Successive Ring Expansion (SuRE) in the synthesis of medium sized ring and macrocycle libraries

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PhD

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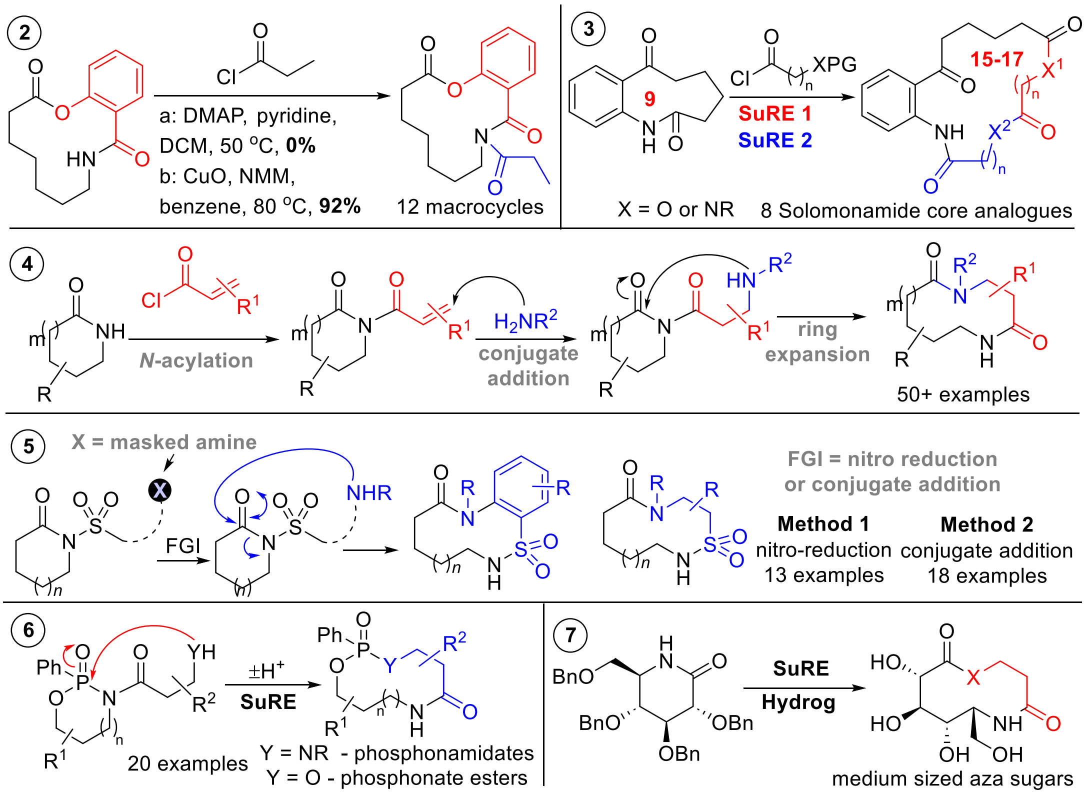
Chemistry

August 2023

Abstract-Successive Ring Expansion (SuRE) in the synthesis of medium sized ring and macrocycle libraries

This thesis describes the development of new methodologies to synthesize different medium sized rings and macrocycles, either using Successive Ring Expansion (SuRE) reactions or SuRE-like reactions. In Chapter 2, new *N*-acylation conditions had been developed for lactams that cannot easily ring expand using previously reported *N*-acylation conditions. In Chapter 3, SuRE reactions were utilised to synthesize the 15-membered macrocyclic core of natural products Solomonamides and a series of analogues. Chapter 4 describes the development of a conjugate addition/ring expansion (CARE) cascade reaction, which allows the synthesis of diverse functionalized medium sized rings and macrocycles. In Chapter 5, two new ring expansion protocols (nitro reduction method and conjugate addition method) to access medium sized and macrocyclic sulfonamides are described. Chapter 6 describes the ring expansion study of P=O containing molecules, which showed quite different reactivity comparing to normal SuRE reaction. Chapter 7 describes a SuRE strategy to synthesize medium sized and macrocyclic aza sugars.



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. The research presented in this Thesis was carried out at the University of York between October 2019 and August 2023.

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.

Zhongzhen Yang

Acknowledgements

Time flies like lightning. Four years of my PhD life are fleeting. First, I want to thank Dr William Unsworth for the opportunity that he accepted me to be one of the international PhD students of his independent academic group. He is so patient, careful, and encouraging that makes me never feel nervous or pushed, and he helps me to become an eligible PhD student. And I want to thank the China Scholarship Council for funding my PhD.

I would also like to thank Dr Alyssa-Jennifer Avestro for her guidance as independent panel member.

I'd like to acknowledge all the members of the Unsworth group that have worked alongside over past 4 years; in no particular order: James Donald, Lee Duff, Aimee Clarke, Hon Eong Ho, James Rossi-Ashton, Ryan Epton, Balasz Pograni, Kleopas Palate, Will Glover Humphreys, Nantachai Inprung, Jack Wootton, Jerry Tam, Will Orukotan, Illya Zalessky.

Many special thanks given to Illya, my best friend in the UK and during these 4 years. The highlight time of my PhD life was when the department reported the news of our paper published in *Angewandte Chemie International Edition*.

I'd like to thank the technical staff in the department, including Mike Keogh and Steve from stores, Karl Heaton from mass spectrometry service, Heather Fish and Alex Heyam from NMR service.

Finally, a huge thank you goes out to my family. My parents always stand behind me and support me to do everything I want. My wife, Xueying Wu, has shown me unlimited love and support since we met. I look forward to spending the rest of our lives together.

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Abbreviations

Ac	acetyl
Alloc	allyloxycarbonyl
AIBN	azobisisobutyronitrile
Ala	alanine
aq	aqueous
Boc	*tert*-butyloxycarbonyl
Bn	benzyl
Bu	butyl
br	broad
b.p.	boiling point
BOP-Cl	bis(2-oxo-3-oxazolidinyl)phosphinic chloride
Cbz	carboxybenzyl
CCDC	Cambridge Crystallographic Data Centre
COSY	correlation spectroscopy
CSA	camphorsulfonic acid
CPME	cyclopentyl methyl ether
DBU	1,8-diazabicyclo(5.4.0)undec-7-ene
DCE	1,2-dichloroethane
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DEPT	distortionless enhancement by polarization transfer
DIPEA	N,N-diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMP	Dess–Martin periodinane
DMF	dimethylformamide
DME	dimethoxyethane
DMEDA	1,2-dimethylethylenediamine
DMSO	dimethyl sulfoxide
DFT	density functional theory
DG	directing group

EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
Et	ethyl
ESI	electrospray ionisation
eq	equivalent(s)
Fmoc	fluorenylmethyloxycarbonyl
Gly	glycine
h	hour(s)
HMBC	heteronuclear multiple bond correlation
HMQC	heteronuclear multiple quantum correlation
HOBt	hydroxybenzotriazole
HRMS	high-resolution mass spectrometry
IR	infrared
KHMDS	potassium bis(trimethylsilyl)amide
LDA	lithium diisopropylamide
LiHMDS	lithium bis(trimethylsilyl)amide
mCPBA	meta-chloroperoxybenzoic acid
Me	methyl
Mes	mesitylene
MMTr	4-monomethoxytrityl
Ms	mesyl
MS	mass spectrometry
MPA	mercaptopropionic acid
NCS	*N*-chlorosuccinimide
NMM	*N*-methylmorpholine
NMR	nuclear magnetic resonance
PG	protecting group
Ph	phenyl
PMB	para-Methoxybenzyl
Pin B	pinacolborane
Pro	proline
PPTS	pyridinium para-toluenesulfonate
4-PPY	4-Pyrrolidinylpyridine
Pr	propyl

p-TSA	para-toluenesulfonic acid
Py	pyridine
quant	quantitative
RC	ring closed
RE	ring expanded
RO	ring opened
RT	room temperature
SM	starting material
Su	succinimide
TBAF	tetra-*n*-butylammonium fluoride
TBSOTf	trimethylsilyl trifluoromethanesulfonate
TBS	*tert*-butyldimethylsilyl
TFA	trifluoroacetic acid
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TLC	thin-layer chromatography
Ts	tosyl
UV-VIS	ultraviolet–visible
XRD	X-ray diffraction

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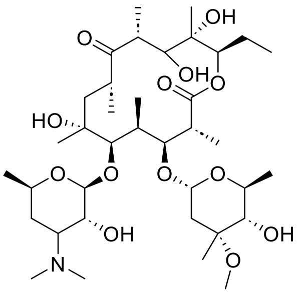
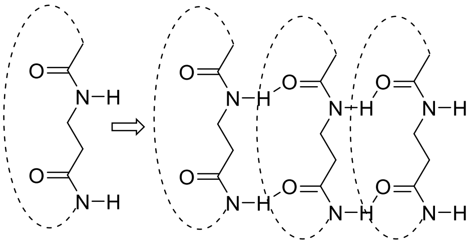
Chapter One: Introduction

1.1 Macrocycles

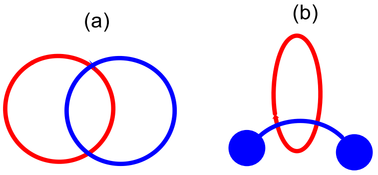
Macrocycles (cyclic molecular frameworks with a ring made up of at least twelve atoms) have attracted widespread interest from chemists due to their significant uses in many scientific fields. For example, macrocycles have distinct molecular shapes and sizes, as well as relatively large surface areas, which in medicinal chemistry can enhance the affinity and selectivity of binding to target receptors. Furthermore, having the atoms held in a large ring scaffold is known to reduce the entropic cost of receptor binding (compared to linear analogues), but compared to smaller cyclic scaffolds, macrocycles do have some degree of flexibility (due to multiple low energy conformations), which can facilitate interactions with protein targets.[1–3] This contributes to why more than 100 macrocyclic drugs are available commercially,[4] for example Erythromycin (**1-1**, Figure 1.1) and other macrolide antibiotics, that are used to treat a wide range of bacterial infections.[5–8] In addition, the self-assembly of peptide macrocycles into drug-transporting nanotubes and other advanced materials is also an important research field,[9,10] and macrocycles are integral components of mechanically interlocked molecules like catenanes and rotaxanes, which have contributed to the development of molecular motors and machines in nanotechnology.[11] Triangular phenanthrenequinone-based macrocycles were reported to be useful in rechargeable aluminium organic batteries recently and also have great potential.[12]



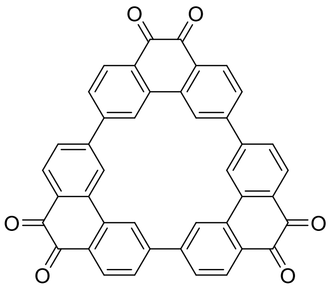
1-1 Erythromycin: macrolide antibiotic



1-2 Macrocyclic peptide nanotubes: drug transport, advanced material



1-3 Simple catenane (a) and rotaxane (b) structures: molecular motors/machines



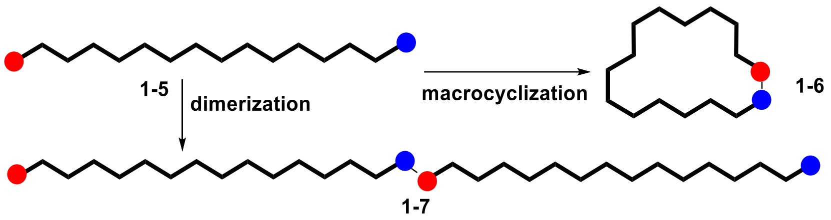
1-4 Triangular phenanthrene- quinone-based macrocycles: used in rechargeable aluminum organic batteries

Figure 1.1 Structures and applications of macrocycles.

Despite the potential to produce medicinally relevant compounds, synthetic macrocycles have been traditionally under-explored in medicinal chemistry and they are also still relatively poorly examined in other relevant subjects.[1–3,9,10,13] One significant reason for this is the difficulty of synthesizing macrocycles,[3,14–16] which can really limit their development prospects in medicinal chemistry and utilities in applied fields.

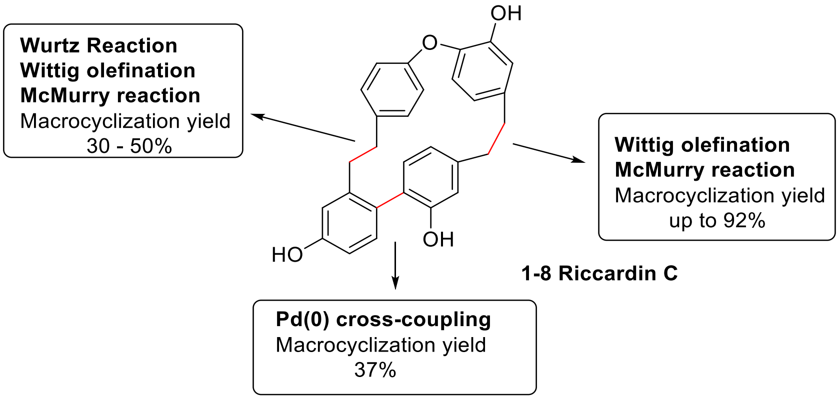
1.2 Macrocyclization strategies towards macrocycles

The efficient synthesis of macrocycles is challenging because of unfavorable entropic and enthalpic effects associated with ring closure (end-to-end macrocyclization). This can make it difficult to avoid unwanted side reactions like dimersation/oligomersation or unwanted transannular side reactions.[3,17] These thermodynamic penalties result from a requirement to access high energy "folded" conformations, that often are not the lowest energy conformations because of lost degrees of freedom and/or destabilising electronic or steric effects. As a result, unwanted side reactions can occur and compete with the macrocyclization pathway, leading to low yields of desired products **1-6** (Scheme 1.1). This is a crucial issue and a number of strategies have been put forward, trying to minimize or completely avoid these unwanted side reactions.



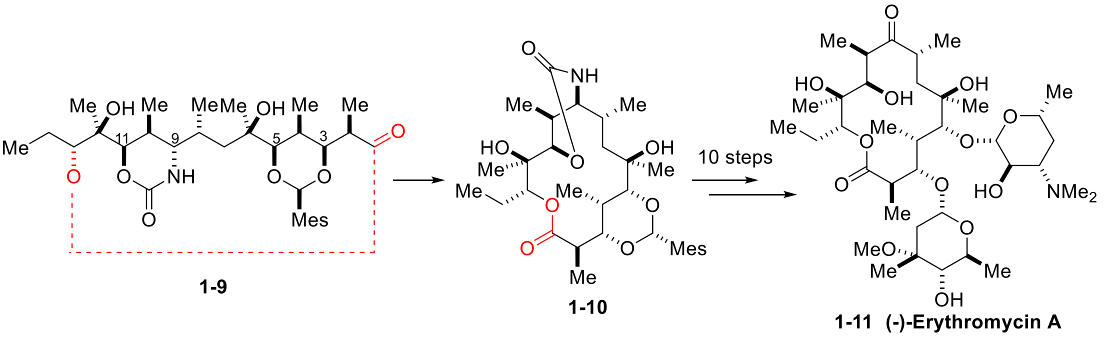
Scheme 1.1 End-to end macrocyclization vs unwanted side reactions.

As many chemical reactions (like amide and ester coupling, ring-closing metathesis (RCM), and “click” chemistry cycloadditions and others) can be used to achieve the key ring-closing step, selecting the appropriate ring-closing reaction is a crucial decision for any synthetic macrocyclization strategy. Sometimes, the selected reaction is associated with the specific functionalities in the target macrocyclic structures, but in other situations, it can dramatically influence the efficiency of the macrocyclization. A good example to illustrate this point can be seen in the multiple synthetic strategies could achieve the crucial macrocyclization step in the synthesis of Riccardin C (compound **1-8**); all are based on the end-to-end macrocyclisation of linear molecules of the same chain length, but they show significantly different yields (Scheme 1.2).[18]



Scheme 1.2 Summary of the position and methods used to effect macrocyclization in Riccardin C.

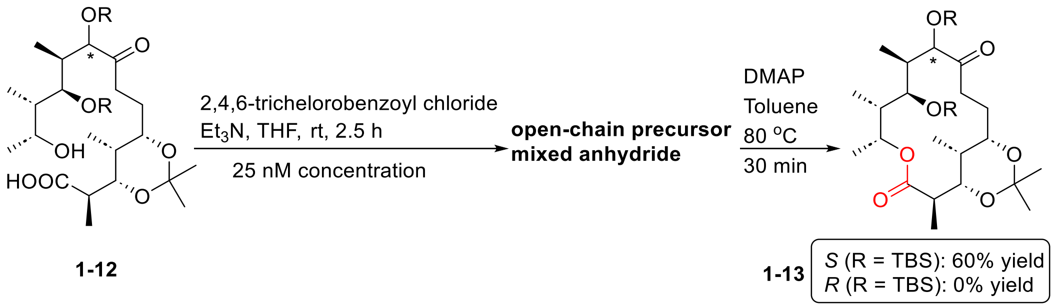
Proper design of the linear precursors to obtain the best pre-cyclization molecule is essential as macrocyclization reactions are often the final step of the synthetic procedure. Entropic and enthalpic effects in the macrocyclization step are key factors that impact the efficiency of the formation of the macrocyclic product, and conformational and configurational preorganization are the main methods used when designing linear precursors better suited to undergo macrocyclisation.[3] The importance of conformational pre-organization in macrocyclization reactions has been recognized for many years, for example in Woodward's synthesis of erythromycin **1-11** in 1981.[19] In this efficient lactonization, *S* configuration at C-9 and cyclic protecting groups at C-3/C5 and C-9/C-11 are necessary to promote macrolactonization.



Scheme 1.3 Woodward's synthesis of (–)-Erythromycin.

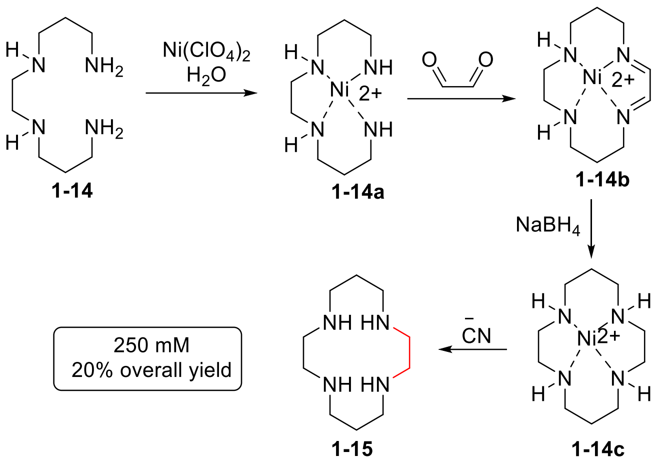
Conformational preorganization in open-chain molecules can favor the presence of folded conformations in which the two reactive centers are close, facilitating macrocyclization and disfavoring the formation of longer oligomers. The forces responsible for one conformation being favored over another are multiple, with covalent bonds, intermolecular hydrogen bonding, steric and different electronic interactions, such as $\pi-\pi$ interactions, polarization and charge transfer all contributing.[20,21] These various factors, with different strengths and different degrees, influence the conformation of molecules and, hence, also the proximity of the reacting centers.[3,19,22]

Configurational preorganization can be considered as a particular case of conformational preorganization in which the conformational preference is associated with the stereochemical configurations of the chiral centers.[17,22] Paterson and co-workers described the synthesis of compounds **1-13** based on the erythromycin core, and this work illustrates this method well. They reported a successful macrolactonization of open-chain precursors **1-12** using the Yamaguchi reaction conditions *via* a high dilution approach. It was found that the configuration of the C-9 in **1-12** (marked with an asterisk in Scheme 1.4) has an large effect on the macrocyclization process, in which the *S* stereoisomer cyclizes in 60% yield while the *R* stereoisomer results in no product under the same reaction conditions.[23] Thus, despite this position being remote from the reaction center, it is a clear demonstration of the difference conformation changes can make in macrocyclization, and how these changes can be brought about by very subtle changes in structure/configuration. Examples like this also illustrate why macrocycle synthesis can be so hard, as predicting the outcome of these changes is extremely challenging.



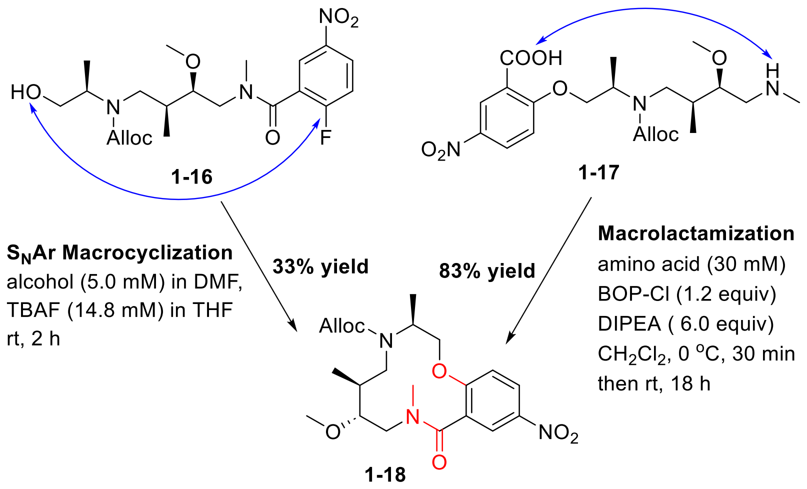
Scheme 1.4 Paterson's synthesis of the erythromycin core.

When conformational and configurational preorganization are not suitable, template-assisted preorganization is an alternative. Metal templated macrocyclizations are the most common reactions based on the application of templates in macrocyclic synthesis, with these reactions benefiting from kinetic and thermodynamic effects to favor cyclization rather than dimerization. A seminal example was reported by Barefield and coworkers, who reported the nickel(II) templated synthesis of cyclam **1-15**, which represented a landmark in this field. In this synthesis, the corresponding metal complex **1-14a** and the diimine macrocycle **1-14b** are the key intermediates allowing cyclam **1-15** to be formed in 20% overall yield (Ni(II) is removed from **1-14c** using cyanide).[24,25]



Scheme 1.5 Ni(II) templated synthesis of cyclam.

Although preorganization of the linear precursors can improve the efficient of macrocyclization, high dilution or pseudo-high dilution conditions are still commonly used in most reactions of this type to increase the yields of the macrocycle. Running the reaction at high dilution (typically about 1–5 mM) can increase the probability of intermolecular macrocyclization occurring and reduce unwanted side reaction pathways. However, the success of high dilution is highly substrate dependent and can be impractical for large scale synthesis. Pseudo-high dilution can be used as an alternative; for example, adding the linear reagent very slowly to create a high dilution condition is the simplest way to do this. But this method isn't always efficient, sometimes higher catalyst loadings or additives are employed in addition to dilution. Other pseudo-high dilution conditions are known, but generally they require relatively specialized techniques and conditions, *e.g.* the use of solid supports[26,27] or biphasic solvent systems.[29,30] The synthesis of macrolactam **1-18** using two different macrocyclization approaches is a good example of high dilution end-to-end cyclisation (Scheme 1.6). The linear analogue **1-16** cyclized *via* intramolecular S_NAr reaction under pseudo-high dilution condition resulting a fairly low yield (33%). However, if the linear precursor is modified to **1-17**, highly yield (83%) can be obtained through the macrolactamization in the presence of DIPEA.[28] The big difference in yield again illustrates the difficulty of predicting macrocyclization efficiency, even using high dilution conditions.



Scheme 1.6 Cyclization *via* two separate approaches under high dilution conditions.

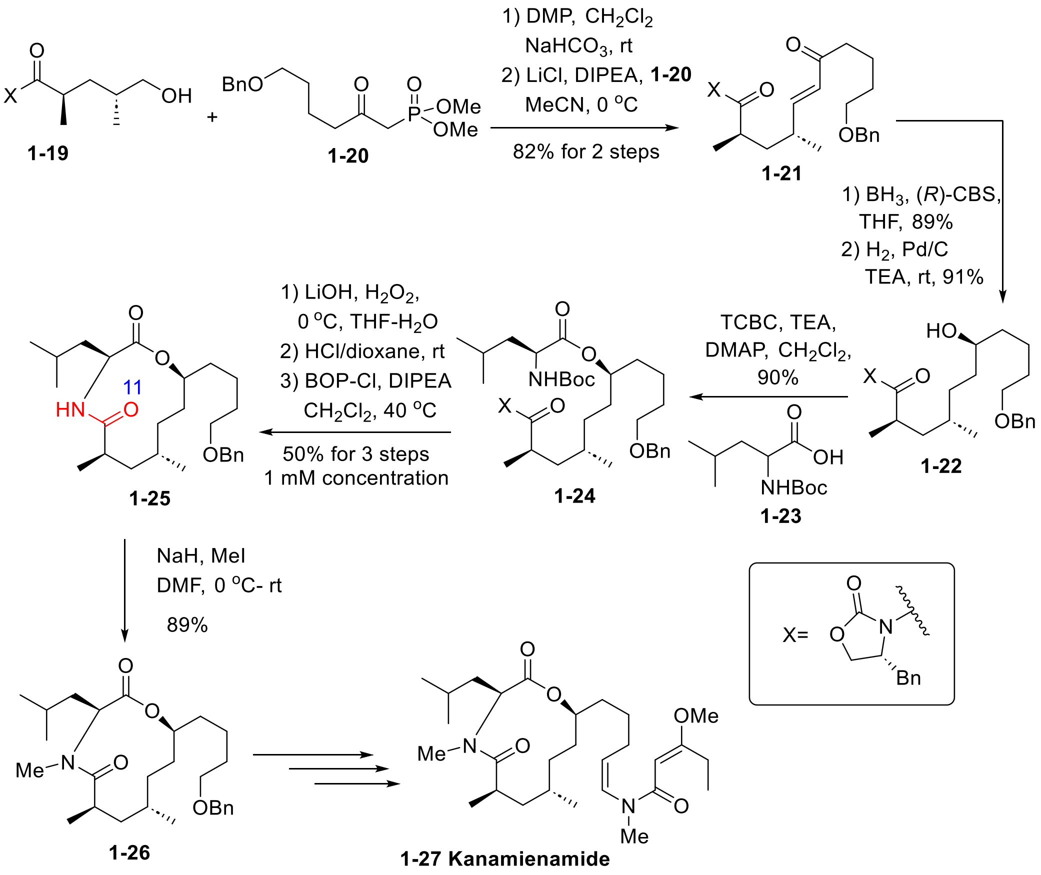
1.3 Macrocyclization reaction types

As mentioned above, many macrocyclization reaction types are reported and have been shown to be efficient in macrocycle synthesis. A few of the most common and efficient reactions are explained below, although this is by no means a comprehensive list.

1.3.1 Macrolactamization reactions

Lactamization is one of the most standard approaches used for macrocycle formation, especially in the peptide chemistry field, driven by the advancement of Solid Phase Peptide Synthesis (SPPS). In SPPS, the initial peptide is connected to the solid phase carrier (polymer resin) and excess reagents can be washed away, thus resulting in high yields and easy separated products when making linear peptides. Hence, peptides of specific length can be rapidly generated using SPPS, and a macrolactamization can afford the desired cyclic peptides.

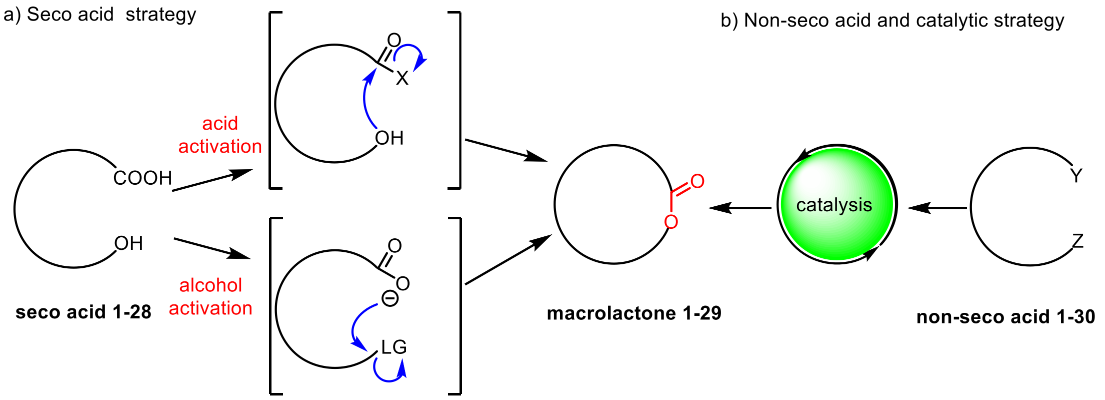
Macrolactamization also plays important role in the synthesis of macrocyclic lactam libraries[28] and natural products such as Kanamienamide **1-27**. Kanamienamide is a structurally unusual enamide isolated from the marine cyanobacterium *Moorea bouillonii*, and displays some anticancer activity.[31] Y. Li et al. reported the total synthesis of Kanamienamide using macrolactamization as the main cyclization step. Fragment **1-19** (synthesized according to reported methods) was condensed with the known phosphonate **1-20** under the conditions described to give enone **1-21**. Corey–Bakshi–Shibata asymmetric reduction and subsequent selective hydrogenation of this ennoe **1-21** furnished the corresponding allylic alcohol **1-22**. Esterification of the secondary alcohol with *L*-leucine analogue **1-23** afforded the corresponding ester **1-24**. Hydrolysis of the chiral auxiliary and subsequent removal of the Boc group afforded a primary amine, which upon treatment of the amino acid with BOP-Cl in refluxing CH_2Cl_2, produced the 11-membered macrocycle **1-25** in good yield (50% over three steps). Kanamienamide **1-27** was obtained after some follow-up procedures including install the required *N*-methyl group, palladium-catalyzed hydrogenation, Stork–Zhao–Wittig olefination homologation and Cu(I) catalyzed cross-coupling.[32,33]



Scheme 1.7 Total synthesis of Kanamienamide using macrolactamization reaction.

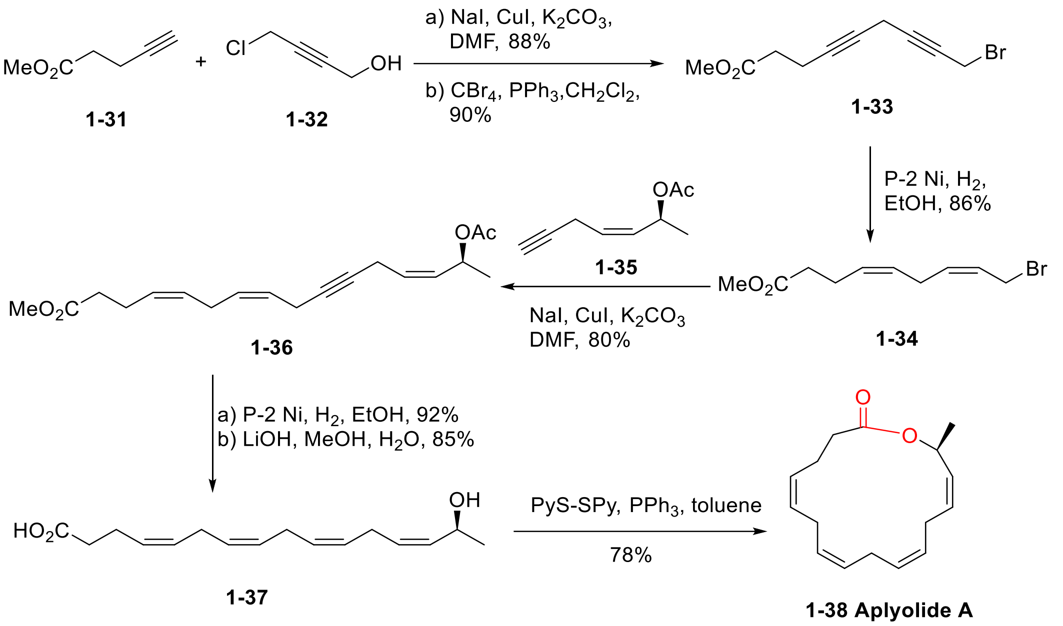
1.3.2 Macrolactonization reactions

The most frequently used approach to obtain macrocyclic lactones is the direct lactonization of linear molecule containing both a carboxylic acid and alcohol (often called seco acids) using various activation modes, and typically involve the activation of one or the other extremity of the seco acid (i.e. acid or alcohol activation). Many commonly used methods such as the Corey–Nicolaou, Boden–Keck, and Mitsunobu macrolactonizations are based on the use of seco-acid strategies (Scheme 1.8a).[34–37] At the same time, non-seco acid and catalytic strategies are known, and have also been proved to be efficient to produce macrocyclic lactones (Scheme 1.8b).[38]



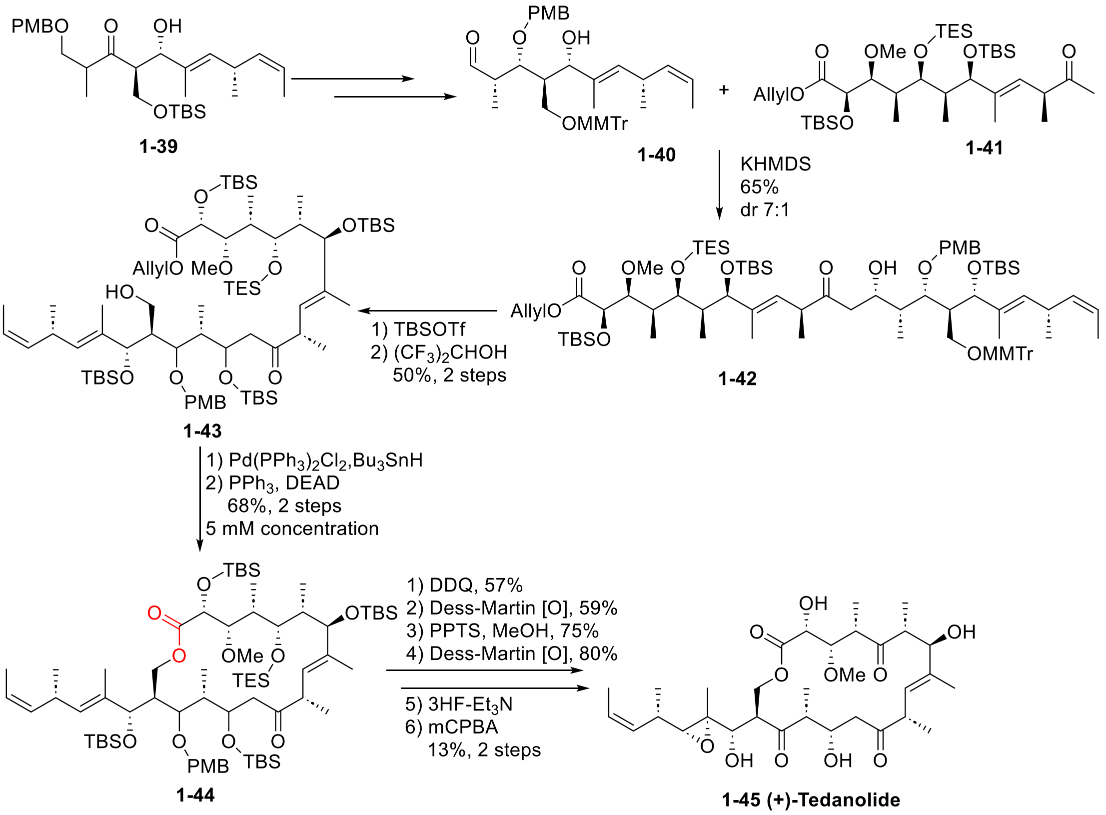
Scheme 1.8 Synthesis of macrolactones using macrolactonization strategies.

The macrolactonization of thioesters is a popular way to obtain macrolides and is a good example of the “acid activation” strategy. Corey and Nicolaou reported the first macrolactonization *via* thioesterification of hydroxyl acid and more advanced protocols were subsequently developed including Corey and Clark, Corey and Brunelle, and Schmidt methods to improve the esterification efficiency.[39–42] The classical Corey−Nicolaou method has been used in a large number of total syntheses and synthetic applications: brefeldin, tylonolide, tricolorin A,[43–46] and in the total syntheses of aplyolide A where other methods failed. [47] Two important fragments **1-31** and **1-32** were obtained through some steps (anion-alkylation, bromination, hydrogenation and so on), which could couple again using an anion-alkylation procedure gave linear compound **1-36**. Stereo- and regiospecific reduction of the remaining triple bond was then accomplished using P-2 nickel hydrogenation and the acetate and methyl ester protecting groups were removed by hydrolysis with lithium hydroxide afforded the seco acid **1-37**, which generated the aplyolide A **1-38** in the presence of 2,2'-dipyridyl disulfide and triphenylphosphine. In addition, a catalytic amount of triethylamine is important to this lactonization, which could decrease the amount of diolide and polymeric side products and led to the synthesis of aplyolide **1-38** in 78% yield.



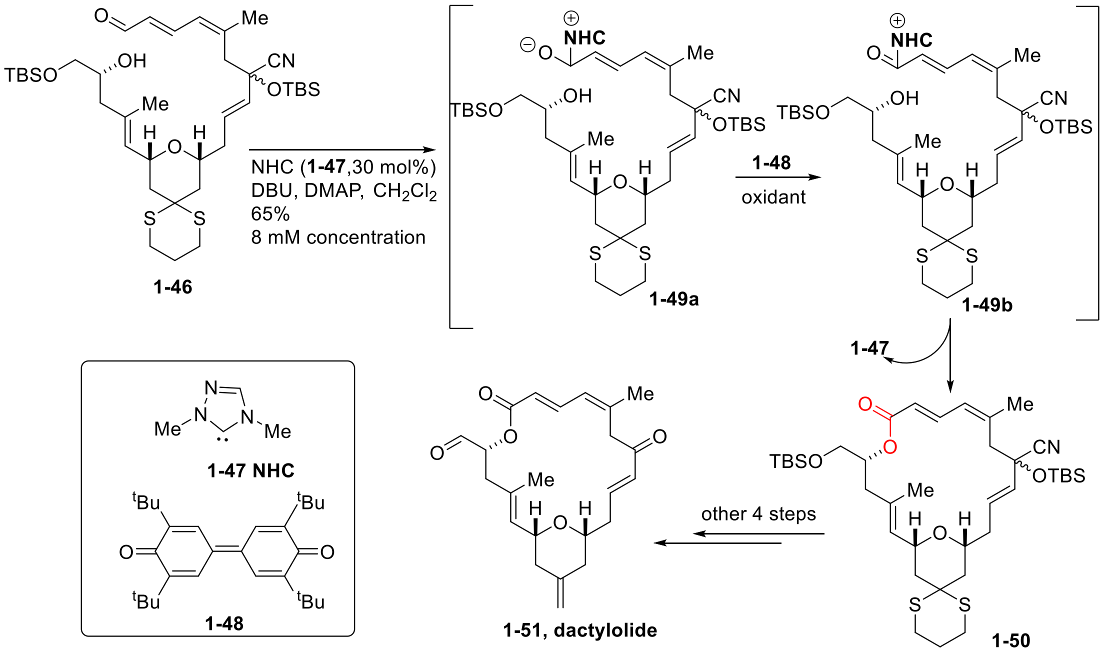
Scheme 1.9 Total synthesis of Aplyolide A using Corey−Nicolaou macrolactonization.

When it comes the to "alcohol activation" of seco acids, the most useful methodology in total synthesis is the Mitsunobu reaction, which involves the substitution of primary or secondary alcohols with nucleophiles mediated by a redox combination of a trialkyl- or triarylphosphine and a dialkyl azodicarboxylate. The most commonly phosphine reagent is triphenylphosphine (PPh_3) and the most common azo coupling partners are diethylazodicarboxylate (DEAD) and diisopropyl azodicarboxylate (DIAD). In the reaction mechanism, the key intermediate is the alkoxyphosphonium salt, and the macrolactonization proceeds *via* an intramolecular S_N2 reaction and with inversion of the alcohol configuration.[47] Furthermore, slow addition of the seco-acid to DEAD−triphenylphosphine is often important to get macrolactone instead of diolide. The Mitsunobu reaction has been used in the synthesis of many 12- to 16-membered macrolactones, for example, in the total syntheses of natural products (+) amphidinolide K745, 19-epi-avermectin B1, (+)-brefeldin C, citreofuran and others.[48–50] As a representative example, the Kalesse group successfully reported the first total synthesis of (+)-tedanolide **1-45** using a Mitsunobu reaction as the core macrocyclization step in 2006.[51] (+)-Tedanolide was isolated from the Caribbean sponge *Tedania ignis* by Schmitz group in 1984, and exhibits remarkable cytotoxicity against murine leukemia cells.[51] In Kalesse's synthesis, the aldol coupling between aldehyde **1-41** and ketone **1-40** gave the compound **1-42** when KHMDS was used as the base. Next, the MMTr group was removed with TBSOTf and hexafluoroisopropanol get the alcohol **1-43**. The ester cleavage was achieved with the palladium catalyzed deprotection of allyl ester **1-43**, then the seco-acid precursor was obtained, followed by Mitsunobu macrolactonization to facilitate the formation of macrocycle **1-44**. (+)-Tedanolide could be obtained following 6 further steps.



Scheme 1.10 First total synthesis of (+)-tedanolide.

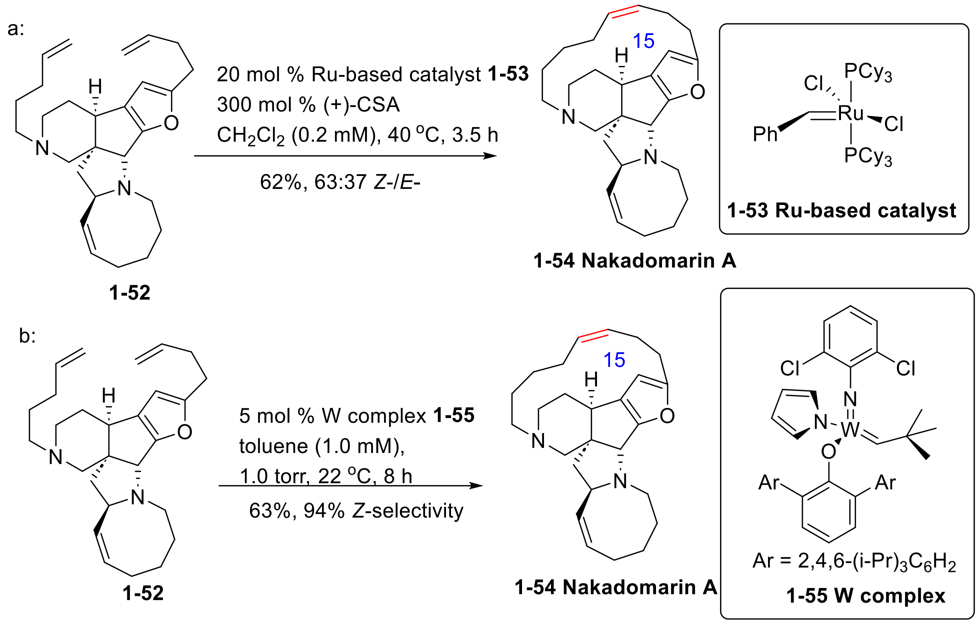
Recently, some catalytic macrolactonization methods have been reported, which do not require seco acid starting materials.[38] For example, in 2012, Hong and co-workers reported an elegant total synthesis of dactylolide, a cytotoxic macrolide isolated from the Vanuatu sponge *Dactylospongia* sp., *via* an *N*-heterocyclic carbene (NHC)-catalyzed oxidative macrolactonization strategy.[51,52] This strategy used an ω-hydroxy aldehyde **1-46** as the linear precursor, which went through 1,2-addition of NHC catalyst **1-47** to aldehyde to form intermediate **1-49a** that was then oxidized *in situ* to **1-49b** by a diphenoquinone derivative **1-48**. Then an intramolecular acyl-transfer from the highly reactive acyl-NHC intermediate to the secondary alcohol completed the catalytic cycle to provide the macrolactonization product **1-50** in 65% yield and released the NHC catalyst for the next cycle. Dactylolide **1-51** was obtained in four more steps. This is the first example of the NHC-catalyzed oxidative macrolactonization of ω-hydroxy aldehydes.[38,53,54]



Scheme 1.11 Total synthesis of dactylolide *via* NHC-catalyzed oxidative macrolactonization.

1.3.3 Ring-Closing Metathesis

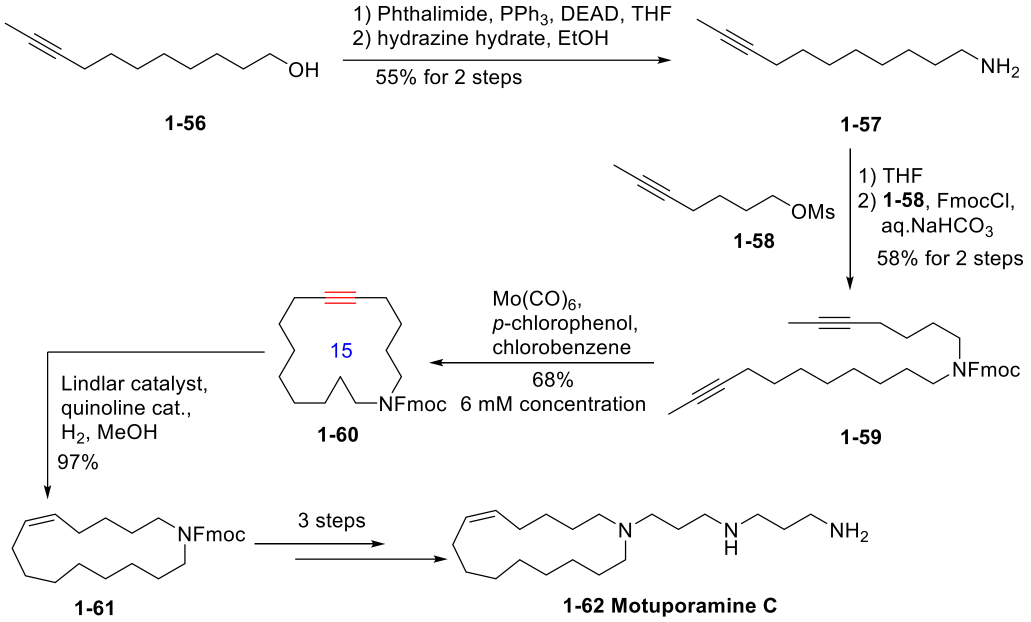
Ring-closing metathesis (RCM) has become a powerful tool to produce macrocycles, especially unsaturated rings, since Dider Villemin first reported the synthesis of Exaltolide precursor using a WCl_6/Me_4Sn catalyzed metathesis cyclization in 1980, and the method was later popularized by Tsuji and especially Grubbs.[55–57] In RCM reactions, the diene proceeds through a series of [2+2] cycloadditions and cycloreversions *via* metallocyclobutane and alkylidene intermediates to complete the cyclization. Ruthenium, molybdenum and tungsten are the most common classes of metal complex used in RCM (most commonly in Grubbs or Schrock catalysts, which have varying reactivity and selectivity and are readily available). RCM has many advantages like (1) broad substrate scope and high functionality tolerance, (2) typically gentle reaction conditions and multiple catalysts available, and (3) the by-product (olefin) usually being volatile and therefore easy to remove.[2,3] Due to its advantages, RCM reactions have been applied to the preparation of a variety of medium sized and macrocyclic natural products like (−)-balanol, manzamine A, (+)-migrastatin and so on.[58–62] However, lack of control of alkene stereochemistry is the main drawback of RCM, with a mixture of *E*- and *Z*- olefins often produced in macrocycles. Generally, the *E*-isomer is thermodynamically more stable than the *Z*-isomer, resulting in *E*-isomer being the major product in RCM reactions, although this is dependent on ring size and other factors. However, some *Z*-selective RCM catalysts have been developed to deal with this problem, an interesting example of *E*- and *Z*- selectivity can be seen in the total synthesis of Nakadomarin A **1-54**, a marine alkaloid isolated from the sponge *Amphimedon* sp..[63–65] In 2009, Pavol reported the total synthesis of Nakadomarin A using Grubbs first-generation catalyst (**1-53** a Ru-based catalyst) RCM reaction in 62% yield and 63:37 *Z*-/*E*- selectivity (Scheme 1.12-a). Then in 2011, Yu and Wang developed a tungsten catalyst controlled stereoselective RCM method and applied it into the total synthesis of Nakadomarin A. From the same pentacycle **1-52**, using the tungsten alkydene catalyst **1-55**, under vacuum to remove the olefin by-products, Nakadomarin A was produced in 63% yield with excellent (94:6) *Z*-/*E*- selectivity.



Scheme 1.12 *Z-/E-* selective synthesis of Nakadomarin A through RCM reactions.

Ring-closing alkyne metathesis (RCAM) is conceptually very similar to alkene RCM but works on the redistribution of alkyne bonds to produce a cyclic alkyne *via* the intermediacy of metal alkylidyne complexes. The important driving force for RACM is the expulsion of small volatile by-products such as acetylene or 2-butyne. Differently to alkene RCM, *Z-/E-* isomerism is not a problem in RCAM due to the *sp*-hybridisation. After the cyclic alkyne is generated, the new triple bond could be stereo-selectively reduced with the Lindlar catalyst in order to obtain the *Z*-alkene or using a Birch-type single electron reduction to afford cyclic *E*-alkenes. RCAM is widely used in a variety of syntheses of macrocyclic natural products like prostaglandins, epilachnenes, epothilones and others.[61,66–68] Motuporamine C **1-62** is a cytotoxic alkaloid isolated from sponge *Xestospongia exigua* in 1998.[69] Furstner reported the total synthesis of it using RCAM strategy in 2000.[70] The commercially available 9-undecyn-1-ol **1-56** was converted into amine **1-57** by a Mitsunobu reaction. *N*-Alkyation of **1-57** with mesylate **1-58** in THF followed by Fmoc-protection of the resulting secondary amine, delivered the linear precursor **1-59** in good overall yield. This diyne was subjected to ring-closing alkyne metathesis using $Mo(CO)_6$ and *p*-chlorophenol in chlorobenzene to provide the desired cyclic product **1-60** in a good yield. Subsequent Lindlar reduction of **1-60** afforded the *Z*-alkene **1-61** in almost quantitative yield with the stereoselective manner.

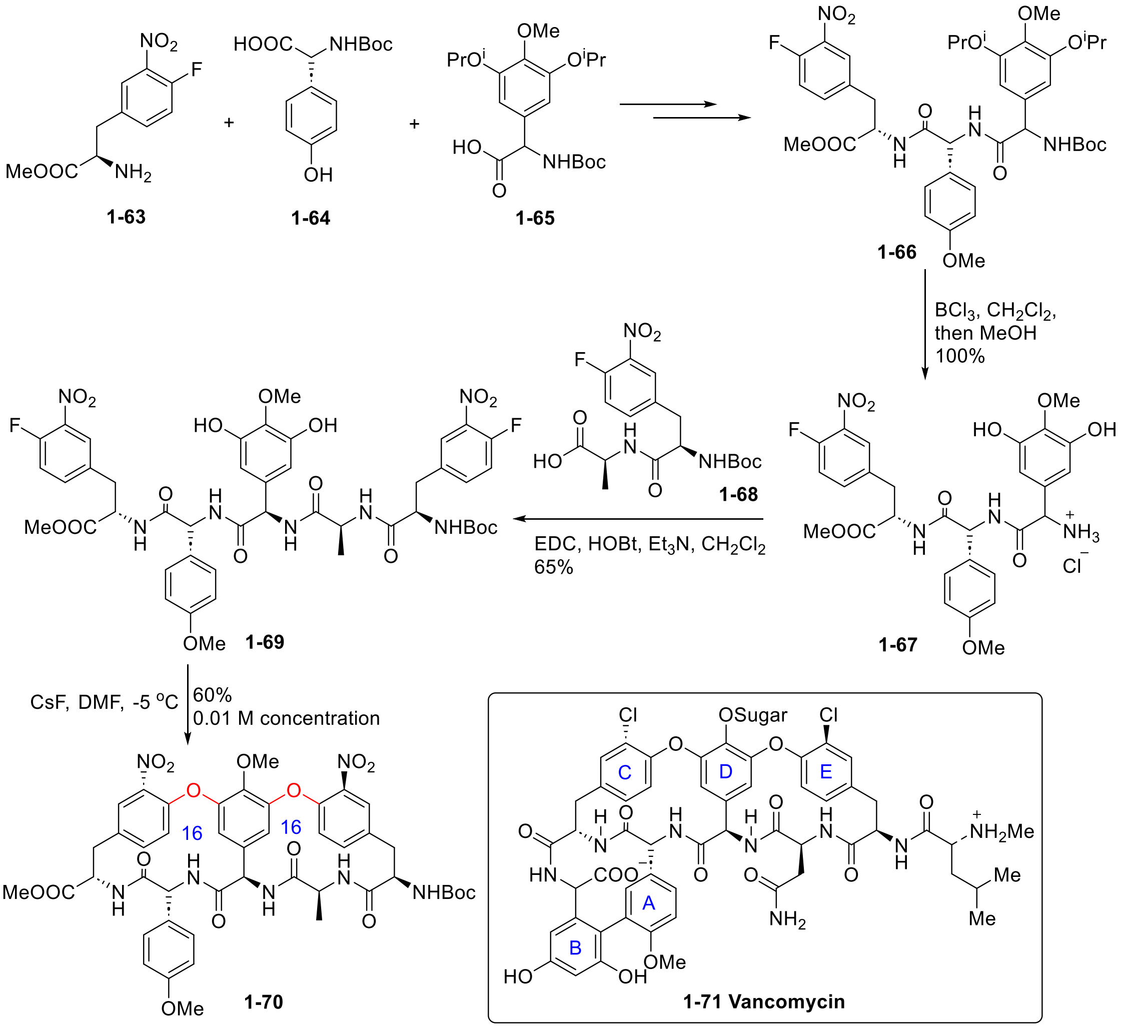
Then the Motuporamine C was generated with further 3 steps in an excellent yield.



Scheme 1.13 Total synthesis of Motuporamine C using RCAM reaction.

1.3.4 Nucleophilic substitution reactions

Nucleophilic substitution reactions (S_N2 and S_NAr substitutions) represent one of the most efficient approaches for macrocyclization, which have been utilized not only for the synthesis of simple macrocyclic structures but also for more complex structures. Despite some requirements of substitution reactions like the need to protect reactive functionalities, and the fact that they generally need to be performed under high dilution conditions, they possess several attractive benefits: (1) multiple reaction conditions and reagents are available, (2) a range of sites of ring closure can be investigated (for S_N2 processes), (3) reactions can be conducted readily on solid supports for diversity generation.[2] The development of Solid Phase Peptide Synthesis (SPPS) has led to the wide application of S_NAr substitution in the construction of constrained macrocyclic peptidomimetics, generally involving S_NAr reactions to link amino acid side chains. In addition, S_NAr-based macrocyclization is an effective method for the synthesis of natural products, especially those containing a biaryl ether in analogy to vancomycin, teicoplanin, bouvardin and piperazinomycin.[71] One interesting example is the synthesis of the model bicyclic C-O-D-O-E ring (16 +16) of vancomycin **1-71** by double intramolecular S_NAr based macrocyclization, which reported by Jieping Zhu in 1997.[71,72] Two coupling of three different amino acid analogues generated the tripeptide **1-66**, which was deprotected (BCl_3) to give the hydrochloride salt **1-67**. Segment coupling of the tripeptide **1-67** and the dipeptide **1-68** gave the pentapeptide **1-69**, which was ready for the double cyclization. They tried some different bases (K_2CO_3, CsF) in different solvents (DMF, Me_2SO) with or without additive (18-crown-6) and found that when dry CsF was used as a promoter in DMF (0.01 M) at –5 °C, the desired biaryl ether product **1-70** was formed and was isolated in 60% yield.

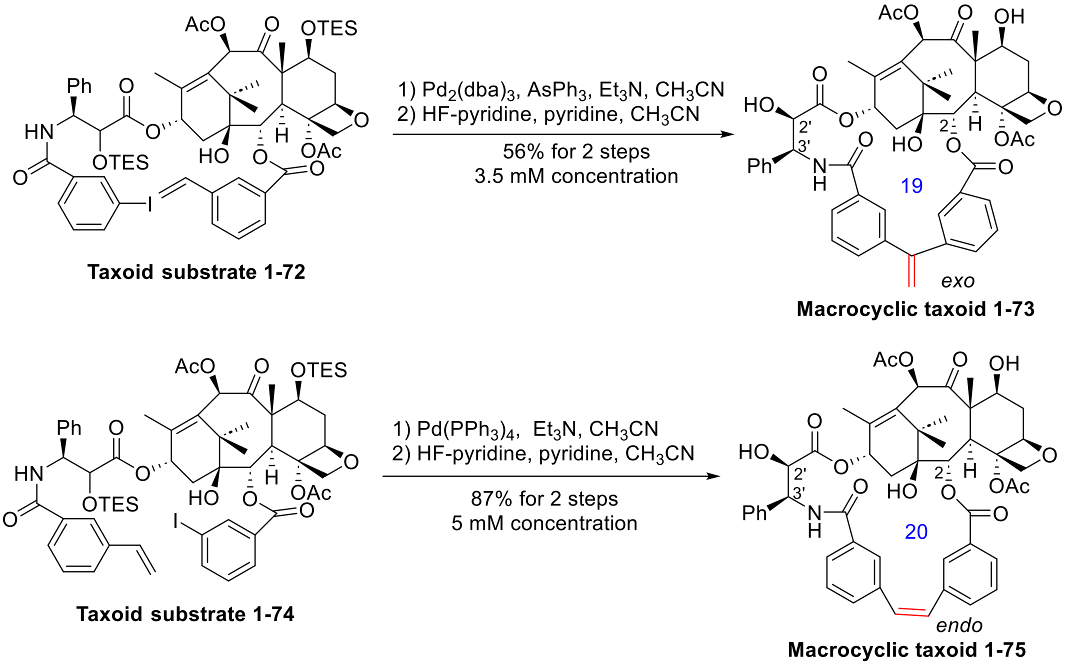


Scheme 1.14 Synthesis of model bicyclic C-O-D-O-E ring of vancomycin.

1.3.5 Palladium catalyzed reactions

During recent decades, palladium-catalyzed cross coupling reactions have evolved as powerful tools in organic synthesis driven by increasing understanding of palladium coupling catalytic cycles and the development of new and effective catalysts. The great significance of palladium-catalyzed C–C coupling reactions has been recognized by the award of the 2010 Nobel Prize in Chemistry to Professors Heck, Negishi, and Suzuki. Among many different palladium-catalyzed coupling reactions, Heck, Stille and Suzuki couplings, amongst others, have all been used to generate complex macrocyclic natural products and pharmaceuticals.[2,3,42,73]

The Heck reaction (Mizoroki-Heck reaction) can be broadly defined as the palladium-catalyzed coupling of alkenyl or aryl (sp^2) halides or triflates with alkenes to yield the substituted alkene products. The Heck reaction has been found to be a very useful approach when functionalized aromatics are a component of the macrocyclic molecule. The Heck reaction can be employed in the solid phase construction of cyclic peptides and the use of microwave irradiation can accelerate the synthesis of peptidomimetic macrocycles using this method.[74] Heck reactions have been applied in the synthesis of macrocyclic taxoids as well as other natural products. Xudong reported the synthesis of novel C2−C3′N-linked macrocyclic taxoids using intramolecular Heck reaction as the key cyclization step.[75] Taxoid bearing an olefin moiety at C2 and an iodide at C3′N gave *exo*-product **1-73**, when switching the positions of the olefin and the iodide moieties gave the *endo*-product **1-75** with up to 100% regioselectivity.



Taxoid substrate 1-72

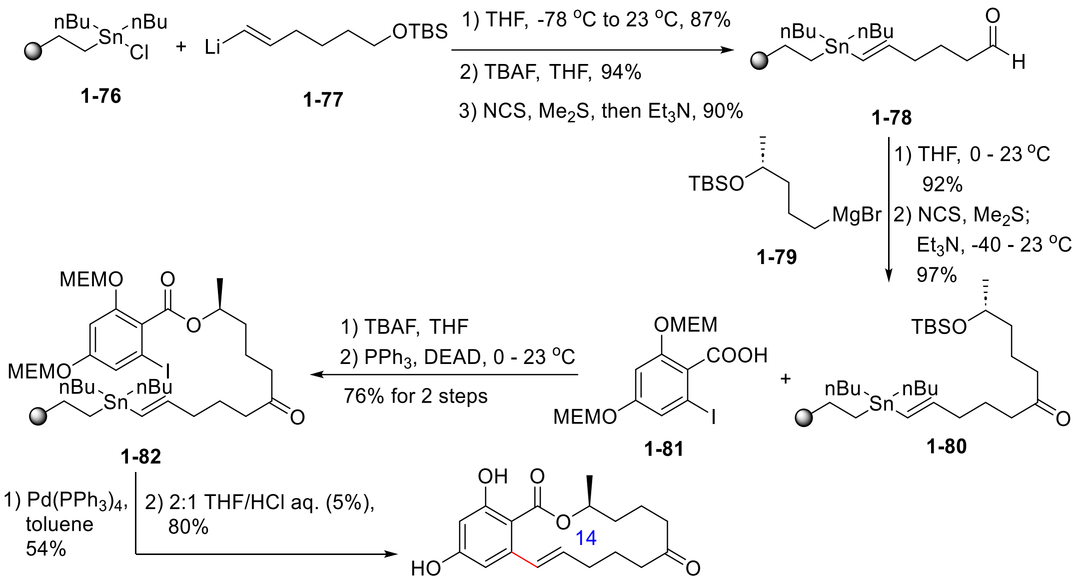
Macrocyclic taxoid 1-73

Taxoid substrate 1-74

Macrocyclic taxoid 1-75

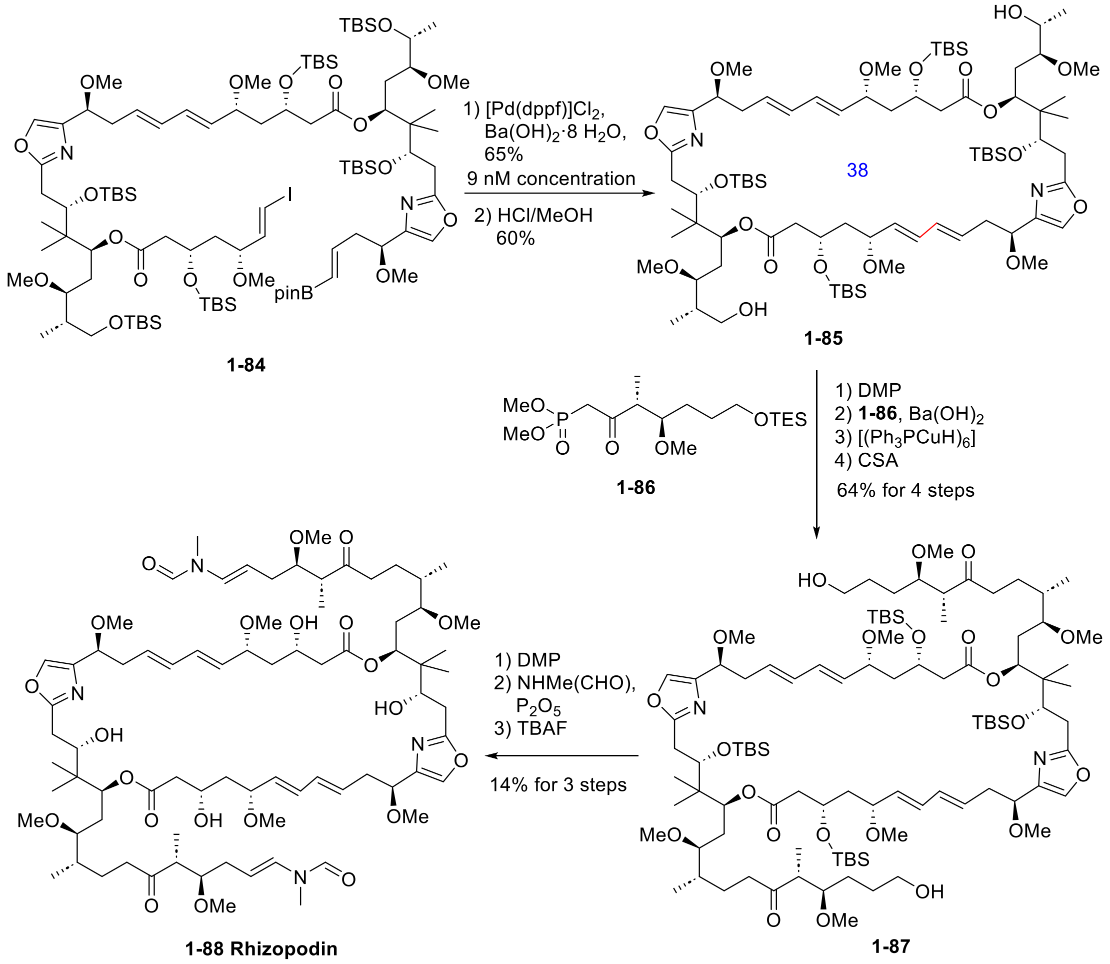
Scheme 1.15 Synthesis of macrocyclic taxoids using different Heck reactions.

The palladium-catalyzed cross-coupling of organic electrophiles with vinyl organotin compounds is today known as the Stille reaction. Due to its typically mild reaction conditions, easily prepared coupling partners, and the tolerance of a wide variety of sensitive functionalities, the Stille reaction is one of the most widely applied palladium-catalyzed C–C bond forming reactions, especially in the synthesis of macrocycles. In addition, Stille coupling was proved to be an efficient strategy in macrocyclic natural products using the cyclization-release solid phase synthesis. Nicolaou reported the total synthesis of the biologically active natural product (*S*)-zearalenone **1-83** using a new solid-phase method for the construction of macrocycles by a novel cyclo-release mechanism that employs the Stille coupling.[76] Using the lithium reagent **1-77** to displace the chloride from PHTC (polystyrene-di-*n*-butyltin chloride) **1-76**, after deprotection and oxidation, the *E*-vinyltin polymer **1-78** was obtained. Nucleophilic addition of Grignard reagent **1-79** to the aldehyde followed by Corey–Kim oxidation afforded **1-80** which was desilylated and coupled to carboxylic acid **1-81** to afford the desired precursor **1-82**. The (*S*)-zearalenone **1-83** was produced after **1-82** exposure to [$Pd(PPh_3)_4$] catalyst in toluene (cyclo-release) and acid-induced deprotection.



Scheme 1.16 Solid-phase total synthesis of (*S*)-zearalenone.

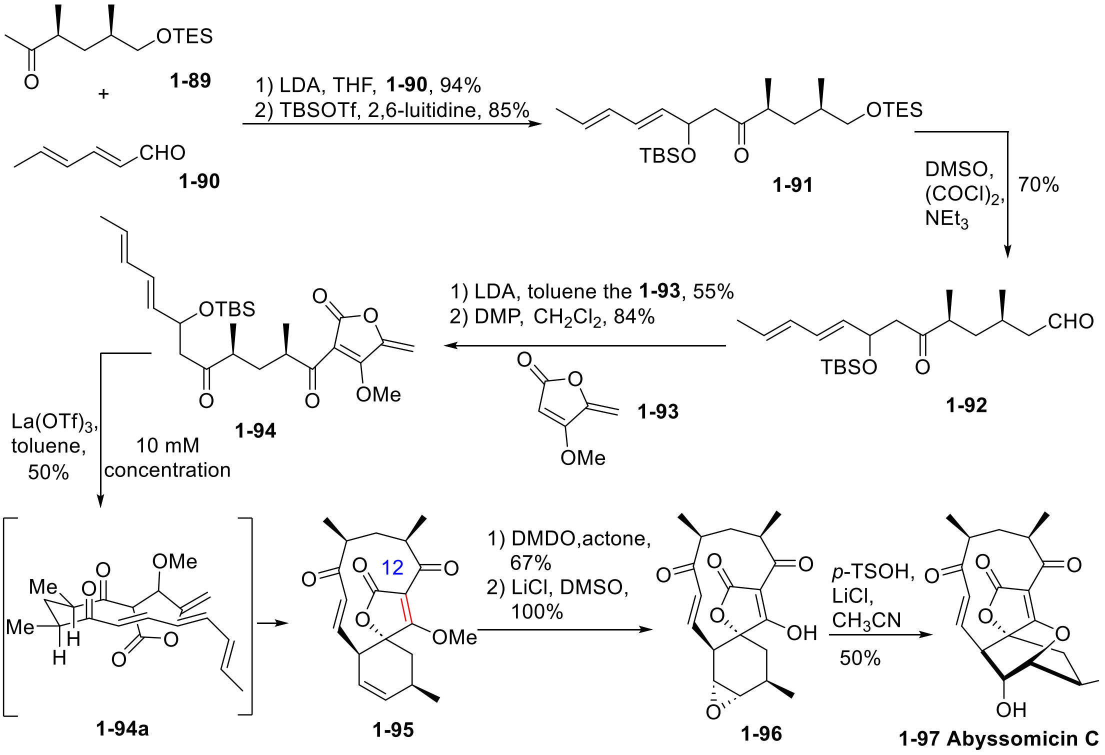
The Suzuki reaction (Suzuki–Miyaura reaction) is the palladium-mediated cross coupling of organic electrophiles, such as aryl or alkenyl halides and triflates, with organoboron compounds in the presence of a base. Suzuki coupling has a number of remarkable advantages, some of which are similar to those in Stille couplings, such as the relative ease of preparation of organoboron compounds, relative stability to air and water, and the use of typically mild reactions conditions. Additionally, and in contrast to the Stille reaction, Suzuki reactions usually lead to the formation of nontoxic by-products (certainly far less toxic than organotin species). That makes Suzuki coupling one of the most general reactions for the synthesis of aryl-containing complex organic structures, and it has been utilized widely for the synthesis of macrocyclic molecules. Dieckmann reported the total synthesis of Rhizopodin **1-88**, which was isolated from the myxobacterium *Myxococcus stipitatus*, applying Suzuki coupling as the final macrocyclization key step.[77,78] The Suzuki macrocyclization of the linear precursor **1-84** proceeded in the presence of catalytic Pd(dppf)Cl_2 in 65% yield, giving the desired C2-symmetric macrocyclic core **1-85**. Finally, the desired Rhizopodin was obtained after the installation of the remaining side chains by Horner-Wadsworth-Emmons (HWE) coupling/hydrogenation reaction sequence.



Scheme 1.17 Total synthesis of Rhizopodin using Suzuki coupling as key cyclization step.

1.3.6 Diels−Alder reactions

The Diels−Alder reaction is a [4+2] cycloaddition between a conjugated diene and a substituted alkene to form a substituted cyclohexene derivative. Through the simultaneous construction of two new carbon–carbon bonds, the Diels–Alder reaction provides a reliable way to form 6-membered rings with good control over the regio- and stereochemical outcomes. Appropriate design of Diels–Alder processes also allows their use for macrocyclization. A remarkable example illustrated this is the synthesis of the natural product Abyssomicin C.[79] First, the deprotonated ketone **1-89** reacted with aldehyde **1-90** gave the silyl ether **1-91**, which provided the aldehyde **1-92** after the Swern oxidation. The linear precursor **1-94** was obtained through the Dess–Martin periodinane oxidation of the aldehyde **1-92** and deprotonated **1-93**. In the presence of lanthanum(III) triflate, the intermolecular Diels–Alder reaction happened (*via* **1-94a**) and afforded the target tricycle **1-95** (50%). Epoxidation and enol ether hydrolysis of macrocycle **1-95** gave the precursor **1-96**, which went through a final step of ring opening of the epoxide to generate the desired product **1-97**.

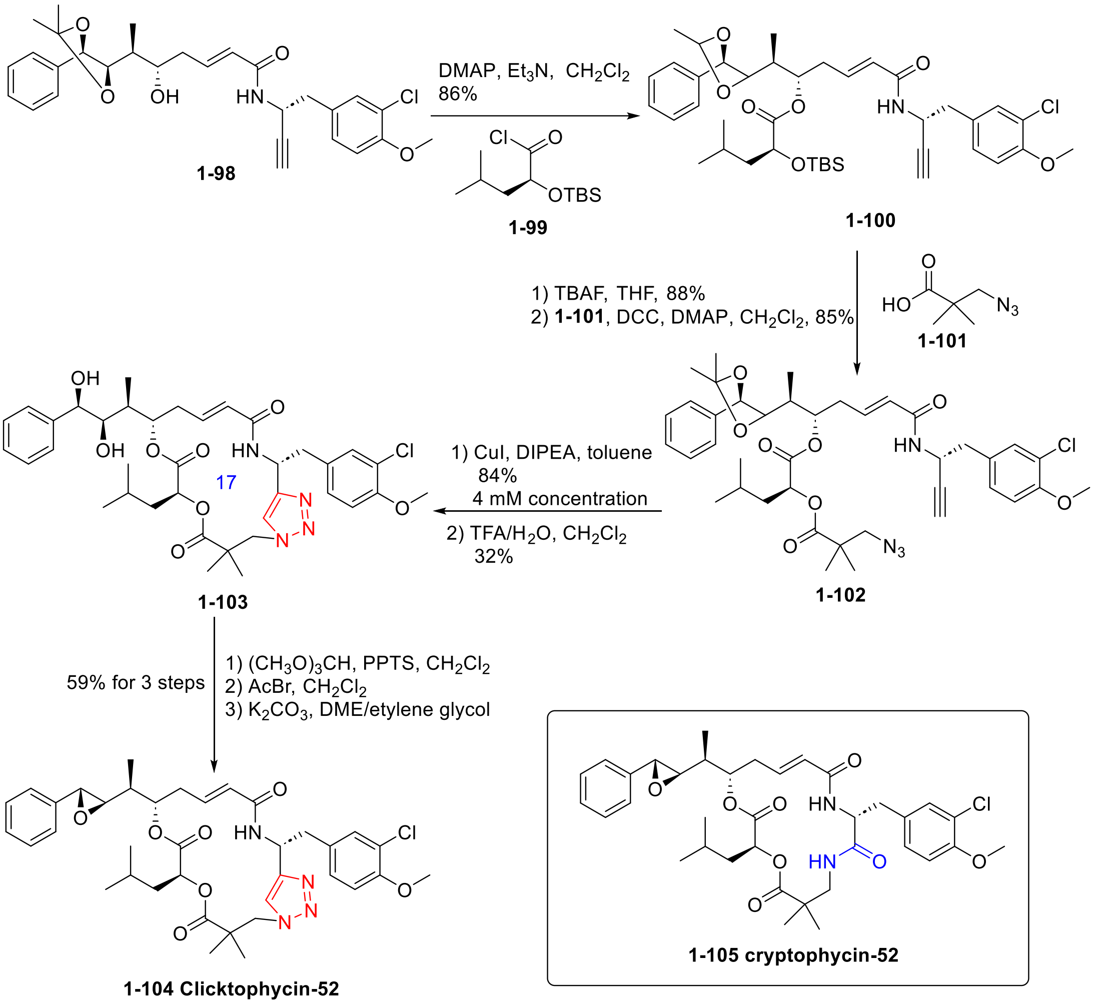


Scheme 1.18 Diels-Alder macrocyclization within the total synthesis of Abyssomicin C.

1.3.7 Copper(I) catalyzed Azide−Alkyne Cycloaddition (CuAAC)

The azide-alkyne Huisgen cycloaddition is a 1,3-dipolar cycloaddition between an azide and a terminal or internal alkyne to give a 1,2,3-triazole, which fulfils the criteria of “click chemistry” well: the reaction must be modular, wide in scope, give very high yields, generate only inoffensive by-products that can be removed by non-chromatographic methods. It should also be stereospecific, involve the use of no solvent or a solvent that is benign or easily removed, and have simple product isolation (the term click chemistry was coined by Sharpless in 2001).[80,81] Copper catalyzed azide−alkyne cycloaddition (CuAAC) is a variant of the Huisgen 1,3-dipolar cycloaddition. Compared to the azide-alkyne Huisgen cycloaddition, the CuAAC can be conducted at room temperature or with only moderate heating, avoiding heating at high temperature and long reaction times. It typically results in the formation of 1,4-regioisomer of 1,2,3-triazoles as sole products, rather than a mixture of the 1,4- and the 1,5-regioisomers. More importantly, the rate of CuAAC is up to 10 million times faster than Huisgen cycloaddition. This makes it a near ideal click reaction and has become incredibly popular in the bio-conjugation of enzymes/peptides, the synthesis of polymers and biopolymers, and in medicinal chemistry, with the 1,2,3-triazole heterocyclic motif commonly found in pharmaceutical and bioactive molecules.[82–85]

CuAAC also provides a valuable tool for the preparation of some macrocyclic structures, primarily peptidomimetic, including a β-turn mimic.[83,86] For example, the Sewald group reported the synthesis of "Clicktophycin-52", a bioactive cryptophycin-52 triazole analogue. They replaced the *trans*-amide peptide linkage in the cryptophycin derivatives with 1,4-disubstituted 1*H*-1,2,3-triazole moiety to probe the bioequivalence.[87] The segment **1-98** was condensed with the acyl chloride **1-99** in the presence of DMAP and Et_3N affording the TBS-protected compound **1-100**. The silyl ether was cleavaged by TBAF then Steglich esterification with azidopivalic acid **1-101** to introduce the azide motif and obtain the seco-precursor **1-102**. The 'Clicktophycin' precursor **1-102** was cyclized through CuAAC at room temperature, the desired cyclomonomer **1-103** was obtained in 32% yield after acidic cleavage of the acetonides, whereas cyclodimer was obtained in 27% yield. Finally, "Clicktophycin-52" **1-104** was obtained after the conversion of *syn*-diol **1-103** into epoxide over further three steps and showed improved activity over cryptophycin-52 when assayed against a broad panel of tumor cells.

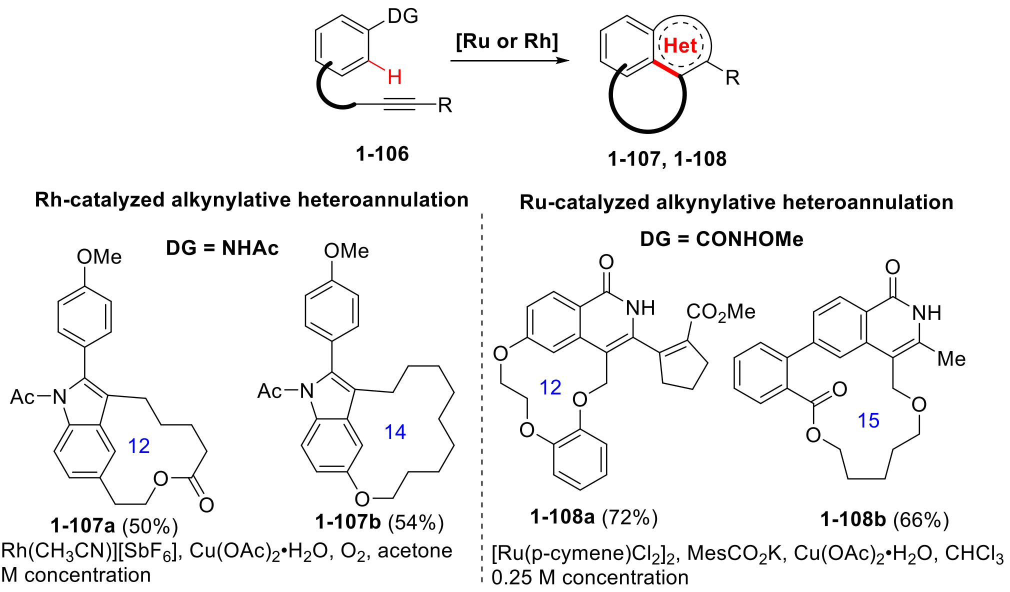


Scheme 1.19 Click reaction for the synthesis of cryptophycin triazole derivative.

1.3.8 C–H functionalization

Carbon–hydrogen bond functionalization (C–H functionalization) has evolved as a powerful synthetic tool for cleaving a C–H bond and forging new C–X bond (where X is usually carbon, oxygen, or nitrogen) *via* transition metal-catalyzed activation. Thus C–H functionalization has also been applied in the synthesis and late-stage modification of amino acids and peptides, and its potential is starting to be seen in the macrocyclization of cyclic peptides and natural macrocycles. The C–H activation macrocyclization strategy has significant benefits like high atom economy, minimum pre-functionalization requirements and site-selectively functionalization. Since the first examples of macrocyclization *via* C–H activation was reported by James in 2012, this approach has been proved to be efficient in the total synthesis of streptorubin B, carbamidocyclophane M, streptide, vancomycin and other natural macrocycles.[88–90]

Macrocyclic alkynylative heteroannulations *via* Rh/Ru- catalyzed directed *ortho*-C(sp^2)–H activation is one of the most efficient strategies in the synthesis of macrocycles using C–H activation. In 2014, Tao developed the first rhodium(III)-catalyzed intramolecular annulation of alkyne tethered acetanilides for the synthesis of fused tricyclic indole scaffolds **1-107** *via* C–H activation.[91] Then in 2016, the Cossy group reported the formation of novel 12- to 20-membered macrocyclic isoquinolones **1-108** *via* Ru-catalyzed alkynylative annulation using *O*-methylarenehydroxamates as directing groups.[92] (Scheme 1.20) This heteroannulative macrocyclization strategy has further extended to 2-pyridone based macrocycles, diarylamine bridged aza-macrocycles and cyclophane type macrocycles.[93–95]



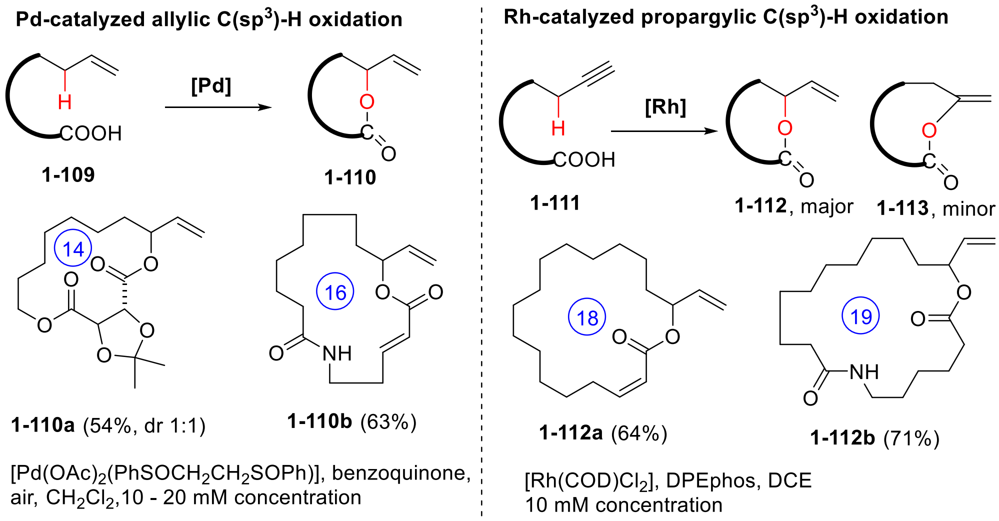
[Cp*Rh(CH$_3$CN)][SbF$_6$], Cu(OAc)$_2$•H$_2$O, O$_2$, acetone
0.01M concentration

[Ru(p-cymene)Cl$_2$]$_2$, MesCO$_2$K, Cu(OAc)$_2$•H$_2$O, CHCl$_3$
0.25 M concentration

Scheme 1.20 C(sp^2)–H activation strategies in macrocyclization.

An alternative strategy is the macrolactonization *via* Pd or Rh catalyzed allylic or propargylic C(sp^3)–H activation. In 2006, White described the first example of Pd-catalyzed macrocyclic oxidation process involving allylic C–H activation using carboxylic acid tethered terminal alkenes to generate 14 to 19 membered macrolides **1-**

110.[96] In an analogous approach, Breit disclosed a Rh-catalyzed propargylic C–H oxidation of terminal alkynes tethered to the carboxylic acid, for regioselective synthesis of vinyl appended macrocyclic lactones **1-112**.[97]



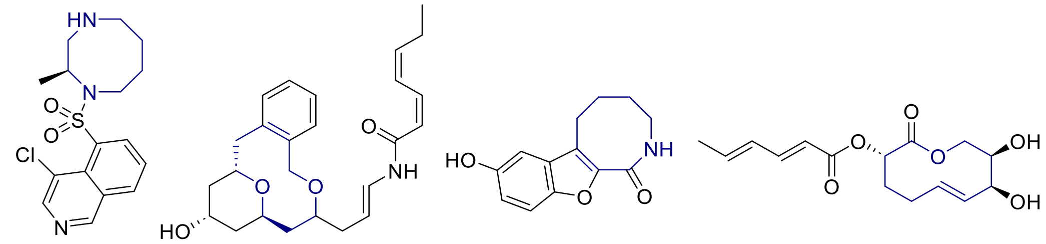
[Pd(OAc)$_2$(PhSOCH$_2$CH$_2$SOPh)], benzoquinone, air, CH$_2$Cl$_2$,10 - 20 mM concentration

[Rh(COD)Cl$_2$], DPEphos, DCE 10 mM concentration

Scheme 1.21 Macrocyclization *via* C(sp^3)-H activation.

1.4 Medium sized rings and their synthesis

Medium sized rings (8-11 membered rings) have important applications in diverse bioactive natural products and therapeutically important molecules (Figure 1.2). Similar to macrocycles, they normally have improved binding affinity to biological receptors and oral bioavailability due to their relative rigidity and diverse 3D spatial properties.[98–105]



1-114
H-0106
ROCK inhibitor

1-115
Apicularen A
anticancer

1-116
kb-NB96-53
PKD inhibitor

1-117
Pinolidoxin
phytotoxin

Figure 1.2 Selected bioactive medium sized rings.

However, despite their promise, the medicinal chemistry of medium sized rings has been underexplored in academia and the pharmaceutical industries, in part due to the well-known challenge of synthesizing them. Cyclization reactions for the synthesis of five- or six-membered rings and macrocycles are not as efficient in the synthesizing medium sized rings, because the kinetic and thermodynamic barriers associated with the synthesis of medium sized rings are typically higher than for other ring sizes.[106–109] On one hand, cyclization strategies are often hampered by entropic factors, as the cyclisation of a long linear precursor is often associated with significant loss of entropy. Furthermore, medium sized rings are small enough to experience unfavorable transannular interactions and strain, which can lead to large enthalpies of activation. One strategy to address this problem is to ‘grow’ medium sized rings *via* ring expansion reactions because the high kinetic barrier associated with direct cyclisation reactions to medium sized rings can be avoided (Figure 1.3).[110–113] Then the thermodynamic challenges became the most crucial problem for the synthesis of medium sized rings, fortunately, different ring expansion reactions can help solve this problem as well.[114,115]

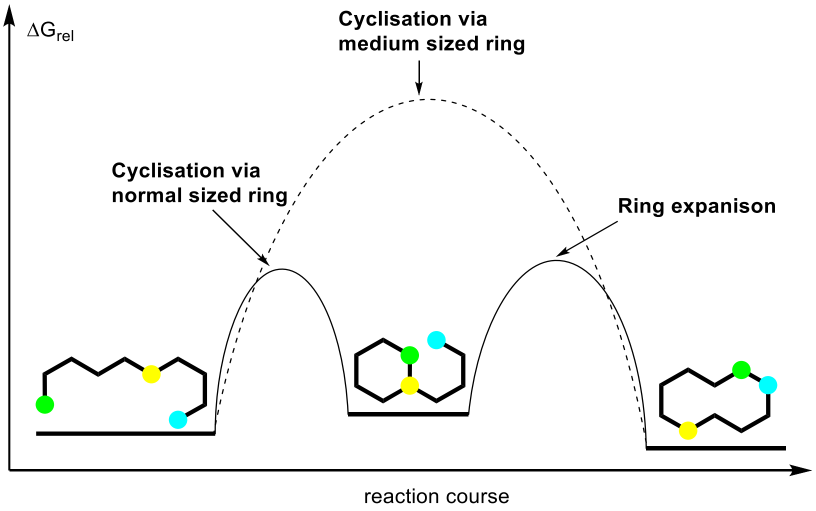


Figure 1.3 Kinetic benefits of direct cyclisation compared with ring expansion.

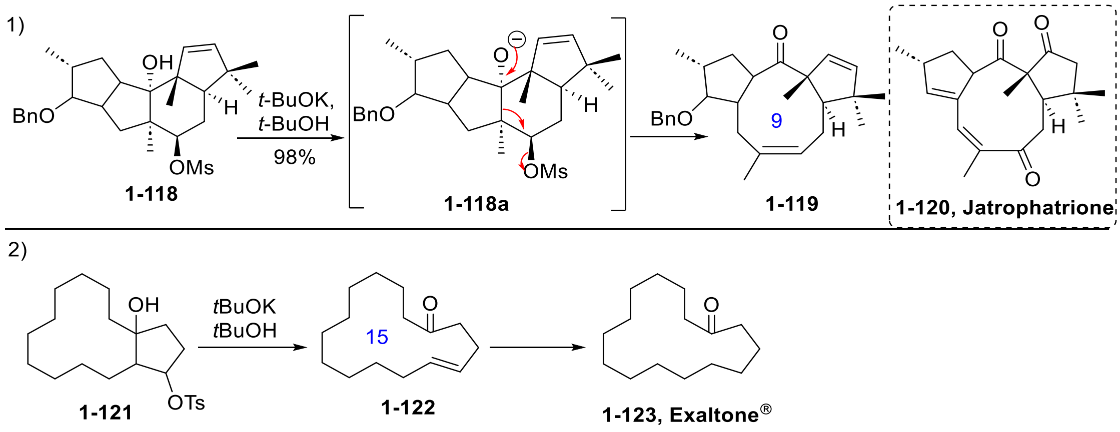
1.5 Ring Expansion reactions

Ring expansion is a conceptually different approach to cyclization reactions to prepare medium sized rings and macrocycles, which based on the enlargement of an existing cyclic scaffold. By “growing” larger ring systems from smaller rings, the most important cyclization step is based on the formation of easily accessible ring sizes (*e.g.*, 5- ,6- or 7-membered ring transition states), which makes the procedure to be more predictable and practical. In this approach, the often-difficult cyclization step can be entirely avoided due to the absence of dimerization/oligomerization pathways thus no need to require high dilution or preorganization. Ring expansion strategy has been used as a solution to produce traditionally difficult ring systems and applied in total synthesis of natural products or pharmaceuticals.

A great number of different ring expansion methodologies have been developed and can be categorized into four types: **fragmentation** reactions, **pericyclic** processes, **radical mediated** ring expansion and **side-chain insertion** processes. This section of the introduction is sub-divided according to these four reaction types, but is not designed to be a comprehensive cover of the topic (an excellent review of this area by Unsworth and Donald can be consulted for more detail[115]). The following sections will only concentrate on reactions in which the ring is expanded by ≥ 3 atoms, as these methods have the greatest potential in the synthesis of medium sized rings and macrocycles with applications.[115]

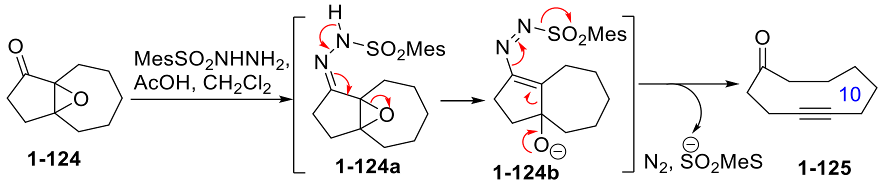
1.5.1 Fragmentation reactions

One of the simplest methods of ring expansion reaction involves the cleavage of the shortest bridge in a fused bicyclic system. Direct fragmentation reactions of pre-prepared fused bicyclic precursors to generate ring enlarged compounds tend to be irreversible processes owing to the loss of a leaving group. Thus, this approach can be used in the synthesis of relatively unstable systems, but sometimes complicated bicyclic precursors are required and unwanted transannular side reactions are sometimes observed following expansion. Grob/Wharton-type fragmentation is the one of most widely used ring expansion reaction, it's an elimination process mediated by an electron donating group extruding a leaving group.[111] A good leaving group can provide a strong thermodynamic driving force for fragmentation, which makes the ring expansion possible because considering ring-size alone, this is generally a thermodynamically unfavourable process. Grob/Wharton-type fragmentation reaction has been applied in a number of natural product synthesis, for example jatrophatrione, vinigrol, macrocyclic musks and others.[116–118] Jatrophatrione is an novel natural medium sized ring compound isolated from the roots of *Jatropha macrorhiza*, with [5.9.5] tricyclic framework and potent antileukemic activity.[116] Paquette and co-workers reported their total synthesis of jatrophatrione using the Grob fragmentation approach in 2002. The tetracyclic product **1-118** went through the fragmentation in the presence of potassium *tert*-butoxide to generate the desired [5.9.5] tricyclic framework **1-119** in an excellent 98% yield. With the main scaffold in hand, jatrophatrione **1-120** was obtained after further structural modification. Grob fragmentation approach also provided a simple method to form macrocyclic musk compounds (high value fragrance components), the fragmentation of the bicyclic **1-121** to form the 15-membered macrocycle **1-122**, which can be converted into the musk compound Exaltone after hydrogenation.[119]



Scheme 1.22 Grob fragmentation ring expansion to synthesize Jatrophatrione and Exaltone.

Another famous fragmentation reaction is Eschenmoser fragmentation reaction, which is the chemical reaction of α, β-epoxyketones with aryl sulfonylhydrazines to the afford the intermediate hydrazine that go through the fragmentation to generate alkynyl ketones. A relatively simple example to illustrate the key features of this reaction is the synthesis of cycloalkyne **1-125** described by Danishefsky.[120,121] Added mesitylene-2-sulfonohydrazide to the solution of the α, β-epoxyketone **1-124** resulting in Eschenmoser fragmentation to give the 10-membered cycloalkyne **1-125**. The stabilized arylsulifinate leaving group and generation of nitrogen gas give even stronger thermodynamic driving force for ring expansion than in the related Grob-type fragmentations.

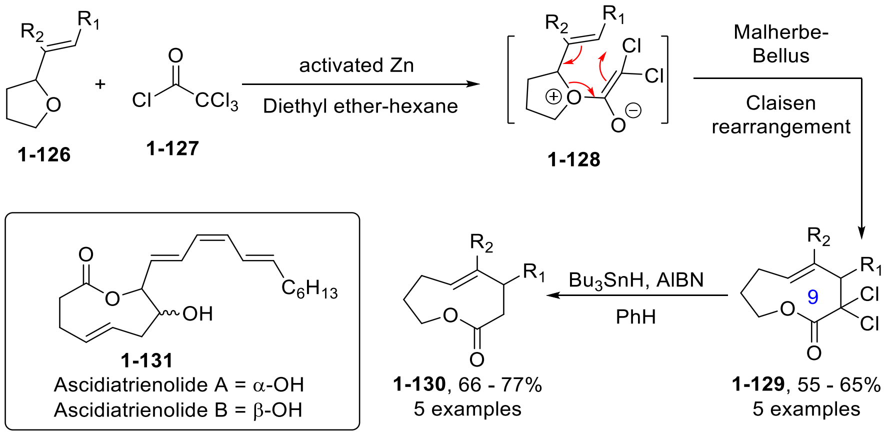


Scheme 1.23 Eschenmoser fragmentation to synthesize cyclodec-4-yn-l-one.

1.5.2 Pericyclic reactions

Pericyclic reactions are concerted reactions that proceed through a cyclic transition state. Pericyclic reactions have the three key characteristics: (1) no ionic, free radical or other discernible intermediates are produced during the reaction; (2) the reaction is relatively unaffected by solvent changes and acid and base catalysts, nor is it affected by free radical initiators and inhibitors; (3) pericyclic reactions require light or heat and are completely stereospecific. Due to these characteristics pericyclic reactions are a popular approach for the synthesis of complex targets including medium sized rings and macrocycles. The major classes of pericyclic reactions are cycloaddition, electrocyclic and sigmatropic rearrangements, each of them has broad application and have been proved to be efficient to form highly functionalized cyclic compounds. One example of the cycloaddition reaction is the Diels-Alder macrocyclization, which was applied in the total synthesis of Abyssomicin C, has already been described in the section **1.3.6**. Electrocyclic reactions, which often occur in nature, have been largely explored in biomimetic syntheses of complex natural product.[122]

However, the most commonly applied class of pericyclic reaction used in the synthesis of medium sized and macrocyclic rings *via* ring expansion are sigmatropic rearrangements. In this molecular rearrangement, one new sigma bond is formed because a σ bond or group shifts from one part of a π-bonded system to another distant adjacent π system in an intramolecular reaction with simultaneous rearrangement of the π system. Among all of the classes of sigmatropic rearrangements, [3,3] sigmatropic rearrangement is the most widely applied to access medium rings and macrocycles *via* ring expansion reactions.[123] One example is that developed by the Taylor group in York, who applied the zwitterionic Malherbe–Bellus–Claisen rearrangement in the synthesis of 9-membered lactone cores **1-130** of bioactive marine metabolites ascidiatrienolides in 1993. The 2-vinyl tetrahydrofurans **1-126** was treated with $CC1_3COCl$ and activated zinc in diethyl ether- hexane, the lactones **1-129** were obtained at 50 °C at good yields, respectively from 55% to 65% for 5 examples. Noteworthy, upon tin hydride-mediated radical dichlorination in the presence of AIBN (azobisisobutyronitrile), olefin *trans–cis* isomerisation was observed to afford exclusively the (*Z*)-isomers, which is thermodynamically preferred in 9-membered rings.

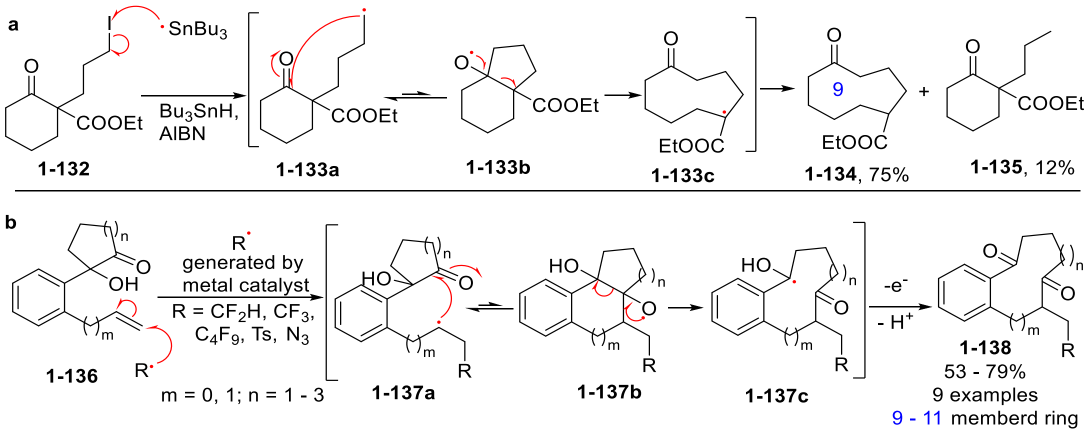


Scheme 1.24 Malherbe-Bellus-Claisen rearrangement in the ring expansion.

1.5.3 Radical Ring Expansion reactions

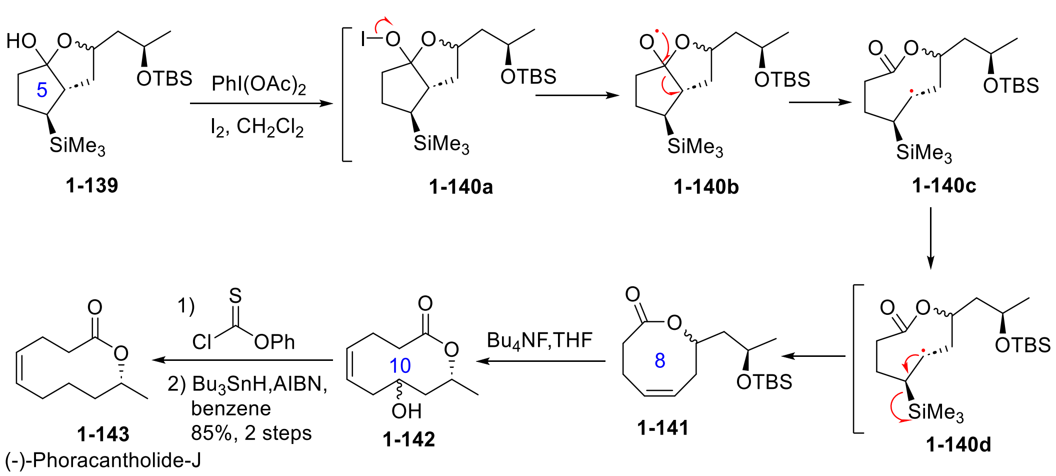
Radical reactions are important tools for the formation of various types of cyclic compounds including biologically active natural products and pharmaceuticals.[124] The typical characteristics of high-energy reactive intermediates and long transition state bonds provide to organic chemist many advantages like mild reaction conditions, high levels of regio- and stereo- control and significant functional group tolerance. With the development in radical chemistry, many practical methods for formation of medium- and large-sized rings *via* radical cyclization strategies have been developed. These reactions can sub-divided into processes initiated by *C*-, *O*- and *N*-centered radicals due to their different mechanisms.

Dowd–Beckwith type reactions are the most versatile and widespread radical ring expansion methods which can generate up to a four-atom ring expansion *via C*-centered radical. Reaction of **1-132** proceeded through the tin hydride promoted production of primary radical **1-133a** followed by attack of the latter on the neighboring carbonyl group. The resulting high-energy oxygen centered radical **1-133b** underwent ring opening to yield the stabilized radical **1-133c** that adjacent to the ester with subsequent reduction to **1-134**. However, the competitive formation of unwanted reduction products **1-135** was commonly detected in many radical processes based on Bu_3SnH.[125–129] As the Bu_3SnH is very toxic, some more modern methods including photochemistry, electrolysis and homolysis of azo compounds have been applied to generate the desired primary radical.[130,131] For example, Liu and co-workers developed an alternative strategy to form radical in the substrate *via* the addition of an external radical to an olefin (Scheme 1.25-b).[132] Sulfonyl, perfluorobutanyl, difluoromethyl and azide radicals were generated by different metal catalysts, their addition to the alkene initiated the Dowd-Beckwith ring expansion and generated 9 – 11 membered medium sized rings.



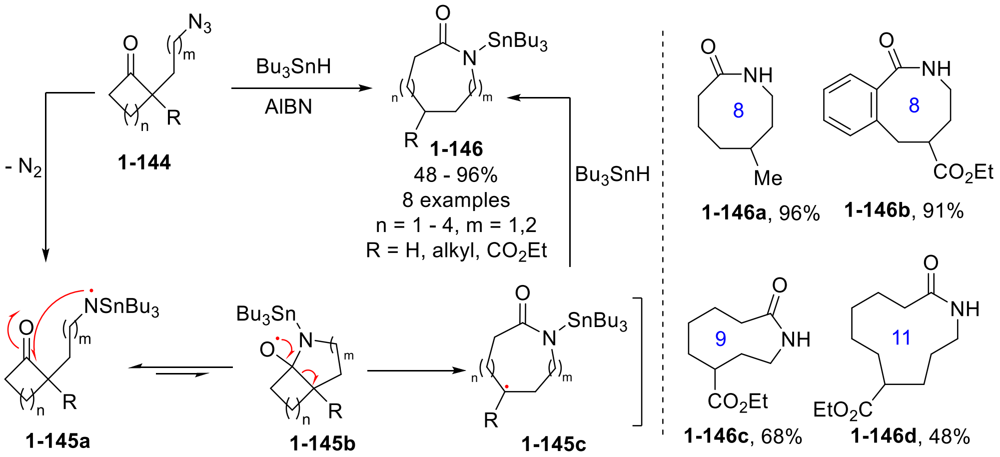
Scheme 1.25 The Dowd-Beckwith *C*-centered radical ring expansion reactions.

As the key step in Dowd–Beckwith type ring expansions is the reversibly generation of high-energy oxygen centered radicals, an oxygen centered radical can be generated directly from a corresponding alcohol and undergo a radical ring expansion in a related fashion. One impressive example is that Posner and coworkers reported a 5 → 8 → 10-membered ring sequential ring-enlargement sequence, toward the total synthesis of 10-membered natural lactone (–)-phoracantholide-J.[133,134] The hemiketal **1-139** together with PhI(OAc)$_2$ to undergo oxidative radical fragmentation to form radical **1-140c**, which reacted further, eliminating a trimethylsilyl radical to form 8-membered lactone **1-141.** After the desilylation, the secondary alcohol spontaneously translactonized into 10-membered lactone **1-142**, which underwent another radical deoxygenation to produce the desired (–)-phoracantholide-J.



Scheme 1.26 Posner’s oxidative radical fragmentation (*O*-centered) ring expansion.

In 1993, Kim and co-workers reported a novel method of aminyl radical formation, in which the action of tributylstannyl radical upon an azide group can generate the nitrogen centered radical and allow the formation of lactams from cyclic ketones.[135] The azide **1-144** was transformed to the nucleophilic aminyl radical **1-145a** (nitrogen centered radical) in the presence of tributylstannyl radical, which can undergo a Dowd–Beckwith type ring expansion (**1-145b** → **1-145c**) to generate different ring sized lactams **1-146**. In this ring expansion, the formation of the more stable tertiary radical **1-145c** provided the driving force.

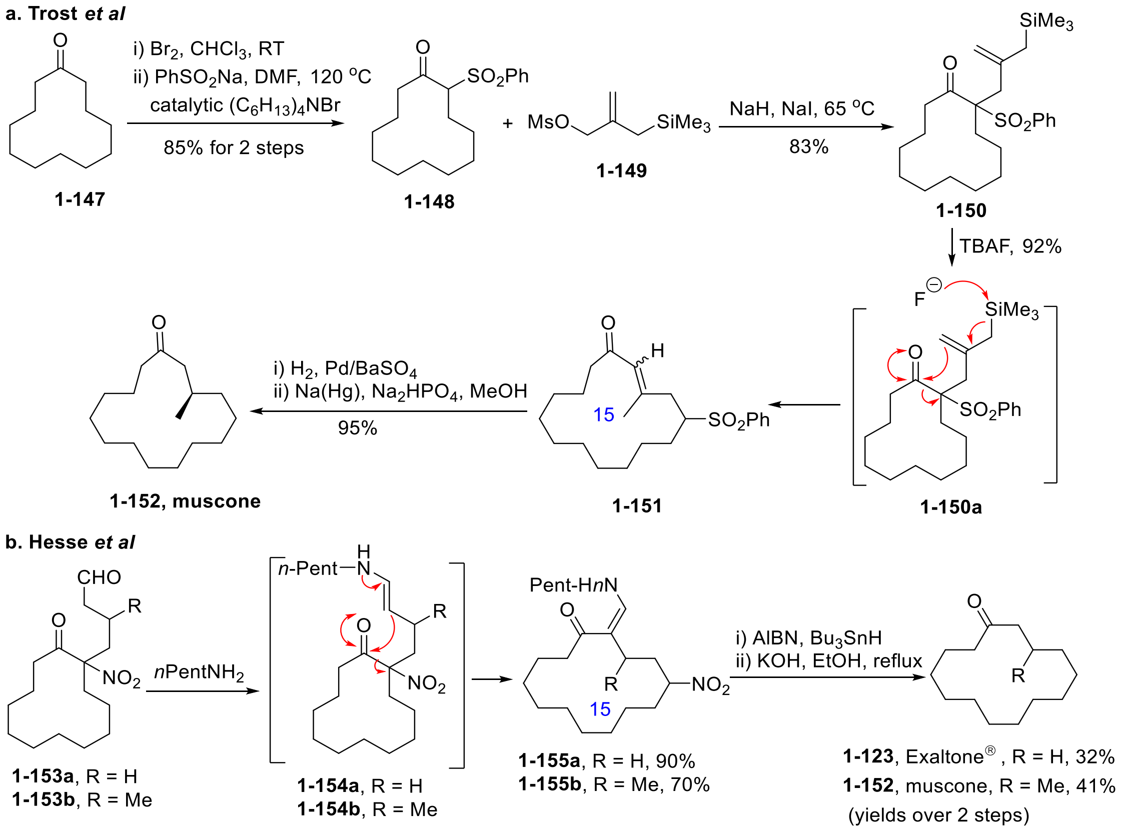


Scheme 1.27 Nitrogen centered radical ring expansion.

1.5.4 Side chain insertion reactions

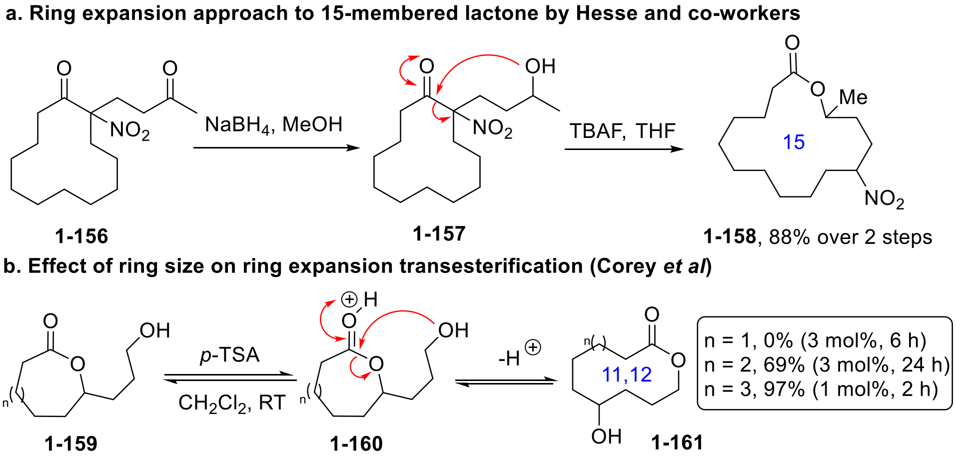
Side chain insertion type ring expansion is a special category of ring expansion reactions, that typically operates *via* three stages: (1) addition of a linear fragment to an already existing cyclic molecule; (2) the formation of a fused bicyclic system; (3) fragmentation of the bridging bond in an elimination type reaction, resulting in an overall ring expansion. Typically, as the side chain insertion process involves the reaction of a nucleophilic side chain with an electrophilic site on the ring to be expanded and forms C–N, C–O and C–C bonds, it can be further divided into reaction modes based on C–N, C–O and C–C bond formation.[115]

Carbon-carbon bond forming ring expansion is the most valuable ring expansion method in organic synthesis, especially in the synthesis of commercially important macrocyclic musk compounds.[118] In 1980, Trost and co-workers reported an innovative three-carbon condensative expansion method and applied it in the synthesis of muscone **1-152** with a high yield (62% overall yield from cyclododecanone **1-147**).[136] The allylation of β-ketosulfone **1-148** with mesylate **1-149** afforded the ring expansion precursor **1-150**. Treatment with catalytic TBAF to **1-150a** initiated ring expansion, *via* an intramolecular carbonyl addition and ring opening fragmentation process, to form the 15-membered enone **1-152** after some reductive steps to complete the synthesis. This methodology is not limited to organosilicon precursor; Hesse reported a related process driven by the formation of the stabilized vinylogous amide functionality intermediate **1-154**, which then converted into macrocyclic musk Exaltone® **1-123** and muscone **1-152** by radical denitration and basic ethanolysis.[137,138]



Scheme 1.28 C–C bond forming side chain insertion in the synthesis of macrocyclic musk.

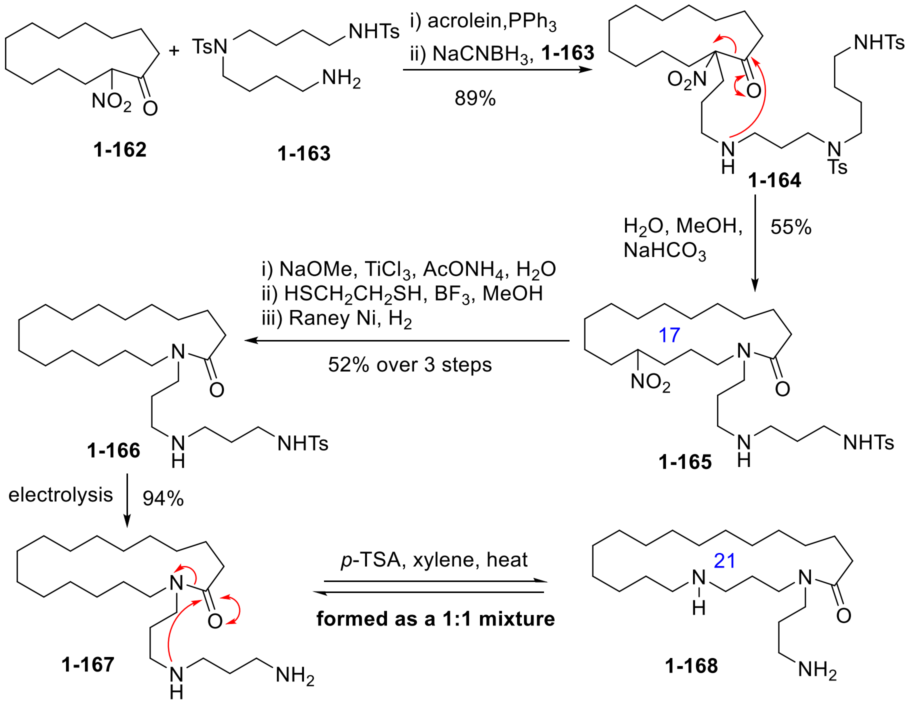
C–O bond formation ring expansion is an efficient tool for the synthesis of macrolactones using basic conditions (TBAF or NaH typically) to promote ring expansion. An early representative example reported by the Hesse group is given in Scheme 1.29-a). The ring expansion precursor **1-157** was produced from the 2-nitrocyclododecanone derivative **1-156**, however, it didn't rearrange spontaneously. Basic conditions (TBAF) were applied to facilitate the ring expansion process and afforded the 15-membered lactone **1-158** in an impressive 88% yield over the two-steps.[139] The electron-withdrawing nitro group plays a key role in facilitating the fragmentation step, and various electron withdrawing groups were later utilized to drive ring expansion in related reactions, including nitriles and sulfones.[140–142] Ring expansion transesterification reactions have also been reported (Corey and co-workers in 1977),[140] however with no overall change in functional group composition during this transformation, the outcome of these reversible reactions is driven almost entirely by ring size. The different yields of lactones **1-161** shows the difficulty in producing thermodynamically unstable ring sizes, especially medium sized rings.


a. Ring expansion approach to 15-membered lactone by Hesse and co-workers

b. Effect of ring size on ring expansion transesterification (Corey *et al*)

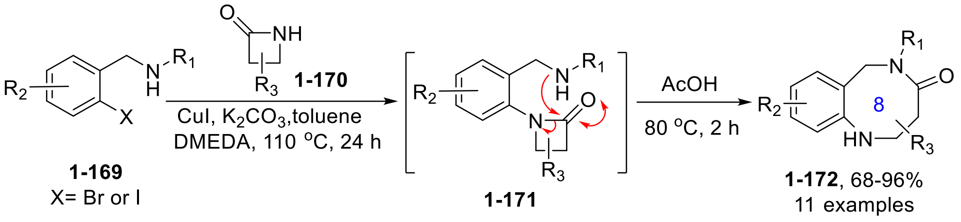
Scheme 1.29 C–O bond forming ring expansion in the synthesis of macrolactones.

Carbon-nitrogen bond forming side chain insertion ring expansion is a very important strategy in the synthesis of natural and pharmaceutical nitrogen-containing macrocyclic compounds, especially macrocyclic peptides and peptide mimetics. Using amines as the pendant nucleophile, many synthetic advantages were introduced in this type reactions. Amine protecting groups have been extensively studied and developed, affording abundant choices for different functional groups and reaction conditions. Therefore, unwanted side reactions such as dimerization or transannular interactions can be avoided once a suitable protecting group was applied and deprotected properly when needed. The revealed amine is also a good nucleophile and has the ability to take part in another ring expansion process with carefully designed. One example is the synthesis of macrocyclic spermidine alkaloids reported by Hesse, which is known as "Zip reaction".[112,143,144] First, the ring expansion precursor **1-164** was prepared *via* Michael addition (between nitrated ketone **1-162** and acrolein) and reductive amination (with amine **1-163**). Intramolecular attack of the proximal amine nucleophile, through a fused six-membered hemiaminal, instigates ring expansion to amide **1-165**. In this step, the nitro group plays an important role in stabilizing the extruded carbanion in the ring expansion process. Then the second ring expansion precursor compound **1-167** was formed after the removal of nitro group and deprotection of the tosyl protecting group. However, this ring expansion was significantly slower and produced a 1:1 equilibrating mixture of compound **1-167** and its ring expanded isomer **1-168**, though it was being heated at reflux in a strong acidic condition. The reversible nature of this type ring expansions really results a major challenge without such conditions.



Scheme 1.30 "Zip reactions" in the synthesis of macrocyclic alkaloid derivative.

One approach reported by Buchwald and co-workers provided a solution: using the release of a strained ring system (4-membered ring) to provide the required driving force for ring expansion.[145] A copper-catalyzed coupling between aryl bromides/iodides with pendant amine groups **1-169** and β-lactams **1-170** generated the ring expansion precursor **1-171**, which afforded the ring expansion products **1-172** after the transamidation by the pendant amine in a good to excellent yields.



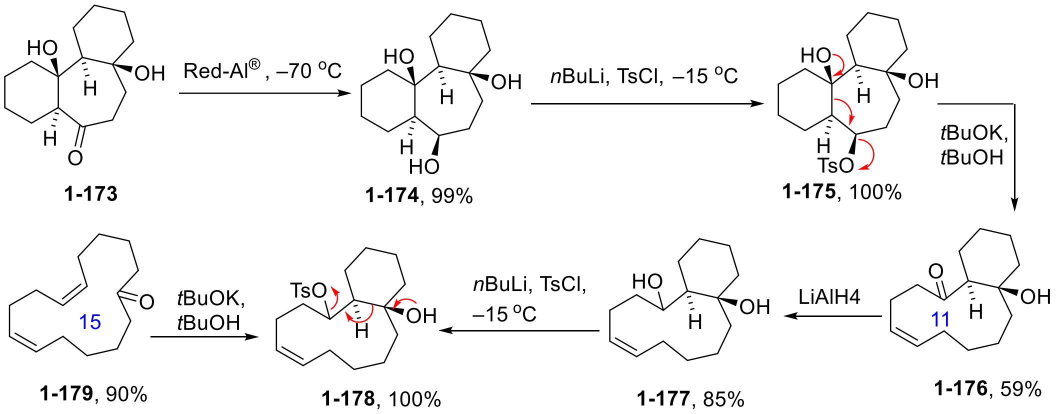
Scheme 1.31 Tandem Cu-catalyzed C-N coupling/ring expansion.

1.6 Consecutive Ring Expansion

As seen in the “Zip reaction” showed in Scheme 1.30, consecutive ring expansion is a powerful way to generate larger medium sized rings or macrocycles quickly. This strategy of ‘growing’ large ring systems *via* the sequential or iterative insertion of smaller linear fragments is known as consecutive ring expansion. Consecutive ring expansion methods are much less common than single ring expansion methods, although there are notable exceptions. Known procedures can be classified into 3 main categories fragmentation, pericyclic process, and side-chain insertion process according to ring expansion types.[114]

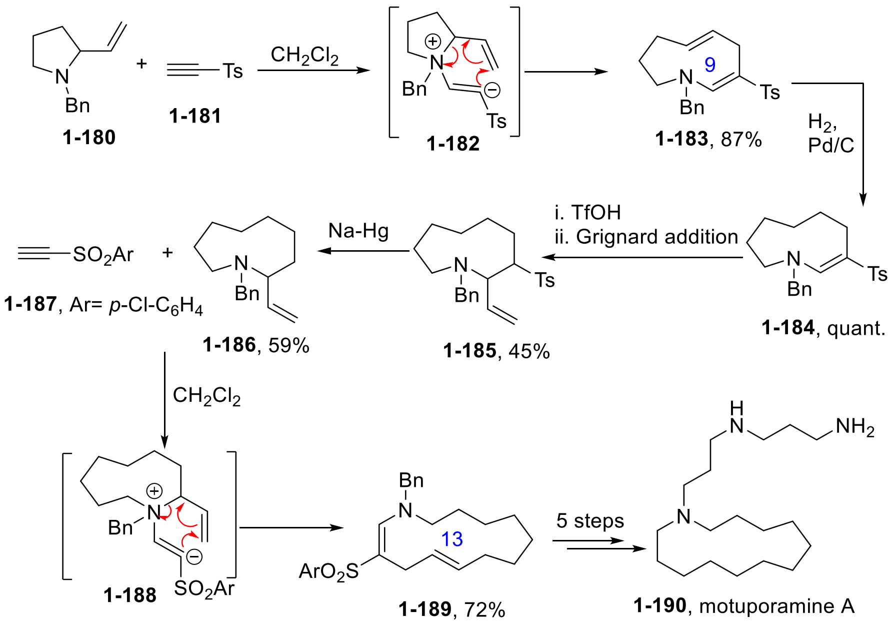
Fragmentation reactions are one of the simplest methods of ring expansion reaction, a selection of carefully designed fragmentation sequences have been developed for the synthesis of medium sized rings and macrocycles. In 2002, Thommen and co-workers reported the synthesis of 15-membered macrocyclic ketone **1-179** *via* consecutive Grob fragmentations, starting from tricyclic diol **1-173**.[146] First, the cis-triol **1-174** was obtained by the diastereoselective reduction of the ketone group of **1-173** using Red-

Al®, which was followed by tosylation using *n*-butyllithium to produce the product **1-175**. Then the first Grob fragmentation was performed upon treatment with potassium *tert*-butoxide to furnish the dicycle product **1-176**. Lithium aluminum hydride reduction of **1-176** followed by tosylation of the secondary alcohol to form **1-178**, which allowed the second Grob fragmentation, promoted by potassium *tert*-butoxide again to afforded 15-membered ring-expanded dienone **1-179** in an excellent yield.



Scheme 1.32 Consecutive Grob fragmentation sequence ring expansion.

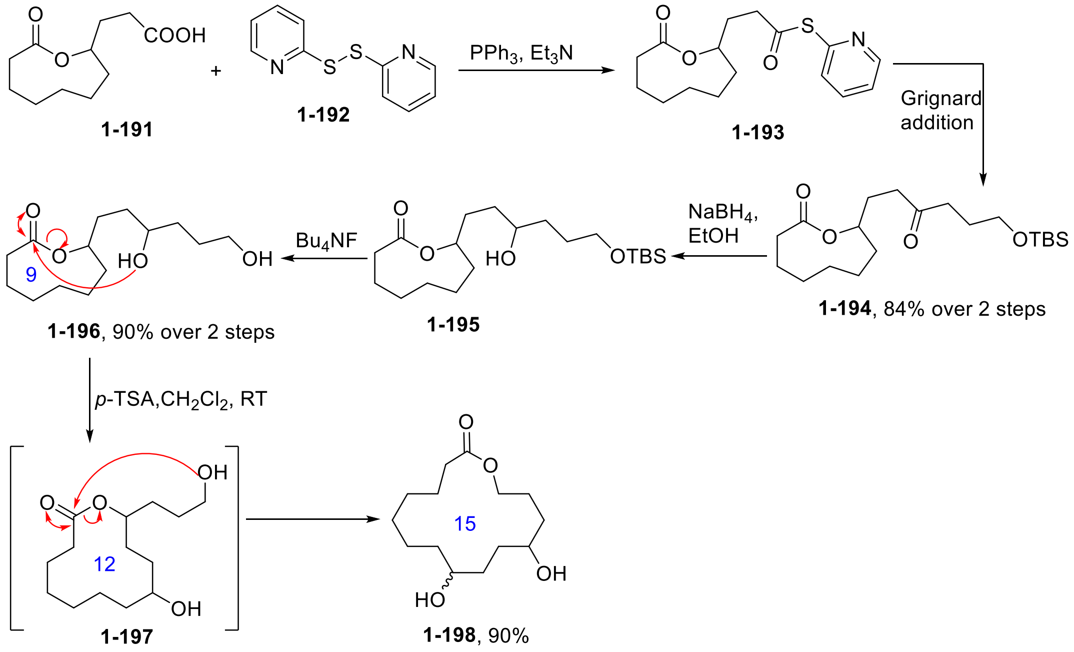
Sigmatropic rearrangements typically require a strong thermodynamic driving force to avoid the formation of multiple products in equilibrium. Sequential sigmatropic rearrangements (both sulfur and nitrogen-mediated rearrangements) have been used in natural product synthesis.[114] An interesting example is that Back and co-workers reported a double 3,3-sigmatropic rearrangement approach as part of the synthesis of 13-membered natural macrocycle motuporamine A.[147] The first zwitterionic species **1-182** was generated from the 2-vinylpyrrolidine **1-180** and acetylenic sulfone **1-181**, which then underwent 3,3-aza-Cope rearrangement *in situ* to produce ring-expanded enamine product **1-183** in the yield of 87%. In order to perform this aza-Cope rearrangement again, a similarly vinyl compound was needed to generate the second zwitterionic species. The 9-membered medium sized ring **1-183** was hydrogenated and then treated with triflic acid and the addition of a vinyl Grignard reagent to generate the product **1-185** with the vinyl group. Using a sodium-mercury amalgam to remove the tosyl group (compound **1-186**), which is not necessary for ring expansion but necessary for the synthesis of motuporamine natural product target. Then the same conjugate addition/aza-Cope rearrangement sequence was performed as the pyrrolidine **1-180** to enlarge the 9-membered ring further to furnish the 13-membered amine **1-189** in a good yield, an additional five steps were performed to complete the total synthesis of motuporamine A.



Scheme 1.33 Consecutive 3,3-aza-Cope rearrangement ring expansion reactions.

Consecutive side-chain insertion reactions are the most common class of ring expansion used in consecutive ring expansion processes. In this category, transamidation- and transesterification-type processes are the most frequently reported reactions. Reactions similar to the “Zip reaction” method described earlier (Scheme 1.30) are representative of many transamidation-type ring expansions to synthesize medium sized rings and macrocycles (macrolactams or polyamides). Related transesterification reactions (translaconization, total synthesis (–)-Phoracantholide-J, Scheme 1.26) can also be used to synthesize medium sized and macrocyclic lactones, although they are less common compared to transamidation ring expansion, perhaps because the low frequency of medium sized and macroclic lactones in nature. In 1977, Corey and Nicolaou performed consecutive transesterifications processes to generate thermodynamically controlled macrocyclic lactone products.[148] The starting lactonic acid **1-191** was treated with dithiobispyridine **1-192** to generate the corresponding pyridine thioester **1-193**, which was reacted with Grignard reagent to produce ketolactone **1-194**. The dihydroxylactone

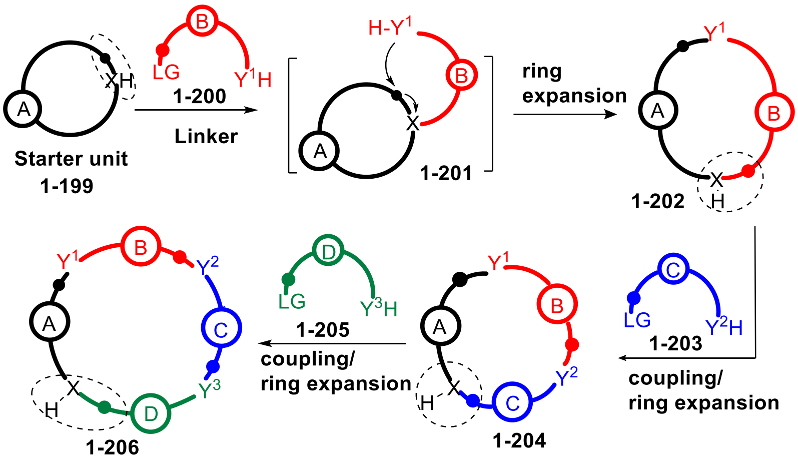
1-196 was produced through reduction and desilyation from keto compound **1-194** in 90% yield over 2 steps. The consecutive ring expansion processes were promoted using catalytic PTSA to produce 15-membered lactone **1-198** in an impressive 90% yield, as a 1:1 mixture of diastereoisomers.



Scheme 1.34 Consecutive transesterification approach to 15-membered lactone.

