Expanding the Scope of Successive Ring Expansion

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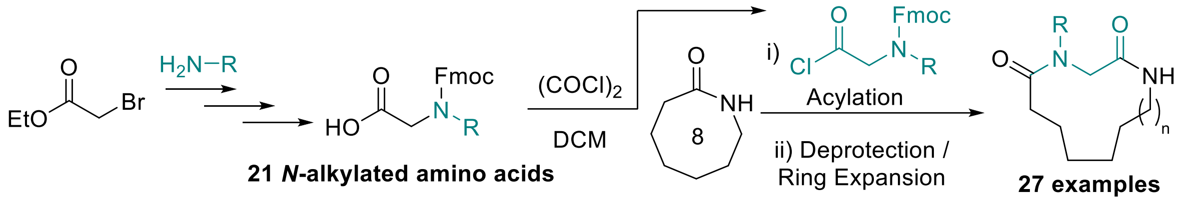
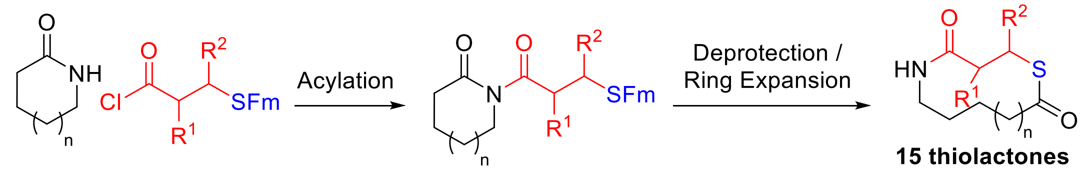
Abstract – Expanding the Scope of Successive Ring Expansion

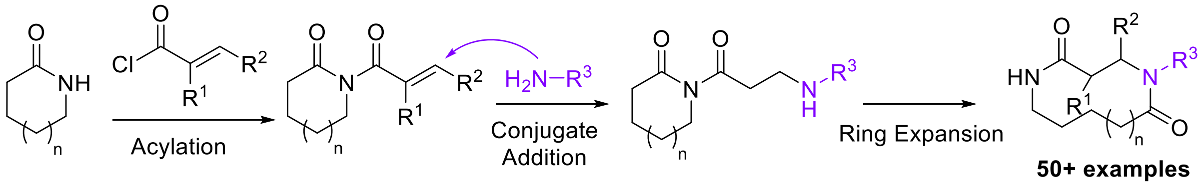
This Thesis describes the development of new methodologies to perform ring expansion reactions to generate novel cyclic molecules. Chapter 1 provides an introduction into methods for the synthesis of cyclic peptides and macrocycles, particularly those utilizing ring expansion reactions, and also outlines the research objectives. In Chapter 2, a study to expand the scope of amino acids compatible with Successive Ring Expansion (SuRE) reactions is reported. A variety of *N*-Fmoc *N*-alkylated amino acids were synthesized and implemented in ring expansions to access functionalized medium sized rings with a peptoid-like structure.



Chapter 3 describes the development of a new SuRE variant utilizing protected thiols to synthesize macrocyclic thiolactones *via* ring expansion, with three complementary protecting group strategies explored. Alongside the synthesis, ring expansions were studied using computational tools, which can be used predictively to assess the viability of the reactions.



Chapter 4 describes efforts to develop a cascade ring expansion methodology to allow many ring expanded products to be formed from a common imide starting materials. The development of a conjugate addition-ring expansion cascade reaction (CARE) allowed the synthesis of functionalized medium sized rings from primary amines in two steps. Using acryloyl imides and a primary amine, an aza-Michael addition occurs followed by concomitant ring expansion. This cascade reaction is protecting-group free, high yielding, and very broad in scope, particularly with respect to the primary amine component, allowing the rapid synthesis of libraries of cyclic peptide mimetics. CARE reactions regenerate a secondary amide, which allows the reaction to be performed iteratively, enabling β-peptoid cyclic peptide mimetics to be 'grown' in sequential reactions with a defined sequence of nitrogen substituent at each stage. CARE reactions using carbon nucleophiles were developed with ring expansion *via* C–C bond formation at the carbonyl. Finally, a dihydroxylation/ring expansion cascade was demonstrated to furnish lactone products.



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 2017 and March 2022.

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 three recent publications, which can be found in the Appendices.

Kleopas Y. Palate

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Abbreviations

Ac	acetyl
Ad	adamantane
AD	Sharpless asymmetric dihydroxylation
AIBN	azobisisobutyronitrile
Ala	alanine
aq	aqueous
Arg	arginine
BI-OAc	acetoxybenziodoxole
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
BOP	(benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate
bpy	bipyridine
br	broad
Bu	butyl
cal	calorie
Cbz	carboxybenzyl
CCDC	Cambridge Crystallographic Data Centre
COSY	correlation spectroscopy
Cy	cyclohexyl
DA	Diels-Alder
DBF	dibenzofulvene
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N,N'*-dicyclohexylcarbodiimide
DCM	dichloromethane
DEPBT	3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3H)-one
DEPT	distortionless enhancement by polarisation transfer
DFT	density functional theory
DIC	*N*,*N'*-diisopropylcarbodiimide
DIPEA	*N*,*N*-diisopropylethylamine
DMA	dimethylacetamide

DMAP	4-dimethylaminopyridine
DMB	2,4-dimethoxybenzyl
DME	dimethoxyethane
DMF	dimethylformamide
DMPU	*N,N′*-dimethylpropyleneurea
DMSO	dimethylsulfoxide
DTT	dithiothreitol
EDCI	*N*-(3-dimethylaminopropyl)-*N′*-ethylcarbodiimide hydrochloride
EDTA	ethylenediaminetetraacetic acid
ee	enantiomeric excess
ESI	electrospray ionisation
Et	Ethyl
eq	equivalent(s)
Fmoc	fluorenylmethyloxycarbonyl
h	hour(s)
HATU	*N,N,N',N'*-tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate
HFIP	hexafluoroisopropanol
HIV	human immunodeficiency virus
HMBC	heteronuclear multiple bond correlation
HMDS	hexamethyldisilazane
HMQC	heteronuclear multiple quantum coherence
HOBt	hydroxybenzotriazole
HRMS	high-resolution mass spectrometry
KAPA	potassium 3-amino-propylamide
Me	methyl
Mes	mesitylene
Ms	mesyl
MS	mass spectrometry
MW	microwave
NMDA	*N*-methyl-D-aspartate receptor
NMP	*N*-methyl-2-pyrrolidone

NMR	nuclear magnetic resonance
Pbf	2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl group
PG	protecting group
Ph	phenyl
Phe	phenylalanine
ppm	parts per million
PMB	para-methoxybenzyl
Pmc	2,2,5,7,8-pentamethyl-chromane-6-sulfonyl
Pr	propyl
p-TSA	para-toluenesulfonic acid
PyAOP	(7-azabenzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (a.k.a. AOP)
PyBOP	(benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate
Pyr	pyridine
RC	ring closed
RE	ring expanded
RO	ring opened
RT	room temperature
SAR	structure activity relationship
SM	starting material
TBDMS	*tert*-butyldimethylsilyl
TEA	triethylamine
Tf	trifluoromethylsulfonyl
TFE	tetrafluoroethylene
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin-layer chromatography
Trt	trityl
Ts	tosyl
XRD	X-ray diffraction

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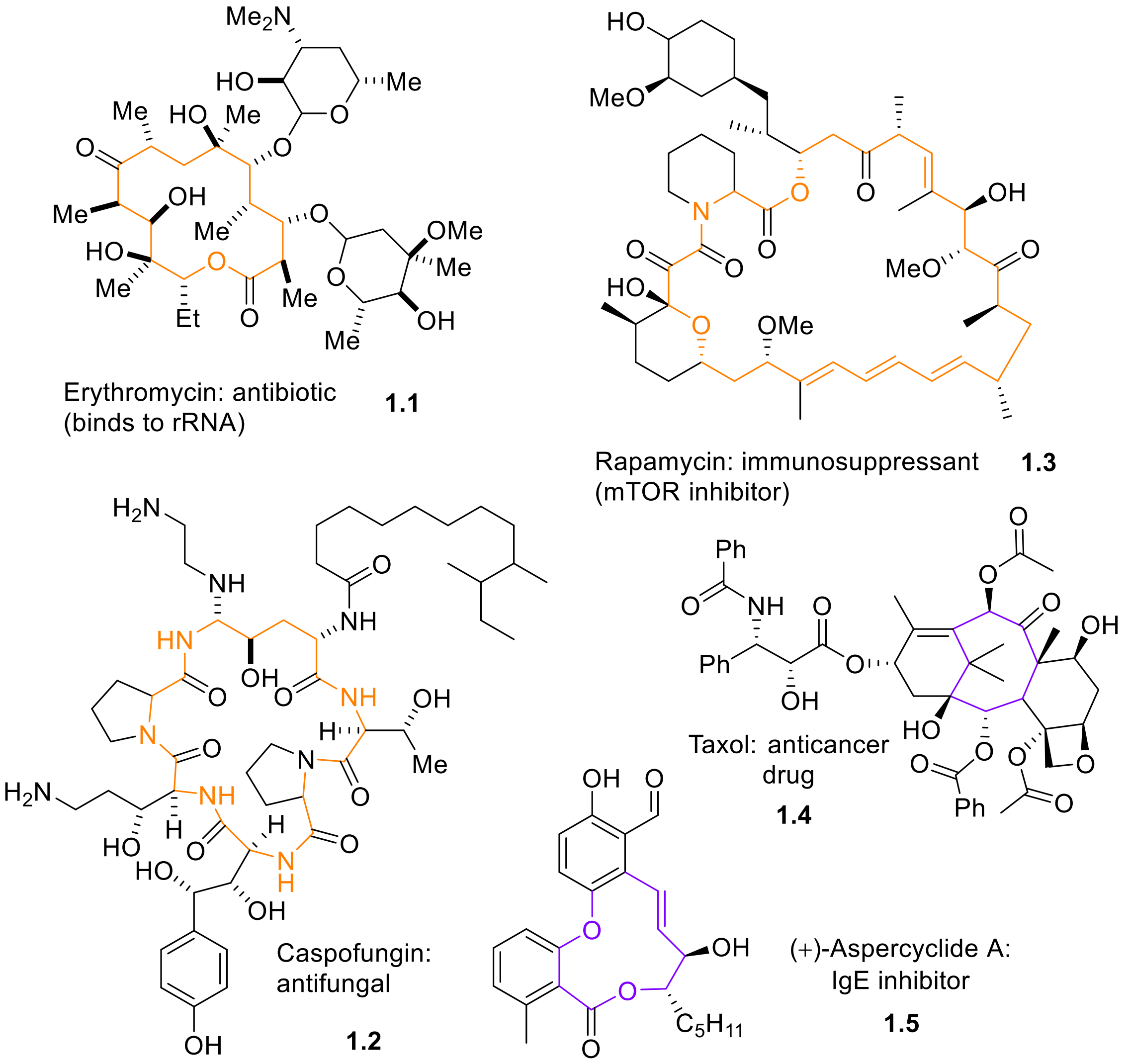
1 Introduction

Macrocycles are defined as being cyclic molecules with a ring size of 12 or more atoms. They have applications in supramolecular chemistry,[1] nanotechnology,[2] and increasingly in medicinal chemistry[3] (Figure 1.1, **1.1**–**1.3**). The 2016 Nobel Prize was awarded 'for the design and synthesis of molecular machines' including catenanes and rotaxanes, which are mechanically bound scaffolds featuring macrocyclic components.[4] Macrocycles are said to 'close the gap' between small molecules and larger biological molecules, possessing desirable pharmacological traits from both classes.[5] Often, they maintain the ability to cross cell membranes, and may be orally bioavailable. Additionally, they may exhibit traits of larger biological molecules (*e.g.* hormones and antibodies), such as conformational flexibility, and 3D character. They inherently have a greater surface area available for interaction compared with low molecular weight small molecules. This is crucial for targeting protein-protein interactions which often span areas too large to be effectively targeted by small molecule drugs.



Erythromycin: antibiotic (binds to rRNA) **1.1**

Rapamycin: immunosuppressant (mTOR inhibitor) **1.3**

Caspofungin: antifungal **1.2**

Taxol: anticancer drug **1.4**

(+)-Aspercyclide A: IgE inhibitor **1.5**

Figure 1.1: Medicinally relevant macrocycles and medium sized rings.

8-11-Membered medium sized rings are also medicinally relevant and are found in many natural products (Figure 1.1, **1.4** and **1.5**). However, the synthesis of medium sized rings is particularly challenging, in large part because the products (and the transition states required to form them *via* cyclization reactions) are often subject to destabilizing transannular interactions. The underpinning challenge may be the reason why 8-11-membered rings are underrepresented in small molecule screening collections and rarely present in top selling drugs;[6,7] indeed, they are usually more difficult to synthesize than both macrocycles (over 12 atoms) or normal sized rings (5-7-membered rings).

Most cyclic compounds are synthesized *via* the cyclization of a linear precursor, typically carried out towards, or at, the end of a synthesis. In the case of cyclic peptides, this is typically a lactamization or disulfide coupling.[8] For instance, in the synthesis of oxytocin, a cyclic peptide hormone, disulfide bridge formation is used to cyclize the linear peptide to form the macrocycle. Alternatively, medium sized rings and macrocycles can be accessed *via* the ring expansion of smaller a cyclic compound. For example, fragmentation reactions of bicyclic systems are a common transformations in natural product synthesis.[9] Both cyclization and ring expansion will be discussed herein, beginning with cyclization reactions.

1.1 Cyclic Peptides

Medicinal interest in cyclic peptides and cyclic peptidomimetics has been on the rise recently for various reasons, such as their resistance to proteolysis, conformational restriction, and favourable pharmacokinetics compared with linear peptides.[10,11] Approximately 85% of the human proteome is considered to be undruggable using traditional small molecule medicinal chemistry due to lack of small molecule binding sites.[12,13] To help address this, libraries of larger cyclic peptides molecules have been synthesized in drug discovery campaigns in order to try to meet this demand.[10,12] For example, larger molecules like cyclic peptides have much potential to interact with extended protein surfaces and be used to inhibit protein-protein interactions.[11,14,15]

This class of compounds is typically synthesized *via* a head-to-tail or side chain-to-side chain cyclization reaction (or another combination thereof). In order to minimize dimerization (Figure 1.2, **1.6** to **1.8**), high dilution conditions are generally required. Alternatively, the linear precursor may be preorganized into a conformational form that favours cyclization by bringing reactive ends together (discussed in more detail later).

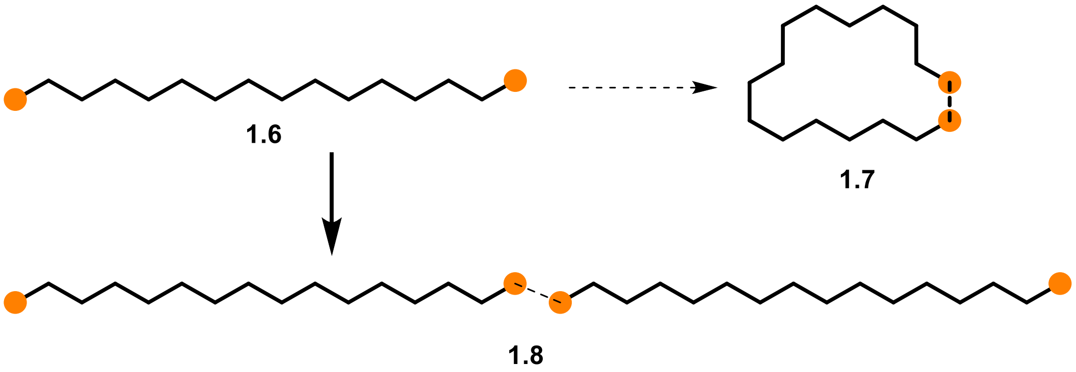
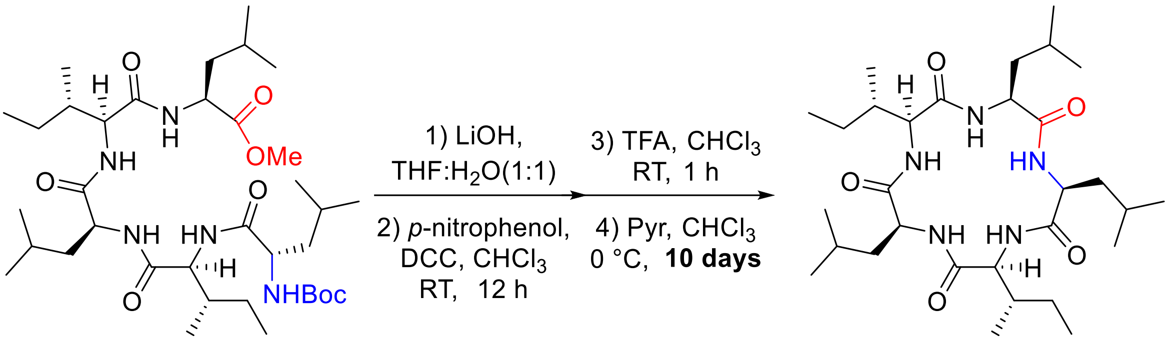


Figure 1.2 : Cyclization of linear molecules is often in competition with dimerization. ***1.8*** *represents the undesired dimer of* ***1.6****.*

1.1.1 Typical Cyclization Reactions for Peptides

Coupling reagents, disulfide bridges, and built-in electrophiles are all used routinely to form cyclic peptides.[8,10] End-to-end cyclization of the C- and N- termini to form an amide bond is a popular approach to forming cyclic peptides. However, the yields of these reactions are highly dependent on the ring size being formed, and the specific sequence of amino acids in the chain.[16] Thioether macrocyclization is a robust method of generating libraries of cyclic peptides,[10,12] and cyclization on resin can also be a very efficient process. For example, using PyBOP as a coupling agent, Pei *et al.* have shown that peptides of 6 to 12 amino acid residues can cyclize nearly quantitatively on resin.[17] Smaller cyclic peptides of 4 or 5 residues were much more likely to undergo dimerization and oligomerization. The same reactions were not as efficient in solution, requiring longer reaction times (as in scheme 1.1) and producing more dimerization side products. An important limitation to consider is that solid state peptide synthesis is not well suited to generating peptides on a large scale. Also, the level of resin loading is often intentionally kept low (2 mmol/g) to effectively isolate each growing peptide preventing intermolecular reactions and promote intramolecular reaction (*i.e*. cyclization). In solution, high-dilution conditions are used to the same effect.[8]



1.9

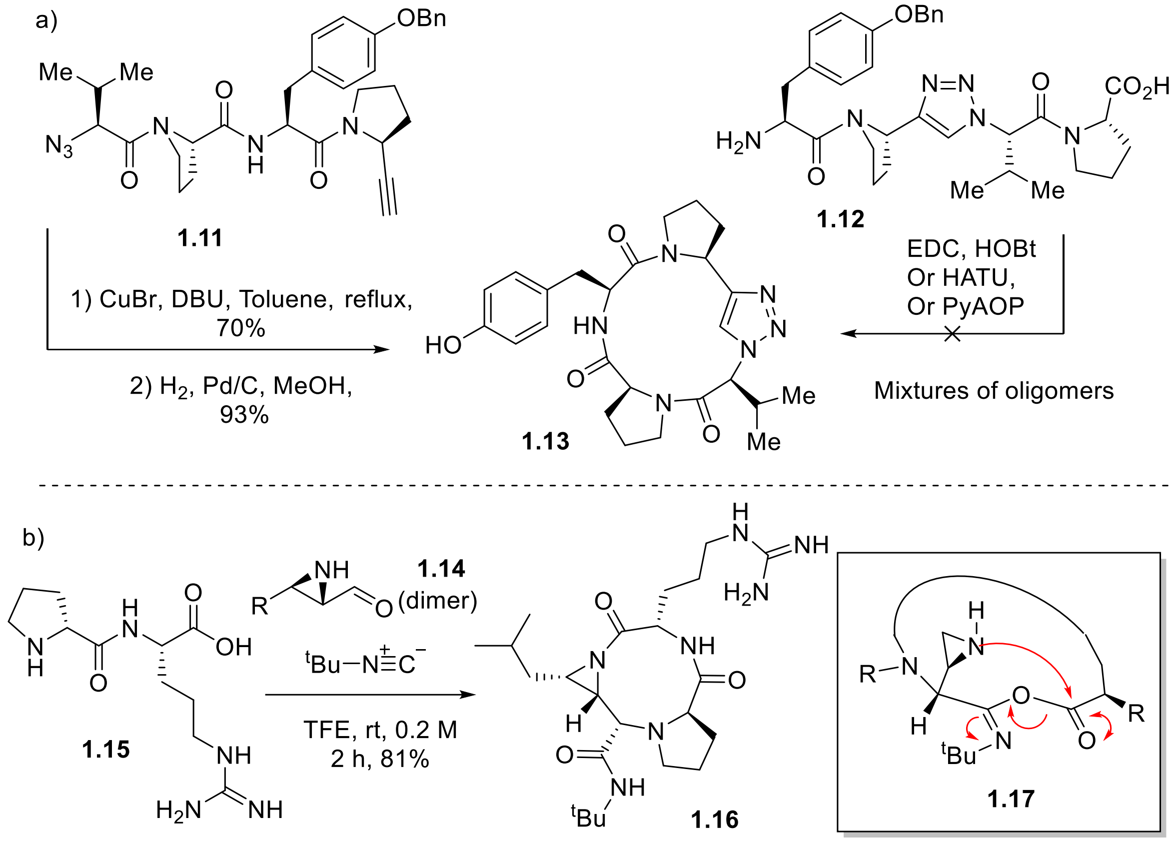
Viscumamide, **1.10**, 57%

Scheme 1.1: End to end cyclization to form cyclic peptide.[18]

1.1.2 Other Cyclization Reactions for Peptides

Many other methods have been used to form cyclic peptides; for instance, copper catalysed "Click" chemistry (Scheme 1.2a), as well as Ugi (multicomponent) reactions (Scheme 1.2b) have been used to access some smaller cyclic peptides.[19,20] Maarseveen *et al.* designed a synthesis where a cyclization and click reaction could be attempted in two different chronological orders in route to a common tetra peptide analogue. When the tetra peptide analogue containing a the internal triazole moiety (**1.12**) was subjected to a variety of coupling conditions, only dimers and higher oligomers could be observed. An alternative cyclization reaction aiming to form the same peptide mimetic (**1.13**) *via* an end-to-end Cu-catayzed click reaction (from **1.11**) was successful in up to 70% yield. The "Click" reaction mechanism may be key to its success; in this reaction a Cu complex brings the azide and alkyne ends of **1.11** close together before a 'ring contraction' generates the triazole.[20–22] The conformation of the respective linear precursors **1.11** and **1.12** may also have played a role.

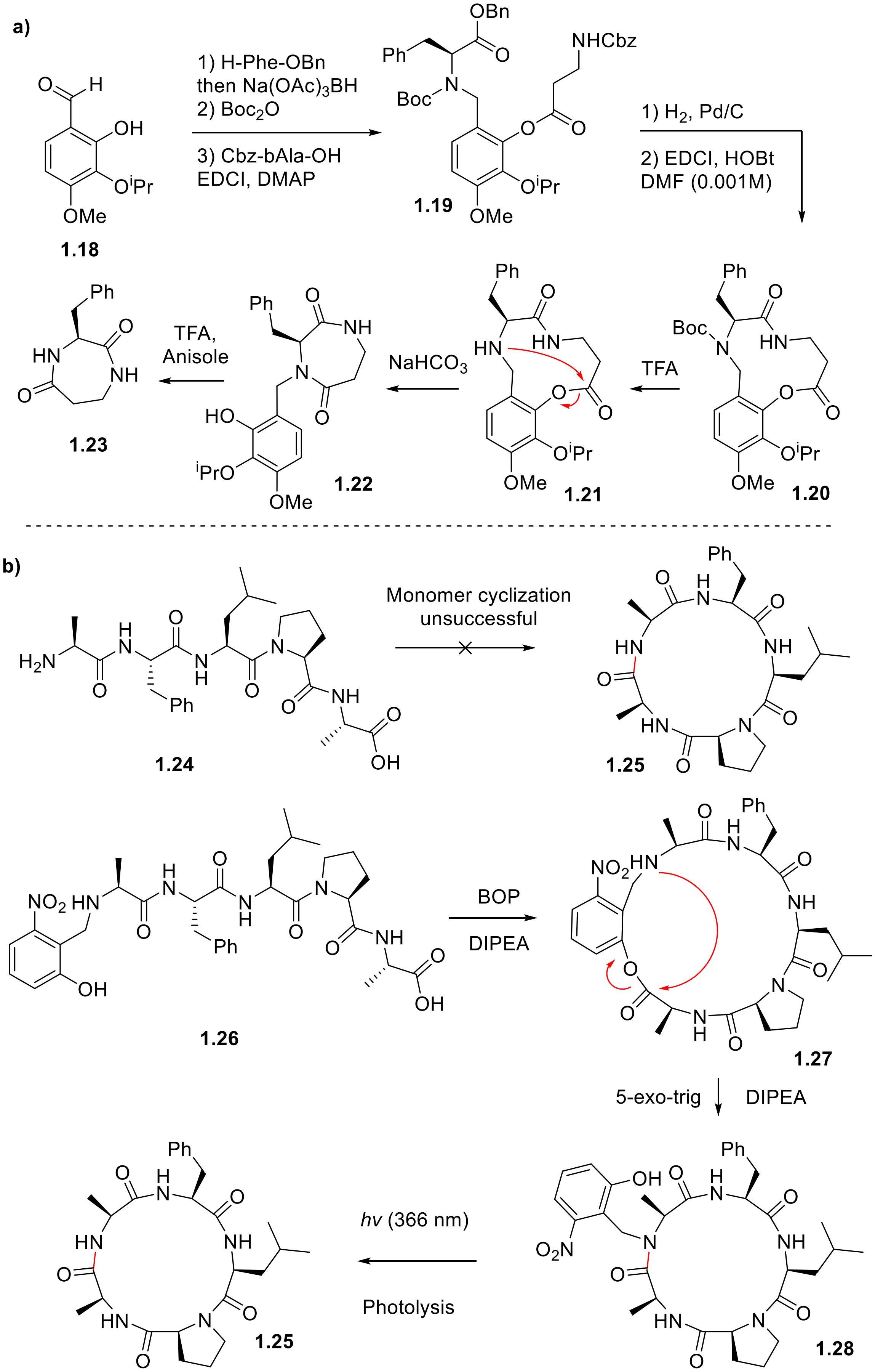
The choice of amphoteric aziridine aldehyde (**1.14**) is key to the reaction in Scheme 1.2b. After the multicomponent step of the reaction, the exocyclic aziradine adds into the carbonyl of the acyl imidate rapidly (**1.17**). It is of note that in a typical Ugi reaction, this rearrangement step is slow, allowing intermolecular reactions to compete, lowering the yield and diastereoselectivity.[19]



Scheme 1.2: Accessing small cyclic peptides via: a) Cu-catalyzed "Click" reaction. b) Ugi reaction using aziridine aldehydes.

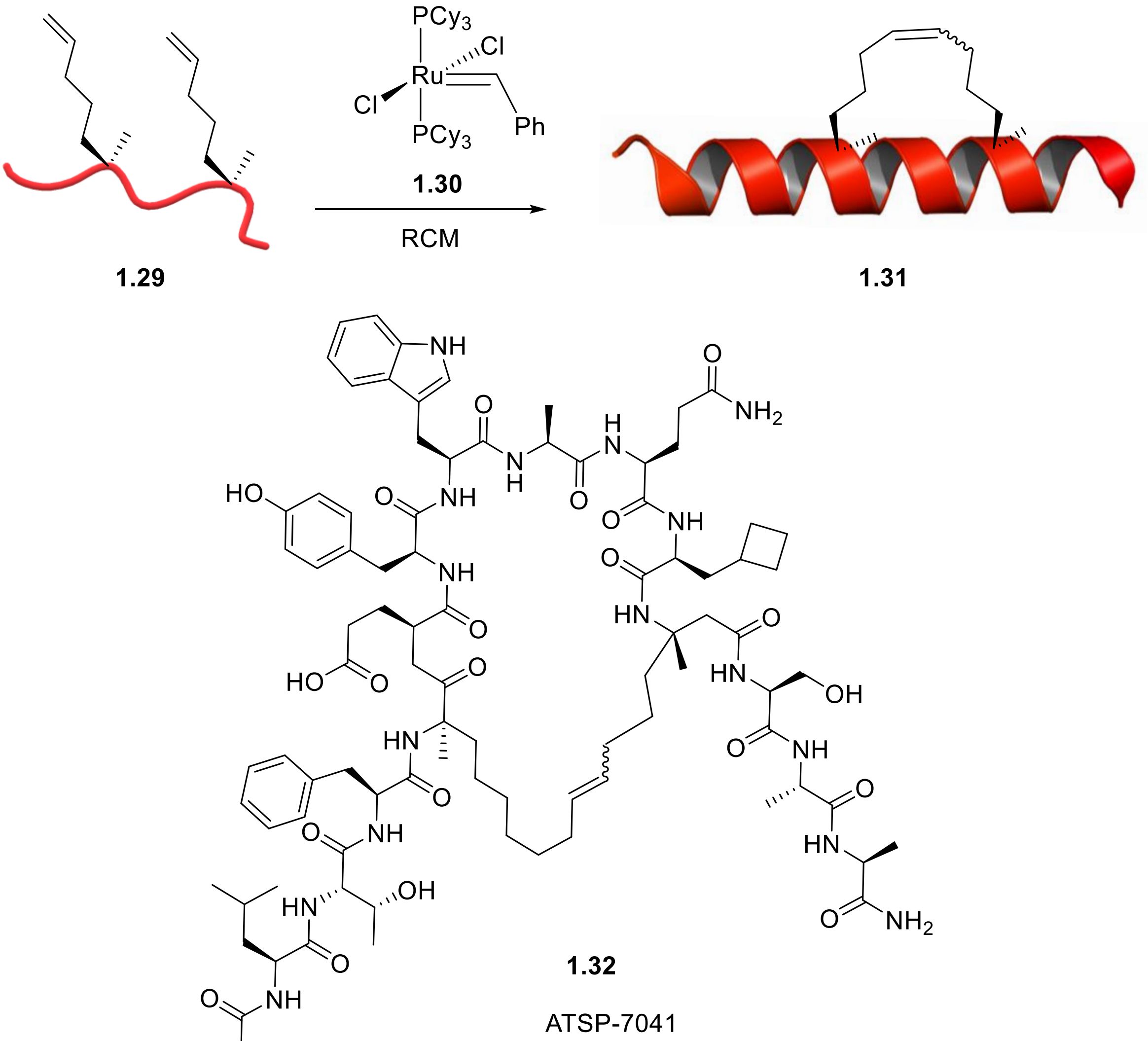
Another approach to access smaller cyclic peptides involves the cyclization of a longer peptide chain followed by a ring contraction. Two such examples are illustrated in Scheme 1.3.[23,24] In Scheme 1.3a, the salicyladehyde derivative (**1.18**) acts to improve the cyclization reaction in two distinct modes. First, by rigidifying the linear precursor **1.19**, the reactive ends of the molecule are held more closely together, thus lowering the entropic hurdle compared to analogous reaction with a more flexible tether. Also, the cleavage of the aryl ester forming **1.22** acts as a thermodynamic driving force to contract the ring (due to the formation of a stable amide and a delocalized phenol).[24]

In Scheme 1.3b, the 5 residue Ala-Phe-Leu-Pro-Ala linear peptide **1.24** could not be cyclized as a single monomer using standard cyclization conditions. Installing a 6-nitro-2-hydroxybenzyl group at the *N*-terminus allows a phenolic ester **1.27** to be formed on subjecting to BOP coupling conditions, which ring contracts in the same way as in Scheme 1.3a to form an amide linkage between the C and N termini. The 6-nitro-2-hydroxybenzyl group is then removed by photolysis to give cyclo Ala-Phe-Leu-Pro-Ala (**1.25**).[23]



Scheme 1.3: Ring contraction approaches via O-to-N acyl transfer.

Finally, advances in transition metal mediated cross coupling have also been used to generate cyclic peptides and peptidomimetics. Ring closing metathesis in particular has been used to cyclize peptides containing alkene handles such as allylglycine.[8,25] The high functional group tolerance of this chemistry has allowed it to be used as a method of 'stapling' together peptides to alter their secondary structure (**1.31**, Scheme 1.4), often enhancing stability and biological activity compared with the parent peptide.[26] ATSP-7041 (**1.32**) is derived from the native p53 alpha helix and acts as to disrupt both MDM2 and MDMX from inhibiting the tumour suppressor p53, leading to suppression of tumour growth in certain cancers.[27]



1.29

1.31

1.32

ATSP-7041
MDM2/MDMX PPI inhibitor

Scheme 1.4: Peptide stapling using RCM.

1.1.3 Preorganization to Aid Cyclization Reactions

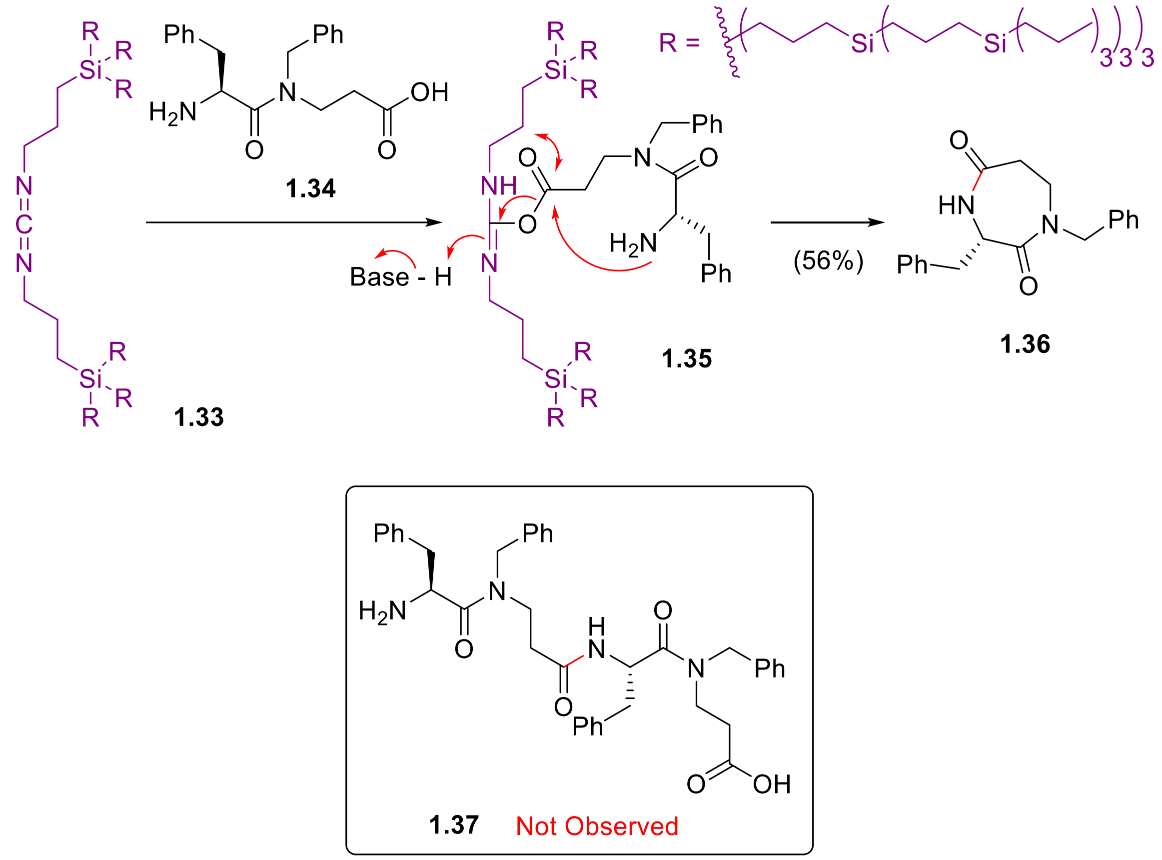
If a linear precursor can be preorganized into a conformational form that favours cyclization (*i.e.* by bringing reactive ends closer together), this can significantly improve the efficiency of macrocyclization reactions by favouring cyclization over dimerization. There are several methods by which this can be achieved, summarized below.

Internal preorganization:

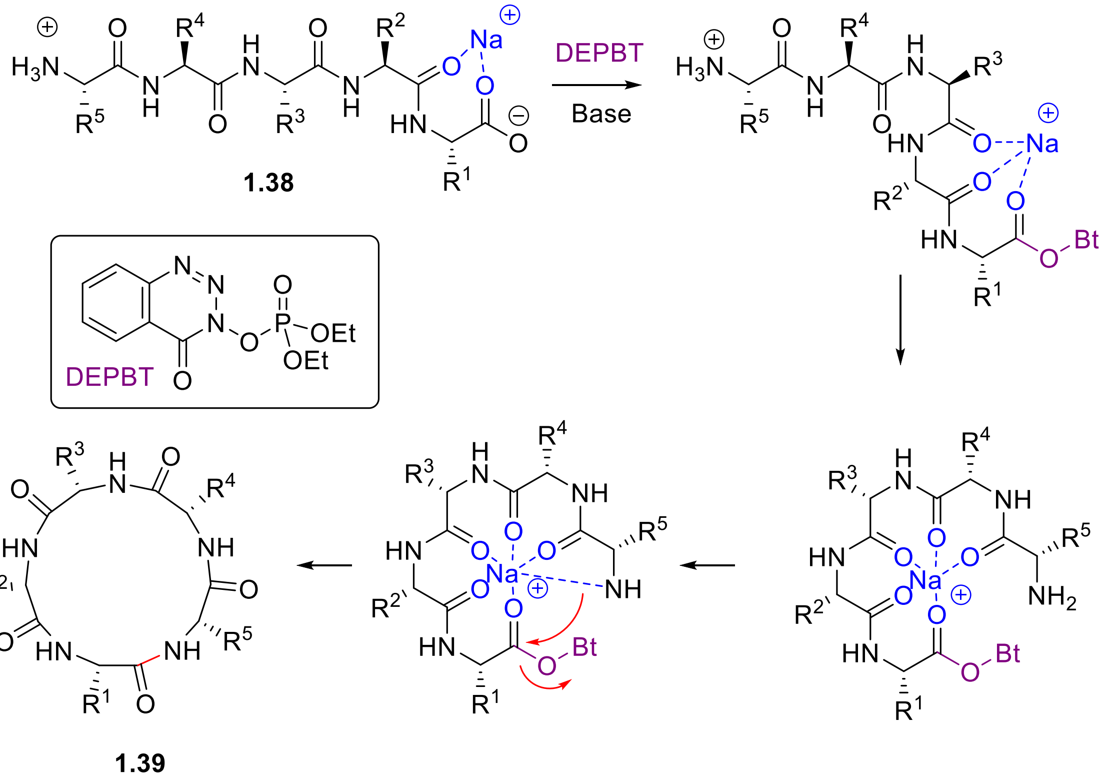
Internal preorganization is achieved by covalent modifications to the peptide chain itself.[8] End-to-end cyclization requires a conformation to be adopted which is often energetically unfavourable. One of the simplest ways to promote the adoption of a conformation more conducive to undergo cyclisation is to introduce a *cis* amide bond at a site where the peptide turning back on itself facilitates the two ‘ends’ becoming closer together in space, and hence promoting cyclization. In nature, proline is commonly used to provide these sharp turns.[8,14] Most amide bonds adopt a *trans* conformation preferentially; however, substitution at nitrogen (such as in proline) tends to remove the energetic bias of one conformer over the other.[8] Other approaches to achieve the same end include incorporation of *D*-amino acids, and *N*-alkylated amino acids (discussed later on). The nature of the substituent on the nitrogen has an important role in determining the geometry of the amide bond.[28]

External preorganization:

External preorganization often involves molecular scaffolds that bring together the reactive ends of a molecule.[8] Bulky coupling reagents, such as the one shown in Scheme 1.5 (**1.33**), effectively isolate a peptide, thus minimizing intermolecular coupling reactions. The crowded dendridic carbosilane (**1.34**) prevents access to a second peptide molecule, and thus helps to prevent dimerization.[29] Metals can be used to coordinate with a peptide in a multidentate fashion (Scheme 1.6, **1.38**).[30] This induced turn structure brings reactive ends in close proximity for cyclization to form **1.39.**

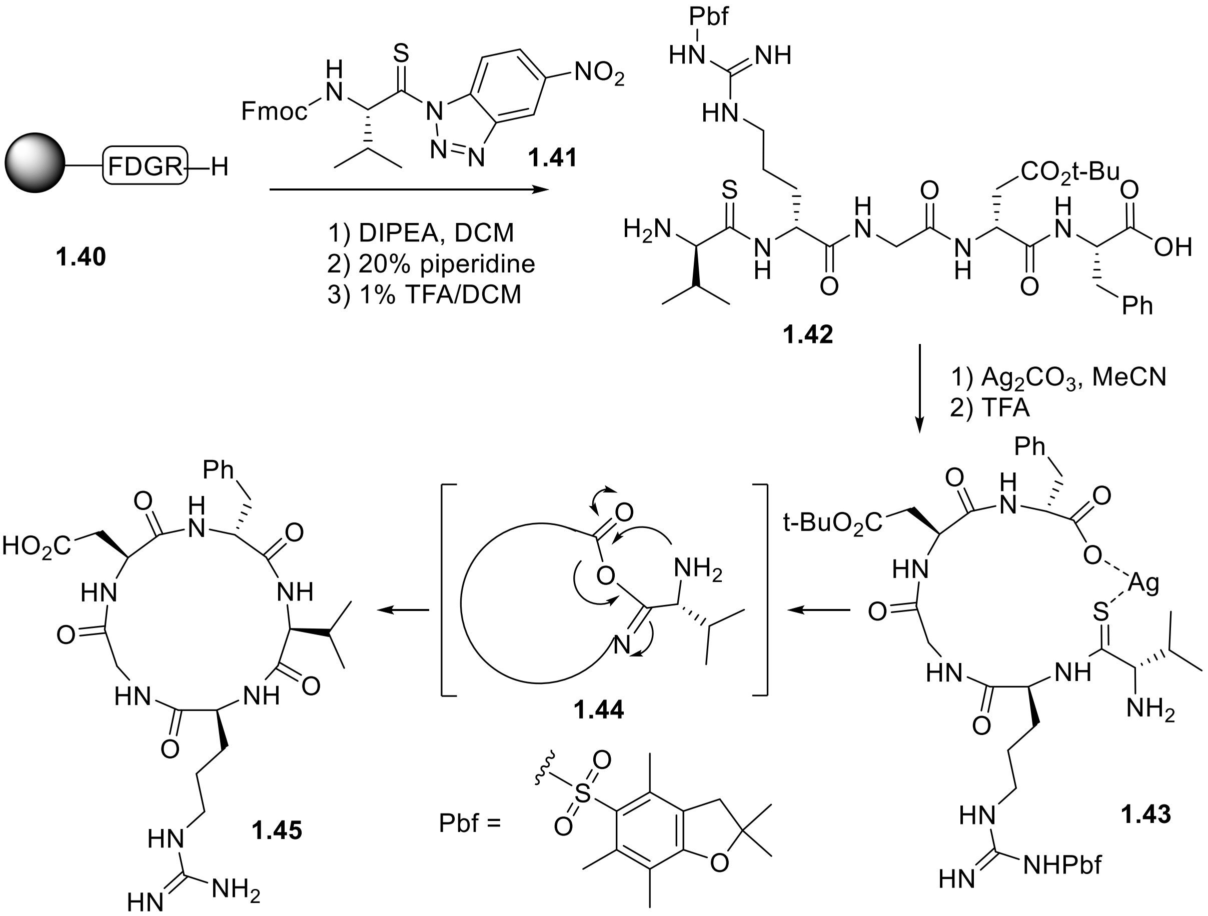


Scheme 1.5: External preorganization using a bulky coupling reagent.



Scheme 1.6: Preorganization via coordination to a metal.

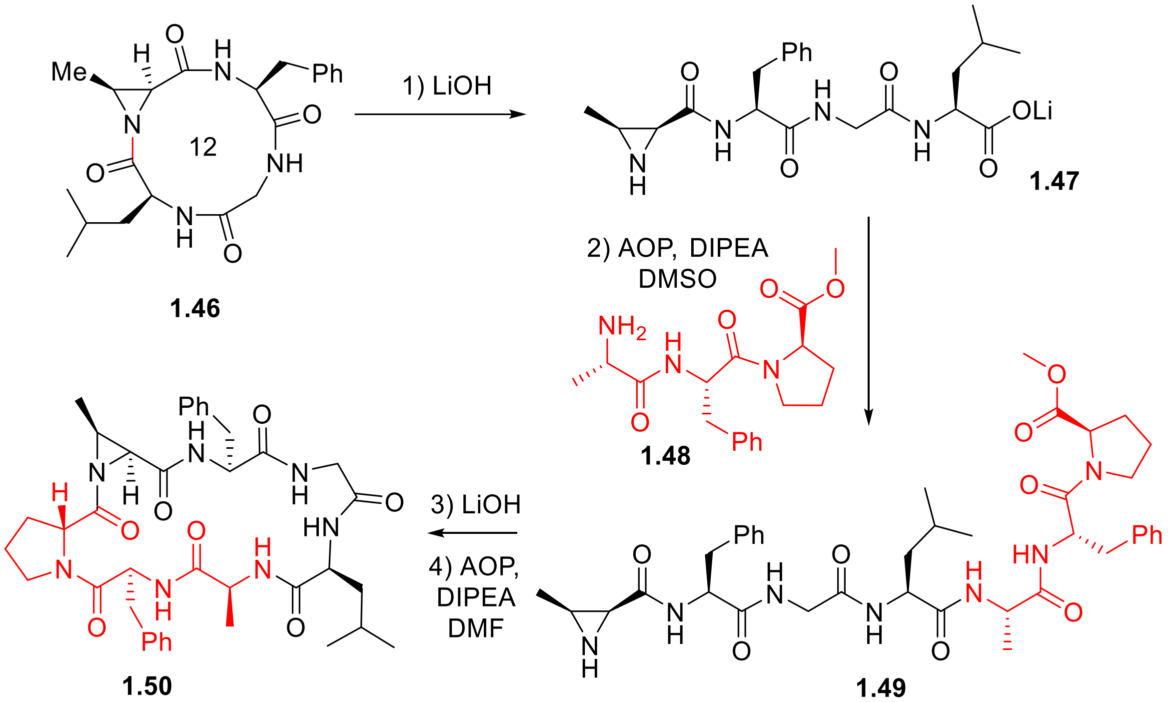
Hutton and co-workers developed an approach which uses metal coordination to both coordinate the two ends of a linear peptide and couple them together (Scheme 1.7). A linear peptide is first assembled on chlorotrityl resin using solid state peptide synthesis. Using thioacylating agent **1.41**, the last residue incorporated into the chain features a thioamide bond, which once cleaved from the resin gives the protected linear peptide **1.42**. When this thioamide is reacted with stoichiometric Ag_2CO_3, the Ag^+ cation serves to coordinate to both the C- terminus and the thioamide to template the macrocyclization and activates the thioamide at the *N*-terminus to form an imine ester **1.44,** which undergoes an O-N acyl shift to complete the head–to–tail cyclization. This method was showcased *via* in the synthesis of an analogue of the anti-integrin drug cilengitide, **1.45**.[31] The authors describe this process as a rapid and traceless method to form cyclic peptides *via* macrocyclization, without any problems relating to cyclodimerization or epimerization. Kinetic studies compared a standard linear octapeptide cyclized using HATU coupling conditions, which cyclized in 35% yield in 16 h, whereas a thioamide analog using Ag(I) conditions was cyclized in 83% yield in less than 1 h (HPLC yields).



Scheme 1.7: Ag⁺ promoted end to end coordination and coupling.

1.1.4 Site selective ring opening, coupling, and recyclization

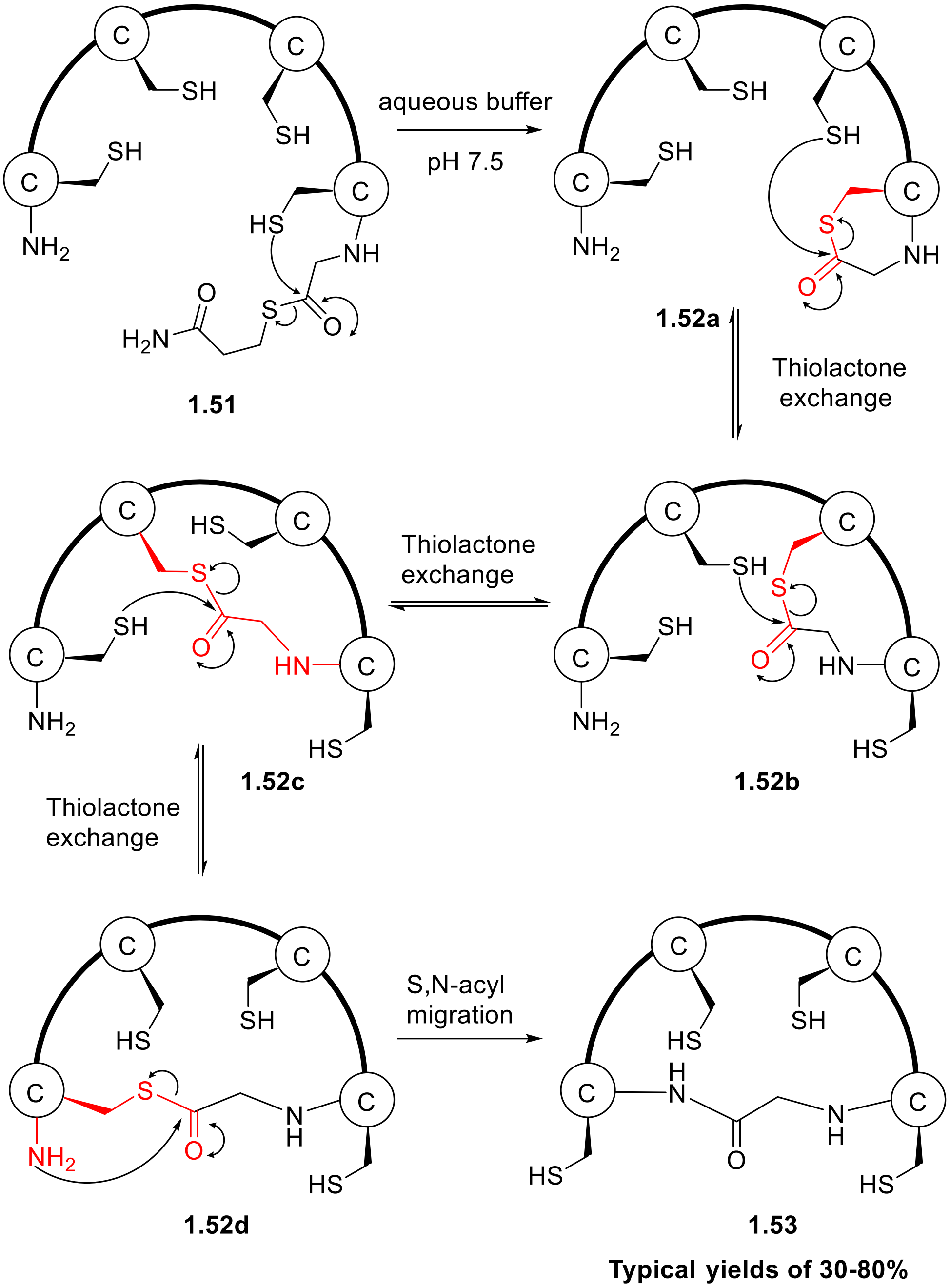
Yudin *et al.* developed a method of ring expansion of cyclic peptides *via* the site selective ring opening at an aziridine amide (highlighted bond in **1.46**) in LiOH conditions, followed by coupling of an additional amino acid residue or short peptide chain (**1.48**) using the coupling agent AOP (scheme 1.8). Repeating this two-step cycle (of LiOH hydrolysis followed by AOP coupling conditions) served to hydrolyze methyl ester **1.49** and recyclize the macrocyclic peptide, incorporating the new fragment in a new, larger macrocyclic product **1.50**.[32]



Scheme 1.8: Site selective amino acid (or peptide) insertion into cyclic peptides.

1.1.5 Thia-zip ring expansion

A biomimetic approach developed by Tam *et al.* utilizes transformations often seen in protein splicing. O-N and S-N acyl shifts allow for segments of a linear peptide to be excised from the whole. This inspired a new approach to peptide cyclization utilizing sequential ring expansion to achieve end-to-end coupling. In a cystine-rich peptide, a thiolactone is first formed at the C terminal end. Then, a series of thiolactone exchange reactions with cystine residues along the chain, sequentially ring expanding the thiolactone, until a thiolactone is formed at the *N*-terminal cystine. A final irreversible S-N acyl transfer completes the end–to–end cyclization of the cyclic peptide. Using this elegant ring expansion approach, cyclopsychotride, a 31-amino acid cyclic peptide, 99 atoms in ring size, could be synthesized.[33] Although depicted in scheme 1.9 as a sequential process with the next cystine along the chain always the following the previous during the thiolactone exchange step, the exact pathways could not be established, and perhaps it is possible that only a few thiols are involved in the thiol-thiolactone exchanges. Thia-zip reactions, as they have been called, were performed in buffered aqueous solution, a stark contrast to the aza-zip reactions discussed later (see Section 1.2.4), which require strong base and organic solvent.



Scheme 1.9: Thia zip reaction. Image reproduced from the literature with authors permission.

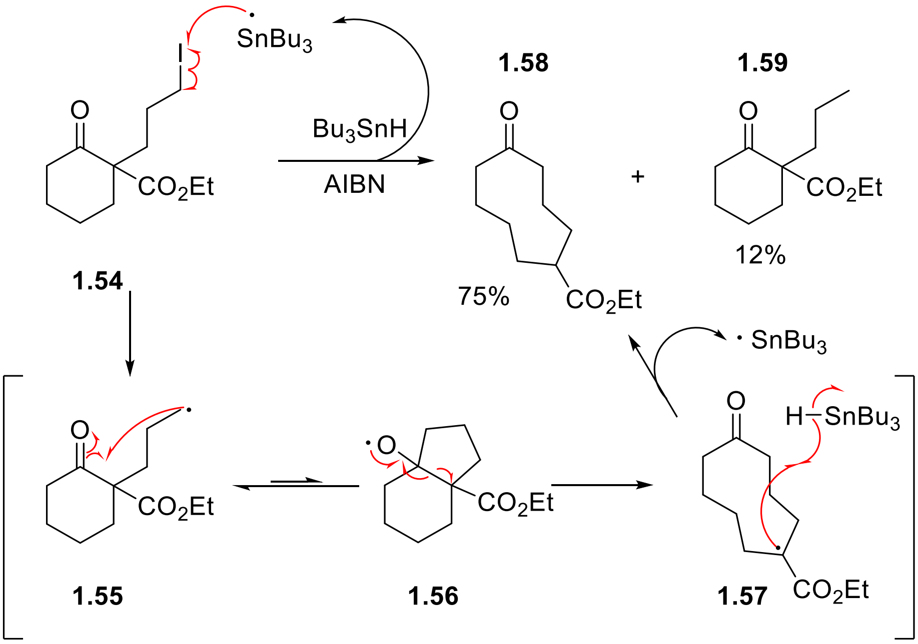
The various creative synthetic methods outlined on the previous pages have found significant success for the synthesis of complex macrocycles. However, the need to employ these strategies also highlights one of the key failings of macrocyclization, namely the challenge of avoiding dimerization. High dilution conditions are still often required, which can slow down macrocyclization reactions substantially. Ring expansion is an alternative approach to forming large cyclic molecules, which avoids the macrocyclization step altogether. Selected approaches are summarized below in Section 1.2.

1.2 Ring Expansion

Ring expansion is the process of taking a cyclic molecule and expanding the size of the ring skeleton by one or more atoms. There are three main types of ring expansion reactions: fragmentation, radical, and pericyclic class ring expansion reactions.[9]

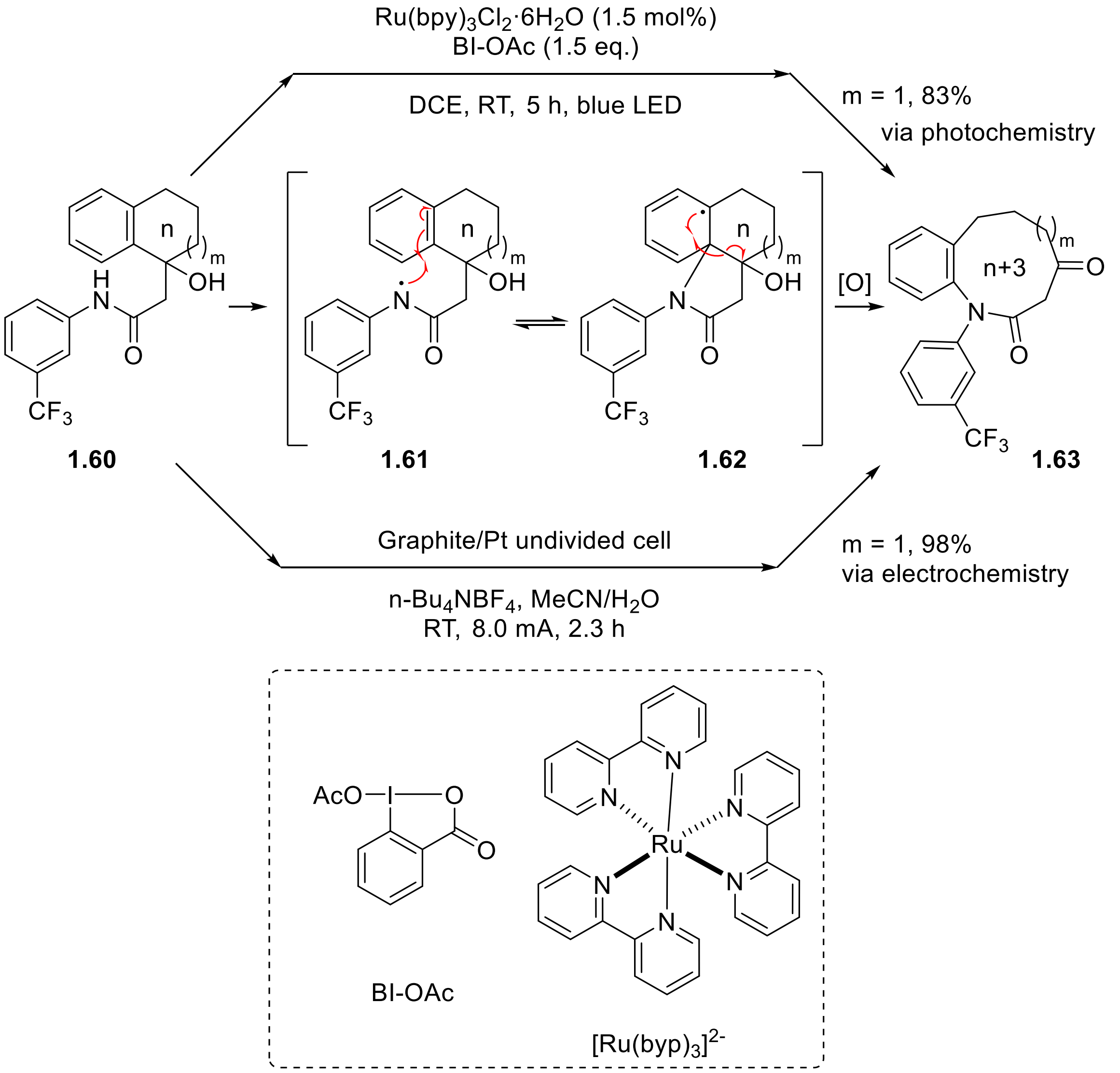
1.2.1 Radical Approaches

A classical example falling under this category is that of the Dowd-Beckwith carbon-centered radical ring expansion (scheme 1.10). This reaction is initiated by generating an alkyl radical on a pendant carbon chain (**1.55**). What follows is a reversible reaction with an electron deficient ketone, and an ensuing fragmentation reaction extruding an electrophilic radical, which is stabilized by an electron withdrawing group, in this case an ester (**1.57**). A final reduction (H abstraction) yields the product (**1.58**) in a good 75% yield. Unfortunately, simple reduction can compete in these reactions, and form side products such as **1.59** (12% yield).



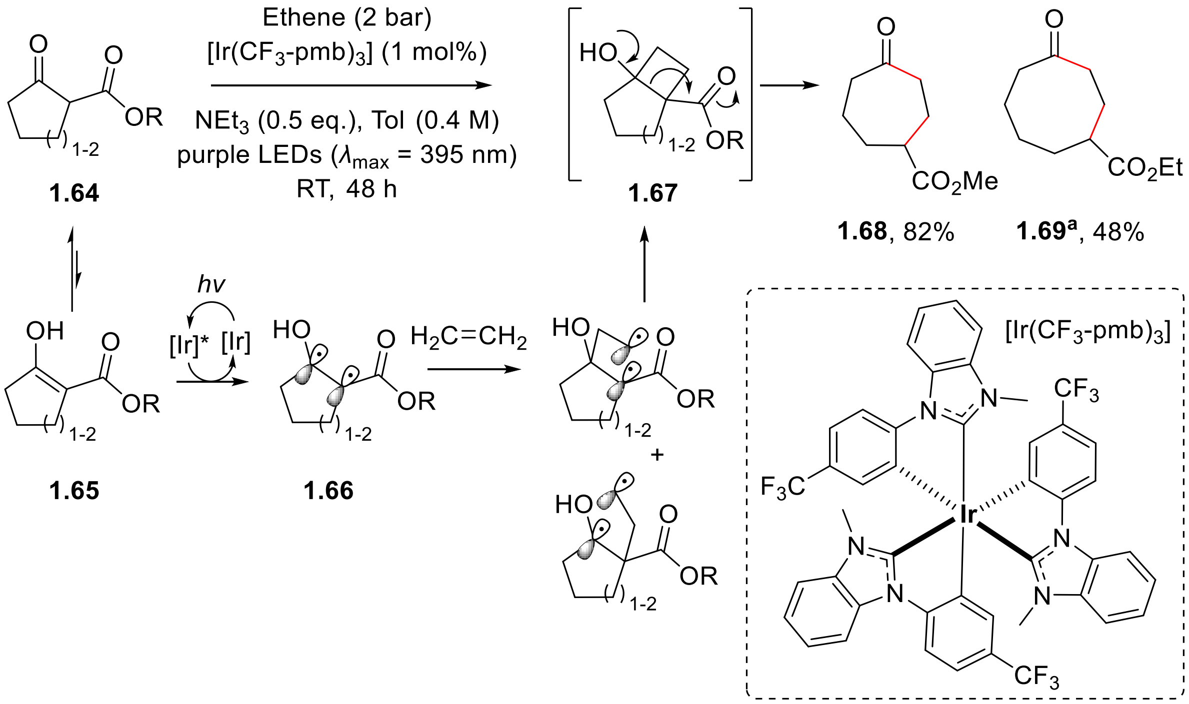
Scheme 1.10: Dowd-Beckwith radical ring expansion.

Modern day radical chemistry is often carried out using photocatalysis or electrochemistry. Liu *et al.* reported a photocatalytic 3-atom ring expansion *via* the generation of a radical on an amide nitrogen (**1.61**). Medium sized rings from 9-11 membered in size were all accessible using this procedure with the 9-membered ring example (**1.63**, n = 6, m = 1) isolated in 83% (scheme 1.11, top conditions).[34] Ackermann *et al.* built upon this work by demonstrating that the reaction can also be performed electrochemically, to give the same 9-membered ring product (**1.63**, n = 6, m = 1) in an improved 98% (scheme 1.11, bottom conditions).[35]



Scheme 1.11: Ring expansion via a Nitrogen centred radical. The same reaction can be performed with photocatalysis or electrochemistry.

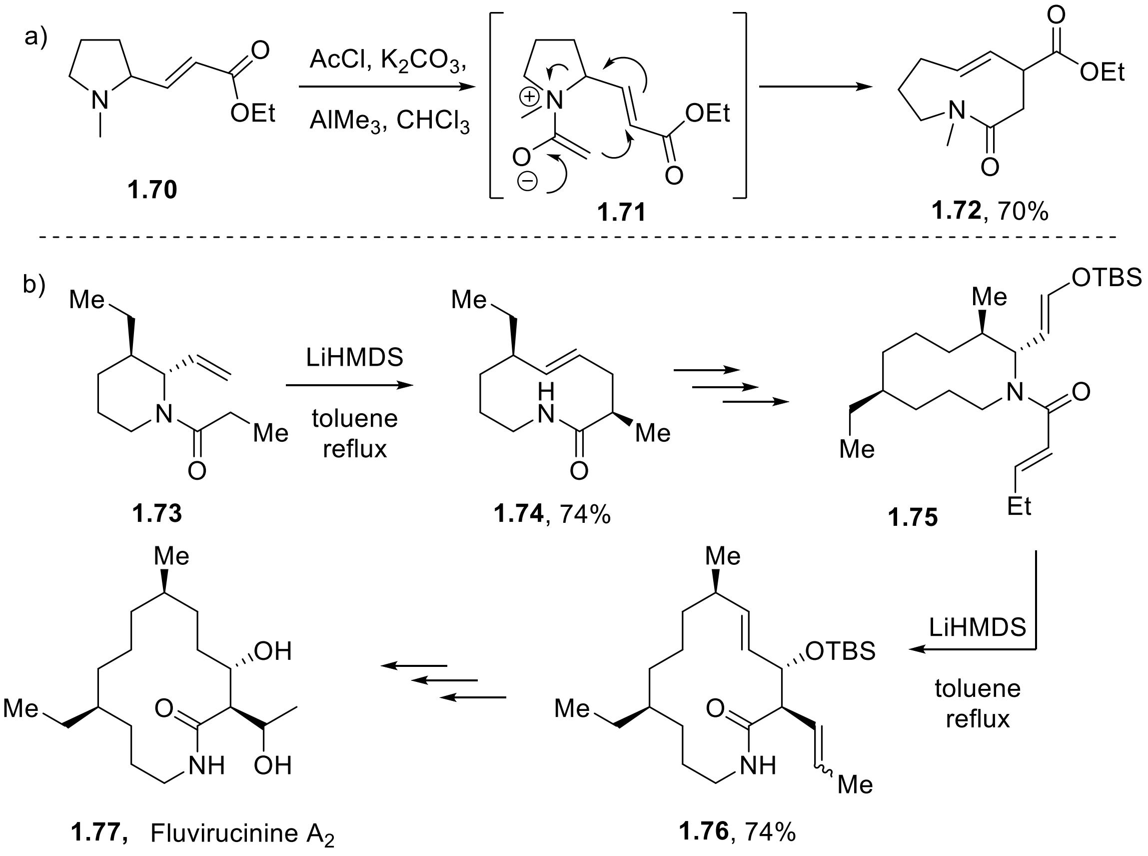
Glorius *et al.* devised a photocatalyzed De Mayo reaction able to ring expand normal 5- and 6-membered dicarbonyl compounds (**1.64**) to 7- and 8-membered rings (scheme 1.12).[36] In this reaction a photocatalyst serves to generate an excited state of enol alkene **1.65**, which can be considered a diradical (**1.66**). Following a reaction with ethene gas, a bicyclic intermediate (**1.67**) is formed that can fragment to form ring expanded products (**1.68** and **1.69**).



Scheme 1.12: Photocatalytic De Mayo-type ring expansion. ^{a} Addition of $LiBF_4$ (0.5 equiv), TEA (1.5 equiv) and heating (70°C).

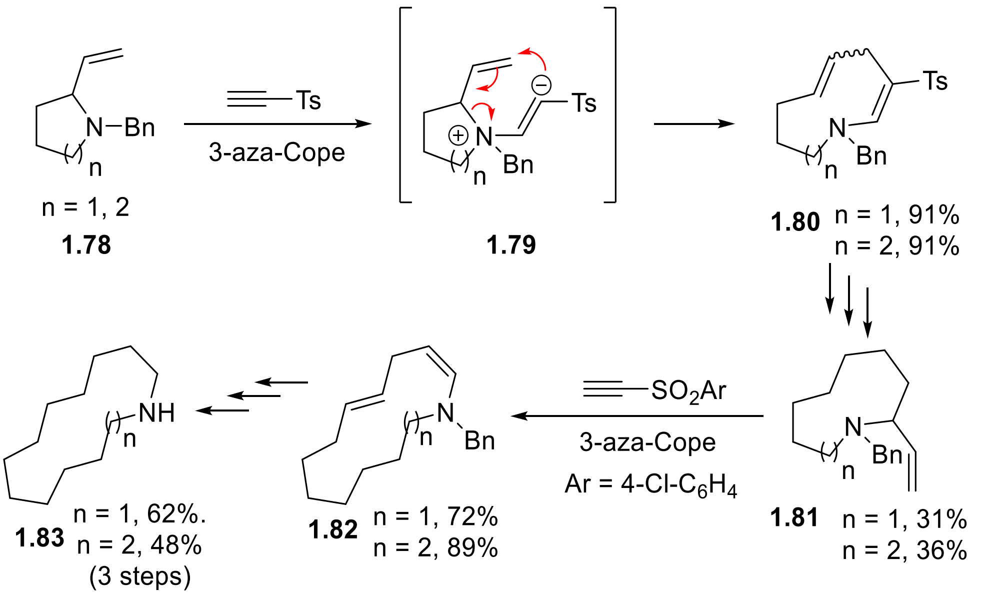
1.2.2 Pericyclic Reactions

Many ring expansions follow a pericyclic route, most commonly *via* [3,3] sigmatropic rearrangements; scheme 1.13 illustrates two such examples. An aza Claisen rearrangement has been used to generate medium-sized rings (*e.g.* **1.72**) *via* acylation to form a quaternary nitrogen in a ring expansion reaction (**1.71**, scheme 1.13a).[37] Suh *et al.* devised a total synthesis of fluvirucinines A_1 and A_2 which featured two aza-Claisen rearrangements to form the 14-membered lactam scaffold from 6-membered **1.73** (scheme 1.13b).[38]



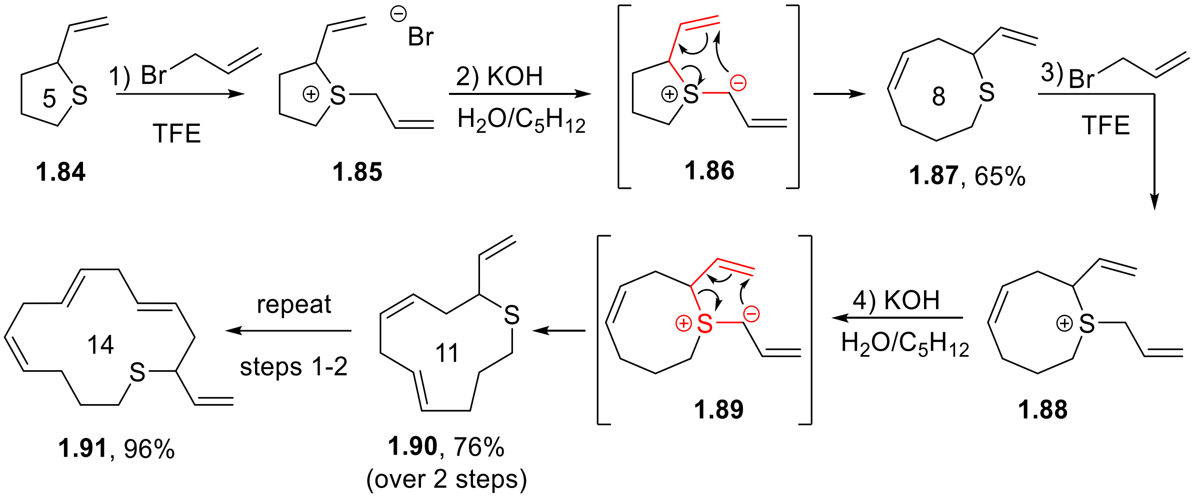
Scheme 1.13: Two examples of aza-Claisen rearrangements to perform ring expansions.

Back *et al.* have used two successive 3-aza Cope rearrangement reactions in order to convert pyrrolidines and piperidines into 13- and 14-membered rings respectively. Each reaction expands the ring by 4 atoms and uses very mild conditions (Scheme 1.14).[39]



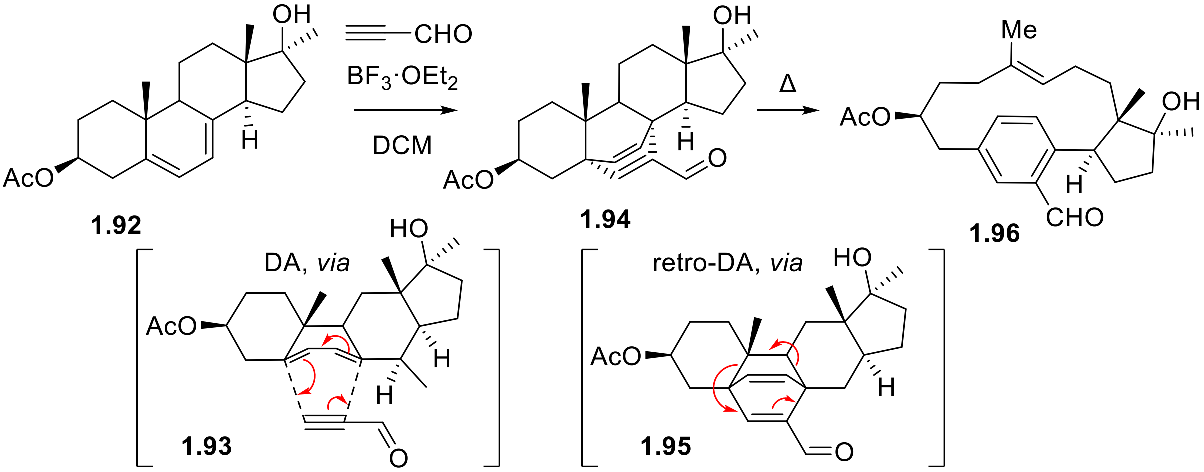
Scheme 1.14: 3-aza-Cope used for iterative ring expansion.

Schmid *et al.* demonstrated that cyclic sulfides (*e.g.* **1.84**) can undergo similar 2,3-sigmatropic rearrangement reactions to form ring expanded products. Each product formed can be used as a starting material to undergo the same two step reaction procedure of allylation followed by deprotonation under aqueous KOH conditions to promote ylide formation and rearrangement/ring expansion. The sequence shown in scheme 1.15 was used to make rings up to 14 membered in size (**1.91**) over 3 iterations.



Scheme 1.15: [2,3]-rearrangements of sulfur ylides in an iterative ring expansion.

Winterfeldt *et al.* developed a Diels-Alder/retro Diels-Alder sequence which can be used to ring-expand readily available steroids and their derivatives (*e.g.* **1.92**) into *p*-cyclophane macrocycles (**1.96**).[40] An initial Diels-Alder reaction with an alkyne forms bridged enal (**1.94**). Upon heating, this undergoes a retro Diels-Alder to open the steroidal B-ring (*via* **1.95**) to yield **1.96** (scheme 1.16).



Scheme 1.16: Diels-Alder / retro Diels-Alder ring expansion sequence of steroid derivatives.

1.2.3 Fragmentation Reactions

The fragmentation of a bicyclic system to cause the cleavage of a bridging bond and generate a larger ring system is a technique that has been used extensively in natural product synthesis. Fragmentation reactions may occur by breaking a central bond on a fused bicyclic system (Figure 1.3a) or *via* the cyclization of a side chain to form a transient bicycle (**1.100**), followed by ring expansion (Figure 1.3b).

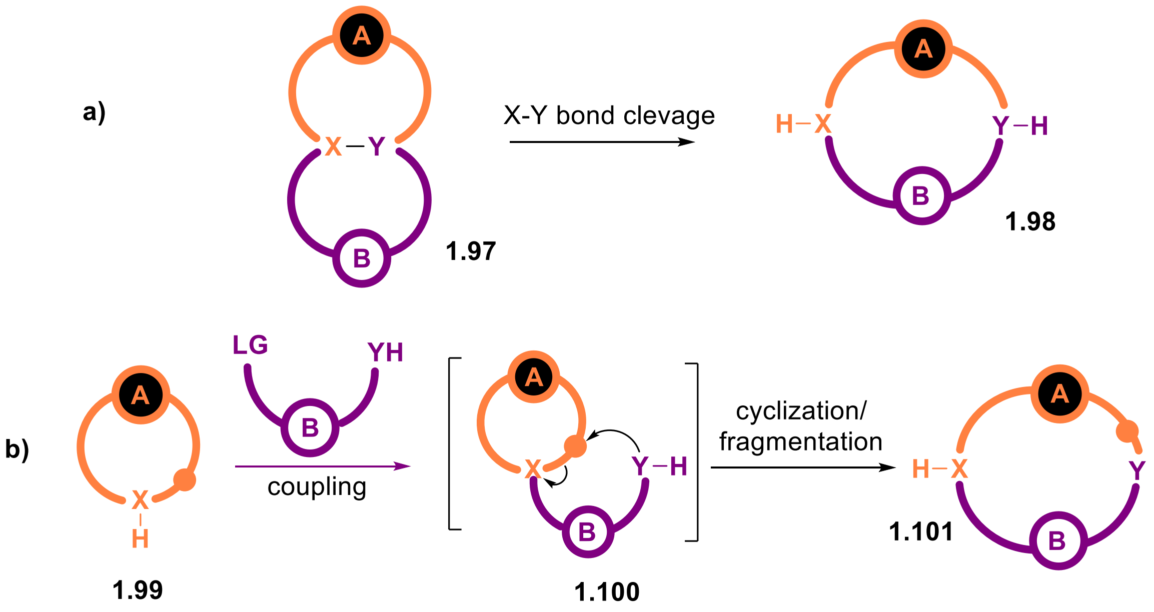
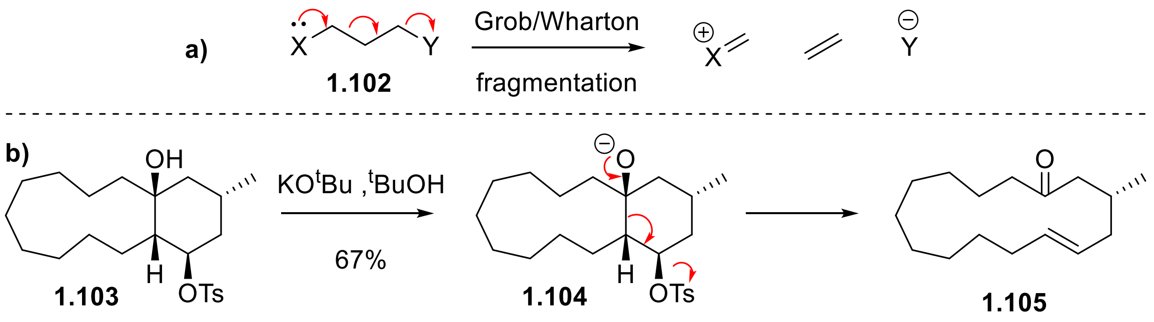


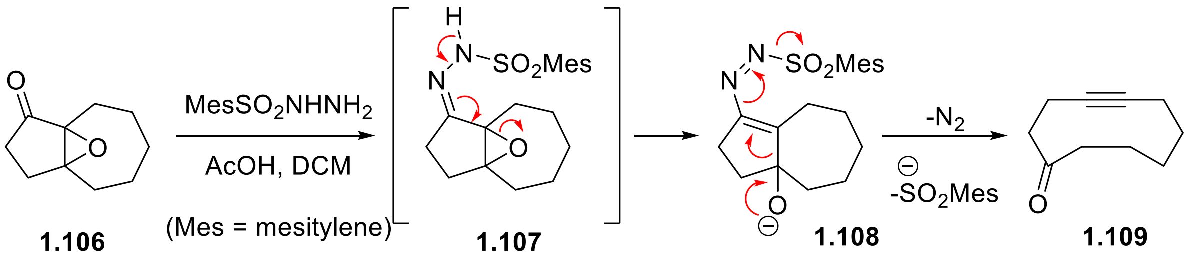
Figure 1.3: Types of fragmentation ring expansion. a) Fragmentation of a bicyclic molecule. b) Side chain insertion followed by fragmentation.

Grob type-eliminations are an attractive way to fragment bicycles due to their irreversible nature. In a typical Grob fragmentation, an electron-donating group "X" pushes electrons towards a leaving group "Y" situated 4 atoms away, and a C–C bond cleavage occurs, as shown in Scheme 1.17a. An example of ring-expansion that employs this methodology is shown in Scheme 1.17b, which is a base–mediated Grob fragmentation whereby the electron donating group is an alcohol (or alkoxide **1.104**) and the leaving group a tosylate yielding 5-muscenone (**1.105**).[41]



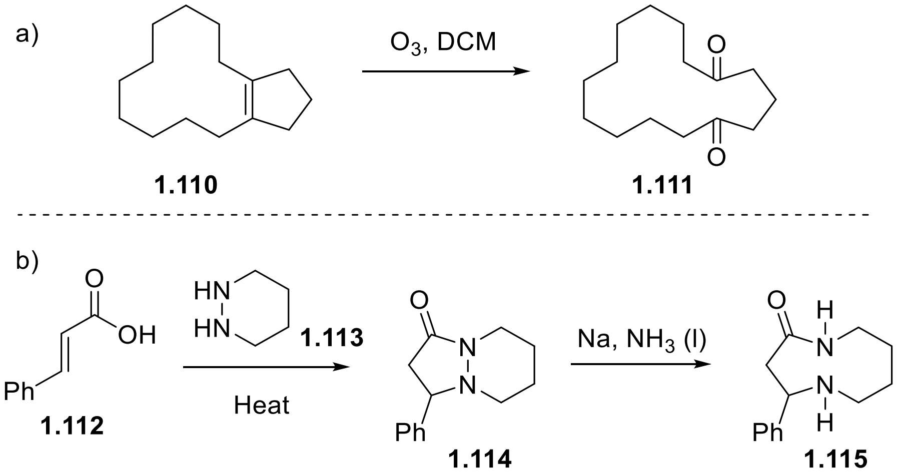
Scheme 1.17: Grob/Wharton fragmentation.

A similar elimination-type reaction is the Eschenmoser fragmentation (Scheme 7) in which α,β-epoxy ketones (**1.106**) react with aryl sulfonyl hydrazines to yield alkynes (**1.109**).[9] In the field of ring expansion it has been used to access highly strained alkyne containing rings aided by the release of nitrogen gas, which acts as a strong thermodynamic driving force (scheme 1.18).



Scheme 1.18: Eschenmoser fragmentation.

Oxidation and reduction have also been used as means to access ring expanded products, in redox driven fragmentation reactions.[6,9] An oxidative approach using ozonolysis is shown in scheme 1.19a,[42] and an example featuring a reductive fragmentation using sodium in liquid ammonia is presented in scheme 1.19b.[43]

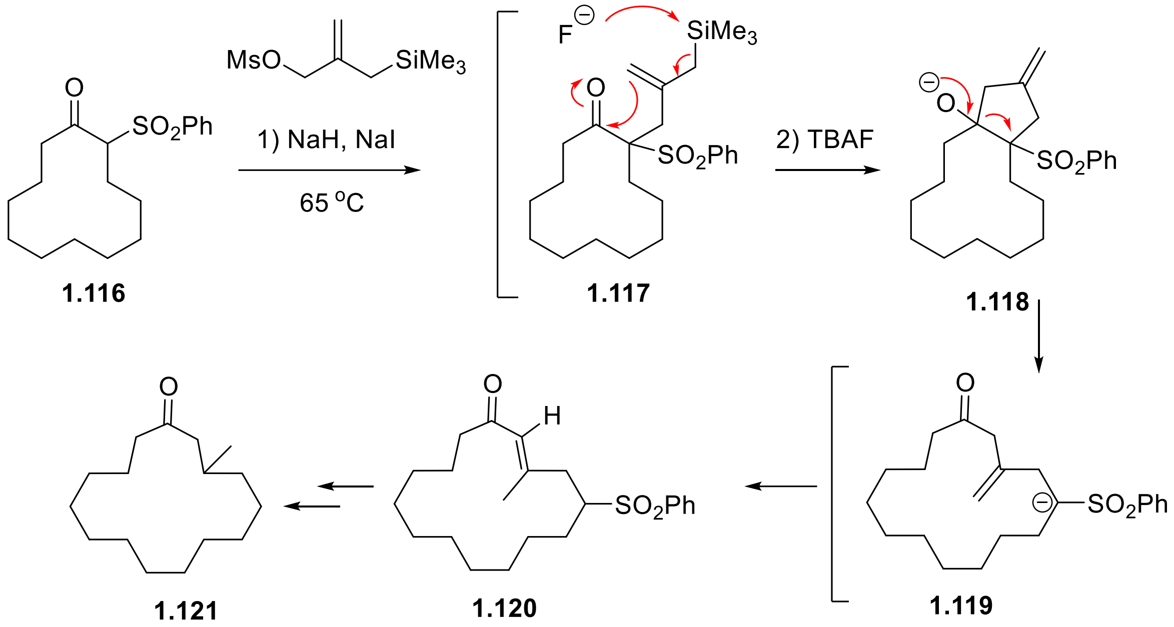


Scheme 1.19: a) Oxidative fragmentation reaction. b) Reductive fragmentation reaction.

1.2.4 Side Chain Insertion

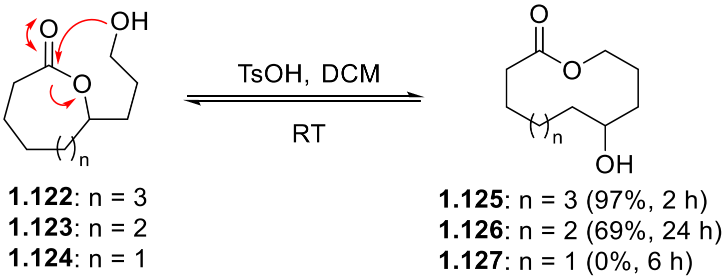
Another type of fragmentation is achieved *via* the insertion of a side chain into the cyclic system, forming a transient bicycle which then undergoes ring expansion (Figure 1.3b). These types of reactions facilitate the formation of a new C–O, C–N or C–C bond, depending on the nature of the pendant nucleophile or pro-nucleophile. Often, ring expansions involving side chain insertion followed by fragmentation are reversible processes and hence are under thermodynamic control. In Scheme

1.20, **1.118** fragments to form **1.119** because electron density is donated towards the electron withdrawing sulfone, driving the equilibrium to favour the expanded product.[9,44]



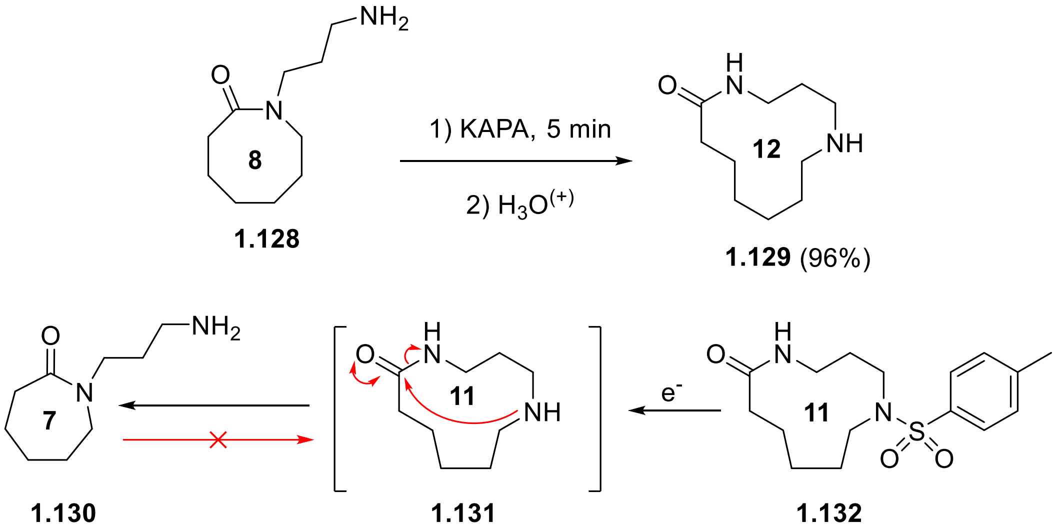
Scheme 1.20: Side chain insertion type fragmentation forming a new C-C bond.

When there is no overall change in the functional group composition from starting material to product, reversible ring expansions are driven largely by the relative stabilities of the ring sizes. An illustrative example of this is shown in Scheme 1.21. Corey *et al.* have demonstrated the stability of different ring sizes in a study looking at reversible transesterification reactions.[9,45] There is a strong thermodynamic driving force associated with the expansion of a 9-membered ring (**1.122**) to a 12-membered one, as illustrated by the near quantitative yield obtained within 2 hours of reaction time (Scheme 1.21, **1.125**). This is due to the release of transannular ring strain associated with medium-sized rings. Conversely, a 7-membered ring (**1.124**) does not expand to a 10-membered ring at all (**1.127**), which can also be rationalized by the higher stability of the normal-sized 7-membered ring isomer, compared to 10-membered **1.127**. The reaction forming **1.126** lies between the two thermodynamic extremes, and proceeds in modest yield.



Scheme 1.21: An acid catalysed intramolecular transesterification demonstrates the relative stability of different ring sizes.

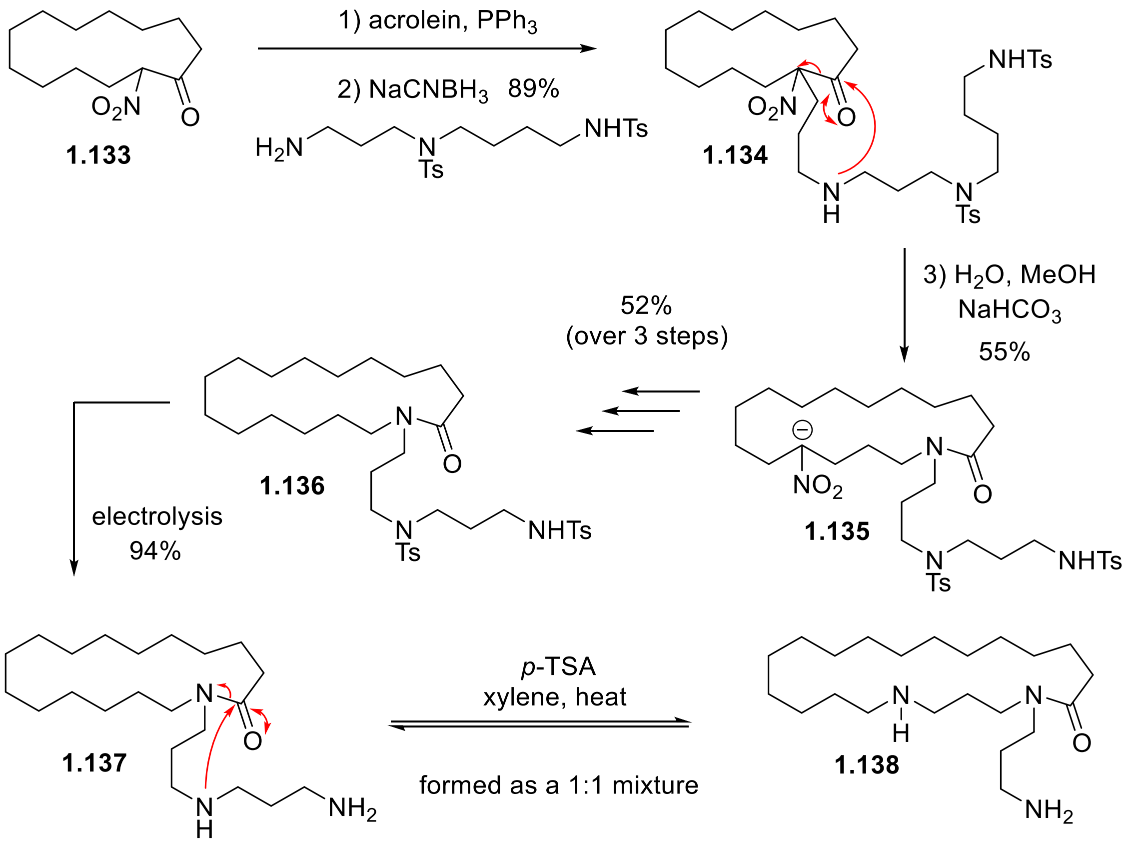
The importance of the relative energy of isomers with respect to ring size is vital to consider in all ring expansion chemistry, and is also demonstrated in transamidation reactions reported by Hesse *et al.* (Scheme 1.22).[46] An expansion from a medium sized 8-membered lactam (**1.128**) to a 12-membered one (**1.129**) is favourable, and proceeds spontaneously under basic conditions, whereas a normal sized 7-membered ring (**1.130**) does not expand to medium sized 11-membered ring (**1.131**) under the same conditions; indeed, when the 11-membered **1.131** was formed *via* an alternative route (electrolysis of **1.132**), a ring contraction reaction occurred to yield the 7-membered lactam (**1.130**), highlighting the greater stability of the smaller ring system in this instance.[46,47]



Scheme 1.22: Transamidation reactions under thermodynamic control. KAPA = potassium 3-aminopropylamide in 1,3-diamino propane.

Pioneering work in the field of ring expansion has been conducted by Prof Manfred Hesse and his research group, who has laid the foundations of much of the work conducted in the Unsworth group.[9,48] Some notable work includes successive transamidation reactions to expand macrocycles, such as the one shown in Scheme 1.23.[49] Sequential transamidation ring expansions have been termed 'aza-zip' reactions.

The reaction begins with a side chain insertion. A pendant amine in **1.134** acts as a nucleophile, adding into the cyclic ketone, which is followed by a fragmentation to yield a ring expanded product, **1.135**. Stabilization of the negative charge adjacent to an electron withdrawing nitro group is key to the formation of **1.135**. Removal of the nitro group and deprotection of the remaining amines resulted in a second, reversible ring expansion reaction under acidic conditions. Once more, without a change of functional group, the ring expansion reaction is driven by the relative stability of the different ring sizes; In this case, a 1:1 mixture of **1.137** and **1.138** was formed, as there is no clear thermodynamic driving force for the expansion of **1.137** into **1.138**, presumably because both are macrocyclic rings.

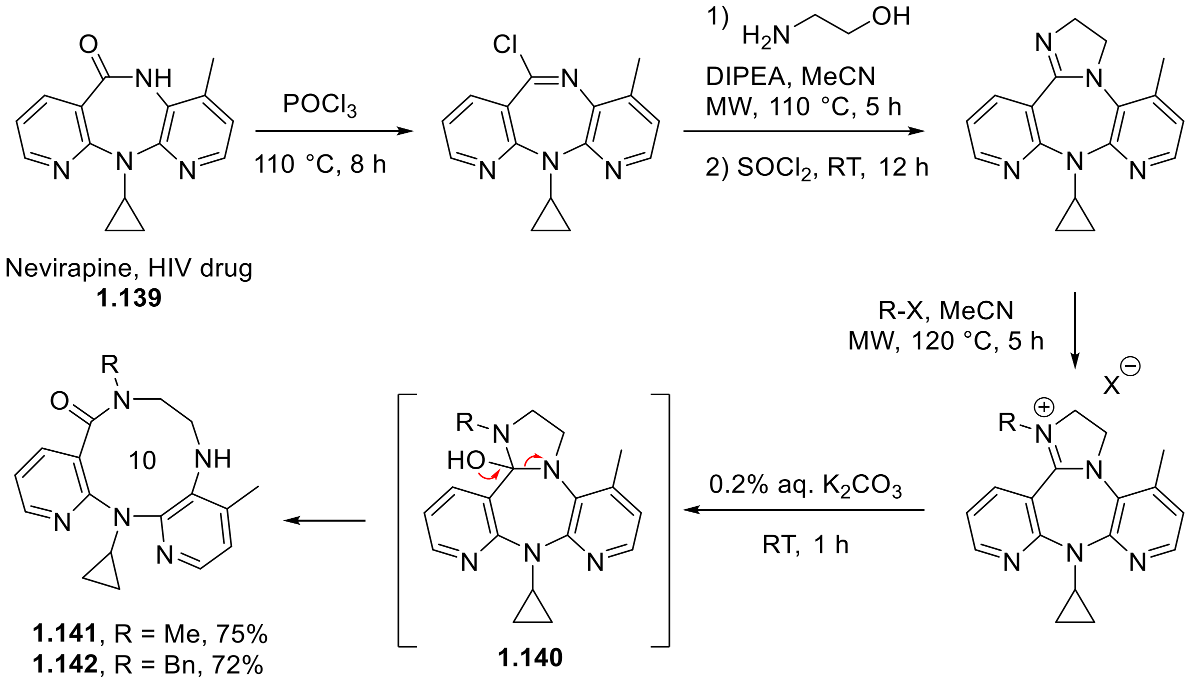


Scheme 1.23: Successive transamidation of a pendent amine chain by Hesse et al.

1.2.5 Recent examples of fragmentation ring expansion

1.2.5.1 Hydrolytic imidazoline ring expansion

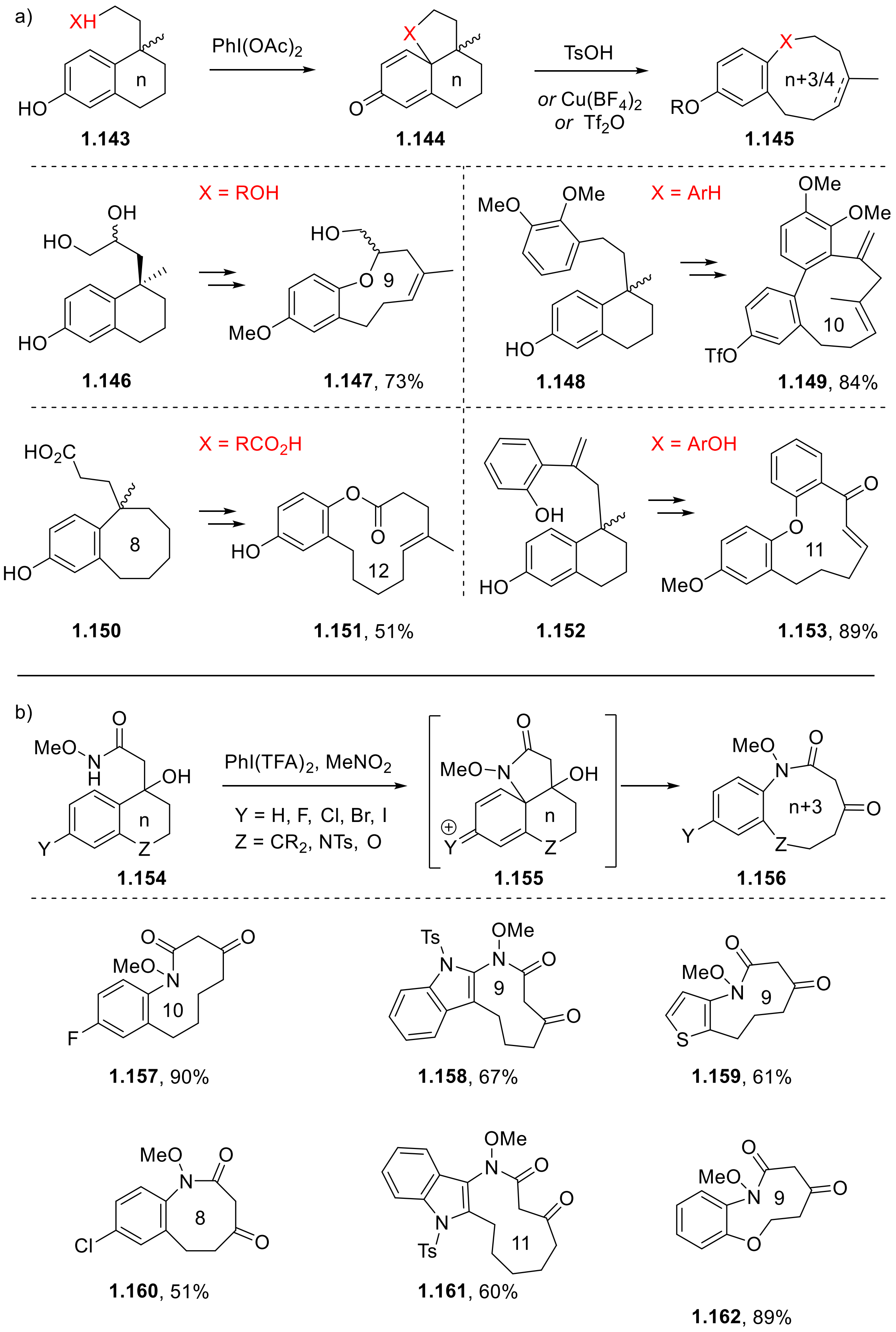
Krasavin *et al.* developed a method to ring expand imidazoline fused rings. Hydrolytic imidazoline ring expansion (HIRE) is a two-step process involving *N*-alkylation of an imidazoline to form a quaternary nitrogen, followed by hydrolysis to form a cyclol intermediate, and finally fragmentation, resulting in a 3-atom ring expansion. Scheme 1.24 shows how this method was used ring expand nevirapine **1.139**, a non-nucleoside reverse transcriptase inhibitor used to treat HIV.[50]



Scheme 1.24: Hydrolytic imidazoline ring expansion (HIRE).

1.2.5.2 Oxidative dearomatization/ring expansion

Tan *et al.* developed two complementary ring expansion approaches driven by the rearomatization of phenols and other aromatic substrates. Oxidative dearomatization/ring expansion (ODRE) has been used to generate medium sized rings of all sizes. In the stepwise ODRE approach (scheme 1.25a), dearomatized intermediates **1.144** are isolated and can be can be further reacted with one of three reagents (TsOH, Tf_2O and $Cu(BF_4)_2$), often resulting in varying mixtures of alkene isomers (varying ratios of endocyclic and exocyclic olefins for instance) and solvent adducts (such as the methoxy adducts formed in **1.147** and **1.153**). In each case, a nucleophile adds in *para* to the phenol during the oxidation reaction to form the cyclohexadienone intermediate **1.144**. This nucleophile can be an alcohol (**1.146**), a phenol (**1.152**), an electron rich aromatic ring (**1.148**), or a carboxylic acid (**1.150**). The second strategy (presented in scheme 1.25b) uses a tandem ODRE reaction where the dearomatized intermediate (**1.155**) is not isolated. The authors describe this as an example of Umpolung reactivity, as the oxidative dearomatization step now leads to attack of an electrophilic *N*-methoxy amide side chain. The advantage of this approach is that the aromatic ring is no longer restricted to phenols, and heteroaromatics can also be used in this approach (*e.g.* **1.158** and **1.159**). Once again, medium sized rings from 8- to 11-membered in size are accessible using this chemistry.

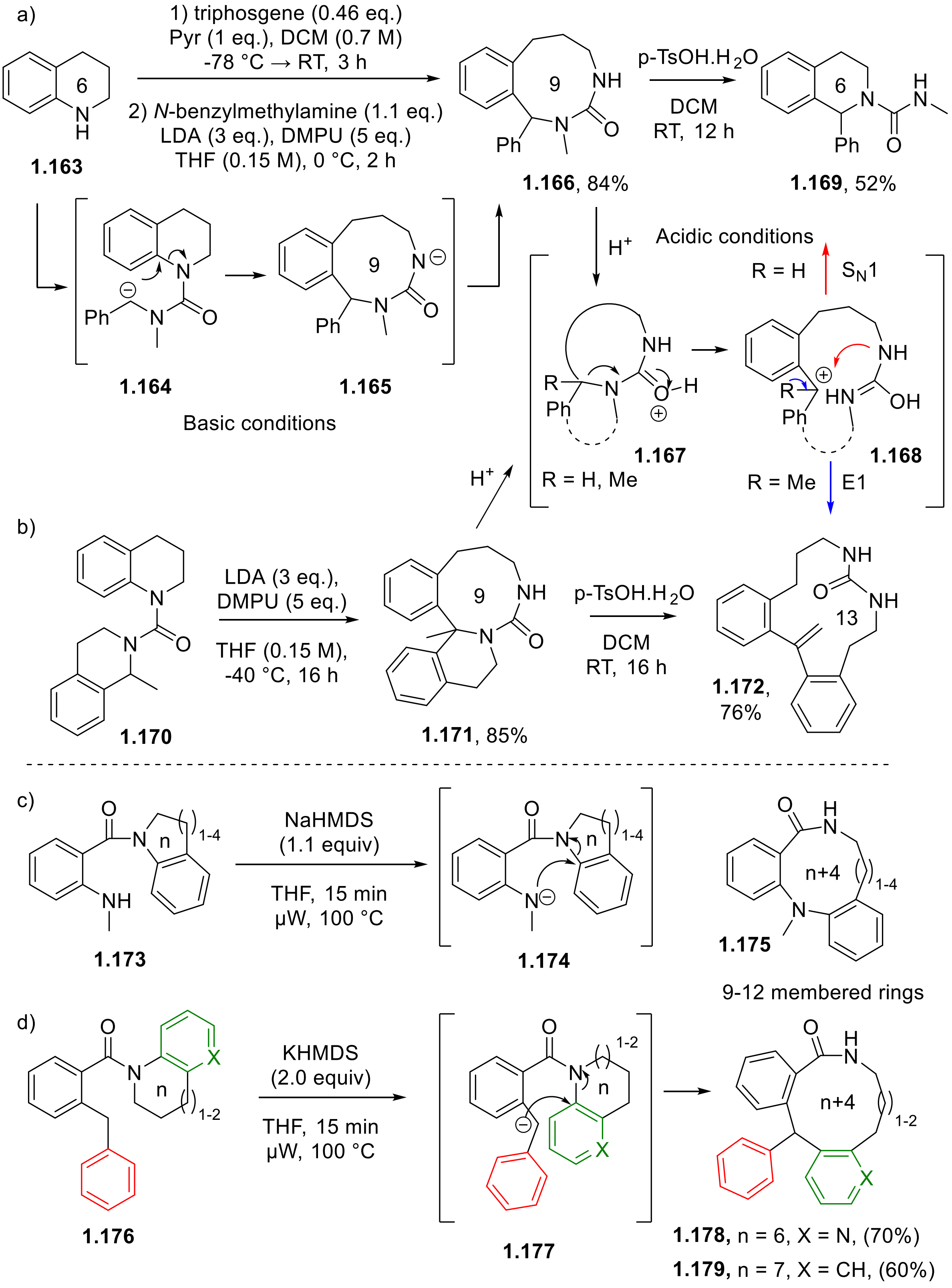


Scheme 1.25: Oxidative dearomatization/ring expansion (ODRE).

1.2.5.3 Metalated ureas and Smiles rearrangements in ring expansions

Clayden *et al.* have developed two conceptually similar migratory ring expansion reactions. The first approach is a 3-atom ring expansion where benzo-fused nitrogen containing heterocycles featuring a tethered aryl substituted urea are reacted under strongly basic conditions to form intermediates of the form **1.164** (scheme 1.26a). The metalated urea can then carry out nucleophilic attack at the aromatic ring to promote ring expansion to form **1.165**; formation of a charged urea group in which the carbanion is significant more stabilized than in the precursor **1.164** is presumably a major driving force for this ring expansion.[51,52] A streamlined procedure used the tetrahydroquinoline **1.163** to form 9-membered **1.166** in 2 steps. Subjecting **1.166** to mildly acidic conditions can also lead to a ring contraction, *via* an S_N1 reaction, from the unsubstituted urea nitrogen to give **1.169** (52%), a precursor to the drug solifenacin.[53] In Scheme 1.26b, two 6-membered nitrogen fused heterocycles (**1.170**) undergo the migratory ring expansion to form a fused bicyclic structure featuring a quaternary center, **1.171**. Exposure of **1.171** to acidic conditions instead proceeds *via* an E1 mechanism to lead to a second ring expansion and formation of a terminal alkene (**1.172**).[53]

A separate study by Clayden *et al*. investigated Smiles-type rearrangements to perform 4-atom ring expansions to form medium sized ring analogues of dibenzodiazepines **1.175** (Scheme 1.26c).[54] Finally, the group also developed an intramolecular nucleophilic aromatic substitution (Truce-Smiles rearrangement) which is able to perform a 4-atom ring expansion and generate medium sized ring lactams such as **1.178** (scheme 1.26d).[55]

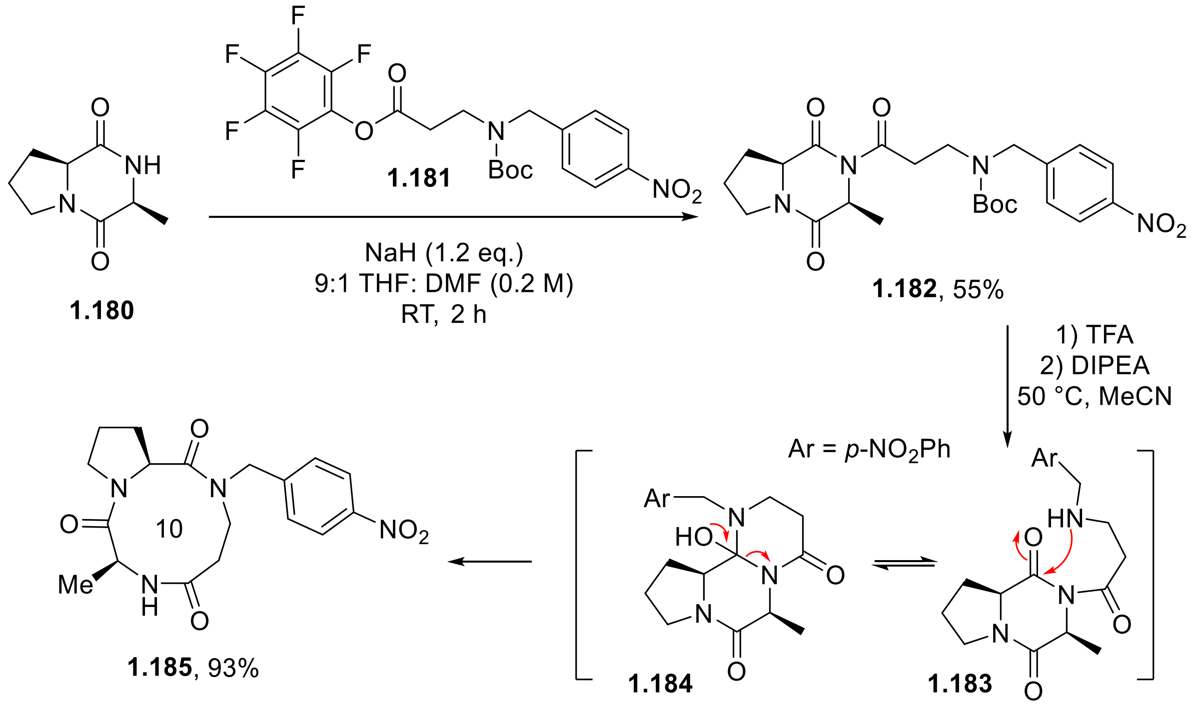


Scheme 1.26: 3-atom and 4-atom ring expansion reactions developed by Clayden et al.

1.2.5.4 Ring expansion of diketopiperazines

Yudin *et al.* developed a ring expansion method that also proceeds via a cyclol intermediate. Using an *N*-Boc protected pentafluorophenol activated amino acid (**1.181**), 6-membered diketopiperazines (*e.g.* **1.180**) were acylated to form imides such as **1.182**. Next, the Boc protecting group was removed under acidic conditions, before returning to basic conditions to promote ring expansion (scheme 1.27).[56]

Yudin also reported a computational chemistry study which supports the experimental evidence that 4-atom ring expansions using imine intermediates are thermodynamically viable, but 3-atom ring expansions are not. The energetic minimum for the latter 3-atom expansion was calculated to be the ring-closed isomer, not the 9 membered ring expanded product. Notably, the methods developed by Krasavin, Yudin, and Unsworth all require basic conditions to promote the promote ring expansion in the final step.

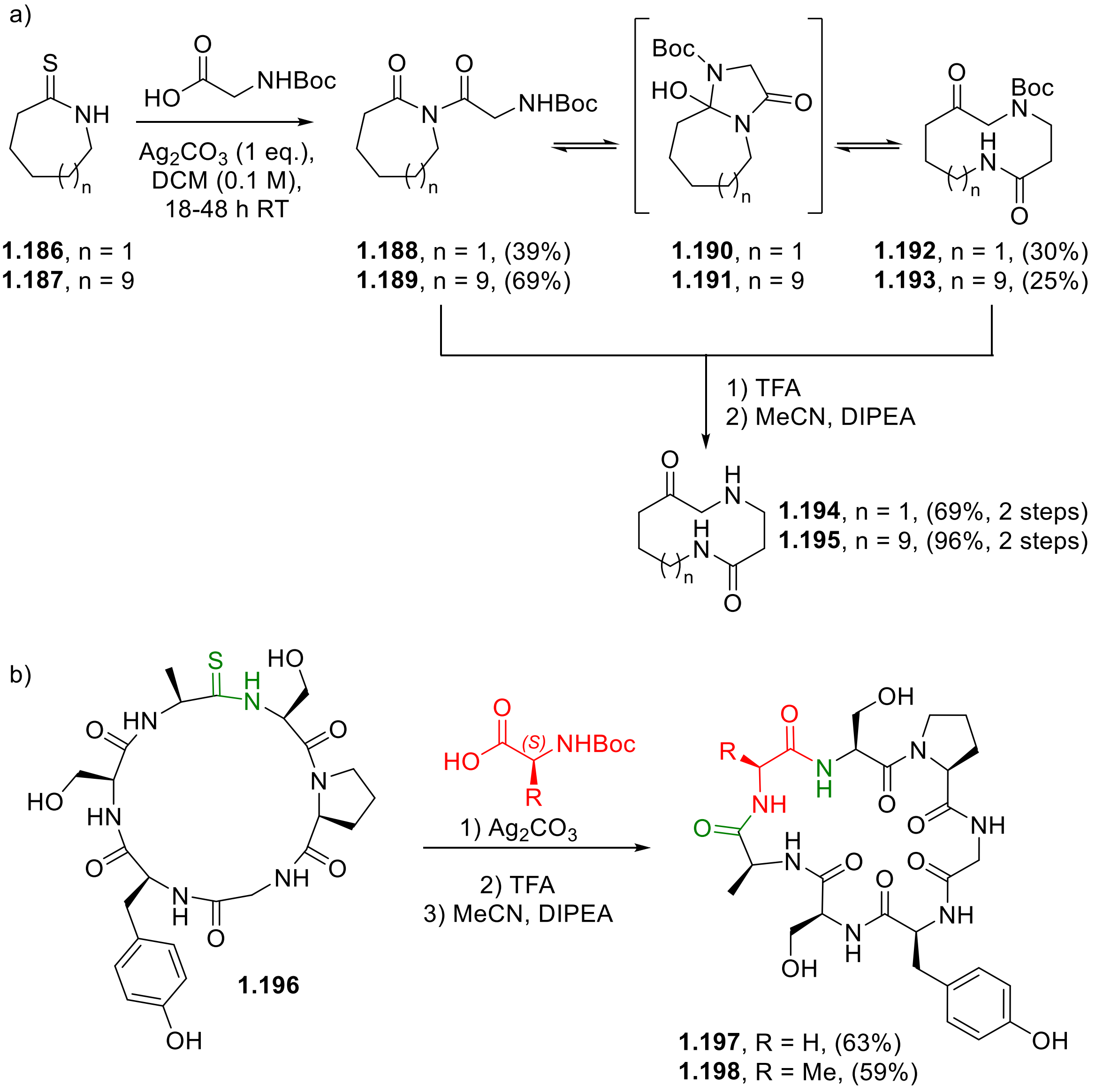


Scheme 1.27: Acylation/Deprotection/Ring expansion methodology developed by Yudin et al.

1.2.5.5 Ring expansion using thiolactams

Another recent publication from the Hutton group is related to the use of thioamides in an acylation/ring expansion cascade.[57] Lactams from 5- to 13-membered in size were first converted into thiolactams using Lawesson's reagent. Treating thiolactams **1.186** and **1.187** with a Boc protected amino acid and Ag_2CO_3 then served to both acylate (to form **1.188** and **1.189**) and partially ring expand the lactam (to form **1.192** and **1.193**), with the Boc protecting group remaining intact. This is noteworthy, as analogous reactions developed in the Unsworth and Yudin groups generally only ring expand upon removal of the protecting group on the amine. When mixtures of ring-opened (**1.188** or **1.189**) and ring expanded isomers (**1.192** or **1.193**) are combined and their protecting groups cleaved, followed by basic conditions, the ring expanded Boc-deprotected bislactams, **1.194** and **1.195**, were isolated in good to excellent yields (scheme 1.28a).

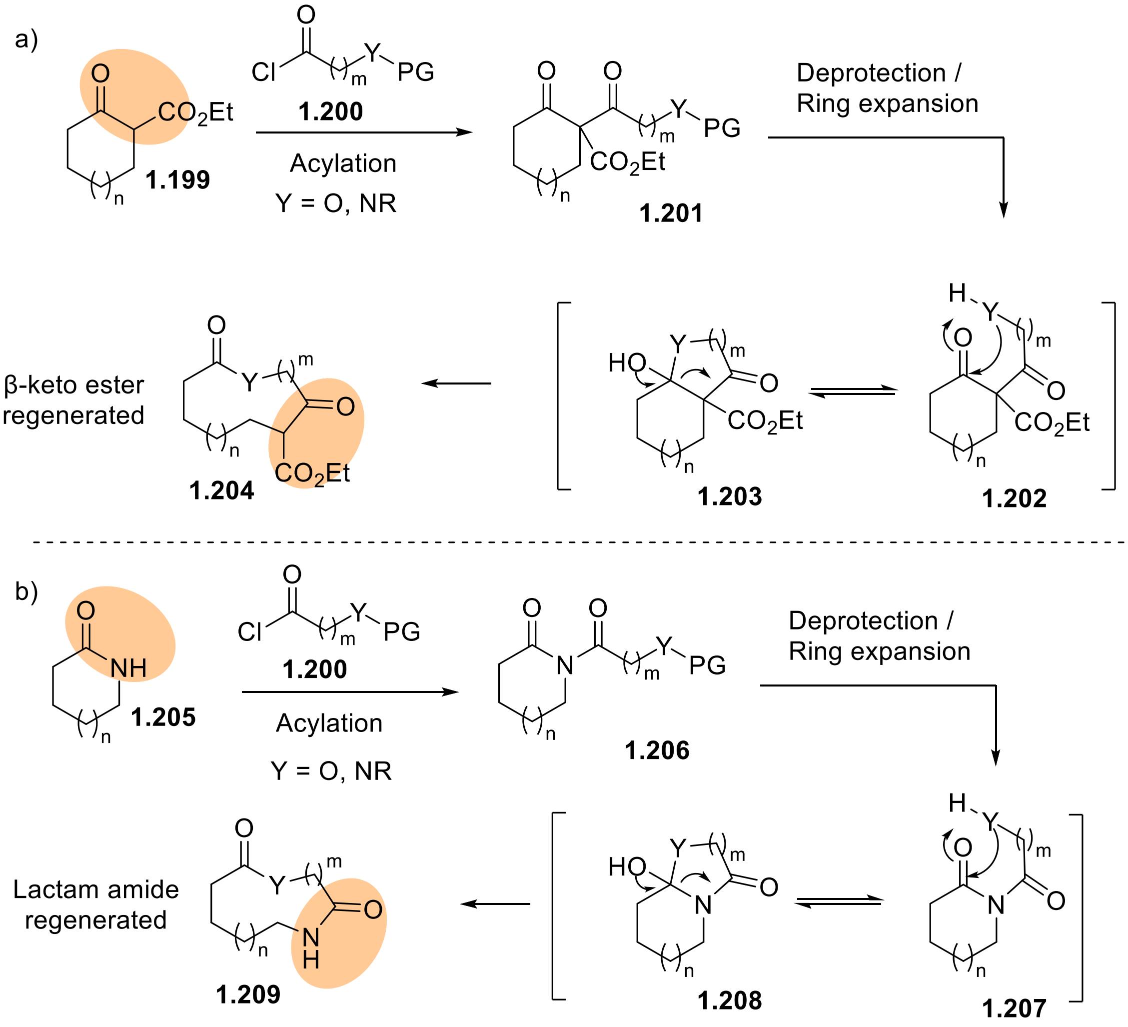
This methodology was applied to the ring expansion of cyclic peptides as well (Scheme 1.28b). By installing a thioamide group in an otherwise unprotected cyclic peptide (**1.196**), this allows late stage incorporation of individual amino acids (to form **1.197** and **1.198**) in a site selective manor via the same acylation/deprotection/ring expansion sequence applied to simple lactams in scheme 1.28a.



Scheme 1.28: Ring expansion using thiolactams.

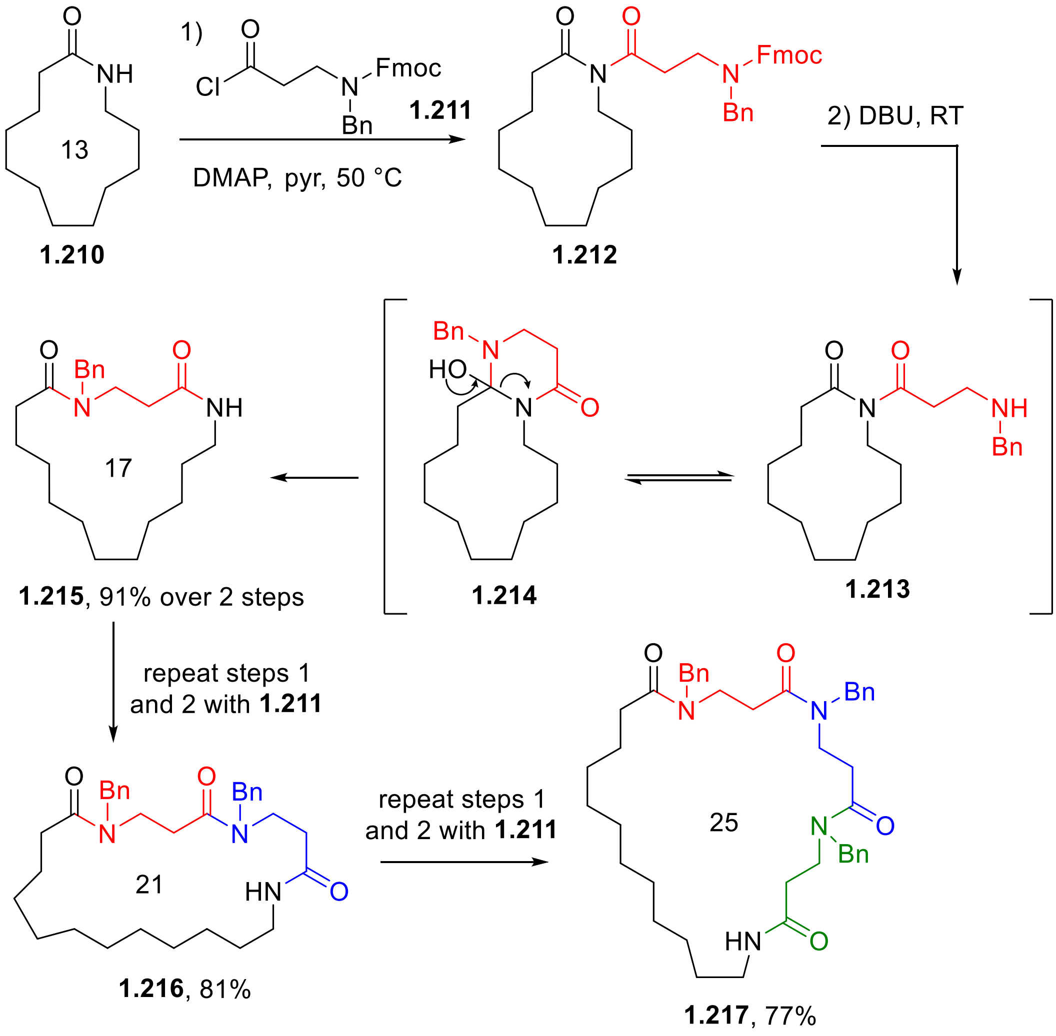
1.2.5.6 Unsworth Group Methodology

Successive Ring Expansion (SuRE) is a term coined in the Unsworth group to refer to a protocol utilized to 'grow' macrocyclic lactams or β-keto esters *via* sequential ring enlargement reactions.[48,58] There are two variations of SuRE, depending on whether a β-keto ester or a lactam is used as a starting material (generation 1 and 2 of SuRE, Scheme , Scheme 1.29a and 1.29b respectively). SuRE reactions occur over two sequential steps. In the first step, the amide nitrogen of the lactam (**1.205**), or α carbon of the beta keto ester (**1.199**), is acylated using a freshly prepared acid chloride of the corresponding amino or hydroxy acid derivative (**1.200**). Following acylation, the protecting group of an internal nucleophile on the pendant unit is cleaved (Fmoc is cleaved using DBU, for example). What ensues is a spontaneous ring expansion which proceeds *via* a bicyclic intermediate (**1.208** and **1.203**). In general, the cyclic molecule can be expanded by 3 or 4 units according to the choice of amino acid derivative or hydroxy-acid. Crucially, this process yields a product with the same functionality as the starting material (highlighted groups in Scheme 1.29), so the product can undergo iterative ring expansions.



Scheme 1.29 : SuRE methodology: a) Generation 1 using β-keto esters, b) Generation 2 using lactams.

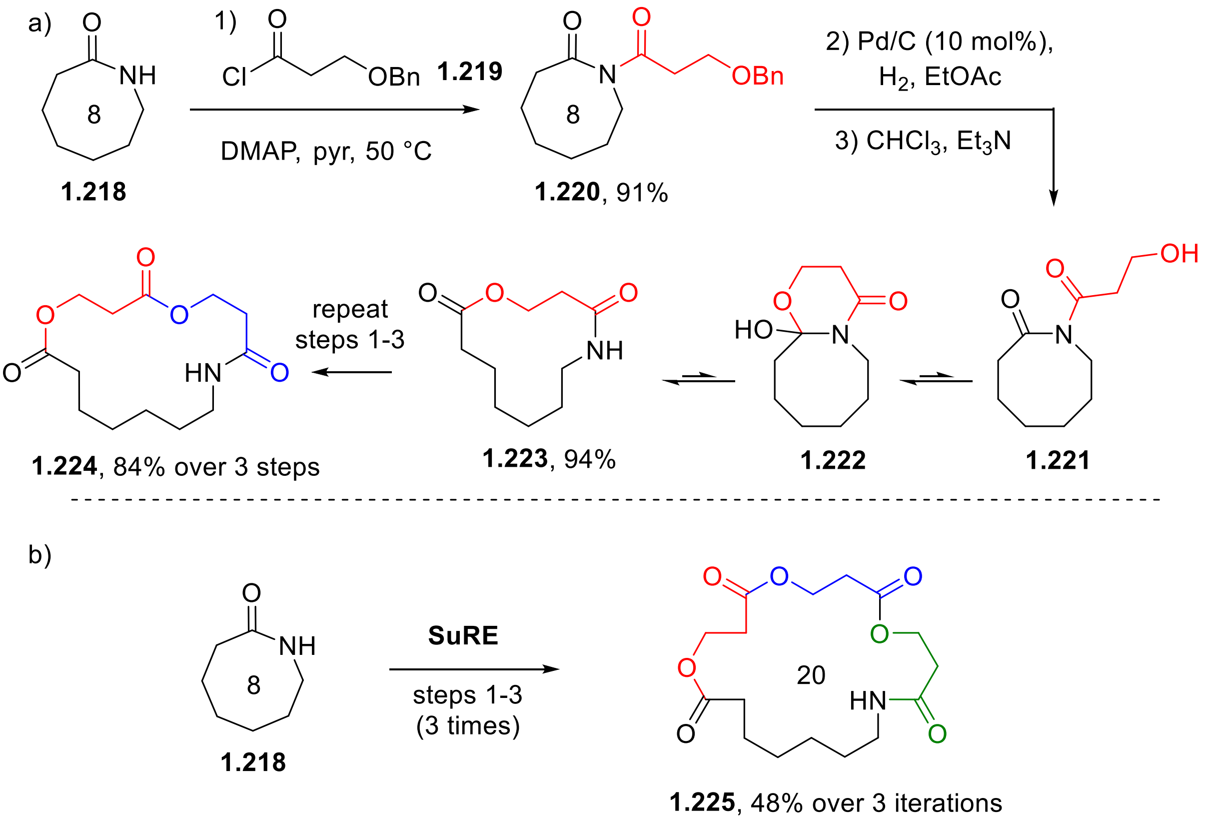
This idea of iterative ring expansion is showcased in Scheme 1.30, *via* the ring expansion of 13-membered **1.210** into 17-membered **1.215**, its subsequent expansion to 21-membered **1.216**, and finally a third ring expansion to form 25-membered ring tetralactam **1.217**.



Scheme 1.30: Iterative ring expansion using SuRE chemistry and beta amino acids.

This methodology has also been expanded for use with α- and β-hydroxy acids, with SuRE reactions developed to form lactones. Benzyl protected hydroxy acids, such as 3-(benzyloxy)propanoic acid, are converted into the corresponding acid chloride (**1.219**) and used in acylation reactions of lactams to form imides (such as **1.220**). The benzyl protecting group is removed under hydrogenation conditions to give an alcohol (**1.221**), which can rearrange under basic conditions to form a form a lactone containing ring expanded product **1.223** (Scheme 1.31a).

These reactions are also repeatable for iterative ring expansion, the utility of which was demonstrated when 8-membered lactam **1.218** was ring expanded over 3 SuRE cycles, forming the 20 membered cyclic depsipeptide **1.225** in 48% yield overall with just one chromatographic purification used at the end of the synthesis (Scheme 1.31b).



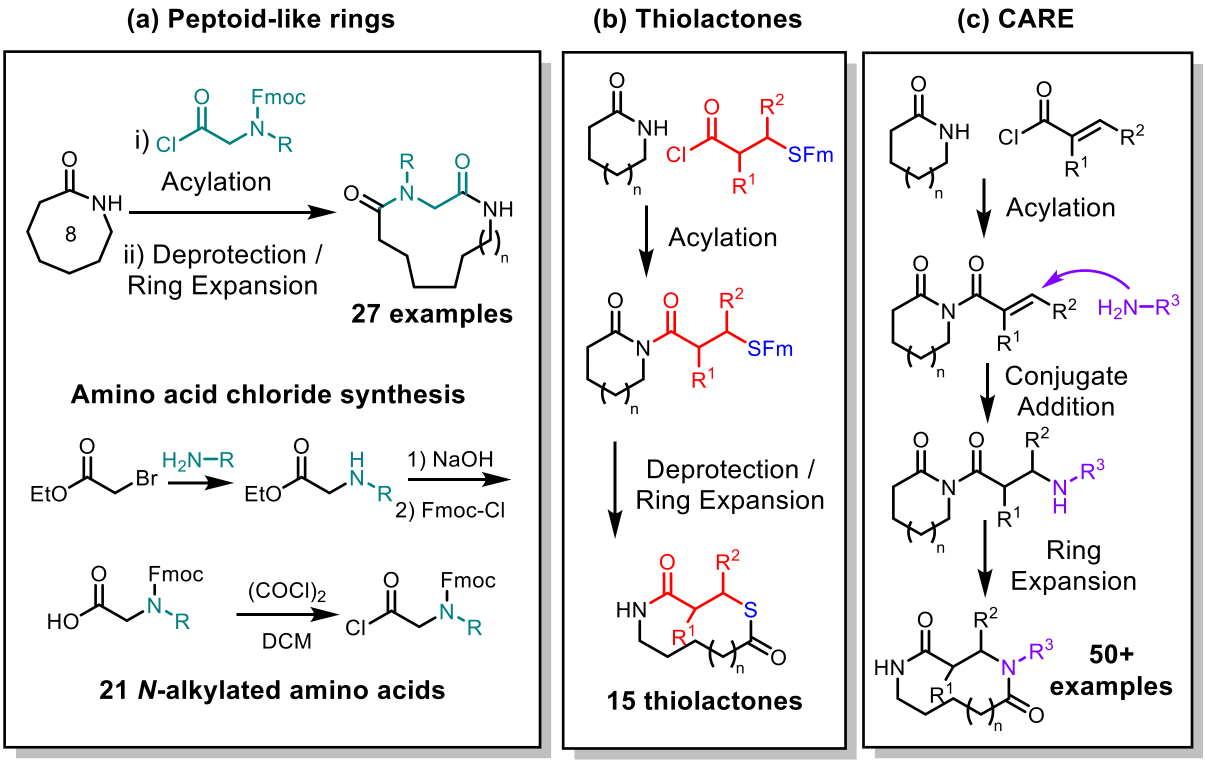
Scheme 1.31: Iterative ring expansion using SuRE chemistry and beta hydroxy acids.

1.3 Project Aims

The overall project aim was to expand the scope of the SuRE approach and to develop new and improved SuRE reactions. This was achieved using three different strategies (Scheme 1.32). The first approach was to expand the range of linear building blocks and lactams that can be used in SuRE reactions. In particular, the key aim was to expand the scope of amino acids that can be used in SuRE reactions. Thus, a variety of *N*-Fmoc *N*-alkylated amino acids were synthesized and implemented in ring expansions to access functionalized medium sized rings and macrocycles with a peptoid-like structure. Chemically and pharmacologically interesting moieties were incorporated into peptoid-like ring expanded products. Benzannulated lactams were also briefly explored as SuRE substrates. This work is described in Chapter 2.

The second project aim was to develop a completely new SuRE variant that is compatible with thiol-tethered carboxylic acids, to synthesize ring enlarged thiolactones using SuRE for the first time. Three complementary protecting group strategies were explored to optimize these often-challenging reactions. The viability of these ring expansions was studied using computational tools (DFT performed by Ryan Epton), which can be used predictively to assess the viability of the reactions before attempting them synthetically. This work is described in Chapter 3.

Finally, we aimed to develop a strategy whereby a common acylating agent could be used to functionalize a lactam that could go on to react with a range of nucleophilic reagents, to allow a variety of different ring expanded products to be formed from a common imide substrate *via* a divergent synthesis strategy. Several systems were considered and investigated, and this approach was ultimately realized with the development of a novel conjugate addition – ring expansion (CARE) cascade reaction. The CARE method allows the synthesis of functionalized medium sized rings from primary amines in just two steps. This methodology can also be applied to carbon nucleophiles, representing a first for SuRE-style reactions, with ring expansion *via* C–C bond formation at the carbonyl now possible. Finally, acryloyl imides were also demonstrated to undergo a one-pot dihydroxylation-ring expansion reaction. This work is described in Chapter 4.



Scheme 1.32: Summary of key project aims realized

2 Expanding the scope of amino acids and lactams used in SuRE

2.1 Types of amino acids

Using the SuRE methodology introduced in Chapter 1, amino acid derivatives can be used as starting materials for side chain insertion/ring expansion cascade reactions. The term amino acid is a broad description of compounds encompassing several classes of molecules as shown in Figure 2.1. Most commonly, amino acid refers to the 21 naturally occurring proteinogenic L-stereoisomer α-amino acids (*e.g.* alanine **2.1** and phenylalanine **2.2**). Other classes of amino acids include β-amino acids (*e.g.* **2.3** and **2.4**) and *N*-alkylated amino acids (*e.g.* **2.5** and **2.6**). β-Alanine (**2.3**) and other β-amino acids can be used in SuRE to perform 4-atom ring expansions, whilst α-amino acid derivatives are used to carry out 3-atom ring expansions.

N-alkylated amino acids are α-amino acids featuring a secondary amine. In the context of SuRE, sarcosine (**2.5**) and *N*-benzyl glycine (**2.6**) have successfully been used in ring expansions. When *N*-alkylated glycines are linked *via* amide bonds, they resemble a peptide secondary structure (**2.7**) and are commonly referred to as peptoids. These can be thought of as peptide mimetics where the functionality is located on the amide nitrogen instead of the α-carbon (**2.8**).

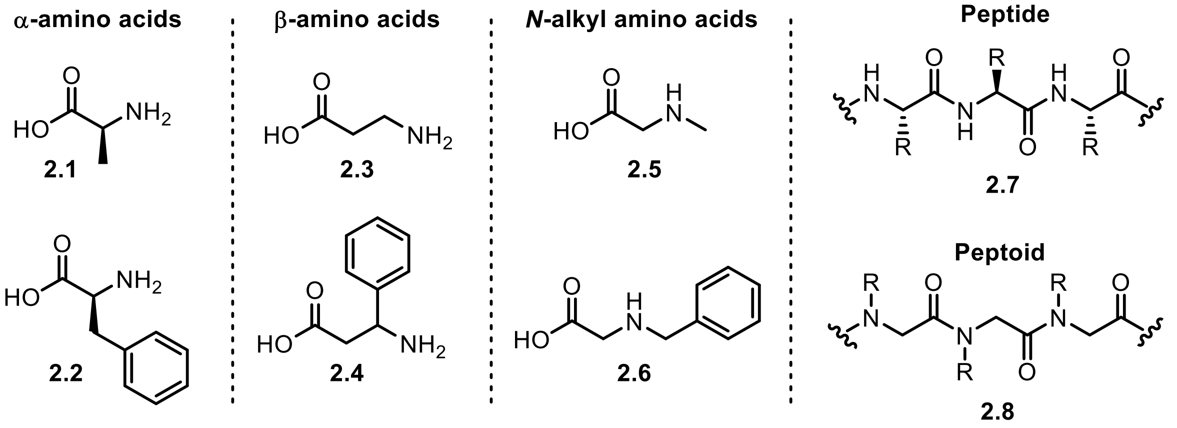
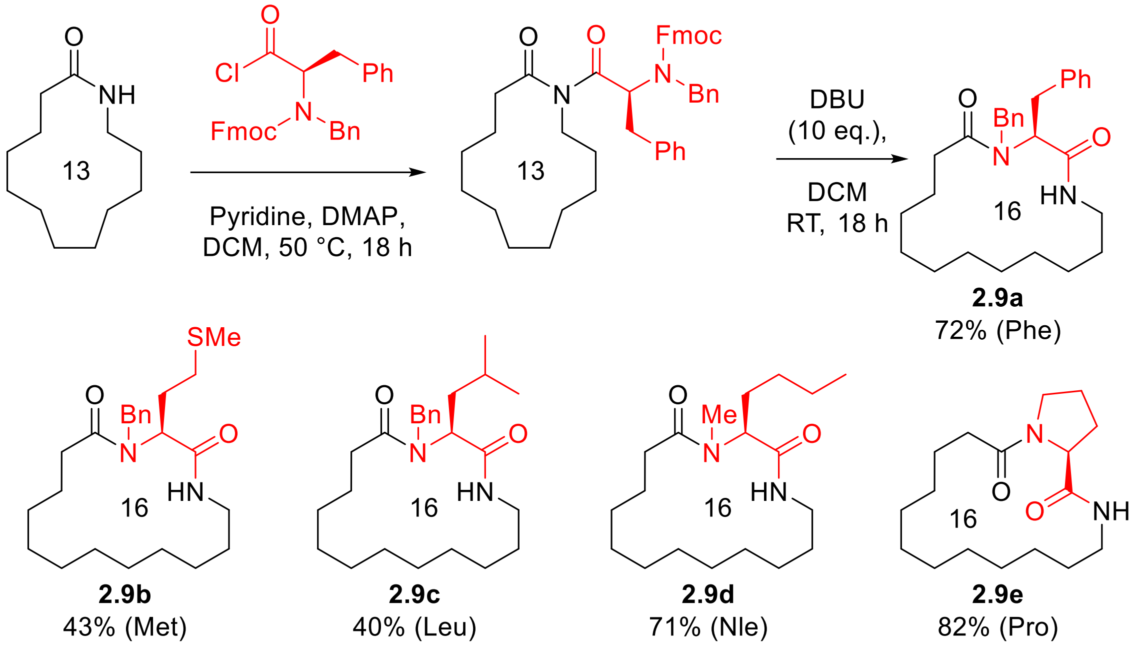


Figure 2.1: Structures depicting various amino acid derivatives.

SuRE has been used to synthesize macrocyclic lactones and lactams with both α- and β- hydroxy and amino-acids. For example, in previous work in the Unsworth group, *N*-benzyl α-amino acids derived from phenylalanine (**2.9a**), methionine (**2.9b**), leucine (**2.9c**) and others have been synthesized and used in SuRE reactions.[48] The macrocyclic products shown in Scheme 2.1 all incorporate peptide functionality (*i.e.* they have a substituent on the α-carbon of the amino acid) while also having an *N*-alkylated moiety.



Scheme 2.1: SuRE reactions with N-alkylated proteinogenic alpha amino acids.[48]

Thus, in the previous work, it had been shown that variation of the amino acid α-position is possible. However, prior to this study, little had been done to explore the scope of SuRE with respect to substitution of the *N*-substituent beyond simple benzyl and methyl groups. This chapter describes efforts to remedy this. Thus, the synthesis of a series of diversely functionalized *N*-alkylated-*N*-Fmoc amino acids is described, starting from ethyl bromoacetate, and their use in ring expansion reactions has been explored. This has enabled the generation of a range of novel 11-membered medium-sized rings containing peptoid-like groups, thus expanding the functionality that has been represented to date in SuRE methodology.

2.2 Synthesis of *N*-alkylated amino acids for use in ring expansion reactions

Before starting the discussion on the new SuRE methodology, a brief background on the importance of *N*-alkylation in peptides is provided below. Peptide therapeutics such as insulin have been in clinical use for over a century.[59] Advances in medical research have taken us from the extraction of peptide hormones from animals in the early 20th century to the current day where over 60 peptide drugs are approved for clinical use in the US, Europe and Japan.[59] More recently, interest has turned to modifying peptides to enhance properties such as their biological half-life or specificity towards a target. Demand in this field has driven research into peptidomimetics, which aim to retain core pharmacological properties of bioactive peptides while improving the bioavailability and selectivity of drug candidates. Covalent modification of bioactive peptides such as the ‘stapling’ of peptides,[26] and incorporation of unnatural amino acids are two such approaches.[60]

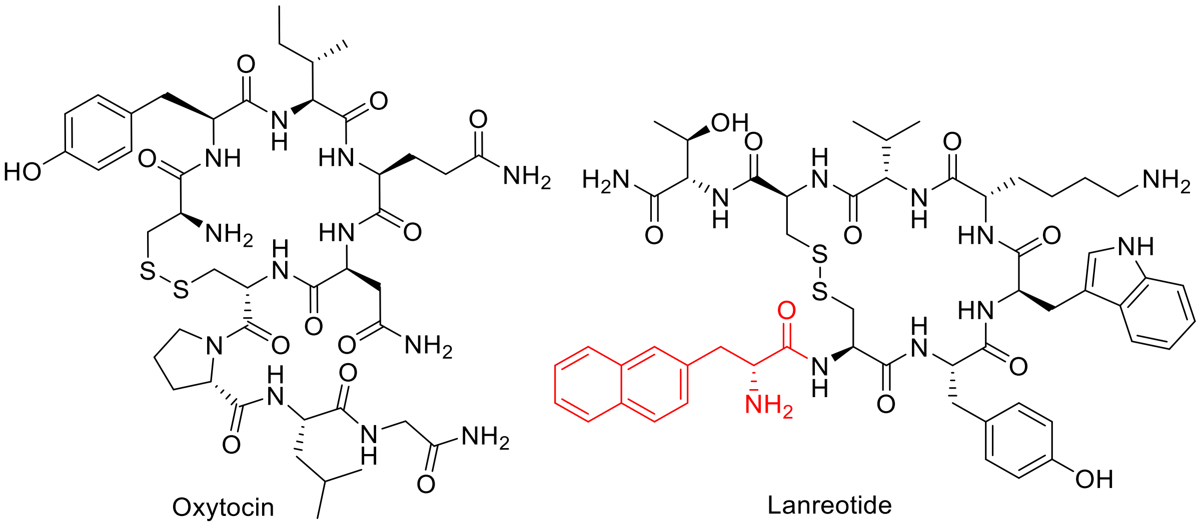
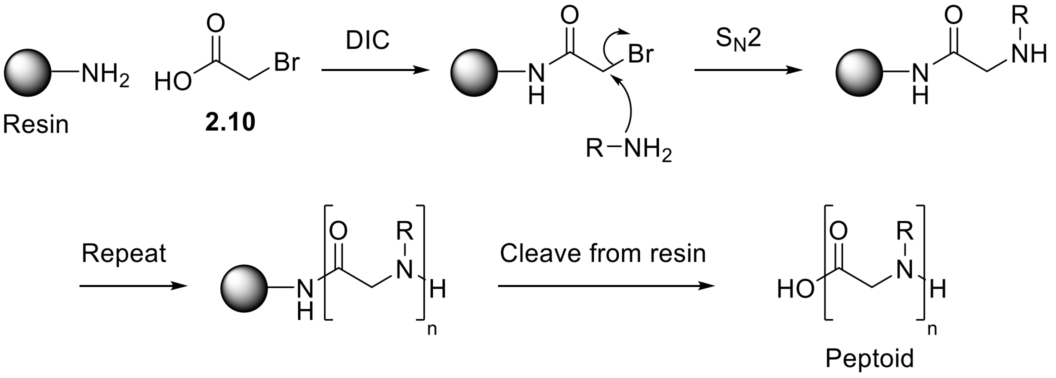


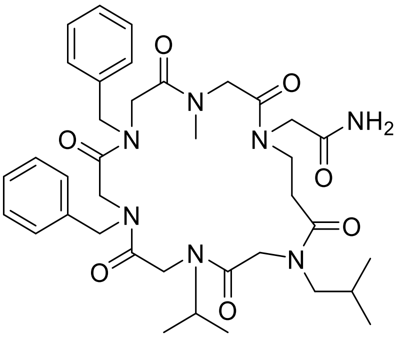
Figure 2.2: Bioactive cyclic peptides. Oxytocin (left) and Lanreotide (right). The latter features D-amino acid residues as well as an unnatural amino acid, highlighted in red.

Peptoids are peptide mimetics which consist of *N*-alkylated glycine residues linked together. Substituents on the amide nitrogen can simulate the functionality that is ordinarily present on the α-carbon of proteinogenic amino acids. Hence, peptoids allow for a greater chemical diversity while exhibiting greater resistance to proteolytic degradation when compared to peptides. The synthesis of peptoids can rapidly be carried out on resin (as shown in Scheme 2.2) using sequential bromoacetic acid (**2.10**) coupling reactions followed by S_N2 reactions with a primary amine.[61]



Scheme 2.2: Solid Phase synthesis of peptides. Scheme adapted from literature.[61]

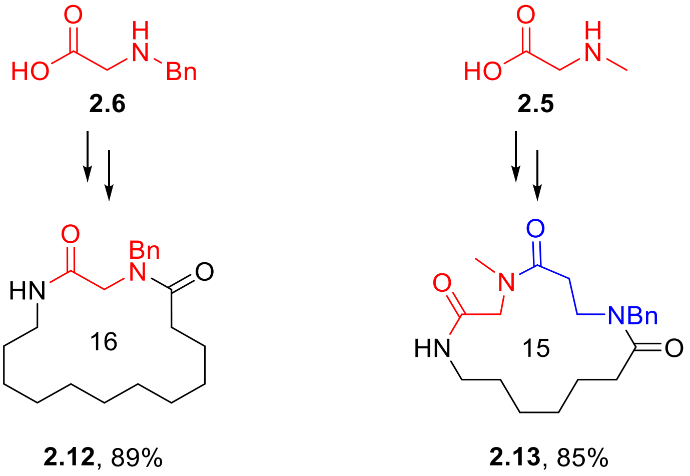
Using this solid phase synthesis strategy, Yong-Uk Kwon and co-workers were able to generate libraries of linear and cyclic peptoids.[61] One of these cyclic peptoids, CPO_Aβ17–21 P (**2.11**), has shown promise as an Alzheimer's disease therapeutic (Figure 2.3).[62]



2.11

Figure 2.3: Structure of cyclic peptoid CPO_Aβ17–21 P.

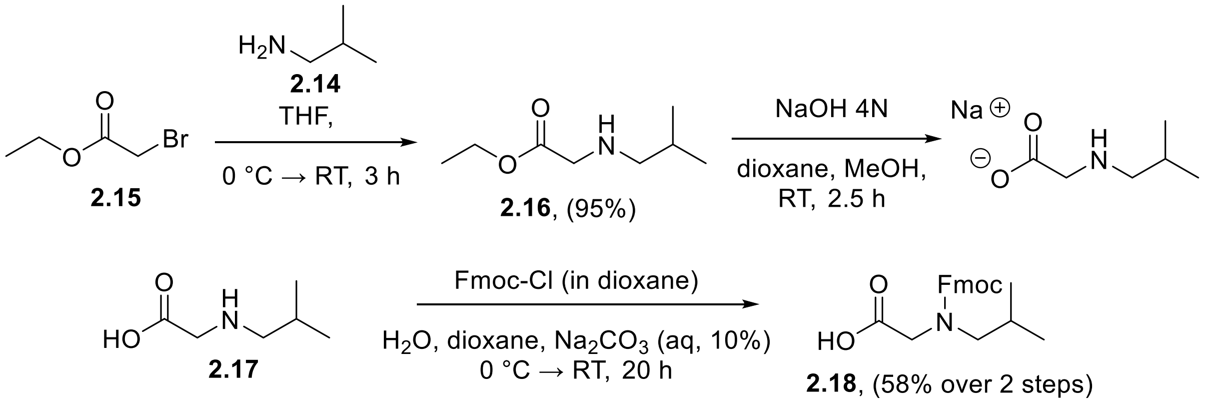
In the Unsworth Group, work has already been completed demonstrating that *N*-alkylated amino acids are compatible with SuRE reactions, with sarcosine (**2.5**) and *N*-benzyl glycine (**2.6**) already having been incorporated into ring expanded products, including sequential examples, to form cyclic peptoid-like macrocycles (Scheme 2.3).



Scheme 2.3: Macrocycles synthesized using sarcosine and N-benzyl glycine.

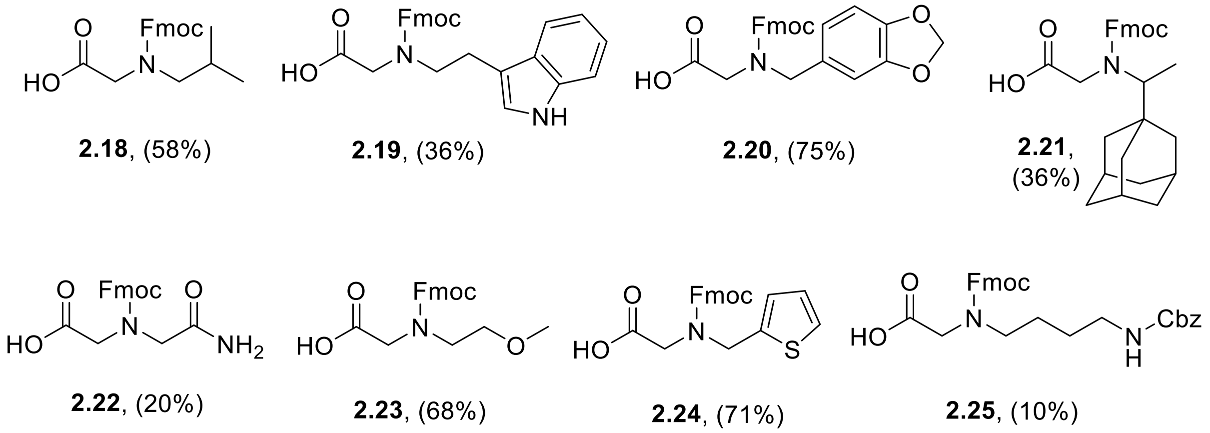
The intention of this study was to create novel ring expanded products using underexplored *N*-alkylated amino acids (*i.e*. beyond **2.5** and **2.6**). Using a diverse range of primary amines, novel *N*-alkylated amino acids were first synthesized with functionality mimicking proteinogenic amino acids (*e.g*. isoleucine, lysine, and tryptophan), as well as other functionality including thiophene and adamantane moieties. Using this flexible and modular approach, a series of *N*-alkylated amino acids with a variety of substituents were successfully synthesized as part of this project. Using an adapted literature procedure,[63] a 3-step synthesis of *N*-alkylated amino acids was trialled using commercially available isobutyl amine (**2.14**) and ethyl bromoacetate (**2.15**) to generate an *N*-isobutyl *N*-Fmoc amino acid (**2.18**) (Scheme 2.4). Bromide **2.15** first undergoes an S_N2 with an excess of amine **2.14**.

Then, after saponification to give **2.17**, the secondary amine is protected with a carbamate Fmoc group, affording **2.18** in 58% yield over 2 steps.



Scheme 2.4. N-alkylated amino acid synthesis.

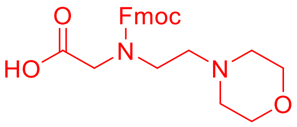
Eight *N*-alkylated *N*-Fmoc amino acids were synthesized successfully using this procedure, with yields ranging from 10–75% as outlined in Figure 2.4. A range of functionality is represented in this collection of amino acid derivatives such as a heteroaromatic group (**2.24**) a primary amide (**2.22**) and an indole moiety (**2.19**), the latter two examples serve as mimics of asparagine and tryptophan respectively. A few of the examples needed an additional synthetic step, such as the conversion of an HCl salt to the freebase. Rimantadine (1-(1-adamantyl)ethanamine hydrochloride) is an antiviral compound and an NMDA antagonist which features a spherical and bulky adamantane moiety. After converting to the freebase, this amine was used to synthesize **2.21** (Figure 2.4). The synthesis of the *N*-alkylated variant of asparagine **2.22** required a slightly adapted protocol,[63] which used EtOH and Et_3N to solubilize and deprotonate the glycinamide HCl salt in the first step of the reaction. An additional synthetic step was required in the route to **2.25**; putrescine was protected with a single Cbz group to generate benzyl *N*-(4-aminobutyl)carbamate, the precursor amine required to synthesize **2.25**.


2.18, (58%) **2.19**, (36%) **2.20**, (75%) **2.21**, (36%)

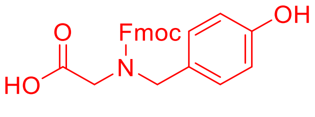
2.22, (20%) **2.23**, (68%) **2.24**, (71%) **2.25**, (10%)

Figure 2.4: Successful examples of N-alkylated N-Fmoc amino-acid synthesis.

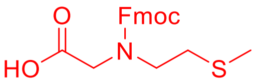
In addition, four *N*-alkylated *N*-Fmoc amino acids were not able to be synthesized using the standard method. For example, the synthesis of a morpholine derived example was unsuccessful (**2.26**); in this case, it is suspected that the basic nitrogen in the morpholine derived amino acid **2.26** was protonated upon acid workup and was lost to the aqueous phase. Basifying the mixture may have resolved this problem, although due to the risk of promoting unwanted Fmoc cleavage this was not attempted. *N*-alkylated amino acids derived from 4-aminomethylphenol (**2.27**) and 2-(methylthio)ethylamine (**2.28**) were also not isolated successfully (Figure 2.5).



