The Synthesis of Medium-sized Rings and Macrocycles *via* Cyclisation/Ring Expansion Cascade Reactions

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PhD

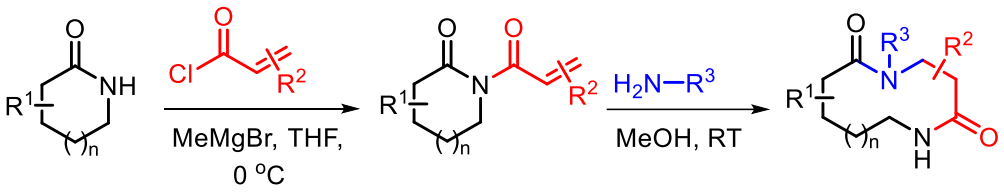
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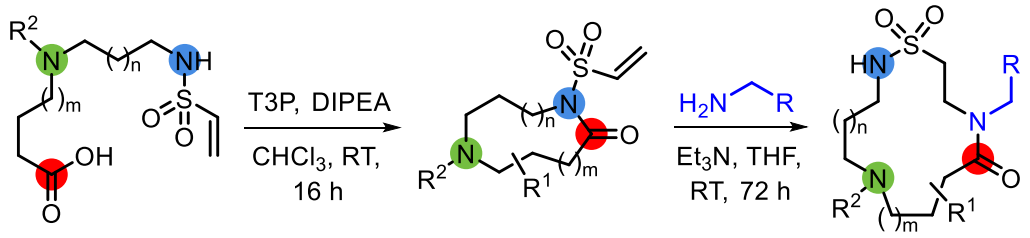
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Abstract

The primary aim of this thesis was to expand the accessibility of medium-sized rings and macrocycles using different ring expansion techniques, developed within the Unsworth group. The scope and limitations of using CARE (Conjugate Addition Ring Expansion), NICE (Nucleophile Induced Cyclisation/Expansion) and SuRE (Successive Ring Expansion) for the formation of these rings were explored and in the case of unsuccessful reactions, side-products were identified. Chapter 2 investigates the use of different nucleophiles in CARE reactions, building upon the published method using nitrogen as the nucleophilic component, by utilising carbon and oxygen nucleophiles.



A novel approach where NICE and CARE reactions were completed consecutively is described in Chapter 3. Various starting material frameworks were developed and converted into medium-sized rings (*via* NICE) and then macrocycles (*via* CARE).



Finally, in Chapter 4, collaborative projects using SuRE reactions in previously unstudied contexts are described. Supplied to the Unsworth group were bicyclic β-lactams from the Docherty group (Lancaster University) and symmetric diamine squaramides from the Elmes group (Maynooth University). Ring expansion was achieved in both cases – including the discovery of a new SuRE-like ring expansion mechanism.

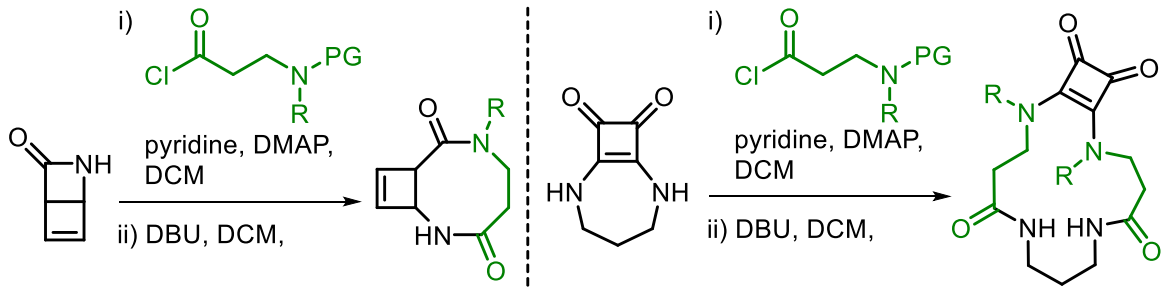


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Finally, but most importantly, the biggest thanks to my family who have done nothing but support me for the duration of my PhD and everything before that (despite neither of you really knowing what I do even when I try and explain it). It hasn't always been straightforward, but your encouragement and the trust you had for me throughout made it so much easier for me. You are both my inspiration and if the people around me think about me the same way as I think about both of you in the future, then I know I'll have done a good job in life, where I'm respected and loved!

Author Declaration

I declare that this thesis is a presentation of original work and I am the sole author. This work has not previously been presented for a degree or other qualification at this University or elsewhere. All sources are acknowledged as references.

Will E. Orukotan

Abbreviations

AIBN	azobisisobutyronitrile
APCI	atmospheric pressure chemical ionization
aq.	aqueous
Ar	aryl
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
calcd.	calculated
CARE	Conjugate Addition Ring Expansion
C-CARE	carbon-Conjugate Addition Ring Expansion
CCDC	Cambridge Crystallographic Data Centre
d	doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N,N'*-dicyclohexylcarbodiimide
DCM	dichloromethane
dd	doublet of doublets
ddd	doublet of doublets of doublets
ddt	doublet of doublets of triplets
DFT	density functional theory
DIPEA	*N,N*-diisopropylethylamine
DMAP	4-(dimethylamino)pyridine
DMF	*N,N*-dimethylformamide
DMPU	*N,N'*-dimethylpropyleneurea
DMSO	dimethyl sulfoxide
dppf	1,1'-bis(diphenylphosphino)ferrocene
dq	doublet of quartets

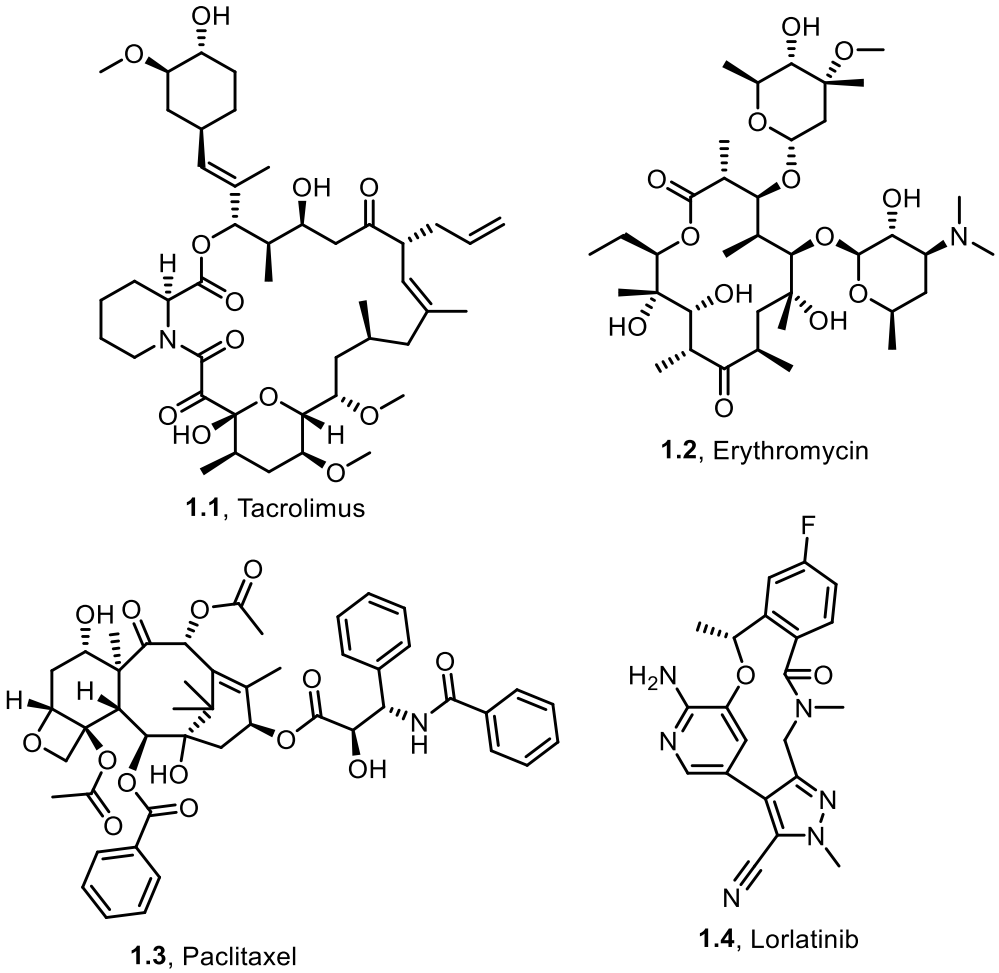
dt	doublet of triplets
dtd	doublet of triplets of doublets
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
ee	enantiomeric excess
ESI	electrospray ionization
Fmoc	fluorenylmethoxycarbonyl
HRMS	high-resolution mass spectrometry
HOBt	1-hydroxybenzotriazole
IPA	isopropyl alcohol
KHMDS	potassium bis(trimethylsilyl)amide
LDA	lithium diisopropylamide
LiHMDS	lithium bis(trimethylsilyl)amide
m	multiplet
Me	methyl
MeMgBr	methylmagneisum bromide
MeOH	methanol
m-CPBA	*meta*-chloroperoxybenzoic acid
MP	melting point
NaHMDS	sodium bis(trimethylsilyl)amide
N-CARE	nitrogen-Conjugate Addition Ring Expansion
NICE	Nucleophile Induced Cyclisation/Expansion
NMR	nuclear magnetic resonance
p	pentet
Ph	phenyl
ppm	parts per million
q	quartet

R_f	retention factor
RT	room temperature
s	singlet
sat.	saturated
SuRE	Successive Ring Expansion
t	triplet
T3P	propanephosphonic acid anhydride
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
td	triplet of doublets
THF	tetrahydrofuran
tt	triplet of triplets

1 Introduction

1.1 Macrocyclisation

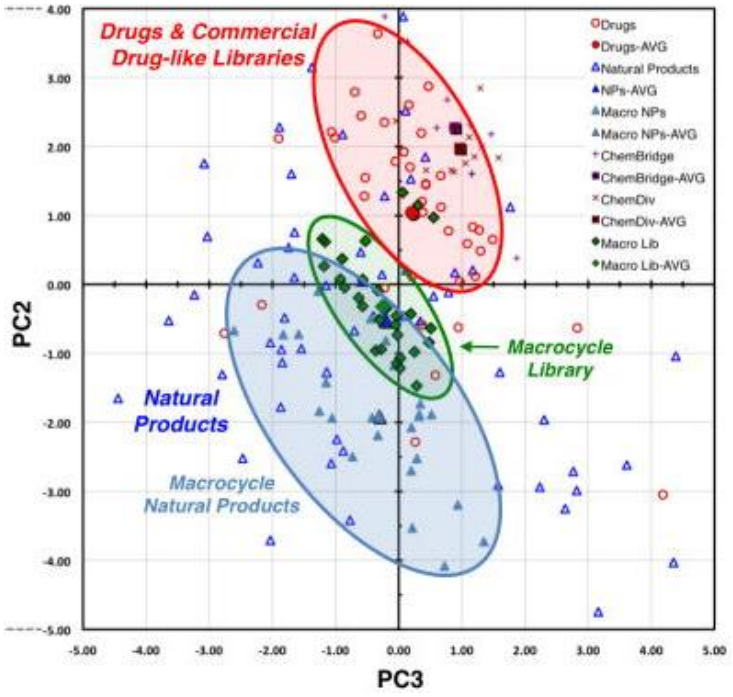
The importance of medium-sized rings (8–11-membered) and macrocycles (12+ membered) has grown significantly over the years.[1,2] Both classes of large ring molecules have several useful applications, for example, in molecular sensing,[3,4] catalysis[5,6] and supramolecular chemistry.[7,8] They have also been found in naturally occurring compounds and have a growing role in medicinal chemistry due to their well-established bioactivity (Scheme 1).[9,10]



Scheme 1. Examples of therapeutic drugs with medium-sized rings and macrocycles within their structure.

Currently, macrocyclic medicinal chemistry is dominated by naturally derived compounds (see above).[11] This is supported by a study carried out by Kopp and co-workers,[12] in which cheminformatic analysis was used to visualise how synthetic macrocyclic compounds overlapped more substantially with natural products than is seen with the current small molecule drugs, and compounds in screening libraries. Using principal component analysis (PCA), the screened compounds were analysed for 20 structural and physiochemical

properties that define the molecule, summarised in Scheme 2. This led to the conclusion that there is a clear area of underrepresentation (highlighted in green) that macrocycles could help to fill.[13]

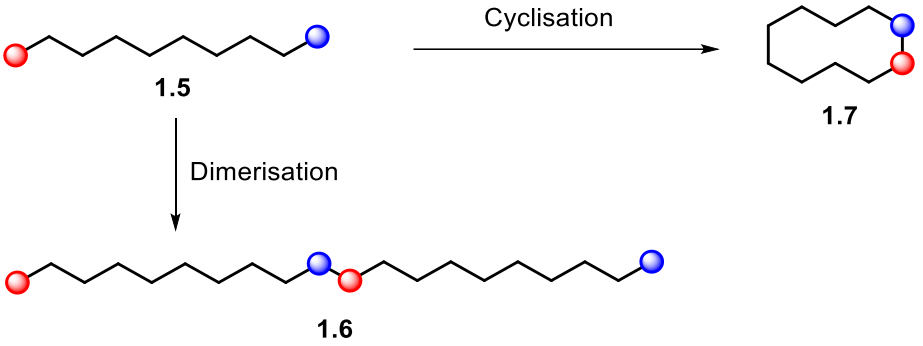


Scheme 2. Hydrophobicity and aromatic ring count shift molecules upward along the y-axis (PC2), while aqueous solubility shifts molecules downward. Notably, larger ring systems shift molecules rearward (negative) along the x-axis (PC3), and stereochemical complexity shifts molecules left and downward.[12]

A major challenge when working with these ring systems lies in their difficult synthesis, with both medium-sized rings and macrocycles suffering from destabilising interactions that are present in the products and the transition states that lead to their formation.[14,15] Pitzer strain (bond opposition forces due to imperfect staggering) and Baeyer strain (deformation of ring bond angles) are seen in all ring sizes, while transannular strain (repulsive interactions between atoms across the ring from one another when forced into close proximity) is particularly pronounced in medium-sized rings.[16]

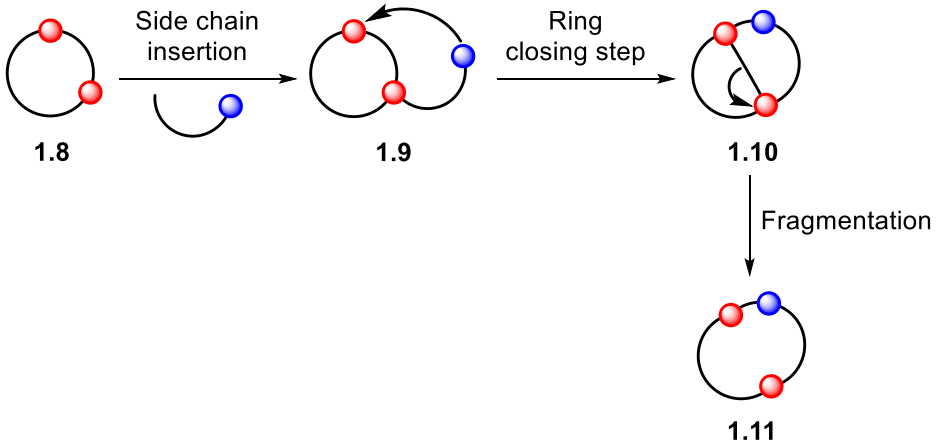
The classical approach used for the synthesis of medium-sized rings and macrocycles is end-to-end cyclisation. This approach relies on two reactive ends of a linear precursor undergoing an intramolecular coupling reaction.[17,18] Unfortunately, using this method, intermolecular side reactions often compete with the desired reaction, resulting in dimerisation and oligomerisation rather than cyclisation (Scheme 3).[19] Negating intermolecular reactions can be achieved *via* the use of high dilution conditions and slow reagent addition; this is due to the decreased chance of separate molecules colliding with one another in the solution, hence promoting the intramolecular pathway.[20,21] Nonetheless,

high dilution approaches have some downfalls: the scalability is reduced, the sustainability and practicality of the synthesis is negatively affected due to large solvent volumes that can cause difficulty in handling these amounts and there are higher reagent costs. Furthermore, yields are still unpredictable and often poor. Therefore, finding effective new methods to synthesise medium-sized rings and macrocycles that do not rely on high dilution is important.



Scheme 3. A general scheme for end-to-end cyclisation, showing the possible macrocyclisation and dimerisation steps.

An alternative method for large ring synthesis in which end-to-end cyclisation can be avoided entirely is ring expansion. Ring expansion methods focus on taking smaller ring systems and enlarging them through rearrangement reactions. Primarily, these transformations rely on the formation of a bicyclic intermediate, of which the bond that connects two rings can be broken to generate larger ring products (Scheme 4). This can enable the problems experienced in end-to-end cyclisation to be bypassed, resulting in fewer side reactions and higher reaction yields, without having to resort to high dilution conditions. Thus, this can enhance the practicality and the potential commercial value of the methods and products produced.[19,22]

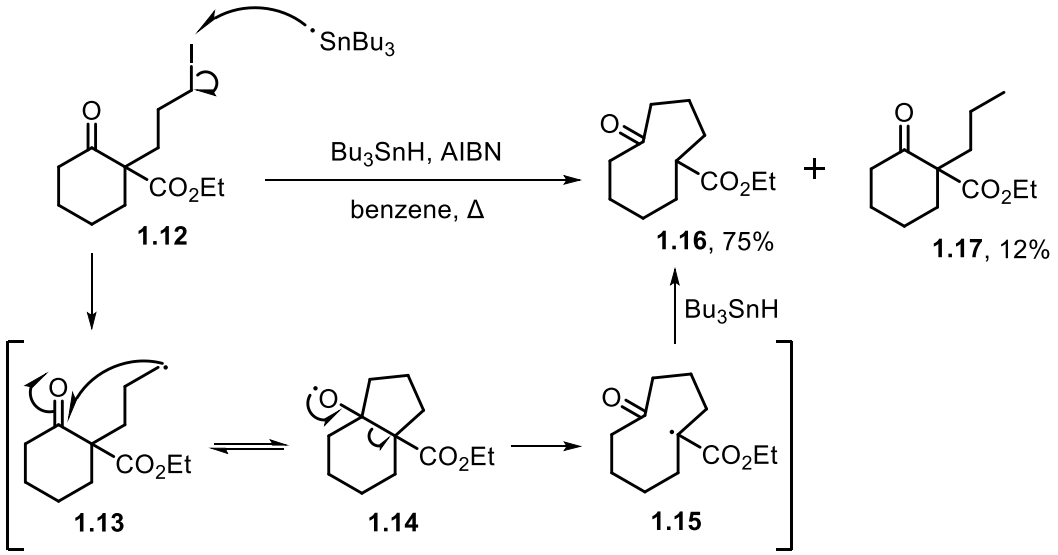


Scheme 4. A general scheme for ring expansion showing the bicyclic intermediate.

In general, ring expansion can be categorised into three main groups: radical-based, fragmentation-based and pericyclic – all of which are discussed in Sections **1.2**–**1.4** below.

1.2 Radical Ring Expansion

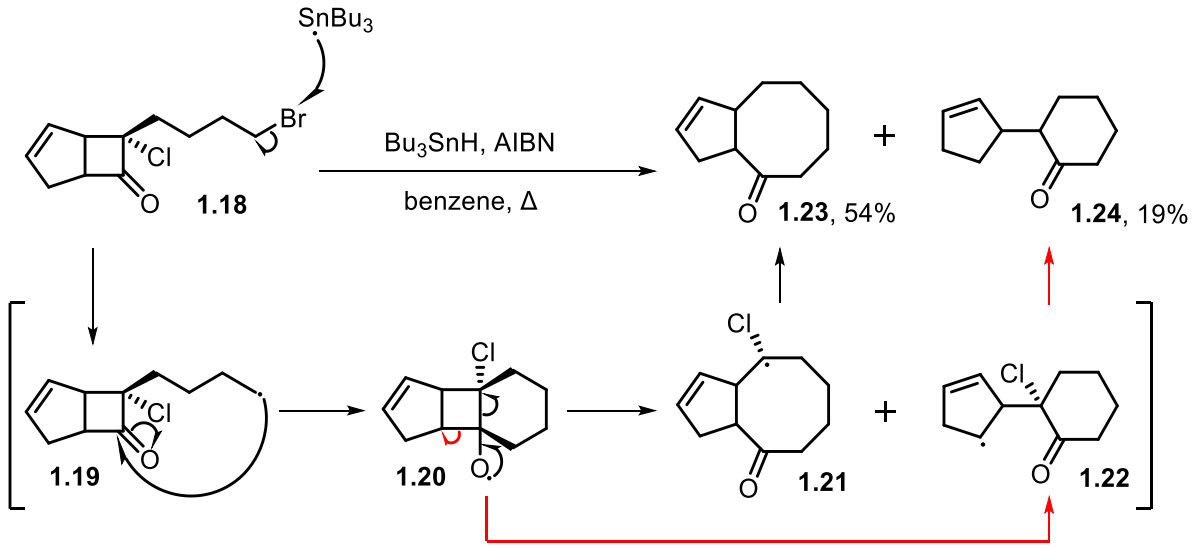
A radical ring expansion reaction involves the generation of a radical species, that goes on to rearrange and form a ring-enlarged product. Such reactions can often be driven by radical stability; for example, the preferential formation of a tertiary radical (more stable) from a primary radical (less stable) following ring expansion.[23] This is demonstrated by work done by Dowd and co-workers where they pioneered a technique that is widely implemented and versatile as a strategy for radical ring expansion of β-keto esters.[24,25] Scheme 5 shows the 3-atom ring expansion[26] where the iodobutyl compound, **1.12**, is treated with tributyltin hydride and AIBN to form the initial primary radical, **1.13**. The free radical will then attack the carbonyl in a reversible cyclisation forming a bicyclic system, **1.14**, with the radical now on oxygen. This is relatively unstable and so the equilibrium will likely lie closer to **1.13**. However, due to the fragmentation step to give the ring-expanded species, **1.15** is irreversible, it means **1.15** can be trapped out as the kinetic product and this process can be repeated until **1.13** is consumed, helping to drive forward the reaction. The radical has now moved to a more stable tertiary carbon position, adjacent to the β-keto ester – this increase in radical stability also provides a key driving force of the ring expansion reaction. A final H-atom abstraction is needed to provide **1.16** in a 75% yield. Reduction product **1.17** is a minor side-product that forms in 12% yield, formed *via* H-atom abstraction from **1.13**.



Scheme 5. Dowd and co-workers' radical ring expansion of cyclic β-keto esters and the side-product generated.

Dowd and co-workers also worked on a similar radical ring expansion reaction (Scheme 6)[27] using tributyltin hydride and AIBN as the reagents to generate a carbon-centred radical **1.19**

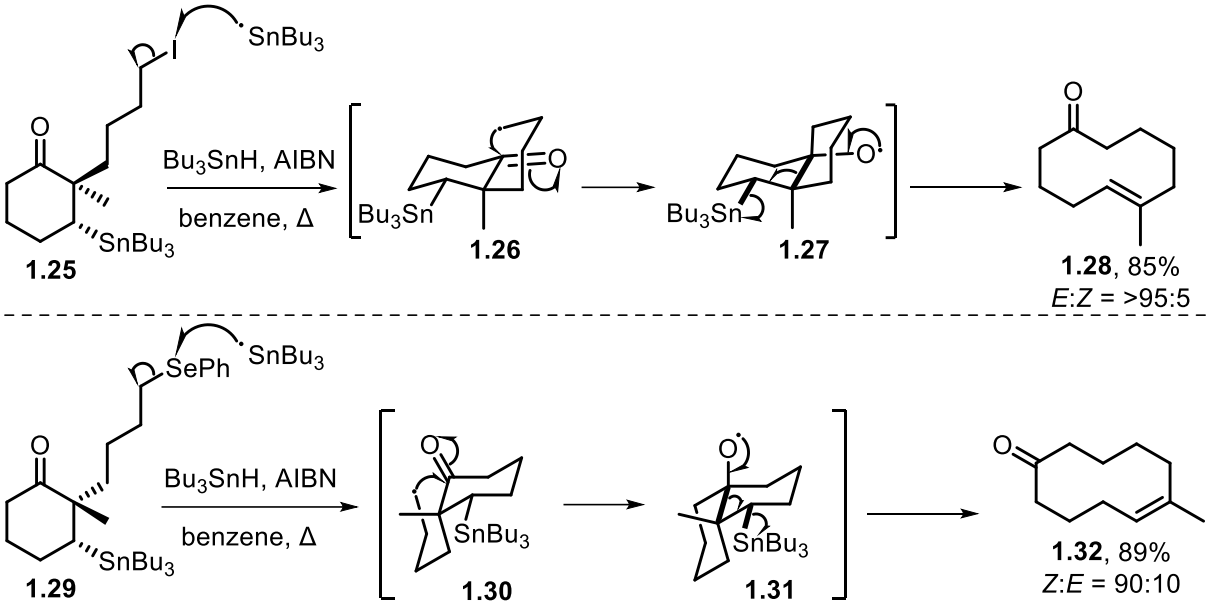
via halogen atom abstraction from **1.18**. The terminal radical in **1.19** attacks the carbonyl in the 4-membered ring, forming a bicyclic intermediate, **1.20**. The alkoxy radical can then fragment in two ways: the first is the desired route where a medium-sized ring radical **1.21** forms. A H-atom abstraction then occurs, followed by the dehalogenation where a tributyltin radical abstracts the chloride atom, before a final further abstraction of a proton from Bu_3SnH provides the final product, **1.23**. The other fragmentation pathway (curly arrow in red) instead forms a pair of normal-sized rings tethered together, **1.22**, which goes on to form **1.24**. Both have the driving force of relieving the strain contained within the 4-membered ring, but the desired product formation (**1.23**) was the major reaction outcome, likely as a result of the greater stability of radical **1.21** compared to **1.22**.



Scheme 6. Dowd and co-workers' radical ring expansion using a cyclobutanone and the side-product generated.

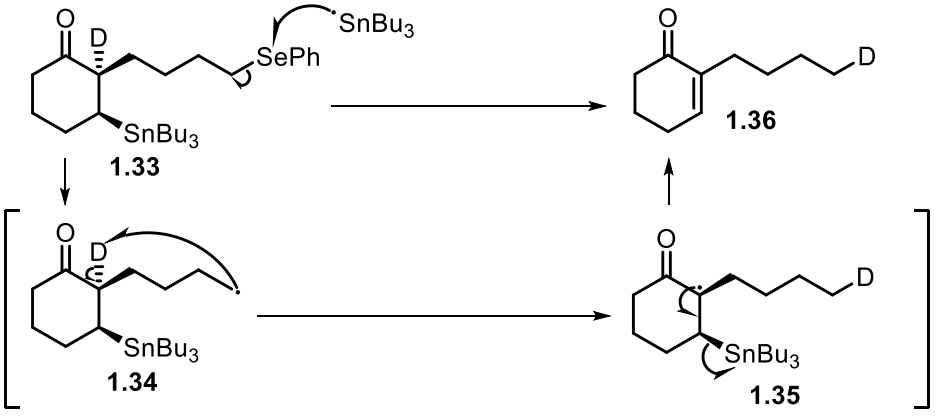
Building on the above principles, Baldwin and co-workers were able to develop a technique that also allowed control of the alkene geometry in the product.[28] In this case, along with the iodide starting materials seen previously, selenides were also used to generate the primary alkyl radicals required for the ring expansion, using tributyltin hydride and AIBN. The attack of the primary radical in **1.26** at the ketone forms a bicyclic intermediate, **1.27**, which can then undergo fragmentation (facilitated by the removal of the stable tributyltin radical) where the ketone is reformed and a 4-atom ring expansion is observed to give **1.28**. Starting with a *cis*-starting material (**1.25**), the *E*-alkene product (**1.28**) is obtained, while the *trans*-starting material (**1.29**) will produce the *Z*-alkene product (**1.32**). Both products (**1.28** and **1.32**) are able to possess defined geometry after the ring expansion due to the bulky tributyltin adopting an equatorial position preferentially when in the intermediate, bicyclic states (**1.27** and **1.31**). These cis-decalin frameworks are now in conformations that allow

the formation of the alternating stereochemistry seen in Scheme 7 upon the tributyltin group leaving.



Scheme 7. Baldwin and co-workers' radical ring expansion with elimination to form cyclic alkenes in both *E* and *Z* conformations.

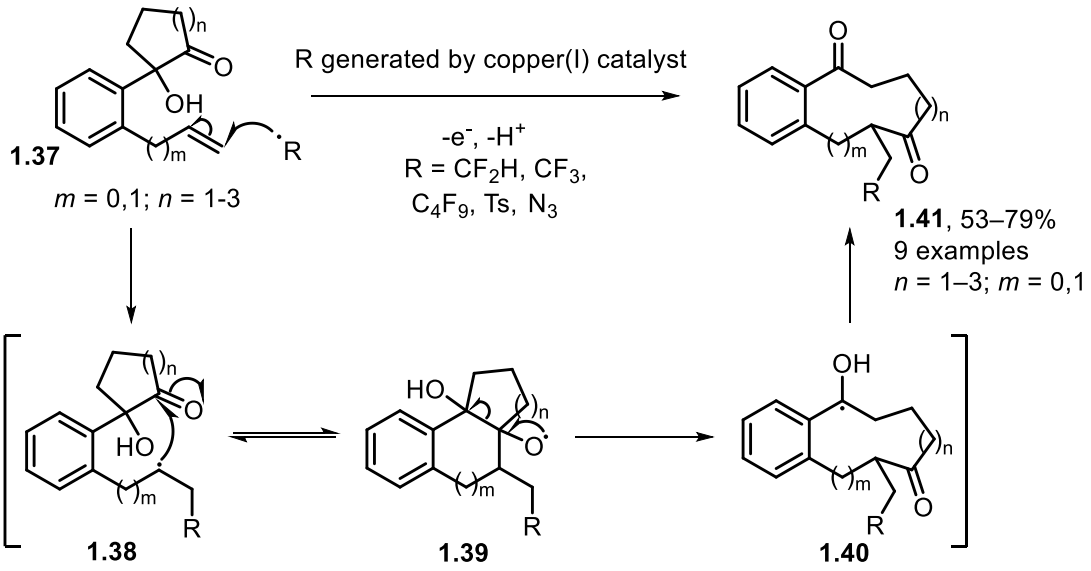
Both instances showcase high yields with **1.28** being formed in 85% and **1.32** formed in 89% yield. There are also other examples where the stereochemistry of the starting material is altered and these are able to maintain the 80+% yields. However, in examples where the yield is lower, this can usually be attributed to the generation of side-products. It was found that the main side reaction was a competing 1,5-hydrogen transfer, shown in Scheme 8,[28] which was determined *via* isotope labelling of the proton at the α-position to the carbonyl.



Scheme 8. The mechanism for the side-product generated from the competing 1,5-hydrogen transfer in the work done by Baldwin and co-workers.

Another example of a radical ring expansion reaction is one developed by Liu and co-workers based on methods in which a single electron reduction occurs to form an electrophilic

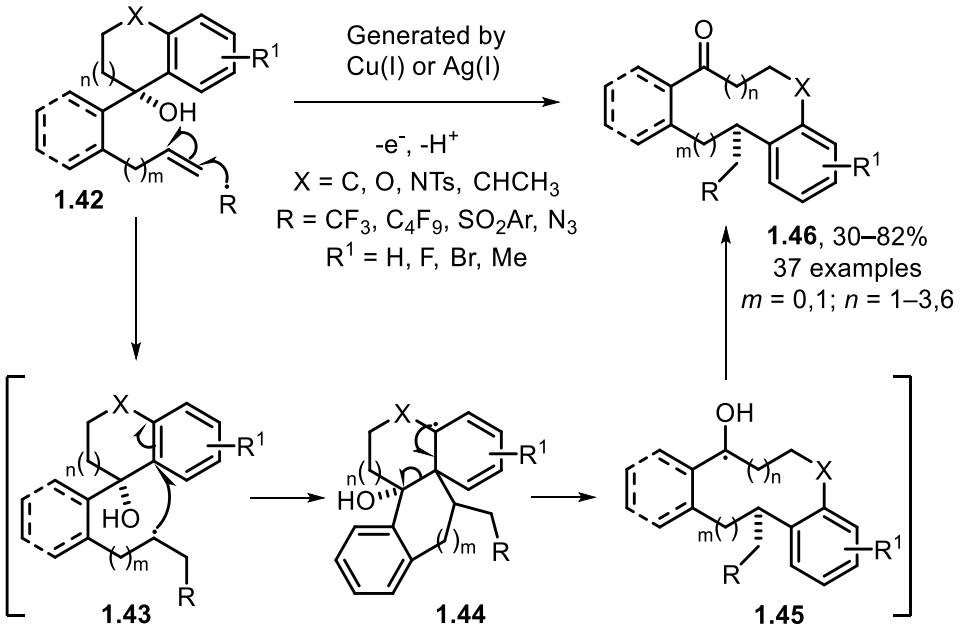
radical.[24,29] Although needing slightly different reaction conditions for each case, electrophilic radicals including azides, sulfonyls and fluoroalkyls were all found to be possible to take the role of 'R' in the reaction and add to the terminal carbon of the alkene to form intermediate radical **1.38**. A reversible carbonyl attack to make **1.39** then follows before the fragmentation which creates the ring-expanded product, **1.40**. As explained previously for Scheme 5, the kinetic product, **1.40**, was able to be gradually trapped out from the equilibrium formed between **1.38** and **1.39**, which aided as a driving force for this reaction. A final oxidation of the benzylic radical is completed by either oxidised-state photocatalyst (if sulfonyl or fluoroalkyl radicals were used) or copper(I) catalyst (if azide radicals were used) to give **1.41** while also regenerating the catalyst (Scheme 9). An additional driving force of this ring expansion reaction is the formation of radical **1.40**, a radical that is stabilised by virtue of being tertiary, benzylic and α- to a hydroxy group.



Scheme 9. Liu and co-workers' radical ring expansion using a terminal alkene and a range of electrophilic radical species.

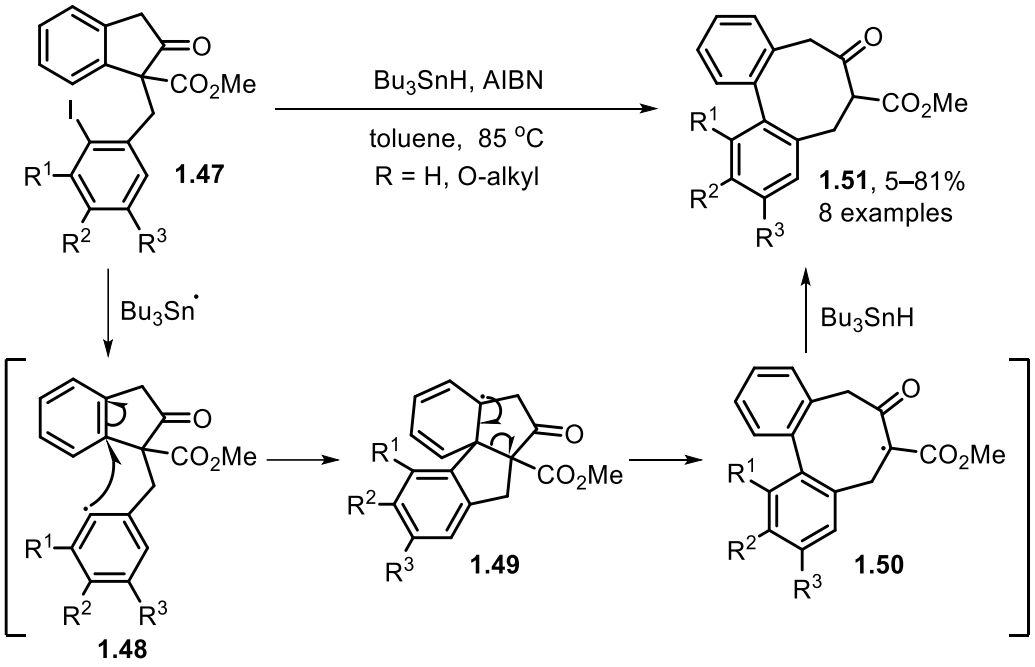
The work by Liu and co-workers was further developed by Li and co-workers, where an aryl migration strategy was used in order to form both medium-sized rings and macrocycles (Scheme 10).[30] Similarly to the previous work, a range of radicals can be used for the reaction. Addition of the in situ-formed radical to **1.42** at the terminal alkene position generates the intermediate radical, **1.43**. This secondary radical is then able to attack the aromatic system to form **1.44** *via* an *ipso*-substitution and then rearomatisation and fragmentation of the bicyclic intermediate, **1.44**, creates **1.45** – a stable benzylic ketyl radical. Oxidation then affords the final, ring-expanded product, **1.46**. Ring sizes ranging from 9–14-membered can be made using this method, with several functional groups also

able to be incorporated into the system whilst maintaining a reasonable yield, highlighting it to be a versatile technique to synthesise medium-sized rings and macrocycles.



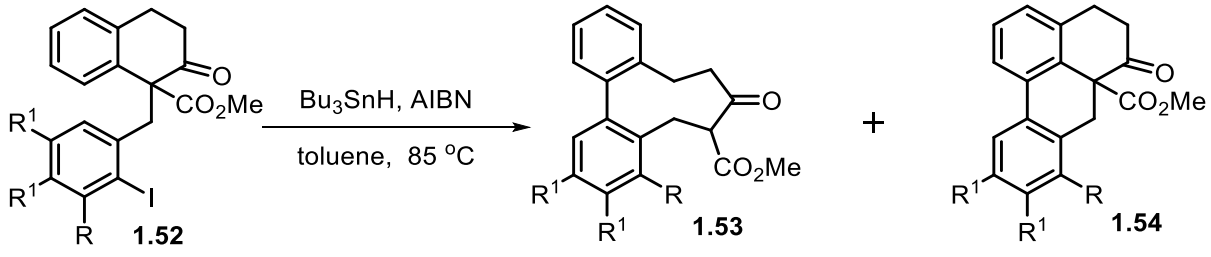
Scheme 10. Li and co-workers' radical ring expansion *via* an *ipso*-substitution.

Likewise, Harrowven and co-workers utilised a strategy that did not require a carbonyl to be directly involved in the radical mechanism (Scheme 11).[31] An aryl radical is first generated from the iodide removal using tributyltin hydride and AIBN, before **1.48** can then initiate a 5-exo-trig-cyclisation. The formation of this polycyclic intermediate, **1.49**, also causes a dearomatisation. However, following fragmentation the aromatic ring is reformed with the radical **1.50** formed and stabilised by the adjacent ketone and ester groups. A final hydrogen atom abstraction provided the final product, **1.51**, in yields ranging from 5–81%.



Scheme 11. Harrowven and co-workers' aryl radical ring expansion, *via* an *ipso*-substitution, to form 8-membered cyclic β-keto esters.

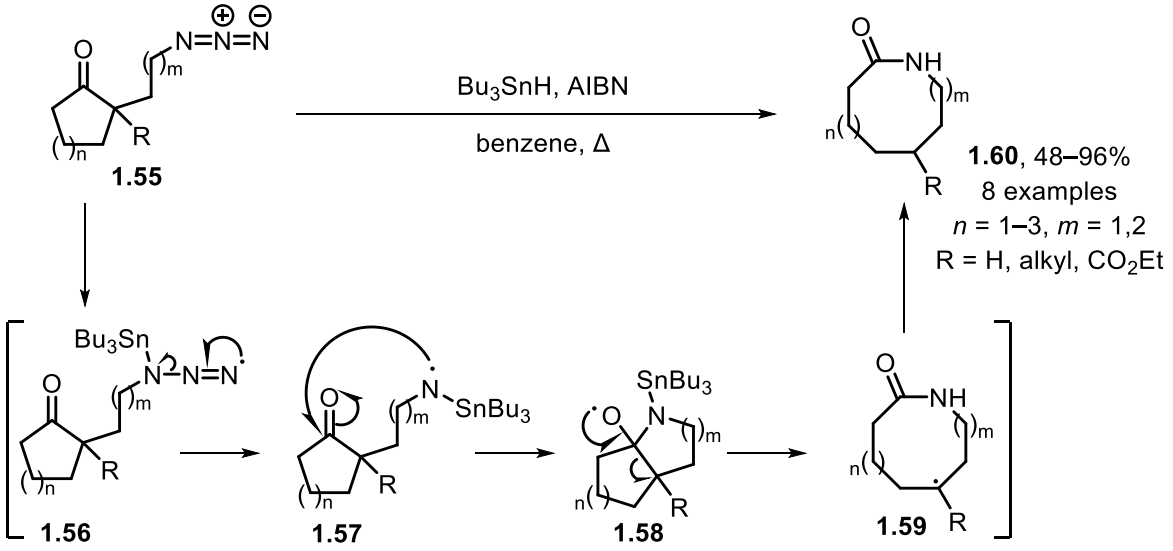
When moving on to the tetralone series, the results were not as positive with less of the expected 9-membered ring product, **1.53**, forming – instead radical addition occurred at the *ortho*-position giving **1.54** preferentially. In other cases where the R groups were altered on the starting material, there was evidence of competition between the two pathways of *ipso*-substitution and *ortho*-cyclisation, with the yields shown in Scheme 12. Disappointingly, no cases favoured the *ipso*-substitution, the best being a 1:1 ratio between the products. Harrowven and co-workers suggested that the indanone series had a higher energy transition state required to bring the aryl radical and *ortho*-carbon together relative to the tetralone series, explaining the emergence of this competing reaction pathway that was not observed in the indanone series.[32]



< 5%	R = R¹ = H	80%
40%	R¹ = OMe, R = H	40%
45%	R¹–R¹ = OCH_2O, R = H	45%
26%	R = R¹ = OMe	53%

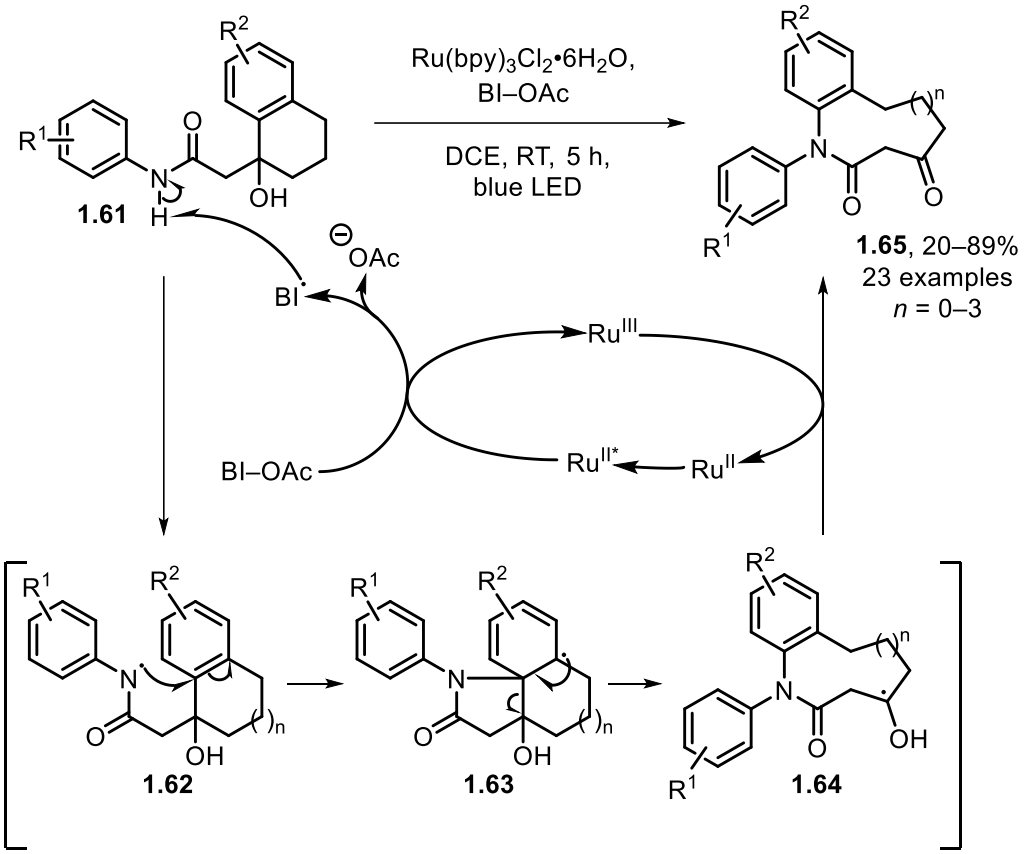
Scheme 12. Harrowven and co-workers' aryl radical ring expansion, displaying the differences in yield of the competing *ipso* and *ortho* cyclisation pathways.

There are also examples of using nitrogen-centred radicals in ring expansion, as investigated by Kim and co-workers in Scheme 13.[33] Reaction of **1.55** with tributyltin hydride and AIBN generated the azide radical (**1.56**) and through the formation of nitrogen gas, a single nitrogen remained in intermediate **1.57**, acting as the radical species. This intermediate then reacted similarly to the Dowd-Beckwith reaction, with radical attack at the ketone occurring, forming the bicyclic intermediate **1.58** and a subsequent fragmentation giving **1.59**. A final hydrogen abstraction gives products **1.60** with a range of ring sizes and varied R groups tested, in yields of 48–96%. Despite the efficiency of this reaction, the use of nitrogen-centred radicals for the synthesis of medium-sized rings is relatively underexplored.[34,35,36]



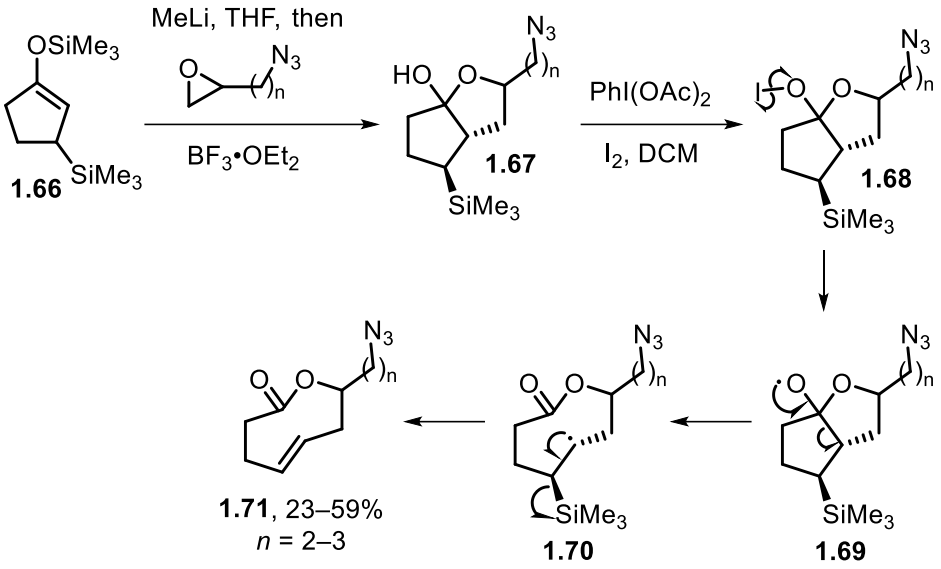
Scheme 13. Kim and co-workers' method utilising a nitrile group to form nitrogen-centred radicals, allowing the synthesis of medium-sized rings.

Nitrogen radicals were also used by Liu and co-workers in photocatalytic ring expansion reactions to form medium-sized rings (Scheme 14).[37] Mechanistic studies were completed to determine a plausible reaction pathway. It was deduced that the reaction is initiated by an oxidation of the photoexcited ruthenium catalyst by the iodine species (which then becomes a radical itself), with the photoexcitation done using blue LED light. H-atom abstraction from **1.61** then provides **1.62** as a nitrogen-centred radical. This radical can then attack the aryl ring, forming intermediate **1.63**, before fragmenting to form **1.64**. The final oxidation of the ketyl radical is done by the ruthenium(III) species formed earlier in the catalytic cycle, thus reducing it back to the +2 oxidation state and regenerating the ground state catalyst. The obtained yields for the rings from 8–11-membered ranged from 20–89% while also changing the R groups attached to the aromatic rings. Some attempts were also made to use an electron donating group (OMe); however, this was unsuccessful due to undesired oxidative decomposition.



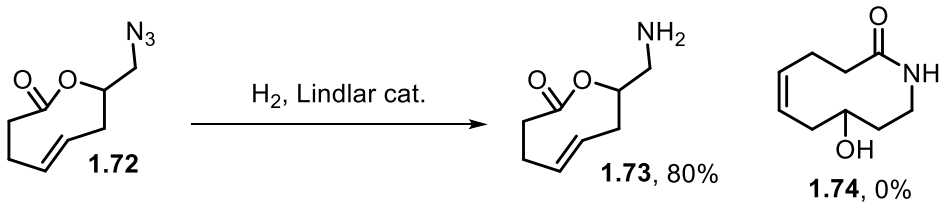
Scheme 14. Liu and co-workers' method of generating amidyl radicals that could then undergo ring expansion, where BI–OAc = 1-acetoxy-1,2-benziodoxol-3(1H)-one.

Another heteroatom that can be utilised to initiate radical ring expansion is oxygen. Oxygen radicals are key intermediates in Dowd-Beckwith ring expansions, and it is also possible to form high energy oxy-radical species from a hydroxyl group *via* oxidation to initiate a radical ring expansion. This method was developed by Posner and co-workers (shown in Scheme 15),[38,39] who were able to demonstrate a series that worked through sequential ring-expansions of functionalised epoxides. The first ring expansion worked through an initial desilylation of **1.66**, with methyllithium acting as the nucleophile to attack the silicon atom and generate a lithium enolate. This then reacts with the epoxide and boron trifluoride etherate (which assists in the epoxide ring opening) to form the hemiacetal, **1.67**. Oxidative radical fragmentation then occurs *via* I–O bond formation followed by homolytic fragmentation, which relocates the radical from the oxygen to a carbon. Radical **1.70** then fragments to eliminate the second silyl group – transferring the radical to it while doing so – and forms the now 8-membered ring.



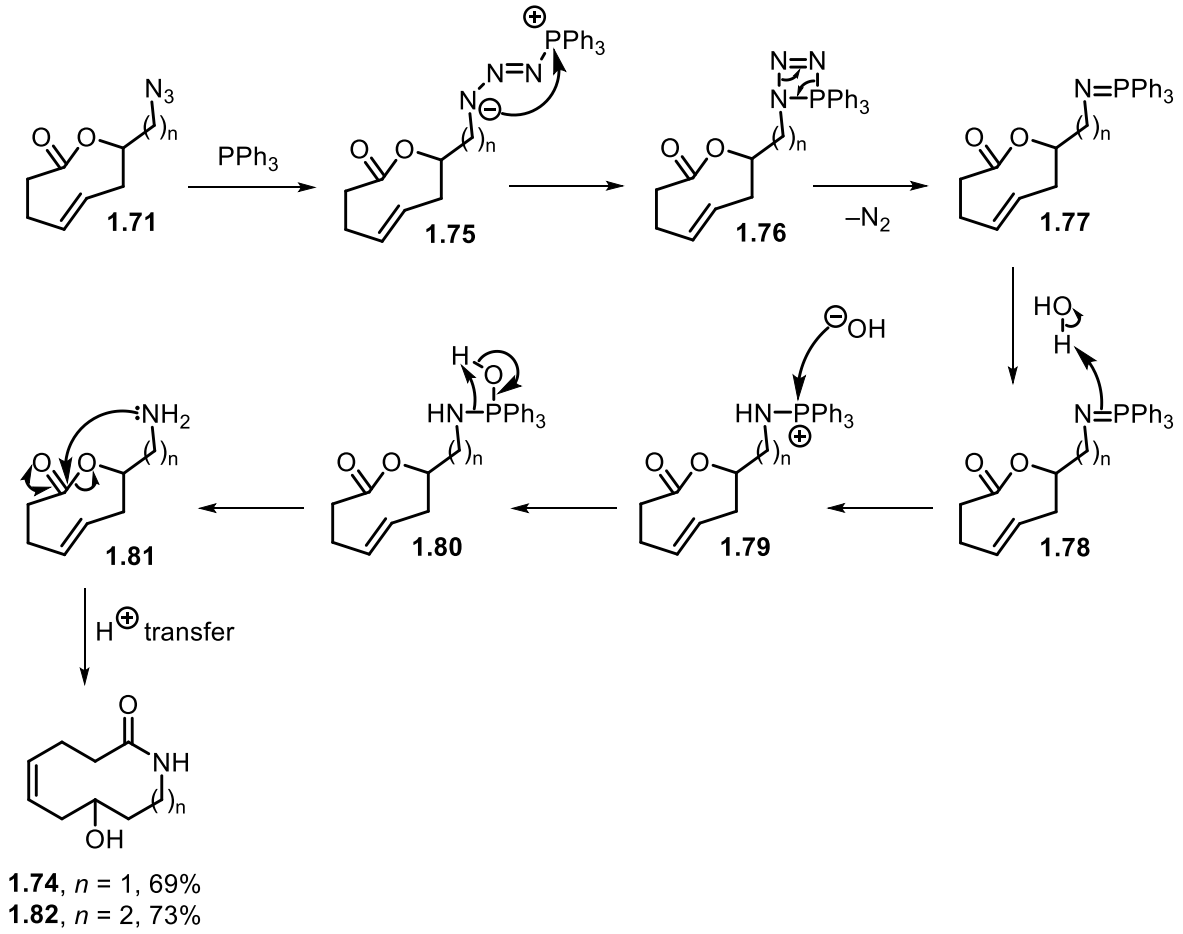
Scheme 15. The first step of Posner and co-workers' silicon-mediated ring expansion with a nitrile branch.

After this, a second ring expansion was explored by Posner and co-workers (Scheme 16). They initially looked at the Corey method for azide reduction and reacted azide **1.72** with hydrogen gas over Lindlar catalyst.[40] While the desired reduction occurred, the expected intramolecular attack and subsequent ring expansion did not take place, and they were left with an 80% yield of amine **1.73** instead. Several other tests were done with different conditions: heat, microwave irradiation, base addition and Lewis acid addition, but all showed no effect on driving the reaction to the desired product, **1.74**.



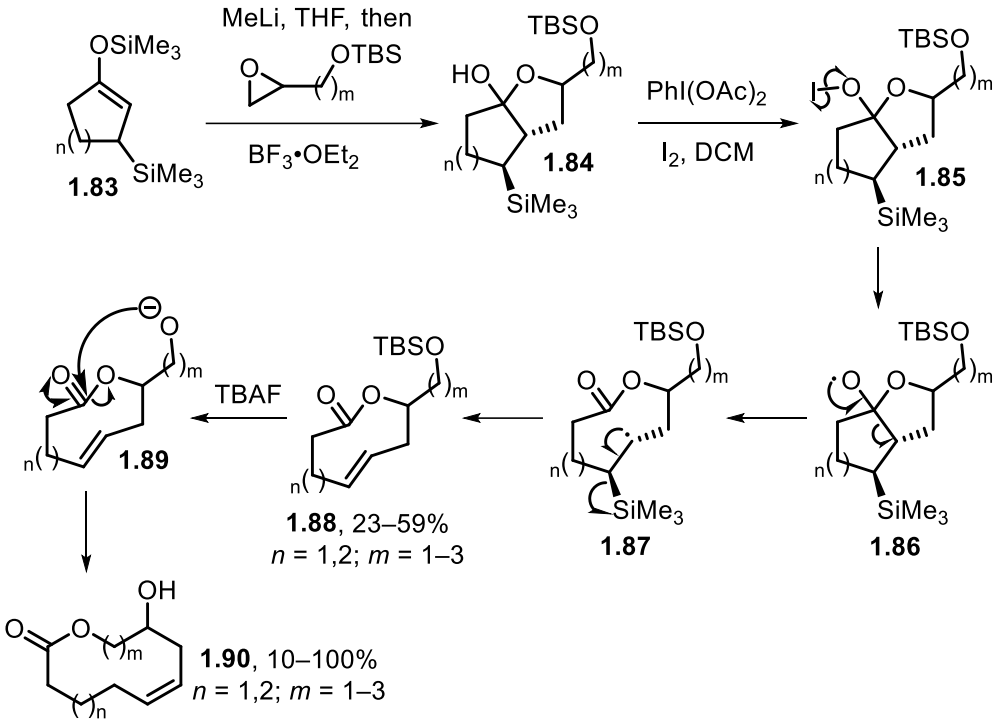
Scheme 16. The unsuccessful second step of Posner and co-workers' ring expansion, where the azide is only reduced to a primary amine.

Posner and co-workers then switched to Staudinger conditions and upon the formation of the primary amine, the desired ring expansion was able to occur (Scheme 17). Pleasingly, good yields for the ring-expanded products (**1.74** and **1.82**) were attained on this occasion with the lack of intramolecular attack now not being an issue. It is thought the driving force for this reaction is the increase in stability going from a lactone to a lactam, as well as the release of some transannular strain upon ring expansion.



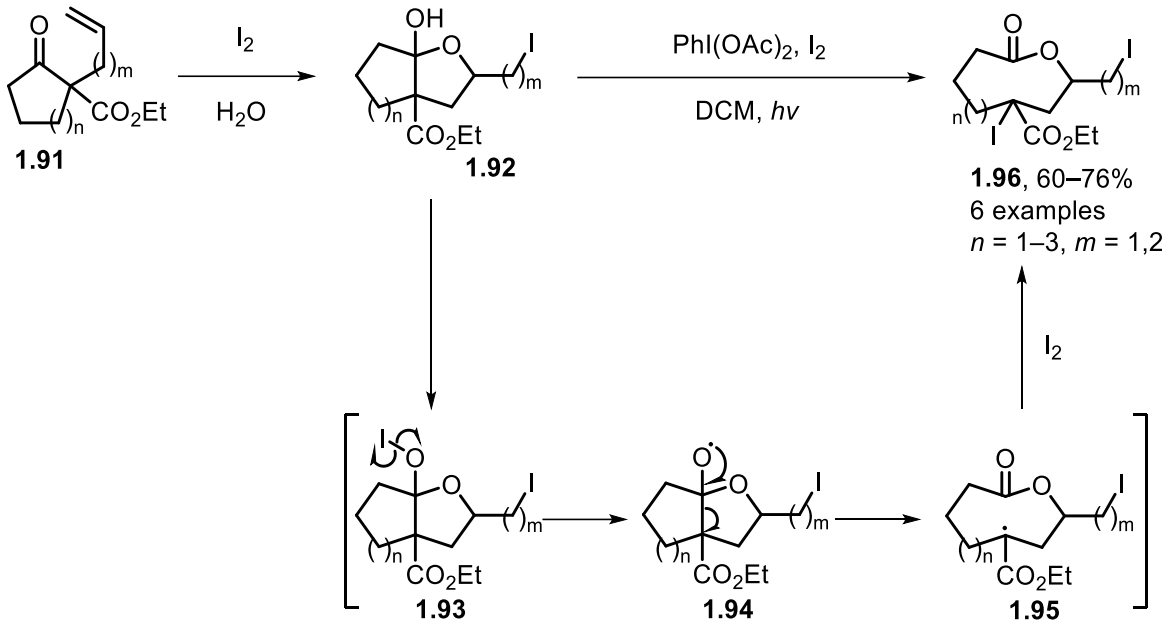
Scheme 17. The successful second step of Posner and co-workers' ring expansion using the Staudinger reaction, converting the lactone to a lactam while increasing ring size.

Posner and co-workers also worked on a similar method, but synthesised medium-sized lactone rings instead, summarised in Scheme 18.[38] Silyl enol ether **1.83** could be lithiated as in the previous example from this group and then treated with an epoxide to form **1.84**. Bicyclic product **1.84** was then subjected to oxidative cleavage (as was displayed in Scheme 15 also) to form the first medium-sized ring from the initial normal-sized ring. This was an irreversible process, ensuring the medium-sized ring formed, **1.87**, was unable to undergo any potentially competing ring contraction reactions that led back to the normal-sized ring. The TBS group could then undergo a facile deprotection with TBAF and the free oxygen could complete the final ring expansion through attack of the lactone to form **1.90**. Due to a release of ring strain, the driving force of the reaction is going from a smaller to larger medium-sized ring making it thermodynamically favourable.



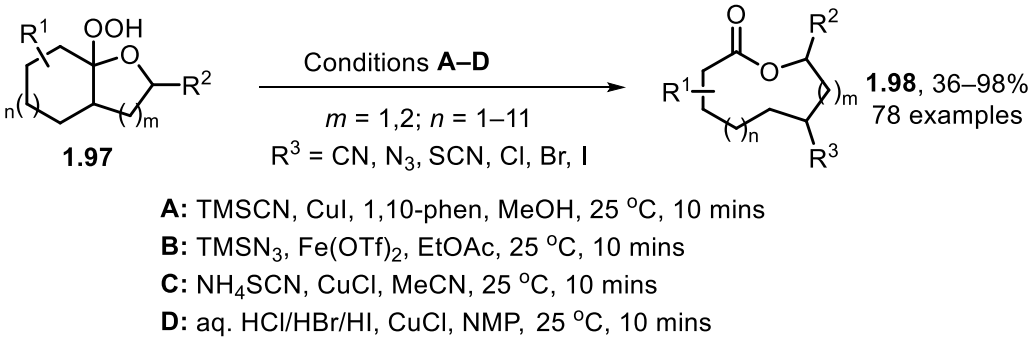
Scheme 18. Posner and co-workers' silicon-mediated ring expansion of 2-cycloalkenones using oxygen-centred radicals to form lactone rings.

Hassner and co-workers were able to build upon the work explored by Posner and co-workers and develop another oxidative ring expansion technique (Scheme 19).[41,42] Using similar conditions as previously, with phenyliodine(III) diacetate (PIDA), the hemiacetal, **1.92**, was synthesised *via* an intramolecular iodoetherification, before iodide-mediated hypoiodite formation (**1.93**). An oxidative ring opening can then occur *via* homolytic cleavage of the I–O bond, followed by fragmentation of the bicyclic intermediate to reposition the radical at the α-position to the ester (**1.95**) and bring about ring expansion. The radical will then react with iodine in the reaction to form the final medium-sized ring in varying ring and branch sizes with yields between 60–76%.



Scheme 19. Hassner and co-workers' method of synthesising lactone rings using photoinduced radical fragmentation.

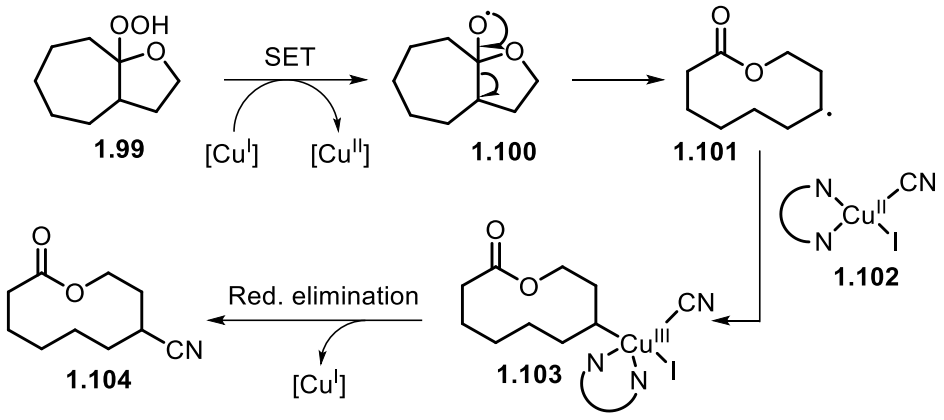
A metal-mediated radical ring expansion was developed by Guo and co-workers, but this time started from a hemiketal hydroperoxide (**1.97** in Scheme 20).[43] **1.97** could either be isolated or a 2-step process could be carried out starting from α-hydroxyalkylketones, forming **1.97** *in situ* and then completing the ring expansion. The yields indicated in Scheme 20 are those of the 1-step reaction from the isolated starting material. This reaction proved to be very effective for the synthesis of rings ranging from 9–19-membered with the yields ranging from 36–98% over 78 examples. Also included in these examples were a number of different functionalities: azide, nitrile, thiocyanate, chloride, bromide and iodide.



Scheme 20. The reaction scheme for Guo and co-workers' radical ring expansion, with four different methods for the experiment.

The proposed mechanism (Scheme 21) was elucidated from DFT calculations. The reaction is proposed to start with a single electron transfer (SET) involving the Cu(I) ligated species and **1.99**. This formed the alkoxyl radical, **1.100**, and Cu(II) species. Following this, a β-scission

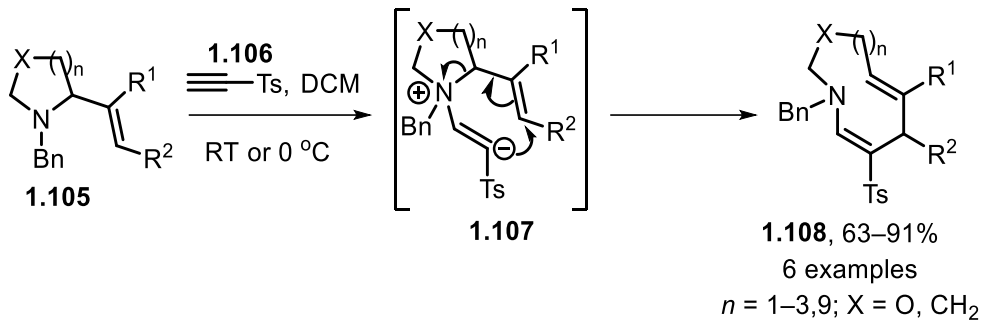
produced the ring-expanded compound, **1.101**, with a carbon-centred radical. Lactone **1.101** is then trapped by the Cu(II) species before forming Cu(III) complex **1.103**. A final reductive elimination then removes the copper from the product to reform the Cu(I) catalyst and the final, functionalised product, **1.104**.



Scheme 21. Guo and co-workers' proposed mechanism for the radical ring expansion reaction using a Cu or Fe catalyst.

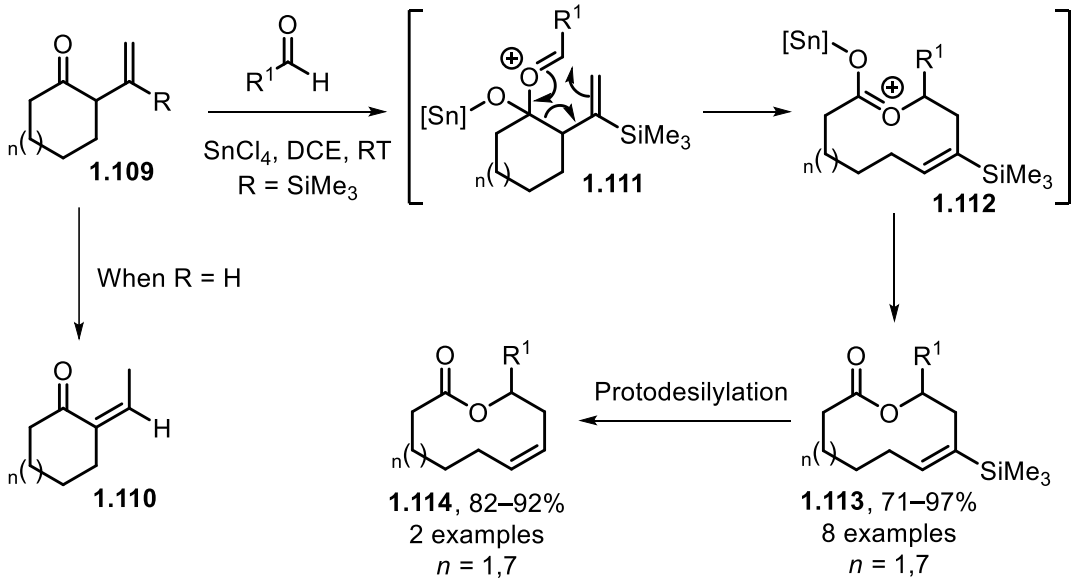
1.3 Pericyclic Ring Expansion

Pericyclic reactions exhibit a flow of electrons through a single, concerted cyclic transition state. Pericyclic reactions can involve the cleavage of a σ-bond which can facilitate ring expansion and the formation of a medium-sized ring or macrocycle, if the starting material is designed accordingly. Back and co-workers utilised a 3-aza-Cope rearrangement to form 9–11-membered rings as well as a single 17-membered macrocycle (depicted in Scheme 22).[44,45] A pyrrolidine derivative, **1.105**, and alkyne, **1.106**, reacts *via* a conjugate addition to form the zwitterionic intermediate **1.107**. Under mild conditions this intermediate can then undergo a 3-aza-Cope rearrangement and produce a ring, **1.108**. This technique provided a convenient method for converting readily available α-vinyl *N*-benzylpyrrolidines, piperidines, morpholines, azepines and other cyclic amines into sulfone-functionalised, medium-sized rings or macrocycles.[24] A key driving force for this reaction is likely to be the neutralisation of the positive charge on the nitrogen.



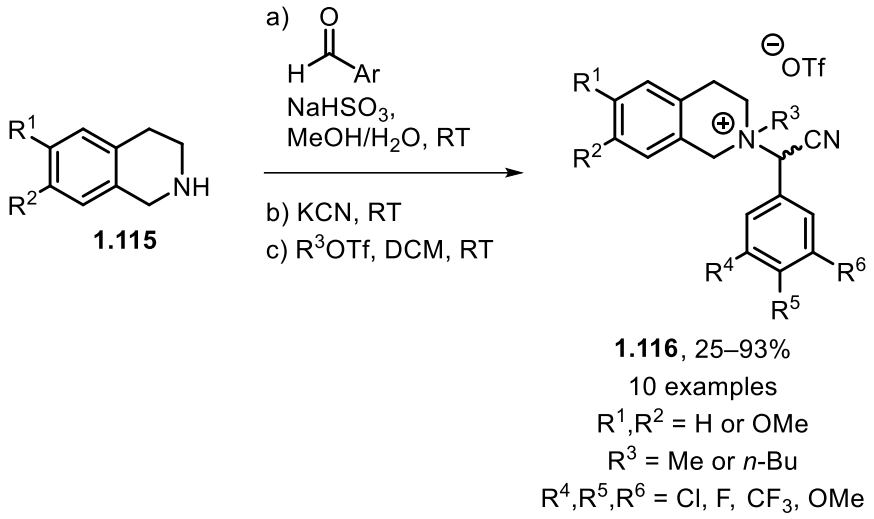
Scheme 22. Back and co-workers' mechanism for the ring expansion reaction using a 3-aza-Cope rearrangement.

Goeke and co-workers developed a reaction to make medium-sized lactones *via* a Lewis acid catalysed oxy-Cope rearrangement (Scheme 23).[46] The Lewis acid used in this case was tin(IV) chloride and this was reacted with the ketone (**1.109**) and aldehyde to form the intermediate (**1.111**). The rearrangement occurs here to give **1.112**. The tin then dissociates from the molecule and, in some cases, protodesilylation was performed which removes the silyl group and gives **1.114**. The yields of both **1.113** and **1.114** were impressive, with a range of 71–97%. These products largely form as the *E*-alkene, with conformational analysis carried out by the group indicating the steric bulk of the silyl group leads to the *E*-alkene being preferred. Previous work on this substrate also showed that when R = H in Scheme 23, isomerisation to the more stable alkene, **1.110** occurs, rather than ring expansion. The placement of a bulky silyl group in this position prevented this isomerisation and increased the rate of rearrangement due to the stabilisation of the intermediate, tertiary oxonium ion, **1.111**.[47,48]



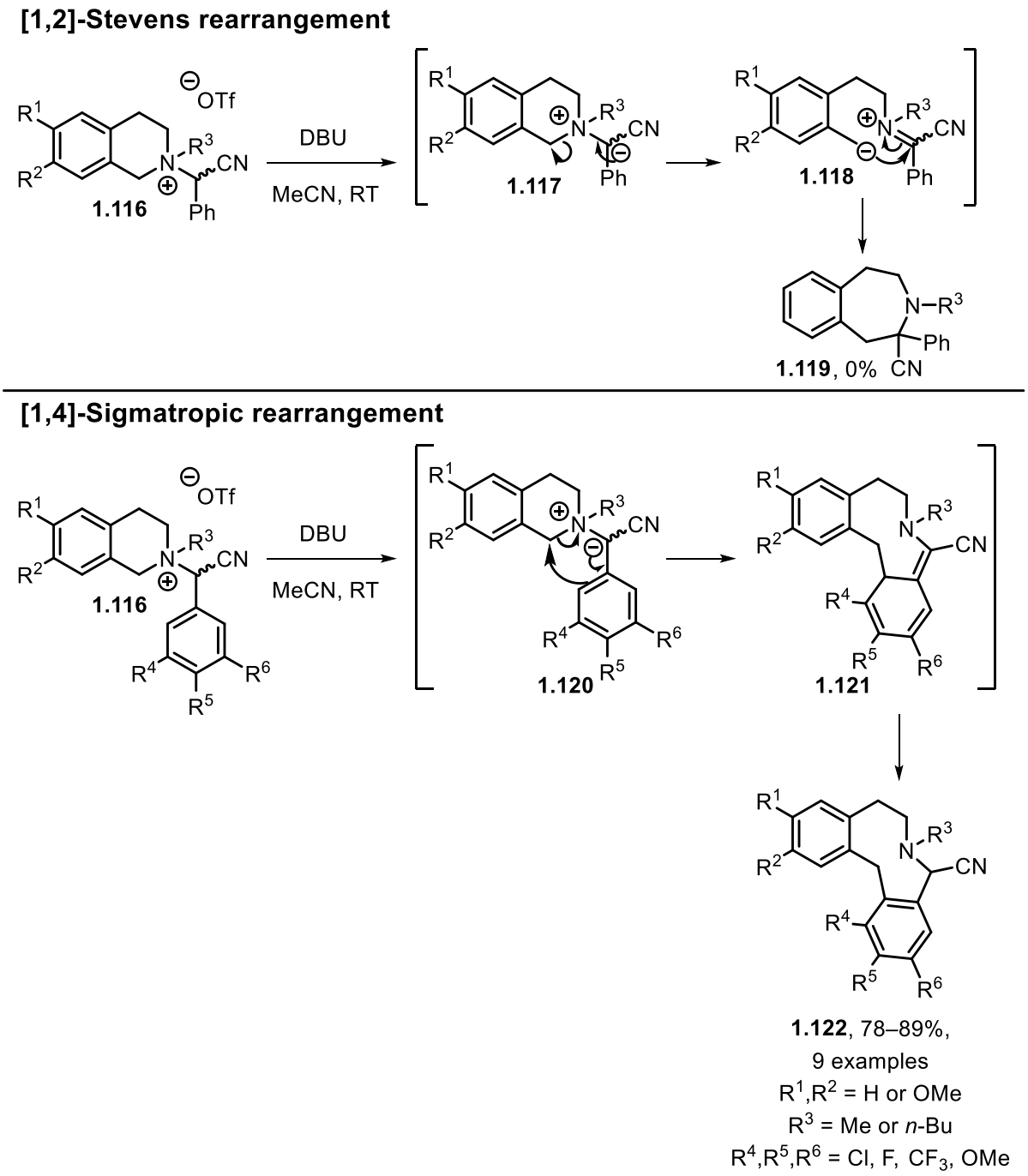
Scheme 23. Goeke and co-workers' mechanism for the Lewis acid catalysed ring expansion reaction using an oxy-Cope rearrangement.

Also forming medium-sized rings, Opatz and co-workers reported a [1,4]-sigmatropic rearrangement to synthesise a range of 9-membered rings (Scheme 24).[49] The initial substrate for the ring expansion was made by *N*-alkylation of Strecker adducts, **1.115**, being reacted with aromatic aldehydes and alkyl triflates to form **1.116**. This generated 10 substrates as indicated in Scheme 24, to be used in the ring expansion step.



Scheme 24. The preparation done by Opatz and co-workers to generate the aminonitrile salts to be used in the subsequent ring expansion reactions.

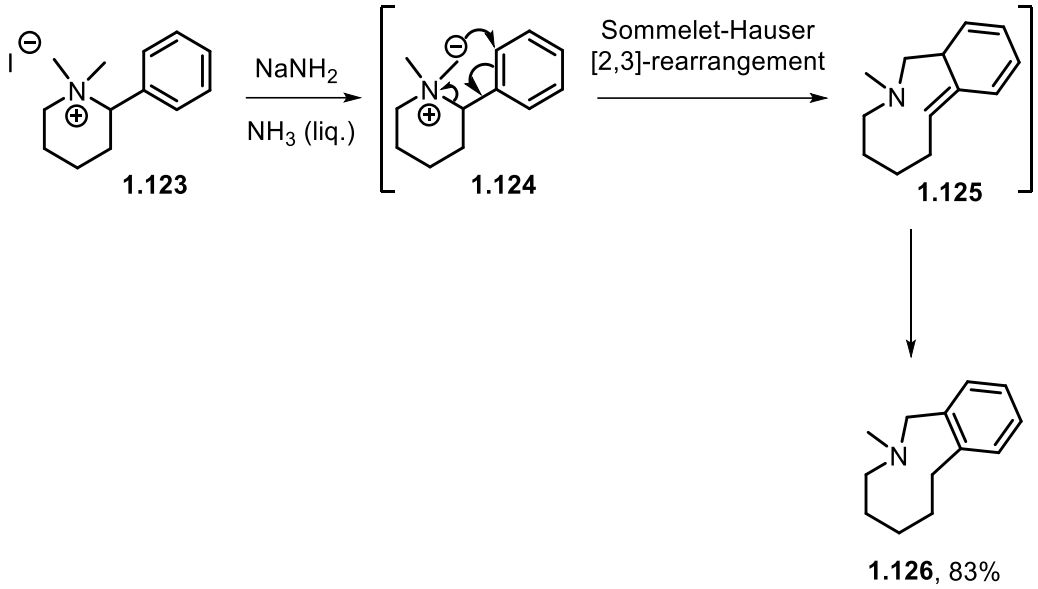
Following this, it was initially expected that addition of base (KHMDS) would facilitate the formation of benzo[*d*]azepines (**1.119**) *via* a [1,2]-Stevens rearrangement. However instead, a [1,4]-sigmatropic rearrangement reaction occurred (Scheme 25) where dibenzo[*c,f*]azonine complexes formed (**1.122**). The base deprotonated at the α-position to the nitrile, forming **1.120**, which could then undergo the [1,4]-sigmatropic rearrangement, rearomatise, then form the final 9-membered product, **1.122**. A total of 9 novel medium-sized rings were synthesised using this method, with variation coming at the R groups and the aryl group attached to the aldehyde. Also, changing the base from KHMDS to DBU facilitated a consistent increase in yield across all substrates with the final range being from 78–89%.



Scheme 25. The expected [1,2]-Stevens rearrangement ring expansion (above) and the actual [1,4]-sigmatropic rearrangement ring expansion (below) completed by Opatz and co-workers to generate the 9-membered rings.

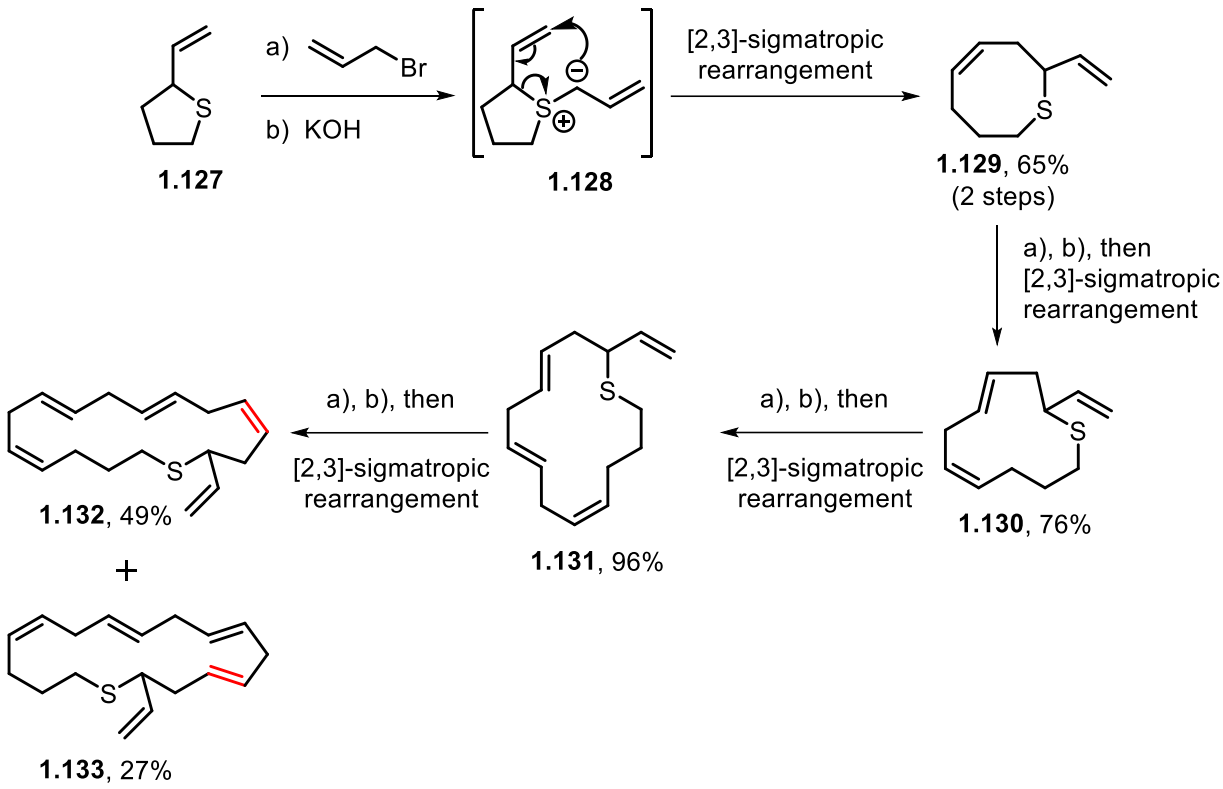
[2,3]-Sigmatropic rearrangements can also lead to ring expansion as shown in the work summarised in Scheme 26,[50,51] carried out by Hauser and co-workers. An initial deprotonation of **1.123** by sodium amide in liquid ammonia gives the ylide intermediate, **1.124**, before undergoing the Sommelet-Hauser [2,3]-sigmatropic rearrangement step. After this, the medium-sized ring can rearomatise to the final product, **1.126**. The lack of side-products is accredited to the close proximity of the methyl groups to the aromatic ring, as

this aids in the rearrangement happening quickly, hence the yield of the 9-membered product is high (83%).



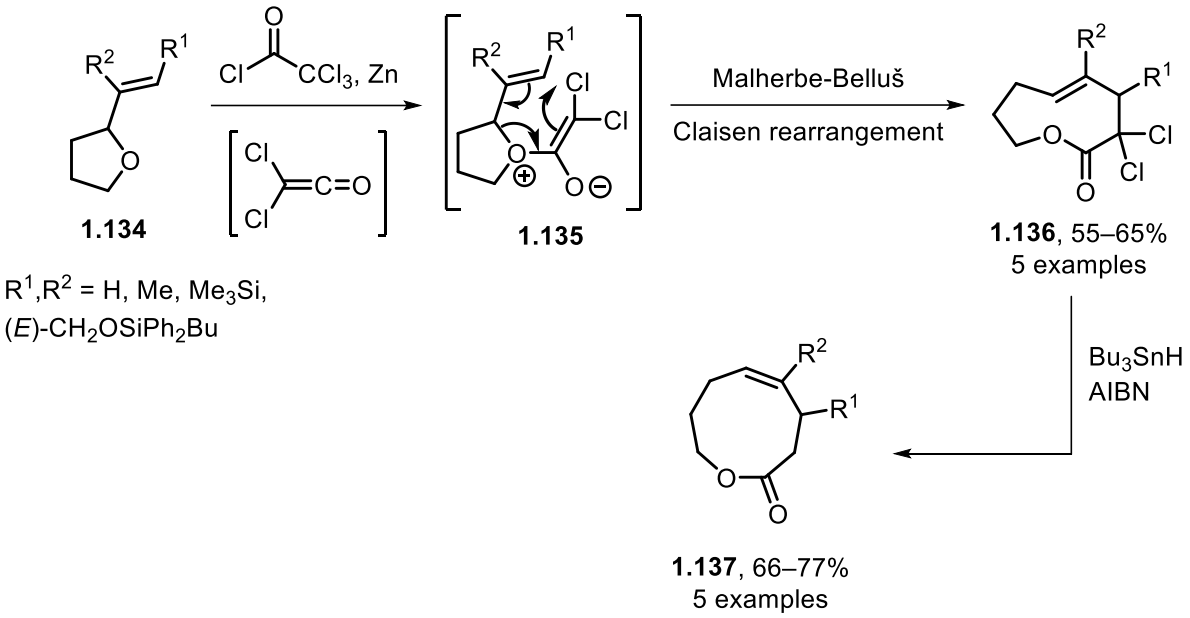
Scheme 26. Hauser and co-workers' mechanism for a Sommelet-Hauser [2,3]-rearrangement to form a 9-membered ring.

Schmid and co-workers also utilised a [2,3]-sigmatropic rearrangement for ring expansion but instead used a sulfur ylide (Scheme 27).[52,53,54] In the first step, the sulfide displaces the bromide through a nucleophilic attack, forming the charged species **1.128**. To neutralise this a [2,3]-sigmatropic rearrangement occurs which also allows a 3-atom ring expansion as shown with the 8-membered product, **1.129**. The starting material's functionality is regenerated in this step and so it means iterative ring expansions are possible, as is displayed in the next two steps where the ring size has sequentially increased from 5- to 17-membered. The reaction to synthesise the final macrocyclic rings (**1.132** and **1.133**) led to the formation of a 2:1 isomeric mix in favour of the compound with the additional *Z*-alkene configuration (**1.132**), in 76% overall yield.



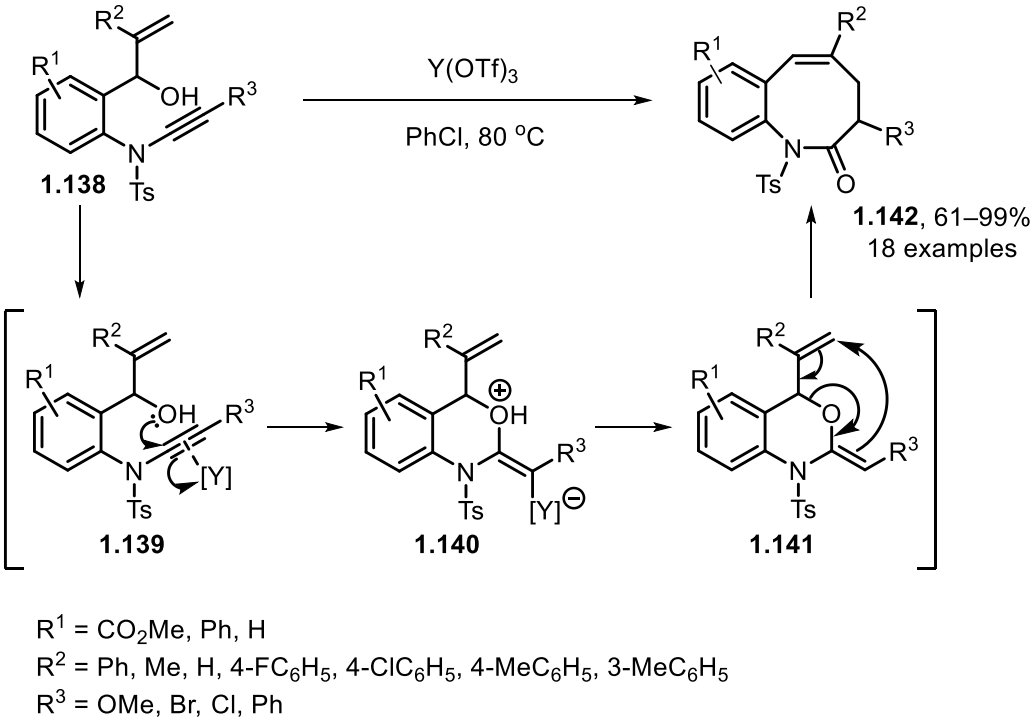
Scheme 27. Schmid and co-workers' mechanism for iterative ring expansion using a sulfur ylide [2,3]-sigmatropic rearrangement.

[3,3]-Sigmatropic rearrangements are a reaction class that has been widely used for the synthesis of medium-sized rings and macrocycles and an example of this was carried out by Taylor and co-workers (Scheme 28).[55,56] Taylor's group used the zwitterionic Malherbe-Belluš-Claisen rearrangement to prepare 9-membered rings with *E*-geometry, from 2-vinyl tetrahydrofurans.[57,58] In the first step, dichloroketene (prepared in situ from trichloroacetyl chloride with activated zinc powder) reacted with **1.134** to form **1.135** which could then undergo the Malherbe-Belluš-Claisen rearrangement to form the ring-expanded product, **1.136**, in reasonable yields and exclusively in the *E*-configuration. Interestingly, following the addition of tributyltin hydride and AIBN to facilitate a radical dechlorination of **1.136**, in addition to dechlorination, isomerisation to the *Z*-alkene **1.137** was also observed, which is thought to occur as this geometry is thermodynamically preferred in 9-membered rings, hence the observed olefin *trans–cis* isomerism.[59]



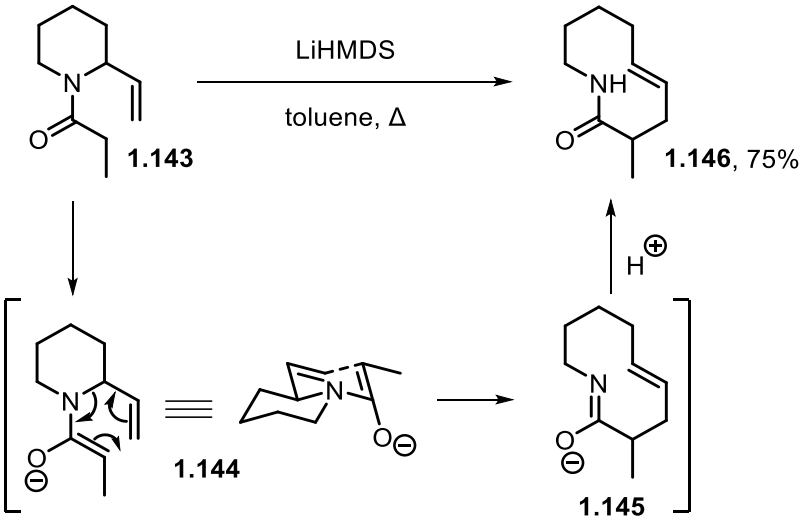
Scheme 28. Taylor and co-workers' mechanism for a ring expansion using the Malherbe-Belluš-Claisen rearrangement to prepare 9-membered rings, with stereochemical control.

Claisen rearrangements can also be used to form medium-sized rings, as demonstrated by Ye and co-workers in Scheme 29.[60] The Ye group took inspiration from recent work of using transition metals for Claisen rearrangements to synthesise normal-sized rings,[61,62,63] as well as their own work using ynamides.[64,65] Yttrium triflate was used as the transition metal catalyst in this reaction and it was able to coordinate to the alkyne of the starting material (**1.138**), giving complex **1.139**. The alcohol could then attack the yttrium-coordinated alkyne, to convert it to an yttrium-alkene intermediate, **1.140**. A proton transfer allows the removal of yttrium and sets up the molecule for a Claisen rearrangement between the two alkenes, allowing **1.142** to be synthesised as the final ring. The driving force of this reaction is thought to be the formation of a stable amide functionality in the product. Using this technique, many 8-membered rings were generated with yields ranging from 61–99%.



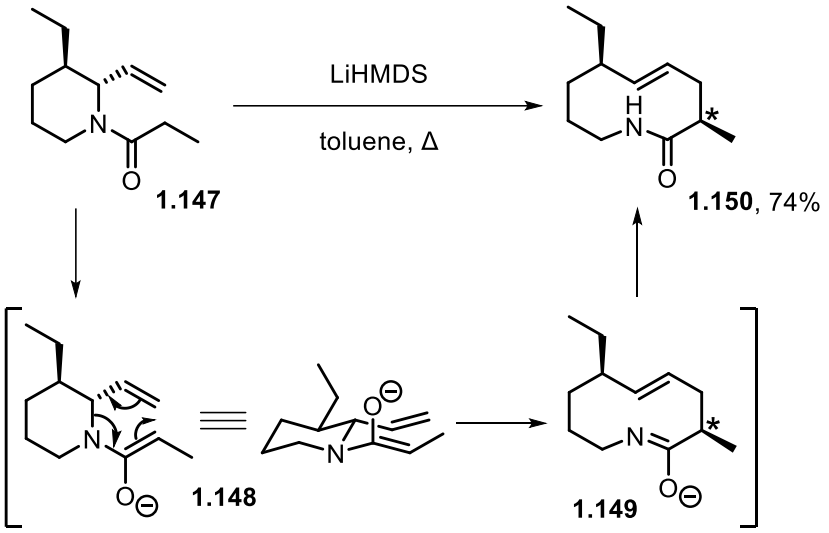
Scheme 29. Ye and co-workers' mechanism to form 8-membered rings using a transition metal to facilitate a Claisen rearrangement reaction.

Suh and co-workers used an aza-Claisen reaction to create 10-membered rings as shown in Scheme 30.[66] LiHMDS was reacted with **1.143** to form the enolate which could then undergo the aza-Claisen rearrangement, causing the ring expansion to the medium-sized ring, **1.145**. A final protonation, using water as the source, generated the product in a yield of 75%. The lactam is formed in the *E*-configuration only, due to the chair-chair-like transition state (**1.144**) and formation of the *Z*-enolate prior to this.



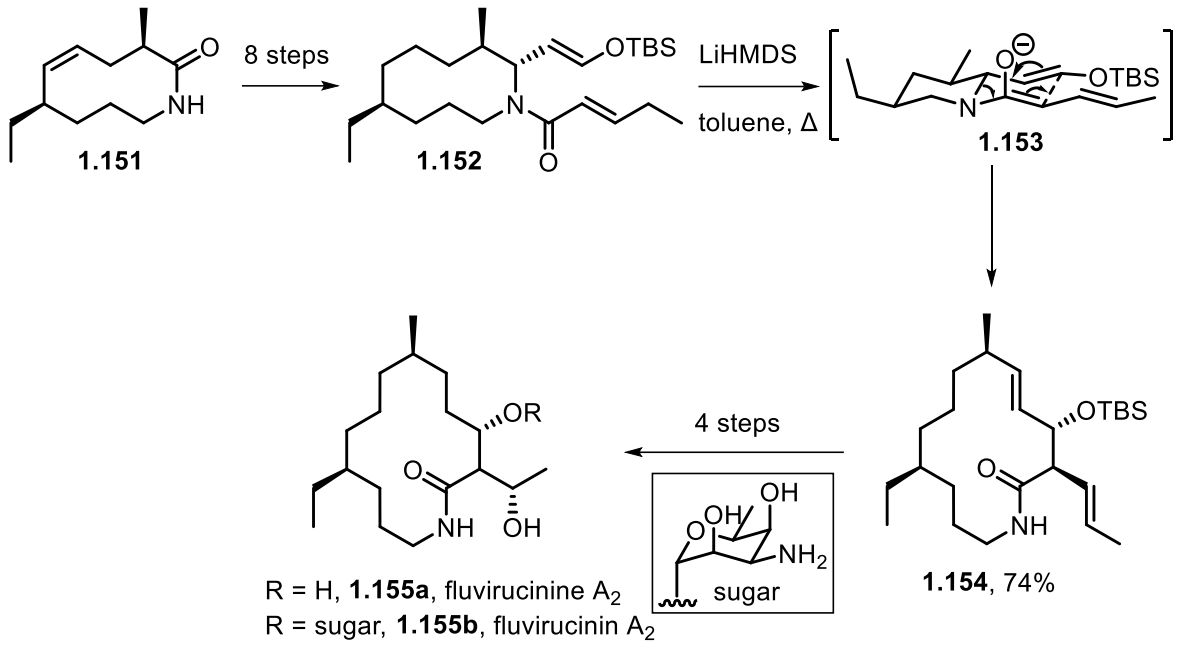
Scheme 30. Suh and co-workers' mechanism to form medium-sized lactams using an aza-Claisen rearrangement approach.

With this success, Suh and co-workers built upon these principles and applied it to the stereoselective synthesis of a natural product, fluvirucinine A_2 (Scheme 31).[67] **1.155** is a molecule of pharmaceutical interest due to its antipathogenic effects and promising antiinfluenza activity[68] and this work was the first report of its total synthesis. Upon initial heating of **1.147** in LiHMDS, the aza-Claisen rearrangement occurred with complete stereoselectivity and **1.150** was isolated as the only product from the reaction. The stereoselectivity was rationalised, like previously, by the formation of a chair-chair-like transition state where all substituents are in the equatorial positions and so the *Z*-enolate was able to form preferentially. The success of this method allowed the group to synthesise a key stereogenic centre (marked by *) in fluvirucinine A_2, which was crucial in the total synthesis.



Scheme 31. Suh and co-workers applying their mechanism for the stereoselective formation of fluvirucinine A_2.

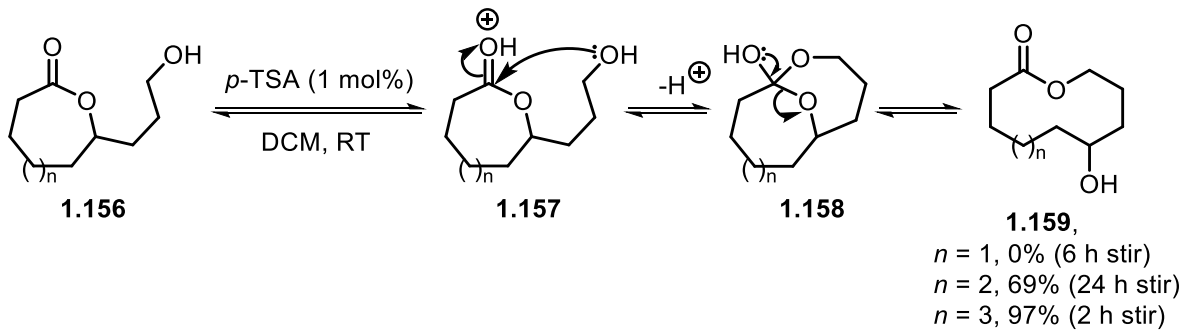
Following this, a further 8 steps allowed the conversion of **1.151** into the exocyclic amide **1.152**. Using LiHMDS, a second aza-Claisen rearrangement could then occur (using the same chair-chair-like transition state as shown for **1.148**) and this then provided the now macrocyclic ring (**1.154**) in a 74% yield with high diastereoselectivity. A final four additional steps completed the syntheses of fluvirucinine A_2 **1.155a** and fluvirucinin A_2 **1.155b**, shown in Scheme 32.



Scheme 32. Following the formation of **1.151**, the continued total synthesis of fluvirucinine A_2 and fluvirucinin A_2.

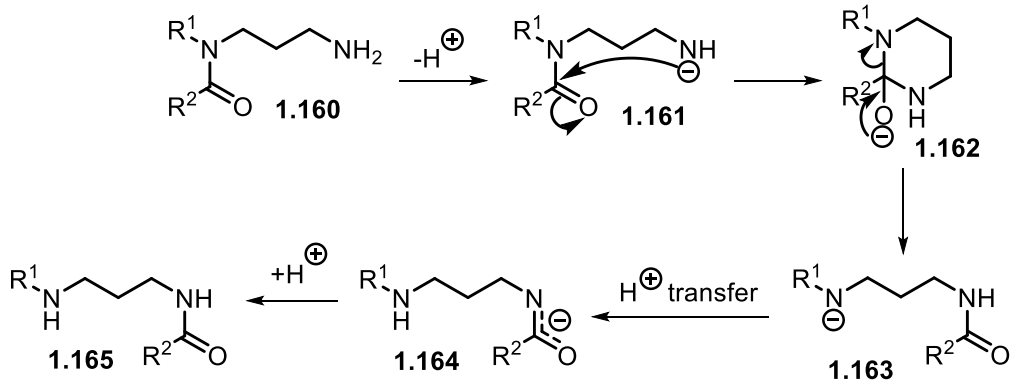
1.4 Fragmentation Ring Expansion

Fragmentation ring expansion involves the formation of a bicyclic intermediate that can successfully undergo a fragmentation reaction *via* a two-electron process to give the ring-expanded products.[69,70] In an early example by Corey and co-workers, a fragmentation ring expansion reaction was completed by translactonisation to form medium-sized rings and macrocycles (Scheme 33).[71] Under acidic conditions, lactone **1.156** undergoes an intramolecular reaction (translactonisation) where the alcohol attacks the protonated carbonyl to form the intermediate, **1.158**, and then fragments to form the *n*+3 product, **1.159**. Three attempts were done (7–9-membered) and this provided information on ring size stability. The 7-membered lactone did not react, indicating the thermodynamic unfavorability of forming a relatively strained medium-sized ring product. Adding a single carbon allows the reaction to occur (69%) but required a longer reaction time, whereas moving to a 9-membered starting material caused an increase in yield (97%) in much less time, showing a higher thermodynamic driving force compared to the others, presumably associated with the 12-membered product being more stable due to reduced strain.



Scheme 33. Corey and co-workers' translactonisation reaction for the synthesis of medium-sized rings and macrocycles.

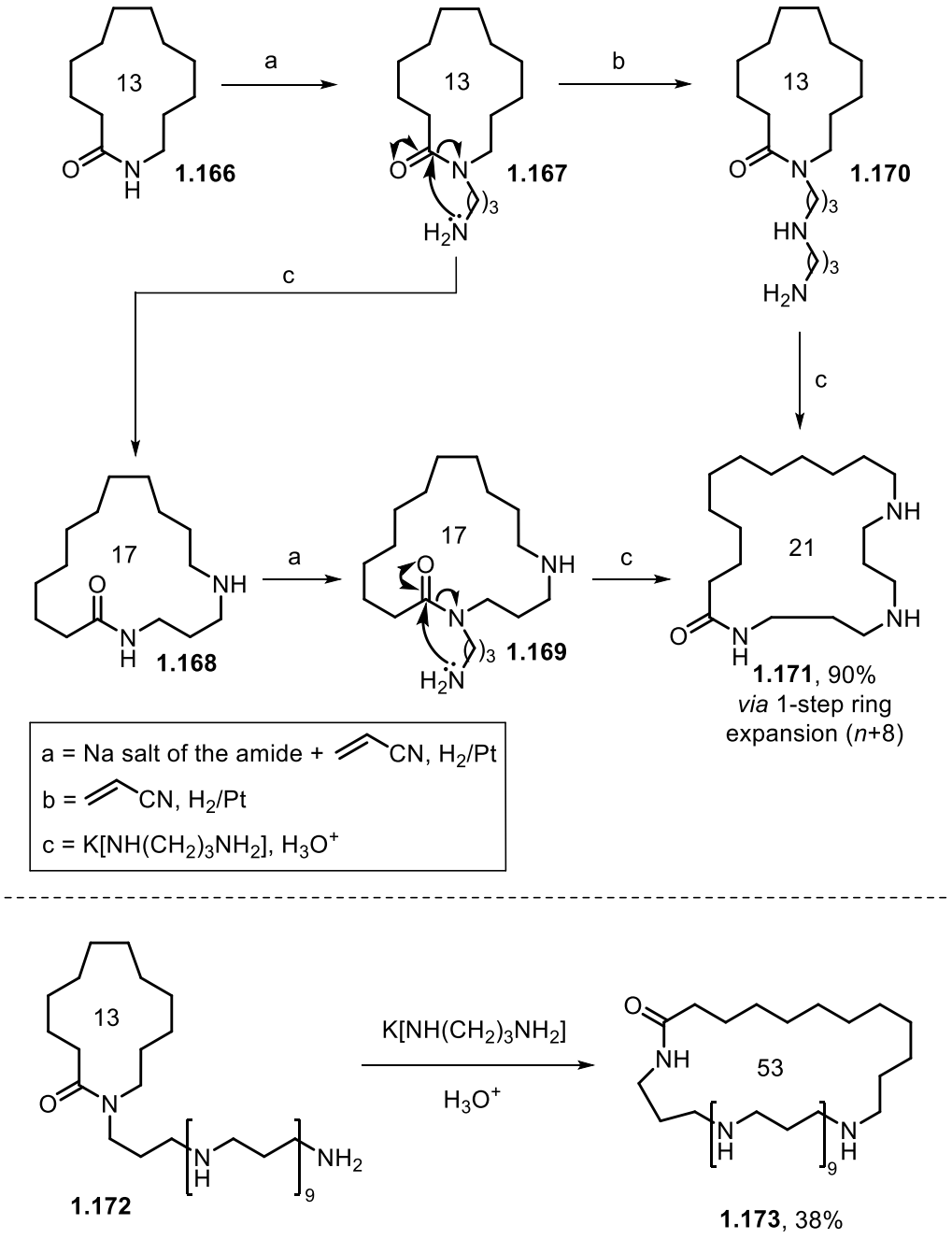
In the same year, Hesse and co-workers published similar work on side chain insertion, but instead used an amine for the attack on the carbonyl resulting in transamidation (Scheme 35).[72] They based their reaction on findings obtained during the structural determination of the *Oncinotis* alkaloids[73,74] where a linear molecule was used but a similar fragmentation reaction could occur through a cyclic intermediate, shown in Scheme 34.



Scheme 34. The type of reaction and mechanism that Hesse and co-workers took inspiration from and were able to apply to their own work.

Hesse and co-workers carried this logic over to their ring expansion work by first converting **1.166** to its sodium salt before reacting with acrylonitrile to create the side chain, followed by a reduction with hydrogen gas and platinum to give **1.167**. To perform the base-catalysed transamidation, **1.167** was then reacted with potassium (3-amino)propylamide to synthesise **1.168**. After this, it is possible to repeat the process again, as seen in Scheme 35, and form the 21-membered ring, **1.171**. They also discovered a 'shortcut' where **1.167** could react with acrylonitrile and H_2/Pt once more, giving the diamine **1.170**. Reaction with potassium (3-amino)propylamide would then generate **1.171** in one fewer step. Further work by the group on this allowed them to follow this procedure in elongating the side chain to produce a 53-membered ring in a yield of 38%, showing the reaction's versatility at even very large

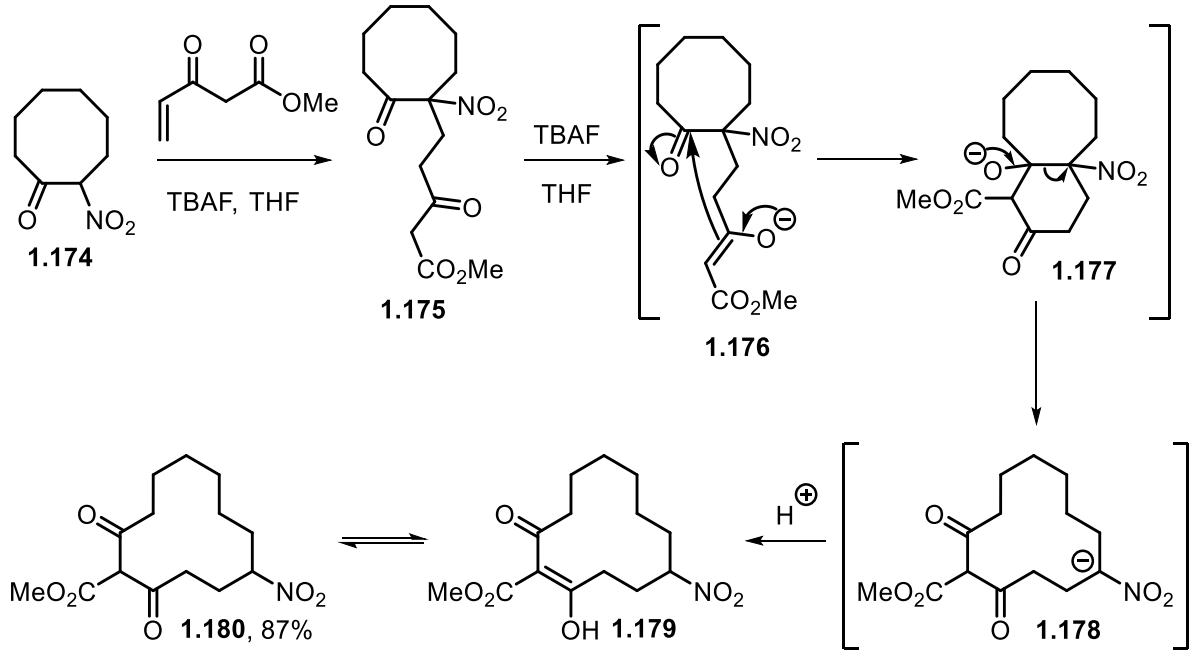
ring sizes.[75] A significant driving force for this reaction is the formation of the amide anion (like **1.162** in Scheme 34) which is resonance stabilised.



Scheme 35. The 'zip' reaction carried out by Hesse and co-workers, showcasing its ability to form macrocycles – up to 53-membered.

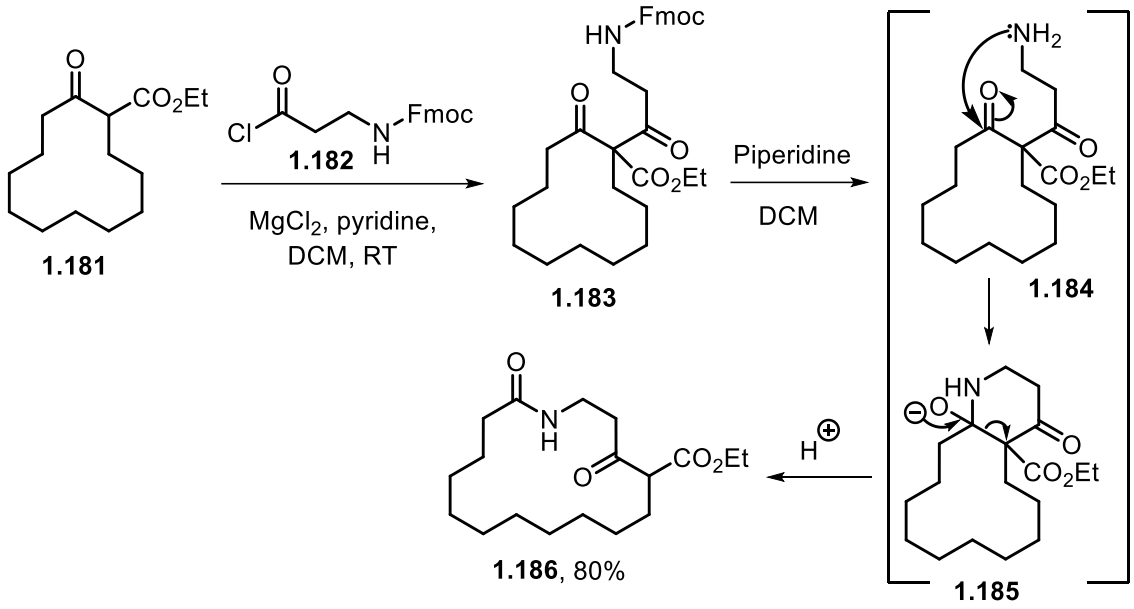
Hesse and co-workers were also able to utilise a carbon pronucleophile for ring expansion, where an 8-membered α-nitroketone was converted into a 12-membered macrocyclic product **1.180** (Scheme 36).[76] An initial Michael addition gave the β-keto ester, **1.175**, which could then be stirred with a base, facilitating a deprotonation to the enolate, **1.176**. The enolate could then attack the carbonyl in the ring and fragmentation of this intermediate

generates the anionic form of the product that could subsequently be protonated to give **1.177**/**1.178** as a mixture of keto and enol tautomers. It was conceivable that the other available ketone in the product could form an additional keto tautomer *via* movement of the double bond, however this was not observed by the group in their analysis.



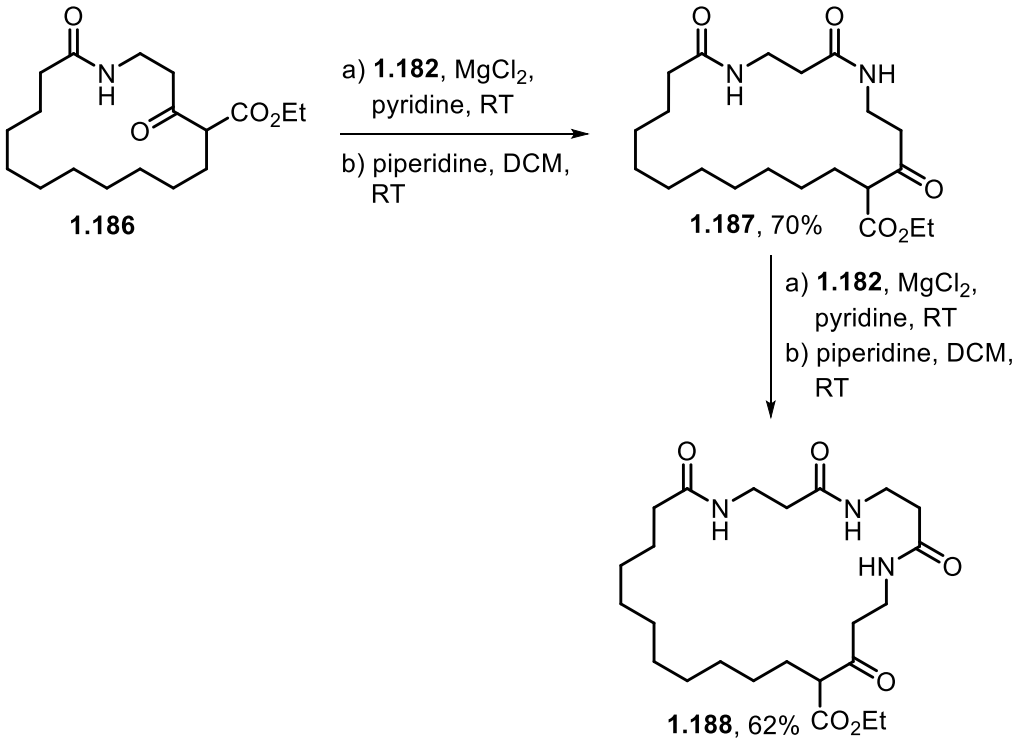
Scheme 36. Hesse and co-workers' ring expansion reaction *via* a side chain insertion, using carbon as the nucleophile.

The idea of implementing iterative ring expansions, as shown above in Scheme 35, was something Unsworth and co-workers used as inspiration for their Successive Ring Expansion (SuRE) concept, summarised in Schemes 37 and 38.[19,77] The idea was to insert amino acid derivatives into cyclic β-keto esters (**1.181**). To achieve this, the cyclic β-keto ester was reacted with a protected acid chloride and base, and this allowed the deprotonation and subsequent attack on the acid chloride to form **1.183**. Using piperidine, the Fmoc protecting group was then cleaved from the branched substituent and under these basic conditions, facilitated the intramolecular attack onto the carbonyl within the ring. The bicyclic intermediate could then undergo a fragmentation to form the macrocyclic product, **1.186**.



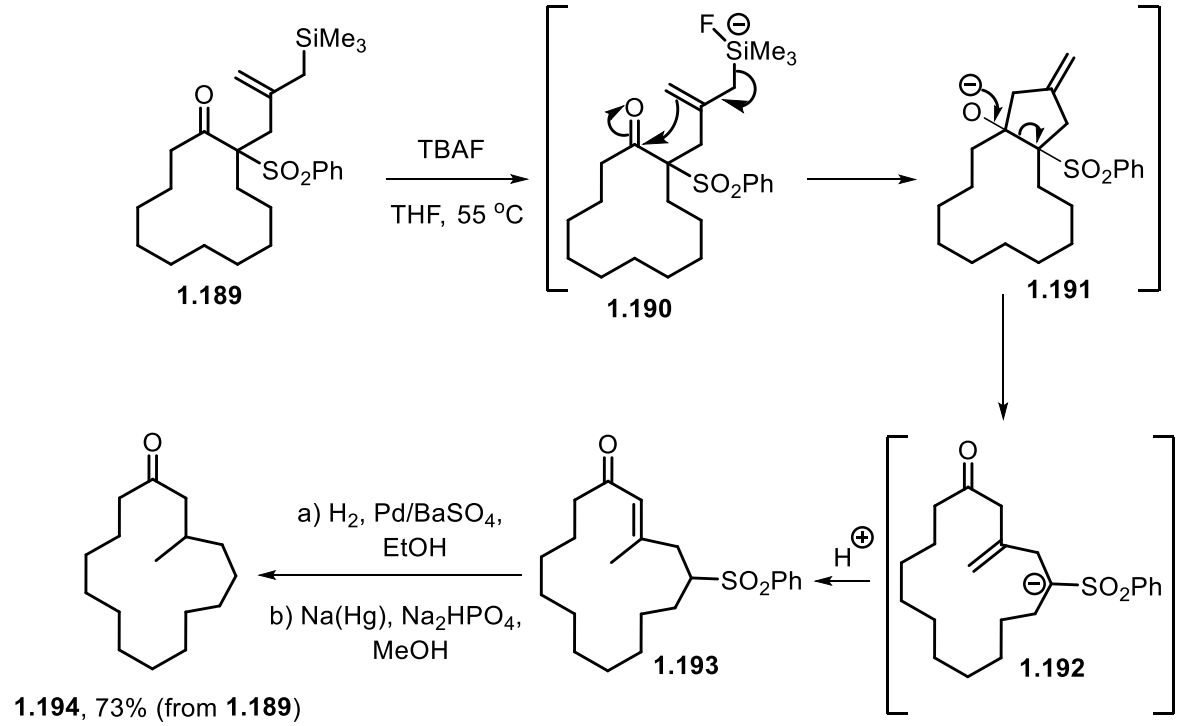
Scheme 37. Unsworth and co-workers' successive ring expansion (SuRE) technique to form a macrocycle *via* addition of an acid chloride.

As the ring-expanded product **1.186** is itself a cyclic β-keto ester, this allows the method to be performed as an iterative process, with additional ring expansions conducted after the initial one. As shown in Scheme 38, if the same steps are followed as before, two further ring expansions can be completed (up to 24-membered macrocycle **1.188** in this example here). Another positive feature of this process was the possibility of being able to use different amino acid derivatives in these next steps at no detriment to the reaction and it has been proven to work within the group with both α- and β-amino acids, at a range of ring sizes.[24]



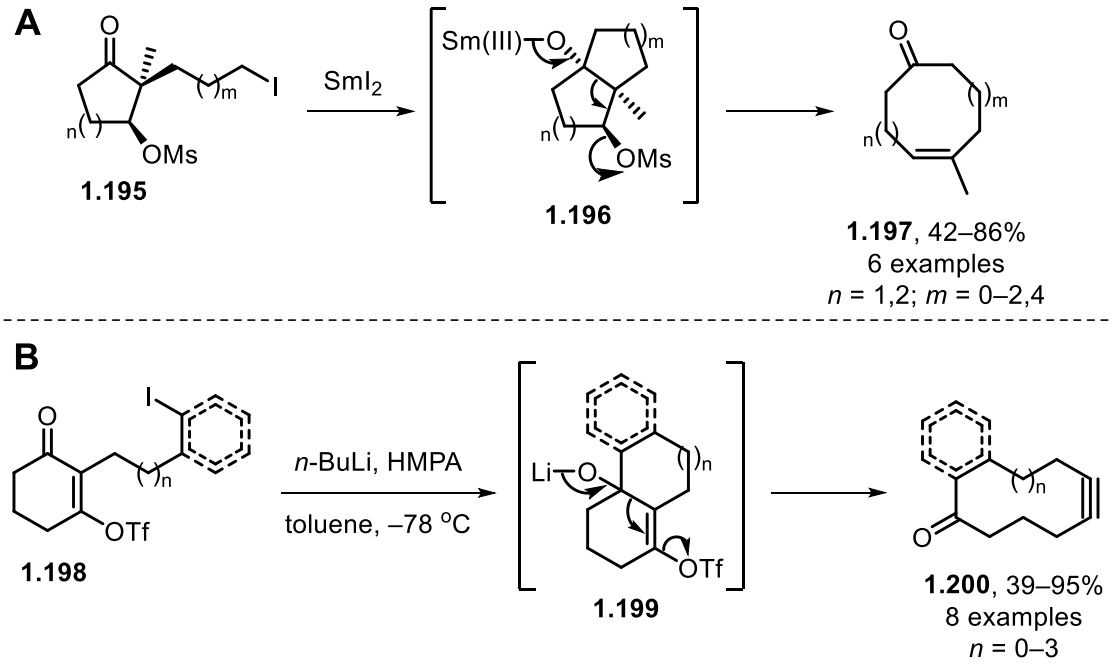
Scheme 38. Unsworth and co-workers' successive ring expansion (SuRE) technique used iteratively, up to a 24-membered macrocycle.

Another example of ring expansion *via* fragmentation with C–C bond formation is the fluoride-initiated technique done by Trost and co-workers to produce a commercially important, macrocyclic musk known as muscone (Scheme 39).[78,79] Silane **1.189** is first reacted with TBAF to form the charged species, **1.190**, before then rearranging to form a 5-membered ring (**1.191**). The ring will then fragment, driven by reformation of the carbonyl (**1.192**), and then protonation and alkene isomerisation will give the ring-expanded species, **1.193**. Muscone, **1.194**, was synthesised by a hydrogenation of the alkene and reduction of the sulfone with sodium amalgam. From **1.189** to **1.194** this was done in an impressive overall yield of 73%.



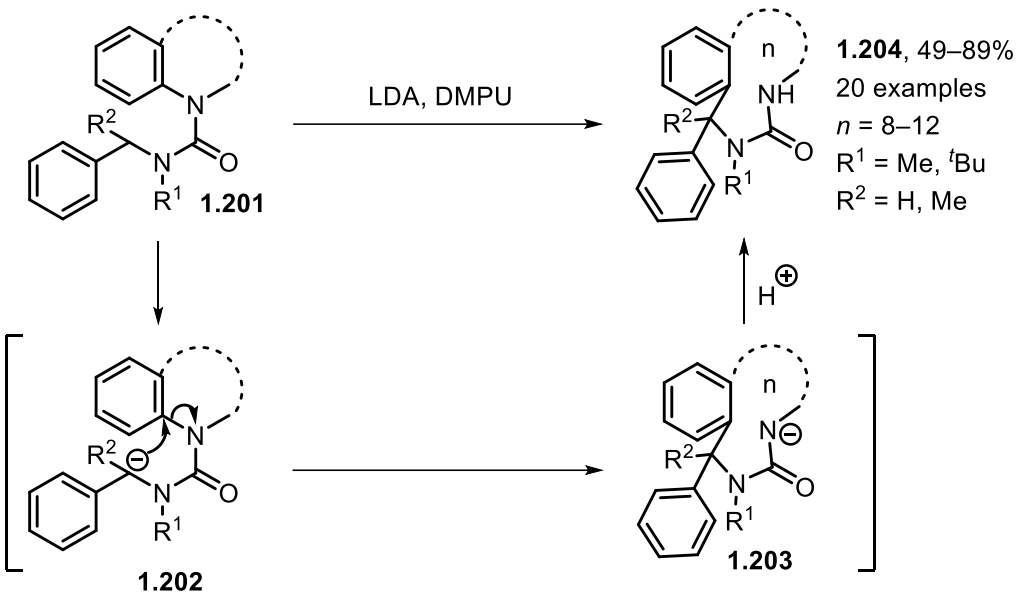
Scheme 39. Trost and co-workers' fluoride-initiated ring expansion to form macrocyclic muscone.

Grob and Eschenmoser fragmentations are both important classical approaches and they have long served as model examples to follow for new methodologies. An example of this was the work done by Molander and co-workers, seen in Scheme 40A,[80] where an SmI_2-mediated Barbier-type reductive coupling was done to form the intermediate, **1.196**. This intermediate then could undergo a Grob-type fragmentation by the removal of the mesylate group to give the product, **1.197**. Through changes to the ring and side chain sizes, a number of examples were completed with a range of 42–86% yields. Similarly, Scheme 40B shows the work done by Dudley and co-workers[81] in which a domino process occurs with the aim of synthesising strained medium-sized ring cycloalkynes in particular – these have known uses in the development and implementation of biorthogonal 'click' reactions.[82] A lithium-halogen exchange occurs first with **1.198** to form the intermediate, **1.199**. After this, a procedure akin to the Eschenmoser fragmentation forms the final alkyne product that has grown in ring size from the original normal-sized ring. The loss of the triflate ion seems to act as a driving force in the reaction, making up for the formation of a strained alkyne group in the ring.



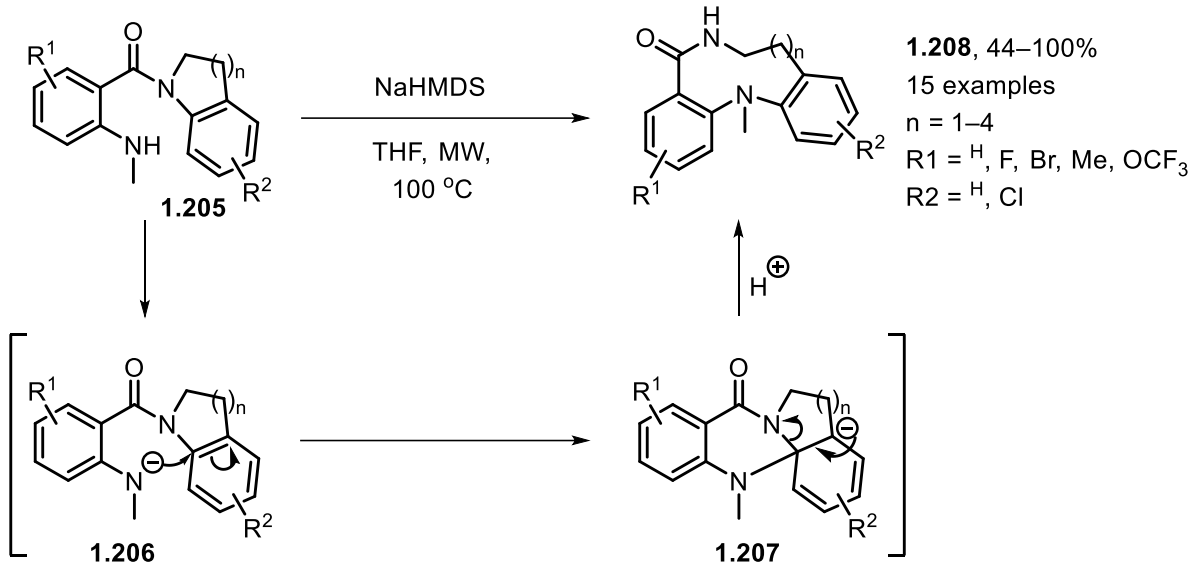
Scheme 40. Fragmentation and domino cyclisation reactions completed by Molander and co-workers (**A**) and Dudley and co-workers (**B**), taking inspiration from classical named reactions.

Clayden and co-workers developed a reaction that involved the aromatic section in the mechanism and was able to form 8–12-membered benzo-fused, nitrogen-containing heterocycles (Scheme 41)[83] and due to the availability of the normal-sized ring precursors, this method was highly useful. An initial lithiation of **1.201** with LDA and deprotonation at the α-site to the nitrogen gives the charged species, **1.202**. Then, through the driving force of moving the negative charge to a more stable location, the carbanion attacks the phenyl ring and moves the charge onto the nitrogen atom. Protonation of **1.203** then gives the ring-expanded product, **1.204**, of which many examples were done in yields ranging from 49–89%. The presence of DMPU was important as it suppressed any competing 1,2-acyl shift that may occur otherwise in the reaction.[84,85] Without DMPU, no product was formed and instead a 66% yield of the acyl shift product was generated.



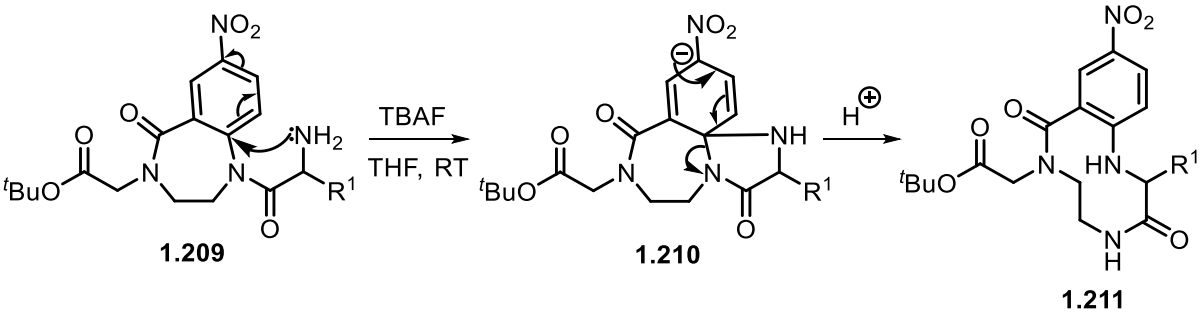
Scheme 41. Clayden and co-workers' migratory ring expansion technique, driven by anion stability, to form 8–12-membered rings.

The same group have also reported a similar reaction where the carbanion is replaced by a nitrogen (Scheme 42).[86] An initial deprotonation is done with NaHMDS under microwave conditions to give **1.206**. This intermediate can then attack the aromatic ring, causing a dearomatisation. Using the driving force of re-establishing the aromatic ring, a fragmentation then occurs to generate the ring, **1.208**, in yields of 44–100% (multiple ring sizes with different substituents attached). Another driving force of this reaction was proposed to be the preorganisation of the compound. It was hypothesised that the tertiary anilide places the nucleophilic nitrogen close to the electrophilic phenyl ring, allowing the reaction to occur faster due to their proximity.



Scheme 42. Clayden and co-workers' ring expansion technique, using aniline as the nucleophile.

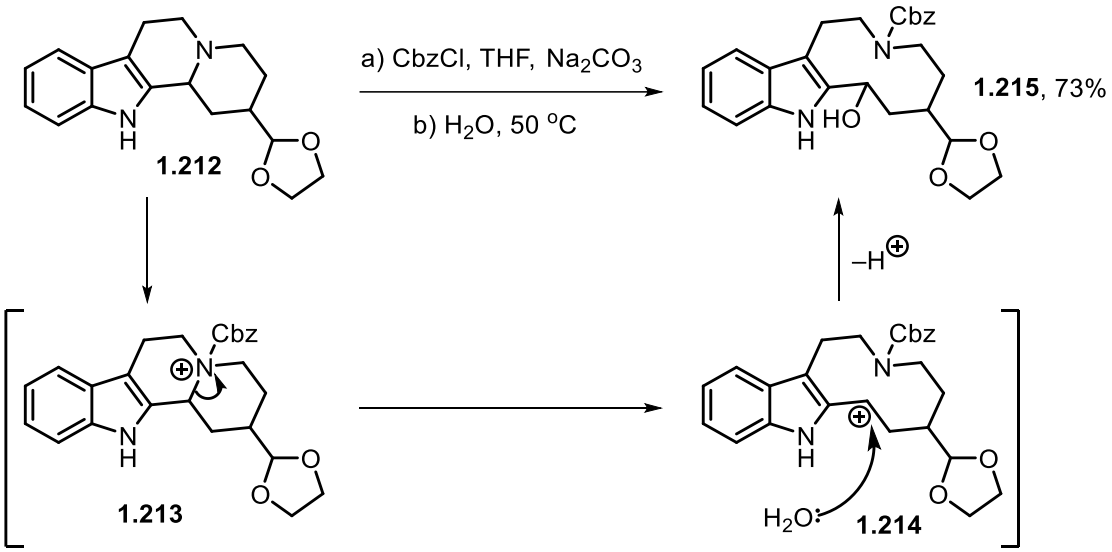
Still and co-workers also developed an analogous reaction for the synthesis of 10-membered lactams (Scheme 43).[87] Amine **1.209** is reacted with TBAF, causing the nucleophilic attack of the free amine into the phenyl ring, with stabilisation being possible due to the nitro group. Intermediate **1.210** will then rearomatise and fragment, with the amide acting as the leaving group over the amine due to being a more stable anion. The electron-withdrawing group at the *para* position in the phenyl ring is essential to allow the resonance stabilisation of the negative charge around the ring which is typical for S_NAr reactions.



Scheme 43. Still and co-workers' ring expansion technique to attach and insert an amino acid derivative into the structure.

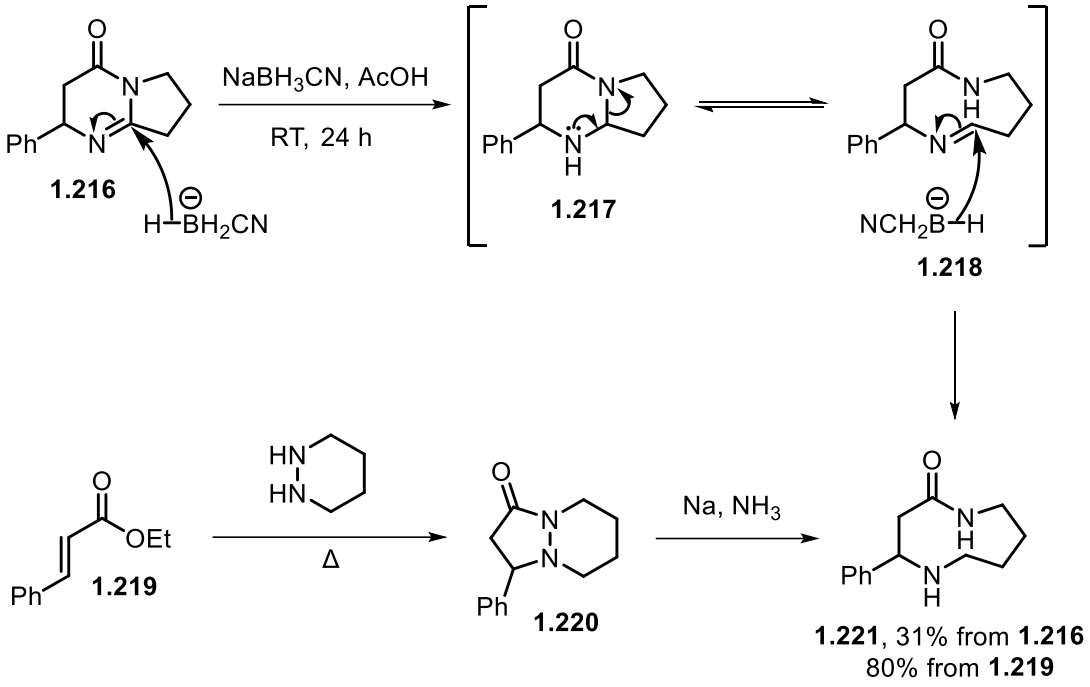
The synthesis of the natural product (±)-deethylibophyllidine *via* a ring expansion reaction was discovered by Bonjoch and co-workers (Scheme 44).[88] The tertiary amine present within the bicyclic structure reacts with benzyl chloroformate to give the ammonium species, **1.213**. This will then fragment in the next step, forming the medium-sized ring, **1.214**. Addition of water was able to allow the trapping of the carbocation intermediate, before adding itself to the positive charge, forming the final product, **1.215**, in a yield of 73%. At the

time of release of this paper, this was the most efficient route to the natural product. The group also developed other routes to the product – but these were lower yielding.[88,89,90]



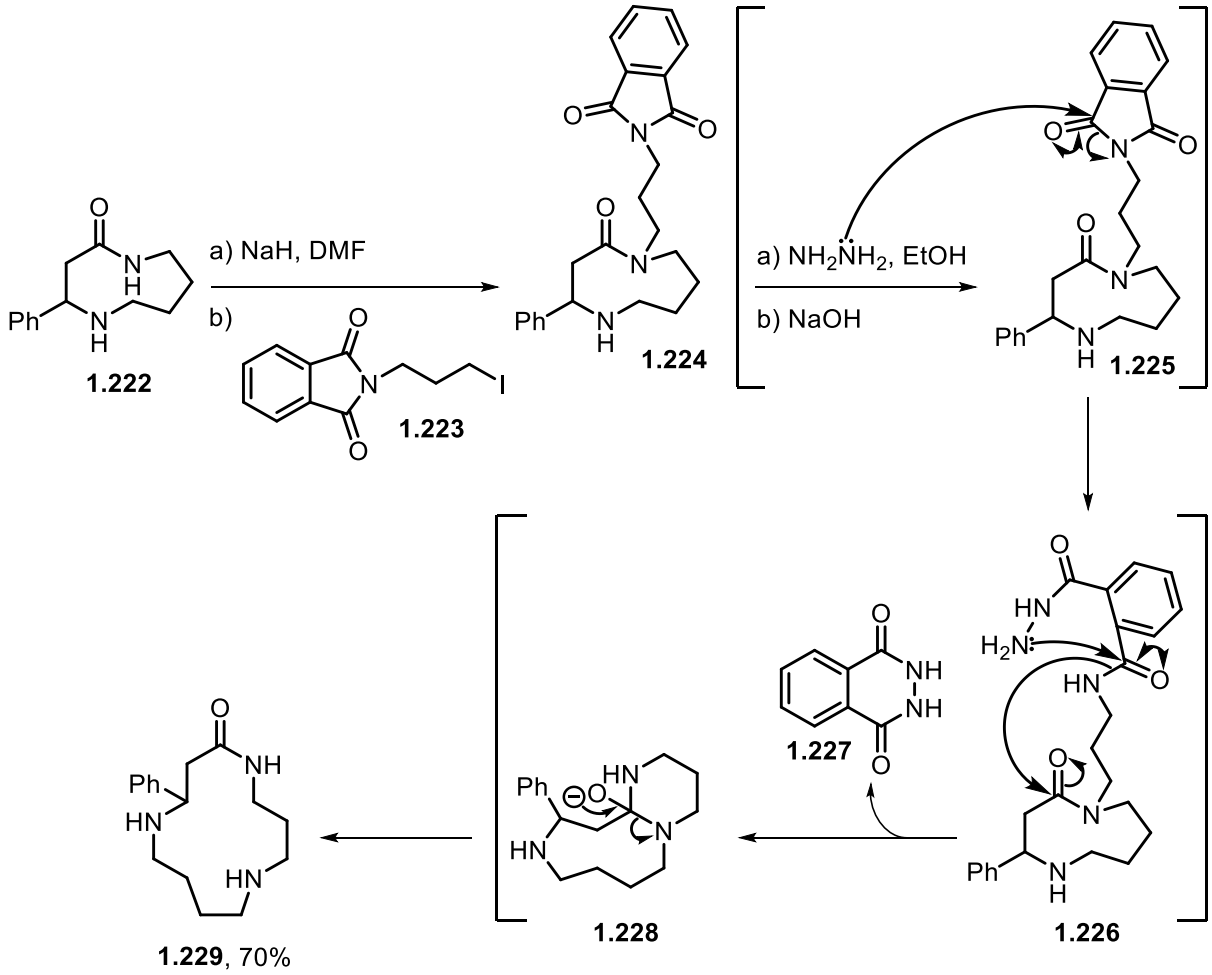
Scheme 44. Bonjoch and co-workers' amine acylation followed by a fragmentation to give a 10-membered ring.

Wasserman and co-workers were able to devise two strategies that use reductive methods for the synthesis of a 9-membered ring (both seen in Scheme 45).[91] The first being the addition of sodium cyanoborohydride to the bicyclic compound, **1.216**. The two intermediate products from this reaction are thought to be in equilibrium with each other and the trapping out of the imine **1.218** meant the ring expansion could be achieved, with 9-membered ring product **1.221** formed in 31% yield. The second strategy initially required the reaction of a cyclic hydrazine with **1.219** to form the bicyclic precursor, **1.220**. Following this, a reductive N–N bond cleavage using sodium and liquid ammonia, generated the 9-membered product, **1.221**, in a much-increased yield of 80%. The reaction time of this second attempt was also much shorter, taking just over an hour as opposed to 24 hours needed for the first strategy.



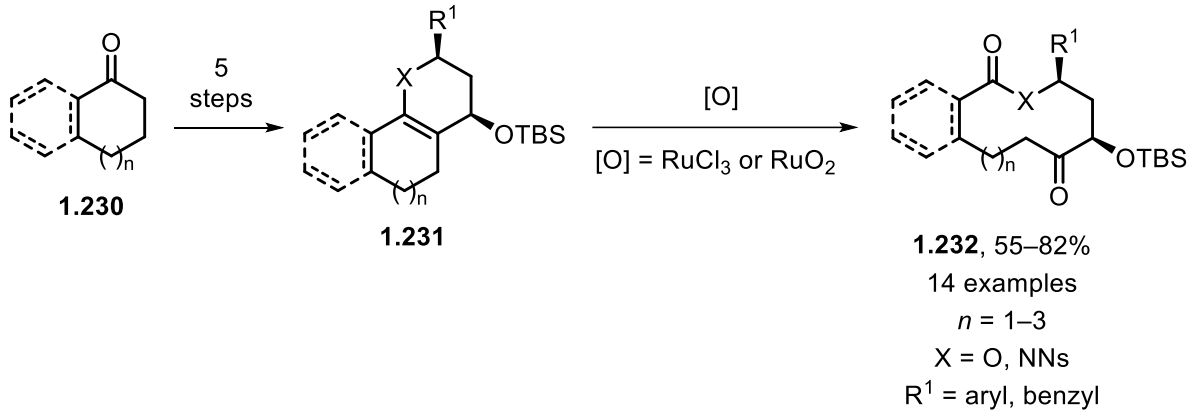
Scheme 45. Wasserman and co-workers' two routes for the synthesis of a medium-sized ring, both involving reductive cleavages.

The same group then enlarged the ring further to a macrocycle (Scheme 46)[91] using a side chain insertion commonly seen in fragmentation ring expansion reactions. The amide was first selectively deprotonated by sodium hydride and then **1.223** was added to the structure *via* an S_N2 alkylation to give **1.224**. Then, using standard conditions for a Gabriel amine synthesis (for the deprotection step),[92] of hydrazine and sodium hydroxide, the phthalimide group was removed to provide the free amine which could then undergo an intramolecular attack on the carbonyl forming a bicyclic intermediate, **1.228**. This could then immediately fragment and the final 13-membered macrocycle **1.229** was obtained.



