$), 2.06-1.95 (m, 2H, 1H -C*H*$_2$CHCH$_2$; -C*H*HCHCNAr), 1.84-1.73 (m, 1H, -C*H*HCHCNAr), 1.45-1.23 (m, 10H, 5 x -C*H*$_2$); ^{13}C-NMR (CDCl$_3$, 75 MHz, δ): 160.1 (C=O), 156.2 (C), 148.5 (C), 139.1 (CH), 131.1 (C), 118.4 (CH), 114.5 (CH), 114.2 (CH$_2$), 109.4 (CH$_2$), 60.5 (CH), 55.5 (CH$_3$), 33.7 (CH$_2$), 30.7 (CH$_2$), 29.5 (CH$_2$), 29.2 (CH$_2$), 28.9 (CH$_2$), 28.8 (CH$_2$), 24.3 (CH$_2$); IR (cm^{-1}): 2927; 2855 (-CH$_2$), 1736 (-CONR$_2$), 1509 (-C=C), 1244

(-CO-CH$_3$), 827 (para disub -ArH); MS-ESI: 336 [M + Na]$^+$; HRMS ES$^+$: [M + Na]$^+$ calcd for C$_{20}$H$_{27}$NNaO$_2$, 336.1934; found, 336.1940; R$_f$ = 0.3 (10% EtOAc in 40-60 °C petroleum ether).

(1Z,13Z)-11,23-Bis(4-methoxyphenyl)-11,23-diazatricyclo[20.2.0.0^{10,13}]tetracosa-1,13-diene-12,24-dione (90)

1-(4-Methoxyphenyl)-3-methylene-4-(non-8-en-1-yl)azetidin-2-one (**176**) (50 mg, 0.16 mmol) was dissolved in CH$_2$Cl$_2$ (80 mL). Grubbs 2nd generation catalyst (13 mg, 0.016 mmol) was added in one portion and the solution heated at reflux for 4 h. The solution was allowed to cool and the solvent removed under reduced pressure. Column chromatography (20% EtOAc in 40-60 °C petroleum ether) yielded the *title compound*, the 20-membered dimer (17 mg, 37%). ^{1}H-NMR (CDCl$_3$, 400 MHz, δ): 7.30-7.23 (m, 4H, -ArH), 6.84-6.78 (m, 4H, -ArH), 5.70-5.57 (m, 2H, -CC*H*CH$_2$-), 4.41-4.31 (m, 2H, -C*H*CNAr), 3.72 (s, 6H, -ArOC*H*$_3$), 2.81-2.68 (m, 2H, -CCHC*H*H), 2.38-2.24 (m, 2H, -CCHC*H*H), 1.98-1.82 (m, 2H -NArCHC*H*H-), 1.82-1.78 (m, 2H -NArCHC*H*H-), 1.54-1.06 (m, 20H, 10 x -C*H*$_2$); ^{13}C-NMR (CDCl$_3$, 100 MHz, δ): 160.8 (C=O), 155.9 (C), 139.8 (C), 131.5 (C) 132.4 (CH), 118.0 (CH), 114.5 (CH), 59.3 (CH), 55.5 (CH$_3$), 30.6 (CH$_2$), 30.4 (CH$_2$), 29.4 (CH$_2$), 29.2 (CH$_2$), 28.9 (CH$_2$), 28.1 (CH$_2$), 27.6 (CH$_2$), 23.6 (CH$_2$), 23.2 (CH$_2$); MS-ESI: 593 [M + Na]$^+$; HRMS ES$^+$: [M + Na]$^+$ calcd for C$_{36}$H$_{46}$N$_2$NaO$_4$, 593.3350; found, 593.3352; R$_f$ = 0.3 (20% EtOAc in 40-60 °C petroleum ether).

3,20-Dihydro-N^1,N^{22}-bis(4-methoxyphenyl)-2,21-dimethylenedocos-11-enediamide (184)
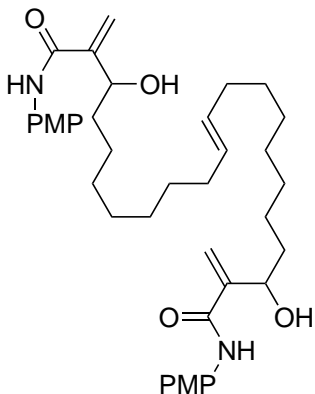
3-Hydroxy-N-(4-methoxyphenyl)-2-methylenedodec-11-enamide (**181**) (20 mg, 60.4 µmol) was dissolved in CH$_2$Cl$_2$ (30 mL). Grubbs 2nd generation catalyst (5 mg, 6.04 µmol) was added in one portion and the solution heated at reflux for 4 h. The solution was allowed to cool and the solvent removed under reduced pressure. Column chromatography (30-100% EtOAc in 40-60 °C petroleum ether) yielded the *title compound* (<1 mg). ^{1}H-NMR (CDCl$_3$, 400 MHz, δ): 8.73 (br s, 2H, -CON*H*-), 7.49-7.46 (m, 4H, -Ar*H*), 6.88-6.85 (m, 4H, -Ar*H*), 5.99 (s, 2H, -CC*H*H), 5.50 (s, 2H, -CC*HH*), 5.35 (t, *J* = 5.4 Hz, 2H, -CHC*H*-), 4.43 (q, *J* = 6.8 Hz, 2H, -C*H*OH), 3.79 (s, 6H, -ArOC*H*$_3$), 3.02 (br s, 2H, -O*H*), 2.02-1.92 (m, 4H, -C*H*$_2$CH=CH$_2$-), 1.79-1.54 (m, 4H, -C*H*$_2$CHOH-), 1.42-1.18 (m, 20H, 10 x -C*H*$_2$); IR (cm^{-1}): 3293 (-OH), 2925; 2853 (-CH$_2$), 1511 (-CONR$_2$), 1245 (-CO-CH$_3$), 828 (para disub -ArH) ; MS-ESI: 657 [M + Na]$^+$.
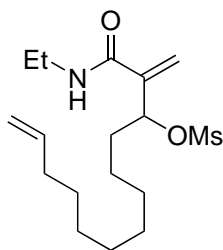
## 3-Hydroxy-N-ethyl-2-methylenetridec-12-enamide (70)
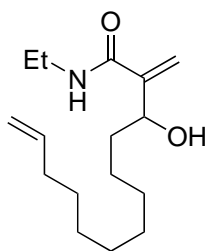
3-Hydroxy-2-methylenetridec-12-enoic acid (0.9 g, 3.54 mmol) and EtNH$_2$ (2M in THF, 1.7 mL, 3.54 mmol) were dissolved in EtOH (35 mL). NMM (0.8 mL, 7.44 mmol) followed by HOBt (72 mg, 0.53 mmol) and EDC·HCl (812 mg, 4.25 mmol). The reaction was allowed to warm to room temperature over 18 h. The solution was diluted with EtOAc (30 mL) and H$_2$O (20 mL) added. The layers were separated and the aqueous extracted with EtOAc (3 x 15 mL), the combined organics were dried (MgSO$_4$), filtered and the volatiles removed under reduced pressure. Column chromatography (30% EtOAc in 40-60 °C petroleum ether) yields the *title compound* as a white solid (901 mg, 95%). ^{1}H-NMR (CDCl$_3$, 300 MHz, δ): 8.54 (br s, 1H, -CON*H*-), 5.89-5.71 (m, 2H, -CC*H*H, -C*H*CH$_2$), 5.40 (s, 1H, -CC*H*H), 5.01-4.90 (m,

2H, -CHCH_2), 4.32 (t, J = 6.7 Hz, 1H, -CHOH), 3.39-3.30 (m, 2H, CH$_3$CH_2N-), 2.03 (q, J, J = 7.3 Hz, 2H, -CH_2CHCH$_2$), 1.73-1.54 (m, 2H, -CH_2CHOH-), 1.43-1.23 (m, 12H, 6 x -CH_2), 1.17 (t, J = 7.3 Hz, CH_3CH$_2$N-); ^{13}C-NMR (CDCl$_3$, 75 MHz, δ): 167.3 (C=O), 145.1 (C), 138.6 (CH), 118.8 (CH$_2$), 113.5 (CH$_2$), 73.4 (CH), 35.1 (CH$_2$), 33.6 (CH$_2$), 33.2 (CH$_2$), 28.9 (CH$_2$), 28.8 (CH$_2$), 28.5 (CH$_2$), 28.3 (CH$_2$), 25.3 (CH$_2$), 14.1 (CH$_3$); IR (cm^{-1}): 3283 (-OH), 2918; 2849 (-CH$_2$), 1612 (-CONR$_2$), 1457 (-C=C); ESI$^+$-MS: 306; mp: 50-53 °C; R_f = 0.3 (30% EtOAc in 40-60 °C petroleum ether).

2-(Ethyl)trideca-1,12-dien-3-yl methanesulfonate (71)

3-Hydroxy-N-ethyl-2-methylenetridec-12-enamide (901 mg, 3.37 mmol), was dissolved in CH_2Cl_2 (20 mL) and cooled to -78 °C. Et_3N (933 μL, 6.75 mmol) was added followed by MsCl (520 μL, 6.75 mmol) dropwise. The solution was allowed to warm to room temperature over 18 h, then quenched with H_2O (20 mL), the organics were separated, dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Column chromatography (40% EtOAc in 40-60 °C petroleum ether) yielded the *title compound* as a clear oil (797 mg, 68%). ^{1}H-NMR (CDCl$_3$, 300 MHz, δ): 6.09 (br s, 1H, N*H*), 5.84-5.69 (m, 2H, -C*H*CH$_2$, -CC*HH*), 5.63 (s, 1H, -CCH*H*), 5.34 (t, *J* = 6.6 Hz, -C*H*OMs), 5.00-4.85 (m, -CHC*H*$_2$), 3.36-3.27 (m, 2H, -CH$_3$C*H*$_2$-), 2.97 (s, 3H, -OSOOC*H*$_3$), 2.02-1.95 (m, 2H, CH$_2$CHC*H*$_2$-), 1.84-1.78 (m, 2H, -C*H*$_2$CHOH-), 1.41-1.20 (m, 12H, 6 x -C*H*$_2$), 1.14 (t, *J* = 7.4 Hz, C*H*$_3$CH$_2$N-); ^{13}C-NMR (CDCl$_3$, 75 MHz, δ): 165.6 (C=O), 142.9 (C), 138.5 (CH), 119.6 (CH$_2$), 113.5 (CH$_2$), 80.8 (CH), 37.8 (CH$_3$), 34.4 (CH$_2$), 34.0 (CH$_2$), 33.2 (CH$_2$), 28.7 (CH$_2$), 28.4 (CH$_2$), 28.2 (CH$_2$), 24.6 (CH$_2$), 14.1 (CH$_3$); MS-ESI: 368 [M + Na]$^+$; HRMS ES$^+$: [M + Na]$^+$ calcd for $C_{17}H_{31}NNaO_4S$, 368.1866; found, 368.1847; R_f = 0.3 (40% EtOAc in 40-60 °C petroleum ether).

4-(Dec-9-enyl)-1-(ethyl)-3-methyleneazetidin-2-one (66)
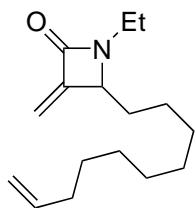
2-(Ethyl)trideca-1,12-dien-3-yl methanesulfonate (797 mg, 2.31 mmol) was dissolved in THF (10 mL) and cooled to 0 °C. KO^{t}Bu (205 mg, 2.54 mmol) was added in one portion. The reaction was allowed to warm to room temperature over 16 h, then quenched with sat. NH$_4$Cl (10 mL). The organics were separated, dried (MgSO$_4$), filtered and the volatiles removed under reduced pressure. Column chromatography (20% EtOAc in 40-60 °C petroleum ether) yielded the *title compound* as a clear oil (416 mg, 72%). ^{1}H-NMR (CDCl$_3$, 300 MHz, δ): 5.78 (ddt, *J* = 16.9 Hz, 10.2 Hz, 6.6 Hz, 1H, -C*H*CH$_2$), 5.57 (s, 1H, -CC*H*H), 5.01 (s, 1H, -CCH*H*), 5.00-4.87 (m, 2H -CHC*H*$_2$), 4.02 (t, *J* = 6.0 Hz 1H, -C*H*CN-), 3.56-3.43 (m, 1H, -NC*H*HCH$_3$), 3.20-3.08 (m, 1H, -NCH*H*CH$_3$), 2.01 (q, *J* = 6.9 Hz, 2H, CH$_2$CHC*H*$_2$-), 1.80-1.67 (m, 1H, -C*H*HCHCN-), 1.62-1.45 (m, 1H,-CH*H*CHCN-), 1.40-1.23 (m, 6H, 3 x CH$_2$), 1.16 (t, *J* = 7.2 Hz, 3H, -NCH$_2$C*H*$_3$); ^{13}C-NMR (CDCl$_3$, 75 MHz, δ): 162.1 (C=O), 149.2 (C), 138.5 (CH), 113.6 (CH$_2$), 107.1 (CH$_2$), 59.2 (CH), 34.6 (CH$_2$), 33.2 (CH$_2$), 31.3 (CH$_2$), 29.1 (CH$_2$), 28.8 (CH$_2$), 28.7 (CH$_2$), 28.4 (CH$_2$), 28.3 (CH$_2$), 24.6 (CH$_2$), 12.8 (CH$_3$); 2926; 2854 (-CH$_2$), 1747 (-CONR$_2$), 1393 (-C=C); MS-ESI: 272 [M + Na]$^+$; HRMS ES$^+$: [M + H]$^+$ calcd for C$_{16}$H$_{28}$NO, 250.2165; found, 250.2165; R$_f$ = 0.3 (20% EtOAc in 40-60 °C petroleum ether).