2.26, (0%)



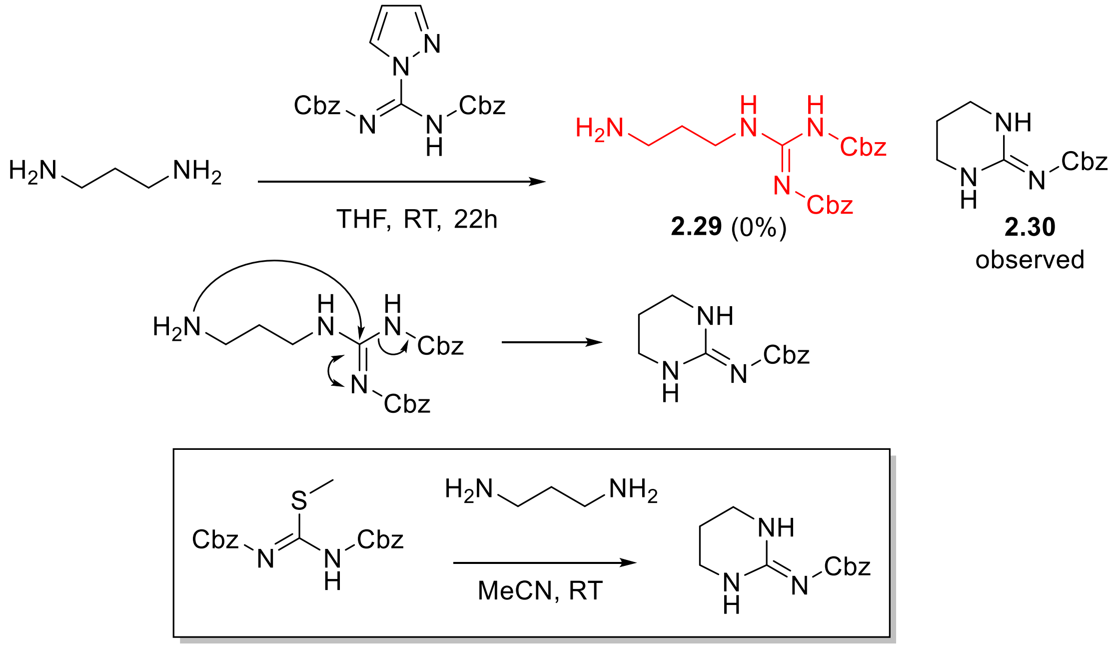
2.27, (0%)



2.28, (0%)

Figure 2.5: Unsuccessful examples of N-alkylated N-Fmoc amino-acid synthesis.

An attempt was also made to synthesize a Cbz-protected *N*-alkylated variant of the amino acid arginine; however, the synthesis of the appropriate amine precursor for this reaction was unsuccessful (Scheme 2.5, **2.29**), as the guanidine group underwent double addition to form a cyclic side product (**2.30**). There is precedent for this reaction in the literature (box, Scheme 2.5).[64]



2.29 (0%)

2.30
observed

Scheme 2.5: Attempt to synthesize N-arginine amine precursor and side product reported in the literature (shown in box).[64]

The successful 3 step route used to synthesize **2.18** – **2.25** (described in Scheme 2.4) was taken on by other Unsworth group members Dr Mahendar Lodi and Dr Katie Lamb to prepare additional *N*-alkylated *N*-Fmoc amino acids. These products are shown in Figure 2.6, and bring the total number of *N*-alkylated amino acids to be tested in SuRE to twenty-one. Some noteworthy examples include proline analogues with rings 4- or 6-membered in size (**2.35** and **2.36**) and unsaturated examples **2.41** and **2.42** that can serve as handles for further functionalization (*e.g*. for alkene metathesis or azide-alkyne click chemistry).

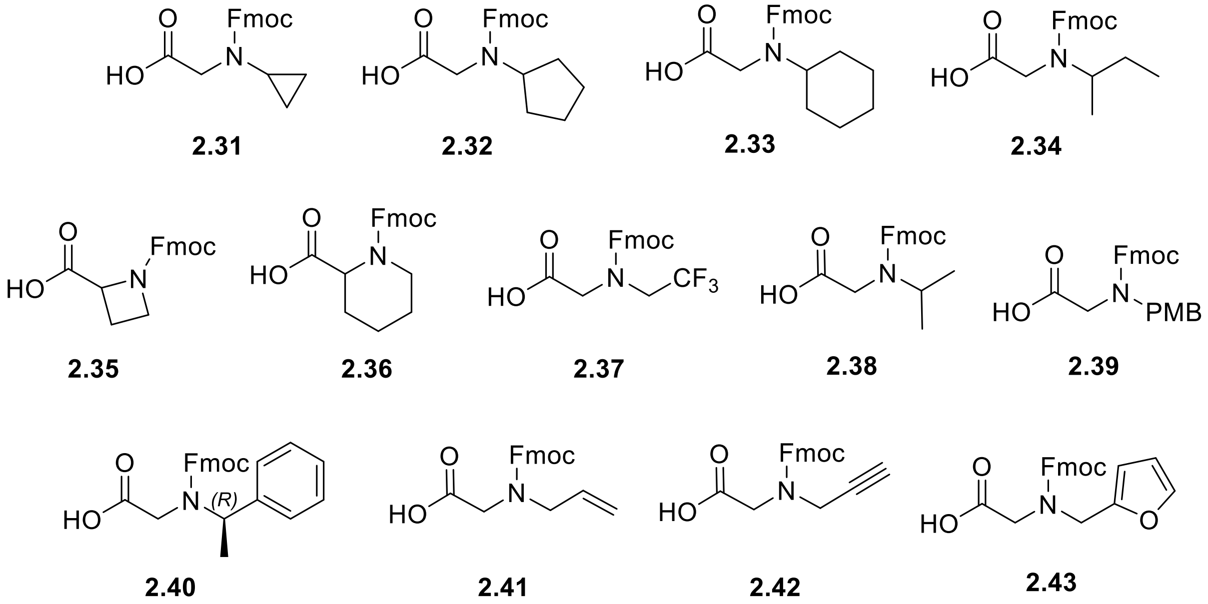
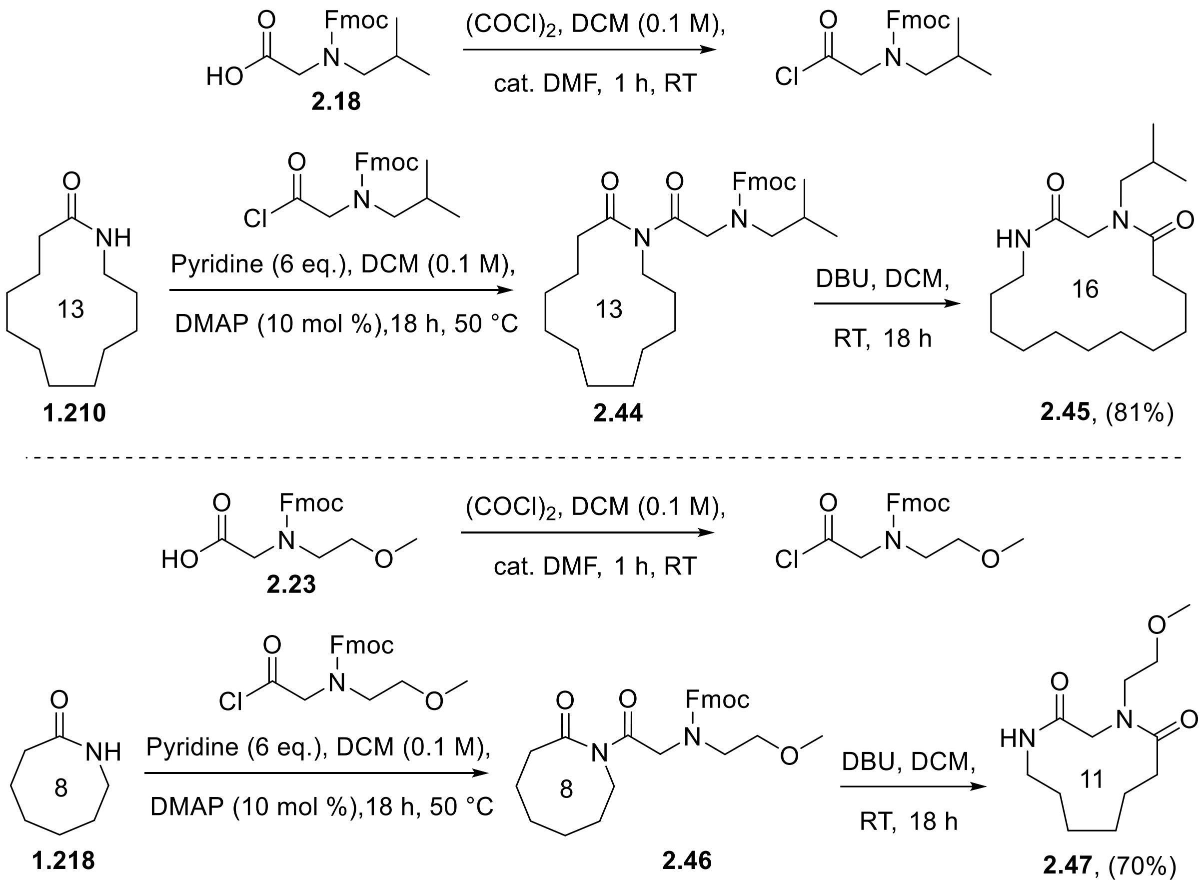

2.31 **2.32** **2.33** **2.34** **2.35** **2.36** **2.37** **2.38** **2.39** **2.40** **2.41** **2.42** **2.43**

Figure 2.6: Library of N-alkylated N-Fmoc amino acids synthesized by Dr M.L. and Dr K.L. PMB is an abbreviation for para-methoxy benzyl.

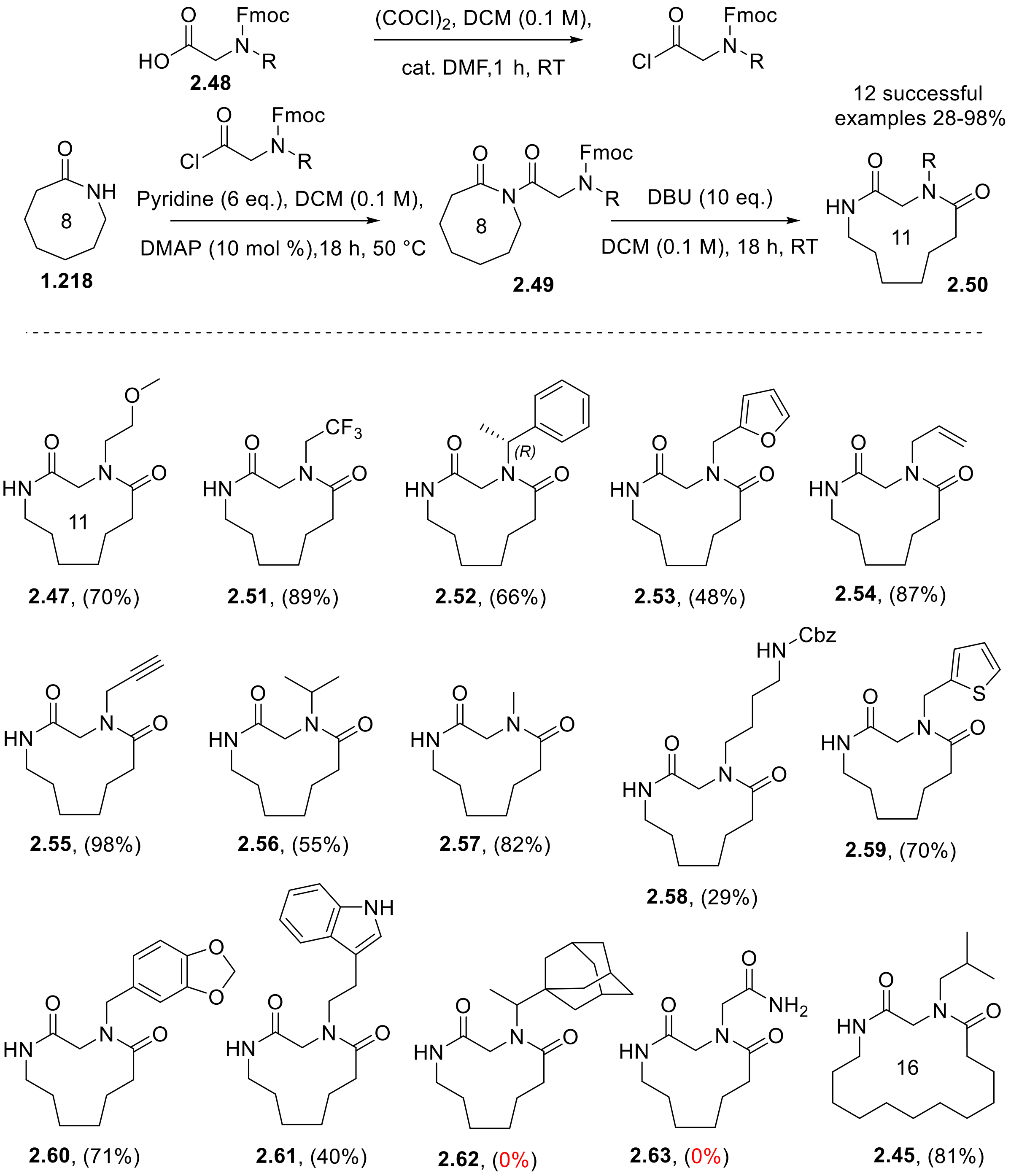
2.3 Ring Expansions

Once the synthesis of the *N*-alkylated *N*-Fmoc amino acids was complete, attention was turned to using these substrates in SuRE reactions to generate ring expanded macrocycles, as illustrated in Scheme 2.6. 13-Membered laurolactam (**1.210**) was the first substrate used in order to test the newly synthesized protected amino acid **2.18** using the group's established protocol.[48] Successful conversion into the 16-membered **2.45** was achieved in 81% yield over 2 steps which validated this new amino acid methodology as being compatible with SuRE. Looking ahead, it was decided that all the available *N*-alkylated *N*-Fmoc amino acids would be tested using the same lactam. In the past, 13-membered laurolactam has been used to test new SuRE reactions (as in Scheme 2.6, above), but in this work 8-membered lactam **1.218** was used as standard. A trial SuRE reaction using **1.218** and **2.23** was also successful, generating 11-membered **2.47** in 70% yield over 2 steps (Scheme 2.6, below). 8-Membered lactams are the smallest that consistently ring expand using the established procedure. Previous work in the group has demonstrated that 3-atom ring expansion from an 8-membered to an 11-membered ring is viable using *N*-alkylated α-amino acids.



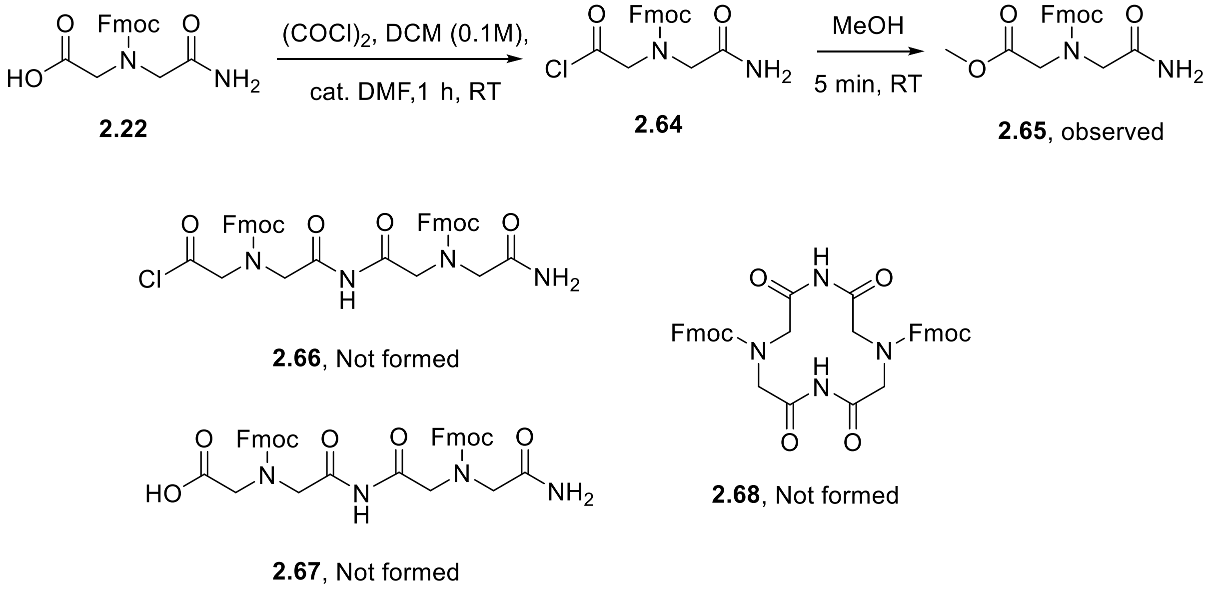
*Scheme 2.6: Initial trial ring expansion using laurolactam and N-Fmoc N-isobutyl glycine **2.18** (above). Trial 8-membered 1-aza-2-cyclooctanone ring expansion using N-alkylated amino acid **2.23** (below).*

The same acylation/deprotection protocol described in Scheme 2.6 was used to expand 8-membered 1-aza-2-cyclooctanone (**1.218**) into a series of 11-membered rings **2.50**. The results of the 14 attempted 8→11 membered acylation and ring expansion reactions are presented in Scheme 2.7. Overall, 12 of the 8→11 membered ring expansions were successful with yields ranging from 29% (**2.58**) to 98% (**2.55**) (and additional 13→16 ring expansion to form **2.45** was also successful in 81%). There does not seem to be an overarching trend relating the reaction yield to structure, except for the observation that some of the bulkier substituents (**2.62**) and the substrates containing reactive functionalities (**2.53**, **2.58**, **2.61**) generally give lower yields (or failed in the case of **2.62**) (Scheme 2.7). For example, the thiophene containing product **2.59** was isolated in 70% yield whereas the analogous furan containing product **2.53** was only obtained in a 50% yield. This is likely be due to the greater reactivity of the furan ring compared with thiophene, hence leading to the furan system having a greater proclivity to undergo unwanted side reactions. For example, the former may decompose or participate in side reactions during the acidic acylation or ring expansion, whereas the latter displays greater aromatic character and hence is usually more stable. The nucleophilic and relatively acid sensitive indole moiety in **2.61** may be participating in side reactions lowering the yield. The formation of **2.58** demonstrates the incorporation of an *N*-protected variant of the amino acid lysine. The low yield (29%) may be due to side reactions involving the terminal Cbz protected nitrogen. This particular reaction produced more side products than usual (based on TLC analysis of the crude reaction), suggesting that Cbz may not be the best choice of protecting group for this *N*-alkylated amino acid.



Scheme 2.7: Products of ring expansion reactions using N-alkylated amino acids.

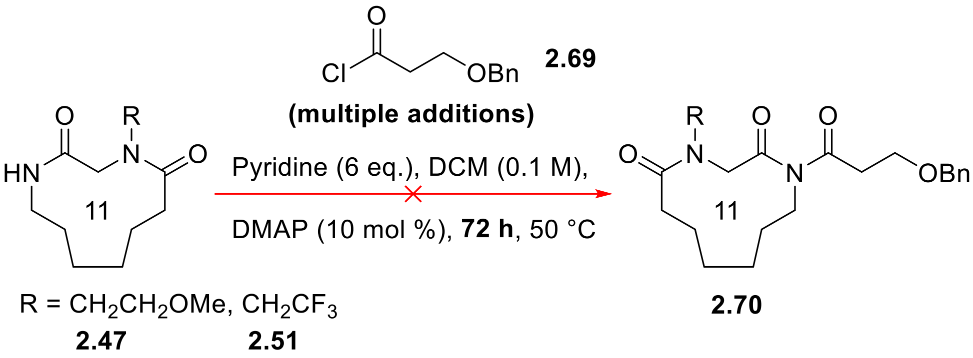
Compound **2.63** represents an *N*-alkylated asparagine mimetic. It was suspected that this reaction was unsuccessful in part due to the incompatibility of the acylation conditions with the primary amide motif. In order to test the viability of this substrate (considering the presence of a primary amide) the corresponding acid chloride was prepared and subsequently stirred in methanol. The aim of this experiment was to test the stability of the acid chloride **2.64**, and in doing so, the reaction appeared to proceed as planned, and did not suffer unwanted dimerization, cyclization or oligomer formation (Scheme 2.8). Characterization following this 'methanol test' indicated that the methyl ester **2.65** is the predominant product. This confirms that acid chloride **2.64** can be prepared, but despite this, the reaction to attempt to form **2.63** was unsuccessful. It is possible that acid chloride **2.64** is unstable under the elevated temperature required for acylation (50 °C).



Scheme 2.8: Acylation test for N-alkyl asparagine analogue. Methanol was used to successfully obtain the methyl ester.

2.3.1 Successive ring expansion attempts

Another Unsworth group member, Dr Lawer, attempted to perform successive ring expansions using lactams **2.47** and **2.51**, two of the 11-membered lactams presented in Scheme 2.7. However, acylation using benzyl protected β-hydroxy acid chloride **2.69** did not proceed to completion, even after repeated additions of additional acid chloride over 3 days (Scheme 2.9). Poor *N*-acylation has been a persistent problem for some larger rings in SuRE reactions. Slow or incomplete *N*-acylation reactions during the first step of the SuRE protocol is a significant problem in these cases despite multiple equivalents of acid chloride being added over the course of 72 hours or longer.[65] The difficulty in forming the required imide for several rings could be down to factors such as the conformation adopted by the lactam, which may or may not be easily accessible during the acylation. Transannular interactions could lead the ring to adopt a conformation where the secondary amide is not easily accessed; for example, a *trans* amide may be a less sterically accessible nucleophile than a *cis* amide. A rough trend has been that substrates that have already been expanded once are usually slower to acylate in subsequent iterations. An ongoing aim of a current PhD candidate (Zhongzhen Yang) in the Unsworth group has been to optimize alternative acylation conditions for some of these challenging substrates that have already undergone at least one SuRE reaction. This will serve as a 'plan b' option when the standard acylation conditions prove ineffective. This work is ongoing in the Unsworth group.



Scheme 2.9: Attempted successive ring expansions.

2.4 Benzannulated lactam starting materials

Expanding the scope of SuRE can be achieved in multiple ways. Two of the simplest approaches are to alter the functionality of the amino acids incorporated in the ring expansion reactions (as described in the Sections 2.2 and 2.3 above) and to alter the structure of the lactam. This subsection investigates efforts towards the latter; as part of a larger study investigating the functionality tolerated in the lactam structures used in SuRE.

This study focused on ring expansion reactions using two commercial benzannulated lactams containing an aromatic ring in the backbone (**2.71** and **2.72** in Table 2.1). Using starting materials that feature motifs to restrict the conformation of the ring expanded products may be favourable in comparison to long alkyl chains favoured by the Unsworth group to date, which generally have relatively poorly defined conformations. From a medicinal chemistry perspective, benzannulated macrocycles may offer greater specificity against biological targets due to restriction of the number of conformations available.

Using two protected β-alanine derivatives and following the standard SuRE acylation protocol, successful acylation of each lactam was achieved. However, the key ring expansion step only proceeded successfully when using a combination of the 7-membered lactam **2.72** and Fmoc-β-alanine acid chloride **2.73** (Table 2.1, entry 3, 58%).

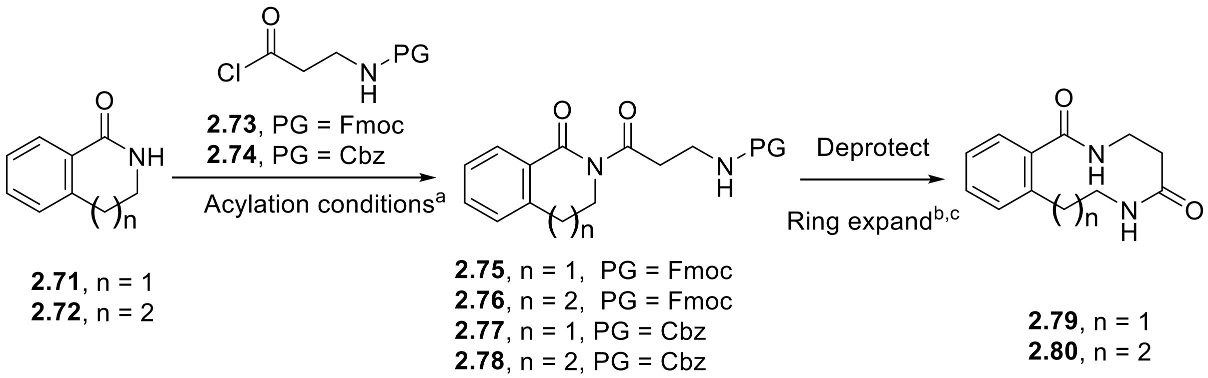
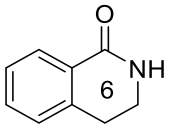
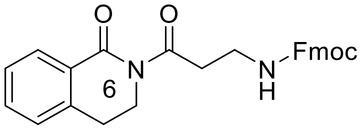
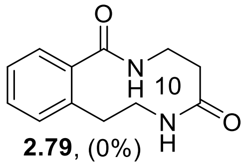
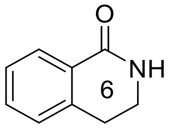
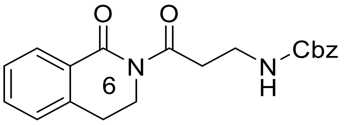
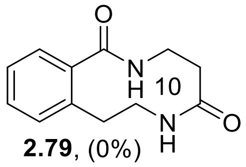
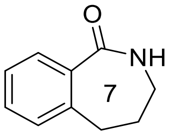
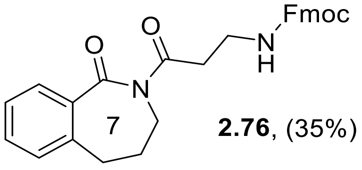
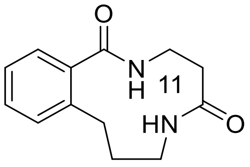
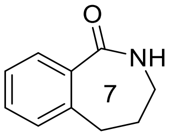
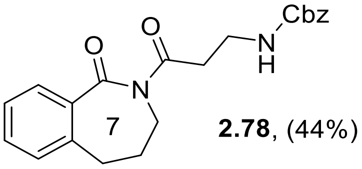
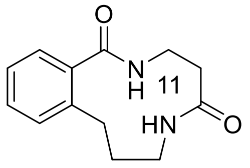


Table 2.1: Ring expansion of benzannulated lactams using SuRE. a) Standard pyridine/DMAP acylation conditions. b) Conditions for Fmoc protected imides: DBU, DCM, RT, 18 h. c) Conditions for Cbz protected imides: Pd/C, $H_{2(g)}$ EtOAc, 22 h. Acylation successful for all substrates.

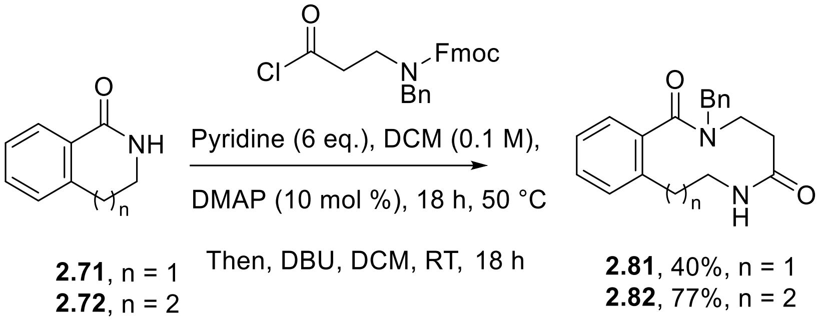
Entry	Lactam	Protecting group	Acylated product	Result of ring expansion
1	 **2.71**	Fmoc	 **2.75** (carried forward without isolation)	 **2.79**, (0%)
2	 **2.71**	Cbz	 **2.77,** (71%)	 **2.79**, (0%)
3	 **2.72**	Fmoc	 **2.76**, (35%)	 **2.80**, (58%)
4	 **2.72**	Cbz	 **2.78**, (44%)	 **2.80**, (0%)

It is worth mentioning that the purification of compounds containing two secondary amides (**2.79** and **2.80**) is usually difficult, due to the high polarity of both these compounds and the DBU reagent used in the second step of the synthesis. In regards to entry 1 (Table 2.1), the reaction was carried through without isolating **2.75** (only performing an acid workup to remove pyridine and DMAP), leading to a mixture of compounds by TLC after treating with DBU. The ring expanded product **2.79** could not be isolated using column chromatography and the mass peak was not detected by mass spectrometry in the crude mixture.

When working with small and highly polar compounds such as these products, changing the amino acid protecting group to Cbz has previously been demonstrated to aid purification as a simple filtration is generally all that is required following hydrogenolysis. Therefore, Cbz-β-alanine acid chloride (**2.74**) was used instead of Fmoc-β-alanine acid chloride (**2.73**) for some experiments, which avoids the need to use DBU in the synthesis, and hence means chromatography can be avoided also (entries 2 and 4, Table 2.1). In the latter approach, the protecting group could be removed using standard hydrogenation conditions (Pd/C and $H_{2(g)}$), as previously demonstrated by similar experiments carried out in the Unsworth group.[48] Unfortunately, in this case, the ^{1}H NMR spectra following hydrogenolysis suggested the formation of a complex mixture.

2.4.1 Further studies on functionalized lactams in the Unsworth group

Further studies on functionalized lactams in SuRE were performed by Dr Tom Stephens and Dr Aggie Lawer. For the benzannulated examples, it was discovered that *N*-Bn beta alanine helps to improve the SuRE sequence (Scheme 2.10).



*Scheme 2.10: Successful SuRE using **2.71** and **2.72** performed using N-Bn beta alanine performed by Dr Tom Stephens.*

Looking beyond benzannulated examples, 6- and 7-membered lactams featuring heteroatoms and branched functionality were synthesized by Dr Aggie Lawer for use in SuRE reactions. The lactams in Figure 2.7 feature in a recent publication exploring the scope of SuRE and the complimentary computational tools used in predicting the viability of these transformations.[66]

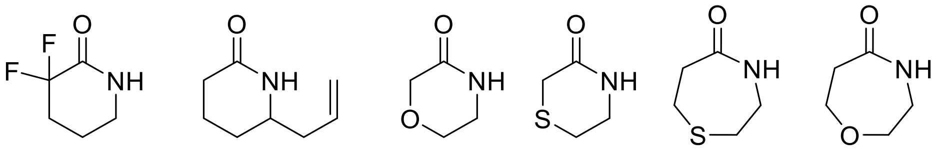


Figure 2.7: Diverse lactams have successfully been ring expanded using SuRE.

2.5 Chapter Summary

In summary, the established SuRE methodology was expanded in two ways; by exploring the viability of two benzannulated lactams for use in ring expansion, and using *N*-alkylated *N*-Fmoc amino acids with a variety of functionalities to form peptoid-like large rings. Each amino acid was synthesized over 3 steps beginning from a commercially available amine and ethyl bromoacetate (**2.15**) to form eight *N*-alkylated *N*-Fmoc amino acids to be added to the group library of 21 synthetic *N*-alkylated *N*-Fmoc α-amino acids (synthesized as part of a collaborative effort between Unsworth group members Kleo Palate, Dr Mahendar Lodi, and Dr Katie Lamb). In total, 15 ring expansion reactions were trialled as part of this doctoral work, with 13 ring expanded products isolated. This allowed access to functionalized macrocycles and medium sized rings with unique structures, complementing previous work installing *N*-alkyl derivatives of proteinogenic α-amino acids, and β-amino acids. The study of benzannulated lactams presented in this work was brief, but formed part of a larger collaborative study in the Unsworth group led by Dr Aggie Lawer exploring functionalized lactams in SuRE.

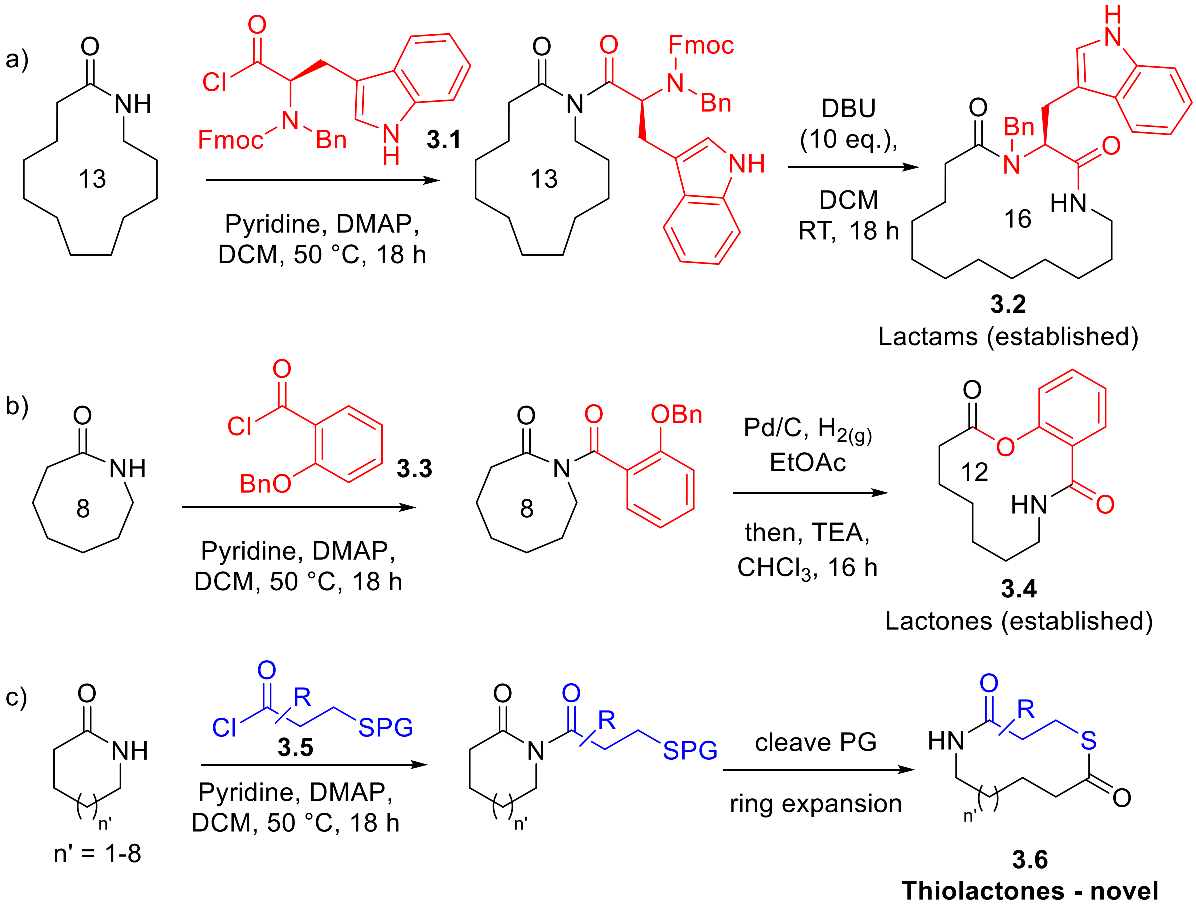
The work described in this Chapter is the subject of one publication.[66]

3 Successive Ring Expansion of Lactams to form Thiolactones

3.1 Extending SuRE to thiol derivatives

In this chapter the synthesis of medium-sized ring and macrocyclic thiolactones using SuRE methodology is described. The progression of this research will be shown from initial proof-of-concept studies, through the evaluation of three different protecting group strategies, expansion of the reaction scope (investigating various ring sizes, branched thiol and α-thiol-tethered carboxylic acid examples), and finally looking at successive examples.

As has already been discussed in Chapter 1, various robust methods for iterative ring expansion of lactams using amino- and hydroxy-acid derivatives have been developed by the Unsworth group (*e.g.* **3.2** and **3.4** in Scheme 3.1a and b). However, one question that had not been explored until the work described in this chapter was the question of whether SuRE methodology could be applied to thiol-tethered carboxylic acid derivatives, to form thiolactone containing macrocycles (**3.6** in Scheme 1c).



Scheme 3.1: SuRE reactions using (a) nitrogen nucleophiles to form lactams[48] and (b) oxygen nucleophiles to form lactones have been established.[67] A novel approach (c) to form thiolactones using sulfur nucleophiles will be explored in this chapter.

3.1.1 Initial concept

Thioesters are an important functional group which feature in essential biosynthetic processes, such as the native chemical ligation of proteins.[68] Key biochemical functions such as fatty acid synthesis and the Krebs Cycle utilize acetyl coenzyme A (**3.7**) which is a thioester.[69] Thioesters are also thought to have played a role in the development of life on earth, as cysteine and homocysteine are believed to have been present in the primitive ocean and may have been involved in early proto-peptide forming reactions (*e.g. via* ring opening of **3.8**).[70] Thiolactones, the cyclic forms of thioesters, can also act as pro-drugs, with the active form revealed *in vivo* following hydrolysis (**3.10** and **3.11**).[71–73] Ring-opening is often a key feature in applications of thiolactones in organic synthesis and polymer chemistry.[74–78] In cases involving hydrolysis, the relative ease of hydrolysis of thiolactones compared to lactones has a significant bearing on these works.

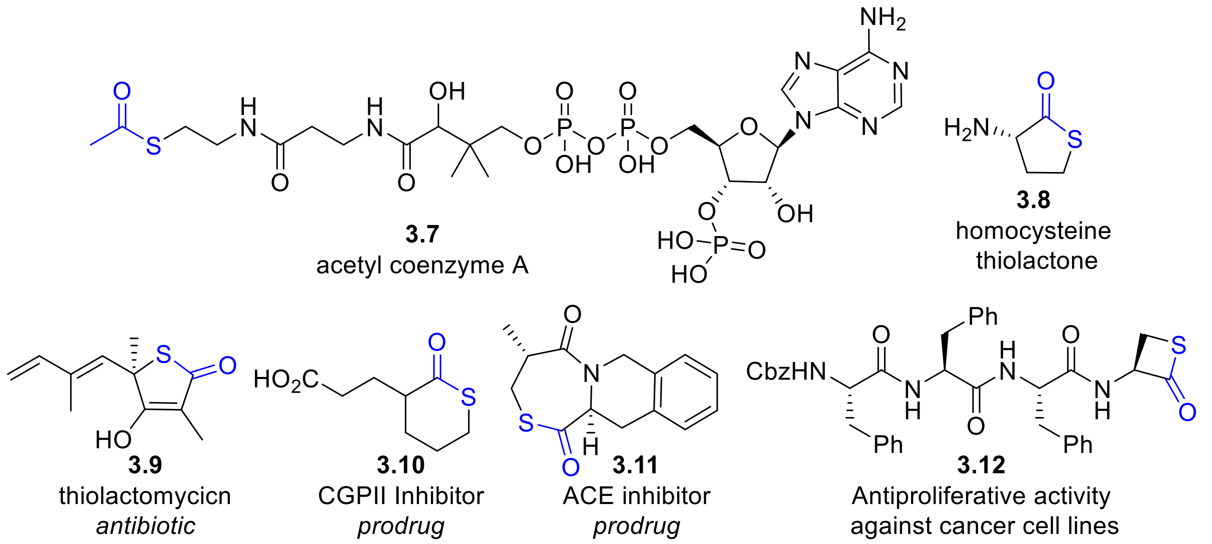

3.7
acetyl coenzyme A
3.8
homocysteine thiolactone
3.9
thiolactomycicn
antibiotic
3.10
CGPII Inhibitor
prodrug
3.11
ACE inhibitor
prodrug
3.12
Antiproliferative activity against cancer cell lines

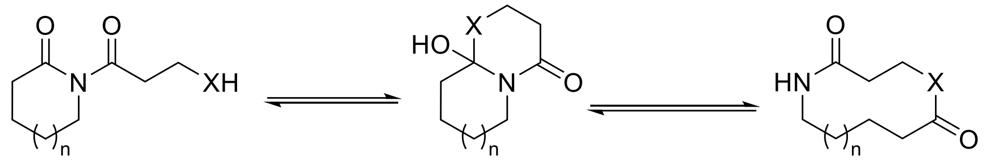
Figure 3.1: Thioesters with biochemical importance.

Despite the importance of thiolactones, thiol ring expansion had been avoided in the Unsworth group's previous work into SuRE up to this point. The reason for not attempting thiol ring expansions earlier was a belief that the side chain insertion of a thiol to ultimately form a thioester would be less thermodynamically favourable than analogous reactions using amino/hydroxy acids to form lactams and lactones. The hypothesis being that the thiolactone-forming reactions could be more challenging to develop, based on chemical intuition and knowledge of the associated bond strengths. However, the Unsworth Group recently established a DFT (Density Functional Theory) based method to help predict whether or not new SuRE type reactions are thermodynamically viable before attempting them in the lab. Therefore, before starting this study, it was decided to use this computational method to model thiol-based SuRE reactions. A summary of the DFT method is provided in the next sub-section, followed by a discussion of the new DFT results.

3.1.2 DFT calculations

The Unsworth Group's DFT method is based on modelling the relative Gibbs free energies of the three isomeric forms that can be formed during a ring expansion reaction, with the calculated energies used to help predict the viability of new SuRE variants. This approach has now been extended to thiol-based ring expansions as well, as shown in Table 3.1 below. After deprotection, a ring opened thiol isomer (RO, **3.13**) can rearrange into its ring closed (RC, **3.14**) form which can in turn rearrange into a ring expanded (RE, **3.15**) product. These processes are thought to be reversible and under thermodynamic control in most cases. If the relative Gibbs free energy of the RE isomer is lower than the other two isomers (by more than 3 kcal mol^{-1}), this is a good indicator that the ring expansion is thermodynamically favourable and will usually work well. The computational studies involved in this work were mostly performed at the B3LYP/6-31G* level of theory, with select examples also completed using M06-2X/6-31G* (and they were benchmarked against various other functionals). The former B3LYP/6-31G* method is sufficient for these relatively simple calculations, with a good record of the theory matching the experimentally observed results.[66]

DFT studies were conducted to model the RO, RC, and RE isomers of a 7→11 ring expansion where the nucleophile (X) is varied (Table 3.1, rows 1–4). The RE isomers were calculated to be lowest in energy for X = O, NH, and NMe as expected. However, for the analogous X = S example (row 4), the RO isomer was calculated to have the lowest relative Gibbs free energy. Investigating other ring sizes for this transformation, it was found that for smaller starting ring sizes (6 and 7-membered), the reaction is indeed likely to be unfavourable, with the RO isomer calculated to be lowest in energy. However, with larger ring homologues (8 and 9 membered) the thermodynamic preference tips in the other direction, with the RE having the lowest calculated free energy, and therefore these ring expansions should be viable, and according to the DFT model, have a good chance of undergoing successful ring expansion to form thiolactones (Table 3.1, entries 5 and 6). Therefore, it was decided to concentrate the subsequent synthetic efforts on larger, commercially available 8- and 13-membered lactams.



Ring-Opened **3.13** Ring-Closed **3.14** Ring-Expanded **3.15**

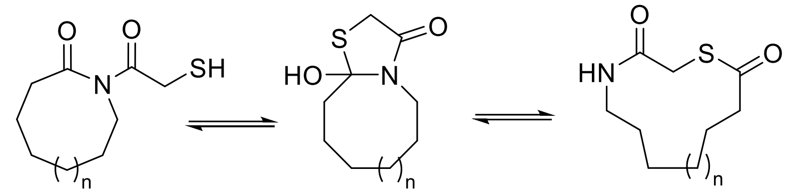
Table 3.1: DFT calculations predicting most energetically favourable isomer in 4-atom ring expansion reactions. Lowest relative energy is shown in bold.

Entry	**RO ring size, n** Nucleophile, X	**Ring expansion**	**ΔG°rel**		
			RO (kcal mol^{-1})	RC (kcal mol^{-1})	RE (kcal mol^{-1})
1	n = 2, X = NH	7 → 11	0.0	12.1	**–8.1**
2	n = 2, X = NMe	7 → 11	0.0	15.0	**–5.6**
3	n = 2, X = O	7 → 11	0.0	9.1	**–6.9**
4	n = 2, X = S	7 → 11	**0.0**	17.1	3.8
5	n = 4, X = S	9 → 13	0.0	17.5	**–7.1**
6	n = 3, X = S	8 → 12	0.0	20.0	**–1.8**
7	n = 1, X = S	6 → 10	**0.0**	15.4	7.5

Additional computational studies were performed to investigate whether a 3-atom thiolactone forming ring expansion would be viable. This is for the same transformation, but using a shorter linear fragment.

In previous studies looking at lactam and lactone formation, the shorter α-amino- and hydroxy- acid linear fragments were also investigated by DFT, and the general finding was they are less favourable than their longer homologues. For example, whilst a 4-atom ring expansion to form a lactone can be performed on lactams as small as 6-membered in size (to form a 10-membered ring), the corresponding 3-atom ring expansion requires lactams of 8-membered or above (to form a 12-membered ring). The key finding from previous work was that the 'switch on' starting ring size was generally larger for these 3-atom ring expansion examples when compared to 4-atom ring expansions.

A similar observation was found here; the DFT results of a 3-atom expansion system to form thiolactones suggested that ring expansion might be favourable for a 13-membered thiol (RO, **3.16**, n = 7) to 16-membered thiolactone (RE, **3.18**, n = 7) ring expansion, but not for the 8- to 11-membered ring variant, as seen in Table 3.2. It was therefore decided to focus on the longer β-thiol acids derivatives.



Ring-opened **3.16**

Ring-closed **3.17**

Ring expanded **3.18**

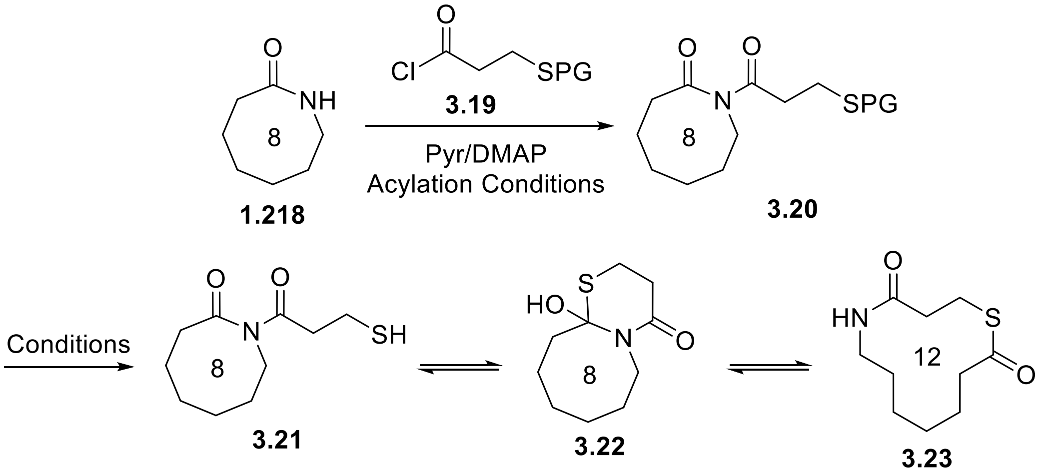
Table 3.2: DFT calculations predicting most energetically favourable isomer (bold) in 3-atom sulfur ring expansion reactions.

n=	Ring expansion	Hybrid functional	RO (kcal mol^{-1})	RC (kcal mol^{-1})	RE (kcal mol^{-1})
7	13 → 16	B3LYP 6-31G*	0.0	11.6	**–12.7**
1	8 → 11	B3LYP 6-31G*	**0.0**	8.1	1.8
1	8 → 11	M06-2X 6-31G*	**0.0**	2.0	1.0

3.2 S-Acetate protecting group

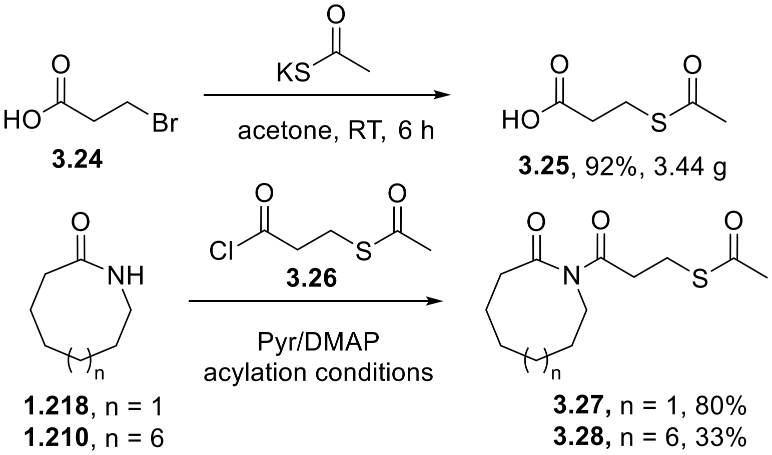
3.2.1 Synthesis of 3-(acetylthio)propanoic acid and acylation

In light of the DFT findings, studies began by investigating the 4-atom ring expansion from 8→12, starting with **1.218** to form **3.23** (Scheme 3.2).



*Scheme 3.2: General scheme for 4 atom ring expansion of **1.218** to form thiolactone **3.23**. Three protecting groups were tested.*

An important decision was the choice of protecting group for the thiol. Three complementary protecting group strategies were explored, the first based on S-acetate protection. To begin with, the required 3-(acetylthio)propanoic acid (**3.25**) was made on a multigram scale. Then, the standard pyridine/DMAP acylation reaction conditions were applied, using acid chloride **3.26** and lactam **1.218**, producing imide **3.27** in 80% yield. An additional 13-membered variant **3.28** was also prepared in the same way in a modest yield (Scheme 3.3).



*Scheme 3.3: Synthesis of 3-(acetylthio)propanoic acid and acylation to form thioacetate imides **3.27** and **3.28**.*

3.2.2 Optimization of thioacetate cleavage and thiolactone formation.

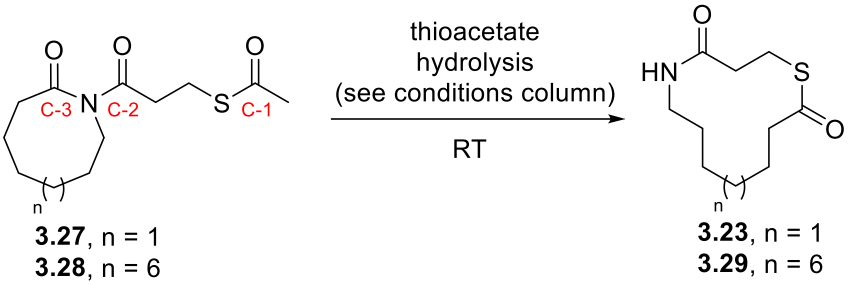
With imides **3.27** and **3.28** successfully in hand, conditions to promote the selective thioacetate deprotection and subsequent ring expansion were examined. To deprotect the thioacetate acyl group, nucleophilic reagents such as sodium and lithium hydroxide as well as secondary amine reagents were tested (Table 3.3 below).

It quickly became clear that *selective* nucleophilic attack of the thioacetate carbonyl was challenging. Chemoselectivity was a significant problem; the difficulty lay in discriminating between the three carbonyl groups of imides **3.27** and **3.28**, labelled C-1 to C-3 in Table 3.3. For instance, the only tractable compounds produced in the reaction of aq. NaOH in methanol were the linear products **3.30** and **3.31** formed by nucleophilic attack of methanol at the C-3 carbonyl (entry 1). Adjusting to milder hydrolysis conditions using LiOH in THF also resulted in C-3 attack (forming **3.31**), in addition to undesired C-2 attack (**3.25** and **1.218**) with only trace quantities of the desired ring expanded product **3.23** formed (entry 2). Evidence for this new transformation was suggested by a new carbonyl peak present in ^{13}C NMR (see section 3.2.4). Repeating the reaction with LiOH in THF at a larger scale and a shortened reaction time yielded the desired thiolactone **3.23** in 6% yield (entry 3). This structure was later confirmed by X-ray crystallography (see section 3.9).

These results prompted a switch to secondary amine reagents, reasoning that a more hindered nucleophile would be more likely to selectively attack at the C-1 carbonyl. Some conditions trialled resulted in no reaction, or poor conversion (*e.g.* DIPA, diethylamine, entries 4–7).

DTT (dithiothreitol) was added in entry 6, as there was some uncertainty as to whether the thiol **3.21** was oxidizing to form a disulphide. This resulted in an improved 16% yield of the desired **3.23** product, with substantially increased thiol **3.21** recovery (43%). However, the addition of DTT made purification more challenging and was not pursued further.

More positively, using piperidine in DCM resulted in a modest yield of the desired ring expanded product **3.23** (29%) as well as side products resulting from C-2 nucleophilic attack (**1.218** and **3.33**), thiol **3.21**, and some unreacted starting material **3.27** (entry 8). A similar outcome was observed when these conditions were used to deprotect the 13-membered imide **3.28**, with 17-membered thiolactone **3.29** isolated in 36% yield, but unproductive side product formation was also observed. The incomplete cleavage of the acetyl group also remained a problem (entry 9). These results represented the first examples of SuRE-style side chain insertion ring expansion reactions being used to synthesize thiolactones. However, problems with competing side reactions and incomplete reactions remained, so alternative protecting group strategies were sought.



Side products deteteced/isolated

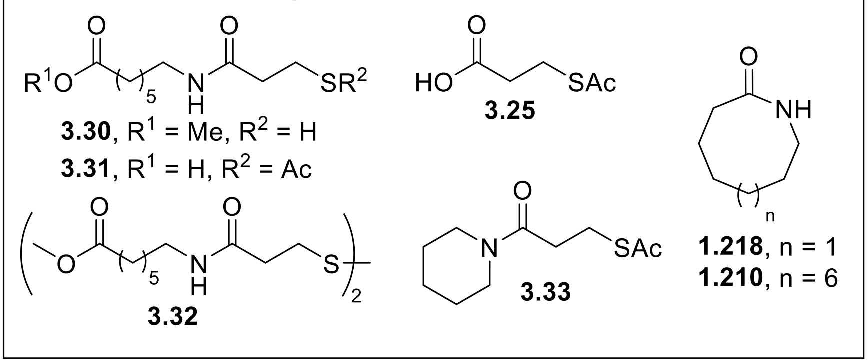


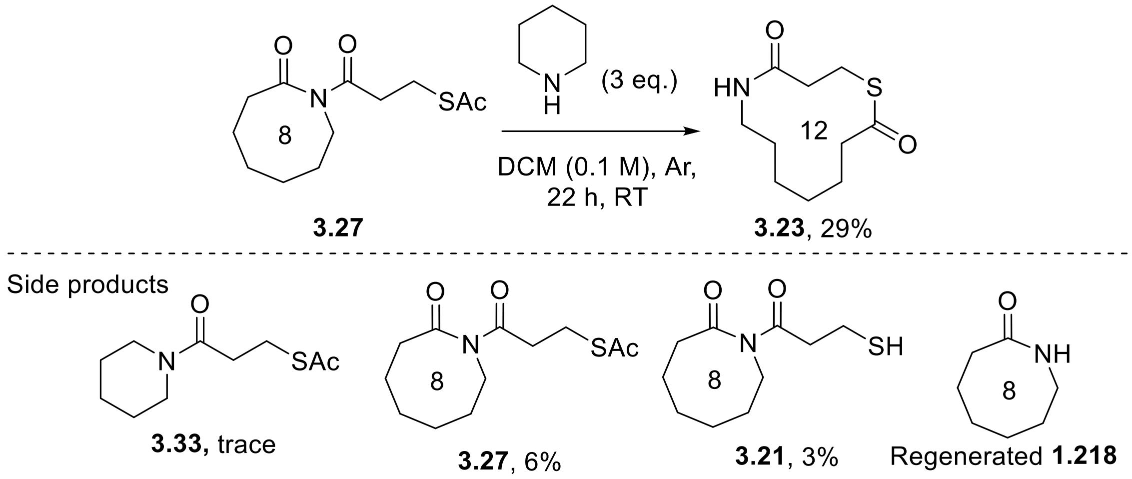
Table 3.3: Optimization experiments for the S-Ac deprotection/ring expansion conditions.

Entry	Conditions	Solvent	Time / h	Yield of **3.23**[a] / %	Side products[b]
1	4 M $NaOH_{(aq)}$	MeOH	2	0	**3.30** (19%) and **3.32** (16%)
2	0.3 M $LiOH_{(aq)}$	THF	3	trace	**3.31**, **3.25** (13%), **1.218** and **3.27** (21%)
3	0.3 M $LiOH_{(aq)}$	THF	0.33	6	**1.218** (10%) and **3.27** (20%)
4	DIPA	THF	24	0	No reaction
5	DIPA	DCM	24	0	No reaction
6	Et_2NH, DTT	DCM	18	16	**3.21** (43%)
7	piperidine	THF	24	0	No reaction
8	piperidine	DCM	22	29	**3.33**, **1.218**, **3.27** (6%) and **3.21** (3%)
9	piperidine	DCM	18	36 (**3.29**) (from **3.28**)	**3.33**, **1.210** and **3.28** (34%)

All reactions were performed at RT. [a] Isolated following column chromatography. [b] Yield (in parentheses) is only reported for side products when the product was isolated without impurities.

3.2.3 Optimized conditions and verification of ring expansion

The optimized acetyl cleavage conditions produced 12-membered and 17-membered thiolactones in synthetically useful yields (29% and 36% respectively). However, side reactions could not be effectively suppressed; for example, in Scheme 3.4, the best conditions for converting **3.27** into ring-expanded product **3.23** are summarized, alongside the various side products also formed.



Scheme 3.4: Optimized thioacetate deprotection/ring expansion conditions and side products isolated.

3.2.4 Summary of acetate protecting group

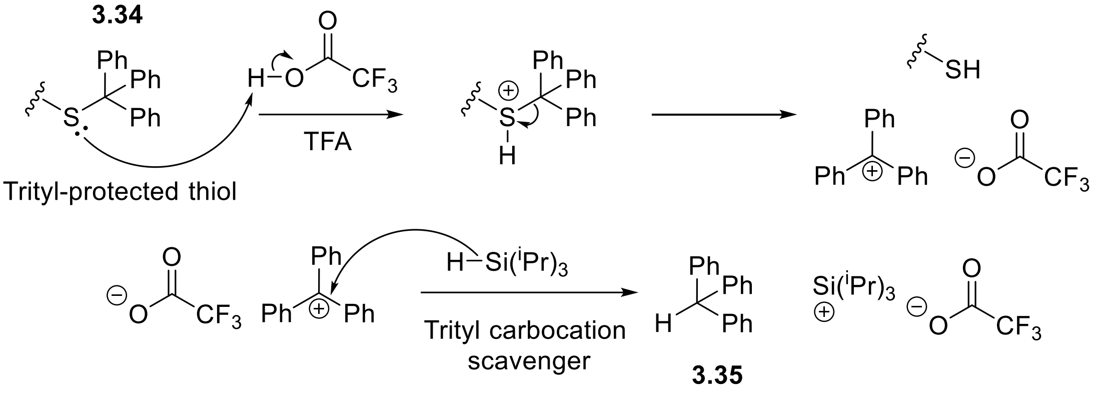
Acetate deprotection of imides **3.27** and **3.28** using the DCM/piperidine conditions produced synthetically useful amounts of **3.23** and **3.29** for the first time. However, it was clear that there were significant challenges with the acetate deprotection strategy that could not easily be resolved. The formation of multiple side products due to lack of selectivity during nucleophilic attack could not be suppressed. Additionally, large quantities of recovered starting material (**3.27** and **3.28**) suggested that even with three equivalents of piperidine the reaction does not go to completion at RT. In order to address these problems, as well as the low yields, an alternative thiol protecting group was sought that would not require a nucleophilic base for its removal.

Although a selective synthesis proved challenging, characterization of **3.23** and **3.29** was comparatively simple. ^{13}C NMR was especially useful in the characterization of novel thiolactones (*e.g.* **3.23**) providing evidence of thiolactone formation. Examining the COS carbonyl signal of these macrocycles showed a signal at *ca.* 200 ppm in each case (200.5 ppm for **3.23** and 201.1 for **3.29**). In comparison, the starting material imides display a signal at *ca.* 196 ppm (195.9 for **3.27** and 195.7 for **3.28**), allowing discrimination of thioacetate and thiolactones. Also, X-ray crystallography provided conclusive evidence of the formation of macrocyclic products **3.23** and **3.29**.

3.3 S-trityl protecting group

The next thiol protecting group examined was triphenylmethyl. Taking inspiration from orthogonal protecting group strategies used to protect cysteine during solid state peptide synthesis, the triphenylmethyl (trityl) group emerged as a promising alternative thiol protecting group.

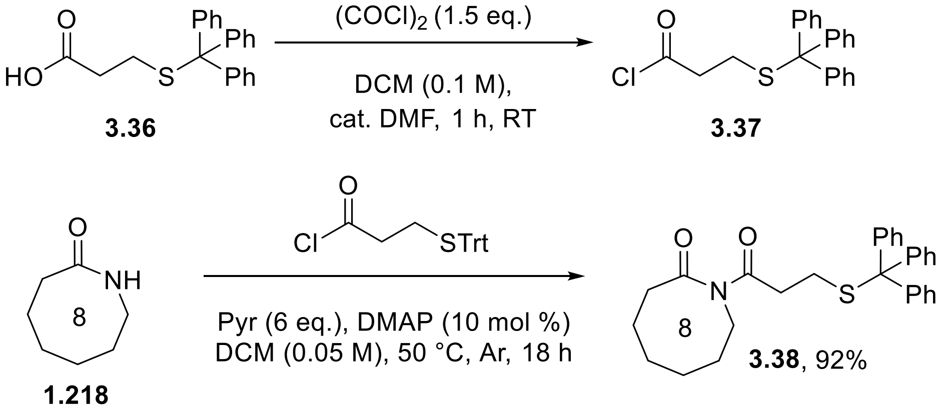
The trityl protecting group is acid-labile and is typically removed using TFA in the presence of a scavenger. The scavenger effectively serves to prevent re-addition of the trityl group by 'quenching' the triphenylmethyl carbocation to form triphenylmethane (Scheme 3.5).



Scheme 3.5: Trityl deprotection mechanism.

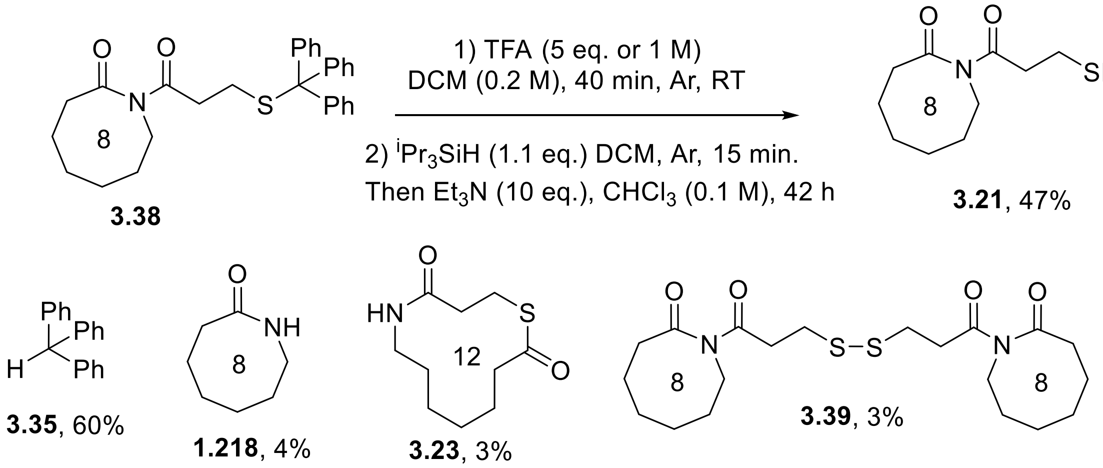
3.3.1 Early studies of the trityl protecting group using 8-membered imide 3.38

An initial acylation of 8-membered lactam using standard conditions and acid chloride **3.37** furnished the desired imide **3.38** in excellent yield (92%, Scheme 3.6).



Scheme 3.6: Acylation of 8-membered lactam using a trityl protected thiol-tethered carboxylic acid.

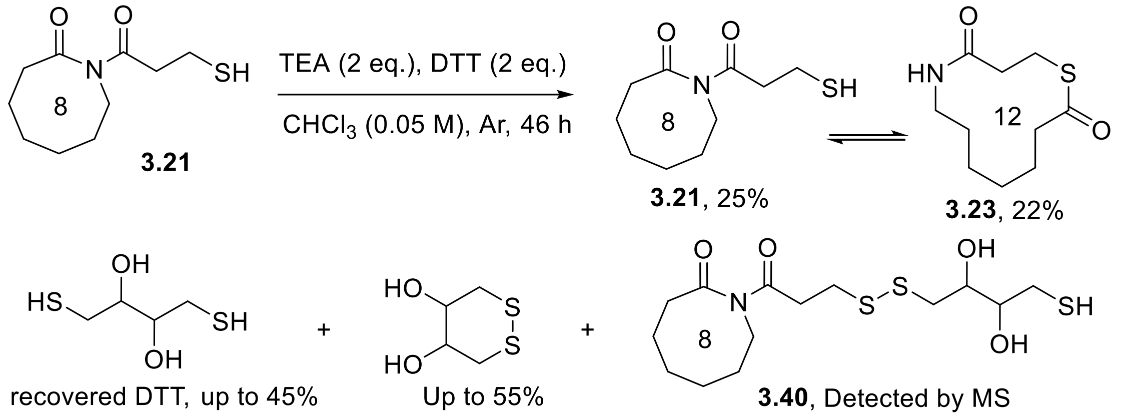
When attention turned to the deprotection/ring expansion reaction using TFA and a silane scavenger, it was observed that mostly thiol **3.21** was isolated, with small amounts of the desired ring expanded product also observed. In addition to this, 8-membered lactam **1.218** and a disulfide side-product (**3.39**) were also formed (Scheme 3.7).



*Scheme 3.7: Trityl deprotection of 8-membered imide generating the unprotected thiol (**3.21**).*

Based on the similarity between the DFT calculated energies of isomers **3.21** and **3.23** (see Table 3.1), the ring expansion of **3.21** into **3.23** was expected to be marginal in terms of whether it would be thermodynamically feasible or not.

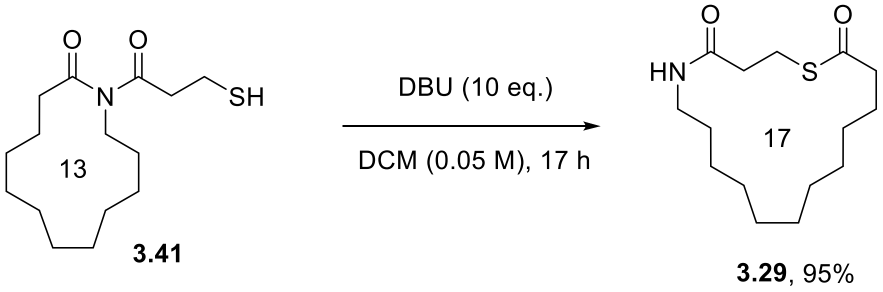
When thiol (**3.21**) was reacted under basic conditions with TEA and DTT in chloroform, some of the desired ring expansion product (**3.23**) was observed, but thiol (**3.21**) also remained in large part unreacted following this reaction, with 25% recovered (Scheme 3.8). DTT was added in this example to reduce any unwanted disulfide that might form during the reaction, and recovered in both linear and cyclic form. A disulfide of thiol **3.21** and DTT was also observed by MS.



*Scheme 3.8: 8-membered thiol (**3.21**) partially undergoing ring expansion when subjected to TEA/$CHCl_3$ cyclization conditions.*

In light of the result above, (*i.e.* with ring expansion of thiol **3.21** slow and incomplete under basic conditions), it was decided to focus optimization efforts on 13-membered laurolactam instead. To confirm the efficiency of the 13→17 membered ring expansion, thiol **3.41** was probed in a series of experiments.

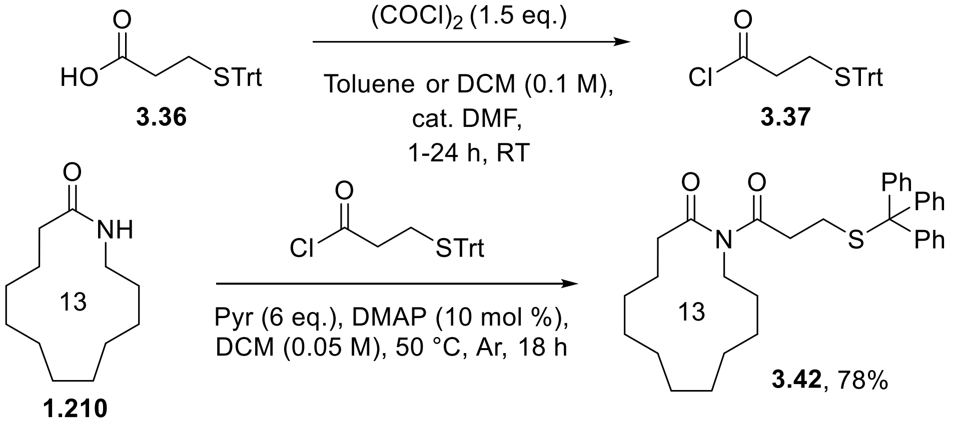
Scheme 3.9 below demonstrates that conversion of thiol **3.41** to **3.29** is near quantitative in 10 eq. of DBU in DCM after 17 hours. Hence this combination of ring size and deprotection conditions was used for further optimization going forward.



*Scheme 3.9: Near quantitative conversion of thiol **3.41** to thiolactone **3.29** under basic conditions.*

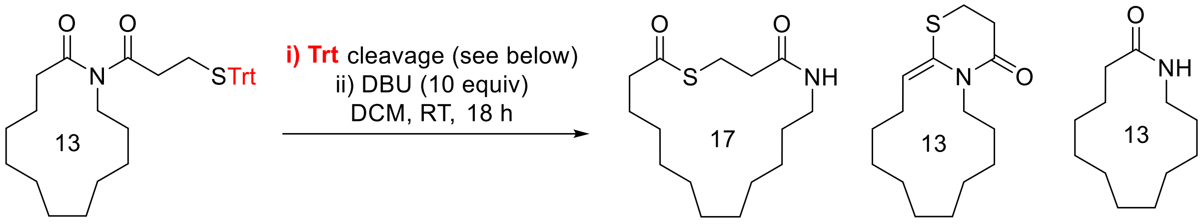
3.3.2 Optimization of S-Trityl deprotection/ring expansion

Exploratory studies focused on the 13-membered to 17-membered ring expansion. First, 3-(tritylthio)propionic acid was converted to the acid chloride **3.37**, and this was used to acylate lactam **1.210** using the standard pyridine / DMAP conditions to form imide **3.42** (Scheme 3.10, 78%).



Scheme 3.10: Acylation of 13-membered lactam using a trityl protected thiol-tethered carboxylic acid

The experiments aiming to optimize the trityl deprotection/ring expansion are detailed in Table 3.4 below.



3.42 **3.29** **3.43** **1.210**

Table 3.4: Optimization experiments for the S-Trt strategy

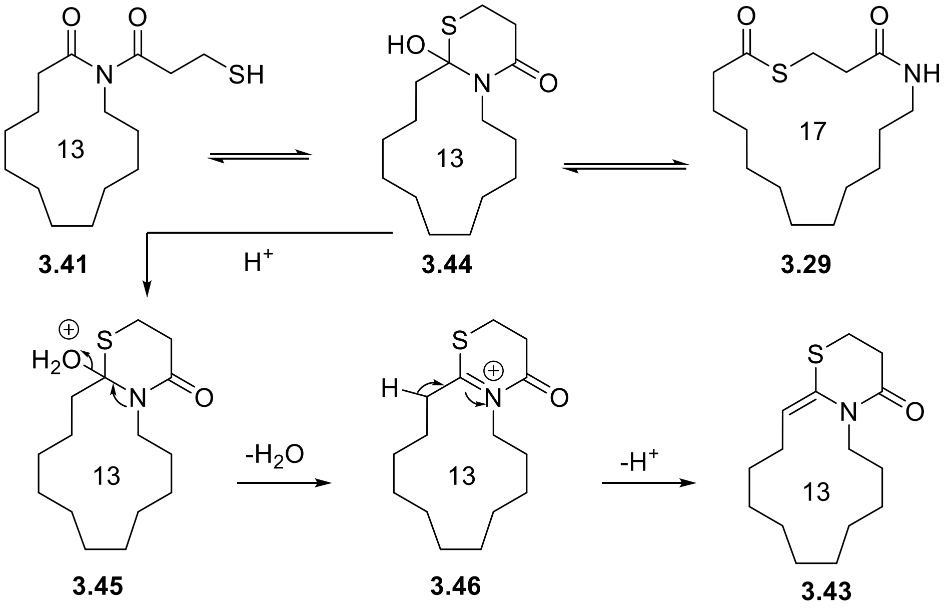
Entry	Scale/mmol of **3.42**	Acid	Scavenger reagent	Yield[b] **3.29**/%	Side products[b]
1[a]	1.9	TFA (8 equiv.)	i-Pr_3SiH (1.4 equiv.)	12	**3.41** (48%), **3.43** (7%)
2	1.9	TFA (13 equiv.)	i-Pr_3SiH (1.2 equiv.)	56	**1.210** (4%), **3.43**[c]
3	0.20	AcOH	i-Pr_3SiH (1.2 equiv.)	0	No reaction
4	0.20	HCl[d]	i-Pr_3SiH (1.2 equiv.)	0	No reaction
5	0.32	TFA[e] (1.1 equiv.)	i-Pr_3SiH (1.2 equiv.)	trace	**1.210** (3%), **3.42** (80%)
6	0.55	TFA (13 equiv.)	Et_3SiH (1.3 equiv.)	36	**1.210** (4%), **3.43** (7%)
7	0.21	TFA[e] (13 equiv.)	i-Pr_3SiH (1.2 equiv.)	44	**1.210** (24%), **3.43** (25%)
8	0.55	TFA[e] (13 equiv.)	i-Pr_3SiH (1.2 equiv.)	51	**1.210** (27%), **3.43** (12%)
9	0.37	Pd/C, H_2, EtOAc, Then $CHCl_3$ / TEA	N/A	0%	No reaction, **3.42** recovered

Unless stated, the following protocol was used for Step i) - the stated acid was added to **3.42** in DCM at RT and stirred for 3 min, before adding the scavenger reagent and stirring at RT for a further 30 min. [a] Step ii not performed. [b] Yields refer to material isolated cleanly following column chromatography. [c] **3.43** observed by TLC but not isolated. [d] 4 M in 1,4-dioxane. [e] at 0 °C.

To begin, imide **3.42** was reacted with an excess of TFA for 3 mins, followed by the addition of $^iPr_3SiH$ to trap the released trityl cation.[79] It was hoped that revealing the thiol nucleophile in this way would promote ring expansion spontaneously; however, ring expanded product **3.29** was isolated in just 12% yield, with thiol **3.41** the major product in this reaction (entry 1). In addition, a new side product **3.43** was isolated, which presumably formed *via* an acid-mediated condensation of thiol **3.41** onto the internal imide carbonyl group. In previous SuRE studies, it was found that a switch to basic reaction conditions can help promote the ring expansion step following protecting group cleavage.[67] Therefore, it was decided to investigate the effect of removing the trityl group under acidic conditions followed by stirring the reaction mixture overnight with an excess of DBU in DCM at RT was investigated (entry 2). Pleasingly, this led to a much-improved yield of the desired ring expanded product **3.29** (56%), along with minor side products. Attempts were made to further improve the yield of **3.29** by varying the silane scavenger, temperature and the acid reagents/equivalents, but none of these changes had a positive impact on the reaction outcome (entries 3–8). Qualitative evidence of trityl deprotection is observed by the rapid intense color change (due to presence of conjugated trityl cation) as acid is added to a solution of **3.42**. In entries 3 and 4 this color change was not observed, indicating that these conditions did not result in complete deprotection. An attempt to suppress side product **3.43** formation by reducing equivalents of TFA used resulted in low conversion (entry 5, 80% of starting material recovered). Reducing temperature to 0 °C also did not suppress **3.43** formation. Some evidence suggested that larger reaction scale would favour product formation. Comparing entries 7, 8 and 2, it would appear that the larger the scale of the reaction, the higher the yield of thiolactone **3.29**. However, a direct comparison cannot be used as the temperature of the reactions differ. An attempt to remove the a trityl protecting group using Pd/C hydrogenation conditions was unsuccessful with only starting material recovered (entry 9).

3.3.3 Mechanism of condensation side product 3.43 formation.

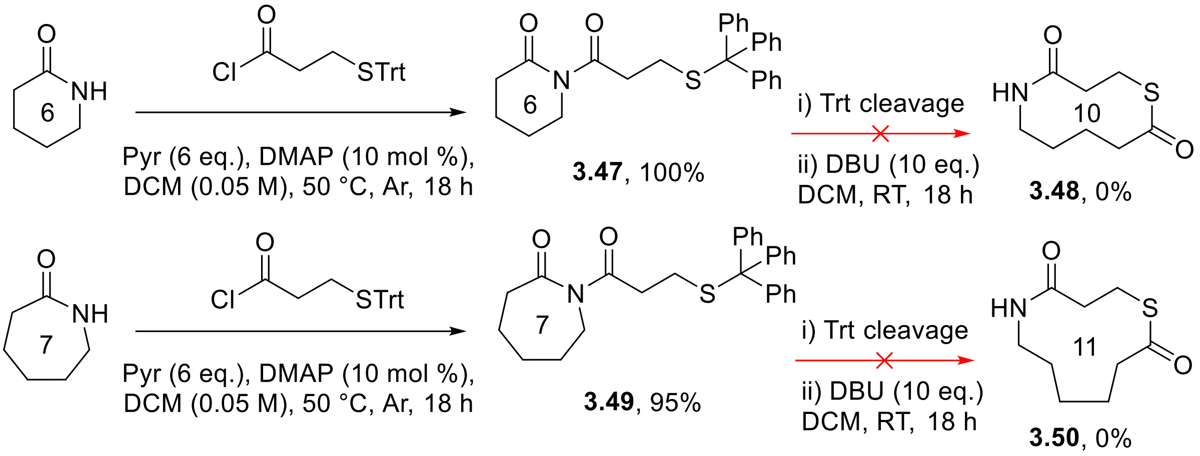
Side product **3.43** is believed to be formed by protonation of the cyclol intermediate formed (**3.44**) following deprotection to reveal the thiol (**3.41**). A condensation reaction results in the formation of **3.43** under acidic conditions (Scheme 3.11). Compound **3.43** is unstable and decomposes in $CDCl_3$ over the course of a few hours at RT. The decomposition products of **3.43** were not elucidated.



Scheme 3.11: Mechanism of **3.43** formation.

3.3.4 Attempts using smaller ring sizes

Smaller lactams were successfully acylated using this strategy, with 6- and 7-membered ring imides **3.47** and **3.49** formed in near quantitative yields. Unfortunately, the deprotection/ring expansion conditions did not result in any ring expanded product formation (Scheme 3.12). This was consistent with what had been predicted by DFT, *i.e*. that 6→10 and 7→11 ring expansions to form thiolactones are not favourable, with the RO isomers calculated to have the lowest relative Gibbs free energy.



3.47, 100%

3.48, 0%

3.49, 95%

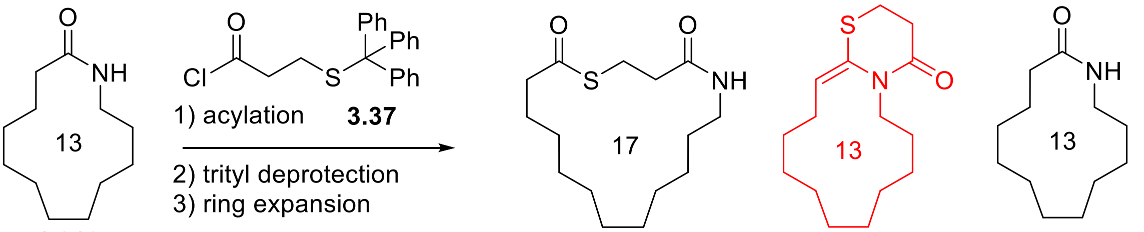
3.50, 0%

*Scheme 3.12: Acylation of 6 and 7-membered lactams with attempted deprotection/ring expansion. **3.47** and **3.49** contained trace impurities, mainly 3-(tritylthio)propionic acid **3.36**, see experimental data chapter for details.*

3.3.5 Consecutive reaction step approach

An attempt to form **3.29** over 3 steps with two chromatographic purifications (the first following acylation to form **3.42** [step 1, Scheme 3.13] and the second following ring expansion [step 3, Scheme 3.13]) was successful resulting in a 34% yield for **3.29** and a 21% yield of recovered laurolactam **1.210** (Scheme 3.13, trial #1). A procedural change for a second attempt involved shortened reaction time for the acid chloride formation (15 min as opposed to the normal 60 min) and with 3 consecutive steps performed with just one chromatographic purification (following step 3, Scheme 3.13, trial #2) led to an improved yield of **3.29** (47% over the 3 steps).

It has been postulated that decomposition of the acid labile Trt group on the acyl chloride **3.37** may occur during its synthesis during which HCl is generated. Therefore, this procedural change involving a shorter duration for the acid chloride formation (from 1 h to 15 mins), as well as leaving the flask on high vacuum for a shortened 30 min, and this is believed to beneficial for the synthesis of the trityl protected acid chloride **3.37**.



1.210

Trial #1: 2 chromatographic purifications **3.29,** (34%, 3 steps) **3.43,** (observed) **1.210,** (21%)

Trial #2: 1 chromatographic purification **3.29,** (47%, 3 steps) **3.43,** (9%) **1.210,** (observed)

Scheme 3.13: 3 consecutive steps to 24b with one chromatographic purification. Trial #2 performed by Dr Will Unsworth.

3.3.6 Summary of S-trityl strategy

There were several advantages to the trityl protecting group strategy compared with S-Ac. First, the use of an acid cleavable protecting group eliminates undesired nucleophilic attack of the imide observed during thioacetate deprotection. Secondly, trityl protected 3-(tritylthio) propanoic acid (**3.36**) is commercially available. Finally, the main by-product formed after deprotection is triphenylmethane, a non-polar unreactive compound which is easily removable using column chromatography.

Some disadvantages must also be considered however. A key consideration is that the *N*-acylation step using 3-(tritylthio) propanoic acid (**3.36**) is capricious and was sometimes unsuccessful. The trityl protected acid chloride may not be completely stable in the acidic conditions required for its synthesis, particularly on large scales, and this was a likely root cause of the inconsistent reaction outcomes. This may be addressed in part by shortening reaction times used to generate the acid chloride. But even so, repeating the acylation, deprotection/ring expansion sequence has often resulted in inconsistent yields of the desired product. Finally, the elimination side-product (**3.43**) forms under the strongly acidic conditions required for deprotection, as well as significant amounts of the regenerated lactam, which negatively impacted the reaction yields.

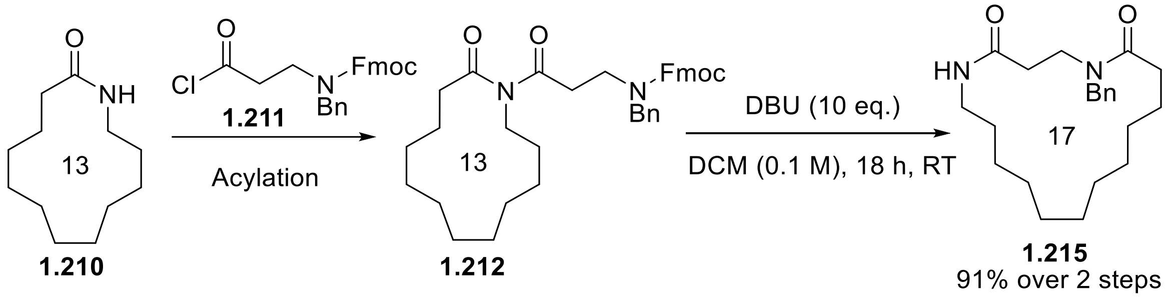
Overall, the trityl protecting group strategy provided an improvement in terms of yields compared with the original thioacetate group approach. This approach addressed a central issue with thioacetate deprotection, namely that of unselective nucleophilic attack. Unfortunately, the trityl strategy also introduced a new set of challenges. This led to the decision to explore another base labile protecting group, more similar to what had been implemented in SuRE chemistry in the past.

3.4 S-Fluorenylmethyl protecting group

Both the S-acetate and S-trityl protecting group strategies were utilized successfully in the synthesis of thiolactone macrocycles. The acetate protecting group required a nucleophile and basic conditions for deprotection, whereas the trityl strategy required acidic conditions to cleave the trityl group followed by basic conditions to promote ring expansion. In order to improve reaction yields a new protecting group was sought that would require neither a nucleophilic reagent (leading to unselective attack, as seen in the acetate strategy) nor acidic conditions (leading to the condensation side product formation of **3.43**, as seen in the trityl strategy). Neutral hydrogenation conditions had been used to successfully in the past to deprotect benzyl protected alcohols. However, this approach was discounted, as it was thought that deprotection to reveal a thiol may potentially lead to poisoning of the palladium catalyst required for hydrogenolysis.

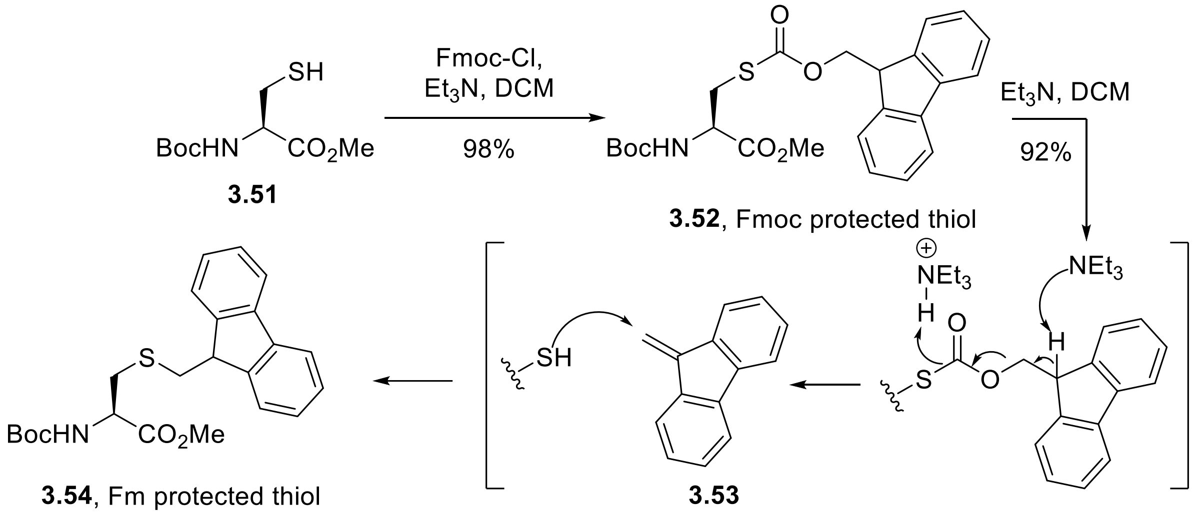
3.4.1 Base cleavable protecting groups

Some of the most efficient ring expansions reported by the Unsworth Group utilize 9-fluorenylmethyloxycarbonyl (Fmoc) protected β-alanine derivatives. These reactions operate *via* a two-step procedure, starting with an acylation reaction to form an imide (using the pyridine/DMAP conditions described earlier), followed by a base induced deprotection and ring expansion by stirring in DBU (10 eq.) over 18 h. The appeal of this approach is that a non-nucleophilic base such as DBU is all that is needed to induce protecting group cleavage and ring expansion. Yields for these reactions are typically around 90% over two steps (Scheme 3.14).



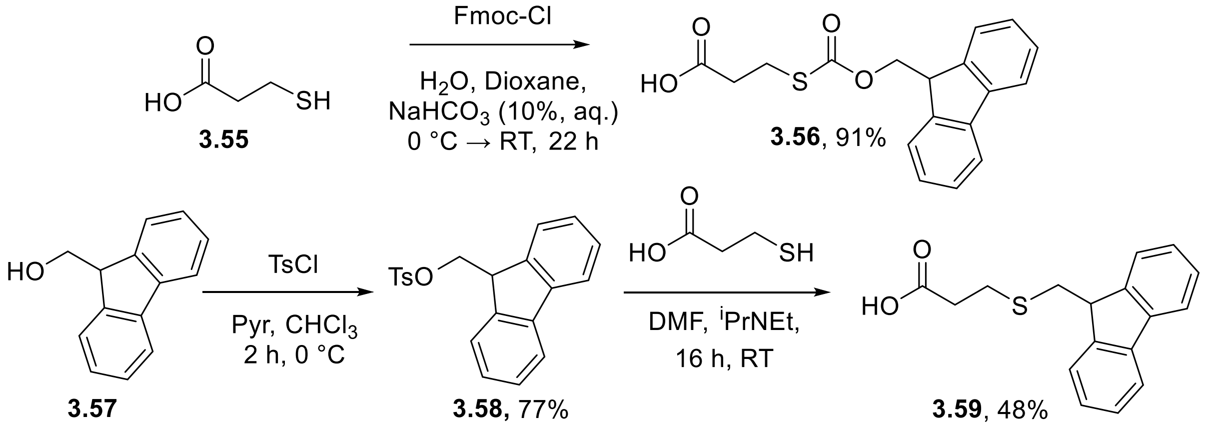
Scheme 3.14: Fmoc protected amino acids are used in efficient acylation and deprotection/ring expansion reactions of lactams. Reaction performed by Dr Stephens.

The aim was to investigate whether the Fmoc protecting group strategy could be applied to thiol-tethered carboxylic acids for use in ring expansion chemistry. In the field of peptide chemistry there is precedent demonstrating that Fmoc protection of cysteine thiols is possible, although it is quite rare.[80] Thiols protected using Fmoc are significantly more labile than Fmoc protected amines. Under weakly basic conditions, Fmoc protected thiols (SFmoc, *e.g.* **3.52**) degrade easily, and often are converted into 9-fluorenylmethyl protected (Fm) thiols, with this group itself an alternative protecting group for thiols (**3.54**) (Scheme 3.15).[81]



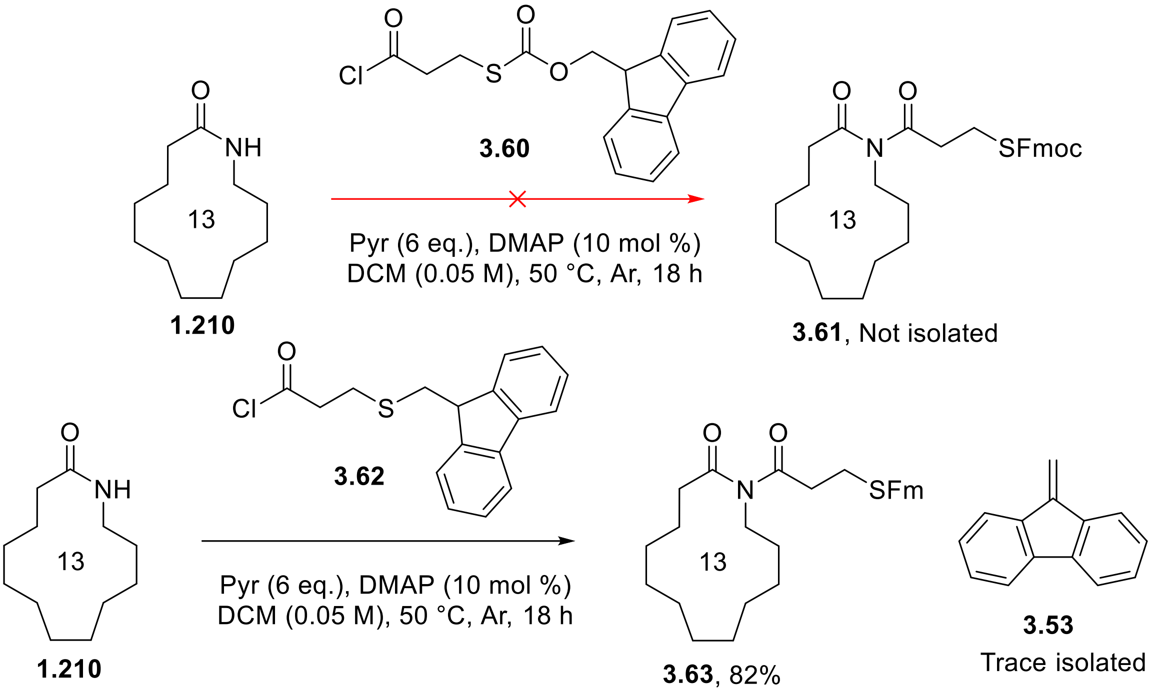
Scheme 3.15: Fmoc protected thiols are unstable to basic conditions and can be readily converted into Fm protected thiols.

Fm protected thiols are more stable than their Fmoc analogues, but can still be deprotected by treating with base, in much the same way as Fmoc protected amines under broadly similar conditions, for example, using piperidine or DBU at RT.[82] Therefore, it was decided to synthesize both *S*-Fmoc-3-thiopropionic acid (**3.56**) and *S*-Fm-3-thiopropionic acid (**3.59**) to test them in SuRE reactions. Each was synthesized following literature conditions as summarized in Scheme 3.16.[81,82]



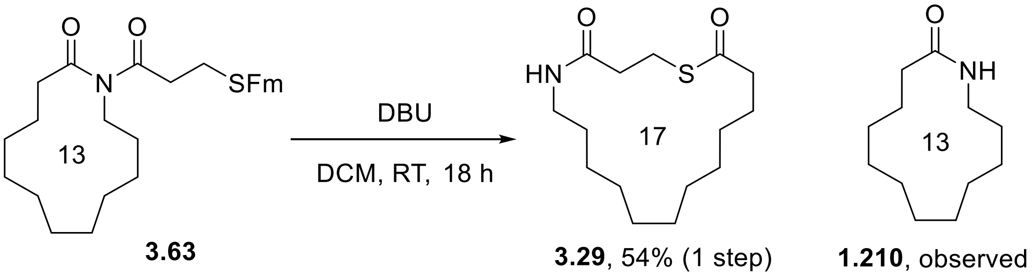
Scheme 3.16: Preparation of Fmoc and Fm protected thiol-tethered carboxylic acids.

The synthesis of both *S*-Fmoc-3-thiopropionic acid (**3.56**) and *S*-Fm-3-thiopropionic acid (**3.59**) were successful. Unfortunately, the acylation reaction using **3.60** to generate Fmoc protected **3.61** failed using the standard *N*-acylation conditions. A clean compound could not be isolated after repeated column chromatography. However, more positively, using Fm protected **3.62** the acylation was successful with the desired imide (**3.63**) isolated in 82% yield. Trace dibenzofulverene (**3.53**) was also isolated.



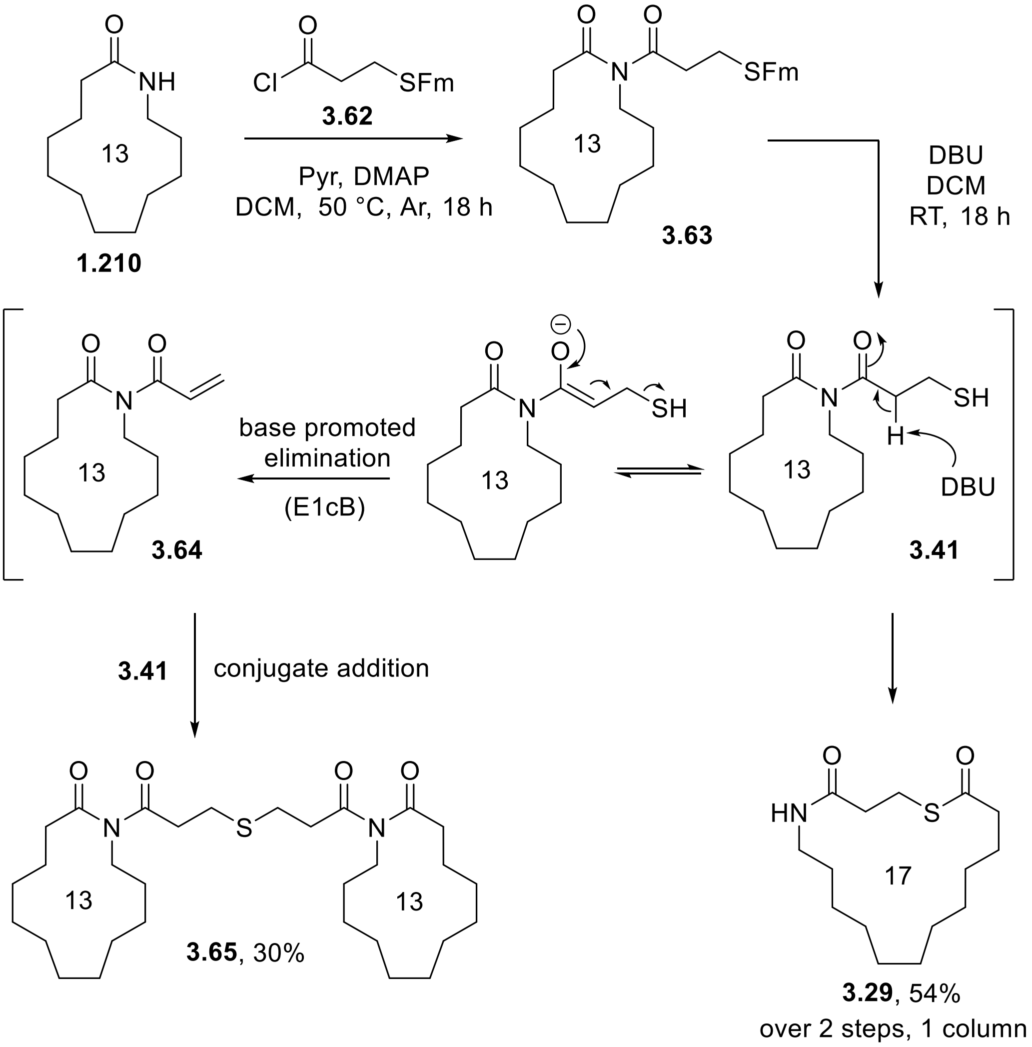
Scheme 3.17: Acylation using Fmoc and Fm protected thiol-tethered carboxylic acids.

Having established that the Fm protecting group was viable for use with the standard acylation conditions, attention turned to the deprotection/ring expansion step. Pleasingly, this step proceeded as planned, with the desired 17-membered macrocycle isolated in 54% yield (Scheme 3.18). This yield was comparable to the highest isolated yields observed using the trityl protected thiol-tethered carboxylic acid strategy described earlier (56% of **3.29** isolated using trityl strategy). Laurolactam was also observed by TLC, suggesting that the imide (**3.63**) might be unstable under basic deprotection conditions. In general, SuRE reactions are performed without isolation of the intermediate imides where possible.



*Scheme 3.18: Deprotection/ring expansion of Fm protected imide **3.63**.*

After some optimization, it was decided to conduct the acylation and deprotection/ring expansion steps of the reaction without intermediate purification of the imide by column chromatography. Using this two-step procedure, the 17-membered macrocycle (**3.29**) was isolated in 54% yield over 2 steps. An additional symmetrical sulfide side-product (**3.65**) was also observed and isolated in 30% yield. A plausible mechanism for its formation is proposed below in Scheme 3.19.



*Scheme 3.19: Highest yielding result of two-step acylation and deprotection/ring expansion using Fm-protected 3-mercaptopropionic acid and laurolactam. A mechanism for the formation of disubstituted side-product **3.65** is proposed.*

3.4.2 Summary of Fm protecting group

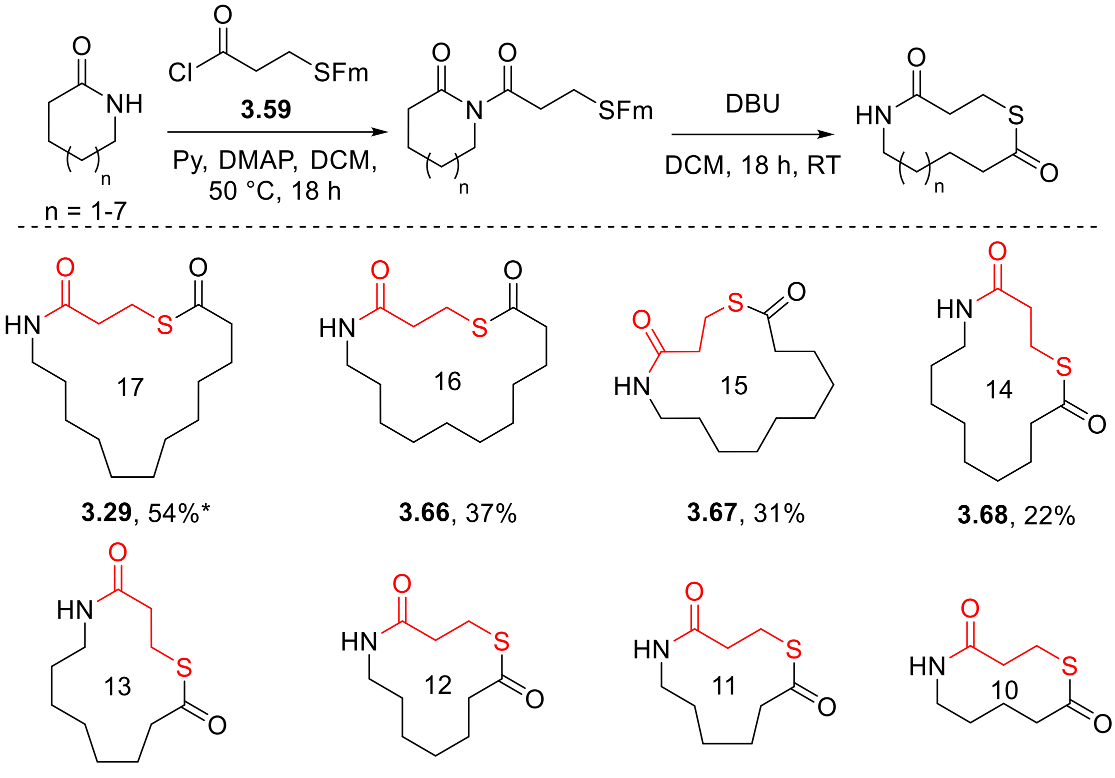
The Fm protecting group strategy has several benefits. The deprotection and ring expansion conditions are one and the same, whereas trityl protected thiols require two steps to be performed (under acidic and basic conditions) in order to achieve deprotection and ring expansion. *N*-Acylation using Fm protected thiol-tethered carboxylic acid was also more reliable in our hands when compared with its trityl protected analogue.

Some disadvantages must also be considered however. A two-step synthesis is required to generate Fm protected thiol-tethered carboxylic acid, although this can be done without column chromatography and the synthesis can be performed on a large scale. Dibenzofulverene (**3.53**) is formed as a by-product, which can make isolation of pure ring expanded products such as **3.29** more difficult. Furthermore, it is believed that **3.53** may reversibly form a polymer with atmospheric oxygen.[83] For instance, it is observed in at least trace amounts in every fraction isolated following column chromatography. Strong alkaline solutions are required to remove this otherwise insoluble polymer from glassware after reactions.

The Fm protecting group strategy produced the highest yields of all the thiol protecting groups trailed, with a yield of 54% obtained for this two-step reaction to form ring expanded thiolactone **3.29**. Comparing all three protecting group strategies, (acetate, trityl and 9-fluorenylmethyl), there are clear advantages and disadvantages to each. S-Fm and S-trityl provided comparable yields of around 50%. Both of these strategies also suffered from side product formation from unproductive pathways (**3.43** and **3.65**). As S-Fm provided the most consistent results (in comparison to the problems with *N*-acylation using S-trityl propionic acid) and was similar to the Fmoc strategy that was used very successfully with amines, it was selected as the preferred protocol moving forward to the ring size screen and substrate scoping phase of work.

3.5 Ring size screen

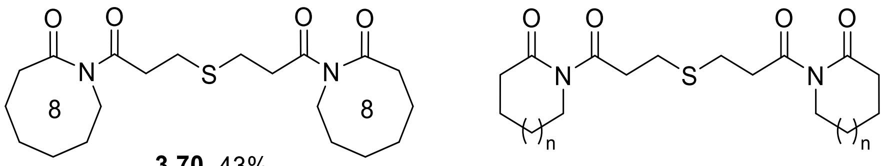
With the optimized procedure in hand, attention turned to applying this chemistry to a ring size screen. Lactams from 13- to 6-membered in size were all subjected to the same acylation/ring expansion protocol using 3 equivalents of Fm protected **3.59**. For the larger rings, the desired 17- to 12-membered ring expanded products were isolated successfully, in 54–15% yield, (Scheme 3.20). However, the two smallest ring systems, 11-membered (**3.50**) and 10-membered (**3.48**) were not isolated under the same conditions.



3.29, 54%*
3.66, 37%
3.67, 31%
3.68, 22%
3.69, 47%
3.23, 15%
3.50, 0%
3.48, 0%

*Scheme 3.20: Ring size scope of sulfur ring expansion. Rings from 17- to 12-membered in size successfully produced. *For the 13 ⟶17 membered ring expansion, 6 equivalents of acid chloride were added in total, in two portions of 3 equivalents.*

This demonstrates that 13- to 8-membered lactams can undergo a 4-atom ring expansion to form novel thioester containing products, with yields ranging from 15–54% over the overall two-step sequence. These results agree with the key findings of the DFT study described earlier, which predict that 4-atom ring expansions starting from an 8-membered thiol to form a 12-membered ring expanded product are favourable. This is what we term the 'switch on' point for the reaction, *i.e.* the smallest ring size in which ring expansion can be observed. The analogous examples starting from the 7- and 6-membered thiols were predicted to favour the RO isomers, *i.e.* ring expansion is not favoured. Once again, the DFT prediction agrees with the experimental findings as 11- and 10-membered thioesters (**3.50** and **3.48**) could not be isolated. In the case of the smaller ring sizes (6–8-membered thiols), symmetrical sulfide side products (**3.71**–**3.72**) were also observed, suggesting that an unproductive mechanistic pathway is occurring, as shown in scheme 3.21 below.

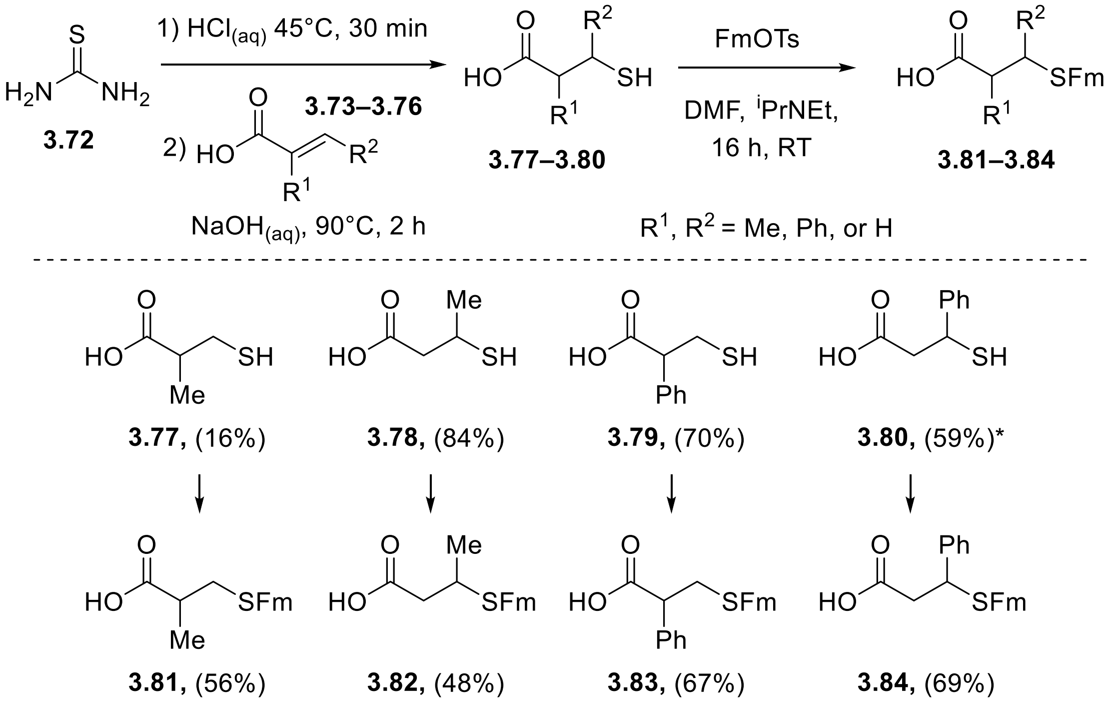


3.70, 43%
3.71, n = 1-2, Observed by MS, NMR

Scheme 3.21: Selection of symmetrical sulfide side-products observed during ring size screen.

3.6 Branched thiol-tethered carboxylic acid derivatives

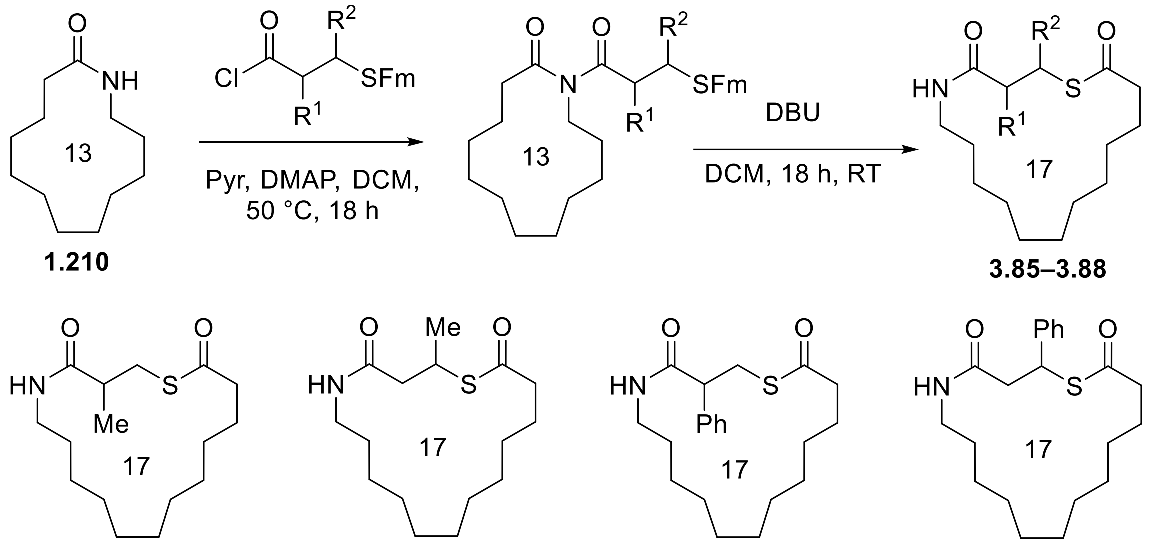
In order to further expand the scope of 4-atom sulfur ring expansion, various branched Fm protected β-thiol-tethered carboxylic acids were prepared and tested. Thiols **3.77**–**3.80** were synthesized from the corresponding methyl or phenyl substituted α,β-unsaturated acids (**3.73**–**3.76**) following conjugate addition reaction with thiourea (**3.72**). This was followed by Fm-protection of the thiol, which proceeded in moderate to good yields for **3.81** to **3.83**. The only example that did not go smoothly was **3.84**; an initial attempt to synthesize thiol **3.80** yielded a 1:1 molar ratio mixture of *trans*-cinnamic acid and **3.80** (Scheme 3.22) using the standard conditions. Therefore, in a subsequent attempt the reaction temperature was raised to 120 °C instead of 90 °C. This led to an improvement, but after workup, some *trans*-cinnamic acid still remained, with **3.80** and *trans*-cinnamic acid isolated in a 4:1 molar ratio. This mixture was carried forward without further purification to the Fm-protection step, and pleasingly pure Fm-protected **3.84** was isolated following protection with no contamination of the previous trans cinnamic acid impurity.



*Scheme 3.22: Synthesis of branched thiol-tethered carboxylic acid derivatives. ****3.80*** *isolated as a 4:1 mixture with starting material* trans-*cinnamic acid.*

With the branched Fm-protected thiol tethered carboxylic acids in hand, efforts turned to using these materials in ring expansion reactions. The established acylation and ring expansion conditions were used to ring expand laurolactam **1.210** using **3.81**–**3.84** as the linear unit. Four different branched 17-

membered thiolactones were synthesized (**3.85**–**3.88**) in 58–8% yield, with a methyl or phenyl substituent in the α- or β-position with respect to the lactam amide (Scheme 3.23).



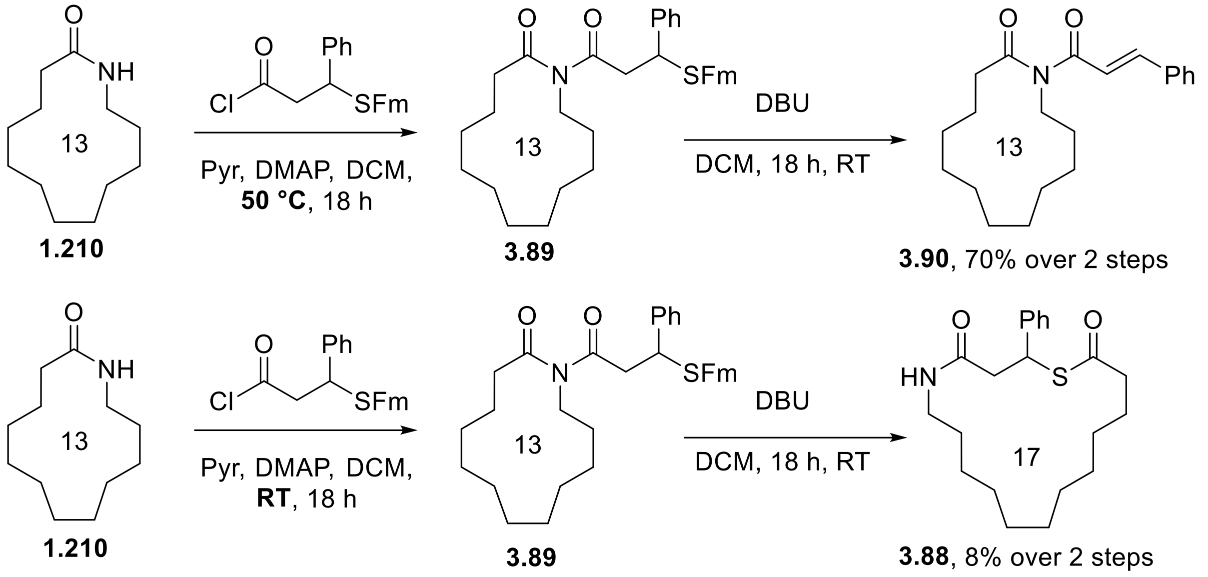
1.210

3.85–3.88

3.85, 58% over 2 steps **3.86**, 58% over 2 steps **3.87**, 29% over 2 steps **3.88**, 8% over 2 steps

Scheme 3.23: Synthesis of branched thiol-tethered carboxylic acids for use in ring expansion reactions.

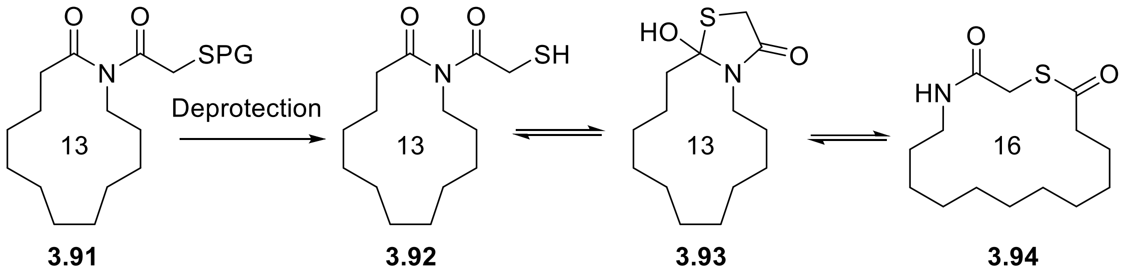
Some problems were encountered during the synthesis of **3.88**. On the first attempt, a significant quantity of a cinnamyl side product **3.90** resulting from base-promoted SFm-elimination was isolated as the major product (Scheme 3.24, top). Repeating the reaction with milder acylation conditions alleviated undesired elimination to some degree and the thiolactone **3.88** product was isolated, albeit in only 8% yield over the two steps. It was concluded that branching is well tolerated for methyl substituents in both alpha and beta positions, whereas phenyl substituents are less well tolerated. It was also concluded that in the case of the synthesis of **3.88**, the standard acylation conditions, which involve heating to 50 °C, promote competing elimination of the S-Fm group. Elimination is favoured in this instance as it forms a conjugated cinnamyl moiety in **3.90**, which would be particularly favourable at elevated temperatures for entropic reasons (Scheme 3.24).



*Scheme 3.24: Synthesis of **3.88** and side product **3.90**.*

3.7 Attempted 3-atom ring expansions using protected thioglycolic acid derivatives

A logical extension of the sulfur ring expansions reported was to attempt a ring expansion using a protected thioglycolic acid. This would lead to a 3-atom ring expansion if successful.



Scheme 3.25: Proposed 3-atom ring expansion using thioglycolic acid derivatives.

Variants of thioglycolic acid (**3.95**) representing each protecting group optimized so far were prepared or purchased (Figure 3.2).

3.95 commercial thiogylcolic acid

3.96 commercially availiable

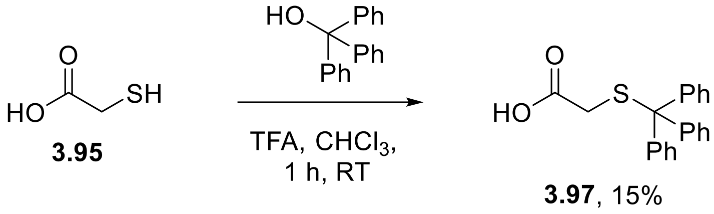
3.97 synthesized

3.98 synthesized

Figure 3.2: Thioglycolic acid and various S-protected variants.

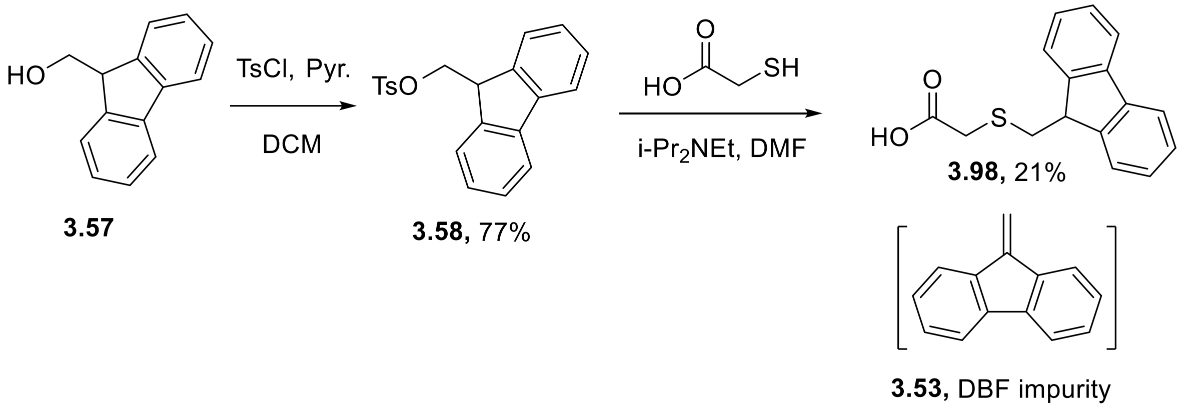
Trityl protected **3.97** and Fm protected **3.98** needed to be synthesized. The S-Ac derivative **3.96** is available commercially and was used as supplied. The synthesis of S-trityl **3.97** (Scheme 3.26) and S-

Fm **3.98** (Scheme 3.27) are outlined here. 2-(Tritylthio)acetic acid **3.97** was synthesized *via* trityl protection of thioglycolic acid. Thioglycolic acid and triphenylmethanol were stirred in chloroform with TFA for 1 hour. Purification *via* repeated recrystallization was successful in removing persistent triphenylmethanol. Trityl protected **3.97** was isolated in 15% yield with ^{1}H NMR data consistent with those previously reported.[84]



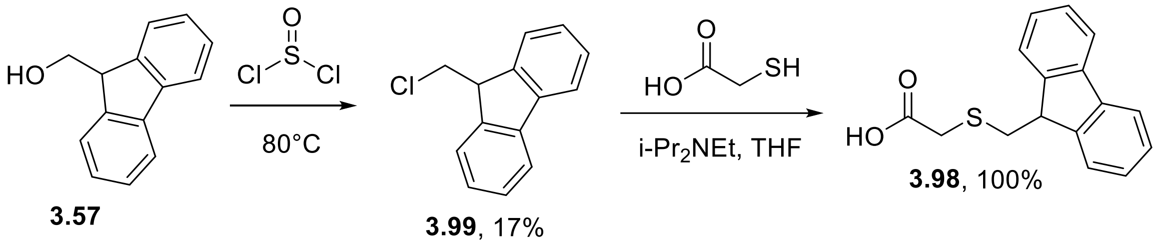
*Scheme 3.26: Synthesis of trityl protected thioglycolic acid **3.97***

Next, the synthesis of S-Fm-thioglycolic acid (**3.98**) was performed using two different methods. The first using the same procedure used to protect 3-mercaptopropionic acid; *via* Fm tosylate (**3.58**) followed by an S_N2 reaction in DMF (Scheme 3.27). This approach was successful, however the desired S-Fm-thioglycolic acid (**3.98**) isolated following aqueous workup was not pure, with significant amounts of the impurity dibenzofulvene (DBF) **3.53** remaining. The approximate yield of the S_N2 step was 21%, accounting for the impurity.



*Scheme 3.27: Synthesis of S-Fm thioglycolic acid **3.98** via tosylate **3.58.***

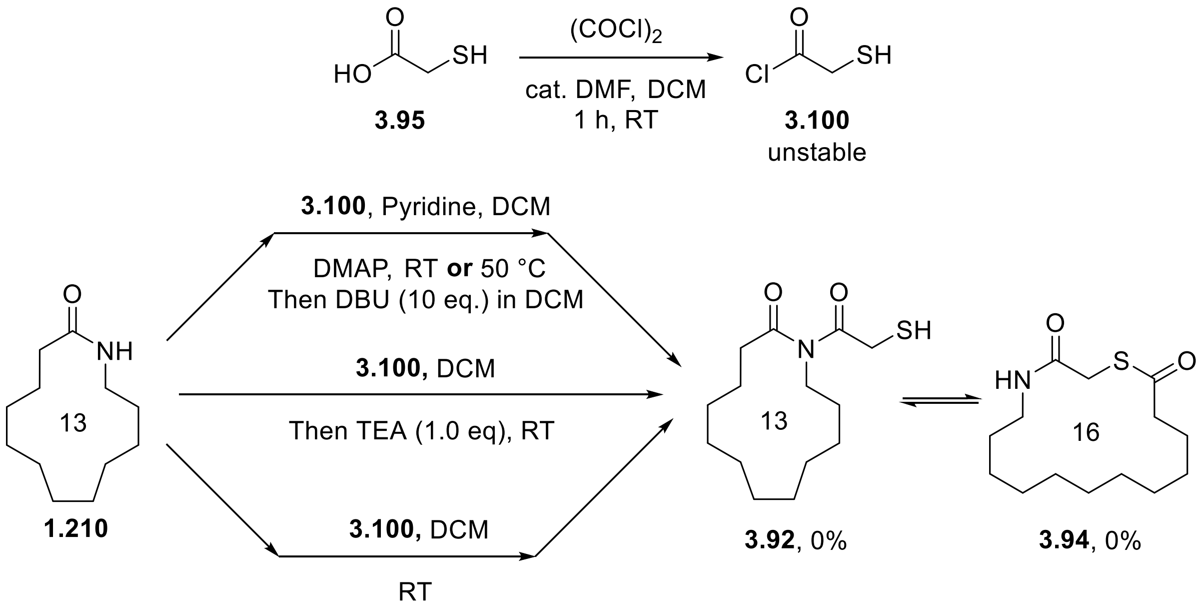
In an alternative approach, 9-fluorenylmethyl chloride (**3.99**) was synthesized from the alcohol (**3.57**) *via* reflux in neat thionyl chloride (Scheme 3.28). Then, an S_N2 reaction using chloride **3.99** and thioglycolic acid furnished the desired S-Fm-thioglycolic acid (**3.98**) in quantitative yield. An improved base/acid aqueous workup was used to remove DBF **3.53** from contaminated **3.98** with excellent results. With all the protected thioglycolic acids in hand, attention turned to attempting 3-atom ring expansions to form thiolactones.



*Scheme 3.28: Synthesis of S-Fm thioglycolic acid via chloride **3.99**.*

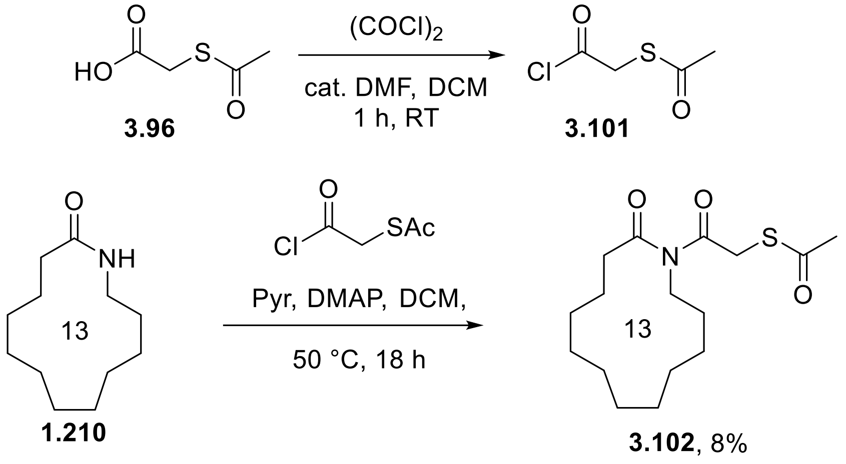
3.7.1 Attempted thioglycolic acid derivative acylation and 3-atom ring expansions

Before attempting the S-protected thioglycolic acid variants in acylation reactions, a protecting group free approach was tested briefly. Three acylation/ring expansion reactions using thioglycolic acid were performed with slightly varying conditions, all unsuccessfully. It is highly probable that acid chloride **3.100** is unstable (Scheme 3.29). Neither thiol **3.92** nor thiolactone **3.94** were observed.



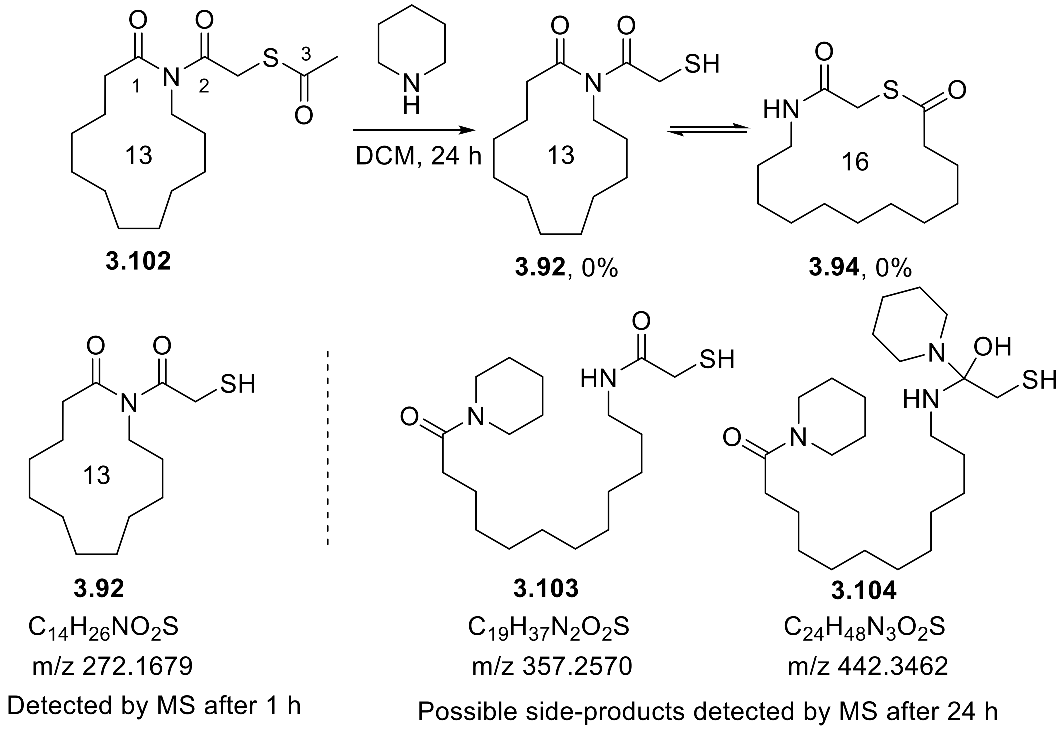
Scheme 3.29: Attempted acylation using unprotected thioglycolic acid.

Moving on to the protected variants, beginning with acetate protected thioglycolic acid (**3.96**), the acylation was performed under standard conditions and found to be successful but low yielding with the imide (**3.102**) isolated in just 8% yield (Scheme 3.30).



Scheme 3.30: Acylation of laurolactam using S-acetyl thioglycolic acid.

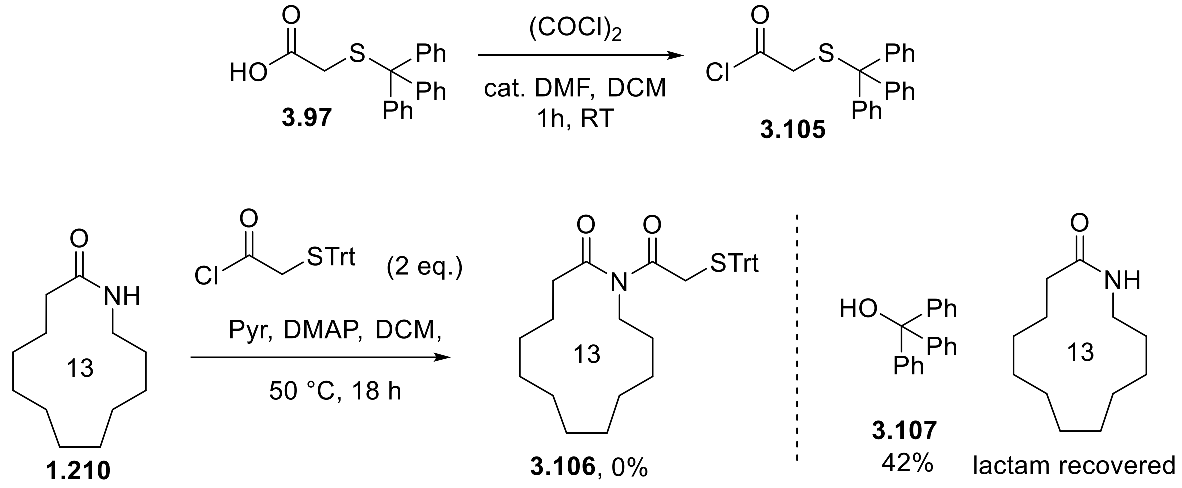
Imide **3.102** was subjected to piperidine deprotection conditions, as previously described in section 3.2. No product thiolactone **3.94** could be isolated, however the molecular ion peak for the thiol (**3.92**) or ring expanded product (**3.94**) was detected after 1 hour when analyzed using mass spectrometry. At 24 hours, there was evidence by mass spectrometry that piperidine caused ring opening of the lactam (attack at carbonyl 1, Scheme 3.31), based on molecular ion peaks detected at m/z 357.2570 and 442.3462; suggested structures **3.103** and **3.104** are proposed in Scheme 3.31.



Scheme 3.31: Attempted ring expansion using acetate protected thioglycolic acid derived imide.

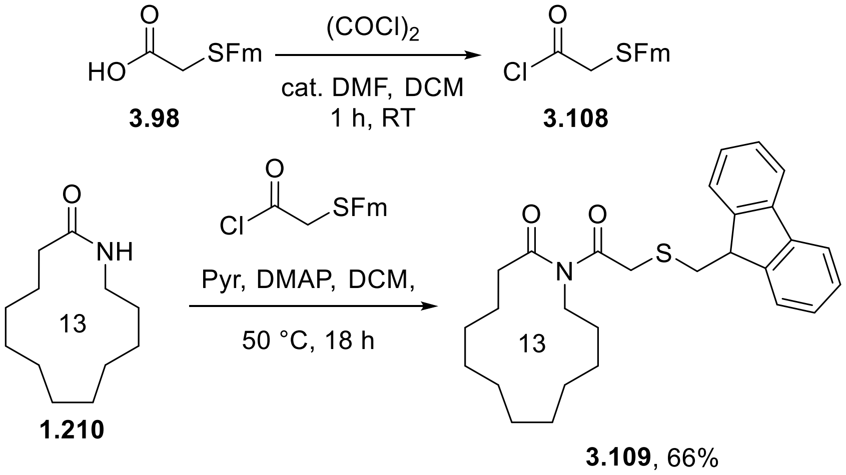
The ring expansion was unsuccessful. Due to the lack of specificity of nucleophilic attack on the three available carbonyls of **3.102** with this protecting group strategy (see section 3.2), it was decided to progress to alternative protecting group strategies, the next being S-trityl protected thioglycolic acid.

An attempted acylation of laurolactam with trityl protected **3.97** was unsuccessful in forming **3.106**, with triphenylmethanol (**3.107**) isolated in 42% yield (with respect to the starting material acid after column chromatography). A second attempt of this acylation was followed by aqueous work up with 10% aq. HCl with only laurolactam recovered following extraction (Scheme 3.32).



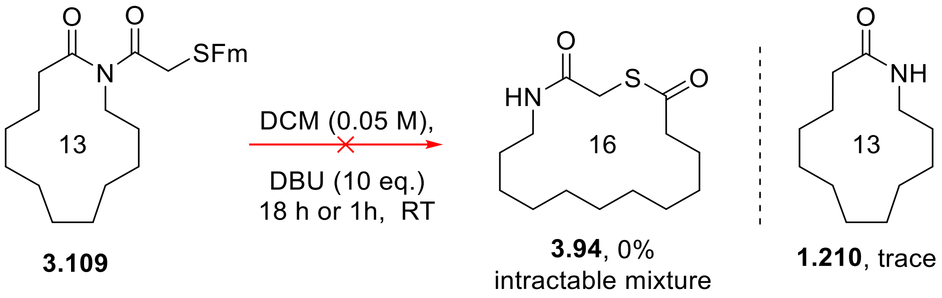
Scheme 3.32: Attempted acylation of laurolactam using tritylthioacetic acid ***3.97****.*

The synthetic difficulties of 2-(tritylthio)acetic acid (**3.97**) synthesis and acylation led to the investigation of one last protecting group for thioglycolic acid, with the *N*-acylation attempted using Fm-protected thioglycolic acid (**3.98**) and our standard pyridine/DMAP conditions. Following column chromatography the product imide **3.109** was formed in 66% yield (Scheme 3.33).



Scheme 3.33: Acylation of laurolactam using S-Fm thioglycolic acid.

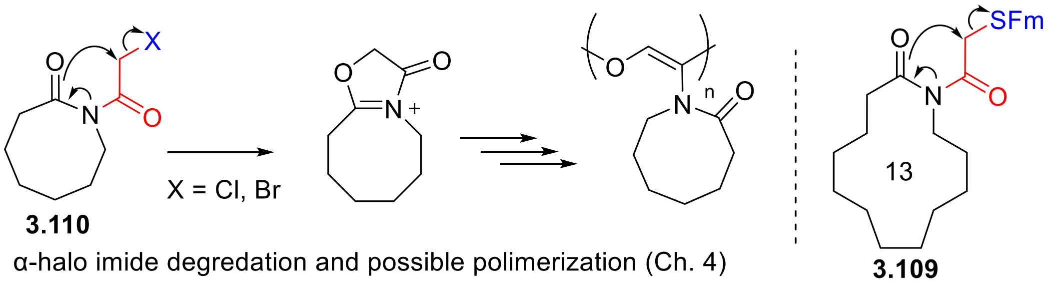
The ring expansion of **3.109** was therefore attempted, but upon reaction with DBU in DCM overnight an intractable mixture was formed. The solution was observed to turn black immediately upon addition of DBU. Repeating the reaction on a larger scale and with a shortened reaction time was done with the hope that some of the desired thiolactone or thiol could be isolated before degradation could occur (Scheme 3.34). The second attempt was also unsuccessful. A trace amount of laurolactam **1.210** was isolated (<5 mg) following chromatography with the remainder of the reaction mixture best described as an intractable mixture. Efforts to perform 3-atom ring expansions to form thiolactones were ceased as a result.



Scheme 3.34: Attempted ring expansion using S-Fm protected thioglycolic acid derived imide

3.7.2 Possible degradation pathway of 3-atom ring expansion attempts to form thiolactones

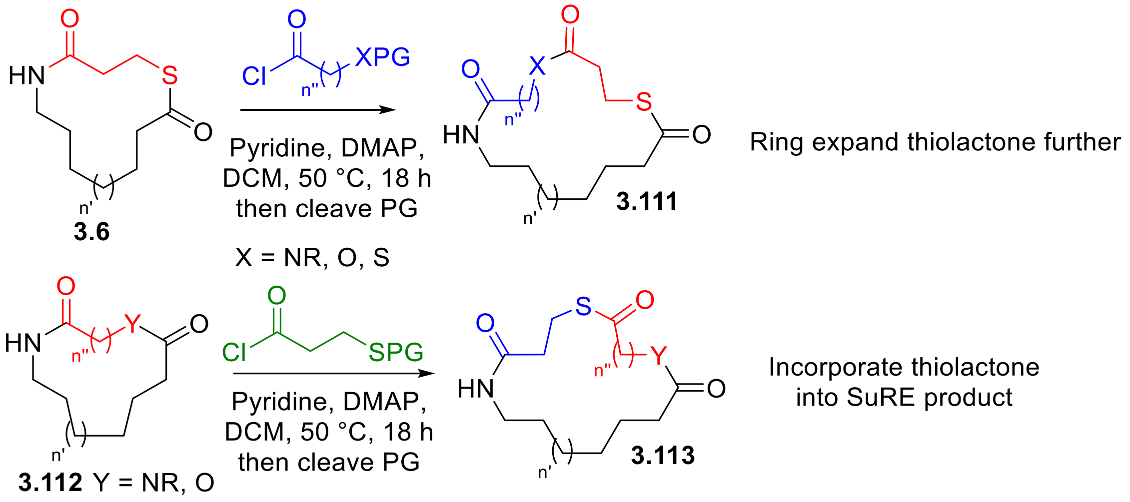
The 3-atom ring expansion using a thiol-tethered carboxylic acids was unsuccessful. None of the desired 16-membered thiolactone **3.94** was isolated in any of the reaction attempts, with several protecting groups trialled. Observations following the reaction described in Scheme 3.34 suggest the imide **3.109** degrades when exposed to basic conditions. This may relate to similar problems encountered during the synthesis of alpha halo imides (which will be discussed in Chapter 4). The synthesis of these imides **3.110** was also problematic, with literature precedent suggesting that alpha halo imides polymerize at ambient temperature over time. While SFm is not as good a leaving group as Cl or Br, we postulate that a similar process can still occur with compound **3.109**, and is accelerated on the presence of base such as DBU (Scheme 3.35).



*Scheme 3.35: Proposed degradation pathway of thioglycolic imides such as **3.109**.*

3.8 Successive ring expansion to form thiolactones

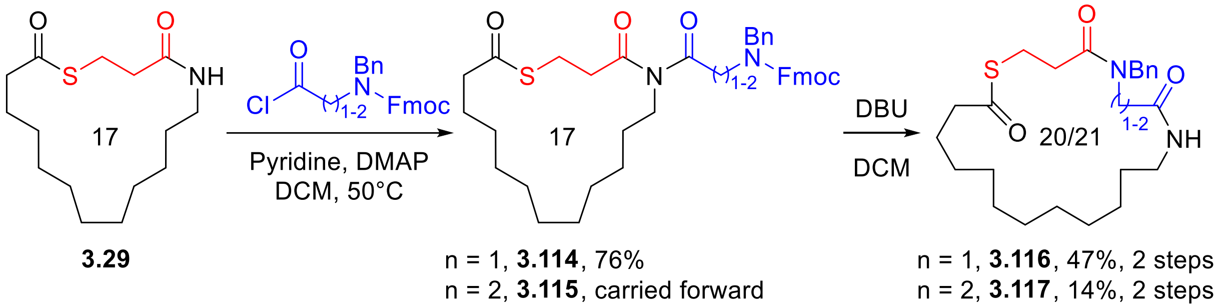
Alongside efforts to study the scope of sulfur ring expansion to expand simple lactams, studies to investigate successive ring expansion to form thiolactone-containing macrocycles were also undertaken. The aim was to incorporate sulfur-based ring expansions into the existing nitrogen- and oxygen-based SuRE methodologies, as well as to attempt a successive sulfur ring expansion to form a macrocycle containing two thiolactones (Scheme 3.36).



Scheme 3.36: Two approaches to SuRE incorporating thiolactones. Top: Thiolactone further expanded using SuRE. Bottom: Lactam or lactone expanded to incorporate a new thiolactone into macrocycle.

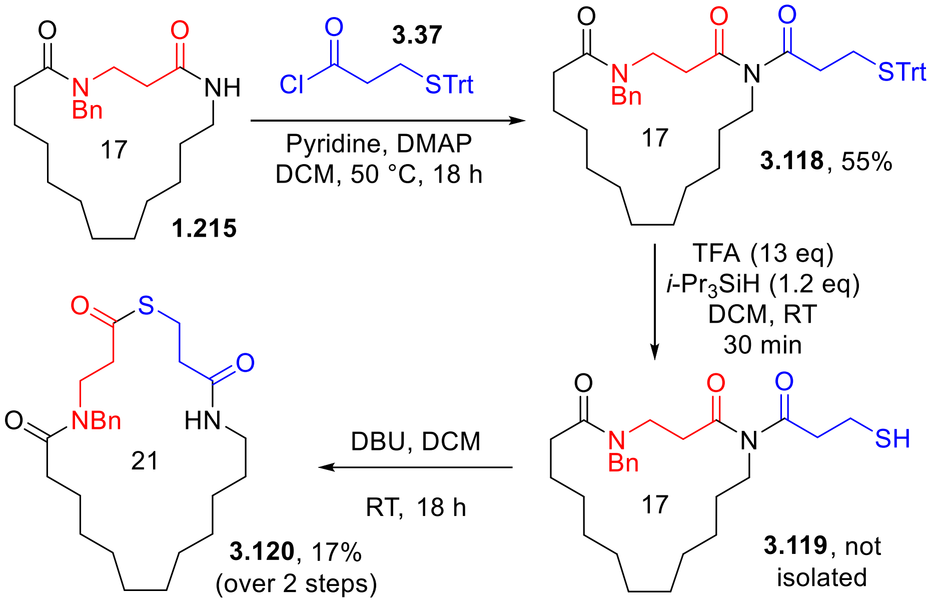
3.8.1 Early proof of concept for thiolactone-containing successive examples

To start, it was decided to test whether thiolactones prepared *via* the SuRE methods discussed in the chapter can themselves be acylated and undergo a 2nd SuRE reaction. Thus, previously expanded thiolactone products, such as **3.29**, were subjected to *N*-acylation and deprotection/ring expansion conditions using various linear fragments. It was demonstrated that **3.29** can be acylated using an α- or β-amino acid derivative using standard SuRE conditions in good yields. This is then capable of undergoing a second ring expansion to form a 20-membered macrocycle (**3.116**) in 47% yield and a 21-membered ring **3.117** in 14% yield over two steps (Scheme 3.37). Therefore, this demonstrates that cyclic products that have been previously expanded with sulfur are able to be expanded a second time.



Scheme 3.37: Successful successive ring expansion examples utilizing thiolactones.

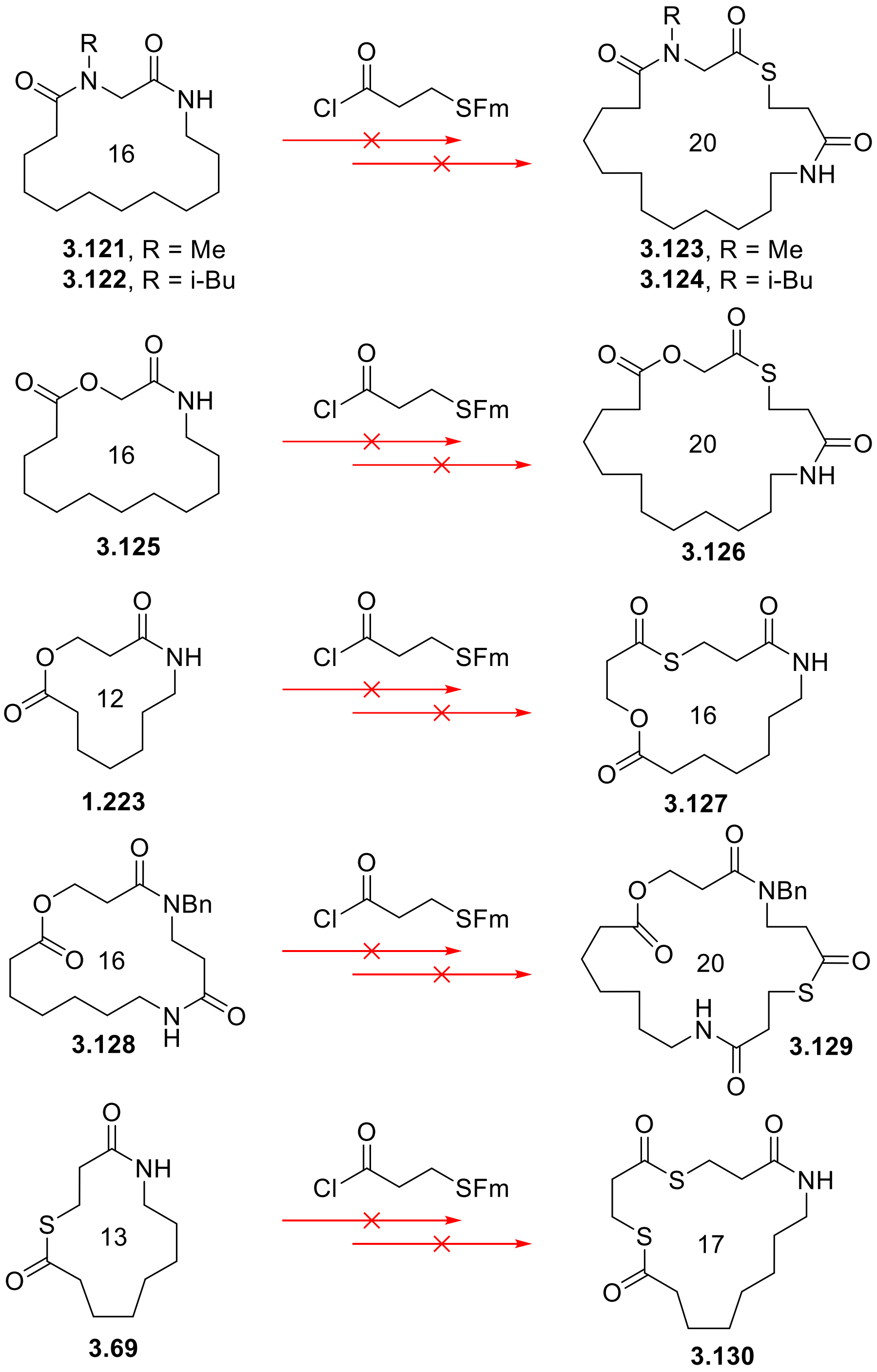
Next, it was shown that lactams that have been previously expanded using amino acid chlorides (*e.g.* **1.215**, can be acylated using thiol-tethered carboxylic acid chlorides, and subsequently ring expanded a second time to install a thiolactone; for example, 21-membered (**3.120**) was formed in this way, albeit in modest yield overall (Scheme 3.38). This example serves as a proof of concept that successive ring expansions to form thiolactone containing macrocycles are also viable.



Scheme 3.38: Successful successive ring expansion example with thiolactone ***3.120*** *formed in the final step.*

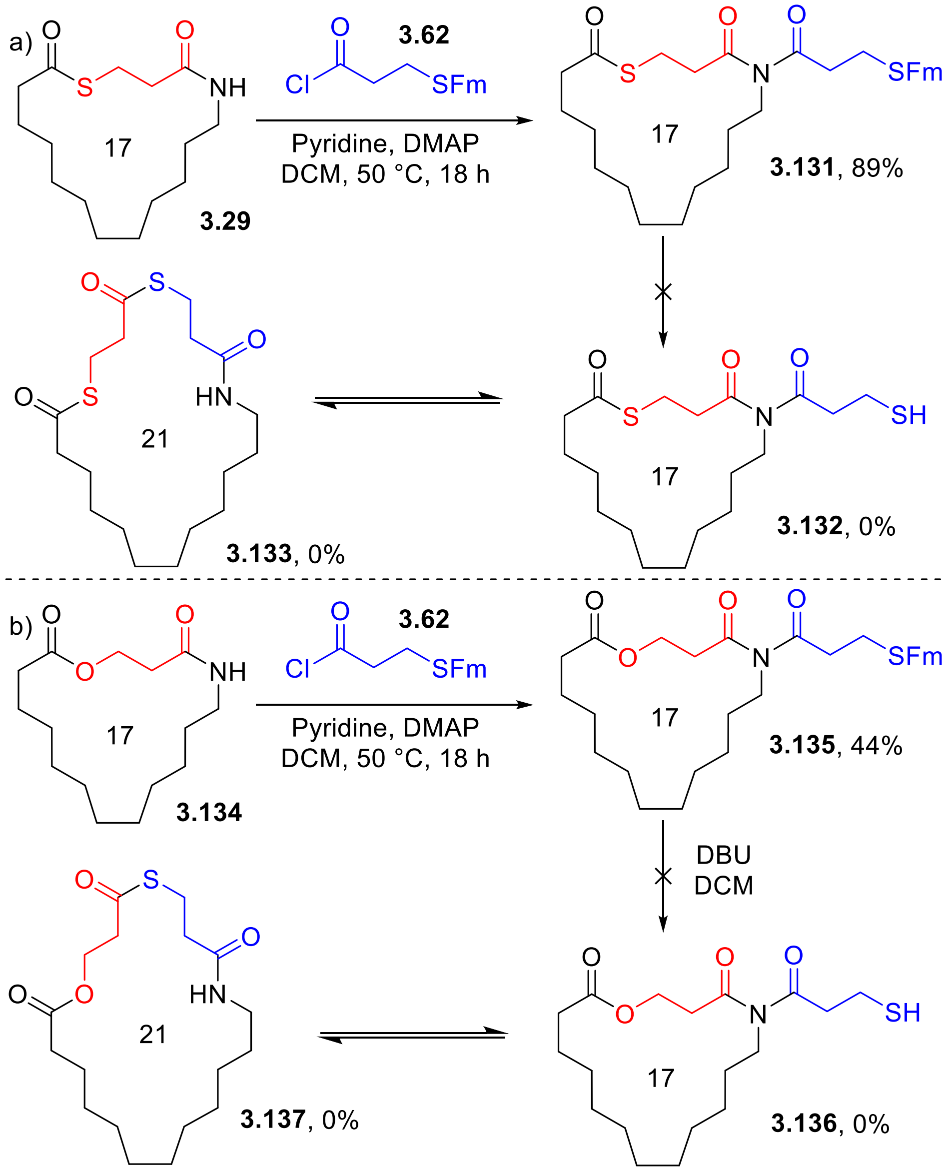
3.8.2 Thiolactone forming successive ring expansion examples attempted using S- Fm protected β-propionic acid

It is important to note that several other successive ring expansion reactions were attempted and were not successful. For example, the 6 reactions in Scheme 3.39 represent attempted acylation/ring expansions of lactams, lactones and thiolactones which all failed to deliver the desired thiolactone containing products. Many suffered problems during the *N*-acylation step. Incomplete acylation observed by TLC resulted in repeated addition of acid chloride solution in attempt to achieve complete acylation. Many reaction mixtures demonstrated the desired mass peak of the corresponding imide, but not all examples. In some instances, starting material was recovered following ring expansion attempts.



Scheme 3.39: Failed attempts at successive ring expansion using S-Fm β propionic acid chloride ***3.37****.*

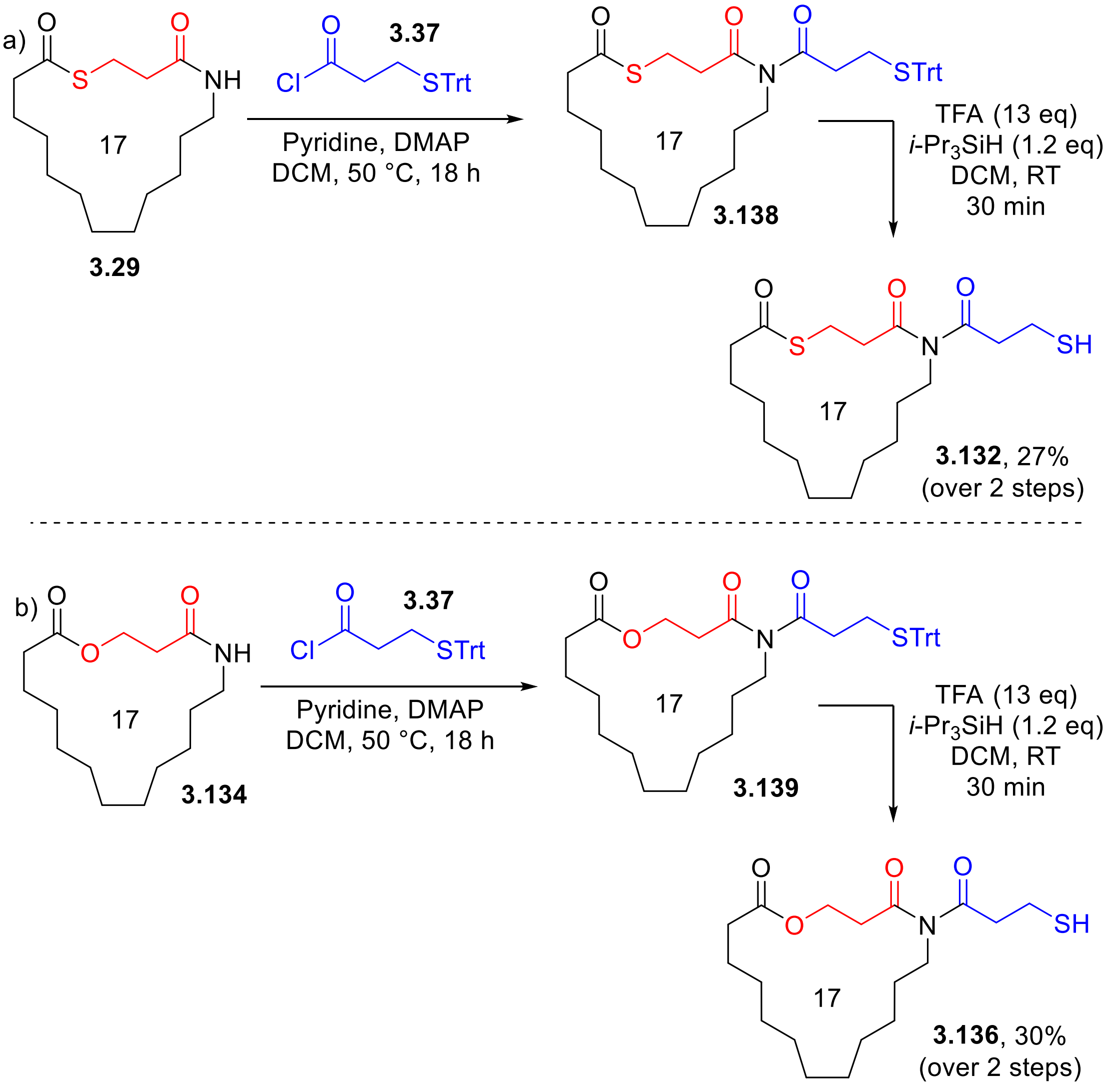
All 6 unsuccessful attempts above used S-Fm protected 3-mecrcapto propionic acid. This was odd, considering the S-Fm approach proved to be the most effective method on the simpler cases, but unfortunately, it appears to be less well suited to promote SuRE on these more complex systems. However, having had success in performing a successive ring expansion where the second fragment was a trityl protected thiol-tethered carboxylic acid (Scheme 3.38 forming **3.120**) it became apparent that the S-trityl approach may be better for more complex systems. In terms of the S-Fm strategy, the *N*-acylation step typically worked as expected, for example imides **3.131** and **3.135** were isolated and characterized before attempting deprotection/ring expansion. But the protecting group cleavage/ring expansion step was unsuccessful in both cases; most likely the basic conditions led to degradation/side reactions of the relatively reactive thiolactone starting materials and/or products (Scheme 3.40).