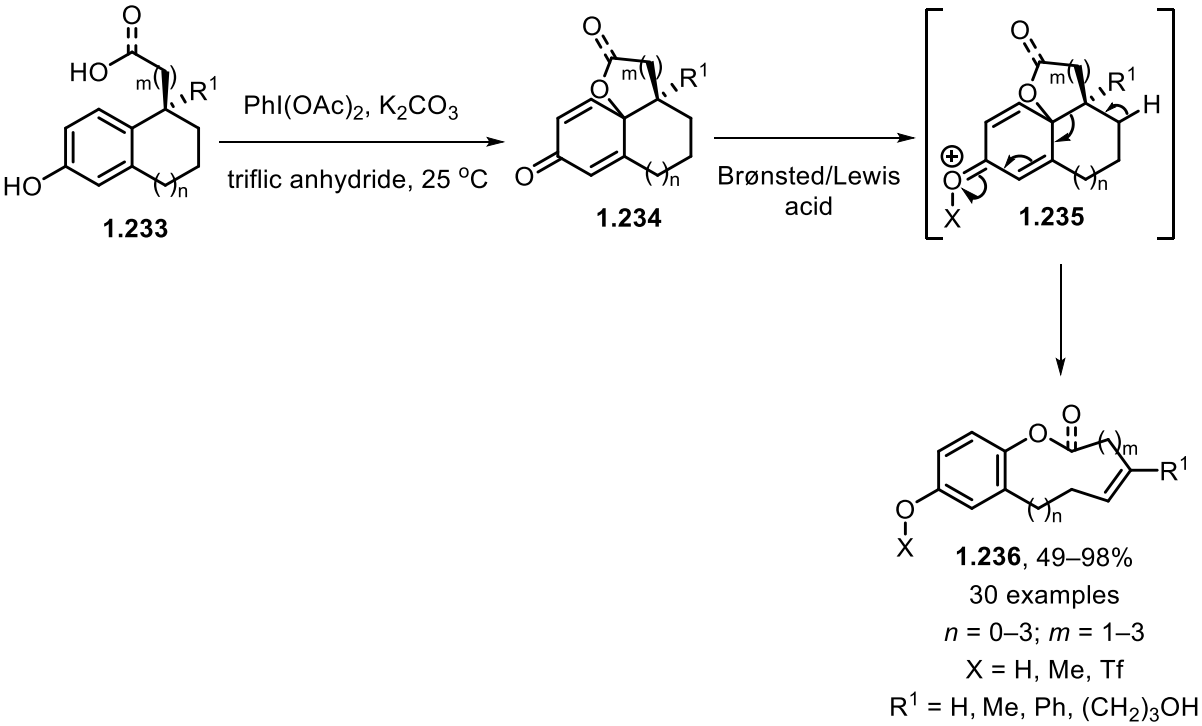
Scheme 46. Wasserman and co-workers' synthesis of a macrocycle, *via* a side chain insertion.

Tan and co-workers developed a way to use oxidation for their ring expansion reactions *via* redox-mediated fragmentation and this allowed the synthesis of medicinally relevant medium-sized rings and macrocycles of 10–12 ring length (see Scheme 47).[12] The initial precursor, **1.230**, was reacted in a number of preliminary steps to reach **1.231** going from: ketone → β-diketone → bis(trimethylsilyloxy)diene → dihydropyrone/dihydropyridone → dihydropyran (**1.231**). Initial studies on this substrate used *m*-CPBA and ozone as the oxidant due to precedent in ring expansion reactions of cyclic enol ethers.[93,94,95,96] However, both were not very effective on a consistent basis. Although with *m*-CPBA, the yield of one example was encouraging (66%), the other attempts all resulted in the formation of a complex mixture of products. With ozone as the oxidative agent, there was some success but only a low 11% of the desired product. The group identified the use of catalytic ruthenium complexes as an alternative, [97,98] and catalytic $RuCl_3$ was attempted for the oxidation with success – the most effective conditions were $RuCl_3$ at 3.5 mol% with oxone (82% yield). These optimum conditions varied slightly for whether **1.231** contained an enol, aryl enol or enamine but all used a ruthenium complex of some sort to form the product, **1.232**, in yields ranging from 55–82%.



Scheme 47. Tan and co-workers' use of an oxidation reaction with a ruthenium complex to synthesise 10–12-membered rings.

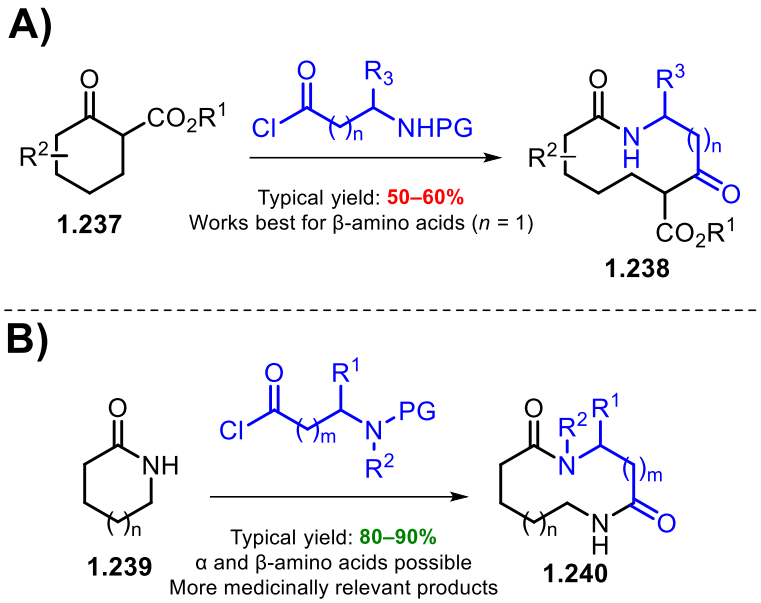
The same group also went on to synthesise more medium-sized rings *via* an approach that involved an oxidative dearomatisation-ring-expanding rearomatisation (ODRE) sequence over two steps (Scheme 48).[99] The phenol undergoes an oxidation that also causes a dearomatisation using phenyliodine(III) diacetate to form **1.234** (a tricyclic enone). This is then reacted with triflic anhydride to give **1.235**, an oxocarbenium. The movement of the positive charge to initially form a tertiary carbocation (before being replaced with an alkene) as well as the opportunity to rearomatise drives the reaction and allows the fragmentation reaction to occur, giving the final product, **1.236**.



Scheme 48. Tan and co-workers' use of a 2-step oxidative dearomatisation-ring-expanding rearomatisation (ODRE) reaction to form medium-sized rings and macrocycles.

1.5 Successive Ring Expansion

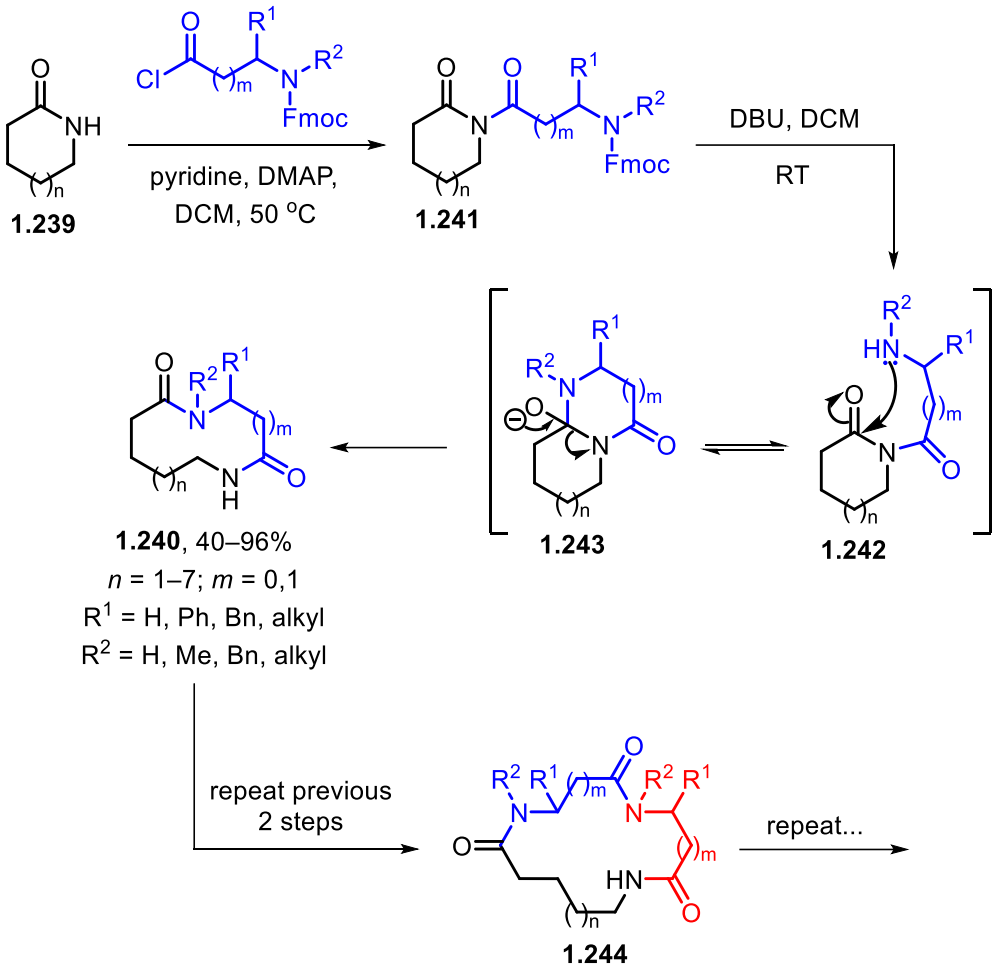
Within the Unsworth group, three general techniques for ring expansion have been developed, the first of which is Successive Ring Expansion (SuRE). The first iteration of SuRE was detailed in section **1.4** above (a simplified version is shown below in Scheme 49A), where a cyclic β-keto ester was used to facilitate the addition of a protected acid chloride, before a deprotection and ring expansion step occurred.[19] The group sought to expand this concept to other, more medicinally relevant substrate classes, and this was done by changing the starting material to a lactam (Scheme 49B).[18,100,101,102] The products generated from this newer technique were higher in yield on average (80–90%), made more medicinally relevant substrates and tolerated a wider range of acid chloride side chains.[103,104]



Scheme 49. A comparison of the techniques for SuRE to synthesise medium-sized and macrocyclic rings.

The method is shown in Scheme 50 and starts with the reaction of lactam **1.239** with an acid chloride, pyridine and DMAP, forming an imide intermediate that now contains the side chain (**1.241**). Following this, **1.241** was reacted with DBU which allowed the deprotection of the Fmoc-protected amine and under these basic conditions, facilitated spontaneous ring expansion. This is thought to go through a bicyclic intermediate, **1.243**, that fragments to provide the final product, **1.240**. Due to the regeneration of the lactam functionality, this ring expansion process can be performed iteratively, *via* the repetition of the previous steps (as shown with the formation of **1.244**). In theory, it could be performed multiple times, although in practice, after a few iterations, the *N*-acylation step tends to become more difficult.[21] Using this methodology, a large number of products of varying sizes, with

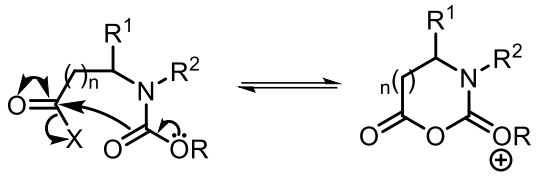
different side chains attached (including amino acids), have been synthesised in yields of 40–96%.



Scheme 50. Using SuRE to complete consecutive ring expansion reactions.

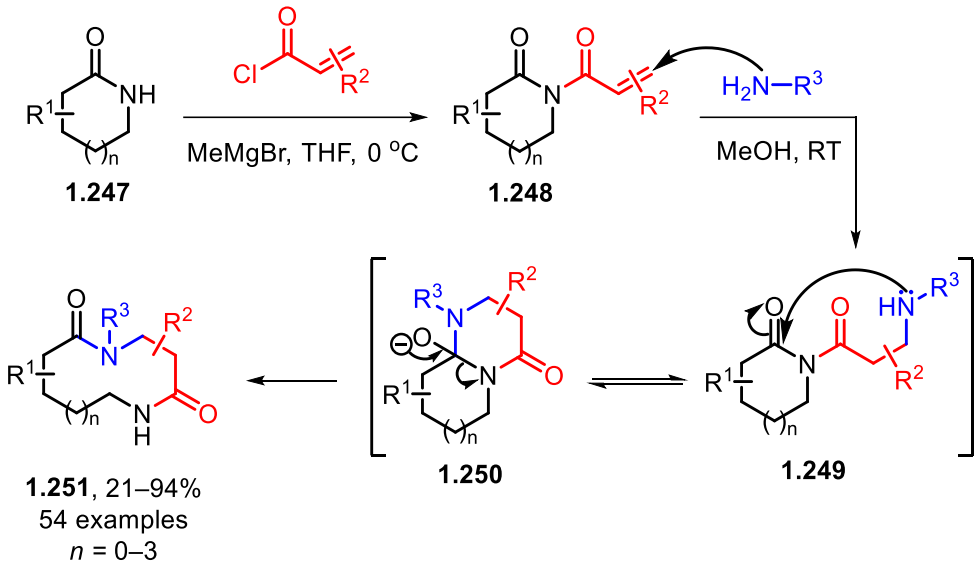
1.6 Conjugate Addition Ring Expansion

A limitation of the SuRE reaction described above, is the need to make protected amino acid chlorides for every new example (often a multi-step process is needed). Moreover, the acid chlorides used are prone to degradation, due to the presence of the carbamate group from the Fmoc protecting group. In cases where the lactam acylation is slow, a competing side reaction takes place to form the 5/6-membered side-product, **1.246**, thus reducing the yield of the *N*-acylation reaction (Scheme 51).[105]



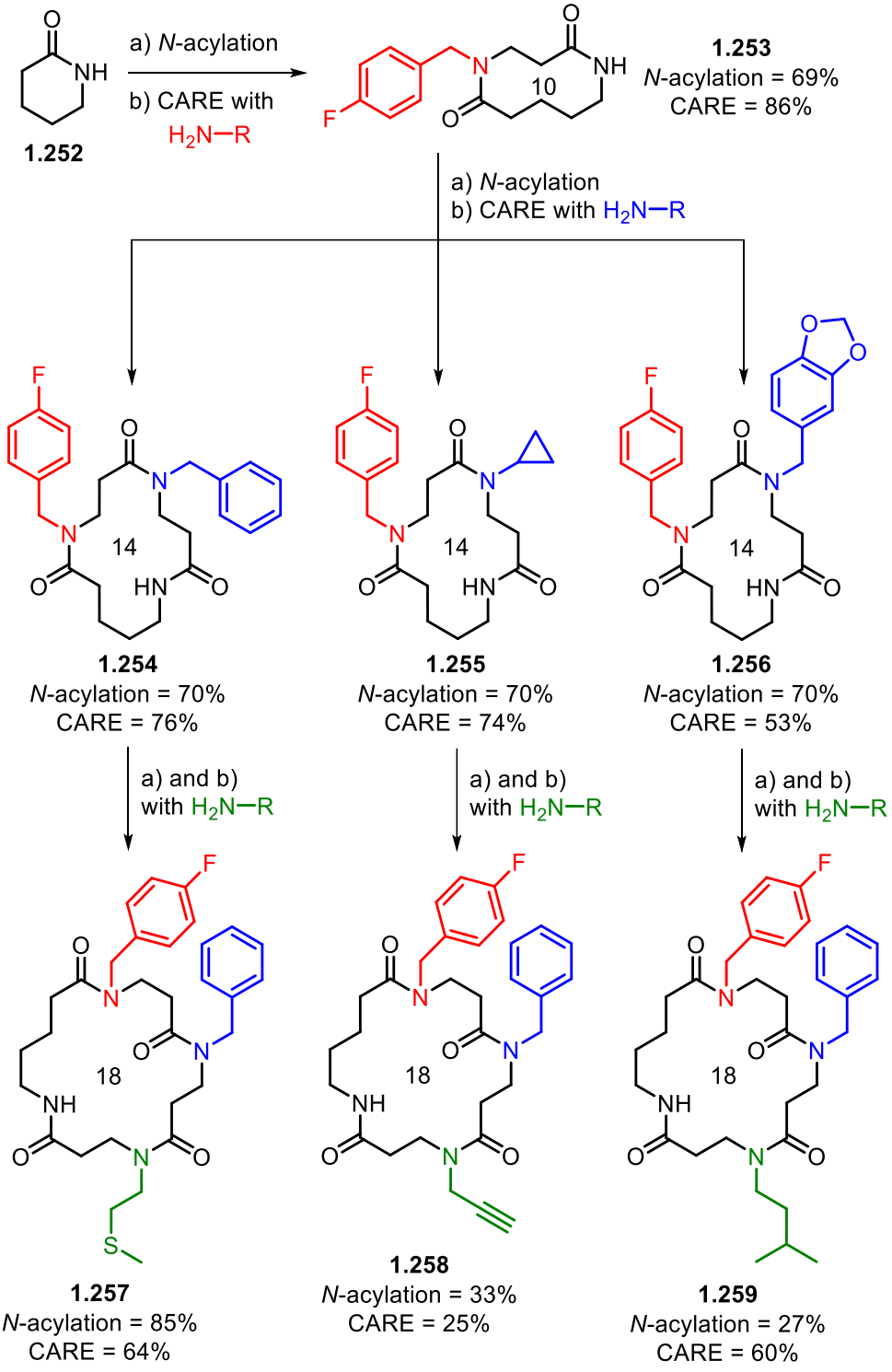
Scheme 51. The competing reaction that causes the consumption of the acid chloride starting material reagent in a SuRE reaction.

With these problems in mind an alternative was devised that had the key consideration of removing protecting groups from the compound. This led to the creation of a new technique called Conjugate Addition Ring Expansion (CARE), shown in Scheme 52.[106,107] This approach involved two simple reactions – the first being an *N*-acylation with acryloyl chloride and methyl magnesium bromide as the base to form the imide, **1.248**. The alkene formed is a strong Michael acceptor, and therefore when reacted with a primary amine, undergoes the conjugate addition to form **1.249**. Under the basic reaction conditions, this intermediate spontaneously rearranges to form the more stable ring-expanded product, **1.251**, as a medium-sized ring or macrocycle. This reaction was found to be incredibly efficient and versatile with a total of 54 novel CARE substrates being generated in the first submitted manuscript on this technique.[106] These substrates included variation on: lactam type, lactam size, branched groups on the Michael acceptor and the amine used (including medicinally relevant examples). Some added benefits of these CARE reactions, were their insensitivity to air and ability to work in a range of solvents, including water. CARE reactions can be done using amino acids, peptides and even proteins as the amine, as was reported in a recent paper published by the group.[108]



Scheme 52. Unsworth and co-workers' general mechanism for the CARE technique devised by the group.

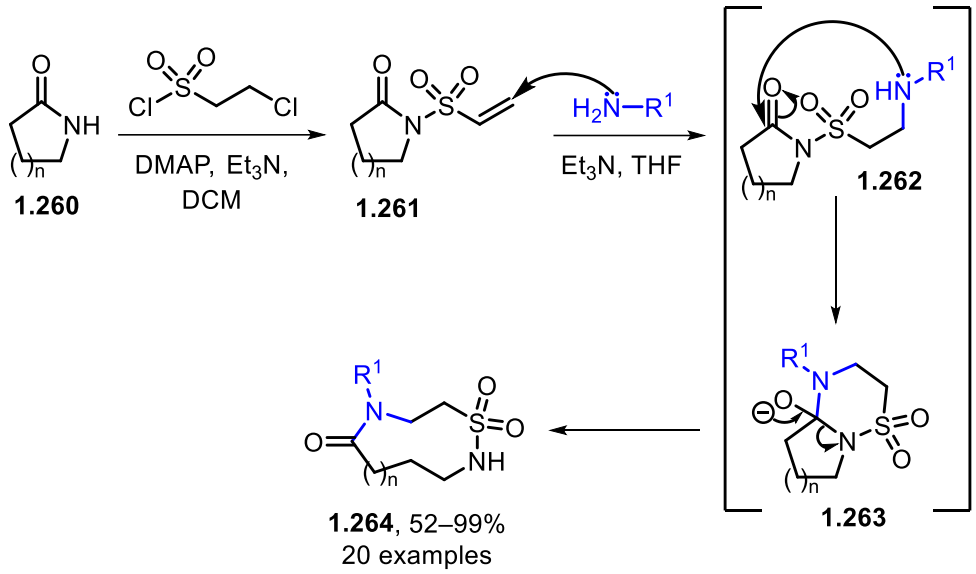
Another key feature of CARE is the regeneration of the starting material's lactam functionality, in the same way as in the previously described SuRE work. This means it is feasible to repeat the *N*-acylation step previously done on the precursor (Scheme 53).[106,109] As shown, **1.253** is able to react with the same reagents, forming the imide in a 69% yield. After this, the CARE step could be completed with a range of amines in yields of 53–76%. A third ring expansion step was also demonstrated (to form **1.257**–**1.259**). The ability to progress from a normal-sized ring to a medium-sized ring and then to macrocycles *via* repeated ring expansions is a major positive of CARE, as well as the capability to install different functionalised building blocks into the ring structure.[110,111,112]



Scheme 53. Unsworth and co-workers' pathway for completing iterative CARE reactions.

The CARE approach is also applicable to sulfonamide containing systems. Medium-sized ring and macrocyclic sulfonamides are relatively rare in the literature and are not well studied in terms of their synthesis and biological activities. Hence, there was interest in the Unsworth group to identify a ring expansion route for their formation.[113,114,115,116] A new sulfonamide-forming ring expansion technique that utilised CARE was therefore developed (Scheme

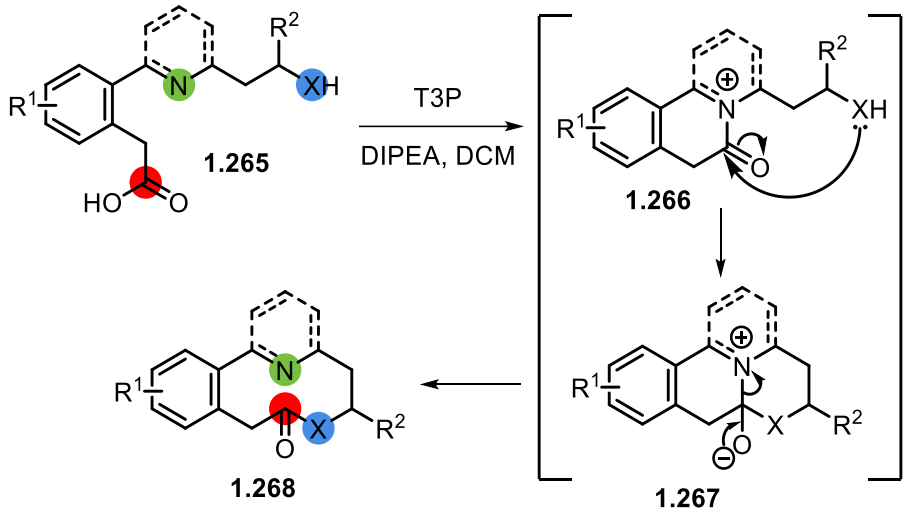
54).[117] The initial sulfonylation was done by reacting lactam **1.260** with DMAP, triethylamine and 2-chloroethanesulfonyl chloride. The resulting compound (**1.261**) could then react with a primary amine (a wide range were successful) with triethylamine acting as the base to form the 9–12-membered cyclic sulfonamide in yields ranging from 52–99%. As shown in Scheme 54, the primary amine is thought to attack the alkene, before rearranging to form the bicyclic intermediate, **1.263** and then the *n*+4 ring-expanded product, **1.264**.



Scheme 54. Unsworth and co-workers' general mechanism for the CARE technique involving a vinyl sulfonamide in its structure.

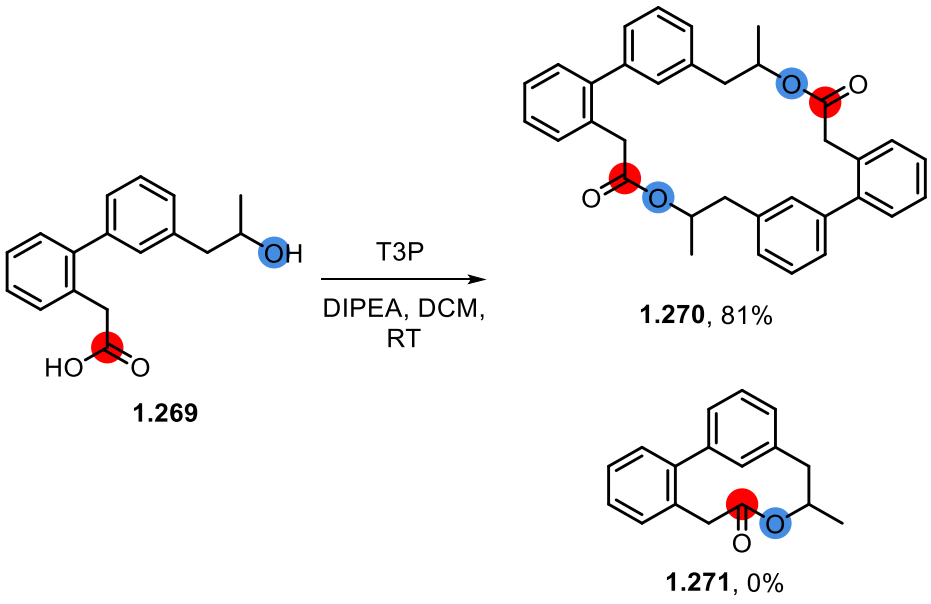
1.7 Nucleophile Induced Cyclisation/Expansion

All the examples described above start from cyclic precursors that undergo a further ring enlargement.[118,119,120] Building on this, the Unsworth group were able to develop a technique to synthesise medium-sized rings and macrocycles directly from linear precursors (Scheme 55),[121] known as Nucleophile Induced Cyclisation/Expansion (NICE). The starting material for a typical reaction, **1.265**, includes an electrophilic end (highlighted in red), a nucleophilic end (highlighted in blue) and an internal nucleophile (highlighted in green). Acid **1.265** is first activated with T3P to form an intermediate that will then be attacked by the internal nucleophile, forming **1.266** (a normal-sized ring).[122,123,124] Once formed, the terminal nucleophile can attack the acyl ammonium salt to generate a bicyclic intermediate **1.267** which then fragments to give the final medium-sized ring (**1.268**).



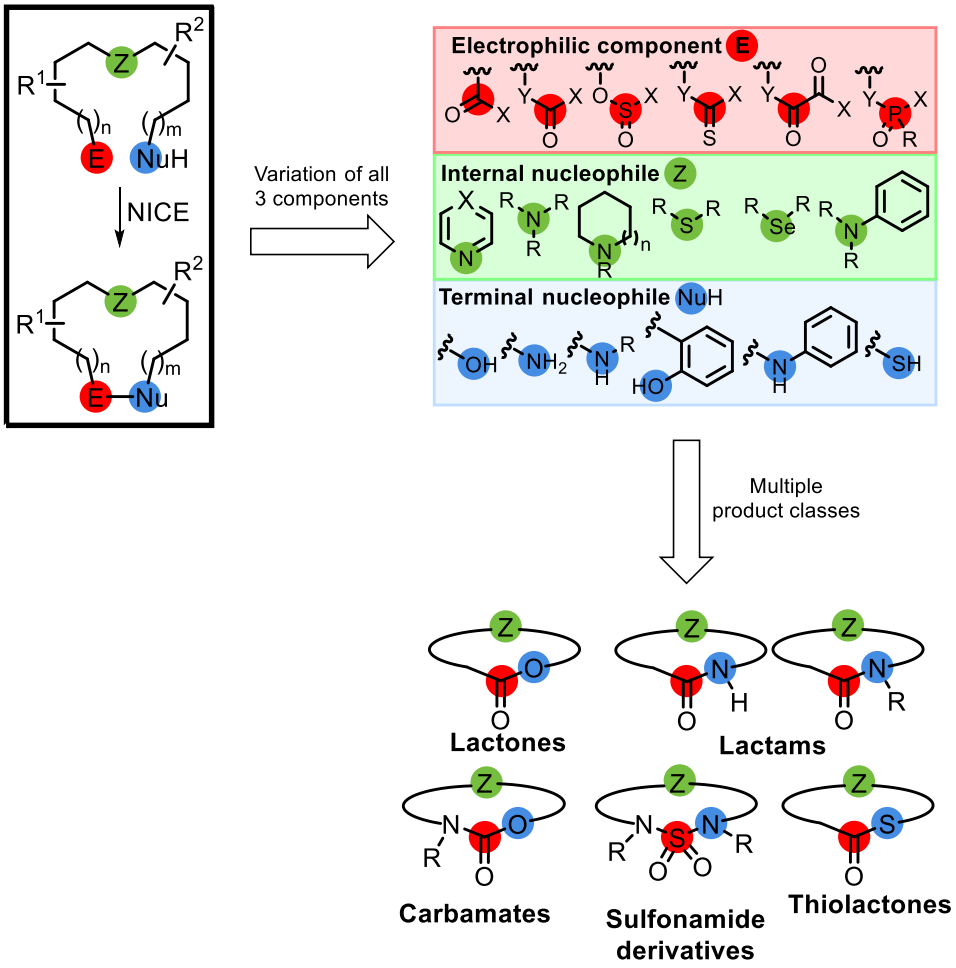
Scheme 55. Unsworth and co-workers' general mechanism for the NICE technique involving an electrophile and two nucleophiles in its structure.

A key design feature of these reactions is that they proceed exclusively *via* normal-sized ring cyclisation steps. Splitting an inefficient end-to-end cyclisation into two steps that are more kinetically favourable, due to them proceeding *via* normal-sized rings, can make the formation of medium-sized rings and macrocycles faster and easier.[16,125] The importance of this internal nucleophile to form the intermediate was tested *via* a control reaction, in which the pyridine was replaced with a benzene ring (Scheme 56). The same reaction conditions were used, but in this case none of the analogous 10-membered ring product, **1.271**, was produced and instead the 'head-to-tail' dimer formed (**1.270**) in a yield of 81%. This confirmed the importance of the internal nucleophile for the synthesis of the medium-sized rings.



Scheme 56. Unsworth and co-workers' control reaction, showing the formation of the head-to-tail dimer.

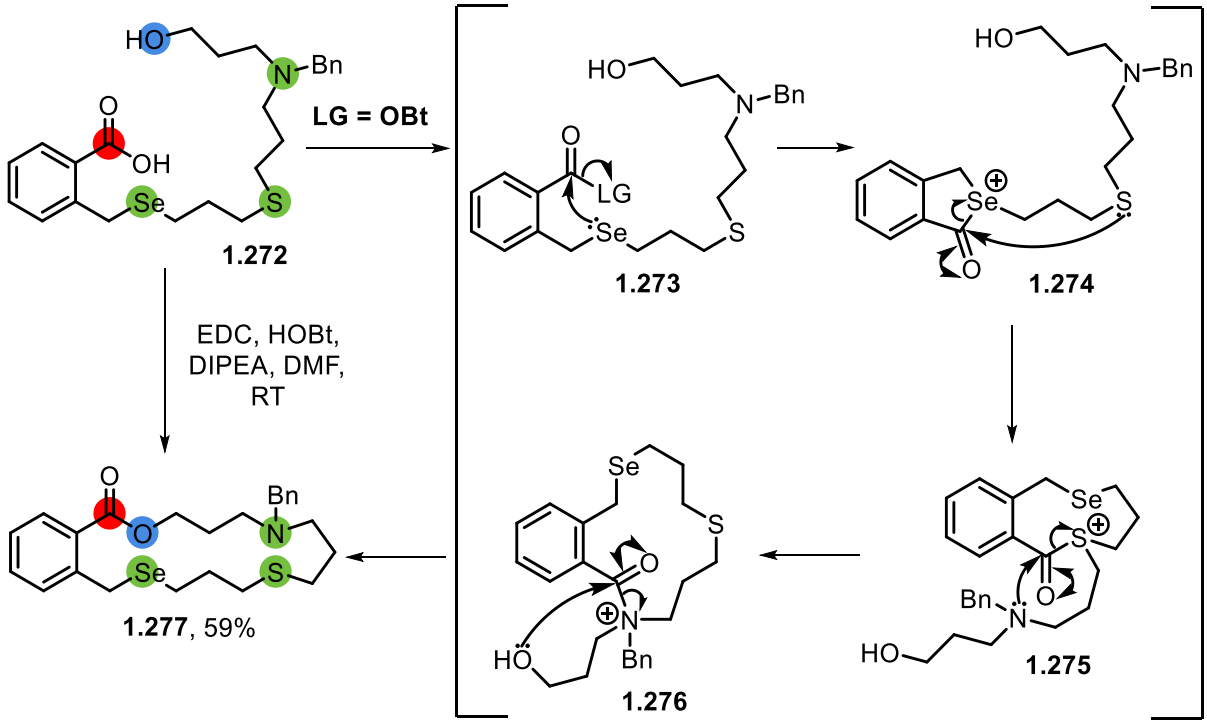
The type of substrate shown in Scheme 55 is just one example done by Unsworth and co-workers – there is broad scope for variation of all three key components of the starting material (Scheme 57).[121,126] The terminal nucleophile has been varied widely, with examples featuring primary, secondary and tertiary alcohols, as well as primary amines, secondary amines and thiols. The internal nucleophile has also been varied with pyridines, aliphatic, tertiary amines, selenides and sulfides all used with success. As for the electrophilic component, carboxylic acids, dicarbonyl species, phosphonic acids, thiocarbonyl species, sulfonic acids and sulfinic acids have all been included in published examples. This huge amount of variation has led to over 150 novel products being made using the technique to date, and many more likely to be possible.



Scheme 57. A scheme showing the different groups utilised for the three key electrophilic/nucleophilic sites.

This methodology was extended to linear starting materials that include multiple internal nucleophiles for the formation of larger macrocyclic systems (Scheme 58).[126] It was hypothesised that having more than one internal nucleophile will allow a sequential reaction where each nucleophile will successively attack the electrophile and form an intermediate at each step. Currently, this idea has been validated with up to 3 internal nucleophiles,

although more, in theory, should be possible and this idea is displayed in Scheme 58. In this example, the EDC and HOBt activate the carboxylic acid, with the 'OBt' group acting as the leaving group (LG) in Scheme 58. It is thought that the selenium atom then attacks the carbonyl to form the selenium salt intermediate (**1.274**). From here, the second internal nucleophile can attack this salt to form the thioester salt, **1.275**. Then, the third internal nucleophile will attack and form an acyl ammonium salt, **1.276**. Finally, the remaining terminal nucleophile (alcohol) will make the last attack on the carbonyl and following a fragmentation will form the final, macrocyclic product, **1.277**.



Scheme 58. Unsworth and co-workers' NICE reaction involving three internal nucleophiles, enlarging the ring to a macrocycle.

1.8 Project Aims

Applications of medium-sized rings and macrocycles have been known for years but in recent times there has been increased interest. This is particularly due to the promise that they have demonstrated in medicinal chemistry,[127,128] and they have also shown potential in a number of other scientific areas including: catalysis,[129] materials science,[130] chiral sensing,[131] self-assembly[132] and nanotechnology.[133] As a result, there has also been an increase in the number of new syntheses for medium-sized rings and macrocycles, as has been shown in the chapter above.

As the increase of applications has grown, the need for a practical and efficient method to synthesise medium-sized rings and macrocycles has also increased. The overriding goal of

the work in this PhD was to develop new methods to make medium-sized rings and macrocycles more easily, using ring expansion approaches. Several different approaches were explored.

In Chapter 2, work focused on the Conjugate Addition Ring Expansion (CARE) approach, and specifically exploring its versatility in enabling ring expansions with multiple nucleophiles. During this investigation, two novel methods were investigated where carbon and oxygen (as well as the already discovered nitrogen) would be used as the nucleophiles in CARE. If successful, there were also aspirations to use these nucleophiles to perform CARE consecutively to synthesise larger macrocycles.

In Chapter 3, the aim was to incorporate two of the widely-used transformations from within the Unsworth group – NICE and CARE – into a single approach. Linear starting materials amenable to Nucleophile Induced Cyclisation/Expansion (NICE) reactions that contained a branched vinyl sulfonamide were hoped to be created. Should precursor synthesis and the following NICE step succeed, the vinyl sulfonamide group would be capable of facilitating the next step (a CARE) and allow a further ring expansion from a medium-sized ring to a macrocycle.

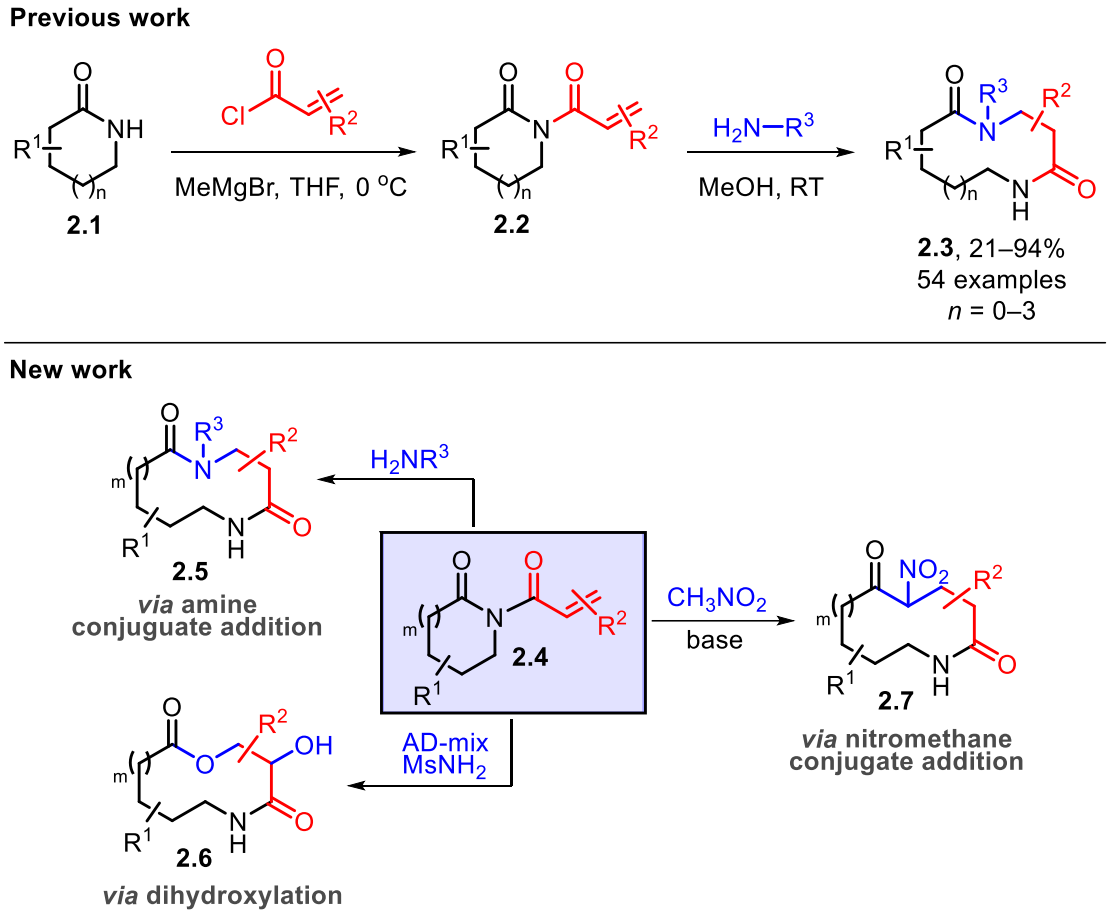
In Chapter 4, attention was primarily switched to work using a third technique developed in the Unsworth group – Successive Ring Expansion (SuRE) – towards different applications. The work in this chapter involved working with different external collaborators interested in utilising the Unsworth group's ring expansion techniques.

2 Divergent Cascade Ring Expansion Reactions of Acryloyl Imides

2.1 Chapter Aims

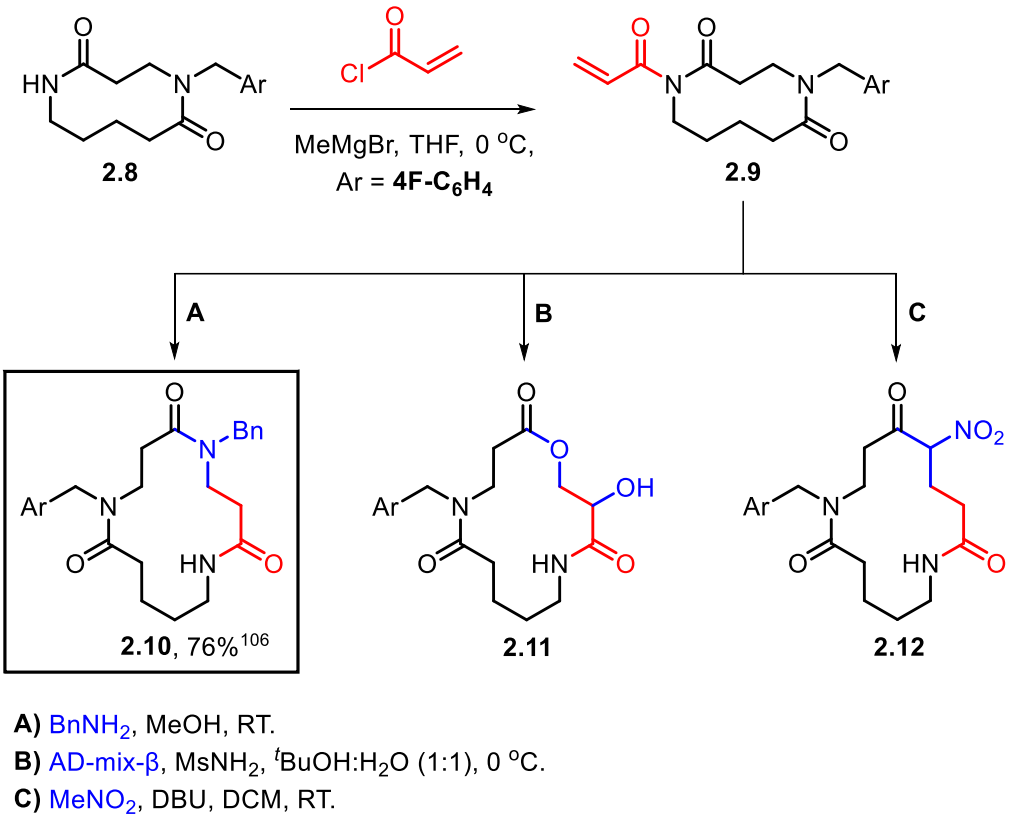
A major aim of the work described in this chapter was to continue the development of the Conjugate Addition Ring Expansion (CARE) approach and expand its scope as a method for the generation of medium-sized rings and macrocycles *via n*+4 ring expansion reactions. A general procedure for CARE using nitrogen as the nucleophile for the conjugate addition step was already established in the Unsworth group before this project (see 'previous work' in Scheme 59). Using this method, Unsworth and co-workers were able to vary the lactam type, lactam size, Michael acceptor and amine, with these results documented in the group's first CARE paper published in 2022.[106]

The work in this chapter is focused on expanding the CARE approach to explore other methods to functionalise the Michael acceptor and enable ring expansion, particularly *via* the introduction of carbon and oxygen-based nucleophiles (see 'new work' in Scheme 59). The early stages of this work were investigated within the Unsworth group during my Master's project, undertaken prior to the commencement of my PhD. This preliminary work uncovered potentially viable procedures using the reagents denoted in Scheme 59 below.[134,135,136] In this project, the aim was to build on these preliminary results and develop new, efficient and versatile CARE approaches.



Scheme 59. A summary of the previous work and the new work described in this chapter.

In the Unsworth group's previous work (also included in the 2022 paper)[106] they were able to confirm the possibility of doing consecutive CARE reactions with a nitrogen nucleophile (**2.10** an example among several). Therefore, there was also interest to see if this idea could be extended and replicated to the new ring expansion methods developed during this project (shown in Scheme 60 with **2.11** and **2.12** as examples). The ability to alternate the type of ring expansion reaction being done in successive reactions would display another level of versatility and further increase the value of CARE reactions.

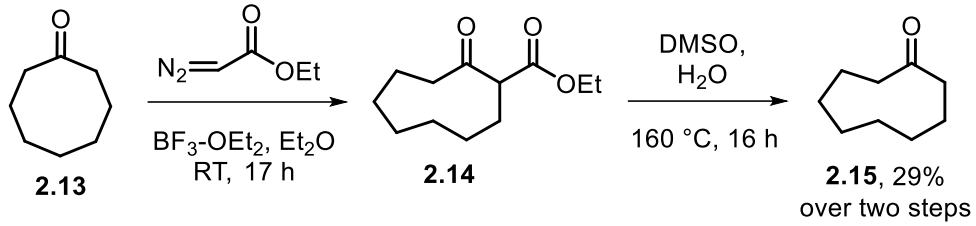


Scheme 60. The potential second ring expansions from **2.9** using nitrogen, oxygen and carbon as the nucleophiles in the CARE reaction.

Note: while the work in this coming chapter built on previous preliminary studies performed during my MChem project, unless stated, all the results described in Section 2.2 onwards were performed during this PhD.

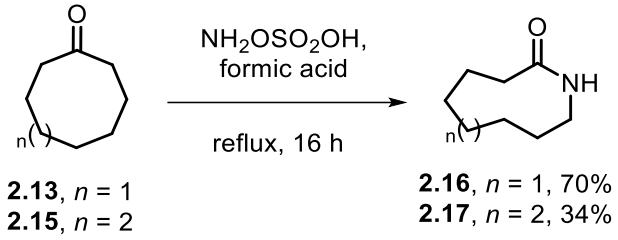
2.2 Synthesis of Imide Precursors

Some medium-sized ring lactams were required to be used as starting materials during the project and their synthesis is described below in Scheme 61. First, starting with cyclooctanone (**2.13**), a Büchner-Curtius-Schlotterbeck reaction[18,137] was carried out to facilitate an *n*+1 ring expansion, following reaction with ethyl diazoacetate and boron trifluoride etherate to form the cyclic β-ketoester **2.14**. Subsequent heating in DMSO and water, as replicated from the literature,[18] then gave the *n*+1 ketone (**2.15**), *via* an initial ester hydrolysis with the water and then a decarboxylation, in an overall 29% yield from ketone **2.13**.



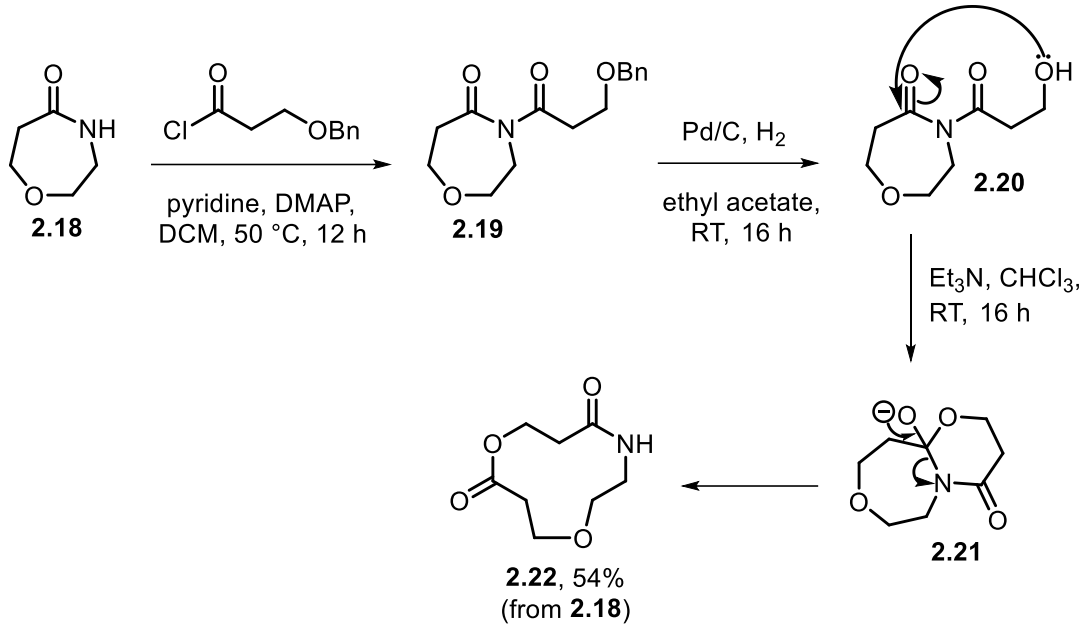
Scheme 61. Synthesis of the *n*+1 cyclic ketone.

With both 8- and 9-membered cyclic ketones, a Beckmann rearrangement was completed to convert the ketone functionality into an *n*+1 lactam.[18,138] Hydroxylamine-O-sulfonic acid and formic acid was reacted with both ketones, **2.13** and **2.15**, to afford the final products (**2.16** and **2.17**) as shown in Scheme 62.



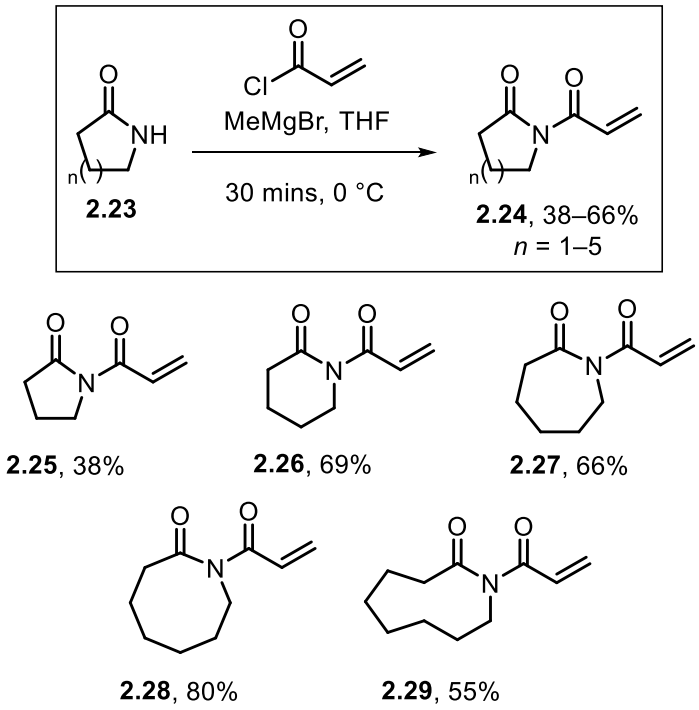
Scheme 62. Synthesis of the *n*+1 lactams.

The final precursor prepared was an 11-membered lactam containing a lactone and ether that was synthesised *via* literature SuRE conditions summarised in Scheme 63.[21,139] The acid chloride (generated in situ) is first reacted with **2.18**, pyridine and DMAP to form imide **2.19**. The second step involves the benzyl deprotection of the alcohol using palladium on carbon and hydrogen gas and then the final step involves a switch to basic conditions that allows **2.20** to rearrange, affording the ring-expanded product **2.22** in a yield of 54% over the three steps.



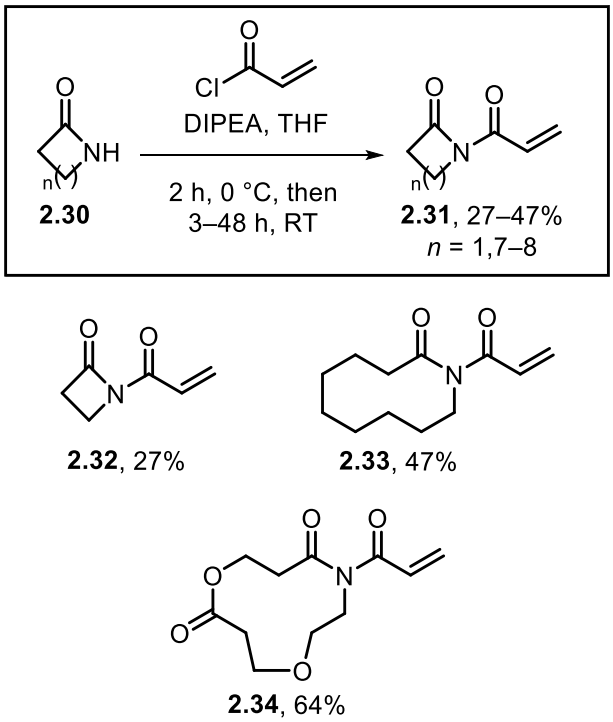
Scheme 63. Synthesis of the functionalised azacycloundecanone.

Following this, acryloyl imide precursors were made, using the general procedure developed by the Unsworth group for the *N*-acylation of different lactam ring sizes (5–9-membered), as shown in Scheme 64.[140,141] Methyl magnesium bromide acted as a base to deprotonate the lactam (**2.23**), enabling the resulting anionic nitrogen to act as a nucleophile and react with the electrophilic acryloyl chloride, allowing the formation of the cyclic imides **2.25**–**2.29**. Yields were quite variable – as has been the case throughout the group with these *N*-acylation reactions, especially as in most cases these were only attempted once. A general reason for some of the poor yields in Scheme 64 and 65 could potentially be the ability of competing polymerisation by the compounds involved, but in most cases they were acceptable.



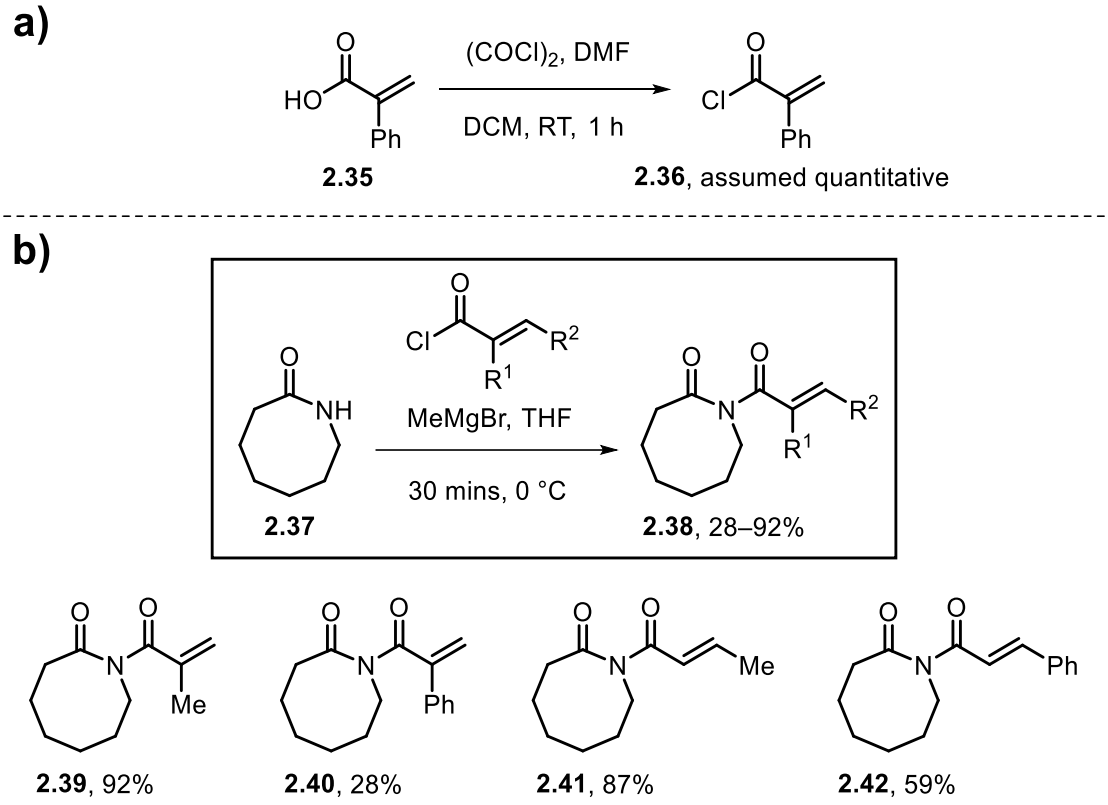
Scheme 64. Synthesis of the acryloyl imides, from lactams.

Different *N*-acylation conditions were used to prepare the 4-,10- and 11-membered ring imides (**2.32, 2.33** and **2.34**). A previously reported procedure for the synthesis of **2.33** used alternate conditions to those in Scheme 64 – the main difference being the use of DIPEA as a milder base relative to methyl magnesium bromide. Initially, **2.33** was synthesised using the general procedure in Scheme 64, but only a 12% yield of **2.33** obtained. However, switching to the DIPEA method in Scheme 65 had a positive effect, increasing the yield to 47%. This milder method was therefore used to make **2.32** and **2.34**.



Scheme 65. Synthesis of the acryloyl imides using DIPEA, from their lactam precursors.

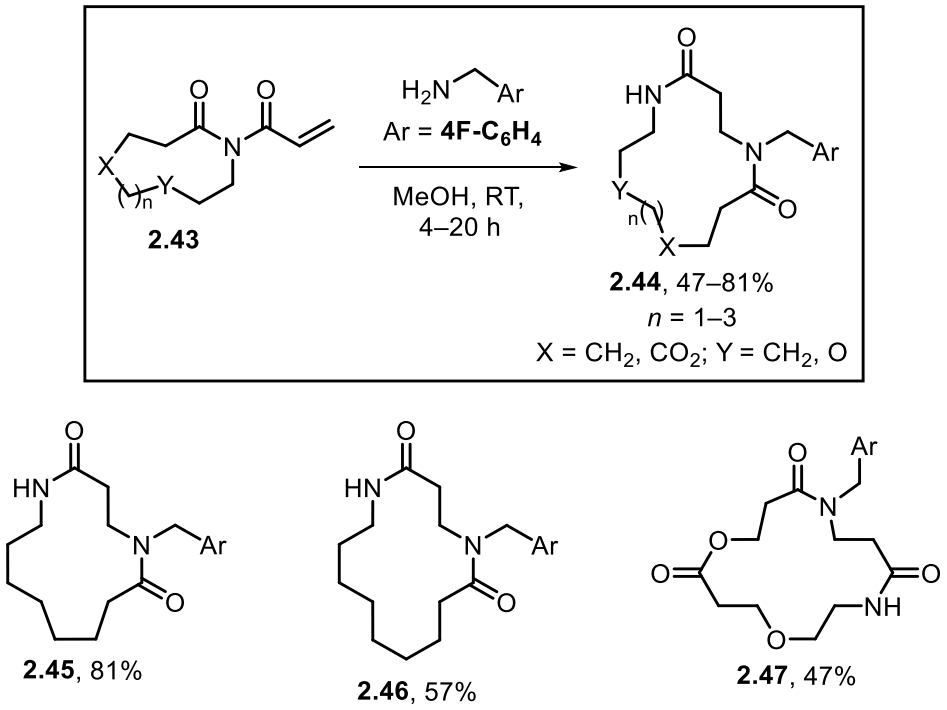
Branched imide precursors were also required, as shown in Scheme 66. Acid chloride **2.36** was made using oxalyl chloride from its carboxylic acid **2.35** (Scheme 66a).[18,142] Scheme 66b summarises the four successful *N*-acylation reactions completed, all using methyl magnesium bromide as base *via* the same general procedure that has been used to make the majority of imides before this. The steric bulk of a phenyl group relative to a methyl may have contributed to the depreciation in yield seen in **2.40** and **2.42**.



Scheme 66. Synthesis of the branched acryloyl imides using MeMgBr, from their lactam precursors.

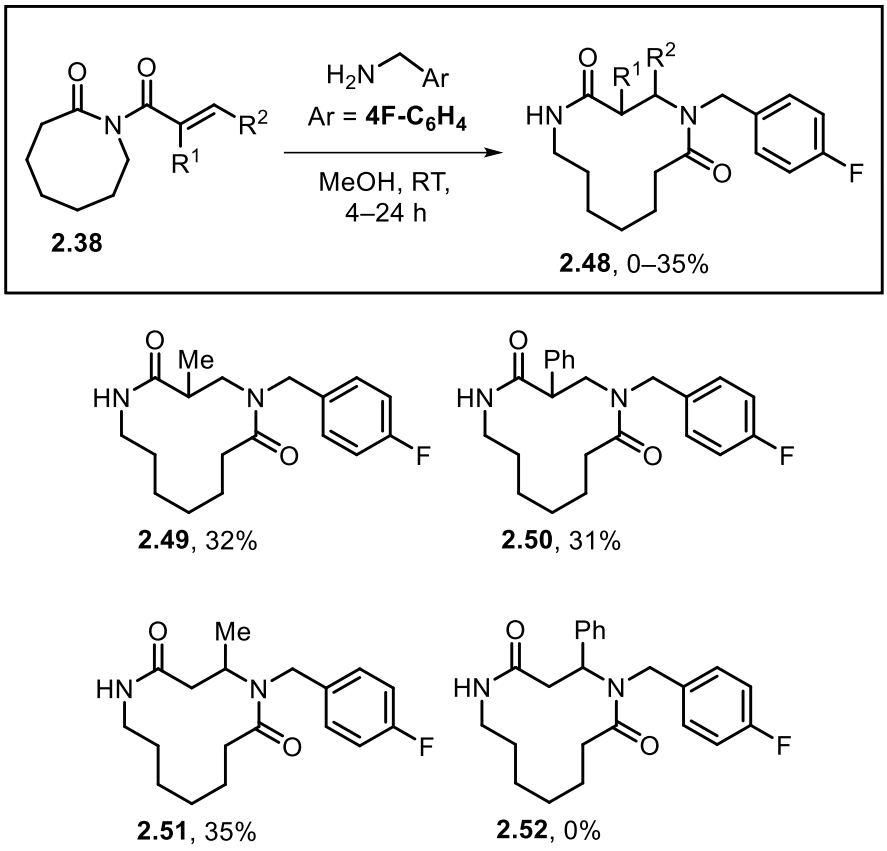
2.3 Nitrogen CARE with the Imide Precursors

Investigations into ring expansion reactions began with the more developed nitrogen CARE method, which had already proven to be successful in published work from the Unsworth group, using 8–12-membered acryloyl imides.[106] Therefore, the focus in this work was on the synthesis of 13–15-membered macrocycles, all novel examples of ring expansion reactions, shown in Scheme 67. These reactions worked well as expected and the yields (which ranged from 47–81%) were broadly in line with the published results.



Scheme 67. Synthesis of the unbranched macrocycles using N-CARE.

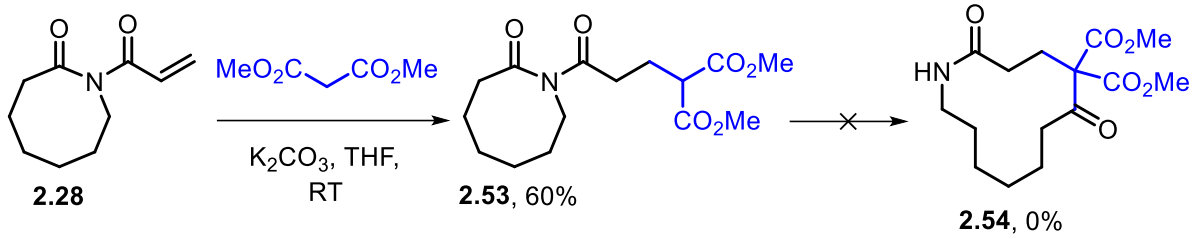
Following this, the four branched imides were tested and pleasingly three of them were successful, albeit in lower yields than the analogous reactions using an unbranched imide (Scheme 68). The unbranched 12-membered analogue of this series worked in a yield of 69%. The lower yields in this series and failure of **2.52** can likely be attributed to the addition of an 'R' group to the alkene meaning the Michael acceptor is deactivated both sterically and electronically; this is corroborated by similar findings in the 2022 CARE paper where similar yield reductions were observed for branched systems.[106]



Scheme 68. Synthesis of the branched macrocycles using N-CARE.

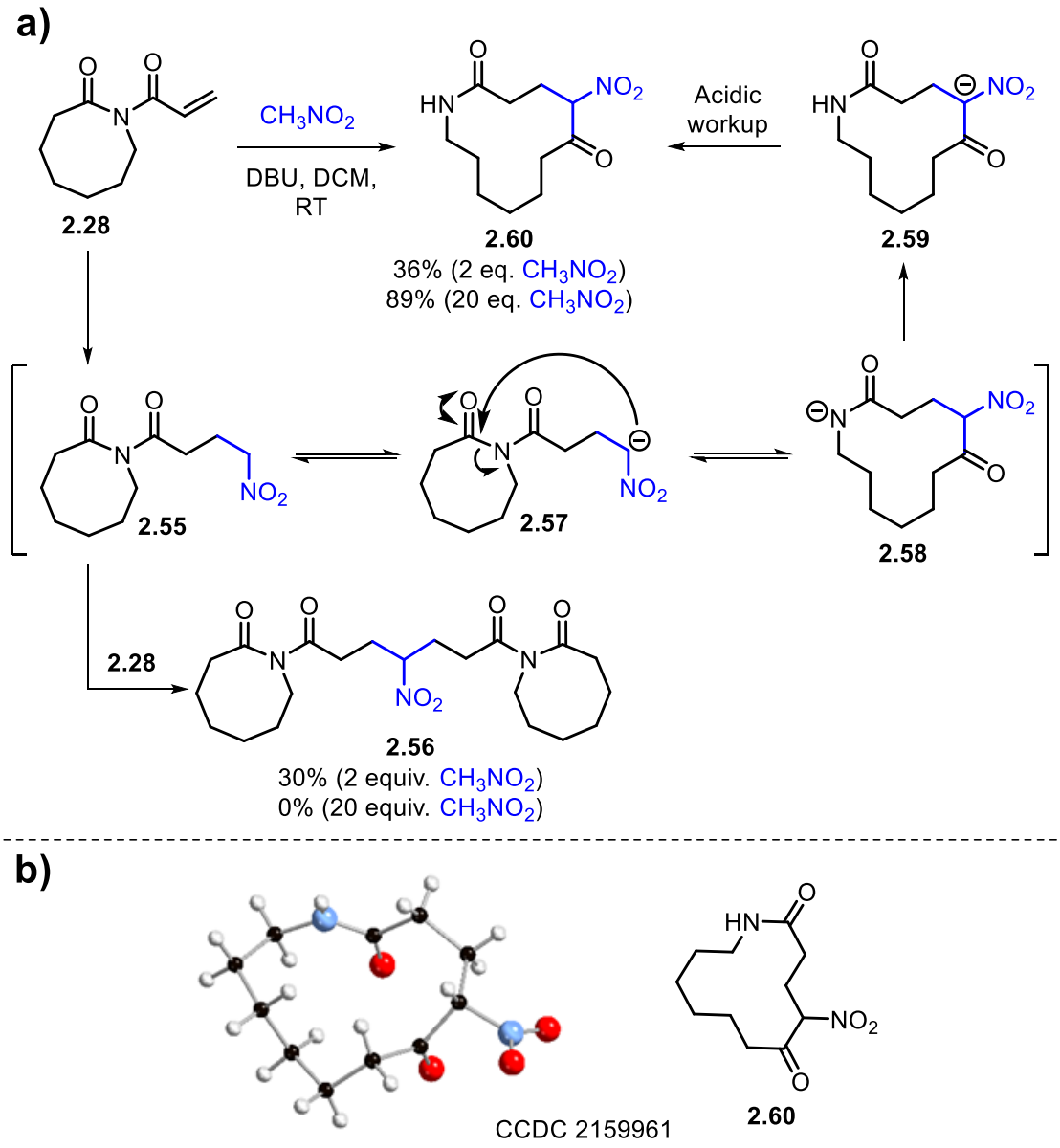
2.4 Carbon CARE with the Imide Precursors

Next, attention turned to developing a new CARE variant in which the primary amine is replaced by a carbon pronucleophile. The hope was that a suitable carbon pronucleophile could be found that is able to undergo both conjugate addition and ring expansion, in the same manner as the established amine CARE method. Investigations in the Unsworth group were therefore started by a member (Kleo Palate) to find a suitable carbon pronucleophile that was able to undergo a conjugate addition into the acryloyl imide **2.28** (Scheme 69).[134,135,143] Dimethyl malonate was the candidate tested with **2.28**. Under basic conditions, the conjugate addition was successful, affording **2**.**53**, but unfortunately it did not undergo the subsequent ring expansion step to form the target macrocycle **2.54** and only unreacted **2.53** was recovered. Deprotonated malonitrile and 1,1,1-trifluoroacetone were also tested as the carbon pronucleophile, with other bases tried too (DBU and NaH), but they did not react with **2.28**.



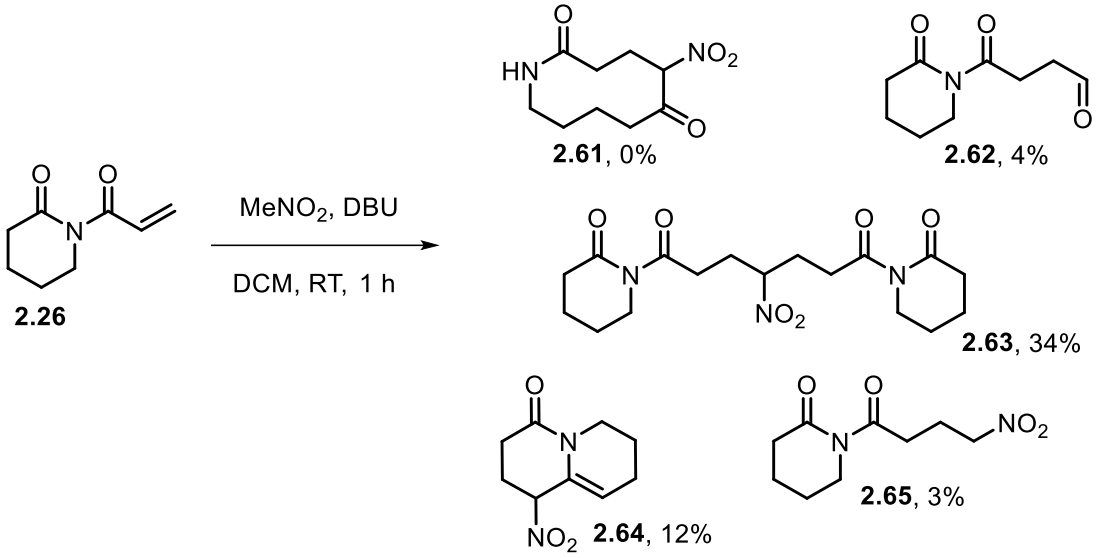
Scheme 69. An unsuccessful CARE reaction using dimethyl malonate as the carbon pronucleophile.

It was reasoned that reducing the bulk around the nucleophilic centre could be beneficial.[144,145] Therefore, attention turned to the use of nitromethane as the pronucleophile, which has a comparable pK_a to dimethyl malonate,[146] but is far less bulky. This approach was successful (Scheme 70a); using 2 equivalents of nitromethane and DBU, the CARE product **2.60** was isolated in 36% yield, with 30% yield of side-product **2.56** also obtained. This side-product forms when a second conjugate addition occurs, in competition with the desired ring expansion. A simple fix for this issue was to increase the amount of nitromethane from 2 to 20 equivalents and this led to a much improved 89% yield of **2.60**, with no requirement for column chromatography – an acidic workup was sufficient for purification. Confirmation of the success of this reaction and product identity was obtained through X-ray crystallographic data (Scheme 70b).[147]



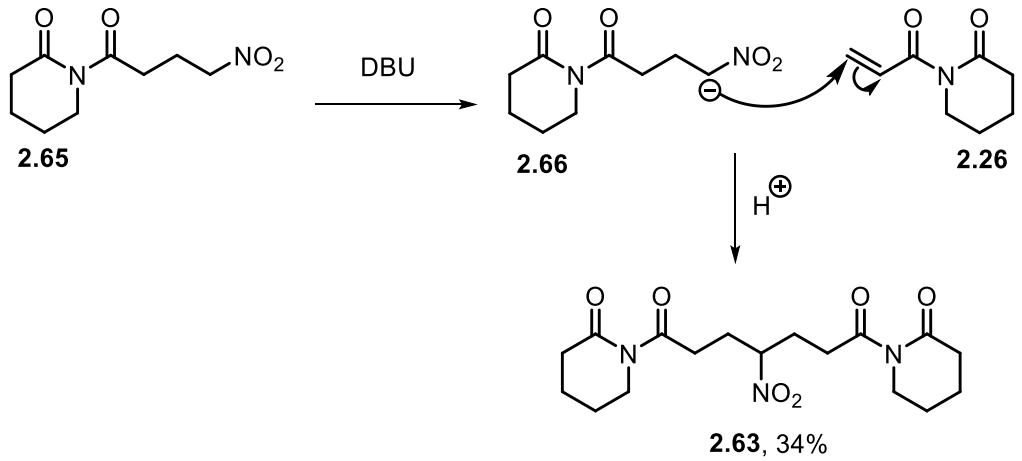
Scheme 70a. The successful CARE reaction using nitromethane as the carbon pronucleophile. **Scheme 70b.** X-ray crystal structure of **2.60**.

With a working procedure established, attention turned to testing the method on other acryloyl imides. The 6-membered imide **2.26** was reacted with nitromethane and DBU, but unfortunately this was unsuccessful with none of the desired ring expansion product (**2.61**) formed. Instead, four side-products **2.62**–**2.65** were made in varying yield (Scheme 71).



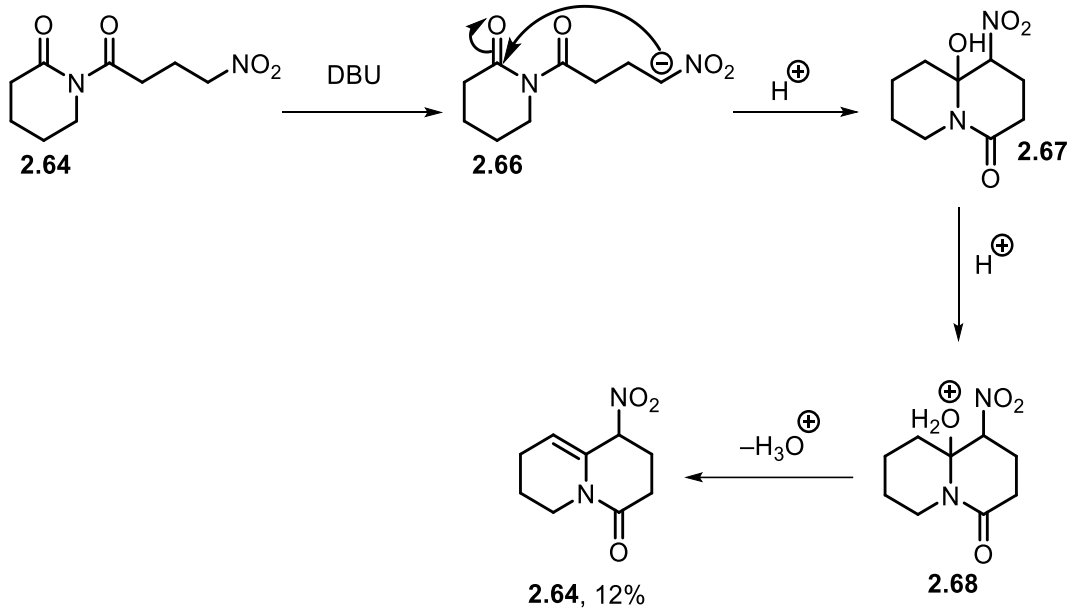
Scheme 71. The unsuccessful CARE reaction of **2.26**, instead forming four side-products.

The isolated side-products indicated that **2.26** did complete the conjugate addition step but was unable to progress further and undergo ring expansion. For example, a small amount of compound **2.65** – a product that is 'stuck' after the conjugate addition step – was isolated. The other three additional side-products were likely to be generated from **2.65** *via* various pathways. First, was a Nef reaction during the acidic workup (with excess HCl) that is thought to have led to the conversion of the nitro group of **2.65** into an aldehyde (**2.62**). The formation of **2.63** is similar to the double conjugate addition product, **2.56**, formed during the initial optimisation. In Scheme 72, it is proposed that **2.65** was deprotonated by DBU after the conjugate addition and rather than reacting *via* the desired ring expansion route (an intramolecular attack), the carbanion reacted with another molecule of starting material (**2.26**) to give **2.63**.



Scheme 72. The mechanism for the formation of **2.63**, a side-product from the CARE reaction.

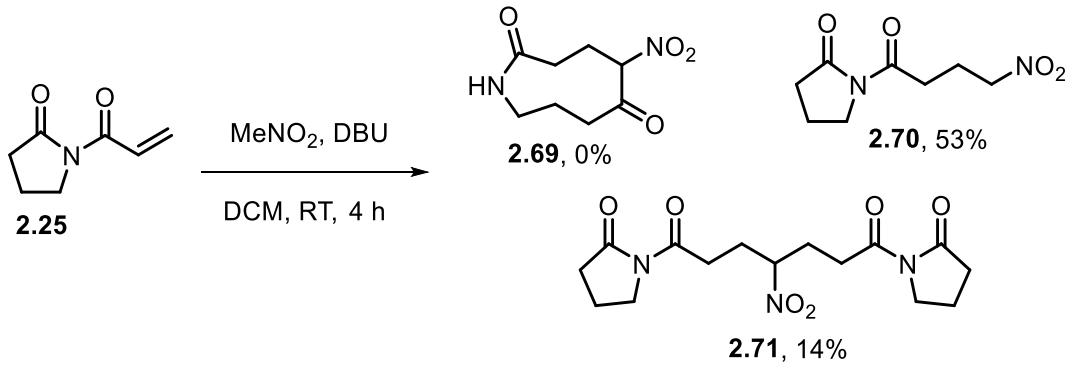
The final side-product is proposed to be generated from the bicyclic intermediate (Scheme 73). Presumably **2.65** was again deprotonated by DBU but this time the desired intramolecular attack of the carbonyl in the ring occurred to give bicycle **2.67**. Unfortunately, from here it seemed to deviate from the expected mechanism, with dehydration leading to the formation of bicyclic side-product, **2.64**.



Scheme 73. The proposed mechanism for the formation of **2.64**, a side-product from the CARE reaction.

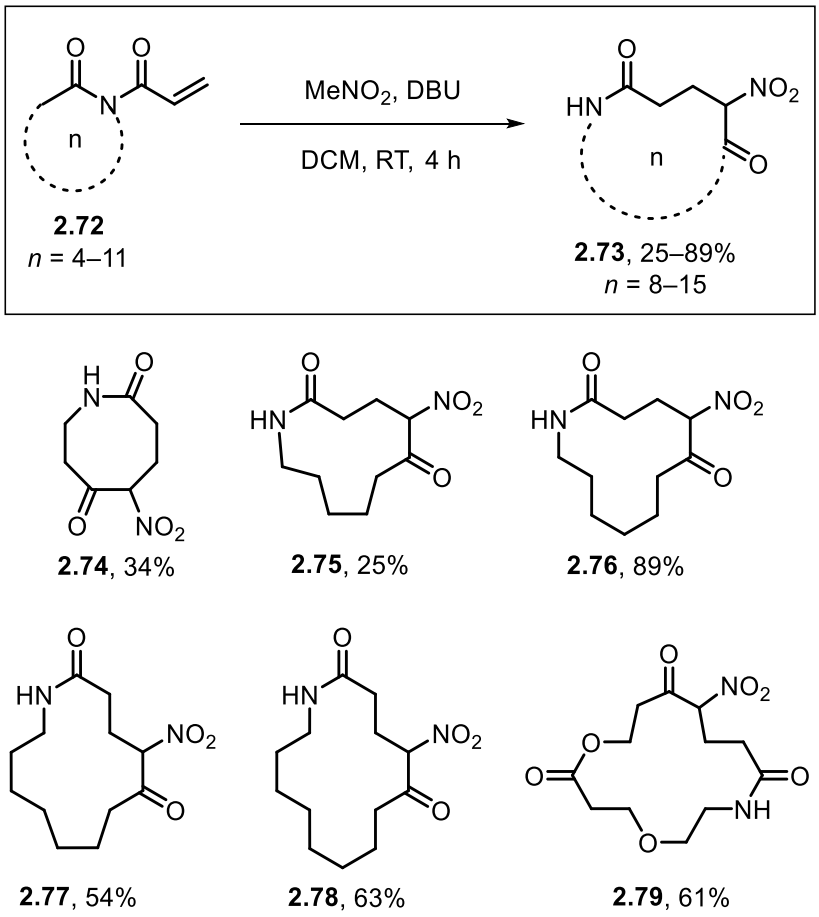
It appeared that some of the side-products were derived from the workup when using excess acid – therefore the workup was changed to just the dropwise addition of acid until pH 2 was reached. This change stopped the formation of **2.62** (the Nef side-product) but the other side-products were still present. A repeat was done with no workup and only **2.65** (the side-product after the conjugate addition is completed) was observed.

Another system that did not work for C-CARE, was the 5-membered lactam, where similar issues arose. The workup was done by adding acid until pH 2 was reached and as shown in Scheme 74, two familiar side-products formed – **2.70** and **2.71**. N-CARE reactions done in the group showed that ring expansion of both the 5- and 6-membered lactams are possible and so we can see a clear change in reactivity when moving to a carbon pronucleophile.



Scheme 74. The unsuccessful CARE reaction of **2.25**, instead forming two side-products.

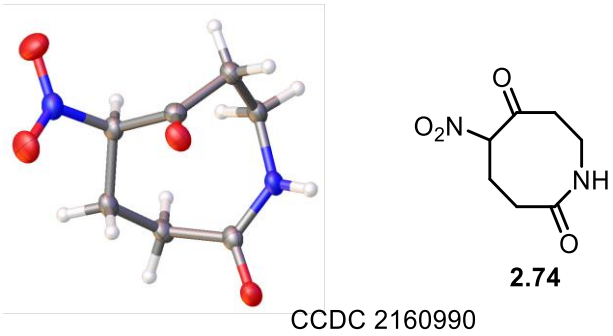
More positively, all the other imide precursors tested up to 11-membered rings (and also including the 4-membered imide) were successful, undergoing the CARE reaction in yields ranging from 25–89% (Scheme 75). Product **2.75** was the lowest yielding, with evidence of the side-product that forms when the reaction halts after the conjugate addition (*n*+2 version of **2.70** in a 39% yield).



Scheme 75. Synthesis of the unbranched medium-sized rings and macrocycles using C-CARE.

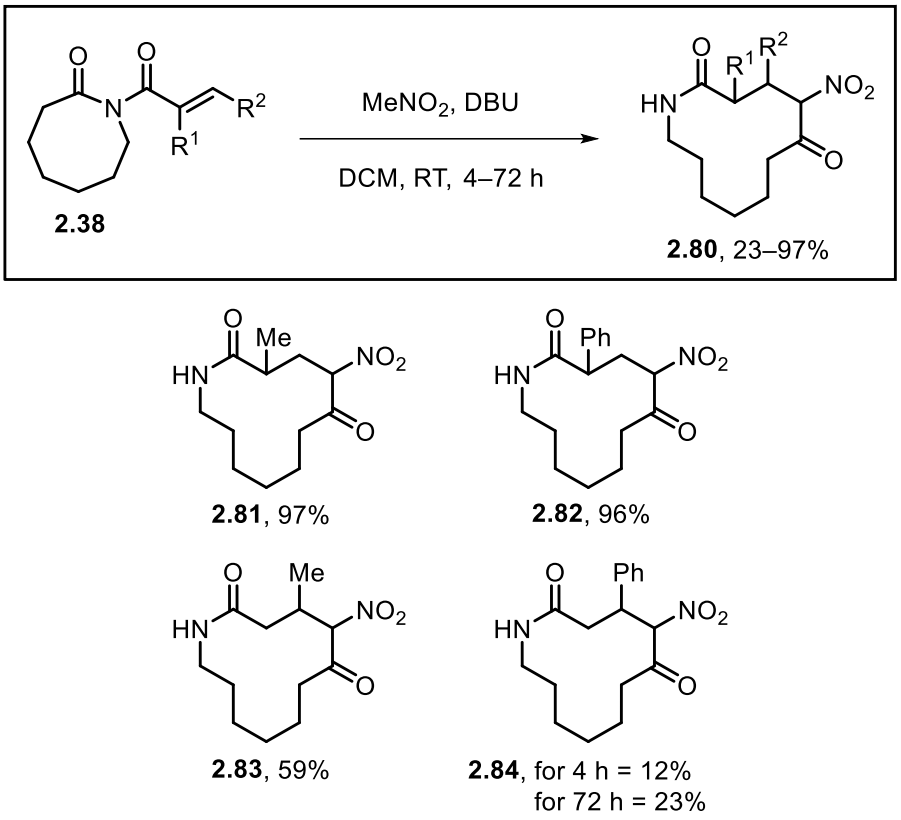
Of particular note in this series was the smallest medium-sized ring formed (**2.74**) from the 4-membered cyclic imide **2.32**. Following the trend of both the 5- and 6-membered rings not

working, it may be expected that the reaction to form **2.74** might also be unsuccessful, but this was not the case. With the bond angles in **2.74** being 90°, they are much lower than would be in an ideal sp^3 hybridised system, which would usually adopt an approximate 109.5° bond angle. Consequently, the 4-membered cyclic imide is not very stable due to the high angle strain it experiences and so there is an additional driving force to rearrange to the 8-membered product we see in Scheme 76. A crystal was also grown from the product, allowing X-ray crystallographic data to be obtained,[147] which further supported the assignment of its structure.



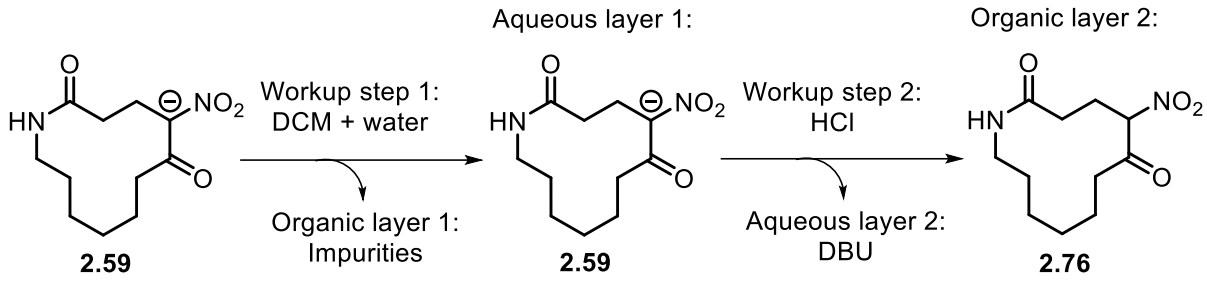
Scheme 76. X-ray crystal structure of **2.74**.

The C-CARE reactions on the imides containing methyl and phenyl branches on the Michael acceptor were all successful (Scheme 77). Product **2.84** was the most troublesome of the four with the standard four hours not being sufficient for the reaction to reach complete consumption of the starting material. It seemed that the phenyl group at the β-position of the Michael acceptor slowed the conjugate addition due to the decreased electrophilicity of the alkene. A second attempt was therefore performed, with the reaction being run for 3 days and this was successful in achieving complete consumption. Despite the yield still being low, there was an increase in yield of **2.84** from 12% to 23%. Within the branched series, the β-phenyl variants were consistently the worst performing; this observation aligns with related ring expansion reactions reported in the literature.[106,148]



Scheme 77. Synthesis of the branched macrocycles using C-CARE.

Of additional note, the workup, or lack thereof, was crucial for the purification of many of the C-CARE products. The optimal workup varied, with it being dependent on the substrate in question and there is no all-encompassing workup procedure that can be used for all reactions that can reliably provide the highest possible yield. In some cases, column chromatography was needed for the purification. This became more common when making larger rings, as the pH-based solubility switches needed for the aqueous workup were generally not applicable to the compounds 13-membered and above. These bigger products were more lipophilic and likely struggled to enter the aqueous layer, even when anionic in the first step of the workup. Therefore, it was easier to simply acidify the mixture, take the organic layer and move on to column chromatography. For information on the specific workup used in all cases, see the Experimental.

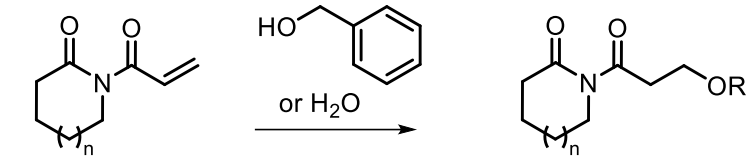


Scheme 78. A visual representation of the original 2-step workup completed following the synthesis of **2.76**.[148]

2.5 Dihydroxylation Ring Expansion with the Imide Precursors

The use of oxygen as a nucleophile in the CARE reactions was something other members of the group had started to investigate prior to the commencement of this project. Initially, members of the Unsworth group tested the possibility of doing an oxa-Michael conjugate addition. These reactions are known to have quite low reactivity and the reaction type as a whole is much less well explored relative to amine conjugate addition.[149] Despite this, there has been some development in its use for synthesis with there being precedent in the literature for oxa-Michael conjugate additions facilitating ring expansion/formation reactions.[150,151,152]

Therefore, a previous Unsworth group member (Kleo Palate) attempted this technique, first using benzyl alcohol as the nucleophile on a standard 6- or 9-membered lactam and the results are shown in Table 1. The first three entries using benzyl alcohol were all unsuccessful – one of which showed no reactivity at all. In entries 1 and 3, de-acylation was observed in the instances where a conjugate addition occurred, giving **2.86** as the major side-product in the reaction. Entries 4–7 utilised water instead and employed a different Lewis acid for each attempt but there was no upturn in results. Rather than doing the conjugate addition, in the presence of water, the lactam simply ring-opened, forming **2.87** as the major side-product from each of these reactions. With these results, it was clear if a ring expansion reaction was to be performed with oxygen as the nucleophile, some changes would need to be made that did not rely on a conjugate addition step to attach the nucleophile to the acryloyl imide.



2.26 or **2.29**
n = 1 or 3

2.85
R = Bn or H

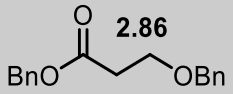
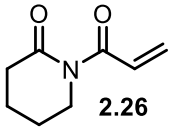
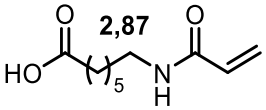
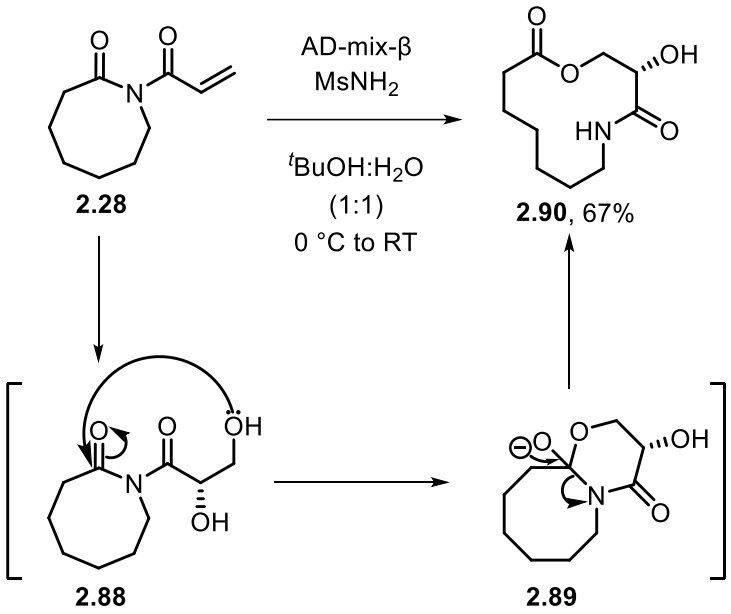
Entry	*n* =	Conditions	Lewis acid	Major product
1	1	Cs_2CO_3 (2 eq), BnOH (4 eq), THF, RT, 26 h	None	 **2.86**
2	1	$Na_2CO_{3\,(aq.)}$ (0.05 M), BnOH (4 eq), RT, 46 h	None	 **2.26**
3	3	Cs_2CO_3 (1 eq), BnOH (1.1 eq), DCM, 50 °C, 12 h	$CuCl_2$ (10 mol%)	**2.86**
4	3	Lewis acid (20 mol%), 2:1 H_2O : MeCN, 80 °C, 12 h	$CrCl_3$-6H_2O	 **2,87**
5	3	Lewis acid (20 mol%), 2:1 H_2O : MeCN, 80 °C, 12 h	$CuCl_2$	**2.87**
6	3	Lewis acid (20 mol%), 2:1 H_2O : MeCN, 80 °C, 12 h	$FeCl_3$-6H_2O	**2.87**
7	3	Lewis acid (20 mol%), 2:1 H_2O : MeCN, 80 °C, 12 h	$In(OTf)_3$	**2.87**

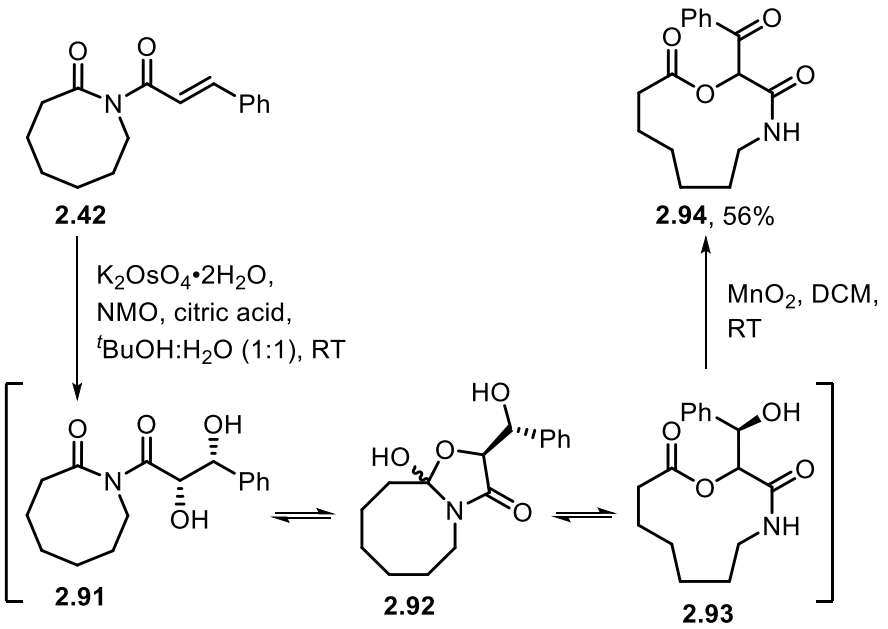
Table 1 – Attempts to complete an oxa-Michael conjugate addition with acryloyl imides.

The same previous member of the Unsworth group (Kleo Palate) therefore explored the possibility of implementing a dihydroxylation of the acryloyl imide to create a 1,2-diol intermediate that could then undergo a ring expansion *via* one of the newly implemented alcohols. The commercial availability of Sharpless AD-mix reagents meant we could also synthesise enantioenriched products and pleasingly this approach was successful.[153] Scheme 79 shows the reaction conditions used as well as the proposed reaction mechanism.[134] Under these conditions **2.90** was formed in a 67% yield. Notably, an alternative product could also have formed, where the secondary alcohol acted as the nucleophile to promote a 3-atom ring expansion. However, none of this product was observed in the reaction. This was later explained by DFT calculations, carried out by Ryan Epton and Jason Lynam, in which the 4-atom ring expansion was calculated to be more energetically favourable than the 3-atom ring expansion when done under thermodynamic control.[148]



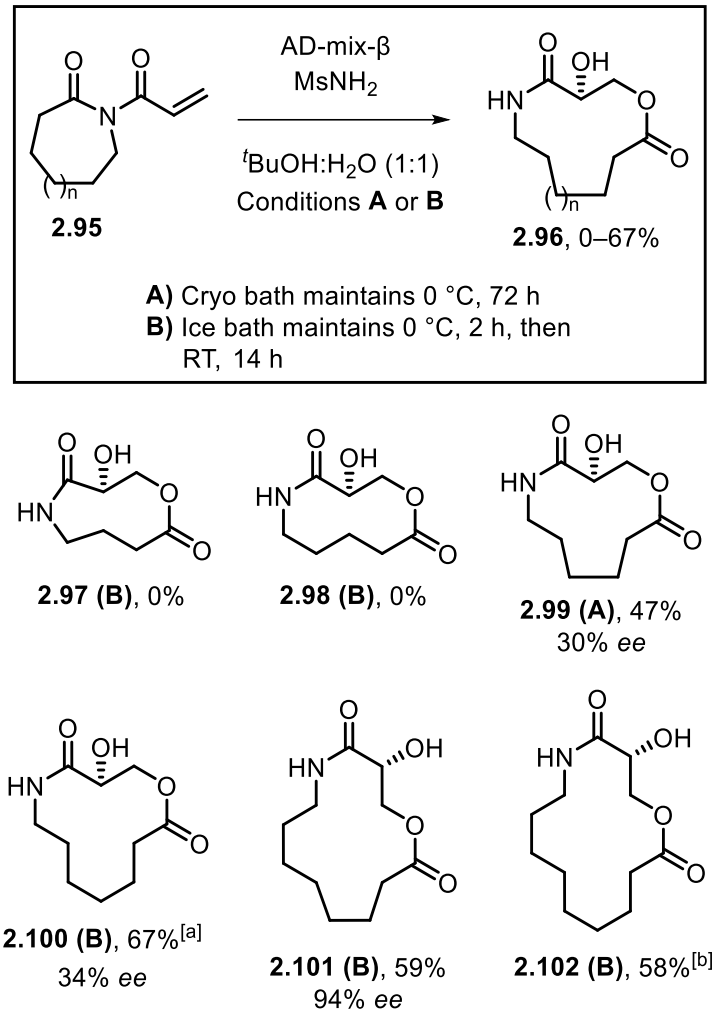
Scheme 79. The successful preliminary test for a dihydroxylation ring expansion reaction.

Interestingly, the DFT calculations also suggested the bicyclic intermediate formed *via* the pathway for the 3-atom ring expansion was lower in energy than the equivalent intermediate in the 4-atom ring expansion pathway. This indicated that 3-atom ring expansion may also be accessible if conditions could be found that favoured kinetic control over thermodynamic. This led to an alternative reaction using Upjohn-type conditions (Scheme 80).[154] A mixture of interconverting products were formed but by then implementing an oxidation with manganese dioxide,[155] the ketone product (**2.94**) was formed, which derived from the desired 3-atom ring expansion in a yield of 56%. The use of citric acid in this reaction was thought to be key in unlocking the kinetic product,[156] as opposed to the use of potassium carbonate which is thought to accelerate the rearrangement step in the thermodynamically controlled 4-atom ring expansion.[157] Despite the discovery of this 3-atom ring expansion technique, this PhD project only focused on expanding the scope of the previously mentioned dihydroxylation method that facilitated a 4-atom ring expansion.



Scheme 80. Evidence for the successful 3-atom ring expansion using Upjohn-type conditions.

This project continued by testing this novel 4-atom ring expansion procedure on the various acryloyl imides synthesised earlier. AD-mix-β and methanesulfonamide were reacted with the starting material (**2.95**) in a 1:1 solvent of *tert*-butyl alcohol and water at 0 °C for two hours, before allowing the mixture to warm to room temperature. As was seen with the C-CARE method, both the 5- and 6-membered lactams did not undergo ring expansion using this technique (**2.97** and **2.98**). But pleasingly, the other four substrates (the 7–10-membered acryloyl imides) all worked in yields of 47–62% (Scheme 81). Lactone **2.99** was made using the same reagents but was done in a cryo bath instead that was able to maintain a constant temperature of 0 °C for longer than a simple ice bath.[158] However, there was no significant increase in yield compared to using a more rudimentary ice bath and so for the remaining examples this was not pursued any further. An enantioselectivity value of 94% for **2.101** was high, as would be expected, in general, for these rings where the alkene is adjacent to an electron withdrawing group as has been observed in the literature.[159,160,161] Rather unexpected were the low *ee* values for **2.99** and **2.100** of 30% and 34% respectively that did not follow the trend, and it is unknown what caused the large decreases in enantioselectivity for these substrates.

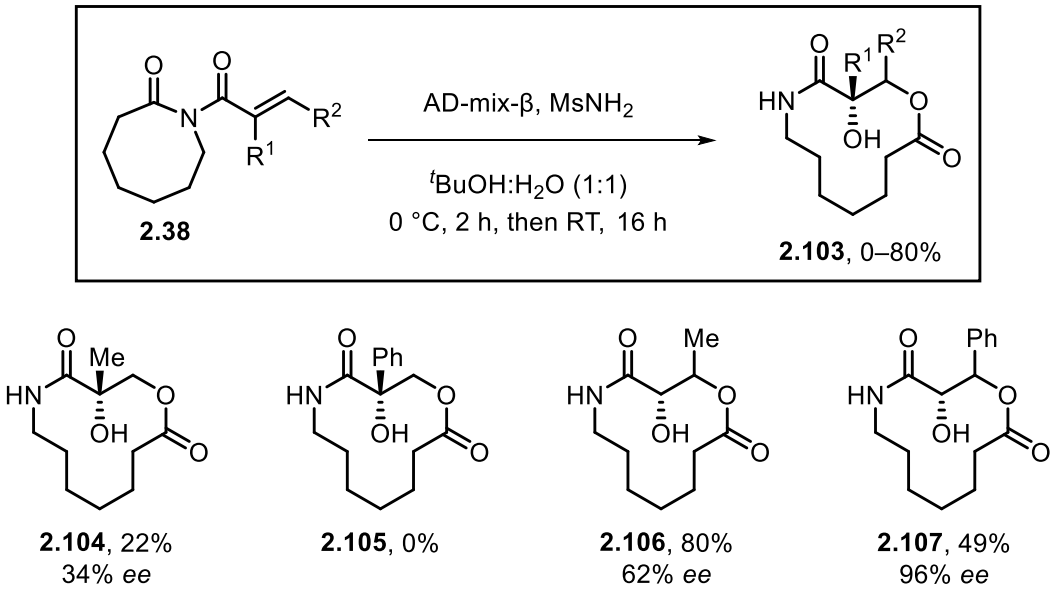


Scheme 81. Synthesis of the unbranched medium-sized rings and macrocycles using dihydroxylation.[a] Synthesised by another member of the Unsworth group. [b] *ee* not measured.

Also encouraging was our ability to synthesise **2.100** on a gram-scale in 57% yield, compared to the 67% yield obtained for the analogous smaller scale reaction. This indicates a good potential for scalability in the process. Another welcome feature of this reaction compared to the previous CARE experiments was the absence of any significant side-products forming in the reaction mixture. In most instances, a relatively simple purification using column chromatography was sufficient to afford pure products.

The branched imides were then tested using the dihydroxylation technique and all but one was successful in forming the 12-membered ring (Scheme 82). As shown, the yields for these were mixed but for **2.107** especially, the enantioselectivity was very high (96%) – it is known that phenyl rings can lead to particularly high *ee*.[162,163] The effect of adding a methyl group is more variable due to being a smaller and less bulky substituent and this is seen with **2.104** and **2.106** where their *ee* values are lower (34% and 62% respectively)[164] – but in the case of **2.104**, maybe still less than would be expected when the *ee* for unbranched **2.100** is

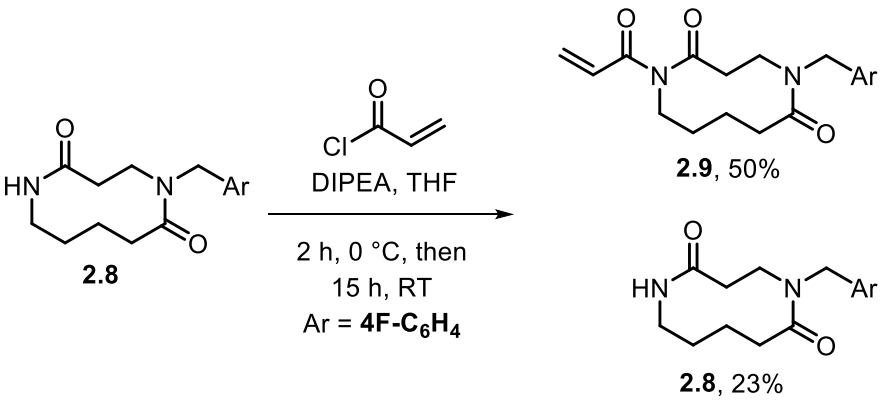
considered. The higher yield of **2.106** compared to **2.107** may point to steric effects, with the bulkier phenyl group potentially inhibiting the oxygen's attack at the carbonyl centre, slowing the ring expansion and leading to the reduced yield. Product **2.105** was not formed in the reaction despite the starting material being consumed – instead it formed a complex mixture of unwanted products that were not able to be identified. The failure to form **2.105** and the low yield of **2.104** indicates low reactivity when the substituent is attached at the α-position to the imide, likely for steric reasons.



Scheme 82. Synthesis of the branched macrocycles using dihydroxylation.

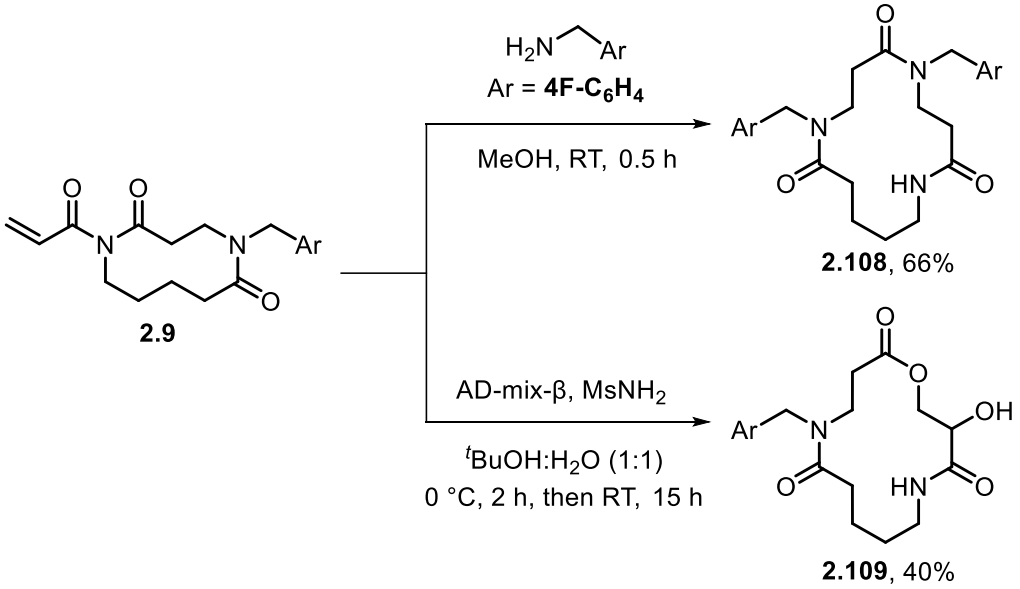
2.6 Consecutive CARE Reaction Attempts and Synthesis of their Imide Precursors

Another goal of this project was to perform ring expansion reactions iteratively using the new CARE methods developed. Ideally, we wanted to perform consecutive ring expansion reactions using the three different nucleophilic atoms that have been mentioned in this report: carbon, nitrogen and oxygen. Previously, it had been established that amine-based ring expansions work well consecutively, and indeed, three consecutive ring expansions had already been reported with success using the N-CARE method.[106] Therefore, this was the starting point for these investigations, where **2.8** (a substrate which was itself prepared *via* an N-CARE reaction) was acylated using the milder *N*-acylation conditions that make use of DIPEA as the base (Scheme 83).



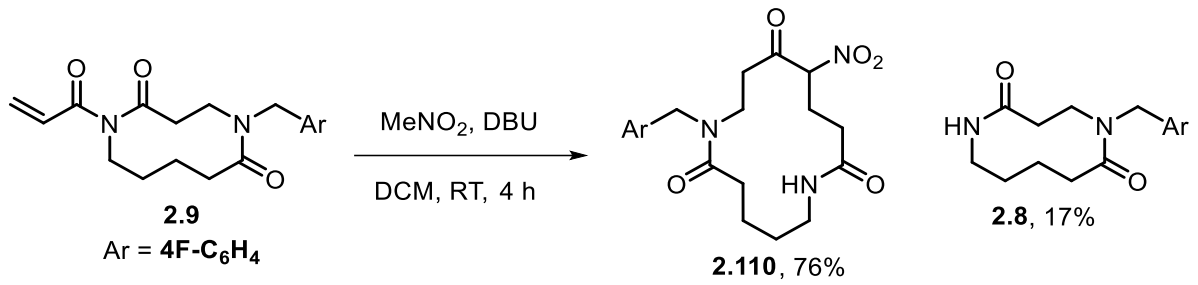
Scheme 83. *N*-Acylation of the medium-sized ring to form the acryloyl imide.

From here, the three ring expansion reactions could be attempted using the conditions discussed earlier in the chapter (Scheme 84). Pleasingly, all three attempts were successful in forming the respective ring-expanded products. Products **2.108** and **2.109** were obtained *via* the N-CARE and dihydroxylation methods respectively, and their purifications afforded products in yields of 66% and 40% respectively. The presence of three amide bonds in **2.108** means that it can exist in several rotameric forms, which led to its NMR data being relatively complex. Variable Temperature (VT) NMR was attempted on one occasion to simplify the spectrum but unfortunately this made no difference with the same peaks being present despite the increased temperature. On the other hand, the NMR data for lactone **2.109** was simpler and easier to assign.



Scheme 84. Two consecutive ring expansion reactions of the 10-membered acryloyl imide using nitrogen and oxygen as the nucleophilic component in the reaction.

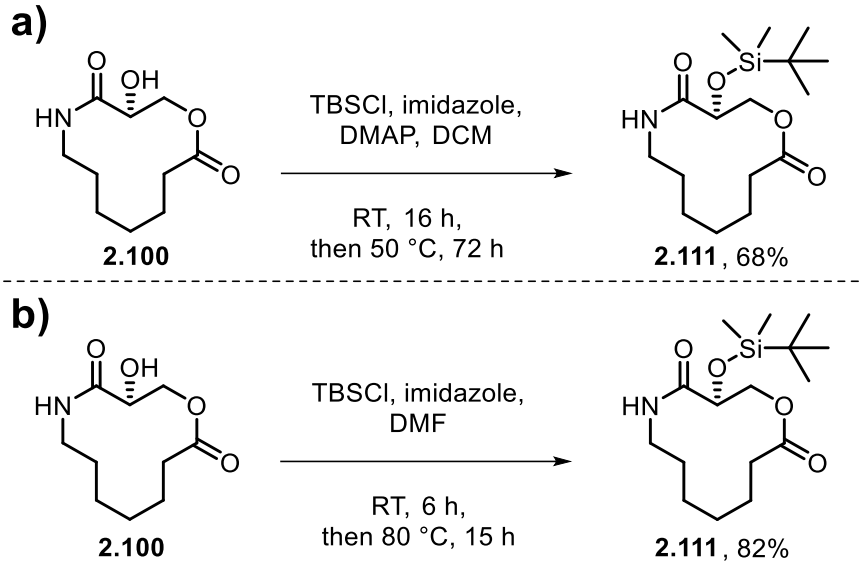
The C-CARE attempt was also successful (76%), but gave rise to some de-acylated starting material, **2.8**, as a side-product, in 17% yield (Scheme 85).



Scheme 85. Consecutive CARE reaction of the 10-membered acryloyl imide using carbon as the nucleophilic component in the reaction.

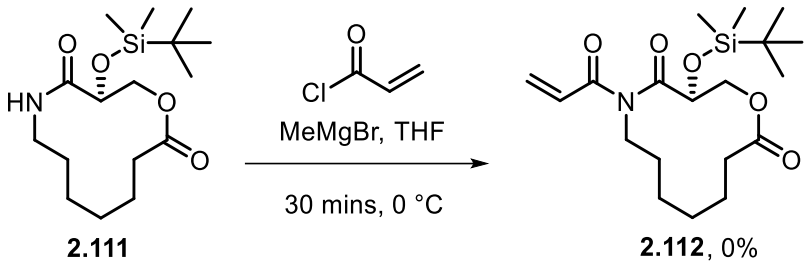
Attention then turned to consecutive CARE reactions where the first ring expansion was completed *via* a dihydroxylation ring expansion with oxygen as the nucleophile. In this case, we reasoned that an extra protection step would be needed (shown in Scheme 86) whereby the alcohol of **2.100** undergoes protection to form TBS derivative **2.111**. Without this, it was considered likely that the free alcohol would react competitively in the *N*-acylation step.[165]

As a result, two similar reactions were devised to protect the alcohol with a silyl group (details of both shown in Scheme 86). The first, devised by Zheng and co-workers,[166] used TBSCl, imidazole and DMAP. The starting material did not dissolve well in DCM and after stirring the reaction overnight there was little change. Therefore, the reaction was heated to reflux and this aided in the dissolution of the visible white precipitate and accelerated the reaction to completion (although it required three days in total), giving a yield of 68%. The second procedure (by Terinek and co-workers)[167] was similar but the main change was their use of DMF as the solvent. This meant higher temperatures could be accessed and subsequently the reaction only needed overnight stirring at 80 °C for **2.100** to be consumed. Visually, the starting material was completely soluble in DMF and this translated to a superior yield with **2.111** forming in an 82% yield.



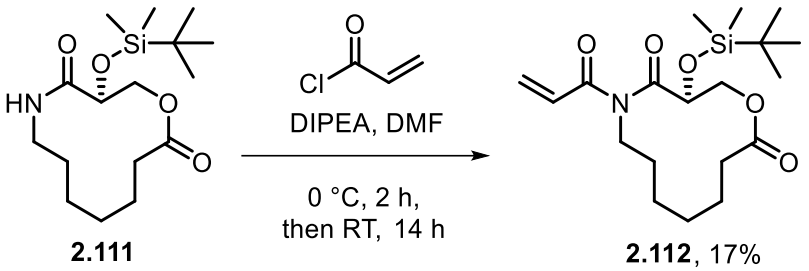
Scheme 86a. Silyl protection method with DCM, devised by Zheng and co-workers.[166] **Scheme 86b.** Silyl protection method with DMF, devised by Terinek and co-workers.[167]

An *N*-acylation reaction (Scheme 87) was now attempted on the protected compound, **2.111**. This step presented great difficulty, with methyl magnesium bromide seeming to cause high levels of degradation of the starting material and any subsequently formed compounds. As a result, no product was able to be gained from this procedure.



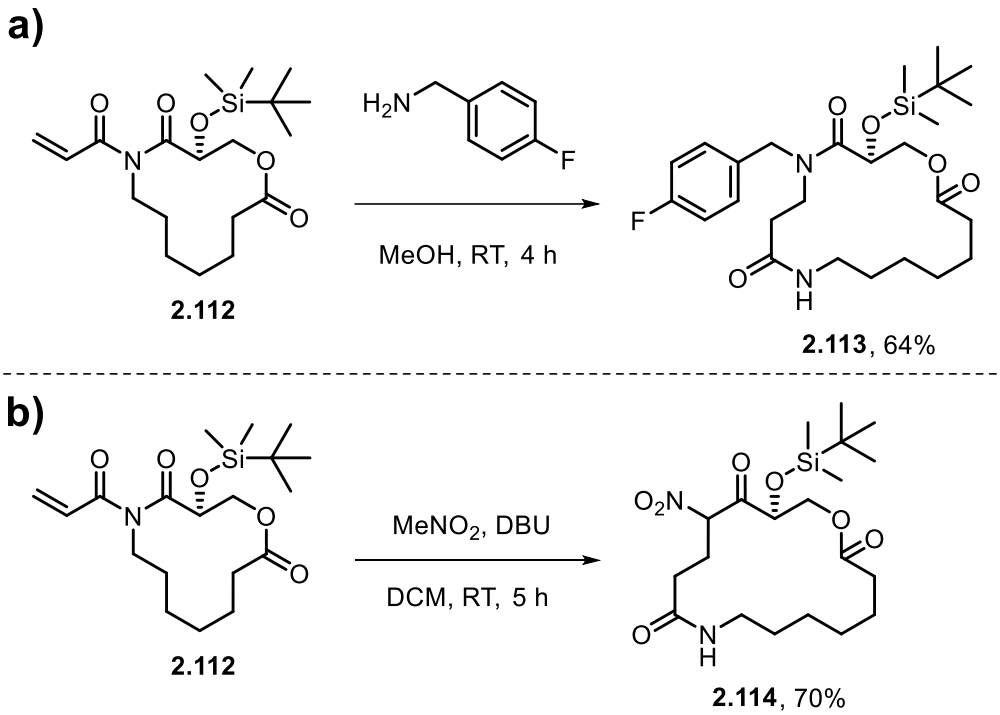
Scheme 87. Unsuccessful *N*-acylation using methyl magnesium bromide.

Milder *N*-acylation conditions were therefore attempted (DIPEA acting as the base instead) but poor solubility of the starting material in THF was observed. Hence, the solvent was changed to DMF and this had a positive overall effect, with **2.111** being completely dissolved in the solution (Scheme 88). This showed some success with **2.112** being formed in 17% yield when the reaction was left for a total of five hours before doing the workup. Unreacted starting material (**2.111**) was also recovered from the reaction.



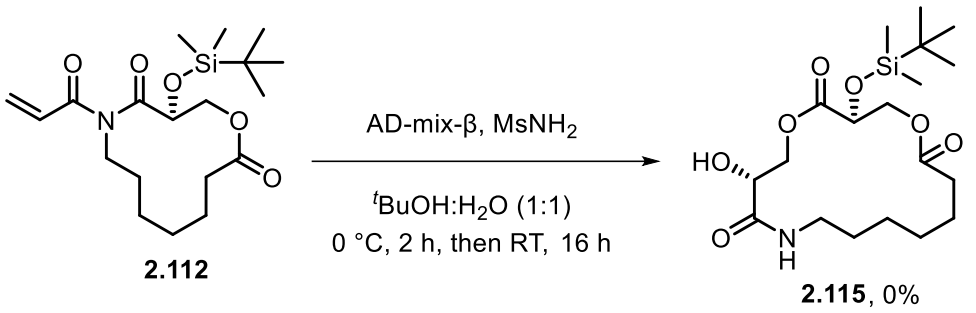
Scheme 88. Successful *N*-acylation using DIPEA.

With imide **2.112** in hand, an N-CARE reaction was attempted with 4-fluorobenzylamine as the amine and this reaction worked well, affording the ring-expanded product **2.113** in a yield of 64% (Scheme 89a). Following this, The C-CARE was then tried, producing the 16-membered ring, **2.114** in a 70% yield (Scheme 89b). After purification, a small amount of the de-acylated compound (**2.111**) was separated from the desired product and identified *via* NMR spectroscopy, albeit not cleanly.



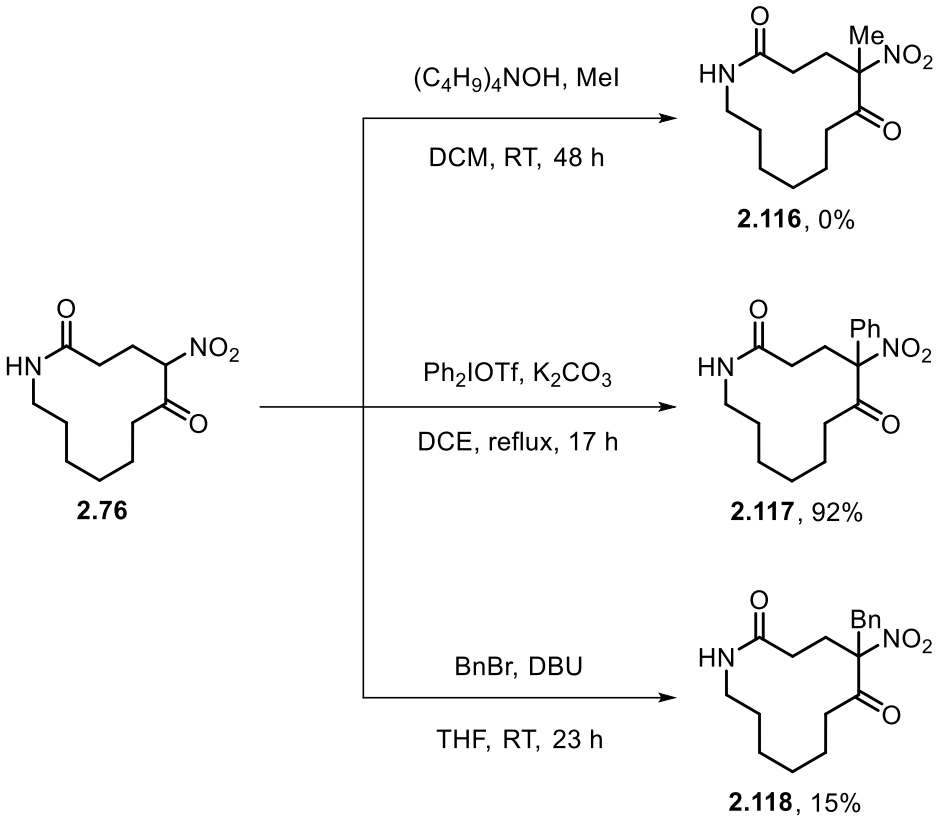
Scheme 89a. Consecutive CARE reaction using nitrogen as the nucleophile. **Scheme 89b.** Consecutive CARE reaction using carbon as the nucleophile.

When the ring expansion of **2.112** was attempted *via* the dihydroxylation ring expansion method (Scheme 90), there was indication of success *via* mass spectrometry data, with a molecular ion consistent with **2.115** present in the crude mixture. However, following purification by column chromatography, the desired product was not isolated. Since only a small amount of **2.112** was synthesised, this reaction was not repeated. In the future, it would be beneficial try to remake **2.112** and optimise its conversion into **2.115**.



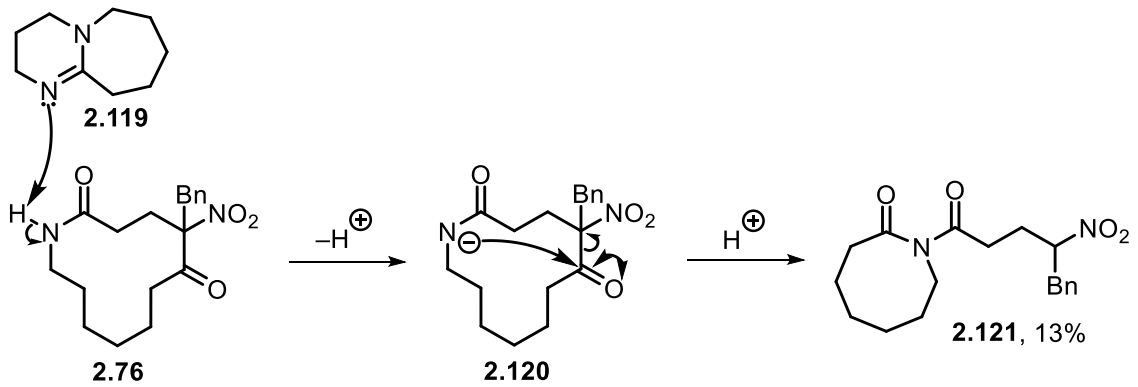
Scheme 90. Unsuccessful consecutive ring expansion reaction using oxygen as the nucleophile.

The final pathway tested in the consecutive ring expansion series, was a sequence starting with a C-CARE reaction. This proved to be the most difficult, due to the challenge of protecting the nitroketone motif that was present in the compound; we reasoned that before undergoing *N*-acylation, the acidic proton at the α-position to the nitro group of **2.76** needed to be blocked with another group. To do this, three alternatives (displayed in Scheme 91) were postulated. The first was a methyl protection using methyl iodide and tetrabutylammonium hydroxide,[168] but this was unsuccessful, giving none of the expected product **2.116** and instead a complex mixture of unknown products was formed. A reaction to insert a phenyl group directly at the α-position was much more encouraging, with a yield of 92% of **2.117** achieved using Ph_2IOTf and potassium carbonate.[169] The final protection attempt was also successful, with **2.118** forming in a 15% yield following benzylation with benzyl bromide and DBU.[170]



Scheme 91. Three attempted protections at the α-position to the nitro group.

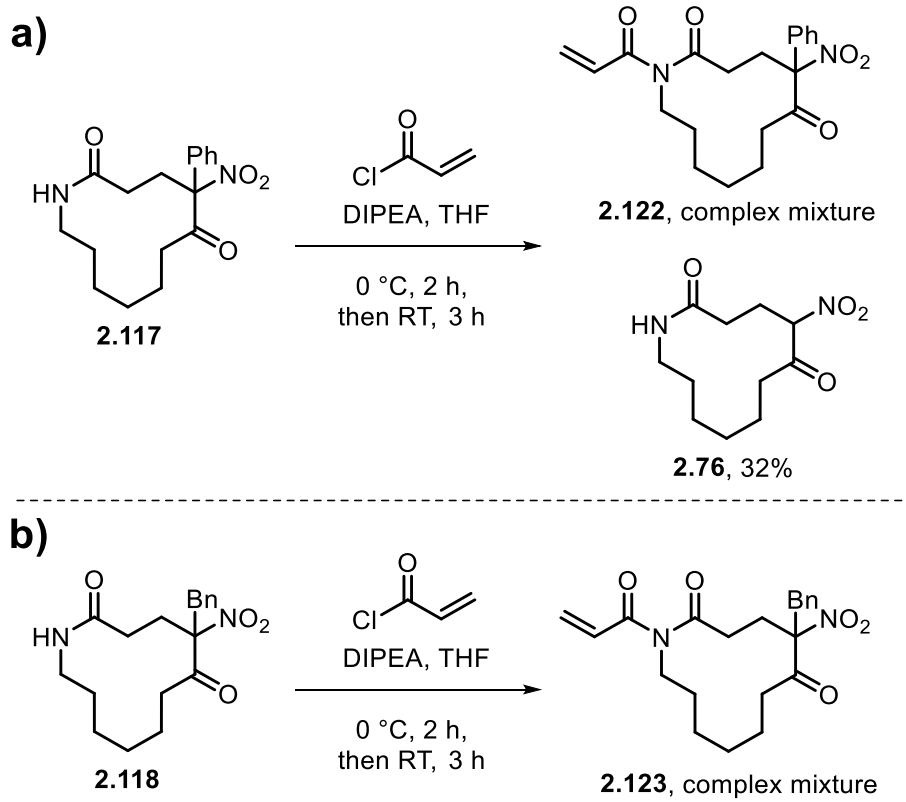
During the synthesis of **2.118**, a number of unknown side-products also formed in the reaction. One that could be identified was a ring-contraction product shown below in Scheme 92. It appeared the lactam was deprotonated by the DBU, before then undergoing an attack on the ketone before the carbon α to the nitro group acted as a leaving group to give the side-product, **2.121** in 13% yield. This was identified *via* the analysis of 2D NMR data and mass spectrometry.



Scheme 92. The ring-contraction side-product that forms during the benzyl protection strategy.

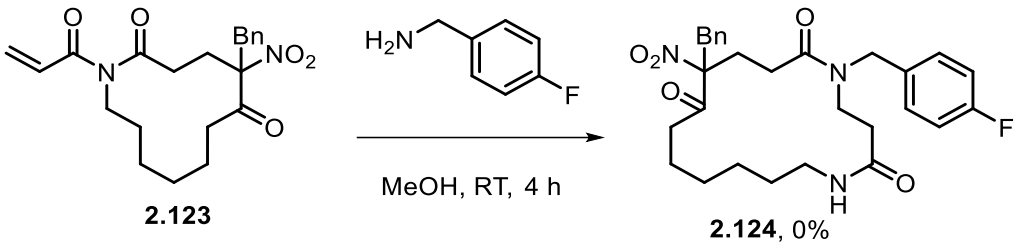
Products **2.117** and **2.118**, were subsequently tested in the *N*-acylation step, starting with the phenyl substrate (**2.117**). Following reaction with acryloyl chloride using the milder base

strategy (DIPEA), the expected product **2.122** was thought to have formed, albeit as part of a complex mixture of compounds that were unable to be separated *via* purification (Scheme 93a). The major product from the reaction appeared to be the deprotected starting material (**2.76**) where the phenyl group had been cleaved, with **2.76** isolated in a yield of 32% (it is unclear how this side-product formed). The *N*-acylation of the benzyl protected compound, **2.118**, similarly formed a complex mixture of products that were unable to be separated. Both **2.122** and **2.123** possessed a few key ^{1}H NMR peaks that are seen consistently in these systems in the region of 5.70–7.00 ppm that denoted the alkene protons and the mass spectrometry data also backed up the assumption that the *N*-acylation reaction had occurred with some success. Therefore, while no data for these two compounds were inputted into the experimental section, the impure sample of **2.123** was still taken forward for an attempted CARE reaction.



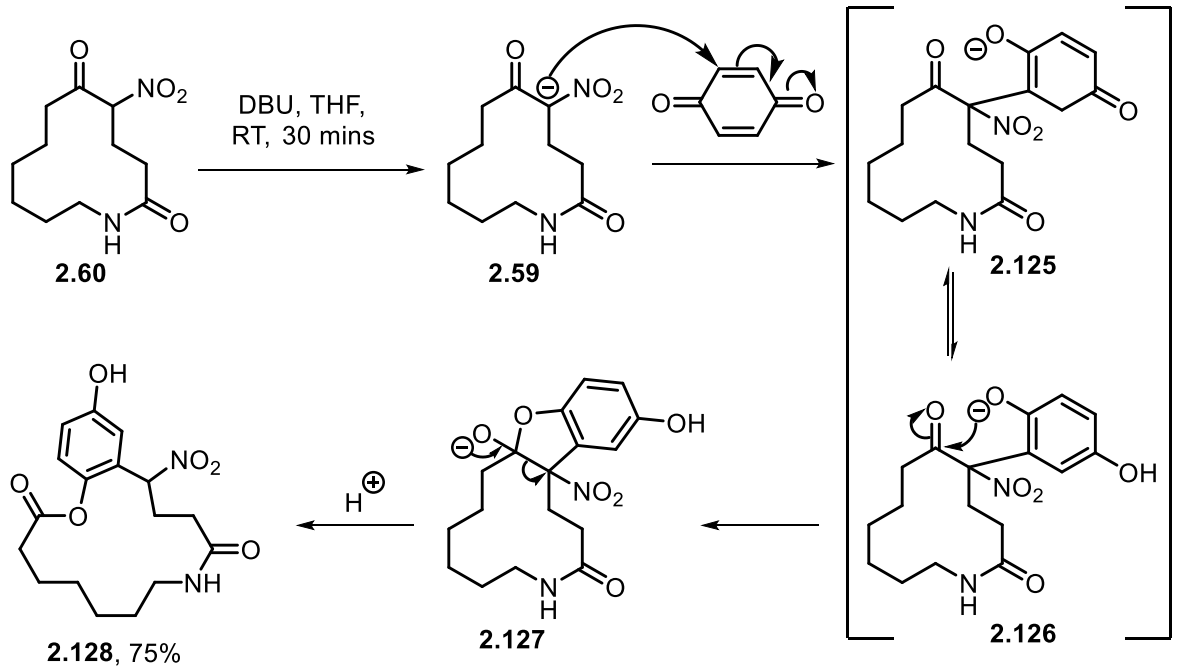
Scheme 93a. *N*-acylation of **2.117** to form the acryloyl imide. **Scheme 93b.** *N*-acylation of **2.118** to form the acryloyl imide.

The complex mixture that was presumed to include **2.123** was used in an N-CARE reaction (Scheme 94). However, unfortunately this reaction was not successful and there were no discernible side-products from the reaction, including any recovered **2.123**.



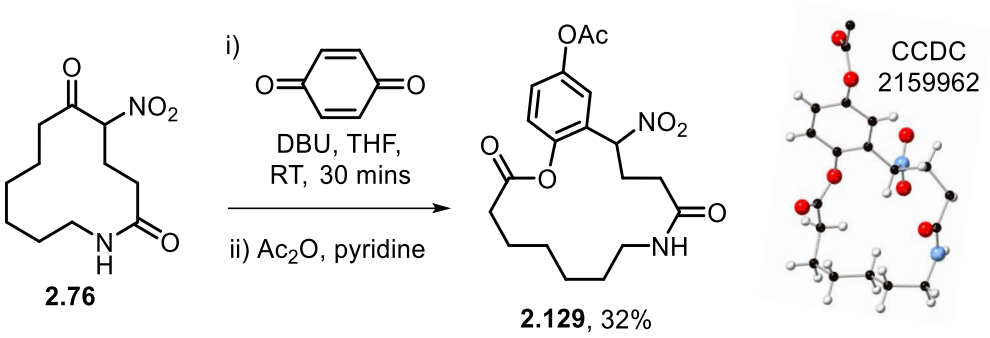
Scheme 94. Unsuccessful CARE attempt using nitrogen as the nucleophile.

Next, an alternative consecutive ring expansion method able make use of the nitroketone motif directly was devised, using product **2.76**. This approach was adapted from a literature method reported by Hesse and co-workers.[171] The reaction is summarised in Scheme 95, whereby the cyclic nitroketone and 1,4-benzoquinone react to facilitate a 3-atom ring expansion. In the first step, DBU is able to deprotonate the α-position to the nitro group before undergoing a conjugate addition attack on 1,4-benzoquinone, giving the phenolate intermediate **2.126**. The negatively charged oxygen can then attack the ketone in the macrocyclic ring, before fragmenting to give the 15-membered ring lactone product, **2.128** in 75% yield.



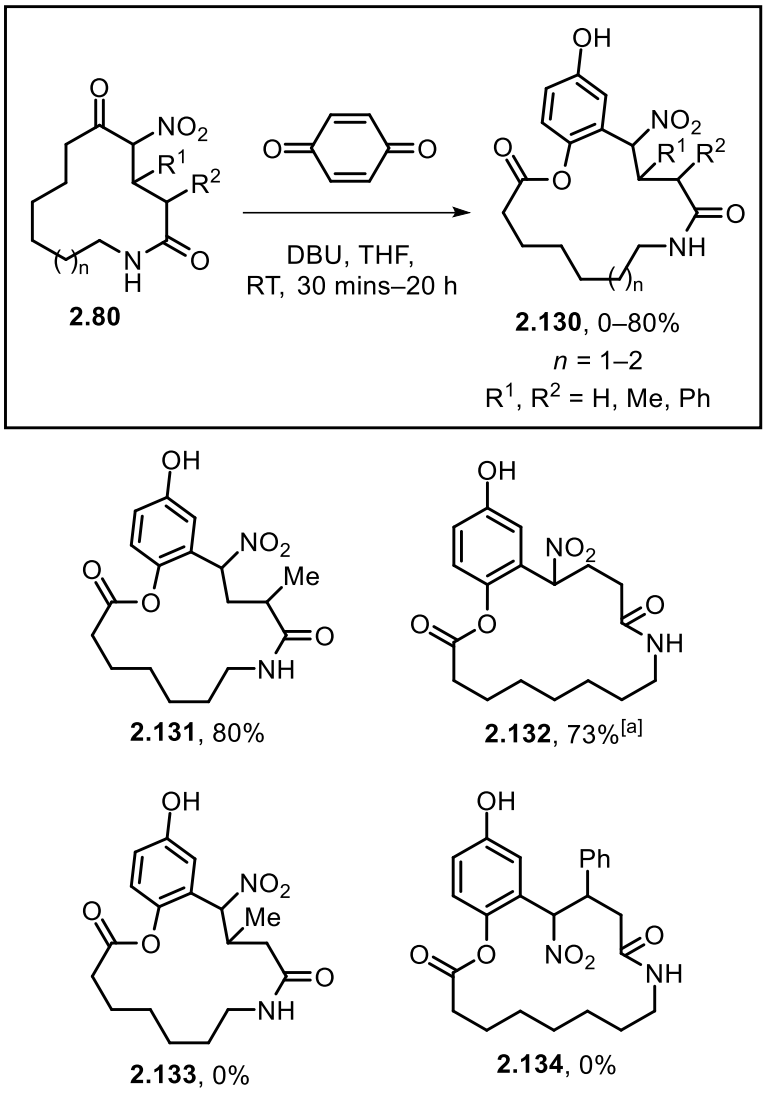
Scheme 95. 3-Atom ring expansion using 1,4-benzoquinone on the 12-membered macrocycle.

The analogous acylated compound **2.129** was also prepared by another member of the group (Phillip Bobinski) and an X-ray structure was obtained for this derivative (Scheme 96).[147]



Scheme 96. 3-Atom ring expansion using 1,4-benzoquinone on the 12-membered macrocycle (with an acetate group attached) and its respective X-ray crystal structure.

The scope of this reaction was explored *via* selected additional examples (Scheme 97). A methyl branched, 15-membered substrate, **2.131**, was successfully synthesised in an 80% yield. However, when the methyl group was moved to the β-position of the amide, the product **2.133** was not isolated. Similarly, with a phenyl group also at the β-position to the amide, none of the 16-membered product **2.134** was generated. Another member of the research group (Phillip Bobinski) then completed a reaction using the analogous unbranched substrate and this was successful, with macrocycle **2.132** obtained in a 73% yield. It is likely that steric repulsion led to the failure of the reactions to form **2.133** and **2.134** and sufficient space is required around the reaction centre for the conjugate addition onto 1,4-benzoquinone to occur.

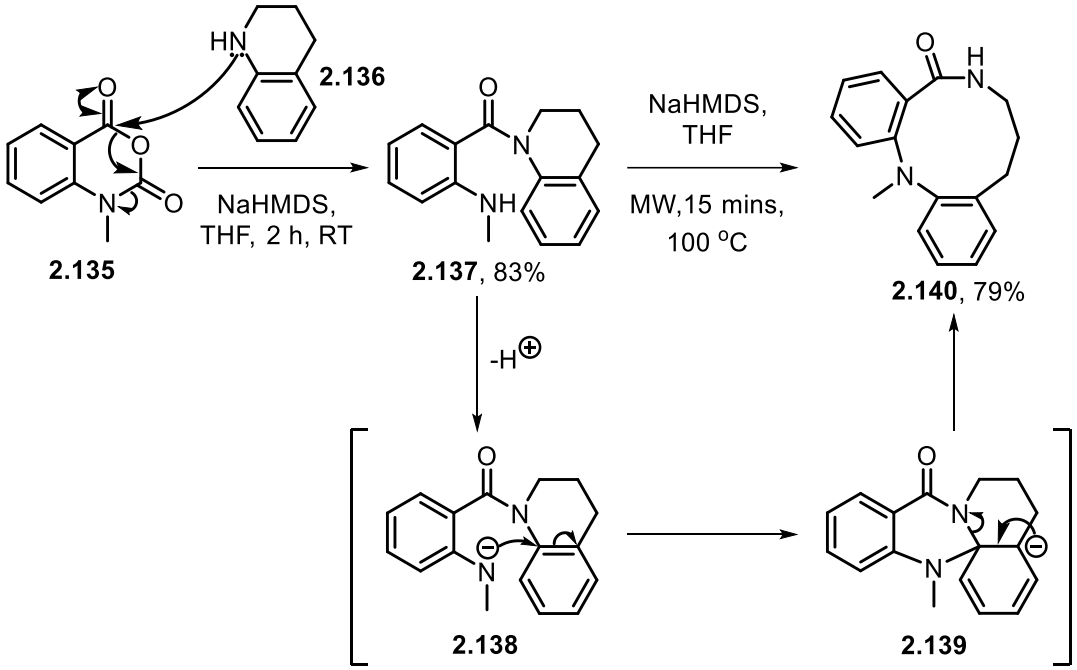


Scheme 97. Synthesis of *n*+3 macrocycles using 1,4-benzoquinone. [a] Synthesised by another member of the group.

2.7 Other Unsuccessful CARE Attempts

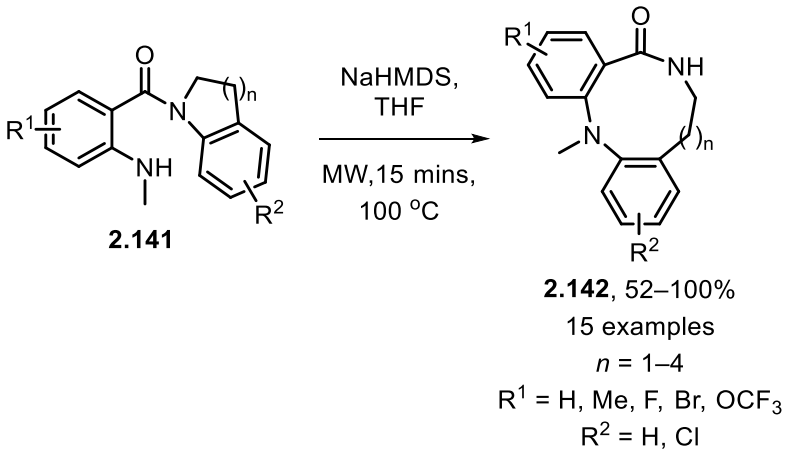
There were some instances of unsuccessful attempts at doing the CARE reactions during this project, summarised in this section. The first was the generation of a dibenzodiazepine starting material that was based on the work done in the Clayden group.[86] The dibenzodiazepine scaffold has been known to be a feature in medicinal compounds used to treat conditions such as: depression, schizophrenia and nocturnal enuresis[172] and so there is some interest in their synthesis as well as derivatives of its structure. We reasoned that if we could take Clayden's work forward and subsequently apply our own ring expansion methods to the compounds seen in Scheme 98, then novel medium-sized rings and macrocycles could be made that all contain the useful dibenzodiazepine functionality.

The Clayden group used isatoic anhydride and tetrahydroquinoline with base to promote nucleophilic attack and ring opening of the anhydride, forming **2.137**. Under microwave conditions and further base, the ring expansion from the 6-membered anthranilamide, to the final, ring-expanded product, **2.140**, was completed.



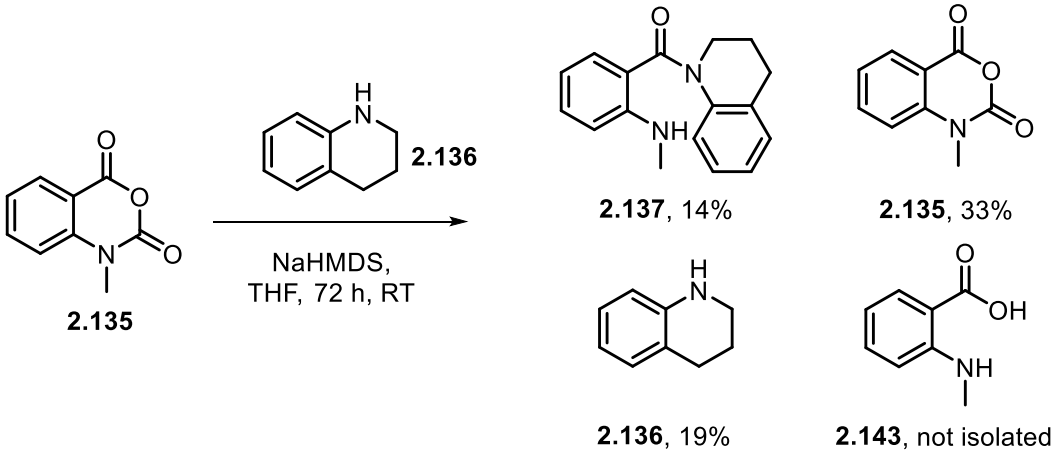
Scheme 98. 2-Step pathway for the synthesis of the 10-membered dibenzodiazepine.