RCM of 4-(Dec-9-enyl)-1-(ethyl)-3-methyleneazetidin-2-one (66)

4-(Dec-9-enyl)-1-(ethyl)-3-methyleneazetidin-2-one (50 mg, 0.20 mmol) was dissolved in CH$_2$Cl$_2$ (100 mL). Grubbs 2nd generation catalyst (17 mg, 0.020 mmol) was added and the solution refluxed for 24 h. The solution was allowed to cool, then the solvent was removed under reduced pressure. Column chromatography (40-50% EtOAc in 40-60 °C petroleum ether) yielded the linear dimer (15 mg, 32%) and the 22-membered dimer which was further purified by semi-preparative HPLC (30% H$_2$O in MeCN) gave the pure dimer (1Z,14Z)-12,25-diethyl-12,25-diazatricyclo[22.2.0.0^{11,14}]hexacosa-1,14-diene-13,26-dione) (<1 mg, approx 2%).
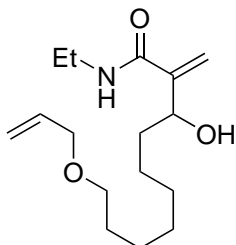
(1Z,14Z)-12,25-diethyl-12,25-diazatricyclo[22.2.0.0^{11,14}]hexacosa-1,14-diene-13,26-dione)
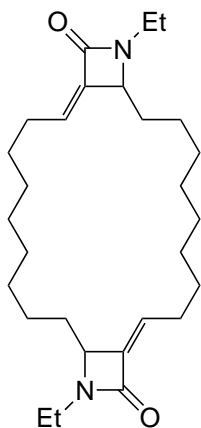
^{1}H-NMR (CDCl$_3$, 600 MHz, δ): 5.44 (td, J = 11.6, 4.4 Hz, 2H, -CC*H*CH$_2$-), 4.05-4.01 (m, 2H, -NC*H*CH$_2$(C)-), 3.53-3.46 (m, 2H, -NC*H*HCH$_3$), 3.13-3.05 (m, 2H, -NC*H*HCH$_3$), 2.91-2.80 (m, 4H, -CCHC*H*$_2$CH$_2$-), 2.17-2.12 (m, 4H, -CCHCH$_2$C*H*$_2$-), 1.69-1.20 (m, 24H, 12 x CH$_2$), 1.17 (t, J = 7.0 Hz, 3H, -NCH$_2$C*H*$_3$); ^{13}C-NMR (CDCl$_3$, 150 MHz, δ): 164.0 (C=O), 163.9 (C=O), 140.7 (C), 140.4 (C), 128.6 (CH), 128.4 (CH), 58.5 (CH), 58.4 (CH), 34.8 (CH$_2$), 30.8 (CH$_2$), 30.6 (CH$_2$), 30.1 (CH$_2$), 29.8 (CH$_2$), 29.7 (CH$_2$), 29.6 (CH$_2$), 29.4 (CH$_2$), 29.2 (CH$_2$), 29.0 (CH$_2$), 28.95 (CH$_2$), 28.88 (CH$_2$), 28.7 (CH$_2$), 28.1 (CH$_2$), 23.8 (CH$_2$), 23.4 (CH$_2$), 13.4 (CH$_3$), 13.3 (CH$_3$); IR (cm^{-1}): 2924; 2852 (-CH$_2$), 1736 (-CONR$_2$), 1392 (-C=C-); MS-ESI: 465 [M + Na]$^+$; HRMS ES$^+$: [M + Na]$^+$ calcd for C$_{28}$H$_{46}$N$_2$NaO$_2$, 465.3451; found, 465.3453.

## 4,4'-(octadec-9-ene-1,18-diyl)bis(1-ethyl-3-methyleneazetidin-2-one) (86)
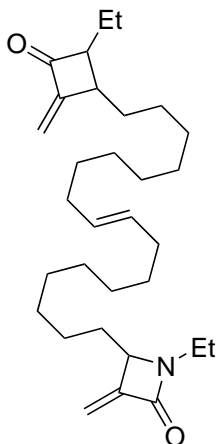
^{1}H-NMR (CDCl$_3$, 700 MHz, δ): 5.54 (s, 2H, -CC*H*H), 5.31 (t, *J* = 3.6 Hz, 2H, -C*H*C*H*-), 5.02 (s, 2H, -CCH*H*), 3.10 (t, *J* = 6.0 Hz, 2H, -NC*H*(C)-), 3.38-3.43 (m, 2H, -NC*H*HCH$_3$), 3.13-3.08 (m, 2H, -NCH*H*CH$_3$), 1.92-1.88 (m, 4H, -CHCHC*H*$_2$CH$_2$-), 1.72-1.65 (m, 4H, -CHC*H*$_2$CH$_2$-), 1.55-1.49 (m, 2H, -CHCH$_2$C*H*H-), 1.34-1.29 (m, 2H, -CHCH$_2$CH*H*-), 1.28-1.18 (m, 20H, 10 x C*H*$_2$), 1.13 (t, *J* = 7.5 Hz, 6H, -NCH$_2$C*H*$_3$); ^{13}C-NMR (CDCl$_3$, 175 MHz, δ): 162.1 (C=O), 148.8 (C), 129.3 (CH), 128.8 (CH), 106.7 (CH$_2$), 58.8 (CH), 34.2 (CH$_2$), 31.6 (CH$_2$), 30.9 (CH$_2$), 28.7 (CH$_2$), 28.6 (CH$_2$), 28.39 (CH$_2$), 28.36 (CH$_2$), 28.1 (CH$_2$), 24.2 (CH$_2$), 12.4 (CH$_3$); IR (cm^{-1}): 2924; 2853 (-CH$_2$), 1747 (-CONR$_2$), 1393 (-C=C-); MS-ESI: 493 [M + Na]$^+$; HRMS ES$^+$: [M + Na]$^+$ calcd for C$_{30}$H$_{50}$N$_2$NaO$_2$, 493.3764; found, 493.3771.

10-(Allyloxy)-3-hydroxy-N-ethyl-2-methylenedecanamide (108)

10-(Allyloxy)-3-hydroxy-2-methylenedecanoic acid (421 mg, 1.64 mmol) was dissolved in EtOH (16 mL). NMM (0.4 mL, 3.62 mmol), HOBt (88%, 40 mg, 0.25 mmol) and EtNH$_2$ (2 M in THF, 0.82 mL, 1.64 mmol) were added and the solution cooled to 5 °C. EDC·HCl (378 mg, 1.97 mmol) was added and the solution allowed to warm to room temperature over 16 h. The solution was diluted with EtOAc (20 mL) and H$_2$O (10 mL) added. The aqueous was extracted with EtOAc (3 x 20 mL), the combined organics were dried (MgSO$_4$), filtered and the solvent removed under reduced pressure. Column chromatography (45% EtOAc + 1% Et$_3$N in 40-60 °C petroleum ether) yielded the *title compound* (339 mg, 72%).

^{1}H-NMR (CDCl$_3$, 400 MHz, δ): 6.92 (s, 1H, N*H*), 5.91 (ddt, *J* = 17.2 Hz, 10.6 Hz, 5.6 Hz, 1H, -C*H*CH$_2$), 5.78 (s, 1H, -CC*H*H), 5.39 (s, 1H, -CCH*H*), 5.26 (dq, *J* = 17.2 Hz, 1.7 Hz, 1H, -CHC*H*H), 5.16 (dq, *J* = 10.4 Hz, 1.3 Hz, -CHCH*H*), 4.31 (t, *J* = 6.9 Hz, 1H, -C*H*OH), 3.95 (dt, *J* = 5.7 Hz, 1.3 Hz, 2H, -C*H*$_2$CHCH$_2$), 3.41 (t, *J* = 6.7 Hz,

2H, -OCH$_2$-), 3.37-3.29 (m, 2H, -NCH$_2$CH$_3$), 1.73-1.25 (m, 12H, 6 x CH$_2$), 1.17 (t,

J = 7.3, 3H, -NCH$_2$CH$_3$); ^{13}C-NMR (CDCl$_3$, 100 MHz, δ): 167.8 (C=O), 145.4 (C),

135.5 (CH), 119.8 (CH$_2$), 116.8 (CH$_2$), 73.9 (CH), 71.8 (CH$_2$), 70.4 (CH$_2$), 35.7 (CH$_2$),

34.2 (CH$_2$), 29.7 (CH$_2$), 29.4 (CH$_2$), 29.3 (CH$_2$), 26.1 (CH$_2$), 25.9 (CH$_2$), 14.7 (CH$_3$);

IR (cm^{-1}): 3321 (-OH), 2928; 2851 (-CH$_2$) 1619 (-CONR$_2$), 1537 (-C=C), 1245 (-CO-

CH$_3$); ESI$^+$-MS: 283 [M + H]$^+$, 306 [M + Na]$^+$; HRMS: ES$^+$ [M + Na]$^+$ calcd for

C$_{16}$H$_{29}$NNaO$_3$, 306.2040; found, 306.2042; mp: 55-58 °C; R$_f$ = 0.3 (45% EtOAc + 1%

Et$_3$N in 40-60 °C petroleum ether).

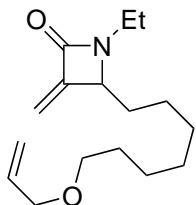## 2-(4-Ethylcarbamoyl)-10-(allyloxy)dec-1-en-3-yl methanesulfonate (109)
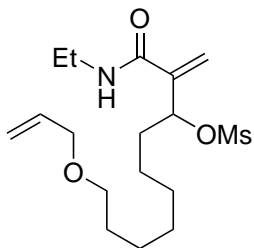
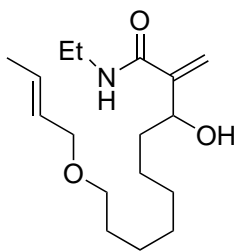10-(Allyloxy)-3-hydroxy-N-ethyl-2-methylenedecanamide

(**108**) (0.339, 2.00 mmol) was dissolved in CH$_2$Cl$_2$ (10 mL)

and cooled to -78 °C. Et$_3$N (0.3 mL, 2.40 mmol) was added

followed by MsCl (0.2 mL, 2.40 mmol) dropwise. The reaction

was stirred at -78 °C for 4 h. The reaction was quenched with

H$_2$O (5 mL). The organics were separated, dried, and the solvent

removed under reduced pressure. Column chromatography (50% EtOAc in 40-60 °C

petroleum ether) yielded the *title compound* as a clear oil (363 mg, 84%). ^{1}H-NMR

(CDCl$_3$, 400 MHz, δ): 6.02 (br s, 1H, N*H*), 5.91 (ddt, J = 17.2 Hz, 10.6 Hz, 5.6 Hz,

1H, -C*H*CH$_2$), 5.80 (s, 1H, -CC*H*H), 5.66 (s, 1H, -CCH*H*), 5.37 (t, J = 6.6 Hz, 1H,

-C*H*OH), 5.26 (dq, J = 17.3 Hz, 1.7 Hz, 1H, -CHC*H*H), 5.66 (dq, J = 10.4 Hz, 1.5 Hz,

-CHCH*H*), 3.95 (dt, J = 5.6 Hz, 1.4 Hz, 2H, -C*H*$_2$CH=CH$_2$), 3.41 (t, J = 6.6 Hz, 2H,

-OC*H*$_2$-), 3.38-3.32 (m, 2H, -NC*H*$_2$CH$_3$), 3.01 (s, 3H, -OSOOC*H*$_3$), 1.86 (q, J = 7.5

Hz, 2H, -C*H*$_2$CHOMs-), 1.60-1.53 (m, 2H, -OCH$_2$C*H*$_2$-), 1.48-1.29 (m, 8H, 4 x C*H*$_2$),

1.19 (t, J = 6.6 Hz, 3H, -NCH$_2$C*H*$_3$); ^{13}C-NMR (CDCl$_3$, 100 MHz, δ): 166.2 (C=O),

143.6 (C), 135.1 (CH), 120.2 (CH$_2$), 116.7 (CH$_2$), 81.4 (CH), 71.8 (CH$_2$), 70.4 (CH$_2$),

38.5 (CH$_3$), 35.0 (CH$_2$), 34.6 (CH$_2$), 29.7 (CH$_2$), 29.2 (CH$_2$), 29.0 (CH$_2$), 26.1 (CH$_2$),

25.3 (CH$_2$), 14.7 (CH$_3$); IR (cm^{-1}): 3337 (-NH), 2933; 2858 (-CH$_2$), 1660 (-C=C), 1536

(-CONR$_2$), 1454 (-C=C), 1352 (-S=O), 1173 (-S=O); MS-ESI: 362 [M + H]$^+$, 384 [M

+ Na]$^+$; HRMS ES$^+$: calcd for $C_{17}H_{31}NNaO_5S$ 384.1815; found, 384.1805; $R_f = 0.3$ (50% EtOAc in 40-60 °C petroleum ether).

4-(7-(Allyloxy)heptyl)-1-ethyl-3-methyleneazetidin-2-one (102)

2-(4-Ethylcarbamoyl)-10-(allyloxy)dec-1-en-3-yl methanesulfonate (**130**) (**109**) (363 mg, 1.01 mmol) was dissolved in THF (10 mL) and cooled to -15 °C. KO^{t}Bu (123 mg, 1.12 mmol) was added in one portion, and stirred for 3.5 h at -15 °C. The solution was quenched with NH_4Cl (10 mL). The organics were separated, dried and the volatiles removed under reduced pressure. Column chromatography (40% EtOAc in 40-60 °C petroleum ether) yielded the *title compound* as a clear oil (85 mg, 32%). ^{1}H-NMR (CDCl$_3$, 400 MHz, δ): 5.92 (ddt, J = 17.2 Hz, 10.8 Hz, 5.6 Hz, 1H, -C*H*CH$_2$), 5.61 (s, 1H, -CC*H*H), 5.27 (dd, J = 17.2 Hz, 1.7 Hz, 1H -CHC*H*H), 5.16 (d, J = 10.4 Hz, 1H, -CHC*H*H), 4.05 (t, J = 5.7 Hz 1H, -C*H*CNAr), 3.95 (dt, J = 5.5 Hz, 1.1 Hz, 2H, -C*H*$_2$CH=CH$_2$), 3.57-3.48 (m, 1H, -NC*H*HCH$_3$) 3.42 (t, J = 6.6 Hz, 2H, -OC*H*$_2$-), 3.22-3.13 (m, 1H, -NC*H*HCH$_3$), 1.82-1.71 (m, 1H, -CH*H*CHCN-), 1.64-1.51 (m, 3H, 1 x -OCH$_2$C*H*$_2$-, 1 x -C*H*HCHCN-), 1.45-1.26 (m, 8H, 4 x C*H*$_2$), 1.19 (t, J = 6.6 Hz, 3H, -NCH$_2$C*H*$_3$); ^{13}C-NMR (CDCl$_3$, 100 MHz, δ): 163.0 (C=O), 149.8 (C), 135.1 (CH), 116.7 (CH$_2$), 107.8 (CH$_2$), 71.8 (CH$_2$), 70.4 (CH$_2$), 59.8 (CH), 35.7 (CH$_2$), 31.9 (CH$_2$), 29.7 (CH$_2$), 29.6 (CH$_2$), 29.3 (CH$_2$), 26.1 (CH$_2$), 25.2 (CH$_2$), 13.4 (CH$_3$); IR (cm^{-1}): 2929; 2856 (-CH$_2$), 1746 (-CONR$_2$), 1457 (-C=C), 1222 (-CO-CH$_3$); MS-ESI: 288 [M + Na]$^+$; HRMS ES$^+$: [M + Na]$^+$ calcd for $C_{16}H_{27}NNaO_2$, 288.1934; found, 288.1938; $R_f = 0.3$ (40% EtOAc in 40-60 °C petroleum ether).