*Scheme 3.40: Initial attempt at successives using S-Fm strategy successfully generate imides **3.131** and **3.135** but failed at the ring expansion step.*

3.8.3 Revisiting S-trityl for successive sulfur ring expansion

With the realization that S-Fm appeared unsuitable for successive ring expansion examples where the second linear unit is an Fm-protected thiol, efforts were focussed on reattempting the most promising reaction systems using the S-trityl strategy. Purification to isolate the imides formed using the S-trityl approach (**3.138** and **3.139**) confirmed both imides were formed successfully, prior to any further reactions being performed (Scheme 3.41). Basic conditions were not used following deprotection to avoid any possible issues with elimination. The aim was to isolate either thiol or **3.132** or **3.136** without introducing 10 equivalents of DBU as per the standard procedure. This was a success with thiol **3.132** isolated in 27% over 2 steps and thiol **3.136** isolated in 30% over 2 steps (Scheme 3.41).



*Scheme 3.41: Successful S-Trityl strategy acylation and Trityl deprotection to form RO thiols **3.132** and **3.136**.*

In order to carefully induce ring expansion of the thiols, a slightly weaker base was selected to attempt the ring expansion reactions: using TEA in place of DBU. Using 2 eq. of TEA in $CDCl_3$, a small-scale ring expansion was attempted using **3.132**. The reaction was monitored at various time points by ^1H and ^{13}C NMR. Over 5 days at RT it became clear that a new compound (**3.133**) was slowly forming, with the presence of new carbonyl peaks visible by ^{13}C NMR at 199.4, 197.7, 174.4 and 170.6 ppm (Figure 3.3).

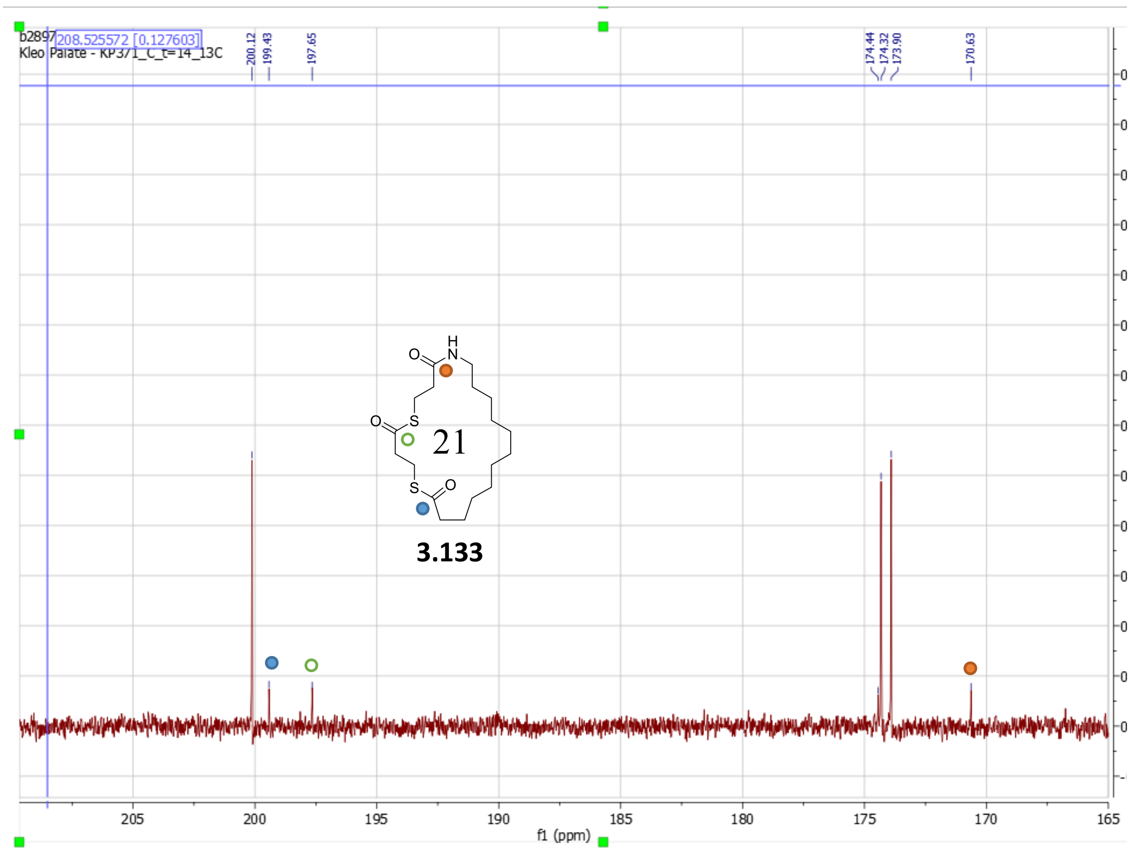


*Figure 3.3: ^{13}C NMR bisithiolactone **3.133** beginning to form in the reaction mixture.*

This NMR sample was then heated in an oil bath at 45°C for 2 h. ^{13}C NMR analysis demonstrated that this resulted in a roughly 1:3 ratio of double thiolactone **3.133** product to thiol starting material **3.132**. The NMR sample was heated again in an oil bath at 55 °C over 8 h. ^{13}C NMR analysis then demonstrated a roughly 1:1 mixture of bisthiolactone product (**3.133**) to thiol starting material (**3.132**) (Figure 3.4). It was decided at this point to isolate the bisthiolactone **3.133** as further heating risked undesired side reactions occurring.

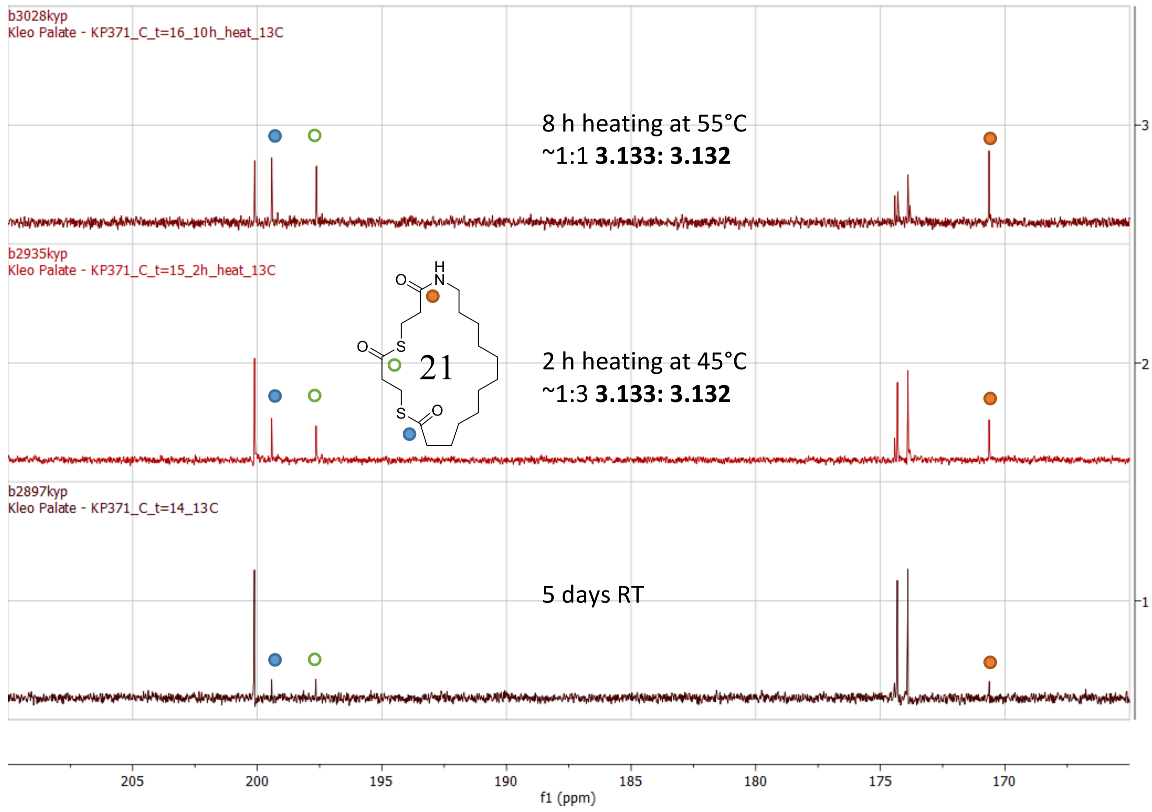
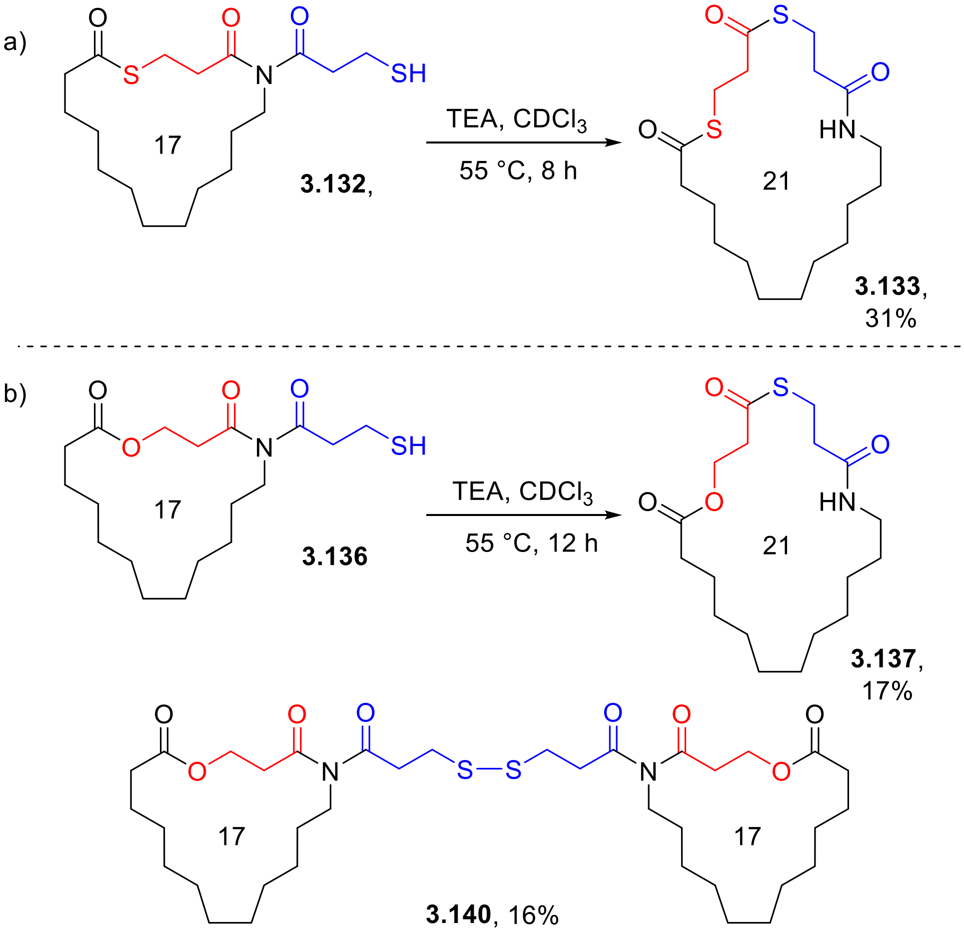


*Figure 3.4: ^{13}C NMR of reaction to form bisthiolactone **3.133** at various time points showing slow conversion and possible equilibrium mixture.*

Following purification by column chromatography, some recovered starting material **3.132** (6.6 mg, 15%) was isolated alongside the desired bisthiolactone **3.133** in 31% yield.

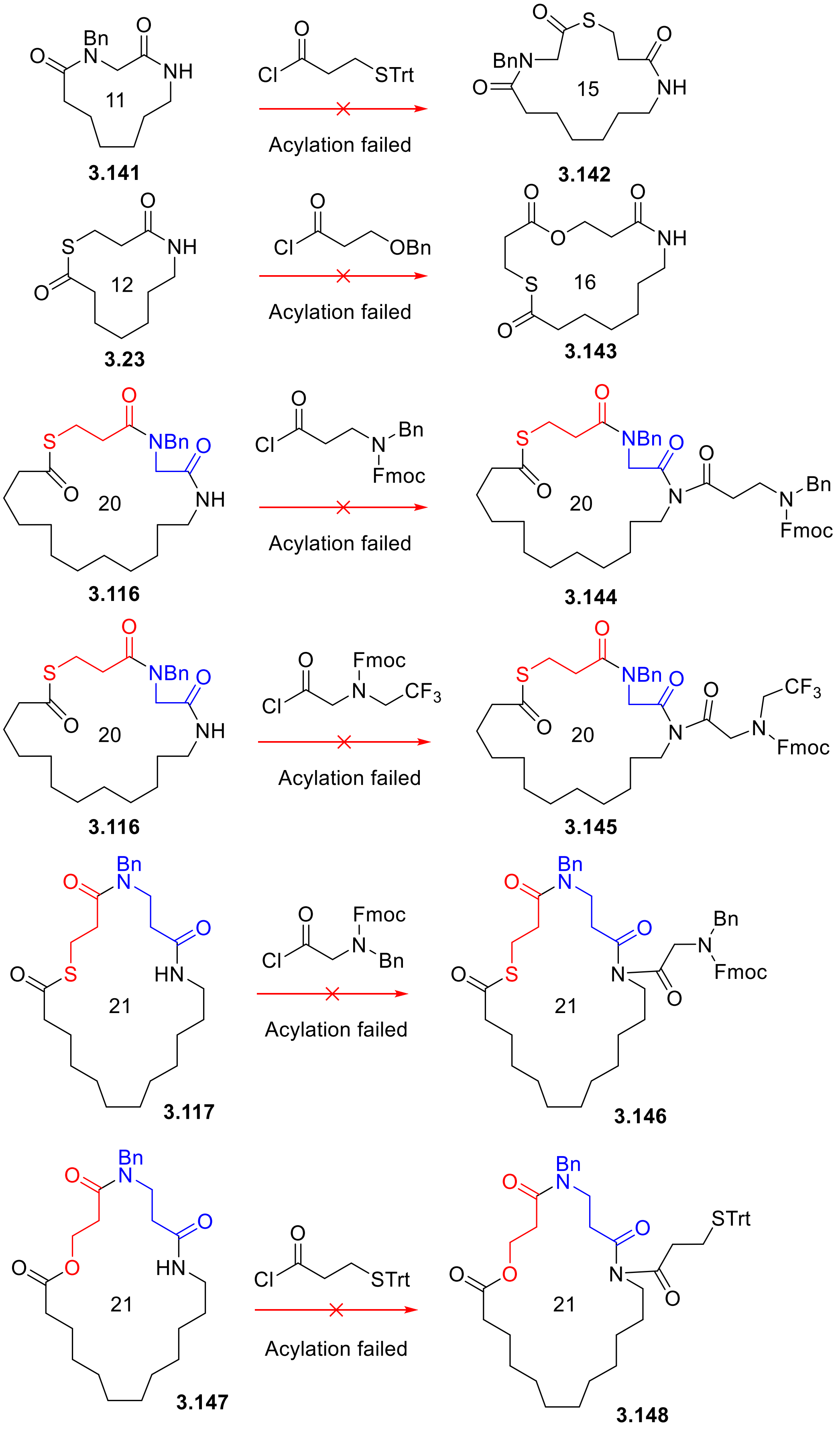
A similar procedure was used to synthesize **3.137**. The thiol **3.136** was isolated in 30% yield over 2 steps, followed by heating in $CDCl_3$ at 55 °C with 2 eq. of TEA, this time for a total of 12 h. At 12 h a mass spectrum of the crude mixture suggested that the disulfide **3.140** was present as well. One procedural difference was that this reaction was performed in a round bottomed flask with stirring as opposed to inside an NMR tube with no stirring, as was the case in the synthesis of **3.133**. Perhaps this allowed more oxygen to enter the flask, which may account for the formation of disulfide **3.140**. Following purification, the desired thiolactone **3.137** was isolated in 17% yield, along with disulfide **3.140** in 16% yield. Disulfide formation is thought to be a minor side product formed in other reactions, however this is one of the few occasions where it was cleanly isolated and fully characterized (Scheme 3.42).



*Scheme 3.42: Successful successive attempts using S-Trityl strategy and isolation of intermediate thiols **3.132** and **3.136**.*

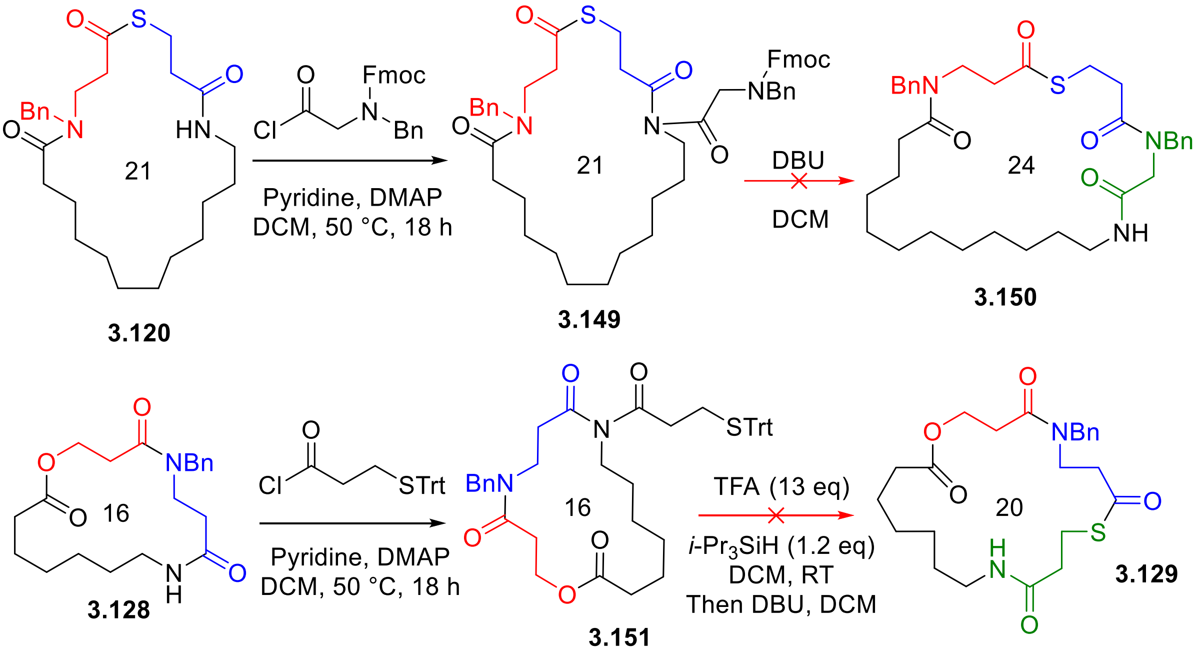
3.8.4 Failed successive ring expansions and triple attempts

Many other attempts at successive ring expansion reactions incorporating the newly developed sulfur chemistry were attempted, including a few attempted triple ring expansions, sadly without success. In most cases, failure of the *N*-acylation step was the main issue. As a record, these are summarized in Scheme 3.43.



Scheme 3.43: Lactams which failed to N-acylate en route to successive ring expansion to form thiolactones.

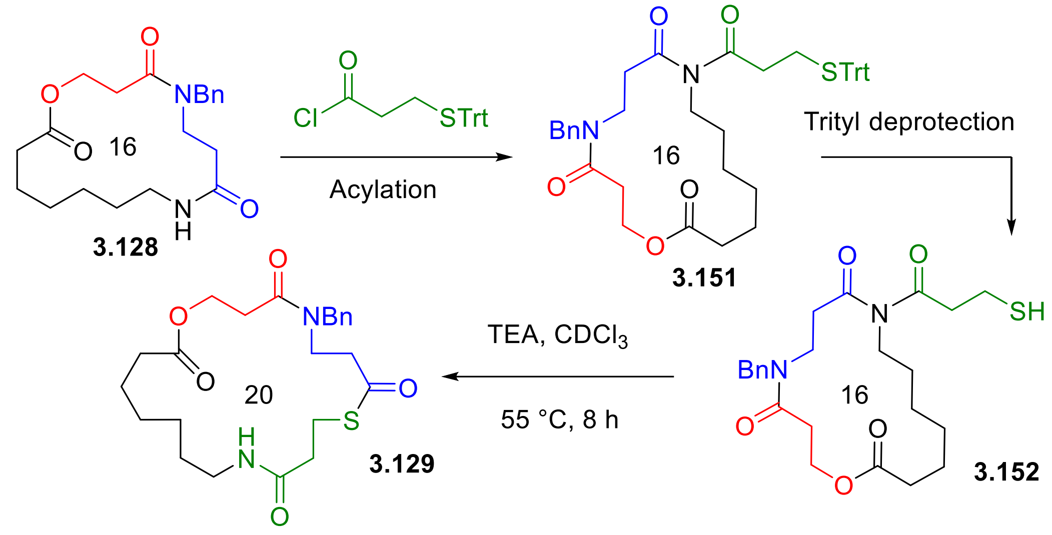
Some *N*-acylations were successful to some degree (for example **3.149**, and **3.151** in Scheme 3.44), with the desired imides seen by TLC and MS, but unfortunately, none of the desired triple ring expansions were not isolated following protecting group cleavage. It is unclear why, but most likely starting material and/or product decomposition when treated with basic or acidic reagents results in the formation of complex mixtures of products.



Scheme 3.44: Successive attempts where acylation appeared partially successful by TLC and MS, but unsuccessful on ring expansion step.

3.8.5 Future work

There was some promise in attempts to perform a triple ring expansion incorporating an amino acid, a hydroxy acid and finally a thio acid (**3.129**). Ultimately, however, material was exhausted in attempts to reach this target and the scale of the reaction performed was too low to properly confirm ring expansion. ^{13}C NMR was unable to unambiguously confirm the presence of a thioester despite an extended run-time on the spectrometer. The desired MS peak of the product was observed however, showing promise that the thiol **3.152** or thiolactone **3.129** could be isolated, given sufficient material. The revised stepwise trityl strategy (Scheme 3.45) is the recommended approach for achieving the final ring expansion to form **3.129** with isolation of the intermediate thiol **3.152** to be performed before attempting the final ring expansion in chloroform/Et_3N.



*Scheme 3.45: Proposed future route to synthesize triple ring expanded product **3.129**.*

3.9 Summary of thiolactone synthesis *via* ring expansion and X-ray crystallography

In conclusion, the synthesis of thiolactones *via* ring expansion was explored in this study, as an extension of the methodology developed for SuRE. Three different protecting groups for thiols were trialled (Ac, Fm, Trt) and optimized. A screen investigating the scope of this ring expansion to different ring sizes and branched examples was performed with DFT complementing experiment for the former study. Five successive examples were also successfully carried out, validating the compatibility of the new sulfur methodology with traditional nitrogen- and oxygen-based SuRE. Finally, three X-ray crystal structures were obtained to confirm ring expansion and deposited in the CCDC (Figure 3.5).

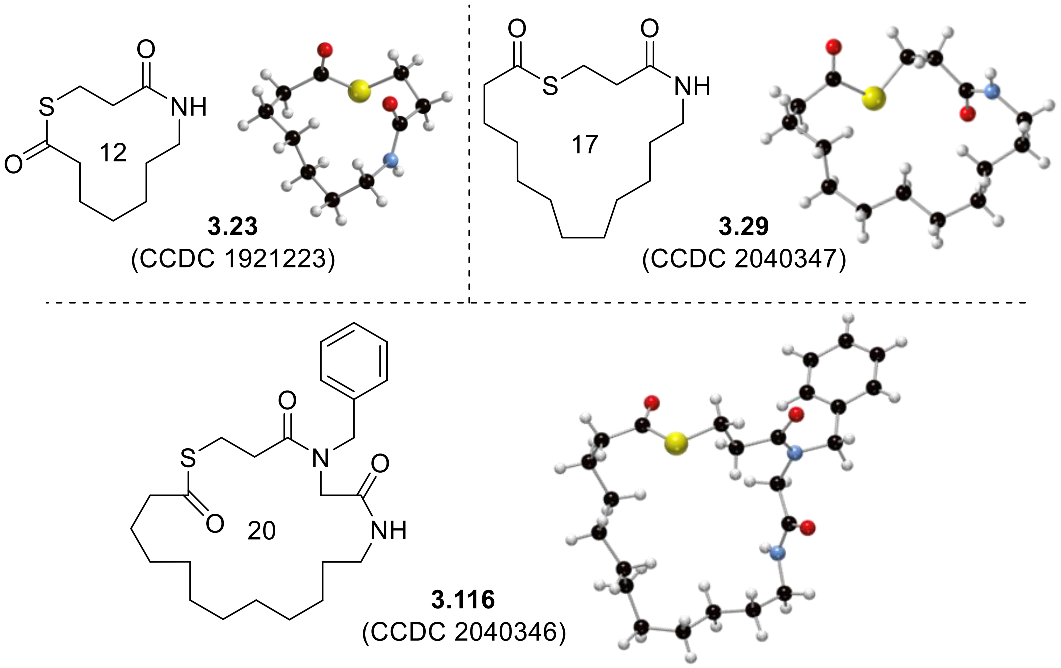


Figure 3.5: The X-ray crystal structures of three thiolactones were solved and deposited in the CCDC.

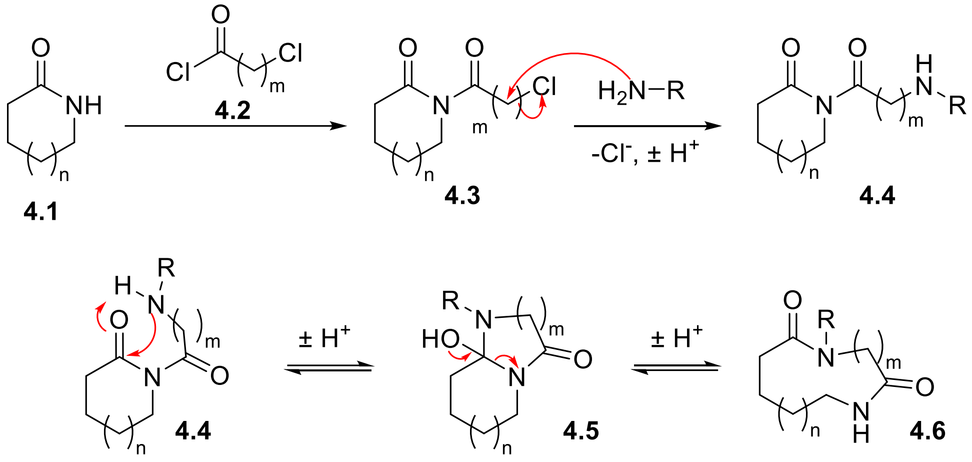
The work described in this chapter is the subject of one publication.[85]

4 Cascade ring expansion reactions using a common electrophilic imide

4.1 Need for new methodology

In this chapter the development of a new cascade ring expansion method based on SuRE is presented, from development and proof of concept, through optimization, and finally to exploration of the scope of the reaction.

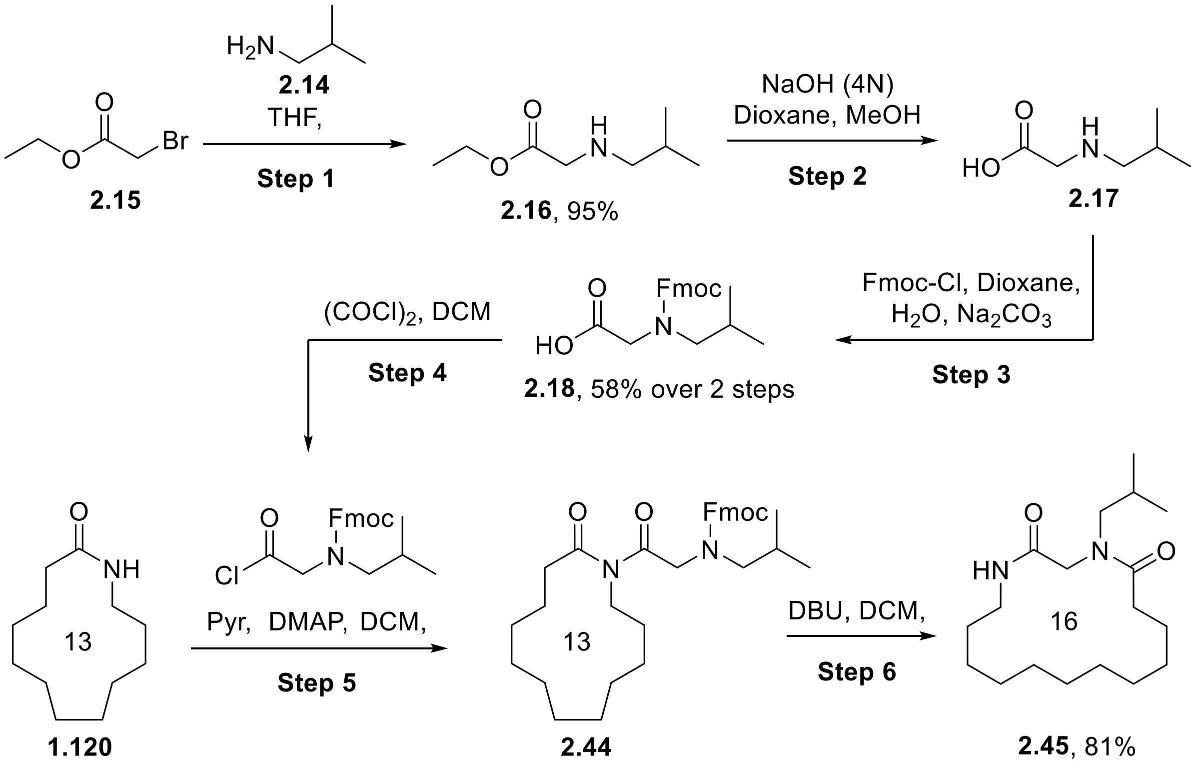
The central idea was to develop a new methodology by which multiple ring expanded products could be formed from a common imide starting material. It was envisaged that this could be achieved through the use of an imide with a pendant electrophilic functionality, for example, a leaving group (such as chloro-substituted imide **4.3**). Introducing a nucleophile, such as a primary amine, could instigate a nucleophilic substitution to yield an amine-tethered imide (**4.4**) which could then undergo concomitant ring expansion (to form **4.6**, Scheme 4.1).



*Scheme 4.1: Proposed SuRE ring expansion using a common imide starting material **4.3***

There are several potential advantages to this approach when compared with the SuRE reactions described in Chapters 1–3. SuRE reactions require protected amino and hydroxy acid chlorides (derived from the parent carboxylic acids), which are generally not commercially available, to be used as acylating agents. In order to alter the functionality of the acylating agent, a bespoke synthesis is required for each new case. This was the approach taken in Chapter 2, where a selection of *N*-alkylated Fmoc-protected amino acids was synthesized to expand the scope of functionality beyond *N*-methyl and *N*-benzyl groups.

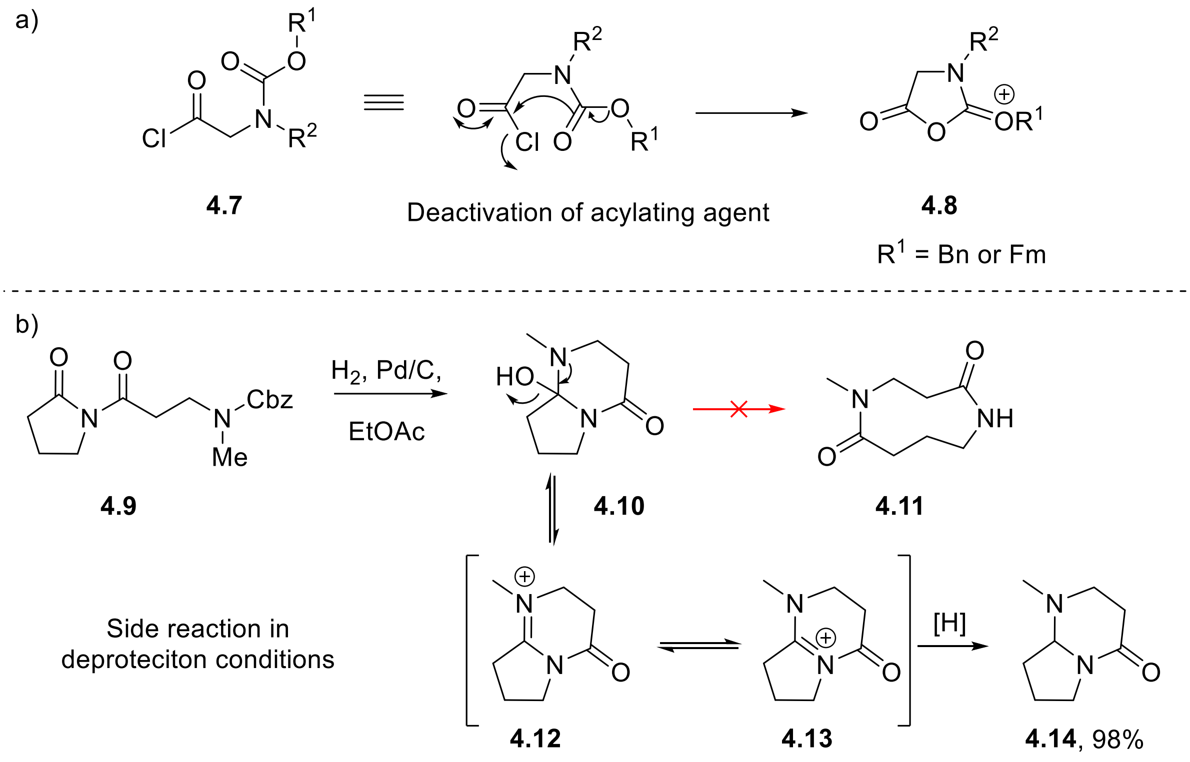
To form a single ring expanded product from this study, 6 synthetic reactions were required in total. Three steps are required to synthesize the protected amino acid (**2.18**) (Steps 1–3). This is followed by an acid chloride formation (Step 4) and *N*-acylation (Step 5), before the final deprotection ring expansion reaction can be performed (Step 6, Scheme 4.2).



Scheme 4.2: 6 step synthesis to form ring expanded products with bespoke N-alkylated amino acids.

Some of the inefficiencies in this process are associated with the need to have a protecting group on the nucleophile. This is required as the acid chloride formation would not be possible for a substrate containing an unprotected nucleophile, as it would quickly react with itself as soon as it is formed. Both alcohols and secondary amines are more nucleophilic than the lactam amide nitrogen in the acylation reaction.

In addition, side reactions have been observed during acylation and protecting group cleavage. Carbamate protecting groups on acid chlorides of amino acids are known to react intramolecularly to form oxazolidine side products such as **4.8** (Scheme 4.3a). A separate issue relating to protecting groups is that the deprotection conditions can lead to the formation of side products, with an example shown in Scheme 4.3b. In this instance, dehydration occurs, forming a transient iminium ion **4.12** (in resonance with **4.13**), which is then further reduced *in situ* under the reductive reaction conditions to form the *N,N*-acetal **4.14** in high yield (reaction performed by Dr Tom Stephens).

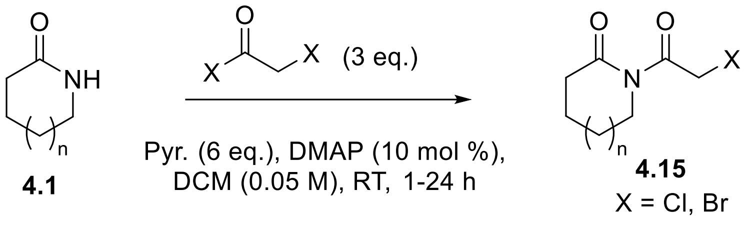


Scheme 4.3: Side reactions relating to protecting groups and deprotection conditions. a) Deactivation of acylation agent by carbamate protecting group. b) Side reaction observed in deprotection conditions (performed by Dr Tom Stephens).

Devising a protecting group free approach was one on the reasons for us deciding to develop a new cascade reaction. By utilizing an acylating agent with two electrophilic sites, this reduces the number of synthetic steps required, as well as allowing the ring expansion to be performed with a variety of nucleophiles at a late stage in the synthesis.

4.2 New acylation protocol

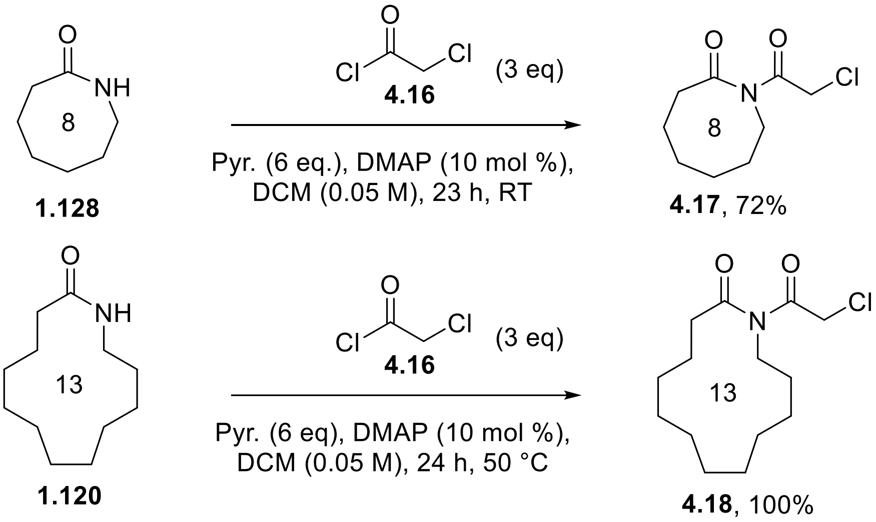
Scheme 4.4 below shows the general acylation protocol used for the α-halo acid halide acylation agents using the standard pyridine/DMAP conditions as done previously.



Scheme 4.4: New acylation procedure using common α-halo acid halides acylation agent

4.2.1 Acylation using chloroacetyl chloride

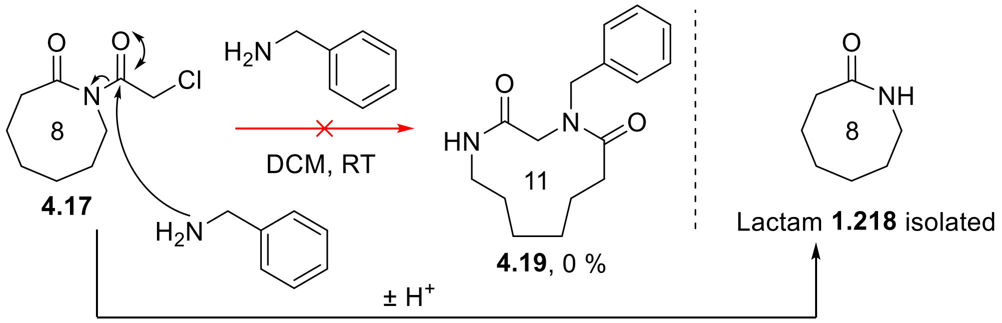
Initially, chloroacetyl chloride **4.16** was chosen as the acylation reagent. This was tested on lactams of two different ring sizes. When an 8–membered lactam **1.128** was employed, the reaction proceeded efficiently to yield 72% of the desired imide **4.17**. To test the robustness of this protocol, a further reaction was performed on the 13-membered lactam **1.120**. Generally, *N*-acylation is less efficient on larger lactams. Indeed, in the case of **1.120**, the reaction did not proceed at RT, however heating at 50 ˚C was beneficial and quantitative conversion into imide **4.18** was achieved (Scheme 4.5).



Scheme 4.5: Acylation using chloroacetyl chloride.

4.2.2 Benzyl amine induced imide cleavage

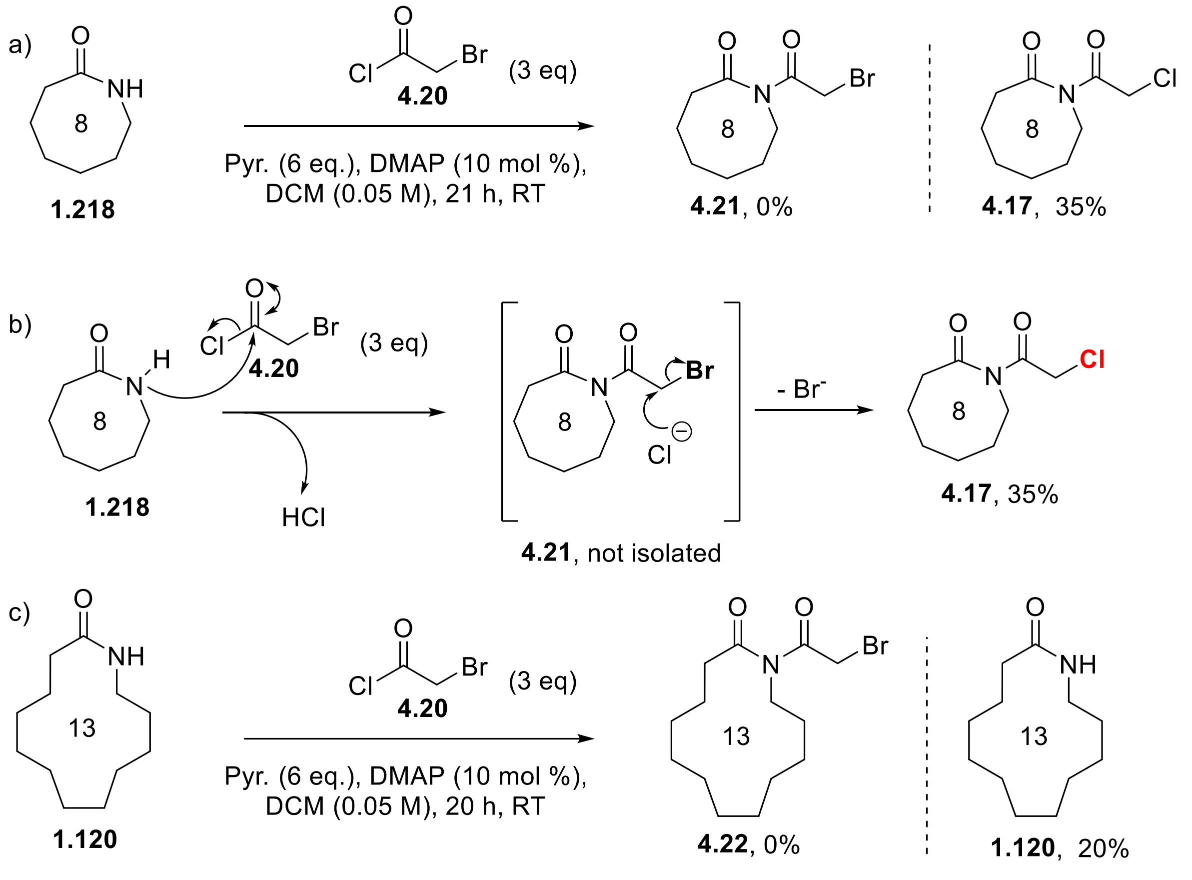
Unfortunately, it was found that attempting to promote the ring expansion of imide **4.17** *via* an initial S_N2 reaction followed by ring expansion using benzyl amine as a nucleophile, did not result in the formation of the desired product. Instead, the imide was cleaved to regenerate the corresponding starting lactams; unfortunately, nucleophilic attack seems to occur preferentially at the carbonyl instead of at the α-carbon (Scheme 4.6, reaction performed by James McNulty). The same result was obtained when using 13–membered imide **4.18** as the starting material (not shown).



Scheme 4.6: Benzyl amine cleaves N-chloroacyl imides regenerating the original lactam. Reaction performed by James McNulty.

4.2.3 Acylation using bromoacetyl chloride

In order to aid the S_N2 step of the reaction, it was thought that changing the leaving group from a chlorine to a bromine would be beneficial. Therefore, a bromoacetyl chloride acylating agent was tested next. However, none of the expected brominated imide product (**4.21**) was observed when 8-membered lactam **1.218** was reacted under the conditions summarized in Scheme 4.7a. Instead, chlorinated imide **4.17** was isolated in low yield, which is believed to form *via* a halogen exchange process. The proposed mechanism for this reaction is shown in Scheme 4.7b. In the first step, the brominated imide is generated, as well as chloride ions. The chloride ions are believed to promote a S_N2 reaction on the α-carbon, substituting bromine for chlorine. Attempting the same reaction of 13-membered **1.210** was unsuccessful in forming either imide, with some starting material recovered (Scheme 4.7c).

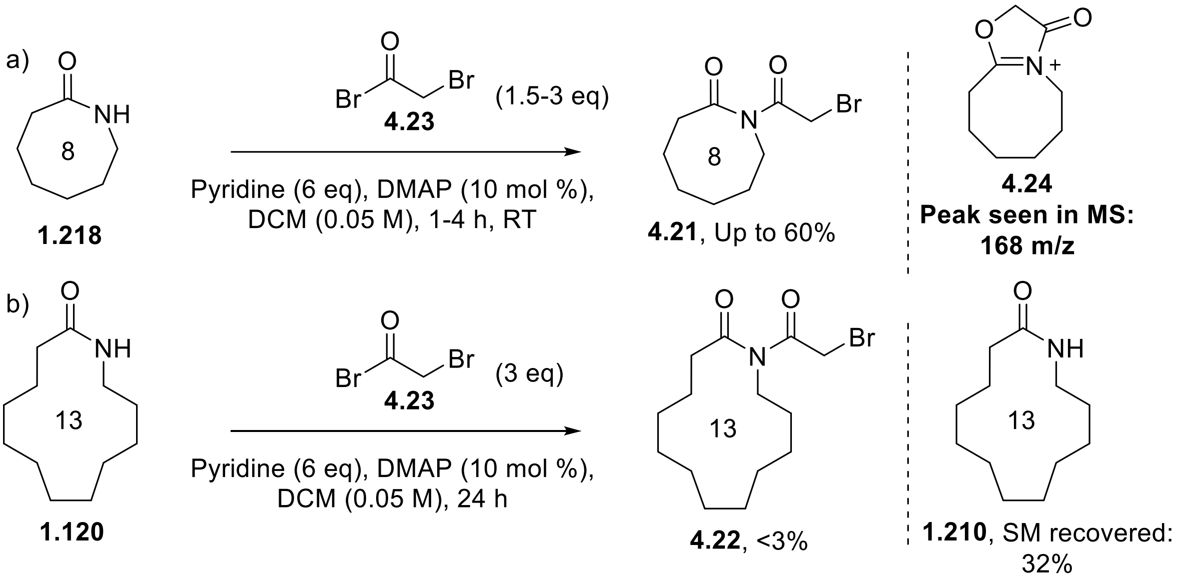


*Scheme 4.7: Acylation using bromoacetyl chloride. A halogen exchange reaction is believed to be responsible for the formation of chlorinated imide **4.17**.*

4.2.4 Acylation using bromoacetyl bromide

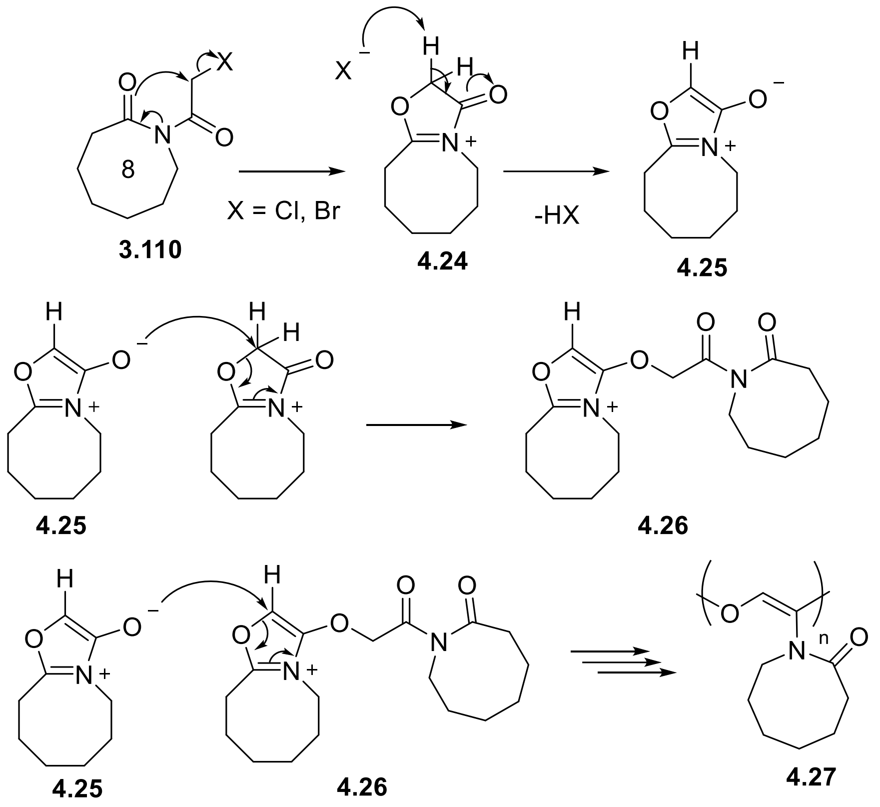
Having been unsuccessful in isolating the desired brominated imide, the acylating agent was then changed to bromoacetyl bromide **4.23**, thus eliminating any source of chloride altogether. The acylation step was attempted multiple times, using various reaction times (ranging from 1 to 4 hours to form **4.21**, Scheme 4.8a, or up to 24 h in attempts to form **4.22**, Scheme 4.8b).

The results of the acylation were inconsistent, with yields of the 8–membered imide **4.21** varying greatly, up to a maximum of 60%. When analyzed using mass spectrometry, all the purified halogenated imides showed a mass peak at m/z 168 (or 238 in the case of 13–membered lactam acylations), which likely corresponds to the formation of the ring closed compound **4.24** (Scheme 4.8).



Scheme 4.8: Acylation using bromoacetyl bromide.

This unwanted intermediate side product (**4.24**) may lead to polymerization,[86,87] thus lowering the yield. Indeed, there is precedent for α-halogenated imides such as **3.110** to eliminate a halide leaving group, forming mesoionic oxazoles known as isomünchnones **4.24**[88] which polymerize over time, as shown in Scheme 4.9. In fact, *N*-haloacyl lactams from 6-to-8-membered in size have been reported to be unstable and polymerize at room temperature, in a study by Mathias and Moore.[86,87,89]

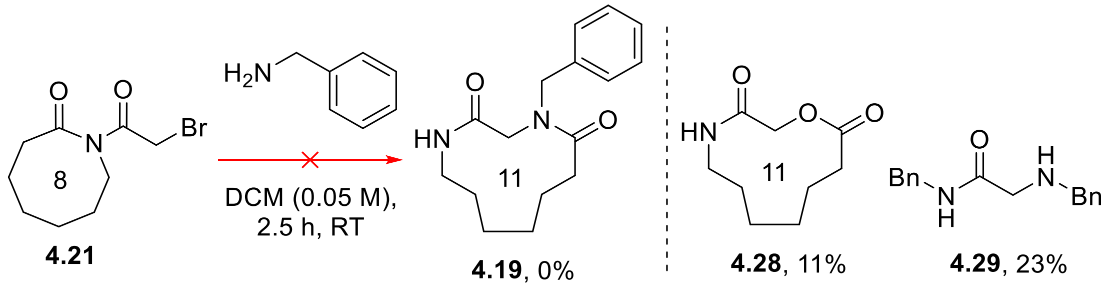


Scheme 4.9: Polymerization of N-haloacyl imides described in the literature.[87]

In our hands, brominated imides (**4.21**, **4.22**) were more challenging to characterize than their chloro derivatives (**4.17**, **4.18**), likely because they are more prone to polymerization of the type described above, which may be responsible for the inconsistent and low yields of these compounds.

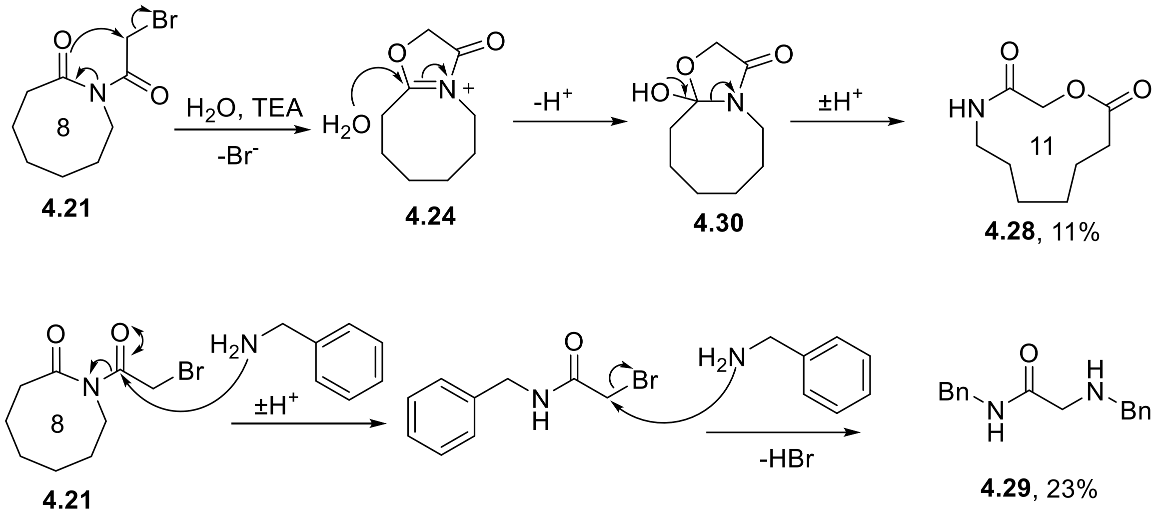
4.2.5 Benzyl amine induced imide cleavage and lactone formation

Although the synthesis of 8–membered *N*-bromoacyl imide **4.21** was problematic, enough material was isolated to test the next step of the reaction. However, when benzyl amine was reacted with imide **4.21** in DCM, in an attempt to induce an S_N2/ring expansion cascade, none of the desired ring expanded product **4.19** could be isolated. Instead, a lactone-containing 11–membered ring **4.28** was isolated in low yield (Scheme 4.10).



*Scheme 4.10: Attempted S_N2/ring expansion of N-bromoacyl imide **4.21** using benzyl amine resulted in formation of mixed lactone/lactam **4.28** and amide **4.29**.*

We propose that trace amounts of water present in the reaction are the cause of this unexpected result, with lactone **4.28** formed *via* the mechanism proposed in Scheme 4.11. Additionally, an amide **4.29** was isolated, suggesting that imide **4.21** can be attacked at the carbonyl by amines as well as at the α-position displacing the bromide (Scheme 4.11).



*Scheme 4.11: Proposed mechanisms of formation of mixed lactone/lactam **4.28** and amide **4.29**.*

4.2.6 Optimization of lactone forming reaction

Based on the unexpected formation of lactone **4.28**, further investigation was made into the effects of intentionally adding water into these reactions, to test whether this could be used productively to induce ring expansion to form lactone products. Thus, imide **4.21** was stirred in the presence of water and conditions were screened, with and without base, in both THF and DCM. The lactone-containing 11–membered ring **4.28** was isolated in up to 43%, with these results presented in Table 4.1. The combination of DCM and TEA resulted in the best yield. An attempt using THF and TEA led to the formation of a bicyclic compound **4.31**. This is believed to be formed *via* the attack of methanol (present during column chromatography) on reactive intermediate **4.24**. Bicyclic compound **4.31** has been observed and reported previously in the literature and its structure was confirmed by comparing its ^{13}C NMR data to those reported previously.[67] The isolation of this bicyclic methanol adduct suggests that reactive intermediate **4.24** is being formed in the reaction or during column chromatography. This evidence is consistent with the polymerization mechanism that has been described above.

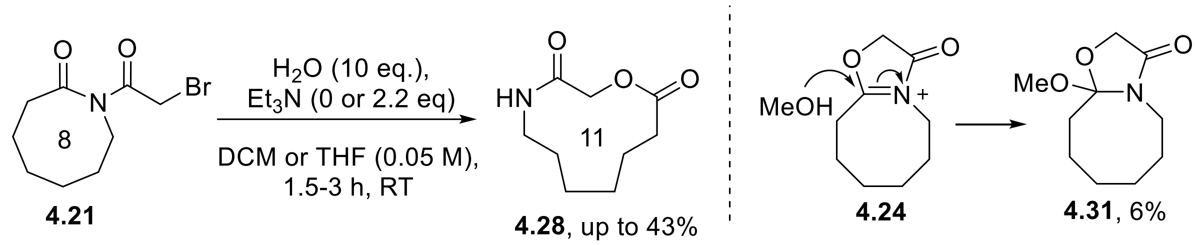
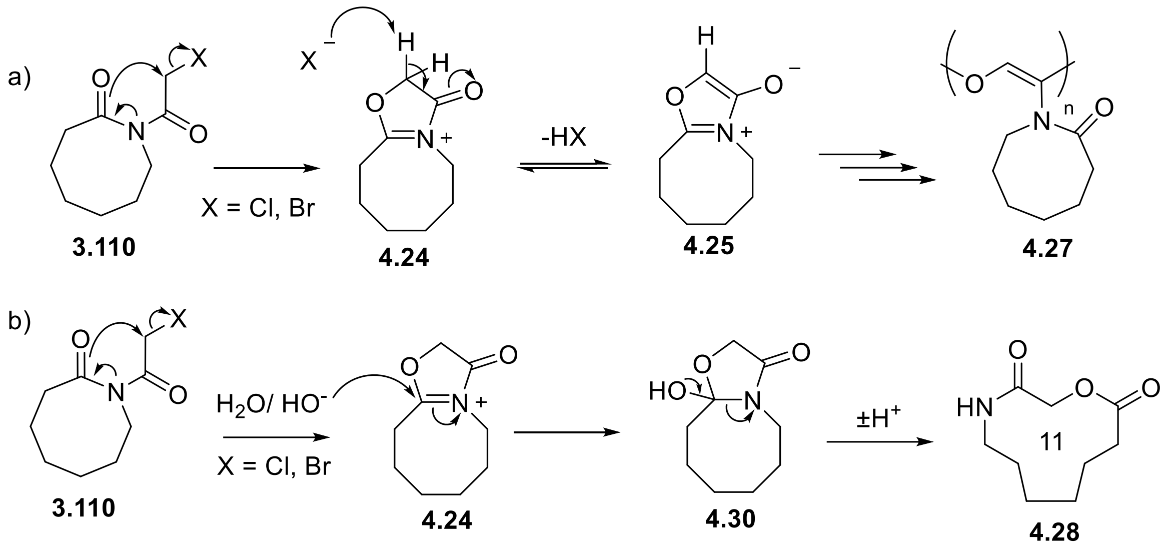


Table 4.1: Water induced ring expansion to form lactone **4.28**.

Solvent	With TEA	Without TEA
DCM	**4.28**, 43%	**4.28**, 25%
THF	**4.31**, 6%	**4.28**, 19%

4.2.6.1 Possible mechanism of oxygen nucleophile incorporation

It is likely that intermediate **4.24** is being formed *via* an intramolecular reaction resulting in the loss of a halogen of *N*-bromoacyl or *N*-chloroacyl imides (**4.21** and **4.17**). There are two possible reaction pathways once this reactive intermediate has formed. The first is an intermolecular reaction leading to polymerization (Scheme 4.12a). However, if this intermediate is exposed to oxygen nucleophiles such as hydroxide or methanol, then nucleophilic attack by water or hydroxide into the reactive bicycle **4.24** may occur, and go on to promote ring expansion (Scheme 4.12b). The evidence is not definitive. A mass peak indicative of bicyclic intermediate **4.24** or isomünchnone **4.25** has been seen in most mass spectra collected when a halogenated imide is synthesized or used in a reaction. This indirect evidence, supported by literature precedent, strongly suggests that halogenated imides of the type investigated are unstable. Hydroxide or water were the only nucleophiles able to induce ring expansion once intermediate **4.24** is formed (Scheme 4.12b), with amines attacking directly at the α-carbon preferentially.

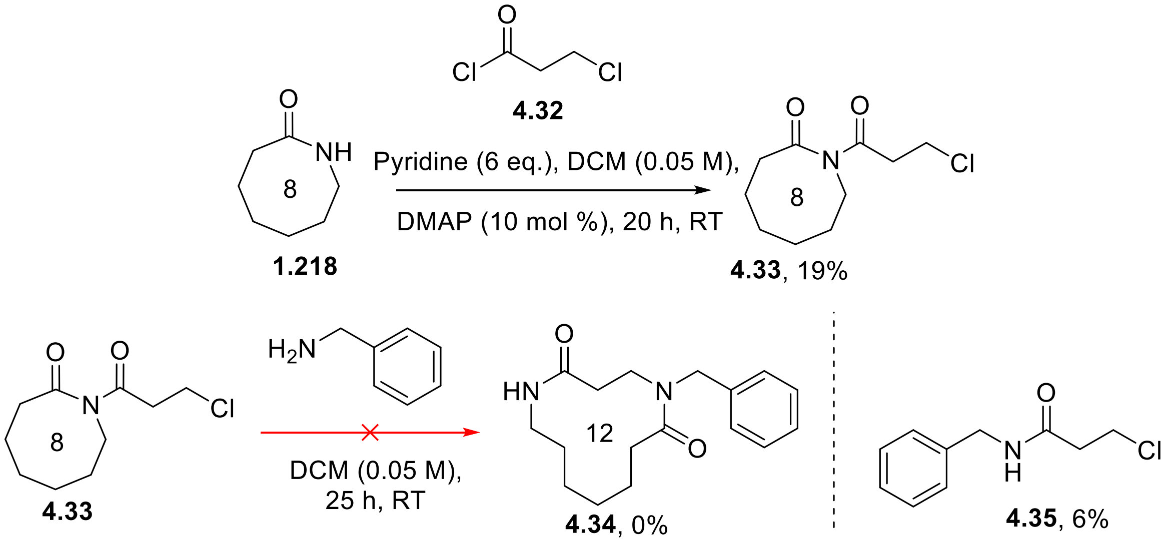


Scheme 4.12: Comparison of reactivity of bicyclic intermediate ***4.24****. a) Polymerization via isomünchnone* ***4.25****. b) Ring expansion in the presence of water or hydroxide to form lactone* ***4.28****.*

To summarize the results in this section, the 8–membered *N*-bromoacetyl imide **4.21** was the main focus of the study of using α-halo carbonyl acylating agents. Inconsistent yields were obtained during the synthesis of this compound, likely due to a tendency for it to react intramolecularly, leading to polymerization. Water can induce ring expansion of this imide to an 11–membered lactone (**4.28**) in moderate yield, likely *via* the same mechanism by which the halogenated imide breaks down (*via* **4.24**). Finally, there is no evidence that the desired S_N2/ring expansion transformation can be induced when benzyl amine is introduced. The result is similar to what was observed in trials using the *N*-chloroacetyl imide **4.17** (Scheme 4.6), in that nucleophilic attack seems to occur preferentially at the carbonyl leading to breakdown of the imide.

4.2.7 Chloropropionyl imide synthesis and reactivity

In order to access a halogenated imide with different reactivity, an imide was synthesized with a halogen at the β-position using commercially available 3-chloropropionyl chloride; the acylation proceeded in low yield, but formed adequate amounts of imide **4.33** to perform further experiments (Scheme 4.13). Reaction of this β-halogenated imide (**4.33**) with benzyl amine once again showed evidence of preferential attack at the carbonyl. In this instance, a halogenated amide (**4.35**) was isolated from the reaction mixture in 6% yield, with none of the desired expanded lactam **4.34** formed.

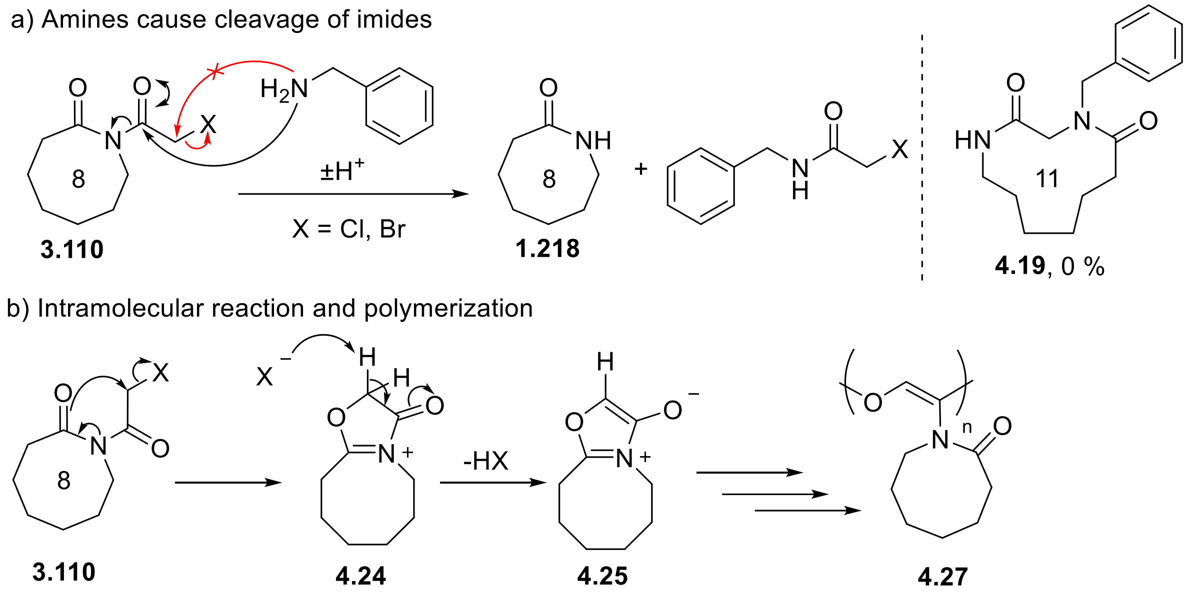


Scheme 4.13: Attempted S_N2/ring expansion using a β-chloride containing imide.

As mentioned, the formation of amide side products **4.29** and **4.35** suggests that nucleophiles of the form RNH_2 do not result in the desired transformation taking place; nucleophilic attack at the carbonyl seems to be favoured in both instances. One strategy that has been employed to address this issue involves changing the leaving group from Br/Cl to iodine (*via* a Finkelstein reaction). Finkelstein reactions on chloride **4.17** were briefly explored, but the results were difficult to interpret. It is thought that if formed, an *N*-iodoacyl imide would even more prone to polymerization than the chloride or bromide analogues.

4.2.8 Conclusion of haloacyl imide studies

Overall, this approach to a new acylation protocol for SuRE was not used to successfully incorporate amine nucleophiles during ring expansion. It appears that *N*-haloacyl imides of the type **3.110** are more prone to reacting in others ways, for example at the imide carbonyl (Scheme 4.14a). The consistently low yields of halogenated imides resulting from polymerization (Scheme 4.14b) was an added challenge.



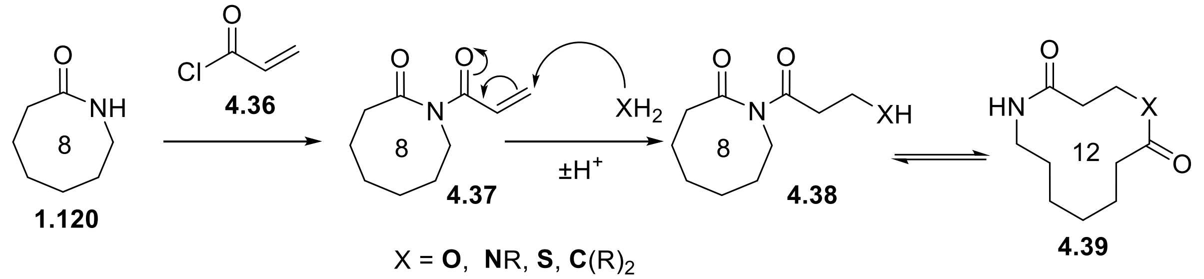
a) Amines cause cleavage of imides

b) Intramolecular reaction and polymerization

Scheme 4.14: Issues with N-haloacyl imides. a) Preferential attack at the carbonyl. b) Halogen loss and polymerization.

4.3 Conjugate addition/ring expansion approach

To overcome these obstacles it was decided that a different type of electrophile would be the best course of action, and α,β-unsaturated electrophiles were considered to be viable alternatives to achieve the desired ring expansion chemistry. New acylating agents such as acryloyl chloride were chosen, thus abandoning the α- or β-halogen leaving groups altogether. Without halide leaving groups, polymerization would not be possible *via* the pathway that had plagued all the halogenated imide reactions described above (Scheme 4.14b). The other major change is that the mechanism of the initial nucleophilic addition reaction will differ. All of the reactions using *N*-haloacyl imides described were intended to undergo an initial S_N2 reaction, displacing the leaving group at the α- or β-position. However, where nitrogen was used as a nucleophile, the predominant site of attack was at the carbonyl in all cases, leading to the imide being cleaved and lactam regenerated. In contrast, an α,β-unsaturated imide could allow 1,4-attack *via* conjugate addition (Scheme 4.15). The different reactivity of these imides may also reduce the chance of unwanted attack at the carbonyl. α,β-Unsaturated systems are also amenable to attack by softer sulfur- and carbon-based nucleophiles, and thus provide opportunity for the development of other reaction types.

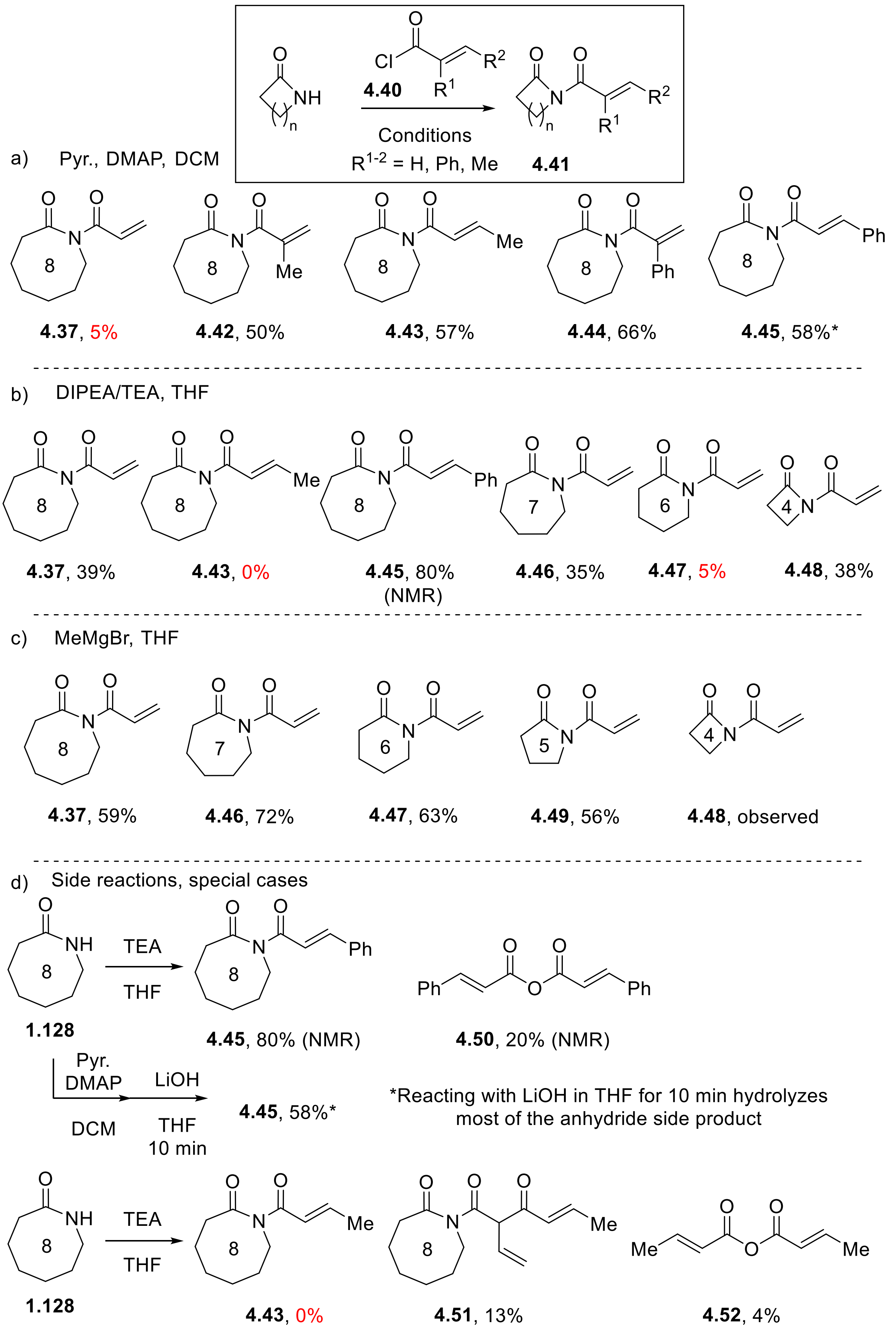


Scheme 4.15: Acryloyl imide formation and conjugate addition reaction.

4.3.1 Synthesis of acryloyl imides

Synthesis of acryloyl imides of the form **4.41** began by attempting acylation with the standard pyridine/DMAP conditions used in SuRE using acryloyl chloride and 8-membered **1.218**. This furnished the desired imide **4.37** in only 5% yield (Scheme 4.16a). A pasty orange solid formed upon addition of excess acryloyl chloride (3 equivalents) which was thought to be sign of polymerization (note, *via* a different mechanism to the polymerization described earlier in Section 4.2.4 – in this case, it is likely polymerization of the acryloyl motif). Indeed, acrylates and acryloyl chloride are well known to be prone to polymerization and often contain a stabilizer, such as phenothiazine, to suppress polymerization during storage. Polymerization can be initiated by elevated temperature, presence of anionic species, or radicals. On the second attempt, the acylation was conducted using fewer equivalents of acryloyl chloride (1.5 equivalents). However, the same orange solid formed again and the reaction was abandoned when product was not detectable by TLC. Attempting the acylation using TEA as a base improved the isolated yield to 39% (**4.37**, Scheme 4.16b). Using the TEA conditions, there is still evidence of polymerization affecting the yields, as an orange putty-like solid is typically formed during reaction or aqueous workup. However, this yield is still synthetically useful and the reaction scales up fairly well. Pyridine/DMAP conditions were used successfully to form substituted acryloyl imides α-methyl **4.42** (50%), α-phenyl **4.44** (66%), β-methyl **4.43** (57%), and β-phenyl **4.45** (58%, although an additional workup was required in this case, see Scheme 4.17c). For both the β-methyl **4.43** and β-phenyl **4.45** examples, anhydride side products were observed when using TEA conditions. In the case of β-phenyl **4.45**, where the anhydride formed a significant proportion of the crude mixture, this was remedied by using pyridine/DMAP conditions followed by a stir in LiOH to promote hydrolysis of the anhydride **4.50** (Scheme 4.17c). In the case of β-methyl **4.43**, TEA conditions did not produce any of the desired product, forming the tri-carbonyl compound **4.51** in 13% yield.

TEA (or DIPEA) were used to synthesize unsubstituted acryloyl imides 8-membered **4.37** (39%) and 7-membered **4.46** (35%), but was unsuccessful in forming the 6-membered imide **4.47** in our hands (only 5% yield). For 6-membered imide **4.47** and other similar unfunctionalized lactams, the highest yielding results were achieved using MeMgBr in THF at 0 °C as the *N*-acylation conditions. This resulted in the highest yields for 8–5 membered lactams (72–56%), however it was not well suited for 4-membered beta lactam **4.48**. The Grignard reagent is believed to partially open the lactam ring in this instance. Reverting to DIPEA in THF conditions resulted in a modest synthetically useful yield of **4.48**, 38%. The methods summarized in Scheme 4.16 were used to make most of the lactams used in the CARE studies described in this thesis, with some exceptions. In the scope exploration (discussed further on), functionalized lactam acylations are presented in Section 4.4.3.3, and some additional branched 6-membered lactams synthesized by Zhongzhen Yang are discussed in section 4.4.3.4.



Scheme 4.16: Synthesis of α,β-unsaturated imides using 3 different conditions.

4.3.2 Sulfur conjugate addition

With acryloyl imides in hand, efforts turned to attempting conjugate addition reactions. The initial aim was to perform a sulfur mediated conjugate addition/ring expansion using 8-membered acryloyl imide **4.37**, to form a 12-membered macrocyclic thiolactone.

To begin, we decided to focus on achieving the conjugate addition reaction separately, using nucleophilic S-containing reagents thiourea, potassium thioacetate, and thioacetic acid. After some optimization, the conjugate addition reaction using thioacetic acid proved to be the most successful, forming **3.27** in up to 96% yield (Table 4.2, entries 3-5). There was also a second, minor conjugate addition product formed in this reaction; a dithioacetate **4.53** was formed as a minor product in the reaction in which is detectable by a characteristic ^{13}C peak at 233 ppm. This is probably simply a result of dithioacetic acid contaminating the thioacetic acid reagent used (Scheme 4.17).

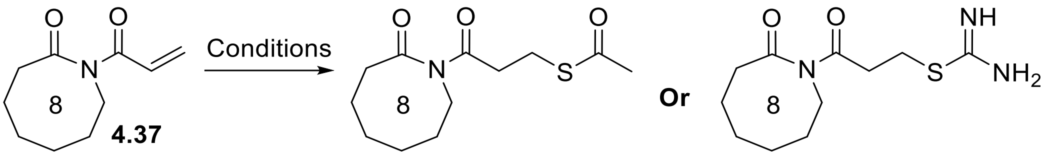
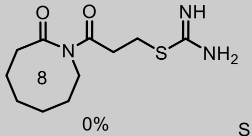
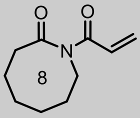
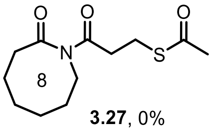
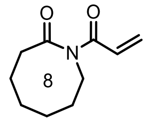
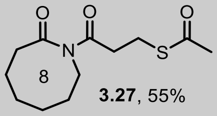
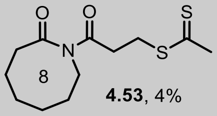
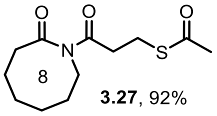
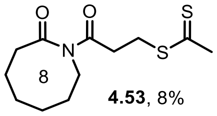
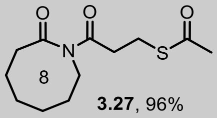
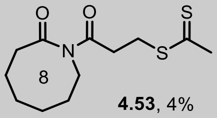
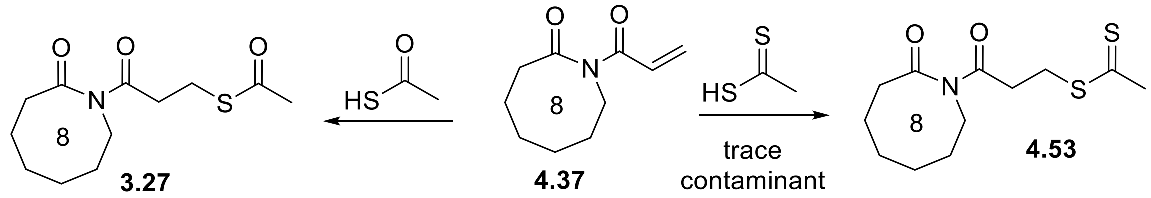


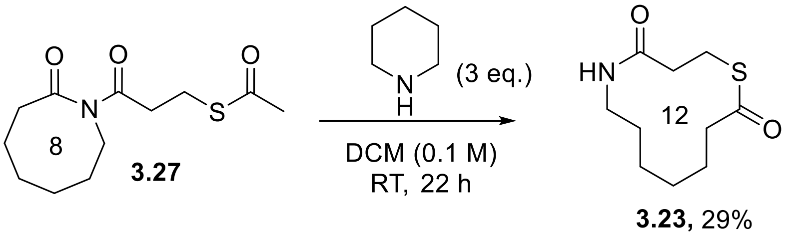
Table 4.2: Sulfur conjugate addition optimization.

Entry	Conditions	Scale / mmol of 4.37	Outcomes
1	Thiourea (1.1 eq.), TEA (3 eq.), MeCN (0.05 M), 4 h, RT, then 1 h, 85 °C	0.25	 0%  SM recovered: 76%
2	KSAc (3 eq.), TEA (0.6 eq.), EtOAc (0.1 M), 20 h, RT	0.25	 **3.27**, 0%  SM recovered: 52%
3	HSAc (3 eq.), TEA (0.4 eq.), EtOAc (0.2 M), 2.5 h	0.50	 **3.27**, 55%  **4.53**, 4%
4	HSAc (3 eq.), TEA (0.4 eq.), EtOAc (0.2 M), 2.5 h	2.0	 **3.27**, 92%  **4.53**, 8%
5	HSAc (3 eq.), TEA (0.4 eq.), EtOAc (0.2 M), 2.5 h	1.0	 **3.27**, 96%  **4.53**, 4%



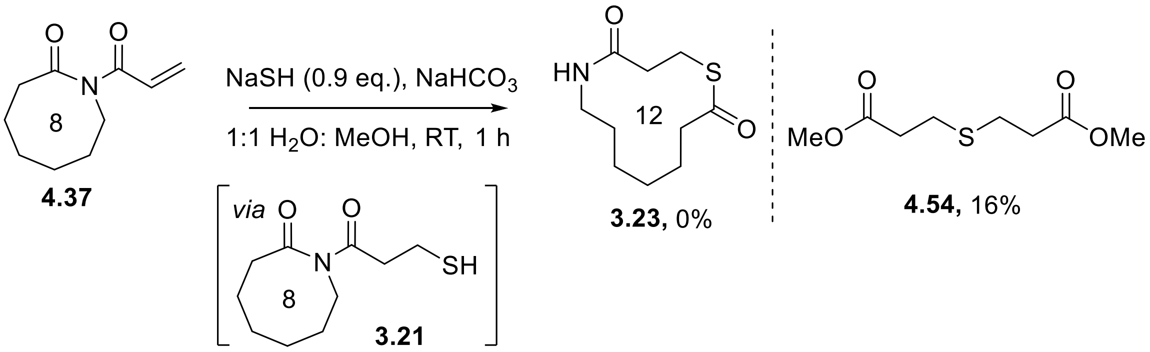
Scheme 4.17: Conjugate addition using thioacetic acid contaminated with trace **dithioacetic** acid forms **4.53** as a minor side product.

With the conjugate addition successfully performed in excellent yields using thioacetic acid, attention turned to deprotection and ring expansion. The aim was to cleave the thioacetate and trigger ring expansion. Indeed, conditions were optimized for this deprotection/ring expansion and described in Chapter 3, Section 3.2, thus enabling the desired thiolactone **3.23** to be formed in 29% (Scheme 4.18).



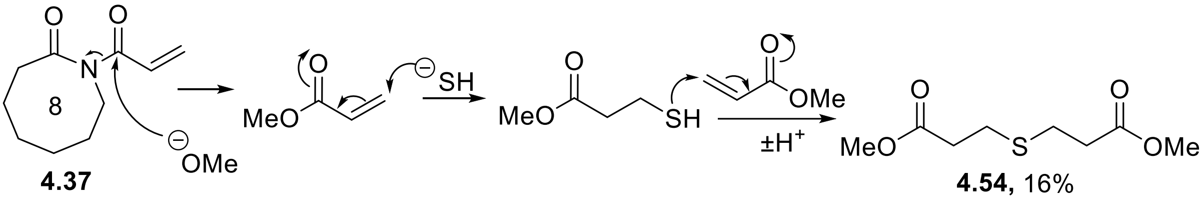
Scheme 4.18: Optimized deprotection ring expansion conditions convert thioacetate **3.27** to thiolactone **3.23**.

Additional studies investigated whether the conjugate addition and ring expansion could be performed in one pot to form **3.23**. As shown in Scheme 4.19 below, sodium hydrogen sulfide was used as the sulfur source, in the hope was that it would induce both these transformations to form thiolactone **3.23** (*via* **3.21**) without the need for a separate protecting group cleavage step. In order to solubilize this salt, a 1:1 mixture of water and methanol was used as solvent.[90] Unfortunately, the methanol solvent promoted a side reaction and cleaved the imide to some degree, forming **4.54**, with no evidence for the formation of macrocycle **3.23** (Scheme 4.19).



Scheme 4.19: Attempted sulfur conjugate addition using sodium hydrogen sulfide.

A proposed mechanism for the formation of **4.54** is indicated in Scheme 4.20. Although unsuccessful in producing the desired product **3.23**, the isolation of side product **4.54** is at least evidence that the conjugate addition step had occurred to some extent, alongside methanolysis of the imide **4.37**.



*Scheme 4.20: Proposed mechanism for the formation of **4.54**.*

A second attempt to perform the conjugate addition and ring expansion in one step was performed in a reaction using hydrogen sulfide gas (Scheme 4.21). This was done by constructing an H_2S generator (from reaction with iron sulfide and conc. HCl) and bleach scrubber as shown in Figure 4.1 below and passing the H_2S gas though a DCM solution of **4.37** (0.05 M with respect to **4.37**) and DBU (10 eq.).

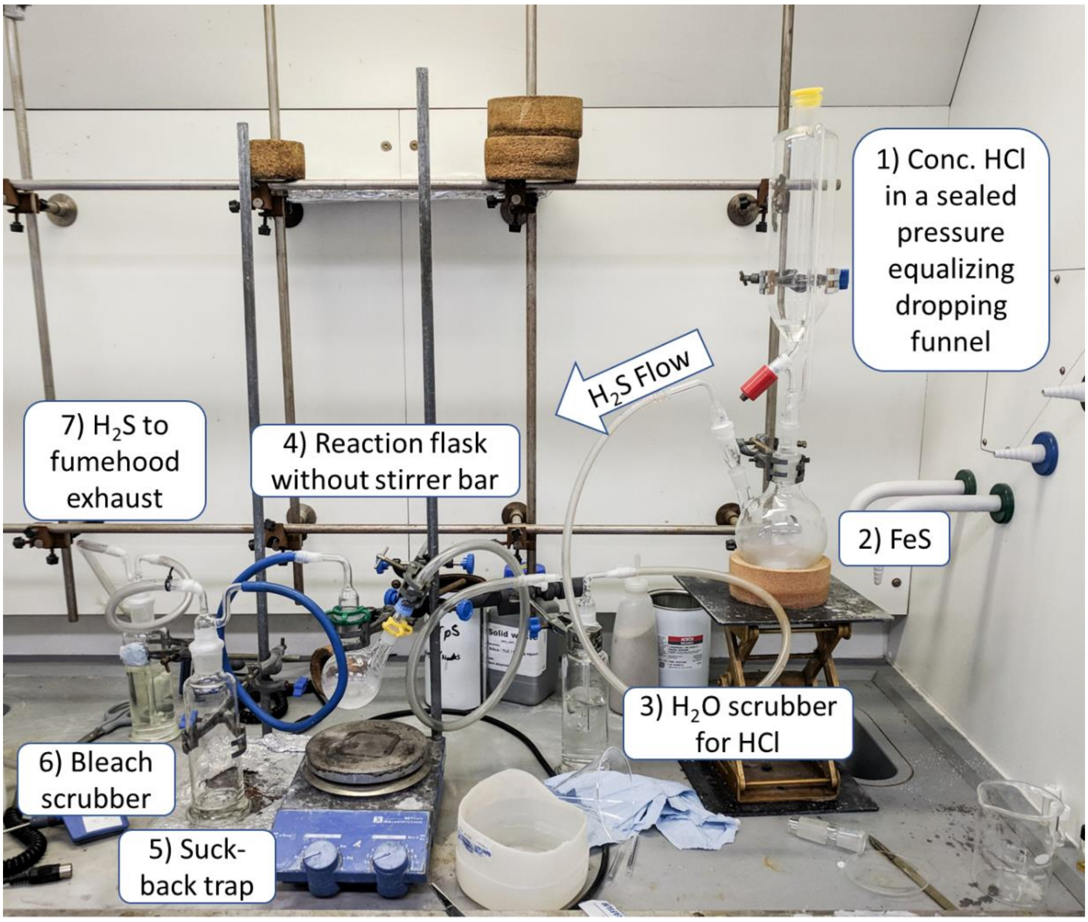
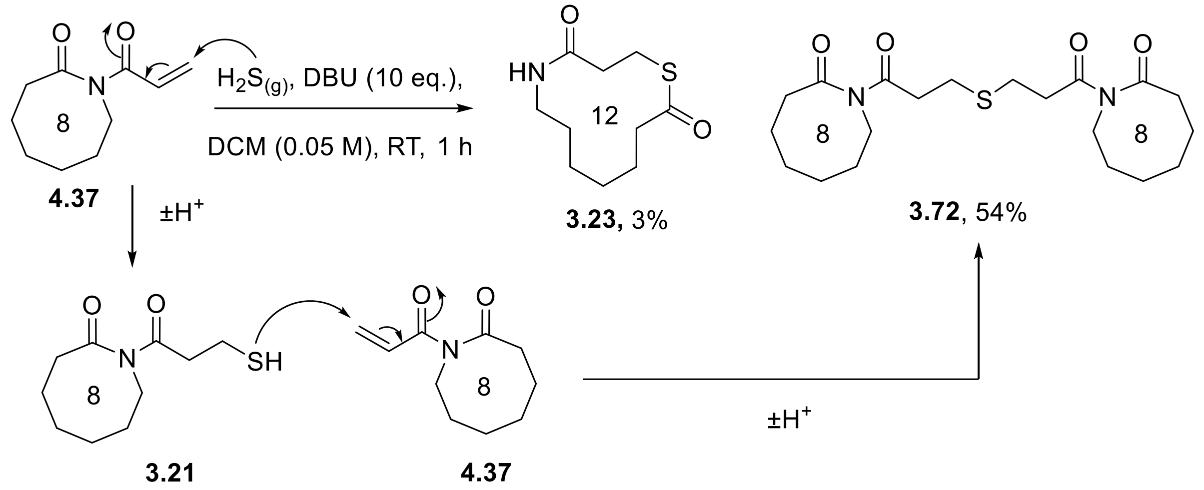


Figure 4.1: Setup of H_2S gas generator for attempted conjugate addition ring expansion (see Scheme 4.21).

This reaction predominantly formed the double conjugate addition product (**3.72**, 54%), as well as trace amounts of ring expanded product (**3.23**, 3%) (Scheme 4.21). Once thiol **3.21** is formed it can undergo an additional conjugate addition reaction to with imide **4.37** to form the symmetrical sulfide **3.72**. Unfortunately, this appears to outcompete ring expansion, in this system.



Scheme 4.21: Attempted Conjugate addition ring expansion using an H_2S gas generator.

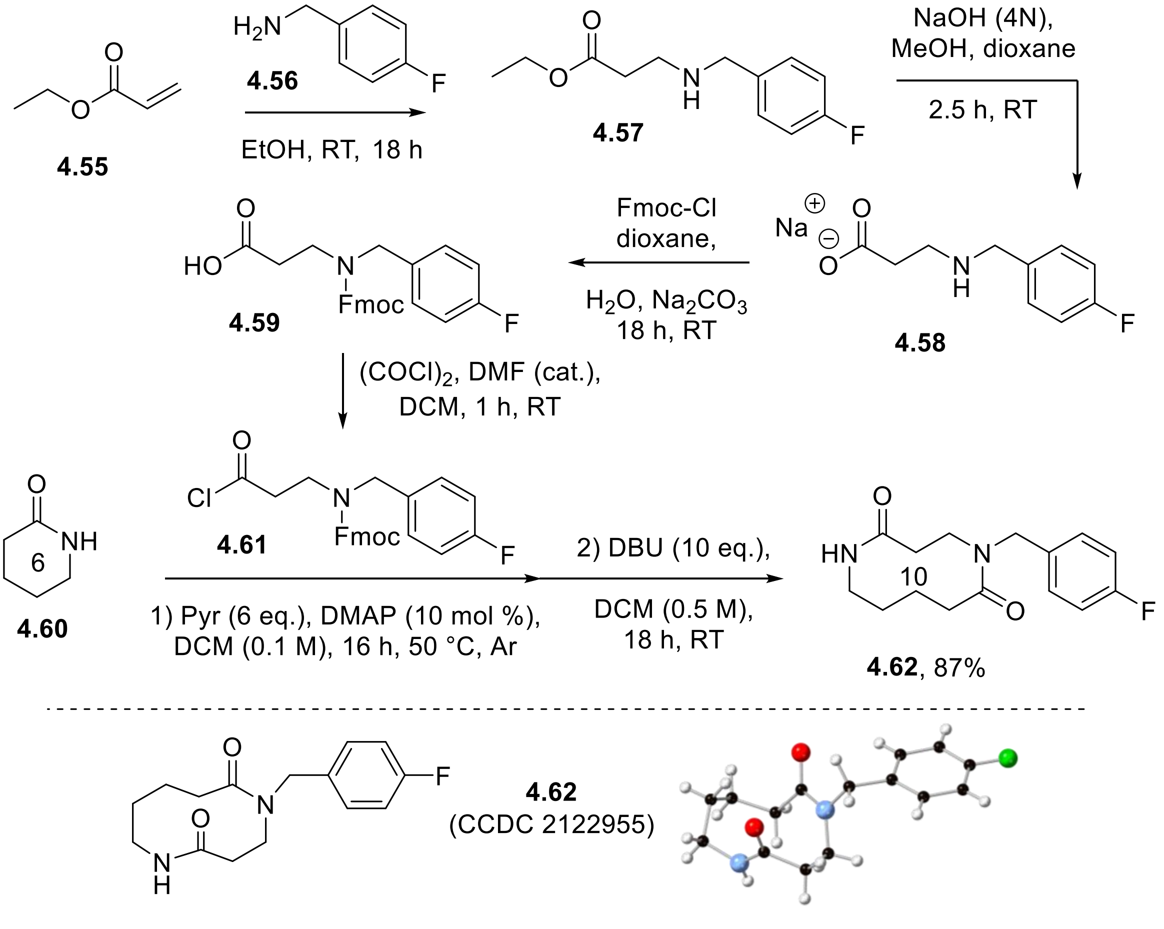
This problem of double conjugate addition effectively makes a cascade conjugate addition ring expansion using sulfur challenging to develop. Given that the SuRE method that makes use of protected thiol imides (described in Ch. 3) enables access to the same product class more effectively, it was therefore decided to move on to other nucleophiles for CARE.

4.4 Nitrogen CARE

4.4.1 Devising a model system for optimization

Attention next turned to developing and optimizing a nitrogen CARE reaction using primary amine nucleophiles. When deciding upon a model amine with which to test this idea, it was envisioned that para fluorobenzyl amine (**4.56**) would be a good choice, as its fluorine group would be unlikely to interfere with the reaction, but provide a convenient handle for reaction monitoring using ^{19}F NMR during condition optimization.

Before commencing optimization, an Fmoc protected, para fluoro benzyl beta alanine (**4.59**) was prepared to trial the desired ring expansion the standard SuRE method (thus establishing whether the ring expansion step is valid), and providing an authentic sample of ring expanded product to aid analysis. Thus, 6-membered lactam **4.60** was then ring expanded using this amino acid to form a 10-membered macrocycle (Scheme 4.22). The 6- to 10-membered ring expansion proceeded as expected with the desired 10-membered ring (**4.62**) isolated in 87% from the 6-membered lactam (**4.60**). This compound was subsequently used as a standard for the optimization of the nitrogen CARE reaction. The structure of **4.62** was also confirmed by XRD as shown Scheme 4.22, bottom.



Scheme 4.22: Synthesis of N-p-fluorobenzyl N-Fmoc beta alanine (**4.59**), and use to synthesize medium sized **4.62** via SuRE.

4.4.1.1 *Notes on NMR spectra and characterization*

Compounds such as **4.62** contain two or more amide functionalities that may adopt a cis or trans conformation. **4.62** has 2 amide bonds and 4 possible rotamers that can be adopted. These are: cis-cis, trans-trans, cis-trans, and trans-cis. In case of **4.62**, only two rotamers are observed, as seen in the ^{1}H, ^{13}C and ^{19}F spectra. For this class of compounds ^{19}F NMR proved to be a useful tool for probing the number of ^{19}F environments and their relative ratios. In CDCl$_3$ at RT the rotamer ratio was determined to be 2:15 by analysis of the ^{19}F NMR (Figure 4.2.b). This can serve as a proxy for rotameric ratio. Analyzing the ^{1}H NMR spectrum, can be challenging, therefore it is simpler to begin with analysis of the ^{13}C NMR spectrum which is often less prone to rotameric broadening. Figure 4.2.a shows that the ^{13}C NMR spectrum is well resolved with all of the carbons in the molecule accounted for (including select minor rotamer signals). Figure 4.2.c. shows ^{1}H NMR spectrum for the same sample of **4.62**. Here there is evidence of the two rotameric environments, most clearly seen in the amide NH environments and the benzylic CH$_2$ environments (highlighted in blue and red/orange respectively). The benzylic protons are particularly of note in this case as they are each in a different chemical environment (diastereotopic) and coupling to each other. This creates two doublets in the spectrum (at ca. 4.9 and 4.2 ppm). The same is true of the minor rotamer, where two doublets of lower integration are

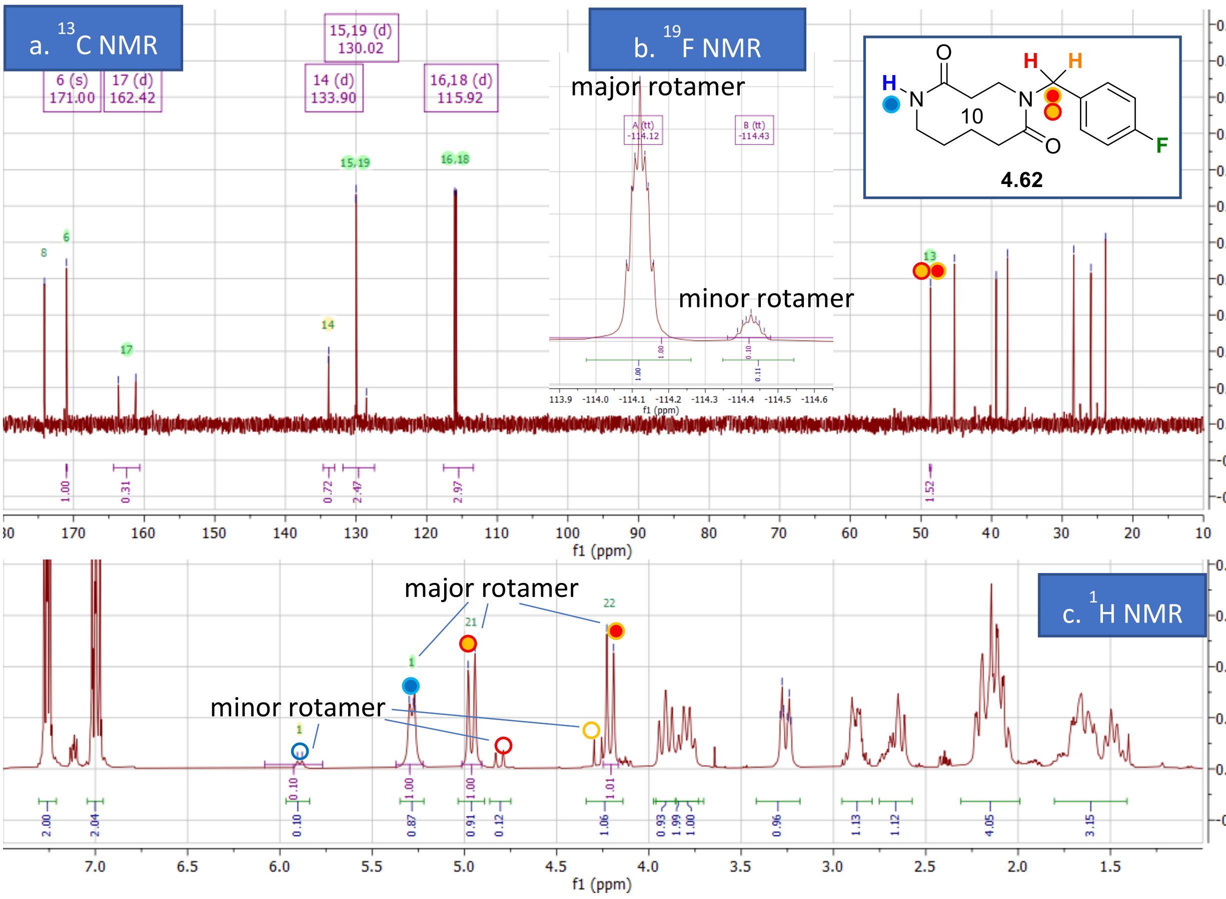


*Figure 4.2: Sample NMR data for **4.62** demonstrating complexity of multiple rotamers and diastereotopic protons.*

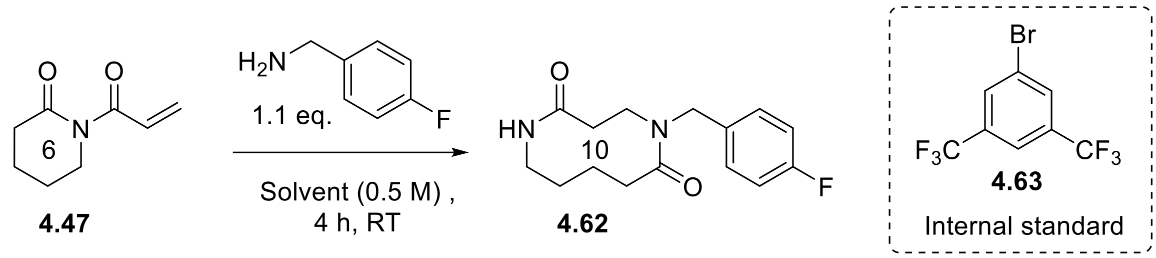
observed (denoted with the hollow circles). With the aid of DEPT and 2D data: COSY, HMQC, and (if available) HMBC, the compound can be assigned.

There are many challenges in characterization of these types of compounds. With multiple rotamers the effective concentration of each is lower than the concentration of total sample in solution. If there are two rotamers of 1:1 ratio observed in the ^{13}C NMR, and the concentration of the NMR sample is 50 mg/mL, then the effective concentration of each rotamer is 25 mg/mL, requiring more concentrated NMR samples, or a more sensitive NMR spectrometer to detect all the signals (especially for quaternary carbons such as carbonyls and ArC carbons). This is particularly a problem with successive examples (see Ch. 5 Experimental data compound **4.133** in $CDCl_3$ at RT for example). If observing each rotamer is not critical, elevated temperature NMR can be used to promote faster rotamer interconversion which may simplify the spectrum (as seen in the d_6-DMSO at 120 °C for compound **4.133**).

The general approach to characterizing these compounds is as follows. Begin by inspecting the ^{13}C NMR spectrum to assess whether the appropriate number of carbon signals are present. If available, inspect the ^{19}F NMR spectrum to estimate the number of rotamers. Next inspect the ^{1}H NMR spectrum and assign beginning with NH, benzylic protons, CH_2 protons adjacent to NH, and CH_2 protons adjacent to amide carbonyl. These signals have been roughly listed in the order that they appear, downfield to upfield. In all instances, the assignments will be verified using 2D data (COSY, HMQC, and HMBC if available) as well as DEPT.

4.4.2 Solvent optimization

With the desired 10-membered ring expanded product standard **4.62** in hand (**4.62**), work began on optimizing the nitrogen CARE reaction. Optimization reactions were set up on 0.5 mmol scale using the conditions indicated in Scheme 4.23. After stirring for 4 hours, 1.1 equivalents of 3,5-bis(trifluoromethyl)bromobenzene (**4.63**) was added as an internal standard. Next, an aliquot of 0.2 mL of the mixture was taken out and to it was added 0.6 mL of $CDCl_3$ (without removal of the reaction solvent) to make an NMR sample. ^{1}H, ^{13}C, and ^{19}F NMR data was acquired for each sample, and the results of optimization reactions were quantified by integration of the ^{19}F NMR signals with respect to the internal standard. Note that despite the presence of large amounts of protic reaction solvents in each sample, there was no issue with regards to ^{19}F NMR analysis, where all but two of the solvents tested do not contain fluorine. In the case of TFE and HFIP (Table 4.3, entry 18–19) ^{19}F solvent signals were observed, but did not overlap with the signals of **4.63** nor **4.62**.

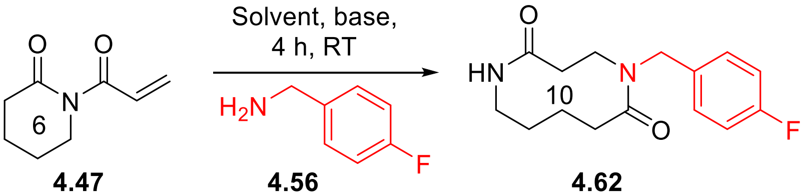


*Scheme 4.23: Model CARE reaction, monitored with **4.63** internal standard by ^{19}F NMR.*

4.4.2.1 Results of solvent optimization

Using the method described in Scheme 4.23, an optimization of solvent conditions was undertaken and the result summarized in Table 4.3. Initially, imide **4.47** (1 equiv) and amine **4.56** (1.1 equiv) were stirred in DCM (0.1 M) at RT with an excess of DBU (10 equiv). These conditions were chosen to begin as they have been used to promote the ring expansion step in the SuRE methodology. Gratifyingly, this resulted in modest conversion (33%) into 10-membered lactam **4.62** (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.[91] This change did not improve conversion, but it had no significant negative impact either so was retained for further optimization. It was then reassessed whether the base was necessary, as the primary amine nucleophile could also act as a base. Performing the same reaction without DBU led to improved conversion (entry 3).

A range of other solvents were then explored (entries 4–20); in total, 18 were tested and remarkably, all resulted in some conversion into 10-membered lactam **4.62**, including solvents compatible with biological systems, most notably water (entry 20). Overall, polar solvents tended 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 **4.62** isolated in 86% following column chromatography. This synthetic reaction was done on a relatively large scale (5.0 mmol) using methanol as the solvent (entry 14, 86%). 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 (with examples provided in the upcoming discussion, see section 4.4.3.1).



4.47 **4.56** **4.62**

Table 4.3: Solvent optimization of Nitrogen CARE reaction.

Entry	Solvent	Conc.	Base	**4.62/%**[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 **4.47** (1 equiv) and amine **4.56** (1.1 equiv) were stirred in the stated solvent (0.5 M) at RT for 4 h unless stated. 3,5-Bis(trifluoromethyl)bromobenzene **4.63** (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 **4.62** was determined by the ratio of the ^{19}F NMR resonance of **4.62** to that of the 3,5-bis(trifluoromethyl)bromobenzene **4.63** internal standard. [b] 18 h reaction time. [c] Isolated yield in parentheses.

Note, to verify that the ^{19}F peak the conversion data were based on belonged to the 10-membered ring product **4.62**, a solution of **4.62** (synthesized as described in Scheme 4.22) in $CDCl_3$ was added to each NMR sample, and the sample analyzed a second time by ^{19}F NMR data. Comparison of the aliquot data before and after doping with additional **4.62** allowed for the ^{19}F signal to be confirmed as belonging to the desired product, as illustrated in Figure 4.3.

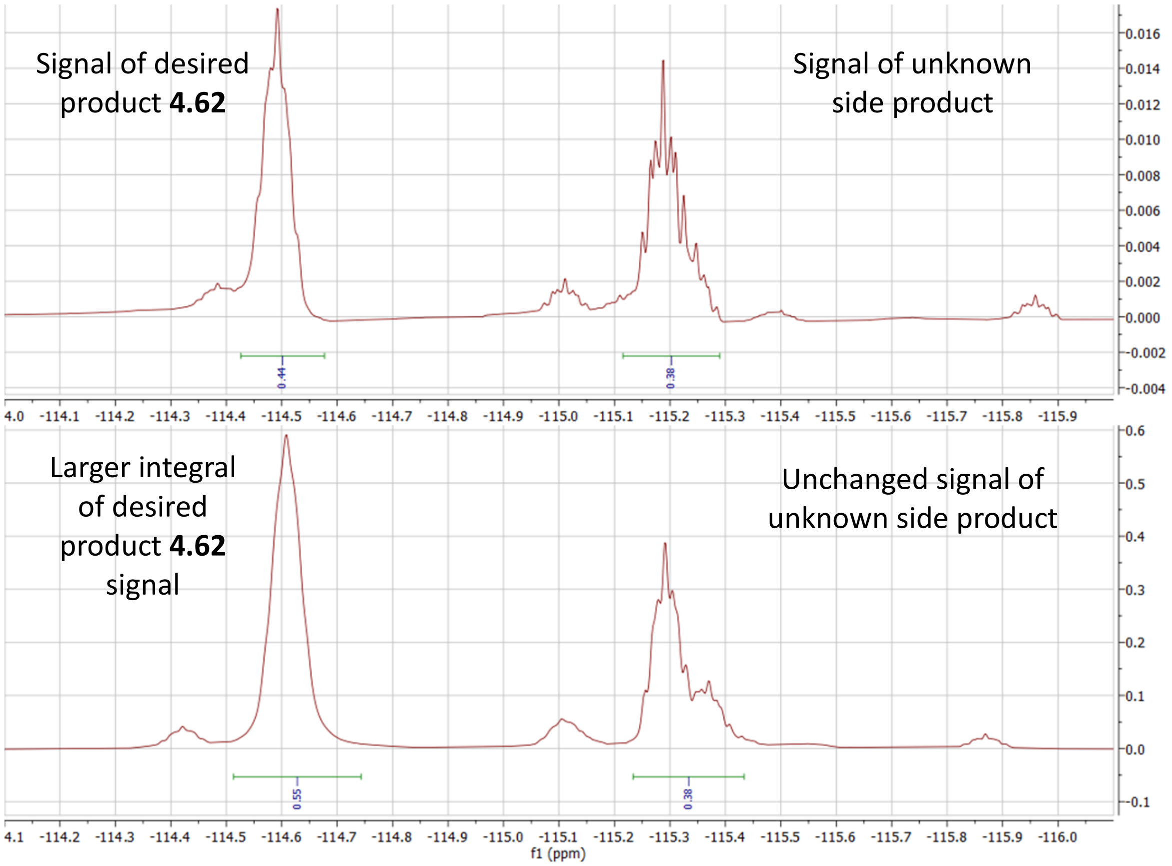
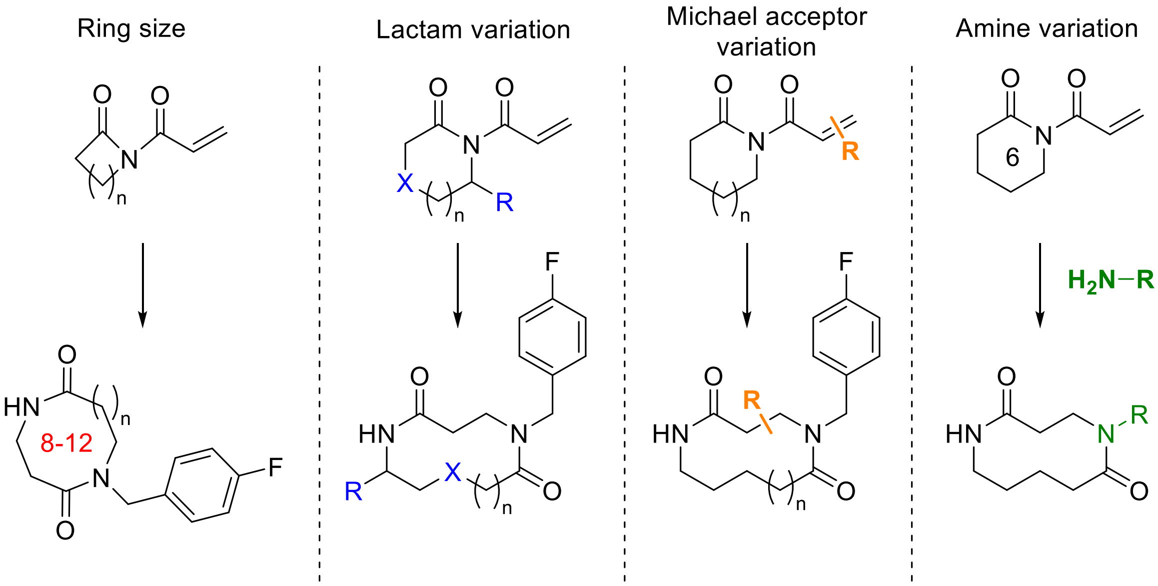


Figure 4.3: Segment of ^{19}F NMR of Et_2O reaction aliquot (above) showing two areas of signals with similar integration. The spectrum of the doped aliquot containing additional 10-membered ***4.62*** *(below) aided confirmation of product signal.*

4.4.3 Scope of Nitrogen CARE reaction

With optimized nitrogen CARE conditions in hand, attention turned to investigating the scope of this reaction. The scope was studied by investigating 4 key variables: ring size, lactam variation, Michael acceptor variation, and amine variation (Scheme 4.24).

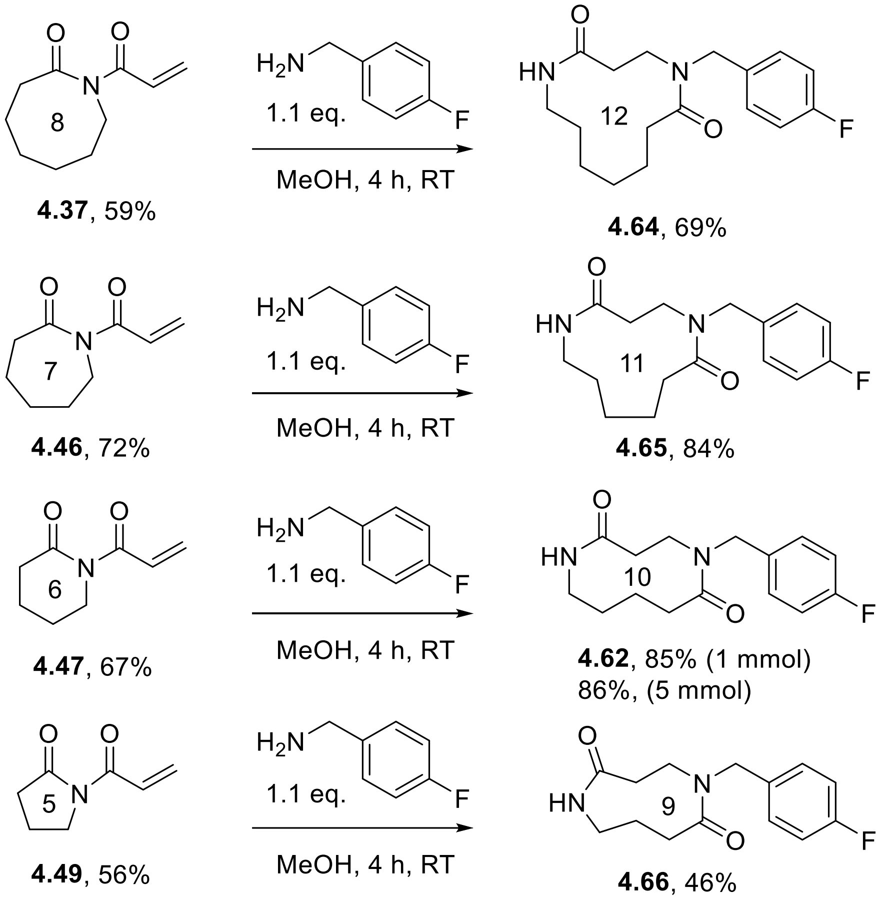


Scheme 4.24: 4 different variables to investigate for scope of nitrogen CARE reaction.

4.4.3.1 Ring size screen

Previous SuRE studies have shown that lactams as small as 4-membered in size and as large as 13-membered (even larger for successive examples) can undergo a 4-atom ring expansion using β-alanine derivatives.[48] It was decided to attempt the nitrogen CARE on lactams from 4-8 membered in size. This would allow a convenient method to access medium sized and macrocyclic rings (8-12 membered).

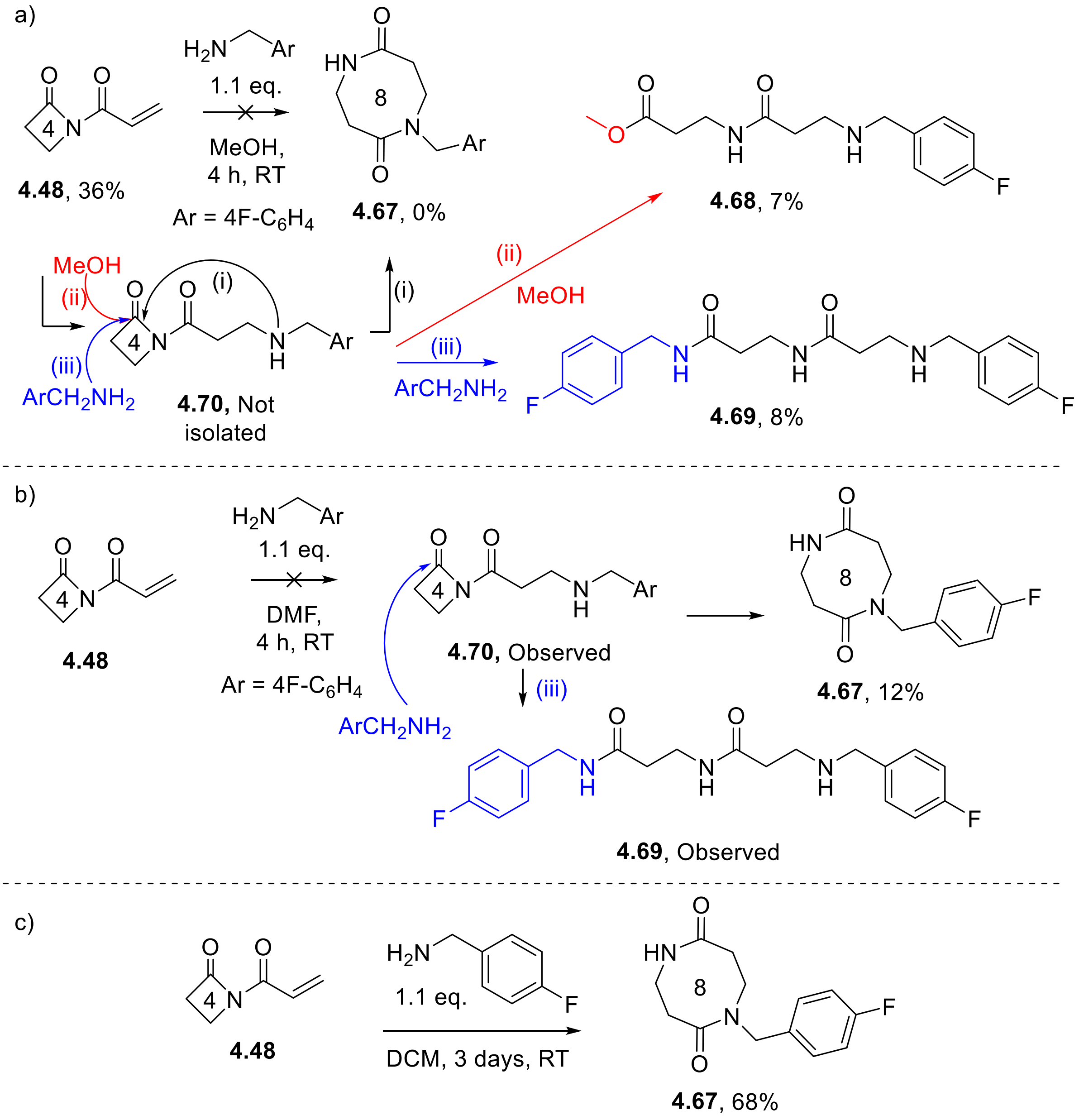
To start, 8-membered **4.37** and 7-membered **4.46** were subjected to the optimized conditions, furnishing the desired 12- and 11-membered bis-lactams in 69% (**4.64**) and 84% (**4.65**) respectively (Scheme 4.25). Next, attention turned to expanding 5-membered **4.49** to 9-membered **4.66**, which proceeded in a more modest 46% yield. It is worth noting that Dr Tom Stephens attempted a similar ring expansion using SuRE to form the *N*-benzyl variant of 9-membered **4.66**, however the analysis of that compound proved to be challenging. Indeed, in the case of **4.66**, both the ^{1}H and ^{13}C NMR data suffered from severe rotameric broadening, but the ^{19}F NMR suggested a new compound was formed and was consistent with ring expansion. Running the ^{13}C NMR at elevated temperature (55 °C in $CDCl_3$) helped to resolve the rotameric broadening and confirm the product identity. In general product identity and purity was best determined by analysis of the ^{13}C NMR data, especially in instances where rotameric broadening was severe.



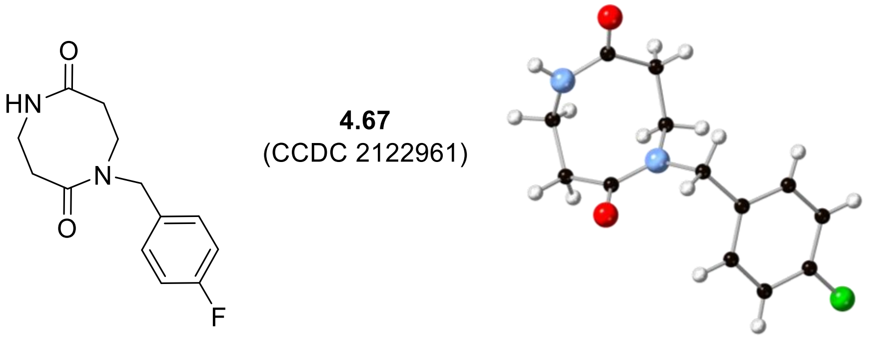
Scheme 4.25: Ring size screen for imides 8-5 membered in size.

The reaction of 4-membered lactam starting material **4.48** was less straightforward, therefore is covered separately. An initial attempt, using the optimized methanol conditions, was unsuccessful, with only ring opening of the β-lactam observed. These side products are believed to form as a result of methanol or para fluorobenzyl amine attacking the β-lactam carbonyl, causing ring opening to form **4.68** and **4.69**, respectively (Scheme 4.26a (ii) and (iii)). A second attempt was performed using DMF as a solvent, and some of the desired 8-membered product **4.67** was observed alongside side product **4.69**. Unexpectedly, the ring opened imide isomer (**4.70**) was also observed and isolated. Imide **4.70** gradually rearranged to form 8-membered **4.67** in $CDCl_3$ NMR solvent and crystallized inside the NMR tube. This was fortuitous, as it allowed an X-ray crystal structure to be obtained for the 8-membered product **4.67** (Figure 4.4).

With the observation that desired conjugate addition was occurring but the ring expansion was not complete in DMF at 4 h, it was decided to attempt the reaction in DCM for an extended time (3 days), and pleasingly, this led to a much-improved yield of 68% of **4.67**.



Scheme 4.26: Optimization of 4→8 ring expansion using different solvent conditions

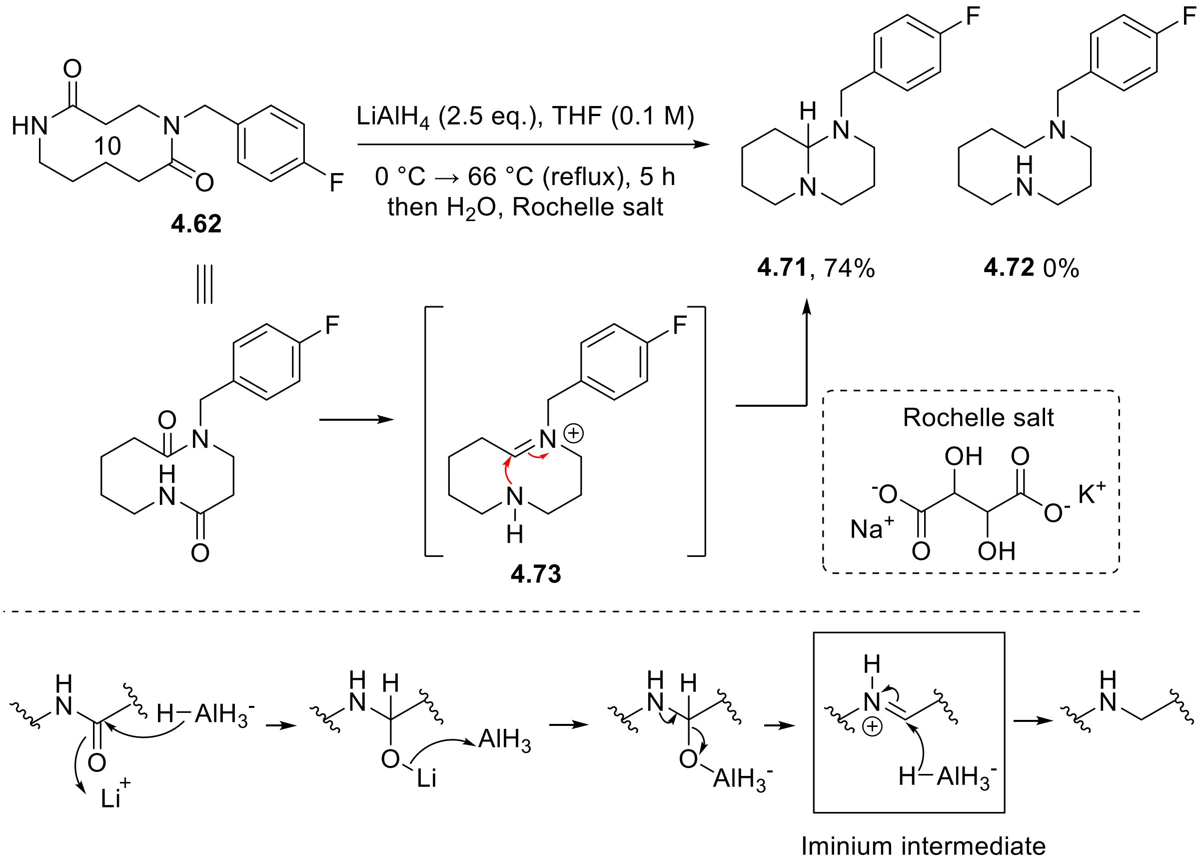


4.67
(CCDC 2122961)

*Figure 4.4: X-ray crystal structure of **4.67**.*

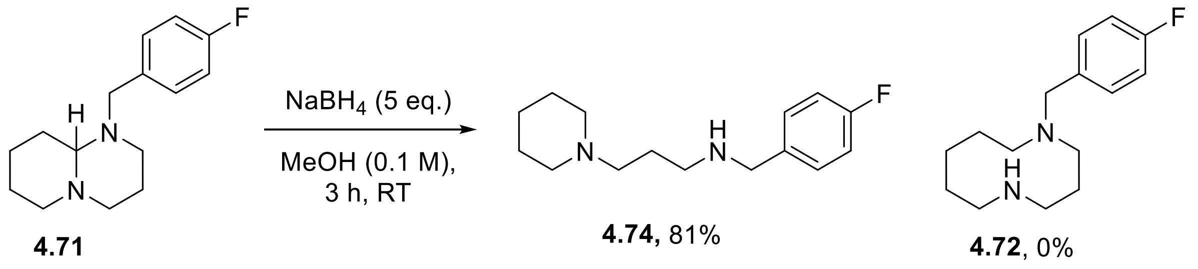
4.4.3.2 Reduction trials of N-CARE products

Following completion of the ring size screen, attempts were made to reduce two CARE bis-lactams to the corresponding cyclic diamines, as we reasoned the reduced products would be useful as synthetic building blocks. Initially, 10-membered **4.62** was reacted with lithium aluminium hydride in THF, but none of the desired diamine product (**4.72**) was observed. Instead, a fused bicyclic side product was isolated in 74% yield (**4.71**) (Scheme 4.27). This is believed to form *via* intermolecular nucleophilic attack from the secondary amine into an iminium intermediate which forms during reduction.



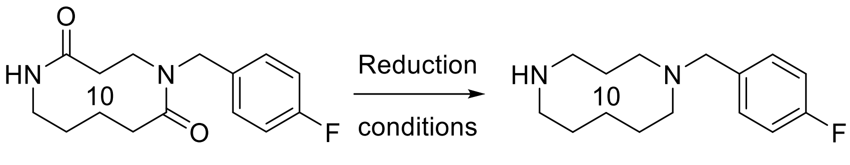
*Scheme 4.27: Attempted $LiAlH_4$ reduction of **4.62** produced side product **4.71** via intramolecular nucleophilic attack of the partially reduced iminium intermediate **4.73**.*

Reacting **4.71** with $NaBH_4$ in methanol led to ring opening to form substituted piperidine side product **4.74** exclusively in 81% yield with none of the desired 10-membered **4.72** observed (Scheme 4.28).



*Scheme 4.28: Attempted $NaBH_4$ reduction of **4.71**.*

Further attempts at reducing 10-membered **4.62** using different conditions are outlined in Table 4.4. BH_3-THF did not produce any of the desired product, with 66% of the starting material recovered following workup (entry 1). The use of a Lewis acid also did not aid the reduction (entry 2). Finally, refluxing BH_3-SMe_2 for 3 days produced reduced product **4.72**, albeit in a modest 23% yield (entry 3).

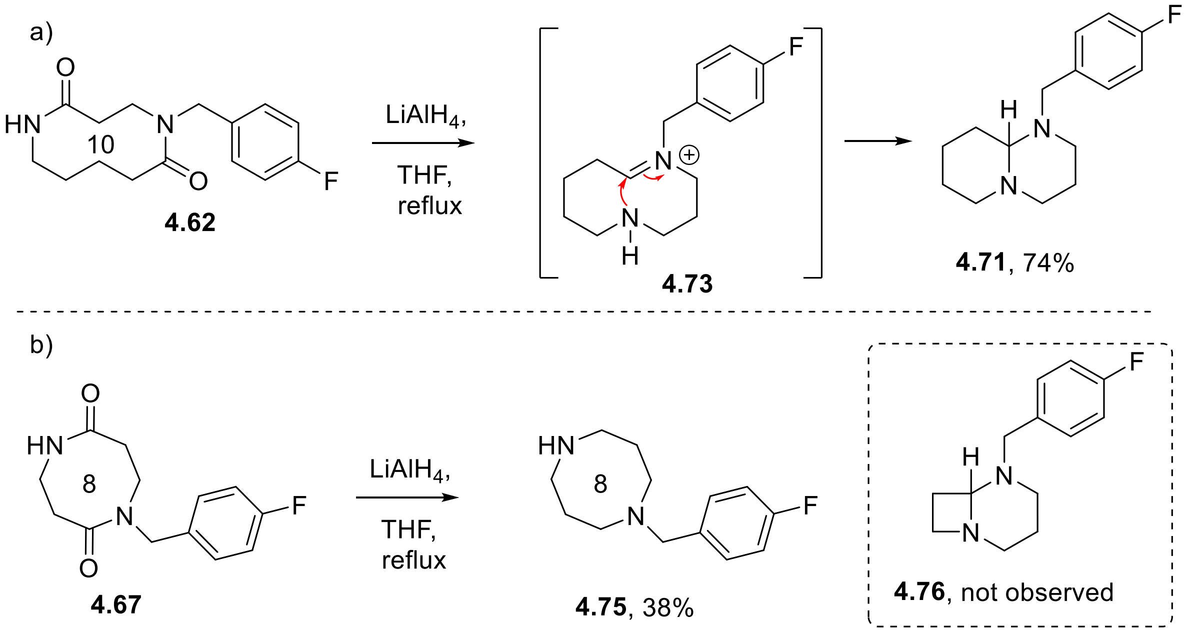


4.62 **4.72**

Table 4.4: Attempted reduction of 10-membered ***4.62****.*

Entry	Conditions	Yield of 4.72 / %
1	BH_3–THF, THF (0.1 M), RT→66 °C, 21 h	0 (66% recov. **4.62**)
2	$TiCl_4$ (1.5 eq.), $NaBH_4$ (3 eq.), DME (0.2 M), 0 °C→RT, 15 h	0
3	BH_3–SMe_2, THF (0.3 M), RT→66 °C, 3 days	**23**

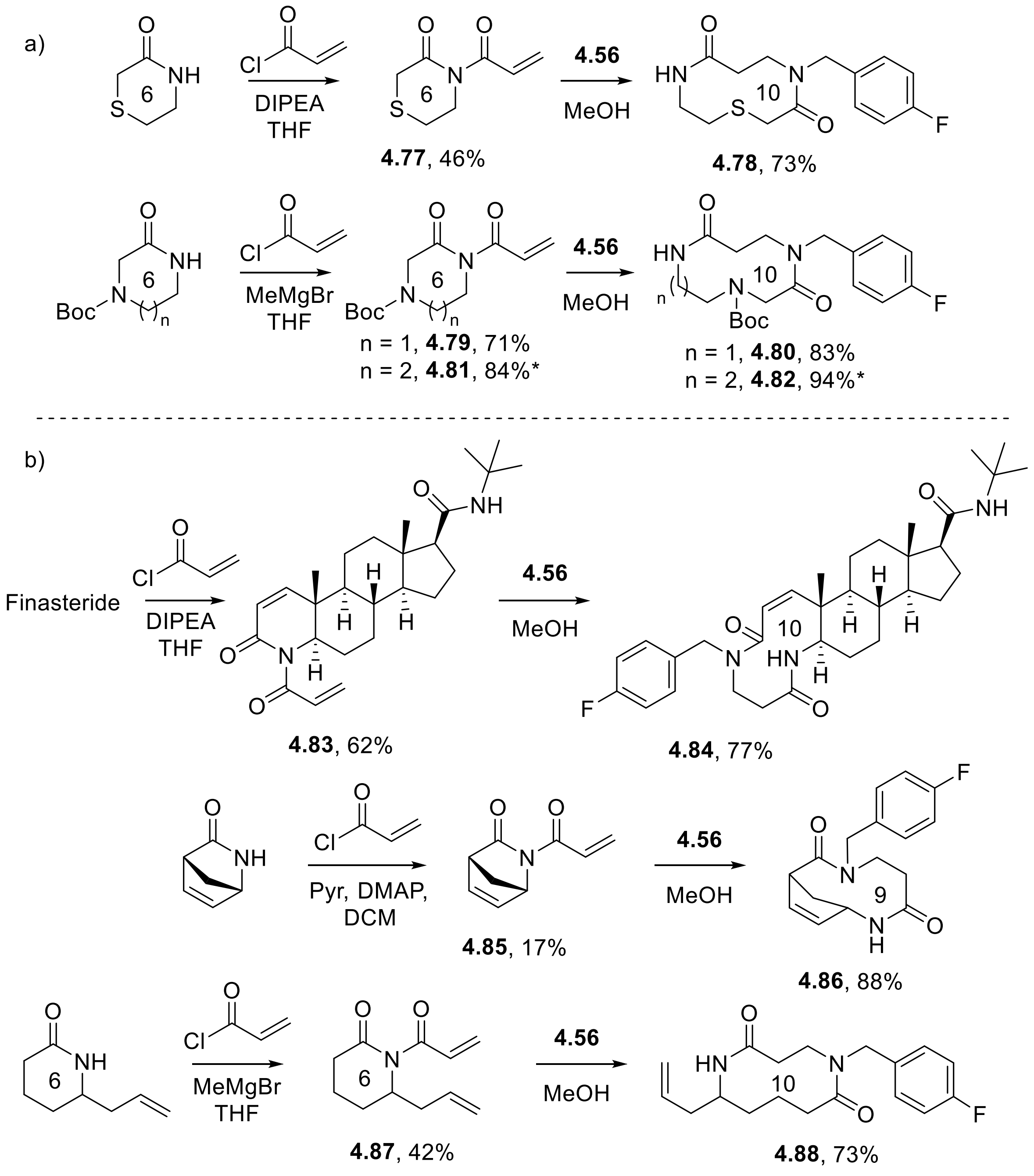
One of the problems with this reaction is that standard $LiAlH_4$ reduction conditions readily leads to side-product formation when 10-membered **4.62** is used as a substrate. This is presumably due to a comparatively low energy side-reaction whereby the medium sized 10-membered ring is converted into two fused 6 membered rings, which is likely to be thermodynamically favourable (Scheme 4.29a). We considered that this pathway might be suppressed if the ring-closing reaction required cyclization *via* a more strained 4-membered ring, as would be the case for the reduction of 8-membered **4.67**. Indeed, using this substrate, the desired reduced product was isolated in 38% yield (Scheme 4.29b).



Scheme 4.29: $LiAlH_4$ reduction conditions applied to different ring sizes of bis-lactam.

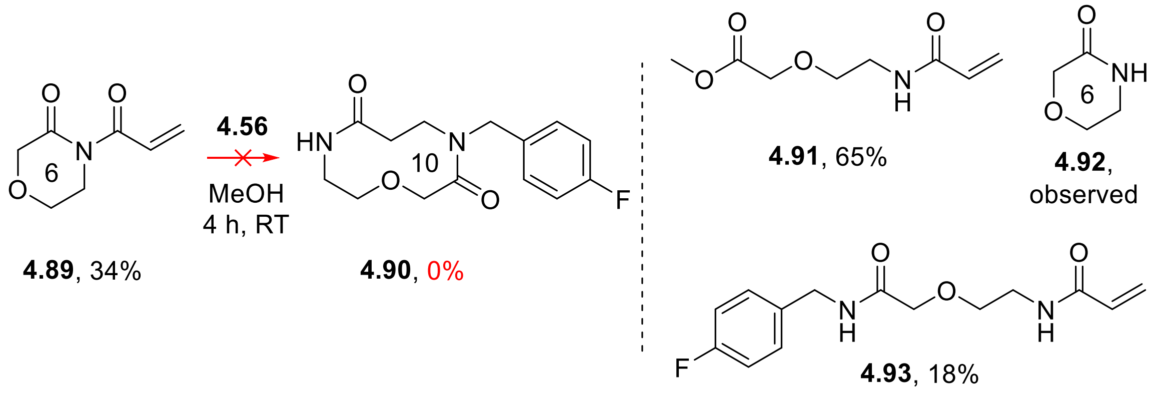
4.4.3.3 Lactam scope for Nitrogen CARE

The next study to probe the scope of CARE investigated the outcome of CARE reactions using functionalized lactam starting materials. Lactams containing heteroatoms in the form of a sulfide (**4.77**), and a carbamate (**4.79** and **4.81**), were investigated and formed the desired CARE products in good yields (11-membered **4.82** was synthesized by Zhongzhen Yang) (Scheme 4.30a). In addition, aza-steriodal (**4.83**), fused ring containing (**4.85**), and alkene containing lactam **4.87** were all utilized successfully to form CARE products **4.84**, **4.86**, and **4.88** in high yields. The acylation of **4.83** was selective for the lactam amide, likely due to the hindered nature of the *t*-Bu amide (Scheme 4.30b).



*Scheme 4.30: Lactam scope for Nitrogen CARE. Reactions denoted with * were performed by Zhongzhen Yang.*

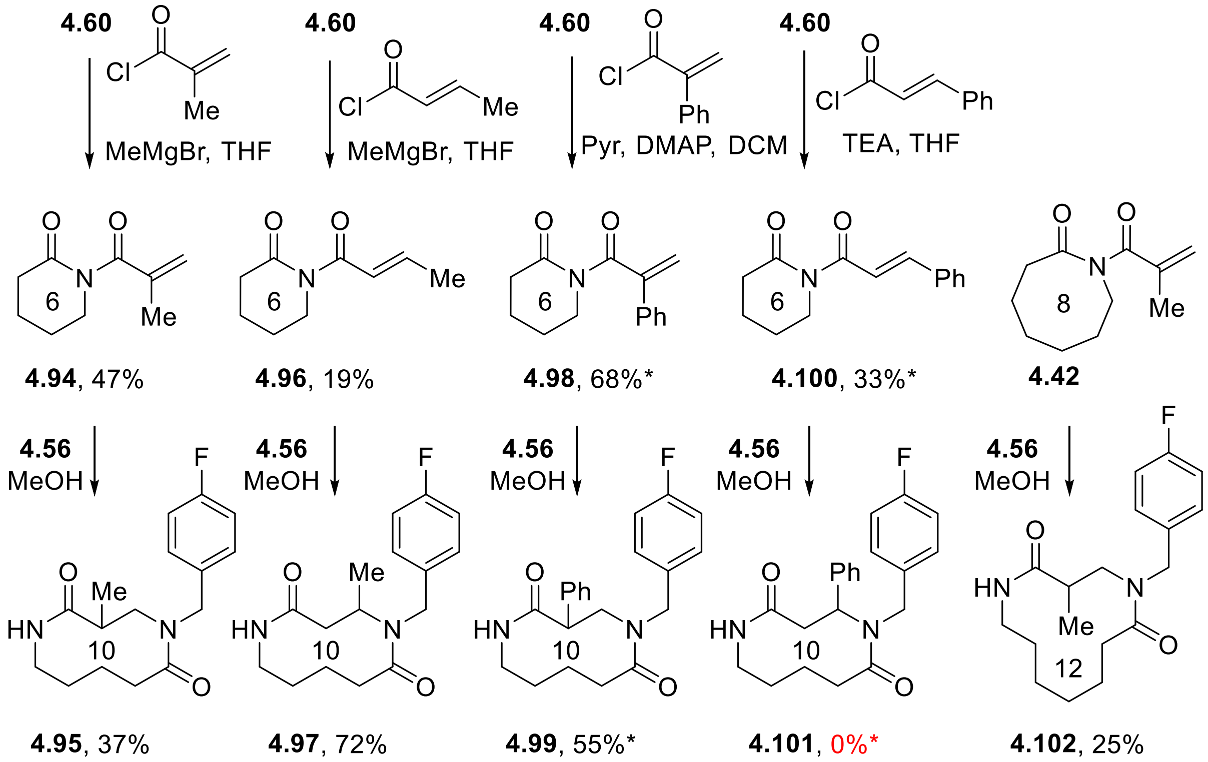
One example in the lactam series was not successful (Scheme 4.31). When morpholinone derived imide **4.89** was reacted using the standard conditions, there was no evidence of the desired product **4.90** being formed. Instead, this imide reacted preferentially at the imide carbonyl instead, to form ring opened side products **4.91** and **4.93**. This highlights one of the limitations of this methodology; in instances where conjugate addition is slow, side reactions are possible, with the two carbonyl groups offering alternative electrophilic sites. The side reactions can include solvolysis by methanol, as well as reaction with the amine nucleophile.



Scheme 4.31: Unsuccessful morpholine CARE example, only side product formation was observed.

4.4.3.4 Scope for branched Michael acceptors

Next the scope of variation on the Michael acceptor was investigated. Four substituted acryloyl imides were synthesized from 6-membered δ-valerolactam (**4.60**). The results shown in Scheme 4.32 indicate that branching is tolerated, except for the β-phenyl cinnamoyl example **4.100**, which failed to produce any of the desired product **4.101**. Some of the acylations and ring expansions presented in Scheme 4.32 were performed by Unsworth group PhD candidate Zhongzhen Yang (denoted with *). Previously synthesized 8-membered methacryloyl imide **4.42** was also trialled in a CARE reaction, leading to a low 25% yield of the desired 12-membered bis-lactam **4.102**. Each of the branched examples in Scheme 4.32 is lower yielding than the unsubstituted acryloyl imide example (up to 86%). However, one advantage of substituted imides is that they are significantly more stable than their unsubstituted acryloyl counterparts. For instance, 8-membered methacryloyl **4.42** remained unreacted after 2 years stored in the fridge. Normally, unsubstituted acryloyl imides have a shelf life of 1−2 weeks at room temperature, or 1−2 months at 4 °C.



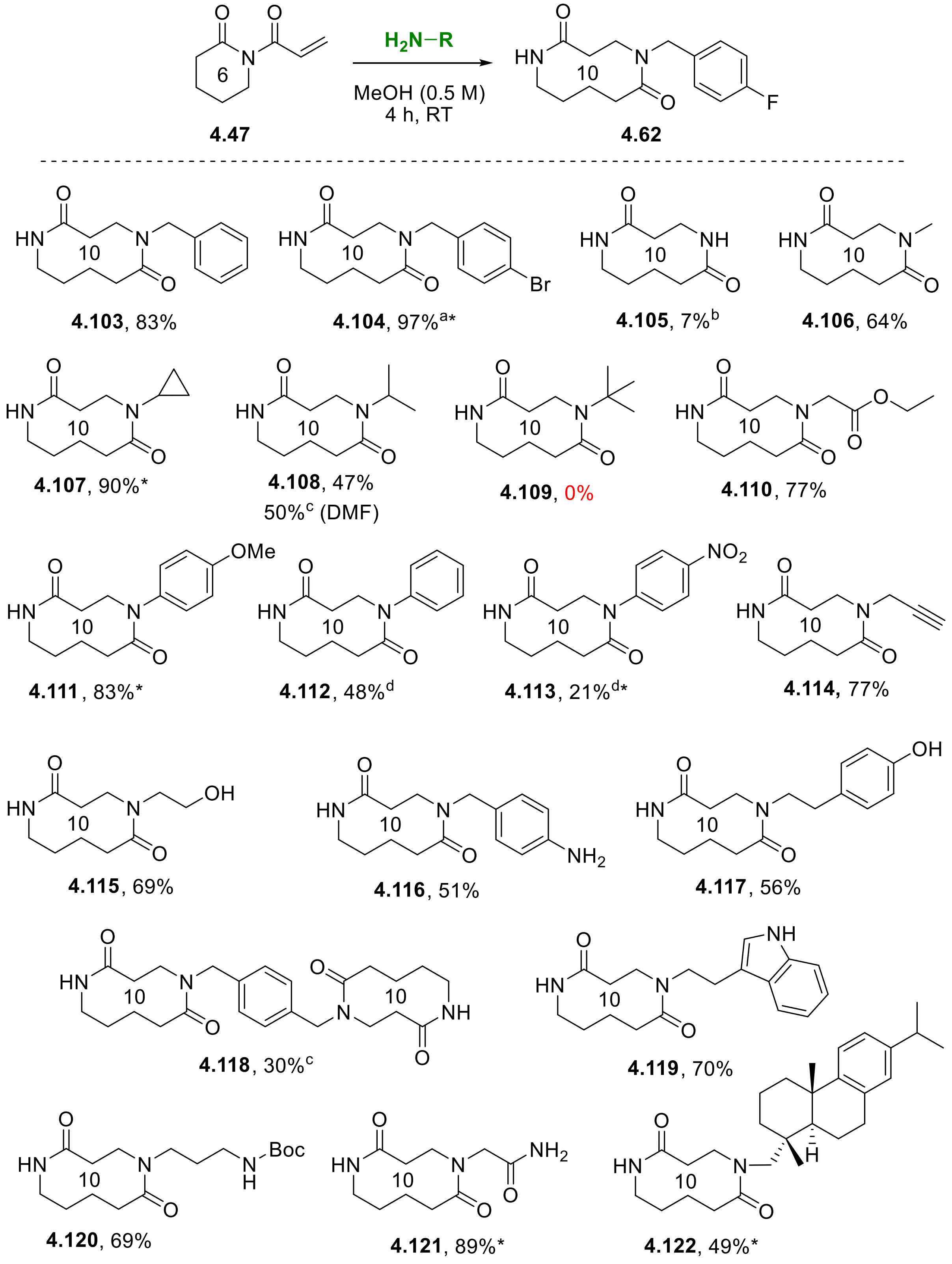
*Scheme 4.32: Scope for branched Michael acceptors. Reactions denoted with * were performed by Zhongzhen Yang.*

4.4.3.5 Scope of primary amine nucleophile

An extensive study was carried out to determine the scope of compatible primary amines in nitrogen CARE reactions, using 6-membered ring imide starting material **4.47** (Scheme 4.33). The ability to vary this nucleophile is a key feature of this chemistry. Trials began by investigating other benzyl amine derivatives (**4.103** and **4.104**) which produced a near quantitative 97% yield in the 4-bromo benzyl amine example (reaction performed by Zhongzhen Yang). In this instance, a precipitate formed which stopped stirring completely after 2 hours, but clearly, based on the high yield, this did not negatively affect the reaction. Next, simple alkyl substituents were trialled, to probe steric effects on the CARE reaction. Here, a clear trend emerges showing that increased steric bulk inhibits reactivity. The relatively unhindered cyclopropylamine takes part in CARE in excellent yield (**4.107**, 90%). In comparison, when using isopropylamine to form **4.108**, a significant quantity of ring opened side product **4.123** was isolated (Scheme 4.34). Repeating this reaction in DMF led to a small improvement in yield. The tertiary butylamine derived product **4.109** was not formed at all, with a mixture of ring opening and de-acylation products observed instead (Scheme 4.34). A series of aniline examples provide insights into the role electronic effects play in the CARE reaction. Electron-rich 4-methoxy aniline produced the desired product **4.111** in good yield in 4 h. Aniline itself only resulted in 48% yield of **4.112** after 3 days, whereas electron poor 4-nitro aniline resulted in even lower yield of **4.113** (21%)

after the same extended reaction duration. The substituent on aniline affects its nucleophilicity and therefore its efficiency in conjugate addition reactions.

Following this a series of diversely functionalized primary amine nucleophiles were trialled in the CARE reaction. Pleasingly, other nucleophilic functionalities such as alcohols, phenols, primary amides and aniline were all well tolerated, with the alkyl amine moiety outcompeting these to perform the aza-Michael reaction and ring expansion in the usual way. A range of other functionalities also performed well in CARE reactions, including terminal alkynes **4.114** and protected amino acids (**4.110**). Leelamine, a bioactive primary amine, was successfully used in a CARE reaction (**4.112**), as was bifunctional p-xylylene diamine, which formed bis-lactam **4.118**. Zhongzhen Yang assisted with the amine scope; these reactions are denoted by *. Additional examples demonstration the amine scope were performed by Zhongzhen Yang are not presented in this Chapter but have been reported in our publication.[92] Additional functionality represented in these successful CARE reactions include heteroaromatic examples, a morpholine containing product, and a hydroxylamine.



4.47

4.62

4.103, 83%

4.104, 97%[a]*

4.105, 7%[b]

4.106, 64%

4.107, 90%*

4.108, 47%
50%[c] (DMF)

4.109, 0%

4.110, 77%

4.111, 83%*

4.112, 48%[d]

4.113, 21%[d]*

4.114, 77%

4.115, 69%

4.116, 51%

4.117, 56%

4.118, 30%[c]

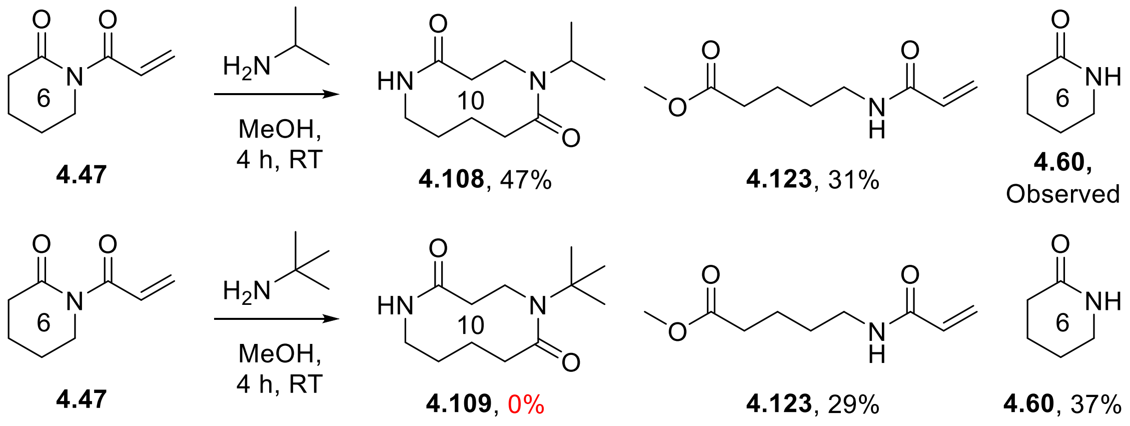
4.119, 70%

4.120, 69%

4.121, 89%*

4.122, 49%*

*Scheme 4.33: Primary amine scope screen for Nitrogen CARE reactions. Reactions denoted with * were performed by Zhongzhen Yang. [a] reaction stirred for 2 h. [b] using NH$_3$ in MeOH (7 M). [c] DMF (0.5 M) used in place of MeOH. [d] reaction stirred for 3 days.*



Scheme 4.34: Side reactions observed with bulky amines.

Overall, the scope for CARE reactions has been demonstrated to be very broad. Ring sizes from 4- to 8-membered in size have been explored, branching of the acryloyl group is tolerated, and the scope of primary amines that can be used in the reaction is very broad. This inspired Figure 4.5 below, which highlights that CARE allows the synthetic chemist to 'mix and match' substituents in order to customize the structure and fuctionality of the final ring expanded product.