In the literature, Clayden and co-workers attempted reactions at lower temperatures (66 °C) and with different bases (LiHMDS and KHMDS), but both changes caused a decrease in the yield and also caused the generation of tetrahydroquinoline as a side-product. Therefore, the original conditions of NaHMDS at 100 °C were optimal for this reaction. Using this procedure, Clayden and co-workers were able to synthesise 15 novel medium-sized rings in yields ranging from 52–100% (Scheme 99). To expand the scope, ring sizes from 9–11 were done, different substituents were applied to the benzene ring and additional amine groups were implemented to the structure.[86]



Scheme 99. Clayden and co-workers' ring expansion method to form several medium-sized rings and macrocycles.

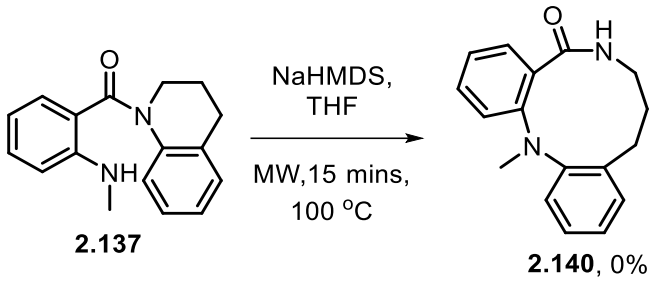
Unfortunately, the synthesis of **2.140** in our hands was not successful. Despite optimisation attempts that included longer reaction times, changing the equivalence of base and changing the ratio of **2.135** and **2.136** in the reaction, similar yields to the literature were unable to be reached for the first step, as shown in Scheme 100 below, where the yield of **2.137** is significantly lower. Instead, a number of side-products were isolated, the majority being the other reagents from the reaction that did not react or were in excess.



Scheme 100. The partially successful synthesis of **2.137**, with its multiple side-products.

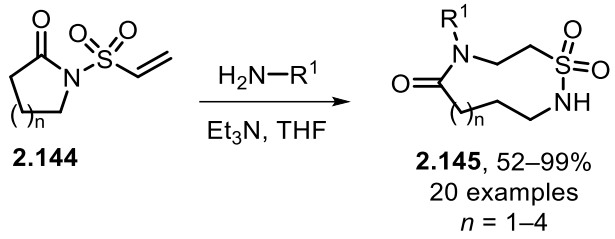
Following this, the ring expansion step to **2.140** was attempted under the microwave conditions denoted in the literature (Scheme 101).[86] Unfortunately, the expected product, **2.140**, was not formed, with just unreacted starting material being recovered from the reaction. This meant the subsequent *N*-acylation and CARE reaction could not be done on this substrate. In both the synthesis of **2.137** and **2.140**, the procedures were followed exactly meaning the fault may have been down to the reagents used. A common feature of

both was NaHMDS and this chemical decomposing over time through the use of an old bottle may have been a valid reason for the reactions being low-yielding/unsuccessful.



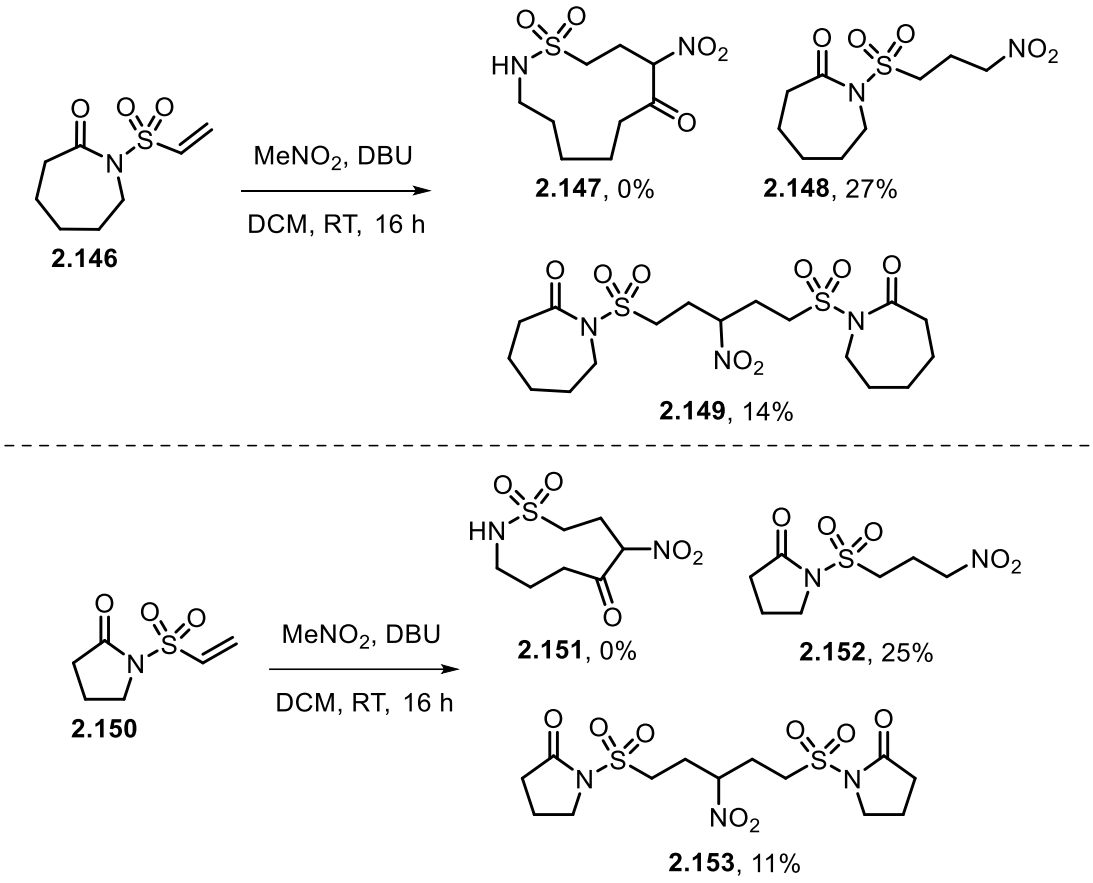
Scheme 101. The unsuccessful ring expansion attempt to form the 10-membered dibenzodiazepine.

Relatively recently, the Unsworth group developed an alternative CARE method using vinyl sulfonamide compounds of the form **2.144**. Scheme 102 summarises this work, with 20 medium-sized and macrocyclic rings that were formed from this procedure.[117] The published work had only used nitrogen as the nucleophile in the CARE reaction and therefore we were interested to test whether the use of carbon and oxygen-based methods developed during this project could be adapted for use on vinyl sulfonamides.



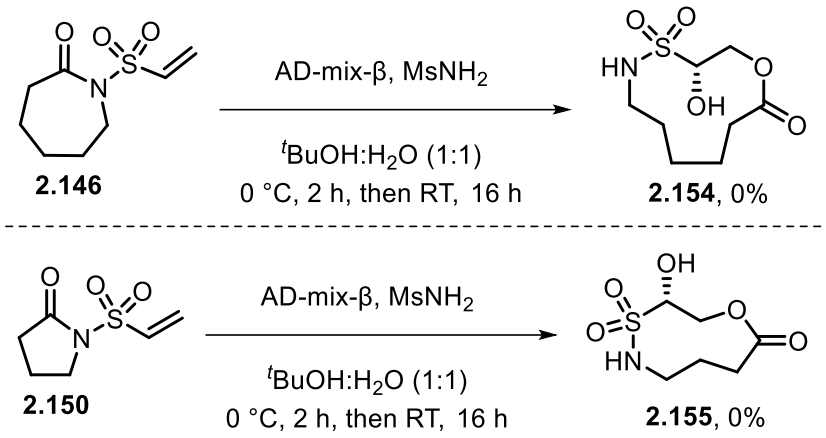
Scheme 102. Unsworth and co-workers' ring expansion method to form several medium-sized rings and macrocycles.

Vinyl sulfonamide precursors **2.146** and **2.150** that had already been made within the Unsworth group were used due to their availability. Both were tested in C-CARE reactions but unfortunately only side-products were formed (Scheme 103), with none of the desired ring expansion products **2.147** or **2.151** being formed. Familiar side-products were seen in these attempted C-CARE reactions, with these forming as a result of the nucleophilic attack on the carbonyl not being favourable enough.



Scheme 103. The unsuccessful C-CARE reactions on both ring sizes, showing the side-products formed.

A similar outcome was observed when attempting the dihydroxylation ring expansions in Scheme 104, with no isolable products formed in either reaction. Starting with ring sizes that led to generally unfavourable transformations in the past (5 → 9-membered and 7 → 11-membered) likely had a negative effect on the reactions and in some ways could have been expected. Despite the disappointing results in this brief study, investigating other vinyl sulfonamides – especially starting with an 8-membered ring or larger – may be a viable option to continue this project in the future.



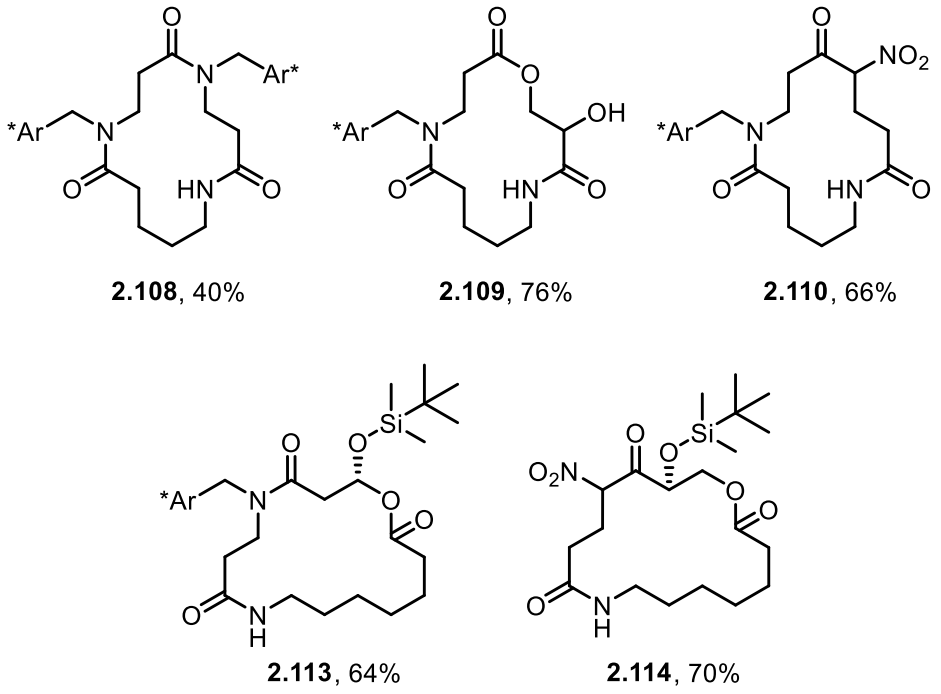
Scheme 104. The unsuccessful dihydroxylation ring expansion reactions on both ring sizes.

2.8 Conclusion

In conclusion, the CARE technique developed within the Unsworth group was successfully expanded, with a number of novel ring-expanded compounds made. All three nucleophiles of interest were applied successfully. The use and scope of N-CARE was further broadened, with a particular focus on exploring more ring sizes, beyond the 10-membered substrates that featured heavily in the 2022 paper.[106]

The development of new procedures that allowed the use of carbon and oxygen as nucleophiles in place of the already used nitrogen was especially pleasing. A range of starting materials were able to be used in both methods, including different ring sizes, heteroatoms within the ring and substituents branching off from the alkene on the vinyl imide.

The CARE reactions were built on by completing consecutive ring expansion reactions. The added challenge here was the requirement to protect the starting substrate in some cases. These macrocyclic structures were made by using a combination of the three aforementioned ring expansion methods, in various combinations and orders, to synthesise the macrocyclic compounds in yields of 40–76% (Scheme 105).



Scheme 105. The five products synthesised from doing consecutive ring expansion reactions using various nucleophiles.

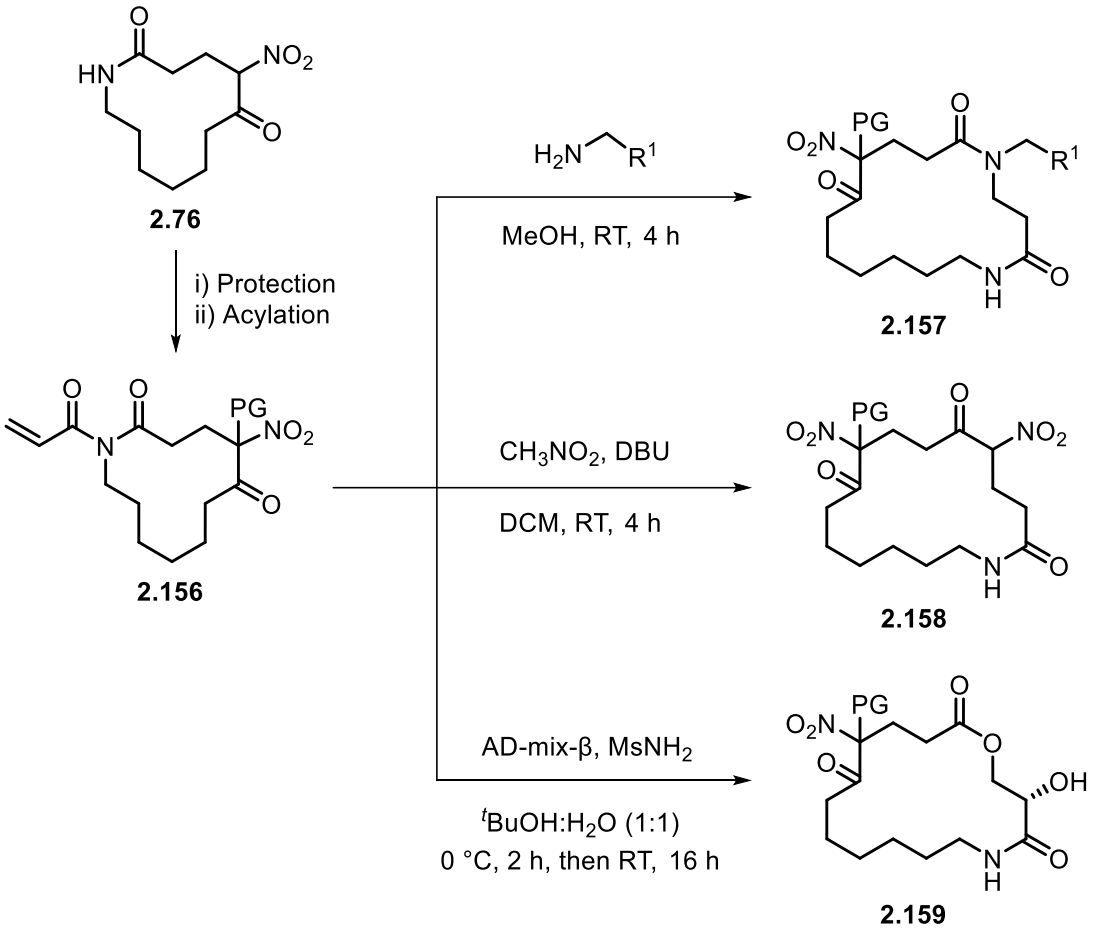
There were a few disappointing results where the ring expansion was unsuccessful or the starting material itself was unable to be made, as detailed in section 2.7. The attempts to do CARE with the compounds containing the vinyl sulfonamide functionality were unsuccessful with a range of unwanted side-products forming instead – the use of unfavourable ring sizes may have been a contributing factor to this, and future work using larger ring sizes is recommended.

The results described in this chapter are published in *Chemistry – A European Journal*.[173]

2.9 Future Work

Continuing the consecutive ring expansion reactions would be of value. The main barrier to progression in this project was the need for a more robust strategy for the protection of a nitroketone and its subsequent *N*-acylation. A reliable method for the synthesis of **2.156** would allow three more possible ring expansions. On top of this, another desire is to use substrates such as the products in Scheme 106 and ring-expand them a third time as this is something that has rarely been done in the Unsworth group and the only examples are based on three consecutive N-CARE reactions completed for the literature.[106] However, the problems we already faced in the protection and *N*-acylation steps previously will likely be

exacerbated in the larger and more complex systems, so it remains to be seen how plausible this will be.

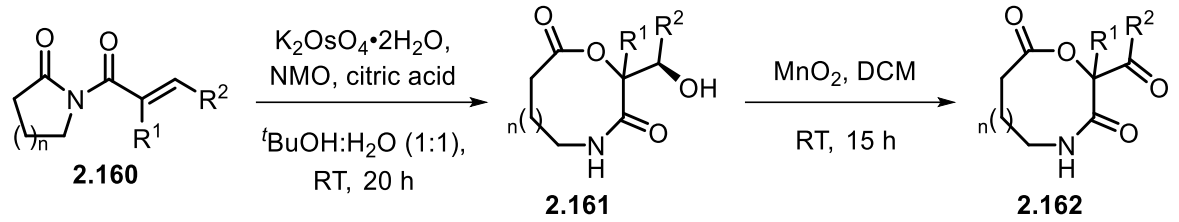


Scheme 106. The proposed pathway to protect then acylate the nitroketone starting material and then complete a subsequent ring expansion using the three different nucleophiles.

A relatively simple project to explore in the future, would be to increase the library of substrates formed *via* CARE, particularly with nitrogen as the nucleophile. An initial screening was done during this project and in the 2022 paper by Unsworth and co-workers (mainly focused on instances where nitrogen is the nucleophile)[106] but there is certainly broad scope to do more related CARE reactions. Varying the amine used, the composition of the lactam ring and substituents on the Michael acceptor functionality are all easy things that can be edited without much trouble but provide novel medium-sized rings and macrocycles to add to the growing library.

Finally, although only touched on briefly during this project, it could be interesting to further investigate the '*n*+3' ring expansion that was done in preliminary testing where NMO was used as a reagent in Upjohn-type conditions for the dihydroxylation reaction (Scheme 107). Of course, this form of ring expansion could only apply when oxygen was being used as the

nucleophile meaning it would slightly limit the possible number of substrates that can form (as opposed to when nitrogen is the nucleophile for example). Despite this, the ability to alter the type of lactam and the substituents on the Michael acceptor offer some options that could be explored in the future.

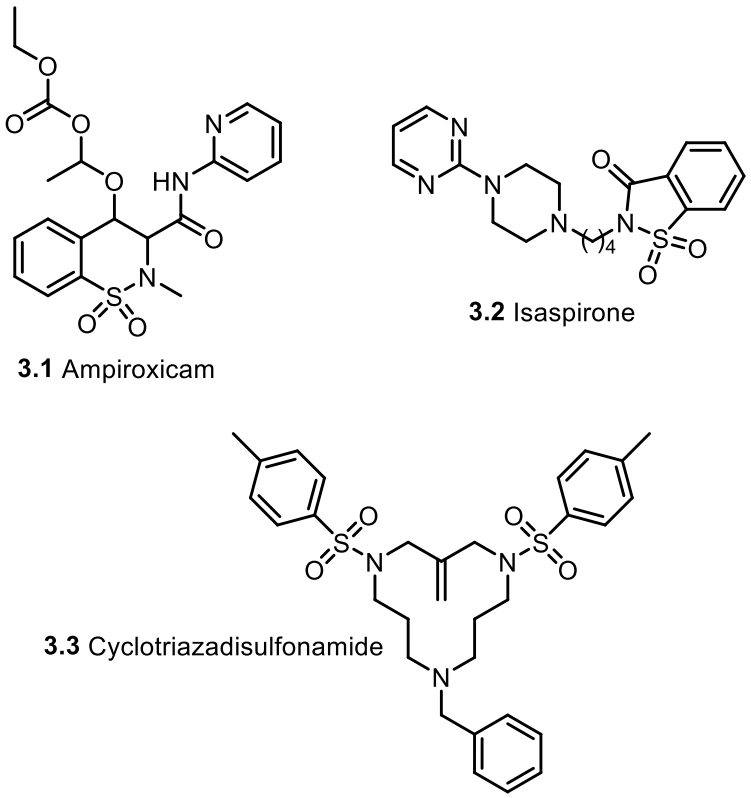


Scheme 107. The proposed pathway to use the Upjohn-type conditions to facilitate the 3-atom ring expansion, with the possible changes that could be made to the structure highlighted.

3 Modular Assembly of Macrocyclic Sulfonamides *via* Consecutive Cascade Ring Expansion Reactions

3.1 Chapter Aims

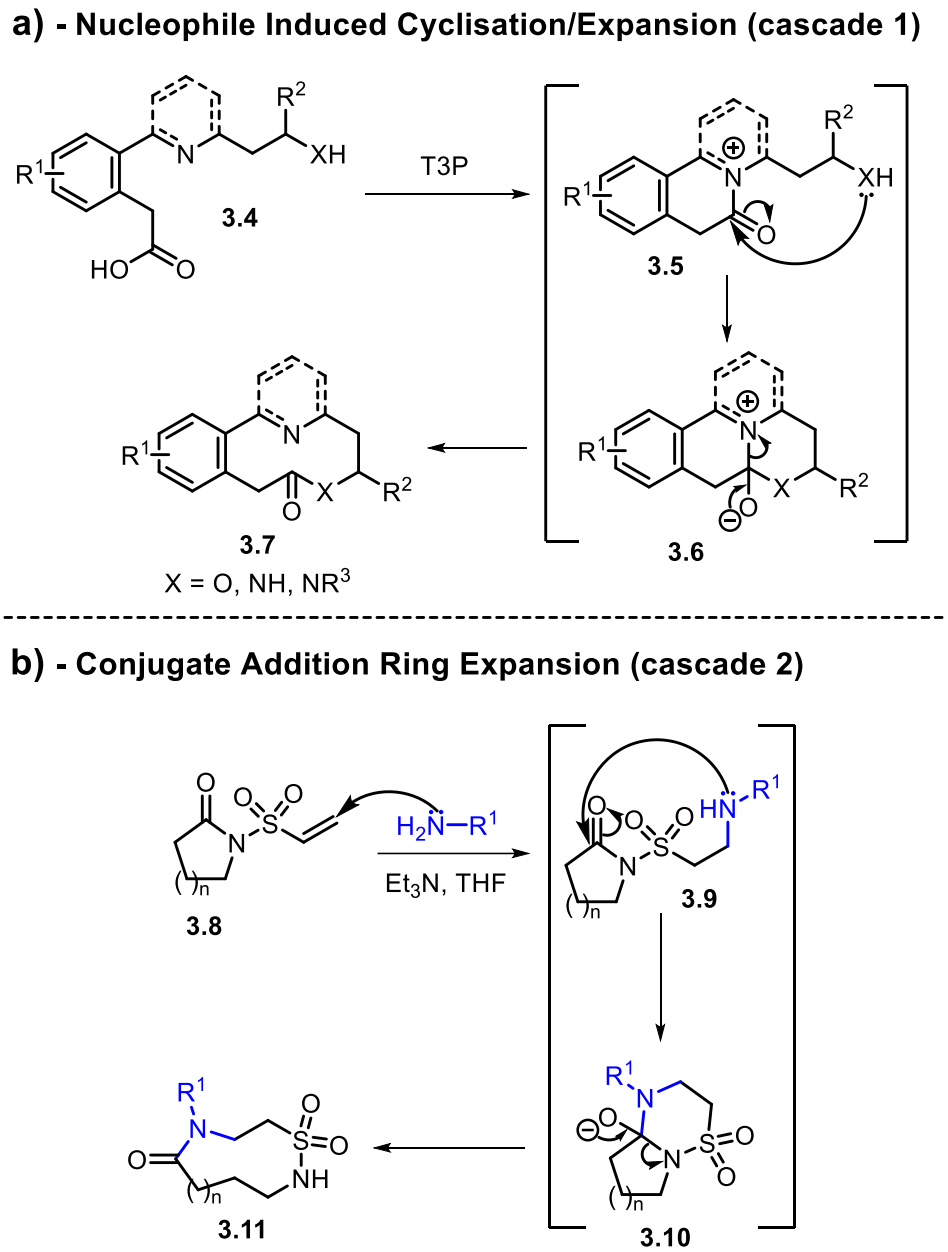
Throughout pharmaceutical research and development, sulfur-containing molecules are prevalent and they are regularly found in FDA approved drugs.[174,175] Within this class of compounds, cyclic sulfonamides (known as sultams) are of particular interest, as it is a functionality that is well-represented in drugs currently on the market, with some examples shown in Scheme 108.[176,177]



Scheme 108. Examples of drugs with the sulfonamide group within their ring structure.

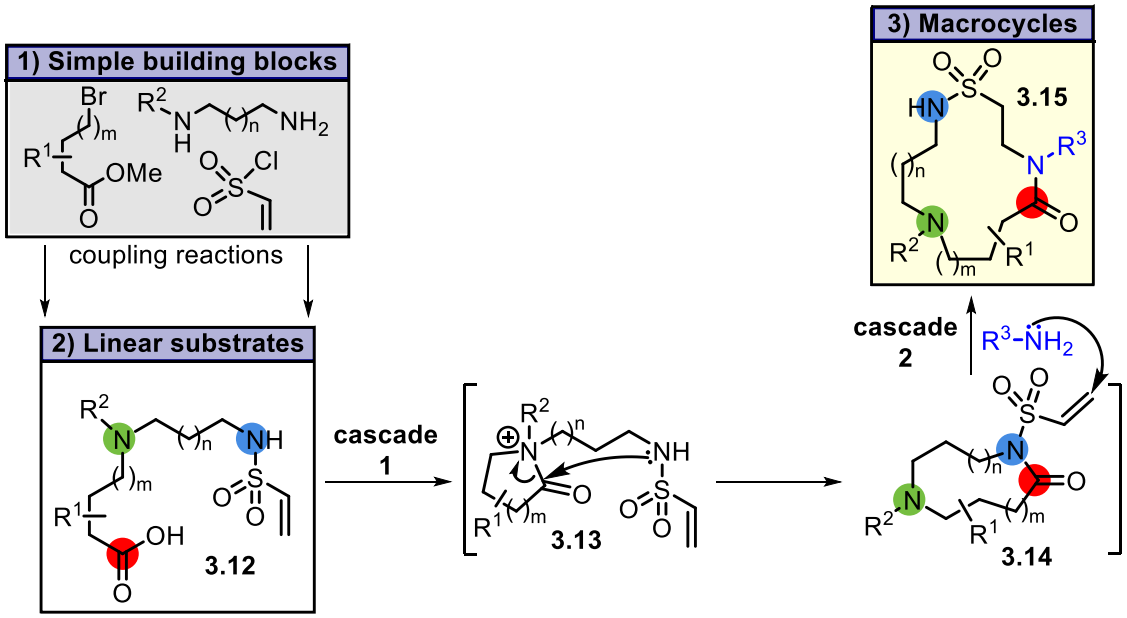
The main aim of the work described in this chapter was to develop a novel pathway for the synthesis of macrocyclic sultams, using methodology based upon the combination of two cascade ring expansion techniques developed by the Unsworth group.[106,121] The first method, Nucleophile Induced Cyclisation/Expansion (NICE), is shown in Scheme 109a. The NICE approach enables an overall end-to-end cyclisation but *via* the use of an internal nucleophile catalyst, built into the linear substrate. For example, when the carboxylic acid group of linear starting material frameworks of the type **3.4** are activated by T3P, it reacts with the internal nucleophile, *via* a normal-sized ring intermediate, **3.5**, before rearranging to give the product, **3.7**, as a medium-sized lactam or lactone.[121] The second strategy is

Conjugate Addition Ring Expansion (CARE). In the context of this project, a primary amine will react with a vinyl sulfonamide group to undergo conjugate addition to give the intermediate **3.9**, before then undergoing an intramolecular attack and fragmentation, providing the ring-expanded product **3.11** in Scheme 109b.[106] Both NICE and CARE alleviate the need for high-dilution conditions and remove many of the unwanted side-products often observed in end-to-end cyclisation reactions when making medium-sized rings and macrocycles.[14,16]



Scheme 109a. Previous work in the group to form rings *via* NICE. **Scheme 109b.** Previous work in the group to form rings *via* CARE.

The focus in this project was to combine these ring expansion methods and develop an approach to generate macrocyclic sulfonamides. Scheme 110 summarises the idea to combine easily accessible building blocks to form the initial linear substrates, **3.12**, containing an electrophile (in red), an internal nucleophile (in green) and a terminal nucleophile (in blue). These features will facilitate the planned NICE reaction (cascade 1) to first form medium-sized rings, **3.14**, and then the presence of the vinyl sulfonamide group will enable it to react further *via* CARE (cascade 2) to form macrocycles like **3.15**.



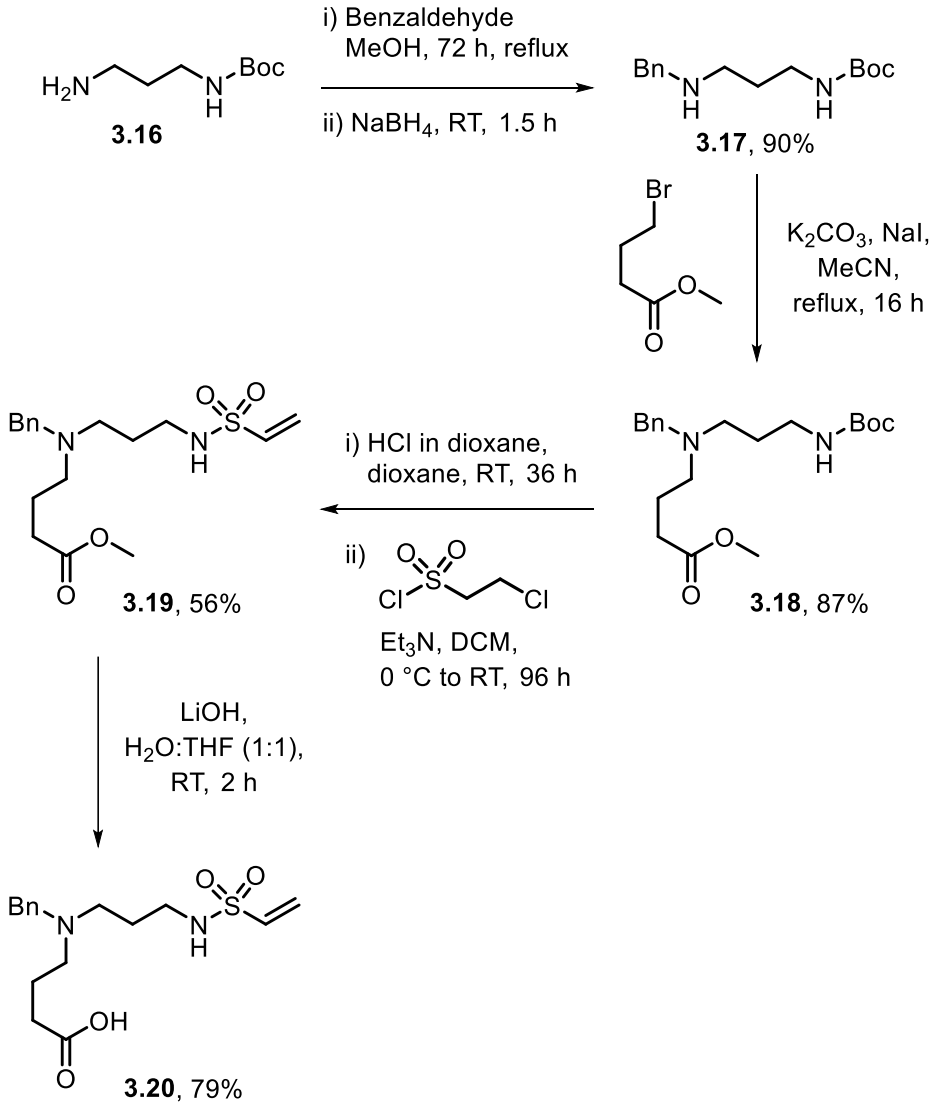
Scheme 110. A summary of the new work that will be described in this chapter.

A key difference from previous work done in the group, is the use of a vinyl sulfonamide as the terminal nucleophile in NICE – something not attempted before. This was done with the idea that, if successful, the vinyl sulfonamide would provide a reactive handle able to undergo CARE.[117] It was hoped that a broad array of starting material frameworks could be synthesised and used for these reactions and by using a variety of primary amines, a large library of macrocyclic sulfonamides could be prepared.

3.2 Synthesis of the Linear Starting Material Frameworks

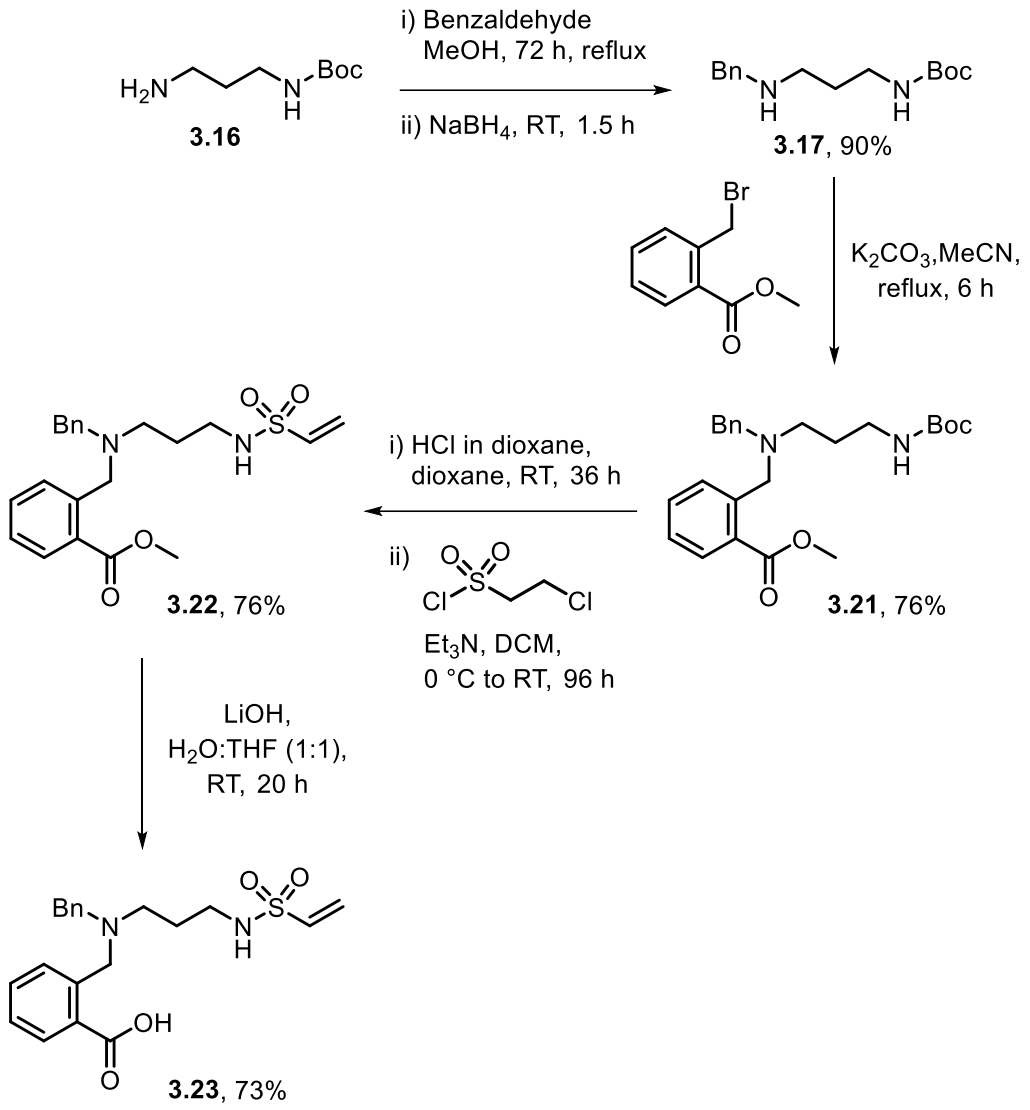
Before the ring expansion reactions could be tested, multiple starting material frameworks needed to be synthesised. The first pathway is shown in Scheme 111, where a reductive amination on protected diamine **3.16** with benzaldehyde was performed, using sodium borohydride as the reducing agent.[178] Then follows an S_N2 reaction on the secondary amine **3.17** with an ester-containing alkyl bromide to produce **3.18** in an 87% yield.[179] Removal of the Boc protecting group with HCl in 1,4-dioxane was immediately followed (with no purification) by sulfonylation and an $E1_{CB}$ elimination to add the vinyl sulfonamide, with **3.19**

formed in a 56% yield over the two steps.[180] Hydrolysis of the ester in **3.19** forms carboxylic acid **3.20** in an overall yield of 35% from the initial starting material, **3.16**. Using this pathway, all three key components essential for a NICE reaction have been incorporated: the carboxylic acid as the electrophile, the tertiary amine as the internal nucleophile and the vinyl sulfonamide as the terminal nucleophile.



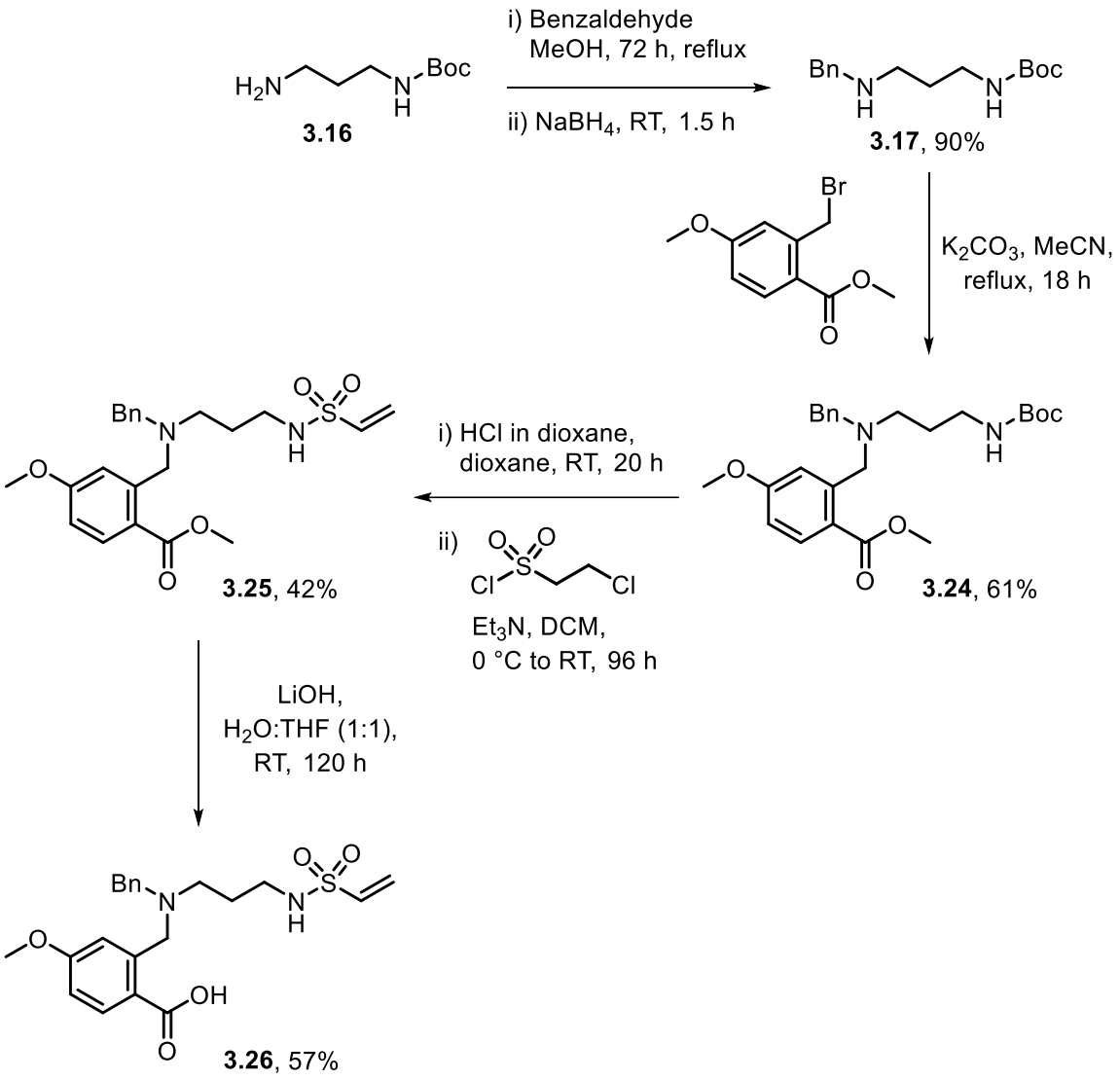
Scheme 111. The reaction pathway from the protected diamine to form the 1st starting material framework, **3.20**.

After this, a related benzannulated system was prepared (Scheme 112). There is evidence in the group's previous work that an aromatic ring in the adjacent position to the electrophilic component can improve the yield of NICE reactions.[126] A similar multi-step synthetic approach was used to generate linear product **3.23** in an overall 38% yield, starting from simple diamine derivative **3.16**.



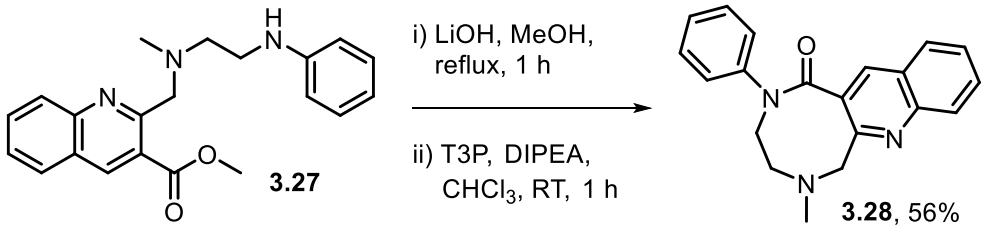
Scheme 112. The reaction pathway from the protected diamine to form the 2nd starting material framework, **3.23**.

Maintaining the same general framework, another benzene-containing starting material was synthesised. This time, a methoxy substituent was attached at the para-position relative to the carboxylic acid, with this sequence shown in Scheme 113, and resulted in an overall 13% yield of framework **3.26**.



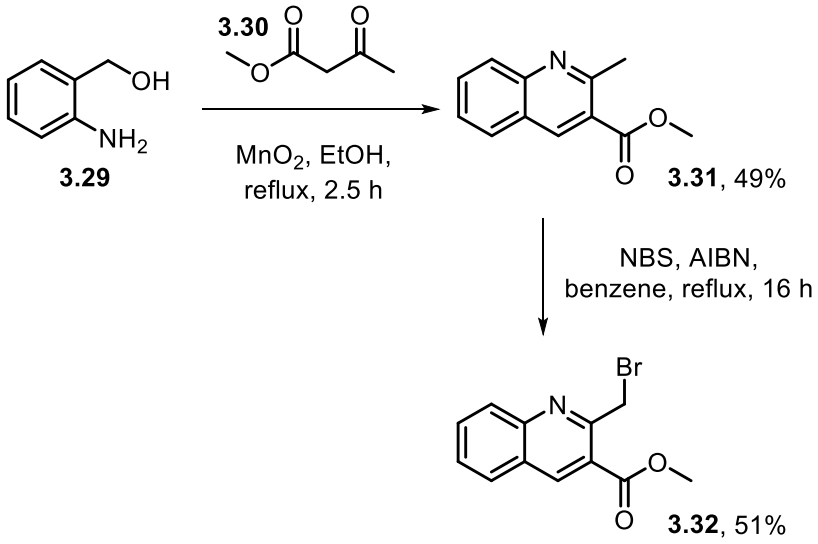
Scheme 113. The reaction pathway from the protected diamine to form the 3rd starting material framework, **3.26**.

Moving on, a quinoline-containing compound was attempted next, using a system very similar to **3.27** below, with the main difference being the replacement of the aniline section with a vinyl sulfonamide group. Scheme 114 shows a successful, published NICE reaction using such a framework.[126]



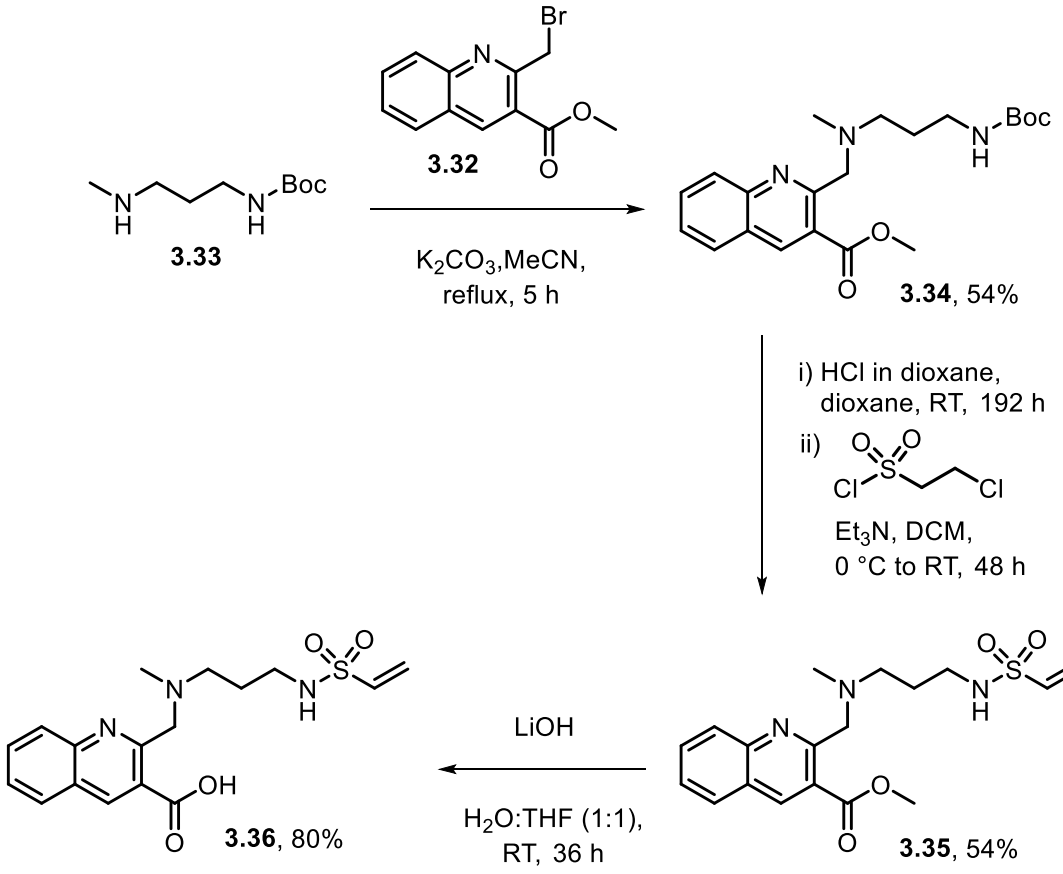
Scheme 114. Literature example by the Unsworth group of using a quinoline-containing compound for a NICE reaction.

An initial synthesis of **3.32** was required (Scheme 115). Using a method previously developed in the Unsworth group,[126] functionalised aniline **3.29** was reacted with methyl acetoacetate and manganese dioxide under reflux, to generate the quinoline **3.31**, which was then brominated with NBS and AIBN, *via* a radical pathway, to afford **3.32**.



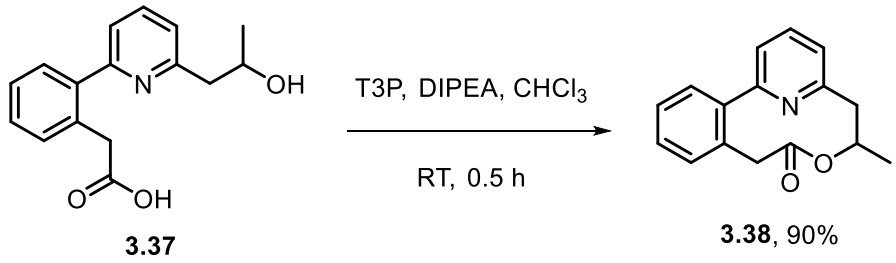
Scheme 115. Reaction pathway for the quinoline-containing reagent.

Following the synthesis of **3.32**, Scheme 116 summarises its conversion into the quinoline-containing starting material framework, **3.36**, in an overall yield of 23% from **3.33**. Despite the unusually long time required for the Boc cleavage step (almost a week), this did not seem to affect the success of the step, with 54% yield being in line with that observed for this step in analogous sequences.



Scheme 116. The reaction pathway from the protected diamine to form the 4th starting material framework, **3.36**.

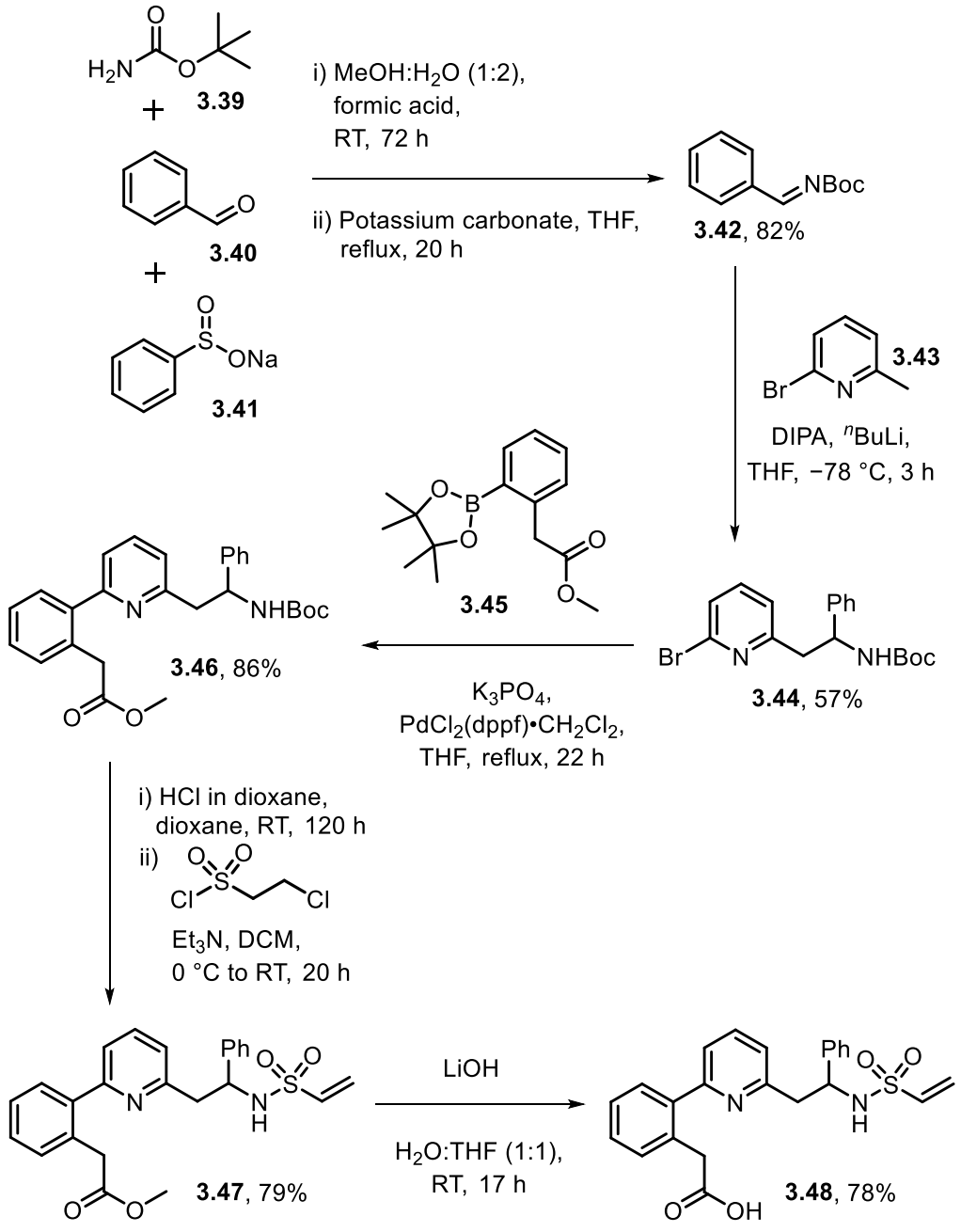
The final starting material framework made contained a pyridine group as its internal nucleophile. Structures of this type have been extensively used in the Unsworth group, with a published example shown in Scheme 117.[121] These reactions are usually high-yielding and reliable, so presented a good alternative to the aliphatic amine substrates described earlier.



Scheme 117. Literature example by the Unsworth group of using a pyridine-containing compound for a NICE reaction.

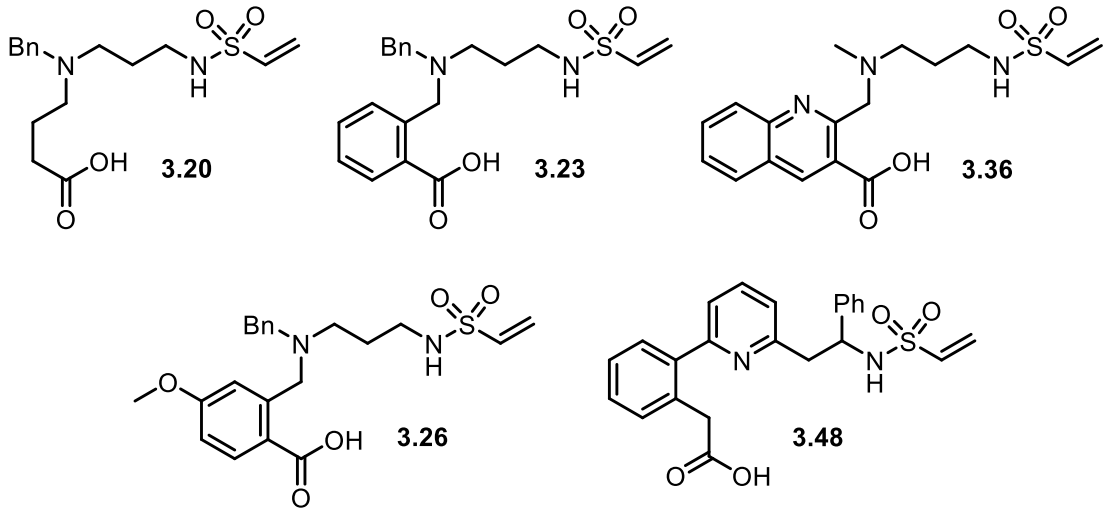
This framework required a different synthesis pathway to install the pyridine and additional benzene group, using the approach shown in Scheme 118. First, protected imine **3.42** was formed from benzaldehyde, *tert*-butyl carbamate and benzenesulfinic acid over two steps. Next, LDA (in situ generation by DIPA and ^{n}BuLi) facilitated the deprotonation of a proton on

the methyl group of 2-bromo-6-methylpyridine, and this lithiated species reacted with imine **3.42** at the carbon position forming **3.44** in a 57% yield. Then, a Suzuki cross-coupling with boronic ester **3.45** enabled the C–C aryl bond-forming reaction producing **3.46**. After this, Boc deprotection, sulfonylation and hydrolysis of the ester afforded the final carboxylic acid **3.48**, in an overall yield of 25%.



Scheme 118. The reaction pathway from the protected amine to form the 5th starting material framework, **3.48**.

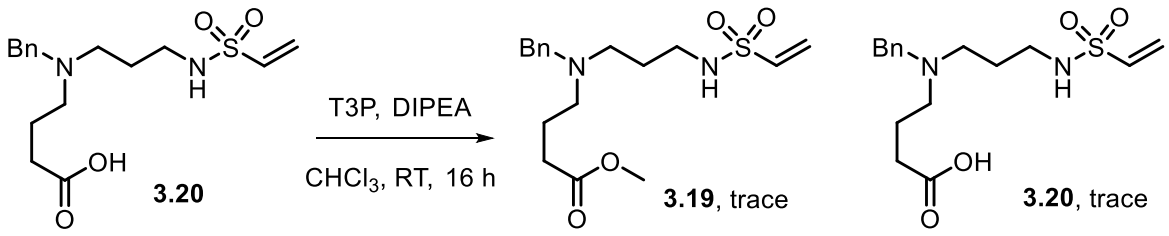
After completing these multi-step pathways, five novel starting material frameworks had been synthesised (all of which are shown in Scheme 119), ready to be tested in the first crucial ring-forming step *via* a NICE reaction.



Scheme 119. The five starting material frameworks that have been synthesised.

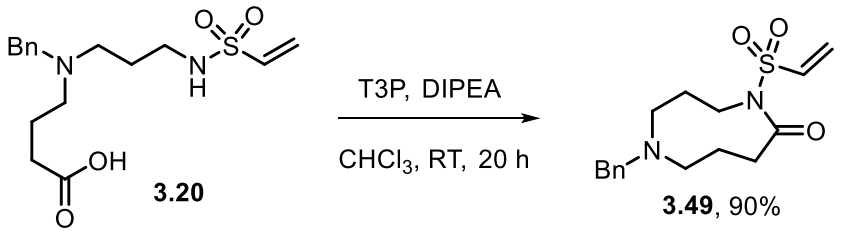
3.3 NICE Reactions of the Linear Precursors

Initial investigations into the NICE step focused on carboxylic acid **3.20** (Scheme 120) and typical conditions developed previously in the group were used: **3.20** was reacted with T3P and DIPEA in chloroform and the reaction was left to stir at room temperature overnight.[121,126] Following reaction completion, mass spectrometry analysis of the unpurified reaction mixture confirmed the presence of a molecular ion peak consistent with the formation of the desired product **3.49**. Therefore, the crude mixture was moved on to purification *via* column chromatography, with a workup usually not necessary for NICE reactions. Unfortunately, the column purification was unsuccessful with the medium-sized ring product appearing to be unstable on silica during chromatography. It seemed that exposure to the methanol and water present during the purification process caused its breakdown; trace amounts of **3.19** and **3.20** were the only observable products.



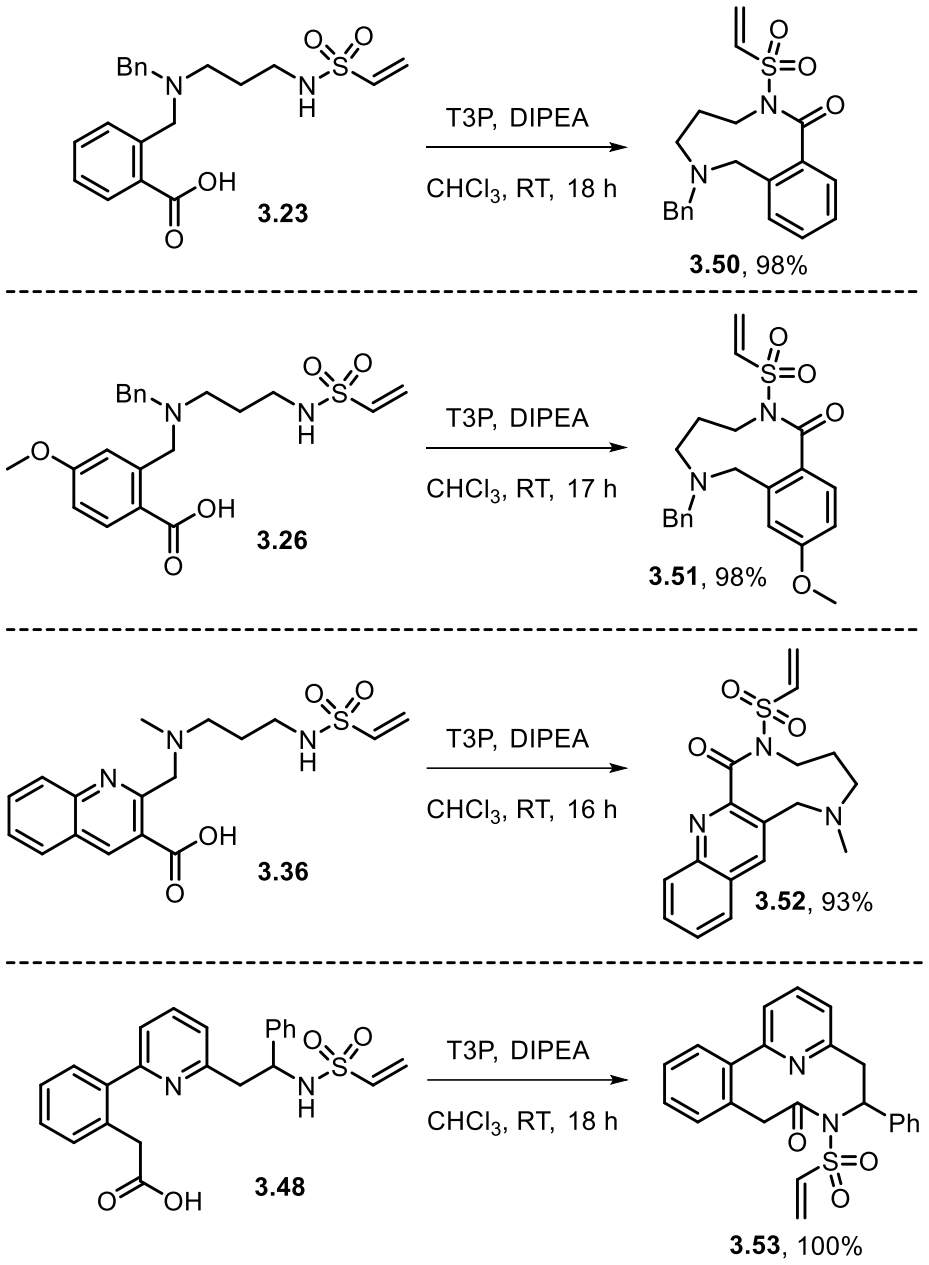
Scheme 120. The unsuccessful NICE reaction with the two identified side-products after a column.

This was a disappointing result as previous examples of NICE did not display this product instability issue. Therefore, a second attempt was done on **3.20**, using the same method but replacing the column with a basic workup of aq. sodium bicarbonate solution and DCM. Pleasingly, this was sufficient and the data collected for **3.49** after workup was of sufficient purity to identify the product (Scheme 121).



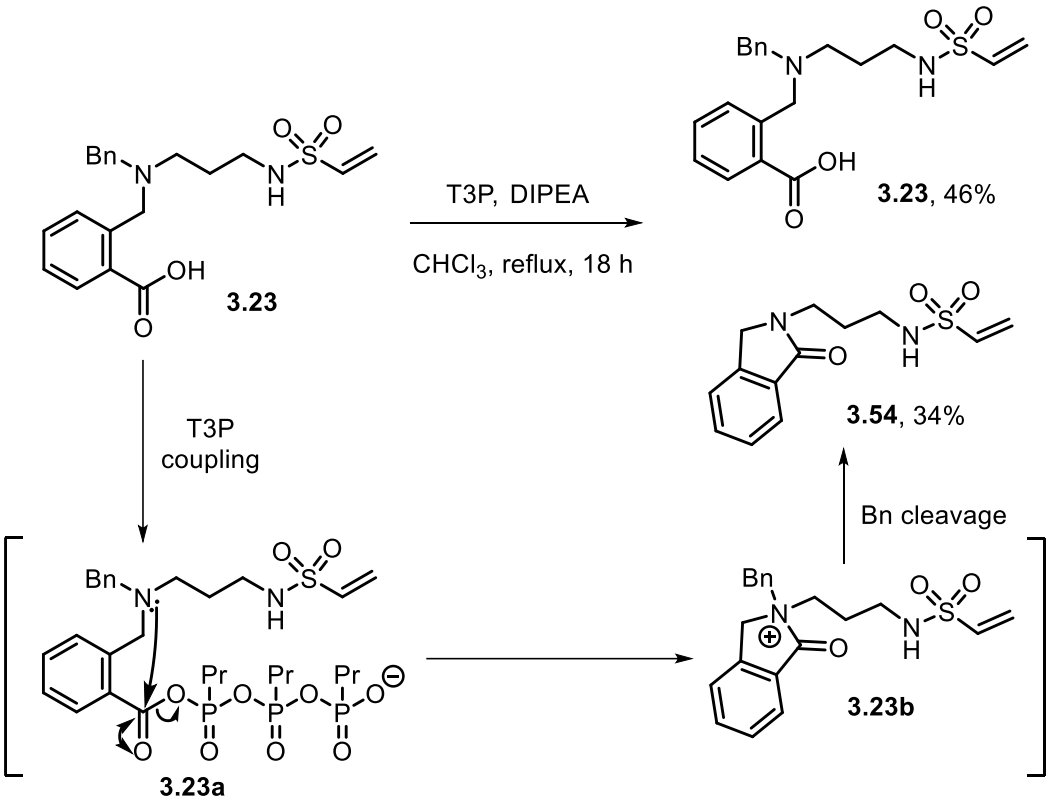
Scheme 121. Successful NICE reaction with **3.20** after a workup for purification.

After this breakthrough, the other starting material frameworks were reacted in the same way, with a basic workup replacing the column that is usually implemented as a purification for these types of compounds. All four other frameworks were successful in their respective NICE reactions forming the medium-sized rings **3.50**–**3.53** (Scheme 122). Also encouraging were their consistently high yields, with the lowest case being 90%.



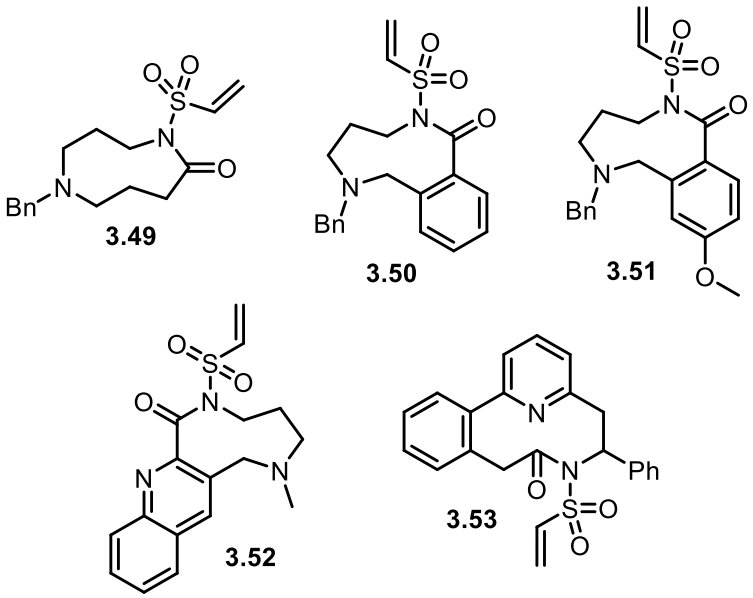
Scheme 122. NICE reactions of vinyl sulfonamide substrates.

A NICE reaction with benzoate **3.23** was also run at reflux rather than the usual room temperature conditions to test if it would run more efficiently. Interestingly, this generated side-product **3.54** that is likely derived from the proposed normal-sized ring intermediate formed during the attack of the internal nucleophile, with a 5-membered side-product, **3.54**, isolated in a 34% yield (Scheme 123). Some starting material was also left unreacted from this reaction. While this was not the desired transformation, it does support our idea that the mechanism operates *via* a 5-membered ring intermediate. In all other examples where the reaction was not heated, the normal-sized ring **3.54** (or any analogous substrate) was not made, indicating the refluxing conditions were the defining factor in its generation.



Scheme 123. Unsuccessful NICE reaction at reflux with the formed side-product highlighted.

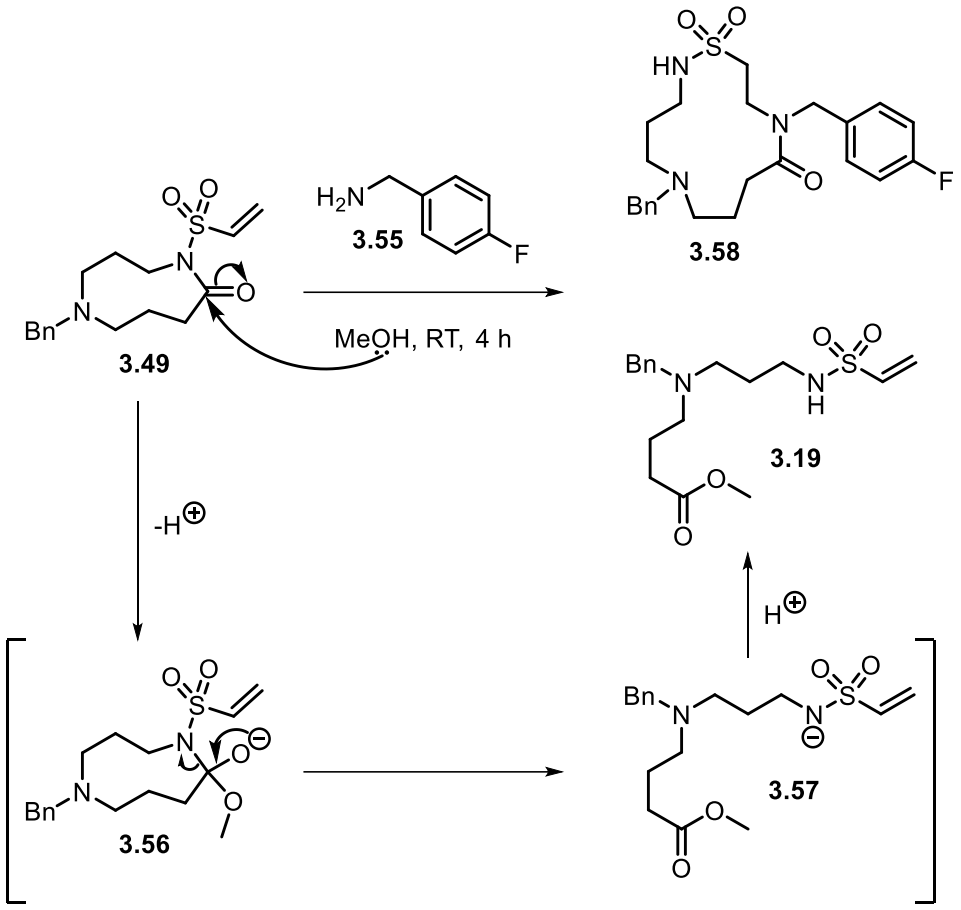
Compounds **3.49**–**3.53** are all unstable on standing in air, with ^{1}H NMR analysis done a day after their generation displaying signs of degradation, seen through a reduction in intensity of product peaks and the formation of new ^{1}H NMR signals. With this in mind, for the following section detailing the completed CARE reactions, it was decided that once the NICE reaction and workup was complete, the medium-sized ring intermediates (Scheme 124) would be immediately taken forward to the CARE reaction as a 2-step telescoped process.



Scheme 124. The five medium-sized rings that have been synthesised using the NICE reaction.

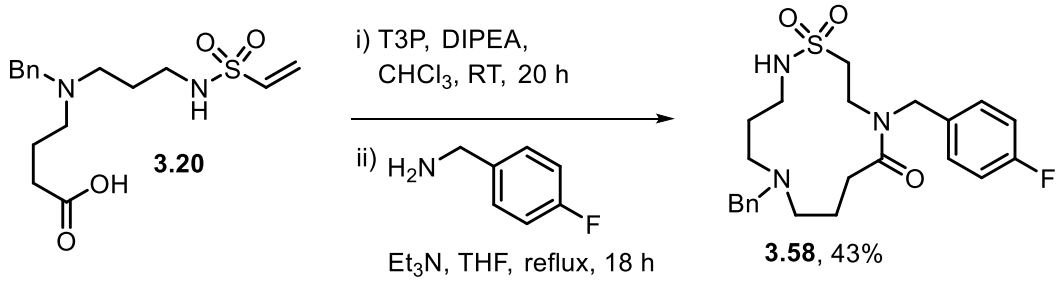
3.4 CARE Reactions on the Medium-sized Rings using the Vinyl Sulfonamide Functionality

Initial investigations began from carboxylic acid **3.20** and following the aforementioned NICE reaction to form **3.49**, the CARE step was attempted using the conditions developed during the group's first CARE paper from 2022, whereby **3.49** was reacted with 4-fluorobenzylamine **3.55** in methanol as the solvent, and stirred at room temperature for 4 hours (Scheme 125 below).[106] Although yields were not quantified for this reaction, it appeared these conditions were partially successful with NMR spectroscopy and mass spectrometry being able to confirm the presence of both the 13-membered ring-expanded product, **3.58**, but also the ring-opened ester starting material, **3.19**. For **3.58**, a distinct NH peak was now present and characteristic carbon-fluorine J-coupling was observed in the ^{13}C NMR spectra. However, using comparisons to previously isolated **3.19**, the peaks for this precursor could also clearly be seen.



Scheme 125. The attempted CARE reaction on **3.49** and the two products formed, including the mechanism for the unwanted ring-opening pathway.

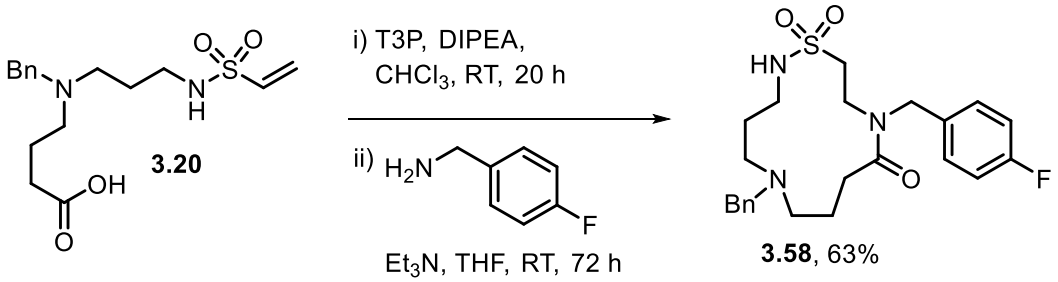
A switch to alternative conditions for CARE used by Unsworth and co-workers was made (Scheme 126),[117] where THF replaced methanol and triethylamine was introduced as a base, with 4-fluorobenzylamine remaining as the amine. These changes provided a much-improved conversion to the desired product, **3.58**, in a 2-step yield (from the carboxylic acid) of 43%.



Scheme 126. The successful NICE and CARE reaction to form the ring-expanded product.

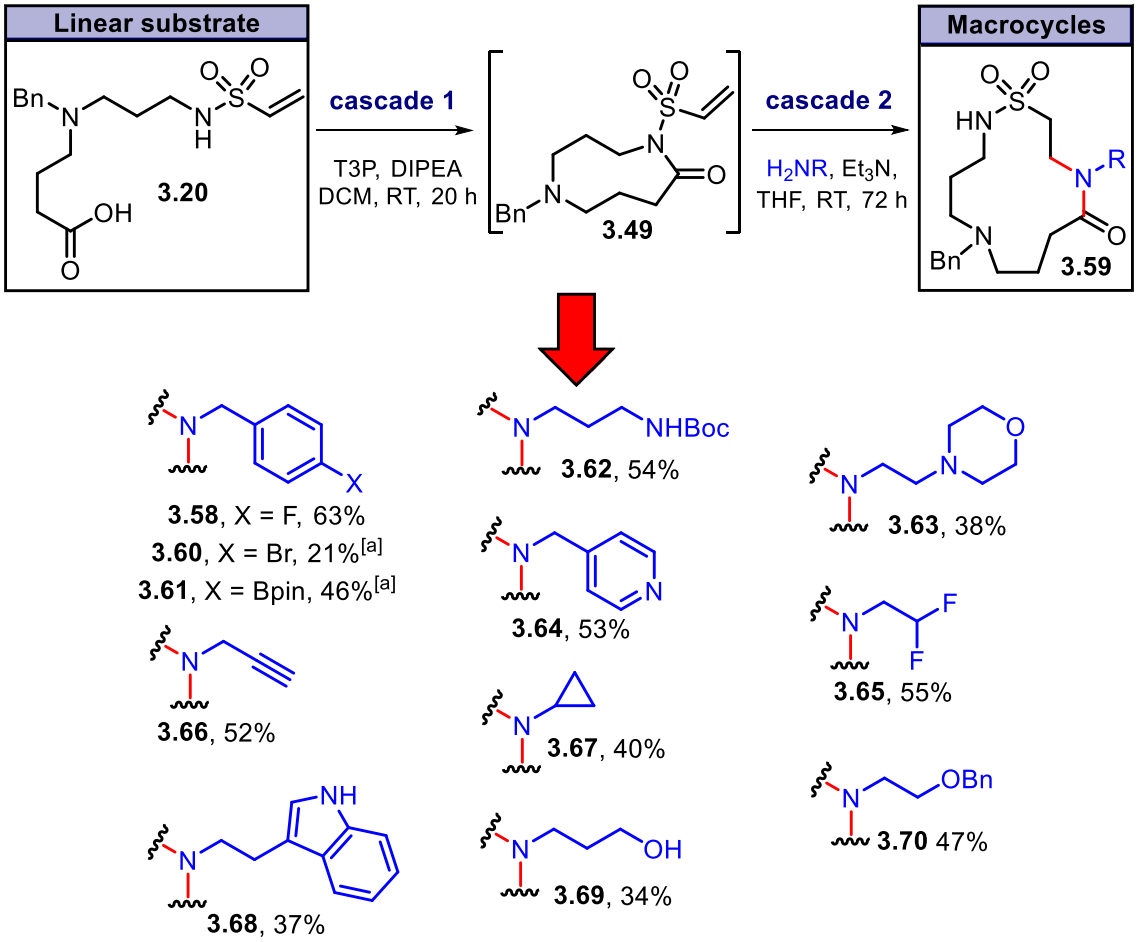
Some optimisation was then performed and it was found that two key changes enhanced the 2-step yield to 63%, with the optimised procedure summarised in Scheme 127: the CARE reaction was left for much longer (72 hours) and the temperature was decreased to room

temperature. Notably, macrocycle **3.58** (and the analogous substrates generated in this series) were able to be purified by column chromatography and there was no longer any notable product instability on silica.



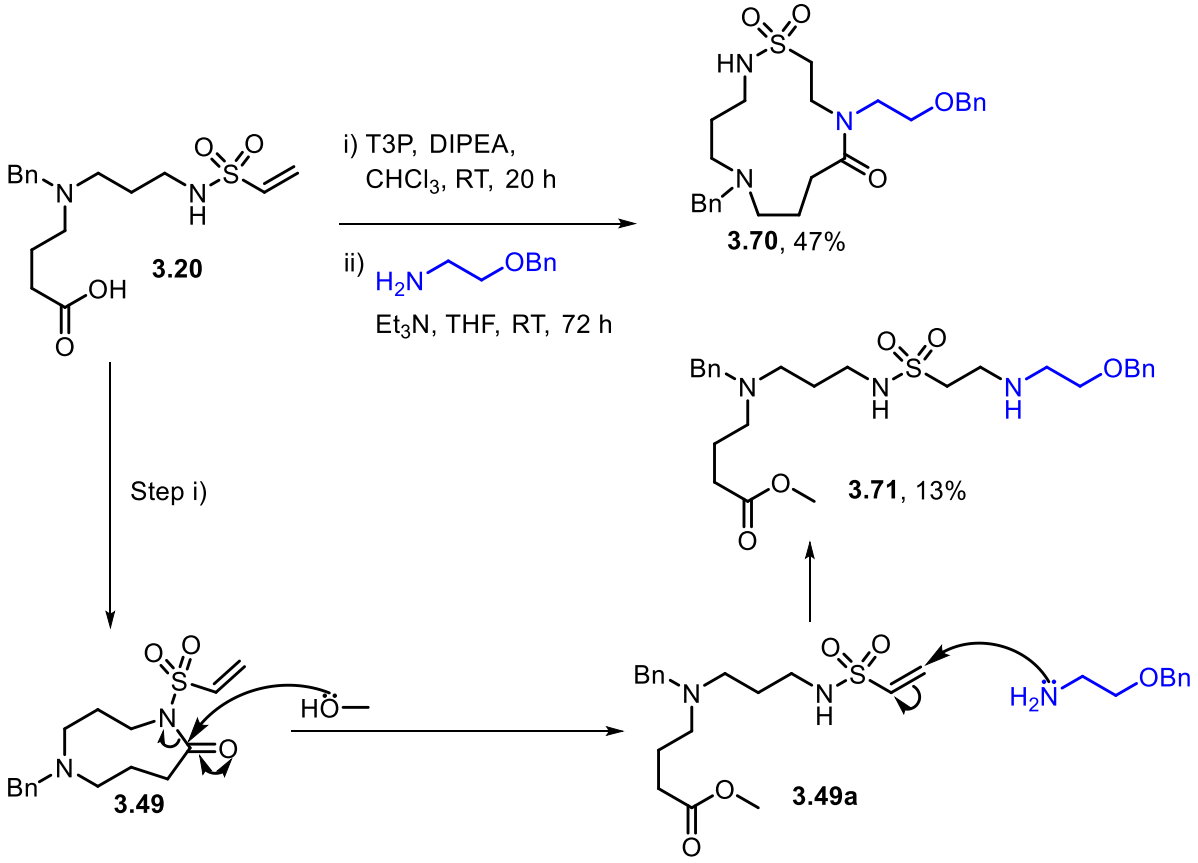
Scheme 127. The successful NICE and optimised CARE reaction to form the ring-expanded product.

Following this first successful CARE reaction, the 2-step sequence from **3.20** was then performed using a number of different primary amines in the CARE step. Scheme 128 summarises 12 successfully completed sequences, with 2-step yields ranging from 21–63%.



Scheme 128. The macrocyclic products formed by the NICE and CARE reactions from starting material **3.20**. [a] Synthesised by another member of the Unsworth group.

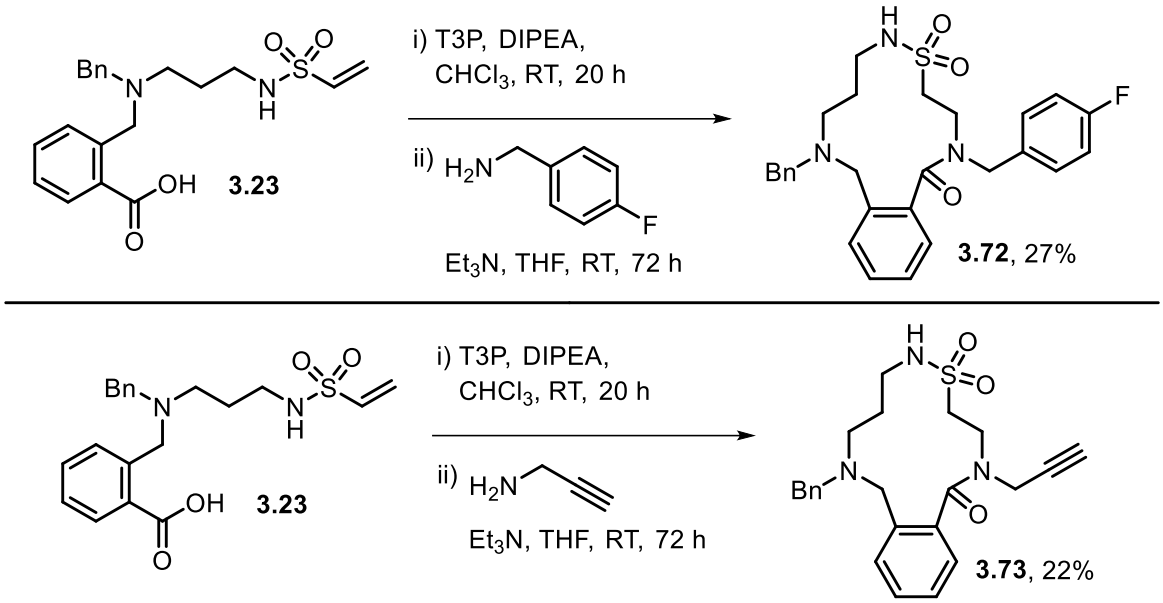
In the lower-yielding examples, a contributing factor was found to be the generation of a side-product (*e.g.* **3.71**, or analogues for different amines) that was identified and isolated after the CARE step when using 2-(benzyloxy)ethan-1-amine (Scheme 129). An explanation for its formation is that ring-opening with methanol must occur to form **3.49a**. Despite the absence of methanol in these reaction conditions, it was present during the previous ester hydrolysis step, so this likely accounts for its involvement in this side reaction. After that, the amine can attach as expected to form side-product **3.71**. While isolated here, for all other examples this side-product was not collected, although TLC analysis showed a minor spot for other examples that potentially represents the analogous side-product.



Scheme 129. The generation of the ring-opened side-product, **3.71**, with the desired product.

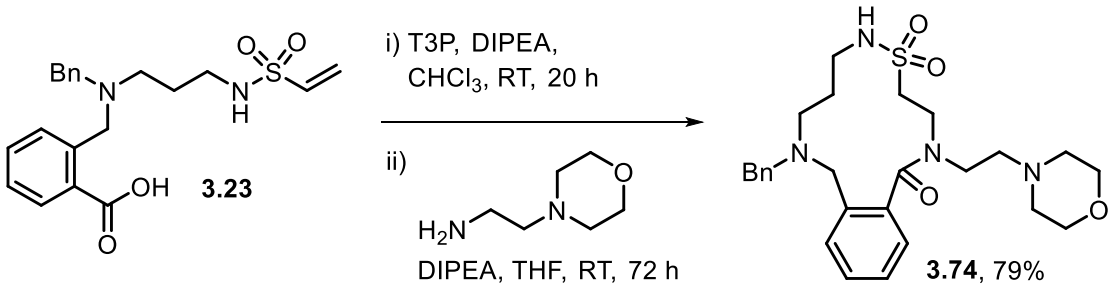
Following the completion of this series, attention moved to the benzoate-containing starting material **3.23** and the same conditions as above were applied for both the NICE and CARE steps. After the successful NICE reaction, forming the medium-sized ring, the CARE reactions for both were attempted and Scheme 130 shows the success of the first two attempts, however both in relatively low yields. Issues arose in the purification step that affected the yield where it appeared there was product degradation by the silica of the column. Basic doping on the column was also attempted with triethylamine as part of the solvent to aid

the product's elution and minimise unwanted stationary phase interactions, but there was no change in results.



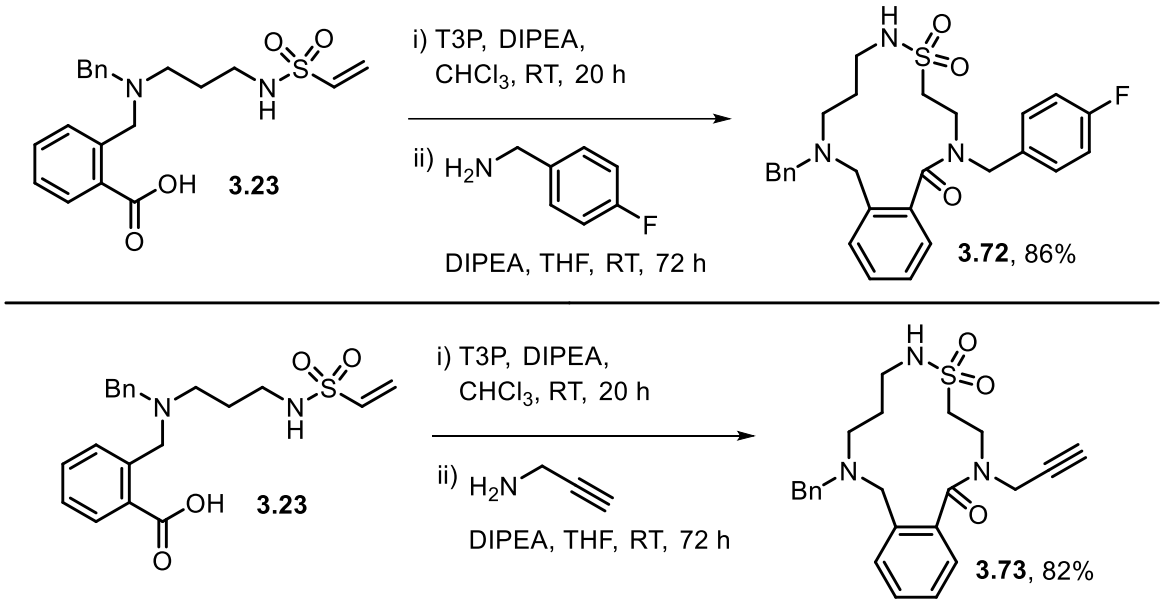
Scheme 130. Low-yielding CARE reactions with two amine reagents.

For the third example tested, a workup was added to the protocol following the CARE step, using aq. sodium bicarbonate solution and extracting with DCM. The first attempt was unsuccessful due to the product containing inseparable triethylamine salt generated in the reaction. Therefore, DIPEA replaced triethylamine as the base and pleasingly this led to a significant improvement, with **3.74** isolated in 79% yield (Scheme 131).



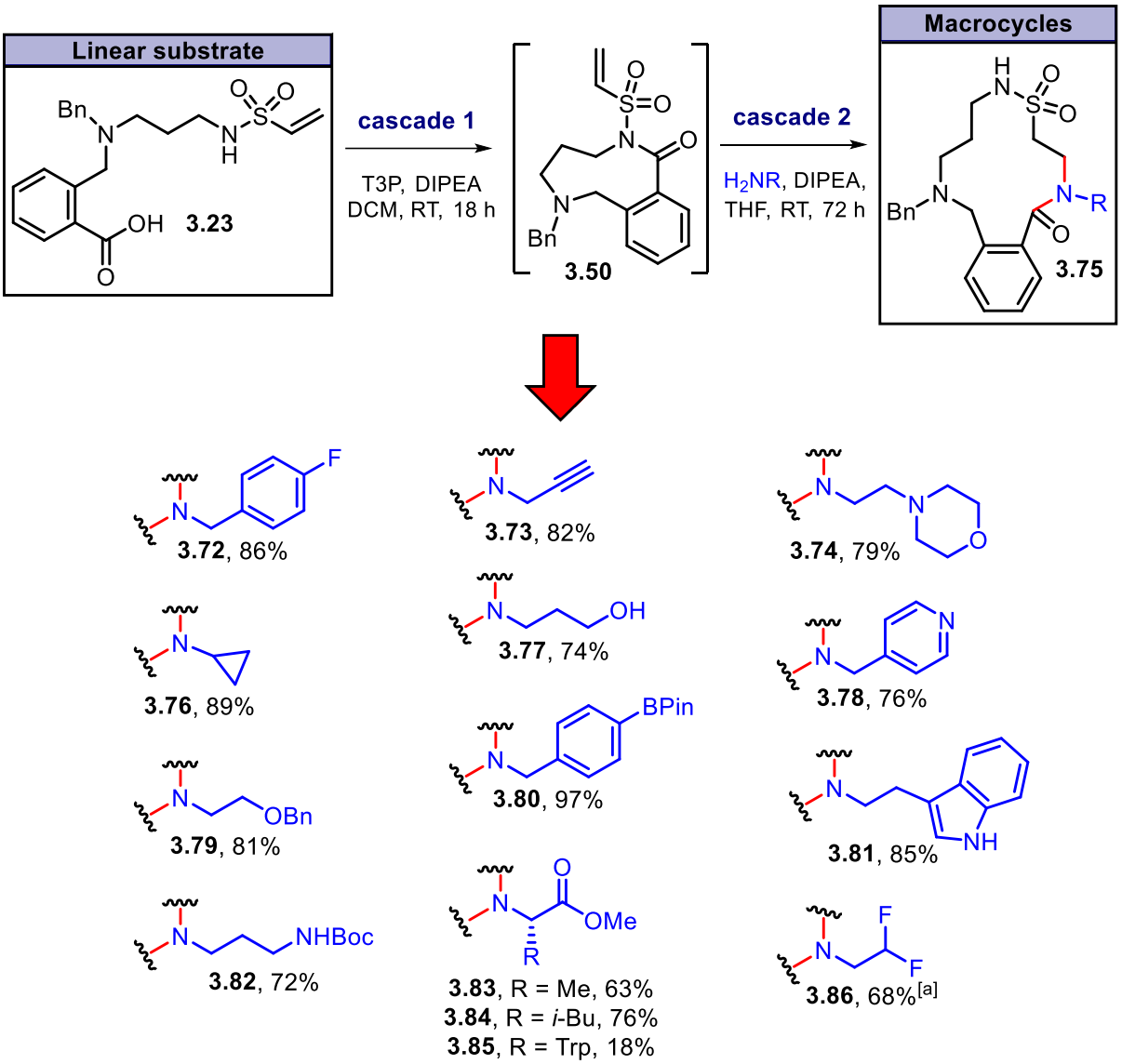
Scheme 131. The optimised, high-yielding reaction conditions used to form **3.74**.

The NICE and CARE reactions to synthesise **3.72** and **3.73** were repeated using the modified protocol, with a workup added, and in both cases the macrocycle formed in yields over 80%, when previously they were under 30%. This was a clear indicator that purification by a workup was superior, hence this method was followed for the remaining examples in this, and future, series (Scheme 132).



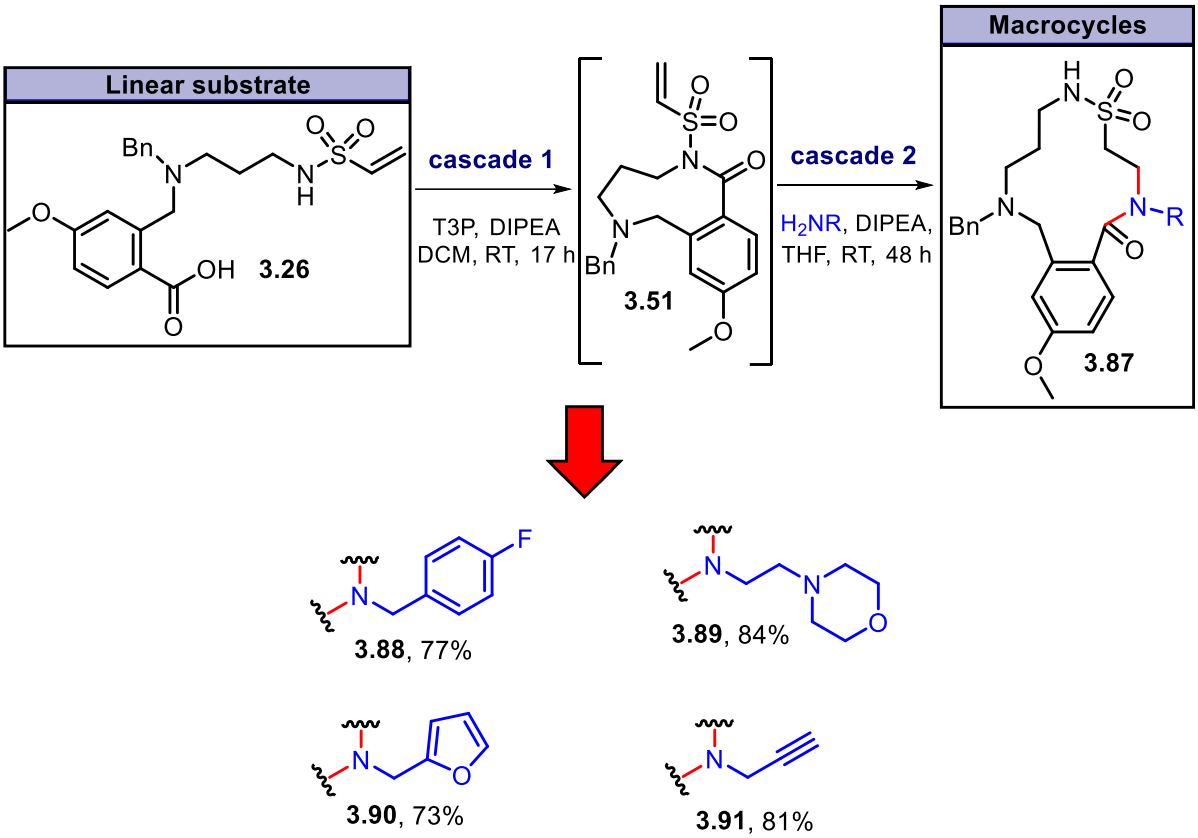
Scheme 132. The optimised CARE reactions with the previous two amine reagents.

With a high-yielding protocol established, more examples were tested using other amines in the CARE step, with a total of 14 ring-expanded macrocycles synthesised, all shown in Scheme 133. An outlier in terms of yield was **3.85** (the reaction using tryptophan methyl ester); this was due to column chromatography being needed for its purification – after the workup it still contained some of the amine reagent – and this significantly reduced the yield to 18%.



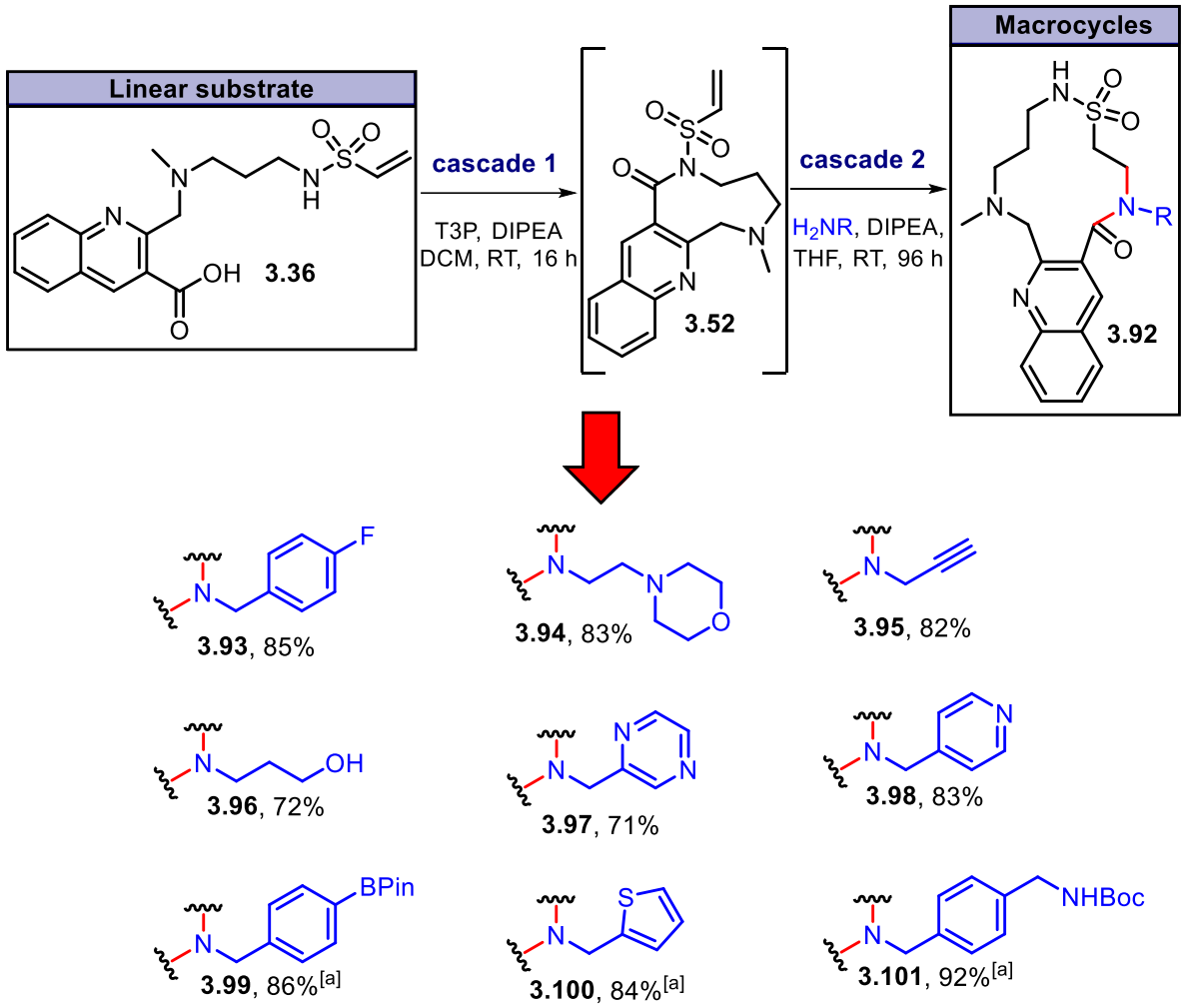
Scheme 133. The macrocyclic products formed by the NICE and CARE reactions from starting material **3.23**. [a] Stirred for 168 hours.

The analogous series using starting material **3.26** (a substrate containing a methoxy group on the benzoate group) was also successful. Four examples were completed in yields ranging from 73–84% (Scheme 134). Similarly to the previous substrates, a column was avoided for purification and only a workup was done with aq. sodium bicarbonate solution and DCM. This was sufficient to isolate the products in high purity.



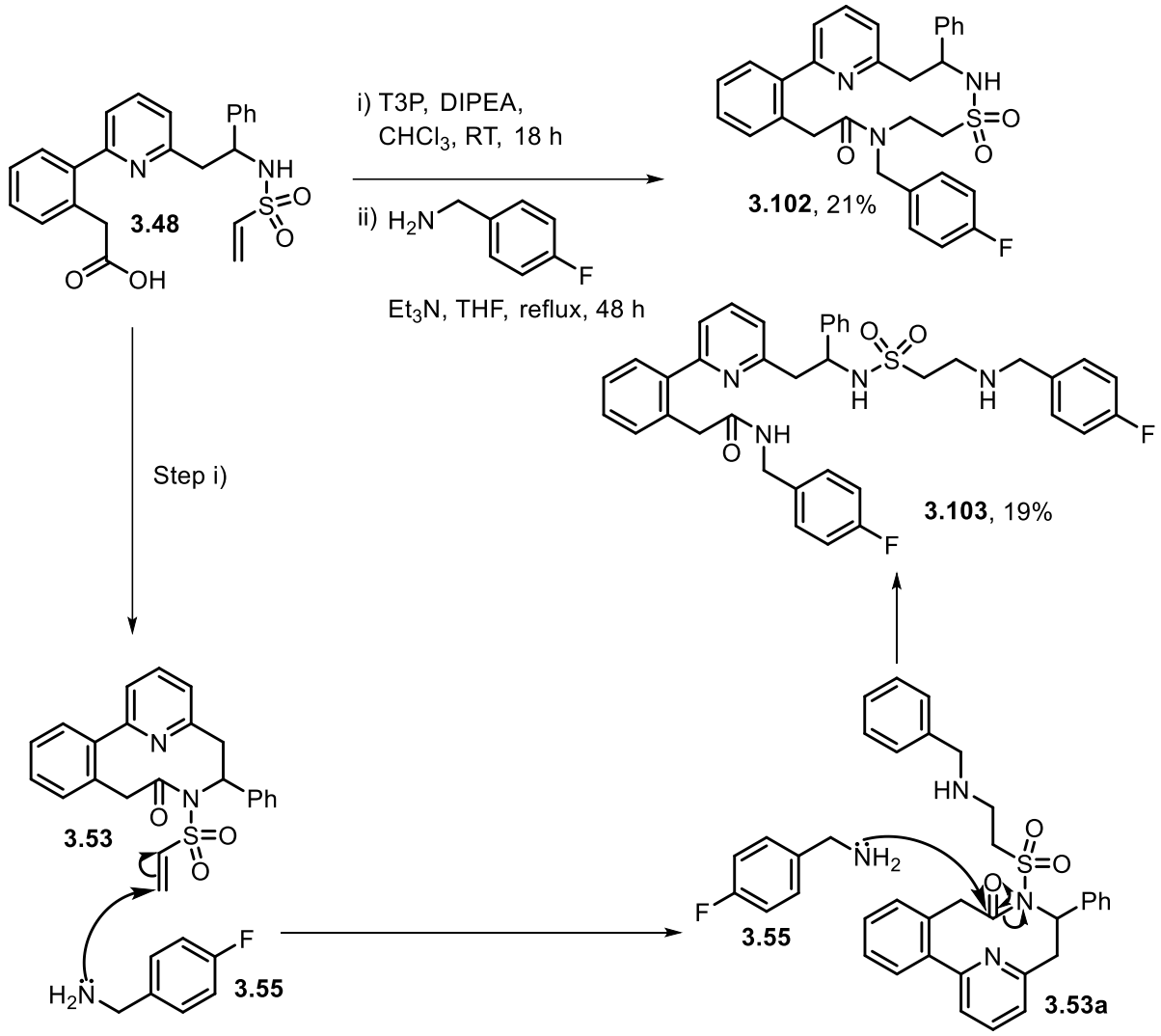
Scheme 134. The macrocyclic products formed by the NICE and CARE reactions from starting material **3.26**.

The quinoline series was attempted next and these reactions worked well, all proceeding in good yields, with the lowest yielding case being **3.97** at 71% (Scheme 135). The three examples on the bottom row were successful but featured a small amount of the primary amine reagent as a minor impurity (see Experimental for full details).



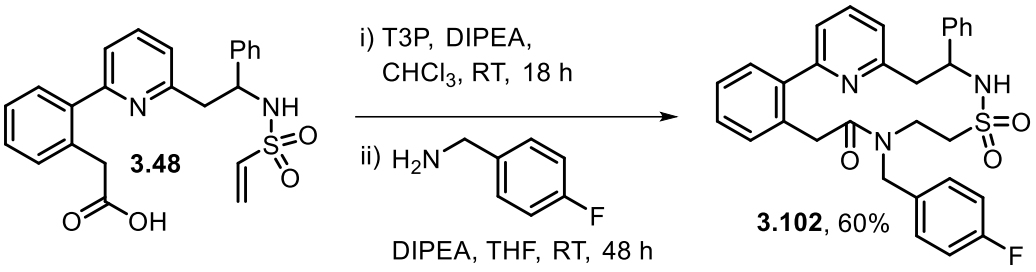
Scheme 135. The macrocyclic products formed by the NICE and CARE reactions from starting material **3.36**. [a] Also contains a small amount of the amine reagent.

The final series was the pyridine-containing compound **3.48**. The NICE reaction was completed and a CARE reaction with 4-fluorobenzylamine was attempted. Due to having a more fundamentally different structure to the previous examples, the original reaction conditions of using triethylamine at reflux were first attempted, including utilising a column for its purification (Scheme 136). An additional compound was identified in an almost 1:1 ratio with the desired product, **3.102**. The side-product, **3.103**, seemed to form *via* a double addition of the amine – one *via* the expected conjugate addition at the vinyl position, but another at the amide carbonyl to promote ring-opening.



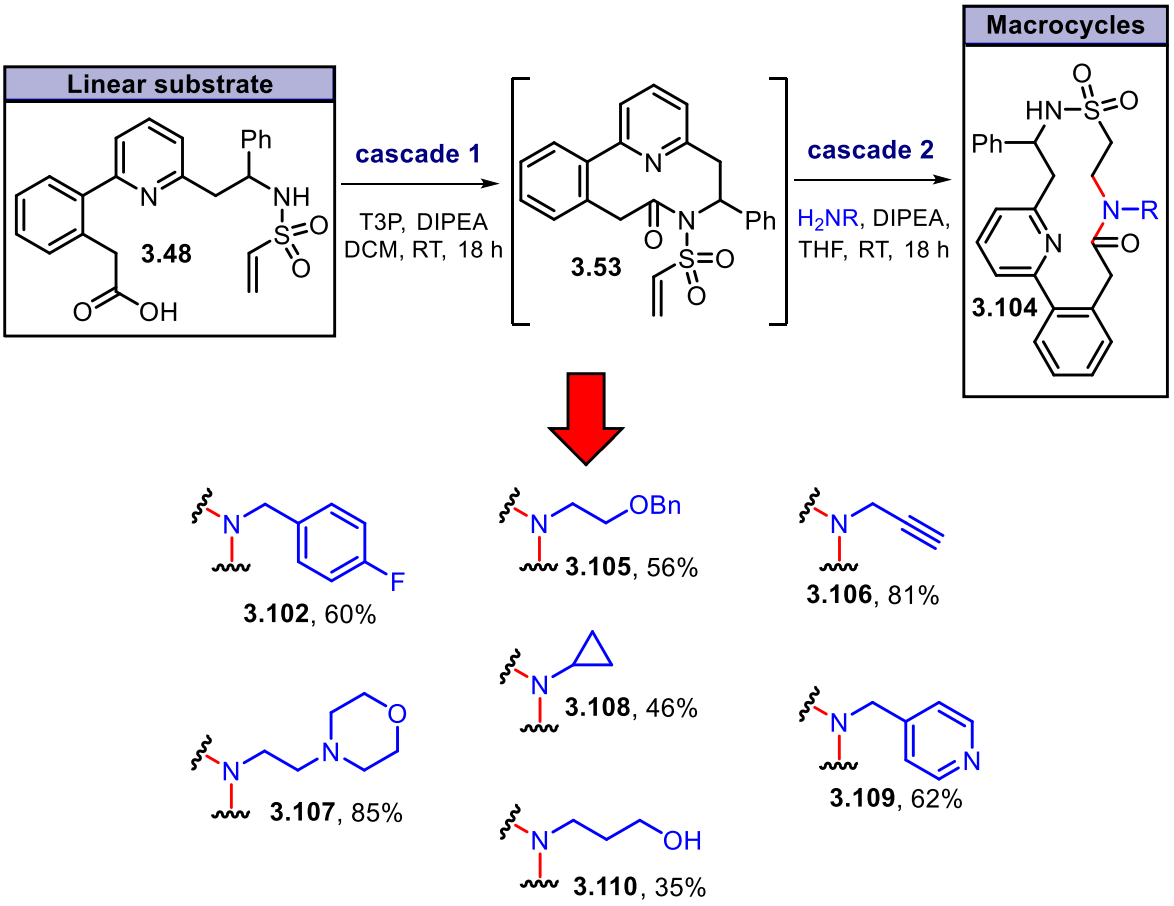
Scheme 136. The NICE and partially successful CARE reaction with 4-fluorobenzylamine to form **3.102** and side-product **3.103**.

It was assumed the harsher, refluxing conditions used for the CARE step may have contributed to the generation of **3.103**. Therefore, the reaction was repeated as shown in Scheme 137, switching back to using DIPEA as the base and performing the CARE step at room temperature (whilst maintaining the use of a column for purification). Pleasingly, this led to an increase in the yield of the desired product, **3.102**, and avoided formation of side-product **3.103**.



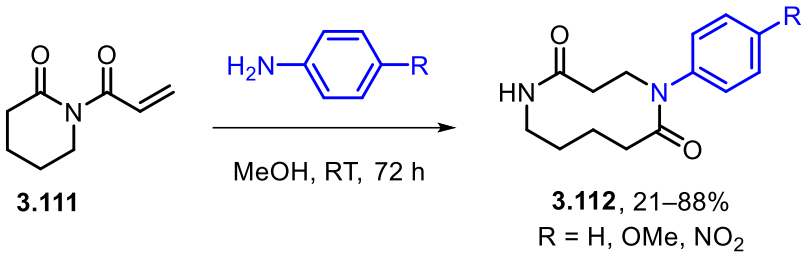
Scheme 137. The optimised NICE and CARE reaction with 4-fluorobenzylamine.

A number of different amines were trialled for the CARE step in this series, with the results summarised in Scheme 138. During their syntheses, some examples showed a trace amount of the double addition product (analogous to **3.103** in Scheme 136), observable by mass spectrometry as a low intensity molecular ion peak. However, the double addition product could not be isolated or identified by NMR analysis.



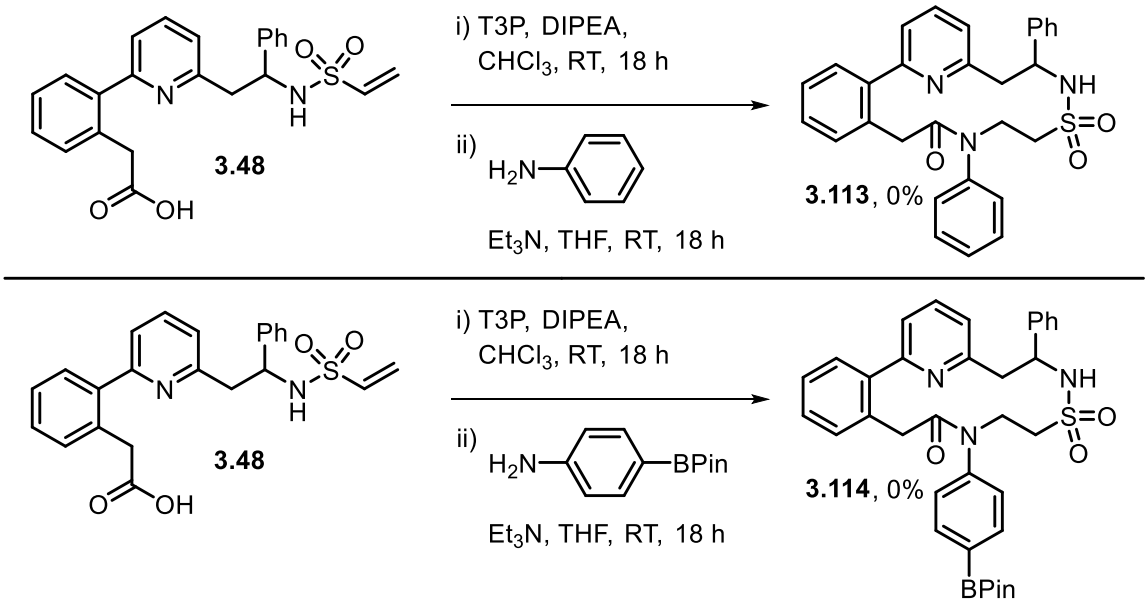
Scheme 138. The macrocyclic products formed by the NICE and CARE reactions from starting material **3.48**.

The success of these reaction sequences prompted attempts using less well studied amines for the CARE step. Reactions using anilines have been demonstrated in the group's published study in 2022, with CARE taking place with imide **3.111** on different anilines to form lactams in the form of **3.112** (Scheme 139).[106]



Scheme 139. The successful CARE reactions completed with aniline derivatives by Unsworth and co-workers.[106]

Two aniline-containing examples were attempted (Scheme 140). Unfortunately, neither were successful and no side-products were recovered from the reaction. The lower nucleophilicity of the aniline nucleophiles compared with the successful aliphatic amine examples likely accounts for the difference in reactivity.

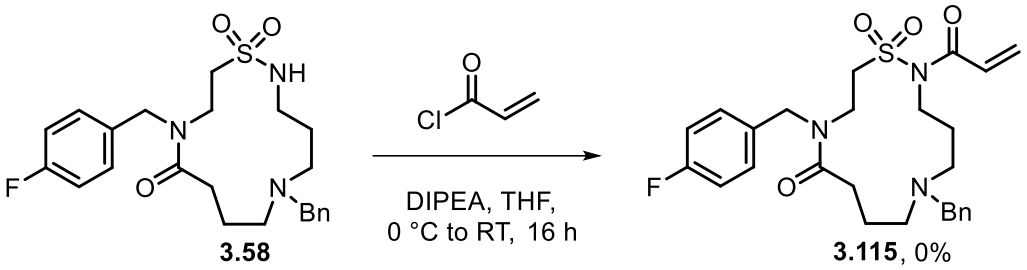


Scheme 140. The unsuccessful CARE reactions with two aniline derivatives.

3.5 Additional Reaction Attempts on the Macrocyclic Products after CARE

Next, attention turned to exploring whether the macrocycles prepared in section 3.4 might be suitable substrates to undergo a second CARE reaction, to enable further ring expansion. As was mentioned in Chapter 2, consecutive CARE reactions have been demonstrated in the group before[106,173] and there was interest to see if this idea could be applied to this project on the macrocyclic library that had been built up.

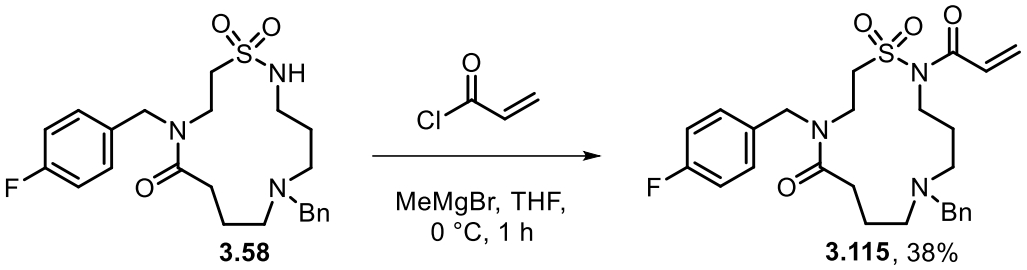
An initial *N*-acylation was needed to provide a position for conjugate addition to take place. The first method tested DIPEA as the base with acryloyl chloride and THF (Scheme 141) but unfortunately, this was unsuccessful, with macrocycle **3.58** unreacted.



3.58 **3.115**, 0%

Scheme 141. Failed *N*-acylation reaction on macrocycle **3.58** with DIPEA.

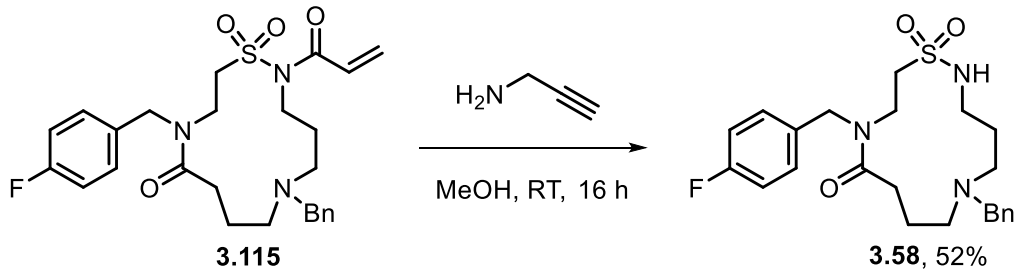
The second attempt replaced DIPEA with methyl magnesium bromide and it was left to stir for an hour at 0 °C (Scheme 142). Usually this Grignard-based method performs poorly for more complex systems, but pleasingly there was success in this instance and the acylated macrocycle **3.115** formed in a 38% yield.



3.58 **3.115**, 38%

Scheme 142. Successful *N*-acylation reaction on macrocycle **3.58** with MeMgBr.

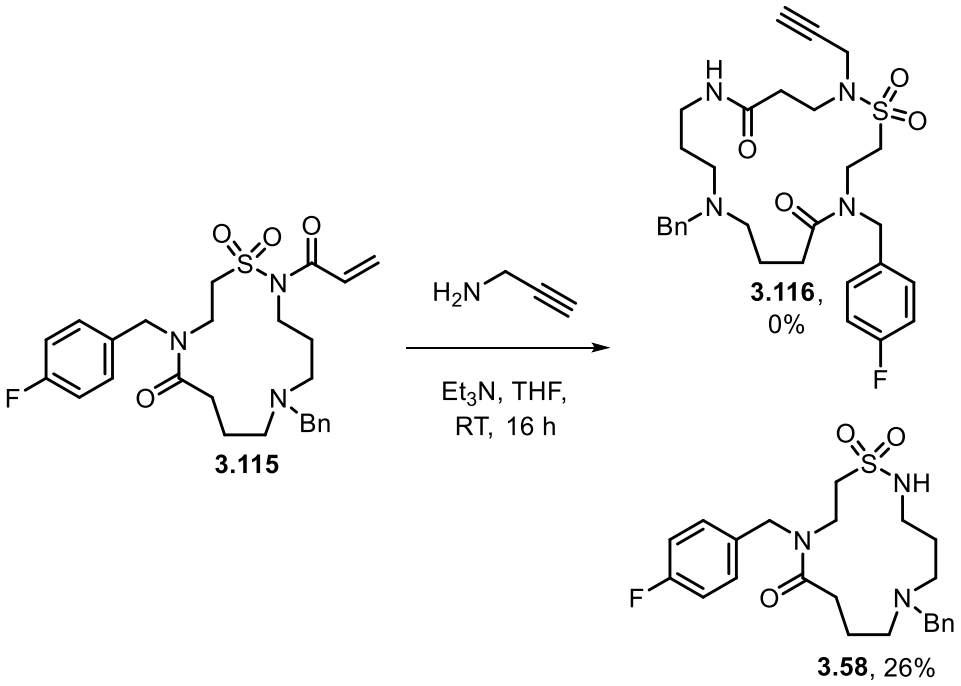
Then, the ring expansion step was attempted, first with methanol used as the solvent and using propargylamine as the amine nucleophile (Scheme 143). This reaction was unsuccessful, with the major product being the de-acylated starting material, **3.58**, formed in 52% yield. This presumably formed *via* attack of either the amine or methanol at the exocyclic carbonyl to cleave the acryloyl group and give **3.58**.



3.115 **3.58**, 52%

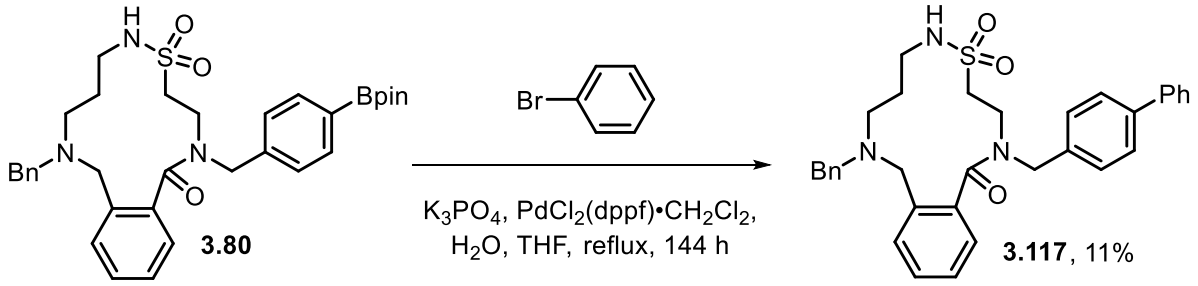
Scheme 143. The unsuccessful consecutive CARE reaction with methanol.

This prompted a change to using THF as the solvent and triethylamine as the base (Scheme 144). This showed more potential, with mass spectrometry data indicating a significant molecular ion peak of a mass consistent with the formation of **3.116**. However, after purification, the 17-membered macrocycle **3.116** could not be isolated and only **3.58** was isolated. In the future, this pathway could be revisited, but this was not continued in this project.



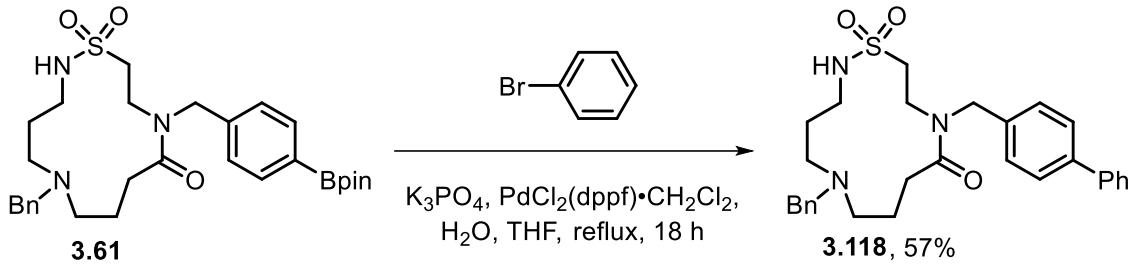
Scheme 144. The unsuccessful consecutive CARE reaction with triethylamine and THF.

Amongst the macrocycles synthesised in this chapter, there were some that contained a Bpin group. Therefore, there was potential to use this functionality for a subsequent Suzuki cross-coupling reaction. This was done with success using macrocycle **3.80**, reacting with bromobenzene as denoted in Scheme 145. The yield was poor and due to a limited amount of **3.80**, the reaction could not be repeated using different reaction conditions. It is likely that the yield could be improved with optimisation.



Scheme 145. Successful Suzuki cross-coupling on macrocycle **3.80**.

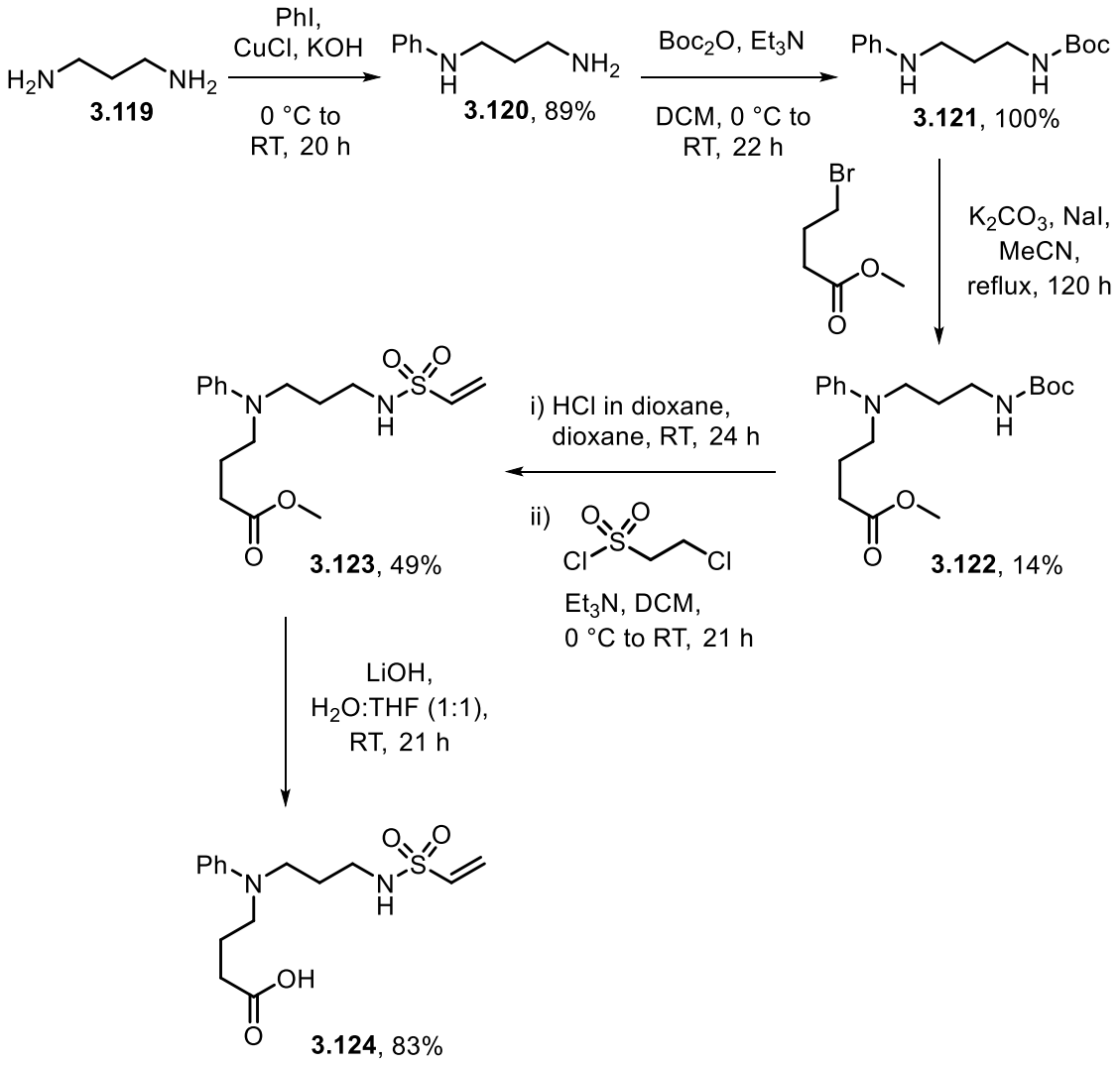
Another member of the Unsworth group (Ben Knapper) also attempted a similar reaction, using macrocycle **3.61** (Scheme 146). In this case, an improved yield of 57% was obtained.



Scheme 146. Successful Suzuki cross-coupling on macrocycle **3.61** by another member of the Unsworth group.

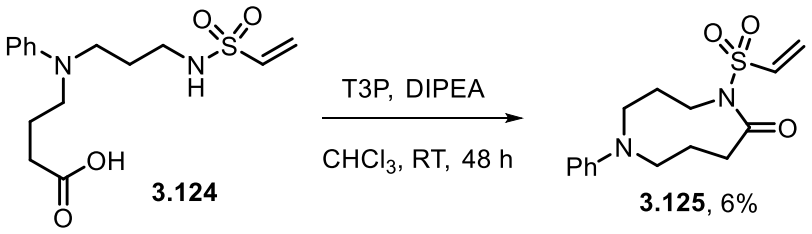
3.6 Unsuccessful Reaction Attempts with Other Starting Material Frameworks

There were several other frameworks that were attempted but did not proceed as planned. First, was an example that replaced the *N*-benzyl group of **3.20** with an aniline as the internal nucleophile. This starting material required a modified synthetic pathway (Scheme 147), that involved a phenylation[181] and Boc protection. The reduced nucleophilicity of anilines compared to aliphatic amines could account for the low yield of **3.122** in this example – however there have been instances in the group where this has not been an issue.[126] Familiar steps of a deprotection, sulfonylation and hydrolysis then followed to give the final starting material framework, **3.124**.



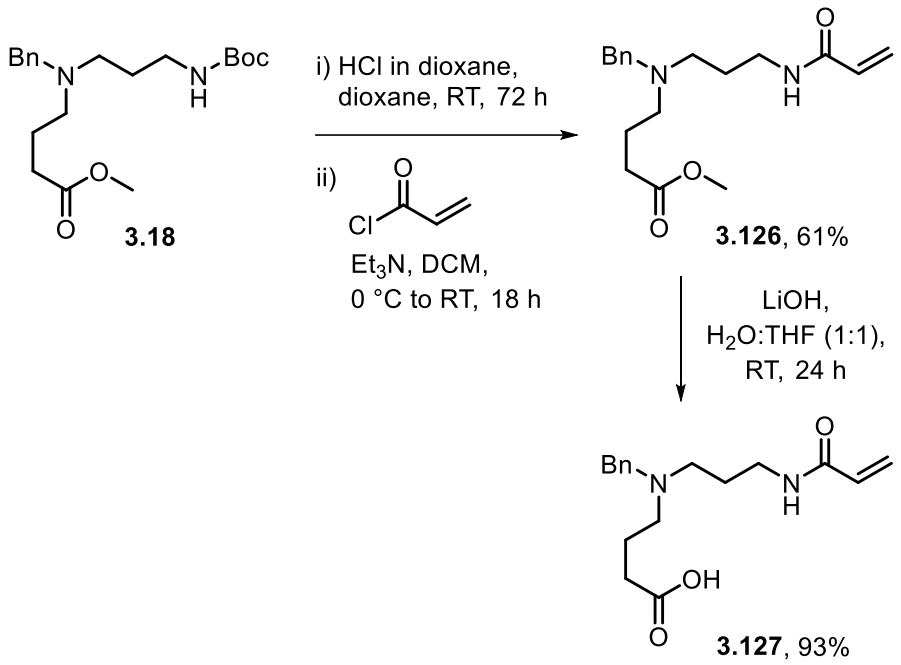
Scheme 147. The reaction pathway from the diamine to form starting material framework, **3.124**.

Partial success was achieved with the NICE step (Scheme 148), albeit with a very low yield achieved. Some starting material, **3.124**, was also recovered, along with the methyl ester, **3.123**, in a combined yield of 13%, likely due to the ring-opening mechanism previously explained once **3.125** had formed. Initially the yield for the NICE product was probably higher than 6%, before the ring-opening side reaction occurred to reduce it. Due to this low yield of **3.125** and **3.122** earlier in the pathway, it was decided not to investigate this series further.



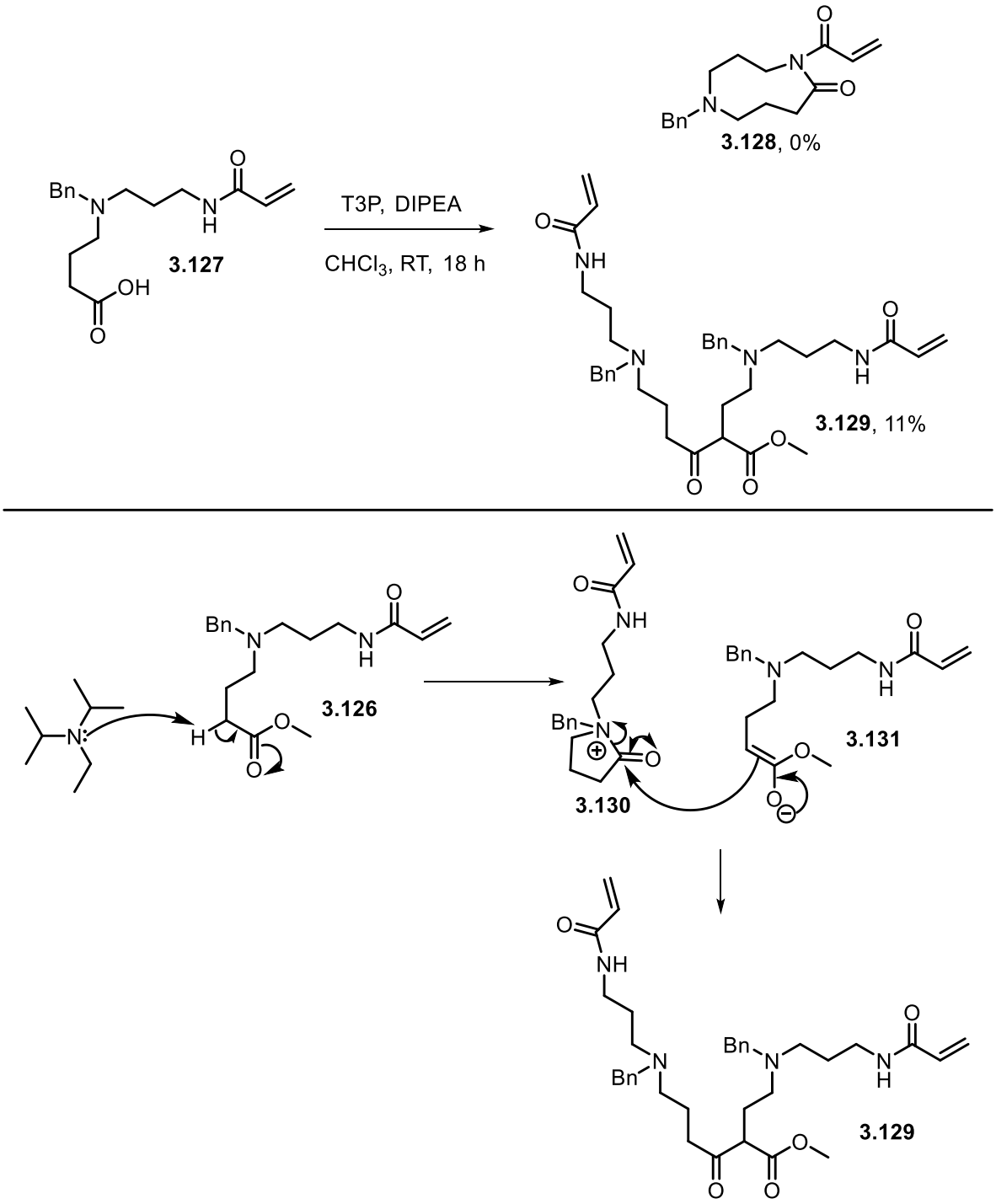
Scheme 148. Low-yielding NICE reaction with **3.124**.

Another attempt involved a deviation from the vinyl sulfonamide that has been used in all previous examples – in its place was a vinyl amide, a system utilised extensively within the group for CARE reactions (Scheme 149).[106,173] The only change made to the synthesis in this case was after the Boc deprotection, where instead of 2-chloroethanesulfonyl chloride, acryloyl chloride is utilised to generate the vinyl amide at the terminal position.



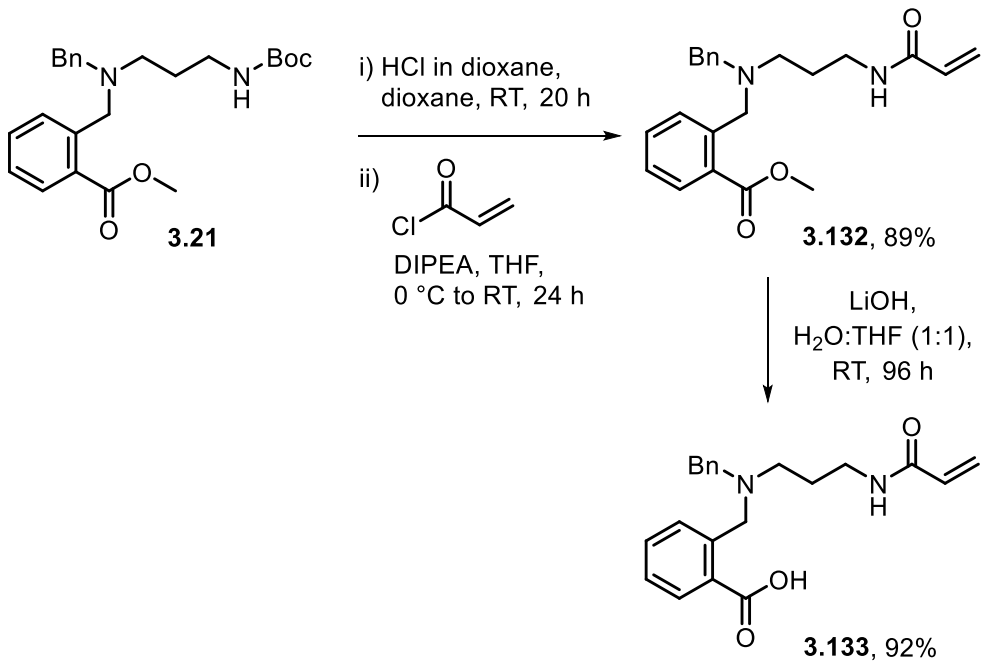
Scheme 149. The reaction pathway starting from the previously synthesised ester to the starting material framework, **3.127**.

With **3.127** in hand, a NICE reaction was attempted with the usual conditions of T3P and DIPEA, but unfortunately the desired product **3.128** was not obtained, and side-product **3.129** formed instead (Scheme 150). The starting material is proposed to first be methylated to produce **3.126**, before then being deprotonated at the α-position to the carbonyl, allowing the creation of its enol product, **3.131**. This can then attack an activated form of the molecule (either through the formation of its 5-membered intermediate or through the coupling to T3P). This process creates the ketone and extended framework we see in the product. An additional attempt to perform the same reaction at reflux formed a complex mixture of unknown products.



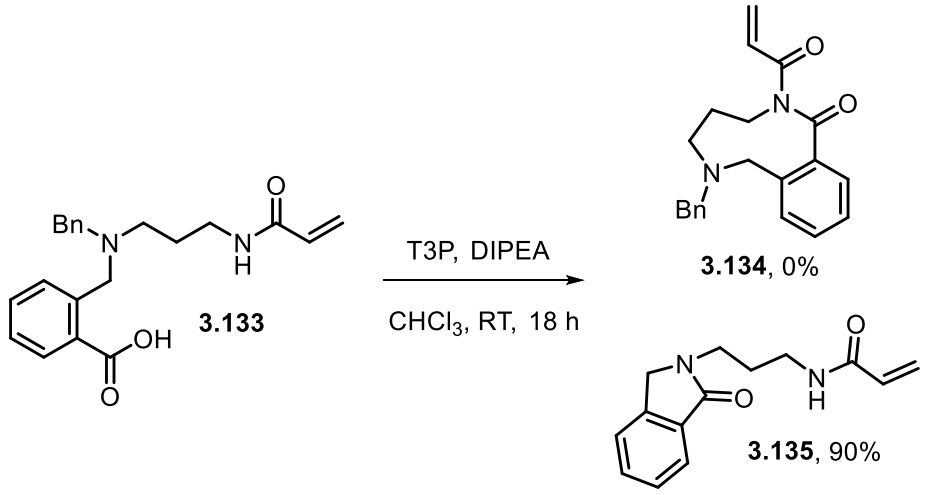
Scheme 150. Unsuccessful NICE reaction with the proposed mechanism for side-product **3.129** shown.

The unexpected side-product formed in Scheme 150 meant an analogous compound was chosen that lacks the enolisable position needed to allow the unwanted dimerisation. This route in Scheme 151 started with compound **3.21** and followed the same steps as previous to form carboxylic acid **3.133**.



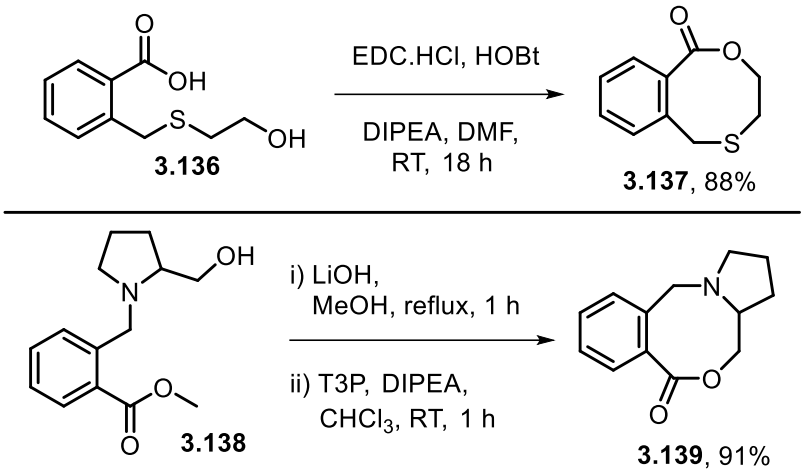
Scheme 151. The reaction pathway starting from the previously synthesised ester to the starting material framework, **3.133**.

Unfortunately, the NICE step was unsuccessful again and it appeared that only the attack of the internal nucleophile was able to occur. The benzyl group was also cleaved, leaving the normal-sized ring **3.135** as the major product in a 90% yield (Scheme 152). Heating of this side-product was also attempted to try and force the reaction to progress as desired but after a day of stirring, there was no change. From these results, it was assumed that the terminal vinyl amide attached was too weak a nucleophile to complete the final step in the NICE cascade, compared to a vinyl sulfonamide.



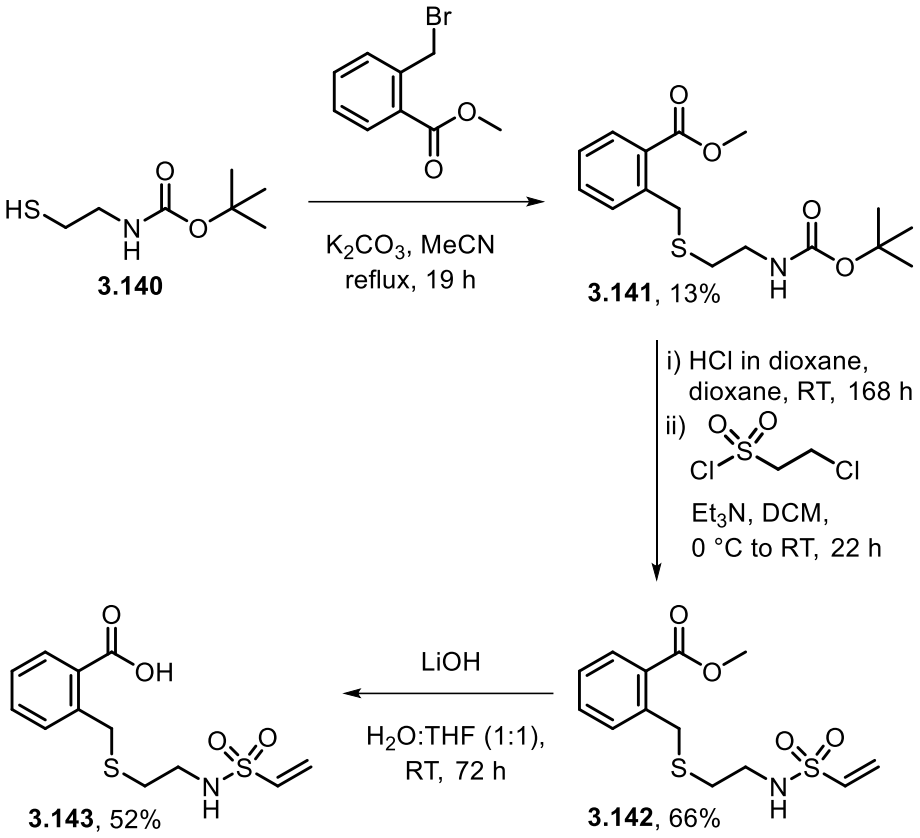
Scheme 152. Unsuccessful NICE reaction with side-product **3.135** shown.