### 10-(But-2-en-1-yloxy)-N-ethyl-3-hydroxy-2-methylenedecanamide (118)

10-(Allyloxy)-3-hydroxy-2-methylenedecanoic acid (421 mg, 1.64 mmol) was dissolved in EtOH (16 mL). NMM (0.4 mL, 3.62 mmol), HOBt (88%, 40 mg, 0.25 mmol) and EtNH$_2$ (2 M in THF, 0.82 mL, 1.64 mmol) were added and the solution cooled to 5 °C. EDC·HCl (378 mg, 1.97 mmol) was added and the solution allowed to warm to room temperature over 16 h. The solution was diluted with EtOAc (20 mL) and H$_2$O (10 mL) added. The aqueous was extracted with EtOAc (3 x 20 mL), the combined organics were dried (MgSO$_4$), filtered and the solvent removed under reduced pressure. Column chromatography (45% EtOAc + 1% Et$_3$N in 40-60 °C petroleum ether) yielded the *title compound* (339 mg, 72%). ^{1}H-NMR (CDCl$_3$, 400 MHz, δ): 7.42 (t, J = 5.6 Hz, 1H, NH), 5.42 (s, 1H, -CCHH), 5.35-5.25 (m, 1H, -CH$_3$CHCH-), 5.23-5.12 (m, 1H, -CH$_3$CHCH-) 5.00 (s, 1H, -CCHH), 4.67 (d, J = 5.0 Hz, -OH), 3.97 (q, J = 6.0 Hz, 1H, -CHOH), 3.49 (d, J = 6.1 Hz, 2H, -OCH_2CH-), 3.00 (t, J = 6.6 Hz, 2H, -CH_2OCH_2-), 2.94-2.87 (m, 2H, -NCH_2CH$_3$), 1.32 (dd, J = 6.3, 1.1 Hz, 3H, CH_3CHCH-), 1.27-0.90 (m, 12H, 6 x -CH_2-) 0.77 (t, J = 7.2 Hz, -NCH$_2$CH_3); ^{13}C-NMR (CDCl$_3$, 100 MHz, δ): 167.5 (C=O), 145.7 (C), 128.3 (CH), 127.6 (CH), 118.9 (CH$_2$), 72.6 (CH), 71.0 (CH$_2$), 69.6 (CH$_2$), 35.6 (CH$_2$), 33.5 (CH$_2$), 29.5 (CH$_2$), 29.4 (CH$_2$), 29.1 (CH$_2$), 29.0 (CH$_2$), 25.8 (CH$_2$), 25.5 (CH$_2$), 20.4 (CH$_3$), 14.2 (CH$_3$); IR (cm^{-1}): ; MS-ESI: 320 [M + Na]$^+$; R$_f$ = 0.3 (45% EtOAc + 1% Et$_3$N in 40-60 °C petroleum ether).

10-(But-2-en-1-yloxy)-2-(ethylcarbamoyl)dec-1-en-3-yl methanesulfonate (119)
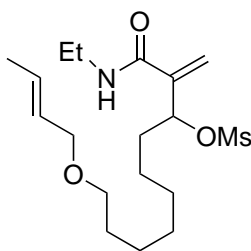
10-(But-2-en-1-yloxy)-N-ethyl-3-hydroxy-2-methylenedecanamide (**244**) (1.08 g, 3.64 mmol) was dissolved in CH$_2$Cl$_2$ (15 mL) and cooled to -78 °C. Et$_3$N (940 μL, 7.27 mmol) was added followed by MsCl (560 μL, 7.27 mmol) drop wise. The solution was allowed to warm to room temperature over 16 h. H$_2$O (10 mL) was added and the solution

separated, and the organics dried (MgSO$_4$), filtered and the volatiles removed under reduced pressure. The crude material was used directly in the next reaction. ^{1}H-NMR (CDCl$_3$, 400 MHz, δ): 6.11 (br s, 1H, N*H*), 5.81 (s, 1H, -CC*H*H), 5.75-5.67 (m, 1H, -CH$_3$C*H*CH-), 5.66 (s, 1H, -CC*H*H), 5.62-5.54 (m, 1H, -CH$_3$CHC*H*-), 5.38 (t, *J* = 6.5 Hz, 1H, -CH$_2$C*H*(C)O-), 3.88 (dt, *J* = 6.2, 1.9 Hz, 2H, -OC*H*$_2$CH-), 3.42-3.32 (m, 4H, -CH$_2$OC*H*$_2$-; -NC*H*$_2$CH$_3$), 3.01 (s, 3H, -SOOC*H*$_3$), 1.88-1.81 (m, 2H, -C*H*$_2$CHOSOOMe), 1.71 (dd, *J* = 6.3, 1.2 Hz, 3H, C*H*$_3$CHCH-), 1.59-1.51 (m, 2H, -CH$_2$OCH$_2$C*H*$_2$-), 1.45-1.28 (m, 8H, 4 x -C*H*$_2$-), 1.19 (t, *J* = 7.3 Hz, -NCH$_2$C*H*$_3$); ^{13}C-NMR (CDCl$_3$, 100 MHz, δ): 166.2 (C=O), 143.5 (C), 129.3 (CH), 127.8 (CH), 120.2 (CH$_2$), 81.4 (CH), 71.6 (CH$_2$), 70.2 (CH$_2$), 38.5 (CH$_3$), 35.0 (CH$_2$), 34.6 (CH$_2$), 29.7 (CH$_2$), 29.2 (CH$_2$), 29.0 (CH$_2$), 26.1 (CH$_2$), 25.2 (CH$_2$), 17.8 (CH$_3$), 14.7 (CH$_3$); MS-ESI: 398 [M + Na]$^+$; HRMS ES$^+$: [M + Na]$^+$ calcd for C$_{18}$H$_{33}$NNaO$_5$S 398.1972; found, 398.1968.

### 4-(7-(But-2-en-1-yloxy)heptyl)-1-ethyl-3-methyleneazetidin-2-one (114)
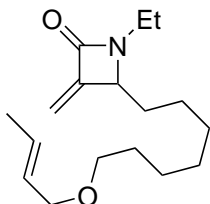
10-(But-2-en-1-yloxy)-2-(ethylcarbamoyl)dec-1-en-3-yl methane-sulfonate (**119**) (1.40 g, 3.73 mmol) was dissolved in THF (12 mL) and the solution cooled to -15 °C. KO^{t}Bu (460 mg, 4.11 mmol) was added in one portion and stirred at -15 °C for 2 h. The reaction was quenched with sat. NH$_4$Cl (10 mL), the organics were separated, dried (MgSO$_4$), filtered and the solvent removed under reduced pressure. Column chromatography (20% EtOAc in 40-60 °C petroleum ether) yielded the *title compound* as a clear oil ^{1}H-NMR (CDCl$_3$, 400 MHz, δ): 5.76-5.70 (m, 1H, -CH$_3$C*H*CH-), 5.60-5.55 (m, 2H, -CC*H*H; -CH$_3$CHC*H*-), 5.09 (s, 1H, -CC*H*H), 4.05 (t, *J* = 6.5 Hz, 1H, -C*H*(N)CH$_2$), 3.88 (d, *J* = 6.2 Hz, 2H, -OC*H*$_2$CH-), 3.17 (ddt, *J* = 14.3, 7.3, 7.3 Hz, 1H, -N*H*HCH$_3$), 3.39 (t, *J* = 6.6 Hz, 2H, -CH$_2$OC*H*$_2$-), 3.52 (ddt, *J* = 14.3, 7.1, 7.1 Hz, 1H, -NH*H*CH$_3$), 1.81-1.73 (m, 1H, -C*H*HCHN-), 1.71 (dd, *J* = 6.3, 0.8 Hz, 3H, C*H*$_3$CHCH-), 1.62-1.52 (m, 3H, -CH$_2$OCH$_2$C*H*$_2$-; -C*H*HCHN-), 1.45-1.28 (m, 8H, 4 x -C*H*$_2$-), 1.19 (t, *J* = 7.3 Hz, -NCH$_2$C*H*$_3$); ^{13}C-NMR (CDCl$_3$, 100 MHz, δ): 163.3

(C=O), 149.5 (C), 129.3 (CH), 127.7 (CH), 108.0 (CH_2), 71.6 (CH_2), 70.3 (CH_2), 59.8 (CH), 35.3 (CH_2), 34.8 (CH_2), 31.8 (CH_2), 29.7 (CH_2), 29.2 (CH_2), CH_2), 26.1 (CH_2), 25.7 (CH_2), 17.8 (CH_3), 13.4 (CH_3); MS-ESI: 302 $[M + Na]^+$; HRMS ES^+: $[M + Na]^+$ calcd for $C_{17}H_{29}NNaO_2$ 302.2091 ; found, 302.2088; R_f = 0.3 (20% EtOAc in 40-60 °C petroleum ether).

**RCM of 4-(7-(But-2-en-1-yloxy)heptyl)-1-ethyl-3-methyleneazetidin-2-one (114)**

4-(7-(But-2-en-1-yloxy)heptyl)-1-ethyl-3-methyleneazetidin-2-one (**114**) (20 mg, 0.07 mmol) was dissolved in CH_2Cl_2 (36 mL). Grubbs 2nd generation catalyst (6 mg, 0.007 mmol) was added and the solution refluxed for 24 h. The solution was allowed to cool and the solvent then removed under reduced pressure. Column chromatography (50% EtOAc in 40-60 °C petroleum ether) yields the monomeric product and dimeric products impure, which were further purified by preparative HPLC (30% H_2O in MeCN, flow rate 1 mL/min) to yield the monomeric product (4 mg, 24%) which was not stable in $CDCl_3$, and the dimer (5 mg, 29%).

(1Z,15Z)-13,27-diethyl-4,18-dioxa-13,27-diazatricyclo[24.2.0.0^{12,15}]octacosa-1,15-diene-14,28dione (120)
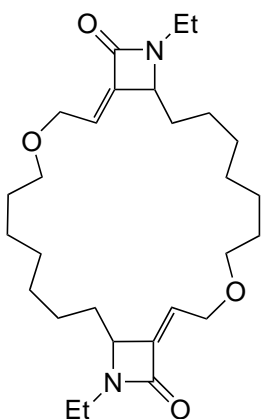

^{1}H-NMR ($CDCl_3$, 700 MHz, δ): 5.69 (t, *J* = 7.0 Hz, 2H, -CC*H*CH$_2$O-), 4.51 (dd, *J* = 12.2, 7,9 Hz, 2H, -CCHC*H*HO-), 4.46 (dd, *J* = 12.7, 7.5 Hz, 2H -CCHC*H*HO-), 4.35 (dd, *J* = 12.8, 6.1 Hz, 1H, -CCHC*H*HO-), 4.31 (dd, *J* = 12.9, 5.7 Hz, 1H, -CCHC*H*HO-), 4.03-4.00 (m, 2H, -NC*H*(C)C-), 3.52-3.46 (m, 6H, -NC*H*HCH$_3$; -OC*H$_2$*CH$_2$-), 3.19-3.13 (m, 2H, -NC*H*HCH$_3$), 1.81-1.25 (m, 20H, 10 x C*H$_2$*), 1.19 (t, *J* = 7.2 Hz, 6H, -NCH$_2$C*H$_3$*); ^{13}C-NMR ($CDCl_3$, 175 MHz, δ): 162.9 (C=O), 143.2 (C), 124.7 (CH), 124.6 (CH), 122.6 (C), 70.3 (CH_2), 70.2 (CH_2), 66.4 (CH_2), 58.6 (CH), 34.9 (CH_2), 31.72 (CH_2), 31.65 (CH_2), 29.9 (CH_2), 29.7 (CH_2), 29.2 (CH_2), 26.00 (CH_2), 25.97 (CH_2), 24.6 (CH_2), 24.5 (CH_2), 13.4

(CH$_3$); IR (cm^{-1}): 2922; 2851 (-CH$_2$), 1733 (-CONR$_2$), 1457 (-C=C); MS-ESI: 497 [M + Na]$^+$; HRMS ES$^+$: [M + Na]$^+$ calcd for C$_{28}$H$_{46}$N$_2$NaO$_2$, 497.3350; found, 497.3355.

3-Ethenyl-1,4-diphenyl-2-azetidinone (203)
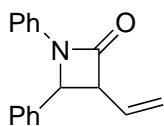
The imine of aniline (0.91 mL, 10.0 mmol) and benzylaldehyde (1.0 mL, 10.0 mmol) was preformed ($MgSO_4$ (0.63 g, 5.00 mmol) in CH_2Cl_2 (10 mL) overnight) was dissolved in CH_2Cl_2 (50 mL). Et_3N (1.37 mL, 10.0 mmol) was added and the imine solution heated to 55 °C at which point crotonyl chloride (0.95 mL, 10.0 mmol) was added dropwise over a period of 45 min. Once the addition was completed the mixture was heated for a further 2 h. The solution was allowed to cool and then washed with H_2O (2 x 50 mL). The CH_2Cl_2 layer was washed with brine (50 mL) dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Column chromatography (4%-6% EtOAc in 40-60 °C petroleum ether) yielded the *title compound* (1.15 g, 46%). Data is consistent with literature values.[105] ^{1}H-NMR (CDCl$_3$, 400 MHz, δ): 7.45-7.20 (m, 9H, 9 x Ar*H*), 7.10-7.00 (m, 1H, Ar*H*), 6.13-5.67 (m, 1H, C*H*), 5.45-5.29 (m, 2H, C*H*$_2$), 4.82-4.81 (m, 1H, C*H*), 3.78-3.71 (m, 1H, C*H*); ^{13}C-NMR (CDCl$_3$, 100 MHz, δ): 164.7 (C), 136.7 (C), 129.9 (CH), 128.6 (CH), 128.6 (CH), 128.0 (CH), 125.2 (CH), 123.4 (CH), 119.4 (CH$_2$), 116.4 (CH), 63.4 (CH), 60.6 (CH); IR (cm^{-1}) 2925 (-CH$_2$), 1751 (-CONR$_2$), 1377 (-C=C-); HRMS ES$^+$ calcd for C$_{17}$H$_{15}$NaNO, 272.1046 [M+Na]$^+$, found 272.1044; R$_f$ = 0.3 (5% EtOAc in 40-60 °C petroleum ether).

3-(2-Oxiranyl)-1,4-diphenyl-2-azetidinone (206)
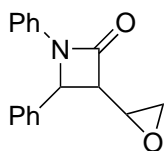
3-Ethenyl-1,4-diphenyl-2-azetidinone (200 mg, 0.80 mmol) was dissolved in CH_2Cl_2 (10 mL). m-CPBA (207 mg, 1.70 mmol) was added and the reaction stirred for 18 h. The reaction was diluted with CH_2Cl_2 (10 mL) then quenched with sat. K_2CO_3 (5 mL). The organics were separated, dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Column chromatography (5%-15% EtOAc in 40-60 °C petroleum ether) yielded the *title compound* as an inseparable mixture of diastereomers (0.17 g, 78%). Data is consistent with literature values.[105] ^{1}H-NMR (CDCl$_3$, 400 MHz, δ): 7.27-7.20 (m, ArH, 9H), 7.07-6.99 (m, ArH, 1H), 4.98 (d, *J* = 2.8 Hz, 0.4H), 4.86 (d, *J* = 2.6 Hz, 0.6H),

3.53 (t, J = 2.7 Hz, 0.4H), 3.44-3.39 (m, 0.6H), 3.39-3.36 (m, 0.4H), 3.22 (q, J = 2.4 Hz,

0.6H), 3.18 (q, J = 2.7 Hz, 0.4H), 2.96 (t, J = 4.2 Hz, 0.6H), 2.89 (t, J = 4.3 Hz, 0.4H),

2.72 (t, J = 2.5 Hz, 0.6H); IR (cm^{-1}) 1745 (-CONR$_2$), 1377 (-C-O), 1265 (-C=C); R$_f$ =

0.3 (10% EtOAc in 40-60 °C petroleum ether).

(S)-N-(2-Bromo-2-propenyl)-l-phenylethylamine (213)
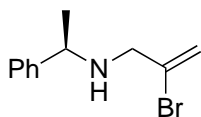
K$_2$CO$_3$ (5.89 g, 42.7 mmol) was made into a suspension with THF (100 mL) and (*S*)-phenylethylamine (10 mL, 77.2 mmol) added. 2,3 dibromopropene (5 mL, 51.4 mmol) was added and the reaction stirred for 18 h. Et$_2$O (200 mL) was added and the solution washed with 10% NaOH (200 mL), H$_2$O (200 mL) and brine (200 mL). The organics were separated, dried (MgSO$_4$), filtered and the solvent removed under reduced pressure. Column chromatography (8% EtOAc in 40-60 °C petroleum ether) yielded the *title compound* (10.5 g, 92%). Data is consistent with literature values.[109] ^{1}H-NMR (CDCl$_3$, 400 MHz, δ): 7.37-7.22 (m, 5H, 5 x ArH), 5.67 (s, 1H), 5.55 (s, 1H), 3.80 (q, J = 6.4 Hz, 1H), 3.36 (d, J = 15.0 Hz, 1H), 3.26 (d, J = 15.3 Hz, 1H), 1.72 (br s, NH), 1.36 (d, J = 7.13, 2H); ^{13}C-NMR (CDCl$_3$, 100 MHz, δ): 144.8 (C), 133.8 (C), 128.5 (CH), 127.1 (CH), 126.9 (CH), 117.8 (CH$_2$), 60.4 (CH$_2$), 55.6 (CH), 55.1 (CH$_2$), 24.3 (CH); R$_f$ = 0.3 (8% EtOAc in 40-60 °C petroleum ether).

