Successive Ring Expansion Reactions

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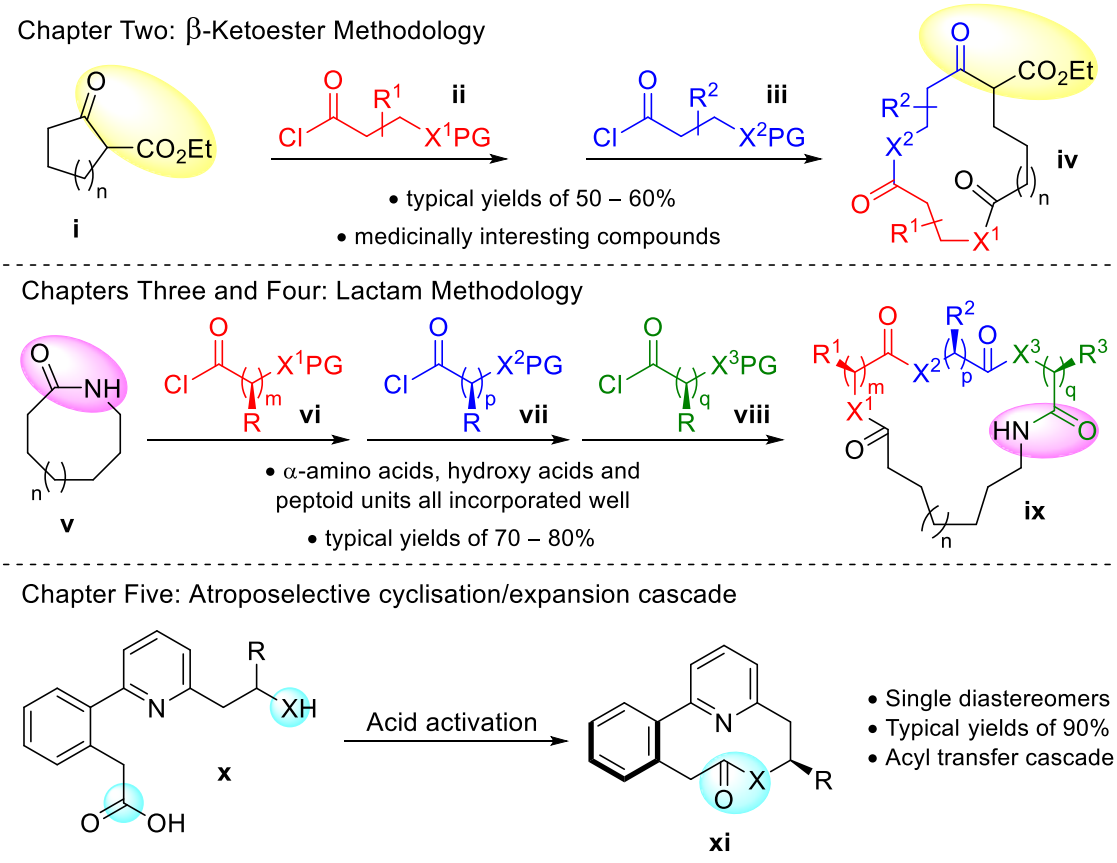
Abstract

This thesis describes the development of a series of methods for performing ring expansion reactions consecutively, either using successive reactions (explored in Chapters 2–4) or cascade sequences (explored in Chapters 5 and 6).

In Chapter two, β-ketoester ring expansion methodology (that has been developed in the Unsworth group) has been extended by incorporating both amino acids and β-hydroxy acids into a range of previously inaccessible cyclic starting materials. The molecular properties of the compounds were then examined to assess their 'lead-likeliness'. In Chapter three, the simple lactam motif was utilised to incorporate α-/β-amino acids to produce macrocyclic peptidiomimetics directly, with a range of natural α-amino acids incorporated. In Chapter four, lactams were then ring enlarged with hydroxy acids forming a diverse array of functionalised macrocyclic lactones. In Chapter five, a cyclisation/expansion cascade was collaboratively explored forming medium-sized bi-aryl lactones/lactams with excellent atroposelectivity. Chapter six describes the preliminary results obtained, for a similar cyclisation/expansion cascade (towards the synthesis of polyamine macrocycles), whereby consecutive acyl transfer reactions must occur.



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Author's Declaration

I declare that this thesis is a presentation of original work, to the best of my knowledge, except where due reference has been made to other workers. This work has not previously been presented for an award at this, or any other, University. All sources are acknowledged as references. This work has been reported in a number of recent publications, which have been included in the Appendices.

Thomas C. Stephens

Abbreviations

Å	Angstrom
AAI	Amino Acid Insertion
Ac_2O	Acetic Anhydride
ACR	Aza-Claisen Rearrangement
AIBN	Azobisisobutyronitrile
Alloc	Allyloxycarbonyl
aq.	Aqueous
ATAB	Ammonium Triacetoxyborohydride
BINOL	1,1'-Bi-2-naphthol
Bn	Benzyl
Boc	*t*-butoxycarbonyl
BOP	Bis(2-oxo-3-oxazolidinyl)phosphonate
bp	Boiling Point
br	Broad
Bu	Butyl
B3LYP	Becke, 3-parameter, Lee–Yang–Parr (functional)
δ	Chemical shift
°C	degree Celsius
CBS	Corey–Bakshi–Shibata
CDI	1,1'-Carbonyldiimidazole
cm^{-1}	Wavenumber
CME	*N*-Cyclohexyl-*N*'-(β-[*N*-methylmorpholino]ethyl)
CN	Cyanide
COSY	Correlated Spectroscopy
18-crown-6	1,4,7,10,13,16-Hexaoxacyclooctadecane
CSA	Camphorsulfonic acid
Cymene	1-Isopropyl-4-methylbenzene

d	Doublet
DBF	Dibenzofulvene
DBU	1,8-Diazabicyclo(5.4.0)undec-7-ene
DCC	*N*,*N*'-Dicyclohexylcarbodiimide
DCE	1,2-Dichloroethane
DEAD	Diethyl azodicarboxylate
DEPT	Distortionless Enhancement by Polarization Transfer
DFT	Density Functional Theory
DEPBT	3-(Diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3*H*)-one
DIAD	Diisopropyl azodicarboxylate
DIBAL	Diisobutylaluminium hydride
(+)-DIPCl	(+)-Chloro-diisopinocampheylborane
DIPEA	Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMDO	Dimethyldioxirane
DMEDA	*N*,*N*'-Dimethylethylenediamine
DMF	Dimethylformamide
DMP	Dess-Martin Periodinane
DMPU	*N*, *N*'-Dimethylpropyleneurea
DMSO	Dimethylsulfoxide
dppf	1,1'-Bis(diphenylphosphino)ferrocene
dr	Diastereomeric ratio
EDCI	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
ee	Enantiomeric excess
EPHP	1-Ethylpiperidine Hypophosphite
equiv.	Equivalent(s)
er	Enantiomeric ratio
ESI	Electrospray ionisation
Et	Ethyl
EtOAc	Ethyl Acetate

Fmoc	Fluorenylmethyloxycarbonyl
FmocOSu	*N*-(9*H*-Fluoren-9-ylmethoxycarbonyloxy)succinimide
g	Gram(s)
G	Gibbs Free Energy
h	Hour(s)
HATU	1-[Bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate
HBTU	*N*,*N*,*N*',*N*'-Tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate
HMBC	Heteronuclear Multiple Bond Correlation
HMDS	Hexamethyldisilazide
HMPA	Hexamethylphosphoramide
HOAT	1-Hydroxy-7-azabenzotriazole
HOBt	Hydroxybenzotriazole
HOSA	Hydroxylamine-*O*-sulfonic Acid
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectrometry
HSQC	Heteronuclear Single Quantum Coherence
Hz	Hertz
i-	Iso-
IC_{50}	Half maximal inhibitory concentration
i-Pr	Isopropyl
IR	Infra-red
J	Coupling constant in Hz
KAPA	Potassium 3-aminopropylamide
kcal	Kilocalorie
K_2CO_3	Potassium carbonate

$LiAlH_4$	Lithium aluminium hydride
LDA	Lithium diisopropylamide
LHMDS	Lithium Hexamethyldisilazide
LLAMA	Lead-Likeliness And Molecular Analysis
M	Molar
M^+	Molecular ion
m	Multiplet
m-	*Meta*-
µW	Microwave Irradiation
mCPBA	*meta*-Chloroperbenzoic acid
Me	Methyl
MeCN	Acetonitrile
MeOH	Methanol
mg	Milligrams
MHz	MegaHertz
min	Minutes
mL	Millilitre
mmol	Millimole
mol	Mole
MOM	2-Methoxyethoxymethyl
m.p.	Melting Point
Ms	Mesyl
m/z	Mass to charge ratio
n-	Normal-
NEt_3	Triethylamine
NHC	*N*-Heterocyclic Carbene
NMR	Nuclear Magnetic Resonance
NTf_2	Triflimide

o-	*Ortho*-
OAc	Acetate
OTf	Triflate
p-	*Para*-
Ph	Phenyl
pin	Pinacolato
PMI	Principal Moments of Inertia
PPI	Protein-Protein Interactions
ppm	Parts Per Million
PPTS	Pyridinium *p*-toluenesulfonate
p-TSA	*para*-Toluenesulfonic acid
pyr	Pyridine
q	Quartet
RBF	Round bottom flask
RCM	Ring Closing Metathesis
Red-Al®	Sodium bis(2-methoxyethoxy)aluminium hydride
R_F	Retention Factor
r.t.	Room temperature
$[\alpha]_D$	Specific Rotation
s	Singlet
sat.	Saturated
S_NAr	Nucleophilic Aromatic Substitution
S_N2	Bimolecular Concerted Nucleophilic Substitution
SPPS	Solid Phase Peptide Synthesis
SuRE	Successive Ring Expansion

t	Triplet
TBAF	Tetrabutylammonium fluoride
TBDPS	*tert*-Butyldiphenylsilyl
TBS	tert-Butyldimethylsilyl
TES	Triethylsilyl
TFA	Trifluoracetic acid
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin Layer Chromatography
TMEDA	Tetramethylethylenediamine
TMS	Trimethylsilyl
Ts	Tosyl
T3P®	Propanephosphonic acid anhydride
VTNMR	Variable Temperature Nuclear Magnetic Resonance
wt.	Weight

Chapter One: Introduction

1.1 The Utility of Macrocycles

Macrocycles (≥12-membered rings) are a unique class of molecule with broad utility, finding application in many scientific fields; for example, they are ubiquitous in mechanically inter-locked catenane/rotaxane systems,[1] can be used as chiral shift reagents,[2] and have many uses in the fields of nanotechnology,[3] catalysis,[4] and medicinal chemistry.[5] With such interdisciplinary function, there is unsurprisingly increasing interest in macrocyclic scaffolds and their synthesis, especially in regards to the generation of compound libraries for lead identification in medicinal chemistry[6] where historically macrocycles have been poorly represented.

Macrocycles often possess distinct molecular shapes and sizes[7] which can enable improved affinity binding to target receptors than their linear analogues.[8] This is rationalised by the decreased entropic penalty upon binding (compared to linear molecules) known as the macrocyclic effect, whilst still offering some degree of flexibility (due to multiple low energy conformations) to accommodate alternative binding modes if required. This can allow macrocycles to be both potent and selective drugs, for example natural products such as erythromycin, vancomycin, and epothilone C (figure 1.1).

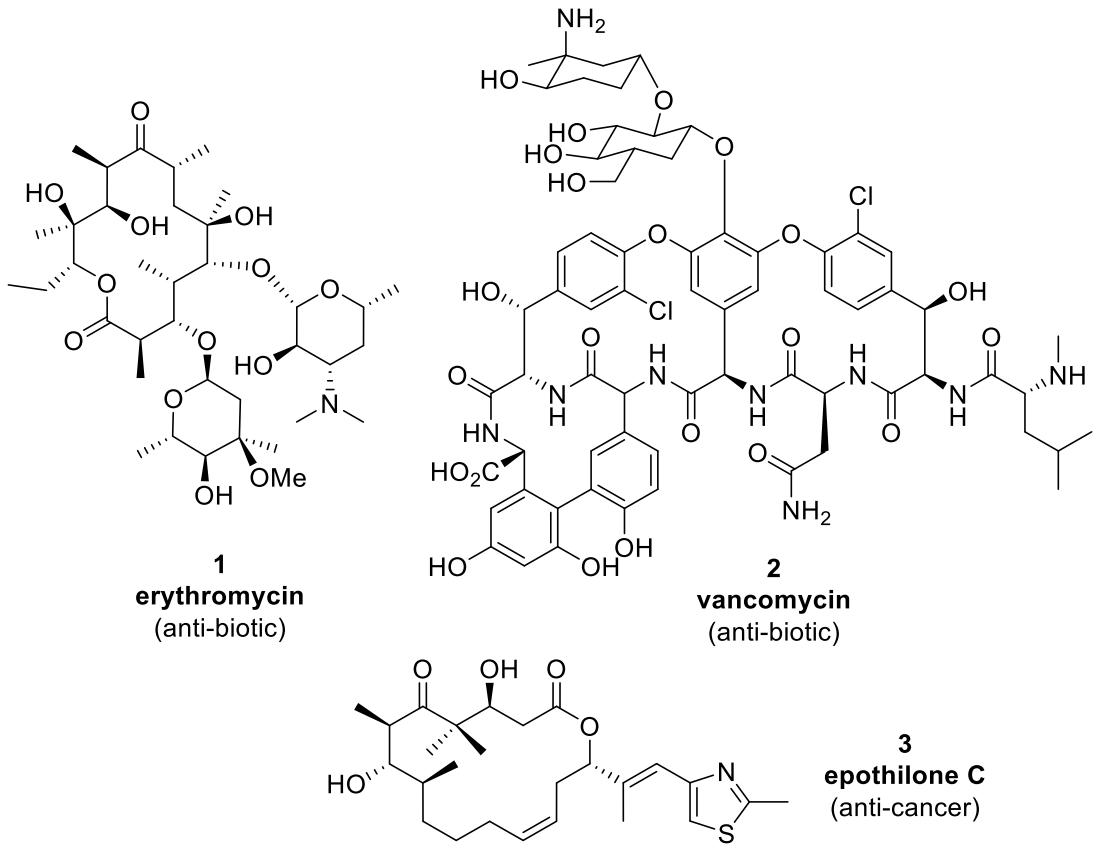


Figure 1.1: Structure of natural products erythromycin, vancomycin and epothilone C.

Macrocyclisation is recognised as a strategy to enhance the druggability of peptides by restricting their conformation, reducing polarity and increasing proteolytic stability and membrane permeability.[9–12] Macrocyclic peptides can serve as structure mimics of large peptidic fragments, for example, in the inhibition of protein-protein interactions (PPIs), but they generally have lower molecular weight than standard peptide-based PPI inhibitors.[13] Macrocycles are also not limited to peptide fragments and can include macrocyclic carbohydrates **4**, calixarenes **5**, and porphyrins **6** (seen in figure 1.2 respectively).

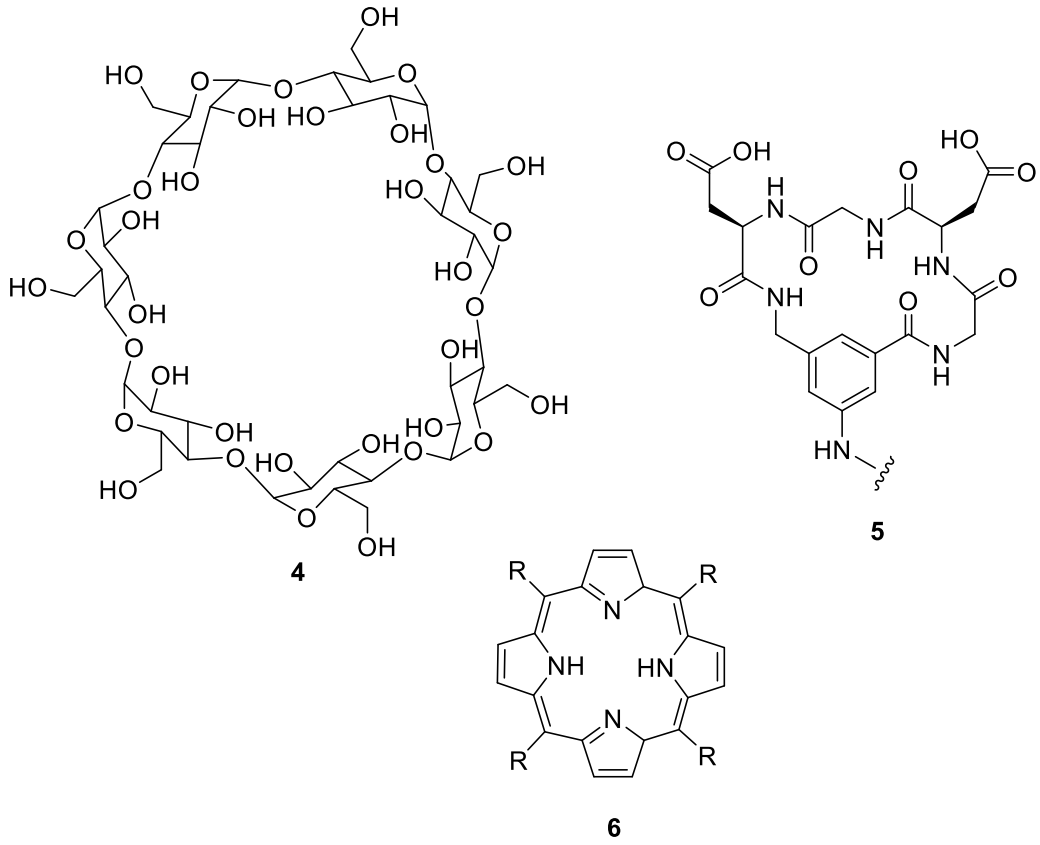


Figure 1.2: Macrocyclic scaffolds: bivalent cyclodextrins, calixarenes and porphyrins.

Structurally diverse macrocycles have been prepared[14] with 'drug-like' physio-chemical properties as defined by Lipinski's rule-of-five,[15] with prominent examples being the macrocyclic libraries developed by the Spring group.[16,17] Although used ubiquitously by medicinal chemists to predict druggability, Lipinski's rules were initially intended to predict the absorption of orally administered compounds. Recent reviews[18–20] have shown that the widespread application of Lipinski's rules has led to, on average, poorer pharmacokinetics than those predicted, often due to poor selectivity, metabolism and absorption. It is now being suggested that such protocols have led to medicinally potent compounds being lost, including macrocyclic compounds which may have missed one criterium.[21,22]

Despite the potential to create medicinally potent compounds, macrocycles have been traditionally under-explored in medicinal chemistry[23] and are still poorly represented in most contemporary screening libraries.[24] One significant factor which has contributed to this, is the difficulty of their synthesis,[25,26] which is pivotal during the drug-discovery process.

1.2 Synthesis of Macrocycles and Medium-Sized Rings

Macrocycles (≥12-membered rings) and medium-sized (8–11 membered) rings both have difficulties associated with their synthesis, which makes these cyclic systems significantly tougher to synthesise than their five- and six-membered counterparts.

1.2.1 Medium-Sized Ring Synthetic Problems

Medium-sized rings often have significant ring strain which is comprised of Baeyer (bond angle distortion), Pitzer (torsional-eclipsing) and Prelog (transannular) strain. For medium-sized rings, Prelog strain is often the major contributing factor to its overall ring strain, where substituents on opposite sides of the ring come in close proximity to each other, resulting in unfavourable steric repulsion. Commonly, this cannot be avoided without significant Baeyer and Pitzer strain being imposed. The ring strain of simple cycloalkanes can be seen in figure 1.3 (derived from the enthalpy of combustion and normalised to their linear counterparts),[27] illustrating the amount of strain that can be present in these ringed systems. A similar study was completed by Illuminati *et al.*[28] on the kinetics of cyclisation reactions. Some methods exist to reduce the amount of strain that exists in medium-sized rings, that include (but are not limited to): changing hybridisation of atoms to reduce Baeyer strain and introducing a methylene bridge to reduce transannular interactions.

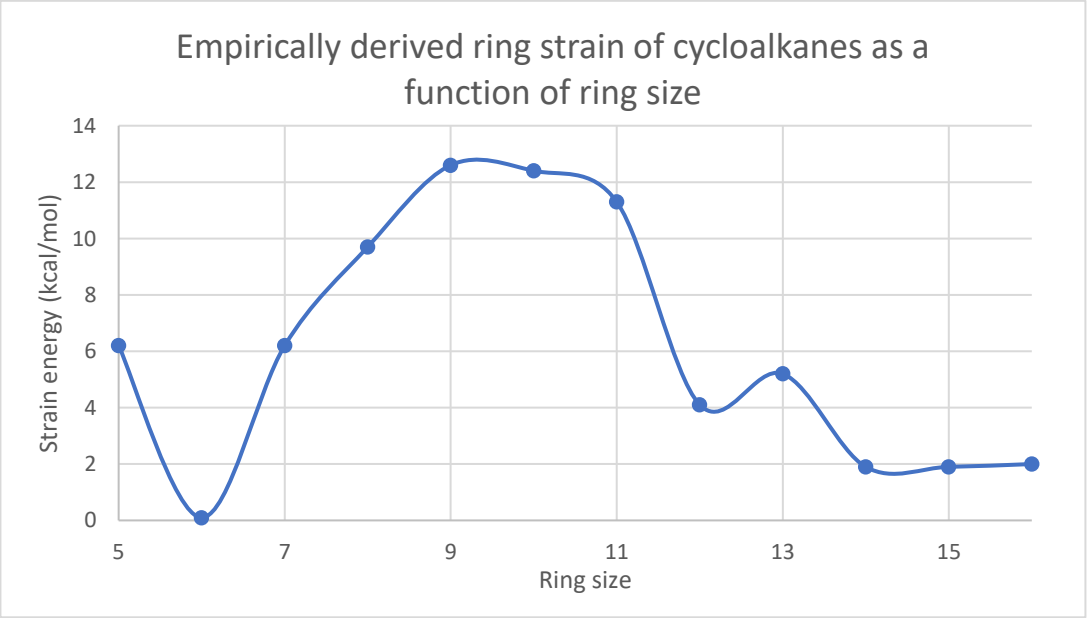
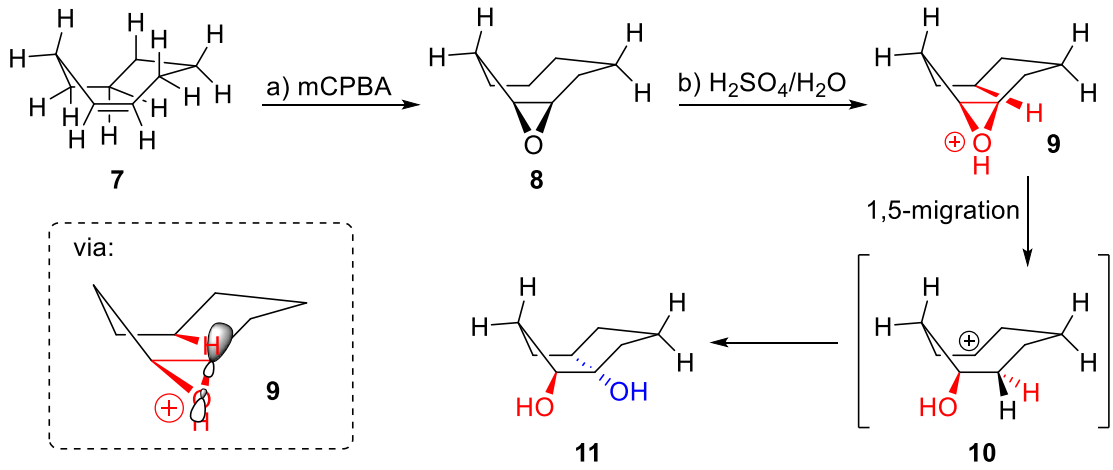


Figure 1.3: Empirically derived ring strain as a function of ring size by Anslyn and Dougherty.

Despite the aforementioned methods known to reduce the strain associated with medium-sized rings, their synthesis remains a significant synthetic challenge. This can be made more difficult when functionality and chirality must be incorporated into these already challenging targets. Side-reactions, from robust organic transformations, are also known to occur in the context of medium-sized rings such as the epoxidation/ring opening of *Z*-octene **7** (shown in scheme 1.1). In this example, epoxidation of the alkene proceeds onto the convex face, using mCPBA, however under acidic aqueous conditions (which would normally deliver a 1,2-diol) migration occurs to deliver the 1,5-diol **11**. This can be explained when considering the direction and position of the C-O σ* anti-bonding orbital of the epoxide. The anti-bonding orbital has a large proportion of a C-H σ bond (on the opposite side of the ring) occupying it. The proximity of substituents (across the ring) normally results in an unfavourable repulsion and overall increase in energy (increase in strain), however here it is the root of this remarkable reactivity. Although drawn stepwise for clarity, via a stabilised tertiary carbenium, it has been shown that the migration occurs in a concerted associative mechanism to deliver diol **11**. This shows how seemingly trivial transformations on these systems can be unexpectedly more challenging.



Scheme 1.1: Formation of 1,5-diol from *Z*-octene via epoxidation, migration, aqueous quench sequence.

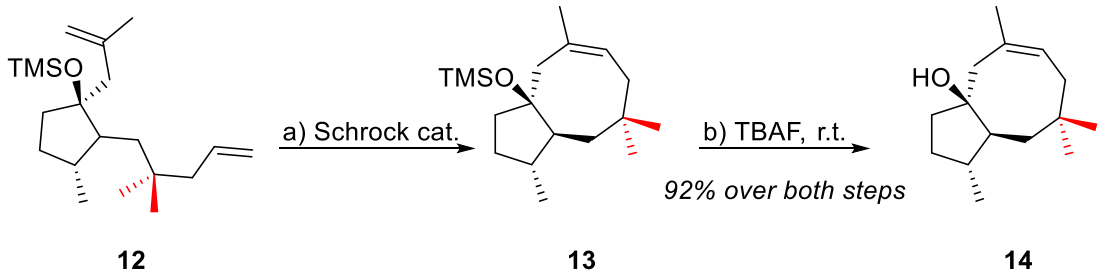
1.2.2 Macrocycle Synthetic Problems

Macrocyclisation reactions are often encumbered by unfavourable entropic and enthalpic effects, associated with bringing the two reactive ends together, which can make it hard to avoid unwanted side reactions. These thermodynamic penalties arise from accessing higher energy 'folded' conformations which are unlikely to be the lowest energy conformations due to losing degrees of freedom and electronic/steric effects. As a result of these thermodynamic penalties, it is common that dimerisation/oligomerisation or unwanted transannular side reactions occur and sometimes outcompete the desired cyclisation pathway. This is a well-documented problem

and a number of strategies have been developed, trying to minimise or completely stop these unwanted side reactions.

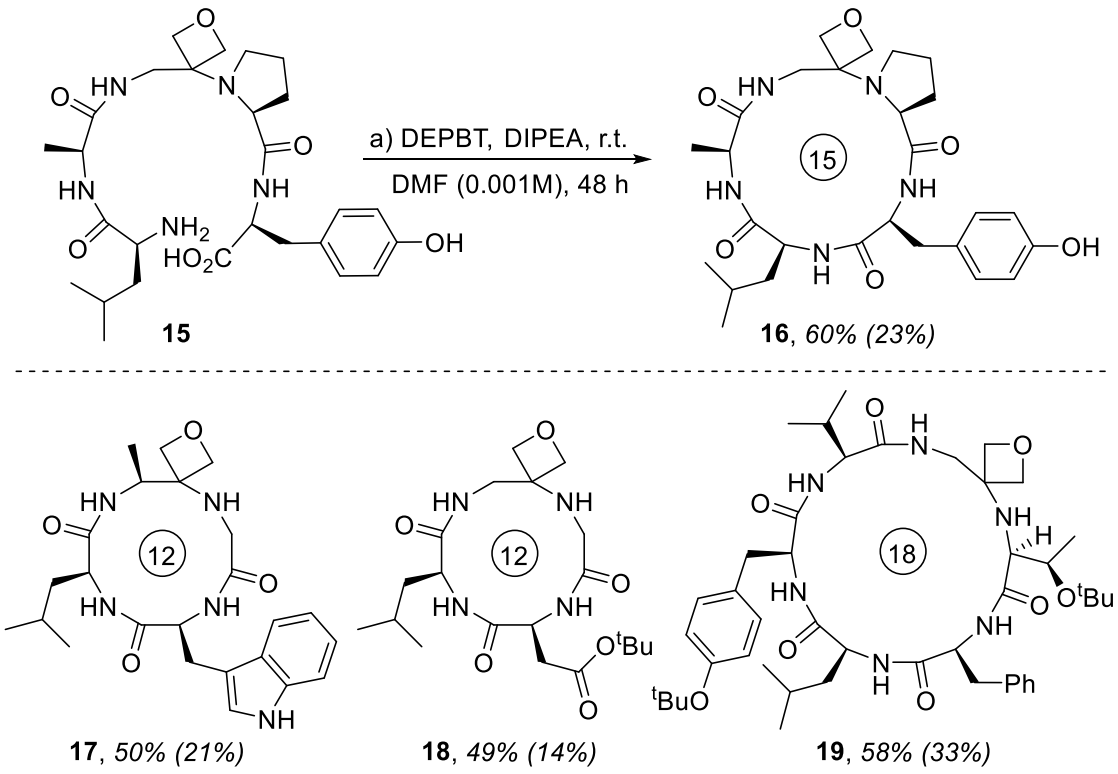
1.2.3 Macrocyclisation Strategies

One of these strategies is to bias the conformation of the substrate, in such a way as to bring together the two reactive ends, thus aiding cyclisation. This can be achieved by inserting sp^2 hybridised centres in the linear precursor to limit flexibility and engineer the conformation such that the reactive ends move closer in proximity. This is known as pre-organisation and can produce a more efficient cyclisation, as there is a higher probability of reactive conformations being occupied. *Z*-Alkenes are commonly used for this reason, however the incorporation of these into the desired linear sequence often produce substrates sensitive to small changes. This is linked to the Thorpe-Ingold effect[29] which has been exploited on numerous medium-sized ring cyclisations, such as a key step in the total synthesis of dactylol reported by Fürstner[30] (seen in scheme 1.2). Diene **12**, undergoes ring closing metathesis to give fused ring system **13**, with the geminal-dimethyl substituent increasing both the rate and yield of this cyclisation.



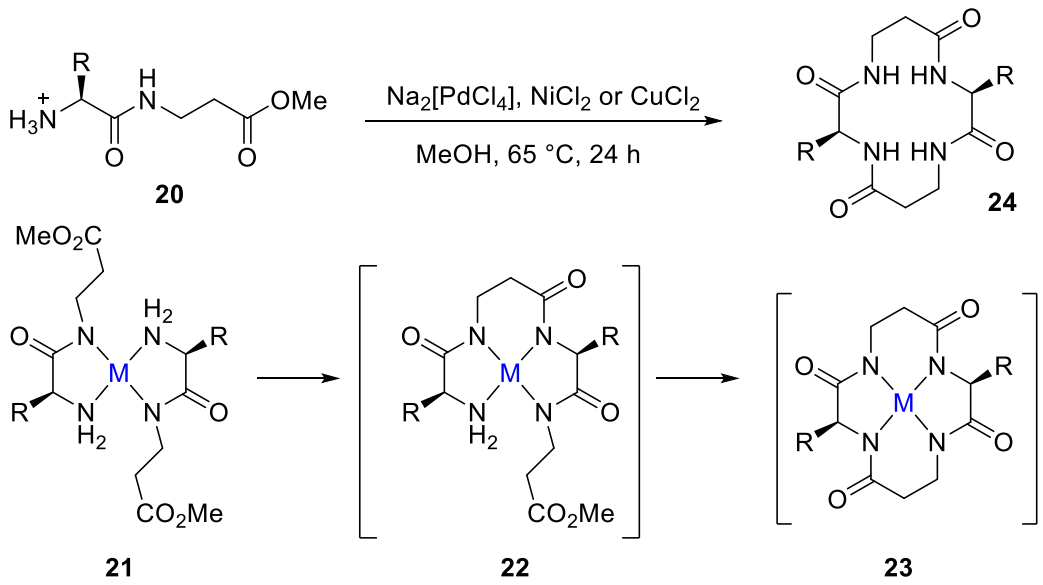
Scheme 1.2: Dactylol synthesis using the Thorpe-Ingold effect in a ring closing metathesis reaction.

Another example of pre-organisation can be demonstrated in the context of cyclic oligopeptides or cyclic peptide mimetics. Although linear peptides can be made expeditiously via solution phase or solid supported synthesis, their cyclisation is typically encumbered due to conformational rigidity from the amide bonds. Linear amides typically adopt a *Z*-geometry due to reduced steric interactions which often does not lead to a reactive conformer for cyclisation. Shipman and co-workers[31] have demonstrated that an oxetane unit can be used in place of an amide as a turn inducing moiety. The amino oxetane fragment mimics an amino acid, and can be introduced using two separate strategies with orthogonal deprotection conditions. They then showed that the oxetane fragment can be introduced at varying points through the linear peptide and enhance cyclisation rates and yields. Multiple oxetane-containing macrocycles in challenging ring sizes were made (tetra-, penta- and hexapeptides) with similar IC_{50} values as those of the parent cyclic peptide (scheme 1.3).



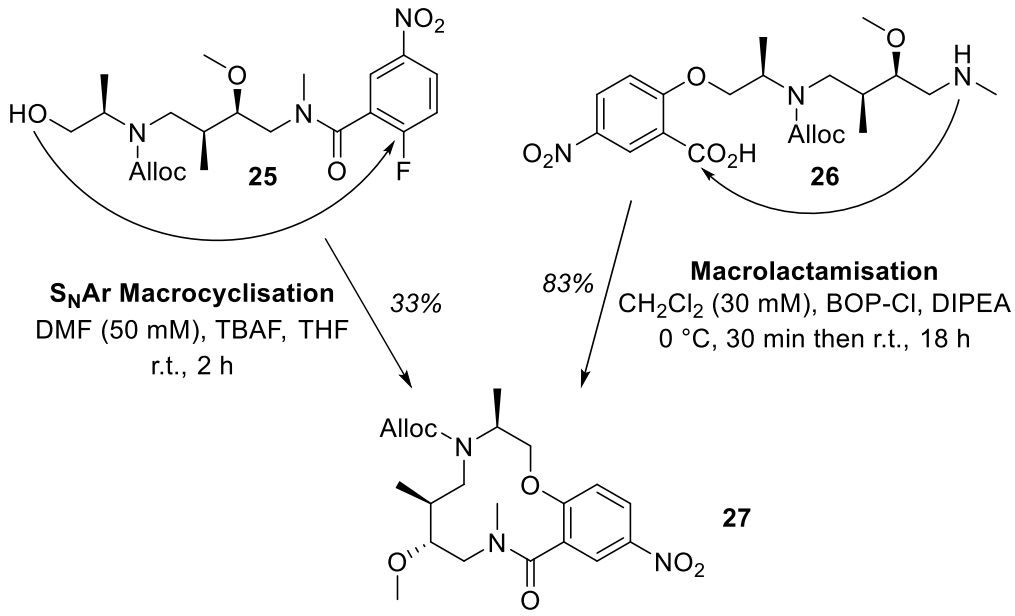
Scheme 1.3: Synthesis of cyclic peptide mimetics via head-to-tail cyclisation using oxetane modified substrates. The yields of the unmodified parent systems are shown in parentheses.

Alternatively, metals can be used to chelate and pre-organise a linear substrate into a reactive conformation, facilitating macrocyclisation.[32] This is typically referred to as 'templated synthesis' and benefits from kinetic and thermodynamic effects which can favour cyclisation over dimerisation.[33] One example, by Beck and co-workers,[34] shows that initial coordination of two amino acid derivatives **20**, can help them to undergo templated cyclisation without the requirement to use an activating additive such as DMAP. Upon acidic work up, the metal can be removed alongside the desired macrocyclic tetrapeptide **24** (scheme 1.4). Coordinating groups are essential and therefore a limitation is that templated synthesis can only produce classes of macrocycles, with these motifs present.



Scheme 1.4: Templated synthesis of cyclic tetrapeptides using palladium, nickel and copper complexes.

Whether or not pre-organisation of a substrate is possible, high dilution or pseudo-high dilution conditions are commonly used as methods to increase the yields of macrocyclisation reactions. Running the reaction at high-dilution decreases the probability of intermolecular reactions occurring and therefore reduces dimerisation/oligomerisation pathways. However, high dilution is usually impractical and not easily scalable. Pseudo-high dilution can also be used as an alternative, for example, where the linear reagent is added very slowly to create a high dilution environment under reaction conditions. This is more effective for some classes of cyclisation reactions (*e.g.* many examples of amidation or esterifications are reported), however, can be less successful on other cyclisation reactions, such a Stille or Sonagashira reaction due to the catalytic cycle being interrupted/halted.[35] In these cases, higher catalyst loadings or additives are commonly employed in addition to dilution. As an example of the reaction dependence on different macrocyclisation protocols, linear analogue **25** was cyclised via a fairly low yielding S_NAr reaction, using pseudo high dilution conditions. However, if the linear precursor is modified to **26**, then a macrolactamisation can be performed at a greatly improved 83% yield. These two strategies appear equally viable on paper, and the large difference in yield highlights the difficulty of predicting macrocyclisation efficiency even using high dilution conditions (scheme 1.5).



Scheme 1.5: Cyclisation via two separate strategies under high dilution conditions.

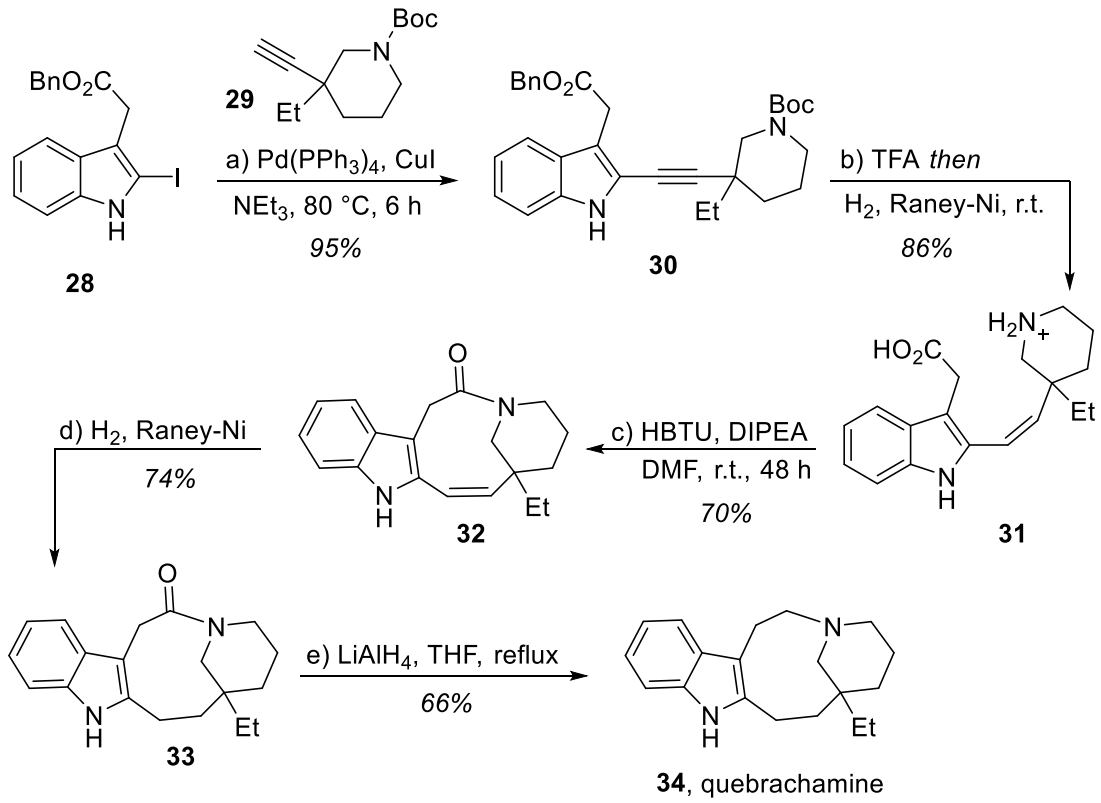
1.2.4 Macrocyclisation Reaction Types

In theory, many retrosynthetic disconnections can be made from a macrocyclic product, which gives rise to many macrocyclisation reaction classes. A few of the most common cyclisation strategies are explained below, although this is by no means a comprehensive list.

1.2.4.1 Macrolactamisation Reaction

Lactamisation reactions have been a staple in cyclic peptide/oligomer synthesis, helped by the advancement in Solid Phase Peptide Synthesis (SPPS). In SPPS, the nascent peptide is covalently bonded to a polymer resin and excess reagents can be washed away, thus avoiding time-consuming purification after each iteration. Therefore, peptides and oligomers can be rapidly made using SPPS, and a single discrete cyclisation can afford the desired cyclic product.

Macrolactamisations can also be utilised to synthesis natural products such as quebrachamine **34**. Using iodinated indole **28**, a Sonagashira coupling was performed with alkyne **29** (itself synthesised using a Seyferth–Gilbert homologation). Subsequent deprotection and hydrogenation afforded the *Z*-olefin **31**, which was amenable to macrolactamisation using coupling reagent HBTU. Final hydrogenation to alkane **33** and amide reduction afforded the natural product quebrachamine.



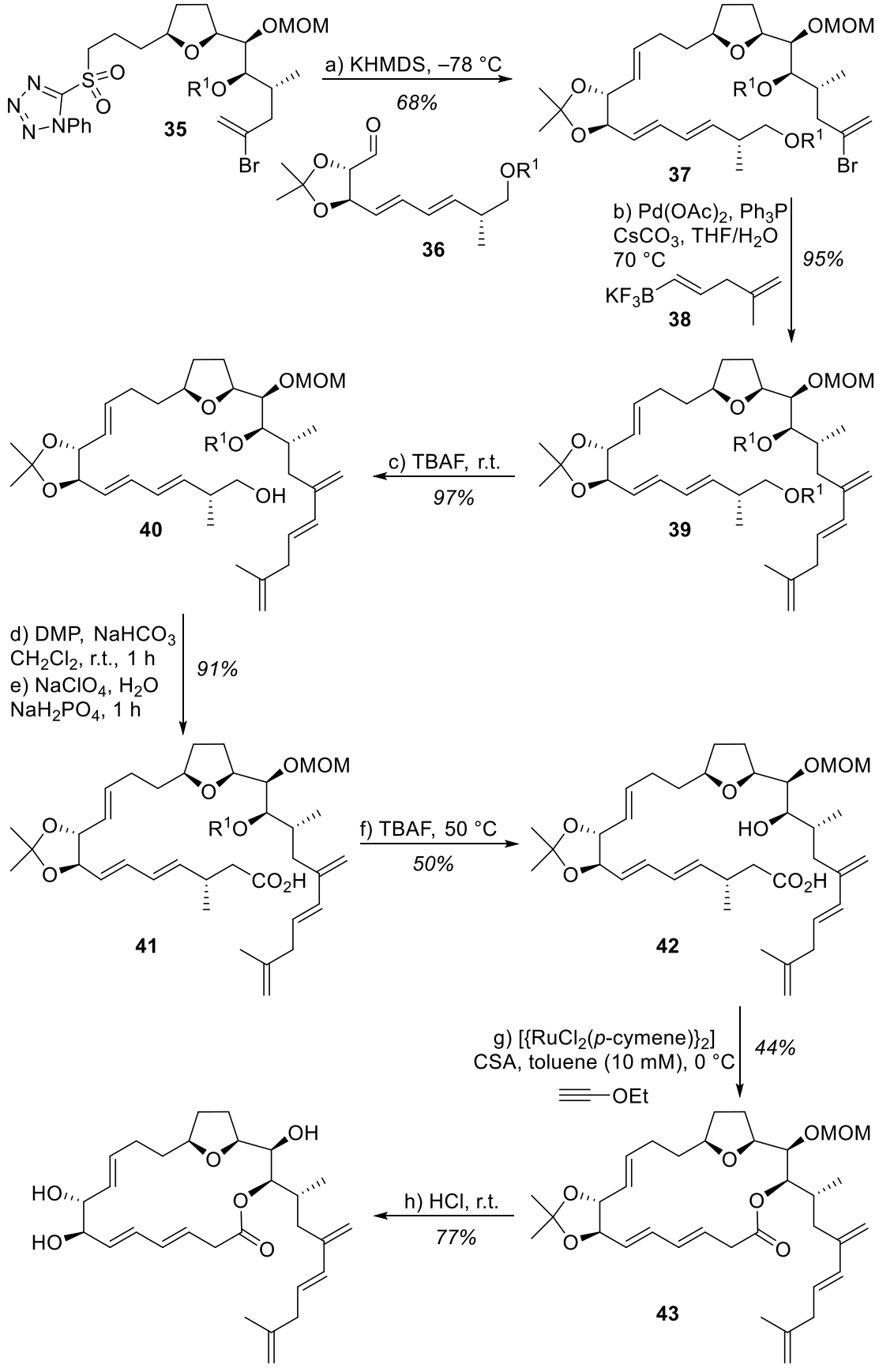
Scheme 1.6: Total synthesis of quebrachamine via macrolactamisation.

1.2.4.2 Macrolactonisation Reaction

Macrolactonisation has been used extensively in multiple total syntheses due to its broad applicability, functional group tolerance and compatibility with high dilution/templating effects. Many different reagents/named reactions/modifications exist which all offer slightly different reactivity; amongst the most notable are Yamaguchi, Steglich and Mukaiyama–Corey–Nicolaou esterifications.[36] These all operate via initial activation of the carboxylic acid, through an anhydride species, followed by lactonisation via the tethered alcohol. These methods were developed to overcome the harsh acidic conditions of Fischer esterification, which would not be applicable in a highly functionalised late stage setting.

One example is in the total synthesis of (−)-amphidinolide E, **44** where a Kita–Trost macrolactonisation is utilised (scheme 1.7). Sulfone **35** was deprotonated using KHMDS and subjected to aldehyde **36** in a Julia–Kocienski olefination, to afford solely the *E*-olefin **37**. Palladium-catalysed Suzuki–Molander coupled trifluoroborate fragment **38** in excellent yield with no olefin isomerisation. Deprotection of the TBDPS using TBAF was performed at room temperature and afforded alcohol **40**. Oxidation of the alcohol to the corresponding carboxylic acid was non-trivial, with Jones oxidation resulting in removal of the acid labile protecting groups and olefin scrambling. Consequently, a two-stage oxidation using Dess–Martin periodinane (to generate the aldehyde) followed by a Pinnick oxidation formed carboxylic acid **41** in 91% over

both steps. Removal of the TBDPS at the highly hindered *C*-17 position required TBAF at elevated temperatures for extended time to afford alcohol **42** in modest yield, with the starting material recoverable. The key macrocyclisation step was initially tested with a Yamaguchi lactonisation and was completely unsuccessful. As a result, alternative lactonisations were tested with the Kita–Trost reaction delivering the highest yield, most reliably, through an ethoxyvinyl ester (not shown). Finally, global deprotection was performed using HCl, producing (−)-amphidinolide E in 77% yield.

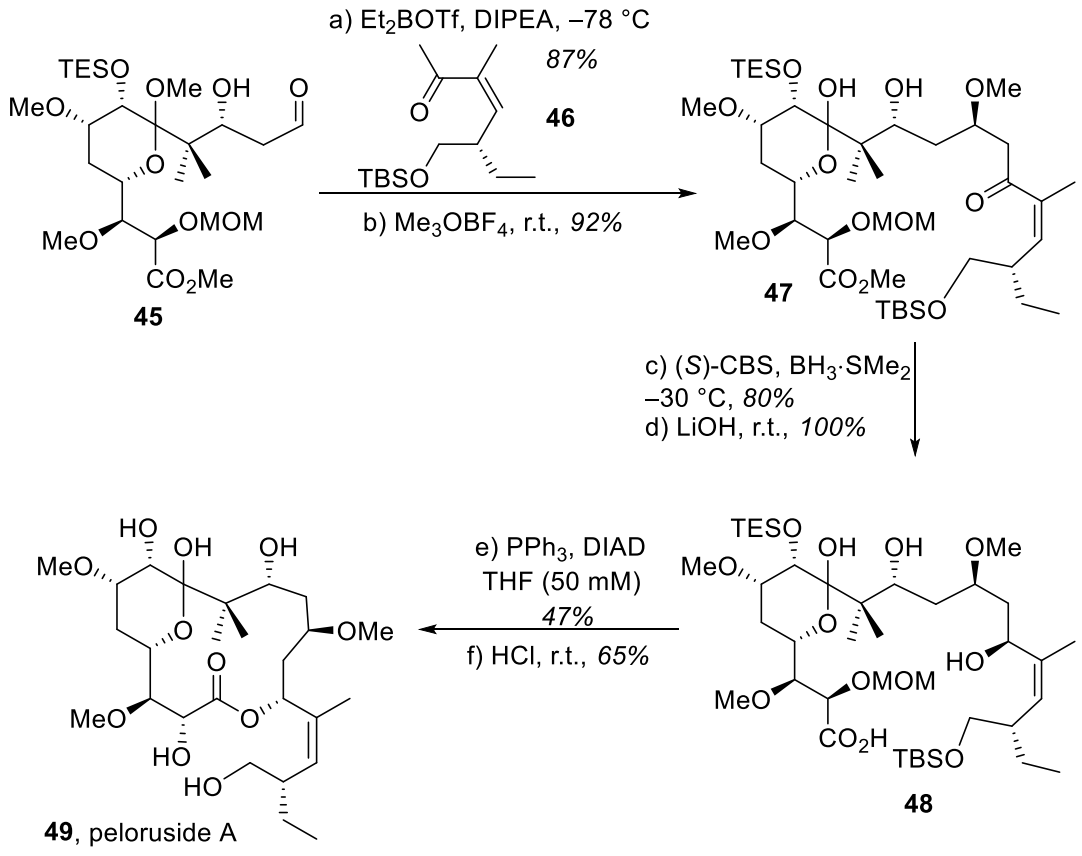


Scheme 1.7: Total synthesis of (–)-amphidinolide E using macrolactonisation. R^1 = TBDPS

1.2.4.3 Mitsunobu Macrocyclisation

An alternative disconnection approach that can be used to produce macrocyclic lactones is the Mitsunobu cyclisation. The Mitsunobu reaction operates by activating the alcohol using a combination of a phosphine reagent (commonly triphenylphosphine) and an azo coupling partner (commonly DIAD or DEAD). Many nucleophiles can be now be used with recent modifications,[37] although they typically must be related to acidic pro-nucleophiles, such as carboxylic acids, phenols, thioethers, and imides. The reaction proceeds with complete, clean inversion of stereochemistry at the alcohol and is usually very reliable, which is useful in stereoselective and total synthesis.

An interesting example was reported in the synthesis of peloruside A, **49** (scheme 1.8). Aldehyde **45** was reacted with the corresponding boron enolate of ketone **46**, in a highly stereoselective aldol addition. Meerwein's salt was then used to methylate this newly formed secondary alcohol in excellent yield and with remarkable selectivity. Enone **47** was reduced using a Corey–Bakshi–Shibata (CBS) reduction, and subsequent ester hydrolysis yielded carboxylic acid **48**. High dilution Mitsunobu cyclisation afforded the macrocyclic lactone in modest yield with some loss of yield, presumably due to side reactions with other unprotected alcohols, although not disclosed in the report. Global acidic deprotection generated peloruside A, **49** in 65% yield.

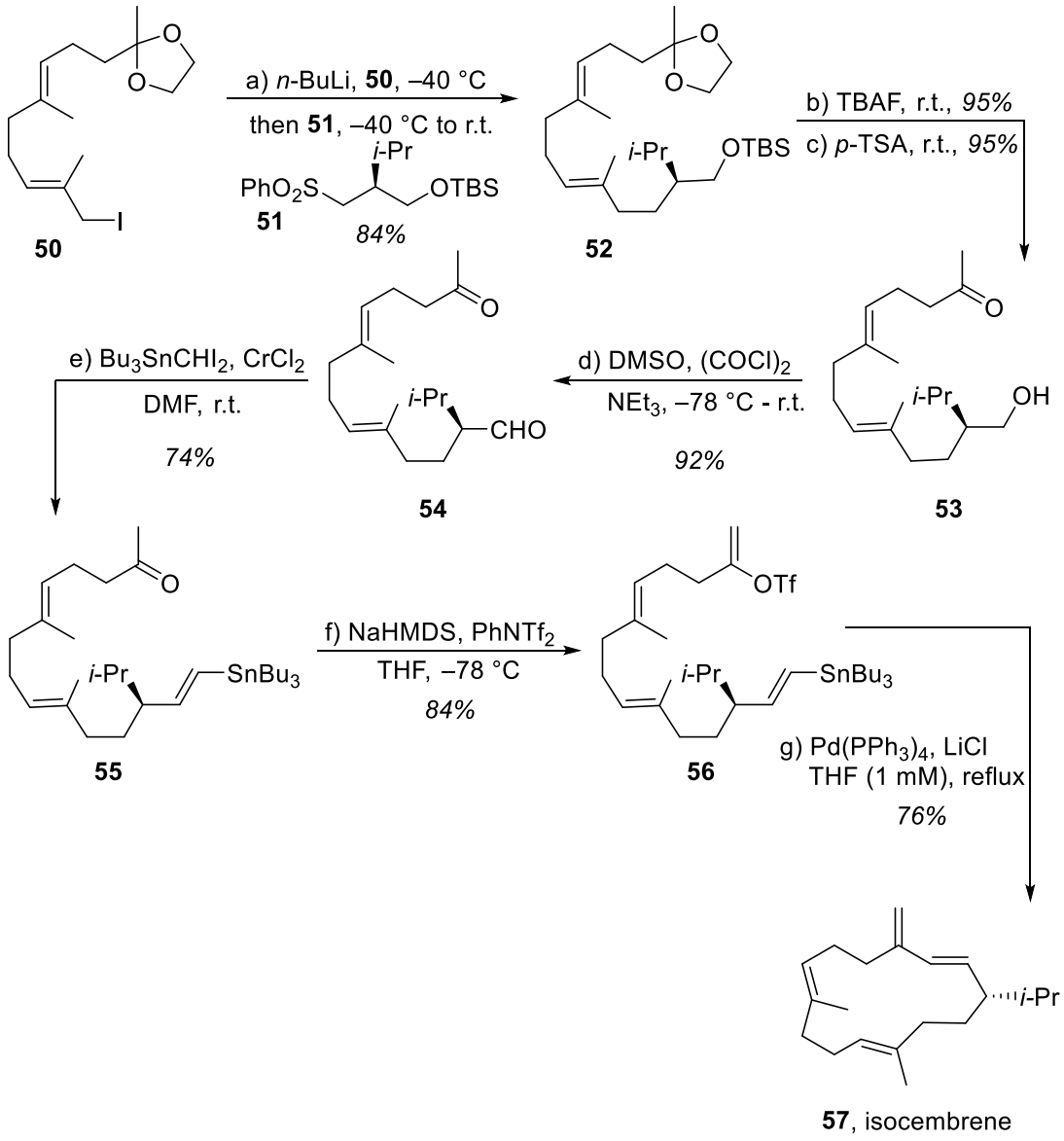


Scheme 1.8: Total synthesis of peloruside A using a Mitsunobu cyclisation.

1.2.4.4 Palladium Catalysed Macrocyclisation

With ever-increasing understanding of palladium coupling catalytic cycles, alongside the design and development of new and improved catalysts, palladium-catalysed cross coupling has drawn significant attention for the macrocyclisation of complex targets. Owing to its orthogonal reactivity, palladium coupling reactions have broad functional group and substrate applicability and therefore multiple disconnections approaches can be envisaged. Suzuki, Heck, Negishi and Stille couplings[38–41] have all been used to generate macrocyclic natural products/pharmaceuticals, sometimes when other macrocyclisation methods were not applicable or successful.

One example is found in the synthesis of highly unsaturated macrocycle isocembrene, **57** (scheme 1.9).[42] Lithium halogen exchange of iodide **50** was followed by S_N2 with fragment **51**. Deprotection of the alcohol and acetal, with TBAF and acid respectively, afforded alcohol **53**. Swern oxidation to generate aldehyde **54**, was followed by Takai-type olefination which proceeded with very high *E*-selectivity, to generate vinyl tin species **55**. Conversion of the ketone to the corresponding enol triflate **56**, was completed with NaHMDS and phenyl triflimide. Stille macrocyclisation was completed with $Pd(PPh_3)_4$ at reflux in THF, under high dilution conditions (1 mM) to access the natural product in 76%. The triflate is used in this context as a pseudo-halide, with oxidative addition into the C-OTf bond being comparable with that of C-Br.



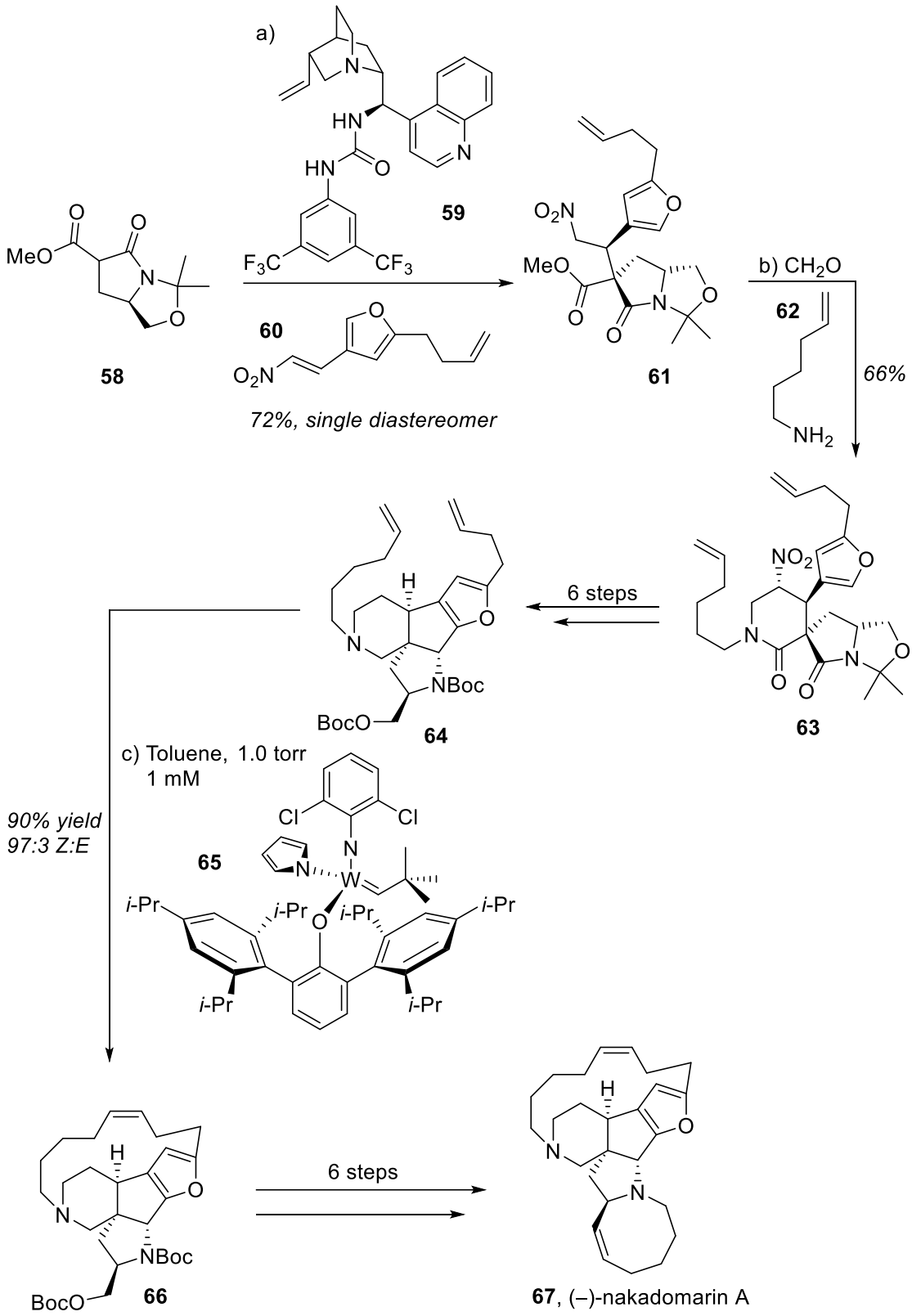
Scheme 1.9: Total synthesis of isocembrene using Stille coupling.

1.2.4.5 Ring-Closing Metathesis

Since its conception by Didier Villemin and co-workers[43] within the synthesis of an Exaltolide precursor in 1980, and later popularised by Grubbs and Schrock, ring closing metathesis (RCM) has become a powerful tool when targeting difficult ring systems.[44] The RCM method has been used in many total syntheses to produce both medium-sized rings and macrocycles such as floresolide B (Nicolaou, 2005),[45] (−)-balanol (Fürstner, 2000)[46] and (+)-migrastatin (Danishefsky, 2003)[46] to highlight a few. It has become a powerful synthetic tool, due to its broad substrate scope and the by-product (olefin) being volatile and therefore easily removable. Ruthenium, molybdenum and tungsten are the most common metals used at the core of the Grubbs and Schrock catalysts, with the mechanism proceeding through a series of formal [2+2] cycloadditions and reversions via metallocyclobutane intermediates. The geometry of the produced olefin has historically been problematic, with mixtures of both *Z*- and *E*-olefins being

produced in large ring sizes. Typically, the reaction is under thermodynamic control with the more stable *E*-olefin generally being the major product. However, in 2013 Grubbs showed that using a ruthenium NHC catalyst excellent *E*-selectivity was achieved, and when using a chelating ruthenium catalyst, the corresponding *Z*-olefin product was formed.[47] Since then, *Z*-selective RCM catalysts have been developed which create a sterically demanding transition state, which give rise to the change in selectivity.[48]

One example of this *Z*-selectivity can be seen within the total synthesis of (−)-nakadomarin A, **67** (scheme 1.10).[48] 1,3-Dicarbonyl **58** was treated with cinchona alkaloid **59** to induce highly stereoselective Michael addition into furan **60**, producing a single observable diastereomer. A Mannich-type reaction with formaldehyde and amine **62** was used to form spirocyclic lactam **63**, which required a further 6 steps to produce tetracyclic diene **64**, which was ready for the key RCM step. Using a tungsten alkydene catalyst, under vacuum to remove olefin by-products, macrocycle **66** was produced in excellent yield with outstanding (97:3) *Z*-/*E*-selectivity. Further manipulation of this core was completed to afford the natural product.

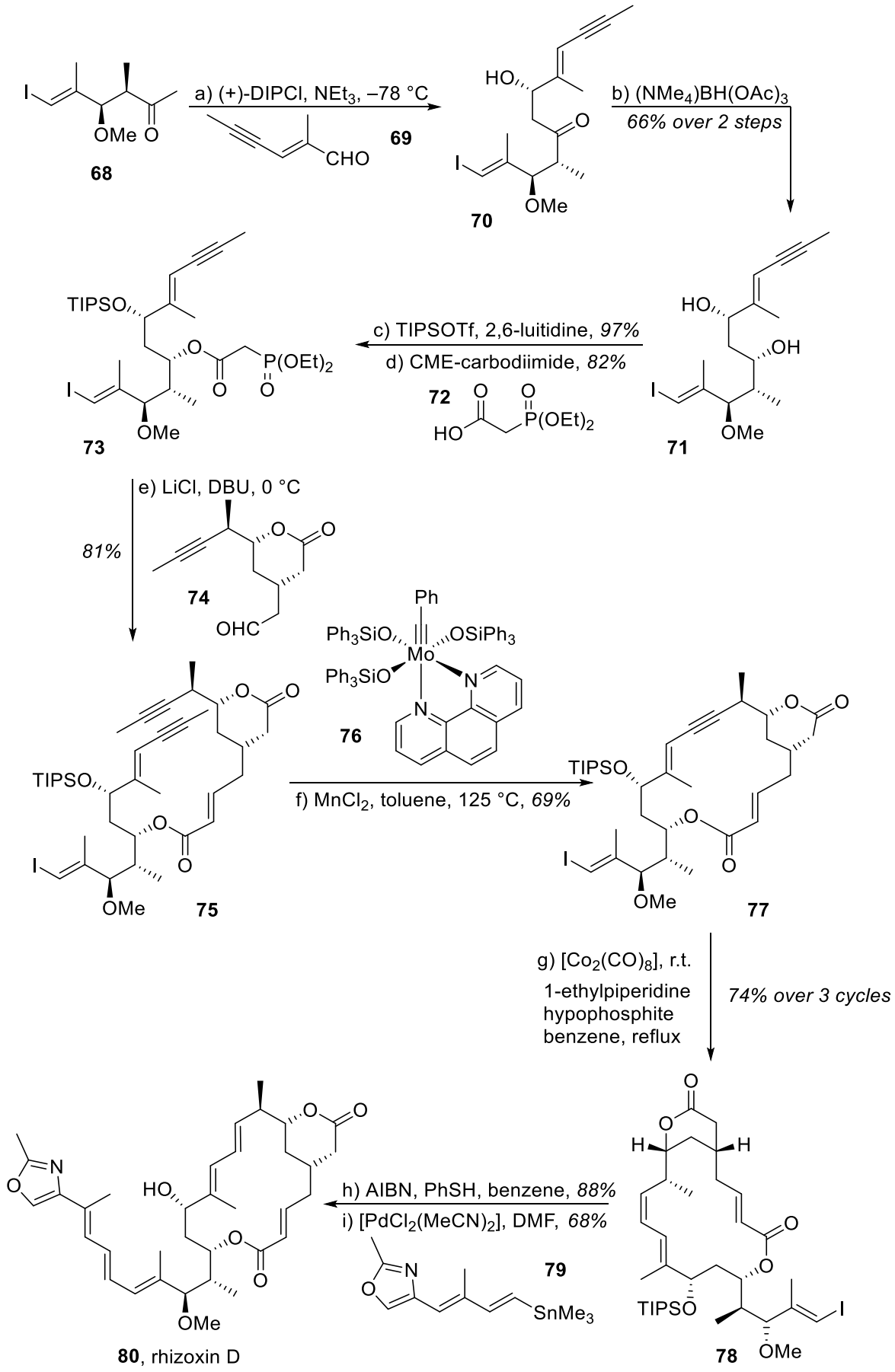


Scheme 1.10: Synthesis of (–)-nakadomarin A using *Z*-selective RCM catalyst.

1.2.4.6 Alkyne Metathesis

This reaction is very closely related to alkene RCM, but works on the principle of rearranging alkyne bonds to produce a cyclic alkyne and a volatile biproduct (commonly ethyne or butyne), which provides an entropic driving force for the reaction. Molybdenum-based catalysts are commonly used, and substrate scope is comparable if not more tolerant than with alkene metathesis.[49,50] One significant advantage, due to sp-hybridisation, is that *Z*-/*E*-isomerism is not a concern. Once the cyclic alkyne is generated, hydrogenation can be performed using Lindlar's catalyst to generate *Z*-olefins and dissolving metal reduction (similar to Birch reduction) can be used to access *E*-olefins. Although two distinct reactions are required to access a desired cyclic olefin via this approach, complete control of geometry can be achieved.

One example of alkyne ring closing metathesis which showcases its advantages, is seen during the synthesis of rhizoxin D, **80** (scheme 1.11).[51] In this synthesis, ketone **68** undergoes a stereoselective aldol reaction with aldehyde **69** mediated by chiral Lewis acid (+)-DIPCl. Using substrate control, reduction of ketone **70** to diol **71** is possible using weak reducing agent ATAB. Protection of the secondary alcohol followed by esterification affords phosphonate **73** in excellent yield. Horner–Wadsworth–Emmons olefination coupled the phosphonate **73** with aldehyde **74**, exclusively observed as the *E*-isomer. Di-alkyne **75** is then subjected to ring closing alkyne metathesis with molybdenum catalyst in good overall yield. Reduction of the newly formed cyclic alkyne **77** was achieved using *in situ* reductive decomplexation of a cobalt complex with EPHP, with satisfactory E:Z selectivity. This alkyne reduction was surprisingly found to be extremely challenging with all attempts of transition metal catalysed hydrogenation, hydroborylation and hydrostannylation being unsuccessful. The *Z*-,*E*-diene **78** was then radically flipped to the corresponding *E*-,*E*-diene. Stille coupling with diene **79** finishes the total synthesis of rhizoxin D in 68% yield.

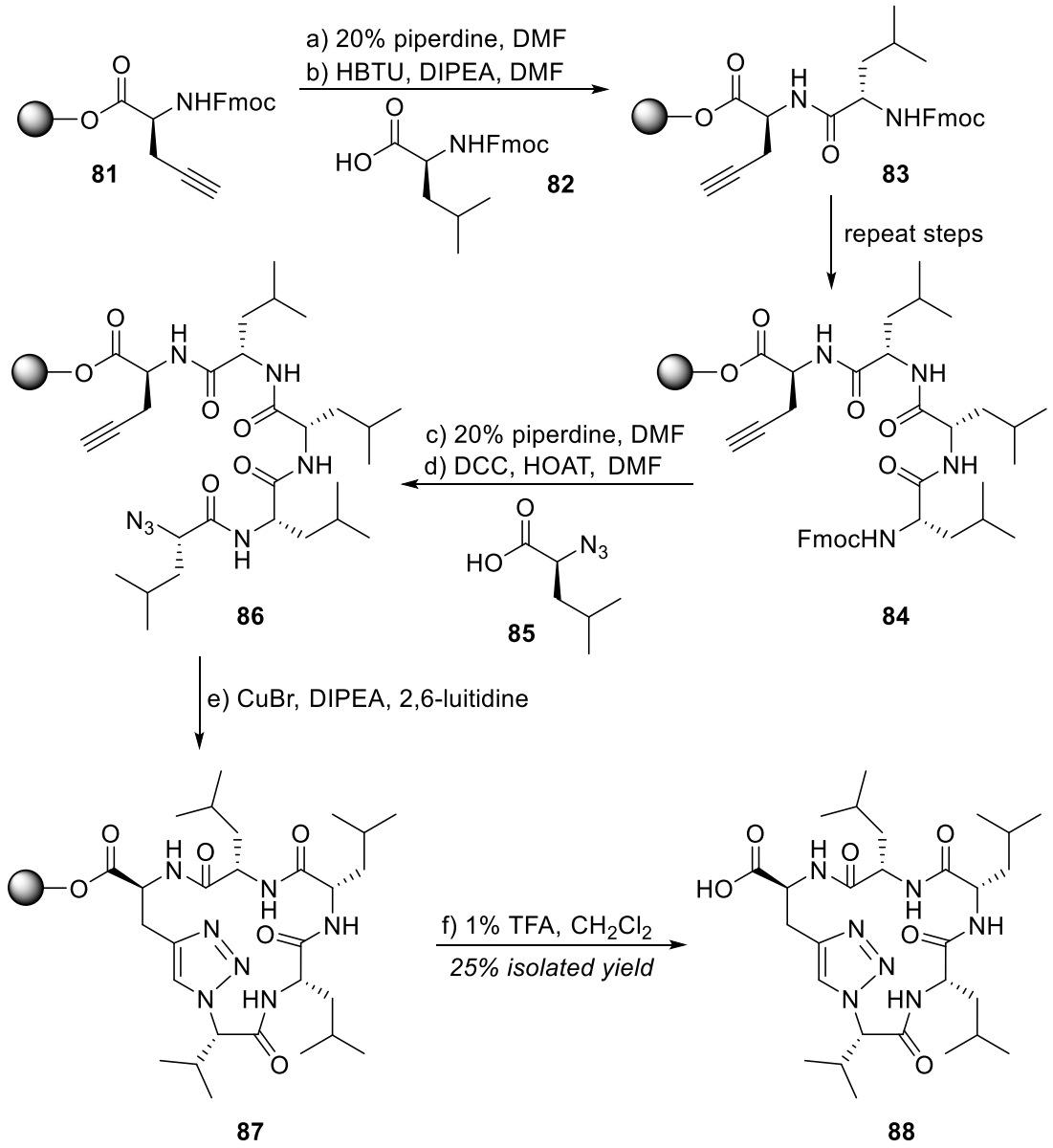


Scheme 1.11: Total synthesis of rhizoxin D via ring closing alkyne metathesis.

1.2.4.7 Cycloaddition of Alkyne and Azide

Huisgen 1,3-dipolar cycloaddition reactions between an azide and alkyne are able to selectively generate 1,2,3-triazoles, often without the requirement to use chromatography to remove by-products. Based on this, the reactions fulfil the pre-requisites of a 'Click' reaction, a concept introduced by Sharpless in 2001[51] to describe reactions which are "high yielding, wide in scope, create only by-products that can be removed without chromatography, stereospecific, operationally simple and can be performed in benign or easily removed solvents." However, thermal 1,3-dipolar cycloadditions usually give a mixture of regioisomers when using unsymmetrical alkynes, and therefore arguably should not be classified as a click reaction in these cases. As a result, a copper-catalysed variation was reported which benefits from greater control of regiochemistry, and operates via a different mechanism, with the reaction completed at room temperature in aqueous conditions. This quickly became incredibly popular due to the huge rate acceleration, broad pH and functional group tolerability and simple isolation of products via filtration.[52] In particular the bio-conjugation of enzymes/peptides, the synthesis of supramolecular structures (such as catenannes and rotaxannes) and the synthesis of pharmaceuticals/natural products use this reaction frequently.

A clever use of this chemistry can be seen within the synthesis of cyclic peptide mimetics. Lokey and co-workers[53] identified that a 1,2,3-triazole can mimic an amide and be constructed regio-selectively through the use of the copper catalysed cycloaddition. Using SPPS, alkyne amino acid **81** was coupled with leucine fragment **82** and repeated twice more to generate tetramer **84**. Azido-leucine **85** was coupled using HOAT and DCC to afforded azido alkyne **86**. Copper catalysed cycloaddition forming macrocycle **87**, was performed whilst the peptide was still attached to the resin, because the acidic conditions required for cleavage would have degraded the azide. Subsequent removal from the resin was completed with 1% TFA, affording the cyclic peptide mimetic, **88**, in 25% overall yield.



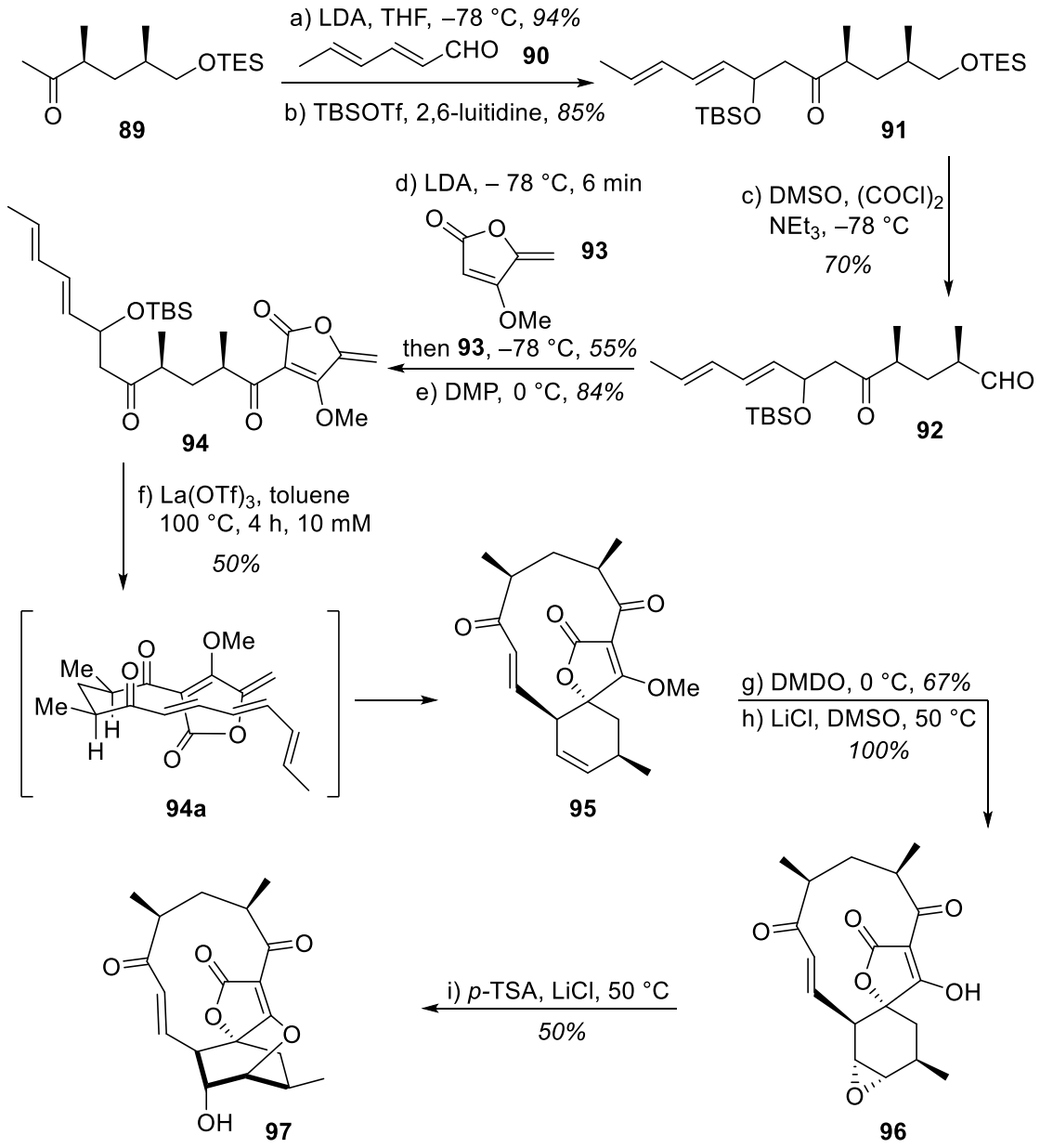
Scheme 1.12: Copper catalysed azide-alkyne cycloaddition towards the synthesis of cyclic peptide mimetics.

1.2.4.8 Diels–Alder Cycloaddition

Another example of a concerted pericyclic reaction that has been used for macrocyclisation is the Diels–Alder reaction. The Diels-Alder reaction is a [4+2] cycloaddition between a diene and dienophile, which results in the formation of an unsaturated six-membered ring. Regioselectivity is dictated by orbital overlap and the electronics of both diene and dienophile. Diastereoselectivity can also be controlled, for example, if a cyclic diene is used, and when operating under kinetic control, the endo product can be preferentially formed if a secondary orbital overlap with a carbonyl is present (this can be seen in scheme 1.13).

Although not commonly utilised in macrocyclisation, an example can be seen within the synthesis of abyssomicin C **97**.[54] First, ketone **89** was kinetically deprotonated using LDA, and

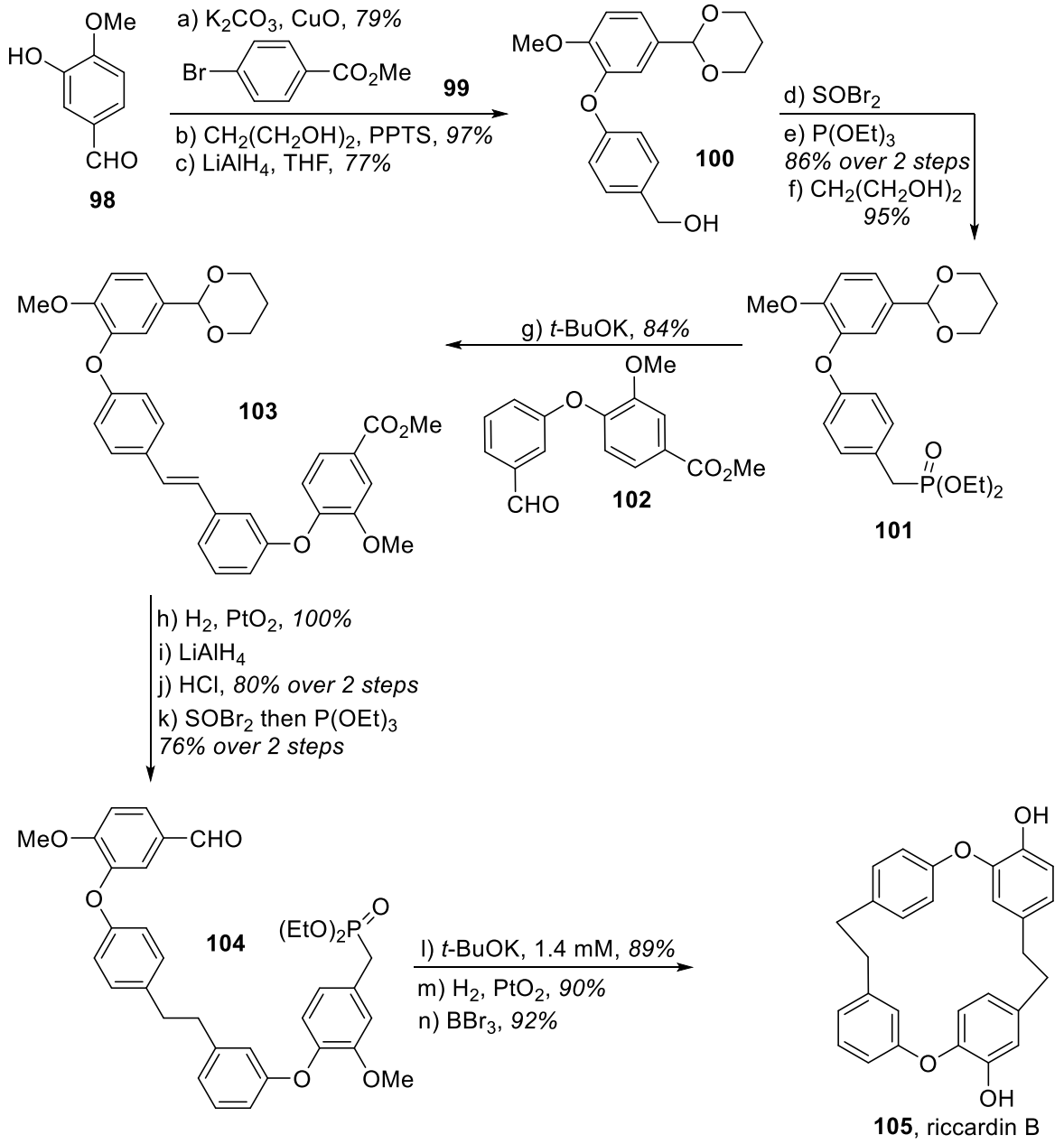
reacted with aldehyde **90** to yield the corresponding alcohol, which was trapped with TBSOTf to generate silyl ether **91**. Swern oxidation conditions were sufficient to deprotect and oxidise primary silyl ether **91** to analogous aldehyde **92**. Deprotonation and subsequent nucleophilic attack of cyclic vinyl ester **93** to aldehyde **92** was followed with Dess–Martin periodinane oxidation to generate 1,3-dicarbonyl **94**. With the use of lanthanum(III) triflate, a Diels–Alder reaction (proceeding via **94a**), afforded macrocycle **95** in modest yield. Epoxidation and enol ether hydrolysis afforded macrocycle **96** which was treated with *p*-TSA to induce ring opening of the activated epoxide with pendant alcohol to generate the natural product **97** in 50% yield.



Scheme 1.13: Diels–Alder macrocyclisation within the total synthesis of 97.

1.2.4.9 Horner–Wadsworth–Emmons/Wittig Olefination

The Horner–Wadsworth–Emmons was successfully employed as a macrocyclisation strategy in the synthesis of riccardin B, **105** (scheme 1.14).[55,56] Initially, an Ullman coupling between phenol **98** and aryl bromide **99** generated the equivalent di-aryl. Acetal protection of the aldehyde was followed with lithium aluminium hydride reduction of the methyl ester to form primary alcohol **100**. Conversion into the alkyl bromide was completed with thionyl bromide (which clumsily deprotected the acetal), which was then subjected to an Arbuzov reaction to generate the phosphonate ester. Protection of the aldehyde was required to generate **101**. Potassium *tert*-butoxide was used to deprotonate the phosphonate ester which was then coupled with bi-aryl aldehyde **102** in the first Horner–Wadsworth–Emmons reaction which proceeded in excellent yield and with complete regio-selectivity. Olefin hydrogenation, ester reduction, acetal deprotection, bromination and Arbuzov reactions were telescoped, generating phosphonate ester **104**. A second Horner–Wadsworth–Emmons reaction was performed which formed the macrocycle, under high dilution, in an excellent 89% yield. Hydrogenation of the produced olefin and demethylation using BBr_3, afforded the natural product riccardin B in 92%.



Scheme 1.14: Horner-Wadsworth-Emmons macrocyclic olefination within the synthesis of riccardin B.

1.2.5 Ring Expansion Reactions

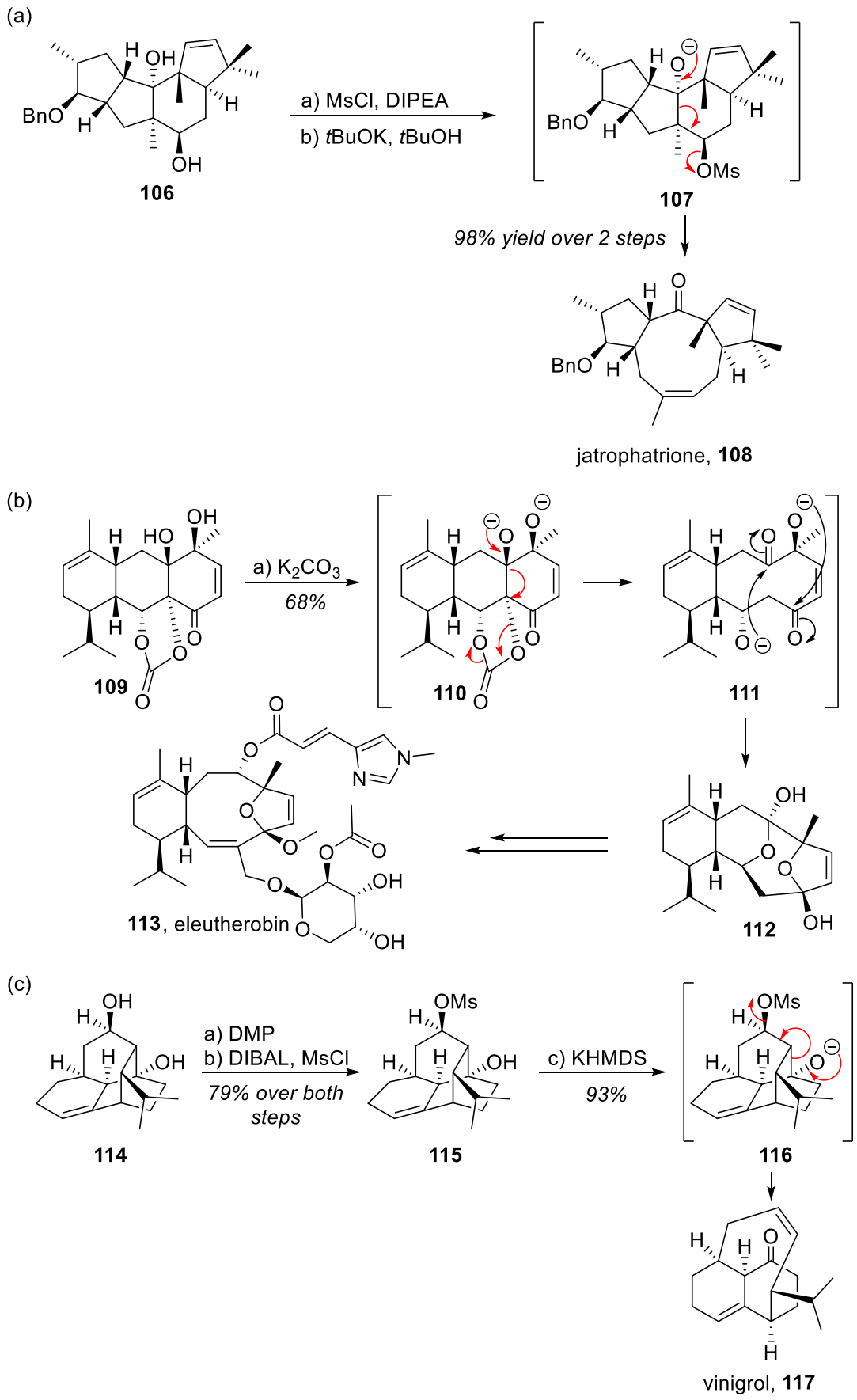
An alternative strategy to the direct cyclisation of a linear precursor is to use ring expansion to enlarge an existing cyclic scaffold. This means that the often-difficult cyclisation step can be entirely avoided, and has been used as an effective tool in total synthesis for many years. The powerful cyclisation reactions outlined thus far have been used in conjunction with at least one macrocyclisation strategy (e.g. high dilution) that minimises the damage of the difficult end-to-end cyclisation. However, utilising a suitable ring expansion can allow access to ringed systems that are traditionally difficult to synthesise (such as 8–11 membered rings or macrocycles), without the requirement of substrate bias or high dilution. This is most effective when a cyclisation step is required, then it is based on the formation of easily accessible cyclic transition states (i.e. 5- ,6- and 7-membered rings). This results in procedures that tend to be more predictable, operationally simple, and importantly scalable, without the competing dimerisation/oligomerisation pathways.

Most published ring expansion processes fall within four categories: **fragmentation**, **pericyclic** rearrangements, **radical** ring expansion and **side-chain insertion** with the following sub-sections split accordingly. This section of the introduction summarises an enormous body of literature and is not designed to be a comprehensive cover of the topic. For an excellent review of the area, the author highlights the subsequent paper.[57] In addition, the following sections will only cover ring expansions based on greater than or equal to 3-atom insertions, unless otherwise stated, as these are generally the most synthetically useful in the synthesis of medium-sized rings and macrocycles.[58–61] This is not done to diminish the importance of 1- and 2- atom ring expansions, however due to the large number of synthetic transformations, a review of this area would be too extensive.

1.2.5.1 Elimination Reactions (Grob/Wharton-type Fragmentation)

Arguably the most direct ring expansion approach, fragmentation involves breaking the bridge in a fused ring structure. Providing that the bicyclic system can be expeditiously prepared, a single fragmentation process is then required. Amongst the most widely used of these is the Grob fragmentation.[62] This elimination reaction profits from its irreversibility and has subsequently been applied to countless examples. Although too many to mention them all, three examples have been selected to illustrate this fragmentation approach. First, in the synthesis of jatrophatrione by Paquette and co-workers,[63,64] 1,3-diol **106** is treated with mesyl chloride which acts upon the less hindered secondary alcohol. Deprotonation causes fragmentation through intermediate **107**, affording the jatrophatrione natural product **108** in excellent yield (scheme 1.15a). Second, tricyclic core **109** was treated with potassium carbonate,

causing reversible deprotonation of both alcohols. A Grob fragmentation occurs generating ketone **111** with the expulsion of carbon dioxide driving the reaction via a large, favourable entropic change. Two separate transannular ring contractions then occur between the alkoxides and ketones to yield the eleutherobin core in a 68% yield.[65] It can be proposed that the first ring contraction occurs to relieve the strain associated with the medium-sized ring, as well as placing the alkoxide and ketone in close proximity in order for the second ring contraction to occur (scheme 1.15b). Finally, in the vinigrol synthesis by Baran,[66] mesylation of secondary alcohol **114** was achieved by an intriguing oxidation-reduction-trapping procedure. Deprotonation of tertiary alcohol with KHMDS initially generates an intermediate alkoxide **116**, and subsequent Grob fragmentation generates vinigrol core **117** in excellent yield, exclusively as the *Z*-olefin due to the geometry required for the elimination (scheme 1.15c).



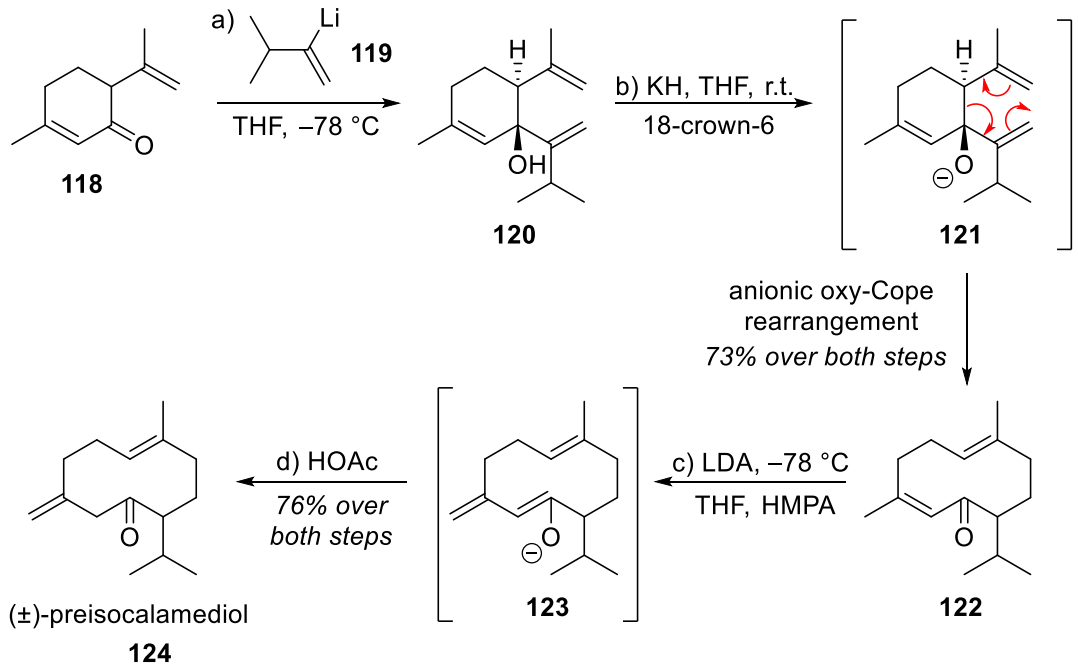
Scheme 1.15: Grob fragmentation reactions in total syntheses.

1.2.5.2 Pericyclic Rearrangements

Characterised by the concerted movement of electrons within a cyclic transition state, pericyclic rearrangements are a popular approach for the synthesis of complex targets.[67] Heterocyclic scaffolds are dominated by this approach due to their efficiency as well as their tuneable regio- and enantioselectivity.[68] This chemistry offers creative and sometimes disguised disconnections, which would otherwise be difficult to perform in a small number of steps. Significant investment has been placed into developing new, broad and interesting pericyclic chemistry with numerous named reactions operating via different reaction modes.

The three most common classes of pericyclic rearrangements are: electrocyclisation, cycloaddition and sigmatropic rearrangements. Each of these reaction classes have broad utility and have been used to create highly functionalised cyclic compounds. One example of a cycloaddition reaction, namely a Diels–Alder macrocyclisation, performed within the total synthesis of abyssomicin C, **97**, has already been described (see section 1.2.4). However, sigmatropic rearrangements are probably the most common class used for ring expansion. This molecular rearrangement involves the formation of a new σ-bond between two atoms not previously directly bonded, with the breaking of an existing σ-bond as defined by IUPAC.[69] [3,3]-Sigmatropic rearrangements have become the most widely used, being involved in many named reactions such as the Claisen, Cope, Carroll and Overman rearrangements. This class of sigmatropic rearrangement often proceeds through a chair-like transition state, which can result in predictable stereocontrol in the product. In addition, the formation of a carbonyl from an alcohol is often utilised as a strong thermodynamic driving force, to push the reaction to completion and avoid any unwanted equilibrium side products.

One example of a [3,3]-sigmatropic rearrangement can be seen in the synthesis of (±)-preisocalamendiol **124** by Still and co-workers.[70] Starting from the monoterpene, isopiperitenone (**118**), 1,2-addition using vinyl lithium reagent **119** afforded diene **120**. Using the anionic oxy-Cope rearrangement, developed by Evans,[71] (which has a substantial rate acceleration, being approximately 10^{17} times faster compared to the neutral oxy-Cope) yielded ketone **122**. Kinetic enolate protonation[72] resulted in deconjugation of the olefin, to produce the natural product in 76% yield.

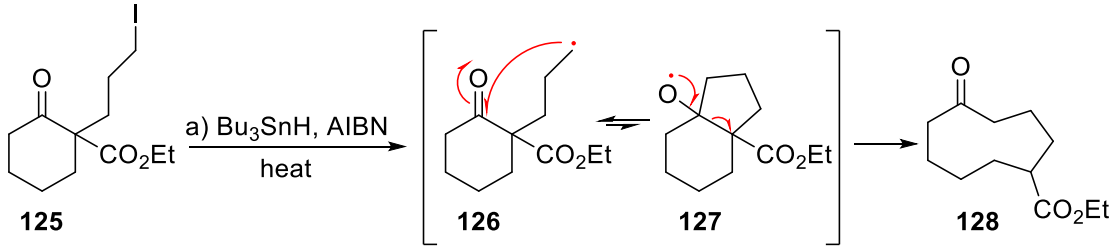


Scheme 1.16: Anionic oxy–Cope rearrangement employed by Still in the synthesis of the germacrene class of natural products.

1.2.5.3 Radical Ring Expansion

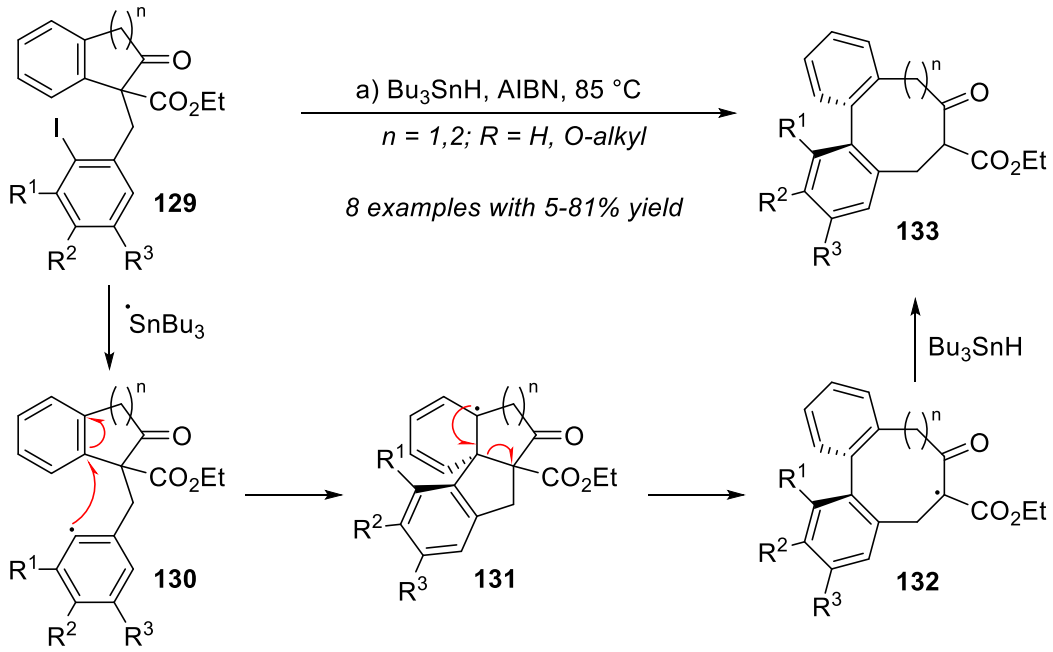
Owing to the short-lived, high-energy nature of radical intermediates in reactions, a plethora of chemistry can be observed ranging from functional group interconversions to highly complex cascade processes.[73] Radical transformations can be performed through many methods such as photochemistry, electrosynthesis and thermal decomposition. *C*- , *O*- and *N*-centred radicals are all possible and open up many different pathways, which can be seen in the ensuing section.

Arguably, the most widely implemented strategy is the Dowd-Beckwith reaction, alongside its variations. Radical generation (from the thermal decomposition of AIBN) has commonly been utilised to produce a primary radical **126** which can cyclise onto a carbonyl moiety (commonly a ketone) and induce a ring expansion via a high-energy *O*-centred radical **127**. The typical alkyl variation is shown in scheme 1.17, however an aminyl radical can also take place in the same reaction sequence if an azide precursor is used.



Scheme 1.17: Classical Dowd–Beckwith ring expansion reaction with primary iodide.

Radical reactions are not limited to variations of carbonyl addition chemistry and sites of radical attack can vary dramatically. An excellent example highlighting this comes from Harrowven et al., who reported an intriguing *ipso*-substitution in the synthesis of atropisomeric bi-aryl medium sized rings (Scheme 1.18).[74] The reaction proceeds via conventional thermal initiation of tributyl tin hydride using AIBN, and the stannyl radical abstracting iodide from the aryl iodide **129**. The resulting aryl radical **130** has the option of attacking into the carbonyl, but opts to attack the adjacent aryl ring. This results in the formation of a more stabilised tertiary allylic radical **131**, which is followed by concerted aromatisation/ring expansion, to generate electrophilic stabilised radical **132**. Tributyltin hydride propagates this radical chain reaction, generating the neutral product **133**. It is noted that the reaction works more effectively with indanone systems than the corresponding tetralones, which undergo unwanted *ortho*-substitution.



Scheme 1.18: Radical ring expansion towards the synthesis of atropisomeric bi-aryl medium sized rings.

1.2.5.4 Side Chain Insertion Reaction

As well as being a radical reaction, the Dowd–Beckwith reaction can also be classified as a side chain insertion reaction. Side chain insertion is best defined by the division into its stages: i) addition of a linear fragment to an already existing cyclic molecule, ii) the formation of a fused bicyclic system, iii) fragmentation of the bridging bond in an elimination type reaction, resulting in an overall ring expansion. Typically, a linear fragment is utilised with both an electrophilic and nucleophilic site to combine the processes into one cascade. Moreover, this can be achieved via both one and two electron processes, and consequently radical ring expansion reactions can also be placed into this category (as seen previously with the Dowd–Beckwith reaction). Commonly, this ring expansion class often proceeds under thermodynamic control, and as a

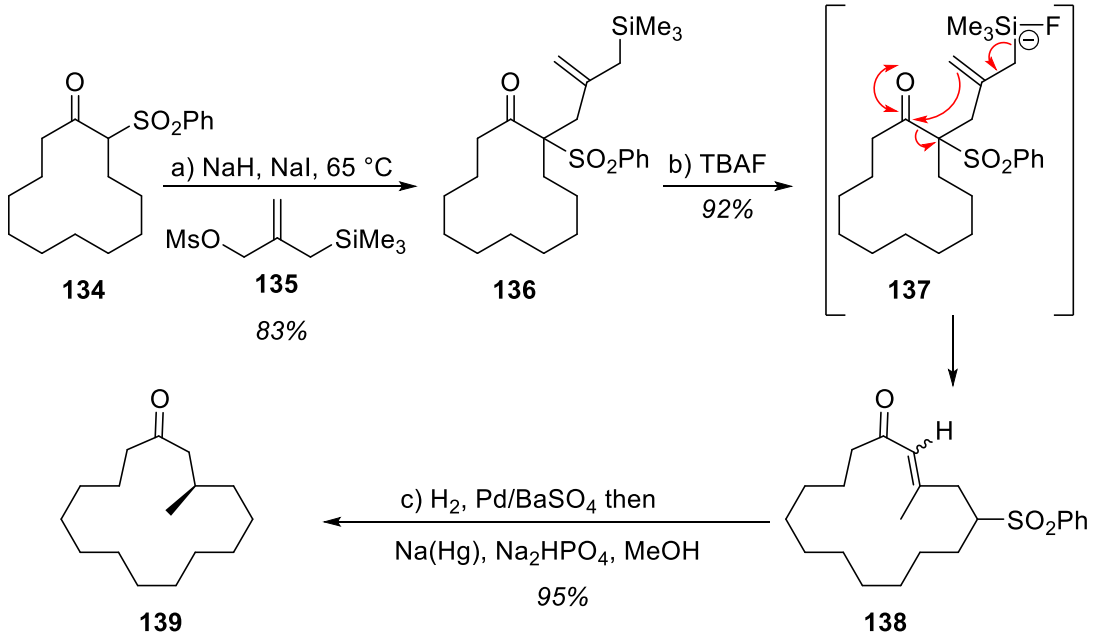
result the reaction must be carefully designed such that there is a clear propensity for expansion. When looking at ring size, functional group conversion or entropy in isolation, some insertion reactions may appear unfavourable, however all thermodynamic aspects must be considered together.

C- , *O*- , and *N*-nucleophiles can all be appended onto the cyclic starting material, which creates a further three sub-divisions of this ring expansion class. It is common that a protecting group strategy is used, to avoid any uncontrolled ring expansion or polymerisation of the linear fragment.

1.2.5.4.1 C-C Bond Forming Side Chain Insertion Ring Expansion

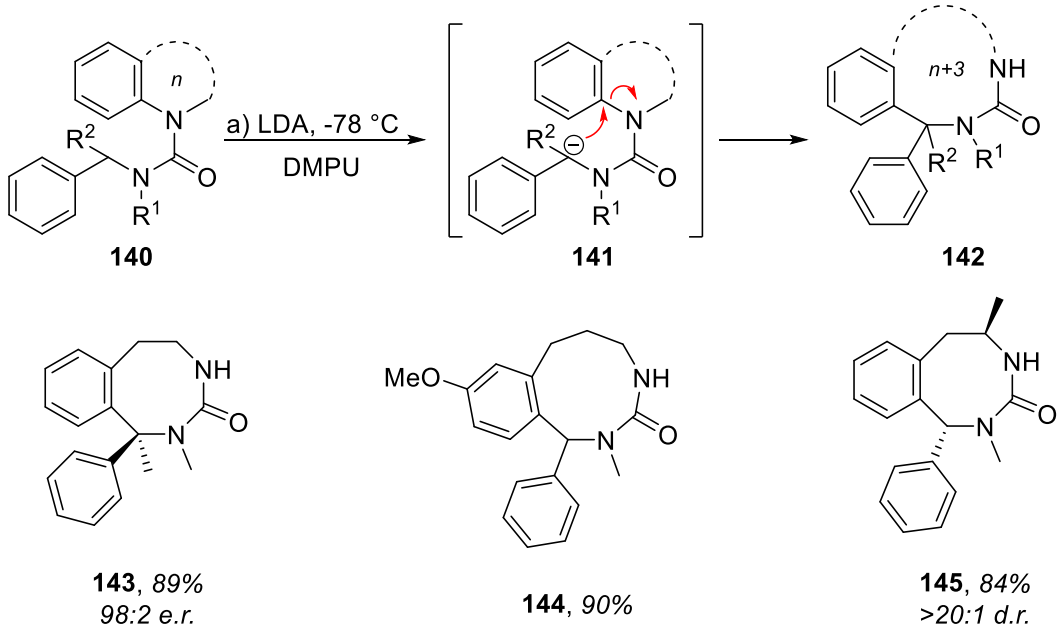
Carbon-carbon bond forming ring expansions are amongst the most valuable ring expansion processes synthetically, as well as being one of the most challenging to achieve through two-electron processes. However, commercially important macrocycles such as the perfume ingredient muscone necessitates a viable and scalable synthesis towards these all carbon macrocyclic scaffolds, and this has led to much interest in the development of such ring expansion approaches. The radical Dowd-Beckwith expansion can be utilised, however this can be problematic with highly functionalised intermediates.

Within the synthesis of muscone, Trost *et al.*[75] reported an astute condensative expansion under mild conditions and excellent selectivity. An initial alkylation of β-keto sulfone **134** with mesylate **135**, assisted via an *in-situ* Finkelstein reaction, generates ketone **136**. Treatment with TBAF is sufficient to initiate ring expansion followed by olefin migration to the thermodynamically stable tri-substituted internal conjugated system **138**. A final hydrogenation affords the natural product muscone **139**.



Scheme 1.19: C-C bond forming side chain insertion within the synthesis of muscone.

This methodology is not limited to organosilicon or radical chemistry; through the use of a suitably strong base, similar transformations can be performed with organometallics. Serious consideration of the acidity and electrophilicity of reactants and products must be taken when handling these reactive intermediates to avoid side reactions, however, with judicious selection of protecting groups and functional groups, transformations which would otherwise be incredibly difficult to perform can be achieved. Exemplifying this reactivity, a host of medium-sized rings have been accessed through a proposed associative concerted mechanism reported by Clayden and co-workers (scheme 1.20).[76] The proposed mechanism proceeds through initial lithiation of cyclic urea **140** at the benzylic position, adjacent to the urea, with hindered base LDA and DMPU used to encumber a 1,2-acyl shift pathway. The benzylic anion **141** undergoes *ipso*-substitution, which results in an overall ring expansion. An associative concerted mechanism (rather than an S_NAr mechanism) is proposed because electron donating groups on the arene, which would destabilise the Meisenheimer complex in a standard S_NAr process, often progress with higher yields (**144**). Exquisite enantioselectivities/diastereoselectivities (**143** and **145**) highlight the influence that lithiated derivatives can have in ring expansion.

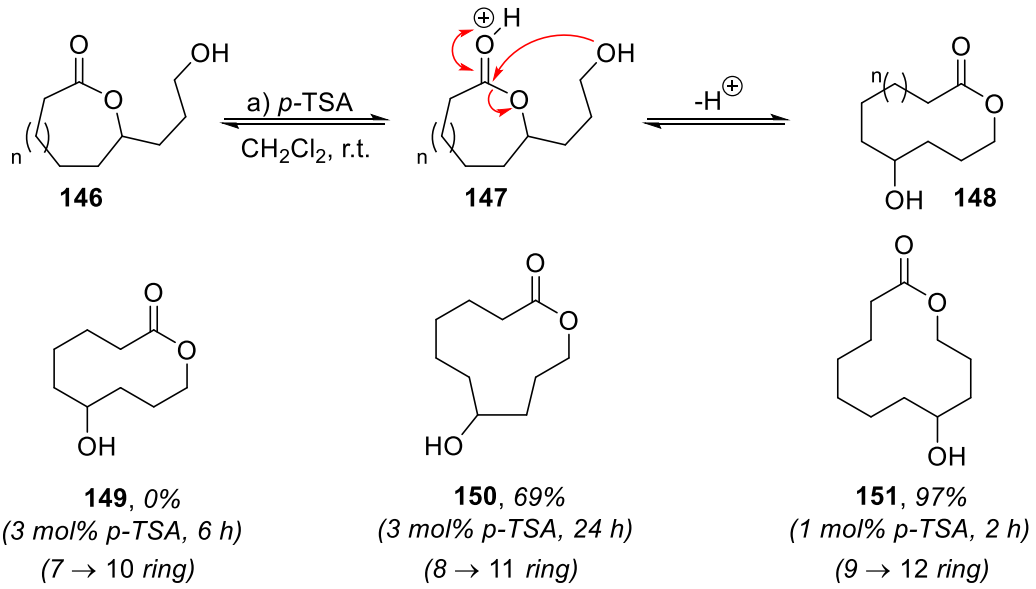


Scheme 1.20: Synthesis of benzodiazepines through organometallic migration of cyclic ureas by Clayden and co-workers.

1.2.5.4.2 C-O Bond Forming Side Chain Insertion Ring Expansion

Since the development of Yamaguchi lactonisation,[77] many more macrocyclic lactonic natural products (such as macrolide antibiotics) have been synthesised. This resulted in significant academic interest in developing streamlined synthetic routes to these valuable targets. Ring expansion was identified as an alternative strategy, which had the potential to access functionalised macrocyclic lactones with continued research. It was quickly understood that basic conditions were commonly required to promote C-O bond forming ring expansion, however some examples have been reported to operate through acid-catalysed mechanisms.[78]

Ring expansion reactions based on transesterifications have been described,[79] however with no change in the functional group composition during such reactions, the driving force for ring expansion must arise from only ring size stability. Corey and co-workers[80] illustrated the challenges associated with medium-sized ring synthesis via a transesterification approach. Treating lactones of the type **146** with *p*-TSA, activated the lactone carbonyl by increasing its reactivity through an oxonium intermediate. At room temperature, an equilibrium between **147** and **148** was achieved, with the position of equilibrium dependant on ring size. Those ring sizes with higher Prelog strain, produced no or very little ring enlarged products under the reaction conditions. However, once the ring size had become significantly large and flexible to reduce the unfavourable transannular interactions, yields of product increased dramatically to near quantitative for macrocyclic lactone **151**. These results highlight the difficulty in synthesising medium-sized rings, however also demonstrate that they can often undergo facile ring expansion to macrocycles, due to the release of ring strain.

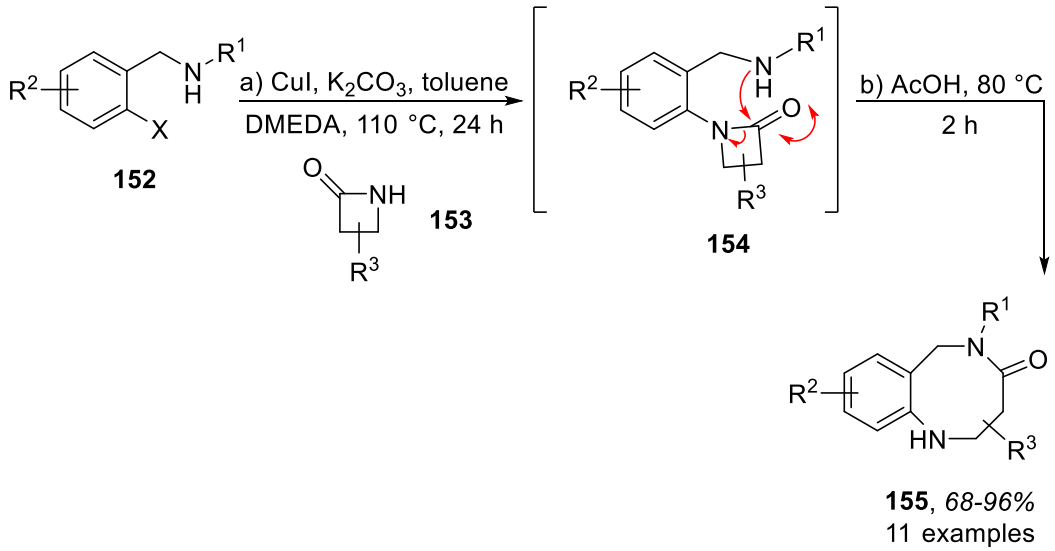


Scheme 1.21: Transesterification of medium-sized rings by Corey and co-workers.

1.2.5.4.3 C-N Bond Forming Side Chain Insertion Ring Expansion

With the prevalence of nitrogen containing heterocycles in Nature and pharmaceuticals, ring expansion methods that incorporate this desirable heteroatom have clear benefits. In addition to the importance/usability of the products, using an amine as a pendant nucleophile has many synthetic advantages. Amine protecting groups have been extensively examined and developed, offering orthogonal stability/lability with regards to other functional groups and reaction conditions. Therefore, a suitable protecting group can often be found, with the amine only revealed when needed, avoiding unwanted side reactions such as dimerisation or transannular interactions. The revealed amine is also usually a good nucleophile and has the ability to partake in a whole host of chemistry such as: carbonyl addition, Michael addition, nucleophilic substitution and Buchwald-Hartwig coupling to name a few.

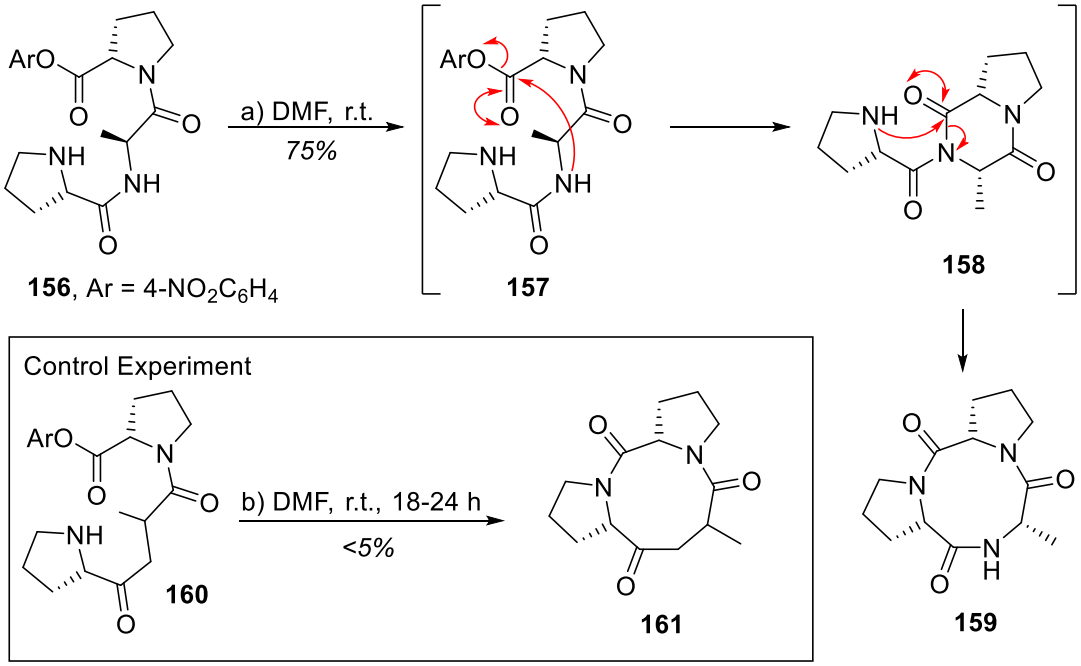
One example, reported by Buchwald and co-workers, uses a telescoped one-pot approach to access benzoazocines.[81] Initially, a copper-catalysed Ullmann-type coupling is performed between aryl halide **152** and azetidinone **153**, forming amine **154**. Although not required in every case, DMEDA was added to ligate the copper catalyst, which increased the reaction yields. Under the coupling conditions used, the amine **154** undergoes transamidation to relieve ring strain of the β-lactam moiety. In some instances, catalytic acetic acid was required for ring expansion to be successful. The real advantage with this chemistry arises from the diversity and ease in which these complex heterocycles can be constructed. Azetidinone **153** and many derivatives are commercially available and benzyl amines **152** can be simply made on large scale in a single step with two further points of modification.



Scheme 1.22: Synthesis of benzoazocines via a domino C-N coupling/ring expansion cascade by Buchwald and co-workers.

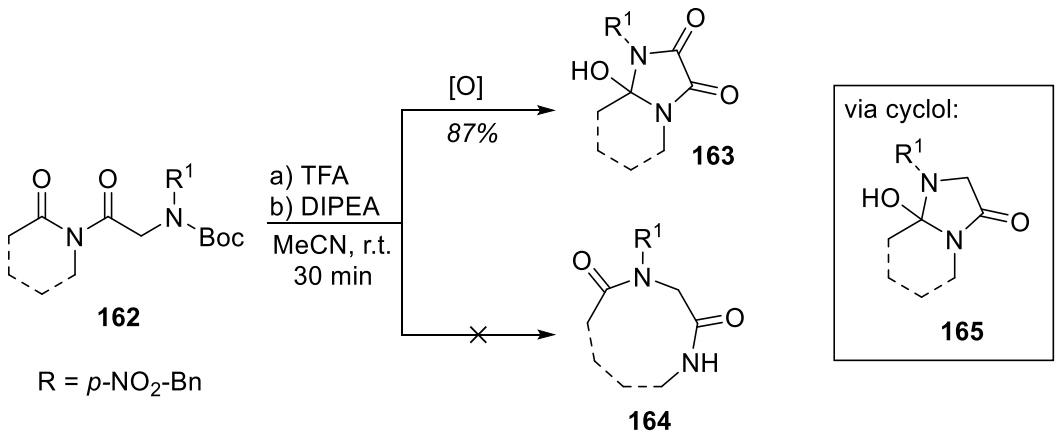
A non-catalytic C-N bond forming ring expansion reaction is the amino acid acyl incorporation (AAI). This involves the incorporation of an amino acid fragment into a cyclic amide, generating a cyclic dipeptide. Despite the power of this reaction, this intriguing intramolecular ring expansion has surprisingly received little attention,[82] with only a few advancements being reported by Shemyakin and co-workers[83–86] until the work reported in this thesis, along with a recent report (published at the same time as the work completed in Chapter three) by Yudin and co-workers.[87]

A generic early example[88] takes tripeptide, synthesised by SPPS, and activated the *C*-terminus via *p*-nitrophenol ester **156** (scheme 1.23). Assisted by the turn-inducing amino acid proline, present in the sequence, cyclisation to diketopiperazine intermediate (**157** → **158**) under extremely mild conditions was possible. If a more activated pentafluorophenol ester is utilised, intermolecular dimerisation/oligomerisation occurs resulting in no observed cyclised product. The diketopiperazine intermediate **158**, was then proposed to undergo spontaneous ring expansion, under neutral conditions, generating 9-membered tripeptide **159** in high yield for sterically unencumbering Pro-Ala-Pro tripeptide. Medium-sized cyclic tripeptides similar to **159** are usually extremely difficult to synthesise via the head-to-tail cyclisation of a linear peptide so this reaction is not viable. The mechanism proposed is supported by a control experiment in which removing the internal nucleophilic amide, resulted in incredibly poor yields (<5%) of the cyclised tripeptide (**160** → **161**).



Scheme 1.23: Synthesis of tripeptide medium-sized rings through AAI reaction.

However, more recent work by Yudin *et al.*[87] sheds significant doubt on the mechanism proposed in scheme 1.23. An extensive study (supported by computational calculations) on direct amino acyl incorporation to produce 8- , 9- , 10- and 11-membered peptides was performed, which contradicted the results obtained by Rothe *et al.*. They found that whilst β-amino acids could undergo ring expansion with lactams of varying ring size, α-amino acids would stop at a tetrahedral intermediate **165** (scheme 1.24), named a cyclol. For 6-membered lactams, including diketopiperazines, the cyclol or open amine form was found to be thermodynamically most stable, rather than the desired ring expanded product **164**. Although the same reaction (**156** → **159**) was not completed, this work opposes a two-step mechanism in the synthesis of cyclic tripeptides, and suggests that direct 9-membered lactamisation aided by a favourable conformation may have been the true mechanism in the study conducted by Rothe *et al.* (scheme 1.23).



Scheme 1.24: Synthesis of medium-sized rings, examining the key cyclol intermediate by Yudin and co-workers.

