NOVEL METHODS TO ACCESS BIOACTIVE MOLECULES

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Finally I want to thank my parents. Without their endless love, support and encouragement I would never have made it this far. So I'd like to dedicate this thesis to my Mum and Dad, who are still my greatest inspiration.

Abstract

This thesis is divided into two chapters detailing research on applying microwave methodology to access aminated nucleosides in significantly reduced time frames, and applying the Belluš-Claisen reaction to produce non-proteogenic dipeptides.

1. Amination of Nucleosides Using Microwave Methodology

2,2'-Anhydrouridine undergoes a ring opening reaction with aliphatic amines to give the corresponding aminated product. Under conventional heating reaction times are extremely lengthy, taking at least 3 to 4 days and up to a month in the case of very hindered amines. A modified procedure using microwave irradiation has proven to drastically reduce reaction time and has allowed access to novel nucleosides on gram scale.

2. Functionalised Amino Acids via the Belluš-Claisen Rearrangement

The Belluš-Claisen reaction is a [3,3] sigmatropic rearrangement of allylic amines, ethers and thioethers to give the corresponding amide, ester of thioester. A modified procedure of the Belluš-Claisen rearrangement was used to prepare functionalised dipeptides by reaction of a ketene prepared from *N*-phthaloylglycyl chloride *in situ* with allylic amino acid derivatives in the presence of a Lewis Acid and di*iso*propylethylamine. Rearrangments were successfully carried out using *N,N*-diallyl alanine and *N*-allyl proline. A range of N-allyl proline derivatives are demonstrated. However, attempts to repeat the reaction with structurally more complex amino acids did not result in successful reactions.

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List of Abbreviations

app	apparent
aq	aqueous
b.p.	boiling point
δ	chemical shift
d	doublet
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	Dichloroethane
DCM	Dichloromethane
DMAP	4-Dimethylaminopyridine
ee	enantiomeric excess
eq	equivalents
g	gram
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
Hz	Hertz
IR	infra red
J	coupling constant
LUMO	lowest unoccupied molecular orbital
m	multiplet
mg	milligram
MHz	megahertz
mL	millilitres
mp	melting point
mmol	millimoles
m/z	mass / charge ratio
NMR	nuclear magnetic resonance
q	quartet
s	singlet
t	triplet
TMS	trimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TLC	thin layer chromatography
ν_{max}	frequency maxima

1. Amination of Nucleosides Using Microwave Methodology

1.1 Introduction

1.1.1 Nucleoside Chemistry

Nucleoside chemistry dates back to 1869 when Miescher discovered a substance that he termed "nuclein".[1] Twenty years later, Altmann isolated a protein-free nuclein which was termed "nucleic acid".[2] Studies in this area continued but since the 1950s, nucleosides and nucleotides have been the subject of a wealth of research when their role in cells was established, most famously as the chemical building blocks of ribonucleic acid (RNA) and deoxyribonucleic acid (DNA) chains.[3]

A nucleotide is comprised of three components (Figure 1):-

- A nitrogen-containing base which is either:-
  1. a purine, **1-2,** a six-membered pyrimidine ring fused to a five membered imidazole ring
     or
  2. a pyrimidine, **3-5**, a six membered heterocyle with two nitrogens in the ring.
- A pentose sugar. In RNA this is ribose **6** and in DNA it is deoxyribose **7**. Arabinose **8** and ribose **6** differ from the relative stereochemistry of the hydroxyl group in the C2' position.
- A phosphate group.[4]

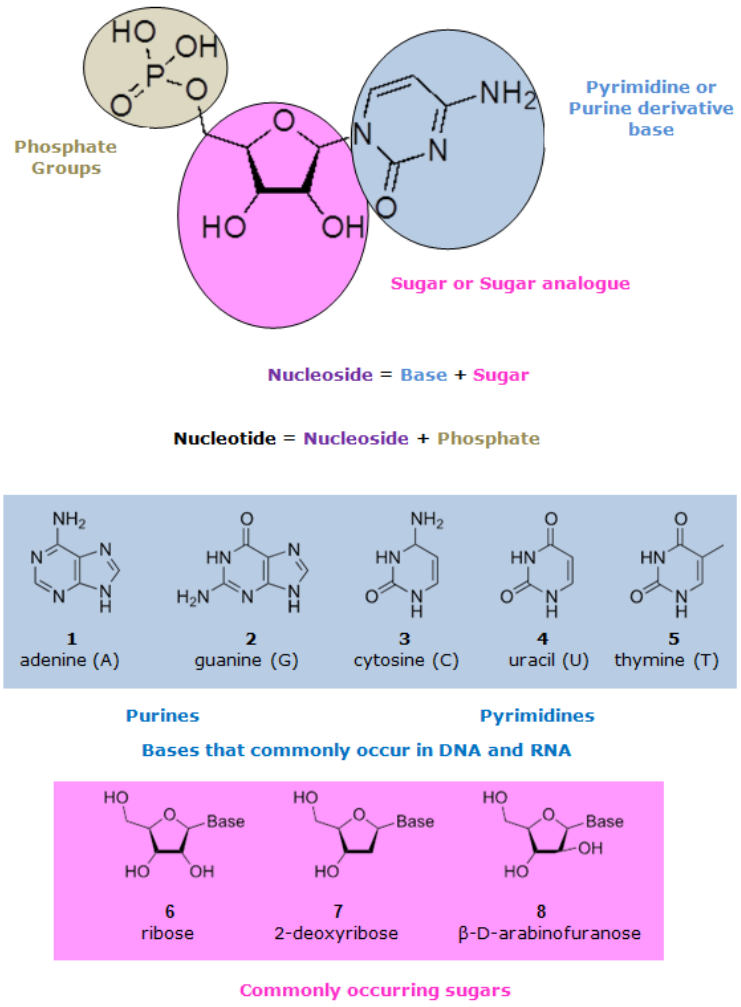


Figure 1: *Nucleoside Structure*[2]

In 1953, using experimental data obtained by Wilkins and Franklin[5], Watson and Crick determined that DNA exists as a double helix.[6] DNA consists of two polynucleotide chains that are held together by hydrogen bonds between the paired bases (Figures 1 and 2). A (adenine **1**) bases are paired with T (thymine **5**) bases and C (Cytosine **3**) are paired with G (guanine **2**). The nucleotides are linked by a phosphodiester bond whereby the 5′ phosphate group of one nucleotide is linked to the 3′-OH group of another.[4,6]

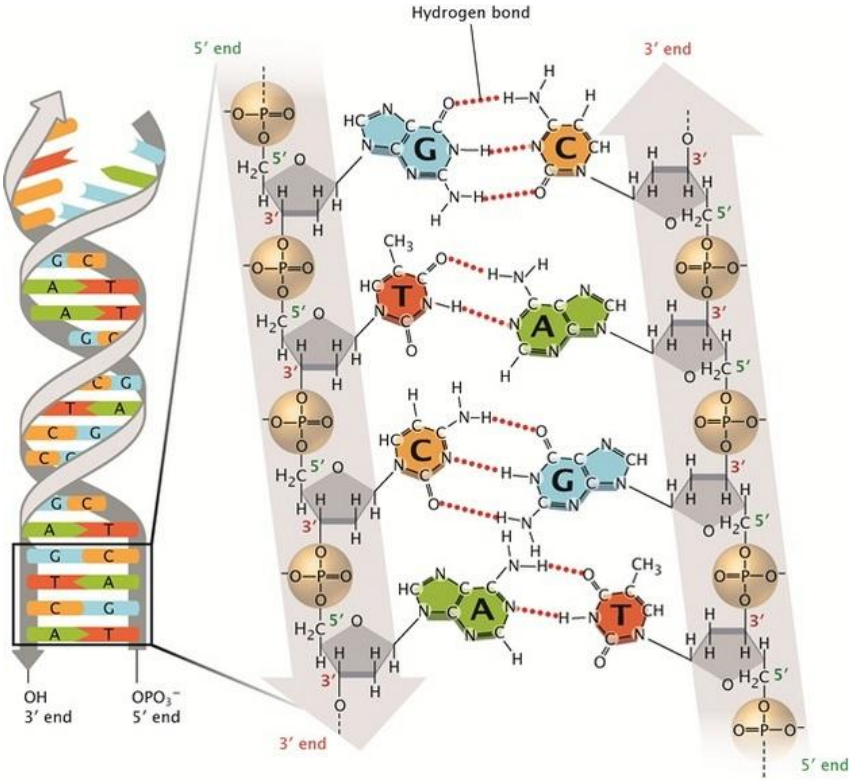
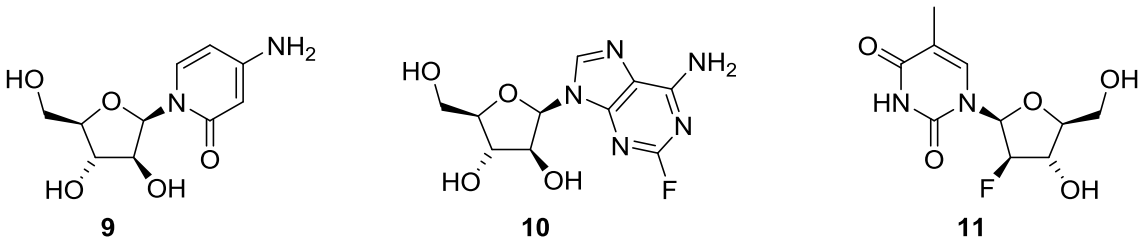


Figure 2: *Schematic model of the double helix (Copied with permission from Pray (2008)*[7]

Nucleoside molecules contain several functional groups within their structure that can be easily modified by chemical transformations.[8] These modified nucleosides have been shown to possess a variety of biological and clinical properties. They mimic physiological nucleosides and can inhibit DNA synthesis causing chain termination which results in cell death.[9] Over the years, numerous modified nucleosides have been used as antiviral, antibiotic and antitumor drugs.[3,9,10] De Clerq affirms that several anti-viral drugs had been developed including some used to treat HIV (human immunodeficiency virus).[11,12] The majority of research pertaining to nucleoside drugs relates to modified heterocyclic components but ribose core modification can lead to advanced biological activity.[13] Examples include the *arabino*-configured nucleosides (or ara-nucleosides): Cytarabine (1-β-D-arabinofuranosylcytosine, ara-C) **9**, Fludarabine (9-(β-D-Arabinofuranosyl)-2-fluoro-9H-purin-6-amine) **10** and Clevudine (1-[2-deoxy-2-fluoro-β-arabinofuranosyl] thymine) **11.**

Cytarabine (Ara-C) **9** (Figure 3) consists of a cytosine base combined with an arabinose sugar. Ara-C **9** was first synthesized in 1959 and since that time it has proven to be a very effective drug in the treatment of non-Hodgkin lymphomas, acute myeloid leukaemias and as an antiviral drug eg to treat the herpes virus.[14,15,16]



9 Cytarabine [15] **10** Fludarabine [17] **11** Clevudine [18]

Figure 3: *Arabino Nucleosides*

Ara-nucleosides are isomeric with ribosyl derivatives but the 2' position of the sugar moiety is epimeric. Thus, they have similar chemical properties to deoxyribosyl derivatives. This is a significant factor in their ability to inhibit DNA synthesis.[15]. In order to be effective, after Ara-C **9** has entered a cell, it must be metabolised to Ara-CTP **12**, (1-β-D-arabinofuranosylcytosine triphosphate) (Figure 4) to become biologically active.[14] Once incorporated into a DNA strands Ara-CTP **12** causes chain termination, resulting in a block of DNA synthesis and subsequent cell death.[19]

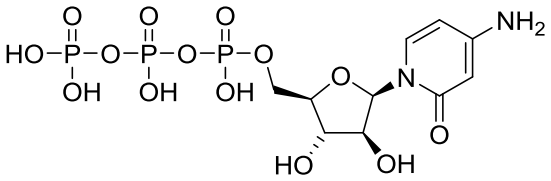


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Figure 4: *Ara-CTP[10]*

The success of Ara-C (cytarabine) **9** in treating acute leukaemias prompted the development of further nucleoside analogues, such as fludarabine **10** (Figure 3). Fludarabine **10** is widely used in the treatment of chronic lymphocytic leukaemia and non-Hodgkins lymphoma.[20,21] Fludarabine **10** must be converted to F-ara-ATP **13** once it is in the cell if it is to be effective. Studies have shown that F-ara-ATP **13** inhibits DNA synthesis and also stalls RNA translation.[22]

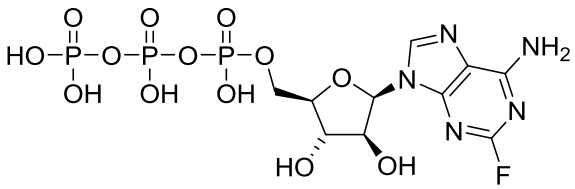

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Figure 5: *F-Ara-ATP*

Clevudine **11** (Figure 3), a pyrimidine L-nucleoside analogue, has proven to have potent activity against HBV.[23] Hepatitis B virus (HBV) infection affects more than 350 million people in the world. It is estimated that over half a million deaths per year are as a result of HBV complications.[24] In general, nucleoside inhibitors interfere with the viral activities by incorporation into DNA chains and competitive inhibition. However, in clinical trials, it was noted that Clevudine was not incorporated into DNA as anticipated.[25] Clevudine inhibits DNA non-competitively by binding to the Hepatitis B Virus active site and thus altering the viral structure.[26,27]

In addition to their therapeutic uses, modified nucleosides are useful as the chemical starting points for functional polynucleotides.[28] As part of an ongoing research program on novel catalytic polynucleotides, a synthetic entry to isocytosines **14,** arabino-configured analogues of the ^{t}RNA nucleoside Lysidine **15** (Figure 6), was required. Polynucleotides, resulting from monomers that are similar to **14**, have been shown to form stable duplexes with DNA containing isoguanosine.[29] Further, related isocytosines have been reported to possess anti-tumour properties.[30]

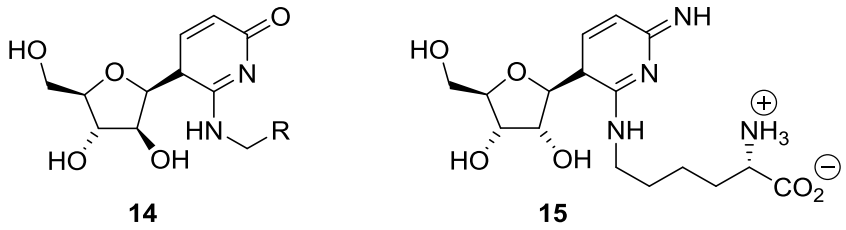
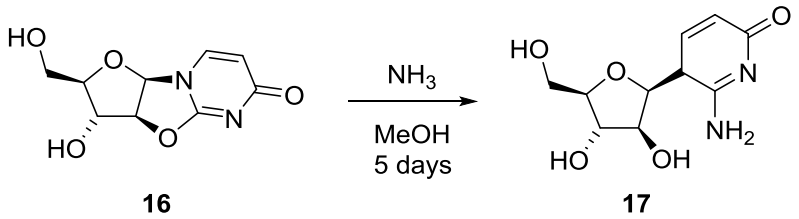


Figure 6: *Lysidine ^{t}RNA nucleobase*

Existing methods to obtain compounds **14** have proven to be lengthy and often low-yielding. The ring-opening of 2,2'-*O*-anhydrouridine **16** by ammonia was first reported by Todd *et al*[31] (Scheme 1).



Scheme 1: *Ring opening of 2,2'-O-anhydrouridine with ammonia*[31]

The method was later refined and generalized to include higher amines.[32] The time required to give the aminated derivatives **14** is very slow, taking at least 3 to 4 days and up to a month in the case of very hindered amines such as cyclohexyl amine. We hoped to produce a more time efficient method of accessing aminated arabinose-anhydrouridines by utilizing microwave technology.

1.1.2 Microwave Chemistry

1.1.2.1 Introduction to Microwaves

Microwave technology has been used in inorganic chemistry since the late 1970s.[33] However, it did not gain widespread acceptance in organic laboratories until the late 1980s. The availability of microwave technology and its adoption in organic chemistry has been relatively slow compared to other fields, for example computational and combinatorial chemistry.[34] This slow uptake could be attributed to safety aspects and issues with control and reproducibility.[35] Since the mid-1990s the number of publications in this field has considerably increased.[36] This development is mainly due to the shorter reaction times afforded by microwave chemistry as well as the availability of improved equipment which included redesigned microwave cavities to improve the heating characteristics.[34,33] A correctly designed cavity will enable uniform heating because cold and hot spots will be eliminated. This is particularly important for organic chemistry because it means that the heating of small samples can be accurately controlled.[37]

Microwave heating possesses certain advantages over conventional heating:

- Energy is imparted directly to the solvent and sample, rather than *via* conduction through the reaction vessel; thus, heating is quicker.
- A correctly designed reactor allows a uniform increase in temperature.
- It is possible to increase the temperature above the boiling point of the solvent, thus solvents with lower boiling points can be used if desired.
- Microwave heating is more energy efficient.[38,39]

1.1.2.2 Microwave Theory

All electromagnetic radiation can be divided into two components: an electric field and a magnetic field. The microwave electric field is responsible for the dielectric heating phenomenon that allows microwave oven technology to function. Dielectric heating occurs using two principal mechanisms, dipolar polarization and conduction.

The first mechanism is dipolar polarization. This is the mechanism most commonly associated with microwave heating. Only substances that contain a dipole moment will generate heat when irradiated with microwaves. Dipoles respond to external electric fields and will rotate and try to align themselves with the electric field.[34] When an

external electric field provides the energy for this rotation, any molecules that contain a dipole will attempt to align themselves with it. The speed with which a molecule will do so depends on the environment. Instantaneous alignment is hindered in liquids due to the proximity of other molecules, causing a transfer of kinetic energy. Conversely, molecules in gases will align rapidly because their molecules are not in such close proximity and thus do not adversely affect the alignment. Gases are therefore not heated as efficiently as liquids within the microwave environment. In most regions of the electromagnetic spectrum, the ability to impart energy *via* the dielectric effect is limited. Low frequency radiation will allow molecules to rotate in alignment with the field, but the heating effect is small. In high frequency radiation there is insufficient time for the molecules to rotate. As the heating is dependent on motion being parted into the component molecules of a material, there is therefore no change in temperature.

Microwave radiation is unique in being between these two extremes. Microwave radiation is not so high that dipoles do not have time to respond to the electric current. The frequency is not, however, low enough for dipoles to fully align before the orientation of the field changes. This creates a phase difference between the orientation of the field and the dipole. This phase difference causes energy to be lost from the dipole by molecular friction and collisions, giving rise to dielectric heating.[34]

If two samples, one containing water and the other dioxane, were irradiated for a fixed time at a fixed power, the sample of water would have a higher temperature at the end of the experiment. Dioxane, as a non-polar solvent, lacks the dipole characteristics necessary for microwave dielectric heating so energy can not be transferred to the sample. However, if two samples containing water, one with tap water, the other distilled water, were used in the same experiment they would not heat uniformly. The sample containing the tap water would be hotter which can be explained by conduction, the second principal mechanism.[34]

When a solution is subjected to an electric field, any ions will be influenced by the field and will move and collide. Due to the increased collision rate this causes, a greater conversion of kinetic energy to heat will result. Heat generated *via* the conductivity is much stronger than that generated solely by dielectric heating. This explains the difference in temperature mentioned above. The sample containing tap water will reach a higher temperature than pure water because the ions, influenced by conduction, will add to the heat produced.

Dielectric heating is dependent on dipole rotation and therefore, it should follow that the higher the solvent dielectric constant (i.e. the more polar a solvent is), the more effective it will be as a solvent for microwave heating. It is possible for two solvents with comparable dielectric constants to have significant differences as microwave solvents. Factors that affect this are the efficiency of a solvent to convert energy into heat, the volume of the reaction and the geometry of the reaction vessel. These latter two are vital in order to create reproducible and uniform heating but volume is the more significant factor. It is important to follow manufacturer guidelines because over or under loading the vessel can result in difficulty obtaining reproducible results.[34]

1.1.2.3 Microwaves and the Effect on the Speed of Reaction.

The major advantage in employing microwave methodology is a decrease in required reaction time.[40] How microwave irradiation alters the outcome of organic synthetic reactions has been the subject of debate.[41,42] Specifically, whether it is simply a thermal effect or if there is something unique to microwave reactions and if any non-thermal effects should also be considered. There is some controversy around the effects of the magnetic field but in most cases of microwave reactions in the literature, the decrease in reaction time can be attributed solely to thermal effects.[34,43]

In well-designed systems, microwave heating is efficient, uniform and rapid which can lead to different reaction profiles when compared to conventional heating, even if the final temperature is the same. The first published examples of microwave assisted organic synthetic chemistry made use of domestic ovens and it is only recently that purpose-built machines have become available. While domestic ovens have the advantage that they are widely available and relatively cheap there are usually major safety concerns with safety, especially when using pressurised vessels.[34]

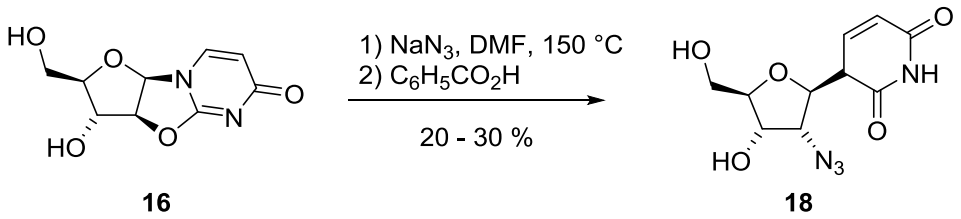
A desire to increase safety led to the development of a number of reflux systems which all broadly have the same advantages and disadvantages. These systems are safer to use and there is minimal risk of an explosion because reactions are performed at atmospheric pressure and flammable products cannot enter the cavity. However, because the reactions are performed at atmospheric pressure, this means that the temperature can only be increased a few degrees (13°C to 26°C), above the boiling point of the solvent being used. This higher temperature will speed up the reaction to some degree but it does not utilise the full potential of microwave heating.[34] Ideally,

reactions will be performed under pressure in a microwave cavity so that they will benefit both from rapid heating rates and remote dielectric microwave heating. Modern apparatus, purpose built for running these reactions, are safe, have good temperature control and accurate pressure measurement.[43]

We therefore planned to apply pressurized microwave system methodology to the amination of anhydrouridine. We hoped that the reaction accelerating effects would drastically reduce the reaction time without the need for harsh conditions. It was also envisaged that this would ease the purification of the product because there would be limited or no side reactions with the reagents and conditions employed.

1.1.3 Aminated Nucleosides

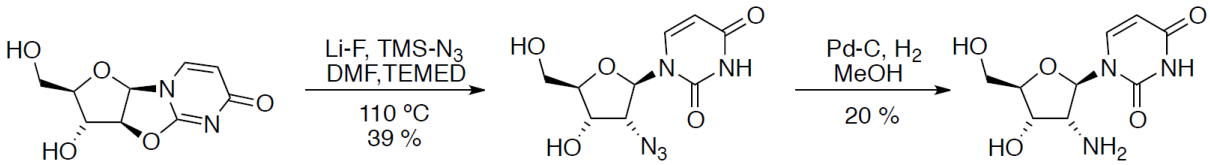
During the 1950s and 1960s, numerous studies were reported relating to the ring opening of 2,2'-anhydronucleosides by nucleophiles but the procedures reported were lengthy and sometimes required harsh conditions.[44,29,45,46] There are literature investigations into nucleophilic attack of ammonia,[31,32] sulfides[31,47] and halides.[48] Amines attack at the 2-position (Scheme 1) giving the corresponding 2-aminated product. Conversely, azides will ring open by attacking at the 2' position. For example, azidation of 2,2'-anhydrouridine **16** will give 2'-azido-2'-deoxyuridine **18** in one step (Scheme 2).[49]



16 **18**

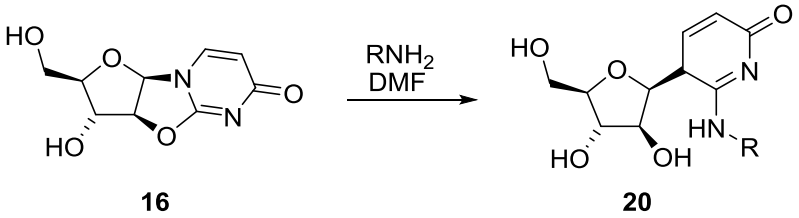
Scheme 2: *Azidation of 2,2-anhydrouridine*[49]

It is possible to access 2'-aminated nucleosides by the formation of intermediate azides that can be later reduced to the corresponding amine[49,50]. Wnuk *et al*.[51] developed a scheme to give the 2'-amino-2'-deoxyuridine **19** in a two-step process (Scheme 3).



Scheme 3: *Synthesis of 2'-amino-2'-deoxyuridine*[51]

Delia and Beranek[44] reported the reaction of 2,2'-anhydrouridine **16** with ammonia, primary aliphatic amines, secondary aliphatic amines and aromatic amines. Their work proved successful with ammonia and primary amines, leading to the corresponding 2-aminated nucleosides **20** (Scheme 4 and Table 1).



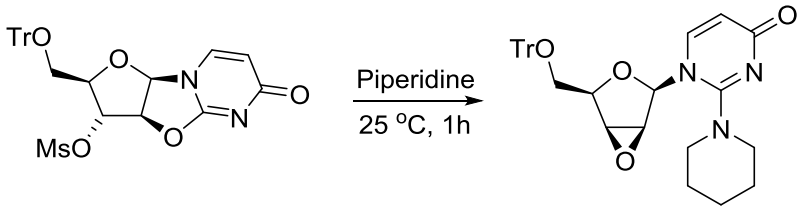
Scheme 4: *Synthesis of 2-aminated nucleosides*

Table 1: *Conventional amination reaction times*[44]

Entry	R	% Yield	Time of Reaction (Hours)
1	*n*-Bu	82	72
2	Allyl	86	96
3	Benzyl	90	360
4	Cyclohexyl	72	768
5	Ph	0	-

Aromatic amines (Scheme 4, Table 1, Entry 5) failed to aminate the nucleoside because they were not sufficiently nucleophilic to effect the reaction under the conditions employed. Secondary amines also only returned starting materials when used. It had been assumed that these would successfully react as they had base strengths similar to the primary amines. The lack of reactivity was presumably due to steric issues. Evidence to support this was the relative rates of reaction of the various primary amines. Butyl amine and allyl amine both reacted relatively quickly (three and four days respectively) while the more bulky cyclohexylamine and benzylamine took considerably longer (almost a month). These results demonstrate a significant steric dependence as the α–branching

increases. It was later reported that some secondary amines were successful in opening the 2,2'-*O*-anhydo-bridge of compounds containing the 3'-O-mesyl group, for example the mesyl protected compound **21** reacted with piperdine to give the 2-aminated product **22**. However, this also resulted in an epoxide ring forming between the 2' and 3' positions (Scheme 5).[52]

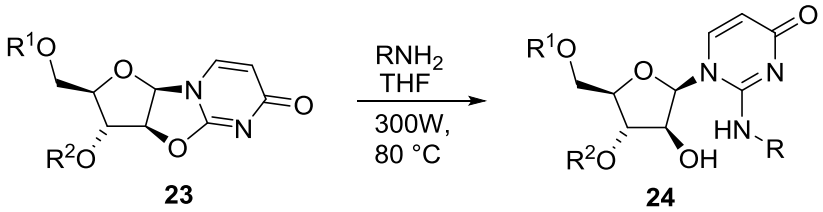


21 **22**

Scheme 5: *2,2'-O-Anhydro-bridge opening with piperidine*[52]

1.1.4 Amination of 2,2'-anhydroarabinouridine (23) and its Derivatives

As part of a research program directed towards novel catalytic polynucleotides, Ochocińska[53] had attempted to apply microwave methodology to the same chemistry (Scheme 6, Table 2) in the hope of cutting the time required to access C2-amine-substituted nucleosides.



23 **24**

Scheme 6: *Initial amination reaction conditions*[53]

Table 2: *Initial Reactions investigated by Ochocińska*[53]

Entry	Reagents	Temp (˚C)	Time (mins)	R	R^1	R^2	Product, Yield %
1	Benzophenone imine	120	60	$C(Ph)_2$	TBS	OH	Trace
2	$MeNH_2$	120	30	Me	TBS	OH	Partial **30**, not isolated
3	$MeNH_2$	80	60	Me	TBS	TBS	**30,** 65
4	$MeNH_2$	80	60	Me	TBS	OH	**30,** 89
5	$MeNH_2$	80	60	Me	TBS	TBS	**0**
6	1)Zinc 2)NH_2Me	120	60	Me	TBS	TBS	**0**
7	NH_2Me $BF_3.Et_2O$	80	30	Me	OH	OH	**0**

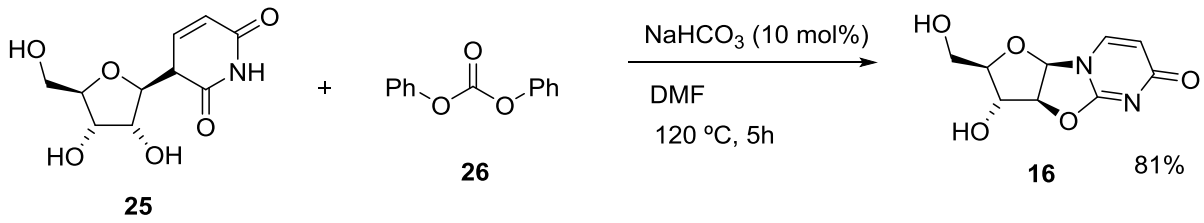
When 5'-*O-tert*-butyldimethylsilyl-2,2'-anhydrouridine was reacted with methylamine using microwave irradiation at 120˚C for 30 minutes, a mixture of products was obtained. ^{1}H NMR analysis of the crude mixture revealed that some of the expected product **24** was present (Entry 2). Several different temperature and reaction times were tried. It was found that 80˚C for 1 hour (Entry 4) gave the expected product **24** in 89% yield. Of particular satisfaction was that to isolate the product as a colourless solid, only concentration of the reaction mixture followed by filtration was required. Addition of a Lewis acid or other modifications of initial conditions failed to give the desired product.

The purpose of this research was to follow up this lead to devise a general protocol for 2-amination of ara-uridines.

1.2 Results and Discussion

5'-*O* Protected 2,2'-anhydrouridine of general structure **23** (Scheme 6) are readily prepared and have served as key intermediates in this research. It was necessary to optimise the synthesis of the starting materials at this point. We wanted to conduct the experiments on a gram scale reactions and the method used did not give sufficient starting materials for the reaction.

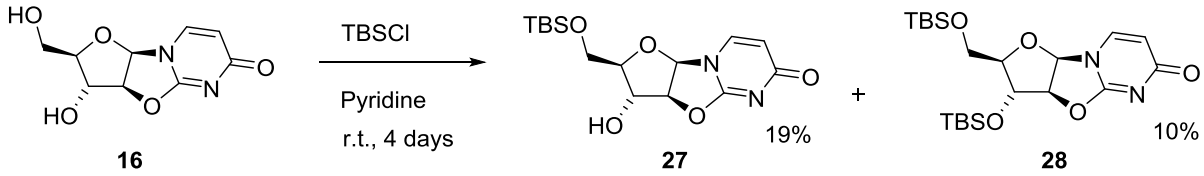
The procedure outlined by Ochocinska[53] was followed and this gave the desired 2,2'-anhydrouridine **16**. (Scheme 7)



***Scheme 7**: Synthesis of 2,2'-anhydrouridine*[53]

Purification by recrystallization in methanol proved difficult because the product was only sparingly soluble and a large excess of methanol was needed to completely dissolve the solution. It was found that simply washing the crude product with cold methanol resulted in a product that was found to be pure by ^{1}H NMR analysis.

When attempting to repeat the TBS protection step a mixture of both the mono and di-protected compound **27** and **28** were obtained.



***Scheme 8**: TBS Protection of 2,2'-anhydrouridine*[53]

Crude ^{1}H NMR analysis showed mono-protected compound was the major product (20:80 ratio) but separation of the two compounds during the column chromatography purification step proved challenging. This meant that the mono-protected compound was isolated with yields of only 5-21%.

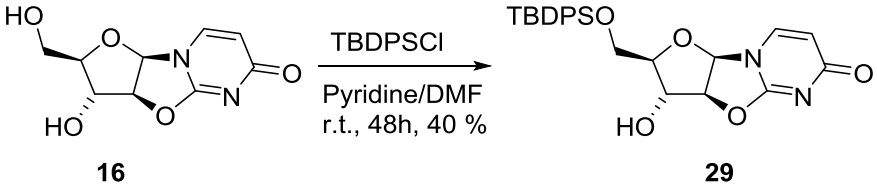
The di-TBS protected compound was also challenging to purify, giving a yield of 65% (Table 2, Entry 3), therefore alternative silyl protecting groups were investigated to determine if this would simplify the purification.

Silyl ethers are widely used protective groups for hydroxyl functional groups because they are stable under a wide range of conditions and are removable with high selectivity.[54,55] Their reactivity can be modulated by carefully selecting the substituents on the silicon atom.[56,57] Originally TBS had been used because it is a very widely used silyl protective group.[58,59] It can be introduced with several reagents and can be easily

removed under conditions that do not affect other functional groups.[57] It is sensitive toward acid but is stable toward base and it can withstand temperatures up to 230 °C.[60] The TBDPS group is far more stable than the TBS group toward acid but is less stable than the TBS group towards base. The TBDPS group has also proven to have better stability to many reagents which are not compatible with the TBS group.[57,61]

1.2.1 Optimization of Protection Step

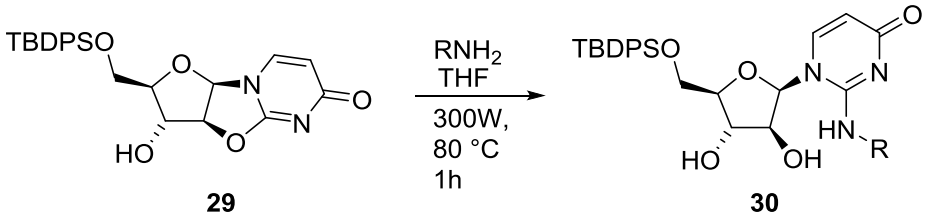
In order to improve the selectivity of the protection step of the starting material the TBS protecting group was changed to the TBDPS group. Following a procedure by Sebesta *et al*.[62] (Scheme 9), the primary alcohol of 2,2′-anhydrouridine **16** was protected with TBDPS-Cl to give the TBDPS protected compound **29**.



