Article:

Grogan, Gideon James orcid.org/0000-0003-1383-7056, Orukotan, Will, Palate, Kleopas et al. (7 more authors) (Accepted: 2023) Divergent Cascade Ring Expansion Reactions of Acryloyl Imides. Chemistry : A European Journal. e202303270. ISSN 1521-3765 (In Press)

https://doi.org/10.1002/chem.202303270

Divergent Cascade Ring Expansion Reactions of Acryloyl Imides

Will E. Orukotan,[a] Kleopas Y. Palate,[a] Balázs Pogrányi,[a] Philipp Bobinski,[b] Ryan G. Epton,[a] Lee Duff,[a] Adrian C. Whitwood,[a] Gideon Grogan,[a] Jason M. Lynam,[a] William P. Unsworth*[a]

[a] W. E. Orukotan, Dr K. Y. Palate, Dr B. Pogrányi, Dr R. G. Epton, L. Duff, Dr A. C. Whitwood, Prof G. Gorgan, Prof J. M. Lynam and Dr W. P. Unsworth
Department of Chemistry, University of York, York, YO10 5DD, UK.
[b] P. Bobinski
Organisch-Chemisches Institut, Universität Heidelberg, Im Neuenheimer Feld 270, 69120 Heidelberg, Germany.

Supporting information for this article is given via a link at the end of the document

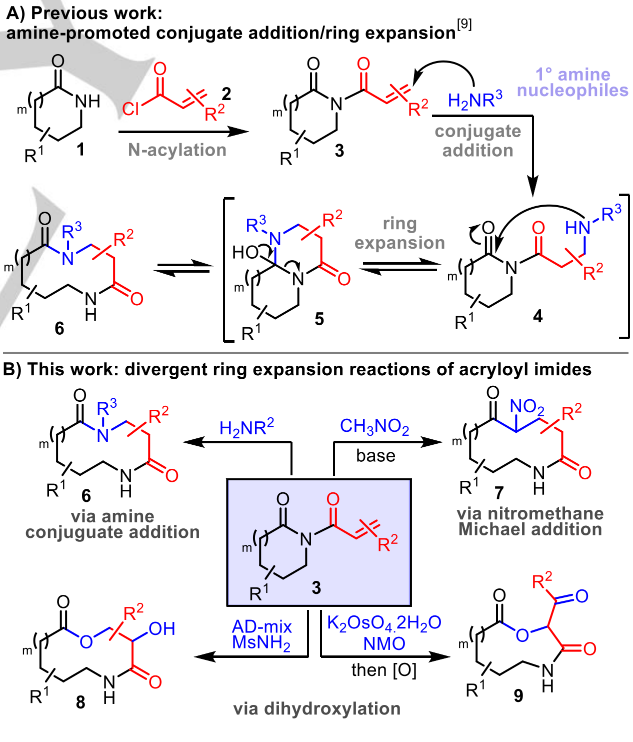
Abstract: Macrocyclic and medium-sized ring ketones, lactones and lactams can all be made from common acryloyl imide starting materials via divergent, one-pot cascade ring expansion reactions. Following either conjugate addition with an amine or nitromethane, or osmium(VIII) catalysed dihydoxylation, rearrangement via a 4-atom ring expansion takes place spontaneously to form the ring expanded products. A second ring expansion can also be performed following a second iteration of imide formation and alkene functionalisation/ring expansion. In the dihydroxylation series, 3- or 4-atom ring expansion can be performed selectively, depending on whether the reaction is under kinetic or thermodynamic control.

Introduction

Reliable methods for the rapid synthesis of diversely functionalised compounds are a cornerstone of lead generation in the discovery of new pharmaceuticals.[1] Divergent synthesis strategies play a key role in this context; for example, being a key design feature of most diversity oriented synthesis (DOS) methods.[2] Divergent synthesis is especially useful when enabling fundamentally different molecular architectures or functional groups to be generated from a simple, common precursor.[3] This manuscript is focused on one such approach, using divergent ring expansion cascade reactions[4,5] for the synthesis of medium-sized rings and macrocycles from acryloyl imides.

Macrocycles and medium-sized rings are of much current interest in medicinal chemistry,[6] but have historically been under-explored in pharmaceutical research and development, in large part due to well-known challenges associated with their synthesis.[7] Ring expansion cascade methods[5,8] offer several practical advantages over using classical end-to-end cyclization, most notably by removing the need to use high dilution conditions. The value of this type of approach was demonstrated in a recently reported study from our group,[9] using a conjugate-addition/ring expansion method (Scheme 1A).[10,11] The alkene moiety of acryloyl imide **3** was shown to react readily with various functionalised primary amines via conjugate addition (**3** → **4**) and subsequent ring expansion (**4** → **5** → **6**) in a cascade reaction, to form ring expanded lactams **6** in high yields in one-pot, with formation of two new C–N bonds.

In this manuscript, we show that this concept can be extended to other alkene reaction modes, establishing acryloyl imides **3** as versatile reactive precursors to diverse large ring scaffolds via divergent cascade ring expansion reactions. In addition to the established amine conjugate addition/ring expansion (**3** → **6**, Scheme 1B), we reveal that nitromethane can also be used to initiate a conjugate addition/ring expansion cascade, to form ring expanded ketones via the formation of two C–C bonds (**3** → **7**, Scheme 1B).[12] Furthermore, we also show that ring expanded lactones can be formed via a dihydroxylation/ring expansion cascade using the Sharpless AD-mix (**3** → **8**, Scheme 1B).[13] By applying all three methods, macrocyclic and medium-sized ring lactam, ketone and lactone products can all be generated, each from a common precursor of the type **3**. We also show that the products themselves can be expanded again, following further ring expansion in the same way. Finally, mechanistic studies (supported by DFT calculations) performed on the lactone series revealed an additional level of divergency, in which either a thermodynamic product **8** can be obtained via a 4-atom ring expansion, or under kinetic control, an alternative 3-atom ring expansion product **9** can be formed and isolated following oxidation (**3** → **9**, Scheme 1B).