1.2.5.5 Consecutive Ring Expansions

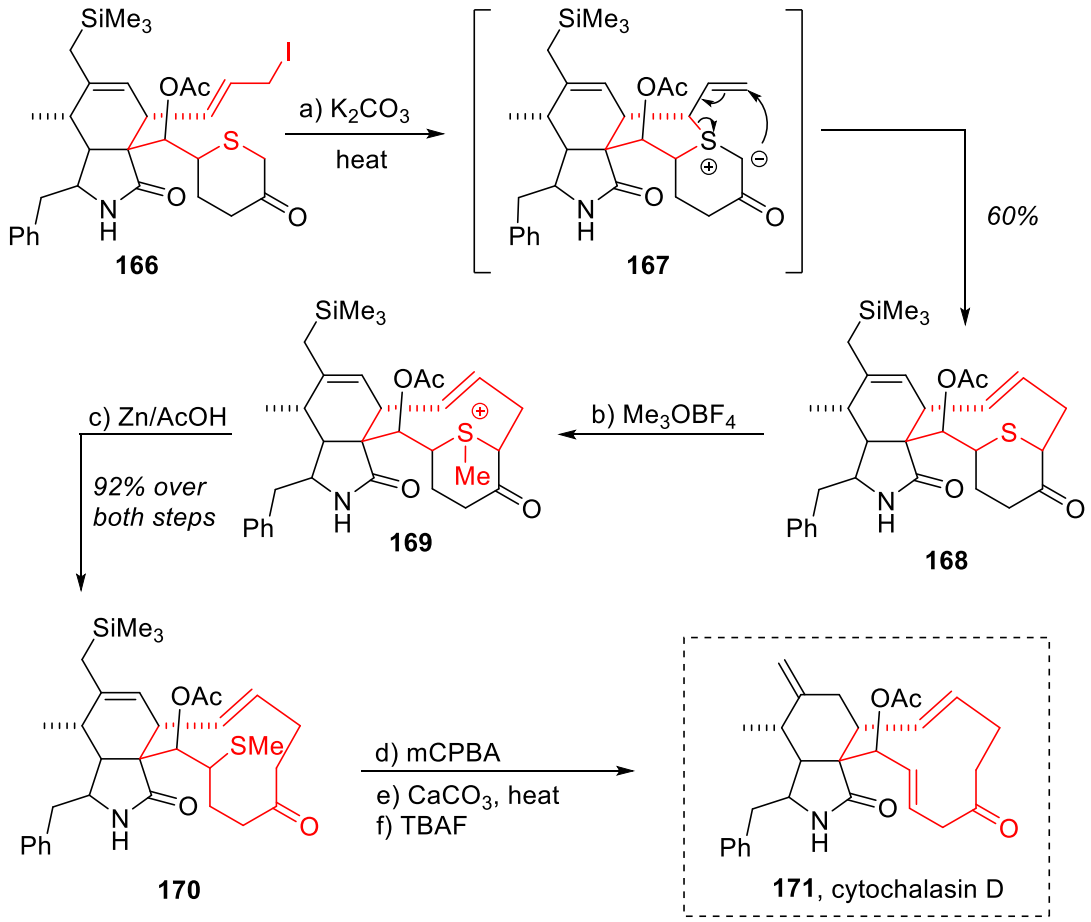
In all the preceding sections, interesting cyclic compounds have been accessed in good to excellent yields that are typically difficult to synthesise via end-to-end cyclisation. Particular emphasis has been placed on the synthesis of medium-sized rings, as their precursors are often commercially available or easy to make, typically with excellent control of regio- and stereochemistry. However, to ensure ring expansion is efficient it is common that reactions proceed via fused 5- ,6- and 7-membered ring intermediates/transition states before expansion, and this can limit the number of atoms (3–5) that can be efficiently added to the ring size during a single ring expansion. This in turn significantly limits the number of molecules that ring expansion methods can access.

One strategy that has emerged to combat this limitation, is the use of *consecutive ring expansions*. There are far fewer examples of this approach being used, however those developed clearly show the potential of this approach. When done well, individual ring expansion can be utilised to incorporate specific functionality, allowing macrocycles to be 'grown' in a programmable and predictable method. We have recently published a full review on this area of ring expansion, which can be consulted for a more detailed account of this topic.[89] Selected highlights are described in this section, with these sequential ring expansion types separated into the same sub-divisions as used previously: *pericyclic rearrangements*, *elimination reactions* and *insertion reactions*.

1.2.5.5.1 Pericyclic Rearrangements

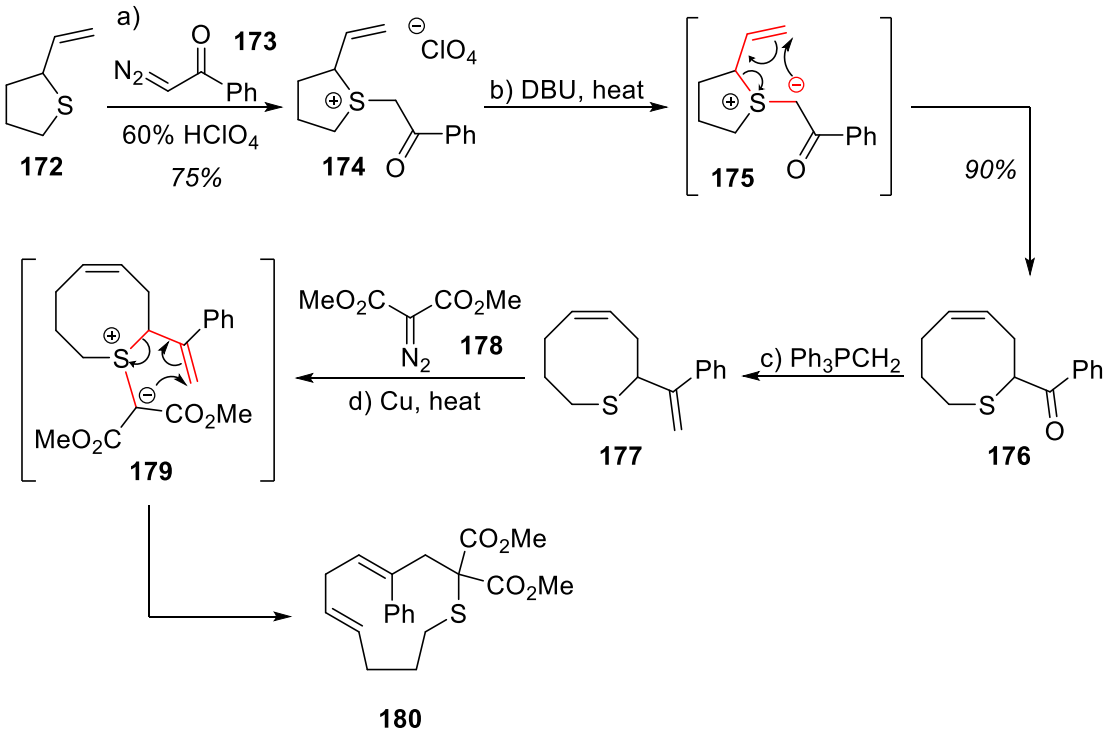
There has been significant interest in this area, with most publications utilising charged intermediates (often acting as a thermodynamic driving force) within sigmatropic rearrangements. Heteroatoms are also commonly employed which can facilitate starting material preparation.

Sulfur can be used to mediate pericyclic rearrangements as sulfonium cations and ylides can be generated with ease, which in turn can result in a facile rearrangement. Sulfur can also be subjected to well-known chemistry to perform functional group interconversion, however the incorporation of sulfur can be advantageous, *e.g.* the sulfone group is often included in medicinal chemistry to act as a hydrogen bond acceptor.[90] The total synthesis of cytochalasan D **171** (scheme 1.25) by Vedejs and Reid[91] utilises these advantages of sulfur mediation, eliminating the heteroatom in a mild fashion at the end of the synthesis. Thus, iodide **166** was heated in acetonitrile/potassium carbonate to produce ylide **167**. Under the reaction conditions used to generate the ylide, spontaneous [2,3]-sigmatropic rearrangement occurred producing 9-membered sulfide **168** in an overall good yield. Methylation with Meerwein's salt afforded sulfonium **169**, which was amenable to zinc/acidic C-S bond cleavage delivering 11-membered sulfide **170**. Oxidation and following elimination formed unconjugated olefin, with TBAF mediated elimination of the silyl group generating the natural product.



Scheme 1.25: Sulfur mediated consecutive ring expansions within the total synthesis of cytochalasan D.

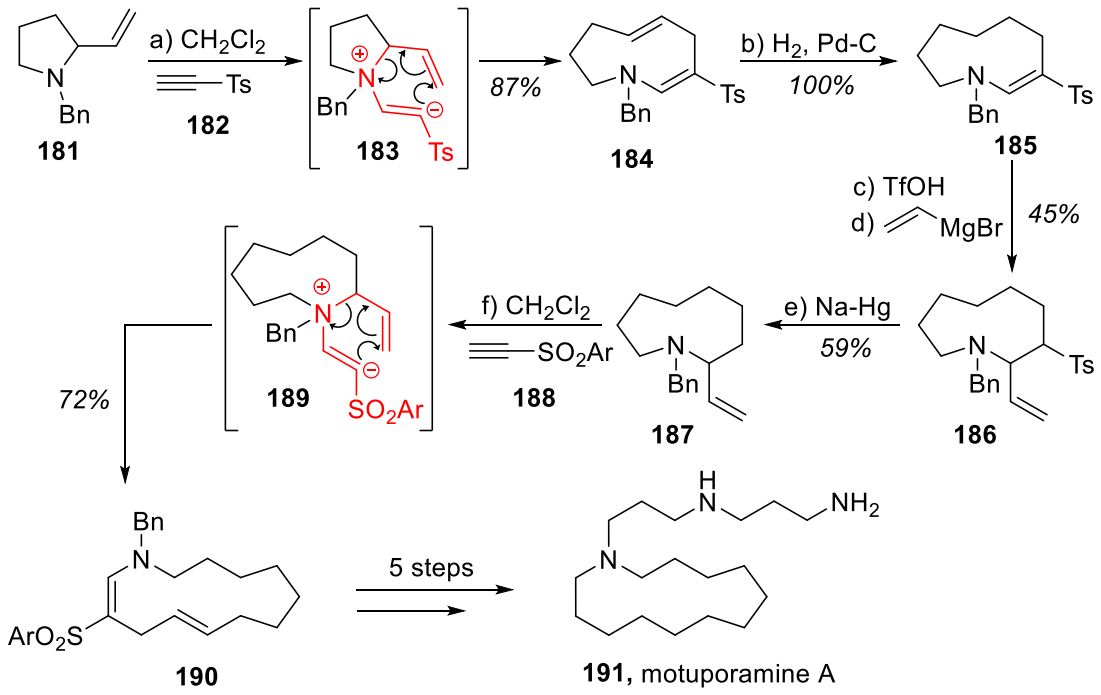
Vedejs and co-workers also pioneered the development of successive [2,3]-sigmatropic rearrangements in order to build ring enlarged products.[92] With only a small number of transformations between each ring expansion iteration, this method illustrates the power of these iterative sigmatropic rearrangements. Starting from allyl sulfide **172**, perchloric acid assisted nucleophilic substitution of diazocarbonyl **173** delivered sulfonium **174**. Treatment with base generated sulfur ylide **175** which efficiently underwent [2,3]-sigmatropic rearrangement in excellent yield to ring enlarged sulfide **176**. Wittig olefination afforded new allyl sulfide **177**, which contained the required functionality for a further iteration. For the second [2,3]-sigmatropic rearrangement, an alternative diazo-compound is utilised however the reaction proceeds in the same fashion. Copper-catalysed coupling of sulfide **177** and diazomalonate **178**, generated 11-membered sulfide **180** in a single step, presumably through the same steps as described previously. Unfortunately, the yields of the final two steps was not disclosed in the report. However, further studies on sulfur mediated [2,3]-sigmatropic rearrangements were completed by Vedejs and co-workers[93–96] as well as Schmid and co-workers,[97] which streamlined this process to an allylation/[2,3]-sigmatropic rearrangement sequence, which could be iterated 3 times, generating a 14-membered highly unsaturated macrocyclic from the same sulfide **172**.



Scheme 1.26: Iterative synthesis of ringed compounds via sequential [2,3]-sigmatropic rearrangements by Vedejs and co-workers.

Nitrogen can also be utilised within sigmatropic rearrangements to mediate consecutive ring expansions. Similar to the sulfur mediated rearrangements, charged intermediates are often utilised, in aza-variations of the carbon rearrangements. One example of this, is the use of two

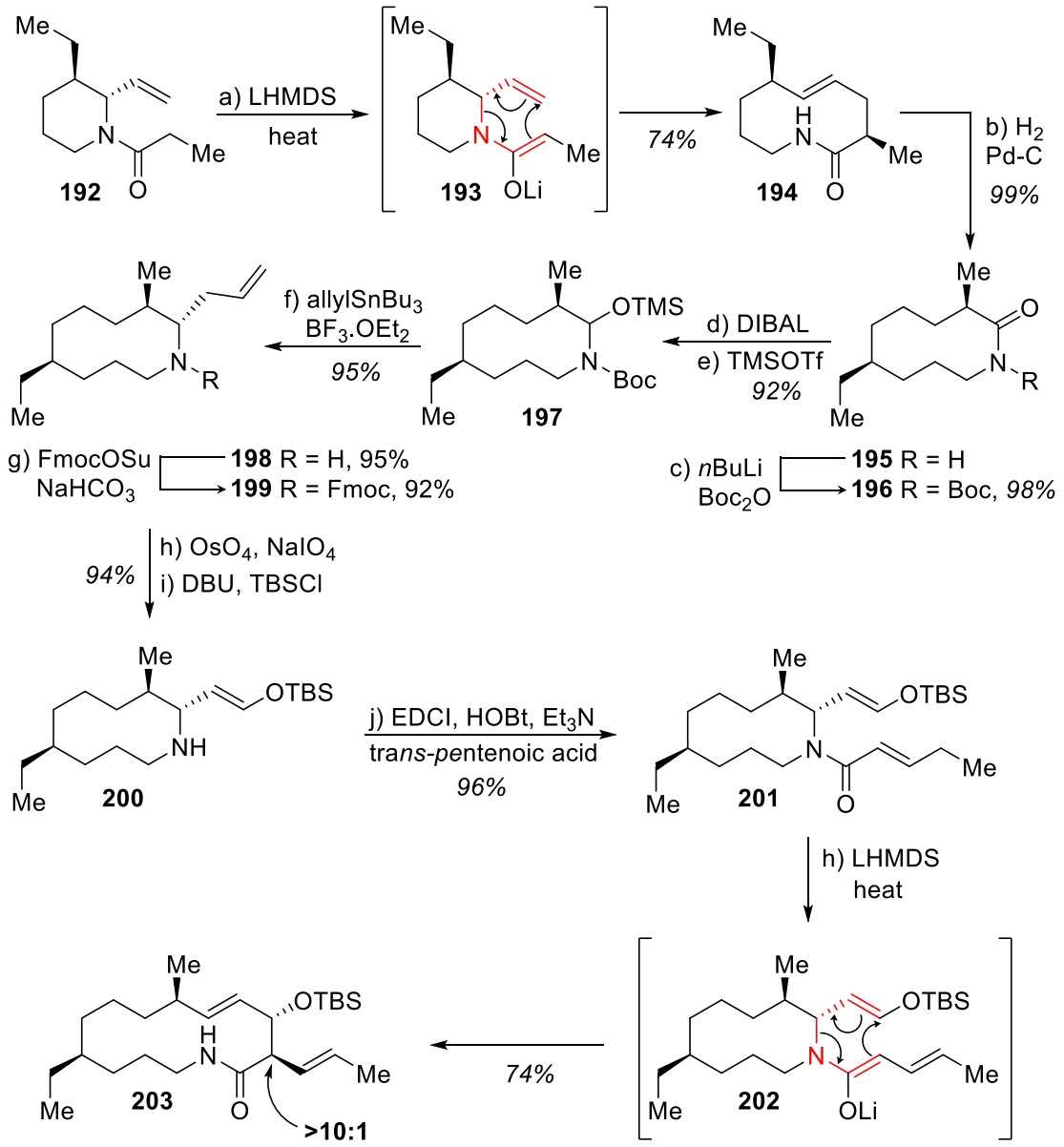
consecutive [3,3]-sigmatropic rearrangements reported by Back and co-workers.[98] Thus, 2-vinylpyrollidine **181** underwent conjugate addition into acetylenic sulfone **182** generating transient zwitterion **183**, which underwent a [3,3]-sigmatropic rearrangement *in situ* in excellent yield. Hydrogenation of isolated olefin **184** was successful with quantitative yield generating cyclic amine **185**. Treatment with triflic acid formed the corresponding iminium intermediate which was immediately quenched with a vinyl-Grignard reagent. This regenerated the α-vinyl moiety, and therefore, this compound could be re-subjected to the same reactions conditions as the initial ring expansion. Using a different acetylenic sulfone **188**, conjugate addition was performed and once again *in situ* [3,3]-sigmatropic rearrangement was performed generating doubly ring expanded product **190**. Additional modifications were required to access the natural product motuporamine A, however the main backbone was introduced using this sequential aza-Cope rearrangement protocol.



Scheme 1.27: Total synthesis of natural product motuporamine A using two sequential aza-Cope rearrangements reported by Back and co-workers. Ar = *p*-Cl-Ph.

Another intriguing example comes from Suh and co-workers[99] which requires somewhat harsher conditions with the use of a strong hindered base and heat, however, excellent yields and diastereomeric control were nonetheless achieved (scheme 1.28). The stereocontrol arises from a 6-membered transition state, demonstrating that these rearrangements can transfer stereochemical information, without the need for chiral reagents or ligands. Thus, α-vinyl lactam **192**, synthesised by use of Evans asymmetric alkylation/stereoselective vinylation, was treated with LHMDS and heated at 110 °C to induce the desired aza-claisen rearrangement (ACR), producing ring enlarged ten-membered lactam **194**. Hydrogenation of the isolated olefin

proceeded in excellent yield to generate saturated lactam **195**. Protection of the amide was required and thus completed in excellent yield using *n*-BuLi and Boc_2O to afford **196**. Reduction of the amide to the corresponding hemi-aminal, followed by trapping with TMSOTf generates the silyl ether **197**, which was amenable to highly selective amidoalkylation producing **198**. Unfortunately, the Lewis acidic BF_3 catalyst used in this step led to unwanted Boc cleavage, and therefore reprotection was required, this time with a base labile Fmoc protecting group. Lemieux–Johnson oxidation was performed generating the aldehyde which was transformed into silyl enol ether **200**. Amidation was achieved using mild *in-situ* coupling conditions with *E*-pentenoic acid producing a newly formed α-vinyl amide **201**. Treatment with LHMDS at 110 °C (identical conditions to those applied previously) generated macrocyclic amide **203** in excellent yield and diastereoselectivity. It was noted that the second ACR exhibited a greatly improved rate compared to that of the first, which was proposed to be as a result of the silyl enol ether.[100] Follow up studies focusing on this were completed shortly afterwards, which confirmed this statement and produced natural product fluvirucinin A2.[101]



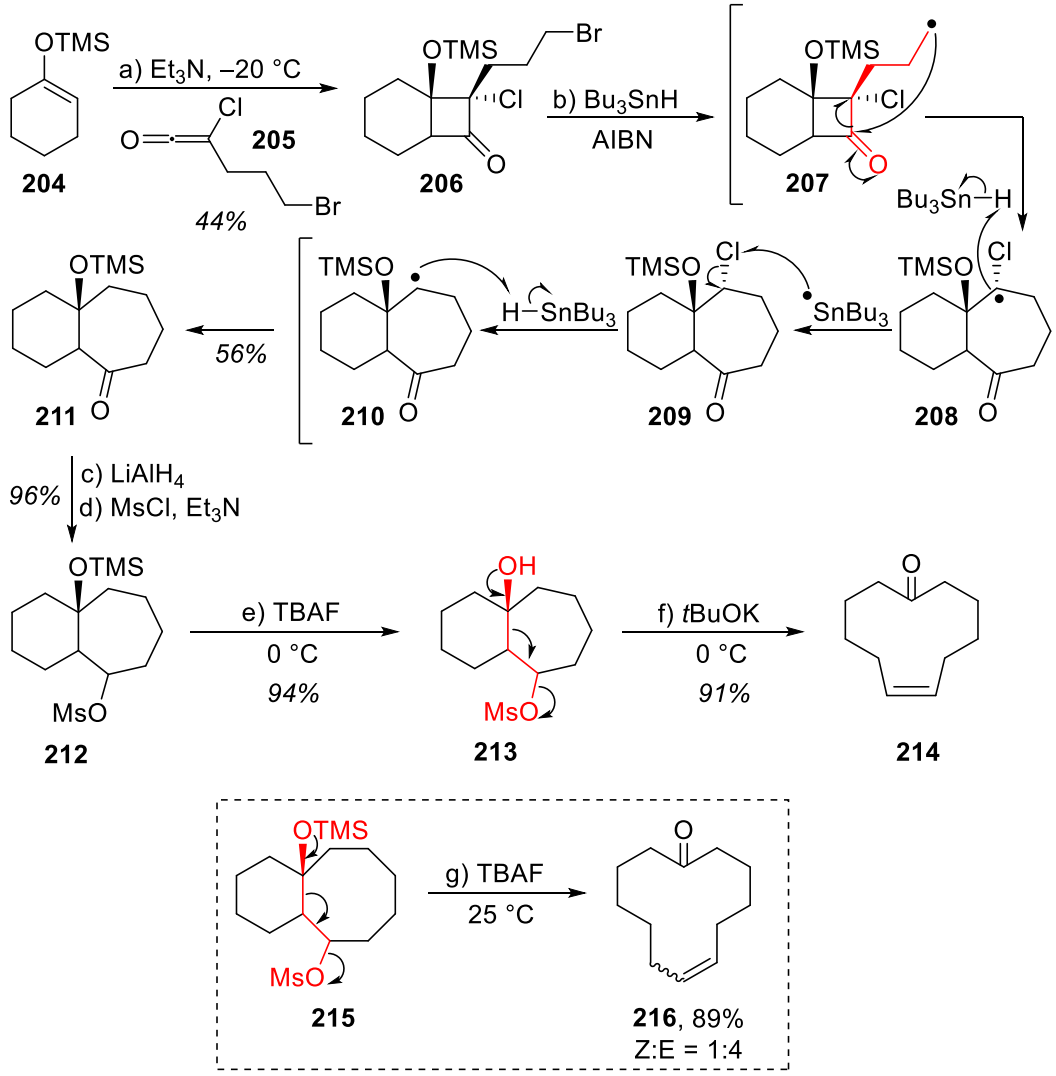
Scheme 1.28: Synthesis of macrocyclic amides via sequential aza-claisen rearrangements by Suh and co-workers.

1.2.5.5.2 Elimination Reactions

These powerful reactions can be used to deliver many different ring sizes, and often benefit from being irreversible reactions. Elimination reactions can be designed to undergo fragmentation only at a specific point within a reaction sequence, when the leaving group is revealed in the required position.

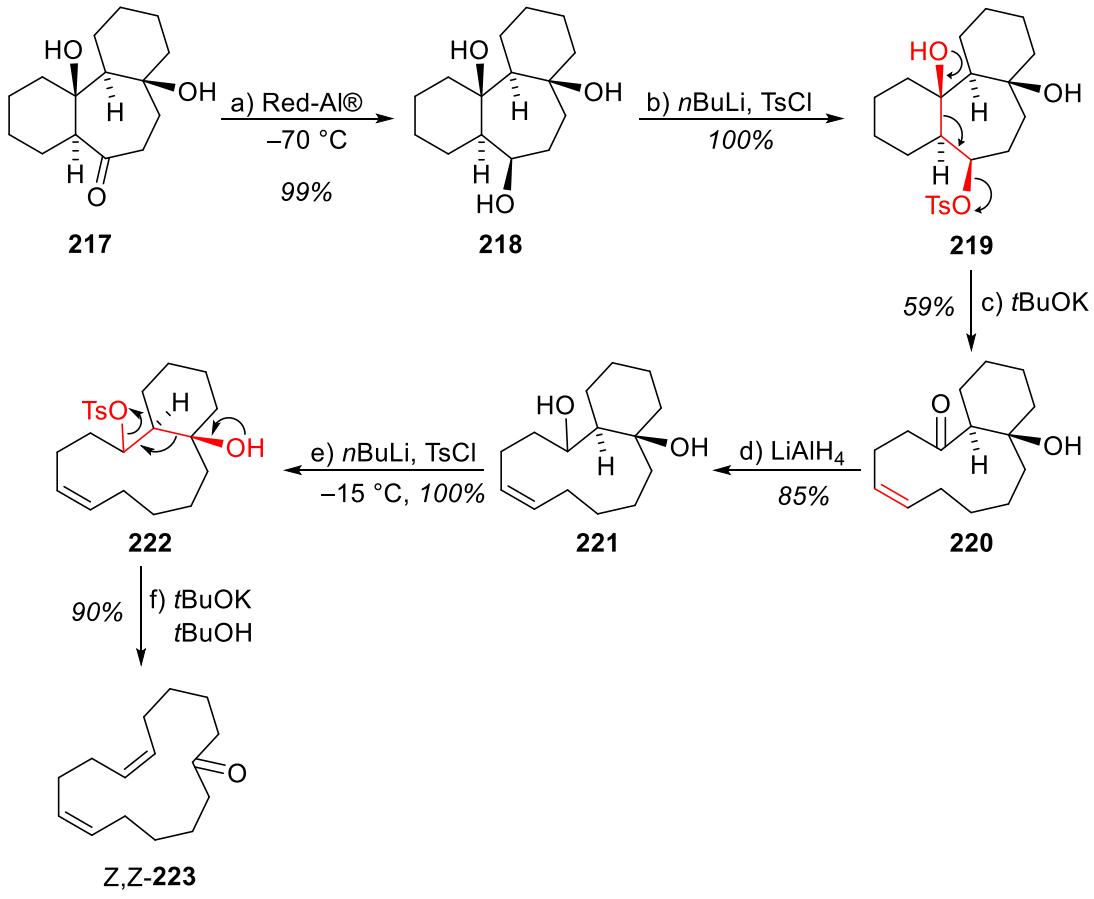
Dowd and Zhang[102] utilised the advantages of a radical expansion/Grob fragmentation sequence in the synthesis of macrocyclic and medium-sized ring ketones. Starting from silyl enol ether **204**, a [2+2]-cycloaddition with ketene **205** was performed generating highly functionalised cyclobutanone **206**. Varying cryogenic temperatures were tested, achieving excellent

diastereoselectivity when −78 °C was utilised, however a significant decrease in the yield was obtained. Classical formation of primary alkyl radical **207** using AIBN and Bu_3SnH was used, promoting a cascade ring expansion/de-chlorination producing fused bicycle **211**. Multiple equivalents of tributyltin hydride were utilised to achieve this transformation in a modest yield, with no mention of whether the chlorine was intentionally removed or alternatively incorporated to improve the preceding cycloaddition. Reduction of the ketone and mesylation of the resulting alcohol formed bicycle **212**, which was then set to undergo Grob fragmentation. However, upon addition of TBAF and cleavage of silyl protecting group, Grob fragmentation did not spontaneously occur and formed alcohol **213**. Only upon addition of strong hindered base, forming the more reactive alkoxide, did fragmentation occur forming 11-membered ketone **214** in excellent yield and *Z*-olefin geometry. Larger ring sizes (e.g. ketone **216)** were produced with an appearance of *E*-olefin geometry, as the ring size can accommodate this motif without significant increase in ring strain.



Scheme 1.29: Radical ring expansion/Grob fragmentation protocol employed by Dowd and Zhang.

Thommen and co-workers[103] utilised a strategy of employing two sequential Grob fragmentations to produce macrocyclic ketone **223**. Starting from tricyclic ketone **217**, stereoselective reduction with Red-Al® generated triol **218**. Other more traditional reducing agents were tested (such as $LiAlH_4$ and $NaBH_4$), with poorer selectivity or yields obtained. The newly formed secondary alcohol was transformed into tosylate **219** using butyllithium/tosyl chloride trap. When *t*-BuOK was used, a mixture of isomers was formed with either of the tertiary alcohols undergoing the functional group conversion, despite the increased steric interaction. The first Grob fragmentation was performed in modest yield, and was followed by a spontaneous olefin migration, presumably due to minimise transannular interactions, to form ketone **220**. Reduction of the ketone with lithium aluminium hydride afforded alcohol **221** as a mixture of diastereomers, which was quickly subjected to slightly modified tosylation conditions generating **222**. The second Grob fragmentation occurred with excellent yield and complete control of olefin geometry, forming macrocyclic ketone **223**.

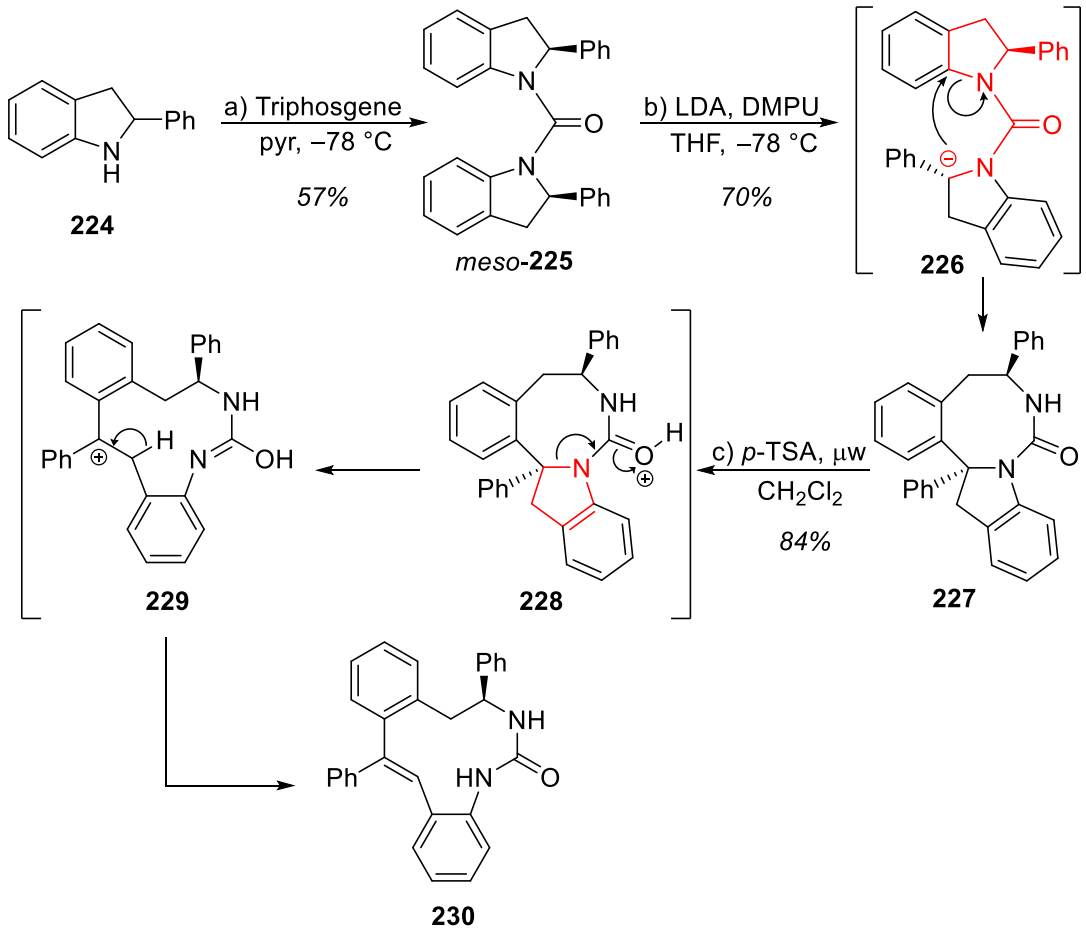


217 218 219 220 221 222 Z,Z-**223**

Scheme 1.30: Synthesis of macrocyclic ketones via sequential Grob fragmentation by Thommen and co-workers.

Clayden and co-workers[104] developed an insertion/fragmentation method to access a medium-sized ringed urea, with the insertion reaction described previously in section 1.2.5.4, whereby a

lithium base mediated insertion reaction is used to form 8-membered urea **227**. Then, simply using *p*-TSA and microwave heating, acidic fragmentation occurs from oxonium **228** to stabilised benzylic carbenium **229**. This fragmentation occurs as the resulting carbenium intermediate is thermodynamically more stable with respect to ring size and cation stability. Elimination then occurs to form enlarged ring product **230**, thus ending the sequence.



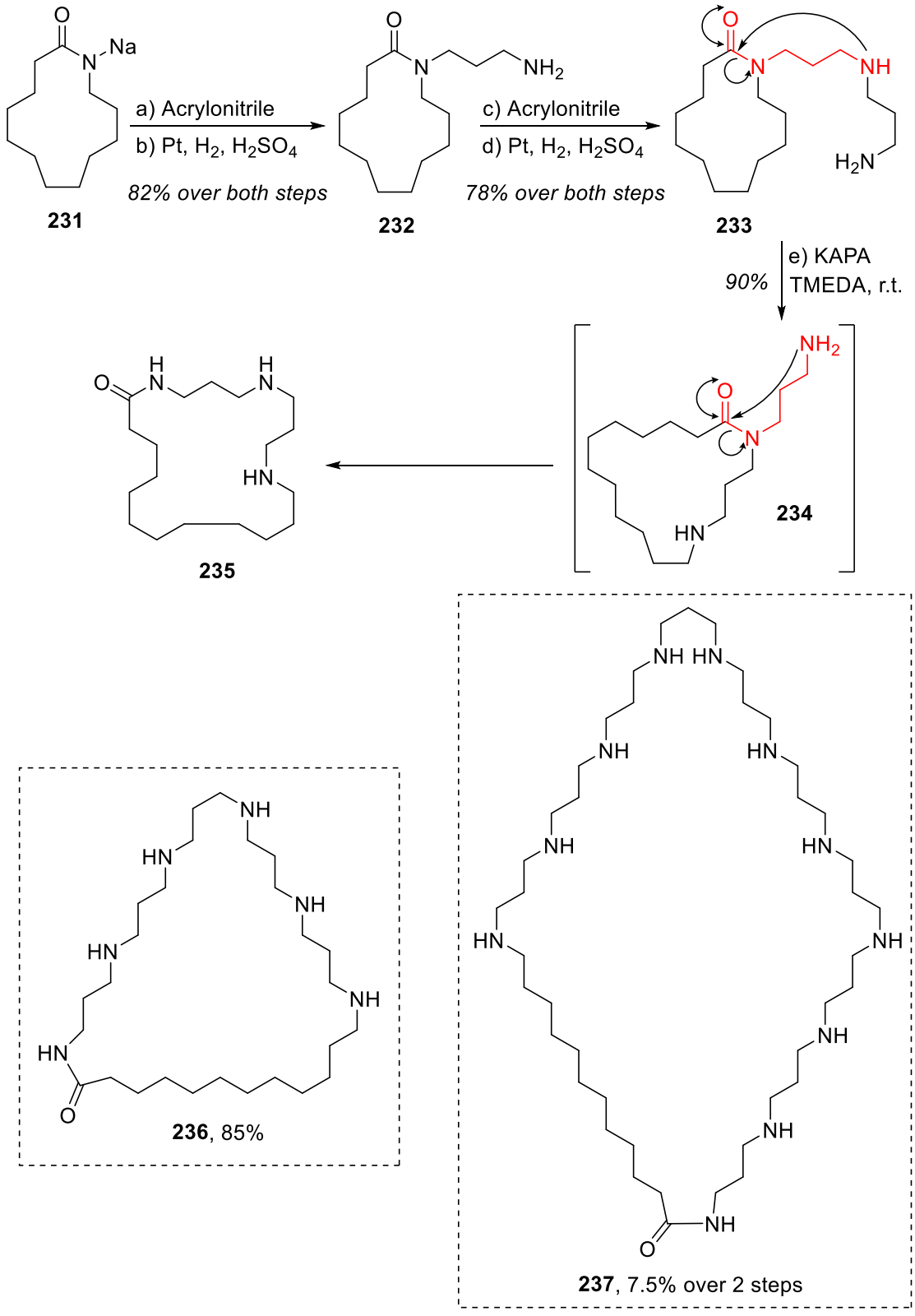
Scheme 1.31: Successive insertion/fragmentation in the synthesis of medium-sized cyclic ureas by Clayden and co-workers.

1.2.5.5.3 Insertion Reactions

Similar to elimination reactions, this sub-division of ring expansion has a very broad definition and therefore many transformations can be included into this classification. It is common that during a sequence with multiple ring expansions, that one step will include the addition of two compounds and thus is an insertion reaction. This is the area with the largest number of examples where multiple ring expansions have been completed, with publications dating back to 1970.[105] Despite the longevity of this reaction class, transformations remain fairly simple with most reports describing lactamisation/lactonisations until the recent resurgence in the area.

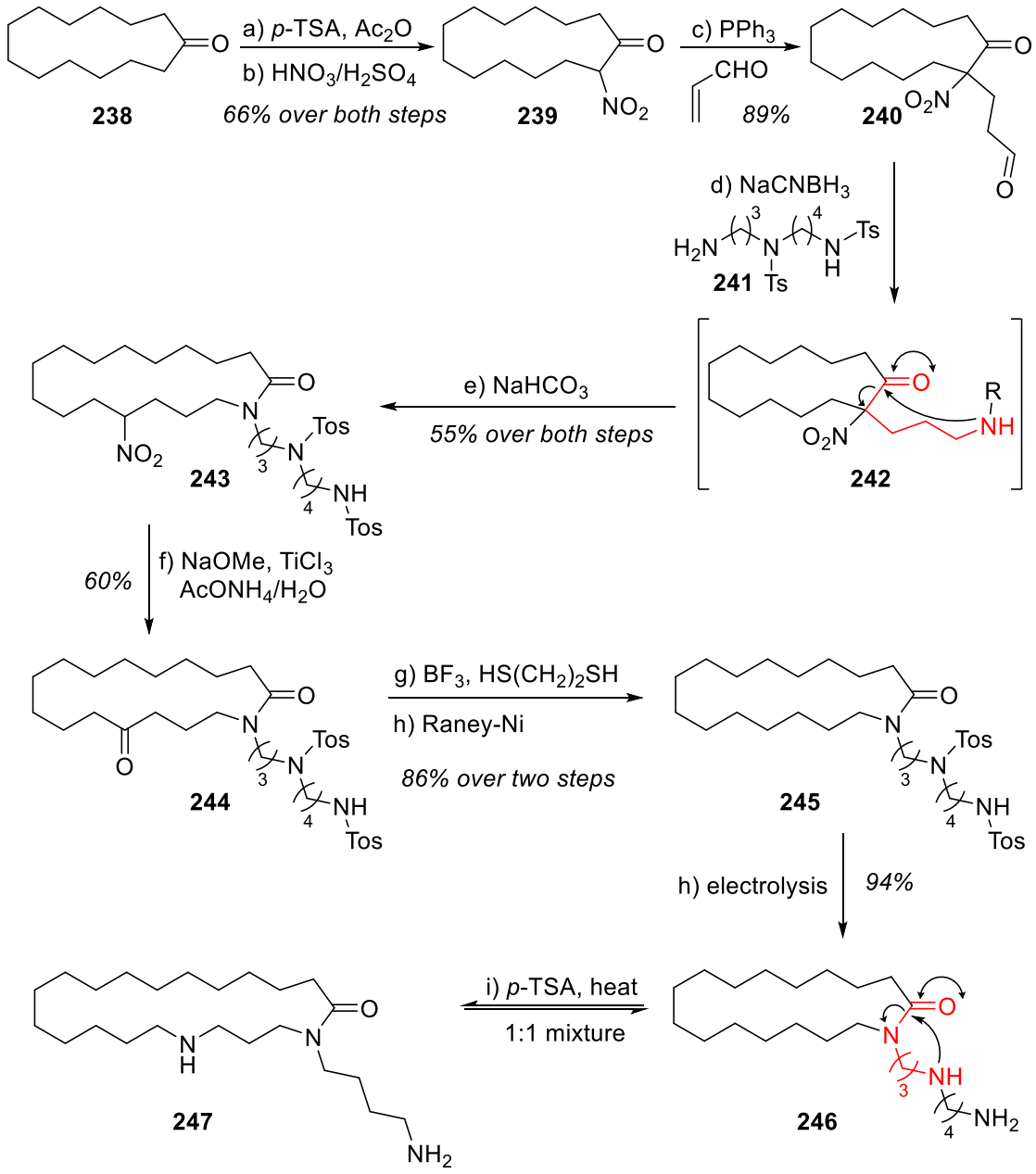
Hesse (one of the most important contributors within the topic of ring expansion) and co-workers[106–109] established a series of transamidation reactions coined as 'zip reactions', which

enabled many different polyamine macrocycles to be accessed in a one-pot cascade procedure. Numerous communications were published from Hesse's group, in both developing the methodology and in natural product synthesis.[110] One early example from this body of work highlights the efficiency of these 'zip reactions' and the synthetic ease in making the starting materials from commercially available building blocks. Deprotonated lactam **231** was alkylated with acrylonitrile and the resulting olefin hydrogenated, without purification, to produce amine **232**. The same reaction conditions were repeated to build diamine **233** in a similarly high yield. Transamidation was accomplished under strong basic conditions (using KAPA = potassium 3-aminopropylamide), and was proposed to proceed through ring enlarged amide **234** (proceeding through 6-membered intermediate) instead of direct transamidation (proceeding through 10-membered intermediate) with the primary amine. This was further supported by the synthesis of 17-membered lactam **234** and subjecting it to the same ring expansion conditions. This resulted in the same 21-membered macrocyclic product **235**, in a similar yield that was obtained for the cascade double-ring expansion. This chemistry was not limited to two-consecutive ring expansions, and was shown to create many large macrocycles in a single step, often in higher yields than the discrete cyclisation of a linear precursor. This is exemplified by the impressive construction of 33- and 54-membered macrocyclic polyamines (**236** and **237** respectively) shown in scheme 1.32.



Scheme 1.32: Typical 'zip reaction' forming polyamine macrocyclic lactams via cascade transamidation reactions by Hesse and co-workers.

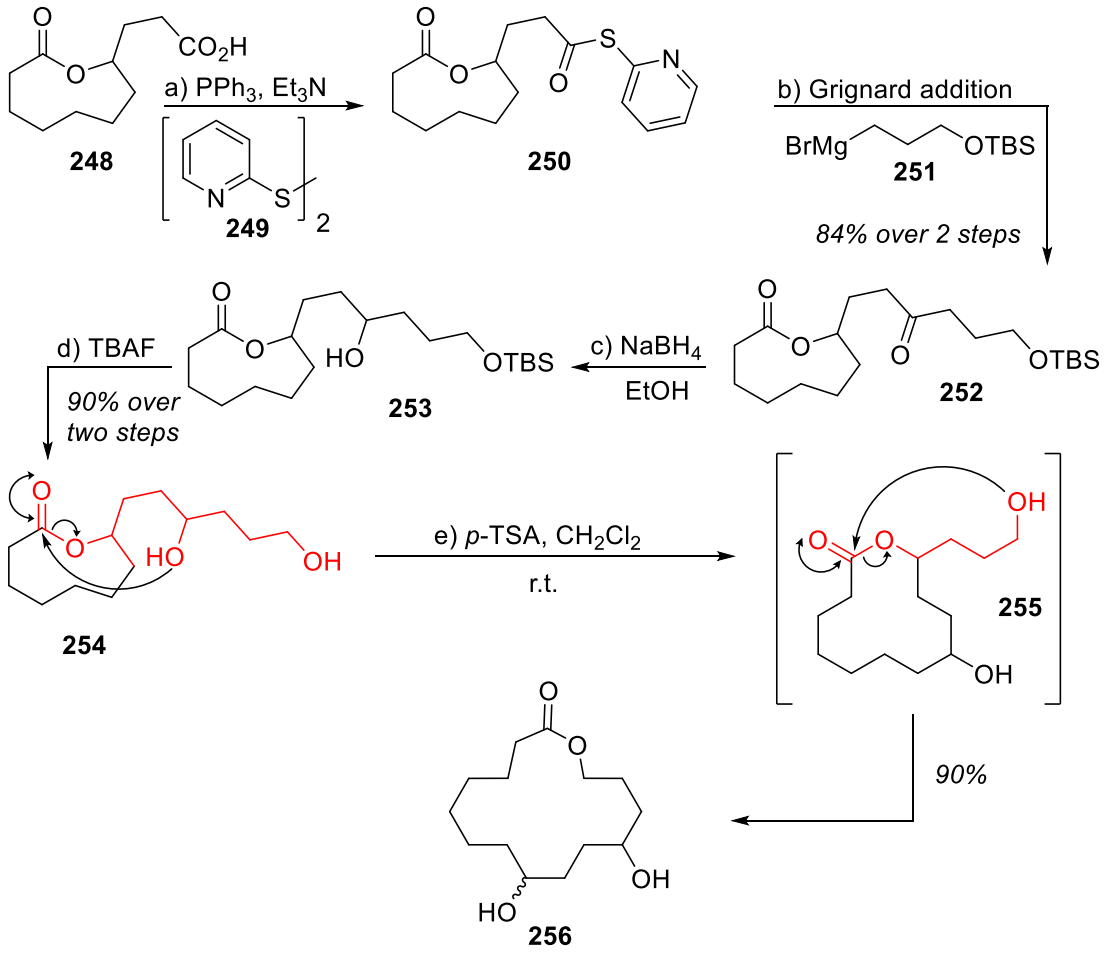
Another example of the 'zip reaction' which proceeds under acidic conditions rather than the strongly basic conditions already established, features in the synthesis of desoxo-indandenine (which is part of the spermidine family of alkaloids).[110] Starting from ketone **238**, α-nitration was accomplished via initial formation of an enol acetate (not shown), to generate ketone **239**. Conjugate addition of α-nitro ketone **239** in acrylaldehyde was performed in excellent yield, in the presence of PPh_3, forming aldehyde **240**. Reductive amination was then performed with the weak reducing agent sodium cyanoborohydride and triamine **241**, forming ketone **242**. An *in-situ* ring expansion insertion reaction was then observed, with weakly basic conditions being used to improve yield of amide **243**, resulting in isolation of the amide in 55% yield. Hydrolysis and reductive Nef reaction were performed to remove the nitro group, via ketone **244**, followed by electrolysis of the tosyl groups forming diamine **246** in excellent yield. Treatment of the newly formed diamine with *p*-TSA, under reflux, formed a 1:1 equilibrium mixture of ring enlarged amide **247** and diamine starting material **246**. This highlights the importance of there being a strong thermodynamic driving force to promote ring expansion, otherwise equilibrium mixtures can be obtained. The acyl transfer reaction between diamine **246** and ring expanded product **247** has no overall change in functional groups, and both macrocyclic ringed systems should have very little ring strain and therefore both compounds should be very similar in energy, resulting in the observed equilibrium. In this case, once cooled and neutralised, the two compounds were separable and a modest yield of the 21-membered macrocycle was achieved, however this could not be generalised for all insertion reactions.



Scheme 1.33: Acidic 'zip reaction' of 21-membered macrocycle towards the synthesis of desoxo-indandenine by Hesse and co-workers.

Although they have less precedent than transamidation reactions, transesterifications reactions can be used sequentially towards the synthesis of macrocycles. This might be explained by the relative scarcity of polylactonic macrocycles found in Nature, compared to commonly found polyamide (peptidyl) macrocycles. Nevertheless, Corey and Nicolaou[80] reported the use of sequential reversible transesterification reactions in the synthesis of macrocyclic lactone **256**, with the thermodynamic driving force arising from the release of ring strain. Thus, acid **248** was coupled with pyridyl sulfide **249** to form thioester **250**, followed by Grignard addition of aliphatic fragment **251**, forming ketone **252** in excellent yield over the telescoped steps. Sodium borohydride reduction of the newly formed ketone, followed by silyl ether deprotection with

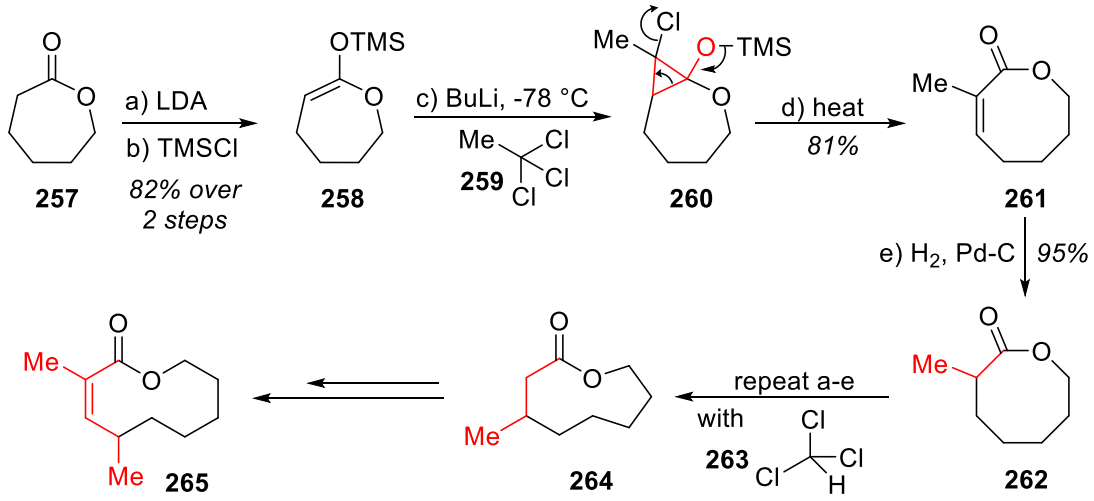
TBAF generated diol **254**. Despite the potential release of ring strain, transesterification did not take place spontaneously and required stoichiometric *p*-TSA to promote the double insertion ring expansion (through 13-membered lactone **255**) to form 15-membered diol **256**.



Scheme 1.34: Synthesis of macrocyclic lactone using sequential translactonisation reactions by Corey and Nicoloau.

Seyden-Penne, Rousseau and Fouque[111] have developed an iterative process to make ring enlarged lactones from commercially available smaller lactones. This work represents one of the first reports which is aimed at developing a multiple ring expansion route towards the synthesis of medium-sized rings and macrocycles. Hence, 7-membered lactone **257**, was converted into labile trimethylsilyl enol ether **258** using an LDA/TMSCl protocol. Preformed carbenoid (from trichloroethane **259** and butyllithium) was engaged in cyclopropanation with the silyl enol ether **258** to form fused bicyclic acetal **260**. Upon heating, de-silylation occurred, instigating carbonyl formation and ring expansion. Release of ring strain and elimination of chloride as a stable leaving group act as both enthalpic and entropic driving forces, for the ring expansion reaction. α,β-Unsaturated ester **261** was formed in 81% yield over the telescoped two steps, which was followed by hydrogenation to form the ring enlarged lactone **262**. The 5-step procedure can be iterated, to produce further ring enlarged lactones. This was demonstrated by two further ring

expansion iterations, which employed two different carbenoids, to form 9- and 10-membered medium-sized rings, **264** and **265** respectively.

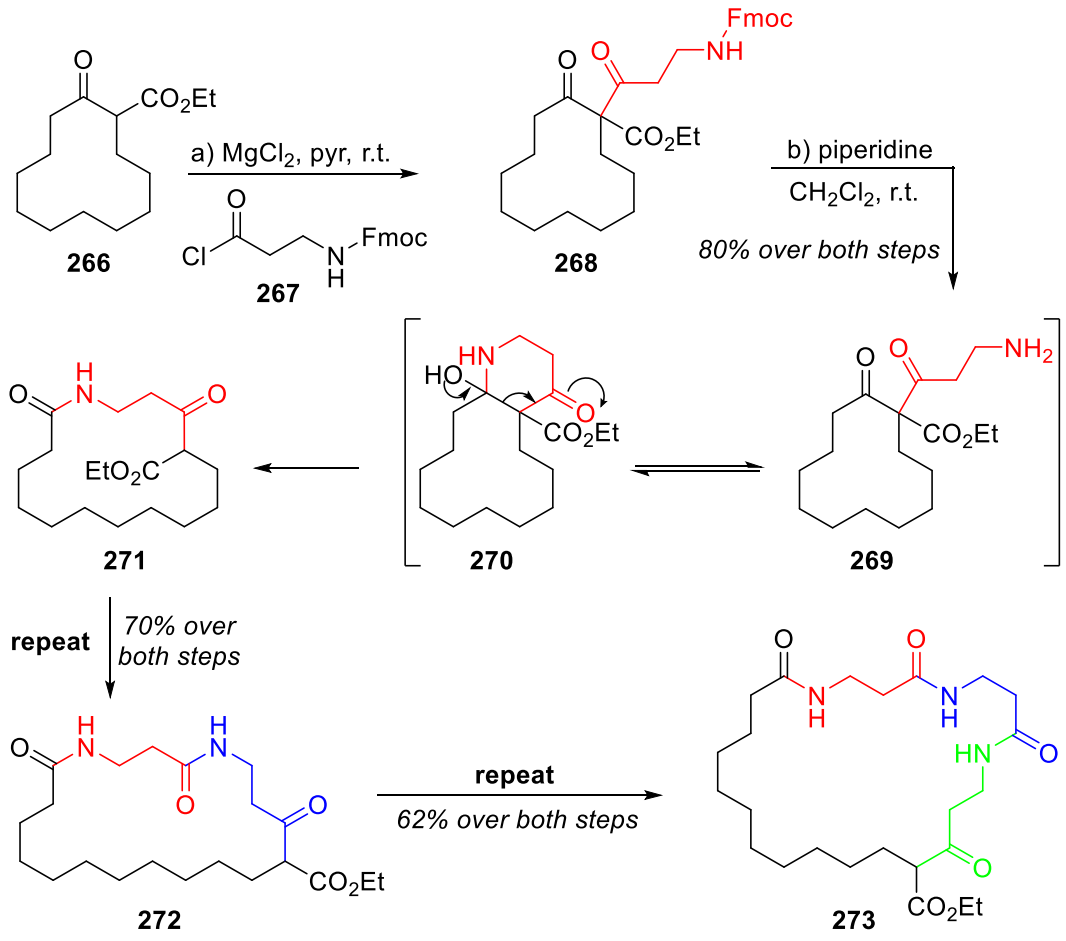


Scheme 1.35: Iterative ring expansion of lactones via cyclopropanation/expansion sequence by Seyden-Penne and co-workers.

Prior to my arrival, the Unsworth group reported a proof-of-concept idea that utilises commercially available building blocks to construct macrocycles in a programmable and predictable fashion.[112] This was based on the Successive Ring Expansion (SuRE) of β-ketoesters, using amino/hydroxy acid fragments to undergo a 3- or 4-atom insertion. The elegant two step procedure was telescoped, with no requirement to purify and isolate the intermediates and with no further functional group manipulation or modification required to complete the next ring enlargement iteration. Each step was synthetically facile and could be completed without cryogenic temperature control, inert atmosphere, elevated temperature/reflux conditions, Schlenk tubes or precious metal catalysts. Therefore, a wide variety of starting materials and linear fragments could be introduced and tolerated, with enantiomerically enriched macrocycles also being accessed.

A representative example of this chemistry can be seen in scheme 1.36, where a triple ring expansion sequence was performed. Starting from 12-membered β-ketoester **266**, which was itself made via a base mediated α-esterification of the 12-membered ketone, *C*-acylation with amino acid chloride **267** was achieved in excellent yield. The use of magnesium chloride was imperative in coordinating the two carbonyls present in the starting material to inhibit unproductive competing *O*-acylation. The tri-carbonyl species **268** was then subjected to basic conditions, cleaving the carbamate protecting group, forming primary amine **269** (although it was never previously observed). It was proposed that spontaneous cyclisation of the amine formed fused bi-cyclic species **270**, which could then undergo subsequent ring expansion to β-ketoester **271**. Although all three species could exist in equilibria, only the desired ring expanded

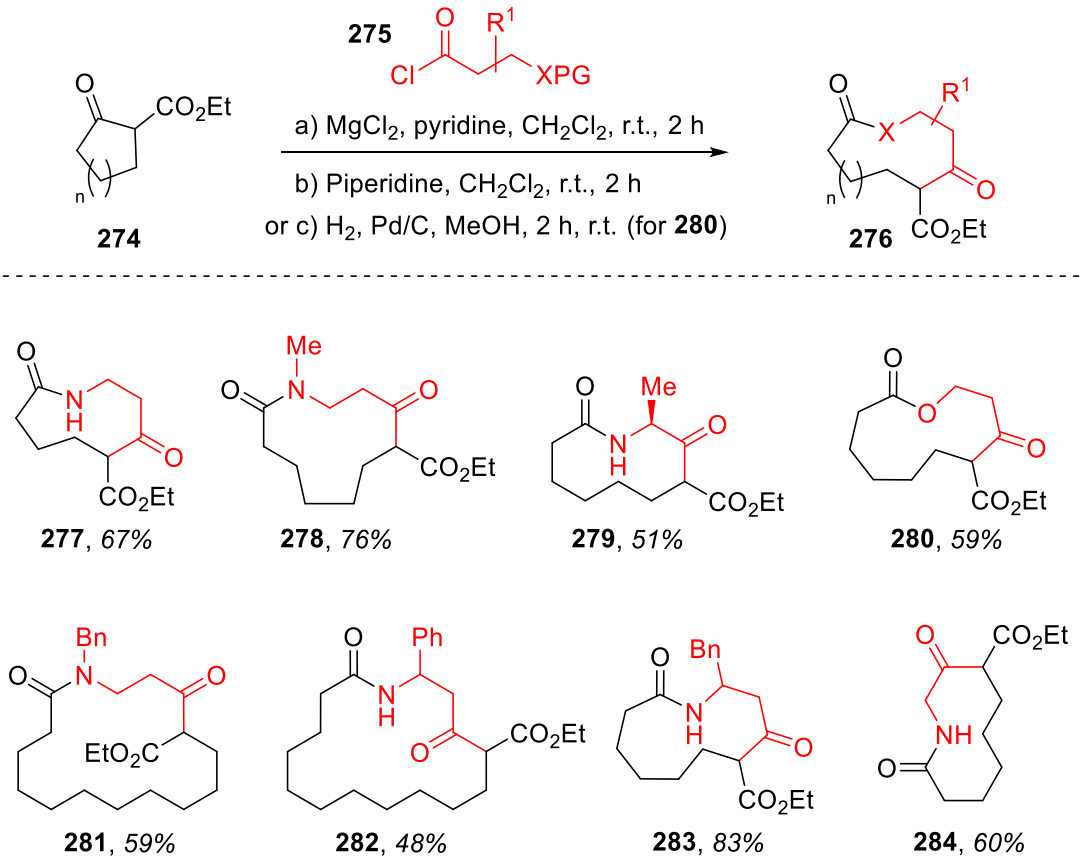
product was observed and obtained in excellent isolated yield. The thermodynamic driving force for the reaction originates from the formation of a strong amide bond and conjugated β-ketoester. The design of the reaction results in the regeneration of the key β-ketoester motif after each ring expansion iteration, and therefore in theory can be repeated indefinitely to generate macrocycles of any size. To prove this concept, the 16-membered ring enlarged β-ketoester **271**, was subjected to the same acylation with amino acid chloride/ring expansion procedure, forming 20-membered macrocycle **272** in 70% yield over both steps. This was repeated once again, to form 24-membered macrocycle tri-amide **273** from 20-membered **272** in good yield. Importantly, all of these reactions do not require high dilution (each was performed at 0.1 M) and therefore are amenable to large scale synthesis, with **266** to **271** performed on 20 mmol scale (approximately 5 g) with no considerable drop in yield.



Scheme 1.36: An example of Successive Ring Expansion (SuRE) of β-ketoesters to form macrocyclic products by Unsworth and co-workers.

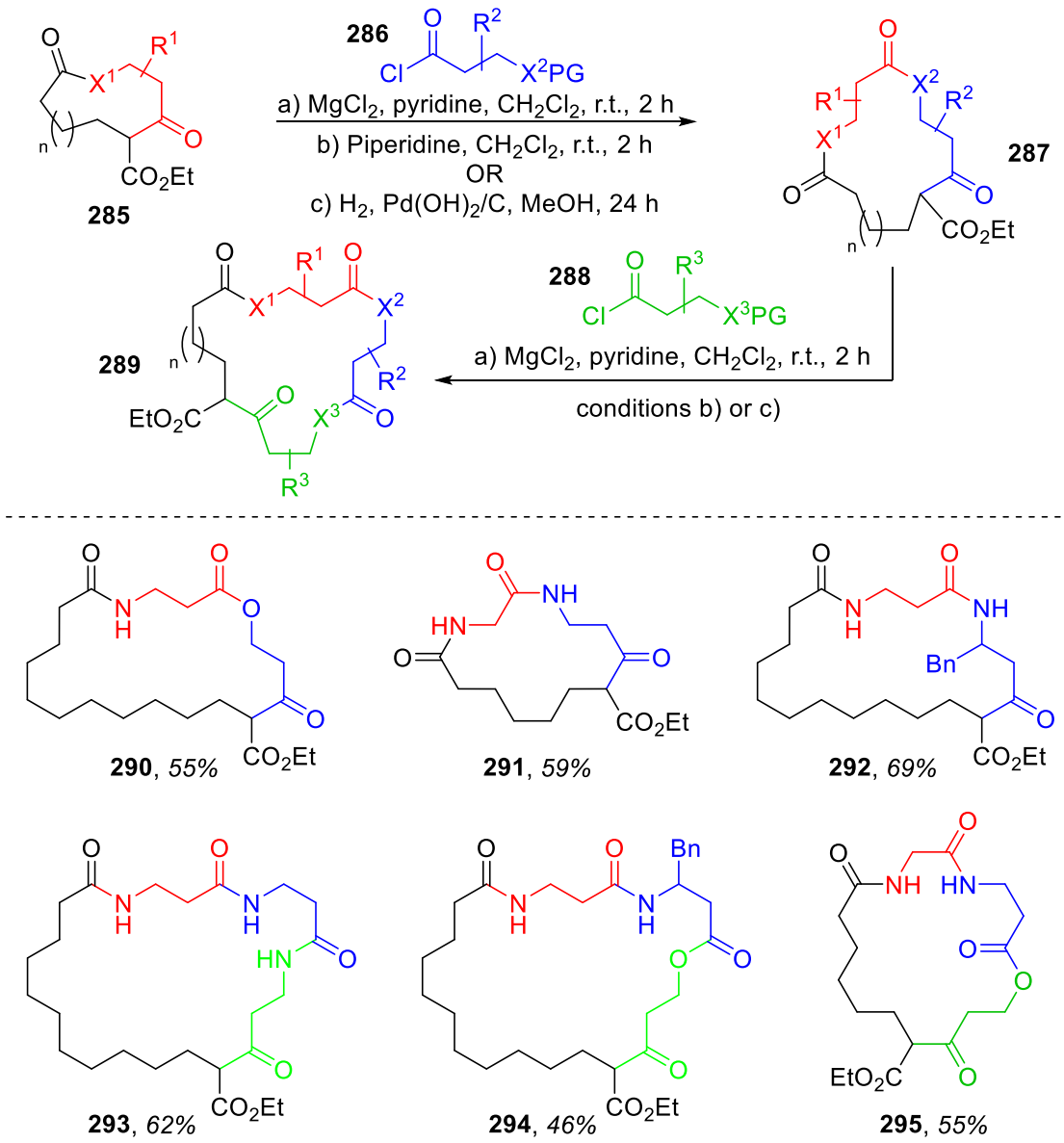
Having established the concept, attention turned towards testing the range of ring sizes that could be accessed and the linear fragments that could be inserted, and it was found that this methodology works well on a range of systems, and despite the well-known difficulties of medium-sized ring synthesis, ring sizes of 9–16 members could be made in generally good yield.

N-Methylated linear fragments were tolerated well, forming 11-membered β-ketoester **278** in high yield, which should encourage the use of this methodology in the synthesis of *N*-methylated peptides, that can benefit from the so-called "magic methyl" effect.[113] However, increasing the steric bulk of the *N*-substituent was noticed to lower the yield of the ring expanded product, as can be seen with benzylated-variant **281**, despite none of the other equilibrium species being observed. Substituents can be introduced onto the backbone of linear fragment, with varying yields obtained, seen in **282** and **283**. In addition to 4-atom insertion, α-amino acid derived linear fragments can also be introduced using this method in comparable yields. Alanine was shown to undergo insertion to make 10-membered ring **279**, with a significant $[\alpha]_D$ value showing that racemisation has not occurred. Using a similar strategy, an ester was produced (**280**) when benzyl protected hydroxy acid was utilised. Hydrogenolysis was performed to remove the benzyl group and induce spontaneous ring expansion. Although the exchange of one heteroatom for another may seem trivial, this example is important in providing access to macrocyclic lactones and may be one of the first examples of C-O bond forming insertion reaction that does not proceed via transesterification. Both C-N and C-O bond forming methodologies operate via similar key intermediates, and were shown to be compatible with each other (see proceeding section), therefore mixed lactone/lactam macrocyclic systems could be produced with this work.



Scheme 1.37: Substrate scope for ring size and linear fragment within SuRE methodology.

A range of macrocycles were also synthesised in which two and three successive ring expansions were completed (seen in scheme 1.38). A series of ring sizes were made with different linear fragments inserted, including both α- and β-amino acids as well as examples with hydroxy acids. Yields for these examples dropped slightly, typically achieving 40–70% using the standard, unoptimised conditions. The loss in yield is accounted for during the acylation step, with some cyclic β-ketoester starting materials acylating slowly/inefficiently. It was proposed that the starting materials exist as less reactive conformers, hence slower acylation is observed. However, the starting material was recoverable, and therefore if desired could be re-subjected to the same reaction conditions to improve the corresponding yield.



Scheme 1.38: Successive ring expansion methodology forming a diverse array of macrocycles.

1.3 Project Outline

First, our aim was to extend the β-ketoester methodology by incorporating more α-amino acids into normal and medium-sized rings, which would produce more functionalised examples. The products molecular properties would then be analysed with respect to their medicinal interest, and manipulation of *in-vivo* labile functional groups would be performed. It was planned that hydroxy acid incorporation would be examined, making this new methodology compatible with varying ring size and linear fragment size.

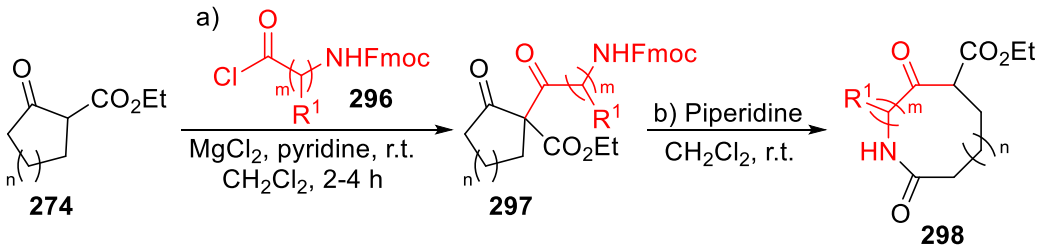
Second, we planned to study the viability of a simple lactam motif, as the regenerating functionality in the successive ring expansion reactions. Optimisation of both acylation and deprotection steps would be completed, to produce a small library of peptidiomimetic macrocycles and medium-sized rings. Significant interest was placed on making these peptide mimetics medicinally interesting, with the intention to incorporate a wider range of α-amino acids than has been achieved previously.

Finally, an examination of whether hydroxy acids were compatible with the lactam motif, which would produce a range of mixed lactam/lactone systems, was planned. Some natural products (i.e. cyclodepsipeptides) were identified which contain both ester and amide functionalities, and therefore we envisaged a direct route to their synthesis, *via* this methodology.

Chapter Two: Extension of β-Ketoester Methodology

2.1 Previous work on β-ketoester methodology

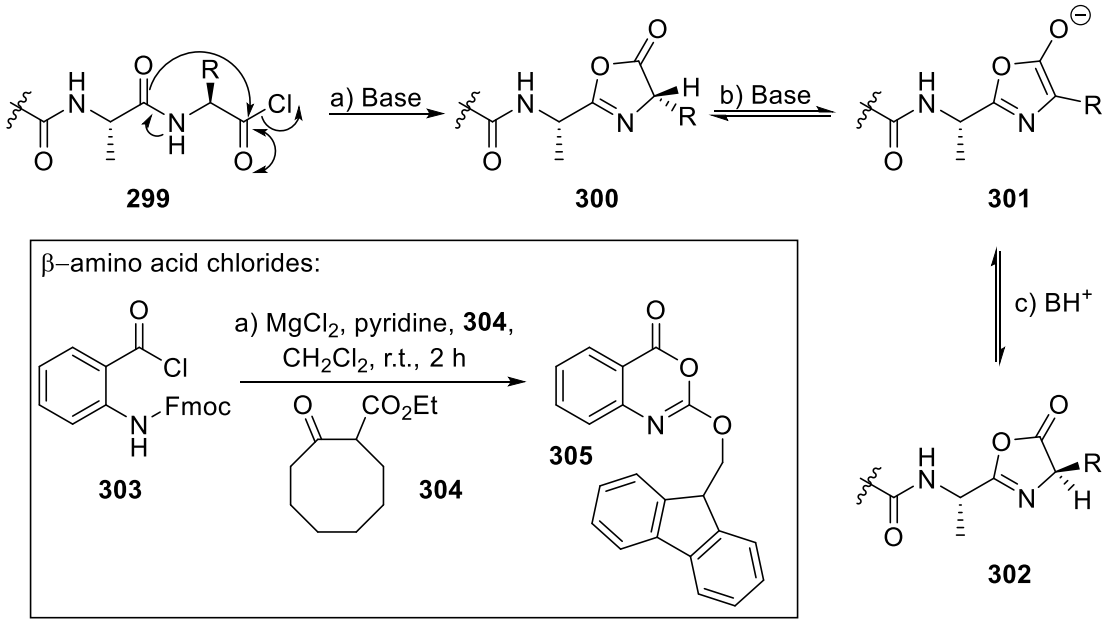
Upon arriving in York, I joined a project close to the end of completion, with the target of synthesising medicinally interesting medium-sized ringed lactams with the β-ketoester motif (scheme 2.1). From previous studies in the group, it was found that β-amino acids (**296**, m = 2) worked well with many different ring sizes and substitution patterns. However, when the natural α-amino acids were utilised (**296**, m = 1), the reactions often produced poorer yields or failed to acylate at all. My first task was to address the gaps in the substrate scope with respect to the amino acid partner.



Scheme 2.1: General scheme for β-ketoester successive ring expansion with amino acid chlorides.

2.2 Oxazolone/Oxazinone Formation

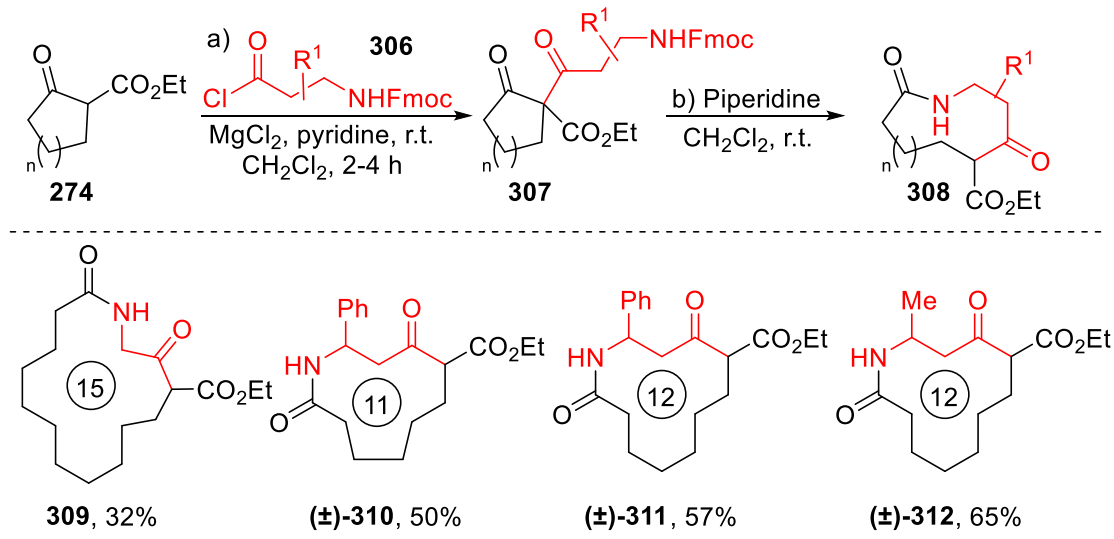
Within peptide chemistry, synthesising the sequence of amino acids often proceeds through a two-step addition/deprotection sequence (commonly on a solid support using SPPS – see section 1.2.4). One such strategy activates the *C*-terminus of the nascent peptide, which is then reacted with an amino acid derivative in an amidation reaction. When an acid chloride **299** is utilised, base-mediated intramolecular cyclisation can occur and form an undesired oxazolone intermediate **300**.[114] This is a major disadvantage, as it is a non-productive pathway and can lead to racemisation (**300** ⟶ **302**) of the peptide chain. We believed that this pathway may have been occurring with the carbamate protected α-amino acid chlorides **296**, as the same pathway was shown to exist in *N*-acyl α-amino acid chlorides, and hence leading to unwanted consumption of the acid chloride.[115] Oxazolone **300** was never isolated to prove this, however the corresponding 6-membered heterocycle (oxazinone) **305** was isolated in high yield, demonstrating that this type of process is viable.



Scheme 2.2: Oxazolone formation/racemisation pathway in peptide chemistry and 6-membered lactone isolated.

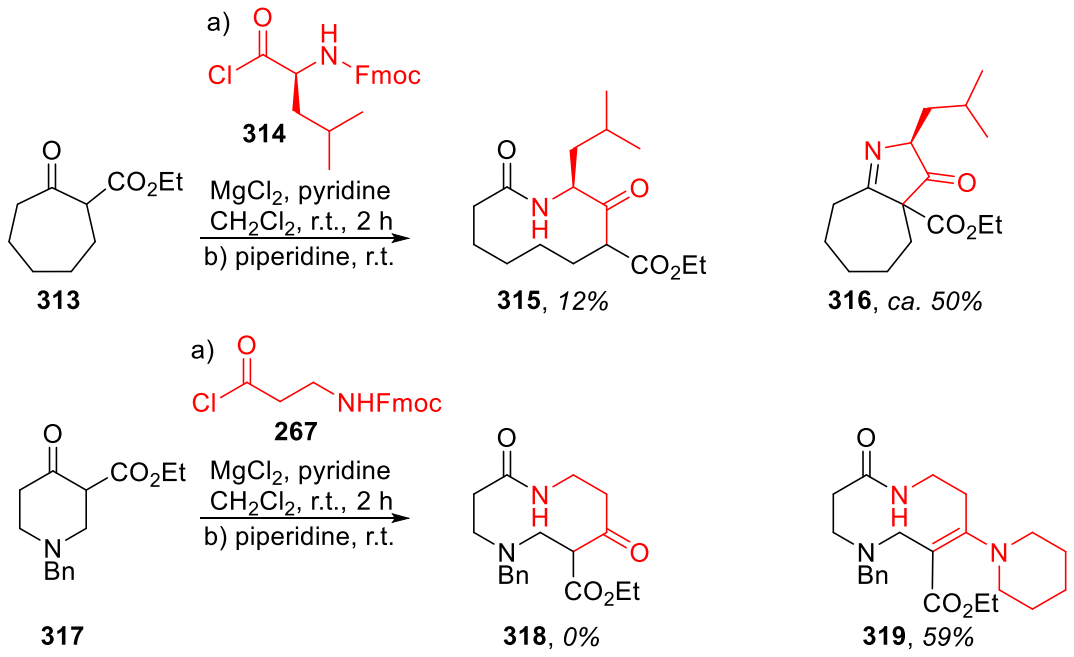
2.3 Ring Expansion of β-Ketoester to form medium-sized rings and macrocycles

In an attempt to combat this problem, three additional equivalents of acid chloride were utilised in ring expansion reactions, where poor acylation of the β-ketoester had been observed. This improvement, led to an additional 4 examples of ring expanded products being formed that were previously unsuccessful. Branched β-amino acid examples **310**–**312** were obtained in modest yields (50–65%). All examples were synthesised using racemic building blocks (with exception to the achiral glycine derivative **309**), however previous work has shown that enantioenriched examples can be produced.



Scheme 2.3: Ring expanded products formed by the insertion of amino acids into cyclic β-ketoesters.

Most of the ring expansion reactions on these cyclic β-ketoesters, proceeded as planned with no observable side-products and only minor/no alterations to the standard conditions. However, two examples differed from the desired reaction pathway, producing two separate side-products. First, 7-membered β-ketoester **313**, was *C*-acylated under the normal reactions conditions with leucine derived amino acid chloride **314** to form tri-carbonyl species (not shown). However, upon piperidine induced cleavage of the Fmoc protecting group (which should spontaneously undergo cyclisation/ring expansion) only small amounts of ring expanded product **315** were isolated. Instead, bi-cyclic imine **316** was isolated and found to be stable towards both acidic and basic hydrolysis. We proposed that the transition state/product must experience significant transannular steric repulsion with the large *iso*-butyl group, increasing the relative energy, therefore rendering this pathway less favourable. Second, 6-membered *N*-benzylpiperidine β-ketoester **317** was *C*-acylated with amino acid chloride **267** forming the corresponding tri-carbonyl species. Again, upon Fmoc cleavage conditions, the desired ring expanded product was not produced. Ring expansion did occur, however a condensation reaction took place between piperidine and the newly formed ketone, to form enamine **319** (this work was completed by Morgan Manning).

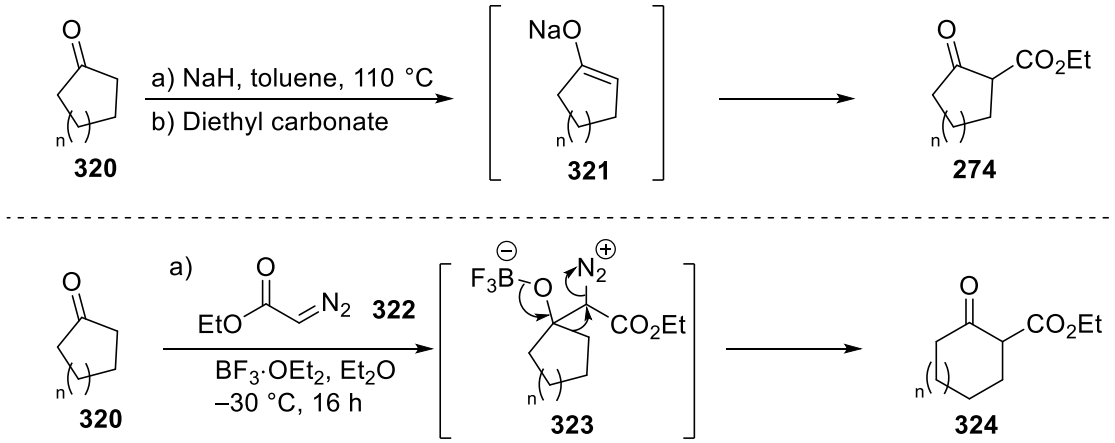


Scheme 2.4: Uncommon examples of side-product formed during ring expansion.

2.3.1 Synthesis of Cyclic β-Ketoester Starting Materials

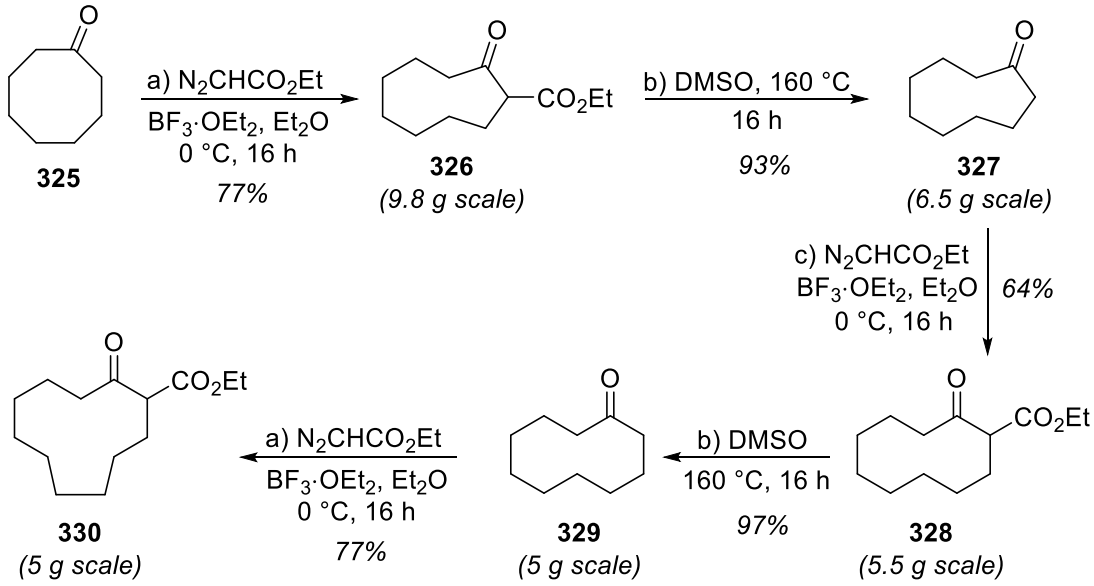
Whilst 5–7-membered cyclic β-ketoester starting materials were easily available from commercial sources, 8-membered cyclic β-ketoesters (and higher) are not, hence a reliable and scalable route to prepare these starting materials was needed. Therefore, starting from the

corresponding ketone **320** two different literature procedures were found to access cyclic β-ketoesters, which could be utilised in successive ring expansion. In one of these methods, deprotonation of a cyclic ketone **320** using sodium hydride formed sodium-enolate **321** and was followed by diethyl carbonate addition, generating the product in typical yields of ≥90% on multigram scale.[112] An alternative homologation approach was also found,[116] which increased the ring size by a single carbon atom and incorporated the ester in one transformation; thus, Lewis acid catalysed addition of ethyl diazoacetate **322** into a cyclic ketone **320**, formed tetrahedral intermediate **323** and through a migration/elimination formed ring-enlarged β-ketoester product **324** (scheme 2.5).



Scheme 2.5: Synthesis of cyclic β-ketoesters via two separate methods.

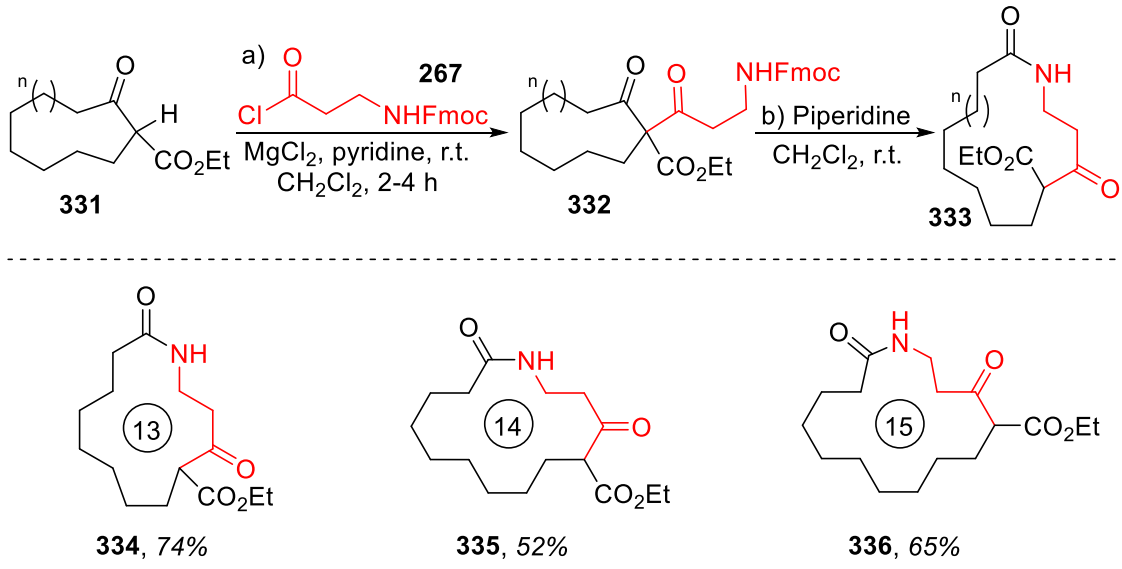
We realised that the medium-sized ring β-ketoesters in which the required cyclic ketones were not commercially available could be synthesised using the ethyl diazoacetate homologation pathway. Starting with cyclooctanone **325**, homologation to 9-membered β-ketoester **326** proceeded in high yield even on multigram scale (up to 9.8 g was made and purified in a single batch). Using reagent grade DMSO (which contains a small amount of water), ester hydrolysis and subsequent decarboxylation was completed in a single pot to form the 9-membered ketone **327** in excellent yield. This two-step procedure was iterated to form the 10-membered ketone (**329** – ketones were also used in Beckmann rearrangements described later in section 3.5) as well as the corresponding β-ketoesters **328** and **330** in good/excellent yield.



Scheme 2.6: Synthesis of medium-sized cyclic β-ketoester starting materials from homologation/hydrolysis pathway.

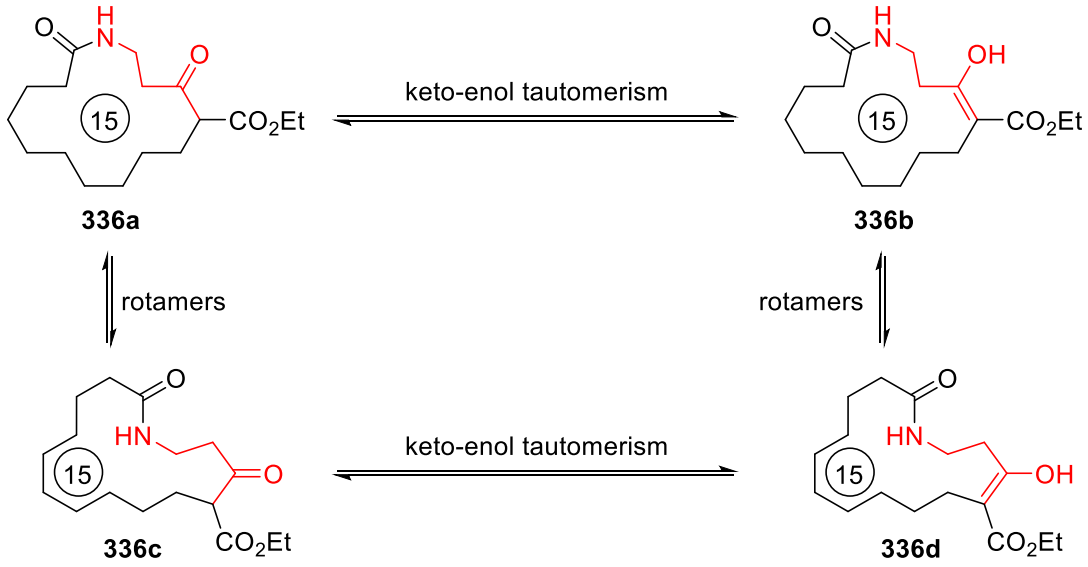
2.3.2 Synthesis of Macrocyclic β-Ketoesters with Medium-Sized Rings

Having gained accessed to the medium-sized ring starting materials, we then wanted to utilise these in ring expansion reactions to produce novel macrocyclic products. Therefore, using standard conditions, *C*-acylation of cyclic β-ketoesters, similar to **331**, formed tri-carbonyl species **332** followed by protecting group cleavage/ring expansion delivering macrocyclic products **333**. Pleasingly, 13- , 14- and 15-membered macrocyclic β-ketoesters were indeed formed **334**–**336** in 52–74% yields with β-amino acid derivative **267**, with no appreciable side-product formation.



Scheme 2.7: Synthesis of macrocyclic ring expanded β-ketoesters from non-commercial medium-sized rings.

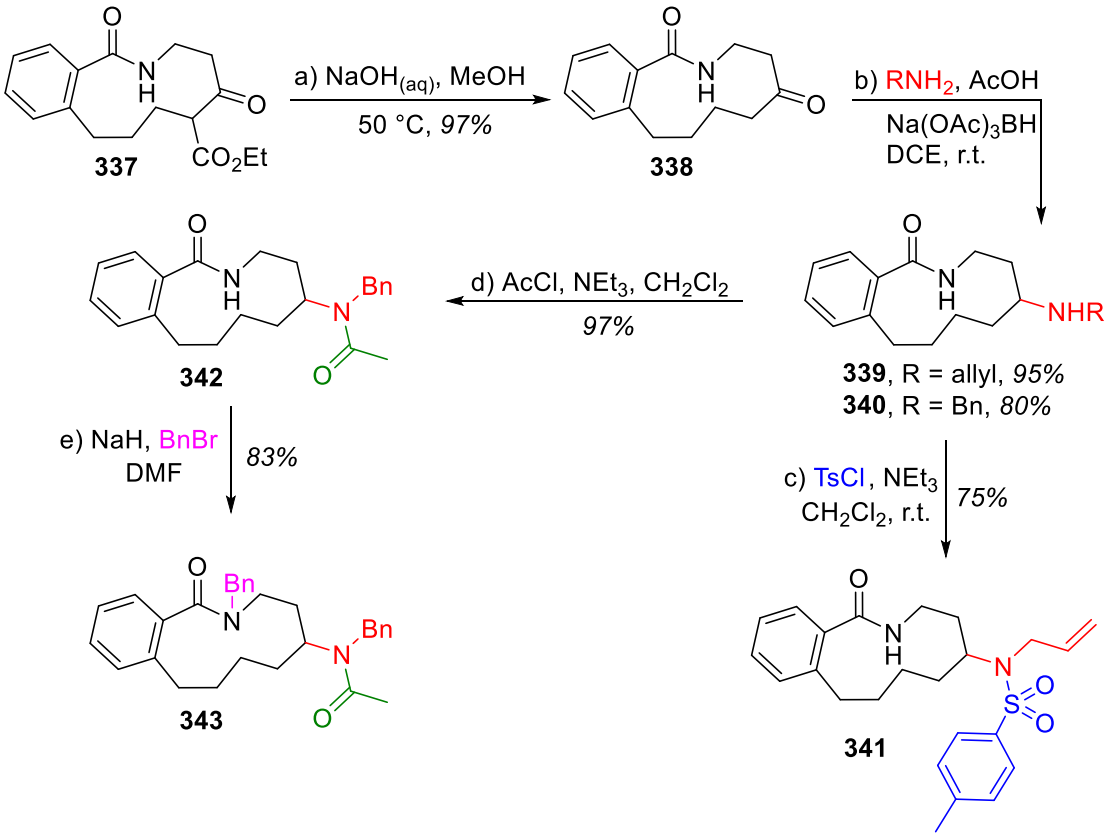
At this point, it is noteworthy to state that while all the ring-expanded products were pure compounds, they commonly existed in $CDCl_3$ as an equilibrating mixture of both keto- and enol tautomers, as well as being rotameric about the amide bond at room temperature. Therefore, up to four isomers (**336a**–**336d**) can be seen in the ^{1}H and ^{13}C NMR spectra for each ring expanded product. The observed mixture of isomers is temperature, solvent and concentration dependant, and thus it is common that only the major constituent is fully characterised with diagnostic resonances in both ^{1}H and ^{13}C NMR spectra highlighting the presence of any of the isomers. Typically, secondary amides did not exhibit rotameric conformations and in the medium-sized rings, but keto-enol tautomerisation was more prominent (presumably to reduce ring strain).



Scheme 2.8: Rotamers and keto/enol tautomers shown for a single ring expanded example.

With a small library of medium-sized rings having been prepared (30 compounds), the physiochemical and spatial properties were analysed using an open-access computational tool called LLAMA.[117] This program judges the 'lead-likeliness' of molecules based on: lipophilicity, functional groups, heavy atoms, the presence of aromatic rings and molecular weight. This is commonly in accordance to Lipinski's rules[118] (which has been previously discussed in section 1.1). LLAMA is also able to predict the three-dimensional spatial properties of molecules using the principal moments of inertia method (PMI).[119] All the ring expanded products contained the metabolically labile β-ketoester moiety and therefore were unlikely to be medicinally applicable in their own right. However, these compounds could be useful within the context of fragment-based drug discovery, in which additional synthetic steps could be completed to afford a suitable lead compound. Therefore, starting from ring expanded product **337**, ester hydrolysis followed

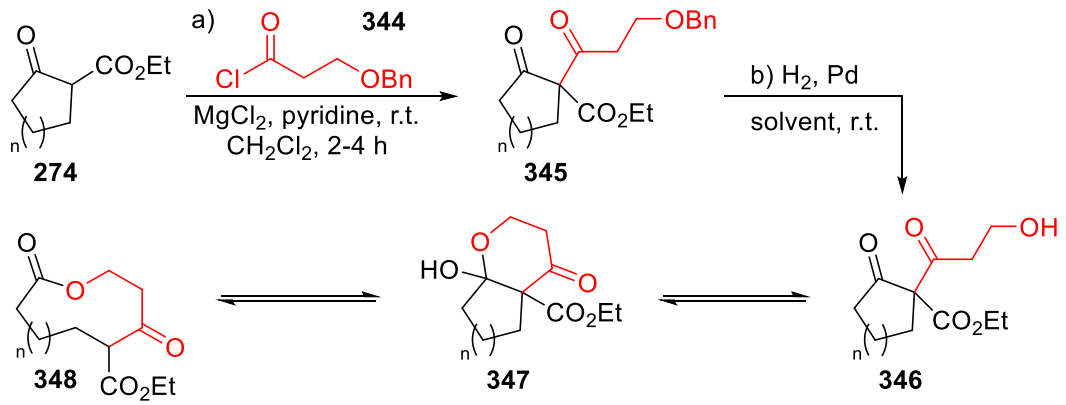
by decarboxylation afforded ketone **338** in excellent yield. The ketone undergoes facile reductive amination to form secondary amines **339** and **340** which were amenable to sulfonylation, acetylation and amide alkylation producing medicinally interesting compounds **341**, **342** and **343** (scheme 2.9, these reactions were completed by Laetitia Baud and Morgan Manning). Therefore, a hydrolysis/decarboxylation procedure was completed virtually on the entire library, and allowing a single transformation from the ketones produced, a virtual library of 402 compounds was generated. Of the virtual library, 200 compounds were found to lie within 'lead-like' space, with favourable molecular properties.



Scheme 2.9: Further synthetic modifications used in virtual library enumerations.

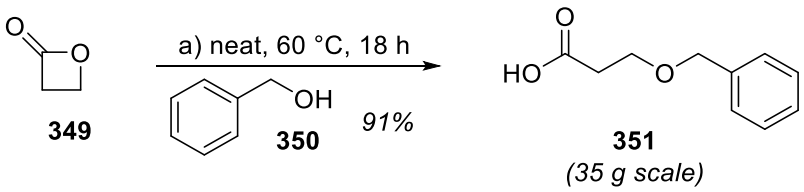
2.3.3 Synthesis of Lactones using Ring Expansion of β-Ketoesters

Next, we turned our attention to the C-O bond forming variant of this ring expansion, which had been previously reported with only two examples. The approach is based on acylation with a benzyl protected hydroxy acid chloride **344**, under otherwise identical acylation conditions to those used for the amino acid reactions, to form a tri-carbonyl species **345**. Under hydrogenolysis conditions, which we predicted could be optimised and improved, cleavage of the benzyl group would occur unveiling the primary alcohol. A systematic study could then probe the effects of ring size upon the position of equilibrium between the three isomeric species **346**, **347** and **348**.



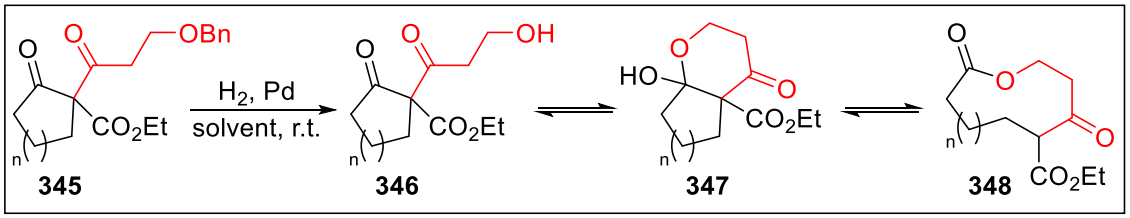
Scheme 2.10: Hydroxy acid methodology, showing three isomers that could be in solution.

To complete this study, a large-scale synthesis of the corresponding hydroxy acid **351** was required. Using literature procedure,[120] β-propiolactone **349** was reacted with benzyl alcohol **350** under neat conditions, affording the desired product in excellent yield directly in a single step.



Scheme 2.11: Synthesis of benzyl protected β-hydroxy acid.

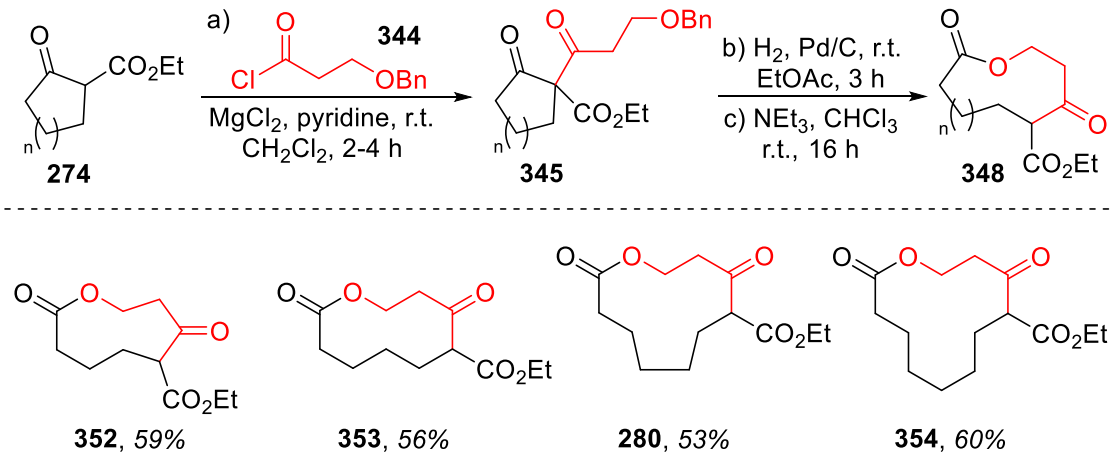
With the desired starting materials in-hand, *C*-acylation was completed to produce tri-carbonyl species **345** with various ring sizes. Table 2.1 shows the results obtained from brief optimisation of the hydrogenolysis conditions. Entry 1 was a repeat of the example reported previously and resulted in an identical yield. However, when these conditions were used on the 5-membered β-ketoester (entry 2), no diagnostic ^{1}H NMR resonances were observed for any of the three isomers. Changing the palladium catalyst (entry 3), had no effect on product formation. This led us to change the solvent, and implement a shorter reaction time to achieve our optimised conditions (entry 5). However, these conditions still led to the formation of all three isomeric forms and it was desirable that only the ring expanded product was produced. Pleasingly, a solvent switch to chloroform and the addition of triethylamine as a base was sufficient to drive the equilibrium to form only ring expanded product **348**. Although this did add a further step, the shorter hydrogenolysis time, higher yields and production of a single product (in the same overall reaction time) was sufficient justification for its incorporation.



Entry	Ring Size	Hydrogenolysis conditions	Yield
1	7 ⟶ 11	$Pd(OH)_2/C$, MeOH, r.t., 16 h	59%
2	5 ⟶ 9	$Pd(OH)_2/C$, MeOH, r.t., 16 h	0%
3	5 ⟶ 9	Pd/C, MeOH, r.t., 16 h	0%
4	5 ⟶ 9	Pd/C, EtOAc, r.t., 16 h	trace
5	**5 ⟶ 9**	**Pd/C, EtOAc, r.t., 4 h**	**90%**

Table 2.1: Optimisation of hydrogenolysis conditions within ring expansion of β-ketoesters. Yields based on analysis by ^{1}H NMR and comparison with signals for 1,3,5-trimethoxybenzene that was used as an internal standard.

Having established reliable conditions, testing the viability of this methodology on different ring sizes was performed. Therefore 5-membered to 8-membered β-ketoesters were subjected to the three-step procedure with the results shown in scheme 2.12. All examples proceeded to exclusively form the ring expanded products, with the yield determined from the success of the acylation step. These results are more significant when considering the ring strain of the medium-sized rings products (**352**, **353** and **280**), which demonstrates that the systems have a large thermodynamic driving force for ring expansion. We propose that the favourable thermodynamic driving force for these challenging transformations originates from the formation of a new lactone, and entropic drive from the loss of toluene in the hydrogenolysis step. For each example, all three isomers were observed after hydrogenolysis in the ^{1}H NMR spectra (via diagnostic resonances) although accurate ratios were not possible to calculate due to similar chemical shifts resulting in overlapping resonances. Interestingly, these intermediates were never identified when inserting amino acids, as spontaneous ring expansion occurred.



Scheme 2.12: Synthesis of ring expanded lactone products using C-O forming SuRE process.

2.4 Chapter Summary

Previously inaccessible cyclic β-ketoesters have been prepared, which could then be ring expanded using the developed SuRE methodology to make novel medium-sized rings and macrocycles. Other challenging α- and β-amino acid derivatives have been incorporated into cyclic β-ketoesters, in an attempt to make the ring enlarged products more medicinally interesting. Hydroxy acid derivatives have also been investigated, improving the ring size scope by modifying the hydrogenolysis conditions used previously, hence generating novel lactone containing ring expanded products.

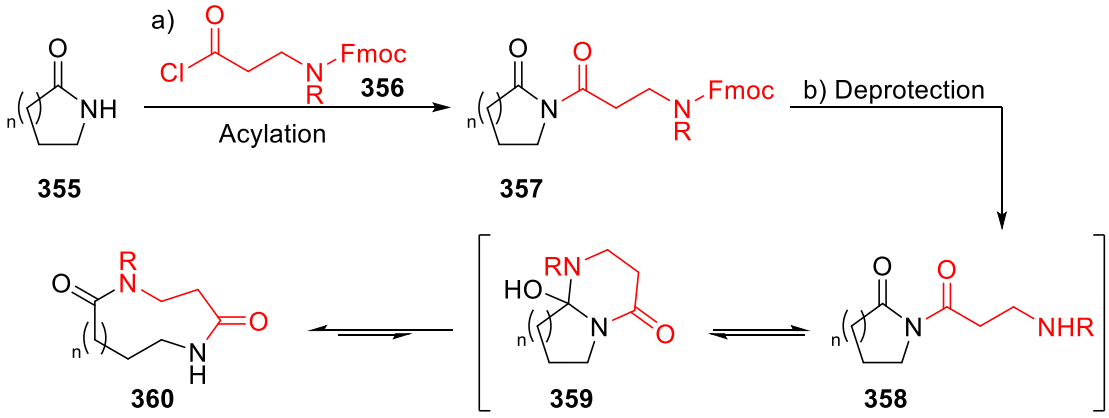
Overall, the work described in this Chapter is the subject of two publications.[6,121]

Chapter Three: Successive Ring Expansion of Lactams

3.1 Lactam SuRE Concept

Taking inspiration from the β-ketoester work and some aspects of the amino acid incorporation (AAI) reaction (of which a large contribution was made by Shemyakin and co-workers[84,87]), we wanted to change the functionality which was regenerated after each ring expansion. We felt that although there was a clear thermodynamic driving force for ring expansion in the cyclic β-ketoester methodology, which was clearly borne out in the experimental results, the final products were not directly medicinally relevant due to the metabolic instability of the key β-ketoester motif; as seen in section 2.3, additional synthetic steps were required to modify the products to achieve appropriate molecular properties for medicinally relevant compounds.

Therefore, we endeavoured to develop a new SuRE procedure that generates medicinally relevant ring expanded products directly. We believed that by starting with a simple lactam, this could be achieved, to produce cyclic peptide mimetics following amino acid incorporation. Thus, if a cyclic lactam **355** could be *N*-acylated with amino acid chloride **356**, then an imide intermediate **357** would be produced and following deprotection, we hoped that spontaneous ring expansion (**358** → **360**) would occur. The integral NH lactam motif would be regenerated upon ring expansion, and therefore we would be able to apply multiple successive ring expansions on these simple compounds.

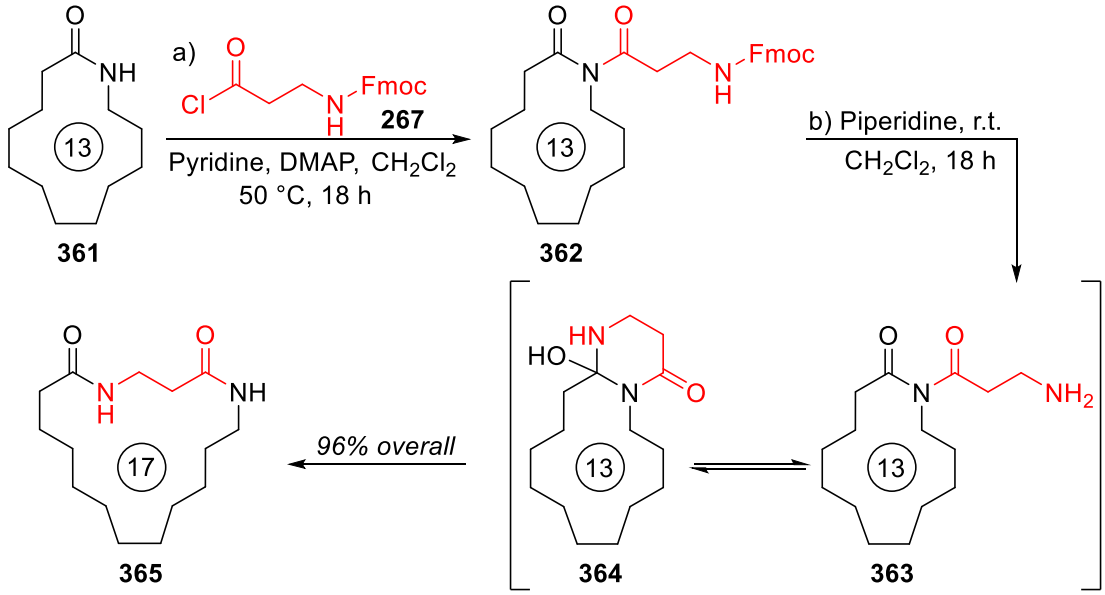


Scheme 3.1: Concept of the synthesis of di-peptides when using lactam as cyclic starting unit.

3.2 Preliminary Results and Optimisation

Starting from 13-membered lactam **361** *N*-acylation was achieved, with modified conditions based on the earlier β-ketoester work (importantly the addition of DMAP), forming imide **362** in excellent yield. This imide is stable to column chromatography, however we found that improved yields were obtained if the acylation and deprotection/ring expansion steps were telescoped. Therefore, crude imide **362** was reacted with piperidine to induce Fmoc cleavage,

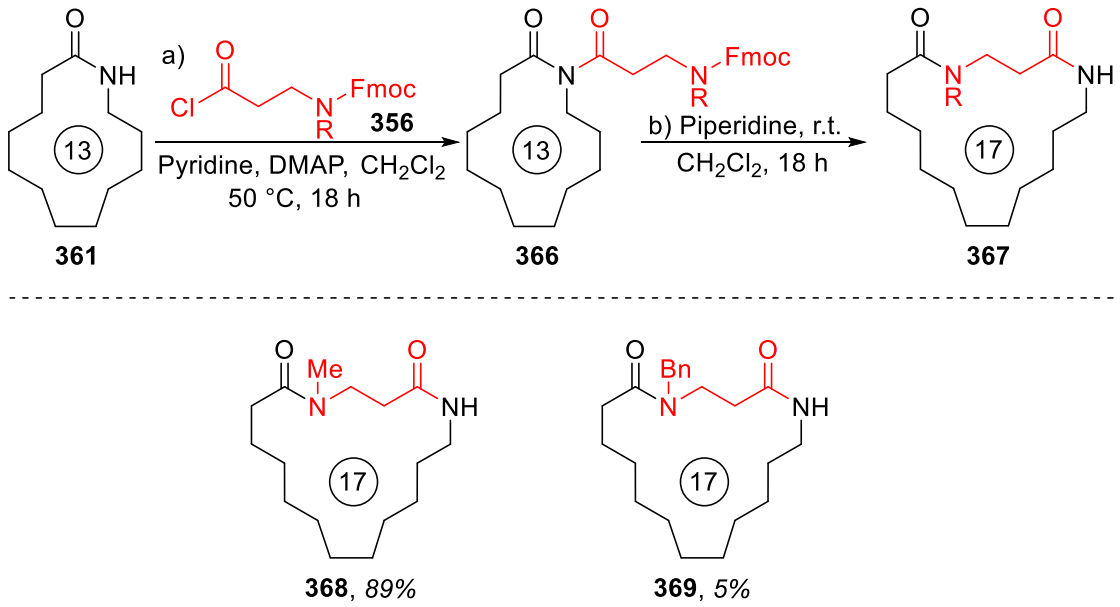
which was followed by spontaneous ring expansion to afford the desired lactam product **365** in excellent yield (scheme 3.2), proving that lactams can be used in these type of ring expansion reactions.



Scheme 3.2: Proof-of-concept ring expansion of 13-membered lactam with an amino acid chloride.

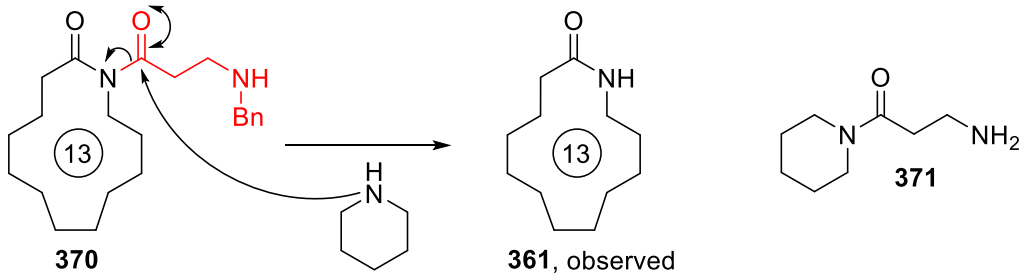
In order to develop a system whereby predictable multiple ring expansions can take place sequentially, it was preferable that only a single secondary lactam be present in the molecule. In the 17-membered ring expanded lactam **365** (scheme 3.2), there are two NH lactam motifs, which was predicted to be a problem in subsequent *N*-acylation reactions. This problem can be circumvented by using a secondary protected amine which would result in the formation of a new tertiary amide which can therefore not acylate.

Thus, if amino acid chlorides, of type **356** (scheme 3.3), were utilised then new ring expanded products, **367**, would be produced which are better suited for further ring expansion iterations. Using a methylated variant, the ring expanded product **368** was formed in excellent yield, however extending this to the benzyl variant was surprisingly poor yielding, with only obtaining 5% of the desired macrocyclic product **369** being isolated. We felt that the benzyl variant was more interesting, as once the ring expansion sequence had been completed, hydrogenolysis of the benzyl groups would be possible. We therefore felt that this problem must be overcome, and reasoned that the loss in yield may be due to the deprotection/ring expansion step, based on the isolation of degradation products.



Scheme 3.3: Ring expansion of 13-membered lactam with secondary protected amino acid chlorides.

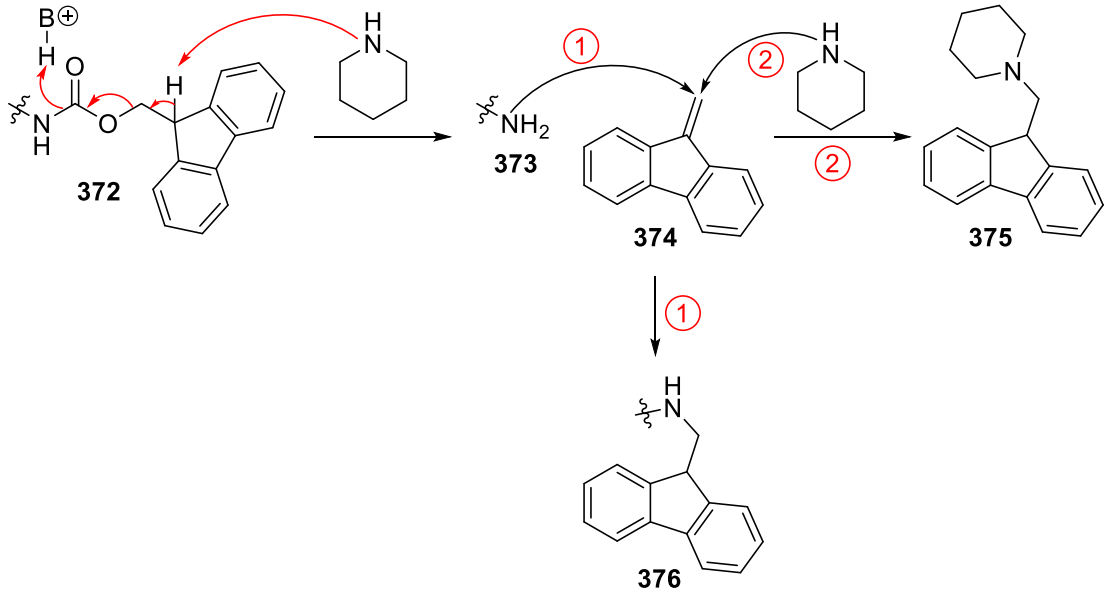
A piperidine induced imide cleavage appeared to be a competing side reaction, whereby after initial Fmoc deprotection, piperidine attacks the exocyclic carbonyl of the imide. This pathway was confirmed by the isolation and characterisation of the 13-membered lactam **361** by ^{1}H NMR, despite starting with purified imide precursor. Presumably, this cleavage only becomes prevalent when the cyclisation/ring expansion of the secondary amine is slow. When the *N*-methyl variant was utilised, presumably the cyclisation/expansion kinetics are more similar to a primary amine example, in which an excellent yield was obtained.



Scheme 3.4: Piperidine induced imide cleavage mechanism.

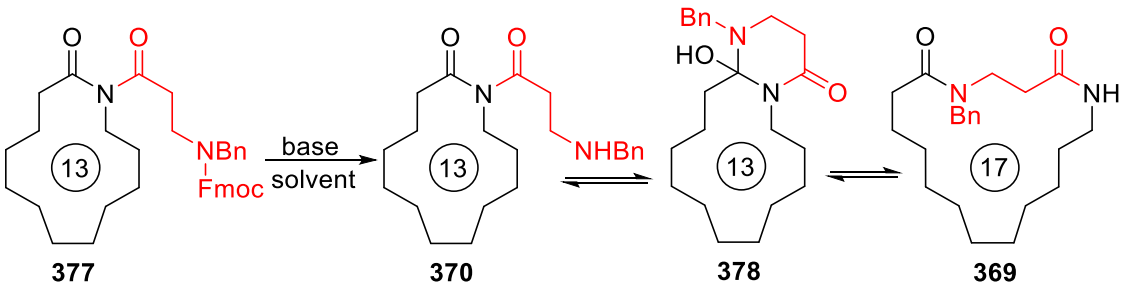
Piperidine is used very commonly for Fmoc cleavage within peptide coupling reactions and, in this context, its nucleophilicity is often an advantage. Piperidine is typically used in large excess during Fmoc deprotection of the *N*-terminus. As seen in scheme 3.5, piperidine initially deprotonates the 'acidic' proton from the Fmoc protecting group (which can form an anionic aromatic species in polar aprotic solvent such as DMF, not shown) which then causes elimination and decarboxylation to form the desired amine **373** in addition to the dibenzofulvene (DBF) side product **374**. If additional equivalents of piperdine are present, then a conjugate addition can

take place and form piperidine adduct **375** (pathway 2), which can be then be removed. However, if all the piperidine is consumed (or a tertiary or non-nucleophilic base is employed) in the deprotection step, then the liberated amine can itself undergo conjugate addition with the DBF (pathway 1) in an unproductive pathway forming amine adduct **376**. In SPPS, this DBF side product is then washed away.



Scheme 3.5: Fmoc deprotection and Michael addition into dibenzofulvene mechanism.

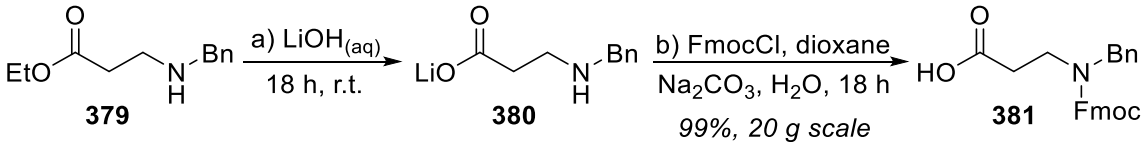
In our work, the liberated amine is consumed within a ring expansion reaction and therefore it may be that alternative non-nucleophilic bases could be utilised which would not normally be suitable in peptide coupling. Therefore, optimisation of the base and solvent for deprotection/ring expansion step were undertaken from a purified sample of the acylated intermediate **377**. Similar to the β-ketoester work, we did not observe either **370** or **378** isomers by ^{1}H NMR and therefore proceeded to optimise through isolated yield of the desired macrocycle **369**. These optimisations are summarised in table 3.1, which shows that the use of non-nucleophilic base DBU in dichloromethane was optimal (entry 6).



Entry	Conditions	Yield of 369
1	Piperidine (10 equiv), CH_2Cl_2, 4 h, 30 °C	0%
2	20% Piperidine in DMF (v/v), 18 h, r.t.	6%
3	20% NEt_3 in DMF (v/v), 5 h, r.t.	0%
4	TBAF (0.1 M), DMF, 4 h, r.t.	0%
5	DBU (10 equiv), DMF, 5 h, r.t.	46%
6	**DBU (10 equiv), CH_2Cl_2, 18 h, r.t.**	**91%**

Table 3.1: Optimisation results for deprotection/ring expansion step using *N,N*-Bn,Fmoc-β-alanine amino acid chloride.

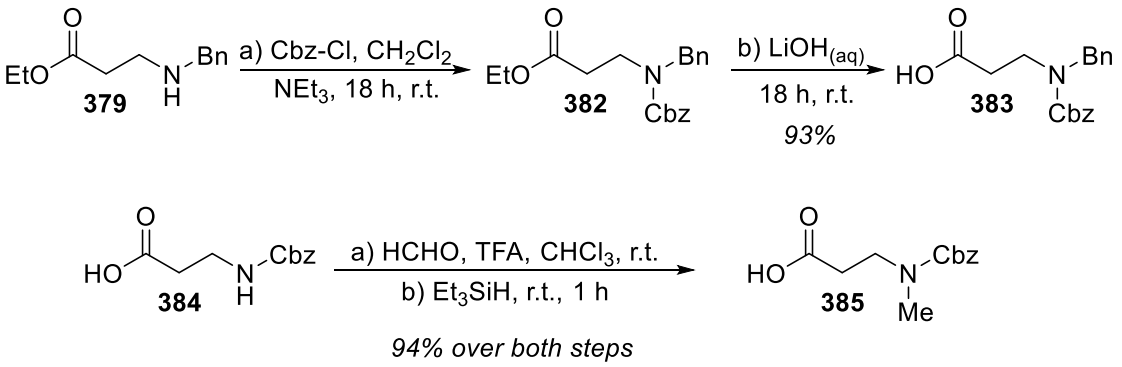
With optimised conditions in hand, the *N,N*-Bn,Fmoc-β-alanine amino acid **381** was produced on gram scale using the following two step procedure from a literature procedure[122] (scheme 3.6). Starting from commercially available amino ester **379**, hydrolysis using lithium hydroxide formed amino acid as lithium carboxylate **380**. Without purification, Fmoc protection was achieved under Schotten-Baumann conditions to produce the desired protected amino acid **381** in excellent yield on multi-gram scale.



Scheme 3.6: Synthesis of *N,N*-Bn,Fmoc-B-alanine amino acid starting material.

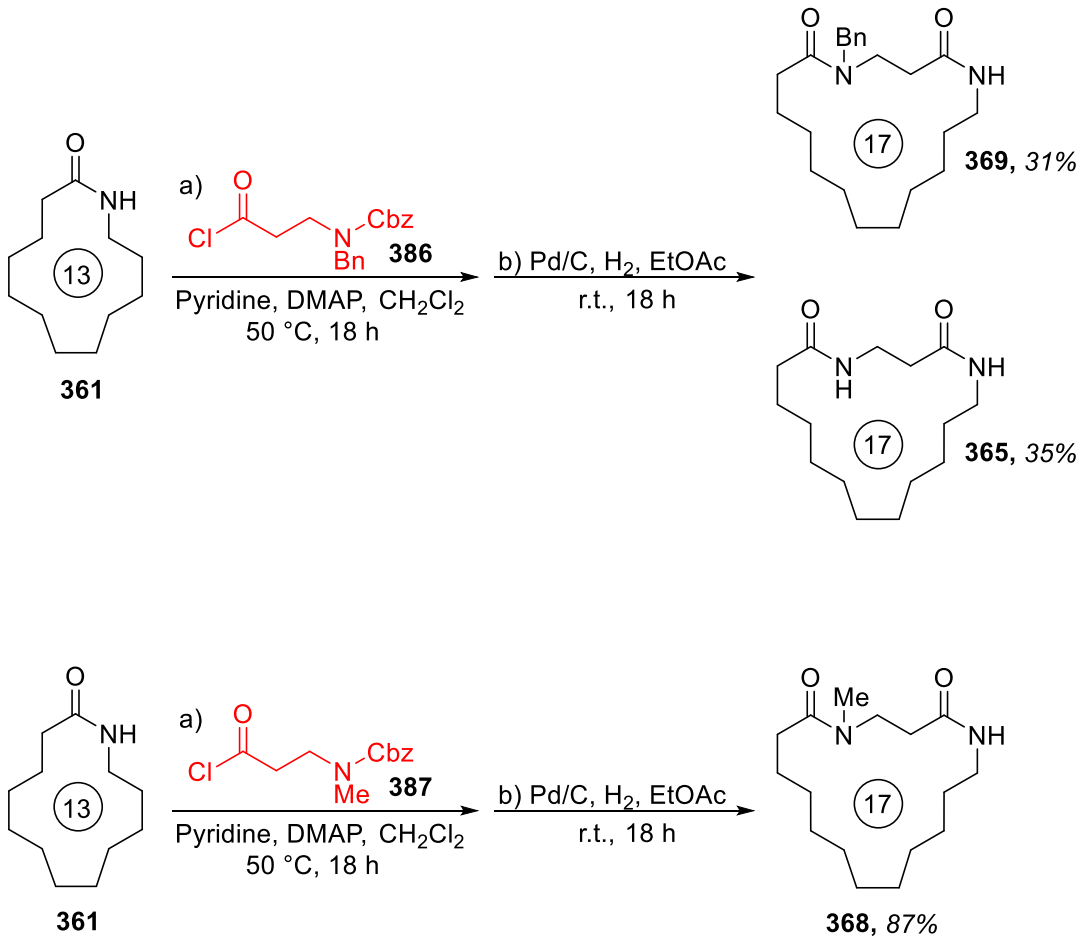
3.3 Protecting Group Scope

Having achieved optimised conditions for the telescoped acyation/deprotection sequence using an Fmoc protecting group, other orthogonal protecting groups were investigated. We proposed that Cbz would work well with our chemistry, with deprotection occurring under hydrogenolysis conditions. Therefore, the Cbz-β-amino acids (**383** and **385**, scheme 3.7) were synthesised on gram scale in excellent yield.



Scheme 3.7: Synthesis of Cbz-protected β-amino acids for protecting group scope testing.