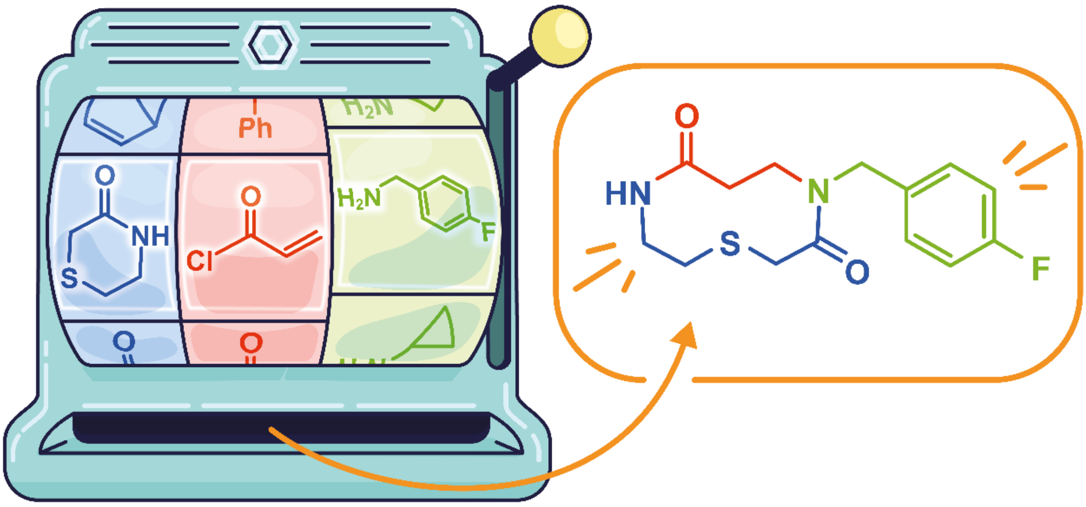
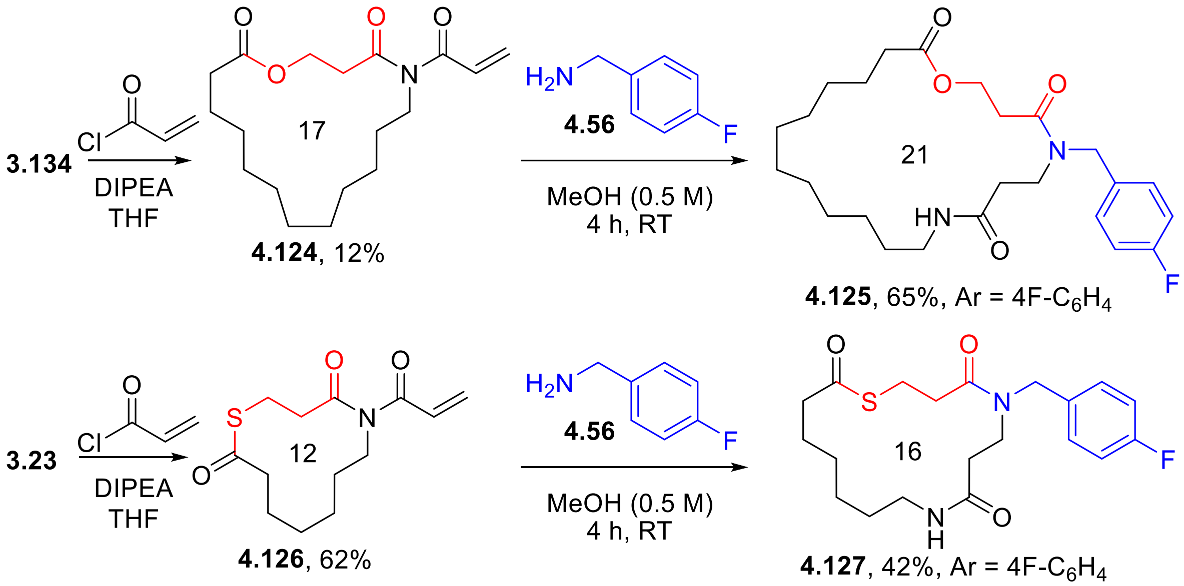


Figure 4.5: Illustrative figure demonstrating the wide scope of CARE reactions, with customizable products. Illustrated by Claudia Flandoli and used as a table of contents graphic for a publication.[92]

4.4.4 Successive ring expansion using CARE

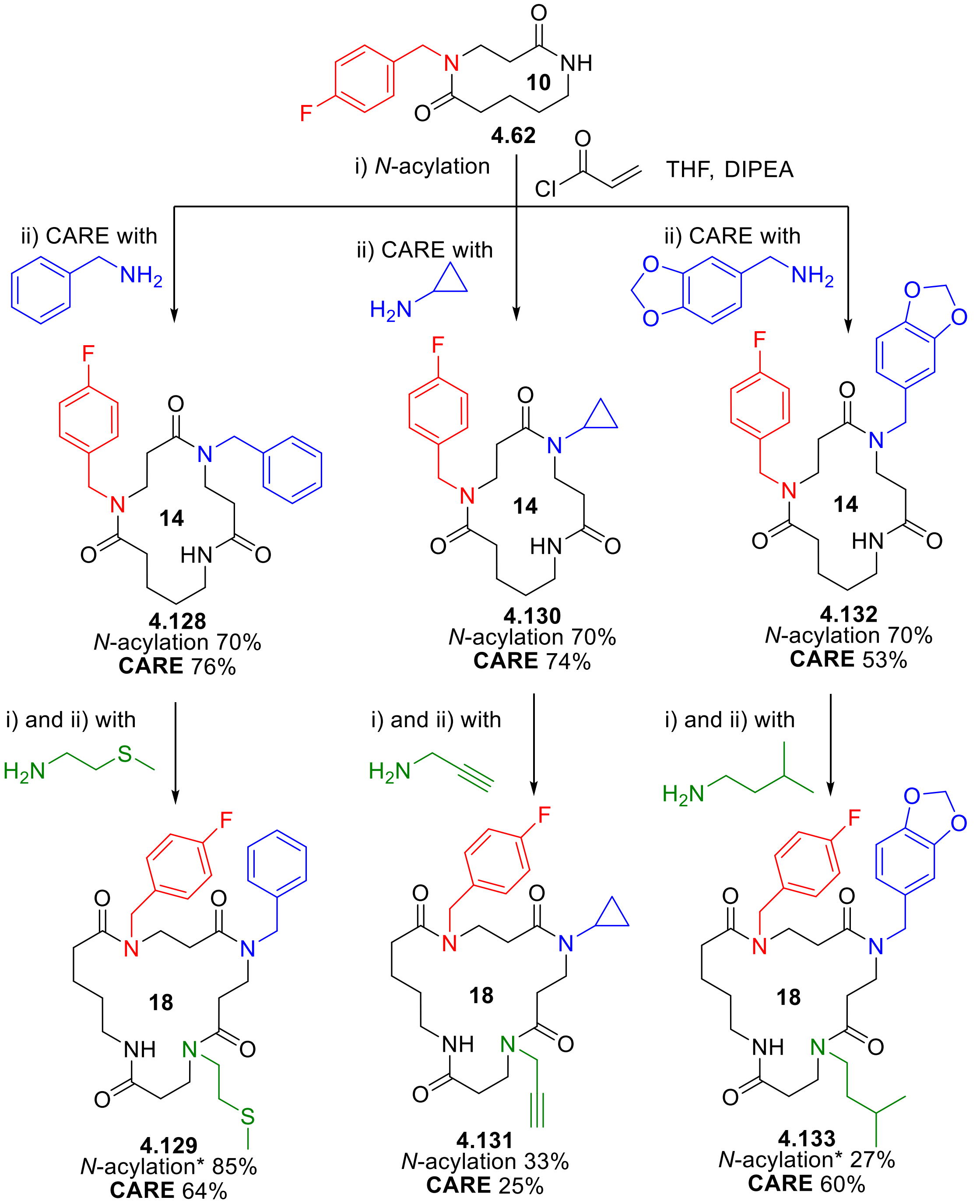
With the scope widely explored, it was decided to extend the CARE methodology to successive ring expansion examples. First, macrocycles **3.134** and **3.23**, themselves prepared *via* SuRE as described in Chapter 3, were tested (Scheme 4.35). Each was acylated using acryloyl chloride to form **4.124** and

4.126 in modest to low yields. Next, each of these cyclic imides was subjected to the optimized CARE conditions using 4-fluoro benzyl amine **4.56** as a nucleophile to furnish 21-membered **4.125** and 16-membered **4.127**, demonstrating that the CARE reaction can be performed in the presence of lactones or thiolactones (possibly with some side reactions occurring particularly in the latter case).



Scheme 4.35: Successive CARE reactions performed macrocycles prepared via SuRE.

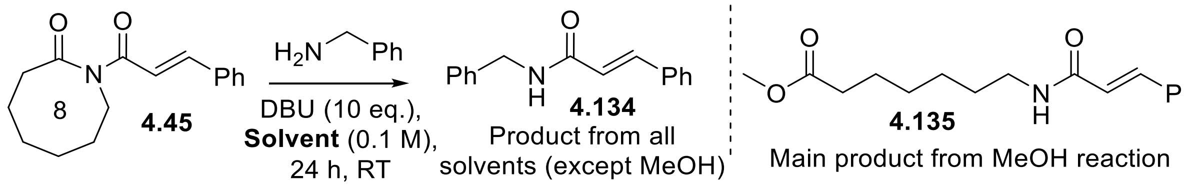
Finally, attempts to perform CARE reactions iteratively were undertaken. To start, 10-membered **4.62** was synthesized on a large scale using a CARE reaction (Scheme 4.36). This was then acylated using acryloyl chloride and DIPEA conditions to form an imide in 70% yield. Using this this imide, three separate CARE reactions were performed with different amine nucleophiles to form **4.128** (76%), **4.130** (74%), and **4.132** (53%) (Scheme 4.36). Each of these 14-membered macrocyclic lactams were then acylated using acryloyl chloride/DIPEA conditions and subjected to another CARE reaction, with a different set of primary amines, forming 18-membered products **4.129** (64%), **4.131** (25%), and **4.133** (60%). This demonstrates that CARE can be used to iteratively 'grow' macrocyclic β-peptoid memetics, with specific amino acid sequences.



*Scheme 4.36: Iterative CARE reactions. *N-acylation used DCM as the solvent.*

4.4.5 Nitrogen CARE solvent screen using β-phenyl imide 4.45

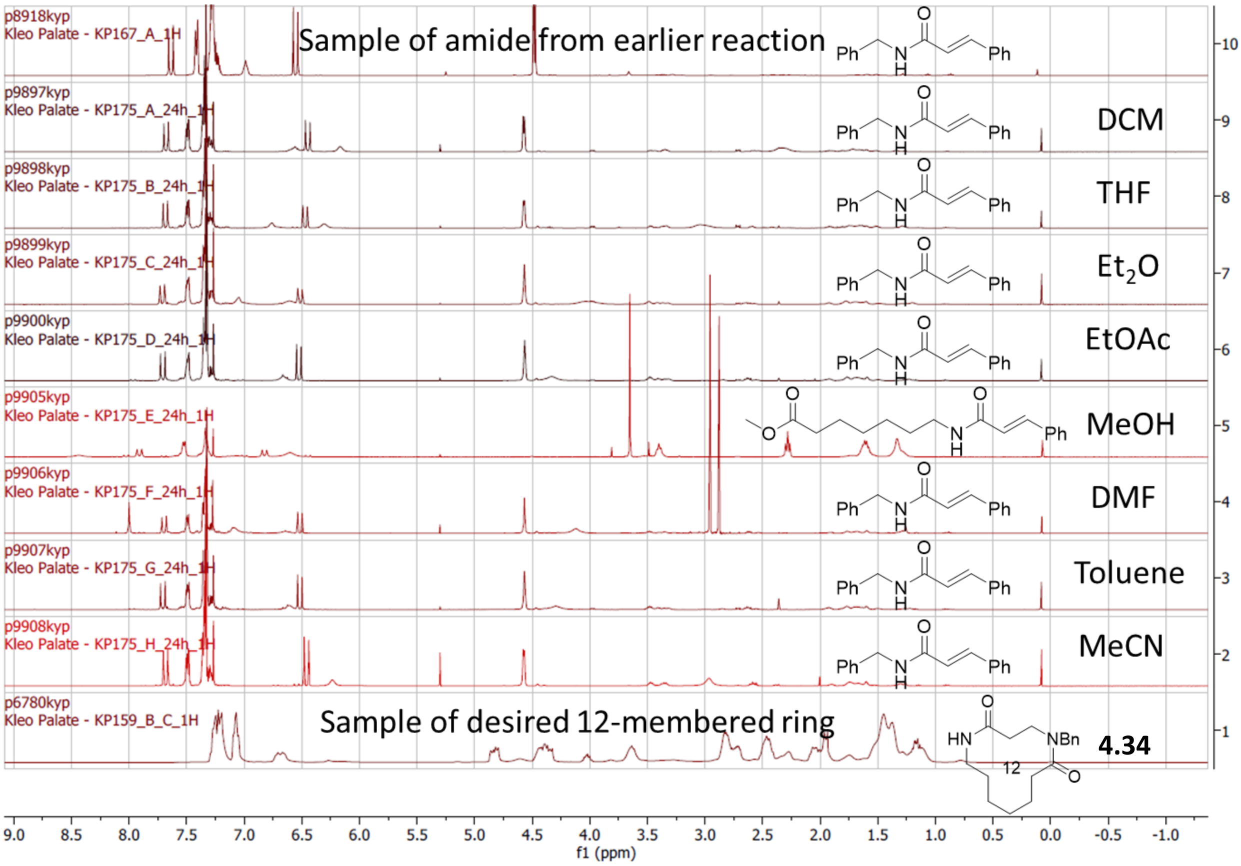
Alongside these studies to probe the scope of the nitrogen CARE reaction, further studies were performed to investigate the CARE reaction of β-phenyl imide (**4.45**), which failed under the standard conditions. These experiments were all done performed using 10 eq. of DBU as a base in the reaction, as they took place before the optimized DBU-free conditions were developed. A solvent screen was conducted using benzyl amine and imide **4.45** as shown in Scheme 4.37.



*Scheme 4.37: Solvent screen using benzyl amine and cinnamoyl imide **4.45**.*

This solvent screen demonstrated that for each of the examples, amide **4.134** is formed preferentially. Using methanol as the solvent resulted in the ring opening of the imide forming the methyl ester **4.135**. None of the desired 12-membered ring expanded product **4.34** was formed in this study.

*Figure 4.6: NMR results from cinnamoyl imide solvent screen. The top NMR spectrum is of pure amide **4.134**, and the overlaid structures are the main component of each solvent screen entry. The solvent used for each reaction is displayed on the right. Amide **4.134** is the main product of the reactions from each solvent tested except for the reaction using methanol as a solvent.*



4.5 Carbon CARE

4.5.1 Carbon nucleophile screening

Reactions testing the viability of CARE reactions of carbon-based nucleophiles have also been attempted and are presented in Table 4.5. Using dimethyl malonate, the conjugate addition was successful in up to 60% yield forming a linear isomer of the form [**A**] (entry 1, Table 4.5). Reaction with malononitrile and K_2CO_3, resulted in a similar outcome (55%, entry 3, Table 4.5), with an additional 'double conjugate addition' product (labelled [**B**]) also observed in 13% yield. No reaction was observed with 1,1,1-trifluoroacetone and DBU as the base (entry 5, Table 4.5). Finally, and more encouraging, reaction with nitromethane and DBU produced some double conjugate addition product [**B**] (14%), but with the desired ring expanded product [**C**] observed in a crude mixture (entry 6, Table 4.5). The presence of the desired product was determined in part by the presence of a characteristic presence of a ketone at 200.3 ppm observed in its ^{13}C NMR spectrum.

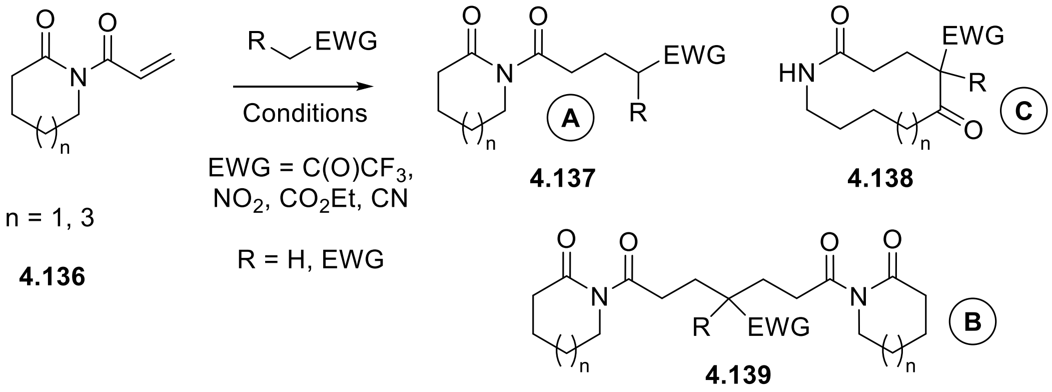
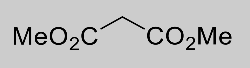
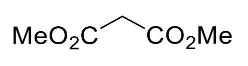
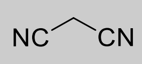
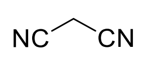
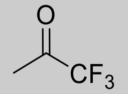


*Table 4.5: Exploratory Carbon-CARE reactions. *Desired product observed in entry 6, [C] was impure and not quantified.*

Entry	n =	Nucleophile	Conditions	A / %	B / %	C / %
1	3		Malonate (1.5 eq.), K_2CO_3 (3 eq.), THF (0.1 M), 18 h, RT	60 (**4.137a**)	0	**0**
2	3		Malonate (1.5 eq.), NaH (2 eq.), THF (0.1 M), 0 °C→RT, 13 h	45 (**4.137a**)	0	**0**
3	1		Malononitrile (1.5 eq.), K_2CO_3 (3 eq.), THF (0.1 M), 4 h, RT	55 (**4.137b**)	13 (**4.139**)	**0**
4	3		Malononitrile (20 eq.) DBU (2 eq.), DCM (0.1 M), RT, 4 h	30 (**4.137c**)	N/A	**0**
5	3		1,1,1-trifluoroacetone (10 eq.), DBU (2 eq.), DCM (0.1 M), RT, 14 h	0	0	**0**
6	3	$MeNO_2$	$MeNO_2$ (2 eq.), DBU (2 eq.), DCM (0.1 M), RT, 4 h	0	14 (**4.140**)	Obs*

This reaction (entry 6, Table 4.5) was the most promising from this brief initial screen, and served as the focus of carbon-CARE optimization moving forward.

4.5.2 Nitromethane Carbon CARE optimization

With a promising carbon nucleophile CARE reaction observed for the first time, efforts began to optimize this reaction to form ring expanded α-nitroketone (**4.141**). Initially, the reaction was repeated on a larger scale (3 mmol, entry 2, Table 4.6), in an attempt generate sufficient material to characterize **4.141** and confirm its identity. In this way, α-nitroketone (**4.141**) was isolated as a mixture with DBU-H$^+$ following column chromatography in approximately 35% yield. High dilution conditions with imide **4.37** added slowly to a mixture of DCM, DBU and nitromethane over 2 hours, resulted in no reaction (entry 4). It was considered at this stage that α-nitroketone (**4.141**) may be sufficiently acidic that it forms a salt with DBU in solution. To test this hypothesis a new acid/base workup was trialled, initially extracting the basic reaction mixture with water to separate the salt of α-nitroketone (**4.141**) and DBU-H$^+$ into the aqueous phase. In the organic layer, the double conjugate addition product (**4.140**) remained. The aqueous layer was then acidified and extracted with DCM, to yield α-nitroketone (**4.141**). Trialling this new workup, followed by column chromatography for the crude mixtures from the first and second organic layers, allowed double conjugate addition product **4.140** [B] and α-nitroketone (**4.141**) [C] to be isolated in 30% and 36% yield respectively (entry 5). In entries 6–8 only the workup was performed without ensuing column chromatography leading to improved yields. It is suspected that α-nitroketone (**4.141**) is moderately unstable on silica, with this notion supported by 2D TLC experiments. Increasing the concentration of nitromethane to 20 equivalents reduced unproductive double conjugate addition observed, with yields of the α-nitroketone (**4.141**) reaching 89% (entry 8). Full details of the work up can be found in Chapter 5 (experimental section).

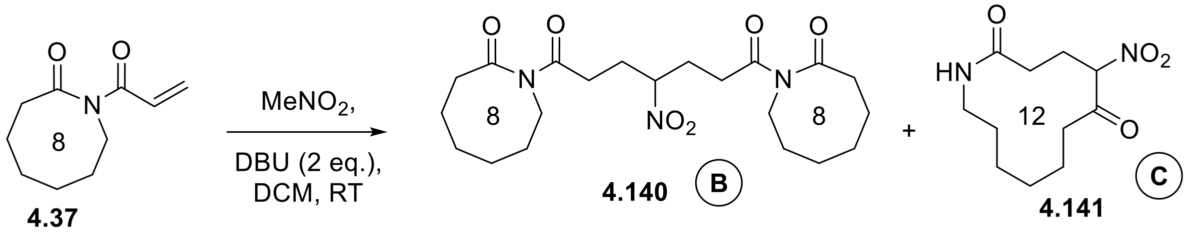


Table 4.6: Optimization of carbon CARE reaction using MeNO$_2$

Entry	MeNO$_2$ / eq.	4.37 / mmol	DCM / M	Time /h	B / %	C / %	Notes
1	2	1	0.1	4	14	Obs.	**4.141** observed in an impure mix
2	2	3	0.1	4	41	35*	***4.141** isolated with DBU-H+ (12% recov.), yield determined by NMR
3	2	1	0.1	4	25*	50*	NMR yields
4	2	1	0.01	18	N/A	0	High dilution, no reaction observed
5	2	1	0.1	4	30	36	New 2 step acid/base workup and subsequent column of each org layer
6	20	0.5	0.1	4	N/A	80	New 2 step acid/base workup only
7	93*	0.5	0.2*	4	N/A	88	New 2 step acid/base workup only, *1:1 mix MeNO$_2$ and DCM
8	20	0.5	0.1	1.5	N/A	**89**	New 2 step acid/base workup only

4.5.2.1 Nitroketone 4.141 tautomerization and X-ray crystal structure

12-Membered α-nitroketone (**4.141**) exists in two tautomeric forms, a major keto tautomer and a minor enol tautomer. Both tautomers can be observed by NMR, with the keto form the predominant species observed in CDCl$_3$ (Figure 4.7).

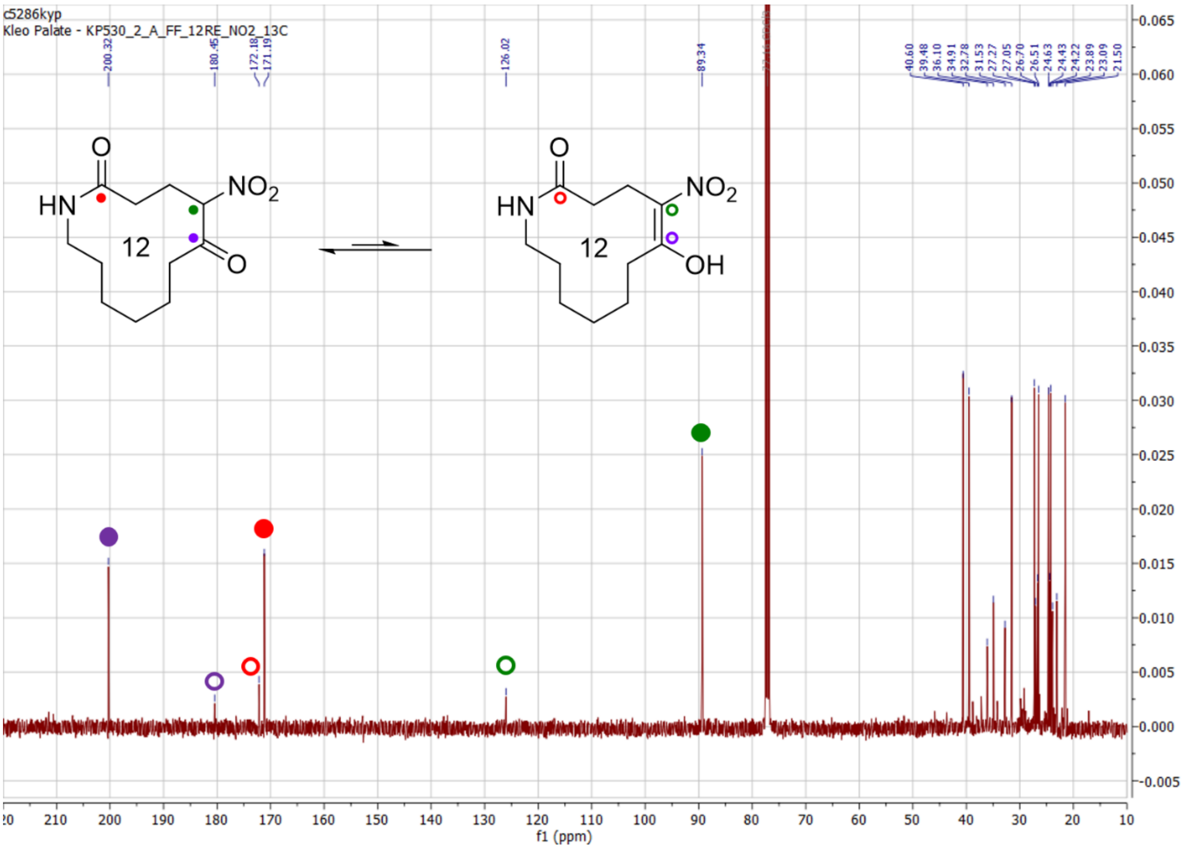
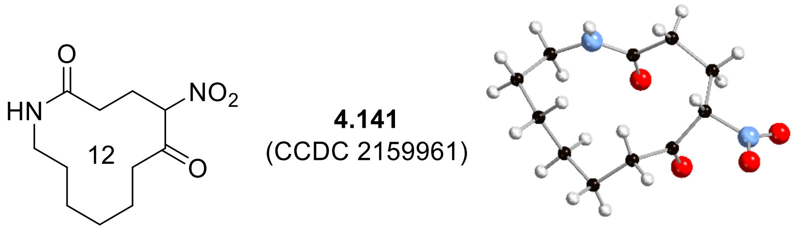


*Figure 4.7: ^{13}C NMR spectrum of **4.141** with characteristic signals for keto and enol tautomer assigned.*

α-Nitroketone (**4.141**) is a crystalline solid, and an XRD structure was solved for it, confirming that ring expansion occurred (Figure 4.8).



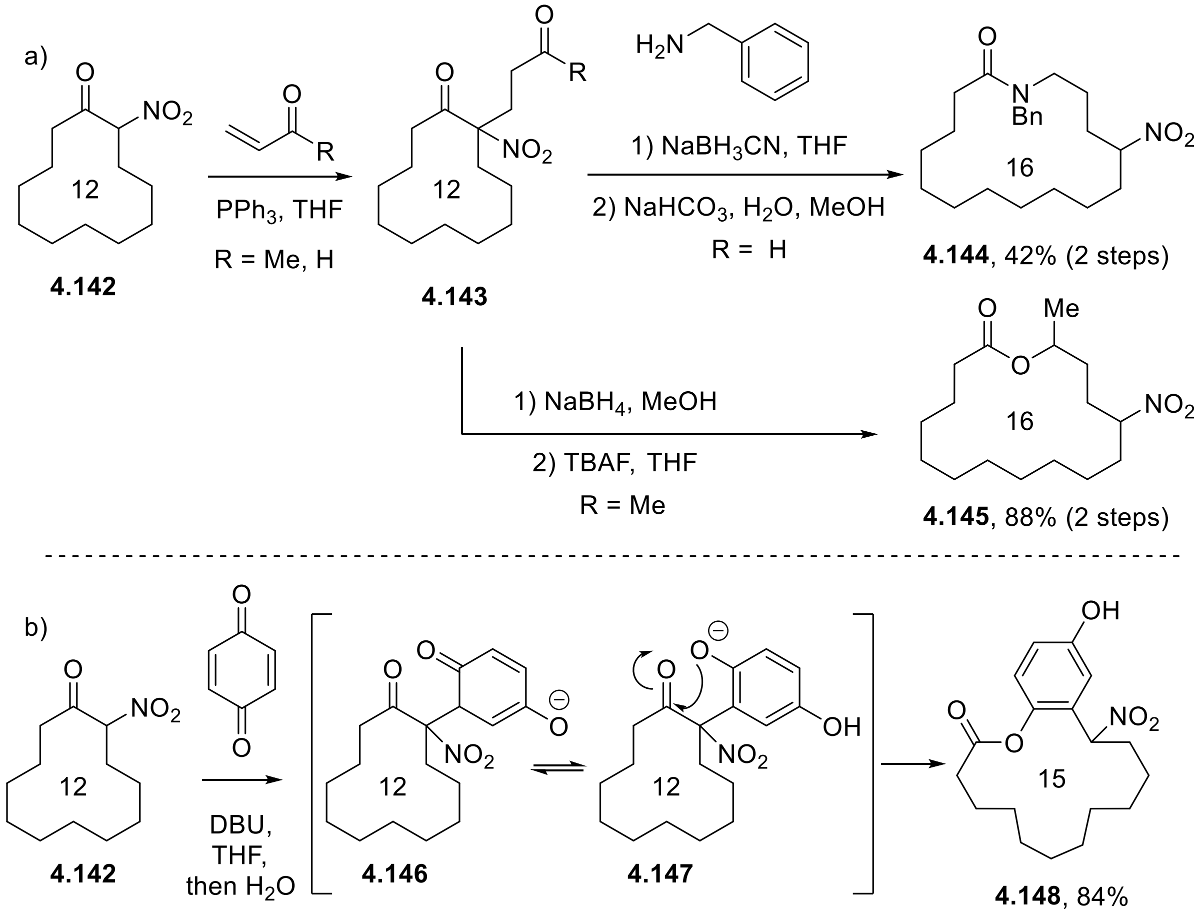
4.141
(CCDC 2159961)

*Figure 4.8: XRD structure of 12-membered α-nitroketone **4.141**, see CCDC 2159961.*

4.5.2.2 Nitroketone successive ring expansion

Cyclic α-nitroketones feature in pioneering ring expansion studies conducted by Hesse *et al.*[93–95] The α-nitroketone moiety can act as carbon-based nucleophile itself to allow for further functionalization at the α-position (Scheme 4.38a). With a pendant nucleophile attached, Hesse was able to ring-expand cyclic nitroketones to form lactam **4.144** and lactone **4.145**.[95,96]

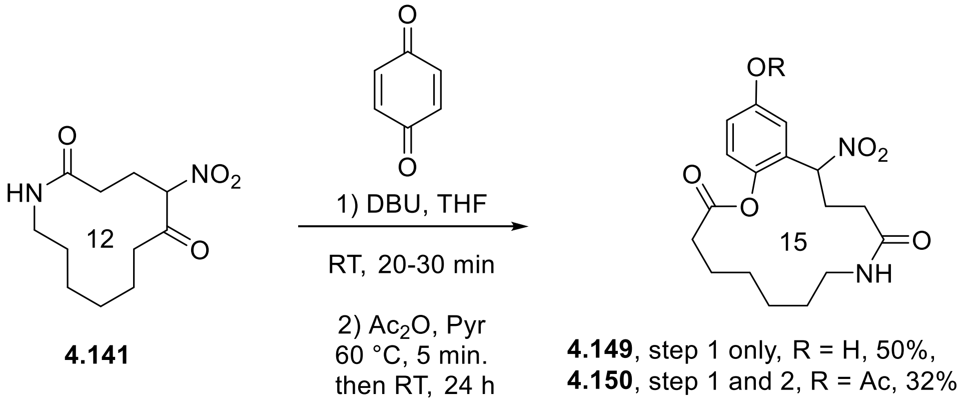
One notable reaction of this type features a ring expansion cascade with 1,4-benzoquinone acting as a Michael acceptor and a masked phenol to form macrocycle **4.148** (Scheme 4.38b).[93]



Scheme 4.38: Stepwise and cascade conjugate addition ring expansion reactions reported by Hesse et al.

This cascade conjugate addition ring expansion reaction developed by Hesse *et al.* is conceptually related to the carbon-CARE chemistry discussed in this chapter, albeit with some key differences. A carbon-based nucleophile performs the initial conjugate addition step to couple the two molecules together, but it is ultimately an oxygen-based nucleophile that performs the ring expansion step of the reaction. In fact, the α-nitroketone **4.142** acts as both a nucleophile (to perform the conjugate addition) and an electrophile (to accept the phenol nucleophile as shown in **4.147**) in this reaction.

We considered that Hesse's 1,4-benzoquinine cascade ring expansion conditions may be compatible with our CARE products, and thus, a reaction trialled was on our newly synthesized 12-membered α-nitroketone lactam (**4.141**). Two iterations of the reaction were attempted, with an additional acyl protection of the phenol added in the second attempt (Scheme 4.39). In each reaction, THF (0.33 M) and 1 equivalent of 1,4-benzoquinone were added to **4.141**, followed by 1 drop of DBU. For the first reaction, where only step 1 was performed, this was then worked up to give **4.149** as an oil in 50% yield. This reaction was repeated with an additional acetyl protection, as the acetate **4.150** was thought to form a crystalline solid, based on analogous findings by Hesse.[93] In the second reaction, acetyl anhydride and pyridine were added straight to the reaction mixture and heated to 60 °C for 5 min before allowing to stir at RT overnight. Following workup and chromatography the desired acetyl protected **4.150** was isolated as a solid in 32% yield.



*Scheme 4.39: Cascade conjugate addition/ring expansion using benzoquinone and **4.141** to form 15-membered rings.*

A crystal structure was later obtained of 15-membered **4.150** (Figure 4.9).

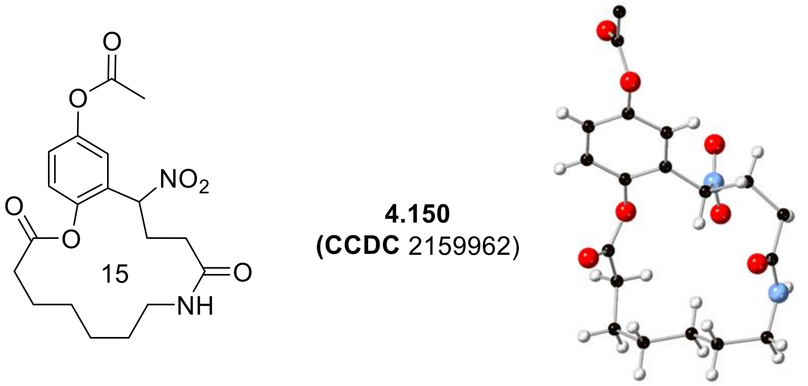
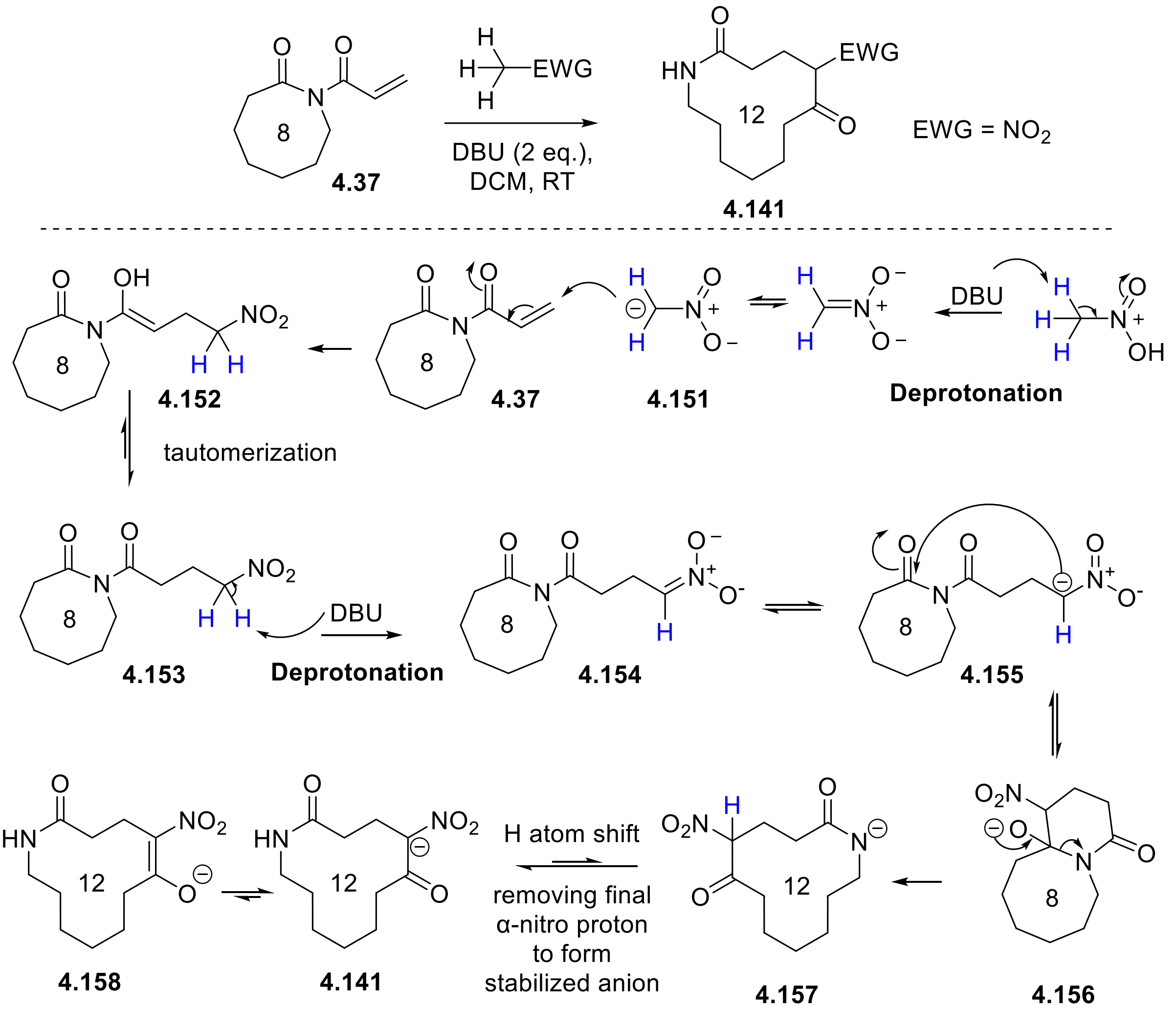


*Figure 4.9: XRD of 15-membered successive product **4.150**, see CCDC 2159962.*

4.5.2.3 Nature of the carbon nucleophile required for CARE and proposed mechanism

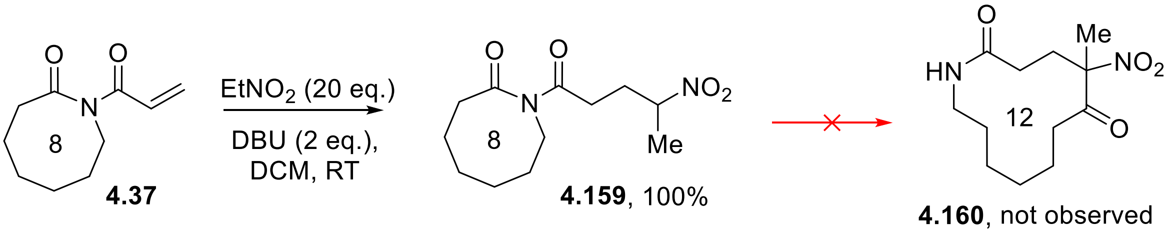
With a reliable procedure developed for carbon-CARE using 8-membered (**4.37**) and nitromethane, the next step was to explore the scope of this reaction. It was thought that the nature of the carbon nucleophile, possessing three acidic protons on the nucleophilic carbon was essential for its reactivity

(Scheme 4.40). The initial deprotonation by DBU forms **4.151**, which acts as a nucleophile in the initial conjugate addition step. A second deprotonation is required to form the nucleophilic intermediate that can attack the imide carbonyl intramolecularly. A final (reversible) deprotonation can then take place, forming a stabilized anion (represented as resonance forms **1.141** and **1.158**), with this resonance form likely to provide a thermodynamic driving force that helps to drive the overall ring expansion.



Scheme 4.40: Carbon CARE mechanism requiring 3-deprotonatable protons.

To probe whether three α-protons must be present in the carbon nucleophile in carbon CARE reactions, an experiment was performed using nitroethane in place of nitromethane (Scheme 4.41). A simple acidic workup to remove DBU revealed the linear conjugate addition product (**4.159**) formed quantitatively with no observed ring expansion. This is consistent with the theory that without the formation of a stabilized carbanion during ring expansion, the thermodynamic driving force for ring expansion is insufficient.



*Scheme 4.41: Carbon CARE with nitroethane only forms RO isomer **4.159**.*

4.6 Oxygen CARE

4.6.1 Conjugate addition attempts with benzyl alcohol and water

With CARE successfully demonstrated on nitrogen and carbon-based nucleophiles it was decided to investigate whether conjugate addition could be used to add oxygen nucleophiles for lactone forming ring expansion reactions. Commonly used oxa-Michael conjugate addition conditions employ strong nucleophilic bases such as NaOH in polar protic solvent, but such conditions were avoided, as in our hands, similar conditions led to side reactions such as ring opening of the lactam and de-acylation with related imide substrates (see section 4.4.5). Initial trials investigated whether benzyl alcohol could be used as a nucleophile in an oxa-Michael conjugate addition reaction (Table 4.7, entries 1-3). This was unsuccessful in each case with de-acylation observed in instances where conjugate addition occurred to form 3-benzyloxy-propionic acid benzyl ester (**4.162**) as a side product (entries 1 and 3). In order to avoid unproductive de-acylation, attempts were made to perform this conjugate addition reaction under acidic conditions with the aid of a Lewis acid. Four Lewis acids were trailed in water/acetonitrile conditions at elevated temperature to attempt to perform a conjugate addition using water as a nucleophile (entries 4-7). Unfortunately, none of these examples were successful in forming the desired conjugate addition product, with the formation of product **4.163**, which results from ring-opening of the lactam, as the predominant outcome in each case (**4.163**).

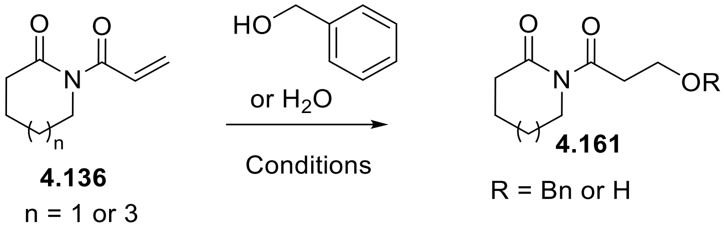
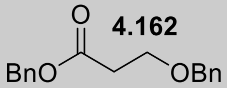
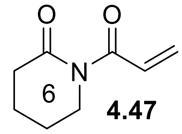
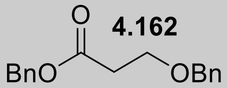
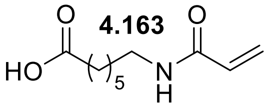
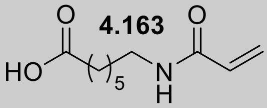
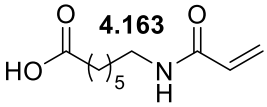
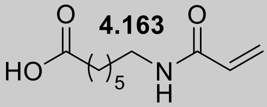


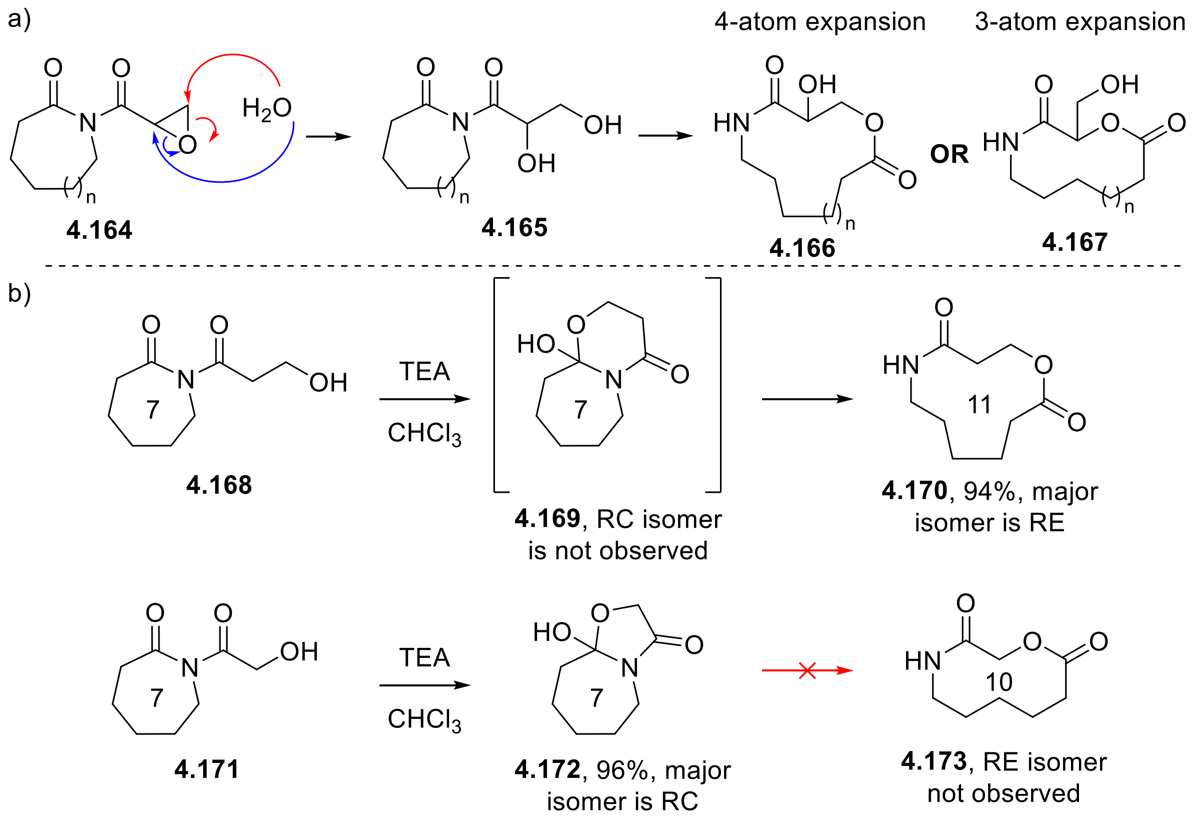
Table 4.7: Substituted acryloyl imide synthesis.

Entry	n =	Conditions	Lewis acid	Main product formed
1	1	Cs_2CO_3 (2 eq.), BnOH (4 eq.), THF (0.5 M), RT, 26 h	None	 **4.162**
2	1	$Na_2CO_{3\,(aq.)}$ (0.05 M), BnOH (4 eq.), RT, 46 h	None	 **4.47** (SM recovered)
3	3	Cs_2CO_3 (1 eq.), BnOH (1.1eq.), DCM (0.5 M), 50 °C, 12 h	$CuCl_2$ (10 mol %)	 **4.162**
4	3	Lewis acid (20 mol %), 2:1 H_2O : MeCN, 80 °C, 12 h	$CrCl_3$-$6H_2O$	 **4.163**
5	3	Lewis acid (20 mol %), 2:1 H_2O : MeCN, 80 °C, 12 h	$CuCl_2$	 **4.163**
6	3	Lewis acid (20 mol %), 2:1 H_2O : MeCN, 80 °C, 12 h	$FeCl_3$-$6H_2O$	 **4.163**
7	3	Lewis acid (20 mol %), 2:1 H_2O : MeCN, 80 °C, 12 h	$In(OTf)_3$	 **4.163**

4.6.2 Alternative one step ring expansion to form lactones

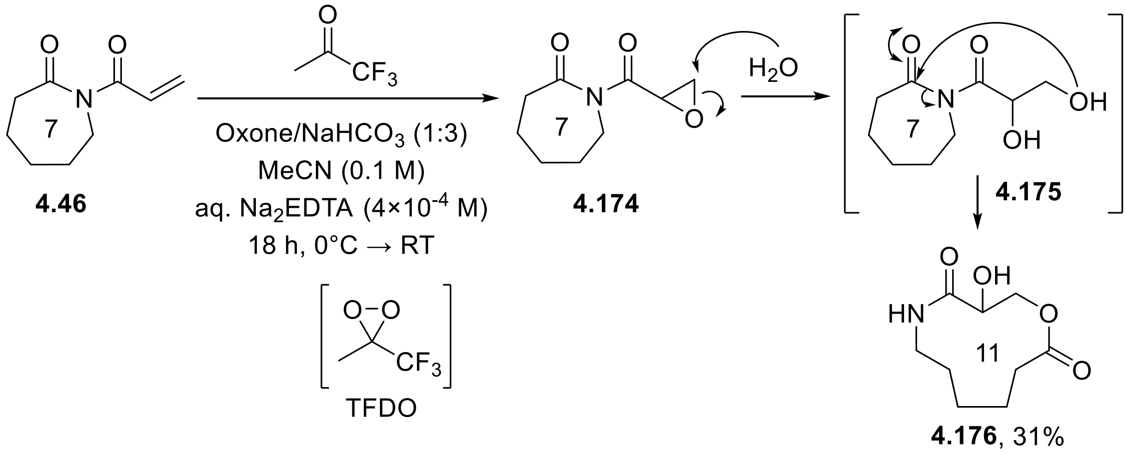
With an oxa-Michael reaction proving difficult to develop, alternative reactions were considered to perform a one-step incorporation of an oxygen nucleophile followed by ring expansion. Focus turned to functionalizing the alkene *via* an epoxidation reaction. Epoxidation seemed an attractive approach as this reactive functional group could be opened *via* a number of nucleophiles, including water. The appeal of ring opening using water as a nucleophile is that attack at either carbon of the epoxide could result in the same diol intermediate (Scheme 4.42a). It was decided to avoid alkaline conditions as they could result in side reactions such as de-acylation and ring opening like those described in section 4.4.5. The choice of ring size for the test system was also carefully considered, as a 1,2-diol imide **4.165** can potentially lead to either a 3-atom or a 4-atom ring expansion. Earlier studies indicated that 7-

membered imides can undergo a 4-atom lactone forming ring expansion, but do not undergo the analogous 3-atom rearrangement (Scheme 4.42b).[67] Therefore, a 7-membered ring system was chosen to start, as only the 4-atom expansion was predicted to be viable, and it was hoped that the formation of a single product would simplify the process.



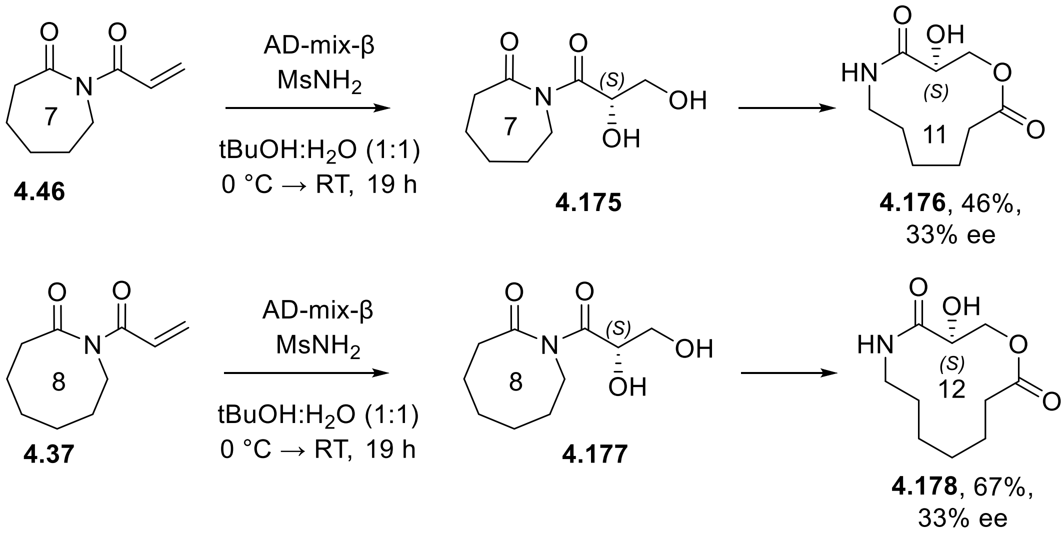
*Scheme 4.42: a) Proposed epoxidation of α,β-unsaturated imide to form an epoxide **4.164**, followed by ring expansion. b) results form a ring size study of lactone forming SuRE reactions.*

A literature search of epoxidation conditions of acrylamide functionalities highlighted an electrophilic epoxidation using methyl(trifluoromethyl)dioxirane (TFDO) formed *in situ*.[97] Pleasingly, applying this procedure to 7-membered acryloyl imide **4.46** yielded lactone **4.176**, albeit in a modest 31% yield (Scheme 4.43). The water present in the reaction or subsequent workup led to ring opening of the epoxide to form diol **4.174**, which subsequently rearranged to perform a 4-atom ring expansion, forming the 11-membered lactone **4.176** exclusively. As expected, none of the 3-atom ring expanded product was observed. This serves as the first example of a 1-step ring expansion forming a lactone from an acryloyl imide.



*Scheme 4.43: Epoxidation/ring expansion of **4.46** to for 11-membered lactone **4.176**.*

Next it was considered whether the diol could be formed directly using Sharpless asymmetric dihydroxylation conditions. This was first trailed with 7-membered imide **4.46** using AD-mix-β and methanesulfonamide. Pleasingly, the desired 4-atom ring expanded lactone **4.176** was isolated directly from this reaction, without the need for additional ring expansion conditions, in 46% yield and in modest enantiomeric excess, as determined by chiral HPLC (see experimental section, Ch. 5, for details). This is a pleasing result, as these substrates often required stirring in $CHCl_3$/TEA to facilitate ring expansion.[67] Repeating this reaction on an 8-membered imide **4.37** again led to 4-atom ring expansion exclusively, to form 12-membered **4.178** in 67% yield and 33% *ee* (Scheme 4.44).



Scheme 4.44: Dihydroxylation/ring expansion reactions using Sharpless dihydroxylation conditions. Absolute stereochemistry assigned by analogy to AD mnemonic.

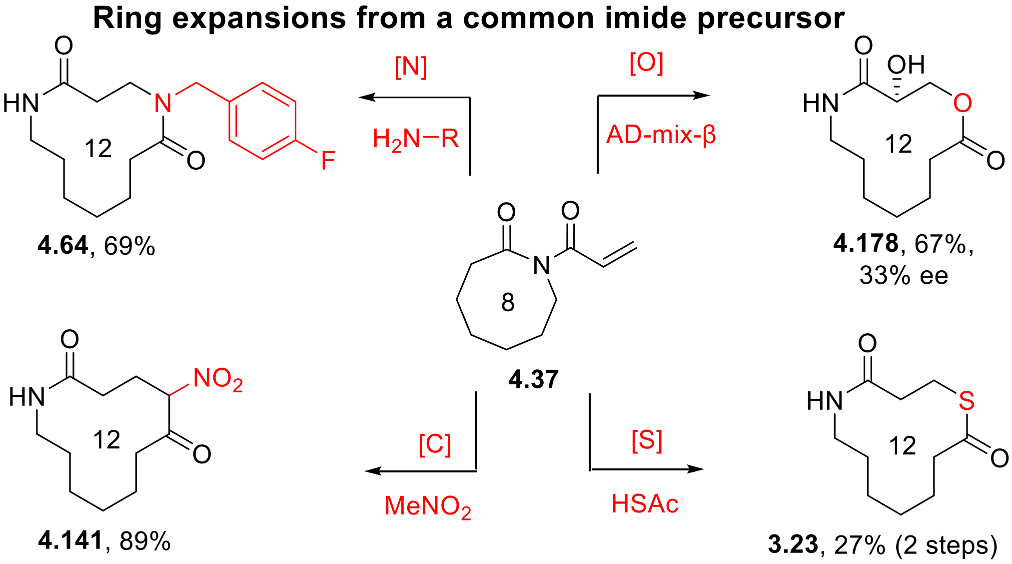
These reactions serve as a proof of concept that dihydroxylation is a viable approach to forming lactone containing medium sized rings and macrocycles from acryloyl imide lactams, and will be explored further in future work in the Unsworth group.

4.7 CARE outlook

4.7.1 Realization of 'common imide' approach to ring expansion

The key objective laid out at the beginning of this chapter was to develop a new ring expansion methodology in which a range of different ring expanded products could be formed from a common imide starting material. This goal has been achieved using α,β-unsaturated imides as the common starting material. Scheme 4.45 shows how four different heteroatoms can be incorporated into ring expanded products from a single starting material. Aza-Michael 'CARE' reactions have been developed to form bislactams, such as **4.64**, in good yields with extensive scope with respect to the primary amine nucleophile (Section 4.4.3.5). Carbon CARE reactions have been demonstrated to access α-nitro ketone products (*e.g.* **4.141**) for the first time. These can be performed in one-step and can be purified with a simple workup that exploits the nature of these compounds. Conjugate addition reactions also extended to sulfur nucleophiles, with thiolacetic acid in excellent yield (96%) in conjugate addition reactions, although selective cleavage of thioacetate proved significantly more challenging to develop (see Chapter 3 for full details). Finally, a dihydroxylation-ring expansion cascade reaction has been demonstrated to form enantioenriched hydroxy-lactones **4.178** in good yields. With the exception of the thiolactones (*e.g.* **3.23**), each of these expanded ring product classes can be formed using mild conditions, room temperature or 0 °C, and without the need for a protecting group.

The applications of this chemistry include late-stage functionalization to form medium sized rings and macrocycles and the capability to rapidly synthesize derivatives required for SAR studies. The work described in this Chapter is the subject of one publication, which is focused solely on the N-CARE reactions.[92]

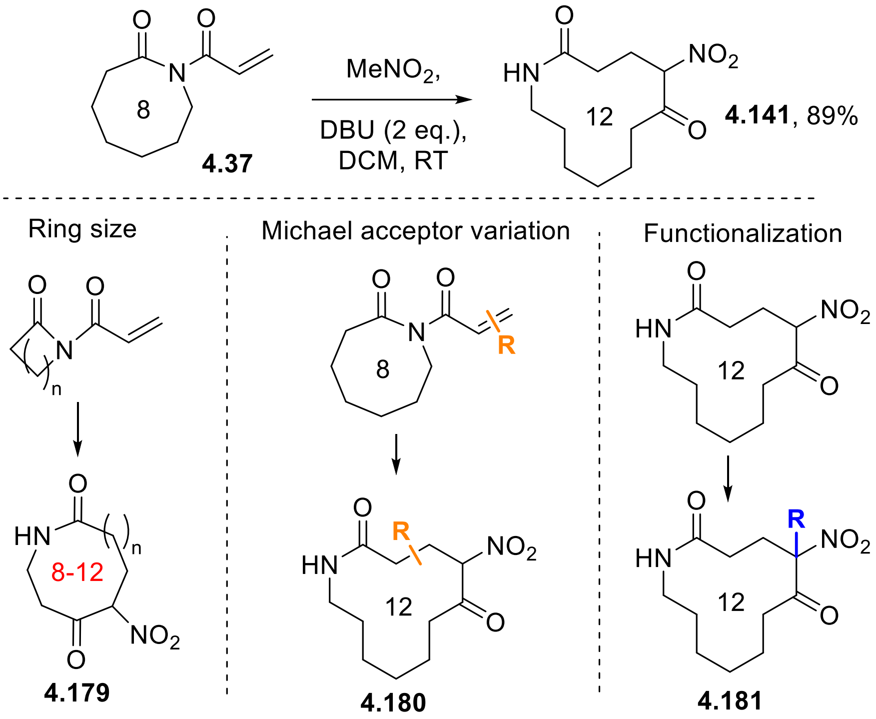


*Scheme 4.45: Ring expansions from **4.37** can be performed using CARE with Nitrogen or carbon nucleophiles. With stepwise conjugate addition and deprotection ring expansion to form thiolactones, and with dihydroxylation to form lactones.*

4.7.2 Future work

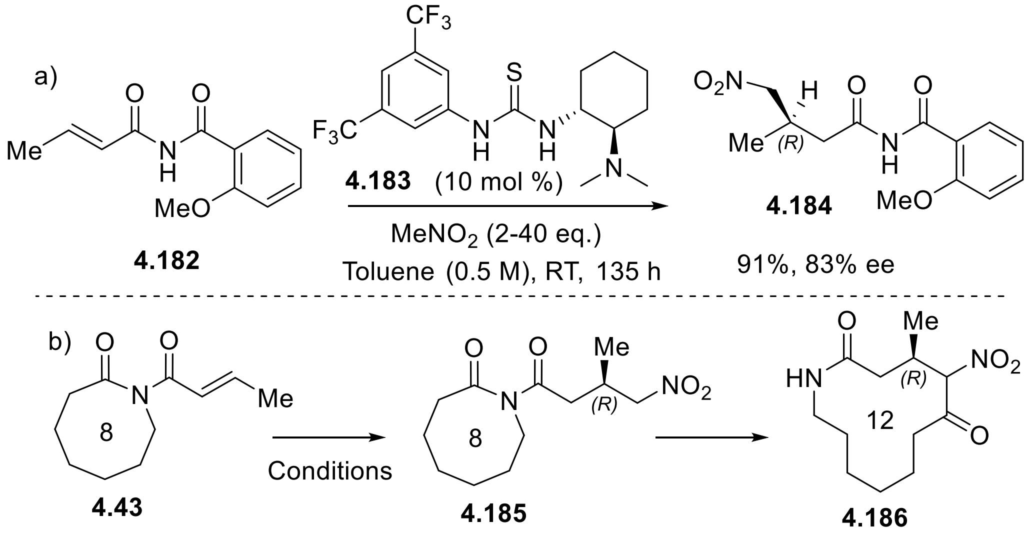
4.7.2.1 Carbon CARE scope

With a successful proof of concept of carbon CARE, this opens up the possibility of further exploration of reaction scope. This is currently being explored by Unsworth group Masters student Will Orukotan (Scheme 4.46).



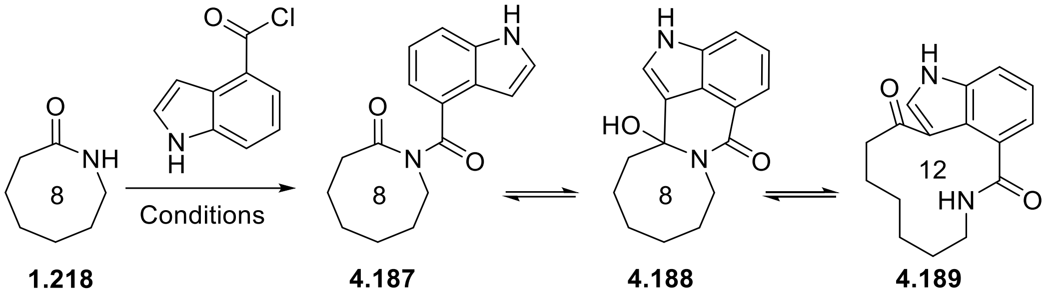
Scheme 4.46: Scope exploration of Carbon CARE reactions

It may also be possible to perform carbon CARE reactions using an organocatalyst to generate enantioenriched products (Scheme 4.47b). There is encouraging precedent for the asymmetric conjugate addition of nitromethane using imides (including cyclic ones as used in carbon CARE reactions)[98] as shown in Scheme 4.47a.



Scheme 4.47: Possible enantioselective Carbon CARE

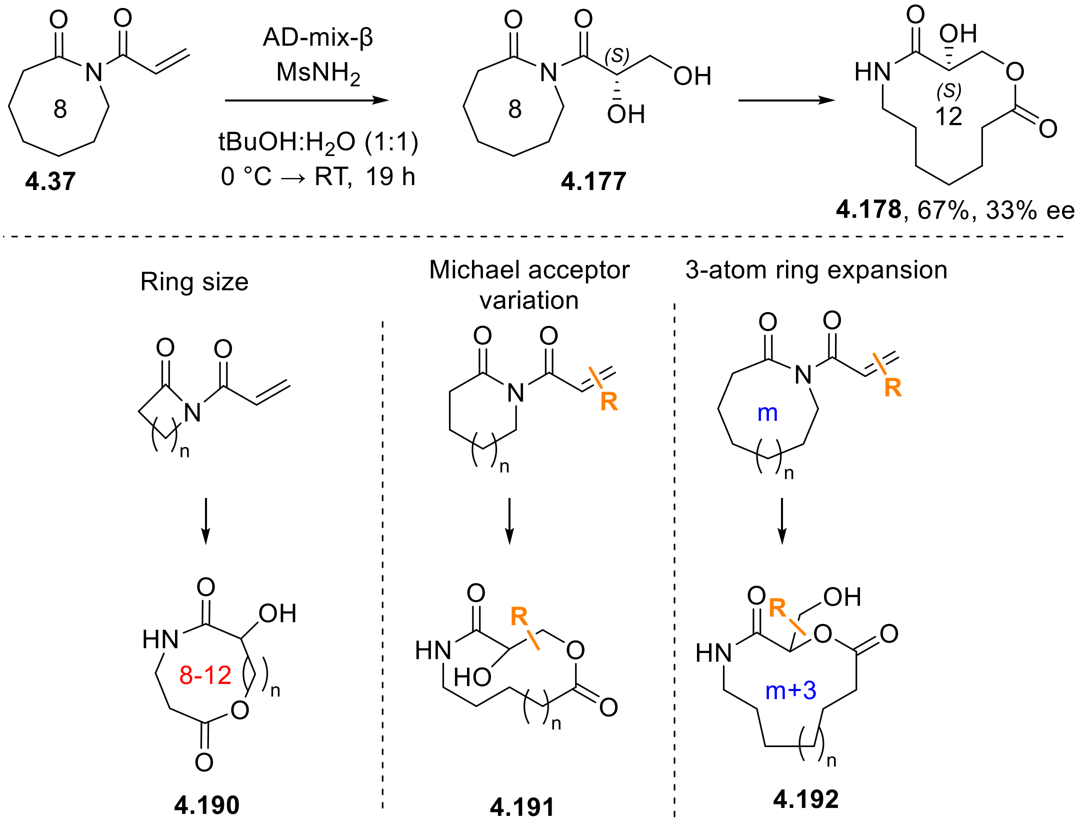
Other carbon nucleophiles may also be used in ring expansion reactions as well. One area to investigate is the use of indoles for SuRE-like acylation/ring expansion reactions (Scheme 4.48).



Scheme 4.48: Indoles could be used for acylation/ring expansion reactions.

4.7.2.2 Dihydroxylation/Ring Expansion scope

A proof of concept for a 1-step Sharpless asymmetric dihydroxylation/ring expansion (DiRE) sequence has been developed as well. There several potential approaches that can be used to explore the scope (Scheme 4.49). As before, ring size scope, and Michael acceptor variation can be explored. Another possibility is to explore conditions for the selective 3-atom ring expansion following dihydroxylation. The low enantiomeric excess observed in the reaction may be due to the terminal nature of the alkene. Preliminary results by Will Orukotan suggest that using a β-phenyl imide may improve the % *ee*.



Scheme 4.49: Dihydroxylation ring expansion scope to explore

4.7.2.3 *Successive CARE and Dihydroxylation examples*

Work showcasing N- and C-CARE as well as DiRE in successive examples has started (Figure 4.10).

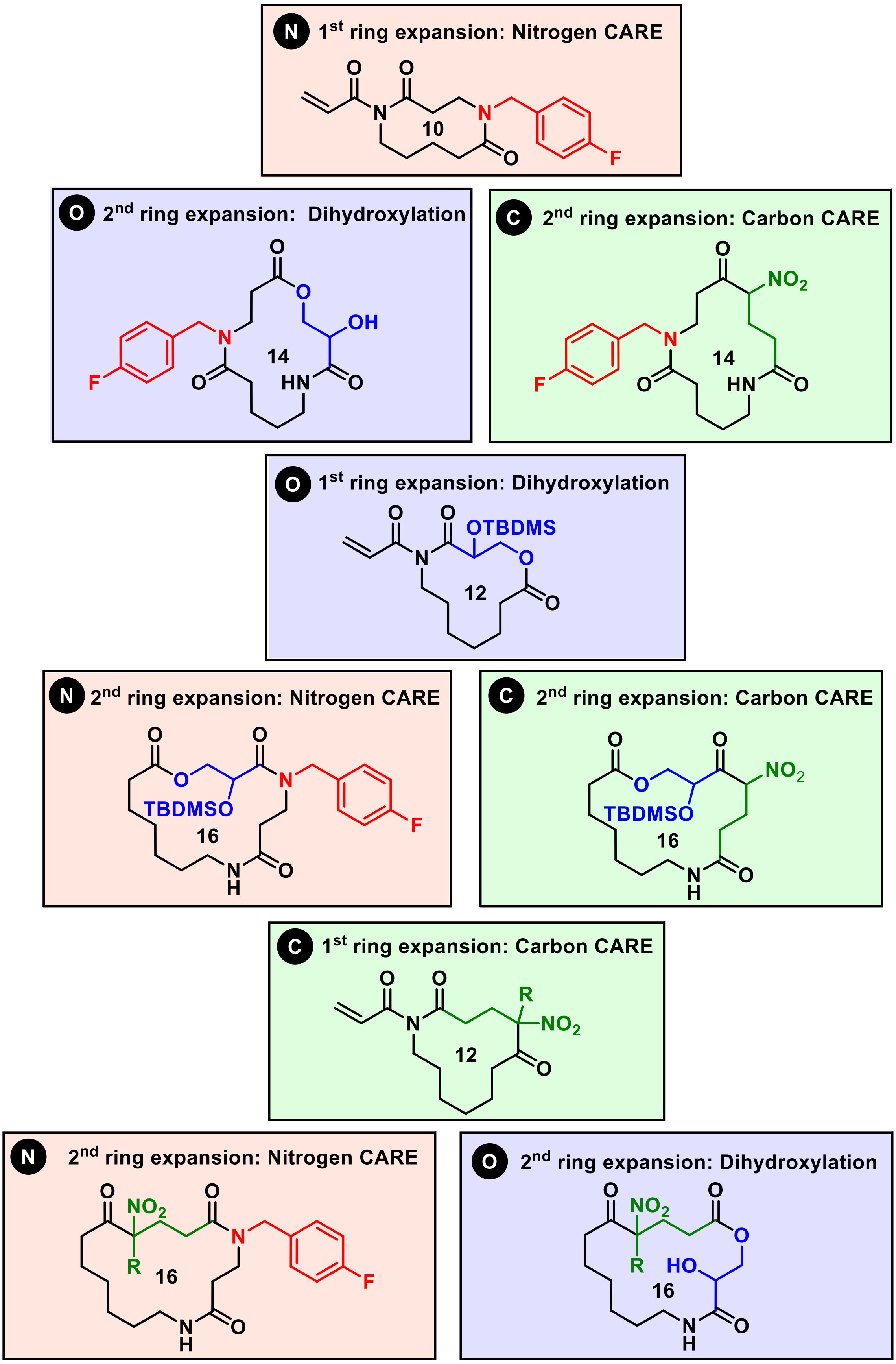


Figure 4.10: 6 potential successive ring expansion reactions, ongoing work with Will Orukotan.

5 Experimental data

5.1 General information

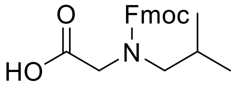
Except where stated, all reagents were purchased from commercial sources and used without further purification. Anhydrous CH_2Cl_2, THF, acetonitrile, hexane, Et_2O and DMF were obtained from an Innovative Technology Inc. PureSolv® solvent purification system. DME, DMSO, DMA, NMP, MeOH, and EtOH, advertised as dry solvents, were purchased from various commercial vendors and used as supplied without additional drying or purification. Standard grade *i*-PrOH, *t*-BuOH, TFE and HFIP (*i.e.* all likely to be wet) were obtained from commercially suppliers and were used as supplied. Water used in reactions was deionized. ^1H NMR, ^{13}C NMR, and ^{19}F spectra were recorded on a JEOL ECX400 or JEOL ECS400 spectrometer (operating at 400 MHz, 100 MHz, and 376 MHz), a Bruker Avance III 300 NMR spectrometer (operating at 300 MHz, 75 MHz, and 282 MHz), a Bruker Avance I 500 MHz spectrometer (operating at 500 MHz, 125 MHz, and 470 MHz), a Bruker Avance III HD 500 NMR spectrometer (operating at 500 MHz, 125 MHz, and 470 MHz), a Bruker Avance III HD 600 NMR spectrometer (operating at 600 MHz, 151 MHz, and 565 MHz), or a Bruker Avance Neo 700 NMR spectrometer (operating at 700 MHz, 176 MHz, and 659 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 Ionization (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 visualized using UV light (254 nm) and stained with basic aqueous potassium permanganate. In most cases, 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. When noted in the procedures, products were purified by using a Teledyne ISCO NextGen 300+ automated flash column chromatography unit equipped with UV–Vis (200–800 nm) and evaporative light scattering (ELS) detectors. Crude materials were loaded onto pre-packed RediSep Rf Gold columns (SiO_2: 40–60 mesh) either by direct liquid injection or dry loading from adsorbed Celite.

General Procedure for Acid Chloride Preparation

Oxalyl chloride (3.0 mmol) was added to a suspension of carboxylic acid (1.0 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 [in general the initial suspension became homogeneous over this period] and concentrated *in vacuo* to remove all solvent and excess oxalyl chloride.

5.2 Characterization Data and Procedures

2-((((9*H*-Fluoren-9-yl)methoxy)carbonyl)(iso-butyl)amino)acetic acid (2.18)

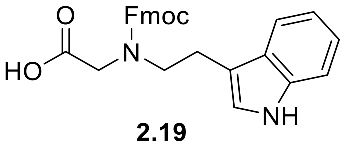


2.18

A solution of ethyl bromoacetate (1.11 mL, 10.0 mmol) in dry THF (5 mL) was added dropwise to a solution of isobutyl amine (2.19 mL, 22.0 mmol) in dry THF (5 mL) at 0 °C. The mixture was allowed to warm to RT and stirred for 3 h. (Following by TLC). The solvent was then removed *in vacuo* and the mixture resuspended in diethyl ether (20 mL). The mixture was filtered and the residue washed with diethyl ether (3 × 10 mL), the filtrate was then concentrated *in vacuo* to afford the amino ester (ethyl isobutylglycinate) as a colorless oil. Aq. NaOH (4 N, 2.75 mL) was added to the solution of amino acetate (isobutylglycinate) in 1,4-dioxane (35 mL) and methanol (12.5 mL). The reaction was stirred at RT for 2.5 h and analysed by TLC. The solvent was removed *in vacuo* to yield crude amino acid sodium salt (sodium isobutylglycinate). The *N*-alkyl amino acid salt was dissolved in a mixture of deionized water (30 mL), 1,4-dioxane (47 mL), and Na_2CO_3 (52 mL, 10% solution). The solution was cooled to 0 °C whilst stirring and a pre-made solution of 9-fluorenylmethyl chloroformate (3.10 g, 12.0 mmol) dissolved in 1,4-dioxane (10 mL) added slowly. The solution was allowed to warm to RT and stirred for 20 h, analysed by TLC. The mixture was diluted with water (50 mL) and acidified to pH 2 using 10% aq. HCl and extracted with EtOAc (3 × 50 mL). The combined organics were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (SiO_2, 1:4 ethyl acetate: hexane → ethyl acetate → 9:1 ethyl acetate: methanol) afforded the *title compound* (as an 1.3:1 mixture of rotamers) as a yellow paste (2.05 g, 58% over 2 steps); R_f 0.19 (9:1 ethyl acetate: methanol) (streaky spot with concentration dependence); ν_{max}/cm^{-1} (neat) 2958, 1697, 1450, 1430, 1212, 1152, 759, 738; δ_H (400 MHz, $CDCl_3$) 9.75 (1H, br s, COO**H**, both rotamers) 7.75 (2H, d, *J* =7.5 Hz, Ar**H**, major), 7.72 (2H, d, *J* =7.5 Hz, Ar**H**, minor), 7.58 (2H, d, *J* = 7.4 Hz, Ar**H**, major), 7.53 (2H, d, *J* = 7.4 Hz, Ar**H**, minor), 7.42–7.23 (4H, m, Ar**H**, both), 4.54 (2H, d, *J* = 5.9 Hz, CHC**H₂**CO₂N major), 4.46 (2H, d, *J* = 6.1 Hz, CHC**H₂**CO₂N, minor), 4.24 (1H, t, *J* = 6.0 Hz, C**H**CH₂CO₂N, major), 4.19 (1H, t, *J* = 6.4 Hz, C**H**CH₂CO₂N, minor), 3.99 (1H, s, C**H₂**COOH, major), 3.87 (1H, s, C**H₂**COOH, minor), 3.13 (2H, d, *J* = 7.3 Hz, N**CH₂**CH(CH₃)₂, minor), 2.94 (2H, d, *J* = 7.5 Hz, N**CH₂**CH(CH₃)₂, major), 1.87–1.76 (1H, m, NCH₂C**H**(CH₃)₂, minor), 1.68–1.54 (1H, m, NCH₂C**H**(CH₃)₂, major), 0.88 (6H, d, *J* = 6.7 Hz, NCH₂CH**(CH₃)₂**, minor), 0.72 (6H, d, *J* = 6.4 Hz, NCH₂CH**(CH₃)₂**, major); δ$_C$ (100 MHz, CDCl₃) data for the major rotamer only, 175.0 (**C**OOH), 157.2 (N**C**OOCH₂CH), 144.0 (Ar**C**), 141.5 (Ar**C**), 127.8 (Ar**C**H), 127.2 (Ar**C**H), 124.9 (Ar**C**H), 120.0 (Ar**C**H), 67.4 (NCOO**C**H₂), 55.8 (N**C**H₂CH(CH₃)₂), 49.6 (N**C**H₂COOH), 47.3 (NCOOCH₂**C**H), 27.5 (NCH₂**C**H(CH₃)₂), 19.9 (NCH₂CH(**C**H₃)₂); Diagnostic ^{13}C NMR resonances for the minor rotamer: 175.3 (**C**OOH), 156.1 (N**C**OOCH₂CH), 56.2 (N**C**H₂CH(CH₃)₂), 48.9 (N**C**H₂COOH); HRMS (ESI): calcd. for $C_{21}H_{23}NNaO_4$, 376.1519. Found: $[MNa]^+$, 376.1528 (2.4 ppm error).

Lab notebook reference: KP019

***N*-(2-(1*H*-Indol-3-yl)ethyl)-*N*-(((9*H*-fluoren-9-yl)methoxy)carbonyl)glycine (2.19)**

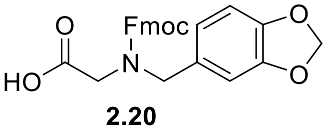


2.19

A solution of ethyl bromoacetate (1.11 mL, 10.0 mmol) in dry DCM (5 mL) was added dropwise to a solution of tryptamine (3.53 g, 22.0 mmol) in dry DCM (10 mL) at 0 °C. The mixture was allowed to warm to RT and stirred for 1.5 h (following by TLC). The solvent was then removed *in vacuo* and the mixture resuspended in diethyl ether (20 mL). The mixture was filtered and the residue washed with diethyl ether (4 × 5 mL), the filtrate was then concentrated *in vacuo* to afford the crude amino ester as a dark orange oil. NaOH (4N aq., 2.5 mL) was added to a solution of amino acetate in 1,4-dioxane (35 mL) and methanol (12 mL). The reaction was stirred at RT for 1.5 h and analysed by TLC. The solvent was removed *in vacuo* to yield crude the *N*-alkyl amino acid as the sodium salt. The *N*-alkyl amino acid salt was dissolved in a mixture of deionized water (30 mL), 1,4-dioxane (45 mL), and Na₂CO₃ (52 mL, 10% solution). The solution was cooled to 0 °C whilst stirring and a pre-made solution of 9-fluorenylmethyl chloroformate (3.20 g, 12.4 mmol) dissolved in 1,4-dioxane (10 mL) added slowly. The solution was allowed to warm to RT and stirred for 18 h, analysed by TLC. The mixture was diluted with water (30 mL) and acidified to pH 1 using 10% aq. HCl and extracted with EtOAc (4 × 50 mL). The combined organics were washed with brine (50 mL), dried over MgSO₄ and concentrated *in vacuo*. Column chromatography (SiO₂, 1:4 ethyl acetate: hexane → ethyl acetate) afforded the *title compound* (as a 3:2 mixture of rotamers) as a light brown crystalline solid, (1.57 g, 36% over 3 steps); m.p. 146–148 °C; R_f 0.17 (9:1 ethyl acetate: methanol) (streaky spot with concentration dependence); ν_{max}/cm^{-1} (neat) 3356, 2926, 1686, 1450, 1248, 1119, 908, 738; δ_H (400 MHz, $CDCl_3$) 8.61 (2H, br s, COO**H**, both rotamers) 8.14–8.11 (2H, m, N**H**, both rotamers), 7.72 (2H, d, *J* = 7.5 Hz, Ar**H**, major rotamer), 7.71 (2H, d, *J* = 7.3 Hz, Ar**H**, minor rotamer), 7.61–7.45 (6H, m, Ar**H**), 7.39–7.23 (10H, m, Ar**H**), 7.19–7.14 (2H, m, Ar**H**), 7.11–7.04 (2H, m, Ar**H**), 6.92 (1H, d, *J* = 2.1 Hz, Ar**H**, minor rotamer), 6.80 (1H, d, *J* = 2.1 Hz, Ar**H**, major rotamer), 4.52–4.44 (4H, m, CHC**H$_2$**CO$_2$N, both rotamers), 4.20–4.13 (2H, m, C**H**CH$_2$CO$_2$N, both rotamers), 3.88 (2H, s, C**H$_2$**COOH, major rotamer), 3.77 (2H, s, C**H$_2$**COOH, minor rotamer), 3.63 (2H, t, *J* = 7.4 Hz, NC**H$_2$**CH$_2$Ar, minor rotamer), 3.55 (2H, t, *J* = 7.1 Hz, NC**H$_2$**CH$_2$Ar, major rotamer), 3.00 (2H, t, *J* = 7.4 Hz, NCH$_2$C**H$_2$**Ar, minor rotamer), 2.82 (2H, t, *J* = 7.1 Hz, NCH$_2$C**H$_2$**Ar, major rotamer); δ_C (100 MHz, $CDCl_3$) 174.9 (**C**OOH), 174.7 (**C**OOH), 156.9 (N**C**OOCH$_2$CH), 156.0 (N**C**OOCH$_2$CH), 143.93 (Ar**C**), 143.92 (Ar**C**), 141.5 (Ar**C**), 141.4 (Ar**C**), 136.4 (Ar**C**), 127.8 (Ar**C**H), 127.7 (Ar**C**H), 127.4 (Ar**C**), 127.2 (Ar**C**H), 127.1 (Ar**C**H), 124.99 (Ar**C**H), 124.96 (Ar**C**H), 122.3 (Ar**C**H), 122.22 (Ar**C**H), 122.20 (Ar**C**H), 122.1 (Ar**C**H), 120.11 (Ar**C**H), 120.06 (Ar**C**H), 119.6 (Ar**C**H), 119.5 (Ar**C**H), 118.7 (Ar**C**H), 118.6 (Ar**C**H), 112.7 (Ar**C**H), 112.5 (Ar**C**H), 111.4 (Ar**C**H), 111.3 (Ar**C**H), 67.7 (N**C**H$_2$COOH), 67.1 (N**C**H$_2$COOH), 49.9 (**C**H$_2$), 49.8 (**C**H$_2$), 49.3 (**C**H$_2$), 49.2 (**C**H$_2$), 47.3 (C**H**CH$_2$CO$_2$N), 24.5 (**C**H$_2$), 24.1 (**C**H$_2$); HRMS (ESI): calcd. for $C_{27}H_{25}N_2O_4$, 441.1809. Found: $[MH]^+$, 441.1816 (1.6 ppm error).

Lab notebook reference: KP035

***N*-(((9*H*-Fluoren-9-yl)methoxy)carbonyl)-*N*-(benzo[d][1,3]dioxol-5-ylmethyl)glycine (2.20)**

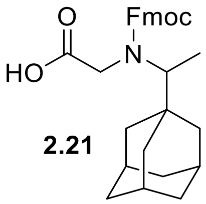


2.20

A solution of ethyl bromoacetate (1.11 mL, 10.0 mmol) in dry DCM (5 mL) was added dropwise to a solution of piperonyl amine (2.15 mL, 17.3 mmol) in dry DCM (10 mL) at 0 °C. The mixture was allowed to warm to RT and stirred for 0.5 h (following by TLC). After 10 min the reaction mixture formed a thick white paste which made stirring difficult. The solvent was then removed *in vacuo* and the mixture resuspended in diethyl ether (20 mL). The mixture was filtered and the residue washed with diethyl ether (3 × 5 mL), the filtrate was then concentrated *in vacuo* to afford the crude amino ester. NaOH (4N aq., 2.5 mL) was added to a solution of amino acetate in 1,4-dioxane (35 mL) and methanol (12.5 mL). The reaction was stirred at RT for 2.5 h and analysed by TLC. The solvent was removed *in vacuo* to yield crude the *N*-alkyl amino acid as the sodium salt. The *N*-alkyl amino acid salt was dissolved in a mixture of deionized water (30 mL), 1,4-dioxane (50 mL), and Na_2CO_3 (50 mL, 10% solution). The solution was cooled to 0 °C whilst stirring and a pre-made solution of 9-fluorenylmethyl chloroformate (3.24 g, 12.4 mmol) dissolved in 1,4-dioxane (10 mL) added slowly. The solution was allowed to warm to RT and stirred for 21 h, analysed by TLC. The mixture was diluted with water (30 mL) and acidified to pH 1 using 10% aq. HCl and extracted with EtOAc (3 × 50 mL). The combined organics were washed with brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (SiO_2, 1:4 ethyl acetate: hexane → 1:1 ethyl acetate: hexane) afforded the *title compound* (as a 1.08:1 mixture of rotamers) as a beige solid, (3.25 g, 75% over 3 steps); m.p. 110–114 °C; R_f 0.17 (9:1 ethyl acetate: methanol) (streaky spot with concentration dependence); ν_{max}/cm^{-1} (neat) 2895, 1700, 1489, 1444, 1232, 1127, 1038, 908, 727; δ_H (400 MHz, $CDCl_3$) 9.91 (2H, br s, COO**H**, both rotamers), 7.73 (4H, t, *J* = 7.4 Hz, Ar**H**), 7.56–7.51 (4H, m, Ar**H**), 7.41–7.33 (4H, m, Ar**H**), 7.28 (4H, tdd, *J* = 7.4, 2.8, 1.2 Hz, Ar**H**), 6.74–6.69 (3H, m, Ar**H**), 6.65–6.61 (1H, m, Ar**H**), 6.54–6.49 (2H, m, Ar**H**), 5.94 (2H, s, OC**H$_2$**O, major rotamer), 5.92 (2H, s, OC**H$_2$**O, minor rotamer), 4.57 (2H, d, *J* = 6.3 Hz, CHC**H$_2$**CO$_2$N, major rotamer), 4.52 (2H, d, *J* = 6.2 Hz, CHC**H$_2$**CO$_2$N, minor rotamer), 4.46 (2H, s, NC**H$_2$**Ar, minor rotamer), 4.36 (2H, s, NC**H$_2$**Ar, major rotamer), 4.27 (1H, t, *J* = 6.3 Hz, C**H**CH$_2$CO$_2$N, major rotamer), 4.21 (1H, t, *J* = 6.2 Hz, C**H**CH$_2$CO$_2$N, minor rotamer), 3.96 (2H, s, NC**H$_2$**COOH, major rotamer), 3.76 (2H, s, NC**H$_2$**COOH, minor rotamer); δ_C (100 MHz, $CDCl_3$) 174.83 (**C**OOH), 174.76 (**C**OOH), 156.6 (N**C**OOCH$_2$CH), 156.4 (N**C**OOCH$_2$CH), 148.2 (2C, Ar**C**), 147.4 (Ar**C**), 147.3 (Ar**C**), 143.84 (2C, Ar**C**), 143.82 (2C, Ar**C**), 141.45 (2C, Ar**C**), 141.43 (2C, Ar**C**), 130.3 (Ar**C**), 130.2 (Ar**C**), 127.9 (2C, Ar**C**H), 127.8 (2C, Ar**C**H), 127.24 (2C, Ar**C**H), 127.19 (2C, Ar**C**H), 125.0 (2C, Ar**C**H), 124.9 (2C, Ar**C**H), 121.8 (Ar**C**H), 121.3 (Ar**C**H), 120.14 (2C, Ar**C**H), 120.08 (2C, Ar**C**H), 108.8 (Ar**C**H), 108.4 (Ar**C**H), 108.30 (Ar**C**H), 108.25 (Ar**C**H), 101.3 (O**C**H$_2$O), 101.2 (O**C**H$_2$O), 68.0 (N**C**H$_2$COOH), 67.9 (N**C**H$_2$COOH), 51.3 (**C**H$_2$), 51.0 (**C**H$_2$), 47.5 (**C**H$_2$), 47.4 (C**H**CH$_2$CO$_2$N), 47.3 (C**H**CH$_2$CO$_2$N), 46.7 (**C**H$_2$); HRMS (ESI): calcd. for $C_{25}H_{21}NNaO_6$, 454.1261. Found: $[MNa]^+$, 454.1263 (–0.4 ppm error).

Lab notebook reference: KP037

N-(((9H-Fluoren-9-yl)methoxy)carbonyl)-N-(1-((3r,5r,7r)-adamantan-1-yl)ethyl)glycine (2.21)

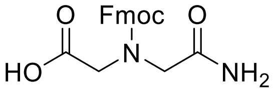


2.21

A solution of NaOH (2 N, 50 mL), was added to 1-(1-adamantyl)ethanamine hydrochloride (2.50 g, 11.6 mmol) and stirred for 10 min. The reaction mixture was then transferred to a separatory funnel using DCM (50 mL) and H_2O (10 mL) and extracted using DCM (3 × 50 mL). The solvent was then removed *in vacuo* to give 1-(1-adamantyl)ethanamine. A solution of ethyl bromoacetate (0.580 mL, 5.23 mmol) in dry THF (2.5 mL) was added dropwise to a solution of 1-(1-adamantyl)ethanamine (2.06 g, 11.0 mmol) in dry THF (2.5 mL) at 0 °C. The mixture was allowed to warm to RT and stirred for 3 h (Following by TLC). The solvent was then removed *in vacuo* and the mixture resuspended in diethyl ether (20 mL). The mixture was filtered and the residue washed with diethyl ether (4 × 15 mL), the filtrate was then concentrated *in vacuo* to afford the amino ester as a white paste. NaOH (4 N, 1.5 mL) was added to a solution of amino acetate (1.47 g) in 1,4-dioxane (18 mL) and methanol (6.5 mL). The reaction was stirred at RT for 3 h and analysed by TLC. The solvent was removed *in vacuo* to yield crude the *N*-alkyl amino acid as the sodium salt. The *N*-alkyl amino acid salt was dissolved in a mixture of deionized water (15 mL), 1,4-dioxane (23 mL), and Na_2CO_3 (26 mL, 10% solution). The solution was cooled to 0 °C whilst stirring and a pre-made solution of 9-fluorenylmethyl chloroformate (1.88 g, 7.27 mmol) dissolved in 1,4-dioxane (5 mL) added slowly. The solution was allowed to warm to RT and stirred for 18 h, analysed by TLC. The mixture was diluted with water (25 mL) and acidified to pH 2 using 10% aq. HCl and extracted with EtOAc (3 × 50 mL). The combined organics were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (SiO_2, 1:4 ethyl acetate: hexane → 1:1 ethyl acetate: hexane) afforded the *title compound* (as an 1:1 mixture of rotamers) as a fine white powder, (874 mg, 36% over 2 steps); 181 – 183 °C ; R_f 0.27 (9:1 ethyl acetate: methanol) (streaky spot with concentration dependence); ν_{max}/cm^{-1} (neat) 2902, 2848, 1689, 1445, 1320, 1191, 907, 727; δ_H (400 MHz, $CDCl_3$) 8.88 (2H, br s, COO**H**, **both** rotamers) 7.76 (2H, br d, J =7.5 Hz, Ar**H**, rotamer **A**), 7.72 (2H, d, J =7.6 Hz, Ar**H**, rotamer **B**), 7.59 (2H, t, J = 8.1 Hz, Ar**H**, rotamer **A**), 7.54 (2H, dd, J = 7.5, 4.0 Hz, Ar**H**, rotamer **B**), 7.42 – 7.24 (8H, m, Ar**H**, **both** rotamers), 4.70 (1H, dd, *J* = 10.7, 5.2 Hz, CHC**H**H'CO_2N, rotamer **A**), 4.54 (2H, m, CHC**H**H'CO_2N, rotamer **B** and CHCH**H'**CO_2N, rotamer **A**), 4.38 (1H, d, *J* = 10.7, 6.1 Hz, CHCH**H'**CO_2N, rotamer **B**), 4.23 (1H, t, *J* = 5.3 Hz, C**H**CH_2CO_2N, rotamer **A**), 4.14 (1H, t, *J* = 6.1 Hz, C**H**CH_2CO_2N, rotamer **B**), 4.08 – 4.01 (1H, m, NC**H**CH_3, rotamer **A**), 4.02 (1H, d, *J* = 18.0 Hz, NC**H**H'COOH, rotamer **A**), 3.94 (1H, d, *J* = 18.0 Hz, NC**H**H'COOH, rotamer **B**), 3.64 (2H, d, *J* = 18.0 Hz, NCH**H’**COOH, **both** rotamers), 3.47 (1H, q, *J* = 7.0 Hz, NC**H**CH$_3$, rotamer **B**), 1.95 (3H, s, Adamantane C**H**, rotamer **A**), 1.84 (3H, s, Adamantane C**H**, rotamer **B**), 1.70 – 1.55 (9H, m, Adamantane C**H**$_2$), 1.54 – 1.43 (9H, m, Adamantane C**H**$_2$), 1.33 – 1.25 (3H, m, Adamantane C**H**$_2$), 1.22 – 1.15 (3H, m, Adamantane C**H**$_2$), 1.06 (3H, d, *J* = 7.2 Hz, C**H**$_3$, rotamer **A**), 3.94 (3H, d, *J* = 7.2 Hz, C**H**$_3$, rotamer **B**); δ_C (100 MHz, $CDCl_3$) data for rotamer B only, 176.0 (**C**OOH), 157.5 (N**C**OOCH$_2$CH), 144.3 (Ar**C**), 144.2 (Ar**C**), 141.7 (Ar**C**), 128.0 (Ar**C**H), 127.4 (Ar**C**H), 125.1 (Ar**C**H), 120.1 (Ar**C**H), 67.6 (NCOO**C**H$_2$), 59.9 (N**C**HCH$_3$), 47.7 (NCOOCH$_2$**C**H), 46.1 (N**C**H$_2$COOH), 39.1 (Adamantane **C**H$_2$), 38.2 (Adamantane **C**), 37.2 (Adamantane **C**H$_2$), 28.5 (Adamantane **C**H), 11.5 (**C**H$_3$); Diagnostic ^{13}C NMR resonances for the rotamer A: 46.8 (N**C**H$_2$COOH), 37.6 (Adamantane **C**), 11.1 (**C**H$_3$); HRMS (ESI): calcd. for $C_{29}H_{33}NNaO_4$, 428.2302. Found: $[MNa]^+$, 428.2308 (1.3 ppm error).

Lab notebook reference: KP031

***N*-(((9*H*-Fluoren-9-yl)methoxy)carbonyl)-*N*-(2-amino-2-oxoethyl)glycine (2.22)**

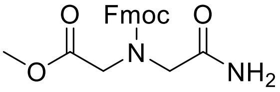


2.22

Glycinamide hydrochloride (1.11 g, 10.0 mmol) was dissolved in ethanol (15 mL) and to this was added Et_3N (2.86 mL, 20.5 mmol). This mixture was cooled to 0 °C and to it was added a solution of ethyl bromoacetate (1.11 mL, 10.0 mmol) in dry THF (10 mL) was added dropwise. The mixture was allowed to warm to RT and stirred for 20 h (following by TLC). The solvent was then removed *in vacuo* and the mixture resuspended in diethyl ether (20 mL). The mixture was filtered and the residue washed with diethyl ether (3 × 5 mL), the filtrate was then concentrated *in vacuo* to afford the crude amino ester as a white paste (2.18 g). Purification by flash column chromatography (SiO_2, 1:4 ethyl acetate: hexane → 1:1 ethyl acetate: hexane) afforded ethyl (2-amino-2-oxoethyl)glycinate as a white crystalline solid (529 mg, 3.30 mmol) which was confirmed by ^{1}H NMR, ^{13}C NMR and HRMS data. Data for ethyl (2-amino-2-oxoethyl)glycinate: δ_H (400 MHz, $CDCl_3$) 7.06 – 6.97 (1H, br m, CONH**H**’), 6.88 – 6.79 (1H, br m, CONH**H’**), 3.89 (2H, q, *J* = 7.1 Hz, C**H**$_2$CH$_3$), 3.14 (2H, s, NHC**H**$_2$CO), 3.01 (2H, s, NHC**H**$_2$CO), 2.31 (1H, s, N**H**CH$_2$CO), 0.98 (3H, t, *J* = 7.2 Hz, CH$_2$C**H**$_3$); δ_C (100 MHz, $CDCl_3$) 174.6 (**C**O), 171.8 (**C**O), 60.3 (**C**H$_2$CH$_3$), 51.3 (NH**C**H$_2$CO), 50.0 (NH**C**H$_2$CO), 13.6 (CH$_2$**C**H$_3$); HRMS (ESI): calcd. for $C_6H_{12}N_2NaO_3$, 183.0740. Found: $[MNa]^+$, 183.0742 (–1.0 ppm error). Next, ethyl (2-amino-2-oxoethyl)glycinate (529 mg, 3.30 mmol) was dissolved in 1,4-dioxane (12 mL) and methanol (4 mL) and NaOH (4 N, 0.85 mL) was added. The reaction was stirred at RT for 1 h and analyzed by TLC. The solvent was removed *in vacuo* to yield crude the *N*-alkyl amino acid as the sodium salt. The *N*-alkyl amino acid salt was dissolved in a mixture of deionized water (10 mL), 1,4-dioxane (16 mL), and Na_2CO_3 (17 mL, 10% solution). The solution was cooled to 0 °C whilst stirring and a pre-made solution of 9-fluorenylmethyl chloroformate (1.02 g, 3.96 mmol) dissolved in 1,4-dioxane (3.5 mL) added slowly. The solution was allowed to warm to RT and stirred for 18 h, analysed by TLC. The mixture was diluted with water (25 mL) and acidified to pH 2 using 10% aq. HCl and extracted with EtOAc (3 × 50 mL). The combined organics were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Recrystallization using hexane and ethyl acetate afforded the *title compound* (as a 2:1 mixture of rotamers) as a pink solid, (719 mg, 20% over 2 steps); R_f 0.00 (4:1 DCM: methanol); ν_{max}/cm^{-1} (neat) 3261, 3062, 1726, 1683, 1615, 1445, 1418, 1402, 1337, 1264, 1106, 1049, 1024, 756, 738, 728, 620, 590; δ_H (400 MHz, d_6-DMSO) data for all rotamers: 7.92 – 7.78 (2H, m, Ar**H**), 7.72 – 7.60 (2H, m, Ar**H**), 7.46 – 7.26 (4H, m, Ar**H**), 4.28 – 4.20 (3H, m, C**H** and C**H**$_2$), 4.14 – 4.10 (1H, m, C**H**$_2$), 4.07 – 4.03 (2H, m, C**H**$_2$ [overlapping]), 4.28 – 4.20 (1H, m, C**H**, minor rotamer, [overlapping]), 3.94 (1H, br s, C**H**$_2$), 3.76 (1H, d, *J* = 7.0 Hz, C**H**$_2$, minor rotamer); δ_C (100 MHz, d_6-DMSO) data for all rotamers: 171.7 (**C**O), 171.5 (**C**O), 171.4 (**C**O), 171.3 (**C**O), 171.2 (**C**O), 171.0 (**C**O), 155.8 (**C**O), 155.7 (**C**O), 145.3 (Ar**C**), 143.74 (Ar**C**), 143.71 (Ar**C**), 140.82 (Ar**C**), 140.80 (Ar**C**), 140.76 (Ar**C**), 127.9 (Ar**C**H), 127.31 (Ar**C**H), 127.27 (Ar**C**H), 126.9 (Ar**C**H), 125.5 (Ar**C**H), 125.35 (Ar**C**H), 125.32 (Ar**C**H), 125.28 (Ar**C**H), 120.3 (Ar**C**H), 120.0 (Ar**C**H), 67.8 (NCOO**C**H$_2$), 67.73 (NCOO**C**H$_2$), 67.68 (NCOO**C**H$_2$), 63.9 (NCOO**C**H$_2$), 51.4 (**C**H$_2$), 51.1 (**C**H$_2$), 50.8 (**C**H$_2$), 50.2 (NCOOCH$_2$**C**H), 49.6 (**C**H$_2$), 49.2 (**C**H$_2$), 46.63 (NCOOCH$_2$**C**H), 46.58 (NCOOCH$_2$**C**H); HRMS (ESI): calcd. for $C_{19}H_{18}N_2NaO_5$, 377.1108. Found: $[MNa]^+$, 377.1104 (1.3 ppm error). This procedure was adapted from a literature method.[63]

Lab notebook reference: KP045

Methyl *N*-(((9*H*-fluoren-9-yl)methoxy)carbonyl)-*N*-(2-amino-2-oxoethyl)glycinate (2.65)



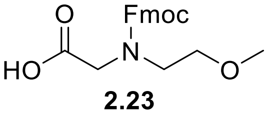
2.65

To a solution of acid chloride (prepared using the general procedure from **2.22** [56.2 mg, 0.159 mmol]) in DCM (1.6 mL) was added MeOH (1.0 mL). After stirring for 1 h, the solvent was removed affording a crude mixture containing the *title compound* as mixture of rotamers as a light brown paste which was analysed without further purification; ν_{max}/cm^{-1} (thin film) 2953, 1745, 1707, 1450, 1407, 1202, 1130, 1005, 909, 759, 728, 539; δ_H (400 MHz, $CDCl_3$) Diagnostic ^{1}H NMR resonances: 6.91 (2H, br s, CON**H$_2$**, both rotamers), 3.75 – 3.72 (3H, m, C**H$_3$**), 3.71 – 3.68 (3H, m, C**H$_3$**); δ_C (100 MHz, $CDCl_3$) data for the major rotamer only, 170.0 (**C**O), 169.8 (**C**O), 156.0 (**C**O), 143.8 (Ar**C**), 141.4 (Ar**C**), 127.8 (Ar**C**H), 127.2 (Ar**C**H), 125.0 (Ar**C**H), 120.1 (Ar**C**H), 68.4 (NCOO**C**H$_2$), 52.4 (**C**H$_3$), 49.4 (N**C**H$_2$), 49.0 (N**C**H$_2$), 47.1

(NCOOCH$_2$**C**H); HRMS (ESI): calcd. for $C_{20}H_{20}N_2NaO_5$, 391.1262. Found: [MNa]$^+$, 391.1263 (0.4 ppm error).

Lab notebook reference: KP081

N-(((9*H*-Fluoren-9-yl)methoxy)carbonyl)-*N*-(2-methoxyethyl)glycine (2.23)

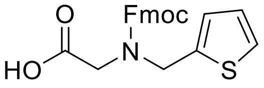


2.23

A solution of ethyl bromoacetate (1.11 mL, 10.0 mmol) in dry THF (5 mL) was added dropwise to a solution of 2-methoxyethylamine (1.91 mL, 22.0 mmol) in dry THF (5 mL) at 0 °C. The mixture was allowed to warm to RT and stirred for 3 h (following by TLC). The solvent was then removed *in vacuo* to afford the crude amino ester as a yellowish oil. NaOH (4N aq., 8.2 mL) was added to a solution of amino acetate in 1,4-dioxane (35 mL) and methanol (12.5 mL). The reaction was stirred at RT for 2.5 h and analysed by TLC. The solvent was removed *in vacuo* to yield crude the *N*-alkyl amino acid as the sodium salt. The *N*-alkyl amino acid salt was dissolved in a mixture of deionized water (30 mL), 1,4-dioxane (50 mL), and Na_2CO_3 (50 mL, 10% solution). The solution was cooled to 0 °C whilst stirring and a pre-made solution of 9-fluorenylmethyl chloroformate (8.67 g, 33.5 mmol) dissolved in 1,4-dioxane (28 mL) added slowly. The solution was allowed to warm to RT and stirred for 18 h, analysed by TLC. The mixture was diluted with water (100 mL) and acidified to pH 2 using 10% aq. HCl and extracted with EtOAc (3 × 50 mL). The combined organics were washed with brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (SiO_2, 1:4 ethyl acetate: hexane → 1:1 ethyl acetate: hexane) afforded the *title compound* (as an 1:1 mixture of rotamers) as a yellow oil which crystalizes under vacuum, (2.40 g, 68% over 3 steps); R_f 0.23 (9:1 ethyl acetate: methanol) (streaky spot with concentration dependence); ν_{max}/cm^{-1} (neat) 2937, 1700, 1450, 1118, 908, 727; δ_H (400 MHz, CDCl$_3$) 10.58 (2H, br s, COO**H**, both rotamers) 7.75 (2H, d, *J* = 7.5 Hz, Ar**H**, single rotamer), 7.72 (2H, d, *J* = 7.5 Hz, Ar**H**, single rotamer), 7.58 (2H, d, *J* = 7.4 Hz, Ar**H**, single rotamer), 7.54 (2H, d, *J* = 7.4 Hz, Ar**H**, single rotamer), 7.42 – 7.25 (8H, m, Ar**H**, both), 4.54 (2H, d, *J* = 6.1 Hz, CHC**H$_2$**CO$_2$N, rotamer A), 4.43 (2H, d, *J* = 6.5 Hz, CHC**H$_2$**CO$_2$N, rotamer B), 4.25 (1H, t, *J* = 6.1 Hz, C**H**CH$_2$CO$_2$N, rotamer A), 4.19 (1H, t, *J* = 6.5 Hz, C**H**CH$_2$CO$_2$N, rotamer B), 4.13 (2H, s, C**H$_2$**COOH, single rotamer), 4.06 (2H, s, C**H$_2$**COOH, single rotamer), 3.54 (4H, s, N**CH$_2$**CH$_2$OCH$_3$, and NCH$_2$**CH$_2$**OCH$_3$, overlapping protons signals from single rotamer), 3.36 (2H, t, *J* = 5.2 Hz N**CH$_2$**CH$_2$OCH$_3$, single rotamer), 3.29 (3H, s, NCH$_2$CH$_2$O**CH$_3$**, single rotamer), 3.25 (2H, t, *J* = 5.2 Hz, NCH$_2$**CH$_2$**OCH$_3$, single rotamer), 3.22 (3H, s, NCH$_2$CH$_2$O**CH$_3$**, single rotamer); δ_C (100 MHz, CDCl$_3$) 174.7 (**C**OOH), 156.4 (N**C**OOCH$_2$CH), 156.0 (N**C**OOCH$_2$CH), 143.9 (Ar**C**), 143.8 (Ar**C**), 141.4 (Ar**C**), 141.3 (Ar**C**), 127.8 (Ar**C**H), 127.7 (Ar**C**H), 127.2 (Ar**C**H), 127.1 (Ar**C**H), 124.9 (Ar**C**H), 124.9 (Ar**C**H), 120.0 (Ar**C**H), 71.7 (**C**H_2), 71.4 (**C**H_2), 68.0 (NCOO**C**H_2), 67.6 (NCOO**C**H_2), 58.7 (O**C**H_3), 50.2 (N**C**H_2COOH), 50.1 (N**C**H_2COOH), 48.7 (**C**H_2), 48.2 (**C**H_2), 47.2 (**C**HC**H₂**CO**₂**N), 47.2 (**C**HC**H₂**CO**₂**N); HRMS (ESI): calcd. for $C_{20}H_{21}NNaO_5$, 378.1312. Found: $[MNa]^+$, 378.1310 (0.4 ppm error).

Lab notebook reference: KP023

_N_-(((9_H_-Fluoren-9-yl)methoxy)carbonyl)-_N_-(thiophen-2-ylmethyl)glycine (2.24)

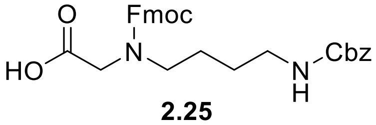


2.24

A solution of ethyl bromoacetate (1.11 mL, 10.0 mmol) in dry THF (5 mL) was added dropwise to a solution of 2-thiophenemethylamine (2.26 mL, 22.0 mmol) in dry THF (5 mL) at 0 °C. The mixture was allowed to warm to RT and stirred for 4 h (following by TLC). The solvent was then removed *in vacuo* and the mixture resuspended in diethyl ether (20 mL) at which point a white precipitate began to form. The mixture was filtered and the residue washed with diethyl ether (3 × 10 mL), the filtrate was then concentrated *in vacuo* to afford the amino ester as a colourless oil. NaOH (4N aq., 2.5 mL) was added to a solution of amino acetate in 1,4-dioxane (35 mL) and methanol (13 mL). The reaction was stirred at RT for 2.5 h and analysed by TLC. The solvent was removed *in vacuo* to yield crude the *N*-alkyl amino acid as the sodium salt. The *N*-alkyl amino acid salt was dissolved in a mixture of deionized water (30 mL), 1,4-dioxane (47 mL), and 10% aq. Na_2CO_3 (52 mL). The solution was cooled to 0 °C whilst stirring and a pre-made solution of 9-fluorenylmethyl chloroformate (3.10 g, 12.0 mmol) dissolved in 1,4-dioxane (10 mL) added slowly. The solution was allowed to warm to RT and stirred for 20 h, analysed by TLC. The mixture was diluted with water (50 mL) and acidified to pH 2 using 10% aq. HCl and extracted with EtOAc (3 × 50 mL). The combined organics were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (SiO_2, 1:4 ethyl acetate: hexane → 1:1 ethyl acetate: hexane) afforded the *title compound* (as an 1.1:1 mixture of rotamers) as a yellow oil which crystalizes under vacuum, (2.79 g, 71% over 3 steps); R_f 0.23 (9:1 ethyl acetate: methanol); ν_{max}/cm^{-1} (neat) 3067, 1702, 1450, 1221, 906, 726; δ_H (400 MHz, $CDCl_3$) 9.14 (2H, br s, COO**H**, both rotamers) 7.76 (2H, d, *J* = 7.5 Hz, Ar**H**, major), 7.73 (2H, d, *J* = 7.5 Hz, Ar**H**, minor), 7.58 (2H, d, *J* = 7.4 Hz, Ar**H**, major), 7.54 (2H, d, *J* = 7.5 Hz, Ar**H**, minor), 7.43 – 7.34 (4H, m, Ar**H**, both), 7.32–7.26 (4H, m, Ar**H**, both), [7.26–7.23 (2H, m), 6.94–6.92 (3H, m,), 6.81–6.78 (1H, m) all thiophene Ar**H**, both rotamers], 4.74 (2H, s, N**CH₂**Ar, minor), 4.67 (2H, s, N**CH₂**Ar, major), 4.56 (2H, d, *J* = 6.6 Hz, CHC**H₂**CO**₂**N, major), 4.52 (2H, d, *J* = 6.4 Hz, CHC**H₂**CO₂N, minor) 4.31 (1H, t, *J* = 6.6 Hz, C**H**CH₂CO₂N, major), 4.23 (1H, t, *J* = 6.3 Hz, C**H**CH₂CO₂N, minor), 4.07 (2H, s, C**H₂**COOH, major), 3.89 (2H, s, C**H₂**COOH, minor); δ_C (100 MHz, $CDCl_3$) 175.1 (**C**OOH), 175.0 (**C**OOH), 156.3 (N**C**OOCH₂CH), 156.0 (N**C**OOCH₂CH), 143.8 (Ar**C**), 141.5 (Ar**C**), 141.4 (Ar**C**), 139.0 (Ar**C**), 139.0 (Ar**C**), 127.9 (Ar**C**H), 127.8 (Ar**C**H), 127.4 (Ar**C**H), 127.3 (Ar**C**H), 127.2 (Ar**C**H), 127.1 (Ar**C**H), 127.0 (Ar**C**H), 126.9 (Ar**C**H), 126.2 (Ar**C**H), 126.0 (Ar**C**H), 125.1 (Ar**C**H), 125.0 (Ar**C**H), 120.2 (Ar**C**H), 120.1 (Ar**C**H), 68.3 (NCOO**C**H₂), 68.1 (NCOO**C**H₂), 47.4 (N**C**H₂Ar), 47.3 (**C**HCH₂CO₂N), 47.2 (**C**HCH₂CO₂N), 46.8 (N**C**H₂Ar), 46.2 (N**C**H₂COOH), 46.1 (N**C**H₂COOH); HRMS (ESI): calcd. for $C_{22}H_{19}NNaO_4S$, 416.0927. Found: $[MNa]^+$, 416.0924 (0.7 ppm error).

Lab notebook reference: KP025

N-(((9*H*-Fluoren-9-yl)methoxy)carbonyl)-*N*-(4-(((benzyloxy)carbonyl)amino)butyl)glycine acid (2.25)

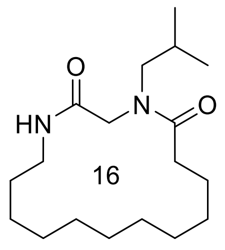


2.25

A solution of ethyl bromoacetate (1.11 mL, 10.0 mmol) in dry THF (5 mL) was added dropwise to a solution of benzyl *N*-(4-aminobutyl) carbamate (4.54 g, 20.4 mmol) in dry THF (15 mL) at 0 °C. The mixture was allowed to warm to RT and stirred for 2 h (following by TLC). The solvent was then removed *in vacuo* and the mixture resuspended in diethyl ether (20 mL). The mixture was filtered and the residue washed with diethyl ether (5 × 5 mL), the filtrate was then concentrated *in vacuo* to afford the amino ester as a pasty white solid. Aq. NaOH (4 N, 2.5 mL) was added to a solution of amino acetate in 1,4-dioxane (35 mL) and methanol (13 mL). The reaction was stirred at RT for 2.5 h and analysed by TLC. The solvent was removed *in vacuo* to yield crude amino acid sodium salt. The *N*-alkyl amino acid salt was dissolved in a mixture of deionized water (30 mL), 1,4-dioxane (47 mL), and Na_2CO_3 (52 mL, 10% solution). The solution was cooled to 0 °C whilst stirring and a pre-made solution of 9-fluorenylmethyl chloroformate (3.21 g, 12.4 mmol) dissolved in 1,4-dioxane (10 mL) added slowly. The solution was allowed to warm to RT and stirred for 18 h, analysed by TLC. The mixture was diluted with water (50 mL) and acidified to pH 2 using 10% aq. HCl and extracted with EtOAc (3 × 50 mL). The combined organics were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (SiO_2, 1:4 ethyl acetate: hexane → 1:1 ethyl acetate: hexane → ethyl acetate) afforded the *title compound* (as a mixture of rotamers) as a white foamy solid (519 mg, 10% over 2 steps); m.p. 45 – 49 °C; R_f 0.13 (9:1 ethyl acetate: methanol) (streaky spot with concentration dependence); ν_{max}/cm^{-1} (thin film) 3334, 2941, 1693, 1524, 1450, 1364, 1235, 1137, 1021, 758, 739, 621, 538; δ_H (400 MHz, $CDCl_3$) 7.80 – 7.65 (2H, m, Ar**H**), 7.64 – 7.47 (2H, m, Ar**H**), 7.44 – 7.20 (8H, m, Ar**H**), 7.16 – 7.02 (1H, m, N**H**), 5.18 – 4.77 (2H, m, ArC**H**$_2$), 4.71 – 4.31 (2H, m, CHC**H**$_2$CO$_2$N), 4.25 – 4.16 (1H, m, C**H**CH$_2$CO$_2$N), 4.04 – 3.82 (2H, m, C**H**$_2$COOH), 3.38 – 2.74 (4H, m, 2×(NC**H**$_2$)), 1.66 – 0.90 (4H, m, (C**H**$_2$)$_2$); δ$_C$ (100 MHz, CDCl$_3$) 171.2 (**C**O), 156.5 (**C**O), 156.2 (**C**O), 155.5 (**C**O), 144.5 (Ar**C**), 144.0 (Ar**C**), 143.8 (Ar**C**), 141.5 (Ar**C**), 141.4 (Ar**C**), 141.3 (Ar**C**), 137.7 (Ar**C**), 136.6 (Ar**C**), 128.5 (Ar**C**H), 128.1 (Ar**C**H), 127.7 (Ar**C**H), 127.6 (Ar**C**H), 127.5 (Ar**C**H), 127.3 (Ar**C**H), 127.2 (Ar**C**H), 127.1 (Ar**C**H), 124.8 (Ar**C**H), 124.7 (Ar**C**H), 120.0 (Ar**C**H), 67.3 (NCOO**C**H$_2$), 66.6 (NCOO**C**H$_2$Ar), 65.1 (NCOO**C**H$_2$), 50.1 (N**C**H$_2$COOH), 50.0 (N**C**H$_2$COOH), 48.3 (N**C**H$_2$CH$_2$), 48.2 (N**C**H$_2$CH$_2$), 47.6 (NCOOCH$_2$**C**H), 47.2 (NCOOCH$_2$**C**H), 40.6 (N**C**H$_2$CH$_2$), 40.5 (N**C**H$_2$CH$_2$), 27.2 (**C**H$_2$), 27.0 (**C**H$_2$), 25.4 (**C**H$_2$), 25.1(**C**H$_2$); HRMS (ESI): calcd. for $C_{29}H_{31}N_2O_6$, 503.2177. Found: $[MH]^+$, 503.2188 (–2.3 ppm error).

Lab notebook reference: KP050

4-Isobutyl-1,4-diazacyclohexadecane-2,5-dione (2.45)



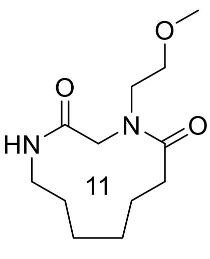
2.45

A mixture of laurolactam (98.7 mg, 0.500 mmol), DMAP (6.1 mg, 0.050 mmol) and pyridine (0.243 mL, 3.00 mmol) in DCM (5 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of (9*H*-fluoren-9-yl)methyl (2-chloro-2-oxoethyl)(isobutyl)carbamate (0.750 mmol, 1.50 eqv. prepared using the general procedure from *N*-(((9*H*-fluoren-9-yl)methoxy)carbonyl)-*N*-isobutylglycine **2.18**) in DCM (4 mL) was added and the resulting mixture was heated to reflux at 40 °C for 24 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 × 20 mL) and the combined organic extracts dried over MgSO$_4$ and concentrated *in vacuo*. The crude material was then re-dissolved in DCM (5 mL) and DBU (0.750 mL, 5.00 mmol) was added, followed by stirring at RT for 14 h, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO$_2$, 1:4 ethyl acetate: hexane → ethyl acetate → 9:1 ethyl acetate: methanol) afforded the *title compound* (as a 5:1 mixture of rotamers) as a yellow oil (126 mg, 81%). ^{1}H and ^{13}C NMR data match those reported in the literature.[48] δ$_H$ (400 MHz, CDCl$_3$) 6.87 (1H, t, *J* = 5.0 Hz, NH, major rotamer), 6.11 (1H, t, *J* = 5.9 Hz, NH, minor rotamer), 3.89 (2H, s, CH$_2$, major rotamer), 3.18 (2H, q, *J* = 5.5 Hz, CH$_2$), 3.15 (2H, d, *J* = 7.6 Hz, CH$_2$), 2.36 – 2.31 (2H, m, CH$_2$, major rotamer) 2.22 – 2.15 (2H, m, CH$_2$, minor rotamer), 2.02 – 1.88 (1H, m, CH, both rotamers), 1.65 – 1.56

(2H, m, CH$_2$, both rotamers), 1.44 – 1.16 (20H, m, CH$_2$), 0.85 (6H, d, *J* = 6.7 Hz, CH$_3$, major rotamer), 0.81 (6H, d, *J* = 6.7 Hz, CH$_3$, minor rotamer).

Lab notebook reference: KP021

4-(2-Methoxyethyl)-1,4-diazacycloundecane-2,5-dione (2.47)

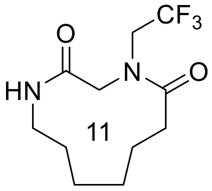


2.47

A mixture of 1-aza-2-cyclooctanone (64.2 mg, 0.505 mmol), DMAP (9.0 mg, 0.074 mmol) and pyridine (0.243 mL, 3.00 mmol) in DCM (5 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride (0.776 mmol, 1.50 equiv. prepared using the general procedure from *N*-(((9*H*-fluoren-9-yl)methoxy)carbonyl)-*N*-(2-methoxyethyl)glycine **2.23**) in DCM (5 mL) was added and the resulting mixture was heated to reflux at 40 °C for 18 h. The mixture was then diluted with DCM (30 mL) and washed with 10% aq. HCl (15 mL). The aqueous layer was then extracted with DCM (3 × 15 mL) and the combined organic extracts dried over MgSO$_4$ and concentrated *in vacuo*. The crude material was then re-dissolved in DCM (5 mL) and DBU (0.747 mL, 5.00 mmol) was added, followed by stirring at RT for 18 h, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO$_2$, 1:9 ethyl acetate: hexane → 19:1 ethyl acetate: methanol) afforded the *title compound* as a pasty orange solid (85.4 mg, 70%); R$_f$ 0.20 (9:1 ethyl acetate: methanol); m.p. 104–105 °C; ν_{max}/cm^{-1} (neat) 3368, 2915, 1667, 1624, 1524, 1470, 1412, 1364, 1213, 1113, 1046, 990, 672); All ^{1}H signals broadened due to rotamer interconversion. δ_H (400 MHz, DMSO-d$_6$, 80 °C) 7.64 (1H, br s, N**H**), 3.97 (2H, s, NC**H$_2$**CO), 3.60 (2H, t, *J* = 5.6 Hz, C**H$_2$**OCH$_3$), 3.52 (2H, t, *J* = 5.6 Hz, C**H$_2$**CH$_2$OCH$_3$), 3.29 (3H, s, CH$_2$OC**H$_3$**), 3.28–3.19 (2H, m, C**H$_2$**NH), 2.18 (2H, t, *J* = 6.8 Hz, C**H$_2$**CON), 1.59–1.45 (4H, m, (C**H$_2$**)$_2$), 1.32–1.21 (4H, m, (C**H$_2$**)$_2$); δ_C (100 MHz, CDCl$_3$): 175.8 (**C**O), 170.7 (**C**O), 69.2 (**C**H$_2$OCH$_3$), 58.3 (O**C**H$_3$), 55.3 (N**C**H$_2$), 49.1 (N**C**H$_2$), 38.9 (**C**H$_2$NH), 30.4 (**C**H$_2$CON), 29.0 (**C**H$_2$), 26.9 (**C**H$_2$), 25.2 (**C**H$_2$), 22.9 (**C**H$_2$); HRMS (ESI): calcd. for $C_{12}H_{22}N_2NaO_3$, 265.1523. Found: [MNa]$^+$, 265.1527 (–1.6 ppm error).

Lab notebook reference: KP052

4-(2,2,2-Trifluoroethyl)-1,4-diazacycloundecane-2,5-dione (2.51)

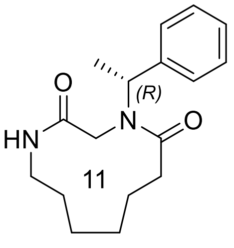


2.51

A mixture of 1-aza-2-cyclooctanone (100 mg, 0.786 mmol), DMAP (10.0 mg, 0.078 mmol) and pyridine (0.382 mL, 4.72 mmol) in DCM (5.5 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride (1.18 mmol, 1.50 equiv. prepared using the general procedure from *N*-(((9*H*-fluoren-9-yl)methoxy)carbonyl)-*N*-(2,2,2-trifluoroethyl)glycine **2.37**) in DCM (3 mL) was added and the resulting mixture was heated to reflux at 40 °C for 24 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*. The crude material was then re-dissolved in DCM (8 mL) and DBU (1.17 mL, 7.86 mmol) was added, followed by stirring at RT overnight, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:4 ethyl acetate: hexane → 1:1 ethyl acetate: hexane) afforded the *title compound* as a white solid (186 mg, 89%); m.p. 188–190 °C; R_f 0.30 (1:1 ethyl acetate: hexane); ν_{max}/cm^{-1} (thin film) 3308, 1657, 1469; δ_H (400 MHz, $CDCl_3$) 8.14 (1H, br s, N**H**), 4.38–4.14 (2H, m, C**H**$_2$), 4.08 (2H, s, C**H**$_2$), 3.29–3.07 (2H, m, C**H**$_2$), 2.23 (2H, t, *J* = 6.9 Hz, C**H**$_2$), 1.60–1.40 (4H, m, 2 × C**H**$_2$), 1.35–1.12 (4H, m, 2 × C**H**$_2$); δ_F (376 MHz, $CDCl_3$) –69.93 (3F, t, *J* = 9.3 Hz, **CF$_3$**); δ_C (100 MHz, DMSO-d_6): 174.6 (**C**O), 169.0 (**C**O), 125.0 (CF_3, q, *J* = 281.1 Hz), 53.0 (**C**H$_2$), 47.8 (**C**H$_2$, q, *J* = 32.1 Hz), 38.0 (**C**H$_2$), 29.4 (**C**H$_2$), 27.2 (**C**H$_2$), 24.4 (**C**H$_2$), 23.1 (**C**H$_2$), 21.3 (**C**H$_2$); HRMS (ESI): calcd. for $C_{11}H_{17}F_3N_2NaO_2$, 289.1134 Found: $[M+Na]^+$, 289.1137 (−0.6 ppm error).

Lab notebook reference: KP054

(*R*)-4-(1-Phenylethyl)-1,4-diazacycloundecane-2,5-dione (2.52)

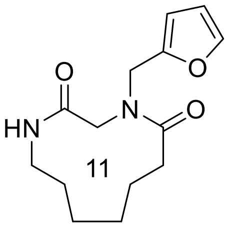


2.52

A mixture of 1-aza-2-cyclooctanone (66.0 mg, 0.519 mmol), DMAP (10.4 mg, 0.085 mmol) and pyridine (0.243 mL, 3.00 mmol) in DCM (5 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride (0.771 mmol, 1.50 equiv. prepared using the general procedure from (*R*)-*N*-(((9*H*-fluoren-9-yl)methoxy)carbonyl)-*N*-(1-phenylethyl)glycine **2.40**) in DCM (5 mL) was added and the resulting mixture was heated to reflux at 40 °C for 19 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 × 15 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was then re-dissolved in DCM (5 mL) and DBU (0.747 mL, 5.00 mmol) was added, followed by stirring at RT for 18 h, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:9 ethyl acetate: hexane → 1:1 ethyl acetate: hexane → ethyl acetate → 19:1 ethyl acetate: methanol) afforded the *title compound* as an off white solid (99.4 mg, 66%); R_f 0.33 (ethyl acetate); m.p. 189–193 °C; ν_{max}/cm^{-1} (neat) 3334, 2933, 1640, 1539, 1450, 1395, 1179, 1151, 748, 697); All ^{1}H signals broadened due to rotamer interconversion. δ_H (400 MHz, $CDCl_3$, 55 °C) 7.39–7.23 (5H, m, Ar**H**), 6.25 (1H, t, *J* = 7.1 Hz, C**H**CH_3), 5.35–5.16 (1H, m, N**H**), 3.81–3.69 (2H, m, NC**H₂**CO), 3.48–3.26 (1H, m, C**H**H′NH), 3.05–2.76 (1H, m, CH**H′**NH), 2.36–2.18 (2H, m, C**H₂**CON), 1.91–1.55 (3H, m, 3 from C**H₂**), 1.48 (3H, d, *J* = 7.1 Hz, CHC**H₃**), 1.43–1.05 (5H, m, 5 from C**H₂**); δ_C (100 MHz, $CDCl_3$) 175.1 (**C**O), 170.0 (**C**O), 140.6 (Ar**C**), 129.3 (2C, Ar**C**H), 128.4 (ArCH), 127.4 (2C, Ar**C**H), 50.6 (**C**HCH_3), 47.6 (N**C**H_2CO), 38.9 (**C**H_2NH), 30.7 (**C**H_2CON), 29.1 (**C**H_2), 26.5 (**C**H_2), 24.8 (**C**H_2), 22.6 (**C**H_2), 16.1 (**C**H_3); HRMS (ESI): calcd. for $C_{17}H_{25}N_2O_2$, 289.1911. Found: $[MH]^+$, 289.1911 (0.1 ppm error).

Lab notebook reference: KP056

4-(Furan-2-ylmethyl)-1,4-diazacycloundecane-2,5-dione (2.53)

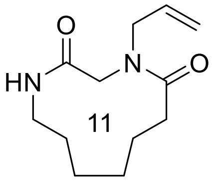


2.53

A mixture of 1-aza-2-cyclooctanone (67.0 mg, 0.527 mmol), DMAP (6.1 mg, 0.050 mmol) and pyridine (0.243 mL, 3.00 mmol) in DCM (5 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride (0.773 mmol, 1.50 equiv prepared using the general procedure from *N*-(((9*H*-fluoren-9-yl)methoxy)carbonyl)-*N*-(furan-2-ylmethyl)glycine **2.43**) in DCM (5 mL) was added and the resulting mixture was heated to reflux at 40 °C for 18 h. The mixture was then diluted with DCM (30 mL) and washed with 10% aq. HCl (15 mL). The aqueous layer was then extracted with DCM (3 × 15 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was then re-dissolved in DCM (5 mL) and DBU (0.747 mL, 5.00 mmol) was added, followed by stirring at RT for 21 h, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:9 ethyl acetate: hexane → 1:1 ethyl acetate: hexane → ethyl acetate → 19:1 ethyl acetate: methanol) afforded the *title compound* as a beige solid (66.4 mg, 48%); R_f 0.21 (ethyl acetate); m.p. 71–87 °C; ν_{max}/cm^{-1} (thin film) 3318, 2934, 1639, 1536, 1463, 1147, 1010, 734, 599); All ^1H signals broadened due to rotamer interconversion. δ_H (400 MHz, $CDCl_3$, 55 °C) 7.34–7.32 (1H, m, Ar**H**), 6.32–6.28 (2H, m, Ar**H**), 5.73 (1H, br s, N**H**), 4.65 (2H, s, NC**H₂**Ar), 3.99 (2H, s, NC**H₂**CO), 3.40–3.18 (2H, m, C**H₂**NH), 2.37–2.21 (2H, m, C**H₂**CON), 1.77–1.14 (8H, m, (C**H₂**)₄); δ_C (100 MHz, $CDCl_3$) 175.0 (**C**O), 169.7 (**C**O), 150.4 (Ar**C**), 142.7 (Ar**C**H), 111.1 (Ar**C**H), 109.8 (Ar**C**H), 53.0 (N**C**H₂CO), 44.1 (N**C**H₂Ar), 39.2 (**C**H₂NH), 30.3 (**C**H₂CON), 29.0 (**C**H₂), 26.3 (**C**H₂), 24.6 (**C**H₂), 22.6 (**C**H₂); HRMS (ESI): calcd. for $C_{14}H_{20}N_2NaO_3$, 287.1366. Found: $[MNa]^+$, 287.1357 (3.0 ppm error).

Lab notebook reference: KP058

4-(Prop-2-en-1-yl)-1,4-diazacycloundecane-2,5-dione (2.54)

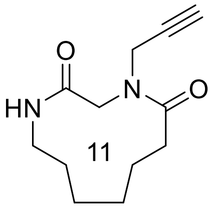


2.54

A mixture of 1-aza-2-cyclooctanone (65.0 mg, 0.511 mmol), DMAP (6.1 mg, 0.050 mmol) and pyridine (0.243 mL, 3.00 mmol) in DCM (5 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride (0.831 mmol, 1.50 equiv prepared using the general procedure form *N*-(((9*H*-fluoren-9-yl)methoxy)carbonyl)-*N*-allylglycine **2.41**) in DCM (5 mL) was added and the resulting mixture was heated to reflux at 40 °C for 18 h. The mixture was then diluted with DCM (30 mL) and washed with 10% aq. HCl (15 mL). The aqueous layer was then extracted with DCM (3 × 15 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was then re-dissolved in DCM (5 mL) and DBU (0.747 mL, 5.00 mmol) was added, followed by stirring at RT for 18 h, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:9 ethyl acetate: hexane → 19:1 ethyl acetate: methanol) afforded the *title compound* (as an 7:1 mixture of rotamers) as an off white solid (99.5 mg, 87%); m.p. 122–125 °C; R_f 0.41 (9:1 ethyl acetate: methanol); ν_{max}/cm^{-1} (neat) 3291, 2933, 1627, 1547, 1465, 1408, 913, 727); δ_H (400 MHz, $CDCl_3$) data for the major rotamer only; 6.03 (1H, br m, N**H**), 5.74 (1H, ddt, *J* = 16.8, 10.2, 6.8 Hz, C**H**CH₂), 5.19–5.12 (2H, m, CHC**H₂**), 4.09–3.97 (2H, m, NC**H₂**CH), 3.92–3.84 (2H, s, NC**H₂**CO), 3.46–3.35 (2H, m, C**H₂**NH), 2.32–2.20 (2H, m, C**H₂**CON), 1.71–1.15 (8H, m, (C**H₂**)₄); Diagnostic ^{1}H NMR resonances for the minor rotamer: 6.53 (1H, br d, N**H**, *J* = 10.2 Hz), 4.81 (1H, dd, NC**H₂**CO, *J* = 13.0, 1.3 Hz), 2.99 (1H, d, NC**H₂**CO, *J* = 13.0 Hz); δ_C (100 MHz, $CDCl_3$): Major rotamer: 174.8 (**C**O), 169.8 (**C**O), 132.6 (**C**HCH₂), 119.4 (CH**C**H₂), 52.3 (N**C**H₂CO), 50.8 (N**C**H₂CH), 39.3 (**C**H₂NH), 30.5 (**C**H₂CON), 28.9 (**C**H₂), 25.9 (**C**H₂), 24.2 (**C**H₂), 22.5 (**C**H₂); Minor rotamer: 176.7 (**C**O), 170.4 (**C**O), 132.4 (**C**HCH₂), 117.7 (CH**C**H₂), 51.7 (N**C**H₂CH), 51.2 (N**C**H₂CO), 39.4 (**C**H₂NH), 32.8 (**C**H₂CON), 27.1 (**C**H₂), 26.9 (**C**H₂), 23.6 (**C**H₂), 23.3 (**C**H₂); HRMS (ESI): calcd. for $C_{12}H_{21}N_2O_2$, 225.1598. Found: $[MH]^+$, 225.1597 (0.1 ppm error).

Lab notebook reference: KP060

4-(Prop-2-yn-1-yl)-1,4-diazacycloundecane-2,5-dione (2.55)

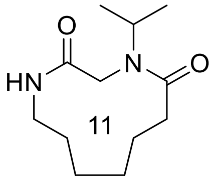


2.55

A mixture of 1-aza-2-cyclooctanone (65.6 mg, 0.516 mmol), DMAP (12.0 mg, 0.096 mmol) and pyridine (0.243 mL, 3.00 mmol) in DCM (5 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride (0.750 mmol, 1.50 equiv prepared using the general procedure from *N*-(((9*H*-fluoren-9-yl)methoxy)carbonyl)-*N*-(prop-2-yn-1-yl)glycine **2.42**) in DCM (5 mL) was added and the resulting mixture was heated to reflux at 40 °C for 18 h. The mixture was then diluted with DCM (30 mL) and washed with 10% aq. HCl (15 mL). The aqueous layer was then extracted with DCM (3 × 15 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was then re-dissolved in DCM (5 mL) and DBU (0.747 mL, 5.00 mmol) was added, followed by stirring at RT for 18 h, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:9 ethyl acetate: hexane → 1:1 ethyl acetate: hexane → ethyl acetate → 9:1 ethyl acetate: methanol) afforded the *title compound* as an off white solid (113 mg, 98%); m.p. 148–150 °C; R_f 0.36 (9:1 ethyl acetate: methanol); ν_{max}/cm^{-1} (neat) 3293, 2944, 1642, 1560, 1458, 1410, 1222, 1186, 914, 762, 596); All ^{1}H signals broadened due to rotamer interconversion. δ_H (400 MHz, $CDCl_3$, 55 °C) 6.16 (1H, br s, N**H**), 4.43–4.21 (2H, m, NC**H₂**CCH), 4.09 (2H, br s, NC**H₂**CO), 3.62–3.26 (2H, m, C**H₂**NH), 2.53–2.23 (3H, m, C**H₂**CON and NCH₂CC**H**), 1.83–1.17 (8H, m, (C**H₂**)₄); δ_C (100 MHz, $CDCl_3$): 174.9 (**C**O), 169.7 (**C**O), 78.9 (CH_2**C**CH), 73.6 (CH_2C**C**H), 53.1 (N**C**H_2CO), 39.1 (**C**H_2NH), 37.3 (N**C**H_2CCH), 30.3 (**C**H_2CON), 29.0 (**C**H_2), 26.4 (**C**H_2), 24.6 (**C**H_2), 22.6 (**C**H_2); HRMS (ESI): calcd. for $C_{12}H_{18}N_2NaO_2$, 245.1260. Found: $[MNa]^+$, 245.1262 (−0.7 ppm error).

Lab notebook reference: KP091

4-Isopropyl-1,4-diazacycloundecane-2,5-dione (2.56)

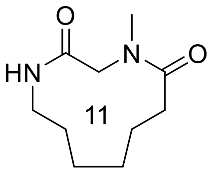


2.56

A mixture of 1-aza-2-cyclooctanone (64.2 mg, 0.505 mmol), DMAP (9.6 mg, 0.079 mmol) and pyridine (0.243 mL, 3.00 mmol) in DCM (5 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride (0.766 mmol, 1.50 equiv prepared using the general procedure from *N*-(((9*H*-fluoren-9-yl)methoxy)carbonyl)-*N*-isopropylglycine **2.38**) in DCM (5 mL) was added and the resulting mixture was heated to reflux at 40 °C for 18 h. The mixture was then diluted with DCM (30 mL) and washed with 10% aq. HCl (15 mL). The aqueous layer was then extracted with DCM (3 × 15 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was then re-dissolved in DCM (5 mL) and DBU (0.747 mL, 5.00 mmol) was added, followed by stirring at RT for 18 h, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:9 ethyl acetate: hexane → 1:1 ethyl acetate: hexane → ethyl acetate → 19:1 ethyl acetate: methanol) afforded the *title compound* as a light brown solid (63.2 mg, 55%); m.p. 132 – 136 °C; R_f 0.38 (9:1 ethyl acetate: methanol); ν_{max}/cm^{-1} (neat) 3321, 2938, 1642, 1540, 1466, 1397, 1196, 1146, 1008, 756, 715, 614, 587; All ^1H signals broadened due to rotamer interconversion. δ_H (400 MHz, $CDCl_3$, 55 °C) 5.93 (1H, br s, N**H**), 5.00–4.85 (1H, m, C**H**$(CH_3)_2$), 3.81 (2H, s, NC**H₂**CO), 3.58–3.18 (2H, m, C**H₂**NH), 2.30–2.16 (2H, m, C**H₂**CON), 1.87–1.18 (8H, m, (C**H₂**)$_4$), 1.09 (6H, d, *J* = 6.8 Hz, CH(C**H₃**)$_2$); Diagnostic ^1H NMR resonances reported at room temperature: δ_H (400 MHz, $CDCl_3$) 4.94 (1H, hept, *J* = 6.8 Hz, C**H**$(CH_3)_2$), 1.07 (6H, d, *J* = 6.8 Hz, CH(C**H₃**)$_2$); δ_C (100 MHz, $CDCl_3$): 175.1 (**C**O), 170.4 (**C**O), 46.6 (N**C**H_2CO), 44.6 (N**C**HCH_2), 39.5 (**C**H_2NH), 30.8 (**C**H_2CON), 29.0 (**C**H_2), 26.2 (**C**H_2), 24.4 (**C**H_2), 22.5 (**C**H_2), 20.4 (2C, **C**H_3); HRMS (ESI): calcd. for $C_{12}H_{22}N_2NaO_2$, 249.1573. Found: $[MNa]^+$, 249.1573 (0.3 ppm error).

Lab notebook reference: KP095

4-Methyl-1,4-diazacycloundecane-2,5-dione (2.57)

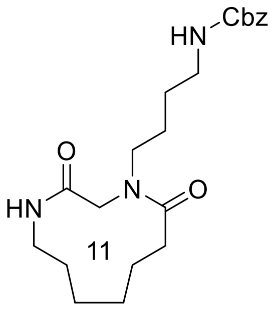


2.57

A mixture of 1-aza-2-cyclooctanone (64.4 mg, 0.505 mmol), DMAP (10.2 mg, 0.082 mmol) and pyridine (0.243 mL, 3.00 mmol) in DCM (5 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride (0.758 mmol, 1.50 equiv., prepared using the general procedure from Fmoc-*N*-methylglycine) in DCM (5 mL) was added and the resulting mixture was heated to reflux at 40 °C for 19 h. The mixture was then diluted with DCM (30 mL) and washed with 10% aq. HCl (15 mL). The aqueous layer was then extracted with DCM (3 × 15 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was then re-dissolved in DCM (5 mL) and DBU (0.747 mL, 5.00 mmol) was added, followed by stirring at RT for 18 h, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:9 ethyl acetate: hexane → 1:1 ethyl acetate: hexane → ethyl acetate → 19:1 ethyl acetate: methanol) afforded the *title compound* (as a 3:1 ratio of rotamers) as a brown yellow solid (81.6 mg, 82%); m.p. 118–121 °C; R_f 0.18 (9:1 ethyl acetate: methanol); ν_{max}/cm^{-1} (neat) 3333, 2931, 1640, 1530, 1464, 1394, 1262, 1094, 799, 728, 647, 584; δ_H (400 MHz, $CDCl_3$, 55 °C) 6.06 (1H, br s, N**H**, major rotamer), 3.92 (2H, s, NC**H₂**CO, major rotamer), 3.49–3.33 (2H, m, C**H₂**NH, major rotamer), 3.04 (3H, s, C**H₃**, major rotamer), 2.27 (2H, m, C**H₂**CON, major rotamer), 1.92–1.18 (16H, m, 4 × C**H₂**, both rotamers); Diagnostic ^{1}H NMR resonance of minor rotamer at reported at room temperature: δ_H (400 MHz, $CDCl_3$) 6.53 (1H, br d, *J* = 9.8 Hz, N**H**, minor rotamer), 4.93 (1H, d, *J* = 12.9 Hz, C**H**H'NMe, minor rotamer), 3.11 (3H, s, C**H₃**, minor rotamer), 2.90 (1H, d, *J* = 12.9 Hz, CH**H'**NMe, minor rotamer); δ_C (100 MHz, $CDCl_3$) data for major rotamer, 175.2 (**C**O), 169.7 (**C**O), 55.2 (N**C**H_2CO), 39.40 (**C**H_2NH), 36.7 (N**C**H_3), 30.4 (**C**H_2CON), 28.7 (**C**H_2), 25.7 (**C**H_2), 24.0 (**C**H_2), 22.7 (**C**H_2); data for minor rotamer, 176.7 (**C**O), 169.9 (**C**O), 53.9 (N**C**H_2CO), 39.42 (**C**H_2NH), 37.7 (N**C**H_3), 33.1 (**C**H_2CON), 27.0 (**C**H_2), 26.9 (**C**H_2), 23.6 (**C**H_2), 22.8 (**C**H_2); HRMS (ESI): calcd. for $C_{10}H_{18}N_2NaO_2$, 221.1260. Found: $[MNa]^+$, 221.1260 (0.3 ppm error).

Lab notebook reference: KP068

Benzyl *N*-(4-(3,11-dioxo-1,4-diazacycloundecan-1-yl)butyl)carbamate (2.58)

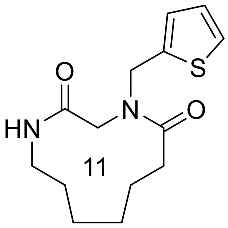


2.58

A mixture of 1-aza-2-cyclooctanone (44.9 mg, 0.353 mmol), DMAP (4.2 mg, 0.035 mmol) and pyridine (0.167 mL, 2.07 mmol) in DCM (3.5 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride (0.259 mmol, 0.75 eqv prepared using the general procedure from *N*-(((9*H*-fluoren-9-yl)methoxy)carbonyl)-*N*-(4-(((benzyloxy)carbonyl)amino)butyl)glycine **2.25**) in DCM (4 mL) was added and the resulting mixture was heated to reflux at 40 °C for 18 h. The acylation reaction was incomplete by TLC so an additional 1.3 eqv of acid chloride (0.455 mmol) was prepared and added to the mixture, refluxing at 50 °C for an additional 18 h. The mixture was then diluted with DCM (30 mL) and washed with 10% aq. HCl (15 mL). The aqueous layer was then extracted with DCM (3 × 15 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was then re-dissolved in DCM (3.5 mL) and DBU (0.527 mL, 3.53 mmol) was added, followed by stirring at RT for 18 h, before the solvent was removed *in vacuo*. Purification by repeated flash column chromatography (SiO_2, 1:9 ethyl acetate: hexane → 1:1 ethyl acetate: hexane → ethyl acetate → 19:1 ethyl acetate: methanol) afforded the *title compound* (as an 2.4:1 mixture of rotamers based on NH) as an orange solid (38.7 mg, 29%); m.p. 114–120 °C; R_f 0.43 (9:1 ethyl acetate: methanol); ν_{max}/cm^{-1} (neat) 3300, 2929, 1708, 1638, 1536, 1454, 1360, 1257, 1161, 1100, 1026, 734, 698, 570, 492); δ_H (400 MHz, $CDCl_3$) 7.38–7.26 (10H, m, Ar**H**), 6.13 (1H, br t, *J* = 5.1 Hz, N**H**, major rotamer), 5.87 (1H, br s, N**H**, minor rotamer), 5.15 (2H, br t, *J* = 5.2 Hz, N**H**), 5.12–5.00 (4H, m, ArC**H₂**), 3.93 (4H, s, NC**H₂**CO), 3.61– 3.11 (12H, m, (C**H₂**N) × 3), 2.33–2.10 (4H, m, NC**H₂**), 1.84–1.17 (24H, m, (C**H₂**)₆); δ_C (100 MHz, $CDCl_3$) 175.2 (**C**O), 169.7 (**C**O), 156.6 (**C**O), 136.6 (Ar**C**), 128.6 (2C, Ar**C**H), 128.2 (3C, Ar**C**H), 66.7 (NCOO**C**H_2Ar), 53.2 (N**C**H_2CO), 48.2 (**C**H_2), 40.5 (**C**H_2), 39.5 (**C**H_2), 30.5 (**C**H_2), 29.0 (**C**H_2), 27.3 (**C**H_2), 26.0 (**C**H_2), 25.3 (**C**H_2), 24.2 (**C**H_2), 22.6 (**C**H_2); HRMS (ESI): calcd. for $C_{21}H_{32}N_3O_4$, 390.2387. Found: $[MH]^+$, 390.2382 (1.4 ppm error).

Lab notebook reference: KP070

4-[(Thiophen-2-yl)methyl]-1,4-diazacycloundecane-2,5-dione (2.59)

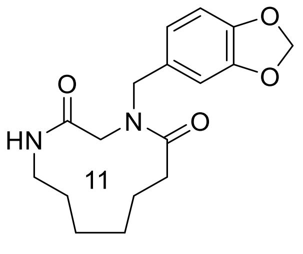


2.59

A mixture of 1-aza-2-cyclooctanone (63.8 mg, 0.502 mmol), DMAP (8.0 mg, 0.066 mmol) and pyridine (0.243 mL, 3.00 mmol) in DCM (5 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride (0.795 mmol, 1.50 equiv. prepared using the general procedure from *N*-(((9*H*-fluoren-9-yl)methoxy)carbonyl)-*N*-(thiophen-2-ylmethyl)glycine **2.24**) in DCM (5 mL) was added and the resulting mixture was heated to reflux at 40 °C for 18 h. The mixture was then diluted with DCM (30 mL) and washed with 10% aq. HCl (15 mL). The aqueous layer was then extracted with DCM (3 × 15 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was then re-dissolved in DCM (5 mL) and DBU (0.747 mL, 5.00 mmol) was added, followed by stirring at RT for 18 h, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:9 ethyl acetate: hexane→19:1 ethyl acetate: methanol) afforded the *title compound* as an off white solid (98.6 mg, 70%); m.p. 123–128 °C; R_f 0.50 (9:1 ethyl acetate: methanol); ν_{max}/cm^{-1} (neat) 3316, 2933, 1633, 1536, 1463, 1186, 911, 702, 591; All ^1H signals broadened due to rotamer interconversion. δ_H (400 MHz, $CDCl_3$, 55 °C) 7.23 (1H, dd, *J* = 5.1, 1.1 Hz, Ar**H**), 7.02–6.98 (1H, m, Ar**H**), 6.92 (1H, dd, *J* = 5.1, 3.4 Hz, Ar**H**), 5.56 (1H, br s, N**H**), 4.78 (2H, s, NC**H₂**Ar), 4.00 (2H, s, NC**H₂**CO), 3.32–3.12 (2H, m, C**H₂**NH), 2.32–2.24 (2H, m, C**H₂**CON), 1.76–1.14 (8H, m, (C**H₂**)₄); δ_C (100 MHz, $CDCl_3$) 174.8 (**C**O), 169.6 (**C**O), 139.4 (Ar**C**), 127.9 (Ar**C**H), 127.2 (Ar**C**H), 126.7 (Ar**C**H), 53.5 (N**C**H₂CO), 46.7 (N**C**H₂Ar), 39.3 (**C**H₂NH), 30.3 (**C**H₂CON), 28.9 (**C**H₂), 26.1 (**C**H₂), 24.5 (**C**H₂), 22.6 (**C**H₂); HRMS (ESI): calcd. for $C_{14}H_{21}N_2O_2S$, 281.1318. Found: $[MH]^+$, 281.1321 (–1.1 ppm error).

Lab notebook reference: KP072

4-(Benzo[d][1,3]dioxol-5-ylmethyl)-1,4-diazacycloundecane-2,5-dione (2.60)

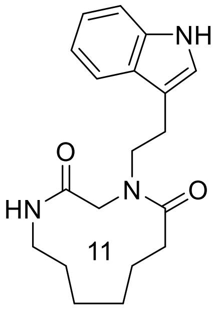


2.60

A mixture of 1-aza-2-cyclooctanone (64.1 mg, 0.504 mmol), DMAP (5.2 mg, 0.043 mmol) and pyridine (0.243 mL, 3.00 mmol) in DCM (5 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride (0.750 mmol, 1.50 eqv. prepared using the general procedure from *N*-(((9*H*-fluoren-9-yl)methoxy)carbonyl)-*N*-(benzo[*d*][1,3]dioxol-5-ylmethyl)glycine **2.20**) in DCM (5 mL) was added and the resulting mixture was heated to reflux at 40 °C for 18 h. The mixture was then diluted with DCM (30 mL) and washed with 10% aq. HCl (15 mL). The aqueous layer was then extracted with DCM (3 × 15 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was then re-dissolved in DCM (5 mL) and DBU (0.747 mL, 5.00 mmol) was added, followed by stirring at RT for 18 h, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:9 ethyl acetate: hexane → 1:1 ethyl acetate: hexane → ethyl acetate → 19:1 ethyl acetate: methanol) afforded the *title compound* as an off white solid (114 mg, 71%); m.p. 134–136 °C; R_f 0.53 (9:1 ethyl acetate: methanol); ν_{max}/cm^{-1} (neat) 3318, 2934, 1634, 1536, 1502, 1489, 1443, 1370, 1244, 1176, 1100, 1037, 926, 808, 730, 578, 492; All ^{1}H signals broadened due to rotamer interconversion. δ_H (400 MHz, $CDCl_3$, 55 °C) 6.85–6.64 (3H, m, Ar**H**), 5.91 (2H, s, OC$\mathbf{H_2}$O), 5.63 (1H, br s, N**H**), 4.59–4.38 (2H, s, NC$\mathbf{H_2}$Ar), 3.98–3.71 (2H, s, NC$\mathbf{H_2}$CO), 3.41–3.13 (2H, m, C$\mathbf{H_2}$NH), 2.36–2.21 (2H, m, C$\mathbf{H_2}$CON), 1.81–1.10 (8H, m, (C$\mathbf{H_2}$)$_4$); δ_C (100 MHz, $CDCl_3$) 175.1 (**C**O), 169.7 (**C**O), 148.4 (Ar**CO**CH$_2$), 147.6 (Ar**CO**CH$_2$), 131.1 (Ar**C**), 122.1 (Ar**C**H), 109.0 (Ar**C**H), 108.7 (Ar**C**H), 101.3 (O**C**H$_2$O), 52.8 (N**C**H$_2$CO), 51.5 (N**C**H$_2$Ar), 39.2 (**C**H$_2$NH), 30.4 (**C**H$_2$CON), 29.0 (**C**H$_2$), 26.1 (**C**H$_2$), 24.5 (**C**H$_2$), 22.6 (**C**H$_2$); HRMS (ESI): calcd. for $C_{17}H_{22}N_2NaO_4$, 341.1472. Found: $[MNa]^+$, 341.1471 (0.1 ppm error).

Lab notebook reference: KP076

4-(2-(1*H*-Indol-3-yl)ethyl)-1,4-diazacycloundecane-2,5-dione (2.61)

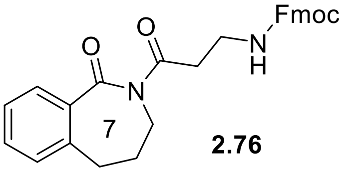


2.61

A mixture of 1-aza-2-cyclooctanone (64.4 mg, 0.506 mmol), DMAP (6.2 mg, 0.050 mmol) and pyridine (0.243 mL, 3.00 mmol) in DCM (5 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride (0.756 mmol, 1.50 eqv prepared using the general procedure from *N*-(2-(1*H*-indol-3-yl)ethyl)-*N*-(((9*H*-fluoren-9-yl)methoxy)carbonyl)glycine **2.19**) in DCM (5 mL) was added and the resulting mixture was heated to reflux at 40 °C for 18 h. The mixture was then diluted with DCM (30 mL) and washed with 10% aq. HCl (15 mL). The aqueous layer was then extracted with DCM (3 × 15 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was then re-dissolved in DCM (5 mL) and DBU (0.747 mL, 5.00 mmol) was added, followed by stirring at RT for 18 h, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:9 ethyl acetate: hexane → 1:1 ethyl acetate: hexane → ethyl acetate → 19:1 ethyl acetate: methanol) afforded the *title compound* as an orange white solid (65.4 mg, 40%); m.p. 180–182 °C; R_f 0.33 (9:1 ethyl acetate: methanol); ν_{max}/cm^{-1} (neat) 3301, 2931, 1635, 1535, 1447, 1101, 908, 731, 646; ^1H signals broadened due to rotamer interconversion. δ_H (400 MHz, $CDCl_3$, 55 °C) 8.20 (1H, br s, ArN**H**), 7.68–7.04 (5H, m, Ar**H**), 5.47 (1H, br s, N**H**), 4.03–3.77 (2H, s, NC**H₂**CO), 3.55–3.26 (2H, m, C**H₂**NH), 3.09 (2H, t, *J* = 6.6 Hz, NCH_2**CH₂**Ar), 2.45–2.37 (2H, m, C**H₂**NH), 2.28–2.13 (2H, m, C**H₂**CON), 1.95–0.87 (8H, m, (C**H₂**)₄); δ_C (100 MHz, $CDCl_3$) 175.7 (**C**O), 169.7 (**C**O), 136.4 (Ar**C**), 127.3 (Ar**C**), 122.8 (Ar**C**H), 122.6 (Ar**C**H), 119.9 (Ar**C**H), 118.6 (Ar**C**H), 111.6 (Ar**C**), 111.4 (Ar**C**H), 54.1 (N**C**H_2CO), 47.6 (N**C**H_2Ar), 39.0 (**C**H_2NH), 30.3 (**C**H_2CON), 29.0 (**C**H_2), 26.0 (**C**H_2), 24.7 (**C**H_2), 23.5 (Ar**C**H_2), 22.5 (**C**H_2); HRMS (ESI): calcd. for $C_{19}H_{25}N_3NaO_2$, 350.1839. Found: $[MNa]^+$, 350.1836 (1.0 ppm error).