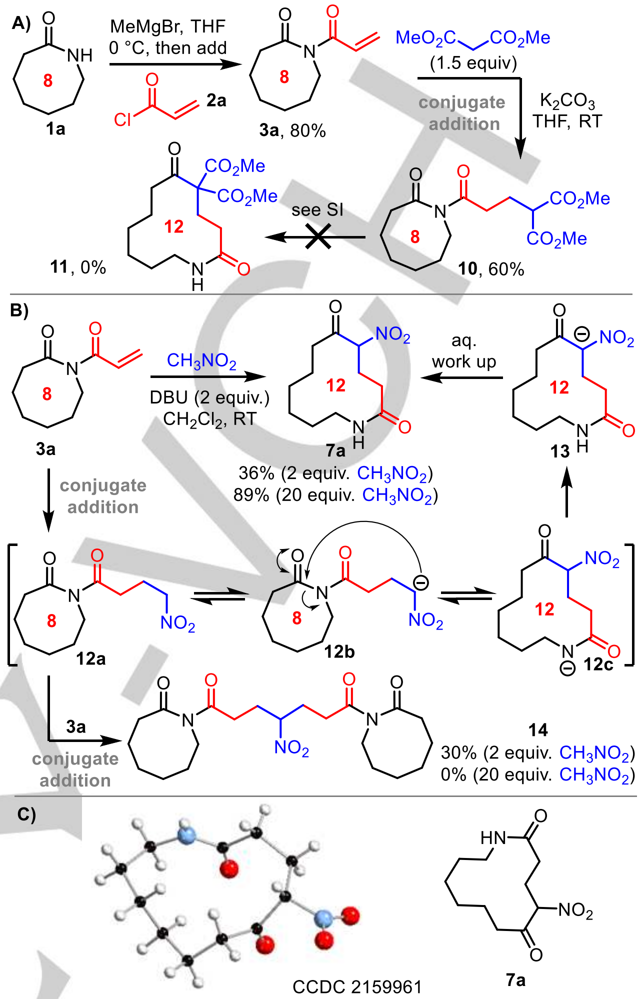


Scheme 1. A) Conjugate-addition/ring expansion using primary amines.[9] B) Divergent ring expansion reactions of acryloyl imides.

Results and Discussion

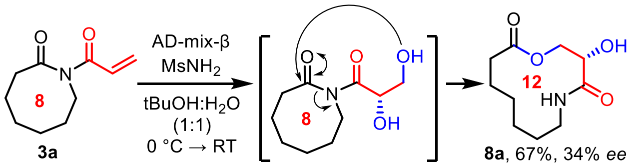
We started by seeking to develop a cascade reaction using a carbon pronucleophile able undergo conjugate addition into an acryloyl imide **3**.[14] As a test system, 8-membered ring acryloyl imide **3a** was synthesised, and reacted with dimethyl malonate under basic conditions (Scheme 2A). The first step of the planned cascade worked well, with imide **10** being formed via conjugate addition of the in situ generated enolate of dimethyl malonate into alkene of **3a**. Product **10** was isolable in 60% yield, but unfortunately there was no evidence of it reacting further to form ring expanded product **11** under any of the conditions tested (see ESI section 2 for details). Similar results were obtained when using malononitrile as the pronucleophile, while 1,1,1-trifluoroacetone failed to react (not shown - see ESI section 2 for details of both).

As steric factors have been shown to influence ring expansion reactions of this type, attention turned to the use of nitromethane as the pronucleophile. Nitromethane has comparable pKa to dimethyl malonate,[15] but with it having only one electron withdrawing substituent, the hope was that the ring expansion step would be less sterically encumbered and hence more favourable. This proved to be the case; following optimisation (see SI) it was found that reacting acryloyl imide **3a** with 2 equivalents of nitromethane and DBU in CH_2Cl_2 at RT promoted the planned conjugate addition (**3a** → **12a**) and ring expansion (**12a** → **12b** → **12c** → **13**). Following aqueous work-up, macrocycle **7a** was isolated in 36% yield, in addition to the formation of a significant quantity (30% yield) of side product **14**, which presumably arises from a second conjugate addition reaction between the intermediate **12b** and unreacted **3a**. Pleasingly, the yield of macrocycle **7a** was improved markedly simply by increasing the number of equivalents of nitromethane in the reaction; using 20 equivalents of nitromethane enabled the isolation of **7a** in 89% yield. The excess nitromethane (a common reaction solvent) is easily removed by evaporation. An additional advantage to this procedure is that prior to acidification, the ring expanded product exists as water soluble anion **13**, which enables its straightforward separation from minor organic impurities by aqueous workup. This meant that column chromatography was not needed to purify **7a** in this case. The structure of macrocycle **7a** is supported by X-ray crystallographic data (Scheme 2C).[16]



Scheme 2. A) Unsuccessful cascade reaction of **3a** and dimethyl malonate; B) Cascade reaction of **3a** and nitromethane; C) X-ray crystal structure of **7a**.