With the Cbz-protected amino acid starting materials **383** and **385** in-hand, they were tested within the standard acylation conditions and pleasingly the corresponding imide was formed in quantitative conversion. In order to remove the Cbz protecting group, hydrogenolysis with Pd/C in ethyl acetate was performed, using similar conditions to those used in the β-ketoester methodology (see Chapter 2). We found that when benzyl β-amino acid chloride **386** was used, two ring expanded products were formed (**365** and **369**, scheme 3.8) with significant amounts of amide debenzylation occurring. Although in this case, this was an undesired pathway, this result supported our previous hypothesis that if benzyl amides were synthesised, they could be removed if required using hydrogenolysis. When the similar methyl β-amino acid chloride **387** was utilised, the 17-membered lactam **368** was exclusively formed in excellent yield, proving that the Cbz protecting group can be utilised successfully.



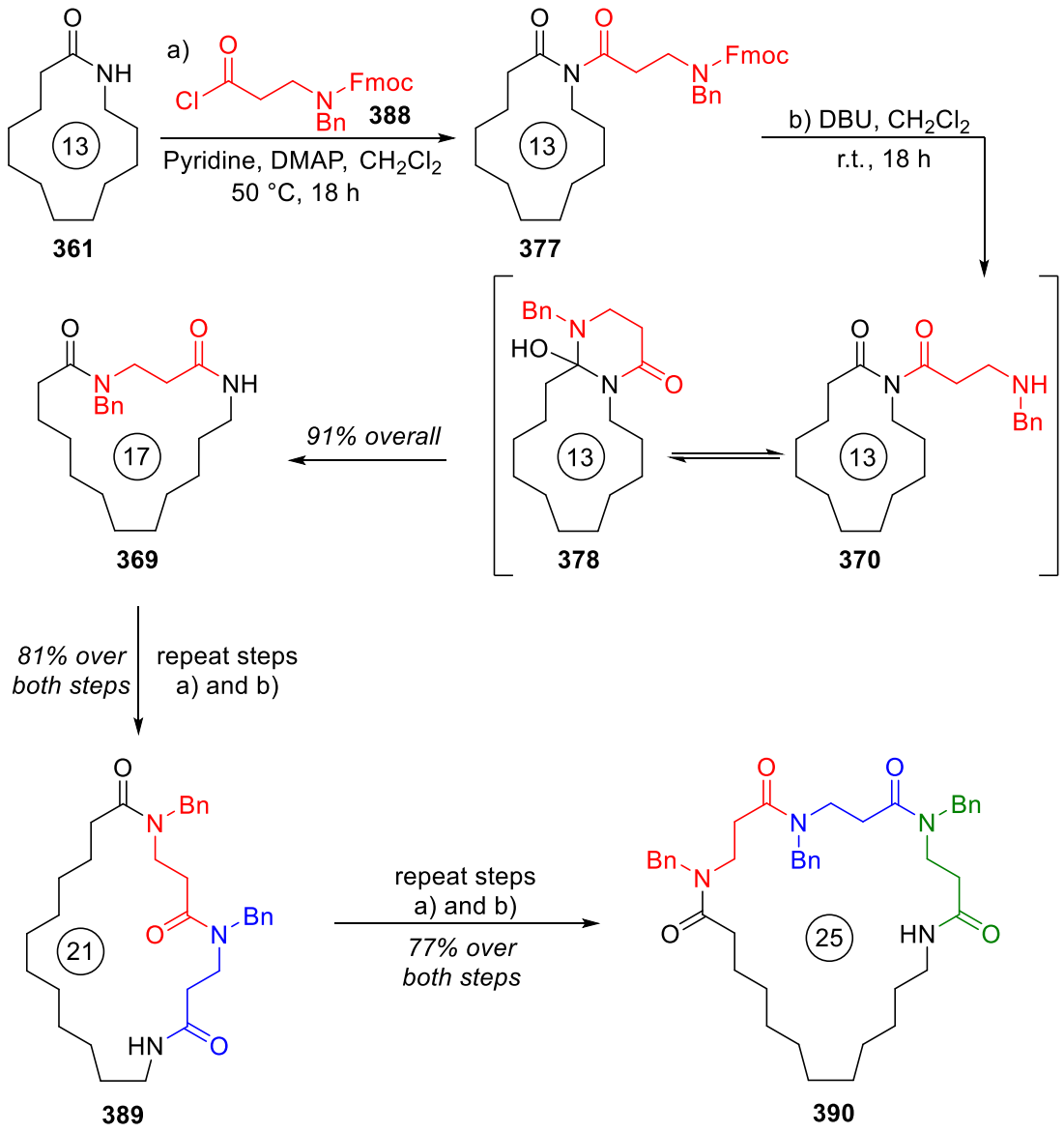
Scheme 3.8: Formation of ring expanded macrocycles using Cbz protecting group.

3.4 Successive Ring Expansion Proof-Of-Concept

With two separate protecting group strategies, we went on to test if the reactions could be performed successively with the regenerating lactam motif. Although Cbz protection worked well, it was decided to prioritise the previous Fmoc protecting group strategy as it was higher yielding and allowed the use of *N*-benzyl amino acids, meaning that after ring expansion, the amides would be amenable to hydrogenolysis.

First, 17-membered lactam **369** was produced using the standard conditions in excellent overall yield (scheme 3.9). As the product contains only a single secondary amide, it could then be re-subjected to our ring expansion sequence with expectation of a selective *N*-acylation reaction, and pleasingly the 21-membered macrocycle **389** was isolated in excellent yield over the telescoped two step protocol. This example proved our design concept is viable, and further, we were able to complete a third ring expansion, producing 25-membered macrocycle **390** in 77% yield over the two steps. This methodology should be useful in the synthesis of medium-sized rings and macrocycles, with a large amount of complexity being introduced to the 25-membered

macrocycle **390** in only three iterations of our ring expansion procedure, from the commercially available 13-membered lactam **361**.



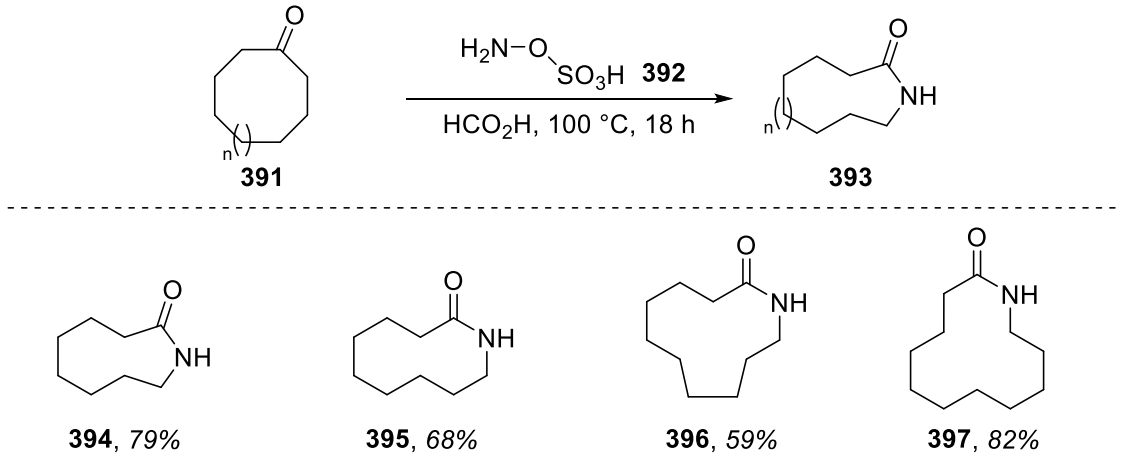
Scheme 3.9: Proof-Of-Concept Successive Ring Expansion examples forming 17- , 21- and 25-membered macrocycles.

3.5 Ring Size Scope

3.5.1 Synthesis of Starting Materials

Having successfully established this new SuRE reaction system, it was important to demonstrate that different ring sizes could be produced using the methodology. Therefore, we set about examining the effect of ring size on the chemistry, and whether medium-sized rings could be synthesised using this methodology. However, despite their simplicity, 9–12-membered lactams **394**–**397** are not commercially available and therefore a route to access them was designed. Fortunately, from the previous β-ketoester methodology (see Chapter 2), the corresponding

ketones had already been prepared on gram scale and thus could be transformed into lactams using a Beckmann rearrangement. Thus, using a single step, ketones **391** were condensed with hydroxylamine-O-sulfonic acid **392** (HOSA), and treated with formic acid under reflux conditions to afford the desired lactam, via a Beckmann rearrangement (scheme 3.10). All lactams **394**–**397** were produced in high to excellent yield, following purification by a series of aqueous work ups and column chromatography.



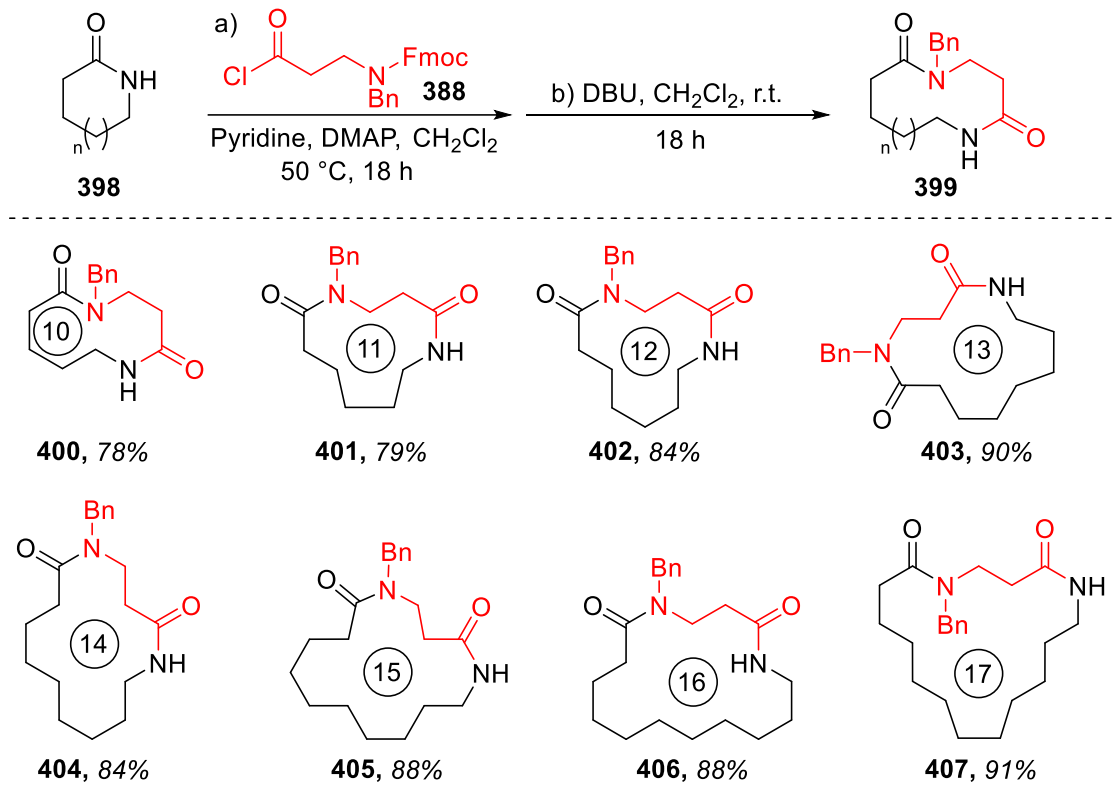
Scheme 3.10: Synthesis of medium-sized ringed lactams using Beckmann rearrangements.

3.5.2 Ring Expansion

With the required lactam starting materials in hand, an examination of how ring size effects the ring expansion reaction was conducted. Using β-amino acid chloride **388**, 6–13-membered lactams were acylated and ring expanded successfully. All ring expanded products were formed clearly, with no observation of other isomers or unwanted side-products. Medium-sized rings **400** and **401** were slightly lower in yield, which we believe is simply as a result of their high polarity making the products more difficult to purify.

The rings **400**–**402** also displayed very interesting ^{1}H NMR spectra with diastereotopic protons throughout the ring system (figure 3.2). A crystal structure of the 10-membered ring enlarged compound **400** was taken (see figure 3.1) which shows a *Z*-,*E*-diamide configuration which causes a twisting in the ring, which might be causing this inequivalence in the proton environments. However, another explanation arises from the conformation of the ring. As the ring is strained (due to transannular strain in medium-sized rings), a single conformation which is significantly more thermodynamically stable than others, may exist which orientates its protons into non-equivalent axial and equatorial environments. Variable temperature NMR was performed in deuterated d_6-DMSO up to 140 °C, and at elevated temperature the diastereotopicity was resolved, however only broad resonances were obtained (see figure 3.3).

14-membered macrocycle **404** was also synthesised on gram scale with no appreciable loss of yield, highlighting the scalability of this reaction.



Scheme 3.11: Ring size scope of ring expansion producing 10- to 17-membered rings.

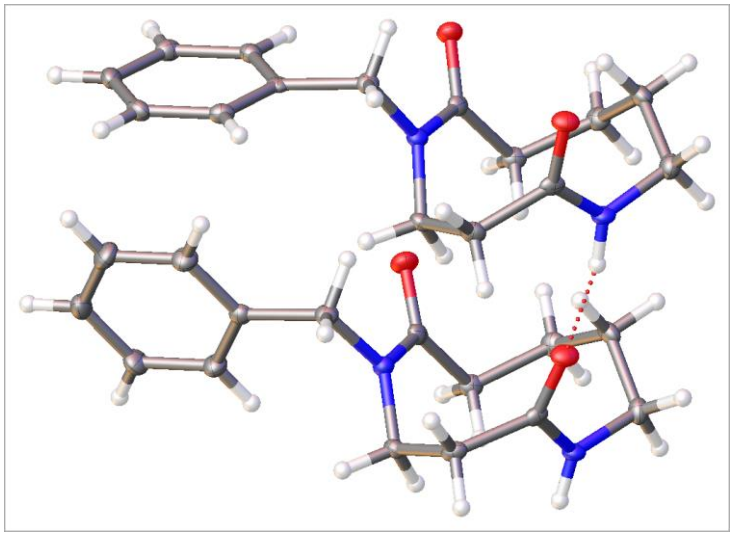


Figure 3.1: Crystal structure of 10-membered ring expanded product.

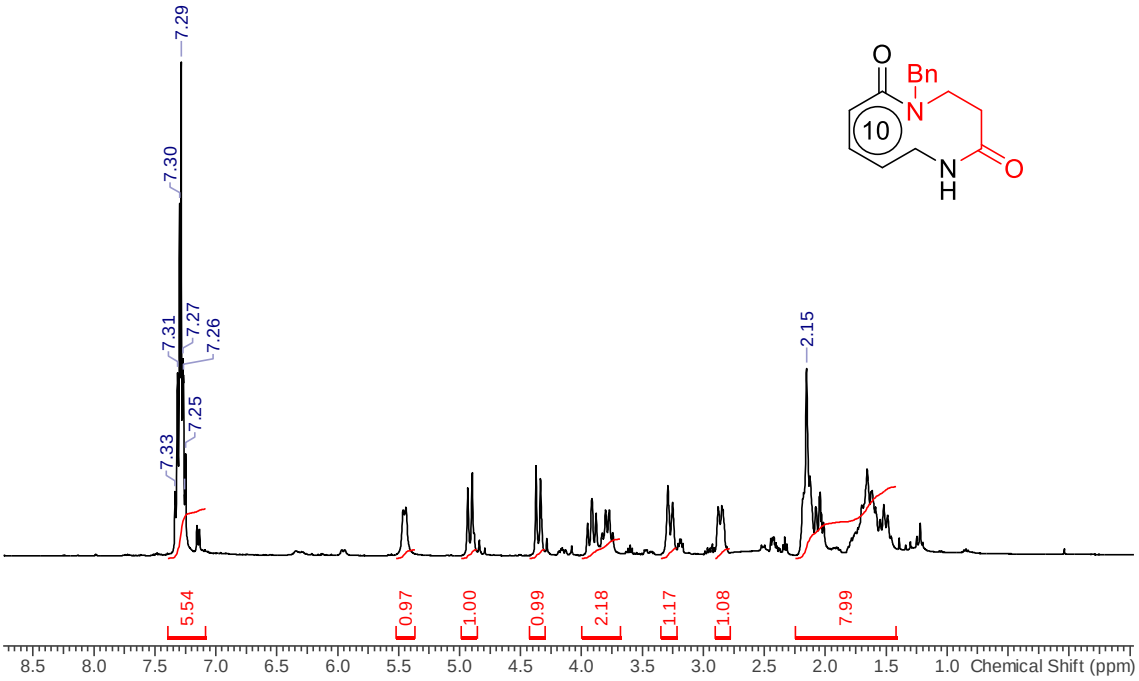


Figure 3.2: ^{1}H NMR of 10-membered ring expanded product 400 at room temperature in $CDCl_3$, which exists as a mixture of rotamers.

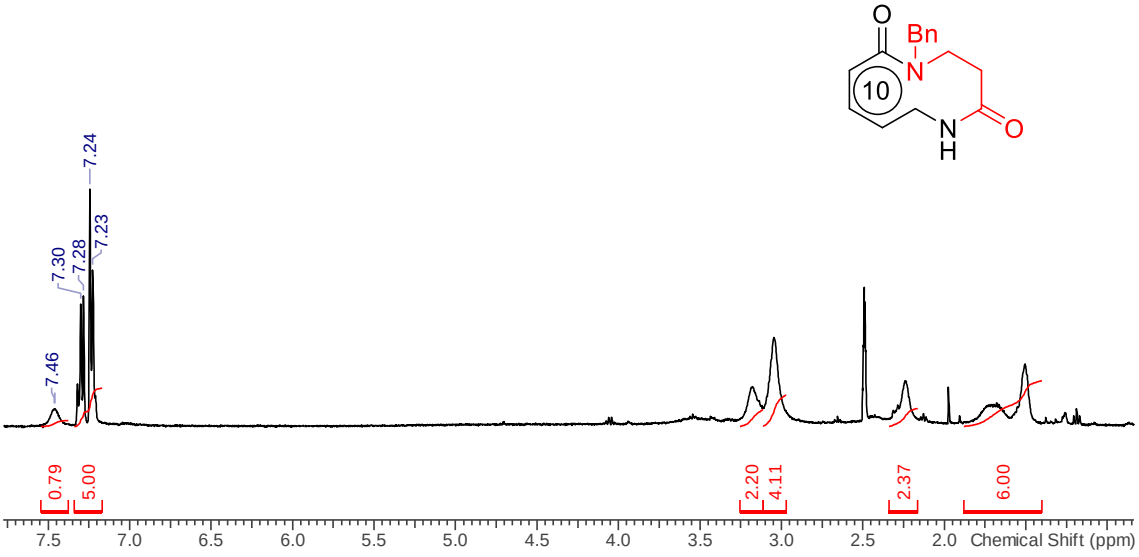
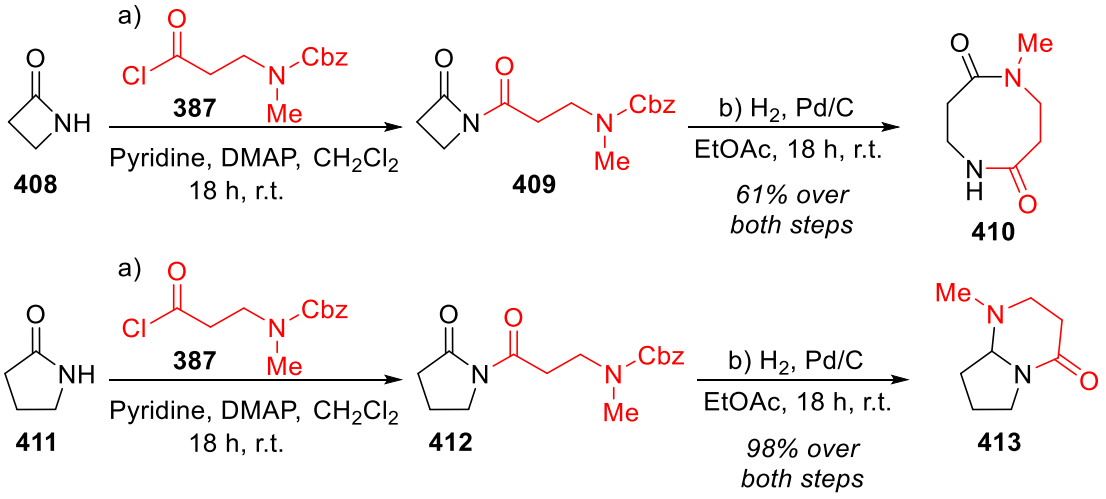


Figure 3.3: ^{1}H NMR of 10-membered ring expanded product 400 at 100° C in d_6-DMSO.

3.5.3 Four and Five Membered Lactam Examples

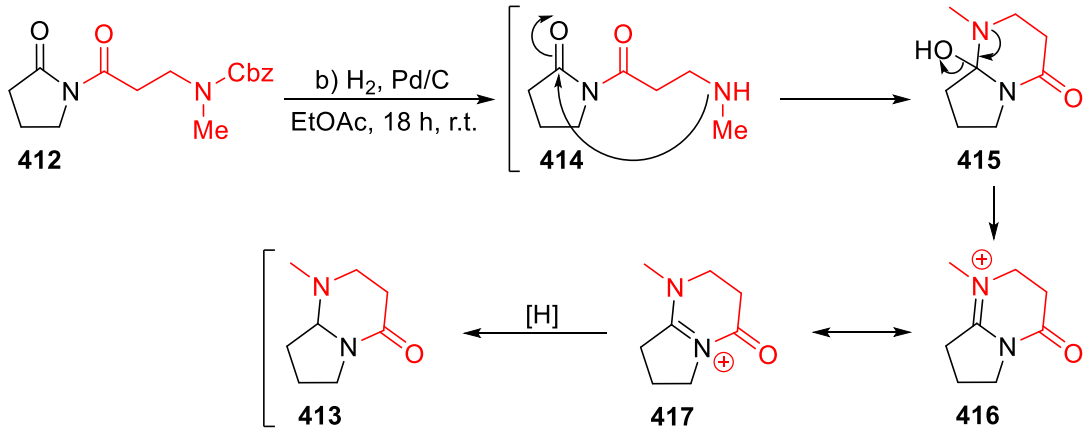
The ring size scope was extended to the smaller four- and five-membered lactams, however we encountered difficulties in determining the reaction outcome. The 4-membered lactam (β-lactam) was successfully *N*-acylated, however, when performing the deprotection/ring expansion step, we believe that the 8-membered enlarged product was formed based on diagnostic resonances in the ^{1}H NMR (in comparison with the product formed later), but was too polar to separate from the excess DBU via column chromatography. The 5-membered lactam was also studied with successful acylation producing the corresponding imide, however upon deprotection no product was observed.

To address this, we decided to use the Cbz protecting group instead, as this would allow us to better understand where the reaction was halting, because column chromatography is not usually required. Therefore both lactams were acylated with *N,N*-Me,Cbz-β-alanine **387**, which produced their corresponding imides **409** and **412** (scheme 3.12). These imides were purified using a silica plug to remove the excess pyridine and amino acid residues. It was important that these amine-based residues were removed from the crude mixture, as they would likely have a high affinity for the palladium catalyst used in the hydrogenolysis step, and could therefore poison the catalyst. The 4-membered imide **409** successfully produced the 8-membered ring enlarged medium-sized ring **410** in a good overall yield of 61%. However, the 5-membered imide **412** did not produce the corresponding ring expanded product, and instead produced fused bicyclic *N,N*-acetal **413** in excellent yield. This was a new reaction pathway which had not been previously observed, and surprisingly this relatively simple compounds were novel.



Scheme 3.12: Using a Cbz protecting group strategy to synthesis medium-sized rings previously unsuccessful when Fmoc was used.

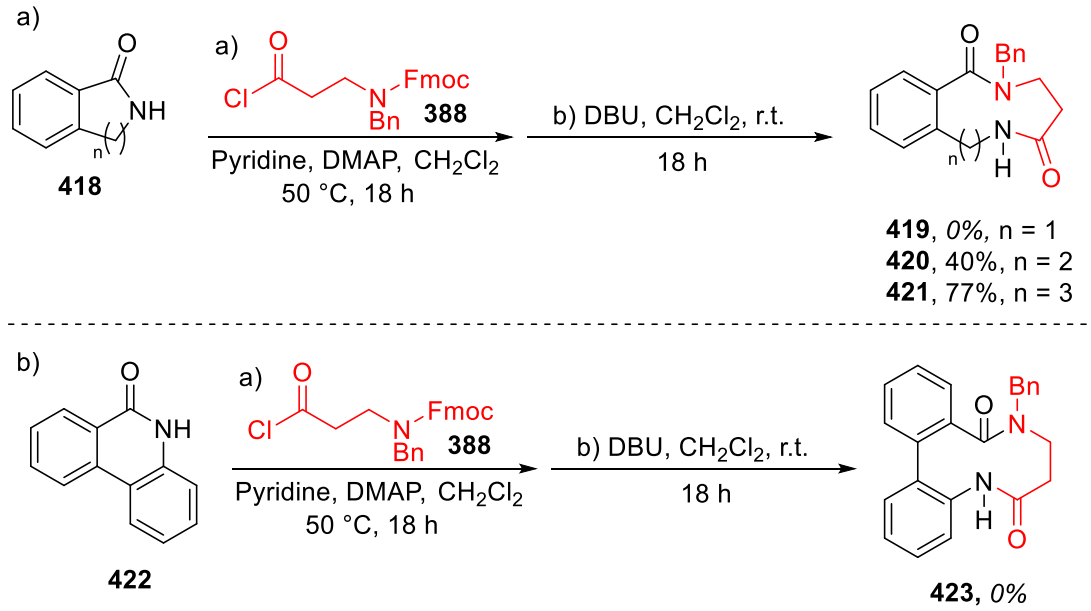
We wanted to understand the mechanism in which this *N,N*-acetal **413** was being formed. We propose the following reaction pathway, seen in scheme 3.13. Initially hydrogenolysis of the Cbz protecting group occurs producing amine **414**. The liberated amine spontaneously cyclises onto the endocyclic carbonyl forming the fused hemi-aminal **415**. This can be followed by dehydration to form iminium ion **416**. This iminium ion is stabilised as another resonance form can be drawn as an *N*-acyl iminium **417**. The iminium is then reduced to the *N,N*-acetal **413** as the reaction is still under reducing conditions.



Scheme 3.13: Formation of *N,N*-acetal 413 from 5-membered lactam using a Cbz protection strategy.

3.5.4 Benzannulated Ring Size Scope

In order to increase the diversity and structural complexity of the products, different sized benzannulated lactams were also tested. The focus was on producing more medicinally interesting ring expanded products, which may have more favourable molecular properties than those produced previously. Introducing the benzannulated motif in the backbone also reduced the polarity of the products which also aided in the purification of these compounds. Thus, 5- , 6- and 7-membered benzannulated systems were tested with the results shown in scheme 3.14. All examples acylated (with varying amounts of conversion), however both **419** and **423** were not successfully produced. However pleasingly, 10- and 11-membered products **420** and **421** produced the ring expanded products in useable and high yields. The poorer yielding 10-membered example suffered from poor acylation, with a significant amount of starting material being recovered and therefore with small reaction optimisation, we are confident that this yield could be improved significantly.



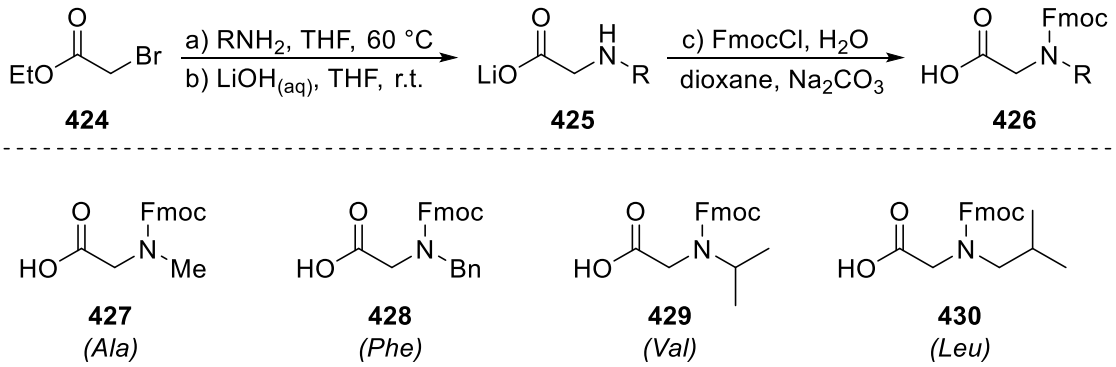
Scheme 3.14: Synthesis of various sized benzannulated ring expanded products.

3.6 Amino Acid Scope

With the ring size scope extensively studied, we turned our attention to varying the linear fragment that is introduced during the ring expansion. Two points of diversification were highlighted: the addition of a group onto the α-carbon of an amino acid and substitution onto the nitrogen of the amino acid. Initially, we examined placing substituents onto the nitrogen, which would create cyclic peptoid mimetics upon ring expansion. Peptoids are a class of peptidiomimetics, in which the amino acid side chain is transposed onto the nitrogen, and can have increased binding affinity compared to the analogous peptides, hence currently there is significant interest in installing peptoid fragments into large ring systems.[123,124]

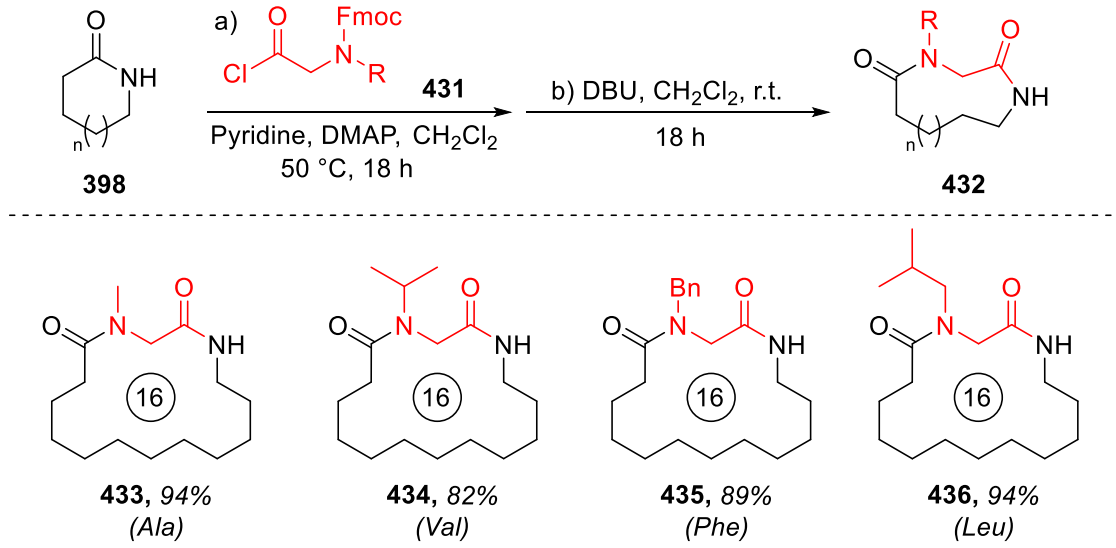
3.6.1 Peptoid-Based Amino Acids

First, we made the peptoid amino acids via a three-step sequence, inspired by how peptoids are made on solid support.[125] Ethyl bromoacetate **424** was treated with excess equivalents of a commercially available primary amine to form an amino ester. Ester hydrolysis was then completed using lithium hydroxide to form the lithium carboxylate **425**. Schotten-Baumann reaction conditions[126] for Fmoc protection produced the desired protected amino acid linear fragments **426**. This sequence could be performed on gram scale if required. The analogous proteinogenic amino acid three letter code is given in brackets underneath the corresponding compound (synthesis of these amino acid starting materials was completed by Dr. Mahendar Lodi).



Scheme 3.15: Synthesis of peptoid amino acid linear fragments via three step procedure.

With the desired linear fragments in-hand, their use within the ring expansion chemistry was tested. All linear fragments were successfully acylated and ring expanded using the standard conditions with no modification to the procedure. All examples produced the cyclic peptoids **433**–**436** in excellent yields with no variation in yields, despite some sterically demanding groups being introduced (such as *iso*-propyl and *iso*-butyl groups). There has been significantly more work (by another PhD student in the group) based on producing these cyclic peptidiomimetic compounds, introducing far more complexity and different functional groups which these aliphatic side chains do not possess.[121]

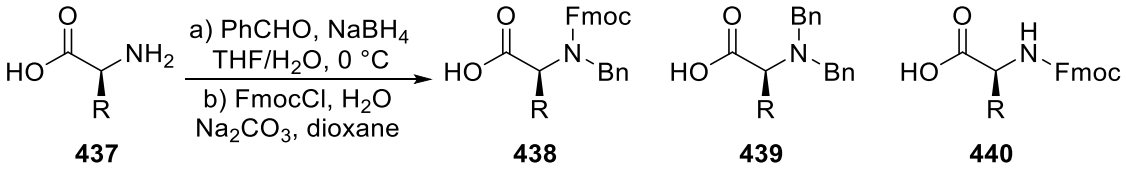


Scheme 3.16: Synthesis of cyclic peptidiomimetic macrocycles using standard ring expansion conditions.

3.6.2 Amino acids

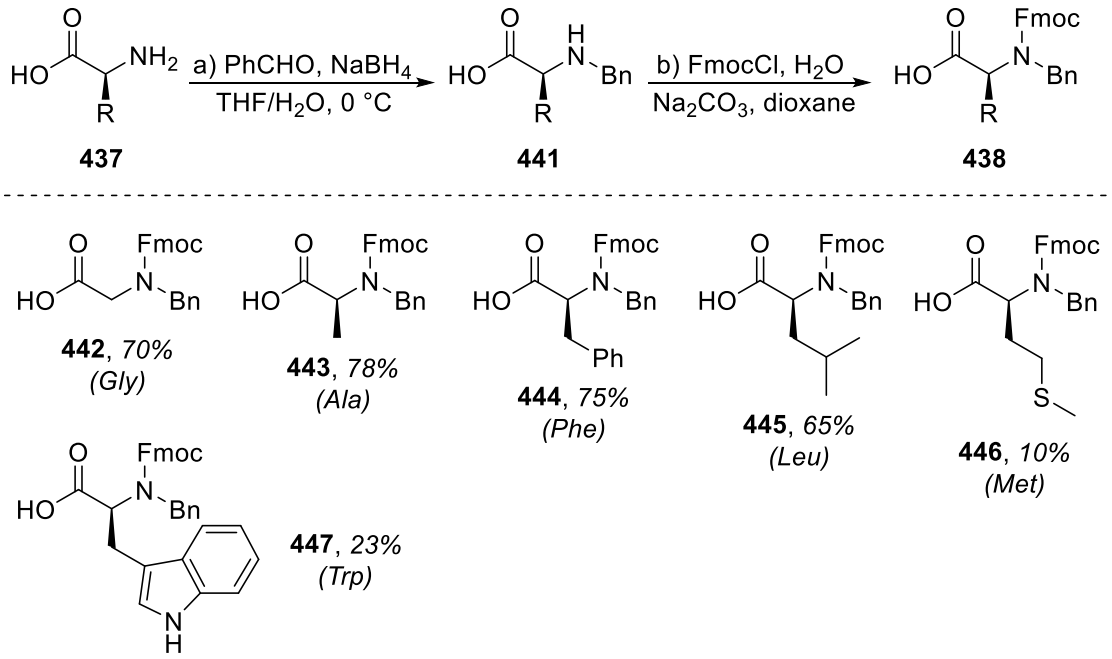
With the success of incorporating the simple peptoid amino acids, we believed that introducing the linear fragment based on proteinogenic amino acids would also be equally viable. There was literature procedure to synthesise *N,N*-Bn,Boc amino acids from the parent unprotected amino acid,[127] and we believed that this could be easily modified to incorporate the Fmoc protecting group instead. Therefore, the amino acid **437** was initially treated with benzaldehyde to form

the imine, which was then reduced using sodium borohydride to form the secondary amine **441**. Due to the zwitterionic nature of the starting material and product, the reaction had to be completed in a bi-phasic mixture of THF and water, which did produce some reproducibility problems (only in this reductive amination step) when scaling this reaction. On account of the reaction being conducted *via* portionwise addition of reagents, a side product where reductive amination occurred twice produced dibenzyl amino acid **439** (scheme 3.17). As a result, the commercially available Fmoc amino acid **440**, was also observed and isolated. We believe that this was because of inefficient mixing of the organic and aqueous phases, which was not a problem with the smaller volumes conducted previously. The desired protected amino acid **438** was purified and the ratio of **438**:**439**:**440** was not calculated.



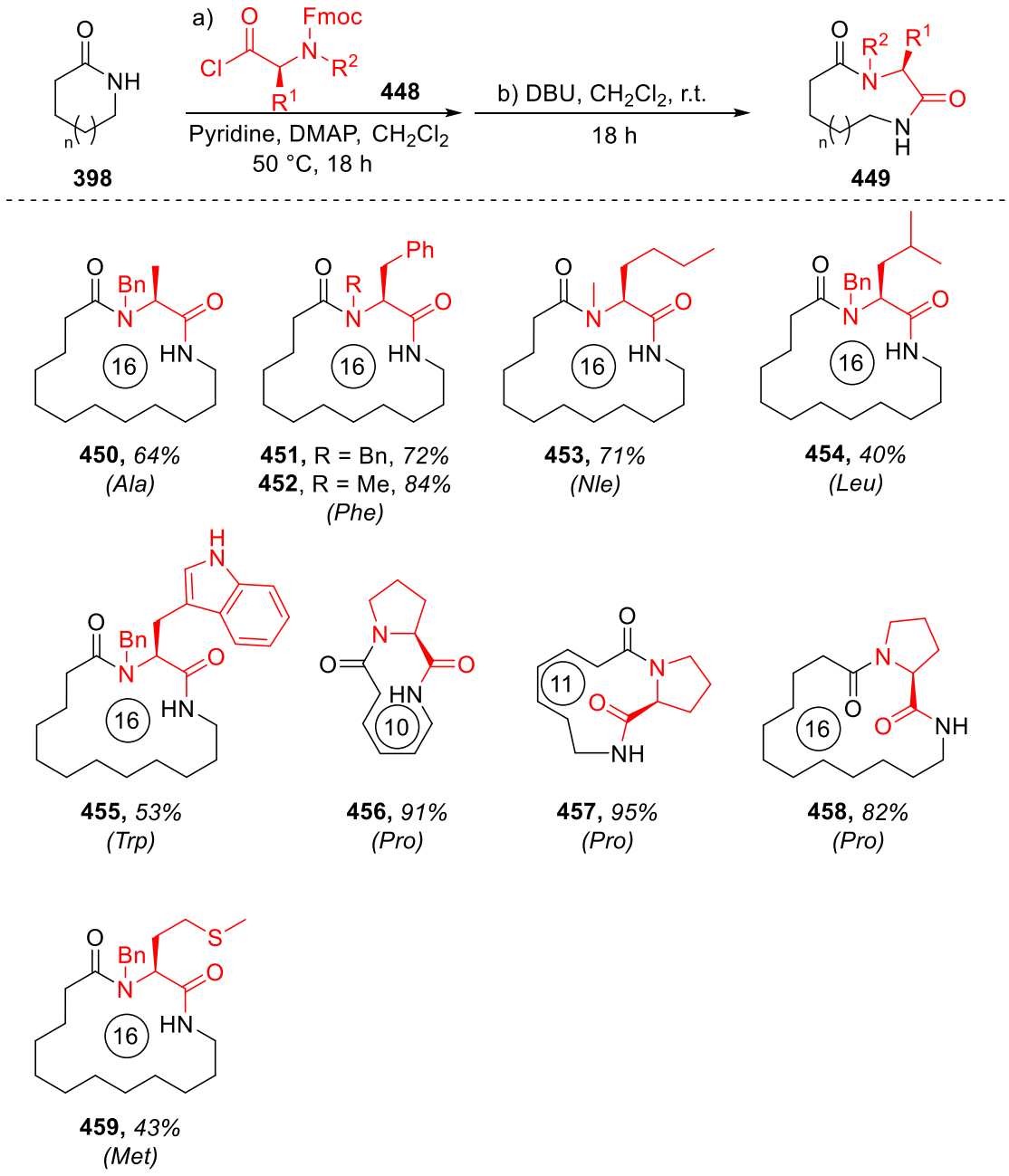
Scheme 3.17: Side-products in the large scale synthesis of *N,N*-Bn,Fmoc amino acids, during the reductive amination step.

With the amino acid derivative **441** (scheme 3.18) from the reductive amination step, Schotten Baumann conditions were utilised for Fmoc protection and was very reliable procedure at this point. Amino acids with aliphatic/lipophilic side chains were successfully produced in good yields, with glycine (**442**), alanine (**443**), phenylalanine (**444**) and leucine (**445**) all being produced with little problem. The methionine derivative **446** was also synthesised and we extended this methodology to create a tryptophan example (**447**). The synthetic steps used to produce these protected amino acids should not epimerise the stereogenic centre, which allowed us to make enantioenriched amino acid linear fragments, when we utilised the enantioenriched amino acid starting materials (depending on commercial availability of the parent amino acid). The $[\alpha]_D$ value measured was always significantly large, illustrating that a racemic sample was not produced.



Scheme 3.18: Synthesis of *N,N*-Bn,Fmoc amino acids using reductive amination/protection sequence.

Having successfully made the derivatised amino acids (and obtaining some commercially available suitable amino acids), we then investigated the viability of these starting materials in the ring expansion chemistry. All amino acids that had been synthesised were successfully incorporated into the lactam starting material, producing a range of cyclic peptide-based medium-sized rings and macrocycles. As a general note, the yields are usually determined by the efficiency of the *N*-acylation step and when acid sensitive functionality such as indole (tryptophan - **447**) and sulfide (methionine - **446**) were incorporated, a significant drop in yield was observed. Although a few yields were modest, the production of these macrocyclic compounds via a head-to-tail cyclisation of the corresponding linear precursor would likely be difficult. There appeared to be some more dependence of the yield obtained and the size of the side-chain of the amino acid. When small side chains such as alanine (**450**), phenylalanine (**451** and **452**) or the unnatural straight-chained norleucine (**453**) were used, good yields were obtained. However, when the steric demand was increased such as leucine (**454**) the yield decreased fairly significantly. We believe that this is again due to a slower acylation and that deviation from using the standard conditions may offer improvements in the future. Pleasingly, a series of examples (**456**–**458**) were produced which incorporated proline as the linear fragment. Both medium-sized ringed and macrocyclic compounds were created in excellent yield, showing good generality.



Scheme 3.19: The synthesis of medium-sized and macrocyclic compounds via ring expansion.

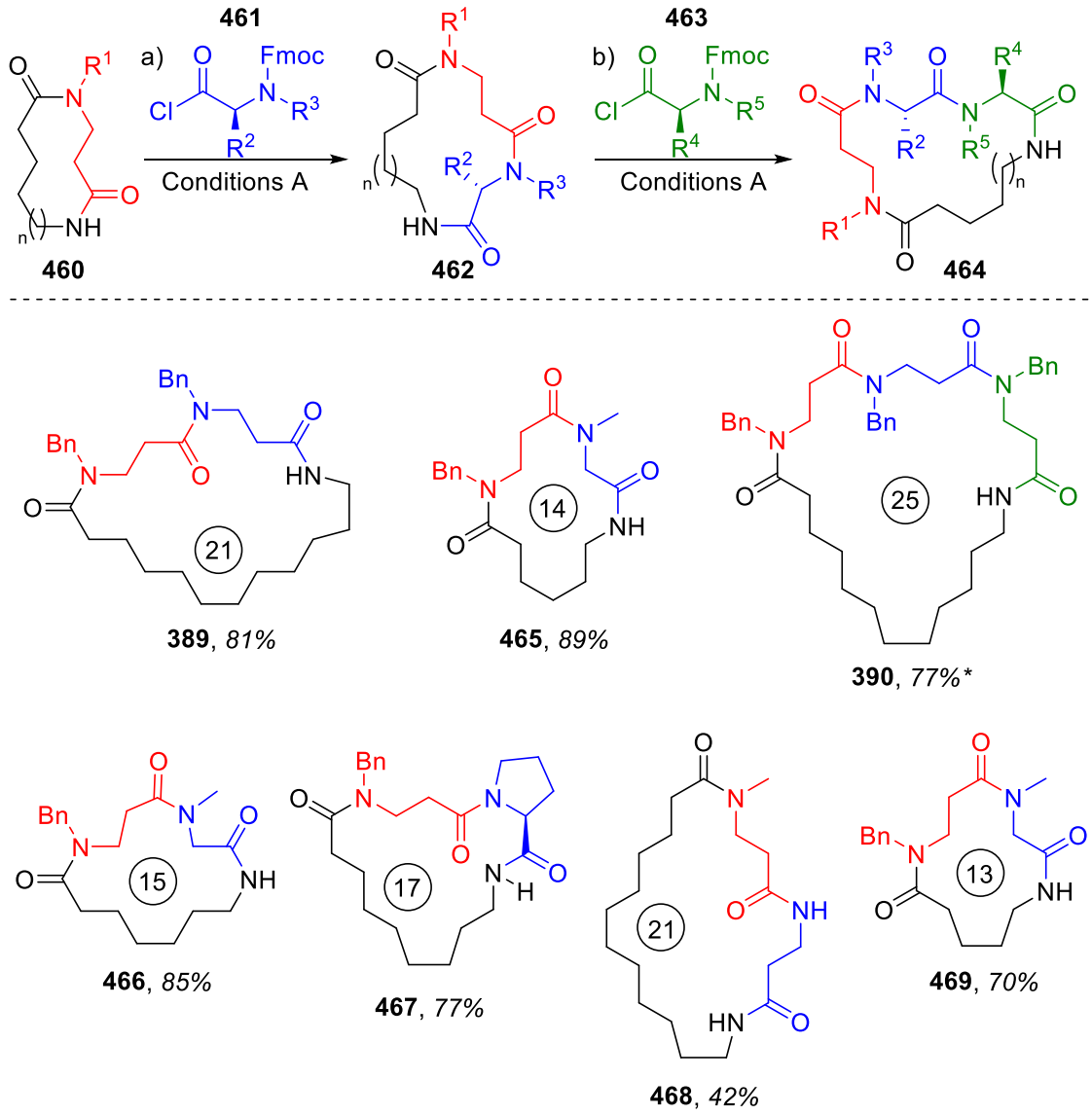
3.7 Successive Ring Expansion

Attention then turned towards making macrocycles based on successive ring expansions. We aimed to make macrocycles of varying ring size, by incorporating different linear fragments in various orders. Initially, there was little success with multiple examples failing to acylate, presumably due to unreactive conformations, arising from rotamers, being the lowest in energy. However, a general trend developed, that 'smaller' sized rings (ranging from 10- to 14-membered) typically did acylate well, under the standard conditions previously optimised. This led to successful examples (**389**–**469**, scheme 3.20) introducing both natural and unnatural

amino acids, with varying ring sizes, all with high to excellent yields. Larger ring sizes, such as the 21-membered macrocycle **468,** were accessed, however the yield was lower than hoped.

Therefore, the reactions were carefully monitored by TLC and if required, additional equivalents of the acid chlorides were used to help improve the yields obtained, as the yields are almost exclusively determined by the conversion during the acylation step. We found that this significantly bolstered the yields obtained, with very similar 21-membered macrocycle **389** being obtained in a much improved 81% yield.

The methodology was then extended to perform three ring expansion reactions in succession, to form 25-membered peptide trimer **390**. An excellent yield was obtained over the same telescoped two-step procedure, and importantly no degradation of the starting materials was observed. Thus, fairly complex macrocycles, which would be difficult to synthesise *via* a traditional end-to-end cyclisation of a linear precursor, can be made reliably *via* the successive ring expansion strategy. Although the same amino acid was utilised in each ring expansion step, this was a controlled series of ring expansions, opposed to an uncontrolled polymerisation-type ring expansion reaction. We believe that different amino acids could be used, and therefore a diverse array of macrocycles can be accessed using this methodology. This work has led to further projects in the group, incorporating more medicinally relevant amino acids and peptoid fragments into cyclic lactams.



Scheme 3.20: Synthesis of peptidiomimetic macrocycles by the use of successive ring expansions with amino acid fragments. *Additional equivalents of the corresponding amino acid chloride were utilised in the *N*-acylation step. Conditions A: a) Pyridine, DMAP, CH_2Cl_2, 50 °C, 18 h. b) DBU, CH_2Cl_2, r.t., 18 h.

3.8 Chapter Summary

The successive ring expansion of simple, commercially available lactams with amino acid derivatives has been developed. A wide range of ring sizes has been prepared, with many different linear fragments successfully incorporated, typically in high yields. Enantioenriched α-amino acid derivatives have been synthesised, and then introduced into lactams to prepare enantioenriched macrocyclic products. Seven examples have been produced, whereby successive ring expansions have taken place, with varying substitution and functionality.

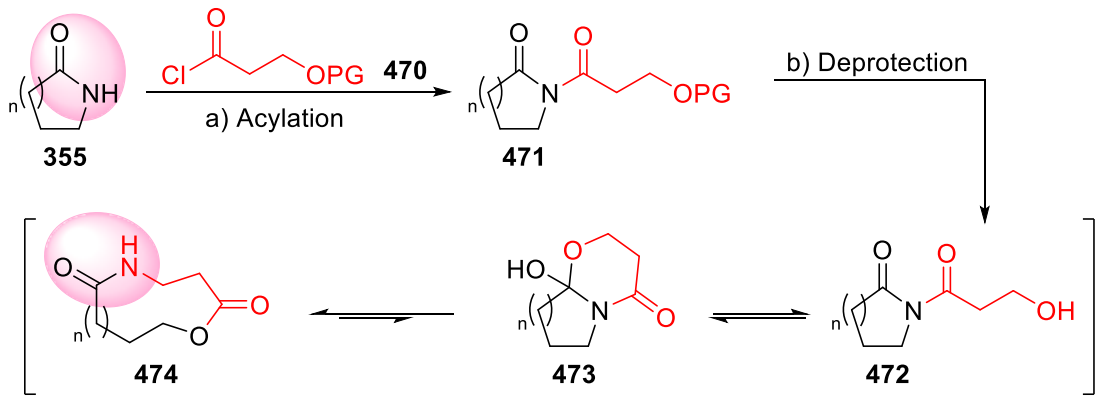
The work described in this Chapter is the subject of one publication.[128]

Chapter Four: Lactone Forming Successive Ring Expansion

4.1 Lactone SuRE Concept

Using a similar approach to the previously described C-N bond forming ring expansion (see Chapter three), we reasoned that a lactone forming reaction would also be possible. There are numerous macrocyclic lactones found in nature, including in cyclic siderophores, and natural products like the epothilones, vancomycin and macrolide antibiotics such as erythromycin. Therefore, a new pathway that can access these targets (as well as analogues) could be incredibly valuable.

Using a two-step procedure, we proposed that *N*-acylation of lactam **355** with a protected hydroxy acid chloride **470** could deliver the corresponding imide **471**. With the use of a suitable protecting group, mild deprotection conditions could then be employed to liberate the pendant alcohol. We proposed that an equilibrium would be established between three isomers (**472**–**474**), with the expectation that the ring expanded product would be the most favourable thermodynamically in most cases (scheme 4.1). Importantly, the NH lactam motif is regenerated upon ring expansion and therefore the ring expansion sequence can be performed successively.

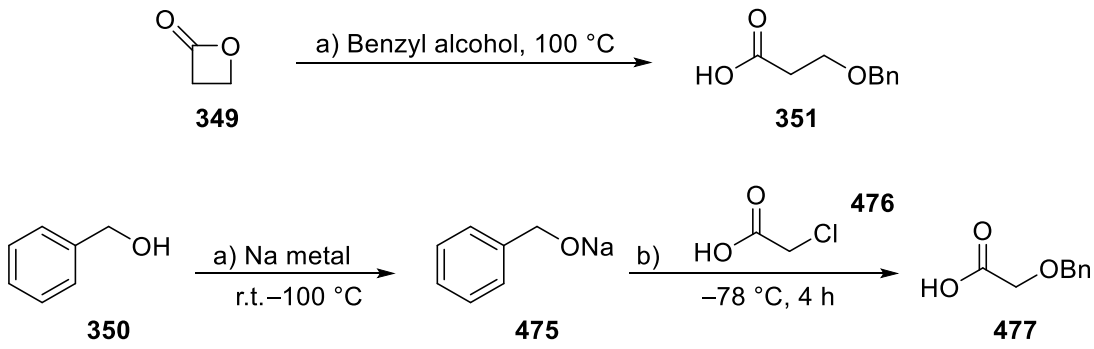


Scheme 4.1: Lactone forming successive ring expansion concept.

4.2 Hydroxy Acid Preparation

A benzyl protecting group was chosen because of its mild cleavage conditions (*via* hydrogenolysis) with the toluene by-product being volatile, whilst the protecting group being stable to the strong acidic conditions of acid chloride formation. The simple α- and β-hydroxy acids, which were required to test our hypotheses, are not commercially available, therefore, using two separate literature procedures were used to make both compounds in excellent yields on gram scale. The procedure to make the β-benzyl protected hydroxy acid **351** from β-propiolactone **349** was discussed previously (see Chapter 2). For the α-hydroxy acid, sodium

metal was used to form the benzyl alkoxide **475**, which was added (in excess) to chloroacetic acid **476**, forming the desired hydroxy acid **477**.

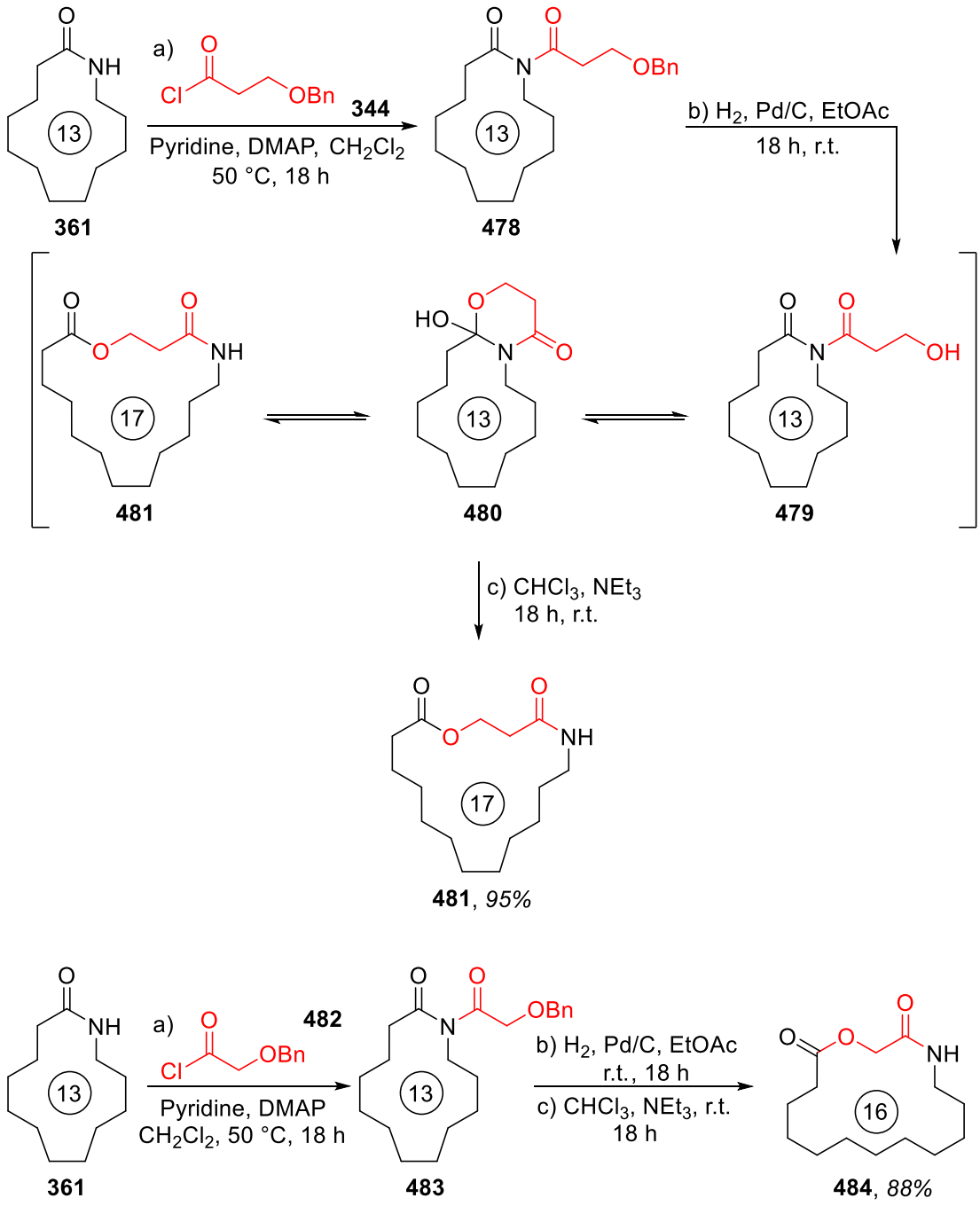


Scheme 4.2: Preparation of benzyl protected hydroxy acid starting materials.

4.3 Reaction Optimisation

With the starting materials in-hand, the ring expansion sequence with hydroxy acid chlorides was investigated. Initially, 13-membered lactam **361** was utilised to avoid the added complication of preparing strained medium-sized rings. Using identical conditions to those used with amino acid chlorides (see section 4.3), successful acylation with β-hydroxy acid chloride **344** was achieved and the imide **478** was purified and characterised (scheme 4.3). Using the optimised conditions, previously obtained from the previous β-ketoester methodology (see Chapter 2), debenzylation occurred delivering a mixture of all three isomers **479**–**481**, which was observed in $CDCl_3$ (NB: an approximate ratio of 10:2:1 was observed, however resonance overlapping in the ^1H NMR spectra makes this ratio inaccurate for further analysis). A solvent switch was then performed to chloroform, and triethylamine added to promote cyclisation and ring expansion. After 18 hours, full conversion to the desired ring expanded product was achieved, and upon purification by column chromatography the product **481** was isolated exclusively with no observation of conversion back to either of the previous isomers **480** or **479**.

When α-hydroxy acid chloride **482** was utilised, imide **483** was prepared via *N*-acylation, and using the same hydrogenolysis conditions, a similar mixture of isomers was obtained. Following a solvent switch to chloroform, with the addition of triethylamine, successfully achieved the 16-membered macrocyclic product **484** in excellent yield.



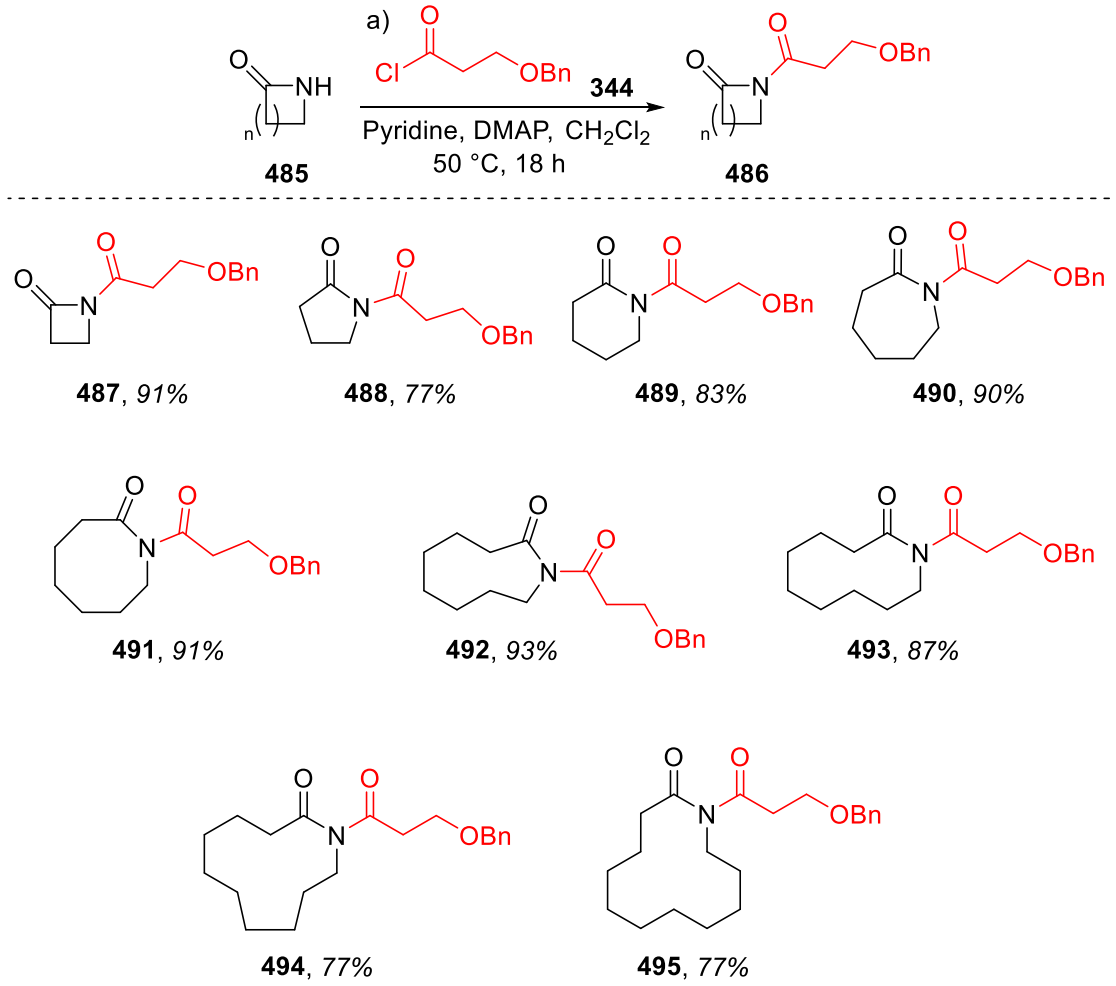
Scheme 4.3: Reaction optimisation for the incorporation of hydroxy acid chloride fragments into 13-membered lactam 361.

4.4 Ring Size Scope

4.4.1 β-Hydroxy Acid Series

After the successful incorporation of linear fragments into the 13-membered lactam, we decided to complete a systematic study of the effects of ring size in this reaction series. Initially, the effect of ring size on product formation was performed using β-hydroxy acid fragment **344**. Using ring sizes from 4- to 13-membered, lactams were *N*-acylated (using the standard reaction conditions), and the imide products **487**–**495** (scheme 4.4) were isolated by column

chromatography and characterised. As some of the starting lactams were not commercially available, these were made via Beckmann rearrangements of the ketones in the same manner as used previously (see Chapter 3).

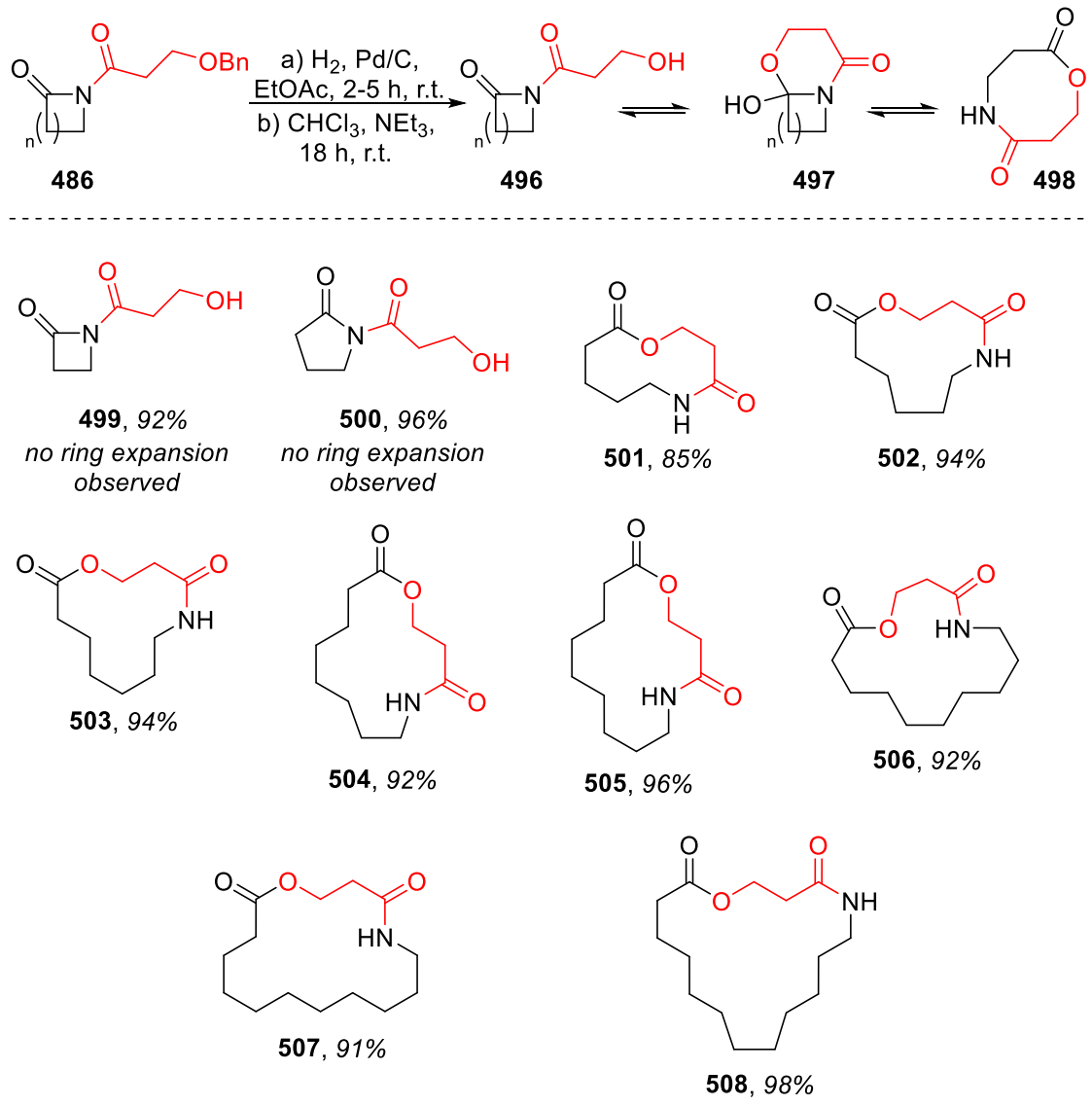


Scheme 4.4: Acylation of lactams of varying sizes using β-hydroxy acid chloride forming the corresponding imides.

Using the standard hydrogenolysis conditions previously developed, the alcohol groups of all imides **487**–**495** were deprotected and after passing through a Celite® plug (to remove palladium catalyst), the reaction mixtures were dissolved in chloroform, triethylamine was added and stirred for 18 h at room temperature. The results obtained were interesting and showed a clear trend. All examples underwent hydrogenolysis successfully however, isomerisation to the desired ring expanded product was not achieved for all ring sizes. For example, 4- and 5-membered lactams formed exclusively the primary alcohols **499** and **500** respectively. These products were heated, treated with acid and base (individually) and multiple different solvents were used in attempt to promote ring expansion. However, ring expansion was not observed and the primary alcohols degraded to the original lactams, presumably via hydrolysis of the imides. Considering the change in ring size required for these transformations, perhaps these

results were unsurprising, as the ring enlarged products would be the highly strained medium-sized rings (8- and 9-membered) and therefore the most difficult to make. This effect was also observed when incorporating amino acids into these small ring sizes. We propose that the ring expanded product is not the lowest energy isomer, and therefore cannot be accessed through this method assuming that the reactions are under thermodynamic control (computational analysis of these reactions will be discussed later).

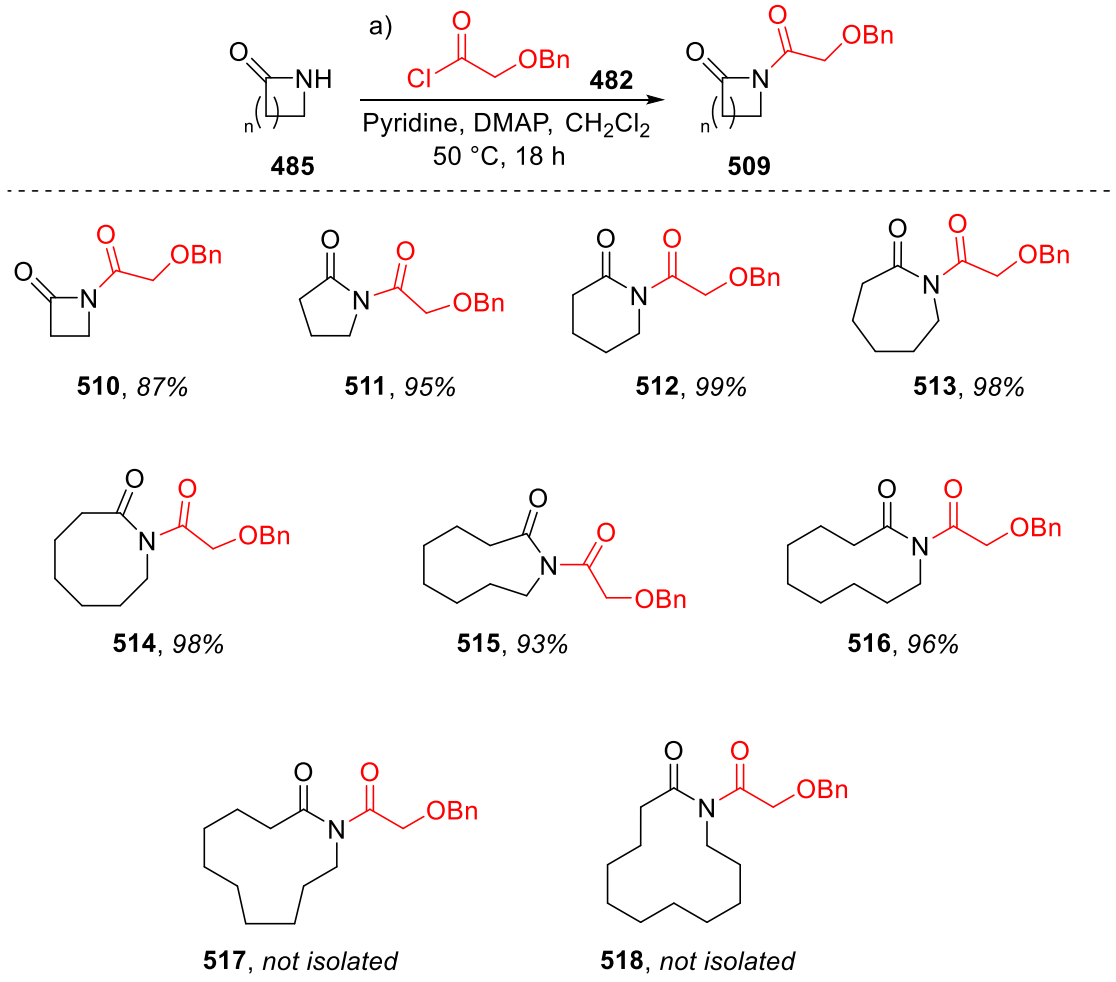
Pleasingly, 10- to 16-membered products (**501**–**508**) were formed in excellent yields without observation of the other isomers. Most examples existed as rotameric mixtures of the desired ring expanded products (in $CDCl_3$), due to the slow rotation of the C-N bond of the secondary amide. This resulted in different environments for most atoms, being observed in both their ^{1}H and ^{13}C NMR spectra.



Scheme 4.5: Ring size scope for β-hydroxy acids making ring expanded products 10- to 17-membered products.

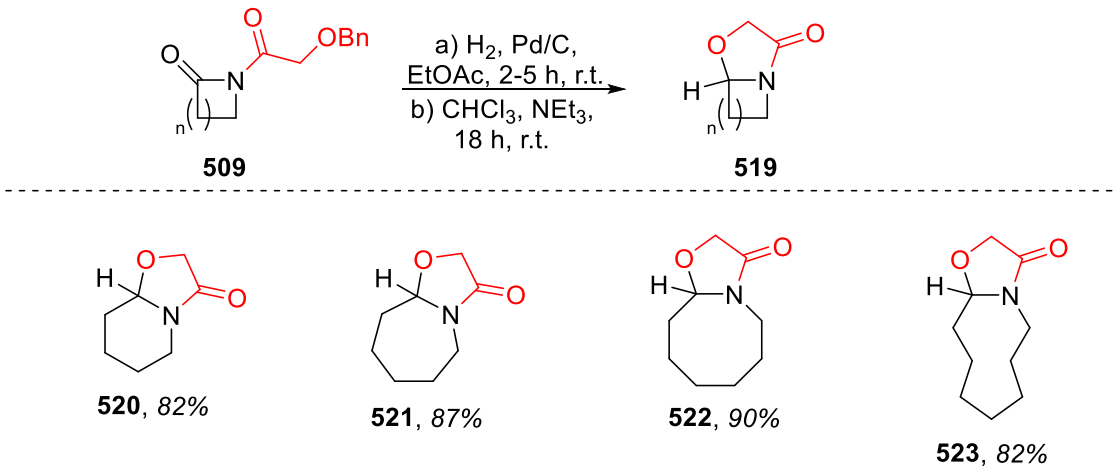
4.4.2 α-Hydroxy Acid Series

Following the success of the ring size study on the β-hydroxy acid series, we then examined the analogous α-hydroxy acid series and the effect of ring size on product formation. Similarly, we decided to separate the acylation and ring expansion steps so that we could examine each step, in isolation. Therefore, 4- to 13-membered lactams were acylated with the α-hydroxy acid chloride **482** to produce the corresponding imides **510**–**518** in good to excellent yields (scheme 4.6). For 11- and 12-membered derivatives **517** and **518**, the two steps were telescoped as the *N*-acylation proceeded to full conversion.



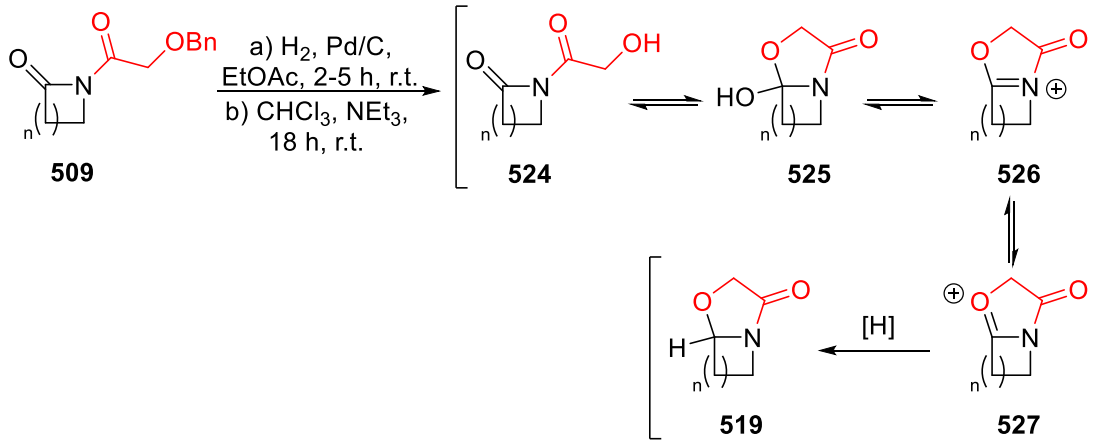
Scheme 4.6: Acylation of 4- to 12-membered lactams with α-hydroxy acid chloride 482.

Next, we turned our attention towards the deprotection/ring expansion of the different sized imides. However, using the previously employed hydrogenolysis conditions (catalysed by palladium on carbon in ethyl acetate), *N,O*-acetals (**520**–**523**, scheme 4.7) were synthesised rather than the ring expanded products.



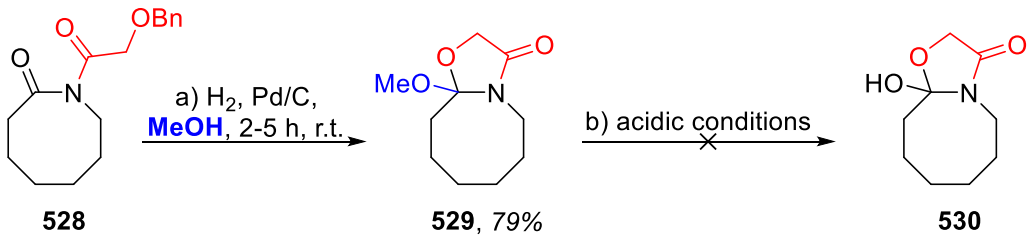
Scheme 4.7: Synthesis of N,O-acetals from a-hydroxy acid imides.

Although this is an interesting pathway to the synthesis of these compounds, it is not desirable when considering the designed ring expansion concept. A similar side-product was also created when using a Cbz protecting group strategy (see Chapter 3), and a similar mechanism is proposed. Thus, upon debenzylation of the imide **509**, the primary alcohol is formed which cyclises to form fused bicycle **525**. Dehydration then occurs to form *N*-acyl iminium **526**, which is reduced again to form the *N,O*-acetal **519**.



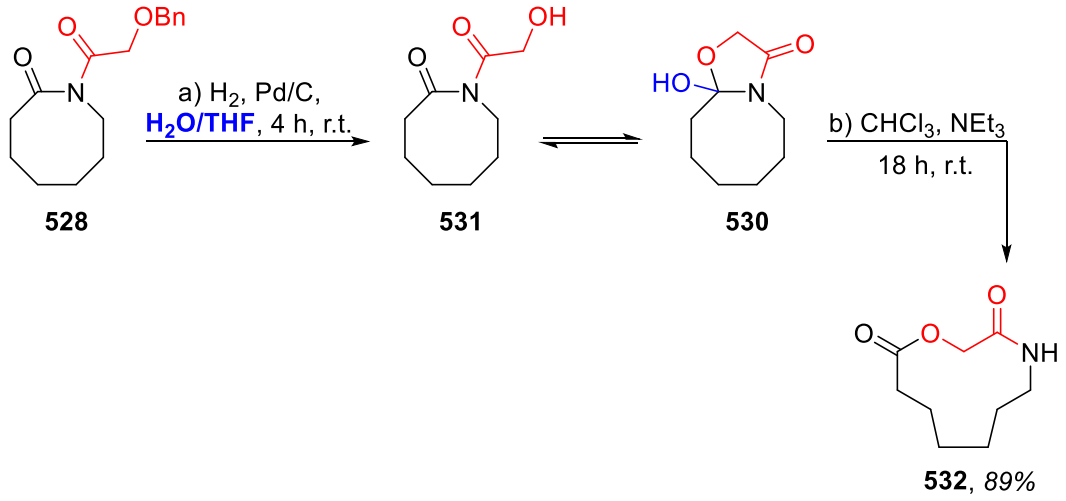
Scheme 4.8: Proposed mechanism of over-reduction to form N,O-acetals via N-acyl iminium intermediate.

We reasoned that if we could trap the proposed *N*-acyl iminium **526**, this would stop the formation of these reduced products. We therefore proposed that judicious choice of hydrogenolysis solvent could form an adduct, hindering the formation of the *N,O*-acetal. Thus, methanol was chosen as a hydrogenolysis solvent and an acetal adduct (**529**) was formed in excellent yield. Acid mediated cleavage of the acetal adduct was attempted, which would deliver a fused bicyclic isomer **530**, however all attempts were unsuccessful with heating causing degradation of the material.



Scheme 4.9: Hydrogenolysis of 8-membered imide using methanol as a solvent to form a hemi-acetal type product 528.

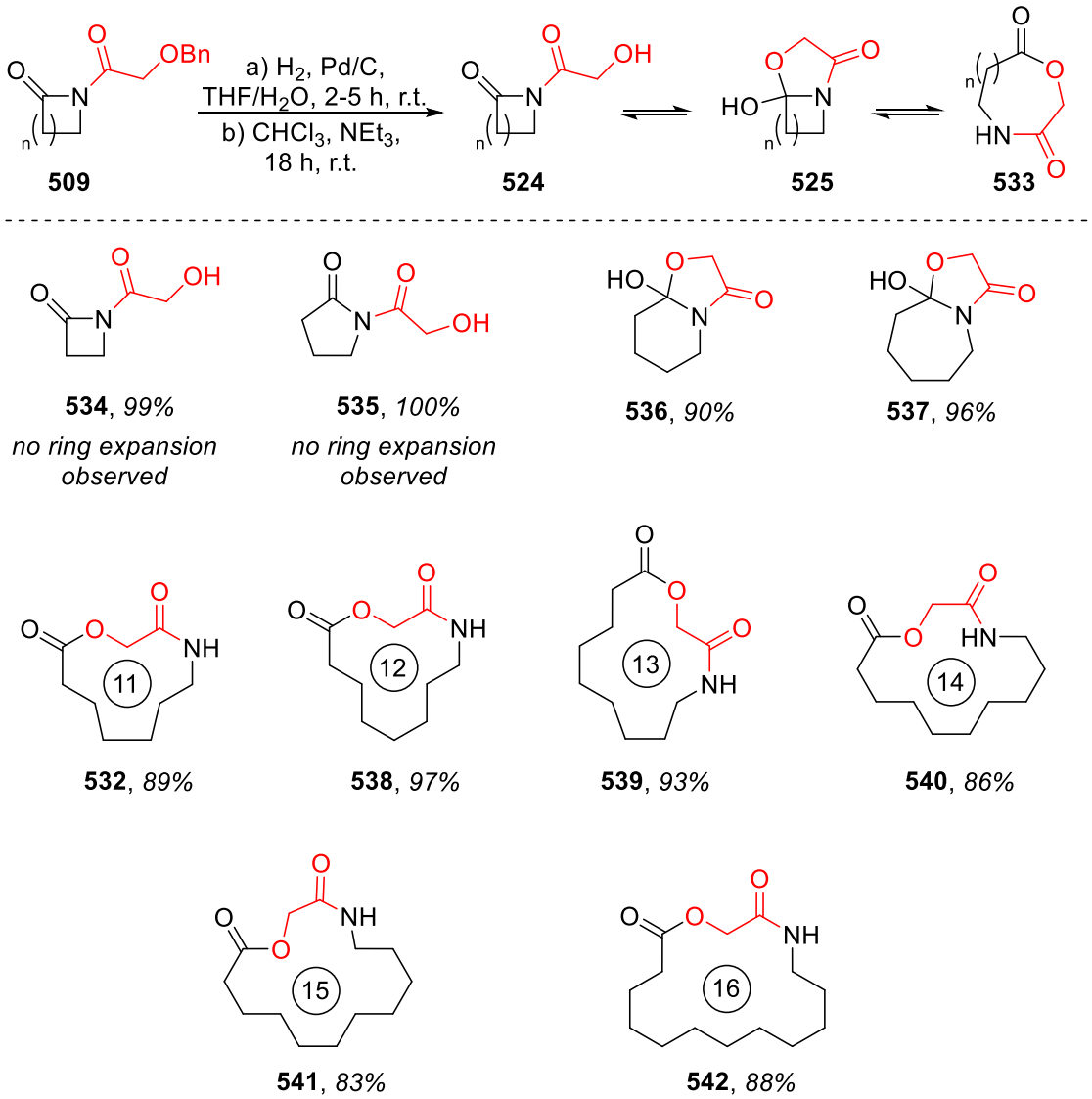
Although changing the solvent to methanol did not achieve ring expanded product, the results highlighted that the proposed *N*-acyl iminium intermediate **526** could be trapped with the hydrogenolysis solvent/reagent *in-situ*. Therefore, we used a mixture of THF and water in a bi-phasic system as the hydrogenolysis solvent, with the aim that water would act as the trapping agent and thus form bicyclic fused isomer **530**, which would be amenable to ring expansion. Using these altered conditions on the 8-membered imide **528**, a mixture of primary alcohol **531** and bicycle **530** was obtained after the hydrogenolysis step. This mixture was then dissolved in chloroform and reacted with triethylamine at room temperature, to exclusively form the 11-membered ring expanded product **532** in excellent yield (scheme 4.10).



Scheme 4.10: Synthesis of 11-membered ring expanded product using THF/H_2O as hydrogenolysis solvent system.

Happy that the reaction pathway was well understood, and that the new optimised conditions were suitable for successive ring expansions, the hydrogenolysis/ring expansion conditions were then applied to 4- to 13-membered imides **510**–**518** (scheme 4.6). Similar to the previous ring size study, not all imides underwent ring expansion. First, 4- and 5-membered examples formed the primary alcohols **534** and **535**; as in the β-hydroxy acid series, these were subjected to high temperatures and both acidic and basic conditions, but still did not ring expand. In contrast, 6- and 7-membered examples were formed as an inseparable mixture of all three isomers, with

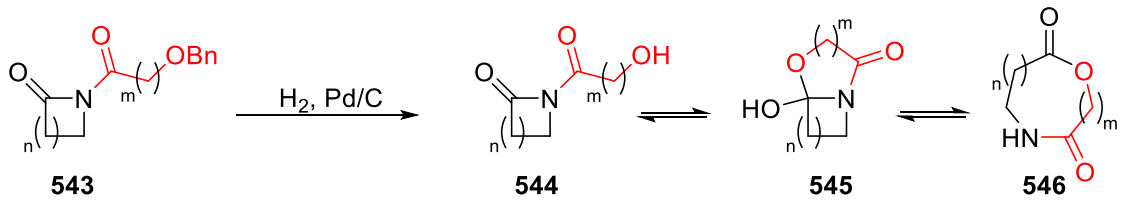
the major component being the fused bicycles **536** and **537** respectively. Via TLC, both of these mixtures appeared as a single spot under many different solvent systems, with attempts to purify the mixtures under different conditions being unsuccessful. This led us to believe that the three isomers exist in equilibrium. This was supported when the ratios of each isomer changed when different deuterated solvent were used. Perhaps it is unsurprising that these examples did not ring expand, as the ring enlarged products would be the challenging medium-sized rings, which have well-known difficulties of formation (which have been previously discussed). However, pleasingly all examples starting from ring sizes 8-membered or larger were successfully ring expanded, forming the desired lactones **532**–**542** in consistently excellent yields. From these results we concluded that as long as the change in ring size is thermodynamically favourable, then ring expansion works well.



Scheme 4.11: Ring size scope using a-hydroxy acids on 4- to 13-membered lactams.

4.4.3 Computational Chemistry

Based on the experimental findings, we believed that we were obtaining the thermodynamic product(s) in the ring expansion reactions, and proposed that a lack of thermodynamic driving force for ring expansion to occur was responsible for the unsuccessful examples. To support this, a postdoctoral researcher in the group (Dr Aggie Lawer), completed a relatively simple computational study using Density Functional Theory (DFT) at the B3LYP/6-31G* level of theory, based on a related study by Yudin and co-workers.[87] Thus, the relative Gibbs free energies of each isomer **544**, **545** and **546** were calculated for the 5–8-membered examples and these results are summarised in table 4.1. These calculations supported the results obtained experimentally. For the α-hydroxy acid series, the 5-membered imide form **544** was shown to be significantly lower in energy than the corresponding bicyclic **545** or ring expanded **546** forms. However, starting from the 8-membered imide, the ring expanded form **546** was significantly lower in energy than the alternate imide **544** or bicyclic **545** forms. The calculations also supported the synthetic results for the β-hydroxy acid series, where the ring expansion became favourable for ring of 6-members or higher, when the relative energy of the ring expanded form **546** was calculated to be lower than the other possible isomers **544** and **545**. The DFT calculations also predicted that the 5-membered imide form would be lower in energy than the ring expanded product **546**. The calculations were done at a relatively modest level of theory, and therefore we believe that the DFT calculations should not be used to make firm conclusions about bond angles, length, conformations because of the relative simplicity of the method. However, as a tool to estimate the probability of a ring expansion proceeding, we feel that this method has value, in advance of committing time and effort into new experiments.



543 **544** **545** **546**

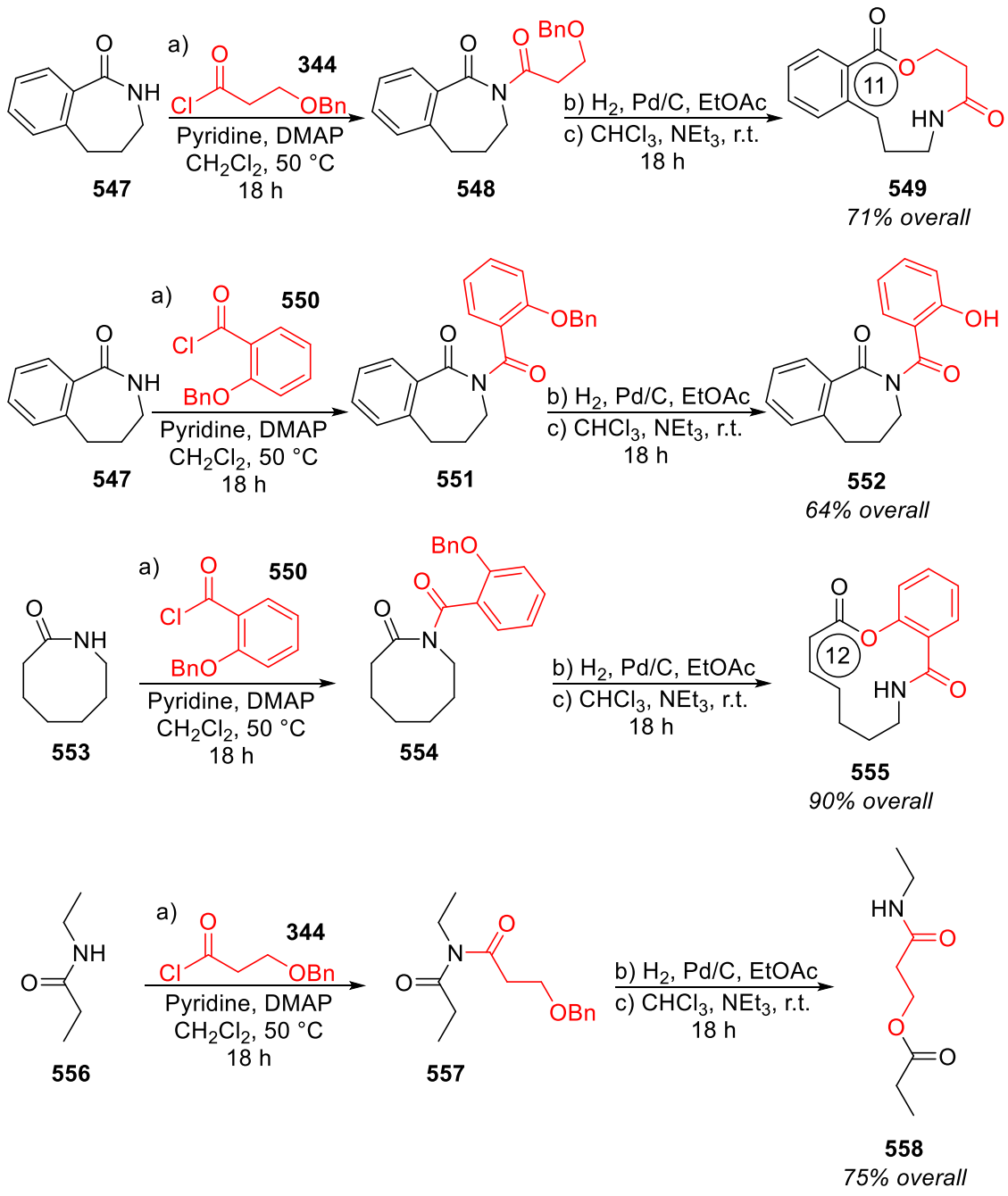
n	m	Ring Sizes	544	545	546
			$\Delta G°_{rel}$ (kcal/mol)		
2	1	5 → 8	**0.0**	13.4	10.3
5	1	8 → 11	6.3	8.9	**0.0**
2	2	5 → 9	**0.0**	11.7	4.1
3	2	6 → 10	2.4	8.1	**0.0**

Table 4.1: Results of computational calculations showing the relative Gibbs free energies of each isomers with varying ring size and linear fragment length.

4.5 Functionalised Examples

With better understanding of which examples would be likely to ring expand based on ring size, we turned our attention towards more complex and medicinally interesting products. Initially, the backbone of the lactam was functionalised to introduce a fused aromatic ring, which would increase the rigidity of the system. Thus, benzannulated lactam **547** was acylated with β-hydroxy acid chloride **344** using the standard conditions, and then hydrogenolysis and subsequent ring expansion formed 11-membered product **549** in high yield. However, when the same benzannulated lactam was treated with phenolic acid chloride **550**, no ring expansion was observed, with phenol isomer **552** isolated in good yield. We propose that increasing the rigidity of both lactam and linear fragment does not permit for a kinetically favourable geometry within the transition state, and therefore was not thermally accessible under the reaction conditions imposed. An alternative could be that the reaction was slow due to the decreased nucleophilicity of the phenol, and prolonged reaction conditions would deliver the ring enlarged product, however this was not tested. Using more flexible 8-membered lactam **553**, the phenol acid chloride **550** was incorporated into the cyclic system in excellent yield, with only the ring enlarged product being observed.

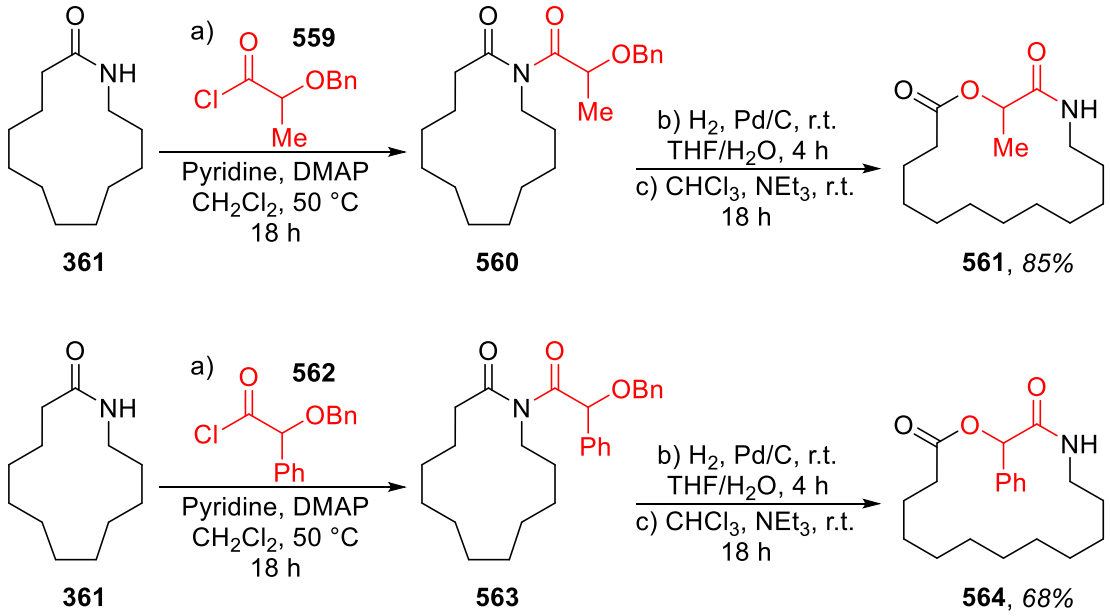
We also extended the methodology past ring expansion, with linear amide **556** successfully being *N*-acylated with β-hydroxy acid chloride **344** and under the standard conditions, hydrogenolysis led to the β-hydroxy acid fragment being inserted into the middle of this linear amide system. Importantly, the insertion operates via an intramolecular cyclisation/extension sequence and therefore the linear amide is not broken into two molecules. Thus, it may be possible to incorporate hydroxy acid fragments into the middle of more complex linear amides, and in the future, there may be potential for this methodology to also be used to modify linear peptides.



Scheme 4.12: Synthesis of functionalised examples via ring expansion/incorporation.

Changes to the linear fragment were examined next, with three different hydroxy acid chlorides already proven to be successfully introduced using this method. Incorporating a larger degree of steric hindrance to the linear fragment was desirable, as this would allow for the derivatisation of the relatively simple hydroxy acid chlorides used so far. Therefore, two different hydroxy acid chlorides were utilised to investigate the reaction tolerability. Methyl and phenyl substituted α-hydroxy acid chlorides **559** and **562** were used to acylate the 13-membered lactam **361**; the *N*-acylation using phenyl substituted hydroxy acid chloride **562** did not proceed to full completion, with the yield in the final isolated product reflecting this. Both imides **560**

and **563** were reacted under the standard hydrogenolysis conditions and ring expanded to generate 16-membered ring enlarged products **561** and **564** in good and excellent yields. With both examples, no over-reduction or side products were observed, with the yields largely reflecting the degree of conversion during the *N*-acylation step.



Scheme 4.13: Synthesis of ring expanded macrocycles incorporating more sterically encumbering hydroxy acid chlorides.

4.6 Successive Ring Expansion

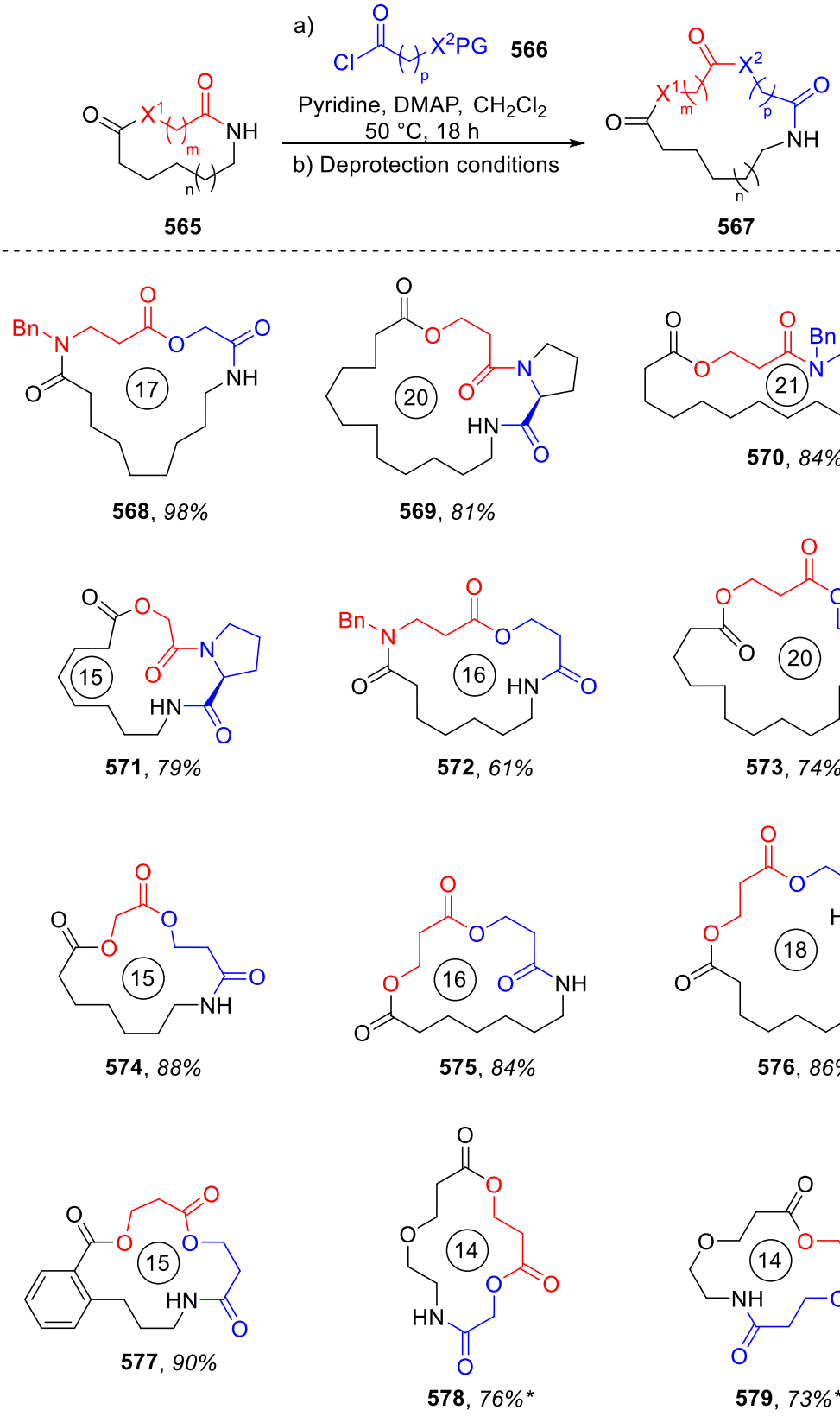
4.6.1 Double Ring Expansion Expansions

Having developed what appeared to be a robust and general protocol that had been used across a broad range of substrates, we attempted to expand our products for a second time. The success of this stage of the project was crucial, as multiple ring expansions would massively increase the number of diverse macrocycles that could be accessed via this method. Pleasingly, the acylation of these ring enlarged lactones was far more successful that the lactam counterparts (discussed in more detail in Chapter 6) and 12 macrocycles were synthesised with typical yields of 80% (seen in scheme 4.14). Many different macrocyclic ring sizes (14- to 21-members) were formed using the standard method with no difficulty, which was expected as all examples proceed through fused 5- or 6-membered transition states and intermediates. Many different linear fragments were utilised, with amino acids also being introduced in either order. Being able to introduce both amino acids and hydroxy acids into macrocycles in sequence was a major achievement, with the number of accessible macrocycles being greatly increased. We also realized that with these compatible procedures, cyclodepsipeptides (a class of natural product

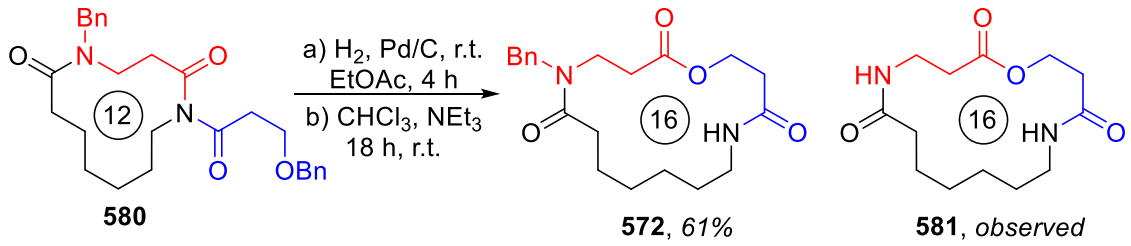
which contain both a lactam and lactone in the molecule) were accessible, which are currently receiving medicinal interest.[129,130]

Natural and non-natural amino acids have been incorporated in conjunction with hydroxy acids to produce mixed lactone/lactam systems in high to excellent yields (**568**–**572**). All the proteinogenic amino acids derivatives, which contain a stereogenic centre were used as enantioenriched starting materials and all the products had a significant non-zero $[\alpha]_D$ value, proving that full racemisation did not occur; we cannot rule out partial epimerisation, although we believe it to be unlikely based on the reaction conditions employed. Lactonic systems were also prepared whereby two hydroxy acids were inserted in succession (**573**–**579**). Different hydroxy acids were commonly used in different orders to show controlled sequential ring expansion rather than a polymerisation type pathway. Linear fragments have also been inserted into more functionalised examples such as benzannulated system **577**, and ether linked examples **578** and **579**. Macrocycle **575** was completed on larger scale (10 mmol) with no appreciable loss in yield. Example **572** was isolated in a lower than expected yield due to debenzylation from the amide resulting in side product **581** (scheme 4.15). This was surprising, as the rate of debenzylation from an oxygen is usually much faster than from a nitrogen (due to electronegativity difference), however in this example the two rates were much closer.

We believe that the macrocycles produced demonstrate that this new technique is compatible with a wide array of starting materials, not limited to those which we have tested.



Scheme 4.14: Successive Ring Expansion examples of inserting both hydroxy acids and amino acids. *Examples made by Dr. Aggie Lawer. Deprotection conditions: (A) i) H_2, Pd/C in THF/H_2O, 2-4 h, r.t. then ii) $CHCl_3$, NEt_3, 18 h, r.t. (for X^2PG = OBn, p = 1); (B) i) H_2, Pd/C in EtOAc, 4 h, r.t. then ii) $CHCl_3$, NEt_3, 18 h, r.t. (for X^2PG = OBn, p = 2); (C) DBU, CH_2Cl_2, 18 h, r.t. (for X_2PG = NFmoc).

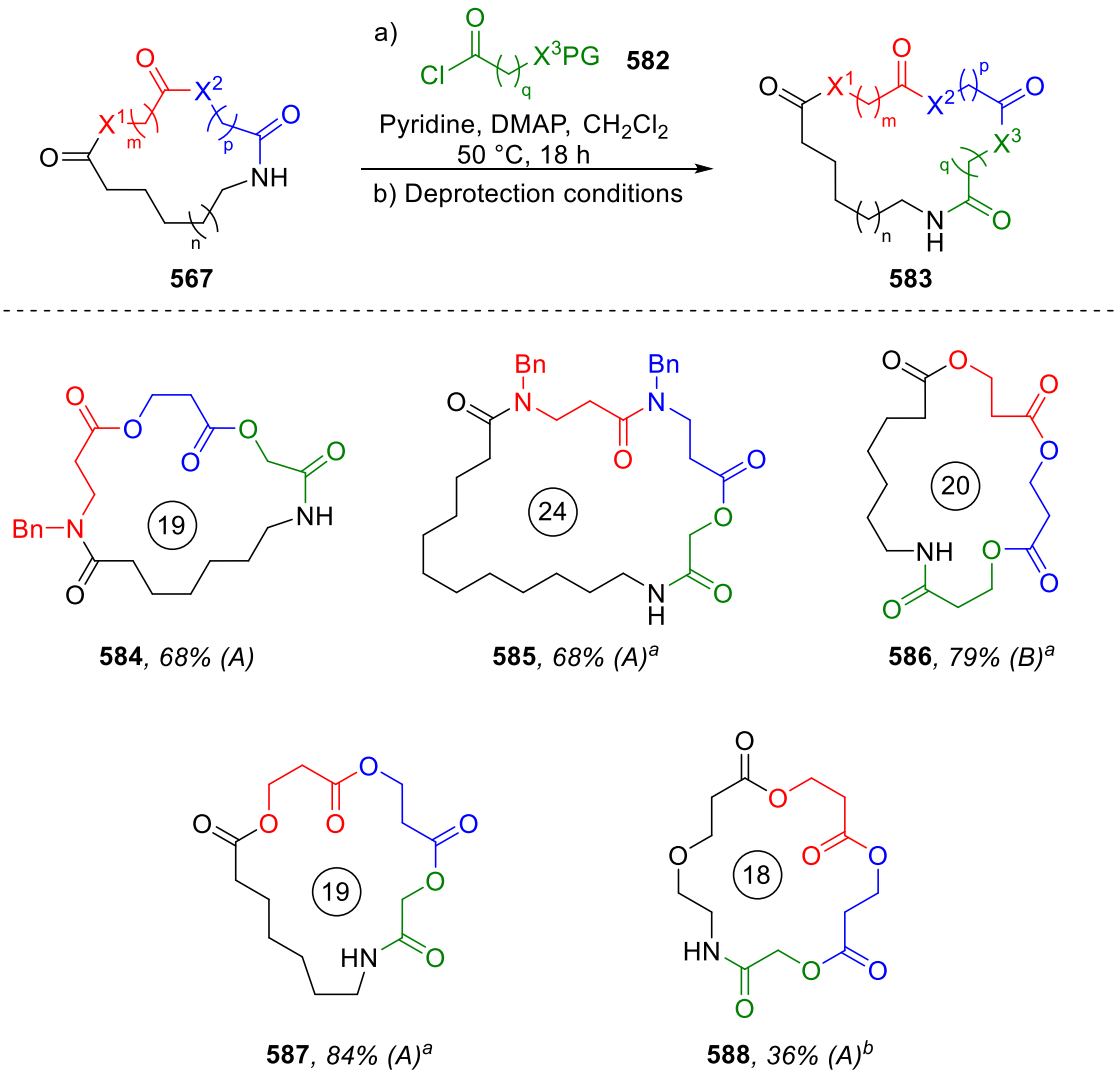


Scheme 4.15: Debenzylation side reaction during successive ring expansion of 572.

4.6.2 Triple Ring Expansion Examples

With the success of making so many macrocycles by performing two consecutive ring expansions, we wanted to extend the methodology further to complete three sequential ring expansion reactions. Once again, it was crucial that different ring sizes were produced and many different linear fragments were utilised to demonstrate the applicability of the method. To our delight, 5 macrocyclic examples were prepared with typical yields of 70%, with no side product formation (see scheme 4.16).

Similar to the previous section, we were able to incorporate both amino acids and hydroxy acids into the same molecule as the methods are compatible. Thus, mixed lactam/lactone systems were produced in good yields (**584** and **585**), with the unnatural β-amino acid being incorporated in both molecules. Both simple, linear α- and β-hydroxy acids were used in varying orders, in all of these examples, showing that these linear fragments can really be 'chopped and changed' at will. Ring expansions using only hydroxy acid chlorides have also been completed making tri-lactone systems in equally high yields (**586** and **587**). The reactions to make **586** and **584** were also repeated on ≥5 mmol scale (with no significant loss in yield) to demonstrate the scalability of these reactions. Finally, highly oxygenated macrocycle **588** was produced (by Dr Aggie Lawer), demonstrating that heteroatoms can be introduced into the backbone and the methodology still works (albeit with a dramatically reduced yield). In general, the *N*-acylation step in these third ring expansion reactions was more difficult, probably owing to less reactive conformations being adoptable, and therefore additional equivalents of the acid chloride were added to improve conversion. This highly oxygenated example (**588**) showed a severely retarded rate of acylation, with an extra 4.5 equivalents still only leading to a 36% yield overall.

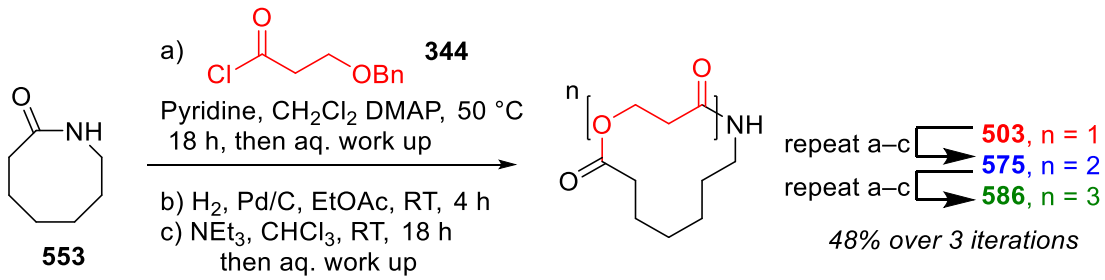


Scheme 4.16: Synthesis of macrocycles by three successive ring expansions with both amino and hydroxy acids. Deprotection conditions: (A) i) H_2, Pd/C in THF/H_2O, 2-4 h, r.t. then ii) $CHCl_3$, NEt_3, 18 h, r.t. (for X^3PG = OBn, q = 1); (B) i) H_2, Pd/C in EtOAc, 4 h, r.t. then ii) $CHCl_3$, NEt_3, 18 h, r.t. (for X^3PG = OBn, q = 2). [a]An additional 1.5 equivalents of acid chloride was used. [b]An additional 4.5 equivalents of acid chloride were used.

4.6.3 Iterative Assembly Line Synthesis

With all the examples which have been previously described, each expanded ring has been isolated after a single operation. Therefore, when completing three successive ring expansions three purifications (by column chromatography) were completed to identify and characterise the individual products. As this can be time consuming, we decided to test whether we could perform multiple ring expansions in sequence. As the chemistry is relatively simple, we thought that we could highlight this practicality in an iterative assembly line type synthesis. Starting from commercially available 8-membered lactam **553**, the standard telescoped ring expansion procedure was performed with β-hydroxy acid chloride **344**. After the first ring expansion iteration, an acidic work up was completed to remove excess triethylamine and hydroxy acid residues. A second and third iteration were then completed with β-hydroxy acid chloride **344** to

form the 20-membered macrocyclic tri-lactone **586**. A single purification was performed after all iterations were complete, to isolate the ring enlarged product in an overall 48% yield. This unoptimised process significantly expedited the synthesis of this macrocycle, and we believe that the freedom to rapidly install precise sequences could have important consequences as an enabling technology in the design of new macrocyclic pharmaceuticals.



Scheme 4.17: Synthesis of 20-membered tri-lactone 586 via an iterative assembly line.

4.7 Chapter Summary

Successive ring expansion reactions have been completed, whereby hydroxy acid derivatives have been incorporated into lactams, typically in high to excellent yield. Both 3- and 4-atom linear fragments have been introduced using a benzyl protecting group, with a novel route to *N,O*-acetals also being discovered. Functionalised examples have been examined, producing a diverse array of macrocycles, with amino acid incorporation (described in Chapter three) being compatible with this lactone forming variant.

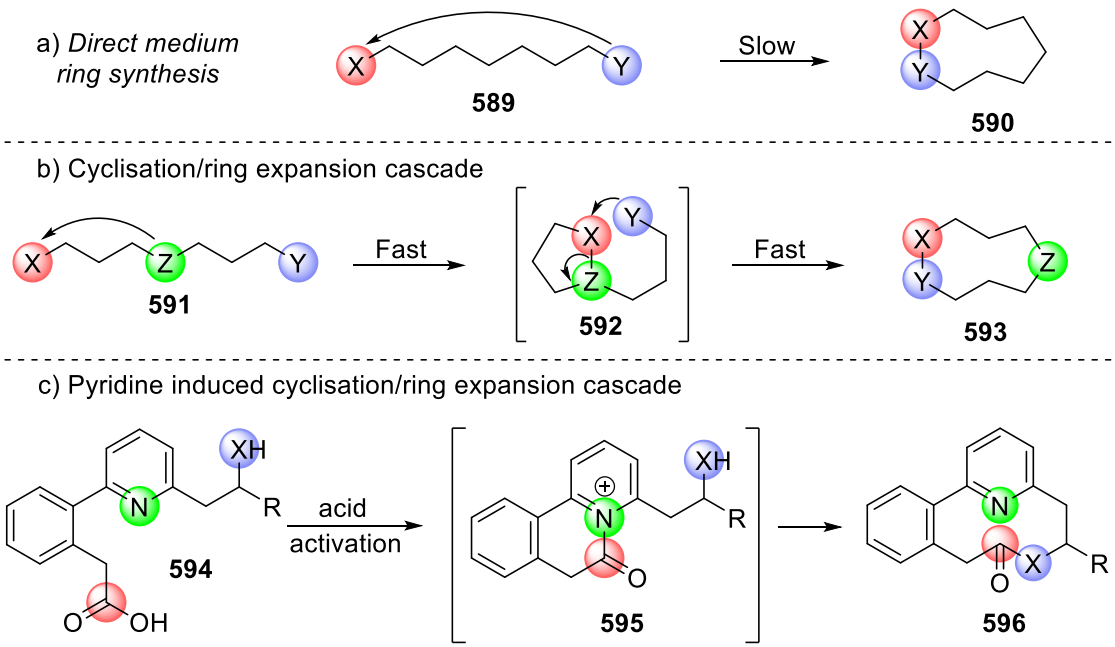
The work described in this Chapter is the subject of one publication.[131]

Chapter Five: Nitrogen-Induced Cyclisation/Expansion Cascade

5.1 Cyclisation/Expansion Cascade Concept

Medium-sized rings have recently received a resurgence in medicinal interest,[132,133] however can be difficult to prepare via the cyclisation of a linear precursor (**589** → **590**, scheme 5.1a). Destabilising transannular strain (Prelog) in addition to the loss of entropy during cyclisation, usually impede the formation of the product. Owing to the difficulties of the synthesis of this class of molecule (see Chapter one), forcing conditions are typically required,[134] hence there is a requirement for alternative milder approaches to the synthesis of medium-sized rings.

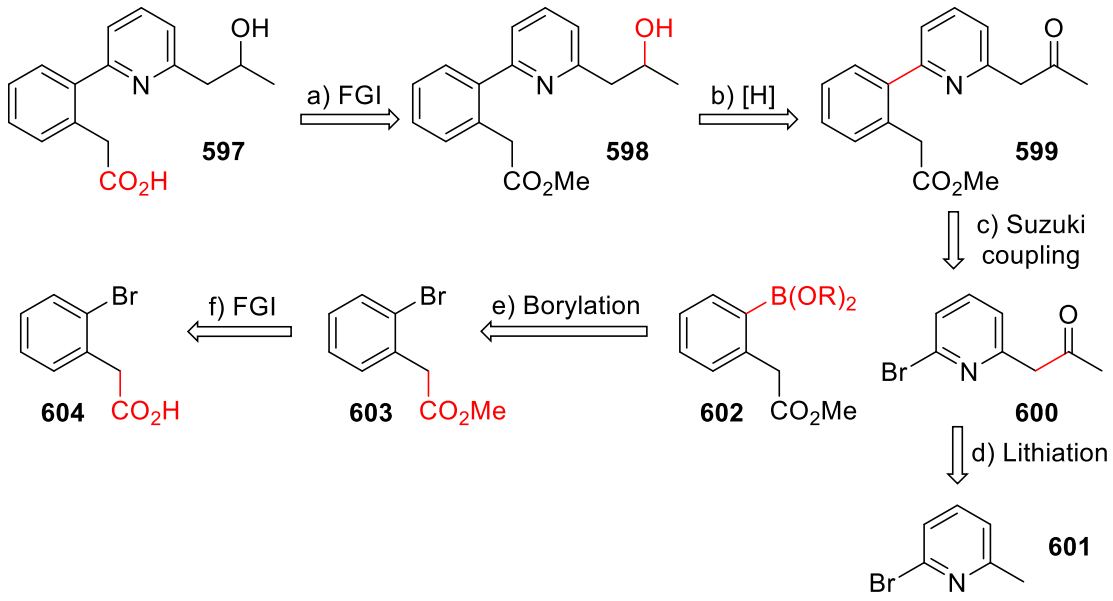
All of the ring expansion methods that have been described previously have started from a cyclic starting material, however, in this chapter, a cyclisation/ring expansion cascade is described in which functionalised medium-sized rings can be accessed directly from a linear precursor. The key design feature when starting this project was to avoid kinetically unfavourable medium-sized ring cyclic transition states/intermediates, by performing a cyclisation followed by a ring expansion with both steps proceeding through 5- , 6- or 7-membered rings. We proposed that by incorporating a nucleophilic motif into the linear starting material (**591**, scheme 5.1b), a slow/difficult cyclisation process could be improved by breaking it down into two easier parts. To do this, a pyridine-based motif was designed to facilitate the lactonisation/lactamisation of a linear precursor (**594**, scheme 5.1c) via a proposed *N*-acyl pyridinium intermediate **595**, with the pyridine effectively acting as an internal nucleophilic catalyst.



Scheme 5.1: a) Direct synthesis of medium-sized ring. b) Cyclisation/ring expansion cascade sequence using an internal nucleophilic motif. c) Pyridine induced cyclisation/expansion cascade.

5.2 Preliminary Work and Optimisation Results

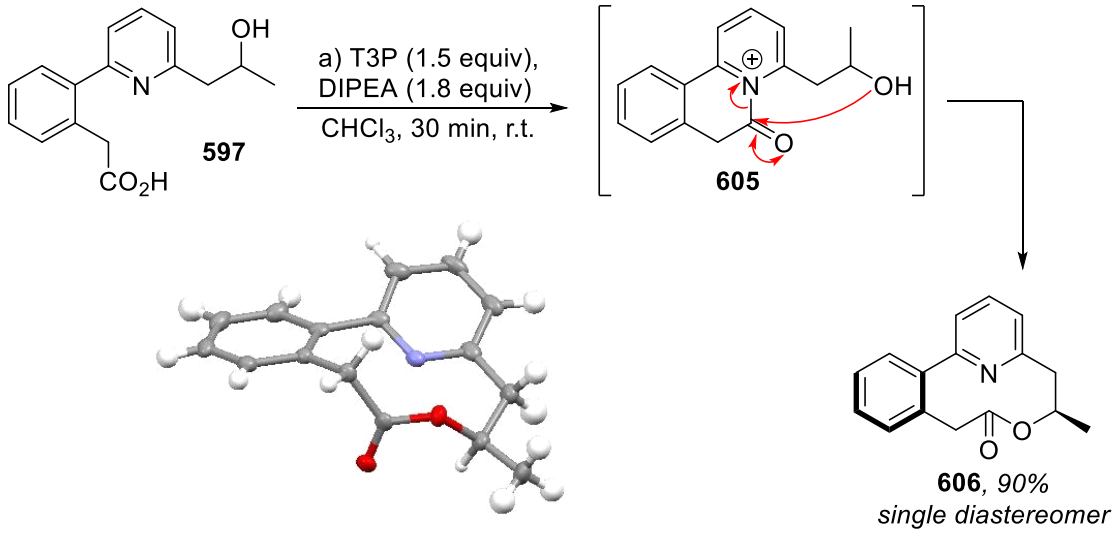
Work completed in the Unsworth lab by Dr Aggie Lawer established a synthetic route to the hydroxy acid starting material (**597**, scheme 5.2) via a six-step procedure. Retrosynthetic analysis of the starting material first required functional group interconversion of the carboxylic acid to ester **598**. Then, alcohol **598** could be formed via reduction of ketone **599**, which in turn can be synthesised via Suzuki-Miyaura coupling of both aryl sub-units **600** and **602**. The pyridine unit was synthesised via a lithiation, followed by trapping with the corresponding Weinreb amide delivering the ketone motif. The aryl boronic ester was made via palladium-catalysed borylation of the aryl bromide **603** and finally conversion to the carboxylic acid **604**, which was a cheap and commercially available building block.



Scheme 5.2: Retrosynthetic analysis of linear starting material 597 via six-step sequence completed by Dr. Aggie Lawer.

Next, the cyclisation/expansion cascade was optimised and it was found that T3P (propanephosphonic acid anhydride) in chloroform with diethylpropylamine (DIPEA) achieved the highest yield of the desired 10-membered lactone **606**, with the added benefit that all the by-products could be removed by aqueous work up. Serendipitously, the product was formed as a single diastereomer, with the relative stereochemistry supported by an X-ray crystal structure (seen in scheme 5.3). An acute angle between the two aryl units can be seen, presumably due to restricted C-C bond rotation, which results in an axis of chirality, making the mirror images non-superimposable. This is called atropisomerism, and is more commonly seen on substituted bi-aryls such as BINOL. This means that, there are two elements of chirality in the 10-membered lactone **606** (the axial chirality and the point stereogenic centre) and therefore two diastereomers can be produced. However, only a single diastereomer was observed and

therefore we reasoned that the relative stereochemistry must be controlled during the cascade reaction.

