**A consecutive ring expansion strategy towards the macrocyclic core of the solomonamide natural products**

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Abstract A synthetic strategy based on the application of three consecutive ring expansion reactions has been used in the synthesis of analogues of the macrocyclic core of the solomonamide natural products. Starting from a simple, readily available tetrahydrocarbazole, oxidative ring expansion is followed by two further 3- and 4-atom ring expansion reactions, enabling the insertion of amino acid- and hydroxyacid-derived linear fragments into 15–17-membered ring-enlarged macrocyclic products.

**Key words** macrocycles; medium-sized rings; ring expansion; natural product analogues; lactams; lactones; Solomonamides

Solomonamides A and B were first isolated in 2011 by Zampella and coworkers from the marine sponge *Theonella swinhoei*.2 Interest in their total synthesis is influenced by their anti-inflammatory properties, and with natural supplies scarce, total synthesis is necessary to facilitate further biological studies. The original structural assignments of solomonamides A and B are depicted in Figure 1 (**1a** and **1b**). However, following the first synthesis of **1b** by Reddy and coworkers in 2016, a structural reassignment of solomonamide B was made (**2b** – with the highlighted stereogenic centres inverted) and this was confirmed unambiguously by total synthesis.3 Reddy’s work also cast doubt on the original assignment of solomonamide A, and indeed, the Reddy group duly reported its total synthesis and structural reassignment as predicted (**2a**) in 2018.4



**Figure 1** Original and revised structures of solomonamides A and B.

Various other synthetic and associated biological studies focused on the solomonamide natural products have also been reported, by Reddy5 and others.6 Assembly of the macrocyclic core is a key step in the synthesis,7 and unsurprisingly, all syntheses to date have focused on end-to-end macrocyclisation strategies (Scheme 1a). For example, in the seminal reports by Reddy and coworkers3–5 a ligand-free Heck macrocyclisation strategy was adopted, typified by the conversion of linear precursor **3** into macrocycle **4** using Pd(OAc)2.3,8 In contrast, Sarabia and coworkers chose to perform the key macrocyclisation via a ring-closing metathesis reaction, using the Hoveyda–Grubbs second generation (HG II) catalyst. This is typified by the high yielding synthesis of macrocycle **6** from diene **5**.6d,9 Notably, both of these impressive reactions are performed under relatively high dilution conditions, which is a common technique used in macrocyclisation reactions to reduce the impact of competing intermolecular coupling and other side reactions.10

To complement these previous approaches, we were inspired to adopt a completely different strategy, whereby end-to-end macrocyclisation is avoided entirely. Our synthetic strategy is based on the use of three consecutive ring expansion reactions, to allow the solomonamide macrocyclic core to be ‘grown’ from a simple, readily available 6-membered ring precursor **7** (Scheme 1b).11-13 The idea was that following an initial oxidative ring expansion reaction (**7** → **8**), the resulting lactam **8** could then undergo two further ring expansion reactions, using our group’s Successive Ring Expansion (SuRE) methodology,14,15 thus enabling amino acid (when X = NR) or hydroxy acid (when X = O) derivatives of the type **9** and **11** to be inserted into ring enlarged products (**8** → **10** → **12**). The main advantages to this strategy are: i) its overall brevity; ii) the divergent nature of the SuRE method, which means that different amino- and hydroxy-acid fragments can be used to facilitate analogue synthesis; iii) as no direct macrocyclisation reactions are needed, high dilution conditions should not be required. The application of this approach is reported herein. An oxidative ring expansion, followed by two consecutive SuRE reactions allows combinations of α- and β- amino and hydroxy acid derived acid chlorides to be inserted into the ring expanded products. This is showcased through the successful synthesis of six macrocyclic (15–17-membered) solomonamide core analogues of the form **12**.



**Scheme 1** Strategies to synthesis the macrocyclic core of the solomonamide natural products. a) Previous macrocyclisation approaches. b) 3 x consecutive ring expansion strategy (this work).