Scheme 9: *Synthesis of 5′-O protected 2,2′-Anhydrouridine*

Analysis of the crude residue by ^{1}H NMR spectroscopy showed that only the mono-protected compound **29** was obtained, which made the resulting purification by column chromatography straightforward.

5′-*O*-TBDPS-2,2′-anhydrouridine **29** was reacted with a variety of amines on 100 mg scale (Scheme 10) using the previously optimised microwave methodology conditions (Scheme 6, Table 2, Entry 4). 5′-*O*-TBDPS-2,2′-anhydrouridine **29** was successfully reacted with a range of primary amines to give compound **30** in yields of 73-51% (Scheme 10 and Table 3). Secondary amines failed to give the desired product, returning the amine and compound **29**.



Scheme 10: *Amination of TBDPS protected 2,2′-Anhydrouridine*

Table 3. *Amination of 5'-O-TBDPS-2,2'-Anhydrouridine*

Entry	Compound	R	% Yield
1	**30a**	Me	73
2	**30b**	Et	65
3	**30c**	Pr	73
4	**30d**	*n*-Bu	68
5	**30e**	*sec*-Bu	64
6	**30f**	Allyl	66
7	**30g**	*n*-Pentyl	61
8	**30h**	*n*-Hexyl	52
9	**30i**	Benzyl	56
10	**30j**	Cyclohexyl	51
11	**30k**	*iso*-Pentyl	58
12*	**30d**	*n*-Bu	74
13	**30l**	*iso*-Pr	0
14	**30m**	*iso*-Bu	0
15	**30n**	*tert*-Bu	0
16	**30o**	2-Ethyl-hexyl	0
17	**30p**	Ph	0
18**	**30b**	Et	0

conditions: *rt, 4 days **reflux, 1 hr

This compares very favourably with amination using conventional methods. When using primary aliphatic amines, this gave a very significant reduction in reaction time compared to similar reactions reported in the literature (Compare Table 1, Entries 1-4 with Table 3, Entries 4, 6, 9 and 10). The reaction was repeated conventionally, being left to stir at room temperature until the starting material was consumed as monitored by TLC analysis (Table 3, Entry 12). This took four days to go to completion, compared to 1 hour with microwave heating (Table 3, Entry 4). The reaction was also repeated using a conventional hot plate for heating. After being refluxed in THF for one hour, TLC analysis showed that there was no conversion of starting material (Table 3, Entry 18). It took four days for unprotected 2,2'-anhydrouridine **16** to undergo the same reaction (Table 1, Entry 1), thus the decrease in reaction time can be explained solely by the application of microwave irradiation.

1.2.2 Amenity To Larger Scale Reactions

The reaction was repeated on a one gram scale using *n*-butyl amine in 10 ml of THF using the standard conditions (1 hr, 80°C, 300 W) but on a 1g scale. When first attempted using butylamine the product had already started to precipitate at the end of the reaction. A final yield was obtained of 90%. Gratifyingly, this was not only a better yield than the 100 mg scale reaction, but also higher than when the reaction was carried out conventionally.[44]

The reaction was then repeated on the same scale using the same amines that had successfully given aminated product **30** (Scheme 10). When attempting the reaction using cyclohexylamine on 1g scale, no improvement in yield was noted. This time the reaction mixture was concentrated *in vacuo* at 1mm pressure. Analysis of the crude residue by ^{1}H NMR spectroscopy revealed that the reaction had not gone to completion. The reaction was repeated on the same scale, with twice the amine loading and double the reaction time. The reaction mixture was again concentrated under 1mm pressure and analysis of the solid residue revealed the remaining material was the 2-aminated product. The total yield obtained was 81%. Overall yields for 1g scale reactions ranged from 70-90% (Table 4).

In summary, the reaction proceeded smoothly with simple and unhindered amines. As observed when performing the reaction under conventional conditions, increasing steric bulk had an adverse effect on the reaction. In the case of cyclo-hexylamine, twice the usual amine load was required and it was also necessary to double the reaction time in order to drive the reaction to completion. However, as the reaction is reported to take one month using conventional methods this still represents a significant improvement.

Table 4. *Amination of 5'-O-TBDPS-2,2'-Anhydrouridine (1g scale)*

Entry	Compound	R	% Yield
1	**30a**	Me	85
2	**30b**	Et	86
3	**30c**	Pr	88
4	**30d**	*n*-Bu	89
5	**30e**	*iso*-Bu	80
6	**30f**	Allyl	87
7	**30g**	Pentyl	85
8	**30h**	Hexyl	79
9	**30i**	Benzyl	70
10	**30j**	Cyclo-hexyl	81
11	**30k**	*iso*-pentyl	81

1.3 Conclusions and Future Work

We have reported a new method of aminating 2,2'-anhydrouridine using a microwave methodology. The presented methodology gave a new, effective, high yielding and neat way of obtaining 2-aminated nucleosides. This discovery offers a means to increase the capacity of these molecules and significantly decreases the required reaction time.

1.4 Experimental

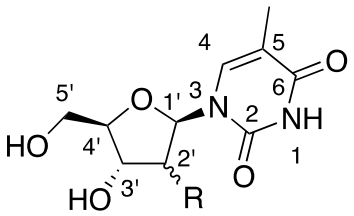
Reagents were purchased from Sigma-Aldrich, Acros, Alfa Aesar or Fisher Scientific and were not purified except where stated. Solvents were purchased anhydrous and stored over molecular sieves, or distilled under nitrogen from an appropriate drying agent. THF and diethyl ether were distilled from sodium benzophenone ketyl radical while DCM and acetonitrile were distilled from calcium hydride. Thin layer chromatography was performed on aluminium sheets coated with Merck silica gel 60 F_{254} with visualisation using potassium permanganate solution and/or scrutinised under 254 nm UV light. Column chromatography was performed using Silica gel 60 (35-70 microns) supplied by Fisher.

Nuclear magnetic resonance (NMR) spectroscopy was performed on a Bruker Advance 400 NMR spectrometer (^{1}H NMR at 400 MHz, ^{13}C NMR at 100 MHz) with the appropriate

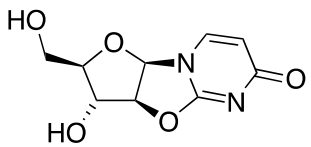
deuterated solvent. Chemical shifts in ^{1}H NMR spectra are expressed as ppm downfield from TMS and in ^{13}C NMR, are relative to internal standard, and reported as singlet (s), doublet (d), triplet (t), quartet (q) and combinations thereof, or multiplet (m). Coupling constants (*J*) are quoted in Hz and are rounded to the nearest 0.5 Hz. Mass spectrometry was performed using a Bruker MicroTOF-Q instrument with electrospray ionisation in the positive mode. FT-IR data was acquired using Thermo Electron Corporation Nicolet 380 FTIR with Smart Orbit diamond window instrument with wavenumbers being reported in cm^{-1}. All melting points were obtained using a Stuart SMP10 melting point instrument. All non-microwave reactions were carried out under an inert atmosphere of nitrogen that was dried by passage through phosphorus pentoxide.

Microwave reactions were performed using a Milestone MicroSYNTH reactor and SK10 vessel with or without three inserts that each contained one magnetic stirring bead depending on volume. Twist control, rotor control, start parameters and continuous power were all selected. T1 control was used with 60 % stirring.

1.4.1 Numbering of atoms in a nucleoside molecule



1.4.2 2,2'-Anhydrouridine 16[63]



Uridine (13.0 g, 53.0 mmol) and diphenyl carbonate (13.0 g, 60.0 mmol) were slurried in DMF (30 mL) and the reaction was heated to 80 °C. After one hour the reagents had

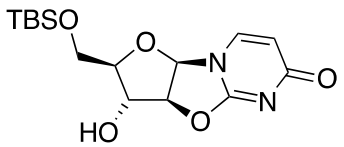
dissolved and sodium hydrogen carbonate (0.53 g, 6.0 mmol) was added followed by heating the reaction to 120 °C. After stirring for five hours the reaction was allowed to cool to room temperature and the resulting precipitate was collected by filtration. The product was washed with MeOH to give the crude as a colourless solid. (9.71g, 42.9 mmol, 81%), mp = 238-40 °C. lit 238-244 °C

δ_H (400 MHz, DMSO-d_6), 3.19 (1H, dd, *J* = 6.0, 11.5 Hz, C5'-H^1), 3.28 (1H, dd, J = 5.0, 11.5 Hz, C5'-H^2), 4.08 (1H, app t, J = 5.0 Hz, C4-H'), 4.38-4.41 (1H, m, C3'-H), 5.00 (1H, br s, C5'-OH), 5.20 (1H, app d, J = 6.0 Hz, C2'-H), 5.85 (1H, d, J = 7.5 Hz, C5-H), 5.91 (1H, br s, C3'-OH), 6.30 (1H, d, J = 6.0 Hz, C1'-H), 7.84 (1H, d, J = 7.5 Hz, C4-H); δ_C (100 MHz, DMSO-d_6), 61.3 (C5'), 75.2 (C3'), 89.2 (C2'), 89.7(C4'), 90.5 (C1'), 109.1 (C5), 137.3 (C4), 160.3 (C2), 171.7 (C6); ν_{max} (thin film), 1650 (C=O); m/z calculated for $C_9H_{10}N_2O_5$ $[M+Na]^+$, 249.0482, found 249.0482.

1.4.3 TBS Protection

2,2'-Anhydrouridine (3.00 g, 13.3 mmol) was dissolved in pyridine (15 mL) at 0 °C. TBDPS chloride (3.64 g, 13.3 mol) was added drop-wise in pyridine (5 mL). After stirring for four days at room temperature, the reaction was treated with ether (30 mL) and the pyridinium salt was removed by filtration. After evaporating the solvents, the crude mixture was dissolved in DCM and washed with water to remove the remaining pyridine. Purification by flash chromatography MeOH:DCM (7.5:92.5) gave 5'-*O*-*tert*-butyldimethylsilyl-2,2'-anhydrouridine (601 mg, 2.50 mmol, 19%), mp = 137-140 °C and 3',5'-di-*O*-*tert*-butyldimethylsilyl-2,2'-anhydrouridine (611 mg, 1.34 mmol, 10%), mp = 100-102 °C, obtained as colourless solids.

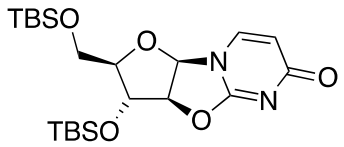
1.4.4 5'-*O*-*tert*-Butyldimethylsilyl-2,2'-anhydrouridine 27



δ_H (400 MHz, DMSO-d_6), -0.03 (3H, s, Si-CH$_3$), -0.03 (3H, s, Si-CH$_3$), 0.83 (9H, s, CCH$_3$), 3.39-3.52 (m, 2H, C5'-H^1, C5'-H^2), 4.09-4.12 (1H, m, C4'-H), 4.37 (1H, m, C3'-H), 5.26 (1H, d, J = 5.5 Hz, C2'-H), 5.90 (1H, d, J = 7.5 Hz, C5-H), 6.00 (1H, d, J = 4.0 Hz, C3'-OH), 6.33 (1H, d, J = 5.5 Hz, C1'-H), 7.47 (d, 1H, J = 7.5 Hz, C4-H); δ_C (100 MHz,

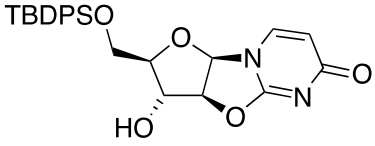
DMSO-d_6), -5.03 (Si-$\underline{C}H_3$), -5.01 (Si-$\underline{C}H_3$), 18.5 (Si$\underline{C}$), 26.2 (Si(C)$\underline{C}H_3$), 62.7 ($\underline{C}$5′), 74.5 ($\underline{C}$3′), 88.4 ($\underline{C}$2′), 89.1 ($\underline{C}$4′), 90.1 ($\underline{C}$1′), 109.2 ($\underline{C}$5), 137.3 ($\underline{C}$4), 160.0 ($\underline{C}$2), 171.4 ($\underline{C}$6); ν_{max} (thin film), 1530 (C=N), 1651 (C=O), 2929 (C-H aliphatic); m/z calculated for $C_{15}H_{24}N_2O_5Si$ $[M+H]^+$, 341.1527, found 341.1528.

1.4.5 3′,5′-Di-*O*-*tert*-butyldimethylsilyl-2,2′-anhydrouridine 28



δ_H (400 MHz, DMSO-d_6), -0.04 (3H, s, Si-C$\underline{H}_3$), -0.03 (3H, s, Si-C$\underline{H}_3$), 0.15 (3H, s, Si-C$\underline{H}_3$), 0.17 (3H, s, Si-C$\underline{H}_3$), 0.81 (9H, s, CC$\underline{H}_3$), 092 (9H, s, CC$\underline{H}_3$), 3.43 (dd, 1H, J = 5.5, 11.5 Hz, C5′-$\underline{H}^1$), 3.55 (1H, dd, J = 5.0, 11.5 Hz, C5′-$\underline{H}^2$), 4.06 (1H, app dd, J = 5.0, 9.0 Hz, C4′-$\underline{H}$) 4.53 (1H, m, C3′-$\underline{H}$), 5.26 (1H, dd, J = 1.0, 5.0 Hz, C2′-$\underline{H}$), 5.90 (1H, d, J = 7.5 Hz, C5-$\underline{H}$), 6.33 (1H, d, J = 6.0 Hz, C1′-$\underline{H}$), 7.47 (d, 1H, J = 7.5 Hz, C4-$\underline{H}$); δ_C (100 MHz, DMSO-d_6), -5.10 (Si-$\underline{C}H_3$), -5.07 (Si-$\underline{C}H_3$), -4.66 (Si-$\underline{C}H_3$), -4.50 (Si-$\underline{C}H_3$), 18.2 (Si$\underline{C}$), 18.4 (Si$\underline{C}$), 26.0 (Si(C)$\underline{C}H_3$), 26.1 (Si(C)$\underline{C}H_3$), 61.7 ($\underline{C}$5′), 76.0 ($\underline{C}$3′), 87.4 ($\underline{C}$4′), 89.1 ($\underline{C}$2′), 89.6 ($\underline{C}$1′), 109.3 ($\underline{C}$5), 137.2 ($\underline{C}$4), 160.0 ($\underline{C}$2), 171.3 ($\underline{C}$6); ν_{max} (thin film), 1468 (C=N), 1656 (C=O), 2929 (C-H aliphatic); m/z calculated for $C_{21}H_{38}N_2O_5Si_2$ $[M+H]^+$, 455.2392, found 455.2393.

1.4.6 5′-*O*-*tert*-Butyldiphenylsilyl-2,2′-anhydrouridine 29[62]



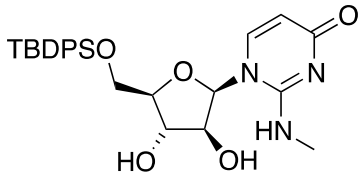
2,2′-Anhydrouridine(3.00 g, 13.3 mmol) was dissolved in pyridine (26 mL) and DMF (12 mL) at 0 °C. TBDPS chloride (3.64 g, 13.3 mol) was added dropwise over five minutes. After stirring for two days at room temperature DCM was added (70 mL) and washed with saturated $NaHCO_3$ solution (3 x 50 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the crude product. Purification by flash chromatography MeOH:DCM (0:100 to 20:80) gave the desired product as colourless crystals. (3.21g, 6.92 mmol, 52%), mp = 181-182°C.

δ_H (400 MHz, DMSO-d_6), 0.92 (9H, s, CC$\underline{H}_3$), 3.47 (dd, 1H, *J* = 6.5, 11.5 Hz, C5′-$\underline{H}^1$), 3.59 (dd, 1H, J = 5.0, 11.5 Hz, C5′-$\underline{H}^2$), 4.15-4.20 (1H, m, C4′-$\underline{H}$), 4.43-4.47 (1H, m, C3′-$\underline{H}$), 5.26 (1H, dd, J = 1.5, 5.5 Hz, C2′-$\underline{H}$), 5.89 (1H, d, J = 7.5 Hz, C5′-$\underline{H}$), 6.01 (1H, d, J = 4.5 Hz, C3′-O$\underline{H}$), 6.33 (1H, d, J = 5.5 Hz, C1′-$\underline{H}$), 7.37-7.49 (6H, m, Ar-$\underline{H}$), 7.50-7.58 (4H, m, Ar-$\underline{H}$), 7.93 (d, 1H, J = 7.5 Hz, C4-$\underline{H}$); δ_C (100 MHz, DMSO-d_6), 19.2 (Si$\underline{C}$), 26.9 (Si(C)$\underline{C}H_3$), 63.1 ($\underline{C}$5′), 74.4 ($\underline{C}$3′), 87.6 ($\underline{C}$4′), 89.1 ($\underline{C}$2′), 89.8 ($\underline{C}$1′), 109.2 ($\underline{C}$5), 128.4 (Ar-$\underline{C}$), 128.4 (Ar-$\underline{C}$), 130.4 (Ar-$\underline{C}$), 130.4 (Ar-$\underline{C}$), 132.8 (Quat. Ar-$\underline{C}$), 133.0 (Quat Ar-$\underline{C}$), 135.4 (Ar-$\underline{C}$), 135.4 (Ar-$\underline{C}$), 137.3 ($\underline{C}$4), 159.9 ($\underline{C}$2), 171.4 ($\underline{C}$6); ν_{max} (thin film), 1533 (C=N), 1650 (C=O), 2157, 2929 (C-H aliphatic); m/z calculated for $C_{25}H_{28}N_2O_5Si$ $[M+Na]^+$, 487.1660, found 487.1666.

1.4.7 General Amination Procedure

5′-*O*-TBDPS-2,2′-anhydrouridine (100 mg, 0.21 mmol, 1.0 eq) was dissolved in THF (0.5 ml) and primary amine (10.0 eq). The mixture was reacted at 80 °C for 1 hour at 300W. After completion the reaction mixture was poured into a flask of ether (100 ml). Filtration of the resulting precipitate gave the product.

1.4.8 3-((2′*R*,3′*S*,4′*S*,5′*R*)-5′-((*tert*-Butyldiphenylsilyl)oxymethyl) -3′, 4′-dihydroxyoxolan-2′-yl)-2-(methylamino)pyrimidin-6(1H)-one 30a

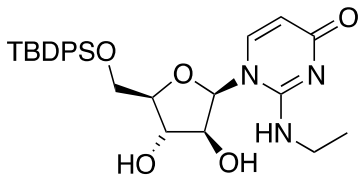


Following general amination procedure from 5′-*O*-TBDPS-2,2′-anhydrouridine (100 mg, 0.21 mmol, 1.0 eq) and methylamine in 2.0M THF solution (1.05 mL, 2.1 mmol, 10.0 eq) 3-((2′*R*,3′*S*,4′*S*,5′*R*)-5′-((*tert*-Butyldiphenylsilyl)oxymethyl)-3′, 4′-dihydroxyoxolan-2′-yl)-2-(methylamino)pyrimidin-6(1H)-one was obtained as a colourless solid (76mg, 0.15 mmol, 73%), mp = 187-188 °C. A drop of D_2O was added to the analytical sample before the ^{1}H NMR analysis.

δ_H (400 MHz, DMSO-d_6), 1.00 (9H, s, C($C\underline{H}_3$)$_3$), 2.71 (3H, s, N-$C\underline{H}_3$), 3.76-3.79 (1H, m, C4′-$\underline{H}$), 3.81-3.84 (1H, m, C5′-$\underline{H}^1$), 3.92 (1H, dd, J = 3.0, 11.5 Hz, C5′-$\underline{H}^2$), 4.07 (1H,

app t, J = 6.5 Hz, C3′-H), 4.25 (1H, app t, J = 6.0 Hz, C2′-H), 5.26 (1H, d, J = 7.5 Hz, C5-H), 5.86 (1H, d, J = 6.0 Hz, C1′-H), 7.38-7.51 (6H, m, Ar-H), 7.58-7.68 (5H, m, Ar-H, C4-*H*); δ_C (100 MHz, DMSO-d_6), 19.3 (Si-C$(CH_3)_3$), 27.0 (Si-C$(CH_3)_3$), 28.7 (N-CH_3), 62.9 (C5′), 74.6 (C3′), 75.9 (C2′), 82.9 (C4′), 85.9 (C1′), 104.9 (C5), 128.4 (Ar-C), 128.4 (Ar-C), 130.4 (Ar-C), 130.5 (Ar-C), 132.9 (Quat. Ar-C), 133.2 (Quat Ar-C), 135.5 (Ar-C), 135.6 (Ar-C), 139.2 (C4), 153.6 (C2), 170.0 (C6); ν_{max} (thin film), 3304 (N-H), 1650 (C=O); m/z calculated for $C_{26}H_{33}N_3O_5Si$ $[M+H]^+$, 496.2262, found 496.2267.

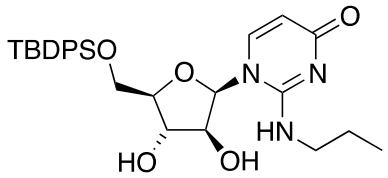
1.4.9 3-((2′*R*,3′*S*,4′*S*,5′*R*)-5′-((*tert*-Butyldiphenylsilyl)oxymethyl)-3′,4′-dihydroxyoxolan-2′-yl)-2- (ethylamino)pyrimidin-6(1H)-one 30b



Following general amination procedure from 5′-*O*-TBDPS-2,2′-anhydrouridine (100mg, 0.21 mmol, 1.0 eq) and ethylamine in 2.0M THF solution (1.05 mL, 2.1 mmol, 10.0 eq) 3-((2′*R*,3′*S*,4′*S*,5′*R*)-5′-((*tert*-Butyldiphenylsilyl)oxymethyl)-3′,4′-dihydroxyoxolan-2′-yl)-2-(ethylamino)pyrimidin-6(1H)-one was obtained as a colourless solid (71mg, 0.14 mmol, 65%), mp = 193-194 °C. A drop of D_2O was added to the analytical sample before the ^{1}H NMR analysis.

δ_H (400 MHz, DMSO-d_6), 0.99 (9H, s, C$(CH_3)_3$), 1.06 (3H, t, J = 7.0 Hz, CH_2CH_3), 3.17-3.33 (2H, m, N-CH_2), 3.76-3.79 (1H, m, C4′-H), 3.82 (1H, dd, J = 4.5, 11.5 Hz, C5′-H^1), 3.91 (1H, dd, J = 3.0, 11.5 Hz, C5′-H^2), 4.07 (1H, app t, J = 6.5 Hz, C3′-H), 4.26 (1H, app t, J = 6.0 Hz, C2′-H), 5.26 (1H, d, J = 7.5 Hz, C5-H), 5.83 (1H, d, J = 6.0 Hz, C1′-H), 7.38-7.49 (6H, m, Ar-H), 7.56-7.67 (5H, m, Ar-H, C4-H); δ_C (100 MHz, DMSO-d_6), 14.9 (CH_2CH_3), 19.3 (Si-C$(CH_3)_3$), 27.1 (Si-C$(CH_3)_3$), 36.2 (N-CH_2), 62.9 (C5′), 74.7 (C3′), 76.0 (C2′), 82.9 (C4′), 85.8 (C1′), 104.4 (C5), 128.4 (Ar-C), 128.4 (Ar-C), 130.4 (Ar-C), 130.5 (Ar-C), 132.9 (Quat. Ar-C), 133.2 (Quat Ar-C), 135.5 (Ar-C), 135.6 (Ar-C), 139.4 (*C*4), 153.1 (C2), 170.0 (C6); ν_{max} (thin film), 3303 (N-H), 1637 (C=O); m/z calculated for $C_{27}H_{35}N_3O_5Si$ $[M+H]^+$, 510.2419, found 510.2432.

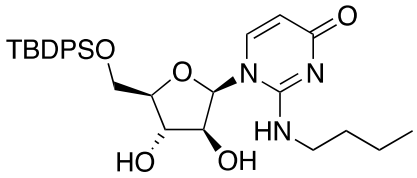
1.4.10 3-((2′*R*,3′*S*,4′*S*,5′*R*)-5′-((*tert*-Butyldiphenylsilyl)oxymethyl)-3′,4′-dihydroxyoxolan-2′-yl)-2-(propylamino)pyrimidin-6(1H)-one 30c



Following general amination procedure from 5′-*O*-TBDPS-2,2′-anhydrouridine (100 mg, 0.21 mmol, 1.0 eq) and propylamine (124 mg, 0.17 mL, 2.1 mmol, 10.0 eq) 3-((2′*R*,3′*S*,4′*S*,5′*R*)-5′-((*tert*-Butyldiphenylsilyl)oxymethyl)-3′,4′-dihydroxyoxolan-2′-yl)-2-(propylamino)pyrimidin-6(1H)-one was obtained as a colourless solid (80mg, 0.15 mmol, 73%), mp = 197-198°C. A drop of D_2O was added to the analytical sample before the ^1H NMR analysis.

δ_H (400 MHz, DMSO-d_6), 0.85 (3H, t, J = 7.5 Hz, $CH_2C\underline{H}_3$), 1.01 (9H, s, $C(C\underline{H}_3)_3$), 1.46-1.55 (2H, m, $C\underline{H}_2CH_3$), 3.09-3.25 (2H, m, N-$C\underline{H}_2$), 3.76-3.79 (1H, m, C4′-$\underline{H}$), 3.83 (1H, dd, J = 4.5, 11.5 Hz, C5′-$\underline{H}^1$), 3.91 (1H, dd, J = 3.0, 11.5 Hz, C5′-$\underline{H}^2$), 4.06 (1H, app t, J = 6.5 Hz, C3′-$\underline{H}$), 4.24 (1H, app t, J = 6.0 Hz, C2′-$\underline{H}$), 5.25 (1H, d, J = 7.5 Hz, C5-$\underline{H}$), 5.87 (1H, d, J = 6.0 Hz, C1′-$\underline{H}$), 7.41-7.50 (6H, m, Ar-$\underline{H}$), 7.57 (1H, J = 7.5 Hz, C4-$\underline{H}$), 7.61-7.65 (4H, m, Ar-$\underline{H}$); δ_C (100 MHz, DMSO-d_6), 11.8 ($CH_2\underline{C}H_3$), 19.3 (Si-$\underline{C}(CH_3)_3$), 22.2 ($\underline{C}H_2CH_3$), 27.1 (Si-C($\underline{C}H_3)_3$), 43.1 (N-$\underline{C}H_2$), 62.9 ($\underline{C}$5′), 74.5 ($\underline{C}$3′), 76.0 ($\underline{C}$2′), 82.8 ($\underline{C}$4′), 85.8 ($\underline{C}$1′), 105.0 ($\underline{C}$5), 128.4 (Ar-$\underline{C}$), 128.4 (Ar-$\underline{C}$), 130.4 (Ar-$\underline{C}$), 130.5 (Ar-$\underline{C}$), 132.9 (Quat. Ar-$\underline{C}$), 133.2 (Quat Ar-$\underline{C}$), 135.5 (Ar-$\underline{C}$), 135.6 (Ar-$\underline{C}$), 139.3 ($\underline{C}$4), 153.2 ($\underline{C}$2), 170.0 ($\underline{C}$6); ν_{max} (thin film), 3333 (N-H), 1636 (C=O); m/z calculated for $C_{28}H_{37}N_3O_5Si$ $[M+H]^+$, 524.2575, found 524.2590.

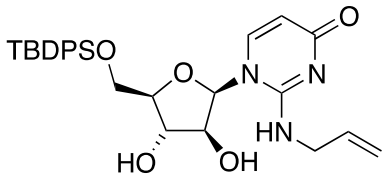
1.4.11 3-((2′*R*,3′*S*,4′*S*,5′*R*)-5′-((*tert*-Butyldiphenylsilyl)oxymethyl)-3′,4′-dihydroxyoxolan-2′-yl)-2-(butylamino)pyrimidin-6(1H)-one 30d



Following general amination procedure from 5′-O-TBDPS-2,2′-anhydrouridine (100mg, 0.21 mmol, 1.0 eq) and butylamine (154 mg, 0.21 mL, 2.1 mmol, 10.0 eq) 3-((2′*R*,3′*S*,4′*S*,5′*R*)-5′-((*tert*-Butyldiphenylsilyl)oxymethyl)-3′,4′-dihydroxyoxolan-2′-yl)-2-(butylamino)pyrimidin-6(1H)-one was obtained as a colourless solid (75mg, 0.14 mmol, 68%), mp = 199-200°C. A drop of D_2O was added to the analytical sample before the ^1H NMR analysis.

δ_H (400 MHz, DMSO-d_6), 0.87 (3H, t, J = 7.0 Hz, $CH_2C\underline{H}_3$), 1.00 (9H, s, $C(C\underline{H}_3)_3$), 1.23-1.32 (2H, m, $C\underline{H}_2CH_3$), 1.43-1.51 (2H, m, $C\underline{H}_2CH_2CH_3$), 3.13-3.29 (2H, m, N-$C\underline{H}_2$), 3.76-3.79 (1H, m, C4′-$\underline{H}$), 3.82 (1H, dd, J = 4.5, 11.5 Hz, C5′-$\underline{H}^1$), 3.91 (1H, dd, J = 3.0, 11.5 Hz, C5′-$\underline{H}^2$), 4.06 (1H, app t, J = 6.5 Hz, C3′-$\underline{H}$), 4.24 (1H, app t, J = 6.0 Hz, C2′-$\underline{H}$), 5.25 (1H, d, J = 7.5 Hz, C5-$\underline{H}$), 5.85 (1H, d, J = 6.0 Hz, C1′-$\underline{H}$), 7.40-7.50 (6H, m, Ar-$\underline{H}$), 7.56-7.66 (5H, m, Ar-$\underline{H}$, C4-$\underline{H}$); δ_C (100 MHz, DMSO-d_6), 14.3($CH_2\underline{C}H_3$), 19.3 (Si-$\underline{C}(CH_3)_3$), 20.1 ($\underline{C}H_2CH_3$), 27.1 (Si-C($\underline{C}H_3)_3$), 31.2 ($\underline{C}H_2CH_2CH_3$), 41.1 (N-$\underline{C}H_2$), 62.9 ($\underline{C}$5′), 74.7 ($\underline{C}$3′), 76.0 ($\underline{C}$2′), 82.9 ($\underline{C}$4′), 85.9 ($\underline{C}$1′), 105.0 ($\underline{C}$5), 128.4 (Ar-$\underline{C}$), 128.4 (Ar-$\underline{C}$), 130.4 (Ar-$\underline{C}$), 130.5 (Ar-$\underline{C}$), 132.9 (Quat. Ar-$\underline{C}$), 133.2 (Quat Ar-$\underline{C}$), 135.5 (Ar-$\underline{C}$), 135.6 (Ar-$\underline{C}$), 139.4 ($\underline{C}$4), 153.2 ($\underline{C}$2), 170.0 ($\underline{C}$6); ν_{max} (thin film), 3362 (N-H), 1636 (C=O); m/z calculated for $C_{29}H_{39}N_3O_5Si$ $[M+H]^+$, 538.2732, found 538.2735.

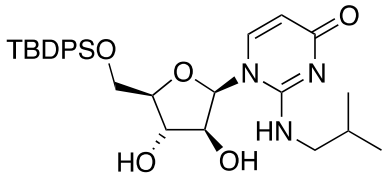
1.4.12 3-((2′*R*,3′*S*,4′*S*,5′*R*)-5′-((*tert*-Butyldiphenylsilyl)oxymethyl)-3′,4′-dihydroxyoxolan-2′-yl)-2-(allylamino)pyrimidin-6(1H)-one 30f



Following general amination procedure from 5′-*O*-TBDPS-2,2′-anhydrouridine (100mg, 0.21 mmol, 1.0 eq) and allylamine (120 mg, 0.17mL, 2.1 mmol, 10.0 eq) 3-((2′*R*,3′*S*,4′*S*,5′*R*)-5′-((*tert*-Butyldiphenylsilyl)oxymethyl)-3′,4′-dihydroxyoxolan-2′-yl)-2-(allylamino)pyrimidin-6(1H)-one was obtained as a colourless solid (72mg, 0.14 mmol, 66%), mp 185-186°C. A drop of D_2O was added to the analytical sample before the ^1H NMR analysis.

δ_H (400 MHz, DMSO-d_6), 1.01 (9H, s, C(C$\underline{H}_3)_3$), 3.78-3.93 (5H, m, C4′-$\underline{H}$, C5′-$\underline{H}^1$, C5′-$\underline{H}^2$, N-C$\underline{H}_2$), 4.08 (1H, app t, J = 6.5, C3′-$\underline{H}$), 4.26 (1H, app t, J = 6.0 Hz, C2′-$\underline{H}$), 5.06 (1H, d, J = 10.0 Hz, cis CH=C$\underline{H}_2$), 5.17 (1H, d, J = 17.0 Hz, trans CH=C$\underline{H}_2$), 5.25 (1H, d, J = 7.5 Hz, C5-$\underline{H}$), 5.82-5.89 (1H, m, CH_2-C$\underline{H}$=CH2), 5.91 (1H, d, J = 6.0 Hz, C1′-$\underline{H}$), 7.41-7.50 (6H, m, Ar-$\underline{H}$), 7.58-7.67 (5H, m, Ar-$\underline{H}$, C4-$\underline{H}$); δ_C (100 MHz, DMSO-d_6), 19.3 (Si-$\underline{C}$(C$H_3)_3$), 27.1 (Si-C(C$\underline{H}_3)_3$), 43.5 (N-$\underline{C}H_2$), 62.9 ($\underline{C}$5′), 74.5 ($\underline{C}$3′), 76.0 ($\underline{C}$2′), 82.9 ($\underline{C}$4′), 85.9 ($\underline{C}$1′), 105.2 ($\underline{C}$5), 115.6 (CH=$\underline{C}H_2$), 128.4 (Ar-$\underline{C}$), 128.4 (Ar-$\underline{C}$), 130.4 (Ar-$\underline{C}$), 130.5 (Ar-$\underline{C}$), 132.9 (Quat. Ar-$\underline{C}$), 133.2 (Quat Ar-$\underline{C}$), 135.5 (Ar-$\underline{C}$), 135.6 (Ar-$\underline{C}$), 135.8 ($\underline{C}$H=CH_2), 139.3 ($\underline{C}$4), 153.0 ($\underline{C}$2), 169.9 ($\underline{C}$6); ν_{max} (thin film), 3336 (N-H), 1638 (C=O); m/z calculated for $C_{28}H_{35}N_3O_5Si$ $[M+H]^+$, 522.2419, found 522.2436.

