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Synthesis of a macrocyclic and medium-sized ring lactam library using cascade ring expansion reactions

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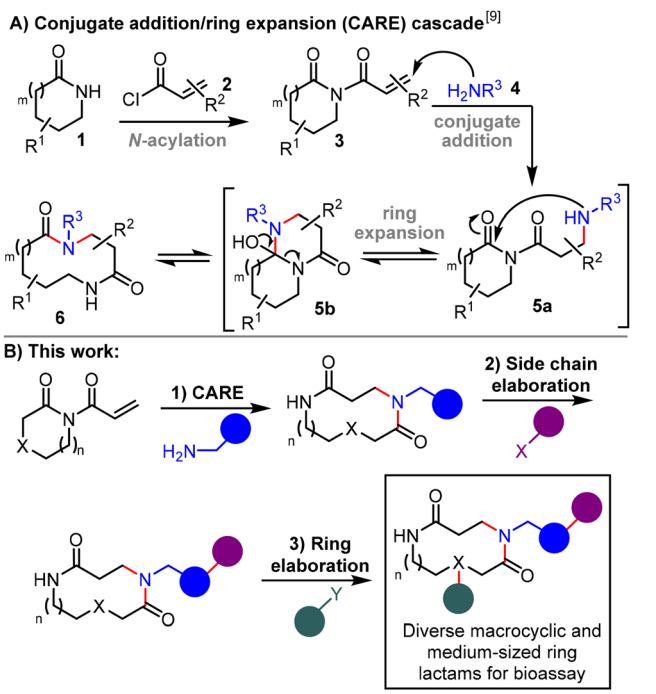
A versatile approach for the synthesis of a diverse library of macrocyclic and medium-sized ring lactams is described. Up to three-sequential synthetic steps were used, starting with a conjugate addition/ring expansion cascade, followed by side-chain and ring elaboration steps. The library was tested for antibacterial activity against *Staphylococcus aureus* and *Escherichia coli*. Although no novel antibacterial agents were uncovered in this study, the utility of the approach to quickly generate diverse lactam libraries for bioassay is confirmed.

Introduction

Access to diverse compound libraries for bioassay is of paramount importance in pharmaceutical research and discovery.[1] The number of compounds and their structural diversity are both key factors in determining the value of compound libraries in lead identification campaigns.[2] The inclusion of compounds with structural features underrepresented in typical compound screening collections is also important as it increases the chance of discovering compounds with novel biological activity. Macrocycles (12+ membered rings) and medium-sized rings (8–11-membered) are important compound classes in this regard. Both have proven potential in medicinal chemistry, being present in various drugs and biologically active natural products.[3] They are also the focus of much current attention in medicinal chemistry.[3] However, synthetic challenges associated with their preparation – most notably, the competition between inter- and intramolecular coupling in end-to-end cyclisation reactions – can provide a barrier to their use.[4,5]

New methods for the efficient preparation of macrocycles and medium-sized rings are therefore of value. The development of versatile methods to make large ring molecules has been a major driver in our group in recent years, with a particular focus on new ring expansion methods.[6,7] Ring expansion reactions can enable macrocycles and medium-sized rings to be prepared without the need to perform a discrete end-to-end cyclisation step; therefore, in well-designed cases, large ring products can be obtained without resorting to high-dilution conditions.[8] One such method is the conjugate addition/ring expansion (CARE) cascade depicted in Scheme 1A.[9,10] The CARE method starts from simple lactams **1**, which upon *N*-acylation are converted into acryloyl imides **3**. Then, reaction of **3** with a primary amine **4** initiates a conjugate addition (**3** → **5a**) and ring expansion (**5a** → **5b** → **6**)



Scheme 1 Synthesis of macrocyclic and medium-sized ring lactams using cascade ring expansion reactions.