Our synthesis started with the NaIO4-mediated oxidative ring expansion of commercially available tetrahydrocarbazole **7**, which led to the formation of 9-membered ring lactam **8** in 98% yield, using a method adapted from that of Dolby and Booth (Scheme 2a).16 Attention then moved to applying our group’s SuRE methodology, starting with an Fmoc-based protecting group strategy. Thus, lactam **8** was reacted with acid chloride **13** in the presence of pyridine and DMAP, which resulted in the formation of imide **14** in 80% yield (Scheme 2a). Then, the idea was that cleavage of the Fmoc protecting group under basic conditions (**14** → **15**) would initiate ring expansion (**15** → **16**).14c-e However, despite trialing this reaction under various basic conditions (see ESI for full details) only trace quantities of the desired macrocycle **16** were observed. The main problem was competing ring opening reactions, promoted by intermolecular nucleophilic attack of the imide by the base used to cleave the Fmoc protecting group; for example, linear amides **17a** and **17b** were isolated when using diethylamine and piperidine respectively. The deviation in reaction outcome here, compared with published SuRE reactions, is thought to be due to the increased electrophilicity of the imide carbonyl groups,17 as a result of conjugation with the adjacent electron deficient aromatic system.

To address this problem, we decided to avoid the use of nucleophilic reagents and switched to a Cbz-based protecting group strategy (Scheme 2b). *N*-Acylation of lactam **8** was performed using Cbz-protected amino acid chloride **18** to form imide **19**. Then, following hydrogenolysis, smooth conversion into macrocycle **21** was observed, which was isolated in 56% overall yield from **8**, across the overall *N*-acylation, protecting group cleavage and ring expansion sequence.



**Scheme 2** Ring expansion of **7** and SuRE reaction **1**. a) Fmoc strategy. B) Cbz strategy.

Attention then turned to the second SuRE reaction. Initially, we focused on using the same Cbz protecting group strategy as above. However, attempts to perform the N-acylation of lactam **21** with acid chloride **18** failed, with unreacted **2**1 the major component of the reaction mixture under all the conditions tested (see ESI for details). It is clear that lactam **21** undergoes *N*-acylation less readily than lactam **8**, and in previous work we have found Cbz-protected amino acid chlorides to be less stable than the analogous Fmoc derivatives. As a result, they tend to perform poorly in cases where the *N*-acylation step is slow. Therefore, we reverted to the Fmoc protecting group strategy. Using this method, *N*-acylation of **21** using the more stable Fmoc-protected amino acid chloride **22** proceeded well (based on full consumption of **21** by tlc analysis) to form imide **23**. Imide **23** was then taken directly onto the ring expansion step; thus, following treatment with piperidine in THF, this promoted Fmoc cleavage and subsequent ring expansion to form of 15-membered macrocycle **25** in 30% overall yield from **21**. The problems associated with unwanted intermolecular side reactions observed in the first SuRE reaction were less pronounced in this case, although notably they were still not wholly avoided, with 12-membered lactam **21** being recovered in 24% yield. Notably, **21** was not present after the *N*-acylation step and is therefore believed to result from cleavage of the exocyclic imide C–N bond, likely following nucleophilic attack of the exocyclic imide carbonyl by piperidine. Nonetheless, the successful isolation of **25** meant that the synthesis of the 15-membered solomonamide macrocyclic core had been completed, serving as proof of principle for our consecutive ring expansion strategy.



**Scheme 3** SuRE reaction 2: ring expansion of **21** to form the 15-membered solomonamide macrocyclic core **25**.

One of the most valuable features of the SuRE method is the ability to vary the linear acid chloride to allow straightforward analogue synthesis. This idea is summarised in Scheme 4. Thus, the SuRE of lactam **8** was tested using acid chlorides derived from various Cbz-protected α- and β-amino acids, including a proline-derivative, to form 12–13-membered bis-lactams **21** and **26**–**28** (SuRE method A). The same starting material **8** could also be converted into macrocyclic lactone products **29** and **30**, by acylating with an O-benzyl functionalised acid chloride. In these cases, hydrogenolysis was used to cleave the benzyl protecting group to reveal an alcohol, and following stirring in chloroform with triethylamine at RT, ring expansion took place in the same manner as for the analogous amines (SuRE method C).14d