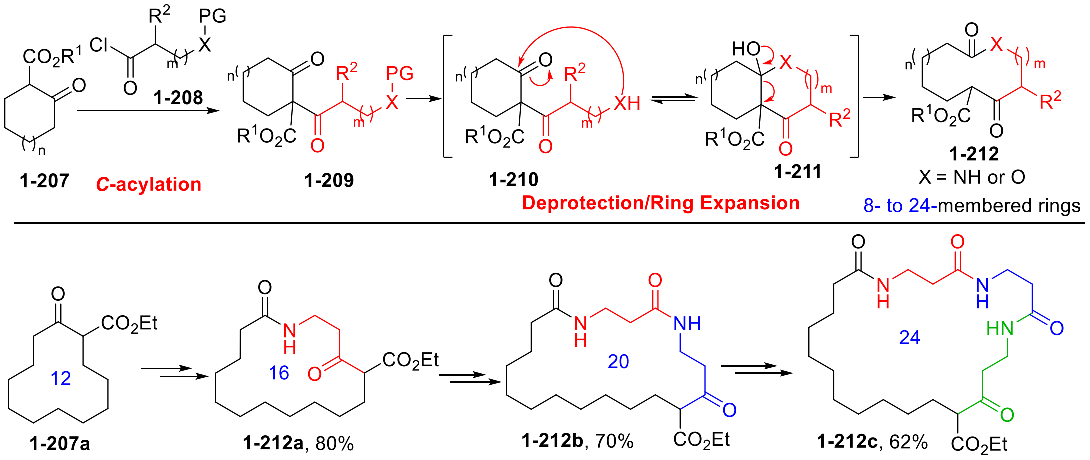
1.7 Successive Ring Expansion (SuRE) in the Unsworth group

The Unsworth group has been working on the development of new ways to prepare medium sized rings and macrocycles for several years and have developed an efficient consecutive ring expansion method, which is known as 'Successive Ring Expansion' (SuRE; Scheme 1.35).[149–152] SuRE is based on the coupling of a starting cyclic starter unit **1-199** with a functionalized linear linker **1-200** which can then rearrange, initiating ring expansion (*via* **1-201**) to generate a larger ring product **1-202**. The reactions are designed so that the same coupling/ring-expansion sequence can then be repeated in the product, to generate much larger ring products, with regeneration of the initial reactive site upon ring expansion being a key design principle (**1-202** → **1-204** → **1-206**). [149]



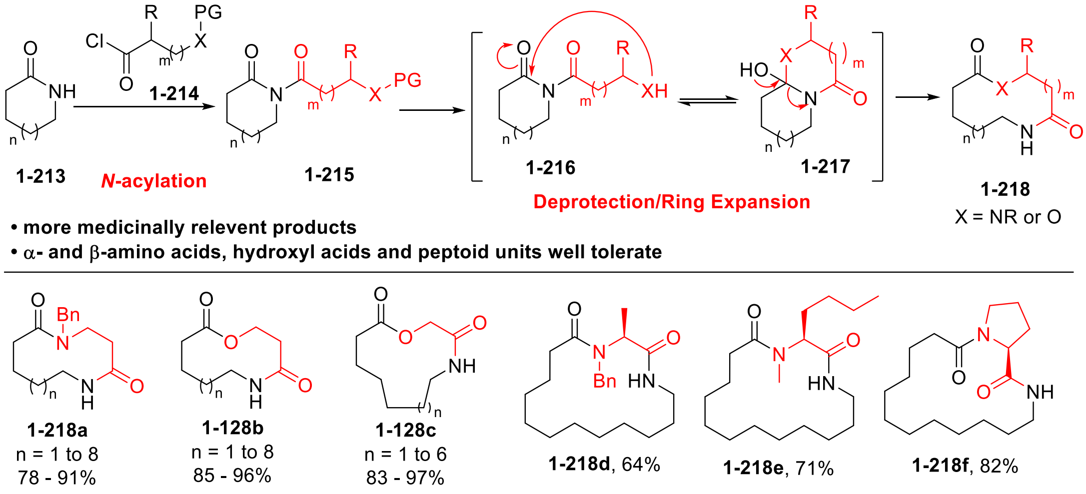
Scheme 1.35 Successive Ring Expansion (SuRE) – general concept.

Before I joined the group, two generations of Successive Ring Expansion reactions (SuRE) had been explored and reported, based on different starting cyclic units. In the group's first generation method, cyclic β-keto esters were used as the cyclic units and acid chlorides were used as the linear linkers to generate medium sized rings and macrocycles (**1-207** → **1-209** → **1-212**).[149,150] A *C*-acylation reaction was performed to generate tricarbonyl species **1-209**, which were deprotected and resulted in spontaneous ring expansion under basic conditions, affording 3- or 4-atom ring expanded products. The driving force of this ring expansion is the formation of a stabilized enolate **1-211** and an amide or a lactone group **1-212**. Importantly, the second (**1-212b**) and even third ring expansion (**1-212c**) could be conducted on the resulting ring expansion products.



Scheme 1.36 Using cyclic β-keto esters as starter unit in SuRE.

Then, a second generation approach was developed based on cyclic lactam starting materials **1-213**, which proved to be a better starter unit to generate both medium sized rings and macrocycles because of the higher yields of the reactions, its much improved substrate scope and its greater potential medicinal utility of the products.[153,154] In this type of SuRE reaction, a *N*-acylation was utilized instead of the *C*-acylation following the same deprotection/ring expansion sequences to produce the ring-expanded lactams and lactones (**1-218**). Also, α-amino acids- or hydroxyl acids-based acid chlorides worked well as β-amino acid/hydroxyl acid derivatives in this cyclic lactam ring expansion.



Scheme 1.37 Using cyclic lactams as starter unit in SuRE.

1.8 Project Aims

The main aim of the work described throughout this thesis was to develop new methods for the synthesis of medium sized rings and macrocycles that make use of SuRE, and SuRE-like reactions. We were keen to expand the range of reactions possible, and to use them to make interesting and important molecules. To do this, a series of novel different methods were developed and explored, with the different projects split by chapter:

In Chapter 2, the aim was to develop new *N*-acylation conditions for these challenging lactams to do ring expansion. The new *N*-acylation conditions would be used for synthesizing a series of novel macrocyclic lactams and lactones, and applied in the SuRE reactions with different starting lactams.

In Chapter 3, the aim was to apply the SuRE reactions to the synthesis of natural product analogues. The plan was that by using our SuRE methodology, the 15-membered macrocyclic core of natural products Solomonamides and a series of analogues could be accessed in just three synthetic steps.

Chapter 4 aimed to develop a strategy whereby the using of protected acyl chlorides could be avoided, in which a common acylating agent could be used and converted into functionalized lactams. The approach was known as conjugate addition/ring expansion (CARE) cascade reaction.

In Chapter 5, the aim was to explore new ring expansion protocols to access the medium sized and macrocyclic sulfonamides from normal cyclic lactams. Both two methods were designed to avoid the use of protecting group reagents, nitro reduction method could allow the synthesis of benzenesulfonamides from 2-nosyl chloride and the conjugate addition method could tolerate various functionalised primary amines.

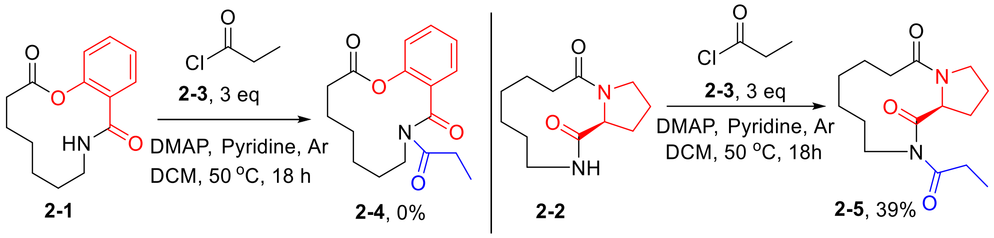
In Chapter 6, ring expansion reactions of P=O containing molecules (cyclic phosphonamidates) have been developed for the first time. Aliphatic amine, aniline, phenol and aliphatic alcohol ring expansion systems were all explored, the high P–O bond strength and the different kinetic barriers could account for the different reactivity of nitrogen- and oxygen ring expansion.

Chapter 7 aimed to explore the possibility of using SuRE strategy to synthesize medium sized and macrocyclic aza sugars. Initial study indicated that this target could be achieved after some side reactions avoided.

Chapter Two: Development of new *N*-acylation conditions for SuRE

2.1 Previous work on SuRE

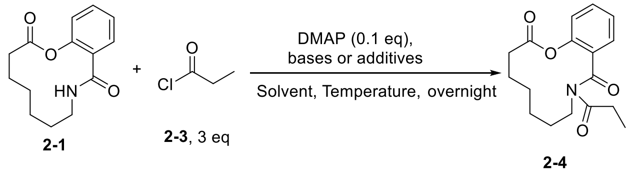
Although the Successive Ring Expansion (SuRE) method developed and published by the Unsworth group in 2017 generally works well for most simple cyclic lactams (various ring sizes or different functional groups) and many ring expanded lactams,[151,152] the established *N*-acylation conditions (DMAP, pyridine in DCM) were not suitable for use with some lactams (*e.g.*, **2-1** and **2-2**, Scheme 2.1), which limited the scope of the SuRE method. Compound **2-1** is a 12-membered macrocycle with a salicylic fragment and compound **2-2** is a 11-membered ring with a proline fragment, their special structures and potential bioactivities make them attractive substrates for which further ring expansion would be of interest. However, when the DMAP and pyridine conditions were used for the acylation of **2-1** with propanoyl chloride **2-3**, none of the imide product **2-4** was detected. Meanwhile, only 39% yield of product **2-5** was obtained from the reaction of **2-2**. Thus, it was decided to attempt to develop improved and efficient *N*-acylation conditions for these compounds to expand the scope of SuRE method and provide alternative *N*-acylation conditions that may also facilitate the SuRE reactions of other more challenging lactam substrates.



Scheme 2.1 The *N*-acylation using propanoyl chloride **2-3** and DMAP conditions.

2.2 Optimization of the new *N*-acylation conditions

The optimization of new *N*-acylation conditions was based on the established DMAP and pyridine conditions, with different temperature, solvents, catalysts, and bases all being explored and optimized. The most obvious way to improve the reaction yield of a slow/incomplete reaction is to increase the temperature, so this was explored first. Increased reaction temperature was tested in DCE, because DCE is a halogen-containing solvent like DCM but has a higher boiling point. Heating lactam **2-1** and acid chloride **2-3** in DCE at 90 °C in presence of DMAP and pyridine gave a 29% yield of the target imide **2-4**, which was a certainly encouraging result (Entry 1, Table 2.1). Then different organic or inorganic bases and additives were tested in DCE at 90 °C, but only the conditions used CuO can give the target product (Entries 2-6). As conditions using 2 eq of CuO gave a similar yield to the 6 eq of pyridine conditions (28% to 27%), the combination of DMAP and CuO conditions were tested in some other high boiling point solvents (toluene, benzene and dioxane), only in benzene the yield of target imide **2-4** has a slightly increase (30%, Entry 8).



Entry	**Solvent and Temperature (°C)**	**Bases and additives**	**Isolated yield of 2-4** (%)
1	DCE, 90	pyridine (6 eq)	**28**
2	DCE, 90	4-picoline (6 eq)	0
3	DCE, 90	NEt$_3$ (6 eq)	0
4	DCE, 90	imidazole (6 eq)	0
5	DCE, 90	CuO (2 eq)	**27**
6	DCE, 90	Zn(OAc)$_2$ (2 eq)	0
7	toluene, 90	CuO (2 eq)	10
8	benzene, 90	CuO (2 eq)	**30**
9	1,4-dioxane, 90	CuO (2 eq)	0

Table 2.1 Initial optimization of the *N*-acylation of lactam **2-1**.

For the reactions in Table 2.1, the outcome of the reactions was assessed by purifying the product mixtures and isolating the desired product **2-4** by column chromatography. While this was helpful to confirm the *N*-acylation was working in some cases, it is quite slow, especially when looking to perform multiple optimization experiments. To help to facilitate the optimizing process, so a ^{1}H NMR analytic approach was introduced to help evaluate the reaction outcomes more quickly, and without the error often associated with column chromatography. In the ^{1}H NMRs of starting lactam **2-1** and target imide **2-4**, the key diagnostic peak of **2-1** is visible at δ_H 3.46 – 3.60 (2H, m, C**H**$_2$NH) and the key diagnostic peak of **2-4** is visible at δ_H 2.20 (2H, q, *J* = 7.2 Hz, C**H**$_2$CH$_3$). By comparing the integral area of these peaks to one another in the crude ^{1}H NMR spectra, the ratio of starting lactam and target product can be calculated easily. Thus, this method was used to evaluate the relative conversion of starting material and the yield of the target product.[155] For example, in the crude ^{1}H NMR shown (Figure 2.1**)**, the integral area of δ_H 3.46 – 3.60 (the key diagnostic peak of **2-1**) is 2.66 relative to the integral area at δ_H 2.20 (the key diagnostic peak of **2-4**) being 1.0. We can therefore determine that the ratio of the starting lactam **2-1** to the target product **2-4** is 2.66:1 (or 73:27), which means that only 27% of the starting lactam **2-1** reacted with propanoyl chloride **2-3** and was converted into the target imide **2-4**. This corresponds to a 27% yield of target product **2-4** was obtained in this condition, with the important caveat that we assume no loss of material or side reactions.

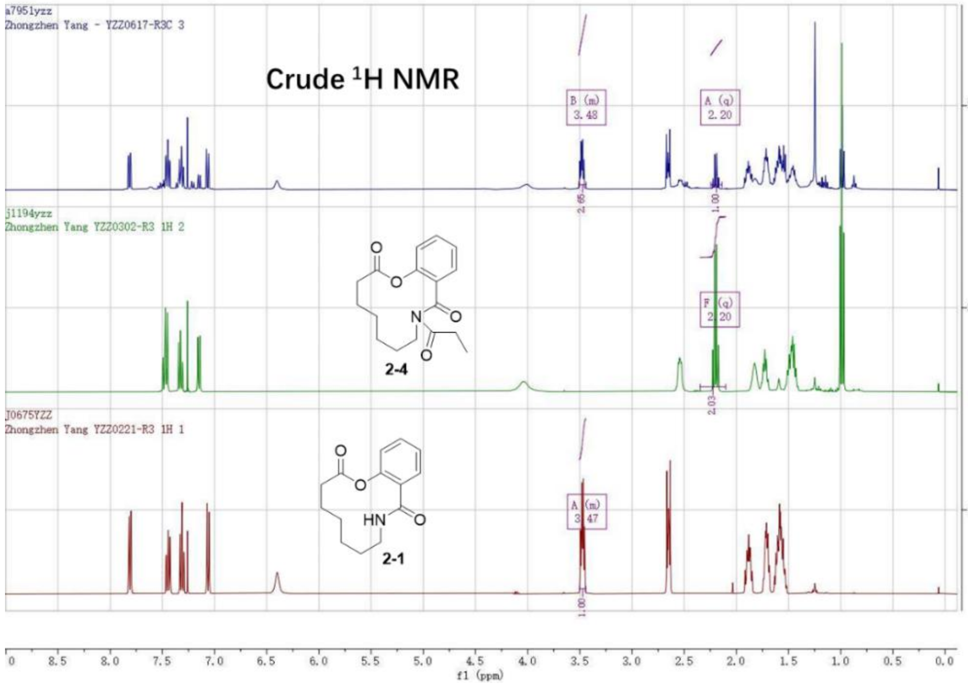
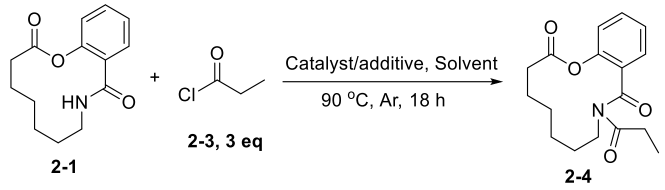


Figure 2.1 Crude NMR method to evaluate the relative conversion and yield of the target product.

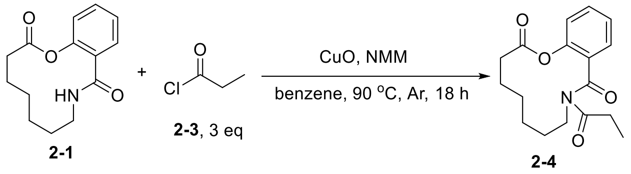
With this more efficient ^{1}H NMR analysis method in hand, DMAP and CuO containing conditions were tested in DCE and benzene using fewer equivalents of them. Using CuO with DMAP in benzene gave a 51: 49 ratio of starting sample **2-1** and the target product **2-4**, which is a much better result than the previous conditions (Entry 2, Table 2.2). It also confirmed that in the presence of CuO, benzene is the better solvent and with or without DMAP giving very similar outcomes. As using CuO in benzene gave a much better result than ever before, we considered whether CuO might be a good catalyst for this *N*-acylation, so some commonly used bases in *N*-acylation reactions were tested, like NEt_3, pyridine and imidazole. 4-Methylmorpholine (NMM) with CuO in benzene gave a good improvement in the ratio (30: 70) of starting lactam **2-1** and product **2-4** (Entry 8).



Entry	Catalyst	additive	solvent	Ratio of 2-1: 2-4
1	CuO (0.4 eq)	DMAP (0.4 eq)	DCE	69: 31
2	CuO (0.4 eq)	DMAP (0.4 eq)	benzene	51: 49
3	CuO (0.4 eq)		DCE	80: 20
4	CuO (0.4 eq)		benzene	**48: 52**
5	CuO (0.4 eq)	Imidazole	benzene	93:7
6	CuO (0.4 eq)	Pyridine	benzene	51:49
7	CuO (0.4 eq)	NEt_3	benzene	100:0
8	CuO (0.4 eq)	NMM	benzene	30:70

Table 2.2 The optimization of different conditions using CuO as a catalyst.

Then different equivalents of CuO and NMM were tested in benzene, and the conditions using catalytic amount of CuO (0.2 eq) with 6.0 equivalent of NMM improved the relative yield of target imide **2-4** to 95% according to the crude ^{1}H NMR analysis (Table 2.3, Entry 3). Besides, the bases used in the previous *N*-acylation conditions (DMAP, pyridine) were tested in the presence of NMM and CuO, but neither gave any improvement. Therefore, at this stage, using CuO as catalyst, NMM as base in benzene at 90 °C were the best conditions for this *N*-acylation reaction.



Entry	CuO (eq)	NMM (eq)	Other bases (eq)	Ratio of 2-3: 3-3
1	2	4.0		42: 58
2	2	1.0		12: 88
3	0.2	6.0		**5:95**
4	0.2	6.0	DMAP (0.1)	9:91
5	0.2	4.0	Pyridine (2.0)	11:89

Table 2.3 Optimization of different equivalents of CuO and NMM in benzene.

However, the ratio of starting lactam **2-1** to the target product **2-4** in the crude ^{1}H NMR just showed the relative proportion of the starting material and product; it does not necessarily represent the real conversion and yield, as it does not account for other side product formation. Also, since the relative yield of the target imide **2-4** was improved to more than 90%, the key diagnostic peak of starting lactam **2-1** at δ_H 3.46 – 3.60 (2H, m, C**H**$_2$NH) was difficult to get an accurate integral area. At this point, we therefore introduced a new analysis method based on absolute concentration determination quantitative NMR method, to measure the NMR yields of the product by using an internal standard. Using this approach, the chemical shifts of the relevant ^{1}H NMR signals of the starting lactam **2-1** and target imide **2-4** noted above were compared to the aromatic signal of 1,3,5-trimethoxybenzene **2-6**, which was selected as an internal NMR standard because its signal at δ_H 6.08 ppm (3H, s, 3 × Ar-C**H**) is well separated from those peaks in the compounds being analyzed. The internal standard **2-6** (1.0 mmol/mL) was added (0.1 mL) into the reaction (0.1 mmol/mL concentration) after the reaction was completed and just before doing the work up to get an accurate result. In the crude ^{1}H NMR spectrum, integrating the specific peak of internal standard **2-6** at δ_H 6.08 ppm as 3.00 (3H, s, 3 × Ar-C**H**), so the integral area of the specific peak of the target product **2-4** at δ_H 2.20 (2H, q, *J* = 7.2 Hz, C**H**$_2$CH$_3$) is 1.87 (see Figure 2.2). The NMR yield was calculated using the following formula:

$$\text{Yield} = \frac{\text{integral area of product}}{\text{integral area of internal}} \times \frac{\text{no.of nuclei (internal)}}{\text{no.of nuclei (product)}} \times \frac{\text{conc. of internal}}{\text{conc. of product}} \times 100\%\,[155]$$

Using this approach, we were pleased to learn that the NMR yield of the target imide **2-4** was be calculated to 94% when using the reaction conditions summarized in Table 2.3, Entry 3 above. Because both the concentration of reaction and internal standard were controlled to 0.1 mmol/mL, the integral area of the target product **2-4** is 1.87 while the internal standard is 3.00, and the nuclei number are 3 (internal standard **2-6**, 3 × Ar-C**H**) and 2 (product **2-4**, 2H at δ_H 2.20).

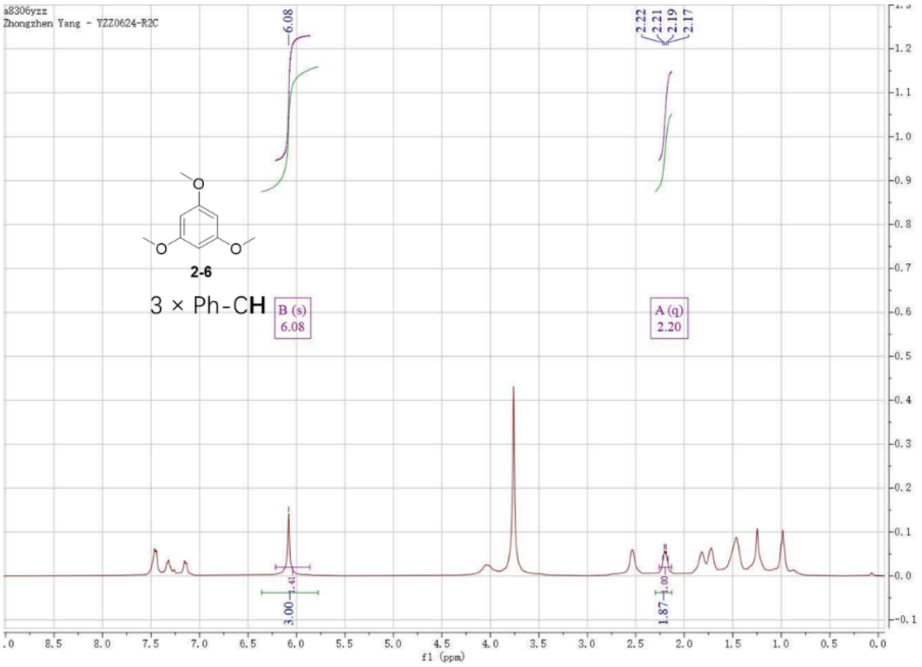
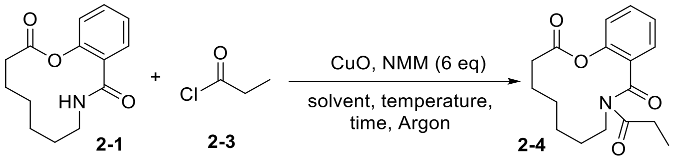


Figure 2.2 The example of calculating the NMR yield in crude ^{1}H NMR using internal standard.

After this convenient analysis methodology proved to be efficient in this model reaction, the last stage of optimization was carried out using this internal standard analysis method. Firstly, different equivalents of CuO were tested in benzene, with cyclohexane also tested as it's a greener and safer (less toxic) solvent than benzene. These experiments showed that 0.1 equivalent of CuO is better than 0.2 eq of CuO but the reaction in cyclohexane was not as good as that in benzene. After optimizing the catalyst (0.1 eq of CuO), base (6 eq of NMM) and solvent (benzene), the target imide **2-4** was obtained in an excellent yield (93% NMR yield) (Entry 2, Table 2.4), then focus was turned to test lower temperatures, shorter reaction times and reduced equivalents of the acyl chloride **2-3**. Different temperatures (50 °C, 65 °C and 80 °C) were tested in benzene (Entry 4 to 6), and the reaction at 80 °C gave an excellent performance in both NMR yield (97%) and isolated yield (92%). Notably, reducing the equivalents of propanoyl chloride **2-3** resulted in the yields of the target imide **2-4** decreasing significantly (Entry 7 and 8), suggesting that the use of 3.0 eq of acyl chlorides is important for this *N*-acylation reaction. The reaction time studies showed that longer reaction time can help improve the yields of the target product (Entry 9 and 10). Finally, the reaction conducted without argon provided **2-4** in a yield of 96%, indicating that this reaction is not sensitive to air (Entry 11). Thus, improved *N*-acylation conditions for the selected starting lactam **2-1** and the model reagent **2-3** had been established.



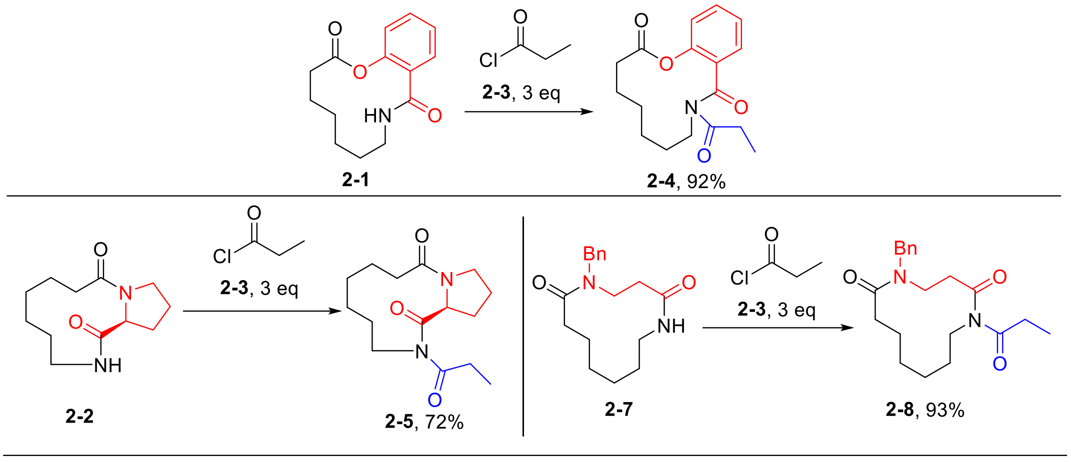
Entry	**CuO (eq)**	**2-3 (eq)**	**Solvent**	**Temperature (°C)**	**Time (hour)**	**Yield of 2-5(%)** [a]
1	0.2	3.0	benzene	90	18	92
2	0.1	3.0	benzene	90	18	**93 (84[b])**
3	0.1	3.0	cyclohexane	90	18	78
4	0.1	3.0	benzene	50	18	82
5	0.1	3.0	benzene	65	18	88
6	0.1	3.0	benzene	80	18	**97 (92)[b]**
7	0.1	2.0	benzene	80	18	60
8	0.1	1.5	benzene	80	18	45
9	0.1	3.0	benzene	80	6	84
10	0.1	3.0	benzene	80	1	82
11	0.1	3.0	benzene	80	18	96[c]

[a] Yields were determined by ^{1}H NMR using 1,3,5-trimethoxybenzene **2-6** as an internal standard.

[b] Isolated yield; [c] Reaction without argon.

Table 2.4 Last stage of optimization of the temperature, time, equivalents of **2-3**.

Before the optimized conditions (CuO, NMM in benzene at 80 °C) were utilized in substrate scope investigations, it was tested on the 11-membered lactam **2-2** and another 12-membered ring expanded lactam **2-7**. Both reactions worked well for acylation with **2-3**, with the target products **2-5** and **2-8** isolated in yields of 72% and 93%, respectively (Scheme 2.2).



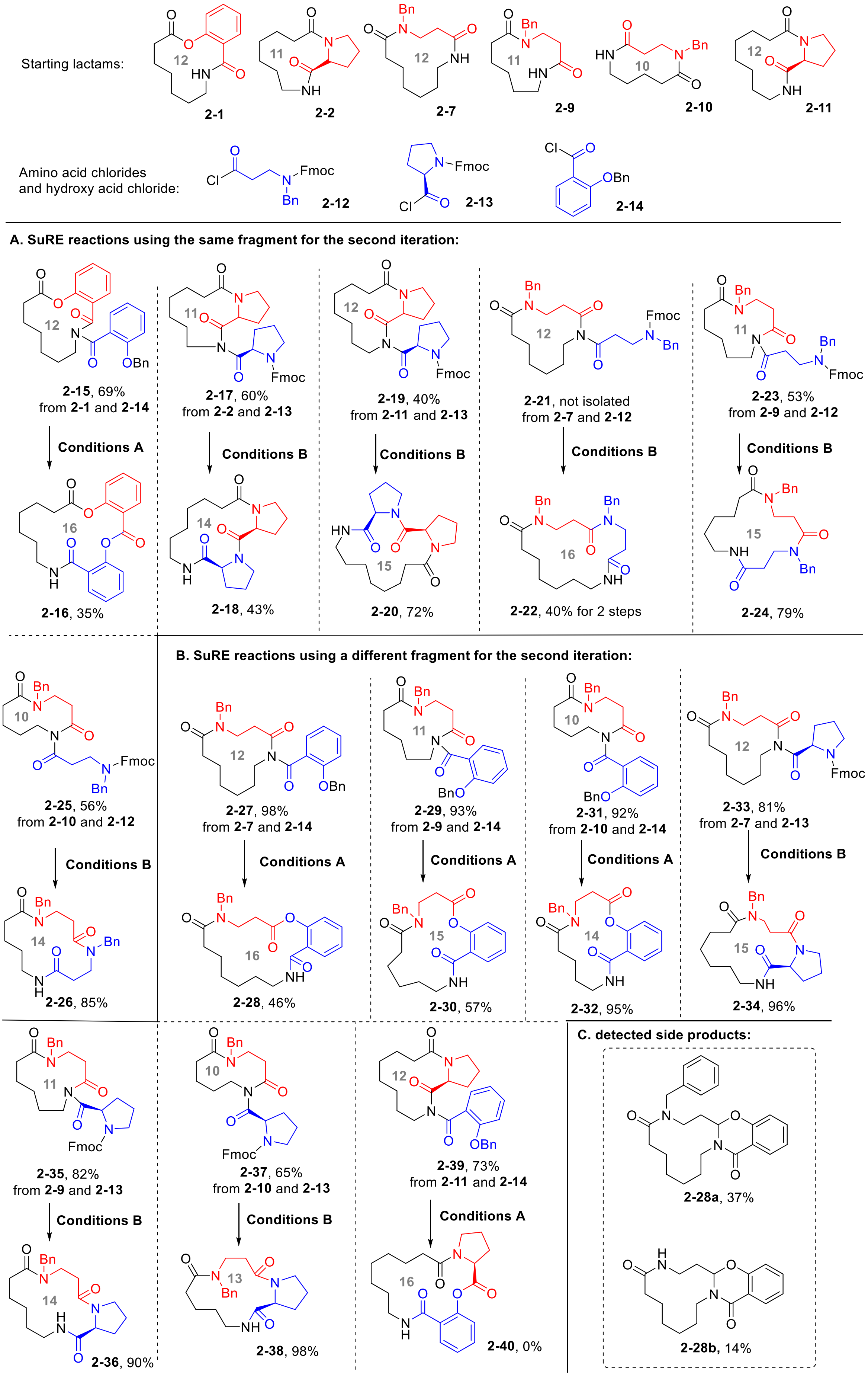
N-acyaltion conditions: CuO (0.1 eq), NMM (6 eq), benzene, 80 °C, 18h; isolated yields

Scheme 2.2 Model reactions of selected lactams using the optimized conditions.

2.3 Substrates scope of new *N*-acylation conditions

As the new *N*-acylation conditions had been proved to be efficient in the model reactions of all these three selected lactams, it was the time to apply it in Successive Ring Expansion (SuRE) reactions to produce larger macrocycles. All of these reactions are summarized in Scheme 2.3.

The starting lactam **2-1** with a salicylic fragment was acylated with the acid chloride **2-14** prepared from the 2-phenoxybenzoic acid, giving the target imide **2-15** in a 69% yield. After the hydrogenation and ring expansion step, the 16-membered macrocycle **2-16** with two same salicylic fragments was generated in the yield of 35%. This reaction proved the new *N*-acylation conditions using CuO and NMM can be used in SuRE reactions to enable further ring expansion reactions and not just in the model *N*-acylation, which was an important discovery. Then macrocycles (14-membered **2-18** and 15-membered **2-20**) with two proline fragments were generated using the Fmoc-protected Pro-OH chloride **2-13** and the stating lactams **2-2** and **2-11**. Also, 12- to 10-membered lactams with a β-alanine fragment (**2-7**, **2-9** and **2-10**) were tested to synthesize the macrocycles in which two β-alanine fragments have been incorporated. Notably, using the published *N*-acylation conditions (DMAP, pyridine in DCM) none of these systems could be ring expanded to larger macrocycles. Pleasingly, these target macrocycles (**2-22**, **2-24** and **2-26**) were generated smoothly after the new acylation conditions and Fmoc-deprotection conditions. Attention then turned to the synthesis of macrocycles containing two different fragments (Scheme 2.3B) , and in general these reactions were easier than the analogous reaction to install the same linear fragment. First, the acyl chloride **2-14** was used to acylate with the 12-membered starting lactam **2-7**, producing the target imide **2-27** in an excellent yield 98%. The 16-membered macrocycle **2-28** was produced after the hydrogenation and ring expansion steps, along with two over-reduced side products **2-28a** and **2-28b**. In the ring expansion reaction of the 11-membered lactam **2-9** to the 15-membered macrocycle **2-30**, a high yield (93%) of imide intermediate **2-29** was obtained in the acylation step, but there was a low yield for the ring expansion product **2-30**, which might result from the over-reduced reaction in the hydrogenation step. Notably, high yields were obtained in both the *N*-acylation step and hydrogenation/ring expansion step from the 10-membered lactam **2-10** to the 14-memered macrocycle **2-32**. The reactions using Fmoc-Pro-OH acid chloride **2-13** acylate with these 10- to 12-membered lactams containing a β-alanine fragment gave good yields in the acylation steps (less than using 2-phenoxybenzoic acid chloride **2-14**) and excellent yields in the Fmoc deprotection/ring expansion steps (**2-34**, **2-36** and **2-38**). The scoping research ended by synthesizing the macrocycle **2-40** containing a proline fragment and a salicylic fragment. The *N*-acylated product **2-39** was generated in a good yield (73%) but no ring expansion product **2-40** was detected after the hydrogenation/ring expansion sequences. In this case, the rigid structure of the proline and salicylic fragments might be responsible for the failure of the ring expansion step; i.e. the rigidity of the system may have prevented the phenol oxygen from being able to attack the imide carbonyl to effect ring expansion.


Starting lactams:
2-1
2-2
2-7
2-9
2-10
2-11
Amino acid chlorides and hydroxy acid chloride:
2-12
2-13
2-14
A. SuRE reactions using the same fragment for the second iteration:
2-15, 69% from 2-1 and 2-14
Conditions A
2-16, 35%
2-17, 60% from 2-2 and 2-13
Conditions B
2-18, 43%
2-19, 40% from 2-11 and 2-13
Conditions B
2-20, 72%
2-21, not isolated from 2-7 and 2-12
Conditions B
2-22, 40% for 2 steps
2-23, 53% from 2-9 and 2-12
Conditions B
2-24, 79%
2-25, 56% from 2-10 and 2-12
Conditions B
2-26, 85%
B. SuRE reactions using a different fragment for the second iteration:
2-27, 98% from 2-7 and 2-14
Conditions A
2-28, 46%
2-29, 93% from 2-9 and 2-14
Conditions A
2-30, 57%
2-31, 92% from 2-10 and 2-14
Conditions A
2-32, 95%
2-33, 81% from 2-7 and 2-13
Conditions B
2-34, 96%
2-35, 82% from 2-9 and 2-13
Conditions B
2-36, 90%
2-37, 65% from 2-10 and 2-13
Conditions B
2-38, 98%
2-39, 73% from 2-11 and 2-14
Conditions A
2-40, 0%
C. detected side products:
2-28a, 37%
2-28b, 14%

Scheme 2.3 Lactams ring expansion scope. i) General conditions to imides: To the starting lactam (1.0 equiv), NMM (6 equiv) and CuO (0.2 equiv) in benzene (0.05 mmol/mL), acid chloride (3.0 equiv) was added in benzene (0.05 mmol/mL), 18 h at 80 °C; ii) Conditions A (hydrogenation and ring expansion): H_2, Pd/C in EtOAc, 16 h, RT then NEt_3, $CHCl_3$, 18 h, RT. iii) Conditions B (deprotection of Fmoc group and ring expansion): DBU (10 equiv) in DCM, RT, 18 h.

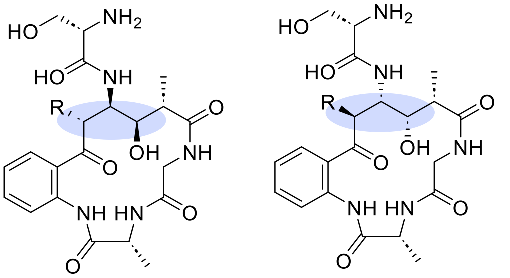
2.4 Chapter 2 summary

In summary, we optimized a new *N*-acylation conditions (CuO, NMM in benzene at 80 °C overnight) for SuRE of lactams which don't work well using the published *N*-acylation conditions. With the new conditions, 12 new macrocycles with different ring sizes (13- to 16-membered), and different fragment combinations (two of the same fragments or two different fragments) were synthesized. This work enriched our macrocycle library, and more importantly, expanded the scope of the SuRE method more generally. Among the products made, some interesting macrocycles with potential medicinally useful structures were made, for example products containing one or two salicylic fragments.

Chapter Three: A consecutive ring expansion strategy towards the macrocyclic core of the Solomonamide natural products

3.1 Solomonamides and consecutive ring expansion strategy

Solomonamides A and B (**3-1a** and **3-1b**) are macrocyclic peptide natural products that were isolated from the marine sponge *Theonella swinhoei* in 2011.[156] Solomonamides display promising anti-inflammatory activity (60% reduction of edema in mice at a dose of 100 µg/kg) but can only be isolated in minute quantities from the sponge, therefore synthesis is needed to enable further biological studies. The original structural assignments of Solomonamides A and B are depicted in Figure 3.1. However, a structural reassignment of Solomonamide B was made (**3-2b** – with the highlighted stereogenic centers inverted) after the first synthesis of **3-1b** by Reddy and coworkers in 2016.[157]



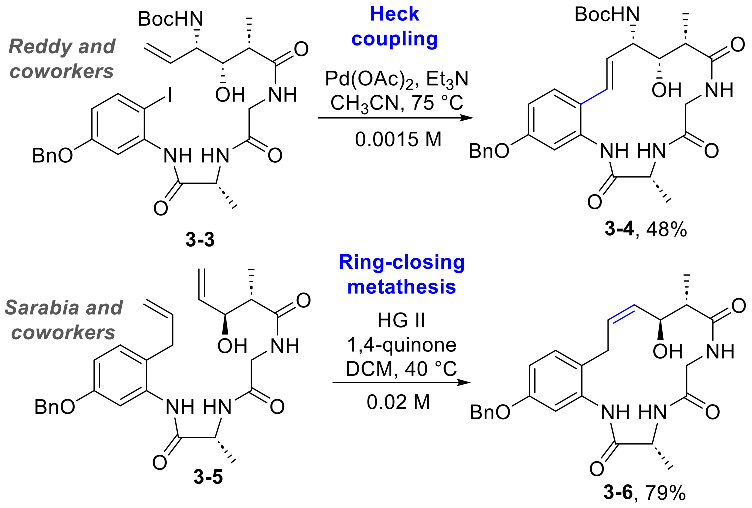
3-1a, R = OH
3-1b, R = H
(original assignments)

3-2a, R = OH solomonamide A
3-2b, R = H solomonamide B
(re-assignments)

Figure 3.1 Structures of Solomonamide A and B.

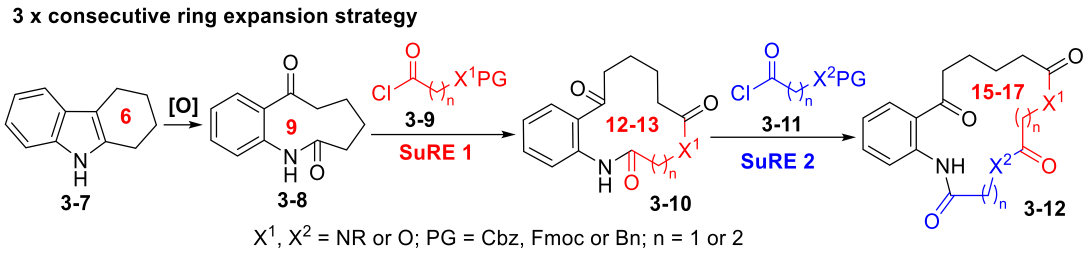
Various synthetic studies focused on the solomonamide natural products have been reported and, unsurprisingly, all syntheses used end-to-end macrocyclisation strategies to form the 15-membered macrocyclic core. For example, Reddy's group has worked on the total synthesis of the solomonamides since 2012 and finished total syntheses in 2016 (Solomonamide B)[158] and 2018 (Solomonamide A)[157] using a ligand-free intermolecular Heck macrocyclization as the key step to form the macrocycle core in both cases. In contrast, Sarabia and coworkers reported using a ring-closing metathesis approach to construct the solomonamide macrocyclic core in the presence of the

Hoveyda–Grubbs second generation (HG II) catalyst.[159,160] Notably, while both macrocyclisation strategies are impressive, both are performed under relatively high dilution conditions.



Scheme 3.1 Previous synthesis methods toward Solomonamide macrocyclic core.

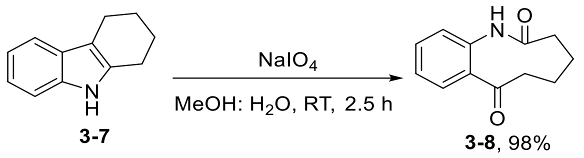
In order to showcase the Successive Ring Expansion (SuRE) strategy introduced in Chapters 1 and 2 this thesis, we considered whether we might be able to use it synthesize the macrocyclic core of the solomonamides. This would represent a completely different approach to the previous end-to-end macrocyclisation strategies. It was proposed that by using SuRE methodology, the 15-membered solomonamide framework could be accessed in just three synthetic steps from commercially available, cheap tetrahydrocarbazole **3-7**. The plan was to first perform an oxidative ring expansion to form the 9-membered lactam **3-8** and then perform two iterations of our lactam SuRE reaction, thus enabling the 15-membered solomonamide framework **3-12** to be prepared *via* the insertion of amino acid (when X = NR) or hydroxy acid (when X = O) derivatives. With this strategy, various solomonamide macrocyclic core analogues could be accessed by inserting different amino- and hydroxy-acid fragments, and high dilution conditions could be avoided as no direct macrocyclisation reactions are needed. Key advantages to this strategy, if successful, would be its overall brevity, the potential to avoid high dilution and the ability to make various derivatives quickly by varying the acid chloride fragments showed in Scheme 3.2 in red and blue.



Scheme 3.2 Consecutive ring expansion strategy towards the macrocyclic core of solomonamides.

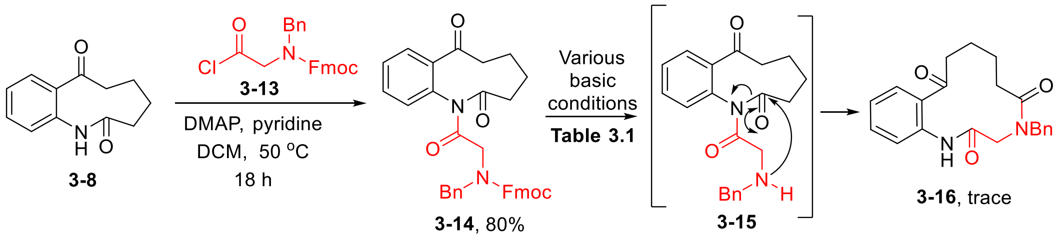
3.2 SuRE strategy towards Solomonamide macrocyclic core: macrolactams

The first step of our synthesis was a published oxidative ring expansion reaction, which was done by treating commercially available tetrahydrocarbazole **3-7** with $NaIO_4$ to cleave the indolic double bond, which in our hands led to the formation of 9-membered ring lactam **3-8** in 98% yield.[161]



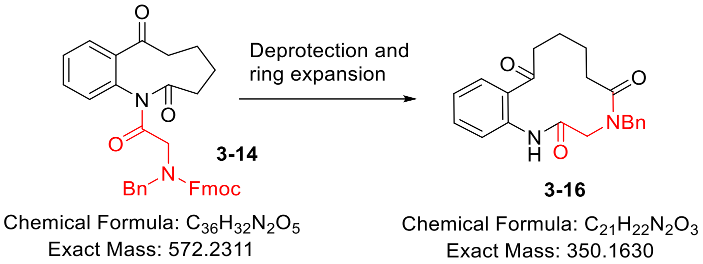
Scheme 3.3 Oxidative ring expansion of tetrahydrocarbazole **3-7** to 9-membered lactam **3-8**.

With the starting lactam **3-8** in hand, attention then moved to applying our group's SuRE methodology, starting with a Fmoc-based protecting group strategy. The lactam **3-8** was reacted with acid chloride **3-13** using the DMAP and pyridine *N*-acylation conditions, which resulted in the formation of imide **3-14** in 80% yield. Then, the idea was that the 12-membered product **3-16** would be generated after the cleavage of the Fmoc protecting group under basic conditions (**3-14** →**3-15**) and ring expansion.



Scheme 3.4 **SuRE 1** reaction using Fmoc strategy.

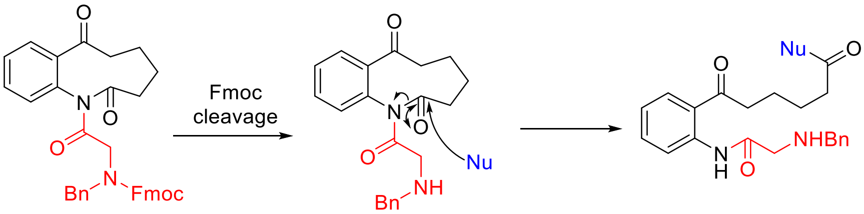
However, in the attempted ring expansion of imide **3-14** to 12-membered macrolactam **3-16**, only trace quantities of the desired macrocycle **3-16** were formed, despite trialing this reaction under various basic conditions (Table 3.1). Firstly, 10 eq of DBU in DCM was used to deprotect the Fmoc group and facilitate the ring expansion. These conditions had proven to be efficient in our previous ring expansion reactions, but less than 5% of the ring expanded product **3-16** was isolated (Entry 1). Then, some small-scale reactions (0.1 mmol) were conducted and analyses by ESI-MS spectrum in an attempt to find the ring expansion product **3-16**. The target molecular ion peaks of **3-16** were observed in the $NHEt_2$, $NH(EtOH)_2$ and TBAF conditions (Entry 3, 6, and 7), but attempts to purify these reactions by column chromatography resulted in less than 5% isolated yields of **3-16**. To give more details of the attempted reactions in Table 3.1, almost all these basic conditions (except NEt_3) were able to remove the Fmoc group of the imide **3-14**, but most of these reactions led to the formation of unwanted/unexpected side products instead of the desired ring expansion product **3-16**.



Entry	Basic Conditions	Detection of 3-16
1	DBU (10 eq) in DCM, RT, 18 h	Yes (< 5%)
2	Piperidine (10 eq) in DCM, RT, 18 h	No
3	20% $NHEt_2$ in dioxane, RT, 1 h	Yes (< 5%)
4	10% NEt_3 in dioxane, RT, 1 h	No
5	50% Morpholine in DCM, RT, 10 h	No
6	1 M TBAF in THF, RT, 16 h	Yes (<5%)
7	10% $NH(EtOH)_2$ in DCM, RT, 1 h	Yes (<5%)
8	10% $NHEt_2$ in DCM, RT, 1 h	No

Table 3.1 Optimization of deprotection and ring expansion conditions of imide **3-14.** Isolated yield.

The main problem is that the bases used to cleave the Fmoc protecting group can also take part in intermolecular nucleophilic addition reactions with the imide, resulting in competing ring-opening reactions. For example, linear amides **3-17a** and **3-17b** were isolated when using diethylamine (Entry 3) and piperidine (Entry 2) to cleavage the Fmoc group, respectively. This unexpected result, which had not been observed before in published SuRE reactions, is thought to be because of the increased electrophilicity of the imide carbonyl groups, as it conjugated with the adjacent electron-deficient aromatic system.



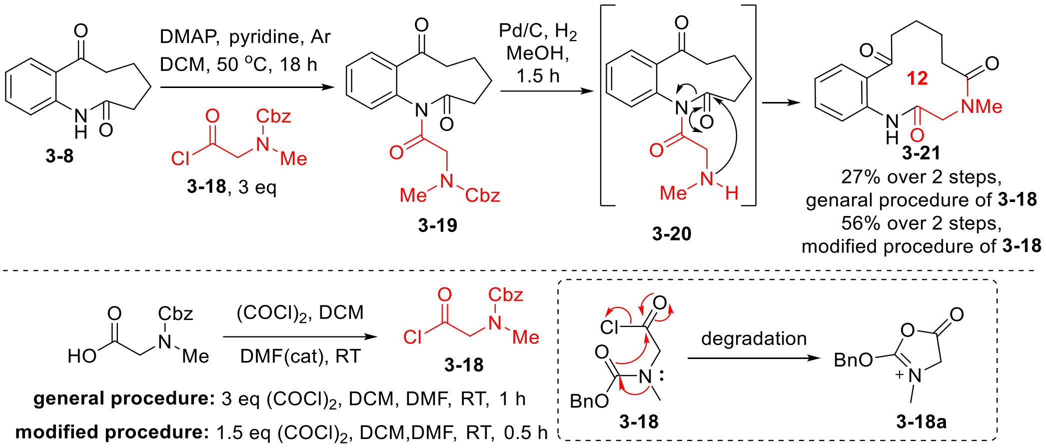
3-14

3-14a

3-17a, 40%, **Nu** = NEt_2, Entry 3
3-17b, 35%, **Nu** = piperidyl, Entry 2

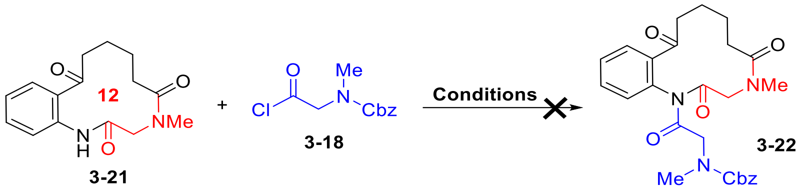
Scheme 3.5 Hypothesized mechanism and structures of byproducts **3-17a** and **3-17b**.

To address this problem, a Cbz-based protecting group strategy was used because the Cbz group can be cleaved using neutral hydrogenolysis conditions, and thus avoids the use of nucleophilic reagents. *N*-acylation of lactam **3-8** with Cbz-protected amino acid chloride **3-18** produced the imide **3-19** smoothly. Then, following hydrogenolysis, conversion into macrocycle **3-21** was observed, which was isolated in 27% overall yield from **3-8**, after the *N*-acylation, protecting group cleavage and ring-expansion sequences. In this reaction, amino acid chloride **3-18** (Cbz-Sar-Cl) was used, which was prepared from the commercial Cbz-Sar-OH using the general procedure for acid chloride formation in our previous ring expansion reactions. Notably, a modified procedure for acid chloride formation (1.5 eq of oxalyl chloride in DCM, DMF as catalyst at RT for 30 mins) was tested, and we were pleased to find that these relatively small changes to the protocol for acid chloride formation improved the yield of the ring expansion product **3-21** from 27% to 56% (over two steps). The key reason was postulated to be the low stability of the α-amino acid chloride **3-18**; it is possible that **3-18** might degrade into an oxazolone type species **3-18a** under longer reaction times, and this likely contributed to the low yield of the *N*-acylation step using the standard conditions. Thus, the first ring expansion (termed here as ‘**SuRE 1**’) had been completed, using the Cbz-based protecting group strategy. Attention then turned to the next ‘**SuRE 2**’ reaction.



Scheme 3.6 **SuRE 1** reaction with Cbz-strategy and hypothesized degradation acid chloride **3-18**.

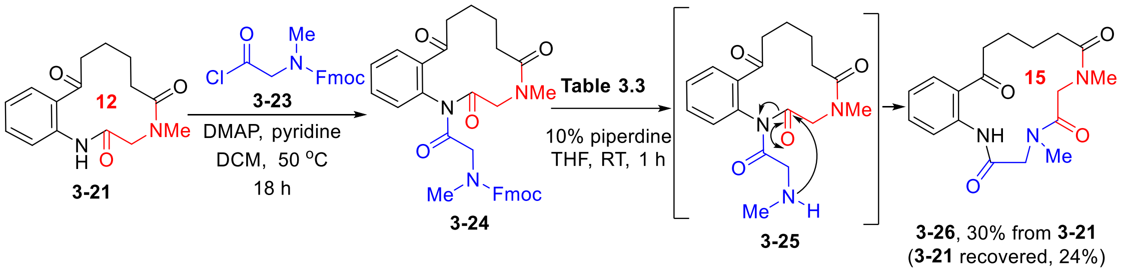
Initially, the same Cbz protecting group strategy as above was used in the **SuRE 2** reaction. However, attempts to generate the imide **3-22** from lactam **3-21** with acid chloride **3-18** failed, with unreacted **3-21** the major component of the reaction mixture under all the conditions tested, including the new *N*-acylation conditions developed in Chapter 2 (CuO, NMM in benzene at reflux).



Entry	Conditions	Yield of 3-22
1	DMAP (0.1 eq), pyridine (6 eq), DCM, 50 °C, 18 h	trace
2	CuO (0.1 eq), NMM (6 eq), benzene, 80 °C, 18 h	0
3	NaH (1.0 eq), THF, RT, 16 h	0
4	MeMgBr (1.1 eq), THF, 0 °C, 2 h	0
5	*n*-BuLi (1.5 eq), THF, 0 °C to RT, 16 h	0

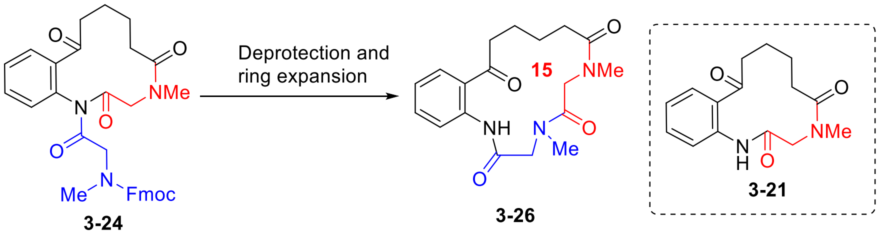
Table 3.2 Optimization of *N*-acylation conditions of lactam **3-21** and acid chloride **3-18**.

It appeared that the macrolactam **3-21** undergoes *N*-acylation less readily than lactam **3-8** might, which is likely because of its larger ring size; larger ring sized lactams have generally been found to acylate more slowly in the group's previous work. Knowing also that Cbz-protected amino acid chlorides tend to be less stable and less reactive in lactam *N*-acylation than their Fmoc derivatives, we reverted to the Fmoc protecting group strategy. Using the more stable Fmoc-protected amino acid chloride **3-23**, *N*-acylation of lactam **3-21** proceeded well (based on full consumption of **3-21** by TLC analysis) to form imide **3-24** (Scheme 3.7). Imide **3-24** was then taken directly onto the ring-expansion step. Then, the deprotection of Fmoc group and ring expansion step became the critical step for synthesizing the solomonamide macrocyclic core **3-26**.



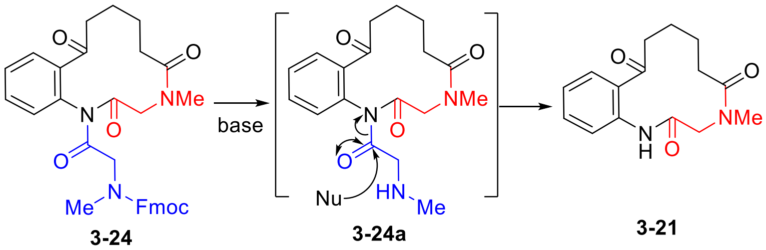
Scheme 3.7 **SuRE 2** reaction of **3-21** to form the solomonamide macrocyclic core **3-26**.

Imide **3-24** was treated with various basic conditions (Table 3.3), and conditions using piperidine in THF formed the 15-membered macrocycle **3-26** in 30% overall yield from **3-21**, which was the highest yield obtained across the nine tested Fmoc cleavage conditions. Based on previous results in the **SuRE 1** sequence, it was not a surprise that the DBU (10 eq) in DCM conditions didn't work for this ring expansion. Then $NHEt_2$, $NH(EtOH)_2$, TBAF, DIPEA and NEt_3 were tested (Table 3.3, Entry 2 to 6), however, only the $NHEt_2$ and NEt_3 conditions gave low yields of the ring expansion product **3-26.** Notably, unwanted ring-opening reactions observed in the **SuRE 1** reaction were not detected in this case; however, in most conditions 12-membered lactam **3-21** being recovered in high yields. It is thought that **3-21** is formed as a result of nucleophilic attack of base into the exocyclic imide carbonyl, which results in cleavage of the exocyclic imide C–N bond *via* **3-24a** (Scheme 3.8). In addition, a novel Fmoc-cleavage strategy with mercaptopropionic acid (MPA) and DBU in CPME[162] and the neutral hydrogenation conditions in MeOH[163] were also tested, but neither improved the yield of macrocycle **3-26**.



Entry	Conditions	Yield of 3-26 (%) from 3-21	Recycle of 3-21 (%)
1	DBU (10 eq), DCM, RT, 16 h	0	88
2	20% $NHEt_2$ in dioxane, RT, 1 h	10	60
3	20% $NH(EtOH)_2$ in DCM, RT, 1 h	0	30
4	1M TBAF in THF, THF, RT, 3 h	0	100
5	20% DIPEA in DCM, RT, 24 h	0	0
6	20% NEt_3 in DCM, RT, 24 h	20	40
7	10% Piperidine in THF, RT, 1 h	**30**	**30**
8	MPA (3 eq), DBU (9 eq), CPME, 0 °C to RT, 1 h	15	0
9	10% Pd/C, H_2, CH_3OH, CH_3CN (5 eq), RT, 18 h	0	0

Table 3.3 Optimization of the deprotection of Fmoc group and ring expansion conditions of **3-24**.



Scheme 3.8 Hypothesized mechanism for the regeneration of **3-21**.

Thus, despite a modest yield for the second SuRE reaction, we had achieved the synthesis of the 15-membered solomonamide macrocyclic core, serving as proof of principle for our consecutive ring expansion strategy to make this compound class. As mentioned in Section 3.1, one of the most valuable advantages of this strategy is the ability to extend it to different linear acid chlorides to allow various analogues to be made. Therefore, a series of macrocycles with different amino acid fragments were prepared by using different acid chlorides in **SuRE 1** and **SuRE 2**, with these results summarized in Figure 3.2. Using the Cbz-protecting protocol, the yield of 12-membered macrolactam **3-16** was improved to 48% compared to 5% using Fmoc-protecting strategy. The 13-membered macrolactam **3-21a** with a β-alanine fragment was obtained in 61% yield and the 12-membered macrolactam with a *Z*-proline fragment (**3-21b**) was generated in 69% from the 9-membered starting lactam **3-8**.

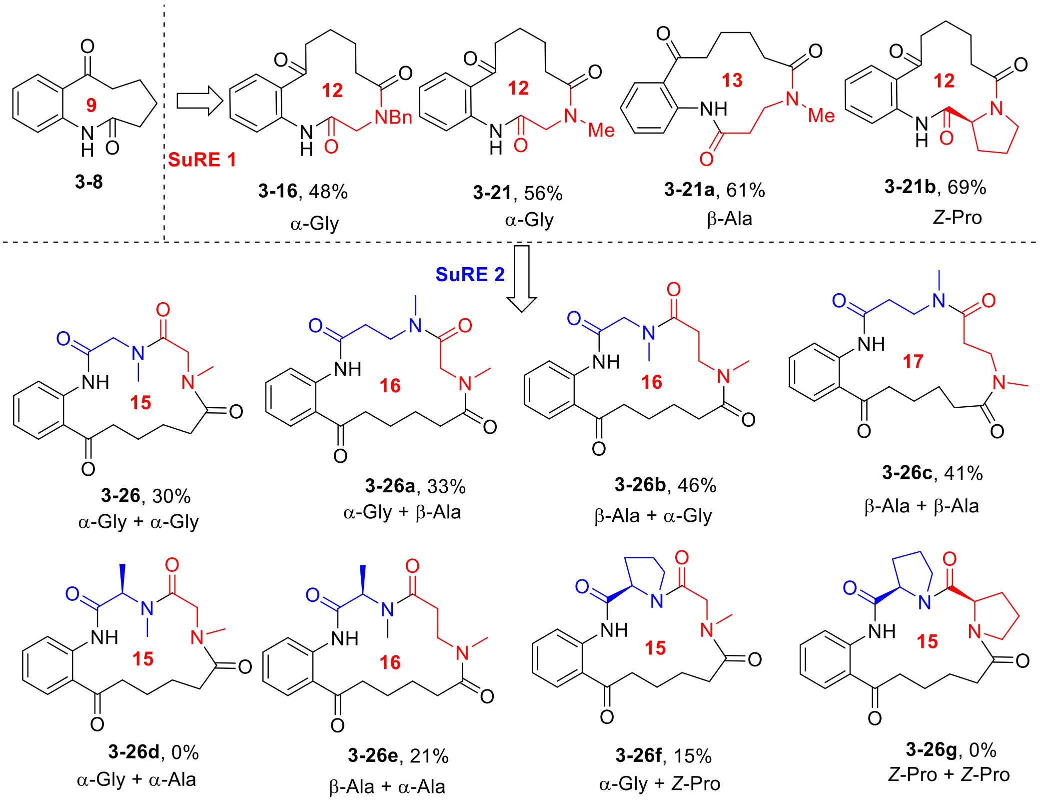


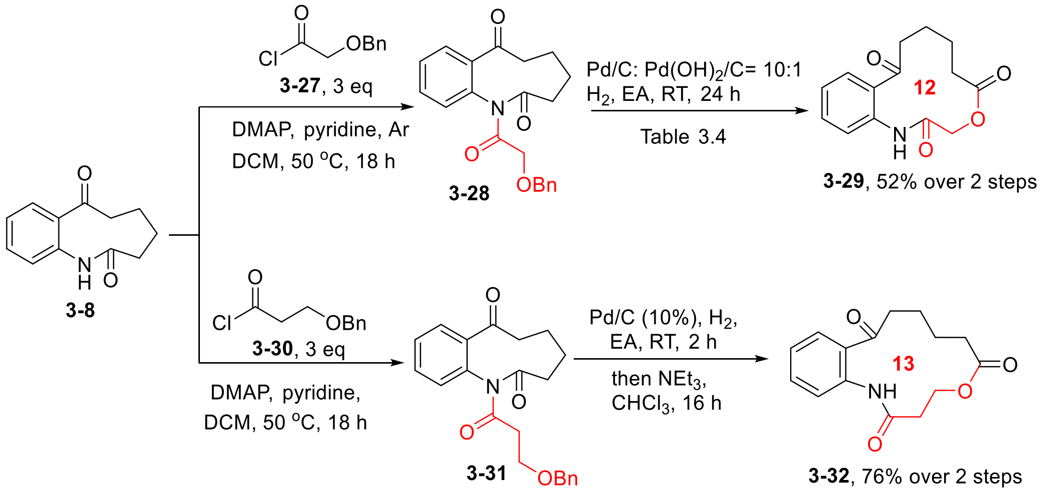
Figure 3.2 Analogues of the Solomonamide macrocyclic core. **SuRE 1**: i) lactam (1 equiv.), acid chloride (3 equiv.), pyridine (6 equiv.), DMAP (0.1 equiv.), DCM, 50 °C; (ii) H_2, Pd/C, MeOH, RT. **SuRE 2**: i) lactam (1 equiv.), acid chloride (3 equiv.), pyridine (6 equiv.), DMAP (0.1 equiv.), DCM (0.1 M), 50 °C; (ii) Piperidine in THF, RT.

After these first SuRE products (12- or 13- membered macrolactams **3-16**, **3-21**, **3-21a**, **3-21b**) had been made, these lactams were then used in additional SuRE reactions with various α- and β-amino acid chloride derivatives (all with the Fmoc protecting group strategy) to do a second iteration of SuRE (**SuRE 2)**. The 15-membered solomonamide core macrolactam **3-26**, was formed by inserting two α-Gly fragments from 9-membered stating lactam **3-8**. Then two 16-membered macrolactams **3-26a** (insertion of α-Gly + β-Ala fragments) and **3-26b** (insertion of β-Ala + α-Gly fragments), and a 17-membered macrolactam **3-26c** (insertion of two β-Ala fragments) were generated in same manner. Notably, all were synthesized in higher yields than macrolactam **3-26** in the **SuRE 2** reactions. The different yields of these four reactions indicated that the 13-membered lactam **3-21a** has better reactivity than the 12-membered lactam **3-21** in the **SuRE 2** reaction. Significant differences in the yields of products **3-26d** and **3-26e** were observed for these homologues; both macrolactams were tested with the *L*-alanine based acid chloride but 15-membered macrocycle **3-26d** was not obtained, while 16-membered **3-26e** was isolated in 21% yield. Then the 15-membered macrolactam **3-26f** with an α-Gly and a *Z*-proline fragments was generated in a yield of 15% from 12-membered macrolactam **3-21**. The substrate scope research ended by attempting to synthesize a 15-membered macrolactam **3-26g** containing two *Z*-proline fragments; however, the reaction failed, possibly due to the very rigid di-proline structure required in the product.

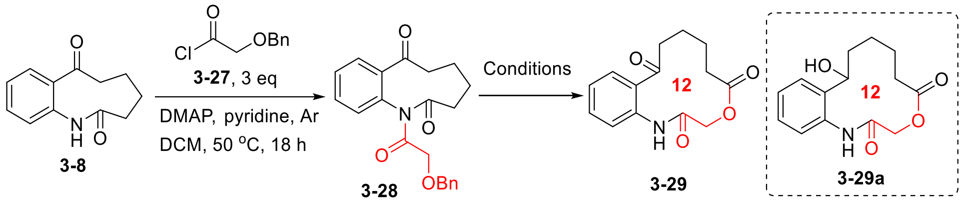
3.3 SuRE strategy towards Solomonamide macrocyclic core: macrolactones

After the cyclic peptide mimetics of solomonamide macrocyclic core were prepared successfully, hydroxy acid chlorides were then tested, in order to make macrolactone analogues of the solomonamide framework.

The 9-membered starting lactam **3-8** was successfully converted into macrocyclic lactone products **3-29** and **3-30** by acylating with *O*-benzyl-functionalized acid chlorides. In these cases, hydrogenolysis was used to cleave the benzyl protecting group to reveal an alcohol, and the ring expansion took place in the same manner as for the analogous amines. With the benzyloxypropanoic acid chloride **3-30**, a 76% yield of the 13-membered macrolactone **3-32** was generated after *N*-acylation and hydrogenation/ring expansion sequences. The 12-membered macrocycle **3-29** only gave a lower 52% yield over 2 steps from the starting lactam **3-8**; in this case, the general hydrogenation conditions using Pd/C could not cleavage the benzyl protecting group, and more forcing conditions using $Pd(OH)_2/C$ combined with Pd/C were required. Nonetheless, an advantage to these conditions was the ring expansion took place spontaneously during the hydrogenation reaction, so there was no need to treat the alcohol intermediate with NEt_3 in chloroform to effect ring expansion, as is usually required in lactone forming SuRE reactions. Optimisation results that led to the discovery of these unusual hydrogenation conditions are shown below in Table 3.4.



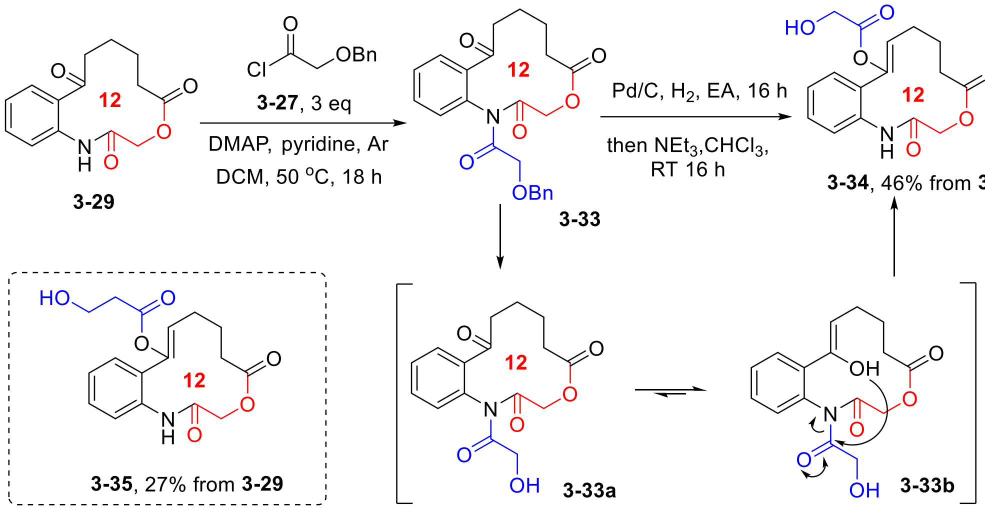
Scheme 3.9 **SuRE 1** reactions using hydroxy acid-based acyl chlorides.



Entry	Hydrogenation conditions	Yield of **3-29** (%) [a]	Yield of **3-29a** (%) [a]
1	Pd/C, H_2, EA, RT, 16 h	0	0
2	Pd/C, H_2, THF, RT, 16 h	0	0
3	Pd/C, H_2, MeOH, RT, 16 h	0	0
4	Pd/C: $Pd(OH)_2/C$ = 1: 1, H_2, THF: IPA, RT, 2 h	18	46
5	Pd/C: $Pd(OH)_2/C$ = 10: 1, H_2, EA, RT, 24 h	**52**	**17**

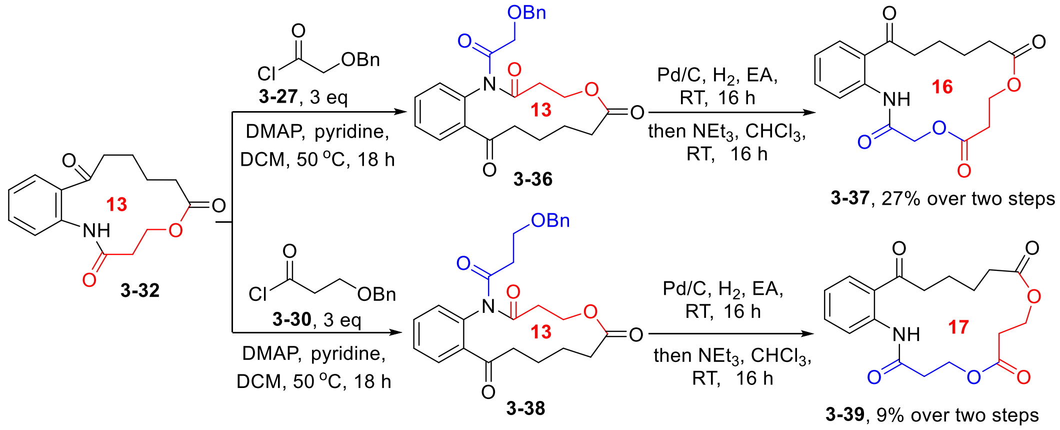
Table 3.4 Optimization of hydrogenation conditions of imide **3-28**. [a] Yield from **3-8**.

Since the SuRE reactions to produce 12- and 13-membered macrolactones **3-29** and **3-32** worked well, the second ring expansion was conducted using same protocol. However, when SuRE reaction of 12-membered macrolactone **3-29** was attempted with α-hydroxy acid chloride **3-27**, instead of giving the expected imide **3-33**, an unexpected acyl transfer product **3-34** was obtained instead after the hydrogenation/ring expansion sequences (Scheme 3.10). It appears that during the hydrogenation step, tautomerization of ketone intermediate **3-33a** into enol **3-33b** enables acyl transfer onto the enol oxygen to form **3-34** as shown in Scheme 3.10. The acyl chain transfer reaction as proposed proceeds *via* a 6-membered ring transition state, and the acyl chain (marked as blue) is transferred from the imide group to the nucleophilic hydroxy group. Similarly, the product **3-35** was generated in the same manner when the same reaction was attempted using the longer chain (β-hydroxy) acid chloride **3-30**.



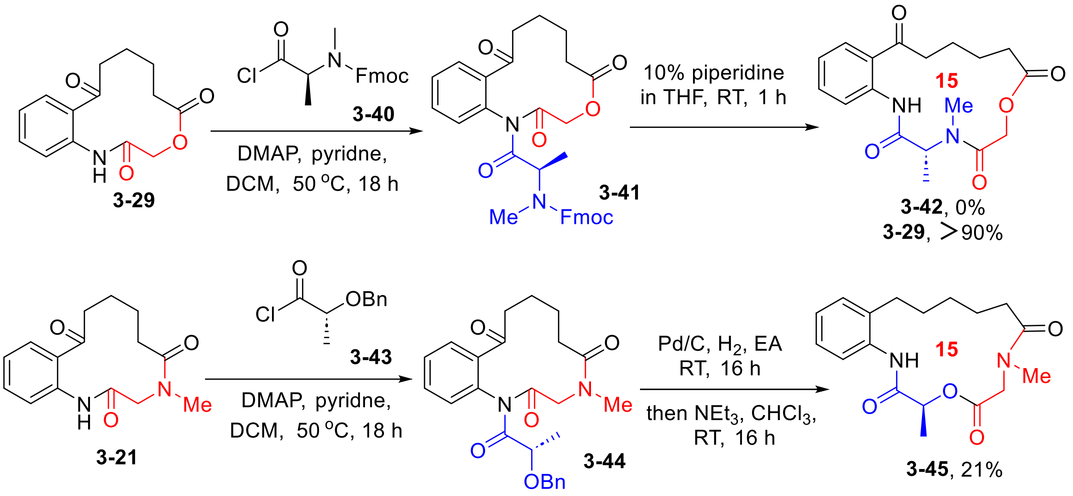
Scheme 3.10 Acyl transferred products generated from the macrocycle **3-29**.

When the 13-membered macrolactone **3-32** was used as the starting lactam, both the 16- and 17-membered macrocycles **3-37** and **3-39** could be produced, although the yields were not high (Scheme 3.11). In these cases, the hydrogenation/ring expansion sequences worked well, with no evidence of the acyl transfer problem that affects the reactions in Scheme 3.11. The low yields were results of the challenging *N*-acylation steps, especially for the 17-membered macrolactone **3-39**.



Scheme 3.11 **SuRE 2** reactions from macrolactone 3-**32** to macrocycles **3-37** and **3-39**.

After the 16- and 17-membered macrolactone analogues of Solomonamide macrocyclic core were synthesized, we tried to generate other 15-membered macrocyclic analogues of Solomonamide core by the combination use of α-amino acid chloride and α-hydroxyacid chloride derivatives. Firstly, 12-membered macrolactone **3-29** was acylated with Fmoc protected *L*-alanine chloride **3-40** successfully, but the imide did not undergo ring expansion and more than 90% of starting macrolactone **3-29** was recovered. Also, in the reaction of 12-membered macrolactam **3-21** with the (*R*)-2-benzyloxypropionic acid chloride **3-43**, after *N*-acylation and hydrogenation/ring expansion sequences, no target ring expansion product (solomonamide macrocyclic core) was detected; instead, an over-reduced product **3-45** with 15-membered ring was obtained with a yield of 21% from starting lactam **3-21**.



Scheme 3.12 Attempts to 15-membered solomonamide macrocycle analogues.

3.4 Chapter 3 summary

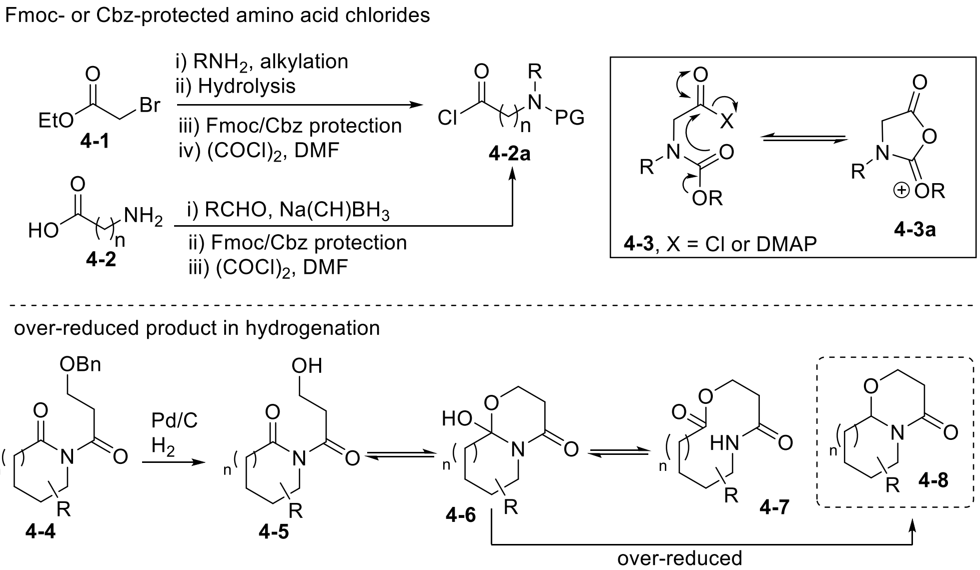
In conclusion, we achieved the synthesis of a series of Solomonamide macrocyclic core analogues using a SuRE strategy. In total, 6 macrolactams and 2 macrolactones with different ring sizes and different amino acid or hydroxy acid fragments were produced. Competitive side reactions were also observed in some cases, but plausible explanations and mechanisms have been suggested, that further our understanding of SuRE reactions in general. Finally, we hope that this study helps to inspire future syntheses of other macrocyclic target molecules using consecutive ring expansion as a synthetic strategy, as an alternative to end-to-end macrocyclisation.

The work described in this Chapter is the subject of one publication.[164]

Chapter Four: Conjugate addition/ring expansion cascade (CARE) reactions to synthesize medium ring lactams and macrocyclic peptide mimetics

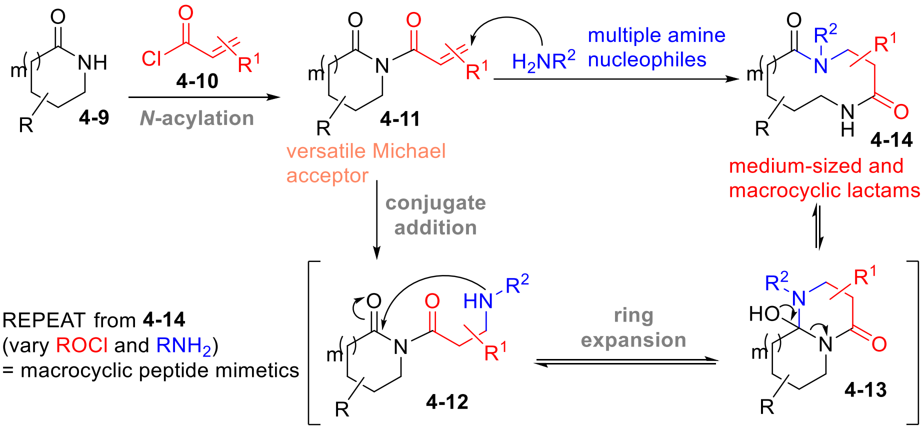
4.1 Introduction to the CARE method

Previous work from our laboratory has established an efficient method for the 3- and 4-atom ring expansion of cyclic lactams upon reaction with acyl chlorides derived from Fmoc- or Cbz-protected amino acids and *O*-benzyl protected hydroxy acid chlorides.[149–152] However, there are limitations associated with the use of the Fmoc- or Cbz-based amino acid chlorides of the type **4-2a**, most notably that a 3- or 4-step synthesis is typically needed to make them (Scheme 4.1). Also, carbamate-mediated acid chloride degradation (discussed earlier in Chapter 3, Scheme 3.6, and summarized below in the Scheme 4.1 box) can negatively affect the *N*-acylation step in reactions that use these reagents. For the *O*-benzyl protected hydroxy acid chlorides, hydrogenation or other conditions to cleavage the benzyl group can lead to the over-reduced products **4-8** sometimes (detected in the Chapter 2).



Scheme 4.1 Limitation of the acyl chlorides.

All of these limitations stem from the need to use protecting groups, which led the Unsworth group to seek a protecting group-free alternative, that could still allow ring expansion to make medium sized ring and macrocyclic products. Thus, a novel conjugate addition/ring expansion cascade (CARE) reaction was developed by a former Unsworth group PhD student Dr Kleopas Palate, in which simple acryloyl chloride derivatives **4-10** were used in the *N*-acylation step instead of the protected amino acid- and hydroxy acid-based chlorides. This enabled the synthesis of the Michael acceptor imide **4-11**, which could then undergo conjugate addition with primary amino nucleophiles (**4-11** → **4-12)** and the ring expansion (**4-12** → **4-13** → **4-14**) takes place spontaneously, furnishing the ring expansion product **4-14**. Using this CARE method, a diverse array of medium sized and macrocyclic peptide mimetics can be generated easily by using different ring sized or functionalised lactams and primary amines with different functional groups.

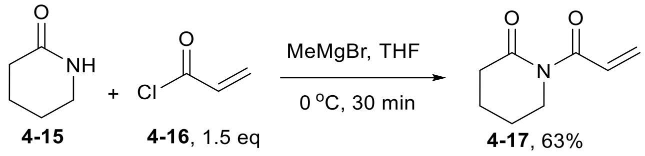


Scheme 4.2 Conjugate Addition/Ring Expansion (CARE) reaction.

The work described in this relatively short chapter is focused on the development of the CARE method, ahead of its publication for the first time.[165] The synthetic work was done together with Dr Kleopas Palate, and throughout the chapter, the reactions performed by Dr Kleopas Palate are clearly acknowledged.

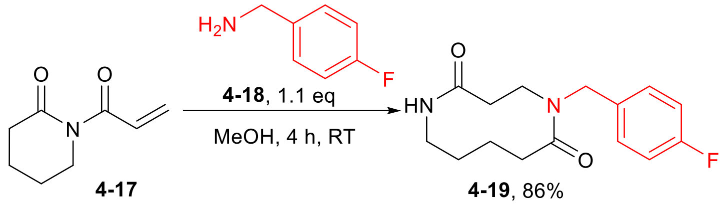
4.2 Preparation of starting material and reaction optimization

The Michael acceptor imide **4-17** was prepared *via* the *N*-acylation of δ-valerolactam with acryloyl chloride **4-16**. In the presence of Grignard reagent in THF at 0 °C for 30 minutes, the acylation completed and generated the imide **4-17** in a yield of 63%, much better than using our standard DMAP, pyridine (0% yield) or DIPEA, NEt_3 (5% yield) conditions.



Scheme 4.3 Preparation of the staring imide **4-17**.

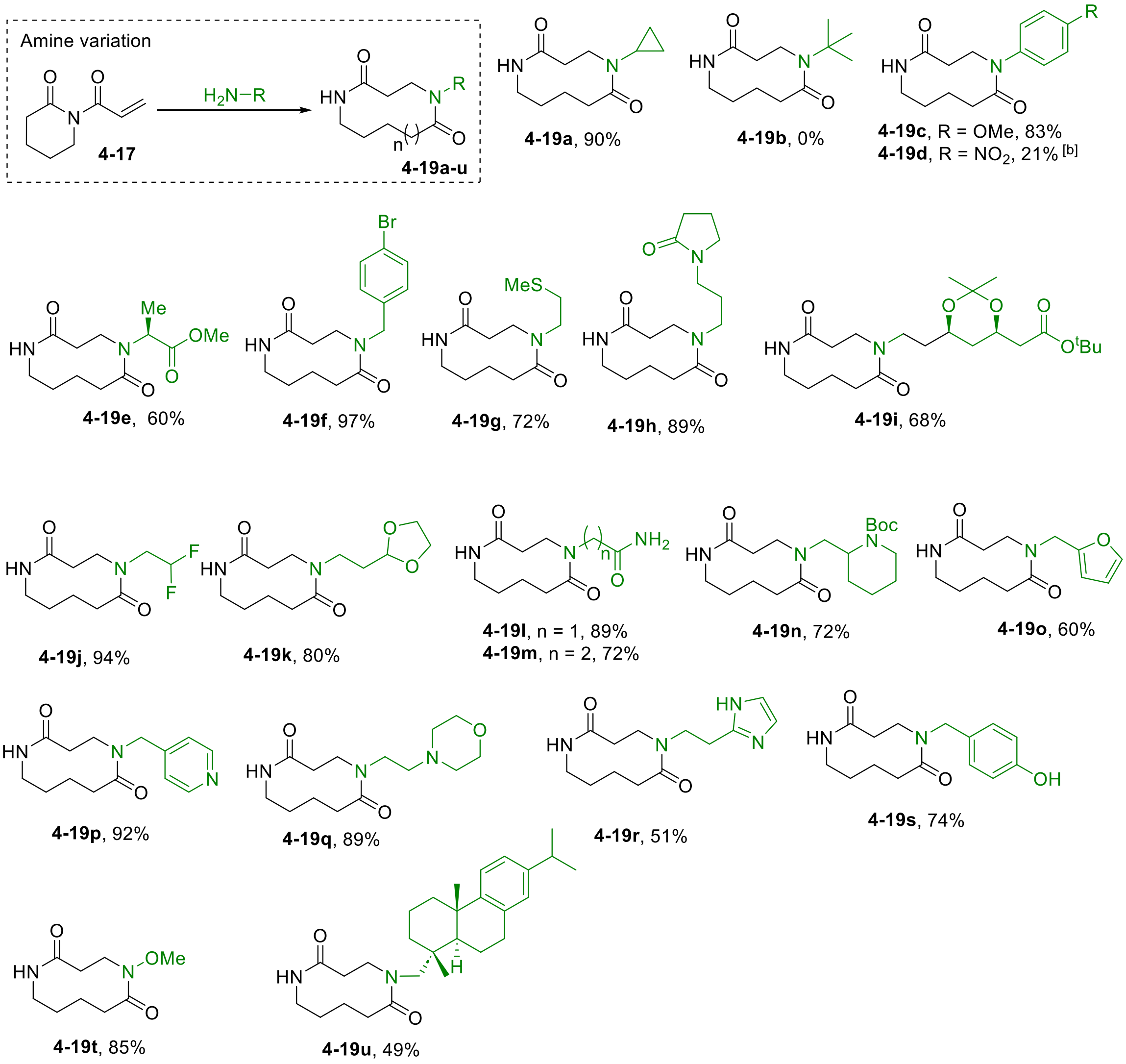
Reaction optimization was performed by Dr Kleopas Palate, using 6-membered starting imide **4-17**. *p*-Fluorobenzylamine **4-18** was chosen as a model primary amine as its fluorine group provided a convenient handle for reaction monitoring using ^{19}F NMR. After many conditions were optimized, using methanol as the solvent was selected to take forward to the substrate scoping phase of the project, with **4-19** isolated yield in 86% following column chromatography, tested on a 5.0 mmol scale reaction.



Scheme 4.4 MeOH as solvent in CARE reaction. Conditions established by Dr Kleopas Palate.

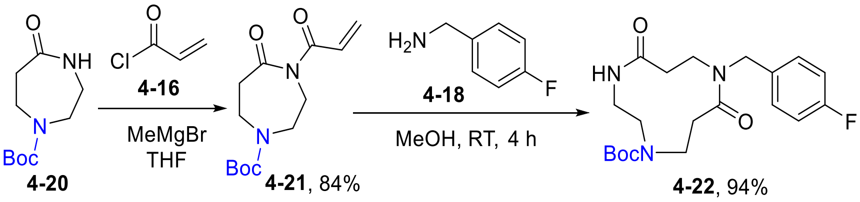
4.3 CARE substrates scope study

My main contribution to this project focused on exploring the scope of this CARE reaction with respect to amine variation. As a test substrate, the 6-membered starting imide **4-17** was used, with the results summarized in Scheme 4.5. The steric influence on the reaction yields is clear when comparing relatively unhindered cyclopropylamine **4-19a** (90%) and bulky *tert*-butylamine **4-19b** (0%). When aniline derivatives were tested, the electron-rich *p*-OMe substituted product was formed in 83% using the standard protocol, but an electron-poor *p*-NO_2 derivative **4-19d** gave only 21% of yield, even when the reaction time was extended to 3 days. Using the 4-bromo benzyl amine as the nucleophile, a 97% yield of 10-membered lactam **4-19f** was generated. *L*-alanine derived primary amine was tolerated and afforded the product **4-19e** in 60% yield. Similarly, a 10-membered peptide mimetic with a cysteamine fragment **4-19g** was obtained in 72% yield. Then a wide array of functional groups, including ester (**4-19i**), halide (**4-19j**), various heterocycles (**4-19h**, **4-19k**, **4-19n**, **4-19o**, **4-19p**, **4-19q** and **4-19r**), amides (**4-19l** and **4-19m**) and hydroxylamine derivative (**4-19s**) were tested and all of them gave the ring expansion products in good to excellent yields. Notably, methoxyamine (free-based from its HCl salt) could be used as the nucleophile amine as well, giving an 85% of the ring expansion product **4-19t**. This amine scope study ended with the CARE reaction of the starting imide **4-17** with the bioactive primary amine leelamine, in which the target product **4-19u** was produced in a 49% yield.



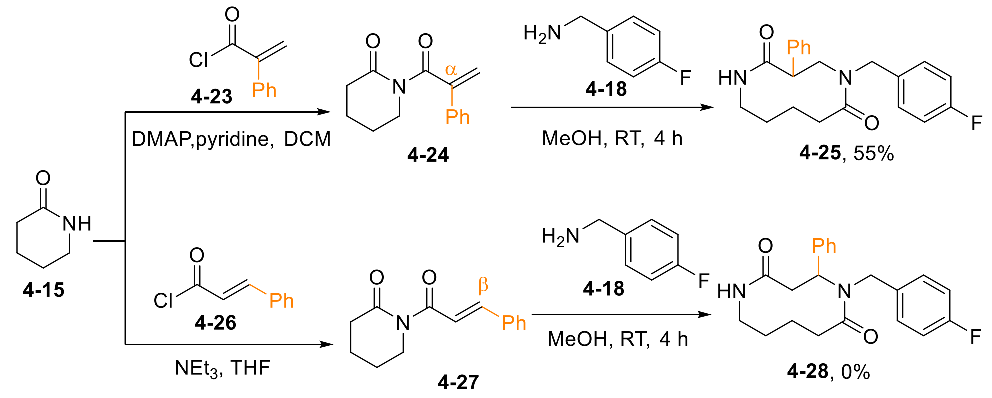
Scheme 4.5 Scope of Conjugate Addition/Ring Expansion (CARE) for medium sized ring lactam synthesis. [a] Unless stated the following procedure was used: Imide (1 equiv) and amine (1.1 equiv) were stirred in methanol (0.5 M) for 4 h at RT, concentrated and purified directly by column chromatography; [b] reaction stirred for 3 days.

Next, different functionalized lactam starting materials were investigated. The 7-membered starting imide **4-21** was prepared from the commercial lactam **4-20** and reacted with fluorobenzylamine **4-18**, affording the CARE product **4-22** in an excellent yield (94%). Other functionalized materials like fused ring containing, alkene containing and sulfide atom containing lactams were also utilized successfully to produce CARE products in work done by Dr Kleopas Palate, with these results not included in this thesis, but they can be found in the publication.[165]



Scheme 4.6 Lactam variation of CARE reaction.

The last part of my contribution to this project was to test substituted Michael acceptors. Substituted imides **4-24** and **4-27** were prepared using standard *N*-acylation methods summarized in Scheme 4.7. The α-substituted Michael acceptor **4-24**, was then converted into ring expansion product **4-25** in 55% yield using the standard CARE protocol. However, no product obtained when the R = Ph at β-position (**4-27**) presumably due to its reduced electrophilicity. Additional examples demonstration different Michael acceptors (R = Me) were performed by Dr Kleopas Palate , with these results included in the publication.[165]



Scheme 4.7 Variation on the Michael accepter.

4.4 Chapter 4 summary

In conclusion, together with Dr Kleopas Palate, I helped to develop the conjugate addition/ring expansion (CARE) reaction as a practical and versatile method for the synthesis of medium sized/macrocyclic lactams and peptide mimetics. The imide precursors can react with a wide array of functionalized amines without the need for protecting groups and produce ring expansion products based on β-peptoid linkages. All these products can be thought of as macrocyclic peptide/peptoid mimetics, which have significant potential applications in medicinal and biological chemistry.

This work was completed collaboratively with Dr Kleopas Palate and published alongside related examples. Those reactions that I didn't participate in (*e.g.* iterative CARE reactions), have not been included in this Chapter, but are reported in the publication.[165]

Chapter Five: Ring Expansion strategies for the synthesis of medium sized ring and macrocyclic sulfonamides

5.1 Sulfonamides and cyclic sulfonamides

Sulfonamides have important applications in medicinal chemistry due to their significant biological activities such as antibiotic and anti-inflammatory agents.[166–169] Cyclic sulfonamides (traditionally known as sultams) are also commonly found in clinical drugs and bioactive compounds. Representative examples of normal sized ring cyclic sulfonamides (5–7-membered rings), medium sized (8–11-membered) and macrocyclic (12+ membered, *e.g.* **5-6**) sulfonamides are shown in Figure 5.1. However, the study of medium sized and macrocyclic sulfonamides is less well explored compared to the normal sized ring cyclic sulfonamides, both in terms of synthetic methods to make them, and their bioactivities.[170–178]

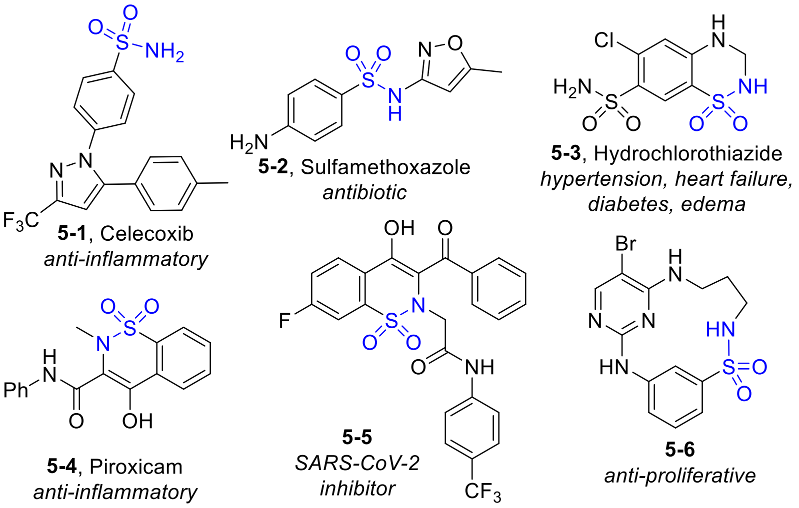
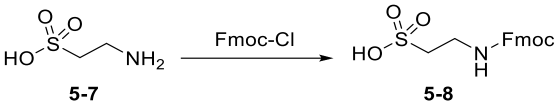


Figure 5.1 Medicinally important acyclic and cyclic sulfonamides.

In the Unsworth group's previous SuRE methodology, various medium sized rings and macrocycles were synthesized, but all these products are belonged to lactam and lactone product classes (including thiolactones[179]). Considering the sulfonyl group can be introduced as bioisostere of the carbonyl group in drug molecules, to remain or improve bioactivity, we wondered if the sulfonyl chlorides could be used instead of acyl chlorides to conduct SuRE type ring expansion reactions and generate medium sized and macrocyclic sulfonamides.

5.2 SuRE strategy towards medium sized and macrocyclic sulfonamides

Synthetic studies started by making Fmoc protected taurine **5-8**. 1 M NaOH was used as the base initially, in different solvents[180], but none of the conditions tested produced the target product. $NaHCO_3$ was also tested but also did not work (Table 5.1).

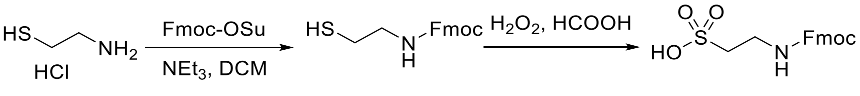


5-7 **5-8**

Entry	conditions	Yield of **5-8** (%)
1	1M NaOH as solvent	0
2	1M NaOH in dioxane	0
3	1M NaOH in CH_3CN	trace
4	$NaHCO_3$ in dioxane	0

Table 5.1 Reactions using taurine to synthesize product **5-8**.

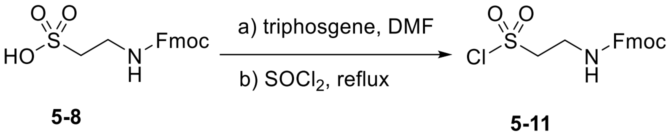
A different strategy towards to the Fmoc protected taurine **5-8** from the cysteamine hydrochloride was therefore tested, and this method could generate the product, in a 25% yield from **5-9**, after Fmoc-protection and thiol oxidation steps.



5-9 **5-10** **5-8**, 25% over 2 steps

Scheme 5.1 Synthesis of the Fmoc protected product **5-8**.

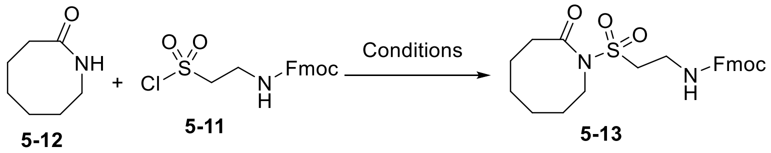
Attention then turned to converting sulfonic acid **5-8** into the sulfonyl chloride **5-11**. Both triphosgene and thionyl chloride conditions were tried,[181,182] because according to the published method, the triphosgene conditions could produce the sulfonyl chloride in a 78% yield, and using thionyl chloride as solvent could give 85% yield of the target sulfonyl chloride as a white solid. Following both methods, the sulfonyl chloride **5-11** was used directly in next step considering its low stability, and no analysis of **5-11** was done (i.e. its formation was assumed to be successful but not confirmed, as is done for acid chloride formation in standard SuRE reactions).



5-8 **5-11**

Scheme 5.2 Synthesis of the Fmoc protected sulfonyl chloride **5-11**.

We found no literature conditions for the *N*-sulfonylation of lactams with Fmoc protected sulfonyl chlorides. Therefore, our optimization started by using our standard conditions for *N*-acylation with acid chlorides. The 8-membered lactam **5-12** was selected as the starting lactam, because the ring expansion from 8-membered lactam to 12-membered products are generally amongst the most favorable reactions in our previous SuRE reactions.[150–152,183] Unfortunately, our established *N*-acylation conditions didn't work for this *N*-sulfonylation reaction (Entry 1 to 3, Table 5.2). Stronger bases were also tested, but in the presence of NaH and *n*-BuLi, no target product **5-13** was detected; with LiHMDS, the ESI-MS analysis of the reaction indicated trace product formation, but more than 90% of the lactam **5-12** was recovered following column chromatography.



5-12 **5-11** **5-13**

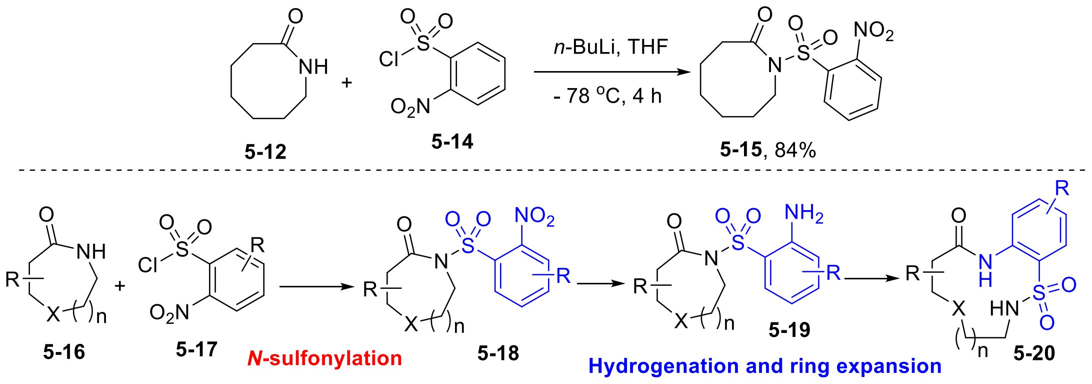
Entry	Conditions	Detection of **5-13**
1	DMAP, pyridine, DCM, 50 °C	no
2	CuO, NMM, benzene, 80 °C	no
3	NEt_3, DCM, rt	no
4	LiHMDS, THF, 0 °C to rt	trace
5	NaH, THF, 0 °C to rt	no
6	NaH, DMF, 0 °C to rt	no
7	*n*-BuLi, THF, - 78 °C to rt	no

Table 5.2 Optimization of *N*-sulfonylation conditions using **5-11**.

Thus, we had to acknowledge that the normal SuRE strategy is not suitable for the synthesis of medium sized and macrocyclic sulfonamides, other approaches should be developed to address this problem.

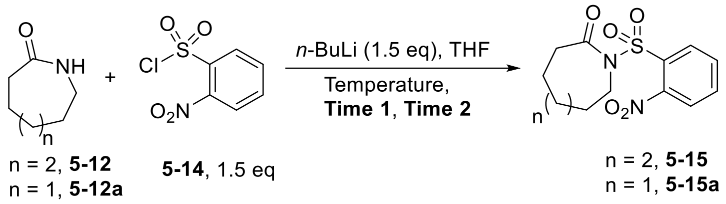
5.3 Nitro reduction method to medium sized and macrocyclic sulfonamides

During a literature research, we found that the commercial 2-nitrobenzenesulfonyl chloride **5-14** (i.e. 2-nosyl chloride) could effect the sulfonylation of cyclic lactams in high yield (84% yield of **5-15**).[184] Taking inspiration from this reaction, our idea was to use nitrobenzenesulfonyl chlorides **5-17** as the sulfonylation reagent towards a ring expansion reaction. It was thought that the nitro product **5-18** can be reduced to the aniline product **5-19**, which we proposed might undergo ring expansion *in situ*, to form medium sized and macrocyclic sulfonamides **5-20** (Scheme 5.3). In this ring expansion, the use of classical protecting groups is avoided, with the nitro group acting as a masked amine, which can be revealed *via* hydrogenation with Pd/C. Notably, anilines were not explored in our previous SuRE methods, so this study also afforded an opportunity to learn how their reactivity compares to aliphatic amine or alcohol ring expansion systems.



Scheme 5.3 Nitro reduction strategy towards sulfonamide medium sized rings macrocycles.

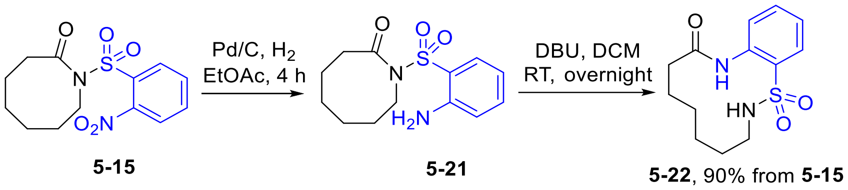
The *N*-sulfonylation of 8-membered cyclic lactam **5-12** with the 2-nitrobenzenesulfonyl chloride **5-14** worked well at both –78 °C (dry ice/acetone bath) and 0 °C (ice bath) when using 1.5 eq of *n*-BuLi and 1.5 eq of nitrobenzenesulfonyl chloride **5-14**, with both reactions giving the target product **5-15** in a yield of up to 86% (Table 5.3). Here, when the temperature was –78 °C, the sulfonyl chloride was added 60 mins after the *n*-BuLi; when the temperature was 0 °C, a 10 mins gap was sufficient (**Time 1**). However, when the 7-membered lactam **5-12a** was used for the sulfonylation at 0 °C, only 44% of target product **5-15a** was isolated. Thus, standard *N*-sulfonylation conditions were established as treating the cyclic lactam with *n*-BuLi at –78 °C in THF for 1 h (**Time 1**) then nitrobenzenesulfonyl chloride added and the reaction mixture was stirred overnight (**Time 2**).



Entry	**Tem (°C)**	**Time 1** (After *n*-BuLi)	**Time 2** (After **5-14**)	**Yield (%)**[a]
1 (n = 2)	-78	10 min	4 h	76
2 (n = 2)	-78	60 min	16 h	**86**
3 (n = 2)	0	10 min	4 h	83
4 (n = 2)	0	10 min	16 h	86
5 (n = 1)	0	10 min	16 h	44
6 (n = 1)	-78	60 min	16 h	**83**

Table 5.3 Optimization of the *N*-sulfonylation conditions using **5-14**. Cyclic lactam (1 eq) in THF (0.25 mmol/mL) was cooled to the **Temperature** (0 or –78 °C) and *n*-BuLi (1.5 eq) was added dropwise, after **Time 1** (10 or 60 min), 2-nitrobenzenesulfonyl chloride (1.5 eq) in THF (1.5 mmol/mL) was added dropwise, the mixture was stirred for **Time 2** (4 h at –78 °C or 16 h from –78 °C to RT). [a] isolated yield reported.

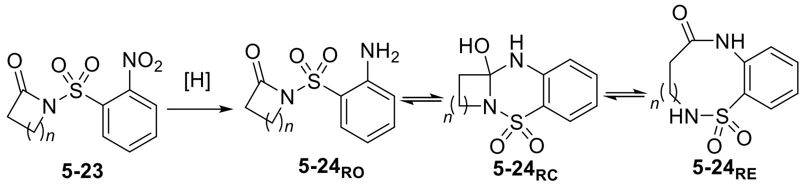
Next, the nitro product **5-15** was reduced to aniline **5-21** *via* hydrogenation with Pd/C in ethyl acetate in a quantitative yield. The resulting aniline was then treated with 10 eq of DBU in DCM at RT to form the ring-expanded macrocyclic sulfonamide **5-24** in 90% overall yield from **5-15** over the reduction/ring expansion sequences. Thus, a synthetic route to macrocyclic sulfonamides *via* ring expansion had been completed and our idea was validated.



Scheme 5.4 Hydrogenation and ring expansion sequences to the sulfonamide macrocycle **5-22**.

Before substrate scope investigations, the viability of ring expansion reactions for different ring sizes was assessed by DFT calculations. The calculations were performed by another Unsworth group member (Dr Ryan Epton) but are discussed herein as they are important when explaining the upcoming synthetic results. The DFT methodology used was validated and benchmarked with imide-based systems developed in the group's previous ring expansion work[151], the relative Gibbs free energies of the ring-opened (**5-24RO**), ring-closed (**5-24RC**) and ring-expanded (**5-24RE**) isomers of different ring size (4- to 8-membered) systems were calculated and the results summarized in Table 5.4. In DFT calculations of ring expansion reactions of this type, the isomer that is calculated to be lowest in energy is typically the final product observed in the synthetic reaction.

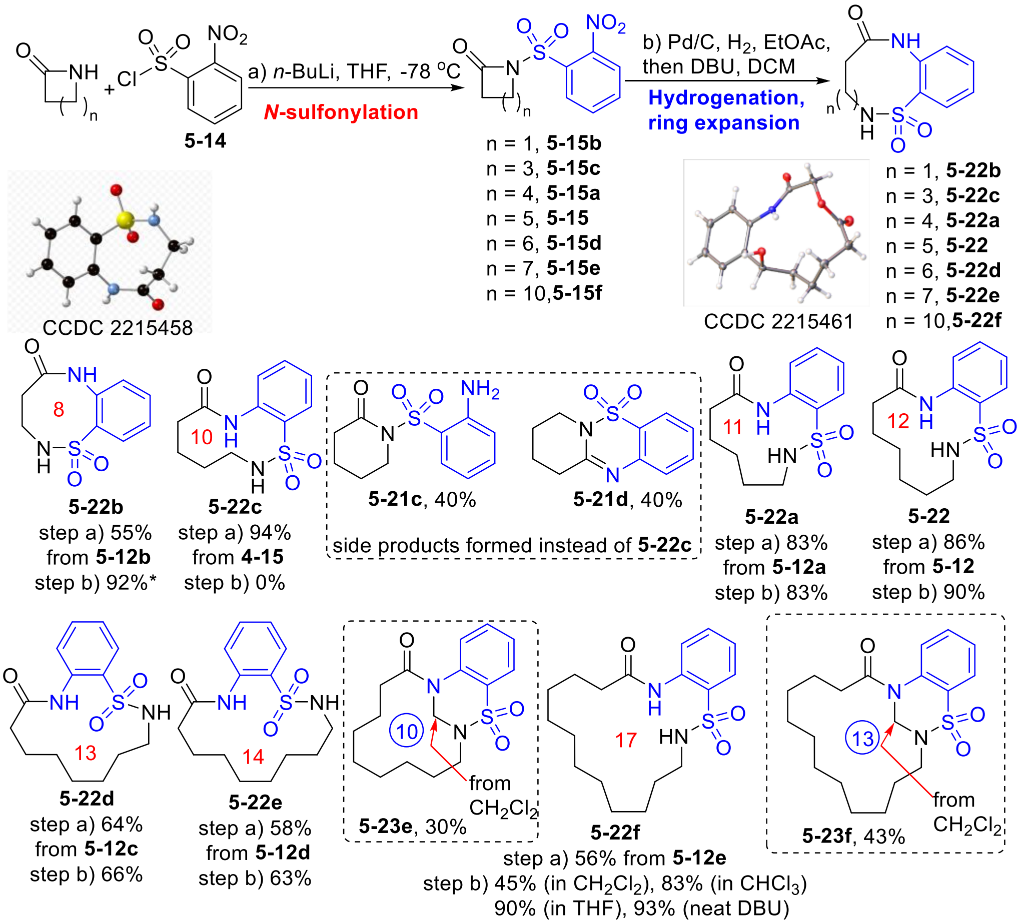
The results are summarized in Table 5.4. The ring expansions of 4- and 8-membered starting materials were calculated to be favorable, indicated by the much lower relative Gibbs free energy of the isomer **5-24RE** (n = 1 and 5, Table 5.4). In contrast, the ring expansion of 5- and 6-membered starting material were predicted to be unfavorable as their aniline isomers **5-24RO** were calculated to have lower relative energies (n = 2 and 3). For the 7-membered starting material, it was difficult to predict the viability of the ring expansion as isomers **5-24RE** and **5-24RO** were very close in energy.



n	ΔGrel 5-24RO	ΔGrel 5-24RC	ΔGrel 5-24RE
1	0.0	+15.9	–6.6
2	0.0	+15.6	+5.8
3	0.0	+11.5	+5.2
4	0.0	+13.9	–0.5
5	0.0	+7.8	–12.5

Table 5.4 DFT calculations to predict the influence of ring size on reaction viability. ΔG_{rel} in kcal/mol; relative energies are Gibbs energies at the B3LYP/6-31G* level of theory in the gas phase, at 298.15 K. These calculations were performed by Unsworth group member Dr Ryan Epton.

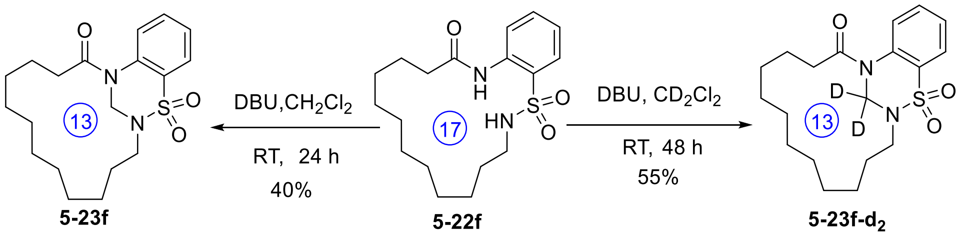
The ring expansion from 8-membered material to 12-membered macrocyclic sulfonamide **5-22** (Table 5.4, n = 5) had already been validated synthetically, and was in line with the DFT calculation. The synthetic reactions of different lactam ring sizes were examined next. Firstly, the 4-membered β-lactam was sulfonated with 2-nitrobenzenesulfonyl chloride **5-14**, and the nitro product was successfully converted into the ring expansion product **5-22b** after reduction/ring expansion sequences, without the need to use base to promote ring expansion (Scheme 5.5, reaction performed and X-ray crystal structure obtained by another PhD student Illya Zalessky in the Unsworth group, CCDC 2215458). This result was in line with the DFT prediction. For the ring expansion of 6-membered lactam **4-15**, the sulfonylation with sulfonyl chloride **5-14** worked very well, giving 94% yield of the target imide product **5-15c**, however, no ring expansion product **5-22c** was detected following nitro reduction and basic treatment; again, this result was as the DFT calculation predicted. Instead, an equilibrium between the aniline product **5-21c** and the thiadiazine product **5-21d** was obtained, when the aniline product was treated with DBU for 48 h. Other bases like NaH and *n*-BuLi were tested for the ring expansion of the aniline **5-21c**, but neither of them led to an improvement, which is consistent with the failure of the ring expansion being a thermodynamic outcome. Notably, all these ring expansions of the >6-membered ring systems worked well – including the 7-membered ring substrate, which was calculated to be a borderline case. In the ring expansion reaction from the 7-membered lactam **5-12a**, both the sulfonylation and hydrogenation/ring expansion steps worked in good yields, and we obtained the X-ray crystal structure of the ring expansion product **5-22a** (CCDC 2215461) as well.



Scheme 5.5 Ring size variation of medium sized and macrocyclic sulfonamides. *Ring expansion took place spontaneously following hydrogenation, the DBU step was not required, reaction and XRD performed by Illya Zalessky.

A trend was noticed that with the increase of cyclic lactam ring sizes, the yields in both *N*-sulfonylation step and hydrogenation/ring expansion step decreased (**5-15d** to **5-15f** and **5-22d** to **5-22f**). Different nucleophilic activities of different ring sized lactams could account for the decrease of the yields in sulfonylation step. However, in the hydrogenation/ring expansion step, the isolation of the side products **5-23e** and **5-23f** was discovered to be responsible for the lower yields of the ring expansion products. Interestingly, these methylene-bridged side products arise from the coupling of the cyclic sulfonamides with CH_2Cl_2 (the solvent used in the ring expansion step). We reasoned that they could easily be avoided by changing the reaction solvent. Thus, a small solvent optimization was performed, and the yield of ring expansion product **5-22f** increased significantly when the solvent was changed to $CHCl_3$, THF or neat DBU (80%, 90% and 93% yields respectively).

The unexpected thiadiazine side products are relatively rare examples of CH_2Cl_2 (which is usually an inert solvent) reacting as a methylene donor, which attracted our interest in the mechanism of this reaction. To prove the methylene came from the solvent, the ring expansion product **5-22f** was reacted in CD_2Cl_2 instead of CH_2Cl_2 with DBU and 55% yield of the d_2-methylene product **5-23f-*d₂*** was obtained (Scheme 5.6). Comparing the ^1H NMRs of **5-23-*d₂*** to **5-23f**, the single peak at 5.50 (s, NC**H₂**N) disappeared, which is consistent with it being deuterated (Figure 5.2). This reaction allowed the synthesis of macrocycles containing a 1,2,4-thiadiazinane 1,1-dioxide motif, which is interesting in its own right, as the products might be biologically active; the thiadiazinane motif has been found in many medicinal agents.[185–187]



Scheme 5.6 Methylene reactions of 17-membered sulfonamide macrocycle **5-22f**.

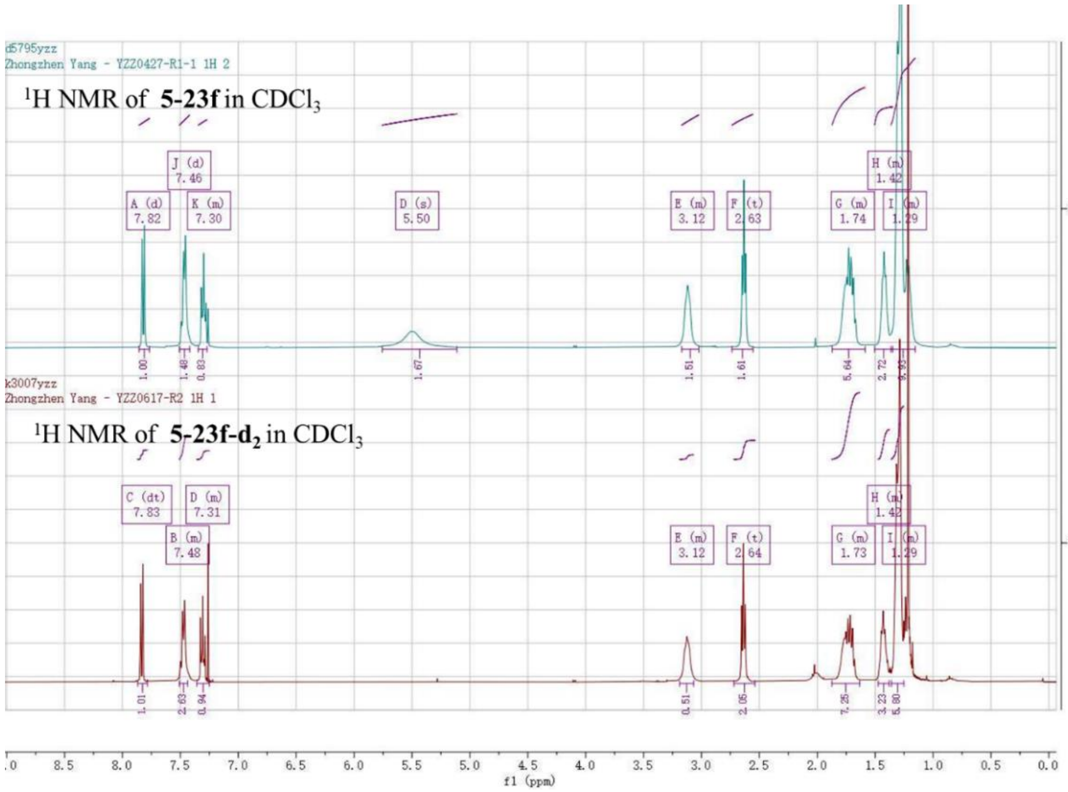
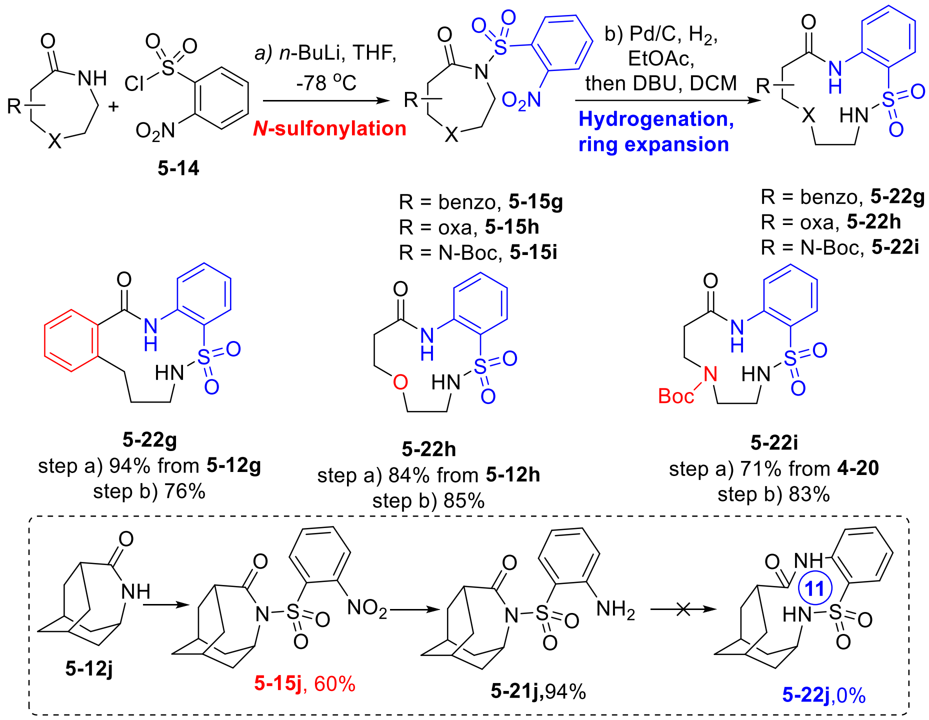


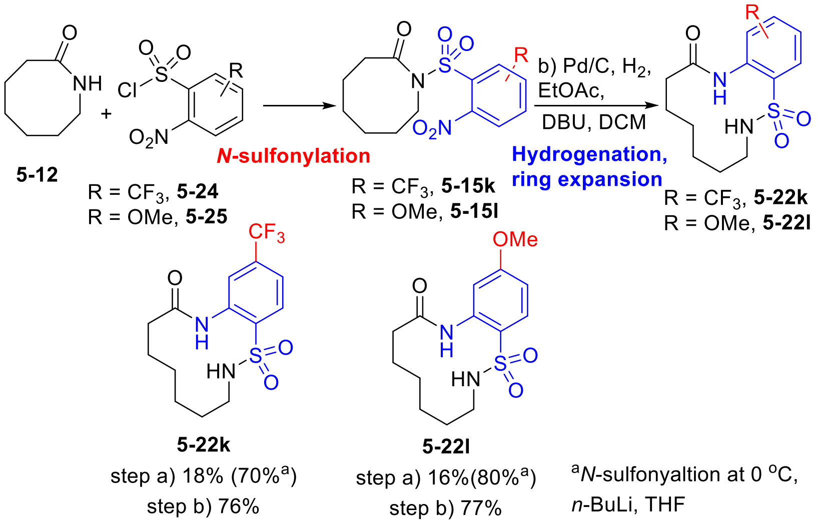
Figure 5.2 ^{1}H NMRs of **5-23f** and **5-23f-*d*$_2$**.

Next, functionalized starting lactams were examined, starting from the 7-membered lactam **5-12g** containing a benzo-motif. The sulfonylation step gave an excellent yield (94%) of the nitro precursor (**5-15g**), and the ring expanded product **5-22g** was generated in a yield of 76% following the hydrogenation/ring expansion sequences. Similarly, the oxa- and carbamate- containing lactams could produce the expected ring expansion products **5-22h** and **5-22i** in good yields (Scheme 5.7). However, the azatricyclo lactam **5-12j** failed in the ring expansion step, while the sulfonylation step and hydrogenation step worked well. This was speculated to be a result of the high rigidity of the tricyclo structure, which may have hindered the ring expansion.



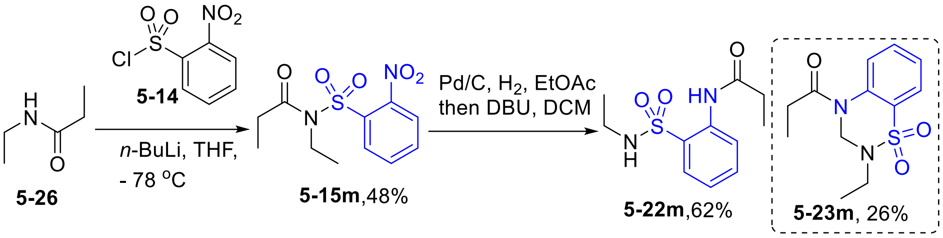
Scheme 5.7 Lactam variation of medium sized sulfonamides.

Substitution on nitrobenzenesulfonyl chloride was also tested (Scheme 5.8). 4-Trifluoromethyl- and 4-methoxy nitrobenzenesulfonyl chlorides **5-24** and **5-25** (both are commercially available) could be sulfonated with the 8-membered lactam **5-12** at 0 °C rather than –78 °C, and the desired ring expansion products **5-22k** and **5-22l** were generated in good yields after reduction/ring expansion steps.



Scheme 5.8 Sulfonyl chloride variation of macrocyclic sulfonamides.

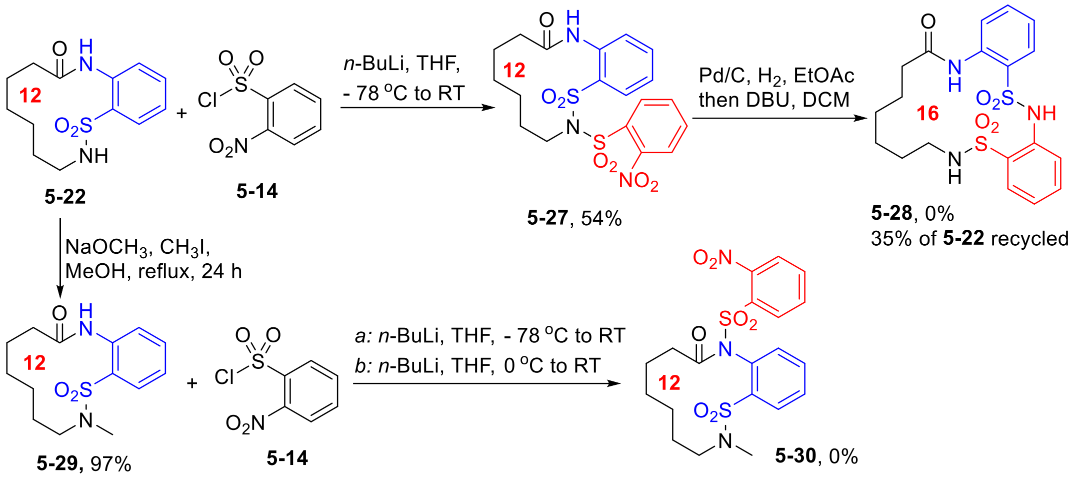
A special case illustrates that this strategy can also be used to introduce a benzenesulfonamide fragment into linear amides (Scheme 5.9). Ethylpropionamide **5-26** reacted with 2-nitrobenzenesulfonyl chloride **5-14** giving the nitrophenylsulfonyl product **5-15m** in a yield of 48%, which underwent hydrogenation and the rearrangement (the same process as the ring expansion reaction) to produce the liner benzenesulfonamide product **5-22m** in a yield of 62%. Notably, the methylene incorporated product was detected again, with the thiadiazinane product **5-23m** isolated in a yield of 26%. This would presumably have been suppressed had one of the alternative solvents been used, but time constraints meant this was not tested.



Scheme 5.9 Synthesis of the linear sulfonamide **5-22m**.

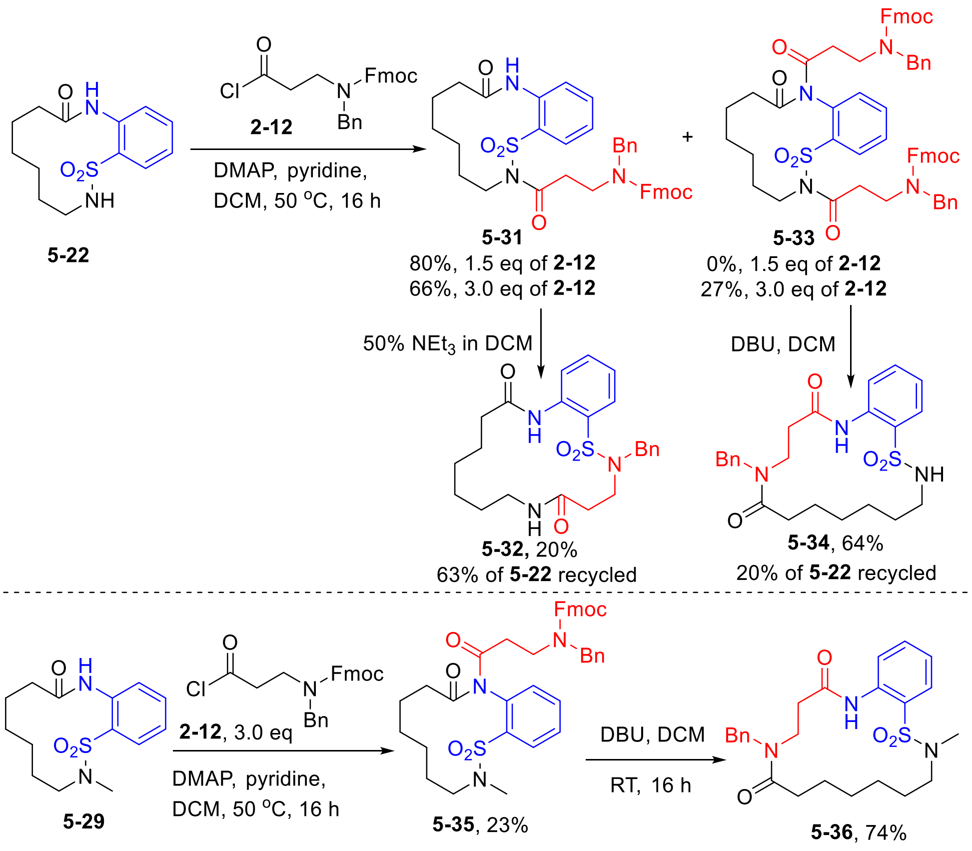
Thus, the method of using ring expansion strategy to make sulfonamide medium sized rings and macrocycles had been demonstrated to work well for a wide range of substrates. Then, we explored the possibility of using this strategy to achieve Successive Ring Expansion (SuRE) by using the ring expansion product **5-22** in a second ring expansion (Scheme 5.10). The macrocycle **5-22** was reacted with 2-nitrobenzenesulfonyl chloride **5-14**, giving a 54% yield of the nitro intermediate **5-27**. This product was then hydrogenated to form the key aniline precursor, but unfortunately it did not ring expand to form 16-membered macrocycle **5-28**. Instead, the 12-membered starting lactam **5-22** was recycled in 35% yield after the reaction being treated with DBU overnight. As the *N*-sulfonylation took place on the sulfonamide nitrogen instead of the lactam nitrogen, it's not wholly surprising that this ring expansion failed, given that this type of ring expansion type has never been studied or achieved in the Unsworth group's previous work. To address this problem, the methylated sulfonamide **5-29** was synthesized as its sulfonamide site has been blocked.

However, the attempts to synthesize the nitro intermediate **5-30** failed; this is thought to be because of the low nucleophilicity of the aniline lactam.



Scheme 5.10 Attempts to the second ring expansion using macrocycle **5-22**.