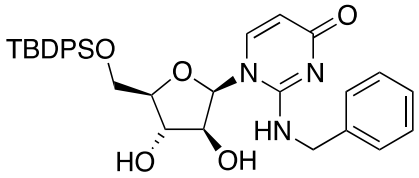
1.4.13 3-((2′*R*,3′*S*,4′*S*,5′*R*)-5′-((*tert*-Butyldiphenylsilyl)oxymethyl) -3′,4′-dihydroxyoxolan-2′-yl)-2-(*iso*-butylamino)pyrimidin-6(1H)-one 30e



Following general amination procedure from 5′-*O*-TBDPS-2,2′-anhydrouridine (100mg, 0.21 mmol, 1.0 eq) and *iso*-butylamine (154mg, 0.21 mL, 2.1 mmol, 10.0 eq) 3-((2′*R*,3′*S*,4′*S*,5′*R*)-5′-((*tert*-Butyldiphenylsilyl)oxymethyl) -3′,4′-dihydroxyoxolan-2′-yl)-2-(*iso*-butylamino)pyrimidin-6(1H)-one was obtained as a colourless solid (72mg, 0.13 mmol, 64%), mp = 197-198°C. A drop of D_2O was added to the analytical sample before the ^1H NMR analysis.

δ_H (400 MHz, DMSO-d_6), 0.91 (6H, d, J = 6.5 Hz, CH(C<u>H</u>$_3$)$_2$), 1.06 (9H, s, C(C<u>H</u>$_3$)$_3$), 1.89-1.99 (1H, m, C<u>H</u>(CH$_3$)$_2$), 3.01-3.16 (2H, m, N-C<u>H</u>$_2$), 3.82-3.85 (1H, m, C4′-<u>H</u>), 3.88 (1H, dd, J = 4.5, 11.5 Hz, C5′-<u>H</u>^{1}), 3.97 (1H, dd, J = 3.0, 11.5 Hz, C5′-<u>H</u>^{2}), 4.12 (1H, app t, J = 6.5 Hz, C3′-<u>H</u>), 4.30 (1H, app t, J = 6.0 Hz, C2′-<u>H</u>), 5.29 (1H, d, J = 7.5 Hz, C5-<u>H</u>), 5.94 (1H, d, J = 6.0 Hz, C1′-<u>H</u>), 7.46-7.56 (6H, m, Ar-<u>H</u>), 7.62 (1H, d, J = 7.5 Hz, C4-<u>H</u>), 7.66-7.72 (4H, m, Ar-<u>H</u>); δ_C (100 MHz, DMSO-d_6), 19.3 (Si-<u>C</u>(CH$_3$)$_3$), 20.6 (CH<u>C</u>H$_3$), 20.7 (CH<u>C</u>H$_3$), 27.1 (Si-C(<u>C</u>H$_3$)$_3$), 27.4 (<u>C</u>H(CH$_3$)$_2$), 48.8 (N-<u>C</u>H$_2$), 62.9 (<u>C</u>5′), 74.7 (<u>C</u>3′), 76.0 (<u>C</u>2′), 83.0 (<u>C</u>4′), 85.9 (<u>C</u>1′), 105.0 (<u>C</u>5), 128.3 (Ar-<u>C</u>), 128.4 (Ar-<u>C</u>), 130.4 (Ar-<u>C</u>), 130.5 (Ar-<u>C</u>), 132.9 (Quat. Ar-<u>C</u>), 133.2 (Quat Ar-<u>C</u>), 135.5 (Ar-<u>C</u>), 135.6 (Ar-<u>C</u>), 139.3 (<u>C</u>4), 153.3 (<u>C</u>2), 169.9 (<u>C</u>6); ν_{max} (thin film), IR 3336 (N-H), 1638 (C=O); m/z calculated for $C_{29}H_{39}N_3O_5Si$ $[M+H]^+$, 538.2732, found 538.2750.

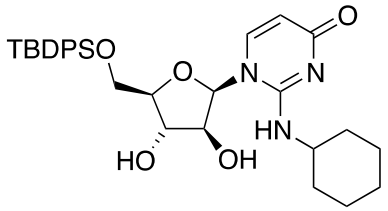
1.4.14 3-((2′*R*,3′*S*,4′*S*,5′*R*)-5′-((*tert*-utyldiphenylsilyl)oxymethyl)-3′,4′-dihydroxyoxolan-2′-yl)-2-(benzylamino)pyrimidin-6(1H)-one 30i



Following general amination procedure from 5′-*O*-TBDPS-2,2′-anhydrouridine (100mg, 0.21 mmol, 1.0 eq) and benzylamine (208 mg, 0.24 mL, 2.1 mmol, 10.0 eq) 3-((2′*R*,3′*S*,4′*S*,5′*R*)-5′-((*tert*-utyldiphenylsilyl)oxymethyl)-3′,4′-dihydroxyoxolan-2′-yl)-2-(benzylamino)pyrimidin-6(1H)-one was obtained as a colourless solid (67mg, 0.12 mmol, 56%), mp = 174-175°C. A drop of D_2O was added to the analytical sample before the ^1H NMR analysis.

δ_H (400 MHz, DMSO-d_6), 1.02 (9H, s, C(C$\underline{H}_3$)$_3$), 3.78-3.82 (1H, m, C4′-$\underline{H}$), 3.85 (1H, dd, J = 4.0, 11.5 Hz, C5′-$\underline{H}^1$), 3.93 (1H, dd, J = 3.0, 11.5 Hz, C5′-$\underline{H}^2$), 4.10 (1H, app t, J = 6.5 Hz, C3′-$\underline{H}$), 4.29 (1H, app t, J = 6.0 Hz, C2′-$\underline{H}$), 4.44-4.53 (2H, m, N-C$\underline{H}_2$), 5.25 (1H, d, J = 7.5 Hz, C5-$\underline{H}$), 5.96 (1H, d, J = 6.0 Hz, C1′-$\underline{H}$), 7.23-7.24 (1H, m, Ar-$\underline{H}$), 7.30-7.32 (3H, m, Ar-$\underline{H}$), 7.42-7.50 (6H, m, Ar-$\underline{H}$), 7.62-7.67 (5H, m, Ar-$\underline{H}$, C4-$\underline{H}$); δ_C (100 MHz, DMSO-d_6), 19.3 (Si-$\underline{C}$(CH$_3$)$_3$), 27.1 (Si-C($\underline{C}$H$_3$)$_3$), 44.2 (N-$\underline{C}$H$_2$), 62.9 ($\underline{C}$5′), 74.5 ($\underline{C}$3′), 76.5 ($\underline{C}$2′), 83.0 ($\underline{C}$4′), 86.0 ($\underline{C}$1′), 105.3 ($\underline{C}$5), 127.0 (Ar-$\underline{C}$), 127.5 (Ar-$\underline{C}$), 128.4 (Ar-$\underline{C}$), 128.5 (Ar-$\underline{C}$), 128.6 (Ar-$\underline{C}$), 130.4 (Ar-$\underline{C}$), 130.5 (Ar-$\underline{C}$), 132.9 (Quat. Ar-$\underline{C}$), 133.2 (Quat Ar-$\underline{C}$), 135.5 (Ar-$\underline{C}$), 135.6 (Ar-$\underline{C}$), 135.8 (Ar-$\underline{C}$), 139.3 ($\underline{C}$4), 140.0 (Quat. Ar-$\underline{C}$), 153.2 ($\underline{C}$2), 169.8 ($\underline{C}$6); ν_{max} (thin film), 3217 (N-H), 1640 (C=O); m/z calculated for $C_{32}H_{37}N_3O_5Si$ $[M+H]^+$, 572.2575, found 572.2600.

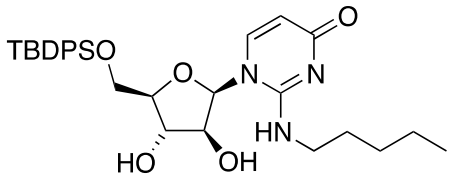
1.4.15 3-((2′*R*,3′*S*,4′*S*,5′*R*)-5′-((*tert*-Butyldiphenylsilyl)oxymethyl) -3′,4′-dihydroxyoxolan-2′-yl)-2-(cyclohexylamino)pyrimidin-6(1H)-one 30j



Following general amination procedure from 5′-*O*-TBDPS-2,2′-anhydrouridine (100mg, 0.21 mmol, 1.0 eq) and cyclohexylamine (183 mg, 2.1 mmol, 10.0 eq) 3-((2′*R*,3′*S*,4′*S*,5′*R*)-5′-((*tert*-Butyldiphenylsilyl)oxymethyl) -3′,4′-dihydroxyoxolan-2′-yl)-2-(cyclohexylamino)pyrimidin-6(1H)-one was obtained as a colourless solid (60mg, 0.11 mmol, 51%), mp = 178-179°C. A drop of D_2O was added to the analytical sample before the ^1H NMR analysis.

δ_H (400 MHz, DMSO-d_6), 0.98 (9H, s, C(C<u>H</u>$_3$)$_3$), 1.14-1.28 (1H, m, aryl-<u>H</u>), 1.13-1.29 (4H, m, aryl-<u>H</u>), 1.50-1.57 (1H, m, aryl-<u>H</u>), 1.61-1.68 (2H, m, aryl-<u>H</u>), 1.73-1.81 (2H, m, aryl-<u>H</u>), 3.72-3.78 (2H, m, C4′-<u>H</u>, NH-C<u>H</u>), 3.81 (1H, dd, J = 4.5, 11.5 Hz, C5′-<u>H</u>^{1}), 3.91 (1H, dd, J = 3.0, 11.5 Hz, C5′-<u>H</u>^{2}), 4.08 (1H, app t, J = 6.5, C3′-<u>H</u>), 4.28 (1H, app t, J = 6.0, C2′-<u>H</u>), 5.26 (1H, d, J=7.5 Hz, C5-<u>H</u>), 5.85 (1H, d, J = 6.0, C1′-<u>H</u>), 7.36-7.48 (6H, m, Ar-<u>H</u>), 7.57-7.61 (4H, m, Ar-<u>H</u>), 7.65 (1H, d, J = 7.5 Hz, C4-<u>H</u>); δ_C (100 MHz, DMSO-d_6), 15.6 (<u>C</u>H$_2$), 19.3 (Si-<u>C</u>(CH$_3$)$_3$), 25.5 (<u>C</u>H$_2$), 25.8 (<u>C</u>H$_2$), 27.1 (Si-C(<u>C</u>H$_3$)$_3$), 32.5 (<u>C</u>H$_2$), 32.7 (<u>C</u>H$_2$), 50.2 (N-<u>C</u>H), 63.0 (<u>C</u>5′), 74.7 (<u>C</u>3′), 76.0 (<u>C</u>2′), 82.9 (<u>C</u>4′), 85.7 (<u>C</u>1′), 105.0 (<u>C</u>5), 128.4 (Ar-<u>C</u>), 128.4 (Ar-<u>C</u>), 130.4 (Ar-<u>C</u>), 130.5 (Ar-<u>C</u>), 132.9 (Quat. Ar-<u>C</u>), 133.2 (Quat Ar-<u>C</u>), 135.4 (Ar-<u>C</u>), 135.6 (Ar-<u>C</u>), 139.7 (<u>C</u>4), 152.5 (<u>C</u>2), 169.9 (<u>C</u>6); ν_{max} (thin film), 3249 (N-H), 1636 (C=O); m/z calculated for $C_{31}H_{41}N_3O_5Si$ $[M+H]^+$, 564.2888, found 564.2912.

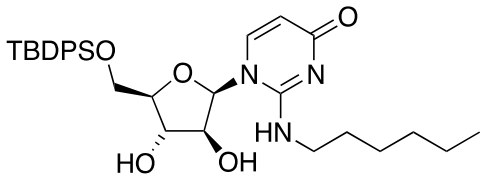
1.4.16 3-((2′*R*,3′*S*,4′*S*,5′*R*)-5′-((*tert*-Butyldiphenylsilyl)oxymethyl) -3′,4′-dihydroxyoxolan-2′-yl)-2-(pentylamino)pyrimidin-6(1H)-one 30g



Following general amination procedure from 5′-*O*-TBDPS-2,2′-anhydrouridine (100mg, 0.21 mmol, 1.0 eq) and amylamine (183 mg, 0.24 mL, 2.1 mmol, 10.0 eq) 3-((2′*R*,3′*S*,4′*S*,5′*R*)-5′-((*tert*-Butyldiphenylsilyl)oxymethyl) -3′,4′-dihydroxyoxolan-2′-yl)-2-(pentylamino)pyrimidin-6(1H)-one was obtained as a colourless solid (71mg, 0.13 mmol, 61%), mp = 185-186°C. A drop of D_2O was added to the analytical sample before the ^1H NMR analysis.

δ_H (400 MHz, DMSO-d_6), 0.86 (3H, t, J = 7.0 Hz, C$\underline{H}_3$), 1.01 (9H, s, C(C$\underline{H}_3$)$_3$), 1.22-1.33 (4H, m, alkyl-$\underline{H}$), 1.46-1.54 (2H, m, NCH$_2$C$\underline{H}_2$), 3.12-3.29 (2H, m, N-C$\underline{H}_2$), 3.76-3.79 (1H, m, C4′-$\underline{H}$), 3.82 (1H, dd, J = 4.5, 11.5 Hz, C5′-$\underline{H}^1$), 3.92(1H, dd, J = 3.0, 11.5 Hz, C5′-$\underline{H}^2$), 4.06 (1H, app t, J = 6.5, C3′-$\underline{H}$), 4.26 (1H, app t, J = 6.0, C2′-$\underline{H}$), 5.24 (1H, d, J = 7.5 Hz, C5-$\underline{H}$), 5.87 (1H, d, J = 6.0, C1′-*H*), 7.40-7.50 (6H, m, Ar-$\underline{H}$), 7.56 (1H, d, J = 7.5 Hz, C4-$\underline{H}$), 7.61-7.67 (4H, m, Ar-$\underline{H}$); δ_C (100 MHz, DMSO-d_6), 14.4 (CH$_2$C$\underline{H}_3$), 19.3 (Si-$\underline{C}$(CH)$_3$), 22.5 (CH$_3$C$\underline{H}_2$), 27.1 (Si-C(C$\underline{H}_3$)$_3$), 28.7 (C$\underline{H}_2$), 29.1 (C$\underline{H}_2$), 41.4 (N-C$\underline{H}_2$), 62.9 (C$\underline{5}$′), 74.7 (C$\underline{3}$′), 76.0 (C$\underline{2}$′), 82.9 (C$\underline{4}$′), 85.8 (C$\underline{1}$′), 104.9 (C$\underline{5}$), 128.4 (Ar-$\underline{C}$), 128.4 (Ar-$\underline{C}$), 130.4 (Ar-$\underline{C}$), 130.5 (Ar-$\underline{C}$), 132.9 (Quat. Ar-$\underline{C}$), 133.2 (Quat Ar-$\underline{C}$), 135.4 (Ar-$\underline{C}$), 135.6 (Ar-$\underline{C}$), 139.4 (C$\underline{4}$), 153.1 (C$\underline{2}$), 170.0 (C$\underline{6}$); ν_{max} (thin film), 3363 (N-H), 1634 (C=O); m/z calculated for $C_{30}H_{41}N_3O_5Si$ $[M+H]^+$, 552.2888, found 552.2911.

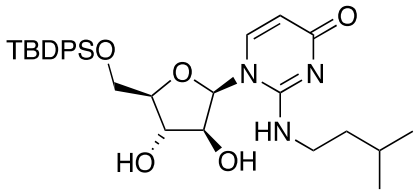
1.4.17 3-((2′*R*,3′*S*,4′*S*,5′*R*)-5′-((tert-Butyldiphenylsilyl)oxymethyl)-3′,4′-dihydroxyoxolan-2′-yl)-2-(hexylamino)pyrimidin-6(1H)-one 30h



Following general amination procedure from 5′-*O*-TBDPS-2,2′-anhydrouridine (100mg, 0.21 mmol, 1.0 eq) and hexylamine (212mg, 0.28 mL, 2.1 mmol, 10.0 eq) 3-((2′*R*,3′*S*,4′*S*,5′*R*)-5′-((tert-Butyldiphenylsilyl)oxymethyl)-3′,4′-dihydroxyoxolan-2′-yl)-2-(hexylamino)pyrimidin-6(1H)-one was obtained as a colourless solid (62mg, 0.11 mmol, 52%), mp = 181-182°C. A drop of D_2O was added to the analytical sample before the ^1H NMR analysis.

δ_H (400 MHz, DMSO-d_6), 0.81 (3H, t, J = 7.0 Hz, C$\underline{H}_3$), 0.98 (9H, s, C(C$\underline{H}_3$)$_3$), 1.19-1.26 (6H, m, alkyl-$\underline{H}$), 1.42-1.50 (2H, m, NCH$_2$C$\underline{H}_2$), 3.12-3.29 (2H, m, N-C$\underline{H}_2$), 3.75-3.79 (1H, m, C4′-$\underline{H}$), 3.82 (1H, dd, J = 4.5, 11.5 Hz, C5′-$\underline{H}^1$), 3.91-3.93 (1H, m, C5′-$\underline{H}^2$), 4.07 (1H, app t, J = 6.5, C3′-$\underline{H}$), 4.26 (1H, app t, J = 6.0, C2′-$\underline{H}$), 5.26 (1H, d, J=7.5 Hz, C5-$\underline{H}$), 5.84 (1H, d, J = 6.0, C1′-$\underline{H}$), 7.38-7.48 (6H, m, Ar-$\underline{H}$), 7.58-7.64 (4H, m, Ar-$\underline{H}$, C4-$\underline{H}$); δ_C (100 MHz, DMSO-d_6), 14.4 (CH$_2$*C*H$_3$), 19.3 (Si-$\underline{C}$(CH$_3$)$_3$), 22.6 (CH$_3$$\underline{C}H_2$), 26.6 ($\underline{C}H_2$), 27.1 (Si-C($\underline{C}H_3$)$_3$), 29.0 ($\underline{C}H_2$), 31.6 ($\underline{C}H_2$), 41.4 (N-$\underline{C}H_2$), 62.9 ($\underline{C}$5′), 74.7 ($\underline{C}$3′), 76.0 ($\underline{C}$2′), 82.9 ($\underline{C}$4′), 85.3 ($\underline{C}$1′), 104.9 ($\underline{C}$5), 128.4 (Ar-$\underline{C}$), 128.4 (Ar-$\underline{C}$), 130.4 (Ar-$\underline{C}$), 130.5 (Ar-$\underline{C}$), 132.9 (Quat. Ar-$\underline{C}$), 133.2 (Quat Ar-$\underline{C}$), 135.4 (Ar-$\underline{C}$), 135.5 (Ar-$\underline{C}$), 139.4 ($\underline{C}$4), 153.1 ($\underline{C}$2), 170.0 ($\underline{C}$6); ν_{max} (thin film), 3364 (N-H), 1635 (C=O); m/z calculated for $C_{31}H_{43}N_3O_5Si$ $[M+H]^+$, 566.3045, found 566.3052.

1.4.18 3-((2′*R*,3′*S*,4′*S*,5′*R*)-5′-((*tert*-Butyldiphenylsilyl)oxymethyl)-3′,4′-dihydroxyoxolan-2′-yl)-2-(*iso*-pentylamino)pyrimidin-6(1H)-one 30k



Following general amination procedure from 5′-*O*-TBDPS-2,2′-anhydrouridine (100mg, 0.21 mmol, 1.0 eq) and *iso*-pentylamine (183 mg, 0.24 mL, 2.1 mmol, 10.0 eq) 3-((2′*R*,3′*S*,4′*S*,5′*R*)-5′-((*tert*-Butyldiphenylsilyl)oxymethyl)-3′,4′-dihydroxyoxolan-2′-yl)-2-(*iso*-pentylamino)pyrimidin-6(1H)-one was as a colourless solid (67mg, 0.12 mmol, 58%), mp = 182-183°C. A drop of D_2O was added to the analytical sample before the ^1H NMR analysis.

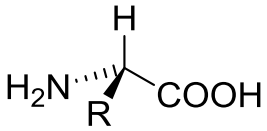
δ_H (400 MHz, DMSO-d_6), 0.89 (6H, d, J = 6.5 Hz, $CH_2(C\underline{H}_3)_2$), 1.02 (9H, s, $C(\underline{C}H_3)_3$), 1.38-1.43 (2H, m, $C\underline{H}_2CH(CH_3)_2$), 1.54-1.64 (1H, m, $\underline{C}H(CH_3)_2$), 3.15-3.32 (2H, m, N-$C\underline{H}_2$), 3.76-3.79 (1H, m, C4′-H), 3.82 (1H, dd, J = 4.5, 11.5 Hz, C5′-$\underline{H}^1$), 3.91 (1H, dd, J = 3.0, 11.5 Hz, C5′-$\underline{H}^2$), 4.06 (1H, app t, J = 6.5, C3′-H), 4.23 (1H, app t, J = 6.0, C2′-H), 5.24 (1H, d, J = 7.5 Hz, C5-H), 5.86 (1H, d, J = 6.0, C1′-H), 7.42-7.48 (7H, m, Ar-H), 7.61-7.66 (5H, m, Ar-H, C4-*H*); δ_C (100 MHz, DMSO-d_6), 19.3 (Si-$\underline{C}(CH_3)_3$), 23.0 ($CH\underline{C}H_3$), 25.8 ($\underline{C}H(CH_3)_2$), 27.1 (Si-C($\underline{C}H)_3$), 38.0 ($NHCH_2\underline{C}H_2$), 39.7 (N-$\underline{C}H_2$), 62.9 (C5′), 74.7 (C3′), 76.0 (C2′), 82.9 (C4′), 85.8 (C1′), 105.0 (C5), 128.4 (Ar-C), 128.4 (Ar-C), 130.4 (Ar-C), 130.5 (Ar-C), 132.9 (Quat. Ar-C), 133.2 (Quat Ar-C), 135.5 (Ar-C), 135.6 (Ar-C), 139.4 (C4), 153.1 (C2), 169.9 (C6); ν_{max} (thin film), 3330 (N-H), 1637 (C=O); m/z calculated for $C_{30}H_{41}N_3O_5Si$ $[M+H]^+$, 552.2888, found 552.2906

2. Functionalised Amino Acids *via* the Belluš-Claisen Rearrangement

2.1 Introduction

2.1.1 Amino Acids and Peptides

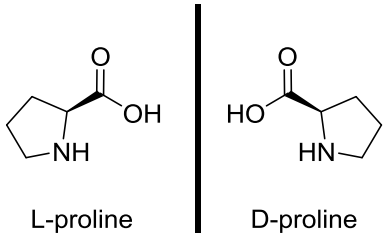
Amino acids are organic molecules that have both an amine (-NH_2) and a carboxyl (-COOH) functional group.[64] Amino acids usually refers to the amino-alkanoic acids, N_3H^+-$(CR^1R^2)_n$-CO_2- where n = 1 for α–amino acids, n = 2 for β–amino acids and so on. Figure 7 depicts the structure of an α–amino acid where R is a side chain. The differing side groups, R, determine the properties of the amino acids.



31

Figure 7: *α–Amino Acid Structure*[65]

Hundreds of amino acids have been discovered which occur in living organisms and the majority are α-amino acids.[66] They can be present as a single amino acid or as components of peptides, proteins and other amides.[64] A peptide consists of a chain of fifty amino acids or less which are joined by peptide bonds. A polypeptide consists of chains of more than fifty amino acids and proteins are formed of several polypeptides.[65] Nineteen α–amino acids and one α–imino acid, proline,[67] are used by cells for protein synthesis. These are called proteogenic, or primary, amino acids and are found within proteins that are coded for the standard genetic code.[65] With the exception of glycine, all proteogenic amino acids have an asymmetric centre and thus can have two enantiomers.[68] Enantiomers are non-superimposable mirror images (Figure 8).[69] Proteins and the majority of naturally occurring peptides contain the L-amino acids.



L-proline **32** D-proline **33**

Figure 8: *Enantiomers of Proline*

Amino acids have shown a wide range of biological activities and are used for a range of treatments. For example, tyrosine is a precursor of the neurotransmitters norepinephrine, epinephrine and dopamine which are used for mood regulation and therefore tyrosine supplements have been used for stress reduction.[70,71] Cysteine is needed for the skin facilitating the production of collagen and it also helps in detoxifying harmful toxins. Cysteine supplements have also been tried in the treatment of arthritis.[72,73] L-Glutamine is used to maintain the lining of the gut as well as other essential functions such as the immune system. L-Glutamine supplements have been used to treat Irritable Bowel Syndrome.[74] Further, in addition to nutritional supplements, amino acids are used in the synthesis of other products such as cosmetics and surfactants.[75,76]

Most proteogenic acids are readily available, and can be bought in gram quantities for a modest cost especially compared to other enantiomerically pure compounds. However, in addition to the primary amino acids, there are hundreds of non-proteogenic amino acids that are not used in protein synthesis.[64] These have become important as tools for modern drug discovery research, particularly when incorporated into peptides.[77,78] It is possible to acquire non-proteogenic amino acids from nature, but this involves harvesting from natural sources that can be time-consuming and expensive. Therefore it is preferable to synthesize these products in the laboratory where possible.

This study investigates the application of Belluš-Claisen rearrangement as a method of producing non-protegenic amino acids and dipeptides in a one-pot reaction.

2.1.2 The Claisen Rearrangement

The Claisen rearrangement has seen wide use in synthetic organic chemistry because of the stereoselective nature of the bond formation, and the potential to obtain useful polyfunctionalised products.[79,80] The reaction's usefulness is reflected in the extensive

library of research that has been published and modern variants have secured the continued reputation of this highly useful synthetic tool.[79]

The process discovered in 1912 by Ludwig Claisen, was the first recorded example of a [3,3]-sigmatropic rearrangement.[81,80] A sigmatropic rearrangement occurs in an intramolecular process whereby a σ-bond is created between atoms that were not linked and a previous bond is broken i.e. the σ-bond migrates (Figure 9 and Figure 10).

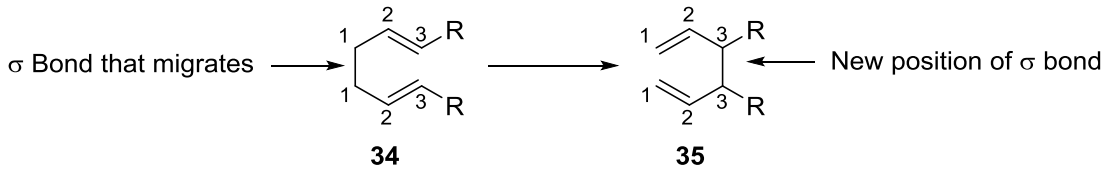


Figure 9: *A [3,3] sigmatropic rearrangement*[82]

Two numbers set in the brackets [i,j] are used to specify the order of a sigmatropic rearrangement. These numbers can be ascertained by counting the atoms from the original position that the σ–bond has moved from. Each of the original termini is given the number 1. Thus in Figure 9, each terminus of the σ-bond has migrated from C-1 to C-3, so the order is [3,3].

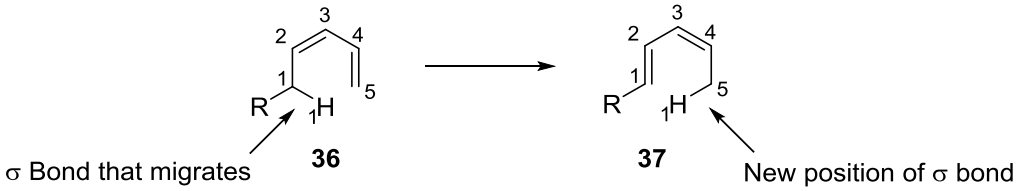
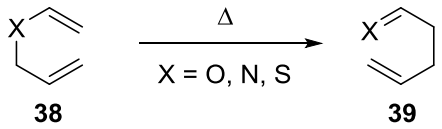


Figure 10: *A [1,5] sigmatropic rearrangement*[82]

In Figure 10, the carbon terminus has moved from C-1 to C-5, but the hydrogen terminus has not moved at all, so the order is [1,5].[82]

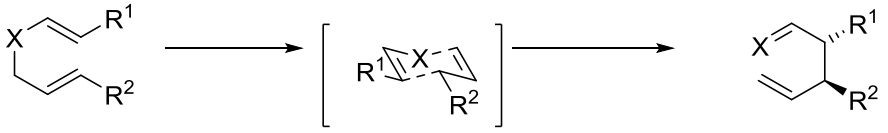
The [3,3]-sigmatropic rearrangement is a reliable and proven method for the stereoselective construction of carbon–carbon or carbon–heteroatom bonds.[83] The Claisen rearrangement is a [3,3]-sigmatropic rearrangement of an allyl vinyl ether **38** to give the corresponding γ,δ-unsaturated carbonyl compound **39** (Scheme 11).[80] Formerly, the Claisen reaction specifically refers to an allylic ether, with the aza-Claisen and thio-Claisen referring to rearrangements of allylic amines and allylic sulphides respectively.



38 **39**

Scheme 11: *The Claisen Rearrangement*[80]

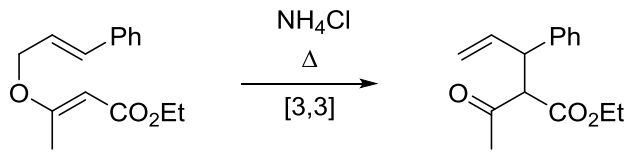
Claisen substrates proceed through highly ordered six-membered transition states allowing control over the stereochemistry depending on the precursors. (Scheme 12).[84]



40 **41** **42**

Scheme 12: *Highly ordered six-membered transition state*[84]

Subsequent research by other groups found that the conditions reported by Claisen on aromatic substrates could be successfully applied to aliphatic skeletons. For example, ethyl β-cinnamyloxycrotonate **43** undergoes a [3,3] rearrangement to give β–keto ester **44** under heating in the presence of ammonium chloride (Scheme 13).[80,85]



43 **44**

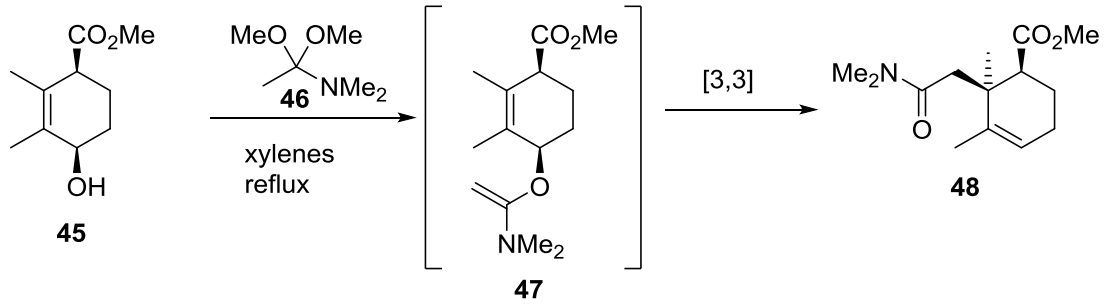
Scheme 13: *Rearrangement of ethyl β-cinnamyloxycrotonate*

Claisen rearrangements of allyl vinyl ethers need high temperatures, about 200 °C.[86] Such harsh conditions can lead to decomposition of the final product. Further, synthesis of the vinyl ether moiety starting material is a challenging process. Many variants have been reported where attempts have been made to enable a synthetically useful process using milder experimental conditions, faster reaction times or generating the intermediate *in situ* to bypass the need to synthesize the starting material separately.[80,85] The methods used included the use of different substituents, different methods to access a suitable intermediate to undergo [3,3] sigmatropic rearrangement and variations in the carbon skeleton of the substrate as well as the catalyst, if any.[80,87] Some examples are discussed below.

2.1.3 Claisen Variants

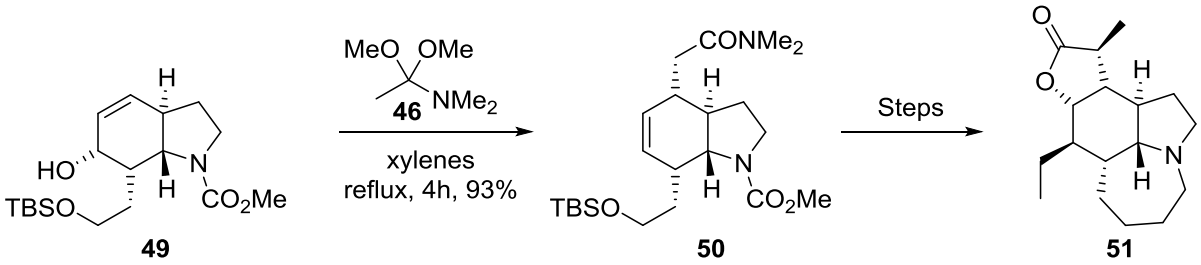
2.1.3.1 The Eschenmoser-Claisen Rearrangement.