Lab notebook reference: KP076

(9*H*-Fluoren-9-yl) methyl (3-oxo-3-(1-oxo-1,3,4,5-tetrahydro-2H-benzo[c]azepin-2-yl)propyl)carbamate (2.76)

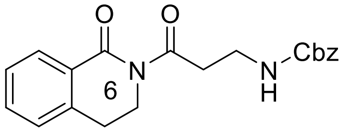


2.76

A mixture of 2,3,4,5-tetrahydro-benzo[c]azepin-1-one (161 mg, 1.00 mmol), DMAP (12.0 mg, 0.100 mmol) and pyridine (0.486 mL, 6.01 mmol) in DCM (10 mL) under an argon atmosphere was stirred at RT for 5 mins. Next, a solution of (9*H*-fluoren-9-yl)methyl (3-chloro-3-oxopropyl)carbamate (1.50 mmol, 1.50 eqv. prepared using the general procedure from *N*-Fmoc-β-alanine) in DCM (7.5 mL) was added and the resulting mixture was heated to reflux at 40 °C for 18 h. The mixture was then diluted with DCM (60 mL) and washed with 10% aq. HCl (60 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*. The crude material was then re-dissolved in DCM (10 mL) and DBU (1.49 mL, 10.0 mmol) was added, followed by stirring at RT for 18 h, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:4 ethyl acetate: hexane) afforded the *title compound* (as a 6:1 mixture of rotamers) as a yellow oil (158 mg, 35%); R_f 0.64 (ethyl acetate); ν_{max}/cm^{-1} (neat) 3357, 2950, 1683, 1360, 1206, 1129, 907, 726; δ_H (400 MHz, $CDCl_3$) 7.76 (6H, m, Ar**H**, both rotamers), 7.60 (4H, d, *J* = 7.5 Hz, Ar**H**, both), 7.48 (2H, t, *J* = 7.5 Hz, Ar**H**, both), 7.43–7.35 (6H, m, Ar**H**, both), 7.31 (4H, t, *J* = 7.5 Hz, Ar**H**, both), 7.19 (2H, d, *J* = 7.5 Hz, Ar**H**, both), 5.44 (1H, br t, *J* = 6.1 Hz, N**H**, major), 5.18 (1H, br s, N**H**, minor), 4.47–4.41 (2H, m, $CO_2C\mathbf{H_2}$, minor), 4.38 (2H, d, *J* = 7.1 Hz, $CO_2C\mathbf{H_2}$, major), 4.30–4.25 (1H, m, $CH_2C\mathbf{H}$, minor), 4.22 (1H, t, *J* = 7.1 Hz, $CH_2C\mathbf{H}$, major), 3.78 (4H, t, *J* = 6.3 Hz, $NC\mathbf{H_2}$, both), 3.62 (2H, q, *J* = 6.0 Hz, $C\mathbf{H_2}NH$, major), 3.57–3.51 (2H, m, $C\mathbf{H_2}NH$, minor), 3.27 (2H, t, *J* = 5.8 Hz, $CH_2C\mathbf{H_2}CON$, major), 3.20–3.13 (2H, m, $CH_2C\mathbf{H_2}CON$, minor), 2.79 (4H, t, *J* = 7.0 Hz, $ArC\mathbf{H_2}$, both), 2.00 (4H, p, *J* = 6.7 Hz, $ArCH_2C\mathbf{H_2}$, both); δ_C (100 MHz, $CDCl_3$) data for the major rotamer only: 174.1 (**C**ON), 172.6 (**C**ON), 156.1 ($N\mathbf{C}O_2$), 143.8 (Ar**C**), 141.1 (Ar**C**), 137.7 (Ar**C**), 134.7 (Ar**C**), 132.7 (Ar**C**H), 129.6 (Ar**C**H), 128.8 (Ar**C**H), 127.4 (Ar**C**H), 127.1 (Ar**C**H), 126.8 (Ar**C**H), 124.9 (Ar**C**H), 119.8 (Ar**C**H), 66.5 ($CO_2\mathbf{C}H_2$), 47.3 ($CH_2\mathbf{C}H$), 41.5 ($N\mathbf{C}H_2$), 38.9 ($\mathbf{C}H_2CON$), 36.6 ($\mathbf{C}H_2NH$), 29.9 ($Ar\mathbf{C}H_2$), 26.5 ($ArCH_2\mathbf{C}H_2$); Diagnostic ^{13}C NMR resonances for the minor rotamer: 171.0 (**C**ON), 168.0 (**C**ON); HRMS (ESI): calcd. for $C_{28}H_{26}N_2NaO_4$, 447.1790. Found: $[MNa]^+$, 447.1785 (1.2 ppm error).

Lab notebook reference: KP006

Benzyl (3-oxo-3-(1-oxo-3,4-dihydroisoquinolin-2(1*H*)-yl)propyl)carbamate (2.77)

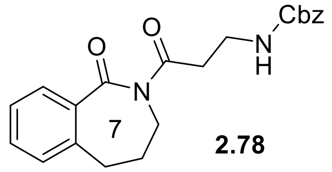


2.77

A mixture of 3,4-dihydroisoquinolin-1(2*H*)-one (73.6 mg, 0.50 mmol), DMAP (6.1 mg, 0.050 mmol) and pyridine (0.243 mL, 3.00 mmol) in DCM (5 mL) under an argon atmosphere was stirred at RT for 5 mins. Next, a solution of benzyl (3-chloro-3-oxopropyl)carbamate (0.750 mmol, 1.50 eqv prepared using the general procedure from *N*-Cbz-β-alanine) in DCM (5 mL) was added and the resulting mixture was heated to reflux at 40 °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 × 15 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:4 ethyl acetate: hexane) afforded the *title compound* (as a 3:4 mixture of rotamers) as a colorless oil (131 mg, 71%); R_f 0.72 (ethyl acetate); ν_{max}/cm^{-1} (neat) 1688, 1514, 1220, 1138, 1000, 748, 697; δ_H (400 MHz, $CDCl_3$) 8.12 (1H, dd, *J* = 7.9, 1.4 Hz, Ar**H**), 7.51 (1H, td, *J* = 7.5, 1.4 Hz, Ar**H**), 7.40 – 7.27 (15H, m, Ar**H**), 7.24 (1H, d, *J* = 7.5 Hz, **ArH**), 5.44 (1H, t, *J* = 6.1 Hz, N**H**), 5.37 (1H, t, *J* = 6.4 Hz, N**H**), 5.08 (4H, s, C**H**$_2$), 4.08 (2H, t, *J* = 6.2 Hz, C**H**$_2$), 3.58 (2H, q, *J* = 6.0 Hz, C**H**$_2$), 3.46 (4H, q, *J* = 6.2 Hz, C**H**$_2$), 3.30 (2H, t, *J* = 6.0 Hz, C**H**$_2$), 2.96 (2H, t, *J* = 6.2 Hz, C**H**$_2$), 2.54 (4H, t, *J* = 6.0 Hz, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) data for the major rotamer only: 175.5 (**C**O), 172.8 (**C**O), 165.7 (**C**O), 156.4 (Ar**C**), 140.2 (Ar**C**), 136.5 (Ar**C**), 133.6 (Ar**CH**), 129.6 (Ar**C**H), 128.8 (Ar**C**H), 128.6 (Ar**C**H), 128.5 (Ar**C**H), 128.2 (Ar**C**H), 128.1 (Ar**C**H), 127.5 (Ar**C**H), 127.4 (Ar**C**H), 66.8 (**C**H$_2$), 41.8), 34.3 (**C**H$_2$), 28.1 (**C**H$_2$); HRMS (ESI): calcd. for $C_{20}H_{20}N_2NaO_4$, 375.1315. Found: [MNa]$^+$, 375.1308 (1.9 ppm error).

Lab notebook reference: KP015

Benzyl (3-oxo-3-(1-oxo-1,3,4,5-tetrahydro-2*H*-benzo[*c*]azepin-2-yl)propyl)carbamate (2.78)

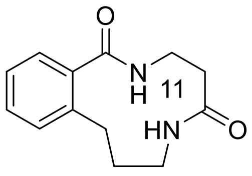


2.78

A mixture of 2,3,4,5-tetrahydro-benzo[c]azepin-1-one (79.6 mg, 0.497 mmol), DMAP (6.1 mg, 0.050 mmol) and pyridine (0.243 mL, 3.00 mmol) in DCM (5 mL) under an argon atmosphere was stirred at RT for 5 mins. Next, a solution of benzyl (3-chloro-3-oxopropyl)carbamate (0.75 mmol, 1.50 eqv prepared using the general procedure from *N*-Cbz-β-alanine) in DCM (5 mL) was added and the resulting mixture was heated to reflux at 40 °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 × 15 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:4 ethyl acetate: hexane) afforded the *title compound* as a colorless oil (78.8 mg, 44%); R_f 0.61 (ethyl acetate); δ_H (400 MHz, $CDCl_3$) 7.75 (1H, d, *J* = 7.7 Hz, Ar**H**), 7.48 (1H, t, *J* = 7.5 Hz, Ar**H**), 7.40 – 7.28 (6H, m, Ar**H**),7.19 (1H, d, *J* = 7.5 Hz, Ar**H**), 5.38 (1H, t, *J* = 7.2 Hz, N**H**), 5.10 (2H, s, C**H**$_2$), 3.75 (2H, t, *J* = 6.3 Hz, C**H**$_2$), 3.59 (2H, q, *J* = 5.9 Hz, C**H**$_2$), 3.25 (2H, t, *J* = 5.9 Hz, C**H**$_2$), 2.77 (2H, t, *J* = 7.1 Hz, C**H**$_2$), 1.98 (2H, p, *J* = 6.6 Hz, C**H**$_2$); HRMS (ESI): calcd. for $C_{21}H_{22}N_2NaO_4$, 389.1472. Found: $[MNa]^+$, 389.1473 (–0.3 ppm error).

Lab notebook reference: KP012

3,4,6,7,8,9-Hexahydro-1H-benzo[g][1,5]diazacycloundecine-1,5(2H)-dione (2.80)

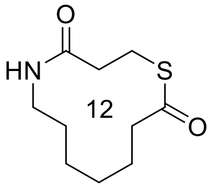


2.80

(9*H*-Fluoren-9-yl)methyl (3-oxo-3-(1-oxo-1,3,4,5-tetrahydro-2*H*-benzo[c]azepin-2-yl)propyl)carbamate **2.78** (77.2 mg, 0.170 mmol) was dissolved in DCM (1.7 mL) and DBU (0.170 mL, 1.14 mmol) was added. The reaction mixture was then left stirring at RT for 18 h, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 2:1 ethyl acetate: hexane→ ethyl acetate → 4:1 ethyl acetate: methanol) afforded the *title compound* as a white solid (22.8 mg, 58%); mp. 229–230 °C; R_f 0.26 (4:1 ethyl acetate: methanol); ν_{max}/cm^{-1} (neat) 3312, 3291, 2928, 1644, 1545, 1442, 1318, 1190, 753, 686; δ_H (400 MHz, CD_3OD) 7.31–7.27 (1H, m, Ar**H**), 7.23–7.16 (3H, m, Ar**H**), 3.63 (2H, t, *J* = 6.5 Hz, Ar(CON)HC**H$_2$**), 3.18–3.14 (2H, m, CH$_2$(CON)HC**H$_2$**), 2.78–2.73 (2H, m, ArC**H$_2$**), 2.53 (2H, t, *J* = 6.5 Hz, CH$_2$C**H$_2$**(CON)), 1.76–1.68 (2H, m, ArCH$_2$C**H$_2$**); δ_C (100 MHz, CD_3OD) 173.5 (**C**ON), 172.5 (**C**ON), 140.0 (Ar**C**), 137.1 (Ar**C**), 129.6 (Ar**C**H), 129.3 (Ar**C**H), 126.4 (Ar**C**H), 125.7 (Ar**C**H), 38.7 (CH$_2$(CON)H**C**H$_2$), 36.8 (Ar(CON)H**C**H$_2$), 35.0 (CH$_2$**C**H$_2$(CON)), 31.8 (ArCH$_2$**C**H$_2$), 28.4 (Ar**C**H$_2$); HRMS (ESI): calcd. for $C_{13}H_{17}N_2O_2$, 233.1285. Found: $[MH]^+$, 233.1287 (1.2 ppm error).

Lab notebook reference: KP011

1-Thia-5-azacyclododecane-4,12-dione (3.23)



3.23

A mixture of 1-[3-(acetylsulfanyl)propanoyl]azocan-2-one **3.27** (130 mg, 0.505 mmol) and piperidine (0.148 mL, 1.50 mmol) in DCM (5 mL) under an argon atmosphere was stirred at RT for 22 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, 1:19 ethyl acetate: hexane → 1:9 ethyl acetate: hexane → 1:4 ethyl acetate: hexane → 1:1 ethyl acetate: hexane → ethyl acetate → 9:1 ethyl acetate: methanol) afforded the *title compound* **3.23** as an off white solid (31.7 mg, 29%), along with recovered **3.27** (8.3 mg, 6%) and thiol **3.21** (3.4 mg, 3%; for characterization data for **3.21** see below). Data for **3.23**: m.p. 152–155 °C; R_f 0.28 (9:1 ethyl acetate: methanol); ν_{max}/cm^{-1} (thin film) 3294, 2924, 2856, 1688, 1638, 1562, 1434, 1035, 977, 729, 629, 566; All ^{1}H signals are broadened due to rotamer interconversion. δ_H (400 MHz, $CDCl_3$) 5.71 (1H, br s, N**H**), 3.42–3.10 (3H, m, 1.5 × C**H$_2$**), 2.85–2.32 (5H, m, 2.5 × C**H$_2$**), 1.67–1.56 (1H, m, 0.5 × C**H$_2$**), 1.56–1.28 (7H, m, 3.5 × C**H$_2$**); δ_C (100 MHz, $CDCl_3$) 200.5 (S**C**O), 169.9 (**C**O), 43.5 (**C**H$_2$COS), 38.4 (**C**H$_2$NH), 37.7 (**C**H$_2$), 27.6 (**C**H$_2$), 26.2 (**C**H$_2$), 24.1 (**C**H$_2$), 23.5 (**C**H$_2$), 22.3 (**C**H$_2$); HRMS (ESI): calcd. for $C_{10}H_{18}NO_2S$, 216.1053. Found: [MH]$^+$, 216.1051 (0.6 ppm error). For X-ray crystallographic data, see CCDC 1921223.

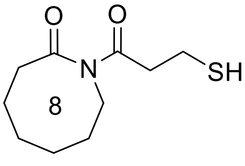
Lab notebook reference: KP187

The same product **3.23** was also prepared using the S-Fm strategy, using the following procedure:

A mixture of 1-aza-2-cyclooctanone (63.7 mg, 0.501 mmol), DMAP (7.5 mg, 0.062 mmol) and pyridine (0.243 mL, 3.00 mmol) in DCM (7 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride **3.62** (3-(((9*H*-fluoren-9-yl)methyl)thio)propanoyl chloride) (1.50 mmol, prepared from 3-(((9*H*-fluoren-9-yl)methyl)thio)propanoic acid **3.59** using the general procedure) in DCM (3 mL) was added and the resulting mixture was heated at reflux 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*. TLC analysis indicated that acylation was complete at this stage. The crude material was then re-dissolved in DCM (10 mL) and DBU (0.747 mL, 5.00 mmol) was added, followed by stirring at RT for 14 h, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:9 ethyl acetate: hexane → 1:2 ethyl acetate: hexane → 1:1 ethyl acetate: hexane → 2:1 ethyl acetate: hexane) afforded the *title compound* **3.23** (for characterization data see above) as a yellow crystalline solid (16.2 mg, 15%).

Lab notebook reference: KP286

1-(3-Mercaptopropanoyl)azocan-2-one (3.21)

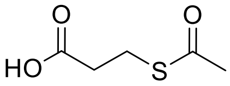


3.21

Data for **3.21** (for synthesis see **3.23** above): colorless oil; R_f 0.74 (9:1 ethyl acetate: methanol); ν_{max}/cm^{-1} (thin film) 2925, 2857, 1685, 1370, 1339, 1285, 1197, 1174, 1125, 1091, 799, 686, 591; δ_H (400 MHz, $CDCl_3$) 3.94–3.88 (2H, m, $C\mathbf{H_2}N$), 3.20 (2H, t, *J* = 6.6 Hz, $C\mathbf{H_2}CH_2SH$), 2.79 (2H, dt, *J* = 8.5, 6.6 Hz, $CH_2C\mathbf{H_2}SH$), 2.67–2.61 (2H, m, $C\mathbf{H_2}CON$), 1.90–1.82 (2H, m, $C\mathbf{H_2}$), 1.74–1.66 (2H, m, $C\mathbf{H_2}$), 1.63 (1H, t, *J* = 8.5 Hz, $CH_2S\mathbf{H}$), 1.61–1.55 (2H, m, $C\mathbf{H_2}$), 1.48–1.40 (2H, m, $C\mathbf{H_2}$); δ_C (100 MHz, $CDCl_3$) 178.4 (**C**ON), 174.8 ($\mathbf{C}OCH_2CH_2$), 43.8 ($COCH_2CH_2S$), 43.5 ($\mathbf{C}H_2N$), 37.2 ($\mathbf{C}H_2CON$), 29.6 ($\mathbf{C}H_2$), 29.2 ($\mathbf{C}H_2$), 26.3 ($\mathbf{C}H_2$), 24.1 ($\mathbf{C}H_2$), 20.1 ($\mathbf{C}H_2SH$); HRMS (ESI): calcd. for $C_{10}H_{17}NNaO_2S$, 238.0872. Found: $[MNa]^+$, 238.0869 (1.3 ppm error).

Lab notebook reference: KP189_B/KP160_A

3-(Acetylthio)propanoic acid (3.25)

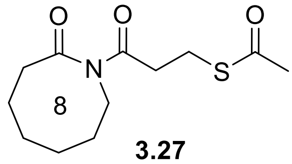


3.25

3-Bromopropionic acid (3.84 g, 25.1 mmol) was added to a stirring solution of potassium thioacetate (3.41 g, 29.9 mmol) in acetone (500 mL) and allowed to stir at RT for 6 h. Afterwards, all solvent was removed *in vacuo* and the residue taken up in ethyl acetate (250 mL) and water (250 mL). The organic layer was collected and the aqueous layer extracted with ethyl acetate (3 × 250 mL). The combined organics were dried over $MgSO_4$ and concentrated *in vacuo* to afford the *title compound* as a brown solid (3.44 g, 92%); R_f 0.43 (2:3 ethyl acetate: hexane); m.p. 49–53 °C; ν_{max}/cm^{-1} (neat) 2925, 1687, 1408, 1355, 1244, 1200, 1131, 1040, 944, 804, 689, 623, 532, 488; δ_H (400 MHz, $CDCl_3$) 10.10 (1H, br s, COO**H**), 3.10 (2H, t, *J* = 6.9 Hz, C**H**$_2$), 2.69 (2H, t, *J* = 6.9 Hz, C**H**$_2$), 2.33 (3H, s, C**H**$_3$); δ_C (100 MHz, CDCl$_3$) 195.7 (S**C**O), 177.9 (**C**OOH), 34.3 (**C**H$_2$), 30.7 (**C**H$_3$), 23.9 (**C**H$_2$); HRMS (ESI): calcd. for $C_5H_8NaO_3S$, 171.0086. Found: $[MNa]^+$, 171.0086 (–0.1 ppm error). This procedure was adapted from a literature method.[99]

Lab notebook reference: KP174

1-[3-(Acetylsulfanyl)propanoyl]azocan-2-one (3.27)



3.27

A mixture of 1-aza-2-cyclooctanone **1.218** (381 mg, 2.97 mmol), DMAP (103 mg, 0.840 mmol) and pyridine (1.44 mL, 17.8 mmol) in DCM (30 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride **3.26** (3-(acetylthio)propanoyl chloride) (4.49 mmol, 1.50 eqv. prepared using the general procedure from 3-(acetylthio)propanoic acid **3.25**) in DCM (30 mL) was added and the resulting mixture was heated at reflux 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 (3 × 25 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:9 ethyl acetate: hexane → 1:1 ethyl acetate: hexane) afforded the *title compound* as a light orange oil (610 mg, 80%); R_f 0.43 (2:5 ethyl acetate: hexane); ν_{max}/cm^{-1} (thin film) 2928, 2859, 1687, 1445, 1372, 1247, 1198, 1175, 1126, 1092, 998, 893, 774, 692, 628, 594; δ_H (400 MHz, CDCl$_3$) 3.92–3.83 (2H, m, C**H**$_2$N), 3.19–3.09 (4H, m, COC**H**$_2$CH$_2$S and COCH$_2$C**H**$_2$S), 2.66–2.58 (2H, m, C**H**$_2$CON), 2.29–2.25 (3H, m, C**H**$_3$), 1.88–1.79 (2H, m, C**H**$_2$), 1.71–1.63 (2H, m, C**H**$_2$), 1.60–1.52 (2H, m, C**H**$_2$), 1.46–1.37 (2H, m, C**H**$_2$); δ_C (100 MHz, CDCl$_3$), 195.9 (**C**OS), 178.3 (**C**ON), 174.8 (**C**OCH$_2$CH$_2$), 43.5 (**C**H$_2$N), 39.9 (CO**C**H$_2$CH$_2$S), 37.2 (**C**H$_2$CON), 30.6 (**C**H$_3$), 29.5 (**C**H$_2$), 29.1 (**C**H$_2$), 26.3 (**C**H$_2$), 24.5 (COCH$_2$**C**H$_2$S), 24.0 (**C**H$_2$); HRMS (ESI): calcd. for $C_{12}H_{19}NNaO_3S$, 280.0978. Found: $[MNa]^+$, 280.0976 (0.8 ppm error).

Lab notebook reference: KP176

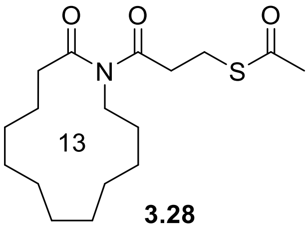
The same product **3.27** was also prepared using a conjugate addition strategy, using the following procedure:

A 10 mL RBF was charged with 1-acryloylazocan-2-one **4.37** (181.3 mg, 1.00 mmol) and EtOAc (5.5 mL). The solution was degassed with argon for 3 min (*via* a balloon) and then thioacetic acid (0.214

mL, 3.00 mmol) was added followed by TEA (0.050 mL, 0.400 mmol). Under an argon atmosphere this mixture was stirred at RT for 2.7 hours. The reaction mixture was then diluted with $CHCl_3$ (20 mL) and washed with $NaHCO_3$. It was then extracted with $CHCl_3$ (3 × 20 mL) and organics washed with brine. The mixture was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:9 ethyl acetate: hexane → 1:1 ethyl acetate: hexane) afforded the *title compound* as a light orange oil (246 mg, 96%); R_f 0.43 (2:5 ethyl acetate: hexane); ν_{max}/cm^{-1} (thin film) 2928, 2859, 1687, 1445, 1372, 1247, 1198, 1175, 1126, 1092, 998, 893, 774, 692, 628, 594; δ_H (400 MHz, $CDCl_3$) 3.92 – 3.83 (2H, m, C**H₂**N), 3.19 – 3.09 (4H, m, COC**H₂**CH₂S and COCH₂C**H₂**S), 2.66 – 2.58 (2H, m, C**H₂**CON), 2.29 – 2.25 (3H, m, C**H₃**), 1.88 – 1.79 (2H, m, C**H₂**), 1.71 – 1.63 (2H, m, C**H₂**), 1.60 – 1.52 (2H, m, C**H₂**), 1.46 – 1.37 (2H, m, C**H₂**); δ_C (100 MHz, $CDCl_3$), 195.9 (**C**OS), 178.3 (**C**ON), 174.8 (**C**OCH₂CH₂), 43.5 (**C**H₂N), 39.9 (CO**C**H₂CH₂S), 37.2 (**C**H₂CON), 30.6 (**C**H₃), 29.5 (**C**H₂), 29.1 (**C**H₂), 26.3 (**C**H₂), 24.5 (COCH₂**C**H₂S), 24.0 (**C**H₂); HRMS (ESI): calcd. for $C_{12}H_{19}NNaO_3S$, 280.0978. Found: $[MNa]^+$, 280.0976 (0.8 ppm error). This procedure was adapted from a literature method.[100]

Lab notebook reference: KP149

1-[3-(Acetylsulfanyl)propanoyl]azacyclotridecan-2-one (3.28)



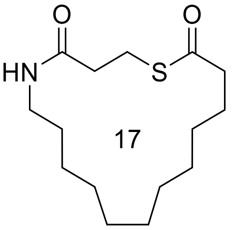
3.28

A mixture of laurolactam **1.210** (592 mg, 3.00 mmol), DMAP (57.4 mg, 0.473 mmol) and pyridine (1.45 mL, 18.0 mmol) in DCM (50 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride **3.26** (3-(acetylthio)propanoyl chloride, 4.49 mmol, 1.50 eqv. prepared using the general procedure from 3-(acetylthio)propanoic acid **3.25**) in DCM (10 mL) was added and the resulting mixture was heated at reflux 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 (3 × 25 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:9 ethyl acetate: hexane → 1:1 ethyl acetate: hexane) afforded the *title compound* as a colorless oil (323 mg, 33%); R_f 0.53 (2:3 ethyl acetate: hexane); ν_{max}/cm^{-1} (thin film) 2930, 2861, 1690, 1364, 1133, 626; δ_H (400 MHz, $CDCl_3$) 3.67 – 3.53 (2H, m, C**H₂**N), 3.14 – 2.95 (4H, m, COC**H₂**CH₂S and COCH₂C**H₂**S), 2.61 – 2.45 (2H, m, C**H₂**CON), 2.24 – 2.22 (3H, m, C**H₃**), 1.84 – 1.62 (2H, m, C**H₂**), 1.58 (2H, p, *J* = 6.6 Hz, C**H₂**), 1.44 – 1.18 (14H, m, C**H₂**); δ_C (100 MHz, $CDzCl_3$), 195.7

(**C**OS), 176.5 (**C**ON), 174.4 (**C**OCH_2CH_2), 43.0 (**C**H_2N), 39.0 (CO**C**H_2CH_2S), 35.9 (**C**H_2CON), 30.4 (**C**H_3), 25.8 (**C**H_2), 25.7 (**C**H_2), 25.6 (**C**H_2), 24.9 (**C**H_2), 24.5 (COCH_2**C**H_2S), 24.5 (**C**H_2), 24.4 (**C**H_2), 24.0 (**C**H_2), 23.8 (**C**H_2), 23.7 (**C**H_2); HRMS (ESI): calcd. for $C_{17}H_{29}NNaO_3S$, 350.1760. Found: $[MNa]^+$, 350.1760 (0.1 ppm error).

Lab notebook reference: KP186

1-Thia-5-azacycloheptadecane-4,17-dione (3.29)



3.29

To a solution of 1-(3-(tritylthio)propanoyl)azacyclotridecan-2-one **3.42** (1.02 g, 1.93 mmol) in DCM (20 mL) under an argon atmosphere was added TFA (1.95 mL, 25.5 mmol) and the solution stirred for 3 min. Next, triisopropylsilane (0.44 mL, 2.15 mmol) was added and the solution stirred for a further 30 min. The solvent and TFA were removed *in vacuo*. The crude material was then re-dissolved in DCM (20 mL) and DBU (2.87 mL, 19.3 mmol) was added, followed by stirring at RT for 18 h, before the solvent was removed *in vacuo*. The reaction mixture was then diluted with DCM (20 mL) and washed with 10% aq. HCl (50 mL). The aqueous layer was then extracted with DCM (3 × 50 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:9 ethyl acetate: hexane → 1:4 ethyl acetate: hexane → 1:1 ethyl acetate: hexane → ethyl acetate) afforded the *title compound* **3.29** as a white crystalline solid (307 mg, 56%), along with a small amount of laurolactam **1.210** (13.3 mg, 4%) and trace **3.43** (see below for data). Data for **3.29**: m.p. 88–95 °C; R_f 0.17 (1:1 ethyl acetate: hexane); ν_{max}/cm^{-1} (thin film) 3299, 2927, 2856, 1684, 1647, 1555, 1459, 1355, 1261, 1203, 1026, 717; δ_H (400 MHz, $CDCl_3$) 5.88 (1H, br s, N**H**), 3.31–3.23 (2H, m, C**H₂**NH), 3.17–3.09 (2H, m, **C**H_2SCO), 2.55–2.47 (4H, m, COC**H₂**CH_2S and C**H₂**COS), 1.64 (2H, apparent pentet, *J* = 7.0 Hz, C**H₂**), 1.51–1.40 (2H, m, C**H₂**), 1.37–1.18 (14H, m, 7 × C**H₂**); δ_C (100 MHz, $CDCl_3$): 201.1 (S**C**O), 171.0 (**C**O), 43.7 (**C**H_2COS), 39.4 (**C**H_2NH), 36.1 (CO**C**H_2CH_2S), 28.8 (**C**H_2), 27.5 (**C**H_2), 27.43 (**C**H_2), 27.40 (**C**H_2), 27.3 (**C**H_2), 27.2 (**C**H_2), 26.4 (**C**H_2), 25.4 (**C**H_2), 25.1 (**C**H_2), 25.0 (**C**H_2); HRMS (ESI): calcd. for $C_{15}H_{27}NNaO_2S$, 308.1655. Found: $[MNa]^+$, 308.1646 (2.9 ppm error). For X-ray crystallographic data see CCDC 2040347.

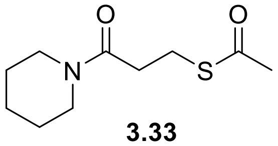
The same product **3.29** was also prepared using the S-Fm strategy, see compound **3.65** for procedure.

The S-Ac strategy was also used to prepare **3.29** *via* a third method, as described below:

A mixture of 1-[3-(acetylsulfanyl)propanoyl]azacyclotridecan-2-one **3.28** (318 mg, 0.972 mmol) and piperidine (0.296 mL, 3.00 mmol) in DCM (10 mL) under an argon atmosphere was stirred at RT 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, 1:19 ethyl acetate: hexane → 1:9 ethyl acetate: hexane → 1:4 ethyl acetate: hexane → 1:1 ethyl acetate: hexane → 2:1 ethyl acetate: hexane → ethyl acetate → 19:1 ethyl acetate: methanol) afforded the *title compound* **3.29** (for characterization data see above) as an off white solid (99.2 mg, 36%), along with recovered **3.28** (109 mg, 34%), and side product **3.33** (23.9 mg, 11%; for characterization data for **3.33** see below).

Lab notebook reference: KP195_F/KP230_A

1-[3-(Acetylsulfanyl)propanoyl]piperidine (3.33)

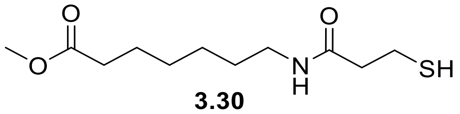


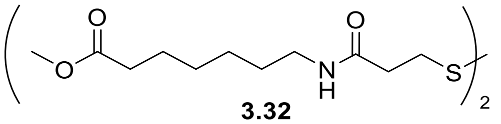
3.33

Data for **3.33** (for synthesis see above, acquired as a mixture containing **3.29**): R_f 0.55 (9:1 ethyl acetate: methanol); δ_H (400 MHz, $CDCl_3$) 3.55 – 3.49 (2H, m, C**H**$_2$), 3.37 – 3.32 (2H, m, C**H**$_2$), 3.11 (2H, t, *J* = 6.9 Hz, C**H$_2$**), 2.60 (2H, t, *J* = 6.9 Hz, C**H$_2$**), 2.30 (3H, s, C**H**$_3$), 1.68 – 1.47 (6H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 196.8 (**C**O), 169.1 (**C**O), 46.5 (**C**H$_2$), 42.9 (**C**H$_2$), 33.5 (**C**H$_2$), 30.7 (**C**H$_3$), 26.5 (**C**H$_2$), 25.6 (**C**H$_2$), 25.0 (**C**H$_2$), 24.6 (**C**H$_2$).

Lab notebook reference: KP187_B/KP188_B

Methyl 7-(3-sulfanylpropanamido)heptanoate (3.30) and methyl 7-[3-({2-[(7-methoxy-7-oxoheptyl)carbamoyl]ethyl}disulfanyl)propanamido]heptanoate (3.32)


3.30


3.32

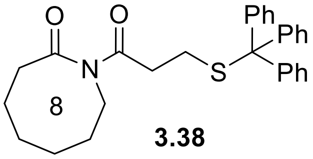
1-[3-(Acetylsulfanyl)propanoyl]azocan-2-one **3.27** (25.7 mg, 0.100 mmol) was dissolved in MeOH (1 mL) and the solution was degassed with argon for 5 min (*via* a balloon) to remove oxygen. To this stirring solution was added NaOH (4N aq., 0.03 mL, 1.2 eqv.) and the solution was stirred for 2 hours at RT. The reaction mixture was then acidified with HCl (10% aq.) to pH 1 and diluted with ethyl acetate (3 mL) and water (5 mL). This was then extracted with ethyl acetate (3 × 5 mL) and the organics washed with $NaHCO_3$. and sat. NaCl. The mixture was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:9 ethyl acetate: hexane → 1:5 ethyl acetate: hexane → 1:1 ethyl acetate: hexane → ethyl acetate → 1:19 methanol: ethyl acetate) afforded crude thiol **3.30** (containing 8% disulfide **3.32** in ^{1}H NMR) as an off white solid (4.7 mg, 19%) and disulfide **3.32** (as a 4.6:1 mixture of rotamers) as light yellow oil (4.0 mg, 16%);

Data for **3.30**: R_f 0.49 (9:1 ethyl acetate: methanol); δ_H (400 MHz, $CDCl_3$), 5.56 (1H, br s, N**H**), 3.65 (3H, s, C**H₃**), 3.25 (2H, q, *J* = 6.8 Hz, C**H₂**N), 2.80 (2H, dt, *J* = 8.2, 6.7 Hz, C**H₂**SH), 2.46 (2H, t, *J* = 6.7 Hz, C**H₂**CON), 2.29 (2H, t, *J* = 7.5 Hz, C**H₂**CO_2CH_3), 1.65 – 1.56 (3H, m, C**H₂** and S**H**), 1.55 – 1.45 (2H, m, C**H₂**), 1.37 – 1.27 (4H, m, C**H₂**); δ_C (100 MHz, $CDCl_3$), 174.3 (**C**O_2CH_3), 170.7 (**C**ON), 51.6 (**C**H_3), 40.6 (**C**H_2CON), 39.6 (**C**H_2N), 34.0 (**C**$H_2CO_2CH_3$), 29.5 (**C**H_2), 28.8 (**C**H_2), 26.6 (**C**H_2), 24.8 (**C**H_2), 20.6 (**C**H_2SH); HRMS (ESI): calcd. for $C_{11}H_{21}NNaO_3S$, 270.1134. Found: $[MNa]^+$, 270.1134 (0.0 ppm error).

Data for **3.32**: R_f 0.39 (9:1 ethyl acetate: methanol); ν_{max}/cm^{-1} (thin film) 3307, 2927, 2853, 1735, 1636, 1546, 1438, 1416, 1365, 1260, 1196, 1018, 800, 726; δ_H (400 MHz, $CDCl_3$) 5.98 (4H, br m, N**H**, both), 3.65 (12H, s, C**H₃**, both rotamers), 3.24 (8H, td, *J* = 7.1, 5.8 Hz, C**H₂**N, both rotamers), 3.15 (4H, t, *J* = 7.0 Hz, C**H₂**S, minor), 2.97 (4H, dt, *J* = 6.9 Hz, C**H₂**S, major), 2.64 (4H, t, *J* = 7.0 Hz, C**H₂**CON, minor), 2.55 (4H, t, *J* = 6.9 Hz, C**H₂**CON, major), 2.29 (8H, t, *J* = 7.5 Hz, C**H₂**CO_2CH_3, both rotamers), 1.67 – 1.56 (8H, m, C**H₂**), 1.55 – 1.46 (8H, m, C**H₂**), 1.38 – 1.27 (16H, m, C**H₂**); Only one rotamer was clearly observable by ^{13}C NMR: δ_C (100 MHz, $CDCl_3$), 174.3 (**C**O_2CH_3), 171.0 (**C**ON), 51.6 (**C**H_3), 39.6 (**C**H_2N), 35.9 (**C**H_2CON), 34.4 (**C**H_2S), 34.0 (**C**$H_2CO_2CH_3$), 29.4 (**C**H_2), 28.8 (**C**H_2), 26.6 (**C**H_2), 24.8 (**C**H_2); HRMS (ESI): calcd. for $C_{22}H_{40}N_2NaO_6S_2$, 515.2220. Found: $[MNa]^+$, 515.2224 (–0.8 ppm error).

Lab notebook reference: KP145_A/B

1-[3-(Tritylthio)propanoyl]azocan-2-one (3.38)

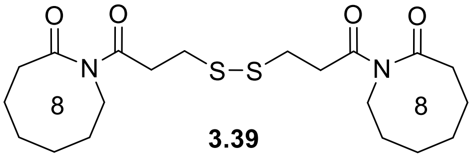


3.38

Oxalyl chloride (0.400 mL, 4.70 mmol) was added to a suspension of 3-(tritylthio)propanoic acid **3.36** (520 mg, 1.49 mmol) in toluene (15 mL), followed by a catalytic amount of DMF (5 drops). The resulting mixture was stirred at RT for 24 h and concentrated *in vacuo* to remove all solvent and excess oxalyl chloride. The resulting 3-(tritylthio)propanoyl chloride **3.37** was dissolved in DCM (3 mL) and added to a pre-stirred mixture of 1-aza-2-cyclooctanone **1.218** (123.4 mg, 0.970 mmol), DMAP (13.3 mg, 0.109 mmol) and pyridine (0.485 mL, 6.00 mmol) in DCM (7 mL) under an argon atmosphere. The reaction mixture was then heated to 50 °C and stirred at for 18 h. The mixture was then diluted with DCM (40 mL) and washed with 10% aq. HCl (40 mL). The aqueous layer was then extracted with DCM (3 × 40 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:19 ethyl acetate: hexane → 1:9 ethyl acetate: hexane → 1:4 ethyl acetate: hexane) afforded the *title compound* as a clear viscous oil (409.8 mg, 92%); R_f 0.74 (1:9 menthol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3056, 2928, 2858, 1687, 1488, 1444, 1369, 1196, 1174, 1125, 1091, 910, 732, 698; δ_H (400 MHz, $CDCl_3$) 7.44 – 7.38 (6H, m, Ar**H**), 7.30 – 7.23 (6H, m, Ar**H**), 7.21 – 7.16 (3H, m, Ar**H**), 3.88 – 3.73 (2H, m, C**H₂**N), 2.84 (2H, t, *J* = 7.0 Hz, COC**H₂**CH₂S), 2.62 – 2.56 (2H, m, C**H₂**CON), 2.48 (2H, t, *J* = 7.0 Hz, COCH₂C**H₂**S), 1.88 – 1.79 (2H, m, C**H₂**), 1.70 – 1.61 (2H, m, C**H₂**), 1.60 – 1.50 (2H, m, C**H₂**), 1.45 – 1.35 (2H, m, C**H₂**); δ_C (100 MHz, $CDCl_3$), 178.1 (**C**ON), 175.0 (**C**OCH₂CH₂), 145.0 (3 × Ar**C**), 129.8 (6 × Ar**C**H), 128.0 (6 × ArCH), 126.7 (3 × Ar**C**H), 66.8 (S**C**(Ph)₃), 43.5 (**C**H₂N), 38.9 (CO**C**H₂CH₂S), 37.2 (**C**H₂CON), 29.5 (**C**H₂), 29.1 (**C**H₂), 27.4 (COCH₂**C**H₂S), 26.3 (**C**H₂), 24.0 (**C**H₂); HRMS (ESI): calcd. for $C_{29}H_{31}NNaO_2S$, 480.1968. Found: $[MNa]^+$, 480.1969 (–0.2 ppm error). The synthetic procedure was adapted from a method reported in a patent.[101]

Lab notebook reference: KP155

1-(3-{[3-Oxo-3-(2-oxoazocan-1-yl)propyl]disulfanyl}propanoyl)azocan-2-one (3.39)

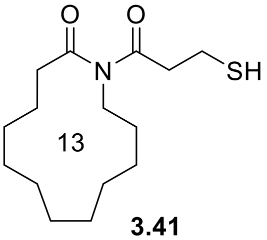


3.39

1-[3-(Tritylthio)propanoyl]azocan-2-one **3.38** (146 mg, 0.319 mmol) was dissolved in DCM (1.6 mL) and sparged using argon for 3 min. TFA (0.160 mL, 2.09 mmol) was added to this stirring solution. After 40 min, triisopropylsilane (0.072 mL, 0.351 mmol) in DCM (0.2 mL) (which was degassed with an argon baloon) was added quickly to the reaction mixture and then allowed to stir for 15 min. Afterwards the reaction mixture was diluted with DCM (5 mL) and to it added water (10 mL). This was then extracted using DCM (3 × 5 mL) and the organic layers dried over $MgSO_4$, filtered, and the solvent was then removed *in vacuo*. A mixture of $CHCl_3$ (3.2 mL) and TEA (0.445 mL, 3.19 mmol) was sparged with argon and then added to the reaction residue and the mixture was allowed to stir for 42 h. Afterwards the reaction mixture was diluted with DCM (5 mL) and 10% aq. HCl (10 mL) was added. This was then extracted with DCM (3 × 10 mL) and the organic layers dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, hexane → 1:19 ethyl acetate: hexane → 1:9 ethyl acetate: hexane → 1:4 ethyl acetate: hexane → 1:1 ethyl acetate: hexane → ethyl acetate → 1:19 methanol: ethyl acetate) afforded the *title compound* **3.39** (2.2 mg, 3%) along with **3.21** (32.3 mg, 47%), **3.23** (2.0 mg, 3%), and **1.218** (1.5 mg, 4%). Data for **3.39**: a colorless oil; R_f 0.76 (9:1 ethyl acetate: methanol); δ_H (400 MHz, $CDCl_3$) 3.94 – 3.88 (4H, m, 2 × C**H$_2$**N), 3.30 (2H, t, *J* = 6.9 Hz, COC**H$_2$**CH$_2$S 3.18 (2H, t, *J* = 7.2 Hz, COC**H$_2$**CH$_2$S), 2.98 (2H, t, *J* = 6.9 Hz, COCH$_2$C**H$_2$**S), 2.84 (2H, t, *J* = 7.2 Hz, COCH$_2$C**H$_2$**S), 2.69 – 2.62 (4H, m, 2 × C**H$_2$**CON), 1.92 – 1.84 (4H, m, 2 × C**H$_2$**), 1.71 (4H, p, *J* = 6.1 Hz, 2 × C**H$_2$**), 1.63 – 1.52 (4H, m, 2 × C**H$_2$**), 1.49 – 1.41 (4H, m, 2 × C**H$_2$**); δ_C (100 MHz, $CDCl_3$) 178.4 (2C, 2 × **C**ON), 175.0 (2C, 2 × **C**OCH$_2$CH$_2$), 43.6 (2C, 2 × CH$_2$N), 40.1 (CO**C**H$_2$CH$_2$S), 39.5 (CO**C**H$_2$CH$_2$S), 37.2 (2C, 2 × **C**H$_2$CON), 33.9 (COCH$_2$**C**H$_2$S), 29.6 (2C, 2 × **C**H$_2$), 29.2 (2C, 2 × **C**H$_2$), 27.6 (COCH$_2$**C**H$_2$S), 26.4 (2C, 2 × **C**H$_2$), 24.1 (2C, 2 × **C**H$_2$); HRMS (ESI): calcd. for $C_{20}H_{32}N_2NaO_4S_2$, 451.1696. Found: $[MH]^+$, 451.1696 (0.1 ppm error).

Lab notebook reference: KP189_C

1-(3-Mercaptopropanoyl)azacyclotridecan-2-one (3.41)

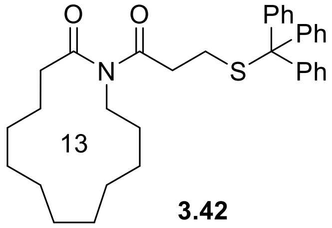


3.41

To a solution of 1-(3-(tritylthio)propanoyl)azacyclotridecan-2-one **3.42** (1.02 g, 1.94 mmol) in DCM (10 mL) under an argon atmosphere was added TFA (1.20 mL, 15.7 mmol) and the solution stirred for 3 min. Next, triisopropylsilane (0.550 mL, 2.69 mmol) was added and the solution stirred for a further 30 min. The mixture was then diluted with DCM (5 mL) and washed with water (20 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, 1:19 ethyl acetate: hexane → 1:9 ethyl acetate: hexane → 1:1 ethyl acetate: hexane → ethyl acetate → 1:19 methanol: ethyl acetate) afforded the *title compound* **3.41** as a yellow oil (268 mg, 48%), along with a small amount of compound **3.43** (38.0 mg, 7%; data for **3.43** is given below). Data for **3.41**: R_f 0.64 (1:1 ethyl acetate: hexane); ν_{max}/cm^{-1} (thin film) 2928, 2860, 1689, 1463, 1445, 1365, 1247, 1230, 1179, 1132, 1121, 1099, 1047; δ_H (400 MHz, $CDCl_3$) 3.63–3.56 (2H, m, C**H₂**N), 3.03 (2H, t, *J* = 6.6 Hz, COC**H₂**CH₂SH), 2.71 (2H, dt, *J* = 8.4, 6.6 Hz, COCH₂C**H₂**SH), 2.53–2.47 (2H, m, C**H₂**CON), 1.73–1.64 (2H, m, C**H₂**), 1.63–1.54 (2H, m, C**H₂** [overlapping]), 1.58 (1H, t, *J* = 8.4 Hz, S**H** [overlapping]), 1.41–1.15 (14H, m, C**H₂**); δ_C (100 MHz, $CDCl_3$), 176.5 (**C**ON), 174.3 (**C**OCH₂CH₂), 42.9 (2 × **C**H₂ (**C**H₂N and CO**C**H₂CH₂S)), 35.8 (**C**H₂CON), 25.8 (**C**H₂), 25.6 (**C**H₂), 25.5 (**C**H₂), 24.8 (**C**H₂), 24.5 (**C**H₂), 24.4 (**C**H₂), 24.0 (**C**H₂), 23.8 (**C**H₂), 23.6 (**C**H₂), 19.8 (COCH₂**C**H₂SH); HRMS (ESI): calcd. for $C_{15}H_{27}NNaO_2S$, 308.1655. Found: $[MNa]^+$, 308.1646 (2.7 ppm error).

Lab notebook reference: KP195_B

1-[3-(Tritylthio)propanoyl]-1-azacyclotridecan-2-one (3.42)



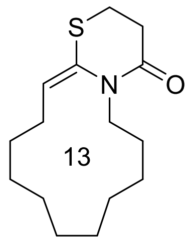
3.42

Oxalyl chloride (1.14 mL, 13.3 mmol) was added to a suspension of 3-(tritylthio)propanoic acid **3.36** (1.57 g, 4.51 mmol) in toluene (45 mL), followed by a catalytic amount of DMF (4 drops). The resulting mixture was stirred at RT for 1 h and concentrated *in vacuo* to remove all solvent and excess oxalyl chloride. The resulting 3-(tritylthio)propanoyl chloride **3.37** was dissolved in DCM (15 mL) and was added to a pre-stirred mixture of laurolactam **1.210** (577 mg, 2.92 mmol), DMAP (49.0 mg, 0.401 mmol) and pyridine (1.44 mL, 17.9 mmol) in DCM (35 mL) under an argon atmosphere. The reaction mixture was then heated to 50 °C and stirred for 18 hours. The mixture was then cooled, diluted with DCM (30 mL) and washed with 10% aq. HCl (90 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, 1:19 ethyl acetate: hexane → 1:9 ethyl acetate: hexane) afforded the *title compound* as a clear viscous oil (1.21 g, 78%)*; R_f 0.74 (1:9 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 2929, 2859, 1691, 1595, 1489, 1445, 1364, 1229, 1180, 1132, 1099, 1034, 909, 737, 699, 676, 620; δ_H (400 MHz, $CDCl_3$) 7.46 – 7.40 (5H, m, ArH), 7.34 – 7.18 (10H, m, ArH), 3.65 – 3.56 (2H, m, C**H₂**N), 2.70 (2H, t, *J* = 6.9 Hz, $COCH_2$C**H₂**S), 2.61 – 2.49 (2H, m, C**H₂**CON [overlapping]), 2.53 (2H, t, *J* = 6.9 Hz, COC**H₂**CH_2S [overlapping]), 1.75 (2H, p, *J* = 6.9 Hz, C**H₂**), 1.65 – 1.56 (2H, m, C**H₂**), 1.48 – 1.25 (14H, m, C**H₂**); δ_C (100 MHz, $CDCl_3$), 176.8 (**C**ON), 174.8 (**C**OCH_2CH_2), 144.9 (3 × Ar**C**), 129.8 (6 × Ar**C**H), 128.0 (6 × Ar**C**H), 126.7 (3 × Ar**C**H), 66.9 (**C**Ph_3), 43.1 (**C**H_2N), 38.2 (**C**H_2CON), 36.3 ($COCH_2$**C**H_2S), 27.3 (CO**C**H_2CH_2S), 26.0 (**C**H_2), 25.9 (**C**H_2), 25.7 (**C**H_2), 25.1 (**C**H_2), 24.9 (**C**H_2), 24.7 (**C**H_2), 24.2 (**C**H_2), 24.1 (**C**H_2), 23.9 (**C**H_2); HRMS (ESI): calcd. for $C_{34}H_{41}NNaO_2S$, 550.2750. Found: $[MNa]^+$, 550.2753 (–0.5 ppm error).

*The purified product also contains traces of triphenylmethanol that we were unable to remove completely, although the purity of **3.42** was sufficient for the product to be used in subsequent steps. Characteristic NMR data for triphenylmethanol can be seen at: δ_C (100 MHz, $CDCl_3$), 147.0 (Ar**C**), 128.04 (Ar**C**H), 127.37 (Ar**C**H), 81.9 (Ph_3**C**OH).

Lab notebook reference: KP191/KP194/KP232

(*E*)-6,7,8,9,10,11,12,13,14,15-Decahydro-2H-[1,3]thiazino[3,2-a][1]azacyclotridecin-4(3H)-one (3.43)

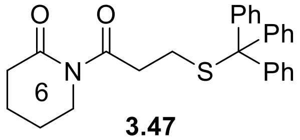


3.43

Data for **3.43** (for synthesis see first procedure for **3.29** above): off white pasty solid; R_f 0.55 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3317, 2927, 2856, 1651, 1549, 1443, 1355, 1258, 1117, 1028, 918, 733, 702, 605; δ_H (400 MHz, $CDCl_3$), 5.47 (1H, t, *J* = 7.8 Hz, C**H**CH_2), 3.82–3.74 (2H, m, C**H₂**N), 3.01–2.96 (2H, m, $COCH_2$C**H₂**S), 2.71–2.65 (2H, m, COC**H₂**CH_2S), 2.22–2.15 (2H, m, CHC**H₂**), 1.69–1.58 (2H, m, C**H₂**), 1.54–1.45 (2H, m, C**H₂**), 1.38–1.24 (12H, m, 6 × C**H₂**); δ_C (100 MHz, $CDCl_3$), 169.8 (**C**ON), 133.0 (**C** quat), 121.1 (**C**HCH_2), 46.2 (**C**H_2N), 35.5 (CO**C**H_2CH_2S), 28.7 (CH**C**H_2), 27.4 (**C**H_2), 27.2 (**C**H_2), 25.6 (**C**H_2), 25.5 (**C**H_2), 25.3 (**C**H_2), 25.1 (**C**H_2), 24.80 (**C**H_2), 24.75 ($COCH_2$**C**H_2S), 24.1 (**C**H_2); HRMS (ESI): calcd. for $C_{15}H_{25}NNaOS$, 290.1549. Found: $[MNa]^+$, 290.1546 (1.1 ppm error).

Lab notebook reference: KP195_C

1-(3-(Tritylthio)propanoyl)piperidin-2-one (3.47)



3.47

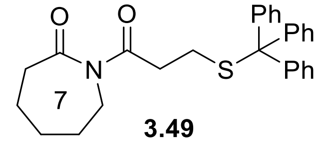
Oxalyl chloride (0.380 mL, 4.50 mmol) was added to a suspension of 3-(tritylthio)propanoic acid **3.36** (520 mg, 1.49 mmol) in DCM (15 mL), followed by a catalytic amount of DMF (1 drop). The resulting mixture was stirred at RT for 1 h and concentrated *in vacuo* to remove all solvent and excess oxalyl chloride. The resulting 3-(tritylthio)propanoyl chloride **3.37** was dissolved in DCM (10 mL) and added to a pre-stirred mixture of δ-valerolactam **4.60** (99.5 mg, 1.00 mmol), DMAP (12.3 mg, 0.100 mmol) and pyridine (0.485 mL, 6.00 mmol) in DCM (15 mL) under an argon atmosphere. The reaction mixture was then heated to 50 °C and stirred for 18 h. The mixture was then diluted with DCM (10 mL) and washed with 10% aq. HCl (30 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, 1:19 ethyl acetate: hexane → 1:9 ethyl acetate: hexane → 1:4 ethyl acetate: hexane) afforded the crude *title compound* as a clear viscous oil (561 mg) [containing some trityl impurities]

Based on the NMR spectra obtained, and the theoretical maximum mass of the *title compound* (431 mg for 100%), it was clear that the product contained some non-product impurities making an accurate yield difficult to calculate. For the purposes of exploring the chemistry of this deprotection/ring expansion, this is not considered to be too important however and therefore the mixture was carried forward, assuming 100% conversion into the imide product for the purposes of reagent calculations in the following deprotection/ring expansion step.

Data for **3.47**: R_f 0.66 (ethyl acetate); ν_{max}/cm^{-1} (neat) 2943, 1689, 1488, 1444, 1357, 1290, 1154, 1083, 1033, 1001, 742, 698, 676, 617, 572, 506; δ_H (400 MHz, $CDCl_3$) 7.50 – 7.43 (6H, m, Ar**H**), 7.33 – 7.25 (6H, m, Ar**H**), 7.24 – 7.18 (3H, m, Ar**H**), 3.70 – 3.62 (2H, m, C**H₂**N), 2.94 (2H, t, *J* = 7.0 Hz, COC**H₂**CH₂S), 2.54 (2H, t, *J* = 7.0 Hz, COCH₂C**H₂**S), 2.51 – 2.44 (2H, m, C**H₂**CON), 1.81 – 1.69 (4H, m, 2 × C**H₂**); δ_C (100 MHz, $CDCl_3$), 175.0 (**C**ON), 173.1 (**C**OCH₂CH₂), 144.8 (3 × Ar**C**), 129.6 (6 × Ar**C**H), 127.8 (6 × Ar**C**H), 126.5 (3 × Ar**C**H), 66.7 (S**C**(Ph)₃), 43.9 (**C**H₂N), 39.0 (CO**C**H₂CH₂S), 34.6 (**C**H₂CON), 27.0 (COCH₂**C**H₂S), 22.2 (**C**H₂), 20.1 (**C**H₂); HRMS (ESI): calcd. for $C_{27}H_{27}NNaO_2S$, 452.1655. Found: $[MNa]^+$, 452.1661 (–1.4 ppm error).

Lab notebook reference: KP222

1-(3-(Tritylthio)propanoyl)azepan-2-one (3.49)



3.49

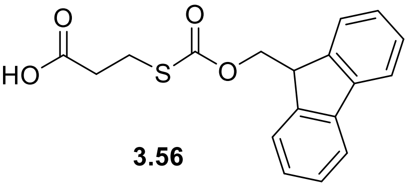
Oxalyl chloride (0.380 mL, 4.50 mmol) was added to a suspension of 3-(tritylthio)propanoic acid **3.36** (520 mg, 1.49 mmol) in DCM (15 mL), followed by a catalytic amount of DMF (1 drop). The resulting mixture was stirred at RT for 1 h and concentrated *in vacuo* to remove all solvent and excess oxalyl chloride. The resulting 3-(tritylthio)propanoyl chloride **3.37** was dissolved in DCM (10 mL) and added to a pre-stirred mixture of aza-2-cycloheptanone (117 mg, 1.03 mmol), DMAP (12.4 mg, 0.101 mmol) and pyridine (0.485 mL, 6.00 mmol) in DCM (15 mL) under an argon atmosphere. The reaction mixture was then heated to 50 °C and stirred at for 18 h. The mixture was then diluted with DCM (10 mL) and washed with 10% aq. HCl (30 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, 1:19 ethyl acetate: hexane → 1:9 ethyl acetate: hexane → 1:4 ethyl acetate: hexane) afforded the *title compound* as a clear viscous oil (487 mg) [containing some trityl impurites];

Based on the NMR spectra obtained, and the theoretical maximum mass of the *title compound* (458 mg for 100%), it was clear that the product contained some non-product impurities making an accurate yield difficult to calculate. For the purposes of exploring the chemistry of this deprotection/ring expansion, this is not considered to be too important however and therefore the mixture was carried forward, assuming 95% conversion into the imide product for the purposes of reagent calculations in the following deprotection/ring expansion step.

Data for **3.49**: R$_f$ 0.68 (ethyl acetate); ν$_{max}$/cm^{-1} (neat) 2930, 1691, 1488, 1443, 1363, 1255, 1206, 1177, 1146, 1081, 1033, 974, 742, 698, 676, 618, 586, 506; δ$_H$ (400 MHz, CDCl$_3$) 7.48 – 7.42 (6H, m, Ar**H**), 7.32 – 7.25 (6H, m, Ar**H**), 7.24 – 7.18 (3H, m, Ar**H**), 3.87 – 3.79 (2H, m, C**H$_2$**N), 2.87 (2H, t, *J* = 7.0 Hz, COC**H$_2$**CH$_2$S), 2.70 – 2.62 (2H, m, C**H$_2$**CON), 2.52 (2H, t, *J* = 7.0 Hz, COCH$_2$C**H$_2$**S), 1.79 – 1.59 (6H, m, 3 × C**H$_2$**); δ$_C$ (100 MHz, CDCl$_3$), 177.5 (**C**ON), 174.4 (**C**OCH$_2$CH$_2$), 144.9 (3 × Ar**C**), 129.7 (6 × Ar**C**H), 127.9 (6 × Ar**C**H), 126.6 (3 × Ar**C**H), 66.8 (S**C**(Ph)$_3$), 43.3 (**C**H$_2$N), 39.7 (**C**H$_2$CON), 38.7 (CO**C**H$_2$CH$_2$S), 29.2 (**C**H$_2$), 28.5 (**C**H$_2$), 27.3 (COCH$_2$**C**H$_2$S), 23.7 (**C**H$_2$); HRMS (ESI): calcd. for $C_{28}H_{29}NNaO_2S$, 466.1811. Found: [MNa]$^+$, 466.1806 (1.1 ppm error).

Lab notebook reference: KP221

3-((((9*H*-Fluoren-9-yl)methoxy)carbonyl)thio)propanoic acid (3.56)



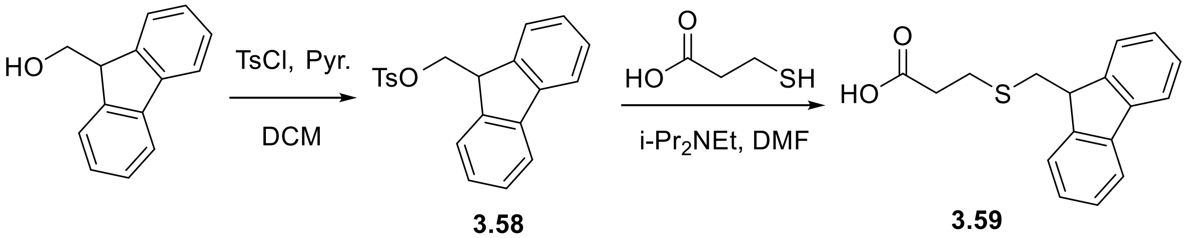
3.56

3-mercaptopropionic acid (2.18 mL, 25.0 mmol) was dissolved in a mixture of deionized water (75 mL), 1,4-dioxane (125 mL), and Na_2CO_3 (125 mL, 10% solution). The solution was cooled to 0 °C whilst stirring and a pre-made solution of 9-fluorenylmethyl chloroformate (8.02 g, 31.0 mmol) dissolved in 1,4-dioxane (25 mL) added slowly. The solution was allowed to warm to RT and stirred for 18 h, analysed by TLC. The mixture was diluted with water (75 mL) and acidified to pH 2 using 10% aq. HCl and extracted with EtOAc (3 × 125 mL). The combined organics were washed with brine (125 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (SiO_2, 1:4 ethyl acetate: hexane → 1:1 ethyl acetate: hexane) afforded the *title compound* as a colorless oil, (7.50 g, 91% over 3 steps); R$_f$ 0.53 (9:1 ethyl acetate: methanol) (streaky spot with concentration dependence); ν$_{max}$/cm^{-1} (neat)

3039, 1698, 1448, 1406, 1242, 1194, 1133, 935, 816, 756, 736, 726, 672, 644, 621, 590, 548; δ_H (400 MHz, CDCl$_3$) 8.99 (1H, br s, COO**H**), 7.78 (2H, d, *J* = 7.1 Hz, Ar**H**), 7.60 (2H, d, *J* = 7.5 Hz, Ar**H**), 7.43 (2H, d, *J* = 7.5 Hz, Ar**H**), 7.37 – 7.31 (2H, m, Ar**H**), 4.51 (2H, d, *J* = 7.3 Hz, CHC**H₂**), 4.21 (1H, t, *J* = 7.3 Hz, C**H**CH$_2$), 3.11 (2H, t, *J* = 6.9 Hz, C**H₂**), 2.78 (2H, t, *J* = 6.9 Hz, C**H₂**); δ_C (100 MHz, CDCl$_3$) 177.7 (**C**O), 170.8 (**C**O), 143.3 (2 × Ar**C**), 141.4 (2 × Ar**C**), 128.1 (2 × Ar**C**H), 127.3 (2 × Ar**C**H), 125.3 (2 × Ar**C**H), 120.2 (2 × Ar**C**H), 69.4 (**C**H$_2$), 46.8 (**C**H), 34.6 (**C**H$_2$), 25.8 (**C**H$_2$); HRMS (ESI): calcd. for $C_{18}H_{16}NaO_4S$, 351.0662. Found: [MNa]$^+$, 351.0664 (–0.9 ppm error).

Lab notebook reference: KP242

3-(((9*H*-Fluoren-9-yl)methyl)thio)propanoic acid (3.59)

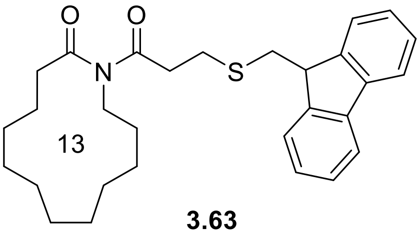


Tosyl chloride (19.6 g, 100 mmol) in anhydrous pyridine (16.1 mL, 200 mmol) was added slowly to a solution of 9-fluorenylmethanol (19.6 g, 100 mmol) in CHCl$_3$ (100 mL) at 0 °C. After stirring for 2 h, the solution was washed with 10% aq. NaHCO$_3$ (2 × 25 mL), and brine (2 × 25 mL) and dried over anhydrous MgSO$_4$. After filtration, the solvent was removed *in vacuo.* The product was recrystallized by dissolving in CHCl$_3$ and adding hexane until loss of transparency in the solution was starting to become apparent. At this point, the mixture was left to stand at room temperature overnight to crystallize. The crystals were filtered by vacuum filtration to yield fluorenylmethyl *p*-toluenesulfonate **3.58** (26.8 g, 76%); δ_H (400 MHz, CDCl$_3$) 7.78–7.69 (4H, m, Ar**H**), 7.53 (2H, dt, *J* = 7.5, 1.0 Hz, Ar**H**), 7.68 (2H, td, *J* = 7.5, 1.0 Hz, Ar**H**), 7.32–7.23 (4H, m, Ar**H**), 4.28–4.18 (3H, m, C**H** and C**H₂**), 2.41 (3H, s, C**H₃**); δ_C (100 MHz, CDCl$_3$) 145.0 (Ar**C**), 142.6 (2 × Ar**C**), 141.3 (2 × Ar**C**), 132.8 (Ar**C**), 130.0 (2 × Ar**C**H), 128.2 (2 × Ar**C**H), 128.0 (2 × Ar**C**H), 127.3 (2 × Ar**C**H), 125.3 (2 × Ar**C**H), 120.2 (2 × Ar**C**H), 72.0 (**C**H$_2$), 46.8 (**C**H), 21.8 (**C**H$_3$). ^{1}H and ^{13}C NMR data matches those reported in the literature.[102]

To a solution of 3-thiopropionic acid (2.48 mL, 28.5 mmol) and fluorenyl methanol *p*-toluenesulfonate **3.58** (9.99 g, 28.5 mmol) in DMF (50 mL) was added ^{i}Pr$_2$NEt (9.93 mL, 57.0 mmol). The reaction was stirred at room temperature for 16 h and DMF was removed under reduced pressure (high vacuum). The residue was dissolved in ethyl acetate (300 mL), washed with 0.2 N aq. HCl (5 × 100 mL), sat. aq. NaHCO$_3$ (2 × 100 mL), water (100 mL), brine (100 mL) and dried over anhydrous Na$_2$SO$_4$. The solvent was removed under reduced pressure and the crude material was then suspended in chloroform and filtered to remove insoluble material (2 × 150 mL). The combined chloroform fractions were then concentrated and the solvent removed *in vacuo* to afford the *title compound* **3.59** as a yellow solid (3.85 g, 48%); R$_f$ 0.27 (ethyl acetate); m.p. 91–95 °C; ν_{max}/cm^{-1} (thin film) 3039, 2912, 1706, 1477, 1448, 1263, 1197, 940, 739, 621; δ_H (400 MHz, CDCl$_3$) 7.76 (2H, dt, *J* = 7.6, 1.0 Hz, Ar**H**), 7.68 (2H, dq, *J* = 7.5, 1.0 Hz, Ar**H**), 7.40 (2H, tt, *J* = 7.6, 1.0 Hz, Ar**H**), 7.32 (2H, td, *J* = 7.5, 1.0 Hz, Ar**H**), 4.12 (1H, t, *J* = 6.4 Hz, SCH$_2$C**H**), 3.11 (2H, d, *J* = 6.4 Hz, SC**H$_2$**CH), 2.80 (2H, t, *J* = 7.3 Hz, CH$_2$C**H$_2$**S), 2.63 (2H, t, *J* = 7.3 Hz, C**H$_2$**CH$_2$S); δ_C (100 MHz, CDCl$_3$) 177.6 (**C**OOH), 146.0 (2 × Ar**C**), 141.2 (2 × Ar**C**), 127.8 (2 × Ar**C**H), 127.2 (2 × Ar**C**H), 124.9 (2 × Ar**C**H), 120.1 (2 × Ar**C**H), 47.0 (SCH$_2$**C**H), 36.9 (S**C**H$_2$CH), 34.7 (**C**H$_2$CH$_2$S), 27.9 (CH$_2$**C**H$_2$S); HRMS (ESI): calcd. for $C_{17}H_{16}NaO_2S$, 307.0763. Found: [MNa]$^+$, 307.0763 (0.2 ppm error). The synthetic procedure was adapted from a literature report.^{82}

Lab notebook reference: KP274/KP254

1-(3-(((9*H*-Fluoren-9-yl)methyl)thio)propanoyl)azacyclotridecan-2-one (3.63)



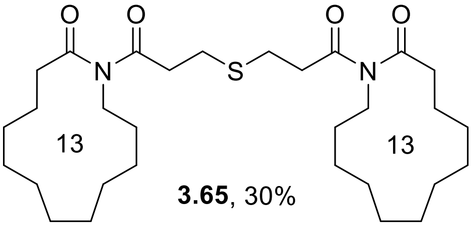
3.63

A mixture of laurolactam (198 mg, 1.00 mmol), DMAP (14.4 mg, 0.118 mmol) and pyridine (0.485 mL, 6.00 mmol) in DCM (10 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride **3.62** (3-(((9*H*-fluoren-9-yl)methyl)thio)propanoyl chloride) (1.50 mmol, prepared from 3-(((9*H*-fluoren-9-yl)methyl)thio)propanoic acid **3.59** using the general procedure) in DCM (10 mL) was added and the resulting mixture was heated at reflux at 50 °C for 18 h. Purification by flash column chromatography (SiO$_2$, 1:9 ethyl acetate: hexane → 1:3 ethyl acetate: hexane → 1:1 ethyl acetate: hexane → 3:1 ethyl acetate: hexane → ethyl acetate) afforded the *title compound* as a yellow-white solid (380 mg, 82%); R$_f$ 0.31 (1:4 ethyl acetate: hexane); m.p. 79–85 °C; ν_{max}/cm^{-1} (thin film) 2930, 2851, 1689, 1447, 1364, 1244, 1179, 1121, 907, 726, 647, 621, 580; δ_H (400 MHz, CDCl$_3$) 7.75 (2H, dt, *J* = 7.6, 1.0 Hz, Ar**H**), 7.68 (2H, dq, *J* = 7.4, 1.0 Hz, Ar**H**), 7.40 (2H, tt, *J* = 7.6, 1.0 Hz, Ar**H**), 7.32 (2H, td, *J* = 7.4, 1.0 Hz, Ar**H**), 4.12 (1H, t, *J* = 6.6 Hz, SCH$_2$C**H**), 3.70–3.62 (2H, m, C**H$_2$**N), 3.12–3.06 (4H, m, COC**H$_2$**CH$_2$S and SC**H$_2$**CH), 2.89 (4H, t, *J* = 7.1 Hz, COCH$_2$C**H$_2$**S), 2.60–2.52 (2H, m, C**H$_2$**CON), 1.82–1.73 (2H, m, C**H$_2$**), 1.70–1.61 (2H, m, C**H$_2$**), 1.50–1.24 (14H, m, 7 × C**H$_2$**); δ_C (100 MHz, CDCl$_3$) 176.8 (**C**ON), 174.8 (**C**OCH$_2$CH$_2$), 146.2 (2 × Ar**C**), 141.1 (2 × Ar**C**), 127.6 (2 × Ar**C**H), 127.1 (2 × Ar**C**H), 125.0 (2 × Ar**C**H), 119.9 (2 × Ar**C**H), 47.0 (SCH$_2$**C**H), 43.1 (**C**H$_2$N), 39.4 (CO**C**H$_2$CH$_2$S), 37.0 (S**C**H$_2$CH), 36.0 (**C**H$_2$CON),

28.4 (COCH$_2$**C**H$_2$S), 25.9 (**C**H$_2$), 25.8 (**C**H$_2$), 25.7 (**C**H$_2$), 24.9 (**C**H$_2$), 24.6 (**C**H$_2$), 24.5 (**C**H$_2$), 24.2 (**C**H$_2$), 24.0 (**C**H$_2$), 23.7 (**C**H$_2$); HRMS (ESI): calcd. for $C_{29}H_{38}NO_2S$, 464.2618. Found: $[MH]^+$, 464.2617 (0.2 ppm error).

Lab notebook reference: KP244

1,1'-(3,3'-Thiobis(propanoyl))bis(azacyclotridecan-2-one) (3.65)

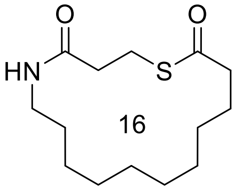


3.65, 30%

A mixture of laurolactam **1.210** (98.1 mg, 0.497 mmol), DMAP (7.4 mg, 0.061 mmol) and pyridine (0.243 mL, 3.00 mmol) in DCM (10 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride **3.62** (3-(((9*H*-fluoren-9-yl)methyl)thio)propanoyl chloride) (1.66 mmol, prepared from 3-(((9*H*-fluoren-9-yl)methyl)thio)propanoic acid **3.59** using the general procedure) in DCM (5 mL) was added and the resulting mixture was heated at reflux at 50 °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*. TLC analysis indicated that acylation was incomplete at this stage, therefore, an additional acylation reaction was performed. Thus, the reaction mixture was dissolved in DCM (15 mL) and to it was added DMAP (11.8 mg, 0.097 mmol) and pyridine (0.243 mL, 3.00 mmol). Then, another solution of acid chloride **3.62** (1.70 mmol, prepared from **3.59** using the general procedure) in DCM (15 mL) was added and the resulting mixture was heated at reflux at 50 °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*. The crude material was then re-dissolved in DCM (10 mL) and DBU (0.747 mL, 5.00 mmol) was added, followed by stirring at RT for 18 h, before the solvent was removed *in vacuo*. The crude product was dry loaded onto Celite and purified by automated flash column chromatography (using a 24 g pre-packed SiO_2 column, 0% → 100% ethyl acetate in hexanes) affording 17-membered ring thiolactone **3.29** (76.7 mg, 54%; for data see above) and the *title compound* **3.65** as a yellow crystalline solid (40.0 mg, 30%). Data for **3.65**: m.p. 53–59 °C; R_f 0.73 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 2928, 2860, 1689, 1463, 1446, 1363, 1243, 1179, 1121, 1099, 1047, 916, 732, 647; δ_H (400 MHz, $CDCl_3$) 3.70–3.62 (4H, m, C**H$_2$**N), 3.08 (4H, t, *J* = 7.2 Hz, C**H$_2$**), 2.83 (4H, t, *J* = 7.2 Hz, C**H$_2$**), 2.60–2.53 (4H, m, C**H**$_2$CON), 1.80–1.71 (4H, m, C**H**$_2$), 1.70–1.60 (4H, m, C**H**$_2$), 1.50–1.22 (28H, m, C**H**$_2$); δ_C (100 MHz, CDCl$_3$), 176.9 (2 × **C**ON), 174.9 (2 × **C**OCH$_2$CH$_2$), 43.2 (2 × **C**H$_2$N), 39.4 (2 × **C**H$_2$), 36.1 (2 × **C**H$_2$CON), 27.6 (2 × **C**H$_2$), 26.0 (2 × **C**H$_2$), 25.8 (2 × **C**H$_2$), 25.7 (2 × **C**H$_2$), 25.0 (2 × **C**H$_2$), 24.6 (4 × **C**H$_2$), 24.2 (2 × **C**H$_2$), 24.0 (2 × **C**H$_2$), 23.8 (2 × **C**H$_2$); HRMS (ESI): calcd. for $C_{30}H_{52}N_2NaO_4S$, 559.3540. Found: [MNa]$^+$, 559.3543 (–0.5 ppm error).

Lab notebook reference: KP255_A

1-Thia-5-azacyclohexadecane-4,16-dione (3.66)

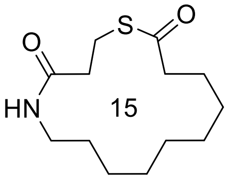


3.66

A mixture of azacyclododecan-2-one[48] (27.5 mg, 0.150 mmol), DMAP (1.8 mg, 0.015 mmol) and pyridine (73 µL, 0.900 mmol) in DCM (1 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride **3.62** (3-(((9*H*-fluoren-9-yl)methyl)thio)propanoyl chloride) (0.469 mmol, prepared from 3-(((9*H*-fluoren-9-yl)methyl)thio)propanoic acid **3.59** using the general procedure) in DCM (2 mL) was added and the resulting mixture was heated at reflux at 50 °C for 18 h. The mixture was then diluted with DCM (5 mL) and washed with 10% aq. HCl (5 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*. The mixture was then re-dissolved in DCM (3 mL) and DBU (0.220 mL, 1.50 mmol) was added, followed by stirring at RT for 18 h, before the solvent was removed under a flow of nitrogen gas. Purification by flash column chromatography (SiO$_2$, hexane → 1:19 ethyl acetate: hexane → 1:9 ethyl acetate: hexane → 1:2 ethyl acetate: hexane → 1:1 ethyl acetate: hexane → 2:1 ethyl acetate: hexane → ethyl acetate) afforded the *title compound* as a yellow crystalline solid (15.2 mg, 37%); m.p. 76–83 °C; R$_f$ 0.38 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3302, 2927, 2856, 1682, 1647, 1552, 1448, 1373, 1259, 1161, 1019, 733, 585; δ_H (400 MHz, CDCl$_3$) 5.53 (1H, br s, N**H**), 3.33–3.26 (2H, m, C**H**$_2$NH), 3.21–3.13 (2H, m, **C**H$_2$SCO), 2.58–2.53 (2H, m, C**H**$_2$COS), 2.52–2.47 (2H, m, COC**H**$_2$CH$_2$S), 1.74–1.66 (2H, m, C**H**$_2$), 1.54–1.46 (2H, m, C**H**$_2$), 1.36–1.27 (2H, m, 6 × C**H**$_2$); δ_C (100 MHz, CDCl$_3$) 200.8 (S**C**O), 170.6 (**C**O), 43.0 (**C**H$_2$COS), 39.3 (**C**H$_2$NH), 36.2 (CO**C**H$_2$CH$_2$S), 28.6 (**C**H$_2$), 27.4 (**C**H$_2$), 26.81 (**C**H$_2$), 26.79 (**C**H$_2$), 26.71 (**C**H$_2$), 26.4 (**C**H$_2$), 25.3 (**C**H$_2$), 25.2 (**C**H$_2$), 25.0 (**C**H$_2$); HRMS (ESI): calcd. for $C_{14}H_{25}NNaO_2S$, 294.1498. Found: [MNa]$^+$, 294.1499 (–0.4 ppm error).

Lab notebook reference: KP270/KP272

1-Thia-5-azacyclopentadecane-4,15-dione (3.67)

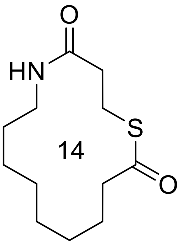


3.67

A mixture of azacycloundecan-2-one[48] (86.7 mg, 0.512 mmol), DMAP (6.8 mg, 0.056 mmol) and pyridine (0.243 mL, 3.00 mmol) in DCM (7 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride **3.62** (3-(((9*H*-fluoren-9-yl)methyl)thio)propanoyl chloride) (1.51 mmol, prepared from 3-(((9*H*-fluoren-9-yl)methyl)thio)propanoic acid **3.59** using the general procedure in DCM (3 mL) was added and the resulting mixture was heated at reflux 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*. TLC analysis indicated that acylation was complete at this stage. The crude material was then re-dissolved in DCM (10 mL) and DBU (0.747 mL, 5.00 mmol) was added, followed by stirring at RT for 18 h, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:9 ethyl acetate: hexane → 1:2 ethyl acetate: hexane → 2:1 ethyl acetate: hexane) afforded the *title compound* as a yellow crystalline solid (40.8 mg, 31%); m.p. 102–104 °C; R_f 0.34 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3299, 2928, 2856, 1680, 1646, 1552, 1442, 1398, 1355, 1258, 1202, 1140, 1008; δ_H (400 MHz, $CDCl_3$) 5.53 (1H, br s, $N\mathbf{H}$), 3.33–3.26 (2H, m, $C\mathbf{H_2}NH$), 3.17–3.12 (2H, m, $\mathbf{C}H_2SCO$), 2.58–2.51 (4H, m, $C\mathbf{H_2}COS$ and $COC\mathbf{H_2}CH_2S$), 1.73–1.64 (2H, m, $C\mathbf{H_2}$), 1.56–1.48 (2H, m, $C\mathbf{H_2}$), 1.42–1.22 (10H, m, 5 × $C\mathbf{H_2}$); δ_C (100 MHz, $CDCl_3$) 201.3 ($S\mathbf{C}O$), 170.6 ($\mathbf{C}O$), 43.1 ($\mathbf{C}H_2COS$), 38.7 ($\mathbf{C}H_2NH$), 35.3 ($CO\mathbf{C}H_2CH_2S$), 28.3 ($\mathbf{C}H_2$), 27.3 ($\mathbf{C}H_2$), 26.5 ($\mathbf{C}H_2$), 26.42 ($\mathbf{C}H_2$), 26.39 ($\mathbf{C}H_2$), 26.0 ($\mathbf{C}H_2$), 25.5 ($\mathbf{C}H_2$), 24.3 ($\mathbf{C}H_2$); HRMS (ESI): calcd. for $C_{13}H_{23}NNaO_2S$, 280.1342. Found: $[MNa]^+$, 280.1344 (–0.9 ppm error).

Lab notebook reference: KP276/KP278

1-Thia-5-azacyclotetradecane-4,14-dione (3.68)

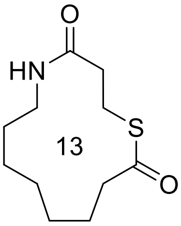


3.68

A mixture of azacyclodecan-2-one[48] (77.6 mg, 0.500 mmol), DMAP (6.4 mg, 0.052 mmol) and pyridine (0.243 mL, 3.00 mmol) in DCM (7 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride **3.62** (3-(((9*H*-fluoren-9-yl)methyl)thio)propanoyl chloride) (1.51 mmol, prepared from 3-(((9*H*-fluoren-9-yl)methyl)thio)propanoic acid **3.59** using the general procedure) in DCM (3 mL) was added and the resulting mixture was heated at reflux 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*. TLC analysis indicated that acylation was complete at this stage. The crude material was then re-dissolved in DCM (10 mL) and DBU (0.747 mL, 5.00 mmol) was added, followed by stirring at RT for 18 h, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, hexane → 1:19 ethyl acetate: hexane → 1:2 ethyl acetate: hexane → 2:1 ethyl acetate: hexane) afforded the *title compound* as a yellow crystalline solid (26.7 mg, 22%); m.p. 55–61 °C; R_f 0.31 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3304, 2929, 2858, 1679, 1649, 1551, 1444, 1376, 1258, 1168, 1043, 920, 731, 595; δ_H (400 MHz, $CDCl_3$) 5.69 (1H, br s, N**H**), 3.30–3.24 (2H, m, $C\mathbf{H_2}NH$), 3.20–3.14 (2H, m, $\mathbf{C}H_2SCO$), 2.58–2.52 (4H, m, 2 × $C\mathbf{H_2}$ ($C\mathbf{H_2}COS$ and $COC\mathbf{H_2}CH_2S$), 1.77–1.59 (4H, m, 2 × $C\mathbf{H_2}$), 1.47–1.31 (8H, m, 4 × $C\mathbf{H_2}$); δ_C (100 MHz, $CDCl_3$) 201.4 (S**C**O), 170.6 (**C**O), 43.9 ($\mathbf{C}H_2COS$), 39.1 ($\mathbf{C}H_2NH$), 35.5 ($CO\mathbf{C}H_2CH_2S$), 28.0 ($\mathbf{C}H_2$), 25.7 ($\mathbf{C}H_2$), 25.45 ($\mathbf{C}H_2$), 25.36 ($\mathbf{C}H_2$), 25.29 ($\mathbf{C}H_2$), 25.26 ($\mathbf{C}H_2$), 23.2 ($\mathbf{C}H_2$); HRMS (ESI): calcd. for $C_{12}H_{22}NO_2S$, 244.1366. Found: $[MH]^+$, 244.1362 (1.4 ppm error).

Lab notebook reference: KP277/KP279

1-Thia-5-azacyclotridecane-4,13-dione (3.69)

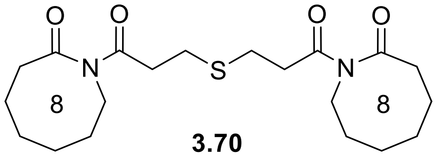


3.69

A mixture of azonan-2-one[48] (87.1 mg, 0.617 mmol), DMAP (8.5 mg, 0.070 mmol) and pyridine (0.243 mL, 3.00 mmol) in DCM (7 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride **3.62** (3-(((9*H*-fluoren-9-yl)methyl)thio)propanoyl chloride) (1.51 mmol, prepared from 3-(((9*H*-fluoren-9-yl)methyl)thio)propanoic acid **3.59** using the general procedure) in DCM (3 mL) was added and the resulting mixture was heated at reflux 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*. TLC analysis indicated that acylation was complete at this stage. The crude material was then re-dissolved in DCM (10 mL) and DBU (0.747 mL, 5.00 mmol) was added, followed by stirring at RT for 18 h, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:9 ethyl acetate: hexane → 1:2 ethyl acetate: hexane → 2:1 ethyl acetate: hexane → ethyl acetate) afforded the *title compound* as a yellow crystalline solid (66.9 mg, 47%); m.p. 129–131 °C; R_f 0.19 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3243, 3080, 2924, 2857, 1678, 1634, 1562, 1459, 1434, 901, 853, 802, 771, 731, 622, 604; δ_H (400 MHz, $CDCl_3$) 5.93 (1H, br s, N**H**), 3.27–3.20 (2H, m, C$\mathbf{H_2}$NH), 3.19–3.13 (2H, m, **C**H$_2$SCO), 2.65–2.56 (2H, m, COC$\mathbf{H_2}$CH$_2$S), 2.54–2.45 (2H, m, C$\mathbf{H_2}$COS), 1.78–1.67 (2H, m, C$\mathbf{H_2}$), 1.55–1.47 (2H, m, C$\mathbf{H_2}$), 1.39 (2H, apparent p, *J* = 6.5 Hz, C$\mathbf{H_2}$), 1.34–1.25 (4H, m, 2 × C$\mathbf{H_2}$); δ_C (100 MHz, $CDCl_3$) 201.6 (S**C**O), 170.3 (**C**O), 44.3 (**C**H$_2$COS), 39.6 (**C**H$_2$NH), 35.6 (CO**C**H$_2$CH$_2$S), 27.9 (**C**H$_2$), 27.4 (2 × **C**H$_2$), 25.5 (**C**H$_2$), 25.1 (**C**H$_2$), 24.5 (**C**H$_2$); HRMS (ESI): calcd. for $C_{11}H_{20}NO_2S$, 230.1209. Found: $[MH]^+$, 230.1209 (0.1 ppm error).

Lab notebook reference: KP284/KP286

1,1'-(3,3'-Thiobis(propanoyl))bis(azocan-2-one) (3.70)



3.70

A mixture of azocan-2-one **1.218** (63.7 mg, 0.501 mmol), DMAP (7.5 mg, 0.061 mmol) and pyridine (0.240 mL, 2.97 mmol) in DCM (5 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride **3.62** (3-(((9*H*-fluoren-9-yl)methyl)thio)propanoyl chloride) (1.50 mmol, prepared from 3-(((9*H*-fluoren-9-yl)methyl)thio)propanoic acid **3.59** using the general procedure) in DCM (10 mL) was added and the resulting mixture was heated to reflux at 40 °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 (10 mL) and DBU (0.747 mL, 5.00 mmol) was added, followed by stirring at RT for 18 h, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:9 ethyl acetate: hexane → 1:2 ethyl acetate: hexane → 1:1 ethyl acetate: hexane → 2:1 ethyl acetate: hexane) afforded the *title compound* **3.70** as an orange oil (42.9 mg, 43%), along with **3.23** (16.2 mg, 15%); Data for **3.70**: R_f 0.66 (1:9 ethyl acetate: methanol); ν_{max}/cm^{-1} (thin film) 2928, 2859, 1689, 1447, 1378, 1245, 1176, 1127, 1092, 738); δ_H (400 MHz, $CDCl_3$) 3.96 – 3.86 (4H, m, 2 × C**H₂**N), 3.18 (4H, t, *J* = 7.2 Hz, 2 × COC**H₂**CH₂S), 2.84 (4H, t, *J* = 7.2 Hz, 2 × COCH₂C**H₂**S), 2.69 – 2.60 (4H, m, 2 × C**H₂**CON), 1.92 – 1.81 (4H, m, 2 × C**H₂**), 1.70 (4H, p, *J* = 6.1 Hz, 2 × C**H₂**), 1.62 – 1.56 (4H, m, 2 × C**H₂**), 1.49 – 1.41 (4H, m, 2 × C**H₂**); δ_C (100 MHz, $CDCl_3$) 178.4 (2C, 2 × **C**ON), 175.2 (2C, 2 × **C**OCH₂CH₂), 43.6 (2C, 2 × CH₂N), 40.1 (2C, 2 × CO**C**H₂CH₂S), 37.2 (2C, 2 × **C**H₂CON), 29.6 (2C, 2 × **C**H₂), 29.2 (2C, 2 × **C**H₂), 27.5 (2C, 2 × COCH₂**C**H₂S), 26.3 (2C, 2 × **C**H₂), 24.1 (2C, 2 × **C**H₂); HRMS (ESI): calcd. for $C_{20}H_{33}N_2O_4S$, 397.2156. Found: $[MH]^+$, 397.2155 (0.1 ppm error).

Lab notebook reference: KP287_A/KP268_A

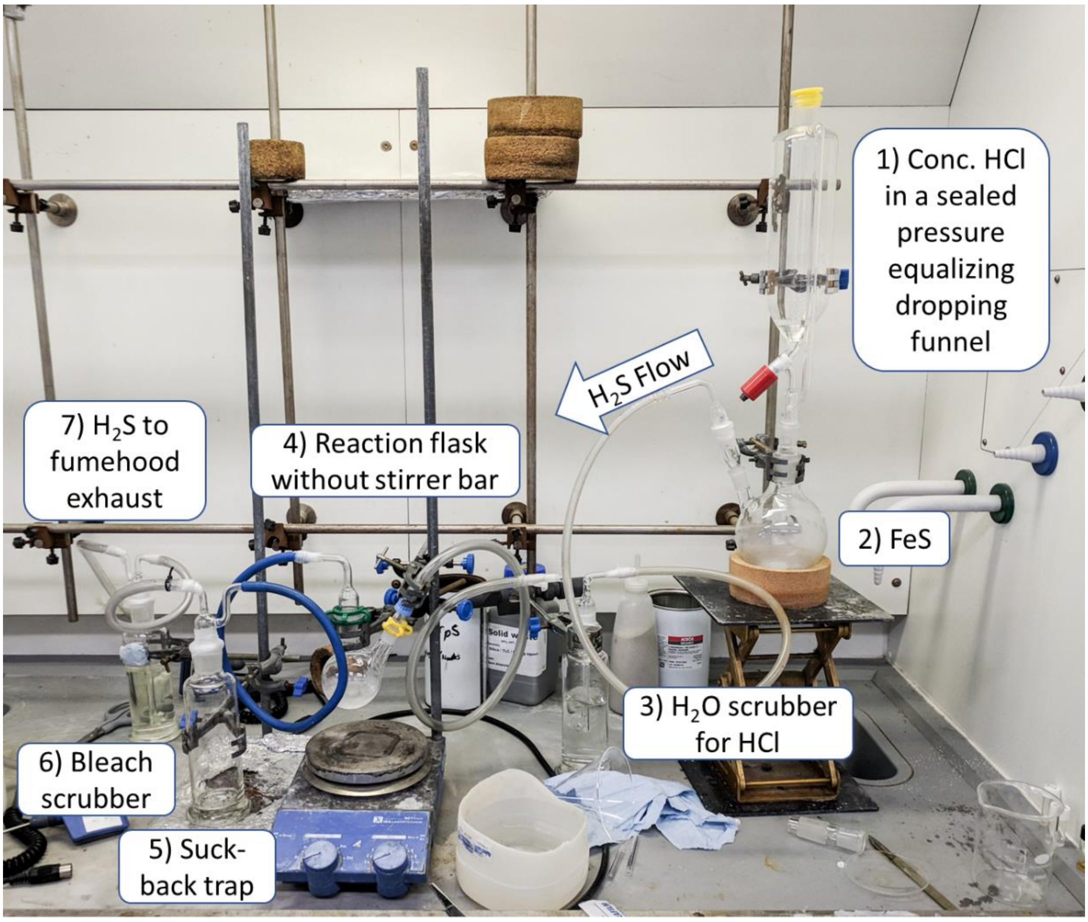
The same product **3.70** was also prepared as the major side product isolated from a conjugate addition reaction using **4.37** in DCM with $H_2S_{(g)}$. Set up of the apparatus is described following the experimental protocol below.

To a two necked round bottomed flask was added 1-acryloylazocan-2-one **4.37** (116 mg, 0.638 mmol), DBU (0.954 mL, 6.38 mmol), and DCM (12.8 mL). H_2S gas was bubbled through this mixture for 1 h, with no additional stirring. After 5 min, the reaction mixture turned a turbid yellow. Then, N_2 was bubbled through the reaction mixture for 2 h to remove H_2S, where a white precipitate had formed. To the crude reaction mixture was added DCM (10 mL) and with 10% aq. HCl (10 mL). The aqueous layer was then extracted with DCM (3 × 10 mL) and the combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*.

Purification by flash column chromatography (SiO_2, 1:9 ethyl acetate: hexane → 1:2 ethyl acetate: hexane → ethyl acetate → 1:19 methanol: ethyl acetate) afforded the *title compound* **3.70** (68.6 mg, 54%), along with trace **3.23** (4.4 mg, 3%) and **3.21** (2.1 mg, 2%).

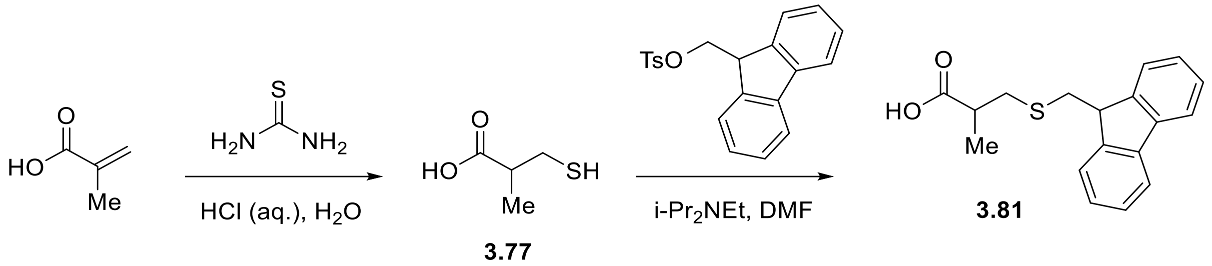
An H_2S gas generator was assembled as shown in Figure 4.1 in Chapter 4 (also reproduced below): Concentrated HCl was added dropwise to a flask containing FeS, using a sealed pressure equalizing dropping funnel. The H_2S gas generated was bubbled through a Drechsel bottle filled with deionized water to remove any HCl, and bubbled through a pipette into the reaction flask, attached through a thermometer adaptor. The off gas from the reaction flask was passed through an empty Drechsel bottle, which acted as a suck-back trap. This was then passed through a third Drechsel bottle filled with bleach solution, and the exhaust pipe was fixed to the back of the fumehood exhaust. To stop the reaction, the dropping funnel was closed and the tubing was purged with air. All of the apparatus was left in the fumehood overnight with each component then rinsed in a container of bleach.

Lab notebook reference: KP550



Setup of H_2S gas generator for attempted conjugate addition ring expansion.

3-(((9*H*-Fluoren-9-yl)methyl)thio)-2-methylpropanoic acid (3.81)

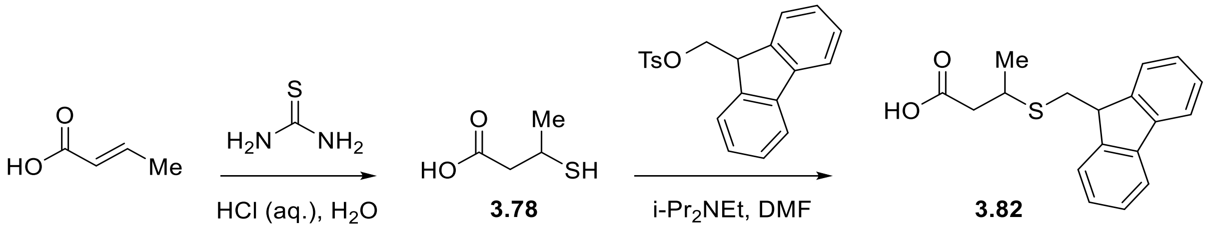


A solution of thiourea (2.65 g, 34.5 mmol), water (5 mL), and concentrated aq. HCl (37%, 3.16 mL) was stirred at 45 °C for 30 min. To this was added methacrylic acid (2.50 g, 2.46 mL) dropwise over 30 min and the temperature was then raised to 90 °C for 2 h with stirring. An aqueous solution of NaOH (4.03 g in 5 mL H_2O) was prepared and added dropwise over 30 min. The reaction mixture was stirred for 30 min and allowed to cool to RT. Concentrated HCl was added to adjust the pH to 5–6 and the reaction mixture extracted using ethyl acetate (3 × 10 mL). The combined organic fractions were collected and the solvent removed *in vacuo* to afford *3-mercapto-2-methylpropanoic acid* **3.77** as a yellow oil which was used without further purification (559 mg, 16%). [Data for *3-mercapto-2-methylpropanoic acid*: R_f 0.47 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 2976, 2936, 1701, 1622, 1461, 1412, 1236, 1185, 1118, 1075, 918, 831, 620, 525; δ_H (400 MHz, $CDCl_3$) 12.04 (1H, s, COO**H**), 2.81–2.56 (3H, m, C**H** and C**H₂**), 1.55 (1H, t, *J* = 8.5 Hz, S**H**), 1.25 (3H, d, *J* = 6.8 Hz, C**H₃**); δ_C (100 MHz, $CDCl_3$) 181.5 (**C**OOH), 43.5 (**C**H), 27.5 (**C**H₂), 16.3 (**C**H₃); HRMS (ESI): calcd. for $C_4H_7O_2S$, 119.0172 Found: $[M-H]^-$, 119.0170 (1.6 ppm error)]. To a solution of 3-mercapto-2-methylpropanoic acid (457 mg, 3.81 mmol) and fluorenyl methanol p-toluenesulfonate **3.58** (1.41 g, 4.02 mmol- see **3.59** for its preparation) in DMF (7 mL) was added $^iPr_2NEt$ (1.39 mL, 8.00 mmol). The reaction was stirred at room temperature for 25 h. The reaction mixture was dissolved in ethyl acetate (40 mL), washed with 0.2 N aq. HCl (5 × 15 mL), sat. aq. $NaHCO_3$ (2 × 15 mL), water (15 mL), brine (15 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the crude material was then suspended in chloroform and filtered to remove insoluble material (2 × 10 mL). The combined chloroform fractions were concentrated and solvent removed *in vacuo* to afford the *title compound* **3.81** as an orange solid (637 mg, 56%); R_f 0.40 (ethyl acetate); m.p. 59–70 °C; ν_{max}/cm^{-1} (thin film) 2933, 1704, 1610, 1477, 1448, 1294, 1232, 1101, 1006, 919, 765, 734, 621; δ_H (400 MHz, $CDCl_3$) 7.81–7.61 (4H, m, Ar**H**), 7.44–7.27 (4H, m, Ar**H**), 4.10 (1H, t, *J* = 6.5 Hz, SCH_2C**H**), 3.14–3.02 (2H, m, SC**H₂**CH), 2.89 (1H, dd, *J* = 12.8, 6.8 Hz, $CH(CH_3)$CH**H’**), 2.69 (1H, apparent sextet, *J* = 6.9 Hz, C**H**(CH_3)CHH’), 2.60 (1H, dd, *J* = 12.8, 6.8 Hz, $CH(CH_3)$C**H**H’), 1.25 (3H, d, *J* = 6.9 Hz, C**H₃**); δ_C (100 MHz, $CDCl_3$) 181.1 (**C**OOH), 146.1 (2 × Ar**C**), 141.1 (2 × Ar**C**), 127.7 (2 × Ar**C**H), 127.1 (2 × Ar**C**H), 125.0 (Ar**C**H), 124.9 (Ar**C**H), 120.0 (2 × Ar**C**H), 47.0 (SCH_2**C**H), 40.2 ((**C**H$(CH_3)CH_2$),), 37.2 (S**C**H₂CH), 36.3 ($CH(CH_3)$**C**H₂), 16.7 (**C**H₃); HRMS (ESI): calcd. for

$C_{18}H_{18}NaO_2S$, 321.0920. Found: [MNa]$^+$, 321.0917 (1.0 ppm error). The synthetic procedure was adapted from a method reported in a patent.[103]

Lab notebook reference: KP271/KP275

3-(((9*H*-Fluoren-9-yl)methyl)thio)-butanoic acid (3.82)

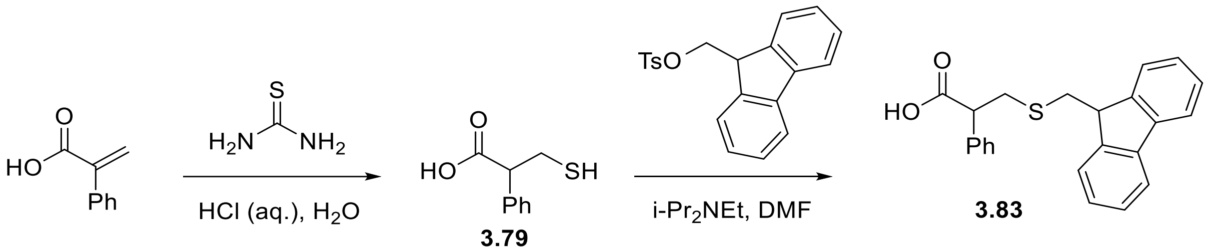


A solution of thiourea (1.75 g, 23.0 mmol), water (25 mL), and concentrated HCl (37%, 15.8 mL) was stirred at 45 °C for 30 min. To this was added crotonoic acid (12.5 g, 145 mmol) and the temperature was then raised to 90 °C for 2 h. An aqueous solution of NaOH (20 g in 25 mL of H_2O) was prepared and added dropwise over 30 min. The reaction mixture was stirred for 30 min and allowed to cool to RT. Concentrated aq. HCl was added to adjust the pH to 5–6 and the reaction mixture extracted using ethyl acetate (3 × 50 mL). The combined organic fractions were collected, and the solvent removed *in vacuo* to afford *3-mercapto-butanoic acid* **3.78** as a yellow oil which was used without further purification (14.6 g, 84%) [Data for *3-mercapto-butanoic* acid: R_f 0.33 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 2969, 2926, 1704, 1408, 1380, 1296, 1263, 1228, 1176, 1115, 1086, 1028, 917, 886, 691, 642, 488; δ_H (400 MHz, $CDCl_3$) 10.47 (1H, s, COO**H**), 3.42–3.29 (1H, m, C**H**), 2.72–2.57 (2H, m, C**H$_2$**), 1.86 (1H, t, *J* = 6.9 Hz, S**H**), 1.39 (3H, d, *J* = 6.9 Hz, C**H$_3$**); δ_C (100 MHz, $CDCl_3$) 177.5 (**C**OOH), 45.7 (**C**H$_2$), 31.0 (**C**H), 24.9 (**C**H$_3$); HRMS (ESI): calcd. for $C_4H_7O_2S$, 119.0172 Found: [M-H]$^-$, 119.0171 (1.1 ppm error)]. To a solution of 3-mercapto-butanoic acid (484 mg, 4.03 mmol) and fluorenyl methanol p-toluenesulfonate **3.58** (1.40 g, 4.03 mmol- see **3.59** for its preparation) in DMF (7.0 mL) was added $^iPr_2NEt$ (1.39 mL, 8.06 mmol). The reaction was stirred at room temperature for 17 h. The reaction mixture was dissolved in ethyl acetate (40 mL), washed with 0.2 N aq. HCl (5 × 15 mL), sat. aq. $NaHCO_3$ (2 × 15 mL), water (15 mL), brine (15 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to afford the *title compound* **3.82** as a yellow solid (582 mg, 48%); R_f 0.51 (ethyl acetate); m.p. 140–152 °C; ν_{max}/cm^{-1} (thin film) 2916, 1706, 1477, 1447, 1374, 1293, 1241, 1166, 1100, 1021, 938, 726, 637, 621, 571; δ_H (400 MHz, $CDCl_3$) 7.77–7.64 (4H, m, Ar**H**), 7.43–7.27 (4H, m, Ar**H**), 4.11 (1H, t, *J* = 6.6 Hz, SCH$_2$C**H**), 3.29–3.18 (1H, m, CHH'C**H**(CH$_3$)), 3.10 (2H, d, *J* = 6.6 Hz, SC**H$_2$**CH), 2.67 (1H, dd, *J* = 15.9, 6.4 Hz, CH**H'**CH(CH$_3$)), 2.51 (1H, dd, *J* = 15.9, 8.0 Hz, C**H**H'CH(CH$_3$)), 1.34 (3H, d, *J* = 6.8 Hz, C**H$_3$**); δ_C (100 MHz, $CDCl_3$) 176.0 (**C**OOH), 146.1 (2 × Ar**C**), 141.1 (2 × Ar**C**), 127.7 (2 × Ar**C**H), 127.2

(2 × Ar**C**H), 125.00 (Ar**C**H), 124.97 (Ar**C**H), 120.0 (2 × Ar**C**H), 47.0 (SCH_2**C**H), 42.0 (**C**$H_2CH(CH_3)$), 37.2 (CH_2**C**$H(CH_3)$), 35.4 (S**C**H_2CH), 21.6 (**C**H_3); HRMS (ESI): calcd. for $C_{18}H_{18}NaO_2S$, 321.0920. Found: $[MNa]^+$, 321.0926 (–2.0 ppm error). The synthetic procedure was adapted from a method reported in a patent.[103]

Lab notebook reference: KP294/KP299

3-(((9*H*-Fluoren-9-yl)methyl)thio)-2-phenylpropanoic acid (3.83)

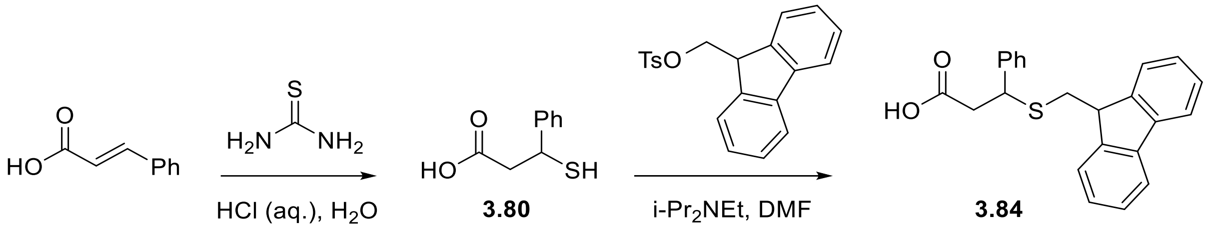


A solution of thiourea (13.3 g, 174 mmol), water (25 mL), and concentrated aq. HCl (37%, 15.8 mL) was stirred at 45 °C for 30 min. To this was added atropic acid (2.96 g, 30.0 mmol) and the temperature was then raised to 90 °C for 2 h. An aqueous solution of NaOH (20.0 g in 25 mL of H_2O) was prepared and added dropwise over 30 min. The reaction mixture was stirred for 30 min and allowed to cool to RT. Concentrated HCl was added to adjust the pH to 5–6 and the reaction mixture extracted using ethyl acetate (3 × 50 mL). The combined organic fractions were collected and the solvent removed *in vacuo* to afford *3-mercapto-2-phenylpropanoic acid* **3.79** as a white paste which was used without further purification (3.72 g, 70%) [Data for *3-mercapto-2-phenylpropanoic acid*: R_f 0.37 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3019, 2259, 1705, 1601, 1496, 1455, 1419, 1277, 1242, 1180, 1005, 924, 717, 697, 645, 615, 503; δ_H (400 MHz, $CDCl_3$) 9.81 (1H, s, COO**H**), 7.40 – 7.22 (5H, m, Ar**H**), 3.77 (1H, dd, *J* = 9.0, 6.4 Hz, C**H**), 3.15 (1H, dt, *J* = 13.8, 9.0 Hz, CHC**H**H'SH), 2.84 (1H, ddd, *J* = 13.8, 7.9, 6.4 Hz, CHCH**H'**SH), 1.54 (1H, dd, *J* = 9.0, 7.9 Hz, S**H**); δ_C (100 MHz, $CDCl_3$) 178.2 (**C**OOH), 136.9 (Ar**C**), 129.1 (2 × Ar**C**H), 128.3 (Ar**C**H), 128.1 (2 × Ar**C**H), 55.8 (**C**H), 27.2 (**C**H_2); HRMS (ESI): calcd. for $C_9H_9O_2S$, 181.0329 Found: $[M-H]^-$, 181.0324 (2.4 ppm error)]. To a solution of 3-mercapto-2-phenylpropanoic acid (1.46 g, 8.00 mmol) and fluorenyl methanol p-toluenesulfonate **3.58** (2.82 g, 8.04 mmol- see **3.59** for its preparation) in DMF (14 mL) was added $^iPr_2NEt$ (2.78 mL, 16.0 mmol). The reaction was stirred at room temperature for 16 h. The reaction mixture was dissolved in ethyl acetate (80 mL), washed with 0.2N HCl (5 × 30 mL), sat. $NaHCO_3$ (2 × 30 mL), water (30 mL), brine (30 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The combined organics were concentrated and solvent removed *in vacuo* to afford the *title compound* as a yellow solid (1.93 g, 67%); R_f 0.45

(ethyl acetate); m.p. 69–85 °C; ν_{max}/cm^{-1} (thin film) 3052, 1714, 1611, 1450, 1012, 736; δ_H (400 MHz, $CDCl_3$) 7.73 (2H, dt, *J* = 7.5, 0.9 Hz, Ar**H**), 7.61 (2H, ddt, *J* = 13.8, 7.5, 0.9 Hz, Ar**H**), 7.44–7.24 (9H, m, Ar**H**), 4.04 (1H, t, *J* = 6.6 Hz, SCH_2C**H**), 3.77 (1H, dd, *J* = 8.9, 6.4 Hz, C**H**(Ph)CHH'), 3.23 (1H, dd, *J* = 13.3, 8.9 Hz, CH(Ph)C**H**H'), 3.06–2.95 (2H, m, SC**H₂**CH), 2.88 (1H, dd, *J* = 13.3, 6.4 Hz, CH(Ph)CH**H'**); δ_C (100 MHz, $CDCl_3$) 177.7 (**C**OOH), 146.1 (Ar**C**), 146.0 (Ar**C**), 141.1 (2 × Ar**C**), 137.4 (Ar**C**), 129.0 (2 × Ar**C**H), 128.1 (3 × Ar**C**H), 127.7 (2 × Ar**C**H), 127.2 (Ar**C**H), 127.1 (Ar**C**H), 125.0 (2 × Ar**C**H), 120.0 (2 × Ar**C**H), 52.5 ((**C**H(Ph)CH_2), 46.9 (SCH_2**C**H), 37.3 (S**C**H_2CH), 36.0 (CH(Ph)**C**H_2); HRMS (ESI): calcd. for $C_{23}H_{19}O_2S$, 359.1111. Found: $[M\text{-}H]^-$, 359.1118 (–1.9 ppm error). The synthetic procedure was adapted from a method reported in a patent.[103]

Lab notebook reference: KP292/KP305

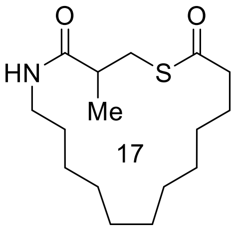
3-(((9*H*-Fluoren-9-yl)methyl)thio)-3-phenylpropanoic acid (3.84)



A solution of thiourea (12.2 g, 160 mmol), water (80 mL), and concentrated aq. HCl (37%, 70.4 mL) was stirred at 120 °C for 2 h. The reaction mixture was then cooled to RT. *Trans*-cinnamic acid (5.92 g, 40 mmol) was added and the temperature was then raised back to 120 °C and stirred for 18 h, before the reaction mixture was then cooled to 0 °C. An aqueous solution of NaOH (62.6 g in 244 mL H_2O) was prepared and added dropwise at 0 °C until the pH was 14. The reaction mixture was stirred and heated to 90 °C for 1.5 h and then was cooled to 0 °C. Concentrated aq. HCl was added to adjust the pH to 5–6 and the reaction mixture extracted using toluene (3 × 100 mL). The combined organic fractions were collected, washed with water (300 mL), dried over anhydrous $MgSO_4$, filtered, and the solvent removed *in vacuo* to afford a sample that is predominantly made up of *3-mercapto-3-phenylpropanoic acid* **3.80**, contaminated with a small amount (*ca.* 20%) *trans*-cinnamic acid, as a white solid, with this mixture was used without further purification (5.21 g of material isolated). [Data for *3-mercapto-3-phenylpropanoic acid*: R_f 0.33 (ethyl acetate); δ_H (400 MHz, $CDCl_3$) 11.21 (1H, s, COO**H**), 7.40 – 7.17 (5H, m, Ar**H**), 4.50 (1H, ddd, *J* = 8.0, 7.0, 6.1 Hz, C**H**), 3.10 – 3.05 (2H, m, C**H₂**), 2.30 (1H, t, *J* = 6.1 Hz, S**H**); HRMS (ESI): calcd. for $C_9H_9O_2S$, 181.0329 Found: $[M\text{-}H]^-$, 181.0329 (1.1 ppm error)]. To a portion of this mixture (calculated to contain 1.19 g, 6.54 mmol, of 3-mercapto-3-phenylpropanoic acid) and fluorenyl methanol p-toluenesulfonate **3.58** (2.33 g, 6.64 mmol- see **3.59** for its preparation) in DMF (12 mL) was added $^{i}Pr_2NEt$ (2.31 mL, 13.3 mmol). The reaction was stirred at room temperature for 72 h. The reaction mixture was dissolved in ethyl acetate (65 mL), washed with 0.2N aq. HCl (5 × 25 mL), sat. aq. $NaHCO_3$ (2 × 25 mL), water (25 mL), brine (25 mL) and dried over anhydrous Na_2SO_4. The combined organics were concentrated and solvent removed *in vacuo* to afford the *title compound* **3.84** as a light orange solid (1.63 g, 69%); R_f 0.48 (ethyl acetate); m.p. 126–140 °C; ν_{max}/cm^{-1} (thin film) 3031, 1704, 1448, 1297, 1153, 918, 733, 698, 666, 621, 528; δ_H (400 MHz, $CDCl_3$) 7.77–7.69 (2H, m, Ar**H**), 7.65 (1H, d, *J* = 7.6 Hz, Ar**H**), 7.43–7.21 (10H, m, Ar**H**), 4.38 (1H, t, *J* = 7.6 Hz, SCH$_2$C**H**), 3.94 (1H, dd, *J* = 6.7 Hz, CHH’C**H**(Ph)), 2.95–2.87 (3H, m, SC**H$_2$**CH and C**H**H’CH(Ph)), 2.73 (1H, dd, *J* = 13.0, 7.3 Hz, CH**H’**CH(Ph)); δ_C (100 MHz, $CDCl_3$) 176.4 (**C**OOH), 146.1 (Ar**C**), 146.0 (Ar**C**), 141.1 (3 × Ar**C**), 128.9 (2 × ArCH), 128.0 (2 × Ar**C**H), 127.9 (Ar**C**H), 127.64 (Ar**C**H), 127.60 (Ar**C**H), 127.1 (2 × Ar**C**H), 125.1 (Ar**C**H), 124.8 (Ar**C**H), 119.9 (2 × Ar**C**H), 46.4 (CH$_2$**C**H(Ph)), 45.6 (SCH$_2$**C**H), 41.4 (S**C**H$_2$CH), 35.5 (**C**H$_2$CH(Ph)); HRMS (ESI): calcd. for $C_{23}H_{20}NaO_2S$, 383.1076. Found: [MNa]$^+$, 383.1077 (–0.2 ppm error). The synthetic procedure was adapted from a method reported in a patent.[104]

Lab notebook reference: KP318/KP320

3-Methyl-1-thia-5-azacycloheptadecane-4,17-dione (3.85)

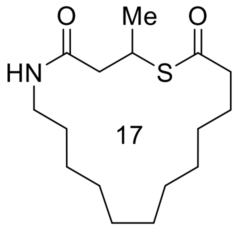


3.85

A mixture of laurolactam **1.210** (98.5 mg, 0.499 mmol), DMAP (6.1 mg, 0.050 mmol) and pyridine (0.243 mL, 3.00 mmol) in DCM (7 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of 3-(((9*H*-fluoren-9-yl)methyl)thio)-2-methylpropanoyl chloride (1.50 mmol, prepared from 3-(((9*H*-fluoren-9-yl)methyl)thio)-2-methylpropanoic acid **3.81** using the general procedure) in DCM (3 mL) was added and the resulting mixture was heated at reflux 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*. TLC analysis indicated that acylation was complete at this stage. The crude material was then re-dissolved in DCM (10 mL) and DBU (0.747 mL, 5.00 mmol) was added, followed by stirring at RT for 18 h, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, hexane → 1:19 ethyl acetate: hexane → 1:2 ethyl acetate: hexane → 1:1 ethyl acetate: hexane → 2:1 ethyl acetate: hexane) afforded the *title compound* as a yellow crystalline solid (86.7 mg, 58%); m.p. 73–80 °C; R$_f$ 0.53 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3297, 2927, 2856, 1684, 1643, 1549, 1456, 1367, 1248, 1189, 1122, 1028, 947, 732; δ_H (400 MHz, CDCl$_3$) 5.74 (1H, br s, N**H**), 3.62–3.52 (1H, m, C**H**H'NH), 3.06–2.91 (3H, m, CH**H'**NH and C**H**$_2$SCO)), 2.62–2.36 (3H, m, COC**H**(CH$_3$)CH$_2$S and C**H$_2$**COS), 1.76–1.50 (3H, m, 1.5 × C**H$_2$**), 1.45–1.24 (15H, m, 7.5 × C**H$_2$**), 1.21 (3H, d, *J* = 6.9 Hz, C**H$_3$**); δ_C (100 MHz, CDCl$_3$) 201.1 (S**C**O), 174.3 (**C**O), 43.7 (**C**H$_2$COS), 42.2 (CO**C**H(CH$_3$)CH$_2$S), 39.4 (**C**H$_2$NH), 32.7 (**C**H$_2$SCO), 28.9 (**C**H$_2$), 27.50 (**C**H$_2$), 27.47 (**C**H$_2$), 27.3 (**C**H$_2$), 27.1 (**C**H$_2$), 27.0 (**C**H$_2$), 26.4 (**C**H$_2$), 25.3 (**C**H$_2$), 25.2 (**C**H$_2$), 18.3 (**C**H$_3$); HRMS (ESI): calcd. for C$_{16}$H$_{29}$NNaO$_2$S, 322.1811. Found: [MNa]$^+$, 322.1808 (1.0 ppm error).

Lab notebook reference: KP281

2-Methyl-1-thia-5-azacycloheptadecane-4,17-dione (3.86)



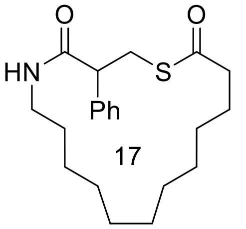
3.86

A mixture of laurolactam **1.210** (98.6 mg, 0.500 mmol), DMAP (6.2 mg, 0.051 mmol) and pyridine (0.243 mL, 3.00 mmol) in DCM (7 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of 3-(((9*H*-fluoren-9-yl)methyl)thio)-butanoyl chloride (1.50 mmol, prepared from 3-(((9*H*-fluoren-9-yl)methyl)thio)-butanoic acid **3.82** using the general procedure) in DCM (3 mL) was added and the resulting mixture was heated at reflux 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*. TLC analysis indicated that acylation was complete at this stage. The crude material was then re-dissolved in DCM (10 mL) and DBU (0.747 mL, 5.00 mmol) was added, followed by stirring at RT for 18 h, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO$_2$, hexane → 1:19 ethyl acetate: hexane → 1:2 ethyl acetate: hexane → 1:1 ethyl acetate: hexane → 2:1 ethyl acetate: hexane) afforded the *title compound* as a yellow crystalline solid (87.2 mg, 58%); m.p. 54–56 °C; R$_f$ 0.48 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3299, 2926, 2856, 1683, 1645, 1553, 1447, 1373, 1291, 1118, 1020, 732; δ_H (400 MHz, CDCl$_3$) 5.86 (1H, br s, N**H**), 3.90–3.80 (1H, m, COCH$_2$C**H**(CH$_3$)S), 3.38–3.16 (2H, m, C**H$_2$**NH), 2.62–2.41 (4H, m, 2 × C**H$_2$** (C**H$_2$**CON and C**H**$_2$COS)), 1.78–1.55 (3H, m, 1.5 × C**H$_2$**), 1.54–1.45

(2H, m, C**H₂**), 1.42 (3H, d, *J* = 7.0 Hz, C**H₃**), 1.40–1.22 (13H, m, 6.5 × C**H₂**); δ$_C$ (100 MHz, CDCl$_3$) 200.5 (**C**OS), 170.3 (**C**ON), 43.9 (**C**H$_2$CO), 43.7 (**C**H$_2$CO), 39.4 (**C**H$_2$NH), 37.0 (COCH$_2$**C**H(CH$_3$)S), 29.0 (**C**H$_2$), 27.6 (**C**H$_2$), 27.4 (**C**H$_2$), 27.1 (**C**H$_2$), 26.99 (**C**H$_2$), 26.97 (**C**H$_2$), 26.4 (**C**H$_2$), 25.5 (**C**H$_2$), 24.6 (**C**H$_2$), 21.8 (**C**H$_3$); HRMS (ESI): calcd. for $C_{16}H_{29}NNaO_2S$, 322.1811. Found: [MNa]$^+$, 322.1812 (–0.2 ppm error).

Lab notebook reference: KP321/KP322

3-Phenyl-1-thia-5-azacycloheptadecane-4,17-dione (3.87)

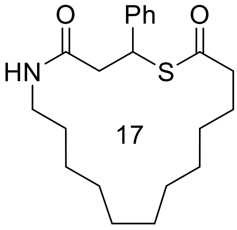


3.87

A mixture of laurolactam **1.210** (99.3 mg, 0.503 mmol), DMAP (8.0 mg, 0.066 mmol) and pyridine (0.243 mL, 3.00 mmol) in DCM (7 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of 3-(((9*H*-fluoren-9-yl)methyl)thio)-2-phenylpropanoyl chloride (1.50 mmol, prepared from 3-(((9*H*-fluoren-9-yl)methyl)thio)-2-phenylpropanoic **3.83** using the general procedure) in DCM (3 mL) was added and the resulting mixture was heated at reflux 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*. TLC analysis indicated that acylation was complete at this stage. The crude material was then re-dissolved in DCM (10 mL) and DBU (0.747 mL, 5.00 mmol) was added, followed by stirring at RT for 18 h, before the solvent was removed *in vacuo*. Purification by repeated flash column chromatography (SiO$_2$, hexane → 1:19 ethyl acetate: hexane → 1:9 ethyl acetate: hexane → 1:4 ethyl acetate: hexane → 1:2 ethyl acetate: hexane → 1:1 ethyl acetate: hexane → ethyl acetate) afforded the *title compound* as a yellow solid (52.5 mg, 29%); m.p. 82–86 °C; R$_f$ 0.73 (ethyl acetate); ν$_{max}$/cm^{-1} (thin film) 3301, 3063, 2927, 2856, 1682, 1647, 1548, 1495, 1450, 1393, 1353, 1243, 1187, 1030, 909, 760, 729, 697; δ$_H$ (400 MHz, CDCl$_3$) 7.42–7.26 (5H, m , Ar**H**), 5.46 (1H, br d, *J* = 8.3 Hz, N**H**), 3.75 (1H, dddd, *J* = 13.3, 8.3, 8.3, 3.4 Hz, C**H**H'NH), 3.58 (1H, dd, *J* = 9.2, 5.4 Hz, COC**H**(Ph)CH$_2$S), 3.31–3.26 (2H, m, C**H₂**SCO), 2.84–2.74 (1H, m, CH**H'**NH), 2.64 (1H, ddd, *J* = 14.2, 8.7, 5.4, C**H**H'COS), 2.50 (1H, ddd, *J* = 14.2, 7.2, 5.4, CH**H'**COS), 1.84–1.71 (2H, m, C**H₂**), 1.70–1.52 (2H, m, C**H₂**), 1.45–1.21 (14H, m, 7 × C**H₂**); δ$_C$ (100 MHz, CDCl$_3$) 201.3 (**C**OS), 171.5 (**C**ON), 139.3 (Ar**C**), 129.0 (2 × Ar**C**H), 127.8 (Ar**C**H), 127.7 (2 × Ar**C**H), 53.5 (CO**C**H(Ph)CH$_2$S), 43.8 (**C**H$_2$COS), 39.5 (**C**H$_2$NH), 32.6 (**C**H$_2$SCO), 29.1 (**C**H$_2$), 27.8 (**C**H$_2$), 27.51 (**C**H$_2$), 27.49 (2 × **C**H$_2$), 27.46 (**C**H$_2$), 26.5 (**C**H$_2$), 25.7 (**C**H$_2$), 25.1 (**C**H$_2$); HRMS (ESI): calcd. for $C_{21}H_{31}NNaO_2S$, 384.1968. Found: [MNa]$^+$, 384.1970 (–0.5 ppm error).

Lab notebook reference: KP316/KP317

2-Phenyl-1-thia-5-azacycloheptadecane-4,17-dione (3.88)

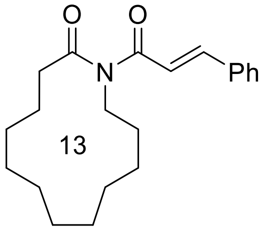


3.88

A mixture of laurolactam **1.210** (156 mg, 0.792 mmol), DMAP (10.5 mg, 0.086 mmol) and pyridine (0.364 mL, 4.50 mmol) in DCM (10 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of 3-(((9*H*-fluoren-9-yl)methyl)thio)-3-phenylpropanoyl chloride (2.25 mmol, prepared from 3-(((9*H*-fluoren-9-yl)methyl)thio)-3-phenylpropanoic acid **3.84** using the general procedure) in DCM (5 mL) was added and the resulting mixture was stirred at RT for 18 h. The solvent was concentrated *in vacuo*, loaded onto a short silica plug and eluted (SiO_2, 1:9 ethyl acetate: hexane → 1:4 ethyl acetate: hexane) to remove the majority of excess carboxylic acid and pyridine residues, and concentrated *in vacuo* to afford the crude imide product 1-(3-(((9H-fluoren-9-yl)methyl)thio)3-phenylpropanoyl)azacyclotridecan-2-one as a yellow oil (273 mg). The crude material was then re-dissolved in DCM (10 mL) and DBU (0.747 mL, 5.00 mmol) was added, followed by stirring at RT for 18 h, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:9 ethyl acetate: hexane → 1:4 ethyl acetate: hexane → 1:2 ethyl acetate: hexane → 1:1 ethyl acetate: hexane) afforded the *title compound* as an orange solid (22.6 mg, 8%); m.p. 79–82 °C; R_f 0.35 (1:1 ethyl acetate: hexane); ν_{max}/cm^{-1} (thin film) 3295, 3078, 2927, 2856, 1689, 1645, 1554, 1494, 1452, 1361, 766, 733, 698; δ_H (400 MHz, CDCl$_3$) 7.38–7.19 (5H, m, ArC**H**), 5.86 (1H, br t, *J* = 5.6 Hz, N**H**), 5.02 (1H, dd, *J* = 9.7, 5.1 Hz, COCH$_2$C**H**(Ph)S), 3.53–3.41 (1H, m, CH**H'**NH), 3.14 (1H, app dq, *J* = 13.2, 5.6 Hz, C**H**H'NH), 2.90–2.74 (2H, m, C**H$_2$**CON), 2.62–2.43 (2H, m, C**H**$_2$COS), 1.90–1.67 (1H, m, 0.5 × C**H$_2$**), 1.61–1.47 (3H, m, 1.5 × C**H$_2$**), 1.45–1.21 (14H, m, 7 × C**H$_2$**); δ_C (100 MHz, CDCl$_3$) 198.7 (**C**OS), 169.5 (**C**ON), 142.0 (Ar**C**), 128.8 (2 × ArCH), 127.7 (ArCH), 127.5 (2 × Ar**C**H), 44.7 (COCH$_2$CH(Ph)S), 43.4 (**C**H$_2$CO), 43.3 (**C**H$_2$CO), 39.5 (**C**H$_2$NH), 29.0 (**C**H$_2$), 27.7 (**C**H$_2$), 27.2 (**C**H$_2$), 27.1 (2 × **C**H$_2$), 26.9 (**C**H$_2$), 26.5 (**C**H$_2$), 25.5 (**C**H$_2$), 24.5 (**C**H$_2$); HRMS (ESI): calcd. for $C_{21}H_{31}NNaO_2S$, 384.1968. Found: [MNa]$^+$, 384.1966 (0.5 ppm error).

Lab notebook reference: KP357/KP358

1-[(2*E*)-3-Phenylprop-2-enoyl]azacyclotridecan-2-one (3.90)

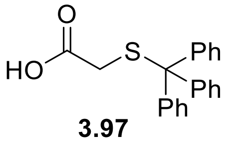


3.90

A mixture of laurolactam **1.210** (98.2 mg, 0.498 mmol), DMAP (6.1 mg, 0.050 mmol) and pyridine (0.243 mL, 3.00 mmol) in DCM (7 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of 3-(((9*H*-fluoren-9-yl)methyl)thio)-3-phenylpropanoyl chloride (1.51 mmol, prepared from 3-(((9*H*-fluoren-9-yl)methyl)thio)-3-phenylpropanoic acid **3.84** using the general procedure) in DCM (3 mL) was added and the resulting mixture was heated at reflux 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*. TLC analysis indicated that acylation was complete at this stage. The crude material was then re-dissolved in DCM (10 mL) and DBU (0.747 mL, 5.00 mmol) was added, followed by stirring at RT for 18 h, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, hexane → 3:97 ethyl acetate: hexane → 1:19 ethyl acetate: hexane → 1:9 ethyl acetate: hexane → 1:5 ethyl acetate: hexane → 1:4 ethyl acetate: hexane) afforded the *title compound* **3.90** as a yellow crystalline solid (115 mg, 70%); m.p. 45–51 °C; R_f 0.40 (1:4 ethyl acetate: hexane); ν_{max}/cm^{-1} (thin film) 2929, 2859, 1675, 1616, 1577, 1449, 1332, 1178, 1135, 1098, 1071, 1047, 910, 763, 729, 684, 563; δ_H (400 MHz, $CDCl_3$) 7.71 (1H, d, *J* = 15.5 Hz, ArC**H**CHCON), 7.57–7.52 (2H, m, Ar**H**), 7.41–7.33 (3H, m, Ar**H**), 7.14 (1H, d, *J* = 15.5 Hz, ArCHC**H**CON), 3.81 (2H, t, *J* = 7.0 Hz, C**H₂**N), 2.69 (2H, t, *J* = 7.2 Hz, C**H₂**CON), 1.84–1.75 (2H, m, C**H₂**), 1.71 (2H, apparent p, *J* = 7.0 Hz, C**H₂**), 1.51–1.24 (14H, m, 7 × C**H₂**); δ_C (100 MHz, $CDCl_3$), 177.5 (**C**ON), 169.5 (**C**OCHCH), 144.1 (ArC**H**CHCON), 134.9 (Ar**C**), 130.3 (Ar**C**H), 128.9 (2 × Ar**C**H), 128.3 (2 × Ar**C**H), 121.3 (ArCHC**H**CON), 43.7 (**C**H_2N), 36.6 (**C**H_2CON), 26.5 (**C**H_2), 26.1 (**C**H_2), 25.4 (2 × **C**H_2), 25.3 (**C**H_2), 25.0 (**C**H_2), 24.6 (**C**H_2), 24.2 (**C**H_2), 23.8 (**C**H_2); HRMS (ESI): calcd. for $C_{21}H_{29}NNaO_2$, 350.2090. Found: $[MNa]^+$, 350.2091 (–0.1 ppm error).

Lab notebook reference: KP333

2-(Tritylthio)acetic acid (3.97)

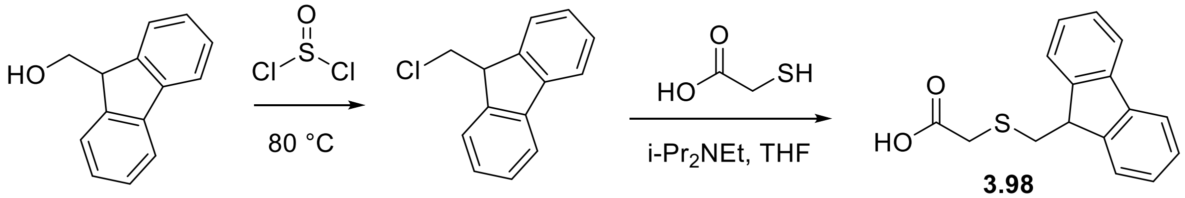


3.97

Mercaptoacetic acid (3.48 mL, 50.0 mmol) and triphenylmethanol (13.0 g, 50.0 mmol) were added to a 100 mL round bottomed flask with $CHCl_3$ (50 mL). To this was added trifluoroacetic (10.0 mL) slowly over the course of 5 min, and mixture stirred at RT. After 1 h, the solvent was and TFA was removed *in vacuo* forming an orange brown paste. This crude reaction mixture was recrystallized using 2:1 hexane: DCM to give the *title compound* as a pale pink solid (2.55 g, 15%); m.p. 159–161 °C; R_f 0.385 (30:70:1 ethyl acetate: petroleum ether: acetic acid); δ_H (400 MHz, $CDCl_3$) 8.35 (1H, br s, COO**H**), 7.46 – 7.37 (6H, m, Ar**H**), 7.34 – 7.26 (6H, m, Ar**H**), 7.25 – 7.19 (3H, m, Ar**H**), 3.02 (2H, s, C**H₂**); δ_C (100 MHz, $CDCl_3$) 175.9 (**C**O), 144.0 (3 × Ar**C**), 129.6 (6 × Ar**C**H), 128.3 (6 × Ar**C**H), 127.1 (3 × Ar**C**H), 67.4 (**C**H), 34.6 (**C**H₂); HRMS (ESI): calcd. for $C_{21}H_{18}NaO_2S$, 357.0920. Found: $[MNa]^+$, 357.0918 (0.3 ppm error). ^1H and ^{13}C NMR data match those reported in the literature.[105]

Lab notebook reference: KP192

2-(((9*H*-Fluoren-9-yl)methyl)thio)acetic acid (3.98)



3.99

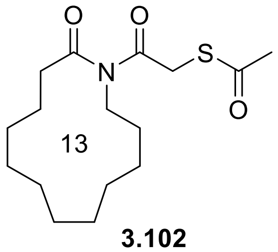
3.98

To 9-fluorenemethanol (9.80 g, 50 mmol) was added thionyl chloride (50 mL) and the solution was heated at reflux at 80 °C for 2 h. Excess thionyl chloride was removed *in vacuo* and the residue was taken up in a pentane: DCM (60:40) mixture. Purification by flash column chromatography (SiO_2, 85:15 pentane: DCM) afforded 9-fluorenylmethyl chloride **3.99** as a pale yellow oil (1.88 g, 17%) [Data for 9-fluorenylmethyl chloride: R_f 0.35 (85:15 pentane: DCM); ν_{max}/cm^{-1} (thin film) 3066, 2952, 1477, 1448, 1303, 1263, 1100, 1031, 936, 814, 763, 736, 706, 638, 621, 579, 530; δ_H (400 MHz, $CDCl_3$) 7.81 – 7.67 (4H, m, Ar**H**), 7.46 – 7.32 (4H, m, Ar**H**), 4.27 (1H, t, *J* = 6.6 Hz, C**H**), 3.92 (1H, t, *J* = 6.6 Hz, C**H₂**); δ_C (100 MHz, $CDCl_3$) 144.2 (2 × Ar**C**), 141.3 (2 × Ar**C**), 128.2 (2 × Ar**C**H), 127.3 (2 × Ar**C**H), 125.1 (2 × Ar**C**H), 120.2 (2 × Ar**C**H), 49.5 (CH₂**C**H), 47.1 (**C**H₂CH); HRMS (APCI): calcd. for $C_{14}H_{12}Cl$, 215.062204. Found: $[MH]^+$, 215.062158 (–0.2 ppm error)]. ^1H and ^{13}C NMR data matches those previously reported.[106]

To a solution of thioglycolic acid (86 µL, 1.23 mmol) and 9-fluorenylmethyl chloride **3.99** (245 mg, 1.14 mmol) in THF (5 mL) was added $^{i}Pr_2NEt$ (0.611 mL, 3.51 mmol). The reaction was stirred at room temperature for 17 h and THF was removed under reduced pressure. The residue was taken up in sat. aq. Na_2CO_3 (10 mL) bringing the pH to 8. The mixture was extracted with $CHCl_3$ (3 × 30 mL), and the aqueous layer acidified with aq. HCl (10%) to pH 1 and extracted with ethyl acetate (5 × 30 mL). The combined ethyl acetate extracts were dried over $MgSO_4$ and concentrated *in vacuo* to afford the *title compound* as an orange-yellow solid paste **3.98** (310 mg, 100%); R_f 0.20 (ethyl acetate); m.p. 94–101 °C; ν_{max}/cm^{-1} (thin film) 2919, 1703, 1477, 1448, 1295, 1129, 1155, 1031, 765, 736, 621; δ_H (400 MHz, $CDCl_3$) 10.24 (1H, br s, COO**H**), 7.80 – 7.64 (4H, m, Ar**H**), 7.44 – 7.29 (4H, m, Ar**H**), 4.17 (1H, t, *J* = 6.3 Hz, SCH_2C**H**), 3.25 (2H, d, *J* = 6.3 Hz, SC**H₂**CH), 3.23 (2H, s, SC**H₂**COOH); δ_C (100 MHz, $CDCl_3$) 176.2 (**C**OOH), 145.7 (2 × Ar**C**), 141.2 (2 × Ar**C**), 127.8 (2 × Ar**C**H), 127.2 (2 × Ar**C**H), 124.9 (2 × Ar**C**H), 120.1 (2 × Ar**C**H), 46.6 (SCH_2**C**H), 36.8 (S**C**H_2CH), 34.2 (S**C**H_2COOH); HRMS (ESI): calcd. for $C_{16}H_{14}NaO_2S$, 293.0607. Found: $[MNa]^+$, 293.0604 (0.9 ppm error). Procedure adapted from a literature method, ^1H data matches those previously reported.[107]

Lab notebook reference: KP300/KP301

S-(2-Oxo-2-(2-oxoazacyclotridecan-1-yl)ethyl) ethanethioate (3.102)



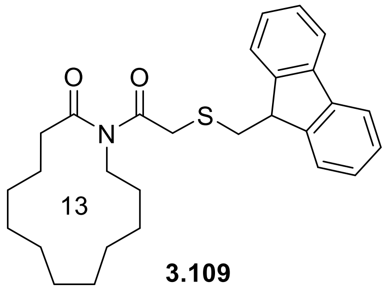
3.102

A mixture of laurolactam **1.210** (498 mg, 2.52 mmol), DMAP (30.5 mg, 0.250 mmol) and pyridine (1.20 mL, 15.0 mmol) in DCM (30 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of 2-(acetylthio)acetoyl chloride (3.75 mmol, 1.50 eqv prepared using the general procedure from (acetylthio)acetic acid (**3.96**) in DCM (20 mL) was added and the resulting mixture was heated at reflux at 50 °C for 18 h. After 5 h a further 50 mL of DCM was added as some had evaporated. 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 (3 × 25 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:19 ethyl acetate: hexane → 1:9 ethyl acetate: hexane → 1:4 ethyl acetate: hexane → 1:1 ethyl acetate: hexane) afforded the *title compound* as an orange crystalline solid (62.8 mg, 8%); m.p. 53–55 °C; R_f 0.66 (1:1 ethyl acetate:

hexane); ν_{max}/cm^{-1} (thin film) 2929, 2861, 1688, 1464, 1446, 1355, 1293, 1282, 1262, 1177, 1129, 1121, 1046, 958, 627; δ_H (400 MHz, CDCl$_3$) 4.19 (2H, s, COC**H$_2$**S), 3.70 – 3.64 (2H, m, C**H$_2$**N), 2.59 – 2.53 (2H, m, C**H$_2$**CON), 2.35 (3H, s, C**H$_3$**), 1.82 – 1.74 (2H, m, C**H$_2$**), 1.72 – 1.62 (2H, m, C**H$_2$**), 1.52 – 1.39 (4H, m, 2 × C**H$_2$**), 1.38 – 1.22 (10H, m, 5 × C**H$_2$**); δ_C (100 MHz, CDCl$_3$), 194.8 (**C**OS), 176.9 (**C**ON), 171.0 (**C**OCH$_2$S), 43.7 (**C**H$_2$N), 37.5 (CO**C**H$_2$S), 35.5 (**C**H$_2$CON), 30.2 (**C**H$_3$), 25.9 (2C, 2 × **C**H$_2$), 25.2 (**C**H$_2$), 24.8 (**C**H$_2$), 24.5 (**C**H$_2$), 24.3 (**C**H$_2$), 24.1 (**C**H$_2$), 23.8 (**C**H$_2$), 23.6 (**C**H$_2$); HRMS (ESI): calcd. for $C_{16}H_{27}NNaO_3S$, 336.1604. Found: [MNa]$^+$, 336.1609 (–0.1 ppm error).

Lab notebook reference: KP219

1-(2-(((9*H*-Fluoren-9-yl)methyl)thio)acetyl)azacyclotridecan-2-one (3.109)

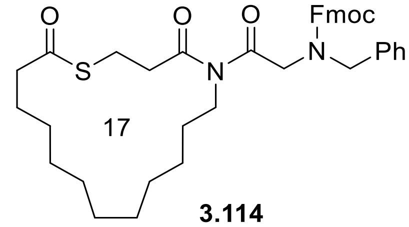


3.109

A mixture of laurolactam **1.210** (198 mg, 1.00 mmol), DMAP (13.6 mg, 0.111 mmol) and pyridine (0.485 mL, 6.00 mmol) in DCM (20 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of 2-(((9*H*-fluoren-9-yl)methyl)thio)acetyl chloride (3.14 mmol, prepared from 2-(((9*H*-fluoren-9-yl)methyl)thio)acetic acid **3.98** using the general procedure) in DCM (20 mL) was added and the resulting mixture was heated at reflux at 50 °C for 18 h. Purification by flash column chromatography (SiO$_2$, hexane → 1:9 ethyl acetate: hexane → 1:4 ethyl acetate: hexane → 1:2 ethyl acetate: hexane → 1:1 ethyl acetate: hexane → 3:1 ethyl acetate: hexane) afforded the *title compound* as an orange solid (299 mg, 66%); R$_f$ 0.31 (1:3 ethyl acetate: hexane); m.p. 65 – 71 °C; ν_{max}/cm^{-1} (thin film) 2929, 2860, 1682, 1447, 1360, 1276, 1177, 1120, 1047, 909, 764, 736, 621; δ_H (400 MHz, CDCl$_3$) 7.73 (4H, t, *J* = 16.3, 7.5 Hz, Ar**H**), 7.42–7.28 (4H, m, Ar**H**), 4.13 (1H, t, *J* = 6.7 Hz, SCH$_2$C**H**), 3.84 (2H, s, SC**H$_2$**CON), 3.71–3.63 (2H, m, C**H$_2$**N), 3.12 (2H, t, *J* = 6.7 Hz, SC**H$_2$**CH), 2.59–2.50 (2H, m, C**H$_2$**CON), 1.83–1.72 (2H, m, C**H$_2$**), 1.71–1.58 (2H, m, C**H$_2$**), 1.52–1.41 (4H, m, 2 × C**H$_2$**), 1.40–1.21 (10H, m, 5 × C**H$_2$**); δ_C (100 MHz, CDCl$_3$) 176.8 (**C**ON), 172.6 (**C**ON), 146.1 (2 × Ar**C**), 141.1 (2 × Ar**C**), 127.7 (2 × Ar**C**H), 127.1 (2 × Ar**C**H), 125.1 (2 × Ar**C**H), 120.0 (2 × Ar**C**H), 46.7 (SCH$_2$**C**H), 43.4 (**C**H$_2$N), 39.1 (S**C**H$_2$CON), 36.3 (S**C**H$_2$CH), 35.7 (**C**H$_2$CON), 25.92 (**C**H$_2$), 25.87 (**C**H$_2$), 25.4 (**C**H$_2$), 24.9 (**C**H$_2$), 24.6 (**C**H$_2$), 24.4 (**C**H$_2$), 24.1 (**C**H$_2$), 23.9 (**C**H$_2$), 23.7 (**C**H$_2$); HRMS (ESI): calcd. for $C_{28}H_{36}NO_2S$, 450.2461. Found: [MH]$^+$, 450.2462 (–0.2 ppm error).

Lab notebook reference: KP328

(9*H*-Fluoren-9-yl)methyl benzyl(2-(4,17-dioxo-1-thia-5-azacycloheptadecan-5-yl)-2-oxoethyl)carbamate (3.114)



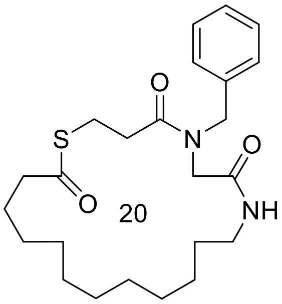
3.114

A mixture of 1-thia-5-azacycloheptadecane-4,17-dione **3.29** (150 mg, 0.526 mmol), DMAP (6.1 mg, 0.050 mmol) and pyridine (0.243 mL, 3.00 mmol) in DCM (2.5 mL) under an argon atmosphere was stirred for 5 mins. Next, a solution of (9*H*-fluoren-9-yl)methyl benzyl(2-chloro-2-oxoethyl)carbamate (0.754 mmol, prepared from *N*-(((9*H*-fluoren-9-yl)methoxy)carbonyl)-*N*-benzylglycine[48] using the general procedure) in DCM (5 mL) was added and the resulting mixture was heated at reflux at 50 °C for 18 h. The crude mixture was concentrated *in vacuo*. Purification by flash column chromatography (SiO$_2$, 1:9 ethyl acetate: hexane → 1:5 ethyl acetate: hexane → 1:2 ethyl acetate: hexane → 1:1 ethyl acetate: hexane → ethyl acetate) afforded the *title compound* **3.114** as a 1:1 mixture of rotamers as a fluffy white solid; m.p. 44–59 °C (261 mg, 76%); R$_f$ 0.56 (1:1 ethyl acetate: hexane); ν_{max}/cm^{-1} (thin film) 2927, 2856, 1694, 1451, 1424, 1389, 1220, 1112, 1004, 953, 892, 759, 740, 699, 621, 598, 534; δ_H (400 MHz, CDCl$_3$) ^{1}H NMR signals are for both rotamers unless stated 7.74 (2H, d, *J* = 7.4 Hz, Ar**H**), 7.72 (2H, d, *J* = 7.6 Hz, Ar**H**), 7.53 (2H, d, *J* = 7.5 Hz, Ar**H**), 7.47 (2H, d, *J* = 7.5 Hz, Ar**H**), 7.42–7.12 (18H, m, Ar**H**), 4.58–4.54 (4H, m, 2 × C$\mathbf{H_2}$Ph), 4.51 (2H, d, *J* = 6.5 Hz, COC$\mathbf{H_2}$CH), 4.49–4.47 (2H, m, NC$\mathbf{H_2}$CNO, [overlapping]), 4.48–4.45 (2H, m, COC$\mathbf{H_2}$CH, [overlapping]), 4.26 (2H, s, NC$\mathbf{H_2}$CNO), 4.26–4.19 (2H, m, 2 × COCH$_2$C**H**), 3.62–3.56 (2H, m, CH$_2$C$\mathbf{H_2}$NCO, rotamer A), 3.51–3.44 (2H, m, CH$_2$C$\mathbf{H_2}$NCO, rotamer B), 3.11 (4H, apparent q, *J* = 6.4 Hz, 2 × SC$\mathbf{H_2}$CH$_2$CON), 2.83 (4H, apparent dt, *J* = 13.8, 6.6 Hz, 2 × SCH$_2$C$\mathbf{H_2}$CON), 2.60 – 2.52 (4H, m, 2 × CH$_2$C$\mathbf{H_2}$COS), 1.73 – 1.62 (4H, m, 2 × C$\mathbf{H_2}$), 1.56 – 1.47 (2H, m, C$\mathbf{H_2}$), 1.45 – 1.14 (30H, m, 15 × C$\mathbf{H_2}$); δ_C (100 MHz, CDCl$_3$), 200.02 (S**C**O), 199.99 (S**C**O), 173.9 (**C**O), 173.8 (**C**O), 172.4 (**C**O), 172.2 (**C**O), 156.72 (N**C**O$_2$), 156.70 (N**C**O$_2$), 144.01 (2 × Ar**C**), 143.95 (2 × Ar**C**), 141.35 (2 × Ar**C**), 141.33 (2 × Ar**C**), 137.3 (Ar**C**), 137.1 (Ar**C**), 128.8 (2 × Ar**C**H), 128.6 (2 × Ar**C**H), 128.0 (2 × Ar**C**H), 127.7 (4 × Ar**C**H), 127.53 (Ar**C**H), 127.51 (Ar**C**H), 127.4 (2 × Ar**C**H), 127.1 (4 × Ar**C**H), 125.1 (2 × Ar**C**H), 124.9 (2 × Ar**C**H), 119.98 (2 × Ar**C**H), 119.95 (2 × Ar**C**H), 67.9 (**C**H$_2$CH), 67.3 (**C**H$_2$CH), 54.2 (N**C**H$_2$CNO), 53.3 (N**C**H$_2$CNO), 51.7 (**C**H$_2$Ph), 51.6 (**C**H$_2$Ph), 47.4 (**C**H), 47.2 (**C**H), 44.5 (CH$_2$**C**H$_2$N), 44.4 (CH$_2$**C**H$_2$N), 43.7 (2 × **C**H$_2$COS), 37.4 (2 × CO**C**H$_2$CH$_2$S), 27.80 (2 × **C**H$_2$), 27.75 (**C**H$_2$), 27.71 (2 × **C**H$_2$), 27.64

(**C**H$_2$), 27.3 (2 × **C**H$_2$), 27.2 (2 × **C**H$_2$), 26.70 (**C**H$_2$), 26.66 (2 × **C**H$_2$), 26.60 (**C**H$_2$), 25.10 (**C**H$_2$), 25.07 (**C**H$_2$), 25.01 (**C**H$_2$), 24.97 (**C**H$_2$), 23.59 (2 × COCH$_2$**C**H$_2$S); HRMS (ESI): calcd. for $C_{39}H_{46}N_2NaO_5S$, 677.3020. Found: [MNa]$^+$, 677.3012 (1.1 ppm error).

Lab notebook reference: KP207

5-Benzyl-5,8-diaza-1-thiacycloicosane-4,7,20-trione (3.116)

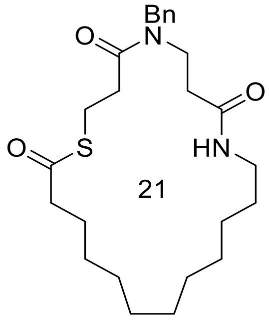


3.116

To a solution of (9*H*-fluoren-9-yl)methyl benzyl(2-(4,17-dioxo-1-thia-5-azacycloheptadecan-5-yl)-2-oxoethyl)carbamate **3.114** (261 mg, 0.398 mmol) in DCM (10 mL) under an argon atmosphere DBU (0.747 mL, 0.500 mmol) was added, followed by stirring at RT for 18 h, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO$_2$, 1:9 ethyl acetate: hexane → 1:4 ethyl acetate: hexane → 1:2 ethyl acetate: hexane → 1:1 ethyl acetate: hexane → ethyl acetate) afforded the *title compound* as a white crystalline solid (106 mg, 62%; 47% over 2 steps from **3.29**) as a 5:4 (A:B) mixture of rotamers; m.p. 84–98 °C; R$_f$ 0.67 (9:1 ethyl acetate: methanol); ν_{max}/cm^{-1} (thin film) 3318, 2927, 2856, 1655, 1543, 1496, 1443, 1358, 1265, 1236, 1198, 1081, 1021, 910, 730, 699; δ_H (400 MHz, CDCl$_3$) 7.34–7.17 (8H, m, Ar**H**), 7.13–7.07 (2H, m, Ar**H**), 6.49 (1H, t, *J* = 5.7 Hz, N**H**, rotamer A), 6.09 (1H, t, *J* = 5.8 Hz, N**H**, rotamer B), 4.60 (2H, s, PhC**H₂**, rotamer B), 4.58 (2H, s, PhC**H₂**, rotamer A), 3.96 (2H, s, NC**H₂**CO, rotamer A), 3.87 (2H, s, NC**H₂**CO, rotamer B), 3.20–3.09 (8H, m, 4 × C**H₂**), 2.71 (2H, t, *J* = 6.2 Hz, C**H₂**), 2.61–2.43 (6H, m, 3 × C**H₂**), 1.71–1.56 (4H, m, 2 × C**H₂**), 1.50–1.12 (32H, m, 16 × C**H₂**); δ_C (100 MHz, CDCl$_3$): 200.2 (S**C**O), 200.1 (S**C**O), 172.7 (**C**O), 171.8 (**C**O), 168.9 (**C**O), 167.7 (**C**O), 136.7 (Ar**C**), 135.5 (Ar**C**), 129.2 (2 × ArCH), 128.9 (2 × Ar**C**H), 128.6 (2 × Ar**C**H), 128.1 (Ar**C**H), 128.0 (Ar**C**H), 126.6 (2 × Ar**C**H), 52.7 (PhC**H₂**, rotamer A), 51.5 (N**C**H$_2$CO, rotamer A), 50.7 (N**C**H$_2$CO, rotamer B), 50.3 (Ph**C**H$_2$, rotamer B), 43.4 (**C**H$_2$), 43.3 (**C**H$_2$), 39.5 (2 × **C**H$_2$), 33.9 (**C**H$_2$), 33.5 (**C**H$_2$), 29.2 (**C**H$_2$), 29.1 (**C**H$_2$), 28.6 (**C**H$_2$), 28.4 (**C**H$_2$), 27.9 (**C**H$_2$), 27.8 (**C**H$_2$), 27.6 (**C**H$_2$), 27.4 (**C**H$_2$), 27.18 (**C**H$_2$), 27.15 (**C**H$_2$), 26.99 (2 × **C**H$_2$), 26.95 (**C**H$_2$), 26.6 (**C**H$_2$), 26.3 (**C**H$_2$), 25.9 (**C**H$_2$), 25.0 (**C**H$_2$), 24.8 (**C**H$_2$), 24.7 (**C**H$_2$), 24.6 (**C**H$_2$); HRMS (ESI): calcd. for $C_{24}H_{36}N_2NaO_3S$, 455.2339. Found: [MNa]$^+$, 455.2332 (1.5 ppm error). For X-ray crystallographic data, see CCDC 2040346.