(S)-N-(l-Phenylethyl)-2-methyleneaziridine (212)
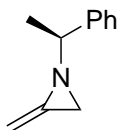
Fe(NO$_3$)$_3$ (cat.) was placed under an atmosphere of NH$_3$ until it had turned red in colour, NH$_3$ (50 mL) was then condensed to which was added fresh cut Na metal (0.48 g, 20.9 mmol). The solution was allowed to stir until a light grey. (S)-N-(2-bromo-2-propenyl)-l-phenylethylamine (2 g, 8.33 mmol) in Et$_2$O (2 mL) was added slowly and the reaction allowed to stir for 30 min. The reaction was diluted with Et$_2$O (20 mL) and quenched slowly with H$_2$O (20 mL). The ammonia was allowed to evaporate overnight. The mixture was washed with NaOH (100 mL, 10%), AcOH (100 mL, 0.1 M) and brine (100 mL). The organics were dried

($MgSO_4$), filtered and the solvent removed under reduced pressure. Bulb to bulb Kughr-Rhor distillation (65 °C, <0 mbar) yielded the *title compound* (0.9 g, 73%). Data was consistent with literature values.[109]

3-Methylene-1-((S)1-phenylethyl)-2-azetidinone (214)
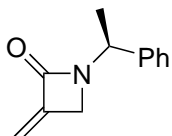
(S)-N-(2-Bromo-2-propenyl)-l-phenylethylamine (600 mg, 2.50) mmol), $Pd(PPh_3)_4$ (289 mg, 10 mol%) and nBu_3N (0.74 mL, 3.12 mmol) were dissolved in DMAc (10 mL). The mixture was placed under an atmosphere of CO (balloon), heated to 100 °C and stirred for 18 h. The solution was allowed to cool and diluted with Et_2O (20 mL). The organics were washed with H_2O (10 x 10 mL), dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Column chromatography (30% EtOAc in 40-60 °C petroleum ether) yielded the *title compound* (0.046 g, 10%). ^{1}H-NMR ($CDCl_3$, 400 MHz, δ): 7.41-7.29 (m, 5H, 5 x ArH), 5.73 (q, J = 1.4 Hz, 1H, CH), 5.16 (q, J = 1.5 Hz, 1H, CH), 5.07 (q, J = 7.1 Hz, 1H, CH), 3.74 (dt, J = 7.6, 1.4 Hz, 1H, CH), 3.55 (dt, J = 7.6, 1.4 Hz, 1H, CH), 1.66 (d, J = 7.1 Hz, 3H, CH_3); ^{13}C-NMR ($CDCl_3$, 100 MHz, δ): 163.0 (C), 144.5 (C), 140.3 (C), 128.8 (CH), 127.4 (CH), 126.7 (CH), 109.4 (CH_2), 51.6 (CH), 46.0 (CH_2), 18.6 (CH_3); Rf = 0.35 (30% EtOAc in 40-60 °C petroleum ether); HRMS ES$^+$ calcd for $C_{12}H_{13}NaNO$, 210.0889 [M+Na]$^+$, found 210.0888; R_f = 0.3 (30% EtOAc in 40-60 °C petroleum ether).

(S)-3-Methylene-1-(1-phenylethyl)azetidin-2-one (214)
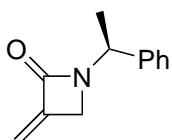
CO was bubbled through a solution of DMAC (5 mL) containing $Pd(PPh_3)_4$ (0.03 mmol, 10 mol%) and (S)-N-(l-Phenylethyl)-2-methyleneaziridine (50 mg, 0.314 mmol). The solution was heated to 100 °C and a CO atmosphere kept overnight via a balloon. The solution was allowed to cool diluted with Et_2O (10 mL) and filtered through Celite. The organics were washed with H_2O (10 x 10 mL) dried ($MgSO_4$), filtered and the solvent removed. Column chromatography (30% EtOAc in 40-60 °C petroleum ether) yielded

the *title compound* (0.001 g, 2%). Data is consistent with those reported above.

1-Iodo-9-decene (215)
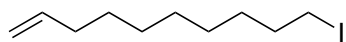
Dec-9en-ol (2.13 mL, 10.9 mmol) and Et_3N (2.30 mL, 16.4 mmol) were combined in CH_2Cl_2 (20 mL), TsCl (2.12 g, 10.9 mmol) was added in one portion and the reaction stirred for 18 h. The solution was diluted with H_2O (50 mL) and the aqueous layer extracted with $CHCl_3$ (3 x 20 mL). The combined organics were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Column chromatography (10% EtOAc in 40-60 °C petroleum ether) yielded dec-9-en-tosylate. Dec-9-en-tosylate (3.45 g, 10.9 mmol) was dissolved in acetone (100 mL) and NaI (16 g, 0.11 mol) was added in one portion. The mixture was stirred for 18 h. The solvent was removed under reduced pressure and EtOAc added to dissolve the solid. The organics were washed with H_2O (150 mL), saturated $Na_2S_2O_4$ (50 mL) and brine (50 mL). The organics were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The resulting oil was filtered through a pad of SiO_2 to give the *title compound* 2.6 g (89% over 2 steps). Data is consistent with literature values. [133] ^{1}H-NMR ($CDCl_3$, 400 MHz, δ): 5.81 (ddt, J = 17.1, 10.2, 6.6 Hz, 1H), 4.99 (ddt, J = 17.1, 1.8, 1.5 Hz, 1H), 4.93 (ddt, J = 10.2, 1.8, 0.9 Hz, 1H), 3.19 (t, J = 7.2 Hz, 2H), 2.03 (q, J = 7.2 Hz, 2H), 1.82 (quintet, J = 7.2 Hz, 2H), 1.29-1.38 (br m, 10H); ^{13}C-NMR ($CDCl_3$, 100 MHz, δ): 139.2 (CH), 114.2 (CH_2), 33.8 (CH_2), 33.6 (CH_2), 30.5 (CH_2), 29.3 (CH_2), 29.0 (CH_2), 28.9 (CH_2), 28.5 (CH_2), 7.3 (CH_2).

**10-1-[(1S)-1-Phenylethyl]-3-methylene-2-aziridinyl-1-decene (218)**
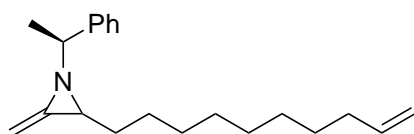
(S)-N-(l-Phenylethyl)-2-methyleneaziridine (200 mg, 1.26 mmol) was dissolved in THF (10 mL). TMEDA (220 μL, 1.51 mmol) was added and the solution cooled to -78 °C. sec-BuLi (1.4 M, 1.2 mL, 1.64 mmol) was added slowly and the solution kept at -78 °C for 5 h. 1-Iodo-9-decene

(300 mg, 1.13 mmol) in THF (2 mL) was added and the solution kept at -78 °C for 10 min before being allowed to warm to room temperature over 18 h. The solution was diluted with Et_2O (10 mL) and H_2O (10 mL) added slowly. The organics were separated and the aqueous extracted with Et_2O (2 x 10 mL). The combined organics were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The crude product, a 1:1 mixture of 1-iodo-9-decene and 1-[(1S)-1-Phenylethyl]-3-methylene-2-aziridinyl-1-decene as a 40:60 ratio of diastereomers, could not be purified by distillation or chromatography. ^{1}H-NMR (CDCl$_3$, 400 MHz, δ): 5.81 (ddt, J = 16.9, 10.0, 6.8 Hz, 1H, CH$_2$CH-), 4.99 (d, J = 17.1 Hz, 1H, CH$_2$C*H*H-), 4.92 (d, J = 10.2 Hz, 1H, CH$_2$C*H*H-), 4.82 (s, 0.3H, C*H*HC-), 4.69 (s, 0.3H, C*H*HC-), 4.50 (s, 0.2H, C*H*HC-), 4.23 (s, 0.2H, C*H*HC-), 2.08-1.96 (m, 1H, CH$_2$C*H*(N)C-), 1.60-1.02 (m, 20H, -C*H*$_2$- x 8; C*H*$_3$$^-$, CH$_3$C*H*$^-$); MS-ESI 298 [M + H]$^+$.

N-Ethylallenimine (219)
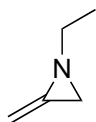
Fe(NO$_3$)$_3$ (cat.) was placed under an atmosphere of NH$_3$ until it had turned red in colour, NH$_3$ (100 mL) was then condensed to which was added fresh cut Na metal (2.24 g, 93.3 mmol) the solution was allowed to stir until a light grey. ethyll propene (8.00 g, 48.8 mmol) in Et$_2$O (10 mL) was added, the solution turned black and was stirred for 3 h. The solution was diluted with Et$_2$O (25 mL) and H$_2$O (25 mL) added slowly. The NH$_3$ was allowed to evaporate overnight. The solution was separated and the aqueous extracted with Et$_2$O (20 mL). The combined organics were dried (NaOH) and flash distilled at atmospheric pressure to leave a concentrated solution (460 mg, 58% N-Ethylallenimine, 12% alkyene and 30% Et$_2$O). Data was consistant with that reported.[108] ^{1}H-NMR (CDCl$_3$, 400 MHz, δ): 4.74 (s, 1H, C*H*HC-), 4.67 (s, 1H, C*H*HC-), 2.53 (q, *J* = 7.2 Hz, 2H, CH$_3$C*H*$_2$N-), 2.02 (s, 2H, CH$_2$N(C)-), 1.21 (t, *J* = 7.2 Hz, 3H, C*H*$_3$CH$_2$N-).

2-(Dec-9-en-1-yl)-1-ethyl-3-methyleneaziridine (225)
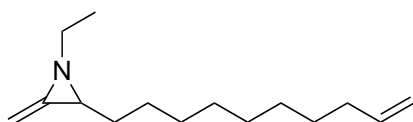
N-Ethylallenimine (230 mg, 2.77 mmol) and TMEDA (440 μL, 3.33 mmol) were dissolved in THF (10 mL) and cooled to -78 °C. sec-BuLi (1.4 M, 2.5 mL, 3.60 mmol) was added and the solution stirred at -78 °C for 5 h. 1-âIodo-9-decene (520 mg, 1.95 mmol) in THF (2 mL) was added and stirred at -78 °C for 10 min before being allowed to warm to room temperature overnight. The solution was diluted with Et$_2$O (10 mL) and H$_2$O (10 mL) added. The layers were separated and the aqueous extracted with Et$_2$O (3 x 10 mL). The combined organics were dried (MgSO$_4$), filtered and the solvent removed under reduced pressure. Analysis of the NMR indicated conversion of 73% to the *title compound* with 10% 1-iodo-9-âdecene remaining. Attempts to purify this by distillation were unsuccessful. ^{1}H-NMR (CDCl$_3$, 400 MHz, δ): 5.81 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H, CH$_2$C*H*CH$_2$-), 4.99 (dq, *J* = 17.1, 1.7 Hz, 1H, C*H*HCHCH$_2$-), 4.92 (dq, *J* = 10.2, 1.3 Hz, 1H, C*H*HCHCH$_2$-

), 4.67 (s, 1H, C*H*HC-), 4.62 (s, 1H, C*H*HC-), 2.66 (dq, J = 11.7, 7.2 Hz, CH$_2$C*H*HN-), 2.43 (dq, J = 11.7, 7.2 Hz, CH$_2$C*H*HN-), 2.03 (qt, J = 6.8, 1.3 Hz, 2H, -C*H*$_2$CH(C)N-), 1.83 (t, J = 6.0 Hz, 1H, -CH$_2$C*H*(C)N-), 1.62-1.26 (m, 14H, -C*H*$_2$ x 7), 1.20 (t, J = 7.2 Hz, 3H, C*H*$_3$CH$_2$N-); MS-ESI 222 [M + H]$^+$.

3-Methylhept-2-en-1-ol (231)
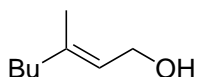
To CuI (0.5 g, 2.63 mmol) was added dry THF (7 mL) and cooled to -45 °C. n-BuLi (2.5 M in hexane, 2.1 mL, 5.26 mmol) was added slowly and the solution kept at -45 °C for 30 min. Ethyl butynoate (0.5 mL, 4.46 mmol) in THF (0.5 mL) was added slowly at -78 °C and the reaction stirred for 30 min. MeOH (0.5 mL) was added carefully followed by sat. NH$_4$Cl (2.5 mL) and the solution allowed to warm to room temperature. The organics were separated, dried (MgSO$_4$), filtered and the solvent removed under reduced pressure. Column chromatography (5% EtOAc in 40-60 °C petroleum ether) yields ethyl 3-methylhept-2-enoate (470 mg, 64%). Ethyl 3-methylhept-2-enoate (470 mg, 2.76 mmol) was dissolved in CH$_2$Cl$_2$ (10 mL) and cooled to -78 °C. DIBAL (1 M in hexane, 7.5 mL, 7.46 mmol) was added and the solution stirred at 0 °C for 1 h. It was then cooled to -78 °C and quenched carefully with 1 M HCl (5 mL). 1 M HCl and CH$_2$Cl$_2$ were added to dissolved the solid. The organic layer was separated, dried (MgSO$_4$), filtered, and the solvent removed under reduced pressure to yield the *title compound* without purification (352 mg, 99%). Data is consistent with literature values.[100] ^{1}H-NMR (CDCl$_3$, 400 MHz, δ): 5.66 (t, J = 1.2 Hz, 1H, -CC*H*-), 4.10 (d, J = 5.4, 2H, C*H*$_2$OH), 1.98 (t, J = 7.2, 2H, -C*H*$_2$CH$_2$CH$_2$CH$_3$), 1.63 (s, 3H, C=CC*H*$_3$), 1.39-1.27 (m, 4H, -C*H*$_2$-), 0.89 (t, J = 6.9, 3H, -CH$_2$C*H*$_3$).