Other vinyl sulfonamide containing starting materials based on frameworks used and published previously in the Unsworth group were also explored (Scheme 153). The effectiveness of both literature NICE reactions gave encouragement that similar substrates could be synthesised that included the necessary vinyl sulfonamide for the subsequent CARE.



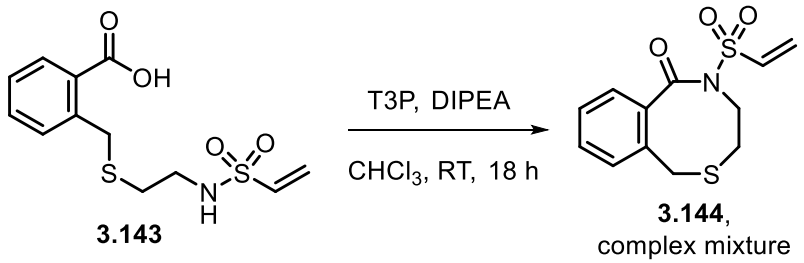
Scheme 153. Two literature NICE reactions forming the medium-sized rings.

Starting with the thioether-containing compound, the usual synthesis pathway was employed to give carboxylic acid **3.143** (Scheme 154).



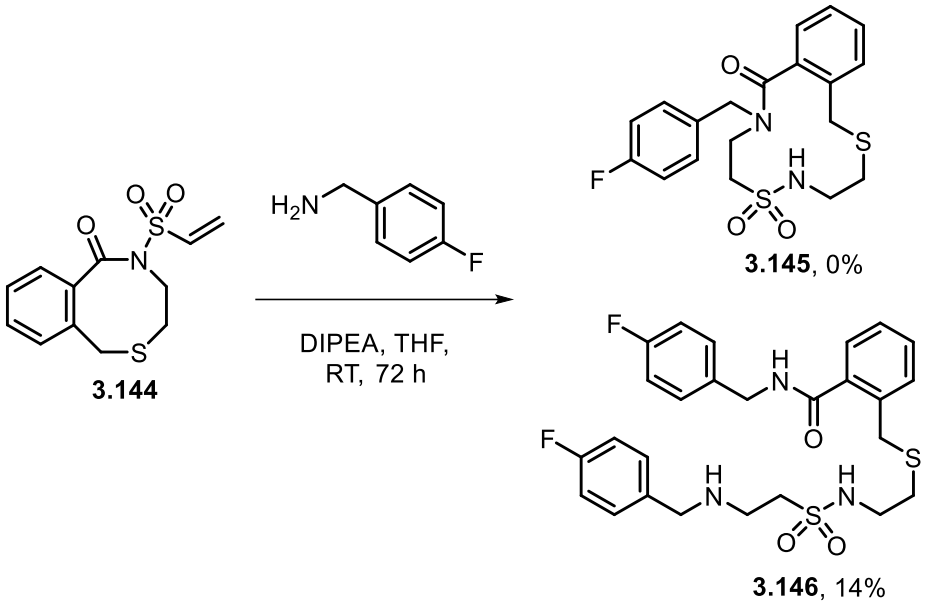
Scheme 154. The reaction pathway from the thiol to form starting material framework, **3.143**.

The NICE reaction was then attempted in Scheme 155, and the reaction appeared to be successful by mass spectrometry (product mass identified) but analysis by ^{1}H NMR spectroscopy was difficult with only the three diagnostic alkene peaks in the region of 5.5–7.0 ppm being able to be reliably identified in the spectrum from a complex mixture.



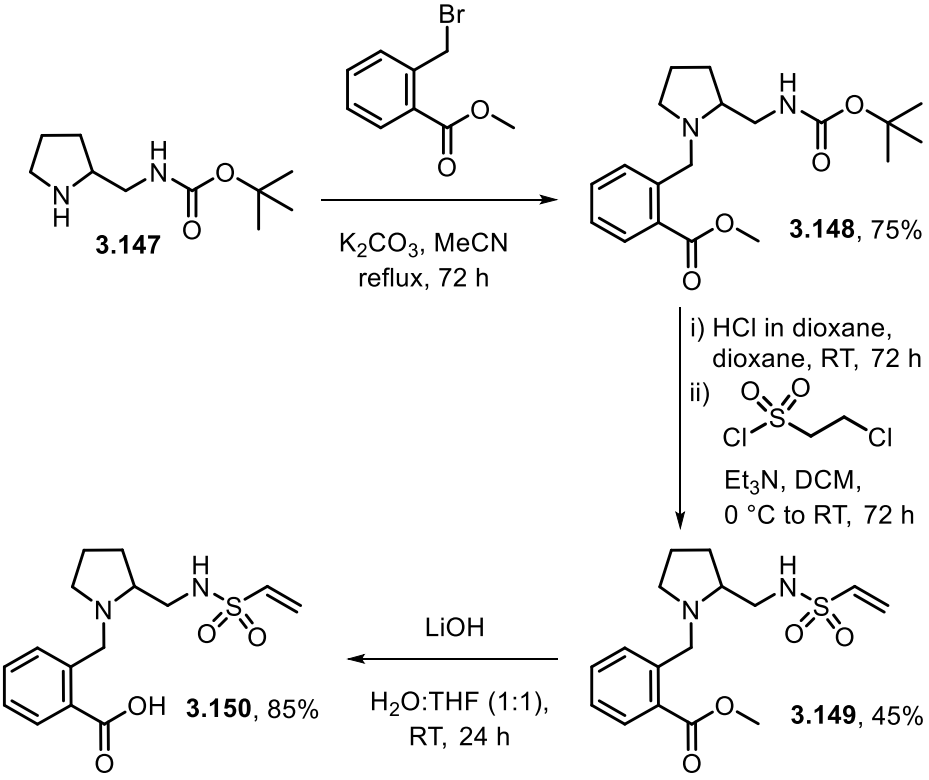
Scheme 155. Partially successful NICE reaction with **3.143**.

Therefore, the impure product from this reaction was immediately taken forward to do the CARE step with 4-fluorobenzylamine (Scheme 156). Unfortunately, this was unsuccessful and only the double addition side-product, **3.146**, was formed in a yield of 14%. This indicated the conjugate addition worked but then an additional amine caused a ring opening at the amide bond to give **3.146**.



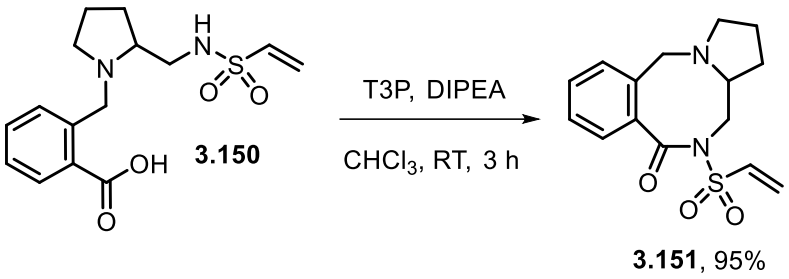
Scheme 156. The unsuccessful CARE reaction with 4-fluorobenzylamine to form side-product **3.146**.

The second example from Scheme 153 depicted the use of a pyrrolidine-containing framework and so this was created through the synthesis pathway shown in Scheme 157 to form carboxylic acid **3.150**.



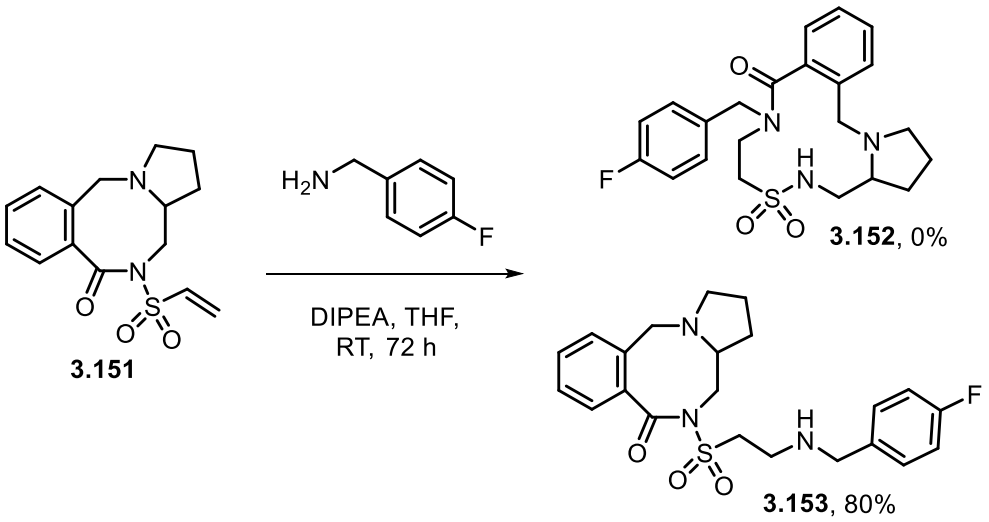
Scheme 157. The reaction pathway from the protected diamine to form starting material framework, **3.150**.

On this occasion, the NICE reaction was successful and product **3.151** was formed in high yield (Scheme 158).



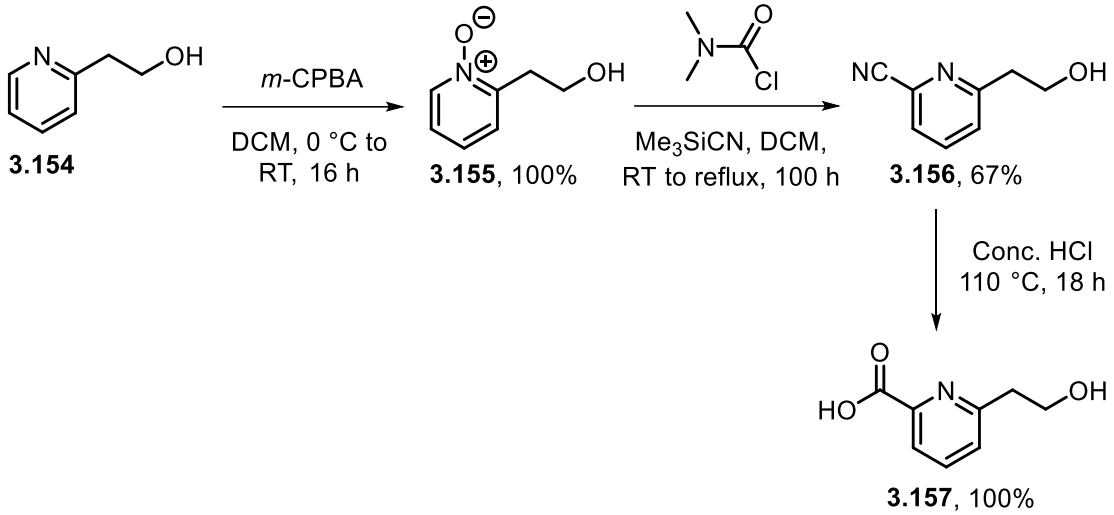
Scheme 158. Successful NICE reaction with **3.150**.

Unfortunately, a similar problem was encountered where **3.151** underwent the conjugate addition but was unable to complete the ring expansion step, affording **3.153** (Scheme 159). To encourage further reaction, compound **3.153** was re-dissolved in THF and heated to reflux for a further four hours. The increased temperature was unable to promote the ring expansion and the conjugate addition product **3.153** was recovered without change.



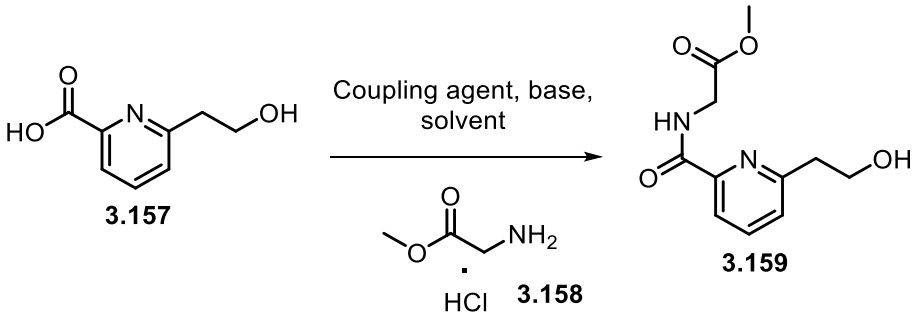
Scheme 159. The unsuccessful CARE reaction with 4-fluorobenzylamine to form side-product **3.153**.

There was interest in testing scaffolds with both a pyridine and an amino acid in the linear framework; if successful, it was hoped that this would allow a number of substrates from different amino acids to be prepared. Shown in Scheme 160, the first step in the pathway was an oxidation with *m*-CPBA,[182] followed by a nitrile addition at the 2-position of the pyridine group whilst also removing the *N*-oxide to give **3.156**.[183] After that, the hydrolysis of the cyanide group to a carboxylic acid was completed to form **3.157**.[184]



Scheme 160. The reaction pathway to form carboxylic acid **3.157**.

The next step involved the coupling of an amino acid onto the compound *via* the newly formed carboxylic acid. Table 2 at the bottom of this section shows the many reagents and reaction conditions trialled to find the optimum conditions for this amino acid coupling. All attempts in Table 2 were completed with glycine methyl ester hydrochloride (Scheme 161).



Scheme 161. General reaction scheme for the amino acid coupling with glycine methyl ester hydrochloride.

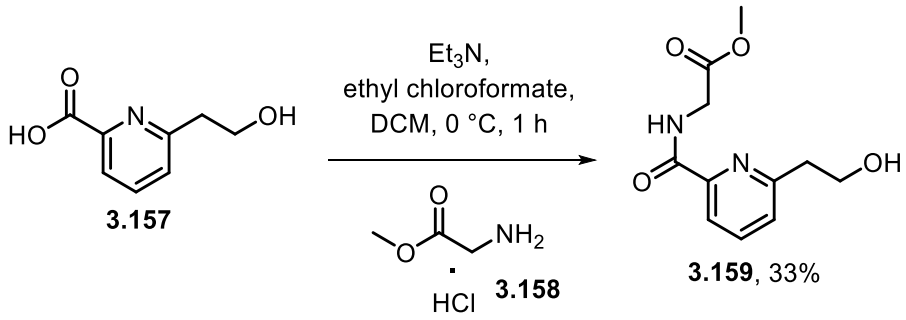
Entry 1 (using DCC and HOBt) was successful but there was coelution of the product with excess DCC and multiple purification attempts were unable to separate the two. Therefore, DCC was replaced with EDC in entry 2 and pleasingly this eliminated any coelution whilst also improving the yield from 14% to 23% – however it was felt the yield could still be improved.

Entry 3 and 4 moved away from carbodiimide coupling agents with T3P and HATU trialled. Unfortunately, both did not work with no **3.159** forming in either reaction. Both reactions consumed the starting material but did not generate any isolable product.

The remaining five entries focused on using ethyl chloroformate as the coupling agent in the reaction due to evidence of this compound being used in the literature for successful amino acid couplings with pyridine-containing compounds.[185] Table 2 shows success in each of

these entries to varying degrees, with the reaction time changes being the main alteration throughout – it was found that leaving the reaction for one hour was optimum (Scheme 162). Leaving it for less time reduced the product generation and a higher ratio of the starting material was recovered. Leaving the reaction for longer seemed to cause the formation of an unknown side-product that was not able to be identified by analysis. However, it was clear that the generation of this unknown side-product was directly linked to the use of ethyl chloroformate as before entry 5 it had never been present.

There were some issues with the solubility of **3.157** in DCM and so a final attempt with DMF (entry 9) was done. This clearly aided solubility but did not seem to help in improving the overall reaction. A final yield could not be quantified due to purification issues, but a crude yield was gathered that already indicated a maximum yield below the 33% yield of entry 5.

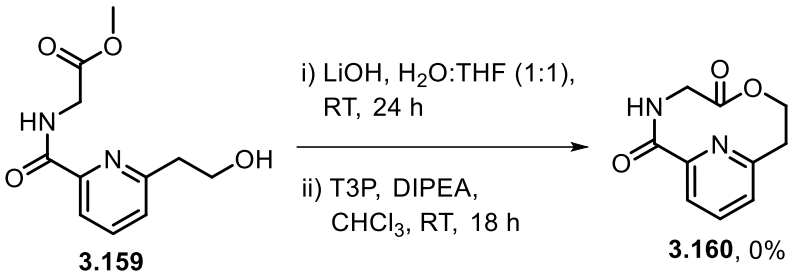


Scheme 162. Optimal reaction conditions for the amino acid coupling.

Entry	Base	Coupling agent	Solvent	Time (h)	Yield of 3.159 (%)
1	Et_3N	DCC + HOBt	DCM	24	14 (impure)
2	Et_3N	EDC + HOBt	DCM	1	23
3	DIPEA	T3P	Chloroform	24	0
4	DIPEA	HATU	DCM	3	0
5	Et_3N	Ethyl chloroformate	DCM	1	33
6	Et_3N	Ethyl chloroformate	DCM	24	20
7	Et_3N	Ethyl chloroformate	DCM	0.5	18
8	Et_3N	Ethyl chloroformate	DCM	3	25
9	Et_3N	Ethyl chloroformate	DMF	1	>33

Table 2 – Attempts to couple an amino acid onto the carboxylic acid of **3.157**.

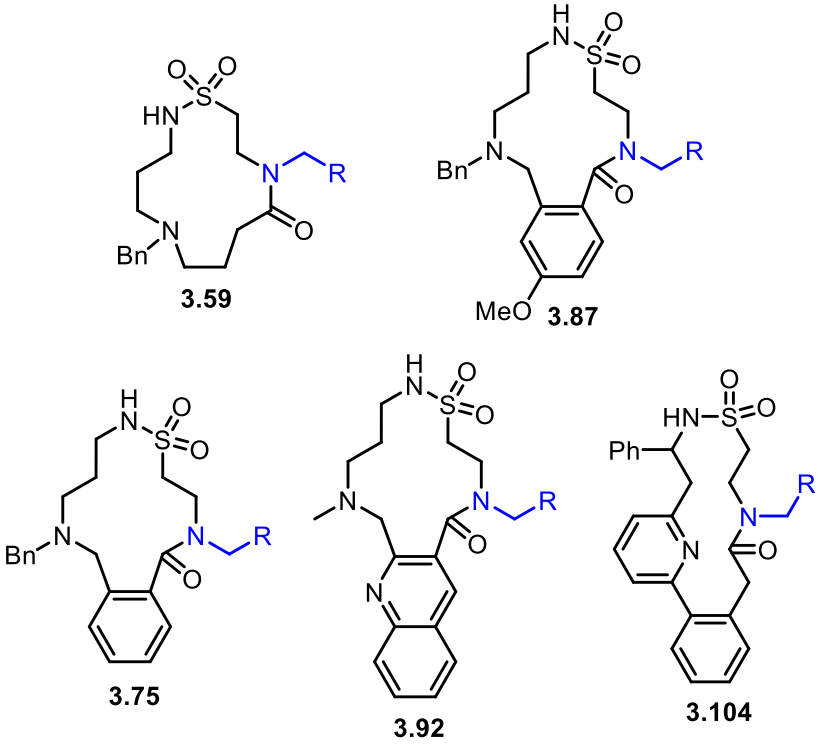
Using the product formed in the optimisation steps, a hydrolysis reaction was done on **3.159** to form the carboxylic acid (Scheme 163). This was successful but a significant impurity was also observed that was unable to be separated or identified during the purification process. Therefore, it was treated as a 2-step process and the NICE reaction immediately followed with the aim of getting an accurate yield after the formation of medium-sized ring **3.160**. Unfortunately, the standard conditions for the NICE reaction were ineffective. The impure carboxylic acid was poorly soluble in the chloroform solvent so this may have contributed to the failure. The data from this reaction was inconclusive, but it was clear the distinctive aryl peaks from the pyridine group were now absent, indicating the compound had undergone a form of degradation during the reaction. Another student in the Unsworth group (Kuanwei Chen) is currently working on optimising this series.



Scheme 163. Attempted hydrolysis and NICE reaction of the ester to form medium-sized ring **3.160**.

3.7 Conclusion

In conclusion, during this project a number of unique starting material frameworks were synthesised, before then undergoing the consecutive NICE and CARE reaction sequence (Scheme 164 shows their general macrocyclic structures). With these methods, a total of 46 novel macrocyclic substrates were generated in yields between 18–97%. The ability to vary the amine in the CARE step means that many more would be possible.



Scheme 164. The five macrocyclic scaffolds produced from the consecutive NICE and CARE reactions.

Some of the starting material frameworks were based upon analogous examples from the literature,[126] while the utilisation of a vinyl sulfonamide was inspired by other work from within the Unsworth group[117] and the combination of these two ideas allowed the formation of these novel macrocycles that further increased the library of rings in the group, many of which also contained medicinally relevant functional groups in their structures.

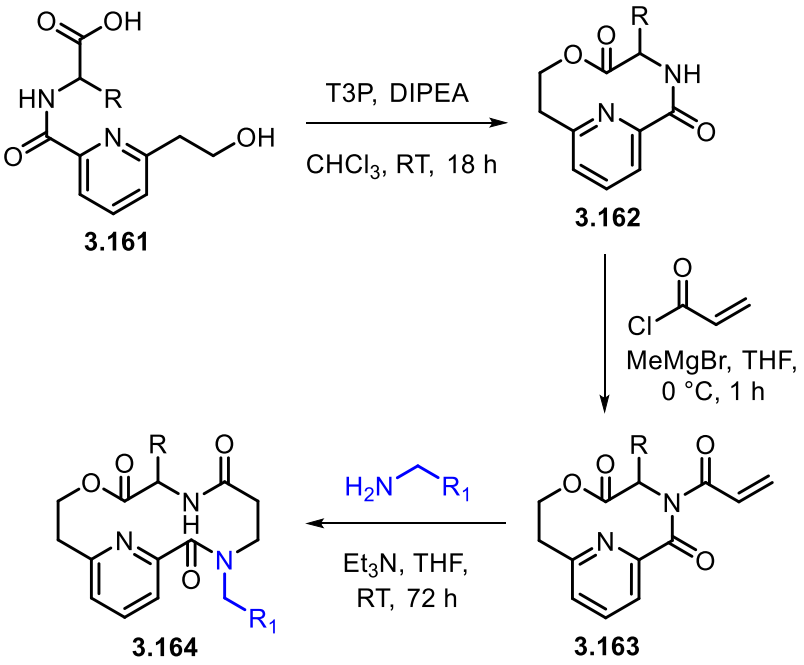
Section 3.6 summarises unsuccessful cases and highlights some limitations of the method. In some instances, it was found that the terminal nucleophile in the NICE step was not strong enough to instigate the final attack, leaving the molecule 'stuck' at the intermediate normal-sized ring. Often the failures would also occur due to some form of ring-opening, where the amide bond would get attacked by the solvent or primary amine during the CARE step.

The results described in this chapter are published in *Chemistry – A European Journal*.[186]

3.8 Future Work

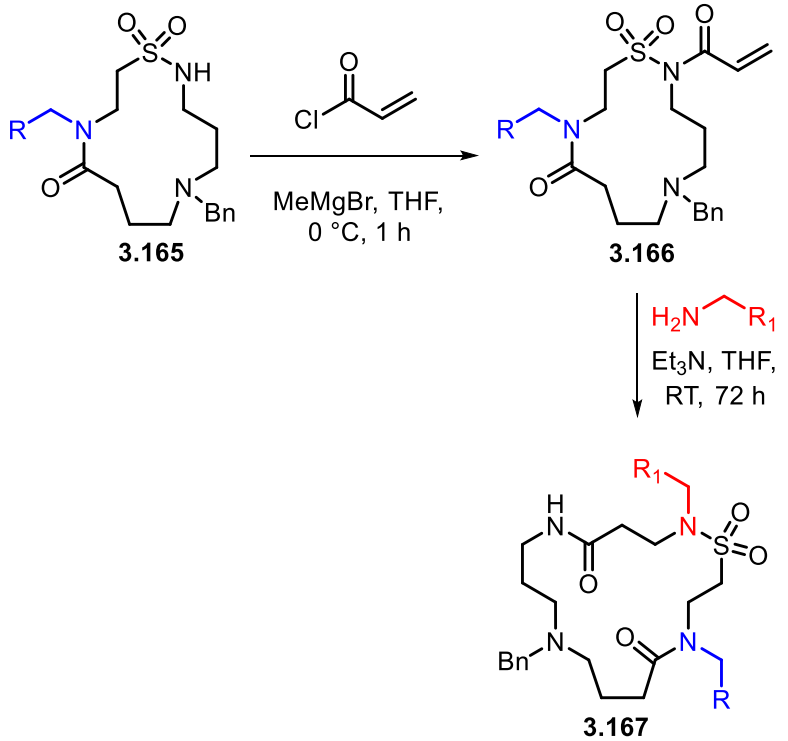
An easy continuation of this work would be to synthesise the same starting material frameworks and attempt some additional CARE reactions with the many different primary amines that are available commercially. Increasing the macrocyclic library within the group is always useful and of interest and this would be a quick and easy way of doing so. Similarly, minor changes to the starting material frameworks could also be made before then attempting the NICE and CARE reactions. Additions like the methoxy group in **3.87** are small but would allow another series of macrocycles to be made.

A specific example from this project that could be investigated further is shown below in Scheme 165. An impure sample of **3.161** (where R = H) had to be used previously for the NICE reaction and so repeating this pathway and ensuring pure **3.161** is obtained for the ring formation step could be crucial for its success. If a way to synthesise **3.164** was found, this could potentially lead to a huge number of substrates through the variation of the amine in CARE, but also the alteration of the amino acid being implemented into the system during the starting material synthesis.



Scheme 165. The pathway to form macrocycle **3.164** *via* NICE and CARE, with an amino acid contained in its structure.

Finally, with the macrocycles that have been produced, more work could go into exploring further *N*-acylation and CARE reactions. These substrates have shown capacity to be further acylated using acryloyl chloride (demonstrated in section 3.5), but more work is needed to optimise the CARE step in Scheme 166.

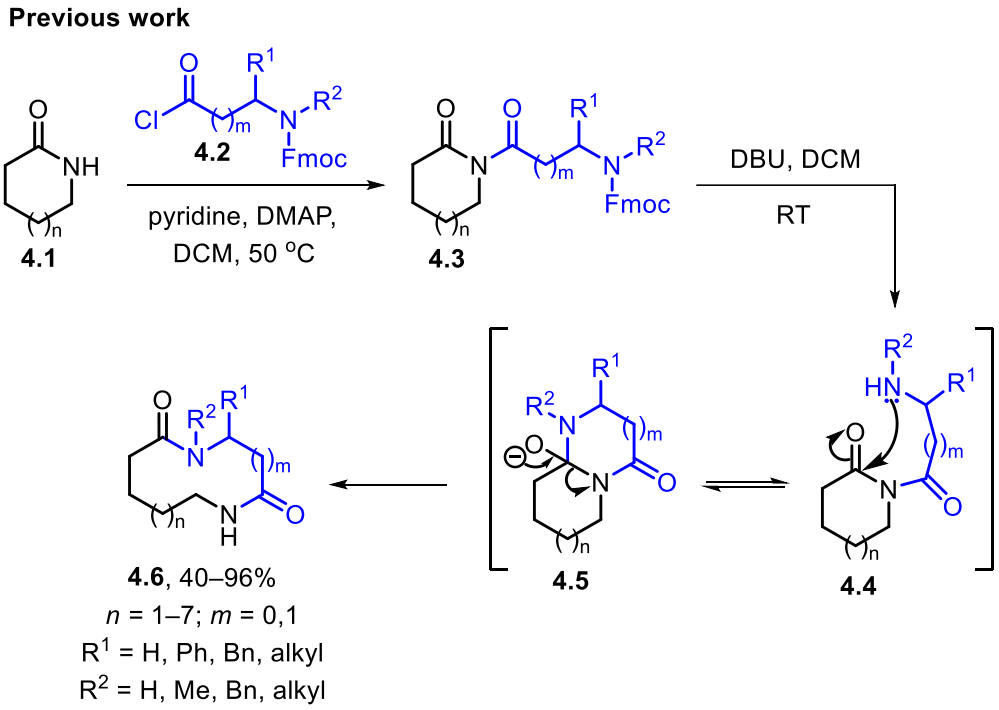


Scheme 166. The *N*-acylation and second CARE on macrocycle **3.165**.

4 Collaborative Work Focusing on Successive Ring Expansion Reactions to Create Medium-sized Rings and Macrocycles

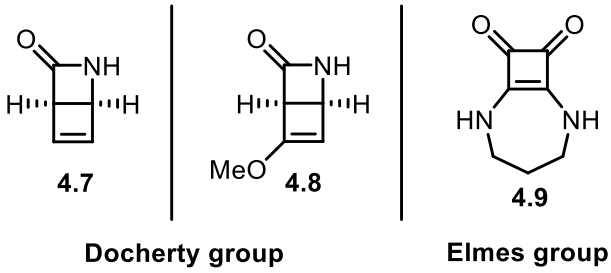
4.1 Chapter Aims

This chapter is focused on efforts to use ring expansion methods in different applied settings, through collaborations with other research groups. The majority of the work in this chapter is based on a third widely-used ring expansion technique developed within the Unsworth group – Successive Ring Expansion (SuRE). Before the work described in this chapter was started, a general procedure for SuRE was already established, based on the reaction of amino acid chlorides with lactams (Scheme 167).[21,187,188] SuRE can be used to prepare medium-sized rings and macrocycles through first an *N*-acylation of the lactam **4.1** with a protected acid chloride (like **4.2** in Scheme 167). Following this, cleavage of the amine protecting group (usually Fmoc, cleaved under basic conditions) allows a subsequent ring expansion, *via* intermediates **4.4** and **4.5**, to form the ring-expanded product, **4.6**.



Scheme 167. A summary of the previous work on SuRE by the Unsworth group.

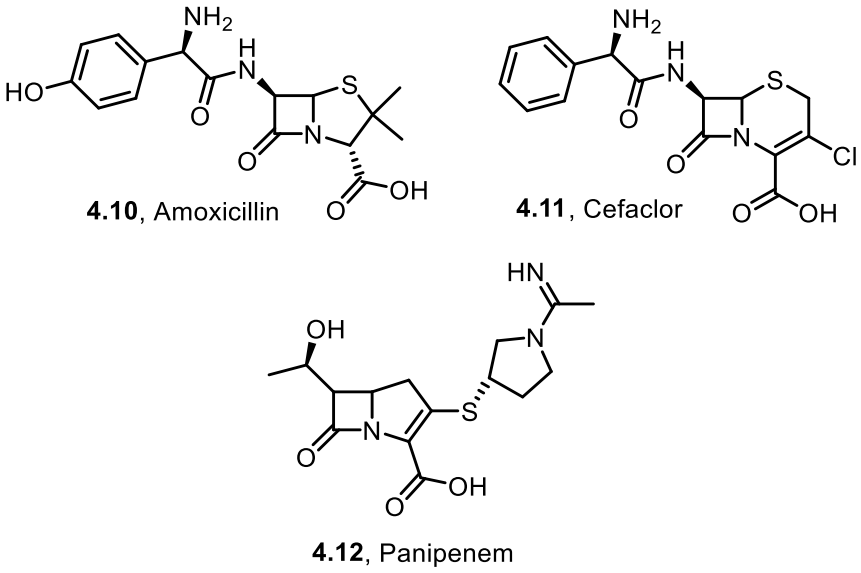
The starting material substrates for the work described in this chapter were provided by collaborators in the Docherty group (based in Lancaster University) and the Elmes group (based in Maynooth University). Both groups supplied us with compounds (shown in Scheme 168) that we postulated had the potential to take part in ring expansion transformations similar to those developed previously in the Unsworth group.



Scheme 168. The three substrates provided by the Docherty group and the Elmes group for use in this project.

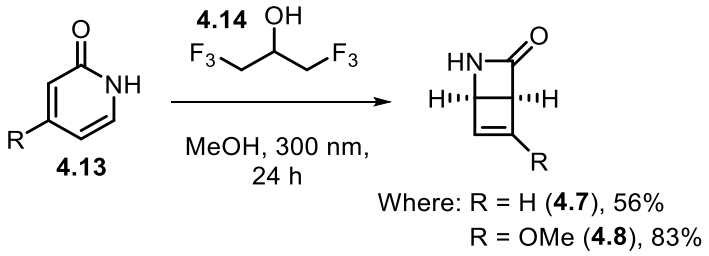
4.2 Ring Expansion Reactions of Bicyclic-β-lactams

The Docherty group provided us with bicyclic β-lactam substrates to explore novel ring expansions. β-Lactams are high value structures in medicinal chemistry and are often a feature in potent antibiotics.[189,190] They are also a useful building block that can be converted into more complex and biologically active compounds.[191,192] Their structural rigidity and high chemical reactivity increase their importance in medicinal chemistry due to their subsequent ease of modification and this can be manipulated to enhance and optimise possible drug properties.[193] Some examples that contain the bicyclic β-lactam functionality are shown in Scheme 169.



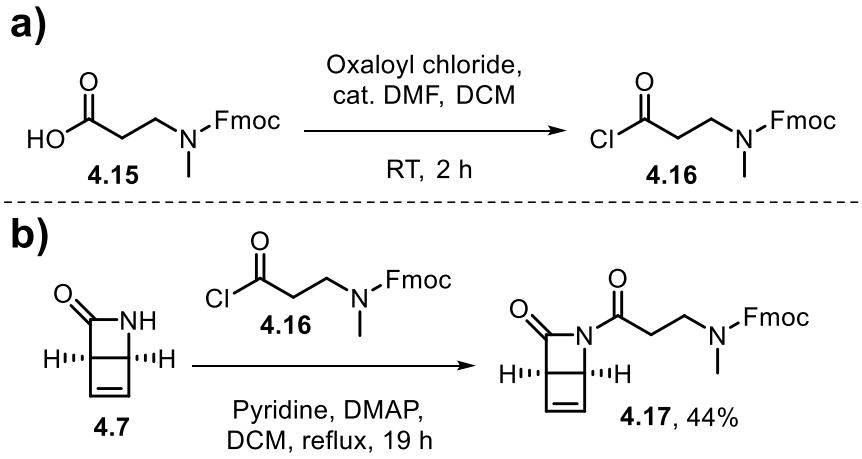
Scheme 169. Examples of pharmaceutical drugs with a bicyclic β-lactam within their structure.

The bicyclic lactams used in this project were synthesised by the Docherty group using the procedure shown in Scheme 170. 2-Pyridone **4.13** and hexafluoropentanol **4.14** were subjected to 300 nm UV radiation for one day to give the two products, **4.7** and **4.8**.[194]



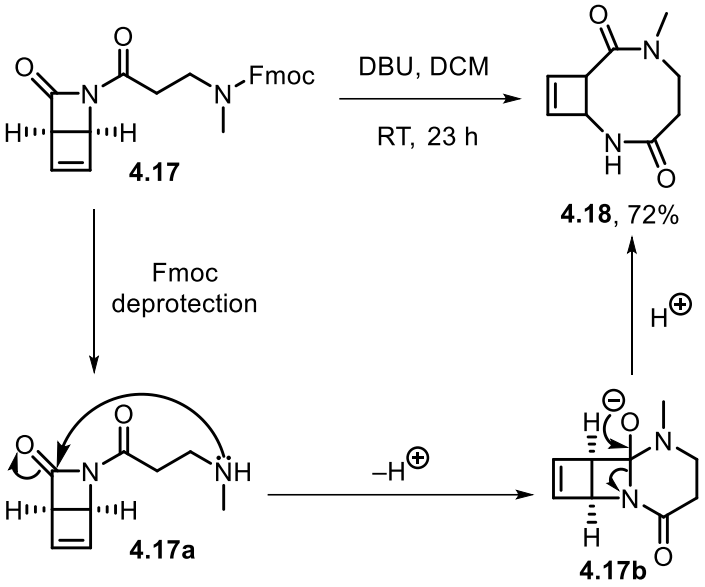
Scheme 170. Literature method to produce the bicyclic lactams used in this project.

With bicyclic lactams **4.7** and **4.8** in hand, the SuRE method that was depicted in Scheme 167 was tested, first on bicyclic β-lactam starting material **4.7**. An initial *N*-acylation was completed first with the acid chloride derived from Fmoc-methyl-β-alanine **4.15**, with the method used to synthesise acid chloride **4.16** shown in Scheme 171a. After this, the *N*-acylation was done using the Unsworth group's published lactam *N*-acylation method (Scheme 171b).[187] Pleasingly, this was a success, with **4.17** formed in 44% yield.



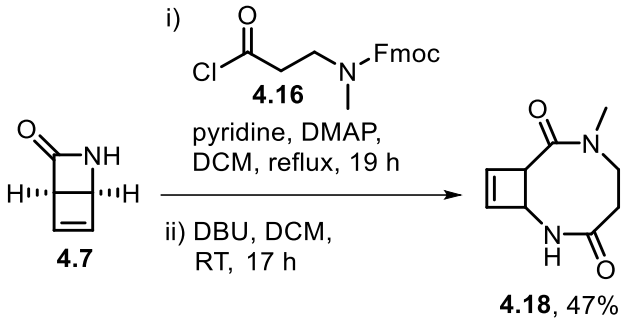
Scheme 171a. Synthesis of the acid chloride from the carboxylic acid. **Scheme 171b.** The successful *N*-acylation with **4.16**.

The addition of excess DBU in DCM to **4.17** facilitated the Fmoc deprotection, releasing the secondary amine, which was followed by the instantaneous attack on the carbonyl and C–N bond fragmentation to give the ring-expanded product, **4.18** in a yield of 72% (Scheme 172). Overall, from the original starting material **4.7**, the yield to **4.18** was 29%.



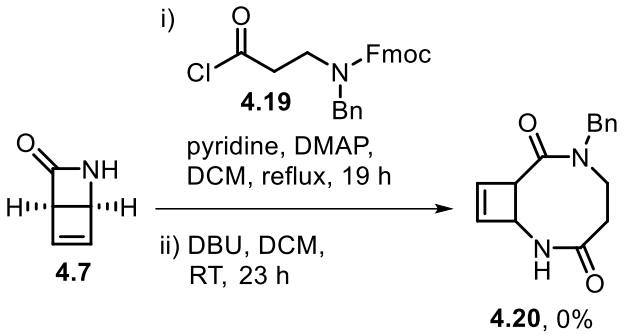
Scheme 172. The successful SuRE reaction of **4.17**, with the mechanism shown.

The overall conversion of **4.7** into **4.18** was improved by modifying the experimental method, by telescoping the *N*-acylation and ring expansion steps, while not performing column chromatography on the acylated imide intermediate **4.17**.[188] Instead, imide **4.17** was purified only *via* an aqueous workup, before it was immediately dissolved in DCM for the next step. This telescoped method worked better, increasing the yield to 47% overall (Scheme 173).



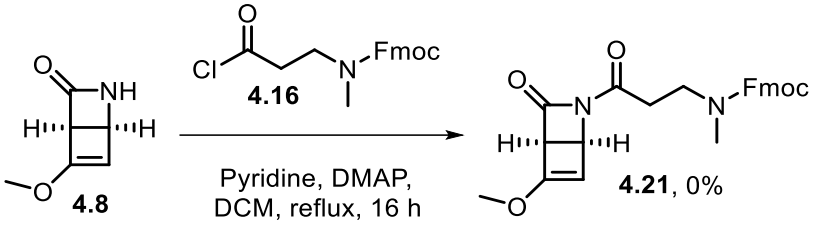
Scheme 173. The consecutive *N*-acylation and SuRE reaction to form **4.18** in an improved yield.

There was interest in testing whether other amino acid chlorides could react similarly with lactam **4.7** – therefore the analogous reaction using **4.19** was next attempted. The formation of the acylated intermediate seemed to work, based on the detection of a molecular ion consistent with the expected product by mass spectrometry. However, following the addition of DBU, none of the expected ring expansion product **4.20** was obtained (Scheme 174).



Scheme 174. The unsuccessful consecutive *N*-acylation and SuRE reaction to form **4.20**.

This was not pursued further and interest instead switched to the bicyclic β-lactam starting material containing a methoxy group, **4.8** (Scheme 175). The lactam was reacted with the Fmoc-methyl-β-alanine derived acid chloride (**4.16**), but this reaction failed, with none of the desired imide product **4.21** formed.

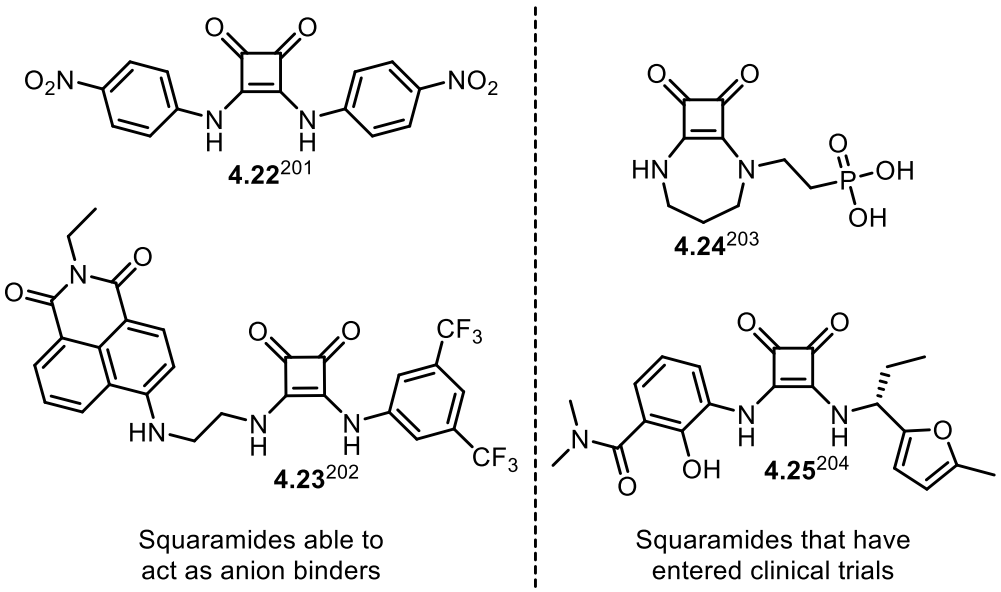


Scheme 175. The unsuccessful *N*-acylation with **4.16**.

While not all the ring expansion reactions tested using bicyclic β-lactams were successful, one novel medium-sized ring was synthesised, showing that the approach had some potential. More success may have been possible with the unbranched bicyclic lactam through attempts of different acid chlorides, for example, using reagents less bulky than the phenylalanine derivative tested.

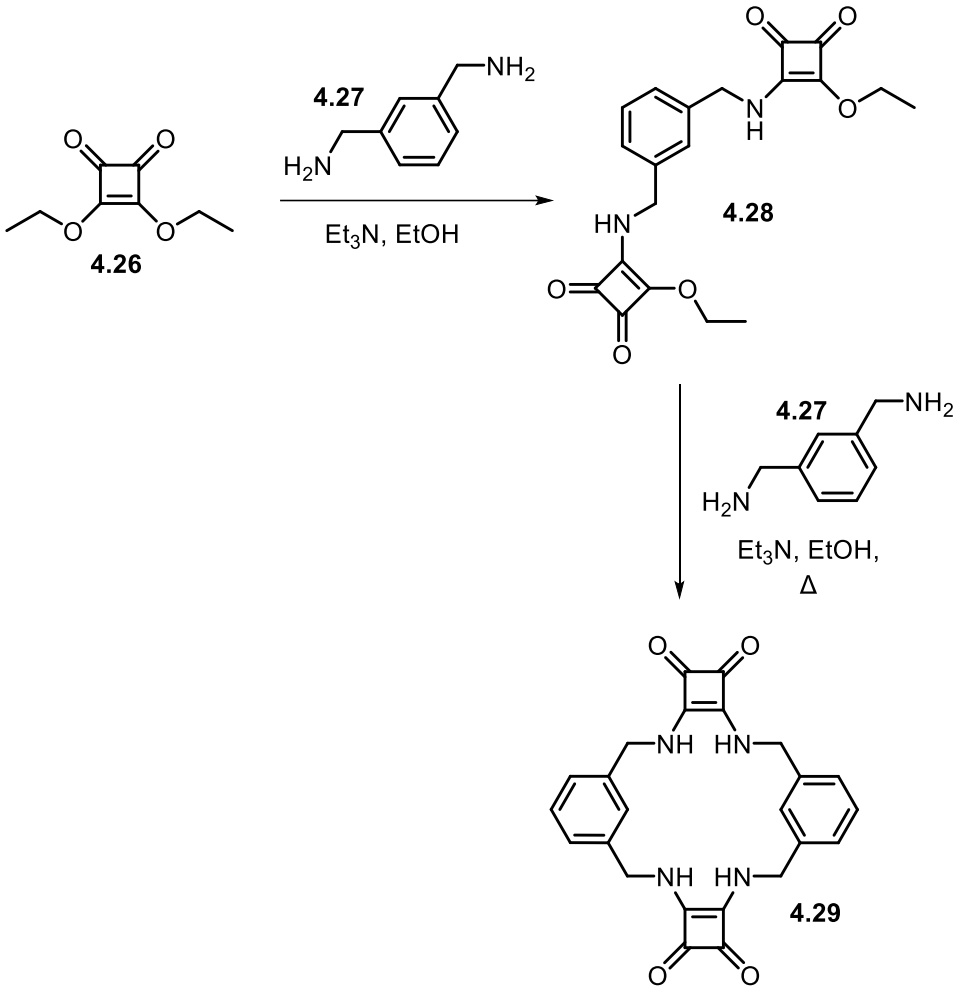
4.3 Ring Expansion Reactions of Cyclic Squaramides

Attention moved to exploring the ring expansion reactions of symmetric diamine complexes provided by the Elmes group. These compounds – known as squaramides – have the ability to form strong bidirectional hydrogen bonds (through the NH groups present) and can act as highly rigid binding motifs[195,196] that can be used in various applications spanning supramolecular chemistry,[197] medicinal chemistry[198] and organocatalysis.[199] Compounds below in Scheme 176 can display binding affinities up to 50 times higher for certain anions compared with other known anion binders like thioureas.[200] This makes them strong candidates for selective recognition and the transport of anions.[200] Some examples that contain the squaramide functionality are shown below in Scheme 176.



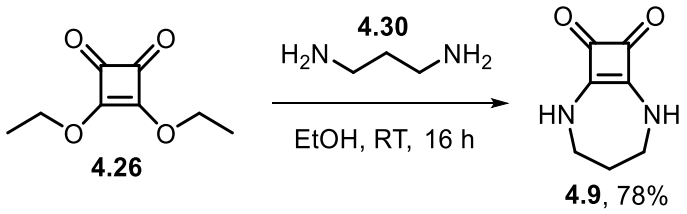
Scheme 176. Examples of squaramides that are able to act as anion binders or are in clinical trials.

The Elmes group demonstrated the anion-binding power of macrocyclic squaramides in a paper from 2016.[205] In this study, macrocyclic squaramide **4.29** was prepared *via* the synthetic pathway shown in Scheme 177. Once synthesised, ^{1}H NMR spectroscopy could be used to monitor the successful binding of SO_4^{2-} ions to macrocycle **4.29**. The change of chemical shift in the macrocycle was able to identify the level of binding by the anion – there were significant changes in the NH protons (downfield shift of 2.21 ppm) and the aromatic protons lying within the macrocyclic cavity (downfield shift of 0.87 ppm) and this proved its efficacy as an anion receptor. **4.29** also showed its ability to bind to SO_4^{2-} in competitive conditions with varying H_2O/DMSO-d_6 conditions (0.5% *v/v* to 50% *v/v*), displaying its impressive selectivity. This reinforced the hopes that these macrocycles could be used in areas where the extraction of sulfate anions is crucial,[205] such as sulfate-selective receptors in nuclear waste remediation[206] or plasma sulfate detection.[207]



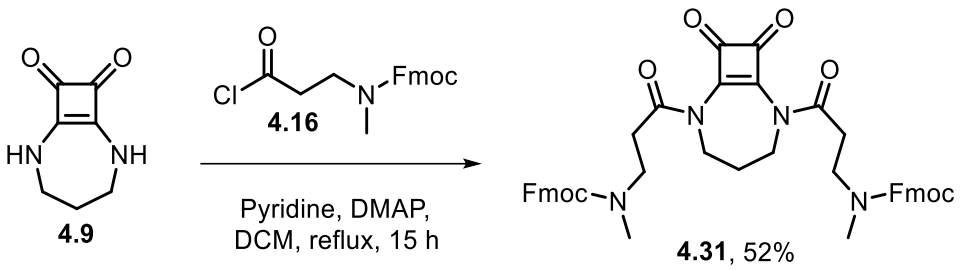
Scheme 177. 2-Step synthesis of the desired macrocyclic squaramide-based receptor framework.

The squaramide used in this project was synthesised by the Elmes group using the procedure shown in Scheme 178. Squaramide **4.26** and propylene diamine **4.30** were dissolved in ethanol and stirred at room temperature overnight to give the 7-membered diamine product as squaramide **4.9**.[208]



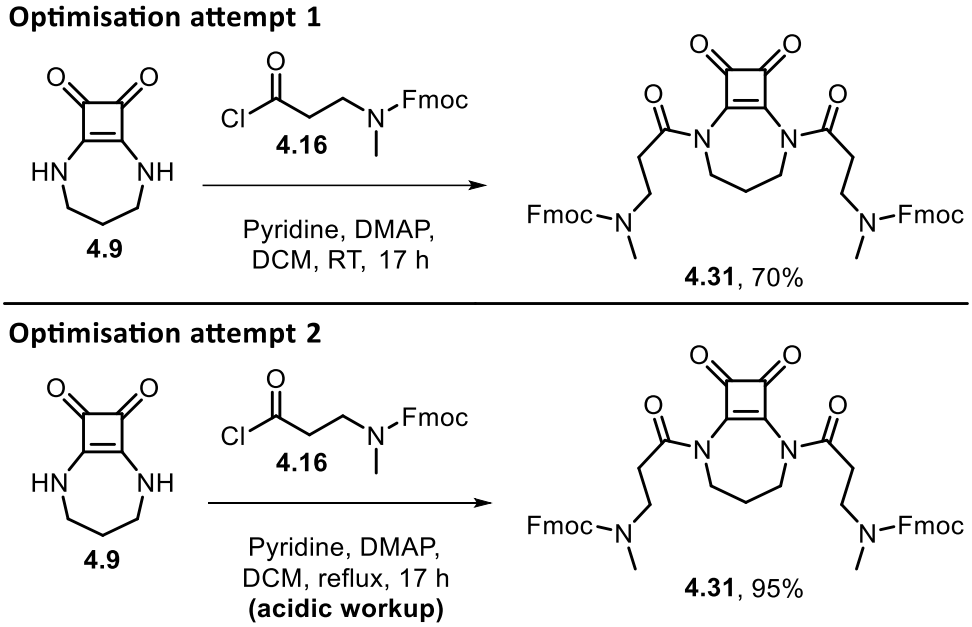
Scheme 178. Method followed by the Elmes group to produce the squaramide in this project.

N-acylation of squaramide **4.9** was next attempted, with the aim to acylate at both NH sites. Scheme 179 shows the standard *N*-acylation conditions used for the reaction of **4.9** with Fmoc-methyl-β-alanine derived acid chloride **4.16**, and this reaction was successful, forming **4.31** in a 52% yield.



Scheme 179. The successful *N*-acylation with **4.16**.

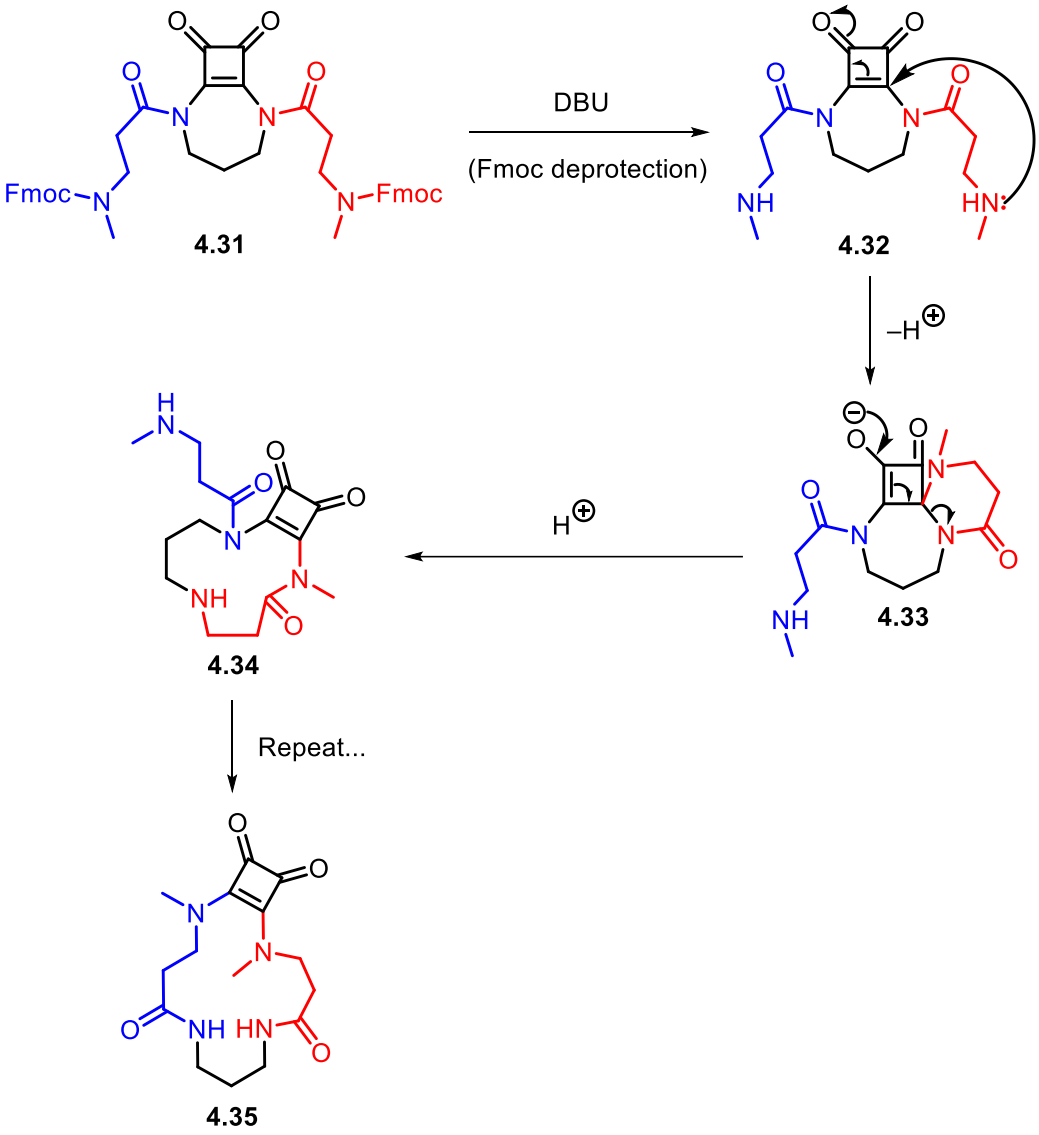
The yield of **4.31** was improved following optimisation. First, reducing the temperature to room temperature had a positive effect, increasing the yield to 70% (Scheme 180). Furthermore, by reverting to refluxing conditions, but adding an acidic workup (see Experimental for full details), instead of just adding methanol to consume the excess acid chloride, further improved the yield to 95%. This indicates that reaction temperature may not have as much bearing on the reaction efficiency as the workup method. As a result, all *N*-acylation reactions in this section used the conditions and altered workup from 'Optimisation attempt 2'.



Scheme 180. The two optimisation attempts for the *N*-acylation step.

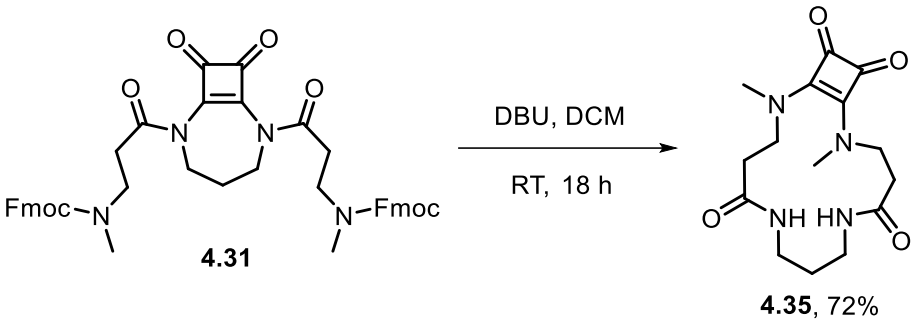
Following this was the SuRE step, with a notable deviation in mechanism from the established SuRE method when using these squaramide complexes for the ring expansion step. Scheme 181 below shows the proposed mechanism for the ring expansion to form **4.35**. First, is the standard Fmoc deprotection stage, where removal of the Fmoc group reveals the secondary amines in **4.32**. After this, in SuRE the amine would usually attack a carbonyl in the ring (look back to Scheme 172 for reference). However, on this substrate an

aza-Michael addition type reaction is proposed to form intermediate **4.33**. From here, a fragmentation is thought to facilitate the first 4-atom ring expansion (to form **4.34**). Repeating the same process with the second acyl branch is then believed to generate the final 15-membered macrocycle, **4.35**.



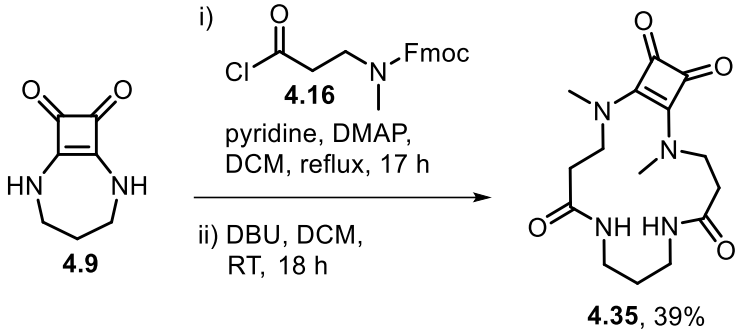
Scheme 181. The proposed mechanism for the SuRE-like reaction to **4.35**.

Pleasingly, the SuRE-like step tested on the doubly acylated compound **4.31**, using DBU and DCM, was successful, with the desired product, **4.35**, forming in 72% yield and in a 2-step yield of 70% from **4.9** (Scheme 182). Notably, this represents a novel ring expansion mechanism, never demonstrated previously in the Unsworth group.



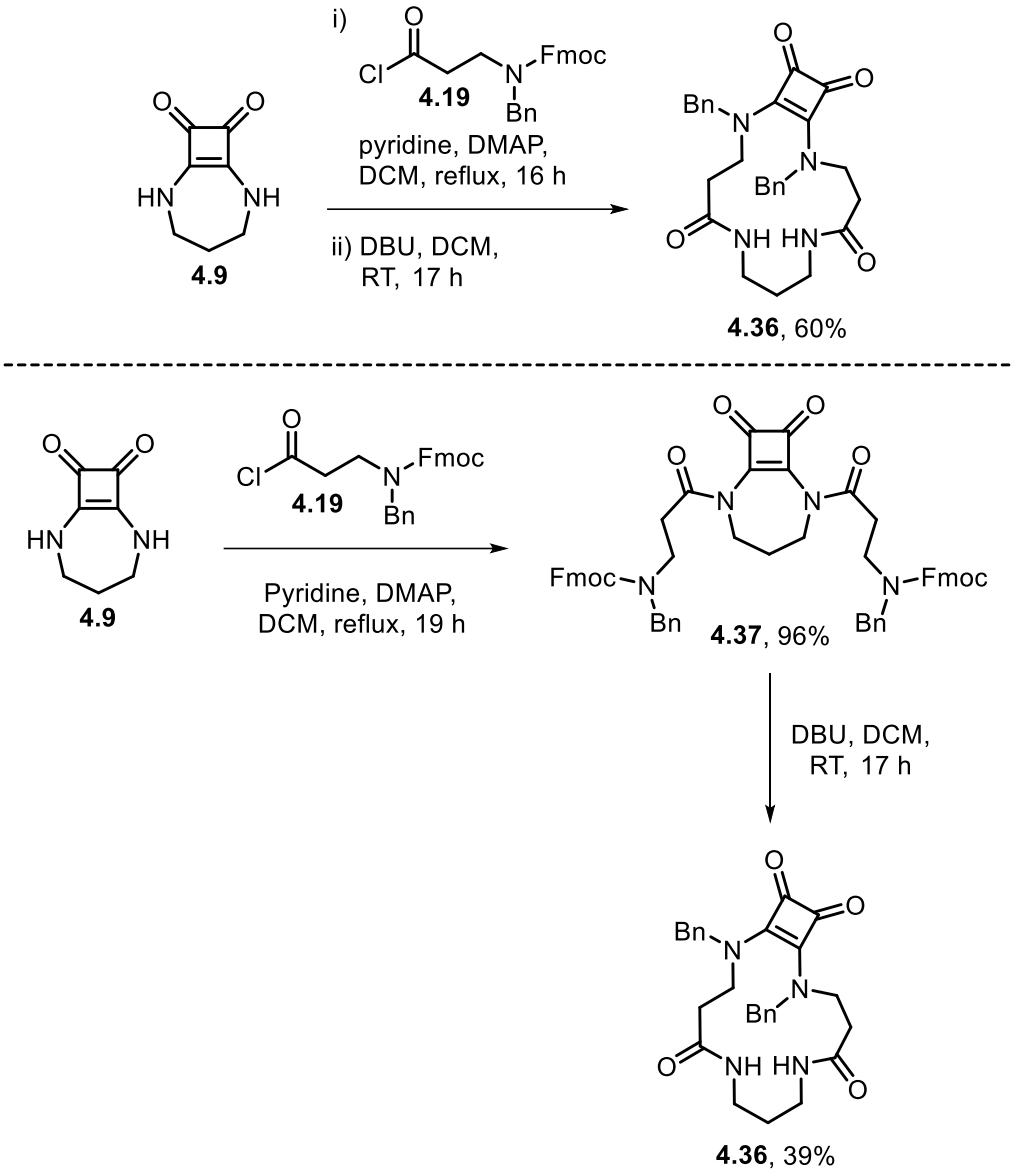
Scheme 182. The successful SuRE-like reaction, to give **4.35**.

After forming **4.35**, the reaction was repeated (from **4.9**) but without isolating the acylated intermediate **4.31** *via* column chromatography (Scheme 183). However, this did not have a positive effect and the 2-step yield achieved here of 39% was lower than the 70% attained previously. Despite this, due to its increased ease and reduction in time taken, it was still positive to see this telescoped process also work to form **4.35** in an acceptable yield.



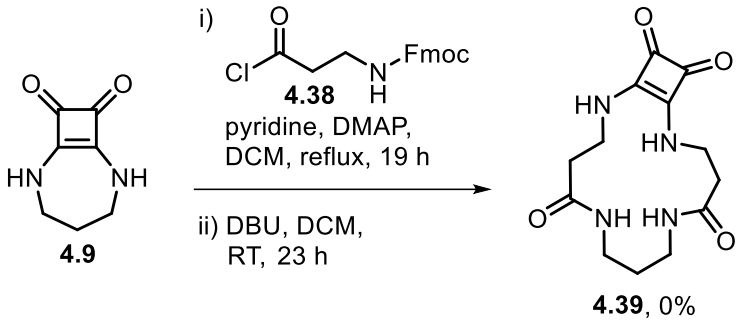
Scheme 183. The consecutive *N*-acylation and SuRE-like reaction to form **4.35** in a decreased yield.

The success in synthesising **4.35** gave encouragement to attempt the ring expansion with different acid chloride reagents. Thus, **4.19** was used in the 2-step method, again starting from **4.9** (Scheme 184). This reaction was successful and the ring-expanded macrocycle **4.36** formed. The alternative approach was also done to obtain data for intermediate **4.37** (can be found in the Experimental) but this gave a lower yield – 60% vs 37%.



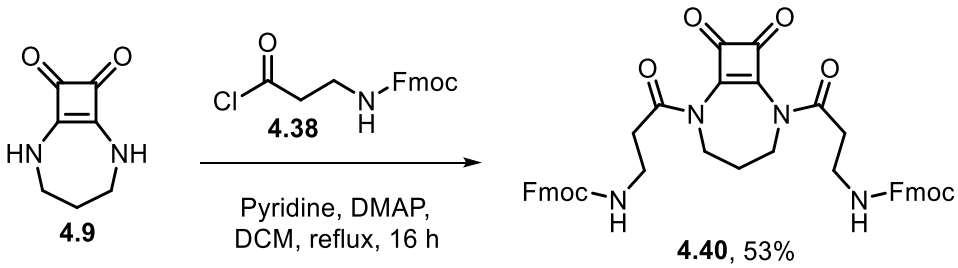
Scheme 184. Both methods attempted to form the 15-membered macrocycle **4.36**.

There was particular interest from the Elmes group in synthesising an analogous product with secondary amines in place of the tertiary ones seen in **4.35** and **4.36**. Therefore, the amino acid chloride of Fmoc-β-alanine (**4.38**) was made and reacted with **4.9**, using the favoured technique of bypassing the purification of the acylated intermediate (Scheme 185). The crude reaction mixture was analysed by mass spectrometry and a molecular ion peak consistent with the expected product **4.39** was observed. However, purification of **4.39** was challenging. The presence of four 'NH' groups in the compound increased the polarity to a level that meant during TLC analysis, the product was stuck on the baseline, even when using very polar conditions (attempts ranged from 10% methanol in ethyl acetate to 100% methanol). Unfortunately, when column chromatography was attempted, the product **4.39** was not isolated.



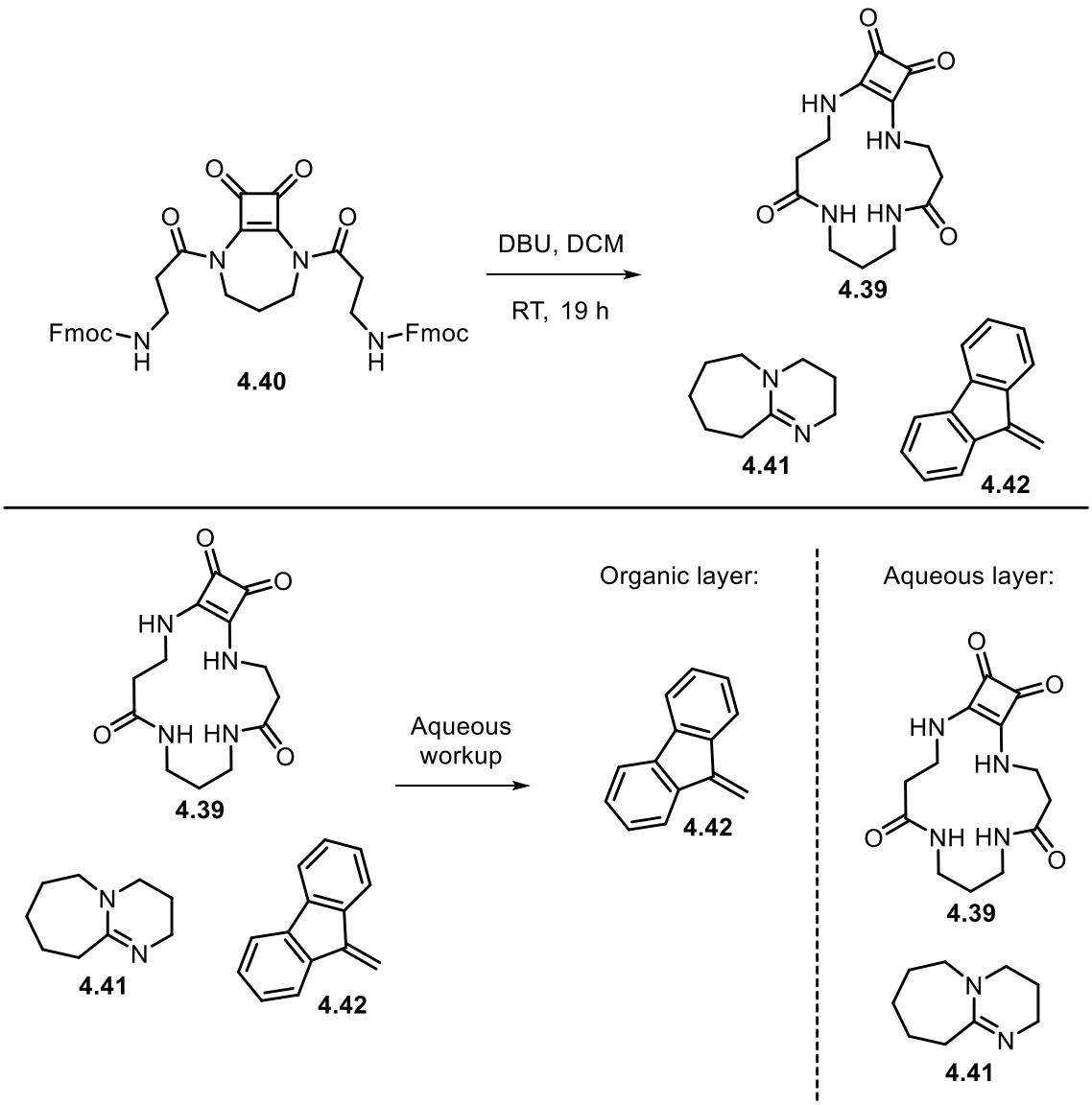
Scheme 185. Unsuccessful consecutive *N*-acylation and SuRE-like reaction to form **4.39**.

The reaction was repeated but this time with the idea to isolate the intermediate prior to the ring expansion step (Scheme 186) and this step worked well, with product **4.40** isolated in 53% yield. The idea was to purify the less polar intermediate, **4.40**, to make it easier to analyse and purify after the ring expansion step.



Scheme 186. The successful *N*-acylation with **4.38**.

The ring expansion reaction was attempted using DBU and DCM, followed by an aqueous workup (Scheme 187). Mass spectrometry and NMR spectroscopy analysis was able to confirm the three main components of the crude reaction mixture. Peaks in the aromatic region of the ^{1}H NMR spectra matched that of the Fmoc cleavage side-product **4.42**. Meanwhile, the ^{1}H NMR signals of DBU **4.41** were clearly visible upfield and masked the region where the macrocycle signals would be expected to appear. However, mass spectrometry was able to confirm the presence of a molecular ion peak that was presumed to be product **4.39**. After the workup, the same analysis was completed and unfortunately it showed that the product entered the aqueous layer along with the DBU, meaning more conventional methods were not going to be able to purify **4.39**.

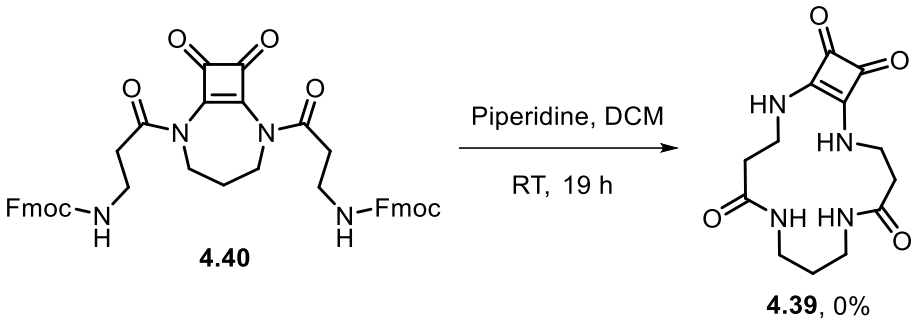


Scheme 187. The SuRE-like reaction, where the products from the reaction were separated *via* an aqueous workup into organic and aqueous layers.

A reverse-phase C18 column was used during an LCMS run completed for analysis by another member of the Unsworth group (Owen Hughes) with the impure sample from the aqueous layer. This was done with the view to conduct preparative HPLC if there was sufficient separation between **4.39** and **4.41**. The eluent used was acetonitrile and water with 1% formic acid. A linear gradient elution was completed with these conditions, starting with 5% water in acetonitrile, before increasing to 90% water over a 13-minute period. However, upon elution of the products, it was observed that the retention times for both **4.39** and **4.41** were very similar and caused strong overlapping peaks when the separation was attempted. This meant the subsequent preparative HPLC was not tried.

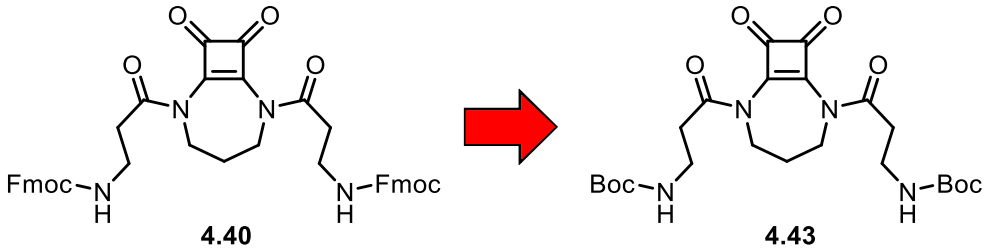
The use of piperidine instead of DBU as the base for the deprotection was briefly explored – the much lower boiling point of piperidine would mean it could be removed under reduced

pressure. However, when attempted, no reaction took place and the starting material remained unreacted in the reaction vessel (Scheme 188).



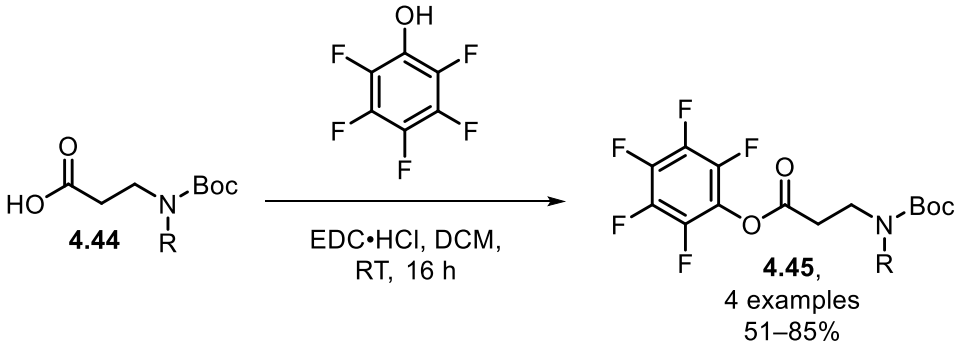
Scheme 188. Unsuccessful SuRE-like reaction with piperidine.

The idea of changing the protecting group was also explored with the use of a Boc group investigated instead (Scheme 189). The deprotection conditions would only require HCl in 1,4-dioxane and this could be removed under reduced pressure rather than necessitating a workup or column for purification.



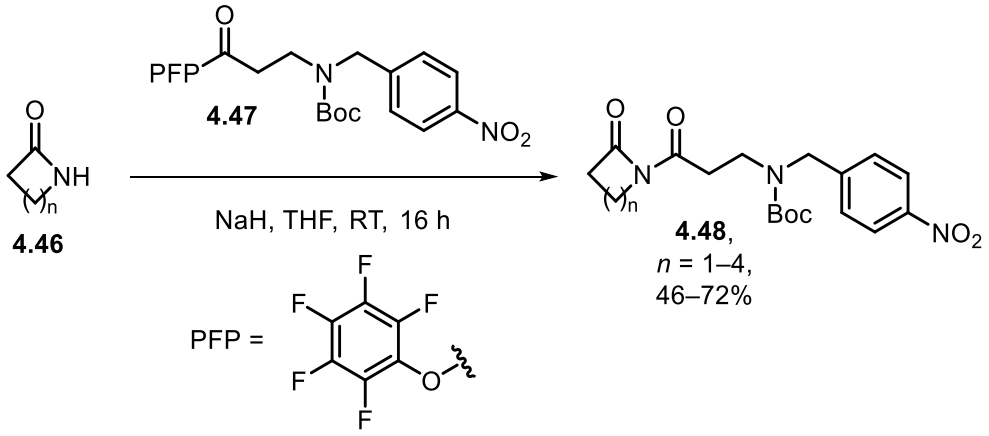
Scheme 189. The conversion of the protecting group from an Fmoc to a Boc.

Inspiration was taken from a paper by Yudin and co-workers in 2017[157] where they were able to synthesise an alternative for the Fmoc-protected acid chlorides needed for the *N*-acylation step (Scheme 190). Pentafluorophenol and EDC in DCM were reacted with **4.44** and this formed a number of substrates, **4.45**, in yields ranging from 51–85%.



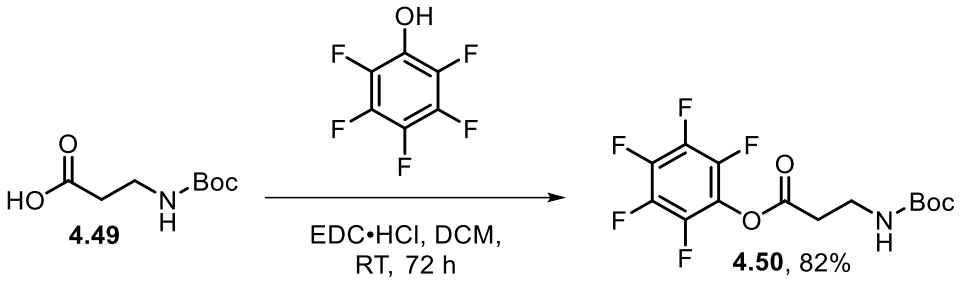
Scheme 190. Reaction of pentafluorophenol with the Boc-protected carboxylic acid **4.44**, completed by Yudin and co-workers.

After this, they were able to utilise these newly formed compounds to make the Boc-protected-β-amino imides through the reaction with a lactam, sodium hydride and **4.47** (Scheme 191).[157]



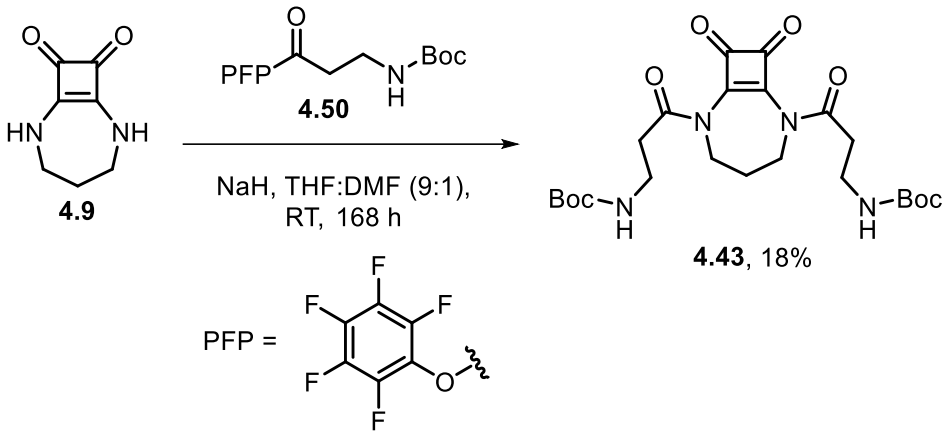
Scheme 191. The *N*-acylation of a lactam using **4.47**, completed by Yudin and co-workers.

The broad success achieved by Yudin and co-workers was encouraging and so using their methodology, **4.50** was synthesised from Boc-β-glycine with success (Scheme 192).



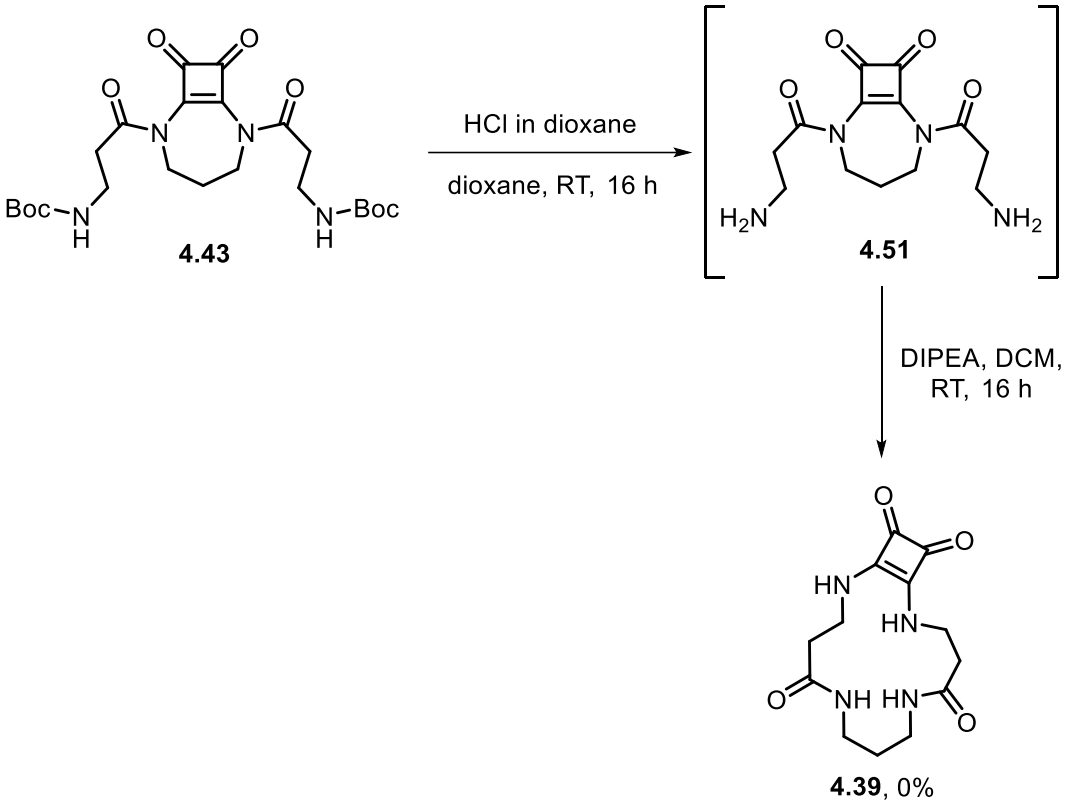
Scheme 192. Reaction of pentafluorophenol with Boc-β-glycine.

From here, the *N*-acylation with squaramide **4.9** was attempted (Scheme 193). A notable change made to the literature method in our case was to add 10% DMF to the reaction solvent – this was done to aid the solubility of **4.9**, which did not dissolve well in pure THF. Pleasingly, the doubly acylated product, **4.43**, was able to form after a week, albeit in a low 18% yield.



Scheme 193. Successful *N*-acylation of the squaramide using **4.50**.

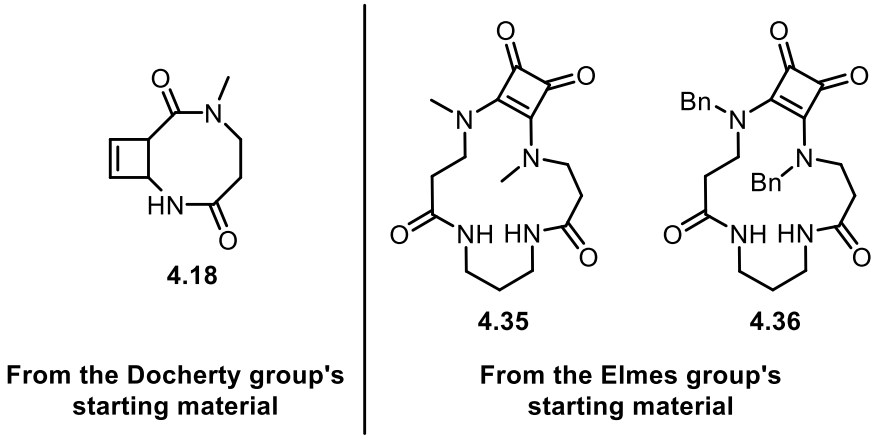
Then, attempts were made to remove the Boc protecting groups, with HCl in 1,4-dioxane (Scheme 194). Mass spectrometry data supported the removal of the Boc groups, through the disappearance of a molecular ion peak for the starting material, and the appearance of a molecular ion consistent with the deprotected product **4.51**. Therefore, DIPEA was then added into the reaction mixture as basic conditions are required for the ring expansion to free-base the amine salt. Unfortunately, after stirring overnight, no product (or side-product) was able to be identified and recovered from the reaction, based on analysis with mass spectrometry and NMR spectroscopy. Ideally, this reaction pathway would have been attempted again on a larger scale, but at this point none of the initial squaramide remained.



Scheme 194. Boc-deprotection and unsuccessful ring expansion of **4.43**.

4.4 Conclusion

In conclusion, the SuRE technique was used to synthesise new medium-sized rings and macrocycles in contexts very different to those the original method was designed for (Scheme 195). This highlights the versatility of the SuRE technique.



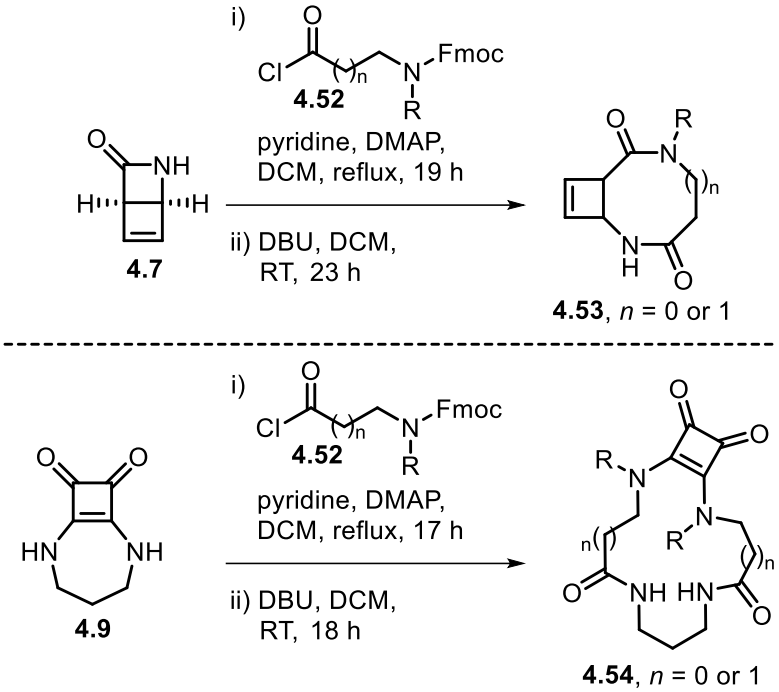
Scheme 195. The three rings synthesised using the starting materials provided by the Docherty and Elmes groups.

When completing the ring expansions for the squaramide complexes (**4.35** and **4.36**), a unique mechanism for the SuRE was identified, where an aza-Michael addition facilitates the

4-atom ring expansion rather than the standard, direct attack at the carbonyl often seen for these reactions. This discovery may open up additional opportunities to use SuRE on similar structures, hence broadening the applicability of SuRE in the group.

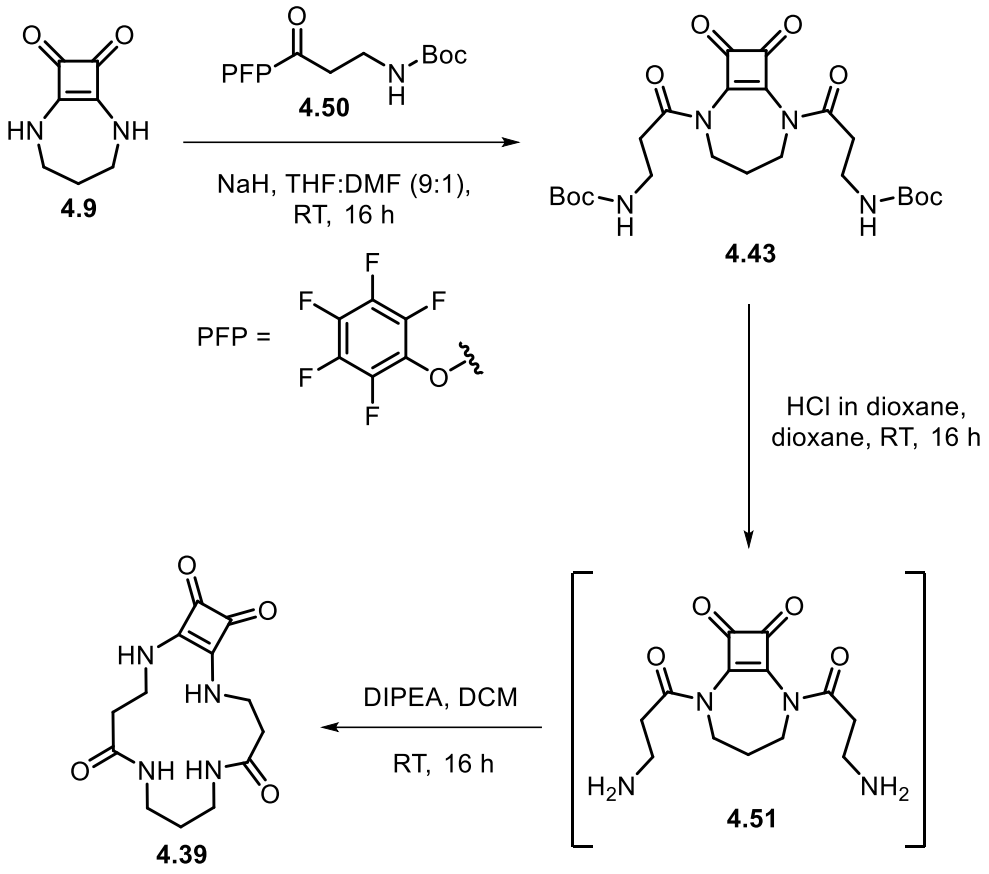
4.5 Future Work

There have been a number of papers published by the Unsworth group that have focused on using a range of different acid chlorides (including α and β amino acids).[188] Applying such acid chlorides to lactams **4.7** and **4.9** explored in this project would allow for the generation of more novel rings from the subsequent SuRE step (Scheme 196) and the squaramides in particular seemed quite amenable to the changes in amino acid chloride structure.



Scheme 196. The two possible starting materials undergoing an *N*-acylation and SuRE with an acid chloride that can be varied.

The attempted route to make macrocycle **4.39** also warrants further investigation (Scheme 197). Although, no success in product separation was possible when using the Fmoc-protected precursor, there was some encouragement when using the Boc-protected precursor instead. However, due to the limited supply of **4.9**, only one attempt was made of the deprotection and ring expansion, so in the future it would be worth exploring this path further. Changing the strategy for deprotection or the base used to instigate the ring expansion step could also be investigated if success is not achieved.



Scheme 197. The pathway from squaramide **4.9** to the macrocycle **4.39**, using the already attempted reagents and conditions.

5 Experimental

5.1 General Experimental Information

Unless otherwise stated, all reactions were carried out at RT under an inert (N_2 or Ar) atmosphere in oven-dried glassware. Except where stated, all reagents were purchased from commercial sources: Merck (Sigma-Aldrich), Alfa Aesar, Acros Organics, Fisher Chemicals, VWR, TCI and Flurorochem and were used without further purification. Anhydrous toluene, Et_2O and DMF were obtained from Innovative Technology Inc. PureSolv® solvent purification system. Dry THF, CH_2Cl_2 and MeCN were obtained from the SPS laboratory system and used immediately after being dispensed. Anhydrous MeOH, DMSO, acetone, ^{t}BuOH and benzene were purchased from Sigma Aldrich and used as supplied.

^{1}H NMR spectra were recorded at 400 MHz on Bruker AV400 or Bruker AMX 400/JEOL ECS-400. ^{13}C NMR spectra were recorded at 101 MHz on Bruker AV400 or Bruker AMX 400 MHz Ultra Shield™. ^{19}F NMR spectra were recorded at 376 MHz on Bruker AV400 or Bruker AMX 400/JEOL ECS-400.

All spectral data was acquired at 298 K (25 °C) unless stated otherwise and samples were dissolved in $CDCl_3$ unless specified otherwise. Chemical shifts (δ) are reported in parts per million (ppm), with residual solvent peaks: $CDCl_3$: δ_H = 7.26, $CDCl_3$: δ_C = 77.0, $(CD_3)_2SO$: δ_H = 2.50, δ_C = 39.5, CD_3OD: δ_H = 3.31, δ_C = 49.0, C_6D_6: δ_H = 7.16, δ_C = 128.1, CD_2Cl_2: δ_H = 5.32, δ_C = 53.8, $(CD_3)_2CO$: δ_H = 2.05, δ_C = 206.3, D_2O: δ_H = 4.79, $DCON(CD_3)_2$: δ_H = 8.03, δ_C = 163.2, being used for internal reference. The multiplicity abbreviations used are: s, singlet; d, doublet; t, triplet; q, quartet; p, pentet; m, multiplet; dd, doublet of doublets; dt doublet of triplets; td, triplet of doublets; tt, triplet of triplets; ddd, doublet of doublets of doublets; where br indicates a broad signal, and app. indicates an apparent. ^{1}H experiments are reported as: chemical shift in ppm, quoted to the nearest 0.01 ppm, (integration, multiplicity, coupling constant and assignment (where possible)). ^{13}C experiments are reported as: chemical shift in ppm, quoted to the nearest 0.1 ppm, (carbon assignment (where possible) or multiplicity, coupling constant and assignment (where applicable)). ^{19}F experiments are reported as: chemical shift in ppm, quoted to the nearest 0.1 ppm, (multiplicity, coupling constant and assignment (where possible)).

Assignment of compounds was achieved through use of ^{135}DEPT, COSY, HMQC and HMBC experiments. Spectra were analysed using MestReNova 12.0.3-21384 software and values of coupling constant (*J*) are reported in Hertz (Hz) to the nearest 0.5 Hz. The term "overlapping" is used to describe a resonance peak, which is behind another resonance peak, *i.e.*, compound resonance behind the solvent peak or combination of two resonance

peaks. The systematic chemical names were generated using the IUPAC name generator tool option that is included within the ChemBioDraw Ultra 19.1 software.

Infrared (IR) spectra were recorded on a PerkinElmer UATR 2 or Pekin Elmer Spectrum 100 spectrometer fitted with a universal Attenuated Total Reflectance (ATR) accessory; data was recorded as a thin film dispersed from either CH_2Cl_2 or $CDCl_3$, neat or solid state by ATR-FTIR. IR-recorded experiments are reported as: IR (method of recorded) ν_{max} (IR absorption maxima) / unit (cm^{-1}) chemical absorption (assignment (where possible)).

High Resolution Mass Spectra (HRMS) were obtained by the University of York Mass Spectrometry Service, recorded on a Waters XEVO G2-XS TOF, Waters Synapt G2S TOF or Bruker Micro-TOF mass spectrometer, with HRMS mode incorporating a lock-in mass into the mobile phase (leucine enkehalin) or on a Bruker Daltonics, Micro-TOF spectrometer, using Electrospray Ionisation (ESI) or Atmospheric Pressure Chemical Ionisation (APCI), positive or negative generative modes.

Thin Layer Chromatography (TLC) was carried out on Merck silica gel $60F_{254}$ pre-coated aluminium foil sheets and was visualised using UV light (λ = 254 nm, short wavelength) or UV light (λ = 366 nm, long wavelength) and stained with basic aqueous potassium permanganate ($KMnO_4$), ninhydrin or vanillin solution dip. Concentration under reduced pressure or *vacuo* was performed using a Büchi® Rotavapor® R-210 evaporator with jack and water bath, 29/32 joint, 240V rotary evaporator using a mixture of acetone and dry ice, ice/water or ethylene glycol/water as the coolant. Flash column chromatography was conducted using Aldrich technical grade silica gel (SiO_2), 60 Å, 230-400 mesh, 40-63 µm particle size, under a light positive pressure of air, eluting with the specified solvent system.

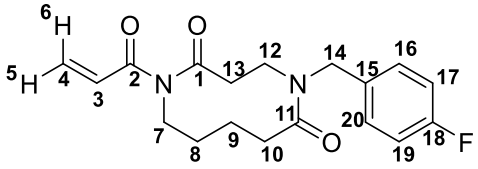
Melting points were recorded as a decomposition temperature range and measured on a Stuart SMP10 or Gallenkamp apparatus using open tubes with no corrections.

X-ray crystallography data was collected, solved, and refined by Dr Adrian C. Whitwood or Dr Richard J. Gammons in the School of Chemistry at the University of York. Diffraction data were collected at 100 K on an Oxford Diffraction SuperNova diffractometer with Cu-K_α radiation (λ = 1.54184 Å) using a HyPix-6000HE detector. The crystal was cooled with an Oxford Instruments Cryojet. Diffractometer control, data collection, initial unit cell determination, frame integration and unit-cell refinement were carried out with CrysAlisPro, face-indexed absorption corrections were applied using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm within CrysAlisPro. OLEX2 was used for overall structure solution, refinement and preparation of computer graphics and publication data. Within OLEX2, the algorithms used for structure solution were Superflip charge-flipping

smtbx-flip charge-flipping ShelXT dual-spaceRefinement by full-matrix least-squares used the SHELXL algorithm within OLEX2. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were placed using a riding model and included in the refinement at calculated positions. CrystalMaker® 10 software was also used to visualise the X-ray structures with their corresponding CCDC deposit numbers given in the manuscript.

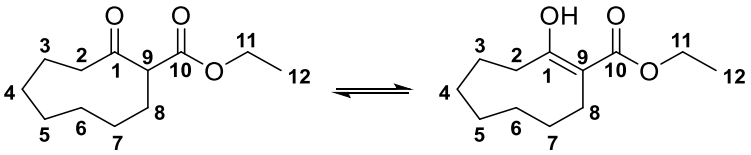
5.2 Experimental Procedures

2.9: 1-Acryloyl-5-(4-fluorobenzyl)-1,5-diazecane-2,6-dione



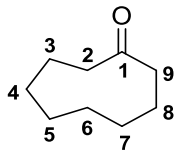
A stirring solution of 5-(4-fluorobenzyl)-1,5-diazecane-2,6-dione (1.02 g, 3.68 mmol) and DIPEA (1.65 mL, 9.47 mmol) in THF (23.0 mL) was cooled to 0 °C. To this was added a 0 °C cooled solution of acryloyl chloride (0.45 mL, 5.52 mmol) in THF (5.0 mL) dropwise. Under an argon atmosphere, this mixture was stirred at 0 °C for 2 hours and a further 15 hours at RT. 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 was washed with sat. aq. $NaHCO_3$ (2 × 15 mL). The organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 2:1 hexane : ethyl acetate → 100% ethyl acetate → 9:1 ethyl acetate : methanol) afforded the title compound, which was obtained as a colourless oil (615 mg, 50%), and exists in $CDCl_3$ as a 10:1 mixture of rotamers. The ^{1}H NMR spectrum is severely affected by rotameric broadening, with product identity and purity best determined using ^{13}C NMR data; R_f = 0.53 (9:1 ethyl acetate : methanol); ν_{max}/cm^{-1} (thin film): 2946, 1682, 1633, 1509, 1458, 1407, 1343, 1257, 1220, 1167, 1143, 1092, 982, 817, 583; δ_H (400 MHz, $CDCl_3$) Data for major rotamer: 7.23 – 7.15 (2H, m, 2 x Ar**H**), 7.00 – 6.91 (2H, m, 2 x Ar**H**), 6.64 (1H, dd, *J* = 16.5, 10.0 Hz, H-3), 6.46 (1H, dd, *J* = 16.5, 1.5 Hz, H-6), 5.89 (1H, dd, *J* = 10.0, 1.5 Hz, H-5), 4.88 – 4.15 (2H, m, C**H₂**), 3.88 (2H, br s, C**H₂**), 3.59 (2H, br s, C**H₂**), 3.28 (2H, br s, C**H₂**), 2.50 – 2.31 (2H, m, C**H₂**), 2.00 – 1.79 (2H, m, C**H₂**), 1.70 (2H, br p, *J* = 5.5 Hz, C**H₂**). Diagnostic data for the minor rotamer: 7.13 – 7.21 (2H, m, 2 x Ar**H**), 6.70 (1H, dd, *J* = 16.5, 10.0 Hz, H-3), 6.41 – 6.35 (1H, m, H-5/6), 5.82 (1H, dd, *J* = 10.5, 1.5 Hz, H-5/6), 4.78 (1H, d, *J* = 16.0 Hz, H-14), 4.21 (1H, d, *J* = 16.0 Hz, H-14'); δ_C (100 MHz, $CDCl_3$) Data for major rotamer: 175.6 (**C**O), 172.9 (**C**O), 168.9 (**C**O), 162.3 (C-18, d, $^1J_{CF}$ = 245.5 Hz), 133.1 (Ar**C**, d, $^4J_{CF}$ = 2.9 Hz), 132.2 (C-4), 130.0 (2 × Ar**C**H, d, $^3J_{CF}$ = 8.5 Hz), 129.5 (C-3), 115.6 (2 × Ar**C**H, d, $^2J_{CF}$ = 21.2 Hz), 46.9 (**C**H$_2$), 45.7 (**C**H$_2$), 43.9 (**C**H$_2$), 38.2 (**C**H$_2$), 29.2 (**C**H$_2$), 24.2 (**C**H$_2$ [overlapping]), 24.1 (**C**H$_2$ [overlapping]). Diagnostic data for minor rotamer: 169.1 (**C**O), 132.3 (Ar**C**, d, $^4J_{CF}$ = 2.6 Hz), 131.2 (C-4), 130.7 (C-3), 128.5 (2 × Ar**C**H, d, $^3J_{CF}$ = 8.4 Hz), 116.0 (2 × Ar**C**H, d, $^2J_{CF}$ = 21.6 Hz), 44.6 (**C**H$_2$), 43.7 (**C**H$_2$), 34.4 (**C**H$_2$), 27.1 (**C**H$_2$), 25.7 (**C**H$_2$), 25.1 (**C**H$_2$); δ_F (376 MHz, $CDCl_3$) Minor rotamer: −114.18 (1F, m, Ar**F**), major rotamer: −114.88 (1F, m, Ar**F**); HRMS (ESI$^+$): calcd. for $C_{18}H_{21}FN_2NaO_3$, 355.1428. Found: $[MNa]^+$, 355.1426 (0.5 ppm error).

2.14: Ethyl 2-oxocyclononane-1-carboxylate



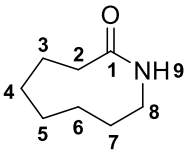
To a round-bottomed flask, cyclooctanone (7.58 g, 60.0 mmol) in diethyl ether (120 mL) at 0 °C, was added boron trifluoride etherate (10.0 mL, 90.0 mmol) in diethyl ether (31.0 mL) over 5 minutes *via* a syringe pump. A solution of ethyl diazoacetate (87% wt in DCM, 9.65 mL, 90.0 mmol) in diethyl ether (30.0 mL) was added over 15 minutes *via* a syringe pump causing a vigorous evolution of gas. The reaction mixture was warmed to RT under an Ar atmosphere and stirred for 17 hours. The reaction mixture was then cooled to 0 °C and neutralised with sat. aq. $NaHCO_3$ (200 mL). This solution was then extracted with $CHCl_3$ (3 x 100 mL) and the organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 20:1 hexane : ethyl acetate) afforded the title compound, which was obtained as a pale orange oil (8.89 g, 70%), and exists in $CDCl_3$ as an approximate 5:1 mixture of keto and enol tautomeric forms; R_f = 0.19 (10:1 hexane : ethyl acetate); ν_{max}/cm^{-1} (thin film): 2929, 2875, 1744, 1705, 1469, 1445, 1227, 1179, 1152, 1027, 858; δ_H (400 MHz, $CDCl_3$) Diagnostic data for keto form: 4.19 (2H, q, *J* = 7.0 Hz, H-11), 3.60 (1H, t, *J* = 7.5 Hz, H-9), 1.28 (3H, t, *J* = 7.0 Hz, H-12). Diagnostic data for enol form: 4.12 (2H, q, *J* = 7.0 Hz, H-11), 1.21 (3H, t, *J* = 7.0 Hz, H-12). Data for keto and enol forms: 2.65 – 2.50 (2H, m, C**H₂**, keto/enol), 2.42 – 2.35 (2H, m, C**H₂**, keto/enol), 2.35 – 2.29 (2H, m, C**H₂**, keto/enol), 2.10 – 2.01 (2H, m, C**H₂**, keto/enol), 1.92 – 1.78 (2H, m, C**H₂**, keto/enol), 1.77 – 1.68 (2H, m, C**H₂**, keto/enol), 1.58 – 1.33 (8H, m, 4 x C**H₂**, keto [overlapping]), 1.58 – 1.33 (8H, m, 4 x C**H₂**, enol [overlapping]); δ_C (100 MHz, $CDCl_3$) Data for keto form: 211.9 (C-1), 170.1 (C-10), 61.3 (C-11), 58.9 (C-9), 42.5 (C-2), 27.1 (**C**H_2), 25.9 (**C**H_2), 25.0 (**C**H_2), 24.6 (**C**H_2), 24.4 (**C**H_2), 24.03 (**C**H_2), 14.2 (C-12). Full data for enol form: 176.0 (C-1/10), 173.5 (C-1/10), 100.3 (C-9), 60.3 (C-11), 42.0 (C-2), 27.0 (**C**H_2), 26.2 (**C**H_2), 25.3 (**C**H_2), 24.72 (**C**H_2), 24.66 (**C**H_2), 23.99 (**C**H_2), 14.4 (C-12); HRMS (ESI^+): calcd. for $C_{12}H_{20}NaO_3$, 235.1305. Found: $[MNa]^+$, 235.1308 (−1.3 ppm error). Characterisation data matched those reported in the literature.[18]

2.15: Cyclononanone



In an argon atmosphere, a solution of ethyl 2-oxocyclononane-1-carboxylate (8.70 g, 41.0 mmol) in DMSO (50.0 mL) and water (12.0 mL) was heated to 160 °C and stirred for 16 hours. The reaction mixture was then cooled and partitioned between water (60 mL) and diethyl ether (3 x 80 mL) before the organic layers were dried, filtered and concentrated *in vacuo*. Purification was done by flash column chromatography (SiO_2, 20:1 hexane : ethyl acetate → 10:1 hexane : ethyl acetate → 2:1 hexane : ethyl acetate) affording the title compound, which was obtained as a yellow oil (2.35 g, 41%); R_f = 0.18 (10:1 hexane : ethyl acetate); ν_{max}/cm^{-1} (thin film): 2925, 2873, 1698, 1471, 1445, 1344, 1220, 1151, 784, 517; δ_H (400 MHz, $CDCl_3$) 2.45 – 2.34 (4H, m, H-2,9), 1.88 – 1.74 (4H, m, 2 x C**H$_2$**), 1.61 – 1.47 (4H, m, 2 x C**H$_2$**), 1.40 – 1.30 (4H, m, 2 x C**H$_2$**); δ_C (100 MHz, $CDCl_3$) 218.5 (C-1), 43.7 (C-2,9), 27.1 (2 x **C**H$_2$), 25.1 (2 x **C**H$_2$), 24.4 (2 x **C**H$_2$); HRMS (APCI$^+$): calcd. for $C_9H_{17}O$, 141.1274. Found: $[MH]^+$, 141.1270 (−2.9 ppm error). Characterisation data matched those reported in the literature.[18]

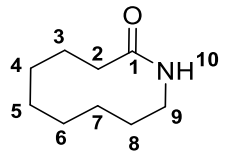
2.16: Azonan-2-one



To a round-bottomed flask, cyclooctanone (1.27 g, 10.1 mmol) in formic acid (10.0 mL) was added hydroxylamine-O-sulfonic acid (1.73 g, 15.3 mmol) in formic acid (5.0 mL) over 30 minutes *via* a syringe pump. The reaction mixture was heated to reflux (100 °C) and stirred for 16 hours. The reaction mixture was quenched with ice-cold water (20 mL), neutralised with 2*N* NaOH (200 mL) and then extracted with $CHCl_3$ (4 x 60 mL). The organic layer was then dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 2:1 hexane : ethyl acetate → 100% ethyl acetate → 9:1 ethyl acetate : methanol) afforded the title compound, which was obtained as a white solid (1.00 g, 70%), and exists in $CDCl_3$ as a 5:1 mixture of rotamers; R_f = 0.38 (9:1 ethyl acetate : methanol); MP = 72 – 75 °C; ν_{max}/cm^{-1} (thin film): 3299, 2926, 2869, 1647, 1548, 1452, 1354, 784, 709; δ_H (400 MHz, $CDCl_3$) Data for major rotamer: 6.44 (1H, br s, H-9), 3.39 – 3.24 (2H, m, H-8), 2.44

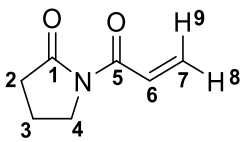
– 2.35 (2H, m, H-2), 1.84 – 1.74 (2H, m, C**H$_2$**), 1.64 – 1.37 (8H, m, 4 x C**H$_2$**). Diagnostic data for the minor rotamer: 5.56 (1H, br s, H-9); δ_C (100 MHz, $CDCl_3$) Data for major rotamer: 178.2 (C-1), 43.4 (C-8), 33.1 (C-2), 30.0 (**C**H$_2$), 27.9 (**C**H$_2$), 25.4 (**C**H$_2$ [overlapping]), 24.5 (**C**H$_2$), 23.1 (**C**H$_2$). Full data for minor rotamer: 176.7 (C-1), 40.4 (C-2/8), 38.7 (C-2/8), 29.4 (**C**H$_2$), 29.2 (**C**H$_2$), 25.9 (**C**H$_2$), 25.4 (**C**H$_2$ [overlapping]), 23.8 (**C**H$_2$); HRMS (ESI$^+$): calcd. for $C_8H_{15}NNaO$, 164.1046. Found: $[MNa]^+$, 164.1046 (0.0 ppm error). Characterisation data matched those reported in the literature.[18]

2.17: Azecan-2-one



To a round-bottomed flask, cyclononanone (1.17 g, 8.35 mmol) in formic acid (10.0 mL) was added hydroxylamine-O-sulfonic acid (1.41 g, 12.5 mmol) in formic acid (6.0 mL) over 30 minutes *via* a syringe pump. The reaction mixture was heated to reflux (100 °C) and stirred for 16 hours. The reaction mixture was quenched with ice-cold water (10 mL), neutralised with 2*N* NaOH (200 mL) and then extracted with $CHCl_3$ (4 x 60 mL). The organic layer was then dried over $MgSO_4$, filtered and concentrated *in vacuo*, affording the title compound, which was obtained as a white solid (445 mg, 34%); R_f = 0.38 (9:1 ethyl acetate : methanol); MP = 117 – 122 °C; ν_{max}/cm^{-1} (thin film): 3307, 3095, 2924, 2867, 1637, 1551, 1467, 1437, 1290, 1231, 759, 702, 647, 619; δ_H (400 MHz, $CDCl_3$) 5.98 (1H, br s, H-10), 3.30 (2H, q, *J* = 6.0 Hz, H-9), 2.24 – 2.17 (2H, m, H-2), 1.74 – 1.59 (4H, m, 2 x C**H$_2$**), 1.52 – 1.42 (4H, m, 2 x C**H$_2$**), 1.40 – 1.29 (4H, m, 2 x C**H$_2$**); δ_C (100 MHz, $CDCl_3$) 174.6 (C-1), 40.7 (C-9), 37.6 (C-2), 26.14 (**C**H$_2$), 26.11 (**C**H$_2$), 24.4 (**C**H$_2$), 24.3 (**C**H$_2$), 23.9 (**C**H$_2$), 23.3 (**C**H$_2$); HRMS (ESI$^+$): calcd. for $C_9H_{18}NO$, 156.1383. Found: $[MH]^+$, 156.1383 (0.0 ppm error). Characterisation data matched those reported in the literature.[18]

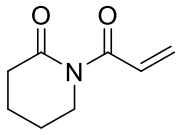
2.25: 1-Acryloylpyrrolidin-2-one



To a round-bottomed flask, MeMgBr (3.0 M in diethyl ether, 1.85 mL, 5.55 mmol) was added dropwise *via* a syringe pump over 30 minutes to a stirring solution of pyrrolidin-2-one (431

mg, 5.06 mmol) in THF (18.0 mL), in an inert atmosphere of Ar, cooled to 0 °C. The reaction mixture was stirred for 10 minutes after the complete addition had occurred. Acryloyl chloride (0.62 mL, 7.59 mmol) was then added in a single portion to the reaction mixture and was stirred for a further 30 minutes at 0 °C. The reaction mixture was then quenched with sat. aq. NH_4Cl (20 mL) and then was extracted with Et_2O (20 mL). The organic layer was then washed with sat. aq. $NaHCO_3$ (2 x 15 mL). The organic layer was extracted and dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 diethyl ether : hexane) afforded the title compound, which was obtained as a colourless liquid (269 mg, 38%); R_f = 0.34 (1:1 ethyl acetate : hexane); ν_{max}/cm^{-1} (thin film): 2985, 1735, 1678, 1617, 1407, 1360, 1313, 1250, 1226, 1193, 799, 587; δ_H (400 MHz, $CDCl_3$) 7.45 (1H, dd, *J* = 17.0, 10.5 Hz, H-6), 6.47 (1H, dd, *J* = 17.0, 2.0 Hz, H-8), 5.82 (1H, dd, *J* = 10.5, 2.0 Hz, H-9), 3.85 (2H, t, *J* = 7.5 Hz, H-4), 2.60 (2H, t, *J* = 7.5 Hz, H-2), 2.04 (2H, p, *J* = 7.5 Hz, H-3); δ_C (100 MHz, $CDCl_3$) 175.7 (C-1), 166.1 (C-5), 130.9 (C-7), 129.2 (C-6), 45.7 (C-4), 33.8 (C-2), 17.3 (C-3); HRMS (ESI^+): calcd. for $C_7H_9NNaO_2$, 162.0525 Found: $[MNa]^+$, 162.0524 (0.6 ppm error).

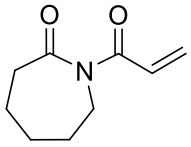
2.26: 1-Acryloylpiperidin-2-one



To a stirring solution of δ-valerolactam (997 mg, 10.1 mmol) in 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 minutes. The reaction mixture was stirred for 10 minutes after complete addition, before acryloyl chloride (1.23 mL, 15.1 mmol) was added in a single portion and the reaction mixture was stirred for an additional 30 minutes at 0 °C. The reaction was then quenched with sat. aq. NH_4Cl (30 mL) and then was extracted with Et_2O (50 mL). The organic layer was washed with sat. aq. $NaHCO_3$ (2 × 30 mL). The organic layer was extracted and dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 diethyl ether : hexane) afforded the title compound, which was obtained as a colourless liquid (1.06 g, 69%); R_f = 0.59 (100% 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**CH_2), 6.32 (1H, dd, *J* = 17.0, 1.5 Hz, NCOCHC**H₂**), 5.69 (1H, dd, *J* = 10.5, 1.5 Hz, NCOCHC**H₂**), 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**HCH₂), 128.0 (NCOCH**C**H₂), 44.7 (N**C**H₂), 34.9 (**C**H₂CON), 22.6 (**C**H₂), 20.8

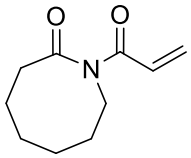
(**C**H_2); HRMS (ESI$^+$): calcd. for $C_8H_{11}NNaO_2$, 176.0682. Found: [MNa]$^+$, 176.0684 (−0.9 ppm error).

2.27: 1-Acryloylazepan-2-one



To a stirring solution of caprolactam (226 mg, 2.00 mmol) in THF (7.3 mL) cooled to 0 °C, was added a solution of MeMgBr (3.0 M in diethyl ether, 0.73 mL, 2.19 mmol) *via* dropwise addition using a syringe pump over 30 minutes. The reaction mixture was stirred for 10 minutes at 0 °C after complete addition was completed. Acryloyl chloride (0.24 mL, 3.00 mmol) was then added in a single portion and the reaction mixture was stirred for an additional 30 minutes at 0 °C. The reaction mixture was then quenched with sat. aq. NH_4Cl (8 mL) and then was extracted with Et_2O (10 mL). The organic layer was washed with sat. aq. $NaHCO_3$ (2 × 10 mL) and the organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 diethyl ether : hexane) afforded the title compound, which was obtained as a colourless oil (219 mg, 66%); R_f = 0.67 (100% 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* = 17.0, 10.5 Hz, NCOC**H**CH_2), 6.28 (1H, dd, *J* = 17.0, 2.0 Hz, NCOCHC**H$_2$**), 5.66 (1H, dd, *J* = 10.5, 2.0 Hz, NCOCHC**H$_2$**), 3.91 – 3.86 (2H, m, NC**H$_2$**), 2.72 – 2.66 (2H, m, C**H$_2$**CON), 1.81 – 1.63 (6H, m, 3 × C**H$_2$**); δ_C (100 MHz, $CDCl_3$) 178.1 (**C**O), 168.9 (**C**O), 131.9 (NCO**C**HCH_2), 128.0 (NCOCH**C**H_2), 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).

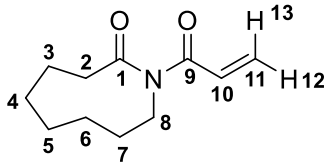
2.28: 1-Acryloylazocan-2-one



To a stirring solution of 1-aza-2-cyclooctanone (561 mg, 4.41 mmol) in THF (18 mL) cooled to 0 °C was added a solution of MeMgBr (3.0 M in diethyl ether, 1.62 mL, 4.86 mmol) *via* dropwise addition using a syringe pump over 30 minutes. The reaction mixture was stirred

for 10 minutes at 0 °C after complete addition was completed. Acryloyl chloride (0.54 mL, 6.61 mmol) was then added in a single portion and the reaction mixture was stirred for an additional 30 minutes at 0 °C. The reaction was then quenched with sat. aq. NH_4Cl (20 mL) and then was extracted with Et_2O (25 mL). The organic layer was washed with sat. aq. $NaHCO_3$ (2 × 25 mL), and organic extracts dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 diethyl ether : hexane) afforded the title compound, which was obtained as a white crystalline solid (640 mg, 80%); R_f = 0.67 (9:1 ethyl acetate : methanol); MP = 29 – 33 °C; ν_{max}/cm^{-1} (thin film): 2926, 2859, 1677, 1616, 1445, 1401, 1378, 1333, 1303, 1248, 1201, 1174, 1126, 1092, 1019, 996, 972, 867, 797, 777, 695, 585; δ_H (400 MHz, $CDCl_3$) 6.81 (1H, dd, *J* = 17.0, 10.5 Hz, NCOC**H**CH_2), 6.24 (1H, dd, *J* = 17.0, 1.5 Hz, NCOCHC**H₂**), 5.61 (1H, dd, *J* = 10.5, 1.5 Hz, NCOCHC**H₂**), 3.89 – 3.82 (2H, m, C**H₂**N), 2.63 – 2.57 (2H, m, C**H₂**CON), 1.86 – 1.77 (2H, m, C**H₂**), 1.74 – 1.65 (2H, m, C**H₂**), 1.58 – 1.50 (2H, m, C**H₂**), 1.44 – 1.36 (2H, m, C**H₂**); δ_C (100 MHz, $CDCl_3$) 178.9 (**C**ON), 169.4 (**C**OCHCH₂), 131.9 (CO**C**HCH₂), 127.6 (COCH**C**H₂), 43.8 (**C**H₂N), 36.7 (**C**H₂CON), 29.9 (**C**H₂), 29.3 (**C**H₂), 26.2 (**C**H₂), 23.9 (**C**H₂); HRMS (ESI^+): calcd. for $C_{10}H_{16}NO_2$, 182.1176. Found: $[MH]^+$, 182.1180 (−2.3 ppm error).

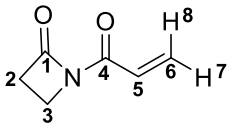
2.29: 1-Acryloylazonan-2-one



To a round-bottomed flask, MeMgBr (3.0 M in diethyl ether, 0.39 mL, 1.17 mmol) was added dropwise *via* a syringe pump over 30 minutes to a stirring solution of azonan-2-one (150 mg, 1.06 mmol) in THF (15.0 mL), under Ar, cooled to 0 °C. The reaction mixture was stirred for 10 minutes at 0 °C after the complete addition had occurred. Acryloyl chloride (0.13 mL, 1.59 mmol) was then added in a single portion to the reaction mixture and stirring continued for a further 30 minutes at 0 °C. The reaction mixture was quenched with sat. aq. NH_4Cl (15 mL) and the mixture was extracted with Et_2O (15 mL). The organic layer was then washed with sat. aq. $NaHCO_3$ (2 x 15 mL). The organic layer was extracted and dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 diethyl ether : hexane) afforded the title compound, which was obtained as a colourless oil (115 mg, 55%), and exists in $CDCl_3$ as a 4:1 mixture of rotamers; R_f = 0.50 (9:1 ethyl acetate : methanol); ν_{max}/cm^{-1} (thin film): 2927, 2868, 1677, 1618, 1402, 1379, 1227, 1164, 1091 1021, 794, 571; δ_H (400 MHz, $CDCl_3$) Data for major rotamer: 6.72 (1H, dd, *J* =

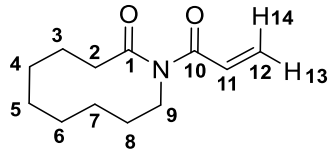
17.0, 10.5 Hz, H-10), 6.31 (1H, dd, *J* = 17.0, 1.5 Hz, H-12), 5.66 (1H, dd, *J* = 10.5, 1.5 Hz, H-13), 3.90 – 3.82 (2H, m, H-8), 2.70 – 2.62 (2H, m, H-2), 1.87 (2H, p, *J* = 6.0 Hz, C**H₂**), 1.77 (2H, p, *J* = 6.0 Hz, C**H₂**), 1.64 (2H, p, *J* = 6.0 Hz, C**H₂**), 1.48 (2H, p, *J* = 6.0 Hz, C**H₂**), 1.39 (2H, p, *J* = 6.0 Hz, C**H₂**). Diagnostic data for the minor rotamer: 3.79 (2H, t, *J* = 7.0 Hz, H-8), 3.25 (2H, t, *J* = 6.5 Hz, H-2); δ_C (100 MHz, $CDCl_3$) Data for major rotamer: 180.4 (C-1), 168.6 (C-9), 131.1 (C-10), 128.0 (C-11), 45.0 (C-8), 38.8 (C-2), 28.5 (**C**H_2), 28.1 (**C**H_2), 26.0 (**C**H_2) 25.51 (**C**H_2), 21.4 (**C**H_2). Diagnostic data for the minor rotamer: 179.7 (C-1), 172.9 (C-9), 41.7 (C-8), 39.6 (C-2), 28.7 (**C**H_2), 27.9 (**C**H_2), 25.8 (**C**H_2) 25.47 (**C**H_2), 21.3 (**C**H_2); HRMS (ESI^+): calcd. for $C_{11}H_{17}NNaO_2$, 218.1151 Found: $[MNa]^+$, 218.1154 (−1.2 ppm error).

2.32: 1-Acryloylazetidin-2-one



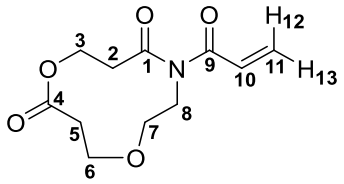
To a round-bottomed flask, DIPEA (2.20 mL, 12.6 mmol) was added to a stirring solution of 2-azetidinone (359 mg, 5.04 mmol) in THF (5.0 mL), in an inert atmosphere of Ar, cooled to 0 °C. Also cooled to 0 °C was a solution of acryloyl chloride (0.61 mL, 7.57 mmol) in THF (5.0 mL) and this was added to the other solution dropwise *via* a syringe pump over 30 minutes. The reaction mixture was stirred for 2 hours at 0 °C, before being allowed to warm to RT and then stirred for a further 3 hours. The reaction mixture was quenched with sat. aq. NH_4Cl (15 mL) and then was extracted with Et_2O (20 mL). The organic layer was then washed with sat. aq. $NaHCO_3$ (2 x 15 mL) and brine (2 x 15 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 diethyl ether : hexane) afforded the title compound, which was obtained as a white, fluffy solid (169 mg, 27%); R_f = 0.64 (9:1 ethyl acetate : methanol); MP = 42 – 45 °C; ν_{max}/cm^{-1} (thin film): 2983, 1794, 1674, 1622, 1421, 1329, 1301, 1264, 1202, 1071, 1005, 989, 916, 784, 604; δ_H (400 MHz, $CDCl_3$) 7.00 (1H, dd, *J* = 17.0, 10.0 Hz, H-5), 6.57 (1H, dd, *J* = 17.0, 1.5 Hz, H-8), 5.90 (1H, dd, *J* = 10.0, 1.5 Hz, H-7), 3.65 (2H, t, *J* = 5.5 Hz, H-3), 3.09 (2H, t, *J* = 5.5 Hz, H-2); δ_C (100 MHz, $CDCl_3$) 165.2 (C-1), 162.7 (C-4), 131.7 (C-6), 129.1 (C-5), 36.6 (**C**H_2), 36.2 (**C**H_2); HRMS (ESI^+): calcd. for $C_6H_7NNaO_2$, 148.0369 Found: $[MNa]^+$, 148.0370 (−0.6 ppm error).

2.33: 1-Acryloylazecan-2-one



A stirring solution of azecan-2-one (801 mg, 5.16 mmol) and DIPEA (2.25 mL, 12.9 mmol) in THF (10.0 mL) was cooled to 0 °C. To this was added a 0 °C cooled solution of acryloyl chloride (0.84 mL, 10.3 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 3 hours. The reaction mixture was then quenched with sat. aq. NH_4Cl (15 mL), extracted with Et_2O (20 mL), then the organic layer was washed with sat. aq. $NaHCO_3$ (2 × 15 mL), and brine (2 × 15 mL). The organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 diethyl ether : hexane) afforded 765 mg of material, which contained the title compound but was contaminated with unreacted starting material. The impure material was therefore dissolved in Et_2O (5 mL) and then washed with $NaHCO_3$ (2 x 5 mL). The organic portion was then dried over $MgSO_4$, filtered and concentrated *in vacuo*. This work-up process was then repeated a second time, to afford a pure sample of the title compound, which was obtained as a colourless oil (503 mg, 47%); R_f = 0.64 (9:1 ethyl acetate : methanol); ν_{max}/cm^{-1} (thin film): 2933, 2872, 1680, 1660, 1618, 1405, 1380, 1242, 1176, 1136, 1083, 977, 795; δ_H (400 MHz, $CDCl_3$) 6.64 (1H, dd, *J* = 17.0, 10.5 Hz, H-11), 6.39 (1H, dd, *J* = 17.0, 1.5 Hz, H-13), 5.77 (1H, dd, *J* = 10.5, 1.5 Hz, H-14), 3.90 (2H, t, *J* = 5.5 Hz, H-9), 2.85 – 2.78 (2H, m, H-2), 1.89 – 1.74 (4H, m, 2 x C**H₂**), 1.55 – 1.36 (8H, m, 4 x C**H₂**); δ_C (100 MHz, $CDCl_3$) 179.9 (C-1), 169.2 (C-10), 130.8 (C-11), 129.4 (C-12), 45.0 (C-9), 37.8 (C-2), 25.2 (**C**H_2), 25.1 (**C**H_2), 24.8 (**C**H_2), 24.5 (**C**H_2), 24.3 (**C**H_2), 22.8 (**C**H_2); HRMS (ESI^+): calcd. for $C_{12}H_{19}NNaO_2$, 232.1308 Found: $[MNa]^+$, 232.1313 (−2.1 ppm error).

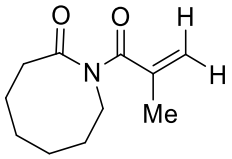
2.34: 5-Acryloyl-1,8-dioxa-4-azacycloundecane-5,9-dione



A stirring solution of 1,8-dioxa-4-azacycloundecane-5,9-dione (145 mg, 0.774 mmol) and DIPEA (0.34 mL, 1.94 mmol) in THF (5.0 mL) was cooled to 0 °C. To this was added a 0 °C cooled solution of acryloyl chloride (0.15 mL, 1.86 mmol) in THF (6.0 mL) dropwise. Under

an argon atmosphere, this mixture was stirred at 0 °C for 2 hours and a further 48 hours at RT. The reaction mixture was then quenched with sat. aq. NH_4Cl (15 mL), extracted with Et_2O (15 mL), then the organic layer was washed with sat. aq. $NaHCO_3$ (2 × 10 mL) and brine (2 x 10 mL). The organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 hexane : ethyl acetate) afforded the title compound, which was obtained as a colourless oil (104 mg, 64%); R_f = 0.60 (9:1 ethyl acetate : methanol); ν_{max}/cm^{-1} (thin film): 2925, 1738, 1682, 1620, 1409, 1352, 1267, 1178, 1121, 1067, 977, 796; δ_H (400 MHz, $CDCl_3$) 6.60 (1H, dd, *J* = 17.0, 10.5 Hz, H-10), 6.37 (1H, dd, *J* = 17.0, 1.5 Hz, H-12), 5.80 (1H, dd, *J* = 10.5, 1.5 Hz, H-13), 4.47 (2H, t, *J* = 5.5 Hz, H-3), 3.91 (2H, t, *J* = 5.0 Hz, H-8), 3.70 (2H, t, *J* = 6.0 Hz, H-6), 3.62 (2H, t, *J* = 5.0 Hz, H-7), 3.09 (2H, t, *J* = 5.5 Hz, H-2), 2.51 (2H, t, *J* = 6.0 Hz, H-5); δ_C (100 MHz, $CDCl_3$) 175.6 (C-1), 171.4 (C-4), 169.1 (C-9), 130.8 (C-11), 130.2 (C-10), 68.0 (C-7), 67.6 (C-6), 61.4 (C-3), 45.2 (C-8), 38.3 (C-2), 35.8 (C-5); HRMS (ESI^+): calcd. for $C_{11}H_{15}NNaO_5$, 264.0842. Found: $[MNa]^+$, 264.0840 (1.0 ppm error).

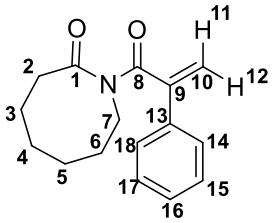
2.39: 1-Methacryloylazocan-2-one



To a round-bottomed flask, MeMgBr (3.0 M in diethyl ether, 0.73 mL, 2.19 mmol) was added dropwise *via* a syringe pump over 30 minutes to a stirring solution of azocan-2-one (255 mg, 2.01 mmol) in THF (10.0 mL), in an inert atmosphere of argon, cooled to 0 °C. The reaction mixture was stirred for 10 minutes at 0 °C after the complete addition had occurred. 1-Methacryloyl chloride (0.29 mL, 3.01 mmol) was then added in a single portion to the reaction mixture and was stirred for a further 30 minutes at 0 °C. The reaction mixture was quenched with sat. aq. NH_4Cl (10 mL) and the mixture was extracted with Et_2O (15 mL). The organic layer was then washed with sat. aq. $NaHCO_3$ (2 x 15 mL). The organic layer was extracted and dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 diethyl ether : hexane) afforded the title compound, which was obtained as a colourless oil (360 mg, 92%); R_f = 0.63 (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, $CDCl_3$) 5.16 (1H, p, *J* = 1.0, NCOC(CH_3)C$\mathbf{H_2}$), 5.12 (1H, p, *J* = 1.5 Hz, NCOC(CH_3)C$\mathbf{H_2}$), 3.87 – 3.80 (2H, m, NC$\mathbf{H_2}$), 2.62 – 2.55 (2H, m, C$\mathbf{H_2}$CON), 1.95 (3H, t, *J* = 1.5 Hz, NCOC(C$\mathbf{H_3}$)CH_2), 1.85 (2H, p, *J* = 6.0 Hz, C$\mathbf{H_2}$), 1.77 (2H, p, *J* = 6.0 Hz, C$\mathbf{H_2}$), 1.59 (2H, p, *J* = 6.5 Hz, C$\mathbf{H_2}$), 1.52 – 1.44 (2H, m, C$\mathbf{H_2}$); δ_C (100 MHz, $CDCl_3$) 178.6 (**C**O), 175.5 (**C**O), 143.2

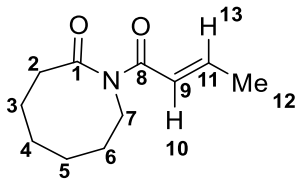
(NCO**C**(CH_3)CH_2), 116.2 (NCOC(CH_3)**C**H_2), 44.0 (N**C**H_2), 36.0 (**C**H_2CON), 30.2 (**C**H_2), 29.0 (**C**H_2), 26.2 (**C**H_2), 23.9 (**C**H_2), 19.2 (**C**H_3); HRMS (ESI^+): calcd. for $C_{11}H_{17}NNaO_2$, 218.1151. Found: $[MNa]^+$, 218.1154 (–1.0 ppm error).

2.40: 1-(2-Phenylacryloyl)azocan-2-one



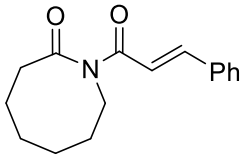
To a round-bottomed flask, MeMgBr (3.0 M in diethyl ether, 0.83 mL, 2.49 mmol) was added dropwise *via* a syringe pump over 30 minutes to a stirring solution of azocan-2-one (288 mg, 2.27 mmol) in THF (10.0 mL), in an inert atmosphere of argon, cooled to 0 °C. The reaction mixture was stirred for 10 minutes at 0 °C after the complete addition had occurred. 2-Phenylacryloyl chloride (0.71 mL, 4.55 mmol) was then added in a single portion to the reaction mixture and was stirred for a further 30 minutes at 0 °C. The reaction mixture was quenched with sat. aq. NH_4Cl (10 mL) and the mixture was extracted with Et_2O (12 mL). The organic layer was then washed with sat. aq. $NaHCO_3$ (2 x 12 mL). The organic layer was extracted and dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 diethyl ether : hexane) afforded the title compound, which was obtained as a colourless oil (122 mg, 28%); R_f = 0.49 (1:1 ethyl acetate : hexane); ν_{max}/cm^{-1} (thin film): 2928, 2859, 1794, 1678, 1445, 1334, 1203, 1175, 1129, 1068, 1011, 777, 701, 593; δ_H (400 MHz, $CDCl_3$) 7.39 – 7.24 (5H, m, 5 x Ar**H**), 5.57 (1H, s, H-11/12), 5.46 (1H, s, H-11/12), 4.01 – 3.95 (2H, m, H-7), 2.46 – 2.40 (2H, m, H-2), 1.85 (2H, p, *J* = 6.0 Hz, H-6), 1.76 (2H, p, *J* = 6.0 Hz, H-3), 1.59 – 1.53 (2H, m, H-4), 1.52 – 1.45 (2H, m, H-5); δ_C (100 MHz, $CDCl_3$) 177.7 (C-1), 173.2 (C-8), 147.8 (C-13), 136.9 (C-9), 128.5 (2 x Ar**C**H), 128.1 (C-16), 126.7 (2 x Ar**C**H), 115.9 (C-10), 43.8 (C-7), 36.0 (C-2), 30.0 (C-6), 28.9 (C-3), 26.2 (C-4), 24.0 (C-5); HRMS (ESI^+): calcd. for $C_{16}H_{19}NNaO_2$, 280.1308. Found: $[MNa]^+$, 280.1307 (0.2 ppm error).

2.41: (*E*)-1-(But-2-enoyl)azocan-2-one



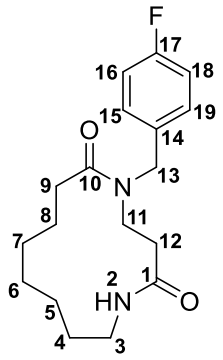
To a round-bottomed flask, MeMgBr (3.0 M in diethyl ether, 1.10 mL, 3.30 mmol) was added dropwise *via* a syringe pump over 30 minutes to a stirring solution of azocan-2-one (383 mg, 3.01 mmol) in THF (12.0 mL), in an inert atmosphere of Ar, cooled to 0 °C. The reaction mixture was stirred for 10 minutes at 0 °C after the complete addition had occurred. (*E*)-But-2-enoyl chloride (0.44 mL, 4.51 mmol) was then added in a single portion to the reaction mixture and was stirred for a further 30 minutes at 0 °C. The reaction mixture was quenched with sat. aq. NH_4Cl (12 mL) and the mixture was extracted with Et_2O (18 mL). The organic layer was then washed with sat. aq. $NaHCO_3$ (2 x 18 mL). The organic layer was extracted and dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 diethyl ether : hexane → 2:1 diethyl ether : hexane) afforded the title compound, which was obtained as a pale yellow oil (510 mg, 87%), and exists in $CDCl_3$ as a 20:1 mixture of rotamers; R_f = 0.72 (1:1 ethyl acetate : hexane); ν_{max}/cm^{-1} (thin film): 2928, 2859, 1678, 1636, 1444, 1334, 1197, 1174, 1130, 1089, 962, 597; δ_H (400 MHz, $CDCl_3$) Data for major rotamer: 6.97 – 6.87 (1H, m, H-13), 6.66 – 6.64 (0.5H, m, H-10), 6.62 – 6.60 (0.5H, m, H-10'), 3.91 – 3.84 (2H, m, H-7), 2.66 – 2.59 (2H, m, H-2), 1.90 – 1.81 (2H, m, H-3 [overlapping]), 1.86 – 1.81 (3H, dd, *J* = 7.0, 1.5 Hz, H-12 [overlapping]), 1.72 (2H, p, *J* = 6.5 Hz, H-6), 1.57 (2H, p, *J* = 6.0 Hz, H-4), 1.47 – 1.40 (2H, m, H-5). Diagnostic data for minor rotamer: 6.45 – 6.42 (0.5H, m, H-10), 6.41 – 6.39 (0.5H, m, H-10'), 6.22 – 6.13 (1H, m, H-13), 4.06 – 4.02 (2H, m, H-7), 2.81 – 2.76 (2H, m, H-2), 2.04 (3H, dd, *J* = 7.5, 2.0 Hz, H-12); δ_C (100 MHz, $CDCl_3$) Data for major rotamer: 178.8 (C-1), 169.3 (C-8), 142.7 (C-11), 126.4 (C-9), 43.7 (C-7), 36.80 (C-2), 30.0 (C-6), 29.23 (C-3), 26.3 (C-4), 23.9 (C-5), 18.3 (C-12). Diagnostic data for minor rotamer: 178.5 (C-1), 169.1 (C-8), 140.9 (C-11), 124.9 (C-9), 43.4 (C-7), 36.76 (C-2), 29.8 (C-6), 29.18 (C-3), 24.0 (C-5), 15.8 (C-12); HRMS (ESI^+): calcd. for $C_{11}H_{17}NNaO_2$, 218.1151. Found: $[MNa]^+$, 218.1150 (2.9 ppm error).

2.42: 1-Cinnamoylazocan-2-one



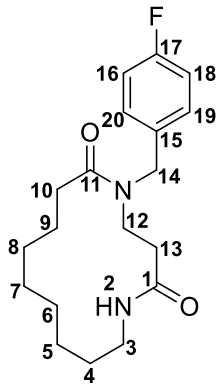
To a round-bottomed flask, MeMgBr (3.0 M in diethyl ether, 1.10 mL, 3.30 mmol) was added dropwise *via* a syringe pump over 30 minutes to a stirring solution of azocan-2-one (379 mg, 2.98 mmol) in THF (12.0 mL), in an inert atmosphere of Ar, cooled to 0 °C. The reaction mixture was stirred for 10 minutes at 0 °C after the complete addition had occurred. Cinnamoyl chloride (681 mg, 4.47 mmol) was then added in a single portion to the reaction mixture and was stirred for a further 30 minutes at 0 °C. The reaction mixture was quenched with sat. aq. NH_4Cl (12 mL) and the mixture was extracted with Et_2O (18 mL). The organic layer was then washed with sat. aq. $NaHCO_3$ (2 x 18 mL). The organic layer was extracted and dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 diethyl ether : hexane → 2:1 diethyl ether : hexane) afforded the title compound, which was obtained as a white solid (345 mg, 59%); R_f = 0.70 (1:1 ethyl acetate : hexane); MP = 78 – 84 °C; ν_{max}/cm^{-1} (thin film): 2925, 2858, 1671, 1614, 1332, 1196, 1174, 1124, 1090, 763, 557; δ_H (400 MHz, $CDCl_3$) 7.69 (1H, dd, *J* = 15.5, 2.0 Hz, ArC**H**CHCON), 7.59 – 7.49 (2H, m, 2 x Ar**H**), 7.40 – 7.32 (3H, m, 3 x Ar**H**), 7.29 (1H, dd, *J* = 20.5, 2.5 Hz, ArCHC**H**CON), 4.03 – 3.89 (2H, m, C**H₂**N), 2.75 – 2.64 (2H, m, C**H₂**CON), 1.97 – 1.86 (2H, m, C**H₂**), 1.86 – 1.74 (2H, m, C**H₂**), 1.68 – 1.57 (2H, m, C**H₂**), 1.55 – 1.43 (2H, m, C**H₂**); δ_C (100 MHz, $CDCl_3$) 179.1 (**C**ON), 169.6 (**C**OCHCH), 143.0 (Ar**C**HCHCON), 135.3 (Ar**C**), 130.0 (2 × Ar**C**H), 128.9 (2 × Ar**C**H), 128.4 (Ar**C**H), 122.2 (ArCH**C**HCON), 44.0 (**C**H_2N), 37.0 (**C**H_2CON), 30.1 (**C**H_2), 29.3 (**C**H_2), 26.4 (**C**H_2), 24.0 (**C**H_2); HRMS (ESI^+): calcd. for $C_{16}H_{19}NNaO_2$, 280.1308. Found: $[MNa]^+$, 280.1308 (0.1 ppm error).