Lab notebook reference: KP208

5-Benzyl-1-thia-5,9-diazacyclohenicosane-4,8,21-trione (3.117)

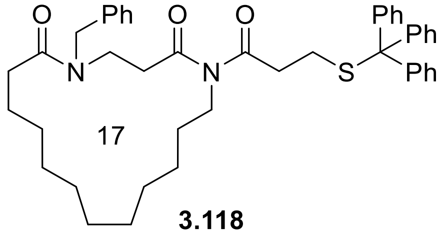


3.117

A mixture of 1-thia-5-azacycloheptadecane-4,17-dione **3.29** (143 mg, 0.502 mmol), DMAP (8.6 mg, 0.070 mmol) and pyridine (0.243 mL, 3.00 mmol) in DCM (5 mL) under an argon atmosphere was stirred for 5 mins. Next, a solution of 3-((((9*H*-fluoren-9-yl)methoxy)carbonyl)(benzyl)amino)propanoyl chloride (0.755 mmol, prepared from 3-((((9*H*-fluoren-9-yl)methoxy)carbonyl)(benzyl)amino)propanoic acid using the general procedure) in DCM (5 mL) was added and the resulting mixture was heated at reflux at 50 °C for 18 h. TLC analysis indicated that the acylation was incomplete, and so another solution of 3-((((9*H*-fluoren-9-yl)methoxy)carbonyl)(benzyl)amino)propanoyl chloride (0.748 mmol) in DCM (10 mL) was prepared and added to the reaction mixture, with heating at reflux for an additional 18 h at 50 °C. The crude mixture was then concentrated *in vacuo*. Rough purification by flash column chromatography (SiO_2, 1:19 ethyl acetate: hexane → 1:9 ethyl acetate: hexane → 1:5 ethyl acetate: hexane → 1:2 ethyl acetate: hexane → 1:1 ethyl acetate: hexane) afforded a crude product consisting of predominantly (9*H*-fluoren-9-yl)methyl benzyl(3-(4,17-dioxo-1-thia-5-azacycloheptadecan-5-yl)-3-oxopropyl)carbamate (**3.115**), as a roughly 1:1 mixture of rotamers, as a light yellow paste (283 mg of material isolated, used directly in the next step). [Selected data for the intermediate (9*H*-fluoren-9-yl)methyl benzyl(3-(4,17-dioxo-1-thia-5-azacycloheptadecan-5-yl)-3-oxopropyl)carbamate (**3.115**): R_f 0.71 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 2927, 2856, 1688, 1451, 1420, 1369, 1210, 1112, 1031, 910, 759, 729, 700, 621; Diagnostic ^{1}H NMR resonances: δ_H (400 MHz, $CDCl_3$), 4.56 (2H, d, *J* = 6.1 Hz, COC**H₂**CH), 4.50 – 4.47 (2H, m, C**H₂**Ph, [overlapping]), 4.50 – 4.45 (2H, m, COC**H₂**CH, [overlapping]), 4.43 (2H, s, C**H₂**Ph), 4.27 (1H, t, *J* = 6.1 Hz, $COCH_2C$**H**), 4.20 (1H, t, *J* = 6.4 Hz, $COCH_2C$**H**); Diagnostic ^{13}C NMR resonances: δ_C (100 MHz, $CDCl_3$), 200.2 (2 × S**C**O), 174.3 (**C**O), 174.0 (**C**O), 173.9 (**C**O), 173.7 (**C**O), 156.6 (N**C**O₂), 156.2 (N**C**O₂), 67.5 (**C**H_2CH), 67.3 (**C**H_2CH), 51.1 (PhC**H₂**), 50.9 (PhC**H₂**), 47.5 (**C**H), 47.4 (**C**H); HRMS (ESI): calcd. for $C_{40}H_{48}N_2NaO_5S$, 691.3176 Found: $[MNa]^+$, 691.3176 (0.0 ppm error)]. To a solution of this sample of (9*H*-fluoren-9-yl)methyl benzyl(3-(4,17-dioxo-1-thia-5-azacycloheptadecan-5-yl)-3-oxopropyl)carbamate (**3.115**) in DCM (8.2 mL) under an argon atmosphere, DBU (0.604 mL, 4.04 mmol) was added, followed by stirring at RT for 18 h, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, hexane → 1:19 ethyl acetate: hexane → 1:9 ethyl acetate: hexane → 1:2 ethyl acetate: hexane → 1:1 ethyl acetate: hexane → 2:1 ethyl acetate: hexane → 4:1 ethyl acetate: hexane → ethyl acetate) afforded the *title compound* as a 2:1 mixture of rotamers as a white pasty solid (31.6 mg, 14% from **3.29**); m.p. 62–75 °C; R_f 0.34 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3311, 2925, 2854, 1638, 1549, 1439, 1365, 1197, 1026, 727, 698; δ_H (400 MHz, $CDCl_3$), 7.37 – 7.22 (8H, m, ArC**H**, both rotamers), 7.15–7.08 (2H, m, ArC**H**, both rotamers), 6.46 (1H, br t, *J* = 5.7 Hz, N**H**, major rotamer), 5.77 (1H, br t, *J* = 5.7 Hz, N**H**, minor rotamer), 4.60 (2H, s, C**H**$_2$Ph, minor rotamer), 4.57 (2H, s, C**H**$_2$Ph, major rotamer), 3.70–3.64 (2H, m, CON(CH$_2$Ph)C**H**$_2$, major rotamer), 3.60–3.54 (2H, m, CON(CH$_2$Ph)C**H**$_2$, minor rotamer), 3.30–3.17 (4H, m, 2 × C**H**$_2$), 3.14 (2H, t, *J* = 6.7 Hz, C**H**$_2$), 2.75–2.69 (2H, m, C**H**$_2$, minor rotamer), 2.63 (2H, t, *J* = 6.7 Hz, C**H**$_2$, major rotamer), 2.58 (2H, t, *J* = 7.0 Hz, C**H**$_2$, minor rotamer), 2.55–2.47 (4H, m, 2 × C**H**$_2$), 2.39 – 2.33 (2H, m, C**H**$_2$, minor rotamer), 1.74–1.61 (4H, m, 2 × C**H**$_2$), 1.59–1.43 (4H, m, 2 × C**H**$_2$), 1.38–1.21 (30H, m, 15 × C**H**$_2$, both rotamers); δ_C (100 MHz, $CDCl_3$) data for major rotamer A, 200.1 (**C**OS), 172.4 (**C**ON), 171.0 (**C**ON), 136.4 (Ar**C**), 129.1 (2 × Ar**C**H), 127.8 (Ar**C**H), 126.3 (2 × Ar**C**H), 52.0 (**C**H$_2$Ph), 43.5 (**C**H$_2$), 43.2 (CON(CH$_2$Ph)**C**H$_2$), 39.8 (**C**H$_2$), 35.5 (**C**H$_2$), 33.9 (**C**H$_2$), 29.4 (**C**H$_2$), 28.9 (**C**H$_2$), 28.2 (**C**H$_2$), 27.8 (**C**H$_2$), 27.52 (**C**H$_2$), 27.49 (**C**H$_2$), 27.2 (**C**H$_2$), 26.7 (**C**H$_2$), 24.9 (**C**H$_2$), 24.6 (**C**H$_2$); Diagnostic ^{13}C NMR resonances for the minor rotamer: δ_C (100 MHz, $CDCl_3$), 201.1 (**C**OS), 171.2 (**C**ON), 169.7 (**C**ON), 49.2 (**C**H$_2$Ph); HRMS (ESI): calcd. for $C_{25}H_{38}N_2NaO_3S$, 469.2495 Found: [MNa]$^+$, 469.2500 (–0.9 ppm error).

Lab notebook reference: KP326

5-Benzyl-1-(3-(tritylthio)propanoyl)-1,5-diazacycloheptadecane-2,6-dione (3.118)



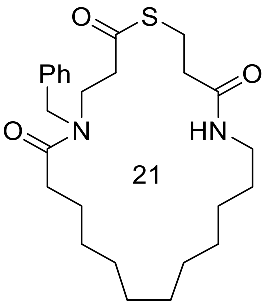
3.118

A mixture of 5-benzyl-1,5-diazacycloheptadecane-2,6-dione[48] (327 mg, 0.912 mmol), DMAP (11.2 mg, 0.092 mmol) and pyridine (0.442 mL, 5.47 mmol) in DCM (10 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride **3.37** (3-(tritylthio)propanoyl chloride) (1.37 mmol, prepared from 3-(tritylthio)propanoic acid **3.36** using the general procedure) in DCM (13 mL) was added and the resulting mixture was heated at reflux at 50 °C for 18 h. The mixture was then diluted with DCM (5 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*. TLC analysis indicated that acylation was incomplete at this stage, so an additional acylation sequence was performed. Thus, the crude reaction mixture was dissolved in DCM (10 mL) and to it was added DMAP (11.2 mg, 0.092 mmol) and pyridine (0.442 mL, 5.47 mmol). Then, another solution of acid chloride **3.37** (1.36 mmol, 1.5 eqv. prepared using the general procedure) in DCM (13 mL) was added and the resulting mixture was heated at reflux at 50 °C for 18 h. The mixture was then diluted with DCM (5 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, 1:19 ethyl acetate: hexane → 1:9 ethyl acetate: hexane → 1:4 ethyl acetate: hexane → 1:1 ethyl acetate: hexane → ethyl acetate → 1:19 methanol: ethyl acetate) afforded the *title compound* as a 2:1 mixture of rotamers as a fluffy white solid (343 mg, 55 %)*; m.p. 38–48 °C; R_f 0.45 (1:1 ethyl acetate: hexane); ν_{max}/cm^{-1} (thin film) 2929, 1694, 1637, 1445, 1371, 1131, 1105, 1034, 907, 726, 698, 647, 619, 506; δ_H (400 MHz, $CDCl_3$) 7.47–7.15 (40H, m, ArH, both rotamers), 4.65 (2H, s, NC**H$_2$**Ph, major), 4.58 (2H, s, NC**H$_2$**Ph, minor), 3.66–3.60 (4H, m, C**H$_2$**, both), 3.54–3.47 (2H, m, C**H$_2$**, major), 3.37–3.30 (2H, m, C**H$_2$**, minor), 2.87 (2H, t, *J* = 6.5 Hz, C**H$_2$**, major), 2.83 (2H, t, *J* = 6.8 Hz, C**H$_2$**, minor), 2.69 (2H, t, *J* = 7.1 Hz, C**H$_2$**, major), 2.54 (2H, t, *J* = 7.0 Hz, C**H$_2$**, minor), 2.51–2.39 (6H, m, C**H$_2$**, both), 2.38–2.33 (2H, m, C**H$_2$**, major), 1.81–1.62 (4H, m C**H$_2$**, both), 1.53–1.18 (32H, m, C**H$_2$**, both); δ_C (100 MHz, $CDCl_3$), 174.4 (**C**O), 174.2 (**C**O), 174.1 (**C**O), 174.0 (**C**O), 173.6 (**C**O), 173.4 (**C**O), 144.8 (Ar**C**), 144.7 (Ar**C**), 138.2 (Ar**C**), 137.1 (Ar**C**), 129.7 (Ar**C**H), 129.6 (Ar**C**H), 129.0 (Ar**C**H), 128.6 (Ar**C**H), 128.0 (Ar**C**H), 127.9 (Ar**C**H), 127.7 (Ar**C**H), 127.2 (Ar**C**H), 126.8 (Ar**C**H), 126.6 (Ar**C**H), 126.5 (Ar**C**H), 67.0 (**C**Ph$_3$), 66.8 (**C**Ph$_3$), 52.7 (NC**H$_2$**Ph, major), 48.7 (NC**H$_2$**Ph, minor), 44.3 (**C**H$_2$), 43.8 (**C**H$_2$), 43.2 (**C**H$_2$), 43.1 (**C**H$_2$), 38.4 (**C**H$_2$), 37.3 (**C**H$_2$), 37.2 (**C**H$_2$), 35.6 (**C**H$_2$), 33.3 (**C**H$_2$), 32.5 (**C**H$_2$), 31.7 (**C**H$_2$), 27.8 (**C**H$_2$), 27.5 (**C**H$_2$), 27.3 (**C**H$_2$), 27.2 (**C**H$_2$), 27.1 (**C**H$_2$), 27.0 (**C**H$_2$), 26.9 (**C**H$_2$), 26.8 (**C**H$_2$), 26.6 (**C**H$_2$), 26.5 (**C**H$_2$), 26.3 (**C**H$_2$), 26.1 (**C**H$_2$), 24.9 (**C**H$_2$), 24.8 (**C**H$_2$), 24.3 (**C**H$_2$); HRMS (ESI): calcd. for $C_{44}H_{52}N_2NaO_3S$, 711.3591. Found: [MNa]$^+$, 711.3614 (–3.2 ppm error).

*Trace trityl impurities were visible in the NMR spectra of this product, but its purity was judged to be sufficient to proceed with the ring expansion sequence.

Lab notebook reference: KP223

5-Benzyl-1-thia-5,18-diazacyclohenicosane-2,6,19-trione (3.120)

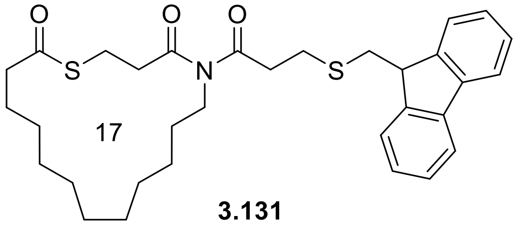


3.120

A mixture of 5-benzyl-1-(3-(tritylthio)propanoyl)-1,5-diazacycloheptadecane-2,6-dione **3.118** (307 mg, 0.445 mmol) in DCM (5 mL) under an argon atmosphere was added TFA (0.460 mL, 6.01 mmol) and the solution stirred for 3 min. Next, triisopropylsilane (0.101 mL, 0.495 mmol) was added and the solution stirred for a further 30 min. The solvent and TFA were removed *in vacuo*. The crude material (containing thiol **3.119**) was then re-dissolved in DCM (5 mL) and DBU (0.672 mL, 4.50 mmol) was added, followed by stirring at RT for 18 h, before the solvent was removed *in vacuo*. The reaction 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, 1:19 ethyl acetate: hexane → 1:9 ethyl acetate: hexane → 1:4 ethyl acetate: hexane → 1:1 ethyl acetate: hexane → ethyl acetate) afforded the *title compound* as a 5:3:1 (A:B:C) mixture of rotamers as a colorless oil (33.5 mg, 17%); R_f 0.34 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3308, 2925, 2854, 1635, 1551, 1495, 1432, 1363, 1260, 1201, 1163, 1059, 1030, 978, 915, 803, 728, 698, 645, 613; δ_H (400 MHz, $CDCl_3$), 7.39 – 7.09 (15H, m, ArC**H**, all rotamers), 7.03 (1H, br t, *J* = 5.7 Hz, N**H**, rotamer C), 6.79 (1H, br t, *J* = 5.9 Hz, N**H**, rotamer A), 5.76 (1H, br m, N**H**, rotamer B), 4.63 (2H, s, C**H₂**Ph, rotamer C), 4.59 (2H, s, C**H₂**Ph, rotamer B), 4.57 (2H, s, C**H₂**Ph, rotamer A), 3.72 – 3.67 (2H, m, CON(CH_2Ph)C**H₂**, rotamer A), 3.66 – 3.61 (2H, m, CON(CH_2Ph)C**H₂**, rotamer C), 3.59 – 3.52 (2H, m, CON(CH_2Ph)C**H₂**, rotamer B), 3.33 – 3.24 (6H, m, 3 × C**H₂**, all rotamers), 3.19 – 3.08 (4H, m, 2 × C**H₂**), 2.76 – 2.66 (4H, m, 2 × C**H₂**), 2.57 – 2.47 (4H, m, 2 × C**H₂**, rotamer C), 2.45 – 2.28 (10H, m, 5 × C**H₂**), 1.78 – 1.57 (8H, m, 4 × C**H₂**), 1.55 – 1.43 (6H, m, 3 × C**H₂**), 1.41 – 1.19 (42H, m, 21 × C**H₂**, all rotamers); δ_C (100 MHz, $CDCl_3$) data for major rotamer A, 197.5 (**C**OS), 174.2 (**C**ON), 171.4 (**C**ON), 136.6 (Ar**C**), 129.1 (2 × Ar**C**H), 127.8 (Ar**C**H), 126.5 (2 × Ar**C**H), 51.2 (**C**H₂Ph), 42.7 (**C**H₂), 42.1 (**C**H₂), 39.4 (**C**H₂), 36.0 (**C**H₂), 33.0 (**C**H₂), 28.9 (**C**H₂), 28.0 (**C**H₂), 27.9 (**C**H₂), 27.8 (**C**H₂), 27.6 (**C**H₂), 27.4 (**C**H₂), 27.0 (**C**H₂), 26.1 (**C**H₂), 25.7 (**C**H₂), 24.6 (**C**H₂); Diagnostic ^{13}C NMR resonances of rotamer B: δ_C (100 MHz, $CDCl_3$), 197.0 (**C**OS), 173.4 (**C**ON), 170.4 (**C**ON), 48.4 (**C**H₂Ph); Diagnostic ^{13}C NMR resonances of rotamer C: δ_C (100 MHz, $CDCl_3$), 175.1 (**C**ON), 171.2 (**C**ON), 52.1 (**C**H₂Ph); HRMS (ESI): calcd. for $C_{25}H_{38}N_2NaO_3S$, 469.2495 Found: [MNa]$^+$, 469.2495 (0.0 ppm error).

Lab Notebook reference: KP234

5-(3-(((9*H*-Fluoren-9-yl)methyl)thio)propanoyl)-1-thia-5-azacycloheptadecane-4,17-dione (3.131)

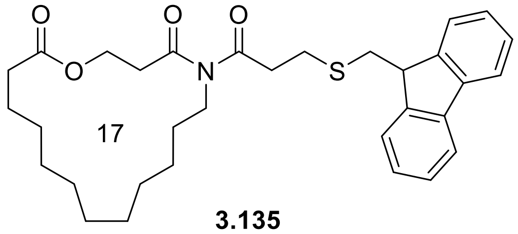


3.131

A mixture of 1-thia-5- azacycloheptadecane-4,17-dione **3.29** (215 mg, 0.755 mmol), DMAP (11.4 mg, 0.094 mmol) and pyridine (0.364 mL, 4.50 mmol) in DCM (10 mL) under an argon atmosphere was stirred for 5 mins. Next, a solution of acid chloride **3.62** (3-(((9*H*-fluoren-9-yl)methyl)thio)propanoyl chloride) (2.27 mmol, 3.01 eq., prepared from 3-(((9*H*-fluoren-9-yl)methyl)thio)propanoic acid **3.59** using the general procedure) in DCM (5 mL) was added and the resulting mixture was heated to reflux at 40 °C for 18 h. The crude mixture was concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:9 ethyl acetate: hexane → 1:4 ethyl acetate: hexane → 2:3 ethyl acetate: hexane) afforded the *title compound* as yellow oil (372 mg, 89%); R_f 0.62 (1:1 ethyl acetate: hexane); ν_{max}/cm^{-1} (thin film) 2928, 2857, 1690, 1449, 1371, 1243, 1132, 1106, 1031, 906, 726, 648, 621); δ_H (400 MHz, $CDCl_3$), 7.76 – 7.70 (4H, m, Ar**H**), 7.41 – 7.28 (4H, m, Ar**H**), 4.15 – 4.09 (1H, m, $SCH_2C\mathbf{H}$), 3.60 – 3.52 (2H, m, $CH_2CH_2C\mathbf{H_2}NCO$), 3.15 – 3.05 (6H, m, 3 × $C\mathbf{H_2}$), 2.90 – 2.83 (4H, m, 2 × $C\mathbf{H_2}$), 2.59 – 2.53 (2H, m, $CH_2C\mathbf{H_2}COS$), 1.73 – 1.63 (2H, m, $C\mathbf{H_2}$), 1.55 – 1.45 (2H, m, $C\mathbf{H_2}$), 1.39 – 1.17 (14H, m, 7 × $C\mathbf{H_2}$); δ_C (100 MHz, $CDCl_3$), 199.8 (**C**OS), 174.3 (**C**O), 173.6 (**C**O), 146.0 (2C, Ar**C**), 140.9 (2C, Ar**C**), 127.4 (2C, Ar**C**H), 126.9 (2C, Ar**C**H), 124.9 (2C, Ar**C**H), 119.7 (2C, Ar**C**H), 46.8 (**C**H), 44.0 ($CH_2CH_2\mathbf{C}H_2NCO$), 43.5 ($\mathbf{C}H_2COS$), 39.6 ($\mathbf{C}H_2$), 37.6 ($\mathbf{C}H_2$), 36.7 ($\mathbf{C}H_2$), 28.1 ($\mathbf{C}H_2$), 27.73 ($\mathbf{C}H_2$), 27.68 ($\mathbf{C}H_2$), 27.6 ($\mathbf{C}H_2$), 27.1 ($\mathbf{C}H_2$), 27.0 ($\mathbf{C}H_2$), 26.6 ($\mathbf{C}H_2$), 26.5 ($\mathbf{C}H_2$), 25.0 ($\mathbf{C}H_2$), 24.9 ($\mathbf{C}H_2$), 23.7 ($\mathbf{C}H_2$); HRMS (ESI): calcd. for $C_{32}H_{41}NNaO_3S_2$, 574.2420. Found: $[MNa]^+$, 574.2427 (–1.2 ppm error).

Lab Notebook reference: KP311_B

5-(3-(((9H-Fluoren-9-yl)methyl)thio)propanoyl)-1-oxa-5-azacycloheptadecane-4,17-dione (3.135)

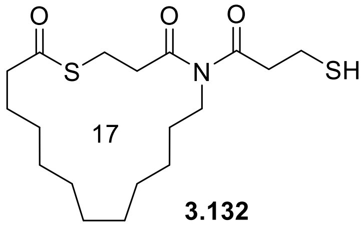


3.135

A mixture of 1-oxa-5-azacycloheptadecane-4,17-dione **3.29** (201 mg, 0.748 mmol), DMAP (14.0 mg, 0.114 mmol) and pyridine (0.364 mL, 4.50 mmol) in DCM (10 mL) under an argon atmosphere was stirred for 5 mins. Next, a solution of acid chloride **3.62** (3-(((9*H*-fluoren-9-yl)methyl)thio)propanoyl chloride) (2.25 mmol, 3.01 eq., prepared from 3-(((9*H*-fluoren-9-yl)methyl)thio)propanoic acid **3.59** using the general procedure) in DCM (5 mL) was added and the resulting mixture was heated to reflux at 40 °C for 18 h. The crude mixture was concentrated *in vacuo*. Purification by flash column chromatography (SiO$_2$, 1:9 ethyl acetate: hexane → 1:4 ethyl acetate: hexane → 1:2 ethyl acetate: hexane) afforded the *title compound* as light brown oil (175 mg, 44%); R_f 0.75 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 2926, 2856, 1731, 1693, 1449, 1366, 1131, 1102, 911, 738, 621); δ_H (400 MHz, CDCl$_3$), 7.76 – 7.64 (4H, m, Ar**H**), 7.40 – 7.27 (4H, m, Ar**H**), 4.42 (2H, t, *J* = 6.2 Hz, CO$_2$C**H$_2$**CH$_2$CON), 4.15 – 4.09 (1H, m, SCH$_2$C**H**), 3.63 – 3.55 (2H, m, CH$_2$CH$_2$C**H$_2$**NCO), 3.09 (2H, d, *J* = 6.6 Hz, SC**H$_2$**CH), 3.02 – 2.96 (4H, m, 2 × C**H$_2$**), 2.85 (2H, t, *J* = 6.9 Hz, C**H$_2$**), 2.34 – 2.28 (2H, m, CH$_2$C**H$_2$**CO$_2$), 1.68 – 1.59 (2H, m, C**H$_2$**), 1.57 – 1.47 (2H, m, C**H$_2$**), 1.39 – 1.21 (14H, m, 7 × C**H$_2$**); δ_C (100 MHz, CDCl$_3$), 174.5 (**C**O), 173.9 (**C**O), 172.9 (**C**O), 146.1 (2C, Ar**C**), 141.1 (2C, Ar**C**), 127.6 (2C, Ar**C**H), 127.1 (2C, Ar**C**H), 125.0 (2C, Ar**C**H), 120.0 (2C, Ar**C**H), 59.6 (CO$_2$**C**H$_2$CH$_2$CON), 47.0 (**C**H), 44.0 (CH$_2$CH$_2$**C**H$_2$NCO), 39.0 (**C**H$_2$), 37.1 (**C**H$_2$), 36.9 (**C**H$_2$), 34.1 (**C**H$_2$), 28.3 (**C**H$_2$), 27.9 (**C**H$_2$), 27.8 (**C**H$_2$), 27.6 (**C**H$_2$), 27.2 (**C**H$_2$), 27.1 (**C**H$_2$), 27.0 (**C**H$_2$), 26.7 (**C**H$_2$), 25.1 (**C**H$_2$), 24.7 (**C**H$_2$); HRMS (ESI): calcd. for $C_{32}H_{41}NNaO_4S$, 558.2649. Found: [MNa]$^+$, 558.2647 (0.3 ppm error).

Lab Notebook reference: KP339_B

5-(3-Mercaptopropanoyl)-1-thia-5-azacycloheptadecane-4,17-dione (3.132)

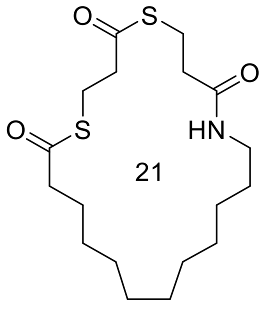


3.132

Oxalyl chloride (0.190 mL, 2.25 mmol) was added to a suspension of 3-(tritylthio)propanoic acid **3.36** (525 mg, 1.51 mmol) in DCM (7.5 mL), followed by a catalytic amount of DMF (1 drop). The resulting mixture was stirred at RT for 30 min and concentrated *in vacuo* to remove all solvent and excess oxalyl chloride. The resulting 3-(tritylthio)propanoyl chloride **3.37** was dissolved in DCM (3 mL) and added to a pre-stirred mixture of 1-thia-5-azacycloheptadecane-4,17-dione **3.29** (149 mg, 0.521 mmol), DMAP (7.0 mg, 0.057 mmol) and pyridine (0.243 mL, 3.00 mmol) in DCM (7 mL) under an argon atmosphere. The reaction mixture was then heated to 50 °C and stirred for 18 h. The solvent was removed *in vacuo*, and the product mixture was loaded onto a short silica plug and eluted (SiO_2, 1:9 ethyl acetate: hexane → 1:4 ethyl acetate: hexane) to remove the majority of the excess carboxylic acid and pyridine residues, and concentrated *in vacuo* to afford a sample of crude 5-(3-(tritylthio)propanoyl)-1-thia-5-azacycloheptadecane-4,17-dione (**3.138**) as a white solid, which was used without further purification, 274 mg of this crude material was obtained. [Data for crude **3.138**: m.p. 31 – 45 °C; R_f 0.79 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3058, 2928, 2856, 1819, 1690, 1595, 1489, 1444, 1370, 1132, 1106, 1034, 908, 730, 698, 676, 619, 506; δ_H (400 MHz, $CDCl_3$), 7.49 – 7.41 (5H, m, Ar**H**), 7.33 – 7.18 (10H, m, Ar**H**), 3.59 – 3.51 (2H, m, $CH_2CH_2\mathbf{CH_2}NCO$), 3.15 (2H, t, *J* = 6.5 Hz, $COS\mathbf{CH_2}CH_2CON$), 2.90 (2H, t, *J* = 6.5 Hz, $COSCH_2\mathbf{CH_2}CON$), 2.76 (2H, t, *J* = 7.0 Hz, $\mathbf{CH_2}CH_2SC(Ph)_3$), 2.62 – 2.57 (2H, m, $CH_2\mathbf{CH_2}COS$), 2.54 (2H, t, *J* = 7.0 Hz, $CH_2\mathbf{CH_2}SC(Ph)_3$), 1.76 – 1.66 (2H, m, $\mathbf{CH_2}$), 1.53 – 1.43 (2H, m, $\mathbf{CH_2}$), 1.41 – 1.18 (14H, m, 7 × $\mathbf{CH_2}$); δ_C (100 MHz, $CDCl_3$), 200.1 (**C**OS), 174.5 (**C**O), 173.7 (**C**O), 144.8 (3 × Ar**C**), 129.7 (6 × Ar**C**H), 127.9 (6 × Ar**C**H), 126.7 (3 × Ar**C**H), 66.9 (**C**Ph_3), 44.1 ($CH_2CH_2CH_2NCO$), 43.7 ($\mathbf{C}H_2COS$), 38.5 ($\mathbf{C}H_2CH_2SC(Ph)_3$), 37.9 ($COSCH_2\mathbf{C}H_2CON$), 27.9 ($\mathbf{C}H_2$), 27.84 ($\mathbf{C}H_2$), 27.77 ($\mathbf{C}H_2$), 27.2 (2 × $\mathbf{C}H_2$), 27.1 ($\mathbf{C}H_2$), 26.8 ($\mathbf{C}H_2$), 26.6 ($\mathbf{C}H_2$), 25.14 ($\mathbf{C}H_2$), 25.05 ($\mathbf{C}H_2$), 23.8 ($COS\mathbf{C}H_2$); HRMS (ESI): calcd. for $C_{37}H_{45}NNaO_3S_2$, 638.2733. Found: $[MNa]^+$, 638.2738 (–0.7 ppm error)]. This mixture was then dissolved in DCM (4.4 mL) under an argon atmosphere, before TFA (0.436 mL, 5.70 mmol) was added and the solution stirred for 3 min. Next, triisopropylsilane (0.109 mL, 0.530 mmol) was added and the solution stirred for a further 30 min. The mixture was then diluted with DCM (1.5 mL) and washed with water (5 mL). The aqueous layer was then extracted with DCM (3 × 1.5 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, hexane → 3:97 ethyl acetate: hexane → 1:19 ethyl acetate: hexane → 1:9 ethyl acetate: hexane) afforded the *title* *compound* as a colorless oil (52.6 mg, 27% from **3.29**); R_f 0.27 (4:1 hexane: ethyl acetate); ν_{max}/cm^{-1} (thin film) 2926, 2855, 1687, 1460, 1371, 1206, 1132, 1105, 1016, 948, 732, 698, 600; δ_H (400 MHz, $CDCl_3$), 3.63–3.56 (2H, m, $CH_2CH_2\mathbf{CH_2}NCO$), 3.18–3.11 (4H, m, $C\mathbf{H_2}CH_2SH$ and $COSC\mathbf{H_2}$), 2.90 (2H, t, *J* = 6.6 Hz, $COSCH_2C\mathbf{H_2}CON$), 2.78 (2H, dt, *J* = 8.4, 6.6 Hz, $CH_2C\mathbf{H_2}SH$), 2.59–2.53 (2H, m, $CH_2C\mathbf{H_2}CO_2$), 1.72–1.60 (2H, m, $C\mathbf{H_2}$ [overlapping]), 1.64 (1H, t, *J* = 8.4 Hz, $CH_2CH_2S\mathbf{H}$ [overlapping]), 1.55–1.45 (2H, m, $C\mathbf{H_2}$), 1.38–1.15 (14H, m, 7 × $C\mathbf{H_2}$); δ_C (100 MHz, $CDCl_3$), 200.2 (**C**OS), 174.3 (**C**O), 173.9 (**C**O), 44.3 ($CH_2CH_2\mathbf{C}H_2NCO$), 43.8 ($\mathbf{C}H_2COS$), 43.6 ($\mathbf{C}H_2CH_2SH$), 37.9 ($COSCH_2\mathbf{C}H_2CON$), 27.94 ($\mathbf{C}H_2$), 27.85 ($\mathbf{C}H_2$), 27.8 ($\mathbf{C}H_2$), 27.3 ($\mathbf{C}H_2$), 27.2 ($\mathbf{C}H_2$), 26.8 ($\mathbf{C}H_2$), 26.7 ($\mathbf{C}H_2$), 25.2 ($\mathbf{C}H_2$), 25.1 ($\mathbf{C}H_2$), 23.9 ($COS\mathbf{C}H_2$), 19.9 ($CH_2\mathbf{C}H_2SH$); HRMS (ESI): calcd. for $C_{18}H_{32}NO_3S_2$, 374.1818. Found: $[MH]^+$, 374.1819 (–0.1 ppm error).

Lab Notebook reference: KP371

1,5-Dithia-9-azacyclohenicosane-4,8,21-trione (3.133)

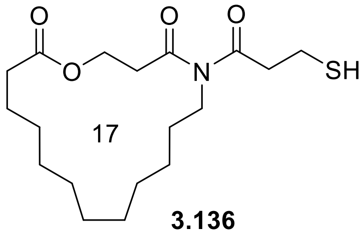


3.133

5-(3-Mercaptopropanoyl)-1-thia-5-azacycloheptadecane-4,17-dione (**3.132**) (45.0 mg, 0.120 mmol) was dissolved in $CDCl_3$ (0.7 mL) and transferred to an NMR tube. To it was added triethylamine (33 µL, 0.240 mmol) in $CDCl_3$ (0.2 mL), and then the reaction mixture was heated to 55 °C in an oil bath for 8 h (doing the reaction in an NMR tube enabled us to monitor progress of the rearrangement using ^1H NMR). The mixture was then concentrated and purified by flash column chromatography (SiO_2, hexane → 3:97 ethyl acetate: hexane → 1:19 ethyl acetate: hexane → 1:9 ethyl acetate: hexane → 1:4 ethyl acetate: hexane → 1:1 ethyl acetate: hexane → 2:1 ethyl acetate: hexane) afforded some recovered starting material **3.132** (6.6 mg, 15%) and the *title compound* **3.133** as a pasty white solid (13.9 mg, 31%). Data for **3.133**: m.p. 87–89 °C; R_f 0.12 (1:1 ethyl acetate: hexane); ν_{max}/cm^{-1} (thin film) 3300, 2925, 2854, 1687, 1645, 1549, 1409, 1262, 1161, 1052, 958, 731, 698, 601; δ_H (400 MHz, $CDCl_3$), 5.79 (1H, br t, *J* = 6.0 Hz, N**H**), 3.28 (2H, q, *J* = 6.0 Hz, $C\mathbf{H_2}NHCO$), 3.22–3.17 (2H, m, $SC\mathbf{H_2}CH_2CONH$), 3.14 (2H, t, *J* = 6.7 Hz, $COSC\mathbf{H_2}CH_2COS$), 2.83 (2H, t, *J* = 6.7 Hz, $COSCH_2C\mathbf{H_2}COS$), 2.58–2.51 (2H, m, $CH_2CH_2C\mathbf{H_2}COS$), 2.50–2.44 (2H, m, $SCH_2C\mathbf{H_2}CONH$), 1.70 (2H, t, *J* = 6.7 Hz, $C\mathbf{H_2}$), 1.55–1.44 (2H, m, $C\mathbf{H_2}$), 1.38–1.18 (14H, m, 7 × C**H₂**); δ_C (100 MHz, $CDCl_3$), 199.6 (**C**OS), 197.8 (**C**OS), 170.9 (**C**ON), 44.0 (CH_2CH_2**C**H_2COS), 43.8 ($COSCH_2$**C**H_2COS), 39.7 (**C**H_2NHCO), 36.6 (SCH_2**C**H_2CONH), 29.3 (**C**H_2), 28.9 (**C**H_2), 28.7 (**C**H_2), 28.5 (**C**H_2), 28.2 (**C**H_2), 28.1 (**C**H_2), 28.0 (**C**H_2), 26.5 (**C**H_2), 25.6 (COS**C**H_2CH_2CONH), 25.3 (**C**H_2), 24.3 (COS**C**H_2CH_2COS); HRMS (ESI): calcd. for $C_{18}H_{32}NO_3S_2$, 374.1818. Found: $[MH]^+$, 374.1812 (1.5 ppm error).

Lab Notebook reference: KP372

5-(3-Mercaptopropanoyl)-1-oxa-5-azacycloheptadecane-4,17-dione (3.136)

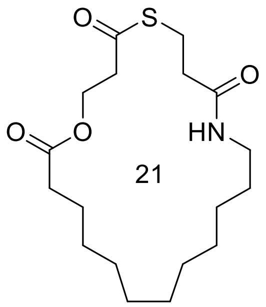


3.136

Oxalyl chloride (0.340 mL, 4.00 mmol) was added to a suspension of 3-(tritylthio)propanoic acid **3.36** (467 mg, 1.34 mmol) in DCM (13.5 mL), followed by a catalytic amount of DMF (1 drop). The resulting mixture was stirred at RT for 30 min and concentrated *in vacuo* to remove all solvent and excess oxalyl chloride. The resulting 3-(tritylthio)propanoyl chloride **3.37** was dissolved in DCM (3 mL) and was added to a pre-stirred mixture of 1-oxa-5-azacycloheptadecane-4,17-dione **3.134**[67] (120 mg, 0.445 mmol), DMAP (6.7 mg, 0.055 mmol) and pyridine (0.216 mL, 2.67 mmol) in DCM (6 mL) under an argon atmosphere. The reaction mixture was then heated at reflux at 50 °C and stirred for 18 h. The solvent was removed *in vacuo*, and the reaction mixture loaded onto a short silica plug and eluted (SiO_2, 1:9 ethyl acetate: hexane → 1:4 ethyl acetate: hexane) to remove the majority of the excess carboxylic acid and pyridine residues, and then concentrated *in vacuo* to afford crude 5-(3-(tritylthio)propanoyl)-1-oxa-5-azacycloheptadecane-4,17-dione (**3.139**) as a colorless oil which was used without further purification, with 220 mg of this crude material obtained. [Data for crude **3.139**: R_f 0.67 (1:1 hexane: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3057, 2929, 2857, 1733, 1696, 1642, 1489, 1445, 1368, 1104, 1034, 910, 742, 699, 676, 620; δ_H (400 MHz, $CDCl_3$), 7.51–7.42 (5H, m, Ar**H**), 7.35–7.17 (10H, m, Ar**H**), 4.42 (2H, t, *J* = 6.0 Hz, CO_2C**H₂**CH_2CON), 3.53 (2H, m, CH_2CH_2C**H₂**NCO), 3.01 (2H, t, *J* = 6.0 Hz, CO_2CH_2C**H₂**CON), 2.59 (4H, m, C**H₂**CH_2S and CH_2C**H₂**S), 2.33 (2H, m, CH_2C**H₂**CO_2), 1.70–1.60 (2H, m, C**H₂**), 1.53–1.43 (2H, m, C**H₂**), 1.42–1.24 (14H, m, 7 × C**H₂**); Diagnostic ^{13}C NMR resonances: δ_C (100 MHz, $CDCl_3$), 174.4 (**C**O), 173.8 (**C**O), 172.7 (**C**O), 59.6 (CO_2**C**H_2CH_2CON), 43.8 (CH_2CH_2**C**H_2NCO), 37.6 (**C**H_2), 37.2 (CO_2CH_2**C**H_2CON), 34.1 (CH_2**C**H_2CO_2); HRMS (ESI): calcd. for $C_{37}H_{45}NNaO_4S$, 622.2962. Found: $[MNa]^+$, 622.2973 (–1.2 ppm error)]. This mixture was then dissolved in DCM (4.3 mL) under an argon atmosphere, before TFA (0.429 mL, 5.60 mmol) was added and the solution stirred for 3 min. Next, triisopropylsilane (0.096 mL, 0.470 mmol) was added and the solution stirred for a further 30 min. The mixture was then diluted with DCM (1.5 mL) and washed with water (5 mL). The aqueous layer was then extracted with DCM (3 × 1.5 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, hexane → 3:97 ethyl acetate: hexane → 1:19 ethyl acetate: hexane → 1:9 ethyl acetate: hexane → 1:4 ethyl acetate: hexane) afforded the *title compound* as a colorless oil (47.3 mg, 30% from **3.134**); R_f 0.14 (4:1 hexane: ethyl acetate); ν_{max}/cm^{-1} (thin film) 2927, 2856, 1732, 1693, 1460, 1367, 1208, 1131, 1102, 732; δ_H (400 MHz, $CDCl_3$), 4.43 (2H, t, *J* = 6.3 Hz, $CO_2C\mathbf{H_2}CH_2CON$), 3.66–3.60 (2H, m, $CH_2CH_2C\mathbf{H_2}NCO$), 3.09 (2H, t, *J* = 6.5 Hz, $C\mathbf{H_2}CH_2SH$), 3.01 (2H, t, *J* = 6.3 Hz, $CO_2CH_2C\mathbf{H_2}CON$), 2.80 (2H, dt, *J* = 8.5, 6.5 Hz, $CH_2C\mathbf{H_2}SH$), 2.35 – 2.29 (2H, m, $CH_2C\mathbf{H_2}CO_2$), 1.67 (1H, t, *J* = 8.5 Hz, $CH_2CH_2S\mathbf{H}$ [overlapping]), 1.68–1.60 (2H, m, $C\mathbf{H_2}$ [overlapping]), 1.59–1.50 (2H, m, $C\mathbf{H_2}$), 1.41–1.21 (14H, m, 7 × $C\mathbf{H_2}$); δ_C (100 MHz, $CDCl_3$), 174.2 ($\mathbf{C}O$), 174.0 ($\mathbf{C}O$), 172.9 ($\mathbf{C}O$), 59.6 ($CO_2\mathbf{C}H_2CH_2CON$), 44.0 ($CH_2CH_2\mathbf{C}H_2NCO$), 42.8 ($\mathbf{C}H_2CH_2SH$), 36.9 ($CO_2CH_2\mathbf{C}H_2CON$), 34.2 ($CH_2\mathbf{C}H_2CO_2$), 27.92 ($\mathbf{C}H_2$), 27.85 ($\mathbf{C}H_2$), 27.6 ($\mathbf{C}H_2$), 27.2 ($\mathbf{C}H_2$), 27.1 ($\mathbf{C}H_2$), 27.0 ($\mathbf{C}H_2$), 26.7 ($\mathbf{C}H_2$), 25.1 ($\mathbf{C}H_2$), 24.8 ($\mathbf{C}H_2$), 19.8 ($CH_2\mathbf{C}H_2SH$); HRMS (ESI): calcd. for $C_{18}H_{32}NO_4S$, 358.2047. Found: $[MH]^+$, 358.2029 (5.0 ppm error).

Lab Notebook reference: KP373

1-Oxa-5-thia-9-azacyclohenicosane-4,8,21-trione (3.137)



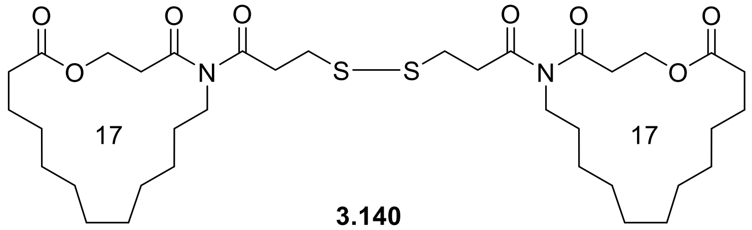
3.137

5-(3-Mercaptopropanoyl)-1-oxa-5-azacycloheptadecane-4,17-dione (**3.136**) (47.3 mg, 0.132 mmol) was dissolved in $CDCl_3$ (1.5 mL) and transferred to a round bottomed flask under argon. To it was added triethylamine (37 µL, 0.265 mmol) in $CDCl_3$ (0.5 mL). The reaction mixture was heated to 55 °C in an oil bath for 12 h. Purification by flash column chromatography (SiO_2, hexane → 3:97 ethyl acetate: hexane → 1:19 ethyl acetate: hexane → 1:9 ethyl acetate: hexane → 1:4 ethyl acetate: hexane → 1:1 ethyl acetate: hexane) afforded the *title compound* **3.137** (8.0 mg, 17%) as an off white solid, along with disulfide **3.140** (7.3 mg, 16%; see below for data for **3.140**). Data for **3.137**: m.p. 78 – 80 °C;

R_f 0.14 (1:1 ethyl acetate: hexane); ν_{max}/cm^{-1} (thin film) 3301, 2926, 2855, 1737, 1690, 1647, 1551, 1459, 1256, 1167, 1097, 1020, 715; δ_H (400 MHz, $CDCl_3$), 5.80 (1H, br s, N**H**), 4.38 (2H, t, *J* = 5.9 Hz, $CO_2C\mathbf{H_2}CH_2COS$), 3.30 (2H, q, *J* = 5.8 Hz, $C\mathbf{H_2}NHCO$), 3.18 (2H, t, *J* = 6.8 Hz, $SC\mathbf{H_2}CH_2$), 2.85 (2H, t, *J* = 5.9 Hz, $CO_2CH_2C\mathbf{H_2}COS$), 2.47 (2H, t, *J* = 6.8 Hz, $SCH_2C\mathbf{H_2}$), 2.34 – 2.27 (2H, m, $CH_2C\mathbf{H_2}CO_2$), 1.67 – 1.58 (2H, m, $C\mathbf{H_2}$), 1.55 – 1.46 (2H, m, $C\mathbf{H_2}$), 1.39 – 1.21 (14H, m, 7 × $C\mathbf{H_2}$); δ_C (100 MHz, $CDCl_3$), 197.0 (**C**OS), 173.8 (**C**O_2), 170.9 (**C**ON), 59.7 ($CO_2\mathbf{C}H_2CH_2COS$), 43.4 ($CO_2CH_2\mathbf{C}H_2COS$), 39.6 ($\mathbf{C}H_2NHCO$), 36.8 ($SCH_2\mathbf{C}H_2$), 34.1 ($CH_2\mathbf{C}H_2CO_2$), 28.9 ($\mathbf{C}H_2$), 28.5 ($\mathbf{C}H_2$), 28.32 (2 × $\mathbf{C}H_2$), 28.28 (2 × $\mathbf{C}H_2$), 27.9 ($\mathbf{C}H_2$), 26.0 ($\mathbf{C}H_2$), 25.7 ($S\mathbf{C}H_2CH_2$), 24.7 ($\mathbf{C}H_2$); HRMS (ESI): calcd. for $C_{18}H_{31}NNaO_4S$, 380.1866. Found: $[MNa]^+$, 380.1866 (0.1 ppm error).

Lab Notebook reference: KP374_B

5,5'-(3,3'-Disulfanediylbis(propanoyl))bis(1-oxa-5-azacycloheptadecane-4,17-dione) (3.140)

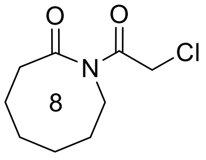


3.140

Data for **3.140** (for synthetic procedure, see above): R_f 0.58 (1:1 ethyl acetate: hexane); ν_{max}/cm^{-1} (thin film) 2926, 2855, 1733, 1695, 1459, 1366, 1260, 1131, 1100, 1020, 913, 802, 732, 470; δ_H (400 MHz, $CDCl_3$), 4.43 (4H, t, *J* = 6.2 Hz, 2 × $CO_2C\mathbf{H_2}CH_2CON$), 3.68 – 3.56 (4H, m, 2 × $CH_2CH_2C\mathbf{H_2}NCO$), 3.18 (4H, t, *J* = 6.8 Hz, 2 × $C\mathbf{H_2}CH_2S$), 3.01 (4H, t, *J* = 6.2 Hz, 2 × $CO_2CH_2C\mathbf{H_2}CON$), 2.96 (4H, t, *J* = 6.8 Hz, 2 × $CH_2C\mathbf{H_2}S$), 2.34–2.28 (4H, m, 2 × $CH_2C\mathbf{H_2}CO_2$), 1.70–1.60 (4H, m, 2 × $C\mathbf{H_2}$), 1.59–1.50 (4H, m, 2 × $C\mathbf{H_2}$), 1.39–1.18 (28H, m, 14 × $C\mathbf{H_2}$); δ_C (100 MHz, $CDCl_3$), 174.4 (2 × **C**O), 174.0 (2 × **C**O), 173.0 (2 × **C**O), 59.7 (2 × $CO_2\mathbf{C}H_2CH_2CON$), 44.2 (2 × $CH_2CH_2\mathbf{C}H_2NCO$), 38.4 (2 × $\mathbf{C}H_2CH_2S$), 37.0 (2 × $CO_2CH_2\mathbf{C}H_2CON$), 34.2 (2 × $CH_2\mathbf{C}H_2CO_2$), 33.3 (2 × $CH_2\mathbf{C}H_2S$), 28.0 (2 × $\mathbf{C}H_2$), 27.9 (2 × $\mathbf{C}H_2$), 27.7 (2 × $\mathbf{C}H_2$), 27.23 (2 × $\mathbf{C}H_2$), 27.19 (2 × $\mathbf{C}H_2$), 27.0 (2 × $\mathbf{C}H_2$), 26.7 (2 × $\mathbf{C}H_2$), 25.2 (2 × $\mathbf{C}H_2$), 24.8 (2 × $\mathbf{C}H_2$); HRMS (ESI): calcd. for $C_{36}H_{60}N_2NaO_8S_2$, 735.3683. Found: $[MNa]^+$, 735.3709 (–3.5 ppm error).

Lab Notebook reference: KP374_A

1-(2-Chloroacetyl)azocan-2-one (4.17)

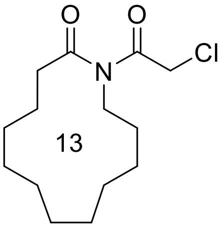


4.17

A mixture of 1-aza-2-cyclooctanone **1.218** (64.6 mg, 0.508 mmol), DMAP (19.0 mg, 0.152 mmol) and pyridine (0.243 mL, 3.00 mmol) in DCM (10 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, chloroacetyl chloride **4.16** (0.119 mL, 1.50 mmol) was added and the resulting mixture was stirred at room temperature for 23 hours. The mixture was concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:9 ethyl acetate: hexane → 1:1 ethyl acetate: hexane → ethyl acetate → 19:1 ethyl acetate: methanol) afforded the *title compound* as an orange oil (73.1 mg, 72%); R_f 0.68 (9:1 ethyl acetate: methanol); ν_{max}/cm^{-1} (neat) 2928, 2859, 1686, 1446, 1379, 1334, 1193, 1174, 1125, 1090, 788, 765, 698, 592); δ_H (400 MHz, $CDCl_3$) 4.68 (2H, s, C**H₂**Cl), 3.95 – 3.88 (2H, m, C**H₂**NCO), 2.66 – 2.60 (2H, m, C**H₂**CON), 1.87 – 1.79 (2H, m, C**H₂**), 1.73 – 1.59 (2H, m, C**H₂**), 1.59 – 1.52 (2H, m, C**H₂**), 1.45 – 1.37 (2H, m, C**H₂**); δ_C (100 MHz, $CDCl_3$) data for major rotamer, 178.4 (**C**ON), 169.7 (**C**OCH₂Cl), 47.9 (CO**C**H₂Cl), 44.3 (**C**H₂N), 36.8 (**C**H₂CON), 29.1 (**C**H₂), 29.0 (**C**H₂), 26.2 (**C**H₂), 24.0 (**C**H₂); HRMS (ESI): calcd. for $C_9H_{14}{}^{35}ClNNaO_2$, 226.0605. Found: $[MNa]^+$, 226.0600 (2.4 ppm error).

Lab notebook reference: KP108

1-(2-Chloroacetyl)-1-azacyclotridecan-2-one (4.18)

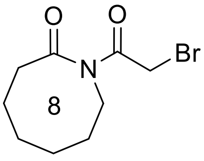


4.18

A mixture of laurolactam **1.210** (102 mg, 0.518 mmol), DMAP (10.0 mg, 0.083 mmol) and pyridine (0.243 mL, 3.00 mmol) in DCM (10 mL) under an argon atmosphere was stirred at 50 °C for 30 mins. Next, chloroacetyl chloride **4.16** (0.119 mL, 1.50 mmol) was added and the resulting mixture was stirred at room temperature for 5 hours. The mixture was concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:9 ethyl acetate: hexane → 1:5 ethyl acetate: hexane → 1:3 ethyl acetate: hexane → 1:1 ethyl acetate: hexane) afforded the *title compound* as an orange oil (147 mg, 100%); R$_f$ 0.73 (9:1 ethyl acetate: methanol); ν$_{max}$/cm^{-1} (neat) 2928, 2860, 1697, 1464, 1446, 1361, 1282, 1261, 1215, 1179, 1121, 1047, 968, 922, 786, 757, 730, 639, 604); δ$_H$ (400 MHz, CDCl$_3$) 4.62 (2H, s, C**H$_2$**Cl), 3.69 – 3.60 (2H, m, C**H$_2$**NCO), 2.52 – 2.45 (2H, m, C**H$_2$**CON), 1.77 – 1.60 (4H, m, 2 × C**H$_2$**), 1.47 – 1.36 (4H, m, 2 × C**H$_2$**), 1.36 – 1.20 (10H, m, 5 × C**H$_2$**); δ$_C$ (100 MHz, CDCl$_3$) 176.6 (**C**ON), 169.7 (**C**OCH$_2$Cl), 47.7 (CO**C**H$_2$Cl), 44.8 (**C**H$_2$N), 35.0 (**C**H$_2$CON), 25.84 (**C**H$_2$), 25.75 (**C**H$_2$), 25.0 (**C**H$_2$), 24.7 (**C**H$_2$), 24.5 (**C**H$_2$), 24.1 (**C**H$_2$), 24.0 (**C**H$_2$), 23.7 (**C**H$_2$), 23.5 (**C**H$_2$); HRMS (ESI): calcd. for $C_{14}H_{24}{}^{35}ClNNaO_2$, 296.1388. Found: [MNa]$^+$, 296.1388 (–0.2 ppm error).

Lab notebook reference: KP111

1-(2-Bromoacetyl)azocan-2-one (4.21)

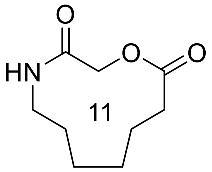


4.21

A mixture of 1-aza-2-cyclooctanone **1.218** (127 mg, 0.995 mmol), DMAP (28.8 mg, 0.236 mmol) and pyridine (0.480 mL, 5.94 mmol) in DCM (20 mL) under an argon atmosphere was stirred at RT for 5 mins. Next, bromoacetyl bromide **4.23** (0.260 mL, 2.99 mmol) was added and the resulting mixture was stirred at room temperature for 2 hours. The mixture was concentrated *in vacuo*. Purification by flash column chromatography (SiO$_2$, 1:9 ethyl acetate: hexane → 1:7 ethyl acetate: hexane → 1:5 ethyl acetate: hexane) afforded the *title compound* as a brown oil (149 mg, 60%); R$_f$ 0.70 (9:1 ethyl acetate: methanol); ν$_{max}$/cm^{-1} (neat) 2930, 2860, 1688, 1445, 1380, 1334, 1285, 1246, 1175, 1126, 1090, 892, 681, 597); δ$_H$ (400 MHz, CDCl$_3$) 4.54 (2H, s, C**H$_2$**Br), 3.95 – 3.90 (2H, m, C**H$_2$**NCO), 2.70 – 2.64 (2H, m, C**H$_2$**CON), 1.90 – 1.82 (2H, m, C**H$_2$**), 1.74 – 1.66 (2H, m, C**H$_2$**), 1.66 – 1.54 (2H, m, C**H$_2$**), 1.47 – 1.41 (2H, m, C**H$_2$**); δ$_C$ (100 MHz, CDCl$_3$) data for major rotamer, 178.4 (**C**ON), 169.2 (**C**OCH$_2$Br), 44.4 (**C**H$_2$N), 36.8 (**C**H$_2$CON), 34.1 (CO**C**H$_2$Br), 29.1 (**C**H$_2$), 29.0 (**C**H$_2$), 26.2 (**C**H$_2$), 24.0 (**C**H$_2$); HRMS (ESI): calcd. for $C_9H_{14}{}^{79}BrNNaO_2$, 270.0100. Found: [MNa]$^+$, 270.0095 (1.9 ppm error).

Lab notebook reference: KP116/KP121

1-Oxa-4-azacycloundecane-3,11-dione (4.28)

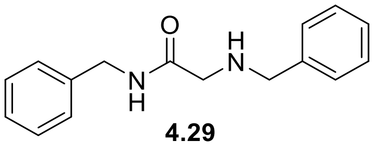


4.28

To a mixture of 1-(2-bromoacetyl)azocan-2-one **4.21** (67.0 mg, 0.270 mmol) and TEA (83 µL, 0.594 mmol) in DCM (5.4 mL) was added water (54 µL, 3.00 mmol) and stirred at RT for 2 hours. The reaction mixture was then diluted with DCM and to it was added 10% aqueous HCl (10 mL) and extracted with DCM (3 × 10 mL). The organics were dried over $MgSO_4$ and the mixture was concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:9 ethyl acetate: hexane → 1:1 ethyl acetate: hexane → ethyl acetate→ 1:19 methanol: ethyl acetate) afforded the *title compound* (as a 10:1 mixture of rotamers) as light yellow crystalline solid (21.4 mg, 43%); R_f 0.44 (9:1 ethyl acetate: methanol); ν_{max}/cm^{-1} (neat) 3289, 2928, 2869, 1732, 1661, 1552, 1437, 1231, 1211, 1143, 1088, 1050, 728, 691; δ_H (400 MHz, $CDCl_3$) 5.86 (1H, br s, NH), 4.66 – 4.56 (2H, m, C**H₂**CON), 3.28 – 3.23 (2H, m, C**H₂**N), 2.45 – 2.40 (2H, m, C**H₂**CO₂), 1.81 – 1.72 (2H, m, C**H₂**), 1.64 – 1.56 (2H, m, C**H₂**), 1.62 – 1.54 (2H, m, C**H₂**), 1.51 – 1.33 (4H, m, C**H₂**); δ_C (100 MHz, $CDCl_3$), 173.5 (**C**O), 168.3 (**C**O), 64.2 (**C**H₂CON), 39.5 (**C**H₂N), 34.8 (**C**H₂CO₂), 25.9 (**C**H₂), 25.24 (**C**H₂), 25.22 (**C**H₂), 23.2 (**C**H₂); HRMS (ESI): calcd. for $C_9H_{16}NO_3$, 186.1125. Found: $[MH]^+$, 186.1124 (0.4 ppm error). Data match those reported previously.[67]

Lab notebook reference: KP130

***N*-Benzyl-2-(benzylamino)acetamide (4.29)**

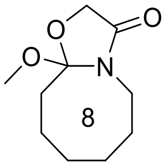


4.29

To a cooled solution of benzylamine (0.066 mL, 0.609 mmol) in DCM (2.2 mL) was added a cold solution of 1-(2-bromoacetyl)azocan-2-one **4.21** (75.5 mg, 0.304 mmol) in DCM (4.0 mL); dropwise over the course of 7 minutes. This warmed to RT and stirred for 2.5 hours. The mixture was concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:9 ethyl acetate: hexane → 1:7 ethyl acetate: hexane → 1:5 ethyl acetate: hexane → 1:3 ethyl acetate: hexane → 1:1 ethyl acetate: hexane) afforded the *title compound* **4.29** as an orange oil (17.5 mg, 23%), as well as **4.28** (6.3 mg, 11%). Data for **4.29**: R_f 0.29 (9:1 ethyl acetate: methanol); ν_{max}/cm^{-1} (neat) 3301, 3030, 2926, 1657, 1529, 1496, 1454, 1256, 1029, 737, 699); δ_H (400 MHz, $CDCl_3$) 7.55 (1H, br s, N**H**), 7.36 – 7.20 (10H, m, Ar**H**), 4.48 – 4.40 (2H, m, C**H₂**NHCO), 3.75 (2H, s, C**H₂**), 3.35 (2H, s, C**H₂**); δ_C (100 MHz, $CDCl_3$) 171.5 (**C**ON), 139.2 (Ar**C**), 138.4 (Ar**C**), 128.8 (2C, Ar**CH**), 128.7 (2C, Ar**CH**), 128.2 (2C, Ar**CH**), 127.8 (2C, Ar**CH**), 127.6 (Ar**CH**), 127.5 (Ar**CH**), 54.1 (**C**H_2N), 52.0 (**C**H_2N), 43.1 (**C**H_2N); HRMS (ESI): calcd. for $C_{16}H_{19}N_2O$, 255.1492. Found: $[MH]^+$, 255.1491 (0.3 ppm error).

Lab notebook reference: KP122_C

10a-Methoxy-octahydro-2H-[1,3]oxazolo[3,2-a]azocin-3-one (4.31)

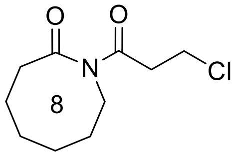


4.31

To a mixture of 1-aza-2-cyclooctanone **1.218** (63.6 mg, 0.500 mmol), DMAP (18.0 mg, 0.148 mmol) and pyridine (0.243 mL, 3.00 mmol) in THF (10 mL) was added bromoacetyl bromide **4.23** (0.131 mL, 1.50 mmol) and stirred at RT for 5 mins. Then H_2O (1.01 mL, 5.60 mmol) and Et_3N (0.105 mL, 0.750 mmol) were added and the mixture was stirred for 1.5 hours. Afterwards the reaction mixture was diluted with DCM (20 mL) and washed with aq. HCl (10%, 20 mL). The aqueous layer was extracted with DCM (3 × 20 mL) and the combined organic layers were dried over $MgSO_4$. The mixture was concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:9 ethyl acetate: hexane → 1:5 ethyl acetate: hexane → 1:1 ethyl acetate: hexane) afforded the *title compound* as an orange solid (6.4 mg, 6%); R_f 0.61 (9:1 ethyl acetate: methanol); δ_C (100 MHz, $CDCl_3$), 170.7 (**C**ON), 115.2 (**C** quat), 68.6 (NC(O)**C**H_2O), 48.3 (**C**H_3), 39.1 (**C**H_2N), 34.6 (**C**H_2C quat), 27.1 (**C**H_2), 26.3 (**C**H_2), 23.9 (**C**H_2), 21.6 (**C**H_2). ^{13}C NMR data matches those previously reported.[67]

Lab notebook reference: KP135_E

1-(3-Chloropropanoyl)azocan-2-one (4.33)

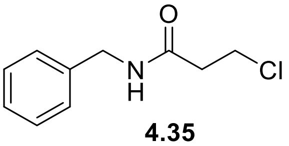


4.33

A mixture of 1-aza-2-cyclooctanone **1.218** (64.4 mg, 0.506 mmol), DMAP (22.3 mg, 0.182 mmol) and pyridine (0.243 mL, 3.00 mmol) in DCM (10 mL) under an argon atmosphere was stirred at RT for 5 mins. Next, 3-chloropropionyl chloride **4.32** (0.143 mL, 1.50 mmol, 3.0 eqv.) was added and the resulting mixture was stirred at room temperature for 20 hours. The mixture was concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:9 ethyl acetate: hexane → 1:5 ethyl acetate: hexane → 1:1 ethyl acetate: hexane) afforded the *title compound* as a light yellow oil (21.1 mg, 19%); R_f 0.68 (9:1 ethyl acetate: methanol); ν_{max}/cm^{-1} (neat) 2928, 2859, 1686, 1446, 1376, 1247, 1199, 1175, 1126, 1092, 998, 684, 593); δ_H (400 MHz, $CDCl_3$) 3.94 – 3.88 (2H, m, C**H₂**N), 3.79 (2H, t, *J* = 6.5 Hz, $CH_2C\mathbf{H_2}Cl$), 3.34 (2H, t, *J* = 6.5 Hz, $C\mathbf{H_2}CH_2Cl$), 2.67 – 2.62 (2H, m, $C\mathbf{H_2}CON$), 1.90 – 1.82 (2H, m, $C\mathbf{H_2}$), 1.73 – 1.64 (2H, m, $C\mathbf{H_2}$), 1.62 – 1.54 (2H, m, $C\mathbf{H_2}$), 1.48 – 1.40 (2H, m, $C\mathbf{H_2}$); δ_C (100 MHz, $CDCl_3$), 178.5 (**C**ON), 173.4 ($\mathbf{C}OCH_2CH_2Cl$), 43.6 ($\mathbf{C}H_2N$), 42.5 ($CO\mathbf{C}H_2CH_2Cl$), 39.6 ($COCH_2\mathbf{C}H_2Cl$), 37.1 ($\mathbf{C}H_2CON$), 29.5 ($\mathbf{C}H_2$), 29.0 ($\mathbf{C}H_2$), 26.2 ($\mathbf{C}H_2$), 24.0 ($\mathbf{C}H_2$); HRMS (ESI): calcd. for $C_{10}H_{16}{}^{35}ClNNaO_2$, 240.0762. Found: $[MNa]^+$, 240.0759 (1.3 ppm error).

Lab notebook reference: KP124

***N*-Benzyl-3-chloropropanamide (4.35)**



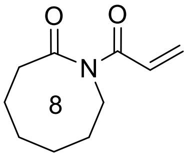
4.35

To a solution of 1-(3-chloropropanoyl)azocan-2-one **4.33** (21.1 mg, 0.096 mmol) in DCM (2 mL) was added benzyl amine (23 µL, 0.214 mmol, 2.2 equiv.) and stirred at room temperature for 26 hours. The mixture was concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:9 ethyl acetate: hexane → 1:2 ethyl acetate: hexane) afforded the *title compound* as a white solid (6.4 mg, 6%); m.p. 79 – 80 °C; R_f 0.57 (9:1 ethyl acetate: methanol); ν_{max}/cm^{-1} (neat) 3290, 3090, 1638, 1557, 1427, 696; δ_H (400 MHz, $CDCl_3$) 7.34 – 7.24 (5H, m, ArH), 5.95 (1H, br s, NH), 4.46 (2H, d, *J* = 5.7 Hz, ArC**H₂**), 3.82 (2H, t, *J* = 6.4 Hz, $CH_2C\mathbf{H_2}Cl$), 2.64 (2H, t, *J* = 6.4 Hz, $C\mathbf{H_2}CH_2Cl$); δ_C (100 MHz, $CDCl_3$), 169.4

(**C**ON), 137.9 (Ar**C**), 128.9 (2C, Ar**C**H), 127.9 (2C, Ar**C**H), 127.8 (Ar**C**H), 43.9 (Ar**C**H$_2$), 40.3 (COCH$_2$**C**H$_2$Cl), 39.7 (CO**C**H$_2$CH$_2$Cl); HRMS (ESI): calcd. for $C_{10}H_{13}{}^{35}ClNO$, 198.0680. Found: $[MH]^+$, 198.0680 (−0.1 ppm error).

Lab notebook reference: KP125

1-Acryloyl-azocan-2-one (4.37)



4.37

To a stirring solution of 1-aza-2-cyclooctanone **1.218** (1.28 g, 10.1 mmol) in dry THF (36 mL) cooled to 0 °C was added a solution of MeMgBr (3.0 M in diethyl ether, 3.65 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 **4.36** (1.22 mL, 15.0 mmol) was then 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 an oil that turned to a white crystalline solid (1.08 g, 59%); m.p. 29–33 °C; R_f 0.67 (9:1 ethyl acetate: methanol); ν_{max}/cm^{-1} (thin film) 2926, 2859, 1677, 1616, 1445, 1401, 1378, 1174, 1126, 1092, 972, 867, 797, 777, 585; δ_H (400 MHz, $CDCl_3$) 6.81 (1H, dd, *J* = 16.9, 10.3 Hz, NCOC**H**CHH’), 6.24 (1H, dd, *J* = 16.9, 1.7 Hz, NCOCHC**H**H’), 5.61 (1H, dd, *J* = 10.3, 1.7 Hz, NCOCHCH**H’**), 3.89 – 3.82 (2H, m, C**H$_2$**N), 2.63 – 2.57 (2H, m, C**H$_2$**CON), 1.86 – 1.77 (2H, m, C**H$_2$**), 1.74 – 1.65 (2H, m, C**H$_2$**), 1.58 – 1.50 (2H, m, C**H$_2$**), 1.44 – 1.36 (2H, m, C**H$_2$**); δ_C (100 MHz, $CDCl_3$), 178.9 (**C**ON), 169.4 (**C**OCHCH$_2$), 131.9 (CO**C**HCH$_2$), 127.6 (COCH**C**H$_2$), 43.8 (**C**H$_2$N), 36.7 (**C**H$_2$CON), 29.9 (**C**H$_2$), 29.3 (**C**H$_2$), 26.2 (**C**H$_2$), 23.9 (**C**H$_2$); HRMS (ESI): calcd. for $C_{10}H_{16}NO_2$, 182.1176. Found: $[MH]^+$, 182.1180 (–2.3 ppm error). Procedure adapted from a literature method.[108]

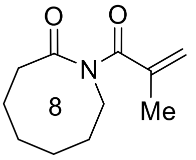
Lab notebook reference: KP526

The same product **4.37** was also prepared using TEA acylation conditions, using the following procedure:

A mixture of 1-aza-2-cyclooctanone **1.218** (127 mg, 0.995 mmol) and TEA (0.347 mL, 2.49 mmol) in THF (1.5 mL) was cooled to 0 °C. To this was added a 0 °C cooled solution of acryloyl chloride **4.36** (0.243 mL, 2.99 mmol) in THF (0.5 mL) dropwise. Under an argon atmosphere this mixture was stirred at 0 °C for 2 hours. Afterwards it was allowed to warm to RT and stirred for a further 3 hours. The reaction mixture was then quenched with aqueous NH_4Cl, extracted with DCM, then washed with $NaHCO_3$ and NaCl. The mixture was concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:9 ethyl acetate: hexane → 1:5 ethyl acetate: hexane) afforded the *title compound* as an oil that turned to a white crystalline film (70.1 mg, 39%). Procedure adapted from a literature method.[109]

Lab notebook reference: KP138

1-Methacryloylazocan-2-one (4.42)

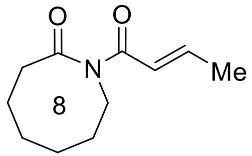


4.42

To a mixture of 1-aza-2-cyclooctanone **1.218** (638 mg, 5.01 mmol), DMAP (74.1 mg, 0.607 mmol) and pyridine (2.25 mL, 28.0 mmol) in DCM (50 mL) under an argon atmosphere was added methacryloyl chloride (0.862 mL, 8.82 mmol). The reaction mixture was stirred at room temperature for 4 hours. The mixture was then diluted with DCM (10 mL) and washed with 10% aq. HCl (50 mL). The aqueous layer was then extracted with DCM (3 × 25 mL) and the combined organic extracts concentrated *in vacuo*. This residue was dissolved in THF (50 mL) and LiOH (25 mL, 0.1 M), and the solution allowed to stir for 10 min. To this was added sat. $NaHCO_3$ (100 mL) and DCM (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*. Purification by automated flash column chromatography (using a 40 g pre-packed SiO_2 column, 0% → 35% ethyl acetate in hexanes) afforded the *title compound* as a white solid (485 mg, 50%); m.p. 25 – 27 °C; R_f 0.46 (1:1 ethyl acetate: hexane); ν_{max}/cm^{-1} (thin film) 2927, 2859, 1682, 1657, 1447, 1359, 1334, 1195, 1127, 1091, 997, 575; δ_H (400 MHz, $CDCl_3$) δ_H (400 MHz, $CDCl_3$) 5.14 (1H, p, *J* = 1.0, NCOC(CH_3)C**H**H’), 5.11 – 5.09 (1H, m, NCOC(CH_3)CH**H’**), 3.86 – 3.79 (2H, m, NC**H₂**), 2.62 – 2.55 (2H, m, C**H₂**CON), 1.95 – 1.93 (3H, m, NCOC(C**H₃**)CHH’), 1.87 – 1.80 (2H, m, C**H₂**), 1.80 – 1.72 (2H, m, C**H₂**), 1.62 – 1.53 (2H, m, C**H₂**), 1.50 – 1.43 (2H, m, C**H₂**); δ_C (100 MHz, $CDCl_3$) 178.6 (**C**O), 175.5 (**C**O), 143.2 (NCO**C**(CH_3)CHH’), 116.2 (NCOC(CH_3)**C**HH’), 44.0 (N**C**H_2), 36.0 (**C**H_2CON), 30.2 (**C**H_2), 29.0 (**C**H_2), 26.2 (**C**H_2), 23.9 (**C**H_2), 19.2 (**C**H_3); HRMS (ESI): calcd. for $C_{11}H_{17}NNaO_2$, 218.1151. Found: $[MNa]^+$, 218.1154 (–1.0 ppm error).

Lab notebook reference: KP180_B

1-[(2E)-But-2-enoyl]azocan-2-one (4.43)

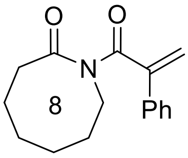


4.43

To a mixture of 1-aza-2-cyclooctanone **1.218** (130 mg, 1.03 mmol), DMAP (13.2 mg, 0.108 mmol) and pyridine (0.485 mL, 6.00 mmol) in DCM (10 mL) under an argon atmosphere was added crotonoyl chloride (0.147 mL, 1.54 mmol). The reaction mixture was stirred at room temperature for 1 hour then heated to 50 °C and stirred for 1 hour. The mixture was then diluted with DCM (5 mL) and washed with 10% aq. HCl (15 mL). The aqueous layer was then extracted with DCM (3 × 5 mL) and the combined organic extracts concentrated *in vacuo*. This residue was dissolved in THF (10 mL) and LiOH (5 mL, 0.1 M), and the solution allowed to stir for 10 min. To this was added sat. $NaHCO_3$ (20 mL) and DCM (20 mL). The aqueous layer was then extracted with DCM (3 × 20 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:9 ethyl acetate: hexane → 1:5 ethyl acetate: hexane) afforded the *title compound* as a yellow oil (106 mg, 53%); R_f 0.65 (9:1 ethyl acetate: methanol); ν_{max}/cm^{-1} (thin film) 2926, 2858, 1677, 1635, 1444, 1380, 1333, 1196, 1174, 1129, 1088; δ_H (400 MHz, $CDCl_3$) 6.88 (1H, dq, *J* = 15.1, 6.9 Hz, $CH_3C\mathbf{H}CHCON$), 6.59 (1H, dd, *J* = 15.1, 1.6 Hz, $CH_3CHC\mathbf{H}CON$), 3.87 – 3.79 (2H, m, $C\mathbf{H_2}N$), 2.62 – 2.55 (2H, m, $C\mathbf{H_2}CON$), 1.85 – 1.78 (2H, m, $C\mathbf{H_2}$ [overlapping]), 1.83 (3H, dd, *J* = 6.9, 1.6 Hz, $C\mathbf{H_3}$ [overlapping]), 1.72 – 1.64 (2H, m, $C\mathbf{H_2}$), 1.57 – 1.49 (2H, m, $C\mathbf{H_2}$), 1.44 – 1.35 (2H, m, $C\mathbf{H_2}$); δ_C (100 MHz, $CDCl_3$), 178.7 ($\mathbf{C}ON$), 169.2 ($\mathbf{C}OCHCH(CH_3)$), 142.5 ($COCH\mathbf{C}H(CH_3)$), 126.3 ($CO\mathbf{C}HCH(CH_3)$), 43.6 ($\mathbf{C}H_2N$), 36.7 ($\mathbf{C}H_2CON$), 29.9 ($\mathbf{C}H_2$), 29.1 ($\mathbf{C}H_2$), 26.1 ($\mathbf{C}H_2$), 23.8 ($\mathbf{C}H_2$), 18.2 ($\mathbf{C}H_3$); HRMS (ESI): calcd. for $C_{11}H_{17}NNaO_2$, 218.1151. Found: $[MNa]^+$, 218.1148 (1.7 ppm error). Also performed on a 10 mmol scale to give **4.43:** 1.11 g, 57%.

Lab notebook reference: KP171/KP179

1-(2-Phenylacryloyl)azocan-2-one (4.44)

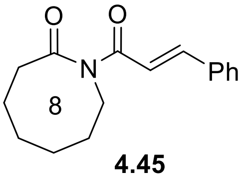


4.44

A mixture of 1-aza-2-cyclooctanone **1.218** (584 mg, 4.59 mmol), DMAP (63.7 mg, 0.521 mmol) and pyridine (2.16 mL, 26.7 mmol) in DCM (30 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of 2-phenylacryloyl chloride (6.75 mmol, 1.50 eqv prepared using the general procedure from atropic acid) in DCM (15 mL) was added and the resulting mixture was stirred as RT for 4 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 × 150 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. Purification by automated flash column chromatography (using an 80 g pre-packed SiO_2 column, 0% → 40% ethyl acetate in hexanes) afforded the *title compound* as a pale orange solid (784 mg, 66%); m.p. 33–38 °C; R_f 0.49 (1:1 ethyl acetate: hexane); ν_{max}/cm^{-1} (thin film) 2929, 2859, 1681, 1496, 1445, 1368, 1334, 1283, 1245, 1205, 1175, 1130, 1088, 897, 777, 703, 593; δ_H (400 MHz, $CDCl_3$-*d*): δ 7.35 – 7.23 (m, 5H, Ph-C**H**), 5.55 (s, 1H, PhC=C**H**H'), 5.44 (s, 1H, PhC=CH**H'**), 4.00 – 3.94 (m, 2H, C**H**$_2$), 2.45 – 2.39 (m, 2H, C**H**$_2$), 1.86 – 1.79 (m, 2H, C**H**$_2$), 1.77 – 1.70 (m, 2H, C**H**$_2$), 1.58 – 1.51 (m, 2H, C**H**$_2$), 1.51 – 1.44 (m, 2H, C**H**$_2$); δ_C (100 MHz, $CDCl_3$-*d*): 177.7 (**C**O), 173.2 (**C**O), 147.8 (Ph**C**=CH_2), 136.9 (Ph-**C**), 128.4 (2 × Ph-**C**H), 128.1 (Ph-**C**H), 126.6 (2 × Ph-**C**H), 115.8 (PhC=**C**H$_2$), 43.7 (**C**H$_2$), 36.0 (**C**H$_2$), 30.0 (**C**H$_2$), 28.9 (**C**H$_2$), 26.1 (**C**H$_2$), 23.9 (**C**H$_2$); HRMS (ESI): calcd. for $C_{16}H_{19}NNaO_2$, 280.1308. Found: $[MNa]^+$, 280.1308 (–0.2 ppm error).

Lab notebook reference: KP181_B

1-[(2E)-3-Phenylprop-2-enoyl]azocan-2-one (4.45)

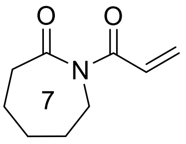


4.45

To a mixture of 1-aza-2-cyclooctanone **1.218** (130 mg, 1.02 mmol), DMAP (13.0 mg, 0.106 mmol) and pyridine (0.485 mL, 6.00 mmol) in DCM (10 mL) under an argon atmosphere was added cinnamoyl chloride (254 mg, 1.53 mmol). The reaction mixture was stirred at room temperature for 1 hour then heated to 50 °C and stirred for 1 hour. The mixture was then diluted with DCM (5 mL) and washed with 10% aq. HCl (15 mL). The aqueous layer was then extracted with DCM (3 × 5 mL) and the combined organic extracts concentrated *in vacuo*. This residue was dissolved in THF (10 mL) and LiOH (5.0 mL, 0.1 M), and the solution allowed to stir for 10 min. To this was added sat. $NaHCO_3$ (20 mL) and DCM (20 mL). The aqueous layer was then extracted with DCM (3 × 20 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:9 ethyl acetate: hexane → 1:5 ethyl acetate: hexane) afforded the *title compound* as a fluffy white solid (151 mg, 58%); m.p. 96–98 °C; R_f 0.52 (1:1 ethyl acetate: hexane); ν_{max}/cm^{-1} (thin film) 2925, 2858, 1671, 1614, 1332, 1196, 1174, 1124, 1090, 763, 557; δ_H (400 MHz, $CDCl_3$) 7.68 (1H, d, *J* = 15.6 Hz, ArC**H**CHCON), 7.59 – 7.52 (2H, m, Ar**H**), 7.38 – 7.34 (3H, m, Ar**H**), 7.33 (1H, d, *J* = 15.6 Hz, ArCHC**H**CON), 4.00 – 3.93 (2H, m, C**H₂**N), 2.75 – 2.66 (2H, m, C**H₂**CON), 1.97 – 1.88 (2H, m, C**H₂**), 1.81 (2H, p, *J* = 6.2 Hz, C**H₂**), 1.68 – 1.58 (2H, m, C**H₂**), 1.53 – 1.46 (2H, m, C**H₂**); δ_C (100 MHz, $CDCl_3$), 179.1 (**C**ON), 169.5 (**C**OCHCH), 143.0 (ArC**H**CHCON), 135.3 (Ar**C**), 130.0 (2 × Ar**C**H), 128.9 (2 × Ar**C**H), 128.4 (Ar**C**H), 122.2 (ArCHC**H**CON), 44.0 (**C**H₂N), 37.0 (**C**H₂CON), 30.1 (**C**H₂), 29.3 (**C**H₂), 26.4 (**C**H₂), 24.0 (**C**H₂); HRMS (ESI): calcd. for $C_{16}H_{20}NNaO_2$, 280.1308. Found: $[MNa]^+$, 280.1308 (0.1 ppm error).

Lab notebook reference: KP170

1-Acryloyl-azepan-2-one (4.46)

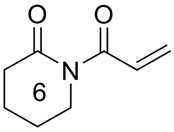


4.46

To a stirring solution of caprolactam (226 mg, 2.00 mmol) in dry THF (7.3 mL) cooled to 0 °C was added a solution of MeMgBr (3.0 M in diethyl ether, 0.73 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 (0.244 mL, 3.00 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 (8 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, 1:1 diethyl ether: hexane) afforded the *title compound* as viscous colorless liquid (219 mg, 72%); R_f 0.67 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 2932, 1701, 1683, 1404, 1383, 1333, 1240, 1209, 1181, 1152, 1098, 980, 795; δ_H (400 MHz, $CDCl_3$), 6.91 (1H, dd, *J* = 16.8, 10.3 Hz, NCOC**H**CHH'), 6.28 (1H, dd, *J* = 16.8, 1.8 Hz, NCOCHC**H**H'), 5.66 (1H, dd, *J* = 10.3, 1.8 Hz, NCOCHCH**H'**), 3.91 – 3.86 (2H, m, NC**H₂**), 2.72 – 2.66 (2H, m, C**H₂**CON), 1.81 – 1.63 (6H, m, 3 × C**H₂**); δ_C (100 MHz, $CDCl_3$), 178.1 (**C**O), 168.9 (**C**O), 131.9 (NCO**C**HCHH'), 128.0 (NCOCH**C**HH'), 43.7 (N**C**H_2), 39.4 (**C**H_2CON), 29.3 (**C**H_2), 28.7 (**C**H_2), 23.7 (**C**H_2); HRMS (ESI): calcd. for $C_9H_{13}NNaO_2$, 190.0838. Found: $[MNa]^+$, 190.0841 (–1.3 ppm error). Procedure adapted from a literature method.[108]

Lab notebook reference: KP398

1-Acryloyl-piperidin-2-one (4.47)

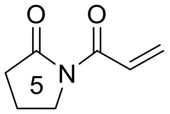


4.47

To a stirring solution of δ-valerolactam **4.60** (991 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 (965 mg, 63%); 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 (1H, dd, *J* = 17.0, 10.5 Hz, NCOC**H**CHH'), 6.33 (1H, dd, *J* = 17.0, 1.7 Hz, NCOCHC**H**H'), (5.69 (1H, dd, *J* = 10.5, 1.7 Hz, NCOCHCH**H'**), 3.76 – 3.71 (2H, m, NC**H₂**), 2.60 – 2.53 (2H, m, C**H₂**CON), 1.90 – 1.81 (4H, m, 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**H_2), 34.9 (**C**H_2CON), 22.6 (**C**H_2), 20.8 (**C**H_2); HRMS (ESI): calcd. for $C_8H_{11}NNaO_2$, 176.0682. Found: $[MNa]^+$, 176.0684 (–0.9 ppm error). Procedure adapted from a literature method.[108]

Lab notebook reference: KP504

1-Acryloyl-pyrrolidin-2-one (4.49)

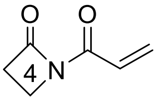


4.49

To a stirring solution of 2-pyrrolidone (426 mg, 5.01 mmol) in dry THF (18.2 mL) cooled to 0 °C was added a solution of MeMgBr (3.0 M in diethyl ether, 1.83 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 (0.610 mL, 7.51 mmol) was then 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 (15 mL) and the mixture was extracted with Et_2O (25 mL). The organic layer was washed with sat. aq. $NaHCO_3$ (2 × 15 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 colorless liquid (391 mg, 56%); R_f 0.19 (1:1 diethyl ether: hexane); ν_{max}/cm^{-1} (thin film) 2980, 1733, 1675, 1617, 1460, 1406, 1359, 1312, 1247, 1223, 1192, 1062, 1021, 980, 930, 887, 839, 799, 674, 639, 587; δ_H (400 MHz, $CDCl_3$) 7.74 (1H, dd, *J* = 17.1, 10.5 Hz, NCOC**H**CHH’), 6.49 (1H, dd, *J* = 17.1, 1.9 Hz, NCOCHC**H**H’), 5.84 (1H, dd, *J* = 10.5, 1.9 Hz, NCOCHCH**H’**), 3.89 – 3.84 (2H, m, NC**H₂**), 2.62 (2H, t, *J* = 8.1 Hz C**H₂**CON), 2.11 – 2.01 (2H, m, C**H₂**); δ_C (100 MHz, $CDCl_3$), 175.7 (**C**O), 166.2 (**C**O), 131.0 (NCOCH**C**HH’), 129.2 (NCO**C**HCHH’), 45.7 (N**C**H₂), 33.9 (**C**H₂CON), 17.4 (**C**H₂); HRMS (ESI): calcd. for $C_7H_9NNaO_2$, 162.0525. Found: $[MNa]^+$, 162.0527 (–0.6 ppm error).

Lab notebook reference: KP482

1-Acryloyl-azetidin-2-one (4.48)

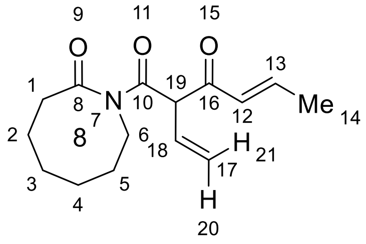


4.48

A stirring solution of 2-azetidinone (357 mg, 5.02 mmol) and DIPEA (2.18 mL, 12.5 mmol) in THF (5.0 mL) was cooled to 0 °C. To this was added a 0 °C cooled solution of acryloyl chloride (0.812 mL, 10.0 mmol) in THF (5.0 mL) dropwise. Under an argon atmosphere this mixture was stirred at 0 °C for 2.5 hours. Afterwards it was allowed to warm to RT and stirred for a further 3.5 hours. The reaction mixture was then quenched with sat. aq. NH_4Cl (15 mL), extracted with Et_2O (20 mL), then the organic layer washed with was washed with sat. aq. $NaHCO_3$ (2 × 15 mL), and sat. aq. NaCl (2 × 15 mL). The organic extracts were 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 fluffy white solid (237 mg, 38%); m.p. 48–50 °C; R_f 0.16 (1:1 diethyl ether: hexane); ν_{max}/cm^{-1} (thin film) 2976, 1783, 1686, 1624, 1409, 1328, 1303, 1264, 1207, 1148, 1072, 1047, 1004, 918, 787, 602; δ_H (400 MHz, $CDCl_3$), 7.00 (1H, dd, *J* = 17.1, 10.4 Hz, NCOC**H**CHH'), 6.58 (1H, dd, *J* = 17.1, 1.6 Hz, NCOCHC**H**H'), 5.90 (1H, dd, *J* = 10.4, 1.6 Hz, NCOCHCH**H'**), 3.65 (2H, t, *J* = 5.4 Hz, C**H₂**), 3.09 (2H, t, *J* = 5.4 Hz, C**H₂**); δ_C (100 MHz, $CDCl_3$) 165.2 (**C**O), 162.7 (**C**O), 131.7 (NCOCH**C**HH'), 129.1 (NCO**C**HCHH'), 36.6 (**C**H₂), 36.2 (**C**H₂); HRMS (ESI): calcd. for $C_6H_7NNaO_2$, 148.0369. Found: $[MNa]^+$, 148.0372 (–2.1 ppm error).

Lab notebook reference: KP512

(4*E*)-2-Ethenyl-1-(2-oxoazocan-1-yl)hex-4-ene-1,3-dione (4.51)



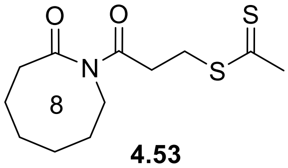
4.51

A mixture of 1-aza-2-cyclooctanone **1.218** (639 mg, 5.02 mmol) and TEA (1.73 mL, 12.5 mmol) in THF (7.5 mL) was cooled to 0 °C. To this was added a 0 °C cooled solution of crotonoyl chloride (0.958 mL, 10.0 mmol) in THF (2.5 mL) dropwise. Under an argon atmosphere this mixture was stirred at 0 °C for 1 hour. Afterwards it was allowed to warm to RT and stirred for a further 23 hours. The reaction mixture was then quenched with aqueous NH_4Cl, extracted with DCM, then washed with $NaHCO_3$ and NaCl. At this point an emulsion formed and HCl (10% aq.) was added to acidify the mixture. The organics were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:9 ethyl acetate: hexane → 1:5 ethyl acetate: hexane → 1:1 ethyl acetate: hexane) afforded the *title compound* **4.51** as a colorless oil (166 mg, 13%) as well as crotonic anhydride **4.52** (27.9 mg, 4%). Data for **4.51**: R_f 0.30 (1:1 ethyl acetate: hexane); ν_{max}/cm^{-1} (thin film) 3357, 2929, 2859, 1736, 1691, 1654, 1447, 1336, 1248, 1196, 1131, 1092; δ_H (400 MHz, $CDCl_3$) 7.05 (1H, dq, *J* = 15.5, 6.9 Hz, H-13), 6.17 (1H, dt, *J* = 17.1, 10.5 Hz, H-18), 5.85 (1H, dq, *J* = 15.5, 1.7 Hz, H-12), 5.75 (1H, dd, *J* = 10.9, 0.9 Hz, H-19), 5.17 (1H, ddd, *J* = 17.1, 1.7, 0.8 Hz, H-21), 5.03 (1H, ddd, *J* = 10.3, 1.7, 0.8 Hz, 1H, H-20), 3.64 – 3.59 (2H, m, H-6), 2.54 – 2.31 (2H, m, H-1), 1.83 (3H, dd, *J* = 7.0, 1.7 Hz, H-14), 1.76 – 1.69 (2H, m, H-2), 1.66 – 1.59 (2H, m, H-5), 1.55 – 1.39 (4H, m, H-3, H-4); δ_C (100 MHz, $CDCl_3$), 175.4 (C-8), 163.6 (C-16), 148.0 (C-13), 140.4 (C-10), 129.4 (C-18), 121.0 (C-12), 118.8 (C-17), 116.4 (C-19), 48.3 (C-6), 34.0 (C-1), 30.0 (C-5), 28.4 (C-2), 26.1 (C-3), 24.1 (C-4), 18.1 (C-14); HRMS (ESI): calcd.

for $C_{15}H_{22}NO_3$, 264.1594. Found: $[MH]^+$, 264.1591 (1.3 ppm error). Procedure adapted from literature.[109]

Lab notebook reference: KP169_C

3-Oxo-3-(2-oxoazocan-1-yl)propyl ethanedithioate (4.53) (formed as an minor side product during the synthesis of compound **3.27** – see above for **3.27** data)

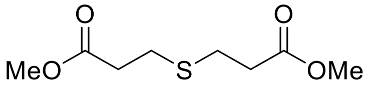


4.53

A 10 mL RBF was charged with 1-acryloyl-azocan-2-one **4.37** (89.1 mg, 0.492 mmol) and EtOAc (2.7 mL). The solution was degassed with argon for 3 min and then thioacetic acid (0.11 mL, 1.54 mmol) was added followed by TEA (0.030 mL, 2.16 mmol). Under an argon atmosphere this mixture was stirred at RT for 2.5 hours. The reaction mixture was then diluted with $CHCl_3$ (10 mL) and washed with $NaHCO_3$. It was then extracted with $CHCl_3$ (3 × 10 mL) and organics washed with sat. NaCl. The mixture was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:9 ethyl acetate: hexane → 1:1 ethyl acetate: hexane) afforded the *title compound* **4.53** as a light orange oil (5.6 mg, 4%) as well as **3.27** (69.9 mg, 55%); Data for **4.53**: R_f 0.25 (1:3 ethyl acetate: hexane); ν_{max}/cm^{-1} (thin film) 2925, 2856, 1688, 1445, 1370, 1247, 1198, 1126, 1092, 998, 895, 592); δ_H (400 MHz, $CDCl_3$) 3.95 – 3.86 (2H, m, C**H₂**N), 3.51 (2H, td, *J* = 6.7, 2.8 Hz, $COCH_2C\mathbf{H_2}S$), 3.27 (2H, td, *J* = 6.7, 2.8 Hz, $COC\mathbf{H_2}CH_2S$), 2.81 – 2.77 (3H, m, C**H₃**), 2.66 – 2.60 (2H, m, C**H₂**CON), 1.91 – 1.81 (2H, m, C**H₂**), 1.74 – 1.66 (2H, m, C**H₂**), 1.62 – 1.52 (2H, m, C**H₂**), 1.48 – 1.40 (2H, m, C**H₂**); δ_C (100 MHz, $CDCl_3$), 233.1 (**C**SS), 178.3 (**C**ON), 174.8 ($\mathbf{C}OCH_2CH_2$), 43.6 ($\mathbf{C}H_2N$), 39.2 ($\mathbf{C}H_3$), 37.8 ($CO\mathbf{C}H_2CH_2S$), 37.2 ($\mathbf{C}H_2CON$), 32.2 ($COCH_2\mathbf{C}H_2S$), 29.5 ($\mathbf{C}H_2$), 29.1 ($\mathbf{C}H_2$), 26.3 ($\mathbf{C}H_2$), 24.0 ($\mathbf{C}H_2$); HRMS (ESI): calcd. for $C_{12}H_{19}NNaO_2S_2$, 296.0749. Found: $[MNa]^+$, 296.0747 (0.8 ppm error). Procedure adapted from literature.[100]

Lab notebook reference: KP144

Dimethyl 3,3'-thiodipropionate (4.54)

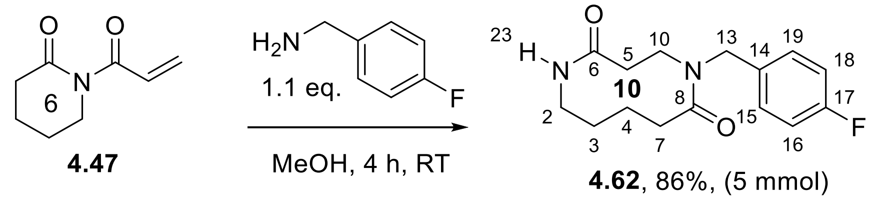


4.54

To a vial containing 1-acryloylazocan-2-one **4.37** (47.5 mg, 0.262 mmol) was added water (2.5 mL), methanol (2.5 mL), $NaHCO_3$ (22.0 mg, 0.262 mmol) and NaSH × H_2O (×≈1.5) (19.6 mg, 0.236 mmol, 0.9 eqv.) and allowed to stir for 5 min. The reaction mixture was then diluted with DCM and water, and the organic layer dried over $MgSO_4$ and the solvent removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:9 ethyl acetate: hexane → 1:4 ethyl acetate: hexane → 1:1 ethyl acetate: hexane → ethyl acetate) afforded the *title compound* as an oil (4.3 mg, 16%); R_f 0.73 (1:9 methanol: ethyl acetate); δ_H (400 MHz, $CDCl_3$) 3.70 (6H, s, 2 × C**H**$_3$), 2.81 (4H, t, *J* = 7.3 Hz, 2 × C**H**$_2$), 2.62 (4H, t, *J* = 7.3 Hz, 2 × C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 172.4 (2 × **C**O), 52.0 (2 × **C**H$_3$), 34.7 (2 × **C**H$_2$), 27.1 (2 × **C**H$_2$). ^1H and ^{13}C NMR data match those previously reported.[110] Procedure adapted from a literature method.[90]

Lab notebook reference: KP139

5-(4-Fluorobenzyl)-1,5-diazecane-2,6-dione (4.62)



4.62, 86%, (5 mmol)

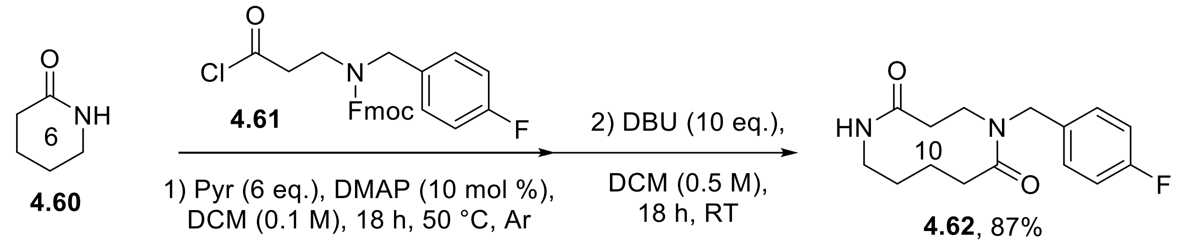
To a solution of 1-acryloyl-piperidin-2-one **4.47** (766 mg, 5.00 mmol) in dry methanol (10.0 mL), was added 4-fluorobenzylamine (0.629 mL, 5.50 mmol) in a single portion. The reaction mixture was allowed to stir for 4 h at RT and then the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:4 ethyl acetate: hexane → 1:1 ethyl acetate: hexane → ethyl acetate → 1:19 methanol: ethyl acetate → 1:9 methanol: ethyl acetate) afforded the *title compound* as a peach-coloured solid (1.20 g, 86%). In solution in $CDCl_3$, this compound exists as a 2:15 mixture of rotameric forms; m.p. 162 – 165 °C, R_f 0.20 (1:9 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3294, 2933, 1620, 1509, 1443, 1350, 1221, 1096, 812, 501; NMR data for the major rotamer only: δ_H (400 MHz, $CDCl_3$) 7.29 – 7.22 (2H, m, Ar**H**-H15, H19), 7.03 – 6.96 (2H, m, Ar**H**-H16, H18), 5.37 – 5.19 (1H, m, N**H**-H23), 4.96 (1H, d, *J* = 14.6 Hz, C**H$_2$**-H13), 4.21 (1H, d, *J* = 14.6 Hz, C**H$_2$**-H13'), 3.95 (1H, t, *J* = 14.0 Hz, C**H$_2$**-H10), 3.84 (1H, td, *J* = 13.4, 7.4 Hz, C**H$_2$**-H2), 3.30 (1H, dt, *J* = 15.8, 3.9 Hz, C**H$_2$**-H10'), 2.96 – 2.79 (1H, m, C**H$_2$**-H2'), 2.76 – 2.57 (1H, m, C**H$_2$**-H7), 2.26 – 2.00 (4H, m, C**H$_2$**-H5, H5', H7', H4), 1.76 – 1.69 (1H, m, C**H$_2$**-H3), 1.69 – 1.61 (1H, m, C**H$_2$**-H4'), 1.52 (1H, q, *J* = 12.8 Hz, C**H$_2$**-H3'); δ_C (100 MHz, $CDCl_3$) 174.1

(**C**O-C8), 171.0 (**C**O-C6), 162.4 (Ar**C**F-C17, $^{1}J_{CF}$ = 246.4 Hz), 133.9 (Ar**C**-C14, $^{4}J_{CF}$ = 3.3 Hz), 130.0 (2 × Ar**C**H-C15, C19, $^{3}J_{CF}$ = 8.1 Hz), 115.9 (2 × Ar**C**H-C16, C18, $^{2}J_{CF}$ = 21.3 Hz), 48.7 (**C**H_2-C13), 45.3 (**C**H_2-C10), 39.3 (**C**H_2-C2), 37.7 (**C**H_2-C5), 28.4 (**C**H_2-C7), 25.9 (**C**H_2-C3), 23.9 (**C**H_2-C4); δ_F (376 MHz, $CDCl_3$) –114.12 (1F, m, Ar**F**); HRMS (ESI): calcd. for $C_{15}H_{19}FN_2NaO_2$, 301.1323. Found: $[MNa]^+$, 301.1321 (0.5 ppm error).

Characteristic NMR data for the minor rotamer can be found at: δ_H (400 MHz, $CDCl_3$) 7.15 – 7.09 (2H, m, Ar**H**), 5.89 (1H, br d, *J* = 10.3 Hz, N**H**), 4.81 (1H, d, *J* = 16.3 Hz, C**H**$_2$), 4.28 (1H, d, *J* = 16.3 Hz, C**H**$_2$), 4.17 – 4.09 (2H, m, C**H**$_2$), 2.43 – 2.36 (2H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 171.3 (**C**O), 128.5 (2 × Ar**C**H, $^{3}J_{CF}$ = 8.2 Hz), 42.4 (**C**H_2), 40.2 (**C**H_2), 35.2 (**C**H_2), 27.5 (**C**H_2), 25.1 (**C**H_2); δ_F (376 MHz, $CDCl_3$) –114.43 (1F, m, Ar**F**).

Lab notebook reference: KP439

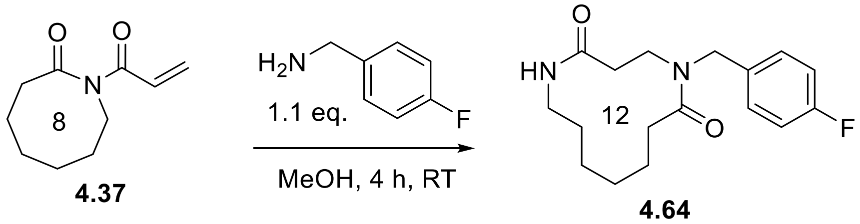
The same compound **4.62** was also made using the group's published SuRE chemistry[48] to provide an authentic product standard prior to optimisation, using the method below.



Oxalyl chloride (0.770 mL, 9.00 mmol) was added to a suspension of 3-((((9*H*-fluoren-9-yl)methoxy)carbonyl)(4-fluorobenzyl)amino)propanoic acid (1.26 g, 3.00 mmol) in DCM (30 mL), followed by a catalytic amount of DMF (3 drops). The resulting mixture was stirred at RT for 1 h and concentrated *in vacuo* to remove all solvent and excess oxalyl chloride. The resulting acid chloride [(9*H*-fluoren-9-yl)methyl (3-chloro-3-oxopropyl)(4-fluorobenzyl)carbamate] was the dissolved in DCM (15 mL) and added to a pre-stirred mixture of δ-valerolactam (200 mg, 2.01 mmol), DMAP (24.2 mg, 0.200 mmol) and pyridine (0.979 mL, 12.1 mmol) in DCM (40 mL) under an argon atmosphere and heated at reflux at 50 °C for 18 h. The crude mixture was concentrated *in vacuo*. The mixture was then diluted with DCM (60 mL) and washed with 10% aq. HCl (60 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* to form crude (9H-fluoren-9-yl)methyl (4-fluorobenzyl)(3-oxo-3-(2-oxopiperidin-1-yl)propyl)carbamate, which was carried forward without further purification. Thus, a solution of this crude imide was dissolved in DCM (40 mL) and DBU (2.99 mL, 20.0 mmol) was added, followed by stirring at RT for 18 h, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:9 ethyl acetate: hexane → 1:1 ethyl acetate: hexane → ethyl acetate → 9:1 ethyl acetate: methanol) afforded the *title compound* **4.62** as an orange solid (489 mg, 87% from δ-valerolactam **4.60**).

Lab notebook reference: KP409/KP410

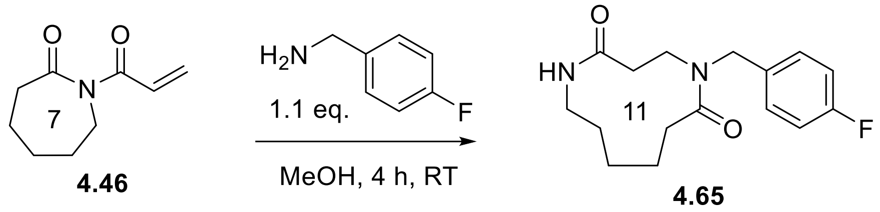
5-(4-Fluorobenzyl)-1,5-diazacyclododecane-2,6-dione (4.64)



To a solution of 1-acryloyl-azocan-2-one **4.37** (103 mg, 0.566 mmol) in dry methanol (1.1 mL), was added 4-fluorobenzylamine (71 µL, 0.622 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, 1:4 ethyl acetate: hexane → 1:1 ethyl acetate: hexane → ethyl acetate → 1:49 methanol: ethyl acetate → 1:19 methanol: ethyl acetate) afforded the *title compound* as a white solid (119 mg, 69%); m.p. 149 – 155 °C, R_f 0.36 (1:9 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3295, 2931, 1640, 1555, 1510, 1456, 1414, 1355, 1222, 1156, 1096, 731; δ_H (400 MHz, $CDCl_3$), 7.15 – 7.09 (2H, m, Ar**H**), 7.07 – 6.97 (2H, m, Ar**H**), 6.39 – 6.28 (1H, br d, *J* = 9.5 Hz, N**H**), 4.86 (1H, d, *J* = 16.7 Hz, 0.5 × ArC**H₂**), 4.54 – 4.46 (1H, m, 0.5 × C**H₂**), 4.38 (1H, d, *J* = 16.7 Hz, 0.5 × ArC**H₂**), 3.81 – 3.70 (1H, m, 0.5 × C**H₂**), 2.91 – 2.74 (3H, m, 1.5 × C**H₂**), 2.61 – 2.39 (2H, m, C**H₂**), 2.30 – 1.99 (2H, m, C**H₂**), 1.66 – 1.31 (6H, m, 3 × C**H₂**), 1.28 – 1.06 (1H, m, 0.5 × C**H₂**); δ_C (100 MHz, $CDCl_3$) 175.9 (**C**O), 170.3 (**C**O), 162.4 (Ar**C**F, $^1J_{CF}$ = 246.5 Hz), 132.3 (Ar**C**, $^4J_{CF}$ = 3.3 Hz), 128.2 (2 × Ar**C**H, $^3J_{CF}$ = 8.0 Hz), 116.1 (2 × Ar**C**H, $^2J_{CF}$ = 21.6 Hz), 51.3 (**C**H₂), 41.0 (**C**H₂), 39.3 (**C**H₂), 35.3 (**C**H₂), 32.5 (**C**H₂), 27.4 (**C**H₂), 25.7 (**C**H₂), 24.0 (**C**H₂), 22.3 (**C**H₂); δ_F (282 MHz, $CDCl_3$), –114.48 (1F, m, Ar**F**); HRMS (ESI): calcd. for $C_{17}H_{23}FN_2NaO_2$, 329.1636. Found: [MNa]$^+$, 329.1639 (–0.9 ppm error).

Lab notebook reference: KP444

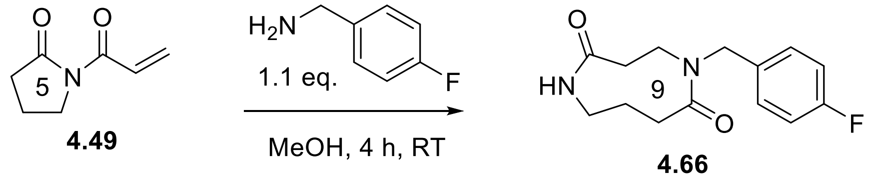
5-(4-Fluorobenzyl)-1,5-diazacycloundecane-2,6-dione (4.65)



To a solution of 1-acryloyl-azepan-2-one **4.46** (156 mg, 0.933 mmol) in dry methanol (2.0 mL), was added 4-fluorobenzylamine (126 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, 1:4 ethyl acetate: hexane → 1:1 ethyl acetate: hexane → ethyl acetate → 1:49 methanol: ethyl acetate → 1:19 methanol: ethyl acetate) afforded the *title compound* as a white solid (228 mg, 84%). In solution in $CDCl_3$, this compound exists as a mixture of rotameric forms (1 major rotamer and 1 minor rotamer based on the ^{19}F NMR data). The ^{1}H NMR spectrum is severely complicated by rotameric broadening, with product identity and purity best determined using ^{13}C NMR data; m.p. 180 – 183 °C, R_f 0.34 (1:9 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3297, 2934, 1625, 1556, 1509, 1452, 1352, 1223, 1183, 1154, 909, 821, 731; δ_H (400 MHz, $CDCl_3$), 7.32 – 7.25 (2H, m, Ar**H**), 7.05 – 6.98 (2H, m, Ar**H**), 5.78 – 5.56 (1H, m, N**H**), 5.23 – 3.07 (5H, m, 2.5 × C**H₂**), 3.03 – 0.65 (11H, m, 5.5 × C**H₂**); δ_C (100 MHz, $CDCl_3$), 173.6 (**C**O), 171.4 (**C**O), 162.4 (Ar**C**F, $^1J_{CF}$ = 246.7 Hz), 134.1 (Ar**C**, $^4J_{CF}$ = 3.2 Hz), 130.1 (2 × Ar**C**H, $^3J_{CF}$ = 8.1 Hz), 115.9 (2 × Ar**C**H, $^2J_{CF}$ = 21.5 Hz), 48.3 (**C**H₂), 44.9 (**C**H₂), 41.9 (**C**H₂), 37.1 (**C**H₂), 28.6 (**C**H₂), 25.3 (**C**H₂), 24.4 (**C**H₂), 22.8 (**C**H₂); δ_F (282 MHz, $CDCl_3$), –114.30 (1F, m, Ar**F**, major rotamer), –114.73 (1F, m, Ar**F**, minor rotamer); HRMS (ESI): calcd. for $C_{16}H_{21}FN_2NaO_2$, 315.1479. Found: [MNa]$^+$, 315.1479 (–0.1 ppm error).

Lab notebook reference: KP497

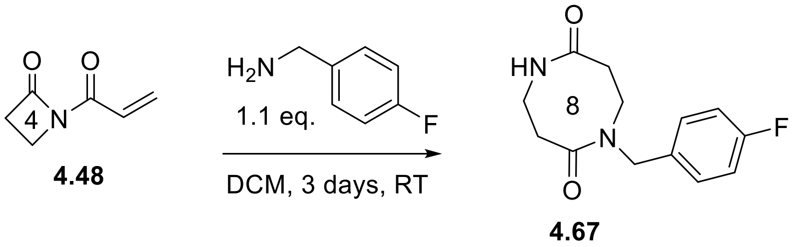
5-(4-Fluorobenzyl)-1,5-diazonane-2,6-dione (4.66)



To a solution of 1-acryloyl-pyrrolidin-2-one **4.49** (139 mg, 0.998 mmol) in dry methanol (2.0 mL), was added 4-fluorobenzylamine (125 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, 1:4 ethyl acetate: hexane → 1:1 ethyl acetate: hexane → ethyl acetate → 1:49 methanol: ethyl acetate → 1:19 methanol: ethyl acetate) afforded the *title compound* as a colourless oil (121 mg, 46%). In solution in $CDCl_3$, this compound exists as a mixture of rotameric forms (1 major rotamer and up to 3 minor rotamers, best seen in the ^{19}F NMR). The ^1H NMR spectrum is significantly affected by rotameric broadening, with product identity and purity best determined using ^{13}C NMR data collected in $CDCl_3$ at 55 °C; R_f 0.06 (1:9 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3280, 2941, 1622, 1508, 1461, 1413, 1359, 1219, 1157, 1098, 1053, 1015, 907, 825, 771, 730, 646, 565, 498; δ_H (400 MHz, $CDCl_3$), 7.26 – 7.14 (2H, m, Ar**H**), 7.00 – 6.90 (2H, m, Ar**H**), 6.69 (1H, br t, *J* = 7.5 Hz, N**H**, major rotamer), 6.35 – 6.27 (1H, br m, N**H**, other rotamers), 5.26 – 2.95 (6H, m, 3 × C**H₂**), 2.90 – 1.64 (6H, m, 3 × C**H₂**); δ_C (100 MHz, $CDCl_3$, 55 °C), 174.7 (**C**O), 173.8 (**C**O), 162.5 (Ar**C**F, $^1J_{CF}$ = 246.3 Hz), 133.2 (Ar**C**, $^4J_{CF}$ = 3.2 Hz), 130.1 (2 × Ar**C**H, $^3J_{CF}$ = 7.9 Hz), 115.7 (2 × Ar**C**H, $^2J_{CF}$ = 21.4 Hz), 49.7 (**C**H_2), 44.6 (**C**H_2), 41.6 (**C**H_2), 34.7 (**C**H_2), 30.6 (**C**H_2), 29.2 (**C**H_2); δ_F (282 MHz, $CDCl_3$), –114.54 (1F, m, ArF, major rotamer), –115.12 (1F, m, ArF), –115.24 (1F, m, ArF), –115.74 (1F, m, ArF); HRMS (ESI): calcd. for $C_{14}H_{17}FN_2NaO_2$, 287.1166. Found: $[MNa]^+$, 287.1171 (–1.5 ppm error).

Lab notebook reference: KP446

1-(4-Fluorobenzyl)-1,5-diazocane-2,6-dione (4.67)



To a solution of 1-acryloyl-azetidin-2-one **4.48** (71.0 mg, 0.568 mmol) in dry DCM (1.1 mL), was added 4-fluorobenzylamine (71 µL, 0.624 mmol) dropwise over the course of 1 min. The reaction mixture was allowed to stir for 3 days at RT and then the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 ethyl acetate: hexane → ethyl acetate → 1:32 methanol: ethyl acetate → 1:14 methanol: ethyl acetate → 1:9 methanol: ethyl acetate→ 1:6 methanol: ethyl acetate) afforded the *title compound* as a white crystalline solid (96.7 mg, 68%); m.p. 179 – 181 °C, R_f 0.38 (1:4 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3266, 1627, 1509, 1476, 1414, 1320, 1220, 1157, 1099, 985, 920, 824, 730, 576, 548; δ_H (500 MHz, $CDCl_3$), 7.25 – 7.19 (2H, m, Ar**H**), 7.02 – 6.96 (2H, m, Ar**H**) 6.64 (1H, br t, *J* = 7.5 Hz, N**H**), 4.55 (2H, s, ArC**H₂**), 3.59 – 3.50 (4H, m, 2 × NC**H₂**), 2.93 (2H, t, *J* = 6.9 Hz, COC**H₂**), 2.78 (2H, t, *J* = 6.9 Hz, COC**H₂**); δ_C (125 MHz, $CDCl_3$), 173.0 (**C**O), 170.9 (**C**O), 162.4 (Ar**C**F, $^1J_{CF}$ = 246.1 Hz), 132.7 (Ar**C**, $^4J_{CF}$ = 3.2 Hz), 130.1 (Ar**C**H, $^3J_{CF}$ = 8.2 Hz), 115.5 (Ar**C**H, $^2J_{CF}$ = 21.5 Hz), 48.3 (Ar**C**H_2), 41.7 (**C**H_2), 38.0 (**C**H_2), 37.5 (**C**H_2), 35.3 (**C**H_2); δ_F (470 MHz, $CDCl_3$), –114.66 (1F, m , Ar**F**); HRMS (ESI):

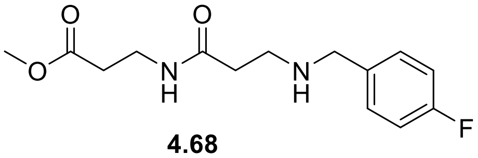
calcd. for $C_{13}H_{15}FN_2NaO_2$, 273.1010. Found: $[MNa]^+$, 273.1013 (–1.3 ppm error). For X-ray crystallographic data, see page 4 and CCDC 2122961.

Lab notebook reference: KP475

The outcome of the reaction when the synthesis of **4.67** was attempted using methanol as the reaction solvent is also described below:

To a solution of 1-acryloyl-azetidin-2-one (58.2 mg, 0.465 mmol) in dry methanol (0.93 mL), was added 4-fluorobenzylamine (58 µL, 0.511 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, 1:4 ethyl acetate: hexane → 1:1 ethyl acetate: hexane → ethyl acetate → 1:49 methanol: ethyl acetate → 1:24 methanol: ethyl acetate → 1:15 methanol: ethyl acetate → 1:9 methanol: ethyl acetate → 1:6 methanol: ethyl acetate → 1:4 methanol: ethyl acetate → 1:3 methanol: ethyl acetate → 1:2 methanol: ethyl acetate → 9:19 methanol: ethyl acetate) afforded methyl 3-(3-((4-fluorobenzyl)amino)propanamido)propanoate **4.68** (9.7 mg, 7%) and *N*-(4-fluorobenzyl)-3-(3-((4-fluorobenzyl)amino)propanamido)propanamide **4.69** (13.6 mg, 8%). Data for each compound is included below.

Methyl 3-(3-((4-fluorobenzyl)amino)propanamido)propanoate (4.68)

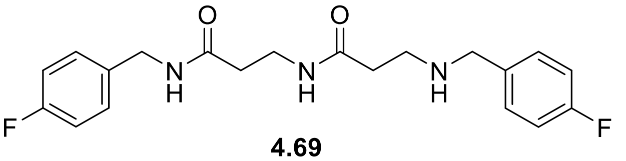


4.68

A brown paste (9.7 mg, 7%). The isolated material contained minor unidentified impurities, but the NMR data obtained were sufficient to identify this unwanted side product. R_f 0.15 (3:7 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3283, 2952, 1735, 1646, 1551, 1510, 1439, 1367, 1221, 825; ^1H and ^{13}C NMR data for the major rotamer only. δ_H (500 MHz, $CDCl_3$), 7.59 – 7.51 (1H, br m, CON**H**), 7.36 – 7.30 (2H, m, Ar**H**), 7.02 (2H, t, *J* = 8.5 Hz, Ar**H**), 3.82 (2H, s, ArC**H₂**), 3.66 (3H, s, C**H₃**), 3.50 (2H, q, *J* = 6.1 Hz, CONHC**H₂**), 3.72 (1H, br s, CH_2N**H**CH_2), 2.92 (2H, t, *J* = 6.0 Hz, C**H₂**NHCH_2Ar), 2.53 (2H, t, *J* = 6.1 Hz, C**H₂**CO_2CH_3), 2.44 (2H, t, *J* = 6.0 Hz, NCOC**H₂**CH_2NHCH_2Ar); δ_C (125 MHz, $CDCl_3$), 173.1 (**C**O), 172.1 (**C**O), 162.4 (Ar**C**F, $^1J_{CF}$ = 246.0 Hz), 133.6 (Ar**C**, $^4J_{CF}$ = 3.3 Hz), 130.4 (Ar**C**H, $^3J_{CF}$ = 8.1 Hz), 115.6 (Ar**C**H, $^2J_{CF}$ = 21.4 Hz), 52.6 (Ar**C**H_2), 51.9 (**C**H_3), 44.8 (NCOCH_2**C**H_2NHCH_2Ar), 35.0 (NCO**C**$H_2CH_2NHCH_2$Ar), 34.9 (CH_2**C**H_2NHCO), 34.1 (C**H₂**CO_2CH_3); δ_F (470 MHz, $CDCl_3$) –114.73 (1F, br s, Ar**F**); HRMS (ESI): calcd. for $C_{14}H_{19}FN_2NaO_3$, 305.1272. Found: $[MNa]^+$, 305.1275 (–1.0 ppm error).

Lab notebook reference: KP450_A

***N*-(4-Fluorobenzyl)-3-(3-((4-fluorobenzyl)amino)propanamido)propenamide (4.69)**

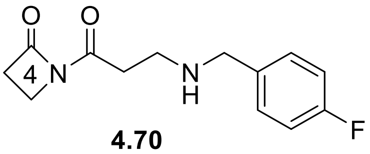


4.69

A white solid (13.6 mg, 8%); m.p. 108 – 110 °C, R_f 0.15 (3:7 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3286, 1644, 1604, 1548, 1509, 1435, 1221, 1158, 1097, 1016, 824; δ_H (400 MHz, $CDCl_3$), 7.84 (1H, br t, *J* = 6.1 Hz, CON**H**), 7.32 – 7.25 (2H, m, Ar**H**), 7.24 – 7.17 (2H, m, Ar**H**), 7.05 – 6.94 (4H, m, Ar**H**), 6.47 (1H, br t, *J* = 5.8 Hz, CON**H**), 4.34 (2H, d, *J* = 5.8 Hz, ArC**H₂**), 3.74 (2H, s, ArC**H₂**), 3.51 (2H, q, *J* = 6.1 Hz, $CONHC\mathbf{H_2}CH_2$), 3.05 (1H, br s, $CH_2N\mathbf{H}CH_2$), 2.83 (2H, dd, *J* = 6.6, 5.4 Hz, $C\mathbf{H_2}NHCH_2Ar$), 2.43 (2H, m, $C\mathbf{H_2}CONCH_2Ar$), 2.34 (2H, t, *J* = 6.6, 5.4 Hz, $NCOC\mathbf{H_2}CH_2NHCH_2Ar$); δ_C (100 MHz, $CDCl_3$), 172.7 (**C**O), 171.5 (**C**O), 162.3 (2 × Ar**C**F, $^1J_{CF}$ = 245.7 Hz), 134.4 (Ar**C**, $^4J_{CF}$ = 3.3 Hz), 134.1 (Ar**C**, $^4J_{CF}$ = 3.3 Hz), 130.2 (2 × Ar**C**H, $^3J_{CF}$ = 8.1 Hz), 129.6 (2 × Ar**C**H, $^3J_{CF}$ = 8.1 Hz), 115.6 (2 × Ar**C**H, $^2J_{CF}$ = 21.4 Hz), 115.5 (2 × Ar**C**H, $^2J_{CF}$ = 21.4 Hz), 52.6 (Ar**C**H_2), 44.9 ($NCOCH_2\mathbf{C}H_2NHCH_2Ar$), 42.9 (Ar**C**$H_2$), 36.1 ($C\mathbf{H_2}CONCH_2Ar$), 34.5 (2 × **C**$H_2$ ($CH_2\mathbf{C}H_2NHCO$ and $NCO\mathbf{C}H_2CH_2NHCH_2Ar$); δ_F (282 MHz, $CDCl_3$) –114.9 (1F, m, ArF), –115.2 (1F, m, ArF); HRMS (ESI): calcd. for $C_{20}H_{24}F_2N_3O_2$, 376.1831. Found: $[MNa]^+$, 376.1832 (–0.2 ppm error).

Lab notebook reference: KP450_B

1-(3-((4-Fluorobenzyl)amino)propanoyl)azetidin-2-one (4.70)

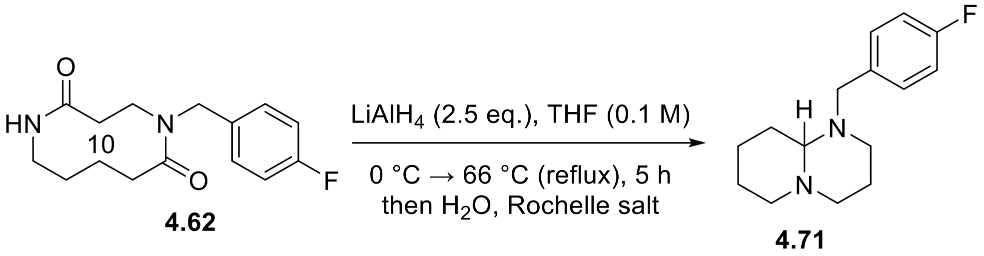


4.70

To a solution of 1-acryloyl-azetidin-2-one (154 mg, 1.23 mmol) in dry DMF (0.93 mL), was added 4-fluorobenzylamine (155 µL, 1.36 mmol) in a single portion. The reaction mixture was allowed to stir for 4 at RT and then the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, ethyl acetate → 1:19 methanol: ethyl acetate → 1:9 methanol: ethyl acetate → 1:6 methanol: ethyl acetate → 1:4 methanol: ethyl acetate → 1:3 methanol: ethyl acetate → 1:2 methanol: ethyl acetate) afforded the *title compound* as a colorless oil (35.6 mg, 12%), R_f 0.36 (3:7 methanol: ethyl acetate); Diagnostic ^{1}H NMR signal: δ_H (400 MHz, $CDCl_3$), 3.79 (2H, s, ArC**H₂**); Diagnostic 13C NMR signals: δ_C (100 MHz, $CDCl_3$), 170.0 (**C**O), 52.7 (Ar**C**H_2). In $CDCl_3$, the title compound ring expanded to form 1-(4-fluorobenzyl)-1,5-diazocane-2,6-dione after 3 days at RT, crystalizing in the process.

Lab notebook reference: KP457_A_8RO

1-[(4-Fluorophenyl)methyl]octahydro-2*H*-pyrido[1,2-*a*]pyrimidine (4.71)



To a 25 mL flask was added $LiAlH_4$ (95.8 mg, 2.52 mmol) and the headspace purged with argon. THF (5 mL) was added and the mixture was cooled down to 0 °C. 5-(4-fluorobenzyl)-1,5-diazecane-2,6-dione **4.62** (138 mg, 0.497 mmol) was added slowly as a neat solid to the chilled open flask, and the flask was fitted with a reflux condenser, purged with argon once more and heated to reflux (66 °C) for 4.5 h. TLC suggested complete conversion after 3 h. The mixture was then cooled to –78 °C and quenched with EtOAc (2 mL). After a few minutes s effervescence as a warming of the reaction flask was observed. Then, a half-saturated solution of aqueous potassium sodium tartrate was added (8 mL) and the mixture was left to stir vigorously overnight (18 h). Following this, the emulsion separated into two layers. It was diluted with DCM (15 mL) and the aqueous layer washed with DCM (2 × 10 mL), the organics were then washed with water (30 mL) and sat. aq. NaCl (30 mL). The organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:4 methanol: DCM) afforded the *title compound* **4.71** as an orange oil (92.0 mg, 74%), R_f 0.23 (1:4 methanol: DCM); ν_{max}/cm^{-1} (thin film) 2937, 2856, 2803, 2752, 1603, 1508, 1445, 1347, 1275, 1220, 1153, 1126, 1103, 1078, 1047, 1016, 963, 839, 501; δ_H (400 MHz, $CDCl_3$) 7.31 – 7.24 (2H, m, Ar**H**), 6.98 – 6.91 (2H, m, Ar**H**), 3.90 (1H, d, *J* = 13.9 Hz, ArC**H₂**), 3.45 (1H, d, *J* = 13.9 Hz, ArC**H₂**), 2.90 (1H, ddt, *J* = 11.3, 4.2, 2.1 Hz, C**H₂**), 2.82 (2H, ddq, *J* = 12.4, 4.2, 1.8 Hz, C**H₂**), 2.68 (1H, dd, *J* = 10.2, 2.8 Hz, C**H**), 2.26 (1H, td, *J* = 12.4, 2.9 Hz, C**H₂**), 2.14 (1H, ddd, *J* = 12.5, 11.3, 3.1 Hz, C**H₂**), 2.09 – 1.92 (2H, m, C**H₂**), 1.90 – 1.82 (1H, m, C**H₂**), 1.82 – 1.73 (1H, m, C**H₂**), 1.65 – 1.42 (3H, m, C**H₂**), 1.39 – 1.17 (2H, m, C**H₂**); δ_C (100 MHz, $CDCl_3$), 161.8 (Ar**C**F, $^1J_{CF}$ = 243.9 Hz), 136.2 (Ar**C**, $^4J_{CF}$ = 3.2 Hz), 130.0 (2 × Ar**C**H, $^3J_{CF}$ = 7.9 Hz), 115.0 (2 × Ar**C**H, $^2J_{CF}$ = 21.2 Hz), 82.5 (**C**H), 56.0 (**C**H₂), 55.7 (**C**H₂), 53.1 (**C**H₂), 51.6 (**C**H₂), 30.3 (**C**H₂), 25.3 (**C**H₂), 24.2 (**C**H₂), 22.8 (**C**H₂); δ_F (282 MHz, $CDCl_3$), –116.75 (1F, br s, Ar**F**); HRMS (ESI): calcd. for $C_{15}H_{22}FN_2$, 249.1762. Found: $[MH]^+$, 249.1758 (1.5 ppm error).

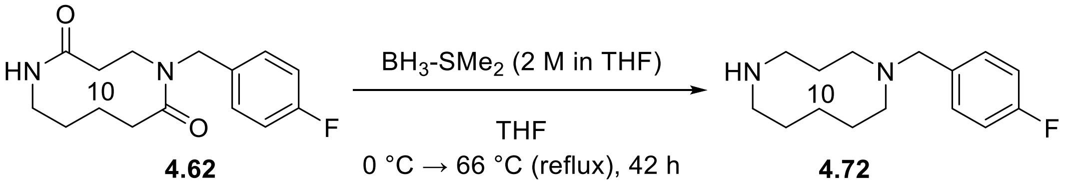
Lab notebook reference: KP449

Alternative procedure using $LiAlH_4$ solution in THF:

A solution of 5-(4-fluorobenzyl)-1,5-diazecane-2,6-dione (125 mg, 0.450 mmol) in THF (4.5 mL) was cooled to 0 °C. A solution of $LiAlH_4$ in THF (2.4 M, 0.375 mL) was added dropwise to the reaction mixture and it was stirred at reflux (66 °C) for 28 h. The reaction was cooled to RT and quenched using water (50 µL), followed by NaOH (15%, aq., 50 µL), and then water again (150 µL). The solution was filtered through Celite, washing with THF. The solvent was removed *in vacuo*, azeotroping with diethyl ether (3 × 5 mL) to give the crude product as a pale yellow oil (113 mg). Purification by flash column chromatography (SiO_2, 1:4 methanol: DCM) afforded the *title compound* **4.71** as an orange oil (79.8 mg, 71%).

Lab notebook reference: KP459

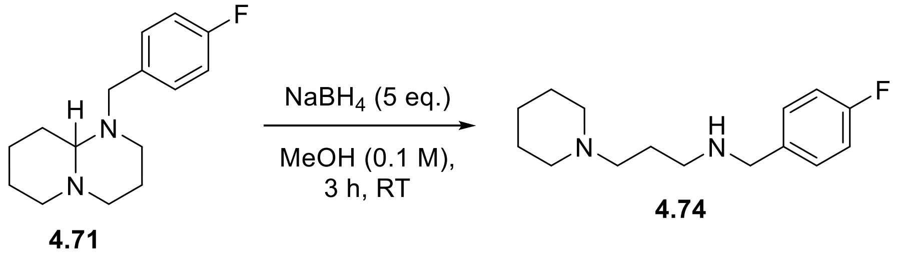
1-(4-Fluorobenzyl)-1,5-diazecane (4.72)



To a solution of 5-(4-fluorobenzyl)-1,5-diazecane-2,6-dione **4.62** (69.5 mg, 0.250 mmol) in anhydrous THF (1 mL) at 0 °C was added 2 M BH_3SMe_2 in THF (0.84 mL, 1.68 mmol) dropwise. Next the reaction mixture was heated to reflux (66 °C) and stirred for 18 hours. At this stage the reaction was judged to be incomplete when analysed by TLC and MS so additional 2 M BH_3SMe_2 in THF (1.68 mL, 3.36 mmol) at 0 °C and then heating was resumed at reflux for an additional 24 hours. The excess borane was destroyed by treating the solution with 6 M HCl (1 mL) at 0 °C, stirring for 1 hour, then adding 15 M ammonium hydroxide at 0 °C until basic pH (14) is reached. The solution was extracted with DCM (3 × 5 mL), the organic layer was washed with sat. $NaHCO_3$ (15 mL) and brine (15 mL) and the organic layers dried over $MgSO_4$, and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, DCM → 1:49 methanol: DCM → 1:19 methanol: DCM → 1:9 methanol: DCM → 1:4 methanol: DCM → 1:2 methanol: DCM → 1:1 methanol: DCM) afforded the *title compound* as a white crystalline solid (14.2 mg, 23%); m.p. 165 – 168 °C; R_f 0.29 (1:4 methanol: DCM); ν_{max}/cm^{-1} (thin film) 3406, 2933, 2844, 1603, 1509, 1453, 1222, 1158, 1094, 831, 604; δ_H (300 MHz, $CDCl_3$) 11.12 (1H, br s, N**H**), 7.35 – 7.24 (2H, m, Ar**H**), 7.16 – 7.06 (2H, m, Ar**H**), 3.87 – 2.34 (10H, m, C**H**$_2$), 2.28 – 1.11 (8H, m, C**H**$_2$); δ_C (75 MHz, $CDCl_3$) 162.7 (Ar**C**F, $^1J_{CF}$ = 247.2 Hz), 131.6 (2 × Ar**C**H, $^3J_{CF}$ = 8.2 Hz), 131.2 (Ar**C**, $^4J_{CF}$ = 3.3 Hz), 116.3 (2 × Ar**C**H, $^2J_{CF}$ = 21.5 Hz), 57.9 (**C**H$_2$), 53.2 (**C**H$_2$), 50.6 (**C**H$_2$), 47.2 (**C**H$_2$), 45.0 (**C**H$_2$), 25.5 (**C**H$_2$), 25.2 (**C**H$_2$), 20.5 (**C**H$_2$), 19.2 (**C**H$_2$); δ_F (282 MHz, $CDCl_3$) –113.69 (1F, m, ArF); HRMS (ESI): calcd. for $C_{15}H_{24}FN_2$, 251.1918. Found: [MH]$^+$, 251.1919 (–0.3 ppm error). This procedure was adapted from a literature method.[111]

Lab notebook reference: KP519_E

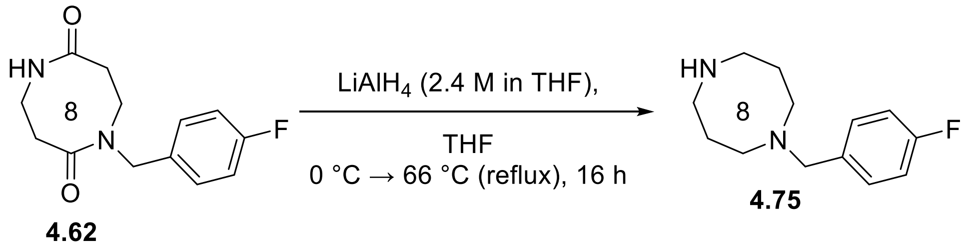
***N*-[(4-Fluorophenyl)methyl]-3-(piperidin-1-yl)propan-1-amine (4.74)**



1-[(4-Fluorophenyl)methyl]octahydro-2*H*-pyrido[1,2-*a*]pyrimidine **4.71** (68.1 mg, 0.274 mmol), dry methanol (2.7 mL) and $NaBH_4$ (55.3 mg, 1.46 mmol) were combined in a flask at RT and allowed to stir for 3 h. TLC indicated complete consumption of starting material after 2.5 h. The reaction mixture was quenched with water (1.2 mL) and extracted with DCM (4 × 5 mL). The organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to afford the *title compound* as a pale yellow oil (55.4 mg, 81%), R_f 0.03 (1:4 methanol: DCM); ν_{max}/cm^{-1} (thin film) 2933, 2853, 2804, 1603, 1509, 1447, 1351, 1221, 1155, 1126, 824; δ_H (400 MHz, $CDCl_3$) 7.30 – 7.19 (2H, m, Ar**H**), 7.00 – 6.92 (2H, m, Ar**H**), 3.71 (2H, s, ArC**H₂**), 2.62 (2H, t, *J* = 6.9 Hz, C**H₂**), 2.40 – 2.23 (6H, m, 3 × C**H₂**), 2.12 (1H, br s, N**H**), 1.72 – 1.61 (2H, m, C**H₂**), 1.53 (4H, app p, *J* = 5.6 Hz, 2 × C**H₂**), 1.43 – 1.34 (2H, m, C**H₂**); δ_C (100 MHz, $CDCl_3$), 161.9 (Ar**C**F, $^1J_{CF}$ = 244.3 Hz), 136.2 (Ar**C**, $^4J_{CF}$ = 2.9 Hz), 129.7 (2 × Ar**C**H, $^3J_{CF}$ = 7.9 Hz), 115.2 (2 × Ar**C**H, $^2J_{CF}$ = 21.2 Hz), 57.9 (**C**H₂), 54.8 (2 × **C**H₂), 53.3 (Ar**C**H₂), 48.4 (**C**H₂), 27.0 (**C**H₂), 26.1 (2 × **C**H₂), 24.5 (**C**H₂); δ_F (282 MHz, $CDCl_3$), –116.23 (1F, m,, Ar**F**); HRMS (ESI): calcd. for $C_{15}H_{24}FN_2$, 251.1918. Found: $[MH]^+$, 251.1920 (–1.0 ppm error).

Lab notebook reference: KP456

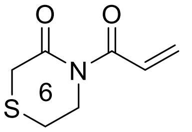
1-(4-Fluorobenzyl)-1,5-diazocane (4.75)



A solution of 1-(4-fluorobenzyl)-1,5-diazocane-2,6-dione **4.62** (37.5 mg, 0.150 mmol) in THF (1.5 mL) was cooled to 0 °C. A solution of $LiAlH_4$ in THF (2.4 M, 0.125 mL) was added dropwise to the reaction mixture and it was stirred at reflux (66 °C) for 4 h at which point additional THF (1 mL) was added and refluxing resumed for 12 more hours. The reaction was cooled to RT and quenched using water (30 µL), followed by NaOH (15%, aq., 30 µL), and then water again (90 µL). The solution was filtered through Celite, washing with THF. The solvent was removed *in vacuo*, azeotroping with diethyl ether (3 × 5 mL) to give the crude product as a colorless oil (12.6 mg, 38%); R_f 0.19 (1:4 methanol: DCM); ν_{max}/cm^{-1} (thin film) 3401, 2929, 1603, 1508, 1463, 1220, 1157, 1017, 836, 502; δ_H (600 MHz, $CDCl_3$) 10.0 (1H, s, N**H**), 7.35 – 7.31 (2H, m, Ar**H**), 7.05 – 7.00 (2H, m, Ar**H**), 3.60 (2H, s, C**H**$_2$), 3.37 – 3.31 (4H, m, 2 × C**H**$_2$), 2.82 – 2.73 (4H, m, 2 × C**H**$_2$), 1.83 (4H, apparent p, *J* = 6.0 Hz, 2 × C**H**$_2$); δ_C (151 MHz, $CDCl_3$) 162.4 (Ar**C**F, $^1J_{CF}$ = 246.2 Hz), 133.6 (Ar**C**, $^4J_{CF}$ = 3.2 Hz), 131.2 (2 × Ar**C**H, $^3J_{CF}$ = 7.9 Hz), 115.6 (2 × Ar**C**H, $^2J_{CF}$ = 21.2 Hz), 62.6 (**C**H$_2$Ar), 52.3 (2 × **C**H$_2$), 45.9 (2 × **C**H$_2$), 23.9 (2 × **C**H$_2$); δ_F (282 MHz, $CDCl_3$), −114.68 (1F, m, ArF); HRMS (ESI): calcd. for $C_{13}H_{20}FN_2$, 223.1605. Found: $[MH]^+$, 223.1609 (–1.6 ppm error).

Lab notebook reference: KP486_WU

4-Acryloylthiomorpholin-3-one (4.77)

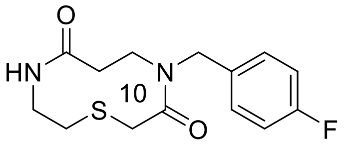


4.77

A stirring solution of thiomorpholin-3-one (56.2 mg, 0.480 mmol) and DIPEA (0.209 mL, 1.20 mmol) in THF (1.9 mL) was cooled to 0 °C. To this was added a 0 °C cooled solution of acryloyl chloride (0.078 mL, 0.960 mmol) in THF (0.9 mL) dropwise. Under an argon atmosphere this mixture was stirred at 0 °C for 3 hours. Afterwards it was allowed to warm to RT and stirred for a further 2 hours. The reaction mixture was then quenched with sat. aq. NH_4Cl (5 mL), extracted with Et_2O (5 mL), then the organic layer washed with washed with sat. aq. $NaHCO_3$ (2 × 5 mL). The organic extracts were 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 colorless oil (37.9 mg, 46%); R_f 0.21 (1:1 diethyl ether: hexane); ν_{max}/cm^{-1} (thin film) 1707, 1684, 1405, 1369, 1334, 1274, 1244, 1198, 1163, 1124, 1021, 977, 869, 794; δ_H (400 MHz, $CDCl_3$), 7.16 (1H, dd, *J* = 16.9, 10.4 Hz, NCOC**H**CHH'), 6.42 (1H, dd, *J* = 16.9, 1.7 Hz, NCOCHC**H**H'), 5.81 (1H, dd, *J* = 10.4, 1.7 Hz, NCOCHCH**H'**), 4.22 – 4.16 (2H, m, SCH$_2$C**H$_2$**N), 3.40 (2H, s, C**H$_2$**CON), 2.99 – 2.94 (2H, m, SC**H$_2$**CH$_2$N); δ_C (100 MHz, $CDCl_3$) 170.3 (**C**O), 167.9 (**C**O), 131.2 (NCO**C**HCHH'), 130.2 (NCOCH**C**HH'), 41.5 (SCH$_2$**C**H$_2$N), 31.5 (**C**H$_2$CON), 26.0 (S**C**H$_2$CH$_2$N); HRMS (ESI): calcd. for $C_7H_9NNaO_2S$, 194.0246. Found: $[MNa]^+$, 194.0248 (–1.1 ppm error).

Lab notebook reference: KP511

4-(4-Fluorobenzyl)-1,4,8-thiadiazecane-3,7-dione (4.78)

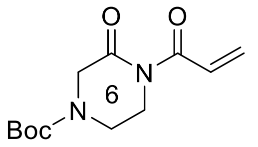


4.78

To a solution of 4-acryloylthiomorpholin-3-one **4.77** (37.9 mg, 0.222 mmol) in dry methanol (0.44 mL), was added 4-fluorobenzylamine (28 µL, 0.244 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 ethyl acetate: hexane → 2:1 ethyl acetate: hexane → ethyl acetate → 1:49 methanol: ethyl acetate → 1:24 methanol: ethyl acetate → 1:16 methanol: ethyl acetate → 1:12 methanol: ethyl acetate) afforded the *title compound* as a colorless oil (48.2 mg, 73%). In solution in $CDCl_3$, this compound exists as a mixture of 2 rotameric forms (5:2 ratio, best seen in the ^{19}F NMR). The ^{1}H NMR spectrum is difficult to interpret due rotameric broadening, even when recorded at 80 °C in d_6-DMSO, with product identity and purity best determined using ^{13}C NMR data; R_f 0.11 (1:9 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3299, 2928, 1628, 1553, 1509, 1413, 1359, 1222, 1156, 1098, 826, 731, 500; δ_H (400 MHz, d_6-DMSO, 80 °C), 8.00 (1H, br s, N**H**), 7.36 – 7.22 (2H, m, Ar**H**), 7.20 – 6.99 (2H, m, Ar**H**), 5.09 – 4.17 (2H, m, C**H₂**), 3.80 – 2.61 (8H, m, C**H₂**), 2.44 – 2.07 (2H, m, C**H₂**); δ_C (100 MHz, $CDCl_3$), 172.3 (**C**O, major rotamer), 172.0 (**C**O, minor rotamer), 171.4 (**C**O, minor), 170.7 (**C**O, major), 162.5 (Ar**C**F, $^{1}J_{CF}$ = 246.5 Hz, minor, [overlapping]), 162.4 (Ar**C**F, $^{1}J_{CF}$ = 246.5 Hz, major [overlapping]), 133.0 (Ar**C**, $^{4}J_{CF}$ = 3.1 Hz, minor), 132.1 (Ar**C**, $^{4}J_{CF}$ = 3.1 Hz, major), 130.1 (2 × Ar**C**H, $^{3}J_{CF}$ = 8.0 Hz, minor), 128.2 (2 × Ar**C**H, $^{3}J_{CF}$ = 8.2 Hz, major), 116.1 (2 × Ar**C**H, $^{2}J_{CF}$ = 21.7 Hz, major, [overlapping]), 115.9 (2 × Ar**C**H, $^{2}J_{CF}$ = 21.7 Hz, minor [overlapping]), 52.4 (**C**H₂, major), 48.6 (**C**H₂, minor), 45.3 (**C**H₂, minor), 43.2 (**C**H₂, minor), 42.4 (**C**H₂, major), 39.5 (**C**H₂, major), 36.9 (**C**H₂, minor), 35.4 (**C**H₂, major), 34.8 (**C**H₂, major), 34.5 (**C**H₂, minor), 32.4 (**C**H₂, major), 30.8 (**C**H₂, minor); δ_F (282 MHz, $CDCl_3$) –114.11 (1F, m, ArF, minor rotamer), –114.13 (1F, m, ArF, major rotamer); HRMS (ESI): calcd. for $C_{14}H_{17}FN_2NaO_2S$, 319.0887. Found: [MNa]$^+$, 319.0891 (–1.4 ppm error).

Lab notebook reference: KP513

***tert*-Butyl 4-acryloyl-3-oxopiperazine-1-carboxylate (4.79)**

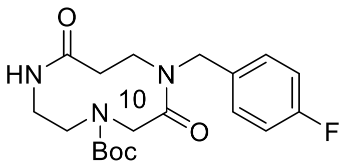


4.79

To a stirring solution of *tert*-butyl 3-oxopiperazine-1-carboxylate (401 mg, 2.00 mmol) in dry THF (7.3 mL) cooled to 0 °C was added a solution of MeMgBr (3.0 M in diethyl ether, 0.733 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 (0.243 mL, 3.00 mmol) was then added in a single portion and the reaction was stirred for an additional 30 min at 0 °C. The reaction was then quenched with sat. aq. NH_4Cl (15 mL) and the mixture was extracted with Et_2O (15 mL). The organic layer was washed with sat. aq. $NaHCO_3$ (2 × 15 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 colourless oil (361 mg, 71%); R_f 0.16 (1:1 hexane: diethyl ether); ν_{max}/cm^{-1} (thin film) 2977, 1685, 1616, 1406, 1389, 1365, 1303, 1243, 1160, 1131, 1097, 1021, 974, 919, 864, 795, 769, 608, 527; δ_H (400 MHz, $CDCl_3$) 7.13 (1H, dd, *J* = 16.9, 10.4 Hz, NCOC**H**CHH'), 6.40 (1H, dd, *J* = 16.9, 1.7 Hz, NCOCHC**H**H'), 5.79 (1H, dd, *J* = 10.4, 1.7 Hz, NCOCHCH**H'**), 4.21 (2H, s, N(Boc)C**H**$_2$CON), 3.89 – 3.84 (2H, m, C**H**$_2$), 3.65 – 3.58 (2H, m, C**H**$_2$), 1.45 (9H, s, 3 × C**H**$_3$); δ_C (100 MHz, $CDCl_3$) 168.8 (**C**O), 168.0 (**C**O), 153.7 (*t*-BuO-**C**O), 131.1 (NCO**C**HCHH'), 130.2 (NCOCH**C**HH'), 81.3 (**C**), 49.3 (**C**H$_2$), 42.3 (**C**H$_2$), 41.7 (**C**H$_2$), 28.4 (3 × **C**H$_3$); HRMS (ESI): calcd. for $C_{12}H_{18}N_2NaO_4$, 277.1159. Found: $[MNa]^+$, 277.1156 (1.0 ppm error).

Lab notebook reference: KP498

***tert*-Butyl 1-(4-fluorobenzyl)-2,8-dioxo-1,4,7-triazecane-4-carboxylate (4.80)**



4.80

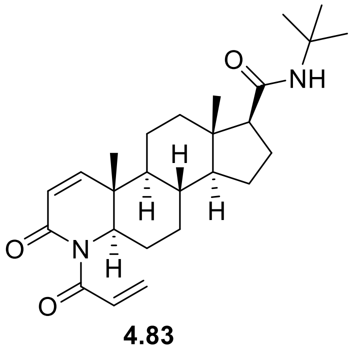
To a solution of *tert*-butyl 4-acryloyl-3-oxopiperazine-1-carboxylate **4.79** (128 mg, 0.503 mmol) in dry methanol (1.0 mL), was added 4-fluorobenzylamine (63 µL, 0.553 mmol) in a single portion. The reaction mixture was allowed to stir for 4 h at RT and then the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 ethyl acetate: hexane → 2:1 ethyl acetate:

hexane → ethyl acetate → 1:49 methanol: ethyl acetate → 1:19 methanol: ethyl acetate → 1:13 methanol: ethyl acetate) afforded the *title compound* as a white solid (158 mg, 83%). In solution in $CDCl_3$, this compound exists as a mixture of 3 rotameric forms (20:5:4 ratio, best seen in the ^{19}F NMR); m.p. 169–172 °C; R_f 0.18 (1:9 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 2977, 1652, 1510, 1405, 1366, 1222, 1159, 910, 832, 728, 646, 499; ^{1}H and ^{13}C NMR data for the major rotamer. δ_H (400 MHz, $CDCl_3$) 7.19 – 7.10 (2H, m, Ar**H**), 7.07 – 6.96 (2H, m, Ar**H**), 5.74 – 5.64 (1H, m, N**H**), 5.11 (1H, d, *J* = 16.3 Hz, C**H**$_2$), 5.03 (1H, d, *J* = 14.2 Hz, C**H**$_2$), 4.28 – 4.04 (3H, m, C**H**$_2$), 3.79 – 3.70 (1H, m, C**H**$_2$), 3.27 (1H, d, *J* = 14.2 Hz, C**H**$_2$), 3.11 – 2.69 (4H, m, C**H**$_2$), 2.52 – 2.39 (1H, m, C**H**$_2$), 1.51 (9H, s, 3 × C**H**$_3$); δ_C (100 MHz, $CDCl_3$) 172.7 (**C**O), 170.8 (**C**O), 155.2 (**C**O), 162.4 (Ar**C**F, $^1J_{CF}$ = 246.3 Hz), 132.7 (Ar**C**, $^4J_{CF}$ = 3.5 Hz), 128.9 (2 × Ar**C**H, $^3J_{CF}$ = 7.9 Hz), 115.8 (2 × Ar**C**H, $^2J_{CF}$ = 21.3 Hz), 81.5 (quat **C**), 52.3 (**C**H$_2$), 51.7 (**C**H$_2$), 49.3 (**C**H$_2$), 41.6 (**C**H$_2$), 38.9 (**C**H$_2$), 35.2 (**C**H$_2$), 28.35 (3 × **C**H$_3$); δ_F (470 MHz, $CDCl_3$), –113.85 (1F, m, ArF, minor rotamer), –114.36 (1F, m, ArF, minor rotamer), –114.87 (1F, m, ArF, major rotamer); HRMS (ESI): calcd. for $C_{19}H_{26}FN_3NaO_4$, 402.1800. Found: [MNa]$^+$, 402.1808 (–2.1 ppm error).

Characteristic NMR data for the minor rotamers can be found at: δ_H (400 MHz, $CDCl_3$) 4.69 (1H, d, *J* = 14.3 Hz, C**H**$_2$), 3.52 (1H, d, *J* = 14.3 Hz, C**H**$_2$), 1.46 (9H, s, 3 × C**H**$_3$), 1.37 (9H, s, 3 × C**H**$_3$); δ_C (100 MHz, $CDCl_3$) 172.0 (**C**O), 130.2 (2 × Ar**C**H, $^3J_{CF}$ = 8.3 Hz), 128.4 (2 × Ar**C**H, $^3J_{CF}$ = 8.3 Hz), 116.1 (2 × Ar**C**H, $^2J_{CF}$ = 22.9 Hz), 42.3 (**C**H$_2$), 41.3 (**C**H$_2$), 38.7 (**C**H$_2$), 34.9 (**C**H$_2$), 28.42 (3 × **C**H$_3$).

Lab notebook reference: KP499

4a*R*,4b*S*,6a*S*,7*S*,9a*S*,9b*S*,11a*R*)-1-Acryloyl-*N*-(*tert*-butyl)-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,7,8,9,9a,9b,10,11,11a-tetradecahydro-1*H*-indeno[5,4-*f*]quinoline-7-carboxamide (4.83)

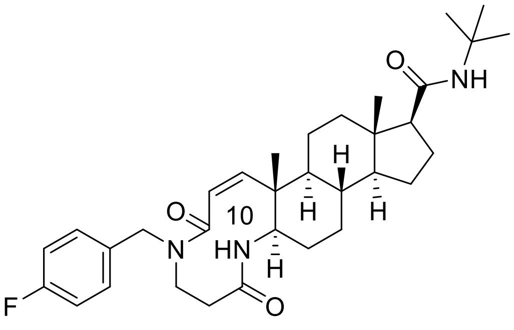


4.83

To a stirring solution of finasteride (125 mg, 0.335 mmol) and DIPEA (0.146 mL, 0.838 mmol) in THF (1.3 mL) was cooled to 0 °C. To this was added a 0 °C cooled solution of acryloyl chloride (0.053 mL, 0.671 mmol) in THF (0.3 mL) dropwise. Under an argon atmosphere this mixture was stirred at 0 °C for 3 hours. Afterwards it was allowed to warm to RT and stirred for a further 2 hours. The reaction mixture was then quenched with sat. aq. NH_4Cl (1.5 mL), extracted with Et_2O (2.0 mL), then the organic layer washed with washed with sat. aq. $NaHCO_3$ (2 × 1.5 mL). The organic extracts were 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 colourless oil (89.3 mg, 62%); R_f 0.63 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3365, 2966, 2940, 2243, 1665, 1619, 1517, 1451, 1391, 1363, 1254, 1196, 1125, 914, 821, 729; δ_H (400 MHz, $CDCl_3$) 6.94 (1H, d, *J* = 10.0 Hz, C**H**CHCONCOCHCHH'), 6.52 (1H, dd, *J* = 17.0, 10.2 Hz, CHCHCONCOC**H**CHH'), 6.27 (1H, dd, *J* = 17.0, 1.5 Hz, CHCHCONCOCHC**H**H'), 5.81 (1H, d, *J* = 10.0 Hz, CH**C**HCONCOCHCHH'), 5.67 (1H, dd, *J* = 10.2, 1.5 Hz, CHCHCONCOCHCH**H'**), 5.12 (1H, s, N**H**), 3.62 (1H, ddd, *J* = 12.2, 3.5, 1.5 Hz), 2.41 (1H, dd, *J* = 13.3, 3.6 Hz), 2.16 – 2.03 (1H, m), 2.03 – 1.89 (2H, m), 1.78 – 1.57 (4H, m), 1.50 – 1.33 (3H, m), 1.30 (9H, s, $CONC(C\mathbf{H_3})_3$), 1.27 – 1.15 (2H, m, $C\mathbf{H_2}$), 1.09 – 0.87 (6H, m), 0.66 (3H, s, $C\mathbf{H_3}$); δ_C (100 MHz, $CDCl_3$) 171.68 (**C**O), 171.66 (**C**O), 166.5 (**C**O), 153.4 (**C**HCHCONCOCHCH$_2$), 133.6 (CHCHCONCO**C**HCH$_2$), 128.1 (CHCHCONCOCH**C**H$_2$), 122.6 (CH**C**HCONCOCHCH$_2$), 65.1 (**C**H), 57.4 (**C**H), 55.6 (**C**H), 51.1 (NH**C**(CH$_3$)$_3$), 47.9 (**C**H), 43.8 (**C**), 40.0 (**C**), 38.4 (**C**H$_2$), 35.0 (**C**H), 29.9 (**C**H$_2$), 29.1 (NHC(**C**H$_3$)$_3$), 24.2 (**C**H$_2$), 23.6 (**C**H$_2$), 23.4 (**C**H$_2$), 21.4 (**C**H$_2$), 13.4 (**C**H$_3$), 13.3 (**C**H$_3$); HRMS (ESI): calcd. for $C_{26}H_{38}N_2NaO_3$, 449.2775. Found: $[MNa]^+$, 449.2779 (–1.0 ppm error).