## 1-(1-Butyl-1-methyl-2-propenylamino)-2,2,2-trichloro-1-ethanone (233)
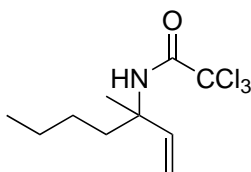
3-Methylhept-2-en-1-ol (**231**) (100 mg, 0.78 mmol) was dissolved in CH_2Cl_2 (5 mL) and cooled to 0 °C. DBU (30 μL, 0.20 mmol) was added followed by CCl_3CN (0.1 mL, 1.17 mmol) and the reaction stirred at room temperature for 2 h. The solution was then filtered through SiO_2, which was washed with Et_2O (25 mL), the combined organics were concentrated to an oil and used with purification. The crude product was dissolved in CH_2Cl_2 (5 mL) and $Pd[(Cl_2)(MeCN)_2]$ (27 mg, 0.078 mmol) added. The solution was stirred for 16 h at room temperature. The solution was then filtered through celite, which was washed with Et_2O (25 mL). The combined organics were concentrated under reduced pressure and the crude oil purified by column chromatography (2% EtOAc in hexane) to give the *title compound* (39 mg, 18%). ^{1}H-NMR ($CDCl_3$, 400 MHz, δ): 6.58 (s, 1H, -N*H*COCCl$_3$), 5.92 (dd, *J* = 17.5, 10.8 Hz, -C*H*CH$_2$), 5.19 (d, *J* = 9.0 Hz, 1H, -CHC*H*H), 5.15 (d, *J* = 15.7 Hz, 1H, -CHCH*H*), 1.81 (appr dt, *J* = 11.0, 8.2 Hz, 2H, -CH$_2$C*H$_2$*C-), 1.50 (s, 3H, C*H$_3$*), 1.38-1.21 (m, 4H, -C*H$_2$*- x 2), 0.91 (t, *J* = , 7.1 Hz, 3H, C*H$_3$*CH$_2$-); ^{13}C-NMR ($CDCl_3$, 100 MHz, δ): 160.1 (C=O), 141.4 (CH), 113.4 (CH$_2$), 93.3 (CCl$_3$), 58.7 (C), 38.7 (CH$_2$), 25.8 (CH$_2$), 23.8 (CH$_3$), 22.8 (CH$_2$), 14.0 (CH$_3$); IR (cm^{-1}): 3429,3358 (-NH), 2958, 2866 (-CH$_2$), 1717 (-COCCl$_3$), 1503 (-C=C); MS-ESI 272, 274 [M + H]$^+$ 294, 296 [M + Na]$^+$; HRMS ES$^+$ [M + Na]$^+$ calcd for $C_1OH_{16}Cl_3NaO$, 294.0190, 296.0160; found, 294.0188, 296.0160; R_f = 0.3 (2% EtOAc in hexane).

1-(2-Bromo-1-butyl-1-methyl-2-propenylamino)-2,2,2-trichloro-1-ethanone (234)
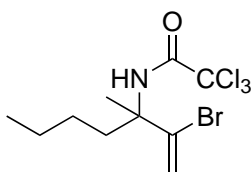
1-(1-Butyl-1-methyl-2-propenylamino)-2,2,2-trichloro-1-ethanone (**233**) (50 mg, 0.17 mmol) was dissolved in MeCN (1 mL) and cooled to 0 °C. PhSeBr (40 mg, 0.17 mmol) was added and the reaction stirred for 3 days. The solution was concentrated under reduced pressure then dissolved in CH_2Cl_2 (15 mL) and cooled to -78 °C. O$_3$ was bubbled through the solution until a fading

of the yellow colour was seen (3 h). The solution was purged with N_2 for 1 h and allowed to warm to room temperature. It was then was added dropwise to a refluxing toluene (40 mL) solution. The solution was then refluxed for 30 min. The solution was cooled to room temperature and the solvent removed under reduced pressure. Column chromatography (2% EtOAc in hexane) yielded the *title product* as a clear oil (13 mg, 20%). ^{1}H-NMR (CDCl$_3$, 400 MHz, δ): 6.62 (s, 1H, -N*H*-), 5.88 (d, J = 2.8 Hz, -C*H*H), 5.74 (d, J = 2.8 Hz, -CH*H*), 2.01-1.91 (m, 1H, -C*H*H-), 1.89-1.78 (m, 1H, -CH*H*-), 1.67 (s, 3H, CH$_3$), 1.43-1.22 (m, 4H, -CH$_2$- x 2), 0.94 (t, J = 7.3 Hz, 3H, C*H*$_3$CH$_2$-); ^{13}C-NMR (CDCl$_3$, 100 MHz, δ): 159.9 (C=O), 136.7 (C), 119.1 (CH$_2$), 91.5 (CCl$_3$), 62.0 (C), 38.2 (CH$_2$), 25.8 (CH$_2$), 22.7 (CH$_2$), 22.2 (CH$_3$), 14.0 (CH$_3$); IR (cm^{-1}): 3429,3358 (-NH), 2933, 2871 (-CH$_2$), 1665 (-COCCl$_3$), 1466 (-C=C); MS-ESI 371, 373 [M + Na]$^+$; R$_f$ = 0.3 (2% EtOAc in hexane).

2-Bromo-N-(4-methoxybenzyl)prop-2-en-1-amine (80)
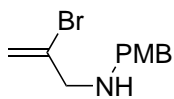
Paramethoxybenzylamine (5 mL, 19.4 mmol) was dissolved in THF and K$_2$CO$_3$ (2.7 g, 19.4 mmol) added. 2,3-dibromopropene (2.5 mL, 38.7 mmol) was added drop w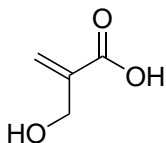ise and the solution stirred for 16 h. The mixture was diluted with Et$_2$O and the excess K$_2$CO$_3$ filtered off. The organics were washed with NaOH (10%, 2 x 20 mL), dried (MgSO$_4$), filtered and the volatiles removed. Column chromatography (20% EtOAc in 40-60 °C petroleum ether) yielded the *title product* as a clear oil (3.3 mg, 99%). Data is consistent with that reported.[134] ^{1}H-NMR (CDCl$_3$, 400 MHz, δ): 7.26-7.24 (m, 2H, ArH), 6.88-6.86 (m, 2H, ArH), 5.79 (d, J = 1.4 Hz, 1H, -C*H*H), 5.60 (d, J = 1.7 Hz, 1H, -CH*H*), 3.80 (s, 3H, -OC*H*$_3$), 3.67 (s, 2H, -C*H*$_2$), 3.45 (s, 2H, -C*H*$_2$) 1.70 (br s, 1H, N*H*); ^{13}C-NMR (CDCl$_3$, 100 MHz, δ): 158.8 (C), 133.6 (C), 131.8 (C), 129.5 (CH$_2$), 117.9 (CH$_2$), 113.8 (CH), 55.3 (CH$_3$); ESI$^+$-MS: 256 [M + H]$^+$; R$_f$ = 0.3 (20% EtOAc in 40-60 °C petroleum ether).

## 3-Methylene-1-(4-methoxybenzyl)-2-azetidinone (74)
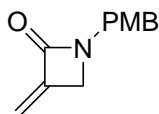
2-Bromo-N-(4-methoxybenzyl)prop-2-en-1-amine (**80** (500 mg, 1.95 mmol), $Pd(PPh_3)_4$ (226 mg, 10 mol%) and nBu_3N (0.58 mL, 2.44 mmol) were dissolved in DMAc (10 mL). The mixture was placed under an atmosphere of CO (balloon), heated to 100 °C and stirred for 18 h. The solution was allowed to cool and diluted with Et_2O (20 mL). The organics were washed with H_2O (10 x 10 mL), dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Column chromatography (30% EtOAc in 40-60 °C petroleum ether) yielded the *title compound* (0.118 g, 30%). ^{1}H-NMR ($CDCl_3$, 400 MHz, δ): 7.19-7.17 (m, 2H, ArH), 6.89-6.88 (m, 2H, ArH), 5.72 (s, 1H, -C*H*H), 5.14 (s, 1H, -CH*H*), 4.45 (s, 2H, -NC*H*$_2$, 3.80 (s, 3H, -OC*H*$_3$), 3.62 (s, 2H, -NC*H*$_2$Ar); ^{13}C-NMR ($CDCl_3$, 100 MHz, δ): 159.3 (C=O), 145.1 (C), 129.5 (CH), 114.2 (CH), 109.5 (CH_2), 55.3 (CH_3), 47.7 (CH_2), 45.5 (CH_2); IR (cm^{-1}): 2952, 2866 (-CH_2), 1736 (-$CONR_2$), 1512 (-C=C); MS-ESI 226 [M + Na]$^+$; HRMS ES$^+$ [M + Na]$^+$ calcd for $C_{12}H_{13}NNaO_2$, 226.0838; found, 226.0836; R_f = 0.3 (30% EtOAc in 40-60 °C petroleum ether).

## Methyl 2-(hydroxymethyl)acrylate (76)
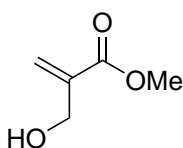
Paraformaldehyde (1.1 g, 37.1 mmol) was dissolved in methyl acrylate (5 mL, 55.6 mmol) and DABCO (410 mg, 3.71 mmol) added. The solution was stirred for 3 days. The solution was diluted with Et_2O, washed with H_2O. The aqueous was extracted with EtOAc (3 x 10 mL) and the combined organics dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Column chromatography (30% EtOAc in 40-60 °C petroleum ether) yielded the *title compound* as a clear oil (1.78 g, 41%). Data is consistent with that reported.[135] ^{1}H-NMR ($CDCl_3$, 400 MHz, δ): 6.26 (s, 1H, -C*H*H), 5.86 (s, 1H, -CH*H*), 4.33 (d, *J* = 5.64 Hz, 2H, -C*H*$_2$), 3.79 (s, 3H, -COOC*H*$_3$), 2.59 (br s, 1H, -O*H*); ^{13}C-NMR ($CDCl_3$, 100 MHz, δ): 166.8 (C=O), 139.3 (C), 125.8 (CH_2), 62.4 (CH_2), 51.9 (CH_3); ESI$^+$-MS: 139 [M + Na]$^+$; R_f = 0.3 (30% EtOAc in 40-60 °C petroleum ether).

2-(Hydroxymethyl)acrylic acid (77)

Methyl 2-(hydroxymethyl)acrylate (**76**) (1.78 mg, 15.3 mmol) was dissolved in THF (20 mL). LiOH·H_2O (3 g, 76.7 mmol) in H_2O (20 mL) was added and the solution stirred for 18 h. The solution was allowed to separate, and the aqueous acidified to pH 1 with 2 M HCl, then extracted with EtOAc (3 x 20 mL). The combined organics were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure to yield the *title compound* as a viscous oil (1.5 g, 99%). Data is consistent with that reported.[135] ^{1}H-NMR (CDCl$_3$, 400 MHz, δ): 6.42 (s, 1H, -C*H*H), 5.98 (s, 1H, -CH*H*), 4.37 (s, 2H, -C*H*$_2$); ^{13}C-NMR (CDCl$_3$, 100 MHz, δ): 171.0 (C=O), 138.6 (C), 128.4 (CH$_2$), 62.2 (CH$_2$); ESI$^+$-MS: 125 [M + Na]$^+$.

2-(Hydroxymethyl)-N-(4-methoxyphenyl)acrylamide (78)
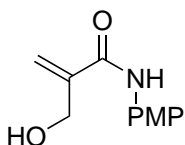
2-(Hydroxymethyl)acrylic acid (**77**) (1 g, 9.80 mmol) and *p*-anisidine (2 g, 9.80 mmol) were dissolved in CH$_2$Cl$_2$ (30 mL). The solution was cooled to −0 °C and DCC (1.2 g, 9.80 mmol) in CH$_2$Cl$_2$ (100 mL) was added slowly. After 2 h at −0 °C the suspension was filtered through Celite and washed with a small amount of CH$_2$Cl$_2$, the solvent removed under reduced pressure. Column chromatography (1:2 Et$_2$O:CH$_2$Cl$_2$) yielded the *title compound* as an off white solid (1.1 g, 50%). Data is consistent with that reported.[53] ^{1}H-NMR (CDCl$_3$, 400 MHz, δ): 8.62 (br s, 1H, N*H*), 7.48-7.45 (m, 2H, ArH), 6.87-6.85 (m, 2H, ArH), 6.08 (s, 1H, -C*H*H), 5.57 (s, 1H, -CH*H*), 4.42 (s, 2H, -CC*H*$_2$, 3.79 (s, 3H, -OC*H*$_3$); ^{13}C-NMR (CDCl$_3$, 100 MHz, δ): 165.1 (C=O), 156.6 (C), 142.1 (C), 130.8 (C), 123.1 (CH$_2$), 122.0 (CH), 114.2 (CH), 63.9 (CH$_2$), 55.5 (CH$_3$); ESI$^+$-MS: 230 [M + Na]$^+$; R$_f$ = 0.3 (1:2 Et$_2$O:CH$_2$Cl$_2$).
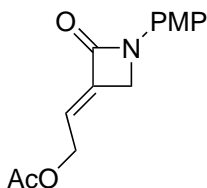
1-(4-Methoxyphenyl)-3-methyleneazetidin-2-one (73)
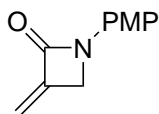
2-((4-Methoxyphenyl)carbamoyl)allyl methanesulfonate (**79**) (156 mg, 0.547 mmol) was dissolved in THF (10 mL). The solution was cooled to -15 °C and KOtBu (67 mg, 0.602 mmol) was added in one portion. After 4 h at -15 °C sat. NH$_4$Cl (10 mL) was added and the organics separated, dried (MgSO$_4$), filtered and the solvent removed under reduced pressure. Column chromatography (30% EtOAc in 40-60 °C petroleum ether) yielded the *title compound* as a white solid (46 mg, 45%). Data is consistent with that reported.[53] ^{1}H-NMR (CDCl$_3$, 400 MHz, δ): 7.33-7.30 (m, 2H, Ar*H*), 6.89-6.86 (m, 2H, Ar*H*), 5.80 (s, 1H, -C*H*H), 5.29 (s, 1H, -CH*H*), 4.06 (s, 2H, -NC*H$_2$*, 3.78 (s, 3H, -OC*H$_3$*); ^{13}C-NMR (CDCl$_3$, 100 MHz, δ): 159.7 (C=O), 156.2 (C), 143.6 (C), 132.0 (C), 117.5 (CH), 114.4 (CH), 110.5 (CH$_2$), 55.5 (CH$_3$), 47.8 (CH$_2$); ESI$^+$-MS: 190 [M + H]$^+$, 212 [M + Na]$^+$; R$_f$ = 0.3 (30% EtOAc in 40-60 °C petroleum ether).

1-(4-Methoxyphenyl)-3-methyleneazetidin-2-one (241)
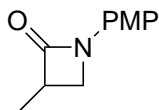
1-(4-Methoxyphenyl)-3-methyleneazetidin-2-one (**73**) (44 mg, 0.232 mmol) was dissolved in MeOH (2 mL). Pd/C (5 mg) was added and the atmosphere replaced with hydrogen via a balloon. The suspension was stirred vigorously for 24 h. The resulting suspension was filtered through Celite, which was washed with CH$_2$Cl$_2$. The volatiles were removed under reduced pressure, to yield the *title compound* as a clear oil (4 mg, 9%). ^{1}H-NMR (CDCl$_3$, 400 MHz, δ): 7.31-7.29 (m, 2H, Ar*H*), 6.88-6.86 (m, 2H, Ar*H*), 3.79 (s, 3H, -OC*H$_3$*), 3.75 (t, *J* = 5.5 Hz, 1H, -NC*H*H), 3.34 (ddq, *J* = 7.4, 2.5, 5.4 Hz, 1H, -C*H*CH$_3$), 3.22 (dd, *J* = 5.5, 2.6 Hz, 1H, -NC*H*H), 1.41 (d, *J* = 7.4 Hz, 3H, -CHC*H$_3$*); ^{13}C-NMR (CDCl$_3$, 100 MHz, δ): 168.4 (C=O), 156.0 (C=O), 132.3 (C), 117.5 (CH), 114.4 (CH), 55.5 (CH$_3$), 46.2 (CH$_2$), 43.6 (CH), 13.8 (CH$_3$); ESI$^+$-MS: 192 [M + H]$^+$, 214 [M + Na]$^+$; IR (cm^{-1}): 1730 (-COOMe), 1519 (-C=C), 825 (para disub -ArH).