With a new C–C bond-forming cascade reaction established, attention next turned to exploring a new process that proceeds via C–O bond formation. A conjugate addition strategy was not feasible in this scenario, with imides like **3a** known to hydrolyse relatively easily when reacted with hydroxide/alkoxide based reagents (see SI). Instead, it was envisaged that dihydroxylation of acryloyl imide **3a** may be used to generate an intermediate 1,2-diol capable of undergoing 3- or 4-atom ring expansion via reaction through either alcohol. Whilst noting that the synthesis of enantiomerically enriched products was not a primary goal of this project, the convenience of commercially available Sharpless AD-mix reagents meant we chose to perform the dihydroxylation using AD-mix-β.[17] The reaction was tested using **3a** and AD-mix-β using the dihydroxylation conditions summarised in Scheme 3.[13] This idea worked well, with macrocyclic lactone **8a** isolated in 67% yield following aqueous workup and column chromatography. The reaction presumably proceeds via an intermediate diol, followed by 4-atom ring expansion via reaction of the terminal alcohol as shown in Scheme 3. In contrast, the alternative 3-atom ring expansion product (which would form through attack of the secondary alcohol) was not observed. The enantiomeric excess of the reaction (34% *ee*) was modest, as was expected for the dihydroxylation of a monosubstituted alkene of this type.[13,17]



Scheme 3. Dihydroxylation ring expansion cascade reaction of **3a**.

With two new ring expansion cascade methods developed (Schemes 2 and 3), in addition to our published amine conjugate addition/ring expansion cascade method,[9] a three branch divergent reaction series had been established. This is exemplified in Scheme 4A (top left corner section) through the reactions of acryloyl imide **3a**; reaction with nitromethane results in its conversion into macrocyclic ketone **7a** (method A), AD-mix-β yields macrocyclic lactone **8a** (method B), while reaction with p-fluorobenzylamine promotes conversion into macrocyclic lactam **6a** (method C). All three methods proceed in one-pot and in good yield.

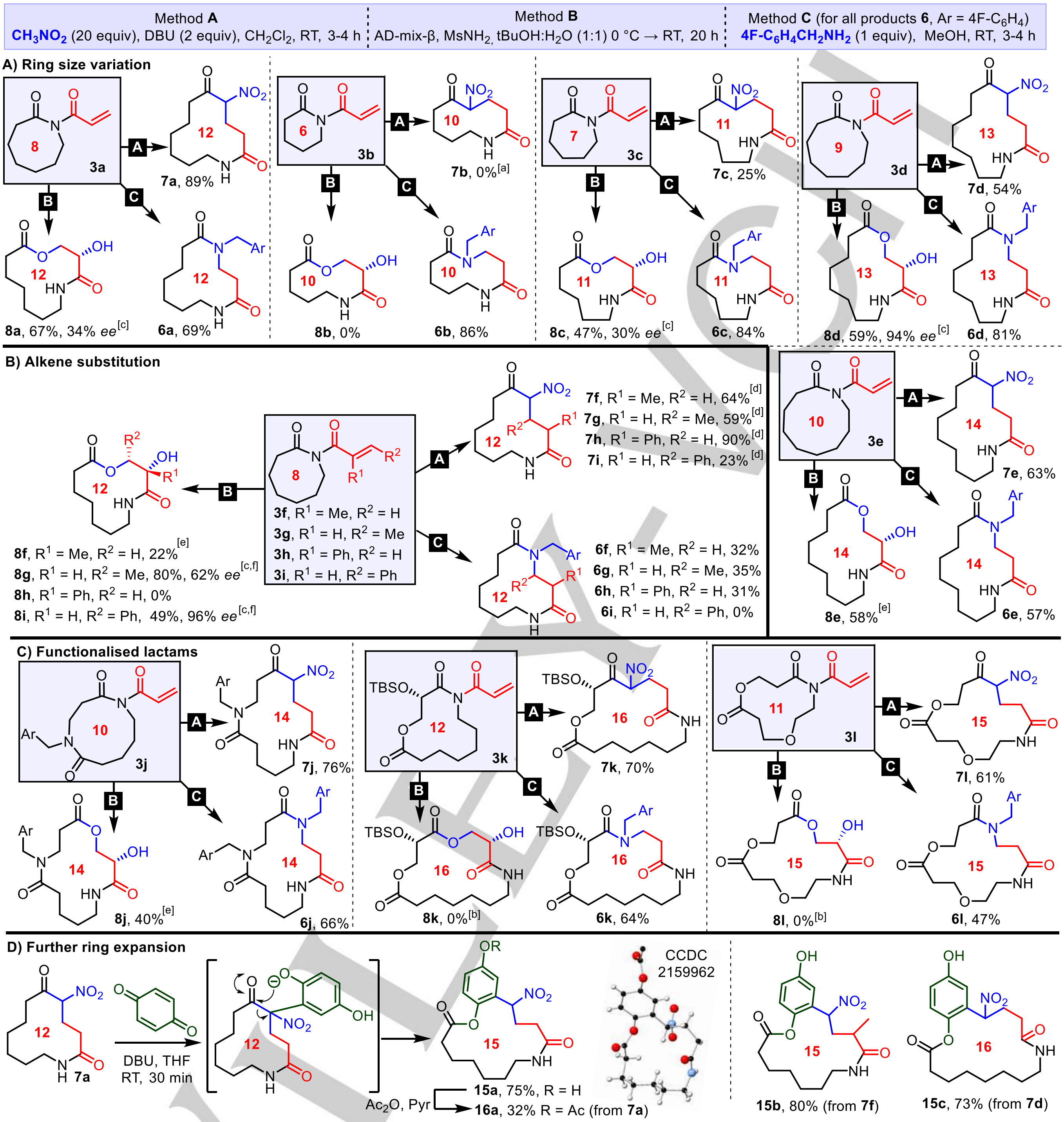
The generality of this divergent series was tested using different imide substrates **3**, starting by examining the effect of ring size (Scheme 4A). 6-Membered ring imide **3b** was not converted into ring expansion products **7b** or **8b** using either of the new methods A or B. These results were somewhat expected; our previous work has shown that ring expansion reactions of this type are usually under thermodynamic control, with their outcomes determined by the relative free energy of their isomeric ring closed and ring expanded forms.[18] These free energies are strongly influenced by ring size, and the conversion of comparatively stable 6-membered rings into 10-membered rings (which are typically more strained) is known to be challenging. Thus, for 6-membered ring imide **3b**, only method C was successful, with this reaction likely enabled by the formation of a particularly stable amide C–N bond.[5e]