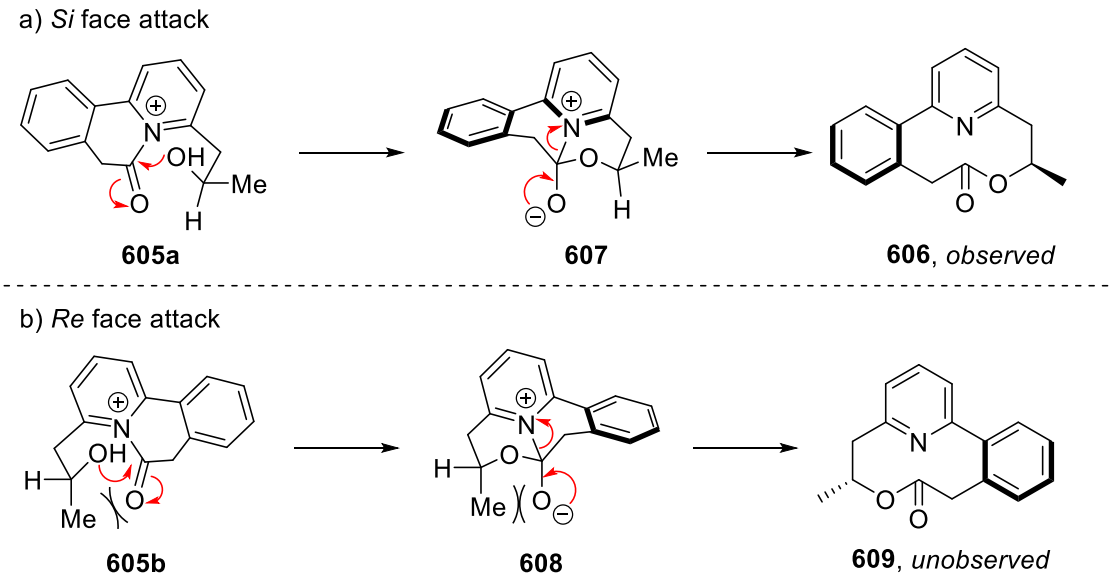


Scheme 5.3: Synthesis of 10-membered bi-aryl lactone 606 in excellent yield via cyclisation/expansion cascade by Dr. Aggie Lawer.

5.3 Origin of Diastereoselectivity

It was proposed that the key to the diastereoselectivity was the point stereogenic centre α- to the alcohol. After formation of the *N*-acyl pyridinium intermediate **605**, a *pseudo* boat-boat conformation can be drawn for the tetrahedral intermediate (scheme 5.4) which via *Si*-face attack, places the methyl group in what we propose to be a relatively favourable *pseudo*-equatorial position **607**. However, for *Re*-face attack to occur, the methyl group would be positioned in a *pseudo*-axial position (**608**), which we predict to be higher in energy, thus increasing the relative energy of this intermediate and encumbering the formation of this diastereomer.

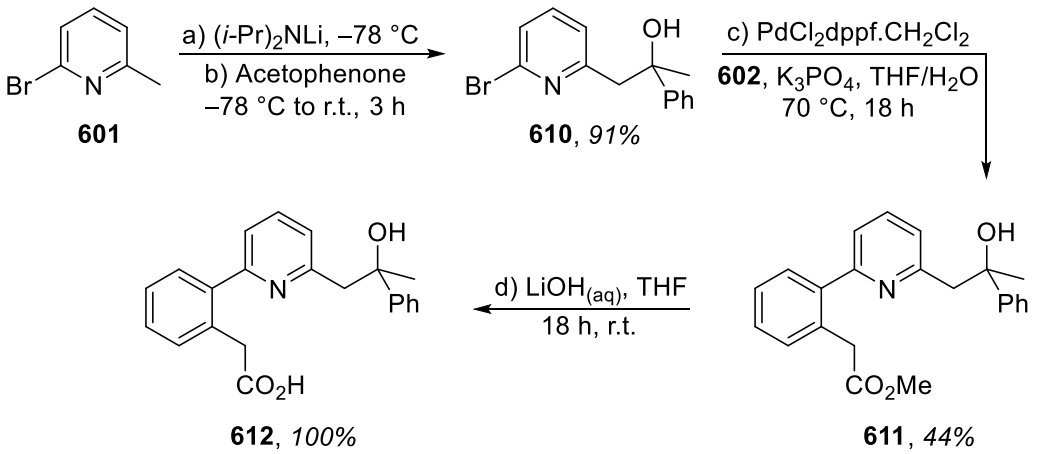
An alternative explanation for the diastereoselectivity observed, could originate from a thermodynamic model. This would require the strained 10-membered lactone product to be reversibly formed and a significant difference in Gibbs energy between the two possible diastereomers resulting in the observed high selectivity. Owing to the mild conditions and short reaction time of this transformation, we postulate that a kinetic model is more likely to be operating in the examples described, however we cannot currently exclude a thermodynamic explanation.



Scheme 5.4: Proposed origin of diastereoselectivity through key transannular interactions in tetrahedral intermediate.

5.4 Examining Diastereoselectivity

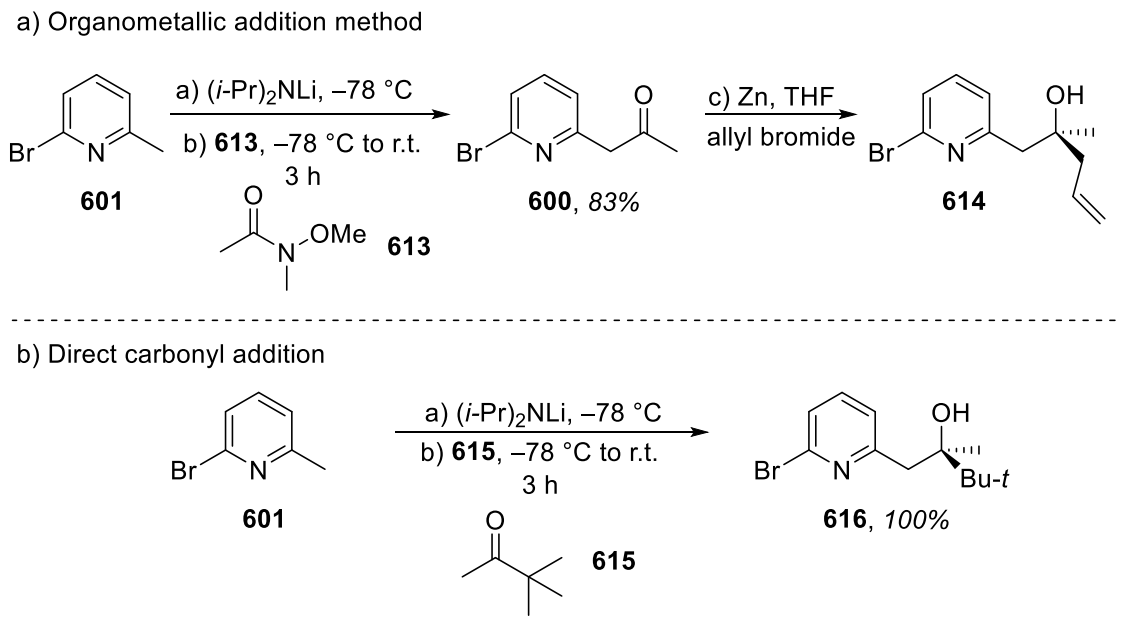
After proposing a model for the diastereoselectivity, a series of chiral tertiary alcohols were investigated with varying substituent sizes to better probe the stereoselectivity. We postulated that when both substituents are of similar size, the diastereoselectivity would be lower as the key steric interaction would be very similar between both *Si*- and *Re*-faces. Thus, via lithiation and trapping with acetophenone (**601** → **610**), pyridine **610** was synthesised in excellent yield. From this building block, linear precursor **612** was synthesised in a similar fashion to those presented previously.



Scheme 5.5: Synthesis of tertiary alcohol linear precursor 612.

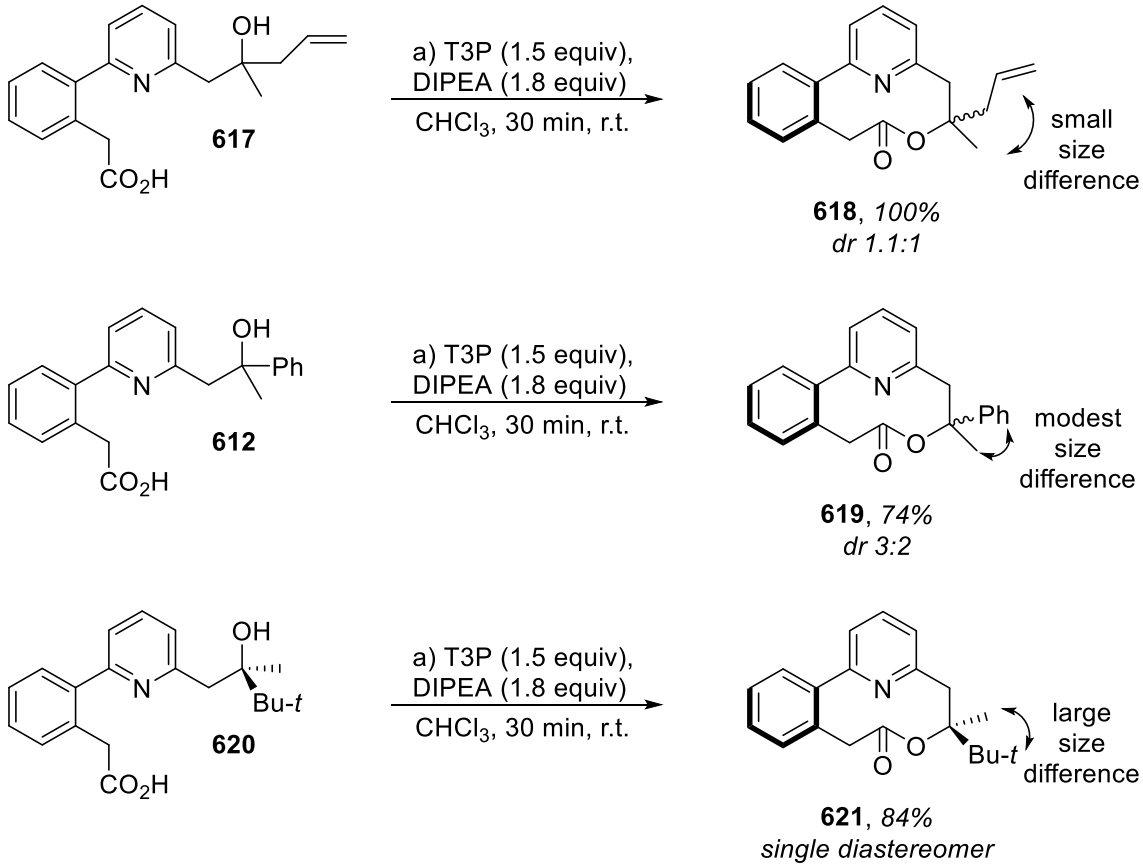
Direct addition of the metallated pyridine intermediate (not shown) into ketones and aldehydes, had been previously unsuccessful for other Unsworth groups members. Therefore, to make tertiary alcohols, ketone **600** (scheme 5.6, synthesised using a Weinreb amide) was reacted with

an organometallic reagent to furnish the desired alcohol. The allyl variant **614** was synthesised via this route however, it was not possible to make the *t*-butyl variant **616** using this method. We believed that direct addition into pinacolone **615**, would be plausible, and pleasingly we obtained the desired tertiary alcohol, in excellent yield, which was previously inaccessible.



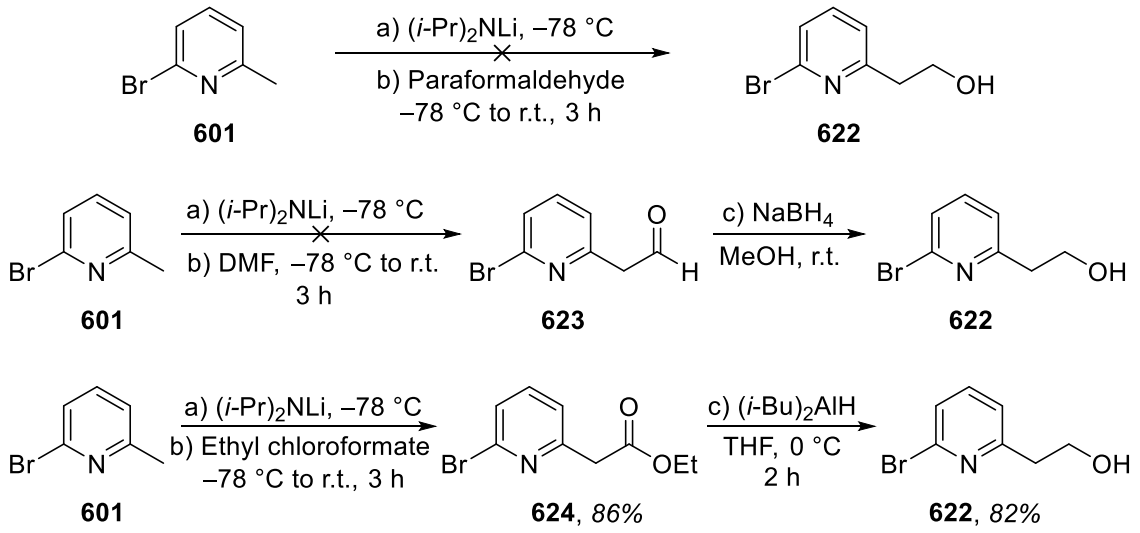
Scheme 5.6: Synthesis of tertiary alcohol from the corresponding pyridine. a) Two step organometallic addition method used previously. b) One step direct addition into ketones/aldehydes.

With tertiary alcohols in-hand, the linear precursors were synthesised and the key cyclisation/expansion cascade reaction was completed (scheme 5.7). Three tertiary alcohols **617**, **612** and **620** were tested and pleasingly all examples furnished the desired medium-sized rings in high to excellent yields. The diastereoselectivity results were also interesting, with varying amounts of selectivity observed. Allyl product **618** was isolated in a 1.1:1 diastereomeric ratio, suggesting that the methyl and allyl substituents are relatively similar in size/steric hindrance which is supported by having similar A-values. A small increase to a 3:2 diastereomeric ratio was observed for the phenyl product **619**, with a difference in A-value of 1.3. Only upon increasing the size of one substituent to a *t*-butyl group (**621**), was complete diastereoselectivity returned and a single diastereomer obtained, with a difference in A-value of 3.2. These results clearly show that the relative size of substitution at this position directly influences the diastereoselectivity.



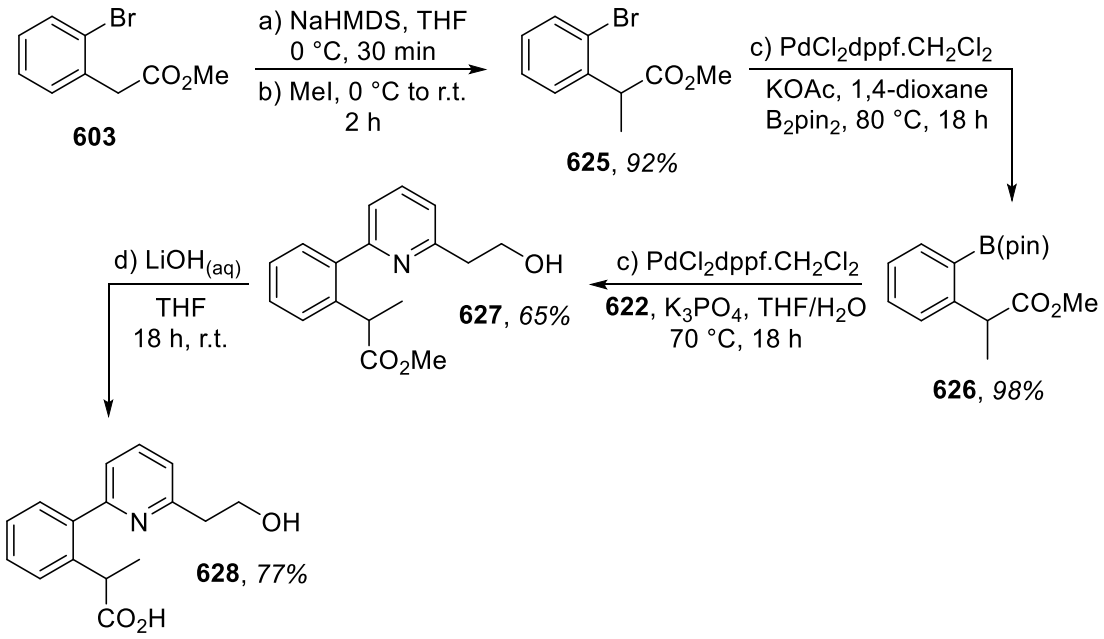
Scheme 5.7: Cyclisation/expansion cascade of tertiary alcohol linear starting materials to examine the diastereoselectivity.

In order to support this hypothesis further, we examined the effect of moving the stereogenic centre to the other two aliphatic positions in the ring. To do this, we required primary alcohol **622**, however, attempted lithiation of **601** and trapping with paraformaldehyde was unsuccessful and delivered only starting material (scheme 5.8). We realised that DMF could be used as the electrophile, delivering aldehyde **623** upon acidic work up which could be reduced to the primary alcohol. However, upon repeated attempts (using dried DMF) an enamine was believed to be produced, which degraded upon acidic workup when trying to isolate the desired aldehyde **623**. Finally, use of ethyl chloroformate successfully produced the ester **624**; in this example, the acidic proton between the ester and pyridine functionalities in the product is removed by the organometallic reagent (lithiated pyridine) forming an enolate, which prevents a second addition. Consequently, multiple equivalents of the organometallic reagent are required as it acts as both nucleophile and base, however can be easily recovered if desired. Conversion of the ester **624** to primary alcohol **622** was completed, in excellent yield, using DIBAL at 0 °C.



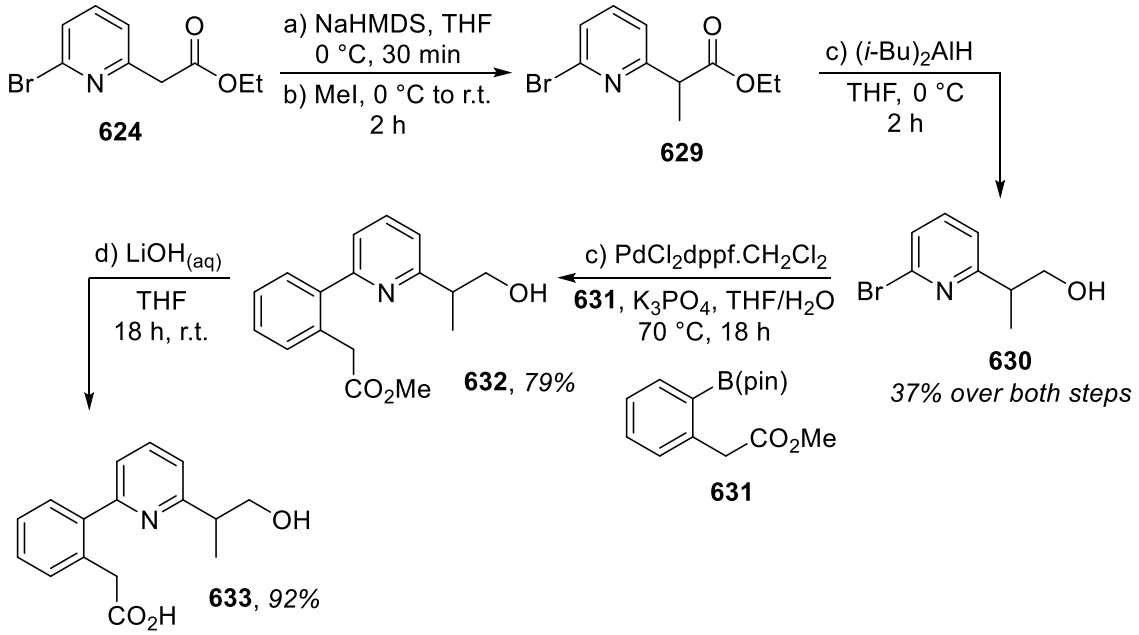
Scheme 5.8: Different synthetic methods attempted to make the primary alcohol 622.

After accessing the primary alcohol **622**, a boronic ester fragment **626** was required to perform a Suzuki-Miyaura cross coupling with the desired stereogenic centre incorporated. Despite its relative simplicity, the boronic ester was not commercially available and therefore was synthesised by the following procedure (scheme 5.9). Thus, bromo ester **603** was treated with methyl iodide using a modified literature procedure[135] to form methylated bromo ester **625**. During this reaction, *O*-methylation was also observed to provide an unwanted side product, which was removed by column chromatography. Palladium-catalysed borylation was then performed to deliver the pinacol boronic ester **626**. Bringing together both fragments, Suzuki-Miyaura cross coupling (with previously optimised conditions by Dr. Aggie Lawer) delivered the hydroxy ester **627**. Finally, hydrolysis was performed to produce carboxylic acid precursor **628**.



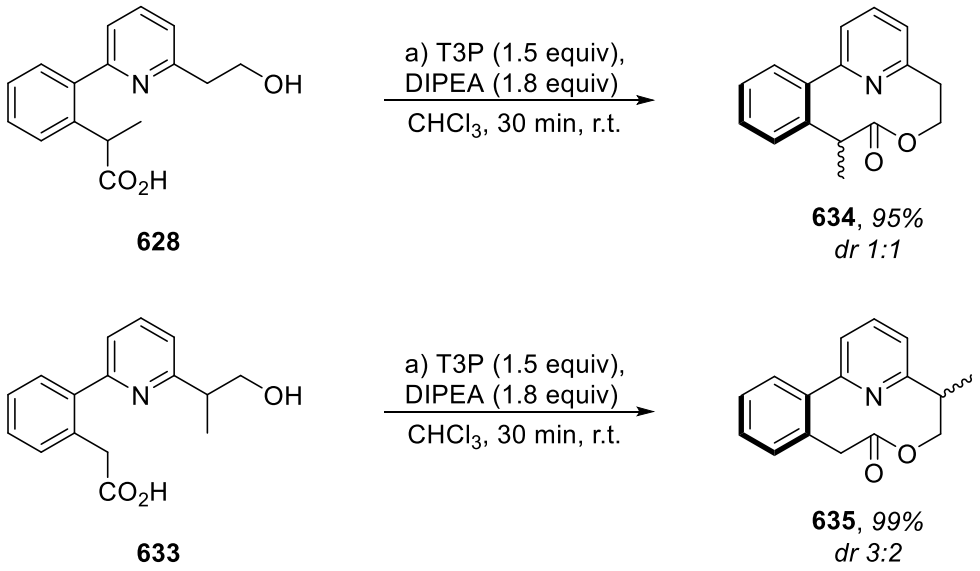
Scheme 5.9: Synthesis of linear fragment with stereogenic centre moved to the α-position of the carboxylic acid.

Introducing the stereogenic centre in the other position (α- to the pyridine) was synthetically simpler with few steps required to make the linear precursor (scheme 5.10). Starting with methylation of the pyridine ester **624** using the conditions stated above. DIBAL reduction formed primary alcohol **630** with the stereogenic centre in the desired position. Suzuki-Miyaura cross coupling and subsequent hydrolysis delivered the linear precursor **633**.



Scheme 5.10: Synthesis of linear fragment moving the stereogenic centre to the a-position of the pyridine.

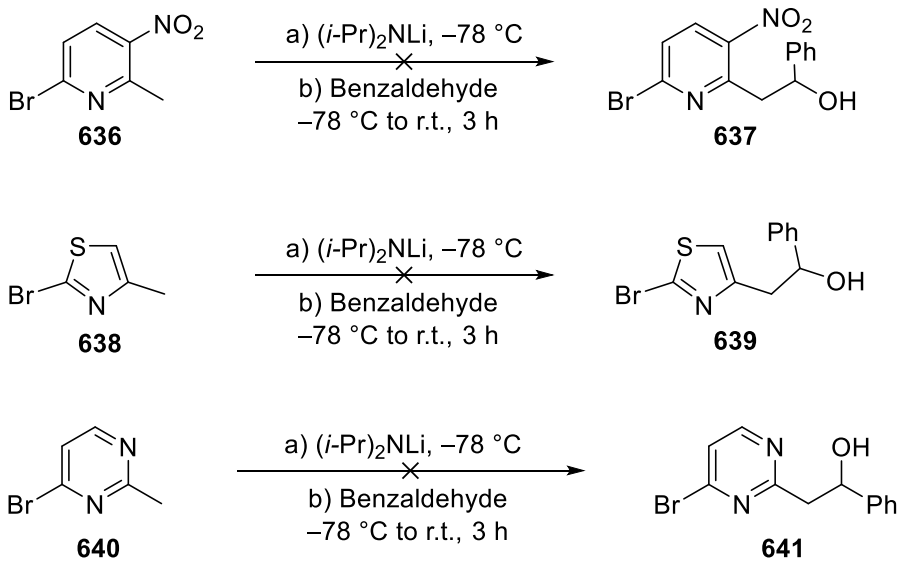
With both linear precursors in-hand, the key cyclisation/expansion cascade was tested. Pleasingly, we found that both examples furnished the desired 10-membered rings (**634** and **635**, scheme 5.11) in excellent yields. However, diastereoselectivity was low, with diastereomeric ratios of 1:1 and 3:2 respectively. This supported our idea that the diastereoselectivity is determined by a key 1,5-steric interaction through a pseudo axial position. Without this key interaction, both pathways are very similar in energy and therefore poor/no selectivity is observed, which is seen through these examples.



Scheme 5.11: Cyclisation/expansion of linear precursors where the stereogenic centre has been moved.

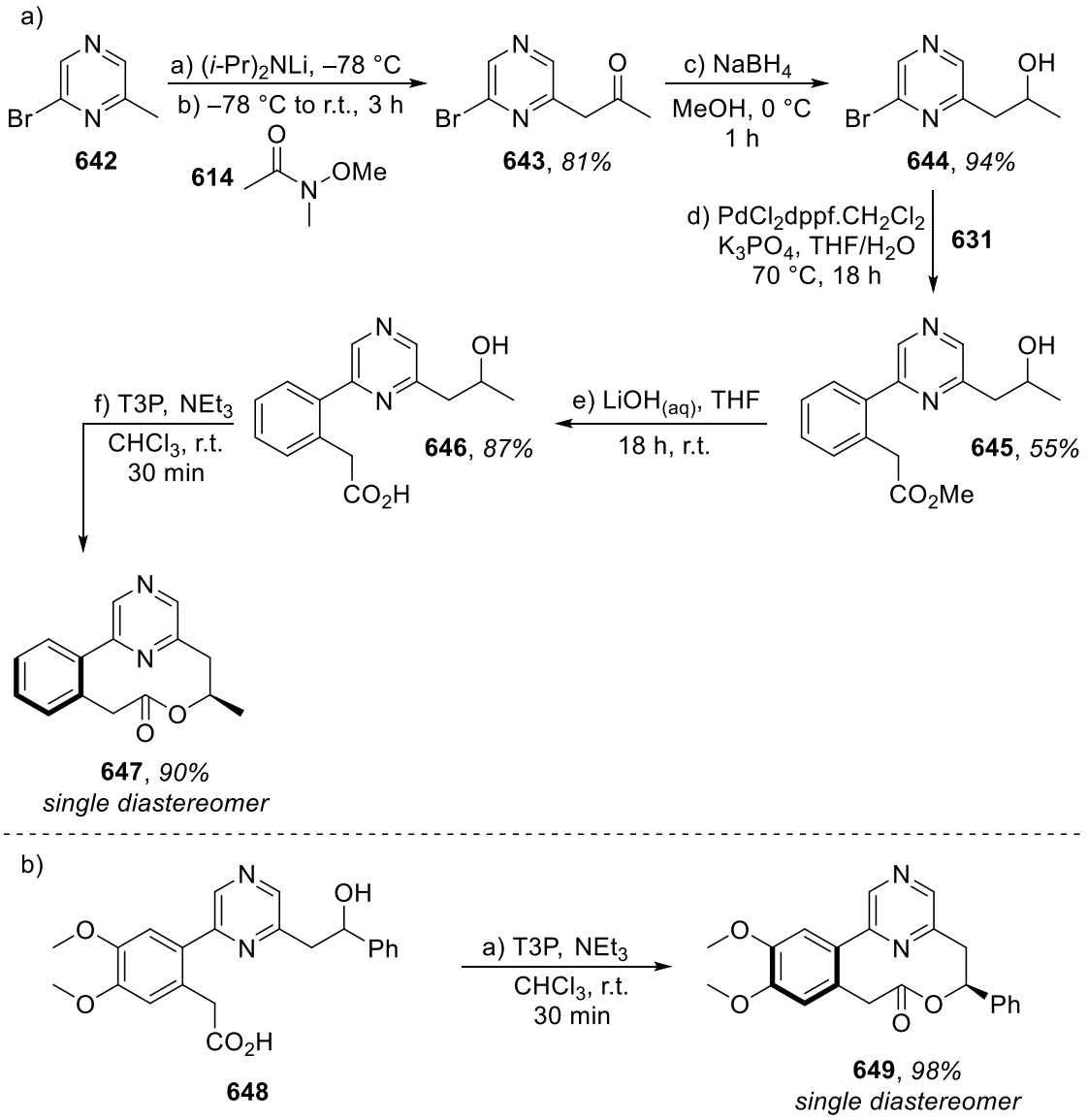
5.5 Heteroaromatic Scope

We moved onto expanding the scope of the pyridine fragment and tested other aromatic systems. The key design principle of the cascade requires a nucleophilic motif instigating a cyclisation event, which can also induce a ring expansion. With the success of the pyridine motif, we envisaged other nitrogen containing heteroaromatics being equally viable. We quickly understood that problems arose from the synthesis of the linear precursor, rather than testing the key cascade reaction. For example, the lithiation/trapping of nitro-substituted pyridine (**636**, scheme 5.12) was unsuccessful with multiple electrophiles, despite the aromatic being electron deficient which should promote the deprotonation. Deprotonation of the thiazole **638** and pyrimidine **640** starting materials were also unsuccessful, delivering only unreacted starting materials with different electrophiles utilised.



Scheme 5.12: Lithiation/trapping procedure tested on other heteroaromatics.

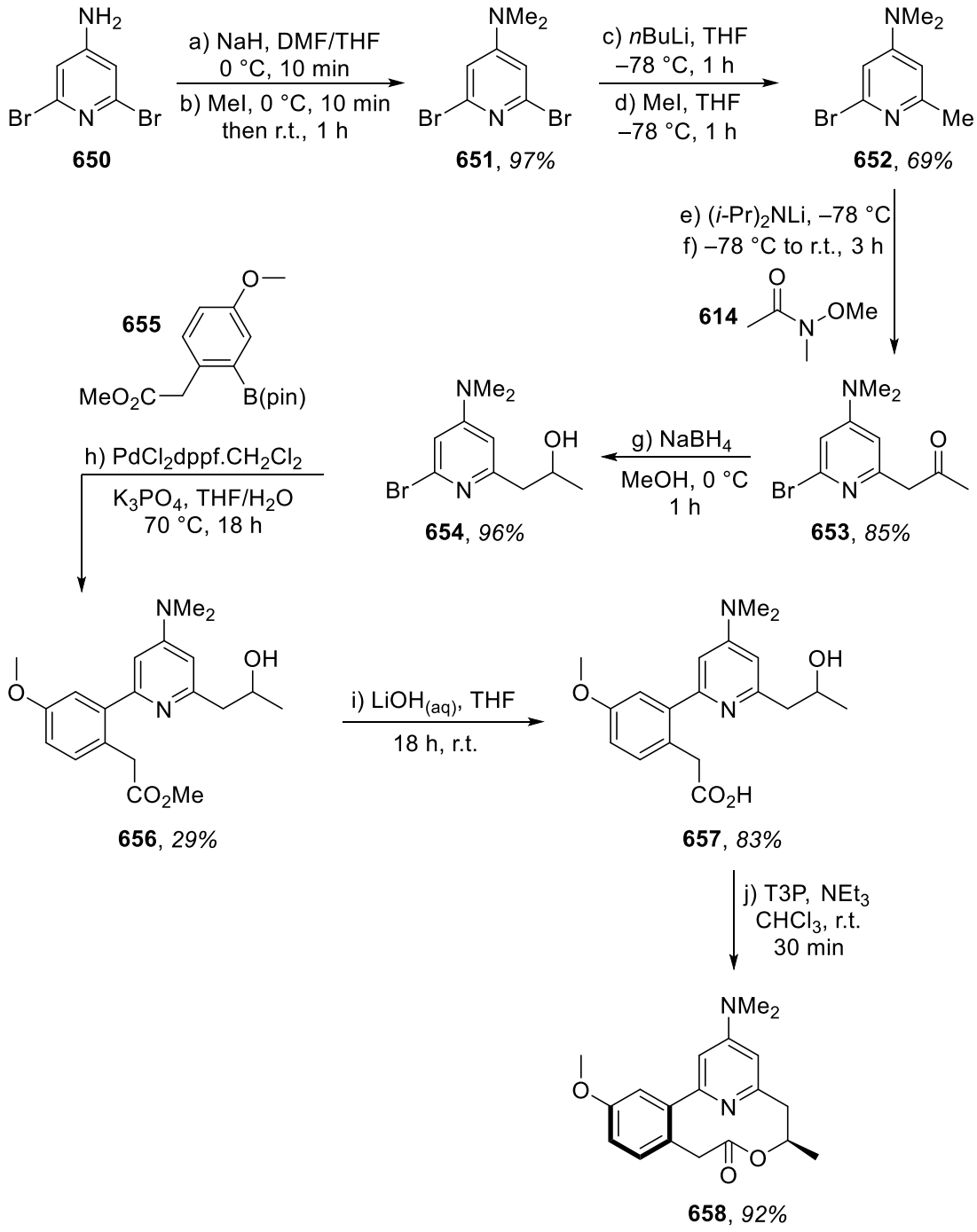
Pyrazines were then investigated, and pleasingly pyrazine **642** formed ketone **643** in excellent yield, using Weinreb amide **614**. Sodium borohydride reduction formed the corresponding alcohol **644** and Suzuki-Miyaura cross coupling delivered the bi-aryl hydroxy ester **645**. Hydrolysis produced the carboxylic acid which successfully formed the 10-membered ring **647** in excellent yield, showing that this heteroaromatic could also be tolerated. Another pyrazine linear precursor **648** was also synthesised, via a similar pathway, and successfully underwent the cascade reaction to form the 10-membered ring **649** in excellent yield, also as a single diastereomer.



Scheme 5.13: a) Pyrazine reaction pathway to linear substrate and successful key cascade reaction. b) Successful cyclisation/expansion reaction of catechol pyrazine substrate.

DMAP is commonly used as a nucleophilic catalyst in lactamisation/lactonisation reactions, operating mechanistically in a similar fashion to the cyclisation/expansion cascade. Therefore, we believed that incorporation of a dimethylaminopyridine unit as the key nucleophilic motif would likely work well to produce the desired medium-sized ring. Thus, amino pyridine **650** was methylated with a modified literature procedure,[136] forming dimethyl pyridine **651**. Lithium/halogen exchange was utilised to introduce methyl substitution, forming **652** in good yield. Importantly, lithium/halogen exchange occurred only once with no di-methylated side product being observed. Lithium/trapping with hindered non-nucleophilic base LDA and Weinreb amide **614** produced ketone **653**, which was then reduced to the alcohol **654** in excellent yields. Suzuki-Miyaura cross coupling with anisole boronic ester **655** was performed, forming electron rich bi-aryl ester **656**. Hydrolysis of the ester produced carboxylic acid

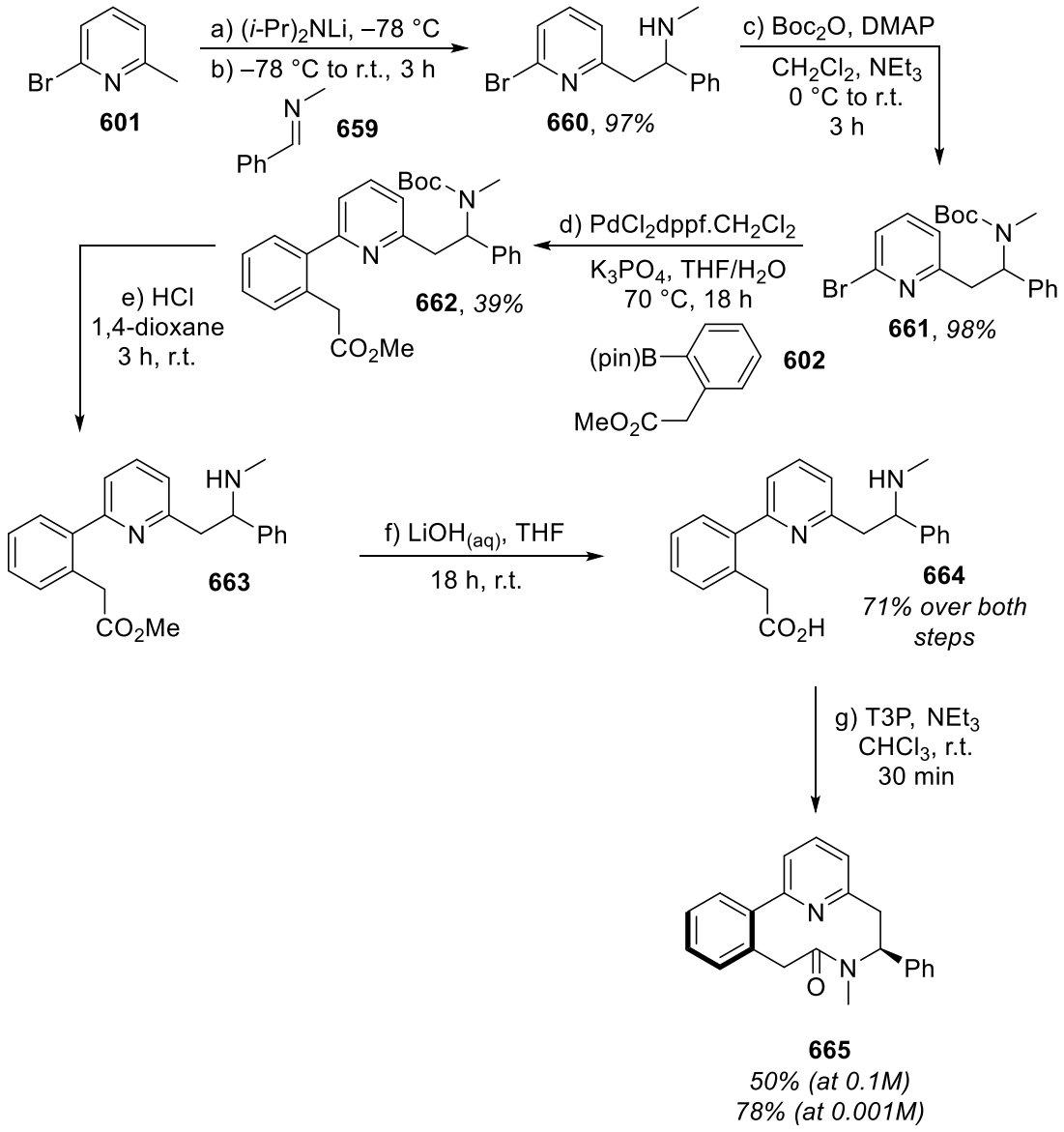
precursor **657**, which as predicted successfully formed the 10-membered ring **658** in excellent yield.



Scheme 5.14: Synthesis of dimethylaminopyridine linear precursor and cyclisation/expansion cascade.

5.6 Lactamisation Cyclisation/Expansion Cascade

Having proved that medium-sized ring lactones can be synthesised by this cascade reaction, we turned our attention to a lactamisation variant. The reaction mechanism should proceed in an identical fashion, with the only difference being the terminal nucleophile. Therefore, an amine linear precursor was synthesised by the following procedure (scheme 5.15). Initially, lithiation/trapping was completed with imine **659** forming secondary amine **660**. Protection of the amine with Boc was completed, in excellent yield, before the Suzuki–Miyaura cross coupling was performed to deliver ester **662** (protection of the amine was required beforehand, otherwise a Buchwald–Hartwig coupling was possible). Deprotection of the amine with HCl in dioxane afforded secondary amine **663**, which was subjected to ester hydrolysis to furnish the amino acid precursor **664**. The key cyclisation/expansion cascade reaction was initially performed under the standard conditions and a modest yield was obtained for the 10-membered lactam **665**. We propose that the increased nucleophilicity of the amine results in competing intermolecular amide-bond formation; this is supported by the fact that when the reaction was repeated under higher dilution, an increased yield was obtained from 50% to 78%.



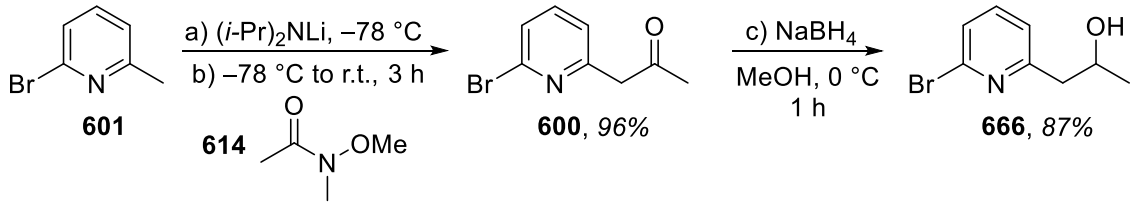
Scheme 5.15: Synthesis of secondary amino acid linear precursor and cyclisation/expansion to form tertiary lactam. High dilution was also tested due to significantly reduced yield using standard conditions for lactonisation.

5.7 Asymmetric Synthesis of Linear Precursor

5.7.1 Asymmetric Synthesis of Alcohol Precursor

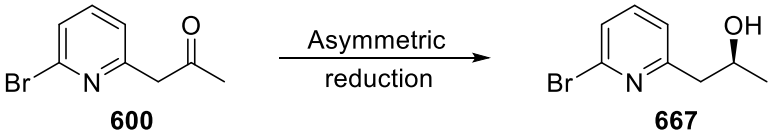
In the atroposelective examples, the relative stereochemistry was controlled by the point stereogenic centre. However, all the products (thus far) utilised racemic building blocks/transformations and therefore, the products are also racemic. As racemisation of the products once formed was deemed unlikely, we realised that enantiomerically enriched medium-sized rings should be accessible by using enantioenriched starting materials. Initially examining the lactonisation cascade reaction, we identified that asymmetric reduction of the ketone **600** (scheme 5.16) would provide an enantioenriched alcohol. Synthesising the racemic

alcohol **666** was simple, and using chiral HPLC, conditions by which the two enantiomers could be separated were established (see Supporting Information for further details).



Scheme 5.16: Synthesis of racemic alcohol through reduction of ketone.

Having produced the racemic alcohol **666**, asymmetric reduction of the corresponding ketone **600** was attempted with the results summarised in table 5.1. Using a literature procedure,[137] Jacobsen's catalyst was used but this was low yielding and formed the product **667** in a disappointing 22% *ee* (entry 1). The procedure was repeated at a lower temperature (−78 °C), in an attempt to improve the enantiomeric excess, but no conversion was achieved. An alternative approach was utilised where the chiral ligand menthol was used with lithium aluminium hydride.[138] An initial 'ligand exchange' between a menthol and hydride should occur, therefore making a chiral reducing agent *in-situ*. However, chiral induction was not achieved with a racemic product formed. Finally, Corey-Bakshi-Shibata reduction was attempted with borane using literature conditions,[139] however no product formation was observed.



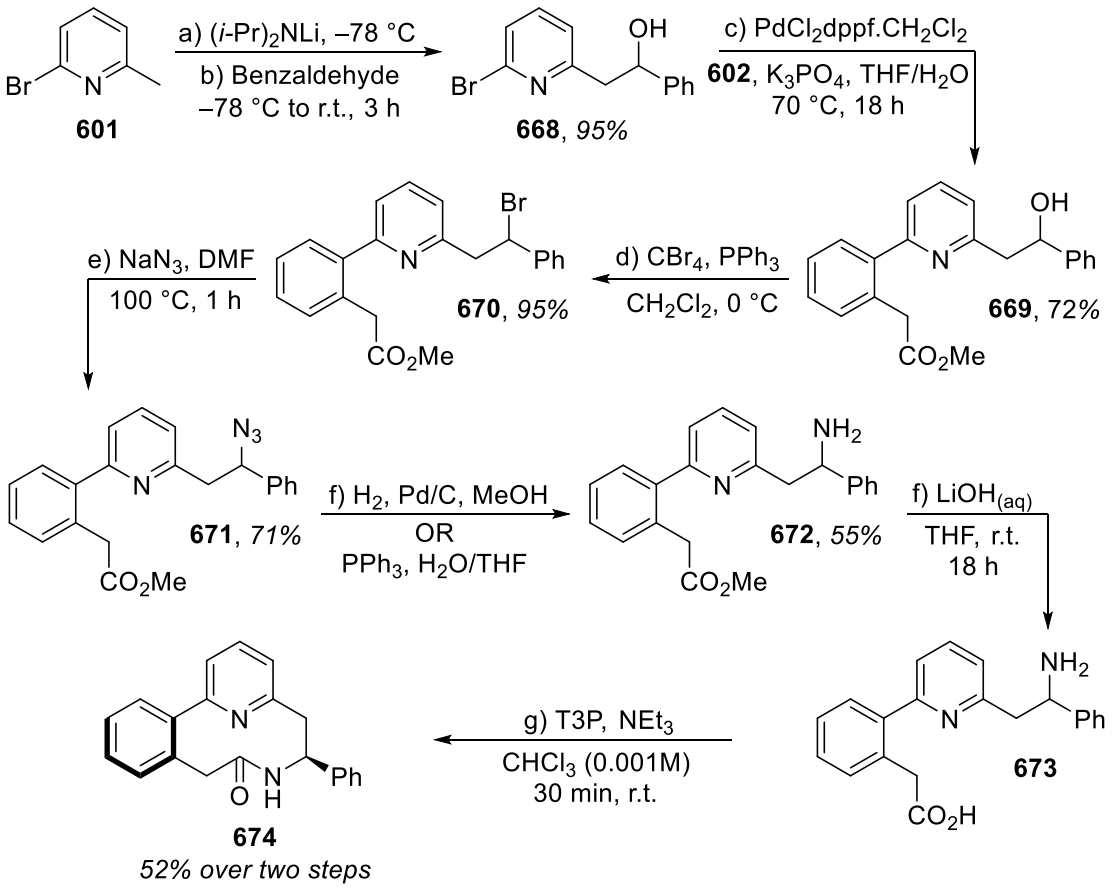
Entry	Conditions	Yield	Enantiomeric Excess
1	Jacobsen's catalyst (4 mol%), EtOH, $NaBH_4$, $CHCl_3$, −40 °C, 18 h	19%	22%
2	Jacobsen's catalyst (4 mol%), EtOH, $NaBH_4$, $CHCl_3$, −78 °C, 18 h	0%	-
3	Menthol, $LiAlH_4$, THF, EtOH, −20 °C	82%	0%
4	CBS catalyst, BH_3, THF, 0 °C	0%	-

Table 5.1: Summarising the results of the asymmetric reduction of the ketone.

5.7.2 Asymmetric Synthesis of Amine Precursor

With the difficulties associated with forming the desired enantioenriched alcohol, we turned our attention to produce an enantioenriched amine precursor. We considered using the well-known Ellman's auxiliary that has been used extensively in the synthesis of chiral amines. The chiral auxiliary acts as a robust directing group for various reactions involving metalation and trapping

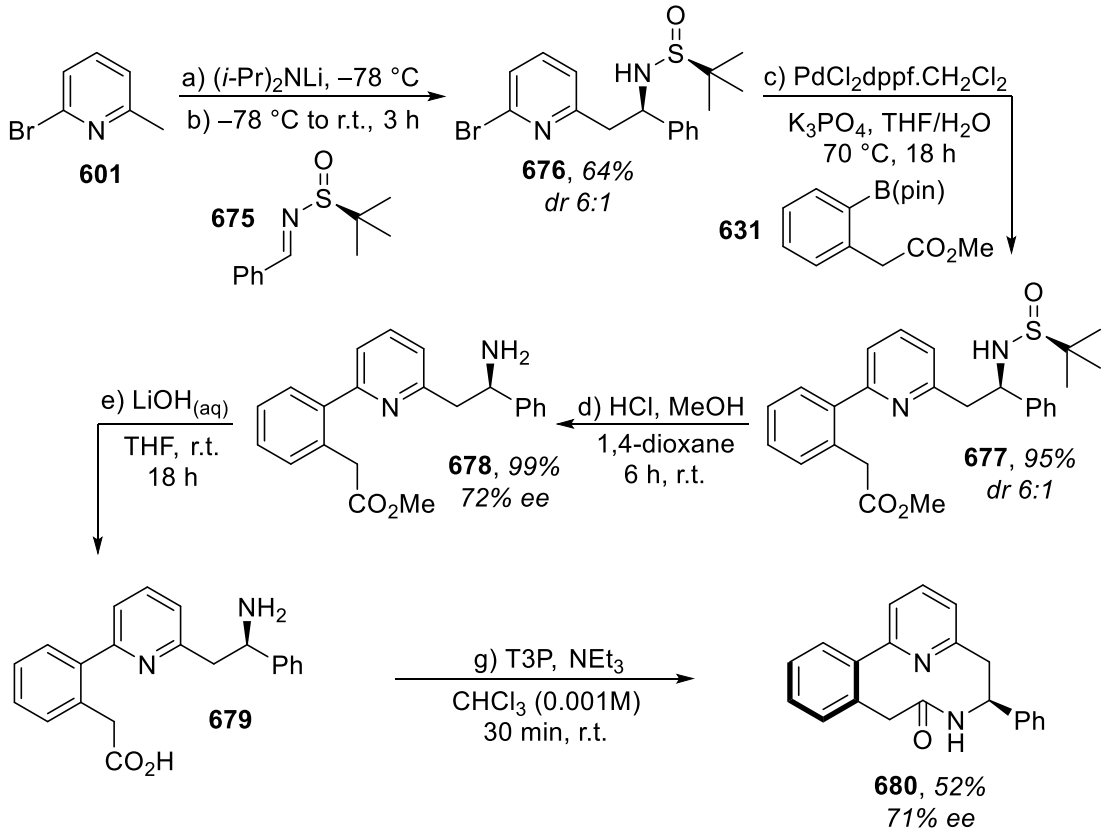
with an electrophile, usually providing products with high diastereoselectivity. The auxiliary can then be removed with mild acidic conditions to furnish the amines in high yield and often high enantiomeric excess. Initially, the racemic amine substrate was synthesised by the following linear procedure (scheme 5.17). Pyridine **601** was lithiated and trapped with benzaldehyde to form alcohol **668** in high yield. Suzuki-Miyaura cross coupling was performed which then delivered hydroxy ester **669**. An Appel reaction was used to convert the alcohol to alkyl bromide **670**, which was subsequently substituted to form azide **671**. Conversion to the corresponding amine **672** was performed by either hydrogenolysis or Staudinger reduction. Hydrolysis to the amino acid was followed by the key cyclisation/expansion cascade, forming the 10-membered lactam **674** in modest yield under high dilution conditions. The lactam was formed as a single diastereomer, however is observed in solution as two rotamers, where the ratio was dependant on both solvent and temperature. HPLC analysis of the compound was performed, with only partial separation of the enantiomers achieved (see Supporting Information).



Scheme 5.17: Synthesis of racemic primary amine and cyclisation/expansion cascade to form medium-sized ring 674 using high dilution.

Then, an asymmetric variant of this route was attempted by the following procedure (scheme 5.18). Pyridine **601** was lithiated and asymmetrically trapped using Ellman's auxiliary (*tert*-butyl sulfinyl imine **675**) to form sulfinamide **676** in a 6:1 diastereomeric ratio in good yield. Suzuki-

Miyaura cross coupling furnished the bi-aryl ester **677**, with a similar mixture of diastereomers observed. The auxiliary was removed using acidic conditions, providing amine **678** in presumably 71% *ee* (matching the diastereomeric ratio in the compounds made beforehand). Ester hydrolysis to the corresponding carboxylic acid **679** was telescoped with the cyclisation/expansion cascade to produce the desired lactam **680** in good yield, with no erosion of the enantiomeric excess.



Scheme 5.18: Synthesis of enantiomerically enriched primary amine using Ellman's auxiliary and the successful cyclisation/expansion cascade.

5.8 Chapter Summary

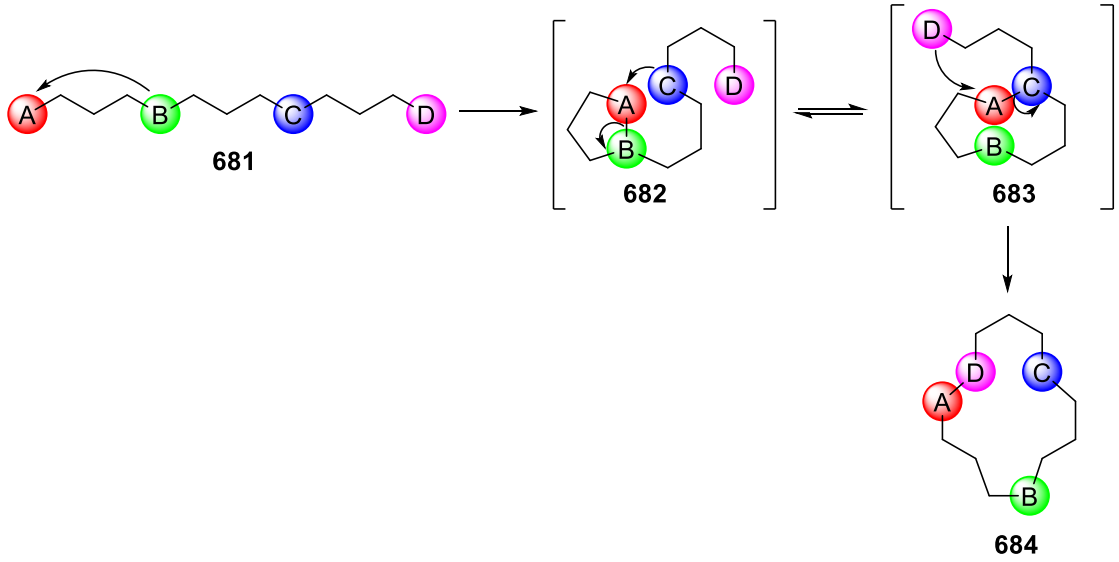
An atroposelective cyclisation/ring expansion cascade reaction has been developed, enabling the formation of 10-membered rings *via* either lactonisation or lactamisation variations. The origin of the diastereoselectivity has been probed, using tertiary alcohols and by moving the point stereogenic centre. Alternative heteroaromatics have been examined, forming the desired 10-membered rings, typically in excellent yields, as single diastereomers. An enantioenriched medium-sized lactam was also prepared using Ellman's auxillary.

This work was completed collaboratively with Dr Aggie Lawer (where stated), and was published alongside related examples. Those examples which I have not participated towards, have not been included in this Chapter, however are reported in the publication.[140]

Chapter Six: *N*-Acyl Transfer Cascade - Current and Future Work

6.1 N-Acyl Transfer Cascade Concept

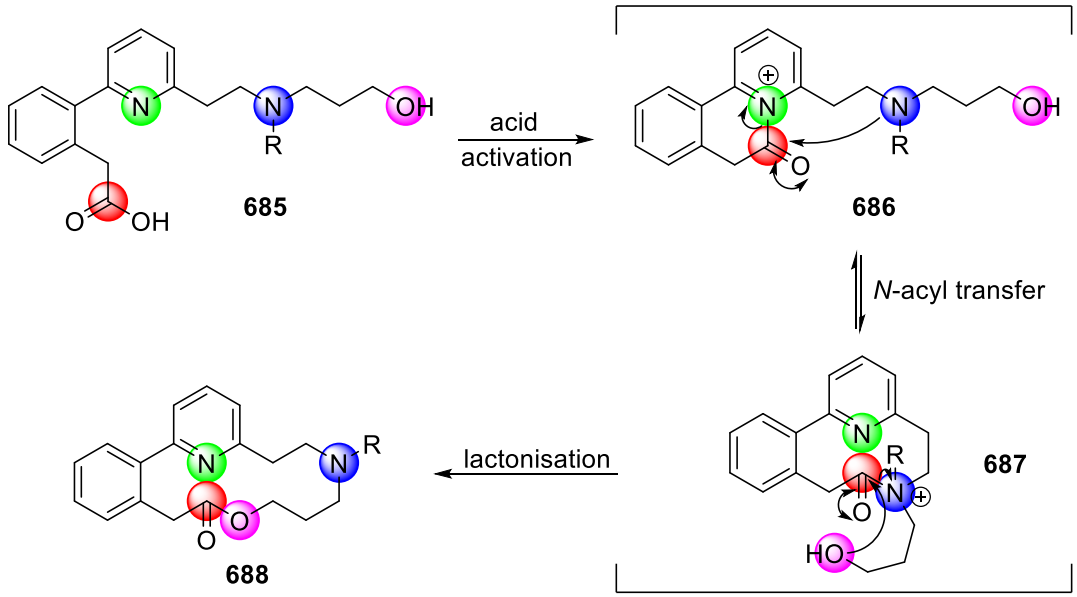
The nitrogen induced cyclisation/expansion cascade described in Chapter five, enables functionalised medium-sized lactams and lactones to be prepared atroposelectivity. This mild cascade reaction exhibits exquisite stereoselectivity, and we envisaged that macrocyclic scaffolds could also be synthesised by a related cascade. The simplified concept can be seen in scheme 6.1, where a nucleophilic motif performs a cyclisation (**681** → **682**), which can reversibly undergo a ring expansion (**682** → **683**), which is quickly trapped in a subsequent irreversible step (**683** → **684**). This would deliver functionalised macrocycles in a pre-determined and programmable fashion, similar to the successive ring expansion chemistry discussed already, however in a single cascade from a linear precursor.



Scheme 6.1: Multiple ring expansion cascade concept.

We highlighted that the first ring expansion step (**682** → **683**) would be the most challenging, as there appears to be no clear thermodynamic driving force. However, we proposed that if an overall lactonisation is performed (similar to Chapter five), even if this *N*-acyl transfer reaction is reversible, the reaction may be driven forward by irreversible lactonisation. Therefore, we imagined starting from substrates similar to carboxylic acid **685** (scheme 6.2) and performing an *in-situ* activation to form *N*-acyl pyridinium intermediate **686**. An equilibrium could be established whereby a 10-membered *N*-acyl ammonium intermediate **687** is produced via an acyl transfer reaction. This equilibrium would lie heavily towards the 6-membered intermediate, due to the transannular strain associated with medium-sized ring formation; however, when the 10-membered ammonium species is formed in small quantities, the fast and irreversible lactonisation ring expansion reaction would form the desired product **688**. We hoped that the

lactonisation step will be sufficiently fast to remove the 10-membered ammonium species **687** from solution, hence we can utilise Le Chatelier's principle to drive the reaction to completion.

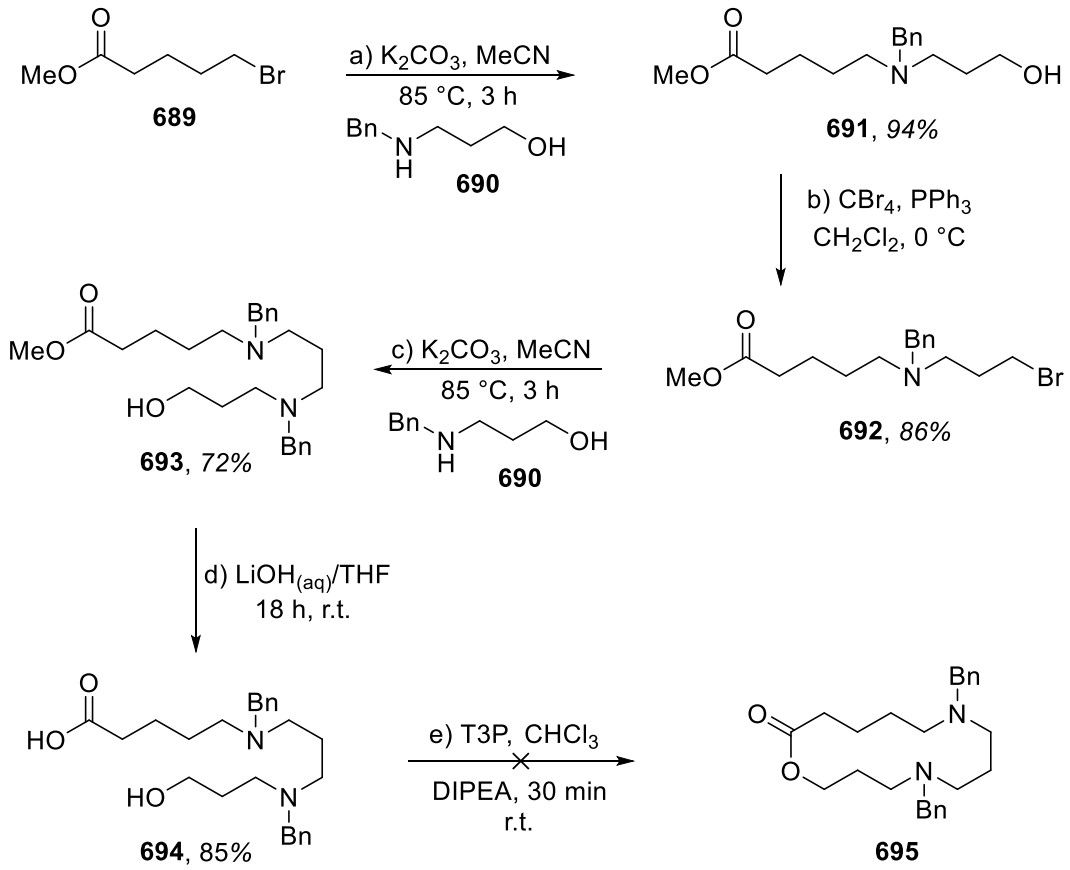


Scheme 6.2: Multi-ring expansion cascade forming lactone 688 using pyridinium/ammonium intermediates.

6.2 Synthesis of Linear Precursors and Cyclisation/Expansion Cascade

Initially, we wanted to test completely aliphatic linear precursors with this new cascade reaction, because the synthesis was simple and they have been shown to undergo the cascade described in Chapter five. Thus, starting from alkyl ester **689** (scheme 6.3), an S_N2 reaction was performed with amino alcohol **690**. Transformation of the alcohol to the alkyl bromide **692** was performed using an Appel reaction with excellent yield. A second S_N2 reaction was then completed, furnishing ester **693**. Finally, ester hydrolysis was performed to deliver the linear carboxylic acid precursor **694**.

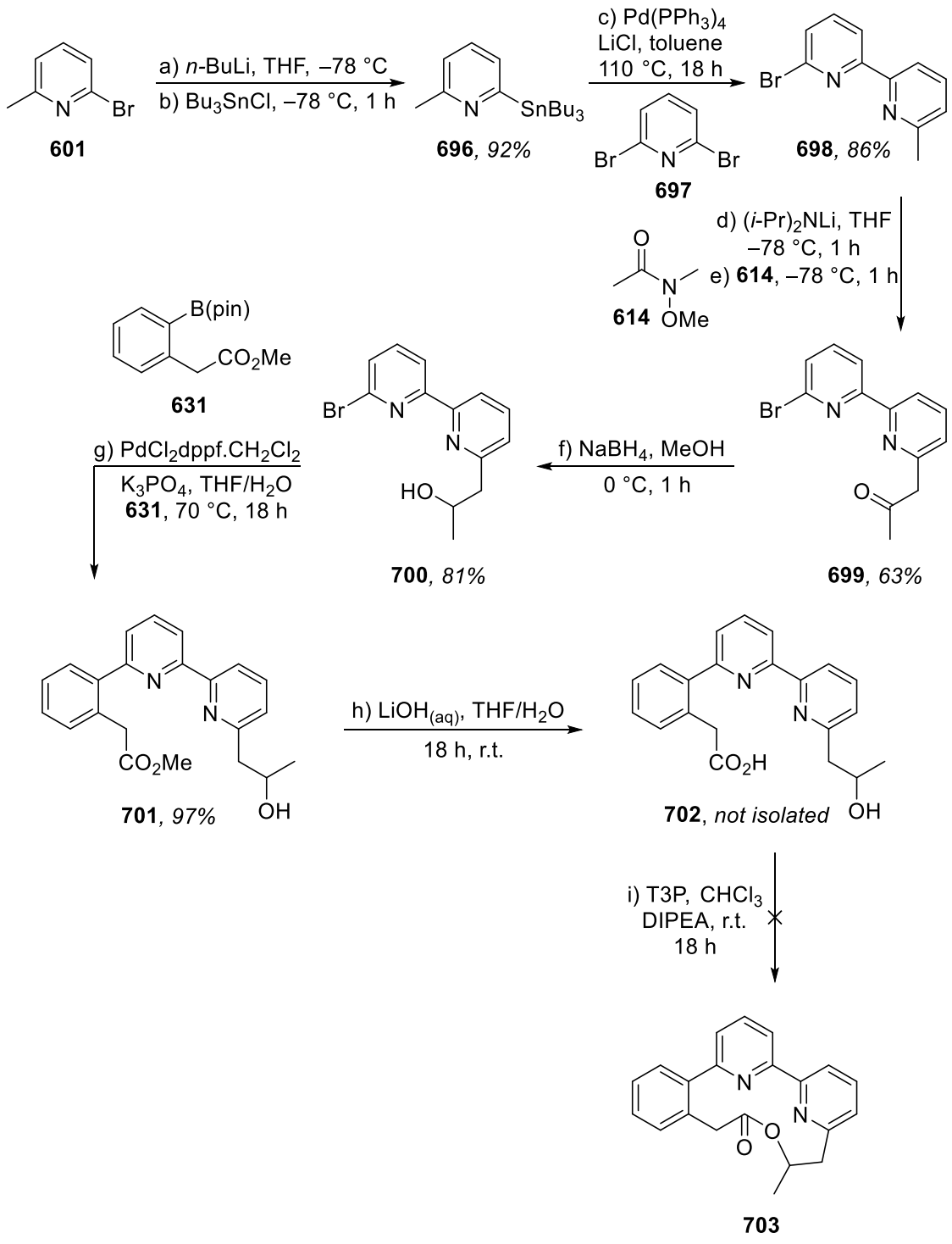
Unfortunately, using the optimised conditions from the nitrogen induced cascade reaction only starting material was observed, with no product formation. Alternative coupling reagents were used, such as HATU and CDI, however only starting material was observed in each case.



Scheme 6.3: Synthesis of aliphatic linear precursor via successive S_N2 reactions and unsuccessful cyclisation/expansion cascade reaction.

Undeterred, we amended the linear precursor to incorporate sp^2 hybridised centres to replicate the more successful systems from the previous cascade sequence. However, with these modifications, the chemistry becomes somewhat long and more laborious, which is shown in scheme 6.4. Thus, bromo pyridine **601** was converted to stannane **696** using lithium halogen exchange and the resultant organometallic trapped with tributyltin chloride. Initially, a literature procedure was utilised to make this stannane,[141] however unidentifiable tin residues plagued the subsequent steps, despite several purifications,[142] and therefore modifications were made. The stannane **696** and dibromo pyridine **697** were then combined using a Stille coupling.[143] Although some tri-pyridine side product (not shown) was observed where Stille coupling had occurred on both bromines, the major product was the mono-coupled product **698**. Deprotonation/trapping with Weinreb amide **614** furnished ketone **699**, which was consequently reduced to the alcohol **700** with sodium borohydride. Suzuki-Miyaura cross coupling with boronic ester **631**, made ester **701** in excellent yield. Hydrolysis to the acid **702** was completed and excess base removed via a silica plug, however due to the polarity of the compound, purification of the compound was not possible. Therefore, the key cascade

expansion reaction utilised the crude product, however was not successful and only the linear carboxylic acid was recovered.



Scheme 6.4: Synthesis of linear precursor with sp^2 hybridised centres, with unsuccessful cyclisation/expansion cascade.

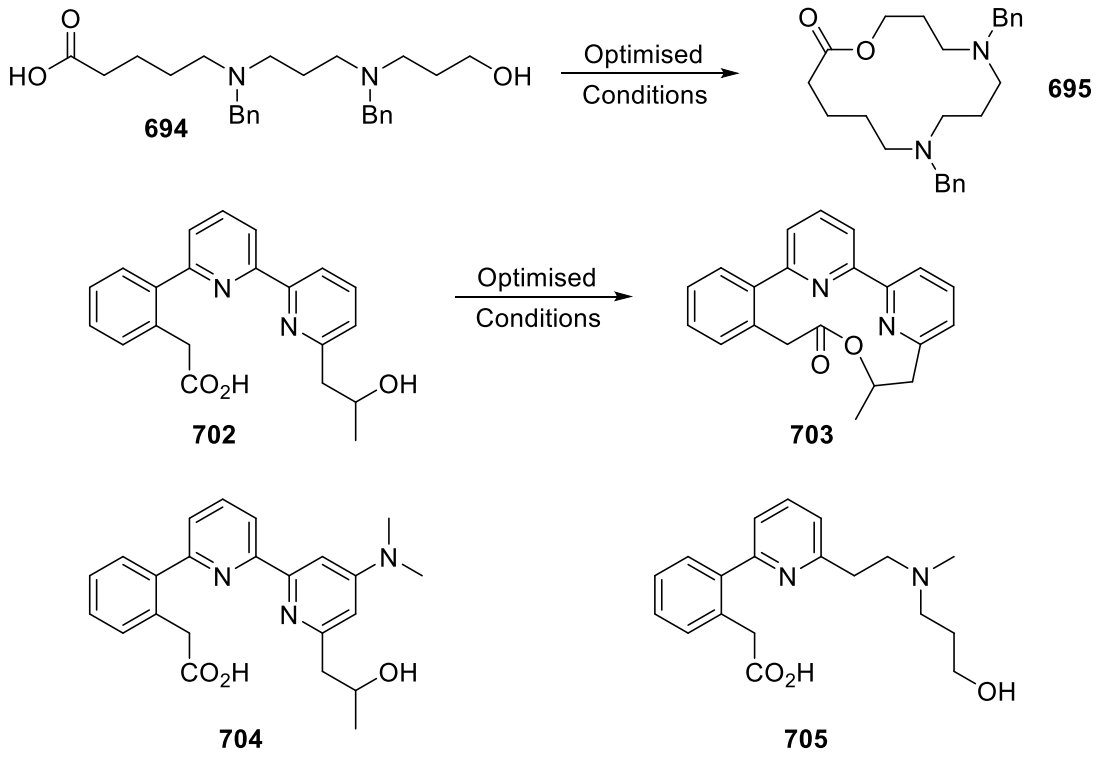
Although the key cyclisation/expansion cascade had been unsuccessful so far, a route to access the starting materials was achieved. We propose from the results obtained, that increased

temperature or longer reaction times will likely be required for the reversible *N*-acyl transfer reaction to occur efficiently and produce the desired product.

6.3 Future Work

6.3.1 *N*-Acyl Transfer Cascade

With a successful route to the linear precursors established, work to find optimised cyclisation/expansion conditions is ongoing. This will include (but not limited to): altering temperature, solvent, base, carboxylic acid activation method and the use of additives such as DMAP. This work will be completed on the linear precursor **694** (scheme 6.5) initially and then extended to the aryl-containing linear precursor **702**. Additional aromatic precursors, with a DMAP bridge (**704**) and tertiary amine (**705**) will also be synthesised.

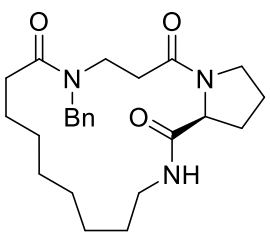


Scheme 6.5: Future work on the *N*-acyl transfer cascade towards the synthesis of macrocyclic lactones.

6.3.2 Acylation Conditions for Successive Ring Expansion of Lactams

When performing a second or third consecutive ring expansion, using either amino acid chlorides or hydroxy acid chlorides, the acylation step was often slow or did not work entirely. To combat this, some examples required additional equivalents and extended reaction times to help improve the conversion obtained. We believe that due to the linear fragments incorporated, the conformation(s) which is most energetically favourable orientates the NH into the internal cavity of the macrocycle. Therefore, when performing a further acylation, the

reaction is sluggish/non-productive as higher energy conformations must be accessed to produce the desired imide. Thus, developing improved acylation conditions for these failed examples is a high priority moving forward. The macrocycles which failed to acylate are shown below (scheme 6.6).



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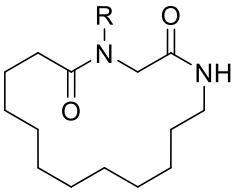
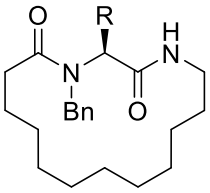
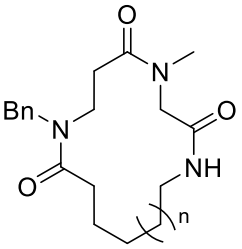


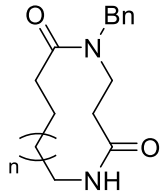
434, **436**
R = *i*-Bu, *i*-Pr



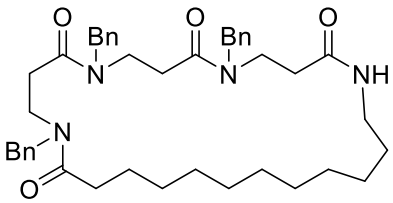
450, **454**
R = *i*-Bu, Me



465, **466**, **469**
n = 1,2,3



400, **401**, **402**
n = 1,2,3



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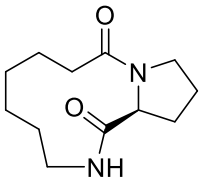

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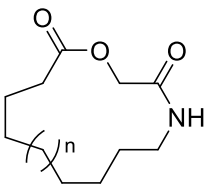
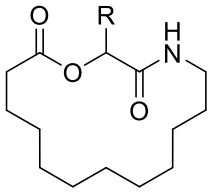
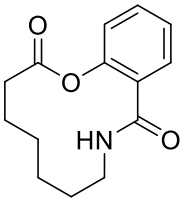


539, **540**, **541**
n = 1,2,3



542, **561**, **564**
R = H, Me, Ph



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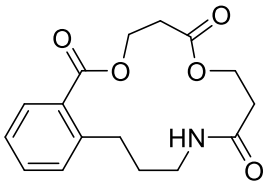

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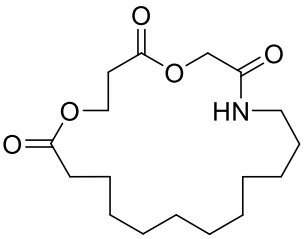

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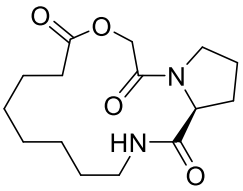

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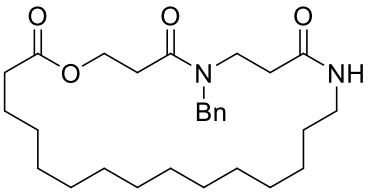

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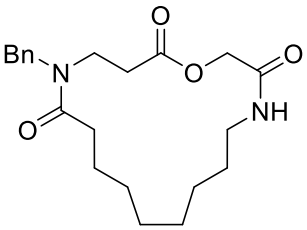

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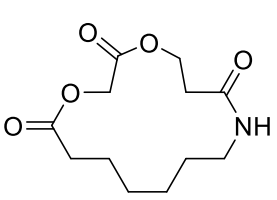

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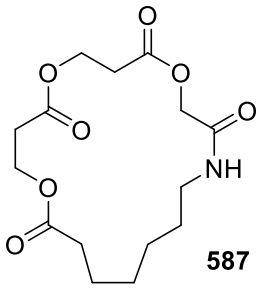
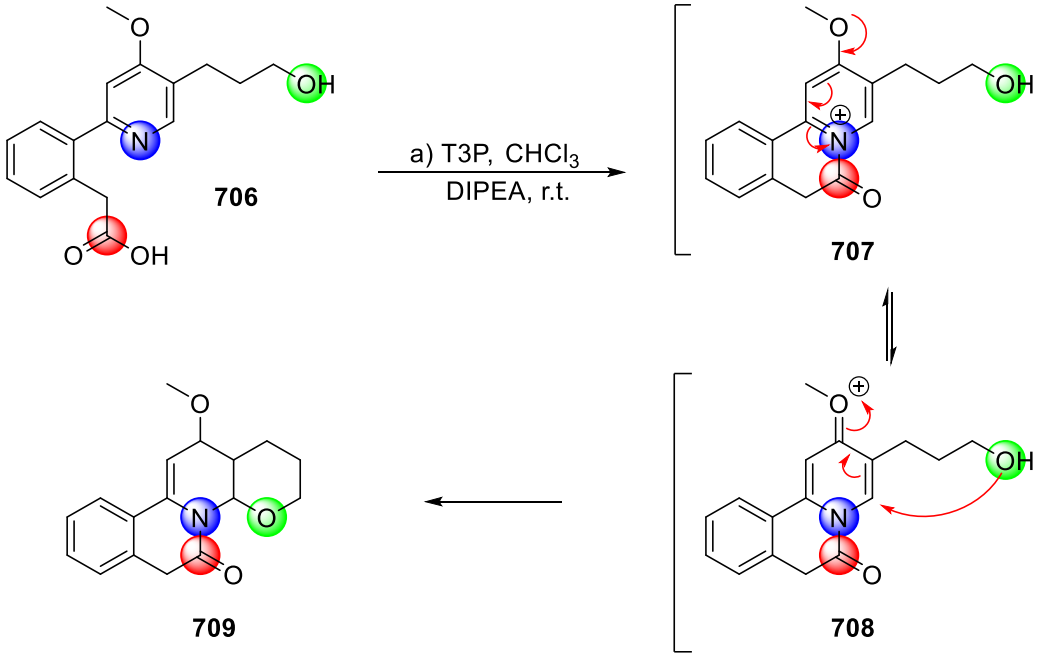


587

Scheme 6.6: Macrocycles that did not acylate for a multiple ring expansion.

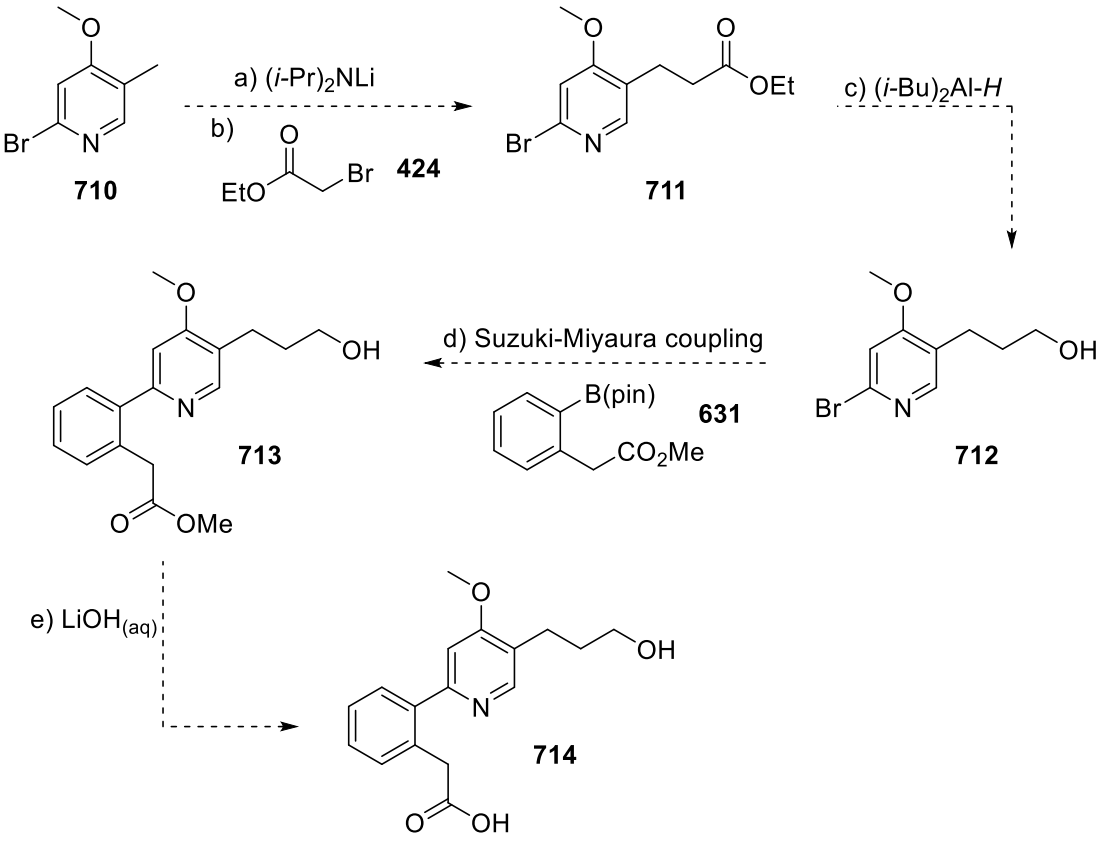
6.3.3 Nitrogen Induced Cyclisation/Annulation Cascade

Following on from Chapter five, an alternative cascade reaction is proposed, that if successful, will produce a tetracyclic annulated system via de-aromatisation of a pyridine (scheme 6.7). Therefore, starting from linear fragment **706**, carboxylic activation could form *N*-acyl pyridinium intermediate **707**. Conversion to the quinone **708** would allow conjugate addition by the pendant alcohol to form tetracyclic *N,O*-acetal **709**.



Scheme 6.7: Pyridine induced cyclisation/de-aromatising annulation cascade reaction.

The linear precursor is very similar to those previously synthesised, with only the initial deprotonation/trapping reaction differing. It is plausible that the deprotonated pyridine (**710**) could attack into bromo ester **424** chemoselectivity to form ester **711**. Reduction of ester using DIBAL could produce alcohol **712**, which would subsequently be subjected to Suzuki–Miyaura coupling and hydrolysis to furnish the desired linear precursor **714**.



Scheme 6.8: Proposed synthesis of amended linear precursor for cyclisation/annulation cascade reaction.

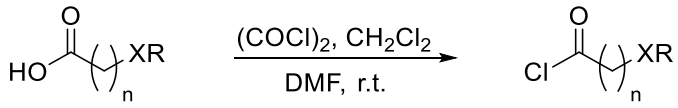
Chapter Seven: Experimental

7.1 General Experimental

Except where stated, all reagents were purchased from commercial sources and used without further purification. Except where stated, all experimental procedures were carried out under an atmosphere of argon. Anhydrous CH_2Cl_2, toluene and acetonitrile were obtained from an Innovative Technology Inc. PureSolv® solvent purification system and stored over activated 5Å molecular sieves. Triethylamine (Et_3N) was purified via distillation and stored over activated 5 Å molecular sieves. ^{1}H NMR and ^{13}C NMR spectra were recorded on a JEOL ECX400 or JEOL ECS400 spectrometer, operating at 400 MHz and 100 MHz, respectively. All spectral data was acquired at 295 K unless stated. Chemical shifts (δ) are quoted in parts per million (ppm). The residual solvent peak, δ_H 7.26 and δ_C 77.0 for $CDCl_3$ was used as a reference. Coupling constants (J) are reported in Hertz (Hz) to the nearest 0.1 Hz. The multiplicity abbreviations used are: s singlet, d doublet, t triplet, q quartet, td triple doublets, tt triple triplets, dq double quartets, m multiplet. Signal assignment was achieved by analysis of DEPT, COSY, NOESY, HMBC and HSQC experiments where required. Infrared (IR) spectra were recorded on a PerkinElmer UATR two spectrometer as a thin film. Mass-spectra (low and high-resolution) were obtained by the University of York Mass Spectrometry Service, using electrospray ionisation (ESI) on a Bruker Daltonics, Micro-tof spectrometer. Melting points were determined using Gallenkamp apparatus and are uncorrected. Thin layer chromatography was carried out on Merck silica gel $60F_{254}$ pre-coated aluminium foil sheets and were visualised using UV light (254 nm) and stained with basic aqueous potassium permanganate. Flash column chromatography was carried out using slurry packed Fluka silica gel (SiO_2), 35–70 µm, 60 Å, under a light positive pressure, eluting with the specified solvent system.

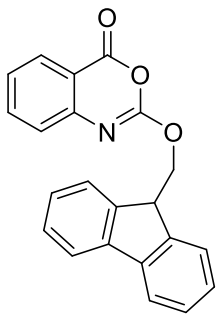
7.2 Characterisation Data and Procedures

General procedure for acid chloride formation:



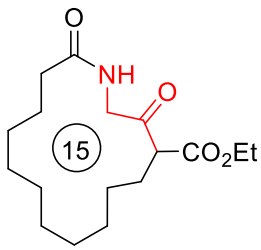
Oxalyl chloride (3 mmol) was added to a suspension of carboxylic acid (1 mmol) in CH_2Cl_2 (5 mL), followed by a catalytic amount of DMF (1 drop/mmol of carboxylic acid). The resulting mixture was stirred at room temperature for 1 h [in general the initial suspension became homogeneous over this period] and concentrated *in vacuo* to remove all of the solvent and excess oxalyl chloride.

2-((9H-Fluoren-9-yl)methoxy)-4H-benzo[d][1,3]oxazin-4-one (305)



A mixture of ethyl 2-oxocyclooctane-1-carboxylate (0.184 g, 0.998 mmol), $MgCl_2$ (0.190 g, 2.00 mmol) and pyridine (0.47 mL, 5.99 mmol) in CH_2Cl_2 (5 mL) under an argon atmosphere was stirred at room temperature for 30 min. Next, a solution of acid chloride (3.00 mmol, prepared using the general procedure) in CH_2Cl_2 (5 mL) was added and the reaction mixture was stirred for 18 h at room temperature. Upon completion, the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 50% ethyl acetate in hexanes → ethyl acetate) afforded the *title compound* as a colourless oil (721 mg, 89%); R_F 0.78 (ethyl acetate); δ_H (400 MHz, $CDCl_3$) 7.83–7.65 (6H, m, 6 × C**H**), 7.45–7.30 (6H, m, 6 × C**H**), 4.66 (2H, d, *J* = 7.6 Hz, C**H**$_2$O), 4.41 (1H, t, *J* = 7.6 Hz, C**H**CH_2O); δ_C (100 MHz, $CDCl_3$) 159.5 (**C**=O), 154.6 (**C**=N), 148.1 (**C**), 143.1 (**C**H), 141.3 (**C**H), 136.9 (**C**H), 129.0 (**C**H), 128.0 (2 × **C**H), 127.2 (2 × **C**H), 126.0 (**C**), 125.4 (**C**), 125.3 (2 × **C**H), 120.1 (2 × **C**H), 114.5 (**C**).

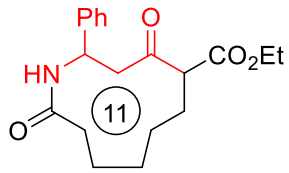
Ethyl 3,15-dioxoazacyclopentadecane-4-carboxylate (309)



A mixture of ethyl 2-oxocyclododecane-1-carboxylate (100 mg, 0.393 mmol), $MgCl_2$ (75 mg, 0.786 mmol) and pyridine (190 µL, 2.35 mmol) in CH_2Cl_2 (3 mL) under an argon atmosphere was stirred at room temperature for 30 min. Next, a solution of acid chloride (1.18 mmol, prepared using the general procedure) in CH_2Cl_2 (2 mL) was added and the reaction mixture was stirred for 2 h at r.t. The mixture was then diluted with CH_2Cl_2 (50 mL) and washed with 10% aq. HCl (25 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was then re-dissolved in CH_2Cl_2 (4 mL) and piperidine (0.39 mL, 3.93 mmol) was added.

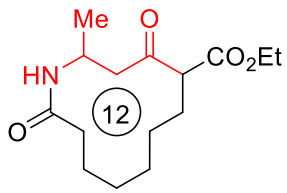
The resulting mixture was stirred for 2 h, at room temperature, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, hexane:ethyl acetate 10:1 → 2:1 → ethyl acetate) afforded the *title compound* (as a 10:1 mixture of keto:enol tautomers) as a colourless oil (62 mg, 50%); R_F 0.35 (50% ethyl acetate in hexanes); δ_H (400 MHz, $CDCl_3$) data for the keto tautomer only: 6.29 (1H, br s, N**H**), 4.22 (2H, s, C**H₂**NH), 4.18 (2H, q, *J* = 6.9 Hz, OC**H₂**CH_3), 3.61 (1H, dd, *J* = 9.2, 5.4 Hz, C**H**CO_2Et), 2.30–2.23 (2H, m, C**H₂**CONH), 2.00–1.90 (2H, m, C**H₂**), 1.72–1.64 (2H, m, C**H₂**), 1.33–1.16 (17H, m, 7 × C**H₂** and C**H₃**). Data is consistent with those previously reported.[112]

Ethyl-4,11-dioxo-2-phenyl-1-azacycloundecane-5-carboxylate (310)



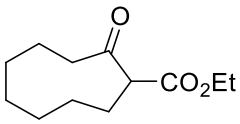
A mixture of ethyl 2-oxocycloheptane-1-carboxylate (184 mg, 0.998 mmol), $MgCl_2$ (0.190 g, 2.00 mmol) and pyridine (0.47 mL, 5.99 mmol) in CH_2Cl_2 (5 mL) under an argon atmosphere was stirred at room temperature for 30 min. Next, a solution of acid chloride (3.00 mmol, prepared using the general procedure) in CH_2Cl_2 (5 mL) was added and the reaction mixture was stirred for 2 h at r.t. The mixture was then diluted with CH_2Cl_2 (50 mL) and washed with 10% aq. HCl (25 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was then re-dissolved in CH_2Cl_2 (10 mL) and piperidine (0.99 mL, 9.98 mmol) was added. The resulting mixture was stirred for 2 h, at room temperature, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, hexane:ethyl acetate 10:1 → 2:1 → ethyl acetate) afforded the *title compound* as a white solid (164 mg, 50%) as a 4:1 mixture of diastereoisomers; m.p. 163–165 °C (chloroform); R_F = 0.35 (hexane:ethyl acetate 1:1); ν_{max}/cm^{-1} (neat) 3303, 2925, 1723, 1708, 1643, 1540, 1454; δ_H (400 MHz, $CDCl_3$) 7.37–7.25 (10H, m, Ph, both diastereoisomers), 6.09 (1H, d, *J* = 9.9 Hz, N**H**, major diastereoisomer), 5.90 (1H, d, *J* = 9.2 Hz, N**H**, minor diastereoisomer), 5.63–5.57 (1H, m, C**H**N, minor) 5.51 (1H, td, *J* = 10.7, 3.5, C**H**N, major), 4.20–4.12 (4H, m, OC**H₂**, both), 3.88 (1H, dd, *J* = 11.4, 3.1 Hz, major), 3.58 (1H, dd, *J* = 12.2, 3.1 Hz, minor), 3.39 (1H, dd, *J* = 13.7, 11.4 Hz, major), 3.30–3.22 (1H, m, minor), 3.01–2.90 (2H, m, both), 2.34–2.13 (5H, m), 1.97–1.88 (2H, m), 1.85–1.45 and 1.31–1.05 (19H, m, both); δ_C (100 MHz, $CDCl_3$) data for the major diastereoisomer only: 205.2 (**C**O, ketone), 172.7 (**C**O, ester/amide), 169.0 (**C**O, ester/amide), 140.7 (**C**), 128.7 (**C**H), 127.7 (**C**H), 126.3 (**C**H), 61.5 (O**C**H_2), 58.9 (**C**HN), 51.9 (**C**HCO_2Et), 47.2 (**C**H_2), 38.0 (**C**H_2), 26.7 (**C**H_2), 26.1 (**C**H_2), 24.7 (**C**H_2), 23.5 (**C**H_2), 14.1 (**C**H_3); HRMS (ESI): calcd. for $C_{19}H_{25}NNaO_4$, 354.1676. Found: $C_{19}H_{25}NaNO_4$ $[MNa]^+$, 354.1672 (1.0 ppm error)].

Ethyl 2-methyl-4,12-dioxoazacyclododecane-5-carboxylate (312)



A mixture of methyl 2-oxocyclooctane-1-carboxylate (193 mg 0.973 mmol), $MgCl_2$ (185 mg, 1.95mmol) and pyridine (0.470 mL, 5.84 mmol) in CH_2Cl_2 (6.8 mL) under an argon atmosphere was stirred at r.t. for 30 min. Next, a solution of acid chloride (2.92 mmol, prepared using the general procedure) in CH_2Cl_2 (2.9 mL) was added and the reaction mixture was stirred for 1 h at r.t. The mixture was then diluted with CH_2Cl_2 (50 mL) and washed with 10% aq. HCl (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL) and the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was then re-dissolved in CH_2Cl_2 (9.7 mL) and piperidine (0.970 mL, 9.73 mmol) was added. The resulting mixture was stirred for 1 h at r.t., before the solvent was removed *in vacuo*. Purification by column chromatography (SiO_2, 10:1 → 1:1 hexane:ethyl acetate → ethyl acetate) afforded the *title compound* (180 mg, 65%) as a white solid as a 4:1 mixture of diastereoisomers; m.p. 116–118 °C (chloroform); R_F = 0.30 (EtOAc); ν_{max} (thin film)/cm^{-1} 3286, 2932, 1742, 1711, 1638, 1540, 1448; δ_H (400 MHz, $CDCl_3$) 5.73 (1H, br s, minor diastereoisomer), 5.65 (1H, br s, major diastereoisomer), 4.52–4.42 (1H, m, NC**H**, major), 4.33–4.26 (1H, m, NC**H**, minor), 4.18–4.11 (4H, m, OC**H₂** both), 3.67 (1H, dd, *J* = 10.7, 3.1 Hz, C**H**, major), 3.41 (1H, dd, *J* = 10.7, 3.8 Hz, C**H**, minor), 3.09 (1H, dd, *J* = 16.8, 4.6 Hz, C**H**, major), 2.99 (1H, dd, *J* = 16.8, 3.8 Hz, C**H**, minor), 2.77 (1H, dd, *J* = 16.8, 6.1 Hz, C**H**, minor), 2.65 (1H, dd, *J* = 16.8, 7.6 Hz, C**H**, major), 2.25–1.98 (6H, m, both), 1.79–1.10 (30H, m, both); δ_C (100 MHz, $CDCl_3$) data for the major diastereoisomer only: 205.8 (**C**O, ketone), 173.7 (**C**O, ester/amide), 169.4 (**C**O, ester/amide), 61.4 (**C**H), 56.0 (**C**H_2), 47.7 (**C**H_2), 42.7 (**C**H), 37.5 (**C**H_2), 27.8 (**C**H_2), 26.4 (**C**H_2), 26.0 (**C**H_2), 25.1 (**C**H_2), 23.3 (**C**H_2), 20.9 (**C**H_3), 14.0 (**C**H_3); HRMS (ESI): Found: 306.1676; $C_{15}H_{25}NNaO_4$ $[MNa]^+$. Requires 306.1676 (0.1 ppm error).

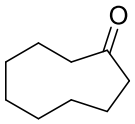
Ethyl 2-oxocyclononane-1-carboxylate (326)



To a solution of cyclooctenone (7.57 g, 60.0 mmol) in Et_2O (120 mL) at 0 °C, was added a solution of $BF_3.OEt_2$ (11.4 mL, 90.0 mmol) in Et_2O (30 mL) over 5 min. A solution of ethyl diazoacetate (87% wt. in CH_2Cl_2, 11.0 mL, 90.0 mmol) in Et_2O (31 mL), was then added over a period of 15 min, causing a vigorous evolution of gas. The resulting solution was allowed to warm to room temperature under an argon atmosphere over 16 h, where the mixture was cooled to 0 °C and neutralised with saturated aqueous solution of $NaHCO_3$. The resulting mixture was extracted with chloroform (3 × 100 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 20:1 hexane:ethyl acetate) afforded the *title compound* (as a 1:1 mixture of ketone:enol tautomers) as an orange oil (9.83 g, 77%); R_f 0.75 & 0.65

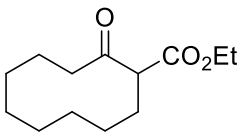
ketone/enol tautomers (CH_2Cl_2); ν_{max}/cm^{-1} (neat); 2927, 1745, 1706, 1640, 1609; δ_H (400 MHz, $CDCl_3$) 12.74 (1H, s, O**H**, enol), [4.19 (2H, q, *J* = 7.3 Hz, OC**H₂**CH_3), 4.12 (2H, q, *J* = 6.9 Hz, OC**H₂**CH_3), ketone and enol], 3.66–3.54 (1H, m, C**H**CO_2Et, ketone), [2.67–2.50 (2H, m, C**H₂**COCH), 2.38 (2H, t, *J* = 6.0 Hz, C**H₂**COH), 2.35–2.28 (2H, m, C**H₂**), 2.13–2.03 (2H, m, C**H₂**), 1.94–1.79 (2H, m, C**H₂**), 1.77–1.67 (2H, m, C**H₂**), 1.67–1.32 (16H, m, 8 × C**H₂**), 1.28 (3H, t, *J* = 7.3 Hz, C**H₃**), 1.21 (3H, t, *J* = 6.9 Hz, C**H₃**), ketone and enol]; δ_C (100 MHz, $CDCl_3$) 212.0 (**C**OCH_2, ketone), 175.9 (**C**O_2Et, ketone), 173.5 (**C**OH, enol), 170.7 (**C**O_2Et, enol), 100.3 (**C**CO_2Et, enol), 61.3 (O**C**H_2, enol), 60.3 (O**C**H_2, ketone), 58.9 (**C**HCO_2Et, ketone), 42.5 (**C**H_2COCH, ketone), [31.5 (**C**H_2), 27.1 (**C**H_2), 27.0 (**C**H_2), 26.2 (**C**H_2), 25.9 (**C**H_2), 25.2 (**C**H_2), 25.0 (**C**H_2), 24.7 (**C**H_2), 24.64 (**C**H_2), 24.56 (**C**H_2), 24.4 (**C**H_2), 24.01 (**C**H_2), 23.96 (**C**H_2), ketone and enol], 14.4 (**C**H_3, enol), 14.1 (**C**H_3, ketone); HRMS (ESI): calcd. for $C_{12}H_{20}NaO_3$, 235.1305. Found: $[MNa]^+$, 235.1304 (0.7 ppm error)]. Data is consistent with those previously reported.[144]

Cyclononanone (327)



A degassed solution of ethyl 2-oxocyclononane-1-carboxylate (10.6 g, 50.0 mmol) in DMSO (50 mL) and H_2O (10 mL) was refluxed at 160 °C for 16 h. After cooling to room temperature, the mixture was partitioned between water (80 mL) and Et_2O (3 × 100 mL), the combined organic phases were dried over $MgSO_4$, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 20:1 hexane:ethyl acetate → 10:1 hexane:ethyl acetate → 2:1 hexane:ethyl acetate) afforded the *title compound* as a yellow oil (6.52 g, 93%); R_f 0.30 (CH_2Cl_2); δ_H (400 MHz, $CDCl_3$) 2.47–2.36 (2H, m, C**H₂**), 1.93–1.76 (2H, m, C**H₂**), 1.61–1.51 (2H, m, C**H₂**), 1.42–1.30 (2H, m, C**H₂**). Data consistent with those reported in the literature.[145]

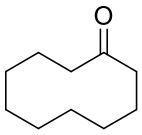
Ethyl 2-oxocyclodecane-1-carboxylate (328)



To a solution of cyclononanone (1.87 g, 13.3 mmol) in Et_2O (26 mL) at 0 °C, was added a solution of $BF_3.OEt_2$ (2.51 mL, 20 mmol) in Et_2O (10 mL) over 5 min. A solution of ethyl diazoacetate (87% wt. in CH_2Cl_2, 2.45 mL, 30.0 mmol) in Et_2O (7.5 mL), was then added over a period of 15 min, causing a vigorous evolution of gas. The resulting solution was allowed to warm to room temperature under an argon atmosphere over 16 h, where the mixture was cooled to 0 °C and neutralised with saturated aqueous solution of $NaHCO_3$. The resulting mixture was extracted with chloroform (3 × 40 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 20:1 hexane:ethyl acetate) afforded the *title compound* (as a 3:2 mixture of ketone:enol tautomers) as a yellow oil (1.72 g, 57%); R_f 0.72 &

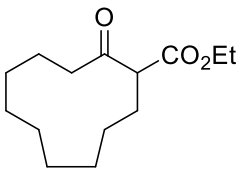
0.64 ketone/enol tautomers (CH_2Cl_2); ν_{max}/cm^{-1} (neat) 2926, 1744, 1707, 1638, 1602; δ_H (400 MHz, $CDCl_3$) 12.95 (1H, s, O**H**, enol), 4.20 (2H, q, *J* = 7.3 Hz, OC**H₂**CH_3, enol), 4.12 (2H, q, *J* = 7.3 Hz, OC**H₂**CH_3, keto), 3.81 (1H, dd, *J* = 3.2, 11.0 Hz, C**H**CO_2Et, keto), 2.76–2.64 (2H, m, C**H₂**CO, keto), [2.45–2.34 (2H), 2.24–2.04 (2H), 2.00–1.87 (2H), 1.86–1.70 (4H), 1.69–1.31 (20H), 7 × C**H₂** (keto and enol) and C**H₂**CO (enol)], 1.29 (3H, t, *J* = 7.3 Hz, $OCH_2C\mathbf{H_3}$, enol), 1.22 (3H, t, *J* = 7.3 Hz, $OCH_2C\mathbf{H_3}$, keto); δ_C (100 MHz, $CDCl_3$) data for the ketone tautomer only: 209.0 (**C**OCH), 169.9 (**C**OOEt), 61.4 (O**C**H_2), 57.9 (**C**H), 42.2 (**C**H_2CO), 30.2 (**C**H_2), 27.3 (**C**H_2), 25.3 (**C**H_2), 25.2 (**C**H_2), 24.5 (**C**H_2), 23.7 (**C**H_2), 21.1 (**C**H_2), 14.1 (**C**H_3). Diagnostic ^{13}C NMR resonances for the enol tautomer: 175.1, 173.7, 99.9 (**C**CO_2Et), 60.3 (O**C**H_2), 38.5 (**C**H_2CO). HRMS (ESI): calcd. for $C_{13}H_{22}NaO_3$, 249.1461. Found: $[MNa]^+$, 249.1463 (−0.7 ppm error)]. Data is consistent with those previously reported.[144]

Cyclodecanone (329)



A degassed solution of ethyl 2-oxocyclodecane-1-carboxylate (1.70 g, 7.52 mmol) in DMSO (7.5 mL) and H_2O (2 mL) was refluxed at 160 °C for 16 h. After cooling to room temperature, the mixture was partitioned between water (30 mL) and Et_2O (3 × 100 mL), where the combined organic phases were dried over $MgSO_4$, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 20:1 hexane:ethyl acetate → 10:1 hexane:ethyl acetate → 2:1 hexane:ethyl acetate) afforded the *title compound* as a yellow oil (1.04 g, 90%); R_f 0.71 (ethyl acetate); δ_H (400 MHz, $CDCl_3$) 2.52–2.46 (4H, m, 2 × C**H₂**CO), 1.89–1.79 (4H, m, C**H₂**CH_2CO), 1.60–1.29 (10H, m, 5 × C**H₂**). Data is consistent with those previously reported in the literature.[146]

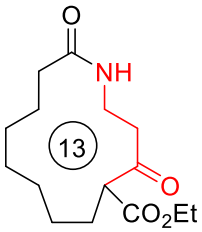
Ethyl 2-oxocyclodecane-1-carboxylate (330)



To a solution of cyclodecanone (4.86 g, 31.5 mmol) in Et_2O (60 mL) at 0 °C, was added a solution of $BF_3.OEt_2$ (5.93 mL, 47.3 mmol) in Et_2O (10 mL) over 5 min. A solution of ethyl diazoacetate (87% wt. in CH_2Cl_2, 5.79 mL, 47.3 mmol) in Et_2O (10 mL), was then added over a period of 15 min, causing a vigorous evolution of gas. The resulting solution was allowed to warm to room temperature under an argon atmosphere over 16 h, where the mixture was cooled to 0 °C and neutralised with sat. aq. solution of $NaHCO_3$. The resulting mixture was extracted with $CHCl_3$ (3 × 100 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 20:1 hexane:ethyl acetate) afforded the *title compound* (as a 2:1 mixture of ketone:enol tautomers) as a yellow oil (5.84 g, 77%); R_F 0.81&0.77(CH_2Cl_2); ν_{max}/cm^{-1} (thin film) 2929, 2865, 1745, 1710, 1638, 1603; δ_H (400 MHz, $CDCl_3$)

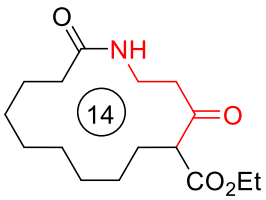
12.96 (1H, s, O**H**, enol tautomer), 4.26–4.07 (4H, m, C**H₂**O, both tautomers), 3.67 (1H, dd, *J* = 10.5, 2.9 Hz, C**H**CO_2Et, keto tautomer), 2.74 (1H, ddd, *J* = 16.4, 9.2, 3.2 Hz, C**H**H', keto), 2.58 (1H, ddd, *J* = 16.4, 9.2, 3.2 Hz, CH**H'**, keto), 2.53–2.42 (2H, m, C**H**H', both), 2.38 (1H, t, *J* = 6.3 Hz, CH**H'**, keto), 2.35–2.30 (1H, m, CH**H'**, enol), 2.14–2.02 (1H, m, C**H**H', keto), 1.97–1.87 (1H, m, CH**H'**, keto), 1.87–1.14 (34H, m, both); δ_C (100 MHz, $CDCl_3$) data for the keto tautomer only: 208.6 (**C**O), 170.0 (**C**O), 61.4 (**C**H_2O), 58.2 (**C**HCO_2Et), 41.5 (**C**H_2CO), 26.5 (**C**H_2), 25.6 (**C**H_2), 25.0 (**C**H_2), 24.69 (**C**H_2), 24.67 (**C**H_2), 24.4 (**C**H_2), 24.3 (**C**H_2), 22.5 (**C**H_2), 14.2 (**C**H_3); HRMS (ESI): calcd. for $C_{14}H_{24}NaO_3$, 263.1618. Found: $[MNa]^+$, 263.1615 (1.1 ppm error). Data is consistent with those previously reported.[144]

Ethyl 4,13-dioxoazacyclotridecane-5-carboxylate (334)



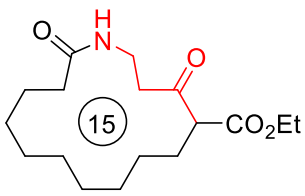
A mixture of ethyl 2-oxocyclononane-1-carboxylate (84 mg, 0.393 mmol), $MgCl_2$ (75 mg, 0.780 mmol) and pyridine (0.190 mL, 2.36 mmol) in CH_2Cl_2 (3 mL) under an argon atmosphere was stirred at room temperature for 30 min. Next, a solution of acid chloride (1.18 mmol, prepared using the general procedure) in CH_2Cl_2 (1 mL) was added and the reaction mixture was stirred for 2 h, at room temperature. The mixture was then diluted with CH_2Cl_2 (20 mL) and washed with 10% aq. HCl (25 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL) and the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was then re-dissolved in CH_2Cl_2 (4 mL) and piperidine (0.390 mL, 3.93 mmol) was added. The resulting mixture was stirred for 2 h, at room temperature, before the solvent was removed *in vacuo*. Purification by column chromatography (SiO_2, 5:1 hexane:ethyl acetate→ethyl acetate) afforded the *title compound* as a white solid (83.0 mg, 74%); m.p. 121–123 °C (chloroform); R_F 0.18 (1:1 hexane:ethyl acetate); ν_{max}/cm^{-1} (thin film) 3395, 3288, 3072, 2932, 2862, 1742, 1709, 1640, 1539; δ_H (400 MHz, $CDCl_3$) 6.38 (1H, br s, N**H**), 4.07 (2H, q, *J* = 6.9 Hz, OC**H₂**CH_3), 3.63–3.50 (1H, m, C**H**H'NH), 3.43–3.30 (2H, m, CH**H'**NH and C**H**CO_2Et), 2.95–2.74 (2H, m, C**H₂**COCH), 2.18–1.99 (2H, m, C**H₂**CONH), 1.88–1.71 (2H, m, C**H₂**CH), 1.67–0.96 (13H, m, 5 × C**H₂** and C**H₃**); δ_C (100 MHz, $CDCl_3$) 207.1 (**C**O), 173.7 (**C**O), 169.5 (**C**O), 61.3 (O**C**H_2), 58.3 (**C**HCO$_2$Et), 42.2 (**C**H_2COCH), 36.5 (**C**H_2CONH), 34.0 (**C**H_2NH), 27.6 (**C**H_2CH), 26.1 (**C**H_2), 25.6 (**C**H_2), 25.5 (**C**H_2), 24.4 (**C**H_2), 24.1 (**C**H_2), 14.1 (**C**H_3); HRMS (ESI): calcd. for $C_{15}H_{25}NNaO_4$, 306.1676. Found: $[MNa]^+$, 306.1679 (−1.1 ppm error).

Ethyl 4,14-dioxoazacyclotetradecane-5-carboxylate (335)



A mixture of ethyl 2-oxocyclodecane-1-carboxylate (89 mg, 0.393 mmol), $MgCl_2$ (75.0 mg, 0.780 mmol) and pyridine (0.190 mL, 2.36 mmol) in CH_2Cl_2 (3 mL) under an argon atmosphere was stirred at room temperature for 30 min. Next, a solution of acid chloride (1.18 mmol, prepared using the general procedure) in CH_2Cl_2 (1 mL) was added and the reaction mixture was stirred for 2 h, at room temperature. The mixture was then diluted with CH_2Cl_2 (20 mL) and washed with 10% aq. HCl (25 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL) and the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was then re-dissolved in CH_2Cl_2 (4 mL) and piperidine (0.390 mL, 3.93 mmol) was added. The resulting mixture was stirred for 2 h, at room temperature, before the solvent was removed *in vacuo*. Purification by column chromatography (SiO_2, 5:1 hexane:ethyl acetate→ethyl acetate) afforded the *title compound* as a colourless oil (60.0 mg, 52%); R_F 0.28 (1:1 hexane:ethyl acetate); ν_{max}/cm^{-1} (thin film) 3300, 3064, 2929, 2859, 1738, 1709, 1643, 1607; δ_H (400 MHz, $CDCl_3$) 6.14 (1H, br s, N**H**), 4.12 (2H, q, *J* = 6.9 Hz, OC**H₂**), 3.59–3.48 (2H, m, C**H₂**NH), 3.44 (1H, dd, *J* = 10.7, 3.8 Hz, C**H**CO_2Et), 2.91–2.66 (2H, m, C**H₂**COCH), 2.12 (2H, t, *J* = 6.1 Hz, C**H₂**CONH), 2.04–1.90 (1H, m, C**H**H'CH), 1.85–1.72 (1H, m, CH**H'**CH), 1.70–1.02 (15H, m, 6 × C**H₂** and CH_2C**H₃**); δ_C (100 MHz, $CDCl_3$) 206.6 (**C**O), 172.9 (**C**O), 169.6 (**C**O), 61.5 (O**C**H_2), 58.3 (**C**HCO_2Et), 41.5 (**C**H_2COCH), 34.7 (**C**H_2CONH), 33.3 (**C**H_2NH), 28.7 (**C**H_2CH), 26.7 (**C**H_2), 26.2 (**C**H_2), 25.3 (**C**H_2), 25.0 (**C**H_2), 24.8 (**C**H_2), 24.5 (**C**H_2), 14.2 (**C**H_3); HRMS (ESI): calcd. for $C_{16}H_{27}NNaO_4$, 320.1832. Found: $[MNa]^+$, 320.1826 (1.7 ppm error).

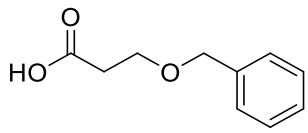
Ethyl 4,15-dioxoazacyclopentadecane-5-carboxylate (336)



A mixture of ethyl 2-oxocycloundecane-1-carboxylate (94.0 mg, 0.393 mmol), $MgCl_2$ (75 mg, 0.780 mmol) and pyridine (0.190 mL, 2.36 mmol) in CH_2Cl_2 (3 mL) under an argon atmosphere was stirred at room temperature for 30 min. Next, a solution of acid chloride (1.18 mmol, prepared using the general procedure) in CH_2Cl_2 (1 mL) was added and the reaction mixture was stirred for 2 h, at room temperature. The mixture was then diluted with CH_2Cl_2 (20 mL) and washed with 10% aq. HCl (25 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL) and the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was then re-dissolved in CH_2Cl_2 (4 mL) and piperidine (0.390 mL, 3.93 mmol) was added. The resulting mixture was stirred for 2 h, at room temperature, before the solvent was removed *in vacuo*. Purification by column chromatography (SiO_2, 5:1 hexane:ethyl acetate → 1:1 hexane:ethyl acetate → ethyl acetate) afforded the *title compound* (as a 3:1 mixture of

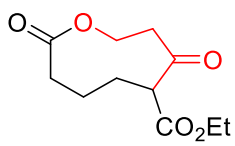
rotamers) as a colourless oil (79 mg, 65%); R_f 0.21 (1:1 hexane:ethyl acetate); ν_{max}/cm^{-1} (thin film) 3300, 2928, 2857, 1740, 1710, 1642, 1538; δ_H (400 MHz, $CDCl_3$) 6.20 (1H, br t, *J* = 5.5 Hz, N**H**, major rotamer), 6.12 (1H, br t, *J* = 5.3 Hz, N**H**, minor rotamer), 4.19–4.08 (4H, m, C**H₂**CH₃, both rotamers), 3.71–3.62 (1H, m, C**H**H'NH, major), 3.56–3.50 (1H, m, C**H**H'NH, minor), 3.45 (1H, dd, *J* = 10.3, 4.0 Hz, C**H**CO₂Et, both), 3.35–3.24 (2H, m, CH**H'**NH, both), 2.91–2.79 (4H, m, C**H₂**COCH, both), 2.37–1.93 (8H, m, 2 × C**H₂**, both), 1.87–1.05 (34H, m, 7 × C**H₂** and C**H₃**, both); δ_C (100 MHz, $CDCl_3$) data for the major rotamer only: 206.7 (**C**O), 173.5 (**C**O), 169.6 (**C**O), 61.7 (**C**H₂CH₃), 58.0 (**C**HCO₂Et), 43.7 (**C**H₂NH), 36.2 (**C**H₂CO), 34.0 (**C**H₂CO), 28.5 (**C**H₂), 28.0 (**C**H₂), 27.6 (**C**H₂), 27.2 (**C**H₂), 26.9 (**C**H₂), 26.8 (**C**H₂), 26.6 (**C**H₂), 25.0 (**C**H₃); HRMS (ESI): calcd. for $C_{17}H_{29}NNaO_4$, 334.1989. Found: $[MNa]^+$, 334.1983 (1.8 ppm error).

3-(Benzyloxy)propanoic acid (351)



This compound has been prepared using the following literature procedure.[120] β-Propiolactone (15.4 g, 0.214 mol) and benzyl alcohol (53.3 mL, 0.514 mol) were stirred at 80 °C for 24 h. Upon completion, the reaction was cooled to room temperature and quenched with 1 m $NaOH_{(aq)}$ (400 mL) and the aqueous phase was washed with CH_2Cl_2 (3 × 50 mL). The aqueous phase was then acidified to pH 1 using 10% $HCl_{(aq)}$ and extracted with ethyl acetate (3 × 150 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent was removed *in vacuo* to afford the *title compound* as a colourless oil (35.1 g, 91%); R_F 0.50 (ethyl acetate); δ_H (400 MHz, $CDCl_3$) 10.2 (1H, br s, CO_2**H**), 7.39–7.24 (5H, m, 5 × C**H**), 4.55 (2H, s, OC**H₂**Ph), 3.75 (2H, t, *J* = 6.1 Hz, C**H₂**OBn), 2.66 (2H, t, *J* = 6.1 Hz, C**H₂**OBn). Data is consistent with those previously reported.[120]

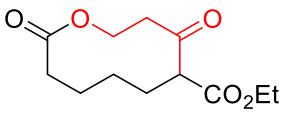
Ethyl 4,9-dioxooxonane-5-carboxylate (352)



A mixture of ethyl 2-oxocyclopentane-1-carboxylate (61 mg, 0.393 mmol), $MgCl_2$ (75 mg, 0.780 mmol) and pyridine (0.190 mL, 2.36 mmol) in CH_2Cl_2 (3 mL) under an argon atmosphere was stirred at room temperature for 30 min. Next, a solution of acid chloride (1.18 mmol, prepared using the general procedure) in CH_2Cl_2 (1 mL) was added and the reaction mixture was stirred for 2 h, at room temperature. The solvent was then concentrated *in vacuo*, loaded onto a short silica plug and eluted with ethyl acetate, to remove the majority of excess carboxylic acid and pyridine residues, and concentrated *in vacuo*. This material was re-dissolved in ethyl acetate (3.9 mL) and placed under an argon atmosphere. Palladium on carbon (39 mg, Pd 10% on carbon) was then added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at room temperature under a slight positive pressure of hydrogen (balloon) for 18 h. The reaction was

then purged with argon, filtered through Celite, washed with ethyl acetate and the solvent was removed *in vacuo*. The crude material was then re-dissolved in chloroform (3.9 mL) and triethylamine (82 µL, 0.590 mmol) added, and stirred at room temperature for 18 h, then reduced *in vacuo*. Purification by flash column chromatography (SiO_2, 2:1 hexane:ethyl acetate) afforded the *title compound* (as a 2:3 mixture of keto:enol tautomeric forms) as a colourless oil (53 mg, 59%); R_F 0.45 (1:1 hexane:ethyl acetate); ν_{max}/cm^{-1} (thin film) 2979, 1738, 1641, 1613; δ_H (400 MHz, $CDCl_3$) 12.81 (1H, s, O**H**, enol tautomer), 4.93–4.84 (1H, m, OC**H**H'CH_2, keto tautomer), 4.36–4.28 (1H, m, OCH**H'**CH_2, keto), 4.27–4.08 (6H, m, O**CH_2**CH_3, both tautomers and O**CH_2**CH_2, enol), 3.57 (1H, dd, *J* = 9.9, 4.0 Hz, C**H**CO_2Et, keto), 3.06–2.98 (1H, m, C**H**H'CO, keto), 2.90–2.81 (1H, m, CH**H'**CO, keto), 2.50–2.27 (6H, m, 3 × C**H_2**, both), 2.21–1.93 (8H, m, 4 × C**H_2**, both), 1.34–1.18 (6H, m, C**H_3**, both); δ_C (100 MHz, $CDCl_3$) 205.4 (**C**O), 175.2 (**C**O), 174.5 (**C**O), 173.1 (**C**O), 170.8 (**C**O), 169.1 (**C**O), 103.5 (**C**CO_2Et, enol), 61.7 (**C**H_2O), 61.5 (**C**H_2O), 60.8 (**C**H_2O), 60.6 (**C**H_2O), 57.8 (**C**HCO_2Et, keto), 41.2 (**C**H_2), 38.2 (**C**H_2), 34.8 (**C**H_2), 33.3 (**C**H_2), 27.5 (**C**H_2), 26.8 (**C**H_2), 23.4 (**C**H_2), 23.3 (**C**H_2), 14.4 (**C**H_3), 14.2 (**C**H_3); HRMS (ESI): calcd. for $C_{11}H_{16}NaO_5$, 251.0890. Found: $[MNa]^+$, 251.0886 (1.6 ppm error).

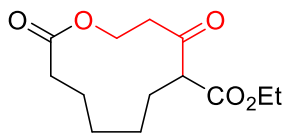
Ethyl 4,10-dioxooxecane-5-carboxylate (353)



A mixture of ethyl 2-oxocyclohexane-1-carboxylate (67 mg, 0.393 mmol), $MgCl_2$ (75 mg, 0.780 mmol) and pyridine (0.190 mL, 2.36 mmol) in CH_2Cl_2 (3 mL) under an argon atmosphere was stirred at room temperature for 30 min. Next, a solution of acid chloride (1.18 mmol, prepared using the general procedure) in CH_2Cl_2 (3 mL) was added and the reaction mixture was stirred for 2 h, at room temperature. The solvent was then concentrated *in vacuo*, loaded onto a short silica plug and eluted with 2:1 hexane:ethyl acetate, to remove the majority of excess carboxylic acid and pyridine residues, and concentrated *in vacuo*. This material was re-dissolved in ethyl acetate (3.9 mL) and placed under an argon atmosphere. Palladium on carbon (39 mg, Pd 10% on carbon) was then added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at room temperature under a slight positive pressure of hydrogen (balloon) for 16 h. The reaction was then purged with argon, filtered through Celite, washed with ethyl acetate and the solvent was removed *in vacuo*. The crude material was then re-dissolved in chloroform (3.9 mL) and triethylamine (82.0 µL, 0.590 mmol) added, and stirred at room temperature for 16 h, then reduced *in vacuo*. Purification by flash column chromatography (SiO_2, 2:1 hexane:ethyl acetate → ethyl acetate) afforded the *title compound* (as a 3:2 mixture of keto:enol tautomeric forms) as a colourless oil (53 mg, 56%); R_f 0.49 (1:1 hexane:ethyl acetate); ν_{max}/cm^{-1} (thin film) 2943, 2874, 1732, 1715, 1642; δ_H (400 MHz, $CDCl_3$) 12.74 (1H, s, O**H**, enol), 4.72–4.62

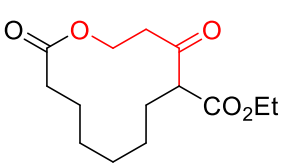
(1H, m, C**H**H'O, keto), 4.32–4.07 (7H, m, CH**H'**O, keto, and C**H₂**O, enol and $CH_3C\mathbf{H_2}O$, both), 3.68 (1H, dd, *J* = 9.9, 4.6 Hz, C**H**CO), 2.99–2.90 (1H, m, C**H**H'COCH, keto), 2.85–2.75 (1H, m, CH**H'**COCH, keto), 2.46–2.36 (1H, m, C**H**H'COO, keto), 2.34–2.10 (5H, m, CH**H'**COO, keto, and C**H₂**COO, enol and C**H₂**COH, enol), 2.02–1.33 (12H, m, 3 × C**H₂**, both), 1.29 (3H, t, *J* = 6.9 Hz, C**H₃**, enol), 1.24 (3H, t, *J* = 6.9 Hz, keto); δ_C (100 MHz, $CDCl_3$) 206.2 (**C**O, keto), 174.6 (**C**OH, enol), 173.2 (**C**O, enol), 173.0 (**C**O, keto), 170.7 (**C**O, enol), 169.4 (**C**O, keto), 102.5 (**C**), 61.53 ($CH_3\mathbf{C}H_2O$, keto/enol), 61.49 ($CH_3\mathbf{C}H_2O$, keto/enol), 61.0 (**C**H_2O, enol), 60.5 (**C**H_2O, keto), 58.3 (**C**H, keto), 39.8 (**C**H_2CO, keto), 35.9 (**C**H_2COO, enol), 34.6 (**C**H_2COO, keto), 31.1 (**C**H_2COH, enol), 27.9 (**C**H_2, enol), 26.6 (**C**H_2, keto), 24.5 (**C**H_2, enol), 24.0 (**C**H_2, keto), 23.3 (**C**H_2, enol), 22.1 (**C**H_2, keto), 14.3 (**C**H_3, enol, 14.2 (**C**H_3, keto); HRMS (ESI): calcd. for $C_{12}H_{18}NaO_5$, 265.1046. Found: $[MNa]^+$, 265.1035 (1.1 ppm error).

