Modular assembly of macrocyclic sulfonamides via consecutive cascade ring expansion reactions

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**Abstract:** Sulfur(IV) groups and macrocycles are both important motifs in bioactive molecules of significant current interest in medicinal chemistry, but methods for the efficient synthesis of macrocyclic sulfur(IV) compounds are rare. In this manuscript, a modular, versatile strategy for the synthesis of macrocyclic sulfonamides is described, using consecutive ring expansion reactions. First, linear starting materials are assembled from simple building blocks. This is followed by two distinct cascade ring expansion reaction steps performed in sequence. The utility of this modular approach is showcased via the synthesis of a library of 42 diversely functionalised 13- and 14-membered macrocyclic sulfonamides. The use of consecutive ring expansions is key to the success of the protocol, ensuring the products are formed in overall good yields without requiring high-dilution conditions.

**Introduction**

Sulfur(IV) motifs are found widely in bioactive small molecules and are of much current interest in pharmaceutical research and development.[1] Amongst these, sulfonamides are one of the most medicinally important, being widely found in FDA approved drugs with broad biological activity.[2] Cyclic sulfonamides (also known as sultams) are very well represented within this class, being present in several drugs and bioactive compounds.[3]

Macrocycles (12+ membered rings)[4] and medium-sized rings[5] (8–11-membered) are also of significant interest in medicinal chemistry, with proven efficacy to address challenging biological targets (*e.g.* protein-protein interaction inhibition).[6] Despite this, the medicinal properties of larger ring scaffolds have been far less well explored than ubiquitous 5–7-membered ring compounds. Macrocyclic and medium-sized ring sulfonamides are no different, with studies focused on their preparation and/or bioassay rare.[7]

This manuscript is focused on the development of a modular strategy for the assembly of macrocyclic sulfonamides, based on the sequential application of novel variants of two distinct cascade ring expansion methods developed in our laboratory. [9-12] The first is the cyclisation/ring expansion cascade summarised in Scheme 1A (cascade 1).[13] This cascade ring expansion approach allows for the conversion of linear carboxylic acid derivatives **1a** into medium-sized rings **2** via an overall end-to-end cyclisation, without requiring high-dilution reaction conditions.[14] Splitting an inefficient end-to-end cyclisation into two more kinetically favourable normal-sized ring cyclisation steps is key to the success of this approach, enabling a cascade of carboxylic acid activation (**1a** → **1b**), cyclisation (**1b** → **1c**) and ring expansion (**1c** → **2**) to form medium-sized lactones and lactams. The second cascade ring expansion strategy used is our conjugate addition/ring expansion[15] method (cascade 2, Scheme 1A). Of most relevance to this study, we have shown that cyclic vinyl sulfonamides **3** react with primary aminesto undergo a conjugate addition (**3** → **4a**), ring expansion (**4a** → **4b**) to form medium-sized cyclic sulfonamides via a high yielding one-pot cascade.[15b]



**Scheme 1.** Modular assembly of macrocyclic sulfonamides via consecutive cascade ring expansion reactions.

This manuscript is focused on combining novel variants of both cascade ring expansion methods into a general, modular approach for the synthesis of macrocyclic sulfonamides (Scheme 1B). Key to this idea is the use of linear substrates of the form **6**, which contain a carboxylic acid group (highlighted in pink), an internal nucleophilic tertiary amine (green) and a terminal vinyl sulfonamide (blue). The assembly of such substrates was expected to be straightforward using well established coupling reactions from simple building blocks, with the resulting substrates **6** containing all the requisite functionality to undergo both cascades. Cyclisation/ring expansion (cascade 1, **6** → **7** → **8**) was then envisioned; a key difference between this work and our previous work is the use of the vinyl sulfonamide group (blue) acting as the terminal nucleophile. Finally, interception of the resulting medium-sized cyclic sulfonamide **8** by reactionwith different functionalised primary amines was planned, to promote conjugate addition/ring expansion (cascade 2) and form macrocyclic sulfonamides **9**.

The successful realisation of this modular approach is described herein, demonstrated via the efficient and scalable synthesis of a library of 42 diversely functionalised 13- and 14-membered macrocyclic sulfonamides in good overall yields.

**Results and Discussion**

Prior to this study, a single example of a cyclisation/ring expansion cascade reaction of a vinyl sulfonamide starting material had been demonstrated, starting from linear substrate **6a** (Scheme 2A).[13b] This system was therefore chosen as the first system to test the generality of this approach. The preparation of **6a**is straightforward from simple building blocks **5c**–**5e** via a sequence of amine alkylation, Boc cleavage, sulfonylation and ester hydrolysis (see SI for preparative details for **6a**, and all linear substrates in the manuscript). This then set up the first cascade reaction (cascade 1), in which carboxylic acid **6a** was activated with T3P under basic conditions, to initiate cyclisation and ring expansion to generate 9-membered ring intermediate **8a**. Following a simple aqueous work-up, this intermediate was then taken directly onto the second cascade (cascade 2), in which **8a** was reacted with different functionalised primary amines to initiate a conjugate addition/ring expansion cascade. Twelve amines bearing various functional groups were used in this series, resulting in the successful synthesis of twelve 13-membered ring sulfonamides **10a**–**l** in 21–63% isolated yields. Notably, the yields quoted are yields starting from **6a** and hence encompass both cascades. Furthermore, in keeping with the approach being designed as a strategy to generate diverse macrocycles quickly, all of these reactions were performed a single time with no additional optimisation performed on a case-by-case basis.