In such cases, the point at which the reactions become thermodynamically viable can usually be found by increasing the ring size of the starting material; indeed, by switching to 7-membered starting material, methods A and B enabled the formation of 11-membered ring products (**7**/**8c**) in moderate yields, while for larger 9- and 10-membered imides both the macrocyclic products **7**/**8d** and **7**/**8e** were isolated in good yields. The corresponding lactam forming reactions (method C, **6c**–**e**) were successful in all cases.

Next, we moved onto substrates with substituted alkenes (Scheme 4B), testing acryloyl imides with methyl and phenyl substituents at the α- and β-position of the alkene (**3f**–**i**). Method A worked in all four cases (**7f**–**i**); the formation of macrocycle **7h** in 90% isolated yield is especially noteworthy, while the yield for **7i** was the lowest obtained, likely due to this styrene-derivative being a poorer Michael acceptor. Yields for the dihydroxylation-based ring expansions (method B) were mixed, but three out of four enabled the expanded lactone product to be isolated (**8f**,**g**,**i**), in all cases via 4-atom ring expansion. When measured, the *ee* of the reactions were broadly in line with those expected for dihydroxylation reactions of the different alkene classes; for example the enantioselectivity was low (34% *ee*) for unsubstituted alkene **3a**, modest (62% *ee*) for methyl substrate **3g**, and high (96% *ee)* for cinnamoyl system **3i**. Yields for method C were generally low for the substituted alkenes, as we reported in the original publication on these reactions, which have been shown to work much better on unsubstituted acryloyl imides.[9]

We then moved onto more functionalised substrates (Scheme 4C). To highlight the potential of the methods to be used in iterative ring expansion reactions,[5d] we decided to focus on starting materials that were themselves made via ring expansion reactions. For example, imide **3j** was made following N-acylation of 10-membered bislactam **6b** – a ring expansion product made during this study – with acryloyl chloride, using our standard method. Imide **3j** was subsequently tested with all three ring expansion procedures (methods A–C), enabling the expected 14-membered ring ketone (**7j**), lactone (**8j**) and lactam (**6j**) products to be isolated. Imide **3k** – which was itself prepared from a ring expanded product, lactone **8a** – was also tested with all three ring expansion methods. In this case, methods A and C both worked well and in good yields (**6k**/**7k**), but the dihydroxylation method led to the formation of a complex mixture of products, from which the desired product **8k** could not be isolated cleanly. The results were similar using 11-membered ring lactone **3l** as starting material, with this substrate made via one of our previously published ring expansion methods;[10c] in this series methods A and C worked well, while method B led to the formation of a complex mixture of products.

Finally, to further highlight the value of the nitroketone motif formed in the method A reactions, their use in a fundamentally different type of conjugate addition/ring expansion cascade reaction was also demonstrated (Scheme 4D). This procedure, which was adapted from a published method by Hesse and coworkers,[19] operates by reacting a cyclic nitroketone with 1,4-benzoquinone and DBU. This promotes a conjugate addition and spontaneous ring expansion cascade reaction, via a phenolate intermediate as summarised in Scheme 4D. For example, using this method 12-membered ring cyclic ketone **7a** was converted into 15-membered ring lactone **15a** in 75% yield. Lactone **15a** was also acetylated using acetic anhydride to form derivative **16a**, a crystalline solid, which allowed for its structural assignment by X-ray crystallography.[16] Macrocycles **15b** and **15c** were also prepared in comparable yields using the same approach.