Lab notebook reference: KP538

(8a*R*,8b*S*,10a*S*,11*S*,13a*S*,13b*S*,15a*R*,Z)-*N*-(*tert*-Butyl)-5-(4-fluorobenzyl)-8a,10a-dimethyl-2,6-dioxo-2,3,4,5,6,8a,8b,9,10,10a,11,12,13,13a,13b,14,15,15a-octadecahydro-1*H*-cyclopenta[5,6]naphtho[2,1-*f*][1,5]diazecine-11-carboxamide trione (4.84)



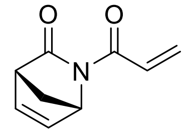
4.84

To a solution of 4a*R*,4b*S*,6a*S*,7*S*,9a*S*,9b*S*,11a*R*)-1-acryloyl-*N*-(*tert*-butyl)-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,7,8,9,9a,9b,10,11,11a-tetradecahydro-1*H*-indeno[5,4-*f*]quinoline-7-carboxamide **4.83** (89.3 mg, 0.209 mmol) in dry methanol (0.42 mL), was added 4-fluorobenzylamine (26 µL, 0.230 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 ethyl acetate: hexane →

ethyl acetate) afforded the *title compound* as a white crystalline solid (83.5 mg, 77%); m.p. 226–229 °C; R_f 0.12 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3319, 2934, 1632, 1542, 1509, 1452, 1414, 1365, 1222, 1157, 910, 821, 729, 645, 537; δ_H (400 MHz, $CDCl_3$) 7.29 (2H, dd, *J* = 8.6, 5.5 Hz, Ar**H**), 7.02 (2H, t, *J* = 8.6 Hz, Ar**H**), 6.03 (1H, d, *J* = 13.4 Hz, =C**H**), 5.48 – 5.42 (1H, m, N**H**), 5.39 (1H, d, *J* = 13.4 Hz, =C**H**), 5.07 (1H, s, N**H**), 4.97 (1H, d, *J* = 14.1 Hz, ArC**H**$_2$), 4.15 (1H, d, *J* = 14.1 Hz, ArC**H**$_2$), 3.84 – 3.67 (2H, m, C**H**$_2$), 3.32 – 3.22 (1H, m, C**H**$_2$), 2.28 – 1.96 (4H, m), 1.90 – 1.60 (7H, m), 1.53 – 1.36 (3H, m), 1.33 (9H, s, CONC(C**H**$_3$)$_3$), 1.27 – 1.16 (2H, m), 1.12 – 0.95 (2H, m, [overlapping] C**H**), 1.06 (3H, s, C**H**$_3$,[overlapping]), 0.66 (3H, s, C**H**$_3$); δ_C (100 MHz, $CDCl_3$) 172.3 (**C**O), 171.8 (**C**O), 169.9 (**C**O), 162.5 (Ar**C**F, $^1J_{CF}$ = 246.6 Hz), 143.3 (**C**H), 133.1 (Ar**C**, $^4J_{CF}$ = 3.2 Hz), 130.4 (2 × Ar**C**H, $^3J_{CF}$ = 7.9 Hz), 125.4 (**C**H), 115.9 (2 × Ar**C**H, $^2J_{CF}$ = 21.3 Hz), 57.6 (**C**H), 55.8 (**C**H), 53.8 (**C**H), 53.6 (**C**H), 51.2 (quat **C**), 48.4 (**C**H$_2$), 47.2 (**C**), 47.0 (**C**H$_2$), 44.1 (**C**), 38.8 (**C**H$_2$), 37.8 (**C**H$_2$), 33.9 (**C**H), 30.2 (**C**H$_2$), 29.2 (NHC(**C**H$_3$)$_3$), 26.6 (**C**H$_2$), 24.3 (**C**H$_2$), 24.0 (**C**H$_2$), 23.2 (**C**H$_2$), 13.3 (**C**H$_3$), 12.5 (**C**H$_3$); δ_F (376 MHz, $CDCl_3$), –113.99 (1F, m, ArF); HRMS (ESI): calcd. for $C_{33}H_{46}FN_3NaO_3$, 574.3415. Found: $[MNa]^+$, 574.3431 (–2.8 ppm error).

Lab notebook reference: KP541

(1*SR*,4*RS*)-2-Acryloyl-2-azabicyclo[2.2.1]hept-5-en-3-one (4.85)



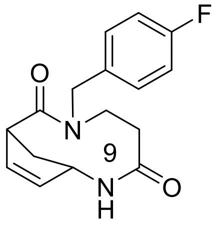
4.85

Acryloyl chloride (0.300 mL, 3.45 mmol), Et_3N (0.480 mL, 3.40 mmol) and DMAP (30.0 mg, 0.230 mmol) were added to a solution of (1*SR*,4*SR*)-2-azabicyclo[2.2.1]hept-5-en-3-one (249 mg, 2.30 mmol) in DCM (11 mL) under argon at 0 °C. The reaction mixture was stirred at RT for 18 h. After this time, 0.5 M aq. HCl was added (15 mL). The crude reaction mixture was washed with sat. aq. $NaHCO_3$ (15 mL) and sat. aq. NaCl (15 mL) and the organic layer dried with $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 diethyl ether: hexane) afforded the *title compound* as a colourless oil (63.8 mg, 17%); R_f 0.28 (1:1 hexane: diethyl ether); ν_{max}/cm^{-1} (thin film) 1734, 1672, 1619, 1405, 1327, 1236, 1174, 1146, 1066, 968, 914, 838, 795, 758, 694, 598; δ_H (400 MHz, $CDCl_3$) 7.28 (1H, dd, *J* = 17.1, 10.4 Hz, NCOC**H**CHH’), 6.89 (1H, ddd, *J* = 5.3, 2.4, 0.8 Hz), 6.62 (1H, ddd, *J* = 5.1, 3.2, 1.5 Hz), 6.44 (1H, dd, *J* = 17.1, 1.9 Hz, NCOCHC**H**H’), 5.77 (1H, dd, *J* = 10.4, 1.9 Hz, NCOCHCH**H’**), 5.29 (1H, ddt, *J* = 4.1, 2.5, 1.6 Hz), 3.42 (1H, ddtd, *J* = 3.2, 2.3, 1.5, 0.7 Hz), 2.30 (1H, dt, *J* = 8.7, 1.8 Hz, 0.5 × C**H**$_2$), 2.19 (1H, dt, *J* = 8.7, 1.5 Hz, 0.5 × C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 177.5 (**C**O), 164.7 (**C**O), 140.5 (**C**H), 138.1 (**C**H), 130.7 (NCOCH**C**H$_2$), 128.7 (NCO**C**HCH$_2$), 60.5 (**C**H), 54.7 (**C**H), 54.5 (**C**H$_2$);

HRMS (ESI): calcd. for $C_9H_9NNaO_2$, 186.0525. Found: $[MNa]^+$, 186.0527 (–0.7 ppm error). ^{1}H and ^{13}C NMR data matches those reported in the literature.[112]

Lab notebook reference: KP520

(1*SR*,8*SR*)-6-(4-Fluorobenzyl)-2,6-diazabicyclo[6.2.1]undec-9-ene-3,7-dione (4.86)

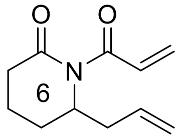


4.86

To a solution of (1*SR*,4*SR*)-2-acryloyl-2-azabicyclo[2.2.1]hept-5-en-3-one **4.85** (63.8 mg, 0.391 mmol) in dry methanol (0.78 mL), was added 4-fluorobenzylamine (49 µL, 0.430 mmol) in a single portion. The reaction mixture was allowed to stir for 5 h at RT and then the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 ethyl acetate: hexane → 3:1 ethyl acetate: hexane → ethyl acetate → 1:19 methanol: ethyl acetate → 1:9 methanol: ethyl acetate) afforded the *title compound* as an off-white solid (98.7 mg, 88%); m.p. 125–131 °C; R_f 0.19 (1:9 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3277, 1627, 1605, 1509, 1413, 1348, 1320, 1220, 1157, 1097, 1049, 992, 965, 910, 841, 727, 645, 550, 494; δ_H (400 MHz, $CDCl_3$) 7.21 – 7.14 (2H, m, Ar**H**), 7.00 (1H, d, *J* = 6.9 Hz, N**H**), 6.98 – 6.91 (2H, m, Ar**H**), 6.15 (1H, ddd, *J* = 5.5, 2.9, 1.4 Hz, CHC**H**=CHCH), 5.84 (1H, dt, *J* = 5.3, 2.5 Hz, CHCH=C**H**CH), 4.61 (1H, d, *J* = 14.4 Hz, 0.5 × C**H₂**), 4.48 – 4.39 (1H, m, C**H**CH=CHCH), 4.36 (1H, d, *J* = 14.4 Hz, 0.5 × C**H₂**), 4.04 – 3.89 (2H, m, 0.5 × C**H₂**, and C**H**CH=CHCH), 3.36 (1H, dt, *J* = 16.6, 7.3 Hz, 0.5 × C**H₂**), 2.75 – 2.50 (3H, m, 1.5 × C**H₂**), 2.31 (1H, ddd, *J* = 14.7, 7.4, 5.6 Hz, 0.5 × C**H₂**); δ_C (100 MHz, $CDCl_3$) 174.7 (**C**O), 171.9 (**C**O), 162.3 (Ar**C**F, $^1J_{CF}$ = 246.3 Hz), 134.9 (CH**C**H=CHCH), 133.8 (CHCH=**C**HCH, **C**H), 133.0 (Ar**C**, $^4J_{CF}$ = 3.3 Hz), 130.1 (2 × Ar**C**H, $^3J_{CF}$ = 8.1 Hz), 115.6 (2 × Ar**C**H, $^2J_{CF}$ = 21.5 Hz), 58.8 (**C**HCH=CHCH), 54.7 (CHCH=CH**C**H), 51.7 (**C**H₂), 40.4 (**C**H₂), 38.6 (**C**H₂), 30.1 (**C**H₂); δ_F (282 MHz, $CDCl_3$), –114.48 (1F, m, ArF); HRMS (ESI): calcd. for $C_{16}H_{17}FN_2NaO_2$, 311.1166. Found: $[MNa]^+$, 311.1169 (–0.7 ppm error).

Lab notebook reference: KP522

1-Acryloyl-6-allylpiperidin-2-one (4.87)

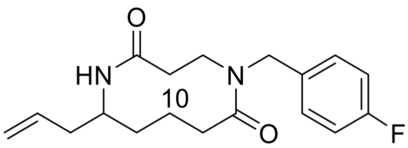


4.87

To a stirring solution of 6-allylpiperidin-2-one (126 mg, 0.903 mmol) in dry THF (3.6 mL) cooled to 0 °C was added a solution of MeMgBr (3.0 M in diethyl ether, 0.370 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 (1.22 mL, 1.36 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 (15 mL) and the mixture was extracted with Et_2O (15 mL). The organic layer was washed with sat. aq. $NaHCO_3$ (2 × 15 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 colourless oil (73.3 mg, 42%); R_f 0.25 (1:1 hexane: diethyl ether); ν_{max}/cm^{-1} (thin film) 3211, 3077, 2944, 1664, 1448, 1406, 1347, 1309, 1209, 1167, 996, 916, 796; δ_H (400 MHz, $CDCl_3$) 6.79 (1H, dd, *J* = 16.8, 10.3 Hz, NCOC**H**=CHH'), 6.28 (1H, dd, J = 16.8, 1.8 Hz, NCOCH=C**H**H'), 5.71 (1H, dddd, *J* = 17.1, 10.2, 8.2, 6.1 Hz, NCHCH$_2$C**H**=CH$_2$), 5.64 (1H, dd, J = 10.3, 1.8 Hz, NCOCH=CH**H'**), 5.11 – 5.01 (2H, m, NCHCH$_2$CHC**H**$_2$), 4.54 – 4.46 (1H, m, NC**H**CH$_2$CHCH$_2$), 2.61 – 2.42 (3H, m, 1.5 × C**H$_2$**), 2.19 (1H, dddt, *J* = 13.7, 10.1, 8.2, 0.9 Hz, 0.5 × C**H$_2$**), 2.00 – 1.87 (2H, m, C**H$_2$**), 1.83 – 1.68 (2H, m, C**H$_2$**); δ_C (100 MHz, $CDCl_3$) 174.3 (**C**O), 169.1 (**C**O), 134.0 (NCHCH$_2$**C**HCH$_2$), 131.9 (NCO**C**HCHH'), 127.7 (NCOCH**C**HH'), 118.1 (NCHCH$_2$CH**C**H$_2$), 53.2 (N**C**HCH$_2$CHCH$_2$), 37.8 (**C**H$_2$), 34.3 (**C**H$_2$), 24.8 (**C**H$_2$), 16.9 (**C**H$_2$); HRMS (ESI): calcd. for $C_{11}H_{15}NNaO_2$, 216.0995. Found: $[MNa]^+$, 216.0996 (–0.3 ppm error).

Lab notebook reference: KP508

10-Allyl-5-(4-fluorobenzyl)-1,5-diazecane-2,6-dione (4.88)



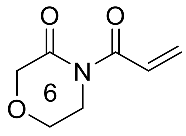
4.88

To a solution of 1-acryloyl-6-allylpiperidin-2-one **4.87** (73.2 mg, 0.379 mmol) in dry methanol (0.76 mL), was added 4-fluorobenzylamine (48 µL, 0.417 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 ethyl acetate: hexane → 2:1 ethyl acetate: hexane → ethyl acetate → 1:49 methanol: ethyl acetate → 1:24 methanol: ethyl acetate → 1:16 methanol: ethyl acetate) afforded the *title compound* as a white solid (88.3 mg, 73%). In solution in $CDCl_3$, this compound exists as a mixture of 2 rotameric forms (12:1 ratio, best seen in the ^{19}F NMR); m.p. 195–198 °C; R_f 0.46 (1:9 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3287, 2933, 1621, 1552, 1509, 1414, 1361, 1221, 1157, 1096, 994, 915, 810, 729, 645, 600, 483; ^1H and ^{13}C NMR data for the major rotamer. δ_H (400 MHz, $CDCl_3$) 7.34 – 7.23 (2H, m, Ar**H**), 6.99 (2H, t, *J* = 8.5 Hz, Ar**H**), 5.68 (1H, ddt, *J* = 17.3, 10.4, 7.1 Hz, $\mathrm{C\mathbf{H}CH_2}$), 5.10 – 4.90 (3H, m, $\mathrm{CHC\mathbf{H_2}}$ and N**H**), 4.82 (1H, d, *J* = 14.5 Hz, $\mathrm{C\mathbf{H_2}}$), 4.34 (1H, d, *J* = 14.5 Hz, $\mathrm{C\mathbf{H_2}}$), 4.05 – 3.84 (2H, m, $\mathrm{C\mathbf{H_2}}$), 3.26 (1H, dt, *J* = 15.6, 3.8 Hz, $\mathrm{C\mathbf{H_2}}$), 2.69 – 2.56 (1H, m, $\mathrm{C\mathbf{H_2}}$), 2.24 – 1.92 (6H, m, $\mathrm{C\mathbf{H_2}}$), 1.71 – 1.53 (2H, m, $\mathrm{C\mathbf{H_2}}$), 1.42 – 1.28 (1H, m, $\mathrm{C\mathbf{H_2}}$); δ_C (100 MHz, $CDCl_3$) 173.9 (**C**O), 170.3 (**C**O), 162.4 (Ar**C**F, $^1J_{CF}$ = 246.7 Hz), 134.1 (Ar**C**, $^4J_{CF}$ = 3.5 Hz), 134.0 ($\mathrm{\mathbf{C}HCH_2}$), 130.1 (2 × Ar**C**H, $^3J_{CF}$ = 8.1 Hz), 118.1 ($\mathrm{CH\mathbf{C}H_2}$), 115.9 (2 × Ar**C**H, $^2J_{CF}$ = 21.4 Hz), 49.2 ($\mathrm{CONH\mathbf{C}HCH_2CHCH_2}$), 49.0 ($\mathrm{\mathbf{C}H_2}$), 45.5 ($\mathrm{\mathbf{C}H_2}$), 41.0 ($\mathrm{\mathbf{C}H_2}$), 37.8 ($\mathrm{\mathbf{C}H_2}$), 31.0 ($\mathrm{\mathbf{C}H_2}$), 28.0 ($\mathrm{\mathbf{C}H_2}$), 23.3 ($\mathrm{\mathbf{C}H_2}$); δ_F (282 MHz, $CDCl_3$), –114.15 (1F, m, ArF, major rotamer), –114.15 (1F, m, ArF, minor rotamer); HRMS (ESI): calcd. for $C_{18}H_{23}FN_2NaO_2$, 341.1636. Found: [MNa]$^+$, 341.1643 (–2.0 ppm error).

Characteristic NMR data for the minor rotamers can be found at: δ_H (400 MHz, $CDCl_3$) 7.14 – 7.09 (2H, m, Ar**H**), 4.75 (1H, d, *J* = 16.3 Hz, $\mathrm{C\mathbf{H_2}}$), 4.26 (1H, d, *J* = 16.3 Hz, $\mathrm{C\mathbf{H_2}}$); δ_C (100 MHz, $CDCl_3$) 176.4 (**C**O), 134.5 ($\mathrm{\mathbf{C}HCH_2}$), 128.5 (2 × Ar**C**H, $^3J_{CF}$ = 8.1 Hz), 117.7 ($\mathrm{CH\mathbf{C}H_2}$), 115.87 (2 × Ar**C**H, $^2J_{CF}$ = 21.4 Hz), 50.2 ($\mathrm{\mathbf{C}H_2}$), 41.7 ($\mathrm{\mathbf{C}H_2}$), 40.2 ($\mathrm{\mathbf{C}H_2}$), 36.0 ($\mathrm{\mathbf{C}H_2}$), 35.2 ($\mathrm{\mathbf{C}H_2}$), 32.5 ($\mathrm{\mathbf{C}H_2}$).

Lab notebook reference: KP509

4-Acryloylmorpholin-3-one (4.89)

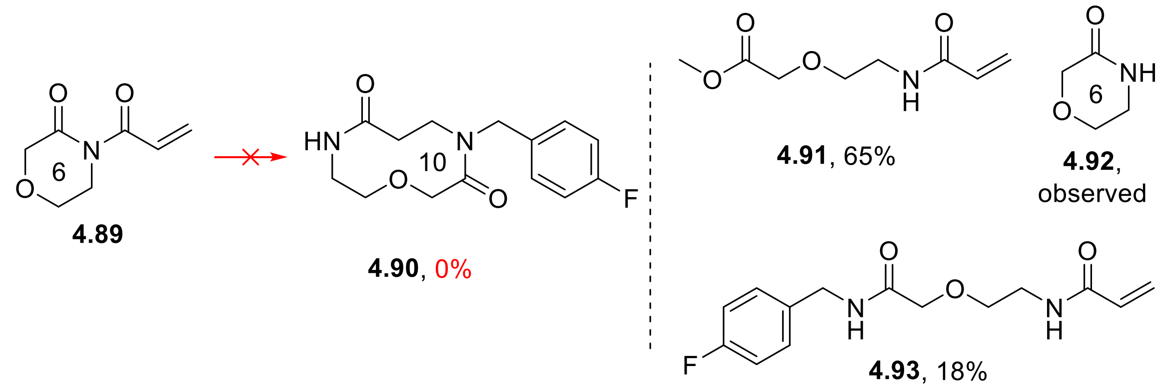


4.89

To a stirring solution of morpholin-3-one (202 mg, 1.99 mmol) in dry THF (7.3 mL) cooled to 0 °C was added a solution of MeMgBr (3.0 M in diethyl ether, 0.731 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 (0.244 mL, 3.00 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 (10 mL). The organic layer was washed with sat. aq. $NaHCO_3$ (2 × 8 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 fluffy white powder (106 mg, 34%); m.p. 44 – 47 °C; R_f 0.16 (1:1 diethyl ether: hexane); ν_{max}/cm^{-1} (thin film) 1686, 1396, 1345, 1312, 1204, 1148, 1114, 940; δ_H (400 MHz, $CDCl_3$), 7.22 (1H, dd, *J* = 16.9, 10.5 Hz, NCOC**H**CHH'), 6.43 (1H, dd, *J* = 16.9, 1.7 Hz, NCOCHC**H**H'), 5.81 (1H, dd, *J* = 10.5, 1.7 Hz, NCOCHCH**H'**), 4.28 (2H, s, OC**H₂**CON), 3.96 – 3.92 (2H, m, OC**H₂**CH₂N), 3.85 – 3.80 (2H, m, OCH₂C**H₂**N); δ_C (100 MHz, $CDCl_3$) 169.8 (**C**O), 168.3 (**C**O), 131.3 (NCO**C**HCHH'), 130.3 (NCOCH**C**HH'), 69.0 (O**C**H₂CON), 64.1 (O**C**H₂CH₂N), 43.8 (OCH₂**C**H₂N); HRMS (ESI): calcd. for $C_7H_9NNaO_3$, 178.0475. Found: [MNa]$^+$, 178.0475 (–0.3 ppm error).

Lab notebook reference: KP451

Methyl 2-(2-acrylamidoethoxy)acetate (4.91) and *N*-(2-(2-((4-fluorobenzyl)amino)-2-oxoethoxy)ethyl)acrylamide (4.93)



To a solution of 4-acryloylmorpholin-3-one **4.89** (77.8 mg, 0.501 mmol) in dry methanol (1.0 mL), was added 4-fluorobenzylamine (63 µL, 0.551 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, 1:4 ethyl acetate: hexane → 1:1 ethyl acetate: hexane → ethyl acetate → 1:49 methanol: ethyl acetate) afforded methyl 2-(2-acrylamidoethoxy)acetate (**4.91**) as a colorless oil (61.4 mg, 65%), *N*-(2-(2-((4-fluorobenzyl)amino)-2-oxoethoxy)ethyl)acrylamide (**4.93**), contaminated with morpholin-3-one, as an orange oil (25.3 mg, 18%).

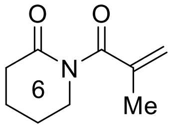
Data for **4.91**: R_f 0.45 (1:9 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3292, 2954, 1742, 1659, 1626, 1543, 1437, 1216, 1139, 985, 888, 806, 705, 580; δ_H (400 MHz, $CDCl_3$) 6.73 (1H, br s, N**H**), 6.27 (1H, dd, *J* = 17.0, 1.6 Hz, NCOC**H**CHH'), 6.14 (1H, dd, *J* = 17.0, 10.2 Hz, NCOCHC**H**H'), 5.62 (1H, dd, *J* = 10.2, 1.6 Hz, NCOCHCH**H'**), 4.10 (2H, s, OC**H**₂CO₂CH₃), 3.74 (3H, s, CO₂C**H₃**), 3.66 – 3.62 (2H, m, C**H₂**), 3.55 – 3.48 (2H, m, C**H₂**); δ_C (100 MHz, $CDCl_3$) 171.5 (**C**O), 165.8 (**C**O), 131.0 (NCO**C**HCHH'), 126.3 (NCOCH**C**HH'), 70.5 (**C**H_2), 68.0 (**C**H_2), 52.1 (**C**H_3), 39.5 (**C**H_2); HRMS (ESI): calcd. for $C_8H_{13}NNaO_4$, 210.0737. Found: [MNa]$^+$, 210.0737 (–0.2 ppm error).

Data for **4.93** (isolated as a roughly 2:1 mixture of **4.93** and morpholin-3-one [**4.92**]): R_f 0.23 (1:9 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3296, 2927, 1660, 1544, 1511, 1414, 1347, 1222, 1124, 983, 822; δ_H (400 MHz, $CDCl_3$) 7.27 – 7.20 (2H, m, Ar**H**), 7.03 – 6.96 (2H, m, Ar**H**), 6.51 (1H, br s, N**H**), 6.30 (1H, br s, N**H**), 6.24 (1H, dd, *J* = 16.9, 1.5 Hz, NCOCHC**H**H'), 6.05 (1H, dd, *J* = 16.9, 10.2 Hz, NCOC**H**CHH'), 5.61 (1H, dd, *J* = 10.2, 1.5 Hz, NCOCHCH**H'**), 4.42 (2H, d, *J* = 6.1 Hz, C**H₂**), 3.99 (2H, s, C**H₂**), 3.63 – 3.58 (2H, m, C**H₂**), 3.55 – 3.48 (2H, m, C**H₂**); δ_C (100 MHz, $CDCl_3$): 169.0 (**C**O), 165.9 (**C**O), 162.3 (Ar**C**F, $^1J_{CF}$ = 245.6 Hz), 134.0 (Ar**C**, $^4J_{CF}$ = 3.5 Hz), 132.6 (NCO**C**HCHH'), 129.6 (2 × Ar**C**H, $^3J_{CF}$ = 7.9 Hz), 127.0 (NCOCH**C**HH'), 115.6 (2 × Ar**C**H, $^2J_{CF}$ = 21.8 Hz), 70.7 (**C**H_2), 70.5 (**C**H_2), 42.2 (**C**H_2), 39.3 (**C**H_2); δ_F (376 MHz, $CDCl_3$), -114.75 (1F, m, ArF); HRMS (ESI): calcd. for $C_{14}H_{17}FN_2NaO_3$, 303.1115. Found: [MNa]$^+$, 303.1116 (–0.1 ppm error).

Data for morpholin-3-one **4.92**: δ_H (400 MHz, $CDCl_3$) 7.06 (1H, br s, N**H**), 4.15 (2H, s, C**H₂**), 3.85 – 3.80 (2H, m, C**H₂**), 3.44 – 3.39 (1H, m, C**H₂**); δ_C (100 MHz, $CDCl_3$) 169.4 (**C**O), 68.1 (**C**H_2), 63.4 (**C**H_2), 41.7 (**C**H_2).

Lab notebook reference: KP453

1-Methacryloylpiperidin-2-one (4.94)

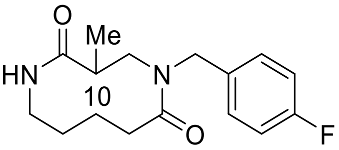


4.94

To a stirring solution of δ-valerolactam **4.60** (300 mg, 3.03 mmol) in dry THF (11.0 mL) cooled to 0 °C was added a solution of MeMgBr (3.0 M in diethyl ether, 1.10 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. Methacryloyl chloride (0.436 mL, 4.50 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, 1:1 diethyl ether: hexane) afforded the *title compound* as a white solid (237 mg, 47%); m.p. 33–39 °C; R_f 0.21 (1:1 hexane: diethyl ether); ν_{max}/cm^{-1} (thin film) 2953, 1677, 1455, 1387, 1324, 1288, 1268, 1196, 1173, 1148, 1111, 1093, 994, 918, 822, 787, 558; δ_H (400 MHz, $CDCl_3$) 5.20 (1H, app h, *J* = 1.0, NCOC(CH$_3$)C**H**H'), 5.15 – 5.13 (1H, m, NCOC(CH$_3$)CH**H'**), 3.65 – 3.57 (2H, m, NC**H$_2$**), 2.51 – 2.43 (2H, m, C**H$_2$**CON), 1.93 – 1.92 (3H, m, NCOC(C**H$_3$**)CHH'), 1.88 – 1.81 (4H, m, 2 × C**H$_2$**); δ_C (100 MHz, $CDCl_3$) 175.8 (**C**O), 173.3 (**C**O), 142.8 (NCO**C**(CH$_3$)CHH'), 117.0 (NCOC(CH$_3$)**C**HH'), 45.3 (N**C**H$_2$), 34.6 (**C**H$_2$CON), 22.6 (**C**H$_2$), 21.3 (**C**H$_2$), 18.9 (**C**H$_3$); HRMS (ESI): calcd. for $C_9H_{13}NNaO_2$, 190.0838. Found: $[MNa]^+$, 190.0841 (–1.3 ppm error).

Lab notebook reference: KP551

5-(4-Fluorobenzyl)-3-methyl-1,5-diazecane-2,6-dione (4.95)



4.95

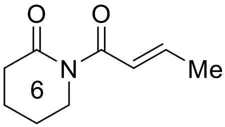
To a solution of 1-methacryloylpiperidin-2-one **4.94** (168 mg, 1.01 mmol) in dry methanol (2.0 mL), was added 4-fluorobenzylamine (126 µL, 1.11 mmol) in a single portion. The reaction mixture was allowed to stir for 4 h at RT and then the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:4 ethyl acetate: hexane → 1:1 ethyl acetate: hexane → 2:1 ethyl acetate: hexane → ethyl acetate) afforded the *title compound* as a colourless oil (78.0 mg, 37%). In solution in $CDCl_3$, this compound exists largely as a single rotamer, along with 3 minor rotamers (most clearly seen in the ^{19}F NMR data); R_f 0.36 (1:9 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3303, 2932, 1621, 1553, 1509, 1442, 1414, 1350, 1219, 1181, 1157, 1097, 1072, 909, 815, 727, 645, 585, 481; NMR data for the major rotamer only. δ_H (400 MHz, $CDCl_3$) 7.25 – 7.19 (2H, m, Ar**H**), 7.01 – 6.94 (2H, m, Ar**H**), 5.46 (1H, d, *J* = 10.0 Hz, N**H**), 5.00 (1H, d, *J* = 14.6 Hz, C**H**$_2$), 4.16 (1H, d, *J* = 14.6 Hz, C**H**$_2$), 3.90 – 3.76 (1H, m, C**H$_2$**), 3.65 – 3.53 (1H, m, C**H**$_2$), 2.95 – 2.77 (2H, m, C**H$_2$**), 2.64 – 2.52 (1H, m, C**H$_2$**), 2.20 – 2.02 (2H, m, C**H$_2$**, [overlapping]), 2.20 – 2.10 (1H, m, C**H**, [overlapping]), 1.70 – 1.38 (3H, m, C**H$_2$**), 1.00 (3H, d, *J* = 6.8 Hz, C**H**$_3$); δ_C (100 MHz, $CDCl_3$) 174.0 (**C**O), 173.3 (**C**O), 162.3 (Ar**C**F, $^1J_{CF}$ = 246.4 Hz), 133.8 (Ar**C**, $^4J_{CF}$ = 3.3 Hz), 129.9 (2 × Ar**C**H, $^3J_{CF}$ = 8.1 Hz), 115.8 (2 × Ar**C**H, $^2J_{CF}$ = 21.2 Hz), 52.2 (**C**H$_2$), 48.9 (**C**H$_2$), 40.5 (**C**H), 38.9 (**C**H$_2$), 28.1 (**C**H$_2$), 25.8 (**C**H$_2$), 23.9 (**C**H$_2$), 13.6 (**C**H$_3$); δ_F (376 MHz, $CDCl_3$), –114.25 (1F, m, ArF); HRMS (ESI): calcd. for $C_{16}H_{21}FN_2NaO_2$, 315.1479. Found: $[MNa]^+$, 315.1480 (–0.2 ppm error).

Characteristic NMR data for the minor rotamers can be found at: δ_H (400 MHz, $CDCl_3$) 5.88 (1H, d, *J* = 10.4 Hz, N**H**), 4.80 (1H, d, *J* = 16.4 Hz, C**H**$_2$), 4.21 (1H, d, *J* = 16.4 Hz, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 176.0 (**C**O), 174.2 (**C**O), 132.5 (Ar**C**, $^4J_{CF}$ = 3.3 Hz), 128.4 (2 × Ar**C**H, $^3J_{CF}$ = 8.1 Hz), 54.9 (**C**H$_2$), 39.95 (**C**H$_2$), 38.8

(**C**H), 35.4 (**C**H_2), 27.6 (**C**H_2), 25.4 (**C**H_2), 15.1 (**C**H_3); δ_F (376 MHz, $CDCl_3$) –114.55 (1F, m, ArF), –115.23 (1F, m, ArF), –116.05 (1F, m, ArF).

Lab notebook reference: KP552

(*E*)-1-(But-2-enoyl)piperidin-2-one (4.96)

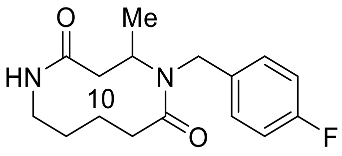


4.96

To a stirring solution of δ-valerolactam **4.60** (300 mg, 3.03 mmol) in dry THF (11.0 mL) cooled to 0 °C was added a solution of MeMgBr (3.0 M in diethyl ether, 1.13 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. Crotonoyl chloride (0.431 mL, 4.50 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, 1:1 diethyl ether: hexane) afforded an impure batch of product (contaminated with crotonic acid), that was further purified by diluting with Et_2O (5 mL) and washing with sat. aq. $NaHCO_3$ (3 × 5 mL). The organic extract dried over $MgSO_4$ and concentrated *in vacuo* to afford the *title compound* as a colourless oil (96.4 mg, 19%). Trace impurities were evident in the ^{1}H NMR data for this compound, but the purity was deemed sufficient to test the subsequent CARE reaction; R_f 0.19 (1:1 hexane: diethyl ether); ν_{max}/cm^{-1} (thin film) 2951, 1679, 1637, 1445, 1385, 1328, 1290, 1202, 1154, 1086, 966, 924, 828, 614; δ_H (400 MHz, $CDCl_3$) 6.98 (1H, dq, *J* = 15.2, 6.9 Hz, CH_3C**H**CHCON), 6.77 (1H, dd, *J* = 15.2, 1.6 Hz, CH_3CHC**H**CON), 3.75 – 3.68 (2H, m, C**H₂**N), 2.59 – 2.51 (2H, m, C**H₂**CON), 1.90 (3H, dd, *J* = 6.9, 1.6 Hz, C**H₃**), 1.87 – 1.81 (4H, m, C**H₂**); δ_C (100 MHz, $CDCl_3$) 173.9 (**C**ON), 169.7 (**C**OCHCH(CH_3)), 143.3 (COCH**C**H(CH_3)), 126.6 (CO**C**HCH(CH_3)), 44.6 (**C**H_2N), 35.0 (**C**H_2CON), 22.7 (**C**H_2), 20.8 (**C**H_2), 18.4 (**C**H_3); HRMS (ESI): calcd. for $C_9H_{14}NO_2$, 168.1019. Found: [MNa]$^+$, 168.1021 (–1.0 ppm error).

Lab notebook reference: KP559

5-(4-Fluorobenzyl)-4-methyl-1,5-diazecane-2,6-dione (4.97)

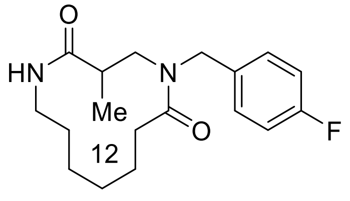


4.97

To a solution of (*E*)-1-(but-2-enoyl)piperidin-2-one **4.96** (92.6 mg, 0.554 mmol) in dry methanol (1.10 mL), was added 4-fluorobenzylamine (70 µL, 0.609 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, 1:4 ethyl acetate: hexane → 1:1 ethyl acetate: hexane → 2:1 ethyl acetate: hexane → ethyl acetate → 1:49 methanol: ethyl acetate) afforded the *title compound* as a colourless oil (84.3 mg, 72%). In solution in $CDCl_3$, this compound exists as a roughly 3:2:1 mixture of rotamers, based on the CH_3 signals in the ^{1}H NMR spectrum; R_f 0.23 (1:9 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3299, 2934, 1607, 1555, 1510, 1463, 1412, 1337, 1221, 1156, 1097, 812, 731, 501; δ_H (400 MHz, $CDCl_3$) 7.28 – 6.91 (4H, m, Ar**H**, all rotamers), 6.12 (1H, d, *J* = 10.5 Hz, N**H**, rotamer), 5.93 (1H, d, *J* = 9.3 Hz, N**H**, rotamer), 5.82 (1H, d, *J* = 15.4 Hz, N**H**, rotamer), 5.46 (1H, dp, *J* = 10.7, 6.8 Hz, C**H**, rotamer), 4.83 – 3.99 (2H, m, C**H₂** overlapping]), 4.51 – 4.41 (1H, m, C**H**, rotamer [overlapping]), 3.90 – 3.56 (1H, m, C$\mathbf{H_2}$), 3.50 (1H, dp, *J* = 10.7, 6.8 Hz, C**H**, rotamer), 3.22 – 2.66 (3H, m, C$\mathbf{H_2}$), 2.41– 2.29 (1H, m, C$\mathbf{H_2}$), 2.21– 1.48 (5H, m, C$\mathbf{H_2}$), 1.22 (3H, d, *J* = 6.8 Hz, C$\mathbf{H_3}$, major rotamer), 1.16 (3H, d, *J* = 6.8 Hz, C$\mathbf{H_3}$, minor rotamer), 1.06 (3H, d, *J* = 6.8 Hz, C$\mathbf{H_3}$, minor rotamer); δ_C (100 MHz, $CDCl_3$) where possible, equivalent signals from the 3 rotamers are grouped in square brackets – [177.7, 176.4, 174.6, 171.8, 170.8 and 170.7 (2 × **C**O from the 3 rotamers)], [162.4 (Ar**C**F, $^1J_{CF}$ = 246.0 Hz), 162.0 (Ar**C**F, $^1J_{CF}$ = 246.0 Hz), 161.9 (Ar**C**F, $^1J_{CF}$ = 246.0 Hz)], [135.4 (Ar**C**, $^4J_{CF}$ = 3.2 Hz), 134.2 (Ar**C**, $^4J_{CF}$ = 3.2 Hz), 132.6 (Ar**C**, $^4J_{CF}$ = 3.2 Hz)], [129.4 (2 × Ar**C**H, $^3J_{CF}$ = 8.1 Hz), 129.15 (2 × Ar**C**H, $^3J_{CF}$ = 8.1 Hz), 129.19 (2 × Ar**C**H, $^3J_{CF}$ = 8.1 Hz)], [115.76 (2 × Ar**C**H, $^2J_{CF}$ = 21.5 Hz), 115.73 (2 × Ar**C**H, $^2J_{CF}$ = 21.5 Hz), 115.57 (2 × Ar**C**H, $^2J_{CF}$ = 21.5 Hz)], 57.1 (**C**H), 56.5 (**C**H_2), 51.8 (**C**H), 46.0 (**C**H), 45.4 (**C**H_2), 44.3 (**C**H_2), 44.1 (**C**H_2), 43.3 (**C**H_2), 42.5 (**C**H_2), 40.2 (**C**H_2), 40.1 (**C**H_2), 39.6 (**C**H_2), 37.1 (**C**H_2), 35.6 (**C**H_2), 28.6 (**C**H_2), 28.0 (**C**H_2), 26.4 (**C**H_2), 25.3 (**C**H_2), 25.1 (**C**H_2), 24.2 (**C**H_2), 24.0 (**C**H_2), [21.4 (**C**H_3), 19.1 (**C**H_3), 18.7 (**C**H_3)]; δ_F (376 MHz, $CDCl_3$), –114.14 (1F, m, ArF, major rotamer), –115.24 (1F, m, ArF, minor rotamer), –115.32 (1F, m, ArF, minor rotamer); HRMS (ESI): calcd. for $C_{16}H_{21}FN_2NaO_2$, 315.1479. Found: [MNa]$^+$, 315.1471 (2.7 ppm error).

Lab notebook reference: KP560

5-(4-Fluorobenzyl)-3-methyl-1,5-diazacyclododecane-2,6-dione (4.102)

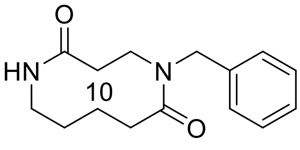


4.102

To a solution of 1-methacryloylazocan-2-one (**4.42**) (197 mg, 1.01 mmol) in dry methanol (2.0 mL), was added 4-fluorobenzylamine (126 µL, 1.11 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 ethyl acetate: hexane → 2:1 ethyl acetate: hexane → ethyl acetate → 1:49 methanol: ethyl acetate) afforded the *title compound* as a colorless oil (81.4 mg, 25%). In solution in $CDCl_3$, this compound exists as a mixture of 4 rotameric forms (10:4:12:1 ratio, best seen in the ^{19}F NMR); R_f 0.36 (9:1 ethyl acetate: methanol); ν_{max}/cm^{-1} (thin film) 3297, 2929, 1632, 1551, 1509, 1453, 1413, 1353, 1219, 1157, 1096, 1078, 1015, 916, 819, 729, 645, 497; δ_H (400 MHz, d_6-DMSO, 120 °C) 7.32 (1H, br s, N**H**), 7.28–7.20 (2H, m, Ar**H**), 7.16–7.06 (2H, m, Ar**H**), 5.14–3.90 (2H, m, C**H**$_2$ / C**H**), 3.61 (1H, br s, C**H**$_2$ / C**H**), 2.97–2.54 (6H, m, C**H**$_2$ / C**H**), 1.81–1.16 (8H, m, C**H**$_2$ / C**H**), 0.95 (1H, d, J = 6.8 Hz, C**H**$_3$); Characteristic ^1H NMR peaks in $CDCl_3$: 3.29 – 3.18 (1H, m, C**H**, rotamer C), 2.86 – 2.71 (1H, m, C**H**, rotamer A), 1.14 (1H, d, J = 7.1 Hz, C**H**$_3$, rotamer A), 1.04 (1H, d, J = 6.9 Hz, C**H**$_3$, rotamer B), 0.99 (1H, d, J = 6.8 Hz, C**H**$_3$, rotamer C); δ_C (100 MHz, $CDCl_3$) 175.7 (**C**O, major rotamers), 175.13 (**C**O, major rotamers), 175.07 (**C**O, minor rotamers), 174.5 (**C**O, major rotamers), 174.1 (**C**O, minor rotamers), 174.0 (**C**O, minor rotamers), 162.33 (Ar**C**F, $^1J_{CF}$ = d, J = 246.5 Hz), 162.25 (Ar**C**F, $^1J_{CF}$ = d, J = 245.9 Hz), 134.18 (Ar**C**, $^4J_{CF}$ = d, J = 3.3 Hz), 132.96 (Ar**C**, $^4J_{CF}$ = d, J = 3.2 Hz), 131.99 (Ar**C**, $^4J_{CF}$ = d, J = 3.3 Hz), 130.29 (2 × ArCH, $^3J_{CF}$ = d, J = 7.9 Hz), 128.29 (2 × Ar**C**H, $^3J_{CF}$ = d, J = 8.0 Hz), 128.01 (2 × ArCH, $^3J_{CF}$ = d, J = 8.0 Hz), 116.11 (2 × Ar**C**H, $^2J_{CF}$ = d, J = 21.6 Hz), 115.8 (2 × Ar**C**H, $^2J_{CF}$ = d, J = 21.5 Hz), 54.85, 52.21, 45.67, 41.34, 40.97, 40.04, 39.28, 38.36, 36.26, 33.71, 31.48, 27.83, 26.60, 26.47, 25.92, 25.53, 24.08, 22.30, 16.89, 16.13, 15.78; δ_F (470 MHz, $CDCl_3$), –114.33 (1F, m, ArF), –114.55 (1F, m, ArF), –115.00 (1F, m, ArF, main rotamer), –115.25 (1F, m, ArF); HRMS (ESI): calcd. for $C_{18}H_{25}FN_2NaO_2$, 343.1792. Found: $[MNa]^+$, 343.1790 (0.7 ppm error).

Lab notebook reference: KP494_B

5-Benzyl-1,5-diazecane-2,6-dione (4.103)



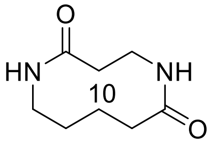
4.103

To a solution of 1-acryloyl-piperidin-2-one **4.47** (153 mg, 1.00 mmol) in dry methanol (2.0 mL), was added benzylamine (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, 1:4 ethyl acetate: hexane → 1:1 ethyl acetate: hexane → ethyl acetate → 1:49 methanol: ethyl acetate → 1:19 methanol: ethyl acetate) afforded the *title compound* as an off-white solid (217 mg, 83%). In solution in $CDCl_3$, this compound exists as a roughly 10:1 mixture of rotamers; m.p. 165–167 °C; R_f 0.21 (1:9 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3293, 2931, 1617, 1559, 1449, 1349, 1204, 1110, 919, 728, 699, 618; δ_H (400 MHz, $CDCl_3$) 7.36 – 7.25 (5H, m, Ar**H**), 5.88 (1H, br d, *J* = 9.9 Hz, N**H**), 4.91 (1H, d, *J* = 14.4 Hz, C**H**H'), 4.39 (1H, d, *J* = 14.4 Hz, CH**H'**), 4.01 – 3.69 (2H, m, C**H**$_2$), 4.21 (1H, dt, *J* = 15.6, 3.8 Hz, C**H**$_2$), 2.92 – 2.80 (1H, m, C**H**$_2$), 2.78 – 2.59 (1H, m, C**H**$_2$), 2.25 – 1.99 (4H, m, C**H**$_2$), 1.84 – 1.43 (3H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 174.1 (**C**O), 171.1 (**C**O), 138.2 (Ar**C**), 129.1 (2 × Ar**C**H), 128.3 (2 × Ar**C**H), 128.0 (Ar**C**H), 49.5 (Ar**C**H$_2$), 45.4 (**C**H$_2$), 39.3 (**C**H$_2$), 37.7 (**C**H$_2$), 28.3 (**C**H$_2$), 25.9 (**C**H$_2$), 23.9 (**C**H$_2$); HRMS (ESI): calcd. for $C_{15}H_{20}N_2NaO_2$, 283.1417. Found: [MNa]$^+$, 283.1421 (–1.3 ppm error).

Characteristic NMR data for the minor rotamers can be found at: δ_H (400 MHz, $CDCl_3$) 5.94 (1H, br d, *J* = 10.4 Hz, N**H**), 4.32 (1H, d, *J* = 16.5 Hz, C**H**$_2$), 4.22 – 4.13 (1H, m, C**H**$_2$), 3.00 – 2.92 (1H, m, C**H**$_2$), 2.42 (1H, ddd, *J* = 12.4, 8.7, 3.5 Hz, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 176.4 (**C**O), 171.4 (**C**O), 136.7 (Ar**C**), 129.0 (2 × Ar**C**H), 127.8 (Ar**C**H), 126.8 (2 × Ar**C**H), 54.4 (**C**H$_2$), 42.5 (**C**H$_2$), 40.2 (**C**H$_2$), 35.2 (**C**H$_2$), 27.4 (**C**H$_2$), 25.1 (**C**H$_2$).

Lab notebook reference: KP442

1,5-Diazecane-2,6-dione (4.105)



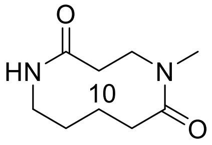
4.105

To a solution of 1-acryloylpiperidin-2-one **4.47** (154 mg, 1.00 mmol) in dry methanol (2.0 mL), was added a solution of NH_3 in methanol (7 M, 0.157 mL, 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 ethyl acetate: hexane → ethyl acetate → 1:19 methanol: ethyl acetate → 1:6 methanol: ethyl acetate → 1:4 methanol: ethyl acetate→ 1:4 methanol: DCM) afforded the *title compound* **4.105** as a white solid (12.4 mg, 7%) as well as methyl 5-acrylamidopentanoate (**4.123**) (95.2 mg, 51%), and δ-valerolactam (**4.60**) (25.1 mg, 25%).

Data for 1,5-diazecane-2,6-dione **4.105**: A white solid (12.4 mg, 7%); m.p. 166 – 170 °C; R_f 0.43 (1:4 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3300, 2929, 1656, 1557, 1434, 1292, 1236, 1188, 1112, 1062, 669, 583; δ_H (400 MHz, $CDCl_3$) 6.76 (1H, br s, N**H**), 6.44 – 5.78(1H, m, N**H**), 4.06 – 2.26 (6H, m, C**H₂**), 2.18 (2H, br s, C**H₂**), 1.92 – 1.55 (4H, m, C**H₂**); δ_C (100 MHz, $CDCl_3$) 176.9 (**C**O), 172.6 (**C**O), 40.4 (**C**H_2), 39.0 (**C**H_2), 37.0 (**C**H_2), 35.5 (**C**H_2), 27.5 (**C**H_2), 25.1 (**C**H_2); HRMS (ESI): calcd. for $C_8H_{14}N_2NaO_2$, 193.0947. Found: $[MNa]^+$, 193.0945 (1.1 ppm error).

Lab notebook reference: KP479_D

5-Methyl-1,5-diazecane-2,6-dione (4.106)



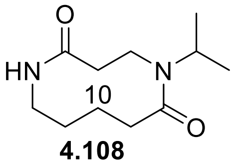
4.106

To a solution of 1-acryloyl-piperidin-2-one **4.47** (154 mg, 1.00 mmol) in dry methanol (2.0 mL), was added methylamine solution (33 wt% in EtOH, 136 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 ethyl acetate: hexane → ethyl acetate → 1:49 methanol: ethyl acetate → 1:19 methanol: ethyl acetate → 1:13 methanol: ethyl acetate → 1:9 methanol: ethyl acetate → 1:6 methanol: ethyl acetate → 1:4 methanol: ethyl acetate) afforded the *title compound* as a sticky white paste (118 mg, 64%); In solution in $CDCl_3$, this compound exists as a roughly 7:1 mixture of rotamers. R$_f$ 0.19 (1:4 methanol: ethyl acetate); ν$_{max}$/cm^{-1} (thin film) 3287, 2933, 1609, 1443, 1401, 1332, 1259, 1198, 1168, 1081, 1033, 729; δ$_H$ (400 MHz, CDCl$_3$) 6.00 – 5.88 (1H, br m, N**H**, minor rotamer), 5.80 – 5.64 (1H, br m, N**H**, major rotamer), 4.11 – 3.94 (2H, m, C**H₂**), 3.81 – 3.65 (2H, m, C**H₂**), 3.33 – 3.13 (2H, m, C**H₂**), 3.06 (3H, s, C**H₃**, minor rotamer), 2.98 (3H, s, C**H₃**, major rotamer), 2.95 – 2.83 (2H, m, C**H₂**), 2.74 – 2.53 (2H, m, C**H₂**), 2.36 – 2.22 (4H, m, 2 × C**H₂**), 2.14 – 1.98 (4H, m, 2 × C**H₂**), 1.75– 1.38 (6H, m, 3 × C**H₂**); δ$_C$ (100 MHz, CDCl$_3$) 174.1 (**C**O), 171.1 (**C**O), 47.9 (**C**H$_2$), 39.5 (**C**H$_2$), 37.3 (**C**H$_2$), 34.0 (**C**H$_3$), 28.3 (**C**H$_2$), 25.7 (**C**H$_2$), 23.8 (**C**H$_2$); HRMS (ESI): calcd. for $C_9H_{16}N_2NaO_2$, 207.1104. Found: [MNa]$^+$, 207.1101 (1.3 ppm error).

Characteristic ^{13}C NMR data for the minor rotamers can be found at: δ$_C$ (100 MHz, CDCl$_3$) 176.2 (**C**O), 171.2 (**C**O), 44.8 (**C**H$_2$), 40.1 (**C**H$_2$), 38.8 (**C**H$_2$), 35.3 (**C**H$_2$), 35.1 (**C**H$_2$), 27.4 (**C**H$_2$), 24.3 (**C**H$_2$).

Lab notebook reference: KP460

5-Isopropyl-1,5-diazecane-2,6-dione (4.108)



4.108

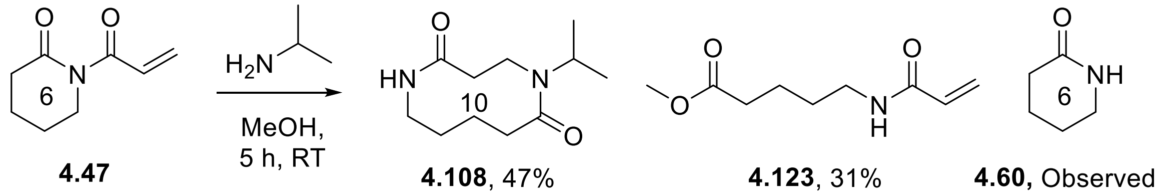
To a solution of 1-acryloyl-piperidin-2-one **4.47** (154 mg, 1.00 mmol) in dry DMF (2.0 mL), was added isopropylamine (95 µL, 1.10 mmol) in a single portion. The reaction mixture was allowed to stir for 4 h at RT and then the solvent was removed *in vacuo*, with dry loading onto Celite using DCM to aid the removal of most of the DMF. Purification of the crude material loaded onto Celite by flash column chromatography (SiO$_2$, ethyl acetate → 1:19 methanol: ethyl acetate → 1:9 methanol: ethyl acetate → 1:6 methanol: ethyl acetate) afforded the *title compound* as a colorless oil (106 mg, 50%). In solution in CDCl$_3$, this compound exists as a roughly 11:1 mixture of rotamers. R$_f$ 0.24 (1:9 methanol: ethyl acetate); ν$_{max}$/cm^{-1} (thin film) 3297, 2932, 1608, 1422, 1368, 1314, 1241, 1212, 1160, 1062, 1043, 922, 727, 644, 581; NMR data for the major rotamer: δ$_H$ (400 MHz, CDCl$_3$) 5.75 – 5.63 (1H, br m, N**H**), 4.77 (1H, hept, *J* = 6.9 Hz, C**H**), 3.81 – 3.56 (2H, m, C**H**$_2$), 3.34 – 3.20 (1H, m, C**H**$_2$), 2.92 – 2.77 (1H, m, C**H**$_2$), 2.61 – 2.46 (1H, m, C**H**$_2$), 2.34 – 1.88 (4H, m, C**H**$_2$), 1.63 – 1.31 (3H, m, C**H**$_2$), 1.17 (3H, d, *J* = 7.0 Hz, C**H**$_3$), 1.10 – 0.99 (3H, m, C**H**$_3$); δ$_C$ (100 MHz, CDCl$_3$) 174.0 (**C**O), 171.2 (**C**O), 45.6 (**C**H), 40.3 (**C**H$_2$), 39.6 (**C**H$_2$), 39.2 (**C**H$_2$), 29.2 (**C**H$_2$), 25.7 (**C**H$_2$), 23.8 (**C**H$_2$), 20.8 (**C**H$_3$), 20.2 (**C**H$_3$); HRMS (ESI): calcd. for $C_{11}H_{20}N_2NaO_2$, 235.1417. Found: [MNa]$^+$, 235.1414 (1.2 ppm error).

Characteristic NMR data for the minor rotamer can be found at: δ_H (400 MHz, $CDCl_3$) 5.97 – 5.86 (1H, br m, N**H**), 3.95 (1H, hept, *J* = 6.7 Hz, C**H**); δ_C (100 MHz, $CDCl_3$) 49.9 (**C**H), 22.5 (**C**H_3), 20.5 (**C**H_3).

The same reaction was also performed using methanol as solvent, as detailed below in the entry for **4.123**.

Lab notebook reference: KP531

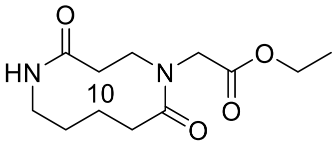
Methyl 5-acrylamidopentanoate (4.123)



To a solution of 1-acryloyl-piperidin-2-one **4.47** (153 mg, 1.00 mmol) in dry methanol (2.0 mL), was added isopropylamine (95 µL, 1.10 mmol) in a single portion. The reaction mixture was allowed to stir for 5 h at RT and then the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, ethyl acetate → 1:49 methanol: ethyl acetate → 1:19 methanol: ethyl acetate → 1:9 methanol: ethyl acetate → 1:6 methanol: ethyl acetate → 1:6 methanol: DCM → 1:4 methanol: DCM → 1:3 methanol: DCM → 1:2 methanol: DCM) afforded 5-isopropyl-1,5-diazecane-2,6-dione **4.108** as a colourless oil (100 mg, 47%), a trace amount of δ-valerolactam (not quantified) and methyl 5-acrylamidopentanoate **4.123** as a pale-yellow oil (57.9 mg, 31%). Data for **4.108** is included above. Data for methyl 5-acrylamidopentanoate **4.123**: R_f 0.56 (1:9 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3285, 2939, 1735, 1658, 1625, 1547, 1437, 1409, 1366, 1242, 1167, 1100, 986, 959, 806, 702; δ_H (400 MHz, $CDCl_3$) 6.30 (1H, dd, *J* = 17.0, 1.5 Hz, NCOC**H**CHH'), 6.11 (1H, dd, *J* = 17.0, 10.2 Hz, NCOCHC**H**H'), 5.81 (1H, br s, N**H**), 5.65 (1H, dd, *J* = 10.2, 1.5 Hz, NCOCHCH**H'**), 3.69 (3H, s, C**H**$_3$), 3.37 (2H, td, *J* = 6.8, 5.8 Hz, NC**H**$_2$), 2.37 (2H, t, *J* = 7.1 Hz, C**H**$_2$$CO_2CH_3$), 1.75 – 1.54 (4H, m, 2 × C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 174.2 (**C**O), 165.7 (**C**O), 131.0 (NCO**C**HCHH'), 126.5 (NCOCH**C**HH'), 51.8 (**C**H_3), 39.2 (N**C**H_2), 33.6 (**C**$H_2CO_2CH_3$), 29.0 (**C**H_2), 22.1 (**C**H_2); HRMS (ESI): calcd. for $C_9H_{15}NNaO_3$, 208.0944. Found: $[MNa]^+$, 208.0940 (1.8 ppm error).

Lab notebook reference: KP470

Ethyl 2-(4,10-dioxo-1,5-diazecan-1-yl)acetate (4.110)

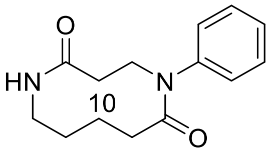


4.110

To a solution of 1-acryloyl-piperidin-2-one **4.47** (159 mg, 1.04 mmol) in dry methanol (2.0 mL), was added glycine ethyl ester (115 µL, 1.14 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 ethyl acetate: hexane → ethyl acetate → 1:49 methanol: ethyl acetate → 1:19 methanol: ethyl) afforded the *title compound* as a white solid (204 mg, 77%); m.p. 143–145 °C; R_f 0.18 (1:9 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3316, 2932, 1721, 1640, 1555, 1477, 1441, 1380, 1212, 1153, 1112, 1071, 1022, 861, 715, 658, 566, 524, 499; δ_H (400 MHz, $CDCl_3$) 7.58 (1H, br d, J = 10.0 Hz, N**H**), 4.74 (1H, d, J = 17.2 Hz, $C\mathbf{H_2}CO_2CH_2CH_3$), 4.23 – 4.14 (2H, m, $CH_2CO_2C\mathbf{H_2}CH_3$), 4.09 (1H, ddd, J = 15.2, 13.0, 1.6 Hz, $C\mathbf{H_2}$), 3.81 (1H, dddd, J = 13.5, 11.6, 10.0, 1.6 Hz, $C\mathbf{H_2}$), 3.32 (1H, d, J = 17.2 Hz, $C\mathbf{H_2}CO_2CH_2CH_3$), 3.24 (1H, dd, J = 15.6, 3.6 Hz, $C\mathbf{H_2}$), 2.95 – 2.86 (1H, m, $C\mathbf{H_2}$), 2.62 (1H, ddd, J = 16.8, 14.0, 4.0 Hz, $C\mathbf{H_2}$), 2.41 (1H, td, J = 12.8, 3.2 Hz, $C\mathbf{H_2}$), 2.21 (1H, ddd, J = 12.6, 4.0, 1.6 Hz, $C\mathbf{H_2}$), 2.12 – 2.00 (2H, m, $C\mathbf{H_2}$), 1.67 – 1.53 (2H, m, $C\mathbf{H_2}$), 1.52 – 1.38 (1H, m, $C\mathbf{H_2}$), 1.29 (3H, t, J = 7.2 Hz, $CH_2CO_2CH_2C\mathbf{H_3}$); δ_C (100 MHz, $CDCl_3$) 174.4 (**C**O), 172.3 (**C**O), 170.7 (**C**O), 62.1 ($CH_2CO_2\mathbf{C}H_2CH_3$), 51.5 ($\mathbf{C}H_2CO_2CH_2CH_3$), 48.9 ($\mathbf{C}H_2$), 39.0 ($\mathbf{C}H_2$), 37.5 ($\mathbf{C}H_2$), 27.9 ($\mathbf{C}H_2$), 25.2 ($\mathbf{C}H_2$), 24.1 ($\mathbf{C}H_2$), 14.1 ($\mathbf{C}H_3$); HRMS (ESI): calcd. for $C_{12}H_{20}N_2NaO_4$, 279.1315. Found: $[MNa]^+$, 279.1316 (–0.2 ppm error).

Lab notebook reference: KP461

5-Phenyl-1,5-diazecane-2,6-dione (4.112)

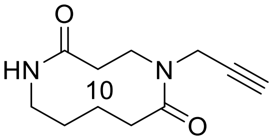


4.112

To a solution of 1-acryloyl-piperidin-2-one **4.47** (153 mg, 1.00 mmol) in dry methanol (2.0 mL), was added aniline (100 µL, 1.10 mmol) in a single portion. The reaction mixture was allowed to stir for 3 days at RT and then the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:4 ethyl acetate: hexane → 1:1 ethyl acetate: hexane → ethyl acetate → 1:49 methanol: ethyl acetate → 1:19 methanol: ethyl acetate) afforded the *title compound* as a fluffy white solid (118 mg, 48%); m.p. 70–75 °C; R_f 0.25 (1:9 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3312, 2933, 1623, 1593, 1548, 1493, 1444, 1416, 1321, 1244, 1165, 1105, 911, 764, 726, 698, 645, 588, 503; δ_H (400 MHz, $CDCl_3$) 7.41 – 7.16 (5H, m, Ar**H**), 6.12 (1H, br d, *J* = 10.2 Hz, N**H**), 4.35 (1H, ddd, *J* = 13.7, 8.5, 1.9 Hz, 0.5 × C**H₂**), 3.81 (1H, ddt, *J* = 14.1, 9.5, 4.5 Hz, 0.5 × C**H₂**), 3.45 (1H, dt, *J* = 13.5, 8.6 Hz, 0.5 × C**H₂**), 3.11 (1H, dt, *J* = 12.4, 8.9 Hz, 0.5 × C**H₂**), 2.57 (1H, ddt, *J* = 13.3, 9.8, 3.2 Hz, 0.5 × C**H₂**), 2.40 (1H, ddd, *J* = 12.4, 8.0, 1.8 Hz, 0.5 × C**H₂**), 2.33 (1H, ddd, *J* = 13.6, 10.3, 3.6 Hz, 0.5 × C**H₂**), 2.00 (1H, ddd, *J* = 13.0, 7.1, 3.1 Hz, 0.5 × C**H₂**), 1.74 – 1.52 (3H, m, 1.5 × C**H₂**), 1.47 – 1.34 (1H, m, 0.5 × C**H₂**); δ_C (100 MHz, $CDCl_3$) 177.0 (**C**O), 172.5 (**C**O), 144.5 (Ar**C**), 129.8 (2 × Ar**C**H), 127.6 (Ar**C**H), 127.3 (2 × Ar**C**H), 49.2 (**C**H₂), 40.1 (**C**H₂), 36.5 (**C**H₂), 35.6 (**C**H₂), 27.8 (**C**H₂), 25.2 (**C**H₂); HRMS (ESI): calcd. for $C_{14}H_{18}N_2NaO_2$, 269.1260. Found: $[MNa]^+$, 269.1260 (0.2 ppm error).

Lab notebook reference: KP452

5-(Prop-2-yn-1-yl)-1,5-diazecane-2,6-dione (4.114)

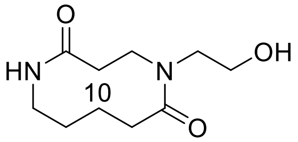


4.114

To a solution of 1-acryloyl-piperidin-2-one **4.47** (123 mg, 0.806 mmol) in dry methanol (1.61 mL), was added propargylamine (57 µL, 0.886 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 ethyl acetate: hexane → ethyl acetate → 1:49 methanol: ethyl acetate) afforded the *title compound* as a colourless oil (128 mg, 77%); R_f 0.25 (1:9 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3288, 2933, 1625, 1560, 1447, 1351, 1205, 1149, 701; δ_H (400 MHz, $CDCl_3$) 6.05 (1H, br s, N**H**), 4.45 – 4.30 (1H, m, C**H**₂), 4.07 – 3.86 (2H, m, C**H**₂), 3.81 – 3.65 (1H, m, C**H**₂), 3.53 – 3.42 (1H, m, C**H**₂), 2.92 – 2.79 (1H, m, C**H**₂), 2.71 – 2.49 (2H, m, C**H**₂), 2.31 – 2.28 (1H, m, C≡C**H**), 2.26 – 2.17 (1H, m, C**H**₂), 2.10 – 1.94 (2H, m, C**H**₂), 1.66 – 1.34 (3H, m, C**H**₂); δ_C (100 MHz, $CDCl_3$) 173.6 (**C**O), 171.0 (**C**O), 80.5 (**C**CH), 72.3 (C**C**H), 46.6 (**C**H₂), 39.2 (**C**H₂), 37.4 (**C**H₂), 36.0 (**C**H₂), 28.2 (**C**H₂), 25.5 (**C**H₂), 23.9 (**C**H₂); HRMS (ESI): calcd. for $C_{11}H_{16}N_2NaO_2$, 231.1104. Found: $[MNa]^+$, 231.1106 (–0.8 ppm error).

Lab notebook reference: KP570

5-(2-Hydroxyethyl)-1,5-diazecane-2,6-dione (4.115)

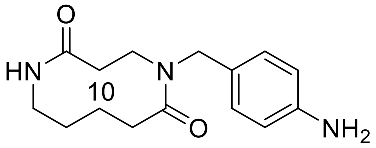


4.115

To a solution of 1-acryloyl-piperidin-2-one **4.47** (154 mg, 1.00 mmol) in dry methanol (2.0 mL), was added ethanolamine (66 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 → 1:39 methanol: ethyl acetate → 1:19 methanol: ethyl acetate → 1:9 methanol: ethyl acetate → 1:6 methanol: ethyl acetate) afforded the *title compound* as a white solid (149 mg, 69%). Rotameric broadening is evident in both the ^{1}H and ^{13}C NMR spectra; m.p. 164–166 °C; R_f 0.11 (1:4 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3351, 2937, 2412, 1604, 1487, 1460, 1442, 1351, 1238, 1203, 1069, 1038, 549, 462; δ_H (400 MHz, d$_4$-MeOD) 4.13 – 3.19 (7H, m, C**H₂**), 3.14 – 2.42 (3H, m, C**H₂**), 2.37 – 1.83 (3H, m, C**H₂**), 1.78 – 1.24 (3H, m, C**H₂**); δ_C (100 MHz, d$_4$-MeOD) 176.4 (**C**O), 173.7 (**C**O), 60.1 (**C**H$_2$), 51.0 (**C**H$_2$), 48.3 (**C**H$_2$), 40.2 (**C**H$_2$), 37.6 (**C**H$_2$), 29.6 (**C**H$_2$), 26.5 (**C**H$_2$), 25.3 (**C**H$_2$); HRMS (ESI): calcd. for $C_{10}H_{18}N_2NaO_3$, 237.1210. Found: [MNa]$^+$, 237.1208 (0.7 ppm error).

Lab notebook reference: KP469

5-(4-Aminobenzyl)-1,5-diazecane-2,6-dione (4.116)



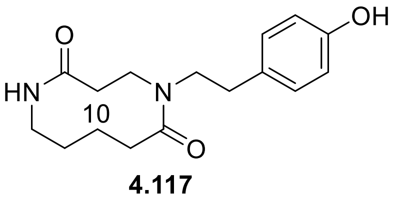
4.116

To a solution of 1-acryloyl-piperidin-2-one **4.47** (154 mg, 1.00 mmol) in dry methanol (2.0 mL), was added 4-aminobenzylamine (125 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, DCM → 1:19 methanol: DCM → 1:9 methanol: DCM) afforded the *title compound* as a white solid (140 mg, 51%). Rotameric broadening is evident in the ^{1}H NMR spectrum. Product identity and purity is best seen in the ^{13}C NMR data; m.p. 165–176 °C; R_f 0.21 (1:9 methanol: DCM); ν_{max}/cm^{-1} (thin film) 3314, 2931, 1613, 1517, 1424, 1282, 1201, 1177, 1140, 910, 729, 506; δ_H (400 MHz, $CDCl_3$) 7.14 – 7.10 (2H, m, Ar**H**), 6.66 – 6.61 (2H, m, Ar**H**), 5.28 (1H, s, ArN**H₂**), 5.25 – 5.17 (1H, m, N**H**), 4.53 (2H, s, ArC**H₂**), 3.96 – 3.66 (3H, m, 1.5 × C**H₂** and 1H, s, ArN**H₂** [overlapping]), 3.30

(1H, dt, *J* = 15.6, 3.8 Hz, 0.5 × C**H**$_2$), 2.90 – 2.79 (1H, m, 0.5 × C**H**$_2$), 2.68 – 2.56 (1H, m, 0.5 × C**H**$_2$), 2.22 – 1.95 (3H, m, 1.5 × C**H**$_2$), 1.73 – 1.42 (3H, m, 1.5 × C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 173.9 (**C**O), 171.2 (**C**O), 146.3 (Ar**C**NH$_2$), 129.7 (2 × Ar**C**H), 128.2 (Ar**C**), 115.5 (2 × Ar**C**H), 49.5 (**C**H$_2$), 45.5 (**C**H$_2$), 39.3 (**C**H$_2$), 37.8 (**C**H$_2$), 28.4 (**C**H$_2$), 25.9 (**C**H$_2$), 24.0 (**C**H$_2$); HRMS (ESI): calcd. for $C_{15}H_{21}N_3NaO_2$, 298.1526. Found: $[MNa]^+$, 298.1515 (3.6 ppm error).

Lab notebook reference: KP493

5-(4-Hydroxyphenethyl)-1,5-diazecane-2,6-dione (4.117)

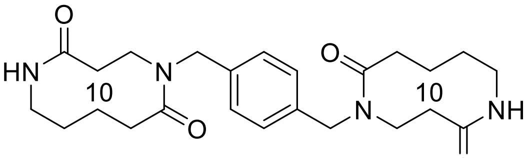


4.117

To a mixture of 1-acryloyl-piperidin-2-one **4.47** (154 mg, 1.00 mmol) and tyramine (151 mg, 1.10 mmol) was added dry methanol (2.0 mL). The reaction mixture was allowed to stir for 4 h at RT and then the solvent was removed *in vacuo*. Purification by automated flash column chromatography (using a 24 g pre-packed SiO_2 column, 0% ⟶ 100% ethyl acetate in hexanes, then 0% ⟶ 15% methanol in ethyl acetate) afforded the *title compound* as a white solid (164 mg, 56%). Rotameric broadening is evident in both the ^{1}H and ^{13}C NMR spectra; m.p. 102–108 °C; R_f 0.21 (1:9 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3271, 2940, 1636, 1613, 1516, 1495, 1447, 1353, 1329, 1232, 1200, 1173, 1111, 940, 830, 526, 460; δ_H (400 MHz, d_4-MeOD) 7.03 (2H, d, *J* = 8.4 Hz, Ar**H**), 6.70 (2H, d, *J* = 8.4 Hz, Ar**H**), 4.10 (1H, dt, *J* = 13.5, 7.6 Hz, 0.5 × **C**H$_2$), 3.88 – 3.71 (1H, m, 0.5 × C**H**$_2$), 3.27 – 3.17 (2H, m, C**H**$_2$), 2.90 (1H, dt, *J* = 13.5, 7.6 Hz, 0.5 × **C**H$_2$), 2.74 (2H, t, *J* = 7.6 Hz, **C**H$_2$), 2.38 – 2.24 (2H, m, C**H**$_2$), 2.21 – 1.97 (2H, m, C**H**$_2$), 1.81 – 1.68 (3H, m, 1.5 × C**H**$_2$), 1.61 – 1.46 (2H, m, C**H**$_2$); δ_C (100 MHz, d_4-MeOD) data for major rotamer: 175.7 (**C**O), 173.5 (**C**O), 157.0 (Ar**C**OH), 131.1 (Ar**C**),130.8 (2 × Ar**C**H), 116.3 (2 × Ar**C**H), 46.8 (**C**H$_2$), 42.9 (**C**H$_2$), 37.7 (**C**H$_2$), 33.7 (**C**H$_2$), 32.0 (**C**H$_2$), 25.0 (**C**H$_2$), 23.0 (**C**H$_2$), 21.7 (**C**H$_2$), Characteristic NMR signal for minor rotamer: 174.9 (**C**O); HRMS (ESI): calcd. for $C_{16}H_{22}N_2NaO_3$, 313.1523. Found: $[MNa]^+$, 313.1527 (–1.3 ppm error).

Lab notebook reference: KP507

5,5'-(1,4-Phenylenebis(methylene))bis(1,5-diazecane-2,6-dione) (4.118)



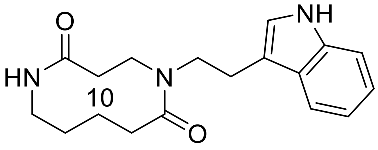
4.118

To a solution of 1,4-phenylenedimethanamine (103 mg, 0.75 mmol) in dry DMF (1.5 mL), was added a solution of 1-acryloyl-piperidin-2-one **4.47** (230 mg, 1.50 mmol) in dry DMF (1.5 mL) dropwise. 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, 1:4 ethyl acetate: hexane → 1:1 ethyl acetate: hexane → ethyl acetate → 1:49 methanol: ethyl acetate → 1:24 methanol: ethyl acetate → 1:16 methanol: ethyl acetate → 1:9 methanol: ethyl acetate → 1:6 methanol: ethyl acetate) afforded the *title compound* as a white solid (98.3 mg, 30%). Severe rotameric broadening is evident in the ^{1}H NMR spectrum. Product identity and purity is best seen in the ^{13}C NMR data. The product exists primarily as a single rotamer, with traces of a minor rotamer also evident; m.p. 163–170 °C; R_f 0.37 (1:4 methanol: DCM); ν_{max}/cm^{-1} (thin film) 3290, 2931, 1615, 1557, 1416, 1349, 1202, 1177, 1145, 1109, 1054, 910, 726, 645, 497; δ_H (400 MHz, $CDCl_3$) 7.21 – 7.05 (4H, m, Ar**H**), 6.19 – 5.80 (2H, m, 2 × N**H**), 5.20 – 4.98 (2H, m, C**H**$_2$), 4.17 – 3.55 (6H, m, C**H**$_2$), 3.28 – 3.10 (2H, m, C**H**$_2$), 2.98 – 2.43 (5H, m, C**H**$_2$), 2.23 – 2.03 (7H, m, C**H**$_2$), 1.81 – 1.38 (6H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 174.1 (2 × **C**O) 171.1 (2 × **C**O), 137.4 (2 × Ar**C**), 128.5 (4 × Ar**C**H), 48.5 (2 × **C**H$_2$), 45.0 (2 × **C**H$_2$), 39.3 (2 × **C**H$_2$), 37.3 (2 × **C**H$_2$), 28.3 (2 × **C**H$_2$), 25.7 (2 × **C**H$_2$), 23.9 (2 × **C**H$_2$); HRMS (ESI): calcd. for $C_{24}H_{34}N_4NaO_4$, 465.2472. Found: $[MNa]^+$, 465.2481 (–1.8 ppm error).

Characteristic NMR data for the minor rotamers can be found at: δ_H (400 MHz, $CDCl_3$) 4.81 (2H, d, *J* = 16.3 Hz, C**H**$_2$), 4.27 (2H, d, *J* = 16.3 Hz, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 176.3 (2 × **C**O), 171.3 (2 × **C**O), 127.3 (4 × Ar**C**H), 35.1 (2 × **C**H$_2$), 27.3 (2 × **C**H$_2$), 24.9 (2 × **C**H$_2$).

Lab notebook reference: KP510

5-(2-(1*H*-Indol-3-yl)ethyl)-1,5-diazecane-2,6-dione (4.119)

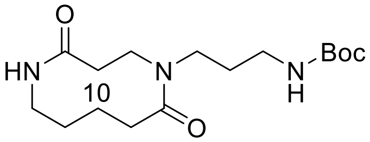


4.119

To a solution of 1-acryloyl-piperidin-2-one **4.47** (153 mg, 1.00 mmol) in dry methanol (1.0 mL), was added a solution of tryptamine (176 mg, 1.10 mmol) in dry methanol (1.0 mL). The reaction mixture was allowed to stir for 4 h at RT and then the solvent was removed *in vacuo*. Purification by automated flash column chromatography (using a 24 g pre-packed SiO_2 column, 0% → 100% ethyl acetate in hexanes, then 0% → 10% methanol in ethyl acetate) afforded the *title compound* as a white solid (220 mg, 70%).; m.p. 189–196 °C; R_f 0.11 (1:9 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3263, 2933, 2404, 1612, 1457, 1351, 1199, 1107, 744; δ_H (400 MHz, d_4-MeOD) 7.59 (1H, dt, *J* = 8.0, 1.1 Hz, Ar**H**), 7.30 (1H, dt, *J* = 8.0, 1.1 Hz, Ar**H**), 7.09 – 7.03 (2H, m, Ar**H**), 7.01 – 6.95 (1H, m, Ar**H**), 4.28 – 4.13 (1H, m, C**H₂**), 3.81 – 3.64 (1H, m, C**H₂**), 3.30 – 3.36 (1H, m, C**H₂**), 3.23 – 3.15 (1H, m, C**H₂**), 3.07 – 2.85 (4H, m, 2 × C**H₂**), 2.76 – 2.55 (1H, m, C**H₂**), 2.34 – 2.19 (1H, m, C**H₂**), 2.14 – 1.93 (3H, m, 1.5 × C**H₂**), 1.61 – 1.38 (3H, m, 1.5 × C**H₂**); δ_C (100 MHz, d_4-MeOD) 175.9 (**C**O), 173.6 (**C**O), 138.1 (Ar**C**), 128.8 (Ar**C**), 123.5 (Ar**C**H), 122.4 (Ar**C**H), 119.7 (Ar**C**H), 119.3 (Ar**C**H), 113.2 (Ar**C**), 112.3 (Ar**C**H), 48.8 (**C**H₂), 46.9 (**C**H₂), 40.5 (**C**H₂), 37.6 (**C**H₂), 29.6 (**C**H₂), 26.2 (**C**H₂), 25.1 (**C**H₂), 24.3 (**C**H₂);; HRMS (ESI): calcd. for $C_{18}H_{23}N_3NaO_2$, 336.1682. Found: [MNa]$^+$, 336.1685 (–0.6 ppm error).

Lab notebook reference: KP506

tert-Butyl (3-(4,10-dioxo-1,5-diazecan-1-yl)propyl)carbamate (4.120)

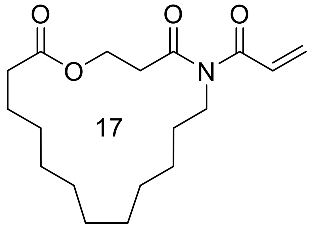


4.120

To a solution of 1-acryloyl-piperidin-2-one **4.47** (153 mg, 1.00 mmol) in dry methanol (2.0 mL), was added *N*-Boc-1,3-diaminopropane (192 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 → 1:19 methanol: ethyl acetate → 1:9 methanol: ethyl acetate → 1:6 methanol: ethyl acetate) afforded the *title compound* as an off-white solid (225 mg, 69%); m.p. 151–153 °C; R_f 0.11 (1:9 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3302, 2934, 1692, 1617, 1513, 1428, 1366, 1250, 1165, 914, 727, 645; δ_H (400 MHz, $CDCl_3$) 6.63 – 6.53 (1H, m, N**H**), 5.42 (1H, t, *J* = 6.3 Hz, N**H**), 4.19 – 3.46 (3H, m, C**H**$_2$), 3.27 – 3.05 (2H, m, C**H**$_2$), 2.99 – 2.72 (3H, m, C**H**$_2$), 2.67 – 2.49 (1H, m, C**H**$_2$), 2.35 – 2.11 (2H, m, C**H**$_2$), 2.07 – 1.87 (2H, m, C**H**$_2$), 1.76 – 1.42 (5H, m, C**H**$_2$), 1.32 (9H, s, 3 × C**H**$_3$); δ_C (100 MHz, $CDCl_3$) 174.5 (**C**O), 171.0 (**C**O), 156.2 (N**C**O$_2$), 79.0 (**C**), 45.4 (**C**H$_2$), 43.1 (**C**H$_2$), 39.1 (**C**H$_2$), 37.8 (**C**H$_2$), 37.5 (**C**H$_2$), 28.4 (3 × **C**H$_3$, and 1 × **C**H$_2$ [overlapping]), 28.2 (**C**H$_2$), 25.7 (**C**H$_2$), 23.7 (**C**H$_2$); HRMS (ESI): calcd. for $C_{16}H_{29}N_3NaO_4$, 350.2050. Found: $[MNa]^+$, 350.2051 (–0.3 ppm error).

Lab notebook reference: KP474

5-Acryloyl-1-oxa-5-azacycloheptadecane-4,17-dione (4.124)

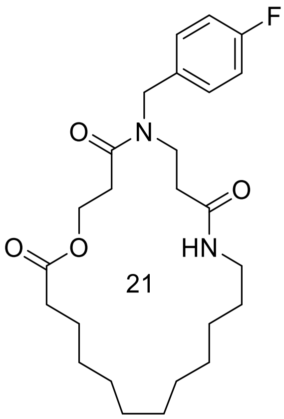


4.124

A stirring solution of 1-oxa-5-azacycloheptadecane-4,17-dione[67] (111 mg, 0.413 mmol) and DIPEA (0.180 mL, 1.03 mmol) in THF (1.6 mL) was cooled to 0 °C. To this was added a 0 °C cooled solution of acryloyl chloride (0.067 mL, 0.825 mmol) in THF (0.8 mL) dropwise. Under an argon atmosphere this mixture was stirred at 0 °C for 3 hours. It was then allowed to warm to RT and stirred for a further 2 hours. The reaction mixture was then quenched with sat. aq. NH_4Cl (2 mL), extracted with DCM (4 mL), and the organic layer washed with washed with sat. aq. $NaHCO_3$ (2 × 2 mL). The organic extracts were 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 colourless oil (21.5 mg, 12%); R_f 0.27 (1:1 hexane: diethyl ether); ν_{max}/cm^{-1} (thin film) 2927, 2857, 1732, 1687, 1618, 1460, 1404, 1365, 1220, 1133, 1103, 1061, 979, 797, 736; δ_H (300 MHz, $CDCl_3$) 6.73 (1H, dd, *J* = 16.7, 10.3 Hz, NCOC**H**CHH'), 6.41 (1H, dd, *J* = 16.7, 1.7 Hz, NCOCHC**H**H'), 5.80 (1H, dd, *J* = 10.3, 1.7 Hz, NCOCHCH**H'**), 4.43 (2H, t, *J* = 5.9 Hz, CO_2C**H$_2$**CH_2CON), 3.75 – 3.65 (2H, m, CH_2CH_2C**H$_2$**NCO), 3.07 (2H, t, *J* = 5.9 Hz, CO_2CH_2C**H$_2$**CON), 2.35 – 2.25 (2H, m, CH_2C**H$_2$**CO_2), 1.72 – 1.51 (4H, m, 2 × C**H$_2$**), 1.41–1.21 (14H, m, 7 × C**H$_2$**); δ_C (75 MHz, $CDCl_3$) 173.9 (**C**O), 173.3 (**C**O), 168.9 (**C**O), 130.6 (**C**HCH$_2$), 130.2 (CH**C**H$_2$), 59.8 (CO_2**C**H$_2$$CH_2$CON), 44.3 ($CH_2CH_2$**C**H$_2$NCO), 37.2 ($CO_2CH_2$**C**H$_2$CON), 34.2 ($CH_2$**C**H$_2$$CO_2$), 28.1 (**C**H$_2$), 27.8 (**C**H$_2$), 27.7 (**C**H$_2$), 27.3 (**C**H$_2$), 27.2 (**C**H$_2$), 27.0 (**C**H$_2$), 26.8 (**C**H$_2$), 25.2 (**C**H$_2$), 24.7 (**C**H$_2$); HRMS (ESI): calcd. for $C_{18}H_{29}NNaO_4$, 346.1989. Found: $[MNa]^+$, 346.1993 (–1.2 ppm error).

Lab notebook reference: KP545

5-(4-Fluorobenzyl)-1-oxa-5,9-diazacyclohenicosane-4,8,21-trione (4.125)

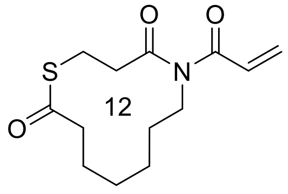


4.125

To a solution of **4.124** (21.5 mg, 0.066 mmol) in dry methanol (0.13 mL), was added 4-fluorobenzylamine (8 µL, 0.073 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, 2:1 hexane: ethyl acetate → ethyl acetate) afforded the *title compound* as a colourless oil (19.3 mg, 65%). In solution in $CDCl_3$, this compound exists as a roughly 2:1 mixture of rotamers; R_f 0.22 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3313, 2927, 2855, 1732, 1638, 1553, 1510, 1460, 1415, 1358, 1222, 1156, 1101, 1016, 824, 732; δ_H (400 MHz, $CDCl_3$) 7.27 – 7.20 (2H, m, Ar**H**, minor rotamer), 7.16 – 7.09 (2H, m, Ar**H**, major rotamer), 7.08 – 7.02 (2H, m, Ar**H**, minor rotamer), 7.01 – 6.95 (2H, m, Ar**H**, minor rotamer), 6.32 (1H, t, *J* = 5.8 Hz, N**H**, major rotamer), 5.64 (1H, t, *J* = 5.8 Hz, N**H**, minor rotamer), 4.56 (4H, s, 2 × C**H**$_2$, both rotamers), 4.45 (2H, t, *J* = 6.9 Hz, C**H**$_2$, minor rotamer), 4.39 (2H, t, *J* = 6.5 Hz, C**H**$_2$, major rotamer), 3.65 – 3.55 (4H, m, C**H**$_2$, both rotamers), 3.31 – 3.20 (4H, m, C**H**$_2$, both rotamers), 2.77 (2H, t, *J* = 6.9 Hz, C**H**$_2$, minor rotamer), 2.66 (2H, t, *J* = 6.5 Hz, C**H**$_2$, major rotamer), 2.49 (2H, t, *J* = 6.4 Hz, C**H**$_2$, major rotamer), 2.38 – 2.24 (6H, m, C**H**$_2$, both rotamers), 1.69 – 1.56 (4H, m, C**H**$_2$, both rotamers), 1.55 – 1.43 (4H, m, C**H**$_2$, both rotamers), 1.37 – 1.18 (28H, m, C**H**$_2$, both rotamers); δ_C (100 MHz, $CDCl_3$) 174.2 (**C**O, minor rotamer), 173.9 (**C**O, major rotamer), 171.0 (**C**O, major rotamer), 170.9 (**C**O, major rotamer), 170.2 (**C**O, minor rotamer), 169.6 (**C**O, minor rotamer), 162.4 (Ar**C**F, $^1J_{CF}$ = 246.0 Hz, major rotamer), 161.3 (Ar**C**F, $^1J_{CF}$ = 246.0 Hz, minor rotamer), 133.5 (Ar**C**F, $^4J_{CF}$ = 3.0 Hz, minor rotamer), 132.1 (Ar**C**F, $^4J_{CF}$ = 3.0 Hz, major rotamer), 130.0 (Ar**C**H, $^3J_{CF}$ = 8.0 Hz, minor rotamer), 128.1 (Ar**C**H, $^3J_{CF}$ = 8.0 Hz, major rotamer), 116.1 (Ar**C**H, $^2J_{CF}$ = 21.5 Hz, major rotamer), 115.6 (Ar**C**H, $^2J_{CF}$ = 21.5 Hz, minor rotamer), 61.1 (**C**H$_2$, minor rotamer), 60.4 (**C**H$_2$, major rotamer), 51.6 (**C**H$_2$, major rotamer), 48.4 (**C**H$_2$, minor rotamer), 44.3 (**C**H$_2$, minor rotamer), 43.7 (**C**H$_2$, major rotamer), 39.7 (**C**H$_2$, major rotamer), 39.3 (**C**H$_2$, minor rotamer), 36.0 (**C**H$_2$, minor rotamer), 35.6 (**C**H$_2$, major rotamer), 34.1 (**C**H$_2$, major rotamer), 32.7 (**C**H$_2$, major rotamer), 32.3 (**C**H$_2$, minor rotamer), 29.3 (**C**H$_2$, major rotamer), 28.9 (**C**H$_2$, minor rotamer), 28.8 (**C**H$_2$, major rotamer), 28.4 (**C**H$_2$, rotamer), 28.3 (**C**H$_2$, rotamer), 28.2 (**C**H$_2$, rotamer), 28.10 (**C**H$_2$, rotamer), 28.07 (**C**H$_2$, rotamer), 27.94 (**C**H$_2$, rotamer), 27.93 (**C**H$_2$, rotamer), 27.89 (**C**H$_2$, rotamer), 27.6 (**C**H$_2$, minor rotamer), 27.2 (**C**H$_2$, minor rotamer), 26.4 (**C**H$_2$, major rotamer), 25.7 (**C**H$_2$, minor rotamer), 24.7 (**C**H$_2$, major rotamer), 24.6 (**C**H$_2$, minor rotamer); δ_F (376 MHz, CDCl$_3$), two rotamers in a 2:1 ratio: −114.34 (1F, m, ArF, major rotamer), −114.76 (1F, m, ArF); HRMS (ESI): calcd. for $C_{25}H_{37}FN_2NaO_4$, 471.2630. Found: [MNa]$^+$, 471.2632 (–0.5 ppm error).

Lab notebook reference: KP547

5-Acryloyl-1-thia-5-azacyclododecane-4,12-dione (4.126)

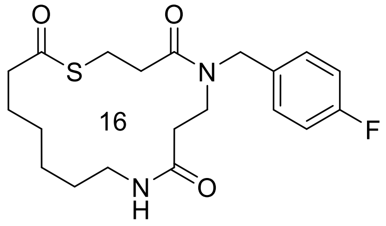


4.126

A stirring solution of 1-thia-5-azacyclododecane-4,12-dione **3.23** (31.5 mg, 0.147 mmol) and DIPEA (0.064 mL, 0.366 mmol) in THF (0.6 mL) was cooled to 0 °C. To this was added a 0 °C cooled solution of acryloyl chloride (0.024 mL, 0.293 mmol) in THF (0.3 mL) dropwise. Under an argon atmosphere this mixture was stirred at 0 °C for 2 hours. It was then allowed to warm to RT and stirred for a further 5 hours. The reaction mixture was then quenched with sat. aq. NH$_4$Cl (1 mL), extracted with DCM (2 mL), then the organic layer washed with washed with sat. aq. NaHCO$_3$ (2 × 1 mL). The organic extracts were 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 colourless oil (24.5 mg, 62%); R_f 0.29 (1:1 hexane: diethyl ether); ν_{max}/cm^{-1} (thin film) 2938, 1683, 1618, 1404, 1352, 1301, 1276, 1210, 1151, 1072, 1032, 978, 870, 795, 694; δ_H (400 MHz, CDCl$_3$) 6.65 (1H, dd, *J* = 16.7, 10.2 Hz, NCOC**H**CHH'), 6.46 (1H, dd, *J* = 16.7, 1.8 Hz, NCOCHC**H**H'), 5.83 (1H, dd, *J* = 10.2, 1.8 Hz, NCOCHCH**H'**), 3.77 (2H, br s, C**H$_2$**), 3.60 – 2.90 (4H, m, 2 × C**H$_2$**), 2.54 – 2.44 (2H, m, C**H$_2$**), 1.82 (2H, br s, C**H$_2$**), 1.65 – 1.52 (2H, m, C**H$_2$**), 1.50 – 1.28 (4H, m, 2 × C**H$_2$**); δ_C (100 MHz, CDCl$_3$) 200.1 (**C**OS), 175.7 (**C**O), 169.4 (**C**O), 130.5 (CH**C**H$_2$), 130.3 (**C**HCH$_2$), 44.3 (**C**H$_2$), 43.7 (**C**H$_2$), 38.8 (**C**H$_2$), 28.3 (**C**H$_2$), 27.4 (**C**H$_2$), 25.0 (**C**H$_2$), 24.8 (**C**H$_2$), 23.5 (**C**H$_2$); HRMS (ESI): calcd. for $C_{13}H_{19}NNaO_3S$, 292.0978. Found: [MNa]$^+$, 292.0981 (–1.1 ppm error).

Lab notebook reference: KP548

5-(4-Fluorobenzyl)-1-thia-5,9-diazacyclohexadecane-4,8,16-trione (4.127)

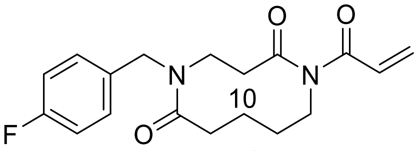


4.127

To a solution of **4.126** (24.5 mg, 0.091 mmol) in dry methanol (0.18 mL), was added 4-fluorobenzylamine (11 µL, 0.100 mmol) in a single portion. The reaction mixture was allowed to stir for 2 h at RT, then the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 2:1 hexane: ethyl acetate → 1:2 hexane: ethyl acetate → ethyl acetate) afforded the *title compound* **4.127** (15.0 mg, 42%) a colourless oil, along with 1-thia-5-azacyclododecane-4,12-dione (2.2 mg, 11%).[8] In solution in $CDCl_3$, compound **4.127** exists as a roughly 3:1 mixture of rotamers; Data for **4.127**: R_f 0.22 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3314, 2931, 2858, 1640, 1548, 1509, 1414, 1364, 1222, 1156, 1098, 982, 823, 731, 597; ^{1}H NMR for the major rotamer: δ_H (400 MHz, $CDCl_3$) 7.31 – 6.95 (4H, m, Ar**H**), 5.89 (1H, t, *J* = 5.6 Hz, N**H**), 4.58 – 4.45 (2H, m, C**H**$_2$), 3.69 – 3.53 (2H, m, C**H**$_2$), 3.32 – 3.21 (2H, m, C**H**$_2$), 3.21 – 3.08 (2H, m, C**H**$_2$), 2.74 – 2.34 (6H, m, C**H**$_2$), 1.97 – 1.66 (2H, m, C**H**$_2$), 1.58 – 1.42 (2H, m, C**H**$_2$), 1.40 – 1.21 (4H, m, C**H**$_2$). Diagnostic ^{1}H NMR shifts for the minor rotamers can be seen at: 7.31 – 7.19 (1H, m, Ar**H**, minor rotamer), 4.55 (2H, s, ArC**H**$_2$, minor rotamer), 7.10 – 7.04 (1H, m, Ar**H**, major rotamer), 4.49 (2H, s, ArC**H**$_2$, major rotamer); δ_C (100 MHz, $CDCl_3$) ^{13}C peaks for the major rotamer: 200.6 (**C**OS), 171.51 (**C**O), 171.45 (**C**O), 162.3 (Ar**C**F, $^1J_{CF}$ = 246.1 Hz), 132.7 (Ar**C**F, $^4J_{CF}$ = 3.2 Hz), 128.1 (2 × Ar**C**H, $^3J_{CF}$ = 8.1 Hz), 116.0 (2 × Ar**C**H, $^2J_{CF}$ = 21.5 Hz), 52.9 (**C**H$_2$), 45.1 (**C**H$_2$), 42.5 (**C**H$_2$), 39.1 (**C**H$_2$), 35.3 (**C**H$_2$), 33.1 (**C**H$_2$), 29.5 (**C**H$_2$), 27.8 (**C**H$_2$), 25.9 (**C**H$_2$), 25.2 (**C**H$_2$), 25.0 (**C**H$_2$). ^{13}C peaks for the minor rotamer: 133.53 (Ar**C**F, $^4J_{CF}$ = 3.2 Hz), 129.9 (2 × Ar**C**H, $^3J_{CF}$ = 8.1 Hz), 115.7 (2 × Ar**C**H, $^2J_{CF}$ = 21.5 Hz), 48.7 (**C**H$_2$), 44.7 (**C**H$_2$), 43.7 (**C**H$_2$), 39.6 (**C**H$_2$), 36.7 (**C**H$_2$), 33.8 (**C**H$_2$), 29.8 (**C**H$_2$), 28.0 (**C**H$_2$), 27.2 (**C**H$_2$), 26.2 (**C**H$_2$), 23.7 (**C**H$_2$); δ_F (376 MHz, $CDCl_3$), −114.77 (1F, m, ArF, both rotamers, overlapping); HRMS (ESI): calcd. for $C_{20}H_{27}FN_2NaO_3S$, 417.1619. Found: [MNa]$^+$, 417.1620 (–0.3 ppm error).

Lab notebook reference: KP549

1-Acryloyl-5-(4-fluorobenzyl)-1,5-diazecane-2,6-dione (5.1)

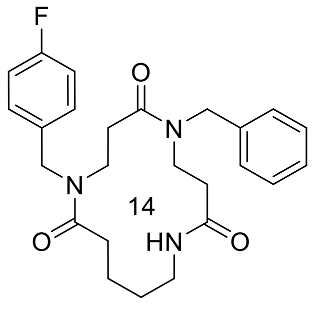


5.1

A stirring solution of **4.62** (1.20 g, 4.30 mmol) and DIPEA (1.87 mL, 10.8 mmol) in THF (20 mL) was cooled to 0 °C. To this was added a 0 °C cooled solution of acryloyl chloride (0.524 mL, 6.45 mmol) in THF (5.0 mL) dropwise. Under an argon atmosphere this mixture was stirred at 0 °C for 2 hours. Afterwards it was allowed to warm to RT and stirred for a further 18 hours. The reaction mixture was then quenched with sat. aq. NH_4Cl (15 mL), extracted with Et_2O (25 mL), then the organic layer washed with washed with sat. aq. $NaHCO_3$ (2 × 15 mL). The organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:2 ethyl acetate: hexane → ethyl acetate) afforded the *title compound* as a pale-yellow oil (997 mg, 70%). In solution in $CDCl_3$, this compound exists largely as a single rotamer, along with a minor rotamer (most clearly seen in the ^{19}F NMR data). The ^{1}H NMR spectrum is significantly affected by rotameric broadening; R_f 0.49 (1:9 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 2943, 1681, 1631, 1509, 1457, 1406, 1342, 1245, 1220, 1158, 1141, 1092, 1063, 981, 905, 816, 767, 730, 582, 498, 474; δ_H (400 MHz, $CDCl_3$) 7.19 – 7.13 (2H, m, Ar**H**), 6.96 – 6.89 (2H, m, Ar**H**), 6.62 (1H, dd, *J* = 16.6, 10.3 Hz, NCOC**H**CHH'), 6.42 (1H, dd, *J* = 16.6, 1.5 Hz, NCOCHC**H**H'), 5.85 (1H, dd, *J* = 10.3, 1.5 Hz, NCOCHCH**H'**), 4.91 – 4.15 (2H, m, C**H₂**), 3.84 (2H, br s, C**H₂**), 3.56 (2H, br s, C**H₂**), 3.24 (2H, br s, C**H₂**), 2.39 (2H, br s, C**H₂**), 1.90 (2H, br s, C**H₂**), 1.66 (2H, br p, *J* = 5.4Hz, C**H₂**); δ_C (100 MHz, $CDCl_3$) 175.4 (**C**O), 172.9 (**C**O), 168.8 (**C**O), 162.1 (Ar**C**F, $^1J_{CF}$ = 245.6 Hz), 133.0 (Ar**C**, $^4J_{CF}$ = 3.1 Hz), 132.1 (NCOCH=**C**HH'), 129.9 (2 × Ar**C**H, $^3J_{CF}$ = 8.1 Hz), 129.4 (NCO**C**H=CHH'), 115.4 (2 × Ar**C**H, $^2J_{CF}$ = 21.5 Hz), 46.8 (**C**H₂), 45.6 (**C**H₂), 43.8 (**C**H₂), 38.0 (**C**H₂), 29.1 (**C**H₂), 24.1 (**C**H₂), 24.0 (**C**H₂); δ_F (376 MHz, $CDCl_3$), −114.32 (1F, m, ArF, minor rotamer), −115.01 (1F, m, ArF, major rotamer); HRMS (ESI): calcd. for $C_{18}H_{21}FN_2NaO_3$, 355.1428. Found: $[MNa]^+$, 355.1423 (1.5 ppm error).

Lab notebook reference: KP564

5-Benzyl-9-(4-fluorobenzyl)-1,5,9-triazacyclotetradecane-2,6,10-trione (4.128)

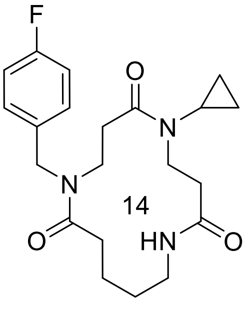


4.128

To a solution of **5.1** (179 mg, 0.537 mmol) in dry methanol (1.07 mL), was added benzylamine (65 µL, 0.591 mmol) in a single portion. After 30 min of stirring a white precipitate formed which turned the solution into a slurry. The reaction mixture was allowed to stir for 3 h in total at RT and then the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, ethyl acetate → 1:49 methanol: ethyl acetate → 1:16 methanol: ethyl acetate → 1:9 methanol: ethyl acetate → 1:6 methanol: ethyl acetate → 1:4 methanol: ethyl acetate) afforded the *title compound* as a white solid (180 mg, 76%). This compound exists as a complex mixture of rotamers at RT in $CDCl_3$, with 4 main rotamers visible in a ratio of roughly 7:5:4:1, based on the ^{19}F NMR data and the NH signals in the ^{1}H NMR spectrum; m.p. 188–190 °C; R_f 0.34 (1:4 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3301, 2933, 1626, 1552, 1509, 1450, 1363, 1221, 1157, 1096, 915, 823, 729, 699, 646; δ_H (400 MHz, $CDCl_3$) 7.39 – 6.91 (9H, m, Ar**H**), 6.88 (1H, br t, *J* = 5.7 Hz, N**H**), 6.76 (1H, br t, *J* = 6.0 Hz, N**H**), 6.46 (1H, br t, *J* = 5.5 Hz, N**H**), 6.05 (1H, br t, *J* = 6.1 Hz, N**H**), 4.69 (2H, s, ArC$\mathbf{H_2}$), 4.62 (2H, s, ArC$\mathbf{H_2}$), 4.56 (2H, s, ArC$\mathbf{H_2}$), 4.55 (2H, s, ArC$\mathbf{H_2}$), 4.48 (2H, s, ArC$\mathbf{H_2}$), 4.38 (2H, s, ArC$\mathbf{H_2}$), 3.74 – 3.47 (4H, m, 2 × C$\mathbf{H_2}$), 3.36 – 3.26 (2H, m, C$\mathbf{H_2}$), 2.66 – 2.23 (6H, m, 6 × C$\mathbf{H_2}$), 1.80 – 1.50 (4H, m, 2 × C$\mathbf{H_2}$); δ_C (100 MHz, $CDCl_3$) 173.9 (**C**O), 173.6 (**C**O), 173.4 (**C**O), 172.9 (**C**O), 172.8 (**C**O), 171.2 (**C**O), 171.1 (**C**O), 170.6 (**C**O), 170.2 (**C**O), 162.3 (Ar**C**F, $^1J_{CF}$ = 246.0 Hz), 162.1 (Ar**C**F, $^1J_{CF}$ = 246.0 Hz), 138.0 (Ar**C**), 137.4 (Ar**C**), 136.9 (Ar**C**), 137.8 (Ar**C**), 133.5 (Ar**C**, $^4J_{CF}$ = 3.0 Hz), 133.4 (Ar**C**, $^4J_{CF}$ = 3.0 Hz), 132.8 (Ar**C**, $^4J_{CF}$ = 3.0 Hz), 129.8 (Ar**C**H, $^3J_{CF}$ = 8.0 Hz), 129.3 (2 × Ar**C**H), 129.0 (2 × Ar**C**H), 128.8 (Ar**C**H), 129.31 (Ar**C**H, $^3J_{CF}$ = 8.0 Hz), 128.32 (Ar**C**H), 128.0 (Ar**C**H), 127.7 (Ar**C**H), 127.6 (Ar**C**H), 126.2 (2 × Ar**C**H), 126.0 (2 × Ar**C**H), 116.0 (Ar**C**H, $^2J_{CF}$ = 21.5 Hz), 115.6 (Ar**C**H, $^2J_{CF}$ = 21.5 Hz), 115.5 (Ar**C**H, $^2J_{CF}$ = 21.1 Hz), 53.4 (Ar**C**H$_2$), 53.0 (Ar**C**H$_2$), 51.5 (Ar**C**H$_2$), 48.3 (Ar**C**H$_2$), 48.0 (Ar**C**H$_2$), 47.9 (Ar**C**H$_2$), 44.5 (**C**H$_2$), 43.9 (**C**H$_2$), 43.7 (**C**H$_2$), 42.9 (**C**H$_2$), 42.4 (**C**H$_2$), 39.6 (**C**H$_2$), 38.5 (**C**H$_2$), 38.3 (**C**H$_2$), 35.4 (**C**H$_2$), 35.2 (**C**H$_2$), 35.0 (**C**H$_2$), 33.6 (**C**H$_2$), 33.2 (**C**H$_2$), 32.5 (**C**H$_2$), 31.7 (**C**H$_2$), 29.1 (**C**H$_2$), 28.1 (**C**H$_2$), 27.8 (**C**H$_2$), 24.0 (**C**H$_2$), 23.3 (**C**H$_2$), 23.0 (**C**H$_2$); δ_F (376 MHz, $CDCl_3$), four rotamers in a 7:5:1:4 ratio: −114.49 (1F, m, ArF, major rotamer), −114.69 (1F, m, ArF), −114.87 (1F, m, ArF), −115.15 (1F, m, ArF); HRMS (ESI): calcd. for $C_{25}H_{30}FN_3NaO_3$, 462.2163. Found: $[MNa]^+$, 462.2160 (0.7 ppm error).

Lab notebook reference: KP467

5-Cyclopropyl-9-(4-fluorobenzyl)-1,5,9-triazacyclotetradecane-2,6,10-trione (4.130)

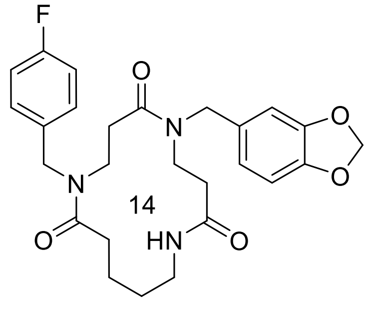


4.130

To a solution of **5.1** (320 mg, 0.963 mmol) in dry methanol (2.0 mL), was added cyclopropyl amine (73 µL, 1.06 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 ethyl acetate: hexane → ethyl acetate → 1:19 methanol: ethyl acetate → 1:9 methanol: ethyl acetate → 3:17 methanol: ethyl acetate) afforded the *title compound* as a colourless oil (279 mg, 74%). This compound exists as a complex mixture of rotamers at RT in $CDCl_3$, with 4 main rotamers based on the carbonyl region of the ^{13}C NMR spectrum. Due to overlapping signals in the ^{1}H and ^{19}F NMR, it is difficult to confidently quote a rotamer ratio; R_f 0.26 (1:4 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3303, 2937, 1736, 1638, 1549, 1509, 1413, 1366, 1221, 1158, 827; δ_H (400 MHz, $CDCl_3$) 7.38 (1H, t, *J* = 5.6 Hz, N**H**, rotamer), 7.33 (1H, t, *J* = 5.7 Hz, N**H**, rotamer), 7.14 – 6.98 (2H, m, Ar**H**), 6.96 – 6.83 (2H, m, Ar**H**), 6.80 (1H, t, *J* = 5.4 Hz, N**H**, rotamer), 4.70 – 4.37 (2H, m, C**H**$_2$), 3.63 – 3.54 (2H, m, C**H**$_2$), 3.52 (1H, d, *J* = 6.6 Hz, C**H**, rotamer), 3.49 – 3.40 (1H, m, C**H**$_2$), 3.20 – 2.99 (2H, m, C**H**$_2$), 2.84 – 2.67 (1H, m, C**H**$_2$), 2.61 – 2.16 (6H, m, C**H** (rotamer) and C**H**$_2$), 1.64 – 1.25 (4H, m, C**H**$_2$), 0.80 – 0.66 (1H, m, cyclopropyl C**H**$_2$, major rotamer), 0.60 – 0.48 (1H, m, cyclopropyl C**H**$_2$, major rotamer), 0.44 – 0.36 (1H, m, cyclopropyl C**H**$_2$, minor rotamer), 0.32 – 0.23 (1H, m, cyclopropyl C**H**$_2$, minor rotamer); δ_C (100 MHz, $CDCl_3$) 174.2 (**C**O), 173.9 (**C**O), 173.7 (**C**O), 173.3 (**C**O), 173.0 (**C**O), 172.8 (**C**O), 172.34 (**C**O), 172.31 (**C**O), 172.2 (**C**O), 171.2 (**C**O), 170.9 (**C**O), 170.7 (**C**O), 162.0 (Ar**C**F, $^{1}J_{CF}$ = 245.6 Hz), 161.92 (Ar**C**F, $^{1}J_{CF}$ = 245.6 Hz), 162.89 (Ar**C**F, $^{1}J_{CF}$ = 245.6 Hz), 133.4 (Ar**C**F, $^{4}J_{CF}$ = 3.2 Hz), 133.2 (Ar**C**F, $^{4}J_{CF}$ = 3.2 Hz), 133.1 (Ar**C**F, $^{4}J_{CF}$ = 3.2 Hz), 132.3 (Ar**C**F, $^{4}J_{CF}$ = 3.2 Hz), 129.6 (2 × Ar**C**H, $^{3}J_{CF}$ = 8.0 Hz), 129.3 (2 × Ar**C**H, $^{3}J_{CF}$ = 8.0 Hz), 129.1 (2 × Ar**C**H, $^{3}J_{CF}$ = 8.0 Hz), 127.8 (2 × Ar**C**H, $^{3}J_{CF}$ = 8.0 Hz), 115.7 (2 × Ar**C**H, $^{2}J_{CF}$ = 21.6 Hz), 115.5 (2 × Ar**C**H, $^{2}J_{CF}$ = 21.6 Hz), 115.3 (2 × Ar**C**H, $^{2}J_{CF}$ = 21.6 Hz), 53.4 (**C**H$_2$), 53.1 (**C**H$_2$), 51.8 (**C**H$_2$), 51.54 (**C**H), 51.51 (**C**H), 51.2 (**C**H$_2$), 48.0 (**C**H$_2$), 47.5 (**C**H$_2$), 43.5 (**C**H$_2$), 43.3 (**C**H$_2$), 43.0 (**C**H$_2$), 42.5 (**C**H$_2$), 41.8 (**C**H$_2$), 38.7 (**C**H$_2$), 38.6 (**C**H$_2$), 38.0 (**C**H$_2$), 36.5 (**C**H), 34.9 (**C**H$_2$), 34.8 (**C**H$_2$), 34.6 (**C**H$_2$), 33.9 (**C**H$_2$), 33.5 (**C**H$_2$), 33.4 (**C**H$_2$), 33.1 (**C**H$_2$), 32.8 (**C**H$_2$), 32.6 (**C**H$_2$), 32.5 (**C**H$_2$), 32.3 (**C**H$_2$), 32.2 (**C**H$_2$), 30.7 (**C**H), 29.2 (**C**H), 28.8 (**C**H$_2$), 28.7 (**C**H$_2$), 28.6 (**C**H$_2$), 28.0 (**C**H$_2$), 23.2 (**C**H$_2$), 22.9 (**C**H$_2$), 22.4 (**C**H$_2$), 22.2 (**C**H$_2$), 9.5 (cyclopropyl **C**H$_2$), 9.0 (cyclopropyl **C**H$_2$), 6.4 (cyclopropyl **C**H$_2$); δ_F (376 MHz, $CDCl_3$), 114.98 (1F, m, ArF), –114.62 (1F, m, ArF); HRMS (ESI): calcd. for $C_{21}H_{28}FN_3NaO_3$, 412.2007. Found: $[MNa]^+$, 412.2008 (–0.2 ppm error).

Lab notebook reference: KP569

5-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-9-(4-fluorobenzyl)-1,5,9-triazacyclotetradecane-2,6,10-trione (4.132)

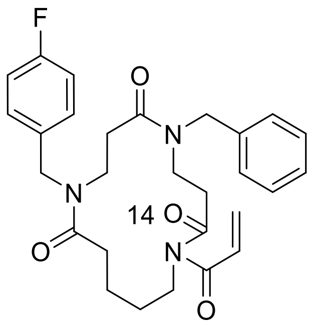


4.132

To a solution of **5.1** (332 mg, 0.998 mmol) in dry methanol (2.0 mL), was added piperonylamine (166 mg, 1.10 mmol) in a single portion. The reaction mixture was allowed to stir for 10 min at RT at which point a white precipitate formed which impeded stirring. To the crude reaction mixture was added DCM (2 mL) and then the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 ethyl acetate: hexane → 2:1 ethyl acetate: hexane → ethyl acetate → 1:49 methanol: ethyl acetate → 1:19 methanol: ethyl acetate → 1:9 methanol: ethyl acetate → 1:4 methanol: ethyl acetate) afforded the *title compound* as a white solid (256 mg, 53%). This compound exists as a complex mixture of rotamers at RT in $CDCl_3$, with 3 main rotamers visible in a ratio of roughly 12:8:6 based on the ^{19}F NMR data and the OC**H₂**O signals in the ^1H NMR spectrum. A more minor fourth rotamer can also be seen in the ^{19}F NMR spectrum; m.p. 216–220 °C; R_f 0.23 (1:4 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 2933, 1633, 1508, 1490, 1443, 1244, 1157, 1038, 928, 705, 503; δ_H (600 MHz, $CDCl_3$) 7.26 – 7.11 (2H, m, Ar**H**), 7.07 – 6.93 (2H, m, Ar**H**), 6.79 – 6.67 (2H, m, Ar**H**), 6.61 (1H, br t, *J* = 5.9 Hz, N**H**, rotamer), 6.59 – 6.46 (1H, m, Ar**H**), 6.01 – 5.87 (2H, s, OC**H₂**O), 5.67 (1H, br t, *J* = 6.2 Hz, N**H**, rotamer), 4.85 – 4.23 (4H, m, ArC**H**$_2$), 3.74 – 3.46 (4H, m, C**H**$_2$), 3.37 – 3.21 (2H, m, C**H**$_2$), 2.69 – 2.40 (5H, m, C**H**$_2$), 1.91 – 1.49 (5H, m, C**H**$_2$), Diagnostic ^1H NMR signals for the 3 major rotamers: 5.97 (2H, s, OC**H₂**O, rotamer B), 5.94 (2H, s, OC**H₂**O, major rotamer A), 5.93 (2H, s, OC**H₂**O, rotamer C); δ_C (151 MHz, $CDCl_3$) 173.9 (**C**O, major rotamer), 173.6 (**C**O), 173.4 (**C**O), 172.8 (**C**O, major rotamer), 172.7 (**C**O), 171.2 (**C**O, major rotamer), 171.0 (**C**O), 170.6 (**C**O), 170.2 (**C**O), 162.4 (Ar**C**F, $^1J_{CF}$ = 246.0 Hz, major rotamer), 162.3 (2 × Ar**C**F, $^1J_{CF}$ = 246.0 Hz, two minor rotamers overlapping), 148.6 (Ar**C**OCH$_2$), 148.4 (Ar**C**OCH$_2$, major rotamer), 148.2 (Ar**C**OCH$_2$), 147.5 (Ar**C**OCH$_2$), 147.3 (Ar**C**OCH$_2$), 147.2 (Ar**C**OCH$_2$, major rotamer), 133.6 (Ar**C**), 133.5 (Ar**C**), 132.9 (Ar**C**, $^4J_{CF}$ = 2.8 Hz, major rotamer), 131.3 (Ar**C**), 130.8 (Ar**C**, major rotamer), 129.9 (Ar**C**H, $^3J_{CF}$ = 8.0 Hz), 129.6 (Ar**C**), 128.4 (Ar**C**H, $^3J_{CF}$ = 8.0 Hz), 128.2 (Ar**C**H, $^3J_{CF}$ = 8.0 Hz), 121.7 (ArCH), 119.6 (Ar**C**H), 119.5 (Ar**C**H), 116.0 (Ar**C**H, $^2J_{CF}$ = 21.5 Hz), 115.7 (Ar**C**H, $^2J_{CF}$ = 21.5 Hz), 115.6 (Ar**C**H, $^2J_{CF}$ = 21.5 Hz), 108.9 (Ar**C**H), 108.8 (Ar**C**H), 108.7 (Ar**C**H, major rotamer), 108.4 (Ar**C**H), 106.8 (Ar**C**H, major rotamer), 106.6 (Ar**C**H), 101.5 (O**C**H$_2$O), 101.32 (O**C**H$_2$O, major rotamer), 101.26 (O**C**H$_2$O), 53.2 (**C**H$_2$), 53.1 (**C**H$_2$), 51.4 (**C**H$_2$), 48.4 (**C**H$_2$), 48.1 (**C**H$_2$), 47.8 (**C**H$_2$), 44.5 (**C**H$_2$), 44.3 (**C**H$_2$), 43.8 (**C**H$_2$), 43.7 (**C**H$_2$), 43.0 (**C**H$_2$), 42.2 (**C**H$_2$), 39.6 (**C**H$_2$), 38.54 (**C**H$_2$), 38.51 (**C**H$_2$), 35.5 (**C**H$_2$), 35.3 (**C**H$_2$), 35.2 (**C**H$_2$), 33.6 (**C**H$_2$), 33.3 (**C**H$_2$), 33.2 (**C**H$_2$), 32.7 (**C**H$_2$), 31.8 (**C**H$_2$), 29.1 (**C**H$_2$), 28.2 (**C**H$_2$), 27.8 (**C**H$_2$), 24.0 (**C**H$_2$), 23.3 (**C**H$_2$), 23.0 (**C**H$_2$); δ$_F$ (376 MHz, CDCl$_3$), four rotamers in a 12:8:3:6 ratio: –114.48 (1F, m, ArF, major rotamer), –114.73 (1F, m, ArF), –114.84 (1F, m, ArF, minor rotamer), –115.19 (1F, m, ArF); HRMS (ESI): calcd. for $C_{26}H_{30}FN_3NaO_5$, 506.2062. Found: [MNa]$^+$, 506.2061 (0.2 ppm error).

Lab notebook reference: KP565

1-Acryloyl-5-benzyl-9-(4-fluorobenzyl)-1,5,9-triazacyclotetradecane-2,6,10-trione (5.2)



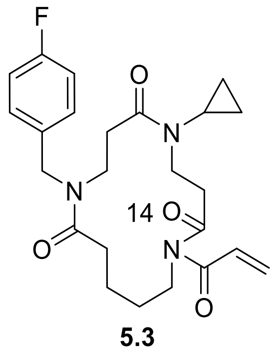
5.2

To a stirring solution of **4.128** (277 mg, 0.630 mmol) and DIPEA (0.274 mL, 1.58 mmol) in DCM (10 mL) was cooled to 0 °C. To this was added a 0 °C cooled solution of acryloyl chloride (0.077 mL, 0.945 mmol) in DCM (3.0 mL) dropwise. Under an argon atmosphere this mixture was stirred at 0 °C for 2 hours. Afterwards it was allowed to warm to RT and stirred for a further 18 hours. The reaction mixture was then quenched with sat. aq. NH$_4$Cl (40 mL), extracted with Et$_2$O (40 mL), then the organic layer washed with washed with sat. aq. NaHCO$_3$ (2 × 40 mL). The organic extracts were dried over MgSO$_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO$_2$, 1:2 ethyl acetate: hexane → 1:1 ethyl acetate: hexane → 2:1 ethyl acetate: hexane → ethyl acetate → 1:9 methanol:

ethyl acetate) afforded the *title compound* as a colorless oil (265 mg, 85%). This compound exists as a complex mixture of rotamers at RT in CDCl$_3$, with at least 3 significant rotameric forms based on the carbonyl region of the ^{13}C NMR spectrum. Due to overlapping signals in the ^{1}H and ^{19}F NMR, it is difficult to confidently quote a rotamer ratio; R_f 0.12 (1:9 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 1681, 1634, 1509, 1408, 1365, 1221, 1141, 1064, 974, 910, 822, 726, 646, 499; δ_H (400 MHz, CDCl$_3$) 7.41 – 7.01 (9H, m, Ar**H**), 6.84 (1H, dd, *J* = 16.6, 10.3 Hz, NCOC**H**CHH') [overlapping]), 6.80 (1H, dd, *J* = 16.6, 10.3 Hz, NCOC**H**CHH'), major rotamer, [overlapping]), 6.40 (1H, dd, *J* = 16.6, 1.5 Hz, NCOCHC**H**H' H-26, major rotamer, [overlapping]), 6.36 (1H, dd, *J* = 16.6, 1.5 Hz, NCOCHC**H**H' H-26, [overlapping]), 5.77 (1H, dd, *J* = 10.3, 1.5 Hz, NCOCHCH**H'** H-25, major rotamer, [overlapping]), 5.74 (1H, dd, *J* = 10.3, 1.5 Hz, NCOCHCH**H'** H-25, [overlapping]), 4.82 (2H, s, ArC**H$_2$**, major rotamer), 4.71 (2H, s, ArC**H$_2$**), 4.69 (2H, s, ArC**H$_2$**, major rotamer), 4.56 (2H, s, ArC**H$_2$**), 4.43 (2H, s, ArC**H$_2$**), 3.97 – 3.60 (5H, m, 2.5 × C**H$_2$**), 3.52 – 3.40 (1H, m, 0.5 × C**H$_2$**), 3.14 – 3.03 (1H, m, 0.5 × C**H$_2$**), 2.92 – 2.74 (2H, m, C**H$_2$**), 2.56 – 2.39 (2H, m, C**H$_2$**), 1.86 – 1.55 (5H, m, 2.5 × C**H$_2$**); δ_C (100 MHz, CDCl$_3$) 175.24 (**C**O), 174.66 (**C**O), 173.70 (**C**O), 173.55 (**C**O), 173.23 (**C**O), 173.10 (**C**O), 172.69 (**C**O), 172.22 (**C**O), 171.73 (**C**O), 170.06 (**C**O), 169.44 (**C**O), 168.91 (**C**O), 168.64 (**C**O), 168.49 (**C**O), 161.98 (Ar**C**F, $^{1}J_{CF}$ = 246.0 Hz), 137.53 (Ar**C**), 137.07 (Ar**C**), 136.88 (Ar**C**), 133.34 (Ar**C**F, $^{4}J_{CF}$ = 3.1 Hz), 133.03 (Ar**C**F, $^{4}J_{CF}$ = 3.1 Hz), 132.89 (Ar**C**F, $^{4}J_{CF}$ = 3.1 Hz), 132.08 (Ar**C**H), 131.31 (Ar**C**H), 131.09 (Ar**C**H), 130.47 (Ar**C**H), 129.71 (Ar**C**H), 129.63 (Ar**C**H), 129.10 (Ar**C**H), 128.90 (Ar**C**H), 129.67 (Ar**C**H, $^{3}J_{CF}$ = 8.1 Hz), 128.53 (Ar**C**H), 128.51 (Ar**C**H), 128.19 (Ar**C**H, $^{3}J_{CF}$ = 8.1 Hz), 128.07 (Ar**C**H, $^{3}J_{CF}$ = 8.1 Hz), 128.01 (Ar**C**H), 127.45 (Ar**C**H), 127.41 (Ar**C**H), 127.35 (Ar**C**H), 126.18 (Ar**C**H), 125.99 (Ar**C**H), 115.62 (Ar**C**H, $^{2}J_{CF}$ = 21.6 Hz), 115.58 (Ar**C**H, $^{2}J_{CF}$ = 21.6 Hz), 115.24 (Ar**C**H, $^{2}J_{CF}$ = 21.6 Hz), 53.45 (**C**H$_2$), 53.18 (**C**H$_2$), 53.09 (**C**H$_2$), 51.91 (**C**H$_2$), 49.88 (**C**H$_2$), 48.13 (**C**H$_2$), 47.72 (**C**H$_2$), 47.57 (**C**H$_2$), 44.21 (**C**H$_2$), 44.13 (**C**H$_2$), 43.45 (**C**H$_2$), 43.37 (**C**H$_2$), 43.15 (**C**H$_2$), 43.04 (**C**H$_2$), 42.38 (**C**H$_2$), 36.41 (**C**H$_2$), 35.55 (**C**H$_2$), 34.98 (**C**H$_2$), 33.83 (**C**H$_2$), 32.76 (**C**H$_2$), 32.54 (**C**H$_2$), 31.72 (**C**H$_2$), 31.24 (**C**H$_2$), 30.80 (**C**H$_2$), 30.77 (**C**H$_2$), 28.65 (**C**H$_2$), 28.29 (**C**H$_2$), 28.16 (**C**H$_2$), 27.22 (**C**H$_2$), 22.77 (**C**H$_2$), 22.60 (**C**H$_2$), 21.32 (**C**H$_2$), Characteristic peaks for major rotamer: 175.24 (**C**O), 168.91 (**C**O), 137.07 (Ar**C**), 133.03 (Ar**C**F, $^{4}J_{CF}$ = 3.1 Hz), 131.09 (Ar**C**H), 53.45 (**C**H$_2$), 53.18 (**C**H$_2$), 44.21 (**C**H$_2$), 43.37 (**C**H$_2$), 43.15 (**C**H$_2$), 34.98 (**C**H$_2$), 33.83 (**C**H$_2$), 30.77 (**C**H$_2$), 28.65 (**C**H$_2$), 22.77 (**C**H$_2$); δ_F (376 MHz, CDCl$_3$), three signals are visible in a 11:23:3 ratio: –114.72 (1F, m, ArF), –114.80 (1F, m, ArF, major rotamer), –115.07 (1F, m, ArF); HRMS (ESI): calcd. for $C_{28}H_{32}FN_3NaO_4$, 516.2269. Found: [MNa]$^+$, 516.2273 (–0.8 ppm error).

Lab notebook reference: KP580

1-Acryloyl-5-cyclopropyl-9-(4-fluorobenzyl)-1,5,9-triazacyclotetradecane-2,6,10-trione (5.3)

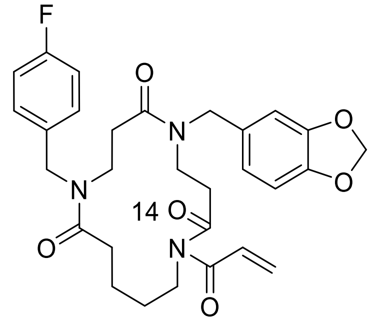


5.3

A stirring solution of **4.130** (278 mg, 0.713 mmol) and DIPEA (0.310 mL, 1.78 mmol) in THF (4.0 mL) was cooled to 0 °C. To this was added a 0 °C cooled solution of acryloyl chloride (0.087 mL, 1.07 mmol) in THF (1.0 mL) dropwise. Under an argon atmosphere this mixture was stirred at 0 °C for 2 hours. Afterwards it was allowed to warm to RT and stirred for a further 2 hours. At this stage additional THF (4 mL) was added to aid solubility and the mixture was allowed to stir for an additional 2 hours. The reaction mixture was then quenched with sat. aq. NH_4Cl (25 mL), extracted with Et_2O (15 mL), then the organic layer washed with washed with sat. aq. $NaHCO_3$ (2 × 25 mL). The organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:2 ethyl acetate: hexane → 2:1 ethyl acetate: hexane → ethyl acetate → 1:19 methanol: ethyl acetate) afforded the *title compound* a colourless oil (105 mg, 33%). This compound exists as a complex mixture of rotamers at RT in $CDCl_3$, with 4 main rotamers visible in a ratio of roughly 10:8:5:1, based on the ^{19}F NMR data; R_f 0.30 and 0.46 (1:4 methanol: ethyl acetate) – the 2 R_f values shows that rotamer interconversion is sufficiently slow that some rotamer separation is possible using chromatography, although for the purpose of this synthetic reaction, the product was isolated and used as a rotameric mixture; ν_{max}/cm^{-1} (thin film) 2937, 1682, 1639, 1509, 1405, 1367, 1221, 1148, 1064, 1036, 977, 917, 823, 798, 729, 646, 533, 499; δ_H (400 MHz, $CDCl_3$) 7.20 – 7.07 (2H, m, Ar**H**), 7.06 – 6.92 (2H, m, Ar**H**), 6.75 – 6.57 (1H, m, NCOC**H**CHH’), 6.43 – 6.32 (1H, m, NCOCHC**H**H’), 5.82 – 5.72 (1H, m, NCOCHCH**H’**), 4.86 – 4.47 (2H, m, ArC**H**$_2$), 3.74 – 3.47 (6H, m, C**H** (rotamer) and C**H**$_2$),3.03 – 2.87 (3H, m, C**H** (rotamer) and C**H**$_2$), 2.58 (1H, t, *J* = 6.8 Hz, C**H**$_2$), 2.54 – 2.28 (3H, m, C**H**$_2$), 1.72 – 1.45 (4H, m, C**H**$_2$), 0.39 – 0.27 (4H, m, cyclopropyl C**H**$_2$). For a diagnostic ^1H NMR signal for one of the individual rotamers: 2.53 (1H, tt, *J* = 6.8, 3.9 Hz, cyclopropyl C**H**); δ_C (100 MHz, $CDCl_3$) 175.5 (**C**O), 174.7 (**C**O), 174.2 (**C**O), 173.4 (**C**O), 172.9 (**C**O), 172.60 (**C**O), 172.54 (**C**O), 171.4 (**C**O), 168.9 (**C**O), 168.8 (**C**O), 162.28 (Ar**C**F, $^1J_{CF}$ = 245.5 Hz), 162.22 (Ar**C**F, $^1J_{CF}$ = 245.5 Hz), 162.15 (Ar**C**F, $^1J_{CF}$ = 245.5 Hz), 133.6 (Ar**C**, $^4J_{CF}$ = 3.2 Hz), 133.4 (Ar**C**, $^4J_{CF}$ = 3.2 Hz), 132.6 (Ar**C**, $^4J_{CF}$ = 3.2 Hz), 130.62 (NCO**C**HCHH’, one rotamer), 130.57 (NCO**C**HCHH’, two rotamers), 130.1 (NCOCH**C**HH’, two rotamers), 129.0 (NCOCH**C**HH’, one rotamer), 129.7 (2 × ArCH, $^3J_{CF}$ = 8.1 Hz), 128.3 (2 × Ar**C**H, $^3J_{CF}$ = 8.1 Hz), 128.0 (2 × Ar**C**H, $^3J_{CF}$ = 8.1 Hz), 116.0 (2 × Ar**C**H, $^2J_{CF}$ = 21.5 Hz), 115.8 (2 × Ar**C**H, $^2J_{CF}$ = 21.5 Hz), 115.6 (2 × Ar**C**H, $^2J_{CF}$ = 21.5 Hz), 53.6 (**C**H$_2$), 52.0 (**C**H), 51.8 (**C**H), 51.5 (**C**H$_2$), 50.8 (**C**H$_2$), 47.7 (**C**H$_2$), 44.30 (**C**H$_2$), 44.25 (**C**H$_2$), 43.8 (**C**H$_2$), 43.6 (**C**H$_2$), 42.9 (**C**H$_2$), 42.7 (**C**H$_2$), 41.8 (**C**H$_2$), 36.0 (**C**H$_2$), 35.6 (**C**H$_2$), 35.5 (**C**H), 33.4 (**C**H$_2$), 32.8 (**C**H$_2$), 32.7 (**C**H$_2$), 32.4 (**C**H$_2$), 32.3 (**C**H$_2$), 29.9 (**C**H), 29.0 (**C**H$_2$), 28.9 (**C**H$_2$), 28.4 (**C**H$_2$), 22.5 (**C**H$_2$), 22.35 (**C**H$_2$), 22.3 (**C**H$_2$), 9.7 (cyclopropyl **C**H$_2$), 7.1 (cyclopropyl **C**H$_2$, two rotamers); δ_F (376 MHz, CDCl$_3$), four major rotamers in a 10:1:8:5 ratio: –114.61 (1F, m, ArF, major rotamer), –114.78 (1F, m, ArF), –115.00 (1F, m, ArF), –115.17 (1F, m, ArF); HRMS (ESI): calcd. for $C_{24}H_{30}FN_3NaO_4$, 466.2113. Found: [MNa]$^+$, 466.2114 (–0.4 ppm error).

Lab notebook reference: KP571

1-Acryloyl-5-(benzo[*d*][1,3]dioxol-5-ylmethyl)-9-(4-fluorobenzyl)-1,5,9-triazacyclotetradecane-2,6,10-trione (5.4)



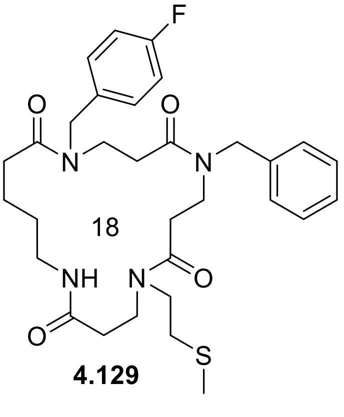
5.4

A stirring solution of **4.132** (73.1 mg, 0.151 mmol) and DIPEA (0.065 mL, 0.372 mmol) in DCM (2.5 mL) was cooled to 0 °C. To this was added a 0 °C cooled solution of acryloyl chloride (0.018 mL, 0.223 mmol) in DCM (0.5 mL) dropwise. Under an argon atmosphere this mixture was stirred at 0 °C for 2 hours. Afterwards it was allowed to warm to RT and stirred for a further 15 hours. The reaction mixture was then quenched with sat. aq. NH$_4$Cl (8 mL), extracted with Et$_2$O (10 mL), then the organic layer was washed with sat. aq. NaHCO$_3$ (2 × 5 mL). The organic extracts were dried over MgSO$_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO$_2$, 1:2 ethyl acetate: hexane → 2:1 ethyl acetate: hexane → ethyl acetate) afforded the *title compound* a colorless oil (22.0 mg, 27%). This compound exists as a complex mixture of rotamers at RT in CDCl$_3$, with 2 major rotameric forms (≈3:2) based on the carbonyl region of the ^{13}C NMR spectrum, and a third more minor rotamer based on the ^{19}F NMR data. Due to overlapping signals in the ^{1}H and ^{19}F NMR, it is difficult to confidently quote a rotamer ratio; R$_f$ 0.68 (1:9 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 2932, 1682, 1637, 1508, 1490, 1443, 1410, 1374, 1223, 1143, 1038, 923, 812, 732; δ_H (400 MHz, CDCl$_3$) 7.24 – 7.10 (2H, m, Ar**H**), 7.07 – 6.94 (2H, m, Ar**H**), 6.84 – 6.65 (3H, m, Ar**H** and C**H**CH$_2$), 6.63 – 6.57 (1H, m, Ar**H**), 6.37 (1H, dd, *J* =

16.8, 1.7 Hz, CHC**H**H’, major rotamer), 5.95 – 5.91 (2H, m, OC**H**$_2$O), 5.74 (1H, dd, J = 10.3, 1.7 Hz, CHCH**H**’, major rotamer), 4.83 – 4.46 (4H, m, ArC**H**$_2$), 3.92 – 3.57 (4H, m, C**H**$_2$), 3.42 (1H, br s, C**H**$_2$), 3.03 (1H, br s, C**H**$_2$), 2.91 – 2.67 (2H, m, C**H**$_2$), 2.53 – 2.33 (2H, m, C**H**$_2$), 1.89 – 1.48 (4H, m, C**H**$_2$). Diagnostic ^{1}H NMR signals for the minor rotamer: 6.34 (1H, dd, J = 16.8, 1.7 Hz, CHC**H**H’, minor rotamer), 5.73 (1H, dd, J = 10.4, 1.6 Hz, CHCH**H**’, minor rotamer [overlapping]); δ_C (100 MHz, CDCl$_3$) 175.5 (**C**O), 173.9 (**C**O), 173.7 (**C**O), 173.6 (**C**O), 172.4 (**C**O), 172.1 (**C**O), 169.2 (**C**O), 168.8 (**C**O), 162.3 (Ar**C**F, $^1J_{CF}$ = 246.0 Hz), 148.3 (Ar**C**OCH$_2$), 148.0 (Ar**C**OCH$_2$), 147.18 (Ar**C**OCH$_2$), 147.15 (Ar**C**OCH$_2$) 134.8 (**C**H$_2$), 133.1 (Ar**C**, $^4J_{CF}$ = 3.1 Hz), 133.0 (Ar**C**, $^4J_{CF}$ = 3.1 Hz), 132.12 (Ar**C**), 132.02 (**C**H$_2$), 131.6 (**C**H), 131.5 (**C**H), 131.3 (**C**H), 131.0 (Ar**C**), 129.9 (Ar**C**H, $^3J_{CF}$ = 8.2 Hz), 129.0 (**C**H$_2$), 128.9 (**C**H$_2$), 128.4 (Ar**C**H, $^3J_{CF}$ = 8.2 Hz), 128.3 (Ar**C**H, $^3J_{CF}$ = 8.2 Hz), 127.6 (Ar**C**H), 121.8 (Ar**C**H), 119.8 (Ar**C**H), 115.92 (Ar**C**H, $^2J_{CF}$ = 21.5 Hz), 115.89 (Ar**C**H, $^2J_{CF}$ = 21.5 Hz), 108.8 (Ar**C**H), 108.6 (Ar**C**H), 108.3 (Ar**C**H), 107.0 (Ar**C**H), 106.6 (Ar**C**H), 101.3 (O**C**H$_2$O), 101.2 (O**C**H$_2$O), 53.8 (**C**H$_2$), 53.6 (**C**H$_2$), 53.2 (**C**H$_2$), 50.0 (**C**H$_2$), 44.6 (**C**H$_2$), 44.5 (**C**H$_2$), 43.9 (**C**H$_2$), 43.7 (**C**H$_2$), 43.2 (**C**H$_2$), 36.7 (**C**H$_2$), 35.2 (**C**H$_2$), 34.1 (**C**H$_2$), 31.6 (**C**H$_2$), 31.2 (**C**H$_2$), 31.1 (**C**H$_2$), 29.8 (**C**H$_2$), 28.9 (**C**H$_2$), 27.5 (**C**H$_2$), 23.0 (**C**H$_2$), 21.6 (**C**H$_2$); δ_F (376 MHz, CDCl$_3$), three signals in a 20:14:1 ratio: –114.74 (1F, m, ArF), –114.77 (1F, m, ArF, major rotamer),–115.05 (1F, m, ArF), –115.19 (1F, m, ArF); HRMS (ESI): calcd. for $C_{29}H_{32}FN_3NaO_6$, 560.2167. Found: [MNa]$^+$, 560.2185 (–3.1 ppm error).

Lab notebook reference: KP567

9-Benzyl-13-(4-fluorobenzyl)-5-(2-(methylthio)ethyl)-1,5,9,13-tetraazacyclooctadecane-2,6,10,14-tetraone (4.129)



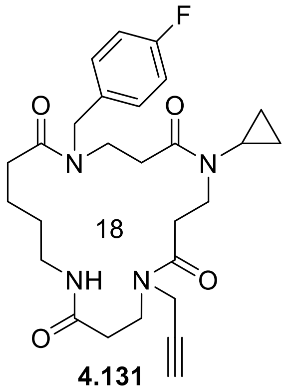
4.129

To a solution of **5.2** (258 mg, 0.523 mmol) in dry methanol (1.04 mL), was added 2-(methylthio)ethylamine (53 µL, 0.575 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 ethyl acetate: hexane → ethyl acetate → 1:19 methanol: ethyl acetate → 1:9 methanol: ethyl acetate) afforded the *title compound* as a white solid (196 mg, 64%). This compound exists as a complex mixture of rotamers at RT in CDCl$_3$, with 8 rotameric forms observable in the ^{19}F NMR data, and 32 (*i.e.* 4 × 8) signals consistent with CO groups in the ^{13}C NMR. Due to overlapping signals in the NMR data, it is not possible to confidently quote a rotamer ratio; m.p. 43–57 °C; R$_f$ 0.11 (1:9 methanol: ethyl acetate); ν$_{max}$/cm^{-1} (thin film) 3310, 2928, 1626, 1551, 1509, 1424, 1364, 1220, 1157, 921, 823, 730, 700, 499; δ$_H$ (400 MHz, CDCl$_3$) 8.08 (1H, br t, *J* = 4.6 Hz, N**H**), 7.61 (1H, br t, *J* = 5.0 Hz, N**H**, rotamer), 7.52 (1H, br t, *J* = 5.6 Hz, N**H**), 7.47 (1H, br t, *J* = 6.0 Hz, N**H**), 7.42 – 6.89 (9H, m, Ar**H**), 4.86 – 4.35 (4H, m, 2 × ArC**H$_2$**), 3.81 – 3.13 (10H, m, 5 × C**H$_2$**), 2.95 – 2.26 (10H, m, 5 × C**H$_2$**), 2.16 – 2.02 (3H, m, C**H$_3$**), 1.91 – 1.44 (4H, m, 2 × C**H$_2$**); δ$_C$ (100 MHz, CDCl$_3$) 174.21 (**C**O), 174.10 (**C**O), 174.02 (**C**O), 173.94 (**C**O), 173.78 (**C**O), 173.70 (**C**O), 173.41 (**C**O), 173.11 (**C**O), 172.69 (**C**O), 172.61 (**C**O), 172.16 (**C**O), 172.08 (**C**O), 172.05 (**C**O), 171.88 (**C**O), 171.52 (**C**O), 171.44 (**C**O), 171.41 (**C**O), 171.29 (**C**O), 171.24 (**C**O), 171.19 (**C**O), 171.16 (**C**O), 171.11 (**C**O), 170.97 (**C**O), 170.72 (**C**O), 170.68 (**C**O), 170.62 (**C**O), 170.49 (**C**O), 170.47 (**C**O), 170.44 (**C**O), 170.32 (**C**O), 170.12 (**C**O), 169.96 (**C**O), 161.97 (Ar**C**F, $^1J_{CF}$ = 246.0 Hz), 161.92 (Ar**C**F, $^1J_{CF}$ = 246.0 Hz), 161.88 (Ar**C**F, $^1J_{CF}$ = 246.0 Hz), 161.83 (Ar**C**F, $^1J_{CF}$ = 246.0 Hz), 161.80 (Ar**C**F, $^1J_{CF}$ = 246.0 Hz), 161.73 (Ar**C**F, $^1J_{CF}$ = 246.0 Hz), 137.51 (Ar**C**), 137.38 (Ar**C**), 137.34 (Ar**C**), 137.13 (Ar**C**), 136.96 (Ar**C**), 136.86 (Ar**C**), 136.78 (Ar**C**), 136.38 (Ar**C**), 136.31 (Ar**C**), 135.84 (Ar**C**), 135.71 (Ar**C**), 133.64 (Ar**C**F, $^4J_{CF}$ = 3.0 Hz), 133.43 (Ar**C**F, $^4J_{CF}$ = 3.0 Hz), 133.18 (Ar**C**F, $^4J_{CF}$ = 3.0 Hz), 133.07 (Ar**C**F, $^4J_{CF}$ = 3.0 Hz), 132.70 (Ar**C**F, $^4J_{CF}$ = 3.0 Hz), 132.32 (Ar**C**F, $^4J_{CF}$ = 3.0 Hz), 132.19 (Ar**C**F, $^4J_{CF}$ = 3.0 Hz), 132.10 (Ar**C**F, $^4J_{CF}$ = 3.0 Hz), 129.63 (Ar**C**H, $^3J_{CF}$ = 8.1 Hz), 129.48 (Ar**C**H), 129.43 (Ar**C**H), 129.39 (Ar**C**H), 129.13 (Ar**C**H, $^3J_{CF}$ = 8.1 Hz), 128.98 (Ar**C**H), 128.90 (Ar**C**H), 128.86 (Ar**C**H), 128.68 (Ar**C**H), 128.63 (Ar**C**H), 128.52 (Ar**C**H), 128.43 (Ar**C**H), 128.33 (Ar**C**H), 128.06 (Ar**C**H, $^3J_{CF}$ = 8.1 Hz), 127.94 (Ar**C**H), 127.88 (Ar**C**H), 127.82 (Ar**C**H), 127.80 (Ar**C**H), 127.71 (Ar**C**H), 127.50 (Ar**C**H), 127.30 (Ar**C**H), 127.14 (Ar**C**H), 126.27 (Ar**C**H), 126.08 (Ar**C**H), 125.91 (Ar**C**H), 125.75 (Ar**C**H), 125.73 (Ar**C**H), 126.27 (Ar**C**H), 126.08 (Ar**C**H), 125.91 (Ar**C**H), 125.75 (Ar**C**H), 115.65 (Ar**C**H, $^2J_{CF}$ = 21.1 Hz), 115.58 (Ar**C**H, $^2J_{CF}$ = 21.1 Hz), 115.54 (Ar**C**H, $^2J_{CF}$ = 21.1 Hz), 115.23 (Ar**C**H, $^2J_{CF}$ = 21.1 Hz), 115.54 (Ar**C**H, $^2J_{CF}$ = 21.1 Hz), 115.23 (Ar**C**H, $^2J_{CF}$ = 21.1 Hz), 115.12 (Ar**C**H, $^2J_{CF}$ = 21.1 Hz), 114.99 (Ar**C**H, $^2J_{CF}$ = 21.1 Hz), 55.86 (**C**H$_2$), 53.22 (**C**H$_2$), 52.93 (**C**H$_2$), 52.67 (**C**H$_2$), 52.33 (**C**H$_2$), 51.92 (**C**H$_2$), 51.83 (**C**H$_2$), 51.23 (**C**H$_2$), 49.96 (**C**H$_2$), 49.11 (**C**H$_2$), 49.01 (**C**H$_2$), 48.81 (**C**H$_2$), 48.59 (**C**H$_2$), 48.28 (**C**H$_2$), 48.25 (**C**H$_2$), 48.10 (**C**H$_2$), 47.80 (**C**H$_2$), 47.49 (**C**H$_2$), 47.18 (**C**H$_2$), 46.91 (**C**H$_2$), 46.79 (**C**H$_2$), 46.42 (**C**H$_2$), 45.89 (**C**H$_2$), 45.60 (**C**H$_2$), 45.45 (**C**H$_2$), 45.33 (**C**H$_2$), 45.02 (**C**H$_2$), 44.89 (**C**H$_2$), 44.62 (**C**H$_2$), 44.26 (**C**H$_2$), 44.17 (**C**H$_2$), 44.03 (**C**H$_2$), 43.75 (**C**H$_2$), 43.65 (**C**H$_2$), 43.58 (**C**H$_2$), 43.54 (**C**H$_2$), 43.48 (**C**H$_2$), 43.36 (**C**H$_2$), 43.23 (**C**H$_2$), 43.11 (**C**H$_2$), 42.87 (**C**H$_2$), 42.68 (**C**H$_2$), 42.47 (**C**H$_2$), 42.33 (**C**H$_2$), 42.25 (**C**H$_2$), 41.20 (**C**H$_2$), 40.24 (**C**H$_2$), 39.41 (**C**H$_2$), 39.22 (**C**H$_2$), 39.13 (**C**H$_2$), 38.66 (**C**H$_2$), 38.58 (**C**H$_2$), 38.20 (**C**H$_2$), 38.06 (**C**H$_2$), 37.56 (**C**H$_2$), 37.51 (**C**H$_2$), 37.33 (**C**H$_2$), 36.91 (**C**H$_2$), 36.20 (**C**H$_2$), 35.33 (**C**H$_2$), 35.27 (**C**H$_2$), 34.93 (**C**H$_2$), 34.79 (**C**H$_2$), 34.15 (**C**H$_2$), 33.99 (**C**H$_2$), 33.52 (**C**H$_2$), 33.44 (**C**H$_2$), 33.23 (**C**H$_2$), 33.05 (**C**H$_2$), 32.78 (**C**H$_2$), 32.74 (**C**H$_2$), 32.64 (**C**H$_2$), 32.53

(**C**H$_2$), 32.49 (**C**H$_2$), 32.41 (**C**H$_2$), 32.32 (**C**H$_2$), 32.24 (**C**H$_2$), 32.14 (**C**H$_2$), 32.05 (**C**H$_2$), 31.98 (**C**H$_2$), 31.81 (**C**H$_2$), 31.75 (**C**H$_2$), 31.65 (**C**H$_2$), 31.56 (**C**H$_2$), 31.52 (**C**H$_2$), 31.44 (**C**H$_2$), 31.34 (**C**H$_2$), 31.24 (**C**H$_2$), 31.20 (**C**H$_2$), 31.05 (**C**H$_2$), 30.93 (**C**H$_2$), 30.76 (**C**H$_2$), 30.67 (**C**H$_2$), 30.58 (**C**H$_2$), 29.34 (**C**H$_2$), 28.76 (**C**H$_2$), 28.56 (**C**H$_2$), 27.96 (**C**H$_2$), 27.87 (**C**H$_2$), 27.73 (**C**H$_2$), 27.61 (**C**H$_2$), 27.41 (**C**H$_2$), 27.20 (**C**H$_2$), 27.03 (**C**H$_2$), 23.60 (**C**H$_2$), 23.12 (**C**H$_2$), 22.99 (**C**H$_2$), 22.68 (**C**H$_2$), 22.18 (**C**H$_2$), 22.08 (**C**H$_2$), 22.03 (**C**H$_2$), 20.65 (**C**H$_2$), 20.49 (**C**H$_2$), 15.58 (**C**H$_3$), 15.22 (**C**H$_3$); δ_F (376 MHz, CDCl$_3$), eight signals in a 14:24:19:7:16:7:7:6 ratio: –114.33 (1F, m, ArF), –114.47 (1F, m, ArF, major rotamer), –114.59 (1F, m, ArF), –114.72 (1F, m, ArF), –114.79 (1F, m, ArF), –115.04 (1F, m, ArF), –115.15 (1F, m, ArF), –115.47 (1F, m, ArF); HRMS (ESI): calcd. for $C_{31}H_{41}FN_4NaO_4S$, 607.2725. Found: [MNa]$^+$, 607.2708 (2.8 ppm error).

Lab notebook reference: KP581

9-Cyclopropyl-13-(4-fluorobenzyl)-5-(prop-2-yn-1-yl)-1,5,9,13-tetraazacyclooctadecane-2,6,10,14-tetraone (4.131)



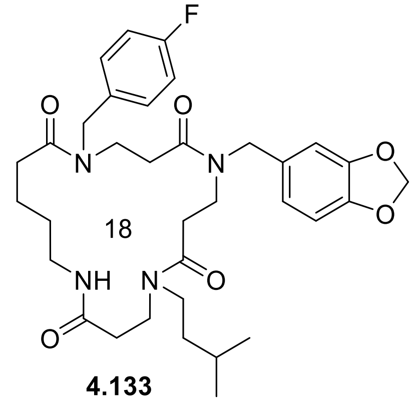
4.131

To a solution of **5.3** (98.1 mg, 0.221 mmol) in dry methanol (0.44 mL), was added propargyl amine (16 µL, 0.243 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 ethyl acetate: hexane → ethyl acetate → 1:19 methanol: ethyl acetate → 1:9 methanol: ethyl acetate → 1:6 methanol: ethyl acetate → 1:4 methanol: ethyl acetate) afforded the *title compound* as a colourless oil (27.6 mg, 25%). This compound exists as a complex mixture of rotamers at RT in CDCl$_3$, with 6 rotameric forms observable in the ^{19}F NMR data. Due to overlapping signals in the NMR data, it is not possible to confidently quote a rotamer ratio; R$_f$ 0.33 (1:4 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3295, 2941, 1733, 1634, 1552, 1510, 1438, 1369, 1219, 1017, 826, 731; δ_H (700 MHz, CDCl$_3$), 7.23 – 7.13 (2H, m, Ar**H**), 7.10 (1H, t, *J* = 6.6 Hz, N**H**, rotamer), 7.06 – 6.95 (2H, m, Ar**H**), 6.92 (1H, t, *J* = 6.0 Hz, N**H**, rotamer), 6.66 (1H, t, *J* = 5.5 Hz, N**H**, rotamer), 4.63 – 4.48 (2H, m, C**H**$_2$), 4.22 – 4.11 (2H, m, C**H**$_2$), 3.81 – 3.50 (4H, m, C**H**$_2$), 3.45 – 3.13 (2H, m, C**H**$_2$), 2.96 – 2.16 (12H, m, C**H**$_2$ and C**H**), 1.87 – 1.43

(4H, m, C**H**$_2$), 0.96 – 0.55 (4H, m, cyclopropyl C**H**$_2$); δ_C (176 MHz, CDCl$_3$), 174.36 (**C**O), 174.10 (**C**O), 173.94 (**C**O), 173.81 (**C**O), 173.78 (**C**O), 173.71 (**C**O), 172.58 (**C**O), 172.49 (**C**O), 171.64 (**C**O), 171.54 (**C**O), 171.50 (**C**O), 171.48 (**C**O), 171.06 (**C**O), 170.37 (**C**O), 170.26 (**C**O), 169.89 (**C**O), 162.35 (Ar**C**F, $^1J_{CF}$ = 246.0 Hz), 162.31 (Ar**C**F, $^1J_{CF}$ = 246.0 Hz), 162.24 (Ar**C**F, $^1J_{CF}$ = 246.0 Hz), 162.20 (Ar**C**F, $^1J_{CF}$ = 246.0 Hz), 162.18 (Ar**C**F, $^1J_{CF}$ = 246.0 Hz), 133.99 (Ar**C**F, $^4J_{CF}$ = 3.2 Hz), 133.91 (Ar**C**F, $^4J_{CF}$ = 3.2 Hz), 133.39 (Ar**C**F), 132.70 (Ar**C**F, $^4J_{CF}$ = 3.2 Hz), 132.54 (ArCF), 129.96 (Ar**C**H, $^3J_{CF}$ = 8.0 Hz), 129.50 (Ar**C**H, $^3J_{CF}$ = 8.0 Hz), 129.22 (Ar**C**H, $^3J_{CF}$ = 8.0 Hz), 128.32 (Ar**C**H, $^3J_{CF}$ = 8.0 Hz), 128.23 (Ar**C**H, $^3J_{CF}$ = 8.0 Hz), 128.09 (Ar**C**H, $^3J_{CF}$ = 8.0 Hz), 116.05 (Ar**C**H, $^2J_{CF}$ = 21.5 Hz), 116.02 (Ar**C**H, $^2J_{CF}$ = 21.5 Hz), 115.95 (Ar**C**H, $^2J_{CF}$ = 21.5 Hz), 115.60 (Ar**C**H, $^2J_{CF}$ = 21.5 Hz), 115.55 (Ar**C**H, $^2J_{CF}$ = 21.5 Hz), 79.22 (**C**CH), 78.98 (**C**CH), 78.80 (**C**CH), 78.63 (**C**CH), 72.85 (C**C**H), 72.45 (C**C**H), 72.06 (C**C**H), 71.89 (C**C**H), 51.50 (**C**H$_2$), 51.44 (**C**H$_2$), 50.05 (**C**H$_2$), 47.94 (**C**H$_2$), 47.82 (**C**H$_2$), 45.92 (**C**H$_2$), 45.52 (**C**H$_2$), 45.48 (**C**H$_2$), 43.99 (**C**H$_2$), 43.93 (**C**H$_2$), 43.82 (**C**H$_2$), 43.64 (**C**H$_2$), 43.15 (**C**H$_2$), 42.97 (**C**H$_2$), 42.47 (**C**H$_2$), 40.58 (**C**H$_2$), 39.65 (**C**H$_2$), 39.55 (**C**H$_2$), 39.43 (**C**H$_2$), 39.32 (**C**H$_2$), 39.09 (**C**H$_2$), 37.53 (**C**H$_2$), 37.22 (**C**H$_2$), 35.75 (**C**H$_2$), 35.11 (**C**H$_2$), 34.81 (**C**H$_2$), 33.42 (**C**H$_2$), 33.27 (**C**H$_2$), 33.25 (**C**H$_2$), 32.84 (**C**H$_2$), 32.73 (**C**H$_2$), 32.69 (**C**H$_2$), 32.64 (**C**H$_2$), 32.40 (**C**H$_2$), 32.11 (**C**H$_2$), 31.94 (**C**H$_2$), 31.87 (**C**H$_2$), 31.51 (**C**H$_2$), 30.90 (**C**H$_2$), 30.53 (**C**H), 30.37 (**C**H), 30.31 (**C**H), 29.79 (**C**H$_2$), 29.71 (**C**H), 28.67 (**C**H$_2$), 28.46 (**C**H$_2$), 28.30 (**C**H$_2$), 27.96 (**C**H$_2$), 27.24 (**C**H$_2$), 23.40 (**C**H$_2$), 22.67 (**C**H$_2$), 22.58 (**C**H$_2$), 22.31 (**C**H$_2$), 9.87 (cyclopropyl **C**H$_2$), 9.67 (cyclopropyl **C**H$_2$), 9.31 (cyclopropyl **C**H$_2$), 9.25 (cyclopropyl **C**H$_2$); δ_F (376 MHz, CDCl$_3$), six rotamers in a 7:5:9:1:12:4 ratio: –114.42 (1F, m, ArF), –114.57 (1F, m, ArF), –114.65 (1F, m, ArF), –114.80 (1F, m, ArF), –114.92 (1F, m, ArF, major rotamer), –115.08 (1F, m, ArF); HRMS (ESI): calcd. for $C_{27}H_{35}FN_4NaO_4$, 521.2535. Found: [MNa]$^+$, 521.2536 (–0.3 ppm error).