2-(1-(4-Methoxyphenyl)-2-oxoazetidin-3-ylidene)ethyl acetate (242)

1-(4-Methoxyphenyl)-3-methyleneazetidin-2-one (**73**) (43 mg, 0.23 mmol) was dissolved in CH_2Cl_2 (1.1 mL). Allyl acetate (50 μL, 0.46 mmol) was added followed by Grubbs 2nd generation catalyst (4 mg, 0.005 mmol). The solution was refluxed for 2 h, at which time an additional 4 mg of Grubbs 2nd generation catalyst was added, and refluxed for 1 h. A final 4 mg of Grubbs 2nd generation catalyst was added and the solution refluxed for 1 h. The solution was allowed to cool and the solvent removed under reduced pressure. Column chromatography (30% EtOAc in 40-60 °C petroleum ether) yielded the starting material (27 mg, 63%), E isomer (4 mg, 7%) and the impure Z isomer (1 mg, 3%).

E isomer: ^{1}H-NMR (CDCl$_3$, 400 MHz, δ): 7.35-7.33 (m, 2H, ArH), 6.91-6.89 (m, 2H, ArH), 6.29 (tt, J = 5.4, 1.6 Hz, 1H, -CH=COCH$_2$-), 4.75 (d, J = 5.4 Hz, 2H, -C=CHCH_2-), 4.20 (s, 2H, -CCH_2NAr), 3.80 (s, 3H, -OCH_3), 2.13 (s, 3H, -OCOMe); ^{13}C-NMR (CDCl$_3$, 100 MHz, δ): 159.3 (C=O), 156.3 (C=O), 138.5 (C), 131.9 (C), 120.0 (CH), 117.7 (CH), 114.5 (CH), 61.2 (CH$_2$), 55.5 (CH$_3$), 47.3 (CH$_2$), 20.8 (CH$_3$); ESI$^+$-MS: 262 [M + H]$^+$, 284 [M + Na]$^+$; HRMS: ES$^+$ [M + Na]$^+$ calcd for C$_{14}$H$_{15}$NNaO$_4$, 284.0893; found, 284.0888; IR (cm^{-1}): 1733 (-CONR$_2$), 1719 (-COOMe), 1509 (-C=C), 1298 (-CO-CH$_3$), 829 (para disub -ArH); mp 115-117 °C (from CH_2Cl_2); R$_f$ = 0.2 (30% EtOAc in 40-60 °C petroleum ether).

3-Heptylidene-1-(4-methoyphenyl)azetidin-2-one
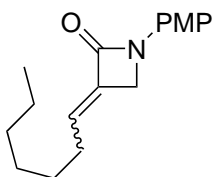
1-(4-Methoxyphenyl)-3-methyleneazetidin-2-one (**73**) (48 mg, 0.27 mmol) and 1-octene (83 μL, 0.53 mmol) were combined in CH_2Cl_2 (1 mL) and Grubbs 2nd generation catalyst (4 mg, 0.005 mmol) added. The solution was heated to reflux for 1 h, then cooled and the solvent removed under reduced pressure. Column chromatography (5% EtOAc in 40-60 °C petroleum ether) yielded the E isomer (43

mg, 62%) and the Z isomer (19 mg, 28%). E (trans): ^{1}H-NMR (CDCl$_3$, 400 MHz, δ): m, 2H, ArH), 6.89-6.86 (m, 2H, ArH), 6.26 (dt, J = 7.5, 1.3 Hz, 1H, -CH=COCH$_2$-), 4.07 (s, 2H, -CCH_2NAr), 3.78 (s, 3H, -OCH_3), 2.15 (q, J = 7.4 Hz, 2H, -C=CHCH_2-), 1.51-1.44 (m, 2H, -CHCH$_2$CH_2-), 1.37-1.24 (m, 6H, 3 x CH_2), 0.92-0.86 (m, 3H, -CH_3); ^{13}C-NMR (CDCl$_3$, 100 MHz, δ): 160.4 (C=O), 156.0 (C), 135.6 (C), 132.4 (C), 128.0 (CH), 117.4 (CH), 114.5 (CH), 55.5 (CH$_3$), 46.8 (CH$_2$), 29.2 (CH$_2$), 28.9 (CH$_2$), 28.5 (CH$_2$), 22.6 (CH$_2$), 14.1 (CH$_3$); IR (cm^{-1}): 2928; 2856 (-CH$_2$), 1734 (-CONR$_2$), 1509 (-C=C), 1241 (-CO-CH$_3$), 825 (para disub -ArH); ESI$^+$-MS: 274 [M + H]$^+$, 296 [M + Na]$^+$; HRMS: ES$^+$ [M + H]$^+$ calcd for C$_{17}$H$_{23}$NNaO$_2$, 296.1621; found, 296.1624; mp 44-46 °C (from CH$_2$Cl$_2$); R$_f$ = 0.3 (5% EtOAc in 40-60 °C petroleum ether).

Z (cis): ^{1}H-NMR (CDCl$_3$, 400 MHz, δ): m, 2H, ArH), 6.89-6.86 (m, 2H, ArH), 5.73 (t, J = 7.8, 1H, -CH=COCH$_2$-), 3.99 (s, 2H, -CCH_2NAr), 3.79 (s, 3H, -OCH3), 2.57 (q, J = 7.5 Hz, 2H, -C=CHCH_2-), 1.51-1.41 (m, 2H, -CHCH$_2$CH2-), 1.40-1.24 (m, 8H, 4 x CH_2), 0.93-0.85 (m, 3H, -CH_3); ^{13}C-NMR (CDCl$_3$, 100 MHz, δ): 160.6 (C=O), 156.0 (C), 134.5 (C), 132.6 (C), 132.0 (CH), 117.3 (CH), 114.6 (CH), 55.5 (CH$_3$), 47.0 (CH$_2$), 31.7 (CH$_2$), 29.4 (CH$_2$), 28.84 (CH$_2$), 28.81 (CH$_2$), 22.6 (CH$_2$), 14.1 (CH$_3$); IR (cm-1): 2925; 2855 (-CH$_2$), 1726 (-CONR$_2$), 1509 (-C=C), 1241 (-CO-CH$_3$), 826 (para disub -ArH); ESI$^+$-MS: 274 [M + H]$^+$, 296 [M + Na]$^+$; HRMS: ES$^+$ [M + H]$^+$ calcd for C$_{17}$H$_{23}$NNaO$_2$, 296.1621; found, 296.1622; mp 41-43 °C (from CHCl$_3$); R$_f$ = 0.2 (5% EtOAc in 40-60 °C petroleum ether).

**3-Heptylidene-1-(4-methoybenzyl)azetidin-2-one**
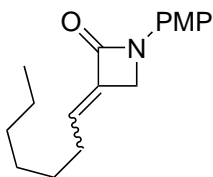
1-(4-Methoxybenzyl)-3-methyleneazetidin-2-one (**74**) (20 mg, 0.099 mmol) and 1-octene (30 μL, 0.20 mmol) were combined in CH$_2$Cl$_2$ (400 μL). Grubbs 2nd generation catalyst (2 mg, 0.002 mmol) was added and the solution reluxed for 1 h. The solution was allowed to cool and the solvent removed under reduced pressure.

Column chromatography (20% EtOAc in 40-60 °C petroleum ether) yielded the E isomer (15 mg, 54%) and the Z isomer (6 mg, 21%). E (trans) ^{1}H-NMR (CDCl$_3$, 400 MHz, δ): 7.13-7.08 (m, 2H, ArH), 6.83-6.78 (m, 2H, ArH), 6.06 (t, J = 7.4 Hz, 1H, -CH$_2$CHC-), 4.36 (s, 2H, ArCH_2N-), 3.73 (s, 3H, -OMe), 3.53 (s, 2H, CH_2(C)N-), 1.95 (q, J = 7.3 Hz, 2H, -CH$_2$CH_2CH-), 1.37-1.14 (m, 8H, -CH_2- x 4), 0.79 (t, J = 6.8 Hz, 3H, CH_3-); ^{13}C-NMR (CDCl$_3$, 100 MHz, δ): 163.9 (C=O), 159.2 (C), 137.0 (C), 129.5 (CH), 127.8 (C), 126.6 (CH), 114.2 (CH), 55.3 (CH$_3$), 46.6 (CH$_2$), 45.4 (CH$_2$), 31.6 (CH$_2$), 29.0 (CH$_2$), 28.8 (CH$_2$), 28.5 (CH$_2$), 22.6 (CH$_2$), 14.1 (CH$_3$); IR (cm-1): ;ESI^{+}-MS: 288 [M + H]$^{+}$, 326 [M + K]$^{+}$; HRMS: ES^{+} [M + Na]$^{+}$ calcd for C$_{18}$H$_{25}$NNaO$_2$, 310.1778; found, 310.1778; R$_f$ = 0.3 (20% EtOAc in 40-60 °C petroleum ether).

Z (cis) ^{1}H-NMR (CDCl$_3$, 400 MHz, δ): 7.23-7.08 (m, 2H, ArH), 6.82-6.78 (m, 2H, ArH), 5.47 (t, J = 7.8 Hz, 1H, -CH$_2$CHC-), 4.34 (s, 2H, ArCH_2N-), 3.73 (s, 3H, -OMe), 3.44 (s, 2H, CH_2(C)N-), 2.44 (q, J = 7.4 Hz, 2H, -CH$_2$CH_2CH-), 1.39-1.17 (m, 8H, -CH$_2$- x 4), 0.81 (t, J = 6.7 Hz, 3H, CH_3-); ^{13}C-NMR (CDCl$_3$, 150 MHz, δ): 164.3 (C=O), 159.1 (C), 136.0 (C), 130.4 (CH), 129.5 (CH), 127.9 (C), 114.1 (CH), 55.3 (CH$_3$), 46.9 (CH$_2$), 45.3 (CH$_2$), 31.6 (CH$_2$), 29.7 (CH$_2$), 29.3 (CH$_2$), 28.8 (CH$_2$), 28.7 (CH$_2$), 22.6 (CH$_2$), 14.1 (CH$_3$); IR (cm-1): ; ESI^{+}-MS: 310 [M + Na]$^{+}$; HRMS: ES^{+} [M + Na]$^{+}$ calcd for C$_{18}$H$_{25}$NNaO$_2$, 310.1778; found, 310.1774; R$_f$ = 0.2 (20% EtOAc in 40-60 °C petroleum ether).

## 2-(1-(4-Methoxyphenyl)-2-oxoazetidin-3-ylidine)ethyl acetate
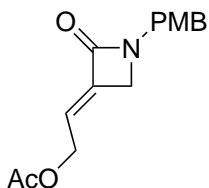
1-(4-Methoxybenzyl)-3-methyleneazetidin-2-one (**74**) (114 mg, 0.56 mmol) and allyl acetate (120 μL, 1.12 mmol) were dissolved in CH_2Cl_2 (2.3 mL). Grubbs 2nd generation catalyst (9 mg, 0.011 mmol) was added and the solution refluxed for 16 h. The solution was cooled and the solvent removed under reduced pressure. Column chromatography (20% then 50% EtOAc in 40-60 °C petroleum ether) yielded the E isomer exclusively (38 mg, 25%). ^{1}H-NMR (CDCl$_3$, 400 MHz, δ): 7.19-7.16 (m, 2H, ArH), 6.90-6.89 (m, 2H, ArH), 6.16 (tt, *J* = 5.3, 1.4 Hz, 1H, -CH$_2$C*H*C-), 4.63 (d, *J* = 5.4 Hz, 2H, -CHC*H*$_2$COAc), 4.44 (s, 2H, ArC*H*$_2$N-), 3.80 (s, 3H, -OMe), 3.71 (s, 2H, C*H*$_2$(C)N-), 2.04 (s, 3H, C*H*$_3$); ^{13}C-NMR (CDCl$_3$, 100 MHz, δ): 170.3 (C=O), 163.0 (C=O), 159.3 (C), 140.0 (C), 129.5 (CH), 127.3 (C), 118.9 (CH), 114.3 (CH), 61.1 (CH$_2$), 55.3 (CH$_3$), 47.0 (CH$_2$), 45.5 (CH$_2$), 20.8 (CH$_3$); IR (cm-1): 1736 (-CONR$_2$), 1610 (-C=O), 1221 (-C=C-); ESI$^+$-MS: 298 [M + Na]$^+$; HRMS: ES$^+$ [M + Na]$^+$ calcd for C$_{15}$H$_{17}$NNaO$_4$, 298.1050; found, 298.1045; R$_f$ = 0.1 (20% EtOAc in 40-60 °C petroleum ether).

3-(2-Hydroxyethylidene)-1-(4-methoybenzyl)azetidin-2-one
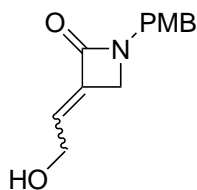
1-(4-Methoxybenzyl)-3-methyleneazetidin-2-one (**74**) (50 mg, 0.25 mmol) and allyl alcohol were dissolved in CH_2Cl_2 (1 mL). Grubbs 2nd generation catalyst (4 mg, 0.005 mmol) was added and the solution refluxed for 48 h. The solution was cooled and the solvent removed under reduced pressure. Column chromatography (50% EtOAc in 40-60 °C petroleum ether) yielded the *title compound* in a 1:1.2 E:Z ratio (<1 mg). ^{1}H-NMR (CDCl$_3$, 400 MHz, δ): 7.19-7.14 (m, 2H, ArH), 6.89-6.85 (m, 2h, ArH), 6.19 (tt, *J* = 4.6, 1.5 Hz, 0.9H, -CH$_2$C*H*C-), 5.88-5.87 (m, 1H, -CH$_2$C*H*C-), 4.42 (s, 2H, ArC*H*$_2$N-), 4.27 (d, *J* = 4.7 Hz, 1.8H, -CHC*H*$_2$COH), 4.15 (d, *J* = 3.8 Hz, 2H, -CHC*H*$_2$COH), 3.80 (s, 3H, -OMe), 3.75 (s, 2H, C*H*$_2$(C)N-); ^{13}C-NMR (CDCl$_3$, 100 MHz, δ): 164.0 (C=O), 159.2 (C), 137.3 (C), 131.0 (CH), 130.5 (CH), 129.5 (CH),

127.5 (C), 124.4 (CH), 114.2 (CH), 62.9 (CH_2), 60.6 (CH_2), 55.3 (CH_3), 47.6 (CH_2), 45.5 (CH_2); ESI^+-MS: 256 [M + Na]$^+$; R_f = 0.3 (50% EtOAc in 40-60 °C petroleum ether).