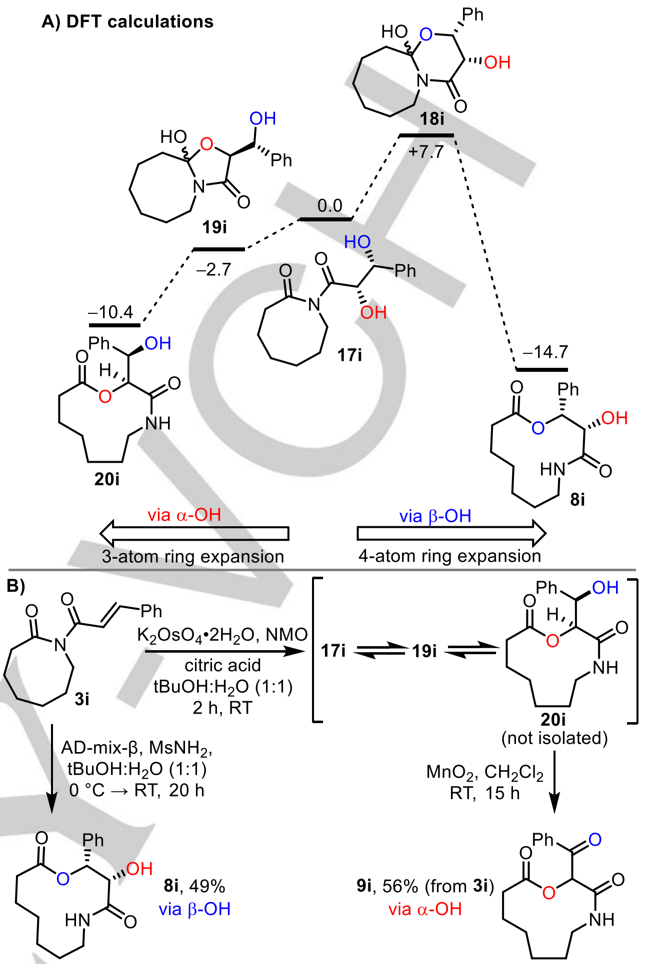


Scheme 4. Divergent ring expansion reactions of acryloyl imides. Reaction conditions A–C are summarised in the pale blue box above and the Experimental section. [a] In total, 4 side products were formed in this reaction, none of which were **7b** - see SI for structures and spectroscopic data of the side products. [b] The molecular ion was observed by mass spectrometry, but the desired product could not be isolated following column chromatography. [c] *ee* was measured by chiral HPLC analysis of the enantioenriched sample; see SI for details. The absolute stereochemistry was not proved explicitly, but the assignment given is made with confidence, based on the well-known stereoselectivity of dihydroxylation using AD-mix-β. [d] In solution in $CDCl_3$, this product exists in an equilibrating mixture of keto/enol tautomers and rotameric forms, meaning that it is not possible to quote a *dr* for this product. [e] *ee* not measured. [f] Isolated as a single diastereoisomer.

The regioselectivity of the dihydroxylation ring expansion cascade reactions (method B) was next investigated. In all cases shown in Scheme 4, the exclusive isolation of 4-atom ring expansion products was observed in this series; for example, following dihydroxylation of **3i**, the resulting diol (**17i**, Scheme 5) was converted into 12-membered ring lactone **8i** only, via reaction through the β-hydroxyl. None of the alternative 11-membered lactone **20i** was observed, which would form via 3-atom ring expansion via cyclisation of the α-hydroxyl.

To better understand this selectivity, relative Gibbs free energies were calculated for diol **17i**, both of the potential ring expanded products (**8i** and **20i**), and also bicyclic intermediates **18i** and **19i**. Our previous studies have demonstrated that the calculated thermodynamic distribution of products is a good model for the experimental outcomes of related ring expansions.[18a] The energies of these isomers are depicted in Scheme 5A, calculated at the B3LYP/6-31G* level of theory, in the gas phase, at 298.15 K. This DFT method was benchmarked against a range of other functionals and was shown to correlate well with reaction outcomes in related ring expansion reactions in our previous work.[18a] Both pathways (**17i** → **8i** and **17i** → **20i**) were calculated to be exergonic, with the 4-atom ring expansion (*i.e.* reaction via the β-OH highlighted in blue) calculated to be more energetically favourable, in line with the observed synthetic outcomes. This suggests that 4-atom ring expansion product **8i** is likely the thermodynamic product of the reaction, and the same logic would reasonably explain the regioselectivity of all the synthetic lactone-forming ring expansion reactions in Scheme 4.

Intriguingly, isomer **19i** (formed via cyclisation of the α-OH, highlighted in red) was calculated to be significantly lower in free energy than **18i**. While it is important to stress that **18i** and **19i** are intermediates and not transition states, based on Hammond's postulate it is reasonable to think that the barrier for conversion of **17i** into **19i** is likely to be lower than the barrier for conversion of **17i** into **18i**. This led us to question whether 3-atom ring expansion product **20i** may also be accessible, if conditions could be found that allow the reaction to proceed under kinetic control. This was achieved by switching to Upjohn-type conditions ($K_2OsO_4 \cdot 2H_2O$, citric acid and NMO)[20] and reducing the reaction time (20 h → 2 h); in contrast to the standard conditions (method B), which produced **8i** via 4-atom ring expansion, these conditions led to the formation of a mixture of products, believed to comprise **17i**, **19i** and **20i**. Isolating pure **20i** from this mixture (which is likely to be in equilibrium) was not possible, but by reacting the mixture with excess manganese dioxide,[21] the 11-membered ring product **20i** could be trapped as ketone **9i** and isolated in 56% overall yield from **3i**. The use of citric acid[22] in the Upjohn-type dihydroxylation is thought to be key to allowing the kinetic product to be accessed; basic reaction conditions (*e.g.* AD-mix β, which contains K_2CO_3) have generally been used to accelerate the rearrangement in thermodynamically controlled ring expansions of this type previously.[10,11,23]



Scheme 5. A) Relative Gibbs free energies for 3- and 4-atom ring expansion pathways from **3i** calculated at the B3LYP/6-31G* level of theory at 298.15 K in kcal mol^{-1}; B) Divergent 3- and 4-atom ring expansion of **3i**.