Ethyl 4,11-dioxooxacycloundecane-5-carboxylate (280)



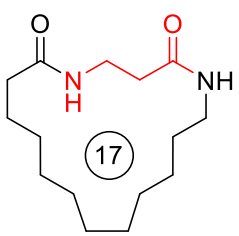
A mixture of ethyl 2-oxocycloheptane-1-carboxylate (72.0 mg, 0.393 mmol), $MgCl_2$ (75.0 mg, 0.780 mmol) and pyridine (0.190 mL, 2.36 mmol) in CH_2Cl_2 (3 mL) under an argon atmosphere was stirred at room temperature for 30 min. Next, a solution of acid chloride (1.18 mmol, prepared using the general procedure) in CH_2Cl_2 (1 mL) was added and the reaction mixture was stirred for 2 h, at room temperature. The mixture was then loaded onto a short silica plug and eluted with 2:1 hexane:ethyl acetate to remove excess pyridine and carboxylic acid residues. The crude material was then dissolved in ethyl acetate (3.9 mL) and placed under an argon atmosphere. Palladium on carbon (39 mg, Pd 10% on carbon) was then added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at room temperature under a slight positive pressure of hydrogen (balloon) for 3 h. The reaction was then purged with argon, filtered through Celite, washed with methanol before the solvent was removed *in vacuo*. The crude material was dissolved in chloroform (3.9 mL) and triethylamine (82.0 µL, 0.590 mmol) added and then stirred at room temperature for 18 h, where the solvent was removed *in vacuo*. Purification by flash column chromatography (2:1 hexane:ethyl acetate) afforded the *title compound* as a colourless oil (54.0 mg, 53%); R_F 0.55 (solvent); δ_H (400 MHz, $CDCl_3$) 4.68–4.62 (1H, m), 4.24–4.11 (3H, m), 3.43 (1H, dd, J = 12.0, 3.0 Hz CH), 3.09 (1H, ddd, J = 14.5, 10.1, 3.7 Hz), 2.58–2.52 (1H, m), 2.46–2.41 (1H, m), 2.18–2.04 (2H, m), 1.82–1.71 (4H, m), 1.53–1.47 (1H, m), 1.43–1.38 (1H, m), 1.30– 1.21 (4H, m). Data is consistent with those reported in the literature.[112]

Ethyl 4,12-dioxooxacyclododecane-5-carboxylate (354)



A mixture of ethyl 2-oxocyclooctane-1-carboxylate (78.0 mg, 0.393 mmol), $MgCl_2$ (75.0 mg, 0.780 mmol) and pyridine (0.190 mL, 2.36 mmol) in CH_2Cl_2 (3 mL) under an argon atmosphere was stirred at room temperature for 30 min. Next, a solution of acid chloride (1.18 mmol, prepared using the general procedure) in CH_2Cl_2 (3 mL) was added and the reaction mixture was stirred for 2 h, at room temperature. The solvent was then concentrated *in vacuo*, loaded onto a short silica plug and eluted with 2:1 hexane:ethyl acetate, to remove the majority of excess carboxylic acid and pyridine residues, and concentrated *in vacuo*. This material was re-dissolved in ethyl acetate (3.9 mL) and placed under an argon atmosphere. Palladium on carbon (39 mg, Pd 10% on carbon) was then added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at room temperature under a slight positive pressure of hydrogen (balloon) for 16 h. The reaction was then purged with argon, filtered through Celite, washed with ethyl acetate and the solvent was removed *in vacuo*. The crude material was then re-dissolved in chloroform (3.9 mL) and triethylamine (82.0 µL, 0.590 mmol) added, and stirred at room temperature for 18 h, then reduced *in vacuo*. Purification by flash column chromatography (SiO_2, 2:1 hexane:ethyl acetate → ethyl acetate) afforded the *title compound* (as a 3:1 mixture of keto:enol tautomers) as a yellow oil (64 mg, 60%); R_F 0.76 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 2928, 2857, 1745, 1706, 1642; δ_H (400 MHz, $CDCl_3$) 12.60 (1H, s, O**H**, enol tautomer), 4.28–4.09 (8H, m, 2 × C**H₂**O, both tautomers), 3.55 (1H, dd, *J* = 11.1, 5.0 Hz, C**H**CO_2Et, keto tautomer), 2.68–2.32 (8H, m, 2 × C**H₂**CO, both), 2.17–2.06 (4H, m, C**H₂**, both), 1.97–1.65 (8H, m, 2 × C**H₂**, both), 1.56–1.19 (14H, m, 2 × C**H₂** and C**H₃**, both); δ_C (100 MHz, $CDCl_3$) data for the ketone tautomer only: 212.2 (**C**O), 175.9 (**C**O), 170.4 (**C**O), 61.3 (**C**H_2O), 60.3 (**C**H_2O), 57.2 (**C**HCO_2Et), 41.8 (**C**H_2CO), 30.0 (**C**H_2CO), 29.1 (**C**H_2), 27.1 (**C**H_2), 25.6 (**C**H_2), 25.4 (**C**H_2), 24.7 (**C**H_2), 14.2 (**C**H_3); HRMS (ESI): calcd. for $C_{14}H_{22}NaO_5$, 293.1359. Found: $[MNa]^+$, 293.1357 (0.7 ppm error).

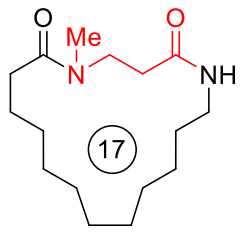
1,5-Diazacycloheptadecane-2,6-dione (365)



A mixture of laurolactam (155 mg, 0.786 mmol), DMAP (10 mg, 0.078 mmol) and pyridine (0.38 mL, 4.72 mmol) in CH_2Cl_2 (5.5 mL) under an argon atmosphere was stirred at room temperature for 30 min. Next, a solution of acid chloride (1.18 mmol, 1.5 equiv., freshly prepared using the general procedure) in CH_2Cl_2 (3 mL) was added and the resulting mixture was refluxed at 50 °C for 16 h. The mixture was then diluted with CH_2Cl_2 (30 mL) and washed with 10% aq. HCl (30 mL). The aqueous layer was then extracted with CH_2Cl_2 (3 × 30 mL)

and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was then re-dissolved in CH_2Cl_2 (8 mL) and piperidine (0.78 mL, 7.86 mmol) was added, followed by stirring at room temperature for 18 h, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 ethyl acetate: hexane → 9:1 ethyl acetate:methanol) afforded the *title compound* as a white crystalline solid (197 mg, 96%); m.p. 101-103 °C; R_F 0.38 (9:1 ethyl acetate:methanol); ν_{max}/cm^{-1} (neat) 3265, 3088, 2927, 2857, 1664, 1636, 1550; δ_H (400 MHz, $CDCl_3$) 6.33 (1H, br s, N**H**), 5.67 (1H, br s, N**H**), 3.60–3.45 (2H, m, C**H₂**), 3.39–3.23 (2H, m, C**H₂**), 2.42 (2H, t, *J* = 5.3 Hz, C**H₂**), 2.14 (2H, t, *J* = 6.9 Hz, C**H₂**), 1.63 - 1.54 (2H, m, C**H₂**), 1.50 - 1.40 (2H, m, C**H₂**), 1.36–1.17 (14H, m, (C**H₂** x 7)); δ_C (100 MHz, $CDCl_3$) 173.8 (**C**O), 171.6 (**C**O), 39.1 (**C**H_2), 37.0 (**C**H_2), 35.6 (**C**H_2), 35.2 (**C**H_2), 29.2 (**C**H_2), 27.94 (**C**H_2), 27.91 (**C**H_2), 27.5 (**C**H_2), 27.3 (**C**H_2), 27.0 (**C**H_2), 26.0 (**C**H_2), 25.7 (**C**H_2), 24.8 (**C**H_2); HRMS (ESI): calcd. for $C_{15}H_{28}N_2O_2Na$, 291.2043. Found $[MNa]^+$, 291.2045 (−1.0 ppm error).

5-Methyl-1,5-diazacycloheptadecane-2,6-dione (368)



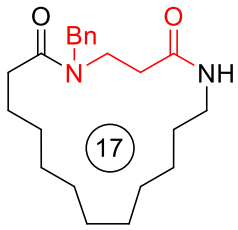
A mixture of laurolactam (155 mg, 0.786 mmol), DMAP (10 mg, 0.0786 mmol) and pyridine (0.380 mL, 4.72 mmol) in CH_2Cl_2 (5.5 mL) under an argon atmosphere was stirred at room temperature for 30 min. Next, a solution of acid chloride (1.18 mmol, 1.50 equiv., freshly prepared using the general procedure) in CH_2Cl_2 (3 mL) was added and the resulting mixture was refluxed at 50 °C for 16 h. The mixture was then diluted with CH_2Cl_2 (30 mL) and washed with 10% aq. HCl (30 mL). The aqueous layer was then extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was then re-dissolved in CH_2Cl_2 (8 mL) and piperidine (0.780 mL, 7.86 mmol) was added, followed by stirring at room temperature for 18 h, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 ethyl acetate:hexane → 9:1 ethyl acetate:methanol) afforded the *title compound* (as a 5:1 mixture of rotamers) as a yellow oil (188 mg, 89%); R_F 0.33 (9:1 ethyl acetate:methanol); ν_{max}/cm^{-1} (neat) 3300, 2928, 2857, 2239, 1626, 1552; δ_H (400 MHz, d_2-CH_2Cl_2) 7.36 (1H, br s, N**H**, major rotamer), 6.45 (1H, br s, N**H**, minor rotamer), 3.71–3.62 (4H, m, C**H₂**, both rotamers), 3.31–3.19 (4H, m, C**H₂**, both), 3.05 (3H, s, NC**H₃**, major), 2.92 (3H, s, NC**H₃**, minor), 2.61–2.52 (2H, m, C**H₂**, major), 2.51–2.45 (2H, m, C**H₂**, minor), 2.43–2.37 (2H, m, C**H₂**, minor), 2.37–2.30 (2H, m, C**H₂**, major), 1.70–1.57 (4H, m, C**H₂**, both), 1.56–1.46 (4H, m, C**H₂**, both), 1.42–1.22 (28H, m, C**H₂** x 7, both); δ_C (100 MHz, $CDCl_3$) data for the major rotamer only: 174.4 (**C**O), 171.0 (**C**O), 44.1 (**C**H_2), 40.0 (**C**H_2), 36.3 (**C**H_2), 35.4 (**C**H_2), 32.9 (**C**H_2), 28.2 (**C**H_2), 27.5 (**C**H_2), 27.0 (**C**H_3), 26.9 (**C**H_2), 26.5 (**C**H_2), 26.1 (**C**H_2), 25.3 (**C**H_2), 25.1 (**C**H_2),

24.2 (**C**H_2). Diagnostic ^{13}C NMR resonances for the minor rotamer: 173.7 (**C**O), 170.2 (**C**O), 46.6 (**C**H_2); HRMS (ESI): calcd. for $C_{16}H_{30}N_2NaO_2$, 305.2199. Found: $[MNa]^+$, 305.2191 (−2.7 ppm error).

The same product was also prepared using an analagous Cbz-protection strategy via the following method:

A mixture of laurolactam (155 mg, 0.786 mmol), DMAP (10 mg, 0.0786 mmol) and pyridine (0.380 mL, 4.72 mmol) in CH_2Cl_2 (5.5 mL) under an argon atmosphere was stirred at room temperature for 30 min. Next, a solution of (((benzyloxy)carbonyl)(methyl)amino)propanoyl chloride (2.36 mmol, 3 equiv., freshly prepared using the general procedure) in CH_2Cl_2 (4 mL) was added and refluxed at 50 °C for 16 h. The mixture was then concentrated *in vacuo*, loaded onto a short silica plug and eluted 2:1 hexane:ethyl actetate, to remove the pyridine and excess carboxylic acid residues, and concentrated *in vacuo*. This material was then re-dissolved in ethyl acetate (5.0 mL) and placed under an argon atmosphere. Palladium on carbon (78.4 mg, Pd 10% on carbon) was then added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at room temperature under a slight positive pressure of hydrogen (balloon) for 16 h. The reaction was then purged with argon, filtered through Celite, washed with methanol and the solvent removed *in vacuo* to afford the title compound (194 mg, 87%). Spectral data as above.

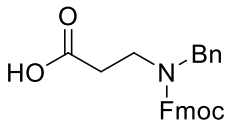
5-Benzyl-1,5-diazacycloheptadecane-2,6-dione (369)



A mixture of laurolactam (155 mg, 0.786 mmol), DMAP (10 mg, 0.0786 mmol) and pyridine (0.380 mL, 4.72 mmol) in CH_2Cl_2 (5.5 mL) under an argon atmosphere was stirred at room temperature for 30 min. Next, a solution of acid chloride (1.18 mmol, 1.50 equiv., freshly prepared using the general procedure) in CH_2Cl_2 (3 mL) was added and the resulting mixture was refluxed at 50 °C for 16 h. The mixture was then diluted with CH_2Cl_2 (30 mL) and washed with 10% aq. HCl (30 mL). The aqueous layer was then extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was then re-dissolved in CH_2Cl_2 (8 mL) and DBU (1.2 mL, 7.86 mmol) was added, followed by stirring at room temperature for 18 h, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 ethyl acetate: hexane → 9:1 ethyl acetate: methanol) afforded the *title compound* (as a 4:1 mixture of rotamers) as a colourless oil (248 mg, 91%); R_F 0.55 (9:1 ethyl acetate: methanol); ν_{max}/cm^{-1} (neat) 3300, 2926, 2856, 1631, 1551; δ_H (400 MHz, $CDCl_3$) 7.38–7.09 (10H, m, Ph, both rotamers), 7.07 (1H, br s, N**H**, major), 5.63 (1H, br s, N**H**, minor), 4.62 (2H, s, C**H₂**Ph, major), 4.58 (2H, s, C**H₂**Ph, minor), 3.62 (4H, t, *J* =

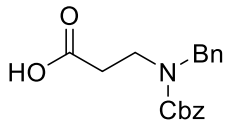
5.3 Hz, C**H₂**, both), 3.30–3.22 (2H, m, C**H₂**, major), 3.22–3.15 (2H, m, C**H₂**, minor), 2.58–2.51 (2H, m, C**H₂**, major), 2.49–2.41 (2H, m, C**H₂**, minor) 2.37–2.27 (2H, m, C**H₂**, major), 2.20–2.13 (2H, m, C**H₂**, minor), 1.74–1.56 (4H, m, C**H₂**, both), 1.55–1.42 (4H, m, C**H₂**, both), 1.42–1.19 (28H, m, C**H₂** × 7, both); δ_C (100 MHz, $CDCl_3$) data for the major rotamer only: 175.1 (**C**O), 171.3 (**C**O), 136.7 (**C**), 129.0 (**C**H), 127.7 (**C**H), 126.3 (**C**H), 52.1 (**C**H_2Ph), 42.6 (**C**H_2), 39.8 (**C**H_2), 35.7 (**C**H_2), 32.9 (**C**H_2), 28.5 (**C**H_2), 27.6 (**C**H_2), 27.2 (**C**H_2), 27.1 (**C**H_2), 26.6 (**C**H_2), 26.5 (**C**H_2), 25.6 (**C**H_2), 25.1 (**C**H_2), 24.8 (**C**H_2). Diagnostic ^{13}C NMR resonances for the minor rotamer: 173.9 (**C**O), 170.1 (**C**O), 128.7 (**C**H), 128.1 (**C**H), 44.2 (**C**H_2); HRMS (ESI): calcd. for $C_{22}H_{35}N_2O_2$, 359.2693. Found: $[MH]^+$, 359.2681 (−3.5 ppm error)].

3-((((9*H*-Fluoren-9-yl)methoxy)carbonyl)(benzyl)amino)propanoic acid (381)



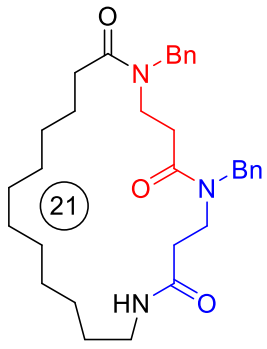
Methyl 3-(benzylamino)propanoate (11.3 g, 54.4 mmol) was dissolved in THF (157 mL) and 1m NaOH(aq) (157 mL) added and stirred at room temperature for 2 h. Upon completion, the solution was acidified with acetic acid (glacial, 6.84 mL, 0.119 mol) then concentrated *in vacuo*. The crude salt was then dissolved in water (200 mL), dioxane (300 mL) and Na_2CO_3 (250 mL, 10% solution) added. The solution was cooled to 0 °C whilst stirring and a pre-made solution of 9-fluorenylmethyl chloroformate (16.9 g, 5.10 mmol) dissolved in dioxane (50 mL) was added slowly. The solution was warmed to room temperature and stirred until reaction completion. The mixture was diluted with water (600 mL) and washed with EtOAc (2 x 500 mL) and then the aqueous layer was acidified to pH 2 using 10% HCl(aq) and extracted with EtOAc (3 x 100 mL). The combined organics were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* which afforded the *title compound* (as a 1:1 mixture of rotamers) as a yellow viscous oil (21.96 g, 99%); R_f 0.35 (9:1 ethyl acetate:methanol); ν_{max}/cm^{-1} (neat) 2964, 1720, 1650; δ_H (400 MHz, $CDCl_3$) 10.95 (1H, br s, CO_2**H**, both rotamers), 7.84–7.68 (4H, m, Ar, both rotamers), 7.61 (2H, d, *J* = 6.9 Hz, Ar), 7.46 (2H, d, *J* = 7.6 Hz, Ar), 7.43–7.20 (14H, m, Ar, both), 7.15 (2H, d, *J* = 6.9 Hz, Ar), 7.10–7.00 (2H, m, Ar), 4.66 (2H, d, *J* = 5.3 Hz, OC**H₂**), 4.55 (2H, d, *J* = 6.1 Hz, OC**H₂**), 4.46 (2H, s, C**H₂**Ph), 4.41 (2H, s, C**H₂**Ph), 4.26 (1H, t, *J* = 5.3 Hz, CH_2C**H**), 4.21 (1H, t, *J* = 6.2 Hz, CH_2C**H**), 3.55 (2H, t, *J* = 6.1 Hz, NC**H₂**), 3.24 (2H, t, *J* = 6.7 Hz, NC**H₂**), 2.62 (2H, t, *J* = 6.2 Hz, HO_2CC**H₂**), 2.18 (2H, t, *J* = 6.7 Hz, HO_2CC**H₂**); δ_C (100 MHz, $CDCl_3$) 177.5 and 177.3 (**C**O_2H), 156.5 and 156.3 (N**C**O), 143.9 (fluorenyl, both rotamers), 141.53 and 141.45 (fluorenyl), 137.4 (Ph, both), 128.81 and 128.76 (Ph), 127.9 and 127.8 (Ph), 127.6 (Ph, both), 127.3 and 127.24 (fluorenyl), 127.24 and 127.18 (fluorenyl), 120.1 (fluorenyl, both), 67.6 and 67.2 (O**C**H_2), 51.3 and 51.2 (N**C**H_2Ph), 47.5 and 47.4 (CH_2**C**H), 43.4 and 42.1 (N**C**H_2CH_2), 32.9 (**C**H_2CO_2H, both); HRMS (ESI): calcd. for $C_{25}H_{23}NNaO_4$, 424.1519. Found: $[MNa]^+$, 424.1506 (3.6 ppm error).

3-(Benzyl-benzyloxycarbonyl-amino)-propionic acid (383)



Ethyl 3-(benzylamino)propanoate (11.25 g, 54.3 mmol) was added to a suspension of $K_2CO_{3(aq)}$ (1.05 m, 62.0 mL, 65.1 mmol) in THF (62 mL), and cooled to 0 °C. Benzyl chloroformate (9.35 g, 59.7 mmol) was added portionwise over 30 min. The mixture was stirred at 0 °C for 30 min and then warmed to room temperature, and stirred for 12 h. Upon completion, the solution was diluted with ethyl acetate (150 mL) and extracted with ethyl acetate (3 × 50 mL) and concentrated *in vacuo*. The crude product was then reacted with NaOH(aq) (1 m, 157 mL, 0.163 mol) and THF (157 mL) and stirred at room temperature for 6 h. The mixture was then diluted with water (100 mL) and washed with CH_2Cl_2 (100 mL). The remaining aqueous phase is acidified with HCl (10% aqueous solution) before being extracted with CH_2Cl_2 (3 × 100 mL) and ethyl acetate (2 × 125 mL). The combined organic layers were then dried over $MgSO_4$, filtered and removed *in vacuo*. Purification by column chromatography (SiO_2, 20% ethyl acetate in hexanes) afforded the *title compound* (as a 1:1 mixture of rotamers) as a yellow oil (15.74 g, 93%); R_f 0.30 (ethyl acetate); δ_H (400 MHz, $CDCl_3$); 7.38–7.17 (20H, m, 10 × C**H**, both rotamers), 5.21 (2H, s, C**H₂**O, rotamer A), 5.18 (2H, s, C**H₂**O, rotamer B), 4.55 (4H, s, NC**H₂**Ph, both), 3.55 (2H, t, *J* = 8.8 Hz, C**H₂**NBn, rotamer A), 3.45 (2H, t, *J* = 6.6 Hz, C**H₂**NBn, rotamer B), 2.65 (2H, t, *J* = 6.6 Hz, C**H₂**CO_2H, rotamer A), 2.54 (2H, t, *J* = 8.8 Hz, C**H₂**CO_2H, rotamer B); HRMS (ESI): calcd. for $C_{18}H_{19}NNaO_4$, 336.1206. Found: $[MNa]^+$, 336.1206 (1.5 ppm error). Data is consistent with those previously reported in the literature.[147]

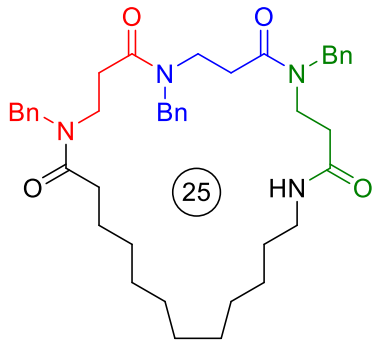
5,9-Dibenzyl-1,5,9-triazacyclohenicosane-2,6,10-trione (389)



A mixture of 5-benzyl-1,5-diazacycloheptadecane-2,6-dione (282 mg, 0.786 mmol), DMAP (10 mg, 0.0786 mmol) and pyridine (0.380 mL, 4.72 mmol) in CH_2Cl_2 (5.5 mL) under an argon atmosphere was stirred at room temperature for 30 min. Next, a solution of acid chloride (1.18 mmol, 1.50 equiv., freshly prepared using the general procedure) in CH_2Cl_2 (3 mL) was added and the resulting mixture was refluxed at 50 °C for 16 h. The mixture was then diluted with CH_2Cl_2 (30 mL) and washed with 10% aq. HCl (30 mL). The aqueous layer was then extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was then re-dissolved in CH_2Cl_2 (8 mL) and DBU (1.2 mL, 7.86 mmol) was added, followed by stirring at room temperature for 18 h, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 ethyl acetate: hexane → 9:1 ethyl acetate: methanol) afforded the *title compound* (as a 1:1:1.5 mixture of rotamers) as a colourless oil (223 mg, 65%); R_F 0.54 (9:1 ethyl acetate: methanol); ν_{max}/cm^{-1} (neat) 3315, 2926, 2855, 1628,

1551; δ_H (400 MHz, $CDCl_3$) 7.55–7.01 (30H, m, 2 × Ph, all rotamers), 7.00–6.96 (1H, m, N**H**, single rotamer), 6.96–6.87 (1H, br s, N**H**, single), 6.56 (1H, br s, N**H**, single), [4.62 (2H, br s), 4.60–4.52 (2H, m), 4.42 (1H, s), 4.40 (2H, s), C**H₂**Ph, all)], 3.73–3.49 (12H, m, 2 × C**H₂**NBn, all), 3.35–3.12 (6H, m, C**H₂**NH, all), 2.76–2.28 (18H, m, 3 × C**H₂**CO, all), 1.76–1.20 (54H, m, 9 × C**H₂**, all); δ_C (100 MHz, $CDCl_3$) data for the major rotamer only: 174.4 (**C**O), 171.1 (**C**O), 170.1 (**C**O), 137.6 (**C**), 136.7 (**C**), 129.3 (**C**H), 129.1 (**C**H), 128.7 (**C**H), 128.2 (**C**H), 127.5 (**C**H), 126.4 (**C**H), 60.5 (**C**H_2Ph), 52.6 (**C**H_2Ph), 49.4 (BnN**C**H_2), 45.3 (BnN**C**H_2), 42.5 (NH**C**H_2), 39.5 (**C**H_2CO), 36.9 (**C**H_2CO), 33.3 (**C**H_2CO), 31.2 (**C**H_2), 28.8 (**C**H_2), 27.6 (**C**H_2), 27.2 (**C**H_2), 26.8 (**C**H_2), 26.3 (**C**H_2), 25.4 (**C**H_2), 24.6 (**C**H_2), 21.2 (**C**H_2). Diagnostic ^{13}C NMR resonances for other rotamers: 175.1 (**C**O), 174.3 (**C**O), 172.1 (**C**O), 171.6 (**C**O), 171.2 (**C**O), 170.6 (**C**O), 137.8 (**C**), 136.9 (**C**), 136.8 (**C**), 136.2 (**C**); HRMS (ESI): calcd. for $C_{32}H_{45}N_3NaO_3$, 542.3353. Found: $[MNa]^+$, 542.3352 (−0.7 ppm error).

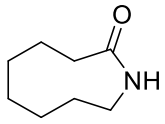
5,9,13-Tribenzyl-1,5,9,13-tetraazacyclopentacosane-2,6,10,14-tetraone (390)



A mixture of 5,9-dibenzyl-1,5,9-triazacyclohenicosane-2,6,10-trione (320 mg, 0.615 mmol), DMAP (8 mg, 0.0615 mmol) and pyridine (0.300 mL, 3.69 mmol) in CH_2Cl_2 (5.0 mL) under an argon atmosphere was stirred at room temperature for 30 min. Next, a solution of acid chloride (0.923 mmol, 1.50 equiv., freshly prepared using the general procedure) in CH_2Cl_2 (3 mL) was added and the resulting mixture was refluxed at 50 °C for 16 h. A further two portions of acid chloride (0.923 mmol, 1.5 equiv) in CH_2Cl_2 (3 mL) were added at 40 h and 64 h until full acylation was achieved, analysed by TLC. The mixture was then diluted with CH_2Cl_2 (30 mL) and washed with 10% aq. HCl (30 mL). The aqueous layer was then extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*, loaded onto a short silica plug and eluted with 1:1 ethyl acetate:hexane to remove excess carboxylic acid and pyridine residues. The crude material was then re-dissolved in CH_2Cl_2 (8 mL) and DBU (0.940 mL, 6.15 mmol) was added, followed by stirring at room temperature for 18 h, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:2 ethyl acetate:hexane → ethyl acetate → 9:1 ethyl acetate:methanol) afforded the *title compound* (as a mixture of 7 rotamers) as a yellow oil (280 mg, 77%). Quantity of rotamers was determined by number of carbonyl resonances in ^{13}C NMR; R_f 0.69 (9:1 ethyl acetate: methanol); ν_{max}/cm^{-1} (thin film) 3299, 2926, 2856, 1648, 1626, 1543; δ_H (400 MHz, $CDCl_3$); δ_H (400 MHz, $CDCl_3$) 7.56–6.39 (112H, m, Ph and N**H**, all rotamers), 4.80–4.34 (40H, m, C**H₂**Ph, all rotamers), 4.20 (2H, s, C**H₂**Ph, single rotamer), 3.83–3.43 (42H, m, C**H₂**NBn, all rotamers), 3.34–3.10 (14H, m, C**H₂**NH), 2.82–2.24 (56H, m, C**H₂**CO, all rotamers), 1.80–1.00 (126H, m, 9 × C**H₂**); δ_C (100 MHz,

$CDCl_3$) 174.5 (**C**O), 174.2 (**C**O), 174.0 (**C**O), 173.94 (**C**O), 173.85 (**C**O), 173.72 (**C**O), 173.67 (**C**O), 172.2 (**C**O), 172.1 (**C**O), 171.9 (**C**O), 171.49 (**C**O), 171.47 (**C**O), 171.4 (**C**O), 171.3 (**C**O), 171.19 (**C**O), 171.16 (**C**O), 171.14–171.06 (m, 3 × **C**O), 171.0 (**C**O), 170.94 (**C**O), 170.88 (**C**O), 170.72 (**C**O), 170.4 (**C**O), 170.3 (**C**O), 170.1 (**C**O), 170.0 (**C**O), 169.9 (**C**O), 138.2 (**C**CH), 137.8 (**C**CH), 137.7 (**C**CH), 137.6 (**C**CH), 137.50 (**C**CH), 137.47(**C**CH), 137.4 (**C**CH), 137.2 (**C**CH), 137.0 (**C**CH), 136.90 (**C**CH), 136.87 (**C**CH), 136.7 (**C**CH), 136.59 (**C**CH), 136.56 (**C**CH), 136.5 (**C**CH), 126.3 (**C**H), 129.20 (**C**H), 129.16 (**C**H), 129.1 (**C**H), 129.02 (**C**H), 129.98 (**C**H), 128.95 (**C**H), 128.9 (**C**H), 128.84 (**C**H), 128.81–128.62 (m, **C**H), 128.60 (**C**H), 128.55 (**C**H), 128.5 (**C**H), 128.42 (**C**H), 128.33 (**C**H), 128.29 (**C**H), 128.27 (**C**H), 128.24 (**C**H), 128.19 (**C**H), 128.16 (**C**H), 128.1 (**C**H), 128.02 (**C**H), 127.99 (**C**H), 127.94 (**C**H), 127.81 (**C**H), 127.78 (**C**H), 127.7 (**C**H), 127.6 (**C**H), 127.54 (**C**H), 127.50 (**C**H), 127.4 (**C**H), 127.3 (**C**H), 127.1 (**C**H), 126.7 (**C**H), 126.59 (**C**H), 126.55 (**C**H), 126.5 (**C**H), 126.39 (**C**H), 126.37 (**C**H), 126.3 (**C**H), 126.19 (**C**H), 126.17 (**C**H), 126.02(**C**H), 126.95 (**C**H), 53.0 (**C**H_2Ph), 52.7 (**C**H_2Ph), 52.6 (**C**H_2Ph), 52.5 (**C**H_2Ph), 52.4 (**C**H_2Ph), 52.22 (**C**H_2Ph), 52.1 (**C**H_2Ph), 52.0 (**C**H_2Ph), 51.9 (**C**H_2Ph), 51.8 (**C**H_2Ph), 49.2 (**C**H_2Ph), 49.14 (**C**H_2Ph), 49.09 (**C**H_2Ph), 48.9 (**C**H_2Ph), 48.8 (**C**H_2Ph), 48.73 (**C**H_2Ph), 48.68 (**C**H_2Ph), 48.6 (**C**H_2Ph), 48.3 (**C**H_2Ph), 45.0 (**C**H_2NBn), 44.73 (**C**H_2NBn), 44.69 (**C**H_2NBn), 44.67 (**C**H_2NBn), 44.4 (**C**H_2NBn), 44.3 (**C**H_2NBn), 44.1 (**C**H_2NBn), 44.05 (**C**H_2NBn), 44.00 (**C**H_2NBn), 43.9 (**C**H_2NBn), 43.82 (**C**H_2NBn), 43.75 (**C**H_2NBn), 43.72 (**C**H_2NBn), 43.66 (**C**H_2NBn), 43.6 (**C**H_2NBn), 43.5 (**C**H_2NBn), 43.4 (**C**H_2NBn), 42.9 (**C**H_2NBn), 39.8 (**C**H_2NH), 39.7 (**C**H_2NH), 39.6 (**C**H_2NH), 39.49 (**C**H_2NH), 39.45 (**C**H_2NH), 36.9 (**C**H_2CO), 36.3 (**C**H_2CO), 36.1 (**C**H_2CO), 35.4 (**C**H_2CO), 35.3 (**C**H_2CO), 35.1 (**C**H_2CO), 34.0 (**C**H_2CO), 33.3 (**C**H_2CO), 33.2 (**C**H_2CO), 32.90 (**C**H_2CO), 32.85 (**C**H_2CO), 32.8 (**C**H_2CO), 32.50 (**C**H_2CO), 32.47 (**C**H_2CO), 32.4 (**C**H_2CO), 32.32 (**C**H_2CO), 32.29 (**C**H_2CO), 32.14 (**C**H_2CO), 32.09 (**C**H_2CO), 31.9 (**C**H_2CO), 31.7 (**C**H_2CO), 31.5 (**C**H_2CO), 31.4 (**C**H_2CO), 31.25 (**C**H_2CO), 31.22 (**C**H_2CO), 31.16 (**C**H_2CO), 31.1 (**C**H_2CO), 29.3 (**C**H_2), 29.19–29.06 (m, **C**H_2), 29.0 (**C**H_2), 28.93 (**C**H_2), 28.86 (**C**H_2), 28.83 (**C**H_2), 28.7 (**C**H_2), 28.59 (**C**H_2), 28.55 (**C**H_2), 28.5 (**C**H_2), 28.4 (**C**H_2), 28.34 (**C**H_2), 28.28 (**C**H_2), 28.1 (**C**H_2), 28.0 (**C**H_2), 27.9 (**C**H_2), 27.83 (**C**H_2), 27.75 (**C**H_2), 27.7 (**C**H_2), 27.6 (**C**H_2), 27.5 (**C**H_2), 27.42 (**C**H_2), 27.38 (**C**H_2), 27.24 (**C**H_2), 27.16 (**C**H_2), 26.9 (**C**H_2), 26.6 (**C**H_2), 26.48–26.27 (m, **C**H_2), 26.2 (**C**H_2), 26.1 (**C**H_2), 25.96–25.84 (m, **C**H_2), 25.5 (**C**H_2), 25.4 (**C**H_2), 25.24 (**C**H_2), 25.21 (**C**H_2), 25.1 (**C**H_2), 25.0 (**C**H_2), 24.83 (**C**H_2), 24.78 (**C**H_2), 24.4 (**C**H_2); HRMS (ESI): calcd. for $C_{42}H_{56}N_4NaO_4$, 703.419377. Found: $[MNa]^+$, 703.420607 (−2.7 ppm error).

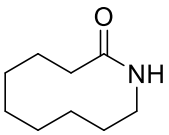
Azonan-2-one (394)



Cyclooctanone (633 mg, 5.0 mmol) in formic acid (5 mL) was added a solution of hydroxylamine-o-sulphonic acid (850 mg, 7.5 mmol) in formic acid (2.5 mL) and heated to 110 °C for 16 h. Purification by flash column chromatography (SiO_2, 2:1 hexane:ethyl acetate → ethyl acetate → 9:1 ethyl acetate:methanol) afforded the *title*

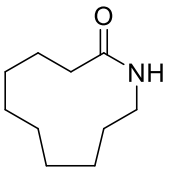
compound as an orange solid (560 mg, 79%). Data consistent with those reported in the literature.[148]

Azecan-2-one (395)



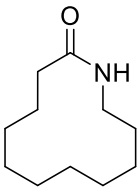
To a magnetically stirred solution of the cyclononanone (462 mg, 3.3 mmol) and formic acid (≥95%, 3.5 mL), a solution of hydroxylamine-o-sulphonic acid (560 mg, 4.95 mmol) in formic acid (1.65 mL) was added dropwise at room temperature over a period of 10 min. The reaction mixture was then heated under reflux for 16 h. After cooling, it was quenched with water, neutralised with NaOH (2M) and then extracted with $CHCl_3$ (4 × 30 mL). The organic extracts were combined, dried over $MgSO_4$, and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 2:1 hexane:ethyl acetate → ethyl acetate → 9:1 ethyl acetate:methanol) afforded the *title compound* as a yellow solid (327 mg, 68%); R_f 0.46 (9:1 ethyl acetate:methanol); δ_H (400 MHz, $CDCl_3$) 5.69 (1H, br s, N**H**), 3.51–3.21 (2H, m, C**H₂**NH), 2.50–2.14 (2H, m, C**H₂**CONH), 1.93–1.17 (12H, m, 6 × C**H₂**); δ_C (100 MHz, $CDCl_3$) 174.5 (**C**O), 40.8 (**C**H_2NH), 37.6 (**C**H_2CO), 26.3 (**C**H_2), 26.1 (**C**H_2), 24.42 (**C**H_2), 24.37 (**C**H_2), 23.9 (**C**H_2), 23.2 (**C**H_2). Data is consistent with those previously reported in the literature.[148]

Azacycloundecan-2-one (396)



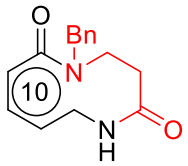
Cyclodecanone (1.240 g, 8.04 mmol) in formic acid (9 mL) was added to a solution of hydroxylamine-o-sulfonic acid (1.37 g, 12.1 mmol) in formic acid (4 mL) and heated to 110 °C for 16 h. Purification by flash column chromatography (SiO_2, 2:1 hexane:ethyl acetate → ethyl acetate → 9:1 ethyl acetate:methanol) afforded the *title compound* as an orange solid (803 mg, 59%). Data consistent with those reported in the literature.[149]

Azacyclododecan-2-one (397)



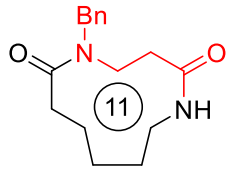
Cycloundecanone (500 mg, 3.0 mmol) in formic acid (4 mL) was added to a solution of hydroxy-o-sulfonic acid (511 mg, 4.51 mmol) in formic acid (2 mL) and heated to 110 °C for 16 h. Purification by flash column chromatography (SiO_2, 50% ethyl acetate in hexanes → ethyl acetate) afforded the *title compound* as a white solid (453 mg, 82%). Data is consistent with those previously reported in the literature.[150]

5-Benzyl-1,5-diazecane-2,6-dione (400)



A mixture of δ-valerolactam (78.0 mg, 0.786 mmol), DMAP (10 mg, 0.0786 mmol) and pyridine (0.380 mL, 4.72 mmol) in CH_2Cl_2 (5.5 mL) under an argon atmosphere was stirred at room temperature for 30 min. Next, a solution of acid chloride (1.18 mmol, 1.50 equiv., freshly prepared using the general procedure) in CH_2Cl_2 (3 mL) was added and the resulting mixture was refluxed at 50 °C for 16 h. The mixture was then diluted with CH_2Cl_2 (30 mL) and washed with 10% aq. HCl (30 mL). The aqueous layer was then extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was then re-dissolved in CH_2Cl_2 (8 mL) and DBU (1.2 mL, 7.86 mmol) was added, followed by stirring at room temperature for 18 h, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 ethyl acetate: hexane → 9:1 ethyl acetate: methanol) afforded the *title compound* (as a 10:1 mixture of rotamers) as a colourless oil (129 mg, 65%); R_F 0.26 (9:1 ethyl acetate: methanol); ν_{max}/cm^{-1} (neat) 3326, 2929, 1645, 1607, 1535; δ_H (400 MHz, $CDCl_3$) 7.35–7.17 (10H, m, Ph, both rotamers), 6.00 (1H, d, *J* = 9.2 Hz, N**H**, minor), 5.85 (1H, br s, N**H**, major), 5.01 (1H, d, *J* = 14.5 Hz, NC**H₂**Ph, major), 4.84 (1H, d, *J* = 16.8 Hz, NC**H₂**Ph, minor), 4.28 (1H, d, *J* = 16.8 Hz, NC**H₂**Ph, minor), 4.20 (1H, d, *J* = 14.5 Hz, NC**H₂**Ph, major), 3.97–3.82 (2H, m, BnNC**H₂**, both), 3.80–3.65 (2H, m, BnNC**H₂**, both), 3.30–3.20 (1H, m, C**H₂**NH, major), 3.19–3.14 (1H, m, C**H₂**NH, minor), 2.97–2.90 (1H, m, C**H₂**NH, minor), 2.89–2.78 (1H, m, C**H₂**NH, major), 2.75–2.59 (2H, m, COC**H₂**, both), 2.50 (1H, m, COC**H₂**, major), 2.43–2.34 (1H, m, COC**H₂**, minor), 2.20–2.04 (8H, m, 2 × C**H₂**, both), 1.69–1.55 (4H, m, C**H₂**, both); δ_C (100 MHz, $CDCl_3$) data for the major rotamer only: 174.1 (**C**O), 171.2 (**C**O), 138.0 (**C**CH), 129.0 (C**C**H), 128.1 (**C**H), 127.8 (**C**H), 49.1 (**C**H_2Ph), 45.2 (**C**H_2), 39.3 (**C**H_2), 37.4 (**C**H_2), 28.3 (**C**H_2), 25.8 (**C**H_2), 24.0 (**C**H_2). Diagnostic ^{13}C NMR **resonances** for the minor rotamer: 179.2 (**C**O), 176.4 (**C**O), 136.7 (Ph), 60.5 (**C**H_2). HRMS (ESI): calcd. for $C_{15}H_{20}N_2NaO_2$, 283.1417. Found: $[MNa]^+$, 283.1417 (−0.1 ppm error)].

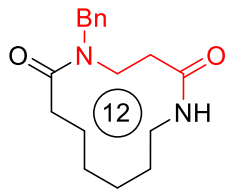
5-Benzyl-1,5-diazacycloundecane-2,6-dione (401)



A mixture of ε-caprolactam (89 mg, 0.786 mmol), DMAP (10 mg, 0.0786 mmol) and pyridine (0.380 mL, 4.72 mmol) in CH_2Cl_2 (5.5 mL) under an argon atmosphere was stirred at room temperature for 30 min. Next, a solution of acid chloride (1.18 mmol, 1.50 equiv, freshly prepared using the general procedure) in CH_2Cl_2 (3 mL) was added and the resulting mixture was refluxed at 50 °C for 16 h. The mixture was then diluted with CH_2Cl_2 (30 mL) and washed with 10% aq. HCl (30 mL). The aqueous layer was then extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was then re-dissolved

in CH_2Cl_2 (8 mL) and DBU (1.20 mL, 7.86 mmol) was added, followed by stirring at room temperature for 18 h, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 5:1 hexane:ethyl acetate → 1:1 hexane:ethyl acetate → 9:1 ethyl acetate:methanol) afforded the *title compound* (as a 6:1 mixture of rotamers determined by ^1H NMR in $CDCl_3$ at room temperature) as a colourless oil (170 mg, 79%). Note, to aid characterisation the ^1H NMR data was recorded at 80 °C, which resolved the rotamer resonances. R_F 0.37 (9:1 ethyl acetate:methanol); ν_{max}/cm^{-1} (thin film) 3289, 2931, 1620, 1554; δ_H (400 MHz, d_6-DMSO, 80 °C) 7.85 (1H, br s, N**H**), 7.39–7.15 (5H, m, Ph), 4.53 (2H, br s, PhC**H₂**), 3.50 (2H, br s, BnNC**H₂**), 2.96 (2H, br s, NHC**H₂**), 2.22 (4H, br s, 2 × C**H₂**), 1.68–1.41 (4H, m, 2 × C**H₂**), 1.27 (2H, br s, C**H₂**). Diagnostic ^1H NMR resonances recorded in $CDCl_3$ at room temperature, which confirm the presence of the two rotamer forms can be found at: 6.10 (1H, br s, N**H**, major), 5.97 (1H, br s, N**H**, minor); δ_C (100 MHz, $CDCl_3$) 173.5 (**C**O), 171.4 (**C**O), 138.5 (**C**), 129.0 (**C**H), 128.3 (**C**H), 127.9 (**C**H), 49.2 (**C**H_2Ph), 45.2 (BnN**C**H_2), 41.8 (NH**C**H_2), 37.07 (**C**H_2CONH), 28.6 (**C**H_2CO), 25.3 (**C**H_2), 24.4 (**C**H_2), 22.8 (**C**H_2); HRMS (ESI): calcd. for $C_{16}H_{22}N_2NaO_2$, 297.1573. Found: $[MNa]^+$, 297.1567 (2.2 ppm error).

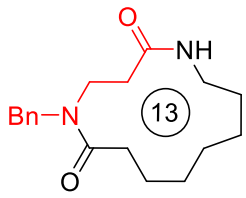
5-Benzyl-1,5-diazacyclododecane-2,6-dione (402)



A mixture of azocan-2-one (100 mg, 0.786 mmol), DMAP (10 mg, 0.0786 mmol) and pyridine (0.380 mL, 4.72 mmol) in CH_2Cl_2 (5.5 mL) under an argon atmosphere was stirred at room temperature for 30 min. Next, a solution of acid chloride (1.18 mmol, 1.50 equiv., freshly prepared using the general procedure) in CH_2Cl_2 (3 mL) was added and the resulting mixture was refluxed at 50 °C for 16 h. The mixture was then diluted with CH_2CH_2 (30 mL) and washed with 10% aq. HCl (30 mL). The aqueous layer was then extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was then re-dissolved in CH_2Cl_2 (8 mL) and DBU (1.2 mL, 7.86 mmol) was added, followed by stirring at room temperature for 18 h, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 ethyl acetate: hexane → 9:1 ethyl acetate: methanol) afforded the *title compound* (as a 5:1 mixture of rotamers determined by ^1H NMR in $CDCl_3$ at room temperature) as a colourless oil (190 mg, 84%). Note, to aid characterisation the ^1H NMR data was recorded at high temperature, which resolved the rotamer resonances. R_F 0.42 (9:1 ethyl acetate: methanol); ν_{max}/cm^{-1} (neat) 3299, 2928, 1623, 1552, 1448; δ_H (400 MHz, d_6-DMSO, 120 °C) 7.60–7.15 (6H, m, Ph, N**H**), 4.57 (2H, br s, PhC**H₂**), 3.15 (2H, s, BnNC**H₂**), 2.57–2.18 (4H, m, NHC**H₂**, C**H₂**CONH), 1.84–1.02 (10H, m, 5 × C**H₂**). Diagnostic ^1H NMR resonances recorded in $CDCl_3$ at room temperature, which confirm the presence of the two rotamer forms can be found

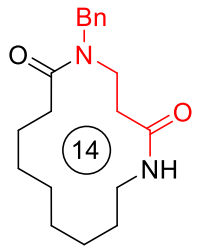
at: 6.57 (1H, br s, N**H**, major), 5.71 (1H, br s, N**H**, minor); δ_C (100 MHz, $CDCl_3$) data for the major rotamer only: 175.9 (**C**O), 170.4 (**C**O), 136.6 (**C**), 129.0 (**C**H), 127.8 (**C**H), 126.5 (**C**H), 51.9 (**C**H_2Ph), 41.1 (BnN**C**H_2), 39.2 (**C**H_2NH), 35.1 (**C**H_2), 32.5 (**C**H_2), 27.3 (**C**H_2), 25.9 (**C**H_2), 24.0 (**C**H_2), 22.3 (**C**H_2). ^{13}C NMR resonances for the minor rotamer: 174.9 (**C**O), 171.0 (**C**O), 138.5 (**C**), 128.8 (**C**H), 128.6 (**C**H), 127.7 (**C**H), 60.5 (**C**H_2), 48.7 (**C**H_2), 44.9 (**C**H_2), 36.7 (**C**H_2), 30.9 (**C**H_2), 26.7 (**C**H_2), 23.6 (**C**H_2), 22.5 (**C**H_2), 14.3 (**C**H_2). HRMS (ESI): calcd. for $C_{17}H_{24}N_2NaO_2$, 311.1730. Found: $[MNa]^+$, 311.1718 (3.4 ppm error).

5-Benzyl-1,5-diazacyclotridecane-2,6-dione (403)



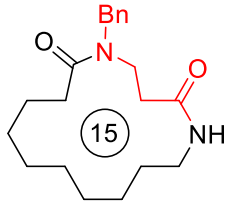
A mixture of azonan-2-one (111 mg, 0.786 mmol), DMAP (10 mg, 0.0786 mmol) and pyridine (0.38 mL, 4.72 mmol) in CH_2Cl_2 (5.5 mL) under an argon atmosphere was stirred at room temperature for 30 min. Next, a solution of acid chloride (1.18 mmol, 1.5 equiv., freshly prepared using the general procedure) in CH_2Cl_2 (3 mL) was added and the resulting mixture was refluxed at 50 °C for 16 h. The mixture was then diluted with CH_2Cl_2 (30 mL) and washed with 10% aq. HCl (30 mL). The aqueous layer was then extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was then re-dissolved in CH_2Cl_2 (8 mL) and DBU (1.2 mL, 7.86 mmol) was added, followed by stirring at room temperature for 18 h, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 ethyl acetate:hexane → 9:1 ethyl acetate:methanol) afforded the *title compound* (as a mixture of two rotamers in a 9:1 ratio) as an orange oil (158 mg, 90%); R_F 0.40 (9:1 ethyl acetate:methanol); δ_H (400 MHz, $CDCl_3$) 7.37–7.19 (6H, m, 3 × aromatic C**H**, both rotamers), 7.14–7.06 (4H, m, 2 × aromatic C**H**, both), 6.91 (1H, br s, N**H**, major rotamer), 5.69 (1H, br s, N**H**, minor rotamer), 4.66 (4H, br s, C**H₂**Ph, both), 3.72–3.60 (4H, m, C**H₂**N, both), 3.33–3.21 (4H, m, C**H₂**N, both), 2.80–2.54 (4H, m, C**H₂**CO, both), 2.42–2.17 (4H, m, C**H₂**CO, both), [1.85–1.66, 1.62–1.49, 1.45–1.24 (20H, m, 5 × C**H₂**, both)]; ν_{max}/cm^{-1} (thin film) 3300, 2928, 2859, 1625, 1552; δ_C (100MHz, $CDCl_3$) 176.0 (**C**O), 170.7 (**C**O), 136.7 (**C**), 129.0 (**C**H), 127.7 (**C**H), 126.4 (**C**H), 52.7 (**C**H_2Ph), 42.5 (**C**H_2NBn), 39.7 (**C**H_2NH), 34.9 (**C**H_2CONH), 32.9 (**C**H_2CONBn), 27.9 (**C**H_2), 27.2 (**C**H_2), 27.0 (**C**H_2), 25.7 (**C**H_2), 24.1 (**C**H_2); HRMS (ESI): calcd. for $C_{18}H_{26}N_2NaO_2$, 325.1886. Found: $[MNa]^+$, 325.1889 (−1.1 ppm error).

5-Benzyl-1,5-diazacyclotetradecane-2,6-dione (404)



A mixture of azecan-2-one (122 mg, 0.786 mmol), DMAP (10 mg, 0.0786 mmol) and pyridine (0.38 mL, 4.72 mmol) in CH_2Cl_2 (5.5 mL) under an argon atmosphere was stirred at room temperature for 30 min. Next, a solution of acid chloride (1.18 mmol, 1.5 equiv., freshly prepared using the general procedure) in CH_2Cl_2 (3 mL) was added and the resulting mixture was refluxed at 50 °C for 16 h. The mixture was then diluted with CH_2Cl_2 (30 mL) and washed with 10% aq. HCl (30 mL). The aqueous layer was then extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was then re-dissolved in CH_2Cl_2 (8 mL) and DBU (1.2 mL, 7.86 mmol) was added, followed by stirring at room temperature for 18 h, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 ethyl acetate:hexane → 9:1 ethyl acetate:methanol) afforded the *title compound* (as a mixture of two rotamers in a 9:1 ratio) as an orange oil (158 mg, 64%); R_F 0.40 (9:1 ethyl acetate:methanol); ν_{max}/cm^{-1} (neat) 3343, 2927, 2854, 1664, 1616, 1534; δ_H (400 MHz, $CDCl_3$) 7.40–7.28 (6H, m, Ph, both rotamers), 7.16 (4H, d, *J* = 6.9 Hz, Ph, both), 6.20 (1H, br s, N**H**, major rotamer), 4.74 (2H, s, C**H₂**Ph, major), 4.64 (2H, s, C**H₂**Ph, minor rotamer), 3.70–3.57 (4H, m, C**H₂**, both), 3.38–3.25 (4H, m, C**H₂**, both), 2.77–2.66 (4H, m, C**H₂**, both), 2.44–2.35 (4H, m, C**H₂**, both), 1.76–1.23 (24H, m, 6 x C**H₂**, both); δ_C (100 MHz, $CDCl_3$) resonances for the major rotamer only observed: 175.0 (**C**O), 171.0 (**C**O), 137.3 (Ph), 128.9 (Ph), 127.6 (Ph), 126.4 (Ph), 53.8 (**C**H_2Ph), 43.72 (**C**H_2), 38.9 (**C**H_2), 34.9 (**C**H_2), 32.9 (**C**H_2), 27.5 (**C**H_2), 25.5 (**C**H_2), 25.3 (**C**H_2), 25.2 (**C**H_2), 24.9 (**C**H_2), 23.1 (**C**H_2); HRMS (ESI): calcd. for $C_{19}H_{28}N_2NaO_2$, 339.2043. Found: $[MNa]^+$, 339.2028 (4.0 ppm error).

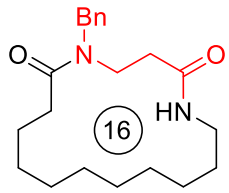
5-Benzyl-1,5-diazacyclopentadecane-2,6-dione (405)



A mixture of azacycloundecan-2-one (100 mg, 0.591 mmol), DMAP (7 mg, 0.0591 mmol) and pyridine (0.285 mL, 3.55 mmol) in CH_2Cl_2 (4 mL) under an argon atmosphere was stirred at room temperature for 30 min. Next, a solution of acid chloride (0.887 mmol, 1.50 equiv. prepared using the general procedure) in CH_2Cl_2 (3 mL) was added and the resulting mixture was refluxed at 50 °C for 16 h. The mixture was then diluted with CH_2Cl_2 (20 mL) and washed with 10% aq. HCl (15 mL). The aqueous layer was then extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was then re-dissolved in CH_2Cl_2 (7.5 mL) and DBU (0.905 mL, 5.91 mmol) was added, followed by stirring at room temperature for 18 h, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 5:1 ethyl acetate:hexane → 1:1 ethyl acetate:hexane → 9:1 ethyl

acetate:methanol) afforded the *title compound* (as a 9:1 mixture of rotamers) as a yellow oil (171 mg, 88%); R_F 0.58 (9:1 ethyl acetate:methanol); ν_{max}/cm^{-1} (thin film); 3314, 2930, 2858, 2240, 1623, 1552; δ_H (400 MHz, $CDCl_3$) 7.33–7.05 (10H, m, Ph, both rotamers), 7.03 (1H, br s, N**H**, major rotamer), 6.46 (1H, br s, N**H**, minor rotamer), 4.72 (2H, s, C**H₂**Ph, major), 4.53 (2H, s, C**H₂**Ph, minor), 3.63–3.43 (4H, m, C**H₂**NBn, both), 3.37–3.07 (4H, m, C**H₂**NH, both), 2.70–2.36 (4H, m, C**H₂**CONH, both), 2.35–2.03 (4H, m, C**H₂**CONBn, both), 1.70–1.10 (28H, m, 7 × C**H₂**, both); δ_C (100 MHz, $CDCl_3$) data for the major rotamer only: 175.0 (**C**O), 171.4 (**C**O), 137.5 (**C**), 128.9 (**C**H), 127.4 (**C**H), 126.3 (**C**H), 53.8 (**C**H_2Ph), 43.8 (**C**H_2NBn), 38.0 (**C**H_2NH), 34.6 (**C**H_2CONH), 32.3 (**C**H_2CONBn), 27.8 (**C**H_2), 26.8 (**C**H_2), 26.6 (**C**H_2), 26.41 (**C**H_2), 26.36 (**C**H_2), 25.6 (**C**H_2), 23.6 (**C**H_2). Diagnostic ^{13}C NMR resonances for the minor rotamer: 174.5 (**C**O), 170.9 (**C**O), 138.3 (**C**), 128.6 (**C**H), 128.1 (**C**H), 60.4 (**C**H_2Ph), 48.5 (**C**H_2NBn), 39.7 (**C**H_2NH), 36.0 (**C**H_2CONBn), 31.8 (**C**H_2CONH); HRMS (ESI): calcd. for $C_{20}H_{30}N_2NaO_2$, 353.2199. Found: $[MNa]^+$, 353.2201 (−0.1 ppm error).

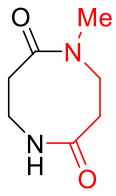
5-Benzyl-1,5-diazacyclohexadecane-2,6-dione (406)



A mixture of azacyclododecan-2-one (144 mg, 0.786 mmol), DMAP (10 mg, 0.0786 mmol) and pyridine (0.380 mL, 4.72 mmol) in CH_2Cl_2 (5.5 mL) under an argon atmosphere was stirred at room temperature for 30 min. Next, a solution of acid chloride (1.18 mmol, 1.50 equiv., freshly prepared using the general procedure) in CH_2Cl_2 (3 mL) was added and the resulting mixture was refluxed at 50 °C for 16 h. The mixture was then diluted with CH_2Cl_2 (30 mL) and washed with 10% aq. HCl (30 mL). The aqueous layer was then extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was then re-dissolved in CH_2Cl_2 (8 mL) and DBU (1.20 mL, 7.86 mmol) was added, followed by stirring at room temperature for 18 h, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 ethyl acetate:hexane → 9:1 ethyl acetate:methanol) afforded the *title compound* (as a 2:1 mixture of rotamers) as a yellow oil (239 mg, 88%); R_F 0.60 (9:1 ethyl acetate:methanol); ν_{max}/cm^{-1} (neat) 3300, 2927, 2857, 1632, 1550; δ_H (400 MHz, $CDCl_3$) 7.37–7.10 (10H, m, Ph, both rotamers), 6.29 (1H, br s, N**H**, major rotamer), 5.67 (1H, br s, N**H**, minor rotamer), 4.65 (2H, s, C**H₂**Ph, major), 4.58 (2H, s, C**H₂**Ph, minor), 3.69–3.58 (4H, m, C**H₂**, both rotamers), 3.36–3.26 (4H, m, C**H₂**, both), 2.58 (2H, t, *J* = 5.3 Hz, C**H₂**, major), 2.46 (2H, t, *J* = 7.6 Hz, C**H₂**, minor), 2.29 (2H, t, *J* = 6.9 Hz, C**H₂**, major), 2.24–2.17 (2H, m, C**H₂**, minor), 1.77–1.20 (32H, m, 8 x C**H₂**, both); δ_C (100 MHz, $CDCl_3$) 174.4 (**C**O), 171.2 (**C**O), 137.2 (**C**CH), 129.0 (**C**H), 127.6 (**C**H), 126.3 (**C**H), 53.1 (**C**H_2), 43.4 (**C**H_2), 39.2 (**C**H_2), 35.2 (**C**H_2), 31.9 (**C**H_2), 28.9 (**C**H_2), 26.6 (**C**H_2), 26.0 (**C**H_2), 25.5 (**C**H_2), 25.2 (**C**H_2), 24.7 (**C**H_2), 24.3 (**C**H_2), 24.0 (**C**H_2). Diagnostic ^{13}C NMR resonances for the minor rotamer: 173.6 (**C**O), 128.7 (**C**H), 128.0 (**C**H), 127.4 (**C**H), 48.9 (**C**H_2),

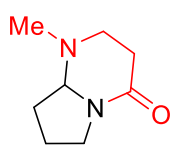
39.4 (**C**H_2), 36.7 (**C**H_2); HRMS (ESI): calcd. for $C_{21}H_{32}N_2NaO_2$, 367.2356. Found: $[MNa]^+$, 367.2348 (2.4 ppm error).

1-Methyl-1,5-diazocane-2,6-dione (410)



A mixture of 2-azetidinone (56 mg, 0.786 mmol), DMAP (10 mg, 0.0786 mmol) and pyridine (0.380 mL, 4.72 mmol) in CH_2Cl_2 (5.5 mL) under an argon atmosphere was stirred at room temperature for 30 min. Next, a solution of acid chloride (1.18 mmol, 1.50 equiv., freshly prepared using the general procedure) in CH_2Cl_2 (3 mL) was added and the resulting mixture was stirred at room temperature for 2 h. The mixture was then concentrated *in vacuo*, loaded onto a short silica plug and eluted ethyl actetate, to remove the pyridine and excess carboxylic acid residues, and concentrated *in vacuo*. This material was then re-dissolved in ethyl acetate (5.0 mL) and placed under an argon atmosphere. Palladium on carbon (55.0 mg, Pd 10% on carbon) was then added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at room temperature under a slight positive pressure of hydrogen (balloon) for 16 h. The reaction was then purged with argon, filtered through Celite, washed with methanol and the solvent removed *in vacuo* to afford the *title compound* as yellow solid (74 mg, 61%); R_F 0.05 (9:1 ethyl acetate:methanol); ν_{max}/cm^{-1} (thin film) 3204, 3079, 2951, 1632, 1480; δ_H (400 MHz, $CDCl_3$) 6.80 (1H, br t, *J* = 6.9 Hz, N**H**), 3.62 (2H, t, *J* = 6.9 Hz, MeNC**H₂**), 3.49 (2H, dt, *J* = 6.9, 7.6 Hz, HNC**H₂**), 2.93 (3H, s, C**H₃**N), 2.87–2.79 (4H, m, 2 × C**H₂**CO); δ_C (100 MHz, $CDCl_3$) 172.9 (**C**O), 170.8 (**C**O), 45.1 (**C**H_2NMe), 38.0 (**C**H_2NH), 37.8 (**C**H_2CONMe), 35.5 (**C**H_2CONH), 34.4 (**C**H_3N). HRMS (ESI): calcd. for $C_7H_{12}N_2NaO_2$, 179.0791. Found: $[MNa]^+$, 179.0793 (−1.3 ppm error).

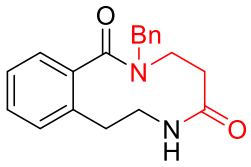
1-Methylhexahydropyrrolo[1,2-a]pyrimidin-4(1H)-one (413)



A mixture of 2-pyrrolidinone (67 mg, 0.786 mmol), DMAP (10 mg, 0.0786 mmol) and pyridine (0.380 mL, 4.72 mmol) in CH_2Cl_2 (5.5 mL) under an argon atmosphere was stirred at room temperature for 30 min. Next, a solution of acid chloride (1.18 mmol, 1.50 eqv prepared using the general procedure) in CH_2Cl_2 (3 mL) was added and the resulting mixture was refluxed at 50 °C for 16 h. The mixture was then diluted with CH_2Cl_2 (30 mL) and washed with 10% aq. HCl (30 mL). The aqueous layer was then extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*, loaded onto a short silica plug and eluted 1:1 hexane:ethyl actetate, to remove the pyridine and excess carboxylic acid residues, and concentrated *in vacuo*. This material was then re-dissolved in ethyl acetate (7.9 mL) and placed under an argon atmosphere. Palladium on carbon (78.6 mg, Pd 10% on carbon) was then added and the reaction vessel was backfilled with

hydrogen (via balloon) several times, then stirred at room temperature under a slight positive pressure of hydrogen (balloon) for 16 h. The reaction was then purged with argon, filtered through Celite, washed with methanol and the solvent was removed *in vacuo* to afford the title compound as a colourless oil (118 mg, 97%); R_f 0.05 (9:1 ethyl acetate:methanol); ν_{max}/cm^{-1} (thin film) 3436, 2953, 2799, 1623; δ_H (400 MHz, $CDCl_3$) 3.59–3.45 (2H, m, C**H** and C**H**H'NCO), 3.44–3.35 (1H, m, CH**H'**NCO), 2.93–2.82 (1H, m, C**H**H'NMe), 2.59–2.28 (3H, m, C**H**H'NMe and C**H$_2$**CH), 2.24 (3H, s, C**H$_3$**N), 2.07 (1H, dt, *J* = 5.3, 11.4 Hz, C**H**H'CO), 1.95–1.84 (1H, m, CH_2C**H**H'CH_2), 1.79–1.61 (1H, m, CH_2C**H**H'CH_2), 1.60–1.46 (1H, m, CH**H'**CO); δ_C (100 MHz, $CDCl_3$) 167.3 (**C**O), 79.8 (**C**HNMe), 52.6 (**C**H_2NMe), 44.7 (**C**H_2NCO), 41.0 (**C**H_3N), 32.4 (**C**H_2CO), 31.3 (CH**C**H_2), 20.6 (CH_2**C**H_2CH_2); HRMS (ESI): calcd. for $C_8H_{14}N_2NaO$, 177.1004. Found: $[MNa]^+$, 177.0997 (−4.0 ppm error).

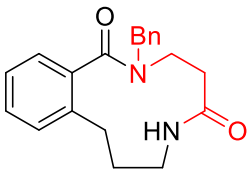
2-Benzyl-3,4,7,8-tetrahydro-2,6-benzodiazecine-1,5-(2*H*,6*H*)-dione (420)



A mixture of 3,4-dihydroisoquinolin-1(2*H*)-one (100 mg, 0.680 mmol), DMAP (8.31 mg, 0.0680 mmol) and pyridine (0.330 mL, 4.08 mmol) in CH_2Cl_2 (4.8 mL) under an argon atmosphere was stirred at room temperature for 30 min. A solution of acid chloride (1.02 mmol, 1.50 equiv., freshly prepared using the general procedure) in CH_2Cl_2 (3.1 mL) was added and the resulting mixture was refluxed at 50 °C for 18 h. An additional solution of acid chloride (1.02 mmol, 1.50 equiv. prepared using the general procedure) in CH_2Cl_2 (3.1 mL) was added and the reaction heated, at reflux at 50 °C for another 12 h to achieve reaction completion. The mixture was then diluted with CH_2Cl_2 (30 mL) and washed with 10% aq. HCl (30 mL). The aqueous layer was then extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was then re-dissolved in CH_2Cl_2 (6.9 mL) and DBU (1.04 mL, 6.97 mmol) was added, followed by stirring at room temperature for 18 h, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, ethyl acetate/hexane 4:1 → 98:2 ethyl acetate:methanol) afforded the *title compound* as a yellow oil (84 mg, 40%); R_f 0.46 (9:1 ethyl acetate: methanol); ν_{max}/cm^{-1} (neat) 3287, 3064, 2936, 2239, 1730, 1655, 1614, 1597, 1551, 1494, 1418 ; δ_H (400 MHz, $CDCl_3$) 7.39–7.24 (7H, m, ArH), 7.20 (1H, t, *J* = 8.0 Hz, ArH), 7.10–7.08 (1H, m, ArH), 5.75 (1H, s, NH), 5.44 (1H, d, *J* = 14.9 Hz, C**H**HPh), 4.13 (1H, d, *J* = 14.9 Hz, CH**H**Ph), 3.90–3.83 (1H, m, C**H**HNBn), 3.48–3.13 (4H, m, CH_2NH and CH**H**NBn and C**H**HCH_2NH), 2.62–2.58 (1H, m, CH**H**CH_2NH), 2.28–2.23 (1H, m, C**H**HCO), 1.97−1.93 (1H, m, CH**H**CO); δ_c (100 MHz, $CDCl_3$) 172.4 (CO), 171.6 (CO), 137.8 (ArC), 137.6 (ArC), 131.6 (ArC), 129.9 (ArC), 129.2 (ArC), 128.4 (ArC), 128.0 (ArC), 126.4 (ArC), 126.3 (ArC), 47.0 (CH_2Ph),

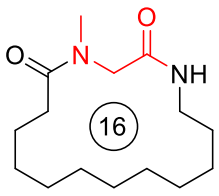
46.9 (CH_2NBn), 40.7 (CH_2NH), 36.2 (**C**H_2CO), 33.1 (**C**H_2CH_2NH). HRMS (ESI): calcd. for $C_{19}H_{20}N_2O_2$, 331.1417. Found; $[MNa]^+$, 331.1416 (1.0 ppm error).

2-Benzyl-3,4,6,7,8,9-hexahydro-1*H*-benzo[*g*][1,5]diazacycloundecine-1,5(2*H*)-dione (421)



A mixture of 2,3,4,5-tetrahydro-1*H*-benzo[c]azepin-1-one (127 mg, 0.786 mmol), DMAP (10.0 mg, 0.0786 mmol) and pyridine (0.380 mL, 4.72 mmol) in CH_2Cl_2 (5.5 mL) under an argon atmosphere was stirred at room temperature for 30 min. A solution of acid chloride (1.18 mmol, 1.50 equiv., freshly prepared using the general procedure) in CH_2Cl_2 (3.0 mL) was added and the resulting mixture was refluxed at 50 °C for 18 h. The mixture was then diluted with CH_2Cl_2 (30 mL) and washed with 10% aq. HCl (30 mL). The aqueous layer was then extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was then re-dissolved in CH_2Cl_2 (8.0 mL) and DBU (1.20 mL, 7.86 mmol) was added, followed by stirring at room temperature for 18 h, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 5:1 → 2:1 → 1:1 hexane:ethyl acetate) afforded the *title compound* (as a 3:1 mixture of rotamers) as a yellow oil (189 mg, 77%); R_f 0.54 (98:2 ethyl acetate: methanol); ν_{max}/cm^{-1} (thin film) 3299, 1646, 1615, 1549, 1495, 1443, 1421, 1351; Data for the major rotamers only: δ_H (400 MHz, $CDCl_3$, 50 °C) 7.40–7.05 (9H, m, ArH), 6.81 (1H, br m, NH), 4.50 (1H, d, *J* = 16.0 Hz, C**H**H-Ph), 4.38–4.28 (2H, m, CH**H**-Ph and C**H**H-NBn), 3.99–3.90 (1H, m, C**H**H-NH), 3.13–3.03 (2H, m, CH**H**-NBn and C**H**H-CO), 2.80–2.72 (2H, m, CH**H**-NH and CH_2-C**H**H-CH_2), 2.67–2.64 (1H, m, CH_2-CH**H**-CH_2), 2.58–2.52 (1H, m, CH**H**-CO), 1.86–1.60 (2H, m, C**H$_2$**-CH_2-CH_2); Data for major rotamer only: δ_c (100 MHz, $CDCl_3$) 172.9 (CO-NBn), 169.9 (CO-NH), 139.2 (ArC), 136.3 (ArC), 136.0 (ArC), 130.0 (ArC), 129.3 (ArC), 128.9 (ArC), 28.4 (ArC), 127.8 (ArC), 127.1 (ArC), 53.8 (CH_2-Ph), 41.0 (CH_2-NBn), 39.1 (CH_2-NH), 34.9 (**C**H_2-CO), 32.2 (**C**H_2-CH_2-CH_2), 29.1 (CH_2-**C**H_2-CH_2); Diagnostic ^{1}H NMR resonances for the minor rotamer: 5.59 (d, *J* = 14.7 Hz, C**H**H-Ph), 5.77 (1H, br m, NH), 4.19 (1H, d, *J* = 14.7 Hz, CH**H**-Ph), 3.85–3.81 (1H, m, C**H**H-NH), 3.22–3.15 (1H, m, CH**H**-NH); Diagnostic ^{13}C NMR resonances for the minor rotamer: 174.9 (CO), 171.6 (CO-NBn), 45.8 (CH_2-Ph), 39.0 (CH_2-NH); HRMS (ESI): calcd. for $C_{20}H_{22}N_2NaO_2$, 345.1573. Found; $[MNa]^+$ 345.1574 (-0.2 ppm error).

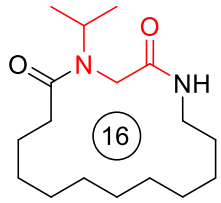
4-Methyl-1,4-diazacyclohexadecane-2,5-dione (433)



A mixture of laurolactam (349 mg, 1.77 mmol), DMAP (21.6 mg, 0.177 mmol) and pyridine (0.860 mL, 10.6 mmol) in CH_2Cl_2 (12.4 mL) under an argon atmosphere was stirred at room temperature for 30 min. Next, a solution of acid chloride (2.65 mmol, 1.50 equiv., freshly prepared using the

general procedure) in CH_2Cl_2 (6.2 mL) was added and the resulting mixture was refluxed at 50 °C for 16 h. The mixture was then diluted with CH_2Cl_2 (100 mL) and washed with 10% aq. HCl (100 mL). The aqueous layer was then extracted with CH_2Cl_2 (3 × 50 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was then re-dissolved in CH_2Cl_2 (17.7 mL) and DBU (2.64 mL, 17.7 mmol) was added, followed by stirring at room temperature for 18 h, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 5:1 hexane:ethyl acetate → 1:1 hexane:ethyl acetate →ethyl acetate) afforded the *title compound* (as a 4:1 (A:B) mixture of rotamers) as a white solid (444 mg, 94%); R_F 0.48 (9:1 ethyl acetate:methanol); ν_{max}/cm^{-1} (thin film) 3315, 2923, 1659, 1636, 1395, 1114, 726; δ_H (400 MHz, $CDCl_3$) 6.52 (1H, br s, N**H**, rotamer A), 5.83 (1H, br s, N**H**, rotamer B), 3.99 (2H, s, NC**H₂**CO, B), 3.95 (2H, s, NC**H₂**CO, B), 3.41–3.35 (2H, m, C**H₂**NH, B), 3.27–3.22 (2H, m, C**H₂**NH, A), 3.13 (3H, s, C**H₃**, A), 2.99 (3H, s, C**H₃**, B), 2.39 (2H, t, *J* = 6.5, COC**H₂**, A), 2.25 (2H, t, *J* = 8.0, COC**H₂**, B), 1.71–1.18 (36H, m, both rotamers); δ_C (100 MHz, $CDCl_3$) data for the major rotamer only: 174.4 (**C**O), 169.5 (**C**O), 53.7 (N**C**H_2CO), 39.0 (**C**H_2NH), 37.3 (**C**H_3), 32.1 (**C**H_2CONCH), 28.5 (**C**H_2), 27.1 (**C**H_2), 26.9 (**C**H_2), 26.3 (**C**H_2), 26.1 (**C**H_2), 25.9 (**C**H_2), 25.1 (**C**H_2), 24.8 (**C**H_2), 24.3 (**C**H_2). Diagnostic ^{13}C NMR resonance for the minor rotamers: 54.9 (N**C**H_2CO); HRMS (ESI): calcd. for $C_{15}H_{28}N_2NaO_2$, 291.2043. Found: $[MNa]^+$, 291.2045 (–0.5 ppm error).

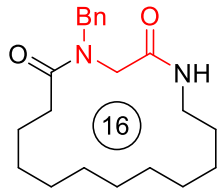
4-*Iso*propyl-1,4-diazacyclohexadecane-2,5-dione (434)



A mixture of laurolactam (130 mg, 0.658 mmol), DMAP (8 mg, 0.065 mmol) and pyridine (0.320 mL, 4.72 mmol) in CH_2Cl_2 (5 mL) under an argon atmosphere was stirred at room temperature for 30 min. Next, a solution of acid chloride (0.988 mmol, 1.50 equiv., freshly prepared using the general procedure) in CH_2Cl_2 (4 mL) was added and the resulting mixture was refluxed at 50 °C for 16 h. The mixture was then diluted with CH_2Cl_2 (20 mL) and washed with 10% aq. HCl (20 mL). The aqueous layer was then extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was then re-dissolved in CH_2Cl_2 (8 mL) and DBU (1.00 mL, 6.58 mmol) was added, followed by stirring at room temperature for 18 h, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 ethyl acetate:hexane → ethyl acetate → 9:1 ethyl acetate: methanol) afforded the *title compound* (as a 10:1:4 (A:B:C) mixture of rotamers) as a white solid (160 mg, 82%); R_F 0.57 (9:1 ethyl acetate:methanol); ν_{max}/cm^{-1} (thin film) 3301, 2926, 2856, 1622, 1547; δ_H (400 MHz, $CDCl_3$) 6.91 (1H, br s, N**H**, rotamer A), 6.02 (1H, br s, N**H**, rotamer B, 5.69 (1H, br s, N**H**, rotamer C), 4.90–4.77 (1H, m, NC**H**$(CH_3)_2$, rotamer B), 4.24–4.07 (2H, m, NC**H**$(CH_3)_2$, rotamers A and C), 3.86 (4H, br s, NC**H₂**CO, rotamers A and B), 3.82 (2H, br s, NC**H₂**CO, rotamer

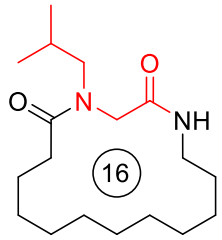
C), 3.37–3.29 (2H, m, C**H₂**NH, rotamer C), 3.29–3.17 (4H, m, C**H₂**NH, rotamers A and B), 2.46–2.37 (2H, m, C**H₂**CONCH, rotamer A), 2.20–2.12 (2H, m, C**H₂**CONCH, rotamer C), 2.04–1.99 (2H, m, C**H₂**CONCH, rotamer B), 1.76–1.23 (48H, m, 9 × C**H₂**, all rotamers), 1.20 (12H, d, *J* = 6.4 Hz, CH**(CH₃)₂**, rotamers A and B), 1.05 (6H, d, *J* = 6.4 Hz, CH**(CH₃)₂**, rotamer B); δ_C (100 MHz, $CDCl_3$) data for the major rotamer only: 174.5 (**C**O), 171.1 (**C**O), 49.4 (N**C**H), 46.1 (N**C**H_2CO), 39.0 (**C**H_2NH), 32.7 (**C**H_2CONCH), 28.7 (**C**H_2), 27.1 (**C**H_2), 26.9 (**C**H_2), 26.4 (**C**H_2), 26.00 (**C**H_2), 25.97 (**C**H_2), 25.1 (**C**H_2), 24.9 (**C**H_2), 24.8 (**C**H_2), 20.9 (**C**H_3). Diagnostic ^{13}C NMR resonances for the minor rotamers: 173.6 (**C**O), 169.5 (**C**O), 37.0 (**C**H_2CONCH), 28.4 (**C**H_2); HRMS (ESI): calcd. for $C_{17}H_{32}N_2NaO_2$, 319.2356. Found: $[MNa]^+$, 319.2353 (0.6 ppm error).

4-Benzyl-1,4-diazacyclohexadecane-2,5-dione (435)



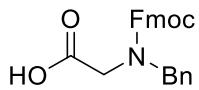
A mixture of laurolactam (155 mg, 0.786 mmol), DMAP (10 mg, 0.0786 mmol) and pyridine (0.380 mL, 4.72 mmol) in CH_2Cl_2 (5.5 mL) under an argon atmosphere was stirred at room temperature for 30 min. Next, a solution of acid chloride (1.18 mmol, 1.50 equiv., freshly prepared using the general procedure) in CH_2Cl_2 (3 mL) was added and the resulting mixture was refluxed at 50 °C for 16 h. The mixture was then diluted with CH_2Cl_2 (30 mL) and washed with 10% aq. HCl (30 mL). The aqueous layer was then extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was then re-dissolved in CH_2Cl_2 (8 mL) and DBU (1.2 mL, 7.86 mmol) was added, followed by stirring at room temperature for 18 h, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 ethyl acetate: hexane → 9:1 ethyl acetate: methanol) afforded the *title compound* (as a 3:1 mixture of rotamers) as a yellow solid (244 mg, 89%); m.p. 119.5–121.0 °C; R_F 0.66 (9:1 ethyl acetate: methanol); ν_{max}/cm^{-1} (thin film) 3301, 2926, 2856, 1632, 1548; δ_H (400 MHz, $CDCl_3$) 7.52–7.07 (10H, m, Ph, both rotamers), 6.66 (1H, br s, N**H**, major), 5.60 (1H, br s, N**H**, minor), 4.67 (2H, s, C**H₂**Ph, major), 4.63 (2H, s, C**H₂**Ph, minor), 3.94 (4H, s, NC**H₂**CO, both), 3.34–3.21 (2H, m, NHC**H₂**, major), 3.20–3.10 (2H, m, NHC**H₂**, minor), 2.43 (2H, t, *J* = 6.8 Hz, C**H**$_2$CONBn, major), 2.27 (2H, t, *J* = 7.6 Hz, C**H**$_2$CONBn, minor), 1.82–1.09 (36H, m, 9 × C**H₂**, both); δ_C (100 MHz, $CDCl_3$) data for the major rotamer only: 175.1 (**C**O), 169.6 (**C**O), 136.0 (**C**), 129.1 (**C**H), 128.0 (**C**H), 126.7 (**C**H), 53.1 (**C**H_2Ph). 51.9 (N**C**H_2CO), 39.2 (NH**C**H_2), 32.2 (**C**H_2CONBn), 28.8 (**C**H_2), 27.2 (**C**H_2), 27.1 (**C**H_2), 26.5 (**C**H_2), 26.2 (**C**H_2), 26.0 (**C**H_2), 25.3 (**C**H_2), 24.9 (**C**H_2), 24.7 (**C**H_2). HRMS (ESI): calcd. for $C_{21}H_{32}N_2NaO_2$, 367.2356. Found: $[MNa]^+$, 367.2331 (4.5 ppm error).

4-*Iso*butyl-1,4-diazacyclohexadecane-2,5-dione (436)



A mixture of laurolactam (70 mg, 0.353 mmol), DMAP (5 mg, 0.035 mmol) and pyridine (0.170 mL, 2.12 mmol) in CH_2Cl_2 (3 mL) under an argon atmosphere was stirred at room temperature for 30 min. Next, a solution of acid chloride (0.530 mmol, 1.50 equiv., freshly prepared using the general procedure) in CH_2Cl_2 (3 mL) was added and the resulting mixture was refluxed at 50 °C for 16 h. The mixture was then diluted with CH_2Cl_2 (20 mL) and washed with 10% aq. HCl (20 mL). The aqueous layer was then extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was then re-dissolved in CH_2Cl_2 (5 mL) and DBU (0.540 mL, 3.53 mmol) was added, followed by stirring at room temperature for 18 h, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 ethyl acetate: hexane → ethyl acetate → 9:1 ethyl acetate: methanol) afforded the *title compound* (as an 8:1 mixture of rotamers) as a yellow oil (105 mg, 94%); R_F 0.69 (9:1 ethyl acetate: methanol); ν_{max}/cm^{-1} (neat) 3300, 2928, 2855, 1648, 1549; δ_H (400 MHz, $CDCl_3$) 6.89 (1H, br s, N**H**, major rotamer), 5.83 (1H, br s, N**H**, minor rotamer), 3.98 (2H, s, NC**H₂**CO, minor), 3.94 (2H, s, NC**H₂**CO, major), 3.50–3.12 (8H, m, NC**H₂**CH and C**H₂**NH, both), 2.45–2.33 (2H, m, C**H₂**CON, major), 2.29–2.19 (2H, m, C**H₂**CON, minor), 2.10–1.92 (2H, m, C**H**$(CH_3)_2$, both), 1.76–1.11 (36H, m, 9 × C**H₂**, both), 0.89 (6H, d, *J* = 6.9 Hz, CH(C**H₃**)₂, major), 0.86 (6H, d, *J* = 6.9 Hz, CH(C**H₃**)₂, minor); δ_C (100 MHz, $CDCl_3$) data for the major rotamer only: 174.8 (**C**O), 170.1 (**C**O), 57.4 (N**C**H_2CO), 52.5 (N**C**H_2CH), 39.3 (**C**H_2NH), 32.1 (**C**H_2CON), 28.6 (**C**H_2), 27.7 (**C**H$(CH_3)_2$), 27.2 (**C**H_2), 27.0 (**C**H_2), 26.4 (**C**H_2), 26.1 (**C**H_2), 25.9 (**C**H_2), 25.3 (**C**H_2), 24.8 (**C**H_2), 24.4 (**C**H_2), 19.9 (2 × CH_3); Diagnostic ^{13}C NMR resonances for the minor rotamer: 54.3 (N**C**H_2CO), 52.2 (N**C**H_2CH), 44.3 (**C**H_2NH), 32.8 (**C**H_2CON); HRMS (ESI): calcd. for $C_{18}H_{34}N_2NaO_2$, 333.2512. Found: $[MNa]^+$, 333.2496 (4.5 ppm error).

***N*-(((9*H*-Fluoren-9-yl)methoxy)carbonyl)-*N*-benzylglycine (442)**



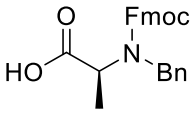
Glycine (300 mg, 4.00 mmol) was dissolved in 2M aq. NaOH (2 mL), and the following procedure was repeated three times: benzaldehyde (0.410 mL, 4.00 mmol), was added and the reaction emulsion stirred for 15 min at room temperature, during which time the solution becomes homogenous. The solution was then cooled to 0 °C and sodium borohydride (51 mg, 1.33 mmol), added over 10 min. The solution was then removed from the ice bath and stirred for 30 min at room temperature, and acidified to pH 11 via dropwise addition of 2M HCl_{aq}. Upon completing the third cycle, the solution was diluted with de-ionised water (50 mL) and washed with ethyl acetate (3 × 50 mL). The aqueous was concentrated *in vacuo* to yield the benzylated amino acid salt. This crude material was re-dissolved in de-ionised water (15 mL)

and 1,4-dioxane (25 mL) and a solution of Na_2CO_3 (10% aq. solution, 20 mL) added. A pre-made solution of 9-fluorenylmethyl chloroformate (1.24 g, 4.8 mmol) in 1,4-dioxane (5 mL) was added at 0 ^oC and the mixture stirred for 16 h. The mixture was diluted with de-ionised water (50 mL), acidified to pH 1, and extracted with ethyl acetate (3 × 100 mL). The combined organics were washed with brine, dried over $MgSO_4$, and solvent removed *in vacuo*. Purification by flash column chromatography (SiO_2, 2:1 hexane:ethyl acetate) afforded the *title compound* (as a 5:4 mixture of rotamers) as a viscous oil (1.09 g, 70%); R_F 0.50 (9:1 ethyl acetate:methanol); δ_H (400 MHz, $CDCl_3$) 7.84–6.99 (26H, m, 13 × aromatic C**H**, both rotamers), 4.63–4.46 (8H, m, C**H₂**Ph and C**H₂**CHO, both rotamers), 4.30–4.19 (2H, m, CH_2C**H**, both rotamers), 3.99 (2H, s, C**H₂**CO_2H, major rotamer), 3.75 (2H, s, C**H₂**CO_2H, minor). Spectral data are consistent with those previously reported.[151]

The same product was also prepared using an alternative substitution strategy via the following procedure:

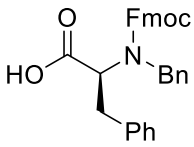
A solution of benzylamine (2.80 mL, 22 mmol) in anhydrous THF (5 mL) was added dropwise to a stirring solution of ethyl bromoacetate (1.12 mL, 10 mmol) in anhydrous THF (5 mL) at 0 °C. The reaction mixture was stirred for 2 h at room temperature, where the reaction mixture was concentrated *in vacuo* to afford a yellow oil. Diethyl ether (20 mL) was added to the oil and the resulting suspension was filtered and washed with ice cold diethyl ether (3 x 10 mL). The collected solute was then concentrated *in vacuo* to afford the desired amino ester intermediate as yellow oil (1.84 g, 88%). Sodium hydroxide (4N aq., 2.5 mL, 10 mmol) was added to a solution of the amino ester intermediate in 1,4-dioxane (35 mL) and methanol (12.5 mL) and stirred at room temperature for 1 h. The reaction mixture was concentrated *in vacuo* to afford the carboxylic acid sodium salt as a white solid. The sodium salt intermediate was then dissolved in a mixture of water (30 mL), 1,4-dioxane (50 mL) and 10% aq. Na_2CO_3 (50 mL) and cooled to 0 °C. A pre-made solution of 9-fluorenylmethyl chloroformate (3.10 g, 12.0 mmol) dissolved in 1,4-dioxane (10 mL) was added dropwise to the sodium salt solution at 0 °C. The solution was then left to warm to room temperature and left stirring for 48 h. The reaction mixture was then diluted with water (50 mL), acidified to approx. pH 2 using 10% aq. HCl and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with sat. aq. brine (2 × 50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a yellow oil (5.60 g). Purification by flash column chromatography (4:1→1:1 ethyl acetate:hexane) afforded the *title compound* as a white solid (2.13 g, 52% over three steps). Data is consistent with those above.

_N_-(((9_H_-Fluoren-9-yl)methoxy)carbonyl)-_N_-benzyl-_L_-alanine (443)



Alanine (356 mg, 4.00 mmol) was dissolved in aq. NaOH (2M, 2 mL), and the following procedure was repeated three times: benzaldehyde (0.410 mL, 4.00 mmol), was added and the reaction emulsion stirred for 15 min at room temperature, during which time the solution became homogenous. The solution was then cooled to 0 °C and sodium borohydride (51 mg, 1.33 mmol), added over 10 min. The solution was then removed from the ice bath and stirred for 30 min at room temperature, and acidified to pH 11 via dropwise addition of 2M HCl_{aq} (then repeat × 2). Upon completing the third cycle, the solution was diluted with de-ionised water (50 mL) and washed with ethyl acetate (3 × 50 mL). The aqueous was concentrated *in vacuo* to yield the benzylated amino acid salt. This crude material was re-dissolved in de-ionised water (15 mL) and 1,4-dioxane (25 mL) and a solution of Na_2CO_3 (10% aq. solution, 20 mL) added. A pre-made solution of 9-fluorenylmethyl chloroformate (1.24 g, 4.8 mmol) in 1,4-dioxane (5 mL) was added at 0 ^oC and the mixture stirred for 16 h. The mixture was diluted with de-ionised water (50 mL), acidified to pH 1, and extracted with ethyl acetate (3 × 100 mL). The combined organics were washed with brine, dried over $MgSO_4$, and solvent removed *in vacuo*. Purification by flash column chromatography (SiO_2, 2:1 hexane:ethyl acetate) afforded the *title compound* (as a 2:1 mixture of rotamers) as a viscous oil (1.24 g, 78%); R_f 0.58 (9:1 ethyl acetate:methanol); δ_H (400 MHz, $CDCl_3$) 8.17–7.06 (26H, m, 13 × aromatic C**H**, both rotamers), 4.79–4.15 (12H, m, C**H₂**Ph, C**H₂**CH, CH_2C**H**, C**H**CO_2H, both), 1.38 (3H, d, *J* = 7.6 Hz, CHC**H₃**, major rotamer), 1.10 (3H, d, *J* = 6.9 Hz, CHC**H₃**, minor rotamer). Data consistent with those previously reported.[152]

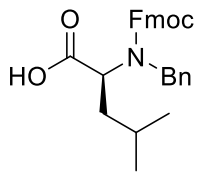
2-((((9H-Fluoren-9-yl)methoxy)carbonyl)(benzyl)amino)-3-phenylpropanoic acid (444)



2-(Benzylamino)-3-phenylpropanoic acid (1.00 g, 4.44 mmol) was dissolved in de-ionised water (18 mL) and 1,4-dioxane (23 mL) and Na_2CO_3 (20 mL, 10% solution) were added. The solution was cooled to 0 °C whilst stirring and a pre-made solution of 9-fluorenylmethyl chloroformate (1.38 g, 5.33 mmol) dissolved in 1,4-dioxane (20 mL) added slowly. The solution was allowed to warm to room temperature and stirred until reaction completion. The mixture was diluted with water (60 mL) and acidified to pH 2 using 10% aq. HCl and extracted with ethyl acetate (3 × 50 mL). The combined organics were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* which afforded the *title compound* (as a 4:1 mixture of rotamers) as a white solid (1.602 g, 75%), m.p. 95–97 °C; $[\alpha]_D^{25}$ −63.1 (c = 1.0, $CHCl_3$); R_F 0.40 (9:1 ethyl acetate:methanol); ν_{max}/cm^{-1} (neat) 3029, 1699, 1451; δ_H (400 MHz, $CDCl_3$) 8.42 (2H, br s, CO_2**H**, both rotamers), 7.80–7.50 (4H, m, Ar, both rotamers), 7.45–6.50 (32H, m, Ar, both rotamers), 5.00–3.70 (12H, m, NC**H**$_2$Ph, OC**H**$_2$CH, OCH_2C**H** and

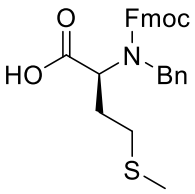
NC**H**CO_2H, both rotamers), 3.50–3.10 (2H, m, PhC**H**$_2$CHN, rotamer A), 3.08–2.30 (2H, m, PhC**H**$_2$CHN, rotamer B); δ_C (100 MHz, $CDCl_3$) 176.6 (CO_2H, rotamer A), 175.6 (**C**O_2H, rotamer B), 156.8 (**C**O, both rotamers), 143.7 (**C**, both rotamers), 141.1 (**C**, both rotamers), 138.4 (CH, rotamer A), 136.9 (CH, rotamer A), 129.1 (**C**H, rotamer A), 129.0 (**C**H, rotamer B), 128.3 (**C**H, rotamer B), 128.2 (**C**H, rotamer A), 127.6 (**C**H, rotamer B), 127.5 (**C**H, rotamer A), 126.9 (**C**H, rotamer A), 126.2 (**C**H, rotamer B), 125.0 (**C**H, rotamer B), 124.9 (**C**H, rotamer B), 119.7 (**C**H, both rotamers), 67.6 (**C**H_2, rotamer A), 66.9 (**C**H_2, rotamer B), 63.9 (**C**H, rotamer A), 61.6 (**C**H, rotamer B), 52.8 (**C**H_2, rotamer A), 51.9 (**C**H_2, rotamer B), 47.3 (**C**H, rotamer B), 47.0 (**C**H, rotamer A), 35.8 (CH, rotamer B), 35.5 (CH, rotamer A); HRMS (ESI)**:** calcd. for $C_{31}H_{27}NNaO_4$, 500.1832. Found: $[MNa]^+$, 500.1814 (3.8 ppm error).

2-((((9H-Fluoren-9-yl)methoxy)carbonyl)(benzyl)amino)-4-methylpentanoic acid (445)



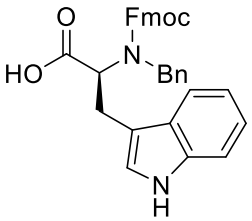
2-(Benzylamino)-4-methylpentanoic acid (1.00 g, 4.48 mmol) was dissolved in de-ionised water (18 mL) and 1,4-dioxane (23 mL) and Na_2CO_3 (20 mL, 10% solution) were added. The solution was cooled to 0 °C whilst stirring and a pre-made solution of 9-fluorenylmethyl chloroformate (1.372 g, 5.4 mmol) dissolved in 1,4-dioxane (20 mL) added slowly. The solution was allowed to warm to room temperature and stirred until reaction completion. The mixture was diluted with water (60 mL) and acidified to pH 2 using 10% HCl(aq) and extracted with ethyl acetate (3 × 50 mL). The combined organics were washed with saturated aqueous brine, dried over $MgSO_4$ and concentrated *in vacuo* which afforded the *title compound* (as a 1:1 mixture of rotamers) as a viscous oil (1.312 g, 65%); $[\alpha]_D^{25}$ −22.6 (c = 1.0, $CHCl_3$); R_F 0.30 (9:1 ethyl acetate:methanol); ν_{max}/cm^{-1} (neat) 2956, 1697, 1450; δ_H (400 MHz, $CDCl_3$) 8.27 (2H, br s, CO_2**H**, both rotamers), 7.90–7.55 (6H, m, Ar, both), 7.53–7.00 (20H, m, Ar, both), 5.00–4.00 (12H, m, OC**H**$_2$C**H** and C**H**NC**H**$_2$Ph, both), 2.00–1.20 (6H, m, C**H**$_2$C**H**, both), 1.10–0.75 and 0.74–0.41 (12H, m, C**H**$_3$CHC**H**$_3$, both); δ_C (100 MHz, $CDCl_3$) 177.5 and 177.2 (**C**O_2H), 157.5 and 156.8 (N**C**O), 143.7 (**C**, both), 141.4 and 141.2 (**C**), 138.1 and 137.9 (**C**), 128.3 and 128.2 (**C**H), 127.9 and 127.5 (**C**H), 127.4 and 127.0 (**C**H), 126.9 (**C**H), 124.9 and 124.8 (**C**H), 119.9 (**C**H, both), 67.7 and 67.3 (N**C**HCO_2H), 59.1 and 57.9 (O**C**H_2), 50.4 (N**C**H_2Ph, both), 47.2 and 47.0 (OCH_2**C**H), 38.6 and 38.2 (NCH**C**H_2), 24.8 and 24.6 (CH_3**C**HCH_3), 22.4 and 22.2 (**C**H_3CHCH_3), 21.7 and 21.4 (CH_3CH**C**H_3); HRMS (ESI): calcd. for $C_{28}H_{29}NNaO_4$, 466.1988. Found: $[MNa]^+$, 466.1994 (−0.9 ppm error).

2-((((9H-Fluoren-9-yl)methoxy)carbonyl)(benzyl)amino)-4-(methylthio)butanoic acid (446)



2-(Benzylamino)-4-(methylthio)butanoic acid (1.00 g, 4.16 mmol) was dissolved in de-ionised water (18 mL) and 1,4-dioxane (23 mL) and Na_2CO_3 (20 mL, 10% solution) were added. The solution was cooled to 0 °C whilst stirring and a pre-made solution of 9-fluorenylmethyl chloroformate (1.29 g, 4.08 mmol) dissolved in 1,4-dioxane (20 mL) added slowly. The solution was allowed to warm to room temperature and stirred until reaction completion. The mixture was diluted with water (60 mL) and acidified to pH 2 using 10% HCl(aq) and extracted with ethyl acetate (3 × 50 mL). The combined organics were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* which afforded the *title compound* (as a 3:1 mixture of rotamers) as a viscous oil (200 mg, 10%); $[\alpha]_D^{25}$ −51.6 (c = 1.0, $CHCl_3$); R_F 0.30 (1:1 ethyl acetate:hexane); ν_{max}/cm^{-1} (neat) 2916, 1698, 1450; δ_H (400 MHz, $CDCl_3$) 8.46 (2H, CO_2**H,** both rotamers), 7.74 (4H, d, *J*=6.9 Hz, Ar, both), 7.65–7.45 (4H, m, Ar, both), 7.42–7.05 (18H, m, Ar, both), 4.90–4.51 (4H, m, OC**H**$_2$, both), 4.50–4.19 (6H, m, OCH_2C**H** and PhC**H**$_2$, both), 4.18–3.40 (2H, m, C**H**CO_2H, both), 2.74–2.17 (4H, m, SC**H**$_2$, both), 2.16–1.70 (8H, m, C**H**$_a$H$_b$$CH_2SCH_3$, both), 1.60–1.18 (2H, m, CH_a**H**$_b$$CH_2$S, both); δ_C (100 MHz, $CDCl_3$) data for the major rotamer only: 176.2 (**C**O_2H), 156.4 (N**C**O), 143.7 (**C**), 141.3 (**C**), 137.0 (**C**), 128.5 (**C**H), 128.3 (**C**H), 127.9 (**C**H), 127.7 (**C**H), 127.0 (**C**H), 124.8 (**C**H), 124.5 (**C**H), 119.9 (**C**H), 67.5 (N**C**HCO_2H), 59.0 (O**C**H_2), 51.9 (**C**H), 47.2 (N**C**H_2Ph), 30.8 (**C**H_2), 28.4 (**C**H_2), 14.9 (**C**H_3). Diagnostic ^{13}C NMR resonances for minor rotamers: 176.3 (**C**O_2H), 156.7 (N**C**O), 143.6 (**C**), 137.3 (**C**), 129.0 (**C**H), 128.4 (**C**H), 127.1 (**C**H), 124.9 (**C**H), 119.9 (**C**H), 67.1 (O**C**H_2), 60.4 (N**C**HCO_2H), 57.8 (O**C**H_2), 47.3 (N**C**H_2Ph), 30.8 (**C**H_2), 28.9 (**C**H_2), 14.8 (**C**H_3); HRMS (ESI): calcd. for $C_{27}H_{27}NNaO_4S$, 484.1553. Found: $[MNa]^+$, 484.1553 (−1.1 ppm error).

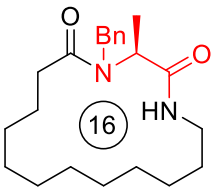
2-((((9H-Fluoren-9-yl)methoxy)carbonyl)(benzyl)amino)-3-phenylpropanoic acid (447)



2-(Benzylamino)-3-(1H-indol-3-yl)propanoic acid (1.00 g, 3.39 mmol) was dissolved in de-ionised water (18 mL) and 1,4-dioxane (23 mL) and Na_2CO_3 (20 mL, 10% solution) were added. The solution was cooled to 0 °C whilst stirring and a pre-made solution of 9-fluorenylmethyl chloroformate (1.05 g, 4.08 mmol) dissolved in 1,4-dioxane (20 mL) added slowly. The solution was allowed to warm to room temperature and stirred until reaction completion. The mixture was diluted with water (60 mL) and acidified to pH 2 using 10% HCl(aq) and extracted with ethyl acetate (3 × 50 mL). The combined organics were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* which afforded the *title compound* (as a 2:1 mixture of rotamers) as a white solid (410 mg, 23%), m.p. 75–77 °C; $[\alpha]_D^{25}$ −57.5 (c = 1, $CHCl_3$); R_F 0.30 (9:1 ethyl acetate:methanol); ν_{max}/cm^{-1} (neat) 3421, 1683, 1452; δ_H (400 MHz, $CDCl_3$) 8.80

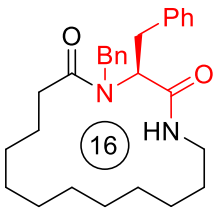
(2H, CO_2**H,** both rotamers), 8.20–7.67 (6H, m, Ar, both), 7.65–7.07 (24H, m, Ar, both), 7.06–6.28 (6H, m, Ar, both), 5.20–4.28 (6H, m, OC**H**$_2$ and C**H**CO_2H, both), 4.25–4.02 (2H, m, OCH_2C**H**, both), 4.01–2.28 (8H, m, PhC**H**$_2$ and C**H**$_2$$CHCO_2$H, both); δ_C (100 MHz, $CDCl_3$) data for the major rotamer: 175.6 (**C**O_2H), 156.6 (N**C**O), 143.7 (**C**), 141.3 (**C**), 136.7 (**C**), 136.0 (**C**), 128.3 (**C**H), 128.1 (**C**H), 127.7 (**C**H), 127.6 (**C**H), 127.2 (**C**H), 127.1 (**C**H), 126.8 (**C**), 124.9 (**C**H), 124.5 (**C**H), 123.3 (**C**H), 121.9 (**C**H), 119.9 (**C**H), 119.4 (**C**H), 118.3 (**C**H), 111.2 (**C**H), 67.6 (O**C**H_2), 59.5 (N**C**HCO_2H), 52.2 (N**C**H_2Ph), 47.1 (NCH_2**C**H), 25.0 (**C**H_2). Diagnostic ^{13}C NMR resonances for minor rotamer: 175.5 (**C**), 156.4 (N**C**O), 143.8 (**C**), 141.2 (**C**), 128.4 (**C**H), 127.6 (**C**H), 127.2 (**C**H), 127.0 (**C**H), 124.9 (**C**H), 124.5 (**C**H), 120.1 (**C**H), 118.1 (**C**H), 111.3 (**C**H), 66.8 (O**C**H_2), 61.5 (N**C**HCO_2H), 52.3 (N**C**H_2Ph), 47.3 (NCH_2**C**H), 25.5 (**C**H_2); HRMS (ESI): calcd. for $C_{33}H_{28}N_2NaO_4$, 539.1941. Found: $[M+Na]^+$, 539.1918 (2.3 ppm error).

(S)-4-Benzyl-3-methyl-1,4-diazacyclohexadecane-2,5-dione (450)



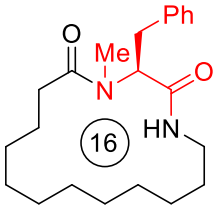
A mixture of laurolactam (24 mg, 0.120 mmol), DMAP (2 mg, 0.0124 mmol) and pyridine (0.060 mL, 0.72 mmol) in CH_2Cl_2 (2.0 mL) under an argon atmosphere was stirred at room temperature for 30 min. Next, a solution of acid chloride (0.36 mmol, 3.0 eqv prepared using the general procedure) in CH_2Cl_2 (1 mL) was added and the resulting mixture was refluxed at 50 °C for 16 h. The mixture was then diluted with CH_2Cl_2 (15 mL) and washed with 10% aq. HCl (10 mL). The aqueous layer was then extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was then re-dissolved in CH_2Cl_2 (2 mL) and DBU (0.180 mL, 1.2 mmol) was added, followed by stirring at room temperature for 18 h, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 5:1 hexane:ethyl acetate → 1:1 hexane:ethyl acetate → ethyl acetate) afforded the *title compound* as a yellow oil (28 mg, 64%); $[\alpha]_D^{25}$ −24.1 (c = 1.0, $CHCl_3$); R_F 0.71 (9:1 ethyl acetate:methanol); ν_{max}/cm^{-1} (thin film) 3319, 2927, 2856, 1717, 1626, 1530; δ_H (400 MHz, $CDCl_3$) 7.42–7.07 (5H, m, Ph), 6.59 (1H, br s, N**H**), 5.11 (1H, q, *J* = 7.3 Hz, C**H**CH_3). 4.63 (2H, s, C**H**$_2$Ph), 3.63–3.48 (1H, m, C**H**H'NH), 3.05–2.88 (1H, m, CH**H'**NH), 2.44–2.29 (1H, m, C**H**H'CONBn), 2.26–2.11 (1H, m, CH**H'**CONBn), 1.89–1.12 (21H, m, 9 × C**H**$_2$ and C**H**$_3$); δ_C (100 MHz, $CDCl_3$) 175.9 (**C**O), 171.8 (**C**O), 138.0 (**C**), 128.8 (**C**H), 127.3 (**C**H), 125.9 (**C**H), 53.1 (**C**H), 48.2 (**C**H_2Ph), 39.3 (**C**H_2NH), 33.2 (**C**H_2CO), 28.9 (**C**H_2), 27.1 (**C**H_2), 26.4 (**C**H_2), 26.2 (**C**H_2), 26.0 (**C**H_2), 25.4 (**C**H_2), 24.9 (**C**H_2), 24.7 (**C**H_2), 14.3 (**C**H_3); HRMS (ESI): calcd. for $C_{22}H_{35}N_2NaO_2$, 381.2512. Found: (MNa^+), 381.2498 (5.0 ppm error).

(S)-3-Benzyl-4-benzyl-1,4-diazacyclohexadecane-2,5-dione (451)



A mixture of laurolactam (78.9 mg, 0.405 mmol), DMAP (4.9 mg, 0.0405 mmol) and pyridine (0.196 mL, 2.43 mmol) in CH_2Cl_2 (2.8 mL) under an argon atmosphere was stirred at room temperature for 30 min. Next, a solution of acid chloride (0.607 mmol, 1.50 equiv., freshly prepared using the general procedure) in CH_2Cl_2 (1.4 mL) was added and the resulting mixture was refluxed at 50 °C for 16 h. The mixture was then diluted with CH_2Cl_2 (50 mL) and washed with 10% aq. HCl (50 mL). The aqueous layer was then extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was then re-dissolved in CH_2Cl_2 (4.1 mL) and DBU (0.607 mL, 4.05 mmol) was added, followed by stirring at room temperature for 18 h, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 10:1 hexane:ethyl acetate → 5:1 hexane:ethyl acetate) afforded the *title compound* as a colourless oil (176 mg, 72%); R_F 0.50 (2:1 hexane:ethyl acetate); $[\alpha]_D^{20}$ −17.0 (c = 1.0, $CHCl_3$); ν_{max}/cm^{-1} (thin film) 2927, 1629, 1453, 908, 727, 696; δ_H (400 MHz, $CDCl_3$) 7.32–7.08 (10H, m, Ph), 6.62 (1H, br s, N**H**), 5.10–4.80 (1H, br m, C**H**Bn), 4.58 (1H, d, *J* = 17.6, NC**H**H'Ph), 4.47 (1H, d, *J* = 17.6, NCH**H'**Ph), 3.49–3.38 (1H, m), 3.22 (1H, dd, *J* = 13.7, 8.4), 3.07–2.87 (2H, m), 2.39–2.30 (1H, m, C**H**H'CO), 2.27–2.17 (1H, m, CH**H'**CO), 1.77–1.16 (18H, m, 9 × C**H₂**); δ_C (100 MHz, $CDCl_3$) 175.7 (**C**O), 170.4 (**C**O), 137.5 (**C**), 137.3 (**C**), 129.1 (**C**H), 128.7 (**C**H), 128.4 (**C**H), 127.3 (**C**H), 126.5 (**C**H), 126.2 (**C**H), 60.9 (broadened, CH), 50.0 (broadened, CH_2), 39.2 (**C**H_2), 34.6 (**C**H_2), 33.1 (**C**H_2), 28.7 (**C**H_2), 27.1 (**C**H_2), 26.9 (**C**H_2), 26.2 (**C**H_2), 26.0 (**C**H_2), 25.9 (**C**H_2), 25.4 (**C**H_2), 24.8 (**C**H_2), 24.3 (**C**H_2); HRMS (ESI): calcd. for $C_{28}H_{38}N_2NaO_2$, 457.2825. Found: $[MNa]^+$, 457.2824 (0.9 ppm error).

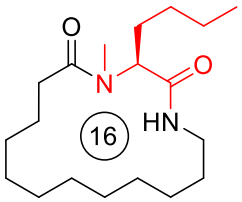
(S)-3-Benzyl-4-methyl-1,4-diazacyclohexadecane-2,5-dione (452)



A mixture of laurolactam (155 mg, 0.786 mmol), DMAP (10 mg, 0.0786 mmol) and pyridine (0.380 mL, 4.72 mmol) in CH_2Cl_2 (5.5 mL) under an argon atmosphere was stirred at room temperature for 30 min. Next, a solution of acid chloride (1.18 mmol, 1.50 equiv., freshly prepared using the general procedure) in CH_2Cl_2 (3 mL) was added and the resulting mixture was refluxed at 50 °C for 16 h. The mixture was then diluted with CH_2Cl_2 (30 mL) and washed with 10% aq. HCl (30 mL). The aqueous layer was then extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was then re-dissolved in CH_2Cl_2 (8 mL) and DBU (1.2 mL, 7.86 mmol) was added, followed by stirring at room temperature for 18 h, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:5 ethyl acetate:hexane → 1:1 ethyl acetate:hexane → ethyl

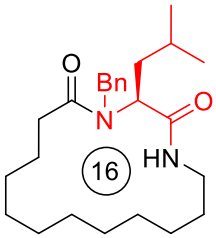
acetate) afforded the *title compound* as a yellow oil (229 mg, 84%); R_F 0.78 (9:1 ethyl acetate: methanol); $[\alpha]_D^{20}$ −18.40 (c = 1.0, $CHCl_3$); ν_{max}/cm^{-1} (thin film) 3315, 2927, 2856, 1626, 1524; δ_H (400 MHz, $CDCl_3$) 7.28–7.20 (3H, m, Ph), 7.19–7.13 (2H, m, Ph), 6.33 (1H, br s, N**H**), 5.37–5.24 (1H, m, C**H**Bn), 3.63–3.50 (1H, m, C**H**H'NH), 3.26 (1H, dd, *J* = 14.5, 7.6 Hz, C**H**H'Ph), 2.98 (1H, dd, *J* = 14.5, 7.6 Hz, CH**H'**Ph), 2.91 (3H, s, C**H₃**), 2.89–2.78 (1H, m, CH**H'**NH), 2.50–2.35 (1H, m, C**H**H'CO), 2.16–1.99 (1H, m, CH**H'**CO), 1.83–1.08 (18H, m, 9 × C**H₂**); δ_C (100 MHz, $CDCl_3$) 174.7 (**C**O), 170.2 (**C**O), 137.4 (**C**), 129.0 (**C**H), 128.5 (**C**H), 126.6 (**C**H), 57.5 (N**C**HBn), 39.2 (**C**H_2NH), 33.8 (**C**H_2Ph), 32.5 (**C**H_2CO), 31.6 (**C**H_3), 28.8 (**C**H_2), 27.2 (**C**H_2), 27.1 (**C**H_2), 26.5 (**C**H_2), 26.3 (**C**H_2), 26.1 (**C**H_2), 25.3 (**C**H_2), 25.1 (**C**H_2), 24.4 (**C**H_2); HRMS (ESI): calcd. for $C_{22}H_{34}N_2NaO_2$, 381.2512. Found: $[MNa]^+$, 381.2498 (3.7 ppm error).

(*S*)-3-Butyl-4-methyl-1,4-diazacyclohexadecane-2,5-dione (453)



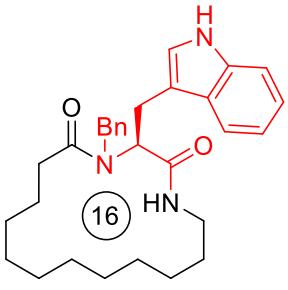
A mixture of laurolactam (155 mg, 0.786 mmol), DMAP (10 mg, 0.0786 mmol) and pyridine (0.380 mL, 4.72 mmol) in CH_2Cl_2 (5.5 mL) under an argon atmosphere was stirred at room temperature for 30 min. Next, a solution of acid chloride (1.18 mmol, 1.50 equiv., freshly prepared using the general procedure) in CH_2Cl_2 (3 mL) was added and the resulting mixture was refluxed at 50 °C for 16 h. The mixture was then diluted with CH_2Cl_2 (30 mL) and washed with 10% aq. HCl (30 mL). The aqueous layer was then extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was then re-dissolved in CH_2Cl_2 (8 mL) and DBU (1.2 mL, 7.86 mmol) was added, followed by stirring at room temperature for 18 h, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 5:1 hexane:ethyl acetate → 1:1 hexane:ethyl acetate → ethyl acetate) afforded the *title compound* (as an 8:1 mixture of rotamers) as a yellow oil (182 mg, 71%); R_F 0.71 (9:1 ethyl acetate: methanol); ν_{max}/cm^{-1} (thin film) 3318, 2927, 2857, 1624, 1529; δ_H (400 MHz, $CDCl_3$) 6.29 (1H, br s, N**H**, major rotamer), 5.91 (1H, br s, N**H**, minor), 5.00–4.89 (2H, m, C**H**NMe, both), 3.64–3.52 (2H, m, C**H**H'NH, both), 2.92 (3H, s, NC**H₃**, major), 2.89–2.80 (2H, m, CH**H'**NH, both), 2.77 (3H, s, NC**H₃**, minor), 2.57–2.45 (2H, m, C**H**H'CONMe, both), 2.26–2.14 (2H, m, CH**H'**CONMe, both), [1.93–1.74 (4H), 1.68–1.54 (4H), 1.51–1.05 (40H), 10 × C**H₂**, both], 0.86 (6H, t, *J* = 6.9 Hz, CH_2C**H₃**, both); δ_C (100 MHz, $CDCl_3$) data for the major rotamer only: 174.7 (**C**O), 170.9 (**C**O), 56.3 (**C**HNMe), 39.1 (**C**H_2NH), 32.6 (**C**H_2CO), 30.9 (N**C**H_3), 28.8 (**C**H_2), 28.2 (**C**H_2), 27.20 (**C**H_2), 27.18 (**C**H_2), 27.0 (**C**H_2), 26.6 (**C**H_2), 26.3 (**C**H_2), 26.1 (**C**H_2), 25.3 (**C**H_2), 25.1 (**C**H_2), 24.6 (**C**H_2), 22.6 (**C**H_2), 14.1 (**C**H_3). Diagnostic ^{13}C NMR resonances for minor rotamer: 175.0 (**C**O), 170.3 (**C**O), 67.2 (**C**HNMe), 62.0 (**C**H_2), 60.5 (**C**H_2); HRMS (ESI): calcd. for $C_{19}H_{36}N_2NaO_2$, 347.2669. Found: $[MNa]^+$, 347.2660 (2.8 ppm error).

(S)-4-Benzyl-3-isobutyl-1,4-diazacyclohexadecane-2,5-dione (454)



A mixture of laurolactam (77.1 mg, 0.391 mmol), DMAP (4.8 mg, 0.0391 mmol) and pyridine (0.189 mL, 2.34 mmol) in CH_2Cl_2 (2.7 mL) under an argon atmosphere was stirred at room temperature for 30 min. Next, a solution of acid chloride (0.586 mmol, 1.50 equiv., freshly prepared using the general procedure) in CH_2Cl_2 (1.3 mL) was added and the resulting mixture was refluxed at 50 °C for 16 h. The mixture was then diluted with CH_2Cl_2 (50 mL) and washed with 10% aq. HCl (50 mL). The aqueous layer was then extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was then re-dissolved in CH_2Cl_2 (3.9 mL) and DBU (0.583 mL, 3.91 mmol) was added, followed by stirring at room temperature for 18 h, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 10:1 hexane:ethyl acetate → 3:1 hexane:ethyl acetate) afforded the *title compound* (as a roughly 10:1 mixture of rotamers) as a colourless oil (63 mg, 40%); R_F 0.40 (2:1 hexane:ethyl acetate); $[\alpha]_D^{20}$ −21.2 (c = 1.0, $CHCl_3$); ν_{max}/cm^{-1} (thin film) 3318, 2927, 1627, 1543, 1451, 730; δ_H (400 MHz, $CDCl_3$) NMR data for the major rotamer only 7.34–7.20 (3H, m, Ph), 7.15 (2H, d, *J* = 7.0, Ph), 6.62 (1H, br s, N**H**), 5.01 (1H, t, *J* = 7.0, C**H**N), 4.66 (1H, d, *J* = 17.6, NC**H**H'Ph), 4.59 (1H, d, *J* = 17.6, NCH**H'**Ph), 3.59–3.49 (1H, m), 2.99–2.90 (1H, m), 2.40–2.32 (1H, m), 2.24–2.16 (1H, m), 1.89–1.70 (2H, m), 1.54–1.10 (19H, m, 9 × C**H₂** and CH), 0.82 (3H, d, *J* = 6.9, C**H₃**), 0.78 (3H, d, *J* = 6.9, C**H₃**); δ_C (100 MHz, $CDCl_3$) 175.8 (**C**O), 171.2 (**C**O), 137.9 (**C**), 128.6 (**C**H), 127.2 (**C**H), 126.1 (**C**H), 56.4 (broadened, CH), 48.6 (**C**H_2), 39.2 (**C**H_2), 37.0 (**C**H_2), 33.0 (**C**H_2), 28.7 (**C**H_2), 27.1 (**C**H_2), 27.0 (**C**H_2), 26.3 (**C**H_2), 26.0 (**C**H_2), 25.8 (**C**H_2), 25.4 (**C**H_2), 25.1 (CH), 24.8 (**C**H_2), 24.4 (**C**H_2), 22.9 (**C**H_3), 22.3 (**C**H_3); HRMS (ESI): calcd. for $C_{25}H_{40}N_2NaO_2$, 423.2982. Found: $[MNa]^+$, 423.2984 (–0.5 ppm error).

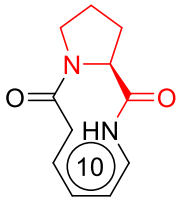
(S)-3-Indolyl-4-benzyl-1,4-diazacyclohexadecane-2,5-dione (455)



A mixture of laurolactam (141 mg, 0.713 mmol), DMAP (8.7 mg, 0.0713 mmol) and pyridine (0.350 mL, 4.28 mmol) in CH_2Cl_2 (5.0 mL) under an argon atmosphere was stirred at room temperature for 30 min. Next, a solution of acid chloride (1.07 mmol, 1.50 equiv., freshly prepared using the general procedure) in CH_2Cl_2 (2.5 mL) was added and the resulting mixture was refluxed at 50 °C for 16 h. The mixture was then diluted with CH_2Cl_2 (50 mL) and washed with 10% aq. HCl (50 mL). The aqueous layer was then extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was then re-dissolved in CH_2Cl_2 (7.1 mL) and DBU (1.06 mL, 7.13 mmol) was added, followed by stirring at room temperature for 18 h, before the

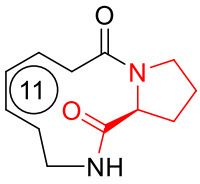
solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 5:1 hexane:ethyl acetate → 1:1 hexane:ethyl acetate) afforded the *title compound* (as a roughly 5:1 mixture of rotamers) as a yellow oil (180 mg, 53%); R_F 0.50 (2:1 hexane:ethyl acetate); $[\alpha]_D^{20}$ −18.5 (c = 1.0, $CHCl_3$); ν_{max}/cm^{-1} (thin film) 3302, 2928, 1657, 1450, 909, 733; δ_H (400 MHz, $CDCl_3$) For the major rotamer only: 8.38 (1H, s, indole N**H**), 7.52 (1H, d, *J* = 7.6, CH), 7.33–7.04 (8H, m, Ar), 6.93 (1H, br s, N**H**), 5.24–5.14 (1H, br m, C**H**N), 4.60 (2H, s, C**H₂**Ph) 3.50–3.34 (2H, m), 3.18–3.08 (1H, m), 2.90–2.81 (1H, m), 2.43–2.32 (1H, m), 2.28–2.20 (1H, m), 1.77–1.15 (18H, m, 9 × C**H₂**); δ_C (100 MHz, $CDCl_3$) 175.7 (**C**O), 170.9 (**C**O), 137.6 (**C**), 136.1 (**C**), 128.7 (**C**H), 127.3 (**C**H), 127.2 (**C**), 126.2 (**C**H), 122.9 (**C**H), 121.8 (**C**H), 119.3 (**C**H), 118.6 (**C**H), 111.2 (**C**), 111.1 (**C**H), 59.5 (broadened, CH), 49.6 (broadened, CH_2), 39.2 (**C**H_2), 33.1 (**C**H_2), 28.7 (**C**H_2), 27.1 (**C**H_2), 26.9 (**C**H_2), 26.3 (**C**H_2), 26.0 (**C**H_2), 25.9 (**C**H_2), 25.3 (**C**H_2), 24.8 (**C**H_2), 24.4 (**C**H_2) 24.3 (**C**H_2); HRMS (ESI): calcd. for $C_{30}H_{39}N_3NaO_2$, 496.2934. Found: $[MNa]^+$, 496.2939 (1.1 ppm error)

(S)-Decahydropyrrolo[1,2-a][1,4]diazecine-1,8-dione (456)



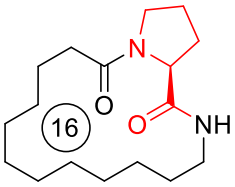
A mixture of ε-caprolactam (200 mg, 1.77 mmol), DMAP (21.6 mg, 0.177 mmol) and pyridine (0.860 mL, 10.6 mmol) in CH_2Cl_2 (12.4 mL) under an argon atmosphere was stirred at room temperature for 30 min. Next, a solution of acid chloride (2.65 mmol, 1.50 equiv., freshly prepared using the general procedure) in CH_2Cl_2 (6.2 mL) was added and the resulting mixture was refluxed at 50 °C for 16 h. The mixture was then diluted with CH_2Cl_2 (100 mL) and washed with 10% aq. HCl (100 mL). The aqueous layer was then extracted with CH_2Cl_2 (3 × 50 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was then re-dissolved in CH_2Cl_2 (17.7 mL) and DBU (2.64 mL, 17.7 mmol) was added, followed by stirring at room temperature for 18 h, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 10:1 hexane:ethyl acetate → 1:1 hexane:ethyl acetate → ethyl acetate) afforded the *title compound* (as a roughly 5:1:1 mixture of rotamers) as a white solid (340 mg, 91%); m.p. 142–145 °C; $[\alpha]_D^{20}$ −25.2 (c = 1.0, $CHCl_3$); R_F 0.18 (19:1 ethyl acetate: methanol); ν_{max}/cm^{-1} (thin film) 3292, 2922, 1635, 1557, 1441, 1155, 735, 519; δ_H (400 MHz, $CDCl_3$) a very broad spectrum was obtained: 6.96 (1H, br s, N**H**, minor rotamer), 6.78 (1H, br s, N**H**, major rotamer) [4.22–4.15 (m), 4.12–3.95 (m), 3.75–3.30 (m), 3.15–3.07 (m), 4H, all rotamers], 2.75–0.80 (13H, m, all rotamers); δ_C (100 MHz, $CDCl_3$) data for the major rotamer only: 174.7 (**C**O), 173.3 (**C**O), 62.7 (N**C**HCO), 46.7 (N**C**H_2), 39.9 (NH**C**H_2), 31.0 (**C**H_2CONCH), 30.7 (**C**H_2), 26.2 (**C**H_2), 25.0 (**C**H_2), 23.4 (**C**H_2), 22.0 (**C**H_2). Diagnostic ^{13}C NMR resonances for the minor rotamers 178.9, 60.3, 60.2, 45.0, 42.5, 36.4, 30.3, 29.5, 27.4, 23.0, 20.6, 14.0. HRMS (ESI): calcd. for $C_{11}H_{18}N_2NaO_2$, 233.1260. Found: $[MNa]^+$, 233.1259 (0.9 ppm error).