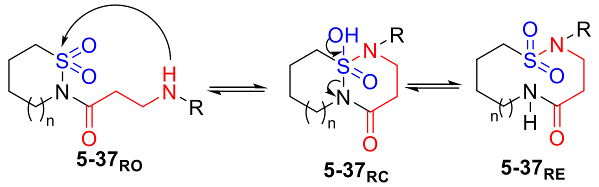
As the attempts to make disulfonamide macrocycles had failed, acyl chlorides used in our previous SuRE were tested on the macrocyclic sulfonamide **5-22** instead, as they are more reactive than sulfonyl chlorides in *N*-acylation reactions. The target imide **5-31** was generated in the yield of 80% by using 1.5 eq of the Fmoc-protected acyl chloride **2-12** reacted with the macrocycle **5-22**, which again showed that the sulfonamide NH is more nucleophilic than the phenylamide NH. Then the 16-membered ring expansion product **5-32** was isolated in 20% yield after the deprotection of the Fmoc group using NEt_3, but with 12-membered sulfonamide **5-22** recycled in 63% yield. Notably, when DBU was used to deprotect Fmoc group of the imide **5-32**, no ring expansion product was observed. As the 12-membered sulfonamide **5-22** has two active NH sites, 3.0 eq of the Fmoc-protected acyl chloride **2-12** was used to produce the diimide product **5-33**. In this deprotection and ring expansion reaction, NEt_3 conditions could remove Fmoc groups slowly but can’t form the ring expansion product, whilst the DBU could deprotect the Fmoc group on the CON side chain but removed the whole β-Ala side chain on SO_2N simultaneously, that’s why only the 16-membered ring expansion product **5-34** was generated and no 20-membered ring expansion product was detected.



Scheme 5.11 Attempts to the second ring expansion using amino acid acyl chloride **51**.

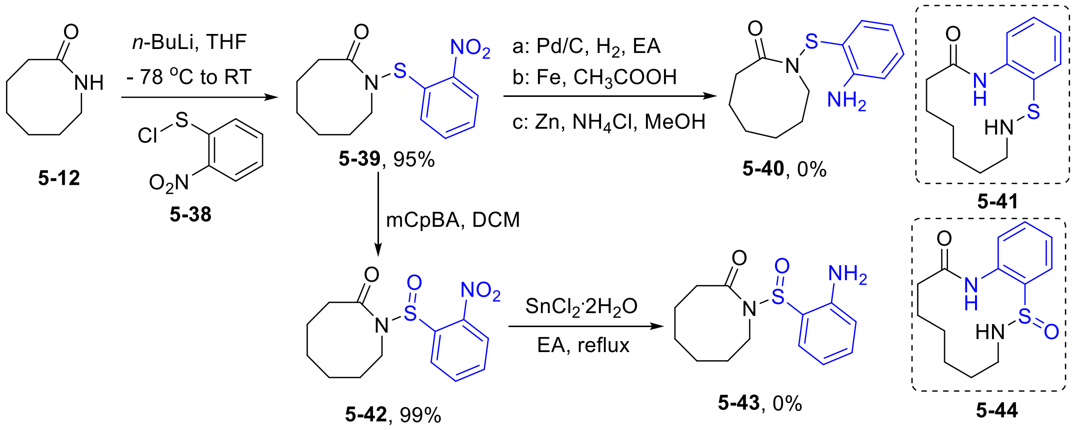
In addition, the methylated sulfonamide **5-29** was acylated with 3.0 eq of acyl chloride **2-12**, producing only 23% yield of desired imide **5-35**; this low yield supported the weak nucleophilic activity of the phenylamide again. But more promising, the ring expansion product **5-36** was isolated after the Fmoc deprotection step in a yield of 74%.

Although some iterative ring expansion products were achieved using our general SuRE conditions, the low overall yields made this process less attractive. Moreover, the ring expansion on the sulfonamide motif has not been achieved. For this to happen, a ring-closed isomer with a very crowded S centre would need to be accessed, which is quite different to our previous SuRE that has a carbon centre with fewer bonds to it (Scheme 5.12).



Scheme 5.12 Speculated mechanism of the ring expansion on sulfonamide motif.

After various medium sized and macrocyclic sulfonamides were synthesized successfully using sulfonyl chlorides, 2-nitrobenzenesulfenyl chloride **5-38** (commercially available) was tested to synthesize ring expansion product containing thiazole (**5-41**) or sulfenamide (**5-44**) fragments. The benzenenitro intermediate **5-39** was generated in an excellent yield (95%) from the 8-membered starting lactam **5-12**. However, several different hydrogenation or reduction conditions to the nitro product **5-39** all failed to access the aniline **5-40**. Then the nitrophenylthio product **5-39** was oxidised to the nitrophenylsulfinyl product **5-42** with 3-chloroperbenzoic acid (mCPBA). Similar to aniline **5-40**, reduction conditions tested failed to give the target aniline product **5-43**, and almost all 8-membered lactam **5-42** was recovered.

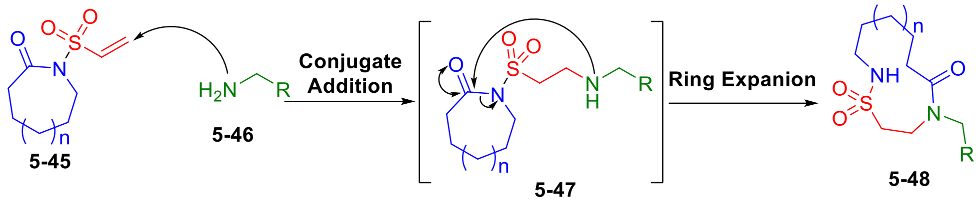


Scheme 5.13 Attempts to do ring expansion using 2-nitrobenzenesulfenyl chloride **5-38.**

As these attempts were not successful, we decided to conclude this work and switch attention to another part of this project (using CARE method to make sulfonamide medium sized rings and macrocycles).

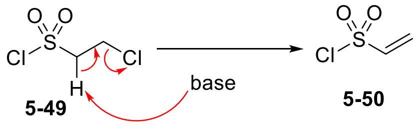
5.4 Conjugate addition method to medium sized and macrocyclic sulfonamides

The conjugate addition/ring expansion cascade (CARE) reactions described in Chapter 4 were proved to be a highly efficient method to synthesize medium sized and macrocyclic lactams. The new idea described in this section was that vinylsulfonyl product **5-45** could act as a Michael acceptor and undergo conjugate addition with a primary amine, then producing the ring expansion product **5-48** with sulfonamide fragment in a similar manner (Scheme 5.14). In this work, I worked cooperatively with another PhD student Illya Zalessky in the Unsworth group. All reactions performed by Illya Zalessky are acknowledged appropriately.

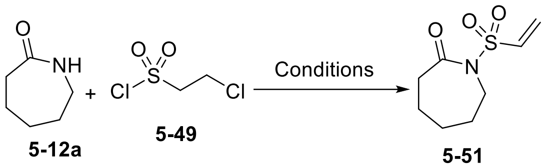


Scheme 5.14 CARE reaction in the synthesis of sulfonamide products.

First, we focused on the synthesis of vinylsulfonyl material **5-51** using the 7-membered lactam **5-12a** with the 2-chloroethanesulfonyl chloride **5-49** (commercially available). In this reaction, the chloroethanesulfonyl chloride **5-49** can be easily converted into the vinylsulfonyl chloride **5-50** under basic conditions (Et_3N or 2,4,6-collidine). The protocols used for the optimization reactions was to first make the crude vinylsulfonyl chloride in the selected solvent with the selected base, then added the mixture of lactam, catalyst, and base into the freshly formed vinylsulfonyl chloride solution. After various bases, catalysts and temperature were tested, the DMAP and NEt_3 conditions (Entry 7, Table 5.5) gave the best yield (16%).



Scheme 5.15 Mechanism of 2-chloroethanesulfonyl chloride to vinylsulfonyl chloride.

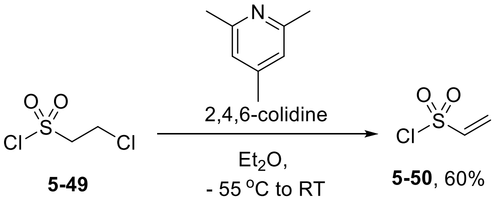


5-12a **5-49** **5-51**

Entry	Conditions	Yield of 5-51 (%)
1	DMAP, Et_3N in DCM, 0 °C to Reflux	0
2	DMAP, Et_3N in DCM, 0 °C to RT	4
3	DMAP, Et_3N in DCM, –60 °C to RT	10
4	DMAP, 2,4,6-collidine in DCM, 0 °C to RT	0
6	NaH, 2,4,6-collidine in THF, 0 °C to RT	0
7	DMAP, Et_3N in DCM, –40 °C to RT	**16**

Table 5.5 Optimization of sulfonylation conditions using **5-49.**

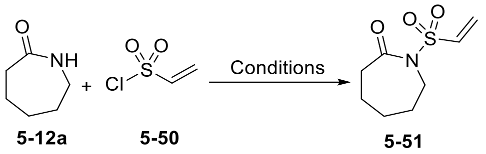
To try to improve this low yield, vinylsulfonyl chloride **5-50** was prepared from the 2-chloroethanesulfonyl chloride **5-49** and isolated. The hope was that using pure **5-50** would lead to an improve sulfonylation reaction. Thus, 2-chloroethanesulfonyl chloride was treated with 2,4,6-colidine in diethyl ether at –55 °C, the target vinylsulfonyl chloride **5-50** could be collected after distillation at 50 – 56 °C at 10 mm Hg.[188] This afforded analytically pure **5-50** in 60% yield.



5-49 **5-50**, 60%

Scheme 5.16 Preparation of the vinylsulfonyl chloride **5-50.**

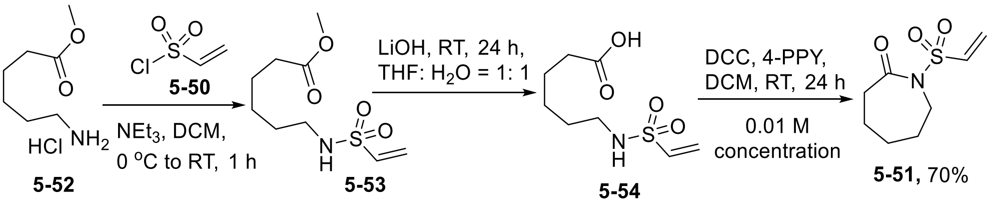
With the vinylsulfonyl chloride **5-50** in hand, the optimisation of the *N*-sulfonylation was started from the DMAP and NEt_3 conditions, but none of the desired product **5-51** was obtained (Table 5.5). Then, different strong bases were tested. Notably, all these strong bases did generate vinylsulfonyl product **5-51**, but all in very low yields (Entry 2 to 5). The best conditions LHMDS in THF at – 78 °C to RT, but only 25% yield of the product was isolated. When the temperature was changed to 0 °C from – 78 °C, none of the target product **5-51** was detected (Entry 6).



Entry	Conditions	Yield of 51 (%)
1	DMAP, Et_3N in DCM, - 40 °C to RT	0
2	NaH in THF, 0 °C to RT	10
3	MeMgBr in THF, 0 °C to RT	9 (11 ^{a})
4	*n*-BuLi in THF, -78 °C to RT	5
5	LHMDS in THF, -78 °C to RT	**25**
6	LHMDS in THF, 0 °C to RT	0

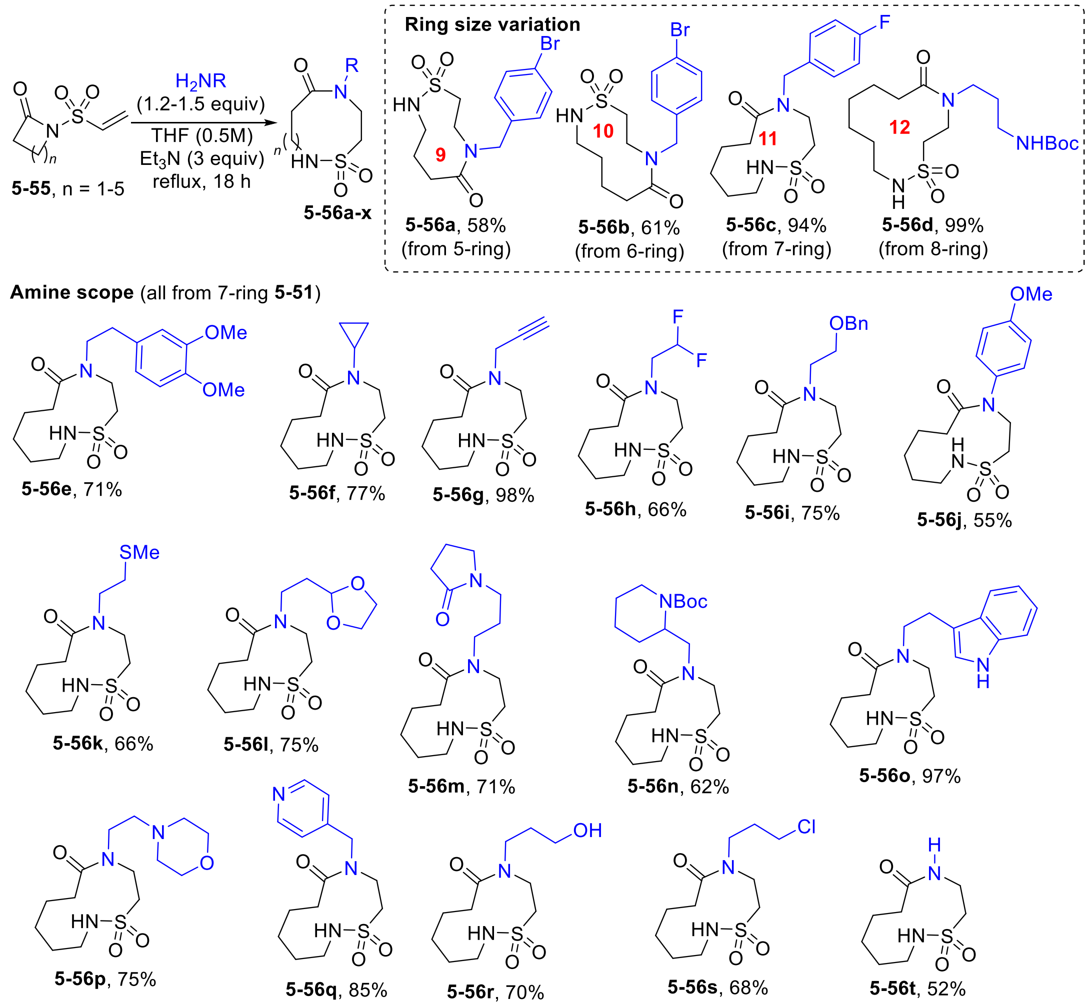
Table 5.6 Optimization of sulfonylation conditions using **5-50**. General conditions: 1.5 eq of bases, 1.5 eq of ethenesulfonyl chloride **5-50**; ^{a} 3.0 eq of ethenesulfonyl chloride **5-50** used.

As the desired vinylsulfonyl product was difficult to produce using the cyclic starting lactams, a ring closing strategy was applied instead. In this way, the vinylsulfonyl product **5-51** was synthesized in a 70% yield from the methyl 6-aminocaproate salt **5-52**, after the sulfonylation, hydrolysis and cyclization sequence summarized in Scheme 5.17.



Scheme 5.17 Ring closing strategy to vinylsulfonyl product **5-51**. Synthesized by Illya Zalessky.

With the desired vinylsulfonyl **5-51** product prepared, in high yield and on large scale, attention turned to the synthesis of medium sized and macrocyclic sulfonamides through the using conjugate addition/ring expansion (CARE) reactions. For these reactions, the vinylsulfonamide starting material was treated with primary amine in THF at reflux in the presence of NEt_3 could generate the ring expansion product in high yield. Pleasingly, different primary amines were tolerated in this CARE reaction and different ring sized systems ring expansion followed the DFT prediction. These scoping results were completed by Illya Zalessky so are not discussed in detail in this thesis. More detail can be found in the published manuscript.[189]



Scheme 5.18 Scope of conjugate addition/ring expansion cascade (CARE) reaction. Synthesized by Illya Zalessky.

5.5 Chapter 5 summary

In summary, we developed two new sulfonamide-forming ring expansion strategies which are protecting group-free methods for the synthesis of medium sized and macrocyclic sulfonamides. The nitro reduction method could access to the benzenesulfonamide medium sized rings and macrocycles from commercially available

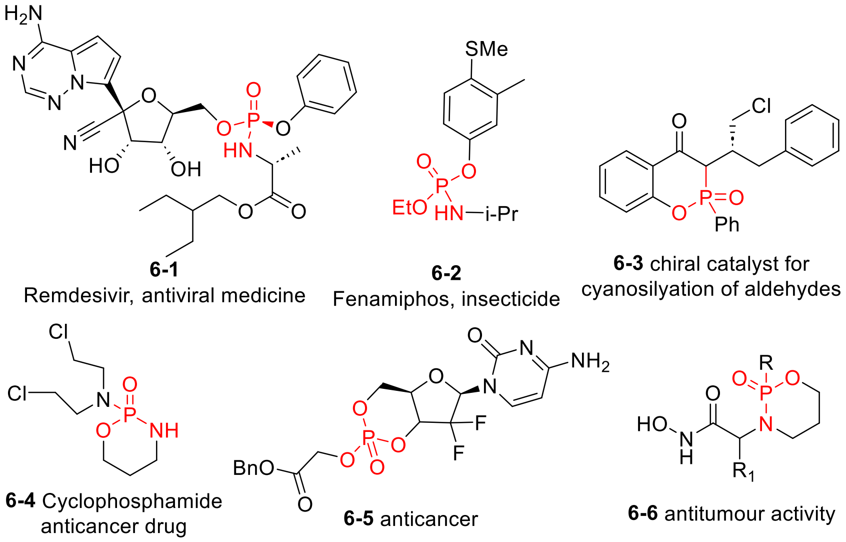
2-nosyl chloride. The conjugate addition method benefited from the diverse range of functionalised primary amines compatible with it. DFT calculation results successfully predicted the viability of the ring expansion reactions of different ring size systems, helping to guide the synthesis of substrates and explain the reaction outcomes. Cyclic sulfonamides are very important medicinal compounds, we hope these medium sized and macrocyclic sulfonamides help expedite the exploration of this compound class in medicinal chemistry.

This work, completed collaboratively with PhD student Illya Zalessky, is included in a published manuscript.[189]

Chapter Six: Ring Expansion reactions of P=O-containing molecules

6.1 P=O-containing molecules

Molecules containing P=O bonds dominate the living world – the genetic materials DNA and RNA, the principal reservoirs of biochemical energy (ATP), and most of the coenzymes are P=O bonds containing molecules.[190] Organophosphorus compounds have many important applications in various research areas, like medicinal chemistry, agrochemistry and asymmetric catalytic reactions (*e.g.* **6-1** to **6-6**, Figure 6.1).[191–197] Cyclic P=O-containing molecules with important medicinal activities have been described, which are recognized for their importance as pro-drugs.[196–199] However, previous research into cyclic P=O compounds has largely focused on 5- or 6-membered ring derivatives, and P=O-containing medium sized rings and macrocycles have rarely been explored.



6-1 Remdesivir, antiviral medicine

6-2 Fenamiphos, insecticide

6-3 chiral catalyst for cyanosilyation of aldehydes

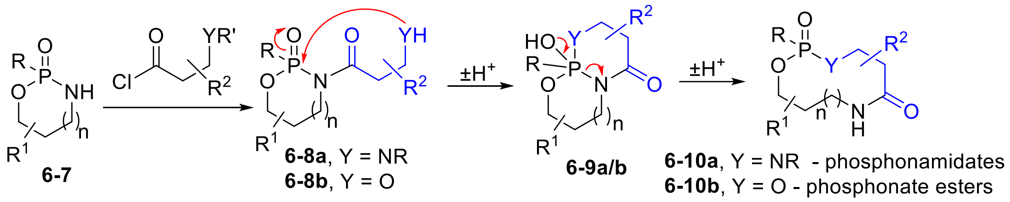
6-4 Cyclophosphamide anticancer drug

6-5 anticancer

6-6 antitumour activity

Figure 6.1 Bioactive or catalytic organophosphorus compounds.

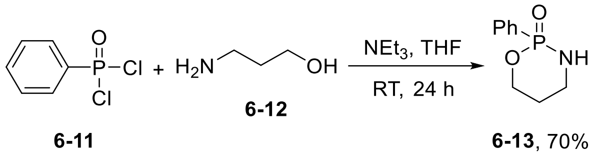
In our previous SuRE research, cyclic β-keto esters and cyclic lactams were used as the cyclic starter units for ring expansion. To extend the method further, we decided to explore ring expansion reaction of the cyclic phosphonamidate derivatives. If established, this ring expansion method would enable a series of medium sized cyclic phosphonamidates and phosphonate esters to be generated; to the best of our knowledge, there are no published examples of the synthesis of either product class using ring expansion.



Scheme 6.1 Ring expansion reactions of cyclic phosphonamidates.

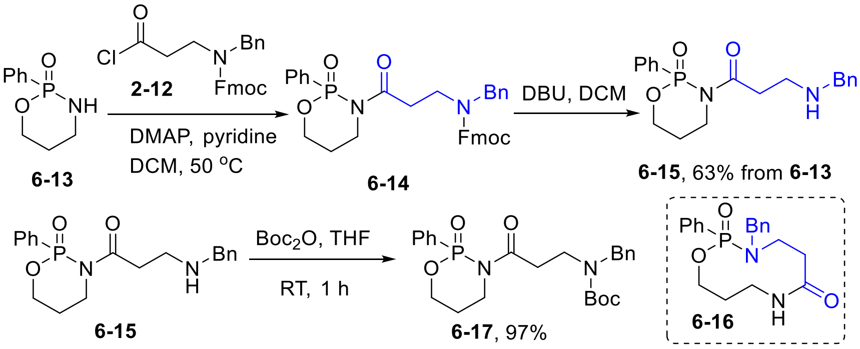
6.2 Nitrogen-nucleophilic ring expansion of cyclic phosphonamidates

The project started from the synthetic of 6-membered phosphonamidate material **6-13**. Phenylphosphinic dichloride was treated with 3-amino-1-propanol in the presence of NEt3, producing the target cyclic product **6-13** in 70% yield.[200] As this material is an analogue of the cyclophosphamide (**6-4**, anticancer drug), which might have similar side effects (including low white blood cell counts, hair loss, vomiting and others) to cyclophosphamide, it was assumed that **6-13** and its derivatives might be toxic, therefore all reactions using this material were performed very carefully.



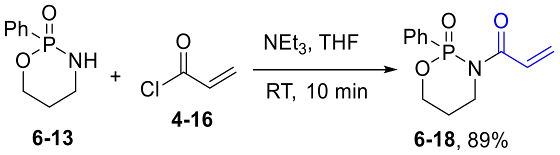
Scheme 6.2 Preparation of the 6-membered phosphonamidate **6-13**.

Cyclic phosphonamidate **6-13** was then reacted with acyl chloride **2-12**, which is an acyl chloride that has been used in earlier lactam SuRE reactions. The *N*-acylation step went well, with the target imide **6-14** generated smoothly and all of the starting material **6-13** was consumed, based on analysis by TLC. However, the ring expansion didn't proceed after the deprotection of Fmoc group using DBU; the Fmoc was cleaved, but the free amine *N*-acyl phosphonamidate product **6-15** did not rearrange and was isolated in 63% yield (Scheme 6.3). Differentiating between **6-15** and the desired ring expansion product **6-16** was challenging, given that they are isomers and would be expected to have similar NMR data. However, after carefully checking the NMR data (especially ^{1}H and HMBC), we realized that it was more likely to be the imide product **6-15** because no lactam NH was detected in the NMRs (which usually seen as a broad singlet around 5 ppm). To confirm this, the product was treated with Boc$_2$O at RT for 1 h, and the isolation of Boc-protected product **6-17** further proved the material is the *N*-acyl phosphonamidate **6-15**.



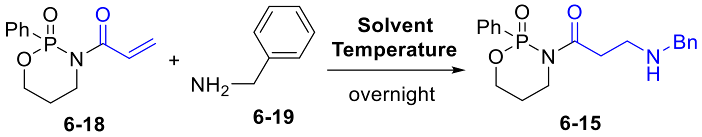
Scheme 6.3 Attempted SuRE method to make medium sized phosphonamidate.

As the SuRE method failed to access the ring-expanded phosphonamidates, attention turned to using the CARE method to prepare the *N*-acyl phosphonamidates, because the CARE method is operationally simple, and the Michael accepter material can be prepared on large scale. The cyclic phosphonamidate **6-13** was acylated with acryloyl chloride **4-16** under the basic conditions, producing the imide **6-18** in 89% yield.



Scheme 6.4 Preparation of the Michael accepter **6-18**.

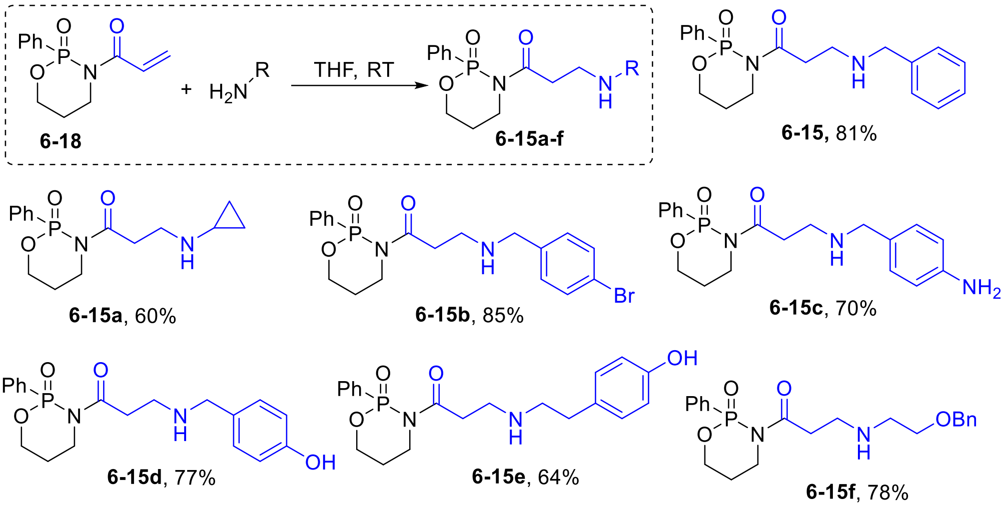
The conjugate addition of the imide **6-18** and primary amine **6-19** could take place in various conditions and the amine product **6-15** could be generated in medium to good yields (Table 6.1). However, no evidence of rearrangement or ring-expanded products was detected under these basic reaction conditions screened. Notably, protic solvent (MeOH) was not favoured for this conjugate addition reaction, which contrasts to our previous CARE method that using MeOH as solvent (Chapter 4).



Entry	Conditions	Yield of 6-15 (%)
1	MeOH, RT	50
2	THF, RT	**81**
3	THF, NEt_3, RT	61
4	DCM, DBU, RT	72
5	MeOH, DBU, RT	40
6	EtOAc, DBU, RT	70
7	THF, DBU, RT	70
8	THF, NEt_3, reflux	61
9	$CHCl_3$, NEt_3, reflux	70

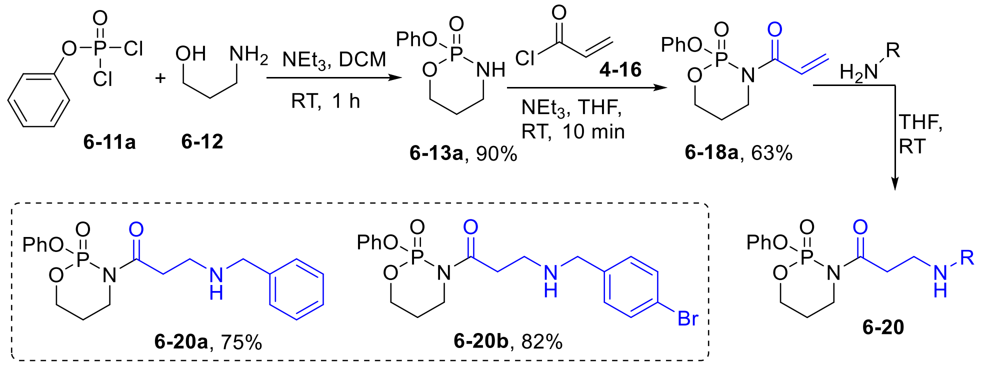
Table 6.1 Optimization of amine conjugate addition conditions of **6-18**. Isolated yields.

At this stage, we realized that this P=O containing ring expansion must be difficult to achieve. We also tested various other primary amines with different functional groups to see if they gave different outcomes, but all went on to produce simple conjugate addition products. For example, cyclopropylamine reacted with the imide **6-18** to generate the product **6-15a** in 60% yield (Scheme 6.5). Halogen-, aniline- and hydroxyl-substituted benzyl amines were all tolerated in this conjugate addition, but none went on to undergo ring expansion. Using tyramine as the nucleophile, product **6-15e** was generated in a yield of 64%, which is lower than the product **6-15d** from 4-hydroxybenzylamine (77% yield). Also, *O*-benzylethanolamine underwent conjugate addition with imide **6-18**, producing the product **6-15f** in 78% yield.



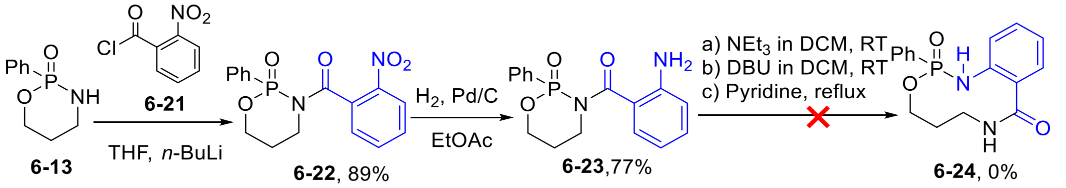
Scheme 6.5 Scope of conjugate addition products from **6-18**.

Then, the cyclic phosphonamidate **6-13a** with a phenoxy group on the P center was tested in these conjugate addition and ring expansion reactions. The cyclization of phosphoric acid phenyl ester dichloride **6-11a** and 3-amino-1-propanol **6-12** gave the cyclic phosphonamidate **6-13a** in 90% yield, which could be converted into imide **6-18a** easily with acryloyl chloride **4-16**. Not unexpectedly, the imide **6-18a** could generate the conjugate addition products in good yields (**6-20a** and **6-20b**, Scheme 6.6) but couldn't initiate ring expansion under various basic conditions (see Table 6.1).



Scheme 6.6 Cyclic phosphonamidate **6-13a** in the conjugate addition reaction.

After the SuRE and CARE methods based on aliphatic amine ring expansion failed to form any ring expansion products, the focus turned to test an aniline system. The nitrobenzene product **6-22** was synthesized from *N*-acylation of cyclic material **6-13** and 2-nitrobenzoyl chloride **6-21**. Aniline derivative **6-23** was prepared *via* reduction of nitrobenzene **6-22** but this substrate could not be converted into ring expansion product **6-24**, despite various basic conditions being tested. NEt_3 and DBU based conditions used in our previous ring expansion reactions didn't work here, and using pyridine as solvent couldn't help this ring expansion either.



Scheme 6.7 Aniline based ring expansion of cyclic phosphonamidate **6-13**.

As all attempts to the ring expansion of cyclic phosphoamidates failed, Density Functional Theory (DFT) calculations were conducted to assess the viability of this ring expansion, using the methodology that was established for lactam ring expansion reactions in our previous work, and introduced in Chapter 5. Both aliphatic amine (analogous to compound **6-15**, labelled with '**a**' and highlighted in red) and aniline (compound **6-23**, labelled with '**b**' and highlighted in pink) systems were assessed (Figure 6.2). The ground state energy of the free amine isomer (**A**), ring-closed (**B**) and ring-expanded isomer (**C**) of different systems were calculated. For the aliphatic amine system, ring expanded isomer (**Ca**) was calculated to be the lowest energy and the ring-closed isomer (**Ba**) had the highest energy. According to the experience from previous DFT calculations of ring expansion reactions, the aliphatic amine system should be possible to achieve because the ring expanded isomer (**Ca**) has the lowest energy. The very high calculated energy (+ 39.4) of ring-closed isomer (**Bb**) was considered to be a problem however, as this may be indicative of a high kinetic barrier to the formation of the ring-closed isomer; this was therefore considered to be the most likely reason for the failure of aliphatic amine system to undergo ring expansion. Similarly, that the ring-closed isomer (**Bb**) had the highest energy in the aniline series, which had a relative energy of + 22.5. However, the ring expanded isomer (**Cb**) had a very similar (slightly higher) energy compared to the free amine isomer (**Ab**), which indicated that the aniline system is at the borderline of being a thermodynamically feasible ring expansion, but could work if the kinetic barrier could be overcome. These calculations were performed by Unsworth group members Jerry Tam and Jack Wootton.

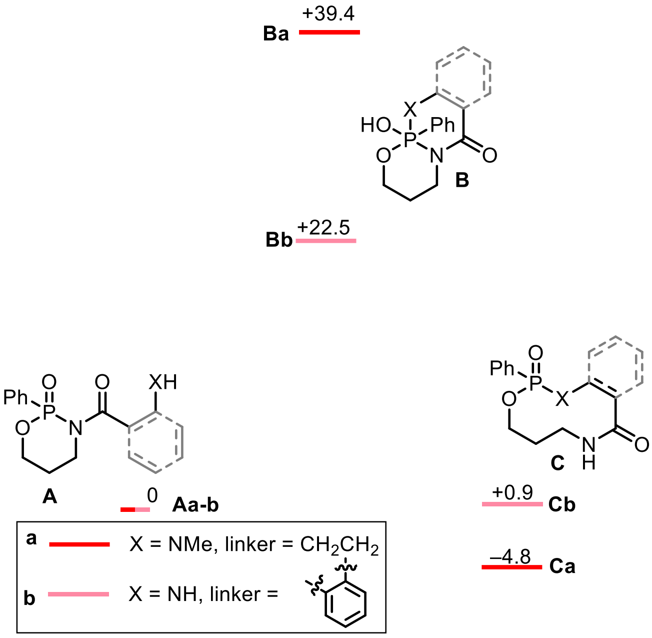
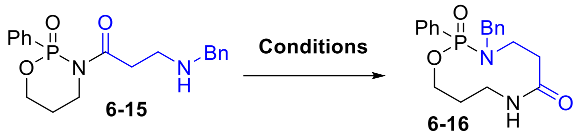


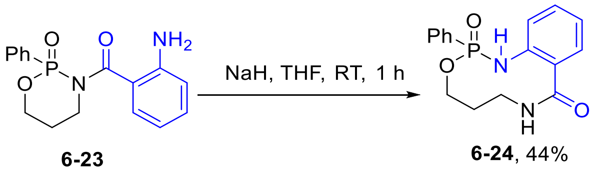
Figure 6.2 Relative energies of isomeric species in nitrogen-based ring expansion using a DFT/B3LYP/6-31G* approach. ΔG°rel values at 298 K are given in kcal mol^{-1}. These calculations were performed by Unsworth group members Jerry Tam and Jack Wootton.

To test the idea that the reactions were being stalled by a high kinetic barrier, we revisited the ring expansion step of imide **6-15** to the ring expansion product **6-16** using much stronger bases. NaH and *n*-BuLi were tested, in the hope that they would allow an anionic reaction system to be accessed to overcome the kinetic barrier. But unfortunately, none of the conditions tested promoted the ring expansion (Table 6.2). However, pleasingly, when the aniline product **6-23** was treated with NaH at RT, and the ring expanded product **6-24** generated in a yield of 44% (Scheme 6.8). Notably this reaction indicated that the kinetic barrier can be overcome using stronger base.



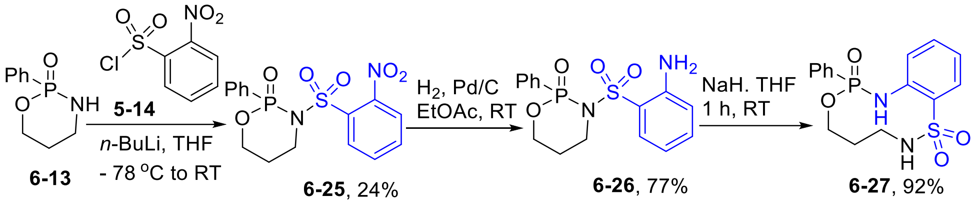
Entry	Conditions	Yield of 6-16
1	NaH, THF, –78 °C to RT, overnight	0%
2	NaH, THF, 0 °C to RT, overnight	0%
3	*n*-BuLi, THF, –78 °C to RT, overnight	0%
4	*n*-BuLi, THF, 0 °C to RT, overnight	0%
5	NaH, THF, RT, 3 h	0%

Table 6.2 Unsuccessful optimization of aliphatic amine ring expansion.



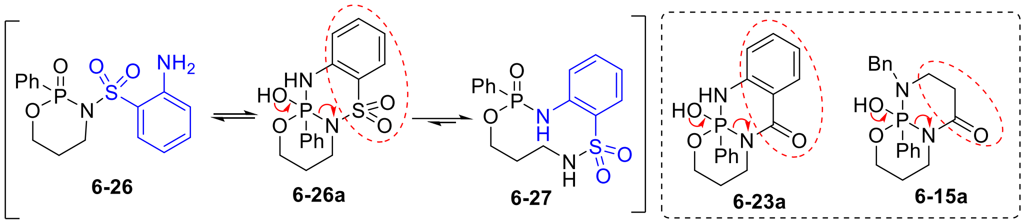
Scheme 6.8 Aniline based ring expansion to the product **6-24**.

Finally, an alternative sulfonyl aniline-based ring expansion was achieved successfully. 2-Nitrobenzenesulfonyl chloride **5-14** was reacted with cyclic phosphonamidate **6-13**, producing the nitrobenzene product **6-25** in a yield of 24%. The aniline precursor **6-26** was reduced from **6-25** in 77% yield, and it could be converted into 10-memebered phosphonamidate **6-27** in the presence of NaH.



Scheme 6.9 Ring expansion of the P=O containing product **6-27** with sulfonamide structure.

The high yield (92%) in the ring expansion of the sulfonyl aniline **6-26** to the product **6-27** is noteworthy, compared to the 44% yield from **6-23** to **6-24** in the aniline system. This difference could be explained by Mulliez and coworkers' research on the aminolysis of phosphorus heterocycles, in which a good leaving group (like sulfonamide) could help to cleavage of the P–N bonds.[201] (Scheme 6.10).



Scheme 6.10 Proposed mechanism of the leaving group affection to the ring expansion.

6.3 Oxygen-nucleophilic ring expansion of cyclic phosphonamidates

Next attention turned to exploring similar reactivity using oxygen-based nucleophiles instead of nitrogen. Before starting the synthesis study, DFT calculations were again conducted to assess the viability of this ring expansion, as we did in the nitrogen-nucleophilic ring expansion, and the results were illuminating. As before, the ground state energy was calculated for the free alcohol isomer (**A**), ring-closed (**B**) and ring-expanded isomer (**C**), in addition to another rearrangement isomer (**D**, which was later isolated in a synthetic reaction). Representative aliphatic alcohol (labelled with '**c**' and highlighted in blue) and phenol systems (labelled with '**d**' and highlighted in pale blue) were both calculated. The isomer with the highest calculated energy in both systems was ring-closed isomer **B** while the lowest energy was the desired ring expanded isomer **C** by a significant margin**.** Notably, the calculated energy of the ring-closed isomer **Bc** and **Bd** were much lower than these in the nitrogen-based ring expansion, which indicated that this series of ring expansion might be easy to achieve because the kinetic barrier might be much lower. Another observation from the calculations is the rearrangement isomer **D** had lower energy than free alcohol isomer (**A**) and ring-closed isomer (**B**) in both ring expansion systems, this means that these rearrangement isomers might be competitive with the ring expansion products. Taken together, the calculations provided encouragement that the alcohol-based substrates should work better than the amine systems in ring expansion, based on their calculated thermodynamic profiles. These calculations were performed by Unsworth group members Jerry Tam and Jack Wootton.

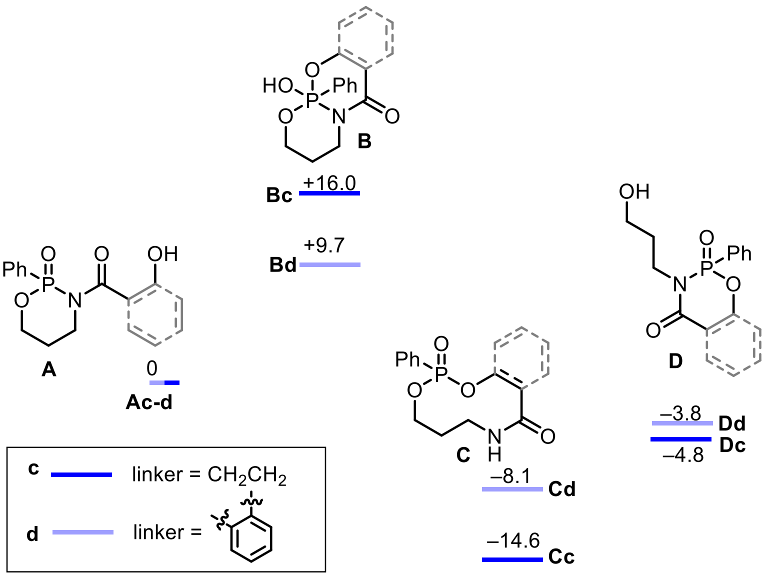
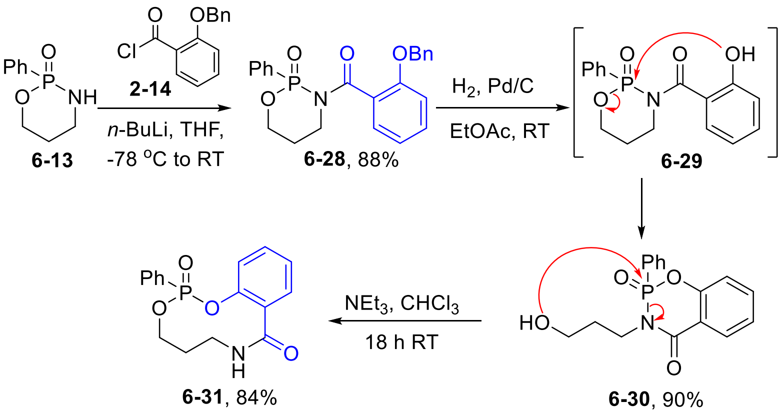


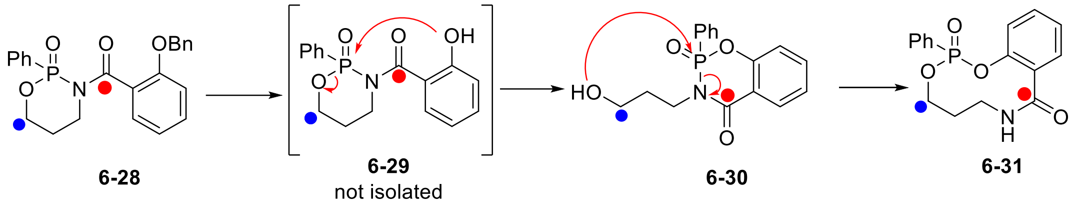
Figure 6.3 Relative energies of isomeric species in oxygen-based ring expansion using a DFT/B3LYP/6-31G* approach. ΔG°rel values at 298 K are given in kcal mol^{-1}.These calculations were performed by Unsworth group members Jerry Tam and Jack Wootton.

The synthesis study started from the *N*-acylation of **6-13** with the acyl chloride **2-14** to generate the imide **6-28** in a yield of 88%. After the hydrogenation step, the expected product was the phenol **6-29**. However, phenol **6-29** rearranged spontaneously *in situ*, but not *via* ring expansion, rather *via* fragmentation of the endocyclic P–O bond to generate the product **6-30** in high yield. However, pleasingly, product **6-30** could be promoted to undergo a further rearrangement to the desired 10-membered ring expansion product by stirring with triethylamine in chloroform at RT, allowing isolation of **6-31** with a yield of 84%. These results are in line with the suggestion that from the DFT calculations, that **6-31** is the thermodynamic product.



Scheme 6.11 Oxygen-nucleophilic ring expansion of the cyclic phosphonamidate **6-13**.

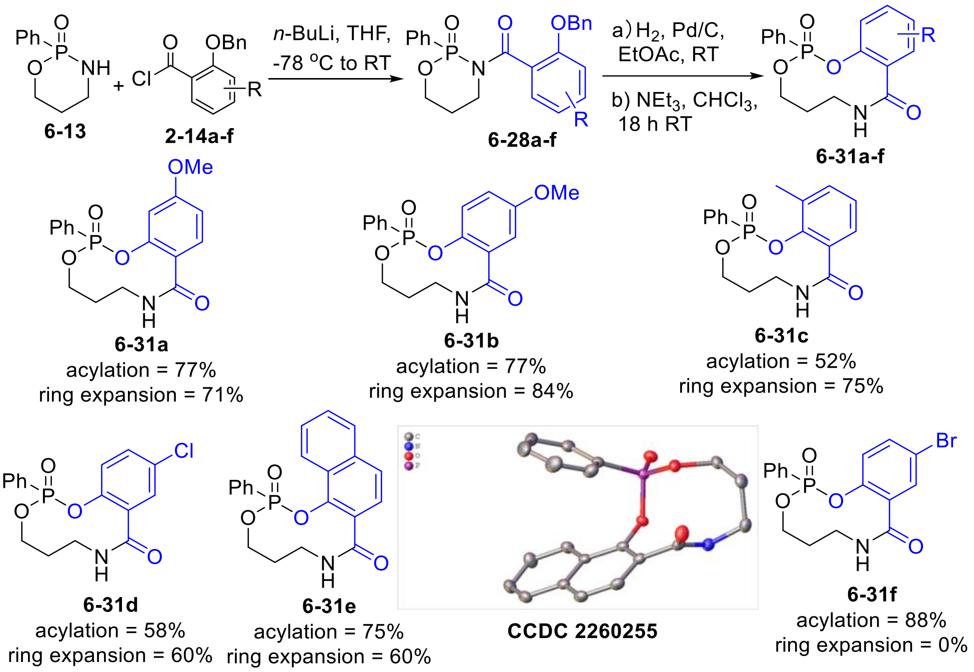
Here, it is useful to note how the different isomers were distinguished spectroscopically. We found that observing which ^{13}C nuclei couple to ^{31}P in the ^{13}C NMR spectra provided a convenient way to distinguish isomer species (**6-28** to **6-31**) in this study, by enabling the proximity of different C-atoms to P to be mapped as the rearrangement progresses. This method is summarized in the Table 6.3 below. The carbonyl peaks (marked with red) in product **6-28** and product **6-30** show coupling to ^{31}P in the ^{13}C NMR spectra, with both of them observed as doublet peaks. In contrast, the carbonyl peak in product **6-31** is a singlet peak in ^{13}C NMR, consistent with the amide being farther away from the P=O center in this structure. Similarly, the **C**H_2OH peak (marked with blue) of product **6-30** is a singlet peak in ^{13}C NMR spectra because it's far away from the P=O center after rearrangement compared to the two endocyclic O**C**H_2 in products **6-28** and **6-31** respectively. For ^{31}P NMRs, the chemical shift of P=O changed from 14.8 (imide **6-28**) to 17.1 ppm (ring expansion product **6-31**). Though the OH and NH protons crowed with other proton peaks, the different chemical shifts were detected. All these data are also indicated in the individual data write ups in experimental section.



	6-28 (50 °C)	**6-30**	**6-31**
^{13}**C** (ppm) **CO**	170.7 d, *J* = 5.8 Hz	162.9 d, *J* = 4.8 Hz	167.0
^{13}**C** (ppm) O**C**H$_2$ or **C**H$_2$OH	65.7 d, *J* = 5.7 Hz, OCH$_2$	58.3 (**C**H$_2$OH)	67.9 d, *J* = 7.8 Hz, OCH$_2$
^{31}**P** (ppm)	14.8	17.7	17.1
^{1}**H** (ppm) OH or NH		3.58 – 3.36 (m, 3H, N**CH$_2$** + **CH$_2$**OH + CH$_2$**OH**)	7.24 – 7.08 (m, 3H, Ar-C**H** + N**H**CO)

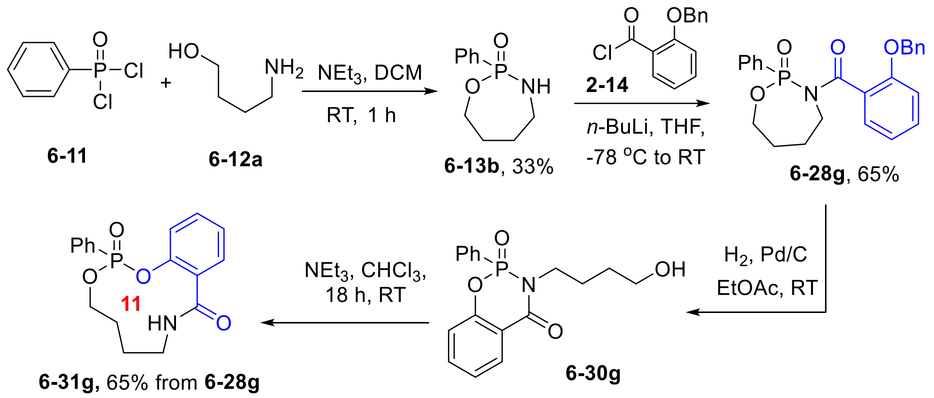
Table 6.3 NMR comparison of different isomers in the phenol ring expansion reaction.

After convincing evidence was obtained that the ring expansion of cyclic phosphonamidate had been achieved, the same sequence (*N*-acylation, hydrogenation, and ring expansion under basic conditions) was used for the substrate scope studies. Different substituted benzyl-salicylate acid chlorides were synthesized from the respective salicylate acids after OBn protection and treated with oxalyl chloride. Most benzyl-salicylate acid chlorides with different position substituted (4- or 5-methoxy) and different functional groups (methyl-, chloro-, and even naphthoic derived) substituted were tolerated in this ring expansion sequence. However, while the 4-bromosalicylate acid chloride acylated cyclic phosphonamidate **6-13** smoothly, producing a high yield of imide **6-28f**, its bromo group was cleaved during in the hydrogenation step, resulting in the 10-membred product **6-31** rather than the target product **6-31f**. Notably, the structure of compound **6-31e** was confirmed by X-ray crystallography (CCDC 2260255), which gave an further evidence that this P=O containing ring expansion had worked as planned.



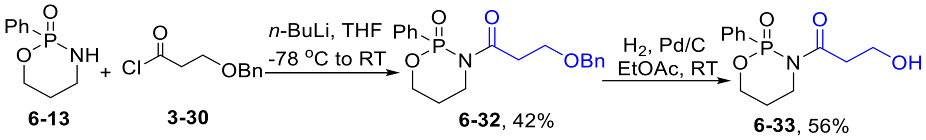
Scheme 6.12 Substituted benzyl-salicylate acid chlorides in the phenol ring expansion reaction.

After the study of the substrate tolerance of 6-membered cyclic phosphonamidate **6-13** was completed, we then tested 7-membered cyclic phosphonamidate **6-13b**. The 7-membered cyclic phosphonamidate **6-13b** was synthesized using similar conditions with the 6-membered one from the phenylphosphinic dichloride **6-11** and 4-aminobutanol **6-12a**. However, the yield of **6-13b** (33%) was much lower than the product **6-13** (70%). *N*-acylation with **6-14** went smmothly, although the larger ring size of starting phosphonamidate affected the yield in the *N*-acylation step, with 7-membered imide **6-28g** isolated in 65% yield compared to the 88% yield of 6-membered imide. Following hydrogenation and basic treatment with NEt_3, ring expansion took place as expected, to form 11-membered ring product **6-31g** in 65% yield.



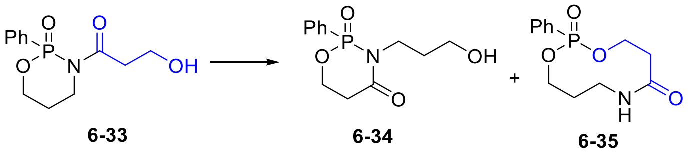
Scheme 6.13 7-membered cyclic phosphonamidate **6-13b** in the phenol ring expansion.

Attention then turned to aliphatic alcohol ring expansion reactions. The imide **6-32** was generated in 42% yield after the *N*-acylation of cyclic phosphonamidate **6-13** and acyl chloride **3-30**. Hydrolysis of the imide **6-32** was performed as before, but the alcohol product **6-33** was isolated which proved that there is no spontaneous rearrangement in the hydrogenation step.



Scheme 6.14 *N*-acylation and hydrogenation steps of the aliphatic alcohol ring expansion.

Alcohol **6-33** was therefore reacted with NEt_3 in chloroform, but this did not result in formation of the ring expansion product **6-35**; instead, the rearranged isomer **6-34** was formed in high yield. Some different bases were then screened to promote the ring expansion (Table 6.4). NMM gave the same result as NEt_3, while DIPEA generated the target ring expansion product **6-35** in low yield but still couldn't avoid the isomer **6-34** as the major product. Sodium hydride was therefore tested, and pleasingly it enabled the conversion of **6-33** into product **6-35** in 68% yield with no unwanted product **6-34** detected. It's supposed that the NaH enables the ring expansion by reacting in an anionic reaction pathway, which is proposed to allow the kinetic barrier to ring expansion to be overcome.



Entry	Conditions	Yield of 6-34 (%)	Yield of 6-35 (%)
1	NEt$_3$, CHCl$_3$, RT, 16 h	90	0
2	NMM, THF, RT, 16 h	80	0
3	DBU, CHCl$_3$, RT, 16 h	0	0
4	DIPEA, THF, RT, 48 h	60	32
5	DIPEA, THF, reflux, 16 h	11	22
6	DIPEA, CHCl$_3$, RT, 16 h	70	20
7	TBAF, THF, RT, 16 h	0	0
8	NaH, THF, RT, 3 h	0	**68**

Table 6.4 Optimization of the ring expansion conditions from **6-33** to **6-35**. Isolated yields.

To explore the NaH effect, DFT calculations of anionic ring expansion intermediates was conducted (Figure 6.4). In this new series of calculations, the five-coordinate phosphorus intermediate **F** was calculated to be lower in energy (–8.8) than its corresponding imide precursor **E** (0.0) and rearrangement isomer **H** (+ 2.6). Notably, the relative energy of rearrangement isomer **H** was higher than the one in the neutral pathway (– 4.8), which could account for the absence of the rearrangement product in the NaH conditions. The transition states for the conversion of **E** into **F** (TS$_{\mathrm{EF}}$) and the conversion of **F** into **H** (TS$_{\mathrm{FH}}$) were found at low energy, 3.3 and 6.7 kcal/mol respectively. These low energy transition states indicated that the reaction could be achieve at RT and that the isomer **H** could be converted back to into **F**. The transition state linking **F** to the ring expanded isomer **G** was not found, but **G** was the lowest energy isomer on the potential energy surface, consistent with the formation of **6-35** as the major product under NaH conditions.

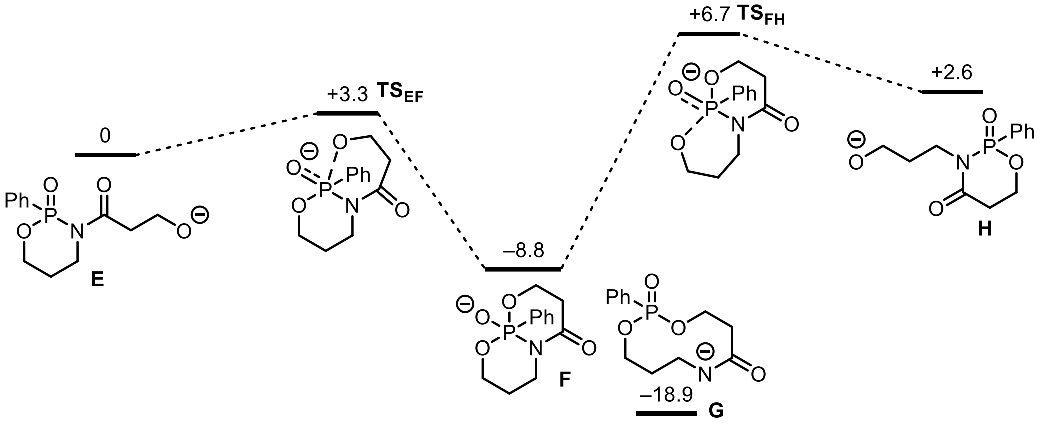
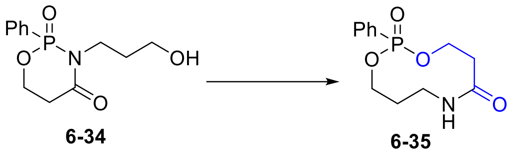


Figure 6.4 Relative energies of isomeric species in an anionic ring expansion manifold, using a DFT/B3LYP/6-31+G* approach. ΔG°rel values at 298 K are given in kcal mol^{-1}. These calculations were performed by Unsworth group members Jerry Tam and Jack Wootton.

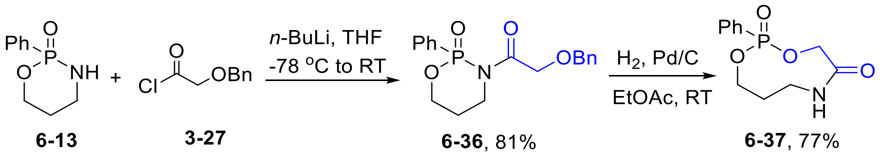
Basic conditions to promote the ring expansion from isomer **6-34** into the product **6-35** were also tested, given that the DFT calculation indicating that the conversion of **H** back into **F** is viable if any **H** forms (Figure 6.4). NEt_3 was tested first and no product **6-35** generated, and DBU didn't work in this reaction either. DIPEA could help to produce the ring expansion product from **6-33** but failed to promote the isomer **6-34** to **6-35** (Entry 3, Table 6.5). NaH was therefore tested as base, which worked well in previous ring expansion failed to achieve the ring-expanded product **6-35**. Thus, it seems that **6-34** is not formed reversibly during the previously discussed ring expansion of **6-33**.



Entry	Conditions	Yield of 6-35 (%)
1	NEt_3, $CHCl_3$, RT, 16 h	0
2	DBU, $CHCl_3$, RT, 16 h	0
3	DIPEA, THF, RT, 16 h	0
4	NaH, THF, RT, 3 h	0

Table 6.5 Optimization of the ring expansion conditions from **6-34** to **6-35**. Isolated yields.

Lastly, α-hydroxy acid chloride **3-27** was used to generate a 9-membered ring phosphonate ester **6-37**. The *N*-acylation of **6-13** with **3-27** gave a high yield of the imide **6-36**, which underwent hydrogenolysis enabling the direct conversion of the ting expansion product **6-37** without further treatment in 77% yield. In this 3-atom ring expansion, the fact that it proceeds *via* 5-membered ring cyclisation as opposed to 6-, likely leads to a lower kinetic barrier and hence precludes the need to add base to promote ring expansion.



Scheme 6.15 Ring expansion to the 9-membered product **6-30**.

6.4 Chapter 6 summary

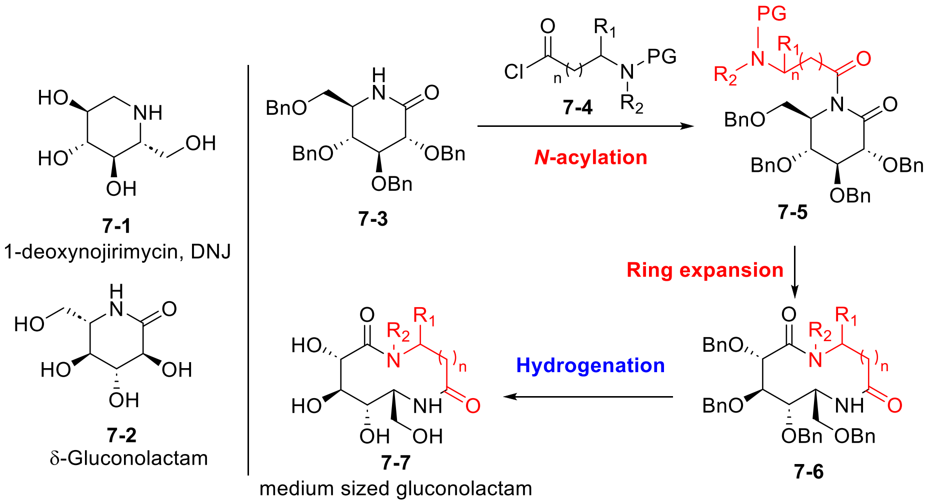
In summary, ring expansion reactions of cyclic phosphonamidates have been developed for the first time, allowing access to medium sized ring cyclic phosphonate esters and phosphonamidates. Compared to our previous ring expansion reactions at C=O bonds, two key differences were concluded that could guide for our further studies of new ring expansions. First, is the greater reactivity of alcohol-tethered systems than the analogous amines. In our previous ring expansions at C=O, amines generally react faster and in higher yields than alcohol systems. This difference is likely due to the change in relative bond strengths on switching from C=O to P=O, in particular the high P–O bond strength. The second key difference is the higher kinetic barriers, which was never a problem in previous ring expansions but needed to be overcome by more basic conditions (NaH) or a more acidic substrate (*e.g.* phenol **6-29**) in this case. An advantage to the higher kinetic barriers is the ability to isolate isomeric species (including rearrangement isomer) to help understanding the whole reaction profile. After this ring expansion was achieved, we have more experience and confidence to explore other types of ring expansion reactions.

The work described in this chapter is the subject of one publication.[202]

Chapter Seven: Ring Expansion in the synthesis of medium sized and macrocycle aza sugars

7.1 Iminosugars (aza sugars)

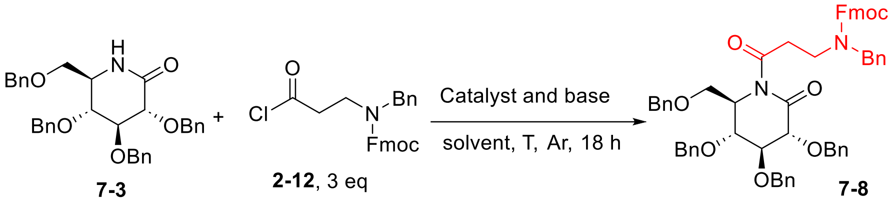
Iminosugars are sugar-like compounds in which the ring oxygen has been replaced with nitrogen and are common components of plants, for example, Mulberry.[203] Iminosugars attracted great deal of attention from chemists and pharmacists because of their powerful inhibition towards carbohydrate processing enzymes glycosidases and glycosyltransferases (GTs).[204–207] For example, DNJ is an alpha-glucosidase inhibitor and was shown to have anti-diabetic and anti-viral activity. Many synthetic analogues like modifications of the hydroxyl groups, branched derivatives, modified five-membered rings or bicyclic rings have been designed to improve the pharmacological properties and selectivity of the parent molecule.[208–211] Gluconolactams are analogues of iminosugars, which might have similar activities as well. It is proposed that by using our SuRE methodology, a series of medium sized and macrocyclic gluconolactams could be produced after an additional hydrogenation step. These larger ring sized gluconolactams might be potent inhibitors of glycosidases.



Scheme 7.1 SuRE strategy in the synthesis of medium sized gluconolactams.

7.2 SuRE in the synthesis of medium sized and macrocycle aza sugars

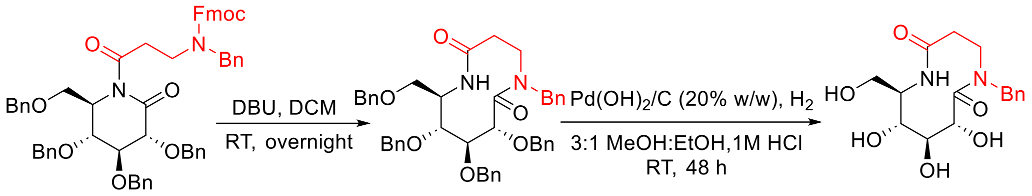
The gluconolactam **7-3** was provided by our collaborating laboratory in France (Prof Philippe Compain, LIMA, ECPM, Université de Strasbourg).[212] The initial optimization of the *N*-acylation conditions was conducted at small scale (0.2 mmol) because the limited amount of material **7-3** was available at the time. Comparing the CuO and NMM conditions, the DMAP and pyridine conditions gave a higher yield (72%) of the imide product **7-8**.



Entry	**Catalyst and base**	**Solvent**	**Temperature (°C)**	**Yield of 7-8 (%)**
1	CuO (0.2 eq), NMM (6 eq)	benzene	RT	trace
2	CuO (0.2 eq), NMM (6 eq)	benzene	80	25
3	DMAP (0.1 eq), pyridine (6 eq)	DCM	50	**72**

Table 7.1 Optimization of *N*-acylation conditions of gluconolactam **7-3** and acyl chloride **2-12**.

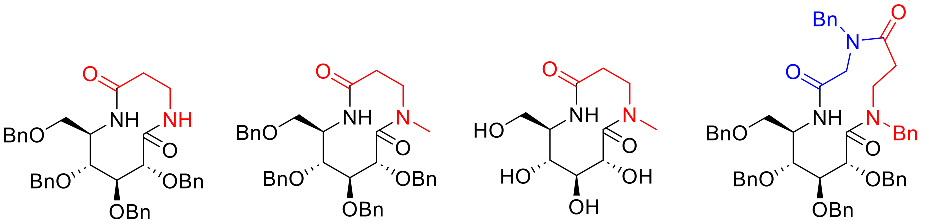
As the acylated product **7-8** obtained, the deprotection/ring expansion process was conducted using DBU in DCM at RT, providing the ring expansion product **7-9** in a yield of 67%. Then, the 10-membered precursor **7-9** was converted into the 10-membered iminosuagr analogue **7-10**, a medium sized ring containing both an amino acid fragment and a sugar fragment, after the hydrogenolysis step. Here, the general hydrogenation conditions using Pd/C didn't work at all, and $Pd(OH)_2/C$ was used instead. The success of this synthetic procedure proved that our SuRE strategy could be used in the synthesis of a series of medium sized gluconolactams.



7-8 **7-9**, 67% **7-10**, 62%

Scheme 7.2 The ring expansion of **7-8** and hydrogenolysis of **7-9**.

The substrate scope study started by testing the viability of the *N*-Fmoc-β-alanine chloride in this ring expansion reaction, in which the 10-membered ring expansion product **7-11** generated in 30% yield from the starting gluconolactam **7-3**. Similarly, the ring expansion product **7-12** with N-Me group was produced in a yield of 53% over 2 steps. And the hydrogenolysis of **7-12** into **7-13** had been performed successfully using $Pd(OH)_2/C$ conditions. Furthermore, a consecutive ring expansion was conducted on the 10-membered lactam **7-10** with the α-amino acid chloride **3-13**, and 18% yield of 13-membered macrolactam **7-14** was generated from the lactam **7-10.**

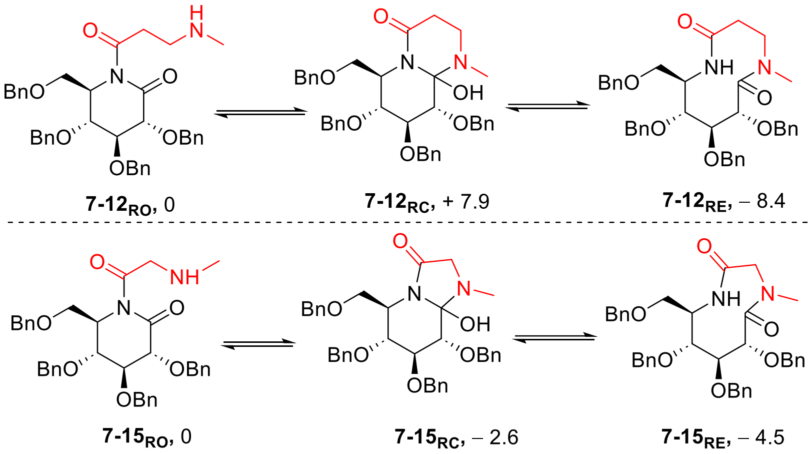


7-11, 30% over 2 steps **7-12**, 53% over 2 steps **7-13**, 72% from **7-12** **7-14**, 18% from **7-10**

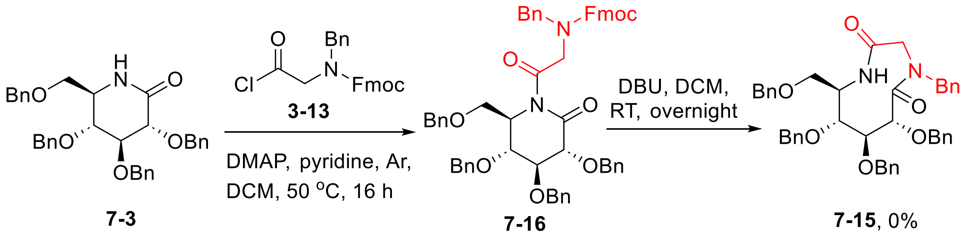
Figure 7.1 Substrates synthesized using ring expansion strategy from **7-3**.

Here, the viability of ring expansion reactions for different side chains (β- or α-amino acid chains) was estimated by DFT calculations that established in our previous research (Scheme 7.3). In the β-amino acid tethered system (4-atom ring expansion), the calculated relative Gibbs free energy of the ring-closed isomer (**7-12RC**) was the highest and the ring-expanded one (**7-12RE**) was the lowest. This indicated that this ring expansion is favorable, and consistent with the synthetic results. For the α-amino acid tethered system (3-atom ring expansion), both the ring-closed (**7-15RC**) and ring-expanded isomer (**7-15RE**) were lower energy than the ring-opened one (**7-15RO**), suggesting this ring expansion should be easy to achieve. However, the synthesis of the

9-membered aza sugar **7-15** failed (see Scheme 7.4). In the *N*-acylation of gluconolactam **7-3** with the acid chloride **3-13**, the target imide **7-16** was generated in good yield as all **7-3** was consumed in the TLC. This imide **7-16** was deprotected by DBU to initiate the ring expansion but no 9-membered product **7-15** was isolated. In this reaction, most starting gluconolactam **7-3** was recycled, which suggested that the exocyclic amide bond was cleaved. These calculations were performed by Unsworth group member Dr Ryan Epton.



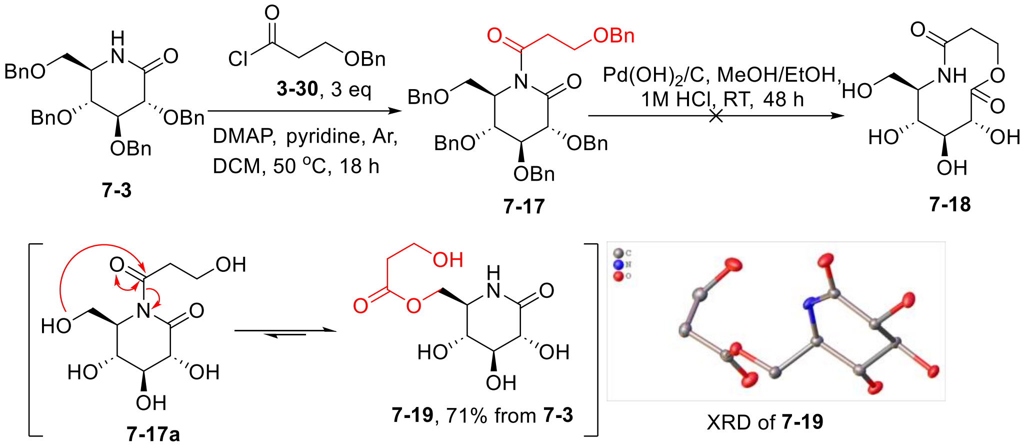
Scheme 7.3 DFT calculations to predict the influence of ring size on reaction viability. ΔG_{rel} in kcal/mol; relative energies are Gibbs energies at the B3LYP/6-31G* level of theory in the gas phase, at 298.15 K. These calculations were performed by Unsworth group member Dr Ryan Epton.



Scheme 7.4 The failed synthesis of 9-membered product **7-15**.

Then the focus turned to studying the ring expansion reactions using hydroxy acid chloride **3-30**, in which we had hoped to synthesize the 10-membered aza sugar **7-18** with both lactam and lactone fragments. However, while the *N*-acylation step worked as expected to form the imide **7-17**, the rearranged product **7-19** was formed, instead of the target 10-membered product **7-18**, after the hydrogenolysis of all of the OBn groups.

This is presumably because of a side chain acyl transfer process, in which the acyl group migrates onto the revealed primary alcohol (**7-17a** → **7-19**) before ring expansion could take place. The structure of **7-19** was confirmed by X-ray crystallography.

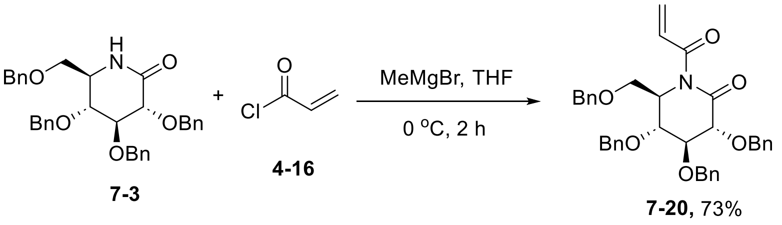


Scheme 7.5 Ring expansion of sugar lactam **7-3** with acid chloride **3-30**.

7.3 CARE in the synthesis of medium sized and macrocycle aza sugars

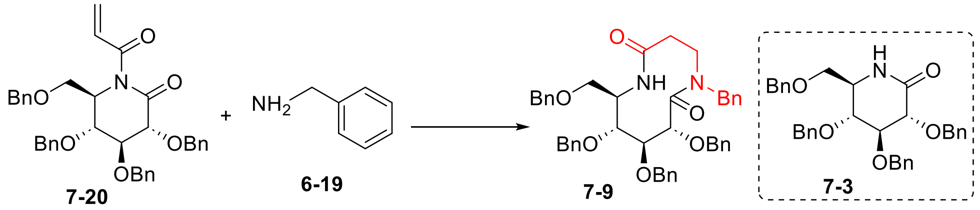
Conjugate addition/ring expansion cascade (CARE) reaction was applied in the synthesis of medium sized aza sugars but worked not very well.

The imide **7-20** was prepared *via* the *N*-acylation of gluconolactam **7-3** with acryloyl chloride **4-16** in a good yield.



Scheme 7.6 Synthesis of the Michael acceptor **7-20** for CARE reaction.

After the Michael acceptor **7-20** was synthesized and the benzylamine **6-19** was chosen as the primary amine, the conditions optimization of this CARE reaction was started from testing MeOH as solvent. However, only 10% yield of product **7-9** was isolated with the majority of 6-membered gluconolactam **7-3** recovered. Other screened conditions couldn’t increase the yield of product **7-9** but recovered the gluconolactam **7-3** in all conditions. This competitive relationship between product **7-9** and the starting material **7-3** indicated that the nucleophilic amine **6-19** might be able to cleave the side amide chain rather than conjugate addition with the terminal olefin.



Entry	**Conditions (overnight)**	**Yield of 7-9 (%)**	**Recovered yield of 7-3 (%)**
1	MeOH, RT	10	76
2	THF, RT	25	**68**
3	DMF, RT	18	54
4	DBU, DCM, RT	20	68
5	NEt_3, THF, RT	15	58

Table 7.2 Optimization of CARE conditions to make the 10-membered product **7-9**. Isolated yield.

7.4 Chapter 7 summary and future work

In summary, the synthesis of medium sized and macrocycle aza sugars could be achieved using ring expansion strategies we developed (SuRE was better than CARE), the only problem was the acyl transfer side reaction in the oxygen-based ring expansion systems.

For future plans, two main keys are highlighted here. Firstly, more medium sized and macrocycle aza sugars could be synthesized and converted into iminosugar analogues to test their glucosidase inhibition activity. Secondly, different starting gluconolactam materials could be developed to generate more iminosugar analogues, which also could help to solve the problem of acyl transfer side reaction or the problem of low yield of ring expansion products in CARE reaction. Three new starting gluconolactams are listed in Figure 7.2. It is supposed that the acyl transfer side reaction could be avoided because the OAc groups couldn’t be deprotected under hydrolysis conditions, when the starting lactam **7-23** with two OAc protecting groups is used in the ring expansion reaction.

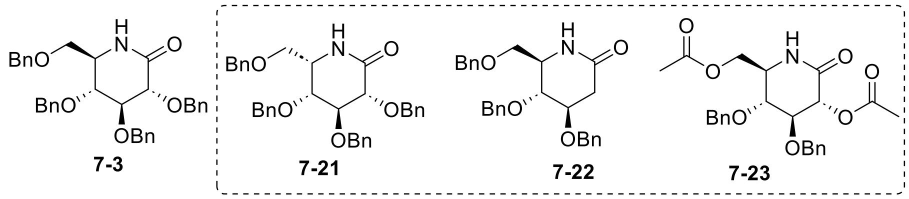

7-3 **7-21** **7-22** **7-23**

Figure 7.2 Starting gluconolactams for further ring expansion study.

Chapter Eight: General conclusion and future perspective

The work described in this thesis is focussed on a series of studies to develop new ring expansion reactions and use them to synthesize diverse medium sized and macrocyclic rings.

In Chapter 2, new *N*-acylation conditions for use in SuRE reactions were been developed to help solve the problem of performing SuRE on lactams that do not react using the published SuRE conditions. With the new *N*-acylation conditions and general deprotection/ring expansion strategies, a series of novel macrocyles that containing different amino acid or hydroxyl acid fragments were produced. Also, the new conditions provide an alternative to other challenging *N*-acylation reactions; this is likely to important in the Unsworth group's ongoing work into SuRE reactions, as its scope is now wider.

In Chapter 3, the SuRE methodology was applied to the synthesis of natural macrocyclic framework (Solomonamide macrocyclic core) and analogues. The overall brevity and the ability to insert different amino- or hydroxy-acid fragments made this approach an efficient alternative to end-to-end macrocyclisation methods to achieve the synthesis of natural macrocycles. While the total synthesis of natural product was not completed, we hope that the general strategy serves as inspiration to others to consider consectuctive ring expansion approaches like ours in target synthesis.

In Chapter 4, the development of a conjugate addition/ring expansion (CARE) reaction was described as an extension to SuRE to synthesize medium sized/macrocyclic lactams and peptide mimetics based on β-peptoid linkages. This approach avoided the use of the acyl chlorides with protecting groups and had good tolerance to a wide array of functionalized amines to produce a series of ring expansion products that have potential medicinal and biological chemistry applications. By avoiding the use of protecting groups, several steps are saved compared with SuRE, as there is not need to prepare protected amino acid derivatives before embarking on the ring expansion. This means that CARE is able to produce diverse libraries far more quickly, and with much improved atom and step economy.

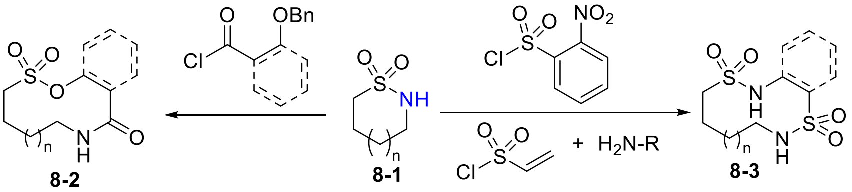
In Chapter 5, two novel ring expansion strategies had been developed to achieve the synthesis of medium sized and macrocyclic sulfonamides. Both methods are protecting group-free and their deisgn was guided by DFT calculations. These methods helped to expedite the exploration of cyclic sulfonamides (especially medium sized and macrocyclic sulfonamides) that we expect to be useful not only synthetic fields but also in medicinal chemistry, given their biological importance.

In Chapter 6, ring expansion reactions of cyclic phosphonamidates had been explored and a series of medium sized cyclic phosphonamidates and phosphonate esters were synthesized for the first time. This type of ring expansion (at P=O bond) was quite different to previous SuRE reactions at C=O bonds, which gave us experience and confidence to explore other types of ring expansion reactions. Key differences include the observation of higher kinetic barriers for ring expansion (that are general not seen in analogous C=O systems) and the higher reactivity of alcohol substartes compared with amines, which is likely driven by the higher bond energy of P–O bonds compared with P–N.

In Chapter 7, the SuRE strategy was applied to the synthesis of medium sized and macrocyclic aza sugars that might be potential glucosidase inhibitors. This uncompleted project had proved the possibility of nitrogen ring expansion of gluconolactams, and suggests that other similarly complex substartes should also be compatible. Problems remain to be solved, such as the acyl transfer side reaction observed in the oxygen ring expansion. Future work in the Unsworth group will explore this.

The novel ring expansion methods and reactions described throughout this thesis enrich the research of different ring expansion reactions and have expanded the product scope of ring expansion reactions to include sulfonamides, phosphonamides, phosphonate esters and aza sugars. All these types of molecules have potential uses in medicinal and biological chemistry, and their efficient synthesis will help with the exploration of their biological activities and possibilities to become drugs.

For further research, more different types of starting cyclic lactams or linear linkers could be explored to produce diverse functional medium sized rings and macrocycles for medicinal chemistry or metarial chemistry. For example, sultams **8-1** could be used as the starting lactam which could lead to medium sized amd macrocyclic sultone (after SuRE reaction) or disulfonamide products (after SuRE-like reactions) (Scheme 8.1). Also, these ring expansion products should be tested the biological activities that could guide their research directions in medicinal chemistry (eg. cyclic sulfonamides and aza suagrs) and should be tested their physical properties to explore their application in material chemistry (eg. diproline macrocycles in Chapter 2 and disulfonamide macrocycles **8-3**).



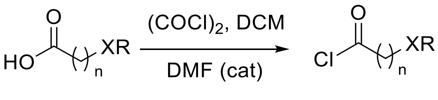
Scheme 8.1 Ring expansion of sultams.

Experimental procedures and data

General information:

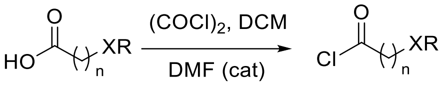
Except where stated, all reagents were purchased from commercial sources and used without further purification. Anhydrous CH_2Cl_2 and THF were obtained from an Innovative Technology Inc. PureSolv® solvent purification system. ^1H NMR, ^{13}C NMR, and ^{19}F spectra were recorded on a JEOL ECX400 or JEOL ECS400 spectrometer (operating at 400 MHz and 100 MHz, or 500 MHz and 125 MHz). All spectral data was acquired at 295 K unless stated otherwise. Chemical shifts (δ) are quoted in parts per million (ppm). The residual solvent peaks, δ_H 7.26 and δ_c 77.16 for $CDCl_3$ were used as a reference. Coupling constants (*J*) are reported in Hertz (Hz) to the nearest 0.1 Hz. The multiplicity abbreviations used are: br s broad singlet, s singlet, d doublet, br d broad doublet, t triplet, br t broad triplet, q quartet, p pentet, dd, doublet of doublets, ddd doublet of doublet of doublets, dddd doublet of doublet of doublet of doublets, dt doublet of triplets, ddt doublet of doublet of triplets, td triplet of doublets, m multiplet. Signal assignment was achieved by analysis of DEPT, COSY, HMBC and HSQC experiments where required. Infrared (IR) spectra were recorded on a PerkinElmer UATR 2 spectrometer as a thin film dispersed from either CH_2Cl_2 or $CDCl_3$. Mass spectra (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. 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.

General procedure for acid chloride formation (Fmoc and OBn derivatives group)



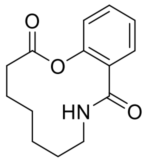
Oxalyl chloride (3 mmol) was added to a suspension of carboxylic acid (1 mmol) in DCM (5 mL), followed by a catalytic amount of DMF (1 drop/mmol of carboxylic acid). The resulting mixture was stirred at RT for 1 h and concentrated *in vacuo* to remove all solvent and excess oxalyl chloride, affording the acid chloride, which was dried with a high vacuum for 1 h at RT before use.

Modified general procedure for acid chloride formation (for use with Cbz-protected derivatives)



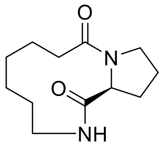
Oxalyl chloride (1.5 mmol) was added to a suspension of carboxylic acid (1 mmol) in DCM (1.5 mL), followed by a catalytic amount of DMF (1 drop/mmol of carboxylic acid). The resulting mixture was stirred at RT for 30 min and concentrated *in vacuo* to remove all solvent and excess oxalyl chloride, affording the acid chloride.

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



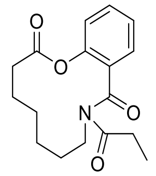
A mixture of azacyclooctan-2-one (500 mg, 3.93 mmol), DMAP (50 mg, 0.393 mmol) and pyridine (1.9 mL, 23.6 mmol) in DCM (30 mL) under an argon atmosphere was stirred at RT for 5 mins. Next, a solution of acid chloride **2-14** (5.89 mmol, 1.50 equiv. prepared using the general procedure) in DCM (15 mL) was added and the resulting mixture was heated, at reflux, at 50 °C for 16 h. An additional solution of acid chloride (5.89 mmol, 1.50 equiv. prepared using the general procedure) in DCM (15 mL) was then added and the mixture was heated at reflux at 50 °C for a further 16 h 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 redissolved in ethyl acetate (40 mL) and placed under an argon atmosphere. Palladium on carbon (390 mg, Pd 10% on carbon) was then added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at RT under a slight positive pressure of hydrogen (balloon) for 1 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 (40 mL) and triethylamine (825 µL, 5.89 mmol) added, and stirred at RT 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 (520 mg, 54%); $R_f = 0.62$ (ethyl acetate); δ_H (400 MHz, $CDCl_3$) 7.74 (dd, *J* = 7.7, 1.8 Hz, 1H, Ar-C**H**), 7.44 (ddd, *J* = 8.2, 7.4, 1.8 Hz, 1H, Ar-C**H**), 7.37 – 7.23 (m, 1H, Ar-C**H**), 7.06 (dd, *J* = 8.2, 1.2 Hz, 1H, Ar-C**H**), 6.46 (brs, 1H, N**H**), 3.60 – 3.36 (m, 2H, C**H**$_2$NH), 2.79 – 2.56 (m, 2H, C**H**$_2$COO), 1.92 – 1.84 (m, 2H, C**H**$_2$), 1.74 – 1.67 (m, 2H, C**H**$_2$), 1.64 – 1.52 (m, 4H, 2 × C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 172.0 (**C**O), 165.4 (**C**O), 147.2 (Ar-**C**), 131.6 (Ar-**C**H), 130.6 (Ar-**C**H), 129.1 (Ar-**C**), 126.6 (Ar-**C**H), 123.3 (Ar-**C**H), 40.2 (**C**H$_2$NH), 34.6 (**C**H$_2$CO), 26.4 (**C**H$_2$), 25.8 (**C**H$_2$), 24.7 (**C**H$_2$), 22.5 (**C**H$_2$); Spectroscopic data are consistent with those previously reported.[154] HRMS (ESI): calcd. For $C_{14}H_{17}NNaO_3$, 270.1101. Found: $[MNa]^+$, 270.1101 (–0.2 ppm error).

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



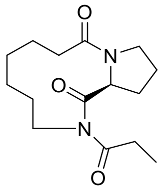
A mixture of azocan-2-one (635 mg, 5 mmol), DMAP (61 mg, 0.5 mmol) and pyridine (2.42 mL, 30 mmol) in DCM (35 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride **2-13** (7.5 mmol, 1.50 equiv., freshly prepared from Fmoc-Pro-OH using the general procedure) in DCM (18 mL) was added and the resulting mixture was refluxed at 50 °C for 16 h. The mixture was then diluted with DCM (150 mL) and washed with 10% aq. HCl (150 mL). The aqueous layer was then extracted with DCM (3 × 100 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was then re-dissolved in DCM (60 mL) and DBU (7.6 mL, 50 mmol) was added, followed by stirring at RT overnight, 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 (430 mg, 52%); R_f = 0.18 (19:1 ethyl acetate: methanol); δ_H (400 MHz, $CDCl_3$) 5.97 (d, *J* = 10.3 Hz, 1H, N**H**), 4.35 (dd, *J* = 9.0 Hz, 3.7 Hz, 1H, NC**H**), 3.95 – 3.85 (m, 1H, NC**H**$_2$), 3.70 – 3.42 (m, 2H, NC**H**$_2$), 3.00 – 2.92 (m, 1H, NC**H**$_2$), 2.47 – 1.25 (m, 10H, 5 × C**H**$_2$), 1.06 – 0.82 (m, 2H, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 174.1 (**C**O), 173.3 (**C**O), 62.5 (N**C**H), 47.2 (**N**CH$_2$), 39.4 (NH**C**H$_2$), 32.0 (**C**H$_2$), 31.8 (**C**H$_2$), 29.1 (**C**H$_2$), 26.0 (**C**H$_2$), 24.3 (**C**H$_2$), 23.2 (**C**H$_2$), 22.5 (**C**H$_2$). Spectroscopic data are consistent with those previously reported.[153] HRMS (ESI): calcd. for $C_{12}H_{20}N_2NaO_2$, 247.1417. Found: $[MNa]^+$, 247.1418 (–0.3 ppm error).

9-Propanoyl-4,5,6,7,8,9-hexahydro-2*H*-1,9-benzoxazacyclododecine-2,10(3*H*)-dione (2-4)



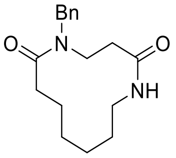
A mixture of lactam **2-1** (49.4 mg, 0.20 mmol), CuO (1.6 mg, 0.02 mmol) and NMM (0.132 mL, 1.20 mmol) in benzene (1.0 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride **2-3** (0.60 mmol, 3 equiv.) in benzene (1.0 mL) was added and the resulting mixture was refluxed at 80 °C for 16 h. The mixture was then directly concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 10:1 hexane: ethyl acetate → 1:1 hexane: ethyl acetate) afforded the *title compound* as a colorless oil (55.5 mg, 92%); R_f = 0.60 (hexane: ethyl acetate = 1:1); δ_H (400 MHz, $CDCl_3$) 7.51 – 7.44 (m, 2H, Ar-C**H**), 7.36 – 7.29 (m, 1H, Ar-C**H**), 7.17 – 7.13 (m, 1H, Ar-C**H**), 4.04 (s, 2H, NC**H**$_2$), 2.65 – 2.39 (m, 2H, C**H**$_2$), 2.20 (q, *J* = 7.2 Hz, 2H, C**H**$_2$), 1.83 (d, *J* = 6.8 Hz, 2H, C**H**$_2$), 1.72 (q, *J* = 6.3 Hz, 2H, C**H**$_2$), 1.56 – 1.39 (m, 4H, 2 × C**H**$_2$), 0.99 (t, *J* = 7.2 Hz, 3H, C**H**$_3$); δ_C (100 MHz, CDCl$_3$) 176.8 (**C**O), 172.3 (**C**O), 169.9 (**C**O), 146.5 (Ar-**C**), 132.2 (Ar-**C**), 131.4 (Ar-**C**H), 128.6 (Ar-**C**H), 126.5 (Ar-**C**H), 123.1 (Ar-**C**H), 44.0 (N**C**H$_2$), 34.1 (**C**H$_2$), 31.4 (**C**H$_2$), 27.4 (**C**H$_2$), 25.6 (**C**H$_2$), 24.0 (**C**H$_2$), 22.9 (**C**H$_2$), 9.6 (**C**H$_3$); HRMS (ESI): calcd. For $C_{17}H_{21}NNaO_4$, 326.1363. Found: $[MNa]^+$, 326.1363 (–0.1 ppm error).

2-Propanoyldecahydro-1*H*-pyrrolo[1,2-*a*][1,4]diazacycloundecine-1,9(2*H*)-dione (2-5)



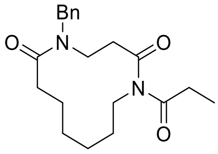
A mixture of lactam **2-2** (22.4 mg, 0.10 mmol), CuO (0.8 mg, 0.01 mmol) and NMM (0.066 mL, 0.60 mmol) in benzene (0.5 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride **2-3** (0.30 mmol, 3 equiv.) in benzene (0.5 mL) was added and the resulting mixture was refluxed at 80 °C for 16 h. The mixture was then diluted with DCM (10 mL) and washed with 10% aq. HCl (10 mL). The aqueous layer was then extracted with DCM (3 × 5 mL) and the combined organic extracts dried over MgSO$_4$ and concentrated *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 (23 mg, 72%); R$_f$ = 0.24 (ethyl acetate); δ_H (400 MHz, CDCl$_3$) 5.08 (dd, *J* = 8.6, 2.7 Hz, 1H, NC**H**), 4.27 (dt, *J* = 14.8, 6.2 Hz, 1H, NC**H**$_2$), 3.37 (ddd, *J* = 14.8, 7.7, 6.1 Hz, 1H, NC**H**$_2$), 3.74 (ddd, *J* = 12.3, 8.5, 4.1 Hz, 1H, NC**H**$_2$), 3.65 (dt, *J* = 11.7, 7.7 Hz, 1H, NC**H**$_2$), 2.64 – 2.51 (m, 2H, C**H**$_2$), 2.47 – 2.37 (m, 1H, C**H**$_2$), 1.89 (dtt, *J* = 12.6, 7.6, 3.9 Hz, 1H, C**H**$_2$), 2.34 – 2.20 (m, 2H, C**H**$_2$), 2.15 – 1.98 (m, 2H, C**H**$_2$), 1.81 – 1.70 (m, 2H, C**H**$_2$), 1.69 – 1.62 (m, 2H, C**H**$_2$), 1.57 – 1.47 (m, 1H, C**H**$_2$), 1.41 – 1.29 (m, 1H, C**H**$_2$), 1.26 – 1.11 (m, 5H, C**H**$_3$ + C**H**$_2$); δ_C (100 MHz, CDCl$_3$) 179.4 (**C**O), 177.4 (**C**O), 172.6 (**C**O), 63.5 (N**C**H), 47.6 (N**C**H$_2$), 42.2 (**N**CH$_2$), 32.0 (**C**H$_2$), 31.0 (**C**H$_2$), 29.6 (**C**H$_2$), 25.1 (**C**H$_2$), 23.2 (**C**H$_2$), 22.4 (**C**H$_2$), 22.3 (**C**H$_2$), 20.3 (**C**H$_2$), 8.9 (**C**H$_3$); HRMS (ESI): calcd. For $C_{15}H_{24}N_2NaO_3$, 303.1679. Found: [MNa]$^+$, 303.1678 (0.5 ppm error).

5-Benzyl-1,5-diazacyclododecane-2,6-dione (2-7)



A mixture of azocan-2-one (500 mg, 3.93 mmol), DMAP (50 mg, 0.393 mmol) and pyridine (1.90 mL, 23.6 mmol) in DCM (30 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride (5.89 mmol, 1.50 equiv., freshly prepared from acid using the general procedure) in DCM (15 mL) was added and the resulting mixture was refluxed at 50 °C for 16 h. The mixture was then diluted with DCM (150 mL) and washed with 10% aq. HCl (150 mL). The aqueous layer was then extracted with DCM (3 × 100 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was then re-dissolved in DCM (40 mL) and DBU (6 mL, 39.3 mmol) was added, followed by stirring at RT overnight, 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 colorless oil (780 mg, 69%); $R_f = 0.42$ (9:1 ethyl acetate: methanol); δ_H (400 MHz, $CDCl_3$) 7.37 – 7.27 (m, 3H, Ar-C**H**), 7.18 – 7.10 (m, 2H, Ar-C**H**), 6.46 (d, *J* = 9.4 Hz, 1H, N**H**), 4.90 (d, *J* = 16.9 Hz, 1H, N**C**H_2), 4.41 (d, *J* = 16.9 Hz, 1H, NC**H**$_2$), 4.55 (dddd, *J* = 14.5, 9.4, 5.1, 1.3 Hz, 1H, C**H**$_2$) , 3.75 (dddd, *J* = 13.4, 9.5, 7.5, 6.2 Hz, 1H, C**H**$_2$), 2.92 – 2.83 (m, 1H, C**H**$_2$), 2.77 (dt, *J* = 15.7, 5.2 Hz, 1H, C**H**$_2$), 2.59 (ddd, *J* = 15.6, 9.5, 5.7 Hz, 1H, C**H**$_2$), 2.49 (ddd, *J* = 14.8, 10.4, 2.0 Hz, 1H, C**H**$_2$), 2.13 (ddd, *J* = 14.8, 8.2, 2.0 Hz, 1H, C**H**$_2$), 1.63 – 1.39 (m, 8H, 4 × C**H$_2$**); δ_C (100 MHz, $CDCl_3$) 176.0 (**C**O), 170.3 (**C**O), 136.5 (Ar-**C**), 129.1 (Ar-**C**H), 127.8 (Ar-**C**H), 126.5 (Ar-**C**H), 51.7 (N**C**H_2Ph), 40.8 (N**C**H_2), 39.1 (**C**H_2), 35.2 (**C**H_2), 32.4 (**C**H_2), 27.5 (**C**H_2), 25.7 (**C**H_2), 23.8 (**C**H_2), 22.1 (**C**H_2). Spectroscopic data are consistent with those previously reported. [153] HRMS (ESI): calcd. for $C_{17}H_{25}N_2O_2$, 289.1911. Found: [MH]$^+$, 289.1907 (1.2 ppm error).

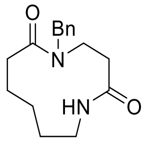
1-(1-Oxopropyl)-5-(phenylmethyl)-1,5-diazacyclododecane-2,6-dione (2-8)



A mixture of lactam **2-7** (28.8 mg, 0.10 mmol), CuO (0.8 mg, 0.01 mmol) and NMM (0.066 mL, 0.60 mmol) in benzene (0.5 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride **2-3** (0.30 mmol, 3.0 equiv.) in benzene (0.5 mL) was added and the resulting mixture was refluxed at 80 °C for 18 h. The mixture was then diluted with DCM (10 mL) and washed with 10% aq. HCl (10 mL). The aqueous layer was then extracted with DCM (3 × 5 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 10:1 hexane: ethyl acetate → 1:1 hexane: ethyl acetate) afforded the *title compound* as a colorless oil (32 mg, as 3:1 mixture of rotamers when analyzed by NMR in $CDCl_3$ at RT, 93%); $R_f = 0.62$ (ethyl acetate); To simplify NMR analysis, the product was analyzed at 120 °C in DMSO which resolved the rotamers; δ_H (400 MHz, DMSO-*d*$_6$, 120 °C) 7.34 (t, *J* = 7.3 Hz, 2H, Ar-C**H**), 7.27 (d, *J* = 6.7 Hz, 1H, Ar-C**H**), 7.22 (d, *J* = 7.6 Hz, 2H, Ar-C**H**), 4.61 (s, 2H, NC**H$_2$**Ph), 3.78 (s, 2H, NC**H$_2$**), 3.00 (s, 2H, NC**H$_2$**), 2.90 (s, 2H, C**H$_2$**), 2.66 (q, *J* = 7.0 Hz, 2H, C**H$_2$**CH_3), 2.30 (s, 2H, C**H$_2$**), 1.72 (s, 2H, C**H$_2$**), 1.62 – 1.48 (m, 2H, C**H$_2$**), 1.44 – 1.34 (m, 2H, C**H$_2$**), 1.26 – 1.18 (m, 2H, C**H$_2$**), 1.10 (t, *J* = 7.3 Hz, 3H, C**H$_3$**); Diagnostic ^{1}H NMR resonances recorded in $CDCl_3$ at RT, which confirm the presence of the two rotamer forms can be found at: 7.36 – 7.23 (m, 5H, Ar-C**H**, major rotamer), 7.16 – 7.11 (m, 5H, Ar-C**H**, minor rotamer), 1.21 (t, *J* = 7.2 Hz, 3H, C**H$_3$**, major rotamer), 1.14 (t, *J* = 7.2 Hz, 3H, C**H$_3$**, minor rotamer); δ_C (100 MHz, $CDCl_3$) data for the major rotamer only: 177.4 (**C**O), 176.7 (**C**O), 175.4 (**C**O), 137.0 (Ar-**C**), 129.0 (Ar-**C**H), 127.7 (Ar-**C**H), 126.5 (Ar-**C**H), 52.0 (N**C**H$_2$Ph), 43.5 (**C**H$_2$), 41.7 (**C**H$_2$), 37.7 (**C**H$_2$), 33.0 (**C**H$_2$), 30.0 (**C**H$_2$), 28.1 (**C**H$_2$), 27.0 (**C**H$_2$), 24.3 (**C**H$_2$), 22.5 (**C**H$_2$), 9.3 (**C**H$_3$); Diagnostic ^{13}C NMR resonances for the minor rotamer: 177.3 (**C**O), 175.1 (**C**O), 174.7 (**C**O), 138.1 (Ar-**C**), 128.7 (Ar-**C**H), 128.5 (Ar-**C**H), 127.5 (Ar-**C**H), 48.9 (N**C**H$_2$Ph), 43.9 (**C**H$_2$), 41.5 (**C**H$_2$), 37.6 (**C**H$_2$), 30.4 (**C**H$_2$), 24.1 (**C**H$_2$), 22.4 (**C**H$_2$), 9.1 (**C**H$_3$); HRMS (ESI): calcd.

for $C_{20}H_{29}N_2O_3$, 345.2173. Found: $[MH]^+$, 345.2178 (–1.6 ppm error).

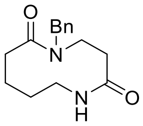
5-Benzyl-1,5-diazacycloundecane-2,6-dione (2-9)



A mixture of ε-caprolactam (565.8 mg, 5.0 mmol), DMAP (61mg, 0.5 mmol) and pyridine (2.42 mL, 30 mmol) in DCM (35 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride **2-12** (7.5 mmol, 1.50 equiv, freshly prepared from 3-[benzyl({[(9H-fluoren-9-yl)methoxy]carbonyl})amino]propanoic acid using the general procedure) in DCM (18 mL) was added and the resulting mixture was refluxed at 50 °C for 16 h. The mixture was then diluted with DCM (100 mL) and washed with 10% aq. HCl (100 mL). The aqueous layer was then extracted with DCM (3 × 100 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was then re-dissolved in DCM (50 mL) and DBU (7.6 mL, 50 mmol) was added, followed by stirring at RT overnight, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 hexane: ethyl acetate → 10:1 ethyl acetate: methanol) afforded the *title compound* (as a 5:1 mixture of rotamers) as a pale yellow solid (1.22 g, 89%). R_f = 0.37 (9:1 ethyl acetate: methanol); δ_H (400 MHz, $CDCl_3$) 7.37 – 7.24 (m, 5H, Ar-C**H**, both rotamers), 5.92 (t, N**H**, *J* = 6.1 Hz, 1H, both rotamers), 5.03 – 4.75 (m, 1H, NC**H₂**Ph, both rotamers), 4.48 – 4.30 (m, 1H, NC**H₂**Ph, both rotamers), 4.05 – 3.17 (m, 8H, NC**H₂** + C**H**₂, both rotamers), 2.74 – 2.34 (m, 6H, C**H₂**, both rotamers); δ_C (100 MHz, $CDCl_3$) data for the major rotamer only: 173.5 (**C**O), 171.5 (**C**O), 138.4 (Ar-**C**), 2 × 129.0 (Ar-**C**H), 2 × 128.3 (Ar-**C**H), 127.9 (Ar-**C**H), 49.0 (N**C**H₂Ph), 45.1 (**C**H₂), 41.7 (**C**H₂), 37.0 (**C**H₂), 28.5 (**C**H₂), 25.3 (**C**H₂), 24.4 (**C**H₂), 22.8 (**C**H₂); Diagnostic ^{13}C NMR resonances for the minor rotamer: 175.4 (**C**O), 171.1 (**C**O), 137.0 (Ar-**C**), 127.7 (Ar-**C**H), 126.6 (Ar-**C**H), 54.0 (N**C**H₂Ph), 42.9 (**C**H₂), 37.5 (**C**H₂), 34.7 (**C**H₂), 33.8 (**C**H₂), 26.0 (**C**H₂), 23.5 (**C**H₂), 22.4 (**C**H₂); HRMS (ESI): calcd. for $C_{16}H_{22}N_2NaO_2$, 297.1573. Found:

[MNa]$^+$, 297.1575 (–0.6 ppm error). Spectroscopic data are consistent with those previously reported.[153]

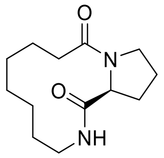
5-Benzyl-1,5-diazecane-2,6-dione (2-10)



A mixture of δ-valerolactam (495.6 mg, 5.0 mmol), DMAP (61 mg, 0.5 mmol) and pyridine (2.42 mL, 30 mmol) in DCM (35 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride **2-12** (7.5 mmol, 1.50 equiv., freshly prepared from 3-[benzyl({[(9H-fluoren-9-yl)methoxy]carbonyl})amino]propanoic acid using the general procedure) in DCM (18 mL) was added and the resulting mixture was refluxed at 50 °C for 16 h. The mixture was then diluted with DCM (100 mL) and washed with 10% aq. HCl (100 mL). The aqueous layer was then extracted with DCM (3 × 100 mL) and the combined organic extracts dried over MgSO4 and concentrated *in vacuo*. The crude material was then re-dissolved in DCM (50 mL) and DBU (7.6 mL, 50 mmol) was added, followed by stirring at RT overnight, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, ethyl acetate → 9:1 ethyl acetate: methanol) afforded the *title compound* (as a 10:1 mixture of rotamers) as a white solid (730 mg, 56%); R_f = 0.26 (9:1 ethyl acetate: methanol); δ_H (400 MHz, $CDCl_3$) 7.35 – 7.17 (m, 5H, Ar-C**H**, both rotamers), 5.95 (d, *J* = 10.3 Hz, 1H, N**H**, minor rotamer), 5.32 (d, *J* = 9.1 Hz, 1H, N**H**, major rotamer), 4.89 (d, *J* = 14.5 Hz, 1H, NC$\mathbf{H_2}$Ph, both rotamers), 4.41 (d, *J* = 14.5 Hz, 1H, NC$\mathbf{H_2}$Ph, both rotamers), 3.97 – 3.82 (m, 2H, C$\mathbf{H_2}$, both rotamers), 3.35 – 3.27 (m, 1H, C$\mathbf{H_2}$, both rotamers), 2.93 – 2.82 (m, 1H, C$\mathbf{H_2}$, both rotamers), 2.74 – 2.61 (m, 1H, C$\mathbf{H_2}$**,** both rotamers), 2.27 – 2.10 (m, 3H, C$\mathbf{H_2}$ + C**H**$_2$, both rotamers), 1.79 – 1.43 (m, 4H, C$\mathbf{H_2}$, both rotamers); δ_C (100 MHz, $CDCl_3$) data for the major rotamer only: 174.1 (**C**O), 171.1 (**C**O), 138.2 (Ar-**C**), 2 × 129.1 (Ar-**C**H), 2 × 128.3 (Ar-**C**H), 128.0 (Ar-**C**H), 49.6 (N**C**H$_2$Ph), 45.5 (**C**H$_2$), 39.3 (**C**H$_2$), 37.7 (**C**H$_2$), 28.4 (**C**H$_2$), 25.9 (**C**H$_2$), 23.9 (**C**H$_2$); ^{13}C NMR resonances for the minor rotamer: 176.4 (**C**O), 171.4 (**C**O), 136.7 (Ar-**C**), 129.0 (Ar-

CH), 127.8 (Ar-**C**H), 126.8 (Ar-**C**H), 60.5 (N**C**H$_2$Ph), 54.4 (**C**H$_2$), 42.6 (**C**H$_2$), 40.2 (**C**H$_2$), 35.2 (**C**H$_2$), 27.4 (**C**H$_2$), 25.1 (**C**H$_2$), 21.2 (**C**H$_2$), 14.3 (**C**H$_2$); HRMS (ESI): calcd. for $C_{15}H_{20}N_2NaO_2$, 283.1417. Found: $[MNa]^+$, 283.1416 (0.3 ppm error). Spectroscopic data are consistent with those previously reported.[153]

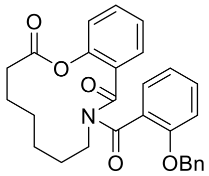
Dodecahydropyrrolo[1,2-*a*][1,4]diazacyclododecine-1,10-dione (2-11)



A mixture of azocan-2-one (706 mg, 5 mmol), DMAP (61 mg, 0.5 mmol) and pyridine (2.42 mL, 30 mmol) in DCM (35 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride **2-13** (7.5 mmol, 1.50 equiv., freshly prepared from Fmoc-Pro-OH using the general procedure) in DCM (18 mL) was added and the resulting mixture was refluxed at 50 °C for 16 h. The mixture was then diluted with DCM (100 mL) and washed with 10% aq. HCl (100 mL). The aqueous layer was then extracted with DCM (3 × 100 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was then re-dissolved in DCM (50 mL) and DBU (7.6 mL, 50 mmol) was added, followed by stirring at RT overnight, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 hexane: ethyl acetate → ethyl acetate → 10:1 ethyl acetate: methanol) afforded the *title compound* (as a 3:2 mixture of rotamers) as a white solid (940 mg, 79%); $R_f = 0.25$ (9:1 ethyl acetate: methanol); δ_H (400 MHz, $CDCl_3$) 7.51 (d, *J* = 9.1 Hz, 1H, N**H**, minor rotamer), 5.85 (d, *J* = 9.6 Hz, 1H, N**H**, major rotamer), 4.81 (dd, *J* = 8.0, 1.5 Hz, 1H, NC**H**, minor rotamer), 4.37 (dd, *J* = 8.7, 2.8 Hz, 1H, NC**H**, major rotamer), 3.88 – 3.50 (m, 4H, C**H$_2$**, both rotamers), 3.45 (dd, *J* = 9.7, 9.1 Hz, 1H, C**H**$_2$, both rotamers), 3.02 (dd, *J* = 14.0, 5.4 Hz, 1H, C**H**$_2$, both rotamers), 2.84 – 2.65 (m, 1H, C**H**$_2$, both rotamers), 2.51 – 2.44 (m, 1H, C**H**$_2$, both rotamers), 2.43 – 2.33 (m, 2H, C**H$_2$**, both rotamers), 2.32 – 2.06 (m, 6H, C**H$_2$**, both rotamers), 1.84 – 1.02 (m, 24H, C**H$_2$**, both rotamers); δ_C (100 MHz, $CDCl_3$) data for the major rotamer: 173.8 (**C**O), 171.8 (**C**O), 62.0 (N**C**H), 47.0 (**C**H$_2$), 39.9 (**C**H$_2$), 31.8 **C**H$_2$), 31.2 (**C**H$_2$), 27.9 (**C**H$_2$), 24.6 (**C**H$_2$), 24.6 (**C**H$_2$), 24.5

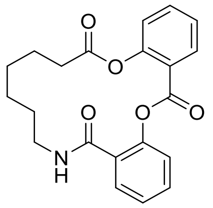
(**C**H_2), 24.4 (**C**H_2), 22.9 (**C**H_2); ^{13}C data for the minor rotamer: 174.7 (**C**O), 171.1 (**C**O), 58.5 (N**C**H), 47.3 (**C**H_2), 39.1 (**C**H_2), 35.0 (**C**H_2), 27.5 (**C**H_2), 26.9 (**C**H_2), 25.2 (**C**H_2), 25.1 (**C**H_2), 25.0 (**C**H_2), 23.8 (**C**H_2), 23.2 (**C**H_2); HRMS (ESI): calcd. for $C_{13}H_{22}N_2NaO_2$, 261.1573. Found: $[MNa]^+$, 261.1570 (1.3 ppm error).

9-[2-(Benzyloxy)benzoyl]-4,5,6,7,8,9,10a,14a-octahydro-2*H*-1,9-benzoxaza-cyclododecine-2,10(3*H*)-dione (2-15)



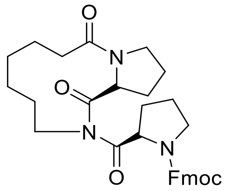
A mixture of lactam **2-1** (247mg, 1.00 mmol), CuO (8.0 mg, 0.10 mmol) and 4-Methylmorpholine (0.660 mL, 6.0 mmol) in benzene (5.0 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride **2-14** (3.0 mmol, 3.00 equiv., prepared from 2-benzyloxybenzoic acid using the general procedure) in benzene (5.0 mL) was added and the resulting mixture was refluxed at 80 °C for 18 h. Purification by flash column chromatography (SiO_2, hexane → 1:10 hexane: dichloromethane → dichloromethane) afforded the title compound as a white solid (315 mg, 69%). $R_f = 0.53$ (1:1 hexane: ethyl acetate); δ_H (400 MHz, $CDCl_3$) 7.41 (d, $J = 4.4$ Hz, 4H, Ar-C**H**), 7.37 – 7.32 (m, 1H, Ar-C**H**), 7.25 – 7.23 (m, 1H, Ar-C**H**), 7.14 – 7.04 (m, 3H, Ar-C**H**), 6.86 (td, $J = 7.6$, 1.1 Hz, 1H, Ar-C**H**), 6.77 (dd, $J = 8.6$, 1.1Hz, 1H, Ar-C**H**), 6.68 (td, $J = 7.5$, 0.9 Hz, 1H, Ar-C**H**), 6.59 (d, $J = 8.4$ Hz, 1H, Ar-C**H**), 4.97 (s, 2H, OC**H**$_2$), 4.09 (d, $J = 6.9$ Hz, 2H, C**H**$_2$), 2.53 (d, $J = 6.7$ Hz, 2H, C**H**$_2$), 1.91 – 1.42 (m, 8H, 4 × C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 172.6 (**C**O), 172.5 (**C**O), 169.8 (**C**O), 154.7 (Ar-**C**), 146.5 (Ar-**C**), 136.1 (Ar-**C**), 132.2 (Ar-**C**H), 131.3 (Ar-**C**H), 130.7 (Ar-**C**), 130.1 (Ar-**C**), 129.8 (Ar-**C**H), 2 × 128.7 (Ar-**C**H), 128.3 (Ar-**C**H), 2 × 127.4 (Ar-**C**H), 126.8 (Ar-**C**H), 125.6 (Ar-**C**H), 122.3 (Ar-**C**H), 121.0 (Ar-**C**H), 111.7 (Ar-**C**H), 70.4 (O**C**H_2), 45.2 (**C**H_2), 33.9 (**C**H_2), 27.7 (**C**H_2), 25.4 (**C**H_2), 23.9 (**C**H_2), 23.0 (**C**H_2); HRMS (ESI): calcd. for $C_{28}H_{28}NO_5$, 458.1962. Found: $[MH]^+$, 458.1963 (–0.1ppm error).

8,9,10,11,12,13-Hexahydro-4a*H*,6*H*-dibenzo[*b*,*f*][1,5,9]dioxazacyclohexadecine-6,14,20(7*H*,20a*H*)-trione (2-16)



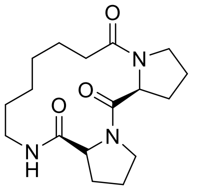
9-[2-(Benzyloxy)benzoyl]-4,5,6,7,8,9,10a,14a-octahydro-2H-1,9-benzoxaza-cyclododecine-2,10(3H)-dione **2-15** (315 mg, 0.689 mmol) was dissolved in ethyl acetate (7.0 mL) and placed under an argon atmosphere. Palladium on carbon (70 mg, Pd 10% on carbon) was then added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at RT under a slight positive pressure of hydrogen (balloon) for 18 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 (7.0 mL) and triethylamine (147 μL, 1.05 mmol) was added, and then stirred at RT for 16 h, then reduced *in vacuo*. Purification by flash column chromatography (SiO_2, 2:1 hexane: ethyl acetate) afforded the *title compound* as a yellow oil (91 mg, 35%); R_f = 0.67 (ethyl acetate); δ_H (400 MHz, $CDCl_3$) 8.36 (dd, *J* = 7.9, 1.7 Hz, 1H, Ar-C**H**), 7.65 (ddd, *J* = 8.1, 7.4, 1.7 Hz, 1H, Ar-C**H**), 7.59 (dd, *J* = 7.6, 1.7 Hz, 1H, Ar-C**H**), 7.49 (ddd, *J* = 8.1, 7.5, 1.7 Hz, 1H, Ar-C**H**), 7.39 (ddd, *J* = 7.9, 7.5, 1.2 Hz, 1H, Ar-C**H**), 7.32 (td, *J* = 7.6, 1.2 Hz, 1H, Ar-C**H**), 7.20 (dd, *J* = 8.1, 1.1 Hz, 1H, Ar-C**H**), 7.15 (dd, *J* = 8.1, 1.1 Hz, 1H, Ar-C**H**), 5.98 (s, 1H, N**H**), 3.56 – 3.32 (m, 2H, C$\mathbf{H_2}$), 2.75 – 2.51 (m, 2H, C$\mathbf{H_2}$), 1.87 – 1.79 (m, 2H, C$\mathbf{H_2}$), 1.66 – 1.59 (m, 2H, C$\mathbf{H_2}$), 1.52 (qd, *J* = 6.5, 2.7 Hz, 2H, C$\mathbf{H_2}$), 1.44 (qd, *J* = 6.5, 2.5 Hz, 2H, C$\mathbf{H_2}$); δ_C (100 MHz, $CDCl_3$) 172.3 (**C**O), 166.6 (**C**O), 162.3 (**C**O), 152.1 (Ar-**C**), 148.0 (Ar-**C**), 134.9 (Ar-**C**H), 133.0 (Ar-**C**H), 131.8 (Ar-**C**H), 130.8 (Ar-**C**), 128.5 (Ar-**C**H), 126.5 (Ar-**C**H), 126.3 (Ar-**C**H), 124.8 (Ar-**C**H), 123.1 (Ar-**C**H), 121.6 (Ar-**C**), 38.5 (**C**H_2), 32.8 (**C**H_2), 28.4 (**C**H_2), 27.2 (**C**H_2), 24.3 (**C**H_2), 23.6 (**C**H_2); HRMS (ESI): calcd. for $C_{21}H_{22}NO_5$, 368.1492. Found: $[MH]^+$, 368.1492 (0.2 ppm error).

(9*H*-Fluoren-9-yl)methyl 2-(1,9-dioxodecahydro-1*H*-pyrrolo[1,2-*a*][1,4]diazacycloundecine-2(3*H*)-carbonyl)pyrrolidine-1-carboxylate (2-17)



A mixture of 11 membered lactam **2-2** (89.7 mg, 0.4 mmol), CuO (3.2 mg, 0.04 mmol) and NMM (0.260 mL, 2.4 mmol) in benzene (2.0 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride **2-13** (1.2 mmol, 3.0 equiv., freshly prepared from Fmoc-Pro-OH using the general procedure) in dry benzene (2.0 mL) was added and the resulting mixture was refluxed at 50 °C for 18 h. The mixture was then diluted with DCM (10 mL) and washed with 10% aq. HCl (10 mL). The aqueous layer was then extracted with DCM (3 × 10 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated in vacuo. Purification by flash column chromatography (SiO_2, ethyl acetate → 9:1 ethyl acetate: methanol) afforded the *title compound* (as a 10:1 mixture of rotamers) as a colorless oil (129 mg, 60%). R_f = 0.60 (9:1 ethyl acetate: methanol); δ_H (400 MHz, $CDCl_3$) 7.75 (d, *J* = 7.2 Hz, 2H, Ar-C**H**, major rotamer), 7.64 – 7.59 (m, Ar-C**H**, 2H, major rotamer), 7.55 – 7.52 (m, 2H, Ar-C**H**, minor rotamer), 7.48 – 7.45 (m, 2H, Ar-C**H**, minor rotamer), 7.39 (t, *J* = 7.4 Hz, 2H, Ar-C**H**, major rotamer), 7.30 (tt, *J* = 7.4, 1.1 Hz, 1H, Ar-C**H**, major rotamer), 4.96 (dd, *J* = 8.6, 1.2 Hz, 1H, NC**H**, major rotamer), 4.75 (dd, *J* = 9.1, 2.8 Hz, 1H, NC**H**, minor rotamer), 4.60 (dd, *J* = 8.4, 4.7 Hz, 1H, NC**H**, major rotamer), 4.36 (dd, *J* = 10.4, 7.3 Hz, 2H, C$\mathbf{H_2}$, major rotamer), 4.24 (t, *J* = 7.2 Hz, 1H, CH_2C**H**, major rotamer), 4.14 (ddd, *J* = 14.2, 5.5, 3.6 Hz, 1H, NC$\mathbf{H}_2$, major rotamer), 3.80 – 3.57 (m, 5H, NC$\mathbf{H_2}$, both rotamers), 3.27 (ddd, *J* = 14.8, 9.9, 4.9 Hz, 1H, C$\mathbf{H}_2$, major rotamer), 2.55 (ddd, *J* = 13.7, 9.5, 4.4 Hz, 1H, C$\mathbf{H_2}$, major rotamer), 2.45 – 1.11 (m, 20H, 8 × C$\mathbf{H_2}$, both rotamers); δ_C (100 MHz, $CDCl_3$) data for the major rotamer only: 179.0 (**C**O), 176.6 (**C**O), 173.3 (**C**O), 154.8 (**C**OO), 2 × 143.8 (Ar-**C**), 2 × 141.3 (Ar-**C**), 2 × 127.8 (Ar-**C**H), 2 × 127.0 (Ar-**C**H), 2 × 125.2 (Ar-**C**H), 2 × 120.0 (Ar-**C**H), 67.7 (O**C**H_2), 62.7 (N**C**H), 59.6 (N**C**H), 47.5 (CH_2**C**H), 47.2 (**C**H_2), 47.1 (**C**H_2), 42.3 (**C**H_2), 32.3 (**C**H_2), 30.7 (**C**H$_2$), 29.8 (**C**H$_2$), 25.4 (**C**H$_2$), 24.6 (**C**H$_2$), 22.9 (**C**H$_2$), 22.4 (**C**H$_2$), 21.7 (**C**H$_2$), 19.2 (**C**H$_2$); ^{13}C NMR resonances for the minor rotamers: 178.9 (**C**O), 175.5 (**C**O), 172.3 (**C**O), 154.2 (**C**OO), 143.9 (Ar-**C**), 143.4 (Ar-**C**), 141.2 (Ar-**C**), 141.2 (Ar-**C**), 125.0 (Ar-**C**H), 120.3 (Ar-**C**H), 68.7 (O**C**H$_2$), 62.6 (N**C**H), 59.5 (N**C**H), 47.5 (CH$_2$**C**H), 47.1 (**C**H$_2$), 46.9 (**C**H$_2$), 32.1 (**C**H$_2$), 31.0 (**C**H$_2$), 30.1 (**C**H$_2$), 24.7 (**C**H$_2$), 23.0 (**C**H$_2$), 22.3 (**C**H$_2$), 21.5 (**C**H$_2$), 19.4 (**C**H$_2$); HRMS (ESI): calcd. for $C_{32}H_{37}N_3NaO_5$, 566.2625. Found: $[MNa]^+$, 566.2636 (–1.8 ppm error).

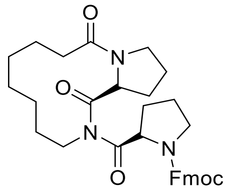
Dodecahydro-1*H*,5*H*-dipyrrolo[1,2-*a*:1',2'-*d*][1,4,7]triazacyclotetradecine 5,13,18(6*H*,18a*H*)-trione (2-18)



The *N*-acylated product **2-17** (129 mg, 0.33 mmol) was re-dissolved in DCM (4 mL) and DBU (0.6 mL, 4.0 mmol) was added, followed by stirring at RT overnight, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO$_2$, 1:1 ethyl acetate: hexane → ethyl acetate → 10:1 ethyl acetate: methanol) afforded the *title compound* (as a 3: 1 mixture of rotamers) as a yellow oil (54mg, 43%); R_f = 0.31 (9:1 ethyl acetate: methanol); δ_H (400 MHz, CDCl$_3$) 6.97 (1H, s, N**H**, major rotamer), 4.51 – 4.56 (2H, m, 2 × NC**H**, both rotamers), 4.12 – 4.19 (m, 1H, NHC**H**$_2$, both rotamers), 3.95 – 4.02 (m, 1H, NHC**H**$_2$, both rotamers), 3.63 –3.72 (m, 1H, COC**H**$_2$, both rotamers), 3.48 – 3.55 (m, 2H, NC**H**$_2$, both rotamers), 3.35 – 3.20 (m, 2H, NC**H**$_2$, both rotamers), 3.17 – 3.04 (m, 1H, COC**H**$_2$, both rotamers), 2.36 – 2.46 (m, 2H, C**H**$_2$, both rotamers), 2.17 – 2.31 (m, 4H, C**H**$_2$, both rotamers), 1.85 – 2.14 (m, 12H, C**H**$_2$, both rotamers); δ_C (100 MHz, CDCl$_3$) data for the major rotamer only: 173.3 (**C**O), 171.9 (**C**O), 171.5 (**C**O), 61.3 (N**C**H), 58.1 (N**C**H), 47.5 (**C**H$_2$), 47.3 (**C**H$_2$), 39.9 (**C**H$_2$), 34.6 (**C**H$_2$), 29.7 (**C**H$_2$), 29.3 (**C**H$_2$), 28.6 (**C**H$_2$), 25.8 (**C**H$_2$), 25.4 (**C**H$_2$), 24.2 (**C**H$_2$), 23.8 (**C**H$_2$), 19.0 (**C**H$_2$). Diagnostic ^{13}C NMR resonances for the minor rotamer: 166.5 (**C**O), 164.4 (**C**O), 61.2 (N**C**H), 60.7 (N**C**H), 45.3 (**C**H$_2$), 44.6 (**C**H$_2$), 30.0 (**C**H$_2$), 27.8

(**C**H$_2$), 23.5 (**C**H$_2$), 22.8 (**C**H$_2$), 21.8 (**C**H$_2$), 14.2 (**C**H$_2$); HRMS (ESI): calcd. for $C_{17}H_{27}NaN_3O_3$, 344.1943. Found: [MNa]$^+$, 344.1945 (0.4 ppm error).

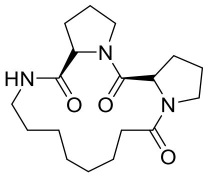
(9*H*-Fluoren-9-yl)methyl 2-(1,10-dioxododecahydropyrrolo[1,2*a*][1,4] diazacyclododecine-2(1*H*)-carbonyl)pyrrolidine-1-carboxylate (2-19)



A mixture of 12 membered lactam **2-11** (95.3 mg, 0.4 mmol), CuO (3.2 mg, 0.04 mmol) and NMM (0.260 mL, 2.4 mmol) in benzene (2.0 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride **2-13** (1.2 mmol, 3.0 equiv., freshly prepared from Fmoc-Pro-OH using the general procedure) in dry benzene (2 mL) was added and the resulting mixture was refluxed at 80 °C for 18 h. The mixture was then diluted with DCM (10 mL) and washed with 10% aq. HCl (10 mL). The aqueous layer was then extracted with DCM (3 × 10 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated in vacuo. Purification by flash column chromatography (SiO_2, 1:1 hexane: ethyl acetate→ ethyl acetate → 9:1 ethyl acetate: methanol) afforded the *title compound* (as a 5:1 mixture of rotamers) as a colorless oil (90 mg, 40%). $R_f = 0.55$ (9:1 ethyl acetate: methanol); δ_H (400 MHz, $CDCl_3$); 7.75 (t, *J* = 7.1 Hz, 3H, Ar-C**H**, both rotamers), 7.65 – 7.55 (m, 3H, Ar-C**H**, both rotamers), 7.43 – 7.34 (m, 3H, Ar-C**H**, both rotamers), 7.33 – 7.26 (m, 3H, Ar-C**H**, both rotamers), 5.54 (d, *J* = 8.8 Hz, 1H, NC**H**, minor rotamer), 5.40 (dd, *J* = 8.8, 1.7 Hz, 1H, NC**H**, major rotamer), 4.77 (dd, *J*= 8.6, 4.0 Hz, 1H, NC**H**, major rotamer), 4.58 (dd, *J* = 10.8, 7.1 Hz, 1H, NC**H**, minor rotamer), 4.49 – 4.30 (m, 3H, OC**H$_2$**, both rotamers), 4.25 (t, *J* = 7.2 Hz, 1H, OCH$_2$C**H**, major rotamer), 3.84 – 3.58 (m, 5H, NC**H$_2$**, both rotamers), 3.29 (ddd, *J* = 14.8, 6.5, 2.8 Hz, 1H, NC**H**$_2$, major rotamer), 2.46 (dt, *J* = 14.5, 7.4 Hz, 1H, NC**H**$_2$, major rotamer), 2.39 – 2.26 (m, 2H, COC**H$_2$**, both rotamers), 2.15 – 1.08 (m, 25H, 9 × C**H$_2$**, both rotamers); δ_C (100 MHz, $CDCl_3$) data for the major rotamer only: 177.6 (**C**O), 176.1 (**C**O), 172.7 (**C**O), 154.8 (**C**OO), 2 × 144.1 (Ar-**C**), 2 × 141.4

(Ar-**C**), 2 × 127.8 (Ar-**C**H), 2 × 127.1 (Ar-**C**H), 2 × 125.3 (Ar-**C**H), 2 × 120.1 (Ar-**C**H), 67.7 (O**C**H$_2$), 62.8 (N**C**H), 59.9 (N**C**H), 47.3 (OCH$_2$**C**H), 47.0 (**C**H$_2$), 47.0 (**C**H$_2$), 44.3 (**C**H$_2$), 32.6 (**C**H$_2$), 31.6 (**C**H$_2$), 30.0 (**C**H$_2$), 27.3 (**C**H$_2$), 26.3 (**C**H$_2$), 25.7 (**C**H$_2$), 25.2 (**C**H$_2$), 24.4 (**C**H$_2$), 23.9 (**C**H$_2$), 21.9 (**C**H$_2$); ^{13}C NMR resonances for the minor rotamers: 177.0 (**C**O), 175.2 (**C**O), 172.2 (**C**O), 154.3 (**C**OO), 144.0 (Ar-**C**), 143.5 (Ar-**C**), 141.3 (Ar-**C**), 141.2 (Ar-**C**), 127.9 (Ar-**C**H), 127.8 (Ar-**C**H), 127.1 (Ar-**C**H), 127.0 (Ar-**C**H), 120.2 (Ar-**C**H), 68.2 (O**C**H$_2$), 47.7 (OCH$_2$**C**H), 47.2 (**C**H$_2$), 46.9 (**C**H$_2$), 44.1 (**C**H$_2$), 31.4 (**C**H$_2$), 31.2 (**C**H$_2$), 29.8 (**C**H$_2$), 27.0 (**C**H$_2$), 25.8 (**C**H$_2$), 25.0 (**C**H$_2$), 23.2 (**C**H$_2$), 22.9 (**C**H$_2$); HRMS (ESI): calcd. for $C_{33}H_{39}N_3NaO_5$, 580.2782. Found: [MNa]$^+$, 580.2790 (–1.4 ppm error).