Conclusion

In summary, this study confirms that acryloyl imides are versatile starting materials able to participate in divergent ring expansion reactions. These methods enable the formation of functionalised macrocyclic and medium-sized ring lactams, lactones and ketones, with further ring expansion of the products themselves also demonstrated. An interesting additional degree of divergency was observed in the dihydroxylation reaction series, with selective 3- or 4-atom ring expansion demonstrated in one case, with the outcome dependent on whether the reaction is performed under kinetic or thermodynamic control. Given the number of other possible alkene functionalisation reactions, it is highly likely that several other novel ring expansion processes will be possible based on this concept. Our hope is that these methods will emerge in time, enabled via the introduction of nucleophilic groups at the α- or β-position of the alkene.

Experimental

Full synthetic detail and spectroscopic data for all compounds are provided in the Supporting Information. Representative **Methods A**, **B** and **C** (Scheme 4, substrate **3a**) are also included below:

Method A.
To a dry round-bottomed flask, DBU (0.15 mL, 1.00 mmol) was added to a stirring solution of 1-acryloyl-azocan-2-one **3a** (89.4 mg, 0.50 mmol) and nitromethane (0.54 mL, 10.0 mmol) in dry DCM (5.0 mL), under an inert atmosphere of Ar, at RT. The reaction mixture was stirred for 3.5 hours at RT, after which time DCM (10 mL) and water (10 mL) were added, and the organic and aqueous layers were separated, with the organic layer discarded. 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 compound **7a** as a white, crystalline solid (106.4 mg, 89%).

Method B.
To a round-bottomed flask was added AD-mix-β (1.41 g), methanesulfonamide (90.0 mg, 0.946 mmol), *t*-BuOH (6.0 mL) and water (6.0 mL), and the mixture was stirred for 15 min at RT and then cooled to 0 °C. 1-Acryloylazocan-2-one **3a** (182 mg, 1.00 mmol) was then added, and the reaction mixture was stirred for 2 h at 0 °C, and 17 h at RT. Na_2SO_3 (1.0 g) was then added, and the mixture was allowed to stir for a further 3 h at RT. The crude reaction mixture was then diluted with EtOAc (8 mL), and the aqueous layer extracted with EtOAc (2 × 4 mL), and the combined organic layers washed with brine (8 mL). The organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 ethyl acetate : hexane → ethyl acetate) afforded compound **8a**, as a white solid (146 mg, 67%).

Method C
To a solution of 1-acryloyl-azocan-2-one **3a** (103 mg, 0.566 mmol) in dry methanol (1.1 mL), was added 4-fluorobenzylamine (71.0 µL, 0.622 mmol) in a single portion. The reaction mixture was allowed to stir for 4 h at RT and then the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:4 ethyl acetate : hexane → 1:1 ethyl acetate : hexane → ethyl acetate → 1:49 methanol : ethyl acetate → 1:19 methanol : ethyl acetate) afforded the compound **6a**, as a white solid (119 mg, 69%).

Acknowledgements

The authors would like to thank the York Graduate Research School for supporting W. E. O with a YGRS PhD scholarship, the University of York for supporting the PhD studentships of K. Y. P. and R. G. E. and the industrial affiliates of the Centre of Excellence for Biocatalysis, Biotransformation and Biomanufacture (CoEBio3) for a studentship for B. P. We also thank the 'Studienstiftung des deutschen Volkes' for funding a research visit to York (P. B.). J. M. L. is supported by a Royal Society Industry Fellowship (INF\R1\221057). The computational work in this project was undertaken on the Viking Cluster, a high-performance computing facility provided by the University of York. We are grateful for computational support from the University of York High Performance Computing service, Viking and the Research Computing team. Finally, special thanks go to Nicola De Mitri for preparing the graphical abstract artwork.

Keywords: medium-sized ring • macrocycle • lactone • ring expansion • DFT

[1] (a) A. H. Lipkus, Q. Yuan, K. A. Lucas, S. A. Funk, W. F. Bartelt, III, R. J. Schenck, A. J. Trippe, *J. Org. Chem.* **2008**, *73*, 4443–4451; (b) P. A. Clemons J. A. Wilson, V. Dančík, S. Muller, H. A. Carrinski, B. K. Wagner, A. N. Koehle, S. L. Schreiber, *Proc. Natl. Acad. Sci. USA*, **2011**, *108*, 6817.

[2] (a) M. D. Burke, S. L. Schreiber, *Angew. Chem. Int. Ed.* **2003**, 43, 46; (b) D. Morton, S. Leach, C. Cordier, S. Warriner, A. Nelson, *Angew. Chem. Int. Ed.* **2009**, *48*, 104-109; (c) K. T. Mortensen, T. J. Osberger, T. A. King, H. F. Sore, D. R. Spring, *Chem. Rev.* 2019, *119*, 10288.

[3] (a) J. Mahatthananchai, A. M. Dumas, J. W. Bode, *Angew. Chem. Int. Ed.* **2012**, *51*, 10954; (b) J. T. R. Liddon, M. J. James, A. K. Clarke, P. O'Brien, R. J. K. Taylor, W. P. Unsworth, *Chem. Eur. J.* **2016**, *22*, 8777; (c) M. J. James, P. O'Brien, R. J. K. Taylor, W. P. Unsworth, *Angew. Chem. Int. Ed.* **2016**, *55*, 9671; (d) J. T. R. Liddon, A. K. Clarke, R. J. K. Taylor, W. P. Unsworth, *Org. Lett.* **2016**, *18*, 6328; (e) J. J. Feng, J. Zhang, *ACS Catal.* **2017**, *7*, 1533; (f) H. E. Ho, A. Pagano, J. A. Rossi-Ashton, J. R. Donald, R. G. Epton, J. C. Churchill, M. J. James, P O'Brien, R. J. K. Taylor, W. P. Unsworth, *Chem. Sci.* **2020**, *11*, 1353; (g) M. Bao, X. Xie, J. Huang, M. P. Doyle, Z. Ren, H. Yue, X. Xu, *Chem. Eur. J.* **2023**, *29*, e202300140.