The Eschenmoser-Claisen rearrangement is considered to be one of the more useful pericyclic reactions.[88] Building on the investigation of amide acetals by Meerwein *et al*.,[89] Eschenmoser reported that heating allylic alcohols **45** with dimethylacetamide dimethyl acetal **46** gave γ,δ-unsaturated amide **48** (Scheme 14).[84,90] Following alcohol exchange and elimination of methanol intermediate ketene *N*,*O*-acetal **47** is formed *in situ*. This undergoes [3,3] sigmatropic rearrangement to give resulting product. The electron donating amino substituent in the intermediate drastically increases the reaction rate of the pericyclic step.[84]



***Scheme 14**: The Eschenmoser–Claisen Rearrangement*

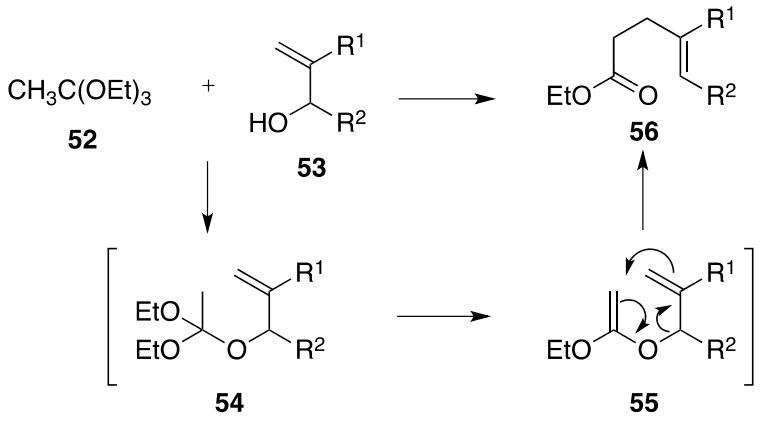
Compared to the Johnson and Ireland variants mentioned below, the Eschenmoser version often provides better yields with superior stereo-selectivity. The reaction also has the advantage of employing neutral conditions in the formation of the *N*,*O*-ketene intermediate which allows sensitive substrates to be used in the reaction, provided that they can withstand the high temperatures that are frequently required. The Eschenmoser–Claisen rearrangement has proven to have extensive scope and has been used in the synthesis of complex molecules,[91] steroids,[92] drugs and natural products.[93,94,] Hart and Chen (1993) employed the Eschenmoser-Claisen rearrangement as one of the key steps in the first total synthesis of stenine **51**[95]. The primary alcohol had to be TBS protected to prevent competitive activation and cyclization. After protection, silyl ether **49** was refluxed with dimethylacetamide dimethyl acetal **46** in xylenes for 4 hours to give the desired amide **50** in excellent 93% yield (Scheme 15).



***Scheme 15**: The Eschenmoser–Claisen Rearrangement used in total synthesis of stenine **51**[95]*

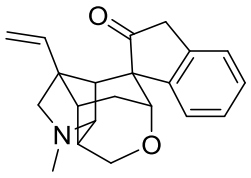
2.1.3.2 The Johnson Rearrangement.

The Johnson-Claisen rearrangement is closely related to the Eschenmoser rearrangement, proceeding through a ketene acetal. Here, an allylic alcohol **53** is heated with ethyl orthoacetate **52** and acid to give mixed ortho ester **54**. The ortho ester **54** then loses ethanol to generate the ketene acetal **55** which proceeds to undergo rearrangement to give to γ,δ-unsaturated ester **56** (Scheme 16).[96] The traditional Claisen rearrangement, namely the allyl vinly ether rearrangement, is typically a two-step process but in the Johnson-Claisen rearrangement the ketene acetal formation and the rearrangement are completed in one step.[90]



***Scheme 16**: The Johnson–Claisen Rearrangement*

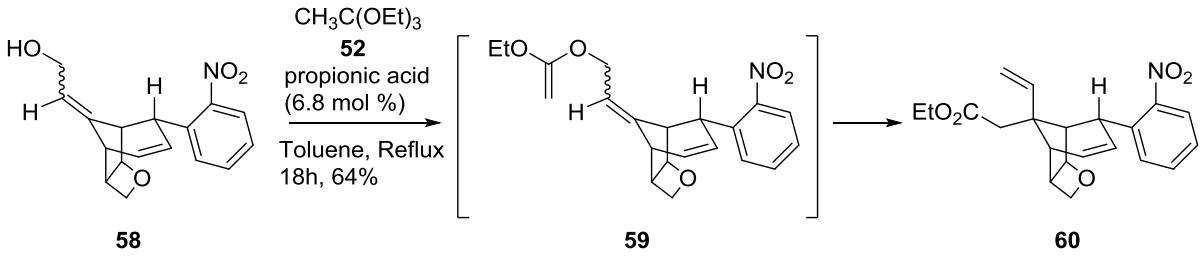
The Johnson-Claisen rearrangement has been used in the synthesis of steroids,[97] prostaglandins,[98] antitumour compounds,[99] and alkaloids.[100,101] Danishefsky *et al.* (2002) used the Johnson-Claisen rearrangement to synthesize a key intermediate in their total synthesis of gelsemine (Figure 11).



57

***Figure 11**: Gelsemine*

A Horner-Wadsworth-Emmons condensation, followed by reduction of the ketone of the allylic alcohol, gave a mixture of stereiosmers **58**. The Johnson-Claisen rearrangement was cleverly employed whereby treatment with triethylorthoacetate and a catalytic amount of propionic acid gave the identical γ,δ-unsaturated ester **60** with both the β-vinyl and α-caroxymethyl functionalities at the correct positions for the following synthetic steps (Scheme 17)[102].

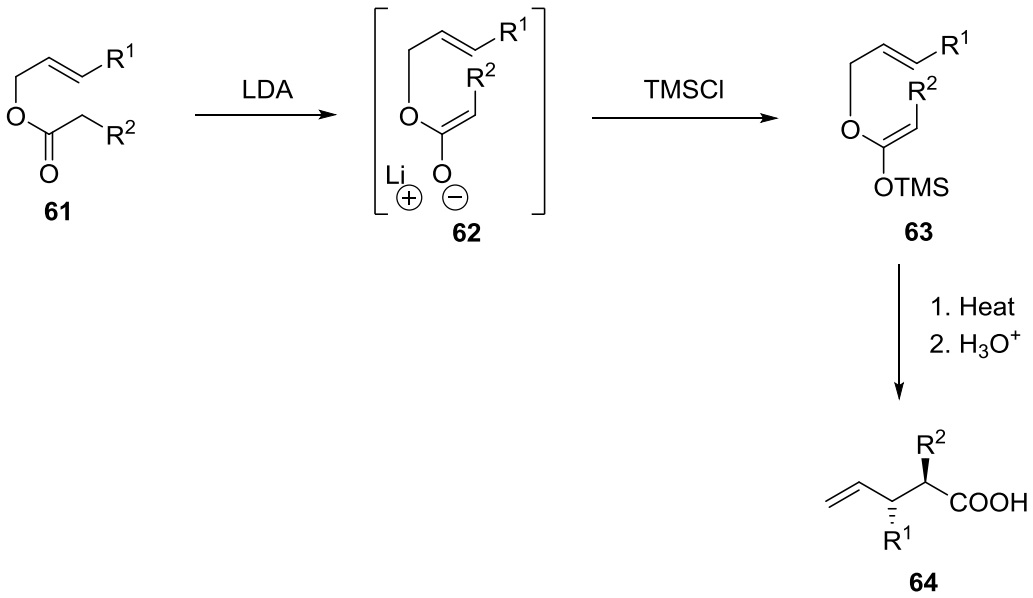


58 **59** **60**

***Scheme 17**: Synthesis of γ,δ-unsaturated ester **60** [102]*

2.1.3.3 The Ireland-Claisen Rearrangement

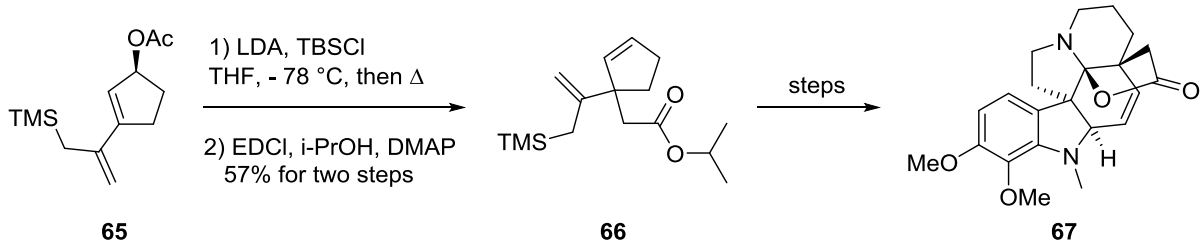
The Ireland-Claisen rearrangement represented a significant development of the Claisen rearrangement because, compared to other rearrangements, this reaction proceeded under milder conditions with temperatures under 100°C.[103,104]The inspiration for this work was a study by Rathke and Lindert in 1971, who demonstrated that it was possible to generate ester enolates under mild conditions.[105,106] Ireland and Mueller reported the rearrangement of allyl trimethylsilyl ketene acetal **63**, prepared by formation of allylic ester enolate **62** from ester **61** followed by reaction with trimethylsilyl chloride. The subsequent rearrangement followed by hydrolysis gave the γ,δ-unsaturated carboxylic acid **64** (Scheme 18).



Scheme 18: *Ireland-Claisen Rearrangement*[103]

The Ireland-Claisen reaction has a number of advantages including the ease of synthesis of the ester enolate, the ability to control E/Z selectivity in the product, a frequently high degree of transference of chirality from the starting material to the newly formed stereocenters in product **64** and a high degree of alkene stereocontrol. It has thus been widely developed in organic syntheses and has been used in various applications including the synthesis of polyether antibiotics[107], natural products[108] and the preparation of polyfunctionalised structures.[80,109]

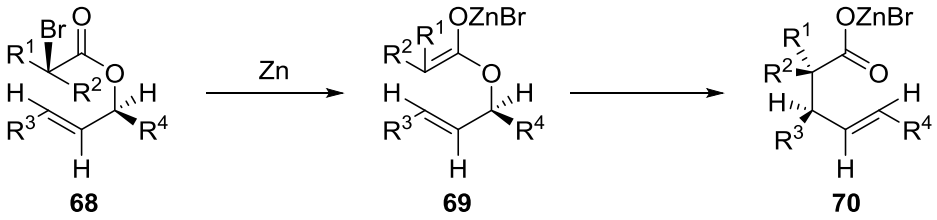
Corey *et al*. (1999) used the Ireland-Claisen rearrangement as part of the first total synthesis of aspidophytine **67** more than a quarter of a century after the elucidation of its structure.[110] A key intermediate, isopropyl ester **66**, was derived by treating allylic acetate **65** with LDA and TBSCl to give a chiral carboxylic acid. Esterification with EDCl as the coupling reagent provided the desired ester in 57% overall yield (Scheme 19).



Scheme 19: *Ireland-Claisen Rearrangement used in total synthesis of aspidophytine* ***67*** [110]

2.1.3.4 The Reformatsky-Claisen Rearrangement.

The [3,3] sigmatropic rearrangement of zinc enolates, termed the Reformatsky-Claisen rearrangement, was reported in 1973.[111] Baldwin's study showed that zinc enolates, generated by the Reformatsky reaction of α–haloesters **68** with zinc dust, at 80 to 140 °C, led to the corresponding γ,δ-unsaturated zinc carboxylates **70** *via* enolate **69** (Scheme 20). This work was significant in that it proceeded under neutral conditions. Yields varied widely depending upon substitution and the solvent used. For example, when R^1=R^2=Me and R^3=R^4=H, using the solvent was benzene and a temperature of 80°C, a stoichiometric yield was reported. The yield drastically changed to less than 15% when R^1=R^2=R^3=R^4=H, xylene was the solvent and the temperature was 140 °C.[111]

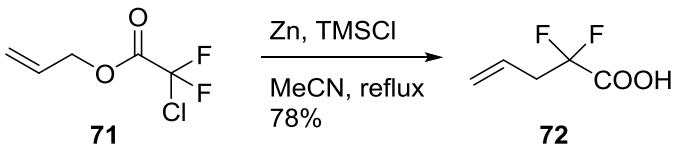


68 **69** **70**

Scheme 20: *Reformatsky-Claisen Rearrangement*[111]

The Reformatsky-Claisen rearrangement will also proceed when a silylating agent is used, where the most probable intermediate is a silyl ketene acetal. The rearrangement most often reported in the literature involve heating a substrate with zinc dust and a silylating reagent in a polar aprotic solvent.[84,112,113]

An example of its synthetic application was the rearrangement of fluorinated substrates. Fluorinated ketones have been found to be effective enzyme inhibitors.[114] With this discovery the ability to synthesize molecules with fluorine substituents adjacent to a carbonyl group became a major research target. This was one of the earliest applications of the Reformatsky-Claisen rearrangement, for example the conversion of allyl chlorodifluoroacetate **71** to difluoroacid **72** (Scheme 21).[115]

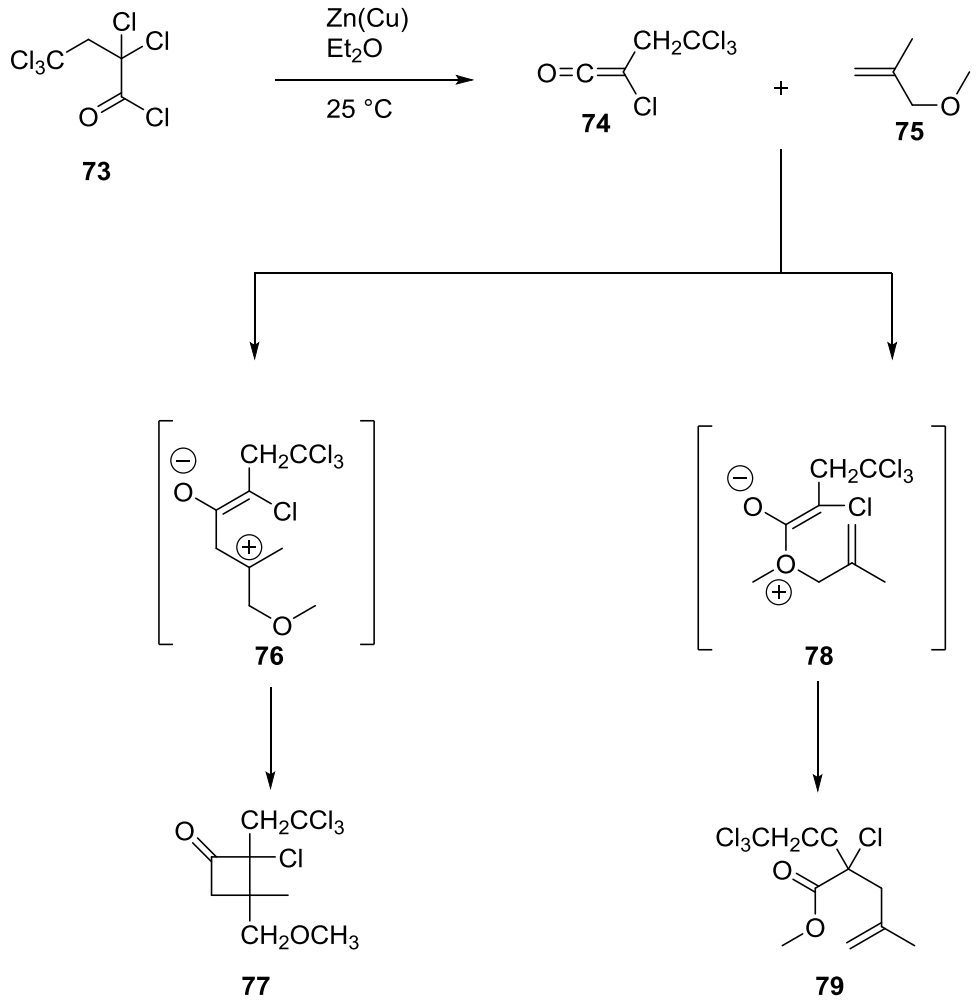


71 **72**

Scheme 21: *Synthesis of difluoroacid* ***72***[115]

2.1.4 The Belluš-Claisen Rearrangement

In 1978, Belluš and Malherbe discovered a new ketene-Claisen reaction during an attempt to prepare the 2-chlorocyclobutanone derivative **77** (Scheme 22).[116,117]



Scheme 22: *First observation of the Belluš-Claisen Rearrangement*[116]

Chloro(trichloroethyl)ketene **74** was prepared from acyl chloride **73** *via* zinc copper couple catalysed dehalogenation. When ketene **74** was then reacted with allylic ether **75** at ambient room temperature a mixture of products was obtained, comprised of the desired [2+2] cycloaddition product **77** and the γ,δ-unsaturated ester **79**. On analysis it was found that this byproduct was the result of an alternate reaction pathway, where the nucleophilic oxygen atom of the allylic ether **75** can compete successfully with the double bond in **75** for the electrophilic ketene. This meant that, as well as expected intermediate **76**, zwitterionic enolate intermediate **78** was also formed. This is perfectly set up to undergo [3,3]-sigmatropic rearrangements to give γ,δ- unsaturated ester **79**.

The original Claisen reaction required high temperatures and since the 1970s, cation-accelerated and anion-accelerated rearrangements have been utilised to reduce the temperature of the reaction, speed up the rate and to enable the synthesis of a wider range of molecules that might otherwise decompose at higher temperatures.[118,119] For example, the Ireland Claisen rearrangement is an anion accelerated process.[103,120] The Belluš-Claisen rearrangement was the first reported rearrangement that had a zwitterionic intermediate.[116] The effect on the reaction is extraordinary and is due to charge neutralisation providing a significant driving force. Whereas a typical Claisen rearrangement needs temperatures in excess of 150°C to proceed, the Belluš-Claisen rearrangement will occur readily at room temperature.

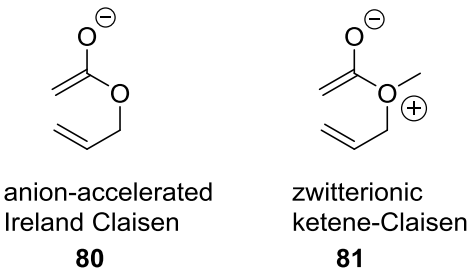
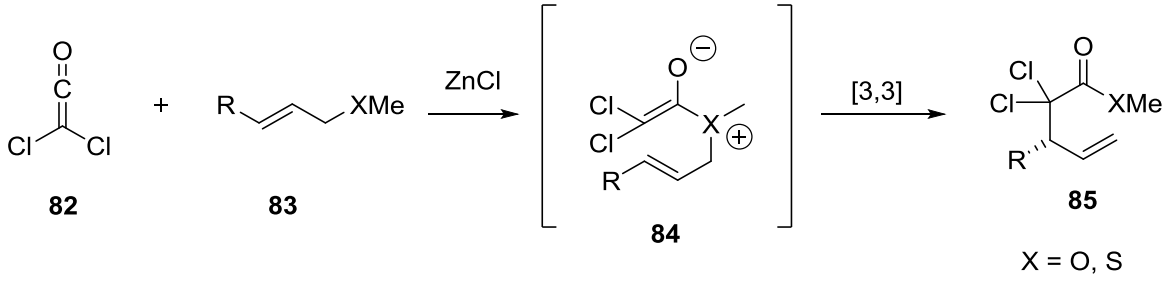


Figure 12: *Dipole Accelerated Claisen Rearrangements*

It was reported that the new reaction could tolerate a broad range of cyclic and acyclic ethers and sulfides **83** to give the corresponding of γ,δ-unsaturated ester and thioester **85** (Scheme 23).[116]

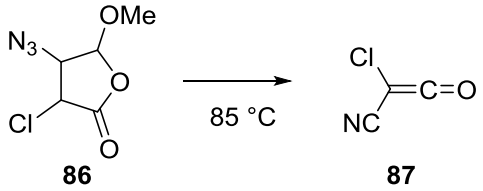


Scheme 23: *General scheme for first reported Belluš-Claisen Rearrangement*[116]

This research inspired work undertaken by the MacMillan group, who conducted a thorough investigation into a novel acyl-Claisen reaction based on the Belluš-Claisen variant. The range of ketenes that could be used were highly limited and it was reported that only highly electrophilic ketenes such as dichloroketene and chloro(trichloroethyl)ketene were found to work satisfactorily.[117] Detailed inspection of these reports by the MacMillan group discovered an alternate explanation. They reported

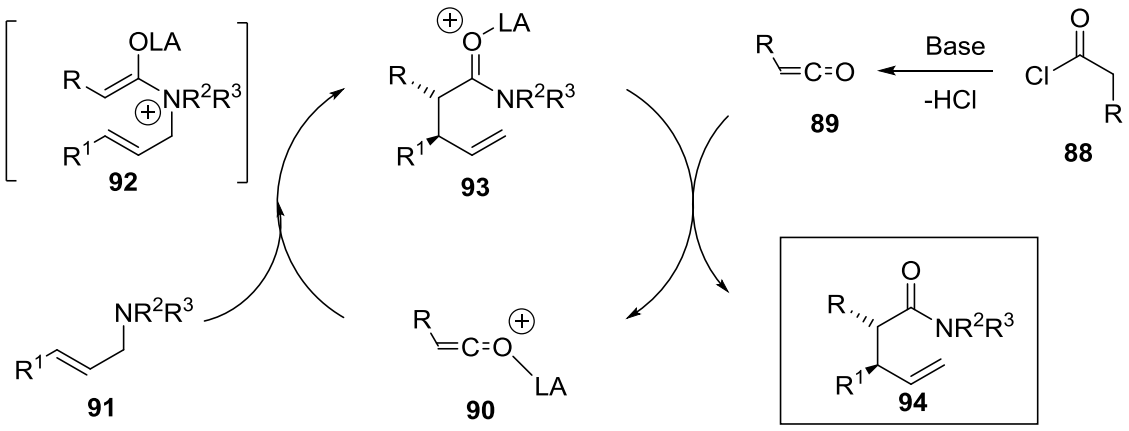
that the only productive reactions were those where the ketenes were generated by *in situ* zinc dehalogenation.[121] The MacMillan group determined that the zinc chloride ($ZnCl_2$) produced during the reaction was not just an unwanted by-product, but in fact, was an essential part of the reaction[122]. Using Lewis acids to activate ketenes is not an unknown process[123] and it seemed likely that a Lewis acid was activating the ketene towards nucleophilic attack.

This theory was supported by attempts to use chlorocyanoketene **87**, a highly electron deficient ketene, in the Belluš-Claisen reaction. The chlorocyanoketene was generated by thermolysis (Scheme 24) and the reaction was therefore performed without any Lewis acidic metal salt to act as a catalyst. Less than 5% of the product arising from a Claisen rearrangement could be isolated, even when elevated temperatures were used.[124]



Scheme 24: *Generation of chlorocyanoketene*[124]

The MacMillan group determined that Lewis acid activated ketene **90** would be susceptible to the addition of a tertiary allylic amine **91** (Scheme 25).[124]

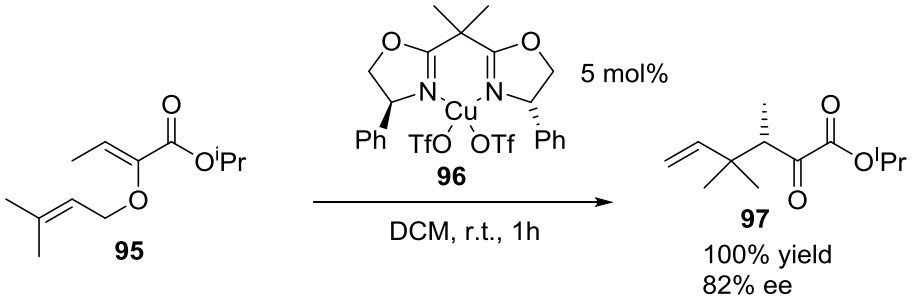


Scheme 25: *New Lewis Acid-Catalysed Claisen Rearrangement*[122]

2.1.4.1 Enantioselective Claisen Rearrangements.

Several studies have reported the fact that, in the presence of Lewis acids, Claisen rearrangements are accelerated.[125,126] This led to the study of the effects of chiral Lewis acids relating to the enantioselectivity of the reaction in an attempt to determine ligands which accelerate the reaction and achieve optimum chirality transfer.[80]

In 2002, Hiersemann and Abraham reported the first successful enantioselective catalytic Claisen Rearrangement (Scheme 26). Chiral bis(oxazoline)copper(II) **96** was used to catalyse the rearrangement of 2-alkoxycarbonyl-substituted allyl vinyl ethers **95** in a bidentate manner. Very high yields were reported (94% to 100%).[127]



Scheme 26: *The catalytic enantioselective Claisen Rearrangement of 2-alkoxycarbonyl-substituted allyl vinyl ethers*[127]

The scope of this reaction is limited because of the necessity for an ester group at the 2-position to act as a chelating group and the difficulties in the synthesis of allyl vinyl ether moieties.[127] The MacMillan group sought to develop an enantioselective catalytic Claisen rearrangement which had general synthetic ability.

2.1.4.2 Enantioselective Acyl-Claisen Rearrangement.

The MacMillan group also looked into developing an enantioselective catalytic Claisen rearrangement as part of their work on the acyl-Claisen rearrangement. This led to the development of several chiral Lewis acids of which **98** was found to be the most effective (Figure 13).

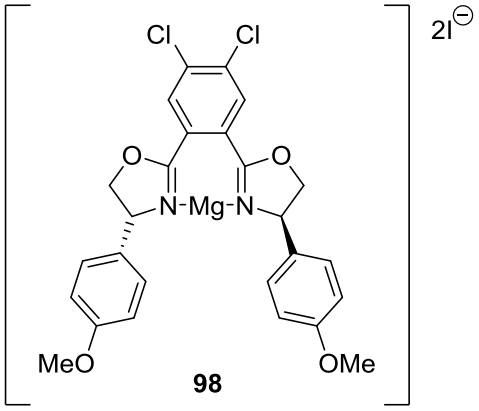
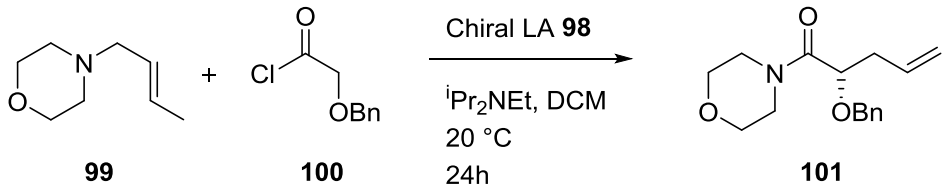


Figure 13: *Chiral Lewis acid complex* ***98***[128]

Using this Lewis acid catalyst the first example of an enantioselective acyl-Claisen reaction was reported[128] However, when published in 2001 this reaction was not catalytic. It required a large excess of the Lewis acid to give good enantiomeric selectivity (Scheme 27 and Table 5). The MacMillan group theorized that this was due to a competing non-metal mediated rearrangement pathway.[124]



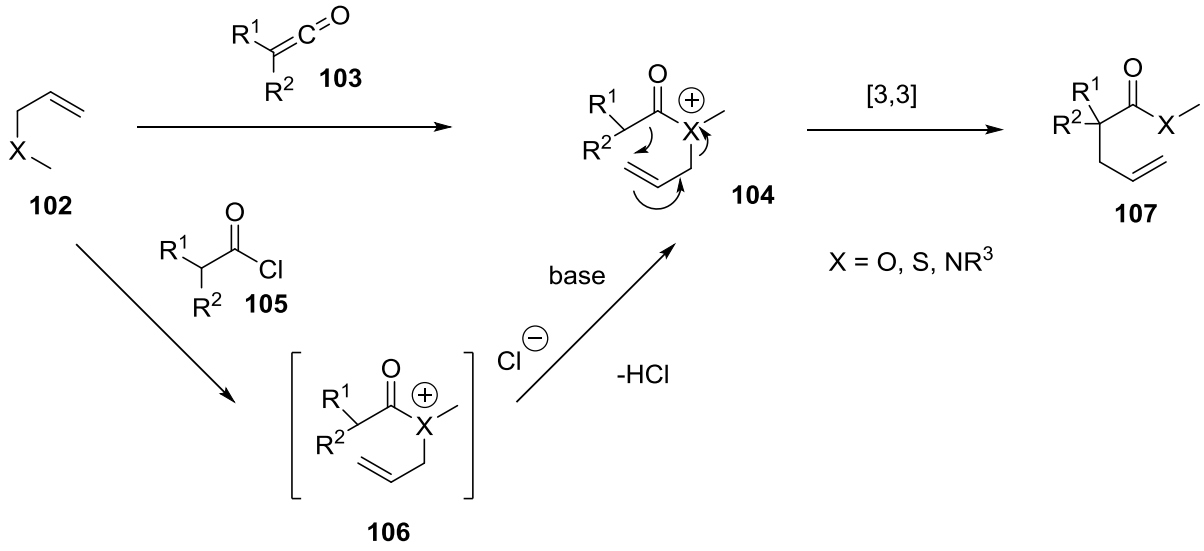
Scheme 27: *Catalysed Acyl-Claisen Rearrangement*[128]

Table 5: *Effect of chiral Lewis acid loading*

Entry	Mol % 98	Yield (%)	ee (%)
1	50	81	42
2	100	63	81
3	200	80	91

When the Belluš-Claisen reaction is performed using allylic amines (Scheme 28)[116] the reaction proceeds *via* zwitterion **104**, formed from the allylic amine **102** upon reaction with a ketene **103**. The ketene used can be an isolated starting material or generated *in*

situ, such as from dehydrohalogenation of an acyl chloride. When using an acyl chloride it is possible that the allylic amine may react with the acyl chloride **105** to form an acyl ammonium salt **106**. This is physically incapable of undergoing the desired [3,3] rearrangement. Only after dehydrohalogenation of the salt can the rearrangement to give the desired amide **107** take place.



Scheme 28: *Mechanism of Belluš-Claisen Rearrangement*[116]

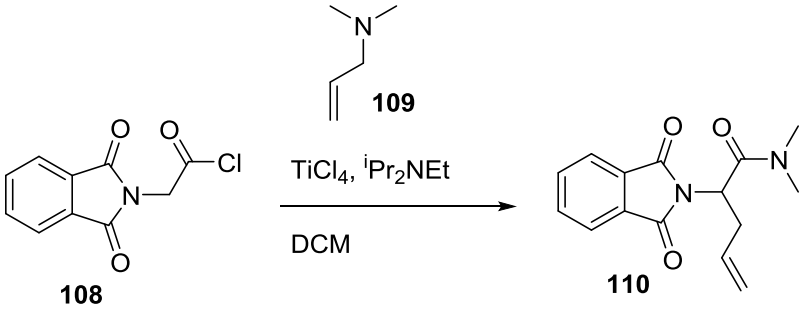
The MacMillan group found that various Lewis acids were able to catalyze the reaction of substituted ketenes with a range of allylic tertiary amine substrates. However their initial method of ketene generation was not ideal. Bromoacetyl bromide was treated with zinc in THF and the resulting ketene was co-distilled with the THF solution at reduced pressure into a liquid nitrogen cooled Schlenk flask. This procedure had two major drawbacks:

1) It was necessary to co-distil the ketenes with ethereal solvents and so the molecular weight of the ketenes had to be low.
2) There was a degree of inaccuracy because it was extremely difficult to work out the concentration of the ketene solution produced and thus it was normally used in considerable excess.

After some research, an alternate method for ketene generation was chosen for the remainder of their investigation. Base-promoted dehydrohalogenation of acid chlorides had been used for over a century and was first demonstrated in 1911 by Staudinger.[129] The method is robust and is capable of generating a broad range of mono and di substituted ketenes. Furthermore, there was evidence of trapping the generated ketenes

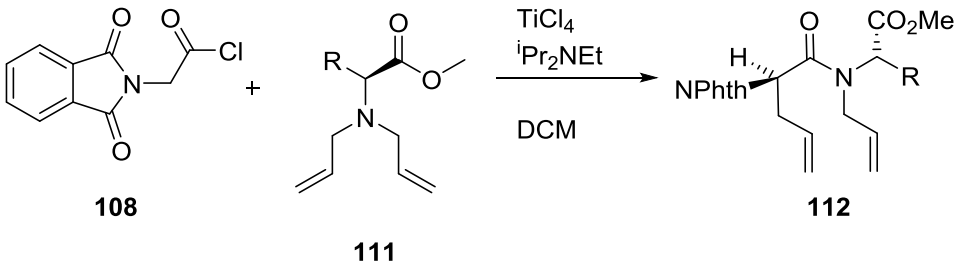
in situ with differing reaction mixtures, for example with enol silanes, alkenes, carbonyl compounds and imines.[130] Most importantly from the view of the MacMillan group, this reaction generated ketenes without generating Lewis acid metal byproducts.[124]

We proposed to extrapolate the Belluš-Claisen rearrangement to prepare functionalised amino acids by C-allylation. As proof of concept the reaction was to be first attempted by reacting *N*-phthaloylglycyl chloride **108** with a *N*,*N*-dimethyl amine **109**. (Scheme 29). This was very similar to the MacMillan work so we expected this to be successful.



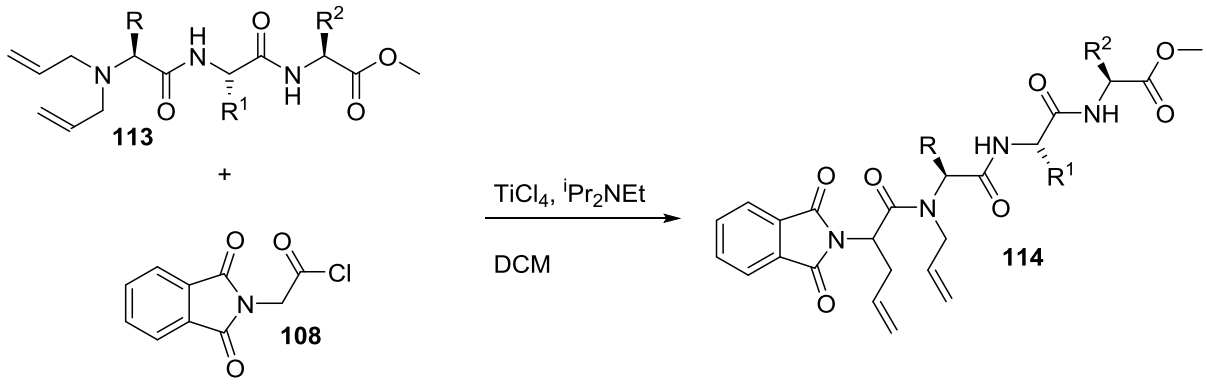
Scheme 29: *Proposed scheme for synthesis of 2-Phthaloyl-N,N-dimethylpent-4-enamide*

If the reaction could be made to work satisfactorily it would then be repeated with suitable allylated amino acid derivatives **111** to synthesize non-proteinogenic dipeptides **112** (Scheme 30).