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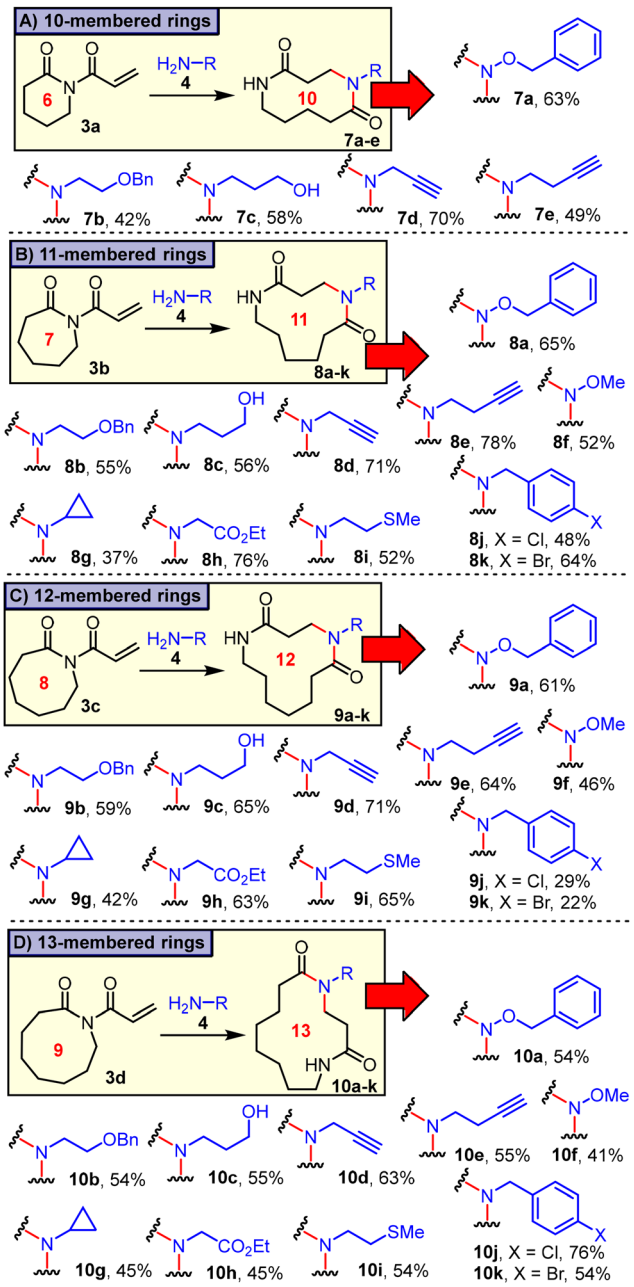
cascade reaction, to form ring expanded lactams **6**. The reactions are typically high yielding and are performed *via* a simple and mild one-pot procedure, that is insensitive to air and moisture. Crucially, CARE has also been shown to work well with a wide array of functionalised primary amines. Thus, multiple ring-expanded products can be generated from a single acryloyl imide precursor by varying the amine **4**.

The CARE method is therefore well suited for the rapid synthesis of lactam libraries. In this manuscript, we demonstrate its use for the rapid generation of a library of diversely functionalised macrocyclic and medium-sized ring lactams for bioassay (Scheme 1B).[11] A three-step approach was conceived, starting with the synthesis of a diverse array of lactams using CARE (step 1). As CARE is proven to work well in the presence of a range of reactive functionalities,[9,10] it is well suited to the formation of lactams containing synthetic handles primed to undergo further elaboration reactions. These handles can be included on the primary amine component used in the CARE, enabling side-chain elaboration (step 2), or on the ring scaffold itself (ring elaboration step 3), using a range of cross coupling, amine and alcohol functionalisation reactions. In total, 67 novel macrocyclic and medium-sized ring lactams were generated during this study, and the majority were assessed for antibacterial activity in Gram-positive *Staphylococcus aureus* and Gram-negative *Escherichia coli* assays.