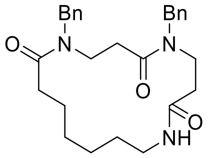
Tetradecahydro-1*H*-dipyrrolo[1,2-*a*:1',2'-*d*][1,4,7]triazacyclopentadecine-5,14,19(19a*H*)-trione (3-25)



The *N*-acylated product **2-19** (85 mg, 0.15 mmol) was then re-dissolved in DCM (4 mL) and DBU (0.6 mL, 4 mmol) was added, followed by stirring at RT overnight, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO$_2$, ethyl acetate → 9:1 ethyl acetate: methanol) afforded the *title compound* as (as a 10:1:1:1 mixture of rotamers, A:B:C:D) a colorless oil (39 mg, 72%); R$_f$ = 0.18 (9:1 ethyl acetate: methanol); δ_H (400 MHz, CDCl$_3$) 8.57 (d, *J* = 4.2 Hz, 1H, N**H**, rotamer A), 7.45 (d, *J* = 7.3 Hz, 1H, N**H**, rotamer B), 6.15 (t, *J* = 5.7 Hz, 1H, N**H**, rotamer C), 4.80 (dd, *J* = 8.4, 2.9 Hz, 1H, NC**H**, rotamer B), 4.71 (dd, *J* = 8.0, 2.0 Hz, 1H, NC**H**, rotamer C), 4.58 – 4.49 (m, 1H, NC**H**, rotamer D), 4.50 – 4.41 (m, 1H, NC**H**, rotamer B), 4.36 (td, *J* = 8.6, 1.6 Hz, 1H, NC**H**, rotamer C), 4.24 (d, *J* = 7.8 Hz, 1H, NC**H**, rotamer A), 4.11 (t, *J* = 7.7 Hz, 1H, NC**H**, rotamer A), 3.77 – 3.20 (m, 8H, NC**H$_2$**+ NHC**H$_2$**, all rotamers), 2.92 – 2.47 (m, 3H, COC**H$_2$**, all rotamers), 2.44 – 0.76 (m, 36H, 7 × C**H$_2$**, all rotamers); δ_C (100 MHz, CDCl$_3$) data for the major rotamer only: 173.2

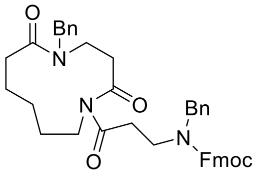
(**C**O), 171.2 (**C**O), 171.0 (**C**O), 61.9 (N**C**H), 59.3 (N**C**H), 47.7 (**C**H$_2$), 47.0 (**C**H$_2$), 38.9 (**C**H$_2$), 34.7 (**C**H$_2$), 32.3 (**C**H$_2$), 28.8 (**C**H$_2$), 28.3 (**C**H$_2$), 28.2 (**C**H$_2$), 26.3 (**C**H$_2$), 25.7 (**C**H$_2$), 24.2 (**C**H$_2$), 22.5 (**C**H$_2$), 22.0 (**C**H$_2$); HRMS (ESI): calcd. for $C_{18}H_{29}N_3NaO_3$, 358.2101. Found: $[MNa]^+$, 358.2104 (–0.7 ppm error).

5,9-Dibenzyl-1,5,9-triazacyclohexadecane-2,6,10-trione (2-22)



A mixture of **2-7** (115.4 mg, 0.40 mmol), CuO (3.2 mg, 0.04 mmol) and NMM (0.260 mL, 2.4 mmol) in benzene (2.0 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride **2-12** (1.2 mmol, 3.00 equiv., prepared using the general procedure) in benzene (2.0 mL) was added and the resulting mixture was refluxed at 80 °C for 18 h. The reaction mixture was concentrated in vacuo, loaded onto a short silica plug and eluted with 2:1 hexane: ethyl acetate to remove the excess carboxylic acid and NMM. The acylated product was concentrated in *vacuo*, re-dissolved in DCM (4 mL) and DBU (0.6 mL, 4.0 mmol) was added, followed by stirring at RT overnight, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 ethyl acetate: hexane → ethyl acetate → 10:1 ethyl acetate: methanol) afforded the *title compound* (as a 4:2:1 mixture of rotamers, A:B:C) as a yellow oil (75 mg, 40%); R_f = 0.42 (9:1 ethyl acetate: methanol); δ_H (400 MHz, $CDCl_3$) 7.43 – 7.07 (m, 20H, Ar-C**H**, all rotamers), 7.00 – 6.96 (m, 1H, N**H**, rotamer A), 6.85 (t, *J* = 5.7 Hz, 1H, N**H**, rotamer B), 6.16 (t, *J* = 5.3 Hz, 1H, N**H**, rotamer C), 4.67 – 4.50 (m, 5H, NC**H**$_2$Ph, all rotamers), 3.73 – 3.56 (m, 7H, NC**H$_2$**, all rotamers), 3.39 – 3.13 (m, 4H, C**H**$_2$NH, all rotamers), 2.76 – 2.28 (m, 12H, 3 × C**H$_2$**, all rotamers), 1.84 – 1.20 (m, 16H, 6 × C**H$_2$**, all rotamers); δ_C (100 MHz, $CDCl_3$) data for the major rotamer only: 174.4 (**C**O), 170.9 (**C**O), 170.5 (**C**O), 137.6 (Ar-**C**), 136.4 (Ar-**C**), 2 × 129.2 (Ar-**C**H), 129.0 (Ar-**C**H), 2 × 128.7 (Ar-**C**H), 2 × 128.2 (Ar-**C**H), 2 ×126.5 (Ar-**C**H), 126.2 (Ar-**C**H), 52.1 (N**C**H$_2$Ph), 49.3 (N**C**H$_2$Ph), 45.9 (**C**H$_2$), 44.9 (**C**H$_2$), 40.3 (**C**H$_2$), 37.4 (**C**H$_2$), 32.8 (**C**H$_2$), 31.1 (**C**H$_2$), 28.4 (**C**H$_2$), 26.5 (**C**H$_2$), 25.6 (**C**H$_2$), 21.6 (**C**H$_2$); ^{13}C NMR resonances for the minor rotamer: 174.1 (**C**O), 173.6 (**C**O), 173.0 (**C**O), 171.9 (**C**O), 171.4 (**C**O), 170.6 (**C**O), 138.2 (Ar-**C**), 138.0 (Ar-**C**), 137.0 (Ar-**C**), 136.0 (Ar-**C**), 128.9 (Ar-**C**H), 128.0 (Ar-**C**H), 127.9 (Ar-**C**H), 127.9 (Ar-**C**H), 127.6 (Ar-**C**H), 127.5 (Ar-**C**H), 127.5 (Ar-**C**H), 127.5 (Ar-**C**H), 126.3 (Ar-**C**H), 54.1 (N**C**H_2Ph), 52.2 (N**C**H_2Ph), 49.3 (N**C**H_2Ph), 44.7 (N**C**H_2Ph), 44.2 (**C**H_2), 43.7 (**C**H_2), 43.2 (**C**H_2), 43.0 (**C**H_2), 39.6 (**C**H_2), 39.1 (**C**H_2), 36.7 (**C**H_2), 35.6 (**C**H_2), 35.4 (**C**H_2), 33.3 (**C**H_2), 32.2 (**C**H_2), 31.4 (**C**H_2), 30.7 (**C**H_2), 28.9 (**C**H_2), 28.1 (**C**H_2), 27.6 (**C**H_2), 26.2 (**C**H_2), 25.4 (**C**H_2), 24.7 (**C**H_2), 24.5 (**C**H_2), 23.3 (**C**H_2); HRMS (ESI): calcd. for $C_{27}H_{36}NO_3$, 450.2751. Found: $[MH]^+$, 450.2757 (–1.2 ppm error).

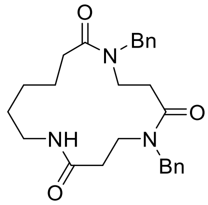
(9*H*-Fluoren-9-yl)methyl benzyl[3-(5-benzyl-2,6-dioxo-1,5-diazacycloundecan-1-yl)-3-oxopropyl]carbamate (2-23)



A mixture of 5-benzyl-1,5-diazacycloundecane-2,6-dione **2-9** (109.7 mg, 0.4 mmol), CuO (6.4 mg, 0.08 mmol) and NMM (0.260 mL, 2.4 mmol) in benzene (3.0 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride **2-12** (1.2 mmol, 3.00 equiv., freshly prepared using the general procedure) in benzene (2 mL) was added and the resulting mixture was refluxed at 80 °C for 18 h. The mixture was then diluted with DCM (30 mL) and washed with 10% aq. HCl (30 mL). The aqueous layer was then extracted with DCM (3 × 30 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated in vacuo. Purification by flash column chromatography (SiO_2, 2:1 hexane: ethyl acetate→1:1 hexane: ethyl acetate) afforded the title compound as a colorless oil (138 mg, 53%). $R_f = 0.65$ (ethyl acetate); δ_H (400 MHz, $CDCl_3$) 7.76 – 7.46 (m, 8H, Ar-C**H**), 7.41 – 7.00 (m, 10H, Ar-C**H**), 4.73 (d, *J* = 4.7 Hz, 1H, NC**H$_2$**Ph), 4.55 (d, *J* = 6.0 Hz, 1H, NC**H$_2$**Ph), 4.53 – 4.41 (m, 2H, NC**H$_2$**Ph), 4.39 (s, 2H, OC**H$_2$**), 4.28 – 4.17 (m, 1H, OCH_2C**H**), 3.60 – 3.21 (m, 6H, 3 × NC**H$_2$**), 3.11 (t, *J* = 6.8 Hz, 1H, C**H$_2$**), 2.80 (t, *J* = 6.8 Hz, 1H, C**H$_2$**), 2.40 – 1.83 (m, 4H, 2 ×

C**H**$_2$), 1.72 – 1.44 (m, 4H, 2 × C**H**$_2$); δ_C (100 MHz, CDCl$_3$) 175.0 (**C**O), 174.5 (**C**O), 172.8 (**C**O), 156.1 (**C**OO), 144.0 (Ar-**C**), 143.9 (Ar-**C**), 141.5 (Ar-**C**), 141.4 (Ar-**C**), 137.5 (Ar-**C**), 137.5 (Ar-**C**), 129.0 (Ar-**C**H), 128.8 (Ar-**C**H), 2 × 128.7 (Ar-**C**H), 2 × 128.2 (Ar-**C**H), 2 × 127.8 (Ar-**C**H), 2 × 127.4 (Ar-**C**H), 127.2 (Ar-**C**H), 127.1 (Ar-**C**H), 2 × 126.7 (Ar-**C**H), 2 × 124.9 (Ar-**C**H), 2 × 120.1 (Ar-**C**H), 67.4 (O**C**H$_2$), 51.7 (N**C**H$_2$Ph), 47.7 (N**C**H$_2$Ph), 47.3 (Fmoc-Ar-**C**H), 44.1 (**C**H$_2$), 44.0 (**C**H$_2$), 43.1 (**C**H$_2$), 37.6 (**C**H$_2$), 35.7 (**C**H$_2$), 31.9 (**C**H$_2$), 26.7 (**C**H$_2$), 25.3 (**C**H$_2$), 22.9 (**C**H$_2$); HRMS (ESI): calcd. for $C_{41}H_{43}N_3NaO_5$, 680.3095. Found: $[MNa]^+$, 680.3110 (–2.2 ppm error).

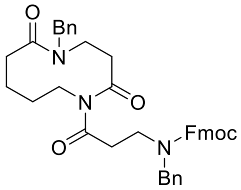
5,9-Dibenzyl-1,5,9-triazacyclopentadecane-2,6,10-trione (2-24)



The *N*-acylated product **2-23** (71.6 mg, 0.11 mmol) was dissolved in DCM (4 mL) and DBU (0.6 mL, 4 mmol) was added, followed by stirring at RT overnight, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO$_2$, 1:1 hexane: ethyl acetate → 10:1 ethyl acetate: methanol) afforded the *title compound* as (as a 2:1 mixture of rotamers) a colorless oil (38 mg, 79%); R_f = 0.32 (9:1 ethyl acetate: methanol); δ_H (400 MHz, CDCl$_3$) 7.40 – 7.04 (m, 15H, Ar-C**H**, both rotamers), 6.72 (t, *J* = 5.9 Hz, 1H, N**H**, major rotamer), 6.49 (t, *J* = 5.8 Hz, 1H, N**H**, minor rotamer), 4.85 (s, 2H, NC**H**$_2$Ph, major rotamer), 4.75 (s, 2H, NC**H**$_2$Ph, minor rotamer), 4.59 (s, 2H, NC**H**$_2$Ph, major rotamer), 4.57 (s, 2H, NC**H**$_2$Ph, minor rotamer), 3.80 – 3.23 (m, 10H, NHC**H**$_2$ + 2 × NC**H**$_2$, both rotamers), 2.88 – 2.37 (m, 10H, 3 × C**H**$_2$, both rotamers), 1.82 – 1.29 (m, 11H, 3 × C**H**$_2$, both rotamers); δ_C (100 MHz, CDCl$_3$) data for the major rotamer only: 174.5 (**C**O), 173.7 (**C**O), 170.8 (**C**O), 137.6 (Ar-**C**), 136.4 (Ar-**C**), 2 × 129.1 (Ar-**C**H), 2 × 129.0 (Ar-**C**H), 128.2 (Ar-**C**H), 126.7 (Ar-**C**H), 2 × 126.6 (Ar-**C**H), 2 × 126.2 (Ar-**C**H), 54.6 (N**C**H$_2$Ph), 51.4 (N**C**H$_2$Ph), 44.4 (**C**H$_2$), 42.0 (**C**H$_2$), 39.0 (**C**H$_2$), 35.2 (**C**H$_2$), 32.5 (**C**H$_2$), 31.5 (**C**H$_2$), 28.5 (**C**H$_2$), 25.6 (**C**H$_2$), 25.0 (**C**H$_2$); ^{13}C NMR resonances for the minor rotamer: 174.5 (**C**O), 171.7 (**C**O), 170.6 (**C**O), 138.0

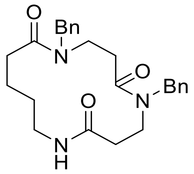
(Ar-**C**), 137.2 (Ar-**C**), 129.0 (Ar-**C**H), 128.7 (Ar-**C**H), 127.7 (Ar-**C**H), 127.6 (Ar-**C**H), 53.7 (N**C**H_2Ph), 49.4 (N**C**H_2Ph), 44.7 (**C**H_2), 44.2 (**C**H_2), 37.6 (**C**H_2), 36.9(**C**H_2), 32.3 (**C**H_2), 31.9 (**C**H_2), 26.8 (**C**H_2), 24.1 (**C**H_2), 23.3 (**C**H_2); HRMS (ESI): calcd. for $C_{26}H_{33}N_3NaO_3$, 458.2414. Found: $[MNa]^+$, 458.2416 (–0.3 ppm error).

(9*H*-Fluoren-9-yl)methyl benzyl[3-(5-benzyl-2,6-dioxo-1,5-diazecan-1-yl)-3-oxopropyl]carbamate (2-25)



A mixture of 5-benzyl-1,5-diazecane-2,6-dione **2-10** (103.7 mg, 0.4 mmol), CuO (6.4 mg, 0.08 mmol) and NMM (0.260 mL, 2.4 mmol) in benzene (3.0 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride **2-12** (1.2 mmol, 3.00 equiv., freshly prepared using the general procedure) in benzene (2 mL) was added and the resulting mixture was refluxed at 80 °C for 18 h. The mixture was then diluted with DCM (30 mL) and washed with 10% aq. HCl (30 mL). The aqueous layer was then extracted with DCM (3 × 30 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 hexane: ethyl acetate) afforded the *title compound* as a yellow oil (144 mg, 56%). R_f = 0.70 (ethyl acetate); δ_H (400 MHz, $CDCl_3$) 7.75 – 7.41 (m, 8H, Ar-C**H**), 7.39 – 7.00 (m, 10H, Ar-C**H**), 4.72 (d, *J* = 4.8 Hz, 1H, NC**H₂**Ph), 4.54 (d, *J* = 6.0 Hz, 1H, NC**H₂**Ph), 4.50 – 4.43 (m, 2H, NC**H₂**Ph), 4.40 (d, *J* = 11.8 Hz, 2H, OC**H₂**), 4.24 – 4.18 (m, 1H, OCH₂C**H**), 3.77 – 3.28 (m, 6H, 3 × NC**H₂**), 3.24 – 3.00 (m, 2H, C**H₂**), 2.89 – 2.46 (m, 2H, C**H₂**), 2.29 – 2.06 (m, 2H, C**H₂**), 1.95 – 1.53 (m, 6H, 3 × C**H₂**); δ_C (100 MHz, $CDCl_3$) 174.1 (**C**O), 172.9 (**C**O), 172.8 (**C**O), 156.1 (**C**OO), 144.0 (Ar-**C**), 143.9 (Ar-**C**), 141.6 (Ar-**C**), 141.5 (Ar-**C**), 137.6 (Ar-**C**), 137.3 (Ar-**C**), 2 × 128.9 (Ar-**C**H), 2 × 128.8 (Ar-**C**H), 2 × 128.1 (Ar-**C**H), 2 × 127.8 (Ar-**C**H), 127.7 (Ar-**C**H), 2 × 127.5 (Ar-**C**H), 127.3 (Ar-**C**H), 2 × 127.2 (Ar-**C**H), 2 × 124.9 (Ar-**C**H), 2 × 120.1 (Ar-**C**H), 67.4 (O**C**H_2), 51.8 (N**C**H_2Ph), 47.6 (Fmoc-Ar-**C**H), 47.4 (N**C**H_2Ph), 44.1 (**C**H_2), 43.5 (**C**H_2), 42.8 (**C**H_2), 38.9 (**C**H_2), 35.6 (**C**H_2), 35.4 (**C**H_2), 29.4 (**C**H_2), 24.3 (**C**H_2); HRMS (ESI): calcd. for $C_{40}H_{41}N_3NaO_5$, 666.2938. Found: $[MNa]^+$, 666.2943 (–0.6 ppm error)

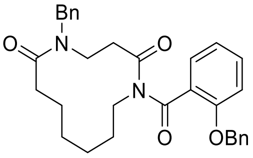
5,9-Dibenzyl-1,5,9-triazacyclotetradecane-2,6,10-trione (2-26)



The *N*-acylated product **2-25** (134 mg, 0.208 mmol) was then re-dissolved in DCM (4 mL) and DBU (0.60 mL, 4.00 mmol) was added, followed by stirring at RT overnight, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, ethyl acetate → 9:1 ethyl acetate: methanol) afforded the *title compound* as (as a 10:5:1 mixture of rotamers, A:B:C) a colorless oil (74 mg, 85%); R_f = 0.72 (ethyl acetate); δ_H (400 MHz, $CDCl_3$) 7.38 – 6.97 (m, 22H, Ar-C**H**, all rotamers), 6.94 (t, *J* = 5.4 Hz, 1H, N**H**, rotamer B), 6.84 (t, *J* = 5.9 Hz, 1H, N**H**, rotamer A), 6.61 (t, *J* = 5.3 Hz, 1H, N**H**, rotamer C), 4.71 (s, 2H, NC**H₂**Ph, rotamer A), 4.62 (s, 2H, NC**H₂**Ph, rotamer C), 4.60 (s, 2H, NC**H₂**Ph, rotamer C), 4.56 (s, 2H, NC**H₂**Ph, rotamer A), 4.54 (s, 2H, NC**H₂**Ph, rotamer B), 4.30 (s, 2H, NC**H₂**Ph, rotamer B), 3.75 – 3.50 (m, 8H, C**H₂**, all rotamers), 3.38 – 3.26 (m, 4H, C**H₂**, all rotamers), 2.68 – 2.37 (m, 12H, C**H₂**, all rotamers), 1.82 – 1.52 (m, 9H, C**H₂**, all rotamers); δ_C (100 MHz, $CDCl_3$) data for the major rotamer only: 174.1 (**C**O), 173.0 (**C**O), 171.3 (**C**O), 137.1 (Ar-**C**), 137.0 (Ar-**C**), 2 × 129.1 (Ar-**C**H), 2 × 129.0 (Ar-**C**H), 128.8 (Ar-**C**H), 2 × 126.6 (Ar-**C**H), 2 × 126.2 (Ar-**C**H), 126.1 (Ar-**C**H), 53.6 (N**C**H_2Ph), 53.4 (N**C**H_2Ph), 44.6 (**C**H_2), 44.0 (**C**H_2), 38.6 (**C**H_2), 35.6 (**C**H_2), 33.5 (**C**H_2), 31.8 (**C**H_2), 29.0 (**C**H_2), 22.8 (**C**H_2); ^{13}C NMR resonances for the minor rotamer: 174.3 (**C**O), 173.5 (**C**O), 173.4 (**C**O), 171.0 (**C**O), 170.7 (**C**O), 170.2 (**C**O), 137.7 (Ar-**C**), 137.6 (Ar-**C**), 137.6 (Ar-**C**), 135.8 (Ar-**C**), 129.2 (Ar-**C**H), 128.7 (Ar-**C**H), 128.7 (Ar-**C**H), 128.3 (Ar-**C**H), 128.1 (Ar-**C**H), 128.1 (Ar-**C**H), 128.0 (Ar-**C**H), 127.8 (Ar-**C**H), 127.7 (Ar-**C**H), 127.6 (Ar-**C**H), 127.6 (Ar-**C**H), 127.4 (Ar-**C**H), 126.5 (Ar-**C**H), 126.1 (Ar-**C**H), 51.3 (N**C**H_2Ph), 50.8

(N**C**H_2Ph), 48.9 (N**C**H_2Ph), 48.7 (N**C**H_2Ph), 44.5 (N**C**H_2), 43.9 (N**C**H_2), 43.1 (N**C**H_2), 42.2 (N**C**H_2), 39.6 (NH**C**H_2), 38.4 (NH**C**H_2), 35.2 (CO**C**H_2), 35.1 (CO**C**H_2), 33.2 (CO**C**H_2), 33.0 (CO**C**H_2), 32.6 (**C**H_2), 32.3 (**C**H_2), 28.1 (**C**H_2), 27.8 (**C**H_2), 24.0 (**C**H_2), 23.3 (**C**H_2); HRMS (ESI): calcd. for $C_{25}H_{31}N_3NaO_3$, 444.2258. Found: $[MNa]^+$, 444.2261 (–0.7 ppm error).

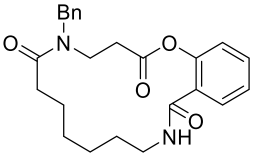
5-Benzyl-1-[2-(benzyloxy) benzoyl]-1,5-diazacyclododecane-2,6-dione (2-27)



A mixture of **2-7** (115.4mg, 0.40 mmol), CuO (6.4 mg, 0.20 mmol) and 4-Methylmorpholine (0.260 mL, 2.4 mmol) in benzene (2.0 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride **2-14** (1.20 mmol, 3.00 equiv., prepared from 2-benzyloxybenzoic acid using the general procedure) in benzene (2.0 mL) was added and the resulting mixture was refluxed at 80 °C for 18 h. Purification by flash column chromatography (SiO_2, hexane → 1:10 hexane: dichloromethane → dichloromethane → 5: 1 dichloromethane: ethyl acetate) afforded the *title compound* (as a 2:1 mixture of rotamers) as a colorless oil (180 mg, 90%). R_f = 0.70 (1: 2 hexane: ethyl acetate); δ_H (400 MHz, $CDCl_3$) 7.60 – 7.18 (m, 27H, Ar-C**H**, both rotamers), 7.12 – 6.92 (m, 6H, Ar-C**H**, both rotamers), 5.10 (s, 2H, OC**H**$_2$Ph, both rotamers), 4.84 (d, *J* = 16.7 Hz, 1H, NC**H**$_2$Ph, both rotamers), 4.63 (s, 1H, NC**H**$_2$Ph, both rotamers), 4.47 (d, *J* = 16.7 Hz, 1H, NC**H**$_2$Ph, both rotamers), 4.27 (s, 1H, NC**H**$_2$Ph, both rotamers), 4.11 – 3.99 (m, 1H, C**H**$_2$, both rotamers), 3.92 – 3.65 (m, 3H, C**H**$_2$, both rotamers), 3.30 (s, 1H, C**H**$_2$, both rotamers), 2.91 (ddd, *J* = 13.3, 8.4, 4.0 Hz, 1H, C**H**$_2$, both rotamers), 2.69 (s, 1H, C**H**$_2$, both rotamers), 2.52 (ddd, *J* = 14.6, 8.6, 2.7 Hz, 1H, C**H**$_2$, both rotamers), 2.40 – 2.28 (m, 1H, C**H**$_2$, both rotamers), 2.11 (ddd, *J* = 14.0, 9.5, 3.1 Hz, 1H, C**H**$_2$, both rotamers), 1.69 – 1.08 (m, 18H, C**H**$_2$, both rotamers), 0.95 – 0.78 (m, 1H, C**H**$_2$, both rotamers); δ_C (100 MHz, $CDCl_3$) data for the major rotamer only: 175.3 (**C**O), 174.4 (**C**O), 171.3 (**C**O), 154.8 (Ar-**C**), 137.3 (Ar-**C**), 136.4 (Ar-**C**), 132.0 (Ar-**C**), 129.4 (Ar-**C**H), 2 × 129.0 (Ar-**C**H), 128.8 (Ar-**C**H), 2 × 128.7 (Ar-**C**H), 128.3

(Ar-**C**H), 2 × 127.6 (Ar-**C**H), 2 × 127.2 (Ar-**C**H), 126.5 (Ar-**C**H), 121.6 (Ar-**C**H), 112.7 (Ar-**C**H), 70.7 (O**C**H$_2$), 48.0 (N**C**H$_2$Ph), 45.2 (**C**H$_2$), 43.9 (**C**H$_2$), 36.5 (**C**H$_2$), 29.8 (**C**H$_2$), 27.8 (**C**H$_2$), 26.2 (**C**H$_2$), 24.5 (**C**H$_2$), 23.2 (**C**H$_2$); Diagnostic ^{13}C NMR resonances for the minor rotamers: 176.7 (**C**O), 174.0 (**C**O), 172.5 (**C**O), 155.1 (Ar-**C**), 137.9 (Ar-**C**), 136.1 (Ar-**C**), 132.6 (Ar-**C**), 129.4 (Ar-**C**H), 128.8 (Ar-**C**H), 128.7 (Ar-**C**H), 128.4 (Ar-**C**H), 128.2 (Ar-**C**H), 127.6 (Ar-**C**H), 127.4 (Ar-**C**H), 126.4 (Ar-**C**H), 121.5 (Ar-**C**H), 112.8 (Ar-**C**H), 43.5 (N**C**H$_2$Ph), 43.4 (**C**H$_2$), 36.9 (**C**H$_2$), 33.7 (**C**H$_2$), 29.4 (**C**H$_2$), 26.7 (**C**H$_2$), 26.5 (**C**H$_2$), 23.6 (**C**H$_2$); HRMS (ESI): calcd. for $C_{31}H_{35}N_2O_4$, 499.2591. Found: [MH]$^+$, 499.2600 (–1.6 ppm error).

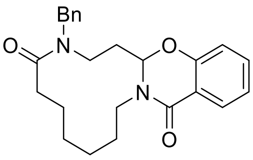
5-Benzyl-4,5,8,9,10,11,12,13-octahydro-2*H*-1,5,13-benzoxadiazacyclohexadecine-2,6,14(3*H*,7*H*)-trione (2-28)



The material **2-27** (176 mg, 0.353 mmol) was dissolved in ethyl acetate (3.5 mL) and placed under an argon atmosphere. Palladium on carbon (35.3 mg, Pd 10% on carbon) was then added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at RT under a slight positive pressure of hydrogen (balloon) overnight. 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 (3.5 mL) and triethylamine (75 µL, 0.52 mmol) was added, and then stirred at RT for 16 h, then reduced *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 hexane: ethyl acetate → 1:2 hexane: ethyl acetate → 10:1 ethyl acetate: menthol) afforded the *title compound* (as a 2:1 mixture of rotamers) as a colorless oil (45.5 mg, 31.5%); $R_f = 0.65$ (9:1 ethyl acetate: menthol); δ_H (400 MHz, $CDCl_3$) 8.09 (dd, *J* = 7.8, 1.8 Hz, 1H, Ar-C**H**, major rotamer), 7.51 – 7.41 (m, 2H, Ar-C**H**, both rotamers), 7.37 – 7.23 (m, 9H, Ar-C**H**, both rotamers), 7.09 (ddt, *J* = 15.8, 8.1, 1.4 Hz, 4H, Ar-C**H**, both rotamers), 6.81 (t, *J* = 5.3 Hz, 1H, CON**H**, major rotamer), 4.78 (s, 2H, NC**H**$_2$Ph, major rotamer), 3.77 – 3.69 (m, 1H, NC**H**$_2$, both rotamers), 3.67

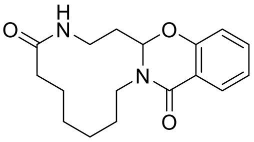
– 3.59 (m, 2H, NHC**H**$_2$, both rotamers), 3.51 – 3.37 (m, 3H, OCOC**H**$_2$ + NC**H**$_2$, both rotamers), 3.15 (dd, J = 5.9, 4.3 Hz, 2H, NC**H**$_2$, both rotamers), 2.79 – 2.70 (m, 1H, C**H**$_2$, both rotamers), 2.53 – 2.44 (m, 1H, C**H**$_2$, both rotamers), 2.38 – 2.26 (m, 2H, C**H**$_2$, both rotamers), 1.80 (dq, J = 17.1, 8.8 Hz, 4H, C**H**$_2$, both rotamers), 1.67 – 1.38 (m, 8H, CH$_2$, both rotamers); Diagnostic ^{1}H NMR resonances for the minor rotamers: 7.63 (dd, J = 7.7, 1.7 Hz, 1H, Ar-C**H**, major rotamer), 6.14 (t, J = 6.2 Hz, 1H, CON**H**, minor rotamer), 4.64 (s, 2H, NC**H**$_2$Ph, minor rotamer); δ_C (100 MHz, CDCl$_3$) data for the major rotamer only: 174.6 (**C**O), 171.4 (**C**O), 164.9 (**C**O), 147.8 (Ar-**C**), 137.6 (Ar-**C**), 132.0 (Ar-**C**H), 131.6 (Ar-**C**H), 2 × 129.0 (Ar-**C**H), 128.2 (Ar-**C**H), 127.6 (Ar-**C**H), 127.0 (Ar-**C**), 2 × 126.5 (Ar-**C**H), 123.1 (Ar-**C**H), 54.1 (N**C**H$_2$Ph), 43.2 (**C**H$_2$), 40.5 (**C**H$_2$), 33.6 (**C**H$_2$), 32.7 (**C**H$_2$), 29.7 (**C**H$_2$), 29.6 (**C**H$_2$), 26.4 (**C**H$_2$), 23.9 (**C**H$_2$); Diagnostic ^{13}C NMR resonances for the minor rotamers: 173.7 (**C**O), 169.4 (**C**O), 166.3 (**C**O), 147.7 (Ar-**C**), 137.7 (Ar-**C**), 131.7 (Ar-**C**H), 129.1 (Ar-**C**H), 127.7 (Ar-**C**H), 127.0 (Ar-**C**), 126.6 (Ar-**C**H), 123.2 (Ar-**C**H), 49.2 (N**C**H$_2$Ph), 42.9 (**C**H$_2$), 39.6 (**C**H$_2$), 34.8 (**C**H$_2$), 31.5 (**C**H$_2$), 29.5 (**C**H$_2$), 27.3 (**C**H$_2$), 25.2 (**C**H$_2$), 24.5 (**C**H$_2$); HRMS (ESI): calcd. for $C_{24}H_{28}N_2NaO_4$, 431.1941. Found: [MNa]$^+$, 431.1939 (0.6 ppm error).

3-Benzyl-1,2,3,5,6,7,8,9,10,17a-decahydro-4*H*,12*H*-[1,5]diazacyclododecino[2,1-*b*][1,3]benzoxazine-4,12-dione (2-28a)



This byproduct was isolated with the product **2-28** (as a 1:1: 0.5 mixture of rotamers) as a colorless oil (52 mg, 37%); R_f = 0.65 (9:1 ethyl acetate: menthol); δ_H (400 MHz, CDCl$_3$) 7.91 (ddd, J = 14.7, 7.8, 1.7 Hz, 2H, Ar-C**H,** all rotamers), 7.45 – 7.18 (m, 15H, Ar-C**H,** all rotamers), 7.16 – 7.03 (m, 3H, Ar-C**H,** all rotamers), 6.88 (dd, J = 8.2, 1.0 Hz, 2H, Ar-C**H,** all rotamers), 5.48 (dd, J = 10.4, 1.1 Hz, 1H, OC**H**N, major rotamer), 5.04 (dd, J = 24.7, 15.6 Hz, 2H, NC**H**$_2$Ph, all rotamers), 4.48 (d, J = 16.5 Hz, 1H, C**H**$_2$, all rotamers), 4.38 (dt, J = 14.6, 8.1 Hz, 1H, **C**H$_2$, all rotamers), 4.23 (dd, J = 15.6, 3.2 Hz, 1H, **C**H$_2$, all rotamers), 4.16 – 3.90 (m, 2H, C**H**$_2$, all rotamers), 3.51 (ddd, J = 15.2, 9.1, 3.7 Hz, 1H, C**H**$_2$, all rotamers), 3.27 – 3.14 (m, 2H, C**H**$_2$, all rotamers), 2.86 – 2.42 (m, 6H, C**H**$_2$, all rotamers), 2.38 – 2.09 (m, 4H, C**H**$_2$, all rotamers), 1.99 – 1.36 (m, 22H, C**H**$_2$, all rotamers); Diagnostic ^{1}H NMR resonances for the minor rotamers: 5.79 (dd, *J* = 7.8, 1.3 Hz, 1H, OC**H**N),5.39 (dd, *J* = 7.9, 2.1 Hz, 1H, OC**H**N); δ_C (100 MHz, CDCl$_3$) data for the major rotamer only: 174.7 (N**C**O), 160.5 (N**C**OPh), 154.5 (Ar-**C**), 137.0 (Ar-**C**), 134.1 (Ar-**C**H), 129.2 (Ar-**C**H), 129.1 (Ar-**C**H), 128.8 (Ar-**C**H), 128.3 (Ar-**C**H), 126.6 (Ar-**C**H), 126.5 (Ar-**C**H), 122.6 (Ar-**C**H), 118.1 (Ar-**C**), 116.9 (Ar-**C**H), 83.2 (O**C**H), 55.2 (N**C**H$_2$Ph), 43.8 (**C**H$_2$), 38.5 (**C**H$_2$), 34.5 (**C**H$_2$), 27.9 (**C**H$_2$), 24.8 (**C**H$_2$), 24.3 (**C**H$_2$), 23.8 (**C**H$_2$), 22.9 (**C**H$_2$); Diagnostic ^{13}C NMR resonances for the minor rotamers: 176.1 (N**C**O), 174.4 (N**C**O), 161.7 (N**C**OPh), 160.9 (N**C**OPh), 155.6 (Ar-**C**), 155.2 (Ar-**C**), 137.6 (Ar-**C**), 136.3 (Ar-**C**), 134.3 (Ar-**C**H), 128.4 (Ar-**C**H), 128.4 (Ar-**C**H), 128.1 (Ar-**C**H), 128.0 (Ar-**C**H), 127.6 (Ar-**C**H), 122.7 (Ar-**C**H), 122.2 (Ar-**C**H), 118.6 (Ar-**C**), 118.3 (Ar-**C**), 117.5 (Ar-**C**H), 116.3 (Ar-**C**H), 87.3 (O**C**H), 85.4 (O**C**H), 51.6 (N**C**H$_2$Ph), 50.4 (N**C**H$_2$Ph), 44.7 (**C**H$_2$), 43.7 (**C**H$_2$), 41.5 (**C**H$_2$), 41.2 (**C**H$_2$), 35.5 (**C**H$_2$), 33.2 (**C**H$_2$), 33.1 (**C**H$_2$), 30.7(**C**H$_2$), 28.3 (**C**H$_2$), 26.8 (**C**H$_2$), 25.8 (**C**H$_2$), 25.3 (**C**H$_2$), 24.5 (**C**H$_2$), 24.2 (**C**H$_2$), 24.1 (**C**H$_2$), 22.8 (**C**H$_2$). HRMS (ESI): calcd. for $C_{24}H_{28}N_2NaO_3$, 415.1992. Found: [MNa]$^+$, 415.1994 (–0.4 ppm error).

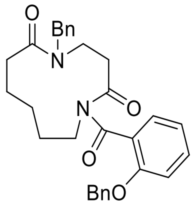
1,2,3,5,6,7,8,9,10,17a-Decahydro-4*H*,12*H*-[1,5]diazacyclododecino[2,1*b*][1,3] benzoxazine-4,12-dione (2-28b)



The byproduct was isolated with the product **2-28** as a colorless solid (15 mg, 14%); R$_f$ 0.50 (9:1 ethyl acetate: menthol); δ_H (400 MHz, CDCl$_3$) 7.92 (dd, *J* = 7.8, 1.7 Hz, 1H, Ar-C**H**), 7.42 (ddd, *J* = 8.2, 7.5, 1.7 Hz, 2H, Ar-C**H**), 7.08 (td, *J* = 1.0, 7.7 Hz, 2H, Ar-C**H**), 6.91 (dd, *J* = 8.2, 1.1 Hz, 1H, Ar-C**H**), 6.08 (t, *J* = 6.3 Hz, 1H, CON**H**), 5.52 (dd, *J* = 8.0, 2.5 Hz, 1H, OC**H**N), 4.20 – 4.00 (m, 1H, C**H**$_2$), 3.74 – 3.23 (m, 4H, 2 × C**H**$_2$), 3.02 (dt, *J* = 14.5, 6.2 Hz, 1H, C**H**$_2$), 2.37 – 2.01 (m, 4H, 2 × C**H**$_2$), 1.85 – 1.68 (m, 6H, 3 × C**H**$_2$); δ_C (100 MHz, CDCl$_3$) 174.5 (**C**O), 161.0 (N**C**OPh), 154.9(Ar-**C**H), 134.2

(Ar-**C**H), 128.3 (Ar-**C**H), 122.5 (Ar-**C**H), 118.4 (Ar-**C**), 117.0 (Ar-**C**H), 84.5(O**C**HN), 40.7 (**C**H$_2$), 37.5 (**C**H$_2$), 35.8 (**C**H$_2$), 31.4 (**C**H$_2$), 25.2 (**C**H$_2$), 24.8 (**C**H$_2$), 22.8 (**C**H$_2$), 14.3 (**C**H$_2$). HRMS (ESI): calcd. for $C_{17}H_{23}N_2NaO_3$, 325.1523. Found: $[MNa]^+$, 325.1518 (1.3 ppm error).

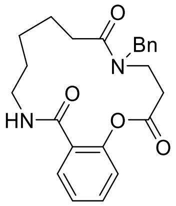
5-Benzyl-1-[2-(benzyloxy)benzoyl]-1,5-diazacycloundecane-2,6-dione (2-29)



A mixture of 11-membered ring lactam **2-9** (109.7 mg, 0.4 mmol), CuO (6.4 mg, 0.08 mmol) and NMM (0.264 mL, 2.4 mmol) in dry benzene (2 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride **2-14** (1.2 mmol, 3.0 equiv., freshly prepared from 2-benzyloxybenzoic acid using the general procedure) in dry benzene (2 mL) was added and the resulting mixture was refluxed at 80 °C for 18 h. The mixture was then diluted with DCM (30 mL) and washed with 10% aq. HCl (30 mL). The aqueous layer was then extracted with DCM (3 × 30 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated in vacuo. Purification by flash column chromatography (SiO_2, 2:1 hexane: ethyl acetate→ 3:2 hexane: ethyl acetate) afforded the *title compound* (as a 10:1 mixture of rotamers) as a colorless oil (180 mg, 93%). R_f = 0.65 (ethyl acetate); δ_H (400 MHz, $CDCl_3$) 7.51 – 7.27 (m, 9H, Ar-C**H**, both rotamers), 7.25 – 7.18 (m, 2H, Ar-C**H**, both rotamers), 7.11 – 6.90 (m, 3H, Ar-C**H**, both rotamers), 5.09 (s, 2H, OC**H$_2$**Ph, both rotamers), 4.82 (d, *J* = 16.6 Hz, 1H, NC**H$_2$**Ph, major rotamer), 4.38 (d, *J* = 16.6 Hz, 1H, NC**H$_2$**Ph, major rotamer), 4.17 – 3.55 (m, 4H, C**H$_2$**, both rotamers), 3.34 – 2.54 (m, 2H, C**H$_2$**, both rotamers), 2.40 – 1.11 (m, 9H, C**H$_2$**, both rotamers); δ_C (100 MHz, $CDCl_3$) for major rotamer: 174.8 (**C**O), 173.1 (**C**O), 172.5 (**C**O), 154.8 (Ar-**C**), 137.6 (Ar-**C**), 136.0 (Ar-**C**), 132.4 (Ar-**C**H), 2 × 128.7 (Ar-**C**H), 2 × 128.6 (Ar-**C**H), 2 × 128.2 (Ar-**C**H), 2 ×127.2 (Ar-**C**H), 126.6 (Ar-**C**), 121.5 (Ar-**C**H), 112.8 (Ar-**C**H), 70.6 (O**C**H$_2$), 47.7 (N**C**H$_2$Ph), 46.4 (N**C**H$_2$), 44.3 (N**C**H$_2$), 37.1 (CO**C**H$_2$), 32.2 (CO**C**H$_2$), 29.1 (**C**H$_2$), 25.3 (**C**H$_2$), 23.8 (**C**H$_2$);

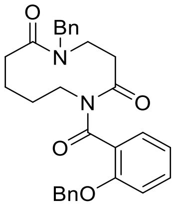
Diagnostic ^{13}C NMR resonances for the minor rotamer: 178.2 (N**C**O), 174.4 (N**C**O), 170.3 (N**C**O), 154.8 (Ar-**C**OBn), 137.3 (Ar-**C**), 136.2 (Ar-**C**), 132.2 (Ar-**C**H), 129.6(Ar-**C**H), 129.2 (Ar-**C**H), 128.9 (Ar-**C**H), 128.3 (Ar-**C**H), 128.1 (Ar-**C**H), 127.6 (Ar-**C**H), 127.3 (Ar-**C**H), 127.2 (Ar-**C**H), 126.3 (Ar-**C)**, 112.9 (Ar-**C**H), 70.7 (O**C**H$_2$Ph), 44.7 (N**C**H$_2$Ph), 36.5 (**C**H$_2$), 26.4 (**C**H$_2$), 22.8 (**C**H$_2$), 22.4 (**C**H$_2$); HRMS (ESI): calcd. for $C_{30}H_{32}N_2NaO_4$, 507.2254. Found: [MNa]$^+$, 507.2261 (–1.3 ppm error).

5-benzyl-4,5,7,8,9,10,11,12-octahydro-1,5,12-benzoxadiazacyclopentadecine-2,6,13(3*H*)-trione (2-30)



This *N*-acylated product **2-29** (175 mg, 0.362 mmol) was re-dissolved in ethyl acetate (4.0 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 RT under a slight positive pressure of hydrogen (balloon) for 16 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 (4.0 mL) and triethylamine (76 µL, 0.543 mmol) added, and stirred at RT for 4 h, then reduced *in vacuo*. Purification by flash column chromatography (SiO_2, 1:3 hexane: ethyl acetate) afforded the *title compound* (as a 10:1 mixture of rotamers) as a colorless oil (82 mg, 57%); R_f = 0.45 (ethyl acetate); δ_H (400 MHz, $CDCl_3$) 7.86 (dd, *J* = 7.8, 1.8 Hz, 1H, Ar-C**H**, major rotamer), 7.44 (td, *J* = 7.8, 1.7 Hz, 1H, Ar-C**H**, major rotamer), 7.53 (dd, *J* = 7.6, 1.8 Hz, 1H, Ar-C**H**, minor rotamer), 7.34 – 7.22 (m, 5H, Ar-C**H**, both rotamers), 7.14 – 7.09 (m, 2H, Ar-C**H**, both rotamers), 6.97 (dd, *J* = 8.1, 1.0 Hz, 1H, Ar-C**H**, major rotamer), 6.49 (t, *J* = 6.0 Hz, 1H, N**H**, major rotamer), 6.24 (t, *J* = 6.1 Hz, 1H, N**H**, minor rotamer), 4.72 (s, 2H, NC**H$_2$**Ph, major rotamer), 4.61 (s, 2H, NC**H$_2$**Ph, minor rotamer), 3.74 (t, *J* = 6.8 Hz, 2H, C**H$_2$**, minor rotamer), 3.61 – 3.55 (m, 3H, C**H$_2$**, major rotamer), 3.44 (q, *J* = 6.0 Hz, 2H, C**H**$_2$, major rotamer), 3.14 – 3.05 (m, 2H, C**H**$_2$, major rotamer), 2.79 (t, *J* = 6.8 Hz, 2H, C**H**$_2$, minor rotamer), 2.51 (t, *J* = 7.4 Hz, 2H, C**H**$_2$, minor rotamer), 2.47 – 2.42 (m, 2H, C**H**$_2$, major rotamer), 1.80 – 1.71 (m, 2H, C**H**$_2$, both rotamers), 1.59 (dt, *J* = 11.6, 6.4 Hz, 2H, C**H**$_2$, both rotamers), 1.46 – 1.35 (m, 2H, C**H**$_2$, both rotamers); δ_C (100 MHz, $CDCl_3$) data for the major rotamer only: 174.5 (**C**O), 171.9 (**C**O), 165.5 (**C**O), 147.6 (Ar-**C**), 137.3 (Ar-**C**), 131.8 (Ar-**C**H), 130.7 (Ar-**C**H), 128.9 (Ar-**C**), 2 × 128.9 (Ar-**C**H), 127.6 (Ar-**C**H), 126.6 (Ar-**C**H), 2 × 126.6 (Ar-**C**H), 122.9 (Ar-**C**H), 54.0 (N**C**H$_2$Ph), 42.6 (**C**H$_2$), 39.5 (**C**H$_2$), 33.1 (**C**H$_2$), 33.1 (**C**H$_2$), 29.2 (**C**H$_2$), 25.4 (**C**H$_2$), 25.1 (**C**H$_2$); Diagnostic ^{13}C NMR resonances for the minor rotamer: 173.9 (**C**O), 169.9 (**C**O), 166.4 (**C**O), 147.9 (Ar-**C**), 137.4 (Ar-**C**), 131.4 (Ar-**C**H), 129.6 (Ar-**C**H), 128.8 (Ar-**C**H), 128.2 (Ar-**C**H), 127.5 (Ar-**C**H), 126.3 (Ar-**C**H), 123.1(Ar-**C**H), 48.7 (N**C**H$_2$Ph), 42.1 (**C**H$_2$), 37.9 (**C**H$_2$), 34.8 (**C**H$_2$), 33.6 (**C**H$_2$), 28.2 (**C**H$_2$), 25.8 (**C**H$_2$), 24.5 (**C**H$_2$); HRMS (ESI): calcd. for $C_{23}H_{26}N_2NaO_4$, 417.1785. Found: [MNa]$^+$, 417.1784 (0.1 ppm error).

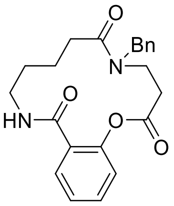
5-Benzyl-1-[2-(benzyloxy)benzoyl]-1,5-diazecane-2,6-dione (2-31)



A mixture of 5-benzyl-1,5-diazecane-2,6-dione **2-10** (103.7 mg, 0.40 mmol), CuO (6.4 mg, 0.08 mmol) and NMM (0.260 mL, 2.4 mmol) in benzene (3.0 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride **2-14** (1.20 mmol, 1.50 equiv., freshly prepared from 2-benzyloxybenzoic acid using the general procedure) in benzene (2 mL) was added and the resulting mixture was refluxed at 80 °C for 18 h. The mixture was then diluted with DCM (30 mL) and washed with 10% aq. HCl (30 mL). The aqueous layer was then extracted with DCM (3 × 30 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 3:2 hexane:ethyl acetate) afforded the *title compound* as a yellow oil (173 mg, 92%). R_f = 0.72 (ethyl acetate); δ_H (400 MHz,

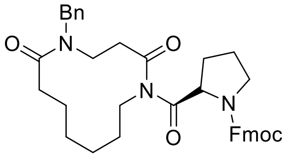
$CDCl_3$) 7.46 – 7.40 (m, 1H, Ar-C**H**), 7.38 – 7.25 (m, 9H, Ar-C**H**), 7.21 – 7.17 (m, 2H, Ar-C**H**), 7.07 – 7.00 (m, 2H, Ar-C**H**), 5.10 (s, 2H, OC**H₂**Ph), 3.90 (s, 2H, NC**H₂**Ph), 3.03 – 2.83 (m, 4H, 2 × C**H₂**), 2.13 – 1.22 (m, 8H, 4 × C**H₂**); δ_C (100 MHz, $CDCl_3$) 173.3 (**C**O), 173.3 (**C**O), 171.3 (**C**O), 155.2 (Ar-**C**), 137.3 (Ar-**C**), 135.9 (Ar-**C**), 132.5(Ar-**C**H), 2 × 128.8 (Ar-**C**H), 2 × 128.7 (Ar-**C**H), 128.5 (Ar-**C**H), 2 × 128.3 (Ar-**C**H), 2 × 127.5 (Ar-**C**H), 126.5 (Ar-**C**), 121.6 (Ar-**C**H), 113.1 (Ar-**C**H), 70.9 (O**C**H₂), 47.8 (N**C**H₂Ph), 46.8 (**C**H₂), 43.0 (**C**H₂), 38.9 (**C**H₂), 29.1 (**C**H₂), 24.7 (**C**H₂), 23.0 (**C**H₂); HRMS (ESI): calcd. for $C_{29}H_{30}N_2NaO_4$, 493.2098. Found: $[MNa]^+$, 493.2099 (–0.1 ppm error).

5-Benzyl-4,5,8,9,10,11-hexahydro-2*H*-1,5,11-benzoxadiazacyclotetradecine-2,6,12(3*H*,7*H*)-trione (2-32)



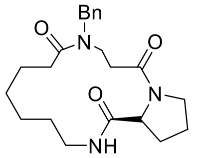
The *N*-acylated product **2-31** (121 mg, 0.257 mmol) was dissolved in ethyl acetate (2.5 mL) and placed under an argon atmosphere. Palladium on carbon (25 mg, Pd 10% on carbon) was then added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at RT under a slight positive pressure of hydrogen (balloon) for 16 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 (2.5 mL) and triethylamine (54 µL, 0.385 mmol) added, and stirred at RT for 16 h, then reduced *in vacuo*. Purification by flash column chromatography (SiO_2, 1:3 hexane: ethyl acetate → ethyl acetate) afforded the *title compound* (as a 10:1 mixture of rotamers) as a colorless oil (93 mg, 95%); R_f = 0.52 (9:1 ethyl acetate: methanol); δ_H (400 MHz, $CDCl_3$) 7.97 (dd, *J* = 7.8, 1.8 Hz, 1H, Ar-C**H**, major rotamer), 7.52 (dd, *J* = 7.6, 1.7 Hz, 1H, Ar-C**H**, minor rotamer), 7.46 (td, *J* = 7.8, 1.8 Hz, 1H, Ar-C**H**, major rotamer), 7.41 (td, *J* = 7.8, 1.7 Hz, 1H, Ar-C**H**, minor rotamer), 7.36 – 7.21 (m, 6H, Ar-C**H**, both rotamers), 7.11 – 7.03 (m, 3H, Ar-**H**, both rotamers), 6.55 (t, *J* = 6.1 Hz, 1H, N**H**, major rotamer), 6.35 (t, *J* = 6.1 Hz, 1H, N**H**, minor rotamer), 4.60 (s, 2H, N**H**$_2$Ph, both rotamers), 3.74 (t, *J* = 7.0 Hz, 2H, C**H**$_2$, minor rotamer), 3.60 (dd, *J* = 6.4, 4.2 Hz, 2H, C**H**$_2$, major rotamer), 3.57 – 3.45 (m, 2H, C**H**$_2$, both rotamers), 3.04 (t, *J* = 5.3 Hz, 2H, C**H**$_2$, major rotamer), 2.69 (t, *J* = 7.0 Hz, 2H, C**H**$_2$, minor rotamer), 2.61 – 2.52 (m, 2H, C**H**$_2$, minor rotamer), 2.46 – 2.32 (m, 2H, C**H**$_2$, major rotamer), 1.85 – 1.55 (m, 5H, 2 × C**H**$_2$, both rotamers); δ_C (100 MHz, $CDCl_3$) data for the major rotamer only: 174.7 (**C**O), 171.4 (**C**O), 165.3 (**C**O), 147.4 (Ar-**C**), 137.3 (Ar-**C**), 131.9 (Ar-**C**H), 131.3 (Ar-**C**H), 2 × 129.0 (Ar-**C**H), 127.9 (Ar-**C**), 2 × 126.7 (Ar-**C**H), 126.4 (Ar-**C**H), 126.4 (Ar-**C**H), 123.1 (Ar-**C**H), 54.4 (N**C**H$_2$Ph), 43.1 (**C**H$_2$), 38.7 (**C**H$_2$), 33.7 (**C**H$_2$), 33.5 (**C**H$_2$), 28.3 (**C**H$_2$), 23.4 (**C**H$_2$); ^{13}C NMR resonances for the minor rotamers: 173.7 (**C**O), 169.4 (**C**O), 166.8 (**C**O), 147.3 (Ar-**C**), 137.2 (Ar-**C**), 130.0 (Ar-**C**), 128.8 (Ar-**C**H), 128.5 (Ar-**C**H), 128.0 (Ar-**C**H), 127.6 (Ar-**C**H), 122.8 (Ar-**C**H), 47.9 (N**C**H$_2$Ph), 42.7 (**C**H$_2$), 37.6 (**C**H$_2$), 34.4 (**C**H$_2$), 33.6 (**C**H$_2$), 29.0 (**C**H$_2$), 22.4 (**C**H$_2$); HRMS (ESI): calcd. for $C_{22}H_{24}N_2NaO_4$, 403.1628. Found: $[MNa]^+$, 403.1634 (–1.5 ppm error).

(9*H*-Fluoren-9-yl)methyl 2-(5-benzyl-2,6-dioxo-1,5-diazacyclododecane-1-carbonyl)pyrrolidine-1-carboxylate (2-33)



A mixture of 12 membered lactam **2-7** (115.4 mg, 0.4 mmol), CuO (6.4 mg, 0.08 mmol) and NMM (0.264 mL, 2.4 mmol) in dry benzene (2 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride **2-13** (1.2 mmol, 3.00 equiv., freshly prepared from Fmoc-Pro-OH using the general procedure) in dry benzene (2 mL) was added and the resulting mixture was refluxed at 80 °C for 18 h. The mixture was then diluted with DCM (30 mL) and washed with 10% aq. HCl (30 mL). The aqueous layer was then extracted with DCM (3 × 30 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated in vacuo. Purification by flash column chromatography (SiO_2, hexane→ 10:1 hexane: ethyl acetate) afforded the *title* *compound* (as 2:1 mixture rotamers) as a colorless oil (198 mg, 81%). R_f = 0.55 (ethyl acetate); δ_H (400 MHz, $CDCl_3$) 7.78 – 7.44 (m, 7H, Ar-C**H**, both rotamers), 7.42 – 7.10 (m, 14H, Ar-C**H**, both rotamers), 4.86 (d, *J* = 17.2 Hz, 1H, NC**H**, major rotamer), 4.77 (dd, *J* = 8.3, 4.4 Hz, 1H, NC**H**, minor rotamer), 4.74 (ddd, *J* = 16.0, 8.4, 3.7 Hz, 1H, NC**H**, major rotamer), 4.51 – 4.21 (m, 7H, COOC$\mathbf{H_2}$ + NC$\mathbf{H_2}$Ph, both rotamers), 4.14 – 4.08 (m, 1H, Fmoc-C**H**, both rotamers), 3.94 – 3.41 (m, 7H, C$\mathbf{H_2}$, both rotamers), 3.27 – 2.70 (m, 3H, C$\mathbf{H_2}$, both rotamers), 2.63 – 2.17 (m, 6H, C$\mathbf{H_2}$, both rotamers), 2.15 – 1.14 (m, 20H, C$\mathbf{H_2}$, both rotamers); δ_C (100 MHz, $CDCl_3$) for major rotamer only: 177.0 (**C**O), 175.1 (**C**O), 174.8 (**C**O), 155.0 (**C**O), 2 × 144.1 (Ar-**C**), 2 × 141.4 (Ar-**C**), 137.1 (Ar-**C**), 129.0 (Ar-**C**H), 2 × 128.8 (Ar-**C**H), 2 × 127.8 (Ar-**C**H), 2 × 127.1 (Ar-**C**H), 2 × 126.6 (Ar-**C**H), 2 × 125.2 (Ar-**C**H), 2 × 120.1 (Ar-**C**H), 67.6 (O**C**H_2), 60.4 (**C**H), 47.3 (Fmoc-**C**H), 47.1 (**C**H_2), 43.8 (**C**H_2), 43.4 (**C**H_2), 37.2 (**C**H_2), 33.0 (**C**H_2), 30.5 (**C**H_2), 27.6 (**C**H_2), 24.6 (**C**H_2), 24.5 (**C**H_2), 23.1 (**C**H_2), 22.3 (**C**H_2); HRMS (ESI): calcd. for $C_{37}H_{41}N_3NaO_5$, 630.2938. Found: $[MNa]^+$, 630.2922 (2.6 ppm error).

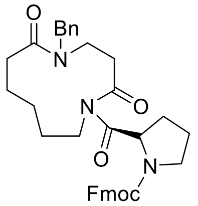
10-Benzyldodecahydro-1*H*-pyrrolo[2,1-*c*][1,4,8]triazacyclopentadecine-1,9,13(2*H*,10*H*)-trione (2-34)



The *N*-acylated product **2-33** (161 mg, 0.265 mmol) was dissolved in DCM (3 mL) and DBU (0.390 mL, 2.6 mmol) was added, followed by stirring at RT overnight, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, ethyl acetate → 9:1 ethyl acetate: methanol) afforded the *title compound* as (as a 10:5:1:1 mixture of rotamers, A:B:C:D) a colorless oil (98 mg, 96%); R_f = 0.25 (9:1 ethyl acetate: methanol); δ_H (400 MHz, $CDCl_3$) 7.35 – 7.08 (m, 10H, Ar-C**H**, all rotamers), 7.05 – 7.00 (m, 2H, N**H**, rotamers A and B), 6.62 (t, *J* = 6.3 Hz, 1H, N**H**, rotamer C), 6.33 (t, *J* = 5.2 Hz, 1H, N**H**, rotamer D), 5.05 – 4.47 (m, 4H, NC$\mathbf{H_2}$Ph, all rotamers), 4.43 (d, *J* = 7.5 Hz, 1H, NC**H**, rotamer A), 4.36 (d, *J* = 3.4 Hz, 1H, NC**H**, rotamer C), 4.34 (d, *J* = 3.5 Hz, 1H, NC**H**, rotamer D), 4.23 – 4.04 (m, 2H, NC$\mathbf{H_2}$Ph +

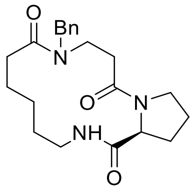
NC**H**, mix rotamers), 3.62 – 2.85 (m, 8H, COC**H**$_2$+ NC**H**$_2$, mix rotamers), 2.57 – 2.00 (m, 12H, NC**H**$_2$ + C**H**$_2$, mix rotamers), 1.97 – 1.16 (m, 22H, C**H**$_2$, all rotamers); δ_C (100 MHz, CDCl$_3$) data for the major rotamer A only: 173.5 (**C**O), 170.8 (**C**O), 170.1 (**C**O), 138.7 (Ar-**C**), 2 × 128.7 (Ar-**C**H), 127.1 (Ar-**C**H), 2 × 126.7 (Ar-**C**H), 60.0 (N**C**H), 49.5 (N**C**H$_2$Ph), 47.2 (**C**H$_2$), 43.8 (**C**H$_2$), 37.6 (**C**H$_2$), 33.3 (**C**H$_2$), 29.6 (**C**H$_2$), 27.7 (**C**H$_2$), 26.8 (**C**H$_2$), 26.1 (**C**H$_2$), 24.8 (**C**H$_2$), 23.6 (**C**H$_2$), 22.7 (**C**H$_2$); ^{13}C NMR resonances for the minor rotamers: 174.9 (**C**O), 174.4 (**C**O), 172.5 (**C**O), 171.7 (**C**O), 171.6 (**C**O), 171.3 (**C**O), 171.0 (**C**O), 169.9 (**C**O), 138.0 (Ar-**C**), 137.4 (Ar-**C**), 137.0 (Ar-**C**), 129.0 (Ar-**C**H), 128.9 (Ar-**C**H), 128.6 (Ar-**C**H), 128.1 (Ar-**C**H), 127.6 (Ar-**C**H), 127.5 (Ar-**C**H), 127.4 (Ar-**C**H), 126.3 (Ar-**C**H), 126.2 (Ar-**C**H), 61.1 (N**C**H), 61.0 (N**C**H), 60.5 (N**C**H), 53.1 (N**C**H$_2$Ph), 52.3 (N**C**H$_2$Ph), 49.0 (N**C**H$_2$Ph), 47.6 (**C**H$_2$), 46.9 (**C**H$_2$), 46.9 (**C**H$_2$), 42.9 (**C**H$_2$), 42.6 (**C**H$_2$), 40.1 (**C**H$_2$), 39.3 (**C**H$_2$), 39.0 (**C**H$_2$), 34.5 (**C**H$_2$), 34.3 (**C**H$_2$), 33.3 (**C**H$_2$), 32.6 (**C**H$_2$), 32.1 (**C**H$_2$), 31.9 (**C**H$_2$), 29.3 (**C**H$_2$), 28.9 (**C**H$_2$), 28.7 (**C**H$_2$), 28.4 (**C**H$_2$), 28.2 (**C**H$_2$), 27.3 (**C**H$_2$), 26.3 (**C**H$_2$), 25.7 (**C**H$_2$), 25.5 (**C**H$_2$), 24.7 (**C**H$_2$), 24.5 (**C**H$_2$), 23.2 (**C**H$_2$), 22.8 (**C**H$_2$), 22.8 (**C**H$_2$), 22.7 (**C**H$_2$); HRMS (ESI): calcd. for $C_{22}H_{31}N_3NaO_5$, 408.2258. Found: [MNa]$^+$, 408.2260 (–0.5 ppm error).

(9*H*-Fluoren-9-yl)methyl 2-(5-benzyl-2,6-dioxo-1,5-diazacycloundecane-1 carbonyl)pyrrolidine-1-carboxylate (2-35)



A mixture of 11-membered ring lactam **2-9** (109.7 mg, 0.4 mmol), CuO (6.4 mg, 0.08 mmol) and NMM (0.264 mL, 2.4 mmol) in dry benzene (2 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride **2-13** (1.2 mmol, 3.0 equiv., freshly prepared from Fmoc-Pro-OH using the general procedure) in dry benzene (2 mL) was added and the resulting mixture was refluxed at 80 °C for 18 h. The mixture was then diluted with DCM (30 mL) and washed with 10% aq. HCl (30 mL). The aqueous layer was then extracted with DCM (3 × 30 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated in vacuo. Purification by flash column chromatography (SiO_2, 2:1 hexane: ethyl acetate→ 2:3 hexane: ethyl acetate) afforded the *title compound* (as a 5:2 mixture of rotamers,) as a colorless oil (194 mg, 82%). R_f = 0.55 (ethyl acetate); δ_H (400 MHz, $CDCl_3$) 7.79 – 7.45 (m, 7H, Ar-C**H**, both rotamers), 7.43 – 7.09 (m, 14H, Ar-C**H**, both rotamers), 4.74 (ddd, *J* = 16.0, 8.4, 3.7 Hz, 1H, NC**H**, major rotamer), 4.67 (dd, *J* = 10.9, 6.4 Hz, 1H, NC**H**, minor rotamer), 4.48 – 4.22 (m, OC**H₂** + NC**H₂**Ph, 7H, both rotamers), 4.11 (t, *J* = 6.1 Hz, 1H, Fmoc-C**H**, minor rotamer), 4.01 – 3.88 (m, 1H, Fmoc-C**H**, major rotamer), 3.84 – 3.01 (m, 9H, C**H₂**, both rotamers), 2.83 – 2.08 (m, 7H, C**H₂**, both rotamers), 2.06 – 1.19 (m, 15H, C**H₂**, both rotamers); δ_C (100 MHz, $CDCl_3$) for major rotamers only: 178.8 (**C**O), 176.2 (**C**O), 173.6 (**C**O), 155.0 (**C**OO), 144.1 (Ar-**C**), 143.9 (Ar-**C**), 2 × 141.4 (Ar-**C**), 137.3 (Ar-**C**), 2 × 129.1 (Ar-**C**H), 2 × 128.7 (Ar-**C**H), 2 × 127.8 (Ar-**C**H), 127.5 (Ar-**C**H), 2 × 127.1 (Ar-**C**H), 2 × 126.7 (Ar-**C**H), 125.3 (Ar-**C**H), 2 × 120.1 (Ar-**C**H), 67.7 (COO**C**H₂), 60.3 (CO**C**H), 47.3 (N**C**H₂Ph), 47.3 (Fmoc-**C**H), 47.1 (**C**H₂), 45.1 (**C**H₂), 44.0 (**C**H₂), 43.2 (**C**H₂), 32.0 (**C**H₂), 30.8 (**C**H₂), 29.6 (**C**H₂), 27.7 (**C**H₂), 24.3 (**C**H₂), 23.6(**C**H₂); HRMS (ESI): calcd. for $C_{36}H_{39}N_3NaO_5$, 616.2782. Found: $[MNa]^+$, 616.3785 (–0.5 ppm error).

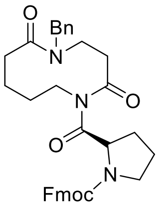
9-Benzyldodecahydropyrrolo[2,1-*c*][1,4,8]triazacyclotetradecine-1,8,12(9*H*)-trione (2-36)



The *N*-acylated product **2-35** (155 mg, 0.261 mmol) was re-dissolved in DCM (3 mL) and DBU (0.390 mL, 2.6 mmol) was added, followed by stirring at RT overnight, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, ethyl acetate → 9:1 ethyl acetate: methanol) afforded the *title compound* as (as a 20:1 mixture of rotamers) a colorless oil (87 mg, 90%); R_f = 0.18 (9:1 ethyl acetate:

methanol); δ_H (400 MHz, $CDCl_3$) 7.36 – 7.27 (m, 3H, Ar-C**H**, both rotamers), 7.20 – 7.16 (m, 2H, Ar-C**H**, both rotamers), 4.83 (d, *J* = 16.8 Hz, 1H, NC**H**$_2$Ph, major rotamer), 4.63 (d, *J* = 16.9 Hz, 1H, NC**H**$_2$Ph, major rotamer), 4.79 – 4.67 (m, 2H, NC**H$_2$**Ph, minor rotamer), 4.57 (d, *J* = 1.9 Hz, 1H, NC**H**, minor rotamer), 4.51 (dd, *J* = 8.5, 2.1 Hz, 1H, NC**H**, major rotamer), 4.43 (ddd, *J* = 13.2, 9.8, 3.2 Hz, 1H, NC**H$_2$**, major rotamer), 4.34 – 4.30 (m, 1H, NC**H**$_2$, minor rotamer), 3.75 (ddd, *J* = 9.7, 8.0, 2.5 Hz, 1H, NC**H**$_2$, major rotamer), 3.40 (qd, *J* = 9.8, 5.8 Hz, 2H, NC**H$_2$**, major rotamer), 3.33 – 3.18 (m, 1H, NHC**H**$_2$, major rotamer), 3.00 (ddd, *J* = 13.6, 6.2, 4.5 Hz, 1H, NHC**H**$_2$, major rotamer), 2.89 (ddd, *J* = 14.8, 6.2, 3.5 Hz, 1H, C**H**$_2$, major rotamer), 2.55 (ddd, *J* = 14.8, 11.5, 3.0 Hz, 1H, C**H$_2$**, major rotamer), 2.41 (ddd, *J* = 14.5, 9.7, 4.5 Hz, 1H, C**H**$_2$, major rotamer), 2.28 (ddt, *J* = 11.4, 8.7, 3.0 Hz, 1H, C**H$_2$**, major rotamer), 2.14 (ddd, *J* = 15.2, 5.7, 3.2 Hz, 1H, C**H**$_2$, major rotamer), 2.08 – 1.73 (m, 4H, C**H$_2$**, both rotamers), 1.69 – 1.58 (m, 1H, C**H**$_2$, major rotamer), 1.43 (dddd, *J* = 16.0, 8.4, 5.5, 2.8 Hz, 1H, C**H**$_2$, major rotamer), 1.38 – 1.14 (m, 3H, C**H$_2$**, both rotamers); δ_C (100 MHz, $CDCl_3$) data for the major rotamer only: 175.0 (**C**O), 171.4 (**C**O), 171.1 (**C**O), 136.9 (Ar-**C**), 2 × 129.0 (Ar-**C**H), 127.7 (Ar-**C**H), 2 × 126.6 (Ar-**C**H), 61.0 (N**C**H), 52.5 (N**C**H$_2$Ph), 47.4 (**C**H$_2$), 42.6 (**C**H$_2$), 36.8 (**C**H$_2$), 33.8 (**C**H$_2$), 32.4 (**C**H$_2$), 28.4 (**C**H$_2$), 26.9 (**C**H$_2$), 24.8 (**C**H$_2$), 23.4 (**C**H$_2$), 21.8 (**C**H$_2$); ^{13}C NMR resonances for the minor rotamers: 173.8 (**C**O), 171.7 (**C**O), 171.5 (**C**O), 137.7 (Ar-**C**), 128.8 (Ar-**C**H), 127.4 (Ar-**C**H), 126.6 (Ar-**C**H), 61.2 (N**C**H), 53.2 (N**C**H$_2$Ph), 46.8 (**C**H$_2$), 42.0 (**C**H$_2$), 38.1 (**C**H$_2$), 34.8 (**C**H$_2$), 31.8 (**C**H$_2$), 29.7 (**C**H$_2$), 26.4 (**C**H$_2$), 25.1 (**C**H$_2$), 24.3 (**C**H$_2$), 22.4 (**C**H$_2$); HRMS (ESI): calcd. for $C_{21}H_{29}N_3NaO_3$, 394.2101. Found: $[MNa]^+$, 394.2101 (0.0 ppm error).

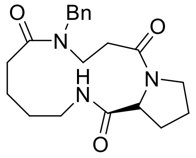
(9*H*-Fluoren-9-yl)methyl 2-(5-benzyl-2,6-dioxo-1,5-diazecane-1-carbonyl)pyrrolidine-1-carboxylate (2-37)



A mixture of 5-Benzyl-1,5-diazecane-2,6-dione **2-10** (103.7 mg, 0.4 mmol), CuO (6.4

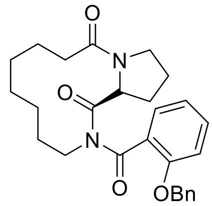
mg, 0.08 mmol) and NMM (0.260 mL, 2.4 mmol) in benzene (3.0 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride **2-13** (1.2 mmol, 1.50 equiv., freshly prepared from Fmoc-Pro-OH using the general procedure) in benzene (2 mL) was added and the resulting mixture was refluxed at 80 °C for 18 h. The mixture was then diluted with DCM (30 mL) and washed with 10% aq. HCl (30 mL). The aqueous layer was then extracted with DCM (3 × 30 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 hexane: ethyl acetate → 1:3 hexane: ethyl acetate) afforded the *title compound* as a pale yellow oil (150 mg, 65%). R_f = 0.20 (9:1 ethyl acetate: methanol); δ_H (400 MHz, $CDCl_3$) 7.77 – 7.11 (m, 13H, Ar-C**H**), 4.79 (dd, *J* = 8.7, 3.6 Hz, 1H, NC**H**), 4.43 – 4.21 (m, 4H, NC**H**$_2$Ph + COOC**H**$_2$), 4.00 – 3.86 (m, 1H, Fmoc-C**H**), 3.82 – 3.48 (m, 4H, C**H**$_2$), 3.34 – 3.02 (m, 4H, C**H**$_2$), 2.46 – 2.14 (m, 4H, C**H**$_2$), 1.86 – 1.54 (m, 6H, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 173.4 (**C**O), 173.4 (**C**O), 171.3 (**C**O), 155.0 (**C**OO), 144.0 (Ar-**C**), 143.8 (Ar-**C**), 141.4 (Ar-**C**), 141.4 (Ar-**C**), 137.3 (Ar-**C**H), 2 × 128.7 (Ar-**C**H), 2 × 128.4 (Ar-**C**H), 2 × 127.8 (Ar-**C**H), 2 × 127.5 (Ar-**C**H), 2 × 125.3 (Ar-**C**H), 2 × 120.1 (Ar-**C**H), 67.8 (O**C**H$_2$), 60.0 (O**C**H), 47.2 (N**C**H$_2$Ph), 47.1 (Fmoc-**C**H), 47.0 (**C**H$_2$), 45.2 (**C**H$_2$), 43.4 (**C**H$_2$), 38.6 (**C**H$_2$), 30.0 (**C**H$_2$), 29.2 (**C**H$_2$), 24.8 (**C**H$_2$), 24.3 (**C**H$_2$), 24.3 (**C**H$_2$); HRMS (ESI): calcd. for $C_{35}H_{37}N_3NaO_5$, 602.2625. Found: $[MNa]^+$, 602.2634 (–1.4 ppm error).

8-Benzyldecahydro-1*H*-pyrrolo[2,1-*c*][1,4,8]triazacyclotridecine-1,7,11(2*H*,8*H*)-trione (2-38)



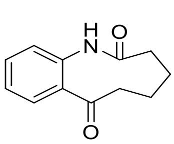
The *N*-acylated product **2-37** (133 mg, 0.23 mmol) was then re-dissolved in DCM (4 mL) and DBU (0.6 mL, 4 mmol) was added, followed by stirring at RT overnight, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 5:4 hexane: ethyl acetate → 9:1 ethyl acetate: methanol) afforded the *title* *compound* as (as a 2:1 mixture of rotamers) a colorless oil (83 mg, 98%); R_f = 0.21 (9:1 ethyl acetate: methanol); δ_H (400 MHz, $CDCl_3$) 7.39 – 7.16 (m, 9H, Ar-C**H**, both rotamers), 7.07 (t, *J* = 4.5 Hz, 1H, N**H**, major rotamer), 4.77 (d, *J* =17.1 Hz, 1H, NC**H**, major rotamer), 4.68 (d, *J* = 6.9 Hz, 1H, NC**H**, minor rotamer), 4.59 – 4.49 (m, 2H, NC**H**$_2$Ph, both rotamers), 3.97 – 3.20 (m, 6H, C**H**$_2$, both rotamers), 3.12 – 2.23 (m, 10H, C**H**$_2$, both rotamers), 2.21 – 1.50 (m, 15H, C**H**$_2$, both rotamers); δ_C (100 MHz, $CDCl_3$) data for the major rotamer: 176.3 (**C**O), 171.4 (**C**O), 170.1 (**C**O), 136.4 (Ar-**C**), 2 × 129.1 (Ar-**C**H), 128.3 (Ar-**C**H), 2 × 126.6 (Ar-**C**H), 61.4 (NC**H**), 49.9 (N**C**H$_2$Ph), 48.0 (**C**H$_2$), 47.5 (NH$_2$), 39.1(**C**H$_2$), 33.5(**C**H$_2$), 32.0 (**C**H$_2$), 29.0 (**C**H$_2$), 25.3 (**C**H$_2$), 25.0 (**C**H$_2$), 22.3 (**C**H$_2$); ^{13}C NMR resonances for the minor rotamer: 172.7 (**C**O), 171.8 (**C**O), 169.8 (**C**O), 137.7 (Ar-**C**), 128.9 (Ar-**C**H), 127.9 (Ar-**C**H), 127.6 (Ar-**C**H), 59.6 (N**C**H$_2$Ph), 47.9 (N**C**H$_2$Ph), 40.7 (**C**H$_2$), 33.5 (**C**H$_2$), 33.0 (**C**H$_2$), 29.1 (**C**H$_2$), 26.8 (**C**H$_2$), 26.3 (**C**H$_2$), 23.8 (**C**H$_2$); HRMS (ESI): calcd. for $C_{20}H_{27}N_3NaO_3$, 380.1945. Found: $[MNa]^+$, 380.1942 (0.6 ppm error).

2-[2-(Benzyloxy)benzoyl]dodecahydropyrrolo[1,2-*a*][1,4]diazacyclododecine-1,10-dione (2-39)



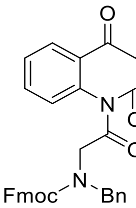
A mixture of 12-membered lactam **2-11** (95.3 mg, 0.4 mmol), CuO (6.4 mg, 0.08 mmol) and NMM (0.264 mL, 2.4 mmol) in dry benzene (2 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride **2-14** (1.2 mmol, 3.0 equiv., freshly prepared from 2-benzyloxybenzoic acid using the general procedure) in dry benzene (2 mL) was added and the resulting mixture was refluxed at 80 °C for 18 h. The mixture was then diluted with DCM (30 mL) and washed with 10% aq. HCl (30 mL). The aqueous layer was then extracted with DCM (3 × 30 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated in vacuo. Purification by flash column chromatography (SiO_2, 1:1 hexane: ethyl acetate→ ethyl acetate) afforded the *title compound* (as a 10:1 mixture of rotamers) as a pale-yellow oil (130 mg, 73%). R_f = 0.40 (ethyl acetate); δ_H (400 MHz, $CDCl_3$) 7.95 (dd, *J* = 7.7, 1.8 Hz, 1H, Ar-C**H**, minor rotamer), 7.44 (ddd, *J* = 8.3, 7.5, 1.7 Hz, 1H, Ar-C**H**, major rotamer), 7.38 – 7.27 (m, 6H, Ar-C**H**, both rotamers), 7.08 – 7.01 (m, 2H, Ar-C**H**, both rotamers), 5.10 – 4.95 (m, 2H, OC**H**$_2$Ph, both rotamers), 4.40 (ddd, *J* = 14.2, 10.9, 3.0 Hz, 1H, NC**H**, major rotamer), 3.96 (ddd, *J* = 13.4, 7.6, 2.7 Hz, 1H, NC**H**, minor rotamer), 3.65 (dt, *J* = 11.8, 5.7 Hz, 2H, C**H**$_2$, both rotamers), 3.53 – 3.42 (m, 1H, C**H**$_2$, both rotamers), 3.25 (dt, *J* = 14.4, 4.0 Hz, 1H, C**H**$_2$, both rotamers), 2.41 (dt, *J* = 13.9, 7.2 Hz, 1H, C**H**$_2$, both rotamers), 2.09 – 1.91 (m, 2H, C**H**$_2$, both rotamers), 1.71 – 1.50 (m, 6H, C**H**$_2$, both rotamers), 1.43 – 1.08 (m, 8H, C**H**$_2$, both rotamers); δ_C (100 MHz, $CDCl_3$) data for the major rotamer only: 175.9 (**C**O), 172.9 (**C**O), 172.6 (**C**O), 154.4 (Ar-**C**), 135.7 (Ar-**C**), 132.3 (Ar-**C**H), 128.7 (Ar-**C**H), 128.7 (Ar-**C**H), 2 × 128.5 (Ar-**C**H), 2 × 127.7 (Ar-**C**H), 125.8 (Ar-**C**), 121.4 (Ar-**C**H), 112.2 (Ar-**C**H), 70.6 (O**C**H$_2$Ph), 61.9 (N**C**H), 46.8 (**C**H$_2$), 46.5 (**C**H$_2$), 32.3 (**C**H$_2$), 30.7 (**C**H$_2$), 26.9 (**C**H$_2$), 26.7 (**C**H$_2$), 26.2 (**C**H$_2$), 24.9 (**C**H$_2$), 23.2 (**C**H$_2$), 22.1 (**C**H$_2$); Diagnostic ^{13}C NMR resonances for the minor rotamer: 177.0 (**C**O), 171.2 (**C**O), 154.8 (Ar-**C**), 135.9 (Ar-**C**), 132.5 (Ar-**C**H), 128.1 (Ar-**C**H), 127.4 (Ar-**C**), 127.2 (Ar-**C**H), 121.8 (Ar-**C**H), 112.4 (Ar-**C**H), 70.8 (O**C**H$_2$Ph), 60.4 (N**C**H), 58.0 (**C**H$_2$), 44.8 (**C**H$_2$), 34.7 (**C**H$_2$), 27.4 (**C**H$_2$), 25.9 (**C**H$_2$), 25.1 (**C**H$_2$), 23.6 (**C**H$_2$), 22.8 (**C**H$_2$), 21.1 (**C**H$_2$); HRMS (ESI): calcd. for $C_{27}H_{32}N_2NaO_4$, 471.2254. Found: $[MNa]^+$, 471.2249 (1.1 ppm error).

3,4,5,6-Tetrahydro-1H-(1)-benzazonin-2,7-dione (3-8)



A solution of 1,2,3,4-Tetrahydrocarbazole (2.16g, 14.7 mmol) in methanol (75 mL) was added a solution of sodium periodate (6.92 g, 32.3 mmol) in water (35 mL). The mixture became warm and stirred for 2.5 h at RT. Upon completion, the aqueous solution was extracted with dichloromethane (100 mL × 2) and the organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Recrystallization from ethyl acetate afforded the *title compound* as a needle-like crystals (2920 mg, 98%); R$_f$ = 0.40 (ethyl acetate); m.p. 155–158 °C; ν_{max} /cm^{-1} (thin film) 3443, 2249, 2124, 1582; δ_H (400 MHz, CDCl$_3$) 8.18 (s, 1H, N**H**), 7.59 (d, *J* = 7.5 Hz, 1H, Ar-C**H**), 7.50 (td, *J* = 7.5, 1.7 Hz, 1H, Ar-C**H**), 7.39 (dd, *J* = 7.8, 7.5 Hz, 1H, Ar-C**H**), 7.24 (dd, *J* = 7.9, 1.2 Hz, 1H, Ar-C**H**), 2.88 (t, *J* =5.7 Hz, 2H, C**H₂**CO), 2.34 – 2.16 (m, 2H, C**H**$_2$), 1.94 – 1.74 (m, 4H, 2 × C**H**$_2$); δ_C (100 MHz, CDCl$_3$) 206.2 (**C**OC), 176.8 (**C**ONH), 139.0 (Ar-**C**), 134.6 (Ar-**C**), 132.3 (Ar-**C**H), 128.8 (Ar-**C**H), 128.5 (Ar-**C**H), 128.1 (Ar-**C**H), 41.4 (**C**H$_2$), 32.4 (**C**H$_2$), 24.8 (**C**H$_2$), 24.6 (**C**H$_2$); HRMS (ESI): calcd. for $C_{12}H_{13}NNaO_2$, 226.0838. Found: [MNa]$^+$, 226.0843 (–1.8 ppm error).

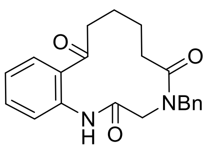
N-(*N*-Fmoc-sarcosine)-3,4,5,6-tetrahydro-1H-(1)-benzazonin-2,7-dione (3-14)



3,4,5,6-Tetrahydro-1H-(1)-benzazonin-2,7-dione **3-8** (203 mg, 1.00 mmol), CuO (8.0 mg, 0.10 mmol) and NMM (0.66 mL, 6.00 mmol) were stirred in benzene (6 mL) under an argon atmosphere at RT for 30 mins. To the stirred solution was added *N*-Fmoc-*N*-benzyl-2-aminoethanoyl chloride (**3-13**, 3.00 mmol, 3.00 eq. prepared using the general procedure) in benzene (4 mL). The resulting mixture was stirred at RT for 18 h. Upon completion by TLC the reaction mixture was concentrated *in vacuo*. Purification by flash column chromatography (SiO$_2$, 2:1 hexane: ethyl acetate → 1:1 hexane: ethyl acetate → ethyl acetate) afforded the *title compound* (as a 2:1 mixture of rotamers) as a yellow oil (400 mg, 70%); R$_f$ = 0.30 (1:1 ethyl acetate: hexane); $_H$ (400 MHz, CDCl$_3$) 7.75 (ddd, *J* = 16.2, 7.5, 2.8 Hz, 2H, Ar-C**H**, both rotamers), 7.63 – 7.44 (m, 5H, Ar-C**H**, both rotamers), 7.42 – 7.16 (m, 10H, Ar-C**H**, both rotamers), 4.88 – 4.56 (m, 2H, CHC**H₂**O, both rotamers), 4.53 – 4.18 (m, 5H, 2 × NC**H**$_2$ + C**H**CH$_2$O, both rotamers), 3.05 – 2.84 (m, 1H, C**H**$_2$, both rotamers), 2.65 – 2.39 (m, 2H, C**H₂**, both rotamers), 2.12 – 1.92 (m, 2H, C**H₂**, both rotamers), 1.89 – 1.66 (m, 2H C**H₂**, both rotamers), 1.63 – 1.49 (m, 1H, C**H**$_2$, both rotamers); δ_C (100 MHz, CDCl$_3$) data for the major rotamer:

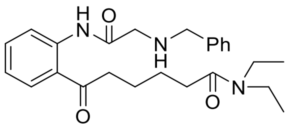
206.0 (**C**OC), 176.6 (N**C**O), 172.7 (NCH$_2$**C**ON), 156.8 (O**C**ON), 144.0 (Ar-**C**), 143.9 (Ar-**C**), 141.4 (Ar-**C**), 141.3 (Ar-**C**), 139.8 (Ar-**C**), 137.3 (Ar-**C**), 135.2 (Ar-**C**), 131.7(Ar-**C**H), 130.4 (Ar-**C**H), 129.3 (Ar-**C**H), 128.8 (Ar-**C**H), 128.7 (Ar-**C**H), 128.4 (Ar-**C**H), 127.7 (Ar-**C**H), 127.2 (Ar-**C**H), 127.2 (Ar-**C**H), 127.0 (Ar-**C**H), 125.2 (Ar-**C**H), 125.1 (Ar-**C**H), 120.0 (Ar-**C**H), 120.0 (Ar-**C**H), 68.0 (**C**H$_2$OCO), 53.4 (N**C**H$_2$CO), 51.7 (N**C**H$_2$Ph), 47.2 (CH$_2$**C**H), 43.2 (**C**H$_2$CON), 37.4 (CO**C**H$_2$), 25.7 (**C**H$_2$), 25.7 (**C**H$_2$); Diagnostic ^{13}C NMR resonances for the minor rotamer: 205.8 (**C**OC), 176.5 (N**C**OCH$_2$), 172.2 (NCH2**C**ON), 156.7 (O**C**ON), 144.3 (Ar-**C**), 144.2 (Ar-**C**), 141.5 (Ar-**C**), 141.4 (Ar-**C**), 139.8 (Ar-**C**), 137.2 (Ar-**C**), 135.0 (Ar-**C**), 131.7 (Ar-**C**H), 130.3 (Ar-**C**H), 129.4 (Ar-**C**H), 127.8 (Ar-**C**H), 127.7 (Ar-**C**H), 127.6 (Ar-**C**H), 127.6 (Ar-**C**H), 127.2 (Ar-**C**H), 127.1 (Ar-**C**H), 125.2 (Ar-**C**H), 125.2 (Ar-**C**H), 120.0 (Ar-**C**H), 67.6 (**C**H$_2$OCO), 52.6 (N**C**H$_2$CO), 51.7 (N**C**H$_2$Ph), 47.5 (CH$_2$**C**H), 43.1 (**C**H$_2$CON), 37.5 (CO**C**H$_2$), 25.7 (**C**H$_2$); HRMS (ESI): calcd. for $C_{36}H_{32}N_2NaO_5$, 595.2203. Found: [MNa]$^+$, 595.2203 (0.1 ppm error).

4-Benzyl-3,4,6,7,8,9-hexahydrobenzo[*e*][1,4]diazacyclododecine-2,5,10(1*H*)-trione (3-16)



3,4,5,6-Tetrahydro-1H-(1)-benzazonin-2,7-dione **3-8** (203.2 mg, 1.0 mmol), DMAP (12.2 mg, 0.2 mmol) and pyridine (0.48 mL, 12.0 mmol) were stirred in DCM (5 mL) under an inert atmosphere at RT for 30 mins. To the stirred solution was added *N*-carboxybenzyl-*N*-methyl-3-aminoethanonyl chloride (3.0 mmol, 3.00 eq. prepared using the modified general procedure) in DCM (5 mL). The resulting mixture was heated, at reflux, at 50 °C for 18 h. The solvent was concentrated in *vacuo*, loaded onto a short silica plug and eluted with 2:1 hexane: ethyl acetate→ 1:1 hexane: ethyl acetate to remove the excess carboxylic acid and pyridine, and concentrated in *vacuo*. This material was redissolved in methanol (10.0 mL) under an inert atmosphere. Palladium on carbon (100 mg, Pd 10% on carbon) was then added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at RT under a slight positive pressure of hydrogen (balloon) for 1.5 h. The reaction was then purged with argon, filtered through Celite, washed with methanol and the solvent removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 hexane: ethyl acetate) afforded the *title compound* (as a 10:3:1 A:B:C mixture of rotamers) as a white solid (168 mg, 48% over 2 steps); R_f = 0.23 (1:2 hexane: ethyl acetate); mp. 135– 137 °C; δ_H (400 MHz, $CDCl_3$-*d*) 9.54 (s, 1H, N**H**, rotamer C), 9.29 (s, 1H, N**H**, rotamer A), 9.03 (s, 1H, N**H**, rotamer B), 7.93 – 6.99 (m, 12H, Ar-C**H**, all rotamers), 5.08 (d, *J* = 16.8 Hz, 1H, NC**H**$_2$, rotamer C), 4.80 (d, *J* = 16.1 Hz, 1H, NC**H**$_2$, rotamer A), 4.65 (d, *J* = 16.1 Hz, 1H, NC**H**$_2$, rotamer A), 4.66 (s, 2H, NC**H$_2$**, rotamer B), 4.36 (d, *J* = 16.9 Hz, 1H, NC**H**$_2$, rotamer C), 4.07 (d, *J* = 15.9 Hz, 1H, NC**H**$_2$, rotamer A), 3.88 (s, 2H, , NC**H$_2$**, rotamer B), 3.44 (d, *J* = 15.8 Hz, 1H, NC**H**$_2$, rotamer A), 3.27 (d, *J* = 15.1 Hz, 1H, NC**H**$_2$, rotamer C), 3.11 – 2.64 (m, 3H, C**H$_2$**, all rotamers), 2.41 – 1.70 (m, 8H, 3 × C**H$_2$**, all rotamers); δ_C (100 MHz, $CDCl_3$-*d*) NMR resonances for the rotamer A: 207.5 (**C**O), 175.3 (**C**O), 170.1 (**C**O), 136.0 (Ar-**C**), 134.6 (Ar-**C**), 133.1 (Ar-**C**), 131.4 (Ar-**C**H), 129.2 (Ar-**C**H), 128.2 (Ar-**C**H), 127.3 (Ar-**C**H), 126.7 (Ar-**C**H), 125.0 (Ar-**C**H), 124.2 (Ar-**C**H), 53.3 (N**C**H$_2$), 53.3 (N**C**H$_2$), 42.2 (**C**H$_2$), 33.8 (**C**H$_2$), 23.0 (**C**H$_2$), 22.1 (**C**H$_2$); ^{13}C NMR resonances for the rotamer B and C: 204.9 (**C**O), 176.7 (**C**O), 173.8 (**C**O), 169.0 (**C**O), 166.9 (**C**O), 137.0 (Ar-**C**), 135.9 (Ar-**C**), 133.5 (Ar-**C**), 131.6 (Ar-**C**), 129.0 (Ar-**C**H), 128.8 (Ar-**C**H), 128.6 (Ar-**C**H), 127.9 (Ar-**C**H), 127.7 (Ar-**C**H), 126.6 (Ar-**C**H), 126.1 (Ar-**C**H), 125.9 (Ar-**C**H), 51.4 (N**C**H$_2$), 51.2 (N**C**H$_2$), 38.8 (**C**H$_2$), 30.0 (**C**H$_2$), 25.0 (**C**H$_2$), 23.8 (**C**H$_2$), 21.3 (**C**H$_2$); HRMS (ESI): calcd. for $C_{21}H_{22}N_2NaO_3$, 373.1523. Found: $[MNa]^+$, 373.1522 (0.1 ppm error).

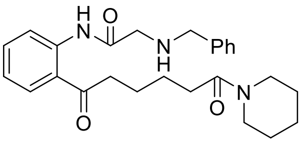
5-(2-[(*N*-benzylglycyl) amino] phenyl)-*N*, *N*-diethyl-5-oxopentanamide (3-17a)



N-(*N*-Fmoc-sarcosine)-3,4,5,6-tetrahydro-1H-(1)-benzazonin-2,7-dione **3-14** (57 mg, 0.1 mmol) was dissolved in 20% $NHEt_2$ in dioxane (1 mL) and stirred at RT for 1 h.

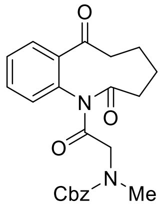
Purification by flash column chromatography (SiO_2, 1:1 hexane: ethyl acetate → ethyl acetate) afforded the *title compound* as a colorless oil (17 mg, 40%); $R_f = 0.30$ (ethyl acetate); δ_H (400 MHz, $CDCl_3$) δ 12.42 (s, 1H, CON**H**), 8.76 (dd, *J* = 8.5, 1.1 Hz, 1H, Ar-C**H**), 7.91 (dd, *J* = 8.0, 1.5 Hz, 1H, Ar-C**H**), 7.52 (ddd, *J* = 8.6, 7.5, 1.5 Hz, 1H, Ar-C**H**), 7.49 – 7.44 (m, 2H, Ar-C**H**), 7.35 – 7.29 (m, 2H, Ar-C**H**), 7.28 – 7.21 (m, 1H, Ar-C**H**), 7.15 – 7.09 (m, 1H, Ar-C**H**), 3.91 (s, 2H, NHC**H$_2$**), 3.50 (s, 2H, NHC**H$_2$**), 3.35 (q, *J* = 7.1 Hz, 2H, NC**H$_2$**CH_3), 3.28 (q, *J* = 7.1 Hz, 2H, NC**H$_2$**CH_3), 3.09 – 3.00 (m, 2H, COC**H$_2$**), 2.76 (brs, 1H, N**H**), 2.34 (t, *J* = 7.0Hz, 2H, NCOC**H$_2$**), 1.87 – 1.63 (m, 4H, C**H$_2$**), 1.15 (t, *J* = 7.1 Hz, 3H, NCH_2C**H$_3$**), 1.09 (t, *J* = 7.1 Hz, 3H, NCH_2C**H$_3$**); δ_C (100 MHz, $CDCl_3$) 204.0 (**C**O), 171.7 (N**C**O), 171.2 (NH**C**O), 140.0 (Ar-**C**), 138.9 (Ar-**C**), 134.7 (Ar-**C**H), 130.7 (Ar-**C**H), 128.7 (Ar-**C**H), 128.6 (Ar-**C**H), 127.5 (Ar-**C**H), 122.8 (Ar-**C**), 122.8 (Ar-**C**H), 121.3 (Ar-**C**H), 53.8 (NH**C**H_2), 52.9 (NH**C**H_2), 42.0 (CO**C**H_2), 40.2 (N**C**H_2CH_3), 40.1 (N**C**H_2CH_3), 33.0 (NCO**C**H_2), 25.1 (**C**H_2), 24.5 (**C**H_2), 14.5 (NCH_2**C**H_3), 13.2 (NCH_2**C**H_3); HRMS (ESI): calcd. for $C_{25}H_{33}N_3NaO_3$, 446.2414. Found: $[MNa]^+$, 446.2419 (–1.1 ppm error).

***N*-Benzyl-*N*-(2-[5-oxo-5-(piperidin-1-yl)pentanoyl]phenyl)glycinamide (3-17b)**



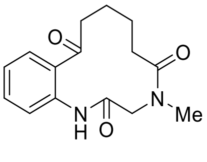
The *N*-(*N*-Fmoc-sarcosine)-3,4,5,6-tetrahydro-1H-(1)-benzazonin-2,7-dione **3-14** (57 mg, 0.1 mmol) was dissolved in DCM (1 mL) and piperidine (99 µL, 10 eq) added, the mixture was stirred at RT for 18 h. Purification by flash column chromatography (SiO_2, 1:1 hexane: ethyl acetate → ethyl acetate) afforded the *title compound* (as a 2:1 mixture of rotamers) as a yellow oil (15 mg, 35%); $R_f = 0.15$ (1:1 hexane: ethyl acetate); δ_H (400 MHz, $CDCl_3$) 12.45 (s, 1H, CON**H**), 8.78 (dd, *J* = 8.5, 1.1 Hz, 1H, Ar-C**H**), 7.91 (dd, *J* = 8.0, 1.5 Hz, 1H, Ar-C**H**), 7.53 (ddd, *J* = 8.6, 7.4, 1.5 Hz, 1H, Ar-C**H**), 7.49 – 7.43 (m, 2H, Ar-C**H**), 7.36 – 7.29 (m, 2H, Ar-C**H**), 7.29 – 7.22 (m, 1H, Ar-C**H**), 7.12 (ddd, *J* = 8.2, 7.4, 1.2 Hz, 1H, Ar-C**H**), 3.88 (s, 2H, NHC**H$_2$**), 3.57 – 3.49 (m, 2H, CONC**H$_2$**), 3.48 (s, 2H, NHC**H$_2$**), 3.42 – 3.33 (m, 2H, CONC**H$_2$**), 3.06 (t, *J* = 7.0 Hz, 2H, C**H**$_2$), 2.42 – 2.30 (m, 2H, C**H**$_2$), 2.13 (s, 1H, N**H**), 1.86 – 1.70 (m, 4H, 2 × C**H**$_2$), 1.67 – 1.46 (m, 6H, 3 × C**H**$_2$); δ_C (100 MHz, CDCl$_3$) 203.9 (**C**O), 171.6 (N**C**O), 170.9 (NH**C**O), 140.0 (Ar-**C**), 139.4 (Ar-**C**), 134.6 (Ar-**C**H), 130.7 (Ar-**C**H), 128.6 (Ar-**C**H), 128.5 (Ar-**C**H), 127.3 (Ar-**C**H), 122.9 (Ar-**C**), 122.7 (Ar-**C**H), 121.2 (Ar-**C**H), 54.0 (NH**C**H$_2$), 53.2 (NH**C**H$_2$), 46.7 (CO**C**H$_2$), 42.7 (CON**C**H$_2$), 40.0 (CON**C**H$_2$), 33.2 (NCO**C**H$_2$), 26.6 (**C**H$_2$), 25.7 (**C**H$_2$), 25.0 (**C**H$_2$), 24.6 (**C**H$_2$), 24.5 (**C**H$_2$); HRMS (ESI): calcd. for $C_{26}H_{34}N_3O_3$, 436.2555. Found: $[MH]^+$, 436.2601 (–3.1 ppm error).

N-(Cbz-sarcosine)-3,4,5,6-tetrahydro-1H-(1)-benzazonin-2,7-dione (3-19)



3,4,5,6-Tetrahydro-1H-(1)-benzazonin-2,7-dione **3-8** (81.3 mg, 0.40 mmol), DMAP (4.8 mg, 0.04 mmol) and pyridine (0.19 mL, 2.4 mmol) were stirred in DCM (2 mL) under an inert atmosphere at RT for 30 mins. To the stirred solution was added *N*-carboxybenzyl-*N*-methyl-3-aminoethanonyl chloride **3-18** (1.2 mmol, 3.00 eq. prepared using the modified general procedure) in DCM (2 mL). The resulting mixture was heated, at reflux, at 50 °C for 20 h, then concentrated *in vacuo*. Purification by flash column chromatography (SiO$_2$, 1:2 hexane: ethyl acetate) afforded the *title compound* (as a 5:6 mixture of rotamers) as a yellow oil (56 mg, 34%); $R_f = 0.42$ (1:2 hexane: ethyl acetate); δ_H (400 MHz, CDCl$_3$) 7.58 – 7.53 (m, 1H, Ar-C**H**, major rotamer), 7.49 – 7.46 (m, 4H, Ar-C**H**, both rotamers), 7.36 – 7.27 (m, 12H, Ar-C**H**, both rotamers), 6.99 – 6.95 (m, 1H, Ar-C**H**, minor rotamer), 5.21 – 5.01 (m, 4H, OC**H**$_2$Ph, both rotamers), 4.73 (d, *J* = 18.3 Hz, 1H, C**H**$_2$NCH$_3$, major rotamer), 4.60 (d, *J* = 18.7 Hz, 1H, C**H**$_2$NCH$_3$, minor rotamer), 4.42 (d, *J* = 18.7 Hz, 1H, C**H**$_2$NCH$_3$, minor rotamer), 4.31 (d, *J* = 18.3 Hz, 1H, C**H**$_2$NCH$_3$, major rotamer), 3.01 – 2.98 (m, 6H, NC**H**$_3$, both rotamers), 2.62 – 2.45 (m, 4H, C**H**$_2$, both rotamers), 2.08 – 1.95 (m, 4H, C**H**$_2$, both rotamers), 1.88 – 1.69 (m, 4H, C**H**$_2$, major rotamers), 1.60 – 1.49 (m, 4H, C**H**$_2$, minor rotamers); δ_C (100 MHz, CDCl$_3$) 206.2 (**C**OC, major rotamer), 205.8 (**C**OC, minor rotamer), 176.6 (N**C**O, minor rotamer), 176.6 (N**C**O, major rotamer), 172.6 (NCH$_2$**C**O, major rotamer), 172.3 (NCH$_2$**C**O, minor rotamer), 156.9 (O**C**O, major rotamer), 156.2 (O**C**O, minor rotamer), 139.6 (2C, m, Ar-**C**, both rotamers), 136.8 (Ar-**C**, minor rotamer), 136.7 (Ar-**C**, major rotamer), 135.0 (Ar-**C**, major rotamer), 134.8 (Ar-**C**, minor rotamer), 131.6 (2C, m, Ar-**C**H, both rotamers), 130.3 (Ar-**C**H, major rotamer), 130.0 (Ar-**C**H, minor rotamer), 129.3 (Ar-**C**H, minor rotamer), 129.2 (Ar-**C**H, major rotamer), 128.4 (2C, m, Ar-**C**H, both rotamers), 127.9 (2C, m, Ar-**C**H, both rotamers), 127.9 (4C, m, 2 × Ar-**C**H, both rotamers), 127.7 (2C, m, Ar-**C**H, both rotamer), 127.0 (Ar-**C**H, minor rotamer), 126.8 (Ar-**C**H, major rotamer), 67.2 (**C**H$_2$O, major rotamer), 67.2 (**C**H$_2$O, minor rotamer), 55.9 (CO**C**H$_2$N, major rotamer), 55.5 (CO**C**H$_2$N, minor rotamer), 43.2 (**C**H$_2$COC, major rotamer), 43.0 (**C**H$_2$COC, minor rotamer), 37.4 (**C**H$_2$CON, major rotamer), 37.3 (**C**H$_2$CON, major rotamer), 36.3 (N**C**H$_3$, minor rotamer), 35.8 (N**C**H$_3$, major rotamer), 25.8 (**C**H$_2$, minor rotamer), 25.6 (**C**H$_2$, minor rotamer), 25.6 (2C, m, **C**H$_2$, major rotamers); HRMS (ESI): calcd. for $C_{23}H_{24}N_2NaO_5$, 431.1577. Found: $[MNa]^+$, 431.1586 (–2.0 ppm error).

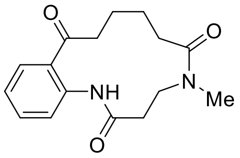
4-Methyl-3,4,6,7,8,9-hexahydrobenzo[e][1,4]diazacyclododecine-2,5,10(1H)-trione (3-21)



3,4,5,6-Tetrahydro-1H-(1)-benzazonin-2,7-dione **3-8** (406.4 mg, 2.0 mmol), DMAP (24.4 mg, 0.2 mmol) and pyridine (0.97 mL, 12.0 mmol) were stirred in DCM (10 mL) under an inert atmosphere at RT for 30 mins. To the stirred solution was added *N*-carboxybenzyl-*N*-methyl-3-aminoethanonyl chloride **3-18** (6.0 mmol, 3.00 eq. prepared using the modified general procedure) in DCM (10 mL). The resulting mixture was heated, at reflux, at 50 °C for 18 h. The solvent was concentrated in *vacuo*, loaded onto a short silica plug and eluted with 2:1 hexane: ethyl acetate→ 1:1 hexane: ethyl acetate to remove the excess carboxylic acid and pyridine, and concentrated in *vacuo*. This material was redissolved in methanol (20.0 mL) under an inert atmosphere.

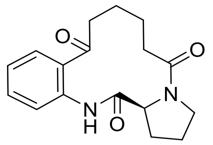
Palladium on carbon (200 mg, Pd 10% on carbon) was then added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at RT under a slight positive pressure of hydrogen (balloon) for 1.5 h. The reaction was then purged with argon, filtered through Celite, washed with methanol and the solvent removed *in vacuo*. Purification by flash column chromatography (SiO_2, 10:1 ethyl acetate: methanol) afforded the *title compound* (as a 10:1 mixture of rotamers) as a colorless oil (300 mg, 56% over 2 steps); R_f = 0.33 (9:1 ethyl acetate: methanol); ν_{max}/cm^{-1} (neat) 3273, 2935, 1690, 1625, 1528, 1482, 1448, 1397, 1304, 1110, 759; δ_H (400 MHz, $CDCl_3$-*d*) 9.24 (s, 1H, N**H**, major rotamer), 9.16 (s, 1H, N**H**, minor rotamer), 7.80 (dd, *J* = 8.0, 1.1 Hz, 1H, Ar-C**H**, major rotamer), 7.49 – 7.45 (m, 4H, Ar-C**H**, minor rotamer), 7.45 – 7.39 (m, 1H, Ar-C**H**, major rotamer), 7.37 – 7.33 (m, 1H, Ar-C**H**, major rotamer), 7.13 (td, *J* = 7.6, 1.2 Hz, 1H, Ar-C**H**, major rotamer), 4.26 (d, *J* = 15.7 Hz, 1H, C**H**H'NCH_3, major rotamer), 3.94 (s, 2H, C**H**$_2$NCH3, minor rotamer), 3.40 (d, *J* = 15.7 Hz, 1H, CH**H'**NCH_3, major rotamer), 3.26 (s, 3H, NC**H**$_3$, major rotamer), 3.06 (s, 3H, NC**H**$_3$, minor rotamer), 3.05 – 2.86 (m, 2H, C**H**$_2$, major rotamer), 2.81 (ddd, *J* = 16.6, 10.3, 1.4 Hz, 1H, C**H**$_2$, major rotamer), 2.70 (t, *J* = 6.7 Hz, 2H, C**H$_2$**, minor rotamer), 2.29 (dd, *J* = 16.1, 7.5 Hz, 1H, C**H**$_2$, major rotamer), 2.08 – 1.69 (m, 5H, C**H$_2$** both rotamers and C**H$_2$**CO, minor rotamer); δ_C (100 MHz, $CDCl_3$-*d*) NMR resonances for the major rotamer: 207.5 (**C**O), 175.2 (**C**O), 170.1 (**C**O), 134.6 (Ar-**C**), 133.2 (Ar-**C**), 131.6 (Ar-**C**H), 126.9 (Ar-**C**H), 124.9 (Ar-**C**H), 124.4 (Ar-**C**H), 55.9 (**C**H$_2$), 42.1 (**C**H$_2$), 37.8 (N**C**H$_3$), 33.7 (**C**H$_2$), 22.9 (**C**H$_2$), 22.2 (**C**H$_2$); ^{13}C NMR resonances for the minor rotamer: 205.3 (**C**OC), 173.8 (**C**O), 169.2 (**C**O), 135.6 (Ar-**C**), 133.6 (Ar-**C**), 131.8 (Ar-**C**H), 127.9 (Ar-**C**H), 126.1 (Ar-**C**H), 126.0 (Ar-**C**H), 54.5 (**C**H$_2$), 39.0 (**C**H$_2$), 36.6 (N**C**H$_3$), 29.9 (**C**H$_2$), 23.7 (**C**H$_2$), 21.3 (**C**H$_2$); HRMS (ESI): calcd. for $C_{15}H_{18}N_2NaO_3$, 297.1210. Found: $[MNa]^+$, 297.1212 (–0.7 ppm error).

5-Methyl-4,5,7,8,9,10-hexahydro-1*H*-1,5-benzodiazacyclotridecine-2,6,11(3*H*)-trione (3-21a)



3,4,5,6-Tetrahydro-1H-(1)-benzazonin-2,7-dione (609.7 mg, 3 mmol), DMAP (36.6 mg, 0.3 mmol) and pyridine (1.46 mL, 18 mmol) in dry DCM (15 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride (9.0 mmol, 3.0 equiv., freshly prepared from Cbz-Sar-β-OH using the modified procedure) in dry DCM (15 mL) was added and the resulting mixture was refluxed at 50 °C for 18 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, and concentrated *in vacuo.* This material was re-dissolved in MeOH (30 mL) and placed under an argon atmosphere. Palladium on carbon (300 mg, Pd 10% on carbon) was added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at RT under a slight positive pressure of hydrogen (balloon) for 1.5 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, 1:2 hexane: ethyl acetate → ethyl acetate) afforded the title compound as a pale-yellow oil (525 mg, 61% over 2 steps); $R_f = 0.43$ (9:1 ethyl acetate: methanol); ν_{max}/cm^{-1} (neat) 3287, 2933, 1664, 1515, 1444, 1406, 759; δ_H (400 MHz, $CDCl_3$-*d*, 50 °C) 9.52 (s, 1H, N**H**CO), 8.10 (d, $J = 8.3$ Hz, 1H, Ar-C**H**), 7.52 (dd, $J = 7.8$, 1.4 Hz, 1H, Ar-C**H**), 7.47 – 7.40 (m, 1H, Ar-C**H**), 7.13 – 7.07 (m, 1H, Ar-C**H**), 3.79 – 3.52 (m, 2H, C**H₂**), 3.08 (s, 3H, NC**H₃**), 3.05 – 2.99 (m, 2H, C**H₂**), 2.57 – 2.46 (m, 4H, C**H₂**), 1.92 – 1.75 (m, 4H, C**H₂**); δ_C (101 MHz, $CDCl_3$-*d*) 207.0 (**C**O), 174.0 (**C**O), 170.4 (**C**O), 136.9 (Ar-**C**), 132.3 (Ar-**C**H), 129.4 (Ar-**C**), 128.2 (Ar-**C**H), 124.2 (Ar-**C**H), 123.6 (Ar-**C**H), 44.8 (**C**H₂), 41.4 (**C**H₂), 36.7 (**C**H₂), 35.1 (N**C**H₃), 33.3 (**C**H₂), 23.3 (**C**H₂), 22.6 (**C**H₂); HRMS (ESI): calcd. for $C_{16}H_{20}N_2NaO_3$, 311.1366. Found: $[MNa]^+$, 311.1364 (0.8 ppm error).

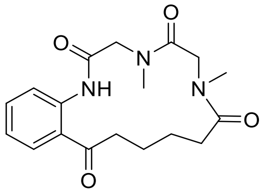
1,2,3,6,7,8,9,16a-octahydrobenzo[*e*]pyrrolo[1,2-*a*][1,4]diazacyclododecine-5,10,16(15*H*)-trione (3-21b)



3,4,5,6-Tetrahydro-1H-(1)-benzazonin-2,7-dione **3-8** (406.4 mg, 2.0 mmol), DMAP (24.4 mg, 0.2 mmol) and pyridine (0.97 mL, 12.0 mmol) in dry DCM (10 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride (6.0 mmol, 3.0 equiv., freshly prepared from Cbz-Pro-OH using the modified procedure) in dry DCM (10 mL) was added and the resulting mixture was refluxed at 50 °C for 18 h. The solvent was then concentrated *in vacuo*, loaded onto a short silica plug and eluted with ethyl acetate, to remove majority of excess carboxylic acid and pyridine residues, and concentrated *in vacuo.* This material was re-dissolved in MeOH (20 mL) and placed under an argon atmosphere. Palladium on carbon (200 mg, Pd 10% on carbon) was added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at RT 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*. Purification by flash column chromatography (SiO_2, ethyl acetate) afforded the *title compound* (as a 5:1 mixture of rotamers) as a colorless oil (414 mg, 69% over 2 steps); $[\alpha]_D^{23}$ –312.13 (c = 1.0, $CHCl_3$); R_f = 0.23 (ethyl acetate); ν_{max}/cm^{-1} (neat) 3252, 2948, 2242, 1691, 1672, 1602, 1505, 1442, 1299, 1238, 910, 756, 725, 644, 580; δ_H (400 MHz, $CDCl_3$-*d*) 9.43 (s, 1H, N**H**, major rotamer), 9.34 (s, 1H, N**H**, minor rotamer), 7.77 – 7.73 (m, 1H, Ar-C**H**, major rotamer), 7.42 – 7.28 (m, 2H, Ar-C**H**, both rotamers), 7.20 – 7.14 (m, 1H, Ar-C**H**, minor rotamer), 7.07 (td, *J* = 7.6, 1.0 Hz, 1H, Ar-C**H**, major rotamer), 4.31 – 4.20 (m, 1H, NC**H**CO, both rotamers), 3.78 (dt, *J* = 10.1, 7.0 Hz, 1H, NC$\mathbf{H}_2$, major rotamer), 3.60 (ddd, *J* = 11.5, 7.3, 4.3 Hz, 1H, NC$\mathbf{H}_2$, minor rotamer), 3.55 – 3.44 (m, 1H, NC$\mathbf{H}_2$, both rotamers), 3.07 – 2.78 (m, 2H, C$\mathbf{H}_2$, both rotamers), 2.68 – 2.49 (m, 1H, C$\mathbf{H}_2$, major rotamer), 2.36 – 2.01 (m, 4H, C$\mathbf{H}_2$, both rotamers), 2.02 – 1.61 (m, 5H, C$\mathbf{H}_2$, both rotamers); δ_C

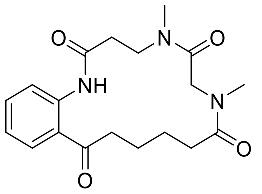
(101 MHz, $CDCl_3$-*d*) for major rotamers only: 207.2 (**C**O), 173.4 (**C**O), 172.8 (**C**O), 134.8 (Ar-**C**), 133.0 (Ar-**C**), 131.4 (Ar-**C**H), 126.9 (Ar-**C**H), 124.5 (Ar-**C**H), 124.1 (Ar-**C**H), 62.6 (CO**C**HN), 47.0 (**C**H_2), 41.8 (**C**H_2), 35.1 (**C**H_2), 28.4 (**C**H_2), 25.3 (**C**H_2), 22.6 (**C**H_2), 22.1 (**C**H_2); Diagnostic ^{13}C NMR resonances for the minor rotamer: 204.8 (**C**O), 172.6 (**C**O), 172.3 (**C**O), 135.9 (Ar-**C**), 133.6 (Ar-**C**), 127.9 (Ar-**C**H), 126.0 (Ar-**C**H), 125.5 (Ar-**C**H), 61.4 (CO**C**HN), 38.5 (**C**H_2), 31.9 (**C**H_2), 31.6 (**C**H_2), 23.6 (**C**H_2), 23.0 (**C**H_2), 21.2 (**C**H_2); HRMS (ESI): calcd. for $C_{17}H_{20}N_2NaO_3$, 323.1366. Found: $[MNa]^+$, 323.1362 (1.3 ppm error).

4,7-Dimethyl-3,4,6,7,9,10,11,12-octahydro-1*H*-1,4,7-benzotriazacyclopentadecine-2,5,8,13-tetrone (3-26)



A mixture of 4-methyl-3,4,6,7,8,9-hexahydrobenzo[e][1,4]diazacyclododecine-2,5,10 (1H)-trione **3-21** (137.2 mg, 0.5 mmol), DMAP (6.1 mg, 0.05 mmol) and pyridine (243 μL, 3.0 mmol) in DCM (3.0 mL) under an argon atmosphere was stirred at RT for 5 mins. Next, a solution of acid chloride **3-23** (1.5 mmol, 3.0 equiv. prepared using the general procedure with Fmoc-Sar-OH) in DCM (3.0 mL) was added and the resulting mixture was heated, at reflux, at 50 °C for 18 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, and concentrated *in vacuo* (230 mg crude material obtained). This crude material (77 mg, 0.136 mmol) was dissolved in 20% piperidine in THF (1.0 mL), the resulting mixture was stirred at RT for 1 h. Purification by flash column chromatography (SiO_2, ethyl acetate → 10:1 ethyl acetate: methanol) afforded the *title compound* as a colorless oil (17 mg, 37%); R_f = 0.32 (9:1 ethyl acetate: methanol); δ_H (400 MHz, $CDCl_3$-*d*, 50 °C) 11.45 (s, 1H, N**H**), 8.71 (d, *J* = 8.3 Hz, 1H, Ar-C**H**), 7.76 (d, *J* = 7.9 Hz, 1H, Ar-C**H**), 7.55 (dd, *J* = 8.3, 4.5 Hz, 1H, Ar-C**H**), 7.13 (dd, *J* = 7.9, 4.5 Hz, 1H, Ar-C**H**), 4.56 – 4.34 (m, 2H, CO**H_2**N), 4.21 – 3.99 (m, 2H, COC**H**$_2$N), 3.39 (s, 3H, NC**H**$_3$), 3.06 – 2.99 (m, 2H, C**H**$_2$), 2.93 (s, 3H, NC**H**$_3$), 2.50 – 2.36 (m, 2H, C**H**$_2$), 1.76 – 1.83 (m, 2H, C**H**$_2$), 1.52 – 1.40 (m, 2H, C**H**$_2$); δ_C (100 MHz, CDCl$_3$-*d*) 208.0 (**C**O), 174.3 (**C**O), 168.9 (**C**O), 167.4 (**C**O), 139.5 (Ar-**C**), 135.3 (Ar-**C**H), 130.5 (Ar-**C**H), 123.3 (Ar-**C**H), 122.8 (Ar-**C**), 120.9 (Ar-**C**H), 54.5 (N**C**H$_2$CO), 52.8 (N**C**H$_2$CO), 38.6 (**C**H$_2$), 36.5 (N**C**H$_3$), 35.2 (N**C**H$_3$), 32.8 (**C**H$_2$), 25.1 (**C**H$_2$), 24.2 (**C**H$_2$); HRMS (ESI): calcd. for $C_{18}H_{23}N_3NaO_4$, 368.1581. Found: [MNa]$^+$, 368.1579 (0.5 ppm error).

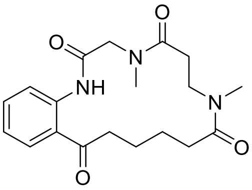
5,8-Dimethyl-4,5,7,8,10,11,12,13-octahydro-1,5,8-benzotriazacyclohexadecine-2,6,9,14(1*H*,3*H*)-tetrone (3-26a)



A mixture of 4-methyl-3,4,6,7,8,9-hexahydrobenzo[e][1,4]diazacyclododecine-2,5,10 (1H)-trione **3-21** (137.2 mg, 0.5 mmol), DMAP (6.1 mg, 0.05 mmol) and pyridine (243 µL, 3.0 mmol) in DCM (3.0 mL) under an argon atmosphere was stirred at RT for 5 mins. Next, a solution of acid chloride (1.5 mmol, 3.0 equiv. prepared using the general procedure with Fmoc-Sar-β-OH) in DCM (3.0 mL) was added and the resulting mixture was heated, at reflux, at 50 °C for 18 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, and concentrated *in vacuo* (218 mg crude material obtained). This crude material (110 mg) was dissolved in THF (2.0 mL) and 25 µL piperidine (0.25 mmol, 1 eq) was added, the resulting mixture was stirred at RT for 1 h. Purification by flash column chromatography (SiO$_2$, ethyl acetate → 10:1 ethyl acetate: methanol) afforded the *title compound* (as a mixture of 10:7 rotamers) as a colorless oil (30 mg, 33%); $R_f = 0.25$ (9:1 ethyl acetate: methanol); ν_{max}/cm^{-1} (neat) 3271, 2930, 1646, 1520, 1447, 1261, 762; δ_H (400 MHz, CDCl$_3$-*d*, 50 °C) 11.33 (s, 1H, N**H**CO, major rotamer), 11.08 (s, 1H, N**H**CO, minor rotamer), 8.68 (d, *J* = 8.4 Hz, 1H, Ar-C**H**, major rotamer), 8.62 (d, *J* = 8.4 Hz, 1H, Ar-C**H**, minor rotamer), 7.81 (d, *J* =

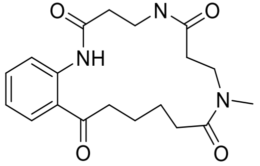
7.9 Hz, 1H, Ar-C**H**, both rotamers), 7.57 – 7.47 (m, 1H, Ar-C**H**, both rotamers), 7.16 – 7.09 (m, 1H, Ar-C**H**, both rotamers), 4.06 (s, 2H, NC**H**$_2$CO, minor rotamer), 3.98 (s, 2H, NC**H**$_2$CO, major rotamer), 3.77 – 3.70 (m, 2H, NC**H**$_2$, both rotamers), 3.05 (s, 3H, NC**H**$_3$, minor rotamer), 3.00 (s, 3H, NC**H**$_3$, major rotamer), 2.96 (s, 3H, NC**H**$_3$, minor rotamer), 2.90 (s, 3H, NC**H**$_3$, major rotamer), 2.78 – 2.71 (m, 2H, C**H**$_2$, major rotamer), 2.71 – 2.65 (m, 2H, C**H**$_2$, minor rotamer), 2.41 – 2.34 (m, 2H, C**H**$_2$, minor rotamer), 2.10 – 2.01 (m, 2H, C**H**$_2$, major rotamer), 1.95 – 1.84 (m, 3H, C**H**$_2$, both rotamers), 1.77 – 1.63 (m, 3H, C**H**$_2$, both rotamers); δ_C (101 MHz, CDCl$_3$-*d*) for major rotamers only: 206.8 (**C**O), 173.6 (**C**O), 170.7 (**C**O), 167.6 (**C**O), 140.2 (Ar-**C**), 135.0 (Ar-**C**H), 134.1 (Ar-**C**H), 130.9 (Ar-**C**H), 124.0 (Ar-**C**), 121.4 (Ar-**C**H), 52.0 (N**C**H$_2$CO), 47.0 (N**C**H$_2$), 40.8 (**C**H$_2$), 37.3 (**C**H$_2$), 36.3 (N**C**H$_3$), 35.4 (N**C**H$_3$), 32.8 (**C**H$_2$), 25.3 (**C**H$_2$), 24.8 (**C**H$_2$); ^{13}C NMR resonances for the minor rotamer: 205.5 (**C**O), 173.3 (**C**O), 170.7 (**C**O), 169.5 (**C**O), 139.5 (Ar-**C**), 134.1 (Ar-**C**H), 130.1 (Ar-**C**H), 123.1 (Ar-**C**H), 122.2 (Ar-**C**), 121.6 (Ar-**C**H), 48.8 (N**C**H$_2$CO), 46.3 (N**C**H$_2$), 37.7 (**C**H$_2$), 37.3 (N**C**H$_3$), 37.1 (N**C**H$_3$), 36.3 (**C**H$_2$), 32.1 (**C**H$_2$), 24.2 (**C**H$_2$), 23.7 (**C**H$_2$); HRMS (ESI): calcd. for $C_{19}H_{25}N_3NaO_4$, 382.1737. Found: [MNa]$^+$, 382.1738 (–0.3 ppm error).

4,8-Dimethyl-3,4,7,8,10,11,12,13-octahydro-1,4,8-benzotriazacyclohexadecine-2,5,9,14(1*H*,6*H*)-tetrone (3-26b)



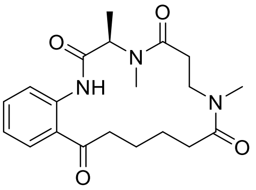
5-Methyl-4,5,7,8,9,10-hexahydro-1H-1,5-benzodiazacyclotridecine-2,6,11(3H)-trione **3-21a** (144.2 mg, 0.5 mmol), DMAP (6.1 mg, 0.05 mmol) and pyridine (243 µL, 3.0 mmol) in DCM (3.0 mL) under an argon atmosphere was stirred at RT for 5 mins. Next, a solution of acid chloride (1.5 mmol, 3.0 equiv. prepared using the general procedure with Fmoc-Sar-OH) in DCM (3.0 mL) was added and the resulting mixture was heated, at reflux, at 50 °C for 18 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, and concentrated *in vacuo* (243 mg crude material obtained). This crude material was dissolved in THF (5.0 mL) and 50 µL piperidine (0.5 mmol, 1 eq) was added, the resulting mixture was stirred at RT for 1 h. Purification by flash column chromatography (SiO_2, ethyl acetate → 10:1 ethyl acetate: methanol) afforded the *title compound* as a colorless oil (82 mg, 46% over 2 steps); R_f = 0.28 (9:1 ethyl acetate: methanol); ν_{max}/cm^{-1} (neat) 3211, 2933, 1651, 1580, 1519, 1450, 1402, 1303, 1210, 1165, 1033, 760, 731, 646; δ_H (400 MHz, $CDCl_3$-*d*, 50 °C) 12.42 (s, 1H, CON**H**), 8.85 (d, *J* = 8.5 Hz, 1H, Ar-C**H**), 7.94 (d, *J* = 8.0 Hz, 1H, Ar-C**H**), 7.56 – 7.50 (m, 1H, Ar-C**H**), 7.12 – 7.07 (m, 1H, Ar-C**H**), 4.34 – 4.07 (m, 2H, NC**H₂**CO), 3.77 – 3.64 (m, 2H, C**H₂**), 3.12 (s, 3H, NC**H₃**), 3.05 (s, 3H, NC**H₃**), 3.06 – 3.01 (m, 4H, C**H₂**), 2.29 – 2.11 (m, 2H, C**H₂**), 2.07 – 1.81 (m, 2H, C**H₂**), 1.67 – 1.47 (m, 2H, C**H₂**); δ_C (101 MHz, $CDCl_3$-*d*) 204.2 (**C**O), 173.4 (**C**O), 173.0 (**C**O), 168.4 (**C**O), 140.8 (Ar-**C**), 135.4 (Ar-**C**H), 130.7 (Ar-**C**H), 122.8 (Ar-**C**H), 121.2 (Ar-**C**), 120.3 (Ar-**C**H), 53.0 (CO**C**H₂N), 45.0 (**C**H₂), 39.1 (**C**H₂), 38.4 (N**C**H₃), 36.6 (N**C**H₃), 32.7 (**C**H₂), 32.5 (**C**H₂), 25.0 (**C**H₂), 19.1 (**C**H₂); HRMS (ESI): calcd. for $C_{19}H_{25}N_3NaO_4$, 382.1737. Found: $[MNa]^+$, 382.1730 (1.8 ppm error).