[4] For key reviews on cascade reactions, see: (a) R. J. K. Taylor, M. Reid, J. Foot, S. A. Raw, *Acc. Chem. Res.*, **2005**, *38*, 851; (b) K. C. Nicolaou, J. S. Chen, *Chem. Soc. Rev.*, **2009**, *38*, 2993; (c) B. Prabagar, N. Ghosh, A. K. Sahoo, *Synlett* **2017**, 2539; (d) J. M. Sperl, V. Sieber, *ACS Catal.* **2018**, *8*, 2385; (e) H.-M. Huang, M. Garduño-Castro, C. Morrill, D. J. Procter, *Chem. Soc. Rev.*, **2019**, *48*, 4626.

[5] For key reviews of ring expansion chemistry, see: (a) M. Hesse in Ring Enlargement in Organic Chemistry, Wiley-VCH, Weinheim, 1991; (b) W. P. Unsworth, J. R. Donald, *Chem. Eur. J.* **2017**, *23*, 8780; (c) K. Prantz, J. Mulzer, *Chem. Rev.* **2010**, *110*, 3741; (d) T. C. Stephens, W. P. Unsworth, *Synlett* **2020**, 133; (e) A. K. Clarke, W. P. Unsworth *Chem. Sci.*, **2020**, *11*, 2876; (f) B. Biletskyi, P. Colonna, K. Masson, J.-L. Parrain, L. Commeiras, G. Chouraqui, *Chem. Soc. Rev.* **2021**, *50*, 7513.

[6] For medium-sized rings and macrocycles in medicinal chemistry, see: (a) K. R. Romines, K. D. Watenpaugh, P. K. Tomich, W. J. Howe, J. K. Morris, K. D. Lovasz, A. M. Mulichak, B. C. Finze, J. C. Lynn, M.-M. Horng, F. J. Schwende, M. J. Ruwart, G. L. Zipp, K.-T. Chong, L. A. Dolak, L. N. Toth, G. M. Howard, B. D. Rush, K. F. Wilkinson, P. L. Possert, R. J. Dalga, R. R. Hinshaw, *J. Med. Chem.* **1995**, *38*, 1884; (b) T. P. Majhi, B. Achari, P. Chattopadhyay, *Heterocycles* **2007**, *71*, 1011; (c) F. Kopp, C. F. Stratton, L. B. Akella, D. S. Tan, *Nat. Chem. Bio.* **2012**, *8*, 358; (d) R. A. Bauer, T. A. Wenderski, D. S. Tan, *Nat. Chem. Bio.* **2013**, *9*, 21; (e) C. Zhao, Z. Ye, Z.-X. Ma, S. A. Wildman, S. A. Blaszczyk, L. Hu, I. A. Guizei, W. Tang, *Nat. Commun.* **2019**, *10*, 4015, DOI: 10.1038/s41467-019-11976-2; (f) E. M. Driggers, S. P. Hale, J. Lee, N. K. Terrett, *Nat. Rev. Drug Discov.* **2008**, 7, 608; (g) E. Marsault, M. L. Peterson, J. *Med. Chem.* **2011**, *54*, 1961; (h) F. Giordanetto, J. Kihlberg *J. Med. Chem.* **2014**, 57, 278; (i) A. K. Yudin, *Chem. Sci.* **2015**, *6*, 30; (j) M. D. Cummings, S. Sekharan, J. *Med. Chem.* **2019**, *62*, 6843.

[7] (a) G. Illuminati, L. Mandolini, *Acc. Chem. Res.* **1981**, *14*, 95; (b) F. Fastrez, *J. Phys. Chem.*, **1989**, *93*, 2635; (c) J. C. Collins, K. James, *Med. Chem. Commun.*, **2012**, *3*, 1489; (d) H. Kurouchi, T. Ohwada, *J. Org. Chem.* **2020**, *85*, 876.

[8] (a) R. Costil, Q. Lefebvre, J. Clayden, *Angew. Chem. Int. Ed.* **2017**, *56*, 14602; (b) T. Guney, T. A. Wenderski, M. W. Boudreau, D. S. Tan, *Chem. Eur. J.* **2018**, *24*, 13150; (c) D. R. Loya, A. Jean, M. Cormier, C. Fressigné, S. Nejrotti, J. Blanchet, J. Maddaluno, M. De Paolis, *Chem. Eur. J.* **2018**, *24*, 2080; (d) A. Lawer, J. A. Rossi-Ashton, T. C. Stephens, B. J. Challis, R. G. Epton, J. M Lynam, W. P. Unsworth, *Angew. Chem., Int. Ed.* **2019**, *58*, 13942; (e) Y. Yuan, Z. Guo, Y. Mu, Y. Wang, M. Xu, Y. Li, *Adv. Synth. Catal.* **2020**, *362*, 1298; (f) J. Shang, V. J. Thombare, C. L. Charron, U. Wille, C. Hutton, *Chem. Eur. J.* **2021**, *26*, 1620; (g) Z.-L. Li, X.-H. Li, N. Wang, N.-Y. Yang, X.Y. Liu, *Angew. Chem. Int. Ed.* **2016**, *55*, 15100; (h) L. Li, Z.-L. Li, Q.-S. Gu, N. Wang, X.-Y. Liu, *Sci. Adv.* **2017**, *3*, e1701487.