(S)-Decahydro-1*H*-pyrrolo[1,2-a][1,4]diazacycloundecine-1,9(2*H*)-dione (457)



A mixture of azocan-2-one (225 mg, 1.77 mmol), DMAP (21.6 mg, 0.177 mmol) and pyridine (0.860 mL, 10.6 mmol) in CH_2Cl_2 (12.4 mL) under an argon atmosphere was stirred at room temperature for 30 min. Next, a solution of acid chloride (2.65 mmol, 1.50 equiv., freshly prepared using the general procedure) in CH_2Cl_2 (6.2 mL) was added and the resulting mixture was refluxed at 50 °C for 16 h. The mixture was then diluted with CH_2Cl_2 (100 mL) and washed with 10% aq. HCl (100 mL). The aqueous layer was then extracted with CH_2Cl_2 (3 × 50 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was then re-dissolved in CH_2Cl_2 (17.7 mL) and DBU (2.64 mL, 17.7 mmol) was added, followed by stirring at room temperature for 18 h, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 10:1 hexane:ethyl acetate → 1:1 hexane:ethyl acetate → ethyl acetate) afforded the *title compound* as a white solid (370 mg, 95%); m.p. 137–141 °C; $[\alpha]_D^{20}$ −50.6 (c = 1.0, $CHCl_3$); R_F 0.18 (19:1 ethyl acetate: methanol); ν_{max}/cm^{-1} (thin film) 3277, 2927, 1674, 1603, 1420, 1238, 729, 688; δ_H (400 MHz, $CDCl_3$) 6.06–5.95 (1H, m, N**H**), 4.35 (1H, dd, *J* = 8.7, 3.2, NC**H**), [3.95 (1H, m), 3.70–3.52 (2H, m) and 3.00–2.90 (1H, m) 2 × NC**H₂**), 2.47–1.22 (10H, m), 1.06–0.84 (2H, m); δ_C (100 MHz, $CDCl_3$) 174.0 (**C**O), 173.1 (**C**O), 62.3 (N**C**HCO), 47.0 (N**C**H₂), 39.3 (NH**C**H₂), 31.8 (**C**H₂CONCH), 31.6 (**C**H₂), 28.9 (**C**H₂), 25.9 (**C**H₂), 24.1 (**C**H₂), 23.1 (**C**H₂), 22.3 (**C**H₂). HRMS (ESI): calcd. for $C_{12}H_{20}N_2NaO_2$, 247.1417. Found: $[MNa]^+$, 247.1422 (0.9 ppm error).

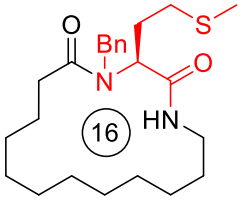
(S)-Hexadecahydropyrrolo[1,2-a][1,4]diazacyclohexadecine-1,14-dione (458)



A mixture of laurolactam (155 mg, 0.786 mmol), DMAP (10 mg, 0.0786 mmol) and pyridine (0.380 mL, 4.72 mmol) in CH_2Cl_2 (5.5 mL) under an argon atmosphere was stirred at room temperature for 30 min. Next, a solution of acid chloride (1.18 mmol, 1.50 equiv., freshly prepared using the general procedure) in CH_2Cl_2 (3 mL) was added and the resulting mixture was refluxed at 50 °C for 16 h. The mixture was then diluted with CH_2Cl_2 (30 mL) and washed with 10% aq. HCl (30 mL). The aqueous layer was then extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was then re-dissolved in CH_2Cl_2 (8 mL) and DBU (1.2 mL, 7.86 mmol) was added, followed by stirring at room temperature for 18 h, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 ethyl acetate:hexane → ethyl acetate) afforded the *title compound* (as a 10:1 mixture of rotamers) as a colourless oil (183 mg, 82%); R_F 0.45 (9:1 ethyl acetate: methanol); $[\alpha]_D^{20}$ −93.3 (c = 1.0, $CHCl_3$); ν_{max}/cm^{-1} (thin film) 3299, 2926, 2856, 1648, 1626, 1543; δ_H (400 MHz, $CDCl_3$) 7.35 (1H, br s, N**H**, major rotamer), 5.96 (1H, br s, N**H**, minor), 4.60 (1H, d, *J*

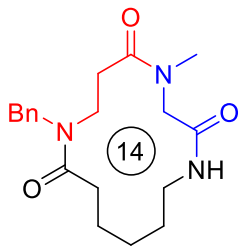
= 7.6 Hz, NC**H**CO, major), 4.34 (1H, dd, *J* = 8.4, 2.3 Hz, NC**H**CO, minor), 3.75–3.63 (2H, m, C**H**H'NCH and C**H**H'NH, minor), 3.62–3.45 (2H, m, C**H**H'NCH and C**H**H'NH, major), 3.42–3.31 (1H, m, CH**H'**NCH, major), 3.30–3.24 (1H, m, CH**H'**NCH, minor), 3.04–2.87 (2H, m, CH**H'**NH, both), 2.53–2.43 (2H, m, C**H**H'CONCH, both), 2.42–2.24 (2H, m, CH**H'**CONCH and C**H**H'CH_2NH, major), [2.23–1.61 (12H), 1.52–1.15 (32H), m, CH**H'**CONCH (minor), C**H**H'CH_2NH (minor), CH**H'**CH_2NH (both), 10 × C**H₂** (both)]. δ_C (100 MHz, $CDCl_3$) data for the major rotamer only: 174.0 (**C**O), 171.3 (**C**O), 59.7 (N**C**HCO), 47.7 (N**C**H_2), 39.5 (NH**C**H_2), 34.0 (**C**H_2CONCH), 28.7 (**C**H_2), 27.2 (**C**H_2), 27.0 (**C**H_2), 26.6 (**C**H_2), 26.2 (**C**H_2), 26.0 (**C**H_2), 25.9 (**C**H_2), 25.4 (**C**H_2), 25.2 (**C**H_2), 24.7 (**C**H_2), 26.3 (**C**H_2). Diagnostic ^{13}C NMR resonances for the minor rotamer: 173.6 (**C**O), 172.1 (**C**O), 61.8 (**C**H), 46.9 (**C**H_2), 34.4 (**C**H_2). HRMS (ESI): calcd. for $C_{17}H_{30}N_2NaO_2$, 317.2199. Found: $[MNa]^+$, 317.2188 (3.3 ppm error).

(S)-4-Benzyl-3-(2-(methylthio)ethyl)-1,4-diazacyclohexadecane-2,5-dione (459)



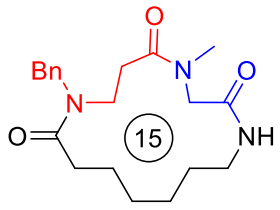
A mixture of laurolactam (49.5 mg, 0.251 mmol), DMAP (3.1 mg, 0.0251 mmol) and pyridine (0.122 mL, 1.51 mmol) in CH_2Cl_2 (1.8 mL) under an argon atmosphere was stirred at room temperature for 30 min. Next, a solution of acid chloride (0.376 mmol, 1.50 equiv., freshly prepared using the general procedure) in CH_2Cl_2 (0.9 mL) was added and the resulting mixture was refluxed at 50 °C for 16 h. The mixture was then diluted with CH_2Cl_2 (30 mL) and washed with 10% aq. HCl (30 mL). The aqueous layer was then extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was then re-dissolved in CH_2Cl_2 (2.5 mL) and DBU (0.370 mL, 2.51 mmol) was added, followed by stirring at room temperature for 18 h, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 10:1 hexane:ethyl acetate → 3:1 hexane:ethyl acetate) afforded the *title compound* (as a roughly 10:1 mixture of rotamers) as a colourless oil (45 mg, 43%); R_F 0.45 (2:1 hexane:ethyl acetate); $[\alpha]_D^{20}$ −48.8 (c = 0.9, $CHCl_3$); ν_{max}/cm^{-1} (thin film) 2925, 1628, 1535, 1452, 728; δ_H (400 MHz, $CDCl_3$) NMR data for the major rotamer only 7.37–7.14 (5H, m, Ph), 6.65 (1H, br s, N**H**), 5.07–5.01 (1H, m, C**H**N), 4.64 (2H, s, C**H₂**Ph), 3.58–3.48 (1H, m), 3.00–2.92 (1H, m), 2.47–2.20 (1H, m), 1.97 (3H, s, SC**H₃**), 1.81–1.70 (2H, m), 1.53–1.20 (18H, m); δ_C (100 MHz, $CDCl_3$) 175.8 (**C**O), 170.5 (**C**O), 137.6 (**C**), 128.8 (**C**H), 127.4 (**C**H), 126.1 (**C**H), 57.3 (broadened, CH), 49.1 (**C**H_2), 39.3 (**C**H_2), 33.0 (**C**H_2), 30.9 (**C**H_2), 28.7 (**C**H_2), 27.8 (**C**H_2), 27.04 (**C**H_2), 27.02 (**C**H_2), 26.3 (**C**H_2), 26.0 (**C**H_2), 25.8 (**C**H_2), 25.4 (**C**H_2), 24.8 (**C**H_2), 24.4 (**C**H_2), 15.2 (**C**H_3); HRMS (ESI): calcd. for $C_{24}H_{38}N_2NaO_2S$, 441.2546. Found: $[MNa]^+$, 441.2531 (3.4 ppm error). Diagnostic NMR resonances for minor rotamer be found at: δ_H (400 MHz, $CDCl_3$) 4.69 (2H, s, C**H₂**Ph), 2.02 (3H, s, SC**H₃**).

8-Benzyl-4-methyl-1,4,8-triazacyclotetradecane-2,5,9-trione (465)



A mixture of 5-benzyl-1,5-diazacycloundecane-2,6-dione (54 mg, 0.197 mmol), DMAP (3 mg, 0.0197 mmol) and pyridine (95.0 µL, 1.18 mmol) in CH_2Cl_2 (1.5 mL) under an argon atmosphere was stirred at room temperature for 30 min. Next, a solution of acid chloride (0.380 mmol, 1.50 equiv., freshly prepared using the general procedure) in CH_2Cl_2 (1 mL) was added and the resulting mixture was heated at 50 °C for 16 h. The mixture was then diluted with CH_2Cl_2 (10 mL) and washed with 10% aq. HCl (10 mL). The aqueous layer was then extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was then re-dissolved in CH_2Cl_2 (3 mL) and DBU (300 µL, 1.97 mmol) was added, followed by stirring at room temperature for 18 h, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 2:1 hexane:ethyl acetate → ethyl acetate → 9:1 ethyl acetate:methanol) afforded the *title compound* (as a 10:1:1 A:B:C mixture of rotamers) as a yellow oil (61 mg, 89%); R_F 0.39 (9:1 ethyl acetate:methanol); ν_{max}/cm^{-1} (neat) 3311, 2933, 2239, 1623, 1538; δ_H (400 MHz, $CDCl_3$) 7.39–7.09 (18H, m, Ph and N**H**, all rotamers), 4.68 (4H, br s, C**H₂**Ph, rotamers A and B), 4.62 (2H, s, C**H₂**Ph. rotamer C), 4.01–3.84 (6H, m, COC**H₂**NMe, all rotamers), 3.83–3.60 (6H, m, C**H₂**NBn, all rotamers), 3.43–3.25 (6H, m, C**H₂**NH, all rotamers), 3.13 (3H, s, NC**H₃**, rotamer A), 3.02 (3H, s, NC**H₃**, rotamer B), 2.93 (3H, s, NC**H₃**, rotamer C), 2.74–2.55 (6H, m, C**H₂**CONMe, all rotamers), 2.43–2.23 (6H, m, C**H₂**CONBn, all rotamers), 1.76–1.55 (6H, m, C**H₂**, all rotamers), 1.54–1.40 (6H, m, C**H₂**, all rotamers), 1.27–1.12 (6H, m, C**H₂**, all rotamers); δ_C (100 MHz, $CDCl_3$) data for the major rotamer only: 175.3 (**C**O), 171.8 (**C**O), 168.6 (**C**O), 136.6 (**C**CH), 129.1 (**C**H), 127.8 (**C**H), 126.6 (**C**H), 53.3 (**C**H_2NMe), 52.1 (**C**H_2Ph), 43.1 (**C**H_2NBn), 37.1 (N**C**H_3), 36.2 (**C**H_2NH), 32.8 (**C**H_2CONMe), 32.3 (**C**H_2CONBn), 26.7 (**C**H_2), 23.5 (**C**H_2), 20.6 (**C**H_2). Diagnostic ^{13}C NMR resonances for minor rotamers: 174.2 (**C**O), 173.5 (**C**O), 172.7 (**C**O), 171.6 (**C**O), 171.2 (**C**O), 168.2 (**C**O), 137.5 (**C**CH), 128.9 (**C**H), 128.3 (**C**H), 127.5 (**C**H), 60.5 (**C**H_2NMe), 14.3 (**C**H_2); HRMS (ESI): calcd. for $C_{19}H_{27}N_3NaO_3$, 368.1945. Found: $[MNa]^+$, 368.1939 (1.7 ppm error).

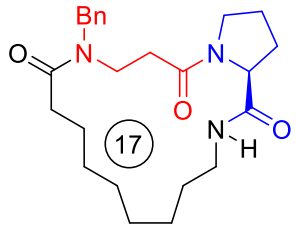
8-Benzyl-4-methyl-1,4,8-triazacyclopentadecane-2,5,9-trione (466)



A mixture of 5-benzyl-1,5-diazacyclododecane-2,6-dione (140 mg, 0.485 mmol), DMAP (6 mg, 0.0485 mmol) and pyridine (235 µL, 2.91 mmol) in CH_2Cl_2 (4 mL) under an argon atmosphere was stirred at room temperature for 30 min. Next, a solution of acid chloride (0.728 mmol, 1.50 equiv. freshly prepared using the general procedure) in CH_2Cl_2 (1 mL) was added and the resulting mixture was heated at 50 °C for 16 h. The mixture was then diluted with CH_2Cl_2 (10 mL)

and washed with 10% aq. HCl (10 mL). The aqueous layer was then extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic extracts dried over $MgSO_4$, concentrated *in vacuo*. The crude material was then re-dissolved in CH_2Cl_2 (6 mL) and DBU (740 µL, 4.85 mmol) was added, followed by stirring at room temperature for 18 h, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 5:1 hexane:ethyl acetate → ethyl acetate → 9:1 ethyl acetate:methanol) afforded the *title compound* (as a 4:2:1:1 mixture of rotamers A:B:C:D) as a yellow oil (158 mg, 85%); R_f 0.44 (9:1 ethyl acetate:methanol); ν_{max}/cm^{-1} (thin film) 3300, 2931, 1630, 1541; δ_H (400 MHz, $CDCl_3$) 7.38–7.05 (20H, m, Ph, all rotamers), 6.99 (1H, br s, N**H**, rotamer A), 6.90 (1H, br s, N**H**, rotamer B), 6.60 (1H, br s, N**H**, rotamer C), 6.28 (1H, br s, N**H**, rotamer D), 4.73 (2H, s, C**H₂**NMe, rotamer B), 4.65 (2H, s, C**H₂**NMe, rotamer A), [4.56 (2H, s, C**H₂**NMe), 4.52 (2H, s, C**H₂**NMe) rotamers C and D], 4.00–3.71 (8H, m, C**H₂**Ph, all rotamers), 3.71–3.47 (8H, m, C**H₂**NBn, all rotamers), 3.46–3.15 (8H, m, C**H₂**NH), 3.05 (3H, s, C**H₃**, rotamer A), 2.98 (3H, s, C**H₃**, rotamer B), [2.94 (3H, s, C**H₃**), 2.66 (3H, s, C**H₃**), rotamers C and D], 2.64–2.50 (8H, m, C**H₂**CONMe, all rotamers), 2.43–2.20 (8H, m, C**H₂**CONBn, all rotamers), 1.81–1.22 (32H, m, 4 × C**H₂**, all rotamers); δ_C (100 MHz, $CDCl_3$) data for the major rotamer only: 175.3 (**C**O), 172.0 (**C**O), 169.0 (**C**O), 136.5 (**C**), 129.1 (**C**H), 127.8 (**C**H), 126.3 (**C**H), 60.5 (**C**H_2NMe), 52.5 (**C**H_2Ph), 51.4 (**C**H_2NBn), 42.4 (**C**H_2CONBn), 40.4 (**C**H_2NH), 36.6 (**C**H_3N), 32.3 (**C**H_2CONMe), 27.8 (**C**H_2), 25.3 (**C**H_2), 22.7 (**C**H_2), 14.3 (**C**H_2). Diagnostic ^{13}C NMR resonances for minor rotamers: 175.9 (**C**O), 174.4 (**C**O), 173.6 (**C**O), 172.8 (**C**O), 172.2 (**C**O), 171.3 (**C**O), 170.4 (**C**O), 168.5 (**C**O), 168.1 (**C**O), 138.4 (**C**), 138.0 (**C**), 137.6 (**C**), 65.2 (**C**H_2NMe); HRMS (ESI): calcd. for $C_{20}H_{29}N_3NaO_3$, 382.2101. Found: $[MNa]^+$, 382.2086 (4.3 ppm error).

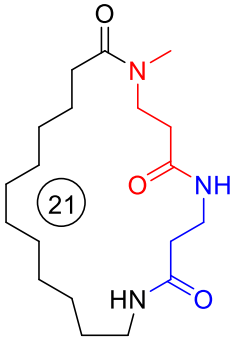
(S)-12-Benzyltetradecahydro-1H-pyrrolo[2,1-c][1,4,8]triazacycloheptadecine-1,11,15(2H,12H)-trione (467)



A mixture of 5-benzyl-1,5-diazacyclotetradecane-2,6-dione (90 mg, 0.284 mmol), DMAP (3 mg, 0.0284 mmol) and pyridine (140 µL, 1.70 mmol) in CH_2Cl_2 (2.5 mL) under an argon atmosphere was stirred at room temperature for 30 min. Next, a solution of acid chloride (0.426 mmol, 1.50 equiv. freshly prepared using the general procedure) in CH_2Cl_2 (1.0 mL) was added and the resulting mixture was heated at 50 °C for 16 h. The mixture was then diluted with CH_2Cl_2 (10 mL) and washed with 10% aq. HCl (10 mL). The aqueous layer was then extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was then re-dissolved in CH_2Cl_2 (3 mL) and DBU (435 µL, 2.84 mmol) was added, followed by stirring at room temperature for 18 h, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 2:1

hexane:ethyl acetate → ethyl acetate → 9:1 ethyl acetate:methanol) afforded the *title compound* (as a mixture of predominantly 3 rotamers) as a pale yellow oil (90 mg, 77%). The number of rotamers was determined by the number of resonances in the carbonyl region of the ^{13}C NMR spectrum; $[\alpha]_D^{25}$ −22.4 (c = 1.0, $CHCl_3$); R_F 0.47 (9:1 ethyl acetate:methanol); ν_{max}/cm^{-1} (thin film); 3301, 2928, 2857, 1624, 1542; δ_H (400 MHz, $CDCl_3$) 7.34–7.07 (5H, m, Ph, all rotamers), 6.61 (1H, br s, N**H**, one of the minor rotamers), [4.89 (1H, d, *J* = 17.5), 4.78 (1H, d, *J* = 17.5), 4.70–4.44 (m), 4.13–3.95 (m), 3.81–3.72 (m), 3.59–3.36 (m), 3.35–3.21 (m) and 3.16–2.88 (m) 9H, 4 × C**H₂**N and C**H**N, all rotamers], 2.71–1.16 (16H, m, 2 × C**H₂**O and 6 × C**H₂**O, all rotamers); δ_C (100 MHz, $CDCl_3$) data for the major rotamer only: 174.8 (**C**O), 172.6 (**C**O), 171.3 (**C**O), 137.6 (**C**), 128.9 (**C**H), 127.8 (**C**H), 126.4 (**C**H), 60.3 (**C**HCONH), 53.7 (**C**H_2NCH), 47.7 (**C**H_2Ph), 43.8 (**C**H_2NBn), 39.0 (**C**H_2NH), 33.9 (**C**H_2CONCH), 32.2 (**C**H_2CONBn), 28.5 (**C**H_2), 27.8 (**C**H_2), 27.6 (**C**H_2), 26.4 (**C**H_2), 26.1 (**C**H_2), 25.4 (**C**H_2), 24.9 (**C**H_2), 24.8 (**C**H_2). Diagnostic ^{13}C NMR resonances for the minor rotamers: 174.5 (**C**O), 174.1 (**C**O), 172.0 (**C**O), 170.6 (**C**O), 170.4 (**C**O), 170.1 (**C**O), 138.0 (**C**), 136.7 (**C**), 60.8 (**C**HCONH), 59.7 (**C**HCONH), 52.5 (**C**H_2NCH), 48.7 (**C**H_2Ph), 47.3 (**C**H_2Ph); HRMS (ESI): calcd. for $C_{24}H_{35}N_{3Na}O_3$, 436.2571. Found: MNa^+, 436.2561 (2.6 ppm error).

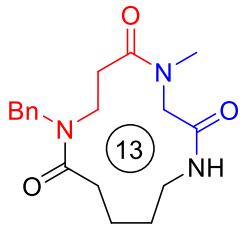
9-Methyl-1,5,9-triazacyclohenicosane-2,6,10-trione (468)



A mixture of 5-methyl-1,5-diazacycloheptadecane-2,6-dione (165 mg, 0.584 mmol), DMAP (8 mg, 0.058 mmol) and pyridine (0.28 mL, 3.5 mmol) in CH_2Cl_2 (5 mL) under an argon atmosphere was stirred at room temperature for 30 min. Next, a solution of acid chloride (0.876 mmol, 1.5 equiv., freshly prepared using the general procedure) in CH_2Cl_2 (2.5 mL) was added and the resulting mixture was refluxed at 50 °C for 16 h. The mixture was then diluted with CH_2Cl_2 (30 mL) and washed with 10% aq. HCl (30 mL). The aqueous layer was then extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was then re-dissolved in CH_2Cl_2 (8 mL) and piperidine (0.59 mL, 5.84 mmol) was added, followed by stirring at room temperature for 18 h, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 ethyl acetate: hexane → 9:1 ethyl acetate:methanol) afforded the *title compound* (as a 3:1.5:1 mixture of 3 rotamers A:B:C) as an orange oil (80 mg, 42%); R_F 0.26 (4:1 ethyl acetate:methanol); δ_H (400 MHz, $CDCl_3$) 6.88 (1H, br s, N**H**, rotamer A), 6.66 (1H, br s, N**H**, rotamer B), 6.48 (1H, br s, N**H**, rotamer C), 6.38 (1H, br s, N**H**, rotamer A), 6.08 (1H, br s, N**H**, rotamer C), 5.95 (1H, br s, N**H**, rotamer B), 3.68–3.57 (6H, m, C**H₂**N, all rotamers), 3.55–3.43 (6H, m, C**H₂**N, all rotamers), 3.30–3.22 (6H, m, C**H₂**N, all rotamers), 3.01 (3H, s, NC**H₃**, rotamer A), 2.96 and 2.94 (3H, s, NC**H₃**, rotamer C), 2.90 (3H, s, NC**H₃**, rotamer B), 2.45–2.36 (6H,

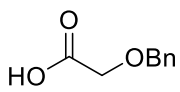
m, C**H₂**CO, all rotamers), 2.35–2.28 (6H, m, C**H₂**CO, all rotamers), 1.70–1.15 (60H, m, 10 × C**H₂**, all rotamers); δ_C (100 MHz, $CDCl_3$) data for the major rotamer only: 173.9 (**C**O), 171.7 (**C**O), 171.1 (**C**O), 44.8 (N**C**H_3), 39.2 (**C**H_2N), 36.3 (**C**H_2N), 36.1 (**C**H_2N), 36.0 (**C**H_2CO), 34.9 (**C**H_2CO), 33.0 (**C**H_2CO), 28.9 (**C**H_2), 28.3 (**C**H_2), 28.1 (**C**H_2), 28.0 (**C**H_2), 27.82 (**C**H_2), 27.79 (**C**H_2), 27.3 (**C**H_2), 25.7 (**C**H_2), 24.5 (**C**H_2).

8-Benzyl-4-methyl-1,4,8-triazacyclotridecane-2,5,9-trione (469)



A mixture of 5-benzyl-1,5-diazecane-2,6-dione (67 mg, 0.269 mmol), DMAP (4 mg, 0.0269 mmol) and pyridine (130 µL, 1.61 mmol) in CH_2Cl_2 (2 mL) under an argon atmosphere was stirred at room temperature for 30 min. Next, a solution of acid chloride (0.403 mmol, 1.50 equiv., freshly prepared using the general procedure) in CH_2Cl_2 (1 mL) was added and the resulting mixture was heated at 50 °C for 16 h. The mixture was then diluted with CH_2Cl_2 (10 mL) and washed with 10% aq. HCl (10 mL). The aqueous layer was then extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic extracts dried over $MgSO_4$, concentrated *in vacuo* and loaded onto a short silica plug eluted with 2:1 (hexane:ethyl acetate) to remove excess carboxylic acid and pyridine residues. The crude material was then re-dissolved in CH_2Cl_2 (4 mL) and DBU (410 µL, 2.69 mmol) was added, followed by stirring at room temperature for 18 h, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 2:1 hexane:ethyl acetate → ethyl acetate → 9:1 ethyl acetate:methanol) afforded the *title compound* (as a 6:1 mixture of rotamers) as a yellow oil (61 mg, 70%); R_F 0.32 (9:1 ethyl acetate:methanol); ν_{max}/cm^{-1} (thin film) 3300, 2933, 1625, 1534; δ_H (400 MHz, $CDCl_3$) 7.50–7.09 (10H, m, Ph, both rotamers), 7.04 (1H, br s, N**H**, major), 6.66 (1H, br s, N**H**, minor), 4.92–4.37 (6H, m, C**H₂**Ph and C**H**H'NMe, both), 3.77–3.26 (4H, m, C**H₂**NBn, both), 3.25–2.90 (12H, m, C**H₃**, CH**H'**NMe and C**H₂**NBn, both), 2.89–2.18 (8H, m, C**H₂**CONMe and C**H₂**CONBn, both), 1.97–1.12 (8H, m, 2 × C**H₂**, both); δ_C (100 MHz, $CDCl_3$) data for the major rotamer only: 176.1 (**C**O), 171.0 (**C**O), 168.1 (**C**O), 136.1 (**C**CH), 129.1 (**C**H), 127.9 (**C**H), 126.5 (**C**H), 53.2 (**C**H_2NMe), 50.1 (**C**H_2Ph), 39.3 (**C**H_2NBn), 39.2 (**C**H_2NH), 37.5 (**C**H_3), 33.6 (**C**H_2CONMe), 32.4 (**C**H_2CONBn), 29.5 (**C**H_2), 22.1 (**C**H_2). Diagnostic ^{13}C NMR resonances for the minor rotamers: 174.6 (**C**O), 172.2 (**C**O), 167.9 (**C**O), 137.3 (**C**CH), 128.8 (**C**H), 128.3 (**C**H), 126.4 (**C**H); HRMS (ESI): calcd. for $C_{18}H_{25}N_3NaO_3$, 354.1788. Found: $[MNa]^+$, 354.1804 (−4.5 ppm error).

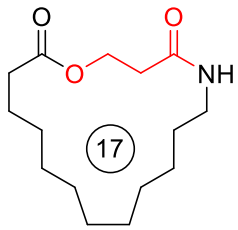
2-(Benzyloxy)acetic acid (477)



This compound has been prepared using the following literature procedure.[153] Sodium metal (6.83 g, 0.297 mol) and benzyl alcohol (48.2 mL, 0.464 mol) was

added to a RBF and heated to 100 °C, until the sodium had dissolved completed. The solution was then cooled to room temperature where a solution of chloroacetic acid (11.4 g, 0.121 mol) in benzyl alcohol (12 mL) was added very slowly. The resulting suspension was stirred, at 120 °C, for 2 h and then cooled to room temperature. The reaction was quenched with water (50 mL) and the aqueous phase was washed with CH_2Cl_2 (3 × 50 mL). The aqueous phase was then acidified to pH 1 with 10% $HCl_{(aq)}$ and extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent was removed *in vacuo* to afford the *title compound* as a colourless oil (16.8 g, 84%); R_F 0.40 (ethyl acetate); δ_H (400 MHz, $CDCl_3$) 9.83 (1H, br s, CO_2**H**), 7.39–7.28 (5H, m, 5 × C**H**), 4.65 (2H, s, C**H**$_2$Ph), 4.15 (2H, s, C**H**$_2$$CO_2$H). Data is consistent with those previously reported in the literature.[153]

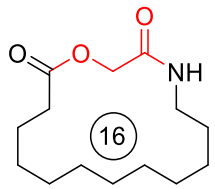
1-Oxa-5-azacycloheptadecane-4,17-dione (481)



A mixture of laurolactam (155 mg, 0.786 mmol), DMAP (10 mg, 0.0786 mmol) and pyridine (0.380 mL, 4.72 mmol) in CH_2Cl_2 (5.5 mL) under an argon atmosphere was stirred at room temperature for 30 min. Next, a solution of acid chloride (1.18 mmol, 1.50 equiv., freshly prepared using the general procedure) in CH_2Cl_2 (3 mL) was added and the resulting mixture was refluxed at 50 °C for 16 h. The mixture was then diluted with CH_2Cl_2 (30 mL) and washed with 10% aq. HCl (30 mL). The aqueous layer was then extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*, loaded onto a short silica plug and eluted 2:1 hexane:ethyl actetate, to remove the pyridine and excess carboxylic acid residues, and concentrated *in vacuo*. This material was then re-dissolved in ethyl acetate (7.9 mL) and placed under an argon atmosphere. Palladium on carbon (78.6 mg, Pd 10% on carbon) was then added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at room temperature under a slight positive pressure of hydrogen (balloon) for 16 h. The reaction was then purged with argon, filtered through Celite, washed with methanol and concentrated *in vacuo.* This material was re-dissolved in $CHCl_3$ and stirred at room temperature for a further 16 h, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 ethyl acetate:hexane → ethyl acetate → 9:1 ethyl acetate:methanol) afforded the *title compound* (as a 5:1 mixture of rotamers) as a colourless oil (100 mg, 47%); R_F 0.53 (9:1 ethyl acetate:methanol); ν_{max}/cm^{-1} (thin film); 3290, 3094, 2926, 2857, 1734, 1643, 1551; δ_H (400 MHz, $CDCl_3$) 6.08–5.84 (2H, m, N**H**, both rotamers), 4.34 (2H, t, *J* = 5.3 Hz, OC**H**$_2$, major), 3.82 (2H, t, *J* = 5.3 Hz, OC**H**$_2$, minor), 3.33–3.21 (4H, m, NHC**H**$_2$, both), 2.55 (2H, t, *J* = 5.3 Hz, C**H**$_2$CONH, minor), 2.46 (2H, t, *J* = 5.3 Hz, C**H**$_2$CONH, major), 2.25 (2H, t, *J* = 7.6 Hz, C**H**$_2$$CO_2$, major), 2.20–2.14 (2H, m, C**H**$_2$$CO_2$, minor), 1.69–1.15 (36H, m, 9 × C**H**$_2$, both);

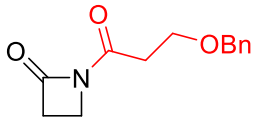
δ_C (100 MHz, $CDCl_3$) 175.3 (**C**O, minor), 174.0 (**C**O, minor), 178.8 (**C**O, major), 170.5 (**C**O, major), 60.6 (CO_2**C**H_2, major), 58.3 (CO_2**C**H_2, minor), 39.5 (NH**C**H_2, major), 39.2 (NH**C**H_2, minor), 39.9 (**C**H_2CONH, minor), 36.5 (**C**H_2CO_2, minor), 36.2 (**C**H_2CONH, major), 34.5 (**C**H_2CO_2, major), 29.2 (**C**H_2, major), 28.3 (**C**H_2, minor), 27.4 (**C**H_2, major), 27.2 (**C**H_2, major), 27.01 (**C**H_2, major), 26.95 (**C**H_2, major), 26.8 (**C**H_2, minor), 26.4 (**C**H_2, minor), 26.3 (**C**H_2, major), 26.2 (**C**H_2, minor), 26.1 (**C**H_2, major), 25.7 (**C**H_2, minor), 25.4 (**C**H_2, major), 25.3 (**C**H_2, minor), 25.0 (**C**H_2, minor), 24.6 (**C**H_2, minor), 24.2 (**C**H_2, major), 23.9 (**C**H_2, minor); HRMS (ESI): calcd. for $C_{15}H_{27}N_2NaO_2$, 292.1883. Found: $[MNa]^+$, 292.1882 (−0.4 ppm error).

1-Oxa-4-azacyclohexadecane-3,16-dione (484)



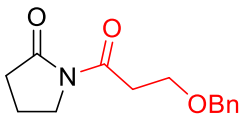
A mixture of laurolactam (155 mg, 0.786 mmol), DMAP (10 mg, 0.0786 mmol) and pyridine (0.380 mL, 4.72 mmol) in CH_2Cl_2 (5.5 mL) under an argon atmosphere was stirred at room temperature for 30 min. Next, a solution of acid chloride (1.18 mmol, 1.50 equiv., freshly prepared using the general procedure) in CH_2Cl_2 (3 mL) was added and the resulting mixture was refluxed at 50 °C for 16 h. The mixture was then diluted with CH_2Cl_2 (30 mL) and washed with 10% aq. HCl (30 mL). The aqueous layer was then extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*, loaded onto a short silica plug and eluted 2:1 hexane:ethyl actetate, to remove the pyridine and excess carboxylic acid residues, and concentrated *in vacuo*. This material was then re-dissolved in ethyl acetate (7.9 mL) and placed under an argon atmosphere. Palladium on carbon (78.6 mg, Pd 10% on carbon) was then added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at room temperature under a slight positive pressure of hydrogen (balloon) for 16 h. The reaction was then purged with argon, filtered through Celite, washed with methanol and concentrated *in vacuo.* This material was re-dissolved in $CHCl_3$ and stirred at room temperature for a further 16 h, where the solvent was removed *in vacuo* to afford the title compound as a white solid (175 mg, 88%); R_F 0.55 (9:1 ethyl acetate:methanol); ν_{max}/cm^{-1} (thin film) 3314, 2927, 2857, 1741, 1659 1538; δ_H (400 MHz, $CDCl_3$) 6.21 (1H, br s, N**H**), 4.54 (2H, s, OC**H₂**CO), 3.48–3.27 (2H, m, C**H₂**NH), 2.39 (2H, t, *J* = 6.9 Hz, C**H₂**CO), 1.74–1.19 (18H, m, 9 × C**H₂**); δ_C (100 MHz, $CDCl_3$) 172.0 (**C**O), 167.2 (**C**O), 63.2 (O**C**H_2CO), 38.5 (NH**C**H_2), 34.6 (**C**H_2CO), 28.2 (**C**H_2), 27.3 (**C**H_2), 27.2 (**C**H_2), 26.5 (**C**H_2), 26.3 (**C**H_2), 25.9 (**C**H_2), 25.1 (**C**H_2), 24.7 (**C**H_2), 24.6 (**C**H_2); HRMS (ESI): calcd. for $C_{14}H_{25}NNaO_3$, 278.1727. Found: $[MNa]^+$, 278.1732 (−2.1 ppm error).

1-(3-(Benzyloxy)propanoyl)azetidin-2-one (487)



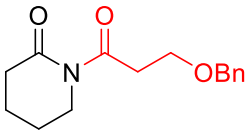
A mixture of 2-azetidinone (56 mg, 0.786 mmol), DMAP (10 mg, 0.0786 mmol) and pyridine (380 µL, 4.72 mmol) in CH_2Cl_2 (5.5 mL) under an argon atmosphere was stirred at room temperature for 5 min. Next, a solution of acid chloride (1.18 mmol, 1.50 equiv. prepared using the general procedure) in CH_2Cl_2 (3 mL) was added and the resulting mixture was stirred at room temperature for 16 h. The mixture was then diluted with CH_2Cl_2 (50 mL), washed with 10% $HCl_{(aq)}$ (15 mL) and $NaHCO_{3(aq)}$ (2 × 20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 2:1 hexane:ethyl acetate) afforded the *title compound* as a yellow oil (167 mg, 91%); R_F 0.64 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 1784, 1698; δ_H (400 MHz, $CDCl_3$) 7.42–7.19 (5H, m, Ph), 4.53 (2H, s, C**H₂**Ph), 3.80 (2H, t, *J* = 6.1 Hz, C**H₂**NH), 3.57 (2H, t, *J* = 5.3 Hz, C**H₂**OBn), 3.06–2.94 (4H, m, C**H₂**CH_2OBn and C**H₂**CON); δ_C (100 MHz, $CDCl_3$) 168.9 (**C**O), 165.1 (**C**O), 138.2 (**C**), 128.5 (**C**H), 127.8 (**C**H), 127.7 (**C**H), 73.1 (**C**H_2Ph), 64.7 (**C**H_2OBn), 37.1 (**C**H_2), 36.7 (**C**H_2), 36.0 (**C**H_2); HRMS (ESI): calcd. for $C_{13}H_{15}NNaO_3$, 256.0944. Found: $[MNa]^+$, 256.0945 (−1.1 ppm error).

1-(3-(Benzyloxy)propanoyl)pyrrolidin-2-one (488)



A mixture of pyrrolidinone (60 µL, 0.786 mmol), DMAP (10 mg, 0.0786 mmol) and pyridine (380 µL, 4.72 mmol) in CH_2Cl_2 (5.5 mL) under an argon atmosphere was stirred at room temperature for 5 min. Next, a solution of acid chloride (1.18 mmol, 1.50 equiv. prepared using the general procedure) in CH_2Cl_2 (3 mL) was added and the resulting mixture was heated, at reflux, at 50 °C for 16 h. The mixture was allowed to cool before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 5:1 hexane:ethyl acetate → 2:1 hexane:ethyl acetate) afforded the *title compound* as a colourless oil (149 mg, 77%). R_F 0.65 (ethyl acetate); ν_{max}/cm^{-1} (thin film); 2870, 1734, 1687; δ_H (400 MHz, $CDCl_3$) 7.38–7.17 (5H, m, Ph), 4.51 (2H, s, C**H₂**Ph), 3.87–3.68 (4H, m, C**H₂**N and C**H₂**OBn), 3.19 (2H, t, *J* = 6.1 Hz, $(CH_2)_2$C**H₂**CO), 2.52 (2H, t, *J* = 8.0 Hz, C**H₂**CH_2OBn), 2.05–1.88 (2H, m, C**H₂**CH_2N); δ_C (100 MHz, $CDCl_3$) 175.6 (**C**O), 172.0 (**C**O), 138.4 (**C**), 128.4 (**C**H), 127.8 (**C**H), 127.7 (**C**H), 73.1 (**C**H_2Ph), 65.1 (**C**H_2OBn), 45.5 (**C**H_2N), 37.4 (**C**H_2CO), 33.7 (**C**H_2CO), 17.2 (**C**H_2CH_2N); HRMS (ESI): calcd. for $C_{14}H_{18}NO_3$, 248.1281. Found: $[MH]^+$, 248.1285 (−1.0 ppm error).

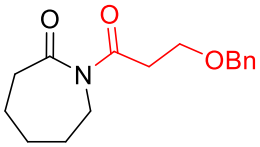
1-(3-(Benzyloxy)propanoyl)piperidin-2-one (489)



A mixture of 2-piperidinone (78 mg, 0.786 mmol), DMAP (10 mg, 0.0786 mmol) and pyridine (380 µL, 4.72 mmol) in CH_2Cl_2 (5.5 mL) under an argon atmosphere was stirred at room temperature for 5 min. Next, a

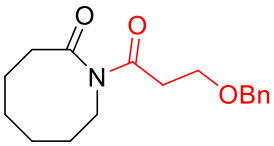
solution of acid chloride (1.18 mmol, 1.50 equiv. prepared using the general procedure) in CH_2Cl_2 (3 mL) was added and the resulting mixture was heated, at reflux, at 50 °C for 16 h. The mixture was allowed to cool before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 5:1 hexane:ethyl acetate → 2:1 hexane:ethyl acetate) afforded the *title compound* as a colourless oil (170 mg, 83%). R_f 0.63 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 2872, 1692; δ_H (400 MHz, $CDCl_3$) 7.40–7.21 (5H, m, Ph), 4.53 (2H, s, C**H₂**Ph), 3.79 (2H, t, *J* = 6.1 Hz, C**H₂**OBn), 3.74–3.67 (2H, m, C**H₂**N), 3.22 (2H, t, *J* = 6.1 Hz, C**H₂**CH_2OBn), 2.57 (2H, m, C**H₂**), 1.87–1.73 (4H, m, 2 × C**H₂**); δ_C (100 MHz, $CDCl_3$) 174.8 (**C**O), 173.5 (**C**O), 138.4 (**C**), 128.5 (**C**H), 127.8 (**C**H), 127.7 (**C**H), 73.2 (**C**H_2Ph), 65.8 (**C**H_2OBn), 44.1 (**C**H_2N), 40.2 (**C**H_2), 34.9 (**C**H_2), 22.5 (**C**H_2), 20.4 (**C**H_2); HRMS (ESI): calcd. for $C_{15}H_{20}NO_3$, 262.1438. Found: $[MH]^+$, 262.1441 (−2.0 ppm error).

1-(3-(Benzyloxy)propanoyl)azepan-2-one (490)



A mixture of ε-caprolactam (90 mg, 0.786 mmol), DMAP (10 mg, 0.0786 mmol) and pyridine (380 µL, 4.72 mmol) in CH_2Cl_2 (5.5 mL) under an argon atmosphere was stirred at room temperature for 5 min. Next, a solution of acid chloride (1.18 mmol, 1.50 equiv. prepared using the general procedure) in CH_2Cl_2 (3 mL) was added and the resulting mixture was heated, at reflux, at 50 °C for 16 h. The mixture was allowed to cool before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 5:1 hexane:ethyl acetate → 2:1 hexane:ethyl acetate) afforded the *title compound* as a colourless oil (194 mg, 90%); R_f 0.70 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 2930, 2860, 1694; δ_H (400 MHz, $CDCl_3$) 7.41–7.20 (5H, m, Ph), 4.52 (2H, s, C**H₂**Ph), 3.94–3.84 (2H, m, C**H₂**N), 3.79 (2H, t, *J* = 6.1 Hz, C**H₂**OBn), 3.19 (2H, t, *J* = 6.1 Hz, C**H₂**CH_2OBn), 2.71–2.65 (2H, m, C**H₂**), 1.80–1.60 (6H, m, 3 × C**H₂**); δ_C (100 MHz, $CDCl_3$) 177.9 (**C**O), 174.1 (**C**O), 138.4 (**C**), 128.4 (**C**H), 127.8 (**C**H), 127.7 (**C**H), 73.2 (**C**H_2Ph), 66.0 (**C**H_2OBn), 43.4 (**C**H_2N), 39.83 (**C**H_2CO), 39.75 (**C**H_2CO), 29.3 (**C**H_2), 28.6 (**C**H_2), 23.7 (**C**H_2); HRMS (ESI): calcd. for $C_{16}H_{22}NO_3$, 276.1594. Found: $[MH]^+$, 276.1598 (−1.4 ppm error).

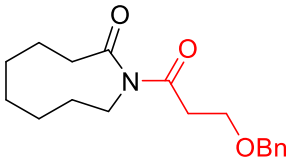
1-(3-(Benzyloxy)propanoyl)azocan-2-one (491)



A mixture of azocan-2-one (100 mg, 0.786 mmol), DMAP (10 mg, 0.0786 mmol) and pyridine (380 µL, 4.72 mmol) in CH_2Cl_2 (5.5 mL) under an argon atmosphere was stirred at room temperature for 5 min. Next, a solution of acid chloride (1.18 mmol, 1.50 equiv. prepared using the general procedure) in CH_2Cl_2 (3 mL) was added and the resulting mixture was heated, at reflux, at 50 °C for 16 h. The mixture was allowed to cool before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 5:1 hexane:ethyl acetate → 2:1 hexane:ethyl acetate)

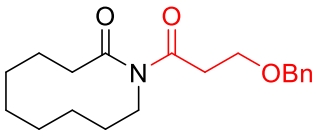
afforded the *title compound* as a colourless oil (206 mg, 91%); R_f 0.72 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 2927, 2859, 1688; δ_H (400 MHz, $CDCl_3$) 7.38–7.20 (5H, m, Ph), 4.52 (2H, s, C**H₂**Ph), 3.93–3.84 (2H, m, C**H₂**N), 3.79 (2H, t, *J* = 6.1 Hz, C**H₂**OBn), 3.17 (2H, t, *J* = 6.1 Hz, C**H₂**CH_2OBn), 2.66–2.58 (2H, m, C**H₂**CO), 1.90–1.81 (2H, m, C**H₂**), 1.74–1.64 (2H, m, C**H₂**), 1.60–1.53 (2H, m, C**H₂**), 1.47–1.39 (2H, m, C**H₂**); δ_C (100 MHz, $CDCl_3$) 178.5 (**C**O), 174.7 (**C**O), 138.4 (**C**), 128.4 (**C**H), 127.8 (**C**H), 127.7 (**C**H), 73.2 (**C**H_2Ph), 66.0 (**C**H_2OBn), 43.5 (**C**H_2N), 39.9 (**C**H_2CH_2OBn), 37.1 (**C**H_2CO), 29.7 (**C**H_2), 29.2 (**C**H_2), 26.3 (**C**H_2), 24.0 (**C**H_2); HRMS (ESI): calcd. for $C_{17}H_{24}NO_3$, 290.1751. Found: $[MH]^+$, 290.1756 (−1.8 ppm error).

1-(3-(Benzyloxy)propanoyl)azonan-2-one (492)



A mixture of azonan-2-one (111 mg, 0.786 mmol), DMAP (10 mg, 0.0786 mmol) and pyridine (380 µL, 4.72 mmol) in CH_2Cl_2 (5.5 mL) under an argon atmosphere was stirred at room temperature for 5 min. Next, a solution of acid chloride (1.18 mmol, 1.50 equiv. prepared using the general procedure) in CH_2Cl_2 (3 mL) was added and the resulting mixture was heated, at reflux, at 50 °C for 16 h. The mixture was allowed to cool before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 5:1 hexane:ethyl acetate → 2:1 hexane:ethyl acetate) afforded the *title compound* as a colourless oil (222 mg, 93%); R_f 0.77 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 2927, 2867, 1688; δ_H (400 MHz, $CDCl_3$) 7.38–7.20 (5H, m, Ph), 4.51 (2H, s, C**H₂**Ph), 3.89–3.82 (2H, m, C**H₂**N), 3.79 (2H, t, *J* = 6.1 Hz, C**H₂**OBn), 3.09 (2H, t, *J* = 6.1 Hz, C**H₂**CH_2OBn), 2.67–2.58 (2H, m, C**H₂**CO), 1.92–1.81 (2H, m, C**H₂**), 1.79–1.70 (2H, m, C**H₂**), 1.69–1.59 (2H, m, C**H₂**), 1.52–1.43 (2H, m, C**H₂**), 1.42–1.33 (2H, m, C**H₂**); δ_C (100 MHz, $CDCl_3$) 180.1 (**C**O), 174.1 (**C**O), 138.4 (**C**), 128.4 (**C**H), 127.8 (**C**H), 127.7 (**C**H), 73.3 (**C**H_2Ph), 66.1 (**C**H-$_2$OBn), 44.8 (**C**H_2N), 39.02 (**C**H_2CO), 38.98 (**C**H_2CO), 28.8 (**C**H_2), 28.0 (**C**H_2), 26.0 (**C**H_2), 25.5 (**C**H_2), 21.2 (**C**H_2); HRMS (ESI): calcd. for $C_{18}H_{26}NO_3$, 304.1907. Found: $[MH]^+$, 304.1908 (−0.2 ppm error).

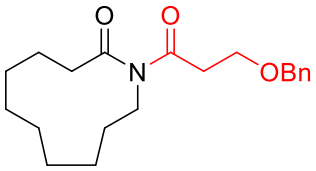
1-(3-(Benzyloxy)propanoyl)azecan-2-one (493)



A mixture of azecan-2-one (122 mg, 0.786 mmol), DMAP (10 mg, 0.0786 mmol) and pyridine (380 µL, 4.72 mmol) in CH_2Cl_2 (5.5 mL) under an argon atmosphere was stirred at room temperature for 5 min. Next, a solution of acid chloride (1.18 mmol, 1.50 equiv. prepared using the general procedure) in CH_2Cl_2 (3 mL) was added and the resulting mixture was heated, at reflux, at 50 °C for 16 h. The mixture was allowed to cool then diluted with CH_2Cl_2 (50 mL), washed with 10% $HCl_{(aq)}$ (15 mL) and $NaHCO_{3(aq)}$ (2 × 20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 5:1 hexane:ethyl acetate → 2:1 hexane:ethyl

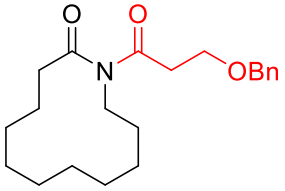
acetate) afforded the *title compound* as a yellow oil (212 mg, 87%); R_f 0.74 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 2927, 2870, 1686; δ_H (400 MHz, $CDCl_3$) 7.40–7.20 (5H, m, Ph), 4.52 (2H, s, C**H₂**Ph), 3.91–3.85 (2H, m, C**H₂**N), 3.82 (2H, t, *J* = 6.1 Hz, C**H₂**OBn), 2.99 (2H, t, *J* = 6.1 Hz, C**H₂**CH_2OBn), 2.84–2.76 (2H, m, $(CH_2)_7$C**H₂**CO), 1.86–1.77 (2H, m, C**H₂**), 1.75–1.67 (2H, m, C**H₂**), 1.52–1.33 (8H, m, 4 × C**H₂**); δ_C (100 MHz, $CDCl_3$) 179.6 (**C**O), 174.5 (**C**O), 138.3 (**C**), 128.5 (**C**H), 127.8 (**C**H), 127.7 (**C**H), 73.4 (**C**H_2Ph), 66.2 (**C**H_2OBn), 44.5 (**C**H_2N), 38.4 (**C**H_2CH_2OBn), 37.0 (**C**H_2CO), 25.6 (**C**H_2), 25.4 (**C**H_2), 25.0 (**C**H_2), 24.3 (**C**H_2), 23.7 (**C**H_2), 22.2 (**C**H_2); HRMS (ESI): calcd. for $C_{19}H_{27}NNaO_3$, 340.1883. Found: $[MNa]^+$, 340.1885 (−0.4 ppm error).

1-(3-(Benzyloxy)propanoyl)azacycloundecan-2-one (494)



A mixture of azacycloundecan-2-one (133 mg, 0.786 mmol), DMAP (10 mg, 0.0786 mmol) and pyridine (380 µL, 4.72 mmol) in CH_2Cl_2 (5.5 mL) under an argon atmosphere was stirred at room temperature for 5 min. Next, a solution of acid chloride (1.18 mmol, 1.50 equiv. prepared using the general procedure) in CH_2Cl_2 (3 mL) was added and the resulting mixture was heated, at reflux, at 50 °C for 16 h. The mixture was allowed to cool then diluted with CH_2Cl_2 (50 mL), washed with 10% $HCl_{(aq)}$ (15 mL) and $NaHCO_{3(aq)}$ (2 × 20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 5:1 hexane:ethyl acetate → 2:1 hexane:ethyl acetate) afforded the *title compound* as a yellow oil (193 mg, 77%); R_f 0.74 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3031, 2929, 2866, 1738, 1689; δ_H (400 MHz, $CDCl_3$) 7.42–7.18 (5H, m, Ph), 4.53 (2H, s, C**H₂**Ph), 3.91–3.79 (4H, m, C**H₂**NH and C**H₂**OBn), 2.94 (2H, t, *J* = 6.4 Hz, C**H₂**CH_2OBn), 2.84–2.74 (2H, m, C**H₂**CO), 1.85–1.75 (2H, m, C**H₂**), 1.73–1.65 (2H, m, C**H₂**), 1.48–1.17 (10H, m, 5 × C**H₂**); δ_C (100 MHz, $CDCl_3$) 179.1 (**C**O), 174.5 (**C**O), 138.2 (**C**), 128.5 (**C**H), 127.8 (**C**H), 127.7 (**C**H), 73.4 (**C**H_2Ph), 66.2 (**C**H_2OBn), 44.1 (**C**H_2NH), 38.1 (**C**H_2CO), 36.8 (**C**H_2CO), 26.3 (**C**H_2), 25.5 (**C**H_2), 25.2 (**C**H_2), 25.1 (**C**H_2), 23.8 (**C**H_2), 23.0 (**C**H_2), 22.7 (**C**H_2); HRMS (ESI): calcd. for $C_{20}H_{29}NNaO_3$, 354.2040. Found: $[MNa]^+$, 354.2040 (−0.1 ppm error).

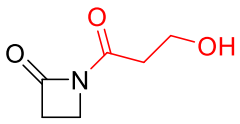
1-(3-(Benzyloxy)propanoyl)azacyclododecan-2-one (495)



A mixture of azacycloundecan-2-one (133 mg, 0.786 mmol), DMAP (10 mg, 0.0786 mmol) and pyridine (380 µL, 4.72 mmol) in CH_2Cl_2 (5.5 mL) under an argon atmosphere was stirred at room temperature for 5 min. Next, a solution of acid chloride (1.18 mmol, 1.50 equiv. prepared using the general procedure) in CH_2Cl_2 (3 mL) was added and the resulting mixture was heated, at reflux, at 50 °C for 16 h. The mixture was allowed to cool then diluted with CH_2Cl_2 (50 mL), washed with 10% $HCl_{(aq)}$ (15 mL) and $NaHCO_{3(aq)}$ (2 × 20 mL), dried over $MgSO_4$ and

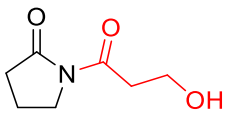
concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 5:1 hexane:ethyl acetate → 2:1 hexane:ethyl acetate) afforded the *title compound* (as a mixture of two rotamers determined by ^{13}C NMR resonances) as a colourless oil (209 mg, 77%); R_f 0.78 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 2928, 2863, 1688; δ_H (400 MHz, $CDCl_3$) 7.39–7.18 (10H, m, Ph, both rotamers), 4.52 (4H, s, C**H₂**Ph, both), 3.88–3.72 (8H, m, C**H₂**OBn and C**H₂**NH, both), 2.96–2.88 (4H, m, C**H₂**CH_2OBn, both), 2.83 (4H, m, C**H₂**CO, both), 1.83–1.15 (32H, m, 8 × C**H₂**, both); δ_C (100 MHz, $CDCl_3$) data for the major rotamer only: 178.2 (**C**O), 174.3 (**C**O), 138.2 (**C**), 128.5 (**C**H), 127.8 (**C**H), 127.7 (**C**H), 73.4 (**C**H_2Ph), 66.2 (**C**H_2OBn), 43.6 (**C**H_2NH), 38.1 (**C**H_2CO), 37.3 (**C**H_2CO), 25.7 (**C**H_2), 25.6 (**C**H_2), 24.8 (**C**H_2), 24.5 (**C**H_2), 24.0 (**C**H_2), 23.8 (**C**H_2), 23.4 (**C**H_2), 23.2 (**C**H_2). Diagnostic ^{13}C NMR resonances for the minor rotamer: 179.1 (**C**O), 174.5 (**C**O), 44.1 (**C**H_2NH), 36.8 (**C**H_2CO), 26.3 (**C**H_2), 25.5 (**C**H_2), 25.2 (**C**H_2), 25.1 (**C**H_2), 23.7 (**C**H_2), 23.0 (**C**H_2), 22.7 (**C**H_2); HRMS (ESI): calcd. for $C_{21}H_{31}NNaO_3$, 368.2196. Found: $[MNa]^+$, 368.2195 (0.1 ppm error).

1-(3-Hydroxypropanoyl)azetidin-2-one (499)



1-(3-(Benzyloxy)propanoyl)azetidin-2-one (153 mg, 0.657 mmol) was dissolved in ethyl acetate (6.6 mL) and placed under an argon atmosphere. Palladium on carbon (66 mg, Pd 10% on carbon) was then added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at room temperature under a slight positive pressure of hydrogen (balloon) for 2 h. The reaction was then purged with argon, filtered through Celite, washed with methanol where the solvent was removed *in vacuo*. The crude material was then re-dissolved in chloroform (6.6 mL) and triethylamine (137 µL, 0.986 mmol) added, and stirred at room temperature for 16 h, then reduced *in vacuo*. Purification by flash column chromatography (SiO_2, 2:1 hexane:ethyl acetate → ethyl acetate) afforded the *title compound* as a colourless oil (86 mg, 92%); R_f 0.28 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3407, 2913, 1777, 1682; δ_H (400 MHz, $CDCl_3$) 3.90 (2H, t, *J* = 5.3 Hz, C**H₂**OH), 3.59 (2H, t, *J* = 5.3 Hz, C**H₂**N), 3.05 (2H, t, *J* = 5.3 Hz, C**H₂**CH_2N), 2.92 (2H, t, *J* = 5.3 Hz, C**H₂**CH_2OH), 2.61 (1H, br s, O**H**); δ_C (100 MHz, $CDCl_3$) 170.4 (**C**O), 165.3 (**C**O), 57.8 (**C**H_2OH), 39.1 (**C**H_2N), 36.7 (**C**H_2CO), 36.2 (**C**H_2CO); HRMS (ESI): calcd. for $C_6H_9NNaO_3$, 166.0475. Found: $[MNa]^+$, 166.0476 (−0.6 ppm error).

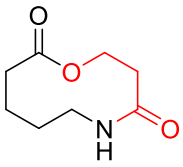
1-(3-Hydroxypropanoyl)pyrrolidin-2-one (500)



1-(3-(Benzyloxy)propanoyl)pyrrolidin-2-one (95 mg, 0.383 mmol) was dissolved in ethyl acetate (3.8 mL) and placed under an argon atmosphere. Palladium on carbon (38 mg, Pd 10% on carbon) was then added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at room

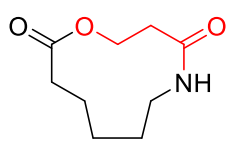
temperature under a slight positive pressure of hydrogen (balloon) for 1 h. The reaction was then purged with argon, filtered through Celite, washed with methanol where the solvent was removed *in vacuo*. The crude material was then re-dissolved in chloroform (3.8 mL) and triethylamine (80 µL, 0.575 mmol) added, and stirred at room temperature for 16 h, then reduced *in vacuo*. Purification by flash column chromatography (SiO_2, 2:1 hexane:ethyl acetate → ethyl acetate) afforded the *title compound* as a colourless oil (58 mg, 96%); R_f 0.30 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3406, 2896, 1732, 1682; δ_H (400 MHz, $CDCl_3$) 3.87 (2H, t, *J* = 5.3 Hz, C**H₂**OH), 3.78 (2H, t, *J* = 7.3 Hz, C**H₂**N), 3.10 (2H, t, *J* = 5.3 Hz, C**H₂**CH_2OH), 2.74 (1H, br s, O**H**), 2.56 (2H, t, *J* = 7.3 Hz, C**H₂**CON), 2.07–1.96 (2H, m, C**H₂**CH_2N); δ_C (100 MHz, $CDCl_3$) 175.8 (**C**O), 173.8 (**C**O), 58.0 (**C**H_2OH), 45.3 (**C**H_2N), 39.6 (**C**H_2CH_2OH), 33.6 (**C**H_2CON), 17.3 (**C**H_2); HRMS (ESI): calcd. for $C_7H_{11}NNaO_3$, 180.0631. Found: $[MNa]^+$, 180.0632 (−1.5 ppm error).

1,5-Oxazecane-4,10-dione (501)



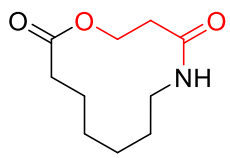
1-(3-(Benzyloxy)propanoyl)piperidin-2-one (80 mg, 0.318 mmol) was dissolved in ethyl acetate (3.2 mL) and placed under an argon atmosphere. Palladium on carbon (32 mg, Pd 10% on carbon) was then added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at room temperature under a slight positive pressure of hydrogen (balloon) for 1 h. The reaction was then purged with argon, filtered through Celite, washed with methanol where the solvent was removed *in vacuo*. The crude material was then re-dissolved in chloroform (3.2 mL) and triethylamine (66 uL, 0.468 mmol) added, and stirred at room temperature for 16 h, then reduced *in vacuo*. Purification by flash column chromatography (SiO_2, 2:1 hexane:ethyl acetate → ethyl acetate → 9:1 ethyl acetate:methanol) afforded the *title compound* (as a 1:3 mixture of rotamers) as a colourless oil (46 mg, 85%); R_f 0.11 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3288, 3088, 2932, 1727, 1647, 1552; δ_H (400 MHz, $CDCl_3$) 5.95 (1H, s, N**H**, minor rotamer), 5.57 (1H, s, N**H**, major rotamer), 4.54–4.40 (4H, m, C**H₂**O, both rotamers), 3.41–3.18 (4H, m, C**H₂**NH, both), 2.60–2.45 (4H, m, C**H₂**CONH, both), 2.38–2.25 (4H, m, C**H₂**CO_2, both), 1.88–1.77 (4H, m, C**H₂**, both), 1.74–1.61 (4H, m, C**H₂**, both); δ_C (100 MHz, $CDCl_3$) data for the major rotamer only: 174.9 (**C**O), 170.1 (**C**O), 61.0 (**C**H_2O), 40.1 (**C**H_2NH), 37.1 (**C**H_2CO), 36.5 (**C**H_2CO), 28.1 (**C**H_2), 24.5 (**C**H_2). Diagnostic ^{13}C NMR resonances for the minor rotamer: 174.3 (**C**O), 173.4 (**C**O), 41.0 (**C**H_2NH), 35.0 (**C**H_2CO), 31.2 (**C**H_2CO), 30.0 (**C**H_2), 20.4 (**C**H_2); HRMS (ESI): calcd. for $C_8H_{14}NO_3$, 172.0968. Found: $[MH]^+$, 172.0970 (0.6 ppm error).

1-Oxa-5-azacycloundecane-4,11-dione (502)



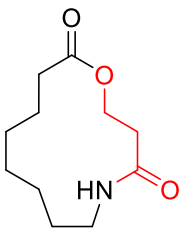
1-(3-(Benzyloxy)propanoyl)azepan-2-one (115 mg, 0.422 mmol) was dissolved in ethyl acetate (4.2 mL) and placed under an argon atmosphere. Palladium on carbon (42 mg, Pd 10% on carbon) was then added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at room temperature under a slight positive pressure of hydrogen (balloon) for 1 h. The reaction was then purged with argon, filtered through Celite, washed with methanol where the solvent was removed *in vacuo* to afford the title compound as a white solid (74 mg, 94%); m.p: 103–105 °C; R_f 0.31 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3288, 2932, 1724, 1637, 1559; δ_H (400 MHz, $CDCl_3$) 6.16 (1H, s, N**H**), 4.51–4.35 (2H, m, C**H₂**O), 3.40–3.23 (2H, m, C**H₂**), 2.54–2.38 (2H, m, C**H₂**CONH), 2.34–2.20 (2H, m, C**H₂**CO_2), 1.69–1.55 (2H, m, C**H₂**), 1.52–1.39 (2H, m, C**H₂**), 1.36–1.24 (2H, m, C**H₂**); δ_C (100 MHz, $CDCl_3$) 173.1 (**C**O), 171.1 (**C**O), 60.9 (**C**H_2O), 39.1 (**C**H_2N), 37.1 (**C**H_2CONH), 34.5 (**C**H_2CO_2), 27.2 (**C**H_2), 25.8 (**C**H_2), 23.9 (**C**H_2); HRMS (ESI): calcd. for $C_9H_{16}NO_3$, 186.1125. Found: $[MH]^+$, 186.1126 (3.7 ppm error).

1-Oxa-5-azacyclododecane-4,12-dione (503)



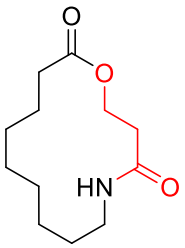
1-(3-(Benzyloxy)propanoyl)azocan-2-one (105 mg, 0.363 mmol) was dissolved in ethyl acetate (3.6 mL) and placed under an argon atmosphere. Palladium on carbon (36 mg, Pd 10% on carbon) was then added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at room temperature under a slight positive pressure of hydrogen (balloon) for 1 h. The reaction was then purged with argon, filtered through Celite, washed with methanol where the solvent was removed *in vacuo*. The crude material was then re-dissolved in chloroform (3.6 mL) and triethylamine (76 uL, 0.545 mmol) was added, and then stirred at room temperature for 16 h, then reduced *in vacuo*. Purification by flash column chromatography (SiO_2, 2:1 hexane:ethyl acetate → ethyl acetate → 9:1 ethyl acetate:methanol) afforded the *title compound* as a white solid (68 mg, 94%); m.p. 128–129 °C; R_f 0.25 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3301, 2922, 2858, 1723, 1639, 1561; δ_H (400 MHz, $CDCl_3$) 6.13 (1H, s, N**H**), 4.54–4.30 (2H, m, C**H₂**O), 3.45–3.21 (2H, m, C**H₂**NH), 2.59–2.43 (2H, m, C**H₂**CO), 2.42–2.21 (2H, m, C**H₂**CO), 1.78–1.11 (8H, m, 4 × C**H₂**); δ_C (100 MHz, $CDCl_3$) 171.7 (**C**O), 168.9 (**C**O), 59.4 (**C**H_2O), 36.7 (**C**H_2NH), 35.4 (**C**H_2CO), 32.0 (**C**H_2CO), 23.9 (**C**H_2), 23.8 (**C**H_2), 23.0 (**C**H_2), 22.4 (**C**H_2); HRMS (ESI): calcd. for $C_{10}H_{17}NNaO_3$, 222.1101. Found: $[MNa]^+$, 222.1103 (−1.5 ppm error).

1-Oxa-5-azacyclotridecane-4,13-dione (504)



1-(3-(Benzyloxy)propanoyl)azonan-2-one (220 mg, 0.725 mmol) was dissolved in ethyl acetate (7.2 mL) and placed under an argon atmosphere. Palladium on carbon (72 mg, Pd 10% on carbon) was then added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at room temperature under a slight positive pressure of hydrogen (balloon) for 1 h. The reaction was then purged with argon, filtered through Celite, washed with methanol where the solvent was removed *in vacuo*. The crude material was dissolved in chloroform (7.2 mL) and trimethylamine (152 µL, 1.09 mmol) was added and stirred at room temperature for 16 h, after which the solvent was then reduced *in vacuo.* Purification by flash column chromatography (SiO_2, 2:1 hexane:ethyl acetate → ethyl acetate → 9:1 ethyl acetate:methanol) to afford the title compound as a white solid (142 mg, 92%); m.p. 129–130 °C; R_f 0.31 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3299, 2928, 2847, 1724, 1641, 1554; δ_H (400 MHz, $CDCl_3$) 5.85 (1H, s, N**H**), 4.36 (2H, t, *J* = 5.3 Hz, C**H₂**O), 3.37–3.21 (2H, m, C**H₂**NH), 2.50 (2H, t, *J* = 5.3 Hz, C**H₂**CH_2O), 2.42–2.30 (2H, m, C**H₂**COO), 1.73–1.60 (2H, m, C**H₂**), 1.59–1.50 (2H, m, C**H₂**), 1.47–1.25 (6H, m, 3 × C**H₂**); δ_C (100 MHz, $CDCl_3$) 173.5 (**C**O), 170.3 (**C**O), 61.7 (**C**H_2O), 40.3 (**C**H_2NH), 36.6 (**C**H_2CO), 34.1 (**C**H_2CO), 27.2 (**C**H_2), 26.8 (**C**H_2), 26.4 (**C**H_2), 25.5 (**C**H_2), 24.2 (**C**H_2); HRMS (ESI): calcd. for $C_{11}H_{19}NNaO_3$, 236.1257. Found: $[MNa]^+$, 236.1257 (−0.6 ppm error).

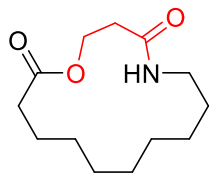
1-Oxa-5-azacyclotetradecane-4,14-dione (505)



1-(3-(Benzyloxy)propanoyl)azecan-2-one (212 mg, 0.630 mmol) was dissolved in ethyl acetate (6.8 mL) and placed under an argon atmosphere. Palladium on carbon (68 mg, Pd 10% on carbon) was then added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at room temperature under a slight positive pressure of hydrogen (balloon) for 1 h. The reaction was then purged with argon, filtered through Celite, washed with methanol where the solvent was removed *in vacuo*. The crude material was then re-dissolved in chloroform (6.3 mL) and triethylamine (131 uL, 0.945 mmol) was added, and then stirred at room temperature for 16 h, then reduced *in vacuo*. Purification by flash column chromatography (SiO_2, 2:1 hexane:ethyl acetate → ethyl acetate → 9:1 ethyl acetate:methanol) afforded the *title compound* as a white solid (137 mg, 96%); m.p. 121–122 °C; R_f 0.40 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3284, 3096, 2929, 2861, 1722, 1646, 1556; δ_H (400 MHz, $CDCl_3$) 5.87 (1H, br s, N**H**), 4.38 (2H, t, *J* = 5.2 Hz, C**H₂**O), 3.35–3.21 (2H, m, C**H₂**NH), 2.54–2.43 (2H, m, C**H₂**CONH), 2.39–2.28 (2H, m, C**H₂**COO), 1.64–1.20 (12H, m, 6 × C**H₂**); δ_C (100 MHz, $CDCl_3$) 173.6 (**C**O), 170.2 (**C**O), 61.4 (**C**H_2O), 38.9 (**C**H_2NH), 36.4 (**C**H_2CO), 34.7 (**C**H_2CO), 28.1 (**C**H_2), 25.9 (**C**H_2), 25.7 (**C**H_2), 25.6 (**C**H_2),

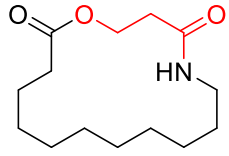
23.9 (**C**H_2), 23.0 (**C**H_2); HRMS (ESI): calcd. for $C_{12}H_{21}NNaO_3$, 250.1414. Found: $[MNa]^+$, 250.1415 (−0.3 ppm error).

1-Oxa-5-azacyclopentadecane-4,15-dione (506)



1-(3-(Benzyloxy)propanoyl)azacycloundecan-2-one (193 mg, 0.582 mmol) was dissolved in ethyl acetate (5.8 mL) and placed under an argon atmosphere. Palladium on carbon (58 mg, Pd 10% on carbon) was then added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at room temperature under a slight positive pressure of hydrogen (balloon) for 1 h. The reaction was then purged with argon, filtered through Celite, washed with methanol where the solvent was removed *in vacuo*. The crude material was then re-dissolved in chloroform (5.5 mL) and triethylamine (115 uL, 0.825 mmol) was added, and then stirred at room temperature for 16 h, then reduced *in vacuo*. Purification by flash column chromatography (SiO_2, 2:1 hexane:ethyl acetate → ethyl acetate → 9:1 ethyl acetate:methanol) afforded the *title compound* (as a 10:1 mixture of rotamers) as a white solid (130 mg, 92%); m.p. 126–128 °C; R_f 0.42 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3311, 2924, 2855, 1725, 1646, 1549; δ_H (400 MHz, $CDCl_3$) 5.90 (1H, s, N**H**, minor rotamer), 5.72 (1H, s, N**H**, major rotamer), 4.46–4.27 (4H, m, C**H₂**O, both rotamers), 3.42–3.20 (4H, m, C**H₂**NH, both), 2.57–2.40 (4H, m, C**H₂**CONH, both), 2.39–2.22 (4H, m, C**H₂**COO, both), 1.69–1.15 (28H, m, 7 × C**H₂**, both); δ_C (100 MHz, $CDCl_3$) data for the major rotamer only: 174.2 (**C**O), 170.1 (**C**O), 61.1 (**C**H_2O), 38.5 (**C**H_2NH), 36.1 (**C**H_2CO), 33.7 (**C**H_2CO), 28.3 (**C**H_2), 26.9 (**C**H_2), 26.7 (**C**H_2), 25.8 (**C**H_2), 25.7 (**C**H_2), 25.1 (**C**H_2), 23.8 (**C**H_2). Diagnostic ^{13}C NMR resonances for minor rotamer: 173.7 (**C**O), 170.3 (**C**O), 61.4 (**C**H_2O), 38.9 (**C**H_2NH), 36.4 (**C**H_2CO), 34.7 (**C**H_2CO); HRMS (ESI): calcd. for $C_{13}H_{23}NNaO_3$, 264.1570. Found: $[MNa]^+$, 264.1578 (−2.7 ppm error).

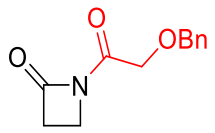
1-Oxa-5-azacyclohexadecane-4,16-dione (507)



1-(3-(Benzyloxy)propanoyl)azacyclododecan-2-one (180 mg, 0.521 mmol) was dissolved in ethyl acetate (5.2 mL) and placed under an argon atmosphere. Palladium on carbon (52 mg, Pd 10% on carbon) was then added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then

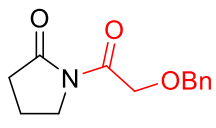
stirred at room temperature under a slight positive pressure of hydrogen (balloon) for 1 h. The reaction was then purged with argon, filtered through Celite, washed with methanol where the solvent was removed *in vacuo*. The crude material was then re-dissolved in chloroform (5.2 mL) and triethylamine (110 µL, 0.782 mmol) was added, and then stirred at room temperature for 16 h, then reduced *in vacuo*. Purification by flash column chromatography (SiO_2, 2:1 hexane:ethyl acetate → ethyl acetate → 9:1 ethyl acetate:methanol) afforded the *title compound* (as a 7:2 mixture of rotamers) as a white solid (119 mg, 91%); m.p. 127–129 °C; R_f 0.45 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3272, 2930, 2860, 1722, 1643, 1559; δ_H (400 MHz, $CDCl_3$) 5.89 (1H, s, N**H**, major rotamer), 5.80 (1H, s, N**H**, minor rotamer), 4.41–4.29 (4H, m, C**H₂**O, both rotamers), 3.36–3.24 (4H, m, C**H₂**NH, both), 2.48 (2H, t, *J* = 5.3 Hz, C**H₂**CONH, minor), 2.43 (2H, t, *J* = 5.3 Hz, C**H₂**CONH, major), 2.34–2.28 (2H, m, C**H₂**COO, minor), 2.24 (2H, t, *J* = 7.7 Hz, C**H₂**COO, major), 1.67–1.56 (4H, m, C**H₂**, both), 1.53–1.42 (4H, m, C**H₂**, both), 1.39–1.15 (24H, m, 6 × C**H₂**, both); δ_C (100 MHz, $CDCl_3$) data for the major rotamer only: 173.7 (**C**O), 170.1 (**C**O), 60.6 (**C**H_2O), 39.2 (**C**H_2NH), 36.2 (**C**H_2CO), 33.6 (**C**H_2CO), 29.1 (**C**H_2), 26.8 (**C**H_2), 26.52 (**C**H_2), 26.46 (**C**H_2), 25.5 (**C**H_2), 25.1 (**C**H_2), 24.8 (**C**H_2), 23.7 (**C**H_2). Diagnostic ^{13}C NMR resonances for minor rotamer: 174.1 (**C**O), 61.0 (**C**H_2O), 38.5 (**C**H_2NH), 36.0 (**C**H_2CO), 33.7 (**C**H_2CO); HRMS (ESI): calcd. for $C_{14}H_{25}NNaO_3$, 278.1727. Found: $[MNa]^+$, 278.1732 (−0.9 ppm error).

1-(2-(Benzyloxy)acetyl)azetidin-2-one (510)



A mixture of 2-azetidinone (56 mg, 0.786 mmol), DMAP (10 mg, 0.0786 mmol) and pyridine (380 µL, 4.72 mmol) in CH_2Cl_2 (5.5 mL) under an argon atmosphere was stirred at room temperature for 5 min. Next, a solution of acid chloride (1.18 mmol, 1.50 eqv prepared using the general procedure) in CH_2Cl_2 (3 mL) was added and the resulting mixture was heated, at reflux, at 50 °C for 16 h. The mixture was allowed to cool before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 5:1 hexane:ethyl acetate → 2:1 hexane:ethyl acetate) afforded the *title compound* as a colourless oil (145 mg, 87%); R_f 0.66 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 2981, 2870, 1781, 1706; δ_H (400 MHz, $CDCl_3$) 7.42–7.22 (5H, m, Ph), 4.63 (2H, s, C**H₂**Ph), 4.42 (2H, s, C**H₂**OBn), 3.55 (2H, t, *J* = 5.3 Hz, C**H₂**N), 2.99 (2H, t, *J* = 5.3 Hz, C**H₂**CO); δ_C (100 MHz, $CDCl_3$) 168.1 (**C**O), 164.7 (**C**O), 137.1 (**C**), 128.6 (**C**H), 128.2 (**C**H), 128.1 (**C**H), 73.6 (**C**H_2Ph), 69.7 (**C**H_2OBn), 36.2 (**C**H_2), 36.0 (**C**H_2); HRMS (ESI): calcd. for $C_{12}H_{13}NNaO_3$, 242.0788. Found: $[MNa]^+$, 242.0787 (0.7 ppm error).

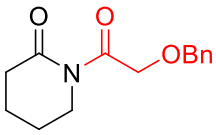
1-(2-(Benzyloxy)acetyl)pyrrolidin-2-one (511)



A mixture of pyrrolidin-2-one (60 µL, 0.786 mmol), DMAP (10 mg, 0.0786 mmol) and pyridine (380 µL, 4.72 mmol) in CH_2Cl_2 (5.5 mL) under an argon

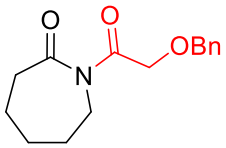
atmosphere was stirred at room temperature for 5 min. Next, a solution of acid chloride (1.18 mmol, 1.50 equiv. prepared using the general procedure) in CH_2Cl_2 (3 mL) was added and the resulting mixture was heated, at reflux, at 50 °C for 16 h. The mixture was allowed to cool before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 2:1 hexane:ethyl acetate) afforded the *title compound* as a colourless oil (137 mg, 75%); Data consistent with those previously reported in the literature.[154]

1-(2-(Benzyloxy)acetyl)piperidin-2-one (512)



A mixture of δ-valerolactam (78 mg, 0.786 mmol), DMAP (10 mg, 0.0786 mmol) and pyridine (380 µL, 4.72 mmol) in CH_2Cl_2 (5.5 mL) under an argon atmosphere was stirred at room temperature for 5 min. Next, a solution of acid chloride (1.18 mmol, 1.50 equiv. prepared using the general procedure) in CH_2Cl_2 (3 mL) was added and the resulting mixture was heated, at reflux, at 50 °C for 16 h. The mixture was allowed to cool before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 2:1 hexane:ethyl acetate) afforded the *title compound* as a yellow oil (193 mg, 99%); R_f 0.65 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 2950, 1690; δ_H (400 MHz, $CDCl_3$) 7.47–7.20 (5H, m, Ph), 4.63 (2H, s, C**H₂**O), 4.62 (2H, s, C**H₂**O), 3.80–3.66 (2H, m, C**H₂**NH), 2.59–2.45 (2H, m, C**H₂**CO), 1.90–1.71 (4H, m, 2 × C**H₂**); δ_C (100 MHz, $CDCl_3$) 174.3 (**C**O), 173.3 (**C**O), 137.8 (**C**), 128.5 (**C**H), 128.1 (**C**H), 127.9 (**C**H), 73.3 (**C**H_2O), 73.0 (**C**H_2O), 44.1 (**C**H_2NH), 34.5 (**C**H_2CO), 22.3 (**C**H_2), 20.2 (**C**H_2); HRMS (ESI): calcd. for $C_{14}H_{17}NNaO_3$, 270.1101. Found: $[MNa]^+$, 270.1105 (−1.8 ppm error).

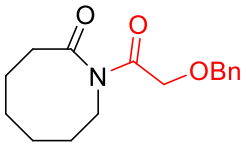
1-(2-(Benzyloxy)acetyl)azepan-2-one (513)



A mixture of ε-caprolactam (90 mg, 0.786 mmol), DMAP (10 mg, 0.0786 mmol) and pyridine (380 µL, 4.72 mmol) in CH_2Cl_2 (5.5 mL) under an argon atmosphere was stirred at room temperature for 5 min. Next, a solution of acid chloride (1.18 mmol, 1.50 equiv. prepared using the general procedure) in CH_2Cl_2 (3 mL) was added and the resulting mixture was heated, at reflux, at 50 °C for 16 h. The mixture was allowed to cool before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 2:1 hexane:ethyl acetate) afforded the *title compound* as a yellow oil (203 mg, 98%); R_f 0.73 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 2931, 2859, 1694; δ_H (400 MHz, $CDCl_3$) 7.48–7.19 (5H, m, Ph), 4.63 (2H, s, C**H₂**Ph), 4.60 (2H, s, C**H₂**OBn), 3.98–3.85 (2H, m, C**H₂**NH), 2.74–2.62 (2H, m, C**H₂**CO), 1.82–1.62 (6H, m, 3 × C**H₂**); δ_C (100 MHz, $CDCl_3$) 177.8 (**C**O), 173.5 (**C**O),

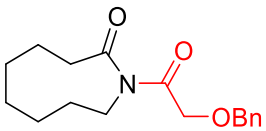
137.8 (**C**), 128.5 (**C**H), 128.1 (**C**H), 127.9 (**C**H), 73.3 (**C**H_2Ph), 72.9 (**C**H_2OBn), 43.1 (**C**H_2NH), 39.5 (**C**H_2CO), 29.2 (**C**H_2), 28.5 (**C**H_2), 23.6 (**C**H_2); HRMS (ESI): calcd. for $C_{15}H_{19}NNaO_3$, 284.1257. Found: $[MNa]^+$, 284.1254 (1.5 ppm error).

1-(2-(Benzyloxy)acetyl)azocan-2-one (514)



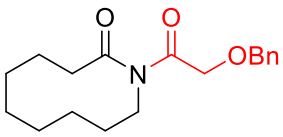
A mixture of azocan-2-one (100 mg, 0.786 mmol), DMAP (10 mg, 0.0786 mmol) and pyridine (380 µL, 4.72 mmol) in CH_2Cl_2 (5.5 mL) under an argon atmosphere was stirred at room temperature for 5 min. Next, a solution of acid chloride (1.18 mmol, 1.50 equiv. prepared using the general procedure) in CH_2Cl_2 (3 mL) was added and the resulting mixture was heated, at reflux, at 50 °C for 16 h. The mixture was allowed to cool before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 2:1 hexane:ethyl acetate) afforded the *title compound* as a yellow oil (216 mg, 98%); R_f 0.74 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 2925, 2859, 1687; δ_H (400 MHz, $CDCl_3$) 7.47–7.19 (5H, m, Ph), 4.63 (2H, s, C**H₂**Ph), 4.61 (2H, s, C**H₂**OBn), 4.00–3.86 (2H, m, C**H₂**NH), 2.68–2.57 (2H, m, C**H₂**CO), 1.91–1.79 (2H, m, C**H₂**), 1.77–1.67 (2H, m, C**H₂**), 1.61–1.52 (2H, m, C**H₂**), 1.48–1.39 (2H, m, C**H₂**); δ_C (100 MHz, $CDCl_3$) 178.2 (**C**O), 173.9 (**C**O), 137.8 (**C**), 128.5 (**C**H), 128.1 (**C**H), 127.9 (**C**H), 73.3 (**C**H_2Ph), 73.0 (**C**H_2OBn), 43.4 (**C**H_2NH), 37.0 (**C**H_2CO), 29.3 (**C**H_2), 29.0 (**C**H_2), 26.3 (**C**H_2), 24.1 (**C**H_2); HRMS (ESI): calcd. for $C_{16}H_{21}NNaO_3$, 298.1414. Found: $[MNa]^+$, 298.1417 (−0.9 ppm error).

1-(2-(Benzyloxy)acetyl)azonan-2-one (515)



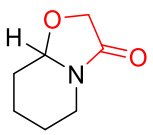
A mixture of azonan-2-one (111 mg, 0.786 mmol), DMAP (10 mg, 0.0786 mmol) and pyridine (380 µL, 4.72 mmol) in CH_2Cl_2 (5.5 mL) under an argon atmosphere was stirred at room temperature for 5 min. Next, a solution of acid chloride (1.18 mmol, 1.50 equiv. prepared using the general procedure) in CH_2Cl_2 (3 mL) was added and the resulting mixture was heated, at reflux, at 50 °C for 16 h. The mixture was allowed to cool before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 2:1 hexane:ethyl acetate) afforded the *title compound* as a yellow oil (213 mg, 93%); R_f 0.77 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3030, 2926, 2864, 1687; δ_H (400 MHz, $CDCl_3$) 7.46–7.17 (5H, m, Ph), 4.62 (2H, s, C**H₂**O), 4.58 (2H, s, C**H₂**O), 3.94–3.82 (2H, m, C**H₂**N), 2.68–2.57 (2H, m, C**H₂**CO), 1.91–1.81 (2H, m, C**H₂**), 1.80–1.72 (2H, m, C**H₂**), 1.65–1.55 (2H, m, C**H₂**), 1.54–1.46 (2H, m, C**H₂**), 1.45–1.37 (2H, m, C**H₂**); δ_C (100 MHz, $CDCl_3$) 179.2 (**C**O), 173.6 (**C**O), 137.7 (**C**), 128.5 (**C**H), 128.1 (**C**H), 127.9 (**C**H), 73.4 (**C**H_2O), 72.5 (**C**H_2O), 45.0 (**C**H_2N), 38.4 (**C**H_2CO), 28.8 (**C**H_2), 27.6 (**C**H_2), 25.7 (**C**H_2), 25.4 (**C**H_2), 21.7 (**C**H_2); HRMS (ESI): calcd. for $C_{17}H_{23}NNaO_3$, 312.1570. Found: $[MNa]^+$, 312.1576 (−2.8 ppm error).

1-(2-(Benzyloxy)acetyl)azecan-2-one (516)



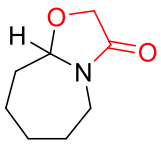
A mixture of azecan-2-one (122 mg, 0.786 mmol), DMAP (10 mg, 0.0786 mmol) and pyridine (380 µL, 4.72 mmol) in CH_2Cl_2 (5.5 mL) under an argon atmosphere was stirred at room temperature for 5 min. Next, a solution of acid chloride (1.18 mmol, 1.50 equiv. prepared using the general procedure) in CH_2Cl_2 (3 mL) was added and the resulting mixture was heated, at reflux, at 50 °C for 16 h. The mixture was allowed to cool before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 2:1 hexane:ethyl acetate) afforded the *title compound* as a yellow oil (229 mg, 96%); R_f 0.78 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 2929, 2869, 1687; δ_H (400 MHz, $CDCl_3$) 7.44–7.21 (5H, m, Ph), 4.61 (2H, s, C**H₂**O), 4.55 (2H, s, C**H₂**O), 3.96–3.85 (2H, m, C**H₂**N), 2.80–2.70 (2H, m, C**H₂**CO), 1.91–1.79 (2H, m, C**H₂**), 1.76–1.67 (2H, m, C**H₂**), 1.52–1.38 (6H, m, 3 × C**H₂**), 1.37–1.23 (2H, m, C**H₂**); δ_C (100 MHz, $CDCl_3$) 178.2 (**C**O), 174.1 (**C**O), 137.6 (**C**), 128.5 (**C**H), 128.1 (**C**H), 127.9 (**C**H), 73.4 (**C**H_2O), 72.5 (**C**H_2O), 43.9 (**C**H_2N), 34.4 (**C**H_2CO), 26.6 (**C**H_2), 26.2 (**C**H_2), 25.3 (**C**H_2), 25.2 (**C**H_2), 22.3 (**C**H_2), 20.2 (**C**H_2); HRMS (ESI): calcd. for $C_{18}H_{25}NNaO_3$, 326.1727. Found: $[MNa]^+$, 326.1728 (−0.6 ppm error).

Tetrahydro-5H-oxazolo[3,2-a]pyridin-3(2H)-one (520)



1-(2-(Benzyloxy)acetyl)piperidin-2-one (54 mg, 0.217 mmol) was dissolved in ethyl acetate (3.2 mL) and placed under an argon atmosphere. Palladium on carbon (22 mg, Pd 10% on carbon) was then added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at room temperature under a slight positive pressure of hydrogen (balloon) for 16 h. The reaction was then purged with argon, filtered through Celite, washed with methanol. The solvent was then removed *in vacuo* to afford the *title compound* as a colourless oil (25 mg, 82%); R_f 0.30 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3477, 2947, 2862, 1694; δ_H (400 MHz, $CDCl_3$) 4.98 (1H, d, *J* = 9.2 Hz, C**H**), 4.23 (2H, s, C**H₂**CO), 4.13 (1H, dd, *J* = 13.1, 4.1 Hz, C**H**H'N), 2.74 (1H, td, *J* = 13.1, 3.1 Hz, CH**H'**N), 2.16–2.04 (1H, m, C**H**H'CH), 1.98–1.88 (1H, m, CH**H'**CH), 1.73–1.62 (2H, m, C**H₂**), 1.49–1.30 (2H, m, C**H₂**); δ_C (100 MHz, $CDCl_3$) 168.2 (**C**O), 89.5 (**C**H), 67.7 (**C**H_2CO), 39.6 (**C**H_2N), 32.9 (**C**H_2CH), 24.0 (**C**H_2), 21.4 (**C**H_2); HRMS (ESI): calcd. for $C_7H_{12}NO_2$, 142.0863. Found: $[MH]^+$, 142.0863 (2.3 ppm error).

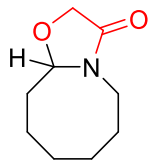
Hexahydrooxazolo[3,2-a]azepin-3(2H)-one (521)



1-(2-(Benzyloxy)acetyl)azepan-2-one (120 mg, 0.459 mmol) was dissolved in ethyl acetate (4.6 mL) and placed under an argon atmosphere. Palladium on carbon (46 mg, Pd 10% on carbon) was then added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at room temperature under a

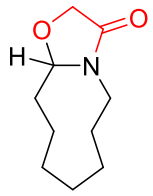
slight positive pressure of hydrogen (balloon) for 16 h. The reaction was then purged with argon, filtered through Celite, washed with methanol. The solvent was then removed *in vacuo* to afford the *title compound* as a colourless oil (62 mg, 87%); R_f 0.37 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 2928, 2855, 1698; δ_H (400 MHz, $CDCl_3$) 5.34–5.20 (1H, m, C**H**), 4.21 (1H, d, *J* = 13.7 Hz, C**H**H'O), 4.12 (1H, d, *J* = 13.7 Hz, CH**H'**O), 3.82–3.66 (1H, m, C**H**H'N), 2.99–2.82 (1H, m, CH**H'**N), 2.02–1.31 (8H, m, 4 × C**H₂**); δ_C (100 MHz, $CDCl_3$) 170.4 (**C**O), 91.7 (**C**H), 68.0 (**C**H_2O), 40.8 (**C**H_2N), 35.5 (**C**H_2), 29.6 (**C**H_2), 28.1 (**C**H_2), 22.0 (**C**H_2); HRMS (ESI): calcd. for $C_8H_{13}NNaO_2$, 178.0838. Found: $[MNa]^+$, 178.0840 (−1.0 ppm error).

Hexahydro-5H-oxazolo[3,2-a]azocin-3(2H)-one (522)



1-(2-(Benzyloxy)acetyl)azocan-2-one (120 mg, 0.436 mmol) was dissolved in ethyl acetate (4.4 mL) and placed under an argon atmosphere. Palladium on carbon (44 mg, Pd 10% on carbon) was then added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at room temperature under a slight positive pressure of hydrogen (balloon) for 16 h. The reaction was then purged with argon, filtered through Celite, washed with methanol. The solvent was then removed *in vacuo* to afford the *title compound* as a colourless oil (66 mg, 90%); R_f 0.42 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 2925, 2856, 1699; δ_H (400 MHz, $CDCl_3$) 5.17–5.10 (1H, m, C**H**), 4.26 (1H, dd, *J* = 13.0, 1.5 Hz, C**H**H'O), 4.13 (1H, dd, *J* = 13.0, 1.5 Hz, CH**H'**O), 3.90–3.77 (1H, m, C**H**H'N), 2.81–2.69 (1H, m, CH**H'**N), 1.92–1.75 (3H, m, C**H**H'CH and C**H₂**), 1.65–1.35 (7H, m, CH**H'**CH and 3 × C**H₂**); δ_C (100 MHz, $CDCl_3$) 170.7 (**C**O), 91.7 (**C**H), 68.0 (**C**H_2O), 39.9 (**C**H_2N), 31.0 (**C**H_2), 27.2 (**C**H_2), 27.0 (**C**H_2), 24.1 (**C**H_2), 20.2 (**C**H_2); HRMS (ESI): calcd. for $C_9H_{15}NNaO_2$, 195.0995. Found: $[MNa]^+$, 195.0999 (−2.6 ppm error).

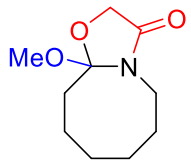
Octahydrooxazolo[3,2-a]azonin-3(2H)-one (523)



1-(2-(Benzyloxy)acetyl)azonan-2-one (64 mg, 0.219 mmol) was dissolved in ethyl acetate (3.2 mL) and placed under an argon atmosphere. Palladium on carbon (22 mg, Pd 10% on carbon) was then added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at room temperature under a slight positive pressure of hydrogen (balloon) for 16 h. The reaction was then purged with argon, filtered through Celite, washed with methanol and the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 2:1 hexane:ethyl acetate → ethyl acetate) afforded the *title compound* as a colourless oil (32 mg, 82%); R_f 0.49 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3424, 2924, 2857, 1694; δ_H (400 MHz, $CDCl_3$) 5.18 (1H, br s, C**H**), 4.34 (1H, d, *J* = 13.7 Hz, C**H**H'CO), 4.18 (1H, d, *J* = 13.7 Hz, CH**H'**CO), 3.86–3.73 (1H, m, C**H**H'N), 2.87–2.74

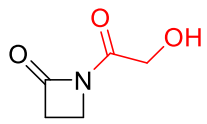
(1H, m, CH**H'**N), 2.01–1.31 (12H, m, 6 × C**H₂**); δ_C (100 MHz, $CDCl_3$) 171.7 (**C**O), 92.7 (**C**H), 68.2 (**C**H_2CO), 41.3 (**C**H_2N), 30.7 (**C**H_2), 25.9 (**C**H_2), 25.5 (**C**H_2), 25.3 (**C**H_2), 24.3 (**C**H_2), 19.8 (**C**H_2); HRMS (ESI): calcd. for $C_{10}H_{18}NO_2$, 184.1332. Found: $[MH]^+$, 184.1331 (0.7 ppm error).

10a-Methoxyhexahydro-5H-oxazolo[3,2-a]azocin-3(2H)-one (529)



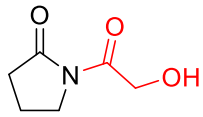
1-(2-(Benzyloxy)acetyl)azocan-2-one (120 mg, 0.436 mmol) was dissolved in methanol (4.4 mL) and placed under an argon atmosphere. Palladium on carbon (44 mg, Pd 10% on carbon) was then added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at room temperature under a slight positive pressure of hydrogen (balloon) for 1 h. The reaction was then purged with argon, filtered through Celite, washed with methanol where the solvent was removed *in vacuo* to afford the *title compound* as a colourless oil (82 mg, 95%); R_f 0.52 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 2928, 2859, 1712; δ_H (400 MHz, $CDCl_3$) 4.29 (2H, s, C**H₂**O), 3.74 (1H, dt, *J* = 13.7, 5.0 Hz, C**H**H'N), 3.03 (3H, s, OC**H₃**), 2.81 (1H, ddd, *J* = 13.7, 9.2, 4.5 Hz, CH**H'**N), 2.05–1.85 (2H, m, C**H₂**C), 1.63–1.30 (8H, m, 4 × C**H₂**); δ_C (100 MHz, $CDCl_3$) 170.5 (**C**O), 115.1 (**C**OMe), 68.5 (**C**H_2O), 48.2 (**C**H_3O), 39.0 (**C**H_2N), 34.5 (**C**H_2C), 27.0 (**C**H_2), 26.2 (**C**H_2), 23.8 (**C**H_2), 21.5 (**C**H_2); HRMS (ESI): calcd. for $C_{10}H_{17}NNaO_3$, 222.1101. Found: $[MNa]^+$, 222.1105 (−1.3 ppm error).

1-(2-Hydroxyacetyl)azetidin-2-one (534)



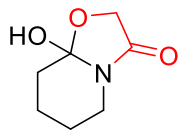
1-(3-(Benzyloxy)propanoyl)azetidin-2-one (147 mg, 0.671 mmol) was dissolved in ethyl acetate (6.7 mL) and placed under an argon atmosphere. Palladium on carbon (67 mg, Pd 10% on carbon) was then added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at room temperature under a slight positive pressure of hydrogen (balloon) for 2 h. The reaction was then purged with argon, filtered through Celite, washed with methanol where the solvent was removed *in vacuo*. The crude material was then re-dissolved in chloroform (6.7 mL) and triethylamine (140 µL, 1.01 mmol) added, and stirred at room temperature for 16 h, then reduced *in vacuo*. Purification by flash column chromatography (SiO_2, 2:1 hexane:ethyl acetate → ethyl acetate → 9:1 ethyl acetate:methanol) afforded the *title compound* as a colourless oil (86 mg, 99%); R_f 0.26 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3425, 2913, 1778, 1694; δ_H (400 MHz, $CDCl_3$) 4.44 (2H, s, C**H₂**OH), 3.62 (2H, t, *J* = 5.3 Hz, C**H₂**N), 3.22 (1H, s, O**H**), 3.08 (2H, t, *J* = 5.3 Hz, C**H₂**CON); δ_C (100 MHz, $CDCl_3$) 170.9 (**C**O), 164.9 (**C**O), 63.4 (**C**H_2OH), 36.5 (**C**H_2N), 36.3 (**C**H_2CON); HRMS (ESI): calcd. for $C_5H_8NO_3$, 130.0499. Found: $[MH]^+$, 130.0498 (0.2 ppm error).

1-(2-Hydroxyacetyl)pyrrolidin-2-one (535)



1-(2-(Benzyloxy)acetyl)pyrrolidin-2-one (135 mg, 0.579 mmol) was dissolved in ethyl acetate (5.8 mL) and placed under an argon atmosphere. Palladium on carbon (58 mg, Pd 10% on carbon) was then added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at room temperature under a slight positive pressure of hydrogen (balloon) for 2 h. The reaction was then purged with argon, filtered through Celite, washed with methanol where the solvent was removed *in vacuo*. The crude material was then re-dissolved in chloroform (5.8 mL) and triethylamine (121 µL, 0.869 mmol) added, and stirred at room temperature for 16 h, then reduced *in vacuo*. Purification by flash column chromatography (SiO_2, 2:1 hexane:ethyl acetate → ethyl acetate) afforded the *title compound* as a white oil (83 mg, 100%); R_f 0.31 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3456, 2905, 1732, 1686; δ_H (400 MHz, $CDCl_3$) 4.56 (2H, s, C**H₂**OH), 3.77 (2H, t, *J* = 7.3 Hz, C**H₂**N), 3.30 (1H, br s, O**H**), 2.53 (2H, t, *J* = 8.0 Hz, C**H₂**CON), 2.12–2.01 (2H, m, C**H₂**CH_2N); δ_C (100 MHz, $CDCl_3$) 176.0 (**C**O), 174.4 (**C**O), 64.2 (**C**H_2OH), 45.0 (**C**H_2N), 32.9 (**C**H_2CO), 18.0 (**C**H_2); HRMS (ESI): calcd. for $C_6H_9NNaO_3$, 166.0475. Found: $[MNa]^+$, 166.0477 (−0.9 ppm error).

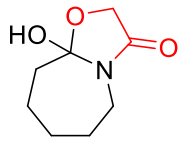
8a-Hydroxytetrahydro-5H-oxazolo[3,2-a]pyridin-3(2H)-one (536)



1-(2-(Benzyloxy)acetyl)piperidin-2-one (188 mg, 0.768 mmol) was dissolved in THF (7.7 mL) and placed under an argon atmosphere. Palladium on carbon (77 mg, Pd 10% on carbon) and water (1.38 mL, 76.8 mmol) was then added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at room temperature under a slight positive pressure of hydrogen (balloon) for 2 h. The reaction was then purged with argon, filtered through Celite, washed with methanol where the solvent was removed *in vacuo*. The crude material was then re-dissolved in chloroform (7.7 mL) and triethylamine (161 µL, 1.15 mmol) added, and stirred at room temperature for 16 h, then reduced *in vacuo*. Purification by flash column chromatography (SiO_2, 2:1 hexane:ethyl acetate → ethyl acetate) afforded an inseparable mixture of the *title compounds* (as a 10:7 mixture of **536**:**524**) as a colourless oil (109 mg, 90%); R_f 0.39 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3375, 2947, 2874, 1688. Data for *8a-hydroxytetrahydro-5H-oxazolo[3,2-a]pyridin-3(2H)-one*: δ_H (400 MHz, $CDCl_3$) 4.91 (1H, br s, O**H**), 4.37 (1H, d, *J* = 13.9 Hz, C**H**H'O), 4.17 (1H, d, *J* = 13.9 Hz, CH**H'**O), 3.97 (1H, dd, *J* = 13.3, 5.0 Hz, C**H**H'N), 3.02–2.90 (1H, m, CH**H'**N), 2.19–2.11 (1H, m, C**H**H'COH), 1.91–1.26 (5H, m, CH**H'**COH and 2 × C**HH'**); δ_C (100 MHz, $CDCl_3$) 168.1 (**C**O), 109.2 (**C**OH), 66.8 (**C**H_2O), 38.4 (**C**H_2N), 36.2 (**C**H_2COH), 24.3 (**C**H_2), 21.3 (**C**H_2). Data for *1-(2-hydroxyacetyl)piperidin-2-one*: 4.61 (1H, s, C**H₂**OH), 3.82–3.72 (2H, m, C**H₂**N), 3.44 (1H, br s, O**H**), 2.60–2.52 (2H, m, C**H₂**CO), 1.94–1.26 (4H, m, 2 × C**H₂**); δ_C (100 MHz, $CDCl_3$) 177.5 (**C**O), 173.1 (**C**O), 66.1 (**C**H_2OH),

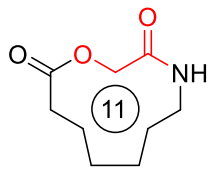
44.6 (**C**H_2N), 34.5 (**C**H_2CO), 22.2 (**C**H_2), 20.0 (**C**H_2); HRMS (ESI): calcd. for $C_7H_{11}NNaO_3$, 180.0631. Found: $[MNa]^+$, 180.0634 (−1.6 ppm error).

9a-Hydroxyhexahydrooxazolo[3,2-a]azepin-3(2H)-one (537)



1-(2-(Benzyloxy)acetyl)azepan-2-one (203 mg, 0.776 mmol) was dissolved in THF (7.7 mL) and placed under an argon atmosphere. Palladium on carbon (77 mg, Pd 10% on carbon) and water (1.40 mL, 77.6 mmol) was then added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at room temperature under a slight positive pressure of hydrogen (balloon) for 2 h. The reaction was purged with argon, filtered through Celite, washed with methanol where the solvent was removed *in vacuo*. The crude material was re-dissolved in chloroform (7.7 mL) and triethylamine (162 µL, 1.16 mmol) added, and stirred at room temperature for 16 h, then reduced *in vacuo*. Purification by flash column chromatography (SiO_2, 2:1 hexane:ethyl acetate → ethyl acetate) afforded an inseparable mixture of the *title compounds* (as a 69:13:1 mixture of 525:524:526 isomers) as a colourless oil (128 mg, 96%); R_f 0.42 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3331, 2932, 2857, 1688; δ_H (400 MHz, $CDCl_3$) data for the 9a-hydroxyhexahydrooxazolo[3,2-a]azepin-3(2H)-one: 5.91 (1H, s, O**H**), 4.29 (1H, d, *J* = 13.7 Hz, C**H**H'O), 4.11 (1H, d, *J* = 13.7 Hz, CH**H'**O), 3.78–3.69 (1H, m, C**H**H'COH), 2.94–2.83 (1H, m, CH**H'**COH), 2.28–2.18 (1H, m, C**H**H'N), 1.90–1.80 (1H, m, CH**H'**N), [1.80–1.55 (3H, m) 1.54–1.39 (1H, m), 1.37–1.23 (1H, m), 1.22–1.09 (1H, m), 3 × C**HH'**]. Diagnostic ^{1}H NMR resonances for 1-(2-hydroxyacetyl)azepan-2-one: 4.52 (2H, d, *J* = 4.6 Hz, C**H$_2$**OH), 3.93–3.86 (2H, m, C**H$_2$**N), 2.79 (1H, br s, O**H**), 2.69–2.59 (2H, m, C**H$_2$**CO). Diagnostic ^{1}H NMR resonances for 1,4-oxazecane-3,10-dione: 6.16 (1H, br s, N**H**), 3.41–3.32 (2H, m, C**H$_2$**NH); δ_C (100 MHz, $CDCl_3$) data for the 9a-hydroxyhexahydrooxazolo[3,2-a]azepin-3(2H)-one only: 170.5 (**C**O), 113.9 (**C**OH), 66.5 (**C**H_2O), [40.2, 39.9 (**C**H_2COH and **C**H_2N)], 29.6 (**C**H_2), 27.9 (**C**H_2), 22.7 (**C**H_2). ^{13}C NMR resonances for 1-(2-hydroxyacetyl)azepan-2-one: 177.7 (**C**O), 176.7 (**C**O), 65.8 (**C**H_2OH), 43.8 (**C**H_2N), 39.3 (**C**H_2CO), 29.1 (**C**H_2), 28.3 (**C**H_2), 23.6 (**C**H_2). Diagnostic ^{13}C NMR resonances for 1,4-oxazecane-3,10-dione: 178.0 (**C**O), 172.5 (**C**O), 68.0 (**C**H_2O), 43.4 (**C**H_2NH), 35.0 (**C**H_2CO), 27.2 (**C**H_2), 22.5 (**C**H_2); HRMS (ESI): calcd. for $C_8H_{13}NNaO_3$, 194.0788. Found: $[MNa]^+$, 194.0788 (−0.9 ppm error).

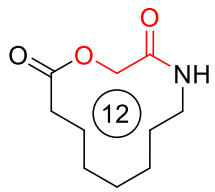
1-Oxa-4-azacycloundecane-3,11-dione (532)



1-(2-(Benzyloxy)acetyl)azocan-2-one (207 mg, 0.751 mmol) was dissolved in ethyl acetate (7.5 mL) and placed under an argon atmosphere. Palladium on carbon (75 mg, Pd 10% on carbon) was then added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at

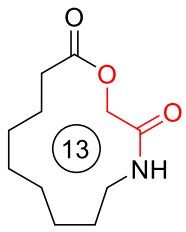
room temperature under a slight positive pressure of hydrogen (balloon) for 1 h. The reaction was then purged with argon, filtered through Celite, washed with methanol where the solvent was removed *in vacuo*. The crude material was then re-dissolved in chloroform (7.5 mL) and triethylamine (157 µL, 1.13 mmol) was added, and then stirred at room temperature for 16 h, and reduced *in vacuo*. Purification by flash column chromatography (SiO_2, 2:1 hexane:ethyl acetate → ethyl acetate → 9:1 ethyl acetate:methanol) afforded the *title compound* (as a 9:1 mixture of rotamers) as a white solid (123 mg, 89%); m.p. 98–99 °C; R_f 0.35 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3287, 2928, 2889, 2868, 2842, 1731, 1659; δ_H (400 MHz, $CDCl_3$) 6.06 (1H, s, N**H**, minor rotamer), 5.94 (1H, s, N**H**, major rotamer), 4.58 (2H, s, C**H₂**O, minor), 4.53 (2H, s, C**H₂**O, major), 3.26–3.12 (4H, m, C**H₂**NH, both rotamers), 2.43–2.29 (4H, m, C**H₂**COO, both), 1.77–1.64 (4H, m, C**H₂**, both), 1.60–1.50 (4H, m, C**H₂**, both), 1.46–1.37 (4H, m, C**H₂**, both), 1.36–1.25 (4H, m, C**H₂**, both); δ_C (100 MHz, $CDCl_3$) data for the major rotamer only: 173.5 (**C**O), 168.3 (**C**O), 64.2 (**C**H_2O), 39.4 (**C**H_2NH), 34.7 (**C**H_2COO), 25.8 (**C**H_2), 25.2 (**C**H_2), 25.1 (**C**H_2), 23.1 (**C**H_2). Diagnostic ^{13}C NMR resonances for the minor rotamer: 172.7 (**C**O), 169.4 (**C**O), 63.9 (**C**H_2O), 40.4 (**C**H_2NH), 28.9 (**C**H_2); HRMS (ESI): calcd. for $C_9H_{16}NO_3$, 186.1125. Found: $[MH]^+$, 186.1129 (−0.4 ppm error).

1-Oxa-4-azacyclododecane-3,12-dione (538)



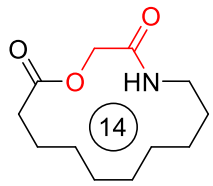
1-(2-(Benzyloxy)acetyl)azonan-2-one (209 mg, 0.729 mmol) was dissolved in THF (7.2 mL) and placed under an argon atmosphere. Palladium on carbon (72 mg, Pd 10% on carbon) and water (1.3 mL, 72.9 mmol) was then added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at room temperature under a slight positive pressure of hydrogen (balloon) for 2 h. The reaction was then purged with argon, filtered through Celite, washed with methanol where the solvent was removed *in vacuo*. The crude material was then re-dissolved in chloroform (7.2 mL) and triethylamine (151 µL, 1.09 mmol) added, and stirred at room temperature for 16 h, then reduced *in vacuo*. Purification by flash column chromatography (SiO_2, 2:1 hexane:ethyl acetate → ethyl acetate → 9:1 ethyl acetate:methanol) afforded the *title compound* as a white solid (139 mg, 97%); m.p. 78–79 °C; R_f 0.43 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3274, 2935, 1733, 1660, 1551; δ_H (400 MHz, $CDCl_3$) 6.26 (1H, s, N**H**), 4.60 (2H, s, C**H₂**O), 3.34–3.23 (2H, m, C**H₂**NH), 2.49–2.38 (2H, m, C**H₂**COO), 1.82–1.70 (2H, m, C**H₂**), 1.55–1.29 (8H, m, 4 × C**H₂**); δ_C (100 MHz, $CDCl_3$) 172.7 (**C**O), 167.2 (**C**O), 62.8 (**C**H_2O), 39.6 (**C**H_2NH), 33.9 (**C**H_2CO), 27.2 (**C**H_2), 25.9 (**C**H_2), 25.3 (**C**H_2), 24.7 (**C**H_2), 24.3 (**C**H_2); HRMS (ESI): calcd. for $C_{10}H_{17}NNaO_3$, 222.1101. Found: $[MNa]^+$, 222.1102 (−1.2 ppm error).

1-Oxa-4-azacyclotridecane-3,13-dione (539)



1-(2-(Benzyloxy)acetyl)azecan-2-one (207 mg, 0.681 mmol) was dissolved in THF (6.8 mL) and placed under an argon atmosphere. Palladium on carbon (68 mg, Pd 10% on carbon) and water (1.2 mL, 68.1 mmol) was then added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at room temperature under a slight positive pressure of hydrogen (balloon) for 2 h. The reaction was then purged with argon, filtered through Celite, washed with methanol where the solvent was removed *in vacuo*. The crude material was then re-dissolved in chloroform (6.8 mL) and triethylamine (142 µL, 1.02 mmol) added, and stirred at room temperature for 16 h, then reduced *in vacuo*. Purification by flash column chromatography (SiO_2, 2:1 hexane:ethyl acetate → ethyl acetate → 9:1 ethyl acetate:methanol) afforded the *title compound* (as a 5:1 mixture of rotamers) as a white solid (135 mg, 93%); m.p. 82.0–83.0 °C; R_f 0.48 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3384, 3282, 2919, 2859, 1720, 1662, 1541; δ_H (400 MHz, $CDCl_3$) 6.01 (1H, br s, N**H**, major rotamer), 4.63 (2H, s, C**H₂**O, major), 4.14 (2H, s, C**H₂**O, minor rotamer), 3.73 (1H, br s, N**H**, minor), 3.53–3.46 (2H, m, C**H₂**NH, minor), 3.33–3.24 (2H, m, C**H₂**NH, major), 3.22–3.16 (2H, m, C**H₂**CO, minor), 2.50–2.39 (2H, m, C**H₂**CO, major), 1.85–1.68 (4H, m, C**H₂**, both rotamers), 1.62–1.28 (20H, m, 5 × C**H₂**, both); δ_C (100 MHz, $CDCl_3$) 172.4 (**C**O), 167.6 (**C**O), 62.8 (**C**H_2O), 38.9 (**C**H_2NH), 34.0 (**C**H_2CO), 26.3 (**C**H_2), 26.0 (**C**H_2), 25.7 (**C**H_2), 25.5 (**C**H_2), 24.0 (**C**H_2), 23.3 (**C**H_2). Diagnostic ^{13}C NMR resonances for minor rotamer: 173.0 (**C**O), 60.5 (**C**H_2O), 48.3 (**C**H_2NH), 25.4 (**C**H_2), 25.2 (**C**H_2), 24.2 (**C**H_2), 23.6 (**C**H_2), 23.0 (**C**H_2); HRMS (ESI): calcd. for $C_{11}H_{19}NNaO_3$, 236.1257. Found: $[MNa]^+$, 236.1259 (−0.6 ppm error).

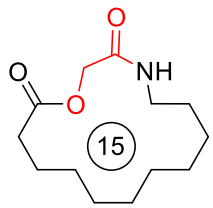
1-Oxa-4-azacyclotetradecane-3,14-dione (540)



A mixture of azacycloundecan-2-one (133 mg, 0.786 mmol), DMAP (10 mg, 0.0786 mmol) and pyridine (380 µL, 4.72 mmol) in CH_2Cl_2 (5.5 mL) under an argon atmosphere was stirred at room temperature for 5 min. Next, a solution of acid chloride (1.18 mmol, 1.50 equiv. prepared using the general procedure) in CH_2Cl_2 (3 mL) was added and the resulting mixture was heated, at reflux, at 50 °C for 16 h. The solvent was concentrated *in vacuo*, loaded onto a short silica plug and eluted with 2:1 hexane:ethyl acetate, to remove the majority of excess carboxylic acid and pyridine residues, and concentrated *in vacuo*. This material was re-dissolved in THF (7.8 mL) and placed under an argon atmosphere. Palladium on carbon (78 mg, Pd 10% on carbon) and water (1.42 mL, 78.6 mmol) was then added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at room temperature under a slight positive pressure of hydrogen (balloon) for 1 h. The reaction was then purged with argon, filtered through Celite, washed with methanol where the solvent was removed *in vacuo*. The crude material was then re-dissolved in

chloroform (7.8 mL) and triethylamine (165 µL, 1.18 mmol) added, and stirred at room temperature for 16 h, then reduced *in vacuo*. Purification by flash column chromatography (SiO_2, 2:1 hexane:ethyl acetate → ethyl acetate) afforded the *title compound* as a white solid (154 mg, 86%); m.p. 97.0–98.0 °C; R_f 0.52 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3397, 2921, 2861, 1722, 1678, 1663, 1534; δ_H (400 MHz, $CDCl_3$) 6.13 (1H, br s, N**H**), 4.58 (2H, s, C**H₂**O), 3.40–3.29 (2H, m, C**H₂**NH), 2.50–2.38 (2H, m, C**H₂**COO), 1.77–1.64 (2H, m, C**H₂**), 1.58–1.48 (2H, m, C**H₂**), 1.44–1.21 (10H, m, 5 × C**H₂**); δ_C (100 MHz, $CDCl_3$) 172.4 (**C**O), 167.2 (**C**O), 63.1 (**C**H_2O), 38.2 (**C**H_2NH), 33.4 (**C**H_2CO), 26.6 (**C**H_2), 26.2 (**C**H_2), 25.8 (**C**H_2), 25.7 (**C**H_2), 25.2 (**C**H_2), 24.2 (**C**H_2), 23.9 (**C**H_2); HRMS (ESI): calcd. for $C_{12}H_{21}NNaO_3$, 250.1414. Found: $[MNa]^+$, 250.1416 (−1.3 ppm error).

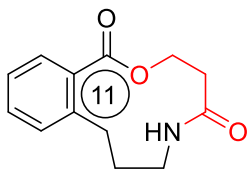
1-Oxa-4-azacyclopentadecane-3,15-dione (541)



A mixture of azacyclododecan-2-one (144 mg, 0.786 mmol), DMAP (10 mg, 0.0786 mmol) and pyridine (380 µL, 4.72 mmol) in CH_2Cl_2 (5.5 mL) under an argon atmosphere was stirred at room temperature for 5 min. Next, a solution of acid chloride (1.18 mmol, 1.50 equiv. prepared using the general procedure) in CH_2Cl_2 (3 mL) was added and the resulting mixture was heated, at reflux, at 50 °C for 16 h. The solvent was concentrated *in vacuo*, loaded onto a short silica plug and eluted with 2:1 hexane:ethyl acetate, to remove the majority of excess carboxylic acid and pyridine residues, and concentrated *in vacuo*. This material was re-dissolved in THF (7.8 mL) and placed under an argon atmosphere. Palladium on carbon (78 mg, Pd 10% on carbon) and water (1.42 mL, 78.6 mmol) was then added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at room temperature under a slight positive pressure of hydrogen (balloon) for 1 h. The reaction was then purged with argon, filtered through Celite, washed with methanol where the solvent was removed *in vacuo*. The crude material was then re-dissolved in chloroform (7.8 mL) and triethylamine (165 µL, 1.18 mmol) added, and stirred at room temperature for 16 h, then reduced *in vacuo*. Purification by flash column chromatography (SiO_2, 2:1 hexane:ethyl acetate → ethyl acetate) afforded the *title compound* (as a 3:1 mixture of rotamers) as a white solid (155 mg, 83%); m.p. 82.0–83.0 °C; R_f 0.54 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3398, 2927, 2857, 1725, 1677, 1530; δ_H (400 MHz, $CDCl_3$) 6.16 (2H, br s, N**H**, both rotamers), 4.58 (2H, s, C**H₂**O, minor rotamer), 4.55 (2H, s, C**H₂**O, major rotamer), 3.40–3.27 (4H, m, C**H₂**NH, both), 2.48–2.37 (4H, m, C**H₂**COO, both), 1.79–1.65 (4H, m, C**H₂**, both), 1.59–1.48 (4H, m, C**H₂**, both), 1.42–1.19 (24H, m, 6 × C**H₂**, both); δ_C (100 MHz, $CDCl_3$) data for the major rotamer only: 172.2 (**C**O), 167.3 (**C**O), 63.0 (**C**H_2O), 38.5 (**C**H_2NH), 33.3 (**C**H_2CO), 29.9 (**C**H_2), 27.3 (**C**H_2), 26.7 (**C**H_2), 26.5 (**C**H_2), 26.4 (**C**H_2), 26.3 (**C**H_2), 24.8 (**C**H_2), 24.3 (**C**H_2). Diagnostic ^{13}C NMR

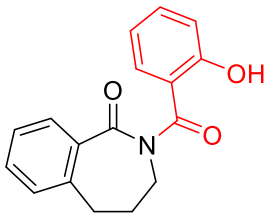
resonances for the minor rotamer: 172.4 (**C**O), 167.2 (**C**O), 63.1 (**C**H_2O), 38.2 (**C**H_2NH), 33.4 (**C**H_2CO), 26.6 (**C**H_2), 26.2 (**C**H_2), 25.8 (**C**H_2), 25.7 (**C**H_2), 25.2 (**C**H_2), 24.2 (**C**H_2), 23.9 (**C**H_2); HRMS (ESI): calcd. for $C_{13}H_{23}NNaO_3$, 264.1570. Found: $[MNa]^+$, 264.1574 (−1.1 ppm error).