Scheme 30: *Proposed scheme for synthesis of non-proteogenic dipeptides*

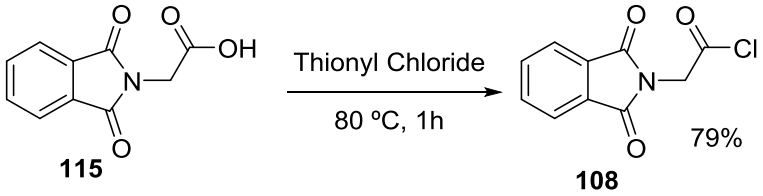
If this general reaction scheme proved viable, it was hoped that the rearrangement could then be applied to more peptides such as **113** (Scheme 31). This would give a process that allows addition of an amino acid to a peptide chain as well as creation of a new stereocentre to give α-allylated peptides like **114** using a single rearrangement reaction.



Scheme 31: *Proposed scheme for [3,3] Belluš Claisen Rearrangement performed on generic peptide*

2.2 Results and Discussion

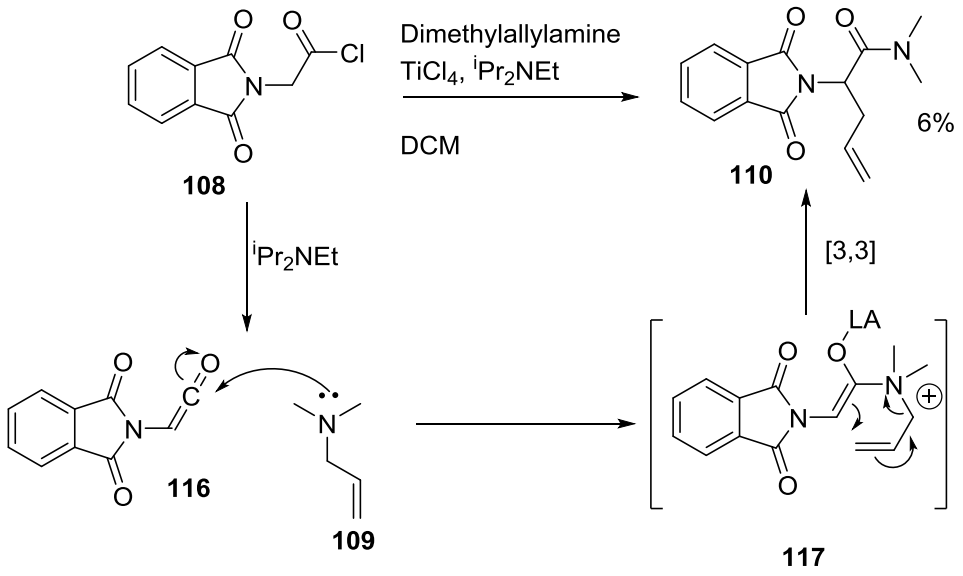
A Belluš-Claisen rearrangement was carried out using *N*,*N*-dimethyl allyl amine **109** (Scheme 33). This reagent was chosen because structurally it was the least complex tertiary amine that could be used in the [3,3] sigmatropic rearrangement. *N*-phthaloyl protected glycyl chloride **108** was chosen for the ketene precursor, which was synthesized from commercially available *N*-phthaloyl glycine **115** following a procedure by Balenovic *et al*.(Scheme 32)[131]



Scheme 32: *Synthesis of N-phthaloylglycyl chloride* ***3***[131]

The MacMillan group had already reported a successful rearrangement using *N*-phthaloylglycyl chloride as the ketene precursor. However, the amine used in their example was an allyl morpholine derivative that had a number of advantages over the dimethylallyl amine that we wished to use. Firstly, the electron-withdrawing ability of the morpholine oxygen can increase the speed of the sigmatropic rearrangement by destabilizing the cationic charge on the nitrogen of the zwitterionic intermediate. Secondly, the separation of the product from the metal centre can be improved. This is due to the relatively weaker electron donating capability of the morpholine nitrogen which will make the amide carbonyl produced in the reaction less Lewis basic. In theory, this improves the rate of the catalyst turnover and also increases the speed of the reaction.[124,128]

Reaction of *N*-phthaloylglycyl chloride **108** with di*iso*propylethylamine gives ketene **116** (Scheme 33). This is followed by nucleophilic attack on the ketene by dimethylallylamine **109** to give zwitterionic intermediate **117**. This underwent [3,3] sigmatropic rearrangement to give amide **110**. Titanium tetrachloride was used as the Lewis acid in this reaction.



Scheme 33: *Synthesis of 2-phthaloyl-N,N-dimethylpent-4-enamide*

^{1}H NMR analysis showed the appearance of the expected product in the reaction mixture. The creation of a new asymmetric centre was supported by the appearance in the ^{1}H NMR of a splitting pattern at 2.78-3.20 characteristic of diastereotopic protons α to an asymmetric center (Figure 14).

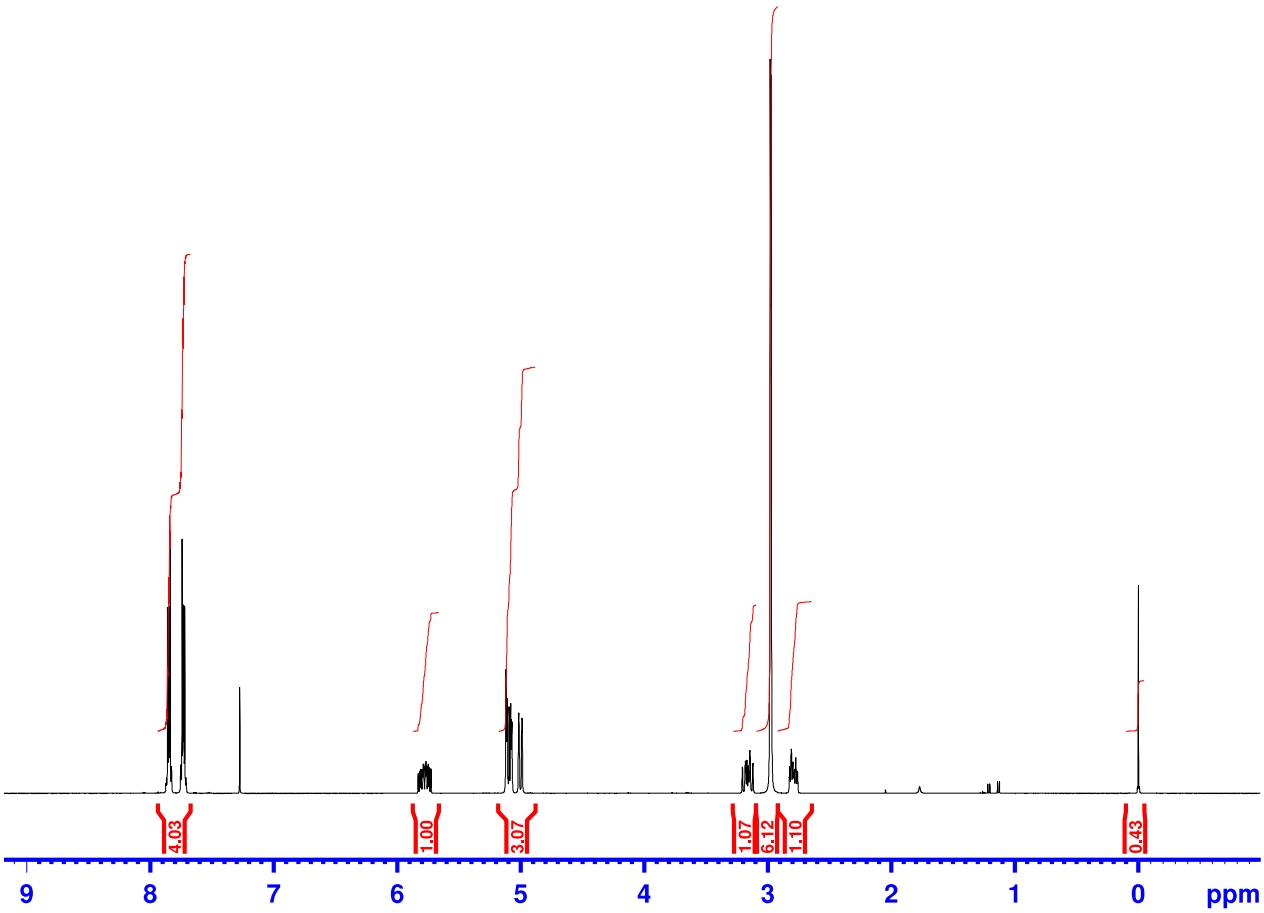
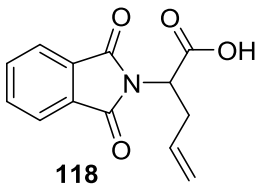


Figure 14: *^{1}H NMR of 2-phthaloyl-N,N-dimethylpent-4-enamide* ***108*** *showing AB splitting pattern at 2.76-3.21 ppm*

A similar splitting pattern is reported for *N*-phthaloylallylglycine **118** at 2.90-3.14 (Figure 15).[132] Following purification by column chromatography an overall yield of 6% was obtained.



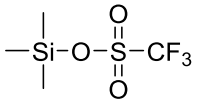
118

Figure 15: *N-phthaloylallylglycine*[132]

Titanium tetrachloride is a strong Lewis acid that has been used to considerably improve the electrophilicity of substrates. It has been successfully utilised in Diels-Alder reactions but it can create side reactions resulting in product decomposition.[133,134,135] Likewise, while it has successfully been used in Belluš-Claisen reactions with a selection

of simple allylic tertiary amines, when used with more complex allylic amines often results in product decomposition or recovery of starting material.[79] Due to this alternate Lewis acids were considered.

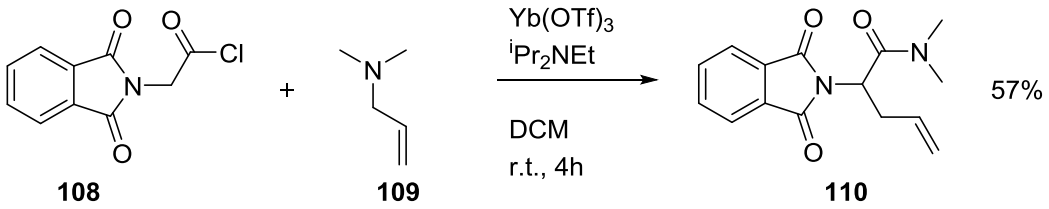
TMS triflate **119** (Figure 16) is a milder Lewis acid which has been used successfully in Belluš-Claisen rearrangements.[79] Repeating the reaction, this time with a stoichiometric quantity of silyl triflate, did give a significant improvement with a final yield of 29%. During these attempts to improve yield it was also noted that the purity of *N*-phthaloylglycyl chloride **108** had a significant effect on the final yield. Either freshly prepared or freshly recrystallized material was necessary to get full conversion of the reaction to the desired starting material.



119

Figure 16: *TMS triflate*

The next attempt to increase the yield was the use of ytterbium triflate as the Lewis acid catalyst. Ytterbium triflate catalyzed Claisen rearrangements in good yields have been reported.[122,136,137] The reaction was repeated using ytterbium triflate (Scheme 34).



108 **109** **110**

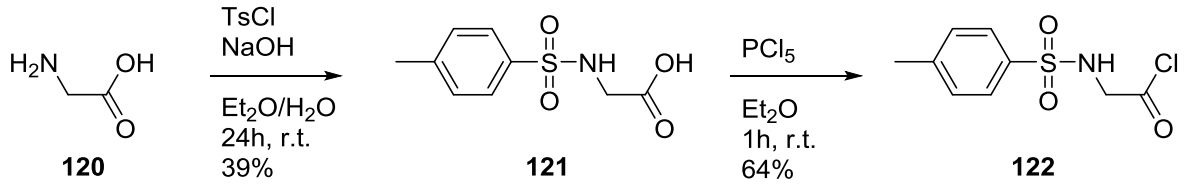
Scheme 34: *Alternate Lewis acid catalyst*

Ytterbium triflate was bought as the hydrate and had to be dried before use. Unless sufficiently dried before use, ytterbium triflate can give poor yields when being used as a Lewis acid.[138] Initially the reaction was attempted using ytterbium triflate hydrate that had been pre-dried under 0.7 mm pressure using a high vacuum oil pump for three hours. However, this failed to give any of the desired product.

After this significantly harsher conditions were used to dry the catalyst. The reaction was repeated using ytterbium triflate that had been left to dry for 16 hours under 0.7 mm vacuum at 140 °C. This gave a quantitative crude yield, with ^{1}H NMR analysis showing the majority to be product. On being left to stand, the crude product solidified. Re-

crystallisation from an IPA/$^{i}Pr_2O$ mixture gave pure 2-phthaloyl-*N*,*N*-dimethylpent-4-enamide, in 57% yield.

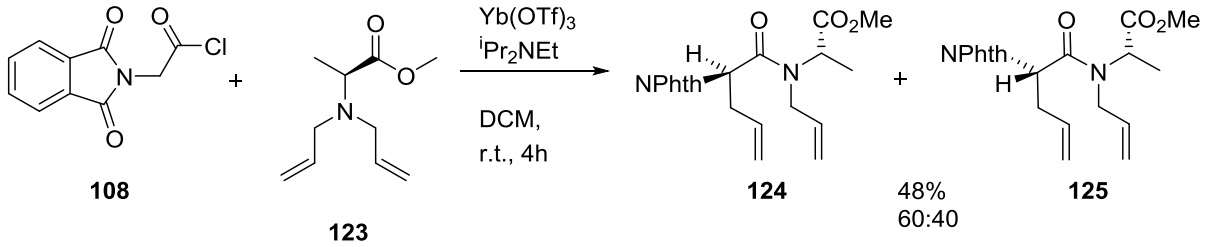
An alternate protecting group for the ketene precursor was also investigated. *N*-Tosyl glycine **121** was synthesized and converted to acid chloride **122** using literature methods.[139] However, attempts to perform the Belluš-Claisen using acid chloride **122** proved unsuccessful. All attempts to perform the rearrangement using acid chloride **122** returned only starting materials and *N*-tosyl glycine **121.**



Scheme 35: *N-Tosyl glycyl chloride synthesis*

2.2.1 Application to Amino Acids

The next step was to apply this chemistry to allylated amino acids anaolgues and to investigate whether a chiral molecule would affect the selectivity of the generating of the new asymmetric centre in the rearranged product. The first experiment was performed on the simplest available chiral amino acid, alanine. The methyl ester hydrochloride salt was refluxed in acetonitrile with allyl bromide and sodium hydrogen carbonate to give the desired allylated analogue. Purification by flash column chromatography gave *N,N*-diallyl alanine methyl ester **123** in 72% yield. The rearrangement reaction was attempted using the previously tried conditions: diisopropylethylamine, *N*-phthalylglycyl chloride and ytterbium triflate as the Lewis acid catalyst (Scheme 36).

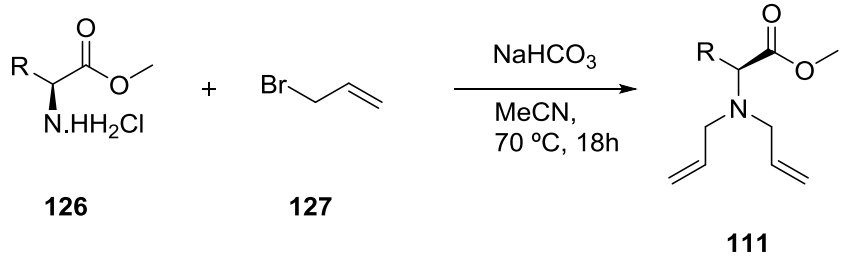


Scheme 36: *Belluš-Claisen Rearrangement of N,N-diallyl alanine methyl ester*

On the first attempted rearrangement, a mixture of starting material and rearranged products **124** and **125** was identified in the crude. An acid wash was used to separate

the starting material and the amide product to give a crude yield of 39% of the two isomeric products. Again, use of freshly re-crystallized *N*-phthalylglycyl chloride resulted in a reaction that gave total conversion by ^{1}H NMR analysis. Purification by column chromatography gave a 60:40 mixture of dipeptides **124** and **125** in a yield of 48%. (Calculation of stereochemistry is discussed below)

Given this encouraging starting point it was hoped to expand the reaction using a diverse range of more complex amino acids. All diallylated amino acid derivatives **111** were synthesized directly from the appropriate amino acid hydrochloride **126** by refluxing in acetronitrile with allyl bromide **127**. (Scheme 37 and Table 6)



126 **127** **111**

Scheme 37: *Synthesis of diallylated amino acid derivatives*

Table 6: *Synthesis of di-allylated amino acid derivatives*

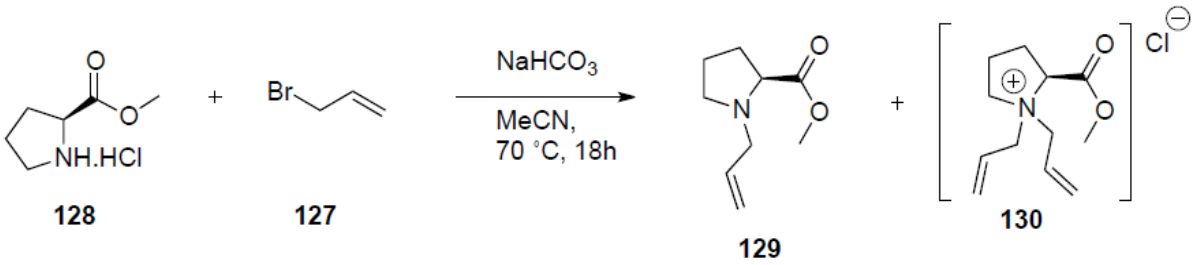
Entry	Compound	R	Yield (%)
1	**111a**	$(CH_3)_2CH$-	70
2	**111b**	$(CH_3)_2CH_2CH$-	61
3	**111c**	$CH_3CH_2(CH_3)CH$-	69

Rearrangements were then attempted, again using di*iso*propylethylamine, *N*-phthalylglycyl chloride and ytterbium triflate as the Lewis acid catalyst. However, all attempts only returned the unreacted diallylated amino acid derivative and phthaloyl glycine. All the reactions were repeated using freshly prepared acyl chlorides and dried ytterbium triflate but again only starting materials were returned.

The lack of the corresponding rearranged product was unexpected. The amino acids derivatives used were not radically different to diallylalanine methyl ester. Alanine derivative **123** had successfully undergone the desired [3,3] rearrangement. Valine, leucine and isoleucine have only a slight increase in the complexity of the carbon chain on the amino acid, with an extra three or four carbons on the chain terminus.

The reaction was then repeated with di-allyl isoleucine methyl ester, refluxing in DCM when the addition of the acyl chloride was complete. This again returned the di-allyl isoleucine methyl ester starting material and *N*-phthaloylglycine. The reaction was then repeated using dichloroethane as the solvent. After refluxing overnight this again returned only di-allyl isoleucine methyl ester starting material and *N*-phthaloylglycine. For avoidance of doubt, the reaction was performed in DCE with di-allyl alanine methyl ester **123** that gave the expected dipeptide product in 45% yield and a diastereoisomeric ratio of 60:40.

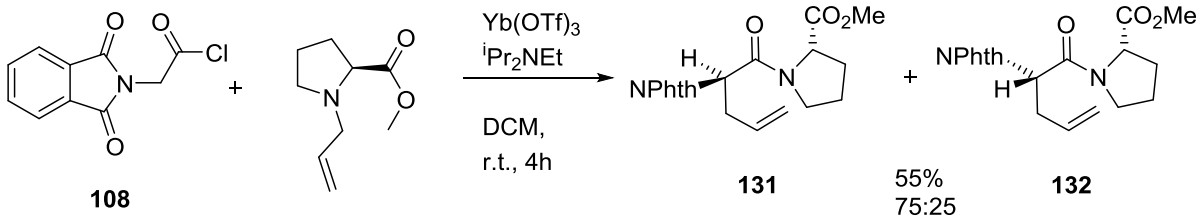
The last amino acid variant tried was *N*-allyl proline methyl ester **129**. The mono-allayted variant of L-proline proved challenging to synthesize at first. Using the previous allyl bromide/sodium hydrogen carbonate conditions with one equivalent of allyl bromide produced a mixture of diallylated quaternary ammonium **130** and the desired *N*-allyl proline methyl ester **129** (Scheme 38). This mixture of products resulted in a very inefficient conversion to the desired product.



128 127 129 130

Scheme 38: *First attempt of synthesis of N-allyl proline methyl ester*

Repeating the reaction at room temperature in DMF proved significantly more selective, giving only the desired mono-allyl product **129**. Purification by flash chromatography gave the product in 46% yield.



108 129 131 55% 75:25 132

Scheme 39: *Belluš-Claisen Rearrangement of allyl proline methyl ester*

Using the same base, ketene precursor and Lewis acid for the reaction, the rearrangement successfully proceeded to give the expected dipeptides **131** and **132** (Scheme 39). The diastereoselectivity of the reaction was significantly better than when using alanine, giving a 75:25 ratio.

Removal of impurities proved straightforward, with flash column chromatography giving a pure mixture of diastereomeric products. However, separation of the major and minor diastereomers proved challenging due to the almost identical rate of elution of the two isomers. HPLC was investigated as a possible method of purification but did not give sufficient separation of the diastereomers. A drastic increase in silica used (100g silica per gram product) finally produced diastereomerically enriched samples. Following controlled crystallization with a combination of IPA and *tert*-butyl ether gave dipeptide **131** in sufficient purity to allow X-ray crystallography (Figure 17). The rearrangement was therefore favouring the generation of an (*R*) stereocentre.

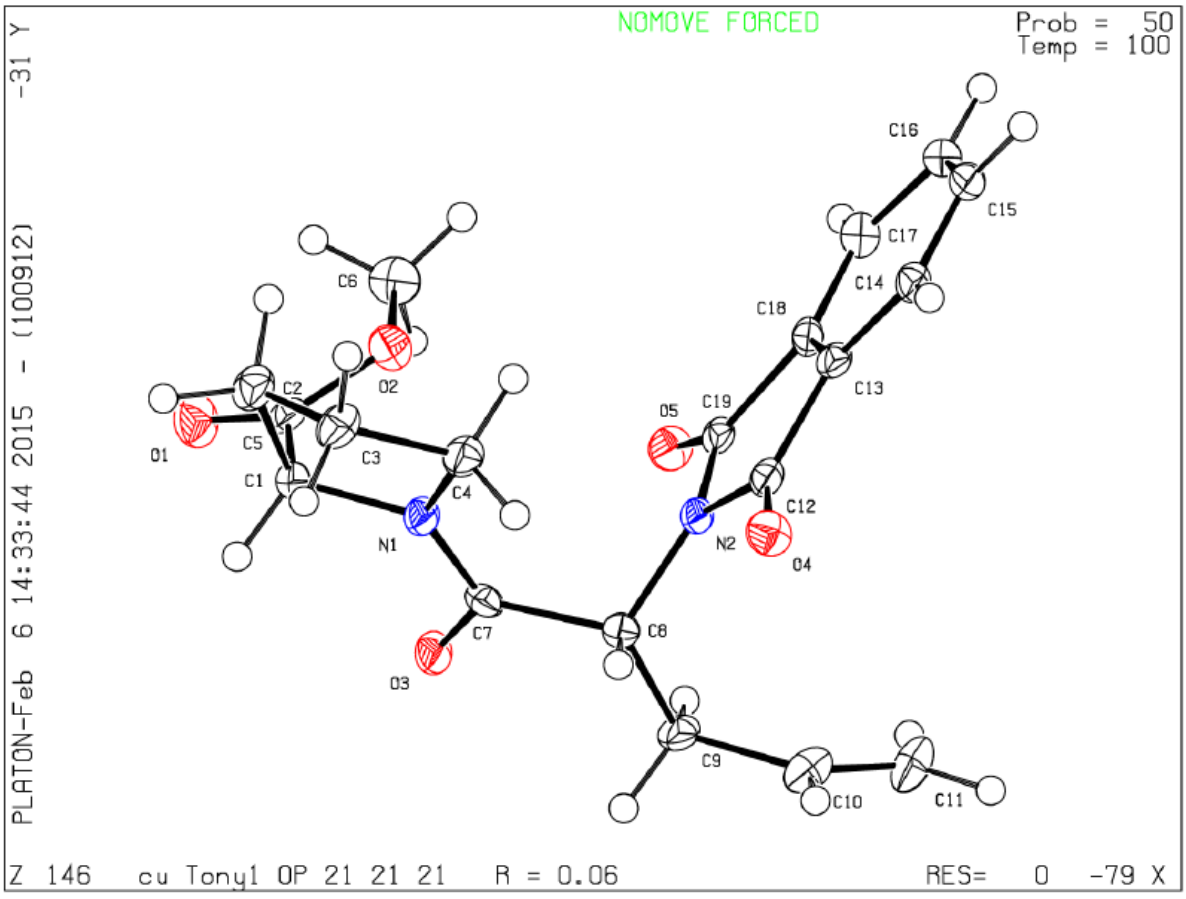
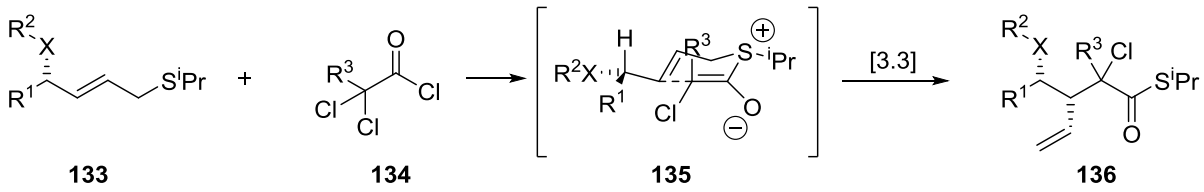


Figure 17: *X-ray data of (S)-methyl 1-((R)-2-(1,3-dioxoisoindolin-2-yl)pent-4-enoyl)pyrrolidine-2-carboxylate* ***131***

[3,3]-Sigmatropic rearrangements proceed through highly ordered six membered transition states which allows for chirality transfer from a stereogenic centre. When the asymmetric centre is incorporated into the cyclic framework of the transition state chiral information can be transferred in a concise and predictable manner.[80] Belluš *et al*. reported the first diastereoisomeric reaction between allyl sulfide **133** and dichloro acyl chloride **134** (Scheme 40). The resulting zwitterionic intermediate **135** then underwent [3,3]-sigmatropic rearrangement to give silyl ester **136**. The rearrangement is directed by substituent X. The resulting 1,3-diaxial repulsive interactions in the intermediate results in the stereochemistry of **136** being preferred.[140]

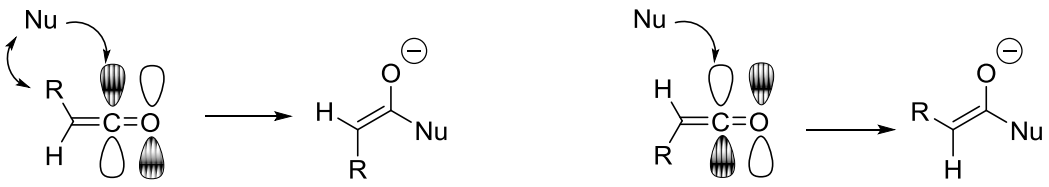


133 **134** **135** **136**

R^1=Me, iPr, $TBSOCH_2CH_2$; R^2=TBS, Boc, Ts, R^3=Cl, Me; X=O, NBn

Scheme 40: *Diasteroselective Ketene-Claisen Rearrangement*[140]

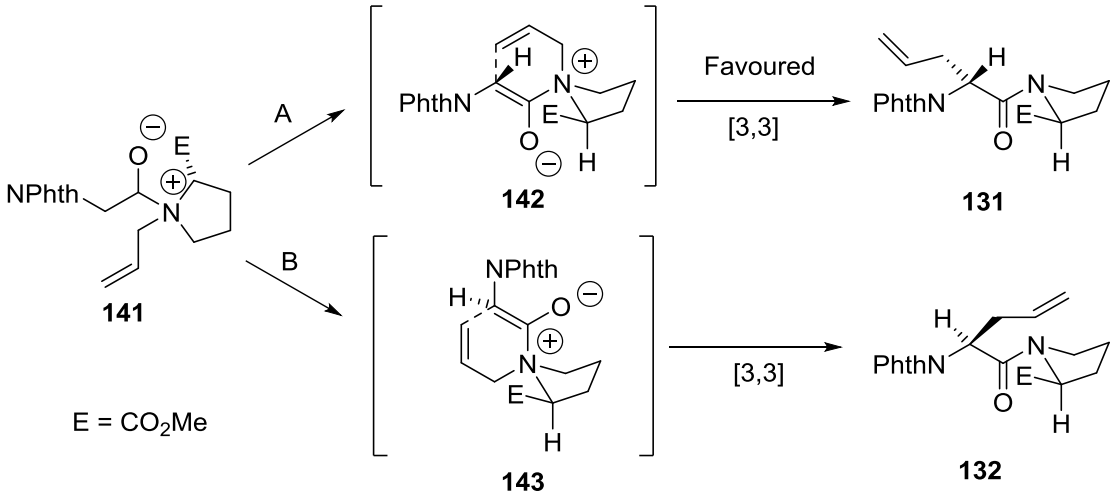
When the asymmetric centre is outside the transition state framework it can be more difficult to achieve high enantioselectivity. For the ketene-Claisen reaction using *N*-allyl proline methyl ester **129** the resulting stereochemistry of the product is determined by two sequential steps. Firstly, the addition of nucleophiles to monosubstituted ketenes usually results in the formation of the (*Z*)-enolate **140** (Scheme 41).[141] The LUMO (lowest unoccupied molecular orbital) of the ketene is the C=O π^* orbital and as a result, nucleophiles that react with the ketene would have to overcome substantial steric interactions with the substituents to form the (*E*)-enolate **138**.[142] Therefore, nucleophiles will prefer to attack opposite the substituent, resulting in (*Z*)-enolate formation.



disfavoured **137** (E)-enolate **138** favoured **139** (Z)-enolate **140**

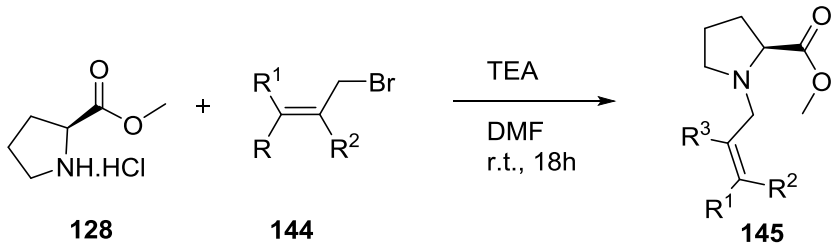
Scheme 41: *Preference for* (*Z*)*-enolate formation in addition to mono-substituted ketene*

The second step, the resulting carbon-carbon bond formation during the [3.3] rearrangement, will be influenced by the stereochemistry of the proline moiety of zwitterionic intermediate **141**. The fused five membered ring will restrict the relative position asymmetric centre, increasing the difficulty of attacking one face of the molecule. This would favour pathway A (Scheme 42), giving the (R) stereocentre.



Scheme 42: *Preference for R stereochemistry*

Following the success with *N*-allyl proline we planned to synthesize a range of allylated proline variants **145** to see if the reaction could tolerate substitutions on the allyl chain. Making the allyl proline anolgues was straight forward. Replacing allyl bromide with a suitably substituted alkyl bromide **144** gave the desired products **145** in yields of 40-62% (Scheme 43 and Table 7).

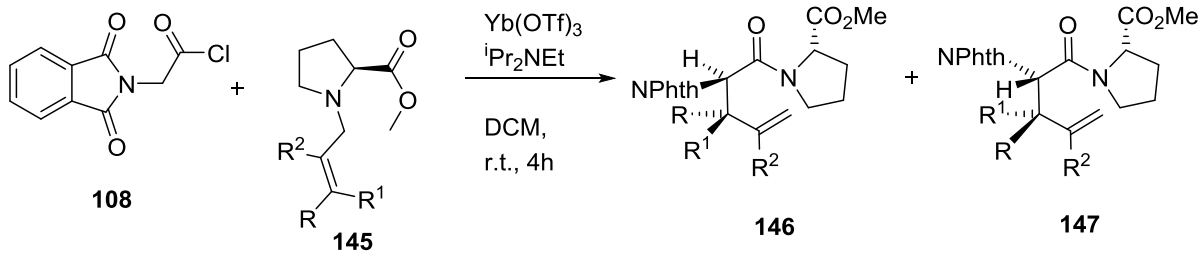


Scheme 43: *Synthesis of N-Allyl Proline Methyl Ester derivatives*

Table 7: *Synthesis of N-Allyl Proline Methyl Ester derivatives*

Entry	Compound	R^1	R^2	R^3	Yield (%)
1	**145a**	Me	H	H	49
2	**145b**	Me	Me	H	62
3	**145c**	H	H	Me	53
4	**145d**	Et	H	H	55
5	**145e**	Ph	H	H	40
6	**145f**	CO_2Me	H	H	59

Once products **145** had been successfully synthesized, Belluš-Claisen rearrangements were attempted with them. The same reaction conditions were used with a stoichiometric amount of ytterbium triflate as the Lewis acid. The reaction proved robust to a variety of allyl anologues, giving the rearranged dipeptides predominately of **146** and **147** in moderate to good yields (40-70 %) (Scheme 44 and Table 8).