[9] K. Y. Palate, Z. Yang, A. C. Whitwood, W. P. Unsworth *RSC Chem. Biol.*, 2022, *3*, 334.

[10] For protecting group based ring expansion methods that preceded the development of the conjugate addition/ring expansion method reported in reference 9, see: (a) C. Kitsiou, J. J. Hindes, P. I'Anson, P. Jackson, T. C. Wilson, E. K. Daly, H. R. Felstead, P. Hearnshaw, W. P. Unsworth, *Angew. Chem. Int. Ed.* **2015**, *54*, 15794; (b) L. G. Baud, M. A. Manning, H. L. Arkless, T. C. Stephens, W. P. Unsworth, *Chem. Eur. J.* **2017**, *23*, 2225; (c) T. C. Stephens, M. Lodi, A. Steer, Y. Lin, M. Gill, W. P. Unsworth, *Chem. Eur. J.* **2017**, *23*, 13314; (d) T. C. Stephens, A. Lawer, T. French, W. P. Unsworth, *Chem. Eur. J.* **2018**, *24*, 13947; (e) Z. Yang, C. R. B. Swanson, W. P. Unsworth, *Synlett* **2023**, 1694.

[11] For related reactions of vinyl sulfonamides, see: Z. Yang, I. Zalessky, R. G. Epton, A. C. Whitwood, J. M. Lynam, W. P. Unsworth, *Angew. Chem., Int. Ed.* **2023**, e202217178

[12] This represents the first C–C bond forming ring expansion based on any of the methods cited in reference 9–11.

[13] K. B. Sharpless, W. Amberg, Y. L. Bennani, G. A. Crispino, J. Hartung, K. S. Jeong, H. L. Kwong, K. Morikawa, Z. M. Wang, D. Xu, X.-L. Zhang, *J. Org. Chem.* **1992**, *57*, 2768.

[14] For conceptually related ring expansion reactions that proceed via C–C bond formation, see: (a) B. M. Trost, J. E. Vincent, *J. Am. Chem. Soc.* **1980**, *102*, 5680; (b) Y. Nakashita, M. Hesse, *Angew. Chem.* **1981**, *93*, 1077; (c) Y. Nakashita, M. Hesse, *Helv. Chim. Acta* **1983**, *66*, 845; (d) S. Bienz, M. Hesse, *Helv. Chim. Acta* **1988**, *71*, 1704.

[15] Bordwell pka tables, see: https://organicchemistrydata.org/hansreich/resources/pka/ (accessed May 2023)

[16] <url href="https://www.ccdc.cam.ac.uk/services/structures?id=doi:10.1002/###.20220XXX"> 2159961 (for **7a**), 2159962 (for **16a**), contain(s) the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe <url href="http://www.ccdc.cam.ac.uk/structures">Access Structures service</url>.

[17] H. C. Kolb, M. S. VanNieuwenhze, K. B. Sharpless, *Chem. Rev.* **1994**, *94*, 2483.

[18] (a) A. Lawer, R. G. Epton, T. C. Stephens, K. Y. Palate, M. Lodi, E. Marotte, K. J. Lamb, J. K. Sangha, J. Lynam, W. P. Unsworth, *Chem. Eur. J.* **2020**, *26*, 12674; (b) K. Y Palate, R. G. Epton, A. C. Whitwood, J. M. Lynam, W. P. Unsworth *Org. Biomol. Chem.*, **2021**, *19*, 1404.

[19] H. Stach, M Hesse, *Helv. Chim. Acta*, **1986**, *69*, 85.

[20] V. Vanrheenen, R. C. Kelly, D. Y. Cha, *Tetrahedron Lett.* **1976**, *17*, 1973.

[21] R. J. K. Taylor, M. Reid, J. Foot, S. A. Raw, *Acc. Chem. Res.* **2005**, *38*, 851.

[22] P. Dupau, R. Epple, A. A. Thomas, V. V. Fokin, K. B. Sharpless, *Adv. Synth. Catal.* **2002**, *344*, 421.

[23] R. Mendoza-Sanchez, V. B. Corless, Q. N. N. Nguyen, M. Bergeron-Brlek, J. Frost, S. Adachi, D. J. Tantillo, A. K. Yudin, *Chem. Eur. J.* **2017**, *23*, 13319.

Entry for the Table of Contents (Please choose one layout)

Layout 1:

RESEARCH ARTICLE

Macrocyclic and medium-sized ring ketones, lactones and lactams can all be made from common acryloyl imide starting materials via divergent, one-pot cascade ring expansion reactions. A second ring expansion can also be performed following a second iteration of imide formation and alkene functionalisation/ring expansion.

*Will E. Orukotan, Kleopas Y. Palate, Balázs Pogrányi, Philipp Bobinski, Ryan G. Epton, Lee Duff, Adrian C. Whitwood, Gideon Grogan, Jason M. Lynam, William P. Unsworth**

Page No. – Page No.

Divergent cascade ring expansion reactions of acryloyl imides

Layout 2:

RESEARCH ARTICLE