Lab notebook reference: KP572

9-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-13-(4-fluorobenzyl)-5-isopentyl-1,5,9,13-tetraazacyclooctadecane-2,6,10,14-tetraone (4.133)



4.133

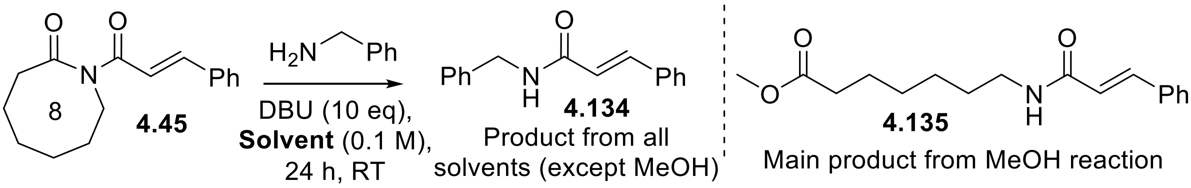
To a solution of **5.4** (53.3 mg, 0.099 mmol) in dry methanol (0.24 mL), was added isopentylamine (15 µL, 0.130 mmol) in a single portion. The reaction mixture was allowed to stir for 4 h at RT and then the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 ethyl acetate: hexane → ethyl acetate → 1:19 methanol: ethyl acetate → 1:9 methanol: ethyl acetate) afforded the *title compound* as a colourless oil (37.1 mg, 60%); R_f 0.45 (1:4 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3308, 2942, 1628, 1557, 1508, 1489, 1442, 1368, 1243, 1221, 1097, 1038, 924, 813, 731; δ_H (600 MHz, $CDCl_3$) 8.01 (1H, br t, *J* = 5.1 Hz N**H**, rotamer), 7.40 – 7.36 (1H, m, N**H**, rotamer), 7.34 (1H, br t, *J* = 5.6 Hz N**H**, rotamer), 7.25 – 7.07 (2H, m, Ar**H**), 7.07 – 6.90 (2H, m, Ar**H**), 6.81 – 6.44 (3H, m, Ar**H**), 5.96 – 5.87 (2H, m, OC**H₂**O), 4.77 – 4.19 (4H, m, 2 × ArC**H₂**), 3.76 – 3.46 (6H, m, 3 × C**H₂**), 3.40 – 2.98 (4H, m, 2 × C**H₂**), 2.87 – 2.24 (8H, m, 4 × C**H₂**), 1.86 – 1.12 (7H, m, 3 × C**H₂** and C**H**, [overlapping]), 0.92 – 0.83 (6H, m, 2 × C**H₃**); δ_C (151 MHz, $CDCl_3$) 174.49 (**C**O), 174.14 (**C**O), 174.05 (**C**O), 173.96 (**C**O), 173.86 (**C**O), 173.84 (**C**O), 173.39 (**C**O), 173.60 (**C**O), 173.39 (**C**O), 173.12 (**C**O), 172.71 (**C**O), 172.64 (**C**O), 172.32 (**C**O), 172.14 (**C**O), 172.02 (**C**O), 171.98 (**C**O), 171.63 (**C**O), 171.46 (**C**O), 171.39 (**C**O), 171.22 (**C**O), 171.01 (**C**O), 170.85 (**C**O), 170.75 (**C**O), 170.55 (**C**O), 170.53 (**C**O), 170.43 (**C**O), 170.37 (**C**O), 170.30 (**C**O), 170.19 (**C**O), 170.04 (**C**O), 170.03 (**C**O), 169.77 (**C**O), 162.36 (Ar**C**F, $^1J_{CF}$ = 246.5 Hz), 162.34 (Ar**C**F, $^1J_{CF}$ = 246.5 Hz), 162.30 (Ar**C**F, $^1J_{CF}$ = 246.5 Hz), 162.23 (Ar**C**F, $^1J_{CF}$ = 246.5 Hz), 148.55 (Ar**C**OCH₂), 148.33 (Ar**C**OCH₂), 148.27 (Ar**C**OCH₂), 148.20 (Ar**C**OCH₂), 148.05 (Ar**C**OCH₂), 147.94 (Ar**C**OCH₂), 147.51 (Ar**C**OCH₂), 147.29 (Ar**C**OCH₂), 147.19 (Ar**C**OCH₂), 147.10 (Ar**C**OCH₂), 147.06 (Ar**C**OCH₂), 147.00 (Ar**C**OCH₂), 133.90 (Ar**C**), 133.74 (Ar**C**F, $^4J_{CF}$ = 3.0 Hz), 133.50 (Ar**C**F, $^4J_{CF}$ = 3.0 Hz), 133.41 (Ar**C**), 132.83 (Ar**C**), 132.59 (Ar**C**F, $^4J_{CF}$ = 3.0 Hz),1 32.38 (Ar**C**F, $^4J_{CF}$ = 3.0 Hz), 132.34 (Ar**C**F, $^4J_{CF}$ = 3.0 Hz),131.83 (Ar**C**), 131.72 (Ar**C**), 131.52 (Ar**C**), 131.18 (Ar**C**), 130.71 (Ar**C**), 130.35 (Ar**C**), 130.03 (Ar**C**H, $^3J_{CF}$ = 8.1 Hz), 129.86 (Ar**C**H, $^3J_{CF}$ = 8.1 Hz), 129.83 (Ar**C**H, $^3J_{CF}$ = 8.1 Hz), 129.70 (Ar**C**), 129.53 (Ar**C**), 129.48 (Ar**C**H, $^3J_{CF}$ = 8.1 Hz), 129.31 (Ar**C**H, $^3J_{CF}$ = 8.1 Hz), 128.31 (Ar**C**H, $^3J_{CF}$ = 8.1 Hz), 128.20 (Ar**C**H), 128.15 (Ar**C**H), 128.10 (Ar**C**H), 128.05 (Ar**C**H), 121.68 (Ar**C**H), 121.61 (Ar**C**H), 121.43 (Ar**C**H), 121.01 (Ar**C**H), 119.84 (Ar**C**H), 119.54 (Ar**C**H), 119.49 (Ar**C**H), 119.42 (Ar**C**H), 116.05 (Ar**C**H, $^2J_{CF}$ = 21.6 Hz), 116.02 (Ar**C**H, $^2J_{CF}$ = 21.6 Hz), 115.95 (Ar**C**H, $^2J_{CF}$ = 21.6 Hz), 115.62 (Ar**C**H, $^2J_{CF}$ = 21.6 Hz), 115.57 (Ar**C**H, $^2J_{CF}$ = 21.6 Hz), 115.46 (Ar**C**H, $^2J_{CF}$ = 21.6 Hz), 108.80 (Ar**C**H), 108.76 (Ar**C**H), 108.66 (Ar**C**H), 108.64 (Ar**C**H), 108.59 (Ar**C**H), 108.55 (Ar**C**H), 108.34 (Ar**C**H), 108.26 (Ar**C**H), 108.21 (Ar**C**H), 107.12 (Ar**C**H), 106.94 (Ar**C**H), 106.79 (Ar**C**H), 106.60 (Ar**C**H), 106.55 (Ar**C**H), 115.53 (O**C**H$_2$O), 115.38 (O**C**H$_2$O), 101.46 (O**C**H$_2$O), 101.43 (O**C**H$_2$O), 101.29 (O**C**H$_2$O), 101.26 (O**C**H$_2$O), 101.22 (O**C**H$_2$O), 101.13 (O**C**H$_2$O), 101.06 (O**C**H$_2$O), 53.52 (**C**H$_2$), 53.12 (**C**H$_2$), 53.03 (**C**H$_2$), 52.62 (**C**H$_2$), 52.50 (**C**H$_2$), 52.27 (**C**H$_2$), 52.16 (**C**H$_2$), 52.06 (**C**H$_2$), 51.81 (**C**H$_2$), 51.53 (**C**H$_2$), 50.56 (**C**H$_2$), 49.80 (**C**H$_2$), 49.42 (**C**H$_2$), 49.26 (**C**H$_2$), 49.11 (**C**H$_2$), 48.63 (**C**H$_2$), 48.27 (**C**H$_2$), 47.99 (**C**H$_2$), 47.85 (**C**H$_2$), 47.68 (**C**H$_2$), 47.23 (**C**H$_2$), 46.94 (**C**H$_2$), 46.74 (**C**H$_2$), 46.33 (**C**H$_2$), 46.15 (**C**H$_2$), 45.82 (**C**H$_2$), 45.34 (**C**H$_2$), 45.25 (**C**H$_2$), 44.96 (**C**H$_2$), 44.89 (**C**H$_2$), 44.85 (**C**H$_2$), 44.74 (**C**H$_2$), 44.52 (**C**H$_2$), 44.25 (**C**H$_2$), 44.09 (**C**H$_2$), 44.04 (**C**H$_2$), 43.85 (**C**H$_2$), 43.74 (**C**H$_2$), 43.68 (**C**H$_2$), 43.52 (**C**H$_2$), 43.23 (**C**H$_2$), 43.07 (**C**H$_2$), 42.98 (**C**H$_2$), 42.77 (**C**H$_2$), 42.39 (**C**H$_2$), 41.88 (**C**H$_2$), 39.65 (**C**H$_2$), 39.51 (**C**H$_2$), 39.18 (**C**H$_2$), 38.94 (**C**H$_2$), 38.49 (**C**H$_2$), 38.34 (**C**H$_2$), 38.07 (**C**H$_2$), 37.83 (**C**H$_2$), 37.68 (**C**H$_2$), 37.64 (**C**H$_2$), 37.52 (**C**H$_2$), 37.28 (**C**H$_2$), 36.96 (**C**H$_2$), 36.75 (**C**H$_2$), 36.68 (**C**H$_2$), 36.57 (**C**H$_2$), 36.22 (**C**H$_2$), 35.88 (**C**H$_2$), 35.86 (**C**H$_2$), 35.79 (**C**H$_2$), 35.37 (**C**H$_2$), 35.12 (**C**H$_2$), 33.60 (**C**H$_2$), 33.52 (**C**H$_2$), 33.46 (**C**H$_2$), 33.21 (**C**H$_2$), 33.11 (**C**H$_2$), 32.96 (**C**H$_2$), 32.83 (**C**H$_2$), 32.65 (**C**H$_2$), 32.53 (**C**H$_2$), 32.31 (**C**H$_2$), 32.19 (**C**H$_2$), 32.12 (**C**H$_2$), 32.02 (**C**H$_2$), 31.98 (**C**H$_2$), 31.94 (**C**H$_2$), 31.91 (**C**H$_2$), 31.84 (**C**H$_2$), 31.69 (**C**H$_2$), 31.34 (**C**H$_2$), 31.10 (**C**H$_2$), 30.95 (**C**H$_2$), 29.69 (**C**H$_2$), 29.07 (**C**H$_2$), 28.78 (**C**H$_2$), 28.12 (**C**H$_2$), 27.95 (**C**H$_2$), 27.74 (**C**H$_2$), 27.23 (**C**H$_2$), 27.05 (**C**H$_2$), 26.38 (**C**H), 26.32 (**C**H), 26.23 (**C**H), 26.14 (**C**H), 26.10 (**C**H), 26.04 (**C**H), 26.00 (**C**H), 25.97 (**C**H), 23.87 (**C**H$_2$), 23.48 (**C**H$_2$), 23.25 (**C**H$_2$), 22.97 (**C**H$_2$), 22.61 (**C**H$_3$), 22.59 (**C**H$_3$), 22.48 (**C**H$_3$), 22.42 (**C**H$_3$), 22.39 (**C**H$_2$), 20.77 (**C**H$_2$); δ_F (376 MHz, CDCl$_3$), eight rotamers in a 42:8:14:13:6:8:5:3 ratio: −114.34 (1F, m, ArF, major rotamer), −114.50 (1F, m, ArF), −114.57 (1F, m, ArF), −114.71 (1F, m, ArF), −114.83 (1F, m, ArF), −115.12 (1F, m, ArF), −115.19 (1F, m, ArF), −115.50 (1F, m, ArF). HRMS (ESI): calcd. for $C_{34}H_{45}FN_4NaO_6$, 647.3215. Found: [MNa]$^+$, 647.3223 (–1.2 ppm error).

NMR data for were also collected in d$_6$-DMSO at 120 °C to reduce the number of rotameric forms, leading greatly simplified NMR spectra:

δ_H (500 MHz, d$_6$-DMSO, 120 °C) 2 major rotamers were observed under these conditions, with most signals broadened; 7.60 (1H, br s, N**H**, minor rotamer), 7.52 (1H, br s, N**H**, major rotamer), 7.31 – 7.23 (2H, m, Ar**H**), 7.15 – 7.06 (2H, m, Ar**H**), 6.65 – 6.68 (3H, m, Ar**H**), 5.96 (2H, s, OC**H$_2$**O), 4.60 – 4.52 (2H, m, ArC**H$_2$**), 4.47 – 4.41 (2H, m, ArC**H$_2$**), 3.65 – 3.43 (6H, m, 3 × C**H$_2$**), 3.30 – 3.20 (2H, m, C**H$_2$**), 3.19 – 3.05 (3H, m, 1.5 × C**H$_2$**), 2.72 – 2.53 (3H, m, 1.5 × C**H$_2$**), 2.45 – 2.30 (4H, m, 2 × C**H$_2$**), 1.68 – 1.44 (4H, m, 2 × C**H$_2$**), [overlapping]), 1.54 (1H, dt, *J* = 13.4, 6.7 Hz, C**H**, [overlapping]), 1.40 – 1.32 (2H, m, C**H$_2$**), 0.91 (6H, d, *J* = 6.7 Hz, 2 × C**H$_3$**); Diagnostic ^{13}C resonances are provided; there is clear evidence for rotemric broadening in the ^{13}C NMR spectrum, which explains why all carbons are not accounted for: δ_C (126 MHz, d$_6$-DMSO, 120 °C); 173.1 (**C**O), 171.1 (**C**O), 170.6 (**C**O), 162.0 (Ar**C**F, $^1J_{CF}$ = 243.2 Hz), 148.1 (Ar**C**OCH$_2$), 147.0 (Ar**C**OCH$_2$), 135.0 (Ar**C**), 129.7 (Ar**C**H), 115.53 (Ar**C**H, $^2J_{CF}$ = 21.3 Hz), 115.46 (Ar**C**H, $^2J_{CF}$ = 21.3 Hz), 108.5 (Ar**C**H), 101.3 (O**C**H$_2$O), 43.8 (**C**H$_2$), 32.2 (**C**H$_2$), 26.1 (**C**H), 22.7 (**C**H$_3$); δ_F (471 MHz, d$_6$-DMSO, 120 °C) two rotamers (broadened, and overlapping) in a 8:5 ratio: −115.99 (1F, m, ArF, major rotamer), −116.07 (1F, m, ArF).

Lab notebook reference: KP568

Methyl 7-cinnamamidoheptanoate (4.135) and (*E*)-*N*-benzylcinnamamide (4.134)



To a vial containing **4.45** (0.500 mmol) was added solvent (5 mL), benzyl amine (55 µL, 0.500 mmol, 1 eq.), and DBU (0.747 mL, 5.00 mmol, 10 eq.), and the reaction mixture allowed to stir for 24 h at RT. The solvent was then removed *in vacuo* and the reaction mixture diluted with DCM (5 mL) and washed with 10% aq. HCl (5 mL). The organic layer was dried over MgSO$_4$ and the solvent removed *in vacuo*. The reaction mixture was submitted for ^{1}H NMR, without further purification. For each solvent tested in this screen (except for methanol), **4.134** was the predominant compound detected. For the reaction in methanol, the main compound detected was **4.135**. For a list of solvents tested, see Figure 4.4 in Section 4.4.5 on page 124.

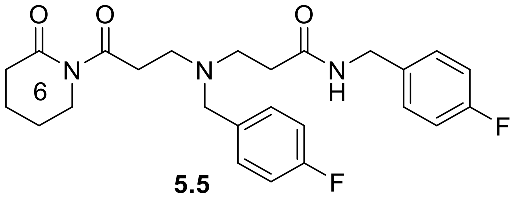
Data for (*E*)-*N*-benzylcinnamamide (**4.134**): δ_H (400 MHz, CDCl$_3$) 7.63 (1H, d, J = 15.6 Hz, ArC**H**CHCON), 7.43 – 7.38 (2H, m, Ar**H**), 7.31 – 7.19 (3H, m, Ar**H**), 6.98 (2H, br t, J = 5.9 Hz, N**H**), 6.55 (1H, d, J = 15.6 Hz, ArCHC**H**CON), 4.47 (2H, d, J = 5.9 Hz, C**H$_2$**); δ_C (100 MHz, CDCl$_3$) 166.2 (**C**O), 141.1 (ArC**H**CHCON), 138.3 (Ar**C**), 134.8 (Ar**C**), 129.6 (Ar**C**H), 128.8 (2 × Ar**C**H), 128.7 (2 × Ar**C**H), 127.82 (2 × Ar**C**H), 128.77 (2 × Ar**C**H), 127.4 (Ar**C**H), 120.8 (ArCHC**H**CON), 43.7 (**C**H$_2$).

Lab notebook reference: KP167_A

Data for methyl 7-cinnamamidoheptanoate (**4.135**): δ_H (400 MHz, CDCl$_3$) 7.90 (1H, d, J = 15.9 Hz, ArC**H**CHCON), 7.56 – 7.48 (2H, m, Ar**H**), 7.40 – 7.28 (3H, m, Ar**H**), 6.81 (1H, d, J = 15.9 Hz, ArCHC**H**CON), 6.59 (1H, br s, N**H**), 3.64 (3H, s, C**H$_3$**), 3.39 (2H, t, J = 7.2 Hz, C**H$_2$**N), 2.27 (2H, t, J = 7.4 Hz, C**H$_2$**CO$_2$CH$_3$), 1.67 – 1.50 (4H, m, 2 × C**H$_2$**), 1.40 – 1.22 (4H, m, 2 × C**H$_2$**); δ_C (100 MHz, CDCl$_3$) 174.4 (**C**O), 168.0 (**C**O), 144.2 (ArC**H**CHCON), 134.3 (Ar**C**), 130.7 (Ar**C**H), 129.0 (2 × Ar**C**H), 128.4 (2 × Ar**C**H), 117.7 (ArCHC**H**CON), 51.7 (**C**H_3), 41.1 (**C**H_2N), 34.0 (**C**H_2CON), 28.9 (**C**H_2), 28.7 (**C**H_2), 26.6 (**C**H_2), 24.8 (**C**H_2).

Lab notebook reference: KP175_E

***N*-(4-Fluorobenzyl)-3-((4-fluorobenzyl)(3-oxo-3-(2-oxopiperidin-1-yl)propyl)amino)propanamide (5.5)**



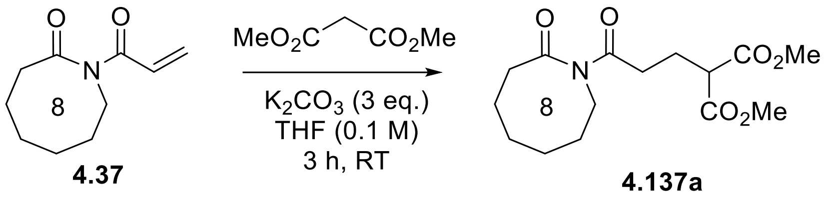
5.5

To a solution of 1-acryloyl-piperidin-2-one **4.47** in $CDCl_3$ (0.7 mL) was added a solution of 4-fluorobenzylamine (27 µL, 0.240 mmol) in $CDCl_3$ (0.3 mL) and allowed to sit at RT for 4 days in an NMR tube. Purification by flash column chromatography (SiO_2, 1:9 ethyl acetate: hexane → 1:2 ethyl acetate: hexane → 2:1 ethyl acetate: hexane → ethyl acetate → 1:9 methanol: ethyl acetate) afforded the *title compound* as a white solid (9.6 mg, 19%); R_f 0.61 (1:9 methanol: ethyl acetate); δ_H (400 MHz, $CDCl_3$) 8.20 (1H, br t, *J* = 5.5 Hz, N**H**), 7.30 – 7.24 (2H, m, Ar**H**), 7.09 – 6.96 (4H, m, Ar**H**), 6.91 – 6.80 (2H, m, Ar**H**), 4.38 (2H, d, *J* = 5.8 Hz, C**H_2**), 3.56 – 3.45 (4H, m, 2 × NC**H_2**Ar), 3.01 (2H, d, *J* = 6.8 Hz, C**H_2**), 2.82 (2H, d, *J* = 6.8 Hz, C**H_2**), 2.74 (2H, dd, *J* = 6.6, 5.2 Hz, C**H_2**), 2.49 – 2.43 (4H, m, 2 × C**H_2**), 1.82 – 1.69 (4H, m, 2 × C**H_2**); δ_C (100 MHz, $CDCl_3$) 175.4 (**C**O), 173.4 (**C**O), 172.4 (**C**O), 130.6 (2 × Ar**C**H, $^3J_{CF}$ = 7.9 Hz), 129.7 (2 × Ar**C**H, $^3J_{CF}$ = 8.0 Hz), 115.5 (2 × Ar**C**H, $^2J_{CF}$ = 21.5 Hz), 115.3 (2 × Ar**C**H, $^2J_{CF}$ = 21.2 Hz), 57.7 ((CH_2)$_2$N**C**H_2Ar), 50.6 (**C**H_2), 49.3 (**C**H_2), 44.1 (CON**C**H_2Ar), 42.6 (**C**H_2), 36.9 (**C**H_2), 34.9 (**C**H_2), 33.3 (**C**H_2), 22.4 (**C**H_2), 20.3 (**C**H_2); δ_F (376 MHz, $CDCl_3$) –115.05 (1F, m, ArF) , –115.45 (1F, m, ArF); HRMS (ESI): calcd. for $C_{25}H_{30}F_2N_3O_3$, 458.2250. Found: $[MH]^+$, 458.2248 (0.5 ppm error).

Note: The four ArC signals in the ^{13}C NMR were not observed, presumbaly as the sample was too dilute. Coupling to F also reducing the height of the peaks by splitting the signal will also have made them more difficult to see.

Lab notebook reference: KP399_B

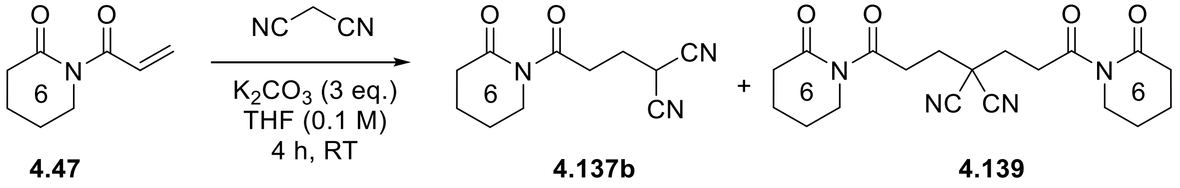
1,3-Dimethyl 2-[3-oxo-3-(2-oxoazocan-1-yl)propyl]propanedioate (4.137a)



A mixture of 1-acryloyl-azocan-2-one **4.37** (90.0 mg, 0.497 mmol), K_2CO_3 (213 mg, 1.54 mmol), and dimethyl malonate (85 µL, 0.746 mmol) in dry THF (5 mL) was allowed to stir at room temperature for 3 hours. Afterwards H_2O (10 mL) and DCM (5 mL) were added to the reaction mixture and the aqueous layer extracted with DCM (3 × 5 mL). The organic layers were dried over $MgSO_4$, and the solvent removed *in vacuo*. Purification by flash column chromatography (SiO_2, hexane → 1:2 ethyl acetate: hexane) afforded the *title compound* as a clear oil (92.9 mg, 60%); R_f 0.20 (1:1 ethyl acetate: hexane); ν_{max}/cm^{-1} (thin film) 2928, 2859, 1734, 1686, 1436, 1378, 1334, 1248, 1197, 1174, 1127; δ_H (400 MHz, $CDCl_3$) 3.88 – 3.82 (2H, m, $C\mathbf{H_2}N$), 3.67 (6H, s, 2 × $C\mathbf{H_3}$), 3.43 (1H, t, *J* = 7.4 Hz, $C\boldsymbol{H}(CO_2CH_3)_2$), 2.89 (2H, q, *J* = 7.4 Hz, $COC\mathbf{H_2}CH_2CH$), 2.63 – 2.56 (2H, m, $C\mathbf{H_2}CON$), 2.19 (2H, q, *J* = 7.4 Hz, $COCH_2C\mathbf{H_2}CH$), 1.87 – 1.75 (2H, m, $C\mathbf{H_2}$), 1.64 (2H, p, *J* = 6.2 Hz, $C\mathbf{H_2}$), 1.59 – 1.48 (2H, m, $C\mathbf{H_2}$), 1.45 – 1.33 (2H, m, $C\mathbf{H_2}$); δ_C (100 MHz, $CDCl_3$), 178.2 (**C**ON), 175.3 ($\mathbf{C}OCH_2CH_2$), 169.6 (2 × $\mathbf{C}O_2CH_3$), 52.5 (2 × $\mathbf{C}H_3$), 50.7 (**C**H), 43.4 ($\mathbf{C}H_2N$), 37.2 ($\mathbf{C}H_2CON$), 36.8 ($CO\mathbf{C}H_2CH_2$), 29.5 ($\mathbf{C}H_2$), 29.1 ($\mathbf{C}H_2$), 26.2 ($\mathbf{C}H_2$), 24.1 ($COCH_2\mathbf{C}H_2$), 23.9 ($\mathbf{C}H_2$); HRMS (ESI): calcd. for $C_{15}H_{24}NO_6$, 314.1598. Found: $[MH]^+$, 314.1598 (-0.0 ppm error). This procedure was adapted from a literature method.[113]

Lab notebook reference: KP177_B

2-(3-Oxo-3-(2-oxopiperidin-1-yl)propyl)malononitrile (4.137b) *and* 2,2-bis(3-oxo-3-(2-oxopiperidin-1-yl)propyl)malononitrile (4.139)



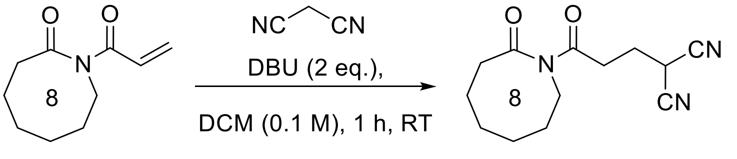
A mixture of 1-acryloyl-piperidin-2-one **4.47** (78.5 mg, 0.513 mmol), K_2CO_3 (211 mg, 1.52 mmol), and malononitrile (0.07 mL, 1.11 mmol) in dry THF (5 mL) was allowed to stir at room temperature for 4 hours. Afterwards water (5 mL), brine (5 mL) and DCM (5 mL) were added to the reaction mixture and the aqueous layer extracted with DCM (3 × 5 mL). The organic layers washed with brine (20 mL) and were dried over $MgSO_4$, with the solvent removed *in vacuo*. Purification by flash column chromatography (SiO$_2$, 1:2 ethyl acetate: hexane → 1:1 ethyl acetate: hexane → 2:1 ethyl acetate: hexane) afforded 2-(3-oxo-3-(2-oxopiperidin-1-yl)propyl)malononitrile (**4.137b**) as a colorless oil (61.4 mg, 55%) along with 2,2-bis(3-oxo-3-(2-oxopiperidin-1-yl)propyl)malononitrile (**4.139**) as a white solid (12.1 mg, 13%). Data for 2-(3-oxo-3-(2-oxopiperidin-1-yl)propyl)malononitrile (**4.137b**): A colorless oil (61.4 mg, 55%); R$_f$ 0.26 (1:1 ethyl acetate: hexane); ν$_{max}$/cm^{-1} (thin film) 2931, 1682, 1461, 1379, 1330, 1291, 1201, 1156, 1113, 1094, 1006, 910, 825, 579; δ$_H$ (400 MHz, CDCl$_3$) 4.17 (1H, t, *J* = 7.6 Hz, C**H**), 3.74 – 3.66 (2H, m, C**H**$_2$N), 3.24 (2H, t, *J* = 6.5 Hz, NCOC**H**$_2$CH$_2$CH(CN)$_2$), 2.60 – 2.53 (2H, m, C**H**$_2$CON), 2.37 (2H, dt, *J* = 7.6, 6.5 Hz, NCOCH$_2$C**H**$_2$CH(CN)$_2$), 1.89 – 1.79 (4H, m, 2 × C**H**$_2$); δ$_C$ (100 MHz, CDCl$_3$) 174.2 (**C**O), 173.6 (**C**O), 112.7 (2 × **C**N), 44.4 (**C**H$_2$N), 35.7 (NCO**C**H$_2$CH$_2$CH(CN)$_2$), 34.9 (**C**H$_2$CON), 26.6 (NCOCH$_2$**C**H$_2$CH(CN)$_2$), 22.3 (**C**H$_2$), 21.7 (**C**H), 20.2 (**C**H$_2$); HRMS (ESI): calcd. for $C_{11}H_{13}N_3NaO_2$, 242.0900. Found: [MNa]$^+$, 242.0901 (–0.3 ppm error).

Lab notebook reference: KP524_B

Data for 2,2-bis(3-oxo-3-(2-oxopiperidin-1-yl)propyl)malononitrile (**4.139**): A white solid (12.1 mg, 13%); m.p. 152–154 °C; R$_f$ 0.13 (1:1 ethyl acetate: hexane); ν$_{max}$/cm^{-1} (thin film) 2953, 1687, 1460, 1381, 1291, 1202, 1158, 1080, 1004, 825, 583; δ$_H$ (400 MHz, CDCl$_3$) 3.76 – 3.69 (4H, m, C**H**$_2$N), 3.32 – 3.27 (4H, m, NCOC**H**$_2$CH$_2$C(CN)$_2$), 2.62 – 2.54 (4H, m, C**H**$_2$CON), 2.43 – 2.34 (2H, m, NCOCH$_2$C**H**$_2$C(CN)$_2$), 1.89 – 1.79 (8H, m, 4 × C**H**$_2$); δ$_C$ (100 MHz, CDCl$_3$) 173.9 (2 × **C**O), 173.5 (2 × **C**O), 115.0 (2 × **C**N), 44.5 (2 × **C**H$_2$N), 36.2 (quat **C**(CN)$_2$), 35.9 (2 × NCO**C**H$_2$CH$_2$C(CN)$_2$), 34.9 (2 × **C**H$_2$CON), 33.1 (2 × NCOCH$_2$**C**H$_2$C(CN)$_2$), 22.4 (2 × **C**H$_2$), 20.3 (2 × **C**H$_2$); HRMS (ESI): calcd. for $C_{19}H_{24}N_4NaO_4$, 395.1690. Found: [MNa]$^+$, 395.1691 (–0.2 ppm error).

Lab notebook reference: KP524_C

2-(3-Oxo-3-(2-oxoazocan-1-yl)propyl)malononitrile (4.137c)



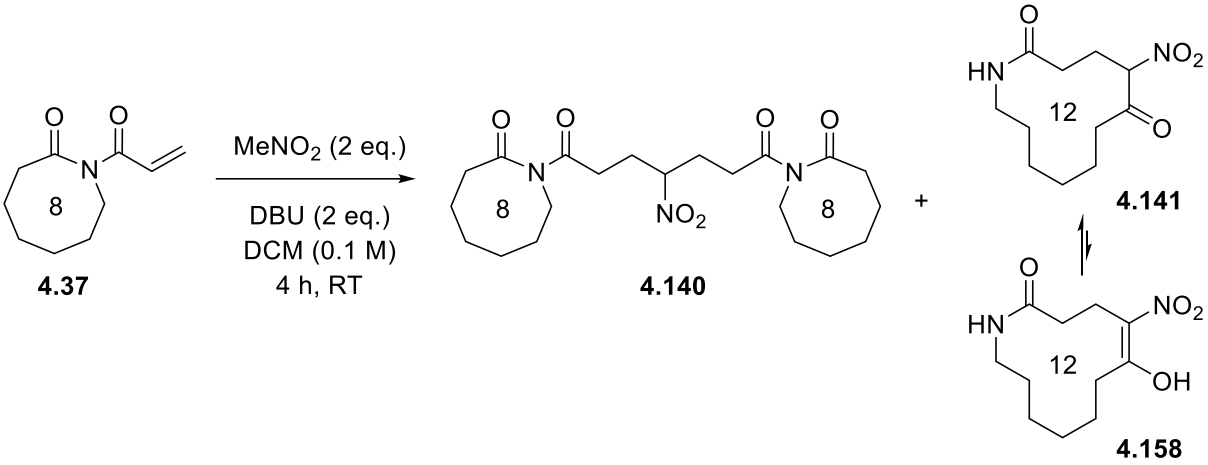
4.37 **4.137c**

To a mixture of 1-acryloylazocan-2-one **4.37** (90.9 mg, 0.501 mmol) and malononitrile (661 mg, 10.0 mmol) in dry DCM (5 mL) was added DBU (0.149 mL, 1.00 mmol) and the mixture was allowed to stir at room temperature for 1 hour. Next, water (5 mL), and DCM (5 mL) were added to the reaction mixture. The organic layer was separated and washed with water (10 mL), then brine (10 mL) and dried over MgSO$_4$, with the solvent removed *in vacuo*. Purification by flash column chromatography

(SiO_2, 1:2 ethyl acetate: hexane → 1:1 ethyl acetate: hexane→ 2:1 ethyl acetate: hexane) afforded the *title compound* as a colorless oil (36.8 mg, 30%); R_f 0.22 (1:1 hexane: ethyl acetate); ν_{max}/cm^{-1} (thin film) 2928, 1682, 1446, 1378, 1333, 1199, 1174, 1126, 1092, 998, 594; δ_H (400 MHz, $CDCl_3$) 4.22 – 4.13 (1H, m, C**H**), 3.95 – 3.88 (2H, m, C**H**$_2$N), 3.26 – 3.17 (2H, m, NCOC**H**$_2$CH$_2$CH(CN)$_2$), 2.72 – 2.63 (2H, m, C**H**$_2$CON), 2.43 – 2.31 (2H, m, NCOCH$_2$C**H**$_2$CH(CN)$_2$), 1.94 – 1.83 (2H, m, C**H**$_2$), 1.75 – 1.65 (2H, m, C**H**$_2$), 1.63 – 1.55 (2H, m, C**H**$_2$), 1.50 – 1.41 (2H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 178.6 (**C**O), 174.0 (**C**O), 112.7 (2 × **C**N), 43.6 (**C**H$_2$N), 37.1 (NCO**C**H$_2$CH$_2$CH(CN)$_2$), 35.5 (**C**H$_2$CON), 29.3 (**C**H$_2$), 29.1 (**C**H$_2$), 26.7 (**C**H$_2$), 26.2 (**C**H$_2$), 24.0 (**C**H$_2$), 21.7 (**C**H); HRMS (ESI): calcd. for $C_{13}H_{17}N_3NaO_2$, 270.1213. Found: $[MNa]^+$, 270.1213 (–0.1 ppm error).

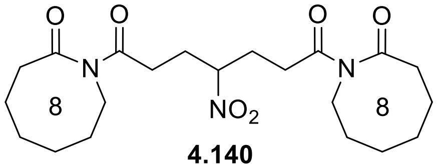
Lab notebook reference: KP587_B

4-Nitro-1,7-bis(2-oxoazocan-1-yl)heptane-1,7-dione (4.140) *and* 4-nitro-1,7-bis(2-oxoazocan-1-yl)heptane-1,7-dione (4.141)



To a stirring solution of 1-acryloyl-azocan-2-one **4.37** (182 mg, 1.00 mmol) and nitromethane (0.107 mL, 2.00 mmol) in DCM (10.0 mL) was added DBU (0.300 mL, 2.01 mmol) and the mixture was stirred at RT for 4 hours. To the reaction mixture was added water (10 mL) and the organics extracted. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to afford crude 4-nitro-1,7-bis(2-oxoazocan-1-yl)heptane-1,7-dione **4.140**. To the aqueous layer was added with 10% aq. HCl (5 mL) (at which point a faint blue emulsion formed) and DCM (10 mL). The aqueous solution was extracted with DCM (2 × 5 mL) and the organics extracts containing 5-nitro-1-azacyclododecane-2,6-dione **4.141** were combined. The organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to yield crude 5-nitro-1-azacyclododecane-2,6-dione **4.141**.

Data for 4-nitro-1,7-bis(2-oxoazocan-1-yl)heptane-1,7-dione (**4.140**):

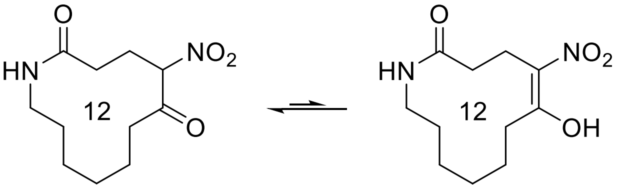


4.140

Purification by flash column chromatography (SiO_2, 1:5 ethyl acetate: hexane → 1:1 ethyl acetate: hexane) afforded pure 4-nitro-1,7-bis(2-oxoazocan-1-yl)heptane-1,7-dione **4.140** as a colorless oil (63.4 mg, 30%); R_f 0.22 (1:1 ethyl acetate: hexane); ν_{max}/cm^{-1} (thin film) 2929, 2859, 1685, 1546, 1445, 1377, 1335, 1248, 1196, 1174, 1126, 1089, 997, 894, 732, 596; δ_H (400 MHz, $CDCl_3$) 4.64 (1H, tt, *J* = 9.2, 4.4 Hz, C**H**), 3.93–3.85 (4H, m, C**H₂**N), 2.97–2.89 (4H, m, C**H₂**), 2.67–2.60 (4H, m, C**H₂**CON), 2.32–2.12 (4H, m, C**H₂**), 1.90–1.81 (4H, m, C**H₂**), 1.72–1.64 (4H, m, C**H₂**), 1.61–1.53 (4H, m, C**H₂**), 1.49–1.38 (4H, m, C**H₂**); δ_C (100 MHz, $CDCl_3$), 178.4 (2 × **C**ON), 174.9 (2 × **C**OCH₂CH₂), 87.1 (**C**H), 43.6 (2 × **C**H₂N), 37.2 (2 × **C**H₂CON), 35.6 (2 × **C**H₂), 29.5 (2 × **C**H₂), 29.2 (4 × **C**H₂), 26.3 (2 × **C**H₂), 24.0 (2 × **C**H₂); HRMS (ESI): calcd. for $C_{21}H_{33}N_3NaO_6$, 446.2262. Found: $[MNa]^+$, 446.2261 (0.1 ppm error).

Lab notebook reference: Proc: KP542_1_A, NMR: KP528_A

Data for 5-nitro-1-azacyclododecane-2,6-dione **4.141**:



4.141 **4.158**

Purification by flash column chromatography (SiO_2, 1:1 ethyl acetate: hexane → ethyl acetate) afforded 5-nitro-1-azacyclododecane-2,6-dione **4.141** as a white crystalline solid as a 4:1 mixture of keto (**4.141**) and enol (**4.158**) tautomers, based on integration of equivalent signals in the ^{13}C NMR spectra in $CDCl_3$ (88.7 mg, 36%); R_f 0.26 (9:1 ethyl acetate: methanol); ν_{max}/cm^{-1} (thin film) 3309, 2936, 1728, 1643, 1553, 1441, 1356, 1186, 1107, 720; m.p. 135–138 °C; δ_H (400 MHz, $CDCl_3$), 5.60 (1H, dd, *J* = 8.0, 4.7 Hz, C**H**), 5.44 (1H, br s, N**H**), 3.85 – 3.72 (1H, m, C**H₂**), 3.59 – 3.15 (1H, m, C**H₂**), 3.05 – 2.30 (10H, m, 5 × C**H₂**), 1.93 – 1.12 (14H, m, 7 × C**H₂**); Diagnostic Keto peak: 5.59 (1H, dd, *J* = 7.9, 4.8 Hz, C**H**); Diagnostic enol peak: 10.48 (1H, br s, O**H**); δ_C (100 MHz, $CDCl_3$) – Data for the keto form, 200.3 (**C**OCHNO₂), 171.2 (**C**ON), 89.3 (COC**H**NO₂), 40.6 (**C**H₂), 39.5 (**C**H₂), 31.5 (**C**H₂), 27.3 (**C**H₂), 26.5 (**C**H₂), 24.6 (**C**H₂), 24.2 (**C**H₂), 21.5 (**C**H₂); Data for enol form, 180.5 (**C**(OH)=C(NO₂)), 172.2 (**C**ON), 126.0 (C(OH)=**C**(NO₂)), 36.1 (**C**H₂), 34.9 (**C**H₂), 32.8 (**C**H₂), 27.1 (**C**H₂), 26.7 (**C**H₂), 24.4 (**C**H₂), 23.9 (**C**H₂), 23.1

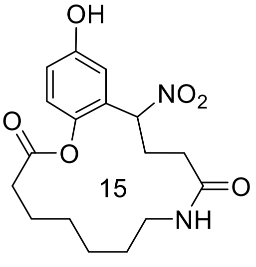
($\mathbf{C}H_2$); HRMS (ESI): calcd. for $C_{11}H_{18}N_2NaO_4$, 265.1159. Found: $[MNa]^+$, 265.1161 (–1.0 ppm error); For X-ray crystallographic data, see CCDC 2159961.

An **improved procedure** using 20 equivalents of $MeNO_2$ is also reported:

To a stirring solution of 1-acryloyl-azocan-2-one (89.9 mg, 0.496 mmol) and nitromethane (0.537 mL, 10.0 mmol) in DCM (5.0 mL) was added DBU (0.15 mL, 1.00 mmol) and the mixture was stirred at RT for 1.5 hours. The solvent was then removed *in vacuo.* To the reaction mixture was added DCM (5 mL) and water (5 mL) and the organics extracted. The organic layer (containing 4-nitro-1,7-bis(2-oxoazocan-1-yl)heptane-1,7-dione **4.140**) was then discarded. To the aqueous layer was added with 10% aq. HCl (5 mL) (at which point a faint blue emulsion formed) and DCM (5 mL). The aqueous solution was extracted with DCM (2 × 5 mL) and the organics extract containing 5-nitro-1-azacyclododecane-2,6-dione **4.141** were combined. The organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* affording 5-nitro-1-azacyclododecane-2,6-dione **4.141** as a white crystalline solid as a mixture of keto and enol tautomers (107 mg, 89%); [data consistent with those reported above for 5-nitro-1-azacyclododecane-2,6-dione **4.141**].

Lab notebook reference: Proc: KP576, NMR: KP530_2_A, XRD: KP542_2_A

15-Hydroxy-13-nitro-4,5,6,7,8,9,12,13-octahydrobenzo[*b*][1]oxa[8]azacyclopentadecine-2,10(3*H*,11*H*)-dione (4.149)

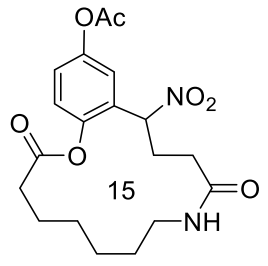


4.149

To a mixture of 5-nitro-1-azacyclododecane-2,6-dione **4.141** (96.7 mg, 0.399 mmol) and 1,4-benzoquinone (43.6 mg, 0.403 mmol) in a round bottomed flask under an argon atmosphere was added dry THF (1.2 mL) then DBU (1 drop) and allowed to stir at RT for 30 min. The crude reaction mixture was concentrated *in vacuo* and taken up in DCM (1.5 mL). This was then washed with water (3 × 1.5 mL) and the organics layer dried over $MgSO_4$, and concentrated *in vacuo* to afford the *title compound* as a brown oil (70.2 mg, 50%); R_f 0.38 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3272, 2933, 1757, 1644, 1552, 1496, 1452, 1359, 1298, 1194, 1132, 1099, 1025, 1004, 765; δ_H (400 MHz, d_6-DMSO) 9.89 (1H, br s, O**H**), 7.97 (1H, dd, *J* = 8.0, 3.5 Hz, N**H**), 7.01 – 6.97 (2H, m, Ar**H**), 6.86 (1H, dd, *J* = 8.8, 2.9 Hz, Ar**H**), 5.39 (1H, dd, *J* = 11.0, 3.0 Hz, $\mathrm{C\mathbf{H}NO_2}$), 3.55 – 3.41 (1H, m, $\mathrm{C\mathbf{H_2}}$), 2.91 – 2.81 (1H, m, $\mathrm{C\mathbf{H_2}}$), 2.68 – 2.53 (2H, m, $\mathrm{C\mathbf{H_2}}$), 2.34 – 2.20 (2H, m, $\mathrm{C\mathbf{H_2}}$), 2.16 – 2.05 (1H, m, $\mathrm{C\mathbf{H_2}}$), 1.78 – 1.56 (3H, m, $\mathrm{C\mathbf{H_2}}$), 1.53 – 1.36 (3H, m, $\mathrm{C\mathbf{H_2}}$), 1.32 – 1.18 (3H, m, $\mathrm{C\mathbf{H_2}}$); δ_C (100 MHz, d_6-DMSO) 171.8 (**C**O), 170.0 (**C**O), 155.7 (Ar**C**OH), 140.7 (Ar**C**), 127.1 (Ar**C**), 123.9 (Ar**C**H), 117.6 (Ar**C**H), 113.5 (Ar**C**H), 83.2 (**C**H), 36.6 ($\mathrm{\mathbf{C}H_2}$), 32.6 ($\mathrm{\mathbf{C}H_2}$), 31.3 ($\mathrm{\mathbf{C}H_2}$), 28.4 ($\mathrm{\mathbf{C}H_2}$), 28.2 ($\mathrm{\mathbf{C}H_2}$), 27.3 ($\mathrm{\mathbf{C}H_2}$), 24.6 ($\mathrm{\mathbf{C}H_2}$), 23.6 ($\mathrm{\mathbf{C}H_2}$); HRMS (ESI): calcd. for $C_{17}H_{22}N_2NaO_6$, 373.1370. Found: $[MNa]^+$, 373.1375 (–1.3 ppm error). This procedure was adapted from a literature method.[93]

Lab notebook reference: KP553

13-Nitro-2,10-dioxo-2,3,4,5,6,7,8,9,10,11,12,13-dodecahydrobenzo[*b*][1]oxa[8]azacyclopentadecin-15-yl acetate (4.150)



4.150

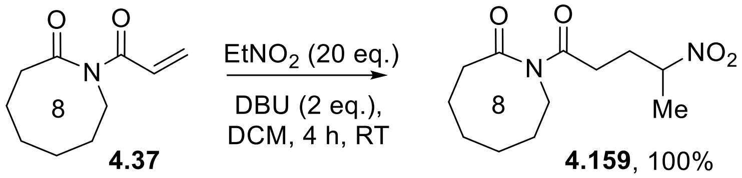
To a mixture of 5-nitro-1-azacyclododecane-2,6-dione **4.141** (172 mg, 0.711 mmol) and 1,4-benzoquinone (76.2 mg, 0.705 mmol) in a round bottomed flask under an argon atmosphere was added dry THF (2.1 mL) then DBU (1 drop) and allowed to stir at RT for 20 min. Next acetic anhydride (0.208 mL, 2.20 mmol), and pyridine (0.114 mL, 0.141 mmol) were added and the reaction heated to 60 °C for 5 min then stirred at RT for 24 hours. To the crude reaction mixture was added DCM (4 mL). This was then washed with washed with 5% aq. HCl (8 mL), and sat. $NaHCO_3$ (8 mL), and finally water (8 mL) and the organic layer dried over $MgSO_4$, and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:2 ethyl acetate: hexane → 1:1 ethyl acetate: hexane → 2:1 ethyl acetate: hexane → ethyl acetate) afforded the *title compound* as a yellow solid (90.3 mg, 32%); m.p. 201–204 °C; R_f 0.39 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3305, 2934, 1763, 1648, 1554, 1493, 1432, 1367, 1207, 1176, 1127, 1097, 1015, 916, 735, 592; δ_H (400 MHz, $CDCl_3$) 7.32 (1H, d, *J* = 2.6 Hz, Ar**H**), 7.19 (1H, dd, *J* = 8.8, 2.6 Hz, Ar**H**), 7.14 (1H, d, *J* = 8.8 Hz, Ar**H**), 5.86 (1H, br dd, *J* = 8.0, 4.4 Hz, N**H**), 5.62 (1H, dd, *J* = 10.8, 4.2 Hz, $\mathrm{C\mathbf{H}NO_2}$), 3.61 (1H, dtd, *J* = 13.6, 7.9, 3.4 Hz, $\mathrm{C\mathbf{H_2}}$), 3.13 – 3.03 (1H, m, $\mathrm{C\mathbf{H_2}}$), 2.71 – 2.60 (3H, m, $\mathrm{C\mathbf{H_2}}$), 2.58 – 2.48 (1H, m, $\mathrm{C\mathbf{H_2}}$), 2.38 (1H, ddd, *J* = 14.8, 5.9, 3.3 Hz, $\mathrm{C\mathbf{H_2}}$), 2.30 (3H, s, $\mathrm{C\mathbf{H_3}}$), 2.11 (1H, ddd, *J* = 14.8, 11.8, 3.0 Hz, $\mathrm{C\mathbf{H_2}}$), 1.95 – 1.84 (1H, m, $\mathrm{C\mathbf{H_2}}$), 1.80 – 1.69 (1H, m, $\mathrm{C\mathbf{H_2}}$), 1.63 – 1.47 (4H, m, 2 × C**H₂**), 1.45 – 1.34 (2H, m, C**H₂**); δ$_C$ (100 MHz, CDCl$_3$) 171.7 (**C**O), 170.6 (**C**O), 169.1 (**C**O), 148.5 (Ar**C**), 146.6 (Ar**C**), 127.1 (Ar**C**), 124.3 (Ar**C**H), 123.8 (Ar**C**H), 121.1 (Ar**C**H), 83.1 (**C**H), 38.6 (**C**H$_2$), 33.0 (**C**H$_2$), 32.7 (**C**H$_2$), 28.9 (**C**H$_2$), 28.8 (**C**H$_2$), 27.7 (**C**H$_2$), 25.0 (**C**H$_2$), 23.5 (**C**H$_2$), 21.2 (**C**H$_3$); HRMS (ESI): calcd. for $C_{19}H_{24}N_2NaO_7$, 415.1476. Found: [MNa]$^+$, 415.1485 (–2.3 ppm error).

For X-ray crystallographic data, see CCDC 2159962.

This procedure was adapted from a literature method.[93]

Lab notebook reference: KP555

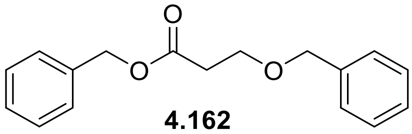
1-(4-Nitropentanoyl)azocan-2-one (4.159)



To a stirring solution of 1-acryloyl-azocan-2-one **4.37** (92.2 mg, 0.509 mmol) and nitroethane (0.718 mL, 10.0 mmol) in DCM (5.0 mL) was added DBU (0.149 mL, 1.00 mmol) and the mixture was stirred at RT for 4 hours. To the reaction mixture was added DCM (5 mL) and 10% aq. HCl (5 mL) (at which point a feint blue emulsion formed). The aqueous solution was extracted with DCM (2 × 5 mL) and the organics extracts combined, dried over MgSO$_4$, and concentrated *in vacuo* to afford the *title compound* as a pale orange oil (130 mg, 100%); R$_f$ 0.33 (1:1 ethyl acetate: hexane); ν$_{max}$/cm^{-1} (thin film) 2931, 1686, 1545, 1446, 1378, 1336, 1248, 1196, 1175, 1125, 1090, 998, 862, 595; δ$_H$ (400 MHz, CDCl$_3$) 4.63 (1H, dqd, *J* = 8.8, 6.7, 4.8 Hz, C**H**), 3.91 – 3.84 (2H, m, C**H₂**), 2.98 – 2.83 (2H, m, C**H₂**), 2.65 – 2.59 (2H, m, C**H₂**), 2.30 – 2.18 (1H, m, 0.5 × C**H₂**), 2.16 – 2.04 (1H, m, 0.5 × C**H₂**), 1.87 – 1.79 (2H, m, C**H₂**), 1.66 (2H, p, *J* = 6.2 Hz, C**H₂**), 1.59 – 1.49 (2H, m, C**H₂**), 1.52 (3H, d, *J* = 6.7 Hz, C**H₃**), 1.45 – 1.37 (2H, m, C**H₂**); δ$_C$ (100 MHz, CDCl$_3$) 178.4 (**C**O), 174.9 (**C**O), 82.7 (**C**H), 43.6 (**C**H$_2$), 37.1 (**C**H$_2$), 35.5 (**C**H$_2$), 30.3 (**C**H$_2$), 29.5 (**C**H$_2$), 29.1 (**C**H$_2$), 26.2 (**C**H$_2$), 24.0 (**C**H$_2$), 19.4 (**C**H$_3$); HRMS (ESI): calcd. for $C_{12}H_{20}N_2NaO_4$, 279.1315. Found: [MNa]$^+$, 279.1310 (1.8 ppm error).

Lab notebook reference: KP556

Benzyl 3-(benzyloxy)propanoate (4.162)

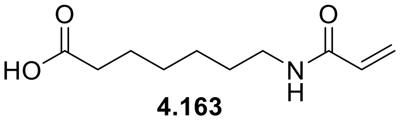


4.162

A mixture of 1-acryloyl-azocan-2-one **4.37** (90.5 mg, 0.500 mmol), Cs_2CO_3 (165 mg, 0.505 mmol), benzyl alcohol (0.057 mL, 0.550 mmol), anhydrous $CuCl_2$ (6.6 mg, 0.049 mmol), and DCM (1.0 mL) were heated to 50 °C for 12 h. Then, the reaction mixture was cooled to RT and flushed through a short silica plug eluting with DCM affording the *title compound* (68.2 mg, 92%); δ_H (400 MHz, $CDCl_3$) 7.39 – 7.26 (10H, m, Ar**H**), 5.16 (2H, s, $PhCH_2OCH_2CH_2CO_2C\mathbf{H_2}Ph$), 4.54 (2H, s, $PhC\mathbf{H_2}OCH_2CH_2CO_2CH_2Ph$), 3.79 (2H, t, J = 6.3 Hz, $PhCH_2OC\mathbf{H_2}CH_2CO_2CH_2Ph$), 2.69 (2H, t, J = 6.3 Hz, $PhCH_2OCH_2C\mathbf{H_2}CO_2CH_2Ph$); δ_C (100 MHz, $CDCl_3$) 171.6 (**C**O), 138.1 (Ar**C**), 136.0 (Ar**C**), 128.6 (2 × Ar**C**H), 128.5 (2 × Ar**C**H), 128.30 (Ar**C**H), 128.28 (2 × Ar**C**H), 127.76 (2 × Ar**C**H), 127.75 (Ar**C**H), 73.2 ($Ph\mathbf{C}H_2OCH_2CH_2CO_2CH_2Ph$), 66.4 (**C**$H_2$O), 65.7 (**C**$H_2$O), 35.3 ($PhCH_2OCH_2\mathbf{C}H_2CO_2CH_2Ph$). This procedure was adapted from a literature method.[114]

Lab notebook reference: KP539

5-Acryloylaminoheptanoic acid (4.163)

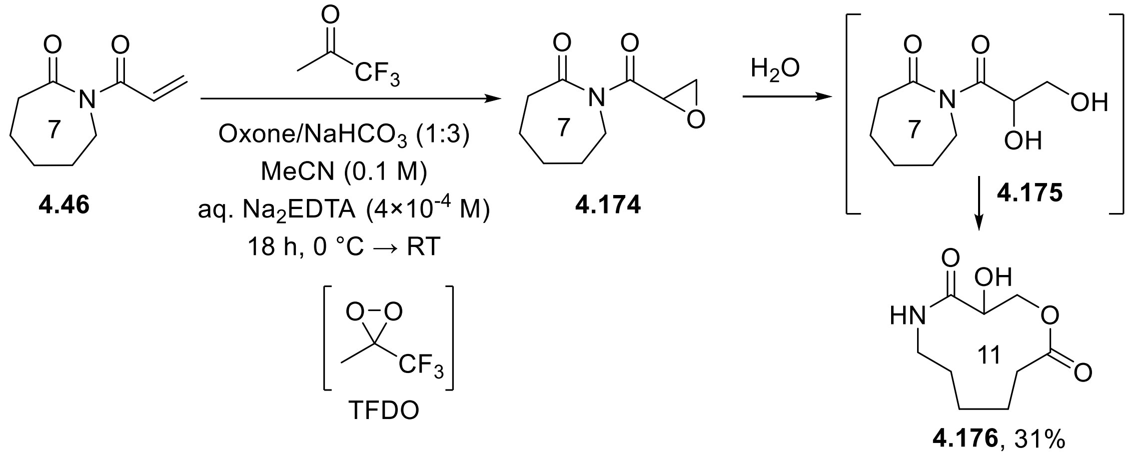


4.163

To a solution of 1-acryloyl-azocan-2-one **4.37** (73.8 mg, 0.407 mmol) in water (0.8 mL) and MeCN (0.4 mL) was added a <u>Lewis acid</u> (*e.g.* $InOTf_3$ (48.8 mg, 0.087 mmol)) (see Table 4.7) (0.08 mmol, 0.2 eq.) and the reaction mixture heated to 80 °C for 24 h. Then, the reaction was allowed to cool to RT, EtOAc (8 mL) and brine (8 mL) were added and the organic layers were separated, dried over Na_2SO_4, and the solvent removed *in vacuo*. To this crude material was added trimethoxybenzene (68.1 mg, 0.4 mmol) as an NMR standard. The crude mixture contained **4.163**. Data for 5-acryloylaminoheptanoic acid (**4.163**): δ_H (400 MHz, $CDCl_3$) 8.17 (1H, br s, COO**H**), 6.37 (1H, br t, J = 5.6 Hz, N**H**), 6.25 (1H, dd, J = 17.0, 1.7 Hz, $CH_2C\mathbf{H}CON$), 6.12 (1H, dd, J = 17.0, 10.1 Hz, C**H**H’CHCON), 5.60 (1H, dd, J = 10.1, 1.7 Hz, CH**H’**CHCON), 3.34 – 3.24 (2H, m, $C\mathbf{H_2}N$), 2.31 (2H, t, J = 7.4 Hz, $C\mathbf{H_2}CO_2H$), 1.65 – 1.45 (4H, m, 2 × $C\mathbf{H_2}$), 1.39 – 1.27 (4H, m, 2 × $C\mathbf{H_2}$); δ_C (100 MHz, $CDCl_3$) 178.2 (**C**O), 166.2 (**C**O), 130.9 ($CH_2\mathbf{C}HCON$), 126.5 ($\mathbf{C}H_2CHCON$), 39.6 ($\mathbf{C}H_2N$), 34.0 ($\mathbf{C}H_2CON$), 29.2 ($\mathbf{C}H_2$), 28.7 ($\mathbf{C}H_2$), 26.5 ($\mathbf{C}H_2$), 24.6 ($\mathbf{C}H_2$).

Lab notebook reference: KP558

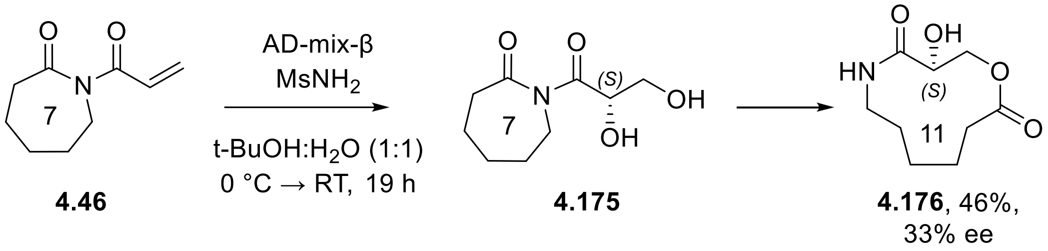
3-Hydroxy-1-oxa-5-azacycloundecane-4,11-dione (4.176)



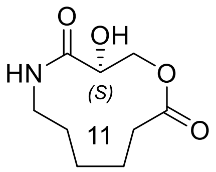
To a solution of 1-acryloyl-azepan-2-one **4.46** (34.0 mg, 0.203 mmol) in acetonitrile (1.5 mL), was added aq. Na_2EDTA (1.0 mL, 4 × 10^{-4} M) and the solution cooled to 0 °C. Then, 1,1,1-trifluoroacetone (0.500 mL, 5.59 mmol), Oxone (210 mg) and $NaHCO_3$ (84.9 mg, 1.01 mmol) were added sequentially, and the reaction allowed to stir for 1.5 h at 0 °C. After this time the starting material was still the predominant component by TLC. The reaction was warmed to RT and allowed to stir for an additional 18 h. Additional 1,1,1-trifluoroacetone (0.500 mL, 5.59 mmol) was added two more times, and additional Oxone/$NaHCO_3$ portions (1/3) (210 mg of Oxone, 84.9 mg of $NaHCO_3$) were added three more times over the course of the reaction. The excess Oxone and TFDO (methyl(trifluoromethyl)dioxirane) were quenched by adding sat. aq. $Na_2S_2O_3$ (5 mL) and stirring for 1 h at RT. The crude reaction mixture was then diluted up with EtOAc (30 mL) the organic layers washed with brine (10 mL), and organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:4 ethyl acetate: hexane → 1:1 ethyl acetate: hexane → ethyl acetate → 1:19 methanol: ethyl acetate) afforded the *title compound* as a white solid (12.6 mg, 31%); m.p. 136 – 139 °C; R_f 0.29 (1:9 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3317, 2935, 2498, 1731, 1643, 1443, 1364, 1311, 1231, 1152, 1128, 1093, 1018, 559; δ_H (400 MHz, MeOD-*d₄*) 8.00 (1H, br s, N**H**), 4.98 (1H, dd, *J* = 11.4, 2.4 Hz, $CH_2CO_2C\mathbf{H}H'CH$), 4.22 (1H, t, *J* = 2.6 Hz, $CH_2CO_2CH_2C\mathbf{H}$), 3.91 (1H, dd, *J* = 11.4, 2.8 Hz, $CH_2CO_2CH\mathbf{H'}CH$), 3.70 (1H, ddd, *J* = 14.1, 10.8, 3.8 Hz, $C\mathbf{H}H'NCO$), 2.99 (1H, dt, *J* = 13.3, 4.1 Hz, $CH\mathbf{H'}NCO$), 2.45 (1H, ddd, *J* = 14.2, 7.4, 3.9 Hz, $C\mathbf{H}H'CO_2CH_2CH$), 2.22 – 2.13 (1H, m, $CH\mathbf{H'}CO_2CH_2CH$), 1.80 – 1.62 (3H, m, $C\mathbf{H}_2$), 1.61 – 1.39 (2H, m, $C\mathbf{H}_2$), 1.22 – 1.09 (1H, m, $C\mathbf{H}_2$); δ_C (100 MHz, MeOD-*d₄*) 174.5 (**C**O), 174.4 (**C**O), 72.7 (**C**H), 66.8 ($CH\mathbf{C}H_2$), 39.7 ($CONH\mathbf{C}H_2$), 35.5 ($\mathbf{C}H_2CO_2CH_2CH$), 28.3 (**C**H$_2$), 27.1 (**C**H$_2$), 25.3 (**C**H$_2$); HRMS (ESI): calcd. for $C_9H_{15}NNaO_4$, 224.0893. Found: [MNa]$^+$, 224.0892 (0.5 ppm error). This procedure was adapted from a literature method.[115]

Lab notebook reference: KP582

Alternative procedure using Sharpless asymmetric dihydroxylation conditions:



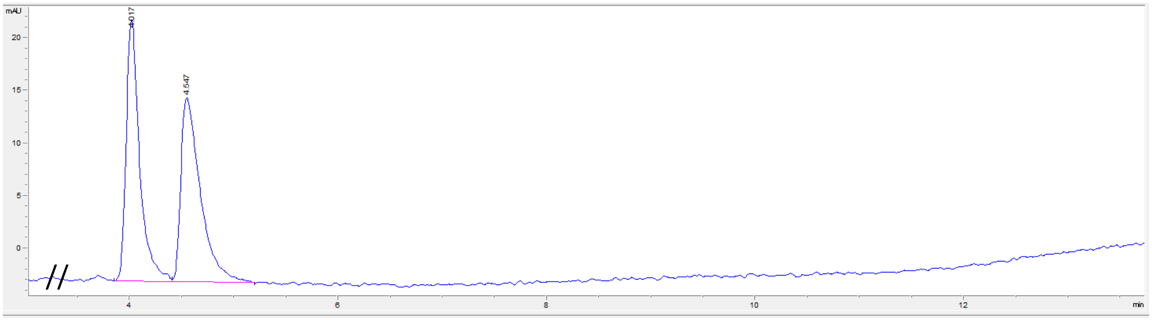
To a 25 mL round bottomed flask was added AD-mix-β (0.716 g), methanesulfonamide (45.3 mg, 0.477 mmol), t-BuOH (2.5 mL) and water (2.5 mL), and the mixture was stirred for 15 min at RT and then cooled to 0 °C. 1-acryloylazepan-2-one (**4.46**) (84.9 mg, 0.508 mmol) was taken up in t-BuOH (0.5 mL) and water (0.5 mL), and added to the AD-mix flask. The reaction mixture was stirred for 2 h at 0 °C, and 19 h at RT. To the reaction mixture was then added wth Na_2SO_3 (7.60 g) and the mixture was allowed to stir for 3 h at RT. The crude reaction mixture was then diluted with EtOAc (4 mL), and the aqueous layer extracted with EtOAc (2 × 2 mL), and the combined organic layers washed with brine (10 mL). The organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 ethyl acetate: hexane → ethyl acetate) afforded the *title compound* as a white solid (46.9 mg, 46%, 33% ee); $[\alpha]_D^{20}$ 21.5 (c = 1.0, MeOH); For data for **4.176** see above. This procedure was adapted from a literature method.[116]



4.176, 46%,
33% ee

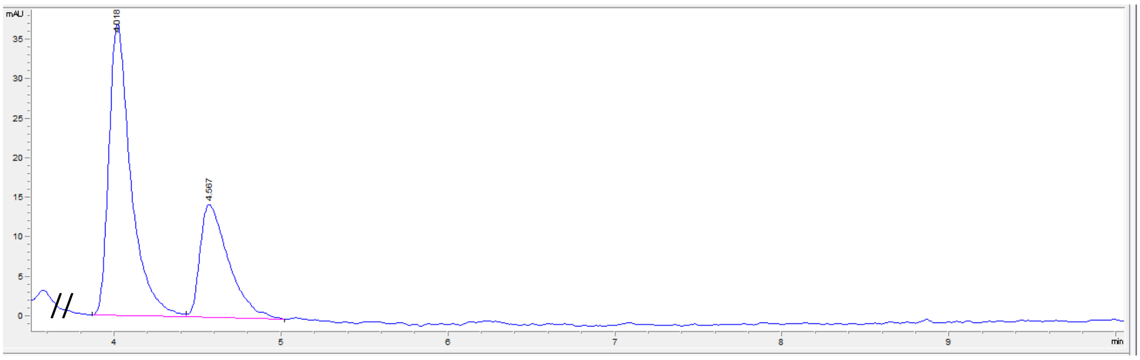
CSP-HPLC of **4.176** using Chiralpak AD-H column, eluting with 20% IPA in hexanes with 1 mL/min flow rate at 25 °C. HPLC spectrum obtained by Balasz Pogranyi.

Racemic **4.176** recorded at 220 nm



Peak No.	Retention Time / min	Peak Area	Peak Area / %
1	4.017	226	49.6
2	4.547	230	50.4

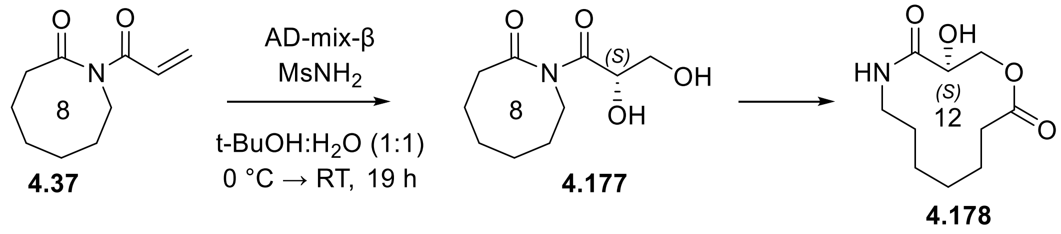
Enantioenriched **4.176** recorded at 220 nm



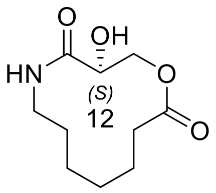
Peak No.	Retention Time / min	Peak Area	Peak Area / %
1	4.018	341	66.4
2	4.567	172	33.6

Lab notebook reference: KP584

3-Hydroxy-1-oxa-5-azacyclododecane-4,12-dione (4.178)



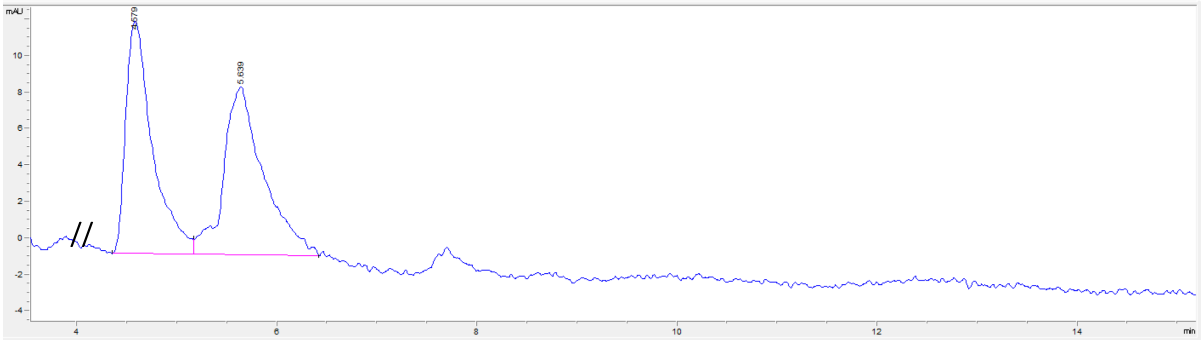
To a 25 mL round bottomed flask was added AD-mix-β (1.41 g), methanesulfonamide (90.0 mg, 0.946 mmol), t-BuOH (6 mL) and water (6 mL), and the mixture was stirred for 15 min at RT and then cooled to 0 °C. 1-acryloylazocan-2-one **4.37** (182.0 mg, 1.00 mmol) was then added directly to the AD-mix flask. The reaction mixture was stirred for 2 h at 0 °C, and 17 h at RT. To the reaction mixture was then added wth Na_2SO_3 (10.7 g) and the mixture was allowed to stir for 3 h at RT. The crude reaction mixture was then diluted with EtOAc (8 mL), and the aqueous layer extracted with EtOAc (2 × 4 mL), and the combined organic layers washed with brine (8 mL). The organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 ethyl acetate: hexane → ethyl acetate) afforded the *title compound* as a white solid (146 mg, 67%, 33% ee); m.p. 122 – 126 °C; R_f 0.44 (1:9 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3349, 2938, 2488, 1727, 1643, 1446, 1371, 1256, 1213, 1118, 1086, 1002, 552; δ_H (400 MHz, MeOD-*d₄*) 4.90 – 4.86 (1H, m, $CH_2CO_2C\mathbf{H}H'CH$ [overlapping with H_2O signal]), 4.26 (1H, td, *J* = 2.5, 0.9 Hz, $CH_2CO_2CH_2C\mathbf{H}$), 3.96 (1H, dd, *J* = 11.4, 2.7 Hz, $CH_2CO_2CH\mathbf{H'}CH$), 3.76 (1H, ddd, *J* = 14.0, 10.6, 3.6 Hz, $C\mathbf{H}H'NCO$), 3.00 (1H, dtd, *J* = 13.6, 4.4, 0.9 Hz, $CH\mathbf{H'}NCO$), 2.47 (1H, ddd, *J* = 14.2, 9.6, 4.9 Hz, $C\mathbf{H}H'CO_2CH_2CH$), 2.29 (1H, ddd, *J* = 13.8, 6.6, 4.3 Hz, $CH\mathbf{H'}CO_2CH_2CH$), 1.81 – 1.54 (5H, m, $C\mathbf{H}_2$), 1.37 – 1.22 (3H, m, $C\mathbf{H}_2$); δ_C (100 MHz, MeOD-*d₄*) 174.6 (**C**O), 173.6 (**C**O), 72.1 (**C**H), 66.8 ($CH\mathbf{C}H_2$), 38.0 ($CONH\mathbf{C}H_2$), 34.0 ($\mathbf{C}H_2CO_2CH_2CH$), 26.7 ($\mathbf{C}H_2$), 25.9 ($\mathbf{C}H_2$), 25.3 ($\mathbf{C}H_2$), 25.2 ($\mathbf{C}H_2$); $[\alpha]_D^{20}$ 23.41 (c = 1.0, MeOH); HRMS (ESI): calcd. for $C_{10}H_{17}NNaO_4$, 238.1050. Found: $[MNa]^+$, 238.1051 (–0.5 ppm error). This procedure was adapted from a literature method.[116]



4.178, 67%,
33% ee

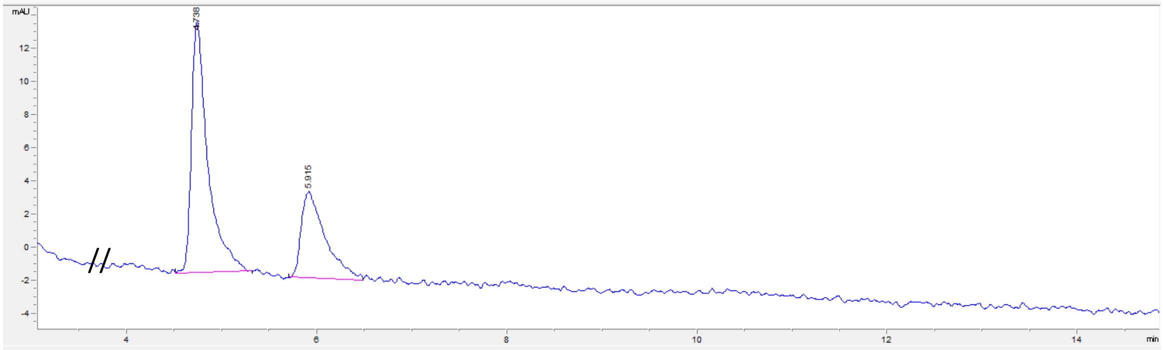
CSP-HPLC of **4.178** using Chiralpak AD-H column, eluting with 20% IPA in hexanes with 1 mL/min flow rate at 25 °C. HPLC spectrum obtained by Balasz Pogranyi.

Racemic **4.178** recorded at 220 nm



Peak No.	Retention Time / min	Peak Area	Peak Area / %
1	4.579	239	48.0
2	5.639	259	52.0

Enantioenriched **4.178** recorded at 220 nm



Peak No.	Retention Time / min	Peak Area	Peak Area / %
1	4.738	183	66.3
2	5.915	93	33.7

Lab notebook reference: KP586_B

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7 Appendices

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Macrocycles |*Hot Paper*|

Evaluating the Viability of Successive Ring-Expansions Based on Amino Acid and Hydroxyacid Side-Chain Insertion

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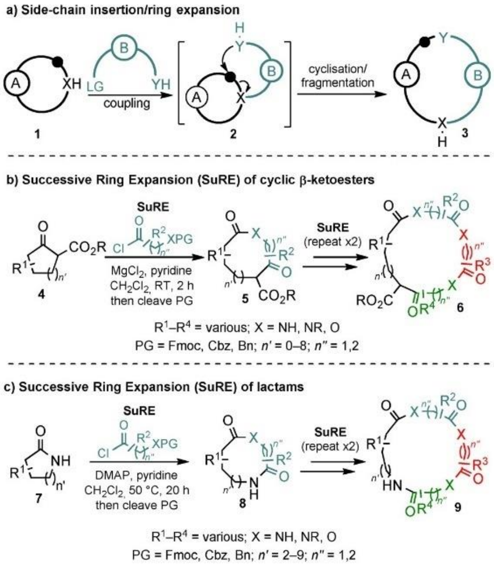
Abstract: The outcome of ring-expansion reactions based on amino/hydroxyacid side-chain insertion is strongly dependent on ring size. This manuscript, which builds upon our previous work on Successive Ring Expansion (SuRE) methods, details efforts to better define the scope and limitations of these reactions on lactam and β-ketoester ring systems with respect to ring size and additional functionality. The synthetic results provide clear guidelines as to which substrate classes are more likely to be successful and are supported by computational results, using a density functional theory (DFT) approach. Calculating the relative Gibbs free energies of the three isomeric species that are formed reversibly during ring expansion enables the viability of new synthetic reactions to be correctly predicted in most cases. The new synthetic and computational results are expected to support the design of new lactam- and β-ketoester-based ring-expansion reactions.

Introduction

Rearrangements that allow ring-enlarged products to be prepared from smaller cyclic systems have much utility in synthetic chemistry.[1,2] Ring expansions are particularly useful for the synthesis of medium-sized rings (8- to 11-membered) and macrocycles (12+ membered), as alternatives to direct end-to-end cyclisations.[3] End-to-end cyclisations can be difficult and unpredictable processes due to competing intermolecular coupling and other side reactions, and they often necessitate the use of impractical high-dilution (or pseudo-high-dilution) conditions.[4] In contrast, high dilution can often be avoided completely in well-designed ring-expansion systems.[1,2,5]

Side-chain insertion ring-expansion reactions (Scheme 1 a) are a useful sub-class of ring expansion, as the requisite precursors are generally straightforward to prepare. Various methods in which the ring expansion is accompanied by concomitant C–O, C–N and C–C bond formation are known, and this topic has been recently reviewed.[1a] Amongst this class of reaction, our group has developed a series side-chain insertion ring expansion processes that can be performed iteratively. These methods, which we have termed "Successive Ring Expansion"



Scheme 1. Side-chain insertion ring-expansion reactions and Successive Ring Expansion (SuRE).

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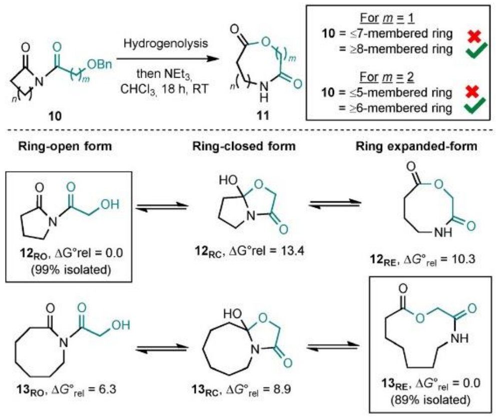
(SuRE) reactions,[5] enable the controlled, iterative insertion of amino acid or hydroxyacid-derived linear sequences into cyclic β-ketoesters (**4**→**6**, Scheme 1 b)[5a,b] or lactams (**7**→**9**, Scheme 1 c).[5c,d]

In our experience, the most important factor in determining the outcome of new ring-expansion reactions of the types summarised in Scheme 1 b and c is ring size. This is well demonstrated by the outcomes of our published lactone-forming ring expansions of imides of the form **10** (Scheme 2).[5d] Thus, for both α- and β-hydroxyacid derived linear fragments (3- and 4-atom ring expansions, respectively), there is a clear point at which ring expansion "switches on"; the reactions work for starting materials with rings that are eight-membered or more for three-atom expansions (*m* = 1) and rings that are six-membered or more for four-atom expansions (*m* = 2). The analogous reactions fail for smaller ring variants. We have previously postulated that these reactions are under thermodynamic control, and hence that the reaction outcomes depend on the relative Gibbs free energies of the three isomeric forms that the substrate must pass through for ring expansion to occur. This idea is supported by calculations performed at the DFT/B3LYP/6-31G* level of theory;[5d,6–8] thus, five-membered ring-open form imide $\mathbf{12_{RO}}$ (RO = ring-opened) was calculated to be significantly lower in Gibbs free energy than its isomeric ring-closed ($\mathbf{12_{RC}}$, RC = ring-closed) and ring-expanded forms ($\mathbf{12_{RE}}$, RE = ring-expanded), and this was replicated in the synthetic results, with imide $\mathbf{12_{RO}}$ being isolated in 99% yield following hydrogenolysis of the parent benzyl protected imide (**10**, where *n* = 2, *m* = 1). Conversely, in the case of the analogous eight-membered starting material (**10**, where *n* = 5, *m* = 1), the ring-expanded form $\mathbf{13_{RE}}$ was calculated to be the most stable isomer, and upon testing the reaction, $\mathbf{13_{RE}}$ was isolated in 89% yield, meaning that the calculations again were in line with the synthetic results.

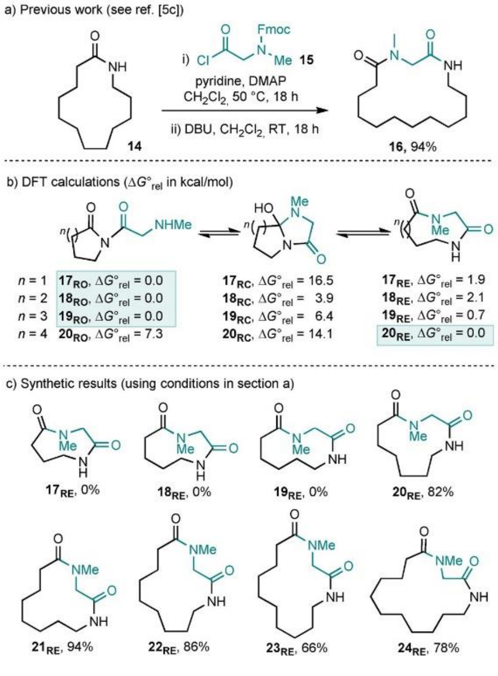
These calculations, which drew inspiration from a similar approach used by Yudin and co-workers,[2d] were done primarily to validate our ideas about the reactions being under thermodynamic control. In this work, we have explored the validity of using calculations of this type predictively. As we continue to develop this research programme, having a reliable predictive tool to inform the likelihood of new SuRE variants working before committing to labour-intensive synthetic efforts will be of value. The utility of this approach is demonstrated herein; in total, 52 new ring-expansion reactions have been attempted, with 48 successfully furnishing the desired ring-expanded product. Our DFT/B3LYP/6-31G* method correctly predicted the reaction outcome in almost all cases, and compared favourably when benchmarked against other alternative methods, including those that model solvation and dispersion interactions. Thus, we believe that this widely available DFT/B3LYP/6-31G* approach will be useful to help assess the viability of new ring-expansion reactions before committing to synthetic efforts.



Scheme 2. Ring-size dependency on the outcome of the ring expansion of imides into aza-lactones. ΔG°_{rel} values are given in kcal mol^{-1}.

Results and Discussion

We started by examining the ring expansion of simple lactams with sarcosine derivative **15**. We had already shown that this acid chloride is compatible with our standard lactam ring expansion method (**14**→**16**, Scheme 3 a), but prior to this work, 13-membered lactam **14** was the smallest aliphatic lactam on



Scheme 3. Ring-size dependency on the outcome of the ring expansion of imides with N-methyl sarcosine derivatives. ΔG°_{rel} values are given in kcal mol^{-1} with thermal corrections at 298 K.

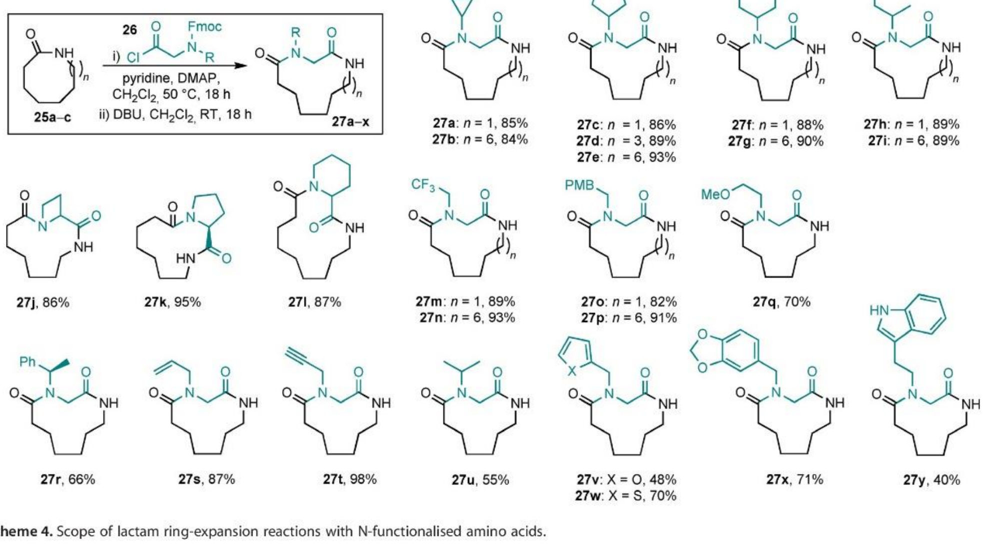
which we have reported a successful ring expansion with any linear α-amino acid chloride.

Prior to doing the synthetic chemistry, we ran DFT calculations based on the method used in our earlier study. To summarise this method, each of the three components of the equilibria deriving from five- to eight-membered ring imide precursors **17**$_{RO}$-**20**$_{RO}$ were optimised at the DFT/B3LYP/6-31G* level of theory in vacuum.[6–8] Conformational searches of the optimised structures were performed at the Molecular Mechanics Force Field level. All the generated structures were retained, and their energies were calculated using DFT/B3LYP/6-31G*. The lowest energy geometry in each case was selected, fully optimised and determined to be minima by the absence of negative vibrational modes, in vacuum using DFT/B3LYP/6-31G*. In each case, the relative free energies of the imide (**17**$_{RO}$–**20**$_{RO}$), ring-closed (**17**$_{RC}$–**20**$_{RC}$), and ring-expanded (**17**$_{RE}$–**20**$_{RE}$) isomers were calculated, with $\Delta G^{\circ}_{\text{rel}}$ values quoted in kcal mol^{-1} (Scheme 3b). More information about the choice of this method and method effects are included later in the manuscript;[7] until then, the discussion will focus on the synthetic aspects and DFT/B3LYP/6-31G* calculations.

In the five- to seven-membered series, the imide isomers **17**$_{RO}$–**19**$_{RO}$ were calculated to be the most stable, thus suggesting that ring expansion is unlikely to proceed in these examples. This prediction was verified by synthetic results; thus, none of the ring-expanded products **17**$_{RO}$–**19**$_{RO}$ were obtained when attempts were made to prepare them using the standard conditions, with no tractable products isolated from these reactions (**17**$_{RO}$–**19**$_{RO,}$ Scheme 3c). Conversely, the ring-expanded isomer **20**$_{RE}$ was calculated to be the lowest in free energy in the eight-membered ring series, and this again was borne out in the synthetic results, with **20**$_{RE}$ isolated in 82% yield. Thus, the use of an eight-membered ring starting material (or larger) appears to be the 'switch on' point for this series, as it was for the analogous lactone systems in Scheme 2. This is supported by the high yielding (66–94%) ring expansions of 9–12-membered lactam systems to form products **21**$_{RE}$–**24**$_{RE}$ under the standard conditions.

Medicinal interest in medium-sized rings and macrocycles has increased significantly in the last decade,[9] and the reaction variant described in Scheme 3 appears to be well suited for use in the preparation of peptoid-containing macrocycles,[10] as long as the starting lactam is an eight-membered ring or larger. Thus, to better demonstrate its potential utility, we went on to investigate the range of N-substituents that can be tolerated on the linear unit **26**, with these results summarised in Scheme 4. In total, 24 new ring-expansion reactions of this type have been performed, to make **27 a**–**y** (**27 k** was described previously)[5c] using various functionalised amino acid-derived linear fragments (**26**). Most of the reactions proceeded in high yield (the yield quoted is for the full N-acylation/protecting group cleavage/rearrangement sequence) under the standard reaction conditions, significantly expanding the range and diversity of amino acid derivatives that have been demonstrated in the SuRE method to date.

All the new SuRE reactions presented in Scheme 4 worked (at least to some degree), although there were a few outliers that were lower yielding (e.g., furan-derivative **27 v**). In these cases, we believe that the lower yield is not caused by an inherent difference in the thermodynamics of the ring expansion equilibrium (i.e., the relative free energies of the analogous isomers **27 v**$_{RO}$, **27 v**$_{RC}$ and **27 v**$_{RE}$ are in line with those for the methyl analogue **20**, see SI for full details)[11] but can be explained by substrate-dependent side reactions or problems

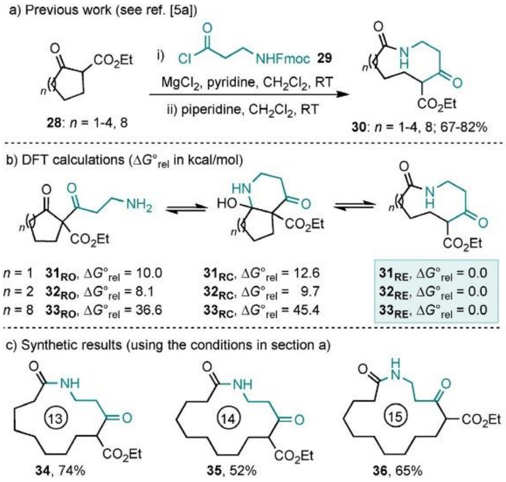


Scheme 4. Scope of lactam ring-expansion reactions with N-functionalised amino acids.

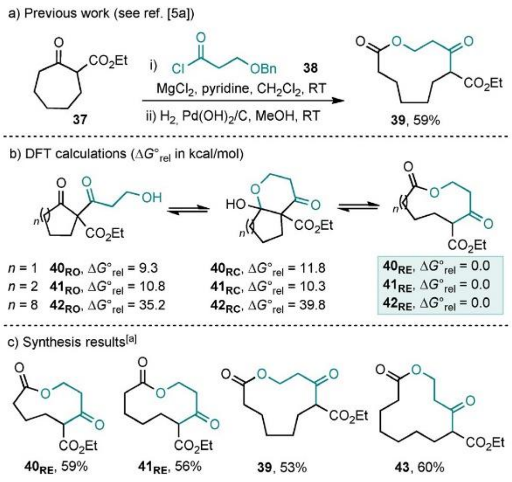
with the preceding N-acylation step. For example, in the case of furan derivative **27 v**, the lower yield is largely due to incomplete N-acylation (step i), which in turn is likely to be a consequence of the relative instability of the acid-sensitive furan motif. Unexpected side reactions/degradation also cannot be ruled out during the ring-expansion reaction (step ii) in cases where more reactive functional groups are involved.

Next, we examined the ring expansions of cyclic β-ketoesters. These reactions were the subject of our first two publications in this area,[5a,b] which focused mainly on the insertion of β-amino acid derived linear fragments; for example, five- to eight- and 12-membered cyclic β-ketoesters (**28**) were all found to undergo smooth ring expansion (to form products of the type **30**) upon reaction under the reported conditions with β-alanine derived acid chloride **29** (Scheme 5 a).[5a] DFT/B3LYP/6-31G* calculations were performed to measure the energies of the equilibrating isomers of the five-, six-, and 12-membered ring systems **31**–**33** as before. Pleasingly, the calculations suggest that the ring-expanded isomers are lowest in energy by a clear margin, suggesting that there is a strong thermodynamic driving force for ring expansion in this series (Scheme 5 b). To complete the synthetic series, we went on to perform the ring expansion of nine- to 11-membered β-ketoesters for the first time, with these new synthetic reactions proceeding well, affording lactams **34**–**36** (52–74 %, Scheme 5 c).

The hydroxyacid-based analogue of this cyclic β-ketoester ring expansion was less well developed, with the expansion of seven-membered **37** the only example of this type featured in our previous publications to have been performed on a simple cyclic β-ketoester (Scheme 6 a). Given the importance of macrocyclic lactones in medicinal chemistry,[12] we decided to test whether the scope of this variant could be expanded. As was done for the analogous amino acid system, DFT/B3LYP/6-31G* calculations were performed to measure the energies of the equilibrating isomers of the five-, six-, and 12-membered ring systems **40**–**42** (Scheme 6 b), which again suggested that there is a clear thermodynamic driving force for ring expansion. Pleasingly, the corresponding synthetic experiments all worked well, with five- to eight-membered β-ketoesters undergoing C-acylation, hydrogenolysis and ring expansion to give ring-expanded lactones **39**, **40**$_{RE}$, **41**$_{RE}$ and **43** all in comparable yields (Scheme 6 c). In a small change to the published conditions shown in Scheme 6 a, we found that performing the hydrogenolysis in ethyl acetate (rather than methanol) and then stirring with triethylamine in chloroform led to superior reaction yields. The main reason the isolated yields are in the 50–60 % range (and not higher) is due to loss of material during the C-acylation step (especially the work-up, during which the magnesium salts can cause problems with phase separation) and these results are in line with typical yields in our previous papers.[5a,b]

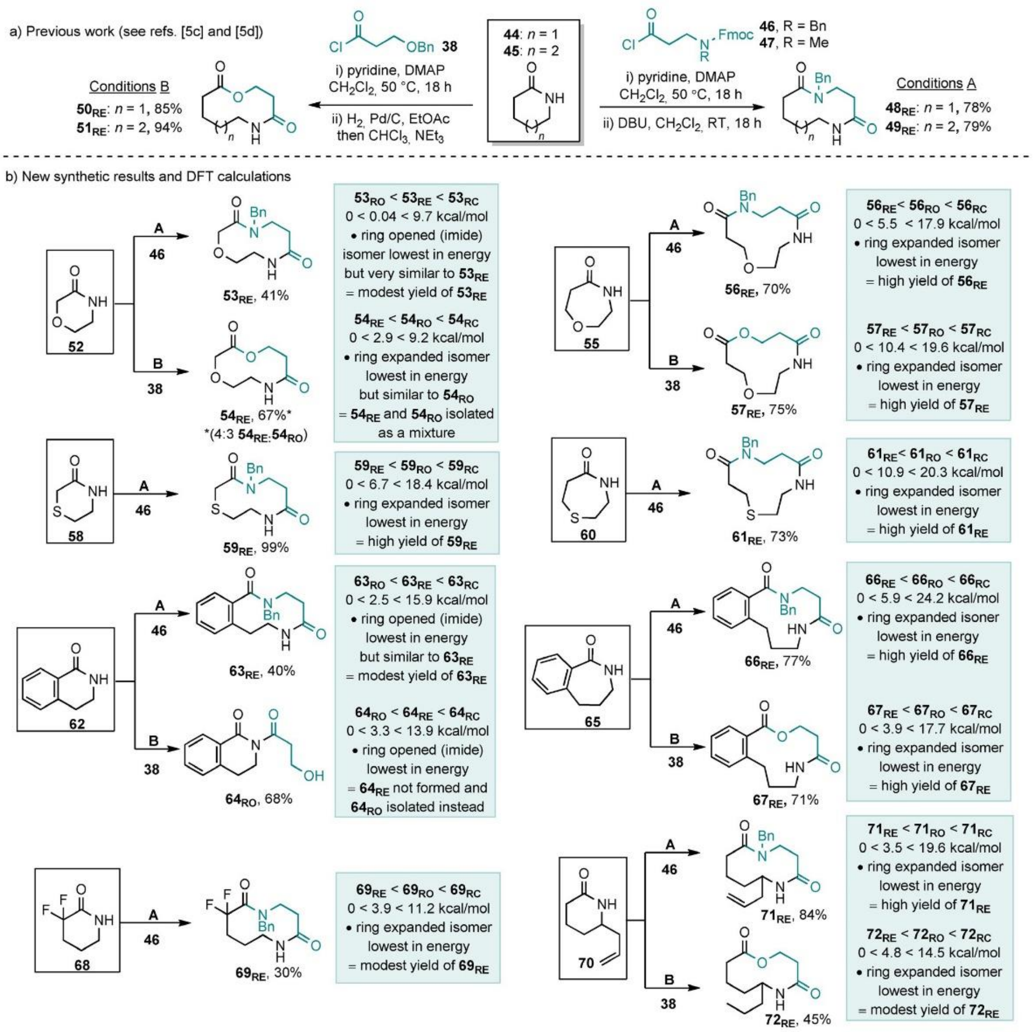


Scheme 5. Ring-size dependency of the outcome of the ring expansion of β-ketoesters with β-alanine-derived acid chloride **29**. ΔG°_{rel} values are given in kcal mol^{-1}.



Scheme 6. Ring-size dependency of the outcome of the ring expansion of β-ketoesters with β-hydroxy acid chloride **38**. ΔG°_{rel} values are given in kcal mol^{-1}. i) β-ketoester, **38**, $MgCl_2$, pyridine, CH_2Cl_2, RT; ii) Pd/C H_2, EtOAc, 3 h, RT; NEt_3, $CHCl_3$, RT, 18 h.

We then went on to test other lactam-based ring expansion systems with additional functionality present in the starting lactams. Hydroxyacid and amino acid derivatives **38** and **46** were used to exemplify the synthetic reactions, and in the calculations for **46**, a simplified N-methyl (rather than N-benzyl) derivative was used (i.e., from **47**) as this significantly reduced the computational time but was found to have very little impact on the calculations.[13] Thus, we started by examining lactams containing α-heteroatoms (**52**, **55**, **58** and **60**) with amino acid and hydroxyacid derivatives **38** and **46**. The analogous heteroatom-free variants of these reactions had been tested in our earlier work (Scheme 7 a) and were shown to be high yielding. Therefore, based purely on our chemical intu-



$53_{RO} < 53_{RE} < 53_{RC}$
0 < 0.04 < 9.7 kcal/mol
- ring opened (imide) isomer lowest in energy but very similar to 53_{RE} = modest yield of 53_{RE}

$54_{RE} < 54_{RO} < 54_{RC}$
0 < 2.9 < 9.2 kcal/mol
- ring expanded isomer lowest in energy but similar to 54_{RO} = 54_{RE} and 54_{RO} isolated as a mixture

$56_{RE} < 56_{RO} < 56_{RC}$
0 < 5.5 < 17.9 kcal/mol
- ring expanded isomer lowest in energy = high yield of 56_{RE}

$57_{RE} < 57_{RO} < 57_{RC}$
0 < 10.4 < 19.6 kcal/mol
- ring expanded isomer lowest in energy = high yield of 57_{RE}

$59_{RE} < 59_{RO} < 59_{RC}$
0 < 6.7 < 18.4 kcal/mol
- ring expanded isomer lowest in energy = high yield of 59_{RE}

$61_{RE} < 61_{RO} < 61_{RC}$
0 < 10.9 < 20.3 kcal/mol
- ring expanded isomer lowest in energy = high yield of 61_{RE}

$63_{RO} < 63_{RE} < 63_{RC}$
0 < 2.5 < 15.9 kcal/mol
- ring opened (imide) lowest in energy but similar to 63_{RE} = modest yield of 63_{RE}

$64_{RO} < 64_{RE} < 64_{RC}$
0 < 3.3 < 13.9 kcal/mol
- ring opened (imide) lowest in energy = 64_{RE} not formed and 64_{RO} isolated instead

$66_{RE} < 66_{RO} < 66_{RC}$
0 < 5.9 < 24.2 kcal/mol
- ring expanded isoner lowest in energy = high yield of 66_{RE}

$67_{RE} < 67_{RO} < 67_{RC}$
0 < 3.9 < 17.7 kcal/mol
- ring expanded isomer lowest in energy = high yield of 67_{RE}

$69_{RE} < 69_{RO} < 69_{RC}$
0 < 3.9 < 11.2 kcal/mol
- ring expanded isomer lowest in energy = modest yield of 69_{RE}

$71_{RE} < 71_{RO} < 71_{RC}$
0 < 3.5 < 19.6 kcal/mol
- ring expanded isomer lowest in energy = high yield of 71_{RE}

$72_{RE} < 72_{RO} < 72_{RC}$
0 < 4.8 < 14.5 kcal/mol
- ring expanded isomer lowest in energy = modest yield of 72_{RE}

Scheme 7. Lactam ring-expansion reactions and DFT calculations. ΔG°_{rel} values are given in kcal mol^{-1}.

ition at this stage, we did not expect to see much variation upon switching to these new systems. However, starting from six-membered lactam **52**, a much lower isolated yield (41 %) of the ring-expanded product **53**$_{RE}$ was obtained in the amino acid series, while the ring-expanded lactone **54**$_{RE}$ was isolated as an inseparable mixture with its ring-opened imide form **54**$_{RO}$. The calculations give clues as to why these reactions did not proceed well; for example, the ring-opened and ring-expanded isomers **53**$_{RO}$ and **53**$_{RE}$ were calculated to have very similar Gibbs free energies, thus suggesting that both may be formed in this reaction, although only the relatively non-polar product **53**$_{RE}$ was isolated after chromatography, in modest yield. Compounds **54**$_{RO}$ and **54**$_{RE}$ were also calculated to be similar in free energy and in this case a mixture of products was isolated. Conversely, upon moving to seven-membered starting material **55**, a clear preference for the ring-expanded isomer was predicted by the calculations, which manifested in much improved synthetic yields for the desired ring-expanded isomers (70 and 75 % for **56**$_{RE}$ and **57**$_{RE}$ respectively).

In contrast to oxygen-containing **52** and **55**, sulfur-containing lactams **58** and **60** both performed well in the synthetic ring-expansion reactions with **46**;[14] ring-expanded products

59$_{RE}$ and **61**$_{RE}$ were each formed in good yield. This was again mirrored in the calculations, with **59**$_{RE}$ and **61**$_{RE}$ calculated to be the lowest energy isomers in each case by clear margins. The difference in reactivity between **52** and **58**, which is presumably a result of some relatively subtle stereoelectronic effects and/or differences in bond lengths, is not something that we would have predicted without the calculations.

We also examined benzannulated, fluorinated and branched lactam starting materials **62**, **65**, **68** and **70**, and as before, the predictive ability of the calculations was retained. Indeed, the ability to predict when reactions will fail completely is also important; for example, the ring-opened imide isomer **64**$_{RO}$ was calculated to be the most stable isomer in this series, and this was corroborated by the synthetic results.

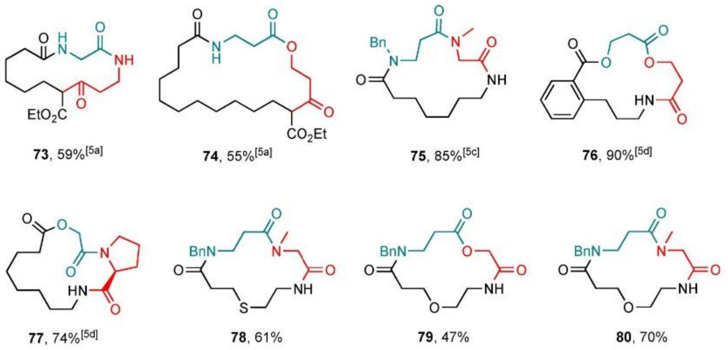
In general, we have found that for systems in which the ring-expanded isomer is calculated to be the lowest in energy by more than 3 kcal mol^{-1}, then the reactions tend to work reliably. In cases where the free energy difference is less than 3 kcal mol^{-1}, the reaction outcomes are less predictable, often giving low yields of ring-expanded products and/or mixtures. The reactions to form ring-expanded products **69**$_{RE}$ and **72**$_{RE}$, which were isolated in modest 30 and 45 % yields, respectively, are outliers in terms of yield, but the lower yields in these cases simply reflect the fact that the N-acylation step did not proceed to completion in either case. Indeed, an important caveat to keep in mind when using this DFT/B3LYP/6-31G* method is that it only gives an indication of the chances of achieving a favourable equilibrium. It does not account for the efficiency of the synthetic steps that take place before the equilibrium, the possibility of off-equilibrium side reactions or other kinetic effects.

As all the ring-expanded products described in this manuscript were made using SuRE methods, they are all, in theory, potential starting materials for further ring-expansion reactions. Representative examples of products (**73**–**77**) that have been expanded for a second time in our earlier work are shown in Figure 1, with the second linear fragment inserted highlighted in red. After undergoing one ring expansion, the rings should all be large enough that they are beyond the "switch on" point for any of the ring-expansion reaction types that we have studied and calculated (not withstanding any effects resulting from the additionally added functional groups) and should therefore be thermodynamically favourable. This is corroborated by our work to date in which several successful successive ring-expansion reactions are reported. This does not mean that performing additional iterations is always routine (e.g., in some cases, the acylation reactions can be more difficult on these more functionalised systems, sometimes requiring additional equivalents of acid chloride),[5c–d] but once acylation has been achieved, ring expansion is typically straightforward. Three new examples of doubly ring-expanded products (**78**–**80**, see the Supporting Information for reaction conditions), based on new substrates made for the first time in this manuscript, have been performed and are reported here for completeness.

Computational chemistry: Method evaluation

The DFT/B3LYP/6-31G* methodology used has demonstrated, in both this and previous work,[5d] good success in predicting the outcome of SuRE reactions. Calculations at the B3LYP/6-31G* level are relatively computationally efficient, but do not take into consideration effects such as solvation and dispersion. These additions are typically used to improve the accuracy of such calculations, therefore, we decided to benchmark their effects, along with a range of functionals, in order to determine any potential method-effects in the calculations.

For this study general gradient approximation, GGA (BP86), hybrid (B3LYP and PBE0) and meta-hybrid (M06 and M06-2X) functionals were used. Solvation effects were applied using a PCM model with either dichloromethane or chloroform as relevant to simulate the reaction conditions. The effects of dispersion are inherently taken into consideration by the M06 and M06-2X functionals.[15] They were also applied using the Grimme's D3 method with Becke-Johnson damping[16] to a PBE0/def2-TZVPP single-point calculation, using the geometry and thermodynamic corrections from a BP86/SV(P) calculation; this method has been used successfully by our groups in previous projects,[17] and also tests the effect of a large triple zeta basis set.[18]



73, 59%[5a] **74**, 55%[5a] **75**, 85%[5c] **76**, 90%[5d]

77, 74%[5d] **78**, 61% **79**, 47% **80**, 70%

Figure 1. Successive ring expansion products.

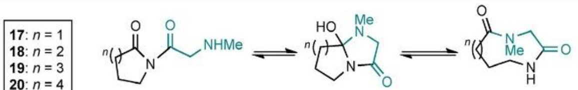
Initially, a wide range of methods were benchmarked against structures **17**–**20**, by reoptimising the structures from the B3LYP/6-31G* calculations and comparing the relative energies with the experimental outcomes (Table 1). Structures with which the ring-closed isomer has a larger energy than the ring-opened or ring-expanded isomers (**17**, **19** and **20**), produced the most comparable results, with there being little difference when using GGA or hybrid functionals with the 6-31G* basis set.

Modelling the effects of solvation also had little effect on the relative energy differences when using the hybrid B3LYP functional. Comparable results are observed both with and without solvent corrections. However, this does not extend to the BP86/SV(P) calculations, with more significant relative energy differences observed when compared to the standard B3LYP/6-31G* calculations, which appears to come from greater stabilisation of the ring-closed and ring-expanded isomers than the ring-opened when solvent is included.

The effects of dispersion had the greatest impact on the expected outcomes of the experiments, with the M06, M06-2X and D3(BJ)-PBE0 calculations showing lower relative energies for the ring-closed and ring-expanded isomers, predicting that ring expansion should be comparatively more thermodynamically favourable in these examples, and in some cases contradicting the experimental results. We believe that due to the side chain present in the ring-opened structures being directed away from the ring, there are fewer stabilising interactions present than compared to the ring-closed or expanded isomers. As a consequence of these different molecule geometries, it appears that modelling the dispersion interactions may result in the stability of the ring-expanded isomer being overpredicted when compared to the ring-opened form. This alters the expected reaction outcome where the B3LYP/6-31G* calculations predict these isomers to be similar in energy.

With dispersion effects having a large effect on the relative energy differences and the predicted thermodynamic out-

Table 1. Relative difference of Gibbs energies at 298 K for structures **17**–**20** at different levels of theory. Solvent corrections were applied using a PCM model. * Geometry from the BP86/SV(P) level.



Compound	Functional	Basis set	Solvent correction	Empirical dispersion correction	RO [kcal mol^{-1}]	RC [kcal mol^{-1}]	RE [kcal mol^{-1}]	Yield RE [%]
17 (n = 1)	B3LYP	6-31G*	N	N	0.0	16.5	1.9	0
	B3LYP	6-31G*	PCM	N	0.0	14.9	0.2	
	BP86	6-31G*	N	N	0.0	14.9	1.6	
	PBE0	6-31G*	N	N	0.0	14.1	1.2	
	M06	6-31G*	PCM	N	0.0	10.8	−2.1	
	M06-2X	6-31G*	PCM	N	0.0	8.7	−1.6	
	BP86	SV(P)	PCM	N	0.0	11.5	−2.1	
	PBE0*	def2-TZVPP	PCM	D3(BJ)	0.0	9.2	−3.3	
18 (n = 2)	B3LYP	6-31G*	N	N	0.0	3.9	2.1	0
	B3LYP	6-31G*	PCM	N	0.0	2.2	−1.1	
	BP86	6-31G*	N	N	0.0	0.5	−1.1	
	PBE0	6-31G*	N	N	0.0	−0.6	−1.6	
	M06	6-31G*	PCM	N	0.0	−3.0	−3.8	
	M06-2X	6-31G*	PCM	N	0.0	−4.5	−4.1	
	BP86	SV(P)	PCM	N	0.0	−1.2	−3.0	
	PBE0*	def2-TZVPP	PCM	D3(BJ)	0.0	−3.0	−5.3	
19 (n = 3)	B3LYP	6-31G*	N	N	0.0	6.4	0.7	0
	B3LYP	6-31G*	PCM	N	0.0	6.2	−0.3	
	BP86	6-31G*	N	N	0.0	5.5	−0.4	
	PBE0	6-31G*	N	N	0.0	4.4	−1.3	
	M06	6-31G*	PCM	N	0.0	1.1	−3.8	
	M06-2X	6-31G*	PCM	N	0.0	−0.5	−3.4	
	BP86	SV(P)	PCM	N	0.0	2.7	−1.8	
	PBE0*	def2-TZVPP	PCM	D3(BJ)	0.0	0.7	−5.0	
20 (n = 4)	B3LYP	6-31G*	N	N	7.3	14.1	0.0	82
	B3LYP	6-31G*	PCM	N	9.9	16.1	0.0	
	BP86	6-31G*	N	N	8.3	13.8	0.0	
	PBE0	6-31G*	N	N	8.8	13.3	0.0	
	M06	6-31G*	PCM	N	12.2	12.8	0.0	
	M06-2X	6-31G*	PCM	N	11.4	10.5	0.0	
	BP86	SV(P)	PCM	N	11.1	13.6	0.0	
	PBE0*	def2-TZVPP	PCM	D3(BJ)	13.4	14.0	0.0	

comes on these examples, the study was extended to include these effects to several other systems, using the M06-2X/6-31G* methodology. A comparison between this method and B3LYP/6-31G* is presented in Table 2. As observed with structures **17**–**20** (Table 1), the main difference between the two methods is that, when compared to the ring-expanded form, the relative energies of the ring-closed forms are lower at the M06-2X/6-31G* level ($\Delta_{ave} = -5.2$ kcal mol^{-1}), and ring-opened isomers increased ($\Delta_{ave} = 3.1$ kcal mol^{-1}). In most instances this doesn't change the expected outcome of the reaction, however, where there is a smaller difference in the energy of the ring-opened and ring-expanded isomers (see **53**, **63** and **64**), this does result in ring expansion being predicted to be favourable. Notably in some examples the intermediate ring-closed isomer becomes lower in energy than the ring-opened, however, this does not seem to correlate to any observable difference in how well the reaction proceeds experimentally (see **32**, **40** and **69** for examples).

Thus, for either method, both the B3LYP and M06-2X functionals correctly predicts the expected reaction outcomes in the majority of cases, although on average, it is the B3LYP method that more closely correlates with the experimental findings, despite the fact that the M06-2X functional usually performs better for organic molecules due to the inclusion of dispersion corrections.[15,19] Therefore, we believe that these results clearly demonstrate that the B3LYP/6-31G* methodology is suitable as an aid for predicting the outcome of SuRE reactions, balancing computational efficiency with good prediction of reaction outcome. The observation that a greater than 3 kcal mol^{-1} energy difference between ring-opened and ring-expanded isomers is needed to more confidently predict the outcome of the reaction, is based upon the inherent computational accuracy of these calculations

Table 2. Relative difference of Gibbs energies at 298 K. Solvent corrections were applied using a PCM model with either dichloromethane or chloroform as relevant for the M06-2X/6-31G* calculations. See the Supporting Information for absolute energies. Blue numbers denotes the most significant differences between the two methods >3 kcal mol^{-1}. Δ_{ave} is defined as the mean value of the energy at M06-2X/6-31G*—energy at B3LYP/6-31G*.

Compound	Functional/ basis set	RO [kcal mol^{-1}]	RC [kcal mol^{-1}]	RE [kcal mol^{-1}]	Yield RE [%]
31	B3LYP/6-31G*	10.0	12.6	0.0	67[5a]
	M06-2X/6-31G*	12.5	10.2	0.0	
32	B3LYP/6-31G*	8.1	9.7	0.0	82[5a]
	M06-2X/6-31G*	10.5	3.7	0.0	
33	B3LYP/6-31G*	36.6	45.4	0.0	80[5a]
	M06-2X/6-31G*	38.0	34.7	0.0	
40	B3LYP/6-31G*	9.3	11.8	0.0	59
	M06-2X/6-31G*	11.7	8.1	0.0	
41	B3LYP/6-31G*	10.8	10.3	0.0	56
	M06-2X/6-31G*	10.3	3.7	0.0	
42	B3LYP/6-31G*	35.2	39.8	0.0	–
	M06-2X/6-31G*	32.6	30.5	0.0	
53	B3LYP/6-31G*	0.0	9.7	0.0	41
	M06-2X/6-31G*	6.9	7.1	0.0	
54	B3LYP/6-31G*	2.9	9.2	0.0	67[a]
	M06-2X/6-31G*	5.0	4.5	0.0	
56	B3LYP/6-31G*	5.5	17.9	0.0	70
	M06-2X/6-31G*	11.7	13.8	0.0	
57	B3LYP/6-31G*	10.4	19.6	0.0	75
	M06-2X/6-31G*	11.2	13.8	0.0	
59	B3LYP/6-31G*	6.7	18.4	0.0	99
	M06-2X/6-31G*	12.0	13.1	0.0	
61	B3LYP/6-31G*	10.9	20.3	0.0	73
	M06-2X/6-31G*	14.5	15.1	0.0	
63	B3LYP/6-31G*	−2.5	13.4	0.0	40
	M06-2X/6-31G*	2.8	10.0	0.0	
64	B3LYP/6-31G*	−3.3	10.6	0.0	0
	M06-2X/6-31G*	0.5	6.8	0.0	
66	B3LYP/6-31G*	5.9	24.2	0.0	77
	M06-2X/6-31G*	9.4	19.1	0.0	
67	B3LYP/6-31G*	3.9	17.7	0.0	71
	M06-2X/6-31G*	6.0	12.8	0.0	
69	B3LYP/6-31G*	3.9	11.2	0.0	30
	M06-2X/6-31G*	9.2	5.7	0.0	
71	B3LYP/6-31G*	3.5	19.6	0.0	84
	M06-2X/6-31G*	9.8	14.5	0.0	
72	B3LYP/6-31G*	4.8	14.5	0.0	45
	M06-2X/6-31G*	6.6	9.2	0.0	
	Δ_{ave}	3.1	−5.2	0.0	

[a] Isolated as a mixture ($\mathbf{54_{RE}}/\mathbf{54_{RO}}$ 4:3).

Conclusions

In summary, we have significantly expanded the scope of various classes of SuRE reaction, and have shown that the reaction outcomes can be predicted based on the relative Gibbs free energies of three isomeric species in equilibrium by using DFT calculations.[20] Useful conclusions can also be drawn from the significantly expanded synthetic scoping reactions and a total of 48 new ring-expanded products are reported in this manuscript. In most cases, the isomer calculated to be lowest in energy was the major product obtained in the corresponding synthetic results.

Of course, any computational predictive method of this type will never be 100 % accurate, especially given how difficult it is to model the properties and conformations of relatively flexible systems like macrocycles.[21] In view of this, the approximations involved in the calculations and the possibility that kinetic effects might prevent equilibrium being reached in some reaction systems, we do not recommend using the calculations to make quantitative predictions on reaction yields or the Boltzmann distribution of the isomers in the presumed equilibria. The guideline that a free energy difference of more than 3 kcal mol^{-1} in favour of the ring-expanded isomer when using the B3LYP/6-31G* methodology usually leads to a successful reaction is a qualitative observation, that this was true in all such cases tested in which the preceding acylation step was efficient. It should not be considered a hard rule. However, as a guide to assessing the viability of new ring-expansion reactions before embarking on synthetic effort, we do believe that this DFT/B3LYP/6-31G* method, which is widely implemented across the vast majority of computational chemistry packages, has practical utility and will be useful in directing future synthetic efforts, in our group and others.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: density functional theory · macrocycles · rearrangement · ring expansion · ring systems

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Synthesis of macrocyclic and medium-sized ring thiolactones *via* the ring expansion of lactams†

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A side chain insertion method for the ring expansion of lactams into macrocyclic thiolactones is reported, that can also be incorporated into Successive Ring Expansion (SuRE) sequences. The reactions are less thermodynamically favourable than the analogous lactam- and lactone-forming ring expansion processes (with this notion supported by DFT data), but nonetheless, three complementary protecting group strategies have been developed to enable this challenging transformation to be achieved.

Introduction

Thioesters are amongst the most important class of small molecules in biology, with thioesters such as acetyl coenzyme A playing central roles in countless biosynthetic processes.[1] The biochemistry of thioesters has also inspired the development of methods in synthetic chemistry, for example in the native chemical ligation of peptides and during protein splicing.[2] Thiolactones (the cyclic analogues of thioesters, Fig. 1) also have important biological functions; for example, homocysteine thiolactone **1** is involved in the post translational modification of proteins,[3a] acts as an allosteric Dopamine D2 receptor antagonist[3b] and may have played a role in the development of life on Earth.[3c] Thiolactones are also relevant in medicinal chemistry; *e.g.* as antibiotics (thiolactomycin **2**), or as pro-drugs, where the relative ease with which they undergo hydrolysis[4] is important in revealing the bioactive form *in vivo* (*e.g.* **3** and **4**).[5] Indeed, the ability of thiolactones to undergo ring-opening *via* reaction with water, and other nucleophiles, is often key to their use as reagents in synthetic chemistry[6] and in polymer science.[7]

Macrocyclic and medium-sized ring thiolactones are relatively rare in the literature. Of those that are known, most are prepared *via* the condensation of an activated linear thiol-tethered carboxylic acid derivative *via* an end-to-end cyclisation reaction (**5** → **6**, Scheme 1a).[8] As is common for larger ring cyclisation processes of this type,[9,10] these methods are often low yielding and usually require high dilution conditions and/or slow addition of reagents to afford the thiolactone products.[8]

Ring expansion represents an attractive alternative strategy for macrocycle/medium sized ring synthesis, as the inefficient end-to-end cyclisation step can be replaced with a more kinetically favourable rearrangement reaction.[11,12] However, published ring expansion approaches to make macrocyclic and medium-sized ring thiolactones are limited to only a handful of examples.[13,14] To the best of our knowledge, the first was reported by Mahajan and Araújo in 1978, and is based on the oxidative cleavage of cyclic vinyl sulfides **7** to form ring expanded thiolactones **8** (Scheme 1b).[13a,b] In addition to two papers on the synthesis of medium-sized thiolactones *via* sigmatropic rearrangements,[13c,d] the work most closely related to the present study was reported by Zhang and co-workers in 2014 (Scheme 1c).[13e] This study was based on classical side chain insertion of thiol-tethered cyclic nitro ketone **9a** to form thiolactone **10**, using a method conceptually related to previous works by Hesse and co-workers.[15]

Our main contribution to the ring expansion field is through the development of an iterative ring expansion strategy known as Successive Ring Expansion (SuRE).[16] As is illustrated in Scheme 2d, a key aspect of SuRE reactions is that the motif present in the starting material (*e.g.* the lactam in **11**) is regenerated upon ring expansion (**11** → **13**),[16c,d] thus enabling additional iterations of the same reaction to be performed to expand the ring further (*e.g.* 2 more iterations enable the conversion of **13** → **14**). To date, our research has focused on

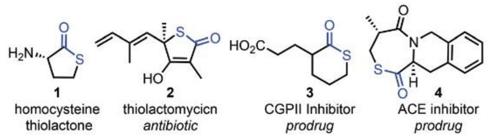

Fig. 1 Biologically important thiolactones **1–4**.

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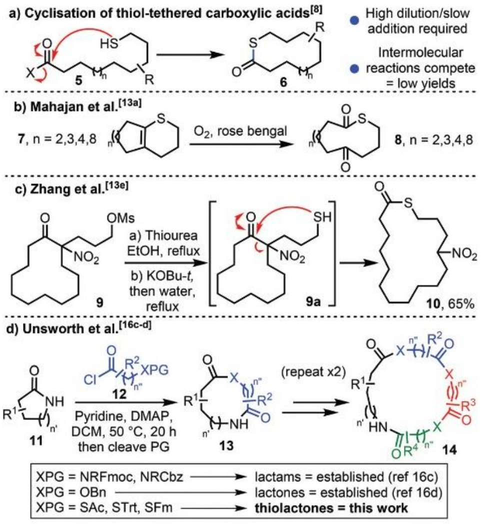
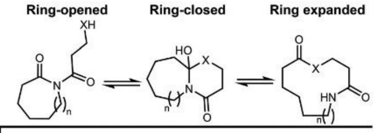
† Electronic supplementary information (ESI) available. CCDC 1921223, 2040346 and 2040347. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d0ob02502j



Scheme 1 Strategies to make medium-sized and macrocyclic thiolactones. (a) End-to-end cyclisation; (b) ring expansion *via* oxidative cleavage; (c) ring expansion *via* side-chain insertion; (d) successive ring expansion (SuRE).



	Ring-opened	Ring-closed	Ring expanded
n = 1, X = S	$\mathbf{15_{RO}}$, $\Delta G°$rel = 0.0	$\mathbf{15_{RC}}$, $\Delta G°$rel = 17.1	$\mathbf{15_{RE}}$, $\Delta G°$rel = 3.8
n = 1, X = NH	$\mathbf{16_{RO}}$, $\Delta G°$rel = 0.0	$\mathbf{16_{RC}}$, $\Delta G°$rel = 12.1	$\mathbf{16_{RE}}$, $\Delta G°$rel = -8.1
n = 1, X = NMe	$\mathbf{17_{RO}}$, $\Delta G°$rel = 0.0	$\mathbf{17_{RC}}$, $\Delta G°$rel = 15.0	$\mathbf{17_{RE}}$, $\Delta G°$rel = -5.6
n = 1, X = O	$\mathbf{18_{RO}}$, $\Delta G°$rel = 0.0	$\mathbf{18_{RC}}$, $\Delta G°$rel = 9.1	$\mathbf{18_{RE}}$, $\Delta G°$rel = -6.9
n = 0, X = S	$\mathbf{19_{RO}}$, $\Delta G°$rel = 0.0	$\mathbf{19_{RC}}$, $\Delta G°$rel = 15.4	$\mathbf{19_{RE}}$, $\Delta G°$rel = 7.5
n = 2, X = S	$\mathbf{20_{RO}}$, $\Delta G°$rel = 0.0	$\mathbf{20_{RC}}$, $\Delta G°$rel = 20.0	$\mathbf{20_{RE}}$, $\Delta G°$rel = -1.8
n = 3, X = S	$\mathbf{21_{RO}}$, $\Delta G°$rel = 0.0	$\mathbf{21_{RC}}$, $\Delta G°$rel = 17.5	$\mathbf{21_{RE}}$, $\Delta G°$rel = -7.1

Scheme 2 Relative energies of isomeric species in SuRE-type rearrangement of imides using a DFT/B3LYP/6-31G* approach. $\Delta G^{\circ}_{\mathrm{rel}}$ values at 298 K are given in kcal mol^{-1}.

SuRE reactions based on the use of amino acid (**12**, where XPG = NRFmoc or NRCbz)^{13c} or hydroxy acid (**12**, where XPG = OBn)^{13d} derivatives, to form ring expanded lactams and lactones respectively. In this manuscript, we describe our efforts to extend this concept to include S-nucleophiles. For various reasons outlined herein, these reactions were considerably more challenging to develop than the analogous processes involving N- and O-nucleophiles. Nonetheless, the successful synthesis of macrocyclic and medium-sized thiolactones *via* the ring expansion of lactams with thiol-tethered carboxylic acid derivatives has been achieved and is described here for the first time.

Results and discussion

Computational chemistry

In our earlier work, we shied away from using thiol derivatives in SuRE, as we thought the reactions would be less thermodynamically favourable than analogous reactions with amino/hydroxy acids (and hence might be harder to develop). This notion was based on a consideration of the ring expansion as an equilibrium of the type depicted in Scheme 2; we reasoned that there would be a lower thermodynamic driving force for ring expansion based on the formation of a thioester (when X = S) than there is for the formation of comparatively more stable lactams/lactones (when X = NR or O), which benefit from greater resonance stabilisation. Indeed, this idea is supported by DFT studies; using a computational method recently established by our groups to assess the viability of SuRE-type reactions,[17,18] the relative free energies isomers $\mathbf{15_{RO}}$, $\mathbf{15_{RC}}$, $\mathbf{15_{RE}}$ were calculated at the DFT/B3LYP/6-31G* level for a potential 7 → 11-membered ring expansion to form $\mathbf{15_{RE}}$. The calculations give a clear steer that this reaction is unlikely to proceed, as the ring opened isomer $\mathbf{15_{RO}}$ was calculated to be lower in energy than the ring expanded isomer $\mathbf{15_{RE}}$ by a significant margin (3.8 kcal mol^{-1}).[19] This is in contrast with calculations for the analogous 7 → 11-membered ring expansion reactions based on lactam and lactone formation (**16–18**), where the ring expanded isomers were calculated to be lower in energy in each case; indeed, these reactions have been shown to work well in our previous synthetic work.[16c,d]

When compared to the S-containing system **15**, the desired ring expanded isomer is 9.4–11.9 kcal mol^{-1} more stable in the N/O-containing analogues **16–18**. This clearly illustrates the significant additional challenge of accessing thiolactones using the SuRE method; for a more visual representation of the stark difference in the S-containing system **15**, see the simplified potential energy surfaces depicted in Fig. 2.

Nonetheless, additional calculations on the higher homologues of sulfur-containing systems gave hope that the approach may still be feasible; for example, S-containing systems **19–21** were treated in the same way, and it was calculated that the ring expanded product is the lowest energy isomer for 8- and 9-membered ring starting materials, suggesting that these larger ringed variants are viable and have a higher chance of success. Therefore, it was decided to focus on larger ring starting materials, starting with readily available 8- and 13-membered ring lactams.

Protecting group strategy selection

A key decision was the choice of protecting group for the thiol. Three complementary strategies were explored, the first based on S-acetate protection. Thus, 8- and 13-membered lactams **21a** and **21b** were both reacted with acid chloride **22** using our

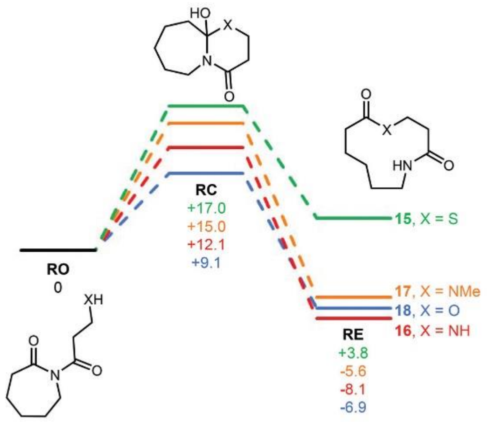
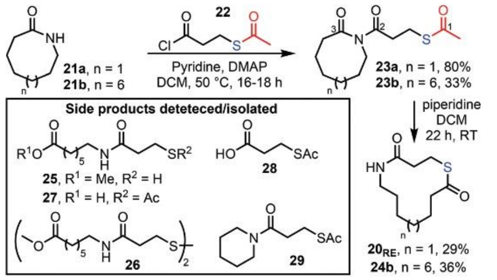


Fig. 2 Simplified potential energy surfaces for **15–18** calculated using a DFT/B3LYP/6-31G* approach. $\Delta G^{\circ}_{\mathrm{rel}}$ values at 298 K are given in kcal mol^{-1}. Note that this diagram depicts the calculated relative Gibbs free energies of the ground states of the three isomeric species in the ring expansion equilibrium only. Transition state energies were not calculated.

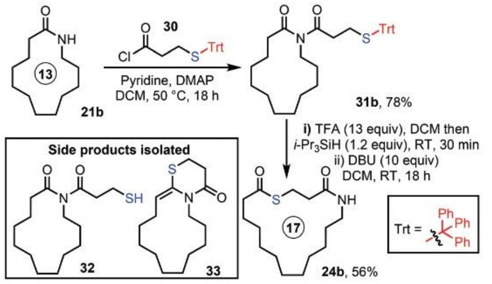
published *N*-acylation conditions to form imides **23a** and **23b** (Scheme 3). We then explored cleavage of the acetyl protecting group *via* the addition of various nucleophilic reagents, in the hope that this would result in concomitant ring expansion to form thiolactones. Of the conditions surveyed, stirring imides **23a** and **23b** with piperidine at RT in DCM were the most effective, forming thiolactones $\mathbf{20_{RE}}$ and **24b** in 29% and 36% yield respectively. However, chemoselectivity was a significant challenge using this approach; in particular, we were unable to fully discriminate between the three carbonyl groups of **23a**. For example, unwanted reaction at the cyclic carbonyl C-3 (*e.g.* to form linear products **25–27**) and/or unwanted C-2 attack (to form **28**/**29** and reform **21a**) led to a reduction in yield for the desired product in all cases (see ESI, Table S1† for a full list of conditions trialled, reaction outcomes and synthetic details).

With the S-Ac method proving difficult, we instead turned to an acid-labile trityl (Trt) protecting group strategy.[20] Exploratory studies focused on 13-membered ring lactam **21b**, which was converted into imide **31b** *via* our standard method, using acid chloride **30**. Various combinations of acids and trityl scavenger reagents were then trialled, to cleave the Trt protecting group and promote ring expansion into **24b** (see ESI, Table S2† for a full list of conditions, reaction outcomes and synthetic details). The best conditions found were those summarised in Scheme 4, in which the Trt group was first cleaved using excess TFA in the presence of a silane scavenger reagent. This was then followed by aqueous workup and finally, stirring the product mixture overnight with an excess of DBU in DCM at RT, which promoted ring expansion to form the desired thiolactone product **24b**. The yield was much-improved (56%) compared to the S-Ac strategy, but side product formation was still not fully avoided, with a new condensation side product **33** observed under some of the conditions tested (likely as a result of the switch to acidic conditions), and thiol **32** was also isolated in some cases.[21]

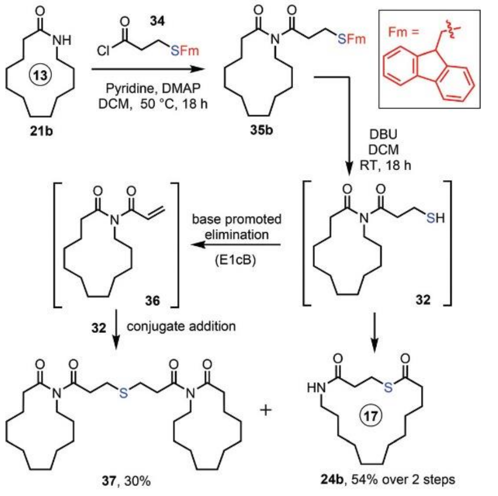
Finally, a third protecting group strategy based on the use of the fluorenylmethyl (Fm) group was explored. The Fm protecting group is used relatively infrequently in organic synthesis (certainly compared to the related Fmoc protecting group) but it has attractive properties for the protections of thiols.[22] The deprotection of Fm-protected thiols is typically done under conditions similar to those used to cleave Fmoc protecting groups from amines (*e.g.* using organic amine bases at RT). Given that such conditions were effective in our earlier work on SuRE using Fmoc-protected amino acid derivatives,[16c,d] we reasoned that this approach might reduce side product formation in the present study. Thus, the *N*-acylation of lactam **21b** with S-Fm-containing acid chloride **34** was performed to form imide **35b** (Scheme 5), which was taken directly onto the next step without purification. A non-nucleophilic base (DBU) was chosen to cleave the Fm protecting group, and pleasingly this promoted concomitant protecting group cleavage/ring expansion to form **24b** in 54% yield over the overall 2 step telescoped sequence from **21b**. Frustratingly however, the product was accompanied by formation of another side product not observed in using the



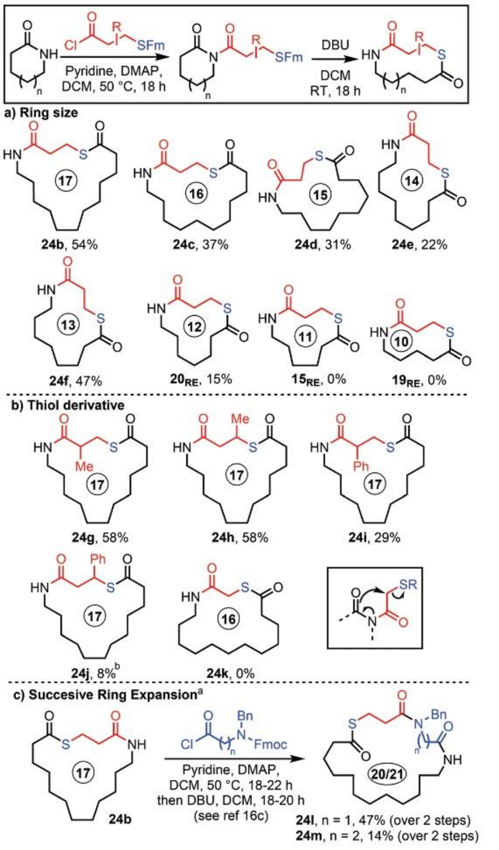
Scheme 3 SuRE using an S-Ac protecting group strategy.



Scheme 4 SuRE using an S-Trt protecting group strategy.



Scheme 5 SuRE using an S-Fm protecting group strategy.



Scheme 6 Scope of the SuRE method using thiol-tethered carboxylic acid derivatives. [a] Using our published method (ref. 16c). [b] *N*-Acylation step performed at RT (see ESI† for full details).

other protecting group strategies, in this case dimer **37**. We presume that **37** is formed *via* base promoted elimination of **32** (or **35b**) to form acrolein derivative **36**, which then reacts with another molecule of thiol **32** *via* conjugate addition.

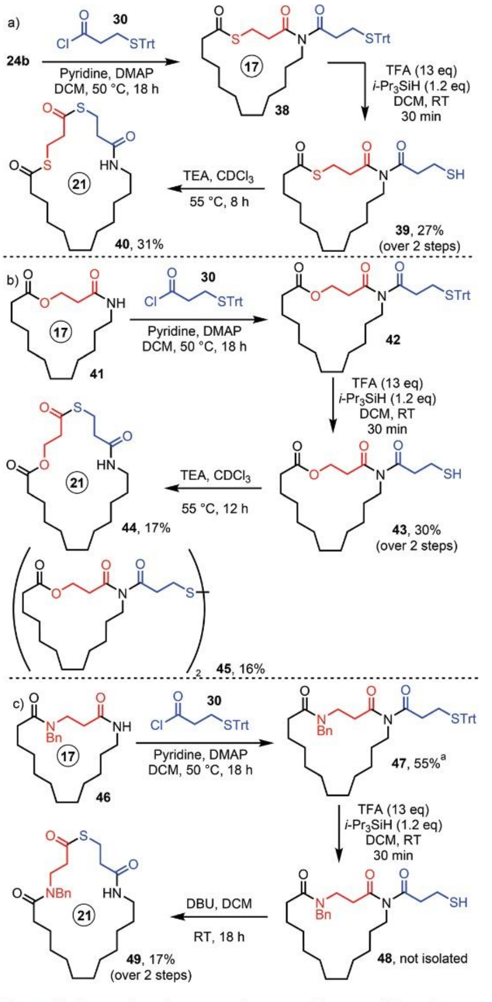
Reaction scope

Despite not being able to fully suppress all side reactions, we were satisfied with the overall yield of **24b** (54% over 2 steps) achievable using the S-Fm protocol. Therefore, this approach was taken forward onto the reaction scoping phase of the project. We started by examining the effect of varying the lactam ring size, with 6–13-membered lactams all tested, using S-Fm-tethered acid chloride **34** and the procedure in Scheme 6. Pleasingly, the ring expanded thiolactone products were obtained for all the 8–13-membered parent lactams (**24b–f** and $\mathbf{20_{RE}}$, 15–54%, Scheme 6a). Overall yields for the telescoped acylation/Fm cleavage/ring expansion sequence were generally modest, with the lowest yield obtained for the 8 → 12-membered ring transformation to form $\mathbf{20_{RE}}$, which is not surprising given that the DFT results discussed earlier (Scheme 2) predicted this to be a borderline case thermodynamically. Conversely, the 10- and 11-membered ring products $\mathbf{15_{RE}}$ and $\mathbf{19_{RE}}$ were not formed at all, which was expected given that the ring opened imide isomers were calculated to be significantly lower in energy than the ring-expanded products for these examples.

Branching is tolerated on the linear fragment, with thiolactones **24g–j** all being formed using the standard protocol (Scheme 6b). The yields were comparatively low for the phenyl-substituted systems, likely due to competing elimination reactions; for example, in forming **24j**, a significant quantity of a cinnamyl side product (resulting from base-promoted S-elimination, *c.f.* Scheme 5) was observed in the reaction mixtures, even upon reducing the temperature for the *N*-acylation step.[23] Unfortunately, we were unable to form 16-membered thiolactone **24k** in the same way, using a shorter α-substituted homologue of the S-Fm-tethered acid chloride, with substrate degradation *via* a pathway known to lead to polymerisation (Scheme 6b box) proposed to be the main problem in this case.[24]

We also confirmed that thiolactone-containing lactams are able to undergo further ring expansion *via* SuRE with amino acid chloride derivatives, with doubly expanded macrocycles **24l** and **24m** both prepared from **24b** using our published method (Scheme 6c). The yields were lower than those of typical amino acid SuRE reactions, which is likely to be a consequence of the relatively reactive thiolactone enabling side reactions of the type already described, but nonetheless we were pleased to learn that thiolactones can be incorporated into larger macrocycles as part of iterative ring expansion sequences.

Other attempts to use the new method as part of longer sequences were more challenging however; for example, we were unable to form a doubly expanded product *via* the sequential insertion of two thiolactones (*e.g.* **40**, Scheme 7) using the standard protocol. Thankfully, we were able to develop a reasonable work-around by using the S-Trt protecting group strategy and adding purification steps at intermediate points in the synthesis (Scheme 7). For example, *N*-acylation of thiolactone-containing lactam **24b** with acid chloride **30**, followed by cleavage of the Trt protecting group furnished imide thiol **39**, with chromatographic purification used after each step. Triethylamine was then used to promote the ring expansion, which was done in $CDCl_3$ to aid reaction monitoring, thus affording bis-thiolactone **40** in modest yield (Scheme 7a).



Scheme 7 Successive ring expansion- special cases. [a] Contains trace impurities (see ESI†).

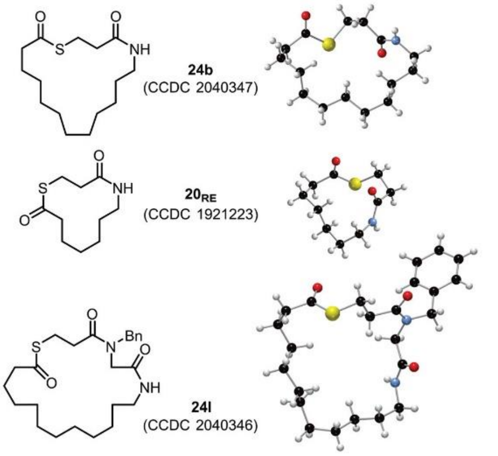


Fig. 3 X-ray crystal structures for **24b**, $\mathbf{20}_{\mathbf{RE}}$ and **24l**.

Macrocycle **44**, a product which contains a lactam, a lactone, and a thiolactone group, was also prepared using a similar strategy, starting from a previously reported lactone SuRE product **41** (Scheme 7b).[16d] Another previously unobserved side product was isolated in this case, disulfide **45**, presumably as a result of oxidation of **43** by adventitious oxygen; incidentally, we believe that disulfide formation may also be a minor side reaction in other reactions featured in this manuscript, although this was the only case where it was confirmed *via* isolation of a pure product. Finally, macrocycle **49** was prepared, starting from bis-lactam **46**;[16c] in this case, the ring expansion step was performed in DCM using DBU as the base (Scheme 7c).

To add additional support to the structural assignments made in this study, X-ray crystal structures were obtained for macrocyclic lactones **24b**, $\mathbf{20}_{\mathbf{RE}}$ and **24l** (Fig. 3).[25]

Conclusions

Ascertaining whether thiol-derivatives can be used in SuRE reactions was a major reason for undertaking this study. In this manuscript we have shown that they can, despite the transformation being more challenging than previous SuRE variants; while yields of >90% are common in our N- and O-SuRE processes, we have been unable to replicate this level of synthetic efficiency in the thiolactone-forming SuRE variants. The reduced thermodynamic driving force (supported by the DFT studies, see Scheme 2 and Fig. 2) for ring expansion is likely to be a significant factor that contributes to this difference; the DFT calculations as performed do not directly probe the reaction kinetics, but given the shift in calculated Gibbs free energy change for ring expansion in the S-containing cases, it is reasonable to predict that there would also be an associated increase in transition state energies (*e.g.* considering Hammond's postulate).[26] A reduced reaction rate is not necessarily a problem when considered in isolation, but it is when kinetically accessible side reactions compete with the desired transformation, which we have clearly demonstrated to be the case for this system.[27]

More positively, thiolactone-forming ring expansion processes are rare in the literature,[13,14] and we are pleased to learn that thiolactones can be incorporated into ring-expanded lactams using SuRE. Three complementary protecting group strategies have been explored and 15 novel macrocyclic thiolactones have been prepared using the new methods, which generally proceed in good overall yield (up to 58%) over the telescoped *N*-acylation/protecting group cleavage/ring expansion sequence (≈83% per transformation). Although we are happy to acknowledge that this study was frustrating at times, observing and appreciating the various unexpected side reactions encountered will certainly help to inform future work on SuRE, as well as related studies on side chain insertion ring expansion reactions.

Experimental

Full synthetic details and spectroscopic data for all compounds are provided in the ESI.† A general synthetic procedure for the S-fluorenylmethyl (S-Fm) method (including *N*-acylation, S-Fm clevage and ring expansion) is provided here: a mixture of lactam (0.5 mmol), DMAP (0.05 mmol) and pyridine (3.0 mmol) in DCM (7 mL) under an argon atmosphere was stirred at RT for 30 min. Next, a solution of acid chloride **34** (1.5 mmol) in DCM (3 mL) was added and the resulting mixture was heated at reflux (50 °C heating block temperature) 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 (10 mL) and DBU (5.00 mmol) was added, followed by stirring at RT for 18 h, before the solvent was removed *in vacuo* and the ring-expanded product purified by flash column chromatography.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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20 P. Majer, P. F. Jackson, G. Delahanty, B. S. Grella, Y.-S. Ko, W. Li, Q. Liu, K. M. Maclin, J. Poláková, K. A. Shaffer, D. Stoermer, D. Vitharana, E. Y. Wang, A. Zakrzewski, C. Rojas, B. S. Slusher, K. M. Wozniak, E. Burak, T. Limsakun and T. Tsukamoto, *J. Med. Chem.*, 2003, **46**, 1989.

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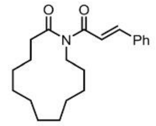

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25 CCDC 2040347 (**24b**), 1921223 ($\mathbf{20_{RE}}$) and 2040346 (**24l**) contain the crystallographic data for these macrocyclic thiolactones, see: † .

26 This is also supported qualitatively by the observation that free-thiol containing imides (*e.g.*, $\mathbf{20_{RO}}$, **32**, **39**, and **43**) were found to be isolable, kinetically stable species, while the analogous amine containing systems cannot be isolated as they ring expand spontaneously at RT (see ref. 16*c*).

27 In total, six mechanistically distinct side reactions were observed during this study: (1) nucleophilic attack at the C-3 carbonyl leading to lactam opening (*e.g.*, **25–27**); (2) nucleophilic attack at the C-2 carbonyl leading to cleavage of the external imide C–N bond (*e.g.* **28**, **29**); (3) condensation (*e.g.* **33**); (4) β-elimination of S (*e.g.* Scheme 5 and **24j**); (5) dimerisation via conjugate addition (*e.g.* Scheme 5); (6) disulfide formation (*e.g.* **45**, Scheme 7).

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Synthesis of medium-ring lactams and macrocyclic peptide mimetics *via* conjugate addition/ring expansion cascade reactions†‡

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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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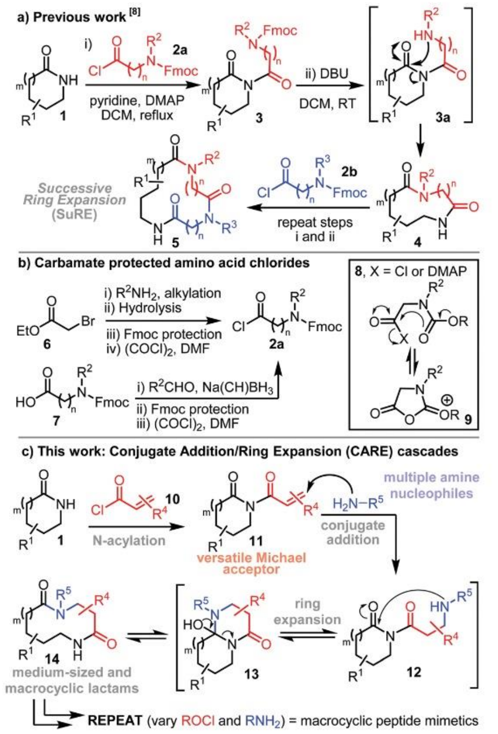
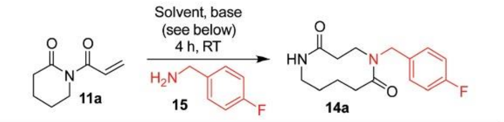
† This manuscript is dedicated to the memory of Prof Eric Marsault, who helped us greatly with scientific advice and encouragement when starting our research into biologically important macrocycles.

‡ 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



Scheme 1 Lactam ring expansion reactions.

Table 1 CARE optimisation and solvent compatibility



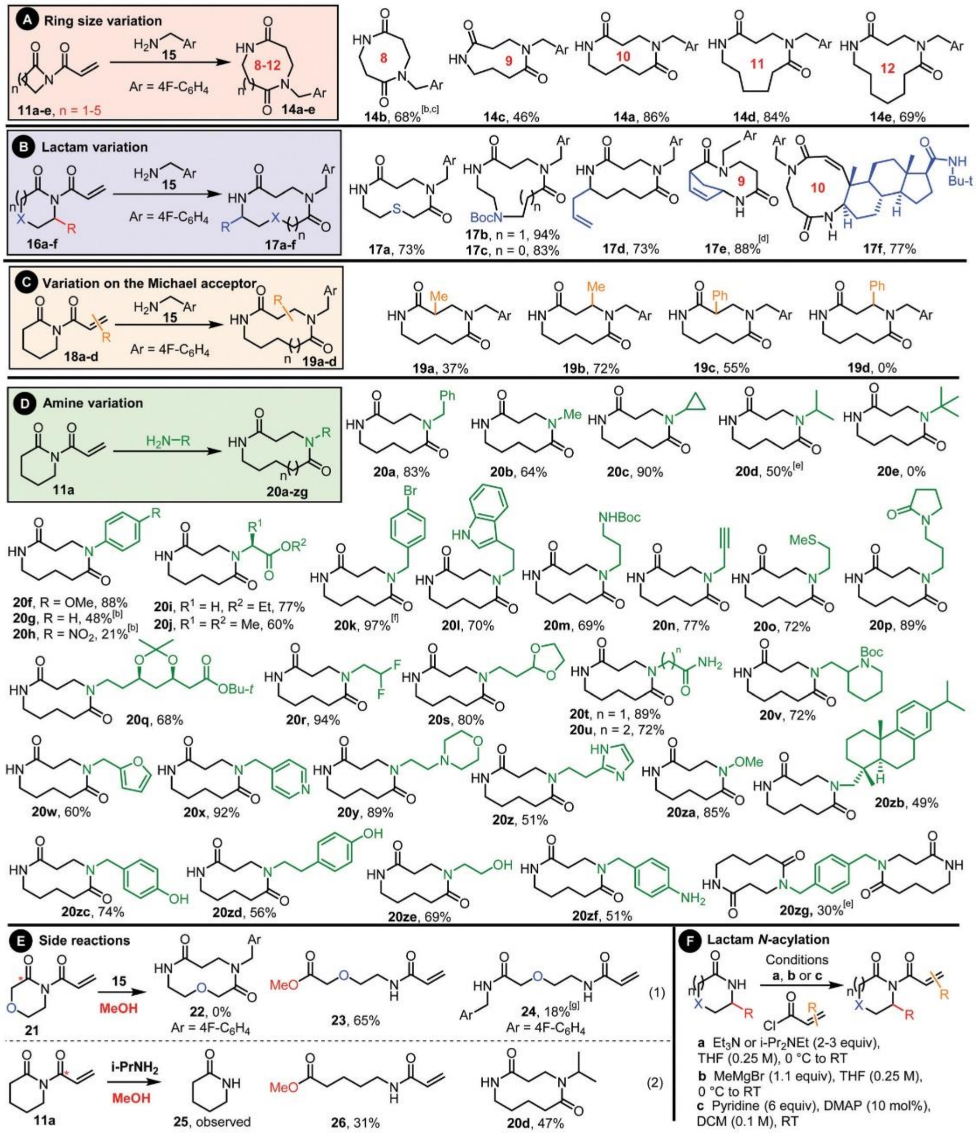
Entry	Solvent	Conc.	Base	14a/%^{a}
1	DCM^b	0.1 M	DBU (10 equiv.)	33
2	DCM^b	0.5 M	DBU (10 equiv.)	32
3	DCM	0.5 M	—	42
4	Toluene	0.5 M	—	48
5	THF	0.5 M	—	52
6	Et_2O	0.5 M	—	41
7	hexane	0.5 M	—	38
8	DME	0.5 M	—	48
9	MeCN	0.5 M	—	51
10	DMSO	0.5 M	—	77
11	DMF	0.5 M	—	77
12	DMA	0.5 M	—	78
13	NMP	0.5 M	—	80
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



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

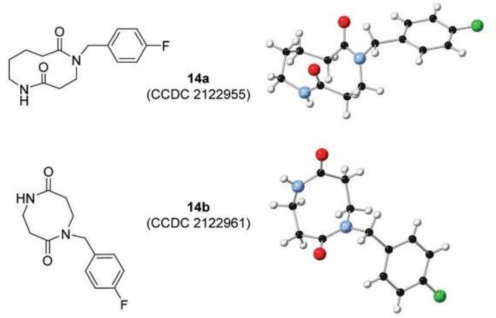


Fig. 1 X-Ray crystal structures of **14a** and **14b**. CCDC 2122955 and 2122961.

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.

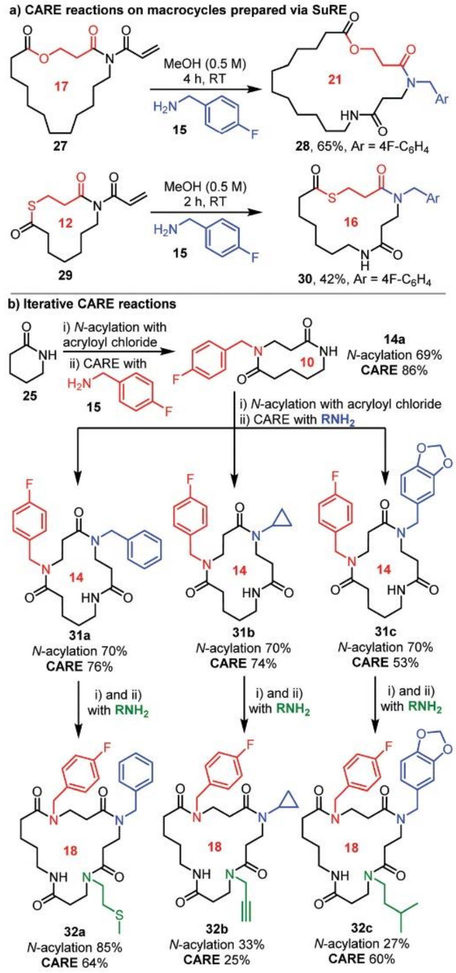
The excellent functional group compatibility of CARE is exemplified by the range of functionalised amines used to make products (**20i–zb**); all were formed in good to excellent yields from amines containing a wide array of functional groups, including esters, halides, carbamates, terminal alkynes, 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



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.

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