Scheme 44: *Belluš-Claisen Rearrangement with N-Allyl Proline Methyl Ester derivatives*

Table 8: *Belluš-Claisen rearrangement with N-Allyl Proline Methyl Ester derivatives*

Entry	Major product	R	R^1	R^2	Yield (%)	Ratio of dipeptides 146 and 147
1	**146a**	Me	H	H	42	66:33
2	**146b**	Me	Me	H	40	54:46
3	**146c**	H	H	Me	49	75:25
4	**146d**	Et	H	H	70	78:22
5	**146e**	Ph	H	H	51	54:46
6	**146f**	CO_2Me	H	H	47	54:46

Purification of these diasteriomeric mixtures again proved challenging. Given the time constraints of the project it was not possible to isolate samples of sufficient purity for X-ray crystallography for all variants of the reaction. However, a sample of **147d** was isolated that allowed crystal data to be collected (Figure 18).

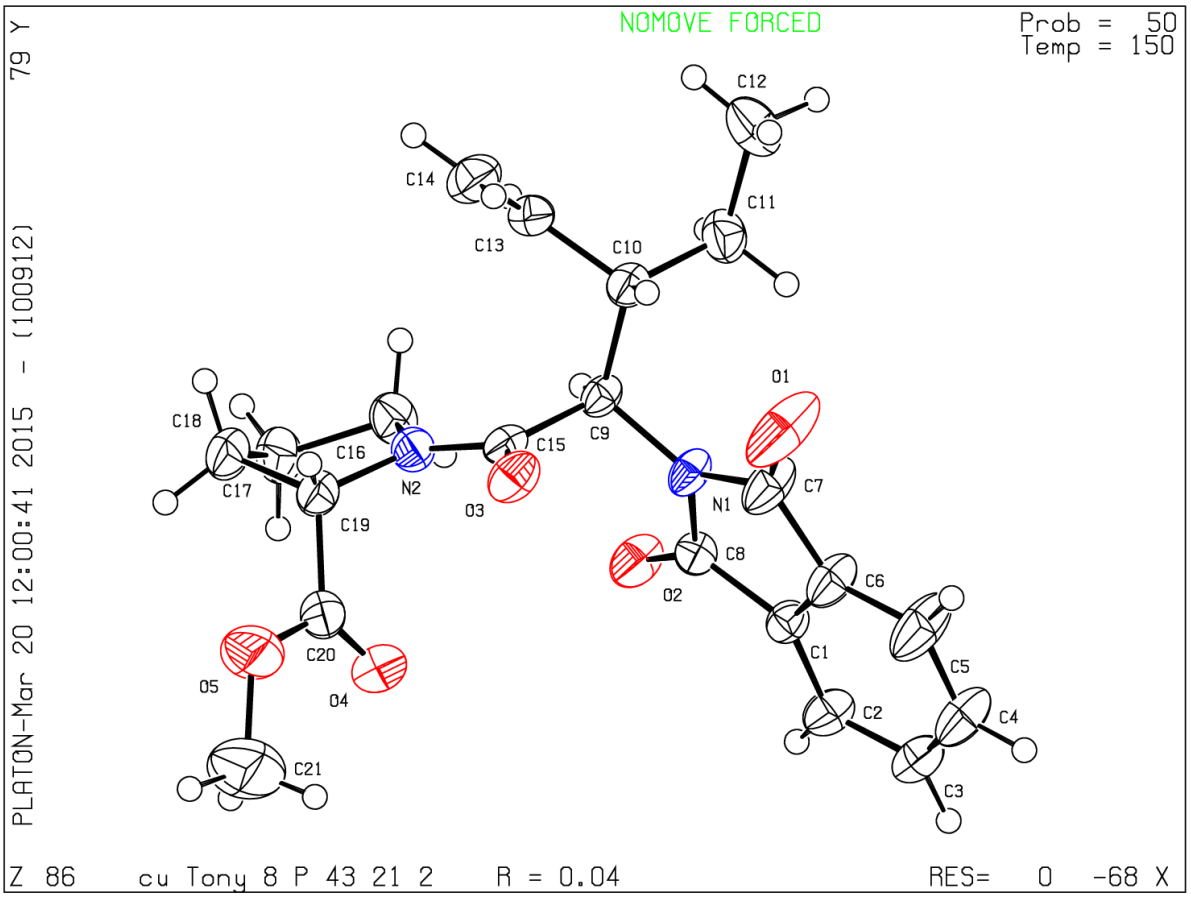
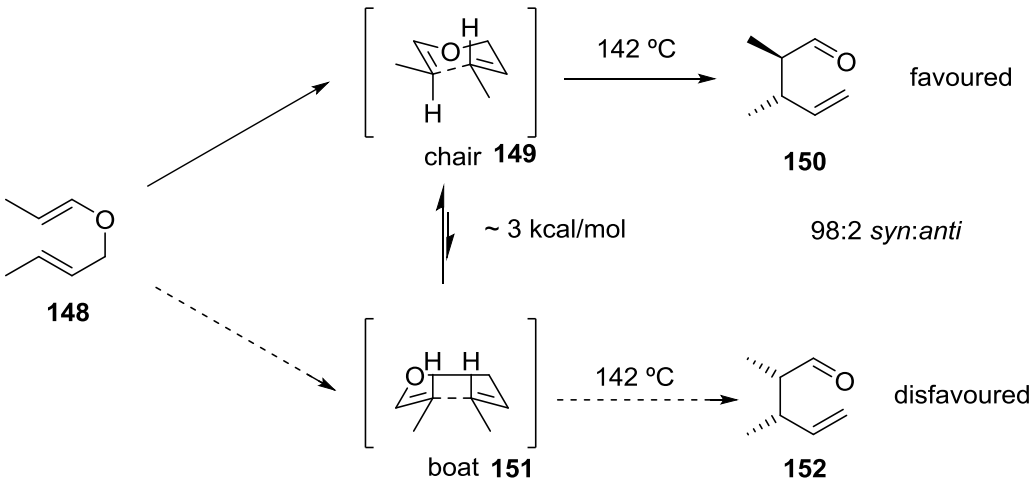


Figure 18: ***147d***

Claisen type rearrangements will preferentially go through a chair-like transition state that will give the corresponding *syn* product (Scheme 45).[97] This is favoured because it is typically lower in energy than that of the corresponding boat transition state. When a second asymmetric centre was created during the rearrangement (Table 8, Entries 1, 4-6) the products were overwhelmingly two diastereomers, even though there are four possible products.

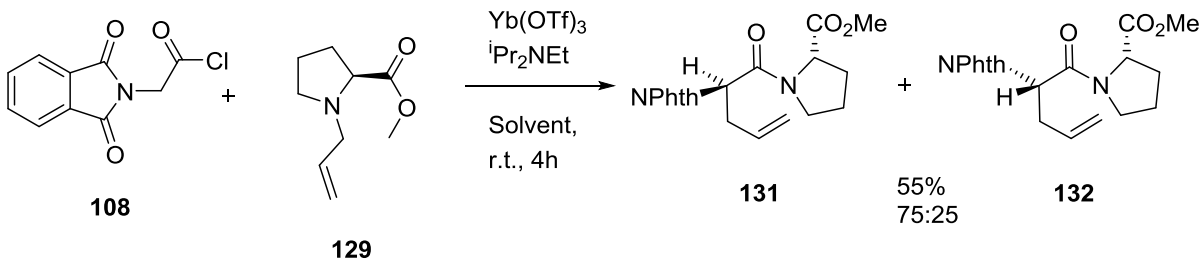


Scheme 45: *Syn/anti control in Claisen type reactions*

2.2.2 Reaction Optimization

2.2.2.1 Solvent Screen

A solvent screen was carried out on the Belluš-Claisen reaction otherwise using the same conditions with *N*-allyl proline methyl ester. Polar protic solvents readily react with acyl chlorides to return carboxylic acids, thus a selection of non-polar and polar aprotic solvents was chosen (Scheme 46 and Table 9). Of those solvents tried, the reaction only went to completion in chlorinated solvents- chloroform and dichloroethane. Yield and selectivity were similar to DCM (Table 9, Entries 1-3). Diethyl ether is a common solvent for Belluš-Claisen type reactions, however some of the reagents used in the reaction were not soluble which almost certainly led to trace yields (Table 9, Entry 4). No conversion was observed when using highly polar solvents such as acetonitrile and DMF (Table 9, Entries 6 and 8).



Scheme 46: *Solvent Screen*

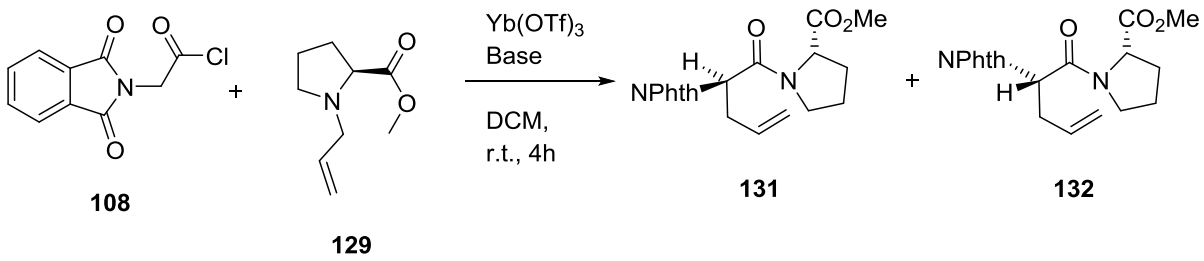
Table 9: *Solvent Screens*

Entry	Solvent	Yield (%)	Diastereoisomeric ratio
1	DCM	44	75:25
2	$CHCl_3$	41	75:25
3	DCE	42	75:25
4	Et_2O	0	-
5	THF	0	-
6	DMF	0	-
7	DMSO	0	-
8	MeCN	0	-
9	EtOAc	0	-

2.2.2.2 Base Screen

For completeness, a base screen was performed to investigate the effect of the base used on the reaction (Scheme 47 and Table 10). Surprisingly of the tertiary amine bases only di*iso*propylethyl amine gave moderate conversion to the desired product. Triethylamine did result in poor conversion to the desired product but showed no improvement in diastereomeric selectivity. Pyridine, DMAP and DBU either gave trace amounts of product or failed to show any conversion. All inorganic bases used failed to show conversion.

The results of the screen were showed no correlation to pKa values, although how hindered the base was did seem to correlate with how effective the conversion was.

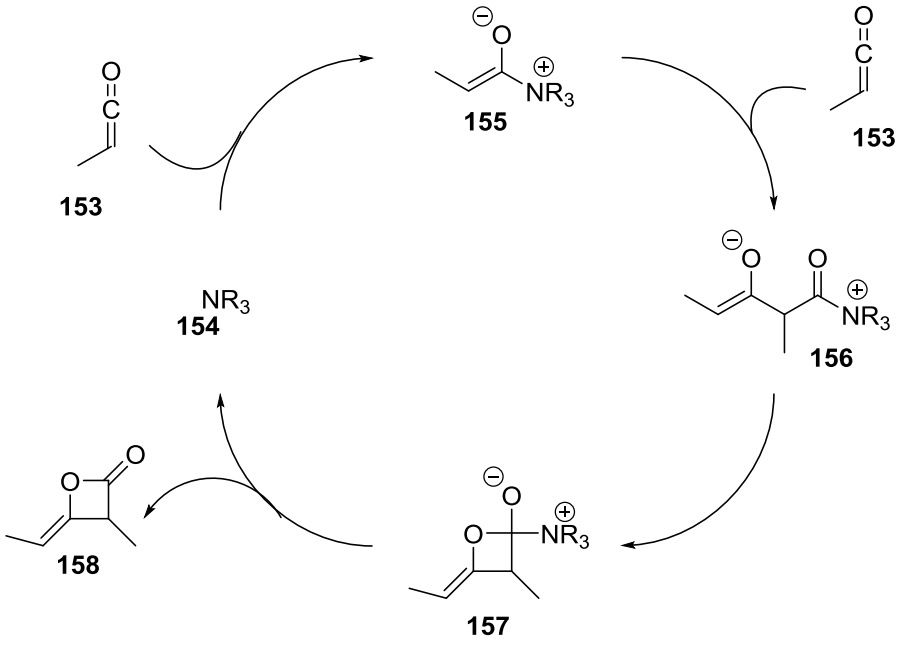


Scheme 47: *Base Screen*

Table 10: *Base Screens*

Entry	Base	pKa[143,144]	Yield (%)	Diastereomeric ratio
1	$^{i}Pr_2EtN$	10.75	51	75:25
2	Et_3N	10.75	18	75:25
3	DBU	12	0	-
4	DMAP	9.2	0	-
5	Pyridine	5.2	0	-
6	NaOH	15.7	0	-
7	KOH		0	-
8	$NaHCO_3$		0	-

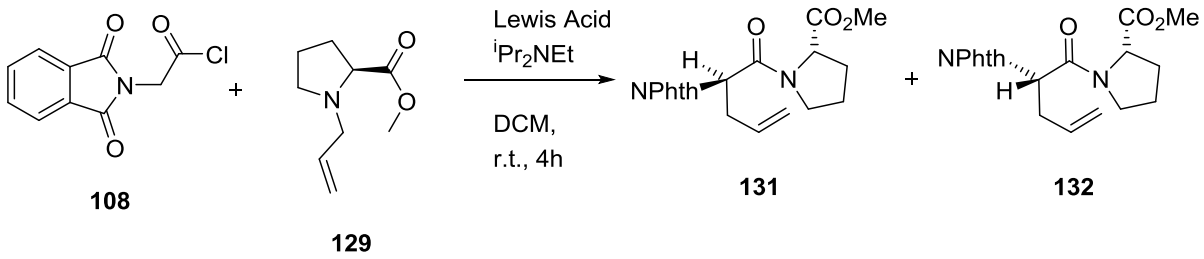
The MacMillan group reported similar problems when they tried alternate bases and speculated that nucleophlic tertiary amines were catalyzing an alternate pathway to give a non-desired side product. Nucleophlic tertiary bases act as a catalyst in the formation of β-lactones by dimerization of ketenes in a known process.[124] This competing pathway could explain the generally poor yield with only hindered tertiary bases given any notable yield.



Scheme 48: *Tertiary amine catalyzed formation of β-lactone*

2.2.2.3 Lewis Acid Screen

Preferably, a catalytic amount of Lewis acid could be used in the reaction. All reactions done until this point had used stoichiometric quantities of ytterbium triflate to drive the reaction to completion. Due to ytterbium triflate having a relatively high molecular mass (620 g/mmol), this made the problem significantly more pronounced because by mass it accounts for nearly 50% of the reaction mixture. A Lewis acid that could get the same yields with a far smaller loading would represent a major improvement. A screen of Lewis acids was attempted (Scheme 49 and Table 11).



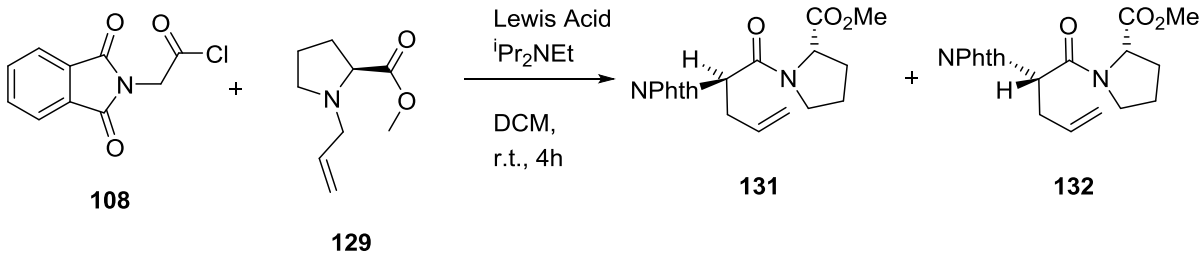
Scheme 49: *Lewis Acid Screen*

Table 11: *Lewis Acid Screens*

Entry	Lewis acid	Yield	Ratio
1	$Yb(OTf)_3$	47	75:25
2	$TiCl_4$	17	80:20
3	$Cu(OTf)_2$	0	-
4	$TiCl_4(THF)_2$	29	80:20
5	$FeCl_3$	0	-
6	$Fe(acac)_3$	0	-
7	$Mg(OTf)_2$	0	-
8	$Sm(OTf)_3$	0	-
9	$Ti(O^iPr)_4$	0	-

Most Lewis acids screened failed to give the desired rearranged products **131** and **132**. Of the Lewis acids tried only titanium tetrachloride and titanium tetrachloride THF complex gave any of the desired dipeptides. Following on from this both ytterbium

triflate and titanium tetrachloride were screened again, this time using increasingly smaller sub-stoichiometric amounts (Scheme 50 and Table 12).



Scheme 50: *Lewis Acid Loading Screen*

Table 12: *Catalyst loading screen*

Entry	Lewis acid	Stochiometry	Yield (%)	Ratio
1	$Yb(OTf)_3$	100	49	75:25
2	$Yb(OTf)_3$	50	26	75:25
3	$Yb(OTf)_3$	25	0	-
4	$Yb(OTf)_3$	10	0	-
5	$TiCl_4$	50	27	80:20
6	$TiCl_4$	25	25	80:20
7	$TiCl_4$	10	19	80:20
8	$TiCl_4(THF)_2$	50	34	75:25
9	$TiCl_4(THF)_2$	25	29	75:25
10	$TiCl_4(THF)_2$	10	17	75:25

The failure of the reaction when a sub-stoichiometric amount of ytterbium triflate was used was cause for concern. The Lewis acid should be able to act as a catalyst in the reaction, being recycled after addition to the ketene and the subsequent rearrangement. The fact that a stoichiometric amount was needed strongly suggests that the Lewis acid was failing to dissociate from the amide after the rearrangement or that it was being poisoned in the reaction. In either case, the catalyst was failing to turnover. Conversely, both $TiCl_4$ and $TiCl_4(THF)_2$ were found to still be effective at sub-stoichiometric amounts. Indeed, there was a small improvement in yield against using titanium tetrachloride in stoichiometric amounts. However, the overall yield of the reactions remained low.

2.2.3 Temperature Control

Further attempts to improve the reaction were employed by investigating the effects of temperature. It was hoped that:-

1. an increase in selectivity could be achieved by using sub zero temperatures

or

2. heating would allow either less Lewis acid to be used or would be able to force re-arrangements to occur that had failed at room temperatures.

2.2.3.1 Conventional Method

Typically the reaction was run at room temperature and went to completion within 4 hours. Some experiments were attempted with various temperature gradients. The reaction was attempted at -78 °C in the hope that a significantly lower temperature would increase the stereo control of the reaction.

A modest increase of the ratio of diastereomers was seen, going from 75:25 to 80:20. This was accompanied by a drastic reduction in conversion. Analysis of the crude mixture revealed that the reaction had not gone to completion and after purification an overall yield of only 17% was obtained. The reaction was repeated with cooling only during the addition of *N*-phthaloylglycyl chloride. After this, it was allowed to warm to room temperature and stirred for an additional 24 hours. ^{1}H NMR analysis of the crude mixture showed an improvement in conversion but nonetheless 47% of the starting material remained. The drastic reduction in yield was not worth the slight increase in stereo-control and further attempts were abandoned.

2.2.3.2 Microwave

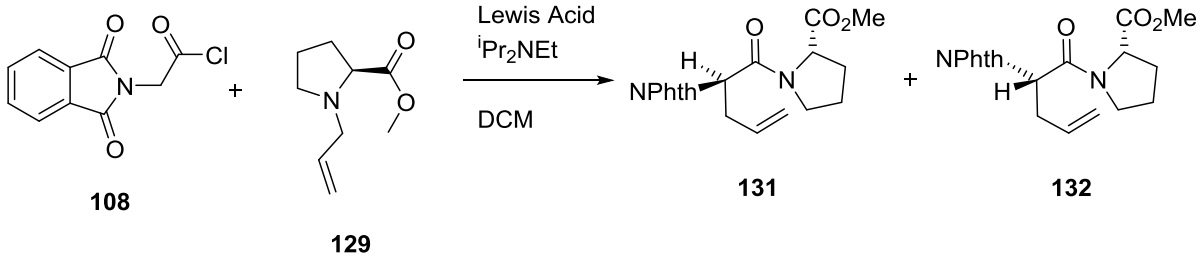
Following the successful use of the microwave to perform aminations of anhydrouridine, it was hoped to apply the same chemistry to the Belluš Claisen rearrangement.

The reaction has been successfully performed with alanine and various allylated proline variants. Unfortunately, attempts to expand the chemistry beyond these reactions have had limited success. Any allylated amino acids with more complicated side chains than alanine failed to rearrange at all, returning only starting material. Further, attempts to use stoichiometric quantities of ytterbium catalyst were also unsuccessful.

It was hoped that higher temperatures and greater pressures achievable by the microwave would provide sufficient activation energy to enable the reaction to work successfully.

As a starting point, the successful *N*-allyl proline methyl ester rearrangement would be performed in the microwave. It takes the reaction at least 4 hours under conventional conditions, including a slow 2 hour addition step. It was hoped that simply performing this reaction in the microwave would, at a minimum, speed up the reaction. If it could be successfully performed then other amino acids would be attempted.

Table 13 summarizes the result of this line of investigation. Because the reactions were performed in DCM, the microwave allowed dramatically higher temperatures than would be possible using conventional conditions. Ultimately, very high temperatures were necessary to drive the reaction to completion in a short time frame. Interestingly, higher temperatures seemed to have no effect on the stereo-control of the reaction, with a 75:25 ratio of diastereoisomers still being obtained in all cases.



Scheme 51: *Microwave Irradiation Screen of Reactions*

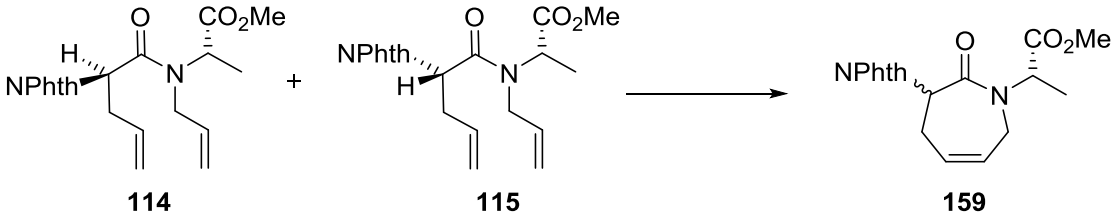
Table 13: *Microwave N-allyl proline methyl ester rearrangement*

Reaction Time (min)	Temperature (˚C)	Yield (%)	Ratio
10	80	0	-
10	90	0	-
20	90	0	-
30	90	0	-
30	100	<5	
60	120	21	75:25
30	140	37	75:25

Despite the acyl chloride being added to the reaction mixture in one portion, it is worth noting that no [2+2] cyclisation products were observable in the reaction mixture. The Belluš Claisen reaction typically requires a controlled addition of the acyl chloride to the reaction mixture as the formation of [2+2] side products from the ketene are a serious detriment to the reaction[124]. It is probable that the phthaloyl protecting group is simply so bulky that it is preventing the [2+2] side reaction from occurring. This is also supported by the fact that the major side products observable by ^{1}H NMR in failed reactions were the unreacted allylated amino acid derivative and *N*-phthaloyl glycine. No cycloadduct was seen in any reaction mixture.

2.2.3.3 Ring Closing Metathesis

Separation of the diastereoisomer mixtures produced during the Belluš-Claisen rearrangement, while not impossible, proved to be very difficult. Besides very time consuming purification methods, one idea investigated was the chemical transformation of un-separated mixtures to aid in purification. Dipeptides **114** and **115**, produced from *N*,*N*-diallyl alanine methyl ester, are perfectly set up for a ring closing metathesis (Scheme 52).



114 **115** **159**

Scheme 52: *Ring closing metathesis of dipeptides **114** and **115***

The reaction proved straightforward, with 2nd Generation Grubbs[145] catalyst giving the expected product **159** on the first attempt in good yield (87%). It had been hoped that the increased rigidity of the seven membered ring would help to differentiate the products, making column chromatography easier. Unfortunately this was not the case because the mixtures were not any easier to separate than the original dipeptide.

2.3 Conclusions and Future Work

A Belluš-Claisen rearrangement carried out with dimethylallylamine **109** with *N*-phthaloylglycyl chloride **108** as the ketene precursor has been initially investigated and a method developed to synthesise 2-phthaloyl-*N,N*-dimethylpent-4-enamide **110**. Out of a variety of Lewis acid catalysts so far tried, it has been found that anhydrous ytterbium triflate catalyst gives the best yield.

The rearrangement has been attempted with a variety of allyated amino acids. *N,N*-diallyl alanine methyl ester **123** and *N*-allyl proline methyl ester **129** both gave successful rearrangements. Use of *N*-allyl proline in particular was found to result in a moderately diastereospecific methodology. However, attempts to repeat the reaction with structurally more complex amino acids did not result in successful rearrangements. Further optimisation of the reaction is required to improve the diastereoselectivity of the reaction.

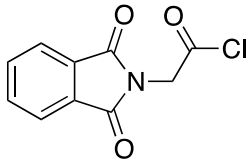
2.4 Experimental

Reagents were purchased from Sigma-Aldrich, Acros, Alfa Aesar, Fisher Scientific, TCI UK or Lancaster Research Chemicals and were not purified except where stated. Solvents were purchased anhydrous and stored over molecular sieves, or distilled under nitrogen from an appropriate drying agent. THF and diethylether were distilled from sodium benzophenone ketyl radical while DCM and acetonitrile were distilled from calcium hydride. Thin layer chromatography was performed on aluminum sheets coated with Merck silica gel 60 F_{254} with visualisation using potassium permanganate solution and/or scrutinised under 254 nm UV light. Column chromatography was performed using Silica 60 (35-70 microns) supplied by Fisher.

Nuclear magnetic resonance (NMR) spectroscopy was performed on a Bruker Advance 400 NMR spectrometer (^{1}H NMR at 400 MHz, ^{13}C NMR at 100 MHz) with the appropriate deuterated solvent. Chemical shifts in ^{1}H NMR spectra are expressed as ppm downfield from TMS and in ^{13}C NMR, are relative to internal standard, and reported as singlet (s), doublet (d), triplet (t), quartet (q) and combinations thereof, or multiplet (m). Coupling constants (*J*) are quoted in Hz and are rounded to the nearest 0.5 Hz. Mass spectrometry was performed using a Bruker MicroTOF-Q instrument with electrospray ionisation in the positive mode. FT-IR data was acquired using Thermo Electron Corporation Nicolet 380 FTIR with Smart Orbit diamond window instrument with

wavenumbers being reported in cm^{-1}. All melting points were obtained using a Stuart SMP10 melting point instrument. Microwave reactions were performed using a Milestone MicroSYNTH reactor and SK10 vessel containing one magnetic stirring bead. Twist control, rotor control, start parameters and continuous power were all selected. T1 control was used with 60 % stirring.

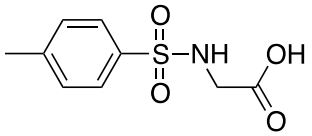
2.4.1 *N*-Phthaloylglycyl Chloride 108 [131]



N-Phthaloylglycine (7.0 g, 34.1 mmol) was refluxed in thionyl chloride (19.6 g, 12 ml, 164.5 mmol) for 1 hour. The solution was then concentrated *in vacuo* and the remaining residue was distilled at 110°C /0.7mm (corrected boiling point of 320 °C at 760 mm) which, on cooling, gave a colourless solid. (6.0 g, 27.1 mmol, 79%) mp = 83-85 °C. (lit 84-85 °C). Lit. boiling point 190-192 °C /15 mm (corrected boiling point of 320 °C at 760 mm).

δ_H (400 MHz, $CDCl_3$), 4.15 (2H, s, NC<u>H</u>$_2$), 7.77 (2H, m, Ar-<u>H</u>), 7.86 (2H, m, Ar-<u>H</u>). δ_C(100 MHz, $CDCl_3$), 38.4 (N<u>C</u>H$_2$), 123.5 (Ar-<u>C</u>), 132.0 (Ar-<u>C</u>), 134.2 (Quat. Ar-<u>C</u>), 167.6 (N<u>C</u>O), 169.2 (<u>C</u>OCl). ν_{max} (thin film, cm^{-1}), 2978 (C-H), 2938 (C-H), 1802 (COCl), 1768 and 1710 (CONCO); m/z (ES^+) calculated for $C_{10}H_7O_4N$ (hydrolysed product) $[M+H]^+$; 206.0448. found 206.0453.

2.4.2 *N*-Tosylglycine 121 [146]

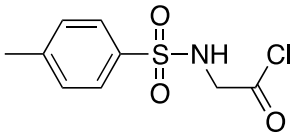


Glycine (2.60g, 30.0 mmol, 1.0 eq) was dissolved in 50 mL of 1.5M NaOH at room temperature and *p*-toluenesulfonyl chloride (6.80 g, 36.0 mmol, 1.2 eq) in Et_2O (30 mL) was added. After leaving to stir overnight 6M HCl was be added until pH = 2. The Et_2O layer was separated and the aqueous layer was extracted with Et_2O (3 x 40 mL). The

combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the product. Recrystallization from Et_2O gave the product as a white powder (2.91 g, 11.8 mmol, 39%). Mp = 146-149 °C. lit 147.6 °C.

δ_H (400 MHz, $(CD_3)_2CO$), 2.27 (3H, s, C<u>H</u>$_3$), 3.64 (2H, d, J = 6.0 Hz, C<u>H</u>$_2$), 6.52 (1H, t, J = 6.0 Hz, N<u>H</u>), 7.25 (2H, d, J = 8.0 Hz, Ar-<u>H</u>), 7.63 (2H, d, J = 8.0 Hz, Ar-<u>H</u>). δ_C (100 MHz, $CDCl_3$), 20.5 (<u>C</u>H$_3$), 43.7 (<u>C</u>H$_2$), 127.0 (Ar-<u>C</u>), 129.5 (Ar-<u>C</u>), 137.9 (Quat. Ar-<u>C</u>), 143.1 (Quat. Ar-<u>C</u>), 169.5 (<u>C</u>OOH). ν_{max} (thin film, cm^{-1}), 3353 (C-H), 1709 (CO); m/z (ES^+) calculated for $C_9H_{11}SO_4N$ $[M+H]^+$; 230.0482. found 230.0485.

2.4.3 *N*-Tosylglycyl Chloride 122[139]



N-Tosylglycine (2.48g, 10.0 mmol, 1.0 eq) was dissolved in Et_2O (25 mL) and PCl_5 (3.09g, 15.0 mmol, 1.5 eq) was added. The reaction was left to stir for 30 minutes until all organic material has dissolved. The reaction was then allowed to stir for a further 30 minutes. Excess PCl_5 was removed by filtration and hexane (100 mL) was added. The solution was set aside at 0°C for four hours.

The crystalline acid chloride will then be filtered off, washed with hexane and dried under vacuum to give the product as a colourless solid (1.59 g, 6.42 mmol, 64%) mp = 81-85 °C. Lit 82-83°C.

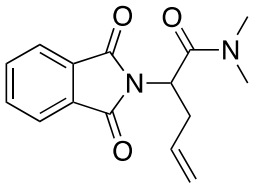
δ_H (400 MHz, $CDCl_3$), 2.44 (3H, s, C<u>H</u>$_3$), 4.27 (2H, s, C<u>H</u>$_2$), 5.25 (1H, br s, N<u>H</u>), 7.34 (2H, d, J = 8.0 Hz, Ar-<u>H</u>), 7.75 (2H, d, J = 8.0 Hz, Ar-<u>H</u>). δ_C (100 MHz, $CDCl_3$), 21.6 (<u>C</u>H$_3$), 53.6 (<u>C</u>H$_2$), 127.1 (Ar-<u>C</u>), 130.0 (Ar-<u>C</u>), 136.1 (Quat. Ar-<u>C</u>), 144.5 (Quat. Ar-<u>C</u>), 171.0 (<u>C</u>OOH). ν_{max} (thin film, cm^{-1}), 2980 (C-H), 1802 (COCl).

2.4.4 General Belluš-Claisen Procedure

Modifying a procedure by MacMillan *et al*[122], to a solution of dried $Yb(OTf)_3$ (1.0 eq) in dry DCM (20 mL) was added *N*,*N*-dimethylallylamine (1.0 eq) followed by *N*,*N*-diisopropylethylamine (2.0 eq). The solution was stirred for 5 min before a solution of *N*-phthaloylglycyl chloride (1.5 eq) in dry DCM (10 mL) was added drop-wise over 2 hours.

The resulting dark orange mixture was then stirred for an additional 2 hours. The reaction was then diluted with diethyl ether (20 mL), treated with aqueous NaOH (1M; 10 mL) and stirred for a further 10 minutes. The aqueous layer was extracted with diethyl ether (3 x 40 mL) and the organic layers combined, washed with brine (3 x 20 mL), and dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by column chromatography and/or re-crystalization gave the desired product

2.4.5 2-Phthaloyl-*N*,*N*-dimethylpent-4-enamide 110



Following general Belluš Claisen procedure from dried $Yb(OTf)_3$ (1.24 g, 2.00 mmol, 1.0 eq), *N*,*N*-dimethylallylamine (170 mg, 0.24 mL, 2.00 mmol, 1.0 eq), *N*,*N*-diisopropylethylamine (517 mg, 0.70 mL, 4.00 mmol, 2.0 eq) and *N*-phthaloylglycyl chloride (670 mg, 3.00 mmol, 1.5 eq) 2-phthaloyl-*N*,*N*-dimethylpent-4-enamide was obtained as a yellow oil that solidified on standing. This was recrystallised from IPA/*tert*-butyl methyl ether to give the product as a pale yellow solid. (311 mg, 1.14 mmol, 57%) mp = 106-107 °C.