3,4,6,7,8,9-Hexahydrobenzo[*i*][1]oxa[5]azacycloundecine-1,5-dione (549)



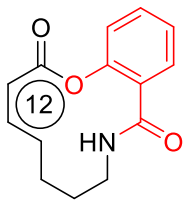
A mixture of 2,3,4,5-tetrahydro-1H-benzo[*c*]azepin-1-one (127 mg, 0.786 mmol), DMAP (10 mg, 0.0786 mmol) and pyridine (380 µL, 4.72 mmol) in CH_2Cl_2 (5.5 mL) under an argon atmosphere was stirred at room temperature for 5 min. Next, a solution of acid chloride (1.18 mmol, 1.50 equiv. prepared using the general procedure) in CH_2Cl_2 (3 mL) was added and the resulting mixture was heated, at reflux, at 50 °C for 16 h. The solvent was concentrated *in vacuo*, loaded onto a short silica plug and eluted with 2:1 hexane:ethyl acetate, to remove the majority of excess carboxylic acid and pyridine residues, and concentrated *in vacuo*. This material was re-dissolved in ethyl acetate (7.8 mL) and placed under an argon atmosphere. Palladium on carbon (78 mg, Pd 10% on carbon) was then added, and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at room temperature under a slight positive pressure of hydrogen (balloon) for 16 h. The reaction was purged with argon, filtered through Celite, washed with methanol where the solvent was removed *in vacuo*. The crude material was then re-dissolved in chloroform (7.8 mL) and triethylamine (165 µL, 1.18 mmol) added, and stirred at room temperature for 16 h, then reduced *in vacuo*. Purification by flash column chromatography (SiO_2, 2:1 hexane:ethyl acetate → ethyl acetate) afforded the *title compound* as a colourless oil (98 mg, 53%). 2-(3-Hydroxypropanoyl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-1-one (48 mg, 26%) was also isolated, and re-subjected to the reaction conditions where it was re-dissolved in chloroform (2.1 mL) and triethylamine (45 µL, 0.309 mmol) was added and stirred at room temperature for 16 h. Purification of this second reaction mixture by flash column chromatography (SiO_2, 2:1 hexane:ethyl acetate → ethyl acetate) afforded the *title compound*, which was combined with the initial purified compound, as a colourless oil (130 mg, 71%); R_f 0.32 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3302, 3071, 2949, 1703, 1651, 1547; δ_H (400 MHz, $CDCl_3$) 7.76 (1H, d, *J* = 6.9 Hz, C**H**), 7.40–7.31 (1H, m, C**H**), 7.23–7.17 (1H, m, C**H**), 7.13 (1H, d, *J* = 7.6 Hz, C**H**), 6.16 (1H, br s, N**H**), 4.57 (2H, t, *J* = 6.1 Hz, C**H**$_2$O), 3.41–3.19 (2H, m, C**H**$_2$NH), 2.86 (2H, t, *J* = 7.6 Hz, C**H**$_2$C), 2.58 (2H, t, *J* = 6.1 Hz, C**H**$_2$CON), 1.80–1.63 (2H, m, C**H**$_2$CH$_2$NH); δ_C (100 MHz, $CDCl_3$) 172.6 (**C**O), 168.8 (**C**O), 142.9 (**C**), 132.1 (**C**H), 131.3 (**C**H), 131.1 (**C**H), 130.0 (**C**), 126.3 (**C**H), 63.2 (**C**H_2O), 40.1 (**C**H_2NH), 37.0 (**C**H_2C), 32.1 (**C**H_2CON), 30.4 (**C**H_2CH$_2$NH); HRMS (ESI): calcd. for $C_{13}H_{15}NNaO_3$, 256.0944. Found: $[MNa]^+$, 256.0945 (−0.2 ppm error).

2-(2-Hydroxybenzoyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepin-1-one (552)



A mixture of 2,3,4,5-tetrahydro-1H-benzo[*c*]azepin-1-one (127 mg, 0.786 mmol), DMAP (10 mg, 0.0786 mmol) and pyridine (380 µL, 4.72 mmol) in CH_2Cl_2 (5.5 mL) under an argon atmosphere was stirred at room temperature for 5 min. Next, a solution of acid chloride (1.18 mmol, 1.50 equiv. prepared using the general procedure) in CH_2Cl_2 (3 mL) was added and the resulting mixture was heated, at reflux, at 50 °C for 16 h. The solvent was concentrated *in vacuo*, loaded onto a short silica plug and eluted with 2:1 hexane:ethyl acetate, to remove the majority of excess carboxylic acid and pyridine residues, and concentrated *in vacuo*. This material was re-dissolved in ethyl acetate (7.8 mL) and placed under an argon atmosphere. Palladium on carbon (78 mg, Pd 10% on carbon) was then added, and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at room temperature under a slight positive pressure of hydrogen (balloon) for 16 h. The reaction was purged with argon, filtered through Celite, washed with methanol where the solvent was removed *in vacuo*. The crude material was then re-dissolved in chloroform (7.8 mL) and triethylamine (165 µL, 1.18 mmol) added, and stirred at room temperature for 16 h, then reduced *in vacuo*. Purification by flash column chromatography (SiO_2, 2:1 hexane:ethyl acetate → ethyl acetate) afforded the *title compound* (as a 4:1 mixture of rotamers) as a colourless oil (142 mg, 73%); R_f 0.71 (ethyl acetate); ν_{max}/cm^{-1} (neat) 3280, 2958, 1649, 1601, 1452; δ_H (400 MHz, $CDCl_3$) 10.01 (1H, br s, O**H**, major rotamer), 9.51 (1H, s, O**H**, minor rotamer), 7.79 (1H, d, *J* = 7.6 Hz, C**H**, major), 7.73 (1H, d, *J* = 7.6 Hz, minor), 7.57–7.23 (11H, m, 5 × C**H**, both rotamers and 1 × C**H**, minor rotamer), 7.22–7.18 (1H, d, *J* = 7.6 Hz, minor), 6.91 (1H, d, *J* = 8.4 Hz, C**H**, major), 6.83–6.75 (1H, m, C**H**, major), 3.87 (2H, t, *J* = 6.4 Hz, C**H₂**N, major), 3.63 (2H, t, *J* = 6.5 Hz, C**H₂**N, minor), 3.03 (2H, t, *J* = 6.9 Hz, C**H₂**C, major), 2.84–2.76 (2H, m, C**H₂**C, minor), 2.09–1.94 (4H, m, C**H₂**CH_2N, both rotamers); δ_C (100 MHz, $CDCl_3$) data for major rotamer only: 175.4 (**C**O), 173.0 (**C**O), 159.8 (**C**OH), 139.2 (**C**), 134.9 (**C**H), 133.7 (**C**), 133.5 (**C**H), 133.3 (**C**), 130.9 (**C**H), 130.8 (**C**H), 129.7 (**C**H), 127.6 (**C**H), 119.1 (**C**H), 118.1 (**C**H), 42.1 (**C**H_2), 30.6 (**C**H_2), 28.0 (**C**H_2). Diagnostic ^{13}C NMR resonances for minor rotamer: 173.4 (**C**O), 162.3 (**C**OH), 138.2 (**C**H), 129.3 (**C**H), 117.9 (**C**H), 38.7 (**C**H_2), 30.1 (**C**H_2), 26.9 (**C**H_2); HRMS (ESI): calcd. for $C_{17}H_{15}N_{Na}O_3$, 304.0944. Found: $[MNa]^+$, 304.0947 (−1.3 ppm error).

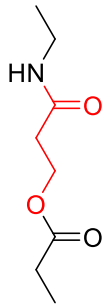
4,5,6,7,8,9-Hexahydro-2H-benzo[b][1]oxa[5]azacyclododecine-2,10(3*H*)-dione (555)



A mixture of azacyclooctan-2-one (100 mg, 0.786 mmol), DMAP (10 mg, 0.0786 mmol) and pyridine (380 µL, 4.72 mmol) in CH_2Cl_2 (5.5 mL) under an argon atmosphere was stirred at room temperature for 5 min. Next, a solution of acid chloride (1.18 mmol, 1.50 equiv. prepared using the general procedure)

in CH_2Cl_2 (3 mL) was added and the resulting mixture was heated, at reflux, at 50 °C for 16 h. An additional solution of acid chloride (1.18 mmol, 1.50 equiv. prepared using the general procedure) in CH_2Cl_2 (3 mL) was added and heated, to reflux, at 50 °C for a further 16 h in order to achieve reaction completion. The solvent was then concentrated *in vacuo*, loaded onto a short silica plug and eluted with 2:1 hexane:ethyl acetate, to remove the majority of excess carboxylic acid and pyridine residues, and concentrated *in vacuo*. This material was re-dissolved in ethyl acetate (7.8 mL) and placed under an argon atmosphere. Palladium on carbon (78 mg, Pd 10% on carbon) was then added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at room temperature under a slight positive pressure of hydrogen (balloon) for 1 h. The reaction was then purged with argon, filtered through Celite, washed with methanol where the solvent was removed *in vacuo*. The crude material was then re-dissolved in chloroform (7.8 mL) and triethylamine (165 µL, 1.18 mmol) added, and stirred at room temperature for 16 h, then reduced *in vacuo*. Purification by flash column chromatography (SiO_2, 2:1 hexane:ethyl acetate → ethyl acetate) afforded the *title compound* as a white solid (174 mg, 90%); m.p. 138.0–140.0 °C; R_f 0.62 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3296, 2939, 2900, 2849, 1742, 1632, 1542; δ_H (400 MHz, $CDCl_3$) 7.74 (1H, d, *J* = 7.7 Hz, C**H**), 7.44–7.35 (1H, m, C**H**), 7.30–7.20 (1H, m, C**H**), 7.01 (1H, d, *J* = 8.1 Hz, C**H**), 6.46 (1H, br s, N**H**), 3.50–3.34 (2H, m, C**H₂**NH), 2.67–2.53 (2H, m, C**H₂**COO), 1.90–1.75 (2H, m, C**H₂**), 1.71–1.61 (2H, m, C**H₂**), 1.59–1.43 (4H, m, 2 × C**H₂**); δ_C (100 MHz, $CDCl_3$) 171.9 (**C**O), 165.4 (**C**O), 147.2 (**C**), 131.5 (**C**H), 130.5 (**C**H), 129.1 (**C**), 126.5 (**C**H), 123.3 (**C**H), 40.1 (**C**H_2NH), 34.6 (**C**H_2CO), 26.3 (**C**H_2), 25.8 (**C**H_2), 24.7 (**C**H_2), 22.5 (**C**H_2); HRMS (ESI): calcd. for $C_{14}H_{17}NNaO_3$, 270.1101. Found: $[MNa]^+$, 270.1107 (−2.1 ppm error).

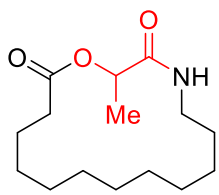
3-(Ethylamino)-3-oxopropyl propionate (558)



A mixture of *N*-ethylpropionamide (80 mg, 0.786 mmol), DMAP (10 mg, 0.0786 mmol) and pyridine (380 µL, 4.72 mmol) in CH_2Cl_2 (5.5 mL) under an argon atmosphere was stirred at room temperature for 5 min. Next, a solution of acid chloride (1.18 mmol, 1.50 equiv. prepared using the general procedure) in CH_2Cl_2 (3 mL) was added and the resulting mixture was heated, at reflux, at 50 °C for 16 h. The solvent was concentrated *in vacuo*, loaded onto a short silica plug and eluted with 2:1 hexane:ethyl acetate, to remove the majority of excess carboxylic acid and pyridine residues, and concentrated *in vacuo*. This material was re-dissolved in ethyl acetate (7.8 mL) and placed under an argon atmosphere. Palladium on carbon (78 mg, Pd 10% on carbon) was then added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at room temperature under a slight positive pressure of hydrogen (balloon) for 1 h. The reaction

was then purged with argon, filtered through Celite, washed with methanol where the solvent was removed *in vacuo*. The crude material was then re-dissolved in chloroform (7.8 mL) and triethylamine (165 µL, 1.18 mmol) added, and stirred at room temperature for 16 h, then reduced *in vacuo*. Purification by flash column chromatography (SiO_2, 2:1 hexane:ethyl acetate → ethyl acetate) afforded the *title compound* as a colourless oil (102 mg, 75%); R_f 0.36 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3299, 3094, 2978, 2941, 1736, 1644, 1551; δ_H (400 MHz, $CDCl_3$) 6.12 (1H, br s, N**H**), 4.36–4.25 (2H, m, C**H₂**O), 3.29–3.16 (2H, m, C**H₂**NH), 2.43 (2H, t, *J* = 6.3 Hz, C**H₂**CONH), 2.25 (2H, q, *J* = 7.6 Hz, C**H₂**COO), 1.15–0.97 (6H, m, 2 × C**H₃**); δ_C (100 MHz, $CDCl_3$) 174.5 (**C**O), 169.9 (**C**O), 60.6 (**C**H_2O), 35.9 (**C**H_2NH), 34.5 (**C**H_2CON), 27.5 (**C**H_2COO), 14.8 (**C**H_3), 9.1 (**C**H_3); HRMS (ESI): calcd. for $C_8H_{15}NNaO_3$, 1986.0944. Found: $[MNa]^+$, 196.0948 (−1.5 ppm error).

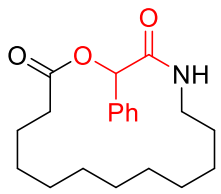
2-Methyl-1-oxa-4-azacyclohexadecane-3,16-dione (561)



A mixture of laurolactam (155 mg, 0.786 mmol), DMAP (10 mg, 0.0786 mmol) and pyridine (380 µL, 4.72 mmol) in CH_2Cl_2 (5.5 mL) under an argon atmosphere was stirred at room temperature for 5 min. Next, a solution of acid chloride (1.18 mmol, 1.50 equiv. prepared using the general procedure) in CH_2Cl_2 (3 mL) was added and the resulting mixture was heated, at reflux, at 50 °C for 16 h. The solvent was concentrated *in vacuo*, loaded onto a short silica plug and eluted with 2:1 hexane:ethyl acetate, to remove the majority of excess carboxylic acid and pyridine residues, and concentrated *in vacuo*. This material was re-dissolved in THF (7.8 mL) and placed under an argon atmosphere. Palladium on carbon (78 mg, Pd 10% on carbon) and water (1.42 mL, 78.6 mmol) was then added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at room temperature under a slight positive pressure of hydrogen (balloon) for 2 h. The reaction was then purged with argon, filtered through Celite, washed with methanol where the solvent was removed *in vacuo*. The crude material was then re-dissolved in chloroform (7.8 mL) and triethylamine (165 µL, 1.18 mmol) added, and stirred at room temperature for 16 h, then reduced *in vacuo*. Purification by flash column chromatography (SiO_2, 2:1 hexane:ethyl acetate → ethyl acetate) afforded the *title compound* as a colourless oil (124 mg, 59%). 1-(2-Hydroxypropanoyl)azacyclotridecan-2-one (82 mg, 38%) was also isolated, and re-subjected to the reaction conditions where it was re-dissolved in chloroform (3.0 mL) and triethylamine (65 µL, 0.452 mmol) was added and stirred at room temperature for 16 h. Purification of this second reaction mixture by flash column chromatography (SiO_2, 2:1 hexane:ethyl acetate → ethyl acetate) afforded the *title compound*, which was combined with the initial purified compound, as a colourless oil (180 mg, 85%); R_f 0.67 (ethyl acetate); ν_{max}/cm^{-}

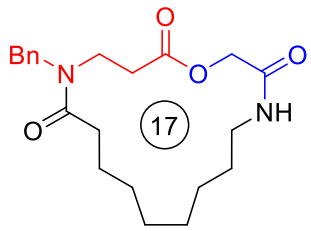
[1] (thin film) 3314, 2928, 2857, 1738, 1659, 1536; δ_H (400 MHz, $CDCl_3$) 6.24 (1H, br s, N**H**), 5.17 (1H, q, *J* = 6.9 Hz, C**H**CH_3), 3.47–3.37 (1H, m, C**H**H'NH), 3.20 (1H, m, CH**H'**NH), 2.39 (2H, m, C**H**$_2$COO), 1.73–1.14 (21H, m, 9 × C**H**$_2$ and C**H**$_3$); δ_C (100 MHz, $CDCl_3$) 172.2 (**C**O), 170.4 (**C**O), 70.8 (**C**HO), 38.6 (**C**H_2NH), 34.8 (**C**H_2COO), 28.5 (**C**H_2), 27.1 (**C**H_2), 27.0 (**C**H_2), 26.40 (**C**H_2), 26.36 (**C**H_2), 25.7 (**C**H_2), 24.9 (**C**H_2), 24.7 (**C**H_2), 24.6 (**C**H_2), 18.1 (**C**H_3); HRMS (ESI): calcd. for $C_{15}H_{28}NO_3$, 270.2064. Found: $[MH]^+$, 270.2065 (−0.1 ppm error).

2-Phenyl-1-oxa-4-azacyclohexadecane-3,16-dione (564)



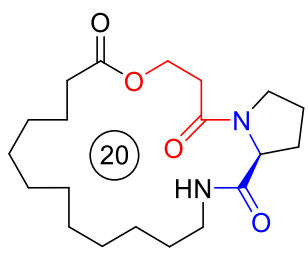
A mixture of laurolactam (155 mg, 0.786 mmol), DMAP (10 mg, 0.0786 mmol) and pyridine (380 µL, 4.72 mmol) in CH_2Cl_2 (5.5 mL) under an argon atmosphere was stirred at room temperature for 5 min. Next, a solution of acid chloride (1.18 mmol, 1.50 equiv. prepared using the general procedure) in CH_2Cl_2 (3 mL) was added and the resulting mixture was heated, at reflux, at 50 °C for 16 h. The solvent was concentrated *in vacuo*, loaded onto a short silica plug and eluted with 2:1 hexane:ethyl acetate, to remove the majority of excess carboxylic acid and pyridine residues, and concentrated *in vacuo*. This material was re-dissolved in THF (7.8 mL) and placed under an argon atmosphere. Palladium on carbon (78 mg, Pd 10% on carbon) and water (1.42 mL, 78.6 mmol) was then added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at room temperature under a slight positive pressure of hydrogen (balloon) for 2 h. The reaction was then purged with argon, filtered through Celite, washed with methanol where the solvent was removed *in vacuo*. The crude material was then re-dissolved in chloroform (7.8 mL) and triethylamine (165 µL, 1.18 mmol) added, and stirred at room temperature for 16 h, then reduced *in vacuo*. Purification by flash column chromatography (SiO_2, 2:1 hexane:ethyl acetate → ethyl acetate) afforded the *title compound* as a white solid (176 mg, 68%); m.p. 126–128 °C; R_f 0.73 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3300, 2927, 2856, 1736, 1654, 1537; δ_H (400 MHz, $CDCl_3$) 7.53–7.16 (5H, m, Ph), 6.41 (1H, br s, N**H**), 6.13 (1H, s, C**H**Ph), 3.61–3.50 (1H, m, C**H**H'NH), 3.21–3.10 (1H, m, CH**H'**NH), 2.49–2.34 (2H, m, C**HH'**COO), 1.83–1.21 (18H, m, 9 × C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 171.7 (**C**O), 168.4 (**C**O), 136.0 (**C**), 128.9 (**C**H), 128.7 (**C**H), 127.3 (**C**H), 75.6 (**C**HPh), 38.7 (**C**H_2NH), 34.8 (**C**H_2CO), 28.8 (**C**H_2), 27.2 (**C**H_2), 27.1 (**C**H_2), 26.6 (**C**H_2), 26.5 (**C**H_2), 25.7 (**C**H_2), 25.0 (**C**H_2), 24.8 (**C**H_2), 24.6 (**C**H_2); HRMS (ESI): calcd. for $C_{20}H_{29}NNaO_3$, 354.2040. Found: $[MNa]^+$, 354.2041 (−0.5 ppm error).

14-Benzyl-1-oxa-4,14-diazacycloheptadecane-3,13,17-trione (568)



A mixture of 5-benzyl-1,5-diazacyclotetradecane-2,6-dione (65 mg, 0.205 mmol), DMAP (3 mg, 0.0205 mmol) and pyridine (100 µL, 1.23 mmol) in CH_2Cl_2 (1.5 mL) under an argon atmosphere was stirred at room temperature for 5 min. Next, a solution of acid chloride (0.308 mmol, 1.50 equiv. prepared using the general procedure) in CH_2Cl_2 (1 mL) was added and the resulting mixture was heated, at reflux, at 50 °C for 16 h. An additional solution of acid chloride (0.308 mmol, 1.50 equiv. prepared using the general procedure) in CH_2Cl_2 (1 mL) was added and heated, to reflux, at 50 °C for a further 16 h in order to achieve reaction completion. The solvent was then concentrated *in vacuo*, loaded onto a short silica plug and eluted with 2:1 hexane:ethyl acetate, to remove the majority of excess carboxylic acid and pyridine residues, and concentrated *in vacuo*. This material was re-dissolved in THF (2.1 mL) and placed under an argon atmosphere. Palladium on carbon (21 mg, Pd 10% on carbon) and water (370 µL, 20.5 mmol) was then added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at room temperature under a slight positive pressure of hydrogen (balloon) for 3 h. The reaction was then purged with argon, filtered through Celite, washed with methanol and the solvent was removed *in vacuo*. The crude material was then re-dissolved in chloroform (2.1 mL) and triethylamine (45 µL, 0.308 mmol) added, and stirred at room temperature for 16 h, then reduced *in vacuo*. Purification by flash column chromatography (SiO_2, 2:1 hexane:ethyl acetate → ethyl acetate → 9:1 ethyl acetate:methanol) afforded the *title compound* as a colourless oil (75 mg, 98%); R_f 0.43 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3331, 2930, 2857, 1744, 1634, 1546; δ_H (400 MHz, $CDCl_3$) 7.56 (1H, br s, N**H**), 7.40–7.07 (5H, m, Ph), 4.61 (2H, s, C$\mathbf{H_2}$O), 4.59 (2H, s, C$\mathbf{H_2}$Ph), 3.72–3.54 (2H, m, C$\mathbf{H_2}$NBn), 3.41–3.27 (2H, m, C$\mathbf{H_2}$NH), 2.65–2.51 (2H, m, C$\mathbf{H_2}$COO), 2.45–2.28 (2H, m, C$\mathbf{H_2}$CONBn), 1.66–1.17 (12H, m, 6 × C$\mathbf{H_2}$); δ_C (100 MHz, $CDCl_3$) 174.3 (**C**O), 171.3 (**C**O), 167.7 (**C**O), 136.4 (**C**), 129.1 (**C**H), 127.9 (**C**H), 126.4 (**C**H), 63.3 (**C**H_2O), 52.4 (**C**H_2Ph), 43.3 (**C**H_2NBn), 38.1 (**C**H_2NH), 34.5 (**C**H_2COO), 32.2 (**C**H_2CONBn), 27.9 (**C**H_2), 26.7 (**C**H_2), 26.0 (**C**H_2), 25.5 (**C**H_2), 23.2 (2 × **C**H_2); HRMS (ESI): calcd. for $C_{21}H_{30}N_2NaO_4$, 397.2098. Found: $[MNa]^+$, 397.2108 (−2.6 ppm error).

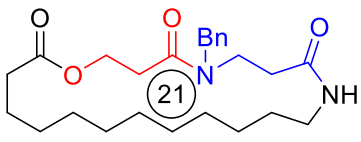
(*S*)-Hexadecahydro-16*H*-pyrrolo[1,2-*e*][1]oxa[5,8]diazacycloicosine-1,14,18(17*H*)-trione (569)



A mixture of 1-oxa-5-azacycloheptadecane-4,17-dione (110 mg, 0.408 mmol), DMAP (5 mg, 0.0408 mmol) and pyridine (0.200 mL, 2.45 mmol) in CH_2Cl_2 (3 mL) under an argon atmosphere was stirred at room temperature for 30 min. Next, a solution of acid chloride (0.613 mmol, 1.50 eqv prepared using the general procedure) in

CH_2Cl_2 (2 mL) was added and the resulting mixture was heated, at reflux, at 50 °C for 16 h. An additional solution of acid chloride (0.613 mmol, 1.50 equiv. prepared using the general procedure) in CH_2Cl_2 (2 mL) was added and heated, to reflux, at 50 °C for a further 24 h in order to achieve reaction completion. The solvent was then concentrated *in vacuo*, loaded onto a short silica plug and eluted with 2:1 hexane:ethyl acetate, to remove the majority of excess carboxylic acid and pyridine residues, and concentrated *in vacuo*. The crude material was then re-dissolved in CH_2Cl_2 (4.1 mL) and DBU (0.620 mL, 4.083 mmol) was added, followed by stirring at room temperature for 16 h, before the solvent was removed *in vacuo*. Purification by flash column chromatography (2:1 hexane:ethyl acetate→ethyl acetate→9:1 ethyl acetate:methanol) afforded the *title compound* (as a 4.4:1 mixture of rotamers) as a colourless oil (119 mg, 81%); $[\alpha]_D^{25}$ −43.6 (c = 1.0, $CHCl_3$); R_f 0.20 (ethyl acetate); ν_{max}/cm^{-1} (neat) 3309, 2917, 1739, 1621, 1551; δ_H (400 MHz, $CDCl_3$) 7.18 (1H, br s, N**H**, major rotamer), 6.16 (1H, br s, N**H**, minor rotamer), 4.59 (1H, d, *J* = 8.4 Hz, C**H**, major), 4.42 (1H, d, *J* = 5.3 Hz, C**H**, minor), 4.40–4.27 (4H, m, C**H₂**NCO, both rotamers), 3.63–3.48 (2H, m, C**H**H'N, both), 3.44–3.25 (4H, m, CH**H'**NCO and C**H**H'NH, both), 3.11–2.96 (2H, m, CH**H'**NH), 2.71–2.53 (4H, m, C**H₂**CON, both), 2.52–2.41 (2H, m, C**H**H'CHN, both), 2.33–2.16 (4H, m, C**H₂**COO), 2.15–2.02 (2H, m, CH**H'**CHN, both), 2.03–1.92 (2H, m, C**H**H'CH_2N, both), 1.87–1.72 (2H, m, CH**H'**CH_2N, both), 1.70–1.54 (4H, m, C**H₂**, both), 1.53–1.40 (4H, m, C**H₂**, both), 1.37–1.16 (28H, m, 7 × C**H₂**, both); δ_C (100 MHz, $CDCl_3$) data for the major rotamer only: 174.1 (**C**O), 170.8 (**C**O), 170.4 (**C**O), [59.8, 59.7 (**C**HN and **C**H_2O)], 47.6 (**C**H_2NCO), 39.5 (**C**H_2NH), 33.9 (**C**H_2CO), 33.8 (**C**H_2CO), 28.7 (**C**H_2), 28.1 (**C**H_2), 27.38 (**C**H_2), 27.36 (**C**H_2), 27.3 (**C**H_2), 27.1 (**C**H_2), 26.9 (**C**H_2), 26.7 (**C**H_2), 26.0 (**C**H_2), 25.1 (**C**H_2), 24.2 (**C**H_2). Diagnostic ^{13}C NMR resonances for the minor rotamer: 173.9 (**C**O), 171.4 (**C**O), 169.9 (**C**O), [61.8, 60.2 (**C**HN and **C**H_2O)], 46.9 (**C**H_2NCO), 39.6 (**C**H_2NH), 33.5 (**C**H_2CO), 32.0 (**C**H_2CO), 29.3 (**C**H_2), 28.2 (**C**H_2), 26.5 (**C**H_2), 26.1 (**C**H_2), 22.7 (**C**H_2); HRMS (ESI): calcd. for $C_{20}H_{34}N_2NaO_4$, 389.2411. Found: $[MNa]^+$, 389.2413 (−0.5 ppm error).

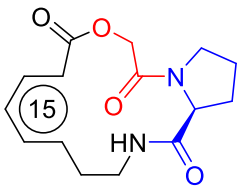
5-Benzyl-1-oxa-5,9-diazacyclohenicosane-4,8,21-trione (570)



A mixture of 1-oxa-5-azacycloheptadecane-4,17-dione (45 mg, 0.167 mmol), DMAP (2 mg, 0.0167 mmol) and pyridine (81 µL, 1.00 mmol) in CH_2Cl_2 (1.5 mL) under an argon atmosphere was stirred at room temperature for 5 min. Next, a solution of acid chloride (0.251 mmol, 1.50 equiv. prepared using the general procedure) in CH_2Cl_2 (1 mL) was added and the resulting mixture was heated, at reflux, at 50 °C for 16 h. The solvent was then concentrated *in vacuo*, loaded onto a short silica plug and eluted with ethyl acetate, to remove the majority of excess carboxylic acid and pyridine residues. The crude material was then re-dissolved in CH_2Cl_2 (1.67 mL) and DBU

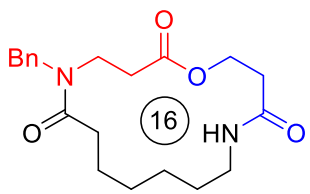
(0.250 mL, 1.67 mmol) was added, followed by stirring at room temperature for 16 h, before the solvent was removed *in vacuo*. Purification by flash column chromatography (2:1 hexane:ethyl acetate→ethyl acetate→9:1 ethyl acetate:methanol) afforded the *title compound* (as a mixture of rotamers) as a colourless oil (58 mg, 84%); R_f 0.13 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3300, 2927, 2856, 1642, 1554; δ_H (400 MHz, $CDCl_3$) 7.40–7.04 (5H, m, Ph), 6.97 (1H, br s, N**H**), 4.62 (2H, s, C**H₂**Ph), 3.76–3.15 (6H, m, 2 × C**H₂**N and C**H₂**O), 2.62–2.14 (6H, m, 3 × C**H₂**CO), 1.94–1.17 (18H, m, 9 × C**H₂**); δ_C (100 MHz, $CDCl_3$) 175.2 (**C**O), 172.9 (**C**O), 171.3 (**C**O), 136.6 (**C**), 129.1 (**C**H), 127.2 (**C**H), 126.3 (**C**H), 66.4 (**C**H_2O), 54.9 (**C**H_2Ph), 52.2 (**C**H_2NBn), 42.7 (**C**H_2NH), 39.9 (**C**H_2CO), 35.6 (**C**H_2CO), 32.9 (**C**H_2CO), 31.4 (**C**H_2), 28.5 (**C**H_2), 27.6 (**C**H_2), 27.2 (**C**H_2), 26.6 (**C**H_2), 25.6 (**C**H_2), 25.1 (**C**H_2), 24.8 (**C**H_2), 24.5 (**C**H_2); HRMS (ESI): calcd. for $C_{25}H_{39}N_2O_4$, 431.2904. Found: $[MH]^+$, 431.2912 (0.1 ppm error).

(*S*)-Dodecahydropyrrolo[1,2-*d*][1]oxa[4,7]diazacyclopentadecine-1,10,13(12*H*)-trione (571)



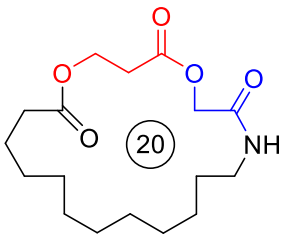
A mixture of 1-oxa-4-azacyclododecane-3,12-dione (80 mg, 0.402 mmol), DMAP (5 mg, 0.0402 mmol) and pyridine (195 µL, 2.41 mmol) in CH_2Cl_2 (3 mL) under an argon atmosphere was stirred at room temperature for 5 min. Next, a solution of acid chloride (0.602 mmol, 1.50 equiv. prepared using the general procedure) in CH_2Cl_2 (1.5 mL) was added and the resulting mixture was heated, at reflux, at 50 °C for 16 h. The solvent was then concentrated *in vacuo*, loaded onto a short silica plug and eluted with 2:1 hexane:ethyl acetate, to remove the majority of excess carboxylic acid and pyridine residues, and concentrated *in vacuo*. This material was re-dissolved in CH_2Cl_2 (4.0 mL) and placed under an argon atmosphere. DBU (615 µL, 4.02 mmol) was then added and stirred at room temperature for 16 h, then reduced *in vacuo*. Purification by flash column chromatography (SiO_2, 2:1 hexane:ethyl acetate → ethyl acetate → 9:1 ethyl acetate:methanol) afforded the *title compound* as a colourless oil (217 mg, 74%); $[\alpha]_D^{25}$ −95.1 (c = 1.0, chloroform); R_f 0.64 (9:1 ethyl acetate:methanol); ν_{max}/cm^{-1} (thin film) 3316, 2856, 1725, 1660, 1544; δ_H (400 MHz, $CDCl_3$) 6.96 (1H, br s, N**H**), 4.88 (1H, d, *J* = 13.3 Hz, C**H**H'O), 4.55 (1H, d, *J* = 6.9 Hz, NC**H**), 4.24 (1H, d, *J* = 13.3 Hz, CH**H'**O), 3.85–3.73 (1H, m, C**H**H'N), 3.46–3.34 (1H, m, CH**H'**N), 3.32–3.20 (1H, m, C**H**H'NH), 3.19–3.04 (1H, m, CH**H'**NH), 2.54–1.10 (16H, m, 8 × C**H₂**); δ_C (100 MHz, $CDCl_3$) 174.8 (**C**O), 170.2 (**C**O), 167.4 (**C**O), 61.9 (**C**H_2O), 60.4 (**C**HN), 46.8 (**C**H_2N), 39.1 (**C**H_2NH), 33.7 (**C**H_2COO), 28.4 (**C**H_2), 28.1 (**C**H_2), 27.3 (**C**H_2), 26.8 (**C**H_2), 25.6 (**C**H_2), 24.8 (**C**H_2), 23.3 (**C**H_2); HRMS (ESI): calcd. for $C_{15}H_{24}N_2NaO_4$, 319.1628. Found: $[MNa]^+$, 319.1633 (−1.5 ppm error).

5-Benzyl-1-oxa-5,13-diazacyclohexadecane-2,6,14-trione (572)



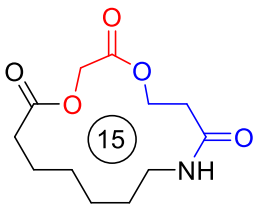
A mixture of 5-benzyl-1,5-diazacyclododecane-2,6-dione (340 mg, 1.179 mmol), DMAP (14 mg, 0.118 mmol) and pyridine (570 µL, 7.07 mmol) in CH_2Cl_2 (8 mL) under an argon atmosphere was stirred at room temperature for 5 min. Next, a solution of acid chloride (1.77 mmol, 1.50 equiv. prepared using the general procedure) in CH_2Cl_2 (4.5 mL) was added and the resulting mixture was heated, at reflux, at 50 °C for 16 h. The solvent was then concentrated *in vacuo*, loaded onto a short silica plug and eluted with 2:1 hexane:ethyl acetate, to remove the majority of excess carboxylic acid and pyridine residues, and concentrated *in vacuo*. This material was re-dissolved in ethyl acetate (11.8 mL) and placed under an argon atmosphere. Palladium on carbon (118 mg, Pd 10% on carbon) was then added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at room temperature under a slight positive pressure of hydrogen (balloon) for 3 h. The reaction was then purged with argon, filtered through Celite, washed with methanol and the solvent was removed *in vacuo*. The crude material was then re-dissolved in chloroform (11.8 mL) and triethylamine (245 µL, 1.77 mmol) added, and stirred at room temperature for 16 h, then reduced *in vacuo*. Purification by flash column chromatography (SiO_2, 2:1 hexane:ethyl acetate → ethyl acetate → 9:1 ethyl acetate:methanol) afforded the *title compound* (as a mixture of 3 rotamers, comprising one major rotamer and two minor rotamers which could not be accurately measured due to overlap of resonances in ^{1}H NMR) as a colourless oil (260 mg, 61%); R_f 0.23 (9:1 ethyl acetate:methanol); ν_{max}/cm^{-1} (thin film) 3311, 2932, 2859, 1732, 1631, 1552; δ_H (400 MHz, $CDCl_3$) 7.35–7.01 (15H, m, Ph, all rotamers), 6.42–6.28 (2H, m, N**H**, two rotamers), 6.15 (1H, br s, N**H**, single rotamer), 4.58 (2H, s, C**H₂**Ph, single rotamer), 4.51 (2H, s, C**H₂**Ph, single rotamer), 4.41–4.24 (8H, m, C**H₂**Ph, single rotamer and C**H₂**O, all rotamers), 3.60–3.51 (2H, m, C**H₂**NBn, single rotamer), 3.48–3.40 (2H, m, C**H₂**NBn, single rotamer), 3.35–3.18 (8H, m, C**H₂**NBn, single rotamer and C**H₂**NH, all rotamers), 2.65–2.19 (18H, m, C**H₂**CONBn and C**H₂**COO and C**H₂**CONH, all rotamers), 1.80–1.13 (24H, m, 4 × C**H₂**, all rotamers); δ_C (100 MHz, $CDCl_3$) data for the major rotamer only: 173.7 (**C**O), 170.1 (**C**O), 169.9 (**C**O), 137.4 (**C**), 128.8 (**C**H), 127.9 (**C**H), 126.4 (**C**H), 61.3 (**C**H_2O), 48.8 (**C**H_2NPh), 43.8 (**C**H_2NBn), 38.9 (**C**H_2NH), 35.1 (**C**H_2CO), 33.6 (**C**H_2CO), 31.6 (**C**H_2CO), 29.4 (**C**H_2), 27.82 (**C**H_2), 25.2 (**C**H_2), 25.1 (**C**H_2). Diagnostic ^{13}C NMR resonances for minor rotamers: 174.2 (**C**O), 173.4 (**C**O), 173.0 (**C**O), 170.5 (**C**O), 170.3 (**C**O), 137.2 (**C**), 129.0 (**C**H), 127.6 (**C**H), 61.5 (**C**H_2O), 61.0 (**C**H_2O), 44.0 (**C**H_2NBn), 38.3 (**C**H_2NH), 37.1 (**C**H_2NH), 36.4 (**C**H_2CO), 35.8 (**C**H_2CO), 33.7 (**C**H_2CO), 32.0 (**C**H_2CO), 29.0 (**C**H_2), 27.78 (**C**H_2), 25.6 (**C**H_2), 25.5 (**C**H_2), 25.4 (**C**H_2), 24.6 (**C**H_2), 24.1 (**C**H_2), 24.0 (**C**H_2); HRMS (ESI): calcd. for $C_{20}H_{28}N_2NaO_4$, 383.1941. Found: $[MNa]^+$, 383.1949 (−1.9 ppm error).

1,17-Dioxa-4-azacycloicosane-3,16,20-trione (573)



A mixture of 1-oxa-5-azacycloheptadecane-4,17-dione (240 mg, 0.891 mmol), DMAP (11 mg, 0.0891 mmol) and pyridine (430 µL, 5.35 mmol) in CH_2Cl_2 (6 mL) under an argon atmosphere was stirred at room temperature for 5 min. Next, a solution of acid chloride (1.34 mmol, 1.50 equiv. prepared using the general procedure) in CH_2Cl_2 (3.5 mL) was added and the resulting mixture was heated, at reflux, at 50 °C for 16 h. An additional solution of acid chloride (1.34 mmol, 1.50 equiv. prepared using the general procedure) in CH_2Cl_2 (3.5 mL) was added and heated, to reflux, at 50 °C for a further 24 h in order to achieve reaction completion. The solvent was then concentrated *in vacuo*, loaded onto a short silica plug and eluted with 2:1 hexane:ethyl acetate, to remove the majority of excess carboxylic acid and pyridine residues, and concentrated *in vacuo*. This material was re-dissolved in THF (8.9 mL) and placed under an argon atmosphere. Palladium on carbon (89 mg, Pd 10% on carbon) and water (1.60 mL, 89.1 mmol) was then added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at room temperature under a slight positive pressure of hydrogen (balloon) for 4 h. The reaction was then purged with argon, filtered through Celite, washed with methanol where the solvent was removed *in vacuo*. The crude material was then re-dissolved in chloroform (8.9 mL) and triethylamine (185 µL, 1.34 mmol) added, and stirred at room temperature for 16 h, then reduced *in vacuo*. Purification by flash column chromatography (SiO_2, 2:1 hexane:ethyl acetate → ethyl acetate) afforded the *title compound* as a colourless oil (217 mg, 74%); R_f 0.64 (9:1 ethyl acetate:methanol); ν_{max}/cm^{-1} (thin film) 3314, 2927, 2856, 1735, 1662, 1545; δ_H (400 MHz, $CDCl_3$) 6.41 (1H, br s, N**H**), 4.51 (2H, s, OC**H₂**CO), 4.35 (2H, t, *J* = 6.0 Hz, OC**H₂**CH_2), 3.34–3.19 (2H, m, C**H₂**NH), 2.66 (2H, t, *J* = 6.0 Hz, CH_2C**H₂**COO), 2.24 (2H, t, *J* = 6.9 Hz, C**H₂**$COOCH_2CH_2$), 1.65–1.06 (18H, m, 9 × C**H₂**); δ_C (100 MHz, $CDCl_3$) 173.8 (**C**O), 169.3 (**C**O), 166.7 (**C**O), 63.3 (O**C**H_2CO), 59.3 (O**C**H_2CH_2), 38.9 (**C**H_2NH), 34.3 (**C**H_2CO), 33.8 (**C**H_2CO), 28.5 (**C**H_2), 27.8 (**C**H_2), 27.6 (**C**H_2), 27.5 (2 × **C**H_2), 27.4 (**C**H_2), 26.9 (**C**H_2), 25.5 (**C**H_2), 24.4 (**C**H_2); HRMS (ESI): calcd. for $C_{17}H_{29}NNaO_5$, 250.1938. Found: $[MNa]^+$, 350.1943 (−1.6 ppm error).

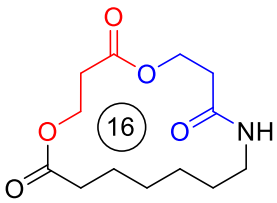
1,4-Dioxa-8-azacyclopentadecane-3,7,15-trione (574)



A mixture of 1-oxa-4-azacycloundecane-3,11-dione (50 mg, 0.270 mmol), DMAP (6 mg, 0.0270 mmol) and pyridine (130 µL, 1.62 mmol) in CH_2Cl_2 (2 mL) under an argon atmosphere was stirred at room temperature for 5 min. Next, a solution of acid chloride (0.405 mmol, 1.50 equiv. prepared using the general procedure) in CH_2Cl_2 (1 mL) was added and the resulting mixture was heated, at reflux, at 50 °C for 16 h. The solvent was concentrated *in vacuo*, loaded

onto a short silica plug and eluted with 2:1 hexane:ethyl acetate, to remove the majority of excess carboxylic acid and pyridine residues, and concentrated *in vacuo*. This material was re-dissolved in ethyl acetate (2.7 mL) and placed under an argon atmosphere. Palladium on carbon (27 mg, Pd 10% on carbon) was then added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at room temperature under a slight positive pressure of hydrogen (balloon) for 4 h. The reaction was then purged with argon, filtered through Celite, washed with methanol where the solvent was removed *in vacuo*. The crude material was then re-dissolved in chloroform (2.7 mL) and triethylamine (56 µL, 0.405 mmol) added, and stirred at room temperature for 16 h, then reduced *in vacuo*. Purification by flash column chromatography (SiO_2, 2:1 hexane:ethyl acetate → ethyl acetate) afforded the *title compound* as a white solid (61 mg, 88%); m.p. 114–116 °C; R_f 0.26 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3290, 3087, 2926, 2858, 1732, 1639, 1566; δ_H (400 MHz, $CDCl_3$) 5.77 (1H, br s, N**H**), 4.60 (2H, s, OC**H₂**CO), 4.46 (2H, t, *J* = 5.2 Hz, OC**H₂**CH_2CO), 3.37–3.26 (2H, m, C**H₂**NH), 2.44 (2H, t, *J* = 5.2 Hz, OCH_2C**H₂**CO), 2.40 (2H, t, *J* = 6.1 Hz, C**H₂**CO), 1.73–1.63 (2H, m, C**H₂**), 1.60–1.51 (2H, m, C**H₂**), 1.44–1.27 (4H, m, 2 × C**H₂**); δ_C (100 MHz, $CDCl_3$) 173.2 (**C**O), 169.8 (**C**O), 168.1 (**C**O), 62.2 (**C**H_2O), 61.1 (**C**H_2O), 39.3 (**C**H_2NH), 36.1 (**C**H_2CO), 32.6 (**C**O), 28.0 (**C**H_2), 27.9 (**C**H_2), 25.2 (**C**H_2), 23.4 (**C**H_2); HRMS (ESI): calcd. for $C_{12}H_{19}NNaO_5$, 280.1155. Found: $[MNa]^+$, 280.1154 (0.4 ppm error).

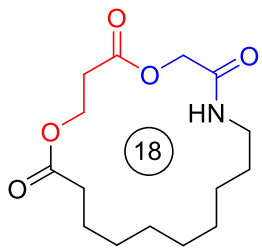
1,5-Dioxa-9-azacyclohexadecane-4,8,16-trione (575)



A mixture of 1-oxa-5-azacyclododecane-4,12-dione (60 mg, 0.301 mmol), DMAP (4 mg, 0.0301 mmol) and pyridine (145 µL, 1.81 mmol) in CH_2Cl_2 (2.5 mL) under an argon atmosphere was stirred at room temperature for 5 min. Next, a solution of acid chloride (0.452 mmol, 1.50 equiv. prepared using the general procedure) in CH_2Cl_2 (1 mL) was added and the resulting mixture was heated, at reflux, at 50 °C for 16 h. An additional solution of acid chloride (0.452 mmol, 1.50 equiv. prepared using the general procedure) in CH_2Cl_2 (1 mL) was added and heated, to reflux, at 50 °C for a further 16 h in order to achieve reaction completion. The solvent was then concentrated *in vacuo*, loaded onto a short silica plug and eluted with 2:1 hexane:ethyl acetate, to remove the majority of excess carboxylic acid and pyridine residues, and concentrated *in vacuo*. This material was re-dissolved in ethyl acetate (3.0 mL) and placed under an argon atmosphere. Palladium on carbon (30 mg, Pd 10% on carbon) was then added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at room temperature under a slight positive pressure of hydrogen (balloon) for 16 h. The reaction was then purged with argon, filtered through Celite, washed with methanol and the solvent was removed *in vacuo*. The crude material was then re-dissolved in chloroform (3.0 mL) and

triethylamine (63 µL, 0.452 mmol) added, and stirred at room temperature for 16 h, then reduced *in vacuo*. Purification by flash column chromatography (SiO_2, 2:1 hexane:ethyl acetate → ethyl acetate) afforded the *title compound* as a yellow oil (69 mg, 84%); R_f 0.31 (9:1 ethyl acetate:methanol); ν_{max}/cm^{-1} (thin film) 3311, 2932, 1735, 1649, 1552; δ_H (400 MHz, $CDCl_3$) 5.80 (1H, s, N**H**), 4.47–4.32 (4H, m, 2 × C**H₂**O), 3.38–3.23 (2H, m, C**H₂**NH), 2.65–2.49 (4H, m, $OCH_2C\mathbf{H_2}CO$), 2.38–2.26 (2H, m, C**H₂**CO), 1.73–1.63 (2H, m, C**H₂**), 1.55–1.43 (2H, m, C**H₂**), 1.39–1.18 (4H, m, 2 × C**H₂**); δ_C (100 MHz, $CDCl_3$) 173.7 (**C**O), 171.3 (**C**O), 170.0 (**C**O), 61.7 (O**C**H_2), 59.6 (O**C**H_2), 39.0 (**C**H_2NH), 36.5 (**C**H_2CO), 34.6 (**C**H_2CO), 32.8 (**C**H_2CO), 29.3 (**C**H_2), 27.6 (**C**H_2), 25.1 (**C**H_2), 24.2 (**C**H_2); HRMS (ESI): calcd. for $C_{13}H_{21}NNaO_5$, 294.1312. Found: $[MNa]^+$, 294.1309 (1.1 ppm error).

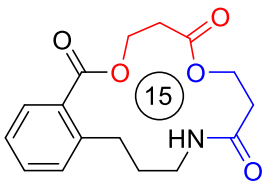
1,15-Dioxa-4-azacyclooctadecane-3,14,18-trione (576)



A mixture of 1-oxa-5-azacyclopentadecane-4,15-dione (50 mg, 0.207 mmol), DMAP (3 mg, 0.0207 mmol) and pyridine (100 µL, 1.24 mmol) in CH_2Cl_2 (1.5 mL) under an argon atmosphere was stirred at room temperature for 5 min. Next, a solution of acid chloride (0.311 mmol, 1.50 equiv. prepared using the general procedure) in CH_2Cl_2 (1 mL) was added and the resulting mixture was heated, at reflux, at 50 °C for 16 h. An additional solution of acid chloride (0.311 mmol, 1.50 equiv. prepared using the general procedure) in CH_2Cl_2 (1 mL) was added and heated, to reflux, at 50 °C for a further 16 h in order to achieve reaction completion. The solvent was then concentrated *in vacuo*, loaded onto a short silica plug and eluted with 2:1 hexane:ethyl acetate, to remove the majority of excess carboxylic acid and pyridine residues, and concentrated *in vacuo*. This material was re-dissolved in THF (2.1 mL) and placed under an argon atmosphere. Palladium on carbon (21 mg, Pd 10% on carbon) and water (380 µL, 20.7 mmol) was then added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at room temperature under a slight positive pressure of hydrogen (balloon) for 16 h. The reaction was then purged with argon, filtered through Celite, washed with methanol and the solvent was removed *in vacuo*. The crude material was then re-dissolved in chloroform (2.1 mL) and triethylamine (45 µL, 0.311 mmol) added, and stirred at room temperature for 16 h, then reduced *in vacuo*. Purification by flash column chromatography (SiO_2, 2:1 hexane:ethyl acetate → ethyl acetate) afforded the *title compound* as a colourless oil (53 mg, 86%); R_f 0.56 (9:1 ethyl acetate:methanol); ν_{max}/cm^{-1} (thin film) 3313, 2929, 2857, 1733, 1662, 1545; δ_H (400 MHz, $CDCl_3$) 6.28 (1H, br s, N**H**), 4.60 (2H, s, O**C**$\mathbf{H_2}$CO), 4.41 (2H, t, *J* = 5.3 Hz, O**C**$\mathbf{H_2}CH_2CO$), 3.40–3.29 (2H, m, C**H₂**NH), 2.70 (2H, t, *J* = 5.3 Hz, $OCH_2C\mathbf{H_2}CO$), 2.30 (2H, t, *J* = 6.9 Hz, C**H₂**CO), 1.71–1.13 (14H, m, 7 × C**H₂**); δ_C (100 MHz, $CDCl_3$) 173.9 (**C**O), 169.7 (**C**O), 166.9 (**C**O),

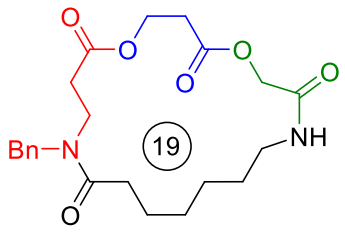
63.5 (O**C**H_2CO), 59.6 (O**C**$H_2$$CH_2$), 39.0 (**C**$H_2$NH), 34.6 (**C**$H_2$CO), 33.4 (**C**$H_2$CO), 28.2 (**C**$H_2$), 27.1 (2 × **C**$H_2$), 26.8 (**C**$H_2$), 26.4 (**C**$H_2$), 25.4 (**C**$H_2$), 23.9 (**C**$H_2$); HRMS (ESI): calcd. for $C_{15}H_{25}NNaO_5$, 322.1625. Found: $[MNa]^+$, 322.1626 (−0.2 ppm error).

7,8,10,11,12,13-Hexahydro-3*H*-benzo[*m*][1,5]dioxa[9]azacyclopentadecine-1,5,9(4*H*)-trione (577)



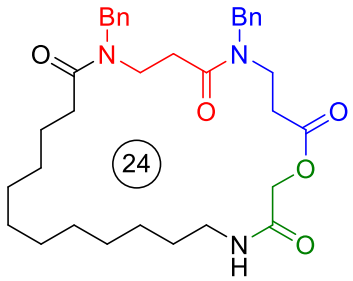
A mixture of 3,4,6,7,8,9-hexahydrobenzo[*i*][1]oxa[5]azacycloundecine-1,5-dione (60 mg, 0.269 mmol), DMAP (4 mg, 0.0269 mmol) and pyridine (130 µL, 1.61 mmol) in CH_2Cl_2 (2.0 mL) under an argon atmosphere was stirred at room temperature for 5 min. Next, a solution of acid chloride (0.403 mmol, 1.50 equiv. prepared using the general procedure) in CH_2Cl_2 (1 mL) was added and the resulting mixture was heated, at reflux, at 50 °C for 16 h. The solvent was then concentrated *in vacuo*, loaded onto a short silica plug and eluted with 2:1 hexane:ethyl acetate, to remove the majority of excess carboxylic acid and pyridine residues, and concentrated *in vacuo*. This material was re-dissolved in ethyl acetate (2.7 mL) and placed under an argon atmosphere. Palladium on carbon (27 mg, Pd 10% on carbon) was then added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at room temperature under a slight positive pressure of hydrogen (balloon) for 16 h. The reaction was then purged with argon, filtered through Celite, washed with methanol and the solvent was removed *in vacuo*. The crude material was then re-dissolved in chloroform (2.7 mL) and triethylamine (56 µL, 0.403 mmol) added, and stirred at room temperature for 16 h, then reduced *in vacuo*. Purification by flash column chromatography (SiO_2, 2:1 hexane:ethyl acetate → ethyl acetate → 9:1 ethyl acetate:methanol) afforded the *title compound* as a colourless oil (74 mg, 90%); R_f 0.50 (9:1 ethyl acetate:methanol); ν_{max}/cm^{-1} (thin film) 3316, 1707, 1640, 1557; δ_H (400 MHz, $CDCl_3$) 7.81 (1H, d, *J* = 7.6 Hz, C**H**), 7.50–7.38 (1H, m, C**H**), 7.29–7.17 (2H, m, 2 × C**H**), 6.09 (1H, br s, N**H**), 4.62 (2H, t, *J* = 4.6 Hz, C**H**$_2$O), 4.45 (2H, t, *J* = 4.6 Hz, C**H**$_2$O), 3.39–3.29 (2H, m, C**H**$_2$NH), 2.96 (2H, t, *J* = 7.6 Hz, C**H**$_2$C), 2.74 (2H, t, *J* = 4.6 Hz, C**H**$_2$$CH_2$O), 2.58 (2H, t, *J* = 4.6 Hz, C**H**$_2$$CH_2$O). 1.88–1.72 (2H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 171.6 (**C**O), 170.2 (**C**O), 168.9 (**C**O), 142.7 (**C**), 132.5 (**C**H), 131.0 (**C**H), 130.8 (**C**H), 129.6 (**C**), 126.3 (**C**H), 61.7 (**C**H_2O), 61.4 (**C**H_2O), 39.0 (**C**H_2NH), 36.7 (**C**H_2CO), 35.2 (**C**H_2CO), 31.5 (**C**H_2), 31.3 (**C**H_2); HRMS (ESI): calcd. for $C_{16}H_{19}NNaO_5$, 328.1155. Found: $[MNa]^+$, 328.1158 (−0.7 ppm error).

12-Benzyl-1,16-dioxa-4,12-diazacyclononadecane-3,11,15,19-tetraone (584)



A mixture of 5-benzyl-1-oxa-5,13-diazacyclohexadecane-2,6,14-trione (90 mg, 0.250 mmol), DMAP (3 mg, 0.0250 mmol) and pyridine (121 µL, 1.50 mmol) in CH_2Cl_2 (2.0 mL) under an argon atmosphere was stirred at room temperature for 5 min. Next, a solution of acid chloride (0.375 mmol, 1.50 equiv. prepared using the general procedure) in CH_2Cl_2 (1 mL) was added and the resulting mixture was heated, at reflux, at 50 °C for 16 h. The solvent was then concentrated *in vacuo*, loaded onto a short silica plug and eluted with 2:1 hexane:ethyl acetate, to remove the majority of excess carboxylic acid and pyridine residues, and concentrated *in vacuo*. This material was re-dissolved in THF (2.5 mL) and placed under an argon atmosphere. Palladium on carbon (25 mg, Pd 10% on carbon) and water (450 µL, 25 mmol) was then added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at room temperature under a slight positive pressure of hydrogen (balloon) for 3 h. The reaction was then purged with argon, filtered through Celite, washed with methanol and the solvent was removed *in vacuo*. The crude material was then re-dissolved in chloroform (2.5 mL) and triethylamine (53 µL, 0.375 mmol) added, and stirred at room temperature for 16 h, then reduced *in vacuo*. Purification by flash column chromatography (SiO_2, 2:1 hexane:ethyl acetate → ethyl acetate → 9:1 ethyl acetate:methanol) afforded the *title compound* (as a 1:1:1.4:2.1 {A:B:C:D} mixture of rotamers) as a yellow oil (71 mg, 68%); R_f 0.18 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3312, 2931, 2858, 1735, 1636, 1548; δ_H (400 MHz, $CDCl_3$) 7.50–7.08 (20H, m, Ph, all rotamers), 7.05 (1H, br s, N**H**, rotamer A), 6.37 (1H, br s, N**H**, rotamer B), 6.09 (1H, br s, N**H**, rotamer C), 5.73 (1H, br s, N**H**, rotamer D), 4.67–4.54 (8H, m, NC**H₂**Ph, all rotamers), 4.49–4.33 (8H, m, $CH_2C\mathbf{H_2}O$, all rotamers), 3.73–3.23 (24H, m, C**H₂**NBn and C**H₂**NH and C**H₂**O, all rotamers), 2.80–2.27 (24H, m, 3 × C**H₂**CO, all rotamers), 1.82–1.20 (32H, m, 4 × C**H₂**, all rotamers); δ_C (100 MHz, $CDCl_3$) 174.22 (**C**O), 174.16 (**C**O), 173.6 (**C**O), 173.4 (**C**O), 173.0 (**C**O), 172.0 (**C**O), 171.0 (**C**O), 170.6 (**C**O), 170.2 (**C**O), 169.7 (**C**O), 169.4 (**C**O), 167.3 (**C**O), 166.9 (**C**O), 137.5 (**C**), 137.4 (**C**), 137.2 (**C**), 136.7 (**C**), 129.1 (**C**H), 129.0 (**C**H), 128.8 (**C**H), 128.0 (**C**H), 127.9 (**C**H), 127.7–127.6 (3 × C**H**), 126.5 (**C**H), 126.4 (**C**H), 63.5 ($\mathbf{C}H_2$), 63.2 ($\mathbf{C}H_2$), 61.6 ($\mathbf{C}H_2$), 61.3 ($\mathbf{C}H_2$), 60.2 ($\mathbf{C}H_2$), 59.9 ($\mathbf{C}H_2$), 53.7 ($\mathbf{C}H_2O$), 51.6 ($\mathbf{C}H_2O$), 48.9 ($\mathbf{C}H_2$), 48.3 ($\mathbf{C}H_2O$), 44.1 ($\mathbf{C}H_2NBn$), 43.8 ($\mathbf{C}H_2NBn$), 42.9 ($\mathbf{C}H_2NBn$), 42.2 ($\mathbf{C}H_2NBn$), 39.1 ($\mathbf{C}H_2NH$), 39.0 ($\mathbf{C}H_2NH$), 38.9 ($\mathbf{C}H_2NH$), 37.5 ($\mathbf{C}H_2CO$), 36.6 ($\mathbf{C}H_2CO$), 36.0 ($\mathbf{C}H_2CO$), 35.2 ($\mathbf{C}H_2CO$), 34.5 ($\mathbf{C}H_2CO$), 34.0 ($\mathbf{C}H_2CO$), 33.8 ($\mathbf{C}H_2CO$), 33.3 ($\mathbf{C}H_2CO$), 32.5 ($\mathbf{C}H_2CO$), 32.14 ($\mathbf{C}H_2CO$), 32.09 ($\mathbf{C}H_2CO$), 31.7 ($\mathbf{C}H_2CO$), 29.5 ($\mathbf{C}H_2$), 29.0 ($\mathbf{C}H_2$), 28.7 ($\mathbf{C}H_2$), 27.92 ($\mathbf{C}H_2$), 27.89 ($\mathbf{C}H_2$), 27.85 ($\mathbf{C}H_2$), 27.81 ($\mathbf{C}H_2$), 26.4 ($\mathbf{C}H_2$), 25.7 ($\mathbf{C}H_2$), 25.5 ($\mathbf{C}H_2$), 25.2 ($\mathbf{C}H_2$), 25.0 ($\mathbf{C}H_2$), 24.62 ($\mathbf{C}H_2$), 24.56 ($\mathbf{C}H_2$), 24.4 ($\mathbf{C}H_2$), 24.0 ($\mathbf{C}H_2$); HRMS (ESI): calcd. for $C_{22}H_{30}N_2NaO_6$, 441.1996. Found: $[MNa]^+$, 441.1994 (1.0 ppm error).

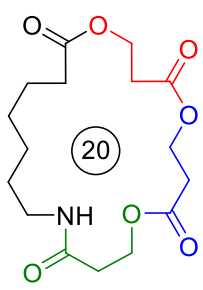
17,21-Dibenzyl-1-oxa-4,17,21-triazacyclotetracosane-3,16,20,24-tetraone (585)



A mixture of 5,9-dibenzyl-1,5,9-triazacyclohenicosane-2,6,10-trione (50 mg, 0.0962 mmol), DMAP (1 mg, 9.62×10^{-3} mmol) and pyridine (46 µL, 0.577 mmol) in CH_2Cl_2 (1 mL) under an argon atmosphere was stirred at room temperature for 5 min. Next, a solution of acid chloride (0.144 mmol, 1.50 equiv. prepared using the general procedure) in CH_2Cl_2 (1 mL) was added and the resulting mixture was heated, at reflux, at 50 °C for 16 h. An additional solution of acid chloride (0.144 mmol, 1.50 equiv. prepared using the general procedure) in CH_2Cl_2 (1 mL) was added and heated, to reflux, at 50 °C for a further 16 h in order to achieve reaction completion. The solvent was then concentrated *in vacuo*, loaded onto a short silica plug and eluted with ethyl acetate, to remove the majority of excess carboxylic acid and pyridine residues, and concentrated *in vacuo*. This material was re-dissolved in THF (1.0 mL) and placed under an argon atmosphere. Palladium on carbon (18 mg, Pd 10% on carbon) and water (173 µL) was then added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at room temperature under a slight positive pressure of hydrogen (balloon) for 5 h. The reaction was then purged with argon, filtered through Celite, washed with ethyl acetate and the solvent was removed *in vacuo*. The crude material was then re-dissolved in chloroform (1.0 mL) and triethylamine (20 µL, 0.144 mmol) added, and stirred at room temperature for 16 h, then reduced *in vacuo*. Purification by flash column chromatography (SiO_2, 2:1 hexane:ethyl acetate→ethyl acetate→9:1 ethyl acetate:methanol) afforded the *title compound* (as a mixture of 2 rotamers) as a yellow oil (38 mg, 68%). The number of rotamers was determined by number of carbonyl resonances in the ^{13}C NMR spectrum; R_f 0.18 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3313, 2927, 2855, 1731, 1637, 1452; δ_H (400 MHz, $CDCl_3$) 7.47–6.93 (22H, m, 2 × Ph and N**H**, both rotamers), 4.76–4.05 (12H, m, C**H₂**O and 2 × NC**H₂**Ph, both), 3.73–3.48 (8H, m, 2 × C**H₂**NBn, both), 3.36–3.10 (4H, m, C**H₂**NH, both), 2.79–2.13 (12H, m, 3 × C**H₂**CO, both), 1.87–0.72 (36H, m, 9 × C**H₂**, both); δ_C (100 MHz, $CDCl_3$) 174.7 (**C**O), 174.5 (**C**O), 172.4 (**C**O), 172.1 (**C**O), 171.9 (**C**O), 171.4 (**C**O), 171.2 (**C**O), 170.4 (**C**O), 137.7 (**C**), 137.6 (**C**), 136.8 (**C**), 136.69 (**C**), 136.65 (**C**), 136.6 (**C**), 136.1 (**C**), 129.3 (**C**H), 129.1 (**C**H), 129.0 (**C**H), 128.7 (**C**H), 128.3 (**C**H), 128.23 (**C**H), 128.19 (**C**H), 128.0 (**C**H), 127.9 (**C**H), 127.7 (**C**H), 127.5 (**C**H), 126.6 (**C**H), 126.43 (**C**H), 126.37 (**C**H), 126.0 (**C**H), 73.5 (**C**H_2O), 66.9 (**C**H_2O), 52.6 (**C**H_2Ph), 52.5 (**C**H_2Ph), 52.0 (**C**H_2Ph), 51.3 (**C**H_2Ph), 49.4 (N**C**H_2CH_2), 48.6 (N**C**H_2CH_2), 45.5 (N**C**H_2CH_2), 45.3 (N**C**H_2CH_2), 44.0 (**C**H_2NH), 42.6 (**C**H_2NH), 39.7 (**C**H_2CO), 39.6 (**C**H_2CO), 39.4 (**C**H_2CO), 36.7 (**C**H_2CO), 35.5 (**C**H_2CO), 35.3 (**C**H_2CO), 33.3 (**C**H_2), 32.9 (**C**H_2), 32.3 (**C**H_2), 31.7 (**C**H_2), 31.2 (**C**H_2), 28.9 (**C**H_2), 28.7 (**C**H_2), 28.6 (**C**H_2), 28.3 (**C**H_2), 28.1 (**C**H_2), 27.8 (**C**H_2), 27.7 (**C**H_2), 27.64 (**C**H_2), 27.57 (**C**H_2), 27.4 (**C**H_2), 27.3 (**C**H_2), 27.1 (**C**H_2), 26.9 (**C**H_2), 26.4 (**C**H_2), 26.1 (**C**H_2), 26.0 (**C**H_2),

25.4 (**C**H_2), 24.9 (**C**H_2), 24.6 (**C**H_2), 24.5 (**C**H_2); HRMS (ESI): calcd. for $C_{34}H_{47}N_3NaO_5$, 600.3408. Found: $[MNa]^+$, 600.3419 (0.9 ppm error).

1,5,9-Trioxa-13-azacycloicosane-4,8,12,20-tetraone (586)



A mixture of 1,5-dioxa-9-azacyclohexadecane-4,8,16-trione (50 mg, 0.184 mmol), DMAP (2 mg, 0.0184 mmol) and pyridine (90 µL, 1.10 mmol) in CH_2Cl_2 (2 mL) under an argon atmosphere was stirred at room temperature for 5 min. Next, a solution of acid chloride (0.276 mmol, 1.50 equiv. prepared using the general procedure) in CH_2Cl_2 (1 mL) was added and the resulting mixture was heated, at reflux, at 50 °C for 16 h. An additional solution of acid chloride (0.276 mmol, 1.50 equiv. prepared using the general procedure) in CH_2Cl_2 (1 mL) was added and heated, to reflux, at 50 °C for a further 16 h in order to achieve reaction completion. The solvent was then concentrated *in vacuo*, loaded onto a short silica plug and eluted with ethyl acetate, to remove the majority of excess carboxylic acid and pyridine residues, and concentrated *in vacuo*. This material was re-dissolved in ethyl acetate (1.8 mL) and placed under an argon atmosphere. Palladium on carbon (18 mg, Pd 10% on carbon) was then added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at room temperature under a slight positive pressure of hydrogen (balloon) for 3 h. The reaction was then purged with argon, filtered through Celite, washed with methanol and the solvent was removed *in vacuo*. The crude material was then re-dissolved in chloroform (1.8 mL) and triethylamine (40 µL, 0.276 mmol) added, and stirred at room temperature for 16 h, then reduced *in vacuo*. Purification by flash column chromatography (SiO_2, ethyl acetate→9:1 ethyl acetate:methanol) afforded the *title compound* as a white solid (49 mg, 79%); m.p. 121–123 °C; R_f 0.50 (9:1 ethyl acetate:methanol); ν_{max}/cm^{-1} (thin film) 3301, 2932, 2858, 1732, 1646, 1551; δ_H (400 MHz, $CDCl_3$) 5.86 (1H, br s, N**H**), 4.49–4.27 (6H, m, 3 × C**H₂**O), 3.36–3.23 (2H, m, C**H₂**NH), 2.68–2.58 (4H, m, 2 × C**H₂**COO), 2.44 (2H, t, *J* = 5.3 Hz, C**H₂**CONH), 2.28 (2H, t, *J* = 6.9 Hz, C**H₂**COO), 1.61–1.53 (2H, m, C**H₂**), 1.52–1.43 (2H, m, C**H₂**), 1.37–1.26 (4H, m, 2 × C**H₂**); δ_C (100 MHz, $CDCl_3$) 173.3 (**C**O), 170.8 (**C**O), 169.93 (**C**O), 169.91 (**C**O), 61.4 (**C**H_2O), 60.0 (**C**H_2O), 59.9 (**C**H_2O), 39.3 (**C**H_2NH), 36.4 (**C**H_2CO), 34.7 (**C**H_2CO), 34.2 (**C**H_2CO), 33.9 (**C**H_2CO), 29.2 (**C**H_2), 28.7 (**C**H_2), 26.4 (**C**H_2), 25.2 (**C**H_2); HRMS (ESI): calcd. for $C_{16}H_{25}NNaO_7$, 366.1523. Found: $[MNa]^+$, 366.1521 (1.0 ppm error).

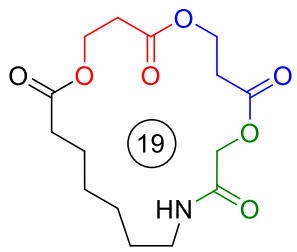
Procedure for one single the synthesis of 586 from 553 with one chromatographic purification

A mixture of azocan-2-one **4f** (100 mg, 0.786 mmol), DMAP (10 mg, 0.0786 mmol) and pyridine (380 µL, 4.72 mmol) in CH_2Cl_2 (5.5 mL) under an argon atmosphere was stirred at room

temperature for 5 min. Next, a solution of acid chloride (2.36 mmol, 3.0 equiv. prepared using the general procedure) in CH_2Cl_2 (3 mL) was added and the resulting mixture was heated, at reflux, at 50 °C for 16 h. The mixture was then diluted with diethyl ether (30 mL) and washed with 10% aq. HCl (15 mL). The aqueous layer was then extracted with diethyl ether (3 × 20 mL) and washed with sat. aq. $NaHCO_3$ (10 mL). The combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was then re-dissolved in ethyl acetate (7.8 mL) and placed under an argon atmosphere. Palladium on carbon (78 mg, Pd 10% on carbon) was then added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at room temperature under a slight positive pressure of hydrogen (balloon) for 4 h. The reaction was then purged with argon, filtered through Celite, washed with ethyl acetate and the solvent was removed *in vacuo*. The crude material was then re-dissolved in chloroform (7.8 mL) and triethylamine (164 µL, 1.18 mmol) added, stirred at room temperature for 16 h, and the solvent was removed *in vacuo*. The residue was dissolved in CH_2Cl_2 (30 mL), washed with sat. aq. $NaHCO_3$ (10 mL) and brine (10 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was added to DMAP (10 mg, 0.0786 mmol) and pyridine (380 µL, 4.72 mmol) in CH_2Cl_2 (5.5 mL) under an argon atmosphere was stirred at room temperature for 5 min. Next, a solution of acid chloride (2.36 mmol, 3.0 equiv. prepared using the general procedure) in CH_2Cl_2 (3 mL) was added and the resulting mixture was heated, at reflux, at 50 °C for 16 h. The mixture was then diluted with diethyl ether (30 mL) and washed with 10% aq. HCl (15 mL). The aqueous layer was then extracted with diethyl ether (3 × 20 mL) and washed with sat. aq. $NaHCO_3$ (10 mL). The combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was then re-dissolved in ethyl acetate (7.8 mL) and placed under an argon atmosphere. Palladium on carbon (78 mg, Pd 10% on carbon) was then added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at room temperature under a slight positive pressure of hydrogen (balloon) for 16 h. The reaction was then purged with argon, filtered through Celite, washed with ethyl acetate and the solvent was removed *in vacuo*. The crude material was then re-dissolved in chloroform (7.8 mL) and triethylamine (164 µL, 1.18 mmol) added, stirred at room temperature for 16 h, and the solvent was removed *in vacuo*. The residue was dissolved in CH_2Cl_2 (30 mL), washed with sat. aq. $NaHCO_3$ (10 mL) and brine (10 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was added to DMAP (10 mg, 0.0786 mmol) and pyridine (380 µL, 4.72 mmol) in CH_2Cl_2 (5.5 mL) under an argon atmosphere was stirred at room temperature for 5 min. Next, a solution of acid chloride (2.36 mmol, 3.0 equiv. prepared using the general procedure) in CH_2Cl_2 (3 mL) was added and the resulting mixture was heated, at reflux, at 50 °C for 16 h. An additional solution of acid chloride (2.36 mmol, 3.0 equiv. prepared using the general procedure) in CH_2Cl_2 (3 mL) was added and

heated, to reflux, at 50 °C for a further 16 h in order to achieve reaction completion. The mixture was then diluted with CH_2Cl_2 (30 mL) and washed with 10% aq. HCl (15 mL). The aqueous layer was then extracted with CH_2Cl_2 (3 × 30 mL) and washed with sat. aq. $NaHCO_3$ (10 mL). The combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was then re-dissolved in ethyl acetate (7.8 mL) and placed under an argon atmosphere. Palladium on carbon (78 mg, Pd 10% on carbon) was then added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at room temperature under a slight positive pressure of hydrogen (balloon) for 16 h. The reaction was then purged with argon, filtered through Celite, washed with ethyl acetate and the solvent was removed *in vacuo*. The crude material was then re-dissolved in chloroform (7.8 mL) and triethylamine (164 µL, 1.18 mmol) added, stirred at room temperature for 16 h, and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 2:1 hexane:ethyl acetate → ethyl acetate→9:1 ethyl acetate:methanol) afforded the *title compound* as a white solid (130 mg, 48%); R_F 0.50 (9:1 ethyl acetate:methanol); δ_H (400 MHz, $CDCl_3$) 5.87 (1H, br s, N**H**), 4.49–4.27 (6H, m, 3 × C**H₂**O), 3.36–3.23 (2H, m, C**H₂**NH), 2.68–2.58 (4H, m, 2 × C**H₂**COO), 2.44 (2H, t, *J* = 5.3 Hz, C**H₂**CONH), 2.28 (2H, t, *J* = 6.9 Hz, C**H₂**COO), 1.76–1.18 (8H, m, 4 × C**H₂**). Data consistent with those reported above.

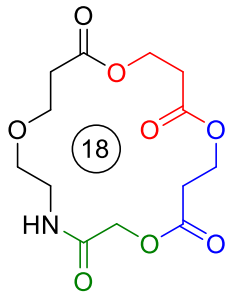
1,12,16-Trioxa-4-azacyclononadecane-3,11,15,19-tetraone (587)



A mixture of 1,5-dioxa-9-azacyclohexadecane-4,8,16-trione (50 mg, 0.184 mmol), DMAP (2 mg, 0.0184 mmol) and pyridine (90 µL, 1.10 mmol) in CH_2Cl_2 (2 mL) under an argon atmosphere was stirred at room temperature for 5 min. Next, a solution of acid chloride (0.276 mmol, 1.50 equiv. prepared using the general procedure) in CH_2Cl_2 (1 mL) was added and the resulting mixture was heated, at reflux, at 50 °C for 16 h. An additional solution of acid chloride (0.276 mmol, 1.50 equiv. prepared using the general procedure) in CH_2Cl_2 (1 mL) was added and heated, to reflux, at 50 °C for a further 16 h in order to achieve reaction completion. The solvent was then concentrated *in vacuo*, loaded onto a short silica plug and eluted with ethyl acetate, to remove the majority of excess carboxylic acid and pyridine residues, and concentrated *in vacuo*. This material was re-dissolved in THF (1.8 mL) and placed under an argon atmosphere. Palladium on carbon (18 mg, Pd 10% on carbon) and water (330 µL, 18.4 mmol) was then added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at room temperature under a slight positive pressure of hydrogen (balloon) for 4 h. The reaction was then purged with argon, filtered through Celite, washed with methanol and the solvent was removed *in vacuo*. The crude material was then re-dissolved in chloroform (1.8 mL) and triethylamine (40 µL, 0.276 mmol) added, and stirred at

room temperature for 16 h, then reduced *in vacuo*. Purification by flash column chromatography (SiO_2, 2:1 hexane:ethyl acetate→ethyl acetate) afforded the *title compound* as a colourless oil (51 mg, 84%); R_f 0.60 (9:1 ethyl acetate:methanol); ν_{max}/cm^{-1} (thin film) 3385, 2935, 2860, 1732, 1667, 1543; δ_H (400 MHz, $CDCl_3$) 6.61 (1H, br s, N**H**), 4.59 (2H, s,OC**H₂**CO), 4.48 (2H, t, *J* = 5.3 Hz, C**H₂**O), 4.32 (2H, t, *J* = 5.3 Hz, C**H₂**O), 3.36–3.27 (2H, m, C**H₂**NH), 2.72 (2H, t, *J* = 5.3 Hz, C**H₂**CH_2O), 2.61 (2H, t, *J* = 5.3 Hz, C**H₂**CH_2O), 2.29 (2H, t, *J* = 6.1 Hz, C**H₂**COO), 1.66–1.57 (2H, m, C**H₂**), 1.56–1.48 (2H, m, C**H₂**), 1.36–1.25 (4H, m, 2 × C**H₂**); δ_C (100 MHz, $CDCl_3$) 173.5 (**C**O), 171.3 (**C**O), 169.4 (**C**O), 167.0 (**C**O), 63.5 (**C**H_2O), 60.3 (**C**H_2O), 59.6 (**C**H_2O), 38.2 (**C**H_2NH), 34.9 (**C**H_2CO), 34.2 (**C**H_2CO), 33.8 (**C**H_2CO), 28.3 (**C**H_2), 27.3 (**C**H_2), 25.2 (**C**H_2), 24.5 (**C**H_2); HRMS (ESI): calcd. for $C_{15}H_{23}NNaO_7$, 352.1367. Found: $[MNa]^+$, 352.1363 (0.7 ppm error).

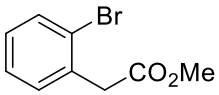
1,7,11,15-Tetraoxa-4-azacyclooctadecane-3,10,14,18-tetraone (588)



A mixture of 1,8,12-trioxa-4-azacyclopentadecane-5,9,13-trione (35 mg, 0.133 mmol), DMAP (2 mg, 0.0133 mmol) and pyridine (0.064 mL, 0.79 mmol) in CH_2Cl_2 (1.0 mL) under an argon atmosphere was stirred at room temperature for 30 min. A solution of acid chloride (0.199 mmol, 1.5 equiv. prepared using the general procedure) in CH_2Cl_2 (1.0 mL) was then added and the resulting mixture was heated, at reflux, at 50 °C for 16 h. A further three portions of acid chloride (0.131 mmol, 1.5 equiv. prepared using the general procedure) in CH_2Cl_2 (0.5 mL) were added at 48 h, 72 h and 96 h. The solvent was concentrated *in vacuo*, loaded onto a short silica plug and eluted with 3:2 hexane:ethyl acetate →1:4 hexane:ethyl acetate to remove the excess carboxylic acid and pyridine. 12 mg of starting material was recovered. The acylated product was concentrated *in vacuo*, re-dissolved in THF (1.5 mL) and placed under an argon atmosphere. Palladium on carbon (13 mg, Pd 10% on carbon) and water (0.24 mL, 13.3 mmol) was added and the reaction vessel was backfilled with hydrogen (*via* balloon) several times. The reaction was stirred at room temperature under a slight positive pressure of hydrogen (balloon) for 18 h. The reaction was then purged with argon, filtered through Celite, washed with methanol and the solvent was removed *in vacuo*. The crude material was re-dissolved in chloroform (1.5 mL) and triethylamine (29 µL, 0.21 mmol) and stirred at room temperature for 18 h, then concentrate *in vacuo.* Purification by flash column chromatography (SiO_2, ethyl acetate → 9:1 ethyl acetate:methanol) afforded the *title compound* as a colourless oil (15 mg, 36% or 54% brsm); R_f 0.55 (4:1 ethyl acetate:methanol); ν_{max} (thin film)/cm^{-1} 3382, 2926, 1736, 1677, 1542; δ_H (400 MHz, $CDCl_3$) 6.93 (1H, br s, NH), 4.66 (2H, s, C**H₂**-CO-NH), 4.49 (2H, t, *J* = 5.3 Hz, COO-C**H₂**-CH_2-COO), 4.41 (2H, t, *J* = 5.5 Hz, OCH_2-CH_2-COO-C**H₂**), 3.72 (2H, t, *J* = 5.3 Hz, OC**H₂**-CH_2-COO), 3.56−3.54 (2H, m, OC**H₂**-CH_2-NH), 3.50−3.46 (2H, m,

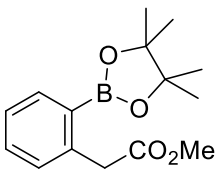
CH_2-NH), 2.73 (2H, t, *J* = 5.3 Hz, C**H**$_2$-COO-CH_2-CO-NH), 2.60 (2H, t, *J* = 5.3 Hz, C**H**$_2$-COO-CH_2-CH_2-COO), 2.53 (2H, t, *J* = 5.3 Hz, OCH_2-C**H**$_2$-COO); δ_C (100 MHz, $CDCl_3$) 172.0 (OCH_2-CH_2-**C**OO), 171.0 (**C**OO-CH_2-CH_2-COO), 169.6 (**C**OO-CH_2-CO-NH), 167.2 (CO-NH), 69.2 (O**C**H$_2$-CH_2-NH), 66.4 (O**C**H$_2$-CH_2-COO), 63.5 (**C**H$_2$-CO-NH), 60.2 (OCH_2-CH_2-COO-**C**H$_2$), 60.0 (COO-**C**H$_2$-CH_2), 39.3 (CH_2-NH), 35.1 (OCH_2-C**H**$_2$-COO), 35.0 (C**H**$_2$-COO-CH_2-CH_2-COO), 34.6 (**C**H$_2$-COO-CH_2-CO-NH); HRMS (ESI^+): calcd. for $C_{13}H_{19}NNaO_8$, 340.1003. Found: [MNa^+], 340.1007 (−1.2 ppm error).

Methyl 2-(2-bromophenyl)acetate (603)



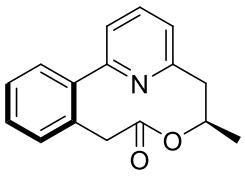
To a stirring solution of 2-(2-bromophenyl)acetic acid (13.2 g, 61.6 mmol) in methanol (130 mL) was added concentrated sulfuric acid (2.50 mL) and the resulting solution was stirred at 70 °C for 18 h. After cooling to room temperature, the reaction was quenched with water (50 mL) and extracted with diethyl ether (3 × 100 mL). The combined organic extracts were washed with brine (30 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford the *title compound* as a clear oil (13.4 g, 95%); δ_H (400 MHz, $CDCl_3$) 7.56 (1H, d, *J* = 8.4 Hz, ArH), 7.28−7.26 (2H, m, ArH), 7.16–7.12 (1H, m, ArH), 3.79 (2H, s, CH_2), 3.71 (3H, s, CH_3). Data is consistent with those reported in the literature.[155]

Methyl 2-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate (631)



To a stirring solution of methyl 2-(2-bromophenyl)acetate (12.5 g, 55.0 mmol) in 1,4-dioxane (200 mL), was added bis(pinacalato)diboron (15.3 g, 60.6 mmol), potassium acetate (19.9 g, 203.7 mmol) and $PdCl_2$(dppf).CH_2Cl_2 (2.25 g, 3.53 mmol). The reaction mixture was purged with argon and heated at 80 °C for 4 h. The reaction mixture was then diluted with ethyl acetate, passed through Celite and concentrated *in vacuo*. Purification *via* flash column chromatography (SiO_2, CH_2Cl_2 → 1:9 ethyl acetate:CH_2Cl_2) afforded the *title compound* as a white solid (8.20 g, 54%); δ_H (400 MHz, $CDCl_3$) 7.83 (dd, *J* = 7.6, 1.5 Hz, 1H, ArH), 7.40−7.36 (m, 1H, ArH), 7.28−7.24 (m, 1H, ArH), 7.18 (d, *J* = 7.6 Hz, 1H, ArH), 3.97 (s, 2H, CH_2), 3.66 (s, 3H, OCH_3), 1.31 (s, 12H, 4 × CH_3). Data is consistent with those reported in the literature.[156]

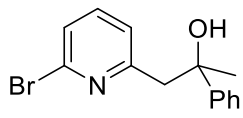
4-Methyl-4,5-dihydro-6,10-(azeno)benzo[*d*][1]oxacyclododecin-2(1*H*)-one (606)



To a stirring solution of 2-(2-(6-(2-hydroxypropyl)pyridin-2-yl)phenyl)acetic acid (44.0 mg, 0.163 mmol) in chloroform (3 mL), was added diisopropylethylamine (50.0 µL, 0.302 mmol), followed by the addition of T3P (78.0 mg, 0.284 mmol, 156 mg of a 50% solution in ethyl acetate). Upon the addition of T3P, the solution rapidly changed from a colourless to an orange solution. After stirring for 30 min at room temperature, the solution was concentrated *in vacuo.*

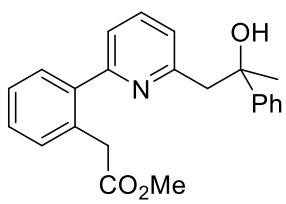
Purification *via* flash column chromatography (SiO_2, 1:1 ethyl acetate:hexane) afforded the *title compound* as a pale yellow solid (37 mg, 90%); R_F 0.45 (3:7 ethyl acetate:hexane); m.p. 110−114 °C; ν_{max}/cm^{-1} (thin film) 3063, 2973, 2928, 1720, 1586, 1575, 1450, 1422; δ_H (400 MHz, $CDCl_3$) 7.80–7.78 (1H, m, ArH), 7.69 (1H, t, *J* = 7.6 Hz, ArH), 7.54 (1H, d, *J* = 7.6 Hz, ArH), 7.43–7.40 (3H, m, ArH), 7.04 (1H, dd, *J* = 7.6, 0.5 Hz, ArH), 5.64–5.55 (1H, m, OCH), 3.65 (1H, d, *J* = 14.5 Hz, C**H**HCO), 3.54 (1H, d, *J* = 14.5 Hz, CH**H**CO), 3.12–3.00 (2H, m, $NCCH_2$), 1.50 (3H, d, *J* = 6.4 Hz, CH_3); δ_C (100 MHz, $CDCl_3$) 174.3 (CO), 155.6 (ArC), 154.9 (ArC), 137.2 (ArC), 135.1 (ArC), 133.9 (ArC), 129.2 (ArC), 127.9 (ArC), 127.7 (ArC), 121.0 (ArC), 118.4 (ArC), 70.4 (OCH), 44.4 (CO-**C**H_2), 40.4 (NC**C**H_2), 21.4 (CH_3); HRMS (ESI): calcd. for $C_{16}H_{16}NO_2$ 254.1176. Found: $[MH]^+$, 254.1173 (1.0 ppm error).

1-(6-Bromopyridin-2-yl)-2-phenylpropan-2-ol (610)



Phenyl magnesium bromide (3.0 m in diethyl ether, 2.34 mL, 7.07 mmol) was added dropwise to a solution of 1-(6-bromopyridin-2-yl)propan-2-one (504 mg, 2.36 mmol) in THF (5.0 mL) at 0 °C. The reaction mixture was slowly warmed to room temperature and stirred for 3 h. Another portion of phenyl magnesium bromide (3.0 m in diethyl ether, 2.34 mL, 7.07 mmol) was added and the reaction was stirred for further 3 h. The reaction was quenched with saturated aq. NH_4Cl (10 mL) and the aqueous layer was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated to afford the *title compound* as a pale-yellow oil (148 mg, 21%), together with (193 mg, 38%) of the starting material recovered. R_f 0.70 (1:1 ethyl acetate:hexane); ν_{max}/cm^{-1} (thin film) 3348, 3060, 2974, 1585, 1554, 1493, 1473, 1436, 1406, 1371, 1276, 1224, 1163, 1119, 1092, 1066, 1028; δ_H (400 MHz, $CDCl_3$) 7.43−7.40 (2H, m, ArH), 7.34 (1H, t, *J* = 7.6 Hz, ArH), 7.27−7.24 (3H, m, ArH), 7.16−7.13 (1H, m, ArH), 6.89 (1H, d, *J* = 6.9 Hz, ArH), 5.39 (1H, s, OH), 3.25 (1H, d, *J* = 14.5 Hz, NCC**H**H), 3.20 (1H, d, *J* = 14.5 Hz, NCCH**H**), 1.56 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 160.4 (ArC), 147.5 (ArC), 140.6 (ArC), 138.8 (ArC), 127.8 (ArC), 126.4 (ArC), 125.9 (ArC), 124.8 (ArC), 123.2 (ArC), 74.5 (COH), 49.2 (NC**C**H_2), 30.5 (CH_3); HRMS (ESI): calcd. for $C_{14}H_{14}{}^{79}BrNNaO$ 314.0151. Found: $[MNa]^+$, 314.0146 (1.7 ppm error).

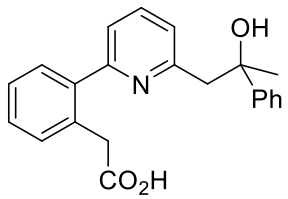
Methyl 2-(2-(6-(2-hydroxy-2-phenylpropyl)pyridin-2-yl)phenyl)acetate (611)



To a microwave vial, methyl 2-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate (218 mg, 0.790 mmol), potassium triphosphate (251 mg, 1.10 mmol) and $Pd(PPh_3)_4$ (45.5 mg, 0.0394 mmol) was added and the vial was purged with argon. Dimethylformamide (3 mL) and 1-(6-bromopyridin-2yl)-2-phenylpropan-2-ol (121 mg, 0.394

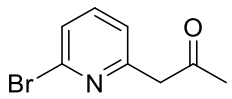
mmol) were added, and the solution was heated and stirred for 90 min at 150 °C in a microwave reactor. The solution was then cooled, diluted with ethyl acetate and passed through Celite®. The solvent was then evaporated *in vacuo*. Water (10 mL), followed by ethyl acetate (30 mL) were added and both layers were separated. The aqueous layers were extracted with ethyl acetate (3 × 30 mL). The combined organic layers were dried with anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification *via* flash column chromatography (SiO_2, 1:4 → 1:3 ethyl acetate:hexane) afforded the *title compound* as a yellow oil (56.5 mg, 44%); R_F 0.58 (3:2 hexane:ethyl acetate); ν_{max}/cm^{-1} (thin film) 3417, 3029, 2951, 1733, 1582, 1571, 1454, 1435, 1340, 1305, 1264, 1210, 1155; δ_H (400 MHz, $CDCl_3$) 7.57 (1H, t, *J* = 7.8 Hz, ArH), 7.45−7.43 (2H, m, ArH), 7.38−7.34 (5H, m, ArH), 7.27−7.23 (3H, m, ArH), 7.16−7.12 (1H, m, ArH), 6.91 (1H, d, *J* = 7.8 Hz, ArH), 6.20 (1H, br s, OH), 3.73 (1H, d, *J* = 16.5 Hz, C**H**H-COO), 3.65 (1H, d, *J* = 16.5 Hz, CH**H**-COO), 3.60 (3H, s, OCH_3), 3.33 (1H, d, *J* = 14.2 Hz, NCC**H**H), 3.27 (1H, d, *J* = 14.2 Hz, NCCH**H**), 1.56 (3H s, CH_3); δ_C (100 MHz, $CDCl_3$) 172.4 (CO), 158.7 (ArC), 158.2 (ArC), 148.3 (ArC), 140.3 (ArC), 137.3 (ArC), 132.3 (ArC), 131.3 (ArC), 130.0 (ArC), 128.8 (ArC), 128.0 (ArC), 127.5 (ArC), 126.3 (ArC), 125.0 (ArC), 122.8 (ArC), 122.1 (ArC), 74.6 (COH), 52.1 (**C**H_2COO), 49.4 (NC**C**H_2), 39.1 (OCH_3), 30.9 (CH_3); HRMS (ESI): calcd. for $C_{23}H_{24}NO_3$ 362.1751. Found: $[MH]^+$, 362.1750 (0.2 ppm error).

2-(2-(6-(2-Hydroxy-2-phenylpropyl)pyridin-2-yl)phenyl)acetic acid (612)



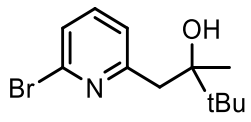
To methyl 2-(2-(6-(2-hydroxy-2-phenylpropyl)pyridin-2-yl)phenyl)acetate (56.5 mg, 0.156 mmol), was added 0.5 m aqueous LiOH (0.4 mL) and THF (0.4 mL) and the resulting solution was stirred for 16 h. The resulting solution was then removed *in vacuo* to afford the crude compound. Purification *via* flash column chromatography (SiO_2, 100% ethyl acetate → 4:1 ethyl acetate:methanol) afforded the *title compound* as a colourless oil (54.2 mg, 100%); R_f 0.45 (95:5 ethyl acetate:methanol); ν_{max}/cm^{-1} (thin film) 3385, 3059, 2976, 2931, 1713, 1598, 1578, 1493, 1447, 1372, 1298, 1263, 1222, 1144, 1120, 1102, 1027, 1016; δ_H (400 MHz, $CDCl_3$) 7.77 (1H, t, *J* = 7.9 Hz, ArH), 7.48−7.33 (7H, m, ArH), 7.28−7.17 (4H, m, ArH), 3.49 (1H, d, *J* = 12.2 Hz, C**H**H-COO), 3.39 (1H, d, *J* = 13.7 Hz, NC-C**H**H), 3.31 (1H, d, *J* = 13.7 Hz, NC-CH**H**), 3.27 (1H, d, *J* = 12.2 Hz, CH**H**-COO), 1.67 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 173.2 (CO), 156.3 (ArC), 155.9 (ArC), 146.2 (ArC), 138.6 (ArC), 137.2 (ArC), 133.1 (ArC), 132.1 (ArC), 131.5 (ArC), 130.6 (ArC), 129.8 (ArC), 128.5 (ArC), 128.2 (ArC), 127.7 (ArC), 126.9 (ArC), 124.9 (ArC), 124.8 (ArC), 122.8 (ArC), 74.7 (C-OH), 50.2 (NC-**C**H_2), 41.8 (**C**H_2-COO), 30.2 (CH_3); HRMS (ESI): calcd. for $C_{22}H_{22}NO_3$ 348.1594. Found: $[MH]^+$, 348.1589.

1-(6-Bromopyridin-2-yl)propan-2-one (600)



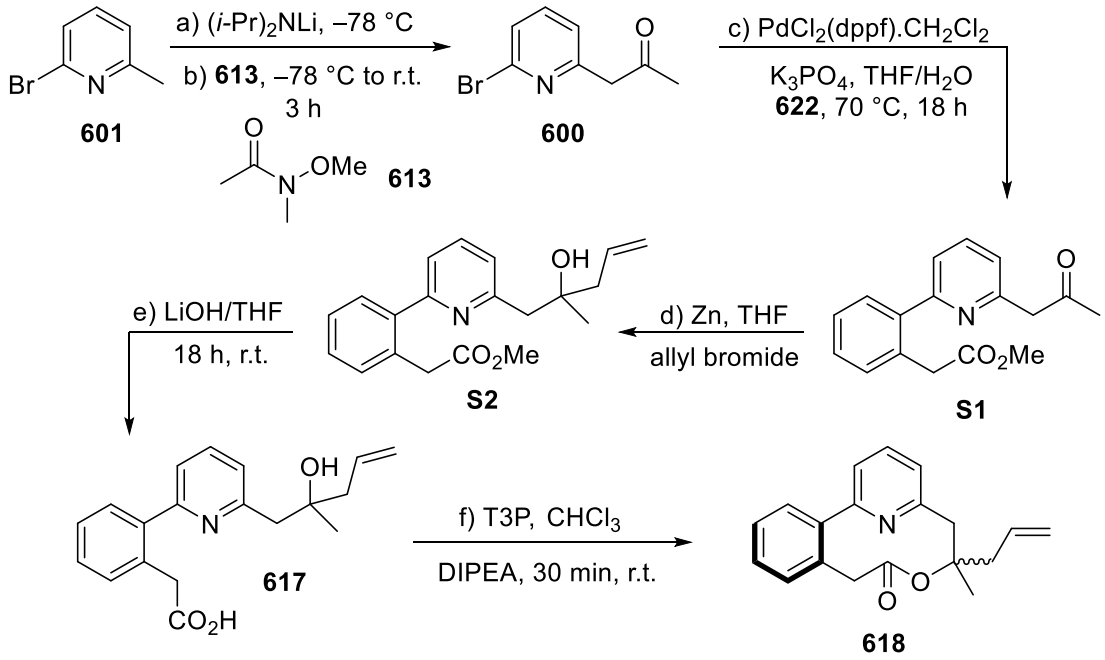
To a stirring solution of *N*,*N*-diisopropylamine (11.0 mL, 78.6 mmol) in dry THF (200 mL), was added *n*-butyllithium (32.7 mL, 78.6 mmol, 2.4 m solution in hexanes) dropwise at −10 °C. The resulting solution was stirred at 0 °C for 30 min, after which the solution was cooled to −78 °C. 6-Bromo-2-methylpyridine (4.44 mL, 39.3 mmol) was then added dropwise and the solution was stirred for 1 h. *N*-Methoxy-*N*-methylacetamide (8.73 mL, 78.6 mmol) was then added and the solution was stirred for a further 2 h. After allowing to warm to room temperature, the solution was quenched with water (150 mL), extracted with diethyl ether (3 × 150 mL) and the organic layer was washed with brine (300 mL). The organic layer was dried ($MgSO_4$), filtered and solvent removed *in vacuo* to yield the crude product. Purification *via* flash column chromatography (SiO_2, 7:3 → 3:2 hexane:ethyl acetate) afforded the *title compound* as a yellow oil (7.00 g, 83%); R_f 0.50 (3:7 ethyl acetate:hexane); ν_{max}/cm^{-1} (thin film) 2976, 1716, 1579, 1554, 1406; δ_H (400 MHz, $CDCl_3$) 7.51 (1H, t, *J* = 7.8 Hz, ArH) 7.38 (1H, d, *J* = 7.8 Hz, ArH), 7.17 (1H, d, *J* = 7.8 Hz, ArH), 3.90 (2H, s, CH_2), 2.24 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 204.0 (CO), 155.6 (ArC), 141.7 (ArC), 139.0 (ArC), 126.5 (ArC), 123.3 (ArC), 52.5 (CH_2), 30.3 (CH_3); HRMS (ESI): calcd. for $C_8H_9{}^{79}BrNO$ 213.9858. Found: $[MH]^+$, 213.9862 (1.7 ppm error).

1-(6-Bromopyridin-2-yl)-2,3,3-trimethylbutan-2-ol (616)



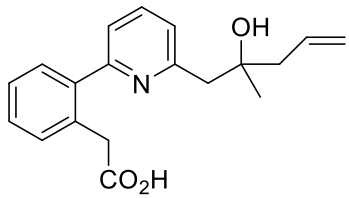
N,N-Diisopropylamine (734 µL, 5.25 mmol) was dissolved in THF (12 mL) and cooled to 0 °C before *n*-BuLi (1.6 m solution in hexanes, 3.28 mL, 5.25 mmol) was added dropwise and stirred for 30 min. The LDA solution was then cooled to −78 °C, where 2-bromo-6-methylpyridine (296 µL, 2.63 mmol) was added dropwise and stirred for 30 min. Pinacolone (665 µL, 5.25 mmol) was added and stirred for a further 30 min at −78 °C before slowly warming to RT. The solution was then quenched with sat. $NH_4Cl_{(aq)}$ (15 mL) and extracted with ethyl acetate (3 × 50 mL) and washed with brine (10 mL). The combined organic extracts were dried over $MgSO_4$, filtered and removed *in vacuo*. Purification by flash column chromatography (SiO_2, 50% ethyl acetate in hexane) afforded the *title compound* as a yellow oil (724 mg, 100%); R_F 0.55 (50% ethyl acetate in hexane); ν_{max}/cm^{-1} (thin film) 3432, 2958, 2874, 1584, 1552; δ_H (400 MHz, $CDCl_3$) 7.47 (1H, t, *J* = 7.8 Hz, C**H**), 7.34 (1H, d, *J* = 7.8 Hz, C**H**), 7.13 (1H, d, *J* = 7.8 Hz, C**H**), 4.43 (1H, br s, O**H**), 3.05 (1H, d, *J* = 13.7 Hz, C**H**H'COH), 2.76 (1H, d, *J* = 13.7 Hz, CH**H'**COH), 1.01 (9H, s, 3 × C**H₃**), 0.97 (3H, s, C**H₃**); δ_C (100 MHz, $CDCl_3$) 162.3 (**C**N), 140.9 (**C**N), 138.9 (**C**H), 125.8 (**C**H), 123.8 (**C**H), 76.4 (**C**OH), 42.5 (**C**H_2COH), 38.1 (**C**$(CH_3)_3$), 25.5 (3 × **C**H_3), 22.0 (**C**H_3); HRMS (ESI): calcd. for $C_{12}H_{19}{}^{79}BrNO$, 272.0645. Found: $[MH]^+$, 272.0642 (0.9 ppm error).

Key to intermediates used to make lactone 618



*Synthesis of S1 and S2 was completed by Dr. Aggie Lawer

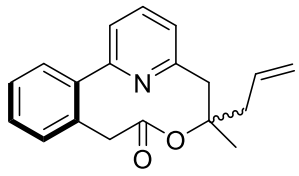
2-(2-(6-(2-Hydroxy-2-methylpent-4-en-1-yl)pyridin-2-yl)phenyl)acetic acid (617)



Zinc (34.1 mg, 0.521 mmol) and allyl bromide (63.0 mg, 0.521 mmol) were added to methyl 2-(2-(6-(2-oxopropyl)pyridin-2-yl)phenyl)acetate (49.2 mg, 0.174 mmol) in THF (1.0 mL). The mixture was stirred at room temperature for 30 min. Excess saturated aq. solution of ammonium chloride was added slowly at 0 °C. It was warmed to room temperature and stirred for 1 h. The mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. Purification *via* flash column chromatography (SiO_2, 1:4 → 1:1 ethyl acetate:hexane) afforded the *title compound* as a yellow oil (22.0 mg, 39%). To methyl 2-(2-(6-(2-hydroxy-2-methylpent-4-en-1-yl)pyridin-2-yl)phenyl)acetate (38.9 mg, 0.119 mmol), was added 0.5 M aqueous LiOH (0.28 mL) and THF (0.28 mL) and the resulting solution was stirred for 18 h. The resulting solution was then removed *in vacuo* to afford the crude *title compound* as a colourless oil (37.1 mg, 100%); R_F 0.72 (4:1 ethyl acetate:methanol); ν_{max}/cm^{-1} (thin film) 3292, 3072, 2974, 2926, 1590, 1444, 1396, 1307, 1162, 1121, 1000; δ_H (400 MHz, $CDCl_3$) 7.63 (1H, t, *J* = 7.6 Hz, ArH), 7.30–7.13 (5H, m, ArH), 7.02 (1H, d, *J* = 8.4 Hz, ArH), 5.80 (1H, m, C**H**=CH_2), 4.97 (2H, m, CH=C**H**$_2$), 3.21 (2H, s, CH_2COO), 2.80 (1H, d, *J* = 14.5 Hz, NCC**H**H), 2.82 (1H, d, *J* = 14.5 Hz, NCCH**H**), 2.15 (2H, br m, C**H**$_2$CH), 1.03 (3H, br s, C**H**$_3$COH); δ_C (100 MHz, $CDCl_3$) 178.7 (COO), 159.8 (ArC), 158.6 (ArC), 139.8 (ArC), 137.6 (ArC), 136.2 (ArC), 134.6 (**C**H=CH_2), 130.5 (ArC), 129.8 (ArC), 128.4 (ArC), 125.9 (ArC), 123.5 (ArC),

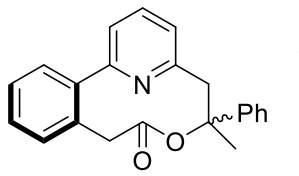
122.9 (ArC), 117.8 (CH=**C**H_2), 72.1 (COH), 47.1 (NC**C**H_2 or **C**H_2CH), 46.9 (NC**C**H_2 or **C**H_2CH), 42.3 (**C**H_2COO), 26.9 (**C**H_3COH); HRMS (ESI): calcd. for $C_{19}H_{21}NNaO_3$ 334.1414 found: $[MNa]^+$, 334.1419.

4-Allyl-4-methyl-4,5-dihydro-6,10-(azeno)benzo[*d*][1]oxacyclododecin-2(1*H*)-one (618)



To a stirring solution of 2-(2-(6-(2-hydroxy-2-methylpent-4-en-1-yl)pyridin-2-yl)phenyl)acetic acid (37.1 mg, 0.119 mmol) in chloroform (2.1 mL), was added diisopropylethylamine (38.0 µL, 0.220 mmol), followed by the addition of T3P (50% solution in ethyl acetate, 0.106 mL, 0.179 mmol). After stirring for 30 min at room temperature, the solution was taken directly to purification with no work-up. Purification *via* flash column chromatography (SiO_2, 3:7 ethyl acetate:hexane) afforded an inseparable mixture of diastereoisomers of the *title compound* as an orange oil (34.9 mg, 100%, *d.r*. 1.1:1); R_F 0.43 (7:3 hexane:ethyl acetate); ν_{max}/cm^{-1} (thin film) 3070, 2976, 2929, 1722, 1586, 1578, 1451; δ_H (400 MHz, $CDCl_3$) 7.75−7.70 (2H, m, ArH), 7.62−7.58 (2H, m, ArH), 7.49−7.46 (2H, m, ArH), 7.40−7.33 (6H, m, ArH), 7.11 (1H, d, *J* = 7.6 Hz, ArH), 7.07 (1H, d, *J* = 7.6 Hz, ArH), 6.00−5.89 (1H, m, C**H**=CH_2), 5.86−5.76 (1H, m, C**H**=CH_2), 5.21–5.11 (4H, m, 2 × CH=C**H**$_2$), 3.59 (1H, d, *J* = 12.9 Hz, NCC**H**H), 3.50−3.44 (3H, m, CH_2CO and NCCH**H**), 3.40 (1H, dd, *J* = 13.7, 6.5 Hz, C**H**H-CH=CH_2), 3.34 (1H, d, *J* = 14.5 Hz, C**H**HCO), 3.28 (1H, d, *J* = 14.5 Hz, CH**H**CO), 2.90 (1H, d, *J* = 13.7 Hz, NCC**H**H), 2.79 (1H, d, *J* = 12.9 Hz, NCCH**H**), 2.75 (1H, dd, *J* = 13.7, 8.2 Hz, C**H**H-CH=CH_2), 2.29 (1H, dd, *J* = 13.7, 6.5 Hz, CH**H**-CH=CH_2), 2.13 (1H, dd, *J* = 13.7, 8.2 Hz, CH**H**-CH=CH_2), 1.83 (3H, s, CH_3), 1.15 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 171.4 (CO), 171.2 (CO), 155.8 (ArC), 155.6 (ArC), 154.9 (ArC), 154.8 (ArC), 139.8 (ArC), 139.4 (ArC), 137.7 (ArC), 137.6 (ArC), 135.3 (ArC), 133.8 (CH=**C**H_2), 133.7 (CH=**C**H_2), 133.5 (ArC), 133.4 (ArC), 129.0 (ArC), 127.8 (ArC), 127.4 (ArC), 121.5 (ArC), 121.3 (ArC), 118.8 (CH=**C**H_2), 118.4 (CH=**C**H_2), 118.2 (ArC), 118.1 (ArC), 83.4 (**C**CH_3), 83.3 (**C**CH_3), 46.3 (**C**H_2-CH=CH_2), 45.4 (**C**H_2-CH=CH_2), 45.1 (**C**H_2CO), 44.9 (**C**H_2CO), 42.5 (NC**C**H_2), 41.2 (NC**C**H_2), 25.9 (CH_3), 25.8 (CH_3); HRMS (ESI): calcd. for $C_{19}H_{20}NO_2$ 294.1491 found: $[MH]^+$, 294.1489.

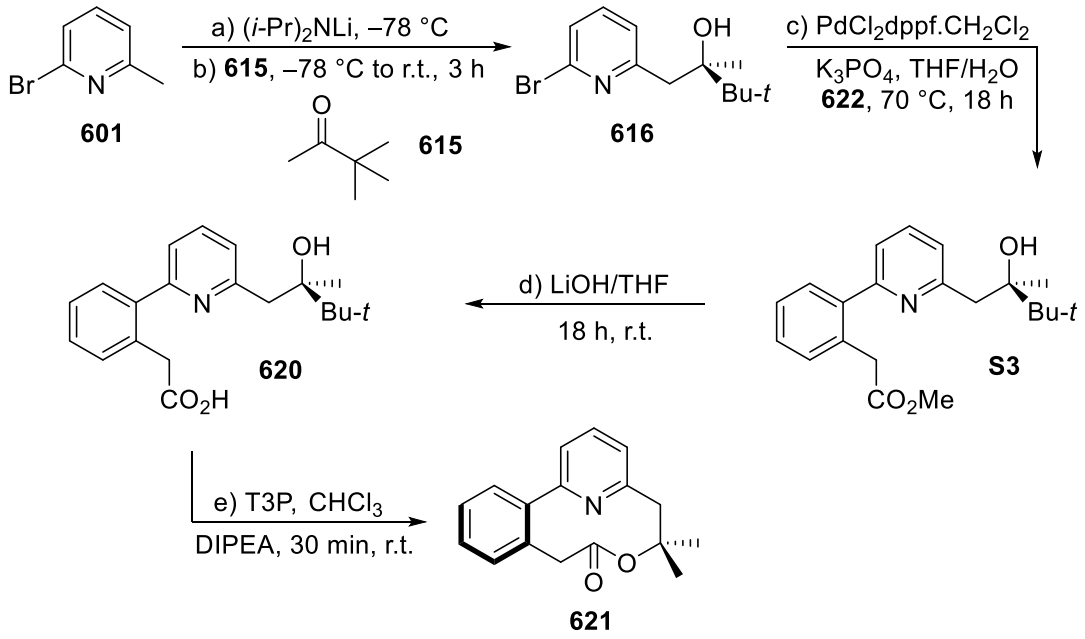
4-Methyl-4-phenyl-4,5-dihydro-6,10-(azeno)benzo[*d*][1]oxacyclododecin-2(1*H*)-one (619)



To a stirring solution of 2-(2-(6-(2-hydroxy-2-phenylpropyl)pyridin-2-yl)phenyl)acetic acid (58.5 mg, 0.168 mmol) in chloroform (3 mL), was added diisopropylethylamine (54.1 µL, 0.312 mmol), followed by the addition of T3P (50% solution in ethyl acetate, 0.150 mL, 0.253 mmol). After stirring for 30 min at room temperature, the solution was taken directly to purification with no work-up. Purification *via* flash column chromatography (SiO_2, 1:4 → 3:7 ethyl

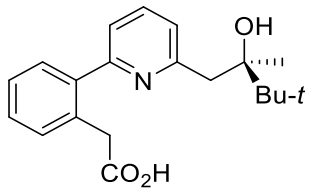
acetate:hexane) afforded an inseparable mixture of the *title compound* as a colourless oil (40.7 mg, 74%, *d.r*. 3:2); R_f 0.70 (3:7 ethyl acetate:hexane); ν_{max}/cm^{-1} (thin film) 3061, 2976, 2244, 1728. 1579, 1451, 1494, 1422, 1372, 1296, 1205, 1086, 1074, 1063, 1029, 1003; δ_H (400 MHz, $CDCl_3$) 7.80 (1H, t, *J* = 7.6 Hz, ArH), 7.64−7.20 (22H, m, ArH), 6.60 (1H, d, *J* = 7.6 Hz, ArH), 4.11 (1H, d, *J* = 12.2 Hz, NC-C**H**H), 3.94 (1H, d, *J* = 12.9 Hz, NC-C**H**H), 3.62 (1H, d, *J* = 14.5 Hz, C**H**H-COO), 3.54 (1H, d, *J* = 14.5 Hz, CH**H**-COO), 3.53 (1H, d, *J* = 14.5 Hz, C**H**H-COO**)**, 3.43 (1H, d, *J* = 14.5 Hz, CH**H**-COO), 3.35 (1H, d, *J* = 12.2 Hz, NC-CH**H**), 3.15 (1H, d, *J* = 12.9 Hz, NC-CH**H**), 2.24 (3H, s, CH_3), 1.41 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 170.9 (CO), 169.5 (CO), 155.7 (ArC), 155.5 (ArC), 154.9 (ArC), 154.4 (ArC), 146.9 (ArC), 146.1 (ArC), 139.9 (ArC), 139.6 (ArC), 137.9 (ArC), 137.5 (ArC), 135.3 (ArC), 135.2 (ArC), 134.1 (ArC), 133.9 (ArC), 129.2 (ArC), 129.1 (ArC), 128.3 (ArC), 128.2 (ArC), 127.9 (ArC), 127.6 (ArC), 127.5 (ArC), 127.1 (ArC), 126.9 (ArC), 124.6 (ArC), 124.2 (ArC), 121.7 (ArC), 121.5 (ArC), 118.4 (ArC), 84.9 (C-Ph), 82.3 (C-Ph), 45.3 (**C**H_2-COO), 44.7 (NC-**C**H_2), 44.6 (**C**H_2-COO), 40.3 (NC-**C**H_2), 32.1 (CH_3), 28.5 (CH_3); HRMS (ESI): calcd. for $C_{22}H_{20}NO_2$ 330.1489 found: $[MH]^+$, 330.1484.

Key to intermediates used to make lactone 621



*Synthesis of S3 was completed by Dr. Aggie Lawer

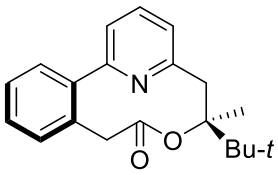
2-(2-(6-(2-Hydroxy-2,3,3-trimethylbutyl)pyridin-2-yl)phenyl)acetic acid (620)



To methyl 2-(2-(6-(2-hydroxy-2,3,3-trimethylbutyl)pyridin-2-yl)phenyl)acetate (87.9 mg, 0.257 mmol), 0.5 M aqueous LiOH (0.6 mL) and THF (0.6 mL) were added and the resulting solution was stirred for 16 h. The resulting solution was then removed *in vacuo*. Purification by column chromatography (SiO_2, 4:1 ethyl acetate:methanol) afforded the *title*

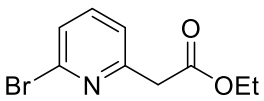
compound as a white solid (66.0 mg, 78%); R_f 0.67 (3:7 ethyl acetate:methanol); m.p. 138−141 °C; ν_{max}/cm^{-1} (thin film) 3422, 2969, 1718, 1598, 1577, 1374, 1301, 1262, 1014; δ_H (400 MHz, $CDCl_3$) 7.88−7.84 (1H, m, ArH), 7.50−7.34 (6H, m, ArH), 3.70−3.60 (2H, m, CH_2CO), 3.16 (1H, d, *J* = 12.9 Hz, NCC**H**H), 2.99 (1H, d, *J* = 12.9 Hz, NCCH**H**), 1.03 (9H, s, $(CH_3)_3$), 0.99 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 173.0 (CO), 157.9 (ArC), 156.6 (ArC), 138.6 (ArC), 137.5 (ArC), 133.1 (ArC), 131.5 (ArC), 130.6 (ArC), 129.7 (ArC), 127.7 (ArC), 125.3 (ArC), 122.6 (ArC), 76.9 (COH), 42.3 (NC**C**H_2), 41.9 (**C**H_2CO), 38.3 (**C**$(CH_3)_3$), 25.3 ($(CH_3)_3$), 21.1 (CH_3); HRMS (ESI): calcd. for $C_{20}H_{26}NO_3$ 328.1907. Found: $[MH]^+$, 328.1909 (−0.4 ppm error).

4-(*tert*-Butyl)-4-methyl-4,5-dihydro-6,10-(azeno)benzo[*d*][1]oxacyclododecin-2(1*H*)-one (621)



To 2-(2-(6-(2-hydroxy-2,3,3-trimethylbutyl)pyridin-2-yl)phenyl)acetic acid (66.0 mg, 0.202 mmol) in chloroform (3.4 mL), was added diisopropylethylamine (0.0652 mL, 0.374 mmol), followed by the addition of T3P (50% solution in ethyl acetate, 0.180 mL, 0.303 mmol). After stirring for 30 min at room temperature, the solution was taken directly to purification with no work-up. Purification *via* flash column chromatography (SiO_2, 3:7 ethyl acetate:hexane) afforded the *title compound* as a colourless oil (52.5 mg, 84%), R_f 0.58 (7:3 hexane:ethyl acetate); ν_{max}/cm^{-1} (thin film) 2960, 1721, 1578, 1451, 1396, 1371, 1325, 1294, 1224, 1208, 1134, 1088, 1011; δ_H (400 MHz, $CDCl_3$) 7.76−7.73 (1H, m, ArH), 7.70 (1H, t, *J* = 7.6 Hz, ArH), 7.55 (1H, d, *J* = 8.4 Hz, ArH), 7.41−7.38 (3H, m, ArH), 7.09 (1H, m, ArH), 3.69 (1H, d, *J* = 14.5 Hz, C**H**HCO), 3.56 (1H, d, *J* = 14.5 Hz, CH**H**CO), 3.30 (1H, d, *J* = 14.5 Hz, NCC**H**H), 3.09 (1H, d, *J* = 14.5 Hz, NCCH**H**), 1.77 (3H, s, CH_3), 1.02 (9H, s, $(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 171.7 (CO), 156.2 (ArC), 154.6 (ArC), 137.6 (ArC), 137.4 (ArC), 135.4 (ArC), 133.9 (ArC), 129.0 (ArC), 127.7 (ArC), 127.3 (ArC), 122.1 (ArC), 117.8 (ArC), 89.1 (CO), 45.7 (**C**H_2CO), 39.5 (**C**$(CH_3)_3$), 38.9 (NC**C**H_2), 25.7 ($(CH_3)_3$), 21.8 (CH_3); HRMS (ESI): calcd. for $C_{20}H_{24}NO_2$ 310.1802. Found: $[MH]^+$, 310.1797 (1.6 ppm error).

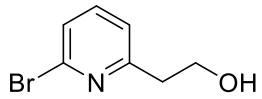
Ethyl 2-(6-bromopyridin-2-yl)acetate (624)



N,N-Diisopropylamine (1.13 mL, 8.00 mmol) was dissolved in THF (20 mL) and cooled to 0 °C before *n*-BuLi (1.6 m solution in hexanes, 5.0 mL, 8.00 mmol) was added dropwise and stirred for 30 min. The LDA solution was then cooled to −78 °C, where a solution of 2-bromo-6-methylpyridine (456 µL, 4.00 mmol) in THF (5.0 mL), was added dropwise and stirred for 30 min. Ethyl chloroformate (191 µL, 2.00 mmol) was added and stirred for a further 30 min at −78 °C before slowly warming to room temperature. The solution was then quenched with sat. $NH_4Cl_{(aq)}$ (20 mL) and extracted with ethyl acetate (3 × 50 mL) and washed with brine (10 mL). The combined organic extracts were dried over $MgSO_4$, filtered and

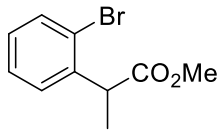
removed *in vacuo*. Purification by flash column chromatography (SiO_2, 33% → 50% diethyl ether in hexanes) afforded the *title compound* (as a 10:1 mixture of ester:enol tautomers) as a yellow oil (419 mg, 86%); R_F 0.71 (ethyl acetate); δ_H (400 MHz, $CDCl_3$) data for the ester tautomer only: 7.51 (1H, t, *J* = 7.6 Hz, C**H**), 7.38 (1H, d, *J* = 7.6 Hz, C**H**), 7.26 (1H, d, *J* = 7.6 Hz, C**H**), 4.16 (2H, q, *J* = 6.9 Hz, OC**H₂**CH_3), 3.80 (2H, s, C**H₂**CO_2Et), 1.24 (3H, t, *J* = 6.9 Hz, CH_2C**H₃**). Data is consistent with those previously reported in the literature.[157]

2-(6-bromopyridin-2-yl)ethan-1-ol (622)



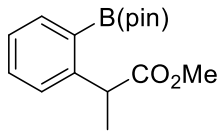
Ethyl 2-(6-bromopyridin-2-yl)acetate (187 mg, 0.766 mmol) was dissolved in anhydrous THF (7.6 mL) and cooled to 0 °C. A solution of DIBAL-*H* (1.0 m, 1.69 mL, 1.69 mmol) was added and stirred at 0 °C for 2 h, where the solution was slowly warmed to room temperature. Upon completion, the reaction was quenched with Rochelle's salt (10 ml) at 0 °C for 10 min, followed by water (10 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. Purification by flash column chromatography (SiO_2, 50% diethyl ether in hexanes → diethyl ether) afforded the *title compound* as a colourless oil (127 mg, 82%); R_F 0.50 (ethyl acetate); δ_H (400 MHz, $CDCl_3$) 7.45 (1H, t, *J* = 7.6 Hz, C**H**), 7.31 (1H, d, *J* = 7.6 Hz, C**H**), 7.12 (1H, d, *J* = 7.6 Hz, C**H**), 4.02–3.93 (2H, m, C**H₂**OH), 3.25 (1H, br s, O**H**), 2.97 (2H, t, *J* = 6.1 Hz, C**H₂**CH_2OH). Data is consistent with those previously reported in the literature.[158]

Methyl 2-(2-bromophenyl)propanoate (625)



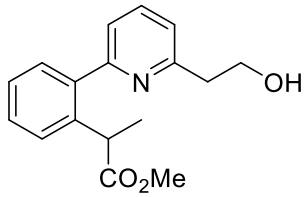
Methyl 2-(2-bromophenyl)acetate (1.00 g, 4.37 mmol) was dissolved in anhydrous THF (14.6 mL) and cooled to 0 °C, where NaHMDS solution (1.0 m in THF, 4.80 mL, 4.80 mmol) was added slowly. The resulting solution was stirred at 0 °C for 30 min where methyl iodide (272 µL, 4.37 mmol) was added and the solution allowed to warm to room temperature over 2 h. Upon completion, the reaction was quenched with 10% $HCl_{(aq)}$ (15 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 50% diethyl ether in hexanes) afforded the *title compound* as a yellow oil (0.976 g, 92%); R_F 0.60 (50% ethyl acetate in hexanes); δ_H (400 MHz, $CDCl_3$) 7.55 (1H, d, *J* = 8.4 Hz, C**H**), 7.31–7.27 (2H, m, 2 × C**H**), 7.14–7.08 (1H, m, C**H**), 4.22 (1H, q, *J* = 6.9 Hz, C**H**CH_3), 3.68 (3H, s, CO_2C**H₃**), 1.48 (3H, d, *J* = 6.9 Hz, CHC**H₃**). Data is consistent with those previously reported in the literature.[159]

Methyl 2-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propanoate (626)



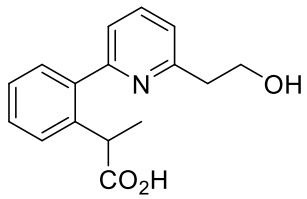
Methyl 2-(2-bromophenyl)propanoate (760 mg, 3.13 mmol), bis(pinacolato)diboron (873 mg, 3.44 mmol), potassium acetate (921 mg, 9.38 mmol) and $PdCl_2(dppf).CH_2Cl_2$ (128 mg, 0.156 mmol) were dissolved in anhydrous 1,4-dioxane (11.0 mL) under an argon atmosphere and heated to 80 °C for 18 h. Upon completion, the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 50% diethyl ether in hexanes→diethyl ether) afforded the *title compound* as an orange oil (887 mg, 98%); R_F 0.59 (50% ethyl acetate in hexanes); ν_{max}/cm^{-1} (thin film) 2978, 1736; δ_H (400 MHz, $CDCl_3$) 7.79 (1H, dd, *J* = 7.6, 1.5 Hz, C**H**), 7.38 (1H, td, *J* = 7.6, 1.5 Hz, C**H**), 7.31–7.18 (2H, m, 2 × C**H**), 4.65 (1H, q, *J* = 6.9 Hz, C**H**CH_3), 3.61 (3H, s, $CO_2C\mathbf{H_3}$), 1.45 (3H, d, *J* = 6.9 Hz, CHC**H₃**), 1.24 (12H, s, 4 × C**H₃**); δ_C (100 MHz, $CDCl_3$) 175.8 (**C**O_2Me), 147.2 (**C**), 136.1 (**C**H), 131.2 (**C**H), 126.2 (**C**H), 126.1 (**C**H), 83.6 (O**C**CH_3), 51.8 ($CO_2\mathbf{C}H_3$), 43.2 (**C**HCO_2Me), 25.0 (C**C**H_3), 19.1 (CH**C**H_3); HRMS (ESI): calcd. for $C_{16}H_{23}BNaO_4$, 313.1582. Found: $[MNa]^+$, 313.1582 (0.7 ppm error).