Results and discussion

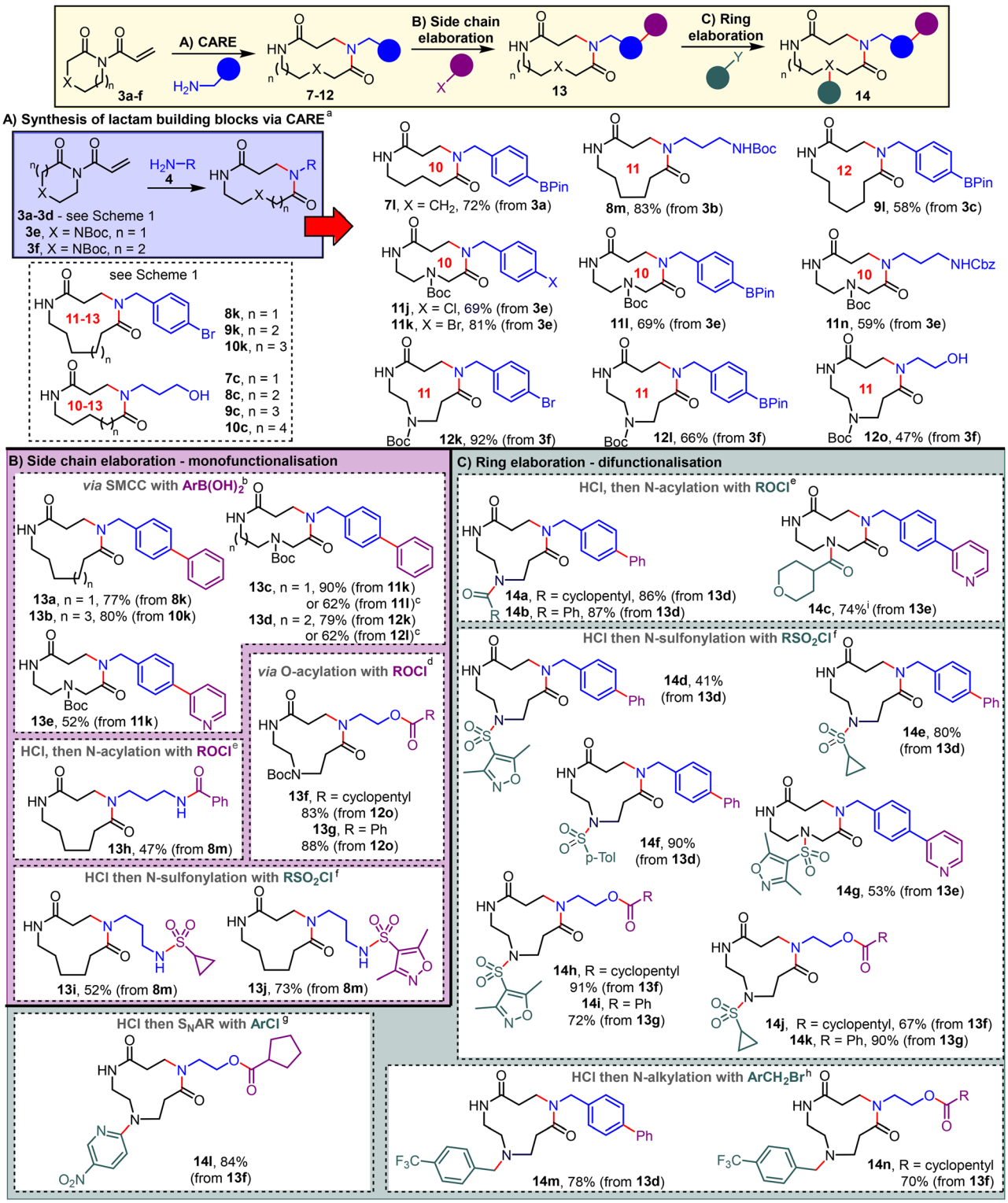
In our first publication on the discovery of the CARE approach,[9] almost all studies focused on varying the amine were done using 6-membered ring acryloyl imide **3a**, to form 10-membered ring lactam products **7**, of the type summarised in Scheme 2A. Five such examples were performed in this study, with the conversion of imide **3a** into 10-membered ring lactams **7a–e** all proceeding in good yield; with the exception of **7d**, the products prepared did not feature in our earlier manuscript. We then moved on to the CARE reactions of other ring-sizes, starting from 7-, 8- and 9-membered acryloyl imides **3b–3d**. Each imide was reacted with the same series of 11 primary amines (Scheme 2B–D). All the results in Scheme 2 were obtained from a single reaction attempt, using the standard conditions (4 h at RT in methanol) with no additional optimisation performed on a case-by-case basis. The expected product was isolated in all cases (**7a–e**, **8a–k**, **9a–k**, **10a–k**, 36 examples, all novel compounds), illustrating the power of the CARE method to quickly generate macrocyclic and medium-sized ring lactams, with different rings sizes formed and a range of functionalised amines used.