 Attention next turned to benzannulated linear substrate **6b**, which was prepared using similar building blocks and synthetic steps as those used to make **6a** (Scheme 2B). The inclusion of cyclic systems such as aromatics into the linear precursor has been shown to improve the efficiency of cyclisation/ring expansion cascades in our previous work, and this improvement was seen in the overall yields in this series. Thus, benzannulated 13-membered ring sulfonamides **11a**–**m** were prepared,using a diverse array of amines, in consistently high isolated yields 63–97% obtained for the overall 2 cascade sequence. A range of functionalised and unprotected primary amine reagents were shown to be compatible and deliver products in good overall yields, with especially notable examples including macrocyclic products containing alkynes (**11b**), aza-heteroaromatics (**11c**, **11i**), alcohols (**11g**) and boronic esters (**11j**).

 Scheme 2C shows the same modular approach being used to prepare pyridine-containing 14-membered ring macrocycles **12**. In this series, the linear substrate **6c** was prepared via a straightforward sequence of lithiation trapping (**5h** and **5i**), Suzuki-Miyaura cross coupling, Boc cleavage, sulfonylation and ester hydrolysis. Both cascade reactions then followed, with 14-membered ring sulfonamides **12a**–**g** in 35–85% overall isolated yields. The pyridine acts as the internal nucleophile in cascade 1 in this series, with a range of reactive primary amines again shown to be compatible with cascade 2. Of additional note, considering that macrocycle sulfonamides **12a**–**g** each contain a chiral biaryl axis and a point stereogenic centre, all were obtained as single atropisomers (racemic). The stereoselectivity is proposed to arise during cascade 1, via point-to-axial chirality transfer,[16] with the assigned relative stereochemistry made based on our published model.[13,17]

 Finally, varying the aromatic group in the scaffold is also possible, with quinoline-containing macrocyclic sulfonamides **13a**–**f** all prepared in high yields (71–85%) from linear substrate **6d** (Scheme 2D). In this series, an *N*-methyl tertiary amine operated as the internal nucleophile in cascade 1, and 6 reactive amines in cascade 2, including a diazine derivative (**13d**). Macrocycles **14a**–**d** were also prepared in good yields from anisole-derivative **6e**; notably, this series includes the formation of furan-containing macrocycle **14d** (Scheme 2E). Considering all reaction series in Scheme 2A–E together, it is notable that little or no variation to the reaction conditions was required to achieve a successful reactions sequence, when compared to the methods used for the previously reported individual reactions.[13,15] Minor modifications to the work-up and purification were required in some cases (associated with the relative instability of intermediates **8a-e**), see SI for details.

 The ability to vary the primary amine freely in cascade 2 is an important feature of our modular approach, as it affords a way to quickly access diversely functionalised macrocycles, often including useful, reactive handles. This means that it is straightforward to envisage further functionalisation reactions for many of the macrocyclic sulfonamides prepared in this manuscript; for example, as a simple demonstration boronic ester containing macrocycle **10c** was converted into **14** via a standard Suzuki-Miyaura cross coupling (SMCC) reaction. The ability to generate macrocycles on scale without resorting to using high dilution conditions is also a key feature of this approach and is demonstrated by scaling up the synthesis of macrocycles **10l** and **11b** to gram-scale, with negligible impact on the isolated yield in each case.



**Scheme 2**  Modular assembly of macrocyclic sulfonamides via consecutive cascade ring expansion reactions. Reaction conditions (see SI for full details): (i) Carboxylic acid **6** (1 equiv.), iPr2NEt (1.85 equiv), T3P (1.5 equiv.), CHCl3, 18 h, RT; (ii) primary amine (≈1.2 equiv.), iPr2NEt or Et3N (≈3 equiv.). THF, RT, 18–96 h; (iii) **10c** (1 equiv.), PhBr (1.5 equiv.), PdCl2(dppf)·CH2Cl2, K3PO4, THF, H2O, 67 °C. T3P = propylphosphonic anhydride

**Conclusion**

In summary, a modular approach has been developed and used to prepare a library of 42 diversely functionalised 13- and 14-membered macrocyclic sulfonamides, via 2 consecutive cascade ring expansion reactions.[18] After synthesis of the linear precursor, cyclisation to form a 5- or 6-membered ring reactive intermediate is followed by ring expansion to a 9/10-membered ring, and then expansion via a different pathway to form a 13- or 14-membered macrocyclic product. Sequentially ‘growing’ the macrocycle via ring expansion reactions in this way – exclusively via 5- or 6-membered ring intermediates – is a key design principle. This ensures that the target macrocycles can be isolated in good overall yields without having to rely on high dilution conditions to avoid intermolecular side reactions. As the toolbox of useful ring expansion reactions grows,[10-12] it is likely that new ways to perform the reactions in parallel, or combine them into single cascade processes, will emerge. As this happens, it is our hope that the use of consecutive ring expansion reactions to ‘grow’ macrocycles will continue to develop, and become established as a go-to synthetic strategy for the synthesis of functionalised macrocycles, as an alternative to high-dilution end-to-end cyclisation.

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**Keywords:** macrocycle • sulfonamide • ring expansion • cascade reaction • rearrangement

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| Methods for the efficient synthesis of macrocyclic sulfur(IV) compounds are rare. In this manuscript, a versatile strategy for the synthesis of macrocyclic sulfonamides is described using a modular three-stage protocol, including two consecutive cascade ring expansion reactions. The utility of this modular approach is showcased via the synthesis of a library of 42 diversely functionalised 13- and 14-membered macrocyclic sulfonamides. |  |  |  | Will E. Orukotan, Ben. J. Knapper, Daniela Dimitrova and William P. Unsworth\*Page No. – Page No.Modular assembly of macrocyclic sulfonamides via consecutive cascade ring expansion reactions |
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