5,9-Dimethyl-4,5,8,9,11,12,13,14-octahydro-1*H*-1,5,9-benzotriazacycloheptadecine-2,6,10,15(3*H*,7*H*)-tetrone (3-26c)



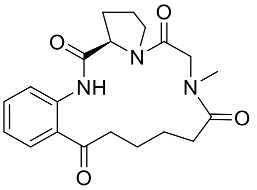
A mixture of 5-methyl-4,5,7,8,9,10-hexahydro-1*H*-1,5-benzodiazacyclotridecine-2,6,11(3*H*)-trione **3-21a** (72 mg, 0.25 mmol), DMAP (3.0 mg, 0.025 mmol) and pyridine (122 µL, 1.5 mmol) in DCM (1.5 mL) under an argon atmosphere was stirred at RT for 5 mins. Next, a solution of acid chloride (0.75 mmol, 3.0 equiv. prepared using the general procedure with Fmoc-Sar-β-OH) in DCM (1.5 mL) was added and the resulting mixture was heated, at reflux, at 50 °C for 18 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, and concentrated *in vacuo* (104 mg crude material obtained). This crude material was dissolved in THF (2.0 mL) and 25 μL piperidine (0.25 mmol, 1 eq) was added, the resulting mixture was stirred at RT for 2 h. Purification by flash column chromatography (SiO_2, ethyl acetate → 10:1 ethyl acetate: methanol) afforded the *title compound* (as a mixture of 3:1 of rotamers) as a colorless oil (37 mg, 41%); R_f = 0.23 (9:1 ethyl acetate: methanol); ν_{max}/cm^{-1} (neat) 2939, 1640, 1583, 1520, 1450, 1306, 1206, 762; δ_H (400 MHz, $CDCl_3$-*d*) 11.90 (s, 1H, CON**H**, major rotamer), 11.30 (s, 1H, CON**H**, minor rotamer), 8.74 (dd, *J* = 8.5, 0.9 Hz, 1H, Ar-C**H**, major rotamer), 8.60 – 8.56 (m, 1H, Ar-C**H**, minor rotamer), 7.92 (dd, *J* = 8.1, 1.3 Hz, 1H, Ar-C**H**, major rotamer), 7.82 (dd, *J* = 8.1, 1.4 Hz, 1H, Ar-C**H**, minor rotamer), 7.60 – 7.48 (m, 1H, Ar-C**H**, both rotamers), 7.16 – 7.09 (m, 1H, Ar-C**H**, both rotamers), 3.82 – 3.59 (m, 6H, C**H**$_2$, both rotamers), 3.22 (s, 3H, NC**H**$_3$, minor rotamer), 3.12 – 2.94 (m, 3H, C**H**$_2$, both rotamers), 2.89 (s, 3H, NC**H**$_3$, minor rotamer), 2.86 (s, 3H, NC**H**$_3$, major rotamer), 2.86 (s, 3H, NC**H**$_3$, major rotamer), 2.72 – 2.56 (m, 4H, C**H**$_2$, both rotamers), 2.54 – 2.35 (m, 5H, C**H**$_2$, both rotamers), 1.90 – 1.75 (m, 3H, C**H**$_2$, both rotamers), 1.64 – 1.44 (m, 3H, C**H**$_2$, both rotamers); δ_C (101 MHz, $CDCl_3$-*d*) for major rotamers only: 204.7 (**C**O), 173.5 (**C**O), 171.6 (**C**O), 170.4 (**C**O), 140.9 (Ar-**C**), 135.4 (Ar-**C**H), 131.0 (Ar-**C**H), 122.9 (Ar-**C**H), 121.3 (Ar-**C**), 120.9 (Ar-**C**H), 47.6 (N**C**H$_2$), 46.9 (N**C**H$_2$), 38.7 (**C**H$_2$), 38.4 (**C**H$_2$), 37.8 (N**C**H$_3$), 35.0 (**C**H$_2$), 33.2 (N**C**H$_3$), 32.8 (**C**H$_2$), 26.3 (**C**H$_2$), 23.8 (**C**H$_2$); Diagnostic ^{13}C NMR resonances for the minor rotamer: 205.8 (**C**O), 173.5 (**C**O), 172.4 (**C**O), 171.3 (**C**O), 139.8 (Ar-**C**), 134.8 (Ar-**C**H), 130.4 (Ar-**C**H), 123.1 (Ar-**C**H), 121.6 (Ar-**C**H), 46.8 (**C**H$_2$), 44.2 (**C**H$_2$), 38.7 (**C**H$_2$), 38.6 (**C**H$_2$), 38.5 (N**C**H$_3$), 33.2 (N**C**H$_3$), 32.9 (**C**H$_2$), 24.5 (**C**H$_2$), 23.2 (**C**H$_2$); HRMS (ESI): calcd. for $C_{20}H_{27}N_3NaO_4$, 396.1894. Found: $[MNa]^+$, 396.1887 (1.8 ppm error).

(*R*)-3,4,8-trimethyl-3,4,7,8,10,11,12,13-octahydrobenzo[*o*][1,4,8]triazacyclohexadecine-2,5,9,14(1*H*,6*H*)-tetraone (3-26e)



A mixture of 3,4,7,8,9,10-hexahydrobenzo[*f*][1]oxa[5]azacyclotridecine-2,6,11(1*H*)-trione **3-21a** (144.2 mg, 0.5 mmol), DMAP (6.1 mg, 0.05 mmol) and pyridine (243 μL, 3.0 mmol) in DCM (2.5 mL) under an argon atmosphere was stirred at RT for 5 mins. Next, a solution of acid chloride (1.5 mmol, 3.0 equiv. prepared using the general procedure with Fmoc-*N*-Me-*L*-Ala-OH) in DCM (2.5 mL) was added and the resulting mixture was heated, at reflux, at 50 °C for 18 h. The solvent was then concentrated *in vacuo*, loaded onto a short silica plug and eluted with 1:1 hexane: ethyl acetate, to remove the majority of excess carboxylic acid and pyridine residues, and concentrated *in vacuo* (130 mg crude material obtained). This crude material was dissolved in THF (5.0 mL) and 500 μL piperidine was added, the resulting mixture was stirred at RT for 1 h. Purification by flash column chromatography (SiO_2, 10:1 ethyl acetate: methanol →3:1 ethyl acetate: methanol) afforded the *title compound* (as a mixture of 10:1 rotamers) as a colorless oil (39 mg, 21% from **3-21a**) which exists as a mixture of 10:1 rotamers in solution in $CDCl_3$; $[\alpha]_D^{22}$ –10.18 (c = 1.0, $CHCl_3$); R_f = 0.25 (9:1 ethyl acetate: methanol); ν_{max}/cm^{-1} (neat) 3211, 2935, 1649, 1580, 1517, 1450, 1404, 1300, 1209, 1164, 1122, 760, 731; δ_H (400 MHz, $CDCl_3$-*d*) 12.47 (s, 1H, N**H**, major rotamer), 12.05 (s, 1H, N**H**, minor rotamer), 8.80 (d, *J* = 8.5 Hz, 1H, Ar-C**H**, major rotamer), 8.71 (d, *J* = 8.5 Hz, 1H, Ar-C**H**, minor rotamer), 7.93 (dd, *J* = 8.1, 1.3 Hz, 1H, Ar-C**H**, major rotamer), 7.86 (dd, *J* = 8.1, 1.3 Hz, 1H, Ar-C**H**, minor rotamer), 7.58 – 7.49 (m, 1H, Ar-CH, both rotamers), 7.17 – 7.04 (m, 1H, Ar-C**H**, both rotamers), 5.58 (q, *J* = 6.9 Hz, 1H, NC**H**, major rotamer), 5.43 (q, *J* = 7.1 Hz, 1H, NC**H**, minor rotamer), 4.31 – 4.11 (m, 1H, C$\mathbf{H}_2$, both rotamers), 3.74 – 3.40 (m, 1H, C$\mathbf{H}_2$, both rotamers), 3.37 – 3.24 (m, 1H, C$\mathbf{H}_2$, both rotamers), 3.22 – 3.13 (m, 1H, C$\mathbf{H}_2$, both rotamers), 3.12 (s, 3H, NC$\mathbf{H}_3$, both rotamers), 3.01 – 2.93 (m, 1H, C$\mathbf{H}_2$, both rotamers), 2.93 (s, 3H, NC$\mathbf{H}_3$, minor rotamer), 2.91 (s, 3H, NC**H**$_3$, major rotamer), 2.57 – 2.43 (m, 2H, C**H**$_2$, both rotamers), 2.36 – 2.18 (m, 1H, C**H**$_2$, both rotamers), 2.15 – 1.98 (m, 1H, C**H**$_2$, both rotamers), 1.82 – 1.68 (m, 1H, C**H**$_2$, both rotamers), 1.66 – 1.51 (m, 1H, C**H**$_2$, both rotamers), 1.44 (d, *J* = 7.2 Hz, 3H, CHC**H**$_3$, both rotamers), 1.40 – 1.26 (m, 1H, C**H**$_2$, both rotamers); δ_C (101 MHz, $CDCl_3$-*d*) for major rotamers only: 204.2 (**C**O), 173.5 (**C**O), 173.1 (**C**O), 171.1 (**C**O), 141.0 (Ar-**C**), 135.4 (Ar-CH), 130.7 (Ar-**C**H), 122.5 (Ar-**C**H), 121.2 (Ar-**C**), 120.2 (Ar-**C**H), 53.8 (N**C**H), 44.8 (**C**H$_2$), 39.0 (N**C**H$_3$), 38.3 (**C**H$_2$), 33.3 (**C**H$_2$), 33.2 (**C**H$_2$), 31.1 (N**C**H$_3$), 24.9 (**C**H$_2$), 19.6 (**C**H$_2$), 13.5 (CH**C**H$_3$); Diagnostic ^{13}C NMR resonances for the minor rotamer: 205.4 (**C**O), 173.2 (**C**O), 171.3 (**C**O), 170.5 (**C**O), 135.3 (Ar-**C**H), 122.7 (Ar-**C**H), 122.2 (Ar-**C**H), 120.5 (Ar-**C**H), 46.2 (**C**H$_2$), 35.2 (**C**H$_2$), 33.9 (**C**H$_2$), 25.2 (**C**H$_2$), 23.3 (**C**H$_2$), 13.2 (CH**C**H$_3$); HRMS (ESI): calcd. for $C_{20}H_{27}N_3NaO_4$, 396.1894. Found: $[MNa]^+$, 396.1891 (0.7 ppm error).

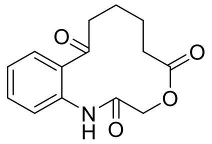
7-Methyl-2,3,6,7,9,10,11,12-octahydro-1*H*-benzo[*n*]pyrrolo[2,1*c*][1,4,7] triazacyclopentadecine-5,8,13,19(18*H*,19a*H*)-tetraone (3-26f)



A mixture of 4-methyl-3,4,6,7,8,9-hexahydrobenzo[e][1,4]diazacyclododecine-2,5,10 (1H)-trione **3-21** (137.2 mg, 0.5 mmol), DMAP (6.1 mg, 0.05 mmol) and pyridine (243 µL, 3.0 mmol) in DCM (3.0 mL) under an argon atmosphere was stirred at RT for 5 mins. Next, a solution of acid chloride (1.5 mmol, 3.0 equiv. prepared using the general procedure with Fmoc-Pro-OH) in DCM (3.0 mL) was added and the resulting mixture was heated, at reflux, at 50 °C for 18 h. The solvent was then concentrated *in vacuo*, loaded onto a short silica plug and eluted with ethyl acetate, to remove majority of excess carboxylic acid and pyridine residues, and concentrated *in vacuo* (270 mg crude material obtained). This crude material was dissolved in THF (5.0 mL) and 500 µL piperidine was added, the resulting mixture was stirred at RT for 1 h. Purification by flash column chromatography (SiO_2, 10:1 ethyl acetate: methanol → 3:1 ethyl acetate:

methanol) afforded the *title compound* as a yellow oil (27 mg, 15%); R_f = 0.28 (3:1 ethyl acetate: methanol); ν_{max}/cm^{-1} (neat) 3263, 2933, 1661, 1643, 1580, 1519, 1448, 1397, 1312, 1206, 1157, 762, 733, 620; δ_H (400 MHz, $CDCl_3$-*d*) 11.65 (s, 1H, N**H**), 8.69 (dd, *J* = 8.4, 1.0 Hz, 1H, Ar-C**H**), 7.76 (dd, *J* = 8.0, 1.4 Hz, 1H, Ar-C**H**), 7.59 – 7.50 (m, 1H, Ar-C**H**), 7.11 (td, *J* = 8.6, 1.1 Hz, 1H, Ar-C**H**), 4.83 (d, *J* = 17.9 Hz, 1H, NC**H**$_2$CO), 4.68 – 4.52 (m, 1H, NC**H**), 4.16 – 4.02 (m, 1H, C**H**$_2$), 3.94 (d, *J* = 17.9 Hz, 1H, NC**H**$_2$CO), 3.68 – 3.53 (m, 1H, C**H**$_2$), 3.46 – 3.33 (m, 1H, C**H**$_2$), 2.92 (s, 3H, NC**H**$_3$), 2.87 – 2.87 (m, 1H, C**H**$_2$), 2.70 – 2.60 (m, 1H, C**H**$_2$), 2.34 – 1.62 (m, 9H, C**H**$_2$); δ_C (101 MHz, $CDCl_3$-*d*): 208.0 (**C**O), 174.3 (**C**O), 170.9 (**C**O), 167.5 (**C**O), 139.7 (Ar-**C**), 135.2 (Ar-**C**H), 130.6 (Ar-**C**H), 123.1 (Ar-**C**H), 122.5 (Ar-**C**), 121.0 (Ar-**C**H), 62.8 (N**C**H), 53.5 (N**C**H$_2$CO), 46.4 (**C**H$_2$), 38.9 (**C**H$_2$), 35.2 (N**C**H$_3$), 32.6 (**C**H$_2$), 29.5 (**C**H$_2$), 25.3 (**C**H$_2$), 25.0 (**C**H$_2$), 24.3 (**C**H$_2$); HRMS (ESI): calcd. for $C_{20}H_{25}N_3NaO_4$, 394.1737. Found: [MNa]$^+$, 394.1736 (0.2 ppm error).

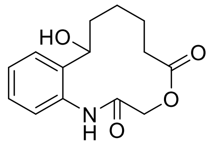
6,7,8,9-Tetrahydro-1*H*-benzo[*e*][1]oxa[4]azacyclododecine-2,5,10(3*H*)-trione (3-29)



3,4,5,6-Tetrahydro-1H-(1)-benzazonin-2,7-dione **3-8** (813 mg, 4.0 mmol), DMAP (49 mg, 0.4 mmol) and pyridine (1.94 mL, 24.0 mmol) were stirred in DCM (20 mL) under an inert atmosphere at RT for 30 mins. To the stirred solution was added benzyloxy acetic acid chloride (12.0 mmol, 3.00 eq. prepared using the modified general procedure) in DCM (20 mL). The resulting mixture was heated, at reflux, at 50 °C for 18 h. The solvent was concentrated in *vacuo*, loaded onto a short silica plug and eluted with 2:1 hexane: ethyl acetate→ 1:1 hexane: ethyl acetate to remove the excess carboxylic acid and pyridine, and concentrated in *vacuo*. This material was redissolved EtOAc (40 mL) under an inert atmosphere. Palladium on carbon (400 mg, Pd 10% on carbon) and palladium hydroxide on carbon (40 mg, 20 wt. %) were then added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at RT under a slight positive pressure of hydrogen (balloon) for 2 h. The reaction was then purged with argon, filtered through Celite, washed with methanol and the solvent removed *in vacuo*. The crude material was then re-dissolved in chloroform (20 mL) and triethylamine (2.10 mL, 10 mmol) was added, and then stirred at RT for 16 h, then reduced in *vacuo*. Purification by flash column chromatography (SiO_2, 2:1 hexane: ethyl acetate → 1: 1 hexane: ethyl acetate) afforded the *title compound* **3-29** (as a 10:1 mixture of rotamers) as a white solid (545 mg, 52% over 2 steps) which exists as a 10:1 mixture of rotamers in solution in $CDCl_3$ along with as a minor product **3-29a** (180 mg, 17% over 2 steps).

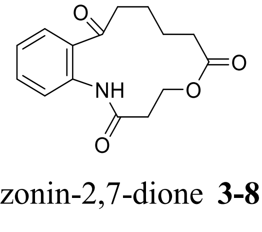
Data for **3-29:** m.p. 120 – 122 °C; R_f = 0.53 (1:2 hexane: ethyl acetate); ν_{max}/cm^{-1} (neat) 3361, 2936, 1743, 1711, 1675, 1517, 1445, 1303, 1139, 1039, 988, 761; δ_H (400 MHz, $CDCl_3$-*d*) 9.03 (s, 1H, CON**H**, major rotamer), 8.27 (d, *J* = 8.2 Hz, 1H, Ar-C**H**, minor rotamer), 7.99 (d, *J* = 8.2 Hz, 1H, Ar-C**H**, major rotamer), 7.85 (s, 1H, CON**H**, minor rotamer), 7.45 (t, *J* = 7.8 Hz, 1H, Ar-C**H**, both rotamers), 7.38 (d, *J* = 7.7 Hz, 1H, Ar-C**H**, both rotamers), 7.15 (t, *J* = 7.6 Hz, 1H, Ar-C**H**, both rotamers), 4.75 (s, 2H, OC$\mathbf{H_2}$CO, minor rotamer), 4.49 (s, 2H, OC$\mathbf{H_2}$CO, major rotamer), 3.01 – 2.85 (m, 2H, C$\mathbf{H_2}$, both rotamers), 2.71 – 2.56 (m, 2H, C$\mathbf{H_2}$, both rotamers), 1.93 – 1.73 (m, 4H, 2 × C$\mathbf{H_2}$, both rotamers); δ_C (100 MHz, $CDCl_3$-*d*) NMR resonances for the major rotamer: 207.6 (**C**O), 174.0 (**C**O), 168.4 (**C**O), 134.3 (Ar-**C**), 132.3 (Ar-**C**), 132.0 (Ar-**C**H), 126.7 (Ar-**C**H), 124.4 (Ar-**C**H), 123.9 (Ar-**C**H), 65.2 (O**C**H_2CO), 42.1 (**C**H_2), 33.7 (**C**H_2), 23.3 (**C**H_2), 21.8 (**C**H_2); Diagnostic ^{13}C NMR resonances for the minor rotamer: 173.0 (**C**O), 165.2 (**C**O), 135.1 (Ar-**C**), 130.6 (Ar-**C**), 130.5 (Ar-**C**H), 127.5 (Ar-**C**H), 124.8 (Ar-**C**H), 120.2 (Ar-**C**H), 63.5 (O**C**H_2CO), 35.0 (**C**H_2), 28.2 (**C**H_2), 27.4 (**C**H_2), 22.8 (**C**H_2); HRMS (ESI): calcd. for $C_{14}H_{16}NO_4$, 262.1074. Found: $[MH]^+$, 262.1072 (0.8 ppm error).

10-Hydroxy-1,6,7,8,9,10-hexahydro-5*H*-benzo[*e*][1]oxa[4]azacyclododecine-2,5(3*H*)-dione (3-29a)



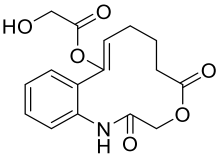
Formed as a minor product during the synthesis of **3-29** (procedure is above). The *title compound* (10:1 mixture of rotamers) was isolated as a white solid (180 mg, 17% over 2 steps); mp. 152 – 155 °C; $R_f = 0.48$ (1:2 hexane: ethyl acetate); δ_H (400 MHz, $CDCl_3$-*d*) 9.58 (s, 1H, N**H**, major rotamer), 9.05 (s, 1H, N**H**, minor rotamer), 8.33 (dd, *J* = 8.2, 0.9 Hz, 1H, Ar-C**H**, major rotamer), 7.99 (dd, *J* = 8.2, 1.0 Hz, 1H, Ar-C**H**, minor rotamer), 7.41 – 7.38 (m, 1H, Ar-C**H**, minor rotamer), 7.31 – 7.23 (m, 1H, Ar-C**H**, major rotamer), 7.11 – 7.01 (m, 2H, Ar-C**H**, both rotamers), 4.88 (d, *J* = 14.6 Hz, 1H, OC**H**$_2$, major rotamer), 4.81 (d, *J* = 8.6 Hz, 1H, C**H**OH, both rotamers), 4.49 (s, 2H, OC**H**$_2$, minor rotamer), 4.32 (d, *J* = 14.6 Hz, 1H, OC**H**$_2$, major rotamer), 3.00 – 2.91 (m, 2H, C**H₂**, minor rotamer), 2.78 (s, 1H, CHO**H**, both rotamers), 2.68 – 2.40 (m, 2H, C**H₂**, major rotamer), 2.29 – 2.15 (m, 6H, 3 × C**H₂**, minor rotamer), 1.99 – 1.66 (m, 6H, 3 × C**H₂**, major rotamer); δ_C (100 MHz, $CDCl_3$-*d*) 174.4 (**C**O), 165.8 (**C**O), 135.9 (Ar-**C**), 132.2 (Ar-**C**), 128.7 (Ar-**C**H), 127.3 (Ar-**C**H), 124.3 (Ar-**C**H), 121.7 (Ar-**C**H), 75.6 (**C**HOH), 64.1 (O**C**H$_2$), 34.8 (**C**H$_2$), 32.6 (**C**H$_2$), 24.9 (**C**H$_2$), 24.7 (**C**H$_2$); Diagnostic ^{13}C NMR resonances for the minor rotamer: 174.0 (**C**O), 132.1 (Ar-**C**), 126.7 (Ar-**C**H), 124.5 (Ar-**C**H), 124.0 (Ar-**C**H), 65.3 (O**C**H$_2$), 33.7 (**C**H$_2$), 23.3 (**C**H$_2$), 21.8 (**C**H$_2$); HRMS (ESI): calcd. for $C_{14}H_{17}NNaO_4$, 286.1050. Found: $[MNa]^+$, 286.1043 (2.3 ppm error).

3,4,7,8,9,10-Hexahydrobenzo[*f*][1]oxa[5]azacyclotridecine-2,6,11(1*H*)-trione (3-32)



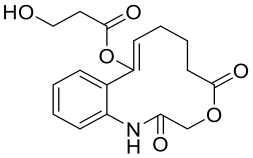
3,4,5,6-Tetrahydro-1H-(1)-benzazonin-2,7-dione **3-8** (203.2 mg, 1.0 mmol), DMAP (12.2 mg, 0.1 mmol) and pyridine (0.48 mL, 6.0 mmol) were stirred in DCM (5 mL) under an inert atmosphere at RT for 30 mins. To the stirred solution was added 3-(benzyloxy) propanoic acid chloride (3.0 mmol, 3.00 eq. prepared using the modified general procedure) in DCM (5 mL). The resulting mixture was heated, at reflux, at 50 °C for 18 h. The solvent was concentrated in *vacuo*, loaded onto a short silica plug and eluted with 2:1 hexane: ethyl acetate to remove the excess carboxylic acid and pyridine, and concentrated in *vacuo*. This material was redissolved in methanol (10 mL) under an inert atmosphere. Palladium on carbon (100 mg, Pd 10% on carbon) was then added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at RT under a slight positive pressure of hydrogen (balloon) for 2 h. The reaction was then purged with argon, filtered through Celite, washed with methanol and the solvent removed *in vacuo*. The crude material was then re-dissolved in chloroform (10 mL) and triethylamine (125 µL, 1.0 mmol) was added, and then stirred at RT for 16 h, then reduced in *vacuo*. Purification by flash column chromatography (SiO$_2$, 1: 1 hexane: ethyl acetate) afforded the *title compound* as a white solid (418 mg, 76% over 2 steps); m.p. 140 – 142 °C; $R_f = 0.45$ (1:2 hexane: ethyl acetate); ν_{max}/cm^{-1} (neat) 3288, 2946, 1733, 1679, 1521, 1481, 1448, 1241, 1147, 1042, 999, 763; δ_H (400 MHz, CDCl$_3$-*d*) 9.72 (s, 1H, CON**H**), 8.05 (d, *J* = 8.1 Hz, 1H, Ar-C**H**), 7.57 (dd, *J* = 7.8, 1.5 Hz, 1H, Ar-C**H**), 7.51 (td, *J* = 8.2, 1.5 Hz, 1H, Ar-C**H**), 7.18 (td, *J* = 7.7, 0.9 Hz, 1H, Ar-C**H**), 4.40 – 4.32 (m, 2H, OC$\mathbf{H_2}$), 2.99 – 2.88 (m, 2H, C$\mathbf{H_2}$), 2.71 – 2.56 (m, 2H, C$\mathbf{H_2}$), 2.48 – 2.32 (m, 2H, C$\mathbf{H_2}$), 1.84 – 1.59 (m, 4H, 2 × C$\mathbf{H_2}$); δ_C (100 MHz, CDCl$_3$-*d*) 207.2 (**C**O), 172.8 (**C**O), 169.7 (**C**O), 136.3 (Ar-**C**), 132.8 (Ar-**C**H), 129.8 (Ar-**C**), 128.2 (Ar-**C**H), 124.3 (Ar-**C**H), 124.1 (Ar-**C**H), 61.4 (O**C**H$_2$), 40.6 (**C**H$_2$), 38.7 (**C**H$_2$), 33.2 (**C**H$_2$), 23.5 (**C**H$_2$), 23.3 (**C**H$_2$); HRMS (ESI): calcd. for $C_{15}H_{17}NNaO_4$, 298.1050. Found: [MNa]$^+$, 298.1054 (–1.5 ppm error).

(*Z*)-2,5-Dioxo-2,3,5,6,7,8-hexahydro-1*H*-benzo[*e*][1]oxa[4]azacyclododecin-10-yl 2-hydroxyacetate (3-34)



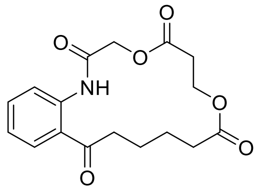
A mixture of 6,7,8,9-tetrahydro-1H-benzo[e][1]oxa[4]azacyclododecine-2,5,10(3H)-trione **3-29** (130.6 mg, 0.5 mmol), DMAP (6.1 mg, 0.05 mmol) and pyridine (243 µL, 3.0 mmol) in DCM (2.5 mL) under an argon atmosphere was stirred at RT for 5 mins. Next, a solution of acid chloride **3-27** (1.5 mmol, 3.0 equiv. prepared using the general procedure with benzyloxyacetic acid) in DCM (2.5 mL) was added and the resulting mixture was heated, at reflux, at 50 °C for 18 h. The solvent was then concentrated *in vacuo*, loaded onto a short silica plug and eluted with 1:1 hexane: ethyl acetate, to remove the majority of excess carboxylic acid and pyridine residues, and concentrated *in vacuo* (255 mg crude material obtained). This crude material was dissolved in EtOAc (5.0 mL) and placed under an argon atmosphere. Palladium on carbon (50 mg, 10% Pd on carbon) was then added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at RT under a slight positive pressure of hydrogen (balloon) for 24 h. The reaction was then purged with argon, filtered through Celite, washed with methanol where the solvent was removed *in vacuo.* The material was re-dissolved in chloroform (5.0 mL) and triethylamine (150 µL, 1.04 mmol) was added and stirred at RT for 16 h. Purification by flash column chromatography (SiO_2, 1:1 hexane: ethyl acetate) afforded the *title compound* as a colorless oil (73 mg, 46%); R_f = 0.13 (1:1 hexane: ethyl acetate); ν_{max}/cm^{-1} (neat) 3358, 2932, 1746, 1692, 1585, 1534, 1451, 1183, 1149, 1097, 769; δ_H (400 MHz, $CDCl_3$-*d*) 8.96 (s, 1H, N**H**), 8.04 (dd, *J* = 8.2, 1.2 Hz, 1H, Ar-C**H**), 7.31 – 7.26 (m, 1H, Ar-C**H**), 7.17 (dd, *J* = 7.7, 1.3 Hz, 1H, Ar-C**H**), 7.06 (td, *J* = 7.7, 1.1 Hz, 1H, Ar-C**H**), 5.23 (t, *J* = 7.3 Hz, 1H, OC=C**H**), 4.64 (s, 2H, OC**H$_2$**CO), 4.31 (s, 2H, C**H$_2$**OH), 3.18 (s, 1H, CH$_2$O**H**), 2.45 – 2.37 (m, 2H, C**H$_2$**), 2.23 (q, *J* = 7.0 Hz, 2H, C**H$_2$**), 2.06 – 1.94 (m, 2H, C**H$_2$**); δ_C (101 MHz, $CDCl_3$-*d*) 173.8 (**C**O), 173.5 (**C**O), 165.2 (**C**O), 142.4 (O**C**=CH), 134.8 (Ar-**C**), 130.1 (Ar-CH), 129.0 (Ar-CH), 126.3 (Ar-**C**), 124.5 (Ar-**C**H), 124.4 (OC=**C**H), 121.8 (Ar-**C**H), 64.0 (O**C**H_2CO), 60.4 (**C**H_2OH), 33.0 (**C**H_2), 26.7 (**C**H_2), 23.0 (**C**H_2); HRMS (ESI): calcd. for $C_{16}H_{17}NNaO_6$, 342.0948. Found: $[MNa]^+$, 342.0950 (–0.7 ppm error).

(*Z*)-2,5-Dioxo-2,3,5,6,7,8-hexahydro-1*H*-benzo[*e*][1]oxa[4]azacyclododecin-10-yl 3-hydroxypropanoate (3-35)



A mixture of 6,7,8,9-tetrahydro-1H-benzo[e][1]oxa[4]azacyclododecine-2,5,10(3H)-trione **3-29** (130.6 mg, 0.5 mmol), DMAP (6.1 mg, 0.05 mmol) and pyridine (243 µL, 3.0 mmol) in DCM (2.5 mL) under an argon atmosphere was stirred at RT for 5 mins. Next, a solution of acid chloride **3-30** (1.5 mmol, 3.0 equiv. prepared using the general procedure with benzyloxypropanoic acid) in DCM (2.5 mL) was added and the resulting mixture was heated, at reflux, at 50 °C for 18 h. The solvent was then concentrated *in vacuo*, loaded onto a short silica plug and eluted with 1:1 hexane: ethyl acetate, to remove majority of excess carboxylic acid and pyridine residues, and concentrated *in vacuo* (152 mg crude material obtained). This crude material was dissolved in EtOAc (5.0 mL) and placed under an argon atmosphere. Palladium on carbon (50 mg, 10% Pd on carbon) was then added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at RT under a slight positive pressure of hydrogen (balloon) for 24 h. The reaction was then purged with argon, filtered through Celite, washed with methanol where the solvent was removed *in vacuo.* The material was re-dissolved in chloroform (3.0 mL) and triethylamine (100 µL, 0.69 mmol) was added and stirred at RT for 16 h. Purification by flash column chromatography (SiO_2, 1:1 hexane: ethyl acetate) afforded the *title compound* as a colorless oil (45 mg, 27%); $R_f = 0.13$ (1:1 hexane: ethyl acetate); ν_{max}/cm^{-1} (neat) 3354, 2954, 1738, 1691, 1585, 1532, 1451, 1146, 1040, 762; δ_H (400 MHz, $CDCl_3$-*d*) 9.02 (s, 1H, N**H**), 8.14 (dd, *J* = 8.2, 1.2 Hz, 1H, Ar-C**H**), 7.36 – 7.30 (m, 1H, Ar-C**H**), 7.20 (dd, *J* = 7.7, 1.5 Hz, 1H, Ar-C**H**), 7.08 (td, *J* = 7.6, 1.1 Hz, 1H, Ar-C**H**), 5.22 (t, *J* = 7.3, 1H, OC=C**H**), 4.66 (s, 2H, COC**H$_2$**O), 3.89 (q, *J* = 5.6 Hz, 2H, C**H$_2$**OH), 2.69 (t, *J* = 5.7 Hz, 2H, C**H**$_2$), 2.48 (t, *J* = 5.7 Hz, 1H, CH$_2$O**H**), 2.46 – 2.38 (m, 2H, C**H**$_2$), 2.27 (q, *J* = 7.0 Hz, 2H, C**H**$_2$), 2.08 – 1.98 (m, 2H, C**H**$_2$); δ_C (101 MHz, CDCl$_3$-*d*) 173.9 (O**C**O), 172.8 (O**C**O), 165.0 (NH**C**O), 142.9 (O**C**=CH), 134.9 (Ar-**C**), 129.9 (Ar-**C**H), 128.9 (Ar-**C**H), 126.8 (Ar-**C**), 124.4 (Ar-**C**H), 124.2 (OC=**C**H), 121.8 (Ar-**C**H), 64.1 (O**C**H$_2$CO), 58.0 (**C**H$_2$OH), 36.8 (**C**H$_2$), 33.1 (**C**H$_2$), 26.8 (**C**H$_2$), 23.1 (**C**H$_2$); HRMS (ESI): calcd. for $C_{17}H_{19}NNaO_6$, 356.1105. Found: $[MNa]^+$, 356.1102 (0.7 ppm error).

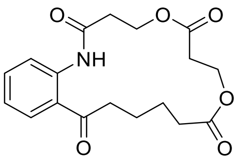
6,7,10,11,12,13-Hexahydro-1*H*,5*H*-benzo[*e*][1,13]dioxa[4]azacyclohexadecine-2,5,9,14(3*H*)-tetraone (3-37)



A mixture of 3,4,7,8,9,10-Hexahydrobenzo[*f*][1]oxa[5]azacyclotridecine-2,6,11(1*H*)-trione **3-32** (138 mg, 0.5 mmol), DMAP (6.1 mg, 0.05 mmol) and pyridine (243 µL, 3.0 mmol) in DCM (2.5 mL) under an argon atmosphere was stirred at RT for 5 mins. Next, a solution of acid chloride (1.5 mmol, 3.0 equiv. prepared using the general procedure with benzyloxyacetic acid) in DCM (2.5 mL) was added and the resulting mixture was heated, at reflux, at 50 °C for 18 h. The solvent was then concentrated *in vacuo*, loaded onto a short silica plug and eluted with 1:1 hexane: ethyl acetate, to remove the majority of excess carboxylic acid and pyridine residues, and concentrated *in vacuo* (140 mg crude material obtained). This crude material was dissolved in EtOAc (5.0 mL) and placed under an argon atmosphere. Palladium on carbon (50 mg, 10% Pd on carbon) was then added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at RT under a slight positive pressure of hydrogen (balloon) for 16 h. The reaction was then purged with argon, filtered through Celite, washed with methanol where the solvent was removed *in vacuo*. The material was re-dissolved in chloroform (3.0 mL) and triethylamine (100 µL, 0.69 mmol) was added and stirred at RT for 16 h. Purification by flash column chromatography (SiO$_2$, 1:1 hexane: ethyl acetate) afforded the *title compound* as a colorless oil (45 mg, 27%); R_f = 0.30 (1:1

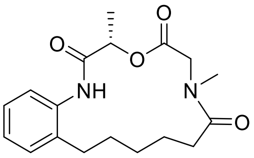
hexane: ethyl acetate); ν_{max}/cm^{-1} (neat) 2925, 1757, 1732, 1693, 1656, 1584, 1525, 1452, 1211, 1161, 1015, 760; δ_H (400 MHz, $CDCl_3$-*d*) 12.40 (s, 1H, N**H**), 8.77 (dd, *J* = 8.5, 1.1 Hz, 1H, Ar-C**H**), 7.92 (dd, *J* = 8.0, 1.5 Hz, 1H, Ar-C**H**), 7.56 (ddd, *J* = 8.6, 7.4, 1.5 Hz, 1H, Ar-C**H**), 7.16 (ddd, *J* = 8.3, 7.5, 1.2 Hz, 1H, Ar-C**H**), 4.82 (s, 2H, OC**H₂**CO), 4.59 – 4.49 (m, 2H, OC**H₂**), 3.14 – 2.97 (m, 4H, 2 × C**H₂**), 2.32 – 2.14 (m, 2H, C**H₂**), 1.97 – 1.83 (m, 2H, C**H₂**), 1.63 – 1.50 (m, 2H, C**H₂**); δ_C (101 MHz, $CDCl_3$-*d*) 204.2 (**C**O), 172.9 (**C**O), 170.8 (**C**O), 166.9 (**C**O), 139.8 (Ar-**C**), 135.2 (Ar-**C**H), 130.6 (Ar-**C**H), 123.2 (Ar-**C**H), 122.5 (Ar-**C**), 120.9 (Ar-**C**H), 62.9 (O**C**H₂CO), 58.7 (O**C**H₂), 38.8 (**C**H₂), 34.0 (**C**H₂), 33.1 (**C**H₂), 24.9 (**C**H₂), 20.2 (**C**H₂); HRMS (ESI): calcd. for $C_{17}H_{19}NNaO_6$, 356.1105. Found: $[MNa]^+$, 356.1105 (–0.2 ppm error).

3,4,7,8,11,12,13,14-Octahydro-6*H*-benzo[*j*][1,5]dioxa[9]azacycloheptadecine-2,6,10,15(1*H*)-tetraone (3-38)



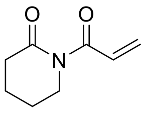
A mixture of 3,4,7,8,9,10-hexahydrobenzo[*f*][1]oxa[5]azacyclotridecine-2,6,11(1*H*)-trione **3-32** (138 mg, 0.5 mmol), DMAP (6.1 mg, 0.05 mmol) and pyridine (243 μL, 3.0 mmol) in DCM (2.5 mL) under an argon atmosphere was stirred at RT for 5 mins. Next, a solution of acid chloride (1.5 mmol, 3.0 equiv. prepared using the general procedure with benzyloxypropanoic acid) in DCM (2.5 mL) was added and the resulting mixture was heated, at reflux, at 50 °C for 18 h. The solvent was then concentrated *in vacuo*, loaded onto a short silica plug and eluted with 1:1 hexane: ethyl acetate, to remove the majority of excess carboxylic acid and pyridine residues, and concentrated *in vacuo* (44 mg crude material obtained). This crude material was dissolved in EtOAc (5.0 mL) and placed under an argon atmosphere. Palladium on carbon (50 mg, 10% Pd on carbon) was then added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at RT under a slight positive pressure of hydrogen (balloon) for 24 h. The reaction was then purged with argon, filtered through Celite, washed with methanol where the solvent was removed *in vacuo*. The material was re-dissolved in chloroform (3.0 mL) and triethylamine (100 µL, 0.69 mmol) was added and stirred at RT for 16 h. Purification by flash column chromatography (SiO_2, 1:1 hexane: ethyl acetate) afforded the *title compound* as a colorless oil (21 mg, 9%); R_f = 0.56 (ethyl acetate); ν_{max}/cm^{-1} (neat) 3227, 2961, 1735, 1660, 1583, 1518, 1449, 1359, 1297, 1211, 1180, 1017, 759; δ_H (400 MHz, $CDCl_3$-*d*) 11.57 (s, 1H, N**H**), 8.69 (dd, *J* = 8.5, 1.1 Hz, 1H, Ar-C**H**), 7.85 (dd, *J* = 8.0, 1.5 Hz, 1H, Ar-C**H**), 7.55 (ddd, *J* = 8.7, 7.4, 1.5 Hz, 1H, Ar-C**H**), 7.14 (ddd, *J* = 8.2, 7.5, 1.2 Hz, 1H, Ar-C**H**), 4.55 – 4.50 (m, 2H, OC$\mathbf{H_2}$), 4.41 – 4.36 (m, 2H, OC$\mathbf{H_2}$), 3.11 – 3.01 (m, 2H, C$\mathbf{H_2}$), 2.86 – 2.79 (m, 2H, C$\mathbf{H_2}$), 2.75 – 2.67 (m, 2H, C$\mathbf{H_2}$), 2.32 (t, *J* = 7.1Hz, 2H, C$\mathbf{H_2}$), 1.83 – 1.73 (m, 2H, C$\mathbf{H_2}$), 1.61 – 1.53 (m, 2H, C$\mathbf{H_2}$); δ_C (101 MHz, $CDCl_3$-*d*) 204.9 (**C**O), 173.0 (**C**O), 171.5 (**C**O), 169.7 (**C**O), 139.9 (Ar-**C**), 134.7 (Ar-**C**H), 130.4 (Ar-**C**H), 123.2 (Ar-**C**), 123.0 (Ar-**C**H), 121.7 (Ar-**C**H), 61.0 (O**C**H$_2$), 59.4 (O**C**H$_2$), 39.2 (**C**H$_2$), 38.2 (**C**H$_2$), 34.5 (**C**H$_2$), 34.0 (**C**H$_2$), 24.5 (**C**H$_2$), 23.3 (**C**H$_2$); HRMS (ESI): calcd. for $C_{18}H_{21}NNaO_6$, 370.1261. Found: $[MNa]^+$, 370.1265 (–1.1 ppm error).

(*S*)-3,7-dimethyl-1,6,7,9,10,11,12,13-octahydrobenzo[*e*][1]oxa[4,13]diazacyclopentadecine-2,5,8(3*H*)-trione (3-45)



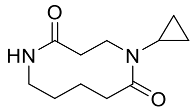
A mixture of 4-methyl-3,4,6,7,8,9-hexahydrobenzo[e][1,4]diazacyclododecine-2,5,10 (1H)-trione **3-21** (137.2 mg, 0.5mmol), DMAP (6.1 mg, 0.05 mmol) and pyridine (243 µL, 3.0 mmol) in DCM (2.5 mL) under an argon atmosphere was stirred at RT for 5 mins. Next, a solution of acid chloride (1.5 mmol, 3.0 equiv. prepared using the general procedure with (*R*)-2-benzyloxypropionic acid) in DCM (2.5 mL) was added and the resulting mixture was heated, at reflux, at 50 °C for 18 h. The solvent was then concentrated *in vacuo*, loaded onto a short silica plug and eluted with ethyl acetate, to remove majority of excess carboxylic acid and pyridine residues, and concentrated *in vacuo* (200 mg crude material obtained). This crude material was dissolved in EtOAc (5.0 mL) and placed under an argon atmosphere. Palladium on carbon (50 mg, 10% Pd on carbon) was then added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at RT under a slight positive pressure of hydrogen (balloon) for 24 h. The reaction was then purged with argon, filtered through Celite, washed with methanol where the solvent was removed in vacuo. The material was re-dissolved in chloroform (3.0 mL) and triethylamine (100 µL, 0.69 mmol) was added and stirred at RT for 16 h. Purification by flash column chromatography (SiO_2, ethyl acetate) afforded *the title compound* (as a 10:1 mixture of rotamers) as a white solid (35 mg, 21%); R_f = 0.30 (1:1 chloroform: acetone); δ_H (400 MHz, DMSO-*d*$_6$) 9.23 (s, 1H, N**H**, major rotamer), 8.89 (s, 1H, N**H**, minor rotamer), 6.93 – 6.67 (m, 5H, Ar-C**H**, both rotamers), 4.88 (q, *J* = 6.5 Hz, 1H, OC**H**CO, minor rotamer), 4.80 (q, *J* = 6.8 Hz, 1H, OC**H**CO, major rotamer), 4.41 (d, *J* = 19.1 Hz, 1H, NC**H**$_2$CO, both rotamers), 3.84 (d, *J* = 19.1 Hz, 1H, NC**H**$_2$CO, both rotamers), 2.73 (s, 3H, NC**H**$_3$, minor rotamer), 2.18 – 2.05 (m, 3H, NC**H**$_3$, major rotamer), 1.89 – 1.77 (m, 1H, C**H**$_2$, both rotamers), 1.59 – 1.34 (m, 2H, C**H**$_2$, both rotamers), 1.24 – 0.78 (m, 10H, CHC**H**$_3$ + C**H**$_2$, both rotamers); δ_C (100 MHz, DMSO-*d*$_6$) for major rotamer only: 173.6 (**C**O), 170.1 (**C**O), 169.9 (**C**O), 140.5 (Ar-**C**), 134.7 (Ar-**C**), 130.0 (Ar-**C**H), 128.3 (Ar-**C**H), 127.4 (Ar-**C**H), 126.3 (Ar-**C**H), 71.4 (O**C**HCO), 51.1 (N**C**H$_2$CO), 34.6 (N**C**H$_3$), 31.0 (**C**H$_2$), 30.0 (**C**H$_2$), 29.3 (**C**H$_2$), 27.2 (**C**H$_2$), 23.7 (**C**H$_2$), 17.4 (CH**C**H$_3$); Diagnostic ^{13}C NMR resonances for the minor rotamer: 168.2 (**C**O), 127.6 (Ar-**C**H), 127.0 (Ar-**C**H), 71.3 (O**C**HCO), 37.1 (N**C**H$_3$), 31.7 (**C**H$_2$), 29.7 (**C**H$_2$), 23.1 (**C**H$_2$), 17.0 (CH**C**H$_3$); HRMS (ESI): calcd. for $C_{18}H_{24}N_2NaO_4$, 355.1628. Found: $[MNa]^+$, 355.1628 (0.1 ppm error).

1-Acryloyl-piperidin-2-one (4-17)



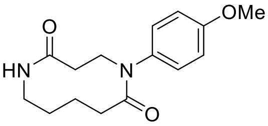
To a stirring solution of δ-valerolactam (992 mg, 10.0 mmol) in dry THF (36.4 mL) cooled to 0 °C was added a solution of MeMgBr (3.0 M in diethyl ether, 3.65 mL, 11.0 mmol) *via* dropwise addition using a syringe pump over 30 min. The reaction mixture was allowed to stir for 10 min at 0 °C after addition was completed, before acryloyl chloride (1.22 mL, 15.0 mmol) was added in a single portion and the reaction mixture was stirred for an additional 30 min at 0 °C. The reaction was then quenched with sat. aq. NH_4Cl (30 mL) and the mixture was extracted with Et_2O (50 mL). The organic layer was washed with sat. aq. $NaHCO_3$ (2 × 30 mL), and organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 diethyl ether: hexane) afforded the *title compound* as a viscous colourless liquid (1.06 g, 69%); $R_f = 0.59$ (ethyl acetate); ν_{max}/cm^{-1} (thin film) 2953, 1679, 1404, 1384, 1289, 1211, 1156, 1004, 796; δ_H (400 MHz, $CDCl_3$), 6.97 (dd, *J* = 17.0, 10.5 Hz, 1H, NCOC**H**CHH'), 6.33 (dd, *J* = 17.0, 1.7 Hz, 1H, NCOCHC**H**H'), 5.69 (dd, *J* = 10.5, 1.7 Hz, 1H, NCOCHCH**H'**), 3.76 – 3.71 (m, 2H, NC**H₂**), 2.60 – 2.53 (m, 2H, C**H₂**CON), 1.90 – 1.81 (m, 4H, 2 × C**H₂**); δ_C (100 MHz, $CDCl_3$), 173.8 (**C**O), 169.7 (**C**O), 132.0 (NCO**C**HCHH'), 128.0 (NCOCH**C**HH'), 44.7 (N**C**H₂), 34.9 (**C**H₂CON), 22.6 (**C**H₂), 20.8 (**C**H₂); HRMS (ESI): calcd. for $C_8H_{11}NNaO_2$, 176.0682. Found: $[MNa]^+$, 176.0684 (–0.9 ppm error).

5-Cyclopropyl-1,5-diazecane-2,6-dione (4-19a)



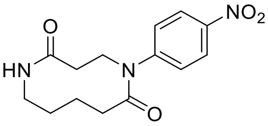
To a solution of 1-acryloylpiperidin-2-one (153.2 mg, 1.00 mmol) in dry methanol (2.0 mL), was added cyclopropylamine (62.8 mg/ 76.2 μL, 1.10 mmol) in a single portion. The reaction mixture was allowed to stir for 4 h at RT then the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 ethyl acetate: hexane →1:50 methanol: ethyl acetate→ 1:10 methanol: ethyl acetate) afforded the *title compound* as a colourless oil (189 mg, 90%). In solution in $CDCl_3$, this compound exists as a roughly 20:1 mixture of rotamers. $R_f = 0.21$ (1:9 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3300, 3087, 2929, 1649, 1550, 1442, 1324, 1270, 1195, 1065; δ_H (400 MHz, $CDCl_3$-*d*) 6.66 (s, 1H, N**H**, minor rotamer), 6.01 (d, *J* = 4.0 Hz, 1H, N**H**, major rotamer), 4.30 (dt, *J* = 14.1, 7.2 Hz, 1H, NC**H₂**, major rotamer), 4.19 – 4.09 (m, 1H, NC**H₂**, minor rotamer), 3.94 – 3.85 (m, 1H, NC**H**, minor rotamer), 3.79 – 3.65 (m, 1H, NC**H**, major rotamer), 3.38 – 3.30 (m, 1H, NC**H₂**, minor rotamer), 3.12 (dt, *J* = 13.5, 7.8 Hz, 1H, NC**H₂**, major rotamer), 3.07 – 2.94 (m, 1H, NC**H₂**, both rotamers), 2.84 – 2.73 (m, 1H, COC**H$_2$**, both rotamers), 2.76 – 2.63 (m, 2H, COC**H$_2$**, both rotamers), 2.52 – 2.41 (m, 1H, NC**H$_2$**, both rotamers), 2.11 – 1.95 (m, 1H, COC**H$_2$**, both rotamers), 1.86 – 1.75 (m, 2H, C**H$_2$**, both rotamers), 1.73 – 1.56 (m, 2H, C**H$_2$**, both rotamers), 1.00 – 0.72 (m, 2H, C**H$_2$**, both rotamers), 0.71 – 0.53 (m, 2H, C**H$_2$**, both rotamers); δ_C (100 MHz, CDCl$_3$-*d*) for the major rotamer: 179.0 (**C**O), 171.5 (**C**O), 43.8 (N**C**H$_2$), 40.0 (N**C**H$_2$), 36.0 (CO**C**H$_2$), 35.5 (CO**C**H$_2$), 30.9 (N**C**H), 27.5 (**C**H$_2$), 24.2 (**C**H$_2$), 12.1 (**C**H$_2$), 7.5 (**C**H$_2$); ^{13}C NMR resonances for the minor rotamer: 176.0 (**C**O), 171.3 (**C**O), 46.6 (N**C**H$_2$), 39.2 (N**C**H$_2$), 38.0 (CO**C**H$_2$), 29.6 (CO**C**H$_2$), 29.1 (N**C**H), 25.0 (**C**H$_2$), 23.2 (**C**H$_2$), 9.2 (**C**H$_2$), 6.6 (**C**H$_2$); HRMS (ESI): calcd. for $C_{11}H_{18}N_2NaO_2$, 233.1260. Found: [MNa]$^+$, 233.1259 (0.6 ppm error).

5-(4-Methoxyphenyl)-1,5-diazecane-2,6-dione (4-19c)



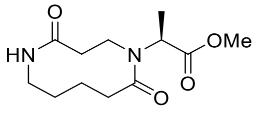
To a solution of 1-acryloylpiperidin-2-one **4-17** (153.2 mg, 1.00 mmol) in dry methanol (2.0 mL), was added 4-methoxybenzenamine (135.5 mg, 1.10 mmol) in a single portion. The reaction mixture was allowed to stir for 4 h at RT and then the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO$_2$, 1:50 methanol: ethyl acetate → 1:10 methanol: ethyl acetate) afforded the *title compound* as a white solid (240 mg, 88%). In solution in CDCl$_3$, this compound largely as a single rotamer, with a trace amount of a minor rotamer visible in the ^{1}H and ^{13}C NMR spectra; $R_f = 0.30$ (1:9 methanol: ethyl acetate); m.p. 52 –55°C, ν_{max}/cm^{-1} (thin film) 3301, 2934, 1622, 1510, 1444, 1244, 1174, 1030, 835, 729; NMR data for the major rotamer only. δ_H (400 MHz, CDCl$_3$-*d*) δ 7.30 – 7.07 (m, 2H, Ar-C**H**), 6.90 – 6.80 (m, 2H, Ar-C**H**), 6.21 (d, *J* = 9.3 Hz, 1H, NH), 4.34 (dd, *J* = 13.6, 7.9 Hz, 1H, NC**H$_2$**), 3.82 (dt, *J* = 13.7, 4.4 Hz, 1H, NC**H$_2$**), 3.76 (s, 3H, OC**H$_3$**), 3.38 (dt, *J* = 14.2, 8.7 Hz, 1H, NC**H$_2$**), 3.09 (dt, *J* = 11.6, 8.6 Hz, 1H, NC**H$_2$**), 2.65 – 2.51 (m, 1H, COC**H$_2$**), 2.46 – 2.24 (m, 2H, COC**H$_2$**), 2.08 – 1.90 (m, 1H, COC**H$_2$**), 1.72 – 1.34 (m, 4H, C**H$_2$**); δ_C (400 MHz, CDCl$_3$-*d*) 177.1 (**C**O), 172.6 (**C**O), 158.7 (Ar-**C**), 137.4 (Ar-**C**), 128.4 (2 × Ar-**C**H), 114.7 (2 × Ar-**C**H), 55.5 (O**C**H$_3$), 49.1 (N**C**H$_2$), 40.1 (N**C**H$_2$), 36.3 (CO**C**H$_2$), 35.6 (CO**C**H$_2$), 27.8 (**C**H$_2$), 25.2 (**C**H$_2$); HRMS (ESI): calcd. for $C_{15}H_{20}N_2NaO_3$, 299.1366. Found: $[MNa]^+$, 299.1358 (2.8 ppm error). Characteristic NMR data for the minor rotamers can be found at: δ_H (400 MHz, CDCl$_3$) 7.13 (2H, m, Ar-C**H**), 6.87 (2H, m, Ar-C**H**), 5.97 (1H, m, N**H**), 3.60 (1H, m, C**H$_2$**); δ_C (100 MHz, CDCl$_3$) 174.2 (**C**O), 171.0 (**C**O), 158.3 (Ar-**C**), 128.6 (Ar-**C**H), 49.4 (**C**H$_2$), 39.6 (**C**H$_2$), 38.2 (**C**H$_2$), 28.8 (**C**H$_2$), 26.0 (**C**H$_2$), 24.0 (**C**H$_2$).

5-(4-Nitrophenyl)-1,5-diazecane-2,6-dione (4-19d)



To a solution of 1-acryloylpiperidin-2-one (60 mg, 0.39 mmol) in dry methanol (2.0 mL), was added 4-nitroaniline (59.2 mg, 0.43 mmol) in a single portion. The reaction mixture was allowed to stir for 72 h at RT and then the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO$_2$, 1:1 hexane: ethyl acetate) afforded the *title compound* as a yellow solid (24 mg, 21%); $R_f = 0.25$ (1:1 hexane: ethyl acetate); m.p. 118 – 120 °C, ν_{max}/cm^{-1} (thin film) 3374, 2958, 1686,1600, 1503, 1474, 1307, 1193, 1110, 835, 754; δ_H (400 MHz, CDCl$_3$-*d*) δ 8.05 (dd, $J = 9.2, 0.6$ Hz, 2H, Ar-C**H**), 6.55 – 6.50 (dd, $J = 9.2, 0.6$ Hz, 2H, Ar-C**H**), 3.75 – 3.70 (m, 2H, NC**H$_2$**), 3.58 (t, $J = 6.0$ Hz, 2H, NC**H$_2$**), 3.21 (t, $J = 6.0$ Hz, 2H, COC**H$_2$**), 2.60 – 2.50 (m, 2H, COC**H$_2$**), 1.88 – 1.80 (m, 4H, 2 × C**H$_2$**); δ_C (400 MHz, CDCl$_3$-*d*) 175.2 (**C**O), 173.9 (**C**O), 153.2 (Ar-**C**), 138.0 (Ar-**C**), 126.6 (2 × Ar-**C**H), 111.1 (2 × Ar-**C**H), 44.3 (N**C**H$_2$), 39.2 (N**C**H$_2$), 38.9 (CO**C**H$_2$), 34.9 (CO**C**H$_2$), 22.4 (**C**H$_2$), 20.3 (**C**H$_2$); HRMS (ESI): calcd. for $C_{14}H_{17}N_3NaO_4$, 314.1111. Found: $[MNa]^+$, 314.1110 (0.5 ppm error).

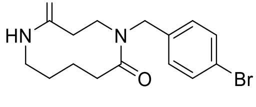
Methyl (*S*)-2-(4,10-dioxo-1,5-diazecan-1-yl)propanoate (4-19e)



To a solution of 1-acryloylpiperidin-2-one (153.2 mg, 1.00 mmol) in dry methanol (2.0

mL), was added *L*-alanine methyl ester (113.4 mg, 1.10 mmol) in a single portion. The reaction mixture was allowed to stir for 4 h at RT and then the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:9 methanol: ethyl acetate) afforded the *title compound* as a colourless oil (154 mg, 60%). In solution in $CDCl_3$, this compound as a roughly 2:1 mixture of rotamers; R_f = 0.23 (1:9 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3320, 2937, 1717, 1633, 1557, 1443, 1316, 1260, 1213, 1159, 1103, 1061, 1030, 719; δ_H (400 MHz, $CDCl_3$-*d*) δ 7.39 (d, *J* = 9.7 Hz, 1H, N**H**, minor rotamer), 7.29 (d, *J* = 9.1 Hz, 1H, N**H**, major rotamer), 4.81 (q, *J* = 7.8 Hz, 1H, NC**H$_2$**, minor rotamer), 3.89 – 3.68 (m, 2H, NC**H$_2$**, major rotamer), 3.67 (s, 3H, OC**H$_3$**, major rotamer), 3.65 (s, 3H, OC**H$_3$**, minor rotamer), 3.60 – 3.58 (m, 1H, NC**H$_2$**, minor rotamer), 3.44 (q, *J* = 6.9 Hz, 1H, NC**H**, major rotamer), 3.43 – 3.31 (m, 1H, NC**H**, minor rotamer), 3.17 (dt, *J* = 15.4, 3.6 Hz, 1H, NC**H**$_2$, both rotamers), 2.78 (dd, *J* =13.7, 3.9 Hz, 1H, NC**H**$_2$, both rotamers), 2.45 – 1.83 (m, 6H, 3 × C**H$_2$**, both rotamers), 1.52 – 1.42 (m, 2H, C**H$_2$**, both rotamers), 1.40 (d, *J* = 6.9 Hz, 3H, C**H$_3$**, major rotamer), 1.35 (d, *J* = 7.9 Hz, 3H, C**H$_3$**, minor rotamer); δ_C (100 MHz, $CDCl_3$-*d*) for major rotamer: 173.3 (**C**O), 173.0 (**C**O), 170.5 (**C**O), 58.5 (O**C**H$_3$), 52.7 (N**C**H), 47.2 (N**C**H$_2$), 38.8 (N**C**H$_2$), 36.7 (CO**C**H$_2$), 27.8 (CO**C**H$_2$), 24.6 (**C**H$_2$), 23.6 (**C**H$_2$), 14.1 (**C**H$_3$); Diagnostic ^{13}C NMR resonances for minor rotamer: 176.0 (**C**O), 174.6 (**C**O), 170.8 (**C**O), 53.1 (N**C**H), 40.4 (N**C**H$_2$), 38.7 (N**C**H$_2$), 38.0 (CO**C**H$_2$), 28.4 (CO**C**H$_2$), 24.9 (**C**H$_2$), 23.8 (**C**H$_2$), 14.6 (**C**H$_3$); HRMS (ESI): calcd. for $C_{12}H_{20}N_2NaO_4$, 279.1315. Found: $[MNa]^+$, 279.1316 (–0.2 ppm error).

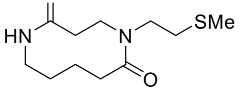
5-(4-Bromobenzyl)-1,5-diazecane-2,6-dione (4-19f)



To a solution of 1-acryloylpiperidin-2-one (153.2 mg, 1.00 mmol) in dry methanol (2.0 mL), was added 4-bromobenzylamine (204.6 mg, 1.11 mmol) in a single portion. The reaction mixture was allowed to stir for 2 h at RT until a white solid precipitated out of solution and then the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 ethyl acetate: hexane → ethyl acetate → 1:50 methanol:

ethyl acetate) afforded the *title compound* as a white solid (330 mg, 97%). In solution in $CDCl_3$, this compound as a roughly 10:1 mixture of rotamers; m.p. 167 – 170 °C, R_f = 0.23 (1:9 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3291, 3092, 2931, 1618, 1560, 1487, 1264, 1010, 731; δ_H (400 MHz, $CDCl_3$-*d*) 7.43 (d, *J* = 8.2 Hz, 2H, Ar**H**, both rotamers), 7.14 (d, *J* = 8.3 Hz, 2H, Ar-C**H**, major rotamer), 7.03 (d, *J* = 8.2 Hz, 2H, Ar-C**H**, minor rotamer), 5.94 (d, *J* = 10.0 Hz, 1H, N**H**, minor rotamer), 5.53 (d, *J* = 9.3 Hz, 1H, N**H**, major rotamer), 5.02 (d, *J* = 14.7 Hz, 1H, NC$\mathbf{H_2}$Ph, major rotamer), 4.79 (d, *J* = 16.6 Hz, 1H, NC$\mathbf{H_2}$Ph, minor rotamer), 4.28 (d, *J* = 16.6 Hz, 1H, NC$\mathbf{H_2}$Ph, minor rotamer), 4.10 (d, *J* = 14.7 Hz, 1H, NC$\mathbf{H_2}$Ph, major rotamer), 3.97 – 3.73 (m, 2H, NC$\mathbf{H_2}$, both rotamers), 3.28 – 3.19 (d, 1H, NC$\mathbf{H_2}$, both rotamers), 2.95 – 2.82 (m, 1H, NC$\mathbf{H_2}$, both rotamers), 2.73 – 2.61 (m, 1H, COC$\mathbf{H_2}$, both rotamers), 2.27 – 2.07 (m, 4H, 2 × C$\mathbf{H_2}$, both rotamers), 1.64 (m, 2H, COC$\mathbf{H_2}$, both rotamers), 1.56 – 1.40 (m, 1H, COC$\mathbf{H_2}$, both rotamers); δ_C (100 MHz, $CDCl_3$-*d*) for major rotamer: 174.2 (**C**O), 171.0 (**C**O), 137.0 (Ar-**C**Br), 132.1 (2 × Ar-**C**H), 129.9 (2 × Ar-**C**H), 121.8 (Ar-**C**), 48.7 (**C**H_2), 45.2 (**C**H_2), 39.3 (**C**H_2), 37.6 (**C**H_2), 28.3 (**C**H_2), 25.9 (**C**H_2), 23.8 (**C**H_2); Diagnostic ^{13}C NMR resonances for the minor rotamer: 176.4 (**C**O), 171.3 (**C**O), 135.8 (Ar-**C**Br), 128.5 (Ar-**C**H), 53.9 (**C**H_2), 42.5 (**C**H_2), 40.2 (**C**H_2), 35.1 (**C**H_2), 27.4 (**C**H_2), 25.0 (**C**H_2); HRMS (ESI): calcd. for $C_{15}H_{19}BrN_2NaO_2$, 361.0519. Found: $[MNa]^+$, 361.0522 (1.0 ppm error).

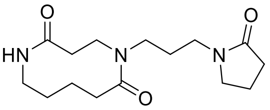
5-(2-(Methylthio)ethyl)-1,5-diazecane-2,6-dione (4-19g)



To a solution of 1-acryloylpiperidin-2-one (153.2 mg, 1.00 mmol) in dry methanol (2.0 mL), was added 2-(methylthio)ethylamine (102.3 µL, 1.10 mmol) in a single portion. The reaction mixture was allowed to stir for 4 h at RT and then the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:10 methanol: ethyl acetate → 1:9 methanol: ethyl acetate) afforded the *title compound* as a colourless oil (178 mg, 72%); R_f = 0.35 (1:9 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3291, 2928, 1617, 1432, 1350, 1199, 1173, 1107, 700; δ_H (400 MHz, $CDCl_3$-*d*) δ 6.67 (d, *J* =

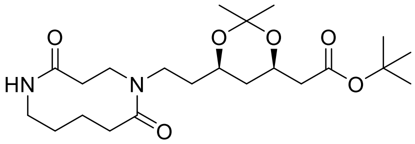
9.2 Hz, 1H, N**H**), 3.92 (t, *J* = 13.7 Hz, 1H, NC**H**$_2$), 3.79 – 3.58 (m, 2H, NC**H$_2$**), 3.41 (dt, *J* = 13.0, 5.6 Hz, 1H, NC**H$_2$**), 3.23 – 3.14 (m, 1H, NC**H**$_2$), 2.85 – 2.70 (m, 2H), 2.64 – 2.47 (m, 2H, C**H$_2$**), 2.32 – 2.14 (m, 2H, C**H$_2$**), 2.07 (s, 3H, SC**H$_3$**), 2.04 – 1.90 (m, 2H, C**H$_2$**), 1.63 – 1.44 (m, 2H, C**H$_2$**), 1.42 – 1.30 (m, 1H, C**H**$_2$); δ$_C$ (400 MHz, CDCl$_3$-*d*) 174.2 (N**C**O), 170.8 (N**C**O), 46.5 (N**C**H$_2$), 46.0 (N**C**H$_2$), 39.0 (N**C**H$_2$), 38.2 (CO**C**H$_2$), 32.2 (CO**C**H$_2$), 28.4 (**C**H$_2$), 25.7 (**C**H$_2$), 23.9 (**C**H$_2$), 15.1 (S**C**H$_3$); HRMS (ESI): calcd. for $C_{11}H_{21}N_2O_2S$, 245.1318. Found: $[MH]^+$, 245.1315 (1.4 ppm error).

5-(3-(2-Oxopyrrolidin-1-yl)propyl)-1,5-diazecane-2,6-dione (4-19h)



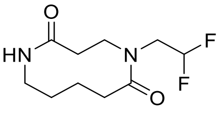
To a solution of 1-acryloylpiperidin-2-one (153.2 mg, 1.00 mmol) in dry methanol (2.0 mL), was added 1-(3-aminopropyl)-2-pyrrolidinone (154 µL, 1.10 mmol) in a single portion. The reaction mixture was allowed to stir for 4 h at RT and then the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO$_2$, 1:1 hexane: ethyl acetate → 1:2 methanol: ethyl acetate → 1:1 methanol: ethyl acetate) afforded the *title compound* as a colourless oil (263 mg, 89%); R$_f$ = 0.22 (1:1 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3288, 2933, 1651, 1614, 1562, 1427, 1295, 1008, 815; δ$_H$ (400 MHz, CDCl$_3$-*d*) δ 7.00 (m, 1H, N**H**), 4.02 – 3.62 (m, 2H, NC**H$_2$**), 3.43 – 3.17 (m, 6H, 3 × NC**H$_2$**), 3.16 – 2.78 (m, 2H, NC**H$_2$**), 2.72 – 2.57 (m, 1H, C**H$_2$**), 2.34 – 2.16 (m, 4H, 2 × C**H$_2$**), 2.07 – 1.88 (m, 4H, 2× C**H$_2$**), 1.85 – 1.73 (m, 1H, C**H$_2$**), 1.66 – 1.28 (m, 4H, 2 × C**H$_2$**); δ$_C$ (100 MHz, CDCl$_3$-*d*) 175.2 (**C**O), 174.3 (**C**O), 171.1 (**C**O), 47.1 (N**C**H$_2$), 46.8 (N**C**H$_2$), 45.3 (N**C**H$_2$), 40.5 (N**C**H$_2$), 39.0 (N**C**H$_2$), 38.9 (CO**C**H$_2$), 30.9 (CO**C**H$_2$), 28.2 (CO**C**H$_2$), 26.7 (**C**H$_2$), 26.1 (**C**H$_2$), 23.9 (**C**H$_2$), 17.9 (**C**H$_2$); HRMS (ESI): calcd. for $C_{15}H_{25}N_3NaO_3$, 318.1788. Found: $[MNa]^+$, 318.1783 (1.6 ppm error).

tert-Butyl 2-((4*R*,6*R*)-6-(2-(4,10-dioxo-1,5-diazecan-1-yl)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate (4-19i)



To a solution of 1-acryloylpiperidin-2-one **4-17** (153.2 mg, 1.00 mmol) in dry methanol (2.0 mL), was added tert-butyl [(4R,6R)-6-aminoethyl-2,2-dimethyl-1,3-dioxan-4-yl]acetate (300.7 mg, 1.10 mmol) in a single portion. The reaction mixture was allowed to stir for 4 h at RT and then the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:20 methanol: ethyl acetate → 1:10 methanol: ethyl acetate) afforded the *title compound* (as a 1:1 mixture of rotamers) as a colourless oil (292 mg, 68%); $R_f = 0.35$ (1:9 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3299, 2979, 2936, 1726, 1614, 1427, 1367, 1267, 1201, 1155, 951, 842, 732; δ_H (400 MHz, Methanol-*d₄*): δ 4.40 – 4.28 (m, 1H, O**C**H), 4.13 – 3.93 (m, 3H, OC**H** + C**H₂**), 3.65 – 3.44 (m, 2H, C**H₂**), 3.22 – 2.72 (m, 3H, C**H**₂ + C**H₂**), 2.49 – 2.20 (m, 4H, 2 × C**H₂**), 2.17 – 1.98 (m, 2H, C**H₂**), 1.88 – 1.54 (m, 6H, 3 × C**H₂**), 1.49 (s, 12H, 3 × COOCC**H₃** + OCC**H₃**), 1.36 (s, 3H, OCC**H₃**), 1.27 – 1.16 (m, 1H, C**H**₂); δ_C (100 MHz, Methanol-*d₄*): 174.4 and 174.3 (**C**O), 172.1 (**C**O, both rotamers), 170.6 (**C**O, both rotamers), 98.7 and 98.6 (O**C**O), 80.4 (COO**C**, both rotamers), 67.3 and 66.7 (O**C**H), 66.3 (O**C**H, both rotamers), 45.6 (N**C**H₂, both rotamers), 44.8 (N**C**H₂, both rotamers), 42.4 (N**C**H₂, both rotamers), 39.2 (**C**H₂, both rotamers), 36.3 (**C**H₂, both rotamers), 36.2 (**C**H₂, both rotamers), 33.9 and 33.8 (**C**H₂), 29.3 (OC**C**H₃, both rotamers), 28.2 (**C**H₂, both rotamers), 27.2 (3 × COOC**C**H₃, both rotamers), 25.0 (**C**H₂, both rotamers), 23.8 (**C**H₂, both rotamers), 18.9 (OC**C**H₃, both rotamers); HRMS (ESI): calcd. for $C_{22}H_{38}N_2NaO_6$, 449.2622. Found: $[MNa]^+$, 449.2628 (−1.3 ppm error).

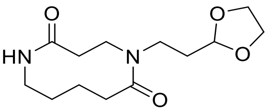
5-(2,2-Difluoroethyl)-1,5-diazecane-2,6-dione (4-19j)



To a solution of 1-acryloylpiperidin-2-one (153.2 mg, 1.00 mmol) in dry methanol (2.0

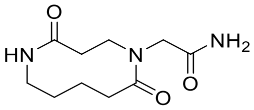
mL), was added 2,2-difluoroethylamine (76.0 µL, 1.10 mmol) in a single portion. The reaction mixture was allowed to stir for 4 h at RT and then the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO$_2$, 1: 1 hexane: ethyl acetate → 1:20 methanol: ethyl acetate → 1:10 methanol: ethyl acetate) afforded the *title compound* as a colourless oil (220 mg, 94%); R$_f$ = 0.40 (1:9 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3285, 2940, 1624, 1438, 1163, 1115, 1056, 860; δ_H (400 MHz, CDCl$_3$-*d*) δ 6.17 (ttd, *J* = 57.0, 4.4, 0.9 Hz, 1 H, C**H**F$_2$), 5.61 (d, *J* = 6.6 Hz, 1H, N**H**), 4.07 (t, *J* = 13.8 Hz, 1H, NC**H**$_2$), 3.95 – 3.68 (m, 2H, NC**H**$_2$), 3.68 – 3.49 (m, 1H, NC**H**$_2$), 3.39 – 3.29 (m, 1H, NC**H**$_2$), 2.95 – 2.86 (m, 1H, NC**H**$_2$), 2.65 (t, *J* = 15.1 Hz, 1H, C**H**$_2$), 2.41 – 2.26 (m, 2H, C**H**$_2$), 2.15 – 2.01 (m, 3H, C**H**$_2$), 1.78 – 1.50 (m, 1H, C**H**$_2$), 1.44 – 1.31 (m, 1H, C**H**$_2$); δ_C (400 MHz, CDCl$_3$-*d*) 175.2 (**C**O), 170.8 (**C**O), 113.7 (**C**HF$_2$, $^1J_{CF}$ = 241.8 Hz), 50.8 (**C**H$_2$CHF$_2$, $^2J_{CF}$ = 26.8 Hz), 48.2 (N**C**H$_2$), 39.2 (N**C**H$_2$), 37.9 (CO**C**H$_2$), 28.3 (CO**C**H$_2$), 26.0 (**C**H$_2$), 23.9 (**C**H$_2$); δ_F (376 MHz, CDCl$_3$-*d*) −120.0 (1F, dddd, *J* = 290, 57, 16, 13 Hz, CH**F**$_2$), −121.4 (1F, dddd, *J* = 290, 57, 16, 13, CH**F**$_2$); HRMS (ESI): calcd. for $C_{10}H_{16}F_2N_2NaO_2$, 257.1072. Found: [MNa]$^+$, 257.1067 (1.8 ppm error).

5-(2-(1,3-Dioxolan-2-yl)ethyl)-1,5-diazecane-2,6-dione (4-19k)



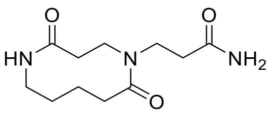
To a solution of 1-acryloylpiperidin-2-one **4-17** (153.2 mg, 1.00 mmol) in dry methanol (2.0 mL), was added 1,3-dioxolane-2-ethanamine (120 µL, 1.10 mmol) in a single portion. The reaction mixture was allowed to stir for 4 h at RT and then the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO$_2$, 1:1 hexane: ethyl acetate → 1:10 methanol: ethyl acetate) afforded the *title compound* as a colourless oil (216 mg, 80%). In solution in CDCl$_3$, this compound exists as a 10:1 mixture of rotamers; R$_f$ = 0.20 (1:9 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3299, 2933, 1615, 1427, 1137, 1025, 942; δ_H (400 MHz, CDCl$_3$-*d*) δ 6.48 (d, *J* = 9.7 Hz, 1H, N**H**, major rotamer), 5.90 (d, *J* = 9.6 Hz, 1H, N**H**, minor rotamer), 4.98 – 4.91 (m, 1H, OC**H**, major rotamer), 4.80 – 4.77 (m, 1H, OC**H**, minor rotamer), 4.02 – 3.65 (m, 7H, OC$\mathbf{H_2}$ + NC$\mathbf{H_2}$, both rotamers), 3.46 – 3.33 (m, 1H, NC$\mathbf{H_2}$, both rotamers), 3.30 – 3.19 (m, 1H, NC$\mathbf{H}_2$, both rotamers), 2.92 – 2.79 (m, 1H, NC$\mathbf{H}_2$, both rotamers), 2.64 – 2.48 (m, 1H, C$\mathbf{H_2}$, both rotamers), 2.40 – 2.20 (m, 2H, C$\mathbf{H_2}$, both rotamers), 2.13 – 1.80 (m, 4H, C$\mathbf{H_2}$, both rotamers), 1.68 – 1.36 (m, 3H, C$\mathbf{H_2}$, both rotamers); δ_C (400 MHz, $CDCl_3$-*d*) for the major rotamer: 174.2 (**C**O), 171.2 (**C**O), 103.6 (O**C**H), 64.8 (O**C**H_2), 64.5 (O**C**H_2), 46.8 (N**C**H_2), 43.9 (N**C**H_2), 39.2 (N**C**H_2), 38.8 (CO**C**H_2), 32.8 (CO**C**H_2), 28.5 (**C**H_2), 25.6 (**C**H_2), 23.9 (**C**H_2); ^{13}C NMR resonances for the minor rotamer: 176.2 (**C**O), 172.3 (**C**O), 101.9 (O**C**H), 65.1 (O**C**H_2), 64.9 (O**C**H_2), 45.8 (N**C**H_2), 42.3 (N**C**H_2), 40.1(N**C**H_2), 35.1 (CO**C**H_2), 31.5 (CO**C**H_2), 25.1 (**C**H_2), 22.3 (**C**H_2), 20.9 (**C**H_2); HRMS (ESI): calcd. for $C_{13}H_{22}N_2NaO_4$, 293.1472. Found: $[MNa]^+$, 293.1471 (0.4 ppm error).

2-(4,10-Dioxo-1,5-diazecan-1-yl)acetamide (4-19l)



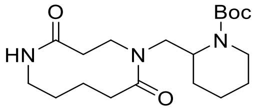
To a solution of 1-acryloylpiperidin-2-one (153.2 mg, 1.00 mmol) in dry methanol (2.0 mL), was added glycinamide (81.5 mg, 1.10 mmol, made from glycinamide hydrochloride using reported method)[213] in a single portion. The reaction mixture was allowed to stir for 4 h at RT and then the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:9 methanol: ethyl acetate → 1:3 methanol: ethyl acetate) afforded the *title compound* as a colourless oil (203 mg, 89%); $R_f = 0.13$ (1:9 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3268, 2933, 1618, 1457, 1308, 1210, 1154, 1110, 1072, 736; δ_H (400 MHz, Methanol-*d*$_4$) δ 4.56 – 3.98 (m, 2H, NC$\mathbf{H_2}$CO), 3.72 (m, 2H, NC$\mathbf{H}_2$), 3.43 (m, 1H, NC$\mathbf{H}_2$), 2.94 (m, 1H, NC$\mathbf{H}_2$), 2.68 – 2.47 (m, 2H, COC$\mathbf{H_2}$), 2.22 – 1.47 (m, 6H, 3 × C$\mathbf{H_2}$); δ_C (100 MHz, Methanol-*d*$_4$) 176.5 (**C**O), 175.0 (**C**O), 173.6 (**C**O), 52.4 (N**C**H_2CO), 49.3 (N**C**H_2), 40.0 (N**C**H_2), 37.5 (CO**C**H_2), 29.1 (CO**C**H_2), 26.0 (**C**H_2), 25.2 (**C**H_2); HRMS (ESI): calcd. for $C_{10}H_{17}N_3NaO_3$, 250.1162. Found: $[MNa]^+$, 250.1165 (−1.3 ppm error).

3-(4,10-Dioxo-1,5-diazecan-1-yl)propenamide (4-19m)



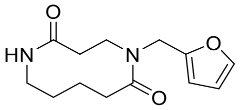
To a solution of 1-acryloylpiperidin-2-one (153.2 mg, 1.00 mmol) in dry methanol (2.0 mL), was added 3-aminopropanamide (97 mg, 1.10 mmol) in a single portion. The reaction mixture was allowed to stir for 4 h at RT and then the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:3 methanol: ethyl acetate → 1:2 methanol: ethyl acetate) afforded the *title compound* as a colourless oil (173 mg, 72%); $R_f = 0.17$ (1:3 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3299, 2934, 1612, 1434, 1349, 1201, 1151, 1108, 1070, 608; δ_H (400 MHz, Methanol-*d*$_4$) δ 4.07 – 3.91 (m, 2H, NC**H$_2$**), 3.66 – 3.43 (m, 2H, NC**H$_2$**), 3.34 – 3.23 (m, 1H, C**H**$_2$), 3.16 – 2.67 (m, 2H, C**H$_2$**), 2.59 – 2.48 (m, 2H, C**H$_2$**), 2.51 – 2.40 (m, 1H, C**H**$_2$), 2.33 – 2.20 (m, 1H, C**H**$_2$), 2.13 – 1.96 (m, 2H, C**H$_2$**), 1.68 – 1.39 (m, 3H, C**H**$_2$ + C**H$_2$**); δ_C (100 MHz, Methanol-*d*$_4$) 176.7 (**C**O), 175.9 (**C**O), 173.4 (**C**O), 47.0 (N**C**H$_2$), 44.6 (N**C**H$_2$), 40.3 (N**C**H$_2$), 37.8 (CO**C**H$_2$), 34.7 (CO**C**H$_2$), 29.4 (CO**C**H$_2$), 26.2 (**C**H$_2$), 25.0 (**C**H$_2$); HRMS (ESI): calcd. for $C_{11}H_{19}N_3NaO_3$, 264.1319. Found: $[MNa]^+$, 264.1315 (1.5 ppm error).

tert-Butyl 2-((4,10-dioxo-1,5-diazecan-1-yl)methyl)piperidine-1-carboxylate (4-19n)



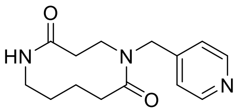
To a solution of 1-acryloylpiperidin-2-one **4-17** (153.2 mg, 1.00 mmol) in dry methanol (2.0 mL), was added 2-(aminomethyl)-1-*N*-Boc-piperidine (232.8 μL, 1.10 mmol) in a single portion. The reaction mixture was allowed to stir for 4 h at RT and then the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:20 methanol: ethyl acetate → 1:10 methanol: ethyl acetate) afforded the *title compound* as a colourless oil (265 mg, 72%). In methanol-*d*$_4$ at 50 °C the 1H NMR spectra is severely broadened due to rotamer interconversion, while the ^{13}C NMR spectrum shows it exists as a roughly 1:1 mixture of rotamers under the same conditions; $R_f = 0.33$ (1:9 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3288, 2933, 1640, 1415, 1364, 1272, 1154, 1089, 927, 767, 729; δ$_H$ (400 MHz, Methanol-*d$_4$* at 50 °C): δ 4.82 – 4.68 (m, 1H, NC**H**), 4.39 – 4.11 (m, 2H, NC**H$_2$**), 3.92 – 3.62 (m, 3H, C**H**$_2$ + C**H$_2$**), 3.53 – 3.16 (m, 2H, C**H$_2$**), 3.17 – 2.87 (m, 1H, C**H**$_2$), 2.84 – 2.18 (m, 4H, 2 × C**H$_2$**), 2.11 – 1.78 (m, 8H, 4 × C**H$_2$**), 1.72 (s, 9H, 3 × CC**H$_3$**), 1.69 – 1.53 (m, 2H, C**H$_2$**); δ$_C$ (100 MHz, Methanol-*d$_4$* at 50 °C): 175.9 and 175.7 (**C**O), 173.4 and 173.3 (**C**O), 156.7 (**C**O, both rotamers), 80.9 and 80.6 (COO**C**), 50.7 (NC**H**, both rotamers), 46.7 and 46.1 (N**C**H$_2$), 40.4 (N**C**H$_2$, both rotamers), 37.6 (N**C**H$_2$, both rotamers), 29.5 (N**C**H$_2$, both rotamers), 28.8 (3 × C**C**H$_3$, both rotamers), 28.4 (**C**H$_2$, both rotamers), 27.6 (**C**H$_2$, both rotamers), 26.5 (**C**H$_2$, both rotamers), 26.1 (**C**H$_2$, both rotamers), 24.8 (**C**H$_2$, both rotamers), 20.6 (**C**H$_2$, both rotamers), 20.2 (**C**H$_2$, both rotamers); HRMS (ESI): calcd. for $C_{19}H_{33}N_3NaO_4$, 390.2363. Found: $[MNa]^+$, 390.2358 (1.4 ppm error).

5-(Furan-2-ylmethyl)-1,5-diazecane-2,6-dione (4-19o)



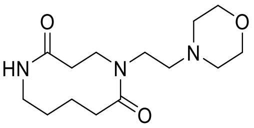
To a solution of 1-acryloylpiperidin-2-one (153.2 mg, 1.00 mmol) in dry methanol (2.0 mL), was added 2-furanylmethyl amine (97 μL, 1.10 mmol) in a single portion. The reaction mixture was allowed to stir for 4 h at RT and then the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO$_2$, 1:1 hexane: ethyl acetate → ethyl acetate → 1:10 methanol: ethyl acetate) afforded the *title compound* as a colourless oil (150 mg, 60%); R$_f$ = 0.35 (1:9 methanol: ethyl acetate); ν$_{max}$/cm^{-1} (thin film) 3288, 2931, 1615, 1442, 1349, 1174, 1011, 813, 730; δ$_H$ (400 MHz, CDCl$_3$-*d*) δ 7.39 – 7.34 (m, 1H, OC**H**), 6.36 – 6.29 (m, 2H, C**H**C**H**), 5.56 (d, *J* = 8.9 Hz, 1H, N**H**), 5.10 (d, *J* = 15.2 Hz, 1H, NC**H**$_2$), 4.16 (d, *J* = 15.2 Hz, 1H, NC**H**$_2$), 4.04 – 3.68 (m, 2H, NC**H$_2$**), 3.41 – 2.78 (m, 2H, NC**H$_2$**), 2.66 – 2.02 (m, 4H, 2 × C**H$_2$**), 1.90 – 1.32 (m, 4H, 2 × C**H$_2$**); δ$_C$ (400 MHz, CDCl$_3$-*d*) 173.9 (**C**O), 171.1 (**C**O), 151.3 (O**C**CH), 142.1 (O**C**HCH), 111.3 (**C**HCH), 109.0 (CH**C**H), 46.4 (N**C**H$_2$), 43.3 (N**C**H$_2$), 39.2 (N**C**H$_2$), 37.6 (CO**C**H$_2$), 28.3 (CO**C**H$_2$), 25.8 (**C**H$_2$), 24.0 (**C**H$_2$); HRMS (ESI): calcd. for $C_{13}H_{18}N_2NaO_3$, 273.1210. Found: $[MNa]^+$, 273.1204 (2.0 ppm error).

5-(Pyridin-4-ylmethyl)-1,5-diazecane-2,6-dione (4-19p)



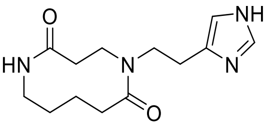
To a solution of 1-acryloylpiperidin-2-one (153.2 mg, 1.00 mmol) in dry methanol (2.0 mL), was added 4-(aminomethyl)pyridine (112 µL, 1.10 mmol) in a single portion. The reaction mixture was allowed to stir for 4 h at RT and then the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:9 methanol: ethyl acetate → 1:3 methanol: ethyl acetate) afforded the *title compound* as a pale-yellow oil (240 mg, 92%). In solution in $CDCl_3$, this compound exists as a 10:1 mixture of rotamers; R_f = 0.36 (1:1 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3285, 2932, 1620, 1561, 1416, 1349, 1205, 1001,794; δ_H (400 MHz, $CDCl_3$-*d*) δ 8.55 – 8.47 (m, 2H, Ar**H**, both rotamers), 7.15 – 7.05 (m, 2H, Ar**H**, both rotamers), 6.21 (d, *J* = 9.1 Hz, 1H, N**H**, major rotamer), 5.96 (d, *J* = 10.1 Hz, 1H, N**H**, minor rotamer), 5.29 (d, *J* = 15.5 Hz, 1H, NC**H**$_2$Py, major rotamer), 4.82 (d, *J* = 17.4 Hz, 1H, NC**H**$_2$Py, minor rotamer), 4.35 (d, *J* = 17.5 Hz, 1H, NC**H**$_2$Py, minor rotamer), 4.03 – 3.91 (m, 1H, NC**H**$_2$, both rotamers), 3.84 (d, *J* = 15.6 Hz, 1H, NC**H**$_2$Py, major rotamer), 3.80 – 3.67 (m, 1H, NC**H**$_2$, both rotamers), 3.18 (m, 1H, NC**H**$_2$, both rotamers), 2.90 (m, 1H, NC**H**$_2$, both rotamers), 2.80 – 2.66 (m, 1H, NC**H**$_2$, both rotamers), 2.31 – 2.21 (m, 2H, C**H**$_2$, both rotamers), 2.21 – 2.05 (m, 2H, C**H**$_2$, both rotamers), 3.68 – 1.44 (m, 2H, C**H**$_2$, both rotamers); δ_C (400 MHz, $CDCl_3$-*d*) for the major rotamer: 174.3 (**C**O), 170.8 (**C**O), 150.1 (2 × Ar-**C**H), 146.9 (Ar-**C**), 122.7 (2 × Ar-**C**H), 48.0 (N**C**H$_2$Py), 45.4 (N**C**H$_2$), 39.3 (N**C**H$_2$), 37.4 (CO**C**H$_2$), 28.2 (CO**C**H$_2$), 25.7 (**C**H$_2$), 23.0 (**C**H$_2$); ^{13}C NMR resonances for the minor rotamer: 176.3 (**C**O), 171.1 (**C**O), 150.2 (Ar-**C**H), 146.3 (Ar-**C**), 121.6 (Ar-**C**H), 53.5 (N**C**H$_2$Py), 43.0 (N**C**H$_2$), 40.1 (N**C**H$_2$), 35.1 (CO**C**H$_2$), 35.0 (CO**C**H$_2$), 27.3 (**C**H$_2$), 24.9 (**C**H$_2$); HRMS (ESI): calcd. for $C_{14}H_{20}N_3O_2$, 262.1550. Found: [MH]$^+$, 262.1555 (−2.0 ppm error).

5-(2-Morpholinoethyl)-1,5-diazecane-2,6-dione (4-19q)



To a solution of 1-acryloylpiperidin-2-one **4-17** (153.2 mg, 1.00 mmol) in dry methanol (2.0 mL), was added 4-(2-aminoethyl)morpholine (143 mg/ 144 µL, 1.10 mmol) in a single portion. The reaction mixture was allowed to stir for 4 h at RT and then the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:9 methanol: ethyl acetate → 1:2 methanol: ethyl acetate → 1:1 methanol: ethyl acetate) afforded the *title compound* as a colourless oil (252 mg, 89%); $R_f = 0.23$ (1:1 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3436, 2927, 2855, 1615, 1443, 1356, 1213, 1171, 1115, 921, 765; δ_H (400 MHz, $CDCl_3$-*d*) δ 7.89 (d, *J* = 10.1 Hz, 1H, N**H**), 4.76 – 4.66 (m, 1H, NC**H**$_2$CH$_2$N), 4.01 (m, 1H, NC**H**$_2$CH$_2$N), 3.96 – 3.80 (m, 1H, NCH$_2$C**H**$_2$N), 3.71 – 3.56 (m, 4H, 2 × OCH2), 3.16 (dt, *J* = 15.5, 3.8 Hz, 1H, NCH$_2$C**H**$_2$N), 2.88 – 2.52 (m, 7H, C**H**$_2$), 2.44 – 2.34 (m, 2H, C**H**$_2$), 2.28 – 2.20 (m, 2H, C**H**$_2$), 2.10 – 1.96 (m, 2H, C**H**$_2$), 1.70 – 1.51 (m, 2H, C**H**$_2$), 1.45 – 1.32 (m, 1H, C**H**$_2$); δ_C (400 MHz, $CDCl_3$-*d*) 174.6 (**C**O), 170.8 (**C**O), 66.6 (2 × O**C**H$_2$), 57.0 (N**C**H$_2$), 53.7 (2 × N**C**H$_2$), 46.6 (N**C**H$_2$), 44.0 (CO**C**H$_2$), 38.5 (2 × N**C**H$_2$), 28.6 (CO**C**H$_2$), 26.0 (**C**H$_2$), 24.3 (**C**H$_2$); HRMS (ESI): calcd. for $C_{14}H_{25}N_3NaO_3$, 306.1788. Found: $[MNa]^+$, 306.1787 (0.4 ppm error).

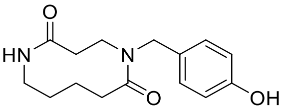
5-(2-(1*H*-Imidazol-4-yl)ethyl)-1,5-diazecane-2,6-dione (4-19r)



To a solution of 1-acryloylpiperidin-2-one (153.2 mg, 1.00 mmol) in dry methanol (2.0 mL), was added histamine (122.2 mg, 1.10 mmol) in a single portion. The reaction mixture was allowed to stir for 4 h at RT and then the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:3 methanol: ethyl acetate → 1:1 methanol: ethyl acetate) afforded the *title compound* as a colourless oil (135 mg, 51%).

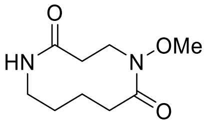
In solution in methanol-*d*$_4$, this compound experiences rotameric broadening; R$_f$ = 0.22 (1:1 methanol: ethyl acetate); ν$_{max}$/cm^{-1} (thin film) 3261, 2934, 1612, 1436, 1199, 1174, 1106, 822, 664, 623; δ$_H$ (400 MHz, Methanol-*d*$_4$) δ 7.34 (d, *J* = 1.2 Hz, 1H, Ar-C**H**), 6.58 (d, *J* = 1.2 Hz, 1H, Ar-C**H**), 3.88 – 3.51 (m, 2H, NC**H$_2$**), 3.45 – 2.77 (m, 4H, 2 × NC**H$_2$**), 2.66 – 2.41 (m, 3H, C**H**$_2$ + C**H$_2$**), 2.19 – 2.06 (m, 1H, C**H**$_2$), 1.98 – 1.87 (m, 1H, C**H**$_2$), 1.85 – 1.70 (m, 2H, C**H$_2$**), 1.39 – 1.16 (m, 3H, C**H$_2$** + C**H$_2$**); δ$_C$ (100 MHz, Methanol-*d*$_4$) 175.8 (**C**O), 173.4 (**C**O), 136.1 (2 × Ar-**C**H), 117.8 (Ar-**C**), 47.7 (N**C**H$_2$), 46.7 (N**C**H$_2$), 40.4 (N**C**H$_2$), 37.7 (CO**C**H$_2$), 29.4 (CO**C**H$_2$), 26.3 (**C**H$_2$), 25.9 (**C**H$_2$Ar), 25.0 (**C**H$_2$); HRMS (ESI): calcd. for $C_{13}H_{21}N_4O_2$, 265.1659. Found: [MH]$^+$, 265.1657 (0.7 ppm error).

(4-Hydroxylbenzyl)-1,5-diazecane-2,6-dione (4-19s)



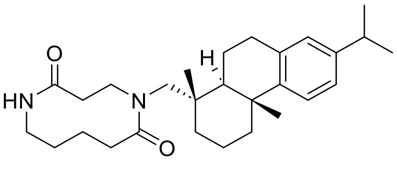
To a solution of 1-acryloylpiperidin-2-one (153.2 mg, 1.00 mmol) in dry methanol (2.0 mL), was added 4-aminomethylphenol (135.5 mg, 1.10 mmol) in a single portion. The reaction mixture was allowed to stir for 4 h at RT and then the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO$_2$, 1:50 methanol: ethyl acetate → 1:20 methanol: ethyl acetate→ 1:10 methanol: ethyl acetate) afforded the *title compound* as a white solid (205 mg, 74%). Rotameric broadening is evident in both the ^{1}H and ^{13}C NMR spectra; m.p. 70–72°C, R$_f$ = 0.32 (1:9 methanol: ethyl acetate); ν$_{max}$/cm^{-1} (thin film) 3275, 2934, 1609, 1514, 1349, 1229, 1101, 813, 776; δ$_H$ (400 MHz, Methanol-*d*$_4$) δ 7.05 (d, *J* = 8.5 Hz, 2H, Ar**H**), 6.70 (d, *J* = 8.5 Hz, 2H, Ar**H**), 5.33 (d, *J* = 14.7 Hz, 1H, NC**H**$_2$Ph), 3.90 – 3.74 (m, 1H, NC**H$_2$**), 3.66 (d, *J* = 14.7 Hz, 1H, NC**H**$_2$Ph), 3.30 – 3.22 (m, 1H, NC**H**$_2$), 3.10 – 2.91 (m, 1H, C**H$_2$**), 2.84 – 2.62 (m, 1H, C**H**$_2$), 2.49 – 2.36 (m, 1H, C**H$_2$**), 2.24 – 2.13 (m, 1H, C**H$_2$**), 2.13 – 1.93 (m, 2H, C**H$_2$**), 1.65 – 1.41 (m, 3H, C**H$_2$**); δ$_C$ (100 MHz, Methanol-*d*$_4$) 175.9 (**C**O), 173.6 (**C**O), 157.9 (Ar-**C**OH), 130.4 (2 × Ar-**C**H), 129.4 (Ar-**C**), 116.4 (2 × Ar-**C**H), 49.9 (N**C**H$_2$Ph), 44.9 (N**C**H$_2$), 40.4 (N**C**H$_2$), 37.1 (CO**C**H$_2$), 29.4 (CO**C**H$_2$), 26.2 (**C**H$_2$), 25.1 (**C**H$_2$); HRMS (ESI): calcd. for $C_{15}H_{20}N_2NaO_2$, 299.1366. Found: [MNa]$^+$, 299.1362 (1.4 ppm error).

5-Methoxy-1,5-diazecane-2,6-dione (4-19t)



To a solution of 1-acryloylpiperidin-2-one (100 mg, 0.65 mmol) in dry methanol (2.0 mL), was added methoxyamine (51.8 mg, 0.95 mmol) in a single portion. The reaction mixture was allowed to stir for 4 h at RT and then the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:9 methanol: ethyl acetate) afforded the *title compound* as a colourless oil (110 mg, 85%). In solution in $CDCl_3$, this compound exists predominantly as a single rotamer, but with rotameric broadening seen in the ^{1}H NMR spectrum and traces of a minor rotamer evident in the ^{13}C NMR spectrum; R_f = 0.18 (1:9 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3317, 3087, 2935, 1652, 1545, 4443, 1318, 1178, 1013, 946, 572; δ_H (400 MHz, $CDCl_3$-*d*) δ 5.60 (d, *J* = 3.0 Hz, 1H, N**H**), 4.61 – 4.49 (m, 1H, NC**H**$_2$), 3.63 (s, 3H, OC**H**$_3$), 3.48 – 3.31 (m, 1H, NC**H**$_2$), 3.32 – 3.16 (m, 1H, NC**H**$_2$), 2.90 (m, 1H, NC**H**$_2$), 2.86 – 2.75 (m, 1H, C**H**$_2$), 2.57 – 2.40 (m, 1H, C**H**$_2$), 2.15 – 2.02 (m, 2H, C**H**$_2$), 1.89 – 1.79 (m, 1H, C**H**$_2$), 1.78 – 1.64 (m, 2H, C**H**$_2$), 1.44 – 1.30 (m, 1H, C**H**$_2$); δ_C (100 MHz, $CDCl_3$-*d*) 178.0 (**C**O), 170.0 (**C**O), 62.1 (O**C**H$_3$), 43.9 (N**C**H$_2$), 39.7 (N**C**H$_2$), 34.1 (CO**C**H$_2$), 31.1 (CO**C**H$_2$), 27.4 (**C**H$_2$), 23.3 (**C**H$_2$); HRMS (ESI): calcd. for $C_9H_{16}N_2NaO_3$, 223.1053. Found: [MNa]$^+$, 223.1053 (0.0 ppm error). Characteristic ^{13}C NMR data for the minor rotamers can be found at: δ_H (400 MHz, $CDCl_3$-*d*) 6.30 (1H, m, N**H**), 4.00 (1H, m, NC**H**$_2$); δ_C (100 MHz, $CDCl_3$) 171.0 (**C**O), 61.0 (O**C**H$_3$), 47.3 (**C**H$_2$), 36.5 (**C**H$_2$), 28.9 (**C**H$_2$), 24.6 (**C**H$_2$), 22.7 (**C**H$_2$).

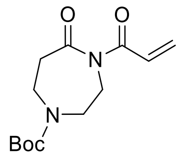
5-(((1*S*,4a*R*,10a*S*)-7-Isopropyl-1,4a-dimethyl-1,2,3,4,4a,9,10,10 aoctahydrophenanthren-1-yl)methyl)-1,5-diazecane-2,6-dione (4-19u)



To a solution of 1-acryloylpiperidin-2-one **4-17** (153.2 mg, 1.00 mmol) in dry methanol

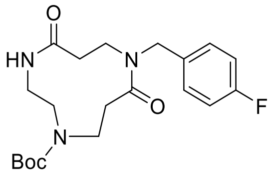
(2.0 mL), was added leelamine (314 mg, 1.10 mmol) in a single portion. The reaction mixture was allowed to stir for 4 h at RT and then the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 hexane: ethyl acetate → ethyl acetate) afforded the *title compound* as a colourless oil (215 mg, 49%). In solution in methanol-*d₄*, this compound exists as a roughly 3:2 mixture of rotamers; $R_f = 0.30$ (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3291, 3085, 2928, 2867, 1768, 1643, 1556, 1448, 1417, 1375, 1304, 1167, 1105, 1046, 820, 733; δ_H (400 MHz, Methanol-*d₄*): δ 7.13 – 7.03 (m, 1H, Ar-C**H**, both rotamers), 6.96 – 6.84 (m, 1H, Ar-C**H**, both rotamers), 6.88 – 6.79 (m, 1H, Ar-C**H**, both rotamers), 4.34 – 4.14 (m, 1H, PhC**H**CH_3, both rotamers), 4.13 – 3.87 (m, 1H, CC**H**C, both rotamers), 3.77 – 3.40 (m, 2H, NC**H$_2$**C, both rotamers), 2.97 – 2.67 (m, 4H, C**H$_2$**, both rotamers), 2.59 – 2.38 (m, 2H, C**H$_2$**, both rotamers), 2.32 – 2.20 (m, 1H, C**H**$_2$, C**H$_2$**, both rotamers), 2.10 – 1.96 (m, 3H, C**H$_3$**, both rotamers), 1.84 – 1.38 (m, 9H, C**H$_2$**, both rotamers), 1.35 – 1.24 (m, 2H C**H$_2$**, both rotamers), 1.20 – 1.14 (m, 9H, C**H$_3$**, both rotamers), 1.02 – 0.78 (m, 4H, C**H$_2$**, both rotamers); δ_C (100 MHz, Methanol-*d₄*): 176.9 and 176.7 (**C**O), 173.5 (**C**O, both rotamers), 148.6 and 148.5 (Ar-**C**), 146.6 and 146.5 (Ar-**C**), 135.8 and 135.3 (Ar-**C**), 127.7 (Ar-**C**H, both rotamers), 124.9 and 124.8 (Ar-**C**H), 124.7 and 124.6 (Ar-**C**H), 49.9 (Ph**C**HCH_3, both rotamers), 48.0 (N**C**H_2C, both rotamers), 47.6 (C**C**HC, both rotamers), 41.3 and 41.0 (**C**CHC), 39.7 and 39.5 (**C**H_2), 38.7 and 38.6 (**C**CHC), 38.2 (**C**H_2, both rotamers), 37.3 (**C**H_2, both rotamers), 34.7 (**C**CH_3, both rotamers), 31.2 and 31.1 (**C**H_2), 29.1 (**C**H_2, both rotamers), 26.5 and 26.4 (**C**H_3), 25.6 (**C**H_2, both rotamers), 24.6 (**C**H_3, both rotamers), 24.4 (**C**H_2, both rotamers), 20.7 (**C**H_2, both rotamers), 20.5 and 20.4 (**C**H_2, both rotamers), 19.7 and 19.6 (**C**H_2, both rotamers), 18.9 (**C**H_3, both rotamers); HRMS (ESI): calcd. for $C_{28}H_{42}N_2NaO_2$, 461.3138. Found: $[MNa]^+$, 461.3152 (−2.8 ppm error).

***tert*-Butyl 4-acryloyl-5-oxo-1,4-diazepane-1-carboxylate (4-21)**



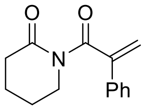
To a stirring solution of *tert*-butyl 5-oxo-1,4-diazepane-1-carboxylate **4-20** (642.8 mg, 3.0 mmol) in dry THF (11 mL) cooled to 0 °C was added a solution of MeMgBr (3.0 M in diethyl ether, 1.1 mL) *via* dropwise addition using a syringe pump over 30 min. The reaction mixture was allowed to stir for 10 min at 0 °C after addition was completed. Acryloyl chloride (0.360 mL, 4.5 mmol) was then added in a single portion and the reaction mixture was stirred for an additional 30 min at 0°C. The reaction mixture was then quenched with sat. aq. NH_4Cl (10 mL) and the mixture was extracted with Et_2O (15 mL). The organic layer was washed with sat. aq. $NaHCO_3$ (2 × 10 mL), and organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 2:1 diethyl ether: hexane) afforded the *title compound* as colourless liquid (676 mg, 84%); $R_f = 0.65$ (ethyl acetate); ν_{max}/cm^{-1} (thin film) 2979, 1685, 1366, 1329, 1245, 1165, 1116, 1042, 957, 795; δ_H (400 MHz, $CDCl_3$-*d*): δ 6.84 (dd, *J* = 16.8, 10.3 Hz, 1H, NCOC**H**CHH'), 6.25 (dt, *J* = 16.9, 2.0 Hz, 1H, NCOCHC**H**H'), 5.64 (dt, *J* = 10.4, 2.0 Hz, 1H, NCOCHCH**H'**), 3.95 – 3.87 (m, 2H, C**H$_2$**), 3.60 – 3.55 (m, 2H, C**H$_2$**), 3.54 – 3.49 (m, 2H, C**H$_2$**), 2.79 – 2.70 (m, 2H, C**H$_2$**), 1.36 (s, 9H, 3 × OCC**H$_3$**); δ_C (100 MHz, $CDCl_3$-*d*, 50 °C): 175.7 (**C**O), 168.4 (**C**O), 154.6 (**C**O), 131.4 (NCOCH**C**HH'), 128.8 (NCO**C**HCHH'), 80.7 (COO**C**), 47.2 (**C**H$_2$), 44.0 (**C**H$_2$), 41.3 (2 × **C**H$_2$), 28.4 (3 × OC**C**H$_3$); HRMS (ESI): calcd. for $C_{13}H_{20}N_2NaO_4$, 291.1315. Found: $[MNa]^+$, 291.1319 (–1.3 ppm error).

***tert*-Butyl 8-(4-fluorobenzyl)-5,9-dioxo-1,4,8-triazacycloundecane-1-carboxylate (4-22)**



To a solution of *tert*-butyl 4-acryloyl-5-oxo-1,4-diazepane-1-carboxylate **4-21** (268.3 mg, 1.00 mmol) in dry methanol (2.0 mL), was added 4-flurobenzylamine (125.7 µL, 1.10 mmol) in a single portion. The reaction mixture was allowed to stir for 4 h at RT and then the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, ethyl acetate → 1:10 methanol: ethyl acetate) afforded the *title* *compound* as a colourless oil (370 mg, 94%). In solution in $CDCl_3$, this compound exists as a mixture of 3 rotameric forms (28:5:1 ratio, based on the ^{19}F NMR data). The ^{1}H NMR and ^{13}C NMR spectra are both affected by rotameric broadening, even when recorded at elevated temperatures; $R_f = 0.22$ (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3304, 2975, 2932, 1644, 1509, 1409, 1365, 1222, 1165, 919, 731, 592; δ_H (400 MHz, DMSO-*d*$_6$ at 50 °C): δ 7.99 (s, 1H, N**H**), 7.35 – 7.05 (m, 4H, Ar-C**H**), 4.89 – 4.12 (m, 2H, NC**H$_2$**Ph), 3.70 – 3.36 (m, 4H, 2 × C**H$_2$**), 3.25 (d, *J* = 9.9 Hz, 2H, C**H$_2$**), 3.19 – 3.07 (m, 2H, C**H$_2$**), 2.66 – 2.03 (m, 4H, 2 × C**H$_2$**), 1.42 (s, 9H, 3 × C**H$_3$**); δ_C (125 MHz, DMSO-*d*$_6$ at 90 °C): 175.4 (**C**O), 171.8 (**C**O), 161.9 (Ar-**C**F, $^1J_{CF}$ = 243.0 Hz), 155.6 (**C**O), 134.8 (Ar-**C**), 130.1 (Ar-**C**H, $^3J_{CF}$ = 7.5 Hz), 115.5 (Ar-**C**H, $^2J_{CF}$ = 23.0 Hz), 79.1 (COO**C**CH3), 48.6 (N**C**H$_2$Ph), 47.1 (**C**H$_2$), 45.2 (**C**H$_2$), 44.1 (**C**H$_2$), 38.5 (**C**H$_2$), 36.1 (**C**H$_2$), 31.7 (**C**H$_2$), 28.7 (3 × **C**H$_3$); Diagnostic ^{13}C NMR resonances for the minor rotamer: 171.3 (**C**O), 79.6 (COO**C**CH$_3$), 28.6 (3 × **C**H$_3$); δ_F (376 MHz, DMSO-*d*$_6$ at 50 °C), 3 rotamers in a 28:5:1 ratio: –115.46 (1F, m, Ar**F**), –115.89 (1F, m, Ar**F**, major rotamer), –16.26 (1F, m, Ar**F**); HRMS (ESI): calcd. for $C_{20}H_{28}FN_3NaO_4$, 416.1956. Found: [MNa]$^+$, 416.1959 (–0.6 ppm error).

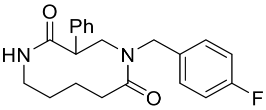
1-(2-Phenylacryloyl)piperidin-2-one (4-24)



A mixture of δ-valerolactam **4-15** (991.3 mg, 10 mmol), DMAP (122.2 mg, 1.0 mmol), and pyridine (4.86 mL, 60 mmol) in dry CH_2Cl_2 (20 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of atropic acid chloride (15 mmol, freshly prepared using a published method)^6 in dry CH_2Cl_2 (20 mL) was added and resulting mixture was refluxed at 50 °C for 18 h. The mixture was then diluted with DCM (50 mL) and washed with 10% aq. HCl (50 mL), the aqueous layer was then extracted with DCM (2 × 30 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 4: 1 hexane: ethyl acetate → 3:1 hexane: ethyl acetate) afforded the *title compound* as a yellow oil

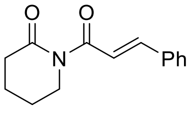
(1.55 g, 68%); $R_f = 0.55$ (1:1 hexane: ethyl acetate); ν_{max}/cm^{-1} (thin film) 2951, 1704, 1674, 1382, 1327, 1288, 1210, 1146, 1090, 996, 904, 775, 697, 595, 555, 459; δ_H (400 MHz, CDCl$_3$-*d*): δ 7.33 – 7.20 (m, 5H, Ar-C**H**), 5.55 (s, 1H, PhC=C**H**H'), 5.48 (s, 1H, PhC=CH**H'**), 3.77 – 3.72 (m, 2H, C**H**$_2$), 2.35 – 2.13 (m, 2H, C**H**$_2$), 1.89 – 1.62 (m, 4H, 2 × C**H**$_2$); δ_C (100 MHz, CDCl$_3$-*d*): 173.2 (**C**O), 172.2 (**C**O), 147.3 (Ph**C**=CH$_2$), 136.5 (Ar-**C**), 128.1 (2 × Ar-**C**H), 127.8 (Ar-**C**H), 126.2 (2 × Ar-**C**H), 116.2 (PhC=**C**H$_2$), 44.8 (**C**H$_2$), 34.1 (**C**H$_2$), 22.3 (**C**H$_2$), 20.7 (**C**H$_2$); HRMS (ESI): calcd. for $C_{14}H_{15}NNaO_2$, 225.0995. Found: [MNa]$^+$, 252.0994 (0.5 ppm error).

5-(4-Fluorobenzyl)-3-phenyl-1,5-diazecane-2,6-dione (4-25)



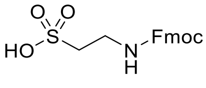
To a solution of 1-(2-phenylacryloyl)piperidin-2-one **4-24** (229.3 mg, 1.00 mmol) in dry methanol (2.0 mL), was added 4-flurobenzylamine (125.7 µL, 1.10 mmol) in a single portion. The reaction mixture was allowed to stir for 4 h at RT and then the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO$_2$, 1: 1 hexane: ethyl acetate → ethyl acetate) afforded the *title compound* as a colourless oil (196 mg, 55%). In solution in CDCl$_3$, this compound exists as a roughly 10:1 mixture of rotamers; $R_f = 0.30$ (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3299, 2931, 1620, 1508, 1442, 1218, 1155, 1095, 816, 700, 590, 502; δ_H (400 MHz, CDCl$_3$-*d*) δ 7.32 – 7.23 (m, 5H, Ar-C**H**, both rotamers), 7.22 – 7.12 (m, 2H, both rotamers), 7.03 – 6.91 (m, 2H, both rotamers), 6.64 – 6.49 (m, 1H, N**H**, major rotamer), 6.26 (d, *J* = 9.9 Hz, 1H, N**H**, minor rotamer), 5.17 (d, *J* = 14.6 Hz, 1H, C**H**Ph, major rotamer), 4.95 (d, *J* = 16.2 Hz, 1H, C**H**Ph, minor rotamer), 4.25 – 4.01 (m, 2H, C**H**$_2$, both rotamers), 3.91 – 3.35 (m, 2H, C**H**$_2$, both rotamers), 3.28 – 3.10 (m, 1H, C**H**$_2$, both rotamers), 2.99 – 2.74 (m, 2H, C**H**$_2$, both rotamers), 2.30 – 2.12 (m, 2H, C**H**$_2$, both rotamers), 1.77 – 1.46 (m, 3H, C**H**$_2$, both rotamers); δ_C (100 MHz, CDCl$_3$-*d*) data for major rotamer: 173.8 (**C**O), 171.2 (**C**O), 162.2 (Ar-**C**F, $^1J_{CF} = 246.4$ Hz), 136.5 (Ar-**C**), 133.5 (Ar-**C**, $^4J_{CF} = 2.7$ Hz), 129.7 (Ar-CH, $^3J_{CF} = 8.0$ Hz), 128.4 (Ar-**C**H), 128.2 (Ar-CH), 127.5 (Ar-**C**H), 115.6 (Ar-**C**H, $^2J_{CF} = 21.4$ Hz), 51.5 (**C**HPh), 51.3 (N**C**H$_2$Ph), 48.5 (**C**H$_2$), 39.0 (**C**H$_2$), 28.0 (**C**H$_2$), 25.8 (**C**H$_2$), 23.9 (**C**H$_2$); Diagnostic ^{13}C NMR resonances for the minor rotamer: 175.9 (**C**O), 171.9 (**C**O), 137.1 (Ar-**C**), 132.3(Ar-**C**), 128.5 (Ar-**C**H), 128.5 (Ar-**C**H), 128.3 (Ar-**C**H), 127.3 (Ar-**C**H), 115.8 (Ar-**C**H), 115.6 (Ar-**C**H), 55.0 (**C**HPh), 52.7 (N**C**H$_2$Ph), 50.1 (**C**H$_2$), 40.1 (**C**H$_2$), 35.4 (**C**H$_2$), 27.5 (**C**H$_2$), 25.2 (**C**H$_2$); δ$_F$ (376 MHz, CDCl$_3$-*d*): –114.15 (s, 1F, Ar-**F**, major rotamer), –114.28 (s, 1F, Ar-**F**, minor rotamer); HRMS (ESI): calcd. for $C_{21}H_{23}FN_2NaO_2$, 377.1636. Found: [MNa]$^+$, 377.1635 (0.1 ppm error).

1-Cinnamoylpiperidin-2-one (4-27)



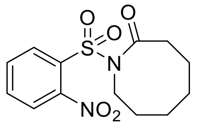
To a solution of cinnamoyl chloride (1666mg, 10 mmol) in CH$_2$Cl$_2$ (20 mL) were added triethylamine (4.18 mL, 30 mmol) and δ-valerolactam (1.19 g, 12 mmol). The reaction mixture was stirred at room temperature overnight before it was quenched with saturated aqueous NH$_4$Cl (30 mL) and extracted with CH$_2$Cl$_2$ (2 × 30 mL). The combined organic phases were washed with brine and dried over MgSO$_4$ then the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO$_2$, 9:1 hexane: ethyl acetate → 5:1 hexane: ethyl acetate) afforded the *title compound* as a white solid (740 mg, 33%); m.p: 40– 42 °C; R$_f$ = 0.55 (1:1 hexane: ethyl acetate); ν$_{max}$/cm^{-1} (thin film) 2951, 1690, 1672, 1617, 1449, 1386, 1332, 1289, 1203, 1154, 1018, 973, 766, 565; δ$_H$ (400 MHz, CDCl$_3$-*d*): δ 7.67 (d, *J* = 15.6 Hz, 1H, COC**H**=CHPh), 7.55 – 7.50 (m, 2H, Ar-C**H**), 7.42 (d, *J* = 15.6 Hz, 1H, COCH=C**H**Ph), 7.35 – 7.28 (m, 3H, Ar-C**H**), 3.85 – 3.64 (m, 2H, C**H$_2$**), 2.58 – 2.45 (m, 2H, C**H$_2$**), 1.94 – 1.67 (m, 4H, 2 × C**H$_2$**); δ$_C$ (100 MHz, CDCl$_3$-*d*): 173.8 (**C**O), 169.6 (**C**O), 142.9 (Ar-**C**H), 135.0 (Ar-**C**), 129.9 (CO**C**H=CHPh), 128.7 (2 × Ar-**C**H), 128.2 (2 × Ar-**C**H), 122.1 (COCH=**C**HPh), 44.5 (**C**H$_2$), 34.8 (**C**H$_2$), 22.4 (**C**H$_2$), 20.5 (**C**H$_2$); HRMS (ESI): calcd. for $C_{14}H_{15}NNaO_2$, 225.0995. Found: [MNa]$^+$, 252.0991 (1.7 ppm error).

2-(9H-Fluoren-9-ylmethoxycarbonylamino)-ethanesulfonic acid (5-8)



To a solution of Fmoc-OSu (3.0 g, 10 mmol) in CH_2Cl_2 (20 mL) was added 1.14 g of 2 -mercaptoethylamine hydrochloride (10 mmol), and the mixture was stirred at 4 °C. To the mixture was added 2 eq of NEt_3 with stirring for 3h at RT. The reaction mixture was washed with 0.1 M HCl (aq.) and water, the organic layer was dried to give the crude Fmoc-thiol. H_2O_2 (30%, 15 mL) was dissolved in 98% formic acid (35 mL) at 0 °C and the mixture was stirred at this temperature for 1 h to afford performic acid. Fmoc-thiol in 98% formic acid (3.0 mL) solution was added dropwise to performic acid solution and the resulting reaction mixture was stirred at RT for 24 h. After removal of the solvent, the product was purified by column chromatography (dichloromethane: methanol 8:1) to afford the product as a pale-yellow solid (870 mg, 25%). δ_H (400 MHz, $CDCl_3$) 7.75 (d, *J* = 7.5 Hz, 2H, Ar-C**H**), 7.61 (d, *J* = 7.5 Hz, 2H, Ar-C**H**), 7.36 (t, *J* = 7.4 Hz, 2H, Ar-C**H**), 7.28 (t, *J* = 7.4 Hz, 2H, Ar-C**H**), 4.31 (d, *J* = 7.0 Hz, 2H, C**H₂**), 4.16 (t, *J* = 7.0 Hz, 1H, C**H**), 3.56 (t, *J* = 7.0 Hz, 2H, C**H₂**), 3.00 (t, *J* = 7.0 Hz, 2H, C**H₂**); Data consistent with those previously reported in the literature. [181]

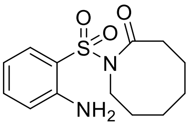
1-((2-Nitrophenyl)sulfonyl)azocan-2-one (5-15)



ω-Heptanolactam (636 mg, 5.00 mmol) was dissolved in THF (20 mL) and the temperature was lowered –78 °C (dry ice/acetone bath). *n*-BuLi (1.6 M in hexanes, 4.7 mL, 7.5 mmol, 1.5 eq) was added dropwise by syringe and the reaction was allowed to stir at –78 °C. After 1 hour, a solution of 2-nitrobenzenesulfonyl chloride **5-14** (1.66 g, 7.5 mmol, 1.5 eq) in THF (5 mL) was transferred to the stirring reaction mixture dropwise by syringe. The reaction was allowed to warm to room temperature overnight before the addition of sat. aq. $NaHCO_3$ solution (30 mL). The aqueous layer was extracted with EtOAc (2 × 30 mL) and the combined organic layers were dried ($MgSO_4$). After filtration, the solvent was removed by rotary evaporation. Purification by flash column chromatography (SiO_2, 1:1 hexane: dichloromethane → 1:1 hexane: ethyl acetate) afforded the title compound as a white solid (1.34 g, 86%); m.p. 110 – 112 °C;

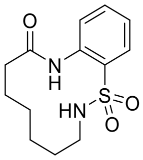
R_f = 0.40 (2:1 hexane: ethyl acetate); ν_{max}/cm^{-1} (neat) 2931, 2861, 1691, 1541, 1360, 1170, 1117, 852, 736, 664, 536; δ_H (400 MHz, $CDCl_3$) 8.47 – 8.42 (m, 1H, Ar-C**H**), 7.79 – 7.69 (m, 3H, Ar-C**H**), 4.14 – 3.94 (m, 2H, C**H₂**), 2.65 – 2.47 (m, 2H, C**H₂**), 1.92 – 1.80 (m, 2H, C**H₂**), 1.73 – 1.54 (m, 4H, 2 × C**H₂**); δ_C (101 MHz, $CDCl_3$) 175.2 (**C**O), 148.0 (Ar-**C**), 134.9 (Ar-**C**H), 134.5 (Ar-**C**H), 133.3 (Ar-**C**), 131.9 (Ar-**C**H), 124.4 (Ar-**C**H), 46.9 (**C**H₂), 36.0 (**C**H₂), 31.6 (**C**H₂), 28.5 (**C**H₂), 26.0 (**C**H₂), 24.1 (**C**H₂); HRMS (ESI): calcd. for $C_{13}H_{16}N_2NaO_5S$, 335.0672. Found: [MNa]$^+$, 335.0670 (0.8 ppm error).

1-((2-Aminophenyl)sulfonyl)azocan-2-one (5-21)



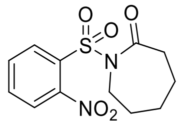
1-((2-Nitrophenyl)sulfonyl)azocan-2-one **5-15** (156.2 mg, 0.5 mmol) was dissolved in ethyl acetate (5 mL) and placed under an argon atmosphere. Palladium on carbon (50 mg, Pd 10% on carbon) was then added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at RT under a slight positive pressure of hydrogen (balloon) overnight. 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, 2:1 hexane: ethyl acetate) afforded the title compound as a colorless oil (149 mg, 105%). R_f = 0.29 (2:1 hexane: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3485, 3380, 2929, 2860, 1683, 1621, 1485, 1328, 1145, 704, 642, 521; δ_H (400 MHz, $CDCl_3$-*d*) 7.58 (dd, *J* = 8.2, 1.5 Hz, 1H, Ph-C**H**), 7.23 (ddd, *J* = 8.3, 7.2, 1.5 Hz, 1H, Ph-C**H**), 6.71 – 6.63 (m, 2H, Ph-C**H**), 5.27 (brs, 2H, Ph-N**H₂**), 4.08 – 4.01 (m, 2H, C**H₂**), 2.52 – 2.38 (m, 2H, C**H₂**), 1.92 – 1.80 (m, 2H, C**H₂**), 1.82 – 1.70 (m, 2H, C**H₂**), 1.61 – 1.46 (m, 4H, 2 × C**H₂**); δ_C (101 MHz, $CDCl_3$-*d*) 175.9 (**C**O), 147.7 (Ph-**C**), 134.8 (Ph-**C**H), 130.5 (Ph-**C**H), 119.6 (Ph-**C**), 117.9 (Ph-**C**H), 116.7 (Ph-**C**H), 46.3 (**C**H₂), 36.3 (**C**H₂), 31.2 (**C**H₂), 28.5 (**C**H₂), 26.1 (**C**H₂), 23.8 (**C**H₂); HRMS (ESI): calcd. for $C_{13}H_{18}N_2NaO_3S$, 305.0930. Found: [MNa]$^+$, 305.0922 (2.7 ppm error).

3,4,5,6,7,8-Hexahydro-2*H*-benzo[*k*][1]thia[2,10]diazacyclododecin-9(10*H*)-one 1,1-dioxide (5-22)



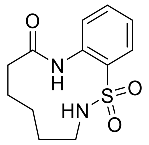
1-((2-Nitrophenyl)sulfonyl)azocan-2-one **5-15** (936 mg, 3.00 mmol) was dissolved in ethyl acetate (30 mL) and placed under an argon atmosphere. Palladium on carbon (300 mg, Pd 10% on carbon) was then added and the reaction vessel was evacuated and backfilled with hydrogen (via balloon) several times, then stirred at RT under a slight positive pressure of hydrogen (balloon) 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 dichloromethane (30 mL) and DBU (4.50 mL, 10 eq) added and stirred at RT overnight, after which time it was reduced in vacuo. Purification by flash column chromatography (SiO_2, 10:1 dichloromethane: ethyl acetate → 9:1 ethyl acetate: methanol) afforded the title compound as a white solid (766 mg, 90%); m.p. 93 – 95 °C; $R_f = 0.41$ (9:1 dichloromethane: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3353, 2936, 1678, 1583, 1520, 1308, 1151, 761, 589; δ_H (400 MHz, $CDCl_3$) 9.30 (s, 1H, CON**H**), 8.22 (d, *J* = 8.2 Hz, 1H, Ar-C**H**), 7.86 (d, *J* = 7.7 Hz, 1H, Ar-C**H**), 7.54 (t, *J* = 8.5 Hz, 1H, Ar-C**H**), 7.15 (t, *J* = 7.6 Hz, 1H, Ar-C**H**), 4.94 (t, *J* = 5.9 Hz, 1H, SO_2N**H**), 3.14 (q, *J* = 6.4 Hz, 2H, NHC**H₂**), 2.48 – 2.36 (m, 2H, C**H₂**), 1.82 – 1.58 (m, 4H, 2 × C**H₂**), 1.47 – 1.33 (m, 4H, 2 × C**H₂**); δ_C (101 MHz, $CDCl_3$) 172.4 (**C**O), 136.3 (Ar-**C**), 134.3 (Ar-**C**H), 129.4 (Ar-**C**H), 127.8 (Ar-**C**), 124.1 (Ar-**C**H), 124.0 (Ar-**C**H), 39.5 (NH**C**H₂), 38.6 (**C**H₂), 27.2 (**C**H₂), 26.0 (**C**H₂), 23.9 (**C**H₂), 23.6 (**C**H₂); HRMS (ESI): calcd. for $C_{13}H_{18}N_2NaO_3S$, 305.0930. Found: $[MNa]^+$, 305.0931 (–0.2 ppm error).

1-((2-Nitrophenyl)sulfonyl)azepan-2-one (5-15a)



Azepan-2-one (283.2 mg, 2.5 mmol) was dissolved in THF (10 mL) and the temperature was lowered to –78 °C (dry ice/acetone bath). *n*-BuLi (1.6 M in hexanes, 2.35 mL, 3.75 mmol, 1.5 eq) was added dropwise by syringe and the reaction was allowed to stir at –78 °C. After 1 hour, a solution of 2-nitrobenzenesulfonyl chloride **5-14** (831 mg, 3.75 mmol, 1.5 eq) in THF (2.5 mL) was transferred to the stirring reaction mixture dropwise by syringe. The reaction was allowed to warm to room temperature overnight before the addition of sat. aq. $NaHCO_3$ solution (15 mL). The aqueous layer was extracted with EtOAc (2 × 15 mL), the combined organic layers were dried ($MgSO_4$). After filtration, the solvent was removed by rotary evaporation. Purification by flash column chromatography (SiO_2, 2:3 hexane: dichloromethane) afforded the *title compound* as a white solid (615 mg, 83%); m.p. 108 – 110 °C; R_f = 0.30 (dichloromethane); ν_{max}/cm^{-1} (neat) 3103, 2934, 1699, 1541, 1357, 1170, 1119, 771, 740, 664, 563; δ_H (400 MHz, $CDCl_3$) 8.45 – 8.36 (m, 1H, Ar-C**H**), 7.78 – 7.66 (m, 3H, Ar-C**H**), 4.03 – 3.92 (m, 2H, C**H$_2$**), 2.60 – 2.54 (m, 2H, C**H$_2$**), 1.93 – 1.84 (m, 2H, C**H$_2$**), 1.81 – 1.73 (m, 4H, 2 × C**H$_2$**); δ_C (101 MHz, $CDCl_3$) 175.4 (**C**O), 147.8 (Ar-**C**), 134.7 (Ar-**C**H), 134.5 (Ar-**C**H), 133.2 (Ar-**C**), 131.9 (Ar-**C**H), 124.3 (Ar-**C**H), 47.3 (**C**H_2), 38.6 (**C**H_2), 29.4 (**C**H_2), 29.2 (**C**H_2), 22.9 (**C**H_2); HRMS (ESI): calcd. for $C_{12}H_{14}N_2NaO_5S$, 321.0516. Found: $[MNa]^+$, 321.0511 (1.3 ppm error).

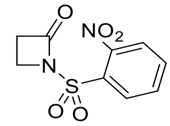
2,3,4,5,6,7-Hexahydrobenzo[*j*][1]thia[2,9]diazacycloundecin-8(9*H*)-one 1,1-dioxide (5-22a)



1-((2-Nitrophenyl)sulfonyl)azepan-2-one **5-15a** (298.3 mg, 1.0 mmol) was dissolved in ethyl acetate (10 mL) and placed under an argon atmosphere. Palladium on carbon (100 mg, Pd 10% on carbon) was then added and the reaction vessel was evacuated and backfilled with hydrogen (via balloon) several times, then stirred at RT under a slight positive pressure of hydrogen (balloon) 4 h. The reaction was then purged with argon, filtered through Celite, washed with methanol and the solvent was removed *in vacuo*.