Efforts to generate more functionalised lactams are summarised in Scheme 3. In this series, in addition to the already mentioned acryloyl imides **3a–3d**, 6- and 7-membered ring acryloyl imides **3e** and **3f** were also used, with each containing a Boc-protected amine group in the ring scaffold. Scheme 3A summarises the synthesis of 10 more lactams using the CARE



Scheme 2 Conjugate addition/ring expansion (CARE) cascade reactions of imides **3a–d** with amines **4**. The following standard reactions conditions were used: imide **3** (1 equiv.), amine **4** (1.1 equiv.), MeOH (0.5 M), 4 h, RT. See SI for full synthetic details.

method, each of which contains a synthetic handle(s) amenable to additional elaboration reactions. Amines containing synthetic handles were used to facilitate the synthesis of lactams primed to undergo subsequent reactions on the side chain; lactams containing boronic ester (**7l**, **9l**, **11l**, **12l**), aryl halide (**11j**, **11k**, **12k**), protected amine (**8m**, **11n**) and free alcohol (**12o**) groups on their side chain were all formed in good yields. The use of imides **3e** and **3f** also enabled the generation lactams containing a Boc-protected amine as part



Scheme 3 Synthesis of a macrocyclic and medium-sized ring lactam library using cascade ring expansion reaction. Reactions conditions: [a] imide **3** (1 equiv.), amine **4** (1.1 equiv.), MeOH (0.5 M), 4 h, RT. See SI for full synthetic details; [b] ArBr (1 equiv.), $ArB(OH)_2$ (1.5 equiv.) $Pd(dppf)Cl_2(CH_2Cl_2)$, Na_2CO_3, water, 1,4-dioxane, 18 h, 50 °C; [c] $ArB(OH)_2$ (1 equiv.), PhBr (1.5 equiv.) $Pd(dppf)Cl_2(CH_2Cl_2)$, Na_2CO_3, water, 1,4-dioxane, 18 h, 50 °C; [d] alcohol (1 equiv.), ROCl (1.2 equiv.), Et_3N, DMAP, CH_2Cl_2, 0 °C → RT, 18 h; [e] Boc-amine compound (1 equiv.), 4 M HCl in 1,4-dioxane, 1 h, RT, concentrate *in vacuo*, then ROCl (1.2 equiv.), Et_3N, DMAP, CH_2Cl_2, 0 °C → RT, 18 h; [f] Boc-amine compound (1 equiv.), 4 M HCl in 1,4-dioxane, 10 min, RT, concentrate *in vacuo*, then RSO_2Cl (1.2 equiv.), Et_3N, DMAP, CH_2Cl_2, 0 °C → RT, 18 h; [g] Boc-amine compound (1 equiv.), 4 M HCl in 1,4-dioxane, 1 h, RT, concentrate *in vacuo*, then 2-chloro-5-nitropyridine (1.2 equiv.), K_2CO_3, CH_3CN, 80 °C, 18 h; [h] Boc-amine compound (1 equiv.), 4 M HCl in 1,4-dioxane, 1 h, RT, concentrate *in vacuo*, then 1-(bromomethyl)-4-(trifluoromethyl) benzene (1.2 equiv.), Et_3N, THF, 70 °C, 18 h. See SI for full synthetic details. [i] **14c** contained a small amount of an unknown impurity.

of the medium-sized ring scaffold (**11j–n**, **12k**, **12l**, **12o**), thus providing an additional synthetic handle for elaboration of ring, *via* protecting group cleavage and *N*-functionalisation.