3-(2-Ethoxyethylidene)-1-(4-methoybenzyl)azetidin-2-one
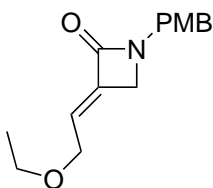
1-(4-Methoxybenzyl)-3-methyleneazetidin-2-one (**74**) (40 mg, 0.20 mmol) and allyl ethyl ether (44 μL, 0.39 mmol) were dissolved in CH_2Cl_2 (1 mL). Grubbs 2nd generation catalyst (3 mg, 0.004 mmol) was added and the solution refluxed for 16 h. The solvent was re-moved under reduced pressure. Column chromatography (20% + 1% Et_3N in 40-60 °C petroleum ether) yielded the *title compound* as the E isomer exclu-sively (6 mg, 12%). ^{1}H-NMR (CDCl$_3$, 400 MHz, δ): 7.19-7.17 (m, 2H, ArH), 6.89-6.87 (m, 2h, ArH), 6.17 (tt, *J* = 4.5, 1.4 Hz, 1H, -CH$_2$C*H*C-), 4.43 (s, 2H, ArC*H*$_2$N-), 4.06 (d, *J* = 4.7 Hz, 2H, -CHC*H*$_2$CO-), 3.80 (s, 3H, -OMe), 3.70 (s, 2H, C*H*$_2$(C)N-), 3.46 (q, *J* = 7.0 Hz, 2H, CH$_3$C*H*$_2$O-), 1.16 (t, *J* = 7.0 Hz, C*H*$_3$CH$_2$O-); ^{13}C-NMR (CDCl$_3$, 100 MHz, δ): 163.7 (C=O), 159.2 (C), 138.7 (C), 129.5 (CH), 127.7 (C), 121.2 (CH), 114.2 (CH), 67.9 (CH_2), 66.4 (CH_2), 55.3 (CH_3), 47.6 (CH_2), 45.5 (CH_2), 15.1 (CH_3); IR (cm^{-1}): 2928; 2851 (-CH_2), 1745 (-CONR$_2$), 1513 (-C=C), 1246 (-CO-CH$_3$); ESI^+-MS: 261 [M + H]$^+$, 284 [M + Na]$^+$; R_f = 0.3 (20% + 1% Et_3N in 40-60 °C petroleum ether).

Appendix I: NMR Spectra of Phyllostictine A

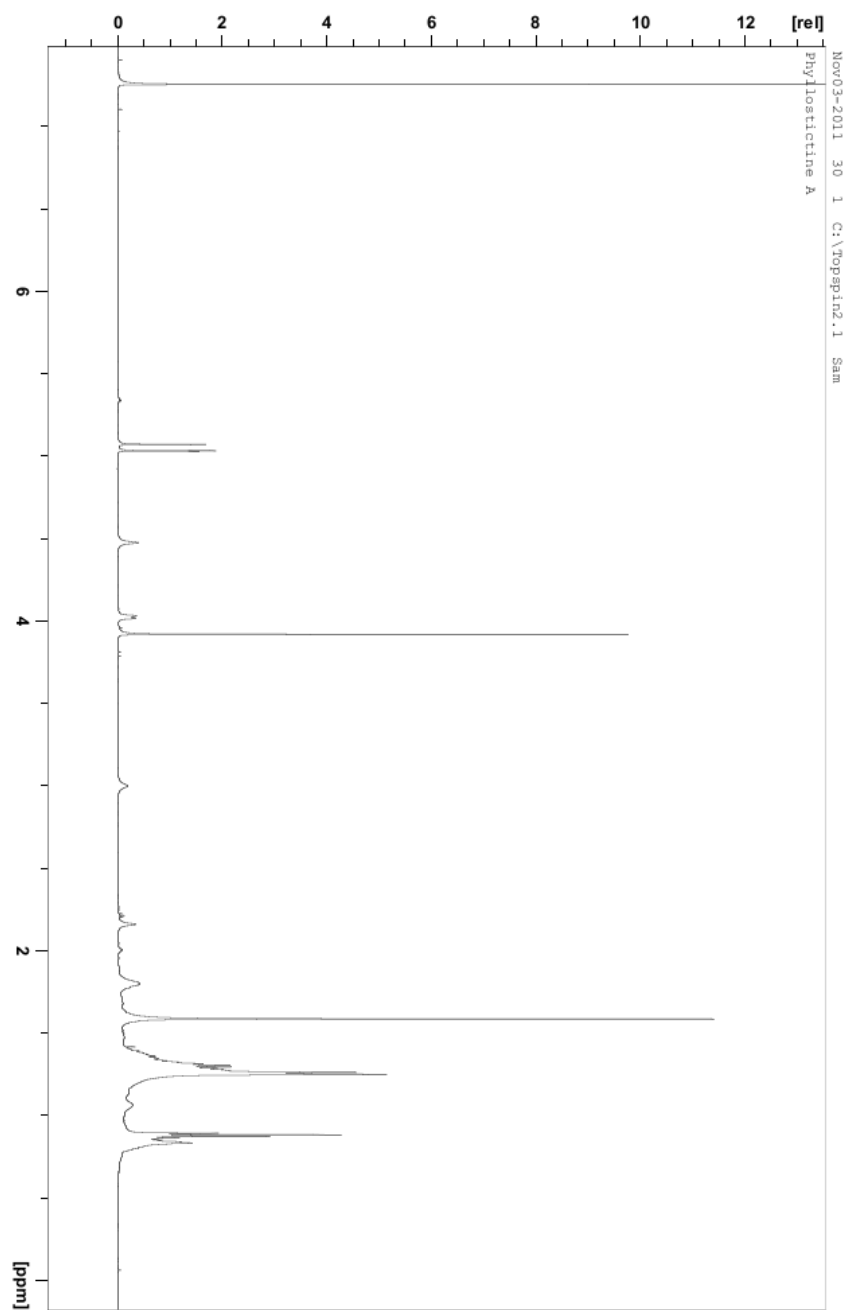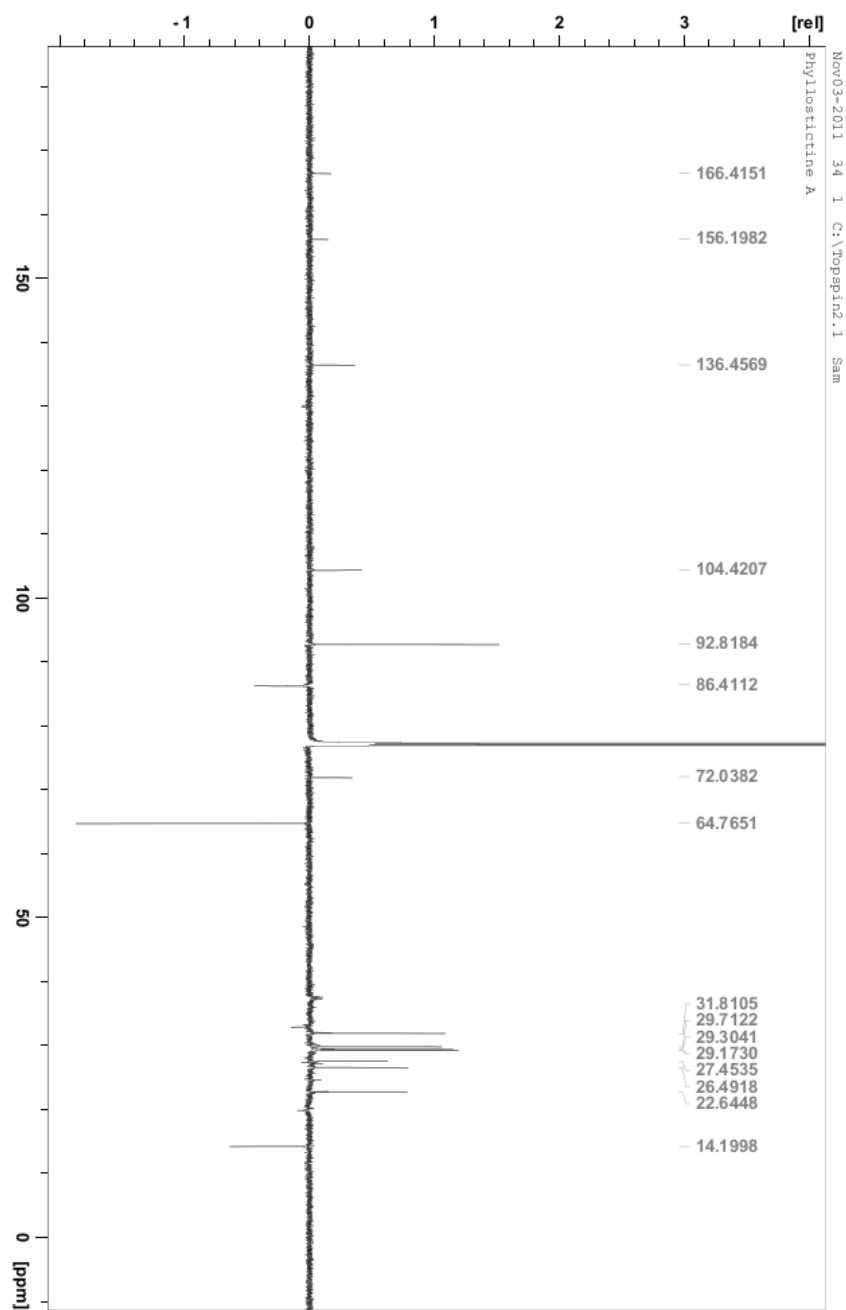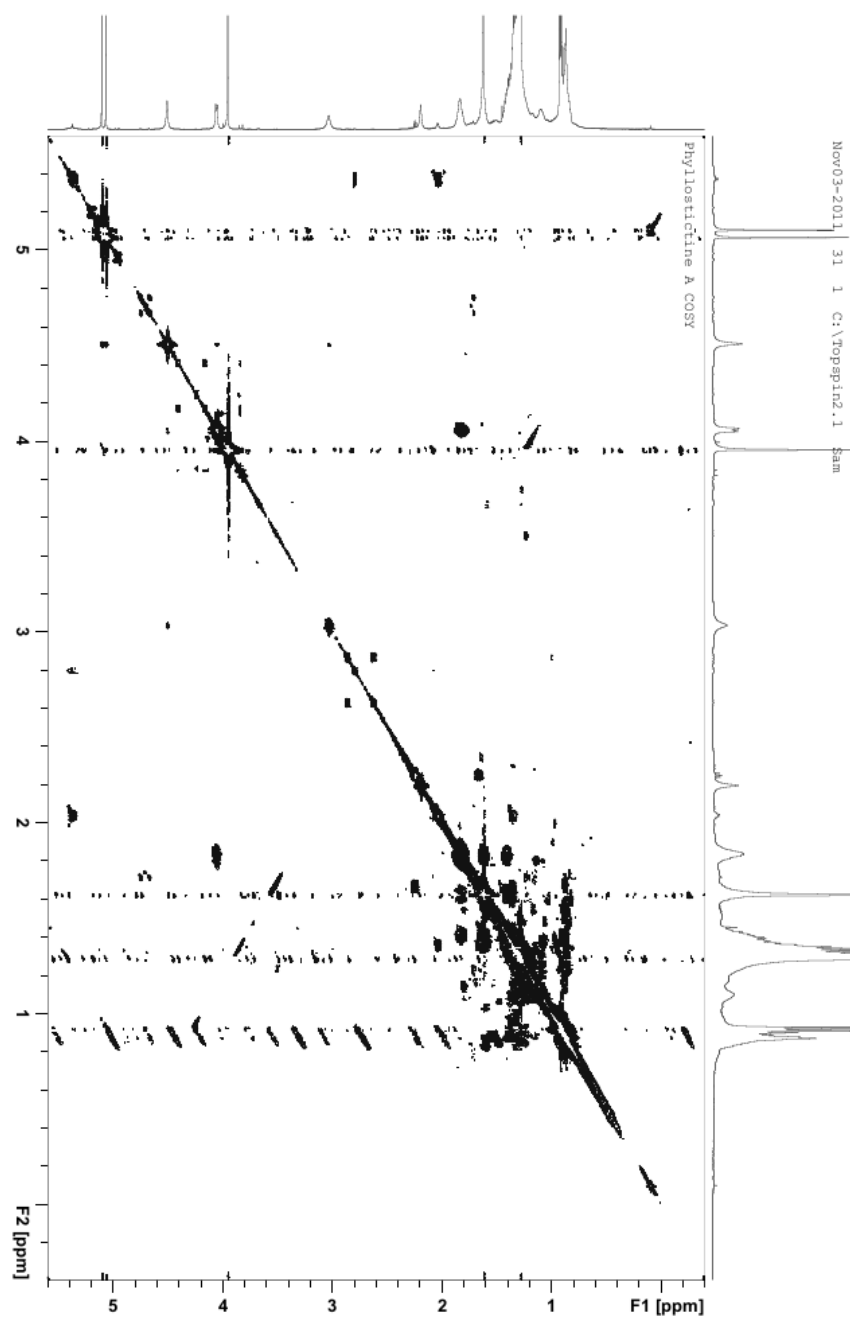**Figure I** – ^{1}H-NMR