Methyl 2-(2-(6-(2-hydroxyethyl)pyridin-2-yl)phenyl)propanoate (627)



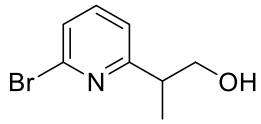
2-(6-Bromopyridin-2-yl)ethan-1-ol (109 mg, 0.539 mmol), methyl 2-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propanoate (235 mg, 0.809 mmol), potassium phosphate (229 mg, 1.08 mmol) and $PdCl_2(dppf).CH_2Cl_2$ (22.0 mg, 26.9 µmol) was dissolved in THF (5.4 mL) under a nitrogen atmosphere. H_2O (49.0 µL, 2.70 mmol) was added and the solution heated, at reflux, to 80 °C for 18 h. Upon completion, the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 50% diethyl ether in hexanes→66% diethyl ether in hexanes) afforded the *title compound* as a colourless oil (100 mg, 65%); R_F 0.50 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3405, 2950, 1732, 1588, 1571, 1446; δ_H (400 MHz, $CDCl_3$) 7.71 (1H, t, *J* = 7.6 Hz, C**H**), 7.48–7.28 (5H, m, 5 × C**H**), 7.16 (1H, d, *J* = 7.6 Hz, C**H**), 4.20–3.97 (4H, m, O**H** and C**H**CH_3 and C**H₂**OH), 3.59 (3H, s, $CO_2C\mathbf{H_3}$), 3.13–3.02 (2H, m, C**H₂**CH_2OH), 1.45 (3H, d, *J* = 7.6 Hz, CHC**H₃**); δ_C (100 MHz, $CDCl_3$) 175.4 (**C**O_2CH_3), 160.0 (**C**N), 158.7 (**C**N), 139.9 (**C**), 138.6 (**C**), 137.1 (**C**H), 130.0 (**C**H), 128.8 (**C**H), 127.4 (**C**H), 126.9 (**C**H), 122.1 (**C**H), 121.7 (**C**H), 61.6 (**C**H_2OH), 52.0 ($CO_2\mathbf{C}H_3$), 41.2 (**C**H_2CH_2OH), 39.1 (**C**HCO_2Me), 24.8 (CH**C**H_3); HRMS (ESI): calcd. for $C_{17}H_{20}NO_3$, 286.1438. Found: $[MH]^+$, 286.1441 (−0.5 ppm error).

2-(2-(6-(2-Hydroxyethyl)pyridin-2-yl)phenyl)propanoic acid (628)



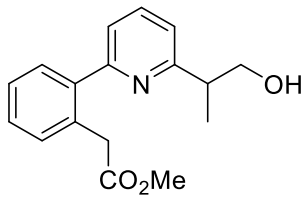
Methyl 2-(2-(6-(2-hydroxyethyl)pyridin-2-yl)phenyl)propanoate (90 mg, 0.315 mmol) was dissolved in THF (0.95 mL) and $LiOH_{(aq)}$ (0.5 m, 0.95 mL, 0.473 mmol) was added and stirred at room temperature for 18 h. Upon completion, the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, diethyl ether→20% methanol in diethyl ether) afforded the *title compound* as a colourless oil (66 mg, 77%); R_F 0.52 (20% methanol in ethyl acetate); ν_{max}/cm^{-1} (thin film) 3411, 2952, 1732, 1589, 1569, 1444; δ_H (400 MHz, $CDCl_3$) 7.88 (1H, t, *J* = 8.4 Hz, C**H**), 7.56–7.48 (2H, m, 2 × C**H**), 7.45–7.29 (4H, m, 4 × C**H**), 4.01–3.87 (3H, m, C**H₂**OH and C**H**CH_3), 3.14–3.06 (2H, m, C**H₂**CH_2OH), 1.44 (3H, d, *J* = 7.6 Hz, CHC**H₃**); δ_C (100 MHz, $CDCl_3$) 175.6 (**C**O_2H), 157.5 (**C**N), 157.3 (**C**N), 139.5 (**C**H), 138.8 (**C**), 137.3 (**C**), 130.6 (**C**H), 129.8 (**C**H), 127.5 (**C**H), 127.3 (**C**H), 123.3 (**C**H), 122.9 (**C**H), 61.9 (**C**H_2OH), 41.0 (**C**H_2CH_2OH), 39.7 (**C**HCH_3), 16.5 (**C**H_3); HRMS (ESI): calcd. for $C_{16}H_{17}NNaO_3$, 294.1101. Found: $[MNa]^+$, 294.1104 (−1.2 ppm error).

2-(6-Bromopyridin-2-yl)propan-1-ol (630)



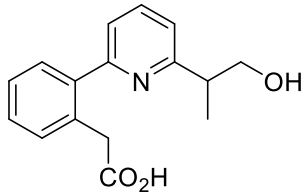
Ethyl 2-(6-bromopyridin-2-yl)acetate (233 mg, 0.955 mmol) was dissolved in THF (3.2 mL) and cooled to 0 °C, before NaHMDS (1.0 m, 1.05 mL, 1.05 mmol) was added dropwise and the solution stirred for 30 min. Then, methyl iodide (60 µL, 0.955 mmol) was added and the solution allowed to slowly warm to room temperature over 2 h. The reaction was quenched with sat. $NH_4Cl_{(aq)}$ (10 mL) and extracted with ethyl acetate (3 × 50 mL) and washed with brine (10 mL). The combined organic extracts were dried over $MgSO_4$, filtered and removed *in vacuo*. This crude material was then re-dissolved in THF (7.4 mL) cooled to 0 °C and DIBAL-H (1.0 m in THF, 1.63 mL, 1.63 mmol) added slowly. The solution was then stirred, at room temperature for 18 h, where upon completion the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 50% diethyl ether in hexanes) afforded the *title compound* as a colourless oil (76 mg, 37% over two steps); R_F 0.54 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3351, 2966, 2931, 2875, 1582, 1552, 1435, 1407; δ_H (400 MHz, $CDCl_3$) 7.40 (1H, t, *J* = 7.6 Hz, C**H**), 7.32 (1H, d, *J* = 7.6 Hz, C**H**), 7.14 (1H, d, *J* = 7.6 Hz, C**H**), 3.89–3.78 (2H, m, C**H₂**OH), 3.11–2.99 (2H, m, O**H** and C**H**CH_3), 1.28 (3H, d, *J* = 7.6 Hz, C**H₃**); δ_C (100 MHz, $CDCl_3$) 166.1 (**C**N), 141.3 (**C**Br), 138.9 (**C**H), 125.8 (**C**H), 121.1 (**C**H), 66.7 (**C**H_2OH), 42.5 (**C**HCH_3), 16.9 (**C**H_3); HRMS (ESI): calcd. for $C_8H_{10}{}^{79}BrNNaO$, 237.9838. Found: $[MNa]^+$, 237.9836 (0.8 ppm error).

Methyl 2-(2-(6-(1-hydroxypropan-2-yl)pyridin-2-yl)phenyl)acetate (632)



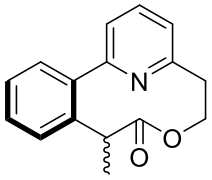
2-(6-Bromopyridin-2-yl)propan-1-ol (70.0 mg, 0.324 mmol), methyl 2-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate (134 mg, 0.486 mmol), potassium phosphate (138 mg, 0.648 mmol) and $PdCl_2(dppf).CH_2Cl_2$ (13.0 mg, 16.2 µmol) was dissolved in THF (3.2 mL) under a nitrogen atmosphere. H_2O (29 µL, 1.62 mmol) was added and the solution heated, at reflux, to 80 °C for 18 h. Upon completion, the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 25% diethyl ether in hexane→50% diethyl ether in hexane) afforded the *title compound* as a yellow oil (73 mg, 79%); R_F 0.60 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3416, 2952, 2875, 1732, 1589, 1569, 1444; δ_H (400 MHz, $CDCl_3$) 7.71 (1H, t, *J* = 7.6 Hz, C**H**), 7.44–7.31 (4H, m, 4 × C**H**), 7.28 (1H, d, *J* = 7.6 Hz, C**H**), 7.15 (1H, d, *J* = 7.6 Hz, C**H**), 3.94–3.78 (5H, m, C**H₂**OH and C**H₂**CO_2Me and O**H**), 3.53 (3H, s, $CO_2C\mathbf{H_3}$), 3.17–3.06 (1H, m, C**H**CH_3), 1.31 (3H, d, *J* = 6.9 Hz, CHC**H₃**); δ_C (100 MHz, $CDCl_3$) 172.4 (**C**O_2Me), 164.0 (**C**N), 158.5 (**C**N), 140.4 (**C**), 137.3 (**C**H), 132.3 (**C**), 131.4 (**C**H), 129.9 (**C**H), 128.5 (**C**H), 127.4 (**C**H), 121.8 (**C**H), 120.4 (**C**H), 67.1 (**C**H_2OH), 51.9 ($CO_2\mathbf{C}H_3$), 42.6 (**C**HCH_2OH), 39.3 (**C**H_2CO_2Me), 17.1 (CH**C**H_3); HRMS (ESI): calcd. for $C_{17}H_{20}NO_3$, 286.1438. Found: $[MH]^+$, 286.1441 (−1.1 ppm error).

2-(2-(6-(1-Hydroxypropan-2-yl)pyridin-2-yl)phenyl)acetic acid (633)



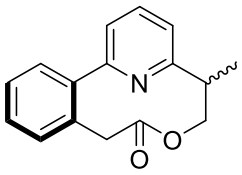
Methyl 2-(2-(6-(1-hydroxypropan-2-yl)pyridin-2-yl)phenyl)acetate (70.0 mg, 0.245 mmol) was dissolved in THF (0.74 mL) and $LiOH_{(aq)}$ (0.5 m, 0.74 mL, 0.368 mmol) was added and stirred at room temperature for 18 h. Upon completion, the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, diethyl ether→25% methanol in diethyl ether) afforded the *title compound* as a colourless oil (61 mg, 92%); R_F 0.51 (20% methanol in ethyl acetate); ν_{max}/cm^{-1} (thin film) 3384, 2934, 1714, 1598, 1578, 1445; δ_H (400 MHz, $CDCl_3$) 7.89 (1H, t, *J* = 7.6 Hz, C**H**), 7.49–7.28 (6H, m, 6 × C**H**), 3.85–3.74 (2H, m, C**H₂**OH), 3.65 (1H, d, *J* = 13.0 Hz, C**H**H'CO_2H), 3.59 (1H, d, *J* = 13.0 Hz, CH**H'**CO_2H), 3.34–3.22 (1H, m, C**H**CH_3), 1.30 (3H, d, *J* = 6.9 Hz, CHC**H₃**); δ_C (100 MHz, $CDCl_3$) 173.6 (**C**O_2H), 162.7 (**C**N), 156.9 (**C**N), 139.9 (**C**H), 137.5 (**C**), 133.2 (**C**), 131.5 (**C**H), 130.8 (**C**H), 129.9 (**C**H), 127.9 (**C**H), 123.2 (**C**H), 121.3 (**C**H), 67.0 (**C**H_2OH), 43.0 (**C**HCH_3), 42.0 (**C**H_2CO_2H), 16.6 (**C**H_3); HRMS (ESI): calcd. for $C_{16}H_{18}NO_3$, 272.1281. Found: $[MH]^+$, 272.1281 (0.2 ppm error).

1-Methyl-4,5-dihydro-6,10-(azeno)benzo[*d*][1]oxacyclododecin-2(1*H*)-one (634)



2-(2-(6-(2-Hydroxyethyl)pyridin-2-yl)phenyl)propanoic acid (61.0 mg, 0.225 mmol) was dissolved in $CHCl_3$ (2.2 mL) where DIPEA (71.0 µL, 0.405 mmol) and T3P (50% solution in ethyl acetate, 201 µL, 0.337 mmol) were added sequentially and stirred at room temperature for 30 min. Upon completion the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 50% diethyl ether in hexanes) afforded the *title compound* (as a 1:1 mixture of diastereomers) as a yellow oil (54 mg, 95%); R_F 0.72 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 2959, 1720, 1587, 1450; δ_H (400 MHz, $CDCl_3$) 7.80–7.75 (1H, m, C**H**, single diastereomer), 7.72–7.59 (4H, m, 4 × C**H**), 7.54–7.44 (3H, m, 3 × C**H**), 7.43–7.34 (4H, m, 4 × C**H**), 7.07 (1H, d, *J* = 7.6 Hz, C**H**, single), 7.04 (1H, d, *J* = 7.6 Hz, C**H**, single), 5.46 (1H, td, *J* = 12.2, 3.1 Hz, C**H**H'O, single), 5.40 (1H, td, *J* = 12.2, 3.8 Hz, CH**H'**O, single), 4.32–4.19 (2H, m, C**H$_2$**O, single), 3.80 (1H, q, *J* = 7.6 Hz, C**H**CH_3, single), 3.63 (1H, q, *J* = 6.9 Hz, C**H**CH_3, single), 3.37–3.23 (2H, m, C**H$_2$**CH_2O, single), 3.05 (1H, dd, *J* = 17.6, 3.1 Hz, C**H**H'CH_2O, single), 3.00–2.91 (1H, m, CH**H'**CH_2O, single), 1.61 (3H, d, *J* = 7.6 Hz, CHC**H$_3$**, single), 1.04 (3H, d, *J* = 6.9 Hz, CHC**H$_3$**, single); δ_C (100 MHz, $CDCl_3$) 178.5 (**C**O_2CH_2) 175.5 (**C**O_2CH_2), 156.4 (**C**N), 155.5 (**C**N), 155.2 (**C**N), 154.8 (**C**N), 141.9 (**C**), 139.1 (**C**), 137.5 (**C**), 137.3 (**C**H), 137.1 (**C**H), 135.3 (**C**), 133.9 (**C**H), 129.4 (**C**H), 129.2 (**C**H), 128.6 (**C**H), 128.1 (**C**H), 127.9 (**C**H), 127.5 (**C**H), 127.1 (**C**H), 121.3 (**C**H), 121.1 (**C**H), 118.8 (**C**H), 118.3 (**C**H), 62.9 (**C**H_2O), 62.7 (**C**H_2O), 49.0 (**C**HCH_3), 45.1 (**C**HCH_3), 32.7 (**C**H_2CH_2O), 32.6 (**C**H_2CH_2O), 17.0 (**C**H_3), 15.2 (**C**H_3); HRMS (ESI): calcd. for $C_{16}H_{16}NO_2$, 254.1176. Found: $[MH]^+$, 254.1179 (−1.3 ppm error).

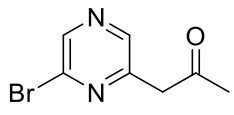
5-Methyl-4,5-dihydro-6,10-(azeno)benzo[*d*][1]oxacyclododecin-2(1*H*)-one (635)



2-(2-(6-(1-Hydroxypropan-2-yl)pyridin-2-yl)phenyl)acetic acid (57.0 mg, 0.210 mmol) was dissolved in $CHCl_3$ (2.1 mL) where DIPEA (66.0 µL, 0.378 mmol) and T3P (50% solution in ethyl acetate, 188 µL, 0.315 mmol) were added sequentially and stirred at room temperature for 30 min. Upon completion, the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 50% diethyl ether in hexanes) afforded the *title compound* (as a 3:2 mixture of diastereomers) as a yellow oil (53 mg, 99%); R_F 0.76 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 2963, 1726, 1587, 1576, 1445; δ_H (400 MHz, $CDCl_3$) 7.85–7.79 (1H, m, C**H**, minor diastereomer), 7.77–7.66 (3H, m, C**H**, major diastereomer and C**H**, both diastereomers), 7.58 (1H, d, *J* = 7.6 Hz, C**H**, minor), 7.48 (1H, d, *J* = 7.6 Hz, C**H**, major), 7.44–7.36 (6H, m, 3 × C**H**, both), 7.18 (1H, d, *J* = 7.6 Hz, C**H**, major), 7.07 (1H, d, *J* = 7.6 Hz, C**H**, minor), 5.40 (1H, dd, *J* = 11.4, 3.1 Hz, C**H**H'O, minor), 5.11 (1H, t, *J* = 11.4 Hz, C**H**H'O, major), 4.13 (1H, dd, *J* = 12.2, 5.3 Hz, CH**H'**O, major), 3.98 (1H, dd, *J* = 12.2, 2.3 Hz, CH**H'**O, minor), 3.85 (1H, d, *J* = 14.5 Hz, C**H**H'CO_2, minor), 3.57 (1H, d, *J* = 14.5

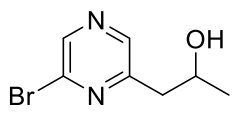
Hz, CH**H'**CO_2, minor), 3.52 (2H, s, C**H₂**CO_2, major), 3.46–3.34 (1H, m, C**H**CH_3, major), 3.16–3.07 (1H, m, C**H**CH_3, minor), 1.52 (3H, d, *J* = 7.6 Hz, CHC**H₃**, minor), 1.32 (3H, d, *J* = 7.6 Hz, CHC**H₃**, major); δ_C (100 MHz, $CDCl_3$) 175.2 (**C**O_2CH_2, major), 174.7 (**C**O_2CH_2, minor), 160.8 (**C**N, minor), 160.7 (**C**N, minor), 155.1 (**C**N, major), 154.3 (**C**N, minor), 137.6 (**C**, major), 137.5 (**C**H, minor), 137.3 (**C**H, major), 136.5 (**C**, minor), 135.1 (**C**, major), 134.8 (**C**, minor), 134.0 (**C**H, minor), 133.6 (**C**H, major), 129.2 (**C**H, minor), 129.1 (**C**H, major), 128.1 (**C**H, major), 127.9 (**C**H, minor), 127.7 (**C**H, both), 120.2 (**C**H, minor), 120.0 (**C**H, major), 118.8 (**C**H, major), 118.3 (**C**H, major) 69.3 (**C**H_2O, both), 44.7 (**C**H_2CO_2, minor), 43.9 (**C**H_2CO_2, major), 37.7 (**C**HCH_3, major), 37.6 (**C**HCH_3, minor), 19.6 (**C**H_3CH, minor), 16.3 (**C**HCH_3, major); HRMS (ESI): calcd. for $C_{16}H_{16}NO_2$, 254.1176. Found: $[MH]^+$, 254.1172 (1.5 ppm error).

1-(6-Bromopyrazin-2-yl)propan-2-one (643)



N,N-Diisopropylamine (282 µL, 2.00 mmol) was dissolved in THF (5 mL) and cooled to 0 °C before *n*-BuLi (1.6 m solution in hexanes, 1.25 mL, 2.00 mmol) was added dropwise and stirred for 30 min. The LDA solution was then cooled to −78 °C, where a solution of 2-bromo-6-methylpyrazine (173 µL, 1.00 mmol) in THF (1.0 mL), was added dropwise and stirred for 30 min. *N*-Methoxy-*N*-methylacetamide (213 µL, 2.00 mmol) was added and stirred for a further 30 min at −78 °C before slowly warming to room temperature. The solution was then quenched with sat. $NH_4Cl_{(aq)}$ (20 mL) and extracted with ethyl acetate (3 × 50 mL) and washed with brine (10 mL). The combined organic extracts were dried over $MgSO_4$, filtered and removed *in vacuo*. Purification by flash column chromatography (SiO_2, 50% ethyl acetate in hexanes→ethyl acetate) afforded the *title compound* (as a 10:1 mixture of keto:enol tautomers) as a colourless oil (174 mg, 81%); R_F 0.59 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 1722, 1639, 1563, 1511; δ_H (400 MHz, $CDCl_3$) 12.1 (1H, s, O**H**, enol), 8.58 (1H, s, C**H**, keto), 8.42 (1H, s, C**H**, keto), 8.28 (1H, s, C**H**, enol), 8.15 (1H, s, C**H**, enol), 5.35 (1H, s, C**H**COH, enol), 3.95 (2H, s, C**H₂**CO, keto), 2.29 (3H, s, C**H₃**, keto), 2.05 (3H, s, C**H₃**, enol); δ_C (100 MHz, $CDCl_3$) data for ketone tautomer only: 203.0 (**C**O), 151.0 (**C**N), 145.6 (**C**HN), 143.4 (**C**HN), 140.1 (**C**Br), 49.3 (**C**H_2), 30.3 (**C**H_3); HRMS (ESI): calcd. for $C_7H_7{}^{79}BrN_2O$, 236.9634. Found: $[MNa]^+$, 236.9630 (1.6 ppm error).

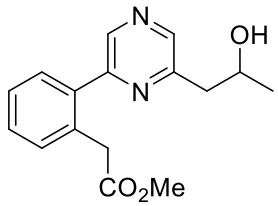
1-(6-Bromopyrazin-2-yl)propan-2-ol (644)



2-(6-Bromopyrazin-2-yl)-1-phenylethan-1-ol (160 mg, 0.744 mmol) was dissolved in methanol (7.4 mL) and cooled to 0 °C. Sodium borohydride (85 mg, 2.23 mmol) was added portionwise and stirred at 0 °C for 1 h then allowed to warm to room temperature. Upon completion, the solvent was removed *in vacuo*.

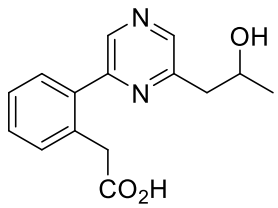
Purification by flash column chromatography (SiO_2, diethyl ether) afforded the *title compound* as a yellow oil (152 mg, 94%); R_F 0.50 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3378, 2968, 2928, 1561, 1508; δ_H (400 MHz, $CDCl_3$) 8.54 (1H, s, C**H**), 8.40 (1H, s, C**H**), 4.33–4.20 (1H, m, C**H**OH), 2.93 (1H, dd, *J* = 14.5, 3.8 Hz, C**H**H'CHOH), 2.86 (1H, dd, *J* = 14.5, 8.4 Hz, CH**H'**CHOH), 2.75 (1H, d, *J* = 3.8 Hz, O**H**), 1.30 (3H, d, *J* = 6.5 Hz, C**H₃**); δ_C (100 MHz, $CDCl_3$) 156.1 (**C**CH_2), 145.2 (**C**H), 143.1 (**C**H), 140.0 (**C**Br), 66.9 (**C**HOH), 43.2 (**C**H_2), 23.3 (**C**H_3); HRMS (ESI): calcd. for $C_7H_9{}^{79}BrN_2NaO$, 238.9790. Found: $[MNa]^+$, 239.9788 (1.0 ppm error).

Methyl 2-(2-(6-(2-hydroxypropyl)pyrazin-2-yl)phenyl)acetate (645)



1-(6-Bromopyrazin-2-yl)propan-2-ol (135 mg, 0.622 mmmol), methyl 2-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate (258 mg, 0.933 mmol), potassium phosphate (264 mg, 1.24 mmol) and $PdCl_2$(dppf).CH_2Cl_2 (26.0 mg, 12.5 µmmol) were dissolved in THF (6.2 mL) under a nitrogen atmosphere. H_2O (56.0 µL, 3.11 mmol) was added and the solution heated, at reflux, to 80 °C for 18 h. Upon completion, the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 33% diethyl ether in hexanes→diethyl ether) afforded the *title compound* as a colourless oil (97 mg, 55%); R_F 0.10 (50% ethyl acetate in hexanes); ν_{max}/cm^{-1} (thin film) 3406, 2967, 1735, 1529; δ_H (400 MHz, $CDCl_3$) 8.59 (1H, s, C**H**N), 8.41 (1H, s, C**H**N), 7.48–7.33 (4H, m, 4 × C**H**), 4.33–4.23 (1H, m, C**H**OH), 3.83 (1H, d, *J* = 16.0 Hz, C**H**H'CO_2Me), 3.75 (1H, d, *J* = 16.0 Hz, CH**H'**CO_2Me), 3.55 (3H, s, OC**H₃**), 3.46 (1H, br s, O**H**), 2.99 (1H, dd, *J* = 14.5, 3.1 Hz, C**H**H'CH), 2.88 (1H, dd, *J* = 14.5, 9.2 Hz, CH**H'**CH), 1.30 (3H, d, *J* = 6.1 Hz, CHC**H₃**); δ_C (100 MHz, $CDCl_3$) 172.2 (**C**O_2Me), 153.8 (**C**N), 153.6 (**C**N), 143.0 (**C**HN), 142.5 (**C**HN), 136.6 (**C**), 133.0 (**C**), 132.0 (**C**H), 129.9 (**C**H), 129.5 (**C**H), 127.8 (**C**H), 67.0 (**C**HOH), 52.1 (O**C**H_3), 43.5 (**C**H_2CHOH), 39.5 (**C**H_2CO_2Me), 23.3 (**C**H_3); HRMS (ESI): calcd. for $C_{16}H_{18}N_2NaO_3$, 309.1210. Found: $[MNa]^+$, 309.1202 (2.4 ppm error).

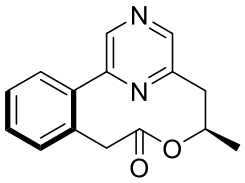
2-(2-(6-(2-Hydroxypropyl)pyrazin-2-yl)phenyl)acetic acid (646)



Methyl 2-(2-(6-(2-hydroxypropyl)pyrazin-2-yl)phenyl)acetate (90.0 mg, 0.314 mmol) was dissolved in THF (1.0 mL) and $LiOH_{(aq)}$ (0.5 m, 0.94 mL, 0.472 mmol) was added and stirred for 18 h. Upon completion, the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, diethyl ether→20% methanol in diethyl ether) afforded the *title compound* as a colourless oil (74 mg, 87%); R_F 0.21 (20% methanol in diethyl ether); ν_{max}/cm^{-1} (thin film) 3360, 2967, 2926, 1711, 1579, 1530; δ_H (400 MHz, $CDCl_3$) 8.63 (1H, s, C**H**N), 8.45 (1H, s, C**H**N), 7.46–7.32 (4H, m, 4 × C**H**), 4.21–4.11 (1H, m, C**H**OH), 3.63 (1H, d, *J* = 15.3 Hz,

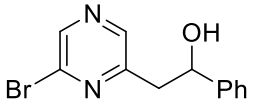
C**H**H'CO_2Me), 3.54 (1H, d, *J* = 15.3 Hz, CH**H'**CO_2Me), 2.95 (1H, dd, *J* = 13.7, 3.8 Hz, C**H**H'CHOH), 2.86 (1H, dd, *J* = 13.7, 8.4 Hz, CH**H'**CHOH), 1.21 (3H, d, *J* = 6.1 Hz, C**H$_3$**); δ_C (100 MHz, $CDCl_3$) 166.3 (**C**O_2H), 153.1 (**C**N), 152.5 (**C**N), 143.5 (**C**HN), 142.9 (**C**HN), 135.6 (**C**), 134.1 (**C**), 132.2 (**C**H), 130.0 (**C**H), 127.6 (**C**H), 127.5 (**C**H), 67.2 (**C**HOH), 43.1 (**C**H_2CH), 41.2 (**C**H_2CO_2H), 23.2 (**C**H_3); HRMS (ESI): calcd. for $C_{15}H_{16}N_2NaO_3$, 295.1053. Found: $[MNa]^+$, 295.1054 (−0.2 ppm error).

4-Methyl-4,5-dihydro-6,10-(azeno)benzo[*i*][1]oxa[6]azacyclododecin-2(1*H*)-one (647)



2-(2-(6-(2-Hydroxypropyl)pyrazin-2-yl)phenyl)acetic acid (65 mg, 0.239 mmol) was dissolved in $CHCl_3$ (2.4 mL), where DIPEA (75 µL, 0.430 mmol) and T3P (50% in ethyl acetate, 213 µL, 0.359 mmol) were added sequentially and stirred for 30 min. Upon completion, the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 50% diethyl ether in hexanes) afforded the *title compound* as a colourless oil (55 mg, 90%); R_F 0.55 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 2975, 2929, 1723, 1546; δ_H (400 MHz, $CDCl_3$) 8.81 (1H, s, C**H**N), 8.34 (1H, s, C**H**N), 7.85–7.78 (1H, m, C**H**), 7.47–7.38 (3H, m, 3 × C**H**), 5.60–5.48 (1H, m, C**H**O), 3.58 (1H, d, *J* = 15.3 Hz, C**H**H'CO_2), 3.54 (1H, d, *J* = 15.3 Hz, CH**H'**CO_2), 3.11 (1H, dd, *J* = 17.6, 3.8 Hz, C**H**H'CH), 3.01 (1H, dd, *J* = 17.6, 9.9 Hz, CH**H'**CH), 1.50 (3H, d, *J* = 6.1 Hz, C**H$_3$**); δ_C (100 MHz, $CDCl_3$) 174.1 (**C**O_2CH), 150.7 (**C**N), 150.0 (**C**N), 141.6 (**C**HN), 139.5 (**C**HN), 135.6 (**C**), 134.4 (**C**), 134.3 (**C**H), 130.2 (**C**H), 127.9 (**C**H), 127.6 (**C**H), 70.3 (**C**HO), 44.1 (**C**H_2CH), 37.9 (**C**H_2CO_2), 21.3 (**C**H_3); HRMS (ESI): calcd. for $C_{15}H_{14}N_2NaO_2$, 277.0947. Found: $[MNa]^+$, 277.0953 (−2.0 ppm error).

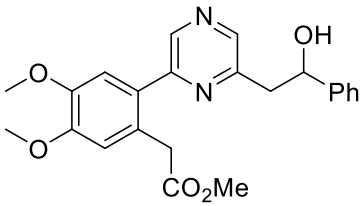
2-(6-Bromopyrazin-2-yl)-1-phenylethan-1-ol (S1)



N,N-Diisopropylamine (564 µL, 4.00 mmol) was dissolved in THF (10 mL) and cooled to 0 °C before *n*-BuLi (1.6 m solution in hexanes, 2.5 mL, 4.00 mmol) was added dropwise and stirred for 30 min. The LDA solution was then cooled to −78 °C, where a solution of 2-bromo-6-methylpyrazine (346 µL, 2.00 mmol) in THF (2.0 mL), was added dropwise and stirred for 30 min. Benzaldehyde (408 µL, 4.00 mmol) was added and stirred for a further 30 min at −78 °C before slowly warming to room temperature. The solution was then quenched with sat. $NH_4Cl_{(aq)}$ (20 mL) and extracted with ethyl acetate (3 × 50 mL) and washed with brine (10 mL). The combined organic extracts were dried over $MgSO_4$, filtered and removed *in vacuo*. Purification by flash column chromatography (SiO_2, diethyl ether) afforded the *title compound* as a yellow oil (524 mg, 94%); R_F 0.68 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3369, 3030, 2927, 1563, 1509; δ_H (400 MHz, $CDCl_3$) 8.54 (1H, s, C**H**N), 8.33 (1H, s, C**H**N), 7.43–7.23 (5H, m, 5 × C**H**), 5.20–5.12 (1H, m, C**H**OH), 4.68 (1H, br s, O**H**), 3.22–3.12 (2H, m, C**H$_2$**CHOH); δ_C (100 MHz, $CDCl_3$) 155.5 (**C**CH_2), 145.3 (**C**H), 143.3 (**C**H), 143.1

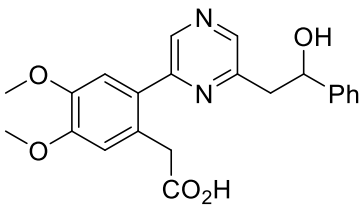
(**C**Br), 140.0 (**C**), 128.6 (**C**H), 125.7 (**C**H), 73.0 (**C**HOH), 43.8 (**C**H_2CHOH); HRMS (ESI): calcd. for $C_{12}H_{11}{}^{79}BrN_2NaO$, 300.9947. Found: $[MNa]^+$, 300.9945 (0.5 ppm error).

Methyl 2-(2-(6-(2-hydroxy-2-phenylethyl)pyrazin-2-yl)-4,5-dimethoxyphenyl)acetate (S2)



2-(6-Bromopyrazin-2-yl)-1-phenylethan-1-ol (240 mg, 0.860 mmmol), methyl 2-(4,5-dimethoxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate (434 mg, 1.29 mmol), potassium phosphate (365 mg, 1.72 mmol) and $PdCl_2(dppf).CH_2Cl_2$ (35.0 mg, 43.0 µmol) were dissolved in THF (8.6 mL) under a nitrogen atmosphere. H_2O (78.0 µL, 4.30 mmol) was added and the solution heated, at reflux, to 80 °C for 18 h. Upon completion, the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 50% diethyl ether in hexanes→diethyl ether) afforded the *title compound* as a colourless oil (194 mg, 55%); R_F 0.46 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3418, 2951, 1732, 1607, 1520; δ_H (400 MHz, $CDCl_3$) 8.60 (1H, s, C**H**N), 8.31 (1H, s, C**H**N), 7.44–7.26 (5H, m, 5 × C**H**), 6.97 (1H, s, C**H**OCH_3), 6.88 (1H, s, C**H**OCH_3), 5.23–5.16 (1H, m, C**H**OH), 3.98 (1H, br d, *J* = 3.8 Hz, O**H**), 3.94 (3H, s, OC**H₃**), 3.91 (3H, s, OC**H₃**), 3.78 (1H, d, *J* = 16.0 Hz, C**H**H'CO_2Me), 3.70 (1H, d, *J* = 16.0 Hz, CH**H'**CO_2Me), 3.62 (3H, s, CO_2C**H₃**), 3.25–3.15 (2H, m, C**H₂**CHOH); δ_C (100 MHz, $CDCl_3$) 176.5 (**C**O_2Me), 157.3 (**C**N), 157.2 (**C**N), 153.7 (**C**OCH_3), 152.2 (**C**OCH_3), 147.5 (**C**CN), 146.6 (**C**HN), 146.4 (**C**HN), 132.8 (**C**), 132.4 (**C**H), 131.5 (**C**H), 129.6 (**C**H), 129.6 (**C**CH_2CO_2Me), 118.6 (**C**H$COCH_3$), 116.6 (**C**H$COCH_3$), 77.0 (**C**HOH), 60.04 (O**C**H_3), 59.99 (O**C**H_3), 56.1 (CO_2**C**H_3), 48.0 (**C**H_2CH), 43.1 (**C**H_2CO_2Me); HRMS (ESI): calcd. for $C_{23}H_{24}N_2NaO_5$, 431.1577. Found: $[MNa]^+$, 431.1582 (−1.0 ppm error).

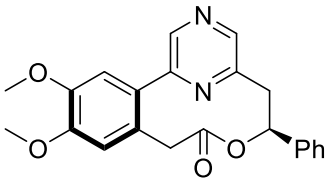
2-(2-(6-(2-Hydroxy-2-phenylethyl)pyrazin-2-yl)-4,5-dimethoxyphenyl)acetic acid (648)



Methyl 2-(2-(6-(2-hydroxy-2-phenylethyl)pyrazin-2-yl)-4,5-dimethoxyphenyl)acetate (180 mg, 0.441 mmol) was dissolved in THF (1.30 mL) and $LiOH_{(aq)}$ (0.5 m, 1.30 mL, 0.661 mmol) was added and stirred for 3 h, at room temperature. Upon completion, the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, ethyl acetate→20% methanol in ethyl acetate) afforded the *title compound* as a colourless oil (166 mg, 95%); R_F 0.44 (20% methanol in ethyl acetate); ν_{max}/cm^{-1} (thin film) 2938, 2253, 1721, 1519; δ_H (400 MHz, $CDCl_3$) 8.66 (1H, s, C**H**N), 8.43 (1H, s, C**H**N), 7.30–7.19 (5H, m, 5 × C**H**), 6.91 (1H, s, C**H**$COCH_3$), 6.90 (1H, s, C**H**$COCH_3$), 5.10 (1H, t, *J* = 6.9 Hz, C**H**OH), 3.88 (6H, s, 2 × OC**H₃**), 3.39 (2H, s, C**H₂**CO_2H), 3.22 (2H, d, *J* = 6.9 Hz, C**H₂**CHOH); δ_C (100 MHz, $CDCl_3$) 177.4 (**C**O_2H), 155.6 (**C**N), 155.2 (**C**N), 154.1 (**C**OCH_3), 152.0 (**C**OCH_3), 147.6 (**C**HN), 146.7 (**C**HN), 146.5

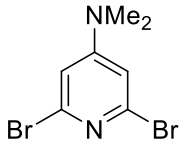
(**C**CN), 132.3 (**C**H), 131.6 (**C**H), 130.6 (**C**), 130.2 (**C**), 129.3 (**C**H), 117.9 (**C**HCOCH$_3$), 116.3 (**C**HCOCH$_3$), 77.0 (**C**HOH), 59.82 (O**C**H$_3$), 58.75 (O**C**H$_3$), 47.5 (**C**H$_2$CHOH), 44.6 (**C**H$_2$CO$_2$H); HRMS (ESI): calcd. for $C_{22}H_{22}N_2NaO_5$, 417.1421. Found: [MNa]$^+$, 417.1417 (0.8 ppm error).

12,13-Dimethoxy-4-phenyl-4,5-dihydro-6,10-(azeno)benzo[*i*][1]oxa[6]azacyclododecin-2-ol (649)



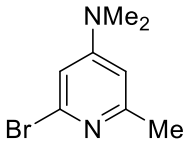
2-(2-(6-(2-Hydroxy-2-phenylethyl)pyrazin-2-yl)-4,5-dimethoxyphenyl)acetic acid (92 mg, 0.232 mmol) was dissolved in $CHCl_3$ (2.3 mL), where DIPEA (73 µL, 0.418 mmol) and T3P (50% solution in ethyl acetate, 208 µL, 0.348 mmol) were added sequentially and stirred at room temperature for 30 min. Upon completion the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, ethyl acetate) afforded the *title compound* as a pink oil (86 mg, 98%); R_F 0.25 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3286, 2937, 1642, 1488; δ_H (400 MHz, $CDCl_3$) 9.41 (1H, s, C**H**N), 7.64 (1H, s, C**H**N), 7.36–7.31 (2H, m, 2 × C**H**), 7.27 (1H, s, C**H**COH), 7.24–7.18 (2H, m, 2 × C**H**), 7.15–7.10 (1H, m, C**H**), 6.75 (1H, s, C**H**COCH$_3$), 6.57 (1H, s, C**H**COCH$_3$), 6.11 (1H, br s, O**H**), 5.10–5.01 (1H, m, O**C**HPh), 3.98 (1H, dd, *J* = 13.7, 9.2 Hz, C**H**H'CHO), 3.89 (3H, s, OC**H$_3$**), 3.88 (3H, s, OC**H$_3$**), 3.77 (1H, dd, *J* = 13.7, 3.8 Hz, CH**H'**CHO); δ_C (100 MHz, $CDCl_3$) 158.6 (**C**OH), 154.8 (CH$_3$O**C**), 149.0 (CH$_3$O**C**), 146.3 (**C**HN), 144.6 (**C**), 138.0 (**C**HN), 137.9 (**C**), 135.2 (**C**N), 132.0 (**C**N), 128.4 (**C**H), 127.4 (**C**H), 125.7 (**C**H), 112.0 (**C**), 108.7 (**C**HCOCH$_3$), 102.1 (**C**HCOCH$_3$), 99.8 (**C**HCOH), 74.5 (**C**H$_2$O), 56.3 (O**C**H$_3$), 56.1 (O**C**H$_3$), 42.2 (**C**H$_2$CH); HRMS (ESI): calcd. for $C_{22}H_{21}N_2O_4$, 377.1496. Found: [MH]$^+$, 377.1501 (−1.3 ppm error).

2,6-Dibromo-4-dimethylaminopyridine (651)



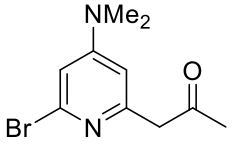
2,6-Dibromo-4-aminopyridine (1.8 g, 7.15 mmol) was dissolved in THF (35 mL) and DMF (35 mL) and cooled to 0 °C. Sodium Hydride (60% in mineral oil, 630 mg, 15.7 mmol) was added and stirred for 10 min. Methyl iodide (980 µL, 15.7 mmol) was then added and the solution was warmed to room temperature and stirred for 2 h. Upon completion, water (25 mL) was added and diluted with diethyl ether (100 mL). The aqueous phase was then extracted with diethyl ether (3 × 50 mL), dried over $MgSO_4$, filtered and the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 50% diethyl ether in hexanes) afforded the *title compound* as a colourless oil (1.94 g, 97%); R_F 0.48 (50% ethyl acetate in hexanes); δ_H (400 MHz, $CDCl_3$) 6.57 (2H, s, 2 × C**H**), 2.96 (6H, s, 2 × NC**H$_3$**). Data is consistent with those reported in the literature.[136]

2-Bromo-6-methyl-4-dimethylaminopyridine (652)



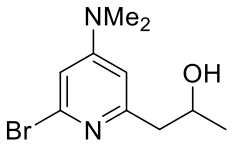
2,6-Dibromo-4-dimethylaminopyridine (400 mg, 1.43 mmol) was dissolved in anhydrous THF (14.2 mL) and cooled to −78 °C. *n*-BuLi (1.6 m, 1.00 mL, 1.6 mmol) was added dropwise and stirred for 1 h, before methyl iodide (134 µL, 2.15 mmol) was added and stirred, at −78 °C for 4 h. The solution was then slowly warmed to room temperature and quenched with sat. $NH_4Cl_{(aq)}$ solution (10 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 50% diethyl ether in hexanes) afforded the *title compound* as a colourless oil (211 mg, 69%); R_F 0.43 (50% ethyl acetate in hexanes); δ_H (400 MHz, $CDCl_3$) 6.48 (1H, d, *J* = 2.3 Hz, C**H**), 6.27 (1H, d, *J* = 2.3 Hz, C**H**), 2.95 (6H, s, 2 × NC**H₃**), 2.38 (3H, s, CC**H₃**); δ_C (100 MHz, $CDCl_3$) 158.7 (**C**NMe_2), 156.1 (**C**CH_3), 142.3 (**C**Br), 106.8 (**C**H), 105.1 (**C**H), 39.3 (N(**C**H_3)$_2$), 24.5 (**C**H_3). Data is consistent with those reported in the literature.[160]

1-(6-Bromo-4-(dimethylamino)pyridin-2-yl)propan-2-one (653)



N,N-Diisopropylamine (302 µL, 2.14 mmol) was dissolved in THF (10.7 mL) and cooled to 0 °C before *n*-BuLi (1.6 m solution in hexanes, 1.34 mL, 2.14 mmol) was added dropwise and stirred for 30 min. The LDA solution was then cooled to −78 °C, where a solution of 2-bromo-6-methyl-4-dimethylaminopyridine (230 mg, 1.07 mmol) was added dropwise and stirred for 30 min. *N*-Methoxy-*N*-methylacetamide (228 µL, 2.14 mmol) was added and stirred for a further 30 min at −78 °C before slowly warming to room temperature. The solution was then quenched with sat. $NH_4Cl_{(aq)}$ (10 mL) and extracted with ethyl acetate (3 × 50 mL) and washed with brine (10 mL). The combined organic extracts were dried over $MgSO_4$, filtered and removed *in vacuo*. Purification by flash column chromatography (SiO_2, diethyl ether) afforded the *title compound* as a colourless oil (234 mg, 85%); R_F 0.56 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 2918, 1713, 1592, 1522; δ_H (400 MHz, $CDCl_3$) 6.52 (1H, d, *J* = 2.3 Hz, C**H**), 6.30 (1H, d, *J* = 2.3 Hz, C**H**), 3.71 (2H, s, C**H₂**CO), 2.94 (6H, s, 2 × NC**H₃**), 2.19 (3H, s, COC**H₃**); δ_C (100 MHz, $CDCl_3$) 205.4 (**C**O), 156.1 (**C**N), 154.7 (**C**N), 142.4 (**C**Br), 107.8 (**C**HCNMe_2), 106.1 (**C**HCNMe_2), 53.0 (**C**H_2CO), 39.3 (N(**C**H_3)$_2$), 29.9 (**C**H_3CO); HRMS (ESI): calcd. for $C_{10}H_{14}{}^{79}BrN_2O$, 257.0284. Found: $[MH]^+$, 257.0282 (0.9 ppm error).

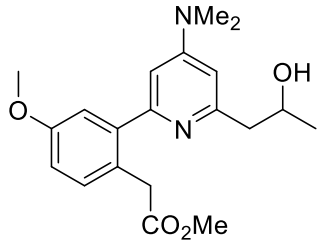
1-(6-Bromo-4-(dimethylamino)pyridin-2-yl)propan-2-ol (654)



1-(6-Bromo-4-(dimethylamino)pyridin-2-yl)propan-2-one (56.0 mg, 0.218 mmol) was dissolved in methanol (2.2 mL) and cooled to 0 °C. Sodium borohydride (25.0 mg, 0.653 mmol) was added portionwise and stirred at

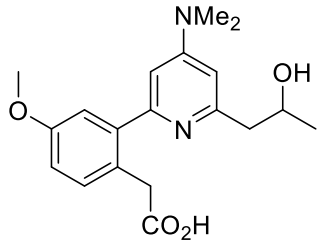
0 °C for 1 h, then allowed to warm to room temperature. Upon completion, the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 50% diethyl ether in hexanes→ethyl acetate) afforded the *title compound* as a colourless oil (54 mg, 96%); R_F 0.42 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3368, 2966, 2926, 1596, 1524; δ_H (400 MHz, $CDCl_3$) 6.50 (1H, d, *J* = 2.3 Hz, C**H**CNMe$_2$), 6.25 (1H, d, *J* = 2.3 Hz, C**H**CNMe$_2$), 4.30 (1H, br s, O**H**), 4.20–4.10 (1H, m, C**H**OH), 2.96 (6H, s, 2 × NC**H$_3$**), 2.72 (1H, dd, *J* = 14.5, 3.0 Hz, C**H**H'CHOH), 2.64 (1H, dd, *J* = 14.5, 8.4 Hz, CH**H'**CHOH), 1.22 (3H, d, *J* = 6.1 Hz, CHC**H$_3$**); δ_C (100 MHz, $CDCl_3$) 160.2 (**C**NMe$_2$), 156.1 (**C**N), 142.0 (**C**Br), 107.4 (**C**HC), 105.4 (**C**HC), 67.1 (**C**HOH), 45.5 (**C**H$_2$CHOH), 39.3 (**C**H$_3$N), 23.0 (**C**H$_3$CH); HRMS (ESI): calcd. for $C_{10}H_{16}{}^{79}BrN_2O$, 259.0441. Found: $[MH]^+$, 259.0442 (−0.4 ppm error).

Methyl 2-(2-(4-(dimethylamino)-6-(2-hydroxypropyl)pyridin-2-yl)-4-methoxyphenyl)acetate (656)



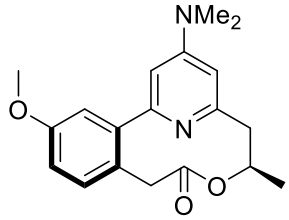
1-(6-Bromo-4-(dimethylamino)pyridin-2-yl)propan-2-ol (215 mg, 0.830 mmmol), methyl 2-(4-methoxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate (398 mg, 1.24 mmol), potassium phosphate (352 mg, 1.66 mmol) and $PdCl_2$(dppf).CH_2Cl_2 (34 mg, 41.5 µmmol) were dissolved in THF (8.3 mL) under a nitrogen atmosphere. H_2O (75 µL, 4.15 mmol) was added and the solution heated, at reflux, to 80 °C for 18 h. Upon completion, the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, ethyl acetate →10% methanol in ethyl acetate) afforded the *title compound* as an orange oil (86 mg, 29%); R_F 0.10 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3327, 2929, 1734, 1597, 1541, 1503; δ_H (400 MHz, $CDCl_3$) 7.21 (1H, d, *J* = 8.4 Hz, C**H**), 6.94 (1H, d, *J* = 3.1 Hz, C**H**), 6.86 (1H, dd, *J* = 8.4, 3.1 Hz, C**H**), 6.50 (1H, d, *J* = 2.3 Hz, C**H**CNMe$_2$), 6.28 (1H, d, *J* = 2.3 Hz, C**H**CNMe$_2$), 4.18 (1H, br s, C**H**OH), 3.78 (3H, s, COC**H$_3$**), 3.71 (1H, d, *J* = 16.0 Hz, C**H**H'CO_2Me), 3.64 (1H, d, *J* = 16.0 Hz, CH**H'**CO_2Me), 3.57 (3H, s, CO_2C**H$_3$**), 2.98 (6H, s, 2 × NC**H$_3$**), 2.79 (1H, dd, *J* = 14.5, 3.1 Hz, C**H**H'CHOH), 2.71 (1H, dd, *J* = 14.5, 9.2 Hz, CH**H'**CHOH), 1.23 (3H, d, *J* = 6.1 Hz. CHC**H$_3$**); δ_C (100 MHz, $CDCl_3$) 171.8 (**C**O$_2$Me), 158.6 (MeO**C**), 157.4 (Me$_2$N**C**), 157.2 (**C**N), 154.2 (**C**N), 141.7 (**C**CN), 131.0 (**C**HCCH$_2$CO$_2$Me), 123.3 (**C**CH$_2$CO$_2$Me), 114.0 (**C**HCOMe), 112.8 (**C**HCOMe), 104.2 (**C**HCN), 103.4 (**C**HCN), 66.2 (**C**HOH), 54.4 (CO**C**H$_3$), 50.9 (CO_2**C**H$_3$), 44.5 (**C**H$_2$CHOH), 38.2 (N(**C**H$_3$)$_2$), 37.3 (**C**H$_2$CO$_2$Me), 23.8 (CH**C**H$_3$); HRMS (ESI): calcd. for $C_{20}H_{27}N_2O_4$, 359.1965. Found: $[MH]^+$, 359.1974 (2.5 ppm error).

2-(2-(4-(Dimethylamino)-6-(2-hydroxypropyl)pyridin-2-yl)-4-methoxyphenyl)acetic acid (657)



Methyl 2-(2-(4-(dimethylamino)-6-(2-hydroxypropyl)pyridin-2-yl)-4-methoxyphenyl)acetate (82.0 mg, 0.220 mmol) was dissolved in THF (0.66 mL) and $LiOH_{(aq)}$ (0.5 m, 0.66 mL, 0.330 mmol) and stirred at room temperature for 3 h. Upon completion, the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, ethyl acetate→50% methanol in ethyl acetate) afforded the *title compound* as a yellow oil (63 mg, 83%); R_F 0.25 (50% methanol in ethyl acetate); ν_{max}/cm^{-1} (thin film) 3279, 2967, 1624, 1541, 1510; δ_H (400 MHz, $CDCl_3$) 7.42 (1H, d, *J* = 8.4 Hz, C**H**), 6.99–6.92 (2H, m, 2 × C**H**), 6.58 (1H, d, *J* = 2.3 Hz, C**H**CNMe$_2$), 6.55 (1H, d, *J* = 2.3 Hz, C**H**CNMe$_2$), 4.22–4.13 (1H, m, C**H**OH), 3.81 (3H, s, OC**H$_3$**), 3.49 (2H, s, C**H$_2$**CO$_2$H), 3.16 (6H, s, 2 × NC**H$_3$**), 2.97 (1H, dd, *J* = 13.7, 4.6 Hz, C**H**H'CHOH), 2.90 (1H, dd, *J* = 13.7, 7.6 Hz, CH**H'**CHOH), 1.26 (3H, d, *J* = 6.1 Hz, CHC**H$_3$**); δ_C (100 MHz, $CDCl_3$) 175.9 (**C**O$_2$H), 158.3 (**C**OCH$_3$), 156.8 (**C**NMe$_2$), 154.1 (**C**N), 153.7 (**C**N), 136.1 (**C**CN), 132.6 (**C**HCHCOCH$_3$), 127.5 (**C**CH$_2$CO$_2$H), 116.2 (**C**HCOCH$_3$), 115.0 (**C**HCOCH$_3$), 106.1 (**C**HCNMe$_2$), 105.0 (**C**HCNMe$_2$), 67.4 (**C**HOH), 55.5 (O**C**H$_3$), 44.1 (**C**H$_2$CHOH), 42.2 (**C**H$_2$CO$_2$H), 39.8 (N(**C**H$_3$)$_2$), 23.1 (CH**C**H$_3$); HRMS (ESI): calcd. for $C_{19}H_{25}N_2O_4$, 345.1809. Found: $[MH]^+$, 345.1812 (−1.0 ppm error).

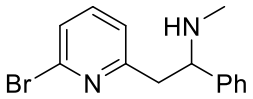
8-(Dimethylamino)-12-methoxy-4-methyl-4,5-dihydro-6,10-(azeno)benzo[*d*][1]oxacyclododecin-2(1*H*)-one (658)



2-(2-(4-(Dimethylamino)-6-(2-hydroxypropyl)pyridin-2-yl)-4-methoxyphenyl)acetic acid (58.0 mg, 0.168 mmol) was dissolved in $CHCl_3$ (1.7 mL) where DIPEA (53.0 µL, 0.303 mmol) and T3P (50% solution in ethyl acetate, 150 µL, 0.253 mmol) were added sequentially at room temperature and stirred for 30 min. Upon completion the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, diethyl ether→5% methanol in diethyl ether) afforded the *title compound* as a colourless oil (51 mg, 92%); R_F 0.10 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 2928, 2244, 1721, 1597; δ_H (400 MHz, $CDCl_3$) 7.28 (1H, d, *J* = 3.0 Hz, C**H**), 7.24 (1H, d, *J* = 8.4 Hz, C**H**), 6.88 (1H, dd, *J* = 8.4, 3.0 Hz, C**H**), 6.68 (1H, d, *J* = 1.5 Hz, C**H**CNMe$_2$), 6.27 (1H, d, *J* = 1.5 Hz, C**H**CNMe$_2$), 5.50–5.39 (1H, m, C**H**OH), 3.85 (3H, s, O**C**H$_3$), 3.59 (1H, d, *J* = 14.5 Hz, C**H**H'CO$_2$), 3.43 (1H, d, *J* = 14.5 Hz, CH**H'**CO$_2$), 3.03 (6H, s, 2 × NC**H$_3$**), 2.95 (1H, dd, *J* = 16.0, 3.8 Hz, C**H**H'CH), 2.87 (1H, dd, *J* = 14.5, 9.9 Hz, CH**H'**CH), 1.44 (3H, d, *J* = 6.1 Hz, CHC**H$_3$**); δ_C (100 MHz, $CDCl_3$) 171.8 (**C**O$_2$CH), 158.7 (MeO**C**), 155.9 (Me$_2$N**C**), 155.8 (**C**N), 155.0 (**C**N), 138.7 (**C**), 134.0 (**C**H), 127.5 (**C**), 114.3 (**C**HCOMe), 113.0 (**C**HCOMe), 104.1 (**C**HCNMe$_2$), 102.1 (**C**HCNMe$_2$), 70.4 (O**C**HCH$_3$), 55.5 (O**C**H$_3$), 42.2 (**C**H$_2$CH), 41.0

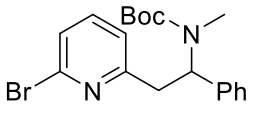
(**C**H_2CO_2), 39.5 (N(**C**$H_3)_2$), 21.4 (CH**C**H_3); HRMS (ESI): calcd. for $C_{19}H_{23}N_2O_3$, 327.1703. Found: $[MH]^+$, 327.1705 (−0.6 ppm error).

2-(6-Bromopyridin-2-yl)-*N*-methyl-1-phenylethan-1-amine (660)



N,N-Diisopropylamine (734 µL, 5.25 mmol) was dissolved in THF (12 mL) and cooled to 0 °C before *n*-BuLi (1.6 m solution in hexanes, 3.28 mL, 5.25 mmol) was added dropwise and stirred for 30 min. The LDA solution was then cooled to −78 °C, where 2-bromo-6-methylpyridine (296 µL, 2.63 mmol) was added dropwise and stirred for 30 min. *N*-Benzylidenemethylamine (656 µL, 5.25 mmol) was added and stirred for a further 30 min at −78 °C before slowly warming to room temperature. The solution was then quenched with sat. $NH_4Cl_{(aq)}$ (15 mL) and extracted with ethyl acetate (3 × 50 mL) and washed with brine (10 mL). The combined organic extracts were dried over $MgSO_4$, filtered and removed *in vacuo*. Purification by flash column chromatography (SiO_2, 50% ethyl acetate in hexane → ethyl acetate) afforded the *title compound* as a yellow oil (749 mg, 97%); R_F 0.15 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3027, 2791; 1582, 1552; δ_H (400 MHz, $CDCl_3$) 7.36–7.17 (7H, m, Ar**H**), 6.84 (1H, d, *J* = 7.9 Hz, Ar**H**), 3.96 (1H, dd, *J* = 8.4, 6.1 Hz, C**H**NHMe), 3.10 (1H, dd, *J* = 13.7, 8.4 Hz, C**H**H'CHPh), 2.98 (1H, dd, *J* = 13.7, 6.1 Hz, CH**H'**CHPh), 2.23 (3H, s, NHC**H₃**); δ_C (100 MHz, $CDCl_3$) 160.7 (**C**CH_2), 142.8 (**C**Br), 141.5 (**C**CHNH), 138.4 (**C**H), 128.3 (**C**H), 127.3 (**C**H), 127.2 (**C**H), 125.7 (**C**H), 122.8 (**C**H), 65.0 (**C**HNH), 46.4 (**C**H_2CH), 34.5 (**C**H_3NH); HRMS (ESI): calcd. for $C_{14}H_{16}{}^{79}BrN_2$, 291.0491. Found: $[MH]^+$, 291.0491 (1.3 ppm error).

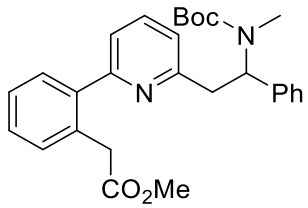
***t*-Butyl (2-(6-bromopyridin-2-yl)-1-phenylethyl)(methyl)carbamate (661)**



2-(6-Bromopyridin-2-yl)-N-methyl-1-phenylethan-1-amine (670 mg, 2.30 mmol) and DMAP (28 mg, 0.231 mmol) was dissolved in anhydrous CH_2Cl_2 (23 mL) and triethylamine (385 µL, 2.76 mmol) was added. The solution was cooled to 0 °C before Boc_2O (603 mg, 2.76 mmol) was added portionwise, and the solution warmed to room temperature and stirred for 18 h. Upon completion, the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 50% ethyl acetate in hexanes) afforded the *title compound* (as a 2:1 mixture of rotamers) as a yellow oil (882 mg, 98%); R_F 0.67 (50% ethyl acetate in hexanes); ν_{max}/cm^{-1} (thin film) 2981, 1784, 1722, 1583, 1555; δ_H (400 MHz, $CDCl_3$) 7.48 (2H, t, *J* = 7.6 Hz, C**H**, both rotamers), 7.42–7.24 (14H, m, 7 × C**H**, both), 5.78 (1H, dd, *J* = 9.9, 6.9 Hz, C**H**NHCH_3, major rotamer), 5.66 (1H, dd, *J* = 10.7, 4.6 Hz, C**H**NCH_3, minor rotamer),3.58–3.27 (4H, m, C**H₂**CH, both), 2.71 (6H, s, NC**H₃**, both), 1.61 (9H, s, 3 × C**H₃**, minor), 1.49 (9H, s, 3 × C**H₃**, major); δ_C (100 MHz, $CDCl_3$) data for the major rotamer only: 159.2 (**C**N), 150.5 (**C**$O_2{}^t$Bu), 147.4 (**C**Br), 141.4 (**C**), 139.0 (**C**H), 128.7 (**C**H), 128.1 (**C**H), 127.6 (**C**H), 126.2

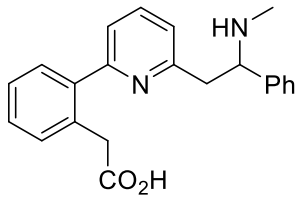
(**C**H), 122.0 (**C**H), 84.7 (**C**CH_3), 58.9 (**C**HNCH_3), 38.2 (**C**H_2CHNCH_3), 30.8 (N**C**H_3), 27.5 (C(**C**H_3)$_3$); HRMS (ESI): calcd. for $C_{19}H_{23}{}^{79}BrN_2NaO_2$, 413.0836. Found: $[MNa]^+$, 413.0832 (0.7 ppm error).

Methyl 2-(2-(6-(2-((*tert*-butoxycarbonyl)(methyl)amino)-2-phenylethyl)pyridin-2-yl)phenyl)acetate (662)



t-Butyl (2-(6-bromopyridin-2-yl)-1-phenylethyl)(methyl)carbamate (410 mg, 1.18 mmol), methyl 2-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate (487 mg, 1.76 mmol), potassium phosphate (500 mg, 2.36 mmol) and $PdCl_2$(dppf).CH_2Cl_2 (48.0 mg, 58.8 µmol) were dissolved in THF (11.7 mL) under a nitrogen atmosphere. H_2O (106 µL, 5.88 mmol) was added and the solution heated, at reflux, to 80 °C for 18 h. Upon completion, the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 20% ethyl acetate in hexanes→33% ethyl acetate in hexanes) afforded the *title compound* (as a 4:5 mixture of rotamers) as a yellow oil (207 mg, 39%); R_F 0.69 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 1736, 1686, 1570, 1448; δ_H (400 MHz, $CDCl_3$) 7.66 (2H, t, *J* = 7.6 Hz, C**H**, both rotamers), 7.52–7.04 (22H, m, 11 × C**H**, both), 5.98 (1H, br s, C**H**NMe, minor rotamer), 5.71 (1H, br s, C**H**NMe, major rotamer), 3.95–3.67 (4H, m, C**H**$_2$$CO_2$Me, both), 3.61–3.31 (10H, m, C**H**$_2$CHNMe and OC**H**$_3$, both), 2.74–2.54 (6H, m, NC**H**$_3$, both), 1.45–1.15 (18H, m, C(C**H**$_3$)$_3$, both); δ_C Data for the major rotamer only (100 MHz, $CDCl_3$) 172.4 (**C**O_2Me), 158.9 (**C**N), 158.0 (**C**N), 155.7 (**C**$O_2{}^t$Bu), 140.3 (**C**), 136.8 (**C**), 132.4 (**C**H), 131.5 (**C**), 131.3 (**C**H), 129.9 (**C**H), 128.4 (**C**H), 127.5 (**C**H), 127.4 (**C**H), 127.3 (**C**H), 127.1 (**C**H), 121.6 (**C**H), 121.3 (**C**H), 51.7 (**C**HNMe), 39.5 (O**C**H_3), 38.9 (N**C**H_3), 29.1 (**C**H_2CHN), 28.3 (**C**H_2CO_2Me), 22.6 (**C**CH_3), 14.1 (C(**C**H_3)$_3$); HRMS (ESI): calcd. for $C_{28}H_{33}N_2O_4$, 461.2435. Found: $[MH]^+$, 461.2433 (0.8 ppm error).

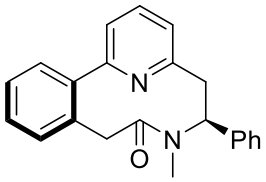
2-(2-(6-(2-(Methylamino)-2-phenylethyl)pyridin-2-yl)phenyl)acetic acid (664)



Methyl 2-(2-(6-(2-((*tert*-butoxycarbonyl)(methyl)amino)-2-phenylethyl)pyridin-2-yl)phenyl)acetate (187 mg, 0.406 mmol) was dissolved in 1,4-dioxane (1.6 mL) and methanol (1.6 mL) where HCl (4.0 m in dioxane, 1.52 mL, 6.08 mmol) was added and stirred at room temperature for 18 h. Upon completion the solution was diluted with ethyl acetate (50 mL) and neutralised using 2 m $NaOH_{(aq)}$. The aqueous layer was extracted with ethyl acetate (3 × 50 mL), and the combined organic extracts were dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude material (140 mg, 0.388 mmol) was dissolved in THF (3.1 mL) and $LiOH_{(aq)}$ (0.5 m, 3.1 mL, 1.55 mmol) was added and the solution was stirred at room temperature for 18 h. Upon completion, the solvent was removed *in vacuo*. Purification by flash column

chromatography (SiO_2, 50% methanol in ethyl acetate) afforded the *title compound* as a white foam (100 mg, 71% over both steps); R_F 0.15 (50% methanol in ethyl acetate); ν_{max}/cm^{-1} (thin film) 3349, 1563, 1415; δ_H (400 MHz, $CDCl_3$) 7.73 (1H, t, *J* = 7.6 Hz, C**H**), 7.50–7.29 (10H, m, 10 × C**H**), 7.12 (1H, d, *J* = 7.6 Hz, C**H**), 4.74–4.66 (1H, m, C**H**NH), 3.64 (1H, dd, *J* = 15.3, 7.6 Hz, C**H**H'CHPh *),* 3.61 (1H, d, *J* = 15.3 Hz, C**H**H'CO_2H), 3.51 (1H, d, *J* = 15.3 Hz, CH**H'**CO_2H), 3.38 (1H, dd, *J* = 15.3, 6.1 Hz, CH**H'**CHPh), 3.32–3.28 (1H, m, N**H**), 2.46 (3H, s, NHC**H₃**); δ_C (100 MHz, $CDCl_3$) 179.0 (**C**O_2H), 160.1 (**C**N), 155.9 (**C**N), 140.4 (**C**), 138.2 (**C**H), 136.3 (**C**), 135.3 (**C**), 131.9 (**C**H), 129.8 (**C**H), 129.6 (**C**H), 129.5 (**C**H), 128.8 (**C**H), 128.6 (**C**H), 126.7 (**C**H), 123.3 (**C**H), 122.9 (**C**H), 63.5 (**C**HNH), 43.3 (**C**H_2CH), 41.2 (**C**H_2CO_2H), 31.0 (N**C**H_3); HRMS (ESI): calcd. for $C_{22}H_{22}N_2O_2$, 347.1754. Found: $[MH]^+$, 347.1758 (−1.0 ppm error).

3-Methyl-4-phenyl-4,5-dihydro-1H-6,10-(azeno)benzo[d][1]azacyclododecin-2(3H)-one (665)



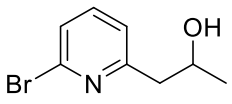
To a stirring solution of 2-(2-(6-(2-(methylamino)-2-phenylethyl)pyridin-2-yl)phenyl)acetic acid (50.0 mg, 0.143 mmol) in chloroform (1.5 mL), was added diisopropylethylamine (45.0 µL, 0.260 mmol) followed by the addition of T3P (50% solution in ethyl acetate, 129 µL, 0.216 mmol). Upon the addition of T3P, the solution rapidly changed from a colourless to an orange solution. After stirring for 30 min at room temperature, the solution was taken directly to purification with no work-up. Purification by flash column chromatography (SiO_2, ethyl acetate → 10% methanol in ethyl acetate) afforded the *title compound* (as a 8.7:1 mixture of rotamers) as a colourless oil (24 mg, 50%); R_F 0.55 (ethyl acetate); δ_H (400 MHz, $CDCl_3$) data for the major rotamer only: 7.95–7.89 (1H, m, C**H**), 7.75–7.69 (1H, m, C**H**), 7.67–7.62 (1H, m, C**H**), 7.46–7.39 (1H, m, C**H**), 7.37–7.32 (2H, m, 2 × C**H**), 7.29–7.19 (3H, m, 3 × C**H**), 7.03 (1H, d, *J* = 6.9 Hz, C**H**), 6.80–6.67 (2H, m, 2 × C**H**), 5.42–5.33 (1H, m, C**H**NMe), 5.29 (1H, d, *J* = 13.7 Hz, C**H**H'CO), 3.44 (1H, d, *J* = 13.7 Hz, CH**H'**CO), 2.97–2.91 (2H, m, C**H₂**CHNMe) 2.31 (3H, s, NCH_3); δ_C (100 MHz, $CDCl_3$) data for the major rotamer only: 173.8 (**C**ONMe), 155.8 (**C**N), 154.5 (**C**N), 137.2 (**C**), 136.4 (**C**H), 136.3 (**C**), 134.7 (**C**), 129.4 (**C**H), 128.2 (**C**H), 128.1 (**C**H), 127.4 (**C**H), 126.2 (**C**H), 126.0 (**C**H), 125.6 (**C**H), 119.1 (**C**H), 116.1 (**C**H), 52.3 (**C**HNMe), 42.4 (**C**O_2NMe), 38.8 (**C**H_2CHNMe), 28.7 (N**C**H_3); HRMS (ESI): calcd. for $C_{22}H_{20}N_2NaO$, 351.1468. Found: $[MNa]^+$, 351.1470 (–0.5 ppm error).

High Dilution Method

To a stirring solution of 2-(2-(6-(2-(methylamino)-2-phenylethyl)pyridin-2-yl)phenyl)acetic acid (50.0 mg, 0.143 mmol) in chloroform (143 mL), was added diisopropylethylamine (45.0 µL, 0.260 mmol) followed by the addition of T3P (50% solution in ethyl acetate, 129 µL, 0.216 mmol). Upon

the addition of T3P, the solution rapidly changed from a colourless to an orange solution. After stirring for 3 h at room temperature, the solution was taken directly to purification with no work-up. Purification by flash column chromatography (SiO_2, diethyl ether → 10% methanol in ethyl acetate) afforded the *title compound* as a colourless oil (36 mg, 78%).

1-(6-Bromopyridin-2-yl)propan-2-ol (666)



Procedure for reduction with $NaBH_4$

1-(6-Bromopyridin-2-yl)propan-2-one (100 mg, 0.467 mmol) was dissolved in methanol (4.7 mL) and cooled to 0 °C. Sodium borohydride (53 mg, 1.40 mmol) was added portionwise and then allowed to warm to room temperature, and stirred for 1 h. Upon completion, the solvent was removed *in vacuo*. Purification by column chromatography (SiO_2, diethyl ether) afforded the *title compound* as a yellow oil (88 mg, 87%); R_F 0.50 (ethyl acetate); δ_H (400 MHz, $CDCl_3$) 7.45 (1H, t, *J* = 7.6 Hz, C**H**), 7.31 (1H, d, *J* = 7.6 Hz, C**H**), 7.10 (1H, d, *J* = 7.6 Hz, C**H**), 4.26–4.16 (1H, m, C**H**OH), 3.71 (1H, br s, O**H**), 2.86 (1H, dd, *J* = 14.5, 3.8 Hz, C**H**H'COH), 2.80 (1H, dd, *J* = 14.5, 8.4 Hz, CH**H'**COH), 1.24 (3H, d, *J* = 6.1 Hz, C**H$_3$**). Data is consistent with those available from commercial sources.

Procedure for reduction with Jacobsen's catalyst

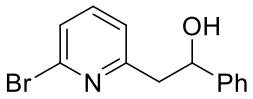
A solution of sodium borohydride (29 mg, 0.75 mmol) and furfuryl alcohol (727 µL, 7.5 mmol) dissolved in ethanol (44 µL, 0.75 mmol) and chloroform (1.5 mL) was prepared under inert conditions and cooled to −20 °C. The pre-made solution was then added dropwise, *via* cannula, to a solution of 1-(6-bromopyridin-2-yl)propan-2-one (137 mg, 0.50 mmol) with Jacobsen's catalyst (13 mg, 4 mol%) in chloroform (4 mL) at −20 °C, under a nitrogen atmosphere. The solution was then stirred at −20 °C for 18 h. Upon completion, the solution was quenched with sat. $NH_4Cl_{(aq)}$ solution (10 mL), extracted with CH_2Cl_2 (3 × 50 mL), washed with brine (10 mL), dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. Purification by column chromatography (SiO_2, diethyl ether) afforded the *title compound* as a colourless oil (31 mg, 19%). Data is consistent with those reported above.

Procedure for reduction with $LiAlH_4$ and menthol

Lithium aluminium hydride (38 mg, 1 mmol) and L-(−)-menthol (782 mg, 5 mmol) was dissolved in anhydrous THF (5 mL) and ethanol (88 µL, 1 mmol), and stirred for 1 h at −20 °C. A solution of 1-(6-bromopyridin-2-yl)propan-2-one (137 mg, 0.5 mmol) in THF (1 mL) was added slowly and the solution stirred, at −20 °C, for 2 h. Purification by column chromatography (SiO_2, diethyl

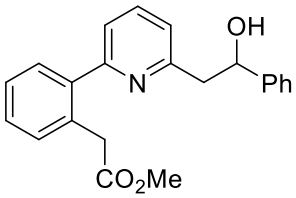
ether) afforded the *title compound* as a yellow oil (88 mg, 82%). Data is consistent with those reported above.

2-(6-Bromopyridin-2-yl)-1-phenylethan-1-ol (668)



N,N-Diisopropylamine (3.67 mL, 26.2 mmol) was dissolved in THF (60 mL) and cooled to 0 °C before *n*-BuLi (1.6 m solution in hexanes, 16.4 mL, 26.2 mmol) was added dropwise and stirred for 30 min. The LDA solution was then cooled to −78 °C, where 2-bromo-6-methylpyridine (1.48 mL, 13.1 mmol) was added dropwise and stirred for 30 min. Benzaldehyde (2.67 mL, 26.2 mmol) was added and stirred for a further 30 min at −78 °C before slowly warming to room temperature. The solution was then quenched with sat. $NH_4Cl_{(aq)}$ (20 mL) and extracted with ethyl acetate (3 × 50 mL) and washed with brine (10 mL). The combined organic extracts were dried over $MgSO_4$, filtered and removed *in vacuo*. Purification by flash column chromatography (SiO_2, 25% ethyl acetate in hexane → ethyl acetate) afforded the *title compound* as a yellow oil (3.02 g, 83%); R_F 0.67 (50% ethyl acetate in hexanes); ν_{max}/cm^{-1} (thin film) 3370, 3062, 3030, 2924, 1584,1553, 1437; δ_H (400 MHz, $CDCl_3$) 7.44 (1H, t, *J* = 7.6 Hz, C**H**), 7.41–7.22 (6H, m, 6 × C**H**), 7.05 (1H, d, *J* = 7.6 Hz, C**H**), 5.19–5.10 (1H, m, C**H**OH), 4.20–4.12 (1H, m, O**H**), 3.18–3.04 (2H, m, C**H₂**CHOH); δ_C (100 MHz, $CDCl_3$) 164.7 (**C**N), 147.4 (**C**Br), 145.1 (**C**), 142.8 (**C**H), 132.3 (**C**H), 131.4 (**C**H), 129.9 (**C**H), 129.6 (**C**H), 126.6 (**C**H), 77.0 (**C**HOH), 49.9 (**C**H_2CHOH); HRMS (ESI): calcd. for $C_{13}H_{12}{}^{79}BrNNaO$, 299.9994. Found: $[MNa]^+$, 299.9994 (0.3 ppm error).

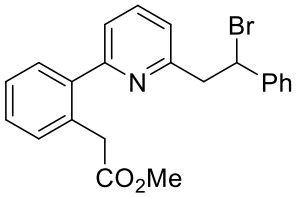
Methyl 2-(2-(6-(2-hydroxy-2-phenylethyl)pyridin-2-yl)phenyl)acetate (669)



2-(6-Bromopyridin-2-yl)-1-phenylethan-1-ol (1.00 g, 3.61 mmol), methyl 2-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl) acetate (1.50 g, 5.41 mmol), potassium phosphate (1.53 g, 7.22 mmol) and $PdCl_2$(dppf).CH_2Cl_2 (16.0 mg, 0.181 mmol) were charged into an RBF purged with nitrogen. THF (36.1 mL) and de-ionised water (324 µL, 18.1 mmol) were added and heated to 80 °C, at reflux, for 18 h. Upon completion the solution was cooled to room temperature, diluted with water (15 mL), extracted with ethyl acetate (3 × 25 mL) and washed with brine (10 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and removed *in vacuo*. Purification by flash column chromatography (SiO_2, CH_2Cl_2 → 1:1 ethyl acetate:hexane) afforded the *title compound* as a yellow oil (898 mg, 72%); R_F 0.39 (1:1 ethyl acetate:hexane); ν_{max}/cm^{-1} (thin film) 3409,3028, 2950, 1735, 1588, 1570; δ_H (400 MHz, $CDCl_3$) 7.69 (1H, t, *J* = 7.6 Hz, C**H**), 7.49–7.22 (10H, m, 10 × C**H**), 7.07 (1H, t, *J* = 8.4 Hz, C**H**), 5.23–5.13 (2H, m, C**H**OH and O**H**), 3.86 (1H, d, *J* = 16.0 Hz, C**H**H'CHOH), 3.78 (1H, d, *J* = 16.0 Hz, CH**H'**CHOH), 3.59 (3H, s, OC**H₃**),

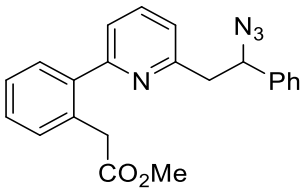
3.19–3.09 (2H, m, C**H₂**CO_2Me); δ_C (100 MHz, $CDCl_3$) 176.2 (**C**O_2Me), 162.8 (**C**N), 162.3 (**C**N), 148.0 (**C**), 144.0 (**C**), 141.2 (**C**H), 136.1 (**C**), 135.3 (**C**H), 133.7 (**C**H), 132.5 (**C**H), 132.2 (**C**H), 132.1 (**C**H), 131.3 (**C**H), 131.0 (**C**H), 129.6 (**C**H), 125.9 (**C**H), 77.0 (**C**HOH), 55.9 (O**C**H_3), 50.1 (**C**H_2CHOH), 43.2 (**C**H_2CO_2Me); HRMS (ESI): calcd. for $C_{22}H_{22}NO_3$, 348.1601. Found: $[MH]^+$, 348.1601 (−1.9 ppm error).

Methyl 2-(2-(6-(2-bromo-2-phenylethyl)pyridin-2-yl)phenyl)acetate (670)



Methyl 2-(2-(6-(2-hydroxy-2-phenylethyl)pyridin-2-yl)phenyl)acetate (800 mg, 2.31 mmol) and tetrabromomethane (841 mg, 2.54 mmol) were dissolved in CH_2Cl_2 (5 mL) and cooled to 0 °C. Triphenylphosphine (665 mg, 2.54 mmol) was added portionwise and the solution allowed to warm to room temperature over 30 min where the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 50% ethyl acetate in hexane) afforded the *title compound* as a yellow oil (896 mg, 95%); R_F 0.58 (50% ethyl acetate in hexane); ν_{max}/cm^{-1} (thin film) 3062, 3030, 2949, 1735, 1584; δ_H (400 MHz, $CDCl_3$) 7.71–7.00 (12H, m, 12 × C**H**), 5.56 (1H, dd, *J* = 9.2, 6.9 Hz, C**H**Br), 3.83 (2H, s, C**H₂**CO_2Me), 3.78–3.60 (2H, m, C**H₂**CHBr), 3.59 (3H, s, OC**H₃**); δ_C (100 MHz, $CDCl_3$) 172.4 (**C**O_2Me), 159.3 (**C**N), 157.0 (**C**N), 141.7 (**C**H), 138.6 (**C**), 136.9 (**C**), 132.4 (**C**), 131.6 (**C**H), 129.6 (**C**H), 128.71 (**C**H), 128.65 (**C**H), 128.4 (**C**H), 127.5 (**C**H), 126.4 (**C**H), 123.0 (**C**H), 122.2 (**C**H), 53.8 (O**C**H_3), 51.9 (**C**HBr), 47.6 (**C**H_2CHBr), 39.2 (**C**H_2CO_2Me); HRMS (ESI): calcd. for $C_{22}H_{21}{}^{79}BrNO_2$, 410.0750. Found: $[MH]^+$, 410.0744 (1.6 ppm error).

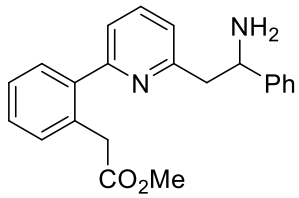
Methyl 2-(2-(6-(2-azido-2-phenylethyl)pyridin-2-yl)phenyl)acetate (671)



Methyl 2-(2-(6-(2-bromo-2-phenylethyl)pyridin-2-yl)phenyl)acetate (350 mg, 0.856 mmol) was dissolved in anhydrous DMF (2.8 mL) and NaN_3 (278 mg, 4.28 mmol) added, under a nitrogen atmosphere, and heater to 100 °C for 1 h. The solution was cooled, diluted with ethyl acetate (50 mL), washed with water (3 × 10 mL) and brine (10 mL). The combined organics were dried over $MgSO_4$, filtered and removed *in vacuo*. Purification by flash column chromatography (SiO_2, 50% ethyl acetate in hexanes) afforded the *title compound* as a yellow oil (225 mg, 71%); R_F 0.60 (50% ethyl acetate in hexane); ν_{max}/cm^{-1} (thin film) 3029, 2949, 2097, 1737, 1583; δ_H (400 MHz, $CDCl_3$) 7.92–6.94 (12H, m, 12 × C**H**), 5.08 (1H, dd, *J* = 8.7, 5.5 Hz, C**H**N_3), 3.83 (2H, s, C**H₂**CO_2Me), 3.58 (3H, s, OC**H₃**), 3.32–3.08 (2H, m, C**H₂**CHN_3); δ_C (100 MHz, $CDCl_3$) 172.3 (**C**O_2Me), 159.2 (**C**N), 156.8 (**C**N), 140.3 (**C**), 139.4 (**C**), 138.7 (**C**), 136.9 (**C**H), 131.6 (**C**H), 129.9 (**C**H), 128.8 (**C**H), 128.6 (**C**H), 128.3 (**C**H), 127.5 (**C**H), 126.9 (**C**H), 122.3 (**C**H),

122.1 (**C**H), 65.7 (**C**N_3), 51.9 (O**C**H_3), 45.0 (**C**H_2CHN_3), 39.3 (**C**H_2CO_2Me); HRMS (ESI): calcd. for $C_{22}H_{21}N_4O_2$, 373.1659. Found: $[MH]^+$, 373.1656 (0.7 ppm error).

Methyl 2-(2-(6-(2-amino-2-phenylethyl)pyridin-2-yl)phenyl)acetate (672)



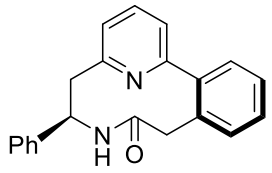
Methyl 2-(2-(6-(2-azido-2-phenylethyl)pyridin-2-yl)phenyl)acetate (175 mg, 0.470 mmol) was dissolved in methanol (5 mL) and placed under a nitrogen atmosphere. Palladium on carbon (47.0 mg, Pd 10% on carbon), was then added and the vessel backfilled with hydrogen (via balloon) several times, then stirred at room temperature under a slight positive pressure of hydrogen (balloon) for 4 h. The reaction was then purged with argon, filtered through Celite, washed with methanol where the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 50% diethyl ether in hexanes → 20% methanol in ethyl acetate) afforded the *title compound* as a yellow oil (89 mg, 55%); R_F 0.25 (20% methanol in ethyl acetate); ν_{max}/cm^{-1} (thin film) 3027, 2923, 1733, 1570, 1553; δ_H (400 MHz, $CDCl_3$) 7.63 (1H, t, *J* = 8.4 Hz, C**H**), 7.47–7.21 (10H, m, 10 × C**H**), 7.02 (1H, d, *J* = 7.6 Hz, C**H**), 4.50 (1H, dd, *J* = 5.3, 9.2 Hz, C**H**NH_2), 3.89 (1H, d, *J* = 16.8 Hz, C**H**H'CO_2CH_3), 3.83 (1H, d, *J* = 16.8 Hz, CH**H'**CO_2CH_3), 3.57 (3H, s, CO_2C**H**$_3$), 3.18 (1H, dd, *J* = 5.3, 13.7 Hz, C**H**H'$CHNH_2$), 3.10 (1H, dd, *J* = 9.2, 13.7 Hz, CH**H'**$CHNH_2$), 2.21 (2H, br s, N**H**$_2$); δ_C (100 MHz, $CDCl_3$) 172.3 (**C**O_2CH_3), 159.0 (**C**N), 158.5 (**C**N), 145.3 (**C**), 140.4 (**C**), 136.8 (**C**H), 132.4 (**C**), 131.5 (**C**H), 129.9 (**C**H), 128.5 (**C**H), 128.4 (2 × C**H**), 127.4 (**C**H), 127.1 (**C**H), 126.5 (2 × C**H**), 122.1 (**C**H), 121.7 (**C**H), 56.0 (**C**HNH_2), 51.9 (CO_2**C**H_3), 47.9 (**C**$H_2CO_2CH_3$), 39.3 (**C**H_2CHNH_2); HRMS (ESI): calcd. for $C_{22}H_{23}N_2O_2$, 347.1754. Found: $[MH]^+$, 347.1754 (0.1 ppm error).

Alternative method via reduction: Methyl 2-(2-(6-(2-azido-2-phenylethyl)pyridin-2-yl)phenyl)acetate **S54** (210 mg, 0.564 mmol) was dissolved in THF/H_2O (40:1 v/v, 5.6 mL) and PPh_3 (192 mg, 0.733 mmol) was added, and heated, at reflux, to 70 °C for 2 h. Once cooled, $NaOH_{(aq)}$ (1.0 m, 10 mL) was added, extracted with ethyl acetate (3 × 25 mL) and washed with brine (5 mL). The combined organics were dried over $MgSO_4$, filtered, and the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 50% ethyl acetate in hexanes→20% methanol in ethyl acetate) afforded the *title compound* (as a 3:2 ratio of diastereomers) as a yellow oil (182 mg, 93%).

The same compound (presumed to be 72% *ee*) was prepared from a diastereomeric mixture (72% *de*) of **677** via the following procedure: methyl 2-(2-(6-(2-(((*S*)-*tert*-butylsulfinyl)amino)-2-phenylethyl)pyridin-2-yl)phenyl)acetate (112 mg, 0.249 mmol) was dissolved in 1,4-dioxane (1 mL) and methanol (1 mL) where HCl in dioxane (4.0 m, 0.93 mL, 3.72 mmol) was added and

stirred at room temperature for 18 h. Upon completion, the solution was diluted with ethyl acetate (50 mL) and neutralised with 2 m $NaOH_{(aq)}$. The aqueous layer was extracted with ethyl acetate (3 × 50 mL), and the combined organic extracts were dried over $MgSO_4$, filtered, and the solvent removed *in vacuo*. Purification by flash column chromatography (SiO_2, diethyl ether→50% methanol in diethyl ether) afforded the *title compound* as a yellow oil (86 mg, 99%). All of the data obtained matched those of the racemic sample above and the optical rotation was also measured: $[\alpha]_D^{298}$ −10.5 (c = 1.0, $CHCl_3$).

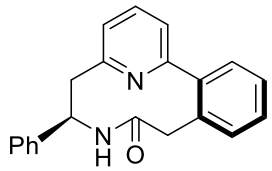
4-Phenyl-4,5-dihydro-1H-6,10-(azeno)benzo[d][1]azacyclododecin-2(3H)-one (674)



To a stirring solution of methyl 2-(2-(6-(2-amino-2-phenylethyl)pyridin-2-yl)phenyl)acetate (55.0 mg, 0.159 mmol) in THF (0.95 mL) was added $LiOH_{(aq)}$ (0.5 m, 0.95 mL, 0.476 mmol). The resulting solution was stirred at room temperature for 18 h, where upon completion the solvent was removed *in vacuo*. The crude salt was passed through a silica plug and eluted with methanol to remove the excess lithium salts and the crude material was used without further purification. The crude material was dissolved in chloroform (159 mL), where diisopropylethylamine (50.0 µL, 0.286 mmol) and T3P (50% solution in ethyl acetate, 142 µL, 0.238 mmol) was added sequentially. Upon the addition of T3P, the solution rapidly changed from a colourless to an orange solution. After stirring for 30 min at room temperature, the solution was taken directly to purification with no work-up. Purification by flash column chromatography (SiO_2, ethyl acetate → 10% methanol in ethyl acetate → 20% methanol in ethyl acetate) afforded the *title compound* (as a 4:1 mixture of rotamers) as a yellow oil (36 mg, 52%); R_F 0.58 (20% methanol in ethyl acetate); ν_{max}/cm^{-1} (thin film) 3288, 2853, 2925, 1646, 1577, 1452; δ_H (400 MHz, $CDCl_3$) 7.99–6.95 (24H, 12 × C**H**, both rotamers), 5.60 (1H, td, *J* = 11.5, 2.8 Hz, C**H**NH, major rotamer), 5.55–5.41 (1H, m, N**H**, major), 5.33–5.25 (1H, m, N**H**, minor rotamer), 4.92 (1H, d, *J* = 13.3 Hz, C**H**NH, minor), 3.86 (1H, d, *J* = 15.1 Hz, C**H**H'CONH, major), 3.72 (1H, d, *J* = 15.1 Hz, CH**H'**CONH, major), 3.69–2.94 (6H, m, C**H₂**CONH, minor and C**H₂**CH, both); δ_C (100 MHz, $CDCl_3$) data for major rotamer only: 176.4 (**C**ONH), 156.4 (**C**N), 155.3 (**C**N), 141.2 (**C**), 137.4 (**C**H), 136.2 (**C**), 135.5 (**C**), 129.4 (**C**H), 128.9 (**C**H), 128.7 (**C**H), 127.5 (**C**H), 126.8 (**C**H), 126.4 (**C**H), 126.2 (**C**H), 120.5 (**C**H), 117.4 (**C**H), 57.3 (**C**HNH), 42.4 (**C**H_2CONH), 29.4 (**C**H_2CHNH); HRMS (ESI): calcd. for $C_{21}H_{18}N_2NaO$, 337.1311. Found: $[MNa]^+$, 337.1310 (0.3 ppm error).

The same compound (71% *ee*) was prepared using the procedure above from an enantioenriched sample of methyl 2-(2-(6-(2-amino-2-phenylethyl)pyridin-2-yl)phenyl)acetate 672 (itself made from **677** - see below). All of the data obtained matched those of the racemic sample above and the optical rotation was also measured: $[\alpha]_D^{298}$ −28.8 (c = 0.5, $CHCl_3$). The *ee*

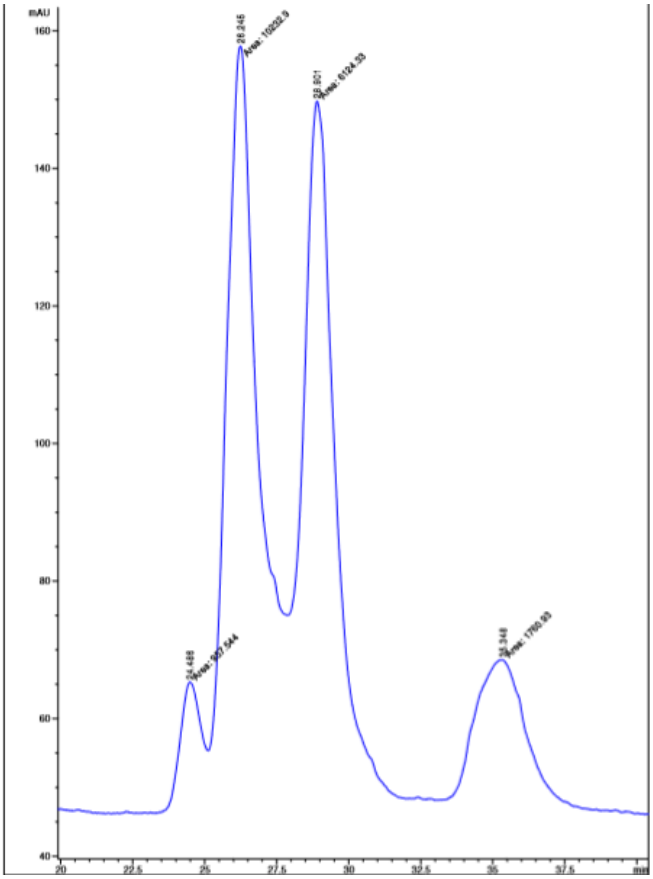
was determined using chiral HPLC as follows. An Agilent HPLC was used alongside an AD-H Chiralpak® column to separate enantiomers. The column temperature was not controlled and a 50 µL injection was completed manually. Diode Array was used to identify the compounds at 5 different wavelengths. For each enantiomerically enriched sample, racemic runs were initially screened to obtain the best separation. As compound **674** exists in two rotameric forms, four peaks in total were obtained (a major and minor enantiomer for each rotameric form). The *ee* of each pair was consistent within experimental error (72% and 70%) and averaged to give an *ee* of 71%.



ee = 71%

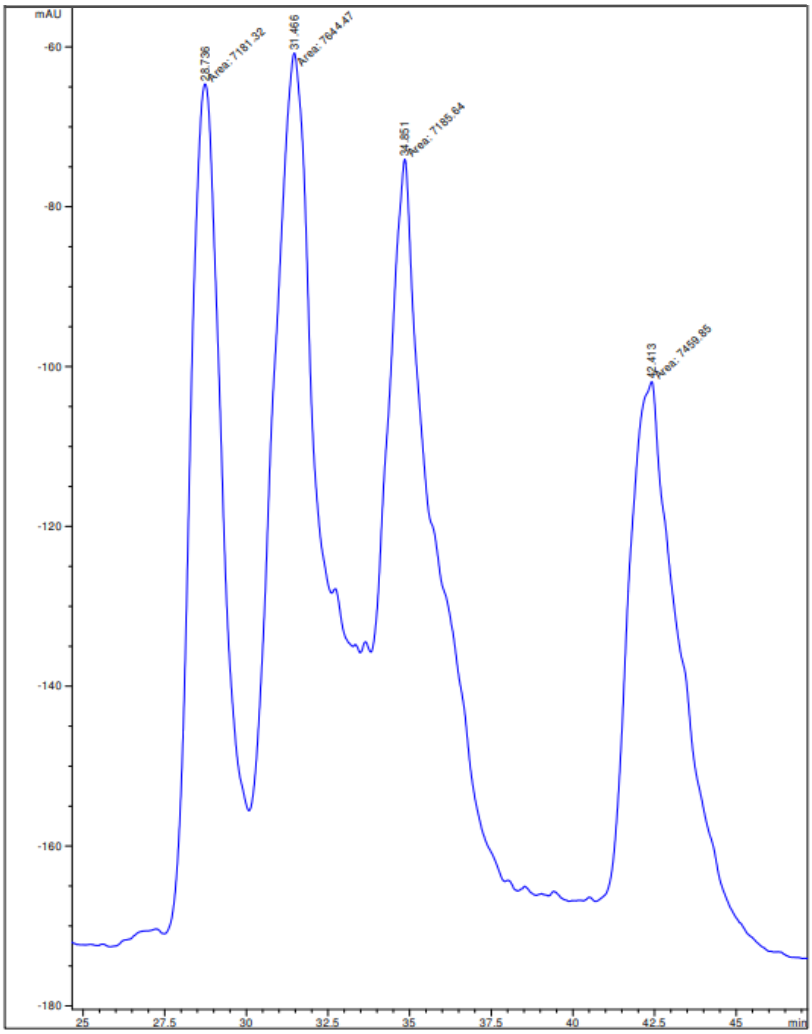
Major enantiomer is drawn, based on the stereochemistry of precursors **672/677**.

HPLC Conditions: AD-H column 80:20 hexane:IPA @ 1.0 mL/min



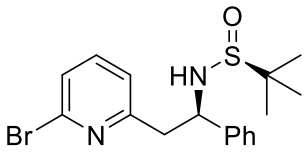
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	24.486	MF	0.8692	957.54443	18.36145	5.0197
2	26.245	MF	1.5545	1.02329e4	109.71237	53.6436
3	28.901	FM	1.0204	6124.33252	100.03528	32.1054
4	35.348	MM	1.6832	1760.92554	17.43647	9.2313

The HPLC trace for a racemic sample of **672** (which had a rotameric ratio) is included below. While we were unable to obtain full separation of all four peaks in either, we believe that the results are sufficient to conform that the enantioenrichment that originates from the Elman's auxiliary derivative **676** and **677** are maintained in the product.



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	28.736	MF	1.1396	7181.32471	105.02475	24.3672
2	31.466	MF	1.1830	7644.46680	107.70275	25.9387
3	34.851	FM	1.2881	7185.63525	92.97271	24.3818
4	42.413	MM	1.8403	7459.84766	67.55851	25.3123

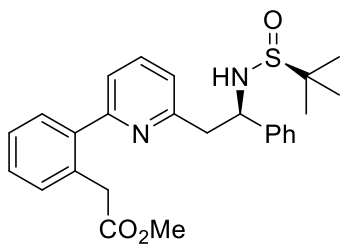
(*S*)-*N*-(2-(6-Bromopyridin-2-yl)-1-phenylethyl)-2-methylpropane-2-sulfinamide (676)



N,N-Diisopropylamine (145 µL, 1.03 mmol) was dissolved in THF (2 mL) and cooled to 0 °C before *n*-BuLi (1.6 m solution in hexanes, 645 µL, 1.03 mmol) was added dropwise and stirred for 30 min. The LDA solution was then cooled to −78 °C, where 2-bromo-6-methylpyridine (59 µL, 0.515 mmol) was added dropwise and stirred for 30 min. Elman's sulfinyl imine (215 mg, 1.03 mmol) was added and stirred for a further 30 min at −78 °C before slowly warming to room temperature. The solution was then quenched with sat. $NH_4Cl_{(aq)}$ (5 mL) and extracted with ethyl acetate (3 × 20 mL) and washed with brine (5 mL). The combined organic extracts were dried over $MgSO_4$,

filtered and removed *in vacuo*. Purification by flash column chromatography (SiO_2, 33% ethyl acetate in hexane → ethyl acetate) afforded the *title compound* (as a 6.1:1 mixture of diastereomers = 72% *de*) as a yellow oil (126 mg, 64%); R_F 0.42 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3217, 2957, 1583, 1552; δ_H (400 MHz, $CDCl_3$) 7.44–7.19 (14H, m, 7 × C**H**, both diastereomers), 6.99 (1H, d, *J* = 7.6 Hz, C**H**, minor diastereomer), 6.92 (1H, d, *J* = 6.9 Hz, C**H**, major diastereomer), 5.56 (1H, br s, N**H**, minor), 4.84 (1H, app dt, *J* = 8.4, 5.3 Hz, C**H**NH, major), 4.72 (1H, ddd, *J* = 9.2, 3.8, 2.3 Hz, C**H**NH, minor), 4.22 (1H, d, *J* = 5.3 Hz, N**H**, major), 3.34 (1H, dd, *J* = 13.7, 8.4 Hz, C**H**H'CHPh, major), 3.19 (1H, dd, *J* = 13.7, 6.9 Hz, CH**H'**CHPh, major), 3.14 (1H, d, *J* = 9.2 Hz, C**H**H'CHPh, minor), 3.08 (1H, dd, *J* = 13.7, 3.8 Hz, CH**H'**CHPh, minor), 1.24 (9H, s, 3 × C**H₃**, minor), 1.10 (9H, s, 3 × C**H₃**, major); δ_C (100 MHz, $CDCl_3$) 159.8 (**C**CH_2, minor diastereomer), 158.7 (**C**CH_2, major diastereomer), 141.6 (**C**Br, minor), 141.4 (**C**Br, major), 141.3 (**C**CHNH, major), 141.2 (**C**CHNH, minor), 139.1 (**C**HCHCBr, minor), 138.5 (**C**HCHCBr, major), 128.5 (**C**H, major), 128.4 (**C**H, minor), 127.74 (**C**H, major), 127.69 (**C**H, minor), 127.3 (**C**H, minor), 127.0 (**C**H, major), 126.3 (**C**H, minor), 125.9 (**C**H, major), 122.9 (**C**H, major), 122.7 (**C**H, minor), 59.4 (**C**HNH, major), 57.8 (**C**HNH, minor), 56.1 (**C**SO, major), 55.6 (**C**SO, minor), 45.4 (**C**H_2, minor), 45.0 (**C**H_2, major), 22.8 (3 × **C**H_3, minor), 22.4 (3 × **C**H_3, major); HRMS (ESI): calcd. for $C_{17}H_{21}{}^{79}BrN_2NaOS$, 403.0450. Found: $[MNa]^+$, 403.0449 (0.2 ppm error).

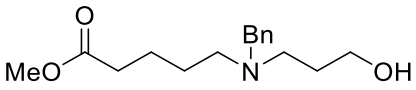
Methyl 2-(2-(6-(2-(((*S*)-*tert*-butylsulfinyl)amino)-2-phenylethyl)pyridin-2-yl)phenyl)acetate (677)



(*S*)-*N*-(2-(6-Bromopyridin-2-yl)-1-phenylethyl)-2-methylpropane-2-sulfinamide (96.0 mg, 0.252 mmol), methyl 2-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate (104 mg, 0.378 mmol), potassium phosphate (107 mg, 0.504 mmol) and $PdCl_2(dppf).CH_2Cl_2$ (10.0 mg, 12.6 µmol) were dissolved in THF (2.5 mL) under a nitrogen atmosphere. H_2O (23.0 µL, 1.26 mmol) was added and the solution was heated, at reflux, to 80 °C for 18 h. Once cooled, the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 50% ethyl acetate in hexanes) afforded the *title compound* (as a 6.1:1 mixture of diastereomers = 72% *de*) as a yellow oil (108 mg, 95%); R_F 0.44 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 1732, 1570, 1448; δ_H (400 MHz, $CDCl_3$) 7.66 (1H, t, *J* = 7.6 Hz, C**H**, minor diasteromer), 7.60 (1H, t, *J* = 7.6 Hz, C**H**, major rotamer), 7.46–7.19 (20H, m, 10 × C**H**, both diasteromers), 7.06 (1H, d, *J* = 7.6 Hz, C**H**, minor), 7.00 (1H, d, *J* = 7.6 Hz, C**H**, major), 5.78 (1H, br s, N**H**, minor), 4.91–4.82 (1H, m, C**H**NH, major), 4.77–4.71 (1H, m, C**H**NH, minor), 4.45 (1H, d, *J* = 5.3 Hz, N**H**, major), 3.83 (2H, d, *J* = 16.8 Hz, C**H₂**CO_2Me, minor), 3.73 (2H, s, C**H₂**CO_2Me, major), 3.60 (3H, s, OC**H₃**, minor), 3.59 (3H, s, OC**H₃**, major), 3.38 (2H, dd, *J* = 13.7,

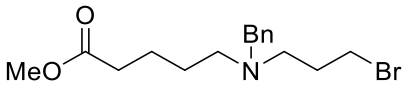
8.4 Hz, C**H**H'CHNH, both), 3.24 (2H, dd, *J* = 13.7, 6.1 Hz, CH**H'**CHNH, both), 1.19 (9H, s, 3 × C**H₃**, minor), 0.99 (9H, s, 3 × C**H₃**, major); δ_C (100 MHz, $CDCl_3$) data for the major diasteromer only: 171.3 (**C**CO_2Me), 157.8 (**C**N), 156.6 (**C**N), 141.0 (**C**), 139.3 (**C**), 135.9 (**C**H), 131.3 (**C**), 130.4 (**C**H), 128.9 (**C**H), 127.5 (**C**H), 126.6 (**C**H), 126.4 (**C**H), 126.2 (**C**H), 121.2 (**C**H), 120.8 (**C**H), 58.7 (**C**HNH), 55.0 (**C**SO), 50.9 (O**C**H_3), 44.7 (**C**H_2CHNH), 38.4 (**C**H_2CO_2Me), 21.4 (3 × **C**H_3); HRMS (ESI): calcd. for $C_{26}H_{31}N_2O_3S$, 451.2050. Found: $[MH]^+$, 451.2044 (1.3 ppm error).

Methyl 5-(benzyl(propan-3-ol)amino)pentanoate (691)



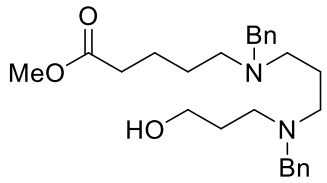
3-(Benzylamino)propan-1-ol (957 µL, 6 mmol), potassium carbonate (415 mg, 3 mmol) and methyl 5-bromovalerate (430 µL, 3 mmol) was dissolved in acetonitrile (6 mL) and heated to 85 °C, at reflux, for 3 h. Upon completion, the reaction was quenched with water (10 mL), and extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 50% ethyl acetate in hexanes → ethyl acetate) afforded the *title compound* as a yellow oil (785 mg, 94%); R_F 0.30 (ethyl acetate); δ_H (400 MHz, $CDCl_3$) 7.33–7.21 (5H, m, 5 × C**H**), 3.71 (2H, t, *J* = 5.5 Hz, C**H₂**OH), 3.64 (3H, s, CO_2C**H₃**), 3.55 (2H, s, C**H₂**Ph), 2.63 (2H, t, *J* = 5.5 Hz, NC**H₂**), 2.42 (2H, t, *J* = 7.3 Hz, NC**H₂**), 2.27 (2H, t, *J* = 6.9 Hz, C**H₂**CO_2Me), 1.74–1.66 (2H, m, C**H₂**), 1.61–1.49 (4H, m, 2 × C**H₂**). Data is consistent with those previously reported in the literature.[140]

Methyl 5-(benzyl(3-bromopropyl)amino)pentanoate (692)



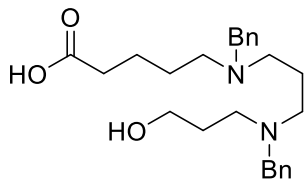
Methyl 5-(benzyl(propan-3-ol)amino)pentanoate (9.80 g, 35.1 mmol) and carbon tetrabromide (12.8 g, 38.6 mmol) was dissolved in CH_2Cl_2 (70 mL) and cooled to 0 °C. Triphenylphosphine (10.1 g, 38.6 mmol) was added portionwise, and then the reaction was stirred for 1 h at 0 °C. Upon completion, the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 50% diethyl ether in hexanes) afforded the *title compound* as a colourless oil (10.4 g, 86%); R_F 0.53 (50% ethyl acetate in hexanes); ν_{max}/cm^{-1} (thin film) 2951, 2807, 1734, 1452; δ_H (400 MHz, $CDCl_3$) 7.29–7.05 (5H, m, 5 × C**H**), 3.57 (3H, s, CO_2C**H₃**), 3.50 (2H, t, *J* = 6.6 Hz, C**H₂**Br), 3.47 (2H, s, C**H₂**Ph), 2.50 (2H, t, *J* = 6.5 Hz, C**H₂**N), 2.40–2.34 (2H, m, C**H₂**N), 2.26 (2H, t, *J* = 7.3 Hz, C**H₂**CO_2Me), 1.88–1.79 (2H, m, C**H₂**), 1.77–1.68 (4H, m, 2 × C**H₂**); δ_C (100 MHz, $CDCl_3$) 174.1 (**C**O), 139.3 (**C**), 128.7 (**C**H), 128.2 (**C**H), 126.9 (**C**H), 58.6 (**C**H_2Ph), 52.8 (**C**H_2N), 51.5 (CO_2**C**H_3), 50.6 (**C**H_2N), 43.1 (**C**H_2Br), 31.5 (**C**H_2CO_2Me), 22.3 (**C**H_2), 20.4 (**C**H_2), 19.5 (**C**H_2); HRMS (ESI): calcd. for $C_{16}H_{25}{}^{79}BrNO_2$, 342.1063. Found: $[MH]^+$, 342.1065 (0.5 ppm error).

Methyl 5-(benzyl(3-(benzyl(3-hydroxypropyl)amino)propyl)amino)pentanoate (693)



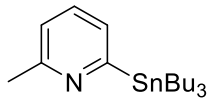
Methyl 5-(benzyl(3-bromopropyl)amino)pentanoate (798 mg, 2.34 mmol), 3-(benzylamino)propan-1-ol (743 µL, 4.68 mmol) and potassium carbonate (323 mg, 2.34 mmol) was dissolved in acetonitrile (23 mL) and stirred at 85 °C, under reflux, for 4 h. Upon completion, the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, ethyl acetate → 33% methanol in ethyl acetate) afforded the *title compound* as a colourless oil (713 mg, 72%); R_F 0.55 (33% methanol in ethyl acetate); ν_{max}/cm^{-1} (thin film) 3416, 2948, 2804, 1736, 1452; δ_H (400 MHz, $CDCl_3$) 7.37–7.14 (10H, m, 2 × Ph), 3.74–3.66 (2H, m, C**H₂**OH), 3.63 (3H, s, CO_2C**H₃**), 3.53 (2H, s, NC**H₂**Ph), 3.49 (2H, s, NC**H₂**Ph), 2.67–2.58 (2H, m, C**H₂**N), 2.46–2.33 (4H, m, 2 × C**H₂**N), 2.30–2.21 (4H, m, C**H₂**N and C**H₂**CO_2Me), 1.75–1.62 (4H, m, 2 × C**H₂**), 1.62–1.52 (2H, m, C**H₂**), 1.48–1.40 (2H, m, C**H₂**); δ_C (100 MHz, $CDCl_3$) 174.2 (**C**O), 139.6 (**C**), 138.2 (**C**), 129.1 (**C**H), 128.7 (**C**H), 128.4 (**C**H), 128.1 (**C**H), 127.2 (**C**H), 126.7 (**C**H), 64.3 (C**H₂**OH), 58.9 (**C**H_2Ph), 58.5 (**C**H_2Ph), 54.2 (**C**H_2N), 52.7 (**C**H_2N), 51.9 (**C**H_2N), 51.7 (**C**H_2N), 51.4 (CO_2**C**H_3), 31.7 (**C**H_2CO_2Me), 27.8 (**C**H_2), 24.3 (**C**H_2), 22.3 (**C**H_2), 20.1 (**C**H_2); HRMS (ESI): calcd. for $C_{26}H_{39}N_2O_3$, 427.2955. Found $[MH]^+$, 427.2960 (1.2 ppm error).

5-(Benzyl(3-(benzyl(3-hydroxypropyl)amino)propyl)amino)pentanoic acid (694)



Methyl 5-(benzyl(3-(benzyl(3-hydroxypropyl)amino)propyl)amino)-pentanoate (703 mg, 1.65 mmol) was dissolved in aqueous lithium hydroxide solution (0.5 m, 4.1 mL, 1.98 mmol) and THF (4.1 mL). The resulting bi-phasic solution was vigorously stirred for 18 h. Upon completion, the solvent was removed *in vacuo*. The crude material was then passed through a silica plug and eluted with 50% methanol in ethyl acetate. The resulting mixture was then re-dissolved in boiling chloroform and filtered (to remove silica) to obtain the *title compound* as a crude colourless oil (576 mg, 85%); R_F 0.14 (50% methanol in ethyl acetate). The crude mixture was then used without further purification.

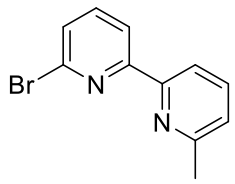
2-(Tributylstannyl)-6-methylpyridine (696)



2-bromo-6-methylpyridine (1.13 mL, 10.0 mmol) was dissolved in THF (10 mL) and cooled to −78 °C before *n*BuLi (1.6 m in hexanes, 6.25 mL, 10.0 mmol) was added dropwise. The solution undergoes an instant colour change from colourless to deep red upon addition of *n*BuLi solution. The solution was stirred at −78 °C for 1 h, where Bu_3SnCl (2.18 mL, 8 mmol) was added slowly. The solution was then allowed to slowly warm to room temperature over 2 h. Upon completion, the reaction was quenched with sat. $NH_4Cl_{(aq)}$

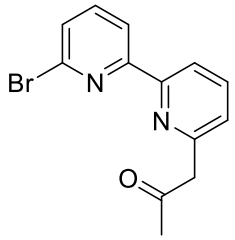
solution (20 mL) and extracted with ethyl acetate (3 × 100 mL). The combined organics were dried over $MgSO_4$, filtered and the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 25% ethyl acetate in hexanes) afforded the *title compound* as a colourless oil (3.53 g, 92%); R_F 0.65 (50% ethyl acetate in hexanes); δ_H (400 MHz, $CDCl_3$) 7.34 (1H, t, *J* = 7.6 Hz, C**H**), 7.16 (1H, d, *J* = 7.6 Hz, C**H**), 6.93 (1H, d, *J* = 7.6 Hz, C**H**), 2.52 (3H, s, CC**H₃**), 1.59–1.49 (6H, m, 3 × C**H₂**), 1.36–1.25 (6H, m, 3 × C**H₂**), 1.07 (6H, t, *J* = 7.6 Hz, 3 × C**H₂**Sn), 0.86 (9H, t, *J* = 6.9 Hz, 3 × CH_2C**H₃**). Data is consistent with those reported in the literature.[161]

6-Bromo-6'-methyl-2,2'-bipyridine (698)



2,6-Dibromopyridine (1.19 g, 5 mmol), lithium chloride (390 mg, 9.3 mmol) and $Pd(PPh_3)_4$ (90 mg, 0.08 mmol) were charged into a RBF and purged with argon. 2-(Tributylstannyl)-6-methylpyridine (1.91 g, 5 mmol) and toluene (20 mL) were added under inert conditions and the solution was stirred at 110 °C, under reflux, for 18 h under an argon atmosphere. Upon completion, the reaction was quenched with sat. $NH_4Cl_{(aq)}$ solution (20 mL) and extracted with ethyl acetate (3 × 100 mL). The combined organics were dried over $MgSO_4$, filtered and the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, CH_2Cl_2 → ethyl acetate) afforded the *title compound* as a white solid (1.07 g, 86%); R_F 0.62 (50% ethyl acetate in hexanes); δ_H (400 MHz, $CDCl_3$) 8.39 (1H, d, *J* = 7.6 Hz, C**H**), 8.18 (1H, d, *J* = 7.6 Hz, C**H**), 7.68 (1H, t, *J* = 7.6 Hz, C**H**), 7.63 (1H, t, *J* = 7.6 Hz, C**H**), 7.45 (1H, d, *J* = 7.6 Hz, C**H**), 7.17 (1H, d, *J* = 7.6 Hz, C**H**), 2.60 (3H, s, C**H₃**); δ_C (100 MHz, $CDCl_3$) 158.0 (**C**), 157.7 (**C**), 153.8 (**C**), 141.5 (**C**Br), 139.1 (**C**H), 137.1 (**C**H), 127.7 (**C**H), 123.8 (**C**H), 119.7 (**C**H), 118.5 (**C**H), 24.6 (**C**H_3). Data is consistent with those previously reported in the literature.[162]

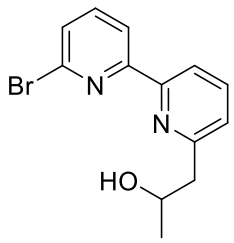
1-(6'-Bromo-[2,2'-bipyridin]-6-yl)propan-2-one (699)



N,N-Diisopropylamine (564 µL, 4.0 mmol) was dissolved in THF (10 mL) and cooled to 0 °C before *n*-BuLi (1.6 m solution in hexanes, 2.5 µL, 4.0 mmol) was added dropwise and stirred for 30 min. The LDA solution was then cooled to −78 °C, where 6-bromo-6'-methyl-2,2'-bipyridine (490 mg, 1.97 mmol) was added dropwise and stirred for 30 min. *N*-Methoxy-*N*-methylacetamide (426 µL, 4.0 mmol) was added and stirred for a further 30 min at −78 °C before slowly warming to room temperature. The solution was then quenched with sat. $NH_4Cl_{(aq)}$ (10 mL) and extracted with ethyl acetate (3 × 100 mL) and washed with brine (5 mL). The combined organic extracts were dried over $MgSO_4$, filtered and removed *in vacuo*. Purification by flash column chromatography (SiO_2, 33% → 50% diethyl ether in hexanes) afforded the *title*

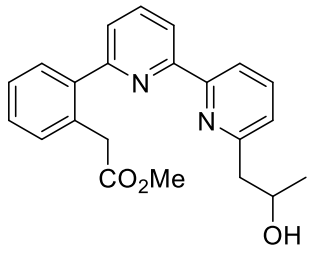
compound as a yellow oil (190 mg, 63%); R_F 0.55 (50% ethyl acetate in hexanes); ν_{max}/cm^{-1} (thin film) 1716, 1574, 1549, 1420; δ_H (400 MHz, $CDCl_3$) 8.39 (1H, d, *J* = 7.6 Hz, C**H**), 8.31 (1H, d, *J* = 7.6 Hz, C**H**), 7.80 (1H, t, *J* = 7.6 Hz, C**H**), 7.66 (1H, t, *J* = 7.6 Hz, C**H**), 7.51–7.47 (1H, m, C**H**), 7.28–7.24 (1H, m, C**H**), 3.99 (2H, s, C$\mathbf{H_2}$CO), 2.27 (3H, s, C$\mathbf{H_3}$CO); δ_C (100 MHz, $CDCl_3$) 205.5 (**C**O), 157.1 (**C**N), 154.3 (**C**N), 154.2 (**C**N), 141.5 (Br**C**N), 139.2 (**C**H), 137.7 (**C**H), 128.0 (**C**H), 124.6 (**C**H), 119.8 (**C**H), 119.7 (**C**H), 53.2 (**C**H_2CO), 30.0 (C$\mathbf{H_3}$CO); HRMS (ESI): calcd. for $C_{13}H_{12}{}^{79}BrN_2O$, 291.0128. Found: $[MH]^+$, 291.0125 (0.8 ppm error).

1-(6'-bromo-[2,2'-bipyridin]-6-yl)propan-2-ol (700)



1-(6'-bromo-[2,2'-bipyridin]-6-yl)propan-2-one (90 mg, 0.310 mmol) was dissolved in methanol (3.1 mL) and sodium borohydride (35 mg, 0.931 mmol) was added portionwise. The solution was stirred at room temperature for 1 h and upon completion the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 50% diethyl ether in hexanes) afforded the *title compound* as a yellow oil (73 mg, 81%); R_f 0.22 (50% ethyl acetate in hexanes); ν_{max}/cm^{-1} (thin film) 3391, 2966, 1572, 1549, 1418; δ_H (400 MHz, $CDCl_3$) 8.29 (1H, d, *J* = 8.3 Hz, C**H**), 8.25 (1H, d, *J* = 7.6 Hz, C**H**), 7.77 (1H, t, *J* = 7.6 Hz, C**H**), 7.66 (1H, t, *J* = 8.3 Hz, C**H**), 7.49 (1H, d, *J* = 8.3 Hz, C**H**), 7.19 (1H, d, *J* = 7.6 Hz, C**H**), 5.18 (1H, br s, O**H**), 4.39–4.28 (1H, m, C**H**OH), 2.99 (1H, dd, *J* = 15.3, 3.1 Hz, C**H**H'CHOH), 2.92 (1H, dd, *J* = 15.3, 8.4 Hz, CH**H'**CHOH), 1.32 (3H, d, *J* = 6.1 Hz, C$\mathbf{H_3}$); δ_C (100 MHz, $CDCl_3$) 159.7 (**C**N), 156.8 (**C**N), 153.5 (**C**N), 141.6 (Br**C**N), 139.3 (**C**H), 137.9 (**C**H), 128.1 (**C**H), 124.4 (**C**H), 119.5 (2 × **C**H), 67.1 (**C**HOH), 44.7 (**C**H_2), 22.9 (**C**H_3); HRMS (ESI): calcd. for $C_{13}H_{14}{}^{79}BrN_2O$, 293.0284. Found: $[MH]^+$, 293.0280 (1.5 ppm error).

Methyl 2-(2-(6'-(2-hydroxypropyl)-[2,2'-bipyridin]-6-yl)phenyl)acetate (701)



1-(6'-bromo-[2,2'-bipyridin]-6-yl)propan-2-ol (50 mg, 0.171 mmol), K_3PO_4 (73 mg, 0.342 mmol), $PdCl_2dppf.CH_2Cl_2$ (7.0 mg, 8.56 µmmol) and methyl 2-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate (71 mg, 0.257 mmol) was charged into a vial and purged with argon. THF (1.7 mL) and water (15 µL, 0.856 mmol) were added under inert conditions and the reaction stirred, at 80 °C for 18 h. Upon completion, the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 50% diethyl ether → diethyl ether) afforded the *title compound* as a yellow oil (60 mg, 97%); R_F 0.19 (50% ethyl acetate in hexanes); ν_{max}/cm^{-1} (thin film) 3421, 3064, 2924, 1711, 1449; δ_H (400 MHz, $CDCl_3$) 8.29–8.22 (2H, m, 2 × C**H**), 7.86 (1H, t, *J* = 7.6 Hz, C**H**), 7.72 (1H, t, *J* = 7.6 Hz, C**H**), 7.52–

7.45 (2H, m, 2 × C**H**), 7.42–7.34 (3H, m, 3 × C**H**), 7.14 (1H, d, *J* = 7.6 Hz, C**H**), 5.50 (1H, br s, O**H**), 4.39–4.29 (1H, m, C**H**OH), 3.93 (2H, s, C**H₂**CO_2Me), 3.50 (3H, s, CO_2C**H₃**), 2.98 (1H, dd, *J* = 15.3, 3.1 Hz, C**H**H'CH), 2.91 (1H, dd, *J* = 15.3, 8.4 Hz, CH**H'**CH), 1.32 (3H, d, *J* = 6.1 Hz, CHC**H₃**); δ_C (100 MHz, $CDCl_3$) 172.2 (**C**O_2Me), 159.5 (**C**), 159.0 (**C**), 155.0 (**C**), 154.7 (**C**), 140.4 (**C**), 137.7 (**C**H), 137.6 (**C**H), 132.4 (**C**), 131.4 (**C**H), 130.1 (**C**H), 128.6 (**C**H), 127.5 (**C**H), 124.2 (**C**H), 123.7 (**C**H), 119.3 (**C**H), 118.9 (**C**H), 67.1 (C**H**OH), 51.7 (CO_2**C**H_3), 44.6 (**C**H_2CO_2Me), 38.9 (**C**H_2CHOH), 22.9 (CH**C**H_3); HRMS (ESI): calcd. for $C_{22}H_{23}N_2O_3$, 363.1703. Found: $[MH]^+$, 363.1700 (0.9 ppm error).

Appendices

Appendix I. Ring-Expansion Approach to Medium-Sized Lactams and Analysis of Their Medicinal Lead-Like Properties

Appendix II. Synthesis of Cyclic Peptide Mimetics by Successive Ring Expansion Reactions of Lactams

Appendix III. Iterative Assembly of Macrocyclic Lactones using Successive Ring Expansion Reactions

Appendix IV. Internal Nucleophilic Catalyst Mediated Cyclisation/Ring Expansion Cascade for the Synthesis of Medium-Sized Lactones and Lactams

Appendix V. Consecutive Ring-Expansion Reactions for the Iterative Assembly of Medium-Sized Rings and Macrocycles

Appendix VI. Merging π-acid and Pd catalysis: dearomatising spirocyclisation/cross coupling cascade reactions of alkyne-tethered aromatics

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