Reactions based on the functionalisation CARE products *via* side chain elaboration are summarised in of Scheme 3B.[12] First, Suzuki–Miyuara cross coupling (SMCC) reactions were demonstrated successfully using phenyl and pyridyl coupling partners to generate derivatives **13a–e**. Notably, SMCC was possible with the CARE product decorated with both bromide and boronic ester handles. Starting from alcohol-substituted CARE product **12o**, facile *O*-acylation can be performed to form esters **13f** and **13g**. Similarly, protected amine derivative **8m** could be functionalised *via* sequential HCl-mediated removal of the Boc protecting group, followed either *N*-acylation to form **13h**, or *N*-sulfonylation to form **13i** and **13j**.

Attention then turned to the formation of difunctionalized products *via* ring elaboration (Scheme 3C). In this series, this was done by performing a second derivatisation of the scaffolds generated *via* side chain elaboration in Scheme 3B.[12] Having established that the lactams are able to tolerate the acidic conditions needed to facilitate cleavage of Boc protecting groups, we focused on the ring elaboration of scaffolds **13d–g**, all of which feature Boc-protected amine within their medium-sized ring/macrocyclic framework.

In all cases, cleavage of the Boc group was followed by immediate *N*-functionalisation, with the yields quoted in Scheme 3C relating to the overall two-step sequence. In this way, diverse difunctionalised products were successfully obtained *via* *N*-acylation with acid chlorides (to form **14a–c**), *N*-sulfonylation (to form **14d–k**), S_NAr (to form **14l**) and *via* *N*-alkylation (to form **14m** and **14n**). The ability of the scaffolds to tolerate the acidic conditions needed to cleave the Boc group and the various *N*-functionalisation conditions is key to enabling the facile generation of the range of derivatised products depicted in Scheme 3.

Macrocycles and medium-sized rings are considered to be underexplored compounds classes in medicinal chemistry lead identification campaigns, compared with ubiquitous 5–7-membered ring scaffolds. Establishing an efficient strategy to generate diverse libraries of macrocyclic and medium-sized lactams for bioassay was therefore a major driving force for undertaking this study. With such a library in hand, the majority (60 compounds) of the lactams synthesised above were assessed in antibacterial activity assays against Gram-positive *Staphylococcus aureus* and Gram-negative *Escherichia coli*. Unfortunately, none of the compounds tested exhibited significant bacterial growth inhibition in either assay (see SI section 3 for full details).

Conclusions

In summary, a cascade ring expansion approach has been successfully applied to the synthesis of a library of 67 novel macrocyclic and medium-sized lactams. The lactam scaffolds were all generated using novel variants of our established CARE method. The broad functional group compatibility of CARE enabled functionalised lactams to be prepared including synthetic handles for further reactions; this allowed subsequent elaboration reactions to be performed to further expand the diversity of lactam library, using a range of cross coupling, amine and alcohol functionalisation reactions.

Unfortunately, none of the lactams synthesised promoted bacterial growth inhibition in the assays performed. Nonetheless, our primary objective in this study was to establish an efficient and general strategy to make libraries of macrocyclic and medium-sized lactams for bioassay, and this objective has been achieved. We anticipate that this approach, and others based on it, could be used to generate larger and more varied lactam libraries. These libraries could then be screened against a much wider array of biological targets and facilitate the discovery of new medicinal lead compound series, in a relatively underexplored area of chemical space.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the SI.

Compound characterisation data, synthetic procedures, bioassay information, NMR spectra and LCMS data. See DOI: **https://doi.org/10.1039/d5ob01048a**.

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We would like to dedicate this publication to the memory of our friend and colleague Prof. Paul A. Clarke. S. Y. started her PhD working in Prof Clarke's team, and this work would not have been possible without his valuable support and training.

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