2.45: 5-(4-Fluorobenzyl)-1,5-diazacyclotridecane-2,6-dione



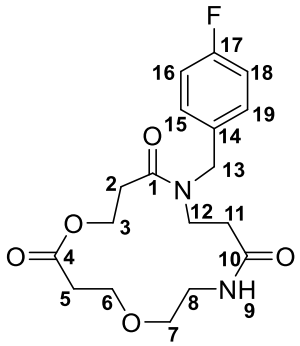
To a solution of 1-acryloylazonan-2-one (96.7 mg, 0.495 mmol) in methanol (1.0 mL), was added 4-fluorobenzylamine (62.5 µL, 0.546 mmol) in a single portion. The reaction mixture was stirred for 4 hours at RT and then the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 ethyl acetate : hexane → 2:1 ethyl acetate : hexane → 100% ethyl acetate → 49:1 ethyl acetate : methanol) afforded the title compound, which was obtained as a white solid (128 mg, 81%), and exists in $CDCl_3$ as a 10:1 mixture of rotamers. The ^{1}H NMR spectrum is severely affected by rotameric broadening, with product identity and purity best determined using ^{13}C NMR data; R_f = 0.27 (9:1 ethyl acetate : methanol); MP = 110 – 114 °C; ν_{max}/cm^{-1} (thin film): 3301, 2929, 2860, 2239, 1627, 1562, 1509, 1440, 1413, 1221, 1156, 909, 818, 728, 499; δ_H (400 MHz, $CDCl_3$) Data for major rotamer: 7.13 – 7.07 (2H, m, 2 x Ar**H**), 7.05 – 6.97 (2H, m, 2 x Ar**H**), 6.71 (1H, br t, *J* = 5.5 Hz, H-2), 4.76 – 4.58 (2H, m, H-13), 3.69 – 3.63 (1H, m, 0.5 × C**H₂**), 3.39 – 3.26 (1H, m, 0.5 × C**H₂**), 2.76 – 2.58 (2H, m, C**H₂**), 2.44 – 2.22 (3H, m, 1.5 x C**H₂**), 1.84 – 1.68 (2H, m, C**H₂**), 1.63 – 1.47 (3H, m, 1.5 × C**H₂**), 1.47 – 1.25 (6H, m, 3 × C**H₂**). Diagnostic data for the minor rotamer: 5.56 (1H, br t, *J* = 6.5 Hz, H-2); δ_C (100 MHz, $CDCl_3$) Data for major rotamer: 175.9 (C-1), 170.6 (C-10), 162.30 (C-17, d, $^1J_{CF}$ = 246.1 Hz), 132.4 (C-14, d, $^4J_{CF}$ = 3.4 Hz), 128.1 (2 × Ar**C**H, d, $^3J_{CF}$ = 7.8 Hz), 116.0 (2 × Ar**C**H, d, $^2J_{CF}$ = 21.3 Hz), 52.3 (C-13), 42.6 (C-11), 39.7 (C-3), 34.9 (C-9/12), 32.8 (C-9/12), 27.9 (**C**H_2), 27.2 (**C**H_2), 27.0 (**C**H_2), 25.8 (**C**H_2), 24.3 (CH_2). Full data for the minor rotamer: 173.8 (C-1), 171.1 (C-10), 162.26 (C-17, d, $^1J_{CF}$ = 245.7 Hz), 134.2 (C-14, d, $^4J_{CF}$ = 3.6 Hz), 130.1 (2 × Ar**C**H, d, $^3J_{CF}$ = 7.8 Hz), 115.6 (2 × Ar**C**H, d, $^2J_{CF}$ = 20.9 Hz), 48.4 (C-13), 44.3 (C-11), 38.3 (C-3), 36.6 (C-9/12), 29.9 (**C**H_2), 29.8 (**C**H_2), 26.7 (**C**H_2), 25.4 (**C**H_2), 25.2 (**C**H_2), 24.7 (**C**H_2); δ_F (282 MHz, $CDCl_3$) Major rotamer: –114.64 (1F, m, Ar**F**); HRMS (ESI^+): calcd. For $C_{18}H_{25}FKN_2O_2$, 359.1532. Found: $[MK]^+$, 359.1532 (0.0 ppm error).

2.46: 5-(4-Fluorobenzyl)-1,5-diazacyclotetradecane-2,6-dione



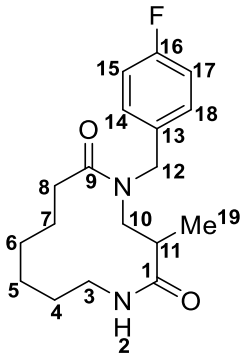
To a solution of 1-acryloylazecan-2-one (105 mg, 0.500 mmol) in methanol (1.0 mL), was added 4-fluorobenzylamine (63.0 µL, 0.551 mmol) in a single portion. The reaction mixture was stirred for 4 hours at RT and then the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 ethyl acetate : hexane → 2:1 ethyl acetate : hexane → 100% ethyl acetate → 49:1 ethyl acetate : methanol) afforded the title compound, which was obtained as a colourless oil (95.7 mg, 57%), and exists in $CDCl_3$ as a 15:1 mixture of rotamers; R_f = 0.36 (9:1 ethyl acetate : methanol); ν_{max}/cm^{-1} (thin film): 3315, 2932, 2860, 2238, 1624, 1552, 1509, 1412, 1361, 1222, 1156, 909, 818, 728, 645, 499; δ_H (400 MHz, $CDCl_3$) Data for major rotamer: 7.16 – 7.09 (2H, m, 2 x Ar**H**), 7.06 – 6.99 (2H, m, 2 x Ar**H**), 6.12 (1H, br t, *J* = 6.0 Hz, H-2), 4.70 (2H, s, H-14), 3.61 – 3.51 (2H, m, H-12), 3.34 – 3.24 (2H, m, H-3), 2.69 (2H, t, *J* = 6.0 Hz, H-13), 2.43 – 2.35 (2H, m, H-10), 1.72 – 1.64 (2H, m, H-9), 1.52 – 1.43 (2H, m, H-4), 1.42 – 1.29 (8H, m, 4 × C**H₂**). Diagnostic data for the minor rotamer: 7.34 – 7.29 (2H, m, 2 x Ar**H**), 4.59 (2H, s, H-14), 3.76 – 3.71 (2H, m, H-12), 2.47 (2H, t, *J* = 6.5 Hz, H-13), 2.26 – 2.22 (2H, m, H-10); δ_C (100 MHz, $CDCl_3$) Data for major rotamer: 174.6 (C-1), 171.1 (C-11), 162.2 (C-18, d, $^1J_{CF}$ = 245.4 Hz), 133.1 (C-15, d, $^4J_{CF}$ = 2.9 Hz), 128.1 (2 × Ar**C**H, d, $^3J_{CF}$ = 8.3 Hz), 115.8 (2 × Ar**C**H, d, $^2J_{CF}$ = 21.2 Hz), 53.4 (C-14), 43.8 (C-12), 38.8 (C-3), 34.7 (C-13), 33.0 (C-10), 27.6 (**C**H_2), 25.6 (**C**H_2), 25.4 (**C**H_2), 25.3 (**C**H_2), 25.1 (**C**H_2), 23.1 (**C**H_2). Diagnostic data for the minor rotamer: 174.0 (C-1), 170.8 (C-11), 130.0 (2 × Ar**C**H, d, $^3J_{CF}$ = 7.5 Hz), 48.2 (C-14), 45.0 (C-12), 40.7 (C-3), 37.6 (C-10/13), 36.3 (C-10/13); δ_F (282 MHz, $CDCl_3$) Major rotamer: −115.03 (1F, m, Ar**F**), minor rotamer: −114.76 (1F, m, Ar**F**); HRMS (ESI^+): calcd. For $C_{19}H_{28}FN_2O_2$, 335.2129. Found: $[MH]^+$, 335.2129 (0.0 ppm error).

2.47: 8-(4-Fluorobenzyl)-1,12-dioxa-4,8-diazacyclopentadecane-5,9,13-trione



To a solution of 5-acryloyl-1,8-dioxa-4-azacycloundecane-5,9-dione (104 mg, 0.430 mmol) in methanol (1.0 mL), was added 4-fluorobenzylamine (54.1 µL, 0.473 mmol) in a single portion. The reaction mixture was stirred for 20 hours at RT and then the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 ethyl acetate : hexane → 100% ethyl acetate → 48:2 ethyl acetate : methanol) afforded the title compound, which was obtained as a colourless oil (73.7 mg, 47%), and exists in $CDCl_3$ as a 10:1 mixture of rotamers; R_f = 0.23 (9:1 ethyl acetate : methanol); ν_{max}/cm^{-1} (thin film): 3314, 2931, 1732, 1635, 1552, 1510, 1414, 1356, 1261, 1220, 1183, 1157, 1119, 823, 729, 645, 499; δ_H (400 MHz, $CDCl_3$) Data for major rotamer: 7.13 – 6.96 (4H, m, 4 x Ar**H**), 6.89 (1H, br t, *J* = 5.5 Hz, H-9), 4.55 (2H, s, H-13), 4.50 – 4.44 (2H, m, H-3), 3.76 – 3.67 (4H, m, H-6/12), 3.58 – 3.53 (2H, m, H-7), 3.45 (2H, q, *J* = 5.0 Hz, H-8), 2.67 – 2.62 (2H, m, H-2), 2.60 – 2.54 (4H, m, H-5,11). Diagnostic data for the minor rotamer: 7.25 – 7.21 (2H, m, 2 x Ar**H**), 6.12 – 6.05 (1H, m, H-9), 4.57 (2H, s, H-13), 3.53 – 3.49 (2H, m, CH_2), 3.38 (2H, q, *J* = 5.0 Hz, H-8), 2.76 (2H, t, *J* = 6.5 Hz, C**H₂**), 2.38 (2H, *J* = 7.0 Hz, C**H₂**); δ_C (100 MHz, $CDCl_3$) Data for major rotamer: 172.0 (C-1/4), 172.0 (C-1/4), 171.3 (C-10), 162.4 (C-17, d, $^1J_{CF}$ = 246.4 Hz), 132.2 (C-14, d, $^4J_{CF}$ = 3.0 Hz), 127.8 (2 × ArCH, d, $^3J_{CF}$ = 7.57 Hz), 116.1 (2 × ArCH, d, $^2J_{CF}$ = 21.9 Hz), 69.2 (C-7), 66.3 (C-6), 61.2 (C-3), 51.8 (C-13), 43.9 (C-12), 39.6 (C-8), 35.6 (C-5/11), 35.4 (C-5/11), 32.8 (C-2). Diagnostic data for the minor rotamer: 170.3 (CO), 170.1 (CO), 130.0 (2 × ArCH, d, $^3J_{CF}$ = 7.9 Hz), 115.7 (2 × ArCH, d, $^2J_{CF}$ = 22.0 Hz), 69.4 (C-7), 66.8 (C-6), 60.6 (C-3), 48.9 (C-13), 44.0 (C-12), 39.4 (C-8), 37.0 (**C**H_2), 35.8 (**C**H_2), 32.9 (**C**H_2); δ_F (282 MHz, $CDCl_3$) Major rotamer: −114.46 (1F, m, Ar**F**), minor rotamer: −114.76 (1F, m, Ar**F**); HRMS (ESI^+): calcd. for $C_{18}H_{23}FN_2NaO_5$, 389.1483. Found: $[MNa]^+$, 389.1483 (0.1 ppm error).

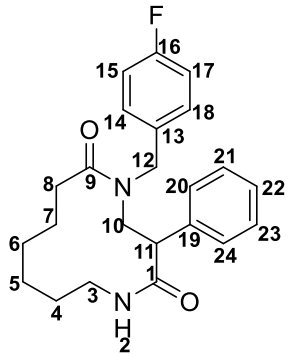
2.49: 5-(4-Fluorobenzyl)-3-methyl-1,5-diazacyclododecane-2,6-dione



To a solution of 1-methacryloylazocan-2-one (92.4 mg, 0.473 mmol) in methanol (1.1 mL), was added 4-fluorobenzylamine (64.0 µL, 0.560 mmol) in a single portion. The reaction mixture was stirred for 4 hours at RT, left overnight and then the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 2:1 ethyl acetate : hexane → 100% ethyl acetate → 48:2 ethyl acetate : methanol) afforded the title compound, which was obtained as a colourless oil (48.6 mg, 32%), and exists in $CDCl_3$ as a 15:12:5 (A:B:C) mixture of rotamers; R_f = 0.39 (9:1 ethyl acetate : methanol); ν_{max}/cm^{-1} (thin film): 3299, 2929, 2863, 2236, 1644, 1623, 1552, 1509, 1454, 1414, 1354, 1219, 1157, 923, 730; δ_H (400 MHz, $CDCl_3$) Data for rotamer A: 7.14 – 7.07 (2H, m, 2 x Ar**H**), 7.07 – 6.96 (2H, m, 2 x Ar**H**), 5.93 (1H, br d, *J* = 9.0 Hz, H-2), 4.81 (1H, d, *J* = 16.5 Hz, H-12), 4.39 (1H, d, *J* = 16.5 Hz, H-12'), 3.87 – 3.77 (1H, m, H-3), 3.71 – 3.60 (1H, m, H-10), 3.30 – 3.19 (1H, m, H-11), 2.94 – 2.76 (1H, m, H-3' [overlapping]), 2.67 – 2.55 (1H, m, H-10' [overlapping]), 2.67 – 2.55 (1H, m, H-8 [overlapping]), 2.25 – 2.14 (1H, m, H-8'), 1.86 – 1.28 (8H, m, 4 x C**H₂**), 1.03 (3H, d, *J* = 7.0 Hz, H-19). Full data for rotamer B: 7.14 – 7.07 (2H, m, 2 x Ar**H**), 7.07 – 6.96 (2H, m, 2 x Ar**H**), 6.45 (1H, br d, *J* = 9.0 Hz, H-2), 4.88 (1H, d, *J* = 17.0 Hz, H-12), 4.67 (1H, t, *J* = 14.0 Hz, H-10), 4.38 (1H, d, *J* = 17.0 Hz, H-12'), 2.94 – 2.76 (1H, m, H-11 [overlapping]), 2.94 – 2.76 (2H, m, H-3 [overlapping]), 2.67 – 2.55 (1H, m, H-10' [overlapping]), 2.42 – 2.30 (1H, m, H-8 [overlapping]), 2.11 – 2.01 (1H, m, H-8' [overlapping]), 1.86 – 1.28 (8H, m, 4 x C**H₂**), 1.18 (3H, d, *J* = 7.0 Hz, H-19). Diagnostic data for rotamer C: 5.09 (1H, br d, *J* = 10.5 Hz, H-2), 4.78 (1H, d, *J* = 14.5 Hz, H-12), 4.41 (1H, d, *J* = 24.5 Hz, H-12'), 2.42 – 2.30 (2H, m, H-11 [overlapping]), 1.07 (3H, d, *J* = 7.0 Hz, H-19); δ_C (100 MHz, $CDCl_3$) Data for all rotamers: 175.8 (C-1, rotamer B), 175.3 (C-1, rotamer A), 175.1 (C-1, rotamer C), 174.5 (C-9A/B), 174.04 (C-9C), 173.97 (C-9A/B), 162.4 (C-16B, d, $^1J_{CF}$ = 246.4 Hz), 162.3 (C-16A, d, $^1J_{CF}$ = 245.4 Hz), 134.3 (C-13C, d, $^4J_{CF}$ = 2.9 Hz), 133.0 (C-13A, d, $^4J_{CF}$ = 2.9 Hz), 132.0 (C-13B, d, $^4J_{CF}$ = 2.9 Hz), 130.4 (2 × Ar**C**H, d, $^3J_{CF}$ = 7.7 Hz, rotamer C), 128.3 (2 × Ar**C**H, d, $^3J_{CF}$ = 7.8 Hz, rotamer A), 128.0 (2 × Ar**C**H, d, $^3J_{CF}$ = 8.1 Hz, rotamer B), 116.1 (2 × Ar**C**H, d, $^2J_{CF}$ = 21.9 Hz, rotamer B), 115.8 (2 × Ar**C**H, d, $^2J_{CF}$ = 21.7 Hz, rotamer A), 115.7 (2 × Ar**C**H, d, $^2J_{CF}$ = 21.2 Hz, rotamer C), 54.9 (C-12A), 52.4 (C-

10A), 49.5 (C-12B), 48.9 (C-12C), 45.7 (C-10B), 41.5 (C-11B), 41.2 (C-11C), 40.0 (C-3A), 39.4 (C-11A), 38.4 (C-3B), 36.4 (**C**H_2, rotamer C), 33.7 (C-8A/B), 31.6 (C-8A/B), 31.1 (C-8C), 28.0 (**C**H_2, rotamer A/B), 26.9 (**C**H_2, rotamer C), 26.7 (**C**H_2, rotamer C), 26.5 (**C**H_2 [overlapping], rotamer A/B), 26.5 (**C**H_2 [overlapping], rotamer A/B), 26.0 (**C**H_2, rotamer A/B), 25.6 (**C**H_2, rotamer A/B), 24.1 (**C**H_2, rotamer A/B), 23.6 (**C**H_2, rotamer C), 22.3 (**C**H_2, rotamer A/B), 21.2 (**C**H_2, rotamer A/B), 17.0 (C-19B), 16.2 (C-19C), 15.8 (C-19A) – not all signals from the minor rotamer C were observed; δ_F (282 MHz, $CDCl_3$) Rotamer A: −114.87 (1F, m, Ar**F**), rotamer B: −114.19 (1F, m, Ar**F**), rotamer C: −114.36 (1F, m, Ar**F**); HRMS (ESI^+): calcd. for $C_{18}H_{25}FN_2NaO_2$, 343.1792. Found: $[MNa]^+$, 343.1797 (−1.4 ppm error).

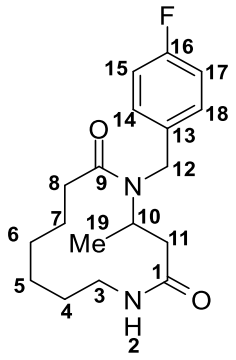
2.50: 5-(4-Fluorobenzyl)-3-phenyl-1,5-diazacyclododecane-2,6-dione



To a solution of 1-(2-phenylacryloyl)azocan-2-one (90.9 mg, 0.354 mmol) in methanol (1.2 mL), 4-fluorobenzylamine (44.4 µL, 0.389 mmol) was added in a single portion. The reaction mixture was stirred for 24 hours 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 → 100% ethyl acetate → 48:2 ethyl acetate : methanol) afforded the title compound, which was obtained as a colourless oil (42.5 mg, 31%), and exists in $CDCl_3$ as a 14:7:1 (A:B:C) mixture of rotamers; R_f = 0.65 (9:1 ethyl acetate : methanol); ν_{max}/cm^{-1} (thin film): 3301, 2927, 2861, 2243, 1647, 1622, 1549, 1509, 1455, 1412, 1221, 1156, 909, 729, 699, 511; δ_H (400 MHz, $CDCl_3$) Data for rotamer A: 7.48 – 6.97 (9H, m, 9 x Ar**H**), 6.10 (1H, br d, *J* = 7.5 Hz, H-2), 4.89 (1H, d, *J* = 16.5 Hz, H-12), 4.63 (1H, d, *J* = 16.5 Hz, H-12'), 4.45 – 4.58 (1H, m, H-11), 3.92 – 3.80 (1H, m, H-10 [overlapping]), 3.92 – 3.80 (1H, m, H-3 [overlapping]), 3.09 (1H, dd, *J* = 13.0, 11.5 Hz, H-10'), 2.86 – 2.66 (1H, m, H-8 [overlapping]), 2.86 – 2.66 (1H, m, H-3' [overlapping]), 2.36 – 2.06 (1H, m, H-8'), 1.93 – 1.33 (8H, m, 4 x C**H₂**). Full data for rotamer B: 7.48 – 6.97 (9H, m, 9 x Ar**H**), 6.90 (1H, br d, *J* = 9.5 Hz, H-2), 5.14 (1H, t, *J* = 14.0 Hz, H-10), 4.97 (1H, d, *J* = 17.0 Hz, H-12), 4.58 – 4.45 (1H, m, H-12'), 4.04 (1H, dd, *J* = 13.5, 5.0 Hz, H-11), 3.79 – 3.63 (1H, m, H-3), 2.99 – 2.87 (1H, m, H-3'), 2.86 – 2.66 (1H, m, H-10' [overlapping]), 2.44 (1H, dd, *J* = 15.5, 11.0 Hz, H-8), 2.36 – 2.06 (1H, m, H-

8'), 1.93 – 1.33 (8H, m, 4 x C**H**$_2$). Diagnostic data for rotamer C: 5.31 (1H, br d, *J* = 10.5 Hz, H-2C), 4.79 (1H, d, *J* = 14.5 Hz, H-12C), 3.38 (1H, dd, *J* = 10.5, 2.0 Hz, H-11C); δ_C (100 MHz, $CDCl_3$) Data for all rotamers: 176.2 (C-9B), 175.3 (C-9A), 175.2 (C-9C), 171.7 (C-1A), 171.6 (C-1C), 170.8 (C-1B), 162.4 (C-16B, d, $^1J_{CF}$ = 246.6 Hz), 162.3 (C-16A, d, $^1J_{CF}$ = 245.5 Hz), 137.6 (C-19C), 137.3 (C-19A), 137.1 (C-19B), 134.3 (C-13C, d, $^4J_{CF}$ = 3.5 Hz), 133.0 (C-13A, d, $^4J_{CF}$ = 3.0 Hz), 131.8 (C-13B, d, $^4J_{CF}$ = 3.5 Hz), 130.3 (2 × Ar**C**H, d, $^3J_{CF}$ = 7.5 Hz, rotamer C), 129.0 (Ar**C**H, rotamer B), 128.7 (2 x Ar**C**H, rotamer A), 128.4 (2 × Ar**C**H, d, $^3J_{CF}$ = 8.5 Hz, rotamer A), 128.1 (2 × Ar**C**H, d, $^3J_{CF}$ = 7.5 Hz, rotamer B), 128.1 (2 x Ar**C**H, rotamer A), 127.8 (Ar**C**H, rotamer A/B), 127.6 (Ar**C**H, rotamer A/B), 116.2 (2 × Ar**C**H, d, $^2J_{CF}$ = 22.0 Hz, rotamer B), 115.8 (2 × Ar**C**H, d, $^2J_{CF}$ = 22.0 Hz, rotamer A), 55.0 (C-12A), 53.0 (C-11B), 52.9 (C-10A), 52.2 (C-10C/12C), 50.8 (C-11C), 50.5 (C-11A), 49.5 (C-12B), 49.0 (C-10C/12C), 45.4 (C-10B), 40.5 (C-3A), 38.6 (C-3B), 36.5 (C-3C), 34.0 (C-8A), 31.7 (C-8B), 30.7 (C-8C), 29.8 (**C**H$_2$, rotamer C), 28.0 (**C**H$_2$, rotamer B), 27.4 (**C**H$_2$, rotamer C), 26.9 (**C**H$_2$, rotamer A), 26.6 (**C**H$_2$, rotamer A), 25.9 (**C**H$_2$, rotamer B), 25.5 (**C**H$_2$, rotamer A), 24.4 (**C**H$_2$, rotamer A), 23.8 (**C**H$_2$, rotamer C), 22.4 (**C**H$_2$, rotamer C), 22.2 (**C**H$_2$, rotamer B), 21.1 (**C**H$_2$, rotamer B); δ_F (282 MHz, $CDCl_3$) Rotamer A: −114.80 (1F, m, Ar**F**), rotamer B: −113.93 (1F, m, Ar**F**), rotamer C: −114.31 (1F, m, Ar**F**); HRMS (ESI$^+$): calcd. for $C_{23}H_{28}FN_2O_2$, 383.2129. Found: [MH]$^+$, 383.2134 (−1.2 ppm error).

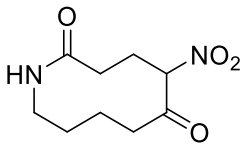
2.51: 5-(4-Fluorobenzyl)-4-methyl-1,5-diazacyclododecane-2,6-dione



To a solution of (*E*)-1-(but-2-enoyl)azocan-2-one (88.3 mg, 0.452 mmol) in methanol (1.1 mL), was added 4-fluorobenzylamine (57.1 µL, 0.500 mmol) in a single portion. The reaction mixture was stirred for 4 hours at RT and then the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 2:1 ethyl acetate : hexane → ethyl acetate → 48:2 ethyl acetate : methanol) afforded the title compound, which was obtained as a colourless oil (50.5 mg, 35%), and exists in $CDCl_3$ as a 5:4 ratio of rotamers; R_f = 0.41 (9:1 ethyl acetate : methanol); ν_{max}/cm^{-1} (thin film): 3300, 2931, 2864, 2237, 1644, 1622, 1552, 1509, 1450, 1409, 1356, 1223, 1155, 910, 729, 499; δ_H (400 MHz, $CDCl_3$) Data for major

rotamer: 7.15 – 7.09 (2H, m, 2 x Ar**H**), 7.06 – 6.98 (2H, m, 2 x Ar**H** [overlapping]), 6.36 (1H, br d, *J* = 9.5 Hz, H-2), 5.64 – 5.53 (1H, m, H-10), 4.67 (1H, d, *J* = 16.0 Hz, H-12), 4.41 (1H, d, *J* = 18.0 Hz, H-12'), 3.85 – 3.65 (2H, m, H-3 [overlapping]), 2.52 (2H, dd, *J* = 16.5, 12.5 Hz, H-11), 2.12 – 2.03 (1H, m, H-8), 1.99 – 1.90 (1H, m, H-8'), 1.88 – 1.26 (8H, m, 4 × C**H₂** [overlapping]), 1.05 (3H, d, *J* = 6.5 Hz, H-19) Full data for minor rotamer: 7.25 – 7.19 (2H, m, 2 x Ar**H**), 7.06 – 6.98 (2H, m, 2 x Ar**H** [overlapping]), 6.09 (1H, br d, *J* = 9.5 Hz, H-2), 4.82 (1H, d, *J* = 16.0 Hz, H-12), 4.19 (1H, d, *J* = 16.0 Hz, H-12'), 3.85 – 3.65 (2H, m, H-3 [overlapping]), 3.61 (1H, dq, *J* = 12.5, 6.5 Hz, H-10), 2.69 – 2.60 (1H, m, H-8), 2.31 (2H, dd, *J* = 13.0, 5.5 Hz, H-11), 2.24 – 2.13 (1H, m, H-8'), 1.88 – 1.26 (8H, m, 4 × C**H₂** [overlapping]), 1.14 (3H, d, *J* = 6.5 Hz, H-19); δ_C (100 MHz, $CDCl_3$) Data for major rotamer: 176.6 (C-9), 169.8 (C-1), 162.0 (C-16, d, $^1J_{CF}$ = 246.3 Hz), 133.9 (C-13, d, $^4J_{CF}$ = 2.9 Hz), 127.3 (2 × Ar**C**H, d, $^3J_{CF}$ = 8.3 Hz), 115.9 (2 × Ar**C**H, d, $^2J_{CF}$ = 22.0 Hz), 45.4 (C-12), 44.7 (C-10), 43.1 (C-11), 38.5 (C-3), 33.1 (C-8), 27.8 (**C**H_2), 26.2 (**C**H_2), 22.7 (**C**H_2), 21.2 (**C**H_2), 19.4 (C-19). Full data for minor rotamer: 175.0 (C-9), 171.2 (C-1), 162.4 (C-16, d, $^1J_{CF}$ = 246.4 Hz), 132.9 (C-13, d, $^4J_{CF}$ = 3.7 Hz), 129.4 (2 × Ar**C**H, d, $^3J_{CF}$ = 7.8 Hz), 115.7 (2 × Ar**C**H, d, $^2J_{CF}$ = 21.5 Hz), 56.3 (C-10), 56.2 (C-12), 42.5 (C-11), 39.8 (C-3), 35.2 (C-8), 26.4 (**C**H_2), 26.3 (**C**H_2), 25.7 (**C**H_2), 23.7 (**C**H_2), 18.6 (C-19); δ_F (282 MHz, $CDCl_3$) Major rotamer: −115.20 (1F, m, Ar**F**), minor rotamer: −114.40 (1F, m, Ar**F**); HRMS (ESI^+): calcd. for $C_{18}H_{26}FN_2O_2$, 321.1973. Found: $[MH]^+$, 321.1975 (−0.7 ppm error).

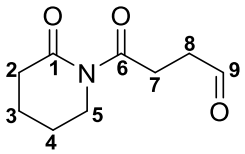
2.61: 5-Nitroazecane-2,6-dione



To a round-bottomed flask, DBU (0.30 mL, 1.99 mmol) was added to a stirring solution of 1-acryloylpiperidin-2-one (152 mg, 0.995 mmol) and nitromethane (1.07 mL, 19.9 mmol) in DCM (8.0 mL), in an inert atmosphere of Ar, at RT. The reaction mixture was stirred for 1 hour at RT, monitoring with TLC. The solvent was then removed *in vacuo* and DCM (5 mL) and water (5 mL) were added, and the organic layer extracted. To the aqueous layer was then added DCM (5 mL) and 10% aq. HCl (5 mL) and the aqueous layer was extracted with DCM (2 x 5 mL). Both organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the first organic layer was done by flash column chromatography (SiO_2, 2:1 hexane : ethyl acetate → 1:1 ethyl acetate : hexane → 100% ethyl acetate) affording products **2.63** and **2.65** (data and yields below). Purification of the second organic layer was done by flash column chromatography (SiO_2, 1:1 ethyl acetate : hexane → 100% ethyl

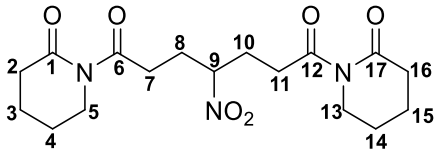
acetate) affording products **2.62** and **2.64** (data and yields below). None of the desired product, **2.61**, was formed.

2.62: 4-Oxo-4-(2-oxopiperidin-1-yl)butanal



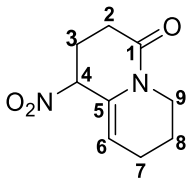
The side-product was obtained as a yellow oil (6.7 mg, 4%), containing minor unknown impurities; R_f = 0.23 (2:1 ethyl acetate : hexane); ν_{max}/cm^{-1} (thin film): 2951, 1689, 1552, 1368, 1292, 1203, 1160, 571; δ_H (400 MHz, $CDCl_3$) 9.82 (1H, s, H-9), 3.76 – 3.68 (2H, m, H-5), 3.27 – 3.21 (2H, m, H-8), 2.82 – 2.77 (2H, m, H-7), 2.60 – 2.53 (2H, m, H-2), 1.88 – 1.79 (4H, m, H-3,4); δ_C (100 MHz, $CDCl_3$) 201.1 (C-9), 175.5 (C-6), 173.6 (C-1), 44.4 (C-5), 38.7 (C-7), 35.0 (C-2), 32.8 (C-8), 22.5 (C-3), 20.4 (C-4); HRMS (ESI^+): calcd. for $C_9H_{13}NNaO_3$, 206.0790 Found: $[MNa]^+$, 206.0788 (−1.0 ppm error).

2.63: 4-Nitro-1,7-bis(2-oxopiperidin-1-yl)heptane-1,7-dione



The side-product was obtained as a colourless oil (62.9 mg, 34%); R_f = 0.24 (2:1 hexane : ethyl acetate); ν_{max}/cm^{-1} (thin film): 3365, 2954, 1687, 1546, 1377, 1291, 1199, 1158, 823; δ_H (400 MHz, $CDCl_3$) 4.66 (1H, tt, *J* = 9.0, 4.5 Hz, H-9), 3.74 – 3.66 (4H, m, H-5,13), 2.97 (4H, t, *J* = 7.0 Hz, H-7,11), 2.57 – 2.50 (4H, m, H-2,16), 2.33 – 2.13 (4H, m, H-8,10), 1.82 (8H, p, *J* = 3.5 Hz, H-3,4,14,15); δ_C (100 MHz, $CDCl_3$) 175.2 (C-6,12), 173.5 (C-1,17), 87.1 (C-9), 44.3 (C-5,13), 35.8 (C-7,11), 34.9 (C-2,16), 29.1 (C-8,10), 22.5 (C-3,15), 20.3 (C-4,14); HRMS (ESI^+): calcd. for $C_{17}H_{25}N_3NaO_6$, 390.1636 Found: $[MNa]^+$, 390.1635 (−0.3 ppm error).

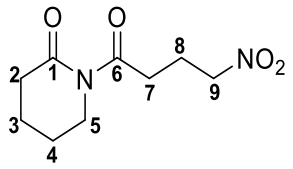
2.64: 1-Nitro-1,2,3,6,7,8-hexahydro-4*H*-quinolizin-4-one



The side-product was obtained as a colourless oil (22.9 mg, 12%), containing minor unknown impurities; R_f = 0.17 (2:1 ethyl acetate : hexane); ν_{max}/cm^{-1} (thin film): 2937, 1678, 1643, 1546, 1446, 1380, 1253, 1203, 911, 780; δ_H (400 MHz, $CDCl_3$) 5.20 (1H, t, *J* = 4.0 Hz, H-6),

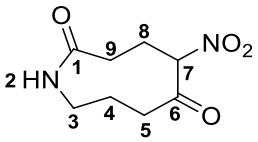
5.15 – 5.10 (1H, m, H-4), 4.11 (1H, ddd, *J* = 13.5, 6.5, 4.0 Hz, H-9), 3.51 (1H, ddd, *J* = 13.0, 9.5, 3.5 Hz, H-9), 2.82 – 2.48 (4H, m, H-2,3), 2.32 – 2.12 (2H, m, H-7), 1.96 – 1.72 (2H, m, H-8); δ_C (100 MHz, $CDCl_3$) 165.9 (C-1), 130.1 (C-5), 114.1 (C-6), 83.4 (C-4), 40.4 (C-9), 27.8 (C-2), 24.1 (C-3), 22.7 (C-7), 20.9 (C-8); HRMS (ESI^+): calcd. for $C_9H_{13}N_2O_3$, 197.0921 Found: $[MH]^+$, 197.0929 (−4.1 ppm error).

2.65: 1-(4-Nitrobutanoyl)piperidin-2-one



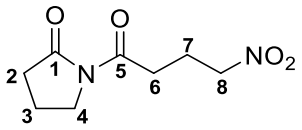
The side-product was obtained as a white/pale solid (6.9 mg, 3%); R_f = 0.36 (100% ethyl acetate); MP = 63 – 68 °C; ν_{max}/cm^{-1} (thin film): 2952, 1685, 1547, 1371, 1290, 1198, 1171, 1156 1005, 576; δ_H (400 MHz, $CDCl_3$) 4.43 (2H, t, *J* = 7.0 Hz, H-9), 3.71 – 3.63 (2H, m, H-5), 3.00 (2H, t, *J* = 7.0 Hz, H-7), 2.54 – 2.47 (2H, m, H-2), 2.30 (2H, p, *J* = 7.0 Hz, H-8), 1.79 (4H, dt, *J* = 6.0, 3.0 Hz, H-3,4); δ_C (100 MHz, $CDCl_3$) 175.0 (C-6), 173.5 (C-1), 74.7 (C-9), 44.1 (C-5), 36.0 (C-7), 34.8 (C-2), 22.5 (C-8), 22.3 (C-3), 20.2 (C-4); HRMS (ESI^+): calcd. for $C_9H_{14}N_2NaO_4$, 237.0846 Found: $[MNa]^+$, 237.0845 (−0.4 ppm error).

2.69: 5-Nitro-1-azacycloundecane-2,6-dione



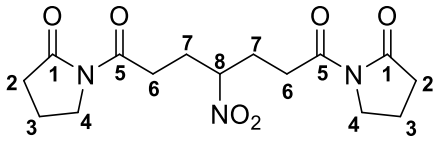
To a round-bottomed flask under Ar, DBU (0.19 mL, 1.30 mmol) was added to a stirring solution of 1-acryloylpyrrolidin-2-one (91.0 mg, 0.650 mmol) and nitromethane (0.70 mL, 13.0 mmol) in DCM (8.0 mL). The reaction mixture was stirred for 4 hours at RT, monitoring with TLC. To the reaction mixture was added DCM (10 mL) and 1M HCl (10 mL) and the aqueous layer was washed with DCM (3 x 10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 ethyl acetate : hexane → 100% ethyl acetate → 9:1 ethyl acetate : methanol) afforded products **2.70** and **2.71** (data and yields below). None of the desired product, **2.69**, was formed.

2.70: 1-(4-Nitrobutanoyl)pyrrolidin-2-one



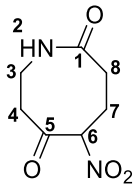
The title compound was a blue oil (68.6 mg, 53%); R_f = 0.59 (9:1 ethyl acetate : methanol); ν_{max}/cm^{-1} (thin film): 2962, 1733, 1684, 1546, 1378, 1360, 1255, 1218, 1187, 1023, 588; δ_H (400 MHz, $CDCl_3$) 4.45 (2H, t, *J* = 7.0 Hz, H-8), 3.76 (2H, *J* = 7.5 Hz, H-4), 2.99 (2H, t, *J* = 7.0 Hz, H-6), 2.56 (2H, t, *J* = 7.5 Hz, H-2), 2.30 (2H, p, *J* = 7.0 Hz, H-7), 2.02 (2H, p, *J* = 7.5 Hz, H-3); δ_C (100 MHz, $CDCl_3$) 175.7 (C-1), 172.3 (C-5), 74.5 (C-8), 45.4 (C-4), 33.5 (**C**H_2), 33.3 (**C**H_2), 21.7 (**C**H_2), 17.2 (**C**H_2); HRMS (ESI^+): calcd. for $C_8H_{12}N_2NaO_4$, 223.0689. Found: $[MNa]^+$, 223.0688 (0.5 ppm error).

2.71: 4-Nitro-1,7-bis(2-oxopyrrolidin-1-yl)heptane-1,7-dione



The title compound was a colourless liquid (15.0 mg, 14%); R_f = 0.49 (9:1 ethyl acetate : methanol); ν_{max}/cm^{-1} (thin film): 2951, 1688, 1547, 1384, 1291, 1200, 1158, 1005; δ_H (400 MHz, $CDCl_3$) 4.72 (1H, tt, *J* = 9.0, 4.5 Hz, H-8), 3.80 (4H, t, *J* = 7.5 Hz, H-4), 2.97 (4H, t, *J* = 7.0 Hz, H-6), 2.59 (4H, t, *J* = 7.5 Hz, H-2), 2.35 – 2.13 (4H, m, H-7), 2.04 (4H, p, *J* = 7.5 Hz, H-3); δ_C (100 MHz, $CDCl_3$) 175.6 (C-1), 172.4 (C-5), 86.8 (C-8), 45.5 (C-4), 33.6 (2 x **C**H_2), 33.1 (2 x **C**H_2), 28.2 (2 x **C**H_2), 17.4 (2 x **C**H_2); HRMS (ESI^+): calcd. for $C_{15}H_{22}N_3O_6$, 340.1503. Found: $[MH]^+$, 340.1504 (−0.2 ppm error).

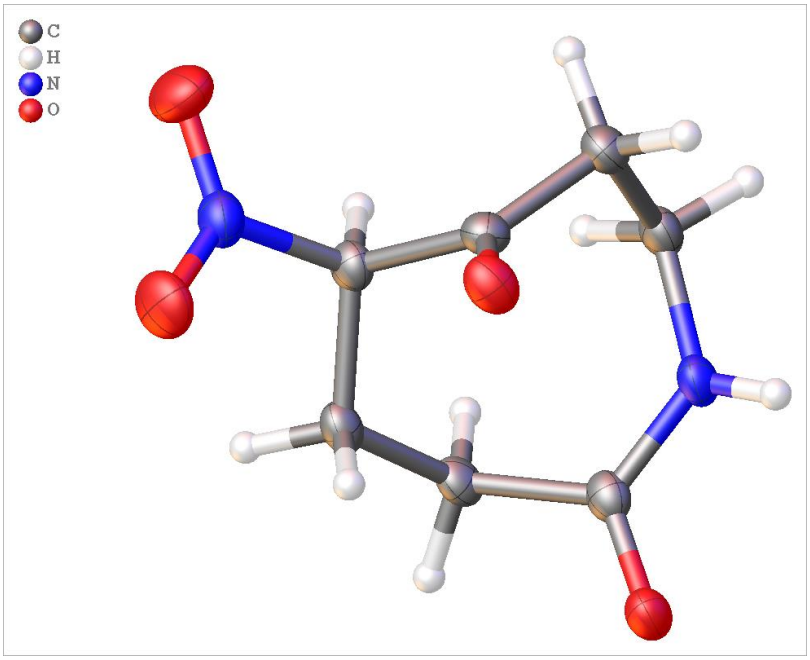
2.74: 5-Nitroazocane-2,6-dione



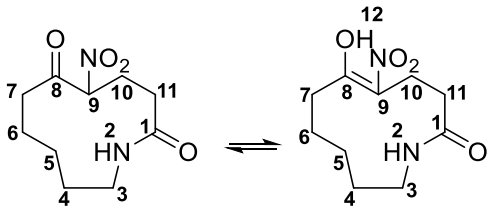
To a round-bottomed flask, DBU (0.15 mL, 1.00 mmol) was added to a stirring solution of 1-acryloylazetidin-2-one (62.6 mg, 0.500 mmol) and nitromethane (0.540 mL, 10.0 mmol) in DCM (5.0 mL), in an inert atmosphere of Ar, at RT. The reaction mixture was stirred for 4

hours, monitoring with TLC. After this, to the reaction mixture was added DCM (5 mL) and water (5 mL) and the organic layer extracted. To the aqueous was added DCM (5 mL), before 1M aq. HCl was added dropwise until pH 2 was reached, monitored *via* universal indicator. The aqueous layer was then extracted with DCM (2 x 5 mL), retaining the organic layer. The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 100% ethyl acetate → 9:1 ethyl acetate : methanol) afforded the title compound, which was obtained as a colourless oil (31.8 mg, 34%); R_f = 0.33 (9:1 ethyl acetate : methanol); ν_{max}/cm^{-1} (thin film): 3315, 2953, 2923, 2854, 1725, 1659, 1556, 1460, 1377, 1216; δ_H (400 MHz, $CDCl_3$) 6.35 (1H, br s, H-2), 5.44 (1H, dd, *J* = 9.5, 5.0 Hz, H-6), 3.69 – 3.60 (2H, m, H-3), 3.00 (1H, dt, *J* = 13.5, 6.0 Hz, H-4), 2.88 (1H, dt, *J* = 13.5, 6.0 Hz, H-4'), 2.69 – 2.43 (4H, m, 2 x C**H₂**); δ_C (100 MHz, $CDCl_3$) 199.9 (C-5), 173.9 (C-1), 89.2 (C-6), 47.4 (C-4), 38.6 (C-3), 28.4 (**C**H_2), 26.2 (**C**H_2); HRMS (ESI^+): calcd. for $C_7H_{11}N_2O_4$, 187.0713 Found: $[MH]^+$, 187.0714 (−0.5 ppm error).

X-ray crystallographic data for **2.74** can be found at CCDC 2160990. The crystal was a non-merohedral twin modelled as two components in a refined ratio of 0.6664:0.3336(17).

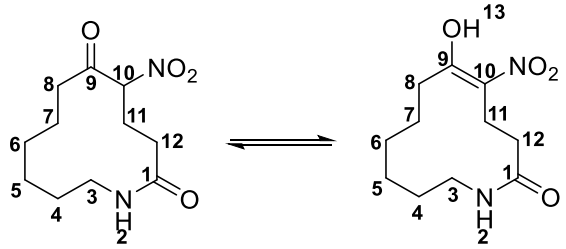


2.75: 5-Nitroazacycloundecane-2,6-dione



In a round-bottomed flask, DBU (0.15 mL, 0.996 mmol) was added to a stirring solution of 1-acryloylazepan-2-one (83.2 mg, 0.498 mmol) and nitromethane (0.53 mL, 9.96 mmol) in DCM (5.5 mL), under an inert atmosphere of Ar. The reaction mixture was stirred for 4 hours at RT. After that, water (5 mL) and DCM (5 mL) were added, the organic layers were separated and the aqueous extracts were retained. DCM (10 mL) was added to the aqueous extracts, followed by 1M aq. HCl, which was added dropwise until the solution reached pH 2. The aqueous layer was then extracted with DCM (2 x 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 ethyl acetate : hexane → 100% ethyl acetate → 9:1 ethyl acetate : methanol) afforded the title compound, which was obtained as a white solid (28.3 mg, 25%), and exists in $CDCl_3$ as an approximate 5:1 mixture of keto and enol tautomeric forms; R_f = 0.22 (9:1 ethyl acetate : methanol); ν_{max}/cm^{-1} (thin film): 3299, 2934, 1634, 1552, 1442, 1297, 1195, 1155, 1080; δ_H (400 MHz, $CDCl_3$) Data for the keto form: 5.80 (1H, br s, H-2), 5.38 (1H, dd, *J* = 6.0, 4.5 Hz, H-9), 3.58 – 3.50 (1H, m, H-3), 3.13 – 3.07 (1H, m, H-3'), 2.98 (1H, t, *J* = 8.0 Hz, H-7), 2.86 – 2.33 (5H, m, 2.5 x C**H$_2$**), 1.91 – 1.39 (6H, m, 3 x C**H$_2$**). Diagnostic data for the enol form: 15.26 (1H, br s, H-12); δ_C (100 MHz, $CDCl_3$) Data for the keto form: 200.3 (C-8), 171.9 (C-1), 91.4 (C-9), 40.6 (**C**H$_2$), 38.1 (**C**H$_2$), 32.3 (**C**H$_2$), 26.2 (**C**H$_2$), 24.4 (**C**H$_2$), 22.2 (**C**H$_2$), 22.1 (**C**H$_2$); HRMS (ESI$^+$): calcd. for $C_{10}H_{16}N_2NaO_4$, 251.1002. Found: $[MNa]^+$, 251.1010 (−3.0 ppm error).

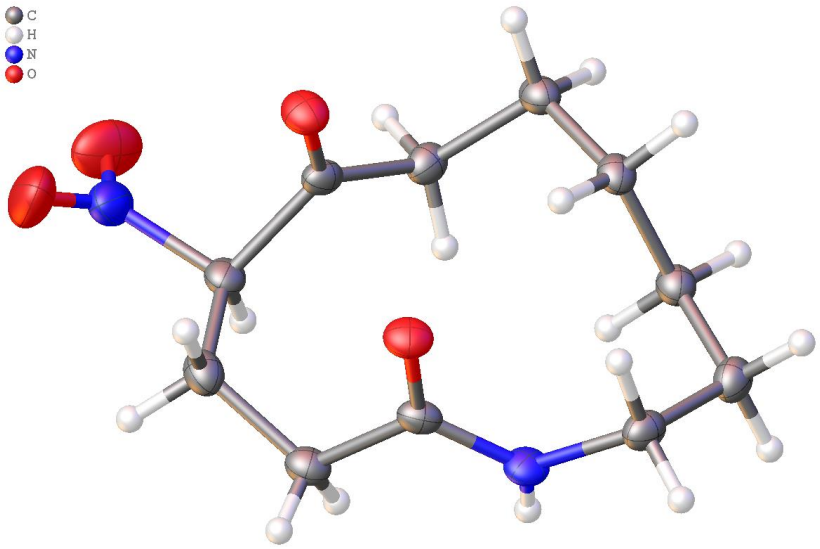
2.76: 5-Nitro-1-azacyclododecane-2,6-dione



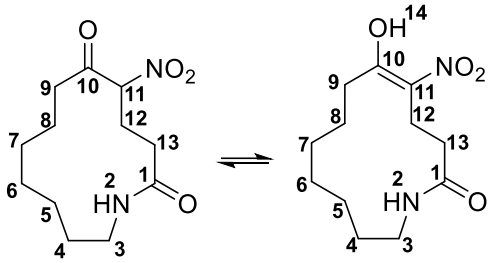
To a round-bottomed flask, DBU (0.15 mL, 1.00 mmol) was added to a stirring solution of 1-acryloylazocan-2-one (89.4 mg, 0.493 mmol) and nitromethane (0.53 mL, 9.86 mmol) in

DCM (5.0 mL), under an inert atmosphere of Ar. The reaction mixture was stirred for 4 hours at RT. After that, DCM (10 mL) and water (10 mL) were added, and the organic and aqueous layers were separated. The aqueous extract was retained, and to this DCM (10 mL) was added, followed by 1M aq. HCl dropwise until the solution reached pH 2. The aqueous layer was then extracted with DCM (2 x 10 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*, affording the title compound, which was obtained as a white, crystalline solid (106.4 mg, 89%), and exists in $CDCl_3$ as an approximate 4:1 mixture of keto and enol tautomeric forms; R_f = 0.22 (9:1 ethyl acetate : methanol); MP = 123 – 128 °C; ν_{max}/cm^{-1} (thin film): 3325, 2934, 1727, 1644, 1551, 1441, 1363, 1112; δ_H (400 MHz, $CDCl_3$) Data for the keto form: 5.71 (1H, br s, H-2), 5.60 (1H, dd, *J* = 8.0, 5.0 Hz, H-10 [overlapping]), 3.80 – 3.65 (1H, m, H-3), 3.03 – 2.82 (1H, m, H-3' [overlapping]), 3.03 – 2.82 (1H, m, H-8 [overlapping]), 2.62 – 2.28 (2H, m, H-12 [overlapping]), 2.74 – 2.33 (1H, m, H-8' [overlapping]), 2.73 – 2.28 (2H, m, H-11 [overlapping]), 1.91 – 1.15 (8H, m, 4 x C**H$_2$**). Diagnostic data for the enol form: 10.92 (1H, br s, H-13), 5.52 (1H, br s, H-2), 3.57 – 3.39 (2H, m, H-3); δ_C (100 MHz, $CDCl_3$) Data for the keto form 200.3 (C-9), 171.3 (C-1), 89.4 (C-10), 40.6 (C-8), 39.5 (C-3), 31.6 (C-12), 27.2 (**C**H$_2$), 26.5 (**C**H$_2$), 24.6 (**C**H$_2$), 24.3 (**C**H$_2$), 21.5 (**C**H$_2$). Full data for the enol form: 180.4 (C-9), 172.3 (C-1), 126.0 (C-10), 36.2 (**C**H$_2$), 34.9 (**C**H$_2$), 32.8 (**C**H$_2$), 27.0 (**C**H$_2$), 26.7 (**C**H$_2$), 24.5 (**C**H$_2$), 23.9 (**C**H$_2$), 23.1 (**C**H$_2$); HRMS (ESI$^+$): calcd. for $C_{11}H_{18}N_2NaO_4$, 265.1159. Found: $[MNa]^+$, 265.1160 (−0.3 ppm error).

X-ray crystallographic data for **2.76** can be found at CCDC 2159961. The crystal was a non-merohedral twin modelled as two components in a refined ratio of 0.5710:0.4290(15).

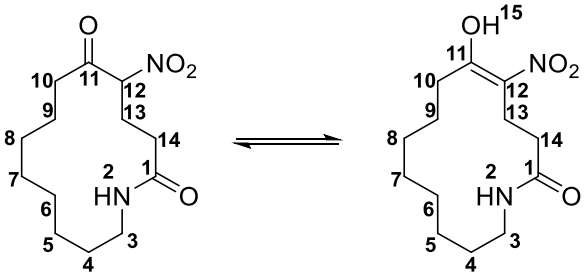


2.77: 5-Nitroazacyclotridecane-2,6-dione



To a round-bottomed flask, DBU (0.15 mL, 1.01 mmol) was added to a stirring solution of 1-acryloylazonan-2-one (98.3 mg, 0.504 mmol) and nitromethane (0.54 mL, 10.1 mmol) in DCM (5.0 mL), under an inert atmosphere of Ar. The reaction mixture was stirred for 4 hours at RT, monitoring with TLC. After that, DCM (5 mL) and water (5 mL) were added and the organic layer was removed. To the aqueous layer was added DCM (5 mL) and 1M aq. HCl dropwise until pH 2 was reached. The aqueous layer was then extracted with DCM (2 x 5 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford the title compound, which was obtained as a colourless oil (69.6 mg, 54%), and exists as a 20:1 mixture of keto and enol tautomeric forms in $CDCl_3$; R_f = 0.42 (9:1 ethyl acetate : methanol); ν_{max}/cm^{-1} (thin film): 3309, 2931, 2860, 1721, 1638, 1549, 1443, 1369, 1254, 731; δ_H (400 MHz, $CDCl_3$) Data for the keto form: 6.32 – 6.24 (1H, br t, H-2), 5.59 (1H, t, *J* = 5.5 Hz, H-11), 3.58 – 3.44 (1H, m, H-3), 3.22 – 3.12 (1H, m, H-3'), 2.71 – 2.60 (1H, m, C**H₂**), 2.55 (2H, t, *J* = 7.0 Hz, C**H₂**), 2.49 – 2.34 (1H, m, C**H₂** [overlapping]), 2.49 – 2.34 (2H, m, C**H₂** [overlapping]), 1.83 – 1.19 (10H, m, 5 x C**H₂**). Diagnostic data for the enol form: 10.39 (1H, br s, H-14); δ_C (100 MHz, $CDCl_3$) Data for the keto form: 200.5 (C-10), 171.3 (C-1), 90.5 (C-11), 39.2 (C-3/9), 38.0 (C-3/9), 32.2 (C-13), 27.2 (**C**H_2), 26.6 (**C**H_2) 24.9 (**C**H_2), 24.8 (**C**H_2), 24.4 (**C**H_2), 21.6 (**C**H_2). Diagnostic data for enol form: 166.4 (C-1), 126.6 (C-10), 54.7 (**C**H_2), 48.8 (**C**H_2), 38.2 (**C**H_2), 32.8 (**C**H_2), 29.1 (**C**H_2), 26.7 (**C**H_2), 23.9 (**C**H_2), 19.5 (**C**H_2); HRMS (ESI^+): calcd. for $C_{12}H_{21}N_2O_4$, 257.1496. Found: $[MH]^+$, 257.1496 (0.1 ppm error).

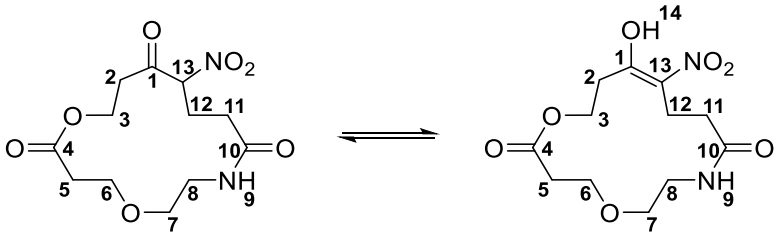
2.78: 5-Nitroazacyclotetradecane-2,6-dione



To a round-bottomed flask, DBU (0.11 mL, 0.745 mmol) was added to a stirring solution of 1-acryloylazecan-2-one (65.0 mg, 0.311 mmol) and nitromethane (0.33 mL, 6.21 mmol) in

DCM (6.0 mL), under an inert atmosphere of Ar. The reaction mixture was stirred for 4 hours at RT, monitoring with TLC. Then, DCM (5 mL) and water (5 mL) were added and the organic layer extracted. To the aqueous layer was added DCM (5 mL) and 1M aq. HCl dropwise until pH 2 was reached. The aqueous layer was then extracted with DCM (2 x 5 mL). The organic layers (from before and after acidification) were then combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 ethyl acetate : hexane → 100% ethyl acetate), afforded the title compound, which was obtained as a white solid (52.9 mg, 63%), and exists as a 5:1 mixture of keto and enol tautomeric forms in $CDCl_3$; R_f = 0.48 (9:1 ethyl acetate : methanol); MP = 106 – 111 °C; ν_{max}/cm^{-1} (thin film): 3300, 2930, 2860, 1726, 1640, 1553, 1440, 1370, 1260, 732; δ_H (400 MHz, $CDCl_3$) Data for the keto form: 5.69 (1H, dd, *J* = 8.0, 5.5 Hz, H-12), 5.52 (1H, br s, H-2), 3.53 – 3.42 (1H, m, H-3), 3.34 – 3.21 (1H, m, H-3'), 2.69 (1H, ddd, *J* = 16.0, 8.5, 4.5 Hz, H-10/14), 2.63 – 2.51 (1H, m, H-10/14), 2.50 – 2.38 (1H, m, H-10/14), 2.27 (1H, ddd, *J* = 15.0, 9.0, 3.5 Hz, H-10/14), 1.86 – 1.16 (14H, m, 7 x C**H$_2$**). Diagnostic data for the enol form: 11.55 (1H, br s, H-15), 4.49 (2H, t, *J* = 6.0 Hz, C**H$_2$**); δ_C (100 MHz, $CDCl_3$) Data for the keto form: 200.2 (C-11), 171.0 (C-1), 89.9 (C-12), 41.0 (C-3/10), 38.0 (C-3/10), 32.4 (C-14), 27.9 (**C**H$_2$), 26.5 (**C**H$_2$), 25.9 (**C**H$_2$), 25.4 (**C**H$_2$), 25.1 (**C**H$_2$), 23.4 (**C**H$_2$), 22.9 (**C**H$_2$). Diagnostic data for the enol form: 122.6 (C-12), 39.0 (**C**H$_2$), 32.7 (**C**H$_2$), 26.2 (**C**H$_2$), 24.7 (**C**H$_2$), 23.9 (**C**H$_2$); HRMS (ESI$^+$): calcd. for $C_{13}H_{22}N_2NaO_4$, 293.1472. Found: $[MNa]^+$, 293.1474 (−0.6 ppm error).

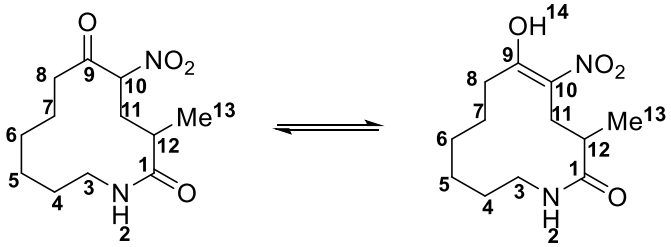
2.79: 8-Nitro-1,12-dioxa-4-azacyclopentadecane-5,9,13-trione



To a round-bottomed flask, DBU (0.12 mL, 0.812 mmol) was added to a stirring solution of 5-acryloyl-1,8-dioxa-4-azacycloundecane-5,9-dione (97.9 mg, 0.406 mmol) and nitromethane (0.44 mL, 8.12 mmol) in DCM (6.0 mL), in an inert atmosphere of Ar. The reaction mixture was stirred for 4 h at RT, monitoring with TLC. Upon completion, the solution was washed with DCM (7 mL) and water (7 mL) and the organic layer removed. To the aqueous layer was added DCM (7 mL) and 1M aq. HCl was added dropwise until the solution reached pH 2, monitored *via* universal indicator paper. The aqueous layer was then extracted with DCM (2 x 7 mL). The organic layer was extracted and dried over $MgSO_4$, filtered and concentrated *in vacuo*, affording the title compound, which was obtained as a yellow oil (74.5 mg, 61%), and

exists in $CDCl_3$ as a 3:1 mixture of rotamers. Evidence of a small amount of an enol tautomeric form was also evident in the ^1H NMR spectrum; R_f = 0.16 (9:1 ethyl acetate : methanol); ν_{max}/cm^{-1} (thin film): 3324, 3302, 2927, 1726, 1647, 1550, 1440, 1381, 1262, 1190, 1113; δ_H (400 MHz, $CDCl_3$) Data for major rotamer: 6.34 (1H, t, *J* = 6.0 Hz, H-9), 5.36 (1H, t, *J* = 7.0 Hz, H-13), 4.60 – 4.52 (1H, m, H-3), 4.31 – 4.24 (1H, m, H-3'), 3.49 – 3.32 (2H, m, H-8 [overlapping]), 3.78 – 3.32 (2H, m, H-7 [overlapping]), 3.78 – 3.32 (2H, m, H-8 [overlapping]), 2.86 (2H, t, *J* = 5.0 Hz, H-2), 2.62 – 2.53 (2H, m, H-5), 2.52 – 2.37 (2H, m, H-12 [overlapping]), 2.52 – 2.19 (2H, m, H-11 [overlapping]). Diagnostic data for the minor rotamer: 6.76 – 6.71 (1H, m, H-9), 5.50 (1H, dd, *J* = 8.0, 5.0 Hz, H-13), 4.44 (2H, t, *J* = 6.5 Hz, H-3), 2.83 – 2.76 (2H, m, H-2). Diagnostic data for an enol tautomer: 10.50 (1H, s, H-14); δ_C (100 MHz, $CDCl_3$) Data for major rotamer: 197.2 (C-1), 172.3 (C-4/10), 171.4 (C-4/10), 91.6 (C-13), 69.2 (C-6/7), 66.3 (C-6/7), 60.5 (C-3), 40.4 (C-2), 39.4 (C-8), 35.3 (C-5), 32.4 (C-11), 25.7 (C-12). Diagnostic data for the minor rotamer: 198.1 (C-1), 172.0 (**C**O), 171.3 (**C**O), 92.6 (C-13), 74.0 (**C**H_2), 66.0 (**C**H_2), 54.7 (**C**H_2), 48.9 (**C**H_2), 39.2 (**C**H_2), 36.5 (**C**H_2), 34.7 (**C**H_2); HRMS (ESI^+): calcd. for $C_{12}H_{18}N_2NaO_7$, 325.1007 Found: $[MNa]^+$, 325.0986 (6.4 ppm error).

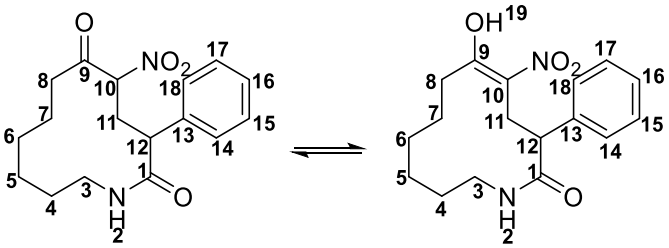
2.81: 3-Methyl-5-nitroazacyclododecane-2,6-dione



To a round-bottomed flask, DBU (0.16 mL, 1.07 mmol) was added to a stirring solution of 1-methacryloylazocan-2-one (104 mg, 0.535 mmol) and nitromethane (0.57 mL, 10.7 mmol) in DCM (5.5 mL), in an inert atmosphere of Ar. The reaction mixture was stirred for 4 hours at RT, monitoring with TLC. Upon completion, to the reaction mixture was added DCM (10 mL) and 1M aq. HCl (10 mL). The aqueous layer was then extracted with DCM (3 x 10 mL). The organic layer was extracted, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 ethyl acetate : hexane → 100% ethyl acetate → 9:1 ethyl acetate : methanol) afforded the title compound (the ^1H NMR spectrum is severely affected by rotameric broadening, with product identity and purity best determined using ^{13}C NMR data), which was obtained as a white solid (133 mg, 97%), and exists in $CDCl_3$ as a 3:1 mixture of rotamers. A trace amount of the enol tautomeric form of one of the rotamers can also be seen in the ^1H NMR data; R_f = 0.30 (9:1 ethyl acetate :

methanol); MP = 126 – 131 °C; ν_{max}/cm^{-1} (thin film): 3288, 2933, 2861, 1687, 1650, 1553, 1446, 1376, 1196, 1126, 1090, 731; δ_H (400 MHz, $CDCl_3$) Data for major rotamer: 5.59 (1H, dd, *J* = 9.0, 4.0 Hz, H-10), 5.46 (1H, br s, H-2), 3.93 – 3.80 (2H, m, H-3), 2.92 – 2.75 (2H, m, H-8), 2.57 – 2.33 (1H, m, H-12 [overlapping]), 2.45 – 2.33 (2H, m, H-11 [overlapping]), 1.91 – 1.80 (2H, m, H-7), 1.78 – 1.66 (2H, m, H-4), 1.65 – 1.54 (2H, m, H-6), 1.52 – 1.39 (2H, m, H-5), 1.24 (3H, d, *J* = 6.5 Hz, H-13). Diagnostic data for minor rotamer: 5.39 (1H, dd, *J* = 7.5, 4.5 Hz, H-10), 5.28 (1H, br s, H-2), 4.19 – 3.99 (2H, m, H-3), 2.71 – 2.61 (2H, m, H-12). Diagnostic ^1H NMR indicating a small amount of an enol tautomer can also be seen at: 10.17 (1H, br s, H-14); δ_C (100 MHz, $CDCl_3$) Data for major rotamer: 200.4 (C-9), 174.8 (C-1), 88.6 (C-10), 41.0 (C-3), 39.9 (C-8), 37.5 (C-12), 32.7 (C-11), 27.6 (**C**H_2), 26.3 (**C**H_2), 25.2 (**C**H_2), 22.0 (**C**H_2), 19.9 (C-13). Diagnostic data for the minor rotamer: 39.2 (**C**H_2), 31.1 (**C**H_2), 29.2 (**C**H_2); HRMS (ESI^+): calcd. for $C_{12}H_{20}N_2NaO_4$, 279.1315. Found: $[MNa]^+$, 279.1312 (0.7 ppm error).

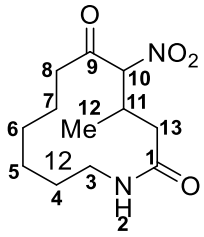
2.82: 5-Nitro-3-phenylazacyclododecane-2,6-dione



To a round-bottomed flask, DBU (0.15 mL, 0.985 mmol) was added to a stirring solution of 1-(2-phenylacryloyl)azocan-2-one (127 mg, 0.493 mmol) and nitromethane (0.53 mL, 9.85 mmol) in DCM (5.5 mL), in an inert atmosphere of Ar. The reaction mixture was stirred for 4 hours at RT, monitoring with TLC. Upon completion, to the reaction mixture was added DCM (10 mL) and 1M aq. HCl (10 mL). The aqueous layer was then extracted with DCM (3 x 10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*, affording the title compound, which was obtained as a white solid (151 mg, 96%), and exists as a 2:1 mixture of keto and enol tautomeric forms in $CDCl_3$; R_f = 0.40 (9:1 ethyl acetate : methanol); MP = 144 – 150 °C; ν_{max}/cm^{-1} (thin film): 3299, 2932, 1731, 1646, 1555, 1449, 1354, 700; δ_H (400 MHz, $CDCl_3$) Data for keto form: 7.39 – 7.27 (5H, m, 5 x Ar**H**), 5.83 (1H, dd, *J* = 9.0, 5.0 Hz, H-10), 5.76 (1H, br d, *J* = 9.5 Hz, H-2), 3.87 (2H, dtd, *J* = 13.5, 10.0, 3.5 Hz, H-3), 3.59 (1H, dd, *J* = 11.0, 4.0 Hz, H-12), 3.07 – 2.86 (1H, m, H-8), 2.84 – 2.67 (1H, m, C**H₂** [overlapping]), 2.62 – 2.52 (1H, m, H-8' [overlapping]), 2.62 – 2.52 (1H, m, C**H₂** [overlapping]), 2.11 – 1.17 (8H, m, 4 x C**H₂**). Diagnostic data for enol form: 11.18 (1H, br s, H-19); δ_C (100 MHz, $CDCl_3$) Data for keto form: 200.6 (C-9), 171.8 (C-1), 139.5 (C-13), 129.2 (2 x Ar**C**H), 127.64 (Ar**C**H), 127.5 (2 x Ar**C**H), 88.2 (C-10), 48.8 (C-12), 41.6 (C-8), 40.3 (C-3), 33.5 (**C**H_2), 28.0 (**C**H_2), 26.4

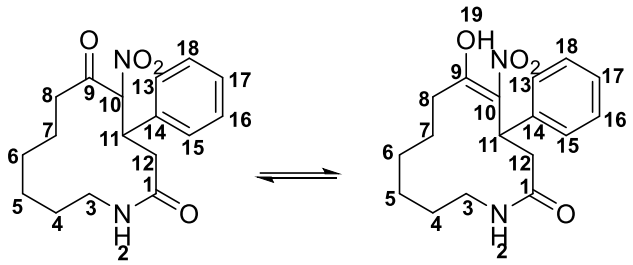
(**C**H_2), 25.7 (**C**H_2), 22.4 (**C**H_2). Diagnostic data for enol form: 181.1 (C-9), 172.6 (C-1), 139.4 (C-13), 128.8 (2 x Ar**C**H), 127.9 (2 x Ar**C**H), 127.59 (Ar**C**H), 51.4 (C-12), 36.0 (**C**H_2), 32.7 (**C**H_2), 27.6 (**C**H_2), 26.9 (**C**H_2), 24.0 (**C**H_2), 23.1 (**C**H_2); HRMS (ESI$^+$): calcd. for $C_{17}H_{22}N_2NaO_4$, 341.1472. Found: [MNa]$^+$, 341.1477 (−1.4 ppm error).

2.83: 4-Methyl-5-nitroazacyclododecane-2,6-dione



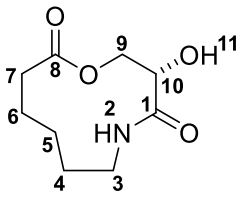
To a round-bottomed flask, DBU (0.16 mL, 1.06 mmol) was added to a stirring solution of (*E*)-1-(but-2-enoyl)azocan-2-one (104 mg, 0.532 mmol) and nitromethane (0.57 mL, 10.6 mmol) in DCM (5.0 mL), under Ar. The reaction mixture was stirred at RT for 4 hours. After that, DCM (10 mL) and water (10 mL) were added and the organic layer was removed. To the aqueous layer was added DCM (10 mL) and 1M aq. HCl was added dropwise until the aqueous solution reached pH 2, monitored *via* universal indicator paper. The aqueous layer was then extracted with DCM (2 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*, affording the title compound, which was obtained as a white, crystalline solid (81.0 mg, 59%), and exists in $CDCl_3$ as a 10:1 mixture of rotamers. The ^{1}H NMR spectrum is severely affected by rotameric broadening, with product identity and purity best determined using ^{13}C NMR data; R_f = 0.45 (9:1 ethyl acetate : methanol); MP = 140 – 146 °C; ν_{max}/cm^{-1} (thin film): 3319, 2933, 2865, 1717, 1641, 1553, 1461, 1440, 1366, 1244, 1106, 734; δ_H (400 MHz, $CDCl_3$) Data for major rotamer: 5.59 – 5.50 (1H, br s, H-2), 5.42 (1H, d, *J* = 4.0 Hz, H-10), 3.96 – 3.84 (1H, m, H-3), 3.36 – 3.25 (1H, m, H-3'), 2.94 – 2.28 (4H, m, 2 x C**H$_2$**), 1.94 – 1.23 (9H, m, 4.5 x C**H$_2$**), 1.21 (3H, d, *J* = 7.0 Hz, H-12). Diagnostic data for the minor rotamer: 5.40 (1H, d, *J* = 4.5 Hz, H-10), 1.25 (3H, d, *J* = 7.0 Hz, H-12); δ_C (100 MHz, $CDCl_3$) Data for major rotamer: 199.5 (C-9), 171.0 (C-1), 95.2 (C-10), 39.2 (C-3/8/13), 39.0 (C-3/8/13), 38.8 (C-3/8/13), 32.3 (C-11), 26.5 (**C**H_2), 26.2 (**C**H_2), 23.8 (**C**H_2), 20.8 (**C**H_2), 18.5 (C-12). Diagnostic data for the minor rotamer: 176.0 (C-1), 39.7 (C-3/8/13), 27.2 (**C**H_2), 26.9 (**C**H_2), 21.3 (**C**H_2), 19.2 (C-12); HRMS (ESI$^+$): calcd. for $C_{12}H_{20}KN_2O_4$, 295.1055. Found: [MK]$^+$, 295.1056 (−0.6 ppm error).

2.84: 5-Nitro-4-phenylazacyclododecane-2,6-dione

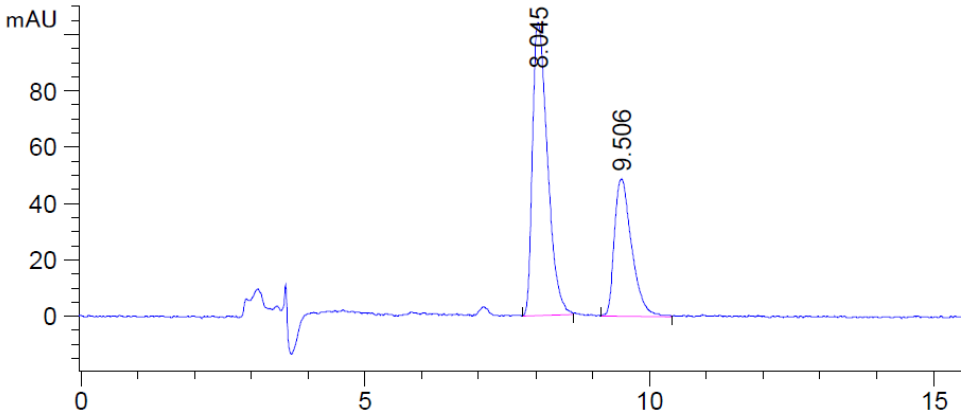


To a round-bottomed flask, DBU (0.15 mL, 1.01 mmol) was added to a stirring solution of 1-cinnamoylazocan-2-one (130 mg, 0.504 mmol) and nitromethane (0.54 mL, 10.1 mmol) in DCM (6.0 mL), in an inert atmosphere of Ar. The reaction mixture was stirred for 72 hours at RT, before DCM (10 mL) and water (10 mL) were added and the organic layer was removed. To the aqueous layer was added DCM (10 mL) and 1M aq. HCl was added dropwise before the solution reached pH 2, monitored *via* universal indicator paper. The aqueous layer was then extracted with DCM (2 x 10 mL). The combined organic layers were then dried over $MgSO_4$, filtered and concentrated *in vacuo*, affording the title compound (a small amount of an enol tautomeric form was also evident in the ^{1}H NMR spectrum), which was obtained as a yellow oil (36.2 mg, 23%), and exists in $(CD_3)_2SO$ as a 5:1 mixture of rotamers; R_f = 0.40 (9:1 ethyl acetate : methanol); ν_{max}/cm^{-1} (thin film): 3301, 2932, 1698, 1644, 1553, 1449, 1359, 1203, 911, 731, 699; δ_H (400 MHz, $(CD_3)_2SO$) Data for major rotamer: 7.88 (1H, br d, *J* = 6.5 Hz, H-2), 7.41 – 7.26 (5H, m, 5 x Ar**H**), 6.29 (1H, d, *J* = 11.0 Hz, H-10), 4.12 (1H, td, *J* = 11.0, 2.0 Hz, H-11), 3.63 – 3.43 (2H, m, H-3), 2.96 (1H, dd, *J* = 20.0, 9.5, 4.0 Hz, H-12), 2.75 – 2.59 (2H, m, H-8), 2.29 (1H, dd, *J* = 16.5, 2.0 Hz, H-12'), 1.86 – 1.06 (8H, m, 4 x C**H$_2$**). Diagnostic data for minor rotamer: 8.16 (1H, br d, *J* = 7.5 Hz, H-2), 7.26 – 7.15 (5H, m, 5 x Ar**H**), 3.76 – 3.64 (2H, m, H-3). Diagnostic data for enol tautomer: 9.53 (1H, br s, H-19); δ_C (100 MHz, $(CD_3)_2SO$) Data for major rotamer: 197.8 (C-9), 168.1 (C-1), 141.5 (C-14), 128.8 (2 x Ar**C**H), 127.5 (2 x Ar**C**H), 127.3 (C-17), 96.3 (C-10), 41.5 (C-11), 40.4 (C-3/12), 39.6 (C-3/12), 35.7 (C-8), 24.4 (**C**H$_2$), 22.5 (**C**H$_2$), 21.3 (**C**H$_2$), 19.9 (**C**H$_2$); HRMS (ESI$^+$): calcd. for $C_{17}H_{22}N_2NaO_4$, 341.1472. Found: $[MNa]^+$, 341.1470 (0.4 ppm error).

2.99: 3-Hydroxy-1-oxa-5-azacycloundecane-4,11-dione



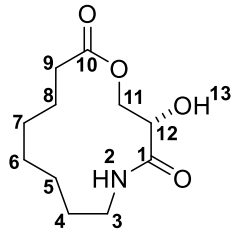
To a round-bottomed flask AD-mix-β (0.722 g), methanesulfonamide (45.3 mg, 0.477 mmol), ^{t}BuOH (3.0 mL) and water (3.0 mL) were added and the mixture was stirred for 15 minutes at RT before cooling to 0 °C. 1-Acryloylazepan-2-one (79.7 mg, 0.477 mmol) was then added and the reaction mixture was stirred for 72 hours at 0 °C. To the reaction mixture was then added Na_2SO_3 (1.0 g) and the mixture was stirred for 1 hour at RT. The crude reaction mixture was then diluted with ethyl acetate (8 mL), and the aqueous layer extracted with ethyl acetate (2 × 4 mL), before the combined organic layers were washed with brine (8 mL). The organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 ethyl acetate : hexane → 100% ethyl acetate) afforded the title compound, which was obtained as a white solid (44.6 mg, 47%); R_f = 0.25 (9:1 ethyl acetate : methanol); MP = 143 – 147 °C; $[\alpha]_D^{20}$ 21.5 (c = 1.0, MeOH); ν_{max}/cm^{-1} (thin film): 3229, 2929, 2865, 2492, 1726, 1639, 1477, 1445, 1312, 1258, 1235, 1152, 1135, 1121, 1094, 1022, 923, 560; δ_H (400 MHz, MeOD-*d*$_4$) 8.00 (1H, br s, H-2), 6.21 (1H, br s, H-11), 5.05 – 4.93 (1H, m, H-9), 4.22 (1H, t, *J* = 2.5 Hz, H-10), 3.91 (1H, dd, *J* = 11.5, 2.5 Hz, H-9'), 3.71 (1H, ddt, *J* = 14.0, 11.0, 4.0, H-3), 3.00 (1H, ddt, *J* = 13.0, 8.5, 4.0, H-3'), 2.46 (1H, ddd, *J* = 14.5, 7.5, 4.0 Hz, H-7), 2.18 (1H, dtd, *J* = 14.0, 8.5, 4.0, H-7'), 1.79 – 1.62 (3H, m, C**H$_2$**), 1.61 – 1.40 (2H, m, C**H$_2$**), 1.23 – 1.09 (1H, m, C**H$_2$**); δ_C (100 MHz, MeOD-*d*$_4$) 174.5 (C-1/8), 174.4 (C-1/8), 72.7 (C-10), 66.8 (C-9), 39.7 (C-3), 35.5 (C-7), 28.2 (**C**H$_2$), 27.1 (**C**H$_2$), 25.3 (**C**H$_2$); HRMS (ESI$^+$): calcd. for $C_9H_{16}NO_4$, 202.1074. Found: $[MH]^+$, 202.1074 (0.1 ppm error).



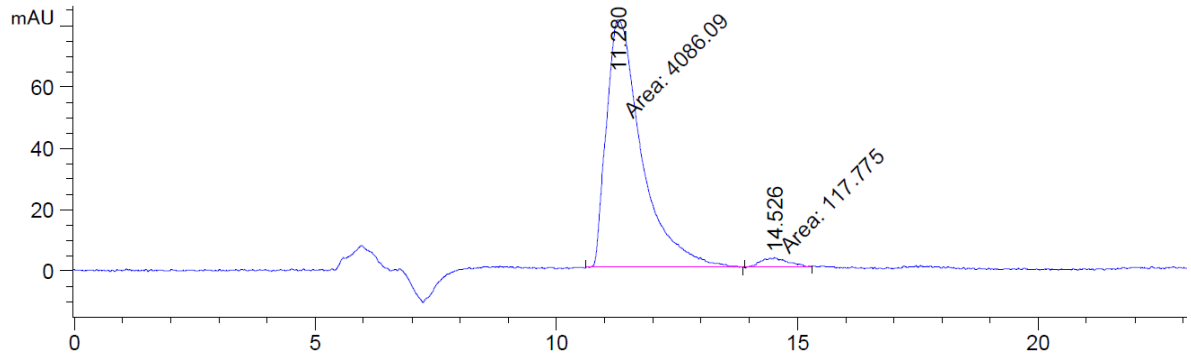
Chirapak IBN-5, 80:20 Hex:IPA, 1 mL/min, 25 °C. ***ee* = 30%**

	Time	Area %
1	8.045	65.0959
2	9.506	34.9041

2.101: 3-Hydroxy-1-oxa-5-azacyclotridecane-4,13-dione



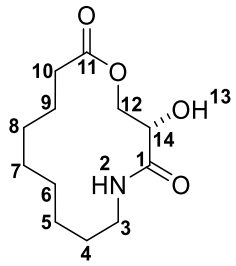
To a round-bottomed flask was added AD-mix-β (0.456 g), methanesulfonamide (29.0 mg, 0.323 mmol), ^{t}BuOH (2.5 mL) and water (2.5 mL), and the mixture was stirred for 15 minutes at RT. This solution was then added to 1-acryloylazonan-2-one (63.0 mg, 0.323 mmol) and stirred for 2 hours at 0 °C and a further 14 hours at RT. To the reaction mixture was then added Na_2SO_3 (0.62 g) and the mixture was stirred for 1 hour at RT. The crude reaction mixture was then diluted with ethyl acetate (8 mL), and the aqueous layer extracted with ethyl acetate (2 × 4 mL), before the combined organic layers were washed with brine (8 mL). The organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 ethyl acetate : hexane → 100% ethyl acetate) afforded the title compound, which was obtained as a white solid (43.8 mg, 59%); R_f = 0.40 (9:1 ethyl acetate : methanol); MP = 120 – 123 °C; $[\alpha]_D^{20}$ 37.5 (c = 1.0, MeOH); ν_{max}/cm^{-1} (thin film): 3399, 2927, 2855, 2522, 2468, 1725, 1691, 1639, 1461, 1250, 1162, 1119, 1031, 929, 540; δ_H (400 MHz, MeOD-*d*$_4$) 4.59 (1H, dd, *J* = 11.5, 2.0 Hz, H-11), 4.22 – 4.19 (1H, m, H-12) 4.05 (1H, dd, *J* = 11.5, 3.0 Hz, H-11'), 3.56 (1H, ddd, *J* = 13.5, 5.5, 3.0 Hz, H-3), 2.92 – 2.82 (1H, m, H-3'), 2.50 (1H, ddd, *J* = 15.5, 7.5, 3.5 Hz, H-9), 2.23 (1H, ddd, *J* = 15.5, 10.5, 3.0 Hz H-9'), 1.87 – 1.63 (2H, m, C**H$_2$**), 1.52 – 1.35 (5H, m, 2.5 x C**H$_2$**), 1.35 – 1.16 (3H, m, 1.5 x C**H$_2$**); δ_C (100 MHz, MeOD-*d*$_4$) 174.8 (C-1/10), 174.2 (C-1/10), 71.3 (C-12), 67.2 (C-11), 40.8 (C-3), 35.0 (C-9), 28.2 (**C**H$_2$), 27.6 (**C**H$_2$), 27.1 (**C**H$_2$), 25.4 (**C**H$_2$), 24.7 (**C**H$_2$); HRMS (ESI$^+$): calcd. for $C_{11}H_{19}NNaO_4$, 252.1206. Found: $[MNa]^+$, 252.1209 (−1.1 ppm error).



Chirapak IA, 80:20 Hex:IPA, 0.5 mL/min, 40 °C. ***ee* = 94%**

	Time	**Area %**
1	11.280	97.1984
2	14.526	2.8016

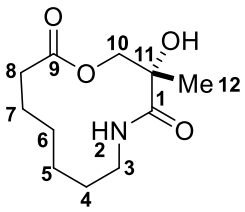
2.102: 3-Hydroxy-1-oxa-5-azacyclotetradecane-4,14-dione



To a round-bottomed flask was added AD-mix-β (0.444 g), methanesulfonamide (28.4 mg, 0.316 mmol), ^{t}BuOH (3.0 mL) and water (3.0 mL), and the mixture was stirred for 15 minutes at RT. This solution was then added to 1-acryloylazecan-2-one (66.0 mg, 0.316 mmol) and stirred for 2 hours at 0 °C and a further 14 hours at RT. To the reaction mixture was then added Na_2SO_3 (0.57 g) and the mixture was stirred for 1 hour at RT. The crude reaction mixture was then diluted with ethyl acetate (8 mL) and the aqueous layer extracted with ethyl acetate (3 × 4 mL). The combined organic layers were washed with brine (8 mL). The organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 ethyl acetate : hexane → 100% ethyl acetate) afforded the title compound, which was obtained as a white solid (44.8 mg, 58%); R_f = 0.37 (9:1 ethyl acetate : methanol); MP = 104 – 107 °C; $[\alpha]_D^{20}$ 19.5 (c = 1.0, MeOH); ν_{max}/cm^{-1} (thin film): 3397, 2929, 2860, 2468, 1726, 1644, 1477, 1444, 1242, 1152, 1118, 1097, 1003, 567, 494; δ_H (400 MHz, MeOD-d_4) 8.03 (1H, br s, H-2), 4.44 (1H, dd, *J* = 11.5, 5.0 Hz, H-12), 4.30 – 4.21 (1H, m, H-14 [overlapping]), 4.30 – 4.21 (1H, m, H-12' [overlapping]), 3.59 (1H, dddt, *J* = 12.0, 8.5, 5.5, 2.5 Hz, H-3), 3.00 (1H, ddq, *J* = 13.0, 6.5, 3.0 Hz H-3'), 2.44 (1H, ddd, *J* = 15.0, 8.0, 4.0 Hz, H-10), 2.35 – 2.24 (1H, m, H-10'), 1.73 – 1.54 (2H, m, CH_2), 1.55 – 1.19

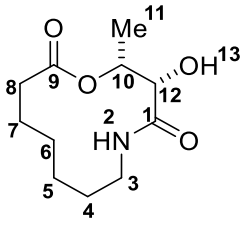
(10H, m, 5 x C**H₂**); δ_C (100 MHz, MeOD-*d₄*) 175.3 (C-1/11), 174.0 (C-1/11), 71.0 (C-14), 67.1 (C-12), 39.5 (C-3), 35.4 (C-10), 29.9 (**C**H₂), 27.0 (**C**H₂), 26.9 (**C**H₂), 26.8 (**C**H₂), 24.5 (**C**H₂), 24.4 (**C**H₂); HRMS (ESI⁺): calcd. for $C_{12}H_{22}NO_4$, 244.1543. Found: $[MH]^+$, 244.1543 (0.3 ppm error).

2.104: 3-Hydroxy-3-methyl-1-oxa-5-azacyclododecane-4,12-dione

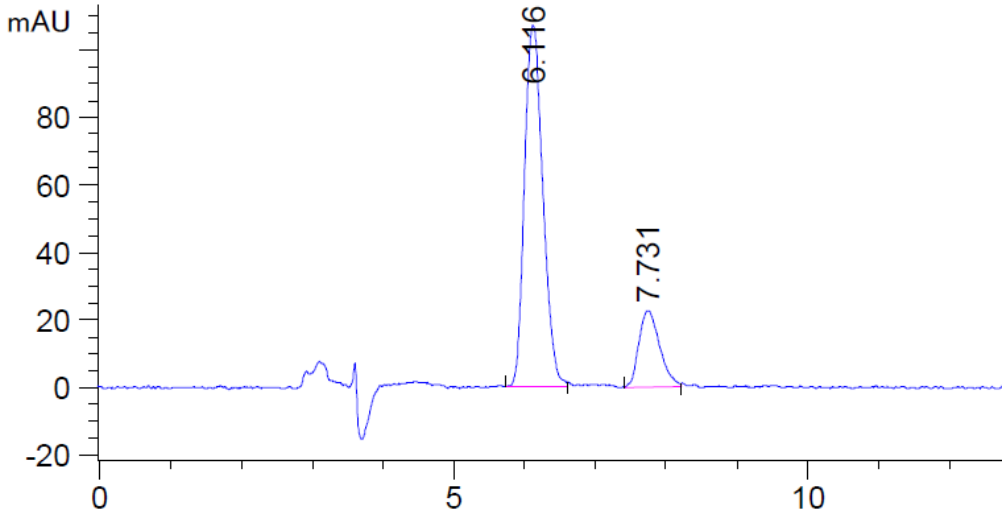


To a round-bottomed flask was added AD-mix-β (1.22 g), methanesulfonamide (81.4 mg, 0.856 mmol), ^{t}BuOH (4.0 mL) and water (4.0 mL), and the mixture was stirred for 15 minutes at RT. This solution was then added to 1-methacryloylazocan-2-one (167 mg, 0.856 mmol) and stirred for 2 hours at 0 °C and then a further 16 hours at RT. To the reaction mixture was then added Na_2SO_3 (1.3 g) and the mixture was stirred for a further 3 hours at RT. The crude reaction mixture was then diluted with ethyl acetate (15 mL) and the aqueous layer extracted with ethyl acetate (2 × 10 mL), before the combined organic layers were washed with brine (15 mL). The organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 ethyl acetate : hexane → 100% ethyl acetate) afforded the title compound, which was obtained as a white solid (42.7 mg, 22%). The title compound was difficult to separate from the methanesulfonamide reagent in this case and was isolated with some methanesulfonamide contaminant. In this low yielding example, we did not make additional effort to separate them; R_f = 0.48 (9:1 ethyl acetate : methanol); MP = 65 – 70 °C; ν_{max}/cm^{-1} (thin film): 3341, 2927, 2860, 2480, 1728, 1648, 1539, 1323, 1261, 1150, 527; δ_H (400 MHz, MeOD-*d₄*) 6.69 (1H, br s, H-2), 4.78 (1H, dd, *J* = 11.0, 2.5 Hz, H-10), 3.78 (1H, ddd, *J* = 13.5, 11.0, 3.0 Hz, H-3), 3.70 (1H, dd, *J* = 11.0, 2.5 Hz, H-10'), 2.98 – 2.89 (1H, m, H-3'), 2.53 – 2.42 (1H, m, H-8), 2.33 – 2.23 (1H, m, H-8'), 1.82 – 1.56 (6H, m, 3 x C**H₂**), 1.36 (3H, s, H-12), 1.34 – 1.24 (2H, m, C**H₂**); δ_C (100 MHz, MeOD-*d₄*) 175.8 (C-1/9), 174.6 (C-1/9), 76.1 (C-11), 70.8 (C-10), 38.2 (C-3), 33.9 (C-8), 26.8 (**C**H₂), 25.9 (**C**H₂), 25.4 (**C**H₂), 25.1 (**C**H₂), 22.3 (C-12); HRMS (ESI⁺): calcd. for $C_{11}H_{19}NNaO_4$, 252.1206. Found: $[MNa]^+$, 252.1207 (−0.4 ppm error).

2.106: 3-Hydroxy-2-methyl-1-oxa-5-azacyclododecane-4,12-dione



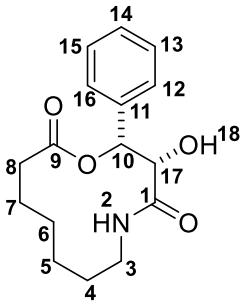
To a round-bottomed flask was added AD-mix-β (0.708 g), methanesulfonamide (46.8 mg, 0.492 mmol), ^{t}BuOH (3.0 mL) and water (3.0 mL) and the mixture was stirred for 15 minutes at RT. This solution was then added to (*E*)-1-(but-2-enoyl)azocan-2-one (96.0 mg, 0.492 mmol) and stirred for 2 hours at 0 °C and then a further 16 hours at RT. To the reaction mixture was then added Na_2SO_3 (0.8 g) and the mixture was stirred for 1 hour at RT. The crude reaction mixture was then diluted with ethyl acetate (8 mL), and the aqueous layer extracted with ethyl acetate (2 × 4 mL), before the combined organic layers were washed with brine (8 mL). The organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 ethyl acetate : hexane → 100% ethyl acetate) afforded the title compound, which was obtained as a white solid (90.7 mg, 80%); R_f = 0.40 (9:1 ethyl acetate : methanol); MP = 199 – 204 °C; $[\alpha]_D^{20}$ 22.9 (c = 1.0, MeOH); ν_{max}/cm^{-1} (thin film): 3261, 2932, 2863, 2480, 1720, 1632, 1472, 1367, 1252, 1218, 1159, 1056, 998; δ_H (400 MHz, MeOD-*d*$_4$) 5.34 (1H, dd, *J* = 6.5, 2.0 Hz, H-10), 4.00 – 3.96 (1H, m, H-12), 3.80 (1H, td, *J* = 13.0, 12.5, 3.5 Hz, H-3), 2.93 – 2.84 (1H, m, H-3'), 2.44 (1H, ddd, *J* = 13.5, 10.0, 5.0, H-8), 2.18 (1H, ddd, *J* = 13.0, 6.0, 4.5, H-8'), 1.85 – 1.47 (6H, m, 3 x C**H$_2$**), 1.29 (3H, d, *J* = 6.6 Hz, H-11), 1.24 – 1.11 (2H, m, C**H$_2$**); δ_C (100 MHz, MeOD-*d*$_4$) 174.7 (C-1/9), 174.1 (C-1/9), 75.2 (C-12), 72.6 (C-10), 37.2 (C-3), 34.1 (C-8), 27.0 (**C**H$_2$), 25.8 (**C**H$_2$), 25.3 (**C**H$_2$), 24.6 (**C**H$_2$), 16.4 (C-11); HRMS (ESI$^+$): calcd. for $C_{11}H_{19}NNaO_4$, 252.1206. Found: $[MNa]^+$, 252.1206 (0.3 ppm error).



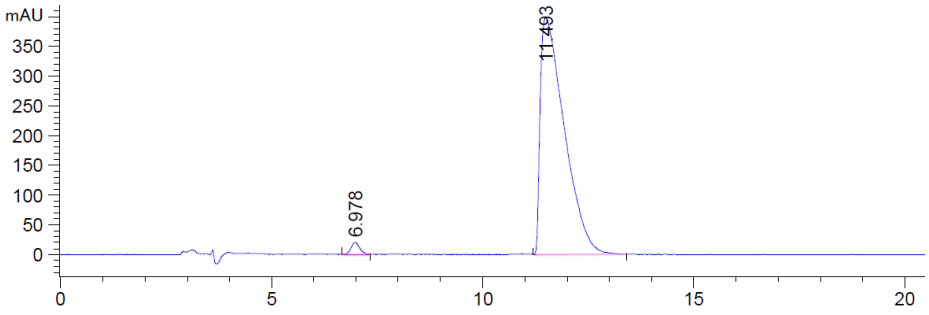
Chirapak IBN-5, 80:20 Hex:IPA, 1 mL/min, 25 °C. ***ee* = 62%**

	Time	**Area %**
1	6.116	80.7199
2	7.731	19.2801

2.107: 3-Hydroxy-2-phenyl-1-oxa-5-azacyclododecane-4,12-dione



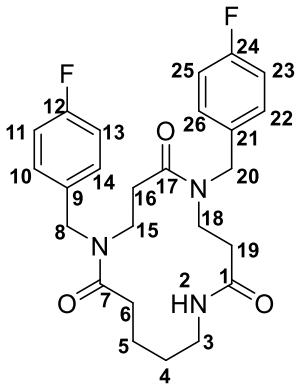
To a round-bottomed flask was added AD-mix-β (0.703 g), methanesulfonamide (47.4 mg, 0.498 mmol), ^{t}BuOH (3.0 mL) and water (3.0 mL), and the mixture was stirred for 15 minutes at RT. Then, 1-cinnamoylazocan-2-one (128 mg, 0.498 mmol) was added and the mixture was stirred for 2 hours at 0 °C and a further 16 hours at RT. To the reaction mixture was then added Na_2SO_3 (0.8 g) and the mixture was stirred for 1 hour at RT. The crude reaction mixture was then diluted with ethyl acetate (8 mL), and the aqueous layer extracted with ethyl acetate (2 × 4 mL), before the combined organic layers were washed with brine (8 mL). The organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 ethyl acetate : hexane → 100% ethyl acetate) afforded the title compound, which was obtained as a white solid (70.6 mg, 49%); R_f = 0.48 (9:1 ethyl acetate : methanol); MP = 227 – 231 °C; $[\alpha]_D^{20}$ 28.7 (c = 1.0, MeOH); ν_{max}/cm^{-1} (thin film): 3264, 2917, 2849, 1727, 1612, 1476, 1317, 1251, 1221, 1150, 985, 768, 703, 526, 497; δ_H (400 MHz, MeOD-*d*$_4$) 7.38 (2H, d, *J* = 7.0 Hz, H-12,16), 7.33 (2H, t, *J* = 7.5 Hz, H-13,15), 7.26 (1H, d, *J* = 7.0 Hz, H-14), 6.23 (1H, s, H-10), 4.23 (1H, s, H-17), 3.85 (1H, td, *J* = 13.0, 4.0 Hz, H-3), 2.92 (1H, dt, *J* = 13.5, 4.0 Hz, H-3' [overlapping]), 2.59 (1H, ddd, *J* = 13.5, 9.0, 6.0 Hz, H-8), 2.22 (1H, dt, *J* = 13.0, 5.5 Hz, H-8'), 1.88 – 1.68 (4H, m, 2 x C**H$_2$**), 1.67 – 1.51 (2H, m, C**H$_2$**), 1.37 – 1.13 (4H, m, 2 x C**H$_2$**); δ_C (100 MHz, MeOD-*d*$_4$) 174.3 (C-1/9), 173.6 (C-1/9), 138.9 (C-11), 129.3 (2 x Ar**C**H), 128.9 (C-14), 127.8 (2 x Ar**C**H), 77.2 (C-10), 76.0 (C-17), 37.3 (C-3), 34.0 (C-8), 27.0 (**C**H$_2$), 25.9 (**C**H$_2$), 25.3 (**C**H$_2$), 24.6 (**C**H$_2$); HRMS (ESI$^+$): calcd. for $C_{16}H_{22}NO_4$, 292.1543. Found: $[MH]^+$, 292.1541 (0.9 ppm error).



Chirapak IBN-5, 80:20 Hex:IPA, 1 mL/min, 25 °C. ***ee* = 96%**

	Time	**Area %**
1	6.978	1.8021
2	11.493	98.1979

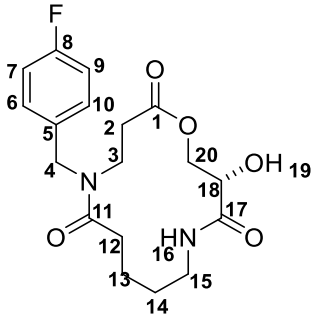
2.108: 5,9-Bis(4-fluorobenzyl)-1,5,9-triazacyclotetradecane-2,6,10-trione



To a solution of 1-acryloyl-5-(4-fluorobenzyl)-1,5-diazecane-2,6-dione (94.5 mg, 0.284 mmol) in methanol (1.0 mL), was added 4-fluorobenzylamine (37.0 µL, 0.324 mmol) in a single portion. The reaction mixture was stirred for 35 minutes at RT and then the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 49:1 ethyl acetate : methanol → 16:1 ethyl acetate : methanol → 9:1 ethyl acetate : methanol → 4:1 ethyl acetate : methanol) afforded the title compound, which was obtained as a white solid (86.2 mg, 66%), and exists in $CDCl_3$ as a complex mixture of rotameric forms; 8 signals are evident in the ^{19}F NMR spectrum, suggesting at least 4 rotamers are present. R_f = 0.27 (9:1 ethyl acetate : methanol); MP = 157 – 160 °C; ν_{max}/cm^{-1} (thin film): 3301, 2933, 1628, 1552, 1509, 1452, 1414, 1220, 1157, 824, 731, 498; δ_H (400 MHz, $CDCl_3$) Data for the rotamers: 7.24 – 6.91 (8H, m, 8 x Ar**H**), 6.74 (1H, br t, *J* = 5.5 Hz, H-2), 6.69 (1H, br t, *J* = 6.0 Hz, H-2), 6.04 (1H, br t, *J* = 6.5 Hz, H-2), 4.70 (2H, s, H-8/20), 4.57 (2H, s, H-8/20), 4.54 (2H, s, H-8/20), 4.53 (2H, s, H-8/20), 4.51 (2H, s, H-8/20), 4.35 (2H, s, H-8/20), 3.72 – 3.48 (4H, m, H-15, H-18), 3.37 – 3.27 (2H, m, H-3), 2.66 – 2.25 (6H, m, H-6, H-16, H-19), 1.75 – 1.50 (4H, m, 2 ×

C**H₂**); δ_C (100 MHz, $CDCl_3$) Data for the rotamers: 173.9 (**C**O), 173.7 (**C**O), 173.4 (**C**O), 172.8 (**C**O), 172.6 (**C**O), 171.2 (**C**O), 170.9 (**C**O), 170.6 (**C**O), 170.3 (**C**O), 162.4 (C-12/24, d, $^1J_{CF}$ = 246.1 Hz), 162.3 (C-12/24, d, $^1J_{CF}$ = 246.9 Hz), 162.2 (C-12/24, d, $^1J_{CF}$ = 246.2 Hz), 133.2 (C-9/21, d, $^4J_{CF}$ = 3.0 Hz), 132.8 (ArC, d, $^4J_{CF}$ = 3.0 Hz), 132.7 (Ar**C**, d, $^4J_{CF}$ = 3.1 Hz), 131.6 (Ar**C**, d, $^4J_{CF}$ = 2.8 Hz), 130.1 (Ar**C**), 130.0 (Ar**C**), 129.9 (Ar**C**), 129.84 (Ar**C**), 129.82 (Ar**C**), 129.8 (Ar**C**), 128.3 (2 x Ar**C**H, d, $^3J_{CF}$ = 7.9 Hz), 128.0 (Ar**C**), 127.9 (2 x Ar**C**H, d, $^3J_{CF}$ = 7.7 Hz), 127.8 (2 x Ar**C**H, d, $^3J_{CF}$ = 8.2 Hz), 116.3 (Ar**C**), 116.0 (2 x Ar**C**H, d, $^2J_{CF}$ = 21.9 Hz), 115.9 (2 x Ar**C**H, d, $^2J_{CF}$ = 21.9 Hz), 115.7 (2 x Ar**C**H, d, $^2J_{CF}$ = 21.3 Hz), 115.5 (2 x Ar**C**H, d, $^2J_{CF}$ = 21.6 Hz), 53.1 (C-8/20), 52.8 (C-8/20), 51.9 (C-8/20), 51.5 (C-8/20), 49.8 (C-8/20), 48.3 (C-8/20), 48.0 (C-8/20), 47.2 (C-8/20), 44.6 (C-15/18), 44.4 (C-15/18), 43.81 (C-15/18), 43.75 (C-15/18), 43.0 (C-15/18), 42.4 (C-15/18), 39.6 (C-3), 38.5 (C-3), 38.2 (C-3), 35.4 (C-19), 35.2 (C-19), 35.0 (C-19), 33.6 (C-6/16), 33.2 (C-6/16), 32.9 (C-6/16), 32.5 (C-6/16), 31.7 (C-6/16), 29.1 (**C**H_2), 28.2 (**C**H_2), 27.8 (**C**H_2), 23.9 (**C**H_2), 23.3 (**C**H_2), 23.0 (**C**H_2), 22.6 (**C**H_2), 22.4 (**C**H_2); δ_F (282 MHz, $CDCl_3$) Data for the rotamers: −115.11 (1F, m, Ar**F**), −114.92 (1F, m, Ar**F**), −114.75 (1F, m, Ar**F**), −114.61 (1F, m, Ar**F**), −114.48 (1F, m, Ar**F**), −114.42 (1F, m, Ar**F**), −114.18 (1F, m, Ar**F**), −113.92 (1F, m, Ar**F**); HRMS (ESI^+): calcd. for $C_{25}H_{30}F_2N_3O_3$, 458.2250. Found: $[MH]^+$, 458.2250 (−0.2 ppm error).

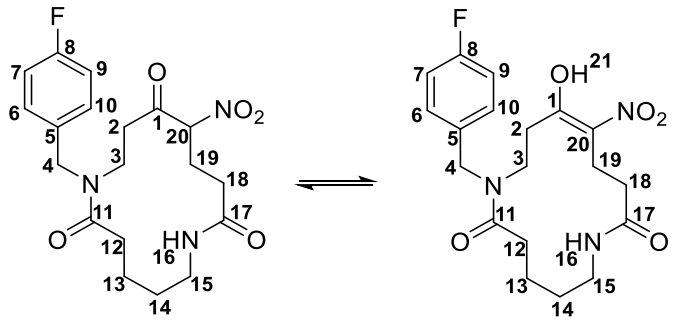
2.109: 5-(4-Fluorobenzyl)-13-hydroxy-1-oxa-5,11-diazacyclotetradecane-2,6,12-trione



To a round-bottomed flask was added AD-mix-β (0.711 g), methanesulfonamide (45.4 mg, 0.504 mmol), ^{t}BuOH (3.0 mL) and water (3.0 mL) and the mixture was stirred for 15 minutes at RT. This solution was then added to 1-acryloyl-5-(4-fluorobenzyl)-1,5-diazecane-2,6-dione (166 mg, 0.500 mmol) and stirred for 2 hours at 0 °C and a further 15 hours at RT. To the reaction mixture was then added Na_2SO_3 (0.7 g) and the mixture was stirred for 1 hour at RT. The crude reaction mixture was then diluted with ethyl acetate (8 mL) and the aqueous layer extracted with ethyl acetate (3 × 4 mL), before the combined organic layers were washed with brine (8 mL). The organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 ethyl acetate : hexane →

100% ethyl acetate → 9:1 ethyl acetate : methanol) afforded the title compound, which was obtained as a white solid (73.6 mg, 40%), and exists in $(CD_3)_2SO$ as a 3:1:1 (A:B:C) mixture of rotamers; R_f = 0.22 (9:1 ethyl acetate : methanol); MP = 185 – 190 °C; $[\alpha]_D^{20}$ 0.81 (c = 1.0, CH_2Cl_2); ν_{max}/cm^{-1} (thin film): 3299, 2929, 1744, 1651, 1615, 1509, 1445, 1361, 1263, 1225, 1158, 1125, 1059, 1005, 828, 573; δ_H (400 MHz, $(CD_3)_2SO$) Data for rotamer A: 7.87 (1H, br t, *J* = 6.0 Hz, H-16), 7.26 – 7.01 (4H, m, 4 x Ar**H**), 5.84 (1H, d, *J* = 5.5 Hz, H-19), 4.49 (1H, d, *J* = 15.5 Hz, H-4), 4.31 (1H, d, *J* = 15.0 Hz, H-4'), 4.39 – 4.17 (1H, m, H-20 [overlapping]), 4.13 – 3.98 (1H, m, H-18 [overlapping]), 4.13 – 3.98 (1H, m, H-20' [overlapping]), 3.89 (1H, t, *J* = 5.5 Hz, H-3), 3.52 (1H, dt, *J* = 15.0, 7.5 Hz, H-3'), 3.44 – 3.26 (1H, m, H-15 [overlapping]), 2.91 – 2.80 (1H, m, H-15'), 2.68 – 2.32 (2H, m, H-2 [overlapping]), 2.68 – 2.32 (1H, m, H-12 [overlapping]), 2.32 – 2.18 (1H, m, H-12'), 1.68 – 1.28 (4H, m, H-13,14). Diagnostic data for rotamer B: 8.06 (1H, br t, *J* = 6.0 Hz, H-16), 5.68 (1H, d, *J* = 4.5 Hz, H-19), 4.44 – 4.36 (1H, m, H-4), 4.27 – 4.23 (1H, m, H-4'), 3.16 – 3.04 (2H, m, H-15). Diagnostic data for rotamer C: 7.95 (1H, br t, *J* = 6.5 Hz, H-16), 2.99 – 2.91 (2H, m, H-15); δ_C (100 MHz, $(CD_3)_2SO$) Data for rotamer A: 172.8 (C-11), 171.2 (C-17), 170.0 (C-1), 161.3 (C-8, d, $^1J_{CF}$ = 242.5 Hz), 134.3 (C-5, d, $^4J_{CF}$ = 3.3 Hz), 129.6 (2 × Ar**C**H, d, $^3J_{CF}$ = 7.9 Hz), 115.2 (2 × Ar**C**H, d, $^2J_{CF}$ = 21.2 Hz), 69.5 (C-18), 66.2 (C-20), 45.9 (C-4), 42.9 (C-3), 37.8 (C-15), 35.1 (C-2), 33.7 (C-12), 27.2 (C-13/14), 22.6 (C-13/14). Diagnostic data for rotamers B and C: 173.2 (**C**O, rotamer B/C), 173.0 (**C**O, rotamer B/C), 172.5 (**C**O, rotamer B/C), 170.6 (**C**O, rotamer B/C), 170.0 (**C**O, rotamer B/C), 161.4 (C-8, d, $^1J_{CF}$ = 242.4 Hz, rotamer B/C), 128.7 (2 × Ar**C**H, d, $^3J_{CF}$ = 8.3 Hz, rotamer B), 115.6 (2 × Ar**C**H, d, $^2J_{CF}$ = 21.5 Hz, rotamer B/C), 115.3 (2 × Ar**C**H, d, $^2J_{CF}$ = 21.0 Hz, rotamer B/C), 69.3 (C-18B), 66.5 (C-20B), 47.1 (C-4B), 42.1 (C-3B), 35.7 (C-15B), 32.5 (C-2B/12B), 32.0 (C-2B/12B), 29.3 (C-13B/14B), 23.9 (C-13B/14B); δ_F (282 MHz, $(CD_3)_2SO$) Rotamer B/C: −115.44 (1F, m, Ar**F**), rotamer B/C: −115.62 (1F, m, Ar**F**), rotamer A: −115.72 (1F, m, Ar**F**); HRMS (ESI^+): calcd. for $C_{18}H_{23}FN_2NaO_5$, 389.1483. Found: $[MNa]^+$, 389.1486 (−0.6 ppm error).

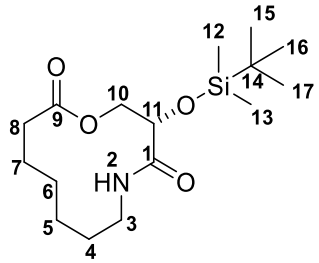
2.110: 1-(4-Fluorobenzyl)-11-nitro-1,7-diazacyclotetradecane-2,8,12-trione



In a round-bottomed flask, DBU (0.16 mL, 1.04 mmol) was added to a stirring solution of 1-acryloyl-5-(4-fluorobenzyl)-1,5-diazecane-2,6-dione (173 mg, 0.500 mmol) and nitromethane (0.56 mL, 10.4 mmol) in DCM (5.5 mL), under an inert atmosphere of Ar. The reaction mixture was stirred for 4 hours at RT. After that DCM (5 mL) and water (5 mL) were then added, and the organic layer was extracted, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 ethyl acetate : hexane → 100% ethyl acetate → 9:1 ethyl acetate : methanol → 85:15 ethyl acetate : methanol) afforded 77.1 mg of the title compound. In addition, to the aqueous layer, DCM (5 mL) was added and 1M aq. HCl was added dropwise until the aqueous solution reached pH 2, monitored *via* universal indicator paper. The aqueous layer was then extracted with DCM (2 x 5 mL), and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford 77.8 mg of product. The two purified samples were combined, affording the title compound, which was obtained as a white solid (155 mg, 76%), and exists in $CDCl_3$ as a 5:4 mixture of rotamers. Evidence of a small amount of an enol tautomeric form was also evident in the ^{1}H NMR data. The ^{1}H NMR spectrum is severely affected by rotameric broadening, with product identity and purity best determined using ^{13}C NMR data; R_f = 0.11 (9:1 ethyl acetate : methanol); MP = 147 – 153 °C; ν_{max}/cm^{-1} (thin film): 3311, 2933, 1732, 1637, 1552, 1509, 1415, 1369, 1220, 1157, 1084, 731; δ_H (400 MHz, $CDCl_3$) Data for major rotamer: 7.15 – 7.09 (2H, m, 2 x Ar**H**), 7.03 – 6.96 (2H, m, 2 x Ar**H**), 6.83 (1H, br s, H-16), 5.44 – 5.33 (1H, m, H-20), 4.67 – 4.49 (2H, m, H-4 [overlapping]), 3.82 (1H, ddd, *J* = 13.5, 8.5, 2.0 Hz, H-3), 3.68 – 3.55 (1H, m, H-15 [overlapping]), 3.26 (1H, ddd, *J* = 14.0, 8.0, 2.0 Hz, H-3'), 2.96 – 2.82 (1H, m, H-15'), 2.78 (2H, ddd, *J* = 16.0, 8.5, 2.5 Hz, H-2), 2.61 – 2.33 (2H, m, C**H₂** [overlapping]), 2.61 – 2.33 (2H, m, C**H₂** [overlapping]), 1.87 – 1.23 (6H, m, 3 x C**H₂** [overlapping]). Full data for the minor rotamer: 7.24 – 7.18 (2H, m, 2 x Ar**H**), 7.08 – 7.03 (2H, m, 2 x Ar**H**), 5.64 (1H, br t, *J* = 5.0 Hz, H-16), 5.32 – 5.24 (1H, m, H-20), 4.67 – 4.49 (2H, m, H-4 [overlapping]), 3.73 (1H, dd, *J* = 9.0, 5.5 Hz, H-3), 3.68 – 3.55 (1H, m, H-3 [overlapping]), 3.53 – 3.32 (2H, m, H-15), 2.71 – 2.63 (2H, m, H-2), 2.61 – 2.33 (2H, m, C**H₂** [overlapping]), 2.61 – 2.33 (2H, m, C**H₂** [overlapping]), 1.87 – 1.23 (6H, m, 3 x C**H₂** [overlapping]). Diagnostic data showing evidence of a small amount of an enol tautomer: 11.48 (1H, br s, H-21); δ_C (100 MHz, $CDCl_3$) Data for major rotamer: 196.4 (C-1), 174.4 (C-11/17), 171.5 (C-11/17), 162.5 (C-8, d, $^1J_{CF}$ = 247.4 Hz), 131.8 (C-5, d, $^4J_{CF}$ = 3.0 Hz), 128.3 (2 × Ar**C**H, d, $^3J_{CF}$ = 7.8 Hz), 116.3 (2 × Ar**C**H, d, $^2J_{CF}$ = 22.0 Hz), 91.4 (C-20), 52.7 (C-4), 44.8 (C-3), 41.0 (C-2), 39.2 (C-15), 32.4 (C-12/18), 32.2 (C-12/18), 28.5 (**C**H_2), 25.0 (**C**H_2), 21.3 (**C**H_2). Full data for the minor rotamer: 197.7 (C-1), 174.2 (C-11/17), 171.5 (C-11/17), 162.3 (C-8, d, $^1J_{CF}$ = 245.2 Hz), 133.3 (C-5, d, $^4J_{CF}$ = 2.8 Hz), 129.8 (2 × Ar**C**H, d, $^3J_{CF}$ = 8.2 Hz), 115.7 (2 × Ar**C**H, d, $^2J_{CF}$ = 21.6 Hz), 91.0 (C-20), 48.1 (C-4), 42.6 (C-3), 41.7 (C-2), 37.2 (C-15), 32.0 (C-12/18), 31.1 (C-12/18), 29.2

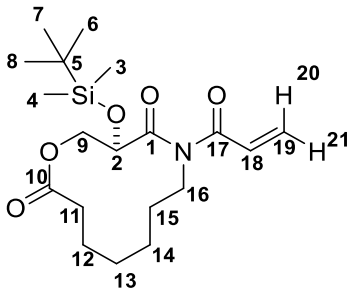
(**C**H_2), 24.4 (**C**H_2), 22.9 (**C**H_2); δ_F (282 MHz, $CDCl_3$) Major rotamer: −113.78 (1F, m, Ar**F**), minor rotamer: −114.79 (1F, m, Ar**F**); HRMS (ESI^+): calcd. for $C_{19}H_{24}FN_3NaO_5$, 416.1592. Found: $[MNa]^+$, 416.1595 (−0.7 ppm error).

2.111: 3-((*tert*-Butyldimethylsilyl)oxy)-1-oxa-5-azacyclododecane-4,12-dione



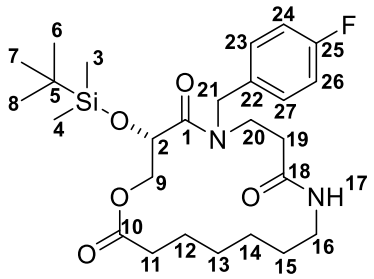
To a round-bottomed flask was added 3-hydroxy-1-oxa-5-azacyclododecane-4,12-dione (107 mg, 0.498 mmol), imidazole (80.7 mg, 1.19 mmol) and TBDMSCl (183 mg, 1.21 mmol) in DMF (3.0 mL) and this solution was stirred at RT for 6 hours, then increased to 80 °C for a further 15 hours under an Ar atmosphere. Then, the reaction mixture was diluted with Et_2O (30 mL) and washed with sat. aq. NH_4Cl solution (3 x 15 mL). The organic layer was washed with brine (5 x 30 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 ethyl acetate : hexane) afforded the title compound, which was obtained as a white, crystalline solid (135 mg, 82%). No optical rotation data was collected for this compound. R_f = 0.64 (9:1 ethyl acetate : methanol); MP = 68 – 72 °C; ν_{max}/cm^{-1} (thin film): 3422, 2930, 2858, 1740, 1685, 1524, 1461, 1252, 1126, 1011, 837, 781; δ_H (400 MHz, $CDCl_3$) 6.52 (1H, d, *J* = 10.5 Hz, H-2), 4.76 (1H, dd, *J* = 11.5, 2.0 Hz, H-10), 4.27 (1H, t, *J* = 2.0 Hz, H-11), 3.91 (1H, dd, *J* = 11.5, 2.0 Hz, H-10'), 3.89 – 3.81 (1H, m, H-3), 2.87 (1H, dt, *J* = 13.5, 4.0 Hz, H-3'), 2.37 (1H, ddd, *J* = 14.5, 10.5, 4.0 Hz, H-8), 2.26 (1H, ddd, *J* = 14.0, 6.5, 4.0 Hz, H-8'), 1.75 – 1.48 (5H, m, 2.5 x C**H₂**), 1.30 – 1.18 (3H, m, 1.5 x C**H₂**), 0.91 – 0.79 (9H, s, H-15,16,17), 0.09 (3H, s, C-12/13), 0.06 (3H, s, C-12/13); δ_C (100 MHz, $CDCl_3$) 172.7 (C-1/9), 170.3 (C-1/9), 72.7 (C-11), 65.9 (C-10), 37.3 (C-3), 33.0 (C-8), 26.0 (**C**H_2), 25.7 (C-15,16,17), 25.0 (**C**H_2), 24.19 (**C**H_2), 24.16 (**C**H_2), 18.0 (C-14), −4.8 (C-12/13), −5.2 (C-12/13); HRMS (ESI^+): calcd. for $C_{16}H_{32}NO_4Si$, 330.2095. Found: $[MH]^+$, 330.2095 (0.0 ppm error).

2.112: 5-Acryloyl-3-((*tert*-butyldimethylsilyl)oxy)-1-oxa-5-azacyclododecane-4,12-dione



A stirring solution of 3-((*tert*-butyldimethylsilyl)oxy)-1-oxa-5-azacyclododecane-4,12-dione **2.111** (110 mg, 0.334 mmol) and DIPEA (0.19 mL, 1.10 mmol) in DMF (3.0 mL) was cooled to 0 °C. To this was added a 0 °C cooled solution of acryloyl chloride (0.080 mL, 0.984 mmol) in DMF (2.0 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 14 hours. The reaction mixture was then quenched with sat. aq. NH_4Cl (10 mL), extracted with Et_2O (20 mL), then the organic layer was washed with sat. aq. $NaHCO_3$ (2 × 10 mL) and brine (5 × 20 mL). The organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 7:3 hexane : diethyl ether) afforded the title compound, which was obtained as a colourless oil (21.2 mg, 17%); R_f = 0.30 (1:1 diethyl ether : hexane); ν_{max}/cm^{-1} (thin film): 2929, 2857, 1734, 1685, 1619, 1462, 1406, 1254, 1203, 1146, 1082, 1006, 979, 836, 780; δ_H (400 MHz, $CDCl_3$) 6.58 (1H, dd, *J* = 16.5, 10.0 Hz, H-18), 6.46 (1H, dd, *J* = 16.5, 2.0 Hz, H-20), 5.85 (1H, dd, *J* = 10.0, 2.0 Hz, H-21), 5.36 (1H, t, *J* = 4.0 Hz, H-2), 4.67 (1H, dd, *J* = 11.5, 3.0 Hz, H-9), 4.29 (1H, ddd, *J* = 14.5, 7.0, 4.5 Hz, H-16), 4.14 (1H, dd, *J* = 11.5, 4.5 Hz, H-9'), 3.44 (1H, ddd, *J* = 14.5, 8.5, 4.0 Hz, H-16'), 2.40 (1H, ddd, *J* = 14.5, 8.5, 3.5 Hz, H-11), 2.28 (1H, ddd, *J* = 15.0, 8.5, 3.5 Hz, H-11'), 1.87 – 1.44 (5H, m, 2.5 x C**H$_2$**), 1.40 – 1.20 (3H, m, 1.5 x C**H$_2$**), 0.91 (9H, s, H-6, 7, 8), 0.15 (3H, s, C-3/4), 0.11 (3H, s, C-3/4); δ_C (100 MHz, $CDCl_3$) 176.3 (C-1/10/17), 174.0 (C-1/10/17), 169.2 (C-1/10/17), 131.4 (C-19), 129.6 (C-18), 73.0 (C-2), 66.7 (C-9), 44.0 (C-16), 34.2 (C-11), 27.4 (**C**H$_2$), 26.5 (**C**H$_2$), 25.9 (C-6,7,8), 23.5 (**C**H$_2$), 22.3 (**C**H$_2$), 18.5 (C-5), −4.5 (C-3/4), −4.9 (C-3/4); HRMS (ESI^+): calcd. for $C_{19}H_{33}NNaO_5Si$, 406.2020. Found: $[MNa]^+$, 406.2024 (–1.1 ppm error).

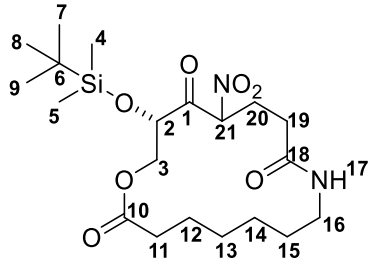
2.113: 3-((*tert*-Butyldimethylsilyl)oxy)-5-(4-fluorobenzyl)-1-oxa-5,9-diazacyclohexadecane-4,8,16-trione



To a solution of 5-acryloyl-3-((*tert*-butyldimethylsilyl)oxy)-1-oxa-5-azacyclododecane-4,12-dione **2.112** (20.7 mg, 0.0540 mmol) in methanol (0.25 mL), was added 4-fluorobenzylamine (14.0 µL, 0.123 mmol) in a single portion. The reaction mixture was stirred for 4 hours 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 → 100% ethyl acetate) afforded the title compound, which was obtained as a colourless oil (17.6 mg, 64%), and exists in $CDCl_3$ as a 5:4 mixture of rotamers; R_f = 0.55 (9:1 ethyl acetate : methanol); ν_{max}/cm^{-1} (thin film): 3330, 2930, 2859, 1739, 1649, 1511, 1465, 1257, 1223, 1157, 1101, 838, 778; δ_H (400 MHz, $CDCl_3$) Data for both rotamers: 7.25 – 7.21 (2H, m, 2 x Ar**H**, minor rotamer), 7.21 – 7.14 (2H, m, 2 x Ar**H**, major rotamer), 7.06 – 6.94 (2H, m, 2 x Ar**H** [overlapping], major), 7.06 – 6.94 (2H, m, 2 x Ar**H** [overlapping], minor), 6.36 (1H, br t, *J* = 6.0 Hz, H-17, major), 5.84 – 5.74 (1H, br m, H-17, minor), 5.13 (1H, d, *J* = 16.0 Hz, H-21, major), 4.81 (1H, t, *J* = 5.5 Hz, H-2, minor), 4.75 (1H, d, *J* = 15.0 Hz, H-21, minor), 4.69 – 4.62 (1H, m, H-2 [overlapping], major), 4.66 – 4.58 (1H, m, H-21' [overlapping], major), 4.56 (1H, dd, *J* = 11.0, 5.0 Hz, H-9, minor), 4.40 – 4.29 (1H, m, H-9 [overlapping], major), 4.40 – 4.29 (1H, m, H-9' [overlapping], minor), 4.38 – 4.24 (1H, m, H-21' [overlapping], minor), 4.24 – 4.16 (1H, m, H-9', major), 3.89 (1H, dq, *J* = 16.5, 9.0, 8.0 Hz, H-20, minor), 3.65 (1H, ddd, *J* = 14.0, 6.5, 4.0 Hz, H-20, major), 3.51 – 3.31 (1H, m, H-20' [overlapping], major), 3.51 – 3.31 (1H, m, H-16 [overlapping], major), 3.51 – 3.31 (1H, m, H-20' [overlapping], minor), 3.51 – 3.31 (1H, m, H-16 [overlapping], minor), 3.22 (1H, dq, *J* = 12.5, 6.0 Hz, H-16', major), 3.12 – 3.02 (1H, m, H-16', minor), 2.56 (2H, dt, *J* = 6.5, 3.0 Hz, H-19, major), 2.40 – 2.34 (2H, m, H-19 [overlapping], minor), 2.50 – 2.28 (2H, m, H-11, [overlapping], major/minor), 2.50 – 2.28 (2H, m, H-11, [overlapping], major/minor), 1.78 – 1.66 (2H, m, C**H₂** [overlapping], major), 1.78 – 1.66 (2H, m, C**H₂** [overlapping], minor), 1.58 – 1.46 (2H, m, C**H₂** [overlapping], major), 1.58 – 1.46 (2H, m, C**H₂** [overlapping], minor), 1.43 – 1.21 (4H, m, 2 x C**H₂** [overlapping], major), 1.43 – 1.21 (4H, m, 2 x C**H₂** [overlapping], minor), 0.87 (9H, s, H-6,7,8, minor), 0.77 (9H, s, H-6,7,8, major), 0.12 (3H, s, C-3/4, minor), 0.10 (3H, s, C-3/4, minor), 0.04 (3H, s, C-3/4, major), −0.05 (3H, s, C-3/4, major); δ_C (100 MHz, $CDCl_3$) Data for both rotamers: 174.7 (C-18/10,

minor rotamer), 173.5 (C-18/10, major rotamer), 171.4 (C-1, minor), 171.2 (C-1, major), 170.3 (C-10/18, minor), 169.9 (C-10/18, major), 162.4 (C-25, d, $^{1}J_{CF}$ = 246.2 Hz, major), 133.2 (C-22, d, $^{4}J_{CF}$ = 2.9 Hz, minor), 132.9 (C-22, d, $^{4}J_{CF}$ = 2.8 Hz, major), 129.9 (2 × Ar**C**H, d, $^{3}J_{CF}$ = 8.3 Hz, minor), 128.7 (2 × Ar**C**H, d, $^{3}J_{CF}$ = 7.8 Hz, major), 115.8 (2 × Ar**C**H, d, $^{2}J_{CF}$ = 21.9 Hz, major), 115.6 (2 × Ar**C**H, d, $^{2}J_{CF}$ = 21.2 Hz, minor), 71.0 (C-2, major), 66.0 (C-9, minor), 65.5 (C-9, major), 51.3 (C-21, major), 48.4 (C-21, minor), 43.9 (C-20, minor), 43.6 (C-20, major), 39.2 (C-16, minor), 38.9 (C-16, major), 36.6 (C-11, major/minor rotamer), 34.9 (C-19, major), 33.7 (C-11, major/minor), 32.7 (C-19, minor), 29.0 (**C**H_2, major), 28.1 (**C**H_2, minor), 27.34 (**C**H_2, minor), 27.30 (**C**H_2, major), 25.8 (C-6,7,8, minor), 25.7 (C-6,7,8, major), 25.3 (**C**H_2, minor), 24.7 (**C**H_2, major), 24.0 (**C**H_2, major), 22.5 (**C**H_2, minor), 18.4 (C-5, minor), 18.1 (C-5, major), −4.2 (C-3/4, minor), −4.4 (C-3/4, major), −4.5 (C-3/4, minor), −4.7 (C-3/4, major); δ_F (282 MHz, $CDCl_3$) Minor rotamer: −114.77 (1F, m, Ar**F**), major rotamer: −114.92 (1F, m, Ar**F**); HRMS (ESI$^+$): calcd. for $C_{26}H_{41}FKN_2O_5Si$, 547.2400. Found: [MK]$^+$, 547.2408 (−1.4 ppm error).

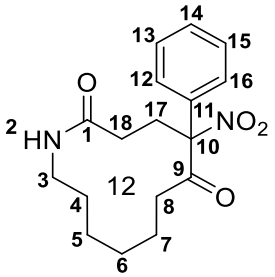
2.114: 15-((*tert*-Butyldimethylsilyl)oxy)-13-nitro-1-oxa-9-azacyclohexadecane-2,10,14-trione



To a round-bottomed flask, DBU (22.5 µL, 0.151 mmol) was added to a stirring solution of 5-acryloyl-3-((*tert*-butyldimethylsilyl)oxy)-1-oxa-5-azacyclododecane-4,12-dione **2.112** (27.7 mg, 0.072 mmol) and nitromethane (81.0 µL, 1.51 mmol) in DCM (0.25 mL), in an inert atmosphere of Ar. The reaction mixture was stirred for 5 hours at RT, monitoring with TLC. After that, to the reaction mixture was added water (5 mL) and extracting with DCM (5 mL), with this extract then dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 ethyl acetate : hexane → 100% ethyl acetate), afforded the title compound, which was obtained as a colourless oil (22.4 mg, 70%), and exists in $CDCl_3$ as a 3:2 mixture of rotamers; R_f = 0.19 (9:1 ethyl acetate : methanol); ν_{max}/cm^{-1} (thin film): 3304, 2928, 2857, 1742, 1657, 1557, 1463, 1363, 1256, 1150, 839, 782; δ_H (600 MHz, $CDCl_3$) Data for major rotamer: 5.74 (1H, br t, *J* = 5.0 Hz, H-17), 5.68 (1H, dd, *J* = 9.5, 4.5 Hz, H-21), 4.56 (1H, dd, *J* = 11.5, 4.0 Hz, H-3), 4.51 (1H, dd, *J* = 4.0, 2.0 Hz, H-2), 4.18 (1H, dd,

J = 11.5, 2.0 Hz, H-3'), 3.53 – 3.47 (1H, m, H-16), 3.24 – 3.18 (1H, m, H-16'), 2.56 – 2.39 (2H, m, H-20 [overlapping]), 2.49 – 2.39 (2H, m, H-11/19 [overlapping]), 2.32 (2H, t, *J* = 7.0 Hz, H-11/19), 1.80 – 1.31 (8H, m, 4 x C**H₂**), 0.91 (9H, s, H-7,8,9), 0.14 (3H, s, H-4/5), 0.11 (3H, s, H-4/5). Diagnostic data for the minor rotamer: 5.79 (1H, dd, *J* = 9.5, 4.0 Hz, H-21), 5.53 (1H, br t, *J* = 6.5 Hz, H-17), 4.53 (1H, dd, *J* = 5.5, 3.0 Hz, H-2), 4.48 (1H, t, *J* = 6.0 Hz, H-3), 4.21 (1H, dd, *J* = 11.5, 3.0 Hz, H-3'), 2.25 – 2.20 (2H, m, H-11/19), 0.92 (9H, s, H-7,8,9), 0.14 (3H, s, H-4/5), 0.19 (3H, s, H-4/5); δ_C (150 MHz, $CDCl_3$) Data for major rotamer: 199.3 (C-1), 173.3 (C-10/18), 171.0 (C-10/18), 87.5 (C-21), 75.9 (C-2), 66.3 (C-3), 38.8 (C-16), 33.0 (C-11/19), 32.45 (C-11/19), 29.0 (**C**H_2), 26.9 (**C**H_2), 26.2 (**C**H_2), 25.8 (C-7,8,9), 25.2 (**C**H_2), 24.2 (**C**H_2), 18.1 (C-6), −4.7 (C-4/5), −5.5 (C-4/5). Full data for the minor rotamer: 198.6 (C-1), 172.2 (C-10/18), 170.6 (C-10/18), 88.7 (C-21), 75.6 (C-2), 65.5 (C-3), 36.8 (C-16), 32.9 (C-11/19), 32.54 (C-11/19), 29.1 (**C**H_2), 27.2 (**C**H_2), 26.3 (**C**H_2), 26.0 (C-7,8,9), 24.8 (**C**H_2), 24.5 (**C**H_2), 18.4 (C-6), −4.6 (C-4/5), −5.0 (C-4/5); HRMS (ESI$^+$): calcd. for $C_{20}H_{36}N_2NaO_7Si$, 467.2184. Found: $[MNa]^+$, 467.2181 (0.7 ppm error).

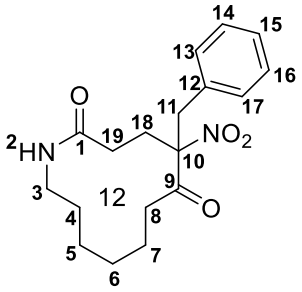
2.117: 5-Nitro-5-phenylazacyclododecane-2,6-dione



5-Nitro-1-azacyclododecane-2,6-dione (223 mg, 0.920 mmol) in DCE (10.0 mL) and K_2CO_3 (130 mg, 0.941 mmol) was placed in an inert atmosphere of Ar and stirred for 10 minutes. Then, diphenyliodonium triflate (482 mg, 1.11 mmol) was added and the reaction mixture was heated to reflux (85 °C) and left to stir for 17 h. Upon completion, the solution was diluted with hexane (10 mL) before being concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 ethyl acetate : hexane → 100% ethyl acetate) afforded the title compound, which was obtained as a yellow oil (268 mg, 92%); R_f = 0.59 (9:1 ethyl acetate : methanol); ν_{max}/cm^{-1} (thin film): 3301, 2933, 2867, 1724, 1647, 1552, 1444, 1349, 1201, 1098, 700; δ_H (400 MHz, $CDCl_3$) 7.50 – 7.46 (2H, m, H-12,16), 7.42 – 7.37 (2H, m, H-13,15 [overlapping]), 7.42 – 7.37 (1H, m, H-14 [overlapping]), 6.16 (1H, dd, *J* = 9.5, 3.5 Hz, H-2), 3.80 – 3.67 (2H, m, H-3), 3.36 (1H, ddd, *J* = 15.5, 8.0, 2.0 Hz, H-17), 3.18 (1H, ddd, *J* = 15.5, 8.0, 2.0 Hz, H-17'), 2.71 – 2.58 (2H, m, H-18), 2.49 – 2.43 (2H, m, H-8), 1.93 – 1.12 (8H, m, 4 x CH_2); δ_C (100 MHz, $CDCl_3$) 202.8 (C-9), 172.3 (C-1), 134.2 (C-11), 130.3 (C-14), 128.9 (C-

13,15), 128.7 (C-12,16), 103.5 (C-10), 39.3 (C-3), 36.4 (C-8), 31.2 (C-18), 28.2 (C-17), 27.4 (CH_2), 27.3 (CH_2), 23.3 (CH_2), 19.8 (CH_2); HRMS (ESI^+): calcd. for $C_{17}H_{22}N_2NaO_4$, 341.1472 Found: $[MNa]^+$, 341.1472 (−0.1 ppm error).

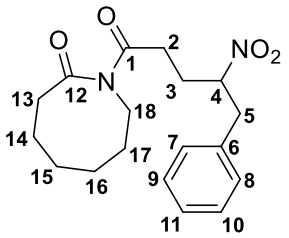
2.118: 5-Benzyl-5-nitroazacyclododecane-2,6-dione



To a round-bottomed flask, 5-nitro-1-azacyclododecane-2,6-dione (205 mg, 0.847 mmol) in THF (10 mL), was added DBU (0.14 mL, 0.940 mmol) in an inert atmosphere of Ar and this was subject to a 5-minute pre-stir. Then, benzyl bromide (0.13 mL, 1.10 mmol) in THF (5.0 mL) was added to the reaction mixture and was left to stir at RT for 23 h. Upon completion, the solution was diluted with DCM (15 mL) and 2 M HCl was added dropwise until the aqueous layer became acidic. The aqueous layer was extracted with DCM (3 x 10 mL). The organic layer was then dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 7:3 hexane : ethyl acetate → 1:1 ethyl acetate : hexane → 7:3 ethyl acetate : hexane → 9:1 ethyl acetate : hexane) afforded two products, the title compound (**2.118**) was obtained as a colourless oil (43.0 mg, 15%) and the side-product (**2.121**) was obtained as a colourless oil (37.3 mg, 13%).

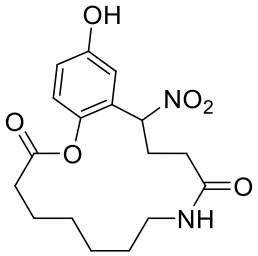
Data for **2.118**: R_f = 0.56 (100% ethyl acetate); ν_{max}/cm^{-1} (thin film) 3224, 2934, 1721, 1643, 1542, 1440, 1355, 909, 728, 701, 648; δ_H (400 MHz, $CDCl_3$) 7.31 – 7.26 (3H, m, H-14,15,16), 7.11 – 7.04 (2H, m, H-13,17), 5.63 (1H, br t, *J* = 6.5 Hz, H-2), 3.67 – 3.55 (1H, m, H-3 [overlapping]), 3.66 (1H, d, *J* = 14.0 Hz, H-11 [overlapping]), 3.40 (1H, d, *J* = 14.0 Hz, H-11'), 3.19 – 3.08 (1H, m, H-3'), 2.70 – 2.57 (2H, m, H-8 [overlapping]), 2.70 – 2.57 (1H, m, H-18 [overlapping]), 2.50 – 2.40 (1H, m, H-18'), 2.34 – 2.28 (2H, m, H-19), 1.67 (2H, q, *J* = 7.0 Hz, H-7), 1.62 – 1.40 (2H, m, H-4), 1.40 – 1.28 (4H, m, H-5,6); δ_C (100 MHz, $CDCl_3$) 203.0 (C-9), 171.7 (C-1), 132.8 (C-12), 130.2 (C-13,17), 128.9 (C-14,16), 128.2 (C-15), 102.2 (C-10), 42.0 (C-11), 38.6 (C-3), 36.1 (C-8), 30.6 (C-19), 27.8 (C-18), 26.9 (C-4), 26.5 (**C**H_2), 23.0 (**C**H_2), 19.8 (C-7); HRMS (ESI^+): calcd. for $C_{18}H_{24}N_2NaO_4$, 355.1628 Found: $[MNa]^+$, 355.1637 (−2.6 ppm error).

Data for **2.121**: **1-(4-Nitro-5-phenylpentanoyl)azocan-2-one**



R_f = 0.67 (9:1 ethyl acetate : methanol); ν_{max}/cm^{-1} (thin film) 2929, 2856, 1692, 1551, 1450, 1379, 1294, 1201, 1127, 700; δ_H (400 MHz, $CDCl_3$) 7.31 – 7.21 (3H, m, H-9,10,11), 7.17 – 7.13 (2H, m, H-7,8), 4.86 – 4.76 (1H, m, H-4), 3.93 – 3.84 (2H, m, H-18), 3.26 (1H, dd, *J* = 14.0, 8.5 Hz, H-5), 3.06 (1H, dd, *J* = 14.0, 8.5 Hz, H-5), 3.02 – 2.84 (2H, m, H-2), 2.66 – 2.60 (2H, m, H-13), 2.36 – 2.17 (2H, m, H-3), 1.85 (2H, p, *J* = 6.0 Hz, H-14), 1.68 (2H, p, *J* = 6.0 Hz, H-17), 1.62 – 1.52 (2H, m, H-16 [overlapping]), 1.62 – 1.52 (2H, m, H-15 [overlapping]); δ_C (100 MHz, $CDCl_3$) 178.4 (C-12), 174.9 (C-1), 136.6 (C-6), 129.0 (C-7,8), 128.9 (C-9,10), 127.5 (C-11), 89.1 (C-4), 43.6 (C-18), 40.3 (C-5), 37.2 (C-13), 35.6 (C-2), 29.5 (C-17), 29.2 (C-14), 28.9 (C-3), 26.3 (C-15), 24.1 (C-16); HRMS (ESI^+): calcd. for $C_{18}H_{24}N_2NaO_4$, 355.1628 Found: $[MNa]^+$, 355.1632 (−0.9 ppm error).

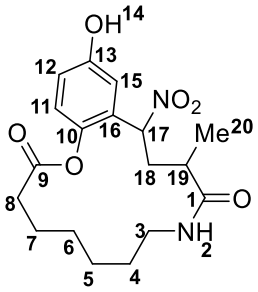
2.128: 15-Hydroxy-13-nitro-4,5,6,7,8,9,12,13-octahydrobenzo[*b*][1]oxa[8]azacyclopentadecine- 2,10(3*H*,11*H*)-dione



To a mixture of 5-nitro-1-azacyclododecane-2,6-dione (82.4 mg, 0.455 mmol) and 1,4-benzoquinone (49.1 mg, 0.455 mmol) in a round-bottomed flask under an argon atmosphere, was added THF (5.0 mL), then DBU (1 drop) and the mixture was stirred at RT for 30 minutes. The crude reaction mixture was then concentrated *in vacuo* and taken up in DCM (10 mL) and water (5 mL). The aqueous layer was acidified with 10% HCl (1 drop) and extracted with DCM (3 × 5 mL) and the combined organic layers were then washed with water (3 × 5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford the title compound, which was obtained as a brown oil (120 mg, 75%); R_f = 0.39 (9:1 ethyl acetate : methanol); 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, $(CD_3)_2SO$) 9.89 (1H, br s, O**H**), 7.97 (1H, dd, *J* = 8.0, 3.5 Hz, N**H**), 7.02 – 6.97 (2H, m, Ar**H**), 6.86 (1H, dd, *J* = 9.0, 3.0 Hz, Ar**H**), 5.39 (1H, dd,

J = 11.0, 3.0 Hz, C**H**NO_2), 3.56 – 3.19 (1H, m, C$\mathbf{H_2}$), 2.92 – 2.81 (1H, m, C$\mathbf{H_2}$), 2.68 – 2.53 (2H, m, C$\mathbf{H_2}$), 2.34 – 2.19 (2H, m, C$\mathbf{H_2}$), 2.16 – 2.05 (1H, m, C$\mathbf{H_2}$), 1.80 – 1.56 (2H, m, C$\mathbf{H_2}$), 1.54 – 1.35 (4H, m, 2 x C$\mathbf{H_2}$), 1.33 – 1.16 (3H, m, 1.5 x C$\mathbf{H_2}$); δ_C (100 MHz, $(CD_3)_2SO$) 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**HNO_2), 36.6 (**C**H_2), 32.6 (**C**H_2), 31.3 (**C**H_2), 28.4 (**C**H_2), 28.2 (**C**H_2), 27.3 (**C**H_2), 24.6 (**C**H_2), 23.6 (**C**H_2); HRMS (ESI^+): calcd. for $C_{17}H_{22}N_2NaO_6$, 373.1370. Found: $[MNa]^+$, 373.1376 (−1.6 ppm error).