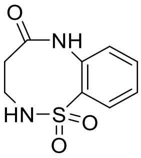
The crude material was then re-dissolved in dichloromethane (10 mL) and DBU (1.5 mL, 10 eq) added, and stirred at RT overnight, then reduced in vacuo. Purification by flash column chromatography (SiO_2, 9:1 dichloromethane: ethyl acetate) afforded the title compound as a white solid (230 mg, 83%); m.p. 120 – 135 °C; $R_f = 0.25$ (9:1 dichloromethane: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3374, 3269, 2938, 2873, 1680, 1516, 1467, 1436, 1292, 1147, 761, 733, 604; δ_H (400 MHz, $CDCl_3$) 8.78 (s, 1H, CON**H**Ph), 8.06 (d, *J* = 8.1 Hz, 1H, Ar-C**H**), 7.89 (d, *J* = 7.8 Hz, 1H, Ar-C**H**), 7.57 (t, *J* = 7.7 Hz, 1H, Ar-C**H**), 7.17 (t, *J* = 7.7 Hz, 1H, Ar-C**H**), 4.50 (t, *J* = 5.7 Hz, 1H, SO_2N**H**), 3.47 (q, *J* = 6.0, 5.9 Hz, 2H, C$\mathbf{H_2}$), 2.47 (t, *J* = 6.6 Hz, 2H, C$\mathbf{H_2}$), 1.83 – 1.61 (m, 4H, 2 × C$\mathbf{H_2}$), 1.52 – 1.38 (m, 2H, C$\mathbf{H_2}$); δ_C (101 MHz, $CDCl_3$) 171.6 (**C**O), 135.7 (Ar-**C**), 134.4 (Ar-**C**H), 129.5 (Ar-**C**), 129.4 (Ar-**C**H), 125.1 (Ar-**C**H), 124.1 (Ar-**C**H), 39.9 (**C**H_2), 36.3 (**C**H_2), 25.2 (**C**H_2), 22.5 (**C**H_2), 21.2 (**C**H_2); HRMS (ESI): calcd. for $C_{12}H_{16}N_2NaO_3S$, 291.0774. Found: $[MNa]^+$, 291.0777 (–0.9 ppm error). X-ray crystallographic data for this compound can be accessed via www.ccdc.cam.ac.uk/data_request/cif (CCDC 2215461)

1-((2-Nitrophenyl)sulfonyl)azetidin-2-one (5-15b)



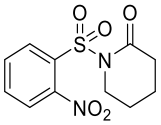
Azetidin-2-one (303 mg, 4.30 mmol) was dissolved in THF (30 mL) and the temperature was lowered to –78 °C (dry ice/acetone bath). *n*-BuLi (1.6 M in hexanes, 4.00 mL, 6.45 mmol, 1.5 eq) was added dropwise by syringe and the reaction was allowed to stir at –78 °C. After 1 hour, a solution of 2-nitrobenzenesulfonyl chloride **5-14** (1.89 g, 8.54 mmol, 1.5 eq) in THF (13 mL) was transferred to the stirring reaction mixture dropwise by syringe. The reaction was allowed to warm to room temperature overnight before the addition of sat. aq. $NaHCO_3$ solution (30 mL). The aqueous layer was extracted with EtOAc (2 × 30 mL), the combined organic layers were dried ($MgSO_4$). After filtration, the solvent was removed by rotary evaporation. Purification by flash column chromatography (SiO_2, ethyl acetate) afforded the title compound as a pale-yellow oil (599 mg, 55%); $R_f = 0.60$ (ethyl acetate); ν_{max}/cm^{-1} (neat) 3097, 2986, 1797, 1731, 1542, 1367, 1173, 1114, 1044, 732, 658, 579; δ_H (400 MHz, $CDCl_3$) 8.23 – 8.20 (m, 1H, Ar-C**H**), 7.83 – 7.72 (m, 3H, Ar-C**H**), 3.94 (t, *J* = 5.3 Hz, 2H, C**H₂**), 3.14 (t, *J* = 5.3 Hz, 2H, C**H₂**); δ_C (101 MHz, $CDCl_3$) 163.6 (**C**O), 147.7 (Ar-**C**), 135.4 (Ar-**C**H), 132.7 (Ar-**C**H), 131.7 (Ar-**C**H), 131.3 (Ar-**C**), 124.5 (Ar-**C**H), 41.9 (**C**H₂), 37.2 (**C**H₂); HRMS (ESI): calcd. for $C_9H_8N_2NaO_5S$, 279.0046. Found: $[MNa]^+$, 279.0043 (1.1 ppm error).

3,4-Dihydro-2*H*-benzo[*g*][1,2,6]thiadiazocin-5(6*H*)-one 1,1-dioxide (5-22b)



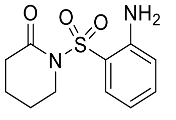
1-((2-Nitrophenyl)sulfonyl)azetidin-2-one (599 mg, 2.34 mmol) was dissolved in ethyl acetate (23.4 mL) and placed under an argon atmosphere. Palladium on carbon (250 mg, Pd 10% on carbon) was then added and the reaction vessel was evacuated and backfilled with hydrogen (via balloon) several times, then stirred at RT under a slight positive pressure of hydrogen (balloon) overnight. 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, ethyl acetate) afforded the title compound as a white solid (487 mg, 92%); m.p. 198 – 200 °C; $R_f = 0.38$ (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3299, 3264, 3044, 2949, 2881, 1680, 1588, 1476, 1428, 1314, 1154, 768, 756, 585; δ_H (400 MHz, DMSO–d_6, at 110 °C) 9.76 (s, 1H, CON**H**Ph), 7.99 (d, *J* = 7.9 Hz, 1H, Ar-C**H**), 7.63 (t, *J* = 7.6 Hz, 1H, Ar-C**H**), 7.47 (t, *J* = 7.7 Hz, 1H, Ar-C**H**), 7.41 (s, 1H, SO_2N**H**), 7.28 (d, *J* = 7.8 Hz, 1H, Ar-C**H**), 3.36 – 3.27 (m, 2H, C**H₂**), 2.27 – 2.08 (m, 2H, C**H₂**); δ_C (101 MHz, DMSO–d_6) 171.5 (**C**O), 137.2 (Ar-**C**), 134.7 (Ar-**C**), 133.4 (Ar-**C**H), 129.4 (Ar-**C**H), 127.6 (Ar-**C**H), 127.0 (Ar-**C**H), 39.3 (**C**H₂), 35.0 (**C**H₂); HRMS (ESI): calcd. for $C_9H_{10}N_2NaO_3S$, 249.0304. Found: $[MNa]^+$, 249.0305 (–0.3 ppm error). X-ray crystallographic data for this compound can be accessed *via* www.ccdc.cam.ac.uk/data_request/cif (CCDC 2215458)

1-((2-Nitrophenyl)sulfonyl)piperidin-2-one (5-15c)

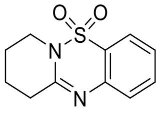


Piperidin-2-one (247.8 mg, 2.5 mmol) was dissolved in THF (10 mL) and the temperature was lowered to –78 °C (dry ice/acetone bath). *n*-BuLi (1.6 M in hexanes, 2.35 mL, 3.75 mmol, 1.5 eq) was added dropwise by syringe and the reaction was allowed to stir at –78 °C. After 1 hour, a solution of 2-nitrobenzenesulfonyl chloride **5-14** (831 mg, 3.75 mmol, 1.5 eq) in THF (2.5 mL) was transferred to the stirring reaction mixture dropwise by syringe. The reaction was allowed to warm to room temperature overnight before the addition of sat. aq. $NaHCO_3$ solution (15 mL). The aqueous layer was extracted with EtOAc (2 × 15 mL), the combined organic layers were dried ($MgSO_4$). After filtration, the solvent was removed by rotary evaporation. Purification by flash column chromatography (SiO_2, 1:2 hexane: dichloromethane → dichloromethane) afforded the title compound as a white solid (670 mg, 94%); m.p. 145 – 147 °C; R_f= 0.22 (dichloromethane); ν_{max}/cm^{-1} (neat) 3103, 2960, 1685, 1541, 1352, 1175, 1154, 1118, 833, 737, 586, 565; δ_H (400 MHz, $CDCl_3$) 8.49 – 8.42 (m, 1H, Ar-C**H**), 7.79 – 7.72 (m, 3H, Ar-C**H**), 3.92 – 3.86 (m, 2H, C**H$_2$**), 2.47 (t, *J* = 6.7 Hz, 2H, C**H$_2$**), 2.05 – 1.93 (m, 2H, C**H$_2$**), 1.92 – 1.80 (m, 2H, C**H$_2$**); δ_C (101 MHz, $CDCl_3$) 170.5 (**C**O), 148.1 (Ar-**C**), 135.2 (Ar-**C**H), 134.6 (Ar-**C**H), 133.2 (Ar-**C**), 132.0 (Ar-**C**H), 124.3 (Ar-**C**H), 47.0 (**C**H$_2$), 33.8 (**C**H$_2$), 22.9 (**C**H$_2$), 20.2 (**C**H$_2$); HRMS (ESI): calcd. for $C_{11}H_{12}N_2NaO_5S$, 307.0359. Found: [MNa]$^+$, 307.0355 (1.2 ppm error).

1-((2-Aminophenyl)sulfonyl)piperidin-2-one (5-21c) and 7,8,9,10-tetrahydrobenzo[*e*]pyrido[1,2-*b*][1,2,4]thiadiazine 5,5-dioxide (5-21d)



5-21c



5-21d

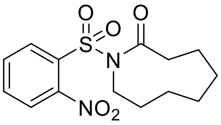
1-((2-Nitrophenyl)sulfonyl)piperidin-2-one **5-15c** (284.3mg, 1.0 mmol) was dissolved in ethyl acetate (10 mL) and placed under an argon atmosphere. Palladium on carbon

(100 mg, Pd 10% on carbon) was then added and the reaction vessel was evacuated and backfilled with hydrogen (via balloon) several times, then stirred at RT under a slight positive pressure of hydrogen (balloon) 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 dichloromethane (10 mL) and DBU (1.5 mL, 10 eq) added, and stirred at RT for 24 h, then reduced in vacuo. Purification by flash column chromatography (SiO_2, 9:1 dichloromethane: ethyl acetate) afforded the compound **5-21c** as a colorless oil (102 mg, 40% over two steps) as well as compound **5-21d** as a colorless oil (100 mg, 40% over two steps).

Data for **5-21c:** $R_f = 0.51$ (9:1 dichloromethane: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3479, 3376, 2954, 1683, 1620, 1484, 1327, 1142, 826, 702, 590; δ_H (400 MHz, $CDCl_3$) 7.66 (dd, *J* = 8.2, 1.5 Hz, 1H, Ar-C**H**), 7.28 (ddd, *J* = 8.7, 7.3, 1.7 Hz, 1H, Ar-C**H**), 6.72 (ddd, *J* = 8.2, 7.2, 1.1 Hz, 1H, Ar-C**H**), 6.68 (dd, *J* = 8.3, 1.0 Hz, 1H, Ar-C**H**), 5.17 (s, 2H, N**H₂**), 3.96 – 3.89 (m, 2H, C**H₂**), 2.43 (t, *J* = 6.8 Hz, 2H, C**H₂**), 1.95 – 1.86 (m, 2H, C**H₂**), 1.84 – 1.72 (m, 2H, C**H₂**); δ_C (101 MHz, $CDCl_3$) 171.1 (**C**O), 147.5 (Ar-**C**), 135.0 (Ar-**C**H), 130.8 (Ar-**C**H), 120.0 (Ar-**C**), 117.9 (Ar-**C**H), 117.1 (Ar-**C**H), 47.3 (**C**H₂), 34.1 (**C**H₂), 23.4 (**C**H₂), 20.4 (**C**H₂); HRMS (ESI): calcd. for $C_{11}H_{14}N_2NaO_3S$, 277.0617. Found: [MNa]$^+$, 277.0615 (0.8 ppm error).

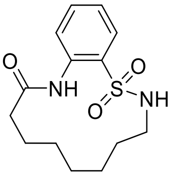
Data for **5-21d**: $R_f = 0.41$ (ethyl acetate); ν_{max}/cm^{-1} (thin film) 2953, 1571, 1462, 1323, 1287, 1181, 1155, 763, 577; δ_H (400 MHz, $CDCl_3$) 7.85 (dd, *J* = 7.9, 1.1 Hz, 1H, Ar-C**H**), 7.65 – 7.59 (m, 1H, Ar-C**H**), 7.46 – 7.35 (m, 2H, Ar-C**H**), 3.96 – 3.84 (m, 2H, C**H₂**), 2.84 (t, *J* = 6.7 Hz, 2H, C**H₂**), 2.06 – 1.97 (m, 2H, C**H₂**), 1.96 – 1.88 (m, 2H, C**H₂**); δ_C (101 MHz, $CDCl_3$) 154.9 (N=**C**), 142.6 (Ar-**C**), 133.8 (Ar-**C**H), 127.3 (Ar-**C**H), 126.4 (Ar-**C**H), 125.4 (Ar-**C**), 121.6 (Ar-**C**H), 41.4 (**C**H₂), 32.7 (**C**H₂), 22.7 (**C**H₂), 19.7 (**C**H₂); HRMS (ESI): calcd. for $C_{11}H_{12}N_2NaO_2S$, 259.0512. Found: [MNa]$^+$, 259.0505 (2.6 ppm error).

1-((2-Nitrophenyl)sulfonyl)azonan-2-one (5-15d)



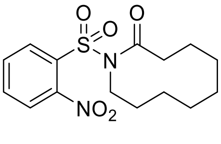
Azonan-2-one (282.4 mg, 2.0 mmol) was dissolved in THF (8 mL) and the temperature was lowered to –78 °C (dry ice/acetone bath). *n*-BuLi (1.6 M in hexanes, 1.88 mL, 3.0 mmol, 1.5 eq) was added dropwise by syringe and the reaction was allowed to stir at –78 °C. After 1 hour, a solution of 2-nitrobenzenesulfonyl chloride **5-14** (664.8 mg, 3.0 mmol, 1.5 eq) in THF (2.0 mL) was transferred to the stirring reaction mixture dropwise by syringe. The reaction was allowed to warm to room temperature overnight before the addition of sat. aq. $NaHCO_3$ solution (15 mL). The aqueous layer was extracted with EtOAc (2 × 15 mL), the combined organic layers were dried ($MgSO_4$). After filtration, the solvent was removed by rotary evaporation. Purification by flash column chromatography (SiO_2, 1:1 hexane: dichloromethane →1:1 hexane: ethyl acetate) afforded the title compound as a white solid (418 mg, 64%); m.p. 110 – 112 °C; R_f = 0.51 (dichloromethane); ν_{max}/cm^{-1} (neat) 3103, 2929, 1686, 1539, 1357, 1167, 740, 664, 535; δ_H (400 MHz, $CDCl_3$) 8.45 – 8.41 (m, 1H, Ar-C**H**), 7.77 – 7.70 (m, 3H, Ar-C**H**), 4.07 – 4.00 (m, 2H, C**H$_2$**), 2.58 – 2.48 (m, 2H, C**H$_2$**), 1.88 (dt, *J* = 11.1, 4.8 Hz, 4H, 2 × C**H$_2$**), 1.72 – 1.63 (m, 4H, 2 × C**H$_2$**), 1.61 – 1.52 (m, 2H, C**H$_2$**); δ_C (101 MHz, $CDCl_3$) 175.7 (**C**O), 147.9 (Ar-**C**), 134.9 (Ar-**C**H), 134.5 (Ar-**C**H), 133.4 (Ar-**C**), 131.8 (Ar-**C**H), 124.3 (Ar-**C**H), 48.7 (**C**H$_2$), 36.3 (**C**H$_2$), 29.4 (**C**H$_2$), 28.2 (**C**H$_2$), 25.0 (**C**H$_2$), 24.8 (**C**H$_2$), 22.6 (**C**H$_2$); HRMS (ESI): calcd. for $C_{14}H_{18}N_2NaO_5S$, 349.0829. Found: $[MNa]^+$, 349.0826 (0.7 ppm error).

2,3,4,5,6,7,8,9-Octahydrobenzo[*l*][1]thia[2,11]diazacyclotridecin-10(11*H*)-one 1,1-dioxide (5-22d)



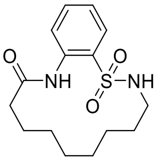
1-((2-Nitrophenyl)sulfonyl)azonan-2-one **5-15d** (326.4 mg, 1.0 mmol) was dissolved in ethyl acetate (10 mL) and placed under an argon atmosphere. Palladium on carbon (100 mg, Pd 10% on carbon) was then added and the reaction vessel was evacuated and backfilled with hydrogen (via balloon) several times, then stirred at RT under a slight positive pressure of hydrogen (balloon) 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 dichloromethane (10 mL) and DBU (1.5 mL, 10 eq) added, and stirred at RT overnight, then reduced in vacuo. Purification by flash column chromatography (SiO_2, dichloromethane → 9:1 dichloromethane: ethyl acetate) afforded the title compound as a colorless oil (195 mg, 66%); $R_f = 0.42$ (9:1 dichloromethane: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3348, 2932, 2861, 1678, 1583, 1522, 1434, 1323, 1286, 1146, 758, 588; δ_H (400 MHz, $CDCl_3$) 9.44 (s, 1H, CON**H**Ph), 8.43 (d, *J* = 8.3 Hz, 1H, Ar-C**H**), 7.87 (d, *J* = 7.9 Hz, 1H, Ar-C**H**), 7.60 – 7.47 (m, 1H, Ar-C**H**), 7.16 (t, *J* = 7.6 Hz, 1H, Ar-C**H**), 4.94 (t, *J* = 6.4 Hz, 1H, $SO_2N\mathbf{H}$), 3.11 (q, *J* = 6.8 Hz, 2H, $C\mathbf{H_2}$), 2.51 – 2.37 (m, 2H, $C\mathbf{H_2}$), 1.84 – 1.75 (m, 2H, $C\mathbf{H_2}$), 1.62 – 1.49 (m, 2H, $C\mathbf{H_2}$), 1.40 – 1.28 (m, 6H, 3 × $C\mathbf{H_2}$); δ_C (101 MHz, $CDCl_3$) 172.2 (**C**O), 136.4 (Ar-**C**), 134.3 (Ar-**C**H), 129.3 (Ar-**C**H), 127.6 (Ar-**C**), 124.1 (Ar-**C**H), 123.0 (Ar-**C**H), 41.0 ($\mathbf{C}H_2$), 37.4 ($\mathbf{C}H_2$), 27.2 ($\mathbf{C}H_2$), 26.7 ($\mathbf{C}H_2$), 24.8 ($\mathbf{C}H_2$), 24.5 ($\mathbf{C}H_2$), 24.4 ($\mathbf{C}H_2$); HRMS (ESI): calcd. for $C_{14}H_{20}N_2NaO_3S$, 319.1087. Found: $[MNa]^+$, 319.1083 (1.2 ppm error).

1-((2-Nitrophenyl)sulfonyl)azecan-2-one (5-15e)



Azecan-2-one (310.5 mg, 2.0 mmol) was dissolved in THF (8 mL) and the temperature was lowered to –78 °C (dry ice/acetone bath). *n*-BuLi (1.6 M in hexanes, 1.88 mL, 3.0 mmol, 1.5 eq) was added dropwise by syringe and the reaction was allowed to stir at –78 °C. After 1 hour, a solution of 2-nitrobenzenesulfonyl chloride (664.8 mg, 3.0 mmol, 1.5 eq) in THF (2.0 mL) was transferred to the stirring reaction mixture dropwise by syringe. The reaction was allowed to warm to room temperature overnight before the addition of sat. aq. $NaHCO_3$ solution (15 mL). The aqueous layer was extracted with EtOAc (2 × 15 mL), the combined organic layers were dried ($MgSO_4$). After filtration, the solvent was removed by rotary evaporation. Purification by flash column chromatography (SiO_2, 1:1 hexane: dichloromethane → 2:1 hexane: ethyl acetate) afforded the title compound as a white solid (395 mg, 58%); m.p. 130 – 132 °C; R_f = 0.40 (1:1 hexane: ethyl acetate); ν_{max}/cm^{-1} (neat) 2929, 1686, 1540, 1358, 1169, 1107, 850, 737, 662, 562, 539; δ_H (400 MHz, $CDCl_3$) 8.45 – 8.36 (m, 1H, Ar-C**H**), 7.78 – 7.68 (m, 3H, Ar-C**H**), 4.04 (t, *J* = 6.0 Hz, 2H, C**H₂**), 2.72 – 2.55 (m, 2H, C**H₂**), 1.92 – 1.76 (m, 4H, 2 × C**H₂**), 1.66 – 1.41 (m, 8H, 4 × C**H₂**); δ_C (101 MHz, $CDCl_3$) 175.1 (**C**O), 147.9 (Ar-**C**), 134.6 (Ar-**C**H), 134.5 (Ar-**C**H), 133.3 (Ar-**C**), 131.9 (Ar-**C**H), 124.5 (Ar-**C**H), 46.7 (**C**H_2), 33.3 (**C**H_2), 28.1 (**C**H_2), 26.8 (**C**H_2), 25.3 (**C**H_2), 25.0 (**C**H_2), 21.9 (**C**H_2), 19.2 (**C**H_2); HRMS (ESI): calcd. for $C_{15}H_{20}N_2NaO_5S$, 363.0985. Found: $[MNa]^+$, 363.0982 (1.0 ppm error).

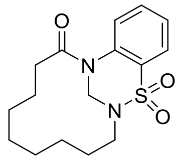
3,4,5,6,7,8,9,10-Octahydro-2*H*-benzo[*m*][1]thia[2,12]diazacyclotetradecin-11(12*H*)-one 1,1-dioxide (5-22e)



1-((2-Nitrophenyl)sulfonyl)azecan-2-one (340.4 mg, 1.0 mmol) was dissolved in ethyl acetate (10 mL) and placed under an argon atmosphere. Palladium on carbon (100 mg, Pd 10% on carbon) was then added and the reaction vessel was evacuated and backfilled with hydrogen (via balloon) several times, then stirred at RT under a slight positive pressure of hydrogen (balloon) 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 dichloromethane (10 mL) and DBU (1.5 mL, 10 eq) added, and stirred at RT overnight, then reduced in vacuo. Purification by flash column chromatography (SiO_2, dichloromethane → 20:1 dichloromethane: ethyl acetate) afforded **5-22e** as a white solid (195 mg, 63%) and **5-23e** as a colorless oil (100 mg, 30%).

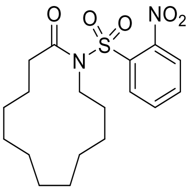
Data for **5-22e**: m.p. 90 – 92 °C; R_f = 0.60 (1:1 dichloromethane: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3337, 2931, 2860, 1680, 1585, 1435, 1321, 1145, 760, 733, 588; δ_H (400 MHz, $CDCl_3$) 9.76 (s, 1H, CON**H**Ph), 8.53 (d, *J* = 8.2 Hz, 1H, Ar-C**H**), 7.82 (dd, *J* = 8.0, 1.2 Hz, 1H, Ar-C**H**), 7.56 – 7.44 (m, 1H, Ar-C**H**), 7.12 (t, *J* = 7.6 Hz, 1H, Ar-C**H**), 5.31 (t, *J* = 6.1 Hz, 1H, SO_2N**H**), 2.99 – 2.88 (m, 2H, C**H**$_2$), 2.58 – 2.34 (m, 2H, C**H**$_2$), 1.83 – 1.70 (m, 2H, C**H**$_2$), 1.63 – 1.48 (m, 2H, C**H**$_2$), 1.42 – 1.19 (m, 8H, 4 × C**H**$_2$); δ_C (101 MHz, $CDCl_3$) 172.1 (**C**O), 136.8 (Ar-**C**), 134.3 (Ar-**C**H), 129.4 (Ar-**C**H), 126.5 (Ar-**C**), 123.9 (Ar-**C**H), 122.2 (Ar-**C**H), 42.0 (**C**H$_2$), 37.4 (**C**H$_2$), 27.5 (**C**H$_2$), 26.5 (**C**H$_2$), 26.3 (**C**H$_2$), 25.0 (**C**H$_2$), 24.4 (**C**H$_2$), 22.8 (**C**H$_2$); HRMS (ESI): calcd. for $C_{15}H_{22}N_2NaO_3S$, 333.1243. Found: [MNa]$^+$, 333.1245 (–0.4 ppm error).

3,4,5,6,7,8,9,10-octahydro-11*H*-2,12-methanobenzo[*m*][1]thia[2,12]diazacyclotetradecin-11-one 1,1-dioxide (5-23e)



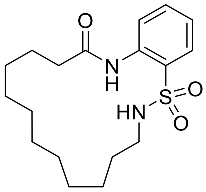
Data for **5-23e**: R_f = 0.80 (1:1 dichloromethane: ethyl acetate); ν_{max}/cm^{-1} (thin film) 2933, 2868, 1676, 1594, 1476, 1335, 1164, 1134, 912, 763, 733, 705; δ_H (400 MHz, $CDCl_3$) 7.83 (dd, *J* = 8.0, 1.5 Hz, 1H, Ar-C**H**), 7.50 – 7.43 (m, 1H, Ar-C**H**), 7.35 – 7.27 (m, 2H, Ar-C**H**), 5.29 (brs, 2H, NC**H**$_2$N), 3.27 (s, 2H, C**H**$_2$), 3.33 – 3.09 (m, 2H, C**H**$_2$), 2.68 (t, *J* = 5.9 Hz, 2H, C**H**$_2$), 1.91 – 1.47 (m, 4H, 2 × C**H**$_2$), 1.43 – 1.09 (m, 8H, 4 × C**H**$_2$); δ_C (101 MHz, $CDCl_3$) 173.8 (**C**O), 136.0 (Ar-**C**), 132.2 (Ar-**C**H), 129.1 (Ar-**C**), 125.9 (Ar-**C**H), 125.7 (Ar-**C**H), 123.9 (Ar-**C**H), 60.0 (**C**H$_2$), 47.0 (**C**H$_2$), 33.2 (**C**H$_2$), 24.6 (2 × **C**H$_2$), 23.5 (**C**H$_2$), 23.4 (**C**H$_2$), 23.0 (**C**H$_2$), 22.8 (**C**H$_2$); HRMS (ESI): calcd. for $C_{16}H_{22}N_2NaO_3S$, 345.1243. Found: [MNa]$^+$, 345.1239 (1.2 ppm error).

1-((2-Nitrophenyl)sulfonyl)azacyclotridecan-2-one (5-15f)



Azacyclotridecan-2-one (986.6 mg, 5.0 mmol) was dissolved in THF (20 mL) and the temperature was lowered to –78 °C (dry ice/acetone bath). *n*-BuLi (1.6 M in hexanes, 4.7 mL, 7.5 mmol, 1.5 eq) was added dropwise by syringe and the reaction was allowed to stir at –78 °C. After 1 hour, a solution of 2-nitrobenzenesulfonyl chloride **5-14** (1.66 g, 7.5 mmol, 1.5 eq) in THF (5.0 mL) was transferred to the stirring reaction mixture dropwise by syringe. The reaction was allowed to warm to room temperature overnight before the addition of sat. aq. $NaHCO_3$ solution (30 mL). The aqueous layer was extracted with EtOAc (2 × 30 mL), the combined organic layers were dried ($MgSO_4$). After filtration, the solvent was removed by rotary evaporation. Purification by flash column chromatography (SiO_2, 1:1 hexane: dichloromethane → dichloromethane) afforded the title compound as a brown solid (1075 mg, 56%); m.p. 79 – 81 °C; R_f = 0.22 (1:1 hexane: dichloromethane); ν_{max}/cm^{-1} (neat) 2931, 2862, 1700, 1542, 1362, 1171, 1117, 852, 781, 739, 572; δ_H (400 MHz, $CDCl_3$) 8.44 – 8.35 (m, 1H, Ar-C**H**), 7.78 – 7.67 (m, 3H, Ar-C**H**), 3.88 – 3.80 (m, 2H, C**H₂**), 2.53 – 2.46 (m, 2H, C**H₂**), 1.95 – 1.78 (m, 2H, C**H₂**), 1.77 – 1.62 (m, 2H, C**H₂**), 1.60 – 1.47 (m, 2H, C**H₂**), 1.46 – 1.28 (m, 12H, 6 × C**H₂**); δ_C (101 MHz, $CDCl_3$) 174.0 (**C**O), 147.9 (Ar-**C**), 134.6 (Ar-**C**H), 134.4 (Ar-**C**H), 133.6 (Ar-**C**), 132.1 (Ar-**C**H), 124.5 (Ar-**C**H), 46.6 (**C**H₂), 34.2 (**C**H₂), 27.5 (**C**H₂), 25.5 (**C**H₂), 25.4 (**C**H₂), 25.2 (**C**H₂), 25.2 (**C**H₂), 24.6 (**C**H₂), 23.9 (**C**H₂), 23.6 (**C**H₂), 23.5 (**C**H₂); HRMS (ESI): calcd. for $C_{18}H_{26}N_2NaO_5S$, 405.1455. Found: $[MNa]^+$, 405.1456 (–0.4 ppm error).

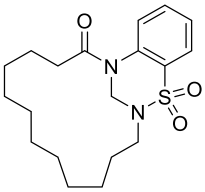
2,3,4,5,6,7,8,9,10,11,12,13- Dodecahydrobenzo [p][1]thia[2,15]diazacycloheptadecin-14(15*H*)-one 1,1-dioxide (5-22f)



1-((2-Nitrophenyl)sulfonyl)azacyclotridecan-2-one **5-15f** (765 mg, 2.0 mmol) was dissolved in ethyl acetate (20 mL) and placed under an argon atmosphere. Palladium on carbon (200 mg, Pd 10% on carbon) was then added and the reaction vessel was evacuated and backfilled with hydrogen (via balloon) several times, then stirred at RT under a slight positive pressure of hydrogen (balloon) 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 dichloromethane (20 mL) and DBU (3.0 mL, 10 eq) added, and stirred at RT overnight, then reduced in vacuo. Purification by flash column chromatography (SiO_2, dichloromethane → 20:1 dichloromethane: ethyl acetate) afforded **5-22f** as a colorless oil (315 mg, 45%) and **5-23f** as a white solid (317 mg, 43%).

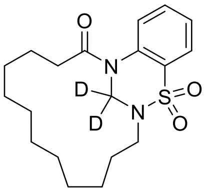
Data for **5-22f**: R_f = 0.13 (dichloromethane); ν_{max}/cm^{-1} (thin film) 3333, 2928, 2857, 1684, 1586, 1529, 1437, 1320, 1148, 760, 588; δ_H (400 MHz, $CDCl_3$) 9.49 (s, 1H, CON**H**Ph), 8.53 (d, J = 8.4 Hz, 1H, Ar-C**H**), 7.82 (dd, J = 8.0, 1.5 Hz, 1H, Ar-C**H**), 7.55 – 7.49 (m, 1H, Ar-C**H**), 7.17 – 7.13 (m, 1H, Ar-C**H**), 5.05 (t, J = 6.2 Hz, 1H, SO_2N**H**), 2.89 (q, J = 6.5 Hz, 2H, C**H₂**), 2.42 (t, J = 6.8 Hz, 2H, C**H₂**), 1.73 (p, J = 6.9 Hz, 2H, C**H₂**), 1.48 – 1.13 (m, 16H, 8 × C**H₂**); δ_C (101 MHz, $CDCl_3$) 172.1 (**C**O), 136.6 (Ar-**C**), 134.2 (Ar-**C**H), 129.3 (Ar-**C**H), 126.4 (Ar-**C**), 123.7 (Ar-**C**H), 122.5 (Ar-**C**H), 42.4 (**C**H_2), 38.3 (**C**H_2), 28.4 (**C**H_2), 27.7 (**C**H_2), 27.2 (**C**H_2), 26.6 (**C**H_2), 26.4 (**C**H_2), 26.0 (**C**H_2), 25.8 (**C**H_2), 25.1 (**C**H_2), 24.4 (**C**H_2); HRMS (ESI): calcd. for $C_{18}H_{28}N_2NaO_3S$, 375.1713. Found: $[MNa]^+$, 375.1713 (–0.0 ppm error).

4,5,6,7,8,9,10,11,12,13-Decahydro-2,15-methanobenzo[*p*][1]thia[2,15]diazacycloheptadecin-14(3*H*)-one 1,1-dioxide (5-23f)



Data for **5-23f**: m.p. 105 – 107 °C; R$_f$ = 0.30 (dichloromethane); ν$_{max}$/cm^{-1} (thin film) 2929, 2858, 1677, 1476, 1337, 1171, 1135, 759, 707, 572; δ$_H$ (400 MHz, CDCl$_3$) 7.82 (d, *J* = 7.9 Hz, 1H, Ar-C**H**), 7.46 (d, *J* = 6.5 Hz, 2H, Ar-C**H**), 7.35 – 7.27 (m, 1H, Ar-C**H**), 5.50 (s, 2H, NC**H$_2$**N), 3.17 – 3.02 (m, 2H, C**H$_2$**), 2.63 (t, *J* = 6.3 Hz, 2H, C**H$_2$**), 1.87 – 1.59 (m, 4H, 2 × C**H$_2$**), 1.50 – 1.35 (m, 2H, C**H$_2$**), 1.36 – 1.15 (m, 12H, 6 × C**H$_2$**); δ$_C$ (101 MHz, CDCl$_3$) 172.8 (**C**O), 135.9 (Ar-**C**), 132.3 (Ar-**C**H), 128.5 (Ar-**C**), 126.0 (Ar-**C**H), 125.9 (Ar-**C**H), 123.8 (Ar-**C**H), 59.2 (N**C**H$_2$N), 46.0 (**C**H$_2$), 34.3 (**C**H$_2$), 27.4 (**C**H$_2$), 26.7 (**C**H$_2$), 26.5 (**C**H$_2$), 26.2 (**C**H$_2$), 26.2 (**C**H$_2$), 25.5 (**C**H$_2$), 25.2 (**C**H$_2$), 25.1 (**C**H$_2$), 23.7 (**C**H$_2$); HRMS (ESI): calcd. for $C_{19}H_{28}N_2NaO_3S$, 387.1713. Found: [MNa]$^+$, 387.1714 (–0.4 ppm error).

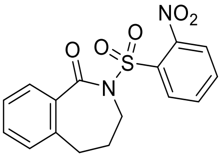
4,5,6,7,8,9,10,11,12,13-Decahydro-2,15-methanobenzo[*p*][1]thia[2,15] diazacycloheptadecin-14(3*H*)-one-20,20-*d*$_2$ 1,1-dioxide (5-23f-*d*$_2$)



The macrocycle **5-22f** (105.2 mg, 0.300 mmol) was dissolved in dichloromethane–*d*$_2$ (3.00 mL) and DBU (0.50 mL, 10 eq) added. The reaction was the stirred at RT for 48 h and reduced in vacuo. Purification by flash column chromatography (SiO$_2$, dichloromethane) afforded the title compound as a white solid (60 mg, 55%); m.p. 100 – 102 °C; R$_f$ = 0.30 (dichloromethane); ν$_{max}$/cm^{-1} (thin film) 2928, 2855, 1663, 1594, 1472, 1330, 1170, 1158, 1075, 758, 695, 568; δ$_H$ (400 MHz, CDCl$_3$) 7.83 (dt, *J* = 7.9, 1.0 Hz, 1H, Ar-C**H**), 7.51 – 7.44 (m, 2H, Ar-C**H**), 7.36 – 7.25 (m, 1H, Ar-C**H**), 3.19 – 3.07 (m, 2H, C**H$_2$**), 2.64 (t, *J* = 6.3 Hz, 2H, C**H$_2$**), 1.87 – 1.63 (m, 4H, 2 × C**H$_2$**), 1.47 –

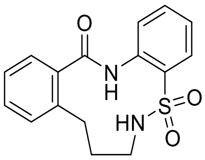
1.38 (m, 2H, C**H₂**), 1.36 – 1.25 (m, 12H, 6 × C**H₂**); δ_C (101 MHz, $CDCl_3$) 172.8 (**C**O), 135.9 (Ar-**C**), 132.3 (Ar-**C**H), 128.5 (Ar-**C**), 126.0 (Ar-**C**H), 125.9 (Ar-**C**H), 123.8 (Ar-**C**H), 75.1 (N**C**D_2N), 46.0 (**C**H_2), 34.3 (**C**H_2), 27.4 (**C**H_2), 26.7 (**C**H_2), 26.6 (**C**H_2), 26.3 (**C**H_2), 26.2 (**C**H_2), 25.5 (**C**H_2), 25.2 (**C**H_2), 25.1 (**C**H_2), 23.7 (**C**H_2); HRMS (ESI): calcd. for $C_{19}H_{26}D_2N_2NaO_3S$, 389.1838. Found: $[MNa]^+$, 389.1844 (–1.5 ppm error).

2-((2-Nitrophenyl)sulfonyl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-1-one (5-15g)



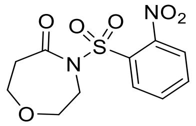
2,3,4,5-Tetrahydro-1*H*-benzo[*c*]azepin-1-one **5-12g** (332 mg, 2.0 mmol) was dissolved in THF (8 mL) and the temperature was lowered to –78 °C (dry ice/acetone bath). *n*-BuLi (1.6 M in hexanes, 1.88 mL, 3.0 mmol, 1.5 eq) was added dropwise by syringe and the reaction was allowed to stir at –78 °C. After 1 hour, a solution of 2-nitrobenzenesulfonyl chloride **5-14** (665 mg, 3.00 mmol, 1.5 eq) in THF (2.0 mL) was transferred to the stirring reaction mixture dropwise by syringe. The reaction was allowed to warm to room temperature overnight before the addition of sat. aq. $NaHCO_3$ solution (15 mL). The aqueous layer was extracted with EtOAc (2 × 15 mL), the combined organic layers were dried ($MgSO_4$). After filtration, the solvent was removed by rotary evaporation. Purification by flash column chromatography (SiO_2, 1:1 hexane: dichloromethane → dichloromethane) afforded the title compound as a pale yellow solid (650 mg, 94%); m.p. 122 – 124 °C; R_f = 0.12 (1:1 hexane: dichloromethane); ν_{max}/cm^{-1} (neat) 3102, 2959, 1684, 1540, 1354, 1169, 1002, 736, 584; δ_H (400 MHz, $CDCl_3$) 8.61 – 8.57 (m, 1H, Ar-C**H**), 7.84 – 7.74 (m, 3H, Ar-C**H**), 7.55 (dd, *J* = 7.7, 1.3 Hz, 1H, Ar-C**H**), 7.47 (td, *J* = 7.5, 1.3 Hz, 1H), 7.30 (td, *J* = 7.6, 1.1 Hz, 1H, Ar-C**H**), 7.21 (d, *J* = 7.5 Hz, 1H, Ar-C**H**), 3.88 (t, *J* = 6.3 Hz, 2H, C**H₂**), 2.99 (t, *J* = 7.0 Hz, 2H, C**H₂**), 2.17 (tt, *J* = 7.2, 7.0 Hz, 2H, C**H₂**); δ_C (101 MHz, $CDCl_3$) 171.1 (**C**O), 148.1 (Ar-**C**), 138.5 (Ar-**C**H), 134.9 (Ar-**C**H), 134.6 (Ar-**C**H), 133.7 (Ar-**C**), 133.5 (Ar-**C**), 133.1 (Ar-**C**H), 132.2 (Ar-**C**H), 129.4 (Ar-**C**H), 129.1 (Ar-**C**H), 127.3 (Ar-**C**H), 124.3 (Ar-**C**H), 46.1 (**C**H_2), 29.8 (**C**H_2), 29.5 (**C**H_2); HRMS (ESI): calcd. for $C_{16}H_{14}N_2NaO_5S$, 369.0516. Found: $[MNa]^+$, 369.0519 (–1.0 ppm error).

6,7,8,9-Tetrahydrodibenzo[*f,j*][1]thia[2,9]diazacycloundecin-14(15*H*)-one 5,5-dioxide (5-22g)



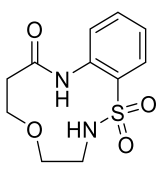
2-((2-Nitrophenyl)sulfonyl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-1-one **5-15g** (346.4 mg, 1.00 mmol) was dissolved in ethyl acetate (10 mL) and placed under an argon atmosphere. Palladium on carbon (100 mg, Pd 10% on carbon) was then added and the reaction vessel was evacuated and backfilled with hydrogen (via balloon) several times, then stirred at RT under a slight positive pressure of hydrogen (balloon) 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 dichloromethane (10 mL) and DBU (1.5 mL, 10 eq) added, and stirred at RT overnight, then reduced in vacuo. Purification by flash column chromatography (SiO_2, dichloromethane → 10:1 dichloromethane: ethyl acetate) afforded the title compound as a colorless oil (241 mg, 76%); R_f = 0.25 (9:1 dichloromethane: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3371, 2935, 2876, 1682, 1508, 1434, 1304, 1151, 1026, 761, 605; δ_H (400 MHz, Acetone–*d6*) 8.22 (d, *J* = 8.1 Hz, 1H, Ar-C**H**), 7.97 – 7.94 (m, 1H, Ar-C**H**), 7.73 (t, *J* = 7.7Hz, 1H, Ar-C**H**), 7.48 (m, 3H, Ar-C**H**), 7.41 – 7.33 (m, 2H, Ar-C**H**), 3.28 – 3.20 (m, 2H, C**H**$_2$), 2.81 (t, *J* = 6.3 Hz, 2H, C**H**$_2$), 2.09 – 2.08 (m, 2H, C**H**$_2$); δ_C (101 MHz, Acetone–*d6*) 169.1 (**C**O), 139.6 (Ar-**C**), 138.1 (Ar-**C**), 136.2 (Ar-**C**), 134.4 (Ar-**C**H), 133.5 (Ar-**C**), 130.9 (Ar-**C**H), 130.3 (Ar-**C**H), 129.4 (Ar-**C**H), 127.2 (Ar-**C**H), 126.7 (Ar-**C**H), 126.2 (Ar-**C**H), 125.5 (Ar-**C**H), 40.3 (**C**H$_2$), 30.6 (**C**H$_2$), 27.6 (**C**H$_2$); HRMS (ESI): calcd. for $C_{16}H_{16}N_2NaO_3S$, 339.0774. Found: $[MNa]^+$, 339.0780 (–1.9 ppm error).

4-((2-Nitrophenyl)sulfonyl)-1,4-oxazepan-5-one (5-15h)



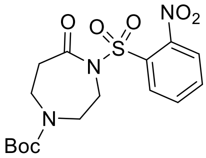
1,4-Oxazepan-5-one **5-12h** (230.3 mg, 2.0 mmol) was dissolved in THF (8 mL) and the temperature was lowered to -78 °C (dry ice/acetone bath). *n*-BuLi (1.6 M in hexanes, 1.88 mL, 3.0 mmol, 1.5 eq) was added dropwise by syringe and the reaction was allowed to stir at -78 °C. After 1 hour, a solution of 2-nitrobenzenesulfonyl chloride (664.8 mg, 3.0 mmol, 1.5 eq) in THF (2.0 mL) was transferred to the stirring reaction mixture dropwise by syringe. The reaction was allowed to warm to room temperature overnight before the addition of sat. aq. $NaHCO_3$ solution (15 mL). The aqueous layer was extracted with EtOAc (2 × 15 mL), the combined organic layers were dried ($MgSO_4$). After filtration, the solvent was removed by rotary evaporation. Purification by flash column chromatography (SiO_2, 2:1 hexane: ethyl acetate) afforded the title compound as a colorless oil (506 mg, 84%); $R_f = 0.25$ (1:1 hexane: ethyl acetate); ν_{max}/cm^{-1} (neat) 3105, 2855, 1699, 1540, 1366, 1355, 1294, 1170, 1125, 954, 852, 663, 583, 565, 530; δ_H (400 MHz, $CDCl_3$) 8.50 – 8.42 (m, 1H, Ar-C**H**), 7.79 – 7.75 (m, 3H, Ar-C**H**), 4.20 – 4.10 (m, 2H, OC**H₂**), 4.01 – 3.94 (m, 2H, OC**H₂**), 3.89 – 3.81 (m, 2H, C**H₂**), 2.85 – 2.78 (m, 2H, C**H₂**); δ_C (101 MHz, $CDCl_3$) 173.7 (**C**O), 147.9 (Ar-**C**), 135.2 (Ar-**C**H), 134.8 (Ar-**C**H), 132.8 (Ar-**C**), 132.1 (Ar-**C**H), 124.5 (Ar-**C**H), 71.1 (O**C**H₂), 64.6 (O**C**H₂), 49.2 (**C**H₂), 42.5 (**C**H₂); HRMS (ESI): calcd. for $C_{11}H_{12}N_2NaO_6S$, 323.0308. Found: $[MNa]^+$, 323.0303 (1.6 ppm error).

3,4,6,7-Tetrahydro-2*H*-benzo[*f*][1]oxa[5]thia[4,8]diazacycloundecin-8(9*H*)-one 1,1-dioxide (5-22h)



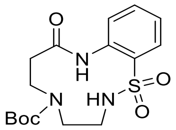
4-((2-Nitrophenyl)sulfonyl)-1,4-oxazepan-5-one **5-15h** (150.2 mg, 0.5 mmol) was dissolved in ethyl acetate (5.0 mL) and placed under an argon atmosphere. Palladium on carbon (50 mg, Pd 10% on carbon) was then added and the reaction vessel was evacuated and backfilled with hydrogen (via balloon) several times, then stirred at RT under a slight positive pressure of hydrogen (balloon) 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 dichloromethane (5.0 mL) and DBU (0.75 mL, 10 eq) added, and stirred at RT overnight, then reduced in vacuo. Purification by flash column chromatography (SiO_2, 2:1 dichloromethane: ethyl acetate → 9:1 ethyl acetate: methanol) afforded the title compound as a white solid (115 mg, 85%); m.p. 162 – 164 °C; R_f = 0.23 (2:1 dichloromethane: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3250, 2874, 1681, 1584, 1537, 1441, 1308, 1155, 1122, 930, 762, 604; δ_H (400 MHz, DMSO–*d*$_6$) 10.43 (s, 1H, CON**H**Ph), 8.46 (d, *J* = 8.0 Hz, 1H, Ar-C**H**), 7.94 (d, *J* = 7.9 Hz, 1H, Ar-C**H**), 7.65 (t, *J* = 7.7 Hz, 1H, Ar-C**H**), 7.25 (t, *J* = 7.6 Hz, 1H, Ar-C**H**), 3.76 (t, *J* = 5.5 Hz, 2H, OC**H**$_2$), 3.57 (t, *J* = 4.7 Hz, 2H, OC**H**$_2$), 3.47 (t, *J* = 4.7 Hz, 2H, C**H**$_2$), 2.60 (t, *J* = 5.6 Hz, 2H, C**H**$_2$); δ_C (101 MHz, DMSO–*d*$_6$) 170.0 (**C**O), 136.3 (Ar-**C**H), 134.2 (Ar-**C**H), 129.4 (Ar-**C**H), 128.7 (Ar-**C**), 123.0 (Ar-**C**H), 121.5 (Ar-**C**), 70.4 (O**C**H$_2$), 66.7 (O**C**H$_2$), 39.6 (**C**H$_2$), 37.8 (**C**H$_2$); HRMS (ESI): calcd. for $C_{11}H_{14}N_2NaO_4S$, 293.0566. Found: $[MNa]^+$, 293.0566 (0.3 ppm error).

tert-butyl 4-((2-nitrophenyl)sulfonyl)-5-oxo-1,4-diazepane-1-carboxylate (5-15i)



Tert-butyl 5-oxo-1,4-diazepane-1-carboxylate **4-20** (214.3 mg, 1.0 mmol) was dissolved in THF (4.0 mL) and the temperature was lowered to -78 °C (dry ice/acetone bath). *n*-BuLi (1.6 M in hexanes, 0.94 mL, 1.5 mmol, 1.5 eq) was added dropwise by syringe and the reaction was allowed to stir at -78 °C. After 1 hour, a solution of 2-nitrobenzenesulfonyl chloride (332.4 mg, 1.5 mmol, 1.5 eq) in THF (1.0 mL) was transferred to the stirring reaction mixture dropwise by syringe. The reaction was allowed to warm to room temperature overnight before the addition of sat. aq. $NaHCO_3$ solution (10 mL). The aqueous layer was extracted with EtOAc (2 × 10 mL), the combined organic layers were dried ($MgSO_4$). After filtration, the solvent was removed by rotary evaporation. Purification by flash column chromatography (SiO_2, 1:1 hexane: dichloromethane → 1:1 hexane: ethyl acetate) afforded the title compound as a pale-yellow solid (282 mg, 71%); m.p. 101 – 103 °C; R_f = 0.32 (1:1 hexane: ethyl acetate); ν_{max}/cm^{-1} (neat) 2975, 1688, 1541, 1359, 1256, 1168, 1127, 1003, 736, 584, 562; δ_H (400 MHz, $CDCl_3$) 8.45 – 8.34 (m, 1H, Ar-C**H**), 7.78 – 7.68 (m, 3H, Ar-C**H**), 4.12 – 3.97 (m, 2H, C$\mathbf{H_2}$), 3.82 – 3.72 (m, 2H, C$\mathbf{H_2}$), 3.68 – 3.56 (m, 2H, C$\mathbf{H_2}$), 2.76 – 2.62 (m, 2H, C$\mathbf{H_2}$), 1.43 (s, 9H, C(C$\mathbf{H_3}$)$_3$); δ_C (101 MHz, $CDCl_3$) 173.6 (**C**O), 154.3 (**C**OO), 147.8 (Ar-**C**), 135.0 (Ar-**C**H), 134.8 (Ar-**C**H), 132.8 (Ar-**C**), 132.1 (Ar-**C**H), 124.4 (Ar-**C**H), 80.9 (O**C**(CH_3)$_3$), 48.1 (2 × **C**H_2), 40.8 (2 × **C**H_2), 28.3 (C(**C**H_3)$_3$); HRMS (ESI): calcd. for $C_{16}H_{21}N_3NaO_7S$, 422.0992. Found: $[MNa]^+$, 422.0989 (0.9 ppm error).

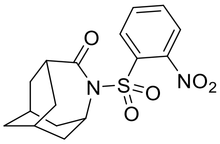
Tert-butyl 8-oxo-3,4,6,7,8,9-hexahydrobenzo[*j*][1]thia[2,5,9]triazacycloundecine-5(2*H*)-carboxylate 1,1-dioxide (5-22i)



tert-Butyl 4-((2-nitrophenyl)sulfonyl)-5-oxo-1,4-diazepane-1-carboxylate (169.7 mg, 0.425 mmol) was dissolved in ethyl acetate (5.0 mL) and placed under an argon atmosphere. Palladium on carbon (50 mg, Pd 10% on carbon) was then added and the reaction vessel was evacuated and backfilled with hydrogen (via balloon) several times, then stirred at RT under a slight positive pressure of hydrogen (balloon) 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 dichloromethane (5.0 mL) and DBU (0.75 mL, 10 eq) added, and stirred at RT overnight, then reduced in vacuo. Purification by flash column chromatography (SiO_2, 9:1 dichloromethane: ethyl acetate → 9:1 ethyl acetate: methanol) afforded the title compound as a white solid (130 mg, 83%); m.p. 163 – 165 °C; R_f = 0.23 (2:1 dichloromethane: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3278, 2975, 1670, 1323, 1155, 1126, 761, 736, 591; δ_H (400 MHz, DMSO–*d*$_6$) δ 9.78 (s, 1H, CON**H**Ph), 7.91 (dd, *J* =

7.9, 1.3 Hz, 1H, Ar-C**H**), 7.66 (t, *J* = 7.3 Hz, 1H, Ar-C**H**), 7.57 (d, *J* = 7.7 Hz, 1H, Ar-C**H**), 7.43 (t, *J* = 7.5 Hz, 1H, Ar-C**H**), 3.59 – 3.50 (m, 2H, C**H**$_2$), 3.33 – 3.11 (m, 4H, 2 × C**H**$_2$), 2.70 – 2.57 (m, 2H, C**H**$_2$), 1.41 (s, 9H, C(C**H**$_3$)$_3$); δ_C (101 MHz, DMSO–*d*$_6$) 171.2 (**C**O), 154.9 (**C**OO), 134.7 (Ar-**C**), 134.4 (Ar-**C**), 132.9 (Ar-**C**H), 129.0 (Ar-**C**H), 128.4 (Ar-**C**H), 126.0 (Ar-**C**H), 79.1(O**C**(CH$_3$)$_3$), 49.1 (**C**H$_2$), 47.0 (**C**H$_2$), 41.6 (**C**H$_2$), 36.7 (**C**H$_2$), 27.9 (OC(**C**H$_3$)$_3$); HRMS (ESI): calcd. for $C_{16}H_{23}N_3NaO_5S$, 392.1251. Found: [MNa]$^+$, 392.1248 (0.6 ppm error).

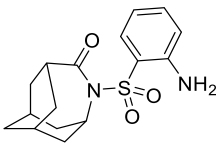
(1*R*,3*r*,8*S*)-4-((2-Nitrophenyl)sulfonyl)-4-azatricyclo[4.3.1.1^{3,8}]undecan-5-one (5-15j)



(1*R*,3*r*,8*S*)-4-azatricyclo[4.3.1.1^{3,8}]undecan-5-one **5-12j** (165.2 mg, 1.0 mmol) was dissolved in THF (4 mL) and the temperature was lowered to –78 °C (dry ice/acetone bath). *n*-BuLi (1.6 M in hexanes, 0.94 mL, 1.5 mmol, 1.5 eq) was added dropwise by syringe and the reaction was allowed to stir at –78 °C. After 1 hour, a solution of 2-nitrobenzenesulfonyl chloride (332.4 mg, 1.5 mmol, 1.5 eq) in THF (1.0 mL) was transferred to the stirring reaction mixture dropwise by syringe. The reaction was allowed to warm to room temperature overnight before the addition of saturated NaHCO$_3$ solution (10 mL). The aqueous layer was extracted with EtOAc (2 × 10 mL), the combined organic layers were dried (MgSO$_4$). After filtration, the solvent was removed by rotary evaporation. Purification by flash column chromatography (SiO$_2$, 1:2 hexane: dichloromethane → 1:1 hexane: ethyl acetate) afforded the title compound as a white solid (208 mg, 60%); R$_f$ = 0.42 (1:1 hexane: ethyl acetate); ν_{max}/cm^{-1} (neat) 3103, 2919, 2854, 1686, 1540, 1360, 1169, 1084, 739, 655, 620, 577; δ_H (400 MHz, CDCl$_3$-*d*) 8.49 – 8.45 (m, 1H, Ph-C**H**), 7.78 – 7.72 (m, 3H, Ph-C**H**), 4.70 (h, *J* = 3.3, 2.9 Hz, 1H, C**H**), 2.86 (tt, *J* = 6.3, 1.8 Hz, 1H, C**H**), 2.12 (d, *J* = 3.6 Hz, 4H, 2 × C**H**$_2$), 2.11 – 2.05 (m, 2H, 2 × C**H**), 2.02 – 1.95 (m, 2H, C**H**$_2$), 1.93 – 1.80 (m, 2H, C**H**$_2$), 1.77

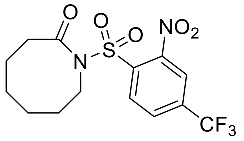
– 1.68 (m, 2H, C**H$_2$**); δ$_C$ (101 MHz, CDCl$_3$-*d*) 179.4 (**C**O), 148.0 (Ph-**C**), 134.7 (Ph-**C**H), 134.5 (Ph-**C**), 134.2 (Ph-**C**H), 132.0 (Ph-**C**H), 124.2 (Ph-**C**H), 50.3 (**C**H), 43.7 (**C**H), 35.9 (2 × **C**H$_2$), 33.8 (**C**H$_2$), 30.7 (2 × **C**H$_2$), 25.8 (2 × **C**H); HRMS (ESI): calcd. for $C_{16}H_{18}N_2NaO_5S$, 373.0829. Found: $[MNa]^+$, 373.0832 (–0.8 ppm error).

(1*R*,3*r*,8*S*)-4-((2-Aminophenyl)sulfonyl)-4-azatricyclo[4.3.1.1^{3,8}]undecan-5-one (5-21j)



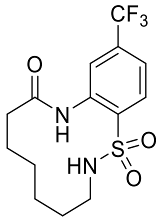
(1*R*,3*r*,8*S*)-4-((2-Nitrophenyl)sulfonyl)-4-azatricyclo[4.3.1.1^{3,8}]undecan-5-one **5-15j** (157.7 mg, 0.4 mmol) was dissolved in ethyl acetate (4.5 mL) and placed under an argon atmosphere. Palladium on carbon (45 mg, Pd 10% on carbon) was then added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at RT under a slight positive pressure of hydrogen (balloon) 3 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 dichloromethane (4.5 mL) and DBU (0.675 mL, 10 eq) added, and stirred at RT overnight, then reduced in vacuo. Purification by flash column chromatography (SiO$_2$, 1: 1 hexane: ethyl acetate) afforded the title compound as a white solid (135 mg, 94%); M.p. 140 – 142 °C; R$_f$ = 0.33 (1: 1 hexane: ethyl acetate); ν$_{max}$/cm^{-1} (thin film) 3449, 3366, 2919, 1668, 1483, 1321, 1192, 1146, 1075, 705, 622, 586, 510; δ$_H$ (400 MHz, CDCl$_3$-*d*) 7.58 (dd, *J* = 8.2, 1.4 Hz, 1H, Ph-C**H**), 7.28 – 7.20 (m, 1H, Ph-C**H**), 6.72 – 6.63 (m, 2H, Ph-C**H**), 5.19 (brs, 2H, N**H$_2$**), 4.90 – 4.83 (m, 1H, C**H**), 2.85 – 2.75 (m, 1H, C**H**), 2.12 – 1.99 (m, 4H, 2 × CH + C**H$_2$**), 1.99 – 1.84 (m, 2H, C**H$_2$**), 1.86 – 1.73 (m, 2H, C**H$_2$**), 1.70 – 1.66 (m, 2H, C**H$_2$**); δ$_C$ (101 MHz, CDCl$_3$-*d*) 179.1 (**C**O), 147.3 (Ph-**C**), 134.6 (Ph-CH), 130.1 (Ph-**C**H), 120.4 (Ph-**C**), 117.9 (Ph-CH), 116.8 (Ph-**C**H), 49.4 (**C**H), 43.5 (**C**H), 36.1 (2 × **C**H$_2$), 33.8 (**C**H$_2$), 30.7 (2 × **C**H$_2$), 25.8 (2 × **C**H); HRMS (ESI): calcd. for $C_{16}H_{20}N_2NaO_3S$, 343.1087. Found: $[MNa]^+$, 343.1088 (–0.3 ppm error).

1-((2-Nitro-4-(trifluoromethyl)phenyl)sulfonyl)azocan-2-one (5-15k)



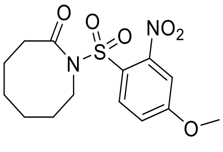
ω-Heptanolactam (127.2 mg, 1.0 mmol) was dissolved in THF (4.0 mL) and the temperature was lowered to 0 °C (ice/water bath). *n*-BuLi (1.6 M in hexanes, 0.94 mL, 1.5 mmol, 1.5 eq) was added dropwise by syringe and the reaction was allowed to stir at 0 °C. After 10 mins, a solution of 2-nitro-4-(trifluoromethyl) benzenesulfonyl chloride **5-24** (434.3 mg, 1.5 mmol, 1.5 eq) in THF (1.0 mL) was transferred to the stirring reaction mixture dropwise by syringe. The reaction was allowed to warm to room temperature overnight before the addition of sat. aq. $NaHCO_3$ solution (110 mL). The aqueous layer was extracted with EtOAc (2 × 10 mL), the combined organic layers were dried ($MgSO_4$). After filtration, the solvent was removed by rotary evaporation. Purification by flash column chromatography (SiO_2, 1:1 hexane: dichloromethane → 2:1 hexane: ethyl acetate) afforded the title compound as a pale-yellow oil (247 mg, 70%). R$_f$ = 0.65 (1:1 hexane: ethyl acetate); ν_{max}/cm^{-1} (neat) 2933, 2863, 1692, 1549, 1365, 1320, 1172, 1140, 1083, 840, 793, 719, 664, 733; δ_H (400 MHz, $CDCl_3$) 8.60 (d, *J* = 8.3 Hz, 1H, Ar-C**H**), 8.06 – 7.93 (m, 2H, Ar-C**H**), 4.18 – 3.97 (m, 2H, C**H**$_2$), 2.65 – 2.40 (m, 2H, C**H**$_2$), 1.94 – 1.80 (m, 4H, 2 × C**H**$_2$), 1.73 – 1.61 (m, 4H, 2 × C**H**$_2$); δ_C (101 MHz, $CDCl_3$) 175.4 (**CO**), 148.1 (Ar-**C**), 136.7 (Ar-**C**), 136.3 (Ar-**C**, d, $^2J_{CF}$ = 34.9 Hz), 136.1 (Ar-**C**H), 128.7 (Ar-**C**H, q, $^3J_{CF}$ = 3.5 Hz), 122.08 (**C**F$_3$, d, $^1J_{CF}$ = 273.7 Hz), 121.8 (Ar-**C**H, q, $^3J_{CF}$ = 3.7 Hz), 47.2 (**C**H$_2$), 36.0 (**C**H$_2$), 31.6 (**C**H$_2$), 28.5 (**C**H$_2$), 26.0 (**C**H$_2$), 24.2 (**C**H$_2$); δ_F (376 MHz, $CDCl_3$) - 63.3 (3F, s, C**F$_3$**); HRMS (ESI): calcd. for $C_{14}H_{15}F_3N_2NaO_5S$, 403.0546. Found: [MNa]$^+$, 403.0546 (0.1 ppm error).

12-(Trifluoromethyl)-3,4,5,6,7,8-hexahydro-2*H*-benzo[*k*][1]thia[2,10]diazacyclododecin-9(10*H*)-one 1,1-dioxide (5-22k)



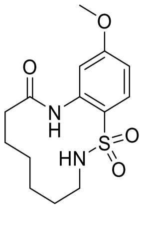
1-((2-Nitro-4-(trifluoromethyl)phenyl)sulfonyl)azocan-2-one **5-15k** (175.2 mg, 0.46 mmol) was dissolved in ethyl acetate (5.0 mL) and placed under an argon atmosphere. Palladium on carbon (50 mg, Pd 10% on carbon) was then added and the reaction vessel was evacuated and backfilled with hydrogen (via balloon) several times, then stirred at RT under a slight positive pressure of hydrogen (balloon) 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 dichloromethane (5.0 mL) and DBU (0.75 mL, 10 eq) added, and stirred at RT overnight, then reduced in vacuo. Purification by flash column chromatography (SiO_2, 20:1 dichloromethane: ethyl acetate → 9:1 ethyl acetate: methanol) afforded the title compound as a white solid (140 mg, 76%); m.p. 138 – 140 °C; $R_f = 0.65$ (9:1 dichloromethane: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3347, 2940, 1683, 1582, 1532, 1424, 1330, 1137, 1090, 705, 631; δ_H (400 MHz, $CDCl_3$) 9.45 (s, 1H, CON**H**Ph), 8.64 (s, 1H, Ar-C**H**), 8.03 (d, J = 8.3 Hz, 1H, Ar-C**H**), 7.43 (d, J = 8.2 Hz, 1H, Ar-C**H**), 4.84 (t, J = 6.3 Hz, 1H, SO_2N**H**), 3.19 (q, J = 6.6 Hz, 2H, C$\mathbf{H_2}$), 2.56 – 2.43 (m, 2H, C$\mathbf{H_2}$), 1.86 – 1.63 (m, 4H, 2 × C$\mathbf{H_2}$), 1.51 – 1.38 (m, 4H, 2 × C$\mathbf{H_2}$); δ_C (101 MHz, $CDCl_3$) 172.6 (**C**O), 137.0 (Ar-**C**), 135.90 (Ar-**C**, q, $^2J_{CF}$ = 33.1 Hz), 130.7 (Ar-**C**), 130.2 (Ar-**C**H), 123.04 (**C**F_3, q, $^1J_{CF}$ = 273.4 Hz), 121.0 (Ar-**C**H), 120.7 (Ar-**C**H), 39.8 (**C**H_2), 38.8 (**C**H_2), 27.2 (**C**H_2), 25.9 (**C**H_2), 23.8 (**C**H_2), 23.5 (**C**H_2); δ_F (376 MHz, $CDCl_3$) - 63.3 (3F, s, C$\mathbf{F_3}$); HRMS (ESI): calcd. for $C_{15}H_{22}N_2NaO_3S$, 333.1243. Found: $[MNa]^+$, 333.1245 (–0.4 ppm error).

1-((4-Methoxy-2-nitrophenyl)sulfonyl)azocan-2-one (5-15l)



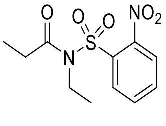
ω-Heptanolactam (127.2 mg, 1.0 mmol) was dissolved in THF (4.0 mL) and the temperature was lowered to 0 °C (ice/water bath). *n*-BuLi (1.6 M in hexanes, 0.94 mL, 1.5 mmol, 1.5 eq) was added dropwise by syringe and the reaction was allowed to stir at 0 °C. After 10 mins, a solution of 4-methoxy-2-nitrobenzenesulfonyl chloride **5-25** (377.5 mg, 1.5 mmol, 1.5 eq) in THF (1.0 mL) was transferred to the stirring reaction mixture dropwise by syringe. The reaction was allowed to warm to room temperature overnight before the addition of sat. aq. $NaHCO_3$ solution (10 mL). The aqueous layer was extracted with EtOAc (2 × 10 mL), the combined organic layers were dried ($MgSO_4$). After filtration, the solvent was removed by rotary evaporation. Purification by flash column chromatography (SiO_2, 1:1 hexane: dichloromethane → 1:1 hexane: ethyl acetate) afforded the title compound as a pale-yellow oil (280 mg, 80%); R_f= 0.42 (1:1 hexane: ethyl acetate); ν_{max}/cm^{-1} (neat) 2931, 2861, 1687, 1602, 1543, 1356, 1240, 1168, 1116, 1049, 803, 685, 560, 536; δ_H (400 MHz, $CDCl_3$) 8.35 (d, *J* = 8.8 Hz, 1H, Ar-C**H**), 7.19 – 7.13 (m, 2H, Ar-C**H**), 4.16 – 4.00 (m, 2H, C**H₂**), 3.91 (s, 3H, OC**H₃**), 2.64 – 2.42 (m, 2H, C**H₂**), 1.89 – 1.80 (m, 4H, 2 × C**H₂**), 1.69 – 1.56 (m, 4H, 2 × C**H₂**); δ_C (101 MHz, $CDCl_3$) 175.1 (**C**O), 163.9 (Ar-**C**), 149.5 (Ar-**C**), 137.1 (Ar-**C**H), 124.6 (Ar-**C**), 116.0 (Ar-**C**H), 110.5 (Ar-**C**H), 56.6 (O**C**H₃), 46.8 (**C**H₂), 36.2 (**C**H₂), 31.5 (**C**H₂), 28.6 (**C**H₂), 26.1 (**C**H₂), 24.1 (**C**H₂); HRMS (ESI): calcd. for $C_{14}H_{18}N_2NaO_6S$, 365.0778. Found: $[MNa]^+$, 365.0783 (–1.4 ppm error).

12-Methoxy-3,4,5,6,7,8-hexahydro-2*H*-benzo[*k*][1]thia[2,10]diazacyclododecin-9(10*H*)-one 1,1-dioxide (5-22l)



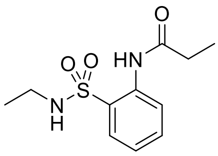
1-((4-Methoxy-2-nitrophenyl)sulfonyl)azocan-2-one (171.2 mg, 0.5 mmol) was dissolved in ethyl acetate (5.0 mL) and placed under an argon atmosphere. Palladium on carbon (50 mg, Pd 10% on carbon) was then added and the reaction vessel was evacuated and backfilled with hydrogen (via balloon) several times, then stirred at RT under a slight positive pressure of hydrogen (balloon) 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 dichloromethane (5.0 mL) and DBU (0.75 mL, 10 eq) added, and stirred at RT overnight, then reduced in vacuo. Purification by flash column chromatography (SiO_2, 9:1 dichloromethane: ethyl acetate → ethyl acetate) afforded the title compound as a white solid (112 mg, 77%); m.p. 95 – 97 °C; R_f = 0.26 (9:1 dichloromethane: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3346, 2936, 1679, 1602, 1577, 1416, 1283, 1127, 1060, 733, 679, 571, 525; δ_H (400 MHz, $CDCl_3$) 9.35 (s, 1H, CON**H**Ph), 7.88 (d, *J* = 2.0 Hz, 1H, Ar-C**H**), 7.76 (d, *J* = 8.9 Hz, 1H, Ar-C**H**), 6.64 (dd, *J* = 8.9, 2.4 Hz, 1H, Ar-C**H**), 4.78 (t, *J* = 6.0 Hz, 1H, SO_2N**H**), 3.82 (s, 3H, OC**H**$_3$), 3.12 (q, *J* = 6.4 Hz, 2H, C**H**$_2$), 2.47 – 2.36 (m, 2H, C**H**$_2$), 1.81 – 1.71 (m, 2H, C**H**$_2$), 1.69 – 1.60 (m, 2H, C**H**$_2$), 1.46 – 1.38 (m, 4H, 2 × C**H**$_2$); δ_C (101 MHz, $CDCl_3$) 172.5 (**C**O), 164.1 (Ar-**C**), 138.2 (Ar-**C**), 131.2 (Ar-**C**H), 119.0 (Ar-**C**), 110.4 (Ar-**C**H), 108.1 (Ar-**C**H), 55.8 (O**C**H$_3$), 39.7 (**C**H$_2$), 38.5 (**C**H$_2$), 27.1 (**C**H$_2$), 26.0 (**C**H$_2$), 24.0 (**C**H$_2$), 23.8 (**C**H$_2$); HRMS (ESI): calcd. for $C_{14}H_{20}N_2NaO_4S$, 335.1036. Found: $[MNa]^+$, 335.1043 (–2.2 ppm error).

***N*-ethyl-*N*-((2-nitrophenyl)sulfonyl)propionamide (5-15m)**



N-ethylpropionamide **5-26** (202.3 mg, 2.0 mmol) was dissolved in THF (8.0 mL) and the temperature was lowered to –78 °C (dry ice/acetone bath). *n*-BuLi (1.6 M in hexanes, 1.88 mL, 3.0 mmol, 1.5 eq) was added dropwise by syringe and the reaction was allowed to stir at -78 °C. After 1 hour, a solution of 2-nitrobenzenesulfonyl chloride (665 mg, 3.0 mmol, 1.5 eq) in THF (2.0 mL) was transferred to the stirring reaction mixture dropwise by syringe. The reaction was allowed to warm to room temperature overnight before the addition of sat. aq. $NaHCO_3$ solution (15 mL). The aqueous layer was extracted with EtOAc (2 × 15 mL), the combined organic layers were dried ($MgSO_4$). After filtration, the solvent was removed by rotary evaporation. Purification by flash column chromatography (SiO_2, 2:3 hexane: dichloromethane → dichloromethane) afforded the title compound as a pale-yellow oil (275 mg, 48%); R_f = 0.12 (1:1 hexane: dichloromethane); ν_{max}/cm^{-1} (neat) 2984, 1704, 1539, 1356, 1173, 1102, 851, 742, 554; δ_H (400 MHz, $CDCl_3$) 8.39 – 8.33 (m, 1H, Ar-C**H**), 7.80 – 7.70 (m, 3H, Ar-C**H**), 3.87 (q, *J* = 7.1 Hz, 2H, C**H**$_2$CH$_3$), 2.55 (q, *J* = 7.2 Hz, 2H, C**H**$_2$CH$_3$), 1.37 (t, *J* = 7.1 Hz, 3H, CH$_2$C**H**$_3$), 1.09 (t, *J* = 7.2 Hz, 3H, CH$_2$C**H**$_3$); δ_C (101 MHz, $CDCl_3$) 173.7 (**C**O), 147.9 (Ar-**C**), 134.6 (Ar-**C**H), 134.1 (Ar-**C**H), 133.4 (Ar-**C**), 132.1 (Ar-**C**H), 124.5 (Ar-**C**H), 42.6 (**C**H$_2$CH$_3$), 29.0 (**C**H$_2$CH$_3$), 16.2 (CH$_2$**C**H$_3$), 8.4 (CH$_2$**C**H$_3$); HRMS (ESI): calcd. for $C_{11}H_{14}N_2NaO_5S$, 309.0516. Found: [MNa]$^+$, 309.0513 (0.7 ppm error).

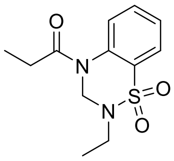
***N*-(2-(*N*-Ethylsulfamoyl)phenyl)propionamide (5-22m)**



N-ethyl-*N*-((2-nitrophenyl)sulfonyl)propionamide **5-15m** (171.8 mg, 0.6 mmol) was dissolved in ethyl acetate (6.0 mL) and placed under an argon atmosphere. Palladium on carbon (60 mg, Pd 10% on carbon) was then added and the reaction vessel was evacuated and backfilled with hydrogen (via balloon) several times, then stirred at RT under a slight positive pressure of hydrogen (balloon) 2 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 dichloromethane (6.0 mL) and DBU (0.90 mL, 10 eq) added, and stirred at RT overnight, then reduced in vacuo. Purification by flash column chromatography (SiO_2, dichloromethane → 20:1 dichloromethane: ethyl acetate) afforded the title compound as a colorless oil (95 mg, 62%); R_f = 0.31 (9:1 dichloromethane: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3346, 2979, 1681, 1585, 1525, 1435, 1317, 1287, 1150, 949, 760, 587, 570; δ_H (400 MHz, $CDCl_3$)

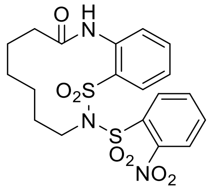
9.39 (s, 1H, CON**H**Ph), 8.39 (d, *J* = 8.3 Hz, 1H, Ar-C**H**), 7.78 (dd, *J* = 8.0, 1.5 Hz, 1H, Ar-C**H**), 7.55 – 7.45 (m, 1H, Ar-C**H**), 7.18 – 7.06 (m, 1H, Ar-C**H**), 5.35 (t, *J* = 5.9 Hz, 1H, SO_2N**H**), 2.91 (p, *J* = 7.2 Hz, 2H, C**H₂**CH₃), 2.40 (q, *J* = 7.6 Hz, 2H, C**H₂**CH₃), 1.19 (t, *J* = 7.6 Hz, 3H, CH₂C**H₃**), 1.03 (t, *J* = 7.2 Hz, 3H, CH₂C**H₃**); δ_C (101 MHz, $CDCl_3$) 172.8 (**C**O), 136.3 (Ar-**C**), 134.0 (Ar-**C**H), 129.1 (Ar-**C**H), 126.9 (Ar-**C**), 123.7 (Ar-**C**H), 122.9 (Ar-**C**H), 38.2 (**C**H₂CH₃), 31.2 (**C**H₂CH₃), 14.9 (CH₂**C**H₃), 9.4 (CH₂**C**H₃); HRMS (ESI): calcd. for $C_{11}H_{16}N_2NaO_3S$, 279.0774. Found: $[MNa]^+$, 279.0771 (1.1 ppm error).

1-(2-Ethyl-1,1-dioxido-2,3-dihydro-4*H*-benzo[*e*][1,2,4]thiadiazin-4-yl)propan-1-one (5-23m)



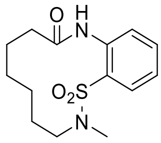
Same procedure to get compound **(5-22m)** as a colorless oil (42 mg, 26%); R_f = 0.70 (9:1 dichloromethane: ethyl acetate); ν_{max}/cm^{-1} (thin film) 2979, 2939, 1679, 1477, 1331, 1178, 1158, 1135, 757, 707, 572; δ_H (400 MHz, $CDCl_3$-*d*) 7.83 (dd, *J* = 7.9, 1.6 Hz, 1H, Ph-C**H**), 7.56 – 7.46 (m, 1H, Ph-C**H**), 7.40 (d, *J* = 8.3 Hz, 1H, Ph-C**H**), 7.36 – 7.30 (m, 1H, Ph-C**H**), 5.44 (s, 2H, NC**H₂**N), 3.16 (q, *J* = 7.2 Hz, 2H, C**H₂**CH₃), 2.61 (q, *J* = 7.4 Hz, 2H, C**H₂**CH₃), 1.25 (t, *J* = 7.2 Hz, 3H, CH₂C**H₃**), 1.21 (t, *J* = 7.4 Hz, 3H, CH₂C**H₃**); δ_C (101 MHz, $CDCl_3$-*d*) 174.3 (**C**O), 136.2 (Ph-**C**), 132.5 (Ph-**C**H), 129.3 (Ph-**C**), 126.2 (Ph-**C**H), 125.9 (Ph-**C**H), 124.4 (Ph-**C**H), 59.5 (N**C**H₂N), 41.9 (**C**H₂CH₃), 28.1 (**C**H₂CH₃), 13.7 (CH₂**C**H₃), 10.2 (CH₂**C**H₃); HRMS (ESI): calcd. for $C_{12}H_{16}N_2NaO_3S$, 291.0774. Found: $[MNa]^+$, 291.0773 (0.3 ppm error).

2-((2-Nitrophenyl)sulfonyl)-3,4,5,6,7,8-hexahydro-2*H*-benzo[*k*][1]thia[2,10]diazacyclododecin-9(10*H*)-one 1,1-dioxide (5-27)



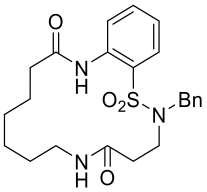
3,4,5,6,7,8-Hexahydro-2*H*-benzo[*k*][1]thia[2,10]diazacyclododecin-9(10*H*)-one 1,1-dioxide **5-22** (282.4 mg, 1.0 mmol) was dissolved in THF (4 mL) and the temperature was lowered to –78 °C (dry ice/acetone bath). *n*-BuLi (1.6 M in hexanes, 0.94 mL, 1.5 mmol, 1.5 eq) was added dropwise by syringe and the reaction was allowed to stir at –78 °C. After 1 hour, a solution of 2-nitrobenzenesulfonyl chloride (0.33 g, 1.5 mmol, 1.5 eq) in THF (1.0 mL) was transferred to the stirring reaction mixture dropwise by syringe. The reaction was allowed to warm to room temperature overnight before the addition of sat. aq. $NaHCO_3$ solution (10 mL). The aqueous layer was extracted with EtOAc (2 × 10 mL), the combined organic layers were dried ($MgSO_4$). After filtration, the solvent was removed by rotary evaporation. Purification by flash column chromatography (SiO_2, 1:2 hexane: dichloromethane → dichloromethane) afforded the title compound as a colorless solid (253 mg, 54%); $R_f = 0.30$ (dichloromethane); δ_H (400 MHz, $CDCl_3$) 9.70 (s, 1H, CON**H**), 8.54 – 8.35 (m, 2H, Ar-C**H**), 7.94 – 7.81 (m, 2H, Ar-C**H**), 7.79 – 7.70 (m, 1H, Ar-C**H**), 7.61 – 7.50 (m, 1H, Ar-C**H**), 6.97 – 6.89 (m, 2H, Ar-C**H**), 3.64 – 3.41 (m, 2H, C**H2**), 2.55 (s, 2H, C**H2**), 2.23 – 2.08 (m, 2H, C**H2**), 1.82 (s, 2H, C**H2**), 1.63 – 1.32 (m, 4H, 2 × C**H2**); δ_C (101 MHz, $CDCl_3$) 171.7 (**C**O), 148.0 (Ar-**C**), 137.8 (Ar-**C**H), 136.0 (Ar-**C**H), 135.3 (Ar-**C**H), 134.2 (Ar-**C**H), 132.4 (Ar-**C**), 132.2 (Ar-**C**H), 129.6 (Ar-**C**H), 124.6 (Ar-**C**H), 124.1 (Ar-**C**), 123.9 (Ar-**C**H), 123.5 (Ar-**C**H), 46.0 (**C**H2), 38.4 (**C**H2), 25.5 (**C**H2), 22.9 (2 × **C**H2), 21.6 (**C**H2); HRMS (ESI): calcd. for $C_{19}H_{21}N_3NaO_7S_2$, 490.0713. Found: $[MNa]^+$, 490.0719 (–1.2 ppm error).

2-Methyl-3,4,5,6,7,8-hexahydro-2*H*-benzo[*k*][1]thia[2,10]diazacyclododecin-9(10*H*)-one 1,1-dioxide (5-29)



3,4,5,6,7,8-Hexahydro-2*H*-benzo[*k*][1]thia[2,10]diazacyclododecin-9(10*H*)-one 1,1-dioxide **5-22** (282.4 mg, 1.0 mmol) was added to a solution of sodium (1.0 mmol) in methyl alcohol (2.5 mL) with stirring. After dissolving, the iodomethane (156.1 mg, 1.1 mmol) was added with stirring, and the resulting solution was kept for 24 h at room temperature. The solvent was removed by rotary evaporation. Purification by flash column chromatography (SiO_2, 3: 2 hexane: ethyl acetate) afforded the title compound as a white solid (280 mg, 94%). M.p. 92 – 94 °C; R_f= 0.35 (1: 1 hexane: ethyl acetate); ν_{max}/cm^{-1} (neat) 3364, 2931, 2862, 1697, 1517, 1307, 1288, 1148, 938, 750, 596; δ_H (400 MHz, $CDCl_3$-*d*) 9.17 (s, 1H, N**H**), 8.24 (d, *J* = 8.3 Hz, 1H, Ar-C**H**), 7.91 (dd, *J* = 8.0, 1.5 Hz, 1H, Ar-C**H**), 7.62 – 7.51 (m, 1H, Ar-C**H**), 7.23 – 7.14 (m, 1H, Ar-C**H**), 3.33 (t, *J* = 6.0 Hz, 2H, C**H₂**), 2.44 (s, 3H, NC**H₃**), 2.43 – 2.33 (m, 2H, C**H₂**), 1.83 – 1.65 (m, 2H, C**H₂**), 1.63 – 1.51 (m, 2H, C**H₂**), 1.50 – 1.32 (m, 4H, 2 × C**H₂**); δ_C (101 MHz, $CDCl_3$-*d*) 172.3 (**C**O), 136.1 (Ar-**C**), 134.5 (Ar-**C**H), 131.0 (Ar-**C**H), 125.3 (Ar-**C**), 124.2 (Ar-**C**H), 123.6 (Ar-**C**H), 46.0 (**C**H₂), 38.8 (**C**H₂), 34.2 (N**C**H₃), 27.6 (**C**H₂), 25.1 (**C**H₂), 24.8 (**C**H₂), 24.3 (**C**H₂); HRMS (ESI): calcd. for $C_{14}H_{20}N_2NaO_3S$, 319.1087. Found: [MNa]$^+$, 319.1085 (0.6 ppm error).

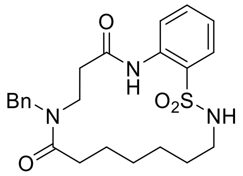
2-Benzyl-3,4,7,8,9,10,11,12-octahydro-2*H*- benzo [*o*][1]thia[2,6,14]triazacyclohexadecine-5,13(6*H*,14*H*)-dione 1,1-dioxide (5-32)



A mixture of 12-membered macrocycle **5-22** (282.4 mg, 1.0 mmol), DMAP (12.2 mg, 0.1 mmol) and pyridine (0.475 mL, 6.0 mmol) in DCM (5 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride **2-12** (1.5

mmol, 1.50 equiv., freshly prepared from Fomc-β-gly using the general procedure) in DCM (5 mL) was added and the resulting mixture was refluxed at 50 °C for 16 h. The mixture was then diluted with DCM (30 mL) and washed with 10% aq. HCl (30 mL). The aqueous layer was then extracted with DCM (3 × 30 mL) and the combined organic extracts dried over MgSO4 and concentrated *in vacuo*. The crude material **73a** (150 mg, 0.225 mmol) was then re-dissolved in DCM (2.5 mL) and NEt$_3$ (1.2 mL) was added, followed by stirring at RT overnight, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO2, 1:1 ethyl acetate: hexane → ethyl acetate) afforded the *title compound* as a yellow oil (20 mg, 20%); R$_f$ = 0.22 (ethyl acetate); δ$_H$ (400 MHz, CDCl$_3$-*d*) 9.88 (s, 1H, CON**H**Ph), 8.44 (d, *J* = 8.4 Hz, 1H, Ar-C**H**), 7.75 (dd, *J* = 8.2, 1.5 Hz, 1H, Ar-C**H**), 7.62 – 7.50 (m, 1H, Ar-C**H**), 7.39 – 7.20 (m, 6H, Ar-C**H**), 7.19 – 7.08 (m, 1H, CON**H**), 4.08 – 4.02 (m, 2H, C**H**$_2$), 3.86 (s, 2H, NC**H**$_2$Ph), 3.05 (t, *J* = 6.3 Hz, 2H, C**H**$_2$), 2.71 (t, *J* = 6.3 Hz, 2H, C**H**$_2$), 2.54 – 2.30 (m, 2H, C**H**$_2$), 1.92 – 1.80 (m, 2H, C**H**$_2$), 1.81 – 1.69 (m, 2H, C**H**$_2$), 1.66 – 1.44 (m, 4H, 2 × C**H**$_2$); δ$_C$ (101 MHz, CDCl$_3$-*d*) 176.5 (**C**O), 170.9 (**C**O), 139.7 (Ar-**C**), 138.6 (Ar-**C**), 134.9 (Ar-**C**H), 129.8 (Ar-**C**H), 128.5 (2 × Ar-**C**H), 128.4 (2 × Ar-**C**H), 127.2 (Ar-**C**H), 126.5 (Ar-**C**), 123.5 (Ar-**C**H), 123.3 (Ar-**C**H), 53.7 (N**C**H$_2$Ph), 46.6 (**C**H$_2$), 44.8 (**C**H$_2$), 37.9 (**C**H$_2$), 36.3 (**C**H$_2$), 31.2 (**C**H$_2$), 28.4 (**C**H$_2$), 26.1 (**C**H$_2$), 23.8 (**C**H$_2$); HRMS (ESI): calcd. for C$_{23}$H$_{30}$N$_3$O$_4$S, 444.1952. Found: [MH]$^+$, 444.1962 (–2.4 ppm error).

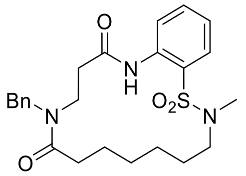
10-Benzyl-3,4,5,6,7,8,11,12-octahydro-2*H*-benzo[*o*][1]thia[2,10,14]triazacyclohexadecine-9,13(10*H*,14*H*)-dione 1,1-dioxide (5-34)



A mixture of 12-membered lactam **5-22** (282.4 mg, 1.0 mmol), DMAP (12.2 mg, 0.1 mmol) and pyridine (0.475 mL, 6.0 mmol) in DCM (5 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride **2-12** (3.0 mmol, 3.0

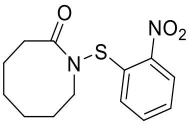
equiv., freshly prepared from Fomc-β-gly using the general procedure) in DCM (5 mL) was added and the resulting mixture was refluxed at 50 °C for 16 h. The mixture was then diluted with DCM (30 mL) and washed with 10% aq. HCl (30 mL). The aqueous layer was then extracted with DCM (3 × 30 mL) and the combined organic extracts dried over MgSO4 and concentrated *in vacuo*. The crude material **73b** (316 mg, 27%) was then re-dissolved in DCM (3.0 mL) and DBU (0.3 mL) was added, followed by stirring at RT overnight, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO2, 1:1 ethyl acetate: hexane → 9: 1 ethyl acetate: methanal) afforded the *title compound* (as a 5:1 mixture of rotamers) as a yellow oil (85 mg, 64%); R_f = 0.32 (9: 1 ethyl acetate: methanal); δ_H (400 MHz, $CDCl_3$-*d*) 9.57 (s, 1H, CON**H**Ph, major rotamer), 9.33 (s, 1H, CON**H**Ph, minor rotamer), 8.36 (dd, *J* = 8.4, 1.2 Hz, 1H, Ar-C**H**, major rotamer), 8.32 (dd, *J* = 8.3, 1.1 Hz, 1H, Ar-C**H**, minor rotamer), 7.92 – 7.90 (m, 1H, Ar-C**H**, minor rotamer), 7.88 (dd, *J* = 7.9, 1.6 Hz, 1H, Ar-C**H**, major rotamer), 7.54 (m, 1H, Ar-C**H**, both rotamers), 7.40 – 7.29 (m, 3H, Ar-C**H**, both rotamers), 7.23 – 7.14 (m, 3H, Ar-C**H**, both rotamers), 6.90 (t, *J* = 5.2 Hz, 1H, SO_2N**H**, major rotamer), 5.31 (t, *J* = 5.2 Hz, 1H, SO_2N**H**, minor rotamer), 4.80 (s, 2H, NC$\mathbf{H_2}$Ph, minor rotamer), 4.67 (s, 2H, NC$\mathbf{H_2}$Ph, major rotamer), 3.98 – 3.69 (m, 2H, C$\mathbf{H_2}$, both rotamers), 2.98 (q, *J* = 5.0Hz, 2H, C$\mathbf{H_2}$, both rotamers), 2.76 (t, *J* = 6.2 Hz, 2H, C$\mathbf{H_2}$, major rotamer), 2.68 – 2.60 (m, 2H, C$\mathbf{H_2}$, minor rotamer), 2.51 – 2.41 (m, 2H, C$\mathbf{H_2}$, minor rotamer), 2.44 – 2.31 (m, 2H, C$\mathbf{H_2}$, major rotamer), 1.64 – 1.53 (m, 2H, C$\mathbf{H_2}$, both rotamers), 1.52 – 1.44 (m, 4H, C$\mathbf{H_2}$, both rotamers), 1.20 – 1.02 (m, 4H, 2 × C$\mathbf{H_2}$, both rotamers); δ_C (101 MHz, $CDCl_3$-*d*) 174.9 (**C**O), 169.6 (**C**O), 136.2 (Ar-**C**), 135.5 (Ar-**C**), 133.7 (Ar-**C**H), 129.6 (Ar-**C**H), 129.2 (2 × Ar-**C**H), 127.9 (Ar-**C**H), 127.3 (Ar-**C**), 126.4 (2 ×Ar-**C**H), 123.6 (Ar-**C**H), 122.8 (Ar-**C**H), 50.4 (N**C**H_2Ph), 43.3 (**C**H_2), 41.0 (**C**H_2), 37.0 (**C**H_2), 32.4 (**C**H_2), 27.3 (**C**H_2), 25.7 (**C**H_2), 25.3 (**C**H_2), 22.1 (**C**H_2); Diagnostic ^{13}C NMR resonances for the minor rotamer: 174.7 (**C**O), 169.2 (**C**O), 134.0 (Ar-**C**H), 128.9 (Ar-**C**H), 128.1 (Ar-**C**H), 127.8 (Ar-**C**H), 42.5 (**C**H_2), 31.1 (**C**H_2), 27.5 (**C**H_2), 20.4 (**C**H_2); HRMS (ESI): calcd. for $C_{23}H_{29}N_3O_4S$, 466.1771. Found: $[MNa]^+$, 466.1775 (–0.9 ppm error).

10-Benzyl-2-methyl-3,4,5,6,7,8,11,12-octahydro-2*H*-benzo[*o*][1]thia[2,10,14]triazacyclohexadecine-9,13(10*H*,14*H*)-dione 1,1-dioxide (5-36)



A mixture of 12-membered lactam **5-29** (148.2 mg, 0.5 mmol), DMAP (6.1 mg, 0.05 mmol) and pyridine (0.243 mL, 3.0 mmol) in DCM (2.5 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride **2-12** (1.5 mmol, 3.0 equiv., freshly prepared from Fomc-β-gly using the general procedure) in DCM (2.5 mL) was added and the resulting mixture was refluxed at 50 °C for 16 h. The mixture was then diluted with DCM (10 mL) and washed with 10% aq. HCl (10 mL). The aqueous layer was then extracted with DCM (3 × 10 mL) and the combined organic extracts dried over MgSO4 and concentrated *in vacuo*. The crude material (158 mg, 23%) was then re-dissolved in DCM (3.0 mL) and DBU (0.3 mL, 10 eq) was added, followed by stirring at RT overnight, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO2, 1:1 ethyl acetate: hexane) afforded the *title compound* (as a mixture of 5:1 rotamers) as a colorless oil (39 mg, 74%, 17% over 2 steps); $R_f = 0.24$ (1: 1 hexane: ethyl acetate); δ_H (400 MHz, $CDCl_3$-*d*) 9.68 (s, 1H, CON**H**Ph, major rotamer), 9.62 (s, 1H, , CON**H**Ph, minor rotamer), 8.52 (d, *J* = 8.3 Hz, 1H, Ar-C**H**, major rotamer), 8.47 (d, *J* = 8.4 Hz, 1H, Ar-C**H**, minor rotamer), 7.82 (dd, *J* = 8.0, 1.4 Hz, 1H, Ar-C**H**, minor rotamer), 7.75 (dd, *J* = 8.0, 1.5 Hz, 1H, Ar-C**H**, major rotamer), 7.61 – 7.51 (m, 1H, Ar-C**H**, both rotamers), 7.38 – 7.26 (m, 3H, Ar-C**H**, both rotamers), 7.23 – 7.12 (m, 3H, Ar-C**H**, both rotamers), 4.76 (s, 2H, NC**H**$_2$Ph, major rotamer), 4.68 (s, 2H, NC**H**$_2$Ph, minor rotamer), 3.76 – 3.58 (m, 2H, C**H**$_2$, both rotamers), 3.12 – 2.84 (m, 4H, 2 × C**H**$_2$, both rotamers), 2.79 (s, 3H, NC**H**$_3$, minor rotamer), 2.73 (s, 3H, NC**H**$_3$, major rotamer), 2.43 (t, *J* = 6.8 Hz, 2H, C**H**$_2$, minor rotamer), 2.40 – 2.35 (m, 2H, 2H, C**H**$_2$, major rotamer), 1.82 – 1.43 (m, 4H, 2 × C**H**$_2$, both rotamers), 1.40 – 1.25 (m, 4H, 2 × C**H**$_2$, both rotamers); δ_C (101 MHz, $CDCl_3$-*d*) for major rotamer only: 174.0 (**C**O), 170.4 (**C**O), 137.7 (Ar-**C**), 136.6 (Ar-**C**), 134.2 (Ar-**C**H), 129.9 (Ar-**C**H), 129.0 (Ar-**C**H), 127.6 (Ar-**C**H), 126.5 (Ar-**C**H), 124.1 (Ar-**C**), 123.7 (Ar-**C**H), 122.4 (Ar-**C**H), 54.0 (N**C**H$_2$Ph), 48.5 (**C**H$_2$), 43.0 (**C**H$_2$), 36.9 (**C**H$_2$), 34.7 (**C**H$_2$), 32.6 (**C**H$_2$), 26.6 (**C**H$_2$), 26.4 (**C**H$_2$), 25.5 (**C**H$_2$), 25.2 (**C**H$_2$); Diagnostic ^{13}C NMR resonances for the minor rotamer: 173.6 (**C**O), 168.6 (**C**O), 134.5 (Ar-**C**H), 128.8 (Ar-**C**H), 128.3 (Ar-**C**H), 49.2 (**C**H$_2$), 48.9 (**C**H$_2$), 42.6 (**C**H$_2$), 35.5 (**C**H$_2$), 27.9 (**C**H$_2$), 26.9 (**C**H$_2$), 24.9 (**C**H$_2$); HRMS (ESI): calcd. for $C_{24}H_{31}N_3O_4S$, 480.1927. Found: [MNa]$^+$, 480.1930 (–0.5 ppm error).

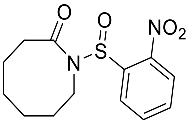
1-((2-Nitrophenyl)thio)azocan-2-one (5-39)



Azocan-2-one **5-12** (636 mg, 5.0 mmol) was dissolved in THF (20 mL) and the temperature was lowered to –78 °C (dry ice/acetone bath). *n*-BuLi (1.6 M in hexanes, 4.7 mL, 7.5 mmol, 1.5 eq) was added dropwise by syringe and the reaction was allowed to stir at –78 °C. After 1 hour, a solution of 2-nitrobenzenesulfenyl chloride **5-38** (1.42 g, 7.5 mmol, 1.5 eq) in THF (5.0 mL) was transferred to the stirring reaction mixture dropwise by syringe. The reaction was allowed to warm to room temperature overnight before the addition of saturated $NaHCO_3$ solution (30 mL). The aqueous layer was extracted with EtOAc (2 × 30 mL), the combined organic layers were dried ($MgSO_4$). After filtration, the solvent was removed by rotary evaporation. Purification by flash column chromatography (SiO_2, 1:1 hexane: ethyl acetate) afforded the title compound as a yellow solid (1335 mg, 95%). R_f = 0.13 (1:1 hexane: ethyl acetate); δ_H (400 MHz, $CDCl_3$-*d*) 8.20 (dd, *J* = 8.3, 1.3 Hz, 1H, Ph-C**H**), 7.56 (ddd, *J* = 8.4, 7.3, 1.4 Hz, 1H, Ph-C**H**), 7.26 – 7.16 (m, 2H, Ph-C**H**), 3.89 – 3.47 (m, 2H, C**H$_2$**), 2.92 – 2.49 (m, 2H, C**H$_2$**), 1.98 – 1.61 (m, 4H, 2 × C**H$_2$**), 1.61 – 1.42 (m, 4H, 2 × C**H$_2$**); δ_C (101 MHz, $CDCl_3$-*d*) 177.3 (**C**O), 142.4 (Ph-**C**), 139.5 (Ph-**C**), 134.4 (Ph-**C**H), 125.7 (Ph-**C**H), 125.2 (Ph-**C**H), 123.3 (Ph-**C**H), 52.2 (**C**H$_2$), 33.8 (**C**H$_2$), 29.3 (**C**H$_2$), 28.5 (**C**H$_2$), 25.6

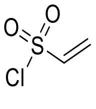
(**C**H$_2$), 23.9 (**C**H$_2$); HRMS (ESI): calcd. for $C_{13}H_{16}N_2NaO_3S$, 303.0774. Found: [MNa]$^+$, 303.0769 (1.7 ppm error).

1-((2-Nitrophenyl)sulfinyl)azocan-2-one (5-42)



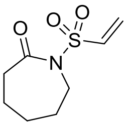
1-((2-Nitrophenyl)thio)azocan-2-one **5-39** (140.2 mg, 0.5 mmol) was dissolved in DCM (7 mL), then 3-chloroperbenzoic acid (mCPBA, 95 mg, 1.1 eq) added. The mixture was stirred at RT for 2 h. The resulting mixture was washed with sat. NaHCO$_3$ and then brine, the organic layer was dried over MgSO$_4$ and filtered to give the product as a pale-yellow solid (147 mg, 99%). R$_f$ = 0.13 (1:1 hexane: ethyl acetate); δ_H (400 MHz, CDCl$_3$-*d*) 8.37 (dd, *J* = 7.9, 1.3 Hz, 1H, Ph-C**H**), 8.29 (dd, *J* = 8.1, 1.1 Hz, 1H, Ph-C**H**), 7.96 (td, *J* = 7.6, 1.0 Hz, 1H, Ph-C**H**), 7.80 – 7.75 (m, 1H, Ph-C**H**), 3.66 (ddd, *J* = 16.4, 6.9, 4.0 Hz, 1H, C**H**$_2$), 3.31 (ddd, *J* = 16.4, 9.0, 3.5 Hz, 1H, C**H**$_2$), 2.63 (ddd, *J* = 13.0, 9.6, 4.6 Hz, 1H, C**H**$_2$), 2.47 (ddd, *J* = 12.5, 7.6, 4.1 Hz, 1H, aC**H**$_2$), 1.90 – 1.70 (m, 2H, C**H$_2$**), 1.68 – 1.25 (m, 5H, 2 × C**H$_2$** + C**H**$_2$), 0.75 (ddp, *J* = 12.9, 8.7, 4.0, 3.9 Hz, 1H, C**H**$_2$); δ_C (101 MHz, CDCl$_3$-*d*) 176.7 (**C**O), 145.6 (Ph-**C**), 140.5 (Ph-**C**), 135.0 (Ph-**C**H), 132.7 (Ph-**C**H), 128.6 (Ph-**C**H), 125.5 (Ph-**C**H), 43.0 (**C**H$_2$), 34.1 (**C**H$_2$), 31.7 (**C**H$_2$), 28.0 (**C**H$_2$), 25.8 (**C**H$_2$), 24.3 (**C**H$_2$); HRMS (ESI): calcd. for $C_{13}H_{16}N_2NaO_4S$, 319.0723. Found: [MNa]$^+$, 319.0726 (–1.0 ppm error).

Ethenesulfonyl chloride (5-50)



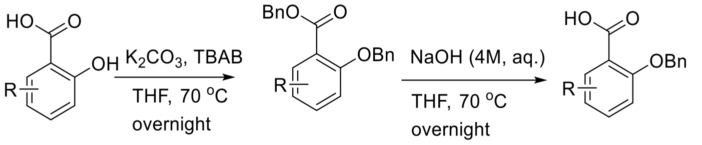
To a stirring solution of 2-chloroethane sulfonyl chloride (1.90 mL, 18.2 mmol) in anhydrous Et$_2$O (12.0 mL) cooled to –60 °C, a solution of 2,4,6-trimethyl-pyridine (2.89 mL, 21.8 mmol) in anhydrous Et$_2$O (5.0 mL) was added dropwise over a period of 30 min via syringe pump. The reaction mixture was stirred at –60 °C under argon for 45 min after the addition was completed and then allowed to warm to RT. The resulting milky white suspension was stirred for an additional 45 min at RT before it was quenched with 1% H_2SO_4 (aq.) (30 mL). The diluted reaction mixture was poured into a separating funnel containing EtOAc (30 mL), and the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* (water bath set 0 °C and pressure to 30 mmHg) to yield crude product as a yellow liquid (2.71 g). The crude product was purified by *vacuo* distillation [17 mmHg] (using a short water condenser) at 60−70 °C affording the title *compound* as a colourless liquid (1.64 g, 70%). δ_H (400 MHz, $CDCl_3$) 7.01 (dd, J = 16.2, 9.4 Hz, 1H, $SO_2C\mathbf{H}CH_2$), 6.53 (dd, J = 16.2, 1.7 Hz, 1H, $SO_2CHC\mathbf{H}H'$), 6.25 (dd, J = 9.4, 1.7 Hz, 1H, $SO_2CHCH\mathbf{H'}$); δ_C (101 MHz, $CDCl_3$) 140.7 ($SO_2\mathbf{C}HCH_2$), 130.11 ($SO_2CH\mathbf{C}H_2$). Spectroscopic data are in agreement with those reported in the literature.[188]

1-(Vinylsulfonyl)azepan-2-one (5-51)



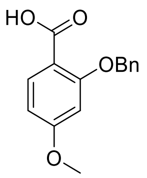
To a stirring solution of caprolactam (269 mg, 2.38 mmol) in anhydrous THF (16.0 mL) cooled to –86 °C, LiHMDS (1.0 M in THF, 3.57 mL, 3.57 mmol) was added dropwise over 30 min, with a colour change to pale yellow noted. The reaction mixture was allowed to stir for 1 hour at –86 °C after the addition was completed. Ethenesulfonyl chloride **5-50** (0.240 mL, 3.00 mmol) as a solution in anhydrous THF (2.0 mL) was added dropwise over a period of 30 min and the reaction mixture was stirred for an additional 1 hour at –78 °C. The reaction was allowed to warm to RT and then stirred for additional 18 hours. After a total of 24 hours, the reaction was deemed to have gone to completion by TLC. The reaction mixture was quenched by the addition of sat. $NH_4Cl_{(aq)}$ (30 mL) and transferred into a separating funnel. The aqueous was extracted with EtOAc (3 × 10 mL), combined with organic layers dried over $MgSO_4$, filtered and concentrated *in vacuo*, to yield crude yield a crude product as an orange oil (701 mg). The crude product was purified by flash column chromatography (SiO_2, 8:2 ethyl acetate: hexane) afforded the *title compound* as a colourless oil (122 mg, 25%). R_f = 0.53 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 2928, 2855, 1651, 1405, 1339, 1197, 1144, 1064, 957, 750, 729, 669, 539; δ_H (400 MHz, CDCl$_3$-*d*) 6.93 (ddd, *J* = 16.7, 9.9, 0.5 Hz, 1H, SO$_2$C**H**CH$_2$), 6.35 (dt, *J* = 16.7, 0.6 Hz, 1H, SO$_2$CHC**H**H'), 6.02 (dt, *J* = 9.7, 0.8 Hz, 1H, SO$_2$CHCH**H'**), 3.87 – 3.80 (m, 2H, C**H$_2$**), 2.64 – 2.52 (m, 2H, C**H$_2$**), 1.75 – 1.67 (m, 6H, 3 × C**H$_2$**); δ_C (101 MHz, CDCl$_3$-*d*) 175.9 (**C**O), 136.4 (SO$_2$**C**HCH$_2$), 128.9 (SO$_2$CH**C**H$_2$), 46.0 (**C**H$_2$), 38.6 (**C**H$_2$), 29.3 (**C**H$_2$), 29.1 (**C**H$_2$), 22.9 (**C**H$_2$); HRMS (ESI): calcd. for $C_8H_{13}NNaO_3S$, 226.0508. Found: [MNa]$^+$, 226.0511 (–1.1 ppm error).

General procedure for OBn-protected carboxylic acids formation:



A mixture of the respective hydroxybenzoic acid (5.0 mmol), anhydrous K_2CO_3 (5.0 mmol), TBAB (10 mol %) and benzyl bromide (10 mmol), in anhydrous THF (25 mL) was stirred at reflux until TLC analysis showed the consumption of the starting materials. The reaction mixture was filtered to remove the solid. Then NaOH (4 M, aq., 5.0 mL, 20.0 mmol) was added to the filtrate and the resulting mixture was heated to reflux. After completion of reaction, the THF was evaporated. Then the crude material was diluted with H_2O (30 mL) and washed with DCM (30 mL). The PH of the aqueous layer was lowered to pH = 2 with 1 M HCl (aq.) and was subsequently extracted three times with DCM (20 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*, purification by flash column chromatography (SiO_2, ethyl acetate) afforded the target compound.[214,215]

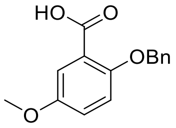
2-(Benzyloxy)-4-methoxybenzoic acid (S1)



A mixture of the 4-methoxysalicyclic acid (841 mg, 5.0 mmol, 1 equiv), anhydrous

K_2CO_3 (691 mg, 5.0 mmol, 1 equiv), TBAB (161.2 mg, 10 mol %) and benzyl bromide (1710 mg, 10.0 mmol, 2 equiv), in anhydrous THF (25 mL) was stirred at ambient temperature until TLC analysis showed the disappearance of the starting materials. The reaction mixture was filtered to remove the solid. NaOH (4 M, aq., 5.0 mL, 20.0 mmol) was added to the filtrate and the resulting mixture was heated to reflux. After completion of reaction, the THF was evaporated. Then the crude material was diluted with H_2O (30 mL) and washed with DCM (30 mL). The pH of the aqueous layer was lowered to pH = 2 with 1 M HCl (aq.) and was subsequently extracted three times with DCM (20 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*, purification by flash column chromatography (SiO_2, ethyl acetate) afforded the *title compound* as a white solid (1060 mg, 82%). m.p. 73 – 75 °C; R_f = 0.62 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3283, 2941, 1726, 1680, 1606, 1442, 1391, 1256, 1166, 1035, 835, 733, 696; δ_H (400 MHz, $CDCl_3$) 8.09 (d, *J* = 8.6 Hz, 1H, Ar-C**H**), 7.45 – 7.31 (m, 5H, Ar-C**H**), 6.62 – 6.57 (m, 2H, Ar-C**H**), 5.20 (s, 2H, OC**H₂**Ph), 3.82 (s, 3H, OC**H₃**); δ_C (100 MHz, $CDCl_3$) 165.9 (**C**O), 165.0 (Ar-**C**), 159.0 (Ar-**C**), 135.4 (Ar-**C**H), 134.5 (Ar-**C**), 129.1 (Ar-**C**H), 129.0 (Ar-**C**H), 127.8 (Ar-**C**H), 110.7 (Ar-**C**), 106.9 (Ar-**C**H), 99.9 (Ar-**C**H), 71.9 (O**C**H₂Ph), 55.7 (O**C**H₃); HRMS (ESI): calcd. for $C_{15}H_{14}NaO_4$, 281.0784. Found: $[MNa]^+$, 281.0785 (–0.2 ppm error). Spectroscopic data are in accordance with those reported in the literature.[216]

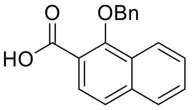
2-(Benzyloxy)-5-methoxybenzoic acid (S2)



A mixture of the 5-methoxysalicyclic acid (841 mg, 5.0 mmol, 1 equiv), anhydrous K_2CO_3 (691 mg, 5.0 mmol, 1 equiv), TBAB (161.2 mg, 0.50 mmol, 10 mol %) and benzyl bromide (1.71 g, 10 mmol, 2 equiv), in anhydrous THF (25 mL) was stirred at ambient temperature until TLC analysis showed the disappearance of the starting materials. The reaction mixture was filtered to remove the solid. NaOH (4 M, aq., 5.0 mL, 20.0 mmol) was added to the filtrate and the resulting mixture was heated to reflux.

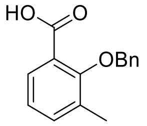
After completion of reaction, the THF was evaporated. Then the crude material was diluted with H_2O (30 mL) and washed with DCM (30 mL). The PH of the aqueous layer was lowered to pH = 2 with 1 M HCl (aq.) and was subsequently extracted three times with DCM (20 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*, purification by flash column chromatography (SiO_2, ethyl acetate) afforded the *title compound* as a white solid (1.08 g, 84%). m.p. 75 – 77 °C; R_f = 0.55 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3247, 1732, 1495, 1426, 1284, 1215, 1039, 814, 732, 697; δ_H (400 MHz, $CDCl_3$) 7.60 (s, 1H, Ar-C**H**), 7.44 – 7.24 (m, 5H, Ar-C**H**), 7.01 (s, 2H, Ar-C**H**), 5.19 (s, 2H, OC**H₂**Ph), 3.73 (s, 3H, OC**H₃**); δ_C (100 MHz, $CDCl_3$) 166.2 (br, **C**O), 154.4 (Ar-**C**), 151.5 (Ar-**C**), 141.0 (Ar-**C**), 134.9 (Ar-**C**), 129.0 (Ar-**C**H), 128.5 (Ar-**C**H), 127.9 (Ar-**C**H), 127.5 (Ar-**C**H), 127.0 (Ar-**C**H), 121.5 (br, Ar-**C**H), 116.2 (Ar-**C**H), 115.3 (br, Ar-**C**H), 72.9 (O**C**H₂Ph), 55.8 (O**C**H₃); HRMS (ESI): calcd. for $C_{15}H_{14}NaO_4$, 281.0784. Found: $[MNa]^+$, 281.0783 (0.4 ppm error). Spectroscopic data are in accordance with those reported in the literature.[217]

1-(Benzyloxy)-2-naphthoic acid (S3)



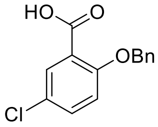
A mixture of the 1-hydroxyl-2-naphthoic acid (941mg, 5.0 mmol, 1 equiv), anhydrous K_2CO_3 (691 mg, 5.0 mmol, 1 equiv), TBAB (161.2 mg, 10 mol %) and benzyl bromide (1.71 g, 10 mmol, 2 equiv), in anhydrous THF (25 mL) was stirred at ambient temperature until TLC analysis showed the disappearance of the starting materials. The reaction mixture was filtered to remove the solid. NaOH (4 M, aq., 5.2 mL, 20.8 mmol) was added to the filtrate and the resulting mixture was heated to reflux. After completion of reaction, the THF was evaporated. Then the crude material was diluted with H_2O (30 mL) and washed with DCM (30 mL). The PH of the aqueous layer was lowered to pH = 2 with 1 M HCl (aq.) and was subsequently extracted three times with DCM (20 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*, purification by flash column chromatography (SiO_2, ethyl acetate) afforded the *title compound* as a white solid (1.01 g, 73%). m.p. 100 – 102 °C; R_f = 0.60 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3065, 1686, 1624, 1467, 1363, 1335, 1289, 1247, 1083, 966, 768, 695; δ_H (400 MHz, $CDCl_3$) 10.87 (brs, 1H, COO**H**), 8.29 (d, *J* = 8.3 Hz, 1H, Ar-C**H**), 8.10 (d, *J* = 8.7 Hz, 1H, Ar-C**H**), 7.90 (d, *J* = 7.8 Hz, 1H, Ar-C**H**), 7.71 (d, *J* = 8.7 Hz, 1H, Ar-C**H**), 7.67 – 7.62 (m, 1H, Ar-C**H**), 7.62 – 7.55 (m, 3H, Ar-C**H**), 7.48 – 7.36 (m, 3H, Ar-C**H**), 5.25 (s, 2H, OC**H**$_2$Ph); δ_C (100 MHz, $CDCl_3$) 169.6 (**C**O), 157.2 (Ar-**C**), 137.5 (Ar-**C**), 136.0 (Ar-**C**), 129.0 (Ar-CH), 128.8 (Ar-**C**H), 128.8 (Ar-**C**H), 128.6 (Ar-**C**H), 128.2 (Ar-**C**H), 128.1 (Ar-**C**), 127.0 (Ar-**C**H), 127.0 (Ar-**C**H), 124.6 (Ar-**C**H), 123.6 (Ar-**C**H), 118.7 (Ar-**C**), 78.7 (O**C**H$_2$Ph); HRMS (ESI): calcd. for $C_{15}H_{14}NaO_4$, 301.0835. Found: [MNa]$^+$, 301.0838 (–1.0 ppm error). Spectroscopic data are in accordance with those reported in the literature.[214]

2-(Benzyloxy)-3-methylbenzoic acid (S4)



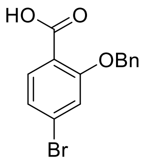
A mixture of the 3-methylsalicylic acid (761mg, 5.0 mmol, 1 equiv), anhydrous K_2CO_3 (691 mg, 5.0 mmol, 1 equiv), TBAB (161.2 mg, 10 mol %) and benzyl bromide (1710 mg, 10 mmol, 2 equiv), in anhydrous THF (25 mL) was stirred at ambient temperature until TLC analysis showed the disappearance of the starting materials. The reaction mixture was filtered to remove the solid. NaOH (4 M, aq., 5.0 mL, 20.0 mmol) was added to the filtrate and the resulting mixture was heated to reflux. After completion of reaction, the THF was evaporated. Then the crude material was diluted with H_2O (30 mL) and washed with DCM (30 mL). The pH of the aqueous layer was lowered to pH = 2 with 1 M HCl (aq.) and was subsequently extracted three times with DCM (20 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*, purification by flash column chromatography (SiO_2, ethyl acetate) afforded the *title compound* as a white solid (717 mg, 60%). m.p. 65 – 67 °C; R_f = 0.65 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3039, 1692, 1592, 1466, 1303, 1220, 1088, 981, 765, 696; δ_H (400 MHz, $CDCl_3$) 11.57 (s, 1H, COO**H**), 7.95 (dd, *J* = 7.9, 1.8 Hz, 1H, Ar-C**H**), 7.54 – 7.33 (m, 6H, Ar-C**H**), 7.18 (t, *J* = 7.7 Hz, 1H, Ar-C**H**), 5.00 (s, 2H, OC**H**$_2$Ph), 2.39 (s, 3H, C**H**$_3$); δ$_C$ (100 MHz, CDCl$_3$) 168.9 (**C**O), 157.0 (Ar-**C**), 136.8 (Ar-**C**H), 135.8 (Ar-**C**), 132.6 (Ar-**C**), 130.6 (Ar-**C**H), 128.8 (3 × Ar-**C**H), 128.7 (2 × Ar-**C**H), 124.7 (Ar-**C**H), 123.1 (Ar-**C**), 76.9 (O**C**H$_2$Ph), 16.4 (**C**H$_3$); HRMS (ESI): calcd. for $C_{15}H_{14}NaO_3$, 265.0835. Found: $[MNa]^+$, 265.0837 (–0.7 ppm error). Spectroscopic data are in accordance with those reported in the literature.[218]

2-(Benzyloxy)-5-chlorobenzoic acid (S5)



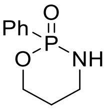
A mixture of the 5-chlorosalicyclic acid (863 mg, 5.0 mmol, 1 equiv), anhydrous K_2CO_3 (691 mg, 5.0 mmol, 1 equiv), TBAB (161.2 mg, 10 mol %) and benzyl bromide (1710 mg, 10 mmol, 2 equiv), in anhydrous THF (25 mL) was stirred at ambient temperature until TLC analysis showed the disappearance of the starting materials. The reaction mixture was filtered to remove the solid. NaOH (4 M, aq., 5.0 mL, 20.0 mmol) was added to the filtrate and the resulting mixture was heated to reflux. After completion of reaction, the THF was evaporated. Then the crude material was diluted with H_2O (30 mL) and washed with DCM (30 mL). The pH of the aqueous layer was lowered to pH = 2 with 1 M HCl (aq.) and was subsequently extracted three times with DCM (20 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*, purification by flash column chromatography (SiO_2, ethyl acetate) afforded the *title compound* as a white solid (790 mg, 60%). m.p. 88 – 90 °C; R_f = 0.55 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3034, 1736, 1697, 1599, 1484, 1415, 1274, 1230, 1116, 986, 812, 736, 697; δ$_H$ (400 MHz, CDCl$_3$) 8.10 (d, *J* = 2.8 Hz, 1H, Ar-C**H**), 7.47 (dd, *J* = 8.9, 2.8 Hz, 1H, Ar-C**H**), 7.44 – 7.34 (m, 5H, Ar-C**H**), 7.06 (d, *J* = 8.8 Hz, 1H, Ar-C**H**), 5.26 (s, 2H, OC**H**$_2$Ph); δ$_C$ (100 MHz, CDCl$_3$) 165.2 (**C**O), 156.2 (Ar-**C**), 134.7 (Ar-**C**H), 134.3 (Ar-**C**), 133.2 (Ar-**C**H), 129.2 (Ar-**C**H), 129.2 (Ar-**C**H), 127.9 (Ar-**C**H), 127.5 (Ar-**C**), 119.6 (Ar-**C**), 114.9 (Ar-**C**H), 72.5 (O**C**H$_2$Ph); HRMS (ESI): calcd. for $C_{14}H_{11}{}^{35}ClNaO_3$, 285.0289. Found: $[MNa]^+$, 285.0283 (1.9 ppm error). Spectroscopic data are in accordance with those reported in the literature.[219]

2-(Benzyloxy)-4-bromobenzoic acid (S6)



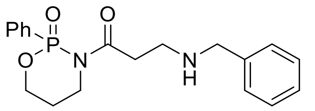
A mixture of the 4-bromosalicyclic acid (651 mg, 3.0 mmol, 1 equiv), anhydrous K_2CO_3 (415 mg, 3.0 mmol, 1 equiv), TBAB (97 mg, 10 mol %) and benzyl bromide (1026 mg, 6 mmol, 2 equiv), in anhydrous THF (15 mL) was stirred at ambient temperature until TLC analysis showed the disappearance of the starting materials. The reaction mixture was filtered to remove the solid. NaOH (4 M, aq., 3.0 mL, 12.0 mmol) was added to the filtrate and the resulting mixture was heated to reflux. After completion of reaction, the THF was evaporated. Then the crude material was diluted with H_2O (20 mL) and washed with DCM (20 mL). The PH of the aqueous layer was lowered to PH = 2 with 1 M HCl (aq.) and was subsequently extracted three times with DCM (20 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*, purification by flash column chromatography (SiO_2, ethyl acetate) afforded the *title compound* as a white solid (653 mg, 71%). m.p. 88 – 90 °C; $R_f = 0.53$ (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3034, 1734, 1690, 1589, 1383, 1242, 1099, 1022, 887, 696; δ_H (400 MHz, DMSO-*d*$_6$) 12.87 (s, 1H, COOH), 7.67 – 7.12 (m, 8H, Ar-C**H**), 5.23 (s, 2H, OC**H**$_2$Ph); δ_C (101 MHz, DMSO-*d*$_6$) 166.7 (**C**O), 157.9 (Ar-**C**), 136.6 (Ar-**C**), 132.4 (Ar-**C**H), 128.5 (Ar-**C**H), 127.8 (Ar-**C**H), 127.2 (Ar-**C**H), 126.0 (Ar-**C**), 123.4 (Ar-**C**H), 121.1 (Ar-**C**), 117.1 (Ar-**C**H), 70.0 (O**C**H$_2$Ph); HRMS (ESI): calcd. for $C_{14}H_{11}BrNaO_3$, 328.9784. Found: $[MNa]^+$, 328.9786 (–0.6 ppm error). Spectral data are in accordance with those reported in the literature.[214,215]

2-Phenyl-1,3,2-oxazaphosphinane 2-oxide (6-13)



Phenylphosphinic dichloride **6-11** (3.90 g, 20 mmol) in THF (90 mL) was added dropwise to a solution of 3-amino-1-propanol **6-12** (1.80 mL, 22 mmol) and triethylamine (5.80 mL, 20 mmol) in THF (30 mL). The mixture was stirred at room temperature for 24 h. The solution was filtered to remove the $NEt_3 \cdot HCl$ salts and the resulting filtrate was concentrated under reduced pressure to give a clear colorless oil. The crude product was purified by flash chromatography (9:1 ethyl acetate: methanol) to give the product as a thick, clear colorless oil (2.76 g, 70%); R_f = 0.48 (ethanol); δ_H (400 MHz, $CDCl_3$) 7.84 – 7.69 (m, 2H, Ar-C**H**), 7.54 – 7.34 (m, 3H, Ar-C**H**), 4.45 – 4.33 (m, 1H, C**H**$_2$), 4.30 – 4.22 (m, 1H, N**H**), 4.11 – 3.99 (m, 1H, C**H**$_2$), 3.45 – 3.29 (m, 1H, C**H**$_2$), 3.20 – 3.03 (m, 1H, C**H**$_2$), 2.09 – 1.93 (m, 1H, C**H**$_2$), 1.71 – 1.57 (m, 1H, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 131.7 (d, *J* = 3.0 Hz, Ar-**C**H), 131.3 (d, *J* = 10.2 Hz, Ar-**C**H), 131.1 (d, *J* = 170.5 Hz, Ar-**C**), 128.6 (d, *J* = 14.4 Hz, Ar-**C**H), 67.8 (d, *J* = 6.8 Hz, O**C**H$_2$), 40.9 (d, *J* = 2.7 Hz, **C**H$_2$), 26.4 (d, *J* = 7.6 Hz, **C**H$_2$); δ_P (162 MHz, $CDCl_3$) 20.1 (Ph**P**=O); HRMS (ESI): calcd. for $C_9H_{12}NNaO_2P$, 220.0498. Found: $[MNa]^+$, 220.0499 (–0.5 ppm error). Spectroscopic data are in accordance with those reported in the literature.[200]

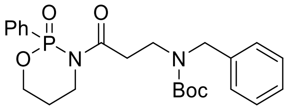
3-(Benzylamino)-1-(2-oxido-2-phenyl-1,3,2-oxazaphosphinan-3-yl)propan-1-one (6-15)



To a solution of 1-(2-oxido-2-phenyl-1,3,2-oxazaphosphinan-3-yl) prop-2-en-1-one (125.6 mg, 0.5 mmol) in dry THF (1.0 mL), was added benzylamine (64.3 mg, 0.6 mmol) in a single portion. The reaction mixture was allowed to stir overnight at RT. Purification by flash column chromatography (SiO_2, 10:1 dichloromethane: methanol) afforded the title compound as a colorless oil (145 mg, 81%); R_f = 0.22 (10:1 dichloromethane: methanol); ν_{max}/cm^{-1} (thin film) 3480, 3324, 2923, 1677, 1439, 1254, 1130, 1022, 914, 747, 696, 540; δ_H (400 MHz, $CDCl_3$) 7.85 – 7.70 (m, 2H, Ar-C**H**), 7.62 – 7.52 (m, 1H, Ar-C**H**), 7.53 – 7.42 (m, 1H, Ar-C**H**), 7.34 – 7.11 (m, 5H, Ar-C**H**), 4.50 (m, 2H, OC**H**$_2$ + C**H**$_2$), 4.21 (dddd, *J* = 14.1, 11.0, 8.9, 5.4 Hz, 1H, OC**H**$_2$), 3.69 (s, 2H, NHC**H**$_2$Ph), 3.32 (ddd, *J* = 13.5, 8.3, 3.0 Hz, 1H, C**H**$_2$), 3.11 (dt, *J* = 16.2, 5.7 Hz, 1H, C**H**$_2$), 2.95 – 2.71 (m, 2H, C**H**$_2$), 2.58 (ddd, *J* = 16.5, 7.2, 5.6 Hz, 1H, C**H**$_2$), 2.20 (ddp, *J* = 14.7, 10.0, 5.2, 5.1 Hz, 1H, N**H**), 2.08 – 1.94 (m, 2H, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 174.3 (d, *J* = 7.9 Hz, **C**O), 140.1 (Ar-**C**), 133.0 (d, *J* = 3.1 Hz, Ar-**C**H), 131.2

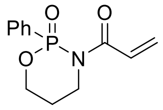
(d, *J* = 10.7 Hz, Ar-**C**H), 129.1 (d, *J* = 176.7 Hz, Ar-**C**), 129.0 (d, *J* = 15.2 Hz, Ar-**C**H), 128.2 (Ar-**C**H), 128.0 (Ar-**C**H), 126.7 (Ar-**C**H), 66.8 (d, *J* = 8.0 Hz, O**C**H_2), 53.5 (NH**C**H_2Ph), 44.6 (**C**H_2), 41.1 (**C**H_2), 37.2 (**C**H_2), 25.7 (d, *J* = 6.0 Hz, **C**H_2); δ_P (162 MHz, $CDCl_3$) 15.8 (Ph**P**=O); HRMS (ESI): calcd. for $C_{19}H_{24}N_2O_3P$, 359.1519. Found: [MH]$^+$, 359.1526 (–2.1 ppm error).

***tert*-Butyl benzyl(3-(2-oxido-2-phenyl-1,3,2-oxazaphosphinan-3-yl)-3-oxopropyl)carbamate (6-17)**



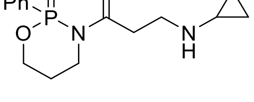
3-(Benzylamino)-1-(2-oxido-2-phenyl-1,3,2-oxazaphosphinan-3-yl)propan-1-one (150 mg, 0.42 mmol) was dissolved in THF (5.0 mL) and Boc anhydride (110 mg, 0.5 mmol) added, the mixture was stirred for 2 h at RT. Purification by flash column chromatography (SiO_2, 1:1 dichloromethane: ethyl acetate) afforded the title compound (a 4:3 mixture of rotamers) as a colorless oil (185 mg, 97%); R_f = 0.28 (1:1 dichloromethane: ethyl acetate); ν_{max}/cm^{-1} (thin film) 2975, 1682, 1413, 1365, 1251, 1163, 1122, 1021, 916, 748, 696, 539; δ_H (400 MHz, $CDCl_3$) 7.69 (dd, *J* = 13.9, 7.5 Hz, 2H, Ar-C**H**, both rotamers), 7.59 – 7.38 (m, 3H, Ar-C**H**, both rotamers), 7.25 – 7.07 (m, 5H, Ar-C**H**, both rotamers), 4.52 – 4.04 (m, 5H, C**H₂**, both rotamers), 3.56 – 2.95 (m, 4H, C**H₂**, both rotamers), 2.84 – 2.40 (m, 1H, C**H₂**, both rotamers), 2.29 – 1.93 (m, 2H, C**H₂**, both rotamers), 1.34 (s, 9H, 3 × C**H₃**, both rotamers); δ_C (100 MHz, $CDCl_3$) for major rotamers only: 173.2 (d, *J* = 7.9 Hz, **C**O), 155.6 (N**C**OO), 138.2 (Ar-**C**), 133.1 (Ar-**C**H), 131.2 (Ar-**C**H), 131.1 (Ar-**C**H), 129.1 (Ar-**C**H), 128.9 (Ar-**C**H), 128.6 (d, *J* = 171.7 Hz, Ar-**C**), 128.3 (Ar-**C**H), 127.6 (Ar-**C**H), 127.0 (Ar-**C**H), 79.7 (O**C**CH_3), 66.7 (d, *J* = 7.7 Hz, O**C**H_2), 50.1 (N**C**H_2Ph), 42.5 (**C**H_2), 41.1 (**C**H_2), 36.0 (**C**H_2), 28.2 (3 × **C**H_3), 25.7 (d, *J* = 6.1 Hz, **C**H_2); Diagnostic ^{13}C NMR resonances for the minor rotamer: 155.1 (N**C**OO), 138.5 (Ar-**C**H), 132.9 (Ar-**C**H), 127.1 (Ar-**C**H), 50.8 (**C**H_2), 42.8 (**C**H_2), 35.4 (**C**H_2); δ_P (162 MHz, $CDCl_3$) 15.4 (Ph**P**=O); HRMS (ESI): calcd. for $C_{24}H_{31}N_2NaO_5P$, 481.1863. Found: [MH]$^+$, 481.1859 (0.8 ppm error). HMBC: NC**H₂**Ph (δ_H 4.27) coupling to the N**C**OO (δ_C 155.6).

1-(2-Oxido-2-phenyl-1,3,2-oxazaphosphinan-3-yl)prop-2-en-1-one (6-18)



To a solution of 2-phenyl-1,3,2-oxazaphosphinane 2-oxide **6-13** (2.09 g, 10.6 mmol) in dry THF (50 mL), was added acryl chloride (1.44 g, 15.9 mmol) in a single portion, then NEt_3 (1.61 g, 15.9 mmol) was added to the mixture. The reaction mixture was allowed to stir for 10 min a RT. The reaction mixture was then quenched with sat. aq. $NaHCO_3$ (100 mL) and the mixture was extracted with Et_2O (2 × 100 mL). The organic extracts dried over $MgSO_4$ and concentrated in vacuo. Purification by flash column chromatography (SiO_2, 1:1 hexane: ethyl acetate → ethyl acetate) afforded the title compound as a pale-brown oil (2.37 g, 89%); R_f = 0.28 (ethyl acetate); δ_H (400 MHz, $CDCl_3$) 7.73 – 7.65 (m, 2H, Ar-C**H**), 7.59 – 7.51 (m, 1H, Ar-C**H**), 7.51 – 7.40 (m, 2H, Ar -C**H**), 7.06 (dd, *J* = 16.6, 10.3 Hz, 1H, C**H**=CHH'), 6.34 (dd, *J* = 16.6, 1.9 Hz, 1H, CH=C**H**H'), 5.63 (dd, *J* = 10.3, 1.9 Hz, 1H, CH=CH**H'**), 4.62 – 4.46 (m, 2H, 1H from OC**H**$_2$ + 1H from C**H**$_2$), 4.23 (dddd, *J* = 12.6, 10.9, 9.2, 5.3 Hz, 1H, OC**H**$_2$), 3.30 (ddt, *J* = 14.0, 11.0, 3.2 Hz, 1H, C**H**$_2$), 2.29 – 2.16 (m, 1H, C**H**$_2$), 2.07 – 1.95 (m, 1H, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 167.5 (d, *J* = 7.6 Hz, **C**O), 133.1 (d, *J* = 3.1 Hz, Ar-**C**H), 131.1 (d, *J* = 10.8 Hz, Ar-**C**H), 130.3 (CO**C**H=CH$_2$), 129.8 (COCH=**C**H$_2$), 129.1 (d, *J* = 174.8 Hz, Ar-**C**), 129.1 (d, *J* = 15.3 Hz, Ar-**C**H), 67.3 (d, *J* = 8.0 Hz, O**C**H$_2$), 41.3 (d, *J* = 1.0 Hz**,** **C**H$_2$), 25.8 (d, *J* = 6.1 Hz, **C**H$_2$); δ_P (162 MHz, $CDCl_3$) 15.9; HRMS (ESI): calcd. for $C_{12}H_{14}NNaO_3P$, 274.0604. Found: $[MNa]^+$, 274.0607 (–1.3 ppm error).