All products formed via SuRE are potentially viable starting materials for a second SuRE reaction. This is highlighted by the synthesis of 15–17-membered ring solomonamide analogues **25** and **31**–**35** (Scheme 4; in these examples, the linear fragment inserted by the first SuRE reaction is highlighted in red, and the second SuRE reaction in blue). For the insertion of amino acid derivatives, the Fmoc protecting group strategy was used (SuRE method B), with both α- and β-amino acids again being compatible (**25**, **31**–**34**).18 The lactone forming ring expansion (SuRE method C) was also successfully used in the synthesis of 16-membered bis-lactone macrocycle **35**. In the lower yielding cases, most of the mass balance is accounted for by side reactions of the types described in Scheme 2 and 3. Notably, all 12 of the novel macrocyclic products in Scheme 4 were isolated cleanly following column chromatography, and the quoted yields relate to the overall SuRE process of *N*-acylation, protecting group cleavage and ring expansion.



**Scheme 4** A consecutive ring expansion approach for the synthesis of the macrocyclic core of the solomonamide natural products and analogues. [a] SuRE method A: i) lactam (1 equiv.), acid chloride (3 equiv.), pyridine (6 equiv.), DMAP (0.1 equiv.), DCM, 50 °C; (ii) H2, Pd/C, MeOH, RT. SuRE method B: i) lactam (1 equiv.), acid chloride (3 equiv.), pyridine (6 equiv.), DMAP (0.1 equiv.), DCM (0.1 M), 50 °C; (ii) Piperidine in THF, RT. SuRE method C: i) lactam (1 equiv.), acid chloride (3 equiv.), pyridine (6 equiv.), DMAP (0.1 equiv.), DCM, 50 °C; (ii) H2, Pd(OH)2/C or Pd/C, EtOAc, RT; (iii) NEt3, CHCl3, RT

In summary, a new synthetic strategy towards the solomonamide natural products has been established, based on the use of three consecutive ring expansion reactions.19 Compared with previously published syntheses, advantages of this new approach are that it does not require high dilution conditions as end-to-end macrocyclisation is avoided, and its divergent nature. This is exemplified by the synthesis of a series of substituted macrocyclic derivatives, larger ring homologues and lactone analogues.

The isolated yields in this study (especially those in the second SuRE reaction) are lower than those typically observed in our group’s published work;13 this is likely due to the lactam nitrogen being an electron-deficient aniline, which promotes the competing side reactions described. Additional challenges that would need to be overcome to complete the total synthesis of **2a** and **2b** are the preparation of more functionalized, protected analogues of tetrahydrocarbazole **7**, and cleavage of the amide *N*-alkyl groups; the latter would likely be achieved via NBn hydrogenolysis, as NBn substituents have been shown to work well in our earlier SuRE work,14 as well as in this study (compound **26**).Nonetheless, despite some challenges remaining, having validated the overall approach through the synthesis of series of 15–17-membered ring solomonamide analogues, the synthesis the solomonamides A and B should be viable using this approach. Useful insight into additional selectivity challenges when using SuRE to expand electron-deficient amide systems has also been uncovered. Finally, and perhaps most importantly, we hope that this study helps to inspire future syntheses of other macrocyclic target molecules using consecutive ring expansion as a synthetic strategy, as an alternative to end-to-end macrocyclisation.

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Supporting Information

YES (this text will be updated with links prior to publication)

Primary Data

NO.

Conflict of Interest

The authors declare no conflict of interest.