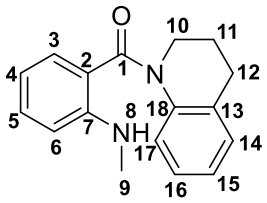
2.131: 15-Hydroxy-11-methyl-13-nitro-4,5,6,7,8,9,12,13-octahydrobenzo[*b*][1]oxa[8]azacyclopentadecine-2,10(3*H*,11*H*)-dione



To a mixture of 3-methyl-5-nitroazacyclododecane-2,6-dione (167 mg, 0.653 mmol) and 1,4-benzoquinone (72.2 mg, 0.668 mmol) in a round-bottomed flask under an argon atmosphere, was added THF (12.0 mL), then DBU (1 drop) and stirred at RT for 20 hours. The crude reaction mixture was concentrated *in vacuo* and taken up in DCM (15 mL) and washed with water (2 x 10 mL). The organic layers were then dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 7:3 hexane : ethyl acetate → 1:1 ethyl acetate : hexane → 100% ethyl acetate → 9:1 ethyl acetate : methanol) afforded the title compound, which was obtained as a brown oil (190 mg, 80%), and exists in $CDCl_3$ as a 5:4 mixture of rotamers; R_f = 0.58 (9:1 ethyl acetate : methanol); ν_{max}/cm^{-1} (thin film): 3287, 2934, 2865, 1758, 1646, 1554, 1497, 1455, 1364, 1300, 1192, 1134, 1099, 911, 733; δ_H (400 MHz, $CDCl_3$) Data for major rotamer: 7.07 – 6.81 (3H, m, 3 x Ar**H**), 5.73 (1H, dd, *J* = 8.5, 3.5 Hz, H-2), 5.51 (1H, dd, *J* = 11.5, 4.0 Hz, H-17), 3.67 (1H, dq, *J* = 14.0, 7.0 Hz, H-3), 3.01 – 2.87 (1H, m, H-3' [overlapping]), 2.85 – 2.54 (1H, m, H-18), 2.47 – 2.22 (1H, m, H-18' [overlapping]), 2.47 – 2.22 (1H, m, H-19 [overlapping]), 1.98 – 1.36 (10H, m, 5 x C$\mathbf{H_2}$), 1.17 (3H, d, *J* = 7.0 Hz, H-20). Diagnostic data for the minor rotamer: 5.96 (1H, dd, *J* = 8.5, 3.0 Hz, H-2), 5.45 (1H, dd, *J* = 10.5, 4.0 Hz, H-17), 3.87 – 3.78 (1H, m, H-3), 3.01 – 2.87 (1H, m, H-3' [overlapping]), 2.47 – 2.22 (2H, m, H-18 [overlapping]), 2.09 – 1.99 (1H, m, H-19), 1.23 (3H, d, *J* = 6.5 Hz, H-20); δ_C (100 MHz, $CDCl_3$) Data for both rotamers: 175.1 (C-1), 175.0 (C-1), 173.9 (C-9), 172.2 (C-9), 155.0 (C-13), 154.7 (C-13), 142.9 (C-10/16), 142.1 (C-10/16), 126.6

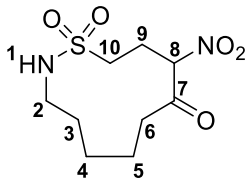
(C-10/16), 125.9 (C-10/16), 124.0 (Ar**C**H), 123.6 (Ar**C**H), 118.4 (Ar**C**H), 118.0 (Ar**C**H), 114.7 (Ar**C**H), 114.1 (Ar**C**H), 83.9 (C-17), 81.5 (C-17), 39.6 (**C**H_2), 38.8 (C-19), 37.9 (C-19), 36.9 (**C**H_2), 36.0 (**C**H_2), 33.5 (**C**H_2), 32.8 (**C**H_2), 28.7 (**C**H_2), 28.6 (**C**H_2), 27.9 (**C**H_2), 27.6 (**C**H_2), 25.0 (**C**H_2), 24.7 (**C**H_2), 23.8 (**C**H_2), 21.4 (**C**H_2), 19.5 (C-20), 18.4 (C-20); HRMS (ESI$^+$): calcd. for $C_{18}H_{24}N_2NaO_6$, 387.1527. Found: [MNa]$^+$, 387.1531 (−1.0 ppm error).

2.137: (3,4-Dihydroquinolin-1(2*H*)-yl)(2-(methylamino)phenyl)methanone



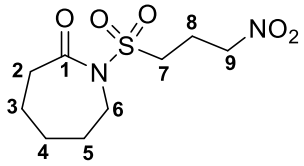
In a round-bottomed flask under argon, isatoic anhydride (887 mg, 5.01 mmol) and tetrahydroquinoline (0.63 mL, 5.01 mmol) were added. To the flask was added THF (10.0 mL) and NaHMDS in THF (2.05 mL, 10.0 mmol) was added dropwise at RT using a syringe pump over 15 minutes. The red mixture was stirred at RT for 72 h, then poured onto 1 M aq. HCl (10 mL). The aqueous layer was extracted with ethyl acetate (2 x 20 mL) and the organics were washed with brine (20 mL). The organic layer was dried over $MgSO_4$, filtered and concentred *in vacuo*. Purification by flash column chromatography (SiO_2, 10:1 hexane : ethyl acetate → 4:1 hexane : ethyl acetate → 100% ethyl acetate) was then done. In order to remove a remaining impurity, a further workup was completed, dissolving the mixture in DCM (20 mL) and washing with 1M NaOH (3 x 30 mL) to afford the title compound, which was obtained as a yellow oil (190 mg, 14%); R_f = 0.56 (1:1 ethyl acetate : hexane); ν_{max}/cm^{-1} (thin film): 3408, 2948, 2246, 1623, 1578, 1514, 1491, 1376, 1292, 1264, 1171, 906, 724, 647; δ_H (400 MHz, $CDCl_3$) 7.23 – 7.18 (1H, m, ArC**H**), 7.13 (1H, d, *J* = 7.5 Hz, ArC**H**), 7.01 – 6.96 (1H, m, ArC**H**), 6.95 – 6.89 (1H, m, ArC**H**), 6.88 – 6.84 (1H, m, ArC**H**), 6.82 (1H, dd, *J* = 7.5, 1.5 Hz, ArC**H**), 6.68 (1H, d, *J* = 7.5 Hz, ArC**H**), 6.40 (1H, t, *J* = 7.5 Hz, ArC**H**), 5.81 (1H, br s, H-8), 3.88 (2H, t, *J* = 6.5, H-10), 2.86 (3H, s, H-9), 2.83 (2H, t, *J* = 6.5 Hz, H-12), 2.03 (2H, p, *J* = 6.5 Hz, H-11); δ_C (100 MHz, $CDCl_3$) 171.4 (C-1), 149.6 (Ar**C**), 139.5 (Ar**C**), 131.6 (Ar**C**H), 131.1 (Ar**C**), 129.8 (Ar**C**H), 128.5 (Ar**C**H), 125.9 (Ar**C**H), 125.2 (Ar**C**H), 124.6 (Ar**C**H), 118.8 (Ar**C**), 115.2 (Ar**C**H), 111.0 (Ar**C**H), 44.6 (C-10), 30.2 (C-9), 27.0 (C-12), 24.4 (C-11); HRMS (ESI$^+$): calcd. for $C_{17}H_{18}N_2NaO$, 289.1311 Found: [MNa]$^+$, 289.1311 (0.3 ppm error). Characterisation data matched those reported in the literature.[86]

2.147: 9-Nitro-1-thia-2-azacycloundecan-8-one 1,1-dioxide



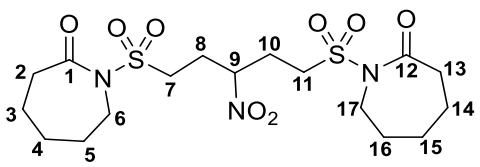
To a round-bottomed flask under Ar, DBU (0.09 mL, 0.606 mmol) was added to a stirring solution of 1-(vinylsulfonyl)azepan-2-one (53.6 mg, 0.264 mmol) and nitromethane (0.28 mL, 5.27 mmol) in DCM (5.0 mL). The reaction mixture was stirred for 16 h at RT, monitoring with TLC. Upon completion, the solution was washed with DCM (5 mL) and water (5 mL) and the organic layer extracted. To the aqueous layer was added DCM (5 mL) and 1M aq. HCl was added dropwise before the solution reached pH 2, monitored *via* universal indicator. The aqueous layer was then extracted with DCM (2 x 5 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The combined organic layers were then purified by flash column chromatography (SiO_2, 7:3 hexane : ethyl acetate → 1:1 hexane : ethyl acetate → 7:3 ethyl acetate : hexane → 100% ethyl acetate → 9:1 ethyl acetate : methanol) affording products **2.148** and **2.149** (data and yields below). None of the title compound, **2.147**, was formed.

2.148: 1-((3-Nitropropyl)sulfonyl)azepan-2-one



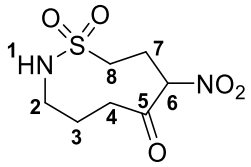
The product was a colourless oil (18.6 mg, 27%); R_f = 0.57 (100% ethyl acetate); ν_{max}/cm^{-1} (thin film): 2927, 2857, 1693, 1552, 1349, 1182, 1151, 1120, 880, 513; δ_H (400 MHz, $CDCl_3$) 4.58 (2H, t, *J* = 7.0 Hz, H-9), 3.96 – 3.86 (2H, m, H-6), 3.67 (2H, t, *J* = 7.0 Hz, H-7), 2.65 – 2.73 (2H, m, H-2), 2.51 (2H, p, *J* = 7.0 Hz, H-8), 1.88 – 1.75 (6H, m, 4 x C**H₂**); δ_C (100 MHz, $CDCl_3$) 176.7 (C-1), 72.9 (C-9), 51.4 (C-7), 46.3 (C-6), 39.0 (C-2), 29.6 (**C**H_2), 29.3 (**C**H_2), 23.2 (**C**H_2), 21.4 (C-8); HRMS (ESI^+): calcd. for $C_9H_{16}N_2NaO_5S$, 287.0672 Found: $[MNa]^+$, 287.0675 (−1.1 ppm error).

2.149: 1,1'-(3-Nitropentane-1,5-diyldisulfonyl)bis(azepan-2-one)



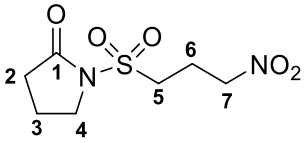
The product was a colourless oil (16.8 mg, 14%); R_f = 0.52 (100% ethyl acetate); ν_{max}/cm^{-1} (thin film): 2930, 2858, 1693, 1552, 1350, 1182, 1154, 1121, 880, 513; δ_H (400 MHz, $CDCl_3$) 4.85 (1H, tt, *J* = 9.0, 4.5 Hz, H-9), 3.94 – 3.82 (4H, m, H-6,17), 3.60 (4H, t, *J* = 7.5 Hz, H-7,11), 2.72 – 2.64 (4H, m, H-2,13), 2.55 – 2.28 (4H, m, H-8,10), 1.87 – 1.74 (12H, m, 6 x CH_2); δ_C (100 MHz, $CDCl_3$) 176.7 (C-1,12), 83.8 (C-9), 50.7 (C-7,11), 46.4 (C-6,17), 38.9 (C-2,13), 29.7 (2 x **C**H_2), 29.3 (2 x **C**H_2), 27.3 (C-8,10), 23.1 (2 x **C**H_2); HRMS (ESI^+): calcd. for $C_{17}H_{29}N_3NaO_8S_2$, 490.1288 Found: $[MNa]^+$, 490.1296 (−1.6 ppm error).

2.151: 7-Nitro-1,2-thiazonan-6-one 1,1-dioxide



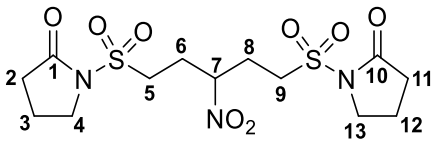
To a round-bottomed flask under Ar, nitromethane (0.80 mL, 14.9 mmol) was added to a stirring solution of 1-(vinylsulfonyl)pyrrolidin-2-one (130 mg, 0.741 mmol) and triethylamine (0.31 mL, 2.22 mmol) in DCM (1.8 mL). The reaction mixture was stirred at RT for 16 h, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 hexane : ethyl acetate → 7:3 ethyl acetate : hexane → 9:1 ethyl acetate : methanol) afforded products **2.152** and **2.153** (data and yields below). None of the title compound, **2.151**, was formed.

2.152: 1-((3-Nitropropyl)sulfonyl)pyrrolidin-2-one



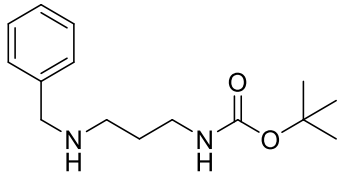
The product was an orange oil (43.4 mg, 25%); R_f = 0.58 (9:1 ethyl acetate : methanol); ν_{max}/cm^{-1} (thin film): 2924, 1732, 1552, 1350, 1212, 1152, 1121, 959, 523; δ_H (400 MHz, $CDCl_3$) 4.58 (2H, t, *J* = 7.0 Hz, H-7), 3.87 (2H, t, *J* = 7.0 Hz, H-4), 3.57 (2H, t, *J* = 7.0 Hz, H-5), 2.59 (2H, t, *J* = 7.0 Hz, H-2), 2.52 (2H, p, *J* = 7.0 Hz, H-6), 2.17 (2H, p, *J* = 7.0 Hz, H-3); δ_C (100 MHz, $CDCl_3$) 174.9 (C-1), 72.8 (C-7), 49.7 (C-5), 47.2 (C-4), 32.3 (C-2), 20.8 (C-6), 18.6 (C-3); HRMS (ESI^+): calcd. for $C_7H_{12}N_2NaO_5S$, 259.0359 Found: $[MNa]^+$, 259.0354 (2.0 ppm error).

2.153: 1,1'-(3-Nitropentane-1,5-diyldisulfonyl)bis(pyrrolidin-2-one)



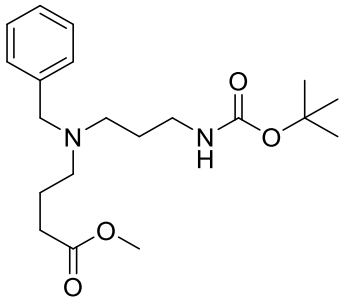
The product was a white solid (32.6 mg, 11%); MP = 144 – 150 °C, R_f = 0.49 (9:1 ethyl acetate : methanol); ν_{max}/cm^{-1} (thin film): 2964, 1732, 1553, 1354, 1212, 1155, 1121, 960, 519; δ_H (400 MHz, $CDCl_3$) 4.89 (1H, tt, *J* = 9.0, 4.5 Hz, H-7), 3.88 (4H, t, *J* = 7.5 Hz, H-4,13), 3.59 – 3.46 (4H, m, *J* = 7.5 Hz, H-5,8), 2.60 (4H, t, *J* = 7.5 Hz, H-2,11), 2.56 – 2.33 (4H, m, H-6,8), 2.18 (4H, p, *J* = 7.5 Hz, H-3,12); δ_C (100 MHz, $CDCl_3$) 175.0 (C-1,10), 83.7 (C-7), 49.1 (C-5,9), 47.2 (C-4,13), 32.3 (C-2,11), 26.9 (C-6,8), 18.6 (C-3,12); HRMS (ESI^+): calcd. for $C_{13}H_{21}N_3NaO_8S_2$, 434.0662 Found: $[MNa]^+$, 434.0666 (−0.9 ppm error).

3.17: *tert*-Butyl (3-(benzylamino)propyl)carbamate



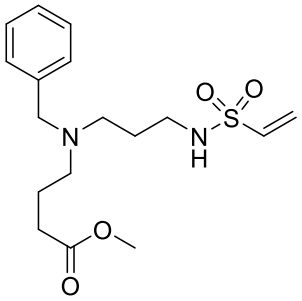
A round-bottomed flask was charged with methanol (20.0 mL), benzaldehyde (1.79 mL, 17.6 mmol) and *tert*-butyl *N*-(3-aminopropyl)carbamate (2.02 mL, 11.6 mmol). The solution was heated to reflux (65 °C) for 72 hours before being cooled to RT. Sodium borohydride (666 mg, 17.6 mmol) was then added portion-wise and the solution stirred for 1.5 hours. The reaction was quenched with ammonium chloride solution (100 mL) and extracted with ethyl acetate (60 mL) and DCM (100 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 100% hexane → 9:1 hexane : ethyl acetate → 8:2 hexane : ethyl acetate) afforded the title compound, which was obtained as a colourless oil (2.76 g, 90%); R_f = 0.50 (20:1 ethyl acetate : triethylamine); ν_{max}/cm^{-1} (thin film): 3335, 2976, 2931, 1691, 1512, 1453, 1365, 1272, 1250, 1167, 735, 698; δ_H (400 MHz, $CDCl_3$) 7.32 – 7.14 (5H, m, 5 x Ar**H**), 5.50 (1H, br s, N**H**CO), 3.71 (2H, s, PhC**H₂**N), 3.16 (2H, q, *J* = 6.5 Hz, C**H₂**NHBoc), 2.64 (2H, t, *J* = 6.5 Hz, C**H₂**NHBn), 1.61 (2H, p, *J* = 6.5 Hz, C**H₂**CH_2NHBoc), 1.41 (9H, s, C(C**H₃**)₃); δ_C (100 MHz, $CDCl_3$) 156.1 (**C**O), 140.2 (Ar**C**), 128.3 (2 x Ar**C**H), 128.1 (2 x Ar**C**H), 126.9 (Ar**C**CH_2N), 78.7 (**C**$(CH_3)_3$), 53.9 (Ph**C**H_2N), 47.2 (**C**H_2NHBn), 39.3 (**C**H_2NHBoc), 29.6 (**C**H_2CH_2NHBoc), 28.4 (C(**C**$H_3)_3$); HRMS (ESI^+): calcd. for $C_{15}H_{25}N_2O_2$, 265.1911. Found: $[MH]^+$, 265.1914 (−1.5 ppm error).

3.18: Methyl 4-(benzyl(3-((*tert*-butoxycarbonyl)amino)propyl)amino)butanoate



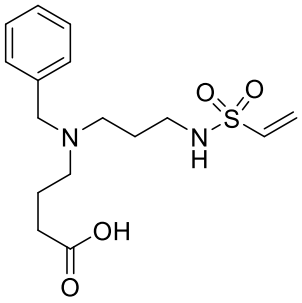
tert-Butyl (3-(benzylamino)propyl)carbamate (2.12 g, 8.01 mmol) was dissolved in acetonitrile (35.0 mL), after which potassium carbonate (1.67 g, 12.1 mmol) and sodium iodide (245 mg, 1.63 mmol) were added. Methyl 4-bromobutyrate (1.11 mL, 8.81 mmol) was then added and the solution heated to reflux (85 °C) for 16 hours. The solution was cooled to RT and diluted with ethyl acetate (80 mL), washed with sodium bicarbonate solution (80 mL) and back-extracted with ethyl acetate (80 mL). The organic layers were combined and dried over magnesium sulfate, filtered and concentrated *in vacuo*. This was purified by column chromatography (SiO_2, 9:1 hexane : ethyl acetate → 7:3 ethyl acetate : hexane) to yield the title compound, which was obtained as a colourless oil (2.55 g, 87%); R_f = 0.27 (1:1 ethyl acetate : hexane); ν_{max}/cm^{-1} (thin film): 3375, 2950, 2807, 1737, 1713, 1512, 1453, 1365, 1249, 1171, 736, 700; δ_H (400 MHz, $CDCl_3$) 7.33 – 7.21 (5H, m, Ar**H**), 5.28 (1H, br s, N**H**), 3.63 (3H, s, OC**H₃**), 3.51 (2H, s, PhC**H₂**N), 3.13 (2H, q, *J* = 6.5 Hz, C**H₂**NHBoc), 2.46 (2H, t, *J* = 6.5 Hz, C**H₂**CH_2CH_2NHBoc), 2.41 (2H, t, *J* = 7.0 Hz, C**H₂**$CH_2CH_2CO_2CH_3$), 2.31 (2H, t, *J* = 7.0 Hz, C**H₂**CO_2CH_3), 1.79 (2H, p, *J* = 7.0 Hz, C**H₂**$CH_2CO_2CH_3$), 1.62 (2H, p, *J* = 6.5 Hz, C**H₂**CH_2NHBoc), 1.43 (9H, s, OC(C**H₃**)₃); δ_C (101 MHz, $CDCl_3$) 174.2 (**C**O_2CH_3), 156.1 (NH**C**O), 139.4 (Ar**C**CH_2N), 129.0 (2 x Ar**C**H), 128.4 (2 x Ar**C**H), 127.1 (Ar**C**H), 78.9 (**C**$(CH_3)_3$), 58.8 (**C**H_2Ph), 53.0 (**C**$H_2CH_2CH_2CO_2CH_3$), 52.2 (**C**$H_2CH_2CH_2$NHBoc), 51.6 (O**C**H_3), 39.7 (**C**H_2NHBoc), 31.8 (**C**$H_2CO_2CH_3$), 28.6 (C(**C**H_3)₃), 26.7 (**C**H_2CH_2NHBoc), 22.4 (**C**$H_2CH_2CO_2CH_3$); HRMS (ESI^+): calcd. for $C_{20}H_{33}N_2O_4$, 365.2435. Found $[MH]^+$ 365.2439 (−1.3 ppm error).

3.19: Methyl 4-(benzyl(3-(vinylsulfonamido)propyl)amino)butanoate



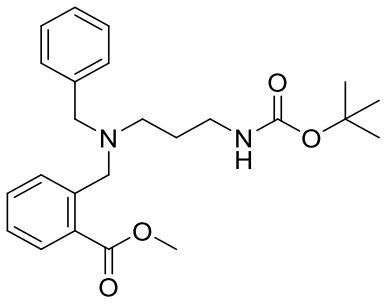
Methyl 4-(benzyl(3-((*tert*-butoxycarbonyl)amino)propyl)amino)butanoate (2.67 g, 7.33 mmol) was dissolved in 1,4-dioxane (45.0 mL) and 4 M HCl in 1,4-dioxane (15.0 mL, 432 mmol) was added. The solution was stirred at RT for 36 hours, after which the solution was concentrated *in vacuo* to yield an amorphous solid. This salt was dissolved in anhydrous DCM (45.0 mL) at RT and the solution was cooled to 0 °C using an ice bath. Triethylamine (10.1 mL, 72.6 mmol) was added dropwise, followed by 2-chloroethane-1-sulfonyl chloride (1.05 mL, 10.8 mmol). The solution was allowed to gradually warm to RT while being stirred for 96 hours. The solution was diluted with DCM (45 mL) and washed with brine (2 x 45 mL). The aqueous layer was then washed with DCM (2 x 45 mL). The organic layers were then combined, dried over magnesium sulfate, filtered and concentrated *in vacuo*. This was purified by column chromatography (SiO_2, 1:1 ethyl acetate : hexane) to yield the title compound, which was obtained as a pale yellow oil (1.44 g, 56%); R_f = 0.24 (1:1 ethyl acetate : hexane); ν_{max}/cm^{-1} (thin film): 3291, 2951, 2815, 1732, 1453, 1436, 1326, 1256, 1146, 1076, 967, 733, 700, 658, 546; δ_H (400 MHz, $CDCl_3$) 7.36 – 7.20 (5H, m, 5 x Ar**H**), 6.37 (1H, dd, *J* = 16.5, 9.5 Hz, C**H**S), 6.15 (1H, d, *J* = 16.5 Hz, **H**C=CHS), 5.87 (1H, d, *J* = 9.5 Hz, **H**C=CHS), 3.64 (3H, s, OC**H₃**), 3.51 (2H, s, PhC**H₂**N), 3.00 (2H, t, *J* = 6.0 Hz, C**H₂**NHS), 2.52 (2H, t, *J* = 6.0 Hz, C**H₂**CH_2CH_2NHS), 2.47 – 2.40 (2H, m, C**H₂**$CH_2CH_2CO_2CH_3$), 2.30 (2H, t, *J* = 7.5 Hz, C**H₂**CO_2CH_3), 1.82 (2H, p, *J* = 7.5 Hz, C**H₂**$CH_2CO_2CH_3$), 1.69 (2H, p, *J* = 6.0 Hz, C**H₂**CH_2NHS); δ_C (100 MHz, $CDCl_3$) 173.9 (**C**O_2CH_3), 138.5 (Ar**C**CH_2N), 135.8 (H_2C=**C**HS), 129.2 (2 x Ar**C**H), 128.5 (2 x Ar**C**H), 127.3 (Ar**C**H), 126.3 (H_2**C**=CHS), 58.7 (Ph**C**H_2N), 52.8 (**C**$H_2CH_2CH_2CO_2CH_3$), 52.4 (**C**$H_2CH_2CH_2$NHS), 51.6 (O**C**H_3), 42.8 (**C**H_2NHS), 31.7 (**C**$H_2CO_2CH_3$), 25.7 (**C**H_2CH_2NHS), 22.0 (**C**$H_2CH_2CO_2CH_3$); HRMS (ESI^+): calcd. for $C_{17}H_{27}N_2O_4S$, 355.1686. Found $[MH]^+$ 355.1685 (0.2 ppm error).

3.20: 4-(Benzyl(3-(vinylsulfonamido)propyl)amino)butanoic acid



Methyl 4-(benzyl(3-(vinylsulfonamido)propyl)amino)butanoate (1.41 g, 4.00 mmol) was dissolved in THF (50.0 mL) and water (50.0 mL). Lithium hydroxide monohydrate (1.01 g, 42.2 mmol) was then added and the solution stirred at RT for 2 hours. The solution was concentrated *in vacuo*. This was purified by column chromatography (SiO_2, 9:1 ethyl acetate : methanol → 7:3 ethyl acetate : methanol) to yield the title compound, which was obtained as a colourless oil (1.08 g, 79%); R_f = 0.20 (1:1 ethyl acetate : methanol); ν_{max}/cm^{-1} (thin film): 2941, 1574, 1322, 1148, 1083, 968, 907, 725, 700, 647, 547; δ_H (400 MHz, $CDCl_3$) 10.04 – 8.72 (1H, br s, O**H**), 7.39 – 7.27 (5H, m, 5 x Ar**H**), 6.48 (1H, dd, *J* = 16.5, 10.0 Hz, C**H**S), 6.11 (1H, d, *J* = 16.5 Hz, **H**C=CHS), 5.84 (1H, d, *J* = 10.0 Hz, **H**C=CHS), 3.84 (2H, s, PhC**H₂**N), 2.97 (2H, t, *J* = 6.5 Hz, C**H₂**NHS), 2.79 (2H, t, *J* = 6.5 Hz, C**H₂**CH_2CH_2NHS), 2.75 (2H, t, *J* = 6.5 Hz, C**H₂**$CH_2CH_2CO_2H$), 2.30 (2H, t, *J* = 6.5 Hz, C**H₂**CO_2H), 1.91 – 1.75 (4H, m, C**H₂**CH_2CO_2H,C**H₂**CH_2NHS); δ_C (100 MHz, $CDCl_3$) 178.4 (**C**O_2H), 136.0 (H_2C=**C**HS), 133.7 (Ar**C**CH_2N), 130.3 (2 x Ar**C**H), 129.0 (2 x Ar**C**H), 128.7 (Ar**C**H), 126.2 (H_2**C**=CHS), 57.7 (Ph**C**H_2N), 53.6 (**C**$H_2CH_2CH_2CO_2H$), 50.9 (**C**$H_2CH_2CH_2$NHS), 41.1 (**C**H_2NHS), 35.1 (**C**H_2CO_2H), 25.1 (**C**H_2CH_2NHS), 21.2 (**C**$H_2CH_2CO_2H$); HRMS (ESI^+): calcd. for $C_{16}H_{24}N_2NaO_4S$, 363.1349. Found $[MNa]^+$ 363.1353 (−1.0 ppm error).

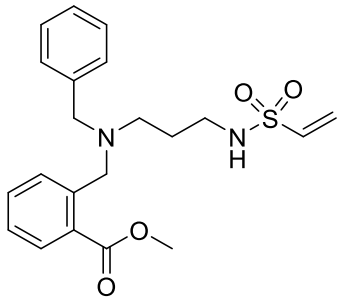
3.21: Methyl 2-((benzyl(3-((*tert*-butoxycarbonyl)amino)propyl)amino)methyl)benzoate



To a stirring suspension of potassium carbonate (9.23 g, 66.8 mmol) in acetonitrile (105 mL), *tert*-butyl (3-(benzylamino)propyl)carbamate (5.86 g, 22.2 mmol) was added followed by methyl 2-(bromomethyl) benzoate (3.65 g, 24.4 mmol). The reaction mixture was refluxed

(85 °C) for 6 hours under argon before filtering through Celite and washing with DCM. The solution was then concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 9:1 hexane : ethyl acetate → 100% ethyl acetate) afforded the title compound, which was obtained as a colourless oil (6.93 g, 76%); R_f = 0.56 (1:1 ethyl acetate : hexane); ν_{max}/cm^{-1} (thin film): 3385, 2950, 2805, 1713, 1507, 1452, 1391, 1365, 1267, 1248, 1168, 1130, 1082, 910, 731, 699; δ_H (400 MHz, $CDCl_3$) 7.77 (1H, dd, *J* = 7.5, 1.5 Hz, Ar**H**), 7.64 (1H, d, *J* = 7.5 Hz, Ar**H**), 7.46 (1H, td, *J* = 7.5, 1.5 Hz, Ar**H**), 7.37 – 7.19 (6H, m, 6 x Ar**H**), 4.86 (1H, br t, *J* = 6.0 Hz, N**H**), 3.90 (2H, s, COCCC**H₂**N), 3.87 (3H, s, OC**H₃**), 3.51 (2H, s, PhC**H₂**N), 3.05 (2H, q, *J* = 6.5 Hz, C**H₂**NHBoc), 2.43 (2H, t, *J* = 6.5 Hz, C**H₂**CH_2CH_2NHBoc), 1.63 (2H, p, *J* = 6.5 Hz, C**H₂**CH_2NHBoc), 1.42 (9H, s, OC(C**H₃**)₃); δ_C (101 MHz, $CDCl_3$) 168.6 (**C**O_2CH_3), 156.0 (NH**C**O), 140.9 (CO**C**CCH_2N), 139.2 (Ar**C**CH_2N), 131.6 (Ar**C**H), 131.0 (COC**C**CH_2N), 130.1 (Ar**C**H), 130.0 (Ar**C**H), 129.0 (2 x Ar**C**H), 128.3 (2 x Ar**C**H), 127.0 (Ar**C**H), 126.8 (Ar**C**H), 78.7 (**C**$(CH_3)_3$), 58.7 (**C**H_2Ph), 56.5 (COCC**C**H_2N), 52.0 (O**C**H_3), 51.3 (**C**$H_2CH_2CH_2$NHBoc), 38.9 (**C**H_2NHBoc), 28.5 (C(**C**$H_3)_3$), 26.6 (**C**H_2CH_2NHBoc); HRMS (ESI^+): calcd. for $C_{24}H_{33}N_2O_4$, 413.2435. Found $[MH]^+$ 413.2429 (1.4 ppm error).

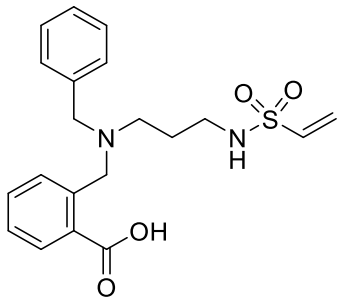
3.22: Methyl 2-((benzyl(3-(vinylsulfonamido)propyl)amino)methyl)benzoate



Methyl 2-((benzyl(3-((*tert*-butoxycarbonyl)amino)propyl)amino)methyl)benzoate (1.09 g, 2.64 mmol) was dissolved in 1,4-dioxane (30.0 mL) and 4 M HCl in 1,4-dioxane (5.40 mL, 156 mmol) was added. The solution was stirred at RT for 36 hours, after which the solution was concentrated *in vacuo* to yield an amorphous solid. This salt was dissolved in anhydrous DCM (40.0 mL) at RT and the solution was cooled to 0 °C using an ice bath. Triethylamine (3.70 mL, 26.6 mmol) was added dropwise, followed by 2-chloroethane-1-sulfonyl chloride (0.52 mL, 5.33 mmol). The solution was allowed to gradually warm to RT while being stirred for 96 hours. After that, the solution was diluted with DCM (30 mL) and washed with brine (2 x 30 mL). The aqueous layer was then washed with DCM (2 x 30 mL). The organic layers were then combined, dried over magnesium sulfate, filtered and concentrated *in vacuo*. This was purified by column chromatography (SiO_2, 7:3 hexane : ethyl acetate) to yield the title compound, which was obtained as a yellow oil (811 mg, 76%). R_f = 0.37 (1:1 ethyl acetate :

hexane); ν_{max}/cm^{-1} (thin film): 3287, 2951, 2819, 1718, 1451, 1433, 1328, 1292, 1269, 1146, 1082, 966, 737, 701, 661, 547; δ_H (400 MHz, $CDCl_3$) 7.80 (1H, dd, *J* = 8.0, 1.5 Hz, C**H**CCO), 7.56 (1H, dd, *J* = 8.0, 1.5 Hz, Ar**H**), 7.50 (1H, td, *J* = 8.0, 1.5 Hz, Ar**H**), 7.36 – 7.23 (6H, m, 6 x Ar**H**), 6.28 (1H, dd, *J* = 16.5, 10.0 Hz, C**H**S), 6.11 (1H, d, *J* = 16.5 Hz, **H**C=CHS), 5.82 (1H, d, *J* = 10.0 Hz, **H**C=CHS), 5.33 (1H, br s, N**H**), 3.91 (2H, s, COCCC**H₂**N), 3.87 (3H, s, OC**H₃**), 3.53 (2H, s, PhC**H₂**N), 2.92 (2H, t, *J* = 6.0 Hz, C**H₂**NHS), 2.50 (2H, t, *J* = 6.0 Hz, C**H₂**CH_2CH_2NHS), 1.68 (2H, p, *J* = 6.0 Hz, C**H₂**CH_2NHS); δ_C (100 MHz, $CDCl_3$) 168.6 (**C**O_2CH_3), 140.3 (**C**CO), 138.6 (**C**CH_2N), 136.0 (H_2C=**C**HS), 131.8 (Ar**C**H), 131.0 (**C**CCO), 130.6 (Ar**C**H), 130.3 (Ar**C**H), 129.4 (2 x Ar**C**H), 128.5 (2 x Ar**C**H), 127.3 (Ar**C**H), 127.2 (Ar**C**H), 126.2 (H_2**C**=CHS), 58.9 (Ph**C**H_2N), 56.7 (**C**$H_2CCCO_2CH_3$), 52.2 (O**C**H_3), 51.5 (**C**$H_2CH_2CH_2$NHS), 42.1 (**C**H_2NHS), 26.1 (**C**H_2CH_2NHS); HRMS (ESI^+): calcd. for $C_{21}H_{27}N_2O_4S$, 403.1686. Found $[MH]^+$ 403.1678 (1.9 ppm error).

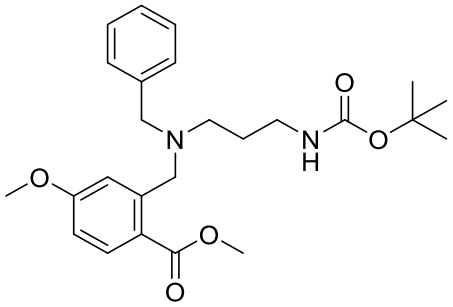
3.23: 2-((Benzyl(3-(vinylsulfonamido)propyl)amino)methyl)benzoic acid



Methyl 2-((benzyl(3-(vinylsulfonamido)propyl)amino)methyl)benzoate (491 mg, 1.22 mmol) was dissolved in THF (20.0 mL) and water (20.0 mL), then lithium hydroxide monohydrate (295 mg, 12.3 mmol) was added and the solution stirred at RT for 20 hours. The solution was concentrated *in vacuo* to give a residue. This was purified by column chromatography (SiO_2, 9:1 ethyl acetate : methanol → 7:3 ethyl acetate : methanol) to yield the title compound, which was obtained as a white solid (348 mg, 73%). R_f = 0.55 (1:1 ethyl acetate : methanol); MP = 209 – 213 °C; ν_{max}/cm^{-1} (thin film): 3064, 2871, 1610, 1593, 1566, 1456, 1383, 1324, 1148, 1088, 967, 911, 813, 745, 701, 663; δ_H (400 MHz, $CDCl_3$) 8.09 (1H, dd, *J* = 7.0, 2.0 Hz, Ar**H**CCO), 7.39 (2H, pd, *J* = 7.0, 2.0 Hz, 2 x Ar**H**), 7.34 – 7.26 (5H, m, 5 x Ar**H**), 7.21 (1H, dd, *J* = 7.0, 2.0 Hz, Ar**H**), 6.92 – 6.66 (1H, br s, O**H**), 6.47 (1H, dd, *J* = 16.5, 10.0 Hz, C**H**S), 6.11 (1H, d, *J* = 16.5 Hz, **H**C=CHS), 5.83 (1H, d, *J* = 10.0 Hz, **H**C=CHS), 4.05 (2H, br s, PhC**H₂**N), 3.87 (2H, br s, COCCC**H₂**N), 2.94 – 2.81 (2H, m, C**H₂**NHS [overlapping]), 2.94 – 2.81 (2H, m, C**H₂**CH_2CH_2NHS [overlapping]), 1.90 (2H, p, *J* = 6.5 Hz, C**H₂**CH_2NHS); δ_C (100 MHz, $CDCl_3$) 171.7 (**C**O_2H), 137.5 (Ar**C**CH_2N), 136.0 (H_2C=**C**HS), 133.1 (Ar**C**H), 131.8 (Ar**C**H), 131.5 (Ar**C**), 131.1 (Ar**C**H), 130.9 (Ar**C**), 130.2 (2 x Ar**C**H), 129.7 (Ar**C**H), 129.3 (2 x Ar**C**H), 129.2 (Ar**C**H), 126.2 (H_2**C**=CHS), 58.5 (Ph**C**H_2N), 55.7 (**C**H_2CCCO_2H), 48.6 (**C**$H_2CH_2CH_2$NHS), 40.4 (**C**H_2NHS),

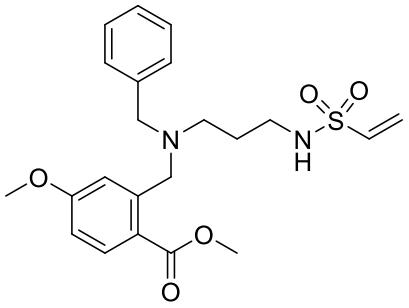
24.6 (**C**H_2CH_2NHS); HRMS (ESI^+): calcd. for $C_{20}H_{24}N_2NaO_4S$, 411.1349. Found $[MNa]^+$ 411.1346 (0.6 ppm error).

3.24: Methyl 2-((benzyl(3-((*tert*-butoxycarbonyl)amino)propyl)amino)methyl)-4-methoxybenzoate



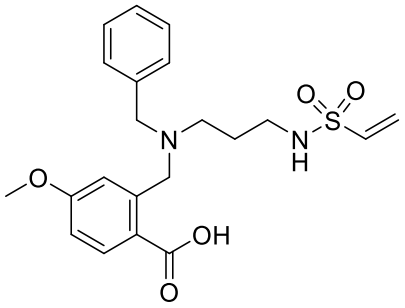
To a stirring solution of potassium carbonate (5.06 g, 36.6 mmol) in acetonitrile (100 mL), *tert*-butyl (3-(benzylamino)propyl)carbamate (3.19 g, 12.1 mmol) was added, followed by methyl 2-(bromomethyl)-4-methoxybenzoate (1.95 g, 7.53 mmol). The reaction mixture was refluxed (85 °C) for 18 hours under argon before filtering through Celite and washing with DCM. The solution was then dried over magnesium sulfate, filtered and concentrated *in vacuo*. This was purified by flash column chromatography (SiO_2, 7:3 hexane : ethyl acetate) affording the title compound, which was obtained as a colourless oil (3.26 g, 61%); R_f = 0.56 (1:1 ethyl acetate : hexane); ν_{max}/cm^{-1} (thin film): 3384, 2949, 1710, 1603, 1496, 1454, 1434, 1365, 1248, 1166, 1123, 1036, 777, 736, 699; δ_H (400 MHz, $CDCl_3$) 7.84 (1H, d, *J* = 8.5 Hz, CO_2CC**H**), 7.37 – 7.20 (6H, m, 6 x Ar**H**), 6.77 (1H, dd, *J* = 8.5, 2.5 Hz, CO_2CCHC**H**), 4.84 (1H, t, *J* = 6.5 Hz, N**H**), 3.95 (2H, s, CO_2CCC**H₂**N), 3.85 (3H, s, ArOC**H₃** [overlapping]), 3.84 (3H, s, CO_2C**H₃** [overlapping]), 3.56 (2H, s, PhC**H₂**N), 3.10 (2H, q, *J* = 6.5 Hz, C**H₂**NHBoc), 2.48 (2H, t, *J* = 6.5 Hz, C**H₂**CH_2CH_2NHBoc), 1.66 (2H, p, *J* = 6.5 Hz, C**H₂**CH_2NHBoc), 1.40 (9H, s, C(C**H₃**)₃); δ_C (101 MHz, $CDCl_3$) 167.9 (**C**O_2CH_3), 162.6 (**C**OCH_3), 156.0 (NH**C**O), 144.7 (Ar**C**), 139.4 (Ar**C**CH_2N), 132.7 (CO_2C**C**H), 129.0 (2 x Ar**C**H), 128.4 (2 x Ar**C**H), 127.1 (Ar**C**H), 122.3 (Ar**C**), 114.8 (NCH_2C**C**HCO), 111.9 (CO_2CCH**C**H), 78.9 (**C**$(CH_3)_3$), 59.1 (Ph**C**H_2N), 56.5 (CO_2CC**C**H_2N), 55.4 (ArO**C**H_3), 51.8 (CO_2**C**H_3 [overlapping]), 51.8 (**C**$H_2CH_2CH_2$NHBoc [overlapping]), 39.1 (**C**H_2NHBoc), 28.5 (C(**C**H_3)₃), 27.0 (**C**H_2CH_2NHBoc); HRMS (ESI^+): calcd. for $C_{25}H_{34}N_2NaO_5$, 465.2360. Found $[MNa]^+$ 465.2367 (−1.5 ppm error).

3.25: Methyl 2-((benzyl(3-(vinylsulfonamido)propyl)amino)methyl)-4-methoxybenzoate



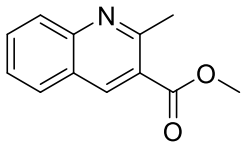
Methyl 2-((benzyl(3-((*tert*-butoxycarbonyl)amino)propyl)amino)methyl)-4-methoxybenzoate (3.21 g, 7.25 mmol) was dissolved in dioxane (75.0 mL) and 4 M HCl in dioxane (18.4 mL, 529 mmol) was added. The solution was stirred at RT for 20 hours, after which the solution was concentrated *in vacuo* to yield an amorphous solid. This salt was dissolved in anhydrous DCM (75.0 mL) at RT and the solution was cooled to 0 °C using an ice bath. Triethylamine (12.5 mL, 89.7 mmol) was added dropwise, followed by 2-chloroethane-1-sulfonyl chloride (1.30 mL, 13.3 mmol). The solution was allowed to gradually warm to RT while being stirred for 96 hours. Then, the solution was diluted with DCM (80 mL) and washed with brine (2 x 80 mL). The aqueous layer was then washed with DCM (2 x 80 mL). The organic layers were then combined, dried over magnesium sulfate, filtered and concentrated *in vacuo*. This was purified by column chromatography (SiO_2, 9:1 hexane : ethyl acetate → 8:2 hexane : ethyl acetate → 7:3 hexane : ethyl acetate → 1:1 ethyl acetate : hexane) affording the title compound, which was obtained as an orange oil (1.32 g, 42%). R_f = 0.38 (1:1 ethyl acetate : hexane); ν_{max}/cm^{-1} (thin film): 3286, 2949, 2838, 1707, 1603, 1572, 1433, 1328, 1254, 1145, 1086, 1035, 968, 778, 741, 701, 660; δ_H (400 MHz, $CDCl_3$) 7.87 (1H, d, *J* = 8.5 Hz, $CO_2CC\mathbf{H}$), 7.38 – 7.23 (5H, m, 5 x Ar**H**), 7.14 (1H, d, *J* = 2.5 Hz, $CH_2CC\mathbf{H}CO$), 6.81 (1H, dd, *J* = 8.5, 2.5 Hz, $CO_2CCHC\mathbf{H}$), 6.25 (1H, dd, *J* = 16.5, 10.0 Hz, C**H**S), 6.10 (1H, d, *J* = 16.5 Hz, **H**C=CHS), 5.81 (1H, d, *J* = 10.0 Hz, **H**C=CHS), 5.43 (1H, br s, N**H**), 3.96 (2H, s, $CO_2CCC\mathbf{H_2}N$), 3.87 (3H, s, $ArOC\mathbf{H_3}$), 3.85 (3H, s, $CO_2C\mathbf{H_3}$), 3.56 (2H, s, $PhC\mathbf{H_2}N$), 2.95 (2H, t, *J* = 6.0 Hz, $C\mathbf{H_2}NHS$), 2.56 (2H, t, *J* = 6.0 Hz, $C\mathbf{H_2}CH_2CH_2NHS$), 1.71 (2H, p, *J* = 6.0 Hz, $C\mathbf{H_2}CH_2NHS$); δ_C (100 MHz, $CDCl_3$) 167.8 ($\mathbf{C}O_2CH_3$), 162.6 ($\mathbf{C}OCH_3$), 143.8 (Ar**C**), 138.7 ($ArCCH_2N$), 135.9 ($H_2C=\mathbf{C}HS$), 133.0 ($CO_2C\mathbf{C}H$), 129.4 (2 x Ar**C**H), 128.6 (2 x Ar**C**H), 127.4 (Ar**C**H), 126.3 ($H_2\mathbf{C}$=CHS), 122.4 (Ar**C**), 115.3 ($CH_2C\mathbf{C}HCO$), 112.5 ($CO_2CCH\mathbf{C}H$), 59.2 ($Ph\mathbf{C}H_2N$), 56.5 ($CO_2CC\mathbf{C}H_2N$), 55.6 ($ArO\mathbf{C}H_3$), 52.1 ($\mathbf{C}H_2CH_2CH_2NHS$), 52.0 ($CO_2\mathbf{C}H_3$), 42.4 ($\mathbf{C}H_2NHS$), 26.1 ($\mathbf{C}H_2CH_2NHS$); HRMS (ESI^+): calcd. for $C_{22}H_{29}N_2O_5S$, 433.1792 Found $[MH]^+$ 433.1789 (0.6 ppm error).

3.26: 2-((Benzyl(3-(vinylsulfonamido)propyl)amino)methyl)-4-methoxybenzoic acid



Methyl 2-((benzyl(3-(vinylsulfonamido)propyl)amino)methyl)-4-methoxybenzoate (1.32 g, 3.05 mmol) was dissolved in THF (50.0 mL) and water (50.0 mL), then lithium hydroxide monohydrate (737 mg, 30.8 mmol) was added and the solution stirred at RT for 120 hours. The solution was concentrated *in vacuo*. This was purified by column chromatography (SiO_2, 9:1 ethyl acetate : methanol → 7:3 ethyl acetate : methanol → 1:1 ethyl acetate : methanol) affording the title compound, which was obtained as a yellow oil (737 mg, 57%); R_f = 0.50 (1:1 ethyl acetate : methanol); ν_{max}/cm^{-1} (thin film): 3063, 2940, 1599, 1456, 1380, 1319, 1283, 1250, 1145, 1086, 1031, 968, 793, 743, 701, 654, 618; δ_H (400 MHz, MeOD-*d*$_4$) 7.98 (1H, d, *J* = 8.5 Hz, C**H**CCO_2H), 7.45 – 7.35 (5H, m, 5 x Ar**H**), 7.03 – 6.94 (2H, m, C**H**$CHCCO_2H$,CH_2CC**H**CO), 6.50 (1H, dd, *J* = 16.5, 10.0 Hz, C**H**S), 6.05 (1H, d, *J* = 16.5 Hz, **H**C=CHS), 5.90 (1H, d, *J* = 10.0 Hz, **H**C=CHS), 4.29 (2H, s, COCCC**H$_2$**N), 4.13 (2H, s, PhC**H$_2$**N), 3.83 (3H, s, ArOC**H$_3$**), 3.03 – 2.94 (2H, m, C**H$_2$**CH_2CH_2NHS), 2.81 (2H, t, *J* = 6.5 Hz, C**H$_2$**NHS), 1.82 (2H, p, *J* = 6.5 Hz, C**H$_2$**CH_2NHS); δ_C (100 MHz, MeOD-*d*$_4$) 174.6 (**C**O_2H), 162.9 (**C**OCH_3), 137.3 (H_2C=**C**HS), 135.5 (**C**$HCCO_2H$), 133.2 (Ar**C**), 132.2 (Ar**C**), 131.5 (Ar**C**), 131.4 (2 x Ar**C**H), 130.6 (Ar**C**H), 130.4 (2 x Ar**C**H), 126.9 (H_2**C**=CHS), 119.3 (CH_2C**C**HCO), 115.2 (**C**$HCHCCO_2H$), 59.3 (CO_2CC**C**H_2N), 57.1 (Ph**C**H_2N), 56.1 (ArO**C**H_3), 49.7 (**C**$H_2CH_2CH_2NHS$), 41.0 (**C**H_2NHS), 25.6 (**C**H_2CH_2NHS); HRMS (ESI^+): calcd. for $C_{21}H_{27}N_2O_5S$, 419.1635. Found $[MH]^+$ 419.1644 (−2.1 ppm error).

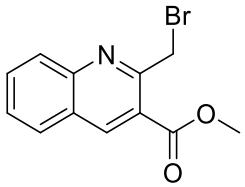
3.31: Methyl 2-methylquinoline-3-carboxylate



2-Amino benzyl alcohol (1.00 g, 8.12 mmol) was added to a solution of MnO_2 (2.12 g, 24.4 mmol) in ethanol (20 mL). Then, methyl acetoacetate (0.89 mL, 8.25 mmol) was added and the solution was stirred at reflux (80 °C) for 2.5 hours. Upon completion, the reaction

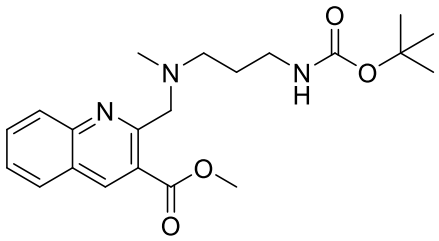
mixture was cooled to RT and filtered through Celite. The filtrate was concentrated *in vacuo* and the title compound was purified by column chromatography (SiO_2, 9.5:0.5 hexane : ethyl acetate → 9:1 hexane : ethyl acetate) to yield the title compound, which was obtained as a yellow solid (806 mg, 49%); R_f = 0.52 (1:1 ethyl acetate : hexane); ν_{max}/cm^{-1} (thin film): 3239, 2951, 1717, 1432, 1420, 1282, 1252, 1201, 1132, 1064, 785, 745; δ_H (400 MHz, $CDCl_3$) 8.72 (1H, s, COCC**H**), 8.02 (1H, d, *J* = 8.0 Hz, Ar**H**), 7.83 (1H, d, *J* = 8.0 Hz, Ar**H**), 7.76 (1H, t, *J* = 8.0 Hz, Ar**H**), 7.51 (1H, t, *J* = 7.5 Hz, Ar**H**), 3.96 (3H, s, OC**H₃**), 2.98 (3H, s, NCC**H₃**); δ_C (101 MHz, $CDCl_3$) 167.0 (**C**O), 158.6 (N**C**CH_3), 148.8 (COCCH**C**), 140.1 (COC**C**H), 131.8 (Ar**C**H), 128.64 (Ar**C**H), 128.58 (Ar**C**H), 126.6 (Ar**C**H), 125.8 (Ar**C**), 123.6 (Ar**C**), 52.5 (O**C**H_3), 25.8 (NC**C**H_3); HRMS (ESI^+): calcd. for $C_{12}H_{12}NO_2$, 202.0863. Found $[MH]^+$ 202.0861 (0.7 ppm error). Characterisation data matched those reported in the literature.[126]

3.32: Methyl 2-(bromomethyl) quinoline-3-carboxylate



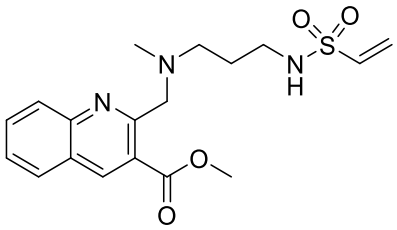
Benzene (20.0 mL) was degassed for 20 minutes using an argon stream passing through the solution, before adding it to a mixture of methyl 2-methylquinoline-3-carboxylate (437 mg, 2.17 mmol), AIBN (18.1 mg, 0.110 mmol) and NBS (503 mg, 2.83 mmol) and then was refluxed (80 °C) for 16 hours. After cooling to RT, the reaction mixture was filtered through Celite, washed with DCM and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 99:1 toluene : ethyl acetate → 98:2 toluene : ethyl acetate) afforded the title compound, which was obtained as a yellow solid (310 mg, 51%); R_f = 0.23 (98:2 toluene : ethyl acetate); ν_{max}/cm^{-1} (thin film): 2953, 1719, 1441, 1278, 1252, 1208, 1134, 1067, 911, 804, 756, 730; δ_H (400 MHz, $CDCl_3$) 8.75 (1H, s, COCC**H**), 8.04 (1H, d, *J* = 8.5 Hz, NCC**H**), 7.82 (1H, d, *J* = 8.5 Hz, COCCHCC**H**), 7.77 (1H, td, *J* = 7.0, 1.5 Hz, NCCHC**H**), 7.55 (1H, td, *J* = 7.0, 1.5 Hz, COCCHCCHC**H**), 5.16 (2H, s, NCC**H₂**Br), 3.98 (3H, s, OC**H₃**); δ_C (101 MHz, $CDCl_3$) 165.9 (**C**O), 156.1 (Ar**C**), 148.4 (Ar**C**), 141.1 (COC**C**H), 132.2 (NCCH**C**H), 129.2 (NC**C**H), 128.5 (COCCHC**C**H), 127.9 (COCCHCCH**C**H), 126.5 (Ar**C**), 122.5 (Ar**C**), 52.8 (O**C**H_3), 33.7 (NC**C**H_2Br); HRMS (ESI^+): calcd. for $C_{12}H_{11}{}^{79}BrNO_2$, 279.9968. Found $[MH]^+$ 279.9961 (2.4 ppm error). Characterisation data matched those reported in the literature.[126]

3.34: Methyl 2-(((3-((*tert*-butoxycarbonyl)amino)propyl)(methyl)amino)methyl)quinoline-3-carboxylate



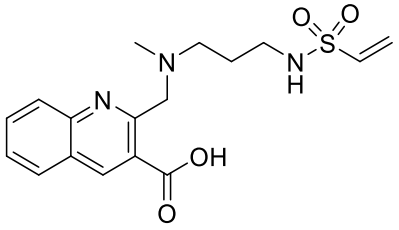
To a stirring suspension of potassium carbonate (284 mg, 2.05 mmol) in acetonitrile (10.0 mL), *tert*-butyl (3-(methylamino)propyl)carbamate (0.20 mL, 1.07 mmol) was added followed by methyl 2-(bromomethyl) quinoline-3-carboxylate (310 mg, 1.11 mmol). The reaction mixture was refluxed (85 °C) for 5 hours under argon before filtering through Celite and washing with DCM. The solution was then concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 100% ethyl acetate) afforded the title compound, which was obtained as an orange oil (211 mg, 54%); R_f = 0.30 (9:1 ethyl acetate : methanol); ν_{max}/cm^{-1} (thin film): 3386, 2951, 1698, 1508, 1439, 1365, 1274, 1244, 1218, 1168, 1065, 919, 756, 729; δ_H (400 MHz, $CDCl_3$) 8.48 (1H, s, COCC**H**), 8.08 (1H, d, *J* = 8.5 Hz, NCC**H**), 7.82 (1H, d, *J* = 7.5 Hz, COCCHCC**H**), 7.74 (1H, td, *J* = 7.0, 1.5 Hz, NCCHC**H**), 7.53 (1H, t, *J* = 7.5 Hz, COCCHCCHC**H**), 5.10 (1H, br t, *J* = 6.0 Hz, N**H**), 4.05 (2H, s, $CH_3NC\mathbf{H_2}CN$), 3.93 (3H, s, $OC\mathbf{H_3}$), 3.04 (2H, q, *J* = 6.5 Hz, $C\mathbf{H_2}NHCO$), 2.39 (2H, t, *J* = 6.5 Hz, $C\mathbf{H_2}CH_2CH_2NHCO$), 2.18 (3H, s, $C\mathbf{H_3}N$), 1.58 (2H, p, *J* = 6.5 Hz, $CH_2C\mathbf{H_2}CH_2NHCO$), 1.32 (9H, s, $C(C\mathbf{H_3})_3$); δ_C (101 MHz, $CDCl_3$) 168.2 (**C**O), 158.8 (Ar**C**), 156.1 (NH**C**O), 147.8 (Ar**C**), 138.8 (COC**C**H), 131.3 (NCCH**C**H), 129.2 (NC**C**H), 128.3 (COCCHC**C**H), 127.1 (COCCHCCH**C**H), 126.3 (Ar**C**), 125.6 (Ar**C**), 78.6 ($\mathbf{C}(CH_3)_3$), 64.0 ($CH_3N\mathbf{C}H_2CN$), 54.8 ($\mathbf{C}H_2CH_2CH_2NHCO$), 52.6 ($O\mathbf{C}H_3$), 41.7 ($\mathbf{C}H_3N$), 38.6 ($\mathbf{C}H_2NHCO$), 28.5 ($C(\mathbf{C}H_3)_3$), 26.8 ($CH_2\mathbf{C}H_2CH_2NHCO$); HRMS ($ESI^+$): calcd. for $C_{21}H_{30}N_3O_4$, 388.2231. Found $[MH]^+$ 388.2236 (−1.2 ppm error).

3.35: Methyl 2-((methyl(3-(vinylsulfonamido)propyl)amino)methyl)quinoline-3-carboxylate



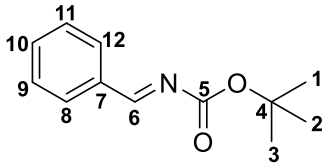
Methyl 2-(((3-((*tert*-butoxycarbonyl)amino)propyl)(methyl)amino)methyl)quinoline-3-carboxylate (164 mg, 0.422 mmol) was dissolved in 1,4-dioxane (15.0 mL) and 4 M HCl in 1,4-dioxane (0.88 mL, 25.4 mmol) was added. The solution was stirred at RT for 48 hours, after which another portion of 4 M HCl in 1,4-dioxane (0.88 mL, 25.4 mmol) was added and stirred for a further 144 hours. Then, the solution was concentrated *in vacuo* to yield an amorphous solid. This salt was dissolved in anhydrous DCM (20 mL) at RT and the solution was cooled to 0 °C using an ice bath. Triethylamine (0.60 mL, 4.22 mmol) was added dropwise, followed by 2-chloroethane-1-sulfonyl chloride (63.0 µL, 0.646 mmol). The solution was allowed to gradually warm to RT while being stirred for 48 hours. The solution was diluted with DCM (15 mL) and washed with brine (2 x 15 mL). The aqueous layer was then washed with DCM (2 x 15 mL). The organic layers were then combined, dried over magnesium sulfate, filtered and concentrated *in vacuo*. This was purified by column chromatography (SiO_2, 100% ethyl acetate) to yield the title compound, which was obtained as a yellow oil (86.8 mg, 54%); R_f = 0.16 (9:1 ethyl acetate : methanol); ν_{max}/cm^{-1} (thin film): 2951, 1721, 1620, 1439, 1326, 1279, 1246, 1218, 1146, 1067, 967, 800, 757, 659; δ_H (400 MHz, $CDCl_3$) 8.65 (1H, s, COCC**H**), 8.19 (1H, d, *J* = 8.5 Hz, NCC**H**), 7.86 (1H, d, *J* = 8.0 Hz, COCCHCC**H**), 7.79 (1H, td, *J* = 7.0, 1.5 Hz, NCCHC**H**), 7.57 (1H, td, *J* = 7.0, 1.5 Hz, COCCHCCHC**H**), 6.45 (1H, dd, *J* = 16.5, 10.0 Hz, H_2C=C**H**S), 6.11 (1H, d, *J* = 16.5 Hz, **H₂**C=CHS), 5.77 (1H, dd, *J* = 10.0 Hz, **H₂**C=CHS), 4.13 (2H, s, CH_3NCH_2CN), 3.98 (3H, s, OC**H₃**), 3.04 (2H, t, *J* = 6.0 Hz, C**H₂**NHS), 2.57 (2H, t, *J* = 6.0 Hz, C**H₂**CH_2CH_2NHS), 2.27 (3H, s, C**H₃**N), 1.68 (2H, p, *J* = 6.0 Hz, CH_2C**H₂**CH_2NHS); δ_C (101 MHz, $CDCl_3$) 167.5 (**C**O), 158.0 (Ar**C**), 148.2 (Ar**C**), 140.0 (COC**C**H), 136.6 (H_2C=**C**HS), 131.8 (NCCH**C**H), 129.3 (NC**C**H), 128.4 (COCCHC**C**H), 127.4 (COCCHCCH**C**H), 126.2 (Ar**C**), 125.5 (H_2**C**=CHS), 124.3 (Ar**C**), 63.6 (CH_3N**C**H_2CN), 56.3 (**C**$H_2CH_2CH_2$NHS), 52.8 (O**C**H_3), 42.8 (**C**H_2NHS), 42.1 (**C**H_3N), 26.1 (CH_2**C**H_2CH_2NHS); HRMS (ESI^+): calcd. for $C_{18}H_{24}N_3O_4S$, 378.1482. Found $[MH]^+$ 378.1485 (−0.8 ppm error).

3.36: 2-((Methyl(3-(vinylsulfonamido)propyl)amino)methyl)quinoline-3-carboxylic acid



Methyl 2-((methyl(3-(vinylsulfonamido)propyl)amino)methyl)quinoline-3-carboxylate (50.4 mg, 0.134 mmol) was dissolved in THF (3.0 mL) and water (3.0 mL), then lithium hydroxide monohydrate (32.4 mg, 1.35 mmol) was added while stirring at RT for 36 hours. The solution was concentrated *in vacuo*. This was purified by column chromatography (SiO_2, 7:3 ethyl acetate : methanol) to yield the title compound, which was obtained as a waxy, white solid (38.7 mg, 80%); R_f = 0.14 (1:1 ethyl acetate : methanol); ν_{max}/cm^{-1} (thin film): 3300, 2925, 2857, 1717, 1609, 1574, 1458, 1382, 1319, 1147, 968, 805, 760, 733; δ_H (400 MHz, $CDCl_3$) 8.83 (1H, s, COCC**H**), 7.97 (1H, d, *J* = 8.5 Hz, NCC**H**), 7.82 (1H, d, *J* = 8.0 Hz, COCCHCC**H**), 7.71 (1H, td, *J* = 7.5, 1.5 Hz, NCCHC**H**), 7.52 (1H, t, *J* = 7.5 Hz, COCCHCCHC**H**), 6.58 (1H, dd, *J* = 16.5, 10.0 Hz, H_2C=C**H**S), 6.14 (1H, d, *J* = 16.5 Hz, **H₂**C=CHS), 5.85 (1H, dd, *J* = 10.0 Hz, **H₂**C=CHS), 4.54 (2H, br s, CH_3NC**H₂**CN), 3.33 (2H, t, *J* = 7.5 Hz, C**H₂**CH_2CH_2NHS), 3.14 (2H, t, *J* = 6.0 Hz, C**H₂**NHS), 2.69 (3H, s, C**H₃**N), 2.12 (2H, p, *J* = 7.0 Hz, CH_2C**H₂**CH_2NHS); δ_C (101 MHz, $CDCl_3$) 170.8 (**C**O), 150.2 (Ar**C**), 147.6 (Ar**C**), 141.5 (COC**C**H), 136.1 (H_2C=**C**HS), 131.3 (NCCH**C**H), 131.0 (Ar**C**), 128.9 (NC**C**H), 128.7 (COCCHC**C**H), 127.9 (COCCHCCH**C**H), 127.7 (Ar**C**), 126.4 (H_2**C**=CHS), 63.5 (CH_3N**C**H_2CN), 54.0 (**C**$H_2CH_2CH_2$NHS), 40.1 (**C**H_2NHS), 39.4 (**C**H_3N), 25.1 (CH_2**C**H_2CH_2NHS); HRMS (ESI^+): calcd. for $C_{17}H_{21}N_3NaO_4S$, 386.1145. Found $[MNa]^+$ 386.1142 (0.7 ppm error).

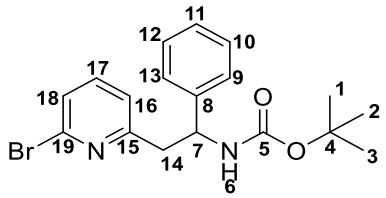
3.42: *tert*-Butyl [(*E*)-phenylmethylidene]carbamate



To a suspension of benzaldehyde (1.85 mL, 18.2 mmol), *tert*-butyl carbamate (1.07 g, 9.13 mmol), sodium benzenesulfinate (3.77 g, 23.0 mmol), methanol (10.0 mL) and water (20.0 mL), was added formic acid (0.70 mL, 18.6 mmol). This solution was stirred at RT for 72 hours. The mixture was then filtered through a glass funnel leaving the solid residue, which was washed with water (15 mL) and hexane. The solid dried on the filter for 5 minutes. This

gave the residue: *tert*-butyl (phenyl(phenylsulfonyl)methyl)carbamate. Following this, the residue was placed in a round-bottomed flask and dissolved in THF (70.0 mL) before addition of K_2CO_3 (6.30 g, 45.6 mmol). The solution was heated to reflux (70 °C) and stirred for 20 hours. The solution then cooled to RT before being filtered through a Celite pad. The residual solid was then washed with THF. The filtrate was concentrated *in vacuo* to give the title compound, which was obtained as a colourless oil (1.55 g, 82%); R_f = 0.53 (1:1 ethyl acetate : hexane); ν_{max}/cm^{-1} (thin film): 2980, 1713, 1628, 1581, 1453, 1368, 1268, 1252, 1214, 1146, 982, 885, 792, 756, 689, 593, 477; δ_H (400 MHz, $CDCl_3$) 8.87 (1H, s, H-6), 7.91 (2H, d, *J* = 7.5 Hz, H-8,12), 7.55 (1H, t, *J* = 7.5 Hz, H-10), 7.46 (2H, t, *J* = 7.5 Hz, H-9,11), 1.58 (9H, s, H-1,2,3); δ_C (100 MHz, $CDCl_3$) 169.8 (C-6), 162.8 (C-5), 134.2 (C-7), 133.6 (C-10), 130.3 (C-8,12), 129.0 (C-9,11), 82.4 (C-4), 28.0 (C-1,2,3); HRMS ($APCI^+$): calcd. for $C_{12}H_{16}NO_2$ Found: $[MH]^+$, 206.1176. Found: 206.1188 (5.8 ppm error).

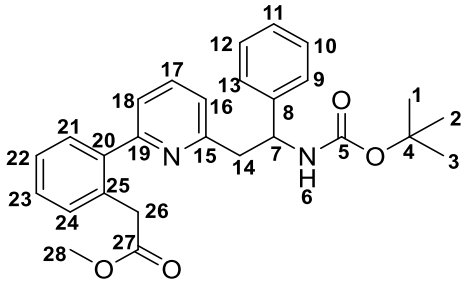
3.44: *tert*-Butyl [2-(6-bromopyridin-2-yl)-1-phenylethyl]carbamate



N,N-Diisopropylamine (1.53 mL, 10.8 mmol) was dissolved in THF (20.0 mL) and cooled to 0 °C before ^{n}BuLi (2.5 M solution in hexanes, 4.35 mL, 10.8 mmol) was added dropwise and stirred for 30 minutes. The LDA solution was then cooled to −78 °C, to which 2-bromo-6-methylpyridine (0.83 mL, 7.30 mmol) was added dropwise *via* a syringe pump and stirred for 1 hour. *tert*-Butyl [(*E*)-phenylmethylidene]carbamate (742 mg, 3.62 mmol) was added and stirred for a further 2 hours at −78 °C before warming to RT. The solution was then quenched with sat. aq. NH_4Cl (70 mL), extracted with ethyl acetate (3 × 60 mL) and washed with brine (70 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 9:1 hexane : ethyl acetate → 100% ethyl acetate) afforded the title compound, which was obtained as a yellow oil (775 mg, 57%); R_f = 0.52 (1:1 ethyl acetate : hexane); ν_{max}/cm^{-1} (thin film): 3331, 2978, 1693, 1495, 1392, 1366, 1245, 1042, 1012, 886, 733, 697; δ_H (400 MHz, MeOD-*d*$_4$) 7.55 (1H, t, *J* = 7.5 Hz, H-17), 7.41 (1H, d, *J* = 7.5 Hz, H-18), 7.38 – 7.20 (5H, m, 5 x Ar**H**), 7.18 (1H, d, *J* = 7.5 Hz, H-16), 5.01 (1H, dd, *J* = 9.0, 5.5 Hz, H-7), 3.17 – 3.03 (2H, m, H-14), 1.34 (9H, s, H-1,2,3); δ_C (100 MHz, MeOD-*d*$_4$) 161.6 (C-15), 157.5 (C-5), 144.0 (C-8), 142.2 (C-19), 140.5 (C-17), 129.5 (C-10,12), 128.2 (C-11), 127.4 (C-9,13), 127.2 (C-18), 124.4 (C-16), 80.2 (C-4), 56.1

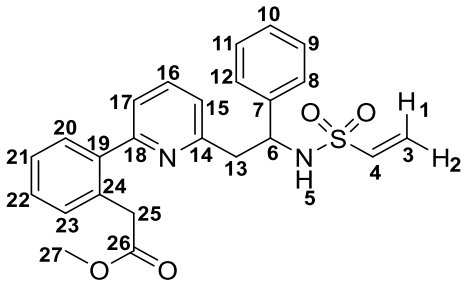
(C-7), 45.6 (C-14), 28.7 (C-1,2,3); HRMS (ESI$^+$): calcd. for $C_{18}H_{21}{}^{79}BrN_2NaO_2$, 399.0679. Found $[MNa]^+$ 399.0680 (−0.4 ppm error).

3.46: Methyl 2-(2-(6-(2-((*tert*-butoxycarbonyl)amino)-2-phenylethyl)pyridin-2-yl)phenyl)acetate



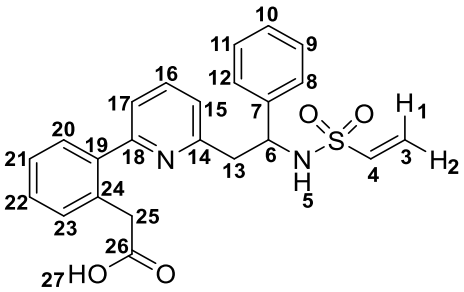
tert-Butyl [2-(6-bromopyridin-2-yl)-1-phenylethyl]carbamate (70.9 mg, 0.203 mmol), methyl 2-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl) acetate (83.5 mg, 0.302 mmol), potassium phosphate (89.4 mg, 0.421 mmol) and $PdCl_2(dppf)\cdot CH_2Cl_2$ (8.30 mg, 10.2 µmol) were charged into a round-bottomed flask purged with argon. THF (7 mL) and de-ionised water (18.5 µL, 1.03 mmol) were added and heated to 70 °C, at reflux, for 22 hours. Upon completion the solution was cooled to RT, diluted with water (5 mL), extracted with ethyl acetate (3 × 10 mL) and washed with brine (10 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 8.5:1.5 hexane : ethyl acetate → 7:3 hexane : ethyl acetate) afforded the title compound, which was obtained as a colourless oil (77.7 mg, 86%); R_f = 0.56 (1:1 ethyl acetate : hexane); ν_{max}/cm^{-1} (thin film): 2977, 2930, 1706, 1590, 1570, 1449, 1401, 1365, 1257, 1211, 1156, 1021, 761, 700; δ_H (400 MHz, MeOD-*d*$_4$) 7.73 (1H, t, *J* = 7.5 Hz, Ar**H**), 7.45 – 7.31 (7H, m, 7 x Ar**H**), 7.28 (2H, t, *J* = 7.5 Hz, 2 x Ar**H**), 7.20 (2H, t, *J* = 7.5 Hz, 2 x Ar**H**), 5.04 (1H, dd, *J* = 10.0, 5.5 Hz, H-7), 3.75 (2H, s, H-26), 3.53 (3H, s, H-28), 3.23 – 3.05 (2H, m, H-14), 1.30 (9H, m, H-1,2,3); δ_C (100 MHz, MeOD-*d*$_4$) 174.2 (C-27), 160.1 (C-19), 159.3 (C-15), 157.5 (C-5), 144.5 (C-8), 141.8 (C-20/25), 138.6 (Ar**C**H), 134.0 (C-20/25), 132.6 (Ar**C**H), 130.9 (Ar**C**H), 129.7 (Ar**C**H), 129.4 (2 x Ar**C**H), 128.4 (Ar**C**H), 128.1 (Ar**C**H), 127.4 (2 x Ar**C**H), 123.6 (Ar**C**H), 123.2 (Ar**C**H), 80.0 (C-4), 56.6 (C-7), 52.4 (C-28), 46.0 (C-14), 40.2 (C-26), 28.7 (C-1,2,3); HRMS (ESI$^+$): calcd. for $C_{27}H_{30}N_2NaO_4$, 469.2098. Found: $[MNa]^+$, 469.2095 (0.6 ppm error).

3.47: Methyl 2-(2-(6-(2-phenyl-2-(vinylsulfonamido)ethyl)pyridin-2-yl)phenyl)acetate



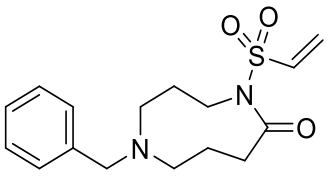
Methyl 2-(2-(6-(2-((*tert*-butoxycarbonyl)amino)-2-phenylethyl)pyridin-2-yl)phenyl)acetate (112 mg, 0.252 mmol) was dissolved in 1,4-dioxane (10.0 mL) and 4 M HCl in 1,4-dioxane (0.53 mL, 15.3 mmol) was added. The solution was stirred at RT for 120 hours, after which the solution was concentrated *in vacuo* to yield an amorphous solid. This salt was dissolved in anhydrous DCM (10.0 mL) at RT and the solution was cooled to 0 °C using an ice bath. Triethylamine (0.35 mL, 2.52 mmol) was added dropwise, followed by 2-chloroethane-1-sulfonyl chloride (50.0 µL, 0.511 mmol). The solution was allowed to gradually warm to RT while being stirred for 20 hours. After that, the solution was diluted with DCM (15 mL) and washed with brine (2 x 15 mL). The aqueous layer was then washed with DCM (2 x 15 mL). The organic layers were then combined, dried over magnesium sulfate, filtered and concentrated *in vacuo*. This was purified by column chromatography (SiO_2, 9:1 hexane : ethyl acetate → 7:3 hexane : ethyl acetate → 7:3 ethyl acetate : hexane → 9:1 ethyl acetate : methanol) to yield the title compound, which was obtained as a colourless oil (87.1 mg, 79%); R_f = 0.63 (1:1 ethyl acetate : hexane); ν_{max}/cm^{-1} (thin film): 3272, 3062, 2951, 1730, 1590, 1569, 1448, 1326, 1256, 1213, 1146, 1064, 964, 762, 701, 554; δ_H (400 MHz, MeOD-*d*$_4$) 7.72 (1H, t, *J* = 7.5 Hz, Ar**H**), 7.44 – 7.32 (7H, m, 7 x Ar**H**), 7.29 (2H, t, *J* = 7.5 Hz, 2 x Ar**H**), 7.24 – 7.13 (2H, m, 2 x Ar**H**), 6.00 (1H, dd, *J* = 16.5, 9.5 Hz, H-4), 5.79 (1H, d, *J* = 16.5 Hz, H-2), 5.44 (1H, d, *J* = 9.5 Hz, H-1), 4.78 (1H, dd, *J* = 8.5, 7.0 Hz, H-6), 3.74 (2H, dd, *J* = 25.0, 15.5 Hz, H-25), 3.54 (3H, s, H-27), 3.21 – 3.16 (2H, m, H-13); δ_C (100 MHz, MeOD-*d*$_4$) 174.3 (C-27), 160.2 (C-18), 158.5 (C-14), 143.6 (C-7), 141.6 (C-19/24), 138.6 (Ar**C**H), 138.5 (C-4), 134.0 (C-19/24), 132.7 (Ar**C**H), 130.9 (Ar**C**H), 129.7 (Ar**C**H), 129.5 (2 x Ar**C**H), 128.54 (Ar**C**H), 128.46 (Ar**C**H), 128.0 (2 x Ar**C**H), 125.0 (C-3), 124.0 (Ar**C**H), 123.4 (Ar**C**H), 59.6 (C-6), 52.5 (C-27), 46.5 (C-13), 40.2 (C-25); HRMS (ESI^+): calcd. for $C_{24}H_{25}N_2O_4S$, 437.1530. Found: $[MH]^+$, 437.1529 (−0.1 ppm error).

3.48: 2-(2-(6-(2-Phenyl-2-(vinylsulfonamido)ethyl)pyridin-2-yl)phenyl)acetic acid



Methyl 2-(2-(6-(2-phenyl-2-(vinylsulfonamido)ethyl)pyridin-2-yl)phenyl)acetate (1.45 g, 3.32 mmol) was dissolved in THF (45.0 mL) and water (45.0 mL), then lithium hydroxide monohydrate (799 mg, 33.4 mmol) was added and the solution stirred at RT for 17 hours. The solution was concentrated *in vacuo*. This was purified by column chromatography (SiO_2, 100% ethyl acetate → 9:1 ethyl acetate : methanol) to yield the title compound, which was obtained as a pink solid (1.09 g, 78%). R_f = 0.49 (9:1 ethyl acetate : methanol); MP = 71 – 76 °C; ν_{max}/cm^{-1} (thin film): 3364, 1716, 1634, 1601, 1580, 1497, 1455, 1328, 1256, 1147, 1066, 965, 764, 733, 700; δ_H (400 MHz, MeOD-*d*$_4$) 7.94 (1H, t, *J* = 7.5 Hz, Ar**H**), 7.55 (1H, d, *J* = 7.5 Hz, Ar**H**), 7.53 – 7.48 (1H, m, Ar**H**), 7.46 – 7.36 (4H, m, 4 x Ar**H**), 7.35 – 7.25 (2H, m, 2 x Ar**H**), 7.27 (2H, t, *J* = 7.5 Hz, 2 x Ar**H**), 7.24 – 7.18 (1H, m, Ar**H**), 6.07 (1H, dd, *J* = 16.5, 10.0 Hz, H-4), 5.81 (1H, d, *J* = 16.5 Hz, H-2), 5.49 (1H, d, *J* = 10.0 Hz, H-1), 4.73 (1H, dd, *J* = 9.0, 6.5 Hz, H-6), 3.54 (2H, s, H-25), 3.33 – 3.18 (2H, m, H-13); δ_C (100 MHz, MeOD-*d*$_4$) 176.2 (C-26), 158.7 (C-18), 157.7 (C-14), 142.9 (C-7), 140.7 (Ar**C**H), 139.5 (C-19/24), 138.5 (C-4), 134.4 (C-19/24), 132.4 (Ar**C**H), 131.7 (Ar**C**H), 130.7 (Ar**C**H), 129.7 (2 x Ar**C**H), 128.9 (Ar**C**H), 128.8 (Ar**C**H), 127.9 (2 x Ar**C**H), 125.4 (Ar**C**H), 125.3 (C-3), 124.4 (Ar**C**H), 59.8 (C-6), 45.8 (C-13), 41.9 (C-25); HRMS (ESI^+): calcd. for $C_{23}H_{22}N_2NaO_4S$, 445.1192. Found: $[MNa]^+$, 445.1194 (−0.3 ppm error).

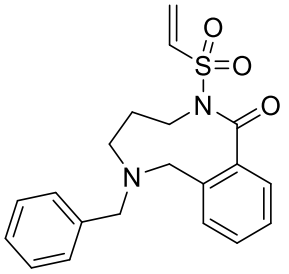
3.49: 1-Benzyl-5-(ethenesulfonyl)-1,5-diazonan-6-one



To a round-bottomed flask 4-(benzyl(3-(vinylsulfonamido)propyl)amino)butanoic acid (63.6 mg, 0.186 mmol) was dissolved in chloroform (5.0 mL) and DIPEA (65.0 µL, 0.374 mmol) was added dropwise. Then, T3P (50% solution in ethyl acetate, 0.19 mL, 0.298 mmol) was added dropwise and the solution stirred at RT for 20 hours. The reaction mixture was diluted with

DCM (10 mL) and washed with $NaHCO_3$ (2 x 10 mL). The organic layer was dried, filtered and concentrated *in vacuo* to yield the title compound, which was obtained as an orange oil (54.2 mg, 90%); ν_{max}/cm^{-1} (thin film): 2929, 2853, 1679, 1454, 1345, 1152, 1127, 1077, 972, 814, 744, 727, 701, 668, 494; δ_H (400 MHz, $CDCl_3$) 7.38 – 7.20 (5H, m, 5 x Ar**H**), 7.02 (1H, dd, *J* = 17.0, 9.5 Hz, C**H**S), 6.40 (1H, d, *J* = 17.0 Hz, **H**C=CHS), 6.04 (1H, d, *J* = 9.5 Hz, **H**C=CHS), 4.10 – 4.04 (2H, m, C$\mathbf{H_2}$NS), 3.59 (2H, s, PhC$\mathbf{H_2}$N), 2.69 (2H, t, *J* = 6.0 Hz, NC$\mathbf{H_2}CH_2CH_2$N), 2.67 – 2.62 (2H, m, C$\mathbf{H_2}$CO), 2.59 (2H, t, *J* = 6.0 Hz, NC$\mathbf{H_2}CH_2CH_2$CO), 1.93 (2H, p, *J* = 6.0 Hz, $NCH_2C\mathbf{H_2}CH_2$CO), 1.72 (2H, p, *J* = 6.0 Hz, $NCH_2C\mathbf{H_2}CH_2$N); δ_C (100 MHz, $CDCl_3$) 176.8 (**C**O), 138.5 (Ar**C**CH_2N), 137.2 (H_2C=**C**HS), 129.2 (2 x Ar**C**H), 128.5 (H_2**C**=CHS), 128.4 (2 x Ar**C**H), 127.2 (Ar**C**H), 58.0 (Ph**C**H_2N), 52.2 (N**C**$H_2CH_2CH_2$CO), 49.5 (N**C**$H_2CH_2CH_2$NHS), 45.2 (**C**H_2NS), 33.0 (**C**H_2CO), 26.9 (NCH_2**C**H_2CH_2NHS), 25.7 (NCH_2**C**H_2CH_2CO); HRMS (ESI^+): calcd. for $C_{16}H_{23}N_2O_3S$, 323.1424. Found $[MH]^+$ 323.1420 (1.2 ppm error).

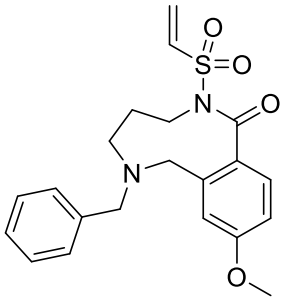
3.50: 6-Benzyl-2-(vinylsulfonyl)-2,3,4,5,6,7-hexahydro-1*H*-benzo[*g*][1,5]diazonin-1-one



To a round-bottomed flask was added 2-((benzyl(3-(vinylsulfonamido)propyl)amino)methyl)benzoic acid (112 mg, 0.288 mmol), which was dissolved in chloroform (7.0 mL) and DIPEA (0.10 mL, 0.575 mmol) was added dropwise. T3P (50% solution in ethyl acetate, 0.27 mL, 0.431 mmol) was added dropwise and the solution stirred at RT for 18 hours. The reaction mixture was diluted with DCM (10 mL) and washed with $NaHCO_3$ (2 x 10 mL). The organic layer was dried, filtered and concentrated *in vacuo* to yield the title compound (^{1}H NMR is severely disrupted and broadened), which was obtained as a beige oil (104 mg, 98%); R_f = 0.71 (100% ethyl acetate); ν_{max}/cm^{-1} (thin film): 2958, 2921, 2853, 1680, 1451, 1346, 1267, 1152, 1047, 1015, 971, 911, 761, 742, 726, 704, 678, 643; δ_H (400 MHz, $CDCl_3$) 7.39 – 7.22 (7H, m, 7 x Ar**H** [overlapping]), 7.39 – 7.22 (1H, m, C**H**S [overlapping]), 7.22 – 7.17 (1H, m, Ar**H**), 7.16 – 7.11 (1H, m, Ar**H**), 6.55 (1H, d, *J* = 17.0 Hz, **H**C=CHS), 6.12 (1H, d, *J* = 10.0 Hz, **H**C=CHS), 3.81 (4H, s, PhC$\mathbf{H_2}$N,COCCC$\mathbf{H_2}$N), 3.79 – 3.48 (2H, m, C$\mathbf{H_2}$NS), 3.26 – 3.12 (2H, m, NC$\mathbf{H_2}CH_2CH_2$N), 1.81 – 1.47 (2H, m, $NCH_2C\mathbf{H_2}CH_2$N); δ_C (100 MHz, $CDCl_3$) 171.9 (**C**O), 139.9 (Ar**C**CH_2N), 137.8 (H_2C=**C**HS), 135.9 (Ar**C**), 135.8 (Ar**C**), 130.0 (2 x Ar**C**H), 129.5 (Ar**C**H), 128.6 (Ar**C**H), 128.4 (2 x Ar**C**H [overlapping]), 128.4 (H_2**C**=CHS

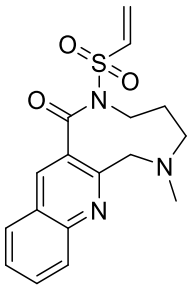
[overlapping]), 127.7 (Ar**C**H), 127.5 (Ar**C**H), 125.2 (Ar**C**H), 56.44 (Ph**C**H_2N/**C**H_2CCCO_2H), 56.38 (Ph**C**H_2N/**C**H_2CCCO), 49.3 (N**C**$H_2CH_2CH_2$NHS), 47.9 (**C**H_2NS), 24.6 (NCH_2**C**H_2CH_2NHS); HRMS (ESI^+): calcd. for $C_{20}H_{22}N_2NaO_3S$, 393.1243. Found $[MNa]^+$ 393.1244 (−0.2 ppm error).

3.51: 6-Benzyl-9-methoxy-2-(vinylsulfonyl)-2,3,4,5,6,7-hexahydro-1*H*-benzo[*g*][1,5]diazonin-1-one



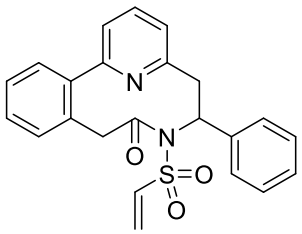
To a round-bottomed flask, 2-((benzyl(3-(vinylsulfonamido)propyl)amino)methyl)-4-methoxybenzoic acid (72.5 mg, 0.173 mmol) was dissolved in chloroform (10.0 mL) and DIPEA (0.06 mL, 0.346 mmol) was added dropwise. T3P (50% solution in ethyl acetate, 0.17 mL, 0.268 mmol) was added dropwise and the solution stirred at RT for 17 hours. The reaction mixture was diluted with DCM (10 mL) and washed with $NaHCO_3$ (2 x 10 mL). The organic layer was dried with $MgSO_4$, filtered and concentrated *in vacuo* affording the title compound (^{1}H NMR is severely disrupted and broadened), which was obtained as a white oil (67.9 mg, 98%); R_f = 0.49 (1:1 ethyl acetate : hexane); ν_{max}/cm^{-1} (thin film): 2960, 2842, 1681, 1607, 1453, 1347, 1257, 1247, 1153, 1012, 774, 731, 670, 551; δ_H (400 MHz, $CDCl_3$) 7.38 – 7.21 (5H, m, 5 x Ar**H** [overlapping]), 7.38 – 7.21 (1H, m, C**H**S [overlapping]), 7.12 (1H, d, *J* = 8.5 Hz, NCOCC**H**), 6.78 (1H, dd, *J* = 8.5, 2.5 Hz, NCOCCHC**H**), 6.66 (1H, d, *J* = 2.5 Hz, NCH_2CC**H**CO), 6.53 (1H, d, *J* = 16.5 Hz, **H**C=CHS), 6.10 (1H, d, *J* = 10.0 Hz, **H**C=CHS), 3.79 (2H, s, PhC**H$_2$**N), 3.76 (3H, s, COC**H$_3$**), 3.16 – 3.03 (1H, m, NC**H$_2$**CH_2CH_2NS), 2.66 – 2.47 (1H, m, NC**H$_2$**CH_2CH_2NS), 1.79 – 1.49 (2H, m, NCH_2C**H$_2$**CH_2NS); δ_C (100 MHz, $CDCl_3$) 172.0 (N**C**O), 160.2 (**C**OCH_3), 142.0 (Ar**C**), 138.0 (H_2C=**C**HS), 135.9 (Ar**C**), 129.9 (2 x Ar**C**H), 128.4 (2 x Ar**C**H [overlapping]), 128.3 (Ar**C** [overlapping]), 128.2 (H_2**C**=CHS), 127.5 (Ar**C**H), 126.6 (NCOC**C**H), 114.1 (NCH_2C**C**HCO), 112.6 (NCOCCH**C**H), 56.6 (Ph**C**H_2N/**C**H_2CCCO_2H), 56.5 (Ph**C**H_2N/N**C**H_2CCHCO), 55.4 (CO**C**H_3), 49.3 (N**C**$H_2CH_2CH_2$NS), 48.0 (**C**H_2NS), 24.7 (NCH_2**C**H_2CH_2NS); HRMS (ESI^+): calcd. for $C_{21}H_{25}N_2O_4S$, 401.1530. Found $[MH]^+$ 401.1528 (0.5 ppm error).

3.52: 2-Methyl-6-(vinylsulfonyl)-1,2,3,4,5,6-hexahydro-7*H*-[1,5]diazonino[7,8-*b*]quinolin-7-one



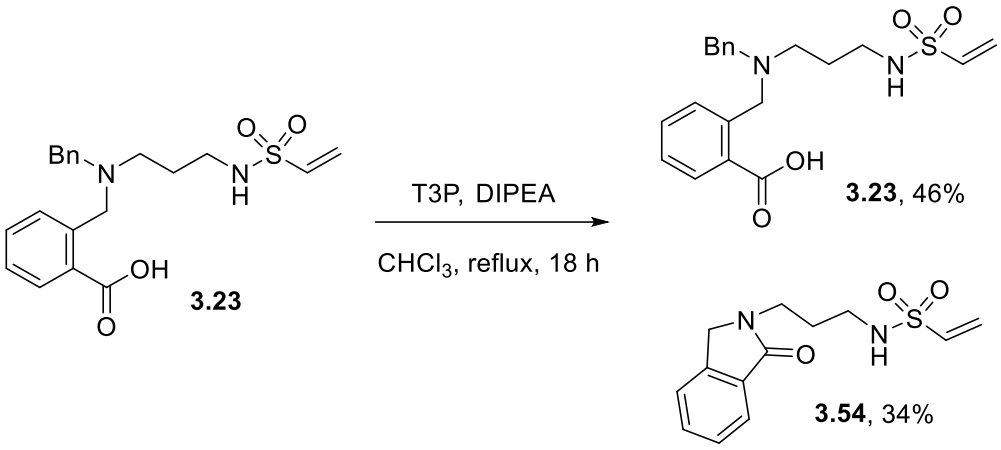
To a round-bottomed flask 2-((methyl(3-(vinylsulfonamido)propyl)amino)methyl)quinoline-3-carboxylic acid (33.7 mg, 0.093 mmol) was dissolved in chloroform (5.0 mL) and DIPEA (30.0 µL, 0.172 mmol) was added dropwise. T3P (50% solution in ethyl acetate, 88.0 µL, 0.139 mmol) was added dropwise and the solution stirred at RT for 16 hours. The reaction mixture was diluted with DCM (5 mL) and washed with $NaHCO_3$ (2 x 10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield the title compound (^{1}H NMR is severely disrupted and broadened), which was obtained as a colourless oil (29.8 mg, 93%); R_f = 0.25 (1:1 ethyl acetate : methanol); ν_{max}/cm^{-1} (thin film): 2954, 2846, 1678, 1347, 1159, 1150, 999, 761, 731, 663, 569; δ_H (400 MHz, $CDCl_3$) 8.03 (1H, s, COCCC**H** [overlapping]), 8.03 (1H, d, *J* = 7.5 Hz, NCC**H** [overlapping]), 7.82 (1H, d, *J* = 8.0 Hz, COCCHCC**H**), 7.76 (1H, t, *J* = 7.5 Hz, NCCHC**H**), 7.58 (1H, t, *J* = 7.5 Hz, COCCHCCHC**H**), 7.28 (1H, dd, *J* = 17.0, 10.0 Hz, H_2C=C**H**S), 6.56 (1H, d, *J* = 17.0 Hz, **H₂**C=CHS), 6.15 (1H, dd, *J* = 10.0 Hz, **H₂**C=CHS), 4.54 – 3.81 (2H, m, CH_3NC**H₂**CN [overlapping]), 4.54 – 3.81 (2H, m, C**H₂** [overlapping]), 2.68 – 2.46 (2H, m, C**H₂**CH_2CH_2NS), 2.41 (3H, s, C**H₃**N), 1.80 – 1.57 (2H, m, CH_2C**H₂**CH_2NS); δ_C (101 MHz, $CDCl_3$) 169.3 (**C**O), 159.7 (Ar**C**), 147.5 (Ar**C**), 138.0 (H_2C=**C**HS), 133.3 (COC**C**H), 131.0 (NCCH**C**H), 129.6 (Ar**C**), 129.0 (NC**C**H), 128.4 (H_2**C**=CHS), 128.1 (COCCHC**C**H), 127.4 (COCCHCCH**C**H), 126.6 (Ar**C**), 61.9 (CH_3N**C**H_2CN), 55.3 (**C**$H_2CH_2CH_2NS$), 48.5 (**C**H_2NS), 41.7 (**C**H_3N), 24.6 (CH_2**C**H_2CH_2NS); HRMS (ESI$^+$): calcd. for $C_{17}H_{20}N_3O_3S$, 346.1220. Found $[MH]^+$ 346.1226 (−1.8 ppm error).

3.53: 4-Phenyl-3-(vinylsulfonyl)-4,5-dihydro-1*H*-6,10-(azeno)benzo[*d*][1]azacyclododecin-2(3*H*)-one



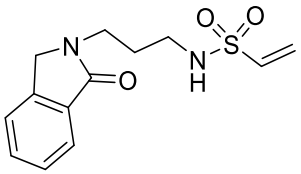
To a round-bottomed flask 2-(2-(6-(2-phenyl-2-(vinylsulfonamido)ethyl)pyridin-2-yl)phenyl)acetic acid (319 mg, 0.755 mmol) was dissolved in chloroform (25.0 mL) and DIPEA (0.24 mL, 1.38 mmol), was added dropwise. T3P (50% solution in ethyl acetate, 0.72 mL, 1.26 mmol) was added dropwise and the solution stirred at RT for 18 hours. The reaction mixture was diluted with DCM (30 mL) and washed with $NaHCO_3$ (2 x 30 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield the title compound, which was obtained as an impure red solid (305 mg, 100%). Column chromatography was not possible with **3.53** due to degradation of the compound on silica. R_f = 0.43 (100% ethyl acetate); ν_{max}/cm^{-1} (thin film): 3264, 3062, 2926, 1716, 1599, 1577, 1454, 1326, 1147, 1064, 964, 764, 734, 701; δ_H (400 MHz, $CDCl_3$) 8.58 (1H, d, *J* = 9.0 Hz, C**H**CCH$_2$CO), 8.42 (1H, d, *J* = 7.0 Hz, Ar**H**), 8.21 (1H, d, *J* = 9.0 Hz, Ar**H**), 7.79 (1H, dd, *J* = 9.0, 7.0 Hz, Ar**H**), 7.60 – 7.27 (7H, m, 7 x Ar**H** [overlapping]), 7.60 – 7.27 (1H, m, C**H$_2$**CO [overlapping]), 7.19 (1H, ddd, *J* = 8.5, 6.0, 2.0 Hz, Ar**H**), 6.65 (1H, s, C**H$_2$**CO), 5.91 – 5.75 (1H, m, H$_2$C=C**H**S [overlapping]), 5.91 – 5.75 (1H, m, **H$_2$**C=CHS [overlapping]), 5.32 (1H, d, *J* = 9.0 Hz, **H$_2$**C=CHS), 5.01 – 4.84 (1H, m, C**H**NS [overlapping]), 5.01 – 4.84 (1H, m, C**H$_2$**CHNS [overlapping]), 3.30 (1H, dd, *J* = 12.5, 4.5 Hz, C**H$_2$**CHNS); δ_C (100 MHz, $CDCl_3$) 159.7 (**C**O), 146.8 (CH$_2$**C**N), 145.4 (**C**CCH$_2$CO), 141.9 (**C**CHNS), 139.5 (N**C**CCCH$_2$CO), 137.3 (H$_2$C=**C**HS), 132.5 (**C**HCHCCH$_2$CO), 131.8 (Ar**C**H), 128.9 (2 x Ar**C**H), 128.1 (Ar**C**H), 127.2 (2 x Ar**C**H), 124.60 (Ar**C**H), 124.56 (Ar**C**H), 124.3 (H$_2$**C**=CHS), 124.2 (Ar**C**H), 122.4 (Ar**C**H), 121.0 (**C**HCCH$_2$CO), 115.9 (**C**CH$_2$CO), 101.1 (**C**H$_2$CO), 59.5 (**C**HNS), 41.8 (**C**H$_2$CHNS); HRMS (ESI$^+$): calcd. for $C_{23}H_{20}N_2NaO_3S$, 427.1087. Found: [MNa]$^+$, 427.1094 (−1.7 ppm error).

3.54: *N*-(3-(1-Oxoisoindolin-2-yl)propyl)ethenesulfonamide and 3.23: 2-((benzyl(3-(vinylsulfonamido)propyl)amino)methyl)benzoic acid



To a round-bottomed flask was added 2-((benzyl(3-(vinylsulfonamido)propyl)amino)methyl)benzoic acid (113 mg, 0.292 mmol), which was dissolved in chloroform (7.0 mL) and DIPEA (0.09 mL, 0.539 mmol) was added dropwise. T3P (50% solution in ethyl acetate, 0.28 mL, 0.438 mmol) was added dropwise and the solution was stirred at reflux (65 °C) for 18 hours. Following this, the reaction mixture was diluted with DCM (10 mL) and washed with $NaHCO_3$ (2 x 10 mL). The organic layer was dried, filtered and concentrated *in vacuo*. This was purified by column chromatography (SiO_2, 1:1 ethyl acetate : hexane → 100% ethyl acetate → 1:1 ethyl acetate : methanol) to afford two products: **3.54** (27.7 mg, 34%) and **3.23** (51.9 mg, 46%), with the data for each provided below.

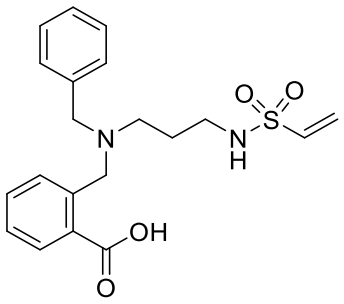
3.54: *N*-(3-(1-Oxoisoindolin-2-yl)propyl)ethenesulfonamide



The product was a colourless oil (27.7 mg, 34%). R_f = 0.31 (100% ethyl acetate); ν_{max}/cm^{-1} (thin film): 3175, 2932, 2871, 1665, 1473, 1457, 1418, 1325, 1145, 1090, 972, 736, 661, 548; δ_H (400 MHz, $CDCl_3$) 7.81 (1H, d, *J* = 7.5 Hz, C**H**CCO), 7.58 – 7.52 (1H, m, C**H**CCCO), 7.47 (2H, t, *J* = 7.5 Hz, 2 x Ar**H**), 6.52 (1H, d, *J* = 16.5, 10.0 Hz, HC=C**H**S), 6.18 (1H, d, *J* = 16.5 Hz, **H**C=CHS), 5.98 (1H, t, *J* = 6.5 Hz, N**H**), 5.85 (1H, d, *J* = 10.0 Hz, **H**C=CHS), 4.40 (2H, s, C$\mathbf{H_2}$CCCO), 3.74 (2H, t, *J* = 6.0 Hz, C$\mathbf{H_2}$NCO), 3.00 (2H, q, *J* = 6.0 Hz, $NCH_2CH_2C\mathbf{H_2}NHS$), 1.89 (2H, p, *J* = 6.0 Hz, $NCH_2C\mathbf{H_2}CH_2NHS$); δ_C (100 MHz, $CDCl_3$) 169.7 (**C**O), 141.3 (**C**CCO), 136.5 (H_2C=**C**HS), 132.3 (**C**CO), 131.8 (**C**HCCCO), 128.4 (**C**HCHCCO), 126.0 ($H_2\mathbf{C}$=CHS), 123.8

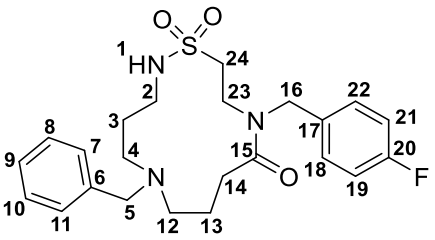
(**C**HCCO), 123.0 (**C**HCHCHCCO), 50.4 (**C**H_2CCCO), 39.6 (NCH_2C**H**$_2$CH$_2$NHS), 39.3 (**C**H_2NCO), 28.9 (NCH_2**C**H_2CH$_2$NHS); HRMS (ESI$^+$): calcd. for $C_{13}H_{16}N_2NaO_3S$, 303.0774. Found [MNa]$^+$ 303.0775 (−0.2 ppm error).

3.23: 2-((Benzyl(3-(vinylsulfonamido)propyl)amino)methyl)benzoic acid



The product was obtained as a white solid (51.9 mg, 46%). See previous **3.23** for the complete assignment of the structure.

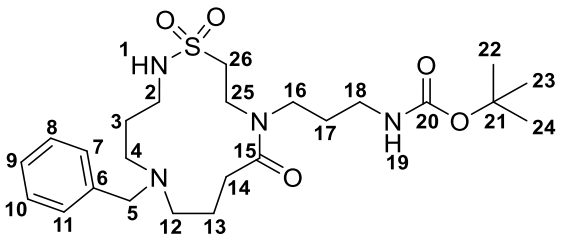
3.58: 6-Benzyl-11-(4-fluorobenzyl)-1-thia-2,6,11-triazacyclotridecan-10-one 1,1-dioxide



To a round-bottomed flask 4-(benzyl(3-(vinylsulfonamido)propyl)amino)butanoic acid (72.1 mg, 0.212 mmol) was dissolved in chloroform (5.0 mL) and DIPEA (68.3 µL, 0.392 mmol) was added dropwise. Then, T3P (50% solution in ethyl acetate, 0.21 mL, 0.324 mmol) was added dropwise and the solution stirred at RT for 20 hours. The reaction mixture was diluted with DCM (10 mL) and washed with $NaHCO_3$ (2 x 10 mL). The organic layer was dried, filtered and concentrated *in vacuo* to remove excess solvent to form 9-membered ring intermediate **3.49**, which was used directly in the next step. To this resulting orange oil was added triethylamine (0.09 mL, 0.641 mmol) in THF (0.31 mL) and 4-fluorobenzylamine (36.0 µL, 0.318 mmol) in THF (0.15 mL) gradually *via* a syringe pump over 10 minutes. The reaction mixture was stirred at RT for 72 hours, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 7:3 hexane : ethyl acetate → 1:1 ethyl acetate : hexane) afforded the title compound, which was obtained as a white solid (59.7 mg, 63%), and exists in $CDCl_3$ as a 5:2 mixture of rotamers; R_f = 0.50 (100% ethyl acetate); MP = 128 – 132 °C; ν_{max}/cm^{-1} (thin film): 3205, 2934, 2811, 1631, 1452, 1414, 1323, 1222, 1139, 1097,

911, 727, 702; δ_H (400 MHz, $CDCl_3$) Data for major rotamer: 7.41 (4H, m, H-7,8,10,11), 7.36 – 7.21 (1H, m, H-9 [overlapping]), 7.02 – 6.94 (2H, m, H-19,21 [overlapping]), 6.90 – 6.84 (2H, m, H-18,22 [overlapping]), 6.47 (1H, d, *J* = 11.5 Hz, H-1), 4.42 (1H, d, *J* = 17.5 Hz, H-16), 4.32 (1H, d, *J* = 17.5 Hz, H-16'), 4.25 – 4.03 (1H, m, H-5 [overlapping]), 4.25 – 4.03 (2H, m, H-23 [overlapping]), 3.43 – 3.34 (1H, m, H-2), 3.27 - 2.91 (1H, m, H-2' [overlapping]), 3.27 – 2.91 (2H, m, H-24 [overlapping]), 3.27 – 2.91 (1H, m, H-4 [overlapping]), 2.74 (1H, d, *J* = 12.5 Hz, H-5'), 2.64 – 2.54 (1H, m, H-12 [overlapping]), 2.44 – 2.31 (1H, m, H-13), 2.27 – 2.12 (1H, m, H-3 [overlapping]), 2.27 – 2.12 (1H, m, H-4' [overlapping]), 2.07 (1H, d, *J* = 13.0 Hz, H-12'), 1.97 (2H, t, *J* = 4.5 Hz, H-14), 1.76 – 1.66 (1H, m, H-3'), 1.47 – 1.36 (1H, m, H-13'). Full data for minor rotamer: 7.91 (1H, br t, *J* = 4.5 Hz, H-1), 7.36 – 7.27 (5H, m, 5 x Ar**H** [overlapping]), 7.27 – 7.21 (2H, m, H-18,22 [overlapping]), 7.02 – 6.84 (2H, m, H-19,21 [overlapping]), 4.57 (2H, s, H-16), 3.78 (2H, t, *J* = 6.0 Hz, H-23), 3.51 (2H, s, H-5), 3.08 (2H, t, *J* = 6.0 Hz, H-24 [overlapping]), 3.04 – 2.91 (2H, m, H-2 [overlapping]), 2.64 – 2.54 (2H, m, H-12 [overlapping]), 2.64 – 2.54 (2H, m, H-14 [overlapping]), 2.51 (2H, t, *J* = 5.5 Hz, H-4), 1.84 (2H, p, *J* = 6.5 Hz, H-13), 1.62 (2H, p, *J* = 5.5 Hz, H-3); δ_C (100 MHz, $CDCl_3$) Data for major rotamer: 176.2 (C-15), 162.1 (C-20, d, $^1J_{CF}$ = 246.4 Hz), 138.2 (C-6), 132.6 (C-17, d, $^4J_{CF}$ = 2.9 Hz), 130.6 (C-7,11), 128.7 (C-8,10), 127.61 (C-18,22, d, $^3J_{CF}$ = 7.8 Hz), 127.69 – 127.53 (C-9), 115.9 (C-19,21, d, $^2J_{CF}$ = 21.2 Hz), 58.5 (C-5), 56.3 (C-12), 55.0 (C-4), 54.2 (C-16), 46.2 (C-24), 45.6 (C-23), 44.8 (C-2), 32.3 (C-14), 24.8 (C-3), 20.8 (C-13). Full data for minor rotamer: 172.7 (C-15), 162.3 (C-20, d, $^1J_{CF}$ = 246.3 Hz), 137.3 (C-6), 133.2 (C-17, d, $^4J_{CF}$ = 3.5 Hz), 130.1 (C-18,22, d, $^3J_{CF}$ = 8.3 Hz), 129.8 (C-7,11), 128.6 (C-8,10), 127.61 (C-9), 115.7 (C-19,21, d, $^2J_{CF}$ = 21.8 Hz), 59.5 (C-5), 54.0 (C-4), 51.9 (C-12), 48.9 (C-24), 48.2 (C-16), 43.3 (C-2), 42.5 (C-23), 29.9 (C-14), 24.1 (C-3), 22.6 (C-13); δ_F (282 MHz, $CDCl_3$) Major rotamer: −114.72 (1F, m, Ar**F**), minor rotamer −114.24 (1F, m, Ar**F**); HRMS (ESI^+): calcd. for $C_{23}H_{31}FN_3O_3S$, 448.2065. Found: $[MH]^+$, 448.2052 (−2.8 ppm error).

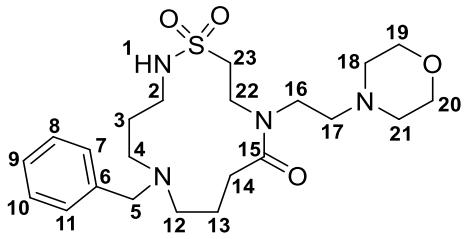
3.62: *tert*-Butyl (3-(6-benzyl-1,1-dioxido-10-oxo-1-thia-2,6,11-triazacyclotridecan-11-yl)propyl)carbamate



To a round-bottomed flask 4-(benzyl(3-(vinylsulfonamido)propyl)amino)butanoic acid (114 mg, 0.334 mmol) was dissolved in chloroform (5.0 mL) and DIPEA (108 µL, 0.618 mmol) was

added dropwise. Then, T3P (50% solution in ethyl acetate, 0.32 mL, 0.501 mmol) was added dropwise and the solution stirred at RT for 20 hours. The reaction mixture was diluted with DCM (10 mL) and washed with $NaHCO_3$ (2 x 10 mL). The organic layer was dried, filtered and concentrated *in vacuo* to remove excess solvent to form 9-membered ring intermediate **3.49**, which was used directly in the next step. To this resulting orange oil was added triethylamine (0.14 mL, 1.03 mmol) in THF (0.30 mL) and *tert*-butyl *N*-(3-aminopropyl)carbamate (71.4 mg, 0.409 mmol) in THF (0.15 mL) gradually *via* a syringe pump over 10 minutes. The reaction mixture was stirred at RT for 72 hours, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 ethyl acetate : hexane → 100% ethyl acetate) afforded the title compound, which was obtained as a colourless oil (81.6 mg, 54%), and exists in $CDCl_3$ as a 2:1 mixture of rotamers; R_f = 0.33 (100% ethyl acetate); ν_{max}/cm^{-1} (thin film): 3374, 2933, 2810, 2249, 1697, 1627, 1511, 1453, 1366, 1323, 1249, 1166, 1140, 1098, 912, 727, 702; δ_H (400 MHz, $CDCl_3$) Data for major rotamer: 7.39 – 7.24 (5H, m, 5 x Ar**H** [overlapping]), 6.39 – 6.32 (1H, m, H-1), 4.39 (1H, br t, *J* = 6.5 Hz, H-19), 4.08 (1H, d, *J* = 12.5 Hz, H-5), 3.36 – 3.29 (1H, m, H-2), 3.24 – 2.90 (1H, m, H-2’ [overlapping]), 3.24 – 2.90 (2H, m, H-18 [overlapping]), 3.24 – 2.90 (2H, m, H-16 [overlapping]), 3.24 – 2.90 (2H, m, H-25 [overlapping]), 3.24 – 2.90 (2H, m, H-26 [overlapping]), 3.24 – 2.90 (2H, m, H-4 [overlapping]), 3.24 – 2.90 (2H, m, H-12 [overlapping]), 2.71 (1H, d, *J* = 12.5 Hz, H-5’), 2.44 – 2.32 (1H, m, H-13), 2.23 – 2.12 (2H, m, H-3), 2.11 – 1.92 (2H, m, H-14), 1.73 – 1.65 (2H, m, H-17 [overlapping]), 1.50 – 1.35 (1H, m, H-13’ [overlapping]), 1.41 (9H, s, H-22,23,24 [overlapping]). Full data for minor rotamer: 7.86 (1H, br s, H-1), 7.39 – 7.24 (5H, m, 5 x Ar**H** [overlapping]), 5.15 (1H, br t, *J* = 6.0 Hz, H-19), 3.79 (2H, t, *J* = 5.5 Hz, H-25), 3.50 (2H, s, H-5), 3.38 (2H, t, *J* = 7.0 Hz, H-16), 3.17 (2H, t, *J* = 6.0 Hz, H-2 [overlapping]), 3.24 – 2.90 (2H, m, H-18 [overlapping]), 3.24 – 2.90 (2H, m, H-26 [overlapping]), 2.60 – 2.47 (2H, m, H-4 [overlapping]), 2.60 – 2.47 (2H, m, H-14 [overlapping]), 2.60 – 2.47 (2H, m, H-12 [overlapping]), 1.79 (2H, p, *J* = 6.5 Hz, H-13), 1.73 – 1.65 (2H, m, H-17 [overlapping]), 1.64 – 1.58 (2H, m, H-3), 1.41 (9H, s, H-22,23,24 [overlapping]); δ_C (100 MHz, $CDCl_3$) Data for major rotamer: 175.7 (C-15), 155.8 (C-20), 138.2 (C-6), 130.7 (C-7,11), 128.6 (C-8,10), 127.5 (C-9), 79.5 (C-21), 58.6 (C-5), 56.5 (C-12), 54.9 (C-4), 46.4 (**C**H_2), 45.0 (**C**H_2), 44.8 (**C**H_2), 43.5 (**C**H_2), 38.0 (C-18), 32.1 (C-14), 29.0 (C-17), 28.47 (C-22,23,24), 24.9 (C-3), 20.9 (C-13). Full data for minor rotamer: 173.0 (C-15), 156.2 (C-20), 137.3 (C-6), 129.8 (C-7,11), 128.7 (C-8,10), 127.7 (C-9), 79.2 (C-21), 59.5 (C-5), 54.0 (C-4), 51.9 (C-12), 49.14 (C-2/26), 49.09 (C-2/26), 42.5 (C-16/25), 42.4 (C-16/25), 37.5 (C-18), 29.9 (C-14), 28.54 (C-22,23,24), 27.8 (C-17), 24.2 (C-3), 22.6 (C-13); HRMS (ESI^+): calcd. for $C_{24}H_{41}N_4O_5S$, 497.2792. Found: $[MH]^+$, 497.2791 (0.3 ppm error).

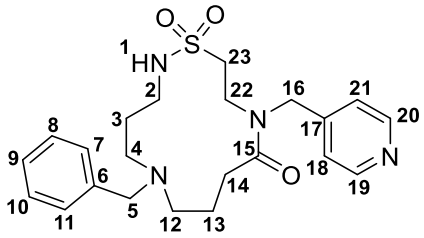
3.63: 6-Benzyl-11-(2-morpholinoethyl)-1-thia-2,6,11-triazacyclotridecan-10-one 1,1-dioxide



To a round-bottomed flask 4-(benzyl(3-(vinylsulfonamido)propyl)amino)butanoic acid (114 mg, 0.334 mmol) was dissolved in chloroform (5.0 mL) and DIPEA (108 µL, 0.618 mmol) was added dropwise. Then, T3P (50% solution in ethyl acetate, 0.32 mL, 0.501 mmol) was added dropwise and the solution stirred at RT for 20 hours. The reaction mixture was diluted with DCM (10 mL) and washed with $NaHCO_3$ (2 x 10 mL). The organic layer was dried, filtered and concentrated *in vacuo* to remove excess solvent to form 9-membered ring intermediate **3.49**, which was used directly in the next step. To this resulting orange oil was added triethylamine (0.14 mL, 1.03 mmol) in THF (0.30 mL) and 4-(2-aminoethyl)morpholine (53.0 µL, 0.404 mmol) in THF (0.15 mL) gradually *via* a syringe pump over 10 minutes. The reaction mixture was stirred at RT for 72 hours, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 9:1 ethyl acetate : methanol) afforded the title compound, which was obtained as a colourless oil (57.3 mg, 38%), and exists in $CDCl_3$ as a 5:2 mixture of rotamers; R_f = 0.54 (1:1 ethyl acetate : methanol); ν_{max}/cm^{-1} (thin film): 3200, 2932, 2854, 2809, 2247, 1626, 1453, 1323, 1300, 1136, 1115, 914, 867, 726, 702; δ_H (400 MHz, $CDCl_3$) Data for major rotamer: 7.39 – 7.22 (5H, m, 5 x Ar**H** [overlapping]), 6.41 – 6.33 (1H, m, H-1), 4.21 – 4.10 (1H, m, C**H₂**), 4.06 (1H, d, *J* = 12.5 Hz, H-5 [overlapping]), 4.09 – 3.96 (1H, m, C**H₂** [overlapping]), 3.64 (4H, t, *J* = 4.5 Hz, H-19,20), 3.41 – 3.19 (2H, m, H-2 [overlapping]), 3.41 – 3.19 (1H, m, C**H₂** [overlapping]), 3.16 – 2.99 (1H, m, C**H₂** [overlapping]), 3.16 – 2.99 (2H, m, C**H₂** [overlapping]), 2.74 (1H, d, *J* = 12.5 Hz, H-5'), 2.63 – 2.51 (2H, m, C**H₂** [overlapping]), 2.44 – 2.34 (1H, m, H-13), 2.31 (4H, t, *J* = 4.5 Hz, H-18,21), 2.27 – 2.05 (1H, m, H-3 [overlapping]), 2.27 – 2.05 (2H, m, H-4 [overlapping]), 2.27 – 2.05 (2H, m, H-12 [overlapping]), 2.27 – 1.95 (2H, m, H-14 [overlapping]), 1.74 – 1.64 (1H, m, H-3'), 1.52 – 1.41 (1H, m, H-13'). Full data for minor rotamer: 7.95 (1H, br s, H-1), 7.39 – 7.22 (5H, m, 5 x Ar**H** [overlapping]), 3.84 (2H, t, *J* = 5.0 Hz, CH_2), 3.69 (4H, t, *J* = 4.5 Hz, H-19,20), 3.50 (2H, s, H-5), 3.46 (2H, t, *J* = 6.5 Hz, C**H₂**), 3.41 – 3.19 (2H, m, C**H₂** [overlapping]), 3.16 – 2.99 (2H, m, H-2 [overlapping]), 2.63 – 2.51 (2H, m, H-14 [overlapping]), 2.63 – 2.51 (2H, m, H-12 [overlapping]), 2.51 – 2.45 (2H, m, H-4 [overlapping]), 2.49 (4H, t, *J* = 5.0 Hz, H-18,21 [overlapping]), 2.27 – 1.95 (2H, m, C**H₂** [overlapping]), 1.79 (2H, p, *J* = 6.5 Hz, H-13), 1.59 (2H,

p, *J* = 5.5 Hz, H-3); δ_C (100 MHz, $CDCl_3$) Data for major rotamer: 175.7 (C-15), 138.3 (C-6), 130.4 (C-7,11), 128.7 (C-9), 128.6 (C-8,10), 67.0 (C-19,20), 58.6 (C-5), 57.0 (C-12), 56.3 (**C**H_2), 54.7 (C-4), 53.91 (C-18,21), 48.5 (C-2), 46.5 (**C**H_2), 45.3 (**C**H_2), 44.6 (**C**H_2), 32.0 (C-14), 25.0 (C-3), 20.8 (C-13). Full data for minor rotamer: 172.6 (C-15), 137.3 (C-6), 129.9 (C-7,11), 127.7 (C-9), 127.4 (C-8,10), 66.9 (C-19,20), 59.6 (C-5), 56.5 (**C**H_2), 54.2 (C-4), 53.94 (C-18,21), 51.8 (C-12), 49.3 (**C**H_2), 43.8 (**C**H_2), 43.5 (C-2,**C**H_2 [overlapping]), 29.7 (C-14), 24.3 (C-3), 22.5 (C-13); HRMS (ESI^+): calcd. for $C_{22}H_{36}N_4NaO_4S$, 475.2349. Found: $[MNa]^+$, 475.2347 (0.5 ppm error).

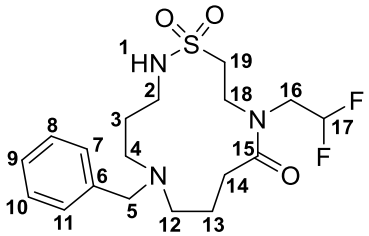
3.64: 6-Benzyl-11-(pyridin-4-ylmethyl)-1-thia-2,6,11-triazacyclotridecan-10-one 1,1-dioxide



To a round-bottomed flask 4-(benzyl(3-(vinylsulfonamido)propyl)amino)butanoic acid (114 mg, 0.334 mmol) was dissolved in chloroform (5.0 mL) and DIPEA (108 µL, 0.618 mmol) was added dropwise. Then, T3P (50% solution in ethyl acetate, 0.32 mL, 0.501 mmol) was added dropwise and the solution stirred at RT for 20 hours. The reaction mixture was diluted with DCM (10 mL) and washed with $NaHCO_3$ (2 x 10 mL). The organic layer was dried, filtered and concentrated *in vacuo* to remove excess solvent to form 9-membered ring intermediate **3.49**, which was used directly in the next step. To this resulting orange oil was added triethylamine (0.14 mL, 1.03 mmol) in THF (0.30 mL) and 4-(aminomethyl)pyridine (40.7 µL, 0.401 mmol) in THF (0.15 mL) gradually *via* a syringe pump over 10 minutes. The reaction mixture was stirred at RT for 72 hours, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 100% ethyl acetate) afforded the title compound, which was obtained as a white solid (76.0 mg, 53%), and exists in $CDCl_3$ as a 5:2 mixture of rotamers; R_f = 0.16 (9:1 ethyl acetate : methanol); MP = 162 – 165 °C; ν_{max}/cm^{-1} (thin film): 2935, 2810, 1638, 1602, 1452, 1414, 1321, 1137, 911, 728, 702, 555, 471; δ_H (400 MHz, $CDCl_3$) Data for major rotamer: 8.50 (2H, d, *J* = 5.0 Hz, H-19,20), 7.46 – 7.24 (5H, m, 5 x Ar**H** [overlapping]), 6.80 (2H, d, *J* = 5.0 Hz, H-18,21), 6.48 (1H, d, *J* = 10.0 Hz, H-1), 4.46 (1H, d, *J* = 19.0 Hz, H-16), 4.32 – 4.19 (1H, m, C**H₂** [overlapping]), 4.24 (1H, d, *J* = 19.0 Hz, H-16' [overlapping]), 4.12 (1H, d, *J* = 12.0 Hz, H-5), 4.17 – 4.07 (1H, m, C**H₂**), 3.46 – 3.36 (1H, m, H-2), 3.25 – 2.91 (1H, m, H-2' [overlapping]), 3.25 – 2.91 (1H, m, C**H₂** [overlapping]), 3.25 – 2.91 (1H, m, C**H₂** [overlapping]), 3.25 – 2.91 (1H, m, H-4 [overlapping]), 2.71 (1H, d, *J* = 12.0 Hz, H-

5’ [overlapping]), 2.76 – 2.49 (1H, m, H-12 [overlapping]), 2.43 – 2.30 (1H, m, H-13), 2.28 – 2.17 (1H, m, H-3 [overlapping]), 2.28 – 2.17 (1H, m, H-4’ [overlapping]), 2.10 – 2.01 (1H, m, H-12’), 1.97 – 1.76 (2H, m, H-14 [overlapping]), 1.76 – 1.67 (1H, m, H-3’), 1.47 – 1.36 (1H, m, H-13’). Full data for minor rotamer: 8.54 (2H, d, *J* = 5.0 Hz, H-19,20), 8.02 (1H, br t, *J* = 4.5 Hz, H-1), 7.46 – 7.24 (5H, m, 5 x Ar**H** [overlapping]), 7.14 (2H, d, *J* = 5.0 Hz, H-18,21), 4.59 (2H, s, H-16), 3.82 (2H, t, *J* = 5.5 Hz, H-22), 3.52 (2H, s, H-5), 3.25 – 2.91 (2H, m, H-2 [overlapping]), 3.25 – 2.91 (2H, m, H-23 [overlapping]), 2.76 – 2.49 (2H, m, H-14 [overlapping]), 2.76 – 2.49 (2H, m, H-4 [overlapping]), 2.76 – 2.49 (2H, m, H-12 [overlapping]), 1.97 – 1.76 (2H, m, H-13 [overlapping]), 1.63 (2H, p, *J* = 5.5 Hz, H-3); δ_C (100 MHz, $CDCl_3$) Data for major rotamer: 176.2 (C-15), 150.4 (C-19,20), 146.4 (C-17), 138.2 (C-6), 130.8 (C-7,11), 128.8 (C-8,10), 128.7 (C-9), 120.9 (C-18,21), 58.6 (C-5), 56.4 (C-12), 55.4 (C-4), 54.3 (C-16), 46.4 (**C**H_2), 46.0 (**C**H_2), 45.2 (C-2), 32.4 (C-14), 24.8 (C-3), 20.9 (C-13). Full data for minor rotamer: 173.0 (C-15), 150.3 (C-19,20), 146.2 (C-17), 137.2 (C-6), 129.8 (C-7,11), 127.7 (C-8,9,10 [overlapping]), 122.7 (C-18,21), 59.5 (C-5), 54.1 (C-4), 51.8 (C-12), 49.1 (C-23), 48.1 (C-16), 43.5 (C-2), 43.1 (C-22), 29.8 (C-14), 24.1 (C-3), 22.5 (C-13); HRMS (ESI^+): calcd. for $C_{22}H_{31}N_4O_3S$, 431.2111. Found: $[MH]^+$, 431.2109 (0.6 ppm error).

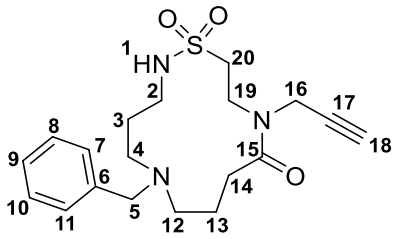
3.65: 6-Benzyl-11-(2,2-difluoroethyl)-1-thia-2,6,11-triazacyclotridecan-10-one 1,1-dioxide



To a round-bottomed flask 4-(benzyl(3-(vinylsulfonamido)propyl)amino)butanoic acid (114 mg, 0.334 mmol) was dissolved in chloroform (5.0 mL) and DIPEA (108 µL, 0.618 mmol) was added dropwise. Then, T3P (50% solution in ethyl acetate, 0.32 mL, 0.501 mmol) was added dropwise and the solution stirred at RT for 20 hours. The reaction mixture was diluted with DCM (10 mL) and washed with $NaHCO_3$ (2 x 10 mL). The organic layer was dried, filtered and concentrated *in vacuo* to remove excess solvent to form 9-membered ring intermediate **3.49**, which was used directly in the next step. To this resulting orange oil was added triethylamine (0.14 mL, 1.03 mmol) in THF (0.30 mL) and 2,2-difluoroethylamine (28.7 µL, 0.407 mmol) in THF (0.15 mL) gradually *via* a syringe pump over 10 minutes. The reaction mixture was stirred at RT for 72 hours, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 ethyl acetate : hexane → 100% ethyl acetate) afforded the title compound, which was obtained as a pale yellow oil (74.5 mg, 55%), and

exists in $CDCl_3$ as a 10:9 mixture of rotamers; R_f = 0.18 (1:1 ethyl acetate : hexane); ν_{max}/cm^{-1} (thin film): 3234, 2939, 2815, 1644, 1452, 1415, 1323, 1302, 1138, 1114, 1094, 910, 728, 701; δ_H (400 MHz, $CDCl_3$) Data for major rotamer: 8.25 (1H, br s, H-1), 7.45 – 7.22 (5H, m, 5 x Ar**H** [overlapping]), 6.11 (1H, tt, *J* = 57.0, 4.5 Hz, H-17), 3.96 – 3.85 (2H, m, H-18/19), 3.60 (2H, td, *J* = 14.0, 4.5 Hz, H-16), 3.50 (2H, s, H-5), 3.19 (2H, t, *J* = 5.5 Hz, H-18/19), 3.14 – 2.88 (2H, m, H-2 [overlapping]), 2.63 (2H, t, *J* = 6.5 Hz, H-14), 2.60 – 2.52 (2H, m, H-12), 2.49 (2H, t, *J* = 5.0 Hz, H-4), 1.84 (2H, p, *J* = 6.5 Hz, H-13 [overlapping]), 1.55 (2H, p, *J* = 5.5 Hz, H-3). Diagnostic data for minor rotamer: 7.45 – 7.22 (5H, m, 5 x Ar**H** [overlapping]), 6.42 – 6.33 (1H, m, H-1), 5.69 (1H, tt, *J* = 55.0, 3.5 Hz, H-17), 4.33 – 4.21 (1H, m, C**H₂**), 4.09 (1H, d, *J* = 12.0 Hz, H-5 [overlapping]), 4.15 – 3.99 (1H, m, C**H₂** [overlapping]), 3.46 – 3.29 (1H, m, H-2 [overlapping]), 3.46 – 3.29 (1H, m, C**H₂** [overlapping]), 3.14 – 2.88 (1H, m, C**H₂** [overlapping]), 3.14 – 2.88 (1H, m, H-2' [overlapping]), 2.72 (1H, d, *J* = 12.0 Hz, H-5'), 2.43 – 2.30 (1H, m, H-3/13), 2.28 – 2.01 (1H, m, H-14 [overlapping]), 2.28 – 2.01 (1H, m, H-3/13 [overlapping]), 2.28 – 2.01 (2H, m, C**H₂** [overlapping]), 1.96 – 1.80 (1H, m, H-14' [overlapping]), 1.77 – 1.64 (1H, m, H-3/13'), 1.51 – 1.38 (1H, m, H-3/13'); δ_C (100 MHz, $CDCl_3$) Data for major rotamer: 173.7 (C-15), 137.1 (C-6), 129.9 (C-7,11), 128.7 (C-8,10), 127.78 (C-9), 113.5 (C-17, d, $^1J_{CF}$ = 242.3 Hz), 59.7 (C-5), 54.5 (C-4), 51.4 (C-12), 50.1 (C-16, d, $^2J_{CF}$ = 27.8 Hz), 49.4 (C-18/19), 45.0 (C-18/19), 43.7 (C-2), 29.4 (C-14), 23.9 (C-3), 22.1 (C-13). Full data for minor rotamer: 175.9 (C-15), 138.2 (C-6), 130.4 (C-7,11), 128.8 (C-8,10), 127.75 (C-9), 113.9 (C-17, d, $^1J_{CF}$ = 243.4 Hz), 58.6 (C-5), 56.4 (**C**H_2), 55.6 (**C**H_2), 52.8 (C-16, d, $^2J_{CF}$ = 24.0 Hz), 46.5 (**C**H_2), 46.1 (**C**H_2), 45.2 (**C**H_2), 32.3 (C-14), 24.7 (C-3/13), 20.7 (C-3/13); δ_F (282 MHz, $CDCl_3$) −120.72 (1F, m, CH**F₂**), −121.73 (1F, ddt, *J* = 234.0, 54.5, 15.0 Hz, CH**F₂**), −122.90 (1F, m, CH**F₂**); HRMS (ESI^+): calcd. for $C_{18}H_{28}F_2N_3O_3S$, 404.1814. Found: $[MH]^+$, 404.1811 (0.6 ppm error).

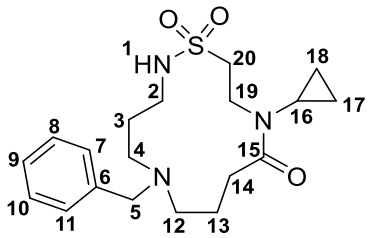
3.66: 6-Benzyl-11-(prop-2-yn-1-yl)-1-thia-2,6,11-triazacyclotridecan-10-one 1,1-dioxide



To a round-bottomed flask 4-(benzyl(3-(vinylsulfonamido)propyl)amino)butanoic acid (114 mg, 0.334 mmol) was dissolved in chloroform (5.0 mL) and DIPEA (108 µL, 0.618 mmol) was added dropwise. Then, T3P (50% solution in ethyl acetate, 0.32 mL, 0.501 mmol) was added dropwise and the solution stirred at RT for 20 hours. The reaction mixture was diluted with DCM (10 mL) and washed with $NaHCO_3$ (2 x 10 mL). The organic layer was dried, filtered and

concentrated *in vacuo* to remove excess solvent to form 9-membered ring intermediate **3.49**, which was used directly in the next step. To this resulting orange oil was added triethylamine (0.14 mL, 1.03 mmol) in THF (0.30 mL) and propargylamine (25.3 µL, 0.398 mmol) in THF (0.15 mL) gradually *via* a syringe pump over 10 minutes. The reaction mixture was stirred at RT for 72 hours, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 ethyl acetate : hexane) afforded the title compound, which was obtained as a white solid (65.4 mg, 52%), and exists in $CDCl_3$ as a 5:3 mixture of rotamers; R_f = 0.54 (100% ethyl acetate); MP = 124 – 127 °C; ν_{max}/cm^{-1} (thin film): 3264, 2932, 2814, 1642, 1452, 1322, 1300, 1136, 975, 911, 726, 702, 536; δ_H (400 MHz, $CDCl_3$) Data for major rotamer: 7.40 – 7.21 (5H, m, 5 x Ar**H** [overlapping]), 6.33 – 6.27 (1H, m, H-1), 4.16 – 3.94 (2H, m, H-19 [overlapping]), 4.16 – 3.94 (2H, m, H-16 [overlapping]), 4.06 (1H, d, *J* = 13.0 Hz, H-5 [overlapping]), 3.37 – 3.23 (2H, m, H-2 [overlapping]), 3.16 – 3.05 (2H, m, H-20 [overlapping]), 2.94 (1H, t, *J* = 12.5 Hz, H-4), 2.75 (1H, d, *J* = 13.0 Hz, H-5'), 2.45 – 2.29 (1H, m, H-13), 2.26 – 1.97 (1H, m, H-3 [overlapping]), 2.26 – 1.97 (1H, m, H-18 [overlapping]), 2.26 – 1.97 (2H, m, H-12 [overlapping]), 2.26 – 1.97 (1H, m, H-4' [overlapping]), 2.26 – 1.97 (2H, m, H-14 [overlapping]), 1.72 – 1.62 (1H, m, H-3'), 1.52 – 1.40 (1H, m, H-13'). Full data for minor rotamer: 8.32 (1H, t, *J* = 5.0 Hz, H-1), 7.40 – 7.21 (5H, m, 5 x Ar**H** [overlapping]), 4.21 (2H, d, *J* = 2.5 Hz, H-16), 4.16 – 3.94 (2H, m, H-19 [overlapping]), 3.50 (2H, s, H-5), 3.37 – 3.23 (2H, m, H-20 [overlapping]), 3.16 – 3.05 (2H, m, H-2 [overlapping]), 2.65 – 2.54 (2H, m, H-14 [overlapping]), 2.65 – 2.54 (2H, m, H-12 [overlapping]), 2.49 (2H, t, *J* = 5.5 Hz, H-4), 2.24 (1H, t, *J* = 2.5 Hz, H-18), 1.82 (2H, p, *J* = 6.0 Hz, H-13), 1.59 (2H, p, *J* = 5.5 Hz, H-3); δ_C (100 MHz, $CDCl_3$) Data for major rotamer: 176.0 (C-15), 138.2 (C-6), 130.2 (C-7,11), 128.7 (C-8,10 [overlapping]), 127.66 (C-9), 78.3 (C-18), 73.0 (C-17), 58.3 (C-5), 56.1 (C-12), 54.6 (C-4), 49.0 (C-2), 46.5 (C-20), 45.2 (C-19), 40.9 (C-16), 32.0 (C-14), 24.9 (C-3), 20.6 (C-13). Full data for minor rotamer: 172.0 (C-15), 137.1 (C-6), 130.0 (C-7,11), 128.7 (C-8,10 [overlapping]), 127.72 (C-9), 79.5 (C-18), 72.3 (C-17), 59.8 (C-5), 54.7 (C-4), 51.5 (C-12), 44.5 (C-20), 43.9 (C-2), 43.7 (C-19), 35.3 (C-16), 29.2 (C-14), 23.9 (C-3), 22.2 (C-13); HRMS (ESI^+): calcd. for $C_{19}H_{27}N_3NaO_3S$, 400.1665. Found: $[MNa]^+$, 400.1665 (0.0 ppm error).

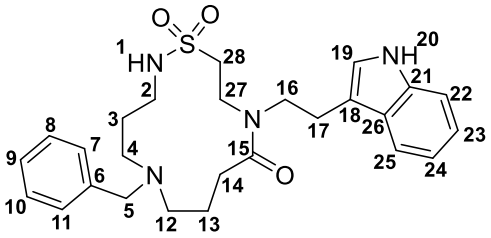
3.67: 6-Benzyl-11-cyclopropyl-1-thia-2,6,11-triazacyclotridecan-10-one 1,1-dioxide



To a round-bottomed flask 4-(benzyl(3-(vinylsulfonamido)propyl)amino)butanoic acid (114 mg, 0.334 mmol) was dissolved in chloroform (5.0 mL) and DIPEA (108 µL, 0.618 mmol) was added dropwise. Then, T3P (50% solution in ethyl acetate, 0.32 mL, 0.501 mmol) was added dropwise and the solution stirred at RT for 20 hours. The reaction mixture was diluted with DCM (10 mL) and washed with $NaHCO_3$ (2 x 10 mL). The organic layer was dried, filtered and concentrated *in vacuo* to remove excess solvent to form 9-membered ring intermediate **3.49**, which was used directly in the next step. To this resulting orange oil was added triethylamine (0.14 mL, 1.03 mmol) in THF (0.30 mL) and cyclopropylamine (28.0 µL, 0.402 mmol) in THF (0.15 mL) gradually *via* a syringe pump over 10 minutes. The reaction mixture was stirred at RT for 72 hours, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 100% ethyl acetate) afforded the title compound, which was obtained as a pale brown solid (51.2 mg, 40%), and exists in $CDCl_3$ as a 20:1 mixture of rotamers; R_f = 0.28 (100% ethyl acetate); MP = 102 – 105 °C; ν_{max}/cm^{-1} (thin film): 3206, 2931, 2807, 1633, 1452, 1416, 1374, 1321, 1298, 1143, 1093, 912, 860, 729, 702, 475; δ_H (400 MHz, $CDCl_3$) Data for major rotamer: 7.38 – 7.20 (5H, m, 5 x Ar**H**), 6.24 (1H, d, *J* = 6.0 Hz, H-1), 4.18 – 4.05 (1H, m, H-19), 4.04 – 3.88 (1H, m, H-5 [overlapping]), 4.04 – 3.88 (1H, m, H-20 [overlapping]), 3.42 – 3.00 (2H, m, H-2 [overlapping]), 3.42 – 3.00 (1H, m, H-19' [overlapping]), 3.21 – 3.00 (1H, m, H-20' [overlapping]), 2.98 – 2.82 (1H, m, H-5' [overlapping]), 2.98 – 2.82 (1H, m, H-4 [overlapping]), 2.67 (1H, p, *J* = 5.5 Hz, H-16), 2.56 – 2.29 (1H, m, H-13 [overlapping]), 2.56 – 2.29 (2H, m, H-12 [overlapping]), 2.28 – 2.13 (2H, m, H-14 [overlapping]), 2.28 – 2.13 (1H, m, H-4' [overlapping]), 2.12 – 1.98 (1H, m, H-3), 1.72 – 1.59 (1H, m, H-3'), 1.53 – 1.39 (1H, m, H-13'), 0.93 – 0.67 (3H, m, 3 x H-17,18), 0.63 – 0.48 (1H, m, 1 x H-17,18). Diagnostic data for minor rotamer: 8.07 (1H, br s, H-1), 4.51 (2H, t, *J* = 5.5 Hz, C**H₂**), 3.64 (2H, t, *J* = 3.0 Hz, C**H₂**), 3.51 (2H, s, H-5), 3.44 (2H, t, *J* = 5.5 Hz, C**H₂**), 1.91 – 1.81 (2H, m, C**H₂**), 1.79 – 1.72 (2H, m, C**H₂**); δ_C (100 MHz, $CDCl_3$) Data for major rotamer: 177.1 (C-15), 138.0 (C-6), 130.2 (C-7,11), 128.5 (C-8,10), 127.4 (C-9), 58.3 (C-5), 55.6 (C-12), 53.7 (C-4), 47.1 (C-20), 44.1 (C-2/19), 43.8 (C-2/19), 33.0 (C-14), 32.3 (C-16), 25.2 (C-3), 19.9

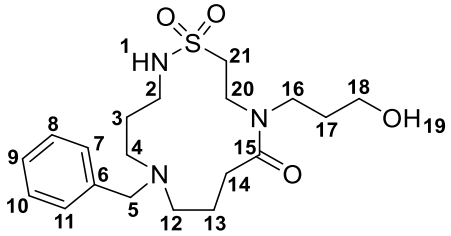
(C-13), 10.6 (C-17/18), 9.0 (C-17/18); HRMS (ESI$^+$): calcd. for $C_{19}H_{30}N_3O_3S$, 380.2002. Found: $[MH]^+$, 380.2005 (−0.7 ppm error).

3.68: 11-(2-(1*H*-Indol-3-yl)ethyl)-6-benzyl-1-thia-2,6,11-triazacyclotridecan-10-one 1,1-dioxide



To a round-bottomed flask 4-(benzyl(3-(vinylsulfonamido)propyl)amino)butanoic acid (114 mg, 0.334 mmol) was dissolved in chloroform (5.0 mL) and DIPEA (108 µL, 0.618 mmol) was added dropwise. Then, T3P (50% solution in ethyl acetate, 0.32 mL, 0.501 mmol) was added dropwise and the solution stirred at RT for 20 hours. The reaction mixture was diluted with DCM (10 mL) and washed with $NaHCO_3$ (2 x 10 mL). The organic layer was dried, filtered and concentrated *in vacuo* to remove excess solvent to form 9-membered ring intermediate **3.49**, which was used directly in the next step. To this resulting orange oil was added triethylamine (0.14 mL, 1.03 mmol) in THF (0.30 mL) and tryptamine (65.6 mg, 0.409 mmol) in THF (0.15 mL) gradually *via* a syringe pump over 10 minutes. The reaction mixture was stirred at RT for 72 hours, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 7:3 hexane : ethyl acetate → 1:1 ethyl acetate : hexane → 100% ethyl acetate) afforded the title compound, which was obtained as a pink solid (59.4 mg, 37%); R_f = 0.48 (100% ethyl acetate); MP = 203 – 206 °C, ν_{max}/cm^{-1} (thin film): 3300, 2928, 1732, 1621, 1456, 1324, 1139, 1097, 911, 741; δ_H (400 MHz, $(CD_3)_2SO$) 10.84 (1H, d, *J* = 2.5 Hz, H-20), 7.58 (1H, d, *J* = 7.5 Hz, H-22/25), 7.33 (1H, d, *J* = 8.0 Hz, H-22/25), 7.39 – 7.21 (5H, m, 5 x Ar**H**), 7.17 (1H, t, *J* = 4.5 Hz, H-1), 7.14 (1H, d, *J* = 2.5 Hz, H-19), 7.06 (1H, t, *J* = 7.5 Hz, H-23/24), 6.98 (1H, t, *J* = 7.5 Hz, H-23/24), 3.45 (2H, s, H-5), 3.48 – 3.35 (6H, m, 3 x CH_2), 3.06 (2H, q, *J* = 5.5 Hz, H-2), 2.85 (2H, t, *J* = 7.5 Hz, H-17), 2.43 (2H, t, *J* = 5.5 Hz, H-4), 2.36 – 2.20 (2H, m, H-14 [overlapping]), 2.36 – 2.20 (2H, m, H-12 [overlapping]), 1.74 – 1.66 (2H, m, C-3), 1.65 – 1.56 (2H, m, C-13); δ_C (100 MHz, $(CD_3)_2SO$) 172.5 (C-15), 139.4 (C-6), 136.3 (C-21), 129.0 (C-7,11), 128.2 (C-8,10), 127.3 (C-26), 126.9 (C-9), 122.8 (C-19), 121.0 (C-23/24), 118.5 (Ar**C**H), 118.3 (Ar**C**H), 111.6 (C-18), 111.5 (C-22/25), 58.1 (C-5), 53.0 (C-12), 49.1 (C-4), 48.1 (**C**H_2), 47.1 (C-16), 43.4 (**C**H_2), 39.5 (C-2 [hidden by NMR solvent]), 32.5 (C-14), 25.1 (C-3), 23.5 (C-17), 23.4 (C-13); HRMS (ESI$^+$): calcd. for $C_{26}H_{34}N_4NaO_3S$, 505.2244. Found: $[MNa]^+$, 505.2257 (−2.7 ppm error).