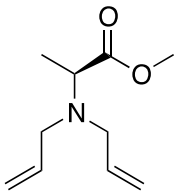
δ_H (400 MHz, $CDCl_3$), 2.76-2.83 (1H, app m, C$\underline{H}_2$), 2.98 (6H, s, C$\underline{H}_3$), 3.12-3.20 (1H, app m, J = 10.5 Hz, C$\underline{H}_2$), 5.00 (1H, app d, J = 10.0 Hz, NC$\underline{H}$), 5.07-5.12 (2H, app m, trans CH=C$\underline{H}_2$, C$\underline{H}$), 5.78 (1H, dddd, J = 4.0 Hz, J = 5.5 Hz, J = 10.0 Hz, J = 17.0 Hz, C$\underline{H}$=CH_2), 7.71-7.76 (2H, m, C=C$\underline{H}$), 7.83-7.87 (2H, m, C=CH-C$\underline{H}$). δ_C (100 MHz, $CDCl_3$), 33.4 (NCH$\underline{C}H_2$), 36.3 (N$\underline{C}H_3$), 37.0 (N$\underline{C}H_3$), 51.1 (N$\underline{C}$HCO), 118.7 (CH=$\underline{C}H_2$), 123.5 (Ar-$\underline{C}$), 131.5 (Quat. Ar-$\underline{C}$), 133.7 (CH_2=$\underline{C}$H), 134.2 (Ar-$\underline{C}$), 167.8 (N$\underline{C}$O), 168.1 ($\underline{C}$ON$(CH_3)_2$. ν_{max} (thin film, cm^{-1}), 2965 (C-H), 1716 (Ester CO_2), 1387 (C-H); m/z (ES^+) calculated for $C_{15}H_{16}O_3N_2$ $[M+H]^+$; 273.1234. found 273.1246.

2.4.6 General Diallylation Procedure [147]

Amino methyl ester hydrochloride (1.0 eq) was added to a mixture of allyl bromide (2.2eq) and sodium hydrogen carbonate (4.0 eq) in acetronitrile (40 mL). The reaction was heated to 70 °C and left to stir overnight under nitrogen. After 18 hours the reaction

was cooled to room temperature and the resulting precipitated salt removed by filtration. The mixture was then concentrated *in vacuo* to give the crude product which was purified by column chromatography (ethyl acetate) to give the product.

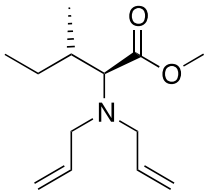
2.4.7 *N,N*-Diallyl alanine methyl ester 123[147]



Following *N*-allylation procedure from L-alanine methyl ester hydrochloride (2.00g, 14.3 mmol, 1.0 eq), allyl bromide (3.81g, 2.73 mL, 31.5 mmol, 2.2 eq) and sodium hydrogen carbonate (4.81g, 57.3 mmol, 4.0 eq) *N*,*N*-diallyl alanine methyl ester was obtained as a pale yellow oil (1.89 g, 10.3 mmol, 72%).

δ_H (400 MHz, $CDCl_3$), 1.26 (3H, d, J = 7.0, $CHC\underline{H}_3$), 3.13 (2H, ddt, J = 1.0, J = 7.0, J = 14.5 Hz, $NC\underline{H}^AH^B$), 3.26 (2H, ddt, J = 1.5, J = 5.5, J =14.5 Hz, $NCH^A\underline{H}^B$), 3.60 (1H, q, J = 7.0 Hz, $C\underline{H}CH_3$), 3.69 (3H, s, OCH_3), 5.10 (2H, ddd, J = 1.0, J = 3.0, J = 10.0 Hz, cis $CH=C\underline{H}_2$), 5.19 (2H, ddd, J = 1.5, J = 3.0, J = 17.0 Hz, trans $CH=C\underline{H}_2$), 5.80 (2H, dddd, J = 5.0, J = 7.0, J = 10.0, J = 17.0, $CH_2=C\underline{H}$). δ_C (100 MHz, $CDCl_3$), 14.6 ($CH\underline{C}H_3$), 51.1 ($O\underline{C}H_3$), 53.4 ($N\underline{C}H_2$), 57.1 ($\underline{C}H$), 117.0 ($CH=\underline{C}H_2$), 136.4 ($\underline{C}H=CH_2$), 174.2 ($\underline{C}O$). m/z (ES^+) calculated for $C_{10}H_{17}NO_2$ $[M+H]^+$; 184.1332. found 184.1339.

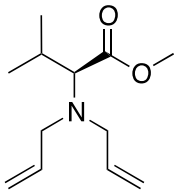
2.4.8 *N,N*-Diallyl isoleucine methyl ester 111c



Following *N*-allylation procedure from L-isoleucine methyl ester hydrochloride (2.0g, 11.0 mmol, 1.0 eq), allyl bromide (2.93g, 2.10 mL, 24.2 mmol, 2.2eq) and sodium hydrogen carbonate (3.70g, 44.0 mmol, 4.0 eq) *N*,*N*-diallyl isoleucine methyl ester was obtained as a pale yellow oil. (1.89 g, 8.25 mmol, 75%)

δ_H (400 MHz, $CDCl_3$), 0.81 (3H, d, J = 6.5 Hz, $CHC\underline{H}_3$), 0.85 (3H, t, J = 7.5 Hz, $CH_2C\underline{H}_3$), 1.10-1.17 (1H, m, $CH_3C\underline{H}^AH^B$), 1.66-1.80 (1H, m, $CH_3CH^A\underline{H}^B$), 1.81-1.93 (1H, m, NCHC$\underline{H}$), 2.82 (2H, app dd, J = 8.0, J = 14.5 Hz, $NC\underline{H}^AH^B$), 3.09 (1H, d, J = 11.0 Hz, NC$\underline{H}$), 3.41 (2H, app dt, J = 2.0, J =14.5 Hz, $NCH^A\underline{H}^B$), 3.69 (3H, s, $OC\underline{H}_3$), 5.09 (2H, app d, J = 10.0 Hz, cis CH=C$\underline{H}_2$), 5.18 (2H, app d, J = 17.0 Hz, trans CH=C$\underline{H}_2$), 5.75 (2H, dddd, J = 4.5, J = 9.0, J = 10.0, J = 17.0 Hz, CH_2=C$\underline{H}$). δ_C (100 MHz, $CDCl_3$), 10.1 ($CH_2\underline{C}H_3$), 15.9 ($CH\underline{C}H_3$), 24.8 ($CH_3\underline{C}H_2$), 33.2 (NCH$\underline{C}$H), 50.5 ($O\underline{C}H_3$), 53.3 ($N\underline{C}H_2$), 67.0 (N$\underline{C}$H), 116.9 (CH=$\underline{C}H_2$), 136. 6 ($\underline{C}H$=CH_2), 173.0 ($\underline{C}$O). m/z (ES^+) calculated for $C_{13}H_{23}NO_2$ $[M+H]^+$; 226.1802. found 226.1812.

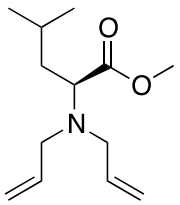
2.4.9 *N*,*N*-Diallyl valine methyl ester 111a



Following *N*-allylation procedure from L-valine methyl ester hydrochloride (2.0g, 11.9 mmol, 1.0 eq), allyl bromide (3.18g, 2.27 mL, 26.2 mmol, 2.2eq) and sodium hydrogen carbonate (4.01g, 143.3 mmol, 4.0 eq) *N*,*N*-diallyl valine methyl ester was obtained as a yellow oil. (1.53 g, 7.26 mmol, 61%)

δ_H (400 MHz, $CDCl_3$), 0.85 (3H, d, J = 6.5 Hz, $CHC\underline{H}_3$), 0.96 (3H, d, J = 6.5 Hz, $CHC\underline{H}_3$), 1.98-2.07 (1H, m, $(CH_3)_2C\underline{H}$), 2.83 (2H, app dd, J = 8.0, J = 15.0 Hz, $NC\underline{H}^AH^B$ x 2), 2.96 (1H, d, J = 11.0 Hz, C$\underline{H}$CO), 3.41 (2H, ddt, J = 2.0, J = 4.0, J = 15.0 Hz, $NCH^A\underline{H}^B$ x 2), 3.69 (3H, s, OCH_3), 5.10 (2H, dd, J = 2.0, 10.0 Hz, cis CH=C$\underline{H}_2$), 5.19 (2H, ddd, J = 1.0, 2.0, 17.0 Hz, trans CH=C$\underline{H}_2$), 5.75 (2H, dddd, J = 4.0, J = 8.0, J = 10.0, J = 17.0 Hz, CH_2=C$\underline{H}$). δ_C (100 MHz, $CDCl_3$), 19.5 ($CH\underline{C}H_3$), 19.9 ($CH\underline{C}H_3$), 27.6 ($\underline{C}H(CH_3)_2$), 50.6 ($O\underline{C}H_3$), 53.3 ($N\underline{C}H_2$), 68.8 (N$\underline{C}$H), 116.8 (CH=$\underline{C}H_2$), 136.6 ($\underline{C}H$=CH_2), 173.0 ($\underline{C}$O). m/z (ES^+) calculated for $C_{12}H_{21}NO_2$ $[M+H]^+$; 212.1645. found 212.1655.

2.4.10 *N*,*N*-Diallyl leucine methyl ester 111b [147]



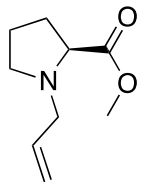
Following *N*-allylation procedure from L-leucine methyl ester hydrochloride (2.0g, 11.0 mmol, 1.0 eq), allyl bromide (2.93g, 2.10 mL, 24.2 mmol, 2.2eq) and sodium hydrogen carbonate (3.70g, 44.0 mmol, 4.0 eq) *N*,*N*-diallyl leucine methyl ester was obtained as a yellow oil. (1.69 g, 7.48 mmol, 68%)

δ_H (400 MHz, $CDCl_3$), 0.87 (3H, d, J = 6.5 Hz, $CHC\underline{H}_3$), 0.90 (3H, d, J = 6.5 Hz, $CHC\underline{H}_3$), 1.46-1.60 (2H, m, $CHC\underline{H}_2$), 1.65-1.73 (1H, m, $C\underline{H}(CH_3)_2$), 3.03 (2H, app dd, J = 7.5, J = 14.5 Hz, $NC\underline{H}^AH^B$), 3.35 (2H, ddt, J = 1.5, J = 4.5, J = 14.5 Hz, $NCH^A\underline{H}^B$), 3.52 (1H, dd, J = 7.0, J = 8.0 Hz, $C\underline{H}CO$), 3.68 (3H, s, OCH_3), 5.10 (2H, app d, J = 10.0 Hz, cis $CH=C\underline{H}_2$), 5.18 (2H, app d, J = 17.0 Hz, trans $CH=C\underline{H}_2$), 5.72 (2H, dddd, J = 5.0, J = 7.0, J = 10.0, J = 17.0 Hz, $CH_2=C\underline{H}$). δ_C (100 MHz, $CDCl_3$), 22.0 ($CH\underline{C}H_3$), 23.0 ($CH\underline{C}H_3$), 24.6 ($\underline{C}H(CH_3)_2$), 38.6 ($NCH\underline{C}H_2$), 50.9 ($O\underline{C}H_3$), 53.4 ($N\underline{C}H_2$), 59.9 ($N\underline{C}H$), 117.0 ($CH=\underline{C}H_2$), 136.7 ($\underline{C}H=CH_2$), 174.2 ($\underline{C}O$). m/z (ES^+) calculated for $C_{16}H_{23}NO_2$ $[M+H]^+$; 226.1802. found 226.1811.

2.4.11 General Mono Allylation Procedure

L-proline methyl ester hydrochloride (1.0 eq) was taken up in DMF (50 mL) and cooled to 0 °C. Allyl bromide (1.1 eq) was then added, followed by triethylamine (2.0 eq). The reaction was allowed to warm to room temperature and left to stir overnight under nitrogen. After 18 hours the reaction was quenched with H_2O (50 mL) and extracted with EtOAc (40 mL x 3). The organic layers were combined, washed with H_2O (30 mL x 3) and dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the crude. The product was purified by column chromatography (90:10 hexanes: ethyl acetate) to give the product.

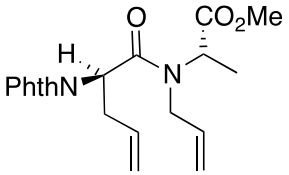
2.4.12 *N*-Allyl proline methyl ester 129[148]



Following mono *N*-allylation procedure from L-proline methyl ester hydrochloride (5.00g, 30.2 mmol, 1.0 eq), allyl bromide (4.02g, 2.87 mL, 33.2 mmol, 1.1 eq) and triethylamine (6.11 g, 8.4 mL, 60.4 mmol, 2.0 eq) *N*-Allyl proline methyl ester was obtained as a pale yellow oil (2.61 g, 5.32 mmol, 44%).

δ_H (400 MHz, $CDCl_3$), 1.75-1.87 (1H, m, NCHCH<u>H</u>), 1.88-1.99 (2H, m, NCHCH<u>H</u> + NCH-$_2$C<u>H</u>H), 2.07-2.20 (1H, m, $NCH_2C\underline{H}H$), 2.38 (1H, q, J = 9.0 Hz, NC<u>H</u>), 3.09-3.19 (2H, m, C<u>H</u>CO + NCH<u>H</u>-CH=CH_2), 3.31 (1H, app dd, J = 6.5, J = 13.0 Hz, NC<u>H</u>H-CH=CH_2), 3.72 (3H, s, $OC\underline{H}_3$), 5.09 (1H, dd, J = 1.0, J = 10.0 Hz, cis CH=C<u>H</u>$_2$), 5.18 (1H, dd, J = 1.0, J = 17.0 Hz, trans CH=C<u>H</u>$_2$), 5.92 (1H, ddt, J = 7.0, J = 10.0, J = 17.0 Hz, CH_2=C<u>H</u>). δ_C (100 MHz, $CDCl_3$), 23.0 (NCH<u>C</u>H_2), 29.5 ($NCH_2\underline{C}H_2$), 51.8 ($O\underline{C}H_3$), 53.5 ($N\underline{C}H_2CH_2$), 57.8 ($N\underline{C}H_2CH$), 65.2 (<u>C</u>HCO), 117.4 (CH=<u>C</u>H_2), 135.2 (<u>C</u>H=CH_2), 174.6 (<u>C</u>O). ν_{max} (thin film, cm^{-1}), 2951 (C-H), 1732 (Ester CO_2), 1435 (Alkene C-H), 1195 and 1167 (C-N); m/z (ES^+), calculated for $C_9H_{15}NO_2$ $[M+H]^+$; 170.1176. found 170.1193.

2.4.13 (*S*)-Methyl 2-((*R*)-*N*-allyl-2-(1,3-dioxoisoindolin-2-yl)pent-4-enamido)propanoate 124

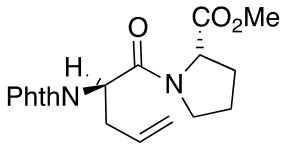


Following general Belluš Claisen procedure from dried $Yb(OTf)_3$ (620 mg, 1.00 mmol, 1.0 eq), *N*,*N*-diallylalanine methyl ester (183 mg, 1.00 mmol, 1.0 eq), *N*,*N*-diisopropylethylamine (258 mg, 0.25 mL, 2.00 mmol, 2.0 eq and *N*-phthaloylglycyl chloride (335 mg, 1.50 mmol, 1.5 eq) (*S*)-Methyl 2-((*R*)-*N*-allyl-2-(1,3-dioxoisoindolin-2-yl)pent-4-enamido)propanoate was obtained as a yellow oil. Purification by column chromatography (diethyl ether) yielded the two diastereoisomers in a 60:40 ratio as a yellow oil. On standing overnight the oil solidified to give a pale yellow solid. (178 mg, 0.48 mmol, 48%). mp = 82-86 °C.

$\delta_{\mathbf{H}}$ (400 MHz, $CDCl_3$), 1.43 (3H, d, J = 7.0 Hz, Minor CHC<u>H</u>$_3$), 1.49 (3H, d, J = 7.0 Hz, Major CHC<u>H</u>$_3$), 2.78-2.81 (1H, m, CHC<u>H</u>^{A}H^B), 3.06-3.22 (1H, m, CHCH^A<u>H</u>^{B}), 3.69 (3H, s, Major $OC\underline{H}_3$), 3.72 (3H, s, Minor $OC\underline{H}_3$), 3.97 (2H, d, J = 5.0 Hz, $NC\underline{H}_2$), 4.14 (1H, q, J = 7.0 Hz, Major C<u>H</u>CH_3), 4.46 (1H, q, J = 7.0 Hz, Minor C<u>H</u>CH_3), 4.88-5.30 (5H, m, CH=C<u>H</u>$_2$ x 2, $(CO)_2NC\underline{H}$), 5.60-5.86 (2H, m, CH_2=C<u>H</u> x 2), 7.71-7.75 (2H, m, Ar-<u>H</u>), 7.81-7.85 (2H, m, Ar-<u>H</u>). $\delta_{\mathbf{C}}$ (100 MHz, $CDCl_3$), (Major diastereoisomer), 14.6 (CH<u>C</u>H_3), 33.5 (CH<u>C</u>H_2), 50.6 ($NC\underline{H}_2$), 51.0 (<u>C</u>HCH_2), 52.2 ($O\underline{C}H_3$), 55.7 (<u>C</u>HCH_3), 117.6 (CH=<u>C</u>H_2), 118.8 (CH=<u>C</u>H_2), 123.5 (Ar-<u>C</u>), 131.7 (Quat. Ar-<u>C</u>), 133.0 (CH_2=<u>C</u>H), 133.5 (CH_2=<u>C</u>H), 134.2 (Ar-<u>C</u>), 167.5 (N(<u>C</u>O)$_2$), 168.9 (CH(<u>C</u>O)NCH), 171.8 (<u>C</u>OCH_3), (Minor diastereoisomer), 14.3 (CH<u>C</u>H_3), 33.3 (CH<u>C</u>H_2), 48.7 ($NC\underline{H}_2$), 54.9 (<u>C</u>HCH_3), 117.0

(CH=CH$_2$), 123.4 (Ar-C), 131.7 (Quat. Ar-C), 133.2 (CH$_2$=CH), 133.5 (CH$_2$=CH), 134.1 (Ar-C), 168.9 (CH(CO)NCH), 171.8 (COCH$_3$). ν_{max} (thin film, cm^{-1}), 2949 (C-H), 1709 (Ester CO$_2$), 1646 (Amide); m/z (ES$^+$) calculated for $C_{20}H_{22}O_5N_2$ [M+H]$^+$; 371.1601. found 371.1604.

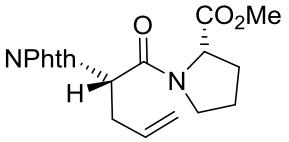
2.4.14 (*S*)-Methyl 1-((*R*)-2-(1,3-dioxoisoindolin-2-yl)pent-4-enoyl)pyrrolidine-2-carboxylate 131



Following general Belluš Claisen procedure from dried Yb(OTf)$_3$ (1.24 g, 2.00 mmol, 1.0 eq), *N*-Allyl proline methyl ester (338 mg, 2.00 mmol, 1.0 eq), *N*,*N*-diisopropylethylamine (517 mg, 0.70 mL, 4.00 mmol, 2.0 eq) and *N*-phthaloylglycyl chloride (670 mg, 3.00 mmol, 1.5 eq) (*S*)-Methyl 1-((*R*)-2-(1,3-dioxoisoindolin-2-yl)pent-4-enoyl)pyrrolidine-2-carboxylate was obtained as a yellow oil. Purification by column chromatography yielded the two diastereoisomers in a 75:25 ratio as a yellow oil. (421 mg, 0.44 mmol, 59%). On standing overnight the product solidified as a yellow solid. Recrystalisation from diisopropylether/IPA isolated the major diasteriosmer as pale colourless crystals. mp = 139-143 °C.

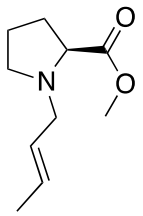
δ_H (400 MHz, CDCl$_3$), 1.83-2.03 (3H, m, NCHCH^{A}H^{B}CH$_2$, NCH$_2$CH^{A}H^B), 2.18-2.25 (1H, m, NCHCH^{A}H^{B}CH$_2$), 2.85 (1H, dtt, J = 1.5, J = 5.5, J = 14.5 Hz, (CO)$_2$NCHCH^{A}H^B), 3.09 (1H, app dt, J = 9.5, J = 14.5 Hz, (CO)$_2$NCHCH^{A}H^B), 3.36-3.42 (1H, m, NCH^{A}H^{B}CH$_2$), 3.56-3.62, (1H, m, NCH^{A}H^{B}CH$_2$), 3.70 (3H, s, OCH$_3$), 4.54 (1H, dd, J = 6.0, J = 8.5 Hz, CHCONCH), 4.96-5.02 (2H, m, (CO)$_2$NCH + CH=CH$_2$ cis), 5.08 (1H, dd, J = 1.0, 17.0 Hz, CH=CH$_2$ trans), 5.76 (1H, dddd, J = 5.5, J = 9.0, J = 10.0, J = 17.0 Hz, CH=CH$_2$), 7.74 (2H, dd, J = 3.0, J = 5.5 Hz, Ar-H), 7.88 (2H, dd, J = 3.0, J = 5.5 Hz, Ar-H). δ_C (100 MHz, CDCl$_3$), 25.3 (NCHCH$_2$CH$_2$), 28.8 (NCH$_2$CH$_2$), 33.0 (CH$_2$CH=CH$_2$), 47.0 (NCH$_2$CH$_2$), 51.9 ((CO)$_2$NCH), 52.2 (OCH$_3$), 59.6 (CONCHCO), 118.8 (CH=CH$_2$), 123.6 (Ar-C), 131.5 (Quat. Ar-C), 133.5 (CH$_2$=CH), 134.2 (Ar-C), 166.9 (CH(CO)NCH), 167.3 (N(CO)$_2$), 172.1 (COCH$_3$). ν_{max} (thin film, cm^{-1}), 2980 (C-H), 1381 (C-H); m/z (ES$^+$) calculated for $C_{15}H_{17}O_3N_2$ [M+H]$^+$; 273.12. found 273.12.

2.4.15 (*S*)-Methyl 1-((S)-2-(1,3-dioxoisoindolin-2-yl)pent-4-enoyl)pyrrolidine-2-carboxylate 132



δ_H (400 MHz, $CDCl_3$), 1.88-2.13 (4H, m, NCHC$\underline{H}^A\underline{H}^BCH_2$, $NCH_2C\underline{H}^A\underline{H}^B$), 2.89 (1H, dtt, J = 1.5, J = 5.5, J = 14.5 Hz, $(CO)_2NCHC\underline{H}^AH^B$), 3.13 (1H, app dt, J = 9.5, J = 14.5 Hz, $(CO)_2NCHCH^A\underline{H}^B$), 3.30-3.37 (1H, m, $NC\underline{H}^AH^BCH_2$), 3.66-3.71, (1H, m, $NCH^A\underline{H}^BCH_2$), 3.74 (3H, s, $OC\underline{H}_3$), 4.50 (1H, dd, J = 6.0, J = 8.5 Hz, CHCONC$\underline{H}$), 5.00-5.06 (2H, m, $(CO)_2NC\underline{H}$ + $CH=C\underline{H}_2$ cis), 5.09 (1H, app dq, J = 1.0, 17.0 Hz, $CH=C\underline{H}_2$ trans), 5.78 (1H, dddd, J = 5.5, J = 9.0, J = 10.0, J = 17.0 Hz, $C\underline{H}=CH_2$), 7.74 (2H, dd, J = 3.0, J = 5.5 Hz, Ar-$\underline{H}$), 7.85 (2H, dd, J = 3.0, J = 5.5 Hz, Ar-$\underline{H}$). δ_C (100 MHz, $CDCl_3$), 24.9 ($NCH\underline{C}H_2CH_2$), 28.7 ($NCH_2\underline{C}H_2$), 33.0 ($\underline{C}H_2CH=CH_2$), 46.9 ($N\underline{C}H_2CH_2$), 52.3 ($(CO)_2N\underline{C}H$), 52.3 ($O\underline{C}H_3$), 59.4 ($CON\underline{C}HCO$), 118.7 ($CH=\underline{C}H_2$), 123.6 (Ar-$\underline{C}$), 131.5 (Quat. Ar-$\underline{C}$), 133.6 ($CH_2=\underline{C}H$), 134.2 (Ar-$\underline{C}$), 167.1 ($CH(\underline{C}O)NCH$), 167.7 ($N(\underline{C}O)_2$), 172.5 ($\underline{C}OCH_3$).

2.4.16 *N*-Crotyl L-proline methyl ester 145a

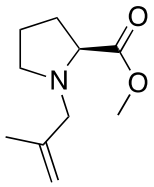


Following mono *N*-allylation procedure from L-Proline methyl ester hydrochloride (2.00g, 12.1 mmol, 1.0 eq), crotyl bromide (1.80g, 1.37 mL, 13.3 mmol, 1.1 eq) and triethylamine (2.47 g, 3.40 mL, 24.2 mmol, 2.0 eq) *N*-Crotyl L-proline methyl ester was obtained as a mix of cis and trans products as a pale yellow oil (1.09 g, 5.93 mmol, 49%).

δ_H (400 MHz, $CDCl_3$), 0.97 (3H, d, J = 7.5 Hz, $CHC\underline{H}_3$), 1.66-1.78 (1H, m, $NCHC\underline{H}^AH^B$), 1.79-1.82 (2H, m, $NCHCH^A\underline{H}^B$ + $NCH_2C\underline{H}^AH^B$), 1.88-1.97 2.09-2.16 (1H, m, $NCH_2CH^A\underline{H}^B$),

2.35 (1H, app q, J = 9.0 Hz, NC$\underline{H}^A$H^{B}CH$_2$), 3.06–3.17 (4H, m, NCH$^A\underline{H}^B$CH$_2$, NC$\underline{H}_2$CH, C$\underline{H}$CO), 3.71 (3H, s, OC$\underline{H}_3$), 5.50-5.63 (2H, m, C$\underline{H}$=CHCH$_3$, CH=C$\underline{H}$CH$_3$). δ_C (100 MHz, $CDCl_3$), 17.7 (CH$\underline{C}$H$_3$), 23.0 (NCH$\underline{C}$H$_2$), 29.5 (NCH$_2\underline{C}$H$_2$), 51.8 (O$\underline{C}$H$_3$), 53.5 (N$\underline{C}$H$_2$CH$_2$), 56.9 (N$\underline{C}$H$_2$CH), 65.3 ($\underline{C}$HCO), 127.8 (CH$_3\underline{C}$H=CH), 128.8 (CH$_3$CH=$\underline{C}$H), 174.8 ($\underline{C}$O). ν_{max} (thin film, cm^{-1}), 2951 (C-H), 1732 (Ester CO_2), 1435 (Alkene C-H), 1195 and 1168 (C-N); m/z (ES$^+$), calculated for $C_{10}H_{17}NO_2$ $[M+H]^+$; 184.1332. found 184.1339.

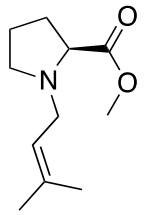
2.4.17 *N*-(2-Methylprop-2-en-1-yl)-L-proline methyl ester 145c



Following mono *N*-allylation procedure from L-Proline methyl ester hydrochloride (2.00g, 12.1 mmol, 1.0 eq), 1-bromo-2-methylpropene (1.80 g, 1.37 mL, 13.3 mmol, 1.1 eq) and triethylamine (2.47 g, 3.40 mL, 24.2 mmol, 2.0 eq) *N*-(2-Methylprop-2-en-1-yl)-L-proline methyl ester was obtained as a pale yellow oil. (1.16 g, 6.41 mmol, 53%)

δ_H (400 MHz, $CDCl_3$), 1.78 (3H, s, CC$\underline{H}_3$), 1.75-1.86 (1H, m, NCHC$\underline{H}^A$H^B), 1.87-2.00 (2H, m, NCHCH$^A\underline{H}^B$ + NCH$_2$C$\underline{H}^A$H^B), 2.09-2.18 (1H, m, NCH$_2$CH$^A\underline{H}^B$), 2.35 (1H, app q, J = 8.0 Hz, 1H, m, NC$\underline{H}^A$H^{B}CH$_2$), 2.96 (1H, d, J = 12.5 Hz, NC$\underline{H}^A$H^B-CH=CH$_2$), 3.05-3.10 (1H, m, NCH$^A\underline{H}^B$CH$_2$), 3.19 (1H, dd, J = 5.5, J = 9.0 Hz, C$\underline{H}$CO), 3.22 (1H, d, J = 12.5 Hz, NCH$^A\underline{H}^B$-CH=CH$_2$), 3.70 (3H, s, OC$\underline{H}_3$), 4.79 (1H, s, cis C=C$\underline{H}_2$), 4.86 (1H, s, trans C=C$\underline{H}_2$). δ_C (100 MHz, $CDCl_3$), 20.8 (C$\underline{C}$H$_3$), 23.1 (NCH$\underline{C}$H$_2$), 29.4 (NCH$_2\underline{C}$H$_2$), 51.6 (O$\underline{C}$H$_3$), 53.5 (N$\underline{C}$H$_2$CH$_2$), 61.7 ($\underline{C}$H$_2$-C=CH), 65.6 ($\underline{C}$HCO), 112.7 (C=$\underline{C}$H$_2$), 143.6 ($\underline{C}$=CH$_2$), 174.8 ($\underline{C}$O). ν_{max} (thin film, cm^{-1}), 2951 (C-H), 1732 (Ester CO_2), 1435 (Alkene C-H), 1195 and 1167 (C-N); m/z (ES$^+$) calculated for $C_{10}H_{17}NO_2$ $[M+H]^+$; 184.1332. found 184.1346.

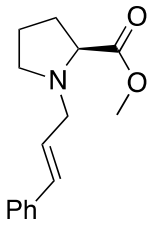
2.4.18 *N*-(3-Methylbut-2-enyl)-L-proline methyl ester 145b



Following mono *N*-allylation procedure from L-Proline methyl ester hydrochloride (2.00g, 12.1 mmol, 1.0 eq), 3,3-dimethylallyl bromide (1.98g, 1.53 mL, 13.3 mmol, 1.1 eq) and triethylamine (2.47 g, 3.40 mL, 24.2 mmol, 2.0 eq) *N*-(3-Methylbut-2-enyl)-L-proline methyl ester product as a pale yellow clear oil. (1.48 g, 7.50 mmol, 62%)

δ_H (400 MHz, $CDCl_3$), 1.65 (3H, s, cis $C\underline{H}_3$), 1.71 (3H, d, J = 1.0 Hz trans $C\underline{H}_3$), 1.71-1.83 (1H, m, $NCHC\underline{H}^AH^B$), 1.88-1.97 (2H, m, $NCHCH^A\underline{H}^B$, $NCH_2C\underline{H}^AH^B$), 2.05-2.17 (1H, m, $NCH_2CH^A\underline{H}^B$), 2.36 (1H, app q, J = 8.0 Hz, 1H, m, $NC\underline{H}^AH^BCH_2$), 3.09 (1H, dd, J = 7.0, J = 13.0 Hz, $NC\underline{H}^AH^BCH{=}C$), 3.11-3.20 (2H, m, $C\underline{H}CO$, $NC\underline{H}^AH^BCH_2$), 3.27 (1H, dd, J = 7.5, J = 13.0 Hz, $NCH^A\underline{H}^BCH{=}C$), 3.71 (3H, s, $OC\underline{H}_3$), 5.29 (1H, app tquin, J = 1.0 , J = 7.0 Hz, $C{=}C\underline{H}$). δ_C (100 MHz, $CDCl_3$), 17,8 (cis $\underline{C}H_3$), 23.0 ($NCH\underline{C}H_2$), 25.8 (trans $\underline{C}H_3$), 29.4 ($NCH_2\underline{C}H_2$), 51.8 ($O\underline{C}H_3$), 51.8 ($N\underline{C}H_2CH{=}C$), 53.5 ($N\underline{C}H_2CH_2$), 65.4 ($\underline{C}HCO$), 121.0 ($CH_2\underline{C}H{=}C$), 135.1 ($CH_2CH{=}\underline{C}$), 174.8 ($\underline{C}O$). ν_{max} (thin film, cm^{-1}), 2951 (C-H), 1732 (Ester CO_2), 1435 (Alkene C-H), 1193 and 1167 (C-N); m/z (ES^+) calculated for $C_{15}H_{19}NO_2$ $[M+H]^+$; 198.1489. found 198.1510.

2.4.19 *N*-Cinnamyl-L-proline methyl ester 145e

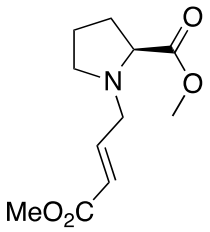


Following mono *N*-allylation procedure from L-Proline methyl ester hydrochloride (5.00g, 30.3 mmol, 1.0 eq) cinnamyl bromide (6.55g, 33.3 mmol, 1.1 eq) and triethylamine

(6.18 g, 8.51 mL, 60.5 mmol, 2.0 eq) *N*-Cinnamyl-L-proline methyl ester was obtained as an orange oil. (4.31 g, 17.6 mmol, 40%)

δ_H (400 MHz, $CDCl_3$), 1.74-1.86 (1H, m, NCHC$\underline{H}^A$H^B), 1,88-2.01 (2H, m, NCHCH$^A\underline{H}^B$, NCH$_2$C$\underline{H}^A$H^B), 2.07-2.20 (1H, m, NCH$_2$CH$^A\underline{H}^B$), 2.41 (1H, app q, J = 8.5 Hz, 1H, NC$\underline{H}^A$H^{B}CH$_2$), 3.16-3.23 (2H, m, NCH$^A\underline{H}^B$CH$_2$, C$\underline{H}$CO), 3.30 (1H, dd, J = 7.0, J = 13.0, NC$\underline{H}^A$H^B-CH), 3.41 (1H, dd, J = 7.0, J = 13.5 Hz, NCH$^A\underline{H}^B$-CH), 3.63 (3H, s, OC$\underline{H}_3$), 6.33 (1H, app dt, J = 7.0 , J = 16.0 Hz, Ph-CH=C$\underline{H}$), 6.50 (1H, d, J = 16.0 Hz, Ph-C$\underline{H}$). δ_C (100 MHz, $CDCl_3$), 23.1 (NCH$\underline{C}$H$_2$), 29.6 (NCH$_2\underline{C}$H$_2$), 51.8 (O$\underline{C}$H$_3$), 53.8 (N$\underline{C}$H$_2$CH$_2$), 57.12 (N$\underline{C}$H$_2$CH), 65.4 ($\underline{C}$HCO), 126.3 (Ar-$\underline{C}$), 126.8 (PhCH=$\underline{C}$H), 127.4 (Ar-$\underline{C}$), 128.5 (Ar-$\underline{C}$), 132.5 (Ph$\underline{C}$H=CH), 136.9 (Quat. Ar-$\underline{C}$), 174.7 (NCH$\underline{C}$O). ν_{max} (thin film, cm^{-1}), 2950 (C-H), 1731 (Ester CO_2), 1435 (Alkene C-H), 1195 and 1167 (C-N); m/z (ES^+) calculated for $C_{15}H_{19}NO_2$ $[M+H]^+$; 246.1489. found 246.1511.