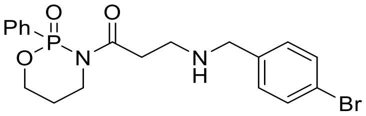
3-(Cyclopropylamino)-1-(2-oxido-2-phenyl-1,3,2-oxazaphosphinan-3-yl)propan-1-one (6-15a)



To a solution of 1-(2-oxido-2-phenyl-1,3,2-oxazaphosphinan-3-yl)prop-2-en-1-one **6-18** (125.6 mg, 0.5 mmol) in dry THF (1.0 mL), was added cyclopropylamide (34.3 mg, 0.6 mmol) in a single portion. The reaction mixture was allowed to stir for overnight at RT. Purification by flash column chromatography (SiO_2, 10: 1 dichloromethane:

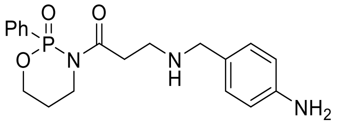
methanol) afforded the title compound as a colorless oil (73 mg, 47%); R$_f$= 0.26 (9:1 dichloromethane: methanol); ν$_{max}$/cm^{-1} (thin film) 3478, 2929, 1677, 1439, 1365, 1253, 1130, 1017, 914, 749, 695, 540; δ$_H$ (400 MHz, CDCl$_3$) 7.78 – 7.66 (m, 2H, Ar-C**H**), 7.58 – 7.50 (m, 1H, Ar-C**H**), 7.48 – 7.42 (m, 1H, Ar-C**H**), 4.55 – 4.39 (m, 2H, OC**H**$_2$ + C**H**$_2$), 4.19 (dddd, *J* = 14.2, 11.0, 8.8, 5.5 Hz, 1H, OC**H**$_2$), 3.30 (tq, *J* = 10.6, 3.2 Hz, 1H, C**H**$_2$), 3.04 (dt, *J* = 16.3, 6.0 Hz, 1H, C**H**$_2$), 2.87 – 2.81 (m, 2H, C**H**$_2$), 2.48 (dt, *J* = 16.5, 6.4 Hz, 1H, C**H**$_2$), 2.19 – 1.99 (m, 3H, N**H** + C**H**$_2$), 1.94 (tt, *J* = 6.6, 3.6 Hz, 1H, NC**H**), 0.31 – 0.15 (m, 4H, 2 × C**H**$_2$); δ$_C$ (100 MHz, CDCl$_3$) 174.4 (d, *J* = 7.8 Hz, **C**O), 133.1 (d, *J* = 3.0 Hz, Ar-**C**H), 131.3 (d, *J* = 10.8 Hz, Ar-**C**H), 129.1 (d, *J* = 176.0 Hz, Ar-**C**), 129.0 (d, *J* = 15.2 Hz, Ar-**C**H), 66.8 (d, *J* = 7.9 Hz, **C**H$_2$), 44.8 (**C**H$_2$), 41.1 (**C**H$_2$), 37.0 (**C**H$_2$), 29.8 (N**C**H), 25.8 (d, *J* = 6.1 Hz, **C**H$_2$), 6.1 (**C**H$_2$), 6.1 (**C**H$_2$); δ$_P$ (162 MHz, CDCl$_3$) 15.7 (Ph**P**=O); HRMS (ESI): calcd. for $C_{15}H_{22}N_2O_3P$, 309.1363. Found: [MH]$^+$, 309.1365 (–0.8 ppm error).

3-((4-Bromobenzyl)amino)-1-(2-oxido-2-phenyl-1,3,2-oxazaphosphinan-3-yl)propan-1-one (6-15b)



To a solution of 1-(2-oxido-2-phenyl-1,3,2-oxazaphosphinan-3-yl) prop-2-en-1-one **6-18** (125.6 mg, 0.5 mmol) in dry THF (1.0 mL), was added 4-bromobenzylamine (111.6 mg, 0.6 mmol) in a single portion. The reaction mixture was allowed to stir for overnight at RT. Purification by flash column chromatography (SiO$_2$, 20:1 dichloromethane: methanol) afforded the title compoud as a colorless oil (186 mg, 85%); R$_f$= 0.45 (10:1 dichloromethane: methanol); ν$_{max}$/cm^{-1} (thin film) 3321, 2907, 1678, 1486, 1439, 1255, 1181, 1130, 1069, 1011, 913, 787, 749, 695, 540; δ$_H$ (400 MHz, CDCl$_3$) 7.75 – 7.66 (m, 2H, Ar-C**H**), 7.57 – 7.49 (m, 1H, Ar-C**H**), 7.49 – 7.38 (m, 2H, Ar-C**H**), 7.36 – 7.29 (m, 2H, Ar-C**H**), 7.11 – 7.04 (m, 2H, Ar-C**H**), 4.46 (m, 2H, OC**H**$_2$ + C**H**$_2$), 4.18 (dddd, *J* = 14.0, 11.0, 8.9, 5.4 Hz, 1H, OC**H**$_2$), 3.59 (s, 2H, NHC**H**$_2$Ph), 3.27 (ddt, *J* = 13.8, 10.6, 3.3 Hz, 1H, C**H**$_2$), 3.06 (dt, *J* = 16.6, 6.0 Hz, 1H, C**H**$_2$), 2.83 – 2.67 (m, 2H, C**H**$_2$), 2.51 (ddd, *J* = 16.5, 7.1, 5.4 Hz, 1H, C**H**$_2$), 2.25 – 2.06 (m, 1H, C**H**$_2$), 1.97 (dddd, *J* = 14.4, 5.1, 3.6, 1.5 Hz, 1H, N**H**), 1.84 (s, 1H, C**H**$_2$); δ_C (100 MHz, CDCl$_3$) 174.2 (d, *J* = 7.9 Hz, **C**O), 139.3 (Ar-**C**), 133.0 (d, *J* = 3.1 Hz, Ar-**C**H), 131.3 (Ar-**C**H), 131.2 (Ar-CH), 131.1 (Ar-**C**H), 129.7 (Ar-**C**H), 129.0 (d, *J* = 176.7 Hz, Ar-**C**), 129.0 (d, *J* = 15.2 Hz, Ar-**C**H), 120.4 (Ar-**C**), 66.8 (d, *J* = 7.9 Hz, O**C**H$_2$), 52.8 (NH**C**H$_2$Ph), 44.5 (**C**H$_2$), 41.1 (**C**H$_2$), 37.2 (**C**H$_2$), 25.8 (d, *J* = 6.1 Hz, **C**H$_2$); δ_P (162 MHz, CDCl$_3$) 15.8 (Ph**P**=O); HRMS (ESI): calcd. for $C_{19}H_{23}{}^{79}BrN_2O_3P$, 437.0624. Found: [MH]$^+$, 437.0633 (–1.9 ppm error).

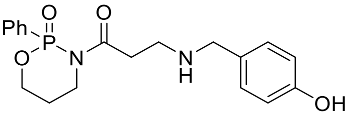
3-((4-Aminobenzyl)amino)-1-(2-oxido-2-phenyl-1,3,2-oxazaphosphinan-3-yl)propan-1-one (6-15c)



To a solution of 1-(2-oxido-2-phenyl-1,3,2-oxazaphosphinan-3-yl) prop-2-en-1-one **6-18** (125.6 mg, 0.5 mmol) in dry THF (1.0 mL), was added 4-aminobenzylamine (73.3 mg, 0.6 mmol) in a single portion. The reaction mixture was allowed to stir for overnight at RT. Purification by flash column chromatography (SiO$_2$, 9:1 dichloromethane: methanol) afforded the title compound as a colorless oil (130 mg, 70%); R$_f$ = 0.15 (10:1 dichloromethane: methanol); ν_{max}/cm^{-1} (thin film) 3347, 2922, 1673, 1517, 1439, 1252, 1129, 1019, 727, 694, 538, 506; δ_H (400 MHz, CDCl$_3$) 7.77 – 7.64 (m, 2H, Ar-C**H**), 7.57 – 7.48 (m, 1H, Ar-C**H**), 7.47 – 7.37 (m, 2H, Ar-C**H**), 6.96 (d, *J* = 8.3 Hz, 2H, Ar-C**H**), 6.59 – 6.44 (m, 2H, Ar-C**H**), 4.51 – 4.34 (m, 2H, OC**H**$_2$ + C**H**$_2$), 4.16 (dddd, *J* = 14.1, 10.9, 8.8, 5.4 Hz, 1H, OC**H**$_2$), 3.50 (s, 2H, NHC**H**$_2$Ph), 3.27 (ddt, *J* = 13.6, 10.2, 3.4 Hz, 1H, C**H**$_2$), 3.03 (dt, *J* = 16.3, 5.5 Hz, 1H, C**H**$_2$), 2.82 – 2.66 (m, 2H, C**H**$_2$), 2.51 (ddd, *J* = 16.6, 7.1, 5.7 Hz, 1H, C**H**$_2$), 2.21 – 2.07 (m, 1H, N**H**), 2.02 – 1.88 (m, 1H, C**H**$_2$); δ_C (100 MHz, CDCl$_3$) 174.3 (d, *J* = 7.7 Hz, **C**O), 145.4 (Ar-**C**), 133.0 (d, *J* = 3.1 Hz, Ar-**C**H), 131.2 (d, *J* = 10.7 Hz, Ar-**C**H), 129.6 (Ar-**C**), 129.1 (Ar-**C**H), 129.0 (d, *J* = 176.7 Hz, Ar-**C**), 128.9 (d, *J* = 15.3 Hz, Ar-**C**H), 114.9 (Ar-**C**H), 66.8 (d, *J* = 8.0 Hz, O**C**H$_2$), 53.0 (NH**C**H$_2$Ph), 44.3 (**C**H$_2$), 41.1 (**C**H$_2$), 37.0 (**C**H$_2$), 25.7 (d, *J* = 6.0 Hz, **C**H$_2$); δ_P (162 MHz, CDCl$_3$) 15.8 (Ph**P**=O); HRMS (ESI): calcd.

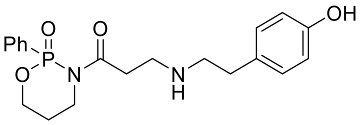
for $C_{19}H_{25}N_3O_3P$, 347.1628. Found: $[MH]^+$, 347.1628 (0.1 ppm error).

3-((4-Hydroxybenzyl)amino)-1-(2-oxido-2-phenyl-1,3,2-oxazaphosphinan-3-yl)propan-1-one (6-15d)



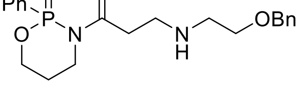
To a solution of 1-(2-Oxido-2-phenyl-1,3,2-oxazaphosphinan-3-yl) prop-2-en-1-one **6-18** (125.6 mg, 0.5 mmol) in dry THF (1.0 mL), was added 4-hydroxybenzylamine (74 mg, 0.6 mmol) in a single portion. The reaction mixture was allowed to stir for overnight at RT. Purification by flash column chromatography (SiO_2, 10:1 dichloromethane: methanol) afforded the title compound as a colorless oil (145 mg, 77%); R_f = 0.14 (10:1 dichloromethane: methanol); ν_{max}/cm^{-1} (thin film) 3243, 2923, 1677, 1516, 1439, 1380, 1251, 1131, 1020, 912, 729, 694, 539; δ_H (400 MHz, $CDCl_3$) 7.75 – 7.66 (m, 2H, Ar-C**H**), 7.55 – 7.47 (m, 1H, Ar-C**H**), 7.46 – 7.34 (m, 2H, Ar-C**H**), 7.00 – 6.91 (m, 2H, Ar-C**H**), 6.62 – 6.52 (m, 2H, Ar-C**H**), 5.67 (s, 2H, Ar-O**H** + OC**H**$_2$), 4.59 – 4.27 (m, 2H, OC**H**$_2$ + C**H**$_2$), 4.17 (dddd, *J* = 14.1, 10.9, 8.6, 5.4 Hz, 1H, C**H**$_2$), 3.55 (s, 2H, NHC**H**$_2$Ph), 3.35 – 3.20 (m, 1H, C**H**$_2$), 3.06 (d, *J* = 16.8 Hz, 1H, C**H**$_2$), 2.81 (ddt, *J* = 19.9, 11.9, 5.6 Hz, 2H, C**H**$_2$), 2.53 (ddd, *J* = 16.7, 7.3, 5.5 Hz, 1H, C**H**$_2$), 2.24 – 2.05 (m, 1H, N**H**), 1.96 (dddd, *J* = 13.4, 11.9, 5.8, 3.7 Hz, 1H, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 174.3 (d, *J* = 7.3 Hz, **C**O), 156.4 (Ar-**C**), 133.2 (d, *J* = 2.8 Hz, Ar-**C**H), 131.3 (d, *J* = 10.9 Hz, Ar-**C**H), 129.6 (Ar-**C**H), 129.4 (Ar-**C**), 129.1 (d, *J* = 15.4 Hz, Ar-**C**H), 128.6 (d, *J* = 177.7 Hz, Ar-**C**), 115.6 (Ar-**C**H), 66.9 (d, *J* = 7.8 Hz, O**C**H$_2$), 52.9 (NH**C**H$_2$Ph), 44.1 (**C**H$_2$), 41.4 (**C**H$_2$), 36.3 (**C**H$_2$), 25.6 (d, *J* = 6.1 Hz, **C**H$_2$); δ_P (162 MHz, $CDCl_3$) 16.1 (Ph**P**=O); HRMS (ESI): calcd. for $C_{19}H_{24}N_2O_4P$, 375.1468. Found: $[MH]^+$, 375.1472 (–1.0 ppm error).

3-((4-Hydroxyphenethyl)amino)-1-(2-oxido-2-phenyl-1,3,2-oxazaphosphinan-3-yl)propan-1-one (6-15e)



To a solution of 1-(2-oxido-2-phenyl-1,3,2-oxazaphosphinan-3-yl) prop-2-en-1-one **6-18** (125.6 mg, 0.5 mmol) in dry THF (1.0 mL), was added tyramine (82 mg, 0.6 mmol) in a single portion. The reaction mixture was allowed to stir for overnight at RT. Purification by flash column chromatography (SiO_2, 5:1 dichloromethane: methanol) afforded the title compound as a colorless oil (125 mg, 64%); R_f = 0.10 (10:1 dichloromethane: methanol); ν_{max}/cm^{-1} (thin film) 2925, 1677, 1515, 1439, 1252, 1130, 1018, 749, 541; δ_H (400 MHz, $CDCl_3$) 7.76 – 7.62 (m, 2H, Ar-C**H**), 7.56 – 7.47 (m, 1H, Ar-C**H**), 7.46 – 7.35 (m, 2H, Ar-C**H**), 6.94 – 6.84 (m, 2H, Ar-C**H**), 6.68 – 6.60 (m, 2H, Ar-C**H**), 5.70 – 5.00 (br m, 2H), 4.62 – 4.30 (m, 2H, OC**H**$_2$ + C**H**$_2$), 4.19 (dddd, *J* = 14.1, 10.9, 8.6, 5.4 Hz, 1H, C**H**$_2$), 3.36 – 3.22 (m, 1H, C**H**$_2$), 3.06 (dt, *J* = 17.1, 5.9 Hz, 1H, C**H**$_2$), 2.90 – 2.77 (m, 2H, C**H**$_2$), 2.76 – 2.67 (m, 2H, C**H**$_2$), 2.62 (t, *J* = 6.7 Hz, 2H, C**H**$_2$), 2.57 – 2.43 (m, 1H, C**H**$_2$), 2.25 – 2.09 (m, 1H, N**H**), 2.05 – 1.90 (m, 1H, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 174.1 (d, *J* = 7.4 Hz, **C**O), 155.6 (Ar-**C**), 133.2 (d, *J* = 2.9 Hz, Ar-CH), 131.3 (d, *J* = 10.9 Hz, Ar-**C**H), 129.9 (Ar-**C**), 129.6 (Ar-**C**H), 129.1 (d, *J* = 15.4 Hz, Ar-**C**H), 128.6 (d, *J* = 176.8 Hz, Ar-**C**), 115.7 (Ar-**C**H), 67.0 (d, *J* = 7.6 Hz, O**C**H$_2$), 50.9 (NH**C**H$_2$), 44.7 (**C**H$_2$), 41.4 (**C**H$_2$), 36.4 (**C**H$_2$), 34.8 (**C**H$_2$), 25.7 (d, *J* = 6.0 Hz, **C**H$_2$); δ_P (162 MHz, $CDCl_3$) 16.1 (Ph**P**=O); HRMS (ESI): calcd. for $C_{20}H_{26}N_2O_4P$, 389.1625. Found: $[MH]^+$, 389.1623 (0.4 ppm error).

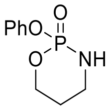
3-((2-(Benzyloxy)ethyl)amino)-1-(2-oxido-2-phenyl-1,3,2-oxazaphosphinan-3-yl)propan-1-one (6-15f)



To a solution of 1-(2-oxido-2-phenyl-1,3,2-oxazaphosphinan-3-yl) prop-2-en-1-one **6-18** (125.6 mg, 0.5 mmol) in dry THF (1.0 mL), was added 2-(benzyloxy)-1-ethanamine

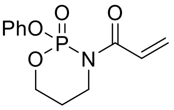
(91 mg, 0.6 mmol) in a single portion. The reaction mixture was allowed to stir for overnight at RT. Purification by flash column chromatography (SiO_2, 10:1 dichloromethane: methanol) afforded the title compound as a colorless oil (158 mg, 78%); R_f = 0.30 (10:1 dichloromethane: methanol); ν_{max}/cm^{-1} (thin film) 3468, 2858, 1678, 1439, 1254, 1130, 1021, 914, 748, 697, 540; δ_H (400 MHz, $CDCl_3$) 7.75 – 7.68 (m, 2H, Ar-C**H**), 7.55 – 7.48 (m, 1H, Ar-C**H**), 7.48 – 7.37 (m, 2H, Ar-C**H**), 7.30 – 7.17 (m, 5H, Ar-C**H**), 4.51 – 4.39 (m, 4H, OC**H**$_2$Ph + OC**H**$_2$ + C**H**$_2$), 4.16 (dddd, *J* = 14.1, 11.0, 8.8, 5.4 Hz, 1H, OC**H**$_2$), 3.46 (t, *J* = 5.3 Hz, 2H, OC**H**$_2$), 3.27 (ddt, *J* = 13.8, 10.3, 3.4 Hz, 1H, C**H**$_2$), 3.05 (dt, *J* = 16.5, 6.2 Hz, 1H, C**H**$_2$), 2.85 – 2.76 (m, 2H, C**H**$_2$), 2.67 (q, *J* = 5.2 Hz, 2H, C**H**$_2$), 2.51 (ddd, *J* = 16.5, 7.1, 6.1 Hz, 1H, C**H**$_2$), 2.24 – 2.10 (m, 2H, N**H** + C**H**$_2$), 1.96 (dddd, *J* = 14.4, 5.1, 3.6, 1.5 Hz, 1H, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 174.1 (d, *J* = 7.8 Hz, **C**O), 138.2 (Ar-**C**), 133.0 (d, *J* = 3.1 Hz, Ar-**C**H), 131.2 (d, *J* = 10.8 Hz, Ar-**C**H), 129.0 (d, *J* = 176.1 Hz, Ar-**C**), 128.9 (d, *J* = 15.2 Hz, Ar-**C**H), 128.3 (Ar-**C**H), 127.6 (Ar-**C**H), 127.5 (Ar-**C**H), 73.0 (O**C**H$_2$Ph), 69.3 (O**C**H$_2$), 66.7 (d, *J* = 8.0 Hz, O**C**H$_2$), 48.9 (**C**H$_2$), 45.0 (**C**H$_2$), 41.1 (**C**H$_2$), 37.1 (**C**H$_2$), 25.7 (d, *J* = 6.0 Hz, **C**H$_2$); δ_P (162 MHz, $CDCl_3$) 15.7 (Ph**P**=O); HRMS (ESI): calcd. for $C_{21}H_{28}N_2O_4P$, 403.1781. Found: [MH]$^+$, 403.1788 (–1.8 ppm error).

2-Phenoxy-1,3,2-oxazaphosphinane 2-oxide (6-13a)



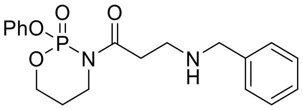
A solution of phosphoric acid phenyl ester dichloride **6-11a** (1.1 g, 5.1 mmol) in DCM (5.0 mL) was added under stirring and cooling at 0 °C to a solution of 3-amino-1-propanol (0.38 g, 5.1 mmol) in 10 mL of DCM. After addition of a solution of triethylamine (1.4 mL, 10.2 mmol) in 10 mL DCM, the reaction mixture was stirred at RT for 1 h and washed with H_2O. The organic solution was dried over $MgSO_4$, the solvent evaporated, and the residue purified by flash chromatography (20:1 dichloromethane: methanol) to give the product as a colorless oil (960 mg, 90%); R_f = 0.43 (10:1 dichloromethane: methanol); δ_H (400 MHz, $CDCl_3$) 7.33 – 7.18 (m, 4H, Ar-C**H**), 7.13 – 7.07 (m, 1H, Ar-C**H**), 4.44 – 4.34 (m, 2H, OC**H**$_2$), 4.32 – 4.24 (m, 1H, N**H**), 3.33 – 3.13 (m, 2H, C**H₂**), 2.08 – 1.91 (m, 1H, C**H**$_2$), 1.62 – 1.54 (m, 1H, C**H**$_2$); δ_C (100 MHz, CDCl$_3$) 150.9 (d, *J* = 7.1 Hz, Ar-**C**), 129.6 (Ar-**C**H), 124.5 (d, *J* = 0.7 Hz, Ar-**C**H), 112.0 (d, *J* = 5.0 Hz, Ar-**C**H), 70.0 (d, *J* = 7.6 Hz, O**C**H$_2$), 41.3 (d, *J* = 3.4 Hz, **C**H$_2$), 26.0 (d, *J* = 7.3 Hz, **C**H$_2$); δ_P (162 MHz, CDCl$_3$) – 0.3 (PhO**P**=O); HRMS (ESI): calcd. for $C_9H_{12}NNaO_3P$, 236.0447. Found: $[MNa]^+$, 236.0452 (–2.1 ppm error). Spectroscopic data are in accordance with those reported in the literature.[197]

1-(2-Oxido-2-phenoxy-1,3,2-oxazaphosphinan-3-yl)prop-2-en-1-one (6-18a)



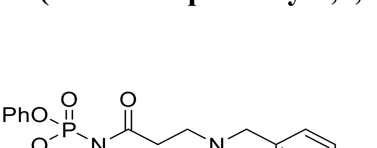
To a solution of 2-phenoxy-1,3,2-oxazaphosphinane 2-oxide **6-13a** (213 mg, 1.0 mmol) in dry THF (5.0 mL), was added acryl chloride (136 mg, 1.5 mmol) in a single portion, then NEt$_3$ (420 μL, 1.5 mmol) was added to the mixture. The reaction mixture was allowed to stir for 10 min a RT. The reaction mixture was then quenched with sat. aq. NaHCO$_3$ (10 mL) and the mixture was extracted with Et$_2$O (2 × 10 mL). The organic extracts dried over MgSO$_4$ and concentrated in vacuo. Purification by flash column chromatography (SiO$_2$, 1:1 hexane: ethyl acetate → ethyl acetate) afforded the title compound as a colorless oil (169 mg, 63%); $R_f = 0.48$ (ethyl acetate); ν_{max}/cm^{-1} (thin film) 2970, 1680, 1488, 1406, 1299, 1182, 1058, 1019, 925, 798, 692, 526; δ_H (400 MHz, CDCl$_3$) 7.33 – 7.22 (m, 3H, Ar-C**H**), 7.21 – 7.11 (m, 3H, Ar-C**H** + C**H**=CHH’), 6.34 (dd, *J* = 16.7, 1.9 Hz, 1H, CH=C**H**H’), 5.69 (dd, *J* = 10.4, 1.9 Hz, 1H, CH=CH**H’**), 4.69 – 4.55 (m, 1H, C**H**$_2$), 4.52 – 4.37 (m, 2H, C**H₂**), 3.32 (ddt, *J* = 14.1, 11.7, 2.7 Hz, 1H, C**H₂**), 2.15 – 1.88 (m, 2H, C**H₂**); δ_C (100 MHz, CDCl$_3$) 166.7 (d, *J* = 9.0 Hz, **C**O), 149.8 (d, *J* = 7.2 Hz, Ar-**C**), 130.5 (COCH=**C**H$_2$), 130.0 (CO**C**H=CH$_2$), 129.8 (d, *J* = 1.0 Hz, Ar-**C**H), 125.6 (d, *J* = 1.1 Hz, Ar-**C**H), 119.8 (d, *J* = 4.9 Hz, Ar-**C**H), 70.9 (d, *J* = 8.6 Hz, O**C**H$_2$), 42.2 (**C**H$_2$), 25.7 (d, *J* = 5.2 Hz, **C**H$_2$); δ_P (162 MHz, CDCl$_3$) –8.8 (PhO**P**=O); HRMS (ESI): calcd. for $C_{12}H_{14}NNaO_3P$, 274.0604. Found: $[MNa]^+$, 274.0607 (–1.3 ppm error).

3-(Benzylamino)-1-(2-oxido-2-phenoxy-1,3,2-oxazaphosphinan-3-yl)propan-1-one (6-20a)



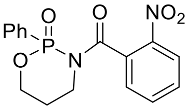
To a solution of 1-(2-oxido-2-phenoxy-1,3,2-oxazaphosphinan-3-yl) prop-2-en-1-one **6-18a** (78 mg, 0.29 mmol) in dry THF (0.6 mL), was added benzylamine (38 mg, 0.36 mmol, 1.2 eq) in a single portion. The reaction mixture was allowed to stir for overnight at RT. Purification by flash column chromatography (SiO_2, 10: 1 dichloromethane: methanol) afforded the title compound as a colorless oil (81 mg, 75%); R_f = 0.23 (10:1 dichloromethane: methanol); ν_{max}/cm^{-1} (thin film) 2925, 1687, 1488, 1300, 1202, 1174, 1026, 926, 800, 691, 531; δ_H (400 MHz, $CDCl_3$) 7.34 – 7.15 (m, 10H, Ar-C**H**), 4.65 – 4.53 (m, 1H, C**H**$_2$), 4.48 – 4.35 (m, 2H, OC**H**$_2$), 3.72 (s, 2H, NHC**H**$_2$Ph), 3.34 – 3.12 (m, 2H, C**H**$_2$), 2.90 – 2.70 (m, 3H, C**H**$_2$ + C**H**$_2$), 2.13 – 1.84 (m, 3H, N**H** + C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 173.6 (d, *J* = 9.6 Hz, **C**O), 149.9 (d, *J* = 7.3 Hz, Ar-**C**), 140.2 (Ar-**C**H), 130.1 (Ar-**C**H), 128.3 (Ar-**C**H), 128.0 (Ar-**C**H), 126.8 (Ar-**C**H), 125.6 (Ar-**C**H), 119.9 (d, *J* = 4.9 Hz, Ar-**C**H), 70.8 (d, *J* = 8.6 Hz, O**C**H$_2$), 53.6 (**C**H$_2$), 44.7 (**C**H$_2$), 41.9 (**C**H$_2$), 37.4 (**C**H$_2$), 25.7 (d, *J* = 5.2 Hz, **C**H$_2$); δ_P (162 MHz, $CDCl_3$) –8.4 (PhO**P**=O); HRMS (ESI): calcd. for $C_{19}H_{24}N_2O_4P$, 375.1468. Found: [MH]$^+$, 375.1473 (–1.2 ppm error).

3-((4-Bromobenzyl)amino)-1-(2-oxido-2-phenoxy-1,3,2-oxazaphosphinan-3-yl)propan-1-one (6-20b)



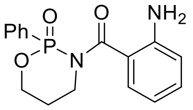
To a solution of 1-(2-oxido-2-phenoxy-1,3,2-oxazaphosphinan-3-yl) prop-2-en-1-one **6-18a** (150 mg, 0.55 mmol) in dry THF (1.1 mL), was added 4-bromobenzylamine (139.5 mg, 0.66 mmol, 1.2 eq) in a single portion. The reaction mixture was allowed to stir for overnight at RT. Purification by flash column chromatography (SiO_2, 20: 1 dichloromethane: methanol) afforded the title compound as a colorless oil (205 mg, 82%); R_f = 0.52 (10:1 dichloromethane: methanol); ν_{max}/cm^{-1} (thin film) 3410, 1591, 1489, 1392, 1265, 1209, 1047, 1025, 1005, 920, 823, 762, 511; δ_H (400 MHz, $CDCl_3$) 7.40 – 7.29 (m, 4H, Ar-C**H**), 7.22 – 7.10 (m, 5H, Ar-C**H**), 4.61 (ddtd, *J* = 15.0, 13.7, 4.2, 1.2 Hz, 1H, C**H**$_2$), 4.44 (dddt, *J* = 12.9, 7.1, 3.7, 1.6 Hz, 2H, OC**H$_2$**), 3.67 (s, 2H, NHC**H$_2$**Ph), 3.30 (ddt, *J* = 14.0, 11.5, 2.8 Hz, 1H, C**H**$_2$), 3.23 – 3.12 (m, 1H, C**H**$_2$), 2.87 – 2.75 (m, 3H, C**H$_2$** + C**H**$_2$), 2.11 – 1.98 (m, 1H, N**H**), 1.95 – 1.81 (m, 2H, C**H$_2$**); δ_C (100 MHz, $CDCl_3$) 173.6 (d, *J* = 9.6 Hz, **C**O), 149.9 (d, *J* = 7.2 Hz, Ar-**C**), 139.3 (Ar-**C**), 131.3 (Ar-**C**H), 130.1 (Ar-**C**H), 129.8 (Ar-**C**H), 125.7 (Ar-**C**H), 120.5 (Ar-**C**), 119.9 (d, *J* = 4.9 Hz, Ar-**C**H), 70.8 (d, *J* = 8.5 Hz, O**C**H$_2$), 52.9 (N**C**H$_2$Ph), 44.6 (**C**H$_2$), 42.0 (**C**H$_2$), 37.4 (**C**H$_2$), 25.7 (d, *J* = 5.2 Hz, **C**H$_2$); δ_P (162 MHz, $CDCl_3$) –8.4 (PhO**P**=O); HRMS (ESI): calcd. for $C_{19}H_{23}{}^{79}BrN_2O_4P$, 453.0573. Found: $[MH]^+$, 453.0575 (–0.3 ppm error).

(2-Nitrophenyl)(2-oxido-2-phenyl-1,3,2-oxazaphosphinan-3-yl)methanone (6-22)



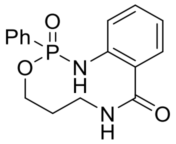
2-Phenyl-1,3,2-oxazaphosphinane 2-oxide **6-13** (197.2 mg, 1.0 mmol) was dissolved in THF (5 mL) and the temperature was lowered –78 °C (dry ice/acetone bath). *n*-BuLi (2.5 M in hexanes, 0.48 mL, 1.2 mmol, 1.2 eq) was added dropwise by syringe and the reaction was allowed to stir at –78 °C. After 1 hour, a solution of 2-nitrobenzoyl chloride (1.5 mmol, 1.5 equiv. prepared using the general procedure with 2-nitrobenzoic acid) in THF (5 mL) was added slowly to the stirring reaction mixture. The reaction was allowed to warm to room temperature overnight before the addition of sat. aq. $NaHCO_3$ solution (20 mL). The aqueous layer was extracted with EtOAc (2 × 10 mL) and the combined organic layers were dried ($MgSO_4$). After filtration, the solvent was then concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, ethyl acetate) afforded the title compound as a colorless oil (308 mg, 89%). R_f = 0.15 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3062, 1667, 1527, 1440, 1346, 1321, 1250, 1129, 1058, 997, 908, 861, 724, 701, 578; δ_H (400 MHz, $CDCl_3$ at 50 °C) 7.91 (d, *J* = 7.7 Hz, 1H, Ar-C**H**), 7.43 – 7.33 (m, 5H, Ar-C**H**), 7.26 – 7.08 (m, 3H, Ar-C**H**), 4.58 – 4.14 (m, 3H, OC**H**$_2$ + C**H**$_2$), 3.78 – 3.45 (m, 1H, C**H**$_2$), 2.42 – 2.23 (m, 1H, C**H**$_2$), 2.16 – 2.01 (m, 1H, C**H**$_2$); δ_C (100 MHz, $CDCl_3$ at 50 °C) 168.5 (d, *J* = 8.0 Hz, **C**O), 145.3 (Ar-**C**), 133.4 (Ar-**C**H), 132.8 (d, *J* = 3.2 Hz, Ar-**C**H), 132.2 (Ar-**C**), 131.5 (d, *J* = 10.7 Hz, Ar-**C**H), 130.1 (Ar-**C**H), 128.8 (br, Ar-**C**H), 128.3 (d, *J* = 15.4 Hz, Ar-**C**H), 128.2 (d, *J* = 180.5 Hz, Ar-**C**), 123.9 (Ar-**C**H), 66.6 (d, *J* = 8.1 Hz, O**C**H$_2$), 41.7 (br, **C**H$_2$), 25.3 (d, *J* = 6.0 Hz, **C**H$_2$); δ_P (162 MHz, $CDCl_3$ at 50 °C) 13.9 (Ph**P**=O); HRMS (ESI): calcd. for $C_{16}H_{15}N_2NaO_5P$, 369.0611. Found: $[MNa]^+$, 369.0608 (0.6 ppm error).

(2-Aminophenyl)(2-oxido-2-phenyl-1,3,2-oxazaphosphinan-3-yl)methanone (6-23)



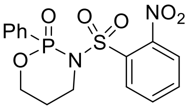
(2-Nitrophenyl)(2-oxido-2-phenyl-1,3,2-oxazaphosphinan-3-yl)methanone **6-22** (200 mg, 0.56 mmol) was dissolved in dry EtOAc (6.0 mL) and placed under an argon atmosphere. Palladium on carbon 60 mg, Pd 10% on carbon) was added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at RT under a slight positive pressure of hydrogen (balloon) for 3 h. The reaction was then purged with argon, filtered through Celite, washed with ethyl acetate where the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, ethyl acetate) afforded the title compound as a colorless oil (180 mg, 77%). R_f = 0.14 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3465, 3440, 2970, 1649, 1621, 1491, 1440, 1326, 1236, 1129, 1056, 994, 748, 725, 693, 504; δ_H (400 MHz, $CDCl_3$) δ 7.66 – 7.52 (m, 2H, Ar-C**H**), 7.41 – 7.30 (m, 1H, Ar-C**H**), 7.26 – 7.17 (m, 3H, Ar-C**H**), 6.96 (ddd, *J* = 8.5, 7.3, 1.6 Hz, 1H, Ar-C**H**), 6.51 (td, *J* = 7.6, 1.1 Hz, 1H, Ar-C**H**), 6.35 (dd, *J* = 8.2, 1.0 Hz, 1H, Ar-C**H**), 4.63 – 4.44 (m, 3H, N**H**$_2$ + OC**H**$_2$), 4.21 (dddd, *J* = 18.9, 10.7, 8.0, 5.8 Hz, 1H, OC**H**$_2$), 3.92 – 3.75 (m, 2H, C**H**$_2$), 2.37 – 2.25 (m, 1H, C**H**$_2$), 2.16 – 2.04 (m, 1H, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 173.3 (d, *J* = 5.5 Hz, **C**O), 147.0 (Ar-**C**), 132.3 (d, *J* = 3.1 Hz, Ar-**C**H), 132.2 (Ar-**C**H), 131.5 (d, *J* = 10.7 Hz, Ar-**C**H), 129.2 (Ar-**C**H), 129.2 (Ar-**C**), 128.3 (d, *J* = 181.5 Hz, Ar-**C**), 127.9 (d, *J* = 15.5 Hz, Ar-**C**H), 117.2 (d, *J* = 2.3 Hz, Ar-**C**), 116.2 (d, *J* = 10.7 Hz, Ar-**C**H), 65.8 (d, *J* = 7.6 Hz, O**C**H$_2$), 43.8 (**C**H$_2$), 25.5 (d, *J* = 7.3 Hz, **C**H$_2$); δ_P (162 MHz, $CDCl_3$) 15.7 (Ph**P**=O); HRMS (ESI): calcd. for $C_{16}H_{17}N_2NaO_3P$, 339.0869. Found: $[MNa]^+$, 339.0864 (1.4 ppm error).

2-Phenyl-1,4,5,6,7-pentahydrobenzo[*d*][1,3,7,2]oxadiazaphosphecin-8-one 2-oxide (6-24)



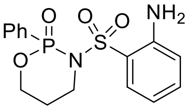
(2-Aminophenyl)(2-oxido-2-phenyl-1,3,2-oxazaphosphinan-3-yl)methanone **6-23** (150 mg, 0.47 mmol) was dissolved in THF (5.0 mL) and NaH (60% in Paraffin oil, 30 mg, 0.75 mmol, 1.5 eq) was added, the mixture was stirred at RT for 1 h. Quenched with sat. NH_4Cl aq. (5 mL), extracted with EtOAc (3 × 10 mL) and the combined organic layers were dried ($MgSO_4$). After filtration, the solvent was then concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 9:1 ethyl acetate: methanol) afforded the title compound (as a 3:2 mixture of rotamers in solution in $CDCl_3$) as a colorless oil (66 mg, 44%); R_f = 0.15 (9:1 ethyl acetate: methanol); ν_{max}/cm^{-1} (thin film) 3152, 1643, 1537, 1454, 1310, 1207, 1126, 1046, 989, 752, 695, 533; δ_H (400 MHz, $CDCl_3$) 8.29 (t, *J* = 6.4 Hz, 1H, Ar-C**H**, minor rotamer), 7.96 (d, *J* = 6.0 Hz, 1H, Ar-C**H**, minor rotamer), 7.91 – 7.76 (m, 1H, Ar-C**H**, both rotamers), 7.62 – 7.30 (m, 7H, Ar-C**H**, both rotamers), 7.24 – 7.01 (m, 5H, Ar-C**H**, both rotamers), 6.94 (td, *J* = 7.7, 1.7 Hz, 1H, N**H**, minor rotamer), 6.76 (dt, *J* = 7.4, 1.6 Hz, 1H, N**H**, major rotamer), 6.72 (d, *J* = 3.9 Hz, 1H, CON**H**, major rotamer), 6.31 (d, *J* = 8.0 Hz, 1H, CON**H**, minor rotamer), 4.93 (qd, *J* = 10.7, 4.1 Hz, 1H, OC**H**$_2$, minor rotamer), 4.65 (dtd, *J* = 10.6, 9.1, 1.2 Hz, 1H, OC**H**$_2$, major rotamer), 4.33 – 4.16 (m, 1H, OC**H**$_2$, major rotamer), 4.06 – 3.01 (m, 2H, C**H$_2$** both rotamers + OC**H**$_2$ minor rotamer), 2.66 – 1.64 (m, 2H, C**H$_2$**, both rotamers); δ_C (100 MHz, $CDCl_3$) 173.5 (NH**C**O, minor rotamer), 169.1 (NH**C**O, major rotamer), 136.4 (d, *J* = 4.3 Hz, Ar-**C**, minor rotamer),136.0 (d, *J* = 2.9 Hz, Ar-**C**, major rotamer), 133.6 (Ar-**C**, both rotamers), 132.3 (Ar-C**H**, both rotamers), 132.1 (d, *J* = 3.1 Hz, Ar-C**H**, both rotamers), 131.9 (d, *J* = 9.5 Hz, Ar-C**H**, minor rotamer), 131.3 (Ar-C**H**, both rotamers), 130.9 (d, *J* = 9.6 Hz, Ar-C**H**, major rotamer), 130.8 (d, *J* = 182.0 Hz, Ar-**C**, minor rotamer), 129.7 (d, *J* = 1.9 Hz, Ar-C**H**, both rotamers), 129.2 (Ar-C**H**, both rotamers), 129.1 (d, *J* = 175.8 Hz, Ar-**C**, major rotamer), 128.5 (d, *J* = 14.7 Hz, Ar-C**H**, minor rotamer), 128.2 (d, *J* = 14.6 Hz, Ar-C**H**, major rotamer), 127.7 (d, *J* = 4.8 Hz, Ar-C**H**, major rotamer), 126.5 (Ar-C**H**, minor rotamer), 126.4 (d, *J* = 2.1 Hz, Ar-C**H**, minor rotamer), 125.6 (d, *J* = 1.9 Hz, Ar-C**H**, major rotamer), 65.9 (d, *J* = 7.1 Hz, O**C**H_2, major rotamer), 58.7 (d, *J* = 5.7 Hz, O**C**H_2, minor rotamer), 39.4 (**C**H_2, minor rotamer), 39.1 (**C**H_2, major rotamer), 28.8 (d, *J* = 6.6 Hz, **C**H_2, minor rotamer), 27.3 (d, *J* = 5.1 Hz, **C**H_2, major rotamer); δ_P (162 MHz, $CDCl_3$) 20.7 (Ph**P**=O, major rotamer), 20.8 (Ph**P**=O, minor rotamer); HRMS (ESI): calcd. for $C_{16}H_{17}N_2NaO_3P$, 339.0869. Found: $[MNa]^+$, 339.0866 (1.0 ppm error).

3-((2-Nitrophenyl)sulfonyl)-2-phenyl-1,3,2-oxazaphosphinane 2-oxide (6-25)



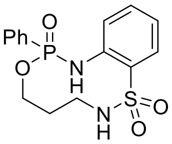
2-Phenyl-1,3,2-oxazaphosphinane 2-oxide **6-13** (197.2 mg, 1.0 mmol) was dissolved in dry THF (8 mL) and the temperature was lowered to –78 °C (dry ice/acetone bath). *n*-BuLi (2.5 M in hexanes, 0.48 mL, 1.2 mmol, 1.2 eq) was added dropwise by syringe and the reaction was allowed to stir at –78 °C. After 1 hour, a solution of 2-nitrobenzenesulfonyl chloride **5-14** (332.4 mg, 1.5 mmol, 1.5 eq) in THF (2.0 mL) was transferred to the stirring reaction mixture dropwise by syringe. The reaction was allowed to warm to room temperature overnight before the addition of sat. aq. $NaHCO_3$ solution (15 mL). The aqueous layer was extracted with EtOAc (2 × 15 mL), the combined organic layers were dried ($MgSO_4$). After filtration, the solvent was removed by rotary evaporation. Purification by flash column chromatography (SiO_2, ethyl acetate) afforded the title compound as a colorless oil (93 mg, 25%). R_f = 0.30 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3096, 1542, 1439, 1362, 1249, 1169, 1129, 1056, 987, 845, 782, 745, 694, 582, 511; δ_H (400 MHz, $CDCl_3$) 8.44 – 8.38 (m, 1H, Ar-C**H**), 7.92 – 7.83 (m, 2H, Ar-C**H**), 7.71 – 7.54 (m, 4H, Ar-C**H**), 7.53 – 7.42 (m, 2H, Ar-C**H**), 4.52 – 4.36 (m, 1H, OC**H**$_2$), 4.29 – 4.05 (m, 2H, C**H**$_2$ + OC**H**$_2$), 3.57 (ddt, *J* = 13.8, 9.9, 3.8 Hz, 1H, C**H**$_2$), 2.43 – 2.23 (m, 1H, C**H**$_2$), 2.10 – 1.95 (m, 1H, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 148.0 (Ar-**C**), 134.3 (Ar-**C**H), 133.6 (Ar-**C**), 133.3 (d, *J* = 3.2 Hz, Ar-**C**H), 133.2 (Ar-**C**H), 132.2 (Ar-**C**H), 131.9 (d, *J* = 11.1 Hz, Ar-**C**H), 128.9 (d, *J* = 15.8 Hz, Ar-CH), 127.7 (d, *J* = 178.0 Hz, Ar-**C**), 123.7 (Ar-**C**H), 67.5 (d, *J* = 7.8 Hz, O**C**H$_2$), 46.2 (**C**H$_2$), 26.0 (d, *J* = 4.6 Hz, **C**H$_2$); δ_P (162 MHz, CDCl$_3$) 14.5 (Ph**P**=O); HRMS (ESI): calcd. for $C_{15}H_{15}N_2NaO_6PS$, 405.0281. Found: [MNa]$^+$, 405.0291 (–2.5 ppm error).

3-((2-Aminophenyl)sulfonyl)-2-phenyl-1,3,2-oxazaphosphinane 2-oxide (6-26)



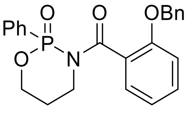
3-((2-Nitrophenyl)sulfonyl)-2-phenyl-1,3,2-oxazaphosphinane 2-oxide **6-25** (85 mg, 0.22 mmol) was dissolved in dry EtOAc (3.0 mL) and placed under an argon atmosphere. Palladium on carbon (30 mg, Pd 10% on carbon) was added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at RT under a slight positive pressure of hydrogen (balloon) for 2 h. The reaction was then purged with argon, filtered through Celite, washed with ethyl acetate where the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO$_2$, ethyl acetate) afforded the title compound as a colorless oil (60 mg, 77%). R_f = 0.44 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3354, 3241, 2926, 1603, 1485, 1454, 1332, 1246, 1153, 1130, 1092, 994, 902, 850, 749, 696, 595, 508; δ_H (400 MHz, CDCl$_3$) 7.99 – 7.85 (m, 2H, Ar-C**H**), 7.70 (dd, *J* = 8.2, 1.6 Hz, 1H, Ar-C**H**), 7.61 – 7.54 (m, 1H, Ar-C**H**), 7.53 – 7.45 (m, 2H, Ar-C**H**), 7.29 (ddd, *J* = 8.5, 7.1, 1.6 Hz, 1H, Ar-C**H**), 6.72 (dd, *J* = 8.3, 1.1 Hz, 1H, Ar-C**H**), 6.65 (ddd, *J* = 8.2, 7.1, 1.1 Hz, 1H, Ar-C**H**), 5.69 (s, 2H, N**H$_2$**), 4.46 – 4.37 (m, 1H, OC**H$_2$**), 4.17 (dddd, *J* = 15.4, 11.1, 7.2, 5.7 Hz, 1H, OC**H$_2$**), 3.64 – 3.43 (m, 2H, C**H$_2$**), 2.07 – 1.91 (m, 2H, C**H$_2$**); δ_C (100 MHz, CDCl$_3$) 146.7 (Ar-**C**), 135.3 (Ar-**C**H), 133.0 (d, *J* = 3.3 Hz, Ar-**C**H), 131.8 (d, *J* = 11.3 Hz, Ar-**C**H), 131.1 (Ar-**C**H), 129.5(d, *J* = 183.5 Hz, Ar-**C**), 128.8 (d, *J* = 16.0 Hz, Ar-**C**H), 117.9 (Ar-**C**H), 117.2 (Ar-**C**), 116.0 (Ar-**C**H), 66.0 (d, *J* = 8.1 Hz, O**C**H$_2$), 45.0 (**C**H$_2$), 25.7 (d, *J* = 5.3 Hz, **C**H$_2$); δ_P (162 MHz, CDCl$_3$) 13.7 (Ph**P**=O); HRMS (ESI): calcd. for $C_{15}H_{17}N_2NaO_4PS$, 375.0539. Found: [MNa]$^+$, 375.0530 (2.3 ppm error).

2-Phenyl-1,4,5,6,7-pentahydrobenzo[*d*][1,6,3,7,2]oxathiadiazaphosphecine 2,8,8-trioxide (6-27)



3-((2-Aminophenyl)sulfonyl)-2-phenyl-1,3,2-oxazaphosphinane 2-oxide **6-26** (60 mg, 0.17 mmol) was dissolved in THF (2.0 mL) and NaH (60% in Paraffin oil, 12 mg, 0.3 mmol, 1.5 eq) was added, the mixture was stirred at RT for 1 h. Quenched with sat. NH_4Cl aq. (5 mL), extracted with EtOAc (3 × 10 mL) and the combined organic layers were dried ($MgSO_4$). After filtration, the solvent was then concentrated *in vacuo* to give the title compound as a colorless oil (55 mg, 92%); R_f = 0.25 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3301, 3135, 2923, 1594, 1481, 1459, 1315, 1273, 1229, 1149, 1127, 1052, 975, 926, 734, 692, 606, 535; δ_H (400 MHz, $CDCl_3$) 7.95 – 7.83 (m, 3H, Ar-C**H**), 7.75 (d, *J* = 8.2 Hz, 1H, Ar-C**H**), 7.64 – 7.57 (m, 1H, Ar-C**H**), 7.55 – 7.44 (m, 3H, Ar-C**H**), 7.18 – 7.09 (m, 1H, Ar-C**H**), 6.15 (d, *J* = 9.3 Hz, 1H, N**H**), 5.38 (dd, *J* = 8.4, 4.1 Hz, 1H, SO_2N**H**), 4.31 – 4.20 (m, 1H, OC**H**$_2$), 3.99 – 3.87 (m, 1H, OC**H**$_2$), 3.68 (dddd, *J* = 14.6, 11.7, 8.4, 3.6 Hz, 1H, C**H**$_2$), 3.35 (dq, *J* = 14.3, 4.2 Hz, 1H, C**H**$_2$), 1.90 – 1.77 (m, 1H, C**H**$_2$), 1.67 – 1.50 (m, 1H, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 137.8 (d, *J* = 2.5 Hz, Ar-**C**), 134.0 (Ar-**C**H), 133.1 (d, *J* = 3.1 Hz, Ar-**C**H), 132.7 (d, *J* = 5.7 Hz, Ar-**C**), 131.2 (d, *J* = 10.1 Hz, Ar-CH), 129.5 (d, *J* = 185.8 Hz, Ar-**C**), 128.9 (Ar-**C**H), 128.8 (d, *J* = 15.0 Hz, Ar-**C**H), 126.1 (Ar-**C**H), 123.6 (Ar-**C**H), 61.8 (d, *J* = 7.0 Hz, O**C**H$_2$), 40.3 (**C**H$_2$), 29.3 (d, *J* = 4.3 Hz, **C**H$_2$); δ_P (162 MHz, $CDCl_3$) 19.3 (Ph**P**=O); HRMS (ESI): calcd. for $C_{15}H_{17}N_2NaO_4PS$, 375.0539. Found: $[MNa]^+$, 375.0532 (1.9 ppm error).

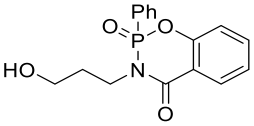
(2-(Benzyloxy)phenyl)(2-oxido-2-phenyl-1,3,2-oxazaphosphinan-3-yl)methanone (6-28)



2-Phenyl-1,3,2-oxazaphosphinane 2-oxide **6-13** (197.2 mg, 1.0 mmol) was dissolved in dry THF (5 mL) and the temperature was lowered –78 °C (dry ice/acetone bath). *n*-

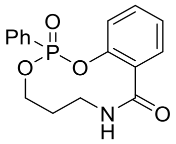
BuLi (2.5 M in hexanes, 0.48 mL, 1.2 mmol, 1.2 eq) was added dropwise by syringe and the reaction was allowed to stir at –78 °C. After 1 hour, a solution of acid chloride **2-14** (1.5 mmol, 1.5 equiv. prepared using the general procedure with 2-benzyloxybenzoic acid) in dry THF (5 mL) was added slowly to the stirring reaction mixture. The reaction was allowed to warm to room temperature overnight before the addition of sat. aq. $NaHCO_3$ solution (20 mL). The aqueous layer was extracted with EtOAc (2 × 10 mL) and the combined organic layers were dried ($MgSO_4$). After filtration, the solvent was then concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, ethyl acetate) afforded the title compound as a colorless oil (357 mg, 88%). R_f = 0.25 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3065, 1662, 1599, 1488, 1449, 1344, 1243, 1132, 1059, 996, 746, 724, 694, 583, 502; δ_H (400 MHz, $CDCl_3$ at 50 °C) 7.49 (dd, *J* = 13.8, 7.4 Hz, 2H, Ar-C**H**), 7.41 – 7.23 (m, 7H, Ar-C**H**), 7.22 – 7.04 (m, 3H, Ar-C**H**), 6.84 (t, *J* = 6.7 Hz, 1H, Ar-C**H**), 6.70 – 6.60 (m, 1H, Ar-C**H**), 4.93 – 4.61 (m, 2H, OC**H**$_2$), 4.44 (dq, *J* = 10.8, 5.3 Hz, 1H, C**H**$_2$), 4.22 – 4.04 (m, 1H, C**H**$_2$), 3.95 – 3.67 (m, 2H, C**H**$_2$), 2.23 – 1.91 (m, 2H, C**H**$_2$); δ_C (100 MHz, $CDCl_3$ at 50 °C) 170.7 (d, *J* = 5.8 Hz, **C**O), 154.8 (Ar-**C**), 136.4 (Ar-**C**), 131.9 (Ar-**C**H), 131.7 (Ar-**C**H), 131.2 (Ar-**C**H), 129.7 (Ar-**C**), 129.0 (Ar-**C**H), 128.3 (Ar-**C**H), 127.9 (Ar-**C**H), 127.6 (Ar-**C**H), 127.2 (Ar-**C**H), 125.2 (Ar-**C**), 120.5 (d, *J* = 8.2 Hz, Ar-**C**H), 111.7 (Ar-**C**H), 69.9 (O**C**H$_2$), 65.7 (d, *J* = 5.7 Hz, O**C**H$_2$), 43.0 (**C**H$_2$), 25.5 (d, *J* = 6.5 Hz, **C**H$_2$); δ_P (162 MHz, $CDCl_3$) 14.8 (Ph**P**=O); HRMS (ESI): calcd. for $C_{23}H_{22}NNaO_4P$, 430.1179. Found: $[MNa]^+$, 430.1186 (–1.7 ppm error).

3-(3-Hydroxypropyl)-2-phenyl-3-hydrobenzo[*e*][1,3,2]oxazaphosphinin-4-one 2-oxide (6-30)



(2-(Benzyloxy)phenyl)(2-oxido-2-phenyl-1,3,2-oxazaphosphinan-3-yl)methanone **6-28** (160 mg, 0.39 mmol) was dissolved in EtOAc (4.0 mL) and placed under an argon atmosphere. Palladium on carbon (40 mg, Pd 10% on carbon) was added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at RT under a slight positive pressure of hydrogen (balloon) for 2 h. The reaction was then purged with argon, filtered through Celite, washed with ethyl acetate where the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, ethyl acetate) afforded the title compound as a colorless oil (110 mg, 90%). R_f = 0.34 (ethyl acetate); δ_H (400 MHz, $CDCl_3$) 8.11 (dd, *J* = 7.9, 1.7 Hz, 1H, Ar-C**H**), 7.75 – 7.68 (m, 2H, Ar-C**H**), 7.62 – 7.52 (m, 2H, Ar-C**H**), 7.49 – 7.42 (m, 2H, Ar-C**H**), 7.27 (td, *J* = 7.9, 1.0 Hz, 1H, Ar-C**H**), 7.09 (d, *J* = 8.3 Hz, 1H, Ar-C**H**), 3.94 (ddt, *J* = 14.0, 12.0, 5.7 Hz, 1H, NC**H**$_2$), 3.64 (ddd, *J* = 12.1, 8.5, 3.8 Hz, 1H, C**H**$_2$OH), 3.58 – 3.36 (m, 3H, NC**H**$_2$ + C**H**$_2$OH + CH$_2$O**H**), 1.98 – 1.70 (m, 2H, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 162.9 (d, *J* = 4.8 Hz, **C**O), 150.7 (d, *J* = 7.4 Hz, Ar-**C**), 135.7 (Ar-**C**H), 134.1 (d, *J* = 3.2 Hz, Ar-**C**H), 131.7 (d, *J* = 11.3 Hz, Ar-**C**H), 130.1 (Ar-**C**H), 129.2 (d, *J* = 15.8 Hz, Ar-**C**H), 126.6 (d, *J* = 178.4 Hz, Ar-**C**), 125.0 (Ar-**C**H), 118.6 (d, *J* = 9.3 Hz, Ar-**C**H), 117.1 (d, *J* = 2.5 Hz, Ar-**C**), 58.3 (**C**H$_2$OH), 39.3 (d, *J* = 4.6 Hz, N**C**H$_2$), 31.2 (**C**H$_2$); δ_P (162 MHz, $CDCl_3$) 17.7 (Ph**P**=O); HRMS (ESI): calcd. for $C_{16}H_{16}NNaO_4P$, 340.0709. Found: [MNa]$^+$, 340.0712 (–1.0 ppm error).

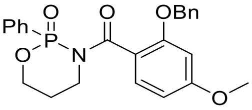
2-Phenyl-4,5,6,7-tetrahydro-8*H*-benzo[*d*][1,3,7,2]dioxazaphosphecin-8-one 2-oxide (6-31)



3-(3-Hydroxypropyl)-2-phenyl-3-hydrobenzo[e][1,3,2]oxazaphosphinin-4-one 2-oxide **6-30** (150 mg, 0.48 mmol) was dissolved in chloroform (5.0 mL) and triethylamine (700 µL, 5.0 mmol, 10 eq) added, the mixture was stirred for 18 h at RT, then reduced *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 hexane: ethyl acetate → ethyl acetate) afforded the *title compound* as a colorless oil (126 mg, 84%). R_f = 0.22 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3434, 2938, 1683, 1439, 1337, 1247, 1129, 1025, 995, 750, 727, 694, 540; δ_H (400 MHz, $CDCl_3$) 7.77 – 7.70 (m, 2H, Ar-C**H**), 7.61 (dd, *J* = 7.4, 2.0 Hz, 1H, Ar-C**H**), 7.58 – 7.48 (m, 1H, Ar-C**H**), 7.46 –

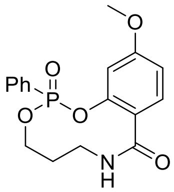
7.35 (m, 2H, Ar-C**H**), 7.24 – 7.08 (m, 3H, Ar-C**H** + N**H**CO), 6.77 – 6.62 (m, 1H, Ar-C**H**), 4.74 – 4.55 (m, 1H, OC**H**$_2$), 4.31 (td, *J* = 12.4, 6.5 Hz, 1H, OC**H**$_2$), 3.96 (td, *J* = 13.0, 5.1 Hz, 1H, NHC**H**$_2$), 3.40 (ddt, *J* = 13.9, 9.3, 4.5 Hz, 1H, NHC**H**$_2$), 2.37 – 2.21 (m, 1H, C**H**$_2$), 2.08 – 1.94 (m, 1H, C**H**$_2$); δ$_C$ (100 MHz, CDCl$_3$) 167.0 (**C**O), 147.6 (d, *J* = 9.1 Hz, Ar-**C**), 133.0 (d, *J* = 3.1 Hz, Ar-**C**H), 131.2 (d, *J* = 10.2 Hz, Ar-**C**H), 129.9 (d, *J* = 2.5 Hz, Ar-**C**), 129.6 (d, *J* = 1.5 Hz, Ar-**C**H), 128.6 (d, *J* = 15.9 Hz, Ar-**C**H), 127.3 (d, *J* = 196.5 Hz, Ar-**C**), 125.8 (d, *J* = 1.5 Hz, Ar-**C**H), 122.2 (d, *J* = 3.7 Hz, Ar-**C**H), 67.9 (d, *J* = 7.8 Hz, O**C**H$_2$), 38.9 (**C**H$_2$), 28.9 (d, *J* = 2.7 Hz, **C**H$_2$); δ$_P$ (162 MHz, CDCl$_3$) 17.1 (Ph**P**=O); HRMS (ESI): calcd. for $C_{16}H_{16}NNaO_4P$, 340.0709. Found: $[MNa]^+$, 340.0710 (–0.3 ppm error).

(2-(Benzyloxy)-4-methoxyphenyl) (2-oxido-2-phenyl-1,3,2-oxazaphosphinan-3-yl) methanone (6-28a)



2-Phenyl-1,3,2-oxazaphosphinane 2-oxide **6-13** (197.2 mg, 1.0 mmol) was dissolved in dry THF (5 mL) and the temperature was lowered –78 °C (dry ice/acetone bath). *n*-BuLi (2.5 M in hexanes, 0.48 mL, 1.2 mmol, 1.2 eq) was added dropwise by syringe and the reaction was allowed to stir at –78 °C. After 1 hour, a solution of acid chloride (1.5 mmol, 1.5 equiv. prepared using the general procedure with the acid **S1**) in THF (5 mL) was added slowly to the stirring reaction mixture. The reaction was allowed to warm to room temperature overnight before the addition of sat. aq. NaHCO$_3$ solution (20 mL). The aqueous layer was extracted with EtOAc (2 × 10 mL) and the combined organic layers were dried (MgSO$_4$). After filtration, the solvent was then concentrated *in vacuo*. Purification by flash column chromatography (SiO$_2$, ethyl acetate) afforded the title compound as a colorless oil (335 mg, 77%). R$_f$ = 0.20 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 2943, 1656, 1608, 1505, 1440, 1341, 1310, 1250, 1166, 1137, 997, 747, 723, 695, 503; δ$_H$ (400 MHz, CDCl$_3$) 7.51 (dd, *J* = 14.4, 7.6 Hz, 1H, Ar-C**H**), 7.44 – 7.31 (m, 7H, Ar-C**H**), 7.25 – 7.14 (m, 2H, Ar-C**H**), 6.43 (d, *J* = 7.9 Hz, 1H, Ar-C**H**), 6.19 (s, 1H, Ar-C**H**), 4.87 (d, *J* = 11.2 Hz, 1H, OC**H**$_2$Ph), 4.76 – 4.63 (m, 1H, OC**H**$_2$Ph), 4.52 (dq, J = 10.6, 5.4 Hz, 1H, OC**H**$_2$), 4.18 (dddd, J = 18.7, 10.7, 7.8, 5.7 Hz, 1H, OC**H**$_2$), 3.95 – 3.81 (m, 2H, C**H**$_2$), 3.74 (s, 3H, OC**H**$_3$), 2.34 – 2.20 (m, 1H, C**H**$_2$), 2.14 – 1.96 (m, 1H, C**H**$_2$); δ_C (100 MHz, CDCl$_3$) 170.9 (d, J = 4.8 Hz, **C**O), 162.6 (Ar-**C**), 156.4 (Ar-**C**), 136.2 (Ar-**C**), 132.2 (d, J = 2.9 Hz, Ar-**C**H), 131.9 (Ar-**C**H), 131.8 (Ar-**C**H), 131.0 (Ar-**C**), 128.6 (Ar-**C**H), 128.2 (Ar-**C**H), 128.0 (Ar-**C**H), 127.8 (Ar-**C**H), 127.5 (Ar-**C**H), 117.7 (Ar-**C**), 104.7 (Ar-**C**H), 99.2 (Ar-**C**H), 70.0 (O**C**H$_2$Ph), 66.0 (d, J = 7.7 Hz, O**C**H$_2$), 55.5 (O**C**H$_3$), 43.4 (**C**H$_2$), 25.7 (d, J = 7.0 Hz, **C**H$_2$); δ_P (162 MHz, CDCl$_3$) 14.9 (Ph**P**=O); HRMS (ESI): calcd. for $C_{24}H_{24}NNaO_5P$, 460.1284. Found: [MNa]$^+$, 460.1286 (–0.3 ppm error).

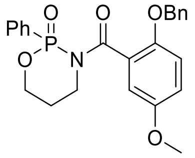
11-Methoxy-2-phenyl-4,5,6,7-tetrahydro-8*H*-benzo[*d*][1,3,7,2]dioxazaphosphecin-8-one 2-oxide (6-31a)



(2-(Benzyloxy)-4-methoxyphenyl) (2-oxido-2-phenyl-1,3,2-oxazaphosphinan-3-yl) methanone **6-28a** (270 mg, 0.60 mmol) was dissolved in dry EtOAc (6.0 mL) and placed under an argon atmosphere. Palladium on carbon (60 mg, Pd 10% on carbon) was then added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at RT 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 where the solvent was removed *in vacuo*. The crude was dissolved in chloroform (6.0 mL) and triethylamine (840 μL, 6.0 mmol, 10 eq) added, the mixture was stirred overnight at RT, then reduced *in vacuo*. Purification by flash column chromatography (SiO$_2$, ethyl acetate) afforded the *title compound* as a colorless oil (147 mg, 71%). R$_f$ = 0.16 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3305, 2964, 1656, 1613, 1500, 1441, 1259, 1131, 992, 978, 866, 696, 522; δ_H (400 MHz, CDCl$_3$) 7.77 – 7.70 (m, 2H, Ar-C**H**), 7.65 (d, J = 8.7 Hz, 1H, Ar-C**H**), 7.59 – 7.49 (m, 1H, Ar-C**H**), 7.48 – 7.37 (m, 2H, Ar-C**H**), 6.97 (t, J = 5.9 Hz, 1H, CON**H**), 6.71 (ddd, J = 8.7, 2.5, 1.1 Hz, 1H, Ar-

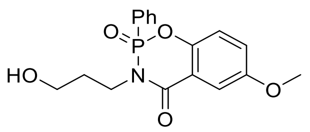
C**H**), 6.13 (dd, *J* = 2.4, 1.5 Hz, 1H, Ar-C**H**), 4.82 – 4.69 (m, 1H, OC**H**$_2$), 4.39 – 4.29 (m, 1H, OC**H**$_2$), 4.01 – 3.88 (m, 1H, C**H**$_2$), 3.61 (s, 3H, OC**H**$_3$), 3.55 – 3.40 (m, 1H, C**H**$_2$), 2.40 – 2.26 (m, 1H, C**H**$_2$), 2.10 – 1.99 (m, 1H, C**H**$_2$); δ_C (100 MHz, CDCl$_3$) 166.8 (**C**O), 162.3 (d, *J* = 1.1 Hz, Ar-**C**), 149.1 (d, *J* = 8.9 Hz, Ar-**C**), 133.1 (d, *J* = 3.2 Hz, Ar-**C**H), 131.4 (d, *J* = 10.1 Hz, Ar-**C**H), 131.4 (d, *J* = 1.6 Hz, Ar-**C**H), 128.7 (d, *J* = 15.9 Hz, Ar-**C**H), 127.2 (d, *J* = 196.3 Hz, Ar-**C**), 121.8 (d, *J* = 2.4 Hz, Ar-**C**H), 111.8 (d, *J* = 1.4 Hz, Ar-**C**H), 107.9 (d, *J* = 3.8 Hz, Ar-**C**H), 68.1 (d, *J* = 7.8 Hz, O**C**H$_2$), 55.6 (O**C**H$_3$), 39.1 (**C**H$_2$), 28.8 (d, *J* = 2.5 Hz, **C**H$_2$); δ_P (162 MHz, CDCl$_3$) 16.9 (Ph**P**=O); HRMS (ESI): calcd. for $C_{17}H_{18}NNaO_5P$, 370.0815. Found: [MNa]$^+$, 370.0819 (–1.1 ppm error).

(2-(Benzyloxy)-5-methoxyphenyl)(2-oxido-2-phenyl-1,3,2-oxazaphosphinan-3-yl)methanone (6-28b)



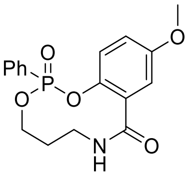
2-Phenyl-1,3,2-oxazaphosphinane 2-oxide **6-13** (197.2 mg, 1.0 mmol) was dissolved in dry THF (5 mL) and the temperature was lowered –78 °C (dry ice/acetone bath). *n*-BuLi (2.5 M in hexanes, 0.48 mL, 1.2 mmol, 1.2 eq) was added dropwise by syringe and the reaction was allowed to stir at –78 °C. After 1 hour, a solution of acid chloride (1.5 mmol, 1.5 equiv. prepared using the general procedure with the acid **S2**) in THF (5 mL) was added slowly to the stirring reaction mixture. The reaction was allowed to warm to room temperature overnight before the addition of sat. aq. NaHCO$_3$ solution (20 mL). The aqueous layer was extracted with EtOAc (2 × 10 mL) and the combined organic layers were dried (MgSO$_4$). After filtration, the solvent was then concentrated *in vacuo*. Purification by flash column chromatography (SiO$_2$, ethyl acetate) afforded the title compound as a colorless oil (335 mg, 77%). R$_f$ = 0.16 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 2937, 2236, 1660, 1498, 1418, 1340, 1247, 1216, 1040, 996, 910, 799, 719, 692, 612, 501; δ_H (400 MHz, CDCl$_3$) 7.57 – 7.45 (m, 2H, Ar-C**H**), 7.38 – 7.22 (m, 6H, Ar-C**H**), 7.19 – 7.07 (m, 2H, Ar-C**H**), 6.95 – 6.62 (m, 3H, Ar-C**H**), 4.90 – 4.56 (m, 2H, OC**H**$_2$Ph), 4.41 (dq, J = 10.6, 5.4 Hz, 1H, OC**H**$_2$), 4.22 – 3.99 (m, 1H, OC**H**$_2$), 3.92 – 3.65 (m, 2H, C**H**$_2$), 3.61 (s, 3H, OC**H**$_3$), 2.32 – 2.10 (m, 1H, C**H**$_2$), 2.04 – 1.86 (m, 1H, C**H**$_2$); δ_C (100 MHz, CDCl$_3$) 170.5 (br, **C**O), 153.2 (Ar-**C**), 148.5 (Ar-**C**), 136.3 (Ar-**C**), 132.0 (Ar-**C**H), 131.6 (Ar-**C**H), 131.5 (Ar-**C**H), 129.3 (Ar-**C**), 128.3 (Ar-**C**H), 127.7 (Ar-**C**H), 127.6 (Ar-**C**H), 127.3 (Ar-**C**H), 124.8 (Ar-**C**), 117.0 (Ar-**C**H), 113.7 (Ar-**C**H), 112.8 (Ar-**C**H), 70.3 (O**C**H$_2$Ph), 65.6 (d, J = 7.1 Hz, O**C**H$_2$), 55.4 (O**C**H$_3$), 43.3 (br, **C**H$_2$), 25.3 (d, J = 7.0 Hz, **C**H$_2$); δ_P (162 MHz, CDCl$_3$) 14.6 (Ph**P**=O); HRMS (ESI): calcd. for $C_{24}H_{24}NNaO_5P$, 460.1284. Found: [MNa]$^+$, 460.1290 (–1.3 ppm error).

3-(3-Hydroxypropyl)-6-methoxy-2-phenyl-3-hydrobenzo[*e*][1,3,2]oxazaphosphinin-4-one 2-oxide (6-30b)



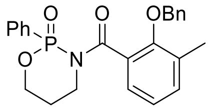
2-(Benzyloxy)-5-methoxyphenyl)(2-oxido-2-phenyl-1,3,2-oxazaphosphinan-3-yl)methanone **6-28b** (230 mg, 0.53 mmol) was dissolved in dry EtOAc (6.0 mL) and placed under an argon atmosphere. Palladium on carbon (60 mg, Pd 10% on carbon) was then added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at RT under a slight positive pressure of hydrogen (balloon) for 2 h. The reaction was then purged with argon, filtered through Celite, washed with ethyl acetate where the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO$_2$, ethyl acetate) afforded the title compound as a colorless oil (170 mg, 92%). R_f = 0.29 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3446, 2942, 1678, 1488, 1428, 1333, 1283, 1247, 1196, 1126, 1029, 916, 728, 717, 692, 576, 558, 507; δ_H (400 MHz, CDCl$_3$) 7.67 (ddd, J = 14.5, 8.3, 1.4 Hz, 2H, Ar-C**H**), 7.55 (tdd, J = 7.0, 2.9, 1.4 Hz, 1H, Ar-C**H**), 7.50 (d, J = 3.1 Hz, 1H, Ar-C**H**), 7.45 – 7.37 (m, 2H, Ar-C**H**), 7.05 (ddd, J = 9.0, 3.2, 0.9 Hz, 1H, Ar-C**H**), 6.98 (d, J = 9.0 Hz, 1H, Ar-C**H**), 3.90 (ddt, J = 14.0, 11.8, 5.7 Hz, 1H, NC**H**$_2$), 3.76 (s, 3H, OC**H**$_3$), 3.71 – 3.56 (m, 2H, OC**H**$_2$ + CH$_2$O**H**), 3.50 (dt, J = 11.8, 5.1 Hz, 1H, OC**H**$_2$), 3.41 (dtd, J = 14.4, 8.5, 6.0 Hz, 1H, NC**H**$_2$), 1.93 – 1.69 (m, 2H, C**H**$_2$); δ_C (100 MHz, CDCl$_3$) 162.8 (d, J = 4.8 Hz, **C**O), 156.3 (Ar-**C**), 144.5 (d, J = 7.2 Hz, Ar-**C**), 134.0 (d, J = 3.2 Hz, Ar-**C**H), 131.6 (d, J = 11.2 Hz, Ar-**C**H), 129.0 (d, J = 15.8 Hz, Ar-**C**H), 126.6 (d, J = 178.1 Hz, Ar-**C**), 123.1 (Ar-**C**H), 119.7 (d, J = 9.4 Hz, Ar-**C**H), 117.4 (d, J = 2.6 Hz, Ar-**C**), 111.7 (Ar-**C**H), 58.2 (**C**H_2OH), 55.8 (O**C**H_3), 39.3 (d, J = 4.6 Hz, N**C**H_2), 31.1 (**C**H_2); δ_P (162 MHz, $CDCl_3$) 17.9 (Ph**P**=O); HRMS (ESI): calcd. for $C_{17}H_{18}NNaO_5P$, 370.0815. Found: $[MNa]^+$, 370.0818 (–0.9 ppm error).

10-Methoxy-2-phenyl-4,5,6,7-tetrahydro-8*H*-benzo[*d*][1,3,7,2]dioxazaphosphecin-8-one 2-oxide (6-31b)



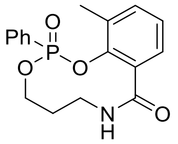
3-(3-Hydroxypropyl)-6-methoxy-2-phenyl-3-hydrobenzo[e][1,3,2]oxazaphosphinin-4-one 2-oxide **6-30b** (160 mg, 0.46 mmol) was dissolved in chloroform (5.0 mL) and triethylamine (700 µL, 5.0 mmol) added, the mixture was stirred overnight at RT, then reduced *in vacuo*. Purification by flash column chromatography (SiO_2, ethyl acetate) afforded the *title compound* as a colorless oil (146 mg, 91%). R_f = 0.15 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3299, 2939, 1655, 1536, 1485, 1249, 1196, 1131, 1033, 993, 919, 730, 695, 526; δ_H (400 MHz, $CDCl_3$) 7.71 – 7.60 (m, 2H, Ar-C**H**), 7.49 – 7.42 (m, 1H, Ar-C**H**), 7.38 – 7.31 (m, 2H, Ar-C**H**), 7.29 – 7.22 (m, 1H, Ar-C**H**), 7.06 (d, J = 3.2 Hz, 1H, CON**H**), 6.64 (dd, J = 9.0, 3.2 Hz, 1H, Ar-C**H**), 6.52 (dd, J = 8.9, 1.6 Hz, 1H, Ar-C**H**), 4.66 – 4.55 (m, 1H, OC**H**$_2$), 4.23 (td, J = 12.1, 11.9, 6.5 Hz, 1H, OC**H**$_2$), 3.92 – 3.80 (m, 1H, C**H**$_2$), 3.66 (s, 3H, OC**H**$_3$), 3.37 (ddt, J = 14.0, 9.5, 4.8 Hz, 1H, C**H**$_2$), 2.31 – 2.17 (m, 1H, C**H**$_2$), 2.01 – 1.88 (m, 1H, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 166.6 (**C**O), 156.7 (d, J = 1.7 Hz, Ar-**C**), 141.0 (d, J = 9.2 Hz, Ar-**C**), 132. 8 (d, J = 3.1 Hz, Ar-**C**H), 131.1 (d, J = 10.0 Hz, Ar-**C**H), 130.1 (d, J = 2.5 Hz, Ar-**C**), 128.4 (d, J = 15.7 Hz, Ar-**C**H), 127.4 (d, J = 195.4 Hz, Ar-**C**), 123.1 (d, J = 3.7 Hz, Ar-**C**H), 117.9 (Ar-**C**H), 113.1 (Ar-**C**H), 67.7 (d, J = 7.7 Hz, O**C**H_2), 55.6 (O**C**H_3), 38.7 (**C**H_2), 28.6 (d, J = 2.9 Hz, **C**H_2); δ_P (162 MHz, $CDCl_3$) 17.1 (Ph**P**=O); HRMS (ESI): calcd. for $C_{17}H_{18}NNaO_5P$, 370.0815. Found: [MNa]$^+$, 370.0822 (–2.0 ppm error).

(2-(Benzyloxy)-3-methylphenyl)(2-oxido-2-phenyl-1,3,2-oxazaphosphinan-3-yl)methanone (6-28c)



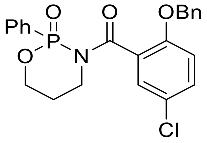
2-Phenyl-1,3,2-oxazaphosphinane 2-oxide **6-13** (197.2 mg, 1.0 mmol) was dissolved in dry THF (5 mL) and the temperature was lowered –78 °C (dry ice/acetone bath). *n*-BuLi (2.5 M in hexanes, 0.48 mL, 1.2 mmol, 1.2 eq) was added dropwise by syringe and the reaction was allowed to stir at –78 °C. After 1 hour, a solution of acid chloride (1.5 mmol, 1.5 equiv. prepared using the general procedure with the acid **S4**) in THF (5 mL) was added slowly to the stirring reaction mixture. The reaction was allowed to warm to room temperature overnight before the addition of sat. aq. $NaHCO_3$ solution (20 mL). The aqueous layer was extracted with EtOAc (2 × 10 mL) and the combined organic layers were dried ($MgSO_4$). After filtration, the solvent was then concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, ethyl acetate) afforded the title compound as a colorless oil (220 mg, 52%). R_f= 0.23 (ethyl acetate); ν_{max}/cm^{-1} (neat) 2923, 2237, 1662, 1462, 1440, 1320, 1245, 1215, 1132, 1068, 995, 908, 726, 692, 645, 596; δ_H (400 MHz, $CDCl_3$ at 50 °C) 7.65 (dd, *J* = 14.5, 7.6 Hz, 2H, Ar-C**H**), 7.46 – 7.09 (m, 10H, Ar-C**H**), 6.98 (t, *J* = 7.5 Hz, 1H, Ar-C**H**), 4.88 – 4.63 (m, 2H, OC**H**$_2$Ph), 4.53 (dq, *J* = 11.3, 5.7 Hz, 1H, OC**H**$_2$), 4.24 (dddd, *J* = 18.4, 10.9, 7.2, 5.7 Hz, 1H, OC**H**$_2$), 4.02 – 3.56 (m, 2H, C**H**$_2$), 2.31 – 2.17 (m, 1H, C**H**$_2$), 2.07 (s, 4H, C**H**$_3$ + C**H**$_2$); δ_C (100 MHz, $CDCl_3$ at 50 °C) 171.5 (br, **C**O), 153.6 (Ar-**C**), 137.5 (Ar-**C**), 133.2 (Ar-**C**H), 132.3 (Ar-**C**H), 132.3 (Ar-**C**H), 132.2 (Ar-**C**H), 132.1 (Ar-**C**H), 131.6 (Ar-**C**), 130.1 (Ar-**C**), 128.3 (Ar-**C**H), 128.0 (Ar-**C**), 127.9 (Ar-**C**H), 127.8 (Ar-**C**H), 127.6 (Ar-**C**H), 126.6 (Ar-**C**), 124.0 (Ar-**C**H), 75.8 (O**C**H$_2$Ph), 65.7 (d, *J* = 7.8 Hz, O**C**H$_2$), 43.0 (br, **C**H$_2$), 25.8 (d, *J* = 6.0 Hz, **C**H$_2$), 16.0 (**C**H$_3$); δ_P (162 MHz, $CDCl_3$ at 50 °C) 14.5 (Ph**P**=O); HRMS (ESI): calcd. for $C_{24}H_{24}NNaO_4P$, 444.1335. Found: [MNa]$^+$, 444.1333 (0.4 ppm error).

12-Methyl-2-phenyl-4,5,6,7-tetrahydro-8*H*-benzo[*d*][1,3,7,2]dioxazaphosphecin-8-one 2-oxide (6-31c)



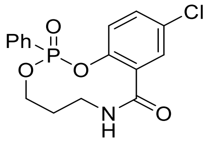
(2-(Benzyloxy)-3-methylphenyl)(2-oxido-2-phenyl-1,3,2-oxazaphosphinan-3-yl)methanone **6-28c** (167 mg, 0.40 mmol) was redissolved in dry EtOAc (4.0 mL) and placed under an argon atmosphere. Palladium on carbon (40 mg, Pd 10% on carbon) was then added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at RT under a slight positive pressure of hydrogen (balloon) for 2 h. The reaction was then purged with argon, filtered through Celite, washed with ethyl acetate where the solvent was removed *in vacuo*. The crude was dissolved in chloroform (4.0 mL) and triethylamine (560 µL, 4.0 mmol, 10 eq) added, the mixture was stirred overnight at RT, then reduced *in vacuo*. Purification by flash column chromatography (SiO_2, ethyl acetate) afforded the *title compound* as a colorless oil (98 mg, 75%). R_f = 0.20 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3300, 2959, 1649, 1536, 1439, 1315, 1254, 1176, 1130, 1045, 992, 921, 730, 696, 561, 543; δ_H (400 MHz, $CDCl_3$) 7.73 (ddd, *J* = 13.8, 8.2, 1.4 Hz, 2H, Ar-C**H**), 7.50 (td, *J* = 7.4, 1.4 Hz, 1H, Ar-C**H**), 7.43 – 7.32 (m, 3H, Ar-C**H**), 7.11 – 6.99 (m, 3H, CON**H** + Ar-C**H**), 4.59 (dddd, *J* = 11.4, 9.9, 8.5, 1.4 Hz, 1H, OC**H**$_2$), 4.24 (dddd, *J* = 13.3, 11.4, 6.8, 1.7 Hz, 1H, OC**H**$_2$), 3.96 – 3.81 (m, 1H, NHC**H**$_2$), 3.42 (ddt, *J* = 14.2, 9.8, 5.0 Hz, 1H, NHC**H**$_2$), 2.34 – 2.20 (m, 1H, C**H**$_2$), 2.02 – 1.89 (m, 1H, C**H**$_2$), 1.78 (s, 3H, C**H**$_3$); δ_C (100 MHz, $CDCl_3$) 167.5 (**C**O), 146.2 (d, *J* = 9.7 Hz, Ar-**C**), 133.2 (Ar-**C**H), 132.8 (d, *J* = 3.3 Hz, Ar-**C**H), 131.2 (d, *J* = 10.1 Hz, Ar-**C**H), 131.0 (d, *J* = 4.2 Hz, Ar-**C**), 130.0 (d, *J* = 2.4 Hz, Ar-**C**), 128.4 (d, *J* = 15.8 Hz, Ar-**C**H), 127.6 (d, *J* = 196.1 Hz, Ar-**C**), 127.1 (d, *J* = 1.8 Hz, Ar-**C**H), 125.4 (d, *J* = 1.7 Hz, Ar-**C**H), 67.5 (d, *J* = 7.7 Hz, O**C**H$_2$), 38.6 (NH**C**H$_2$), 28.5(d, *J* = 3.2 Hz, **C**H$_2$), 17.0 (**C**H$_3$); δ_P (162 MHz, $CDCl_3$) 15.5 (Ph**P**=O); HRMS (ESI): calcd. for $C_{17}H_{18}NNaO_4P$, 354.0866. Found: $[MNa]^+$, 354.0863 (0.7 ppm error).

(2-(Benzyloxy)-5-chlorophenyl)(2-oxido-2-phenyl-1,3,2-oxazaphosphinan-3-yl)methanone (6-28d)



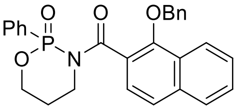
2-Phenyl-1,3,2-oxazaphosphinane 2-oxide **6-13** (197.2 mg, 1.0 mmol) was dissolved in dry THF (5 mL) and the temperature was lowered –78 °C (dry ice/acetone bath). *n*-BuLi (2.5 M in hexanes, 0.48 mL, 1.2 mmol, 1.2 eq) was added dropwise by syringe and the reaction was allowed to stir at –78 °C. After 1 hour, a solution of acid chloride (1.5 mmol, 1.5 equiv. prepared using the general procedure with the acid **S5**) in THF (5 mL) was added slowly to the stirring reaction mixture. The reaction was allowed to warm to room temperature overnight before the addition of sat. aq. $NaHCO_3$ solution (20 mL). The aqueous layer was extracted with EtOAc (2 × 10 mL) and the combined organic layers were dried ($MgSO_4$). After filtration, the solvent was then concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, ethyl acetate) afforded the title compound as a colorless oil (255 mg, 58%). R_f = 0.11 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3062, 1663, 1596, 1484, 1407, 1318, 1247, 1127, 1058, 997, 911, 745, 725, 693, 594, 502; δ_H (400 MHz, $CDCl_3$) 7.67 – 7.01 (m, 12H, Ar-C**H**), 6.60 (s, 1H, Ar-C**H**), 5.15 – 4.59 (m, 2H, OC**H**$_2$Ph), 4.46 (dq, *J* = 11.1, 5.6 Hz, 1H, OC**H**$_2$), 4.16 (dddd, *J* = 18.6, 10.9, 7.8, 5.6 Hz, 1H, OC**H**$_2$), 4.09 – 3.31 (m, 2H, C**H$_2$**), 2.42 – 1.77 (m, 2H, C**H$_2$**); δ_C (100 MHz, $CDCl_3$) 168.9 (br, **C**O), 153.1 (br, Ar-**C**), 135.8 (br, Ar-**C**), 132.4 (Ar-**C**H), 131.7 (Ar-**C**H), 131.6 (Ar-**C**H), 130.9 (Ar-**C**H), 128.5 (Ar-**C**H), 128.0 (Ar-**C**H), 127.9 (Ar-**C**H), 127.3 (Ar-**C**H), 125.3 (Ar-**C**), 112.9 (Ar-**C**), 70.2 (O**C**H$_2$Ph), 65.9 (d, *J* = 7.7 Hz, O**C**H$_2$), 42.9 (br, **C**H$_2$), 25.4 (d, *J* = 6.7 Hz, **C**H$_2$); δ_P (162 MHz, $CDCl_3$) 14.5 (Ph**P**=O); HRMS (ESI): calcd. for $C_{23}H_{21}{}^{35}ClNNaO_4P$, 464.0789. Found: $[MNa]^+$, 464.0798 (–2.0 ppm error).

10-Chloro-2-phenyl-4,5,6,7-tetrahydro-8*H*-benzo[*d*][1,3,7,2]dioxazaphosphecin-8-one 2-oxide (6-31d)



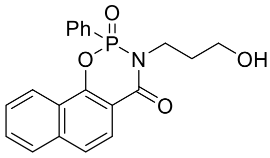
(2-(Benzyloxy)-5-chlorophenyl)(2-oxido-2-phenyl-1,3,2-oxazaphosphinan-3-yl)methanone **6-28d** (212 mg, 0.48 mmol) was dissolved in dry EtOAc (5.0 mL) and placed under an argon atmosphere. Palladium on carbon (50 mg, Pd 10% on carbon) was then added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at RT under a slight positive pressure of hydrogen (balloon) for 2 h. The reaction was then purged with argon, filtered through Celite, washed with ethyl acetate where the solvent was removed *in vacuo*. The crude was dissolved in chloroform (5.0 mL) and triethylamine (700 μL, 5.0 mmol, 10 eq) added, the mixture was stirred overnight at RT, then reduced *in vacuo*. Purification by flash column chromatography (SiO_2, ethyl acetate) afforded the *title compound* as a colorless oil (100 mg, 60%). R_f= 0.19 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3294, 2932, 1653, 1547, 1470, 1439, 1252, 1215, 1131, 1043, 994, 922, 827, 730, 694, 558, 534; δ_H (400 MHz, $CDCl_3$) 7.80 – 7.69 (m, 2H, Ar-C**H**), 7.64 – 7.52 (m, 2H, Ar-C**H**), 7.50 – 7.40 (m, 2H, Ar-C**H**), 7.24 – 7.13 (m, 2H, CON**H** + Ar-C**H**), 6.65 (dd, *J* = 8.7, 1.6 Hz, 1H, Ar-C**H**), 4.78 – 4.56 (m, 1H, OC**H**$_2$), 4.42 – 4.25 (m, 1H, OC**H**$_2$), 4.03 – 3.86 (m, 1H, NHC**H**$_2$), 3.51 – 3.34 (m, 1H, NHC**H**$_2$), 2.38 – 2.23 (m, 1H, C**H**$_2$), 2.10 – 1.95 (m, 1H, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 165.6 (**C**O), 146.2 (d, *J* = 9.1 Hz, Ar-**C**), 133.3 (d, *J* = 3.3 Hz, Ar-**C**H), 131.7 (Ar-**C**H), 131.4 (d, *J* = 2.2 Hz, Ar-**C**), 131.3 (d, *J* = 10.2 Hz, Ar-**C**H), 129.6 (d, *J* = 1.7 Hz, Ar-**C**H), 129.1 (d, *J* = 15.7 Hz, Ar-**C**), 128.8 (d, *J* = 15.9 Hz, Ar-**C**H), 127.1 (d, *J* = 196.8 Hz, Ar-**C**), 123.7 (d, *J* = 3.8 Hz, Ar-**C**H), 68.2 (d, *J* = 7.8 Hz, O**C**H$_2$), 39.0 (**C**H$_2$), 29.0 (d, *J* = 2.7 Hz, **C**H$_2$); δ_P (162 MHz, $CDCl_3$) 17.5 (Ph**P**=O); HRMS (ESI): calcd. for $C_{16}H_{15}ClNNaO_4P$, 374.0319. Found: $[MNa]^+$, 374.0319 (0.2 ppm error).

(1-(Benzyloxy)naphthalen-2-yl)(2-oxido-2-phenyl-1,3,2-oxazaphosphinan-3-yl)methanone (6-28e)



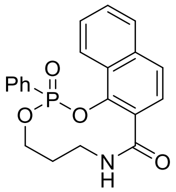
2-Phenyl-1,3,2-oxazaphosphinane 2-oxide **6-13** (197.2 mg, 1.0 mmol) was dissolved in dry THF (5 mL) and the temperature was lowered –78 °C (dry ice/acetone bath). *n*-BuLi (2.5 M in hexanes, 0.48 mL, 1.2 mmol, 1.2 eq) was added dropwise by syringe and the reaction was allowed to stir at –78 °C. After 1 hour, a solution of acid chloride (1.5 mmol, 1.5 equiv. prepared using the general procedure with the acid **S3**) in THF (5 mL) was added slowly to the stirring reaction mixture. The reaction was allowed to warm to room temperature overnight before the addition of sat. aq. $NaHCO_3$ solution (20 mL). The aqueous layer was extracted with EtOAc (2 × 10 mL) and the combined organic layers were dried ($MgSO_4$). After filtration, the solvent was then concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, ethyl acetate) afforded the title compound as a colorless oil (345 mg, 75%). R_f = 0.34 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3061, 1660, 1439, 1358, 1253, 1131, 1060, 998, 745, 722, 694, 623, 533; δ_H (400 MHz, $CDCl_3$) 8.15 – 6.76 (m, 16H, Ar-C**H**), 5.24 – 4.79 (m, 2H, OC**H$_2$**Ph), 4.60 (dtd, *J* = 11.0, 5.5, 2.6 Hz, 1H, OC**H**$_2$), 4.37 – 4.14 (m, 1H, OC**H**$_2$), 4.08 – 3.60 (m, 2H, C**H$_2$**), 2.38 – 1.98 (m, 2H, C**H$_2$**); δ_C (100 MHz, $CDCl_3$) 171.9 (br, **C**O), 151.9 (Ar-**C**), 137.2 (Ar-**C**), 135.7 (Ar-**C**H), 132.5 (d, *J* = 3.0 Hz, Ar-**C**H), 132.1 (d, *J* = 10.9 Hz, Ar-**C**H), 128.5 (Ar-**C**H), 128.0 (Ar-**C**H), 127.9 (Ar-**C**), 127.5 (Ar-**C**H), 127.5 (Ar-**C**), 126.6 (Ar-**C**H), 124.9 (Ar-**C**), 124.5 (Ar-**C**), 122.6 (Ar-**C**H), 77.4 (O**C**H$_2$Ph), 65.8 (d, *J* = 4.9 Hz, O**C**H$_2$), 44.0 (br, **C**H$_2$), 25.9 (d, *J* = 6.6 Hz, **C**H$_2$); δ_P (162 MHz, $CDCl_3$) 14.5 (Ph**P**=O); HRMS (ESI): calcd. for $C_{27}H_{24}NNaO_4P$, 480.1335. Found: [MNa]$^+$, 480.1336 (–0.1 ppm error).

3-(3-Hydroxypropyl)-2-phenyl-3-hydronaphtho[2,1-*e*][1,3,2]oxazaphosphinin-4-one 2-oxide (6-30e)



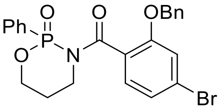
(1-(Benzyloxy)naphthalen-2-yl)(2-oxido-2-phenyl-1,3,2-oxazaphosphinan-3-yl)methanone **6-28e** (252 mg, 0.55 mmol) was redissolved in dry EtOAc (6.0 mL) and placed under an argon atmosphere. Palladium on carbon (60 mg, Pd 10% on carbon) was then added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at RT 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 where the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, ethyl acetate) afforded the *title compound* as a colorless oil (190 mg, 94%). R_f= 0.32 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3457, 1677, 1438, 1383, 1352, 1295, 1265, 1196, 1128, 1089, 928, 822, 761, 732, 693, 567; δ_H (400 MHz, $CDCl_3$) 8.19 (dd, *J* = 8.3, 1.2 Hz, 1H, Ar-C**H**), 8.04 (d, *J* = 8.7 Hz, 1H, Ar-C**H**), 7.83 – 7.73 (m, 3H, Ar-C**H**), 7.64 (dd, *J* = 8.9, 0.9 Hz, 1H, Ar-C**H**), 7.63 – 7.50 (m, 2H, Ar-C**H**), 7.50 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H, Ar-C**H**), 7.46 – 7.39 (m, 2H, Ar-C**H**), 4.12 – 3.95 (m, 1H, NC**H**$_2$), 3.77 – 3.65 (m, 2H, C**H**$_2$OH + CH_2O**H**), 3.62 – 3.44 (m, 2H, C**H**$_2$OH + NC**H**$_2$), 2.07 – 1.77 (m, 2H, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 163.2 (d, *J* = 4.8 Hz, **C**O), 148.5 (d, *J* = 7.5 Hz, Ar-**C**), 137.1 (Ar-**C**), 134.1 (d, *J* = 3.1 Hz, Ar-**C**H), 131.6 (d, *J* = 11.4 Hz, Ar-**C**H), 129.7 (Ar-**C**H), 129.1 (d, *J* = 15.7 Hz, Ar-**C**H), 127.8 (Ar-**C**H), 127.3 (Ar-**C**H), 126.7 (d, *J* = 178.2 Hz, Ar-**C**), 124.4 (Ar-**C**H), 123.8 (Ar-**C**H), 123.7 (d, *J* = 8.1 Hz, Ar-**C**), 122.6 (Ar-**C**H), 111.9 (d, *J* = 2.6 Hz, Ar-**C**), 58.3 (**C**H_2OH), 39.3 (d, *J* = 4.5 Hz, N**C**H_2), 31.3 (**C**H_2); δ_P (162 MHz, $CDCl_3$) 18.9 (Ph**P**=O); HRMS (ESI): calcd. for $C_{20}H_{18}NNaO_4P$, 390.0866. Found: [MNa]$^+$, 390.0868 (–0.6 ppm error).

2-Phenyl-4,5,6,7-tetrahydro-8*H*-naphtho[1,2-*d*][1,3,7,2]dioxazaphosphecin-8-one 2-oxide (6-31e)



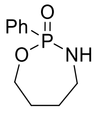
(1-(Benzyloxy)naphthalen-2-yl)(2-oxido-2-phenyl-1,3,2-oxazaphosphinan-3-yl)methanone **6-28e** (230 mg, 0.50 mmol) was redissolved in dry EtOAc (5.0 mL) and placed under an argon atmosphere. Palladium on carbon (50 mg, Pd 10% on carbon) was then added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at RT 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 where the solvent was removed *in vacuo*. The crude was dissolved in chloroform (5.0 mL) and triethylamine (700 μL, 5.0 mmol, 10 eq) added, the mixture was stirred overnight at RT, then reduced *in vacuo*. Purification by flash column chromatography (SiO_2, ethyl acetate) afforded the *title compound* as a colorless oil (110 mg, 60%). R_f= 0.17 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3300, 3065, 2935, 1650, 1536, 1439, 1370, 1252, 1190, 1130, 1039, 993, 907, 814, 749, 695, 512; δ_H (400 MHz, $CDCl_3$) 7.76 – 7.54 (m, 5H, Ar-C**H**), 7.50 – 7.27 (m, 6H, CON**H** + Ar-C**H**), 7.19 (ddd, *J* = 8.2, 6.8, 1.2 Hz, 1H, Ar-C**H**), 4.73 (dddd, *J* = 11.5, 10.2, 8.8, 1.4 Hz, 1H, OC$\mathbf{H}_2$), 4.37 – 4.21 (m, 1H, OC$\mathbf{H}_2$), 3.95 – 3.82 (m, 1H, NHC$\mathbf{H}_2$), 3.59 – 3.42 (m, 1H, NHC$\mathbf{H}_2$), 2.44 – 2.29 (m, 1H, C$\mathbf{H}_2$), 2.03 – 1.86 (m, 1H, C$\mathbf{H}_2$); δ_C (100 MHz, $CDCl_3$) 167.3 (**C**O), 144.2 (d, *J* = 9.9 Hz, Ar-**C**), 135.4 (Ar-**C**), 132.9 (d, *J* = 3.1 Hz, Ar-**C**), 131.4 (d, *J* = 10.1 Hz, Ar-**C**H), 128.4 (d, *J* = 15.9 Hz, Ar-**C**H), 127.6 (d, *J* = 12.5 Hz, Ar-**C**H), 127.0 (d, *J* = 197.5 Hz, Ar-**C**), 126.8 (d, *J* = 3.6 Hz, Ar-**C**), 126.7 (Ar-**C**H), 125.6 (d, *J* = 1.3 Hz, Ar-**C**H), 125.3 (d, *J* = 1.7 Hz, Ar-**C**H), 125.1 (d, *J* = 3.2 Hz, Ar-**C**H), 122.7 (Ar-**C**H), 67.7 (d, *J* = 7.6 Hz, O**C**H_2), 38.7 (**C**H_2), 28.4 (d, *J* = 2.9 Hz, **C**H_2); δ_P (162 MHz, $CDCl_3$) 16.3 (Ph**P**=O); HRMS (ESI): calcd. for $C_{20}H_{18}NNaO_4P$, 390.0866. Found: [MNa]$^+$, 390.0863 (0.8 ppm error).

(2-(Benzyloxy)-4-bromophenyl)(2-oxido-2-phenyl-1,3,2-oxazaphosphinan-3-yl)methanone (6-28f)



2-Phenyl-1,3,2-oxazaphosphinane 2-oxide **6-13** (197.2 mg, 1.0 mmol) was dissolved in THF (5 mL) and the temperature was lowered –78 °C (dry ice/acetone bath). *n*-BuLi (1.6 M in hexanes, 0.44 mL, 1.1 mmol, 1.1 eq) was added dropwise by syringe and the reaction was allowed to stir at –78 °C. After 1 hour, a solution of acid chloride (1.5 mmol, 1.5 equiv. prepared using the general procedure from **S6**) in THF (5 mL) was added slowly to the stirring reaction mixture. The reaction was allowed to warm to room temperature overnight before the addition of sat. aq. $NaHCO_3$ solution (20 mL). The aqueous layer was extracted with EtOAc (2 × 10 mL) and the combined organic layers were dried ($MgSO_4$). After filtration, the solvent was then concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, ethyl acetate) afforded the title compound as a colorless oil (357 mg, 88%). $R_f = 0.15$ (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3061, 1666, 1588, 1484, 1404, 1317, 1246, 1132, 1104, 1057, 996, 884, 747, 724, 694, 602, 536; δ_H (400 MHz, $CDCl_3$) 7.72 – 6.50 (m, 13H, Ar-C**H**), 4.99 – 4.28 (m, 3H, OC**H₂**Ph + OC**H₂**), 4.24 – 3.19 (m, 3H, C**H₂** + OC**H₂**), 2.32 – 1.74 (m, 2H, C**H₂**); δ_C (101 MHz, $CDCl_3$) 169.4 (br, **C**O), 155.2 (br, Ar-**C**), 135.4 (Ar-**C**), 132.1 (Ar-**C**H), 131.5 (Ar-**C**H), 131.4 (Ar-**C**H), 130.1 (br, Ar-**C**), 128.9 (br, Ar-**C**), 128.4 (Ar-**C**H), 128.0 (Ar-**C**H), 127.7 (Ar-**C**H), 127.6 (Ar-**C**H), 127.2 (Ar-**C**H), 123.9 (br, Ar-**C**), 123.3 (Ar-**C**H), 114.8 (Ar-**C**H), 69.8 (O**C**H₂Ph), 65.9 (d, *J* = 6.5 Hz, O**C**H₂), 42.6 (br, **C**H₂), 25.2 (d, *J* = 6.8 Hz, **C**H₂); δ_P (162 MHz, $CDCl_3$) 14.5 (Ph**P**=O); HRMS (APCI): calcd. for $C_{23}H_{22}BrNO_4P$, 486.046433. Found: $[MH]^+$, 486.047816 (–2.8 ppm error).

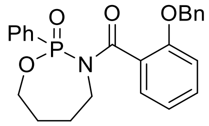
2-Phenyl-1,3,2-oxazaphosphepane 2-oxide (6-13b)



A solution of phenylphosphinic dichloride **6-11**(0.995 g, 5.1 mmol) in DCM (5.0 mL) was added under stirring and cooling at 0 °C to a solution of 4-aminobutan-1-ol **6-12a**

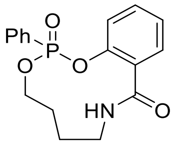
(0.45 g, 5.1 mmol) in 10 mL of DCM. After addition of a solution of triethylamine (1.40 mL, 10.2 mmol) in 10 mL DCM, the reaction mixture was stirred at RT for 1 h and washed with H_2O. The organic solution was dried over $MgSO_4$, the solvent evaporated, and the residue purified by flash chromatography (10:1 dichloromethane: methanol) to give the product as a colorless oil (350 mg, 33%); R_f = 0.31 (10:1 dichloromethane: methanol); δ_H (400 MHz, $CDCl_3$) 7.85 – 7.72 (m, 2H, Ar-C**H**), 7.49 – 7.35 (m, 3H, Ar-C**H**), 4.53 (q, *J* = 11.5 Hz, 1H, OC**H**$_2$), 4.20 – 4.08 (m, 1H, N**H**), 4.03 (q, *J* = 8.5 Hz, 1H, NHC**H**$_2$), 3.19 – 3.01 (m, 1H, OC**H**$_2$), 2.82 – 2.68 (m, 1H, NHC**H**$_2$), 1.91 – 1.52 (m, 4H, 2 × C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 131.5 (d, *J* = 2.9 Hz, Ar-**C**H), 131.5 (d, *J* = 182.5 Hz, Ar-**C**), 130.9 (d, *J* = 9.6 Hz, Ar-CH), 128.3 (d, *J* = 14.6 Hz, Ar-**C**H), 65.4 (d, *J* = 6.7 Hz, O**C**H$_2$), 41.1 (**C**H$_2$), 31.9 (**C**H$_2$), 30.0 (**C**H$_2$); δ_P (162 MHz, $CDCl_3$) 27.7 (Ph**P**=O); HRMS (ESI): calcd. for $C_{10}H_{14}NNaO_2P$, 234.0654. Found: $[MNa]^+$, 234.0656 (–0.6 ppm error).

(2-(Benzyloxy)phenyl)(2-oxido-2-phenyl-1,3,2-oxazaphosphepan-3-yl)methanone (6-28g)



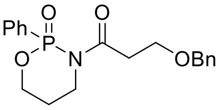
2-Phenyl-1,3,2-oxazaphosphepane 2-oxide **6-13b** (211.2 mg, 1.0 mmol) was dissolved in dry THF (5 mL) and the temperature was lowered to –78 °C (dry ice/acetone bath). *n*-BuLi (2.5 M in hexanes, 0.48 mL, 1.2 mmol, 1.2 eq) was added dropwise by syringe and the reaction was allowed to stir at –78 °C. After 1 hour, a solution of acid chloride **2-12** (1.5 mmol, 1.5 equiv. prepared using the general procedure with 2-benzyloxybenzoic acid) in THF (5 mL) was transferred to the stirring reaction mixture slowly. The reaction was allowed to warm to room temperature overnight before the addition of sat. aq. $NaHCO_3$ solution (20 mL). The aqueous layer was extracted with EtOAc (2 × 20 mL), the combined organic layers were dried ($MgSO_4$). After filtration, the solvent was removed by rotary evaporation. Purification by flash column chromatography (SiO_2, ethyl acetate) afforded the title compound as a colorless oil (276 mg, 65%). R_f = 0.35 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 2929, 1665, 1599, 1490, 1448, 1326, 1250, 1130, 1019, 955, 747, 721, 695, 579, 542; δ_H (400 MHz, $CDCl_3$ at 50 °C) 7.73 – 7.53 (m, 2H, Ar-C**H**), 7.48 – 7.38 (m, 1H, Ar-C**H**), 7.34 – 7.18 (m, 8H, Ar-C**H**), 7.18 – 7.01 (m, 1H, Ar-C**H**), 6.93 – 6.78 (m, 2H, Ar-C**H**), 5.04 – 4.74 (m, 2H, OC**H**$_2$Ph), 4.51 (tt, *J* = 11.7, 5.8 Hz, 1H, OC**H**$_2$), 4.26 (ddd, *J* = 19.5, 14.0, 4.9 Hz, 1H, C**H**$_2$), 4.05 (ddt, *J* = 18.1, 11.1, 3.3 Hz, 1H, OC**H**$_2$), 3.27 – 3.05 (m, 1H, C**H**$_2$), 1.92 – 1.61 (m, 4H, 2 × C**H**$_2$); δ_C (100 MHz, $CDCl_3$ at 50 °C) 171.6 (d, *J* = 7.5 Hz, **C**O), 155.1 (Ar-**C**), 136.7 (Ar-**C**), 132.1 (d, *J* = 3.0 Hz, Ar-**C**H), 131.1 (d, *J* = 10.1 Hz, Ar-**C**H), 130.4 (Ar-**C**H), 129.2 (d, *J* = 181.6 Hz, Ar-**C**), 128.2 (Ar-**C**H), 128.0 (d, *J* = 15.3 Hz, Ar-**C**H), 127.6 (Ar-**C**H), 127.2 (Ar-**C** + Ar-**C**H), 120.3 (Ar-**C**H), 112.1 (Ar-**C**H), 70.1 (O**C**H$_2$Ph), 66.5 (d, *J* = 6.8 Hz, O**C**H$_2$), 45.5 (br, **C**H$_2$), 28.5 (**C**H$_2$), 27.8 (**C**H$_2$); δ_P (162 MHz, $CDCl_3$ at 50 °C) 19.6 (Ph**P**=O); HRMS (ESI): calcd. for $C_{24}H_{24}NNaO_4P$, 444.1333. Found: [MNa]$^+$, 444.1335 (0.6 ppm error).

2-Phenyl-5,6,7,8-tetrahydrobenzo[*d*][1,3]dioxa[7]aza[2]phosphacycloundecin-9(4*H*)-one 2-oxide (6-31g)



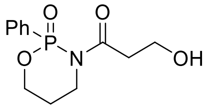
(2-(Benzyloxy)phenyl)(2-oxido-2-phenyl-1,3,2-oxazaphosphepan-3-yl)methanone (118 mg, 0.28 mmol) **6-28g** was redissolved in dry EtOAc (3.0 mL) and placed under an argon atmosphere. Palladium on carbon (30 mg, Pd 10% on carbon) was then added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at RT 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 where the solvent was removed *in vacuo*. The crude was dissolved in chloroform (3.0 mL) and triethylamine (420 µL, 3.0 mmol) added, the mixture was stirred overnight at RT, then reduced *in vacuo*. Purification by flash column chromatography (SiO_2, ethyl acetate) afforded the *title compound* as a colorless oil (60 mg, 65%). R_f = 0.19 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3299, 2928, 1645, 1606, 1542, 1481, 1440, 1312, 1252, 1211, 1131, 1008, 993, 923, 741, 695, 531; δ_H (400 MHz, $CDCl_3$) 7.93 – 7.86 (m, 2H, Ar-C**H**), 7.74 (dd, *J* = 7.5, 1.9 Hz, 1H, Ar-C**H**), 7.67 – 7.59 (m, 1H, Ar-C**H**), 7.58 – 7.47 (m, 2H, Ar-C**H**), 7.36 (t, *J* = 5.7 Hz, 1H, CON**H**), 7.33 – 7.27 (m, 1H, Ar-C**H**), 7.25 – 7.19 (m, 1H, Ar-C**H**), 6.80 (dt, *J* = 8.0, 1.1 Hz, 1H, Ar-C**H**), 4.51 – 4.33 (m, 2H, OC**H$_2$**), 3.86 – 3.68 (m, 1H, NHC**H**$_2$), 3.60 – 3.43 (m, 1H, NHC**H**$_2$), 2.00 – 1.92 (m, 4H, 2 × C**H$_2$**); δ_C (100 MHz, $CDCl_3$) 165.7 (**C**O), 147.7 (d, *J* = 8.6 Hz, Ar-**C**), 133.3 (d, *J* = 3.1 Hz, Ar-**C**H), 131.9 (d, *J* = 1.4 Hz, Ar-CH), 131.7 (d, *J* = 10.4 Hz, Ar-**C**H), 130.5 (d, *J* = 1.3 Hz, Ar-**C**H), 129.3 (d, *J* = 3.2 Hz, Ar-**C**), 128.9 (d, *J* = 15.9 Hz, Ar-**C**H), 127.7 (d, *J* = 196.7 Hz, Ar-**C**), 125.9 (d, *J* = 1.5 Hz, Ar-**C**H), 122.0 (d, *J* = 2.9 Hz, Ar-**C**H), 67.4 (d, *J* = 8.0 Hz, O**C**H$_2$), 39.7 (**C**H$_2$), 29.4 (d, *J* = 4.6 Hz, **C**H$_2$), 24.2 (**C**H$_2$); δ_P (162 MHz, $CDCl_3$) 17.3 (Ph**P**=O); HRMS (ESI): calcd. for $C_{17}H_{18}NNaO_4P$, 354.0866. Found: $[MNa]^+$, 354.0863 (0.8 ppm error).

3-(Benzyloxy)-1-(2-oxido-2-phenyl-1,3,2-oxazaphosphinan-3-yl)propan-1-one (6-32)



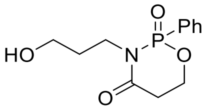
2-Phenyl-1,3,2-oxazaphosphinane 2-oxide **6-13** (394.4 mg, 2.0 mmol) was dissolved in THF (10 mL) and the temperature was lowered –78 °C (dry ice/acetone bath). *n*-BuLi (2.5 M in hexanes, 0.88 mL, 2.2 mmol, 1.1 eq) was added dropwise by syringe and the reaction was allowed to stir at –78 °C. After 1 hour, a solution of acid chloride **3-30** (3.0 mmol, 1.5 equiv. prepared using the general procedure with 3-(benzyloxy)propanoic acid) in THF (10 mL) was added slowly to the stirring reaction mixture. The reaction was allowed to warm to room temperature overnight before the addition of sat. aq. $NaHCO_3$ solution (20 mL). The aqueous layer was extracted with EtOAc (2 × 20 mL) and the combined organic layers were dried ($MgSO_4$). After filtration, the solvent was then concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, ethyl acetate) afforded the title compound as a colorless oil (300 mg, 42%). R_f = 0.24 (ethyl acetate); δ_H (400 MHz, $CDCl_3$) 7.80 – 7.66 (m, 2H, Ar-C**H**), 7.57 – 7.50 (m, 1H, Ar-C**H**), 7.46 – 7.36 (m, 2H, Ar-C**H**), 7.31 – 7.20 (m, 5H, Ar-C**H**), 4.56 – 4.45 (m, 2H, OC**H**$_2$ + C**H**$_2$), 4.45 – 4.35 (m, 2H, OC**H**$_2$), 4.24 – 4.13 (m, 1H, OC**H**$_2$), 3.80 – 3.63 (m, 2H, OC**H**$_2$), 3.34 – 3.20 (m, 1H, C**H**$_2$), 3.09 (dt, *J* = 16.5, 5.6 Hz, 1H, C**H**$_2$), 2.86 (ddd, *J* = 16.5, 7.5, 6.0 Hz, 1H, C**H**$_2$), 2.26 – 2.10 (m, 1H, C**H**$_2$), 2.06 – 1.89 (m, 1H, C**H**$_2$); δ_C (100 MHz, CDCl$_3$) 173.1 (d, *J* = 7.7 Hz, **C**O), 138.3 (Ar-**C**), 133.0 (d, *J* = 3.1 Hz, Ar-**C**H), 131.3 (d, *J* = 10.9 Hz, Ar-**C**H), 129.0 (d, *J* = 15.4 Hz, Ar-**C**H), 128.9 (d, *J* = 175.1 Hz, Ar-**C**), 128.3 (Ar-**C**H), 127.6 (Ar-**C**H), 127.5 (Ar-**C**H), 72.9 (O**C**H$_2$), 67.1 (d, *J* = 7.9 Hz, O**C**H$_2$), 65.8 (O**C**H$_2$), 41.2 (**C**H$_2$), 37.5 (**C**H$_2$), 25.8 (d, *J* = 5.9 Hz, **C**H$_2$); δ_P (162 MHz, CDCl$_3$) 15.9 (Ph**P**=O); HRMS (ESI): calcd. for $C_{19}H_{22}NNaO_4P$, 382.1179. Found: [MNa]$^+$, 382.1184 (–1.3 ppm error).

3-Hydroxy-1-(2-oxido-2-phenyl-1,3,2-oxazaphosphinan-3-yl)propan-1-one (6-33)



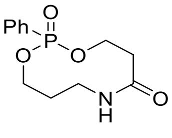
3-(Benzyloxy)-1-(2-oxido-2-phenyl-1,3,2-oxazaphosphinan-3-yl)propan-1-one **6-32** (90 mg, 0.25 mmol) was dissolved in dry EtOAc (3.0 mL) and placed under an argon atmosphere. Palladium on carbon (30 mg, Pd 10% on carbon) was then added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at RT under a slight positive pressure of hydrogen (balloon) for 3 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$_2$, 9:1 ethyl acetate: methanol) afforded the *title compound* as a colorless oil (50 mg, 56%); R_f = 0.20 (9:1 ethyl acetate: methanol); ν_{max}/cm^{-1} (thin film) 3396, 2890, 1674, 1439, 1381, 1250, 1130, 1018, 912, 749, 727, 695, 539; δ_H (400 MHz, CDCl$_3$) 7.78 – 7.66 (m, 2H, Ar-C**H**), 7.59 – 7.53 (m, 1H, Ar-C**H**), 7.53 – 7.42 (m, 2H, Ar-C**H**), 4.49 (tt, *J* = 10.9, 5.3 Hz, 2H, OC**H**$_2$ + C**H**$_2$), 4.21 (dddd, *J* = 14.1, 11.0, 8.8, 5.4 Hz, 1H, OC**H**$_2$), 3.81 (ddd, *J* = 11.1, 6.9, 4.0 Hz, 1H, C**H**$_2$OH), 3.71 (ddd, *J* = 11.2, 6.9, 4.0 Hz, 1H, C**H**$_2$OH), 3.36 – 3.02 (m, 3H, C**H**$_2$ + CH$_2$O**H**), 2.50 (ddd, *J* = 16.7, 6.9, 4.1 Hz, 1H, C**H**$_2$), 2.19 (dtt, *J* = 14.8, 10.3, 5.2 Hz, 1H, C**H**$_2$), 2.07 – 1.94 (m, 1H, C**H**$_2$); δ_C (100 MHz, CDCl$_3$) 174.7 (d, *J* = 7.9 Hz, **C**O), 133.3 (d, *J* = 3.1 Hz, Ar-**C**H), 131.2 (d, *J* = 10.8 Hz, Ar-C**H**), 129.1 (d, *J* = 15.3 Hz, Ar-C**H**), 128.7 (d, *J* = 176.1 Hz, Ar-**C**), 67.0 (d, *J* = 7.9 Hz, OCH_2), 58.6 (O**C**H_2), 41.1 (**C**H_2), 39.5 (**C**H_2), 25.7 (d, *J* = 6.0 Hz, **C**H_2); δ_P (162 MHz, $CDCl_3$) 16.3 (Ph**P**=O); HRMS (ESI): calcd. for $C_{12}H_{16}NNaO_4P$, 292.0709. Found: $[MNa]^+$, 292.0710 (–0.3 ppm error).

3-(3-Hydroxypropyl)-2-phenyl-1,3,2-oxazaphosphinan-4-one 2-oxide (6-34)



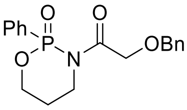
3-Hydroxy-1-(2-oxido-2-phenyl-1,3,2-oxazaphosphinan-3-yl)propan-1-one **6-33** (50 mg, 0.185 mmol) was dissolved in $CHCl_3$ (2.0 mL) and NEt_3 (280 μL, 2.0 mmol, 10 eq) was added, the mixture was stirred at RT overnight. Purification by flash column chromatography (SiO_2, 10:1 ethyl acetate: methanol) afforded the *title compound* as a colorless oil (35 mg, 70%); R_f = 0.40 (9:1 ethyl acetate: methanol); ν_{max}/cm^{-1} (thin film) 3415, 2950, 1683, 1440, 1336, 1282, 1244, 1127, 1024, 994, 943, 725, 693, 539; δ_H (400 MHz, $CDCl_3$) 7.82 – 7.70 (m, 2H, Ar-C**H**), 7.65 – 7.58 (m, 1H, Ar-C**H**), 7.55 – 7.47 (m, 2H, Ar-C**H**), 4.68 (tdd, *J* = 11.5, 8.8, 3.2 Hz, 1H, OC**H**$_2$), 4.36 (dddd, *J* = 22.1, 11.5, 5.5, 3.2 Hz, 1H, OC**H**$_2$), 3.79 – 3.58 (m, 3H, C**H**$_2$ + CH_2O**H**), 3.58 – 3.47 (m, 1H, C**H**$_2$), 3.18 (dtd, *J* = 14.2, 9.2, 5.1 Hz, 1H, C**H**$_2$), 3.01 (ddd, *J* = 17.0, 11.2, 5.6 Hz, 1H, C**H**$_2$), 2.84 (dt, *J* = 17.9, 3.0 Hz, 1H, C**H**$_2$), 1.84 (tdd, *J* = 14.4, 5.3, 3.5 Hz, 1H, C**H**$_2$), 1.68 (ddq, *J* = 14.1, 9.3, 4.7 Hz, 1H, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 170.2 (d, *J* = 3.9 Hz, **C**O), 133.9 (d, *J* = 3.1 Hz, Ar-**C**H), 132.4 (d, *J* = 10.8 Hz, Ar-**C**H), 129.1 (d, *J* = 15.4 Hz, Ar-**C**H), 126.4 (d, *J* = 179.9 Hz, Ar-**C**), 61.7 (d, *J* = 6.3 Hz, O**C**H_2), 58.3 (**C**H_2OH), 39.2 (d, *J* = 4.7 Hz, N**C**H_2), 35.2 (**C**H_2), 30.7 (**C**H_2); δ_P (162 MHz, $CDCl_3$) 19.9 (Ph**P**=O); HRMS (ESI): calcd. for $C_{12}H_{16}NNaO_4P$, 292.0709. Found: $[MNa]^+$, 292.0712 (–0.8 ppm error).

2-Phenyl-1,3,7,2-dioxazaphosphecan-6-one 2-oxide (6-35)



3-Hydroxy-1-(2-oxido-2-phenyl-1,3,2-oxazaphosphinan-3-yl)propan-1-one **6-33** (150 mg, 0.56 mmol) was dissolved in THF (6.0 mL) and NaH (60% in paraffin oil, 36 mg, 0.9 mmol, 1.5 eq) was added, the mixture was stirred at RT for 3 h. Quenched with sat. NH_4Cl aq. (5 mL), extracted with EtOAc (3 × 10 mL) and the combined organic layers were dried ($MgSO_4$). After filtration, the solvent was then concentrated *in vacuo* to give the *title compound* (as a 10:1 mixture of rotamers in solution in $CDCl_3$) as a colorless oil (102 mg, 68%); R_f = 0.15 (9:1 ethyl acetate: methanol); ν_{max}/cm^{-1} (thin film) 3291, 2960, 1654, 1559, 1439, 1235, 1132, 1071, 1006, 936, 748, 697, 562; δ_H (400 MHz, $CDCl_3$) 7.76 – 7.67 (m, 2H, Ar-C**H**, both rotamers), 7.57 – 7.50 (m, 1H, Ar-C**H**, both rotamers), 7.50 – 7.38 (m, 2H, Ar-C**H**, both rotamers), 6.74 (t, *J* = 6.1Hz, 1H, CON**H**, major rotamer), 6.35 (s, 1H, CON**H**, minor rotamer), 4.88 – 4.75 (m, 1H, C**H**$_2$, minor rotamer), 4.73 – 4.44 (m, 2H, OC**H**$_2$, both rotamers), 4.35 – 4.04 (m, 2H, OC**H**$_2$, both rotamers), 3.81 – 3.56 (m, 1H, C**H**$_2$, major rotamer), 3.51 – 3.24 (m, 1H, C**H**$_2$, both rotamers), 2.80 – 2.44 (m, 2H, C**H**$_2$, both rotamers), 2.32 – 2.13 (m, 1H, C**H**$_2$, both rotamers), 1.99 – 1.69 (m, 1H, C**H**$_2$, both rotamers); δ_C (100 MHz, $CDCl_3$) data for major rotamer only: 171.3 (**C**O), 132.6 (d, *J* = 3.0 Hz, Ar-**C**H), 131.1 (d, *J* = 10.1 Hz, Ar-**C**H), 128.7 (d, *J* = 15.6 Hz, Ar-**C**H), 128.6 (d, *J* = 196.3 Hz, Ar-**C**), 67.5 (d, *J* = 7.0 Hz, O**C**H$_2$), 64.7 (d, *J* = 7.6 Hz, O**C**H$_2$), 39.2 (**C**H$_2$), 38.8 (**C**H$_2$), 28.6 (d, *J* = 4.5 Hz, **C**H$_2$); Diagnostic ^{13}C NMR resonances for the minor rotamer: 173.4 (**C**O), 132.7 (d, *J* = 3.0 Hz, Ar-**C**H), 131.2 (d, *J* = 9.8 Hz, Ar-**C**H), 128.7 (d, *J* = 15.3 Hz, Ar-**C**H), 64.4 (d, *J* = 7.1 Hz, O**C**H$_2$), 30.3 (d, *J* = 6.3 Hz, **C**H$_2$); δ_P (162 MHz, $CDCl_3$) 19.0 (Ph**P**=O, major rotamer), 18.7 (Ph**P**=O, minor rotamer); HRMS (ESI): calcd. for $C_{12}H_{16}NNaO_4P$, 292.0709. Found: $[MNa]^+$, 292.0713 (–1.2 ppm error).

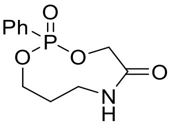
2-(Benzyloxy)-1-(2-oxido-2-phenyl-1,3,2-oxazaphosphinan-3-yl)ethan-1-one (6-36)



2-Phenyl-1,3,2-oxazaphosphinane 2-oxide **6-13** (197.2 mg, 1.0 mmol) was dissolved in dry THF (5 mL) and the temperature was lowered –78 °C (dry ice/acetone bath). *n*-BuLi (2.5 M in hexanes, 0.48 mL, 1.2 mmol, 1.2 eq) was added dropwise by syringe and the reaction was allowed to stir at –78 °C. After 1 hour, a solution of acid chloride

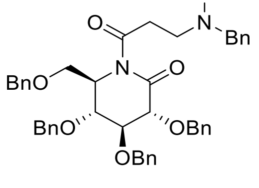
3-27 (1.5 mmol, 1.5 equiv. prepared using the general procedure with benzyloxyacetic acid) in THF (5 mL) was added slowly to the stirring reaction mixture. The reaction was allowed to warm to room temperature overnight before the addition of sat. aq. $NaHCO_3$ solution (20 mL). The aqueous layer was extracted with EtOAc (2 × 20 mL) and the combined organic layers were dried ($MgSO_4$). After filtration, the solvent was then concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 hexane: ethyl acetate → ethyl acetate) afforded the *title compound* as a yellow oil (280 mg, 81%). R_f= 0.22 (ethyl acetate); δ_H (400 MHz, $CDCl_3$) 7.63 – 7.53 (m, 2H, Ar-C**H**), 7.50 – 7.43 (m, 1H, Ar-C**H**), 7.42 – 7.30 (m, 2H, Ar-C**H**), 7.20 – 7.11 (m, 5H, Ar-C**H**), 4.59 – 4.45 (m, 2H, 1 H each from OC**H**$_2$ + C**H**$_2$), 4.45 (s, 2H, OC**H**$_2$), 4.37 (ddt, *J* = 15.5, 10.2, 5.1 Hz, 1H, OC**H**$_2$), 4.25 (d, *J* = 16.1 Hz, 1H, OC**H**$_2$), 4.08 (tdd, *J* = 11.1, 9.5, 4.9 Hz, 1H, OC**H**$_2$), 3.10 (ddt, *J* = 13.9, 11.2, 3.0 Hz, 1H, C**H**$_2$), 2.04 (dtq, *J* = 14.8, 10.2, 5.0 Hz, 1H, C**H**$_2$), 1.84 (dq, *J* = 14.3, 4.5, 3.9 Hz, 1H, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 171.8 (d, *J* = 7.6 Hz, **C**O), 137.0 (Ar-**C**), 132.8 (d, *J* = 3.1 Hz, Ar-**C**H), 130.7 (d, *J* = 10.8 Hz, Ar-**C**H), 128.8 (d, *J* = 173.7 Hz, Ar-**C**), 128.8 (d, *J* = 15.1 Hz, Ar-**C**H), 128.0 (Ar-**C**H), 127.7 (Ar-**C**H), 127.5 (Ar-**C**H), 73.0 (O**C**H$_2$), 70.1 (O**C**H$_2$), 67.3 (d, *J* = 8.0 Hz, O**C**H$_2$), 40.8 (**C**H$_2$), 25.3 (d, *J* = 5.5 Hz, **C**H$_2$); δ_P (162 MHz, $CDCl_3$) 15.4 (Ph**P**=O); HRMS (ESI): calcd. for $C_{18}H_{20}NNaO_4P$, 368.1022. Found: $[MNa]^+$, 368.1023 (–0.2 ppm error).

2-Phenyl-1,3,6,2-dioxazaphosphonan-5-one 2-oxide (6-37)



2-(Benzyloxy)-1-(2-oxido-2-phenyl-1,3,2-oxazaphosphinan-3-yl)ethan-1-one **6-36** (300 mg, 0.87 mmol) was dissolved in dry EtOAc (9.0 mL) and placed under an argon atmosphere. Palladium on carbon (90 mg, Pd 10% on carbon) was then added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at RT 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, 9:1 ethyl acetate: methanol) afforded the *title compound* (a 5:3:1 mixture of rotamers at RT) as a colorless oil (170 mg, 77%); R_f = 0.22 (9:1 ethyl acetate: methanol); ν_{max}/cm^{-1} (thin film) 3476, 3278, 2963, 1664, 1475, 1439, 1235, 1132, 1078, 1051, 977, 828, 750, 695, 580, 548, 508; δ_H (400 MHz, $CDCl_3$ at 50 °C, exists in $CDCl_3$ solution as a roughly 3:2 mixture of rotamers based on analysis of the ^{13}C NMR spectrum) 7.84 – 7.37 (m, 11H, Ar-C**H** both rotamers + CON**H** one rotamer), 6.91 (d, *J* = 8.4 Hz, 1H, CON**H** one rotamer), 5.10 (dd, *J* = 14.4, 9.4 Hz, 1H, OC**H**$_2$, one rotamer), 4.78 – 4.36 (m, 4H, C**H**$_2$, both rotamers), 4.29 – 3.79 (m, 5H, C**H**$_2$ both rotamers + OC**H**$_2$ one rotamer), 3.53 (td, *J* = 11.8, 5.1 Hz, 1H, C**H**$_2$, one rotamer), 3.16 – 2.25 (m, 2H, C**H**$_2$, both rotamers), 2.00 – 1.43 (m, 3H, C**H**$_2$ both rotamers + C**H**$_2$ one rotamer); δ_C (100 MHz, $CDCl_3$ at 50 °C, a 3:2 mixture of rotamers) 170.4 (NH**C**O, major rotamer), 169.1 (NH**C**O, minor rotamer), 132.8 (d, *J* = 3.3 Hz, Ar-**C**H, both rotamers), 131.2 (d, *J* = 10.0 Hz, Ar-**C**H, both rotamers), 128.5 (d, *J* = 15.8 Hz, Ar-**C**H, both rotamers), 126.6 (Ar-**C**, both rotamers), 67.7 (brs, O**C**H$_2$, minor rotamer), 67.0 (brs, O**C**H$_2$, minor rotamer), 64.7 (d, *J* = 7.8 Hz, O**C**H$_2$, major rotamer), 62.2 (d, *J* = 7.5 Hz, O**C**H$_2$, major rotamer), 38.8 (**C**H$_2$, minor rotamer), 38.2 (**C**H$_2$, major rotamer), 30.6 (**C**H$_2$, major rotamer), 25.5 (**C**H$_2$, minor rotamer); δ_P (162 MHz, $CDCl_3$) 20.2 (Ph**P**=O): 20.7 (Ph**P**=O): 21.4 (PhP=O) = 5:3:1; HRMS (ESI): calcd. for $C_{11}H_{14}NNaO_4P$, 278.0553. Found: [MNa]$^+$, 278.0551 (0.5 ppm error).