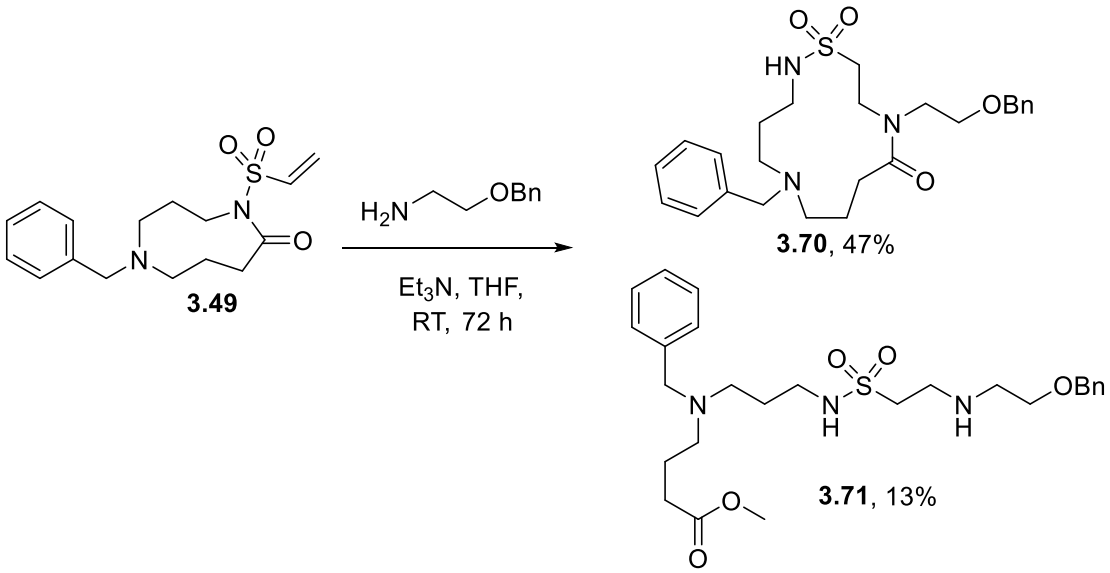
3.69: 6-Benzyl-11-(3-hydroxypropyl)-1-thia-2,6,11-triazacyclotridecan-10-one 1,1-dioxide



To a round-bottomed flask 4-(benzyl(3-(vinylsulfonamido)propyl)amino)butanoic acid (114 mg, 0.334 mmol) was dissolved in chloroform (5.0 mL) and DIPEA (108 µL, 0.618 mmol) was added dropwise. Then, T3P (50% solution in ethyl acetate, 0.32 mL, 0.501 mmol) was added dropwise and the solution stirred at RT for 20 hours. The reaction mixture was diluted with DCM (10 mL) and washed with $NaHCO_3$ (2 x 10 mL). The organic layer was dried, filtered and concentrated *in vacuo* to remove excess solvent to form 9-membered ring intermediate **3.49**, which was used directly in the next step. To this resulting orange oil was added triethylamine (0.14 mL, 1.03 mmol) in THF (0.30 mL) and 3-amino-1-propanol (30.9 µL, 0.404 mmol) in THF (0.15 mL) gradually *via* a syringe pump over 10 minutes. The reaction mixture was stirred at RT for 72 hours, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 9:1 ethyl acetate : methanol) afforded the title compound, which was obtained as a pale brown oil (44.5 mg, 34%), and exists in $CDCl_3$ as a 5:4 mixture of rotamers; R_f = 0.26 (9:1 ethyl acetate : methanol); ν_{max}/cm^{-1} (thin film): 3226, 2930, 2809, 1619, 1453, 1322, 1260, 1138, 1095, 1054, 912, 727, 701, 539; δ_H (400 MHz, $CDCl_3$) Data for major rotamer: 7.88 (1H, br s, H-1), 7.39 – 7.23 (5H, m, 5 x Ar**H** [overlapping]), 3.80 (2H, t, *J* = 5.5 Hz, H-20), 3.55 – 3.45 (4H, m, H-16,18 [overlapping]), 3.51 (2H, s, H-5 [overlapping]), 3.20 (2H, t, *J* = 5.5 Hz, H-21), 3.16 – 3.08 (2H, m, H-2), 2.62 – 2.54 (2H, m, H-14 [overlapping]), 2.62 – 2.54 (2H, m, H-12 [overlapping]), 2.52 (2H, t, *J* = 5.0 Hz, H-4), 1.81 (2H, p, *J* = 6.5 Hz, H-13), 1.72 (2H, p, *J* = 6.0 Hz, H-17), 1.64 (2H, p, *J* = 5.0 Hz, H-3). Full data for minor rotamer: 7.39 – 7.23 (5H, m, 5 x Ar**H** [overlapping]), 6.41 – 6.34 (1H, m, H-1), 4.18 – 3.97 (1H, m, H-20/21 [overlapping]), 4.18 – 3.97 (1H, m, H-20/21 [overlapping]), 4.06 (1H, d, *J* = 13.0 Hz, H-5 [overlapping]), 3.55 – 3.45 (2H, m, H-18 [overlapping]), 3.28 (2H, t, *J* = 8.0 Hz, H-16 [overlapping]), 3.37 – 3.23 (2H, m, H-2 [overlapping]), 3.37 – 3.23 (1H, m, H-20'/21' [overlapping]), 3.07 – 2.99 (1H, m, H-20'/21'), 2.99 – 2.90 (1H, m, H-4), 2.75 (1H, d, *J* = 13.0 Hz, H-5'), 2.45 – 2.31 (1H, m, H-13), 2.23 – 2.03 (2H, m, H-3 [overlapping]), 2.23 – 2.03 (2H, m, H-14 [overlapping]), 2.23 – 2.03 (2H, m, H-12 [overlapping]), 2.23 – 2.03 (1H, m, H-4' [overlapping]), 1.59 – 1.52 (2H, m, H-17), 1.51 – 1.41 (1H, m, H-13'); δ_C (100 MHz, $CDCl_3$) Data for major rotamer: 174.0 (C-15), 137.3 (C-6), 129.9 (C-7,11), 128.7 (C-8,10), 127.8 (C-9), 59.7 or 59.5 (C-5), 58.4 (C-18), 54.0 (C-4), 51.9 (C-12), 49.1 (C-21), 43.5 (C-2), 42.5 (C-20),

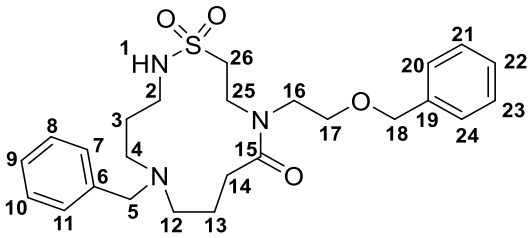
41.5 (C-16), 30.0 (C-17), 29.9 (C-14), 24.2 (C-3), 22.6 (C-13). Full data for minor rotamer: 175.8 (C-15), 138.3 (C-6), 130.5 (C-7,11), 128.6 (C-8,10), 127.4 (C-9), 59.7 or 59.5 (C-18), 58.6 (C-5), 56.4 (C-12), 54.5 (C-4), 48.2 (C-16), 46.6 (C-20/21), 44.6 (C-20/21), 44.5 (C-2), 32.0 (C-14), 31.4 (C-17), 25.0 (C-3), 20.9 (C-13); HRMS (ESI$^+$): calcd. for $C_{19}H_{31}N_3NaO_4S$, 420.1927. Found: $[MNa]^+$, 420.1928 (−0.1 ppm error).

3.70: 6-Benzyl-11-(2-(benzyloxy)ethyl)-1-thia-2,6,11-triazacyclotridecan-10-one 1,1-dioxide and 3.71: methyl 4-(benzyl(3-((2-((2-(benzyloxy)ethyl)amino)ethyl)sulfonamido)propyl)amino)butanoate



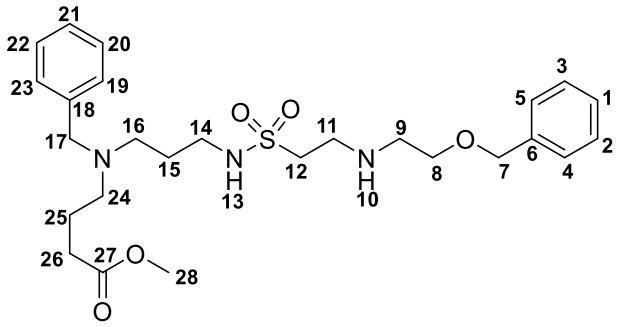
To a round-bottomed flask 4-(benzyl(3-(vinylsulfonamido)propyl)amino)butanoic acid (107 mg, 0.313 mmol) was dissolved in chloroform (5.0 mL) and DIPEA (101 µL, 0.579 mmol) was added dropwise. Then, T3P (50% solution in ethyl acetate, 0.30 mL, 0.500 mmol) was added dropwise and the solution stirred at RT for 20 hours. The reaction mixture was diluted with DCM (10 mL) and washed with $NaHCO_3$ (2 x 10 mL). The organic layer was dried, filtered and concentrated *in vacuo* to remove excess solvent to form 9-membered ring intermediate **3.49**, which was used directly in the next step. To this resulting orange oil was added triethylamine (0.13 mL, 0.939 mmol) in THF (0.30 mL) and 2-(benzyloxy)-1-ethanamine (51.8 µL, 0.376 mmol) in THF (0.15 mL) gradually *via* a syringe pump over 10 minutes. The reaction mixture was stirred at RT for 72 hours, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 ethyl acetate : hexane) afforded the two products: **3.70** (69.0 mg, 47%) and **3.71** (19.0 mg, 13%), with the data for each provided below.

3.70: 6-Benzyl-11-(2-(benzyloxy)ethyl)-1-thia-2,6,11-triazacyclotridecan-10-one 1,1-dioxide



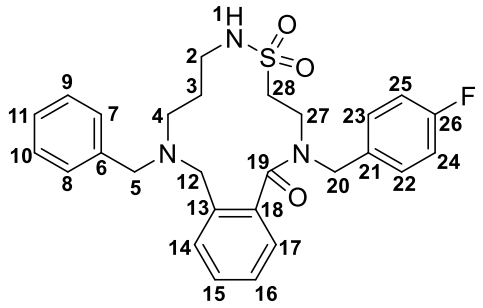
The title compound was obtained as a colourless oil (69.0 mg, 47%), and exists in $CDCl_3$ as a 2:1 mixture of rotamers; R_f = 0.50 (1:1 ethyl acetate : methanol); ν_{max}/cm^{-1} (thin film): 3280, 2930, 1640, 1453, 1324, 1143, 1099, 739, 700; δ_H (400 MHz, $CDCl_3$) Data for major rotamer: 7.39 – 7.19 (10H, m, 10 x Ar**H** [overlapping]), 6.39 – 6.31 (1H, m, H-1), 4.43 (2H, d, *J* = 5.0 Hz, H-18), 4.20 – 4.08 (1H, m, H-25/26), 4.04 (1H, d, *J* = 13.0 Hz, H-5 [overlapping]), 4.08 – 3.95 (1H, m, H-25/26 [overlapping]), 3.48 – 3.39 (2H, m, H-17 [overlapping]), 3.48 – 3.39 (2H, m, H-16 [overlapping]), 3.35 – 3.23 (1H, m, H-2 [overlapping]), 3.35 – 3.23 (1H, m, H-25/26 [overlapping]), 3.16 – 3.08 (1H, m, H-2'), 3.06 – 2.97 (1H, m, H-25/26 [overlapping]), 2.96 – 2.86 (1H, m, H-4), 2.77 (1H, d, *J* = 12.5 Hz, H-5'), 2.42 – 2.29 (1H, m, H-13), 2.23 – 2.14 (1H, m, H-4' [overlapping]), 2.23 – 1.98 (1H, m, H-3 [overlapping]), 2.23 – 1.98 (2H, m, H-14 [overlapping]), 2.23 – 1.98 (2H, m, H-12 [overlapping]), 1.84 – 1.62 (1H, m, H-3' [overlapping]), 1.47 – 1.36 (1H, m, H-13'). Full data for minor rotamer: 8.01 (1H, br t, *J* = 4.5 Hz, H-1), 7.39 – 7.19 (10H, m, 10 x Ar**H** [overlapping]), 4.48 (2H, s, H-18), 3.89 (2H, t, *J* = 5.0 Hz, H-25/26), 3.67 (2H, t, *J* = 5.0 Hz, H-17), 3.53 (2H, t, *J* = 5.0 Hz, H-16), 3.50 (2H, s, H-5), 3.35 – 3.23 (2H, m, H-25/26 [overlapping]), 3.06 – 2.97 (2H, m, H-2 [overlapping]), 2.62 – 2.53 (2H, m, H-14 [overlapping]), 2.62 – 2.53 (2H, m, H-12 [overlapping]), 2.51 – 2.43 (2H, m, H-4), 1.80 (2H, p, *J* = 6.5 Hz, H-13), 1.54 (2H, p, *J* = 5.5 Hz, H-3); δ_C (100 MHz, $CDCl_3$) Data for major rotamer: 176.1 (C-15), 138.3 (C-6), 137.7 (C-19), 130.2 (C-7,11), 128.60 (C-8,10,21,23) 127.6 (C-20,24), 73.3 (C-18), 67.9 (C-17), 58.5 (C-5), 56.2 (C-12), 54.63 (C-4), 50.9 (C-16), 46.6 (C-25/26), 44.9 (C-25/26), 44.5 (C-2), 32.2 (C-14), 25.0 (C-3), 20.7 (C-13). Diagnostic data for minor rotamer: 172.6 (C-15), 137.8 (C-19), 137.3 (C-6), 129.9 (C-7,11), 127.99 (C-9/22), 127.7 (C-9/22), 73.5 (C-18), 68.8 (C-19), 59.7 (C-5), 54.57 (C-4), 51.7 (C-12), 49.5 (C-25/26), 47.6 (C-16), 44.7 (C-25/26), 43.6 (C-2), 29.6 (C-14), 24.1 (C-3), 22.4 (C-13). The remaining aryl peaks are indistinguishable between the major (Ar**C**H) and minor (2 x Ar**C**H) rotamers: 128.7, 128.63, 127.95, 127.9, 127.5; HRMS (ESI^+): calcd. for $C_{25}H_{36}N_3O_4S$, 474.2421. Found: $[MH]^+$, 474.2423 (−0.3 ppm error).

3.71: Methyl 4-(benzyl(3-((2-((2-(benzyloxy)ethyl)amino)ethyl)sulfonamido)propyl)amino)butanoate



The product was obtained as a pale yellow oil (19.9 mg, 13%); R_f = 0.51 (1:1 ethyl acetate : methanol); ν_{max}/cm^{-1} (thin film): 3289, 2929, 1649, 1542, 1453, 1324, 1140, 1112, 1028, 738, 699; δ_H (400 MHz, $CDCl_3$) 7.38 – 7.22 (10H, m, 10 x Ar**H**), 6.16 (1H, br t, *J* = 6.0 Hz, H-10), 4.52 (2H, s, H-7), 3.73 (2H, t, *J* = 6.0 Hz, H-12), 3.55 (2H, t, *J* = 6.0 Hz, H-8), 3.52 (2H, s, H-17), 3.44 (2H, q, *J* = 6.0 Hz, H-9), 3.33 (3H, s, H-28), 3.17 (2H, t, *J* = 6.0 Hz, H-11), 3.11 (2H, t, *J* = 6.0 Hz, H-14), 2.53 (2H, t, *J* = 6.0 Hz, H-16), 2.43 (2H, t, *J* = 7.0 Hz, H-24), 2.19 (2H, t, *J* = 7.0 Hz, H-26), 1.84 (2H, p, *J* = 7.0 Hz, H-25), 1.69 (2H, p, *J* = 6.0 Hz, H-15); δ_C (100 MHz, $CDCl_3$) 173.0 (C-27), 138.7 (C-18), 138.1 (C-6), 129.3 (C-19,23), 128.6 (2 x Ar**C**H), 128.6 (2 x Ar**C**H), 128.0 (C-4,5), 127.9 (C-1/21), 127.4 (C-1/21), 73.2 (C-7), 69.0 (C-8), 66.9 (C-12), 59.1 (C-28), 58.8 (C-17), 53.1 (C-24), 52.6 (C-16), 51.4 (C-11), 42.9 (C-14), 39.4 (C-9), 34.2 (C-26), 26.3 (C-15), 22.8 (C-25); HRMS (ESI^+): calcd. for $C_{26}H_{40}N_3O_5S$, 506.2683. Found: $[MH]^+$, 506.2687 (−0.7 ppm error).

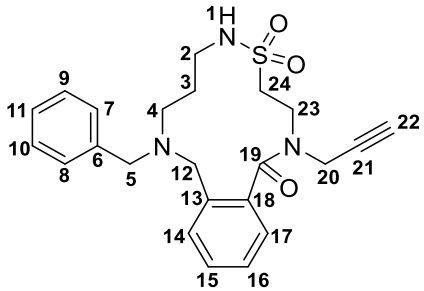
3.72: 10-Benzyl-2-(4-fluorobenzyl)-3,4,6,7,8,9,10,11-octahydrobenzo[*h*][1]thia[2,6,11]triazacyclotridecin-1(2*H*)-one 5,5-dioxide



To a round-bottomed flask was added 2-((benzyl(3-(vinylsulfonamido)propyl)amino)methyl)benzoic acid (97.1 mg, 0.250 mmol), which was dissolved in chloroform (7.0 mL) and DIPEA (0.09 mL, 0.520 mmol) was added dropwise. T3P (50% solution in ethyl acetate, 0.24 mL, 0.375 mmol) was added dropwise and the solution

stirred at RT for 18 hours. The reaction mixture was diluted with DCM (10 mL) and washed with $NaHCO_3$ (2 x 10 mL). The organic layer was dried, filtered and concentrated *in vacuo* to remove excess solvent to form 9-membered ring intermediate **3.50**, which was used directly in the next step. To this resulting beige oil was added DIPEA (0.13 mL, 0.725 mmol) in THF (2.0 mL) and 4-fluorobenzylamine (34.3 µL, 0.300 mmol) in a single portion. The reaction mixture was stirred at RT for 72 hours. Then, the solution was diluted in DCM (15 mL) and washed with $NaHCO_3$ (2 x 10 mL). The organic layer was dried, filtered and concentrated *in vacuo* to yield the title compound, which was obtained as a colourless oil (107 mg, 86%), and exists in $CDCl_3$ as a 10:1 mixture of rotamers. The ^{1}H NMR spectrum is severely affected by rotameric broadening, with product identity and purity best determined using ^{13}C NMR data; R_f = 0.26 (1:1 ethyl acetate : hexane); ν_{max}/cm^{-1} (thin film): 2953, 2927, 1718, 1673, 1509, 1452, 1308, 1221, 1141, 1086, 824, 734, 701; δ_H (400 MHz, $CDCl_3$) 7.39 – 7.21 (9H, m, 9 x Ar**H**), 7.15 (1H, d, *J* = 7.0 Hz, Ar**H**), 7.05 – 6.96 (3H, m, 3 x Ar**H**), 4.03 – 3.80 (7H, m, 3.5 x C**H$_2$**), 3.19 (2H, t, *J* = 6.0 Hz, C**H$_2$**); δ_C (100 MHz, $CDCl_3$) 172.2 (C-19), 162.1 (C-26, d, $^1J_{CF}$ = 244.5 Hz), 139.9 (C-18), 136.03 (C-6/13), 135.97 (C-6/13), 135.4 (C-21, d, $^4J_{CF}$ = 3.3 Hz), 130.1 (C-7,8), 129.9 (C-22,23, d, $^3J_{CF}$ = 7.7 Hz), 129.5 (Ar**C**H), 128.7 (Ar**C**H), 128.4 (C-9,10), 127.7 (Ar**C**H), 127.4 (Ar**C**H), 125.2 (Ar**C**H), 115.4 (C-24,25, d, $^2J_{CF}$ = 21.1 Hz), 56.6 (**C**H$_2$), 56.3 (**C**H$_2$), 54.8 (**C**H$_2$), 52.7 (**C**H$_2$), 49.4 (**C**H$_2$), 47.5 (**C**H$_2$), 43.2 (C-2), 25.2 (C-3); δ_F (282 MHz, $CDCl_3$) Major rotamer: −115.54 (1F, m, Ar**F**), minor rotamer −116.18 (1F, m, Ar**F**); HRMS (ESI$^+$): calcd. for $C_{27}H_{31}FN_3O_3S$, 496.2065. Found $[MH]^+$ 496.2064 (0.1 ppm error).

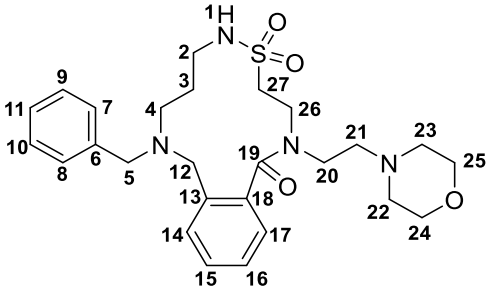
3.73: 10-Benzyl-2-(prop-2-yn-1-yl)-3,4,6,7,8,9,10,11-octahydrobenzo[*h*][1]thia[2,6,11]triazacyclotridecin-1(2*H*)-one 5,5-dioxide



To a round-bottomed flask was added 2-((benzyl(3-(vinylsulfonamido)propyl)amino)methyl)benzoic acid (97.1 mg, 0.250 mmol), which was dissolved in chloroform (7.0 mL) and DIPEA (0.09 mL, 0.520 mmol) was added dropwise. T3P (50% solution in ethyl acetate, 0.24 mL, 0.375 mmol) was added dropwise and the solution stirred at RT for 18 hours. The reaction mixture was diluted with DCM (10 mL) and washed with $NaHCO_3$ (2 x 10 mL). The organic layer was dried, filtered and concentrated *in vacuo* to

remove excess solvent to form 9-membered ring intermediate **3.50**, which was used directly in the next step. To this resulting beige oil was added DIPEA (0.13 mL, 0.725 mmol) in THF (2.0 mL) and propargylamine (19.1 µL, 0.300 mmol) in a single portion. The reaction mixture was stirred at RT for 72 hours. Then, the solution was diluted in DCM (15 mL) and washed with $NaHCO_3$ (2 x 10 mL). The organic layer was dried, filtered and concentrated *in vacuo* to yield the title compound, which was obtained as a colourless oil (87.1 mg, 82%). The ^{1}H NMR spectrum is severely affected by rotameric broadening, with product identity and purity best determined using ^{13}C NMR data; R_f = 0.28 (1:1 ethyl acetate : hexane); ν_{max}/cm^{-1} (thin film): 3284, 2927, 2842, 1716, 1676, 1452, 1306, 1141, 1085, 1016, 736, 702; δ_H (400 MHz, $CDCl_3$) 7.39 – 7.22 (8H, m, 8 x Ar**H**), 7.19 – 7.14 (1H, m, Ar**H**), 4.21 – 3.71 (6H, m, 3 x C**H$_2$**), 3.51 (2H, d, *J* = 2.5 Hz, H-20), 3.31 (2H, t, *J* = 6.5 Hz, H-23), 2.26 (1H, t, *J* = 2.5 Hz, H-22), 1.73 (2H, br s, H-3); δ_C (100 MHz, $CDCl_3$) 172.3 (C-19), 140.0 (C-6), 136.1 (C-13/18), 136.0 (C-13/18), 130.1 (C-7,8), 129.6 (Ar**C**H), 128.7 (Ar**C**H), 128.4 (C-9,10), 127.7 (Ar**C**H), 127.5 (Ar**C**H), 125.3 (Ar**C**H), 81.6 (C-22), 72.2 (C-21), 56.6 (C-5), 56.3 (**C**H$_2$), 54.8 (C-24), 49.5 (**C**H$_2$), 47.6 (**C**H$_2$), 42.9 (C-23), 38.1 (C-20), 25.3 (C-3); HRMS (ESI$^+$): calcd. for $C_{23}H_{27}N_3NaO_3S$, 448.1665. Found: $[MNa]^+$, 448.1666 (−0.3 ppm error).

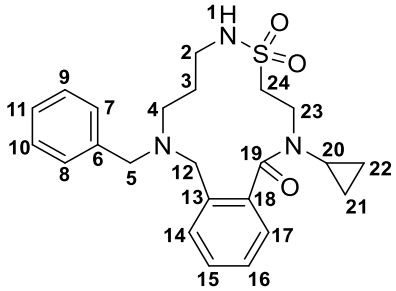
3.74: 10-Benzyl-2-(2-morpholinoethyl)-3,4,6,7,8,9,10,11-octahydrobenzo[*h*][1]thia[2,6,11]triazacyclotridecin-1(2*H*)-one 5,5-dioxide



To a round-bottomed flask was added 2-((benzyl(3-(vinylsulfonamido)propyl)amino)methyl)benzoic acid (97.1 mg, 0.250 mmol), which was dissolved in chloroform (7.0 mL) and DIPEA (0.09 mL, 0.520 mmol) was added dropwise. T3P (50% solution in ethyl acetate, 0.24 mL, 0.375 mmol) was added dropwise and the solution stirred at RT for 18 hours. The reaction mixture was diluted with DCM (10 mL) and washed with $NaHCO_3$ (2 x 10 mL). The organic layer was dried, filtered and concentrated *in vacuo* to remove excess solvent to form 9-membered ring intermediate **3.50**, which was used directly in the next step. To this resulting beige oil was added DIPEA (0.13 mL, 0.725 mmol) in THF (2.0 mL) and 4-(2-aminoethyl)morpholine (40.0 µL, 0.303 mmol) in a single portion. The reaction mixture was stirred at RT for 72 hours. Then, the solution was diluted in DCM (10

mL) and washed with water (2 x 10 mL) and brine (10 mL). The organic layer was dried, filtered and concentrated *in vacuo* to yield the title compound, which was obtained as a pale orange oil (98.5 mg, 79%). The ^{1}H NMR spectrum is severely affected by rotameric broadening, with product identity and purity best determined using ^{13}C NMR data; R_f = 0.06 (9:1 ethyl acetate : methanol); ν_{max}/cm^{-1} (thin film): 2934, 2816, 1717, 1677, 1452, 1300, 1140, 1116, 1086, 735, 702; δ_H (400 MHz, $CDCl_3$) 7.38 – 7.23 (7H, m, 7 x Ar**H**), 7.22 – 7.18 (1H, m, Ar**H**), 7.17 – 7.12 (1H, m, Ar**H**), 4.06 – 3.79 (2H, m, H-5 [overlapping]), 4.06 – 3.79 (2H, m, H-12 [overlapping]), 3.68 (4H, t, *J* = 4.5 Hz, H-24,25), 3.25 (2H, t, *J* = 6.5 Hz, H-26), 2.77 (2H, t, *J* = 6.0 Hz, H-20), 2.51 (2H, t, *J* = 6.0 Hz, H-21), 2.44 (4H, t, *J* = 4.5 Hz, H-22,23); δ_C (100 MHz, $CDCl_3$) 172.2 (C-19), 139.9 (C-6), 136.1 (C-13/18), 135.9 (C-13/18), 130.0 (C-7,8), 129.5 (Ar**C**H), 128.7 (Ar**C**H), 128.3 (C-9,10), 127.7 (Ar**C**H), 127.4 (Ar**C**H), 125.2 (Ar**C**H), 67.0 (C-24,25), 58.0 (C-21), 56.5 (C-5/12), 56.2 (C-5/12), 54.6 (C-27), 53.7 (C-22,23), 49.4 (**C**H_2), 47.5 (**C**H_2), 45.7 (C-20), 43.9 (C-26), 25.2 (C-3); HRMS (ESI^+): calcd. for $C_{26}H_{37}N_4O_4S$, 501.2530. Found: $[MH]^+$, 501.2530 (0.1 ppm error).

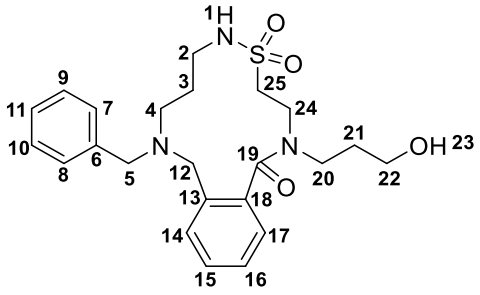
3.76: 10-Benzyl-2-cyclopropyl-3,4,6,7,8,9,10,11-octahydrobenzo[*h*][1]thia[2,6,11]triazacyclotridecin-1(2*H*)-one 5,5-dioxide



To a round-bottomed flask was added 2-((benzyl(3-(vinylsulfonamido)propyl)amino)methyl)benzoic acid (97.1 mg, 0.250 mmol), which was dissolved in chloroform (7.0 mL) and DIPEA (0.09 mL, 0.520 mmol) was added dropwise. T3P (50% solution in ethyl acetate, 0.24 mL, 0.375 mmol) was added dropwise and the solution stirred at RT for 18 hours. The reaction mixture was diluted with DCM (10 mL) and washed with $NaHCO_3$ (2 x 10 mL). The organic layer was dried, filtered and concentrated *in vacuo* to remove excess solvent to form 9-membered ring intermediate **3.50**, which was used directly in the next step. To this resulting beige oil was added DIPEA (0.10 mL, 0.575 mmol) in THF (2.0 mL) and cyclopropylamine (24.7 mg, 0.355 mmol) in a single portion. The reaction mixture was stirred at RT for 16 hours. Then, the solution was diluted in DCM (10 mL) and washed with $NaHCO_3$ (2 x 10 mL). The organic layer was dried, filtered and concentrated *in vacuo* to yield a residue. ^{1}H NMR indicated the reaction had not reached completion, so the

residue was dissolved in THF (2.0 mL) and cyclopropylamine (24.7 µL, 0.355 mmol) was added in a single portion. The solution was stirred for a further 72 hours at RT. Then, the reaction mixture was diluted in DCM (10 mL) and washed with $NaHCO_3$ (2 x 10 mL). The organic layer was dried, filtered and concentrated *in vacuo* to yield the title compound, which was obtained as a pale yellow oil (94.7 mg, 89%). The ^{1}H NMR spectrum is severely affected by rotameric broadening, with product identity and purity best determined using ^{13}C NMR data; R_f = 0.70 (9:1 ethyl acetate : methanol), and exists in $CDCl_3$ as a 10:1 mixture of rotamers; ν_{max}/cm^{-1} (thin film): 2923, 2850, 1674, 1450, 1335, 1268, 1148, 1014, 779, 758, 727, 704; δ_H (400 MHz, $CDCl_3$) 7.38 – 7.25 (7H, m, 7 x Ar**H**), 7.22 – 7.19 (1H, m, H-17), 7.17 – 7.13 (1H, m, H-14), 4.11 – 3.81 (3H, m, 1.5 x C**H$_2$** [overlapping]), 4.11 – 3.81 (2H, m, H-5 [overlapping]), 3.30 (2H, t, *J* = 6.5 Hz, H-23), 2.23 (1H, tt, *J* = 7.0, 3.5 Hz, H-20), 0.51 – 0.46 (2H, m, H-21/22), 0.41 – 0.35 (2H, m, H-21/22); δ_C (100 MHz, $CDCl_3$) Data for major rotamer: 172.2 (C-19), 140.0 (C-18), 136.1 (C-6/13), 136.0 (C-6/13), 130.0 (C-7,8), 129.5 (C-16), 128.7 (C-14), 128.4 (C-9,10), 127.7 (C-15), 127.42 (C-11), 125.2 (C-17), 56.6 (**C**H$_2$), 56.3 (**C**H$_2$), 54.7 (C-24), 49.4 (**C**H$_2$), 47.5 (**C**H$_2$), 43.7 (C-23), 29.9 (C-20), 25.2 (C-3), 6.5 (C-21,22). Diagnostic data for minor rotamer: 172.1 (C-19), 139.9 (C-18), 129.4 (C-16), 127.36 (C-11), 59.0 (**C**H$_2$), 54.1 (**C**H$_2$), 47.6 (**C**H$_2$), 25.4 (**C**H$_2$); HRMS (ESI$^+$): calcd. for $C_{23}H_{29}N_3NaO_3S$, 450.1822. Found: [MNa]$^+$, 450.1820 (0.4 ppm error).

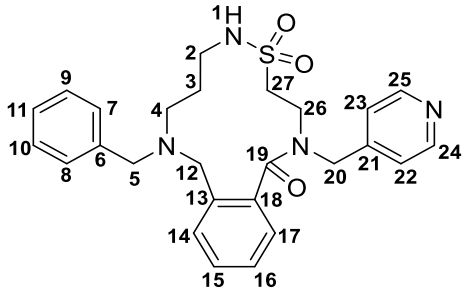
3.77: 10-Benzyl-2-(3-hydroxypropyl)-3,4,6,7,8,9,10,11-octahydrobenzo[*h*][1]thia[2,6,11]triazacyclotridecin-1(2*H*)-one 5,5-dioxide



To a round-bottomed flask was added 2-((benzyl(3-(vinylsulfonamido)propyl)amino)methyl)benzoic acid (97.1 mg, 0.250 mmol), which was dissolved in chloroform (7.0 mL) and DIPEA (0.09 mL, 0.520 mmol) was added dropwise. T3P (50% solution in ethyl acetate, 0.24 mL, 0.375 mmol) was added dropwise and the solution stirred at RT for 18 hours. The reaction mixture was diluted with DCM (10 mL) and washed with $NaHCO_3$ (2 x 10 mL). The organic layer was dried, filtered and concentrated *in vacuo* to remove excess solvent to form 9-membered ring intermediate **3.50**, which was used directly in the next step. To this resulting beige oil was added DIPEA (0.13 mL, 0.725 mmol) in THF

(2.0 mL) and 3-amino-1-propanol (23.1 µL, 0.303 mmol) in a single portion. The reaction mixture was stirred at RT for 72 hours. Then, the solution was diluted in DCM (15 mL) and washed with $NaHCO_3$ (2 x 10 mL). The organic layer was dried, filtered and concentrated *in vacuo* to yield the title compound, which was obtained as a peach oil (82.4 mg, 74%). The ^1H NMR spectrum is severely affected by rotameric broadening, with product identity and purity best determined using ^{13}C NMR data; R_f = 0.07 (9:1 ethyl acetate : methanol); ν_{max}/cm^{-1} (thin film): 3329, 2927, 2851, 1675, 1452, 1335, 1268, 1150, 1015, 780, 759, 730, 705; δ_H (400 MHz, $CDCl_3$) 7.38 – 7.22 (7H, m, 7 x Ar**H**), 7.21 – 7.17 (1H, m, H-17), 7.17 – 7.12 (1H, m, H-14), 4.02 – 3.81 (4H, m, 2 x C**H₂** [overlapping]), 4.02 – 3.81 (2H, m, H-5 [overlapping]), 3.78 (2H, t, *J* = 5.5 Hz, H-22), 3.24 (2H, t, *J* = 6.0 Hz, H-24), 2.90 (1H, t, *J* = 5.5 Hz, H-20), 1.72 (1H, p, *J* = 5.5 Hz, H-21); δ_C (100 MHz, $CDCl_3$) 172.3 (C-19), 139.9 (C-18), 136.0 (C-6/13), 135.9 (C-6/13), 130.0 (C-7,8), 129.6 (C-16), 128.7 (C-14), 128.3 (C-9,10), 127.8 (C-15), 127.4 (C-11), 125.2 (C-17), 63.5 (C-22), 56.5 (**C**H_2), 56.3 (**C**H_2), 54.6 (C-25), 49.4 (**C**H_2), 48.8 (C-20), 47.6 (**C**H_2), 43.8 (C-24), 31.1 (C-21), 25.2 (C-3); HRMS (ESI^+): calcd. for $C_{23}H_{31}N_3NaO_4S$, 468.1927. Found: $[MNa]^+$, 468.1927 (0.2 ppm error).

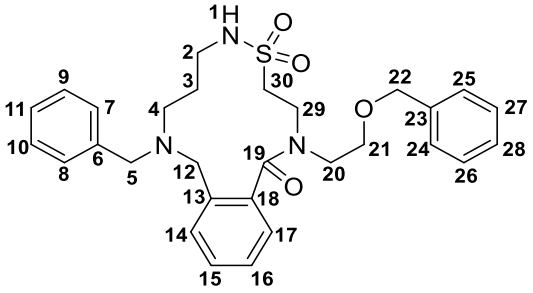
3.78: 10-Benzyl-2-(pyridin-4-ylmethyl)-3,4,6,7,8,9,10,11-octahydrobenzo[*h*][1]thia[2,6,11]triazacyclotridecin-1(2*H*)-one 5,5-dioxide



To a round-bottomed flask was added 2-((benzyl(3-(vinylsulfonamido)propyl)amino)methyl)benzoic acid (97.1 mg, 0.250 mmol), which was dissolved in chloroform (7.0 mL) and DIPEA (0.09 mL, 0.520 mmol) was added dropwise. T3P (50% solution in ethyl acetate, 0.24 mL, 0.375 mmol) was added dropwise and the solution stirred at RT for 18 hours. The reaction mixture was diluted with DCM (10 mL) and washed with $NaHCO_3$ (2 x 10 mL). The organic layer was dried, filtered and concentrated *in vacuo* to remove excess solvent to form 9-membered ring intermediate **3.50**, which was used directly in the next step. To this resulting beige oil was added DIPEA (0.13 mL, 0.725 mmol) in THF (2.0 mL) and 4-(aminomethyl)pyridine (30.9 µL, 0.304 mmol) in a single portion. The reaction mixture was stirred at RT for 72 hours. Then, the solution was diluted in DCM (10 mL) and washed with $NaHCO_3$ (2 x 10 mL). The organic layer was dried, filtered and

concentrated *in vacuo* to yield the title compound, which was obtained as a colourless oil (90.9 mg, 76%) and exists in $CDCl_3$ as a 10:1 mixture of rotamers. The ^1H NMR spectrum is severely affected by rotameric broadening, with product identity and purity best determined using ^{13}C NMR data; R_f = 0.46 (9:1 ethyl acetate : methanol); ν_{max}/cm^{-1} (thin film): 3027, 2919, 2848, 1674, 1502, 1451, 1336, 1268, 1148, 1014, 779, 759, 727, 704; δ_H (400 MHz, $CDCl_3$) Data for major rotamer: 8.53 (2H, d, *J* = 6.0 Hz, H-24,25), 7.36 – 7.21 (9H, m, 9 x Ar**H**), 7.13 (1H, d, *J* = 7.5 Hz, H-14), 7.04 (1H, d, *J* = 7.5 Hz, H-17), 4.25 – 3.75 (2H, m, H-20 [overlapping]), 4.25 – 3.75 (2H, m, H-5 [overlapping]), 4.25 – 3.75 (6H, m, 3 x C**H₂** [overlapping]), 3.20 (2H, t, *J* = 6.0 Hz, H-26). Diagnostic data for minor rotamer: 8.49 (2H, d, *J* = 5.5 Hz, H-24,25); δ_C (100 MHz, $CDCl_3$) Data for major rotamer: 172.2 (C-19), 149.9 (C-24,25), 148.8 (C-21), 139.8 (C-18), 135.9 (C-6/13), 135.8 (C-6/13), 130.0 (C-7,8), 129.5 (C-16), 128.7 (C-14), 128.31 (C-9,10), 127.7 (C-15), 127.4 (C-11), 125.0 (C-17), 123.0 (C-22,23), 56.5 (C-5), 56.2 (**C**H_2), 54.8 (C-27), 52.1 (C-20), 49.4 (**C**H_2), 47.5 (**C**H_2), 43.3 (C-26), 25.1 (C-3). Diagnostic data for minor rotamer: 172.1 (C-19), 137.8 (C-18), 136.2 (C-6/13), 136.1 (C-6/13), 129.9 (C-7,8), 129.3 (C-16), 128.27 (C-9,10), 127.6 (C-15), 127.3 (C-11), 125.1 (C-17), 59.0 (**C**H_2), 56.6 (**C**H_2), 54.0 (**C**H_2), 47.8 (**C**H_2), 25.3 (C-3); HRMS (ESI^+): calcd. for $C_{26}H_{30}N_4NaO_3S$, 501.1931. Found: $[MNa]^+$, 501.1933 (−0.5 ppm error).

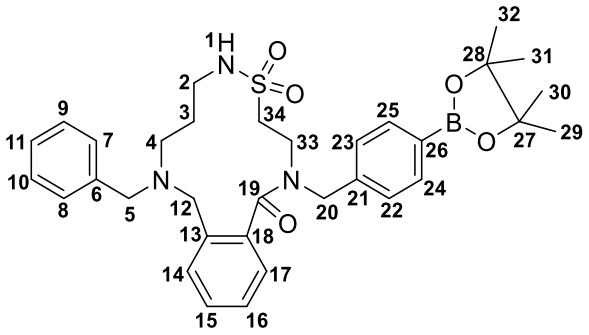
3.79: 10-Benzyl-2-(2-(benzyloxy)ethyl)-3,4,6,7,8,9,10,11-octahydrobenzo[*h*][1]thia[2,6,11]triazacyclotridecin-1(2*H*)-one 5,5-dioxide



To a round-bottomed flask was added 2-((benzyl(3-(vinylsulfonamido)propyl)amino)methyl)benzoic acid (97.1 mg, 0.250 mmol), which was dissolved in chloroform (7.0 mL) and DIPEA (0.09 mL, 0.520 mmol) was added dropwise. T3P (50% solution in ethyl acetate, 0.24 mL, 0.375 mmol) was added dropwise and the solution stirred at RT for 18 hours. The reaction mixture was diluted with DCM (10 mL) and washed with $NaHCO_3$ (2 x 10 mL). The organic layer was dried, filtered and concentrated *in vacuo* to remove excess solvent to form 9-membered ring intermediate **3.50**, which was used directly in the next step. To this resulting beige oil was added DIPEA (0.13 mL, 0.725 mmol) in THF (2.0 mL) and 2-(benzyloxy)-1-ethanamine (41.4 µL, 0.300 mmol) in a single portion. The

reaction mixture was stirred at RT for 72 hours. Then, the solution was diluted in DCM (15 mL) and washed with $NaHCO_3$ (2 x 10 mL). The organic layer was dried, filtered and concentrated *in vacuo* to yield the title compound, which was obtained as a colourless oil (105 mg, 81%), and exists in $CDCl_3$ as a 3:1 mixture of rotamers. The ^1H NMR spectrum is severely affected by rotameric broadening, with product identity and purity best determined using ^{13}C NMR data; R_f = 0.44 (9:1 ethyl acetate : methanol); ν_{max}/cm^{-1} (thin film): 3028, 2920, 2854, 1676, 1453, 1336, 1268, 1150, 1110, 1014, 779, 738, 700; δ_H (400 MHz, $CDCl_3$) Data for major rotamer: 7.39 – 7.24 (12H, m, 12 x Ar**H**), 7.23 – 7.19 (1H, m, H-17), 7.17 – 7.13 (1H, m, H-14), 4.53 (2H, s, H-22), 4.08 – 3.83 (6H, m, 3 x C**H₂**), 3.61 (2H, t, *J* = 5.0 Hz, H-21), 3.52 (2H, t, *J* = 5.0 Hz, C**H₂**), 3.24 (2H, t, *J* = 6.5 Hz, H-29), 2.88 (2H, t, *J* = 5.0 Hz, H-20). Diagnostic data for minor rotamer: 4.52 (2H, s, H-22); δ_C (100 MHz, $CDCl_3$) Data for major rotamer: 172.2 (C-19), 139.9 (C-18), 138.2 (C-23), 136.1 (C-6/13), 136.0 (C-6/13), 130.0 (C-7,8), 128.5 (C-9,10), 128.3 (C-24,25), 127.81 (C-26,27), 125.2 (C-17), 73.3 (C-22), 69.5 (C-21), 56.6 (**C**H_2), 56.2 (**C**H_2), 54.8 (C-30), 49.4 (**C**H_2), 49.1 (C-20), 47.5 (**C**H_2), 43.9 (C-29), 25.2 (C-3). Diagnostic data for minor rotamer: 138.3 (Ar**C**), 128.0 (Ar**C**H), 127.9 (Ar**C**H), 73.2 (C-22), 71.7 (C-21). The remaining aryl peaks are indistinguishable between the major and minor rotamers: 129.5 (Ar**C**H), 128.6 (Ar**C**H), 127.9 (Ar**C**H), 127.78 (Ar**C**H), 127.71 (Ar**C**H), 127.67 (Ar**C**H), 127.4 (Ar**C**H); HRMS (ESI^+): calcd. for $C_{29}H_{36}N_3O_4S$, 522.2421. Found: $[MH]^+$, 522.2421 (0.1 ppm error).

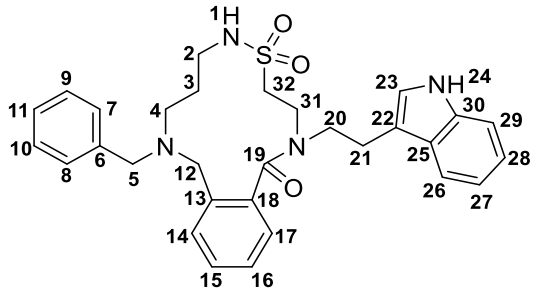
3.80: 10-Benzyl-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-3,4,6,7,8,9,10,11-octahydrobenzo[*h*][1]thia[2,6,11]triazacyclotridecin-1(2*H*)-one 5,5-dioxide



To a round-bottomed flask was added 2-((benzyl(3-(vinylsulfonamido)propyl)amino)methyl)benzoic acid (97.1 mg, 0.250 mmol), which was dissolved in chloroform (7.0 mL) and DIPEA (0.09 mL, 0.520 mmol) was added dropwise. T3P (50% solution in ethyl acetate, 0.24 mL, 0.375 mmol) was added dropwise and the solution stirred at RT for 18 hours. The reaction mixture was diluted with DCM (10 mL) and washed

with $NaHCO_3$ (2 x 10 mL). The organic layer was dried, filtered and concentrated *in vacuo* to remove excess solvent to form 9-membered ring intermediate **3.50**, which was used directly in the next step. To this resulting beige oil was added DIPEA (0.13 mL, 0.725 mmol) in THF (2.0 mL) and (4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanamine (71.3 mg, 0.306 mmol) in a single portion. The reaction mixture was stirred at RT for 72 hours. Then, the solution was diluted in DCM (15 mL) and washed with $NaHCO_3$ (2 x 15 mL). The organic layer was dried, filtered and concentrated *in vacuo* to yield the title compound, which was obtained as an orange oil (146 mg, 97%). The ^{1}H NMR spectrum is severely affected by rotameric broadening, with product identity and purity best determined using ^{13}C NMR data; R_f = 0.55 (9:1 ethyl acetate : methanol); ν_{max}/cm^{-1} (thin film): 2978, 2927, 2853, 1675, 1612, 1452, 1398, 1358, 1321, 1269, 1143, 1088, 1015, 859, 728, 704, 658; δ_H (400 MHz, $CDCl_3$) 7.82 – 7.72 (2H, m, H-24,25), 7.38 – 7.19 (9H, m, 9 x Ar**H**), 7.13 (1H, d, *J* = 7.5 Hz, H-14), 6.94 (1H, d, *J* = 7.0 Hz, H-17), 4.07 – 3.81 (4H, m, 2 x C**H$_2$** [overlapping]), 4.07 – 3.81 (2H, m, H-5 [overlapping]), 4.07 – 3.81 (2H, m, H-20 [overlapping]), 3.16 (2H, t, *J* = 6.0 Hz, H-33), 1.36 – 1.31 (12H, m, H-29,30,31,32); δ_C (100 MHz, $CDCl_3$) 172.1 (C-19), 145.1 (C-26), 142.9 (C-21), 139.9 (C-18), 136.0 (C-6,13 [overlapping]), 135.2 (C-24,25), 130.0 (C-7,8), 129.4 (C-16), 128.6 (C-14), 128.3 (C-9,10), 127.8 (C-15), 127.6 (C-22,23), 127.4 (C-11), 125.2 (C-17), 83.8 (C-27,28), 56.5 (C-5), 56.2 (**C**H$_2$), 54.7 (C-34), 53.5 (C-20), 49.4 (**C**H$_2$), 47.5 (**C**H$_2$), 43.2 (C-33), 25.2 (C-3), 25.0 (C-29,30,31,32); HRMS (ESI$^+$): calcd. for $C_{33}H_{43}BN_3O_5S$, 604.3011. Found: $[MH]^+$, 604.3035 (−3.0 ppm error).

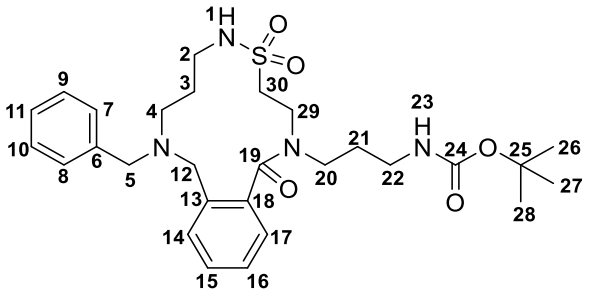
3.81: 2-(2-(1*H*-Indol-3-yl)ethyl)-10-benzyl-3,4,6,7,8,9,10,11-octahydrobenzo[*h*][1]thia[2,6,11]triazacyclotridecin-1(2*H*)-one 5,5-dioxide



To a round-bottomed flask was added 2-((benzyl(3-(vinylsulfonamido)propyl)amino)methyl)benzoic acid (97.1 mg, 0.250 mmol), which was dissolved in chloroform (7.0 mL) and DIPEA (0.09 mL, 0.520 mmol) was added dropwise. T3P (50% solution in ethyl acetate, 0.24 mL, 0.375 mmol) was added dropwise and the solution stirred at RT for 18 hours. The reaction mixture was diluted with DCM (10 mL) and washed with $NaHCO_3$ (2 x 10 mL). The organic layer was dried, filtered and concentrated *in vacuo* to

remove excess solvent to form 9-membered ring intermediate **3.50**, which was used directly in the next step. To this resulting beige oil was added DIPEA (0.13 mL, 0.725 mmol) in THF (2.0 mL) and tryptamine (48.4 mg, 0.302 mmol) in a single portion. The reaction mixture was stirred at RT for 72 hours. Then, the solution was diluted in DCM (15 mL) and washed with $NaHCO_3$ (2 x 10 mL). The organic layer was dried, filtered and concentrated *in vacuo* to yield the title compound, which was obtained as a white solid (113 mg, 85%). The ^1H NMR spectrum is severely affected by rotameric broadening, with product identity and purity best determined using ^{13}C NMR data; R_f = 0.34 (9:1 ethyl acetate : methanol); MP = 57 – 63 °C; ν_{max}/cm^{-1} (thin film): 2923, 1671, 1455, 1335, 1268, 1151, 1015, 909, 730, 704; δ_H (400 MHz, $CDCl_3$) 8.29 (1H, s, H-24), 7.79 (1H, d, *J* = 8.5 Hz, H-26), 7.62 (1H, d, *J* = 8.0 Hz, H-29), 7.41 – 7.08 (9H, m, 9 x Ar**H** [overlapping]), 7.35 (1H, d, *J* = 8.5 Hz, H-27 [overlapping]), 7.10 (1H, d, *J* = 8.0 Hz, H-28), 7.05 (1H, d, *J* = 2.5 Hz, H-23), 4.18 – 3.80 (4H, m, 2 x C**H₂** [overlapping]), 4.18 – 3.80 (2H, m, H-5 [overlapping]), 3.25 (2H, t, *J* = 6.5 Hz, H-31), 3.02 (4H, dd, *J* = 7.5, 4.5 Hz, H-20,21); δ_C (100 MHz, $CDCl_3$) 172.3 (C-19), 139.9 (C-18), 136.5 (C-30), 136.1 (C-6/13), 136.0 (C-6/13), 130.1 (C-7,8), 129.5 (Ar**C**), 128.7 (Ar**C**), 128.4 (C-9,10), 127.8 (Ar**C**), 127.4 (Ar**C**), 126.5 (C-26), 125.2 (C-17), 122.3 (C-23), 122.1 (Ar**C**), 119.3 (C-28), 118.8 (C-29), 113.4 (C-22), 111.4 (C-27), 56.5 (C-5), 56.2 (**C**H_2), 54.9 (C-32), 49.6 (C-20/32), 49.4 (C-20/32), 47.5 (**C**H_2), 43.8 (C-31), 25.7 (C-21), 25.2 (C-3); HRMS (ESI^+): calcd. for $C_{30}H_{35}N_4O_3S$, 531.2424. Found: $[MH]^+$, 531.2434 (−1.8 ppm error).

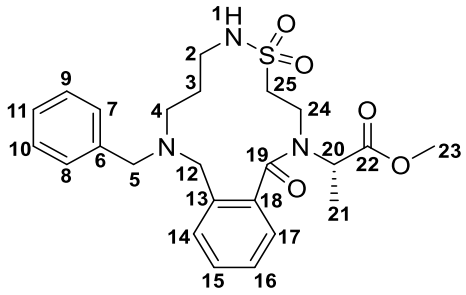
3.82: *tert*-Butyl (3-(10-benzyl-5,5-dioxido-1-oxo-3,4,6,7,8,9,10,11-octahydrobenzo[*h*][1]thia[2,6,11]triazacyclotridecin-2(1*H*)-yl)propyl)carbamate



To a round-bottomed flask was added 2-((benzyl(3-(vinylsulfonamido)propyl)amino)methyl)benzoic acid (97.1 mg, 0.250 mmol), which was dissolved in chloroform (7.0 mL) and DIPEA (0.09 mL, 0.520 mmol) was added dropwise. T3P (50% solution in ethyl acetate, 0.24 mL, 0.375 mmol) was added dropwise and the solution stirred at RT for 18 hours. The reaction mixture was diluted with DCM (10 mL) and washed with $NaHCO_3$ (2 x 10 mL). The organic layer was dried, filtered and concentrated *in vacuo* to remove excess solvent to form 9-membered ring intermediate **3.50**, which was used directly

in the next step. To this resulting beige oil was added DIPEA (0.13 mL, 0.725 mmol) in THF (2.0 mL) and *tert*-butyl *N*-(3-aminopropyl)carbamate (58.5 mg, 0.300 mmol) in a single portion. The reaction mixture was stirred at RT for 72 hours. Then, the solution was diluted in DCM (15 mL) and washed with $NaHCO_3$ (2 x 10 mL). The organic layer was dried, filtered and concentrated *in vacuo* to yield the title compound, which was obtained as an orange oil (98.1 mg, 72%). The ^{1}H NMR spectrum is severely affected by rotameric broadening, with product identity and purity best determined using ^{13}C NMR data; R_f = 0.14 (9:1 ethyl acetate : methanol); ν_{max}/cm^{-1} (thin film): 2936, 1683, 1512, 1452, 1335, 1269, 1154, 1014, 909, 727, 704; δ_H (400 MHz, $CDCl_3$) 7.38 – 7.23 (7H, m, 7 x Ar**H**), 7.21 – 7.18 (1H, m, H-17), 7.17 – 7.12 (1H, m, H-14), 4.99 (1H, t, *J* = 6.0 Hz, H-23), 4.16 – 3.78 (4H, m, 2 x C**H$_2$** [overlapping]), 4.16 – 3.78 (2H, m, H-5 [overlapping]), 3.22 (2H, t, *J* = 6.5 Hz, H-29 [overlapping]), 3.27 – 3.11 (2H, m, H-22 [overlapping]), 2.72 (2H, t, *J* = 6.5 Hz, H-20), 1.67 (2H, p, *J* = 6.5 Hz, H-21), 1.42 (9H, s, H-26,27,28); δ_C (100 MHz, $CDCl_3$) 172.3 (C-19), 156.2 (C-24), 139.9 (C-18), 136.1 (C-6/13), 135.9 (C-6/13), 130.0 (C-7,8), 129.5 (C-16), 128.7 (C-14), 128.4 (C-9,10), 127.8 (C-15), 127.4 (C-11), 125.2 (C-17), 79.2 (C-25), 56.6 (C-5), 56.2 (**C**H$_2$), 54.7 (C-30), 49.4 (**C**H$_2$), 47.6 (**C**H$_2$), 47.0 (C-20), 43.9 (C-29), 38.8 (C-22), 30.0 (C-21), 28.5 (C-26,27,28), 25.2 (C-3); HRMS (ESI$^+$): calcd. for $C_{28}H_{40}N_4NaO_5S$, 567.2612. Found: [MNa]$^+$, 567.2606 (0.9 ppm error).

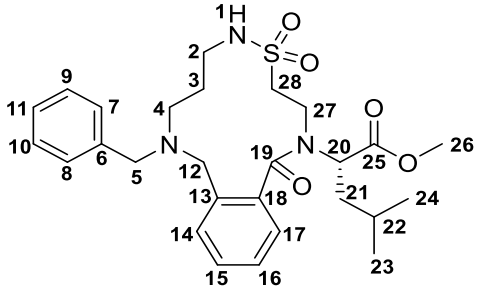
3.83: Methyl 2-(10-benzyl-5,5-dioxido-1-oxo-3,4,6,7,8,9,10,11-octahydrobenzo[*h*][1]thia[2,6,11]triazacyclotridecin-2(1*H*)-yl)propanoate



To a round-bottomed flask was added 2-((benzyl(3-(vinylsulfonamido)propyl)amino)methyl)benzoic acid (97.1 mg, 0.250 mmol), which was dissolved in chloroform (7.0 mL) and DIPEA (0.09 mL, 0.520 mmol) was added dropwise. T3P (50% solution in ethyl acetate, 0.24 mL, 0.375 mmol) was added dropwise and the solution stirred at RT for 18 hours. The reaction mixture was diluted with DCM (10 mL) and washed with $NaHCO_3$ (2 x 10 mL). The organic layer was dried, filtered and concentrated *in vacuo* to remove excess solvent to form 9-membered ring intermediate **3.50**, which was used directly in the next step. To this resulting beige oil was added DIPEA (0.27 mL, 1.53 mmol) in THF (2.0 mL) and L-alanine methyl ester hydrochloride (44.0 mg, 0.315 mmol) in a single portion. The

reaction mixture was stirred at RT for 72 hours. Then the solution diluted in DCM (15 mL) and washed with $NaHCO_3$ (2 x 15 mL). The organic layer was dried, filtered and concentrated *in vacuo* to yield the title compound, which was obtained as an orange oil (74.3 mg, 63%). The ^1H NMR spectrum is severely affected by rotameric broadening, with product identity and purity best determined using ^{13}C NMR data; R_f = 0.67 (9:1 ethyl acetate : methanol); $[\alpha]_D^{20}$ −9.10 (c = 1.0, $CHCl_3$); ν_{max}/cm^{-1} (thin film): 2924, 2851, 1733, 1676, 1451, 1337, 1268, 1148, 1048, 1014, 912, 780, 728, 704; δ_H (400 MHz, $CDCl_3$) 7.38 – 7.23 (7H, m, 7 x Ar**H**), 7.22 – 7.18 (1H, m, H-17), 7.17 – 7.12 (1H, m, H-14), 4.17 – 3.80 (5H, m, 2.5 x C**H₂** [overlapping]), 3.73 (3H, s, H-23), 3.45 – 3.38 (1H, m, H-20), 3.30 – 3.20 (1H, m, H-24), 3.10 – 3.00 (1H, m, H-24'), 1.33 (2H, d, *J* = 7.0 Hz, H-21); δ_C (100 MHz, $CDCl_3$) 175.6 (C-22), 172.2 (C-19), 140.0 (C-18), 136.1 (C-6/13), 136.0 (C-6/13), 130.1 (C-7,8), 129.5 (C-16), 128.7 (C-14), 128.4 (C-9,10), 127.7 (C-15), 127.4 (C-11), 125.2 (C-17), 56.6 (C-5,20), 56.2 (**C**H_2), 55.0 (C-25), 52.1 (C-23), 49.5 (**C**H_2), 47.6 (**C**H_2), 42.3 (C-24), 25.2 (C-3), 19.1 (C-21); HRMS (ESI^+): calcd. for $C_{24}H_{31}N_3NaO_5S$, 496.1877. Found: $[MNa]^+$, 496.1885 (−1.8 ppm error).

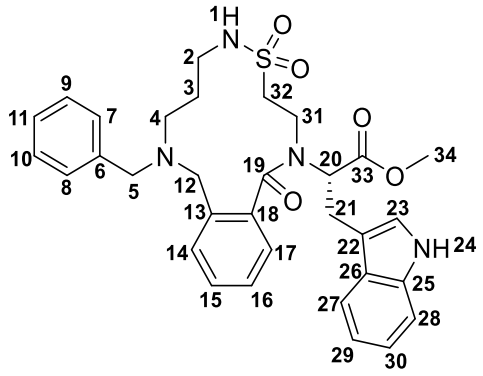
3.84: Methyl 2-(10-benzyl-5,5-dioxido-1-oxo-3,4,6,7,8,9,10,11-octahydrobenzo[*h*][1]thia[2,6,11]triazacyclotridecin-2(1*H*)-yl)-4-methylpentanoate



To a round-bottomed flask was added 2-((benzyl(3-(vinylsulfonamido)propyl)amino)methyl)benzoic acid (97.1 mg, 0.250 mmol), which was dissolved in chloroform (7.0 mL) and DIPEA (0.09 mL, 0.520 mmol) was added dropwise. T3P (50% solution in ethyl acetate, 0.24 mL, 0.375 mmol) was added dropwise and the solution stirred at RT for 18 hours. The reaction mixture was diluted with DCM (10 mL) and washed with $NaHCO_3$ (2 x 10 mL). The organic layer was dried, filtered and concentrated *in vacuo* to remove excess solvent to form 9-membered ring intermediate **3.50**, which was used directly in the next step. To this resulting beige oil was added DIPEA (0.27 mL, 1.53 mmol) in THF (2.0 mL) and L-leucine methyl ester hydrochloride (56.5 mg, 0.311 mmol) in a single portion. The reaction mixture was stirred at RT for 72 hours. Then, the solution was diluted in DCM (15 mL) and washed with $NaHCO_3$ (2 x 15 mL). The organic layer was dried, filtered and concentrated *in vacuo* to yield the title compound, which was obtained as an orange oil

(98.3 mg, 76%), and exists in $CDCl_3$ as a 10:1 mixture of rotamers. The ^1H NMR spectrum is severely affected by rotameric broadening, with product identity and purity best determined using ^{13}C NMR data; R_f = 0.77 (9:1 ethyl acetate : methanol); $[\alpha]_D^{20}$ −7.62 (c = 1.0, $CHCl_3$); ν_{max}/cm^{-1} (thin film): 2955, 2869, 1733, 1677, 1452, 1336, 1268, 1148, 1048, 1014, 780, 730, 704; δ_H (400 MHz, $CDCl_3$) 7.39 – 7.22 (7H, m, 7 x Ar**H**), 7.21 – 7.11 (2H, m, H-14,17), 4.20 – 3.79 (3H, m, 1.5 x C**H₂** [overlapping]), 4.20 – 3.79 (2H, m, H-5 [overlapping]), 3.72 (2H, s, H-26), 3.70 (1H, s, H-26'), 3.32 (1H, t, *J* = 7.0 Hz, H-20), 3.27 – 3.19 (1H, m, H-27), 3.06 – 2.95 (1H, m, H-27'), 1.75 (1H, dp, *J* = 13.5, 6.5 Hz, H-22), 1.48 (2H, td, *J* = 7.0, 3.0 Hz, H-21), 0.91 (6H, td, *J* = 6.5, 4.0 Hz, H-23,24); δ_C (100 MHz, $CDCl_3$) Data for major rotamer: 175.9 (C-25), 172.2 (C-19), 140.0 (C-18), 136.1 (C-6/13), 136.0 (C-6/13), 130.0 (C-7,8), 129.5 (C-16), 128.7 (C-14), 128.3 (C-9,10), 127.7 (C-15), 127.4 (C-11), 125.2 (C-17), 60.0 (C-20), 56.6 (C-5), 56.2 (**C**H_2), 55.1 (C-28), 51.9 (C-26), 49.4 (**C**H_2), 47.5 (**C**H_2), 42.62 (C-21/27), 42.61 (C-21/27), 25.2 (C-3), 24.9 (C-22), 22.9 (C-23/24), 22.2 (C-23/24). Diagnostic data for minor rotamer: 24.8 (C-22), 23.0 (C-23/24), 21.9 (C-23/24); HRMS (ESI^+): calcd. for $C_{27}H_{38}N_3O_5S$, 516.2527. Found: $[MH]^+$, 516.2534 (−1.4 ppm error).

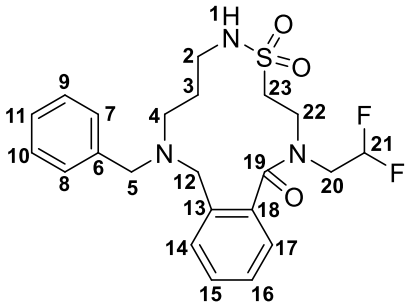
3.85: Methyl 2-(10-benzyl-5,5-dioxido-1-oxo-3,4,6,7,8,9,10,11-octahydrobenzo[*h*][1]thia[2,6,11]triazacyclotridecin-2(1*H*)-yl)-3-(1H-indol-3-yl)propanoate



To a round-bottomed flask was added 2-((benzyl(3-(vinylsulfonamido)propyl)amino)methyl)benzoic acid (97.1 mg, 0.250 mmol), which was dissolved in chloroform (7.0 mL) and DIPEA (0.09 mL, 0.520 mmol) was added dropwise. T3P (50% solution in ethyl acetate, 0.24 mL, 0.375 mmol) was added dropwise and the solution stirred at RT for 18 hours. The reaction mixture was diluted with DCM (10 mL) and washed with $NaHCO_3$ (2 x 10 mL). The organic layer was dried, filtered and concentrated *in vacuo* to remove excess solvent to form 9-membered ring intermediate **3.50**, which was used directly in the next step. To this resulting beige oil was added DIPEA (0.27 mL, 1.53 mmol) in THF (2.0 mL) and L-tryptophan methyl ester hydrochloride (78.1 mg, 0.307 mmol) in a single portion.

The reaction mixture was stirred at RT for 72 hours. Then, the solution was diluted in DCM (15 mL) and washed with $NaHCO_3$ (2 x 15 mL). The organic layer was dried, filtered and concentrated *in vacuo* to yield a residue. Purification *via* flash column chromatography (100% ethyl acetate) afforded the title compound, which was obtained as a colourless oil (27.0 mg, 18%). The ^{1}H NMR spectrum is severely affected by rotameric broadening, with product identity and purity best determined using ^{13}C NMR data; R_f = 0.70 (9:1 ethyl acetate : methanol); $[\alpha]_D^{20}$ −0.11 (c = 1.0, $CHCl_3$); ν_{max}/cm^{-1} (thin film): 3351, 2925, 2854, 1729, 1671, 1454, 1336, 1264, 1148, 1015, 909, 731, 703; δ_H (400 MHz, $CDCl_3$) 8.14 (1H, s, H-24), 7.60 (1H, d, *J* = 8.0 Hz, H-27/28), 7.19 – 7.11 (2H, m, H-14/17 [overlapping]), 7.09 (1H, d, *J* = 2.0 Hz, H-23 [overlapping]), 7.38 – 7.05 (12H, m, 12 x Ar**H** [overlapping]), 4.17 – 3.80 (6H, m, 3 x C**H₂** [overlapping]), 4.17 – 3.80 (2H, m, H-5 [overlapping]), 3.67 (3H, s, H-34 [overlapping]), 3.71 – 3.63 (1H, m, H-20 [overlapping]), 3.29 – 3.20 (1H, m, H-31 [overlapping]), 3.29 – 3.20 (1H, m, H-21 [overlapping]), 3.13 (1H, dd, *J* = 15.0, 7.0 Hz, H-21' [overlapping]), 3.17 – 3.10 (1H, m, C**H₂** [overlapping]), 3.07 – 2.99 (1H, m, H-31'); δ_C (100 MHz, $CDCl_3$) 174.8 (C-33), 172.2 (C-19), 140.0 (C-18), 136.3 (C-25), 136.12 (C-6/13), 136.06 (C-6/13), 130.1 (C-7,8), 129.5 (C-16), 128.7 (C-14), 128.4 (C-9,10), 127.7 (C-15), 127.4 (C-11,26), 125.3 (C-17), 123.2 (C-23), 122.2 (Ar**C**H), 119.6 (Ar**C**H), 118.8 (C-27/28), 111.4 (Ar**C**H), 111.0 (C-22), 62.0 (C-20), 56.6 (C-5), 56.2 (**C**H_2), 55.0 (C-32), 52.1 (C-34), 49.4 (**C**H_2), 47.5 (**C**H_2), 42.7 (C-31), 29.3 (C-21), 25.2 (C-3); HRMS (ESI^+): calcd. for $C_{32}H_{36}N_4NaO_5S$, 611.2299. Found: $[MNa]^+$, 611.2304 (−0.9 ppm error).

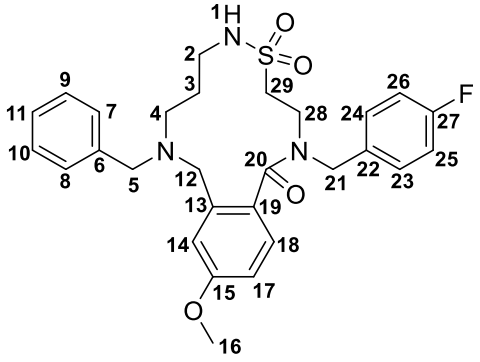
3.86: 10-Benzyl-2-(2,2-difluoroethyl)-3,4,6,7,8,9,10,11-octahydrobenzo[*h*][1]thia[2,6,11]triazacyclotridecin-1(2*H*)-one 5,5-dioxide



To a round-bottomed flask was added 2-((benzyl(3-(vinylsulfonamido)propyl)amino)methyl)benzoic acid (97.1 mg, 0.250 mmol), which was dissolved in chloroform (7.0 mL) and DIPEA (0.09 mL, 0.520 mmol) was added dropwise. T3P (50% solution in ethyl acetate, 0.24 mL, 0.375 mmol) was added dropwise and the solution stirred at RT for 18 hours. The reaction mixture was diluted with DCM (10 mL) and washed

with $NaHCO_3$ (2 x 10 mL). The organic layer was dried, filtered and concentrated *in vacuo* to remove excess solvent to form 9-membered ring intermediate **3.50**, which was used directly in the next step. To this resulting beige oil was added 2,2-difluoroethylamine (21.1 µL, 0.300 mmol) in THF (2.0 mL) in a single portion. The reaction mixture was stirred at RT for 168 hours. Then, the solution was diluted in DCM (15 mL) and washed with $NaHCO_3$ (2 x 15 mL). The organic layer was dried, filtered and concentrated *in vacuo* to yield the title compound, which was obtained as a brown oil (76.6 mg, 68%). The ^{1}H NMR spectrum is severely affected by rotameric broadening, with product identity and purity best determined using ^{13}C NMR data; R_f = 0.66 (9:1 ethyl acetate : methanol); ν_{max}/cm^{-1} (thin film): 2924, 2853, 1673, 1452, 1336, 1268, 1150, 1116, 1048, 1014, 910, 779, 730, 704; δ_H (400 MHz, $CDCl_3$) 7.39 – 7.24 (7H, m, 7 x Ar**H**), 7.21 – 7.18 (1H, m, H-17), 7.18 – 7.14 (1H, m, H-14), 5.85 (1H, tt, *J* = 56.0, 4.0 Hz, H-21), 4.16 – 3.79 (5H, m, 2.5 x C**H$_2$** [overlapping]), 4.16 – 3.79 (2H, m, H-5 [overlapping]), 3.31 (2H, t, *J* = 6.0 Hz, H-22), 3.04 (2H, td, *J* = 15.5, 4.0 Hz, H-20); δ_C (100 MHz, $CDCl_3$) 172.3 (C-19), 140.0 (C-18), 136.0 (C-6/13), 135.9 (C-6/13), 130.1 (C-7,8), 129.6 (C-16), 128.8 (C-14), 128.4 (C-9,10), 127.8 (C-15), 127.5 (C-11), 125.2 (C-17), 116.0 (C-21, d, $^1J_{CF}$ = 241.2 Hz), 56.6 (C-5), 56.3 (**C**H$_2$), 55.0 (C-23), 51.2 (C-20, d, $^2J_{CF}$ = 24.3 Hz), 49.5 (**C**H$_2$), 47.6 (**C**H$_2$), 44.1 (C-22), 25.2 (C-3); δ_F (282 MHz, $CDCl_3$) −121.56 (2F, dt, *J* = 56.0, 15.5 Hz, CH**F$_2$**); HRMS (ESI$^+$): calcd. for $C_{22}H_{28}F_2N_3O_3S$, 452.1814. Found: $[MH]^+$, 452.1816 (−0.4 ppm error).

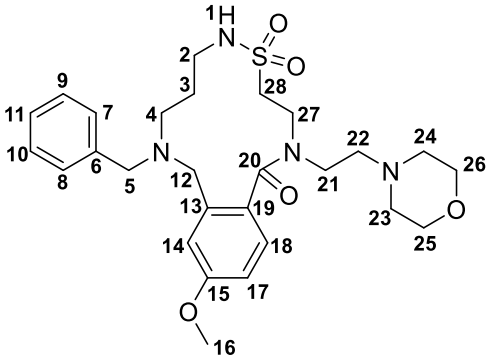
3.88: 10-Benzyl-2-(4-fluorobenzyl)-13-methoxy-3,4,6,7,8,9,10,11-octahydrobenzo[*h*][1]thia[2,6,11]triazacyclotridecin-1(2*H*)-one 5,5-dioxide



To a round-bottomed flask, 2-((benzyl(3-(vinylsulfonamido)propyl)amino)methyl)-4-methoxybenzoic acid (92.1 mg, 0.220 mmol) was dissolved in chloroform (10.0 mL) and DIPEA (0.08 mL, 0.440 mmol) was added dropwise. T3P (50% solution in ethyl acetate, 0.22 mL, 0.341 mmol) was added dropwise and the solution stirred at RT for 17 hours. The reaction mixture was diluted with DCM (10 mL) and washed with $NaHCO_3$ (2 x 10 mL). The

organic layer was dried with $MgSO_4$, filtered and concentrated *in vacuo* to remove excess solvent to form 9-membered ring intermediate **3.51**, which was used directly in the next step. To this resulting white oil was added DIPEA (0.10 mL, 0.569 mmol) in THF (3.0 mL) and 4-fluorobenzylamine (27.0 µL, 0.237 mmol) in a single portion. The reaction mixture was allowed to stir at RT for 48 hours. Then, the solution diluted in DCM (10 mL) and washed with $NaHCO_3$ (2 x 10 mL). The organic layer was dried with $MgSO_4$, filtered and concentrated *in vacuo* to afford the title compound, which was obtained as a white oil (88.8 mg, 77%). The ^{1}H NMR spectrum is severely affected by rotameric broadening, with product identity and purity best determined using ^{13}C NMR data; ν_{max}/cm^{-1} (thin film): 2922, 2841, 1674, 1604, 1508, 1454, 1333, 1248, 1220, 1150, 1120, 1012, 822, 763, 732, 703, 610, 499; δ_H (400 MHz, $CDCl_3$) 7.39 – 7.24 (7H, m, 7 x Ar**H**), 7.05 – 6.97 (2H, m, H-25,26), 6.94 (1H, d, *J* = 8.5 Hz, H-18), 6.74 (1H, dd, *J* = 8.5, 2.5 Hz, H-17), 6.68 (1H, d, *J* = 2.5 Hz, H-14), 3.84 (2H, m, H-5 [overlapping]), 3.82 (2H, m, H-21 [overlapping]), 3.92 – 3.81 (2H, m, H-25 [overlapping]), 3.78 (3H, s, H-16), 3.18 (2H, t, *J* = 6.5 Hz, H-28); δ_C (100 MHz, $CDCl_3$) 172.2 (C-20), 162.0 (C-27, d, $^1J_{CF}$ = 245.2 Hz), 160.2 (C-15), 141.9 (C-13/19), 135.9 (C-6), 135.4 (C-22, d, $^4J_{CF}$ = 3.0 Hz), 130.0 (C-7,8), 129.8 (C-23,24, d, $^3J_{CF}$ = 7.8 Hz), 128.4 (13/19), 128.3 (C-9,10), 127.4 (C-11), 126.4 (C-18), 115.3 (C-25,26, d, $^2J_{CF}$ = 21.1 Hz), 114.1 (C-14), 112.5 (C-17), 56.7 (C-12), 56.3 (C-5), 55.4 (C-16), 54.7 (C-29), 52.7 (C-21), 49.4 (C-4), 47.5 (C-2), 43.2 (C-28), 25.3 (C-3); δ_F (282 MHz, $CDCl_3$) major rotamer: −115.54 (1F, m, Ar**F**), minor rotamer −116.22 (1F, m, Ar**F**); HRMS (ESI^+): calcd. for $C_{28}H_{32}FN_3NaO_4S$, 548.1990. Found $[MNa]^+$ 548.2001 (−2.1 ppm error).

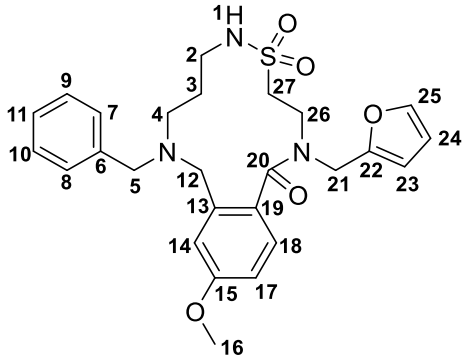
3.89: 10-Benzyl-13-methoxy-2-(2-morpholinoethyl)-3,4,6,7,8,9,10,11-octahydrobenzo[*h*][1]thia[2,6,11]triazacyclotridecin-1(2*H*)-one 5,5-dioxide



To a round-bottomed flask, 2-((benzyl(3-(vinylsulfonamido)propyl)amino)methyl)-4-methoxybenzoic acid (102 mg, 0.243 mmol) was dissolved in chloroform (10.0 mL) and DIPEA (0.08 mL, 0.486 mmol) was added dropwise. Then, T3P (50% solution in ethyl acetate,

0.23 mL, 0.365 mmol) was added dropwise and the solution stirred at RT for 17 hours. The reaction mixture was diluted with DCM (10 mL) and washed with $NaHCO_3$ (2 x 10 mL). The organic layer was dried, filtered and concentrated *in vacuo* to remove excess solvent to form 9-membered ring intermediate **3.51**, which was used directly in the next step. To this resulting white oil was added DIPEA (0.13 mL, 0.729 mmol) in THF (2.0 mL), followed by 4-(2-aminoethyl)morpholine (38.5 µL, 0.294 mmol) in a single portion. The reaction mixture was allowed to stir at RT for 48 hours. Then the solution was diluted in DCM (10 mL) and washed with $NaHCO_3$ (2 x 10 mL). The organic layer was dried, filtered and concentrated *in vacuo* to yield the title compound, which was obtained as a white oil (108 mg, 84%). The ^{1}H NMR spectrum is severely affected by rotameric broadening, with product identity and purity best determined using ^{13}C NMR data; ν_{max}/cm^{-1} (thin film): 2920, 2852, 1675, 1606, 1454, 1334, 1258, 1148, 1116, 1011, 764, 730, 704, 611; δ_H (400 MHz, $CDCl_3$) 7.37 – 7.22 (6H, m, 6 x Ar**H**), 7.12 (1H, d, *J* = 8.5 Hz, H-18), 6.77 (1H, dd, *J* = 8.5, 2.5 Hz, H-17), 6.67 (1H, d, *J* = 2.5 Hz, H-14), 3.90 – 3.80 (2H, m, H-12 [overlapping]), 3.84 (2H, m, H-5 [overlapping]), 3.76 (3H, s, H-16), 3.68 (4H, t, *J* = 4.5 Hz, H-25,26), 3.23 (2H, t, *J* = 6.5 Hz, H-27), 2.76 (2H, t, *J* = 6.0 Hz, H-21), 2.49 (2H, t, *J* = 6.0 Hz, H-22), 2.43 (4H, t, *J* = 4.5 Hz, H-23,24); δ_C (100 MHz, $CDCl_3$) 172.3 (C-20), 160.2 (C-15), 141.9 (C-13/19), 135.9 (C-6), 130.0 (C-7,8), 128.5 (13/19), 128.3 (C-9,10), 127.4 (C-11), 126.4 (C-18), 114.1 (C-14), 112.6 (C-17), 67.0 (C-25,26), 58.1 (C-22), 56.7 (C-12), 56.3 (C-5), 55.4 (C-16), 54.6 (C-28), 53.7 (C-23,24), 49.3 (C-4), 47.6 (C-2), 45.6 (C-21), 44.0 (C-27), 25.3 (C-3); HRMS (ESI^+): calcd. for $C_{27}H_{39}N_4O_5S$, 531.2636. Found $[MH]^+$ 531.2643 (−1.3 ppm error).

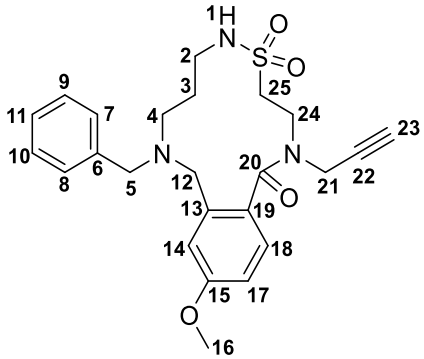
3.90: 10-Benzyl-2-(furan-2-ylmethyl)-13-methoxy-3,4,6,7,8,9,10,11-octahydrobenzo[*h*][1]thia[2,6,11]triazacyclotridecin-1(2*H*)-one 5,5-dioxide



To a round-bottomed flask, 2-((benzyl(3-(vinylsulfonamido)propyl)amino)methyl)-4-methoxybenzoic acid (102 mg, 0.243 mmol) was dissolved in chloroform (10.0 mL) and DIPEA (0.08 mL, 0.486 mmol) was added dropwise. Then, T3P (50% solution in ethyl acetate,

0.23 mL, 0.365 mmol) was added dropwise and the solution stirred at RT for 17 hours. The reaction mixture was diluted with DCM (10 mL) and washed with $NaHCO_3$ (2 x 10 mL). The organic layer was dried, filtered and concentrated *in vacuo* to remove excess solvent to form 9-membered ring intermediate **3.51**, which was used directly in the next step. To this resulting white oil was added DIPEA (0.13 mL, 0.729 mmol) in THF (2.0 mL), followed by furan-2-ylmethanamine (27.0 µL, 0.304 mmol) in a single portion. The reaction mixture was allowed to stir at RT for 48 hours. Then, the solution was diluted in DCM (10 mL) and washed with $NaHCO_3$ (2 x 10 mL). The organic layer was dried, filtered and concentrated *in vacuo* to yield the title compound, which was obtained as a white oil (88.0 mg, 73%). The ^{1}H NMR spectrum is severely affected by rotameric broadening, with product identity and purity best determined using ^{13}C NMR data; ν_{max}/cm^{-1} (thin film): 2920, 2841, 1674, 1606, 1453, 1334, 1258, 1147, 1120, 1011, 762, 733, 704; δ_H (400 MHz, $CDCl_3$) 7.41 – 7.33 (1H, m, H-25 [overlapping]), 7.41 – 7.22 (5H, m, 5 x Ar**H** [overlapping]), 7.04 (1H, d, *J* = 8.5 Hz, H-18), 6.76 (1H, dd, *J* = 8.5, 2.5 Hz, H-17), 6.67 (1H, d, *J* = 2.5 Hz, H-14), 6.31 (1H, dd, *J* = 3.0, 2.0 Hz, H-24), 6.21 (1H, d, *J* = 3.0 Hz, H-23), 3.84 (4H, s, H-5,21 [overlapping]), 3.92 – 3.81 (2H, m, H-12 [overlapping]), 3.77 (3H, s, H-16), 3.19 (2H, t, *J* = 6.5 Hz, H-26); δ_C (100 MHz, $CDCl_3$) 172.2 (C-20), 160.2 (C-15), 153.2 (C-22), 142.1 (C-25), 141.9 (C-13/19), 136.0 (C-6), 130.0 (C-7,8), 128.5 (13/19), 128.3 (C-9,10), 127.4 (C-11), 126.5 (C-18), 114.0 (C-14), 112.7 (C-17), 110.3 (C-24), 107.5 (C-23), 56.7 (C-12), 56.3 (C-5), 55.4 (C-16), 54.7 (C-27), 49.4 (C-4), 47.6 (C-2), 45.8 (C-21), 43.1 (C-26), 25.3 (C-3); HRMS (ESI^+): calcd. for $C_{26}H_{31}N_3NaO_5S$, 520.1877. Found: $[MNa]^+$, 520.1877 (0.0 ppm error).

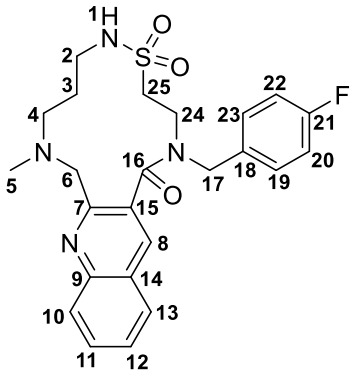
3.91: 10-Benzyl-13-methoxy-2-(prop-2-yn-1-yl)-3,4,6,7,8,9,10,11-octahydrobenzo[*h*][1]thia[2,6,11]triazacyclotridecin-1(2*H*)-one 5,5-dioxide



To a round-bottomed flask, 2-((benzyl(3-(vinylsulfonamido)propyl)amino)methyl)-4-methoxybenzoic acid (109 mg, 0.260 mmol) was dissolved in chloroform (10.0 mL) and DIPEA (0.09 mL, 0.520 mmol) was added dropwise. T3P (50% solution in ethyl acetate, 0.25

mL, 0.390 mmol) was added dropwise and the solution stirred at RT for 17 hours. The reaction mixture was diluted with DCM (10 mL) and washed with $NaHCO_3$ (2 x 10 mL). The organic layer was dried with $MgSO_4$, filtered and concentrated *in vacuo* to remove excess solvent to form 9-membered ring intermediate **3.51**, which was used directly in the next step. To this resulting white oil was added DIPEA (0.12 mL, 0.693 mmol) in THF (3.0 mL) and propargylamine (18.0 μL, 0.283 mmol) in a single portion. The reaction mixture was allowed to stir at RT for 168 hours. Then, the solution was diluted in DCM (10 mL) and washed with $NaHCO_3$ (2 x 10 mL). The organic layer was dried with $MgSO_4$, filtered and concentrated *in vacuo* to afford the title compound, which was obtained as an orange oil (95.5 mg, 81%). The ^{1}H NMR spectrum is severely affected by rotameric broadening, with product identity and purity best determined using ^{13}C NMR data; ν_{max}/cm^{-1} (thin film): 2921, 2852, 1673, 1607, 1498, 1453, 1335, 1258, 1149, 1119, 1011, 909, 763, 729, 703, 610; δ_H (400 MHz, $CDCl_3$) 7.39 – 7.22 (5H, m, 5 x Ar**H**), 7.16 (1H, d, *J* = 8.5 Hz, H-18), 6.78 (1H, dd, *J* = 8.5, 2.5 Hz, H-17), 6.68 (1H, d, *J* = 2.5 Hz, H-14), 3.84 (2H, m, H-5 [overlapping]), 3.90 – 3.82 (2H, m, H-25 [overlapping]), 3.76 (3H, s, H-16), 3.48 (2H, d, *J* = 3.0 Hz, H-21), 3.28 (2H, t, *J* = 6.5 Hz, H-24), 2.25 (1H, t, *J* = 3.0 Hz, H-23); δ_C (100 MHz, $CDCl_3$) 172.3 (C-20), 160.2 (C-15), 141.9 (C-13/19), 136.0 (C-6), 130.0 (C-7,8), 128.5 (13/19), 128.3 (C-9,10), 127.4 (C-11), 126.5 (C-18), 114.1 (C-14), 112.6 (C-17), 81.6 (C-23), 72.1 (C-22), 56.8 (C-12), 56.4 (C-5), 55.4 (C-16), 54.6 (C-25), 49.4 (C-4), 47.6 (C-2), 42.8 (C-24), 38.0 (C-21), 25.3 (C-3); HRMS (ESI^+): calcd. for $C_{24}H_{29}N_3NaO_4S$, 478.1771. Found: $[MNa]^+$, 478.1780 (−1.8 ppm error).

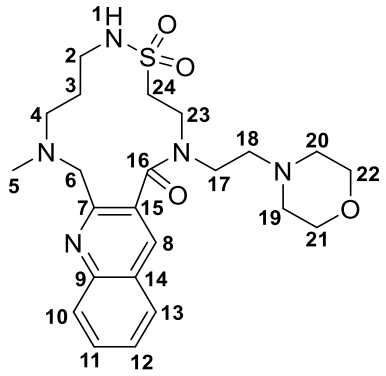
3.93: 2-(4-Fluorobenzyl)-10-methyl-3,4,6,7,8,9,10,11-octahydro-[1]thia[2,6,11]triazacyclotridecino[9,8-*b*]quinolin-1(2*H*)-one 5,5-dioxide



To a round-bottomed flask 2-((methyl(3-(vinylsulfonamido)propyl)amino)methyl)quinoline-3-carboxylic acid (72.7 mg, 0.200 mmol) was dissolved in chloroform (5.0 mL) and DIPEA (65.0 μL, 0.373 mmol) was added dropwise. T3P (50% solution in ethyl acetate, 0.19 mL, 0.302 mmol) was added dropwise and the solution stirred at RT for 16 hours. The reaction

mixture was diluted with DCM (5 mL) and washed with $NaHCO_3$ (2 x 10 mL). The organic layer was dried, filtered and concentrated *in vacuo* to remove excess solvent to form 9-membered ring intermediate **3.52**, which was used directly in the next step. To this resulting colourless oil was added DIPEA (0.11 mL, 0.628 mmol) in THF (2.0 mL) and 4-fluorobenzylamine (28.8 µL, 0.252 mmol) in a single portion. The reaction mixture was stirred at RT for 96 hours. Upon completion, the solution was diluted with DCM (10 mL) and washed with $NaHCO_3$ (2 x 10 mL). The organic layer was dried, filtered and concentrated *in vacuo* to yield the title compound, which was obtained as a yellow oil (80.4 mg, 85%). The ^{1}H NMR spectrum is severely affected by rotameric broadening, with product identity and purity best determined using ^{13}C NMR data; ν_{max}/cm^{-1} (thin film): 2847, 1672, 1509, 1335, 1220, 1145, 999, 908, 755, 726, 646; δ_H (400 MHz, $CDCl_3$) 8.03 (1H, d, *J* = 8.5 Hz, H-10), 7.90 (1H, s, H-8 [overlapping]), 7.73 (1H, d, *J* = 8.5 Hz, H-13 [overlapping]), 7.79 – 7.69 (1H, m, H-11 [overlapping]), 7.57 (1H, t, *J* = 7.5 Hz, H-12), 7.32 (2H, dd, *J* = 8.5, 5.5 Hz, H-19,23), 7.00 (2H, t, *J* = 8.5 Hz, H-20,22), 3.84 (2H, s, H-17), 3.24 (2H, t, *J* = 6.0 Hz, H-24), 2.45 (3H, s, H-5); δ_C (100 MHz, $CDCl_3$) 169.5 (C-16), 162.1 (C-21, d, $^1J_{CF}$ = 244.6 Hz), 159.6 (Ar**C**), 147.5 (Ar**C**), 135.4 (C-18, d, $^4J_{CF}$ = 3.5 Hz), 133.1 (C-8), 131.0 (C-11), 129.8 (C-19,23, d, $^3J_{CF}$ = 7.7 Hz), 129.6 (Ar**C**), 129.0 (C-10), 128.0 (C-13), 127.4 (C-12), 126.4 (Ar**C**), 115.4 (C-20,22, d, $^2J_{CF}$ = 21.3 Hz), 61.9 (C-6), 55.3 (C-4/25), 55.2 (C-4/25), 52.7 (C-17), 47.9 (C-2), 43.1 (C-24), 41.4 (C-5), 25.4 (C-3); δ_F (282 MHz, $CDCl_3$) −115.45 (1F, m, Ar**F**); HRMS (ESI$^+$): calcd. for $C_{24}H_{28}FN_4O_3S$, 471.1861. Found $[MH]^+$ 471.1861 (−0.1 ppm error).

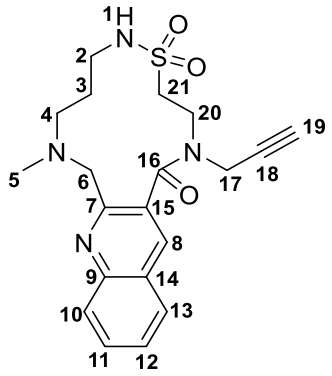
3.94: 10-Methyl-2-(2-morpholinoethyl)-3,4,6,7,8,9,10,11-octahydro-[1]thia[2,6,11]triazacyclotridecino[8,9-*b*]quinolin-1(2*H*)-one 5,5-dioxide



To a round-bottomed flask 2-((methyl(3-(vinylsulfonamido)propyl)amino)methyl)quinoline-3-carboxylic acid (72.7 mg, 0.200 mmol) was dissolved in chloroform (5.0 mL) and DIPEA (65.0 µL, 0.373 mmol) was added dropwise. T3P (50% solution in ethyl acetate, 0.19 mL, 0.302 mmol) was added dropwise and the solution stirred at RT for 16 hours. The reaction

mixture was diluted with DCM (5 mL) and washed with $NaHCO_3$ (2 x 10 mL). The organic layer was dried, filtered and concentrated *in vacuo* to remove excess solvent to form 9-membered ring intermediate **3.52**, which was used directly in the next step. To this resulting colourless oil was added DIPEA (0.11 mL, 0.628 mmol) in THF (2.0 mL) and 4-(2-aminoethyl)morpholine (31.5 µL, 0.240 mmol) in a single portion. The reaction mixture was stirred at RT for 96 hours. Upon completion, the solution was diluted with DCM (10 mL) and washed with $NaHCO_3$ (2 x 10 mL). The organic layer was dried, filtered and concentrated *in vacuo* to yield the title compound, which was obtained as an orange oil (79.3 mg, 83%). The ^{1}H NMR spectrum is severely affected by rotameric broadening, with product identity and purity best determined using ^{13}C NMR data; ν_{max}/cm^{-1} (thin film): 2942, 2849, 1674, 1453, 1337, 1244, 1144, 1116, 999, 915, 756, 729; δ_H (400 MHz, $CDCl_3$) 8.03 (1H, d, *J* = 8.5 Hz, H-10), 8.01 (1H, s, H-8), 7.80 (1H, d, *J* = 8.0 Hz, H-13), 7.76 (1H, d, *J* = 7.5 Hz, H-11), 7.57 (1H, t, *J* = 7.5 Hz, H-12), 3.69 (4H, t, *J* = 4.5 Hz, H-21,22 [overlapping]), 4.36 – 3.58 (6H, m, 3 x C**H$_2$** [overlapping]), 3.29 (2H, t, *J* = 6.5 Hz, H-23), 2.79 (2H, t, *J* = 6.0 Hz, H-17), 2.52 (2H, t, *J* = 6.0 Hz, H-18), 2.46 (3H, s, H-5 [overlapping]), 2.48 – 2.41 (4H, m, H-19,20 [overlapping]); δ_C (100 MHz, $CDCl_3$) 169.5 (C-16), 159.6 (Ar**C**), 147.5 (Ar**C**), 133.2 (C-8), 130.9 (C-11), 129.7 (Ar**C**), 129.0 (C-10), 128.0 (C-13), 127.4 (C-12), 126.5 (Ar**C**), 67.1 (C-21,22), 61.9 (C-6), 58.2 (C-18), 55.24 (C-4/24), 55.20 (C-4/24), 53.8 (C-19,20), 47.9 (C-2), 45.7 (C-17), 43.9 (C-23), 41.4 (C-5), 25.4 (C-3); HRMS (ESI$^+$): calcd. for $C_{23}H_{34}N_5O_4S$, 476.2326. Found $[MH]^+$ 476.2344 (−3.7 ppm error).

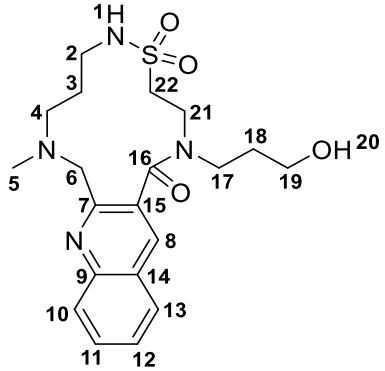
3.95: 10-Methyl-2-(prop-2-yn-1-yl)-3,4,6,7,8,9,10,11-octahydro-[1]thia[2,6,11]triazacyclotridecino[8,9-*b*]quinolin-1(2*H*)-one 5,5-dioxide



To a round-bottomed flask 2-((methyl(3-(vinylsulfonamido)propyl)amino)methyl)quinoline-3-carboxylic acid (72.7 mg, 0.200 mmol) was dissolved in chloroform (5.0 mL) and DIPEA (65.0 µL, 0.373 mmol) was added dropwise. T3P (50% solution in ethyl acetate, 0.19 mL, 0.302 mmol) was added dropwise and the solution stirred at RT for 16 hours. The reaction

mixture was diluted with DCM (5 mL) and washed with $NaHCO_3$ (2 x 10 mL). The organic layer was dried, filtered and concentrated *in vacuo* to remove excess solvent to form 9-membered ring intermediate **3.52**, which was used directly in the next step. To this resulting colourless oil was added DIPEA (0.11 mL, 0.628 mmol) in THF (2.0 mL) and propargylamine (15.9 µL, 0.248 mmol) in a single portion. The reaction mixture was stirred at RT for 96 hours. Upon completion, the solution was diluted with DCM (10 mL) and washed with $NaHCO_3$ (2 x 10 mL). The organic layer was dried, filtered and concentrated *in vacuo* to yield the title compound, which was obtained as a yellow oil (66.0 mg, 82%). The ^{1}H NMR spectrum is severely affected by rotameric broadening, with product identity and purity best determined using ^{13}C NMR data; ν_{max}/cm^{-1} (thin film): 3281, 2847, 1975, 1672, 1337, 1244, 1145, 1117, 1058, 999, 794, 756, 729, 647; δ_H (400 MHz, $CDCl_3$) 8.05 (1H, s, H-8), 8.03 (1H, d, *J* = 8.5 Hz, H-10), 7.80 (1H, d, *J* = 8.0 Hz, H-13), 7.75 (1H, td, *J* = 7.0, 1.5 Hz, H-11), 7.57 (1H, t, *J* = 7.5 Hz, H-12), 4.33 – 3.56 (6H, m, 3 x C**H$_2$**), 3.51 (2H, d, *J* = 2.5 Hz, H-17), 3.33 (2H, t, *J* = 6.0 Hz, H-20), 2.85 – 2.55 (2H, m, C**H$_2$**), 2.47 (3H, s, H-5), 2.27 (1H, t, *J* = 2.5 H-19); δ_C (100 MHz, $CDCl_3$) 169.5 (C-16), 159.7 (Ar**C**), 147.5 (Ar**C**), 133.3 (C-8), 130.9 (C-11), 129.7 (Ar**C**), 129.0 (C-10), 128.0 (C-13), 127.4 (C-12), 126.5 (Ar**C**), 81.6 (C-19), 72.2 (C-18), 61.9 (C-6), 55.3 (C-4/21), 55.1 (C-4/21), 47.9 (C-2), 42.8 (C-20), 41.4 (C-5), 38.1 (C-17), 25.4 (C-3); HRMS (ESI^+): calcd. for $C_{20}H_{25}N_4O_3S$, 401.1642. Found: $[MH]^+$, 401.1643 (−0.3 ppm error).

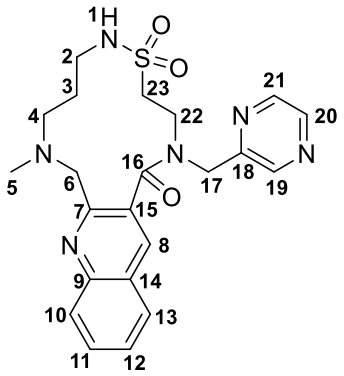
3.96: 2-(3-Hydroxypropyl)-10-methyl-3,4,6,7,8,9,10,11-octahydro-[1]thia[2,6,11]triazacyclotridecino[8,9-*b*]quinolin-1(2*H*)-one 5,5-dioxide



To a round-bottomed flask 2-((methyl(3-(vinylsulfonamido)propyl)amino)methyl)quinoline-3-carboxylic acid (72.7 mg, 0.200 mmol) was dissolved in chloroform (5.0 mL) and DIPEA (65.0 µL, 0.373 mmol) was added dropwise. T3P (50% solution in ethyl acetate, 0.19 mL, 0.302 mmol) was added dropwise and the solution stirred at RT for 16 hours. The reaction mixture was diluted with DCM (5 mL) and washed with $NaHCO_3$ (2 x 10 mL). The organic layer was dried, filtered and concentrated *in vacuo* to remove excess solvent to form 9-

membered ring intermediate **3.52**, which was used directly in the next step. To this resulting colourless oil was added DIPEA (0.11 mL, 0.628 mmol) in THF (2.0 mL) and 3-amino-1-propanol (18.4 µL, 0.240 mmol) in a single portion. The reaction mixture was stirred at RT for 96 hours. Upon completion, the solution was diluted with DCM (10 mL) and washed with $NaHCO_3$ (2 x 10 mL). The organic layer was dried, filtered and concentrated *in vacuo* to yield the title compound, which was obtained as a pale yellow oil (60.3 mg, 72%). The ^1H NMR spectrum is severely affected by rotameric broadening, with product identity and purity best determined using ^{13}C NMR data; ν_{max}/cm^{-1} (thin film): 3318, 2931, 2847, 1674, 1357, 1337, 1244, 1146, 999, 756, 730, 647; δ_H (400 MHz, $CDCl_3$) 8.03 (1H, d, *J* = 9.0 Hz, H-10 [overlapping]), 8.02 (1H, s, H-8 [overlapping]), 7.82 (1H, d, *J* = 8.5 Hz, H-13), 7.76 (1H, t, *J* = 8.0 Hz, H-11), 7.58 (1H, t, *J* = 8.0 Hz, H-12), 3.81 (2H, t, *J* = 5.5 Hz, H-19 [overlapping]), 4.33 – 3.56 (5H, m, 2.5 x C**H₂** [overlapping]), 3.29 (2H, t, *J* = 6.0 Hz, H-21), 2.93 (2H, t, *J* = 6.0 Hz, H-17), 2.46 (3H, s, H-5), 1.75 (2H, p, *J* = 5.5 Hz, H-18); δ_C (100 MHz, $CDCl_3$) 169.6 (C-16), 159.5 (Ar**C**), 147.5 (Ar**C**), 133.2 (C-8), 131.0 (C-11), 129.6 (Ar**C**), 129.0 (C-10), 128.1 (C-13), 127.5 (C-12), 126.5 (Ar**C**), 63.7 (C-19), 61.9 (C-6), 55.3 (C-4/22), 55.2 (C-4/22), 49.0 (C-17), 48.0 (C-2), 43.7 (C-21), 41.5 (C-5), 31.0 (C-18), 25.3 (C-3); HRMS (ESI^+): calcd. for $C_{20}H_{29}N_4O_4S$, 421.1904. Found $[MH]^+$ 421.1913 (−2.1 ppm error).

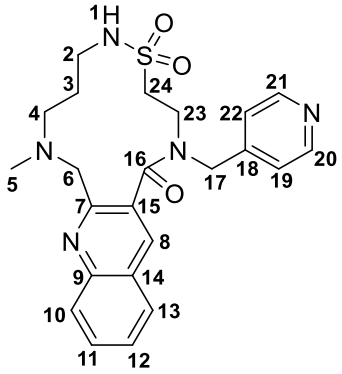
3.97: 10-Methyl-2-(pyrazin-2-ylmethyl)-3,4,6,7,8,9,10,11-octahydro-[1]thia[2,6,11]triazacyclotridecino[8,9-*b*]quinolin-1(2*H*)-one 5,5-dioxide



To a round-bottomed flask 2-((methyl(3-(vinylsulfonamido)propyl)amino)methyl)quinoline-3-carboxylic acid (72.7 mg, 0.200 mmol) was dissolved in chloroform (5.0 mL) and DIPEA (65.0 µL, 0.373 mmol) was added dropwise. T3P (50% solution in ethyl acetate, 0.19 mL, 0.302 mmol) was added dropwise and the solution stirred at RT for 16 hours. The reaction mixture was diluted with DCM (5 mL) and washed with $NaHCO_3$ (2 x 10 mL). The organic layer was dried, filtered and concentrated *in vacuo* to remove excess solvent to form 9-membered ring intermediate **3.52**, which was used directly in the next step. To this resulting

colourless oil was added DIPEA (0.11 mL, 0.628 mmol) in THF (2.0 mL) and 2-aminomethylpyrazine (29.2 mg, 0.268 mmol) in a single portion. The reaction mixture was stirred at RT for 96 hours. Upon completion, the solution was diluted with DCM (10 mL) and washed with $NaHCO_3$ (2 x 10 mL). The organic layer was dried, filtered and concentrated *in vacuo* to yield the title compound, which was obtained as a yellow oil (64.9 mg, 71%). The ^1H NMR spectrum is severely affected by rotameric broadening, with product identity and purity best determined using ^{13}C NMR data; ν_{max}/cm^{-1} (thin film): 2847, 1672, 1338, 1244, 1145, 1058, 999, 794, 757, 729, 646, 582; δ_H (400 MHz, $CDCl_3$) 8.66 – 8.63 (1H, m, H-19), 8.53 – 8.49 (1H, m, H-21), 8.46 (1H, d, *J* = 2.5 Hz, H-20), 8.02 (1H, d, *J* = 8.5 Hz, H-10), 7.95 (1H, s, H-8), 7.73 (1H, d, *J* = 7.5 Hz, H-13 [overlapping]), 7.78 – 7.70 (1H, m, H-11 [overlapping]), 7.55 (1H, t, *J* = 7.5 Hz, H-12), 4.04 (2H, s, H-17 [overlapping]), 4.36 – 3.80 (6H, m, 3 x C**H₂** [overlapping]), 3.32 (2H, t, *J* = 6.5 Hz, H-22), 2.45 (3H, s, H-5 [overlapping]), 2.75 – 2.36 (2H, m, C**H₂** [overlapping]); δ_C (100 MHz, $CDCl_3$) 169.5 (C-16), 159.6 (Ar**C**), 154.7 (C-18), 147.5 (Ar**C**), 144.3 (C-19/21), 144.2 (C-19/21), 143.5 (C-20), 133.2 (C-8), 130.9 (C-11), 129.6 (Ar**C**), 129.0 (C-10), 128.0 (C-13), 127.4 (C-12), 126.4 (Ar**C**), 61.9 (C-6), 55.4 (C-4/23), 55.2 (C-4/23), 52.4 (C-17), 47.9 (C-2), 43.6 (C-22), 41.4 (C-5), 25.3 (C-3); HRMS (ESI^+): calcd. for $C_{22}H_{26}N_6NaO_3S$, 477.1679. Found: $[MNa]^+$, 477.1679 (0.0 ppm error).

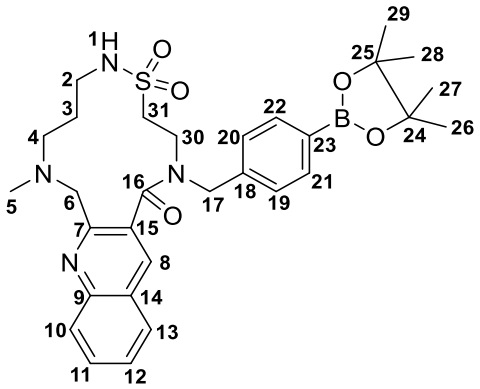
3.98: 10-Methyl-2-(pyridin-4-ylmethyl)-3,4,6,7,8,9,10,11-octahydro-[1]thia[2,6,11]triazacyclotridecino[8,9-*b*]quinolin-1(2*H*)-one 5,5-dioxide



To a round-bottomed flask 2-((methyl(3-(vinylsulfonamido)propyl)amino)methyl)quinoline-3-carboxylic acid (72.7 mg, 0.200 mmol) was dissolved in chloroform (5.0 mL) and DIPEA (65.0 µL, 0.373 mmol) was added dropwise. T3P (50% solution in ethyl acetate, 0.19 mL, 0.302 mmol) was added dropwise and the solution stirred at RT for 16 hours. The reaction mixture was diluted with DCM (5 mL) and washed with $NaHCO_3$ (2 x 10 mL). The organic layer was dried, filtered and concentrated *in vacuo* to remove excess solvent to form 9-membered ring intermediate **3.52**, which was used directly in the next step. To this resulting

colourless oil was added DIPEA (0.11 mL, 0.628 mmol) in THF (2.0 mL) and 4-(aminomethyl)pyridine (24.4 µL, 0.240 mmol) in a single portion. The reaction mixture was stirred at RT for 96 hours. Upon completion, the solution was diluted with DCM (10 mL) and washed with $NaHCO_3$ (2 x 10 mL). The organic layer was dried, filtered and concentrated *in vacuo* to yield the title compound, which was obtained as an orange oil (75.3 mg, 83%). The ^1H NMR spectrum is severely affected by rotameric broadening, with product identity and purity best determined using ^{13}C NMR data; ν_{max}/cm^{-1} (thin film): 2931, 2846, 1673, 1600, 1416, 1337, 1244, 1145, 1058, 999, 915, 794, 756, 729, 646; δ_H (400 MHz, $CDCl_3$) 8.55 (1H, d, *J* = 4.5, 1.5 Hz, H-20,21), 8.03 (1H, d, *J* = 8.5 Hz, H-10), 7.91 (1H, s, H-8), 7.75 (1H, d, *J* = 7.5 Hz, H-11 [overlapping]), 7.80 – 7.72 (1H, m, H-13 [overlapping]), 7.57 (1H, t, *J* = 7.5 Hz, H-12), 7.30 (1H, dd, *J* = 4.5, 1.5 Hz, H-19,22), 3.90 (2H, s, H-17 [overlapping]), 4.35 – 3.61 (6H, m, 3 x C**H₂**), 3.26 (2H, t, *J* = 6.0 Hz, H-23), 2.46 (3H, s, H-5); δ_C (100 MHz, $CDCl_3$) 169.6 (C-16), 159.5 (Ar**C**), 150.1 (C-20,21), 148.8 (C-18), 147.5 (Ar**C**), 133.1 (C-8), 131.0 (C-11), 129.6 (Ar**C**), 129.0 (C-10), 128.0 (C-13), 127.5 (C-12), 126.4 (Ar**C**), 123.0 (C-19,22), 61.9 (C-6), 55.4 (C-24), 55.2 (C-4), 52.2 (C-17), 47.9 (C-2), 43.3 (C-23), 41.4 (C-5), 25.3 (C-3); HRMS (ESI^+): calcd. for $C_{23}H_{28}N_5O_3S$, 454.1907. Found $[MH]^+$ 454.1906 (0.4 ppm error).

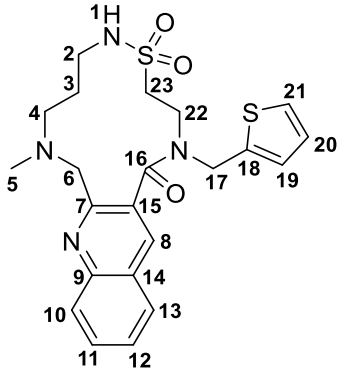
3.99: 10-Methyl-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-3,4,6,7,8,9,10,11-octahydro-[1]thia[2,6,11]triazacyclotridecino[8,9-*b*]quinolin-1(2*H*)-one 5,5-dioxide



To a round-bottomed flask 2-((methyl(3-(vinylsulfonamido)propyl)amino)methyl)quinoline-3-carboxylic acid (72.7 mg, 0.200 mmol) was dissolved in chloroform (5.0 mL) and DIPEA (65.0 µL, 0.373 mmol) was added dropwise. T3P (50% solution in ethyl acetate, 0.19 mL, 0.302 mmol) was added dropwise and the solution stirred at RT for 16 hours. The reaction mixture was diluted with DCM (5 mL) and washed with $NaHCO_3$ (2 x 10 mL). The organic layer was dried, filtered and concentrated *in vacuo* to remove excess solvent to form 9-membered ring intermediate **3.52**, which was used directly in the next step. To this resulting

colourless oil was added DIPEA (0.11 mL, 0.628 mmol) in THF (2.0 mL) and (4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanamine (56.9 mg, 0.244 mmol) in a single portion. The reaction mixture was stirred at RT for 96 hours. Upon completion, the solution was diluted with DCM (10 mL) and washed with $NaHCO_3$ (2 x 10 mL). The organic layer was dried, filtered and concentrated *in vacuo* to yield the title compound, which was obtained as an orange oil (99.4 mg, 86%). Contains a small amount of (4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanamine. The ^{1}H NMR spectrum is severely affected by rotameric broadening, with product identity and purity best determined using ^{13}C NMR data; ν_{max}/cm^{-1} (thin film): 2975, 1675, 1613, 1399, 1358, 1322, 1270, 1143, 1088, 999, 859, 755, 730, 658; δ_H (400 MHz, $CDCl_3$) 8.01 (1H, d, *J* = 8.5 Hz, H-10), 7.87 (1H, s, H-8), 7.77 (2H, d, *J* = 7.5 Hz, H-21,22 [overlapping]), 7.80 – 7.70 (1H, m, H-11 [overlapping]), 7.70 (1H, d, *J* = 8.0 Hz, H-13), 7.54 (1H, t, *J* = 7.5 Hz, H-12), 7.35 (2H, d, *J* = 7.5 Hz, H-19,20), 4.29 – 3.97 (2H, m, C**H$_2$**), 3.89 (2H, s, H-17), 3.77 – 3.53 (2H, m, C**H$_2$**), 3.23 (2H, t, *J* = 6.0 Hz, H-30), 2.43 (3H, s, H-5), 1.31 (12H, s, H-26,27,28,29); δ_C (100 MHz, $CDCl_3$) 169.4 (C-16), 159.6 (Ar**C**), 147.4 (Ar**C**), 142.9 (C-18), 135.2 (C-21,22), 133.2 (C-8), 130.8 (C-11), 129.6 (Ar**C**), 128.9 (C-10), 128.1 (C-13), 127.5 (C-19,20), 127.3 (C-12), 126.5 (Ar**C**), 126.4 (Ar**C**), 83.8 (C-24,25), 61.9 (C-6), 55.2 (C-4,31), 53.5 (C-17), 47.8 (C-2), 43.2 (C-30), 41.3 (C-5), 25.3 (C-3), 24.9 (C-26,27,28,29); HRMS (ESI^+): calcd. for $C_{30}H_{39}BN_4NaO_5S$, 601.2626. Found: $[MNa]^+$, 601.2637 (−0.8 ppm error).

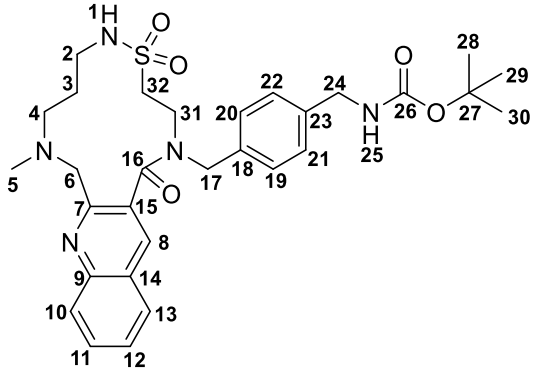
3.100: 10-Methyl-2-(thiophen-2-ylmethyl)-3,4,6,7,8,9,10,11-octahydro-[1]thia[2,6,11]triazacyclotridecino[8,9-*b*]quinolin-1(2*H*)-one 5,5-dioxide



To a round-bottomed flask 2-((methyl(3-(vinylsulfonamido)propyl)amino)methyl)quinoline-3-carboxylic acid (72.7 mg, 0.200 mmol) was dissolved in chloroform (5.0 mL) and DIPEA (65.0 µL, 0.373 mmol) was added dropwise. T3P (50% solution in ethyl acetate, 0.19 mL, 0.302 mmol) was added dropwise and the solution stirred at RT for 16 hours. The reaction mixture was diluted with DCM (5 mL) and washed with $NaHCO_3$ (2 x 10 mL). The organic

layer was dried, filtered and concentrated *in vacuo* to remove excess solvent to form 9-membered ring intermediate **3.52**, which was used directly in the next step. To this resulting colourless oil was added DIPEA (0.11 mL, 0.628 mmol) in THF (2.0 mL) and 2-aminomethylthiophene (24.6 µL, 0.240 mmol) in a single portion. The reaction mixture was stirred at RT for 96 hours. Upon completion, the solution was diluted with DCM (10 mL) and washed with $NaHCO_3$ (2 x 10 mL). The organic layer was dried, filtered and concentrated *in vacuo* to yield the title compound, which was obtained as a yellow oil (77.3 mg, 84%). Contains a small amount of 2-aminomethylthiophene. The ^{1}H NMR spectrum is severely affected by rotameric broadening, with product identity and purity best determined using ^{13}C NMR data; ν_{max}/cm^{-1} (thin film): 2927, 2846, 1672, 1452, 1335, 1244, 1144, 1058, 999, 910, 794, 755, 728, 646; δ_H (400 MHz, $CDCl_3$) 8.03 (1H, d, *J* = 8.5 Hz, H-10), 7.92 (1H, s, H-8), 7.80 – 7.72 (1H, m, H-13 [overlapping]), 7.80 – 7.72 (1H, m, H-11 [overlapping]), 7.57 (1H, t, *J* = 7.5 Hz, H-12), 7.22 (2H, dd, *J* = 5.0, 1.5 Hz, H-20), 7.00 – 6.87 (2H, m, H-19,21), 4.08 (2H, s, H-17 [overlapping]), 4.31 – 3.78 (4H, m, 2 x C**H$_2$** [overlapping]), 3.27 (2H, t, *J* = 6.5 Hz, H-22), 2.46 (3H, s, H-5); δ_C (100 MHz, $CDCl_3$) 169.5 (C-16), 159.7 (Ar**C**), 147.5 (Ar**C**), 143.4 (C-18), 133.2 (C-8), 130.9 (C-11), 129.7 (Ar**C**), 129.0 (C-10), 128.1 (C-13), 127.3 (C-12), 126.9 (C-21), 126.5 (Ar**C**), 125.5 (C-19), 124.8 (C-20), 61.9 (C-6), 55.2 (C-4/23), 55.1 (C-4/23), 48.0 (C-2/17), 47.9 (C-2/17), 42.9 (C-22), 41.3 (C-5), 25.4 (C-3); HRMS (ESI$^+$): calcd. for $C_{22}H_{26}N_4NaO_3S_2$, 481.1339. Found $[MNa]^+$ 481.1342 (−0.8 ppm error).

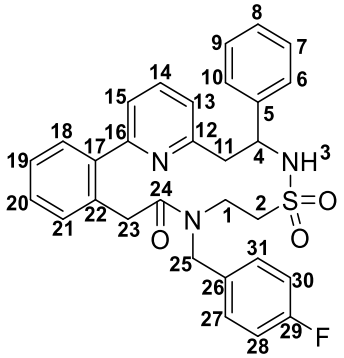
3.101: *tert*-Butyl (4-((10-methyl-5,5-dioxido-1-oxo-3,4,6,7,8,9,10,11-octahydro-[1]thia[2,6,11]triazacyclotridecino[8,9-*b*]quinolin-2(1*H*)-yl)methyl)benzyl)carbamate



To a round-bottomed flask 2-((methyl(3-(vinylsulfonamido)propyl)amino)methyl)quinoline-3-carboxylic acid (72.7 mg, 0.200 mmol) was dissolved in chloroform (5.0 mL) and DIPEA (65.0 µL, 0.373 mmol) was added dropwise. T3P (50% solution in ethyl acetate, 0.19 mL, 0.302 mmol) was added dropwise and the solution stirred at RT for 16 hours. The reaction mixture was diluted with DCM (5 mL) and washed with $NaHCO_3$ (2 x 10 mL). The organic

layer was dried, filtered and concentrated *in vacuo* to remove excess solvent to form 9-membered ring intermediate **3.52**, which was used directly in the next step. To this resulting colourless oil was added DIPEA (0.11 mL, 0.628 mmol) in THF (2.0 mL) and *tert*-butyl 4-(aminomethyl)benzylcarbamate (58.2 mg, 0.246 mmol) in a single portion. The reaction mixture was stirred at RT for 96 hours. Upon completion, the solution was diluted with DCM (10 mL) and washed with $NaHCO_3$ (2 x 10 mL). The organic layer was dried, filtered and concentrated *in vacuo* to yield the title compound, which was obtained as a yellow oil (107 mg, 92%). Contains a small amount of *tert*-butyl 4-(aminomethyl)benzylcarbamate. The ^{1}H NMR spectrum is severely affected by rotameric broadening, with product identity and purity best determined using ^{13}C NMR data; ν_{max}/cm^{-1} (thin film): 2971, 1690, 1514, 1365, 1338, 1246, 1158, 999, 915, 866, 780, 756, 730, 646; δ_H (400 MHz, $CDCl_3$) 8.01 (1H, d, *J* = 8.5 Hz, H-10), 7.89 (1H, s, H-8), 7.74 (1H, t, *J* = 8.0 Hz, H-11), 7.68 (1H, d, *J* = 8.0 Hz, H-13), 7.55 (1H, t, *J* = 7.5 Hz, H-12), 7.28 (2H, t, *J* = 7.5 Hz, H-19,20), 7.25 – 7.14 (2H, m, H-21,22), 5.02 – 4.89 (1H, m, H-25), 4.25 (2H, d, *J* = 6.0 Hz, H-24 [overlapping]), 4.33 – 3.95 (5H, m, 2.5 x C**H$_2$** [overlapping]), 3.83 (2H, s, H-17), 3.76 – 3.52 (2H, m, C**H$_2$**), 3.23 (2H, t, *J* = 6.0 Hz, H-31), 2.44 (3H, s, H-5), 1.43 (9H, s, H-28,29,30); δ_C (100 MHz, $CDCl_3$) 169.4 (C-16), 159.6 (Ar**C**), 155.9 (C-26), 147.4 (Ar**C**), 138.7 (C-18), 138.0 (C-23), 133.1 (C-8), 130.9 (C-11), 129.6 (Ar**C**), 128.9 (C-10), 128.5 (C-19,20), 128.0 (C-13), 127.7 (C-21,22), 127.3 (C-12), 126.4 (Ar**C**), 79.5 (C-27), 61.9 (C-6), 55.2 (C-4,32), 53.1 (C-17), 47.8 (C-2), 44.4 (C-24), 43.2 (C-31), 41.3 (C-5), 28.5 (C-28,29,30), 25.3 (C-3); HRMS (ESI$^+$): calcd. for $C_{30}H_{40}N_5O_5S$, 582.2745. Found: $[MH]^+$, 582.2742 (0.5 ppm error).

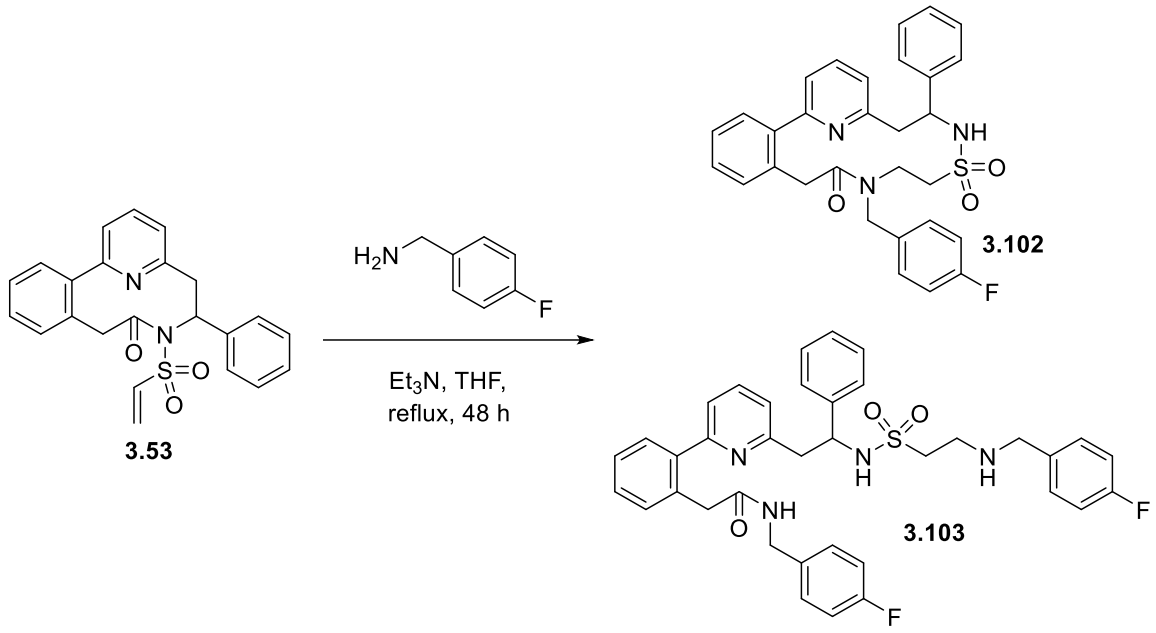
3.102: 5-(4-Fluorobenzyl)-10-phenyl-8-thia-5,9-diaza-1(2,6)-pyridina-2(1,2)-benzenacycloundecaphan-4-one 8,8-dioxide



To a round-bottomed flask 2-(2-(6-(2-phenyl-2-(vinylsulfonamido)ethyl)pyridin-2-yl)phenyl)acetic acid (84.5 mg, 0.200 mmol) was dissolved in chloroform (5.0 mL) and DIPEA (63.8 µL, 0.366 mmol), was added dropwise. T3P (50% solution in ethyl acetate, 0.19 mL,

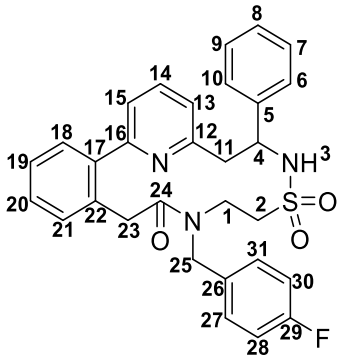
0.300 mmol) was added dropwise and the solution stirred at RT for 18 hours. The reaction mixture was diluted with DCM (10 mL) and washed with $NaHCO_3$ (2 x 10 mL). The organic layer was dried, filtered and concentrated *in vacuo* to remove the excess solvent to form 10-membered ring intermediate **3.53**, which was used directly in the next step. To this resulting red solid was added triethylamine (0.09 mL, 0.620 mmol) in THF (2.5 mL) and 4-fluorobenzylamine (27.7 µL, 0.242 mmol) in a single portion. The reaction mixture was stirred at RT for 18 hours, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 ethyl acetate : hexane) afforded the title compound, which was obtained as an orange oil (48.7 mg, 60%); R_f = 0.23 (1:1 ethyl acetate : hexane); ν_{max}/cm^{-1} (thin film): 3063, 2926, 1651, 1571, 1510, 1451, 1414, 1325, 1260, 1221, 1146, 1063, 910, 807, 730, 701; δ_H (400 MHz, $CDCl_3$) 7.75 (1H, t, *J* = 7.5 Hz, H-14), 7.55 – 7.51 (1H, m, Ar**H**), 7.40 (1H, d, *J* = 7.5 Hz, H-15 [overlapping]), 7.44 – 7.38 (3H, m, 3 x Ar**H** [overlapping]), 7.35 – 7.31 (4H, m, H-6,7,9,10), 7.23 (1H, d, *J* = 7.5 Hz, H-13 [overlapping]), 7.30 – 7.18 (1H, m, Ar**H** [overlapping]), 7.13 (2H, dd, *J* = 8.5, 5.5 Hz, H-27,31), 6.85 (2H, t, *J* = 8.5 Hz, H-28,30), 5.94 – 5.81 (2H, m, H-1/2 [overlapping]), 5.94 – 5.81 (1H, m, H-1/2 [overlapping]), 5.39 (1H, dd, *J* = 8.5, 1.0 Hz, H-1/2), 4.74 – 4.65 (1H, m, H-4), 4.44 (2H, qd, *J* = 15.0, 6.0 Hz, H-25), 3.86 (1H, d, *J* = 15.5 Hz, H-23), 3.59 (1H, d, *J* = 15.5 Hz, H-23‘), 3.11 – 2.94 (2H, m, H-11); δ_C (100 MHz, $CDCl_3$) 173.5 (C-24), 162.1 (C-29, d, $^1J_{CF}$ = 245.4 Hz), 158.3 (C-16), 157.2 (C-12), 141.9 (C-5), 140.0 (C-17/22), 137.8 (C-14), 137.2 (C-1/2), 134.5 (C-26, d, $^4J_{CF}$ = 3.6 Hz), 133.8 (C-17/22), 131.9 (Ar**C**H), 130.4 (Ar**C**H), 129.3 (Ar**C**H), 129.2 (C-27,31, d, $^3J_{CF}$ = 7.7 Hz), 128.8 (C-7,9), 128.0 (Ar**C**H), 127.9 (Ar**C**H), 126.8 (C-6,10), 124.5 (C-1/2), 122.2 (C-15), 122.0 (C-13), 115.4 (C-28,30, d, $^2J_{CF}$ = 21.2 Hz), 59.3 (C-4), 45.5 (C-11), 42.9 (C-23/25), 42.7 (C-23/25); δ_F (282 MHz, $CDCl_3$) −115.43 (1F, m, Ar**F**); HRMS (ESI^+): calcd. for $C_{30}H_{29}FN_3O_3S$, 530.1908. Found: $[MH]^+$, 530.1912 (−0.6 ppm error).

3.102: 5-(4-Fluorobenzyl)-10-phenyl-8-thia-5,9-diaza-1(2,6)-pyridina-2(1,2)-benzenacycloundecaphan-4-one 8,8-dioxide and 3.103: *N*-(4-fluorobenzyl)-2-(2-(6-(2-((2-((4-fluorobenzyl)amino)ethyl)sulfonamido)-2-phenylethyl)pyridin-2-yl)phenyl)acetamide



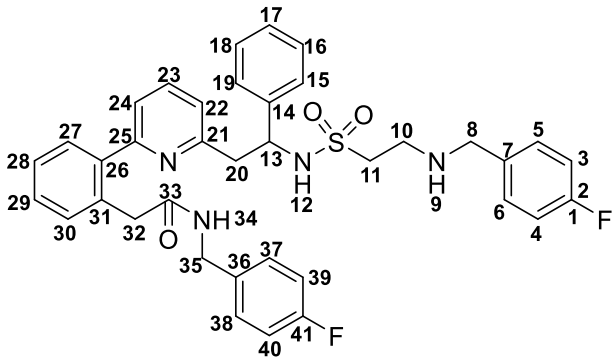
To a solution of 4-phenyl-3-(vinylsulfonyl)-4,5-dihydro-1*H*-6,10-(azeno)benzo[*d*][1]azacyclododecin-2(3*H*)-one (132 mg, 0.325 mmol) and triethylamine (0.14 mL, 1.01 mmol) in THF (1.5 mL), was added 4-fluorobenzylamine (45.0 µL, 0.394 mmol) in a single portion. The reaction mixture was stirred at reflux (70 °C) for 48 hours, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 ethyl acetate : hexane → 100% ethyl acetate) afforded two products: **3.102** (35.7 mg, 21%) and **3.103** (40.9 mg, 19%), with the data for each provided for in turn below.

3.102: 5-(4-Fluorobenzyl)-10-phenyl-8-thia-5,9-diaza-1(2,6)-pyridina-2(1,2)-benzenacycloundecaphan-4-one 8,8-dioxide



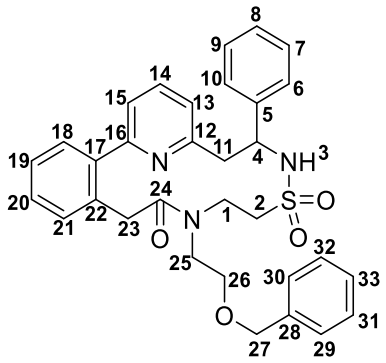
The title compound was obtained as an orange oil (35.7 mg, 21%). See previous **3.102** for the complete assignment of the structure.

3.103: *N*-(4-Fluorobenzyl)-2-(2-(6-(2-((2-((4-fluorobenzyl)amino)ethyl)sulfonamido)-2-phenylethyl)pyridin-2-yl)phenyl)acetamide



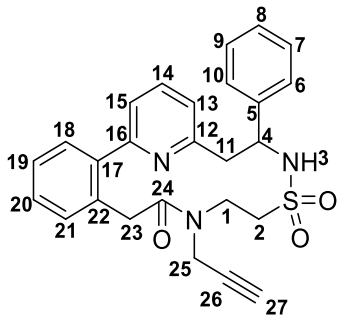
The product was obtained as an orange oil (40.9 mg, 19%); R_f = 0.37 (9:1 ethyl acetate : methanol); ν_{max}/cm^{-1} (thin film): 3064, 2926, 1653, 1602, 1571, 1509, 1451, 1318, 1221, 1142, 1064, 911, 823, 762, 731, 703; δ_H (400 MHz, $CDCl_3$) 7.73 (1H, t, *J* = 7.5 Hz, H-23), 7.55 – 7.49 (1H, m, Ar**H**), 7.38 (1H, d, *J* = 7.5 Hz, H-24 [overlapping]), 7.23 (1H, d, *J* = 7.5 Hz, H-22 [overlapping]), 7.46 – 7.21 (8H, m, 8 x Ar**H** [overlapping]), 7.19 – 7.09 (4H, m, H-5,6,37,38), 6.95 (2H, t, *J* = 8.5 Hz, H-3,4/39,40), 6.85 (2H, t, *J* = 8.5 Hz, H-3,4/39,40), 4.82 – 4.73 (1H, m, H-13), 4.51 – 4.35 (2H, m, H-35), 3.87 (1H, d, *J* = 15.5 Hz, H-32), 3.56 (1H, d, *J* = 15.5 Hz, H-32' [overlapping]), 3.53 (2H, s, H-8 [overlapping]), 3.11 – 2.96 (2H, m, H-20), 2.87 – 2.68 (2H, m, H-10 [overlapping]), 2.87 – 2.68 (1H, m, H-11 [overlapping]), 2.64 – 2.52 (1H, m, H-11'); δ_C (100 MHz, $CDCl_3$) 173.6 (C-33), 162.0 (C-1,41, d, $^1J_{CF}$ = 244.7 Hz), 158.3 (C-25), 157.1 (C-21), 142.0 (C-14), 140.1 (C-26/31), 137.8 (C-23), 135.4 (C-7, d, $^4J_{CF}$ = 2.8 Hz), 134.5 (C-36, d, $^4J_{CF}$ = 2.8 Hz), 133.8 (C-26/31), 131.9 (Ar**C**H), 130.4 (Ar**C**H), 129.7 (C-5,6, d, $^3J_{CF}$ = 8.0 Hz), 129.3 (Ar**C**H), 129.1 (C-37,38, d, $^3J_{CF}$ = 7.8 Hz), 129.0 (H-16,18), 128.1 (Ar**C**H), 128.0 (Ar**C**H), 126.7 (H-15,19), 122.2 (C-24), 122.0 (C-22), 115.4 (C-3,4/39,40, d, $^2J_{CF}$ = 21.1 Hz), 115.3 (C-3,4/39,40, d, $^2J_{CF}$ = 21.1 Hz), 59.3 (C-13), 53.4 (C-11), 52.6 (C-8), 45.6 (C-20), 43.2 (C-10), 42.8 (C-35), 42.7 (C-32); δ_F (282 MHz, $CDCl_3$) −115.40 (1F, m, Ar**F**), −115.72 (1F, m, Ar**F**); HRMS (ESI^+): calcd. for $C_{37}H_{37}F_2N_4O_3S$, 655.2549. Found: $[MH]^+$, 655.2535 (2.1 ppm error).

3.105: 5-(2-(Benzyloxy)ethyl)-10-phenyl-8-thia-5,9-diaza-1(2,6)-pyridina-2(1,2)-benzenacycloundecaphan-4-one 8,8-dioxide



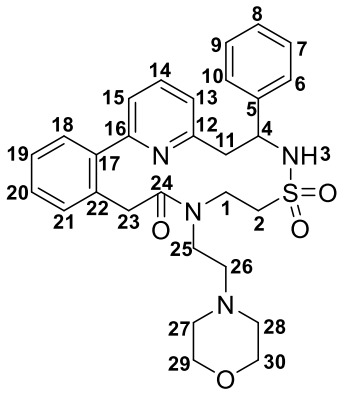
To a round-bottomed flask 2-(2-(6-(2-phenyl-2-(vinylsulfonamido)ethyl)pyridin-2-yl)phenyl)acetic acid (84.5 mg, 0.200 mmol) was dissolved in chloroform (5.0 mL) and DIPEA (63.8 µL, 0.366 mmol), was added dropwise. T3P (50% solution in ethyl acetate, 0.19 mL, 0.300 mmol) was added dropwise and the solution stirred at RT for 18 hours. The reaction mixture was diluted with DCM (10 mL) and washed with $NaHCO_3$ (2 x 10 mL). The organic layer was dried, filtered and concentrated *in vacuo* to remove the excess solvent to form 10-membered ring intermediate **3.53**, which was used directly in the next step. To this resulting red solid was added triethylamine (0.08 mL, 0.600 mmol) in THF (2.5 mL) and 2-(benzyloxy)-1-ethanamine (33.3 µL, 0.241 mmol) in a single portion. The reaction mixture was stirred at RT for 18 hours, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 8:2 hexane : ethyl acetate → 1:1 ethyl acetate : hexane) afforded the title compound, which was obtained as an orange oil (61.9 mg, 56%); R_f = 0.12 (1:1 ethyl acetate : hexane); ν_{max}/cm^{-1} (thin film): 3062, 2926, 2863, 1648, 1570, 1451, 1326, 1146, 1097, 1066, 963, 911, 762, 731, 699; δ_H (400 MHz, $CDCl_3$) 7.74 (1H, t, *J* = 8.0 Hz, H-14), 7.57 – 7.52 (1H, m, Ar**H**), 7.49 – 7.19 (13H, m, 13 x Ar**H**), 7.12 – 7.06 (2H, m, H-29,30), 5.93 – 5.80 (2H, m, H-1/2 [overlapping]), 5.93 – 5.80 (1H, m, H-1/2 [overlapping]), 5.37 (1H, d, *J* = 8.0, 1.0 Hz, H-1/2), 4.78 – 4.70 (1H, m, H-4), 4.34 (2H, d, *J* = 2.5 Hz, H-27), 3.82 (1H, d, *J* = 15.5 Hz, H-23), 3.58 (1H, dd, *J* = 15.5 Hz, H-23‘), 3.54 – 3.44 (4H, m, H-25,26), 3.24 – 3.10 (2H, m, H-11); δ_C (100 MHz, $CDCl_3$) 173.5 (C-24), 158.2 (C-16), 157.2 (C-12), 142.2 (C-5), 139.9 (C-17/22), 137.9 (C-28), 137.7 (C-14), 137.3 (C-1/2), 134.0 (C-17/22), 131.9 (Ar**C**H), 130.3 (Ar**C**H), 129.2 (Ar**C**H), 128.7 (C-7,9), 128.4 (C-31,32), 127.84 (Ar**C**H), 127.76 (Ar**C**H), 127.73 (Ar**C**H), 127.68 (C-29,30), 126.9 (C-6,10), 124.3 (C-1/2), 122.1 (C-15), 121.9 (C-13), 73.0 (C-27), 69.0 (C-26), 59.4 (C-4), 45.7 (C-11), 42.7 (C-23), 39.5 (C-25); HRMS (ESI^+): calcd. for $C_{32}H_{34}N_3O_4S$, 556.2265. Found: $[MH]^+$, 556.2281 (−2.9 ppm error).