2.4.20 *N*-(4-Methoxy-4-oxobut-2-en-1-yl)-L-Proline methyl ester 145f

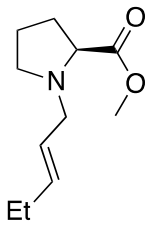


Following mono *N*-allylation procedure from L-Proline methyl ester hydrochloride (1.00g, 6.04 mmol, 1.0 eq), methyl *trans*-4-bromo-2-butenoate (1.19 g, 2.87 mL, 6.67 mmol, 1.1 eq) and triethylamine (1.23 g, 1.69 mL, 12.1 mmol, 2.0 eq) *N*-(4-Methoxy-4-oxobut-2-en-1-yl)-L-Proline methyl ester was obtained as a pale yellow oil. (810 mg, 3.56 mmol, 59%)

δ_H (400 MHz, $CDCl_3$), 1.79-2.19 (3H, m, NCHC$\underline{H}^A$H^B, NCHCH$^A\underline{H}^B$, NCH$_2$C$\underline{H}^A$H^B), 2.09-2.19 (1H, m, NCH$_2$CH$^A\underline{H}^B$), 2.45 (1H, app q, J = 8.0 Hz, 1H, m, NC$\underline{H}^A$H^{B}CH$_2$), 3.12-3.17 (1H, m, NCH$^A\underline{H}^B$CH$_2$), 3.23-3.26 (1H, m, C$\underline{H}$CO), 3.27 (1H, ddd, J = 1.5, J = 6.5, J = 15.0 Hz, NC$\underline{H}^A$H^B-CH=CH$_2$), 3.51 (1H, ddd, J = 1.5, J = 6.0, J = 15.0 Hz, NCH$^A\underline{H}^B$-CH=CH$_2$), 3.71 (3H, s, NCHC(O)OC$\underline{H}_3$), 3.73 (3H, s, CH=CHC(O)OC$\underline{H}_3$), 5.99 (1H, dt, J = 1.5 , J = 15.5 Hz, cis C=C$\underline{H}_2$), 7.0 (1H, dt, J = 6.5, J = 15.5 Hz, trans C=C$\underline{H}_2$). δ_C (100 MHz, $CDCl_3$),

23.1 (NCH$\underline{C}$H$_2$), 29.3 (NCH$_2\underline{C}$H$_2$), 51.4 (CH=CHC(O)O$\underline{C}$H$_3$), 51.8 (NCHC(O)O$\underline{C}$H$_3$), 53.4 (N$\underline{C}$H$_2$CH$_2$), 54.9 (N$\underline{C}$H$_2$-CH=CH), 65.1 ($\underline{C}$HCO), 122.6 (CH$_2$CH=$\underline{C}$H), 145.2 (CH$_2\underline{C}$H=CH), 166.5 (CH=CH$\underline{C}$O), 174.1 (NCH$\underline{C}$O). ν_{max} (thin film, cm^{-1}), 2951 (C-H), 1732 (Ester CO$_2$), 1435 (Alkene C-H), 1195 and 1167 (C-N); m/z (ES$^+$) calculated for $C_{11}H_{17}NO_4$ [M+H]$^+$; 228.1230. found 228.1237.

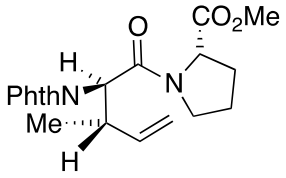
2.4.21 *N*-(Pent-2-enyl)-L-proline methyl ester 145d



Pent-2-en-1-ol (1.15 g, 1.38 mL, 13.3 mmol, 1.1 eq) was taken up in Et$_2$O (15 mL) and cooled to 0 °C. Phosphorus tribromide (1.80 g, 0.63 mL, 6.66 mmol, 0.55 eq) was then added dropwise and allowed to stir at room temperature for 18h. On completion the reaction was quenched with H$_2$O and extracted with Et$_2$O (3 x 20 mL). The organic layers were combined, dried over Na$_2$SO$_4$, filtered and concentrated *in vacuo.* Following mono *N*-allylation procedure from the resulting oil, L-proline methyl ester hydrochloride (2.00g, 12.1 mmol, 1.0 eq) and triethylamine (2.47 g, 3.40 mL, 24.2 mmol, 2.0 eq) *N*-(Pent-2-enyl)-L-proline methyl ester was obtained as a pale yellow oil. (1.31 g, 6.66 mmol, 55%)

δ_H (400 MHz, CDCl$_3$), 0.97 (3H, t, J = 7.5 Hz, CH$_2$C$\underline{H}_3$), 1.77-1.82 (1H, m, NCHC$\underline{H}^A$H^B), 1.88-1.95 (2H, m, NCHCH$^A\underline{H}^B$ + NCH$_2$C$\underline{H}^A$H^B), 1.99-2.06 (2H, m, CH$_2$CH$_3$), 2.09-2.16 (1H, m, NCH$_2$CH$^A\underline{H}^B$), 2.34 (1H, app q, J = 9.0 Hz, NC$\underline{H}^A$H^{B}CH$_2$), 3.07 – 3.22 (4H, m, NCH$^A\underline{H}^B$CH$_2$, NC$\underline{H}_2$, C$\underline{H}$CO), 3.71 (3H, s, OC$\underline{H}_3$), 5.52 (1H, ddt, J = 1.0, J = 6.5, J = 15.5 Hz, NCH$_2$C$\underline{H}$=CH), 5.65 (1H, dt, J = 6.0, J = 15.5 Hz, NCH$_2$CH=C$\underline{H}$). δ_C (100 MHz, CDCl$_3$), 13.4 (CH$_2\underline{C}$H$_3$), 23.1 (NCH$\underline{C}$H$_2$), 25.3 ($\underline{C}$H$_2$CH$_3$), 29.6 (NCH$_2\underline{C}$H$_2$), 51.8 (O$\underline{C}$H$_3$), 53.6 (N$\underline{C}$H$_2$CH$_2$), 57.1 (N$\underline{C}$H$_2$CH), 65.3 ($\underline{C}$HCO), 125.5 (NCH$_2\underline{C}$H=CH), 135.8 (NCH$_2$CH=$\underline{C}$H$_2$), 174.9 ($\underline{C}$O). ν_{max} (thin film, cm^{-1}), 2951 (C-H), 1732 (Ester CO$_2$), 1435 (Alkene C-H), 1195 and 1167 (C-N); m/z (ES$^+$) calculated for $C_{11}H_{19}NO_2$ [M+H]$^+$; 198.1489. found 198.1493.

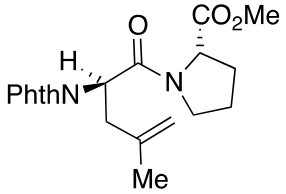
2.4.22 (*S*)-Methyl 1-((2*R*,3*S*)-2-(1,3-dioxoisoindolin-2-yl)-3-methylpent-4-enoyl)pyrrolidine-2-carboxylate 146a



Following general Belluš Claisen procedure from dried $Yb(OTf)_3$ (620 mg, 1.00 mmol, 1.0 eq), *N*-Crotyl-L-proline methyl ester (183 mg, 1.00 mmol, 1.0 eq), *N*,*N*-di*iso*propylethylamine (258 mg, 0.35 mL, 2.00 mmol, 2.0 eq) and *N*-phthaloylglycyl chloride (335 mg, 1.50 mmol, 1.5 eq) (*S*)-Methyl 1-((2*R*,3*S*)-2-(1,3-dioxoisoindolin-2-yl)-3-methylpent-4-enoyl)pyrrolidine-2-carboxylate was obtained following purification by column chromatography (Et_2O) that yielded the two major diastereoisomers in a 1.9:1.0 ratio as a yellow oil. (157 mg, 0.42 mmol, 42%).

δ_H (400 MHz, $CDCl_3$), 0.99 (3H, s, J = 7.0 Hz, $CHC\underline{H}_3$), 1.83-2.21 (4H, m, $NCHC\underline{H}^A\underline{H}^BCH_2$, $NCH_2C\underline{H}^A\underline{H}^B$), 3.50-3.80 (3H, m, $NC\underline{H}_2CH_2$, $C\underline{H}CH_3$), 3.63 (2H, s, major diastereoisomer $OC\underline{H}_3$), 3.72 (1H, s, minor diastereoisomer $OC\underline{H}_3$), 4.43-4.54 (1H, m, $NC\underline{H}CH_2$), 4.68-4.80 (1H, m, $(CO)_2NC\underline{H}$), 5.08-5.27 (2H, m, $CH=C\underline{H}_2$), 5.89 (1H, ddd, J = 7.5, J = 10.5, J = 17.5 Hz, $C\underline{H}=CH_2$), 7.75-7.77 (2H, m, Ar-$\underline{H}$), 7.88-7.90 (2H, m, Ar-$\underline{H}$). δ_C (100 MHz, $CDCl_3$), 16.3 ($CH\underline{C}H_3$), 25.1 ($NCH\underline{C}H_2$), 28.8 ($NCH_2\underline{C}H_2$), 35.9 ($\underline{C}HCH=CH_2$), 47.1 ($N\underline{C}H_2CH_2$), 52.1 ($O\underline{C}H_3$), 56.5 ($(CO)_2N\underline{C}H$), 59.1 ($NC\underline{H}CH_2$), 116.4 ($CH=\underline{C}H_2$), 123.6 (Ar-$\underline{C}$), 131.4 (Quat. Ar-$\underline{C}$), 134.3 (Ar-$\underline{C}$), 139.6 ($CH_2=\underline{C}H$), 166.3 ($CH(\underline{C}O)NCH$), 167.5 ($N(\underline{C}O)_2$), 172.1 ($\underline{C}OCH_3$). m/z (ES^+) calculated for $C_{20}H_{22}O_5N_2$ $[M+H]^+$; 371.1601. found 371.1602.

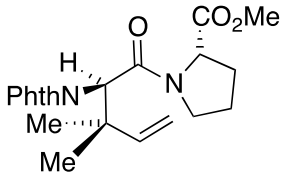
2.4.23 (*S*)-Methyl 1-((*R*)-2-(1,3-dioxoisoindolin-2-yl)-4-methylpent-4-enoyl)pyrrolidine-2-carboxylate 146c



Following general Belluš Claisen procedure from dried $Yb(OTf)_3$ (620 mg, 1.00 mmol, 1.0 eq), *N*-(2-methylprop-2-en-1-yl)-L-proline methyl ester (183 mg, 1.00 mmol, 1.0 eq), *N*,*N*-diisopropylethylamine (258 mg, 0.35 mL, 2.00 mmol, 2.0 eq) and *N*-phthaloylglycyl chloride (335 mg, 1.50 mmol, 1.5 eq) (*S*)-Methyl 1-((*R*)-2-(1,3-dioxoisoindolin-2-yl)-4-methylpent-4-enoyl)pyrrolidine-2-carboxylate was obtained following purification by column chromatography yielding the two diastereoisomers in a 3.0:1 ratio as a yellow oil. (182 mg, 0.49 mmol, 49%). On standing the product solidified to give a yellow solid mp = 146-148 °C.

δ_H (400 MHz, $CDCl_3$), 1.77 (3H, s, $CC\underline{H}_3$), 1.77-2.25 (4H, m, $NCHC\underline{H}^A\underline{H}^B$, $NCH_2C\underline{H}^A\underline{H}^B$), 2.64-2.72 (1H, m, $CC\underline{H}^AH^B$), 3.19-3.45 (2H, m, $NC\underline{H}^AH^BCH_2$, $CCH^A\underline{H}^B$), 3.58-3.62 (1H, m, $NCH^A\underline{H}^BCH_2$), 3.69 (2.2H, s, major diastereoisomer $OC\underline{H}_3$), 3.74 (0.8H, s, minor diastereoisomer $OC\underline{H}_3$), 4.50-5.56 (1H, m, $CHCONC\underline{H}$), 4.65 (1H, s, $CH=C\underline{H}_2$ cis), 4.69 (1H, s, $CH=C\underline{H}_2$ trans), 5.16 (1H, dt, J = 3.5, J = 14.5 Hz, $(CO)_2NC\underline{H}$), 7.73-7.74 (2H, m, Ar-$\underline{H}$), 7.83-7.87 (2H, m, Ar-$\underline{H}$). δ_C (100 MHz, $CDCl_3$), (major diastereoisomer), 21.9 ($C\underline{C}H_3$), 25.3 ($NCH\underline{C}H_2CH_2$), 28.8 ($NCH_2\underline{C}H_2$), 36.5 ($\underline{C}H_2C=CH_2$), 47.0 ($N\underline{C}H_2CH_2$), 50.5 ($(CO)_2N\underline{C}H$), 52.2 ($O\underline{C}H_3$), 59.7 ($CONC\underline{H}CO$), 114.4 ($C=\underline{C}H_2$), 123.6 (Ar-$\underline{C}$), 131.6 (Quat. Ar-$\underline{C}$), 134.1 (Ar-$\underline{C}$), 141.1 ($CH_2=\underline{C}$), 167.3 ($CH(\underline{C}O)NCH$), 167.6 ($N(\underline{C}O)_2$), 172.1 ($\underline{C}OCH_3$), (minor diastereoisomer), 22.0 ($C\underline{C}H_3$), 25.0 ($NCH\underline{C}H_2CH_2$), 28.7 ($NCH_2\underline{C}H_2$), 36.3 ($\underline{C}H_2C=CH_2$), 47.9 ($N\underline{C}H_2CH_2$), 50.8 ($(CO)_2N\underline{C}H$), 52.3 ($O\underline{C}H_3$), 59.4 ($CONC\underline{H}CO$), 114.2 ($C=\underline{C}H_2$), 123.5 (Ar-$\underline{C}$), 131.5 (Quat. Ar-$\underline{C}$), 134.2 (Ar-$\underline{C}$), 141.2 ($CH_2=\underline{C}$), 167.2 ($CH(\underline{C}O)NCH$), 167.4 ($N(\underline{C}O)_2$), 172.6 ($\underline{C}OCH_3$). ν_{max} (thin film, cm^{-1}), 2973 (C-H), 1711 (Ester CO_2), 1655 (Amide); m/z (ES^+) calculated for $C_{20}H_{22}O_5N_2$ $[M+H]^+$; 371.1601. found 371.1602.

2.4.24 (*S*)-Methyl 1-((*R*-2-(1,3-dioxoisoindolin-2-yl)-3,3-dimethylpent-4-enoyl)pyrrolidine-2-carboxylate 146b

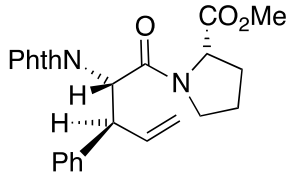


Following general Belluš Claisen procedure from dried $Yb(OTf)_3$ (620 mg, 1.00 mmol, 1.0 eq), *N*-(3-methylbut-2-enyl)-L-proline methyl ester (197 mg, 1.00 mmol, 1.0 eq), *N*,*N*-

di*iso*propylethylamine (258 mg, 0.35 mL, 2.00 mmol, 2.0 eq) and *N*-phthaloylglycyl chloride (335 mg, 1.50 mmol, 1.5 eq) (*S*)-Methyl 1-((*R*-2-(1,3-dioxoisoindolin-2-yl)-3,3-dimethylpent-4-enoyl)pyrrolidine-2-carboxylate was obtained following purification by column chromatography (diethyl ether) yielding the two diastereoisomers in a 1.1:1 ratio as a yellow oil that solidified on standing. (155 mg, 0.40 mmol, 40%) mp = 142-145 °C.

δ_H (400 MHz, $CDCl_3$), 1.27 (3H, s, CC$\underline{H}_3$), 1.28 (3H, s, CC$\underline{H}_3$), 1.76-2.22 (4H, m, NCHC$\underline{H}^A\underline{H}^B$, NCH$_2C\underline{H}^A\underline{H}^B$), 2.83-3.06 (1H, m, NC$\underline{H}^A$H^{B}CH$_2$), 3.46-3.61 ((1H, m, NCH$^A\underline{H}^B$CH$_2$), 3.70 (1.6H, s, major diastereoisomer OC$\underline{H}_3$), 3.73 (1.4H, s, minor diastereoisomer OC$\underline{H}_3$), 4.44-4.59 (1H, m, NC$\underline{H}$CH$_2$), 4.78 (1H, s, (CO)$_2$NC$\underline{H}$), 4.94-5.00 (2H, m, CH=C$\underline{H}_2$), 6.27-6.36 (1H, m, C$\underline{H}$=CH$_2$), 7.74 -7.78 (2H, m, Ar-$\underline{H}$), 7.84-7.91 (2H, m, Ar-$\underline{H}$). δ_C (100 MHz, $CDCl_3$), (major diastereoisomer), 24.5 (C$\underline{C}$H$_3$), 25.2 (C$\underline{C}$H$_3$), 25.2 (NCH$\underline{C}$H$_2$), 28.6 (NCH$_2\underline{C}$H$_2$), 42.3 ($\underline{C}$(CH$_3$)$_2$), 46.9 (N$\underline{C}$H$_2$CH$_2$), 52.2 (O$\underline{C}$H$_3$), 58.1 (NC$\underline{H}$CH$_2$), 59.4 ((CO)$_2$N$\underline{C}$H), 112.3 (CH=$\underline{C}$H$_2$), 123.7 (Ar-$\underline{C}$), 131.1 (Quat. Ar-$\underline{C}$), 134.4 (Ar-$\underline{C}$), 145.5 (CH$_2$=$\underline{C}$H), 165.2 (CH($\underline{C}$O)NCH), 167.6 (N($\underline{C}$O)$_2$), 172.2 ($\underline{C}$OCH$_3$), (minor diastereoisomer), 24.1 (C$\underline{C}$H$_3$), 24.9 (C$\underline{C}$H$_3$), 24.9 (NCH$\underline{C}$H$_2$), 28.6 (NCH$_2\underline{C}$H$_2$), 42.4 ($\underline{C}$(CH$_3$)$_2$), 46.9 (N$\underline{C}$H$_2$CH$_2$), 58.4 (NC$\underline{H}$CH$_2$), 59.4 ((CO)$_2$N$\underline{C}$H), 112.2 (CH=$\underline{C}$H$_2$), 123.7 (Ar-$\underline{C}$), 131.3 (Quat. Ar-$\underline{C}$), 134.4 (Ar-$\underline{C}$), 145.4 (CH$_2$=$\underline{C}$H), 165.9 (N($\underline{C}$O)$_2$), 172.7 ($\underline{C}$OCH$_3$). ν_{max} (thin film, cm^{-1}), 2980 (C-H), 1388 (C-H); m/z (ES$^+$) calculated for $C_{21}H_{24}O_5N_2$ $[M+H]^+$; 385.1758 found 385.1760.

2.4.25 (*S*)-Methyl 1-((2*S*,3*S*)-2-(1,3-dioxoisoindolin-2-yl)-3-phenylpent-4-enoyl)pyrrolidine-2-carboxylate 147e

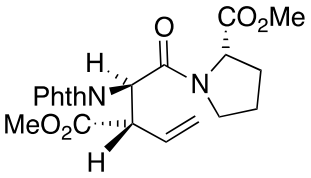


Following general Belluš Claisen procedure from dried Yb(OTf)$_3$ (620 mg, 1.00 mmol, 1.0 eq), *N*-Cinnamyl-L-proline methyl ester (245 mg, 1.00 mmol, 1.0 eq), *N*,*N*-diisopropylethylamine (258 mg, 0.35 mL, 2.00 mmol, 2.0 eq) and *N*-phthaloylglycyl chloride (335 mg, 1.50 mmol, 1.5 eq) (*S*)-Methyl 1-((2*S*,3*S*)-2-(1,3-dioxoisoindolin-2-yl)-3-phenylpent-4-enoyl)pyrrolidine-2-carboxylate was obtained following purification by column chromatography (diethyl ether) yielding the two diastereoisomers in a 1.1:1

ratio as a colourless oil. (222 mg, 0.51 mmol, 51%). A second column managed to isolate a sample of the minor diastereoisomer in a 3:1 ratio.

δ_H (400 MHz, $CDCl_3$), 1.83-2.21 (4H, m, NCHC$\underline{H}^A\underline{H}^BCH_2$, $NCH_2C\underline{H}^A\underline{H}^B$), 3.49-3.56 (1H, m, $NC\underline{H}^AH^BCH_2$), 3.68-3.74 (1H, m, $NC\underline{H}^AH^BCH_2$), 3.64 (3H, s, major diastereoisomer $OC\underline{H}_3$), 3.74 (3H, s, minor diastereoisomer $OC\underline{H}_3$), 4.57 (1H, dd, J = 5.5, J = 8.5 Hz, $NC\underline{H}CH_2$), 4.96 (1H, dd, J = 7.5, J = 11.0 Hz, $C\underline{H}CH=CH_2$), 5.15-5.30 (3H, m, $(CO)_2NC\underline{H}$, $CH=C\underline{H}_2$), 6.06 (1H, ddd, J = 7.5, J = 10.5, J = 17.5 Hz, $C\underline{H}=CH_2$), 7.60 (2H, dd, J = 3.0, J = 5.5 Hz, Ar-$\underline{H}$), 7.68 (2H, dd, J = 3.0, J = 5.5 Hz, Ar-$\underline{H}$). δ_C (100 MHz, $CDCl_3$), 25.2 ($NCH\underline{C}H_2$), 28.9 ($NCH_2\underline{C}H_2$), 47.2 ($N\underline{C}H_2CH_2$), 48.0 ($\underline{C}HCH=CH_2$), 52.2 ($O\underline{C}H_3$), 54.6 ($(CO)_2N\underline{C}H$), 59.3 ($NC\underline{H}CH_2$), 117.7 ($CH=\underline{C}H_2$), 123.3 (Ar-$\underline{C}$), 126.9 (Ar-$\underline{C}$), 128.5 (Ar-$\underline{C}$), 128.6 (Ar-$\underline{C}$), 131.1 (Quat. Ar-$\underline{C}$), 133.9 (Ar-$\underline{C}$), 137.9 ($CH_2=\underline{C}H$), 139.0 (Quat, Ar-$\underline{C}$), 165.9 ($CH(\underline{C}O)NCH$), 167.1 ($N(\underline{C}O)_2$), 172.1 ($\underline{C}OCH_3$). ν_{max} (thin film, cm^{-1}), 2979 (C-H), 1716 (Ester CO_2); m/z (ES^+) calculated for $C_{25}H_{24}O_5N_2$ $[M+H]^+$; 433.1758. found 433.1760.

2.4.26 (*S*)-Methyl 1-((2*R*,3*S*)-2-(1,3-dioxoisoindolin-2-yl)-3-(methoxycarbonyl)pent-4-enoyl)pyrrolidine-2-carboxylate 146f

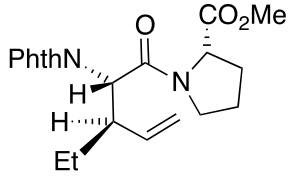


Following general Belluš Claisen procedure from dried $Yb(OTf)_3$ (620 mg, 1.00 mmol, 1.0 eq), *N*-(4-methoxy-4-oxobut-2-en-1-yl)-L-proline methyl ester (227 mg, 1.00 mmol, 1.0 eq), *N*,*N*-diisopropylethylamine (258 mg, 0.35 mL, 2.00 mmol, 2.0 eq) and *N*-phthaloylglycyl chloride (335 mg, 1.50 mmol, 1.5 eq) (*S*)-Methyl 1-((2*R*,3*S*)-2-(1,3-dioxoisoindolin-2-yl)-3-(methoxycarbonyl)pent-4-enoyl)pyrrolidine-2-carboxylate was obtained as a viscous oil. Purification by column chromatography (diethyl ether) yielded the two diastereoisomers in a 1.1:1 ratio as a yellow oil. (194 mg, 0.47 mmol, 47%).

δ_H (400 MHz, $CDCl_3$), 1.84-2.12 (4H, m, NCHC$\underline{H}^A\underline{H}^BCH_2$, $NCH_2C\underline{H}^A\underline{H}^B$), 3.58 (3H, s, $OC\underline{H}_3$), 3.65 (3H, s, $OC\underline{H}_3$), 4.45-4.61 (2H, m, $(CO)_2NC\underline{H}$, $CONC\underline{H}CO$), 5.24-5.38 (2H, m, $CH_2=CHC\underline{H}$ + $CH=C\underline{H}_2$), 5.99 (1H, ddd, J = 9.0, J = 10.0, J = 17.0 Hz, $C\underline{H}=CH_2$), 7.74 (2H, dd, J = 3.0, J = 5.5 Hz, Ar-$\underline{H}$), 7.87 (2H, dd, J = 3.0, J = 5.5 Hz, Ar-$\underline{H}$). δ_C (100 MHz, $CDCl_3$), 25.1 ($NCH\underline{C}H_2$), 28.9 ($NCH_2\underline{C}H_2$), 47.2 ($N\underline{C}H_2CH_2$), 48.9 ($N\underline{C}H$), 52.2 ($O\underline{C}H_3$), 52.3 ($O\underline{C}H_3$), 53.0 ($CH_2=CH\underline{C}H$), 59.3 ($N\underline{C}H$), 121.1 ($CH=\underline{C}H_2$), 123.7 (Ar-$\underline{C}$), 131.4 (Quat. Ar-$\underline{C}$), 131.9 ($CH_2=\underline{C}H$), 134.3 (Ar-$\underline{C}$), 165.1 ($CH(\underline{C}O)NCH$), 167.0

(N(C=O)$_2$), 171.6 (C=OCH$_3$), 171.9 (C=OCH$_3$); ν_{max} (thin film, cm^{-1}), 2980 (C-H), 1717 (Ester CO$_2$), 1657 (Amide); m/z (ES$^+$) calculated for $C_{21}H_{22}O_7N_2$ [M+H]$^+$; 415.1500. found 415.1500.

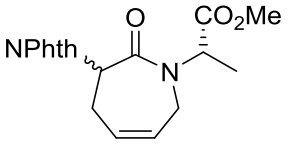
2.4.27 (*S*)-Methyl 1-((2*S*,3*R*)-2-(1,3-dioxoisoindolin-2-yl)-3-ethylpent-4-enoyl)pyrrolidine-2-carboxylate 147d



Following general Belluš Claisen procedure from dried Yb(OTf)$_3$ (620 mg, 1.00 mmol, 1.0 eq), *N*-(pent-2-enyl)-L-proline methyl ester (197 mg, 1.00 mmol, 1.0 eq), *N*,*N*-diisopropylethylamine (258 mg, 0.35 mL, 2.00 mmol, 2.0 eq) and *N*-phthaloylglycyl chloride (335 mg, 1.50 mmol, 1.5 eq) (*S*)-Methyl 1-((2*S*,3*R*)-2-(1,3-dioxoisoindolin-2-yl)-3-ethylpent-4-enoyl)pyrrolidine-2-carboxylate was obtained as a viscous oil. Purification by column chromatography (diethyl ether) yielded the two major diastereoisomers in a 3.5:1.0 ratio as a yellow oil. (271 mg, 0.70 mmol, 70%). Recrystallization from diisopropylether/IPA gave an isolated sample as a pale colourless solid of the minor diastereomer. mp = 135-140 °C.

δ_H (400 MHz, CDCl$_3$), 0.87 (3H, t, J = 7.5 Hz, CH$_2$C=H$_3$), 1.21-1.32 (1H, m, C=H^{A}H^{B}CH$_3$), 1.51-1.57 (1H, m, CH^A=H^{B}CH$_3$), 1.87-1.98 (2H, m, NCHC=H^{A}H^{B}CH$_2$, NCH$_2$C=H^{A}H^B), 2.01-2.14 (2H, m, NCHCH^A=H^{B}CH$_2$, NCH$_2$CH^A=H^B), 3.46-3.54 (1H, m, C=HCH=CH$_2$), 3.61-3.75 (2H, m, NC=H^{A}H^{B}CH$_2$), 3.69 (2.3H, s, major diastereoisomer OC=H$_3$), 3.70 (0.7H, s, minor diastereoisomer OC=H$_3$), 4.42 (1H, dd, J = 4.0, J = 8.0 Hz, NC=HCH$_2$), 4.86 (1H, d, J = 10.0 Hz, (CO)$_2$NC=H), 5.22-5.27 (2H, m, CH=C=H$_2$), 5.69-5.78 (1H, m, C=H=CH$_2$), 7.73 (2H, dd, J = 3.0, J = 5.5 Hz, Ar-=H), 7.85 (2H, dd, J = 3.0, J = 5.5 Hz, Ar-=H). δ_C (100 MHz, CDCl$_3$), 11.1 (CH$_2$C=H$_3$), 23.4 (C=H$_2$CH$_3$), 24.9 (NCHC=H$_2$), 29.0 (NCH$_2$C=H$_2$), 43.9 (C=HCH=CH$_2$), 47.2 (NC=H$_2$CH$_2$), 52.0 (OC=H$_3$), 55.9 ((CO)$_2$NC=H), 59.3 (NC=HCH$_2$), 119.0 (CH=C=H$_2$), 123.5 (Ar-C=), 131.6 (Quat. Ar-C=), 134.2 (Ar-C=), 136.5 (CH$_2$=C=H), 167.1 (CH(C=O)NCH), 168.0 (N(C=O)$_2$), 172.3 (C=OCH$_3$). m/z (ES$^+$) calculated for $C_{21}H_{24}O_5N_2$ [M+H]$^+$; 385.1758. found 385.1758.

2.4.28 Methyl (2*S*)-2-(3-(1,3-dioxoisoindolin-2-yl)-2-oxo-2,3,4,7-tetrahydro-1*H*-azepin-1-yl)propanoate 159



Grubbs second generation catalyst (229 mg, 0.027 mmol, 0.1 eq) in DCM (2.5 mL) was added to a solution of (*S*)-Methyl 2-(*N*-allyl-2-(1,3-dioxoisoindolin-2-yl)pent-4-enamido)propanoate (100 mg, 0.27 mmol, 1.0 eq) in DCM (2.5 mL). The reaction was allowed to stir at room temperature until consumption of starting material as monitored by TLC. The reaction mixture was then concentrated *in vacuo* and purified by column chromatography (diethyl ether) to give the product as a mixture of diastereoisomers (75 mg, 0.24 mmol, 87%).

$\delta_{\mathbf{H}}$ (400 MHz, $CDCl_3$), 1.17 (0.9H, app t, J = 7.0 Hz, Minor $CHC\underline{H}_3$), 1.33 (2.1H, app t, J = 7.5 Hz, Major $CHC\underline{H}_3$), 2.44-2.48 (1H, m, $CHC\underline{H}^AH^B$), 3.43-3.57 (1H, m, $NCH^A\underline{H}^B$), 3.61 (3H, s, $OC\underline{H}_3$), 3.62-3.73 (1H, m, $CHCH^A\underline{H}^B$), 3.30-3.34 (0.3H, m, Minor $NCH^A\underline{H}^B$), 4.38-4.42 (0.7H, m, Major $NCH^A\underline{H}^B$), 5.20 (0.3H, q, J = 7.0 Hz, Minor $C\underline{H}CH_3$), 5.52 (0.7H, q, J = 7.5 Hz, Major $C\underline{H}CH_3$), 5.47 (0.3H, dd, J = 3.0, J = 13.5 Hz, Minor $NC\underline{H}$), 5.57 (0.7H, dd, J = 3.0, J = 13.5 Hz, Major $NC\underline{H}$) 5.73-5.85 (2H, m, $C\underline{H}$=$C\underline{H}$), 7.63-7.65 (2H, m, Ar-$\underline{H}$), 7.77-7.79 (2H, m, Ar-$\underline{H}$). $\delta_{\mathbf{C}}$ (100 MHz, $CDCl_3$), (Major diastereoisomer), 14.4 ($CH\underline{C}H_3$), 28.7 ($CH\underline{C}H_2$), 40.8 ($N\underline{C}H_2$), 50.1 ($\underline{C}HCH_2$), 51.3 ($O\underline{C}H_3$), 51.6 ($\underline{C}HCH_3$), 123.4 ($\underline{C}H$=CH), 122.4 (Ar-$\underline{C}$), 128.1 (Quat. Ar-$\underline{C}$), 129.0 (CH=$\underline{C}H$), 133.0 (Ar-$\underline{C}$), 167.2 ($N(\underline{C}O)_2$), 169.2 ($CH(\underline{C}O)NCH$), 171.0 ($\underline{C}OCH_3$), (Minor diastereoisomer), 13.9 ($CH\underline{C}H_3$), 28.3 ($CH\underline{C}H_2$), 41.4 ($N\underline{C}H_2$), 50.3 ($\underline{C}HCH_2$), 51.2 ($O\underline{C}H_3$), 52.2 ($\underline{C}HCH_3$), 123.0 ($\underline{C}H$=CH), 122.4 (Ar-$\underline{C}$), 128.1 (Quat. Ar-$\underline{C}$), 130.9 (CH=$\underline{C}H$), 133.0 (Ar-$\underline{C}$), 167.2 ($N(\underline{C}O)_2$), 169.0 ($CH(\underline{C}O)NCH$), 171.0 ($\underline{C}OCH_3$). ν_{max} (thin film, cm^{-1}), 2952 (C-H), 1713 (Ester CO_2), 1660 (Amide); m/z (ES^+) calculated for $C_{18}H_{18}O_5N_2$ $[M+H]^+$; 343.1288. found 343.1296.

3. References

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