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18. In the cases of products **28** and **33** (both prepared from enantiopure proteinogenic amino acids), the enantiopurity of the products was not measured in this study, but epimerisation is considered to be unlikely based on our previous studies (refs 14), in which such epimerisation was not observed in related systems.
19. **Representative procedure for SuRE method A** (synthesis of **28**): 3,4,5,6-tetrahydro-1H-(1)-benzazonin-2,7-dione 8 (406.4 mg, 2.00 mmol), DMAP (24.4 mg, 0.200 mmol) and pyridine (0.970 mL, 12.0 mmol) in dry DCM (10 mL) under an argon atmosphere were stirred at RT for 30 mins. Next, a solution of acid chloride (6.0 mmol, 3.0 equiv., prepared from Cbz-proline using the procedure described in the ESI) in dry DCM (10 mL) was added and the resulting mixture was heated at reflux (50 °C) for 18 h. The solvent was then concentrated in vacuo, loaded onto a short silica plug and eluted with ethyl acetate, to remove majority of excess carboxylic acid and pyridine residues, and concentrated in vacuo. This material was re-dissolved in MeOH (20 mL) and placed under an argon atmosphere. Palladium on carbon (200 mg, 10% Pd on carbon) was added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at RT under a slight positive pressure of hydrogen (balloon) for 1 h. The reaction was then purged with argon, filtered through Celite, washed with methanol and the solvent was removed in vacuo. Purification by flash column chromatography (SiO2, ethyl acetate) afforded the title compound as a colorless oil (414 mg, 69% over 2 steps from **8**) which exists as a 5:1 mixture of rotamers in solution in CDCl3; [α]D23 ﹣312.13 (c = 1.0, CHCl3); Rf = 0.23 (ethyl acetate); νmax/cm–1 (neat) 3252, 2948, 2242, 1691, 1672, 1602, 1505, 1442, 1299, 1238, 910, 756, 725, 644, 580; δH (400 MHz, CDCl3) 9.43 (s, 1H, NH, major rotamer), 9.34 (s, 1H, NH, minor rotamer), 7.77 – 7.73 (m, 1H, Ph-CH, major rotamer), 7.42 – 7.28 (m, 2H, Ph-CH, both rotamers), 7.20 – 7.14 (m, 1H, Ph-CH, minor rotamer), 7.07 (td, *J* = 7.6, 1.0 Hz, 1H, Ph-CH, major rotamer), 4.31 – 4.20 (m, 1H, NCHCO, both rotamers), 3.78 (dt, *J* = 10.1, 7.0 Hz, 1H, NCH2, major rotamer), 3.60 (ddd, *J* = 11.5, 7.3, 4.3 Hz, 1H, NCH2, minor rotamer), 3.55 – 3.44 (m, 1H, NCH2, both rotamers), 3.07 – 2.78 (m, 2H, CH2, both rotamers), 2.68 – 2.49 (m, 1H, CH2, major rotamer), 2.36 – 2.01 (m, 4H, CH2, both rotamers), 2.02 – 1.61 (m, 5H, CH2, both rotamers); δC (100 MHz, CDCl3) for the major rotamer only: 207.2 (CO), 173.4 (CO), 172.8 (CO), 134.8 (Ph-C), 133.0 (Ph-C), 131.4 (Ph-CH), 126.9 (Ph-CH), 124.5 (Ph-CH), 124.1 (Ph-CH), 62.6 (COCHN), 47.0 (CH2), 41.8 (CH2), 35.1 (CH2), 28.4 (CH2), 25.3 (CH2), 22.6 (CH2), 22.1 (CH2); Diagnostic 13C NMR resonances for the minor rotamer: 204.8 (CO), 172.6 (CO), 172.3 (CO), 135.9 (Ph-C), 133.6 (Ph-C), 127.9 (Ph-CH), 126.0 (Ph-CH), 125.5 (Ph-CH), 61.4 (COCHN), 38.5 (CH2), 31.9 (CH2), 31.6 (CH2), 23.6 (CH2), 23.0 (CH2), 21.2 (CH2); HRMS (ESI): calcd. for C17H20N2NaO3, 323.1366. Found: [MNa]+, 323.1362 (1.3 ppm error). For stereoscopic data and procedures for all novel compounds prepared in this manuscript, see the Supporting Information.

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