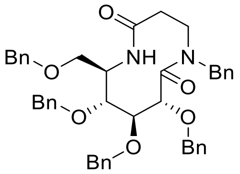
(9*H*-Fluoren-9-yl)methyl 3,4,5-tris(benzyloxy)-2-[(benzyloxy)methyl]-6-oxopiperidine-1-carboxylate (7-8)



A mixture of sugar lactam **7-3** (107.5 mg, 0.2 mmol), DMAP (2.4 mg, 0.02 mmol) and pyridine (0.097 mL, 1.2 mmol) in dry DCM (1.0 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride **2-12** (0.6 mmol, 3.0 equiv., freshly prepared from acid using the general procedure) in dry DCM (1.0 mL) was added and the resulting mixture was refluxed at 50 °C for 18 h. The mixture was then diluted with DCM (10 mL) and washed with 10% aq. HCl (10 mL). The aqueous layer was then extracted with DCM (3 × 10 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 2:1 hexane: ethyl acetate → 1:1 hexane: ethyl acetate) afforded the *title compound* (as a 5:4 rotamers) as a colorless oil (132 mg, 72%). R_f = 0.60 (1:1 hexane: ethyl acetate); δ_H (400 MHz, $CDCl_3$) 7.77 – 7.71 (m, 2H, Fmoc-C**H**, both rotamers), 7.63 (d, *J* = 7.1 Hz, 1H, Fmoc-C**H**, both rotamers), 7.49 – 7.19 (m, 36H, Ar-C**H**, both rotamers), 7.12 (d, *J* = 6.4 Hz, 1H, Fmoc-C**H**, both rotamers), 5.04 – 4.93 (m, 2H, OC**H**$_2$Ph, both rotamers), 4.75 (dd, *J* = 13.7, 10.1 Hz, 1H, CONC**H**, major rotamer), 4.65 (t, *J* = 10.3 Hz, 1H, COOCH$_2$C**H**, major rotamer), 4.60 – 4.36 (m, 11H, 3 × OC**H**$_2$Ph + NC**H**$_2$Ph + OC**H**$_2$CH, both rotamers), 4.24 (dt, *J* = 12.9, 6.6 Hz, 1H, OC**H**, both rotamers), 4.01 (dd, *J* = 4.0, 2.2 Hz, 1H, OC**H**, major rotamer), 3.88 (dd, *J* = 8.9, 4.3 Hz, 1H, OC**H**, major rotamer), 3.78 (dd, *J* = 10.5, 8.8 Hz, 1H, OC**H**, minor rotamer), 3.67 – 3.56 (m, 2H, BnOC**H**$_2$, both rotamers), 3.47 (td, *J* = 9.8, 5.3 Hz, 2H, NC**H**$_2$, both rotamers), 3.40 – 3.09 (m, 2H, COC**H**$_2$, both rotamers); δ_C (101 MHz, $CDCl_3$) for major rotamer only: 173.6 (N**C**O), 172.1 (N**C**O), 156.2 (O**C**O), 144.1 (Ar-**C**), 141.4 (Ar-**C**), 138.0 (Ar-**C**), 137.8 (Ar-**C**), 137.7 (Ar-**C**), 137.5 (Ar-**C**), 128.8 (Ar-**C**H), 128.6 (Ar-**C**H), 128.5 (Ar-**C**H), 128.3 (Ar-**C**H), 128.1 (Ar-**C**H), 128.0 (Ar-**C**H), 128.0 (Ar-**C**H), 127.8 (Ar-**C**H), 127.7 (Ar-**C**H), 127.4 (Ar-**C**H), 127.3 (Ar-**C**H), 127.2 (Ar-**C**H), 125.1 (Ar-**C**H), 120.0 (Ar-**C**H), 81.7 (O**C**H), 79.8 (O**C**H), 76.5 (O**C**H), 74.4 (O**C**H$_2$), 73.6 (O**C**H$_2$), 73.3 (O**C**H$_2$), 71.7 (O**C**H$_2$), 69.3 (O**C**H$_2$), 67.6 (O**C**H$_2$), 55.5 (N**C**H$_2$), 50.6 (N**C**H), 47.4 (Ar-C**C**H), 43.2 (N**C**H$_2$), 37.7 (CO**C**H$_2$); Diagnostic ^{13}C NMR resonances for the minor rotamer: 173.5 (N**C**O), 172.1 (N**C**O), 156.6 (O**C**O), 144.2 (Ar-**C**), 141.4 (Ar-**C**), 137.8 (Ar-**C**), 137.8 (Ar-**C**), 137.7 (Ar-**C**), 137.4 (Ar-**C**), 128.7 (Ar-**C**H), 128.6 (Ar-**C**H), 128.0 (Ar-**C**H), 127.7 (Ar-**C**H), 127.5 (Ar-**C**H), 127.2 (Ar-**C**H), 125.1 (Ar-**C**H), 120.1 (Ar-**C**H), 81.5 (O**C**H), 79.6 (O**C**H), 74.5 (O**C**H$_2$), 73.8 (O**C**H$_2$), 73.4 (O**C**H$_2$), 71.9 (O**C**H$_2$), 69.6 (O**C**H$_2$), 67.6 (O**C**H$_2$), 55.7 (N**C**H$_2$), 50.8 (N**C**H$_2$), 47.5

(Ar-C**C**H), 42.2 (N**C**H$_2$), 38.2(CO**C**H$_2$); HRMS (ESI): calcd. for $C_{59}H_{56}N_2NaO_8$, 943.3929. Found: [MNa]$^+$, 943.3966 (–4.0 ppm error).

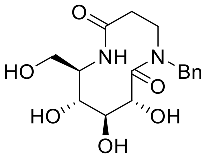
5-Benzyl-7,8,9-tris(benzyloxy)-10-[(benzyloxy)methyl]-1,5-diazecane-2,6-dione (7-9)



The *N*-acylated product **7-8** (120 mg, 0.13 mmol) was then re-dissolved in DCM (1.3 mL) and DBU (0.194 mL, 1.3 mmol) was added, followed by stirring at RT overnight, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 10:1 hexane: ethyl acetate →1:2 hexane: ethyl acetate) afforded the *title compound* as (as a 10:3:2 mixture of rotamers A:B:C) a colorless oil (61 mg, 67%); R_f = 0.24 (1:1 hexane: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3408, 3062, 3030, 2924, 2864, 1660, 1453, 1098, 736, 698; δ_H (400 MHz, $CDCl_3$) 7.56 – 7.06 (m, 57H, Ar-C**H**, all rotamers), 6.90 (dd, *J* = 7.2, 2.3 Hz, 2H, Ar-C**H**, all rotamers), 5.93 (d, *J* = 10.3 Hz, 1H, CON**H**, rotamer A), 5.56 (d, *J* = 10.3 Hz, 1H, CON**H**, rotamer C), 5.43 (d, *J* = 10.2 Hz, 1H, CON**H**, rotamer B), 5.22 – 3.68 (m, 36H, 5 × OC**H$_2$** + NC**H$_2$**+ 3 × OC**H** + NHC**H**, all rotamers), 3.63 – 3.23 (m, 3H, NC**H$_2$**, all rotamers), 2.84 – 2.71 (m, 2H, C**H$_2$**, rotamer A), 2.50 – 2.41 (m, 2H, C**H$_2$**, rotamer B), 2.34 – 2.25 (m, 2H, C**H$_2$**, rotamer C); δ_C (101 MHz, $CDCl_3$) data for the major rotamer only: 172.0 (NH**C**O), 169.6 (N**C**O), 138.9 (Ar-**C**), 138.2 (Ar-**C**), 138.2 (Ar-**C**), 137.8 (Ar-**C**), 136.1 (Ar-**C**), 128.9 (Ar-**C**H), 128.8 (Ar-**C**H), 128.6 (Ar-**C**H), 128.5 (Ar-**C**H), 128.5 (Ar-**C**H), 128.4 (Ar-**C**H), 128.3 (Ar-**C**H), 128.1 (Ar-**C**H), 127.9 (Ar-**C**H), 126.9 (Ar-**C**H), 78.8 (O**C**H), 78.5 (O**C**H), 74.2 (O**C**H$_2$), 74.0 (O**C**H$_2$), 73.2 (O**C**H$_2$), 72.7 (O**C**H), 72.2 (O**C**H$_2$), 69.2 (O**C**H$_2$), 53.1 (NH**C**H), 51.2 (N**C**H$_2$Ph), 41.1 (N**C**H$_2$), 34.9 (CO**C**H$_2$); Diagnostic ^{13}C NMR resonances for the minor rotamer: 171.8 (NH**C**O), 171.7 (NH**C**O), 171.5 (N**C**O), 166.2 (N**C**O), 151.9 (Ar-**C**), 138.5 (Ar-**C**), 138.2 (Ar-**C**), 138.1 (Ar-**C**), 138.1 (Ar-**C**), 138.0 (Ar-**C**), 138.0 (Ar-**C**), 137.4 (Ar-**C**), 137.4 (Ar-**C**), 135.9 (Ar-**C**), 129.4 (Ar-**C**H), 129.2

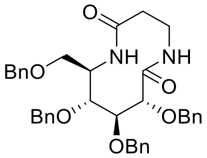
(Ar-**C**H), 129.0 (Ar-**C**H), 128.7 (Ar-**C**H), 128.7 (Ar-**C**H), 128.4 (Ar-**C**H), 128.3 (Ar-**C**H), 128.2 (Ar-**C**H), 128.2 (Ar-**C**H), 128.2 (Ar-**C**H), 128.0 (Ar-**C**H), 128.0 (Ar-**C**H), 128.0 (Ar-**C**H), 127.9 (Ar-**C**H), 127.5 (Ar-**C**H), 127.5 (Ar-**C**H), 105.9 (O**C**H), 90.6 (O**C**H), 81.9 (O**C**H), 81.5 (O**C**H), 76.2 (O**C**H), 75.8 (O**C**H), 75.8 (O**C**H), 74.9 (O**C**H$_2$), 74.2 (O**C**H), 73.9 (O**C**H$_2$), 73.6 (O**C**H$_2$), 73.1 (O**C**H$_2$), 71.6 (O**C**H$_2$), 70.1 (O**C**H$_2$), 68.2 (O**C**H$_2$), 67.3 (O**C**H$_2$), 53.3 (NH**C**H), 52.6 (NH**C**H), 50.8 (N**C**H$_2$Ph), 50.4 (N**C**H$_2$Ph), 49.9 (N**C**H$_2$Ph), 47.3 (N**C**H$_2$), 44.9 (N**C**H$_2$), 44.1 (N**C**H$_2$), 37.9 (CO**C**H$_2$), 37.7 (CO**C**H$_2$), 36.0 (CO**C**H$_2$), 29.8 (CO**C**H$_2$); HRMS (ESI): calcd. for $C_{44}H_{46}N_2NaO_6$, 721.3248. Found: $[MNa]^+$, 721.3268 (–2.7 ppm error).

5-Benzyl-7,8,9-trihydroxy-10-(hydroxymethyl)-1,5-diazecane-2,6-dione (7-10)



The 5-benzyl-7,8,9-tris(benzyloxy)-10-[(benzyloxy)methyl]-1,5-diazecane-2,6-dione **7-9** (122 mg, 0.175 mmol) was dissolved in methanol (3 mL) and ethanol (1 mL), then palladium hydroxide on carbon (20 mg, 20% w/w) was added, together with 1 drop 1 M aqueous HCl solution. The mixture was stirred for 48 hours under a positive pressure of hydrogen (via balloon). The mixture was then filtered through Celite, washed with methanol where the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 9:1 ethyl acetate: methanol →3:1 ethyl acetate: methanol) afforded the *title compound* as a pale yellow oil (37 mg, 62%); R_f = 0.26 (3:1 ethyl acetate: methanol); ν_{max}/cm^{-1} (thin film) 3307, 1634, 1496, 1453, 1364, 1076, 1049, 735, 698; δ_H (400 MHz, methanol-*d$_4$*) 7.37 – 7.10 (m, 5H, Ar-C**H**), 5.38 (d, *J* = 15.1 Hz, 1H, CON**H**), 4.82 – 4.92 (m, 1H, COC**H**OH), 4.17 (s, 1H, C**H**OH), 3.96 (s, 1H, C**H**OH), 3.86 – 3.67 (m, 4H, C**H$_2$**OH + NC**H$_2$**Ph), 3.54 (dd, *J* = 8.8, 3.5 Hz, 1H, NHC**H**), 3.47 – 3.24 (m, 2H, NC**H$_2$**), 2.51 (td, *J* = 12.4, 2.9 Hz, 1H, COC**H$_2$**), 2.21 (dd, *J* = 12.5, 4.2 Hz, 1H, COC**H$_2$**); δ_C (101 MHz, methanol-*d$_4$*) 176.2 (NH**C**O), 174.3 (**N**CO), 138.2 (Ar-**C**), 129.7 (Ar-**C**H) × 2, 128.8 (Ar-**C**H) × 2, 128.6 (Ar-**C**H), 81.0 (CO**C**HOH), 75.2 (**C**HOH), 65.0 (**C**HOH), 63.2 (**C**H$_2$OH), 52.8 (NH**C**H), 49.8 (N**C**H$_2$Ph), 45.6 (N**C**H$_2$), 37.4 (CO**C**H$_2$); HRMS (ESI): calcd. for $C_{16}H_{22}N_2NaO_6$, 361.1370. Found: [MNa]$^+$, 361.1372 (–0.5 ppm error).

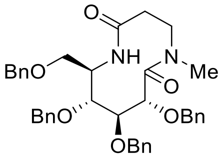
7,8,9-Tris(benzyloxy)-10-[(benzyloxy)methyl]-1,5-diazecane-2,6-dione (7-11)



A mixture of sugar lactam **7-3** (107.5 mg, 0.2 mmol), DMAP (2.4 mg, 0.02 mmol) and pyridine (0.097 mL, 1.2 mmol) in dry DCM (1.0 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride (0.6 mmol, 3.0 equiv., freshly prepared from Fmoc-β-alanine using the general procedure) in dry DCM (1.0 mL) was added and the resulting mixture was refluxed at 50 °C for 18 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 (28% starting lactam left), and concentrated *in vacuo*. The crude material (128 mg) was then re-dissolved in DCM (2 mL) and DBU (300 mL, 2.0 mmol) was added, followed by stirring at RT for 30 min, 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 colorless oil (36 mg, 30%); R_f = 0.21 (1:1 hexane: ethyl acetate); δ_H (400 MHz, $CDCl_3$-*d*) 7.31 – 7.08 (m, 20H, Ar-C**H**), 6.78 (dd, *J* = 10.2, 2.8 Hz, 1H, N**H**), 5.85 (d, *J* = 10.4 Hz, 1H, N**H**), 4.82 (t, *J* = 10.7 Hz, 2H, OC**H$_2$**CH), 4.60 – 4.50 (m, 3H, OC**H$_2$** + OC**H**), 4.46 – 4.33 (m, 4H, OC**H$_2$**), 4.26 – 4.04 (m, 1H, OC**H**), 3.92 – 3.82 (m, 3H,OC**H$_2$** + OC**H**), 3.61 (dd, *J* = 8.8, 6.3 Hz, 1H, NHC**H**), 3.31 (dd, *J* = 9.2, 2.8 Hz, 1H, COC**H$_2$**), 3.15 – 3.02 (m, 1H, COC**H$_2$**), 2.68 (ddd, *J* = 14.2, 8.1, 3.4 Hz, 1H, NHC**H$_2$**), 2.39 (dt, *J* = 14.3, 8.6 Hz, 1H, NHC**H$_2$**); δ_C (101 MHz, $CDCl_3$-*d*) 173.6 (NH**C**O), 169.5 (NH**C**O), 138.6 (Ar-**C**), 138.4 (Ar-**C**), 138.2 (Ar-**C**), 137.3 (Ar-**C**), 128.5 (Ar-**C**H), 128.3 (Ar-**C**H), 128.3 (Ar-**C**H), 128.3 (Ar-**C**H), 128.1 (Ar-**C**H), 127.8 (Ar-**C**H), 127.7 (Ar-**C**H), 127.7 (Ar-**C**H), 127.6 (Ar-**C**H), 127.6 (Ar-**C**H), 85.1 (O**C**H), 83.6 (O**C**H), 76.1 (O**C**H), 75.6 (O**C**H$_2$), 75.3 (O**C**H$_2$), 73.4 (O**C**H$_2$), 73.3 (O**C**H$_2$), 69.5 (O**C**H$_2$CH), 53.0 (NH**C**H), 36.9 (CO**C**H$_2$), 34.0 (NH**C**H$_2$); HRMS (ESI): calcd. for

$C_{37}H_{40}N_2NaO_6$, 631.2779. Found: $[MNa]^+$, 631.2786 (–1.2 ppm error).

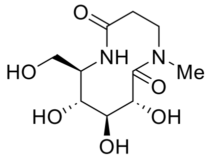
7,8,9-Tris(benzyloxy)-10-[(benzyloxy)methyl]-5-methyl-1,5-diazecane-2,6-dione (7-12)



A mixture of sugar lactam **7-3** (107.5 mg, 0.2 mmol), DMAP (2.4 mg, 0.02 mmol) and pyridine (0.097 mL, 1.2 mmol) in dry DCM (1.0 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride (0.6 mmol, 3.0 equiv., freshly prepared from Fmoc-*N*-methyl-β-alanine using the general procedure) in dry DCM (1.0 mL) was added and the resulting mixture was refluxed at 50 °C for 18 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 (no starting lactam left), and concentrated *in vacuo*. The crude material (166 mg) was then re-dissolved in DCM (2 mL) and DBU (300 mL, 2.0 mmol) was added, followed by stirring at RT for 30 min, before the solvent was removed in vacuo. Purification by flash column chromatography (SiO_2, 2:1 dichloromethane: ethyl acetate) afforded the title compound (as a 10:1:1:1 mixture of rotamers in $CDCl_3$) as a colorless oil (66 mg, 53%); δ_H (400 MHz, $CDCl_3$-*d*) 7.51 – 7.18 (m, 30 H, Ar-C**H**, all rotamers), 6.29 (d, *J* = 10.1 Hz, 1H, N**H**, minor rotamer), 5.89 (d, *J* = 10.0 Hz, 1H, N**H**, major rotamer), 5.64 (d, *J* = 10.2 Hz, 1H, N**H**, minor rotamer), 5.28 (d, *J* = 10.4 Hz, 1H, N**H**, minor rotamer), 5.02 – 4.83 (m, 3H, 3 × OC**H**, all rotamers), 4.72 – 4.32 (m, 10H, 5 × OC**H₂**, all rotamers) 4.26 – 4.11 (m, 2H, C**H₂**, all rotamers), 3.83 – 3.35 (m, 3H, C**H** + C**H₂**, all rotamers), 3.00 (s, 3H, NC**H₃**, minor rotamer), 2.90 (s, 3H, NC**H₃**, minor rotamer), 2.84 (s, 3H, NC**H₃**, minor rotamer), 2.59 (s, 3H, NC**H₃**, major rotamer); δ_C (101 MHz, $CDCl_3$-*d*) 171.7 (NH**C**O), 169.4 (NH**C**O), 138.9 (Ar-**C**), 138.4 (Ar-**C**), 138.2 (Ar-**C**), 138.0 (Ar-**C**), 128.5 (Ar-**C**H), 128.5 (Ar-**C**H), 128.4 (Ar-**C**H), 128.4 (Ar-**C**H), 128.2 (Ar-**C**H), 128.0 (Ar-**C**H), 127.9 (Ar-**C**H), 127.7 (Ar-**C**H), 127.7 (Ar-**C**H), 78.4 (O**C**H), 78.2 (O**C**H), 74.1 (O**C**H₂), 74.1 (O**C**H₂), 73.2 (O**C**H₂), 72.4 (O**C**H), 72.0

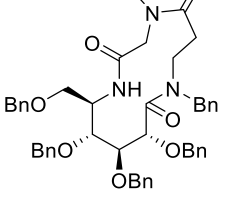
(OCH2), 69.1 (OCH2CH), 53.0 (NHCH), 43.7 (COCH2), 35.7 (NCH3), 34.9 (NHCH2); HRMS (ESI): calcd. for $C_{38}H_{42}N_2NaO_6$, 645.2935. Found: $[MNa]^+$, 645.2939 (–0.7 ppm error).

(7*R*,8*S*,9*R*,10*R*)-7,8,9-trihydroxy-10-(hydroxymethyl)-5-methyl-1,5-diazecane-2,6-dione (7-13)



The 7,8,9-tris(benzyloxy)-10-[(benzyloxy)methyl]-5-methyl-1,5-diazecane-2,6-dione **7-12** (66 mg, 0.106 mmol) was dissolved in methanol (1 mL) and ethanol (0.3 mL), then palladium hydroxide on carbon (10 mg, 20% w/w) was added, together with 1 drop 1 M aqueous HCl solution. The mixture was stirred for 48 hours under a positive pressure of hydrogen (via balloon). The mixture was then filtered through Celite, washed with methanol where the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 3:1 ethyl acetate: methanol) afforded the *title compound* as a pale-yellow oil (20 mg, 72%); $R_f = 0.26$ (3:1 ethyl acetate: methanol); δ_H (400 MHz, methanol-*d4*) 4.64 – 3.98 (m, 4H, 4 × C**H**), 3.96 – 3.58 (m, 2H, C**H2**OH), 3.29 – 3.22 (m, 2H, C**H2**), 3.07 – 2.86 (m, 2H, C**H2**), 2.72 (s, 3H, NC**H3**); δ_C (101 MHz, methanol-*d4*) 174.8 (**C**O), 171.5 (**C**O), 73.3 (**C**HOH), 72.8 (**C**HOH), 68.6 (**C**HOH), 63.4 (**C**H2OH), 54.5 (**C**HNH), 45.9 (N**C**H3), 34.3 (**C**H2), 31.5 (**C**H2); HRMS (ESI): calcd. for $C_{10}H_{19}N_2O_6$, 263.1238. Found: $[MH]^+$, 263.1232 (2.2 ppm error).

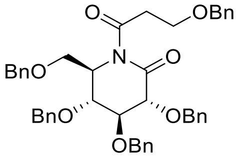
4,8-Dibenzyl-10,11,12-tris(benzyloxy)-13-[(benzyloxy)methyl]-1,4,8-triazacyclotridecane-2,5,9-trione (7-14)



5-benzyl-7,8,9-tris(benzyloxy)-10-[(benzyloxy)methyl]-1,5-diazecane-2,6-dione **7-10**

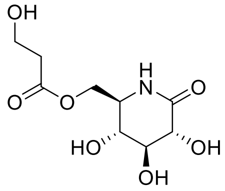
(130 mg, 0.186 mmol), DMAP (2.4 mg, 0.02 mmol) and pyridine (0.097 mL, 1.2 mmol) in dry DCM (1.0 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride (0.6 mmol, 3.0 equiv., freshly prepared from Fmoc-*N*-methyl-alanine using the general procedure) in dry DCM (1.0 mL) was added and the resulting mixture was refluxed at 50 °C for 18 h. The mixture was then diluted with DCM (10 mL) and washed with 10% aq. HCl (10 mL). The aqueous layer was then extracted with DCM (3 × 10 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated in vacuo. The crude material was then re-dissolved in DCM (2 mL) and DBU (300 mL, 2.0 mmol) was added, followed by stirring at RT for 30 min, before the solvent was removed in vacuo. Purification by flash column chromatography (SiO_2, 2:1 hexane: ethyl acetate → 1:1 hexane: ethyl acetate) afforded the title compound (as a 10:7:7:3:3 mixture of rotamers A:B:C:D:E in $CDCl_3$) as a colorless oil (28 mg, 18%); $R_f = 0.40$ (1:1 hexane: ethyl acetate); δ_H (400 MHz, $CDCl_3$) 7.39 – 7.12 (m, 45H, Ar-C**H**, all rotamers), 5.72 (d, *J* = 10.1 Hz, 1H, N**H**, rotamer B), 5.46 (d, *J* = 15.1 Hz, 1H, N**H**, rotamer C), 5.18 (d, *J* = 11.2 Hz, 1H, N**H**, rotamer D), 5.09 (d, *J* = 14.2 Hz, 1H, N**H**, rotamer A), 4.95 (d, *J* = 10.1 Hz, 1H, N**H**, rotamer E), 4.89 – 4.15 (m, 17 H, OC**H**$_2$ + NC**H**$_2$Ph, all rotamers), 4.04 – 3.36 (m, 11H, OC**H** + C**H** + C**H**$_2$, all rotamers), 2.46 – 1.96 (m, 2H, C**H**$_2$, all rotamers); δ_C (101 MHz, $CDCl_3$) 171.6 (N**C**O), 171.5 (N**C**O), 167.3 (NH**C**O), 138.0 (Ar-**C**), 137.9 (Ar-**C**), 137.9 (Ar-**C**), 137.7 (Ar-**C**), 137.6 (Ar-**C**), 137.0 (Ar-**C**), 128.8 (Ar-**C**H), 128.7 (Ar-**C**H), 128.7 (Ar-**C**H), 128.6 (Ar-**C**H), 128.6 (Ar-**C**H), 128.5 (Ar-**C**H), 128.5 (Ar-**C**H), 128.4 (Ar-**C**H), 128.4 (Ar-**C**H), 128.3 (Ar-**C**H), 128.3 (Ar-**C**H), 128.2 (Ar-**C**H), 128.1 (Ar-**C**H), 128.0 (Ar-**C**H), 128.0 (Ar-**C**H), 127.9 (Ar-**C**H), 127.8 (Ar-**C**H), 127.6 (Ar-**C**H), 82.4 (OC**H**), 78.9 (OC**H**), 76.0 (OC**H**), 74.1 (OC**H**$_2$), 73.4 (OC**H**$_2$), 72.2 (OC**H**$_2$), 71.4 (OC**H**$_2$), 69.5 (OC**H**$_2$CH), 51.1 (NHC**H**), 50.7 (N**C**H$_2$), 50.0 (N**C**H$_2$), 49.9 (CO**C**H$_2$N), 45.5 (CO**C**H$_2$), 32.6 (N**C**H$_2$); HRMS (ESI): calcd. for $C_{53}H_{55}N_3NaO_7$, 868.3932. Found: $[MNa]^+$, 868.3979 (–5.4 ppm error).

3,4,5-Tris(benzyloxy)-6-[(benzyloxy)methyl]-1-[3(benzyloxy) propanoyl] piperidin-2-one (7-17)



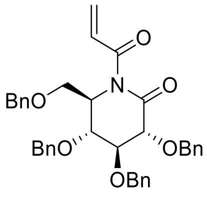
A mixture of sugar lactam **7-3** (161.3 mg, 0.3 mmol), DMAP (3.7 mg, 0.03 mmol) and pyridine (0.146 mL, 1.8 mmol) in dry DCM (1.5 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride **3-30** (0.9 mmol, 3.0 equiv., freshly prepared from xxx using the general procedure) in dry DCM (1.5 mL) was added and the resulting mixture was refluxed at 50 °C for 18 h. The solvent was concentrated *in vacuo*, purification by flash column chromatography (SiO_2, 3:1 hexane: ethyl acetate→ ethyl acetate) afforded the title compound as a colorless oil (135 mg, 50%) and 27% stating lactam left. R_f = 0.70 (1:2 hexane: ethyl acetate); δ_H (400 MHz, $CDCl_3$) 7.41 – 7.18 (m, 25H, Ar-C**H**), 4.97 (d, *J* = 11.3 Hz, 2H, OC**H**$_2$), 4.72 (d, *J* = 11.4 Hz, 1H, OC**H**$_2$), 4.61 (d, *J* = 11.4 Hz, 1H, OC**H**$_2$), 4.54 (s, 5H, OC**H**$_2$), 4.39 (d, *J* = 1.9 Hz, 2H, OC**H**$_2$), 4.35 (d, *J* = 8.5 Hz, 1H, OC**H**$_2$), 4.00 (dd, *J* = 4.1, 2.0 Hz, 1H, OC**H**), 3.88 – 3.74 (m, 3H, 2 × OC**H** + NC**H**), 3.60 (dd, *J* = 9.6, 6.5 Hz, 1H, OC**H**$_2$CH), 3.46 (dd, *J* = 9.6, 3.9 Hz, 1H, OC**H**$_2$CH), 3.29 (td, *J* = 6.2, 3.7 Hz, 2H, COC**H**$_2$); δ_C (101 MHz, $CDCl_3$) 173.6 (N**C**O), 172.2 (N**C**O), 138.4 (Ar-**C**), 138.0 (Ar-**C**), 137.7 (Ar-**C**), 137.6 (Ar-**C**), 137.5 (Ar-**C**), 128.6 (Ar-**C**H), 128.5 (Ar-**C**H), 128.5 (Ar-**C**H), 128.3 (Ar-**C**H), 128.1 (Ar-**C**H), 128.0 (Ar-**C**H), 128.0 (Ar-**C**H), 128.0 (Ar-**C**H), 127.9 (Ar-**C**H), 127.8 (Ar-**C**H), 127.8 (Ar-**C**H), 127.7 (Ar-**C**H), 81.8 (O**C**H), 79.8 (O**C**H), 76.5 (O**C**H), 74.4 (O**C**H$_2$), 73.7 (O**C**H$_2$), 73.4 (O**C**H$_2$), 73.2 (O**C**H$_2$), 71.7 (O**C**H$_2$), 69.5 (O**C**H$_2$), 65.7 (O**C**H$_2$), 55.6 (N**C**H), 39.7 (CO**C**H$_2$).

3,4,5-Trihydroxy-6-(hydroxymethyl)-1-(3-hydroxypropanoyl)piperidin-2-one (7-19)



This material **7-17** (0.5 mmol, 135 mg) was re-dissolved in MeOH (5.0 mL)/EtOH (1.5 mL) and placed under an argon atmosphere. Palladium hydroxide on coal (30 mg, 20% w/w) was added, together with a few aqueous HCl solution (1M). Then the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at RT under a slight positive pressure of hydrogen (balloon) for 48 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 (3.0 mL, not dissolved well) and triethylamine (60 µL, 0.3 mmol) added, and stirred at RT for 16 h, then reduced *in vacuo*. Purification by flash column chromatography (SiO_2, ethyl acetate → 3:1 ethyl acetate: methanol) afforded the title compound as a colorless oil (53 mg, 71%); R_f = 0.20 (3:1 ethyl acetate: methanol); δ_H (400 MHz, methanol-*d₄*) 4.39 (dd, *J* = 11.6, 2.6 Hz, 1H, HOC**H**), 4.21 (dd, *J* = 11.6, 5.2 Hz, 1H, HOC**H**), 3.91 – 3.86 (m, 1H, HOC**H**), 3.83 (t, *J* = 6.0 Hz, 2H, HOC$\mathbf{H_2}$), 3.67 – 3.59 (m, 2H, OC$\mathbf{H_2}$), 3.47 – 3.42 (m, 1H, NHC**H**), 2.61 – 2.56 (m, 2H, COC$\mathbf{H_2}$); δ_C (101 MHz, methanol-*d₄*) 174.0 (NH**C**O), 173.5 (**C**OO), 75.3 (HO**C**H), 72.5 (HO**C**H), 69.7 (HO**C**H), 64.7 (HO**C**H_2), 58.6 (O**C**H_2), 56.5 (NH**C**H), 38.3 (CO**C**H_2); HRMS (ESI): calcd. for $C_9H_{14}NO_7$, 248.0776. Found: $[MH]^+$, 248.0762 (5.4 ppm error).

(3*R*,4*S*,5*R*,6*R*)-1-acryloyl-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)piperidin-2-one (7-20)



To a stirring solution of aza-sugar **7-3** (538 mg, 1.0 mmol) in dry THF (3.6 mL) cooled to 0°C was added a solution of MeMgBr (3.0 M in diethyl ether, 0.36 mL) via dropwise addition using a syringe pump. The reaction mixture was allowed to stir for 10 min at 0°C after addition was completed. Acryloyl chloride (136 mg, 1.5 mmol) was then added in a single portion and the reaction mixture was stirred for an additional 2 h at 0°C. The reaction mixture was then quenched with sat. aq. NH_4Cl (10 mL) and the mixture was extracted with Et_2O (10 mL). The organic layer was washed with sat. aq. $NaHCO_3$ (2 × 10 mL), and organic extracts dried over $MgSO_4$ and concentrated in vacuo. Purification by flash column chromatography (SiO_2, 4:1 hexane: ethyl acetate) afforded the title compound as a colorless oil (430 mg, 73%); R_f = 0.42 (2:1 hexane: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3063, 3030, 2866, 1722, 1684, 1402, 1185, 1091, 1069, 1027, 735, 696; δ_H (400 MHz, $CDCl_3$-*d*) 7.50 – 7.27 (m, 20H, Ar-C**H**), 7.17 (dd, *J* = 16.9, 10.4 Hz, 1H, C**H**=CH_2), 6.50 (dd, *J* = 16.9, 1.7 Hz, 1H, CH=C**H**H'), 5.86 (dd, *J* = 10.4, 1.7 Hz, 1H, CH=CH**H'**), 5.10 (d, *J* = 11.2 Hz, 1H, OC**H**$_2$Ph), 5.09 – 5.00 (m, 1H, NC**H**), 4.84 (d, *J* = 11.4 Hz, 1H, OC**H**$_2$), 4.72 (d, *J* = 11.4 Hz, 1H, OC**H**$_2$), 4.69 – 4.60 (m, 3H, OC**H**$_2$Ph + OC**H**$_2$), 4.54 – 4.43 (m, 3H, OC**H**$_2$ + OC**H**), 4.09 (dd, *J* = 4.6, 2.3 Hz, 1H, OC**H**), 3.98 (ddd, *J* = 8.8, 4.6, 0.8 Hz, 1H, OC**H**), 3.74 (dd, *J* = 9.7, 6.0 Hz, 1H, OC**H**$_2$), 3.59 (dd, *J* = 9.7, 4.0 Hz, 1H, OC**H**$_2$); δ_C (100 MHz, $CDCl_3$-*d*) 172.5 (**C**O), 168.1 (**C**O), 137.9 (Ar-**C**), 137.6 (Ar-**C**), 137.4 (Ar-**C**), 137.4 (Ar-**C**), 131.1 (**C**H=CH_2), 129.3 (CH=**C**H$_2$), 128.5 (Ar-**C**H), 128.4 (Ar-**C**H), 128.4 (Ar-**C**H), 128.4 (Ar-**C**H), 128.3 (Ar-**C**H), 128.0 (Ar-**C**H), 127.9 (Ar-**C**H), 127.9 (Ar-**C**H), 127.8 (Ar-**C**H), 127.7 (Ar-**C**H), 81.7 (O**C**H), 79.4 (O**C**H), 76.6 (O**C**H), 74.4 (O**C**H$_2$), 73.7 (O**C**H$_2$), 73.3 (O**C**H$_2$), 71.8 (O**C**H$_2$), 69.7 (O**C**H$_2$), 56.1(N**C**H); HRMS (ESI): calcd. for $C_{37}H_{37}NNaO_6$, 614.2513. Found: [MNa]$^+$, 614.2528 (–2.5 ppm error).

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Appendices

Appendix I. A Consecutive Ring-Expansion Strategy towards the Macrocyclic Core of the Solomonamide Natural Products

Appendix II. Synthesis of medium-ring lactams and macrocyclic peptide mimetics *via* conjugate addition/ring expansion cascade reactions

Appendix III. Ring Expansion Strategies for the Synthesis of Medium Sized Ring and Macrocyclic Sulfonamides

Appendix IV. Ring expansion reactions of P=O-containing molecules

A Consecutive Ring-Expansion Strategy towards the Macrocyclic Core of the Solomonamide Natural Products

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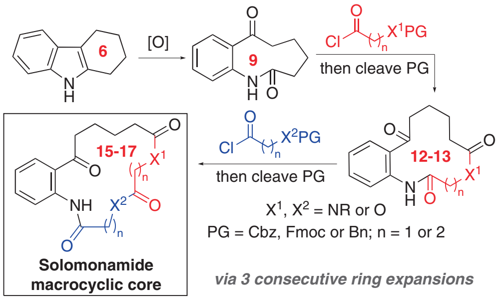
Published as part of the Special Section
13th EuCheMS Organic Division Young Investigator Workshop



Received: 21.07.2022
Accepted after revision: 29.08.2022
Published online: 29.08.2022 (Accepted Manusript), 30.09.2022 (Version of Record)
DOI: 10.1055/a-1932-9717; Art ID: ST-2022-07-0334-L

Crowd-Reviewed

Abstract A synthetic strategy based on the application of three consecutive ring-expansion reactions has been used in the synthesis of analogues of the macrocyclic core of the solomonamide natural products. Starting from a simple, readily available tetrahydrocarbazole, oxidative ring expansion is followed by two further 3- and 4-atom ring-expansion reactions, enabling the insertion of amino acid and hydroxy acid derived linear fragments into 15- to 17-membered-ring-enlarged macrocyclic products.

Key words macrocycles, medium-sized rings, ring expansion, natural product analogues, lactams, lactones, solomonamides

Solomonamides A and B were first isolated in 2011 by Zampella and coworkers from the marine sponge *Theonella swinhoei*.[2] Interest in their total synthesis is influenced by their anti-inflammatory properties and with natural supplies scarce, total synthesis is necessary to facilitate further biological studies. The original structural assignments of solomonamides A and B are depicted in Figure 1 (**1a** and **1b**). However, following the first synthesis of **1b** by Reddy and coworkers in 2016, a structural reassignment of solomonamide B was made (**2b** – with the highlighted stereogenic centres inverted) and this was confirmed unambiguously by total synthesis.[3] Reddy's work also cast doubt on the original assignment of solomonamide A, and indeed, the Reddy group duly reported its total synthesis and structural reassignment as predicted (**2a**) in 2018.[4]

Various other synthetic and associated biological studies focused on the solomonamide natural products have also been reported, by Reddy[5] and others.[6] Assembly of the macrocyclic core is a key step in the synthesis,[7] and unsurprisingly, all syntheses to date have focused on end-to-end macrocyclisation strategies (Scheme 1a). For example, in the seminal reports by Reddy and coworkers[3–5] a ligand-free Heck macrocyclisation strategy was adopted, typified by the conversion of linear precursor **3** into macrocycle **4** using Pd(OAc)$_2$.[3,8] In contrast, Sarabia and coworkers chose to perform the key macrocyclisation via a ring-closing metathesis reaction, using the Hoveyda–Grubbs second-generation (HG II) catalyst. This is typified by the high-yielding synthesis of macrocycle **6** from diene **5**.[6d,9] Notably, both of these impressive reactions are performed under relatively high dilution conditions, which is a common technique used in macrocyclisation reactions to reduce the impact of competing intermolecular coupling and other side reactions.[10]

William P. Unsworth After completing his Ph.D. in Oxford, Will moved to his current institution, the University of York, first as a postdoctoral research associate in the group of Prof. Richard Taylor, before moving onto a Research and Teaching Fellowship in 2013. In 2016 he started his independent career as a Leverhulme Trust early career fellow, and then later as holder of the inaugural Eleanor Dodson Fellowship. He is now a Senior Lecturer in Organic Chemistry. His current research interests include ring expansion approaches for the synthesis of medium-sized rings and macrocycles, catalyst selective synthesis and biocatalysis. Will also has won several prizes for his research, most notably the RSC Hickinbottom Award for his work on the synthesis of spirocycles and macrocycles.

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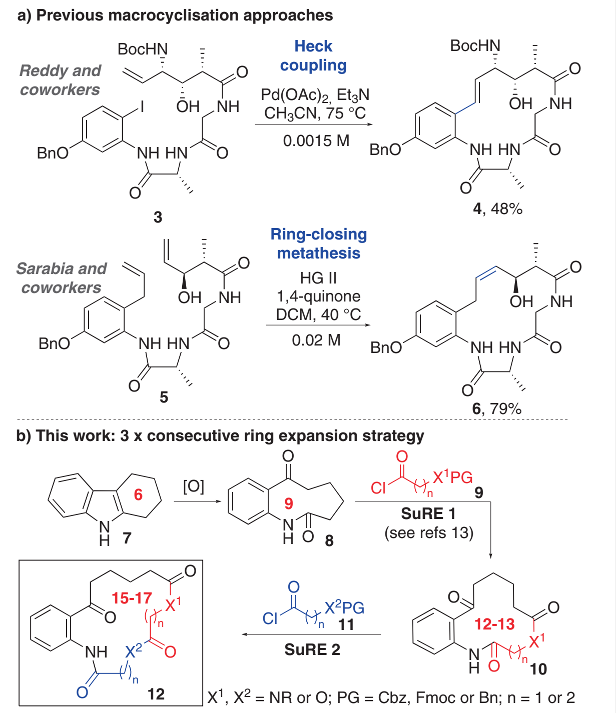
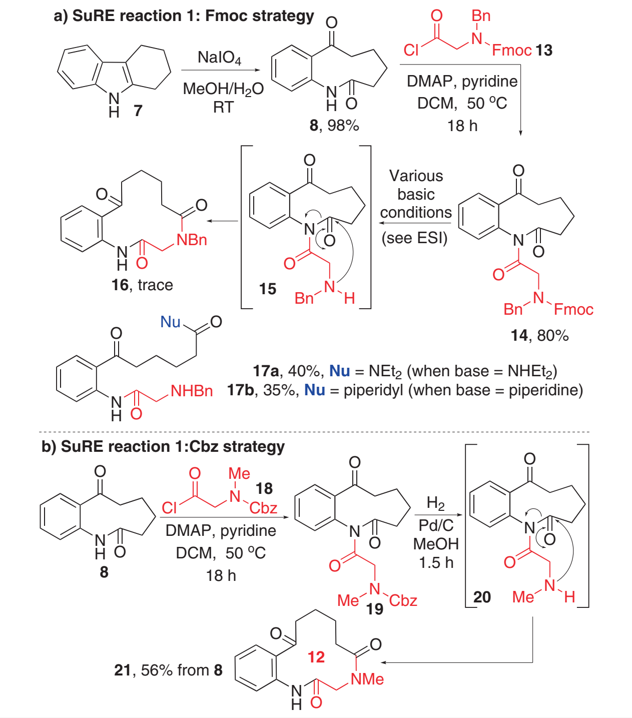


Scheme 1 Strategies to synthesis the macrocyclic core of the solomonamide natural products. a) Previous macrocyclisation approaches. b) 3 × consecutive ring-expansion strategy (this work).

To complement these previous approaches, we were inspired to adopt a completely different strategy, whereby end-to-end macrocyclisation is avoided entirely. Our synthetic strategy is based on the use of three consecutive ring-expansion reactions, to allow the solomonamide macrocyclic core to be 'grown' from a simple, readily available 6-membered ring precursor **7** (Scheme 1b).[11–13] The idea was that following an initial oxidative ring-expansion reaction (**7** → **8**), the resulting lactam **8** could then undergo two further ring-expansion reactions, using our group's Successive Ring Expansion (SuRE) methodology,[14,15] thus enabling amino acid (when X = NR) or hydroxy acid (when X = O) derivatives of the type **9** and **11** to be inserted into ring-enlarged products (**8** → **10** → **12**). The main advantages to this strategy are: i) its overall brevity; ii) the divergent nature of the SuRE method, which means that different amino- and hydroxy acid fragments can be used to facilitate analogue synthesis; iii) as no direct macrocyclisation reactions are needed, high-dilution conditions should not be required. The application of this approach is reported herein. An oxidative ring expansion, followed by two consecutive SuRE reactions allows combinations of α- and β-amino and hydroxy acid derived acid chlorides to be inserted into the ring-expanded products. This is showcased through the successful synthesis of six macrocyclic (15- to 17-membered) solomonamide core analogues of the form **12**.

Our synthesis started with the $NaIO_4$-mediated oxidative ring expansion of commercially available tetrahydrocarbazole **7**, which led to the formation of 9-membered ring lactam **8** in 98% yield, using a method adapted from that of Dolby and Booth (Scheme 2a).[16] Attention then moved to applying our group's SuRE methodology, starting with an Fmoc-based protecting group strategy. Thus, lactam **8** was reacted with acid chloride **13** in the presence of pyridine and DMAP, which resulted in the formation of imide **14** in 80% yield (Scheme 2a). Then, the idea was that cleavage of the Fmoc protecting group under basic conditions (**14** → **15**) would initiate ring expansion (**15** → **16**).[14c–e] However, despite trialing this reaction under various basic conditions (see the Supporting Information for full details) only trace quantities of the desired macrocycle **16** were observed. The main problem was competing ring-opening reactions, promoted by intermolecular nucleophilic attack of the imide by the base used to cleave the Fmoc protecting group; for example, linear amides **17a** and **17b** were isolated when using diethylamine and piperidine, respectively. The deviation in reaction outcome here, compared with published SuRE reactions, is thought to be due to the increased electrophilicity of the imide carbonyl groups,[17] as a result of conjugation with the adjacent electron-deficient aromatic system.



Scheme 2 Ring expansion of **7** and SuRE reaction **1**: a) Fmoc strategy; b) Cbz strategy.

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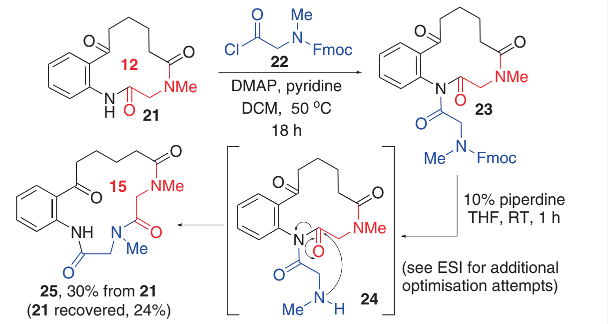
To address this problem, we decided to avoid the use of nucleophilic reagents and switched to a Cbz-based protecting group strategy (Scheme 2b). *N*-Acylation of lactam **8** was performed using Cbz-protected amino acid chloride **18** to form imide **19**. Then, following hydrogenolysis, smooth conversion into macrocycle **21** was observed, which was isolated in 56% overall yield from **8**, across the overall *N*-acylation, protecting group cleavage and ring-expansion sequence.



25, 30% from **21**
(**21** recovered, 24%)

Scheme 3 SuRE reaction 2: ring expansion of **21** to form the 15-membered solomonamide macrocyclic core **25**

Attention then turned to the second SuRE reaction. Initially, we focused on using the same Cbz protecting group strategy as above. However, attempts to perform the *N*-acylation of lactam **21** with acid chloride **18** failed, with unreacted **21** as the major component of the reaction mixture under all the conditions tested (see the Supporting Information for details). It is clear that lactam **21** undergoes *N*-acylation less readily than lactam **8**, and in previous work we have found Cbz-protected amino acid chlorides to be less stable than the analogous Fmoc derivatives. As a result, they tend to perform poorly in cases where the *N*-acylation step is slow. Therefore, we reverted to the Fmoc protecting group strategy. Using this method, *N*-acylation of **21** using the more stable Fmoc-protected amino acid chloride **22** proceeded well (based on full consumption of **21** by TLC analysis) to form imide **23** (Scheme 3). Imide **23** was then taken directly onto the ring-expansion step; thus, following treatment with piperidine in THF, this promoted Fmoc cleavage and subsequent ring expansion to form of 15-membered macrocycle **25** in 30% overall yield from **21**. The problems associated with unwanted intermolecular side reactions observed in the first SuRE reaction were less pronounced in this case, although notably they were still not wholly avoided, with 12-membered lactam **21** being recovered in 24% yield. Notably, **21** was not present after the *N*-acylation step and is therefore believed to result from cleavage of the exocyclic imide C–N bond, likely following nucleophilic attack of the exocyclic imide carbonyl by piperidine. Nonetheless, the successful isolation of **25** meant that the synthesis of the 15-membered solomonamide macrocyclic core had been completed, serving as proof of principle for our consecutive ring-expansion strategy.

One of the most valuable features of the SuRE method is the ability to vary the linear acid chloride to allow straightforward analogue synthesis. This idea is summarised in Scheme 4. Thus, the SuRE of lactam **8** was tested using acid chlorides derived from various Cbz-protected α- and β-amino acids, including a proline derivative, to form 12–13-membered bislactams **21** and **26**–**28** (SuRE method A). The same starting material **8** could also be converted into macrocyclic lactone products **29** and **30**, by acylating with an O-benzyl-functionalised acid chloride. In these cases, hydrogenolysis was used to cleave the benzyl protecting group to reveal an alcohol, and following stirring in chloroform with triethylamine at RT, ring expansion took place in the same manner as for the analogous amines (SuRE method C).[14d]

All products formed via SuRE are potentially viable starting materials for a second SuRE reaction. This is highlighted by the synthesis of 15- to 17-membered ring solomonamide analogues **25** and **31**–**35** (Scheme 4; in these examples, the linear fragment inserted by the first SuRE reaction is highlighted in red, and the second SuRE reaction in blue). For the insertion of amino acid derivatives, the Fmoc protecting group strategy was used (SuRE method B), with both α- and β-amino acids again being compatible (**25**, **31**–**34**).[18] The lactone-forming ring expansion (SuRE method C) was also successfully used in the synthesis of 16-membered bislactone macrocycle **35**. In the lower-yielding cases, most of the mass balance is accounted for by side reactions of the types described in Scheme 2 and 3. Notably, all 12 of the novel macrocyclic products in Scheme 4 were isolated cleanly following column chromatography, and the quoted yields relate to the overall SuRE process of *N*-acylation, protecting group cleavage, and ring expansion.

In summary, a new synthetic strategy towards the solomonamide natural products has been established, based on the use of three consecutive ring-expansion reactions.[19] Compared with previously published syntheses, advantages of this new approach are that it does not require high dilution conditions as end-to-end macrocyclisation is avoided, and its divergent nature. This is exemplified by the synthesis of a series of substituted macrocyclic derivatives, larger-ring homologues and lactone analogues.

The isolated yields in this study (especially those in the second SuRE reaction) are lower than those typically observed in our group's published work;[13] this is likely due to the lactam nitrogen being an electron-deficient aniline, which promotes the competing side reactions described. Additional challenges that would need to be overcome to complete the total synthesis of **2a** and **2b** are the preparation of more functionalized, protected analogues of tetrahydrocarbazole **7**, and cleavage of the amide *N*-alkyl groups; the latter would likely be achieved via NBn hydrogenolysis, as NBn substituents have been shown to work well

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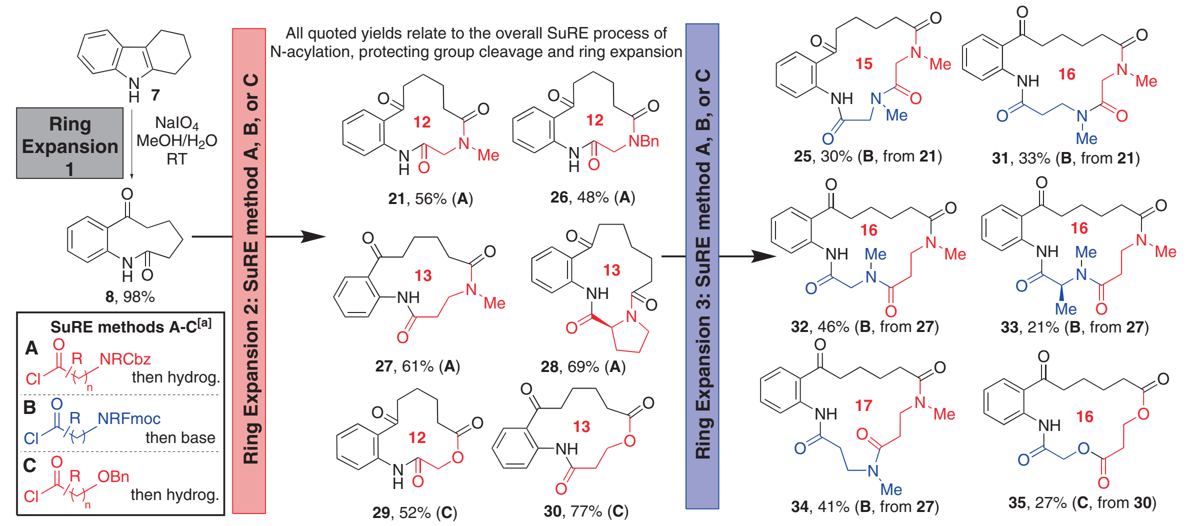

Scheme 4 A consecutive ring-expansion approach for the synthesis of the macrocyclic core of the solomonamide natural products and analogues. [a] SuRE method A: i) lactam (1 equiv.), acid chloride (3 equiv.), pyridine (6 equiv.), DMAP (0.1 equiv.), DCM, 50 °C; (ii) H_2, Pd/C, MeOH, RT. SuRE method B: i) lactam (1 equiv.), acid chloride (3 equiv.), pyridine (6 equiv.), DMAP (0.1 equiv.), DCM (0.1 M), 50 °C; (ii) piperidine in THF, RT. SuRE method C: i) lactam (1 equiv.), acid chloride (3 equiv.), pyridine (6 equiv.), DMAP (0.1 equiv.), DCM, 50 °C; (ii) H_2, $Pd(OH)_2$/C or Pd/C, EtOAc, RT; (iii) NEt_3, $CHCl_3$, RT.

in our earlier SuRE work,[14] as well as in this study (compound **26**). Nonetheless, despite some challenges remaining, having validated the overall approach through the synthesis of series of 15- to 17-membered ring solomonamide analogues, the synthesis of the solomonamides A and B should be viable using this approach. Useful insight into additional selectivity challenges when using SuRE to expand electron-deficient amide systems has also been uncovered. Finally, and perhaps most importantly, we hope that this study helps to inspire future syntheses of other macrocyclic target molecules using consecutive ring expansion as a synthetic strategy, as an alternative to end-to-end macrocyclisation.

Conflict of Interest

The authors declare no conflict of interest.

Funding Information

The authors would like to thank the University of York for the provision of an Eleanor Dodson Fellowship (to W.P.U.) and the China Scholarship Council for a funding the PhD studentship of Z.Y.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/a-1932-9717.

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(19) **Representative Procedure for SuRE Method A (Synthesis of 28)**

3,4,5,6-Tetrahydro-1*H*-(1)-benzazonin-2,7-dione **8** (406.4 mg, 2.00 mmol), DMAP (24.4 mg, 0.200 mmol), and pyridine (0.970 mL, 12.0 mmol) in dry DCM (10 mL) under an argon atmosphere were stirred at RT for 30 min. Next, a solution of acid chloride (6.0 mmol, 3.0 equiv., prepared from Cbz-proline using the procedure described in the Supporting Information) in dry DCM (10 mL) was added, and the resulting mixture was heated at reflux (50 °C) for 18 h. The solvent was then concentrated in vacuo, loaded onto a short silica plug and eluted with ethyl acetate, to remove majority of excess carboxylic acid and pyridine residues, and concentrated in vacuo. This material was redissolved in MeOH (20 mL) and placed under an argon atmosphere. Palladium on carbon (200 mg, 10% Pd on carbon) was added, and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at RT under a slight positive pressure of hydrogen (balloon) for 1 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, ethyl acetate) afforded the title compound as a colorless oil (414 mg, 69% over 2 steps from **8**) which exists as a 5:1 mixture of rotamers in solution in $CDCl_3$; $[\alpha]_D^{23}$ –312.13 (c = 1.0, $CHCl_3$); R_f = 0.23 (ethyl acetate). IR (neat) ν_{max} = 3252, 2948, 2242, 1691, 1672, 1602, 1505, 1442, 1299, 1238, 910, 756, 725, 644, 580 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.43 (s, 1 H, NH, major rotamer), 9.34 (s, 1 H, NH, minor rotamer), 7.77–7.73 (m, 1 H, PhCH, major rotamer), 7.42–7.28 (m, 2 H, PhCH, both rotamers), 7.20–7.14 (m, 1 H, PhCH, minor rotamer), 7.07 (td, *J* = 7.6, 1.0 Hz, 1 H, PhCH, major rotamer), 4.31–4.20 (m, 1 H, NCHCO, both rotamers), 3.78 (dt, *J* = 10.1, 7.0 Hz, 1 H, NCH_2, major rotamer), 3.60 (ddd, *J* = 11.5, 7.3, 4.3 Hz, 1 H, NCH_2, minor rotamer), 3.55–3.44 (m, 1 H, NCH_2, both rotamers), 3.07–2.78 (m, 2 H, CH_2, both rotamers), 2.68–2.49 (m, 1 H, CH_2, major rotamer), 2.36–2.01 (m, 4 H, CH_2, both rotamers), 2.02–1.61 (m, 5 H, CH_2, both rotamers). ^{13}C NMR (100 MHz, $CDCl_3$) for the major rotamer only: δ = 207.2 (CO), 173.4 (CO), 172.8 (CO), 134.8 (PhC), 133.0 (PhC), 131.4 (PhCH), 126.9 (PhCH), 124.5 (PhCH), 124.1 (PhCH), 62.6 (COCHN), 47.0 (CH_2), 41.8 (CH_2), 35.1 (CH_2), 28.4 (CH_2), 25.3 (CH_2), 22.6 (CH_2), 22.1 (CH_2). Diagnostic ^{13}C NMR resonances for the minor rotamer: δ = 204.8 (CO), 172.6 (CO), 172.3 (CO), 135.9 (PhC), 133.6 (PhC), 127.9 (PhCH), 126.0 (PhCH), 125.5 (PhCH), 61.4 (COCHN), 38.5 (CH_2), 31.9 (CH_2), 31.6 (CH_2), 23.6 (CH_2), 23.0 (CH_2), 21.2 (CH_2). HRMS (ESI): *m*/*z* calcd for $C_{17}H_{20}N_2NaO_3$: 323.1366; found $[MNa]^+$: 323.1362 (1.3 ppm error). For spectroscopic data and procedures for all novel compounds prepared in this manuscript, see the Supporting Information.

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Synthesis of medium-ring lactams and macrocyclic peptide mimetics *via* conjugate addition/ring expansion cascade reactions†‡

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Received 17th December 2021,
Accepted 8th February 2022

DOI: 10.1039/d1cb00245g

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A novel conjugate addition/ring expansion (CARE) cascade reaction sequence is reported that enables medium-sized ring and macrocyclic bis-lactams to be prepared from primary amines and cyclic imides. The reactions are simple to perform, generally high yielding, and very broad in scope, especially with respect to the primary amine component. CARE reactions can also be performed iteratively, enabling β-peptoid-based macrocyclic peptide mimetics to be 'grown' *via* well controlled, sequential 4-atom ring expansion reactions, with the incorporation of varied functionalised amines during each iteration.

Introduction

Cascade reaction sequences are widely used in synthetic chemistry to streamline the preparation of complex molecules.[1,2] Performing multiple reaction steps in a single operation brings obvious benefits in terms of the overall brevity of synthetic routes and can obviate the need to directly handle reactive and/or toxic intermediates. This strategy can also lead to the development of synthetic cascades greater than the sum of their parts, whereby the overall cascade reaction proceeds more efficiently than the analogous stepwise process.[3] Ring expansion reactions are also important in synthetic chemistry,[4,5] especially for the synthesis of biologically relevant medium-sized rings and macrocycles,[6] compounds that can be difficult to make using classical end-to-end cyclisation methods.[7] This manuscript is focused on combining these two individually powerful approaches for the synthesis of macrocyclic peptide mimetics, using a novel Conjugate Addition/Ring Expansion (CARE) cascade reaction sequence.

Previous work from our laboratory has established a robust method for the 3- and 4-atom ring expansion of lactams **1** upon reaction with acyl chlorides derived from Fmoc-protected amino acids (*e.g.* **2a**); following *N*-acylation of the lactam to form imide **3**, reaction with base promotes Fmoc-cleavage (**3** → **3a**) and spontaneous ring expansion (**3a** → **4**, Scheme 1a).[8] The reactions typically proceed in good yield over two steps, and the lactams products **4** can themselves be expanded further by repeating the same two-step sequence (*e.g.* **4** → **5**), thus enabling Successive Ring Expansion (SuRE).[8,9] However, there are limitations associated with the use of acid chlorides of the type **2a**, most notably that a 3- or 4-step synthesis is typically needed to make them (**6** or **7** → **2a**, Scheme 1b), and that carbamate-mediated acid chloride deactivation/degradation (**8** → **9**, Scheme 1b box) can negatively affect the reactions in cases where lactam acylation is sluggish.[10]

Avoiding the use of protecting groups was therefore a key factor when designing the new method in this manuscript. We postulated that *N*-acylation of a lactam **1** using a simple acryloyl chloride derivative **10** would generate imide **11**, and that this Michael acceptor could engage in a conjugate addition (**11** → **12**) ring expansion (**12** → **13** → **14**, Scheme 1c) cascade reaction sequence upon treatment with primary amine nucleophiles.[11] The successful realisation of this approach is described herein. The method is extremely broad in scope, with 54 novel CARE reactions reported in this manuscript, demonstrated across a diverse array of functionalised lactams and amines. The reactions are easy to perform, they are insensitive to air and moisture, and work in a wide range of solvents, including water. CARE reactions can also be performed iteratively, to enable the synthesis of macrocyclic peptide mimetics, based on β-peptoid linkages,[12] by performing sequential *N*-acylation and CARE reactions.

Results and discussion

Reaction optimisation (Table 1) was performed using 6-membered ring imide **11a**, itself prepared *via* the *N*-acylation

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† This manuscript is dedicated to the memory of Prof Eric Marsault, who helped us greatly with scientific advice and encouragement when starting our research into biologically important macrocycles.

‡ Electronic supplementary information (ESI) available. CCDC 2122955 and 2122961. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1cb00245g

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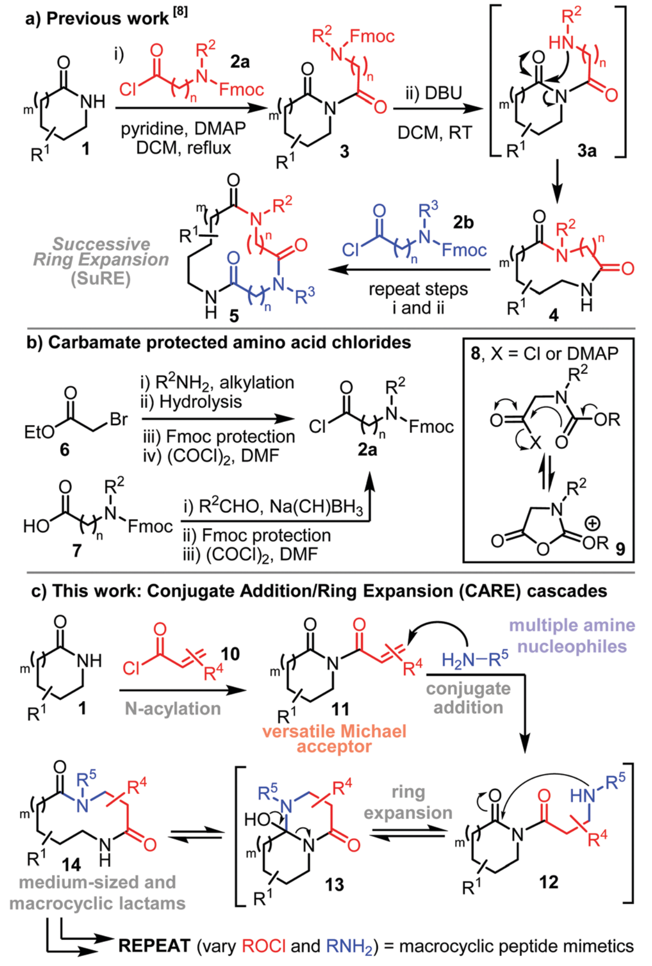
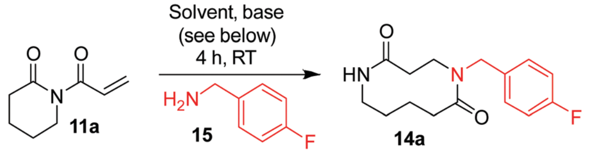


Scheme 1 Lactam ring expansion reactions.

Table 1 CARE optimisation and solvent compatibility



Entry	Solvent	Conc.	Base	14a/%[a]
1	DCM[b]	0.1 M	DBU (10 equiv.)	33
2	DCM[b]	0.5 M	DBU (10 equiv.)	32
3	DCM	0.5 M	—	42
4	Toluene	0.5 M	—	48
5	THF	0.5 M	—	52
6	Et_2O	0.5 M	—	41
7	hexane	0.5 M	—	38
8	DME	0.5 M	—	48
9	MeCN	0.5 M	—	51
10	DMSO	0.5 M	—	77
11	DMF	0.5 M	—	77
12	DMA	0.5 M	—	78
13	NMP	0.5 M	—	80
14	MeOH	0.5 M	—	82 (86)[c]
15	EtOH	0.5 M	—	80
16	i-PrOH	0.5 M	—	71
17	*t*-BuOH	0.5 M	—	73
18	TFE	0.5 M	—	52
19	HFIP	0.5 M	—	58
20	H_2O	0.5 M	—	69

[a] Imide **11a** (1 equiv.) and amine **15** (1.1 equiv.) were stirred in the stated solvent at RT for 4 h unless stated, performed on a 0.5 mmol scale. 3,5-Bis(trifluoromethyl)bromobenzene (1 equiv.) was then added before an aliquot of the reaction mixture (*ca.* 0.2 mL) was taken, diluted with $CDCl_3$ and analyzed directly by ^{19}F NMR. Conversion to **14a** was determined by the ratio of the ^{19}F NMR resonance of **14a** to that of the 3,5-bis(trifluoromethyl)bromobenzene internal standard. [b] 18 h reaction time. [c] isolated yield in parentheses, performed on a 5.0 mmol scale.

of δ-valerolactam with acryloyl chloride.[13] *p*-Fluorobenzylamine **15** was chosen as a model primary amine as its fluorine group provided a convenient handle for reaction monitoring using ^{19}F NMR. Initially, imide **11a** (1 equiv.) and amine **15** (1.1 equiv.) were stirred in DCM (0.1 M) at RT with an excess of DBU (10 equiv.). These conditions were chosen to start as they were used to promote the ring expansion step in our published SuRE chemistry,[8] and pleasingly, resulted in modest conversion (33%) into 10-membered lactam **14a** (entry 1). Next, the reaction concentration was increased (0.1 M → 0.5 M, entry 2) as increasing the concentration has been shown to promote amine conjugate addition in related systems;[14] this change did not improve conversion, but it had no significant negative impact either so was retained for further optimisation. We then questioned whether the base was necessary, and indeed, performing the same reaction without DBU led to improved conversion (entry 3).

A range of alternative solvents were then explored (entries 4–20); in total, 18 were tested and remarkably, all resulted in some conversion into 10-membered lactam **14a**, including solvents compatible with biological systems, most notably water (entry 20). Overall, polar solvents tend to perform better, with alcohol solvents particularly effective (entries 14–17). Importantly, the conversion as measured using ^{19}F NMR translates into a comparable synthetic yield, with **14a** isolated in 86% following column chromatography, tested on a 5.0 mmol scale reaction using methanol as the solvent (entry 14). Methanol was therefore selected to take forward to the substrate scoping phase of the project, but the versatility of the reaction in terms of solvent is also notable and is important in scenarios where methanol is less effective (see later for examples).

The scope with respect to lactam ring size was examined first, with 4–8-membered ring imides **11a–e** prepared from the corresponding lactams and acryloyl chloride. All were reacted with *p*-fluorobenzylamine **15** and in all cases the desired ring-expanded products were formed (**14a–e**, Scheme 2A). The standard protocol (methanol, 0.5 M, 4 h) was used in all examples, except for the expansion of 4-membered imide **11b** into 8-membered **14b**. In this case, a complex mixture of products was formed when the reaction was done in methanol, with the only tractable products arising from unwanted ring opening of the β-lactam, both by the amine **15** and methanol (see ESI† for details). However, by performing the reaction in DCM instead of methanol and increasing the reaction time, the desired ring expanded product **14b** could be isolated in 68% yield. This result highlights the value of the wide solvent compatibility of CARE in finding contingencies for substrates that have chemical functionality not compatible with the

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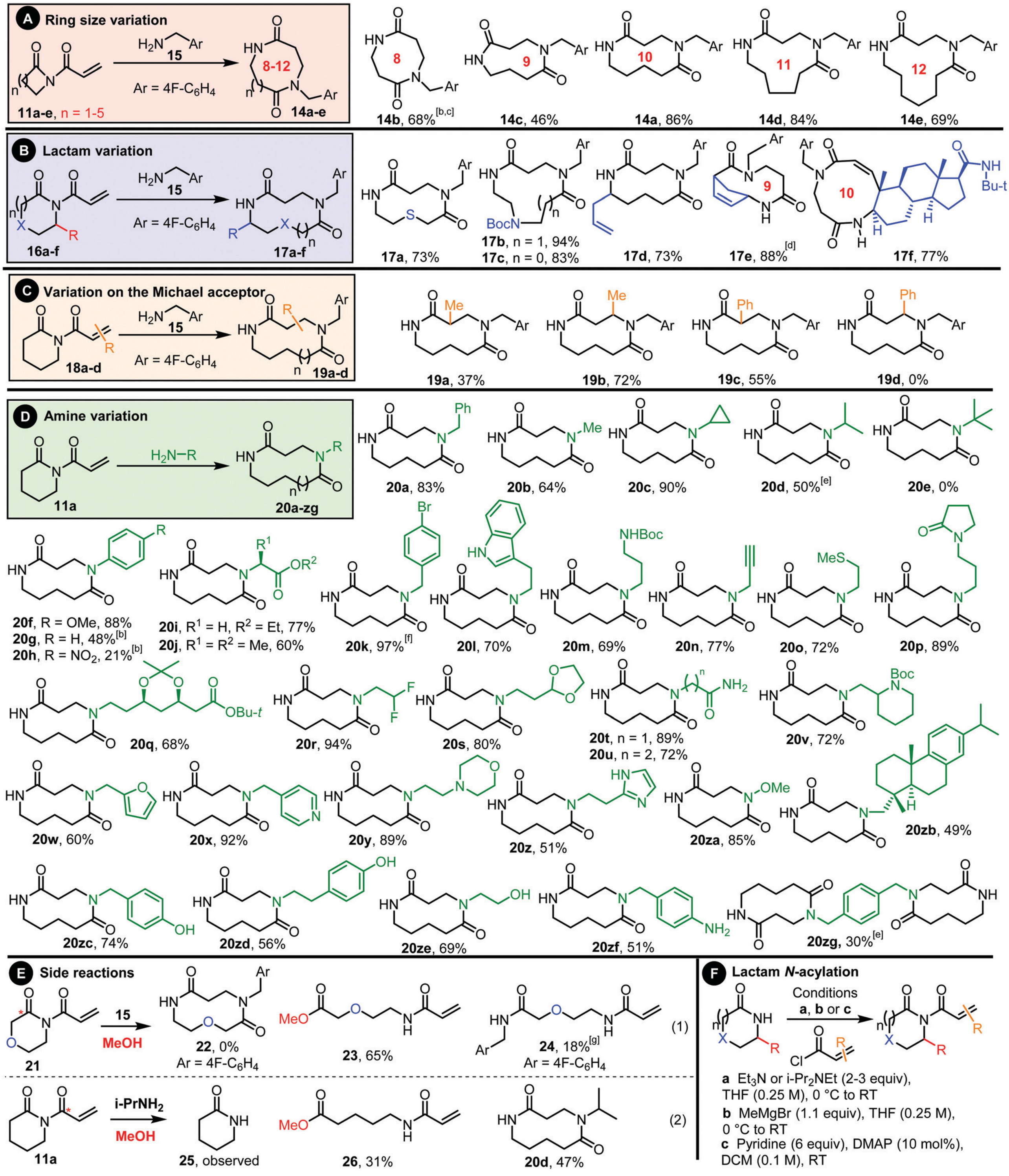

Scheme 2 Scope of Conjugate Addition/Ring Expansion (CARE).[a] Unless stated the following procedure was used: Imide (1 equiv.) and amine (1.1 equiv.) were stirred in methanol (0.5 M) for 4 h at RT, concentrated and purified directly by column chromatography; [b] reaction stirred for 3 days; [c] DCM (0.5 M) used in place of methanol; [d] reaction stirred for 5 h; [e] DMF (0.5 M) used in place of methanol; [f] reaction stirred for 2 h; [g] contaminated with morpholin-3-one.

standard methanol conditions. The assigned structures of products **14a** and **14b** were both confirmed *via* X-ray crystallography (Fig. 1).[15]

Functionalised lactam starting materials (**16a–f**) were also examined, with the expected ring expanded products **17a–f** all formed in good yields; this series includes sulfide-, carbamate- and

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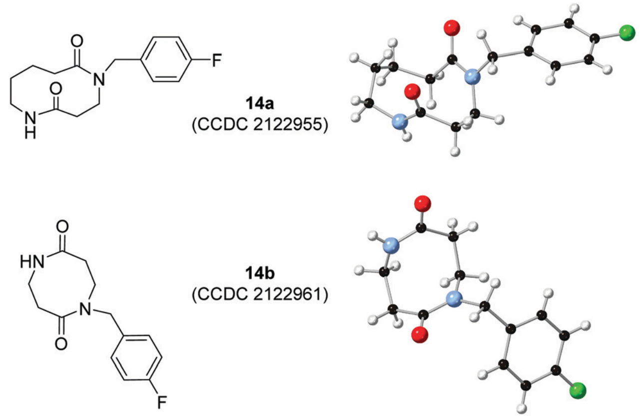

Fig. 1 X-Ray crystal structures of **14a** and **14b**. CCDC 2122955 and 2122961.

alkene-containing lactams, as well as bicyclic and steroidal lactams (Scheme 2B). Substitution on the Michael acceptor is also tolerated both at the α- and β-position (**19a–c**, Scheme 2C), although a notable exception is cinnamoyl-derivative **18d** (R = Ph at the β-position) which failed to react, presumably due to its lower electrophilicity as a Michael acceptor.

The ability to freely vary the primary amine coupling partner is arguably the most powerful feature of the CARE method (Scheme 2D). Aliphatic primary amines typically work well, provided they are not too bulky; the steric influence on the reaction yields is clear when comparing relatively unhindered cyclopropylamine (**20c**, 90%), moderately bulky iso-propylamine (**20d**, 50%) and bulky *tert*-butylamine (**20e**, 0%). Unsurprisingly, electronics also influence the CARE reactions, presumably by modulated the amine's nucleophilicity; for example, when comparing aniline derivatives, the electron-rich *p*-OMe substituted product **20f** was formed in 83% using the standard protocol, but there was a drop in yield when moving to aniline itself (**20g**, 48%) and an electron-poor *p*-NO_2 derivative (**20h**, 21%), even when using longer reaction times.

The excellent functional group compatibility of CARE is exemplified by the range of functionalised amines used to make products (**20i–zb**); all were formed in good to excellent yields from amines containing a wide array of functional groups, including esters, halides, carbamates, terminal alkynes, sulfides, amides, acetals, furans, various aza-heterocycles, hydroxylamine derivatives and others. Notably, the primary amine motif can also out-compete other unprotected nucleophiles like phenols, alcohols and anilines (**20zc–f**), while the diamine-tethered bis-lactam **20zg** was also made from *p*-xylylene diamine.

Thus, the CARE method has been demonstrated to work well across a wide range of substrates, with most reactions tested working well. However, as well as highlighting the successful cases, it is instructive to consider the relatively rare cases in which the reaction does not proceed in the typical way (Scheme 2E). The biggest challenge relates to chemoselectivity, specifically that the imide starting materials typically contain three electrophilic centres. One of these is the β-position of the Michael acceptor (*i.e.* the required site for conjugate addition), and based on our previous ring expansion work, which includes detailed DFT studies,[8c] we are confident that once conjugate addition has taken place the ring expansion step should be facile. However, both carbonyl groups of the imide are also electrophilic and can react competitively with the primary amine and/or nucleophilic solvent molecules. For example, when imide **21** was reacted under the standard conditions, none of the expected ring expanded product **22** was formed; instead linear products **23** and **24** were isolated, arising from nucleophilic ring opening through attack at the internal imide carbonyl (highlighted with a star) by methanol or *p*-fluorobenzylamine respectively (Scheme 2E, eqn (1)). Presumably, the cyclic ether oxygen increases the electrophilicity of the adjacent carbonyl and changes the typical kinetic preference for conjugate addition. This is a similar observation to that described earlier, during the CARE of the β-lactam-based imide **11b** into 8-membered **14b** (Scheme 2A).

Competing nucleophilic attack at the external imide carbonyl has also been observed in cases where the conjugate addition step is sluggish; for example, when imide **11a** was reacted with relatively bulky i-propylamine under the standard conditions, de-acylated lactam **25** was formed in the reaction, presumably as a result of nucleophilic attack by methanol and/or the amine at the highlighted carbonyl, alongside ring-opened side product **26** and the desired ring expanded product **20d** (Scheme 2E, eqn (2)). In situations like this, where the methanol solvent promotes side reactions, alternative solvents can be considered, and in this case a solvent switch to DMF resulted in a modest increase in yield of the ring expanded product **20d** (50%, Scheme 2D).

The requisite imides used for all the CARE reactions in this manuscript were prepared using basic reaction conditions, using one of the three related *N*-acylation methods summarised in Scheme 2F, with full details for all imide preparations included in the ESI.‡

The products in Scheme 2 are all lactams that can potentially be used in CARE reactions themselves. Therefore, the possibility of using CARE in iterative ring expansion processes was explored. First, lactone- and thiolactone-containing macrocyclic imides **27** and **29** were tested, with the precursor lactams prepared using our published SuRE method (with the section inserted *via* the first ring expansion highlighted in red).[8b,d] Pleasingly, both imides were converted into the ring-expanded products **28** and **30** respectively using amine **15** and the standard conditions (Scheme 3a). It is also possible to perform CARE reactions iteratively (Scheme 3b). For example, starting from δ-valerolactam **25**, *N*-acylation with acryloyl chloride followed by CARE with *p*-fluorobenzylamine **15** delivered 10-membered bis-lactam **14a**. Then, another *N*-acylation/CARE sequence was performed starting from **14a** using three different amines (shown in blue) to afford 14-membered products **31a–c** in good yields. Each of compounds **31a–c** were then expanded a third time in the same way (amine shown in green) to furnish 18-membered β-peptoid-based tetra-peptide mimetics **32a–c**. This ability to use CARE to install different functionalised building blocks in sequence was a major driving force when developing the reaction. Sequence specific cyclic peptides have numerous important biochemical applications, for example arginine-glycine-aspartic acid (RGD) peptides, that have found wide utility in cell

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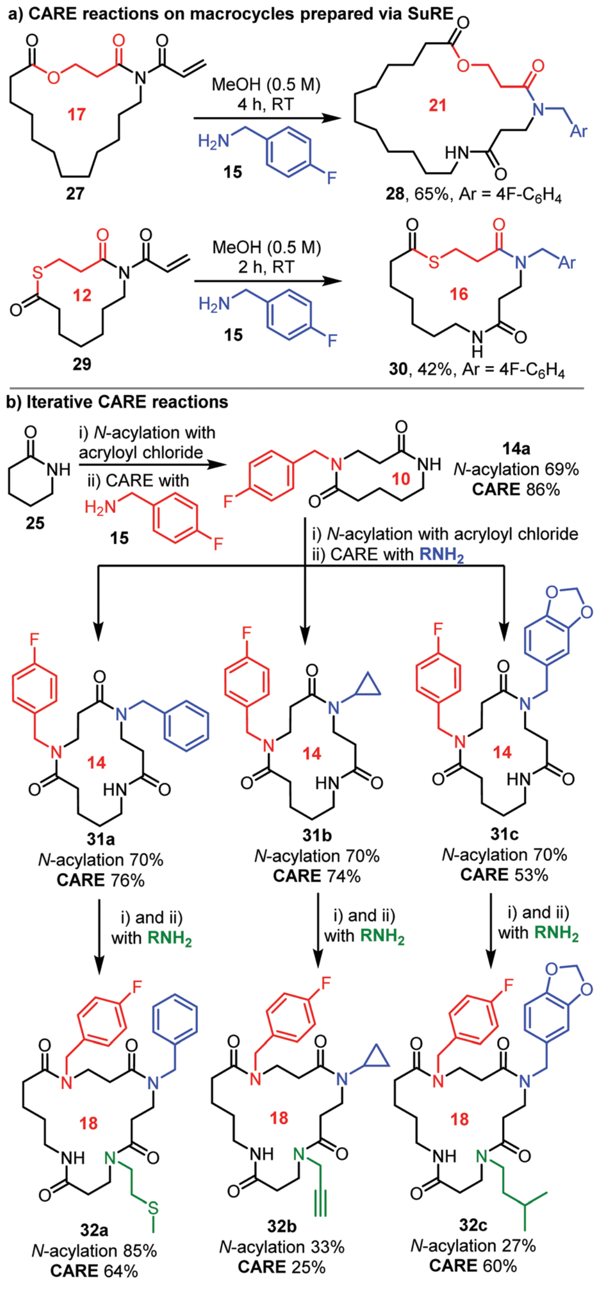

Scheme 3 Iterative CARE reactions.

culture models and as targeted therapeutic agents.[16] Of course, the CARE method can only be used to promote 4-atom ring expansion, and hence cannot be used to target cyclic peptides based on proteinogenic amino acids. Nonetheless, what is does offer is a versatile route to sequence specific β-peptoid-based macrocycles, that could become similarly useful in future biochemical studies.

Conclusions

In summary, a practical and versatile iterative conjugate addition/ring expansion sequence is described for the synthesis of medium-sized/macrocyclic lactams and peptide mimetics based on β-peptoid linkages. The imide precursors that undergo the CARE cascade can react with a wide array of functionalised amines without the need for protecting groups. The products can be thought of as macrocyclic peptide/peptoid mimetics, a compound class with significant potential for use in medicinal and biological chemistry applications.[17] The iterative nature of the CARE reactions will be of value when optimising the properties of the macrocyclic products (*e.g.* in structure activity relationship studies), and its operational simplicity and wide scope should ensure that the CARE method is well-used, both by specialist synthetic chemists, and by researchers working in more applied fields.

The demonstrated wide solvent compatibility of CARE should also have important implications. For example, CARE reactions have been successfully applied in solvents like DMSO and water, that are commonly used to handle biologically relevant molecules like peptides or proteins. This, coupled with the demonstrated high selectivity for reaction on primary amines in the presence of a wide array of other functional groups, provides encouragement that CARE reactions based on the selective functionalisation amines in complex macromolecules (*e.g.* lysine residues in peptides/proteins) could emerge over time.

Author contributions

The project was conceived by WPU and KYP. Initial method development and optimisation was done by KYP. Reaction scope and further method development was done by KYP and ZY. The manuscript was written through contributions from all authors. X-ray crystallography data acquisition, processing and analysis was done by ACW. The project was directed and managed by WPU.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The authors would like to thank the University of York for the provision of an Eleanor Dodson Fellowship (to W. P. U.) and for supporting K. Y. P. with a PhD studentship, and the China Scholarship Council for funding (Z. Y.). Special thanks to Claudia Flandoli for preparing the graphical abstract artwork.

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How to cite: *Angew. Chem. Int. Ed.* **2023,** *62,* e202217178
International Edition: doi.org/10.1002/anie.202217178
German Edition: doi.org/10.1002/ange.202217178

Synthetic Methods

Ring Expansion Strategies for the Synthesis of Medium Sized Ring and Macrocyclic Sulfonamides

Zhongzhen Yang[+], *Illya Zalessky*[+], *Ryan G. Epton, Adrian C. Whitwood, Jason M. Lynam, and William P. Unsworth**

Abstract: Two new ring expansion strategies are reported for the synthesis of medium sized ring and macrocyclic sulfonamides. Both methods can be performed without using classical protecting groups, with the key ring expansion step initiated by nitro reduction and amine conjugate addition respectively. Each method can be used to make diversely functionalised cyclic sulfonamides in good to excellent yields, in a range of ring sizes. The ring size dependency of the synthetic reactions is in good agreement with the outcomes modelled by Density Functional Theory calculations.

Introduction

Sulfonamides are amongst the most important structural motifs in medicinal chemistry, being widely present in FDA approved small molecule drugs with broad spectrum biological activity.[1,2] Cyclic sulfonamides—traditionally known as "sultams"—are also commonly found in drugs and bioactive compounds, with representative examples of both classes shown in Figure 1.[3]

Compared to normal sized ring cyclic sulfonamides (5–7-membered rings), medium sized (8–11-membered) and macrocyclic (12+ membered, e.g. **7**) sulfonamides are far less well explored, both in terms of synthetic methods to prepare them, and their biological activities.[4,5] Indeed, this mirrors a trend seen across other compound classes, where larger ring systems are often underexplored due the additional challenges associated with their synthesis.[6,7] Given growing interest in the study of medium sized rings and macrocycles in medicinal chemistry,[8,9] the development of effective new methods to prepare them is important, especially for compounds classes like sulfonamides for which existing synthetic methods are limited.

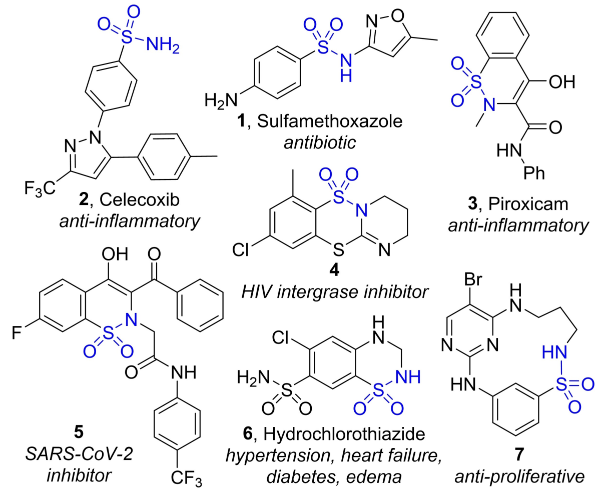

Figure 1. Medicinally important acyclic and cyclic sulfonamides.

This manuscript is focused on the development of two new methods to prepare medium sized and macrocyclic sulfonamides using ring expansion reactions.[10,11] Ring expansion reactions offer significant advantages for large ring syntheses, most notably by removing the need to perform an end-to-end cyclisation via a medium sized ring or macrocyclic transition state. Our group has experience designing new ring expansion methods for large ring synthesis, generally using a sequence of acylation, protecting group cleavage and ring expansion to make lactams and lactones of the type summarised in Scheme 1A (**8**→**9c**).[12] However, we had not reported any sulfonamide-forming ring expansion reactions prior to this study. Furthermore, to the best of our knowledge, we are aware of only one other published study in which a ring expansion reaction of any type has been used to prepare a medium sized or macrocyclic sulfonamide.[13]

Two new sulfonamide-forming ring expansion protocols are reported herein. Both rely on the use of sulfonylated precursors of the form **10**, which contain a group "X" that can be converted into an amine (**10**→**11**) capable of initiating ring expansion (**11**→**12**/**13**, Scheme 1B). In contrast to our previous work,[12] in this study we were keen to avoid the use of classical protecting group chemistry, and have developed complementary strategies to achieve this using redox chemistry (nitro reduction, Method 1) and amine

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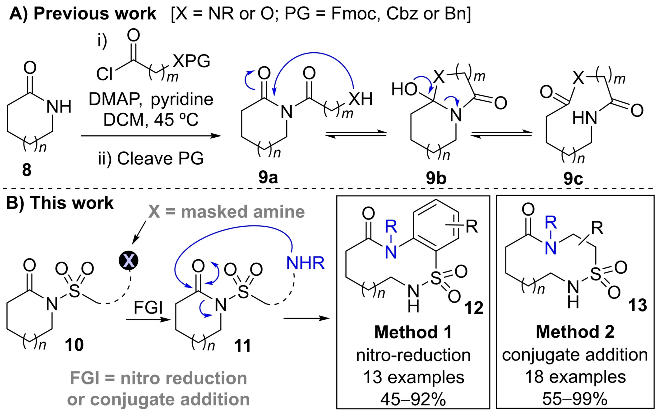
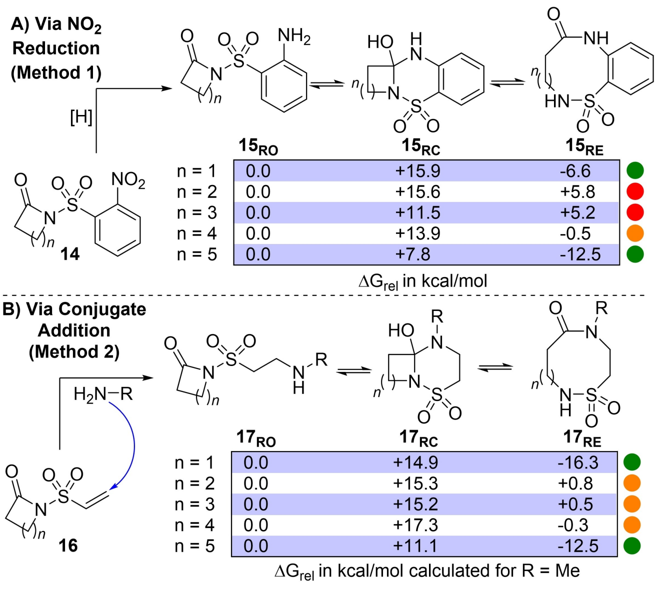


Scheme 1. A) Previous work; B) Ring expansion strategies for the synthesis of medium sized and macrocyclic sulfonamides.

coupling (conjugate addition, Method 2) respectively. Both methods can be used to make diversely functionalised cyclic sulfonamides in good to excellent yields, and work well across a range of ring sizes, with the ring size dependency of the synthetic reactions in good agreement with the outcomes predicted by Density Functional Theory (DFT) calculations.

Results and Discussion

Our reaction design strategies are summarised in Scheme 2. The first method (Scheme 2A, Method 1) is based on the reduction of 2-nitro sulfonamide precursors of the form **14**; reduction of the nitro group was expected to form aniline $\mathbf{15_{RO}}$, and this ring-opened form was predicted to rearrange via cyclisation to form ring closed isomer $\mathbf{15_{RC}}$ and subsequent ring expansion to form $\mathbf{15_{RE}}$. This approach allows access to benzannulated products and has the added advantage that the 2-nitro sulfonamide moiety in the starting material can be easily introduced by reacting lactams with commercially available 2-nosyl chloride. To access non-benzannulated systems an alternative reaction design was envisioned, starting from vinyl sulfonamide precursors of the form **16** (Scheme 2B, Method 2); in this case, a conjugate addition reaction between **16** and an added primary amine was proposed, to set up a system capable of undergoing cyclisation ($\mathbf{17_{RO}}\rightarrow\mathbf{17_{RC}}$) and ring expansion ($\mathbf{17_{RC}}\rightarrow\mathbf{17_{RE}}$) in the same way.



	$\mathbf{15_{RO}}$	$\mathbf{15_{RC}}$	$\mathbf{15_{RE}}$	
n = 1	0.0	+15.9	-6.6	🟢
n = 2	0.0	+15.6	+5.8	🔴
n = 3	0.0	+11.5	+5.2	🔴
n = 4	0.0	+13.9	-0.5	🟠
n = 5	0.0	+7.8	-12.5	🟢

ΔG_{rel} in kcal/mol

	$\mathbf{17_{RO}}$	$\mathbf{17_{RC}}$	$\mathbf{17_{RE}}$	
n = 1	0.0	+14.9	-16.3	🟢
n = 2	0.0	+15.3	+0.8	🟠
n = 3	0.0	+15.2	+0.5	🟠
n = 4	0.0	+17.3	-0.3	🟠
n = 5	0.0	+11.1	-12.5	🟢

ΔG_{rel} in kcal/mol calculated for R = Me

Scheme 2. Reaction design and DFT calculations to predict the influence of ring size on reaction viability. Relative energies are Gibbs energies at the B3LYP/6-31G* level of theory in the gas phase, at 298.15 K.

Before embarking on synthetic studies, the viability of both proposed ring expansion reactions was assessed by DFT calculations, using methodology validated and benchmarked with imide-based systems during our previous ring expansion work.[12e] For both reaction series, the ground state energies of the ring-opened ($\mathbf{15/17_{RO}}$), ring-closed ($\mathbf{15/17_{RC}}$) and ring-expanded ($\mathbf{15/17_{RE}}$) isomers were calculated; our previous work shows that the isomer calculated to be lowest in energy typically aligns well to synthetic outcomes. As the ring-size of the starting material is known to have a major influence on the outcomes of ring expansion reactions, these calculations were performed for starting material ring sizes ranging from 4–8-membered (**14/16**, $n=1$–5), with the results summarised in Scheme 2. A traffic light colour coding system is depicted, with green indicating a reaction calculated to be thermodynamically viable, red indicating a reaction calculated to be not viable, and amber for borderline cases.

For the nitro reduction series (**14**→**15**, Scheme 2A), a clear thermodynamic driving force for ring expansion was revealed for 4- and 8-membered starting materials (**14**, $n=1$ and 5), indicated by the much lower relative energy of the isomer $\mathbf{15_{RE}}$. In contrast, the expansion of 5- and 6-membered starting materials (**14**, $n=2$ and 3) were predicted to be not viable; this is not wholly surprising, as "normal-to-medium" ring expansions of this type are usually the most challenging.[10d] The ring expansion of the 7-membered starting material (**14**, $n=4$) was calculated to be a borderline case. For the conjugate addition series (**16**→**17**, Scheme 2B), a clear driving force for expansion was again seen for the 4- and 8-membered starting materials (**16**, $n=1$ and 5). The calculated energies for $\mathbf{17_{RO}}$ and $\mathbf{17_{RE}}$ for the 5–7-membered systems (**16**, $n=2$–4) were too close to make a confident prediction on the most likely synthetic outcome, but notably they were all sufficiently encouraging to justify testing synthetically (vide infra).

Synthetic studies started by examining the nitro-reduction series (Method 1). Guided by the DFT results, we started by testing the expansion of 8-membered lactam **18a**, as the ring expansion was calculated to be highly exergonic for this ring size. Conditions were established whereby lactam **18a** could be sulfonylated using *n*-BuLi and 2-nosyl chloride **19a** to form **20a** in 86% yield (see Supporting Information for optimisation). Reduction of the nitro group was then done via hydrogenation with Pd/C in ethyl acetate, and the resulting aniline was converted directly into the

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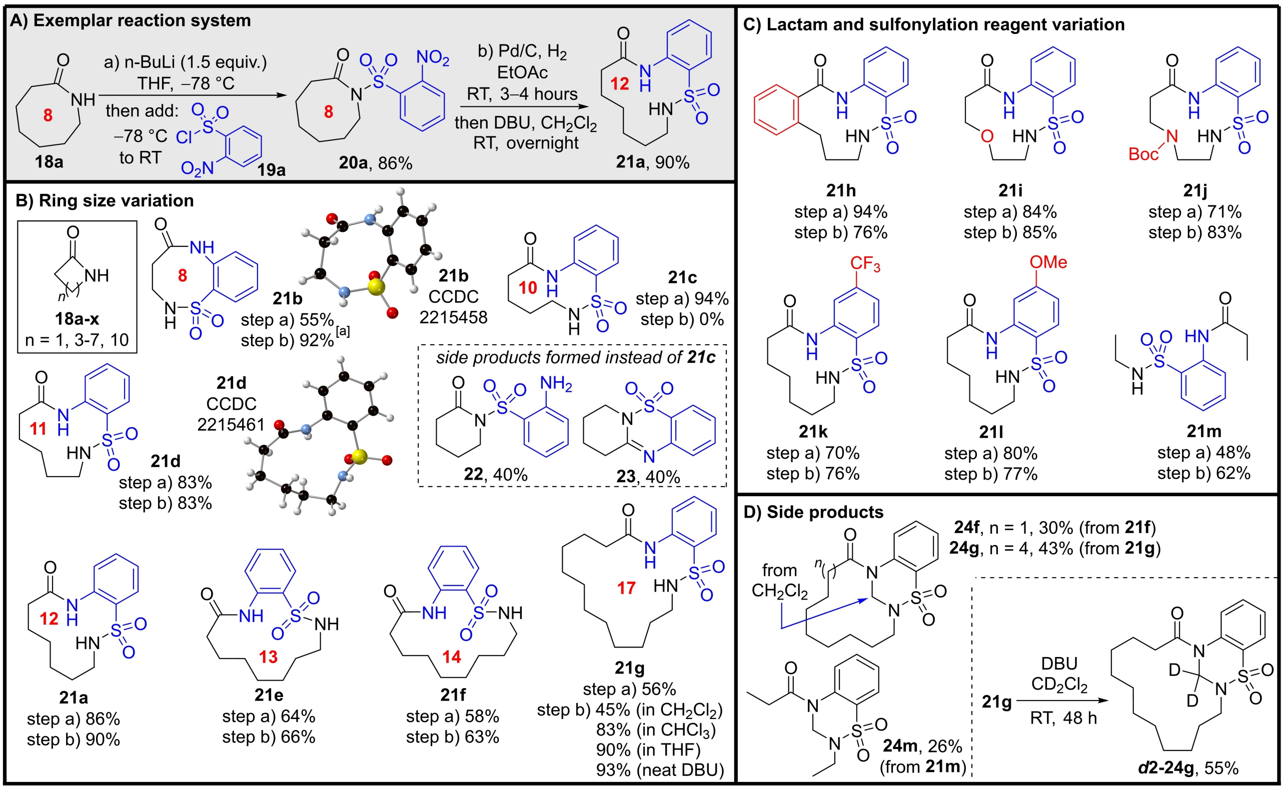
ring-expanded macrocyclic sulfonamide **21a** following RT stirring with DBU in CH_2Cl_2, in 90 % overall yield over the reduction/ring expansion sequence (Scheme 3A).

With reaction conditions established, the scope of the reaction was next examined, starting with the effect of ring size (Scheme 3B). As predicted by the DFT calculations, the expansion of β-lactam **18b** to form 8-membered ring sulfonamide **21b** worked well, with the reduction/ring expansion step proceeding in 92 % yield. The DFT calculations also correctly predicted that the expansion of 6-membered valerolactam would fail; none of the ring expanded product **21c** was formed, with aniline **22** and condensation side product **23** the only tractable products isolated from the reaction. Pleasingly, all >6-membered ring systems tested worked well, with ring expanded sulfonamides **21d–g** all formed in good yields. Variation to the lactam precursor (to form **21h–j**) and sulfonylation reagent (to form **21k–l**) was also well tolerated, enabling the synthesis of more functionalised derivatives using the same method (Scheme 3C). Interestingly, the method is also applicable to linear amide precursors; for example, linear sulfonamide **21m** was prepared using the same sequence, starting from *N*-ethylpropanamide, via the overall insertion the 2-amino sulfonyl benzene unit highlighted in blue.

Notably, in cases where the yield of the ring expansion products was lower than in ideal systems, the bulk of the mass balance accounted for by the formation of methylene-bridged side products (e.g. **24f/g**, **24m** Scheme 3D). These products presumably arise from an unusual coupling of the ring-expanded cyclic sulfonamide product with CH_2Cl_2 (the solvent used for the ring expansion step). This notion was corroborated by the fact that deuterated analogue **d2–24g** was formed upon stirring **21g** with DBU in CD_2Cl_2.[14] Whilst not intended, this unexpected side reaction allows 1,2,4-thiadiazinane 1,1-dioxides to be incorporated into the macrocyclic products. This may prove to be a useful discovery, given that these motifs are present in a range of bioactive compounds.[15] With respect to the desired ring expansion, this side reaction can easily be avoided simply by changing the reaction solvent; for example, product **21g** was formed in a modest 46 % yield when the ring expansion step was performed in CH_2Cl_2, but the yield increased markedly when done in $CHCl_3$, THF or neat DBU (80 %, 90 % and 93 % yields respectively).

The use of hydrogenation to reduce the nitro group presumably precludes the inclusion of hydrogenation-sensitive groups like alkenes or benzyl alcohols in the starting materials. We therefore briefly examined alternative reduction conditions that do not require hydrogenation, and found that reacting **20a** with zinc and ammonium chloride in a water/methanol mixture enabled reduction and ring expansion to form **21a** in modest (29 %) unoptimised yield. Attempts to reduce **20a** using $SnCl_2{\cdot}2H_2O$ and HCl were unsuccessful (for full synthetic details of both alternative methods, see Supporting Information).



Scheme 3. Ring expansion method for the synthesis of medium sized and macrocyclic sulfonamides initiated via nitro reduction (Method 1). All examples were performed using the conditions summarised in (A) (see Supporting Information for full synthetic details) and yields are of isolated product.[a] In this example the ring expansion took place spontaneously following hydrogenation, so the DBU step was not required.

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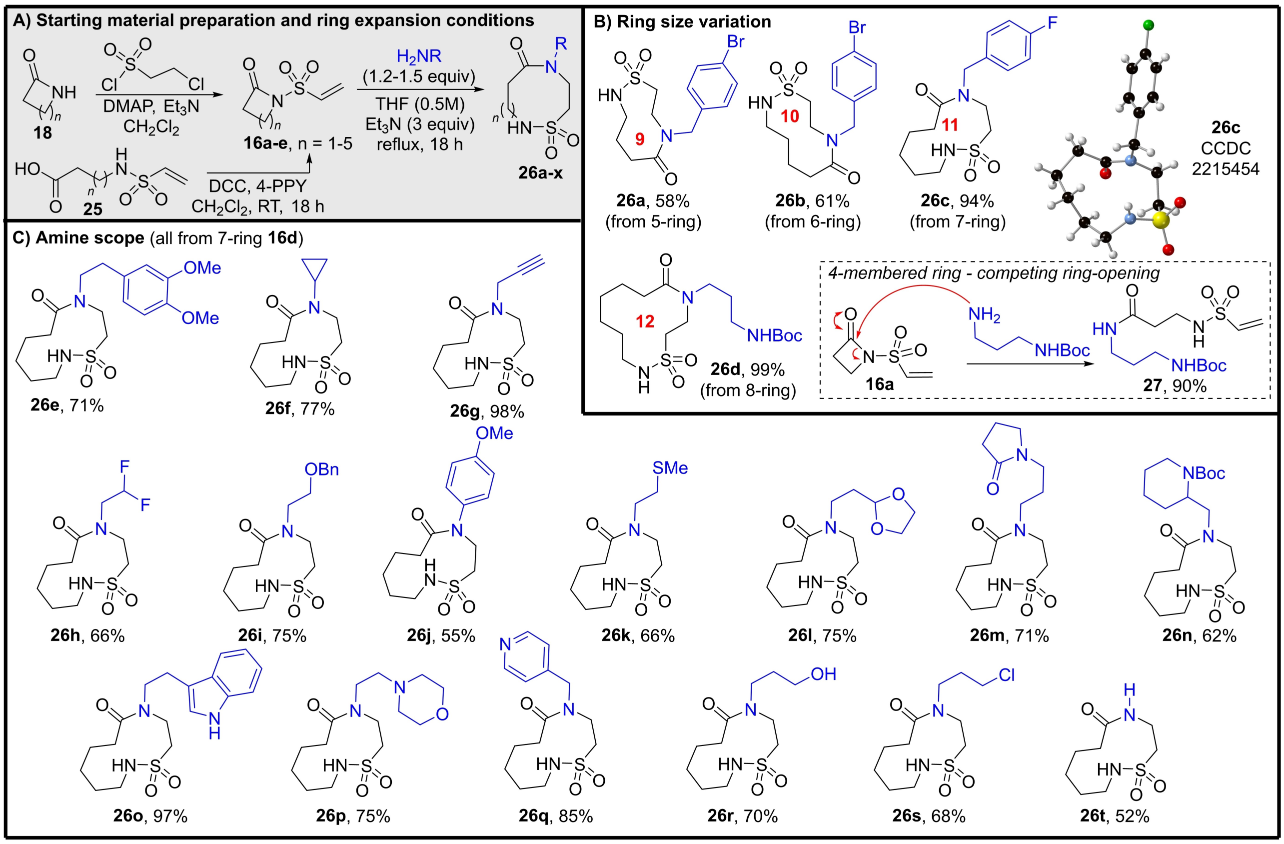
We also briefly explored the possibility using ring-expended product **21a** in a second iteration of the sulfonylation/ring expansion sequence.[12] Unfortunately, attempts to *N*-sulfonylate **21a** with **19a** on its lactam moiety failed, with *N*-sulfonylation of the sulfonamide nitrogen taking place instead. Similar reaction via the sulfonamide nitrogen was also observed when **21a** was reacted with an acid chloride (see Supporting Information for full synthetic details and characterization data for the products formed in each case).

Of final note, several of the products in this series are crystalline solids, and the structures of two of these (**21b** and **21d**) are supported by X-ray crystallographic data.[16]

Next, attention turned to examining the conjugate addition/ring expansion reaction series (Method 2). The requisite sulfonylated lactam starting materials **16a–e** were prepared using two different approaches (Scheme 4A); either the parent lactam was reacted with 2-chloroethanesulfonyl chloride under basic conditions, or they were made via cyclisation of *N*-sulfonylated amino acid derivatives of the form **25** (see Supporting Information for full synthetic details).[17]

The effect of variation in the ring size of the starting material was then explored. The DFT results (vide supra) suggested that 4–8-membered ring precursors **16a–e** could all be viable substrates for this process. Pleasingly, this proved to be the case for 5–8-membered starting materials **16b–e**; simply heating the sulfonylated lactam with the appropriate primary amine and triethylamine in THF enabled smooth conversion into the expected ring expanded 9–12-membered cyclic sulfonamides **26a–d** in good to excellent yields (Scheme 4B). The only substrate that did not react as expected was 4-membered lactam derivative **16a** (see Scheme 4B box). In this case, the ring expansion was calculated to be highly exergonic using our DFT method. However, the DFT method does not account for the possibility of side products being formed if more kinetically favourable pathways are available. In this instance, ring-opening of the strained 4-memebred ring, presumably via the mechanism shown in the Scheme 4B box, was found to be the dominant reaction pathway, leading to the formation of linear amide **27** in 90% yield. A similar side reaction was also observed when the synthesis of **26c** was attempted using methanol as the reaction solvent rather than THF.[18] These results highlight the delicate balance required to achieve the desired reactivity when using starting materials of the type **16**, which contain more than one electrophilic site.

Notwithstanding the 4-membered ring system, the ability to perform the conjugate addition/ring expansion method on all of the other ring sizes tested is notable, especially as it works well to promote challenging "normal-to-medium"



Scheme 4. Ring expansion method for the synthesis of medium sized and macrocyclic sulfonamides initiated via conjugate addition (Method 2). All examples were performed using the conditions summarised in (A) (see Supporting Information for full synthetic details) and yields are of isolated product.

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ring expansions.[10d] Furthermore, another key feature of this approach is the freedom with which the primary amine component can be varied. Of the 20 examples shown in Scheme 3B and C, 19 different diversely functionalised primary amines were used,[19] and in choosing these amines, we actively sought to challenge the method with varied chemical functionality.[20] For example, in addition to comparatively simple aliphatic amines (e.g. **26a–c**, **26e,f**), ring-expanded sulfonamides have been generated in good to excellent yields from an amine bearing a terminal alkyne (**26g**), a fluorinated amine (**26h**), a sulfide-tethered amine (**26k**), an aniline derivative (**26j**), amines containing protected alcohols, aldehydes and amines (**26d**, **26i**, **26l**, **26n**), amines tethered to aza-heterocycles (**26m–q**), a free amino alcohol (**26r**) and an alkyl chloride (**26s**). The conjugate addition/ring expansion cascade also works using ammonia (added as a solution in 1,4-dioxane) to form secondary lactam **26t**. The freedom to introduce varied functionality into the ring expanded products from a common precursor, using a simple and robust procedure,[21] is likely to be useful when preparing compound libraries for bioassay or structure activity relationship (SAR) studies.

Conclusion

In summary, two complementary protecting group-free ring expansion methods have been developed for the synthesis of medium sized ring and macrocyclic sulfonamides. The first (Method 1) is initiated via simple nitro reduction, and benefits from the fact that the starting materials can be easily prepared from commercially available 2-nosyl chloride. The second (Method 2) is initiated by conjugate addition with a diverse array of functionalised primary amines. Both new methods work on a range of ring sizes, with the ring size dependence of both synthetic series in good agreement with the reaction outcomes predicted by DFT calculations. Established methods to make medium sized ring and macrocyclic sulfonamides are relatively rare, particularly so for methods involving ring expansion. Therefore, our hope is that the two new methods reported herein will help expedite the exploration of this compound class in a range of applied fields, especially in medicinal chemistry.

Acknowledgements

The authors would like to thank the University of York for the provision of an Eleanor Dodson Fellowship (to W.P.U.) and the China Scholarship Council for a funding the PhD studentship of Z.Y. We are also grateful to Dr Tony Wild for supporting I.Z. through the University of York Wild Fund. J.M.L. is funded through a Royal Society Industrial Research fellowship. The computational work in this project was undertaken on the Viking Cluster, a high-performance computing facility provided by the University of York. We are grateful for computational support from the University of York High Performance Computing service, Viking and the Research Computing team. Finally, we would like to thank the reviewers, whose insightful ideas and suggestions during the peer review process improved this manuscript markedly.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: Density Functional Calculations · Macrocycles · Medium-Sized Rings · Ring Expansion · Sulfonamides

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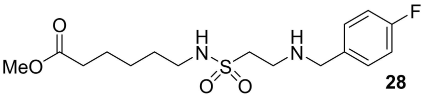

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[19] In most examples free amine reagents were used, but in cases where the amine is more readily available commercially as its HCl salt, the HCl was used directly in the reaction, with an extra equivalent of Et_3N also added to freebase the amine in situ. See Supporting Information for full synthetic details.

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Manuscript received: November 22, 2022
Accepted manuscript online: January 30, 2023
Version of record online: February 15, 2023

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Cite this: *Chem. Commun.*, 2023, 59, 7927

Received 28th April 2023,
Accepted 30th May 2023

DOI: 10.1039/d3cc02087h

rsc.li/chemcomm

Ring expansion reactions of P═O-containing molecules†

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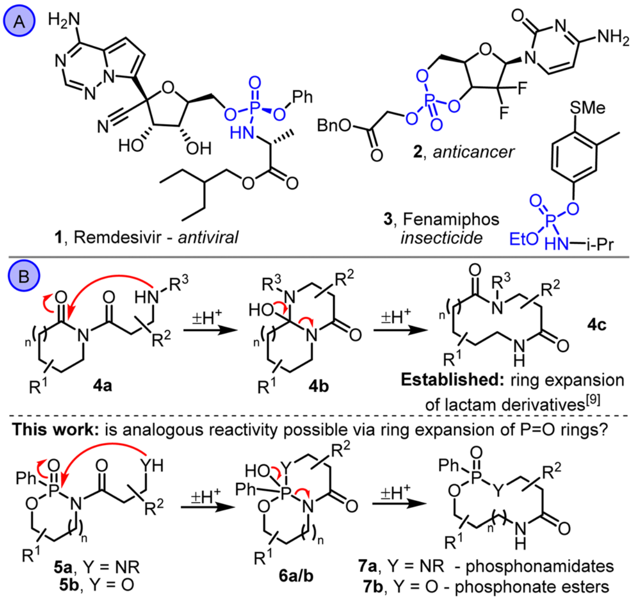
A series of ring expansion reactions of P═O-containing molecules have been developed for the synthesis of medium-sized ring cyclic phosphonate esters and phosphonamidates. The reactivity trends initially appear to be counter-intuitive, compared with more well established ring expansion reactions of lactam derivatives, but are explained by considering the differences in heteroatom bonding to P and C respectively.

Molecules containing P═O bonds (*e.g.* DNA, RNA and ATP) are essential to all life on earth.[1] Organophosphorus compounds are also important in medicinal chemistry and agrochemistry, with various biologically active P═O-containing molecules known (*e.g.* **1–3**, Scheme 1A).[2] Their potential to be used as therapeutic and crop protection agents has therefore been well studied, often using prodrug approaches.[3]

Cyclic P═O-containing molecules are routinely used in prodrug-based medicinal chemistry studies, but almost always as 5- or 6-membered ring derivatives (*e.g.* the recently reported anti-tumor candidate **2**).[4] In view of this, and interest in medium-sized rings and macrocycles in medicinal chemistry more generally,[5] our aim in this study was to develop new methods to synthesise P═O-containing medium-sized rings using ring expansion reactions (Scheme 1B).[6,7] Synthetic methods to make medium-sized ring P═O compounds are rare,[8] and to the best of our knowledge there are no published examples that make use of ring expansion reactions. We therefore set out to explore whether strategies similar to those able to promote the ring expansion of lactam derivatives (*e.g.* **4a** → **4b** → **4c**, Scheme 1B)[9,10] can be applied to phosphonamidate derivatives of the type **5**. By testing amine (**5a**) and alcohol (**5b**) tethered substrates, a reactivity trend was revealed that contrasts that seen in the established lactam ring expansions; the more nucleophilic amine derivatives **5a** rearrange less easily (or not at all), while less nucleophilic alcohol derivatives **5b** rearrange well to form cyclic phosphonate esters **7b**. Calculated Gibbs free energy data for the isomeric intermediates **5**, **6** and **7** indicate that while both reaction series are exergonic, there is a much stronger thermodynamic force for ring expansion, and a lower kinetic barrier, in alcohol derivatives **5b** compared with the analogous amine substrates **5a**.

Synthetic studies started by exploring amine-based substrates of the type **5a**; our previous work showed that related ring expansions are generally faster, more exergonic and higher yielding using amine side chains compared with alcohol-[11] or thiol-based systems.[12] A Conjugate Addition/Ring Expansion (CARE)[13] cascade was devised, with phosphonamidate derivative **9** reacted with different nucleophilic primary amines



Scheme 1 (A) Bioactive P═O containing small organic molecules. (B) Ring expansion reactions of lactams vs cyclic phosphonamidates.

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† Electronic supplementary information (ESI) available. CCDC 2260255. For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d3cc02087h

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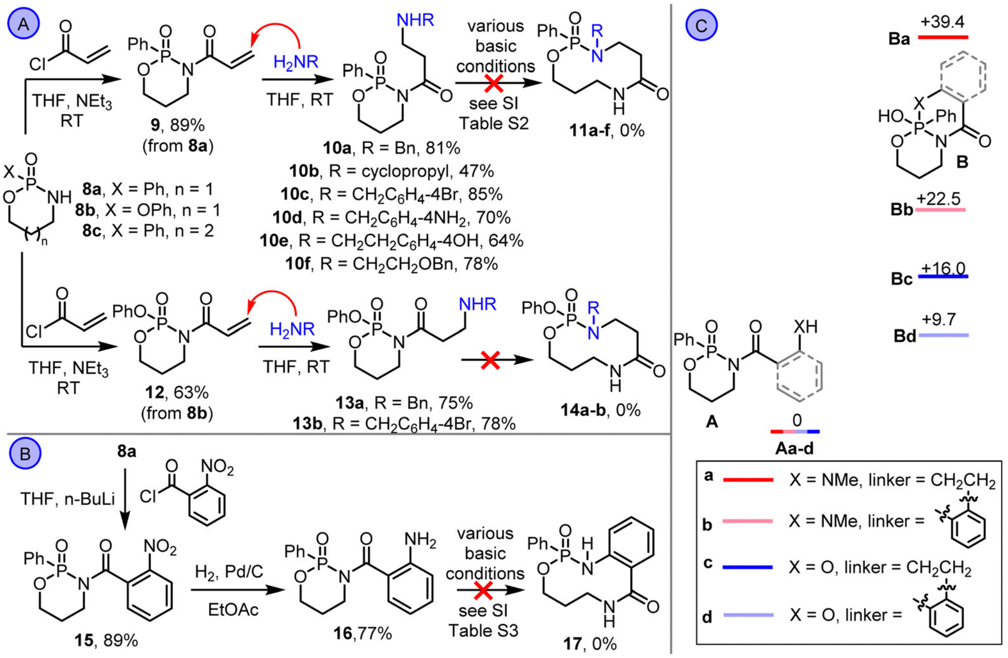

Scheme 2 (A) Unsuccessful ring expansion of *N*-acyl phosphonamidates with tethered aliphatic amines. (B) Unsuccessful ring expansion of **16**. (C) Relative energies of isomeric species in ring expansion of *N*-acyl phosphonamidates using a DFT/B3LYP/6-31G* approach. ΔG°rel values at 298 K are given in kcal mol^{-1}.

(Scheme 2A). The first part of the CARE cascade reaction proceeded as expected, with amine conjugate addition taking place in each case to form amines **10a–f** in good yields.[14] However, no evidence of rearrangement to ring expanded products **11a–f** was obtained under any of the basic reaction conditions screened (see ESI,† Table S2). Similar results were obtained starting from phosphoramidate derivative **12**, with conjugate addition products (**13a,b**) isolated. Aniline derivative **16** was also prepared *via* reduction of nitrobenzene **15** but this substrate also failed to undergo ring expansion (Scheme 2B).

At this point, with the planned ring expansion reactions not proceeding as hoped, their viability was assessed using Density Functional Theory (DFT), using a method that was established and benchmarked for lactam ring expansion reactions in our previous work (Scheme 2C).[15] Thus, the ground state energy of the free amine isomer (**A**), ring-closed (**B**) and ring-expanded isomer (**C**) were calculated for a representative aliphatic amine (analogous to compounds **10a–f**, labelled with '**a**' and highlighted in red) and aniline systems (compound **16**, labelled with '**b**' and highlighted in pink). The energy of a fourth isomer (**D**), accessible *via* an alternative fragmentation of the endocyclic P–O bond, was also calculated, in addition to analogous calculations for aliphatic alcohol (labelled with '**c**', highlighted in dark blue) and phenol (labelled with '**a**', highlighted in pale blue) for comparison. The energies are in kcal/mol and relative to reference states **A**.

Several observations emerge from the calculations. First, ring expanded isomer (**C**) was calculated to be the lowest energy in three out of the four series, and borderline for the aniline system (**Ab**, **Cb**, **Db** all have similar energy). Notably, the unwanted isomer **D** was significantly higher in energy than **C** in three out of four cases. The isomer with the highest calculated energy in all systems was ring-closed isomer **B**, with this especially marked for the aliphatic amine series (isomer **Ba**). With the caveat that these data are calculated for intermediates and not transition states, this may be indicative of a high kinetic barrier to cyclisation being the reason for the failure of **10a–f** and **16** to rearrange. Finally, the energies of states **B–D** were all significantly lower relative to the reference state for the analogous alcohol and phenol systems compared to the analogous amines; this is best visualised in Scheme 2C by comparing the alcohol states depicted in dark/pale blue (**c** and **d**) to the amines depicted in red/pink (**a** and **b**).

These data provide three key learnings that informed subsequent synthetic studies: (1) the ring expansion reactions are thermodynamically viable based on the calculated energy of states **Ca–d**; (2) there appears to be a significant kinetic barrier to ring expansion, in contrast to our previous work on lactam systems which are under thermodynamic control;[15] (3) alcohol-based substrates should work better than the analogous amines, based on their calculated thermodynamic profiles. At this point, we switched attention to alcohol-based substrates, starting with protected-phenol derivative **18a**, which was synthesised *via* the *N*-acylation of phosphonamidate **8a** (Scheme 3A). Hydrogenolysis of **18a** followed, to form phenol **19a**, which rearranged spontaneously *in situ*. However, rather than rearrange *via* ring expansion, we instead isolated product **20a**, *via* fragmentation of the endocyclic P–O bond. This observation was surprising, considering that this isomer was calculated to be higher in energy than ring expanded product **21a** (compare **Cd** and **Dd** in Scheme 2C). But pleasingly, stirring **20a** with triethylamine in chloroform at RT promoted further

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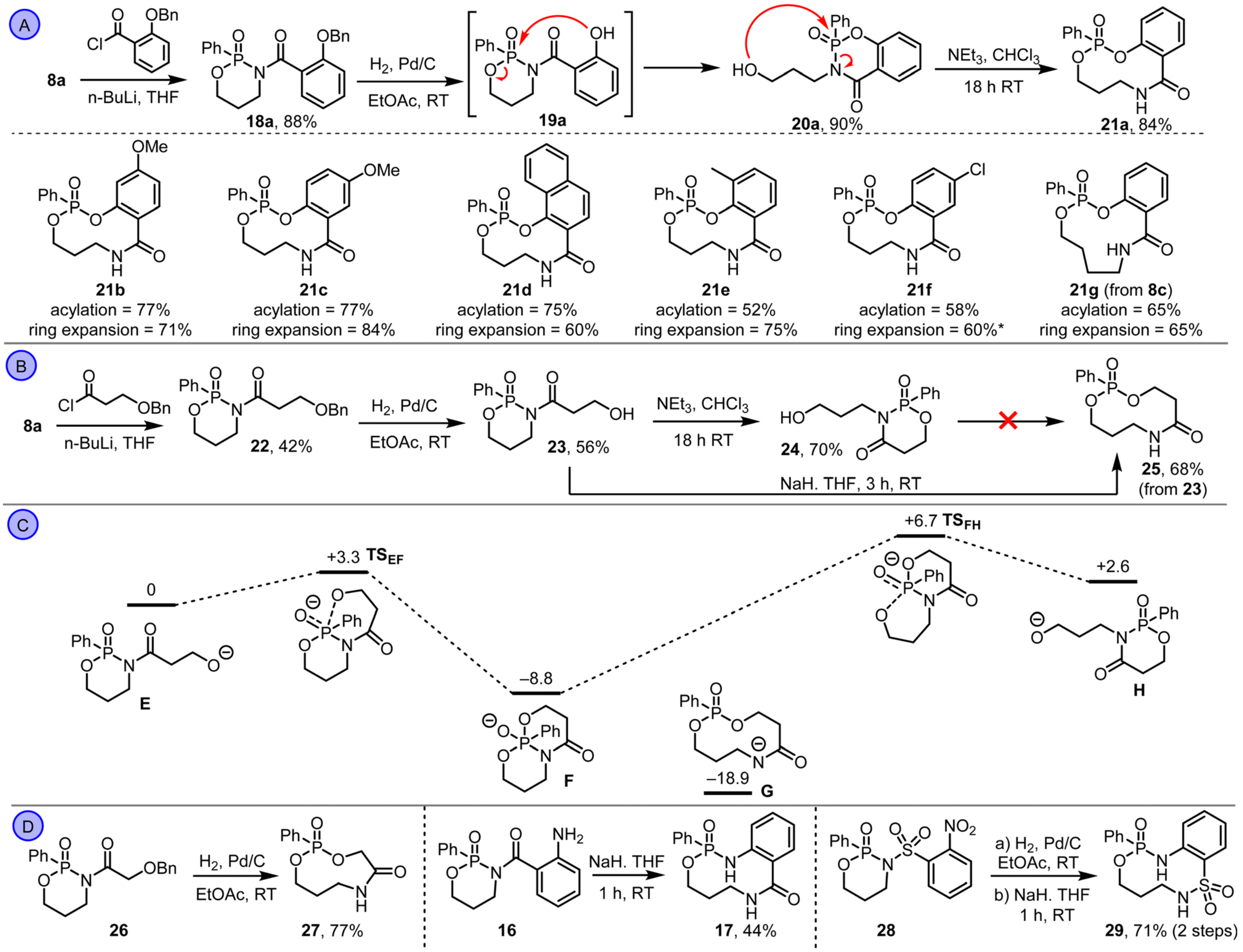

Scheme 3 (A) The ring expansion of *N*-acyl phosphonamidates with tethered phenols. (B) The ring expansion of *N*-acyl phosphonamidates **23**. (C) Relative energies of isomeric species in an anionic ring expansion manifold, using a DFT/B3LYP/6-31+G* approach. $\Delta G°$rel values at 298 K are given in kcal mol^{-1}. (D) Other ring expansion reactions of P=O containing molecules. *Contaminated with ≈10% **21a**, presumably as a result of hydrogenolysis of the C–Cl bond.

rearrangement into the thermodynamic product **21a**, which was isolated in 84% yield. The same sequence (*N*-acylation, hydrogenolysis and ring expansion under basic conditions) was also used to form medium-sized ring phosphonate esters **21b–g** (Scheme 3A).[16] The structure of compound **21d** was confirmed by X-ray crystallography.[17]

Attention then turned to aliphatic alcohol derivative **22** (Scheme 3B). Hydrogenolysis of **22** was performed as before, but there was no evidence of spontaneous rearrangement, with alcohol **23** the only product isolated. This suggests a higher kinetic barrier compared to the phenol systems, which aligns with the calculated energies for **Bc** and **Bd** in Scheme 2C. In an attempt to overcome the kinetic barrier, alcohol **23** was reacted with triethylamine in chloroform at RT; this did promote rearrangement, but again led to the formation of unwanted isomer **24**. Sodium hydride was therefore tested as base in place of triethylamine, and pleasingly this enabled the smooth conversion of **23** into ring-expanded product **25** in 68% yield. It is likely that the use of this stronger base enables an anionic reaction manifold to be accessed that allows the kinetic barrier to ring expansion to be overcome; notably, in the case of the phenol substrates (*e.g.* **19a**) their lower pK_a presumably enables a similar anionic pathway to be accessed when using triethylamine. Calculations performed for the aliphatic alcohol system (Scheme 3C) reinforce the notion that accessing an anionic pathway is important, with the five-coordinate phosphorus intermediate **F** calculated to be *lower* in energy than its corresponding precursor **E**, in stark contrast to the neutral pathway (Scheme 2C). A transition state (**TS$_{EF}$**) for the conversion of **E** into **F** was found at just 3.3 kcal mol^{-1}, consistent with a facile reaction at RT, and a low energy transition state (**TS$_{FH}$**) linking isomers **F** and **H** was also found, indicating that the conversion of **H** back into **F** is also viable if any **H** forms. We were unable to find a transition state linking **F** to the ring expanded isomer **G**, but notably **G** was comfortably the lowest energy isomer on the potential energy surface, in line with the formation of **25** as the reaction product.[18]

We ended by testing two new reaction systems and revisiting one that had previously failed. First, hydrogenolysis

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of **26** enabled its direct conversion into 9-membered ring phosphonate ester **27** in 77% yield. In this 3-atom ring expansion, the fact that it proceeds *via* 5-membered ring cyclisation as opposed to 6-, likely leads to a lower kinetic barrier and hence precludes the need to add base to promote ring expansion. We also found that by using sodium hydride as base, aniline **16** could be converted into **17** in 44% yield. Notably this reaction failed using the less basic condition tested previously and confirms that ring expansion *via* amine nucleophiles is viable provided the kinetic barrier can be overcome. Finally, an alternative aniline-based ring expansion was achieved successfully from sulfonamide derivative **28**; nitro reduction followed by treatment with sodium hydride in THF promoted its conversion into 10-memebered ring phosphonamidate **29** in 71% yield over two steps.

In summary, ring expansion reactions of P═O-containing starting materials have been developed, allowing access to medium-sized ring cyclic phosphonate ester and phosphonamidates. Compared to more well-established ring expansion reactions at C═O bonds (*e.g.* lactam derivatives **4**, Scheme 1B), two key differences emerged. First is the greater reactivity of alcohol-tethered systems than the analogous amines. This contrasts to reactivity at C═O, where amines generally react faster and in higher yields, and is likely due to the change in relative bond strengths on switching from C to P, in particular the high P–O bond strength. The second key difference is the higher kinetic barriers, which in most cases can be overcome by using either a more acidic substrate (*e.g.* phenol **19a**) or more basic reaction conditions to access an anionic rearrangement pathway. An advantage to the higher kinetic barriers is the ability to isolate isomeric species (*e.g.* **23**, **24** and **25**, in Scheme 3C) in high yields under appropriate kinetically controlled conditions.

The synthetic chemistry featured in the manuscript was done by Z. Y., with guidance from W. P. U. The computational chemistry was done by J. K. F. T. and J. M. W., with guidance from J. M. L. The manuscript was written through contributions from all authors. The project was directed and managed by W. P. U. and J. M. L. The authors are grateful for funding from the China Scholarship Council (Z. Y.), the University of York Wild Fund (J. K. F. T.), GSK (J. M. W.) and the Royal Society (J. M. L.) for an Industry Fellowship (INF\R1\221057).

Conflicts of interest

There are no conflicts to declare.

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17 CCDC 2260255† (**21d**) contains the crystallographic data see: www.ccdc.cam.ac.uk/data_request/cif.

18 For all novel products synthesised in this manuscript, the reliable assignment of isomeric species was aided by the observation of $^{13}C–^{31}P$ coupling in their ^{13}C NMR spectra. This allowed the proximity of different carbon atoms to phosphorus to be easily observed and hence provide a simple method to map the progress of the rearrangement (*e.g.* to distinguish **23**, **24** and **25**). See ESI,† Tables S6 and S7 for additional detail.

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