Figure II – ^{13}C-NMR

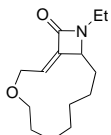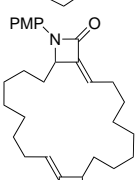**Figure III** – COSY NMR
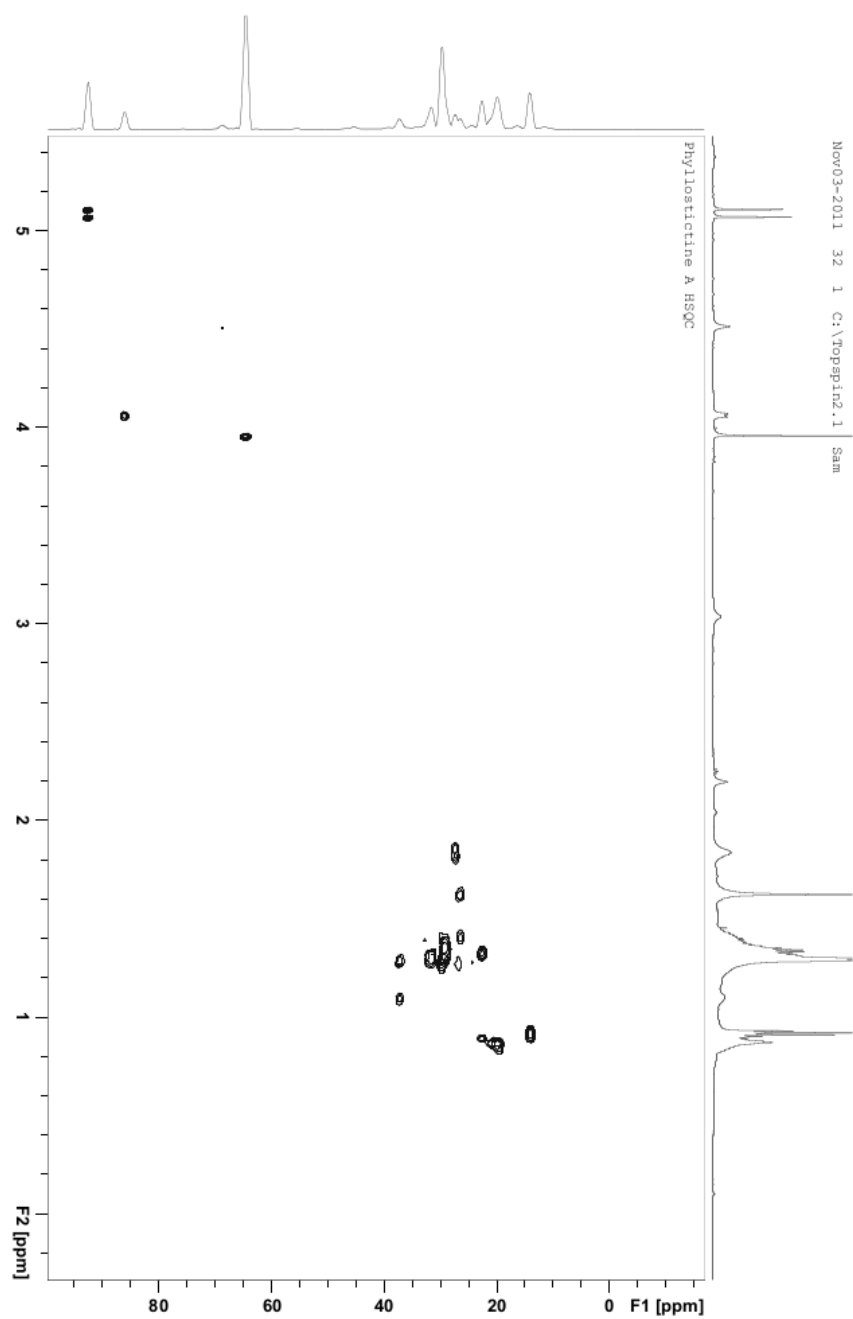
Figure IV – HSQC NMR
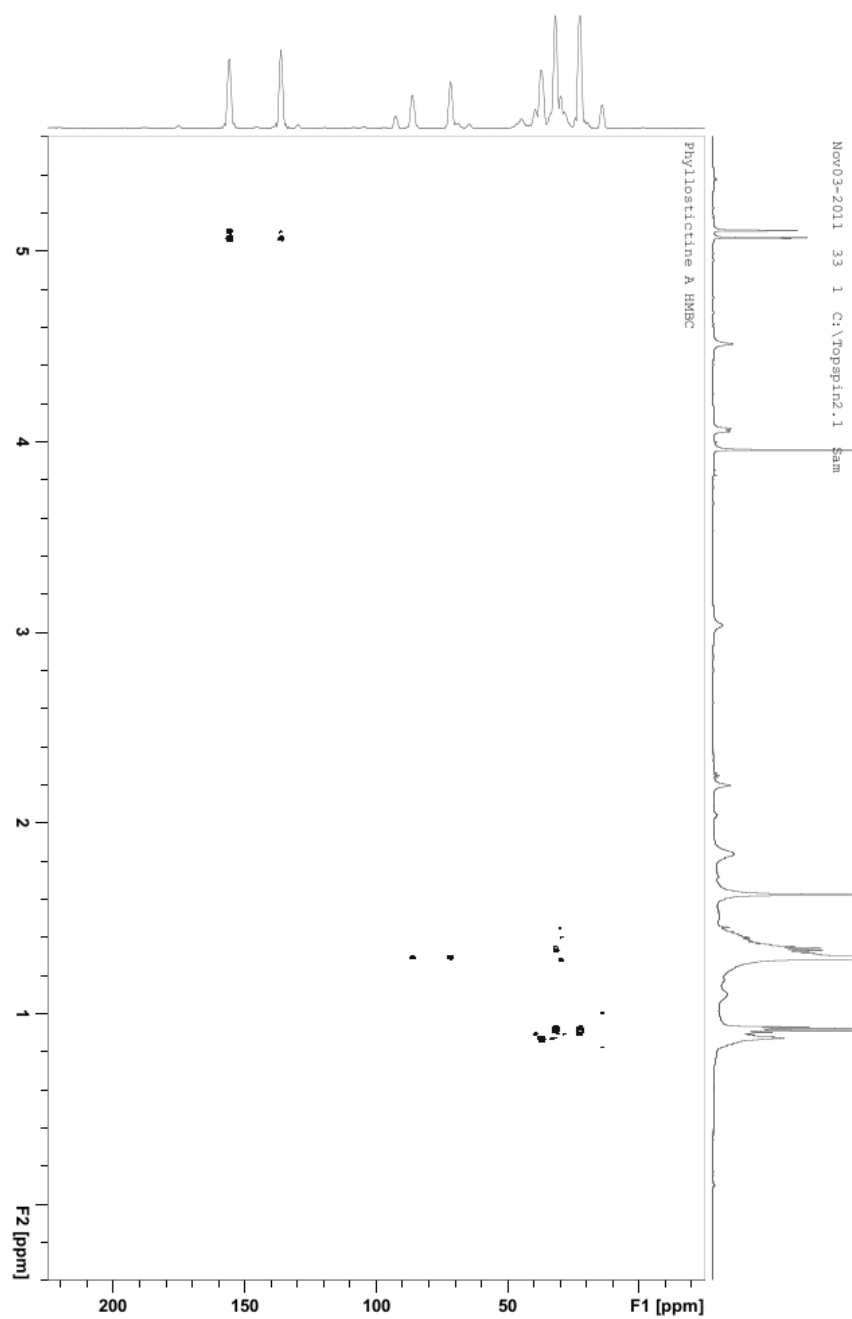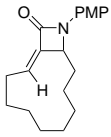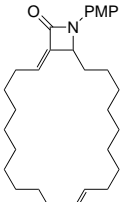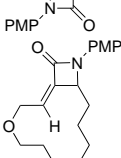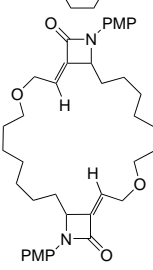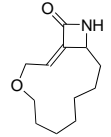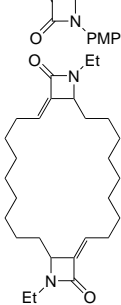
Figure V – HMBC NMR

Appendix II: α-Methylene-β-Lactam

E/Z Shifts

α-Methylene-β-Lactam	E-Shift (ppm)	Z-Shift (ppm)
	-	5.71
	-	5.52
	6.25	5.88
	-	5.86-5.8
	-	5.89
	-	5.78
	-	5.70-5.57
	-	5.44

	-	5.69
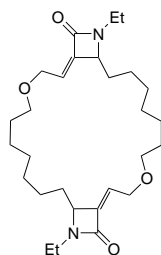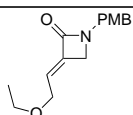
α-Methylene-β-Lactam	*E*-Shift (ppm)	*Z*-Shift (ppm)
	6.29	-
	6.26	5.73
	6.06	5.47
	6.16	-
	6.19	5.88-5.87
	6.17	-
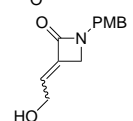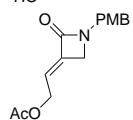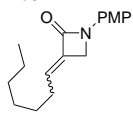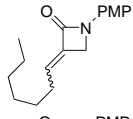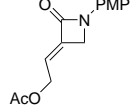
Appendix III: HPLC Traces

Figure I
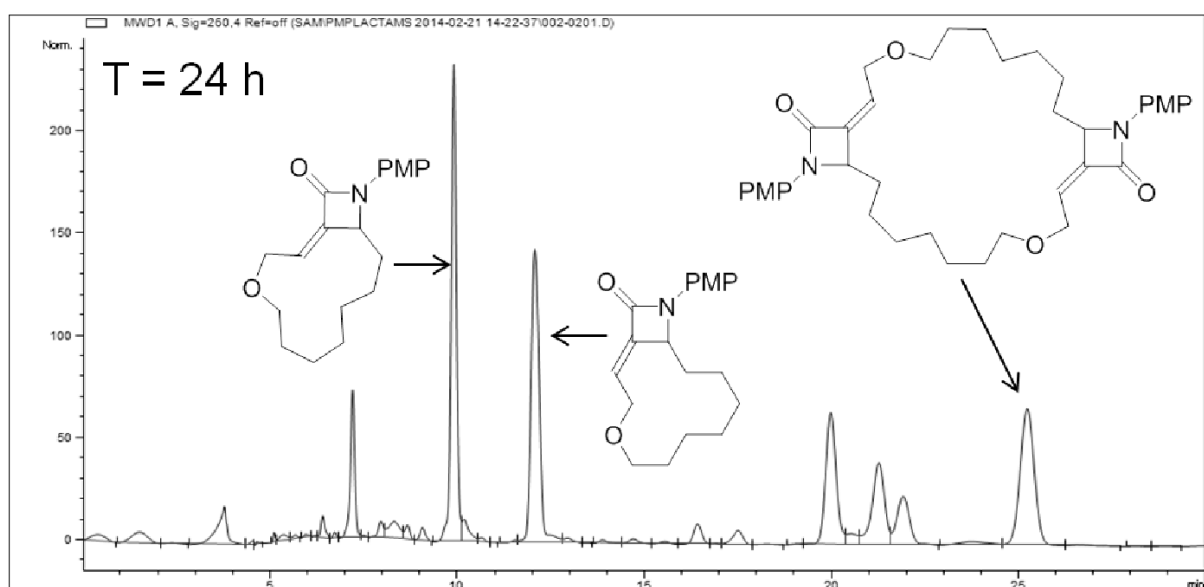
Figure II
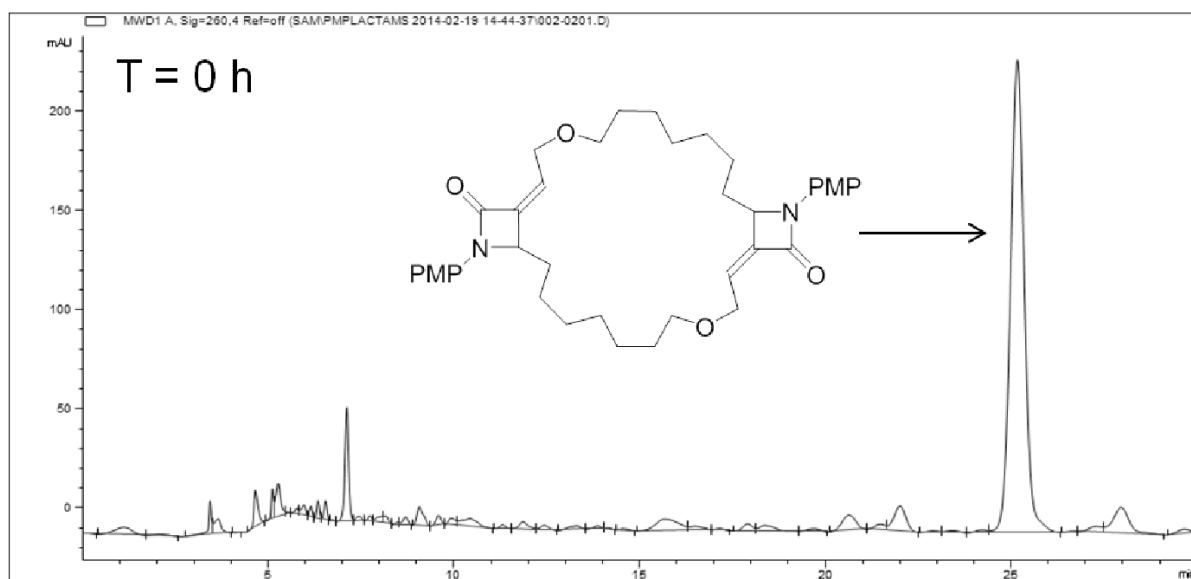
Figure III
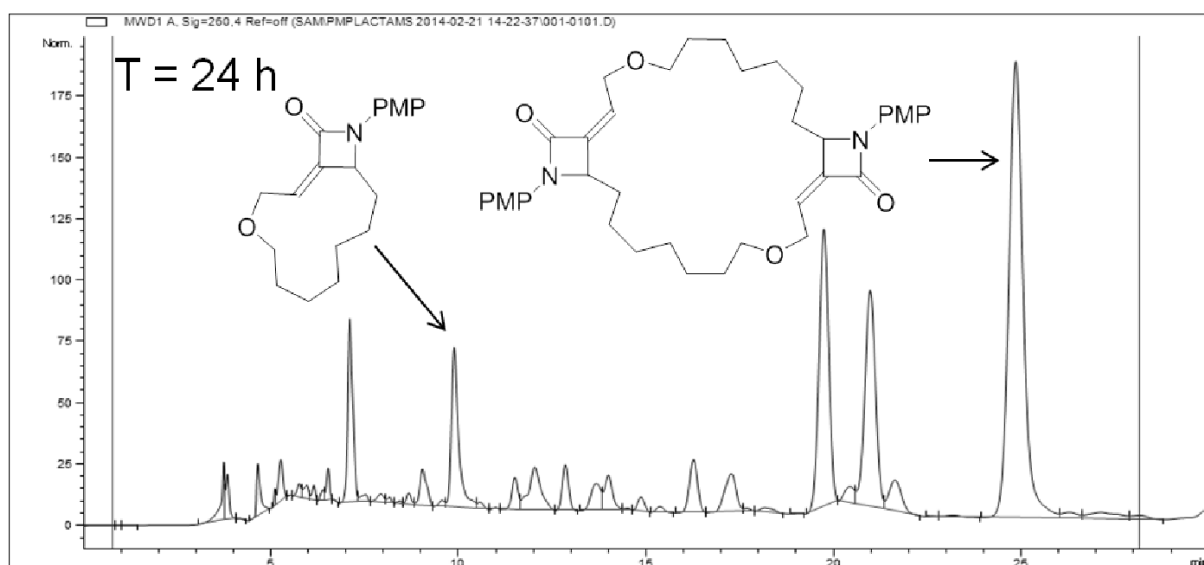
Figure IV

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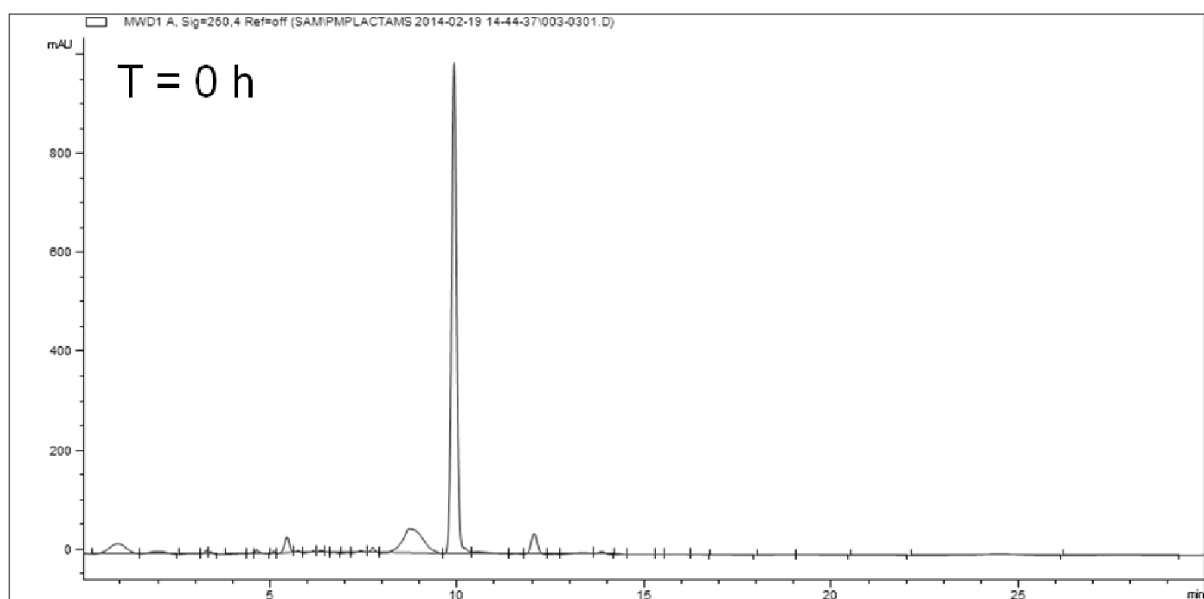
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