3.106: 10-Phenyl-5-(prop-2-yn-1-yl)-8-thia-5,9-diaza-1(2,6)-pyridina-2(1,2)-benzenacycloundecaphan-4-one 8,8-dioxide



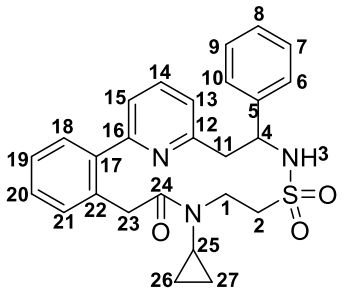
To a round-bottomed flask 2-(2-(6-(2-phenyl-2-(vinylsulfonamido)ethyl)pyridin-2-yl)phenyl)acetic acid (84.5 mg, 0.200 mmol) was dissolved in chloroform (5.0 mL) and DIPEA (63.8 µL, 0.366 mmol), was added dropwise. T3P (50% solution in ethyl acetate, 0.19 mL, 0.300 mmol) was added dropwise and the solution stirred at RT for 18 hours. The reaction mixture was diluted with DCM (10 mL) and washed with $NaHCO_3$ (2 x 10 mL). The organic layer was dried, filtered and concentrated *in vacuo* to remove the excess solvent to form 10-membered ring intermediate **3.53**, which was used directly in the next step. To this resulting red solid was added triethylamine (0.08 mL, 0.600 mmol) in THF (2.5 mL) and propargylamine (15.9 µL, 0.250 mmol) in a single portion. The reaction mixture was stirred at RT for 18 hours, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 7:3 hexane : ethyl acetate → 1:1 ethyl acetate : hexane) afforded the title compound, which was obtained as a yellow oil (74.5 mg, 81%); R_f = 0.21 (1:1 ethyl acetate : hexane); ν_{max}/cm^{-1} (thin film): 3282, 3028, 2866, 2251, 1655, 1591, 1571, 1450, 1324, 1145, 1065, 961, 910, 762, 729, 700, 651; δ_H (400 MHz, $CDCl_3$) 7.77 (1H, t, *J* = 8.0 Hz, H-14), 7.52 – 7.47 (1H, m, Ar**H**), 7.46 – 7.23 (10H, m, 10 x Ar**H**), 6.89 (1H, d, *J* = 8.0 Hz, H-3), 5.99 – 5.84 (2H, m, H-1/2 [overlapping]), 5.99 – 5.84 (1H, m, H-1/2 [overlapping]), 5.43 (1H, d, *J* = 9.0 Hz, H-1/2), 4.80 – 4.71 (1H, m, H-4), 4.13 – 3.96 (2H, m, H-25), 3.71 (1H, d, *J* = 15.0 Hz, H-23), 3.50 (1H, d, *J* = 15.0 Hz, H-23‘), 3.39 – 3.24 (2H, m, H-11), 2.08 (1H, t, *J* = 2.5 Hz, H-27); δ_C (100 MHz, $CDCl_3$) 172.9 (C-24), 158.2 (C-16), 157.0 (C-12), 141.6 (C-5), 139.6 (C-17/22), 138.1 (C-14), 137.0 (C-1/2), 133.6 (C-17/22), 131.7 (Ar**C**H), 130.4 (Ar**C**H), 129.4 (Ar**C**H), 128.8 (C-7,9), 128.0 (Ar**C**H), 127.9 (Ar**C**H), 126.9 (C-6,10), 124.8 (C-1/2), 122.5 (C-15), 122.4 (C-13), 80.1 (C-27), 71.7 (C-26), 59.3 (C-4), 45.5 (C-11), 42.1 (C-23), 29.4 (C-25); HRMS (ESI^+): calcd. for $C_{26}H_{26}N_3O_3S$, 460.1689. Found: $[MH]^+$, 460.1698 (−1.8 ppm error).

3.107: 5-(2-Morpholinoethyl)-10-phenyl-8-thia-5,9-diaza-1(2,6)-pyridina-2(1,2)-benzenacycloundecaphan-4-one 8,8-dioxide



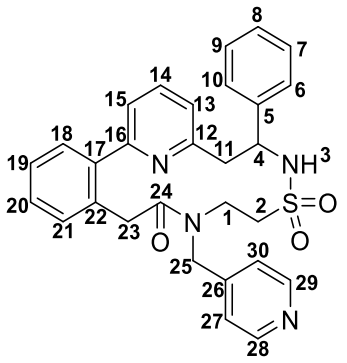
To a round-bottomed flask 2-(2-(6-(2-phenyl-2-(vinylsulfonamido)ethyl)pyridin-2-yl)phenyl)acetic acid (84.5 mg, 0.200 mmol) was dissolved in chloroform (5.0 mL) and DIPEA (63.8 µL, 0.366 mmol), was added dropwise. T3P (50% solution in ethyl acetate, 0.19 mL, 0.300 mmol) was added dropwise and the solution stirred at RT for 18 hours. The reaction mixture was diluted with DCM (10 mL) and washed with $NaHCO_3$ (2 x 10 mL). The organic layer was dried, filtered and concentrated *in vacuo* to remove the excess solvent to form 10-membered ring intermediate **3.53**, which was used directly in the next step. To this resulting red solid was added triethylamine (0.08 mL, 0.600 mmol) in THF (2.5 mL) and 4-(2-aminoethyl)morpholine (31.7 µL, 0.241 mmol) in a single portion. The reaction mixture was stirred at RT for 18 hours, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 100% ethyl acetate → 49:1 ethyl acetate : methanol → 48:2 ethyl acetate : methanol) afforded the title compound, which was obtained as a brown oil (91.2 mg, 85%); R_f = 0.19 (9:1 ethyl acetate : methanol); ν_{max}/cm^{-1} (thin film): 3063, 2926, 1646, 1570, 1450, 1326, 1145, 1067, 912, 763, 729, 701, 650; δ_H (400 MHz, $CDCl_3$) 8.01 (1H, d, *J* = 8.5 Hz, H-3), 7.76 (1H, t, *J* = 7.5 Hz, H-14), 7.62 – 7.54 (1H, m, Ar**H**), 7.54 – 7.23 (10H, m, 10 x Ar**H**), 5.97 – 5.79 (2H, m, H-1/2 [overlapping]), 5.97 – 5.79 (1H, m, H-1/2 [overlapping]), 5.36 (1H, d, *J* = 9.0 Hz, H-1/2), 4.79 – 4.69 (1H, m, H-4), 3.86 (1H, d, *J* = 16.0 Hz, H-23), 3.57 (1H, d, *J* = 16.0 Hz, H-23‘), 3.48 – 3.27 (4H, m, H-29,30 [overlapping]), 3.48 – 3.27 (2H, m, H-25 [overlapping]), 3.25 – 3.09 (2H, m, H-11), 2.49 – 2.30 (2H, m, H-26), 2.30 – 2.15 (4H, m, H-27,28); δ_C (100 MHz, $CDCl_3$) 174.1 (C-24), 158.1 (C-16), 157.4 (C-12), 142.6 (C-5), 140.2 (C-17/22), 137.7 (C-14), 137.5 (C-1/2), 134.0 (C-17/22), 132.4 (Ar**C**H), 130.2 (Ar**C**H), 129.1 (Ar**C**H), 128.8 (C-7,9), 128.0 (Ar**C**H), 127.8 (Ar**C**H), 126.9 (C-6,10), 124.0 (C-1/2), 121.8 (C-15), 121.6 (C-13), 66.8 (C-29,30), 59.6 (C-4), 56.2 (C-26), 52.9 (C-27,28), 46.0 (C-11), 43.2 (C-23), 36.1 (C-25); HRMS (ESI^+): calcd. for $C_{29}H_{35}N_4O_4S$, 535.2374. Found: $[MH]^+$, 535.2379 (−1.0 ppm error).

3.108: 5-Cyclopropyl-10-phenyl-8-thia-5,9-diaza-1(2,6)-pyridina-2(1,2)-benzenacycloundecaphan-4-one 8,8-dioxide



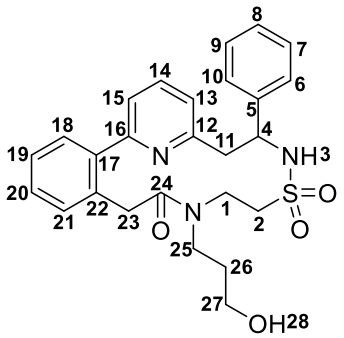
To a round-bottomed flask 2-(2-(6-(2-phenyl-2-(vinylsulfonamido)ethyl)pyridin-2-yl)phenyl)acetic acid (84.5 mg, 0.200 mmol) was dissolved in chloroform (5.0 mL) and DIPEA (63.8 µL, 0.366 mmol), was added dropwise. T3P (50% solution in ethyl acetate, 0.19 mL, 0.300 mmol) was added dropwise and the solution stirred at RT for 18 hours. The reaction mixture was diluted with DCM (10 mL) and washed with $NaHCO_3$ (2 x 10 mL). The organic layer was dried, filtered and concentrated *in vacuo* to remove the excess solvent to form 10-membered ring intermediate **3.53**, which was used directly in the next step. To this resulting red solid was added triethylamine (0.08 mL, 0.600 mmol) in THF (2.5 mL) and cyclopropylamine (16.7 µL, 0.240 mmol) in a single portion. The reaction mixture was stirred at RT for 18 hours, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 ethyl acetate : hexane) afforded the title compound, which was obtained as an orange oil (42.9 mg, 46%); R_f = 0.38 (100% ethyl acetate); ν_{max}/cm^{-1} (thin film): 3062, 2926, 1653, 1570, 1451, 1324, 1145, 1061, 963, 910, 762, 729, 701, 652; δ_H (400 MHz, $CDCl_3$) 7.75 (1H, t, *J* = 8.0 Hz, H-14), 7.54 – 7.21 (11H, m, 11 x Ar**H**), 6.36 (1H, br s, H-3), 5.99 – 5.81 (2H, m, H-1/2 [overlapping]), 5.99 – 5.81 (1H, m, H-1/2 [overlapping]), 5.40 (1H, d, *J* = 9.0 Hz, H-1/2), 4.76 (1H, q, *J* = 8.0 Hz, H-4), 3.77 (1H, d, *J* = 16.0 Hz, H-23), 3.51 (1H, d, *J* = 16.0 Hz, H-23‘), 3.29 – 3.18 (2H, m, H-11), 2.72 (1H, tq, *J* = 7.5, 3.5 Hz, H-25), 0.75 – 0.62 (2H, m, H-26/27), 0.43 – 0.32 (2H, m, H-26/27); δ_C (100 MHz, $CDCl_3$) 175.0 (C-24), 158.3 (C-16), 157.2 (C-12), 142.1 (C-5), 140.1 (C-17/22), 137.8 (C-14), 137.3 (C-1/2), 133.8 (C-17/22), 131.9 (Ar**C**H), 130.3 (Ar**C**H), 129.2 (Ar**C**H), 128.8 (C-7,9), 127.90 (Ar**C**H), 127.86 (Ar**C**H), 126.9 (C-6,10), 124.4 (C-1/2), 122.1 (C-15), 122.0 (C-13), 59.4 (C-4), 45.8 (C-11), 42.7 (C-23), 23.0 (C-25), 6.6 (C-26/27), 6.5 (C-26/27); HRMS (ESI^+): calcd. for $C_{26}H_{27}N_3NaO_3S$, 484.1665. Found: $[MNa]^+$, 484.1670 (−0.9 ppm error).

3.109: 10-Phenyl-5-(pyridin-4-ylmethyl)-8-thia-5,9-diaza-1(2,6)-pyridina-2(1,2)-benzenacycloundecaphan-4-one 8,8-dioxide



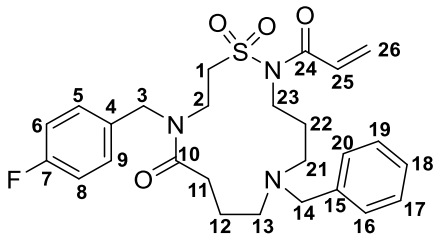
To a round-bottomed flask 2-(2-(6-(2-phenyl-2-(vinylsulfonamido)ethyl)pyridin-2-yl)phenyl)acetic acid (84.5 mg, 0.200 mmol) was dissolved in chloroform (5.0 mL) and DIPEA (63.8 µL, 0.366 mmol), was added dropwise. T3P (50% solution in ethyl acetate, 0.19 mL, 0.300 mmol) was added dropwise and the solution stirred at RT for 18 hours. The reaction mixture was diluted with DCM (10 mL) and washed with $NaHCO_3$ (2 x 10 mL). The organic layer was dried, filtered and concentrated *in vacuo* to remove the excess solvent to form 10-membered ring intermediate **3.53**, which was used directly in the next step. To this resulting red solid was added triethylamine (0.08 mL, 0.600 mmol) in THF (2.5 mL) and 4-(aminomethyl)pyridine (24.6 µL, 0.242 mmol) in a single portion. The reaction mixture was stirred at RT for 18 hours, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 ethyl acetate : hexane → 100% ethyl acetate) afforded the title compound, which was obtained as a brown oil (63.9 mg, 62%); R_f = 0.32 (9:1 ethyl acetate : methanol); ν_{max}/cm^{-1} (thin film): 3054, 2872, 1658, 1591, 1569, 1450, 1418, 1325, 1146, 1066, 964, 911, 762, 730, 701; δ_H (400 MHz, $CDCl_3$) 8.36 (2H, d, *J* = 5.5 Hz, H-28,29), 7.74 (1H, t, *J* = 7.5 Hz, H-14), 7.59 (1H, t, *J* = 6.0 Hz, Ar**H**), 7.55 – 7.51 (1H, m, Ar**H**), 7.40 (1H, d, *J* = 7.5 Hz, H-15 [overlapping]), 7.50 – 7.23 (7H, m, 7 x Ar**H** [overlapping]), 7.20 (1H, d, *J* = 7.5 Hz, H-13), 7.04 (2H, d, *J* = 5.5 Hz, H-27,30), 5.94 – 5.80 (2H, m, H-1/2 [overlapping]), 5.94 – 5.80 (1H, m, H-1/2 [overlapping]), 5.40 (1H, d, *J* = 9.0 Hz, H-1/2), 4.72 (1H, q, *J* = 8.0 Hz, H-4), 4.54 (1H, dd, *J* = 16.0, 6.5 Hz, H-25), 4.40 (1H, dd, *J* = 16.0, 6.5 Hz, H-25‘), 3.86 (1H, d, *J* = 15.0 Hz, H-23), 3.64 (1H, d, *J* = 15.0 Hz, H-23‘), 3.13 – 2.99 (2H, m, H-11); δ_C (100 MHz, $CDCl_3$) 173.5 (C-24), 158.4 (C-16), 156.9 (C-12), 149.6 (C-28,29), 148.2 (C-26), 141.6 (C-5), 139.8 (C-17/22), 137.8 (C-14), 137.0 (C-1/2), 133.8 (C-17/22), 131.6 (Ar**C**H), 130.4 (Ar**C**H), 129.3 (Ar**C**H), 128.7 (C-7,9), 127.9 (2 x Ar**C**H [overlapping]), 126.7 (C-6,10), 124.6 (C-1/2), 122.4 (C-15), 122.3 (C-13), 122.2 (C-27,30), 59.1 (C-4), 45.6 (C-11), 42.2 (C-23 [overlapping]), 42.2 (C-25 [overlapping]); HRMS (ESI^+): calcd. for $C_{29}H_{28}N_4NaO_3S$, 535.1774. Found: $[MNa]^+$, 535.1773 (0.2 ppm error).

3.110: 5-(3-Hydroxypropyl)-10-phenyl-8-thia-5,9-diaza-1(2,6)-pyridina-2(1,2)-benzenacycloundecaphan-4-one 8,8-dioxide



To a round-bottomed flask 2-(2-(6-(2-phenyl-2-(vinylsulfonamido)ethyl)pyridin-2-yl)phenyl)acetic acid (84.5 mg, 0.200 mmol) was dissolved in chloroform (5.0 mL) and DIPEA (63.8 µL, 0.366 mmol), was added dropwise. T3P (50% solution in ethyl acetate, 0.19 mL, 0.300 mmol) was added dropwise and the solution stirred at RT for 18 hours. The reaction mixture was diluted with DCM (10 mL) and washed with $NaHCO_3$ (2 x 10 mL). The organic layer was dried, filtered and concentrated *in vacuo* to remove the excess solvent to form 10-membered ring intermediate **3.53**, which was used directly in the next step. To this resulting red solid was added triethylamine (0.08 mL, 0.600 mmol) in THF (2.5 mL) and 3-amino-1-propanol (18.2 µL, 0.238 mmol) in a single portion. The reaction mixture was stirred at RT for 18 hours, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 ethyl acetate : hexane → 100% ethyl acetate) afforded the title compound, which was obtained as an orange oil (33.4 mg, 35%); R_f = 0.20 (100% ethyl acetate); ν_{max}/cm^{-1} (thin film): 3071, 2935, 2873, 1648, 1622, 1589, 1571, 1449, 1324, 1145, 1066, 961, 910, 727, 648; δ_H (400 MHz, $CDCl_3$) 7.77 (1H, t, *J* = 8.0 Hz, H-14), 7.52 – 7.47 (1H, m, Ar**H**), 7.46 – 7.23 (10H, m, 10 x Ar**H**), 5.97 – 5.79 (2H, m, H-1/2 [overlapping]), 5.97 – 5.79 (1H, m, H-1/2 [overlapping]), 5.41 (1H, d, *J* = 9.0 Hz, H-1/2), 4.76 (1H, q, *J* = 8.0 Hz, H-4), 3.78 (1H, d, *J* = 15.5 Hz, H-23), 3.58 (1H, d, *J* = 15.5 Hz, H-23‘), 3.49 (2H, t, *J* = 5.5 Hz, H-27), 3.45 – 3.34 (2H, m, H-25), 3.28 – 3.16 (2H, m, H-11), 1.60 (2H, p, *J* = 5.5 Hz, H-26); δ_C (100 MHz, $CDCl_3$) 174.3 (C-24), 158.3 (C-16), 157.1 (C-12), 141.8 (C-5), 139.9 (C-17/22), 138.1 (C-14), 137.1 (C-1/2), 133.8 (C-17/22), 131.8 (Ar**C**H), 130.4 (Ar**C**H), 129.4 (Ar**C**H), 128.9 (C-7,9), 128.0 (2 x Ar**C**H), 126.8 (C-6,10), 124.7 (C-1/2), 122.6 (C-15), 122.3 (C-13), 59.4 (C-27), 59.3 (C-4), 45.7 (C-11), 42.2 (C-23), 36.6 (C-25), 32.1 (C-26); HRMS (ESI^+): calcd. for $C_{26}H_{30}N_3O_4S$, 480.1952. Found: $[MH]^+$, 480.1951 (0.0 ppm error).

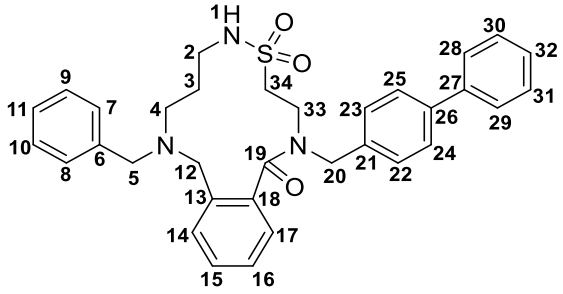
3.115: 2-Acryloyl-6-benzyl-11-(4-fluorobenzyl)-1-thia-2,6,11-triazacyclotridecan-10-one 1,1-dioxide



To a round-bottomed flask, MeMgBr (3.0 M in diethyl ether, 0.09 mL, 0.270 mmol) was added dropwise *via* a syringe pump over 30 minutes to a stirring solution of 6-benzyl-11-(4-fluorobenzyl)-1-thia-2,6,11-triazacyclotridecan-10-one 1,1-dioxide (107 mg, 0.239 mmol) in THF (10.0 mL), in an inert atmosphere of Ar, cooled to 0 °C. The reaction mixture was stirred for 10 minutes at 0 °C after the complete addition had occurred. Acryloyl chloride (29.0 µL, 0.357 mmol) was then added in a single portion to the reaction mixture and was stirred for a further 50 minutes 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 then washed with sat. aq. $NaHCO_3$ (2 x 10 mL). The organic layer was extracted and dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 ethyl acetate : hexane) afforded the title compound, which was obtained as a colourless oil (45.6 mg, 38%), and exists in $CDCl_3$ as a 2:1 mixture of rotamers; R_f = 0.62 (100% ethyl acetate); ν_{max}/cm^{-1} (thin film): 2935, 2808, 1683, 1641, 1509, 1452, 1405, 1350, 1221, 1155, 976, 912, 729, 700; δ_H (400 MHz, $CDCl_3$) Diagnostic data for major rotamer: 7.44 – 6.95 (9H, m, 9 x Ar**H** [overlapping]), 6.77 (1H, dd, *J* = 16.5, 10.5 Hz, H-25), 6.42 (1H, dd, *J* = 16.5, 1.5 Hz, H-26), 5.80 (1H, dd, *J* = 10.5, 1.5 Hz, H-26), 4.86 (2H, br s, H-1/13), 2.01 – 1.85 (2H, m, H-12 [overlapping]), 1.75 – 1.54 (2H, m, H-22 [overlapping]). Full data for minor rotamer: 7.44 – 6.95 (9H, m, 9 x Ar**H** [overlapping]), 6.53 (1H, dd, *J* = 16.5, 10.0 Hz, H-25), 6.44 (1H, dd, *J* = 16.5, 2.0 Hz, H-26), 5.83 (1H, dd, *J* = 10.0, 2.0 Hz, H-26), 4.58 (2H, s, H-3), 3.90 – 3.84 (2H, m, H-2), 3.84 – 3.78 (2H, m, H-1), 3.74 (2H, t, *J* = 6.5 Hz, H-23), 3.53 (2H, s, H-14), 2.64 (2H, t, *J* = 6.0 Hz, H-11 [overlapping]), 2.47 (2H, t, *J* = 6.0 Hz, H-13), 2.34 – 2.20 (2H, m, H-21), 2.01 – 1.85 (2H, m, H-12 [overlapping]), 1.69 (2H, p, *J* = 6.5 Hz, H-22 [overlapping]); δ_C (100 MHz, $CDCl_3$) Data for major rotamer: 174.1 (C-10), 166.0 (C-24), 162.4 (C-7, d, $^1J_{CF}$ = 246.7 Hz), 139.5 (C-15), 132.9 (C-4, d, $^4J_{CF}$ = 2.8 Hz [overlapping]), 131.4 (C-26), 128.9 (C-16,20), 128.7 (C-25), 128.5 (C-17,19 [overlapping]), 128.27 (C-5,9, d, $^3J_{CF}$ = 8.3 Hz [overlapping]), 127.2 (C-18), 116.1 (C-6,8, d, $^2J_{CF}$ = 21.7 Hz), 58.8 (C-14), 55.4 (C-1/13), 53.9 (C-1/13 [overlapping]), 50.7 (C-3/21), 50.0 (C-3/21), 44.6 (C-2/23), 43.3 (C-2/23), 29.9 (C-11), 26.3 (C-22), 22.4 (C-12). Full data for minor rotamer: 173.6 (C-10), 166.7 (C-24), 162.5 (C-7, d, $^1J_{CF}$ = 246.8 Hz), 138.8 (C-15), 132.9 (C-4, d, $^4J_{CF}$ = 2.8 Hz [overlapping]), 132.1 (C-26), 130.2 (C-5,9, d, $^3J_{CF}$ =

8.5 Hz), 129.4 (C-16,20), 128.5 (C-17,19 [overlapping]), 128.28 (C-25 [overlapping]), 127.4 (C-18), 115.9 (C-6,8, d, $^2J_{CF}$ = 21.2 Hz), 58.5 (C-14), 54.2 (C-13), 53.9 (C-1 [overlapping]), 51.1 (C-21), 48.0 (C-3), 43.4 (C-23), 41.5 (C-2), 29.4 (C-11), 27.9 (C-22), 23.3 (C-12); δ_F (282 MHz, $CDCl_3$) Major rotamer: −114.45 (1F, m, Ar**F**), minor rotamer: −114.06 (1F, m, Ar**F**); HRMS (ESI^+): calcd. for $C_{26}H_{33}FN_3O_4S$, 502.2170. Found: $[MH]^+$, 502.2182 (−2.4 ppm error).

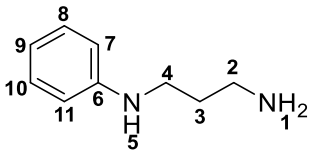
3.117: 2-([1,1'-Biphenyl]-4-ylmethyl)-10-benzyl-3,4,6,7,8,9,10,11-octahydrobenzo[*h*][1]thia[2,6,11]triazacyclotridecin-1(2*H*)-one 5,5-dioxide



10-Benzyl-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-3,4,6,7,8,9,10,11-octahydrobenzo[*h*][1]thia[2,6,11]triazacyclotridecin-1(2*H*)-one 5,5-dioxide (193 mg, 0.319 mmol), bromobenzene (0.05 mL, 0.479 mmol), potassium phosphate (135 mg, 0.638 mmol) and $PdCl_2$(dppf)·CH_2Cl_2 (13.0 mg, 16.0 µmol) were charged into a round-bottomed flask purged with argon. THF (5.0 mL) and de-ionised water (29.0 µL, 1.61 mmol) were added and heated to 80 °C, at reflux, for 24 hours. Upon completion the solution was cooled to RT, diluted with water (10 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 ethyl acetate : hexane → 100% ethyl acetate) afforded the title compound. Data suggests starting material was still present so the reaction was put back on. To the mixture of product and starting material (26.7 mg, 0.044 mmol), bromobenzene (7.0 µL, 0.067 mmol), potassium phosphate (19.7 mg, 0.093 mmol) and $PdCl_2$(dppf)·CH_2Cl_2 (2.8 mg, 3.43 µmol) were charged into a round-bottomed flask purged with argon. THF (3.0 mL) and de-ionised water (4.0 µL, 0.223 mmol) were added and heated to 65 °C, for 120 hours. Upon completion the solution was cooled to RT, diluted with water (10 mL), extracted with ethyl acetate (3 × 10 mL) and washed with brine (10 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 100% ethyl acetate → 1:1 ethyl acetate : methanol) afforded the title compound, which was obtained as a brown oil (18.9 mg, 11%). The ^{1}H NMR spectrum is severely affected by rotameric broadening, with product identity and purity best determined using ^{13}C NMR data; R_f = 0.71 (100% ethyl acetate); ν_{max}/cm^{-1}

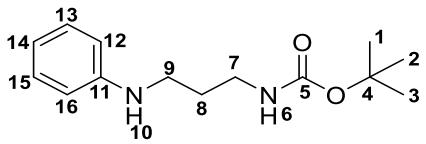
(thin film): 2926, 1973, 1676, 1452, 1398, 1338, 1150, 1016, 761, 701; δ_H (400 MHz, $CDCl_3$) 7.62 – 7.54 (4H, m, 4 x Ar**H**), 7.47 – 7.39 (4H, m, 4 x Ar**H**), 7.37 – 7.23 (7H, m, 7 x Ar**H**), 7.19 (1H, t, *J* = 7.5 Hz, H-15), 7.14 (1H, d, *J* = 7.5 Hz, H-14), 7.06 (1H, d, *J* = 7.5 Hz, H-17), 3.92 (2H, s, H-20), 3.86 (2H, s, H-5), 3.25 (2H, t, *J* = 6.5 Hz, H-33); δ_C (100 MHz, $CDCl_3$) 172.3 (C-19), 141.0 (C-26/27), 140.3 (C-26/27), 140.0 (C-18), 138.7 (C-21), 136.1 (C-6/13), 136.0 (C-6/13), 130.1 (C-7,8), 129.5 (C-16), 128.9 (2 x Ar**C**H), 128.8 (2 x Ar**C**H), 128.7 (C-14), 128.4 (C-9,10), 127.8 (C-15), 127.5 (C-11/32), 127.42 (2 x Ar**C**H), 127.37 (C-11/32), 127.2 (2 x Ar**C**H), 125.2 (C-17), 56.6 (C-12), 56.3 (C-5), 54.8 (C-34), 53.2 (C-20), 49.5 (**C**H_2), 47.5 (**C**H_2), 43.3 (C-33), 25.3 (C-3); HRMS (ESI^+): calcd. for $C_{33}H_{35}N_3NaO_3S$, 576.2291. Found: $[MNa]^+$, 576.2299 (−1.2 ppm error).

3.120: *N*-(3-Aminopropyl)aniline



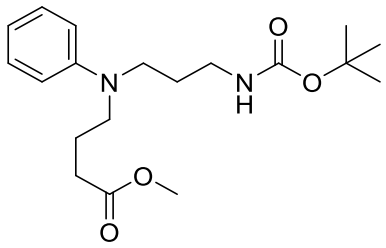
Copper(I) chloride (200 mg, 2.02 mmol), iodobenzene (2.23 mL, 20.0 mmol), and potassium hydroxide (2.24 g, 39.9 mmol) were added to a round-bottomed flask. 1,3-Diaminopropane (4.46 mL, 60.1 mmol) was then added and the reaction mixture was stirred at 0 °C while gradually allowing to heat to RT for 20 hours. The resulting mixture was diluted with water (20 mL) before extracted with DCM (4 x 20 mL). The organics were then dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 20:1 DCM : methanol → 100% methanol) gave the title compound, which was obtained as an orange oil (2.68 g, 89%); R_f = 0.07 (1:1 ethyl acetate : methanol); ν_{max}/cm^{-1} (thin film): 3338, 2930, 1603, 1502, 1432, 1318, 1261, 1179, 750, 694; δ_H (400 MHz, $CDCl_3$) 7.21 – 7.14 (2H, m, 2 x Ar**H**), 6.69 (1H, t, *J* = 7.5 Hz, H-9), 6.62 (2H, d, *J* = 7.5 Hz, 2 x Ar**H**), 3.20 (2H, t, *J* = 7.0 Hz, H-4), 2.86 (2H, t, *J* = 7.0 Hz, H-2), 2.51 – 2.11 (2H, br s, H-1), 1.78 (2H, p, *J* = 6.5 Hz, H-3); δ_C (100 MHz, $CDCl_3$) 148.6 (C-6), 129.4 (2 x Ar**C**H), 117.4 (C-9), 112.9 (2 x Ar**C**H), 42.2 (C-4), 40.4 (C-2), 32.8 (C-3); HRMS (ESI^+): calcd. for $C_9H_{15}N_2$, 151.1230. Found $[MH]^+$ 151.1232 (−1.3 ppm error). Characterisation data matched those reported in the literature.[181]

3.121: *tert*-Butyl *N*-[3-(phenylamino)propyl]carbamate



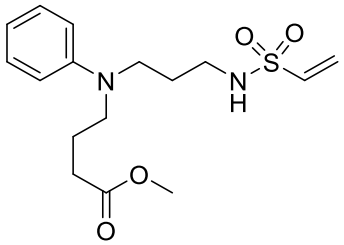
A round-bottomed flask was charged with anhydrous DCM (10.0 mL) and *N*-(3-aminopropyl)aniline (1.74 g, 11.6 mmol), after which triethylamine (4.00 mL, 28.7 mmol) was added under argon. The solution was cooled to 0 °C in an ice bath, before di-*tert*-butyl dicarbonate (5.06 g, 23.2 mmol), dissolved in DCM (10.0 mL), was added dropwise *via* a syringe pump over 10 minutes. Upon complete addition, the solution was allowed to warm to RT and stirred for 22 hours. Upon completion, the solution was diluted with DCM (20 mL). The organic layer was washed with 0.1 M HCl (2 x 20 mL), water (2 x 20 mL) and brine (2 x 20 mL) before being dried over magnesium sulfate, filtered and concentrated *in vacuo*. This was purified by column chromatography (SiO_2, 1:1 ethyl acetate : hexane) to yield the title compound, which was obtained as a colourless oil (2.91 g, 100%), and exists in $CDCl_3$ as a 10:7:4 (A:B:C) mixture of rotamers; R_f = 0.55 (1:1 ethyl acetate : hexane); ν_{max}/cm^{-1} (thin film): 3364, 2977, 2933, 1685, 1600, 1498, 1393, 1366, 1251, 1169, 750, 697; δ_H (400 MHz, $CDCl_3$) Data for rotamer A: 7.20 (2H, t, *J* = 7.0 Hz, H-13,15), 6.69 (1H, t, *J* = 7.5 Hz, H-14), 6.61 (2H, d, *J* = 8.0 Hz, H-12,16), 5.07 (1H, br s, H-10), 4.66 (1H, br s, H-6), 3.24 (2H, q, *J* = 6.5 Hz, H-7), 3.18 (2H, t, *J* = 6.5 Hz, H-9 [overlapping]), 1.77 (2H, p, *J* = 6.5 Hz, H-8), 1.43 (9H, s, H-1,2,3). Full data for rotamer B and C: 7.33 (4H, t, *J* = 7.5 Hz, 4 x Ar**H**, rotamer B,C), 7.18 – 7.11 (6H, m, 6 x Ar**H**, rotamer B,C), 3.90 (1H, br s, H-10B), 3.70 (4H, t, *J* = 6.5 Hz, 2 x C$\mathbf{H_2}$, rotamer B,C), 3.20 – 3.10 (4H, m, 2 x C$\mathbf{H_2}$, rotamer B,C [overlapping]), 1.64 (4H, p, *J* = 6.5 Hz, H-8B,C), 1.44 (9H, s, H-1C,2C,3C), 1.41 (9H, s, H-1B,2B,3B); δ_C (100 MHz, $CDCl_3$) Data for rotamer A: 156.1 (C-5), 148.3 (C-11), 129.4 (C-13,15), 117.4 (C-14), 113.0 (C-12,16), 79.1 (C-4), 41.1 (C-9), 38.2 (C-7), 29.8 (C-8), 28.4 (C-1,2,3). Diagnostic data for rotamer B and C: 156.3 (C-5C), 155.2 (C-5B), 142.2 (C-11), 129.0 (Ar**C**H), 127.3 (Ar**C**H), 126.4 (Ar**C**H), 117.0 (Ar**C**H), 80.5 (C-4B), 79.4 (C-4C), 47.1 (**C**H_2), 37.6 (**C**H_2), 31.4 (**C**H_2), 28.6 (C-1B,2B,3B), 28.5 (C-1C,2C,3C), 27.5 (**C**H_2); HRMS (ESI$^+$): calcd. for $C_{14}H_{23}N_2O_2$, 251.1754. Found $[MH]^+$ 251.1757 (−1.0 ppm error).

3.122: Methyl 4-((3-((*tert*-butoxycarbonyl)amino)propyl)(phenyl)amino)butanoate



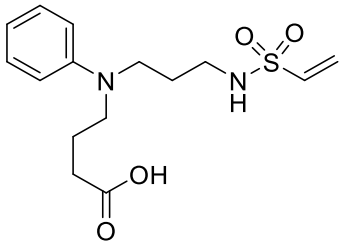
tert-Butyl *N*-[3-(phenylamino)propyl]carbamate (2.85 g, 11.4 mmol) was dissolved in acetonitrile (80.0 mL), after which potassium carbonate (2.37 g, 17.2 mmol) and sodium iodide (344 mg, 2.30 mmol) were added. Methyl 4-bromobutyrate (1.60 mL, 12.7 mmol) was then added and the solution heated to reflux (85 °C) for 120 hours. The solution was cooled to RT and diluted with ethyl acetate (80 mL), washed with sodium bicarbonate solution (80 mL) and the aqueous fraction was back-extracted with ethyl acetate (80 mL). The organic layers were combined and dried over magnesium sulfate, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 9:1 hexane : ethyl acetate → 1:1 ethyl acetate : hexane) afforded the title compound, which was obtained as a colourless oil (543 mg, 14%); R_f = 0.54 (1:1 ethyl acetate : hexane); ν_{max}/cm^{-1} (thin film): 3375, 2974, 1735, 1692, 1598, 1505, 1365, 1247, 1161, 1038, 866, 746, 694; δ_H (400 MHz, $CDCl_3$) 7.24 – 7.18 (2H, m, 2 x Ar**H**), 6.72 – 6.65 (3H, m, 3 x Ar**H**), 4.65 (1H, br s, N**H**), 3.67 (3H, s, OC**H₃**), 3.35 – 3.27 (4H, m, C**H₂**CH_2CH_2NHBoc,C**H₂**$CH_2CH_2CO_2CH_3$), 3.17 (2H, q, *J* = 6.5 Hz, C**H₂**NHBoc), 2.35 (2H, t, *J* = 7.0 Hz, C**H₂**CO_2CH_3), 1.89 (2H, p, *J* = 7.0 Hz, C**H₂**$CH_2CO_2CH_3$), 1.76 (2H, p, *J* = 7.0 Hz, C**H₂**CH_2NHBoc), 1.45 (9H, s, OC(C**H₃**)₃); δ_C (101 MHz, $CDCl_3$) 173.8 (**C**O_2CH_3), 156.1 (NH**C**O), 147.9 (Ar**C**N), 129.4 (2 x Ar**C**H), 116.4 (Ar**C**H), 112.6 (2 x Ar**C**H), 79.3 (**C**$(CH_3)_3$), 51.7 (O**C**H_3), 50.4 (**C**$H_2CH_2CH_2CO_2CH_3$), 48.6 (**C**$H_2CH_2CH_2$NHBoc), 38.7 (**C**H_2NHBoc), 31.3 (**C**$H_2CO_2CH_3$), 28.5 (C(**C**$H_3)_3$), 27.8 (**C**H_2CH_2NHBoc), 22.5 (**C**$H_2CH_2CO_2CH_3$); HRMS (ESI^+): calcd. for $C_{19}H_{31}N_2O_4$, 351.2278. Found $[MH]^+$ 351.2276 (0.6 ppm error).

3.123: Methyl 4-(phenyl(3-(vinylsulfonamido)propyl)amino)butanoate



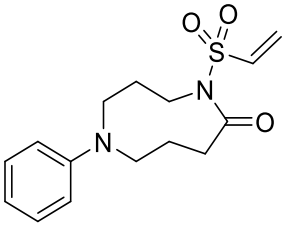
Methyl 4-((3-((*tert*-butoxycarbonyl)amino)propyl)(phenyl)amino)butanoate (477 mg, 1.36 mmol) was dissolved in 1,4-dioxane (15.0 mL) and 4 M HCl in 1,4-dioxane (2.85 mL, 82.2 mmol) was added. The solution was stirred at RT for 24 hours, after which the solution was concentrated *in vacuo* to yield an amorphous solid. This salt was dissolved in anhydrous DCM (15.0 mL) at RT and the solution was cooled to 0 °C using an ice bath. Triethylamine (1.90 mL, 13.6 mmol) was added dropwise, followed by 2-chloroethane-1-sulfonyl chloride (0.27 mL, 2.76 mmol). The solution was allowed to gradually warm to RT while being stirred for 21 hours. After that, the solution was diluted with DCM (20 mL) and washed with brine (2 x 20 mL). The aqueous layer was then washed with DCM (2 x 20 mL). The organic layers were then combined, dried over magnesium sulfate, filtered and concentrated *in vacuo*. This was purified by column chromatography (SiO_2, 7:3 hexane : ethyl acetate → 1:1 ethyl acetate : hexane → 100% ethyl acetate) to yield the title compound, which was obtained as a yellow oil (227 mg, 49%); R_f = 0.24 (1:1 ethyl acetate : hexane); ν_{max}/cm^{-1} (thin film): 3287, 2952, 2880, 1733, 1599, 1506, 1367, 1328, 1195, 1150, 1079, 971, 749; δ_H (400 MHz, $CDCl_3$) 7.25 – 7.19 (2H, m, 2 x Ar**H**), 6.75 – 6.68 (3H, m, 3 x Ar**H**), 6.46 (1H, dd, *J* = 16.5, 10.0 Hz, C**H**S), 6.22 (1H, d, *J* = 16.5 Hz, **H**C=CHS), 5.92 (1H, d, *J* = 10.0 Hz, **H**C=CHS), 4.69 (1H, br t, *J* = 6.0 Hz, N**H**), 3.68 (3H, s, OC**H₃**), 3.37 (2H, t, *J* = 7.0 Hz, C**H₂**CH_2CH_2NHS), 3.33 – 3.27 (2H, m, C**H₂**$CH_2CH_2CO_2CH_3$), 3.08 (2H, q, *J* = 6.5 Hz, C**H₂**NHS), 2.35 (2H, t, *J* = 7.0 Hz, C**H₂**CO_2CH_3), 1.93 – 1.78 (4H, m, C**H₂**CH_2NHS,C**H₂**$CH_2CO_2CH_3$); δ_C (101 MHz, $CDCl_3$) 173.9 (**C**O_2CH_3), 147.9 (Ar**C**N), 135.8 (H_2C=**C**HS), 129.5 (2 x Ar**C**H), 127.0 (H_2**C**=CHS), 117.2 (Ar**C**H), 113.4 (2 x Ar**C**H), 51.8 (O**C**H_3), 50.9 (**C**$H_2CH_2CH_2CO_2CH_3$), 48.6 (**C**$H_2CH_2CH_2$NHS), 41.3 (**C**H_2NHS), 31.3 (**C**$H_2CO_2CH_3$), 27.5 (**C**H_2CH_2NHS), 22.4 (**C**$H_2CH_2CO_2CH_3$); HRMS (ESI^+): calcd. for $C_{16}H_{25}N_2O_4S$, 341.1530. Found $[MH]^+$ 341.1527 (−0.6 ppm error).

3.124: 4-(Phenyl(3-(vinylsulfonamido)propyl)amino)butanoic acid



Methyl 4-(phenyl(3-(vinylsulfonamido)propyl)amino)butanoate (181 mg, 0.531 mmol) was dissolved in THF (10.0 mL) and water (10.0 mL), then lithium hydroxide monohydrate (133 mg, 5.54 mmol) was added and the solution stirred at RT for 21 hours. The solution was concentrated *in vacuo*. This was purified by column chromatography (SiO_2, 100% ethyl acetate → 9:1 ethyl acetate : methanol → 7:3 ethyl acetate : methanol) to yield the title compound, which was obtained as a yellow oil (144 mg, 83%); R_f = 0.42 (9:1 ethyl acetate : methanol); ν_{max}/cm^{-1} (thin film): 3280, 2938, 1709, 1599, 1506, 1326, 1149, 1081, 905, 724, 696, 648, 547; δ_H (400 MHz, $CDCl_3$) 11.26 – 9.16 (1H, br s, O**H**), 7.23 (2H, t, *J* = 8.0 Hz, 2 x Ar**H**), 6.80 – 6.70 (3H, m, 3 x Ar**H**), 6.48 (1H, dd, *J* = 16.5, 10.0 Hz, C**H**S), 6.20 (1H, d, *J* = 16.5 Hz, **H**C=CHS), 5.91 (1H, d, *J* = 10.0 Hz, **H**C=CHS), 3.36 (2H, t, *J* = 7.0 Hz, C**H₂**CH_2CH_2NHS), 3.30 (2H, t, *J* = 7.5 Hz, C**H₂**$CH_2CH_2CO_2$H), 3.03 (2H, t, *J* = 6.5 Hz, C**H₂**NHS), 2.38 (2H, t, *J* = 7.0 Hz, C**H₂**CO_2H), 1.86 (2H, p, *J* = 7.0 Hz, C**H₂**CH_2CO_2H), 1.79 (2H, p, *J* = 7.0 Hz, C**H₂**CH_2NHS); δ_C (101 MHz, $CDCl_3$) 179.0 (**C**O_2H), 147.3 (Ar**C**N), 135.7 (H_2C=**C**HS), 129.6 (2 x Ar**C**H), 127.1 (H_2**C**=CHS), 117.7 (Ar**C**H), 113.8 (2 x Ar**C**H), 51.3 (**C**$H_2CH_2CH_2CO_2$H), 48.8 (**C**$H_2CH_2CH_2$NHS), 40.9 (**C**H_2NHS), 32.0 (**C**H_2CO_2H), 27.2 (**C**H_2CH_2NHS), 22.2 (**C**$H_2CH_2CO_2$H); HRMS (ESI^+): calcd. for $C_{15}H_{22}N_2NaO_4S$, 349.1192. Found $[MNa]^+$ 349.1186 (1.9 ppm error).

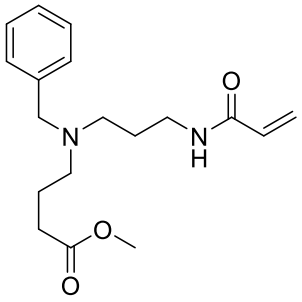
3.125: 1-Phenyl-5-(vinylsulfonyl)-1,5-diazonan-6-one



To a round-bottomed flask 4-(phenyl(3-(vinylsulfonamido)propyl)amino)butanoic acid (134 mg, 0.410 mmol) was dissolved in chloroform (8.0 mL) and DIPEA (0.13 mL, 0.758 mmol) was added dropwise. T3P (50% solution in ethyl acetate, 0.40 mL, 0.635 mmol) was then added dropwise and the solution stirred at RT for 48 hours. The reaction mixture was diluted with DCM (15 mL) and washed with $NaHCO_3$ (2 x 15 mL). The organic layer was dried, filtered and

concentrated *in vacuo*. This was purified by column chromatography (SiO_2, 1:1 ethyl acetate : hexane → 100% ethyl acetate → 8:2 ethyl acetate : methanol) to yield the title compound, which was obtained as a colourless oil (8.0 mg, 6%); R_f = 0.56 (100% ethyl acetate); ν_{max}/cm^{-1} (thin film): 2925, 2855, 1685, 1599, 1503, 1462, 1345, 1329, 1233, 1159, 1123, 1085, 969, 801, 748, 695, 666; δ_H (400 MHz, $CDCl_3$) 7.23 (2H, dd, *J* = 9.0, 7.0 Hz, 2 x Ar**H**), 6.79 (1H, t, *J* = 7.5 Hz, Ar**H**), 6.68 (2H, d, *J* = 8.5 Hz, 2 x Ar**H**), 6.52 (1H, dd, *J* = 16.5, 10.0 Hz, C**H**S), 6.18 (1H, d, *J* = 16.5 Hz, **H**C=CHS), 5.66 (1H, d, *J* = 10.0 Hz, **H**C=CHS), 4.11 (2H, t, *J* = 5.5 Hz, C$\mathbf{H_2}$NS), 3.57 (2H, t, *J* = 5.5 Hz, NC$\mathbf{H_2}CH_2CH_2N$), 3.40 (2H, t, *J* = 6.5 Hz, C$\mathbf{H_2}CH_2CH_2CO$), 2.71 – 2.65 (2H, m, C$\mathbf{H_2}$CO), 2.29 (2H, p, *J* = 6.5 Hz, $NCH_2C\mathbf{H_2}CH_2CO$), 2.05 – 1.97 (2H, m, $NCH_2C\mathbf{H_2}CH_2N$); δ_C (100 MHz, $CDCl_3$) 174.9 (**C**O), 148.5 (Ar**C**), 136.7 (H_2C=**C**HS), 129.3 (2 x Ar**C**H), 128.3 ($H_2\mathbf{C}$=CHS), 118.0 (Ar**C**H), 113.4 (2 x Ar**C**H), 56.9 (**C**$H_2CH_2CH_2CO$), 54.3 (N**C**$H_2CH_2CH_2CO$), 46.1 (**C**H_2NHS), 31.2 (**C**H_2CO), 27.8 ($NCH_2\mathbf{C}H_2CH_2CO$) 26.6 ($NCH_2\mathbf{C}H_2CH_2N$); HRMS (ESI^+): calcd. for $C_{15}H_{20}N_2NaO_3S$, 331.1087. Found $[MNa]^+$ 331.1091 (−1.3 ppm error).

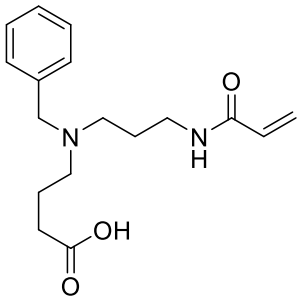
3.126: Methyl 4-((3-acrylamidopropyl)(benzyl)amino)butanoate



Methyl 4-(benzyl(3-((*tert*-butoxycarbonyl)amino)propyl)amino)butanoate (65.2 mg, 0.179 mmol) was dissolved in 1,4-dioxane (5.0 mL) and 4 M HCl in 1,4-dioxane (0.50 mL, 14.5 mmol) was added. The solution was stirred at RT for 72 hours, after which the solution was concentrated *in vacuo* to yield an amorphous solid. This salt was dissolved in THF (5.0 mL), cooled to 0 °C and DIPEA (0.31 mL, 1.79 mmol) was added. To this was added a 0 °C cooled solution of acryloyl chloride (22.0 µL, 0.271 mmol) in THF (1.0 mL) dropwise. Under an argon atmosphere this mixture was stirred at 0 °C for 2 hours and a further 16 hours at RT. The reaction mixture was then quenched with sat. aq. NH_4Cl (10 mL), extracted with Et_2O (15 mL), then the organic layer was washed with sat. aq. $NaHCO_3$ (2 × 10 mL) and NaCl (2 x 10 mL). The organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 ethyl acetate : hexane → 9:1 ethyl acetate : methanol) afforded the title compound, which was obtained as a colourless oil (34.5 mg, 61%); R_f = 0.33 (9:1 ethyl acetate : methanol); ν_{max}/cm^{-1} (thin film): 3284, 2950, 2805, 1735, 1658, 1625, 1548, 1453, 1437, 1366, 1245, 1173, 1125, 987, 737, 700; δ_H (400

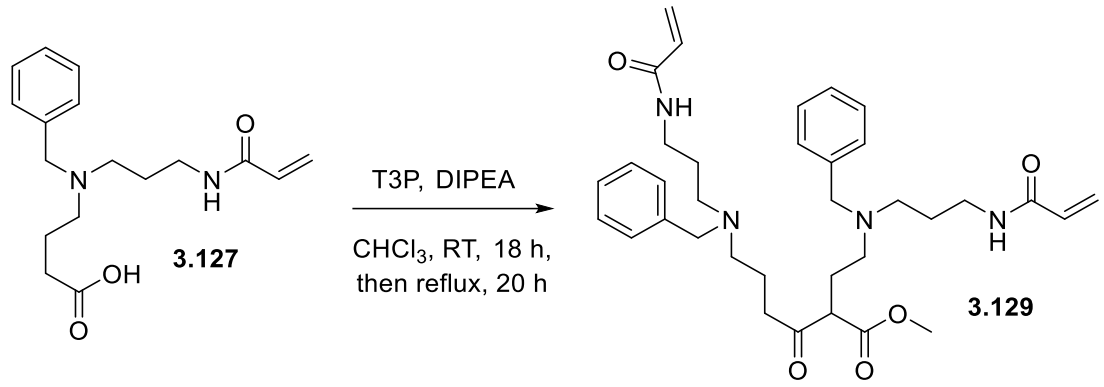
MHz, $CDCl_3$) 7.34 – 7.22 (5H, m, 5 x Ar**H**), 6.42 (1H, br t, *J* = 5.0 Hz, N**H**), 6.18 (1H, dd, *J* = 17.0, 1.5 Hz, HC=C**H$_2$**), 5.92 (1H, dd, *J* = 17.0, 10.5 Hz, **H**C=CH_2), 5.55 (1H, dd, *J* = 10.5, 1.5 Hz, HC=C**H$_2$**), 3.64 (3H, s, OC**H$_3$**), 3.51 (2H, s, PhC**H$_2$**N), 3.33 (2H, q, *J* = 6.0 Hz, C**H$_2$**NHCO), 2.47 (2H, t, *J* = 5.5 Hz, C**H$_2$**CH_2CH_2NHCO), 2.44 (2H, t, *J* = 5.5 Hz, C**H$_2$**$CH_2CH_2CO_2CH_3$), 2.32 (2H, t, *J* = 7.5 Hz, C**H$_2$**CO_2CH_3), 1.82 (2H, p, *J* = 7.5 Hz, C**H$_2$**$CH_2CO_2CH_3$), 1.65 (2H, p, *J* = 6.5 Hz, C**H$_2$**CH_2NHCO); δ_C (100 MHz, $CDCl_3$) 174.2 (**C**O_2CH_3), 165.5 (NH**C**O), 139.4 (Ar**C**CH_2N), 131.1 (H_2C=**C**HCO), 129.2 (Ar**C**H), 128.5 (2 x Ar**C**H), 127.2 (2 x Ar**C**H), 125.9 (H_2**C**=CHCO), 58.7 (Ph**C**H_2N), 53.0 (**C**$H_2CH_2CH_2CO_2CH_3$), 51.7 (O**C**H_3), 51.5 (**C**$H_2CH_2CH_2$NHCO), 38.3 (**C**H_2NHCO), 31.8 (**C**$H_2CO_2CH_3$), 26.0 (**C**H_2CH_2NHCO), 22.3 (**C**$H_2CH_2CO_2CH_3$); HRMS (ESI^+): calcd. for $C_{18}H_{27}N_2O_3$, 319.2016. Found $[MH]^+$ 319.2021 (−1.4 ppm error).

3.127: 4-((3-Acrylamidopropyl)(benzyl)amino)butanoic acid



Methyl 4-((3-acrylamidopropyl)(benzyl)amino)butanoate (133 mg, 0.416 mmol) was dissolved in THF (5.0 mL) and water (5.0 mL), then lithium hydroxide monohydrate (101 mg, 4.23 mmol) was added and the solution stirred at RT for 24 hours. The solution was concentrated *in vacuo*. This was purified by column chromatography (SiO_2, 9:1 ethyl acetate : methanol → 1:1 ethyl acetate : methanol) to yield the title compound, which was obtained as a colourless oil (118 mg, 93%); R_f = 0.12 (1:1 ethyl acetate : methanol); ν_{max}/cm^{-1} (thin film): 3268, 2942, 2240, 1659, 1625, 1553, 1454, 1406, 1245, 984, 959, 908, 726, 699, 644; δ_H (400 MHz, $CDCl_3$) 12.00 – 10.98 (1H, br s, O**H**), 7.53 (1H, br t, *J* = 5.5 Hz, N**H**), 7.34 – 7.24 (5H, m, 5 x Ar**H**), 6.20 (1H, dd, *J* = 17.0, 2.0 Hz, HC=C**H$_2$**), 6.11 (1H, dd, *J* = 17.0, 10.0 Hz, **H**C=CH_2), 5.51 (1H, dd, *J* = 10.0, 2.0 Hz, HC=C**H$_2$**), 3.71 (2H, s, PhC**H$_2$**N), 3.27 (2H, q, *J* = 6.5 Hz, C**H$_2$**NHCO), 2.69 – 2.58 (4H, m, C**H$_2$**CH_2CH_2NHCO,C**H$_2$**$CH_2CH_2CO_2H$), 2.28 (2H, t, *J* = 6.5 Hz, C**H$_2$**CO_2H), 1.78 (4H, p, *J* = 7.0 Hz, C**H$_2$**CH_2CO_2H,C**H$_2$**CH_2NHCO); δ_C (100 MHz, $CDCl_3$) 178.6 (**C**O_2H), 166.2 (NH**C**O), 135.0 (Ar**C**CH_2N), 131.2 (H_2C=**C**HCO), 130.0 (2 x Ar**C**HCCH_2N), 128.9 (2 x Ar**C**HCHCCH_2N), 128.3 (Ar**C**H), 126.0 (H_2**C**=CHCO), 57.9 (Ph**C**H_2N), 53.7 (**C**$H_2CH_2CH_2CO_2H$), 50.8 (**C**$H_2CH_2CH_2$NHCO), 37.5 (**C**H_2NHCO), 35.4 (**C**H_2CO_2H), 25.2 (**C**H_2CH_2NHCO), 21.7 (**C**$H_2CH_2CO_2H$); HRMS (ESI^+): calcd. for $C_{17}H_{25}N_2O_3$, 305.1865. Found $[MH]^+$ 305.1860 (−1.7 ppm error).

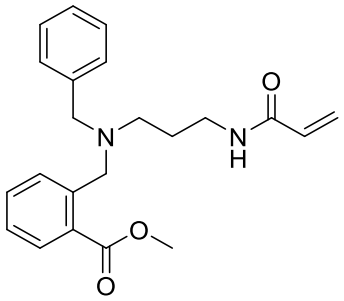
3.129: Methyl 6-((3-acrylamidopropyl)(benzyl)amino)-2-(2-((3-acrylamidopropyl)(benzyl)amino)ethyl)-3-oxohexanoate



To a round-bottomed flask 4-((3-acrylamidopropyl)(benzyl)amino)butanoic acid (118 mg, 0.388 mmol) was dissolved in chloroform (7.0 mL) and DIPEA (0.13 mL, 0.746 mmol) was added dropwise. T3P (50% solution in ethyl acetate, 0.36 mL, 0.567 mmol) was added dropwise and the solution stirred at RT for 18 hours. The reaction mixture was diluted with DCM (10 mL) and washed with $NaHCO_3$ (2 x 10 mL). The organic layer was dried, filtered and concentrated *in vacuo*. This was purified by column chromatography (SiO_2, 100% ethyl acetate → 7:3 ethyl acetate : methanol → 1:1 ethyl acetate : methanol). This was then re-dissolved chloroform (7.0 mL) and DIPEA (0.13 mL, 0.746 mmol) was added in a single portion. The solution was stirred at reflux (65 °C) for 20 hours. This was purified by column chromatography (SiO_2, 9:1 ethyl acetate : methanol) to yield the side-product, which was obtained as a pale orange oil (26.3 mg, 11%); R_f = 0.61 (1:1 ethyl acetate : methanol); ν_{max}/cm^{-1} (thin film): 3281, 2928, 2806, 1740, 1712, 1657, 1625, 1548, 1452, 1406, 1242, 1135, 1074, 985, 958, 806, 734, 700; δ_H (400 MHz, $CDCl_3$) 7.35 – 7.19 (10H, m, 10 x Ar**H**), 6.50 (1H, br t, *J* = 5.5 Hz, N**H**), 6.40 (1H, br t, *J* = 5.5 Hz, N**H**), 6.21 (1H, dd, *J* = 17.0, 1.5 Hz, HC=C**H₂**), 6.19 (1H, dd, *J* = 17.0, 1.5 Hz, HC=C**H₂**), 6.00 (1H, dd, *J* = 17.0, 10.0 Hz, **H**C=CH_2), 5.95 (1H, dd, *J* = 17.0, 10.0 Hz, **H**C=CH_2), 5.56 (1H, dd, *J* = 10.0, 1.5 Hz, HC=C**H₂**), 5.55 (1H, dd, *J* = 10.0, 1.5 Hz, HC=C**H₂**), 3.65 (3H, s, OC**H₃**), 3.53 (1H, t, *J* = 7.0 Hz, COC**H** [overlapping]), 3.51 (2H, s, PhC**H₂**N [overlapping]), 3.48 (2H, d, *J* = 3.5 Hz, PhC**H₂**N), 3.37 – 3.28 (4H, m, 2 x C**H₂**NHCO), 2.59 – 2.29 (10H, m, 5 x C**H₂**), 2.05 – 1.95 (2H, m, C**H₂**$CHCOCH_3$), 1.70 (2H, p *J* = 8.0 Hz, C**H₂**$CH_2COCHCOCH_3$ [overlapping]), 1.77 – 1.60 (4H, m, 2 x C**H₂**CH_2NHCO [overlapping]); δ_C (100 MHz, $CDCl_3$) 205.3 (**C**O$CHCOCH_3$), 170.5 (**C**O_2CH_3), 165.7 (NH**C**O), 165.6 (NH**C**O), 139.3 (Ar**C**CH_2N), 139.2 (Ar**C**CH_2N), 131.2 (H_2C=**C**HCO), 131.1 (H_2C=**C**HCO), 129.3 (2 x Ar**C**HCH_2N), 129.2 (2 x Ar**C**HCH_2N), 128.5 (4 x Ar**C**HCH_2N), 127.3 (2 x Ar**C**H), 126.1 (H_2**C**=CHCO), 126.0 (H_2**C**=CHCO), 58.8 (Ph**C**H_2N), 58.6 (Ph**C**H_2N), 56.5 (CO**C**H), 52.8 (**C**H_2), 52.6 (O**C**H_3), 51.50 (**C**H_2 [overlapping]), 51.49 (**C**H_2 [overlapping]), 51.1 (**C**H_2), 39.8 (**C**$H_2COCHCOCH_3$), 38.3 (**C**H_2NHCO), 37.9 (**C**H_2NCO), 26.4 (**C**H_2CH_2NHCO), 26.2

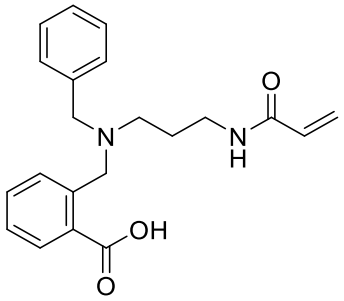
(**C**H_2CH_2NHCO), 25.8 (**C**$H_2CHCOCH_3$), 20.8 (**C**$H_2CH_2COCHCOCH_3$); HRMS (ESI$^+$): calcd. for $C_{35}H_{49}N_4O_5$, 605.3697. Found [MH]$^+$ 605.3705 (−1.2 ppm error).

3.132: Methyl 2-(((3-acrylamidopropyl)(benzyl)amino)methyl)benzoate



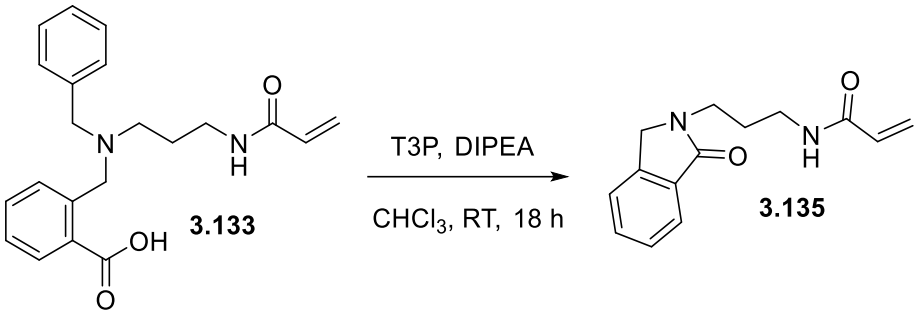
Methyl 2-((benzyl(3-((*tert*-butoxycarbonyl)amino)propyl)amino)methyl)benzoate (1.52 g, 4.17 mmol) was dissolved in 1,4-dioxane (30.0 mL) and 4 M HCl in 1,4-dioxane (11.7 mL, 337 mmol) was added. The solution was stirred at RT for 20 hours, after which the solution was concentrated *in vacuo* to yield an amorphous solid. This salt was dissolved in THF (30.0 mL), cooled to 0 °C and DIPEA (7.25 mL, 41.6 mmol) was added. To this was added a solution of acryloyl chloride (0.51 mL, 6.30 mmol) dropwise *via* a syringe pump over 10 minutes. Under an argon atmosphere this mixture was stirred at 0 °C for 2 hours and a further 22 hours at RT. The reaction mixture was then quenched with sat. aq. NH_4Cl (40 mL), extracted with Et_2O (2 x 50 mL), then the organic layer was washed with sat. aq. $NaHCO_3$ (2 × 40 mL) and NaCl (2 x 40 mL). The organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 7:3 hexane : ethyl acetate → 100% ethyl acetate) to yield the title compound, which was obtained as a yellow oil (1.20 g, 89%); R_f = 0.42 (100% ethyl acetate); ν_{max}/cm^{-1} (thin film): 3283, 3064, 2949, 2805, 1721, 1657, 1625, 1546, 1452, 1434, 1292, 1267, 1248, 1128, 1082, 982, 959, 737, 699; δ_H (400 MHz, $CDCl_3$) 7.77 (1H, dd, *J* = 7.5, 1.5 Hz, C**H**CCO), 7.55 (1H, d, *J* = 7.5 Hz, C**H**CCH_2N), 7.46 (1H, td, *J* = 7.5, 1.5 Hz, C**H**CHCCH_2N), 7.35 – 7.22 (6H, m, 6 x Ar**H**), 6.14 (1H, dd, *J* = 17.0, 1.5 Hz, HC=C**H$_2$**), 5.81 (1H, dd, *J* = 17.0, 10.5 Hz, **H**C=CH_2), 5.73 (1H, br t, *J* = 6.0 Hz, N**H**), 5.52 (1H, dd, *J* = 10.5, 1.5 Hz, HC=C**H$_2$**), 3.90 (2H, s, COCCC**H$_2$**N), 3.86 (3H, s, OC**H$_3$**), 3.51 (2H, s, PhC**H$_2$**N), 3.25 (2H, q, *J* = 6.0 Hz, C**H$_2$**NHCO), 2.42 (2H, t, *J* = 6.5 Hz, C**H$_2$**CH_2CH_2NHCO), 1.66 (2H, p, *J* = 6.5 Hz, C**H$_2$**CH_2NHCO); δ_C (100 MHz, $CDCl_3$) 169.0 (**C**O_2CH_3), 165.5 (NH**C**O), 140.7 (**C**CCO), 139.1 (Ar**C**CH_2N), 131.6 (H_2C=**C**HCO), 131.3 (**C**CO), 131.1 (**C**HCHCCH_2N), 130.6 (**C**HCCH_2N), 130.1 (**C**HCCO), 129.4 (2 x Ar**C**H), 128.5 (2 x Ar**C**H), 127.3 (Ar**C**H), 127.1 (Ar**C**H), 125.9 (H_2**C**=CHCO), 58.7 (Ph**C**H_2N), 57.1 (COCC**C**H_2N), 52.2 (O**C**H_3), 50.4 (**C**$H_2CH_2CH_2$NHCO), 37.4 (**C**H_2NHCO), 26.0 (**C**H_2CH_2NHCO); HRMS (ESI$^+$): calcd. for $C_{22}H_{26}N_2NaO_3$, 389.1836. Found [MNa]$^+$ 389.1836 (−0.1 ppm error).

3.133: 2-(((3-Acrylamidopropyl)(benzyl)amino)methyl)benzoic acid



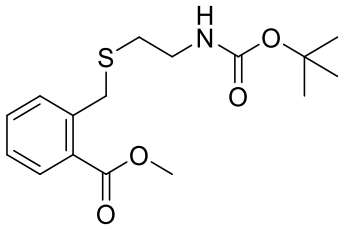
Methyl 2-(((3-acrylamidopropyl)(benzyl)amino)methyl)benzoate (1.09 g, 2.98 mmol) was dissolved in THF (25.0 mL) and water (25.0 mL), then lithium hydroxide monohydrate (726 mg, 30.3 mmol) was added and the solution stirred at RT for 96 hours. The solution was concentrated *in vacuo*. This was purified by column chromatography (SiO_2, 9:1 ethyl acetate : methanol → 1:1 ethyl acetate : methanol) to yield the title compound, which was obtained as an orange oil (971 mg, 92%). R_f = 0.46 (1:1 ethyl acetate : methanol); ν_{max}/cm^{-1} (thin film): 3264, 3064, 2952, 2233, 1662, 1625, 1595, 1551, 1456, 1375, 1243, 985, 910, 808, 729, 700; δ_H (400 MHz, $CDCl_3$) 8.12 (1H, dd, *J* = 7.0, 2.0 Hz, C**H**CCO), 7.48 – 7.34 (1H, m, N**H** [overlapping]), 7.42 (2H, pd, *J* = 7.5, 1.5 Hz, 2 x Ar**H** [overlapping]), 7.34 – 7.23 (5H, m, 5 x Ar**H**), 7.19 (1H, dd, *J* = 7.5, 1.5 Hz, C**H**CCCO), 6.25 (1H, dd, *J* = 17.0, 2.0 Hz, **H**C=CHCO), 6.16 (1H, d, *J* = 17.0, 10.0 Hz, C**H**CO), 5.57 (1H, d, *J* = 10.0, 2.0 Hz, **H**C=CHCO), 4.01 (2H, br s, PhC**H₂**N), 3.81 (2H, br s, COCCC**H₂**N), 3.22 (2H, q, *J* = 6.0 Hz, C**H₂**NHCO), 2.76 (2H, t, *J* = 8.0 Hz, C**H₂**CH_2CH_2NHCO), 1.88 (2H, p, *J* = 7.0 Hz, C**H₂**CH_2NHCO); δ_C (100 MHz, $CDCl_3$) 171.4 (**C**O_2H), 166.4 (NH**C**O), 137.0 (**C**CCO), 133.3 (**C**HCCO), 131.9 (Ar**C**CH_2N), 131.6 (**C**CO), 131.3 (**C**HCCCO,H_2C=**C**HCO [overlapping]), 131.1 (Ar**C**H), 130.2 (2 x Ar**C**H), 129.7 (Ar**C**H), 129.3 (2 x Ar**C**H), 129.2 (Ar**C**H), 126.2 (H_2**C**=CHCO), 58.8 (Ph**C**H_2N), 55.8 (**C**H_2CCCO_2H), 48.5 (**C**$H_2CH_2CH_2$NHCO), 36.8 (**C**H_2NHCO), 24.0 (**C**H_2CH_2NHCO); HRMS (ESI^+): calcd. for $C_{21}H_{24}N_2NaO_3$, 375.1679. Found $[MNa]^+$ 375.1666 (3.4 ppm error).

3.135: *N*-(3-(1-Oxoisoindolin-2-yl)propyl)acrylamide



To a round-bottomed flask 2-(((3-acrylamidopropyl)(benzyl)amino)methyl)benzoic acid (110 mg, 0.311 mmol) was dissolved in chloroform (7.0 mL) and DIPEA (0.10 mL, 0.575 mmol) was added dropwise. T3P (50% solution in ethyl acetate, 0.30 mL, 0.473 mmol) was added dropwise and the solution stirred at RT for 18 hours. After that, the reaction mixture was diluted with DCM (15 mL) and washed with $NaHCO_3$ (2 x 15 mL). The organic layer was dried, filtered and concentrated *in vacuo*. This was purified by column chromatography (SiO_2, 9:1 ethyl acetate : methanol) to yield the side-product, which was obtained as an orange oil (68.3 mg, 90%). R_f = 0.68 (1:1 ethyl acetate : methanol); ν_{max}/cm^{-1} (thin film): 3288, 3072, 2929, 1657, 1624, 1544, 1472, 1456, 1413, 1304, 1237, 1212, 986, 734, 684; δ_H (400 MHz, $CDCl_3$) 7.78 (1H, d, *J* = 7.5 Hz, C**H**CCO), 7.55 – 7.48 (1H, m, C**H**CCH_2N), 7.44 (2H, t, *J* = 7.5 Hz, C**H**CHCCO,C**H**CHCCH_2N), 7.23 (1H, br t, *J* = 5.5 Hz, N**H**), 6.25 (1H, d, *J* = 17.0, 2.0 Hz, **H**C=CHCO), 6.16 (1H, dd, *J* = 17.0, 10.0 Hz, HC=C**H**CO), 5.58 (1H, dd, *J* = 10.0, 2.0 Hz, **H**C=CHCO), 4.38 (2H, s, PhC**H₂**N), 3.67 (2H, t, *J* = 6.0 Hz, NC**H₂**CH_2CH_2NH), 3.27 (2H, q, *J* = 6.5 Hz, C**H₂**NHCO), 1.83 (2H, p, *J* = 6.0 Hz, NCH_2C**H₂**CH_2NH); δ_C (100 MHz, $CDCl_3$) 169.6 (N**C**O), 165.8 (NH**C**O), 141.2 (**C**CCO), 132.3 (**C**CO), 131.6 (**C**HCCH_2N), 131.4 (H_2C=**C**HCO), 128.3 (Ar**C**H), 125.8 (H_2**C**=CHCO), 123.6 (**C**HCCO), 122.9 (Ar**C**H), 50.2 (Ph**C**H_2N), 39.5 (N**C**$H_2CH_2CH_2$NHCO), 35.6 (**C**H_2NHCO), 27.7 (NCH_2**C**H_2CH_2NHCO); HRMS (ESI^+): calcd. for $C_{14}H_{17}N_2O_2$, 245.1285. Found $[MH]^+$ 245.1285 (−0.0 ppm error).

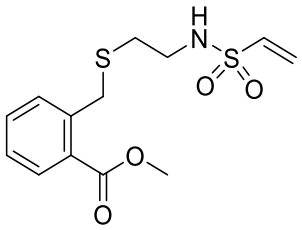
3.141: Methyl 2-(((2-((*tert*-butoxycarbonyl)amino)ethyl)thio)methyl)benzoate



To a stirring suspension of potassium carbonate (3.20 g, 23.2 mmol) in acetonitrile (30 mL), 2-[(*tert*-butoxycarbonyl)amino]-1-ethanethiol (1.37 g, 7.73 mmol) was added followed by

methyl 2-(bromomethyl) benzoate (1.26 g, 5.50 mmol). The reaction mixture was refluxed (85 °C) for 19 hours under argon before filtering through Celite and washing with DCM. The solution was then concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 9:1 hexane : ethyl acetate → 100% ethyl acetate) afforded the title compound, which was obtained as a colourless oil (339 mg, 13%); R_f = 0.43 (7:3 hexane : ethyl acetate); ν_{max}/cm^{-1} (thin film): 3383, 2977, 2951, 1710, 1506, 1449, 1435, 1365, 1263, 1164, 1124, 1078, 954, 769, 716; δ_H (400 MHz, $CDCl_3$) 7.90 (1H, d, *J* = 8.0 Hz, COCC**H**), 7.44 (1H, t, *J* = 7.5 Hz, Ar**H**), 7.36 – 7.28 (2H, m, 2 x Ar**H**), 4.97 (1H, br s, N**H**), 4.11 (2H, s, COCCC**H₂**S), 3.91 (3H, s, OC**H₃**), 3.28 (2H, q, *J* = 6.5 Hz, $CH_2C\mathbf{H_2}NHBoc$), 2.56 (2H, t, *J* = 6.5 Hz, $C\mathbf{H_2}CH_2NHBoc$), 1.43 (9H, s, $OC(C\mathbf{H_3})_3$); δ_C (101 MHz, $CDCl_3$) 167.9 (**C**O_2CH_3), 155.9 (NH**C**O), 140.4 (CO**C**CCH_2S), 132.1 (Ar**C**H), 131.3 (Ar**C**H), 131.2 (Ar**C**H), 129.5 (COC**C**CH_2S), 127.4 (Ar**C**H), 79.4 (**C**$(CH_3)_3$), 52.3 (O**C**H_3), 39.5 (**C**H_2NHBoc), 34.2 (COCC**C**H_2S), 32.2 (**C**H_2CH_2NHBoc), 28.5 ($C(\mathbf{C}H_3)_3$); HRMS (ESI^+): calcd. for $C_{16}H_{23}NNaO_4S$, 348.1240. Found $[MNa]^+$ 348.1241 (−0.2 ppm error).

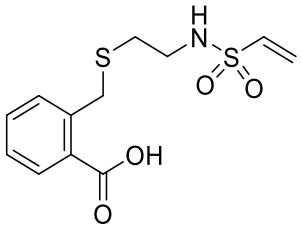
3.142: Methyl 2-(((2-(vinylsulfonamido)ethyl)thio)methyl)benzoate



Methyl 2-(((2-((*tert*-butoxycarbonyl)amino)ethyl)thio)methyl)benzoate (275 mg, 0.844 mmol) was dissolved in 1,4-dioxane (20 mL) and 4 M HCl in 1,4-dioxane (1.80 mL, 51.9 mmol) was added. The solution was stirred at RT for 72 hours, after which another portion of 4 M HCl in 1,4-dioxane (1.80 mL, 51.9 mmol) was added and stirred for a further 96 hours at RT. Then, the solution was concentrated *in vacuo* to yield an amorphous solid. This salt was dissolved in anhydrous DCM (20 mL) at RT and the solution was cooled to 0 °C using an ice bath. Triethylamine (1.20 mL, 8.61 mmol) was added dropwise, followed by 2-chloroethane-1-sulfonyl chloride (0.12 mL, 1.27 mmol). The solution was allowed to gradually warm to RT while being stirred for 22 hours. The solution was diluted with DCM (30 mL) and washed with brine (2 x 30 mL). The aqueous layer was then washed with DCM (2 x 30 mL). The organic layers were then combined, dried over magnesium sulfate, filtered and concentrated *in vacuo*. This was purified by column chromatography (SiO_2, 9:1 hexane : ethyl acetate → 7:3 hexane : ethyl acetate → 1:1 ethyl acetate : hexane) to yield the title compound, which was obtained as a colourless oil (175 mg, 66%); R_f = 0.34 (1:1 ethyl acetate : hexane); ν_{max}/cm^{-1} (thin film): 3285, 2951, 1713, 1433, 1326, 1264, 1144, 1126, 1077, 965,

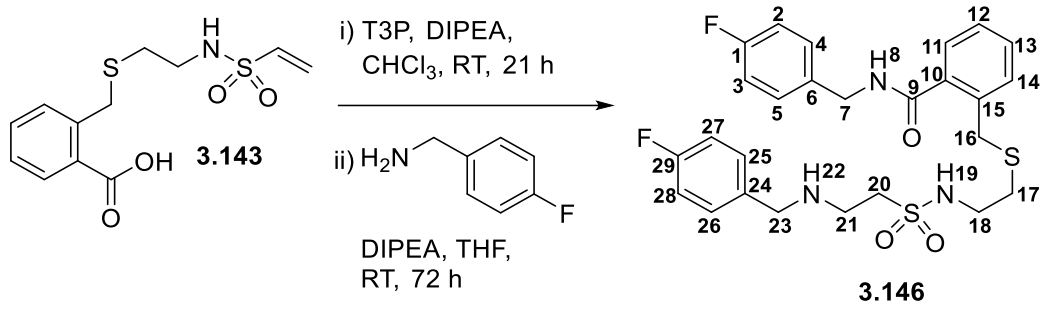
769, 715, 659, 548; δ_H (400 MHz, $CDCl_3$) 7.88 (1H, dd, *J* = 7.5, 1.5 Hz, COCC**H**), 7.42 (1H, td, *J* = 7.5, 1.5 Hz, C**H**CCH$_2$S), 7.31 (2H, d, *J* = 7.5 Hz, 2 x Ar**H**), 6.48 (1H, dd, *J* = 16.5, 9.5 Hz, H$_2$C=C**H**S), 6.17 (1H, d, *J* = 16.5 Hz, **H$_2$**C=CHS), 5.87 (1H, d, *J* = 9.5 Hz, **H$_2$**C=CHS), 5.15 (1H, br t, *J* = 6.0 Hz, N**H**), 4.08 (2H, s, COCCC**H$_2$**S), 3.88 (3H, s, OC**H$_3$**), 3.11 (2H, q, *J* = 6.5 Hz, CH$_2$C**H$_2$**NHS), 2.62 (2H, t, *J* = 6.5 Hz, C**H$_2$**CH$_2$NHS); δ_C (101 MHz, $CDCl_3$) 167.8 (**C**O$_2$CH$_3$), 139.9 (Ar**C**), 136.0 (H$_2$C=**C**HS), 132.2 (**C**HCCH$_2$S), 131.22 (Ar**C**H), 131.18 (Ar**C**H), 129.2 (Ar**C**), 127.4 (Ar**C**H), 126.6 (H$_2$**C**=CHS), 52.3 (O**C**H$_3$), 41.8 (**C**H$_2$NHS), 34.0 (COCC**C**H$_2$S), 31.9 (**C**H$_2$CH$_2$NHS); HRMS (ESI$^+$): calcd. for $C_{13}H_{17}NNaO_4S_2$, 338.0491. Found $[MNa]^+$ 338.0495 (−1.1 ppm error).

3.143: 2-(((2-(Vinylsulfonamido)ethyl)thio)methyl)benzoic acid



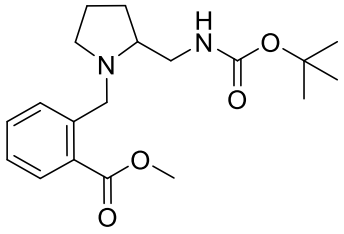
Methyl 2-(((2-(vinylsulfonamido)ethyl)thio)methyl)benzoate (151 mg, 0.478 mmol) was dissolved in THF (5.0 mL) and water (5.0 mL), then lithium hydroxide monohydrate (114 mg, 4.74 mmol) was added and the solution stirred at RT for 72 hours. The solution was concentrated *in vacuo*. This was purified by column chromatography (SiO_2, 9:1 ethyl acetate : methanol) to yield the title compound, which was obtained as a colourless oil (74.5 mg, 52%); R_f = 0.46 (9:1 ethyl acetate : methanol); ν_{max}/cm^{-1} (thin film): 3278, 2927, 1689, 1602, 1581, 1554, 1395, 1324, 1272, 1145, 1132, 1079, 967, 911, 768, 730, 654, 551, 487; δ_H (400 MHz, $CDCl_3$) 7.97 – 8.80 (1H, br s, O**H**), 7.97 – 7.71 (1H, m, COCC**H**), 7.46 – 7.33 (2H, m, 2 x Ar**H**), 7.33 – 7.13 (1H, m, C**H**CCH$_2$S), 6.38 (1H, dd, *J* = 16.5, 10.0 Hz, H$_2$C=C**H**S), 6.11 (1H, d, *J* = 16.5 Hz, **H$_2$**C=CHS), 5.79 (1H, d, *J* = 10.0 Hz, **H$_2$**C=CHS), 5.61 (1H, br s, N**H**), 4.32 – 3.94 (2H, br s, COCCC**H$_2$**S), 3.09 – 2.88 (2H, br s, CH$_2$C**H$_2$**NHS), 2.67 – 2.44 (2H, br s, C**H$_2$**CH$_2$NHS); δ_C (101 MHz, $CDCl_3$) 167.8 (**C**OOH), 139.6 (Ar**C**), 135.8 (H$_2$C=**C**HS), 131.9 (Ar**C**), 131.5 (Ar**C**), 131.3 (Ar**C**), 131.1 (Ar**C**), 127.4 (Ar**C**), 127.0 (H$_2$**C**=CHS), 42.2 (**C**H$_2$NHS), 34.3 (COCC**C**H$_2$S), 31.9 (**C**H$_2$CH$_2$NHS); HRMS (ESI$^+$): calcd. for $C_{12}H_{15}NNaO_4S_2$, 324.0335. Found $[MNa]^+$ 324.0331 (1.1 ppm error).

3.146: *N*-(4-Fluorobenzyl)-2-(((2-((2-((4-fluorobenzyl)amino)ethyl)sulfonamido)ethyl)thio)methyl)benzamide



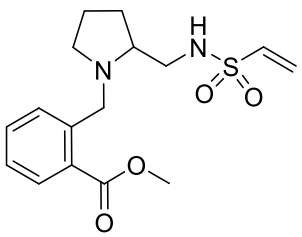
To a round-bottomed flask 2-(((2-(vinylsulfonamido)ethyl)thio)methyl)benzoic acid (61.2 mg, 0.203 mmol) was dissolved in chloroform (7.0 mL) and DIPEA (0.07 mL, 0.406 mmol) was added dropwise. T3P (50% solution in ethyl acetate, 0.19 mL, 0.305 mmol) was added dropwise and the solution stirred at RT for 21 hours. After that, the reaction mixture was diluted with DCM (10 mL) and washed with $NaHCO_3$ (2 x 10 mL). The organic layer was dried, filtered and concentrated *in vacuo* to remove excess solvent to form 8-membered ring intermediate, which was used directly in the next step. To this resulting beige oil was added DIPEA (0.13 mL, 0.756 mmol) in THF (2.0 mL) and 4-fluorobenzylamine (35.0 µL, 0.307 mmol) in a single portion. The reaction mixture was allowed to stir at RT for 72 hours. Then, the solution was diluted in DCM (10 mL) and washed with $NaHCO_3$ (2 x 10 mL). The organic layer was dried, filtered and concentrated *in vacuo* to yield the side-product, which was obtained as a colourless oil (17.9 mg, 14%); R_f = 0.17 (100% ethyl acetate); ν_{max}/cm^{-1} (thin film): 3287, 2925, 1643, 1602, 1509, 1316, 1221, 1140, 1094, 824, 766, 732; δ_H (400 MHz, $CDCl_3$) 7.47 – 7.20 (8H, m, 8 x Ar**H**), 7.04 (2H, t, *J* = 8.5 Hz, H-4,5/25,26), 6.98 (2H, t, *J* = 8.5 Hz, H-4,5/25,26), 6.64 (1H, t, *J* = 6.0 Hz, H-8), 4.57 (2H, d, *J* = 6.0 Hz, H-7), 3.95 (2H, s, H-16), 3.74 (2H, s, H-23), 3.18 – 3.10 (2H, m, H-18 [overlapping]), 3.18 – 3.10 (2H, m, H-21 [overlapping]), 3.07 – 3.01 (2H, m, H-20), 2.60 (2H, t, *J* = 6.5 Hz, H-17); δ_C (100 MHz, $CDCl_3$) 169.6 (C-9), 162.4 (C-1/29, d, $^1J_{CF}$ = 245.8 Hz), 162.2 (C-1/29, d, $^1J_{CF}$ = 245.3 Hz), 136.8 (C-15), 135.8 (C-10), 134.9 (C-24, d, $^4J_{CF}$ = 3.9 Hz), 134.0 (C-6, d, $^4J_{CF}$ = 3.9 Hz), 131.2 (Ar**C**H), 130.6 (Ar**C**H), 129.91 (C-4,5/25,26, d, $^3J_{CF}$ = 7.7 Hz), 129.90 (C-4,5/25,26, d, $^3J_{CF}$ = 8.3 Hz), 127.8 (Ar**C**H), 127.7 (Ar**C**H), 115.8 (C-2,3/27,28, d, $^2J_{CF}$ = 21.2 Hz), 115.5 (C-2,3/27,28, d, $^2J_{CF}$ = 21.2 Hz), 52.9 (C-23), 52.1 (C-18), 43.5 (C-7 [overlapping]), 43.5 (C-20 [overlapping]), 42.2 (C-21), 33.4 (C-16), 32.4 (C-17); δ_F (282 MHz, $CDCl_3$) −114.4 (1F, m, Ar**F**), −115.1 (1F, m, Ar**F**); HRMS (ESI^+): calcd. for $C_{26}H_{30}F_2N_3O_3S_2$, 534.1691. Found $[MH]^+$ 534.1685 (1.1 ppm error).

3.148: Methyl 2-((2-(((*tert*-butoxycarbonyl)amino)methyl)pyrrolidin-1-yl)methyl)benzoate



To a stirring suspension of potassium carbonate (2.19 g, 15.9 mmol) in acetonitrile (30 mL), *tert*-butyl (pyrrolidin-2-ylmethyl)carbamate (1.06 g, 5.29 mmol) was added followed by methyl 2-(bromomethyl) benzoate (873 mg, 5.84 mmol). The reaction mixture was refluxed (85 °C) for 72 hours under argon before filtering through Celite and washing with DCM. The solution was then dried over magnesium sulfate, filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 100% ethyl acetate → 9:1 ethyl acetate : methanol) afforded the title compound, which was obtained as an orange oil (1.38 g, 75%); R_f = 0.44 (9:1 ethyl acetate : methanol); ν_{max}/cm^{-1} (thin film): 3396, 2971, 2797, 1710, 1513, 1450, 1435, 1365, 1268, 1249, 1167, 1084, 744; δ_H (400 MHz, $CDCl_3$) 7.72 (1H, d, *J* = 8.0 Hz, COCC**H**), 7.45 – 7.35 (2H, m, 2 x Ar**H**), 7.29 (1H, t, *J* = 8.0 Hz, COCCHC**H**), 5.37 – 5.28 (1H, m, N**H**), 4.47 (1H, d, *J* = 13.0 Hz, COCCC**H₂**N), 3.91 (3H, s, OC**H₃**), 3.40 – 3.32 (1H, m, C**H₂**NHCO [overlapping]), 3.32 (1H, d, *J* = 12.5 Hz, COCCC**H₂**N [overlapping]), 3.09 (1H, td, *J* = 14.0, 3.5 Hz, C**H₂**NHCO), 2.73 (1H, t, *J* = 8.0 Hz, C**H₂**NCH), 2.59 – 2.51 (1H, m, C**H**CH_2NHCO), 2.12 – 2.03 (1H, m, C**H₂**NCH), 1.89 – 1.78 (1H, m, C**H₂**$CHCH_2$NHCO), 1.68 – 1.53 (3H, m, C**H₂**$CHCH_2$NHCO,C**H₂**CH_2NCH), 1.43 (9H, s, OC(C**H₃**)₃); δ_C (101 MHz, $CDCl_3$) 169.2 (**C**O_2CH_3), 156.8 (NH**C**O), 140.8 (Ar**C**), 131.4 (Ar**C**H), 130.9 (Ar**C**), 130.4 (Ar**C**H), 129.9 (COC**C**H), 127.1 (COCCH**C**H), 78.7 (**C**$(CH_3)_3$), 64.1 (**C**HCH_2NHCO), 57.1 (COCC**C**H_2N), 54.8 (**C**H_2NCH), 52.2 (O**C**H_3), 41.0 (**C**H_2NHCO), 28.6 (C(**C**H_3)₃), 27.5 (**C**H_2CHCH_2NHCO), 22.8 (**C**H_2CH_2NCH); HRMS (ESI^+): calcd. for $C_{19}H_{29}N_2O_4$, 349.2122. Found $[MH]^+$ 349.2126 (−1.2 ppm error).

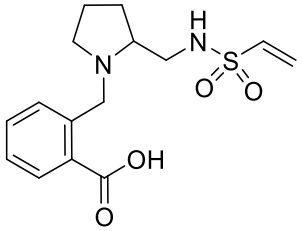
3.149: Methyl 2-((2-(vinylsulfonamidomethyl)pyrrolidin-1-yl)methyl)benzoate



Methyl 2-((2-(((*tert*-butoxycarbonyl)amino)methyl)pyrrolidin-1-yl)methyl)benzoate (1.28 g, 3.68 mmol) was dissolved in 1,4-dioxane (20 mL) and 4 M HCl in 1,4-dioxane (7.75 mL, 223

mmol) was added. The solution was stirred at RT for 72 hours. Then, the solution was concentrated *in vacuo*. This salt was dissolved in anhydrous DCM (20 mL) at RT and the solution was cooled to 0 °C using an ice bath. Triethylamine (5.00 mL, 35.9 mmol) was added dropwise, followed by 2-chloroethane-1-sulfonyl chloride (0.54 mL, 5.53 mmol). The solution was allowed to gradually warm to RT while being stirred for 72 hours. The solution was diluted with DCM (50 mL) and washed with brine (2 x 50 mL). The aqueous layer was then washed with DCM (2 x 50 mL). The organic layers were then combined, dried over magnesium sulfate, filtered and concentrated *in vacuo*. This was purified by column chromatography (SiO_2, 1:1 ethyl acetate : hexane) to yield the title compound, which was obtained as a yellow oil (566 mg, 45%); R_f = 0.27 (1:1 ethyl acetate : hexane); ν_{max}/cm^{-1} (thin film): 3283, 2954, 2876, 2804, 1713, 1434, 1330, 1295, 1272, 1150, 1085, 967, 743, 665, 544; δ_H (400 MHz, $CDCl_3$) 7.75 (1H, dd, *J* = 7.5, 1,5 Hz, COCC**H**), 7.42 (1H, td, *J* = 7.5, 1.5 Hz, COCCHC**H**), 7.32 (2H, td, *J* = 7.5, 1.5 Hz, 2 x Ar**H**), 6.58 (1H, dd, *J* = 16.5, 10.0 Hz, H_2C=C**H**S), 6.19 (1H, d, *J* = 16.5 Hz, **H₂**C=CHS), 5.88 (1H, d, *J* = 10.0 Hz, **H₂**C=CHS), 5.34 (1H, br s, N**H**), 4.44 (1H, d, *J* = 12.5 Hz, COCCC**H₂**N), 3.92 (3H, s, OC**H₃**), 3.28 (1H, d, *J* = 12.5 Hz, COCCC**H₂**N), 3.07 – 2.91 (2H, m, C**H₂**NHS), 2.74 – 2.66 (1H, m, C**H₂**NCH), 2.62 (1H, t, *J* = 8.0 Hz, C**H**CH_2NHS), 2.11 (1H, q, *J* = 9.5 Hz, C**H₂**NCH), 1.95 – 1.83 (2H, m, C**H₂**$CHCH_2$NHS), 1.68 – 1.55 (2H, m, C**H₂**CH_2NCH); δ_C (101 MHz, $CDCl_3$) 169.5 (**C**O_2CH_3), 140.4 (CO**C**CCH_2N), 135.9 (H_2C=**C**HS), 131.7 (COCCH**C**H), 130.8 (Ar**C**H), 130.5 (COC**C**CH_2N), 130.2 (COC**C**H), 127.5 (Ar**C**H), 126.3 (H_2**C**=CHS), 63.2 (**C**HCH_2NHS), 57.3 (COCC**C**H_2N), 55.0 (**C**H_2NCH), 52.6 (O**C**H_3), 43.3 (**C**H_2NHS), 27.7 (**C**H_2CHCH_2NHS), 22.8 (**C**H_2CH_2NCH); HRMS (ESI^+): calcd. for $C_{16}H_{23}N_2O_4S$, 339.1373. Found $[MH]^+$ 339.1369 (1.3 ppm error).

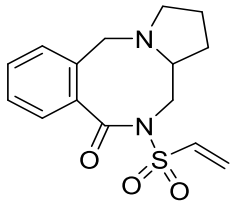
3.150: 2-((2-(Vinylsulfonamidomethyl)pyrrolidin-1-yl)methyl)benzoic acid



Methyl 2-((2-(vinylsulfonamidomethyl)pyrrolidin-1-yl)methyl)benzoate (508 mg, 1.50 mmol) was dissolved in THF (5.0 mL) and water (15.0 mL), then lithium hydroxide monohydrate (364 mg, 15.2 mmol) was added and the solution stirred at RT for 24 hours. The solution was concentrated *in vacuo*. This was purified by column chromatography (SiO_2, 9:1 ethyl acetate : methanol → 7:3 ethyl acetate : methanol → 1:1 ethyl acetate : methanol) to yield the title compound, which was obtained as a waxy, white solid (413 mg, 85%); R_f = 0.29 (1:1 ethyl

acetate : methanol); MP = 101 – 110 °C; ν_{max}/cm^{-1} (thin film): 3069, 1610, 1593, 1566, 1450, 1382, 1328, 1148, 971, 757, 730, 664; δ_H (400 MHz, $CDCl_3$) 8.06 (1H, d, *J* = 7.5 Hz, COCC**H**), 7.43 (1H, t, *J* = 7.5 Hz, COCCHC**H**), 7.37 (1H, t, *J* = 7.5 Hz, COCCHCHC**H**), 7.18 (1H, d, *J* = 7.5 Hz, COCCC**H**), 6.56 (1H, dd, *J* = 16.5, 10.0 Hz, H_2C=C**H**S), 6.15 (1H, d, *J* = 16.5 Hz, **H₂**C=CHS), 5.87 (1H, d, *J* = 10.0 Hz, **H₂**C=CHS), 4.69 (1H, d, *J* = 11.5 Hz, COCCC**H₂**N), 3.78 (1H, d, *J* = 11.5 Hz, COCCC**H₂**N), 3.46 (1H, br s, C**H**CH_2NHS), 3.34 (2H, br s, C**H₂**NHS), 3.18 (1H, br s, C**H₂**NCH), 2.76 (1H, q, *J* = 8.5 Hz, C**H₂**NCH), 2.26 – 2.14 (1H, m, C**H₂**$CHCH_2$NHS), 2.12 – 2.01 (1H, m, C**H₂**$CHCH_2$NHS), 2.01 – 1.90 (2H, m, C**H₂**CH_2NCH); δ_C (101 MHz, $CDCl_3$) **C**O peak was not detected, 137.7 (Ar**C**), 135.8 (H_2C=**C**HS), 133.0 (COC**C**H), 131.0 (COCC**C**H [overlapping]), 131.0 (Ar**C** [overlapping]), 130.8 (COCCHCH**C**H), 129.8 (COCCH**C**H), 126.6 (H_2**C**=CHS), 66.3 (**C**HCH_2NHS), 59.6 (COCC**C**H_2N), 52.6 (**C**H_2NCH), 43.5 (**C**H_2NHS), 27.9 (**C**H_2CHCH_2NHS), 22.7 (**C**H_2CH_2NCH); HRMS (ESI^+): calcd. for $C_{15}H_{21}N_2O_4S$, 325.1217. Found $[MH]^+$ 325.1217 (−0.3 ppm error).

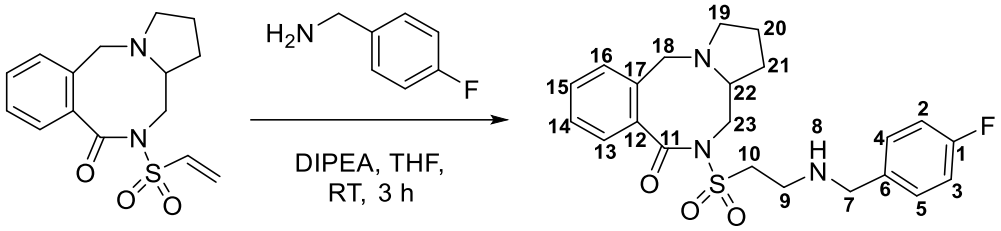
3.151: 5-(Vinylsulfonyl)-1,2,3,3a,4,5-hexahydrobenzo[*f*]pyrrolo[1,2-*a*][1,4]diazocin-6(11*H*)-one



To a round-bottomed flask 2-((2-(vinylsulfonamidomethyl)pyrrolidin-1-yl)methyl)benzoic acid (80.3 mg, 0.247 mmol) was dissolved in chloroform (10.0 mL) and DIPEA (0.08 mL, 0.458 mmol) was added dropwise. T3P (50% solution in ethyl acetate, 0.24 mL, 0.379 mmol) was added dropwise and the solution stirred at RT for 3 hours. After that, the reaction mixture was diluted with DCM (10 mL) and washed with $NaHCO_3$ (2 x 10 mL). The organic layer was dried, filtered and concentrated *in vacuo* to yield the title compound, which was obtained as a white oil (72.1 mg, 95%); R_f = 0.66/0.28 (1:1 ethyl acetate : methanol); ν_{max}/cm^{-1} (thin film): 2961, 2812, 1676, 1345, 1303, 972, 910, 772, 727, 662; δ_H (400 MHz, $CDCl_3$) 7.36 (1H, td, *J* = 7.0, 2.0 Hz, C**H**$CHCH_2$N), 7.32 – 7.24 (2H, m, 2 x Ar**H**), 7.21 – 7.12 (1H, m, C**H**CCH_2N [overlapping]), 7.17 (1H, dd, *J* = 17.0, 10.0 Hz, H_2C=C**H**S [overlapping]), 6.47 (1H, d, *J* = 17.0 Hz, **H₂**C=CHS), 6.13 (1H, d, *J* = 10.0 Hz, **H₂**C=CHS), 4.16 (1H, d, *J* = 16.0 Hz, COCCC**H₂**N), 3.80 (1H, dd, *J* = 15.5, 3.5 Hz, C**H₂**NHS), 3.78 (1H, d, *J* = 16.0 Hz, COCCC**H₂**N), 3.40 (1H, dd, *J* = 15.5, 3.5 Hz, C**H₂**NHS), 3.13 – 3.04 (1H, m, C**H₂**NCH), 2.81 – 2.73 (1H, m, C**H**CH_2NHS), 2.69 (1H, q, *J* = 8.0 Hz, C**H₂**NCH), 2.12 – 2.01 (1H, m, C**H₂**$CHCH_2$NHS), 1.88 – 1.59

(2H, m, C**H**$_2$CH$_2$NCH [overlapping]), 1.88 – 1.59 (1H, m,C**H**$_2$CHCH$_2$NHS [overlapping]); δ_C (101 MHz, $CDCl_3$) 172.5 (**C**O), 137.6 (Ar**C**), 136.7 (H_2C=**C**HS), 133.8 (Ar**C**), 130.4 (**C**HCHCCH$_2$N), 128.9 (H_2**C**=CHS), 128.6 (Ar**C**H), 127.6 (**C**HCCH$_2$N), 127.5 (Ar**C**H), 64.2 (**C**HCH$_2$NHS), 56.4 (COCC**C**H$_2$N), 55.1 (**C**H$_2$NCH), 49.2 (**C**H$_2$NHS), 30.3 (**C**H$_2$CHCH$_2$NHS), 22.8 (**C**H$_2$CH$_2$NCH); HRMS (ESI^+): calcd. for $C_{15}H_{18}N_2NaO_3S$, 329.0930. Found $[MNa]^+$ 329.0930 (0.2 ppm error).

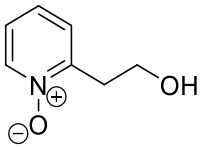
3.153: 5-((2-((4-Fluorobenzyl)amino)ethyl)sulfonyl)-1,2,3,3a,4,5-hexahydrobenzo[*f*]pyrrolo[1,2-*a*][1,4]diazocin-6(11*H*)-one



3.151 **3.153**

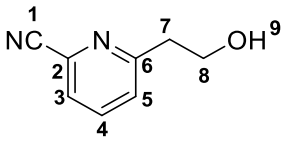
To a round-bottomed flask 5-(vinylsulfonyl)-1,2,3,3a,4,5-hexahydrobenzo[*f*]pyrrolo[1,2-*a*][1,4]diazocin-6(11*H*)-one **3.151** (72.1 mg, 0.235 mmol) and DIPEA (0.12 mL, 0.690 mmol) in THF (2.0 mL), was added 4-fluorobenzylamine (32.5 µL, 0.284 mmol) in a single portion. The reaction mixture was stirred at RT for 3 hours. Then, the solution was diluted in DCM (15 mL) and washed with $NaHCO_3$ (2 x 10 mL). The organic layer was dried, filtered and concentrated *in vacuo* to yield the side-product, which was obtained as a colourless oil (81.2 mg, 80%); R_f = 0.64 (1:1 ethyl acetate : hexane); ν_{max}/cm^{-1} (thin film): 2957, 2814, 1673, 1602, 1509, 1343, 1307, 1219, 1149, 1123, 823, 773, 735, 557; δ_H (400 MHz, $CDCl_3$) 7.43 – 7.36 (1H, m, H-16), 7.31 – 7.22 (4H, m, H-4,5,13,14), 7.18 (1H, d, *J* = 7.5 Hz, H-16), 6.97 (2H, t, *J* = 8.5 Hz, H-2,3), 4.15 (1H, d, *J* = 15.5 Hz, H-18), 4.01 – 3.92 (1H, m, H-10), 3.79 (1H, d, *J* = 15.5 Hz, H-18 [overlapping]), 3.78 (2H, s, H-7 [overlapping]), 3.73 (1H, dd, *J* = 15.5, 3.5 Hz, H-23 [overlapping]), 3.87 – 3.69 (1H, m, H-10' [overlapping]), 3.42 (1H, dd, *J* = 15.5, 3.5 Hz, H-23'), 3.22 – 3.07 (2H, m, H-9 [overlapping]), 3.22 – 3.07 (1H, m, H-19 [overlapping]), 2.82 – 2.74 (1H, m, H-22), 2.69 (1H, q, *J* = 8.0 Hz, H-19'), 2.14 – 2.02 (1H, m, H-21), 1.93 – 1.63 (2H, m, H-20 [overlapping]), 1.93 – 1.63 (1H, m, H-21' [overlapping]); δ_C (100 MHz, $CDCl_3$) 173.1 (C-11), 162.0 (C-1, d, $^1J_{CF}$ = 245.4 Hz), 137.5 (C-12/17), 135.3 (C-6, d, $^4J_{CF}$ = 3.6 Hz), 133.8 (C-12/17), 130.6 (C-15), 129.7 (C-4,5, d, $^3J_{CF}$ = 7.7 Hz), 128.7 (C-13/14), 128.1 (C-16), 127.5 (C-13/14), 115.3 (C-2,3, d, $^2J_{CF}$ = 21.1 Hz), 64.3 (C-22), 56.4 (C-18), 55.1 (C-19), 54.2 (C-10), 52.6 (C-7), 49.1 (C-23), 43.0 (H-9), 30.1 (C-21), 22.8 (C-20); HRMS (ESI^+): calcd. for $C_{22}H_{27}FN_3O_3S$, 432.1752. Found $[MH]^+$ 432.1750 (0.5 ppm error).

3.155: 2-(Hydroxyethyl)pyridine-*N*-oxide



3-Chloroperoxybenzoic acid (1.29 g, 15.0 mmol) was added to a solution of 2-(2-hydroxyethyl)pyridine (1.12 mL, 10.0 mmol) in DCM (40.0 mL) at 0 °C. The resulting reaction mixture was gradually warmed to RT and stirred for 16 hours. The solution was concentrated *in vacuo*. Then, purification by flash column chromatography (SiO_2, 9:1 ethyl acetate : methanol → 7:3 ethyl acetate : methanol) afforded the title compound, which was obtained as a colourless oil (1.39 g, 100%); R_f = 0.22 (1:1 ethyl acetate : methanol); ν_{max}/cm^{-1} (thin film): 3257, 2884, 1659, 1491, 1440, 1213, 1110, 1050, 838, 769; δ_H (400 MHz, $CDCl_3$) 8.24 (1H, dd, *J* = 6.5 Hz, C**H**NO), 7.34 – 7.25 (2H, m, C**H**CHCHNO,C**H**CHCHCHNO), 7.19 (1H, td, *J* = 7.0, 2.5 Hz, C**H**CHNO), 5.14 (1H, br s, O**H**), 3.98 (2H, t, *J* = 6.0 Hz, C**H₂**OH), 3.22 (2H, t, *J* = 6.0 Hz, C**H₂**CH_2OH); δ_C (100 MHz, $CDCl_3$) 151.3 (**C**NO), 139.7 (**C**HNO), 127.5 (**C**HCHCHNO), 127.2 (**C**HCHCHCHNO), 124.3 (**C**HCHNO), 61.9 (**C**H_2OH), 34.8 (**C**H_2CH_2OH); HRMS (ESI^+): calcd. for $C_7H_9NNaO_2$, 162.0525. Found $[MNa]^+$ 162.0527 (−1.1 ppm error). Characterisation data matched those reported in the literature.[182]

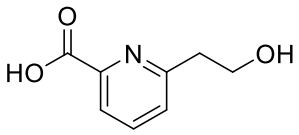
3.156: 6-(2-Hydroxyethyl)pyridine-2-carbonitrile



To a solution of 2-(hydroxyethyl)pyridine-*N*-oxide (221 mg, 1.74 mmol) in DCM (20.0 mL), *N,N*-dimethylcarbamoyl chloride (0.16 mL, 1.74 mmol) was added dropwise. After 2.5 hours, trimethylsilyl cyanide (0.26 mL, 2.09 mmol) was also added. The mixture was stirred at RT for 20 hours, followed by 8 hours at reflux (45 °C) and then cooled back to RT. A further portion of *N,N*-dimethylcarbamoyl chloride (0.16 mL, 1.74 mmol) and trimethylsilyl cyanide (0.22 mL, 1.74 mmol) were added and stirring continued at reflux (45 °C) for a further 72 hours. Then, the reaction was quenched by addition of a sat. aq. Na_2CO_3 (20 mL). The aqueous layer was extracted with DCM (2 x 15 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 100% ethyl acetate → 9:1 ethyl acetate : methanol) afforded the title compound, which was obtained as a pale yellow solid (173 mg, 67%); R_f = 0.46 (9:1 ethyl

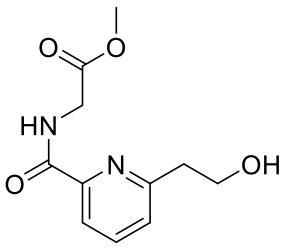
acetate : methanol); MP = 60 – 64 °C; ν_{max}/cm^{-1} (thin film): 3369, 2928, 2884, 2238, 1589, 1452, 1046, 990, 802, 740; δ_H (400 MHz, $CDCl_3$) 7.74 (1H, t, *J* = 8.0 Hz, H-4), 7.53 (1H, d, *J* = 8.0 Hz, H-3), 7.42 (1H, d, *J* = 8.0 Hz, H-5), 3.95 (2H, t, *J* = 6.0 Hz, H-8), 3.49 (1H, br s, H-9), 3.02 (2H, t, *J* = 6.0 Hz, H-7); δ_C (100 MHz, $CDCl_3$) 162.2 (C-6), 137.5 (C-4), 132.8 (C-2), 127.5 (C-5), 126.4 (C-3), 117.2 (C-1), 61.0 (C-8), 39.9 (C-7); HRMS (ESI^+): calcd. for $C_8H_8N_2NaO$, 171.0529. Found $[MNa]^+$ 171.0532 (−2.0 ppm error). Characterisation data matched those reported in the literature.[183]

3.157: 6-(2-Hydroxyethyl)pyridine-2-carboxylic acid



To a solution of 6-(2-hydroxyethyl)pyridine-2-carbonitrile (139 mg, 0.940 mmol) was added conc. HCl (1.41 mL, 12 M). After 18 hours of stirring at 110 °C, the solution was allowed to cool to RT, before being concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 ethyl acetate : methanol) afforded the title compound, which was obtained as a white solid (427 mg, 100%); R_f = 0.15 (1:1 ethyl acetate : methanol); MP = 156 – 162 °C; ν_{max}/cm^{-1} (thin film): 3369, 2506, 1651, 1611, 1385, 1294, 1048, 776; δ_H (400 MHz, MeOD-*d*$_4$) 8.53 (1H, t, *J* = 7.5 Hz, C**H**CHCN), 8.32 (1H, d, *J* = 7.5 Hz, ArC**H**), 8.09 (1H, d, *J* = 7.5 Hz, ArC**H**), 3.87 (2H, t, *J* = 5.5 Hz, C$\mathbf{H_2}$OH), 3.26 (2H, t, *J* = 5.5 Hz, C$\mathbf{H_2}$$CH_2OH$); δ_C (100 MHz, MeOD-*d*$_4$) 161.6 (**C**O), 159.7 (Ar**C**), 148.1 (**C**HCHCN), 142.4 (Ar**C**), 132.5 (**C**HCCOOH), 126.7 (**C**$HCCH_2CH_2OH$), 61.1 (**C**H_2OH), 37.1 (**C**H_2CH_2OH); HRMS (ESI^+): calcd. for $C_8H_{10}NO_3$, 168.0655. Found $[MH]^+$ 168.0656 (−0.2 ppm error). Characterisation data matched those reported in the literature.[184]

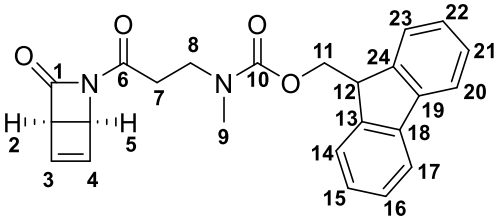
3.159: Methyl (6-(2-hydroxyethyl)picolinoyl)glycinate



6-(2-Hydroxyethyl)pyridine-2-carboxylic acid (98.8 mg, 0.591 mmol) was dissolved in DCM (7.0 mL) and cooled to 0 °C, before triethylamine (0.16 mL, 1.15 mmol) was added. Ethyl

chloroformate (0.08 mL, 0.887 mmol) in DCM (0.5 mL) was then added dropwise and the solution was stirred for a further 30 minutes at 0 °C. Upon complete addition, glycine methyl ester hydrochloride (90.4 mg, 0.720 mmol) was added and the solution was stirred at 0 °C for 1 hour. The reaction mixture was then concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 7:3 ethyl acetate : hexane) yielded the title compound, which was obtained as a colourless oil (45.9 mg, 33%); R_f = 0.33 (9:1 ethyl acetate : methanol); ν_{max}/cm^{-1} (thin film): 3374, 2955, 1744, 1662, 1593, 1528, 1454, 1373, 1212, 1178, 1049, 763; δ_H (400 MHz, $CDCl_3$) 8.40 (1H, t, *J* = 6.0 Hz, N**H**), 8.03 (1H, d, *J* = 7.5 Hz, C**H**CCONH), 7.78 (1H, t, *J* = 7.5 Hz, C**H**CHCCONH), 7.36 (1H, d, *J* = 7.5 Hz, C**H**CCH_2CH_2OH), 4.25 (2H, d, *J* = 5.5 Hz, C**H₂**NHCO), 4.07 (2H, t, *J* = 6.0 Hz, C**H₂**OH), 3.79 (3H, s, CO_2C**H₃**), 3.08 (2H, t, *J* = 6.0 Hz, C**H₂**CH_2OH); δ_C (100 MHz, $CDCl_3$) 170.4 (**C**O_2CH_3), 164.7 (**C**ONH), 158.6 (**C**CH_2CH_2OH), 148.9 (**C**CONH), 138.0 (**C**HCHCCONH), 126.8 (**C**HCCH_2CH_2OH), 120.5 (**C**HCCONH), 61.8 (**C**H_2OH), 52.6 (CO_2**C**H_3), 41.4 (**C**H_2NHCO), 40.3 (**C**H_2CH_2OH); HRMS (ESI^+): calcd. for $C_{11}H_{14}N_2NaO_4$, 261.0846. Found $[MNa]^+$ 261.0844 (0.8 ppm error).

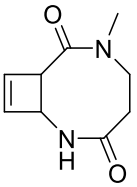
4.17: (9*H*-Fluoren-9-yl)methyl methyl(3-oxo-3-(3-oxo-2-azabicyclo[2.2.0]hex-5-en-2-yl)propyl)carbamate



A mixture of 2-azabicyclo[2.2.0]hex-5-en-3-one (49.2 mg, 0.517 mmol), DMAP (14.0 mg, 0.115 mmol) and pyridine (0.25 mL, 3.10 mmol) in DCM (5.0 mL), under an argon atmosphere, was stirred at RT for 30 minutes. Next, a solution of 9*H*-fluoren-9-yl)methyl (3-chloro-3-oxopropyl)(methyl)carbamate (0.27 mL, 0.786 mmol) in DCM (2.0 mL) was added and the resulting mixture was refluxed (50 °C) for 19 hours. After cooling, the mixture was then diluted with DCM (15 mL) and washed with 10% aq. HCl (20 mL). The aqueous layer was then extracted with DCM (3 × 15 mL) and the combined organic extracts dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 9:1 hexane : ethyl acetate → 7:3 hexane : ethyl acetate → 9:1 ethyl acetate : methanol) afforded the title compound, which was obtained as a yellow oil (91.0 mg, 44%); R_f = 0.40 (1:1 ethyl acetate : methanol); ν_{max}/cm^{-1} (thin film): 2944, 1781, 1693, 1480, 1450, 1401, 1344, 1282, 1239, 1203, 1137, 1111, 1048, 909, 759, 727; δ_H (400 MHz, $CDCl_3$) 7.76 (2H, t, *J* = 7.5 Hz, H-17,20), 7.59 (2H, d, *J* = 7.5 Hz, H-14,23), 7.40 (2H, t, *J* = 7.5 Hz, H-16,21), 7.32 (2H, t, *J* = 7.5 Hz, H-15,22), 6.69 – 6.50 (2H, m, H-3,4), 4.73 (1H, t, *J* = 2.5 Hz, H-2/5),

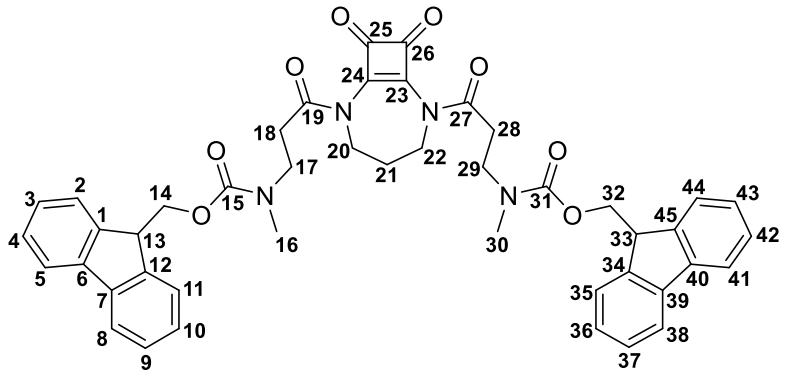
4.44 (1H, d, *J* = 7.0 Hz, H-11), 4.38 (1H, d, *J* = 7.0 Hz, H-11'), 4.24 (1H, t, *J* = 7.0 Hz, H-12), 4.18 (1H, d, *J* = 6.0 Hz, H-2/5), 3.70 – 3.60 (1H, m, H-8), 3.50 (1H, t, *J* = 7.0 Hz, H-8'), 3.01 – 2.88 (3H, m, H-9 [overlapping]), 3.01 – 2.88 (1H, m, H-7 [overlapping]), 2.77 (1H, t, *J* = 7.5 Hz, H-7'); δ_C (100 MHz, $CDCl_3$) 171.2 (C-1), 170.0 (C-6), 156.1 (C-10), 144.1 (C-13,24), 142.2 (C-3/4), 141.3 (C-18,19), 140.4 (C-3/4), 127.7 (C-16,21), 127.1 (C-15,22), 125.1 (C-14,23), 120.0 (C-17,20), 67.5 (C-11), 56.7 (C-2/5), 51.9 (C-2/5), 47.3 (C-12), 44.1 (C-8), 35.2 (C-9), 34.4 (C-7); HRMS (ESI^+): calcd. for $C_{24}H_{22}N_2NaO_4$, 425.1472. Found: $[MNa]^+$, 425.1459 (3.0 ppm error).

4.18: 6-Methyl-2,6-diazabicyclo[6.2.0]dec-9-ene-3,7-dione



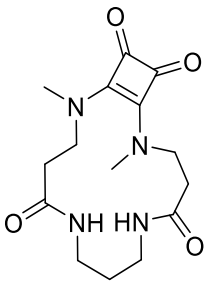
A mixture of 2-azabicyclo[2.2.0]hex-5-en-3-one (60.6 mg, 0.637 mmol), DMAP (15.8 mg, 0.129 mmol) and pyridine (0.31 mL, 3.82 mmol) in DCM (10.0 mL), under an argon atmosphere, was stirred at RT for 30 minutes. Then, a solution of 9*H*-fluoren-9-yl)methyl (3-chloro-3-oxopropyl)(methyl)carbamate **4.17** (657 mg, 1.91 mmol) in DCM (6.5 mL) was added and the resulting mixture was refluxed (50 °C) for 19 hours. After cooling, the mixture was then diluted with DCM (10 mL) and washed with 10% aq. HCl (20 mL). The aqueous layer was then extracted with DCM (3 x 10 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The intermediate product was then dissolved in DCM (15.0 mL) and DBU (0.95 mL, 6.37 mmol) was added. The reaction mixture was stirred at RT for 17 hours before removing the solvent by concentrating *in vacuo*. This was purified by flash column chromatography (SiO_2, 8:2 hexane : ethyl acetate → 9:1 ethyl acetate : methanol) affording the title compound, which was obtained as a yellow oil (54.3 mg, 47%); R_f = 0.38 (1:1 ethyl acetate : methanol); ν_{max}/cm^{-1} (thin film): 3251, 2926, 1628, 1488, 1406, 1284, 1082, 805, 733, 507; δ_H (400 MHz, $CDCl_3$) 6.54 (1H, br s, N**H**), 6.49 – 6.46 (1H, m, COCHCH=C**H**), 6.15 (1H, br d, *J* = 3.5 Hz, COCHC**H**=CH), 4.69 (1H, t, *J* = 3.5 Hz, NHC**H**), 4.16 (1H, d, *J* = 3.5 Hz, COC**H**), 4.10 – 4.00 (1H, m, $CH_3NC\mathbf{H_2}$), 3.22 (1H, ddd, *J* = 15.5, 8.5, 2.5 Hz, $CH_3NC\mathbf{H_2}$), 2.95 (3H, s, $C\mathbf{H_3}N$), 2.93 – 2.83 (2H, m, $CH_3NCH_2C\mathbf{H_2}$); δ_C (100 MHz, $CDCl_3$) 171.6 (**C**ONH), 169.9 (**C**ONCH_3), 140.2 (COCHCH=**C**H), 135.3 (COCH**C**H=CH), 55.5 (NH**C**H), 53.8 (CO**C**H), 42.5 ($CH_3N\mathbf{C}H_2$), 34.8 ($CH_3NCH_2\mathbf{C}H_2$), 33.2 ($\mathbf{C}H_3N$); HRMS (ESI^+): calcd. for $C_9H_{12}N_2NaO_2$, 203.0791. Found: $[MNa]^+$, 203.0787 (2.1 ppm error).

4.31: Bis((9*H*-fluoren-9-yl)methyl) ((8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-ene-2,6-diyl)bis(3-oxopropane-3,1-diyl))bis(methylcarbamate)



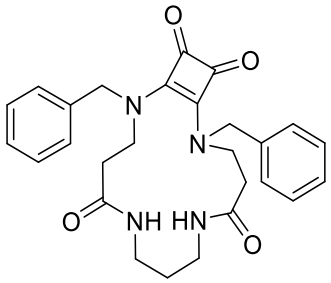
A mixture of 2,6-diazabicyclo[5.2.0]non-1(7)-ene-8,9-dione (154 mg, 1.01 mmol), DMAP (12.6 mg, 0.103 mmol) and pyridine (0.49 mL, 6.08 mmol) in DCM (20.0 mL), under an argon atmosphere, was stirred at reflux (50 °C) for 30 minutes. Next, a solution of 9*H*-fluoren-9-yl)methyl (3-chloro-3-oxopropyl)(methyl)carbamate (2.50 g, 6.08 mmol) in DCM (10.0 mL) was added and the resulting mixture was refluxed (50 °C) for 17 hours. After cooling, the mixture was then diluted with DCM (15 mL) and washed with 10% aq. HCl (20 mL). The aqueous layer was then extracted with DCM (3 × 15 mL) and the combined organic extracts dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 ethyl acetate : hexane → 7:3 ethyl acetate : hexane) afforded the title compound, which was obtained as a white solid (737 mg, 95%); R_f = 0.10 (1:1 ethyl acetate : hexane); MP = 77 – 86 °C; ν_{max}/cm^{-1} (thin film): 2952, 1793, 1747, 1693, 1564, 1450, 1403, 1208, 1170, 1033, 760, 737; δ_H (400 MHz, $CDCl_3$) 7.81 – 7.69 (4H, m, H-5,8,38,41), 7.56 (4H, d, *J* = 7.5 Hz, H-2,11,35,44), 7.44 – 7.34 (4H, m, H-4,9,37,42), 7.34 – 7.27 (4H, m, H-3,10,36,43), 4.48 (1H, d, *J* = 6.0 Hz, H-14/32), 4.32 (3H, d, *J* = 7.0 Hz, H-14'/32'), 4.27 – 4.18 (2H, t, *J* = 7.0 Hz, H-13,33), 4.06 – 3.89 (4H, m, H-20/22), 3.62 (4H, t, *J* = 7.0 Hz, H-17,29), 3.24 – 3.14 (4H, m, H-18,28), 3.05 – 2.83 (6H, s, H-16,30), 2.04 – 1.92 (2H, m, H-21); δ_C (100 MHz, $CDCl_3$) [Missing C-23,24,25,26], 170.4 (C-19,27), 156.5 (C-15,31), 144.0 (C-1,12,34,45), 141.4 (C-6,7,39,40), 127.9 (C-4,9,37,42), 127.2 (C-3,10,36,43), 125.1 (C-2,11,35,44), 120.1 (C-5,8,38,41), 67.7 (C-14/32), 67.3 (C-14/32), 47.3 (C-13,33), 45.8 (C-17,29), 45.3 (C-20,22), 34.7 (C-16,30), 34.4 (C-18,28), 24.2 (C-21); HRMS (ESI^+): calcd. for $C_{45}H_{42}N_4NaO_8$, 789.2895. Found: $[MNa]^+$, 789.2922 (−3.4 ppm error).

4.35: 2,14-Dimethyl-2,6,10,14-tetraazabicyclo[13.2.0]heptadec-1(15)-ene-5,11,16,17-tetraone



Bis((9H-fluoren-9-yl)methyl) ((8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-ene-2,6-diyl)bis(3-oxopropane-3,1-diyl))bis(methylcarbamate) **4.31** (376 mg, 0.490 mmol) was dissolved in DCM (15.0 mL) and DBU (0.73 mL, 4.90 mmol) was added. The reaction mixture was stirred at RT for 18 h before removing the solvent by concentrating *in vacuo*. Purification by flash column chromatography (SiO_2, 9:1 ethyl acetate : methanol → 1:1 ethyl acetate : methanol) afforded the title compound, which was obtained as a yellow oil (114 mg, 72%); R_f = 0.20 (1:1 ethyl acetate : methanol); ν_{max}/cm^{-1} (thin film): 3394, 2943, 2506, 1794, 1746, 1692, 1564, 1449, 1403, 1208, 1171, 1143, 977, 760, 740; δ_H (400 MHz, $(CD_3)_2SO$) 8.16 (2H, t, *J* = 5.5 Hz, 2 x N**H**), 3.78 (4H, t, *J* = 6.5 Hz, 2 x $CH_3NC\mathbf{H_2}$), 3.12 (6H, s, 2 x $C\mathbf{H_3}N$ [overlapping]), 3.14 – 3.07 (4H, m, 2 x $NHC\mathbf{H_2}$ [overlapping]), 2.37 (4H, t, *J* = 6.5 Hz, 2 x $COC\mathbf{H_2}$), 1.57 – 1.48 (2H, m, $NHCH_2C\mathbf{H_2}$); δ_C (100 MHz, $(CD_3)_2SO$) 183.8 (2 x C=C**C**O), 170.0 (2 x **C**ONH), 169.2 (2 x **C**=C), 49.6 (2 x $CH_3N\mathbf{C}H_2$), 39.7 (2 x $\mathbf{C}H_3N$), 37.5 (2 x $NH\mathbf{C}H_2$), 34.8 (2 x $CO\mathbf{C}H_2$), 27.9 ($NHCH_2\mathbf{C}H_2$); HRMS (ESI^+): calcd. for $C_{15}H_{22}N_4NaO_4$, 345.1533. Found: $[MNa]^+$, 345.1537 (−1.1 ppm error).

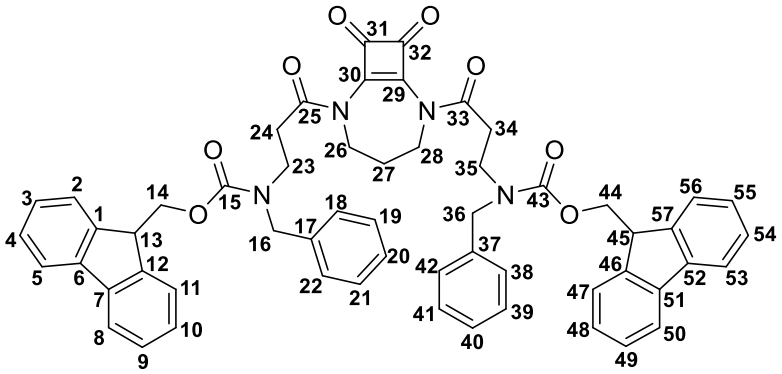
4.36: 2,14-Dibenzyl-2,6,10,14-tetraazabicyclo[13.2.0]heptadec-1(15)-ene-5,11,16,17-tetraone



A mixture of 2,6-diazabicyclo[5.2.0]non-1(7)-ene-8,9-dione (75.1 mg, 0.494 mmol), DMAP (12.7 mg, 0.104 mmol) and pyridine (0.24 mL, 2.96 mmol) in DCM (10.0 mL), under an argon atmosphere, was stirred at RT for 30 minutes. Then, a solution of (9*H*-fluoren-9-yl)methyl benzyl(3-chloro-3-oxopropyl)carbamate **4.37** (1.24 mL, 2.96 mmol) in DCM (3.0 mL) was added and the resulting mixture was refluxed (50 °C) for 16 hours. After cooling, the mixture

was then diluted with DCM (15 mL) and washed with 10% aq. HCl (20 mL). The aqueous layer was then extracted with DCM (3 × 15 mL) and the combined organic extracts dried over $MgSO_4$, filtered and concentrated *in vacuo*. The intermediate product was then dissolved in DCM (20.0 mL) and DBU (0.37 mL, 2.48 mmol) was added. The reaction mixture was stirred at RT for 17 hours before removing the solvent by concentrating *in vacuo*. This was purified by flash column chromatography (SiO_2, 100% ethyl acetate → 9:1 ethyl acetate : methanol) affording the title compound, which was obtained as a colourless oil (140 mg, 60%); R_f = 0.58 (1:1 ethyl acetate : methanol); ν_{max}/cm^{-1} (thin film): 3301, 2932, 2245, 1779, 1662, 1563, 1495, 1482, 1363, 1244, 908, 725, 698, 645; δ_H (400 MHz, ($CDCl_3$) 7.55 (2H, t, *J* = 5.5 Hz, 2 x N**H**), 7.37 – 7.28 (6H, m, 6 x Ar**H**), 7.22 – 7.15 (4H, m, 4 x Ar**H**), 4.75 (4H, s, 2 x PhC**H₂**), 3.76 (4H, t, *J* = 6.5 Hz, 2 x NC**H₂**), 3.38 (4H, q, *J* = 5.5 Hz, 2 x CONHC**H₂**), 2.55 (4H, t, *J* = 6.5 Hz, 2 x NCH_2C**H₂**), 1.78 (2H, p, *J* = 5.5 Hz, $CONHCH_2C$**H₂**); δ_C (100 MHz, $CDCl_3$) 185.1 (2 x C=C**C**O), 170.6 (2 x **C**ONH), 170.5 (2 x **C**=C), 135.6 (2 x Ar**C**), 129.2 (4 x Ar**C**H), 128.4 (2 x Ar**C**H), 128.0 (4 x Ar**C**H), 55.2 (2 x Ph**C**H_2), 47.0 (2 x N**C**H_2), 38.7 (2 x CONH**C**H_2), 35.7 (2 x NCH_2**C**H_2), 28.4 ($CONHCH_2$**C**H_2); HRMS (APCI⁺): calcd. for $C_{27}H_{31}N_4O_4$, 475.2340. Found: $[MH]^+$, 475.2346 (−1.3 ppm error).

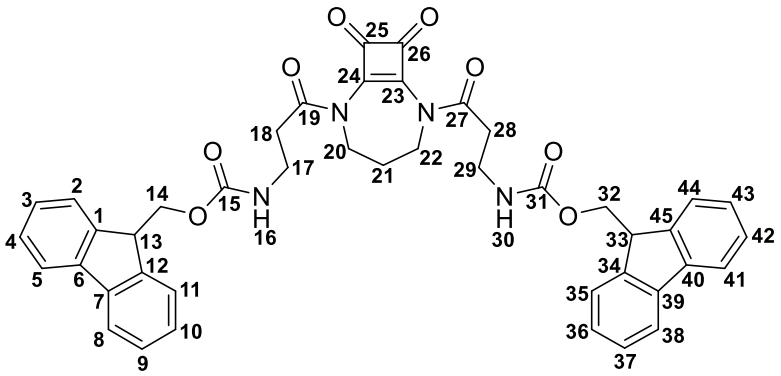
4.37: Bis((9*H*-fluoren-9-yl)methyl) ((8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-ene-2,6-diyl)bis(3-oxopropane-3,1-diyl))bis(benzylcarbamate)



A mixture of 2,6-diazabicyclo[5.2.0]non-1(7)-ene-8,9-dione (75.7 mg, 0.498 mmol), DMAP (12.0 mg, 0.099 mmol) and pyridine (0.24 mL, 2.99 mmol) in DCM (10.0 mL), under an argon atmosphere, was stirred at RT for 30 minutes. Next, a solution of (9*H*-fluoren-9-yl)methyl benzyl(3-chloro-3-oxopropyl)carbamate (1.24 g, 2.99 mmol) in DCM (5.0 mL) was added and the resulting mixture was refluxed (50 °C) for 19 hours. After cooling, the mixture was then diluted with DCM (15 mL) and washed with 10% aq. HCl (20 mL). The aqueous layer was then extracted with DCM (3 x 15 mL) and the combined organic extracts dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 7:3 hexane : ethyl acetate → 1:1 ethyl acetate : hexane → 100% ethyl acetate) afforded the title

compound, which was obtained as a colourless oil (439 mg, 96%), as a mixture of rotamers in the ratio of 3:1; R_f = 0.24 (1:1 ethyl acetate : hexane); ν_{max}/cm^{-1} (thin film): 2955, 1795, 1748, 1693, 1567, 1477, 1451, 1419, 1236, 1166, 1119, 905, 723, 648; δ_H (400 MHz, $CDCl_3$) Full data for major rotamer: 7.79 – 7.71 (4H, m, H-5,8,50,53), 7.45 (4H, d, *J* = 7.5 Hz, H-2,11,47,56), 7.44 – 7.34 (4H, t, *J* = 7.5 Hz, H-4,9,49,54 [overlapping]), 7.35 – 7.15 (10H, m, 10 x Ar**H** [overlapping]), 7.12 (4H, d, *J* = 7.0 Hz, H-18,22,38,42), 4.58 – 4.45 (4H, m, H-14,44 [overlapping]), 4.58 – 4.45 (4H, m, H-16,36 [overlapping]), 4.21 (2H, t, *J* = 6.5 Hz, H-13,45), 4.01 – 3.79 (4H, m, H-26,28), 3.61 (4H, t, *J* = 7.0 Hz, H-23,35), 3.15 (4H, t, *J* = 7.0 Hz, H-24,34), 2.00 – 1.90 (2H, m, H-27). Diagnostic data for minor rotamer: 7.62 (4H, d, *J* = 7.5 Hz, H-2,11,47,56), 7.06 (4H, d, *J* = 7.0 Hz, H-18,22,38,42), 4.68 – 4.61 (4H, m, H-14,44), 4.55 (4H, s, H-16,26), 4.34 – 4.25 (2H, m, H-13,45), 3.54 (4H, t, *J* = 7.0 Hz, H-23,35), 2.61 (4H, t, *J* = 7.0 Hz, H-24,34); δ_C (100 MHz, $CDCl_3$) Full data for major rotamer: 184.9 (C-31,32), 175.7 (C-29,30), 170.4 (C-25,33), 156.3 (C-15,43), 143.8 (C-1,12,46,57), 141.3 (C-6,7,51,52), 137.2 (C-17,37), 128.8 (C-19,21,39,41), 127.7 (C-4,9,49,54), 127.5 (C-20,40), 127.3 (C-18,22,38,42), 127.1 (C-3,10,48,55), 124.9 (C-2,11,47,56), 120.0 (C-5,8,50,53), 67.7 (C-14,44), 50.8 (C-16,36), 47.2 (C-13,45), 45.2 (C-26,28), 43.5 (C-23,35), 34.4 (C-24,34 [overlapping]), 24.1 (C-27). Diagnostic data for minor rotamer: 175.2 (C-29,30), 170.2 (C-25,33), 156.5 (C-15,43), 143.9 (C-1,12,46,57), 137.5 (C-17,37), 128.7 (C-19,21,39,41), 127.8 (C-4,9,49,54), 67.2 (C-14,44), 51.3 (C-16,36), 47.5 (C-13,45), 45.3 (C-26,28), 43.4 (C-23,35), 32.8 (C-24,34); HRMS (ESI^+): calcd. for $C_{57}H_{51}N_4O_8$, 919.3701. Found: $[MH]^+$, 919.3671 (−3.3 ppm error).

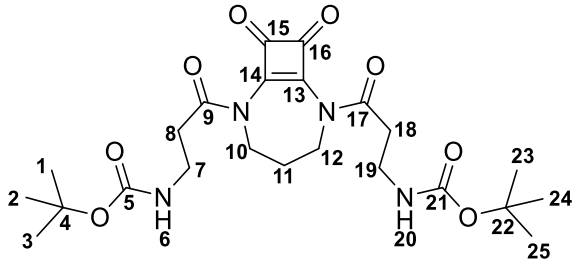
4.40: Bis((9*H*-fluoren-9-yl)methyl) ((8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-ene-2,6-diyl)bis(3-oxopropane-3,1-diyl))dicarbamate



A mixture of 2,6-diazabicyclo[5.2.0]non-1(7)-ene-8,9-dione (100 mg, 0.657 mmol), DMAP (16.3 mg, 0.133 mmol) and pyridine (0.32 mL, 3.96 mmol) in DCM (10.0 mL), under an argon atmosphere, was stirred at RT for 30 minutes. Then, a solution of (9*H*-fluoren-9-yl)methyl (3-chloro-3-oxopropyl)carbamate (1.30 g, 3.94 mmol) in DCM (4.0 mL) was added and the resulting mixture was refluxed (50 °C) for 16 hours. After cooling, the mixture was then

diluted with DCM (15 mL) and washed with 10% aq. HCl (20 mL). The aqueous layer was then extracted with DCM (2 × 15 mL) and the combined organic extracts dried over $MgSO_4$, filtered and concentrated *in vacuo*. This was purified by flash column chromatography (SiO_2, 7:3 hexane : ethyl acetate → 1:1 ethyl acetate : hexane → 7:3 ethyl acetate : hexane → 100% ethyl acetate) affording the title compound, which was obtained as a brown oil (257 mg, 53%); R_f = 0.73 (9:1 ethyl acetate : methanol); ν_{max}/cm^{-1} (thin film): 3385, 2954, 2252, 1796, 1704, 1566, 1246, 1175, 905, 724, 648; δ_H (400 MHz, $CDCl_3$) 7.74 (4H, d, *J* = 7.5 Hz, H-5,8,38,41), 7.56 (4H, d, *J* = 7.5 Hz, H-2,11,35,44), 7.38 (4H, d, *J* = 7.5 Hz, H-4,9,37,42), 7.29 (4H, d, *J* = 7.5 Hz, H-3,10,36,43), 5.46 (2H, t, *J* = 6.0 Hz, H-16,30), 4.34 (4H, d, *J* = 7.0 Hz, H-14,32), 4.17 (2H, t, *J* = 7.0 Hz, H-13,33), 3.95 (4H, t, *J* = 6.0 Hz, H-20,22), 3.55 (4H, q, *J* = 6.0 Hz, H-17,29), 3.07 (4H, t, *J* = 6.0 Hz, H-18,28), 2.01 (2H, p, *J* = 6.0 Hz, H-21); δ_C (100 MHz, $CDCl_3$) 185.0 (C-25,26), 175.0 (C-23,24), 170.9 (C-19,27), 156.5 (C-15,31), 143.9 (C-1,12,34,45), 141.3 (C-6,7,39,40), 127.8 (C-4,9,37,42), 127.1 (C-3,10,36,43), 125.1 (C-2,11,35,44), 120.1 (C-5,8,38,41), 66.9 (C-14,32), 47.2 (C-13,33), 45.5 (C-20,22), 36.7 (C-17,29), 36.1 (C-18,28), 24.4 (C-21); HRMS ($APCI^+$): calcd. for $C_{43}H_{38}N_4NaO_8$, 761.2582. Found: $[MNa]^+$, 761.2586 (−0.5 ppm error).

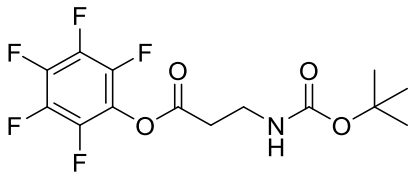
4.43: Di-*tert*-butyl ((8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-ene-2,6-diyl)bis(3-oxopropane-3,1-diyl))dicarbamate



In a round-bottomed flask, under an inert atmosphere, was added 2,6-diazabicyclo[5.2.0]non-1(7)-ene-8,9-dione (75.0 mg, 0.493 mmol) in THF (22.5 mL) and DMF (2.5 mL). To this, sodium hydride (49.7 mg, 1.24 mmol, 60% suspension in mineral oil) was added in a single portion and stirred at RT for 15 minutes. Then, perfluorophenyl 3-((*tert*-butoxycarbonyl)amino)propanoate (1.05 g, 2.96 mmol) in THF (10.0 mL) and DMF (1.0 mL) was added in a single portion and the solution stirred at RT for 168 hours. The reaction mixture was then quenched with 0.5 M citric acid (10.0 mL) and stirred for 5 minutes. The reaction mixture was then diluted with DCM (20 mL) and washed with water (5 x 30 mL). The solution was dried with $MgSO_4$, filtered and concentrated *in vacuo*. This was purified by flash column chromatography (SiO_2, 7:3 hexane : ethyl acetate → 1:1 ethyl acetate : hexane

→ 7:3 ethyl acetate : hexane → 9:1 ethyl acetate : methanol) affording the title compound, which was obtained as a colourless oil (42.9 mg, 18%); R_f = 0.25 (1:1 ethyl acetate : hexane); ν_{max}/cm^{-1} (thin film): 3384, 2978, 2933, 1795, 1750, 1693, 1565, 1518, 1415, 1367, 1249, 1165, 1102, 731; δ_H (400 MHz, $CDCl_3$) 5.06 (2H, t, *J* = 6.0 Hz, H-6,20), 4.04 (4H, t, *J* = 6.0 Hz, H-10,12), 3.46 (4H, q, *J* = 6.0 Hz, H-7,19), 3.06 (4H, t, *J* = 6.0 Hz, H-8,18), 2.08 (2H, p, *J* = 6.0 Hz, H-11), 1.40 (18H, s, H-1,2,3,23,24,25); δ_C (100 MHz, $CDCl_3$) 184.9 (C-15,16), 175.3 (C-13,14), 171.1 (C-9,17), 156.0 (C-5,21), 79.7 (C-4,22), 45.5 (C-10,12), 36.5 (C-8,18 [overlapping]), 36.4 (C-7,19 [overlapping]), 28.5 (C-1,2,3,23,24,25), 24.4 (C-11); HRMS (ESI^+): calcd. for $C_{23}H_{34}N_4NaO_8$, 517.2269. Found: $[MNa]^+$, 517.2291 (−4.3 ppm error).

4.50: Perfluorophenyl 3-((*tert*-butoxycarbonyl)amino)propanoate



In a round-bottomed flask, under an inert atmosphere, was added 3-(*tert*-butyloxycarbonylamino)propionic acid (246 mg, 1.30 mmol) and EDC.HCl (250 mg, 1.31 mmol) and this was dissolved in DCM (10.0 mL). The reaction mixture was stirred at RT for 30 minutes. Then, pentafluorophenol (194 mg, 1.05 mmol) was added to the mixture and stirred at RT for a further 72 hours. The reaction mixture was concentrated *in vacuo*. This was purified by flash column chromatography (SiO_2, 1:1 ethyl acetate : hexane) affording the title compound, which was obtained as a colourless oil (307 mg, 82%); R_f = 0.64 (1:1 ethyl acetate : hexane); ν_{max}/cm^{-1} (thin film): 3340, 2990, 1797, 1704, 1519, 1373, 1251, 1168, 1105, 993, 857; δ_H (400 MHz, $CDCl_3$) 5.13 (1H, t, *J* = 6.5 Hz, N**H**), 3.49 (2H, q, *J* = 6.5 Hz, C$\mathbf{H_2}$NH), 2.90 (2H, t, *J* = 6.5 Hz, C$\mathbf{H_2}CH_2$NH), 1.41 (9H, m, C(C$\mathbf{H_3}$)$_3$); δ_C (100 MHz, $CDCl_3$) 168.5 (**C**OOAr), 156.1 (NH**C**O), 142.4 (Ar**C**), 139.9 (Ar**C**), 139.2 (Ar**C**), 138.5 (Ar**C**), 136.8 (Ar**C**), 125.0 (Ar**C**), 80.0 (**C**(CH$_3$)$_3$), 36.1 (**C**H$_2$NH), 33.9 (**C**H$_2$CH$_2$NH), 28.3 (C(**C**H$_3$)$_3$); δ_F (282 MHz, $CDCl_3$) −152.77 (1F, d, *J* = 18.5 Hz, Ar**F**), −157.92 (1F, t, *J* = 21.5 Hz, Ar**F**), −162.39 (1F, t, *J* = 21.0 Hz, Ar**F**), −162.89 (1F, dd, *J* = 17.5, 5.5 Hz, Ar**F**), −165.09 (1F, t, *J* = 21.0 Hz, Ar**F**); HRMS (ESI^+): calcd. for $C_{14}H_{14}F_5NNaO_4$, 378.0735. Found: $[MNa]^+$, 378.0729 (1.6 ppm error).

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