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Synthesis of a natural product-inspired eight-membered ring lactam library via ring-closing metathesis

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ABSTRACT

We have prepared a novel speculative eight-membered lactam demonstration library based on the skeletal structure of the potent antitumor marine natural product octalactin A. The basic scaffold was readily constructed in a convergent fashion via ring-closing metathesis chemistry from the corresponding diene amides. A cursory examination of the biological properties of the library validates the relevance and significance of these structures.

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Libraries of compounds based on natural products have gained in importance in recent years.[1,2] Although the structures contained in these libraries tend to be fairly diverse, one class of compound remains to be fully exploited, namely, the monocyclic medium-ring.[3,4] An interesting natural product from the standpoint of structural architecture and biological profile is the powerful antitumor marine natural product octalactin A, **1** (Fig. 1).[5,6] This fascinating natural product which features a rare saturated eight-membered lactone core continues to receive considerable attention in total synthesis efforts from many laboratories.[7]

We have previously constructed this lactone by means of an especially facile and direct lactonization from the corresponding seco acid ('zip-up' approach),[7a,8] and by an equally facile ring-closing metathesis (RCM) route ('zip-down' approach) to afford the unsaturated oxocene.[9] These enabling technologies prompted us to investigate the feasibility of generating a speculative eight-membered ring library inspired by octalactin A.

In order to simplify the synthesis, we elected in the present work to construct a simpler lactam scaffold that at a minimum retained the eight-membered core feature of the octalactins. The strategy is depicted in Scheme 1.

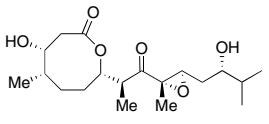

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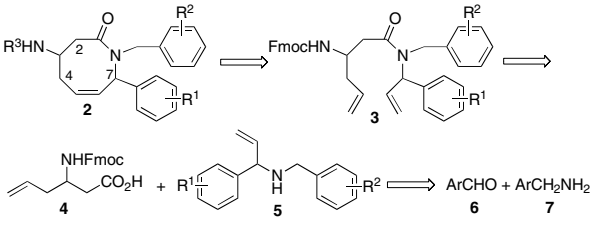
Figure 1. Octalactin A.



Scheme 1. Retrosynthetic analysis of the lactam scaffold.

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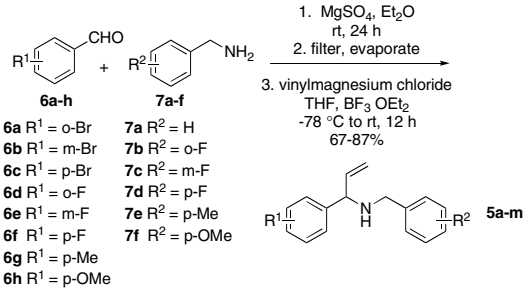
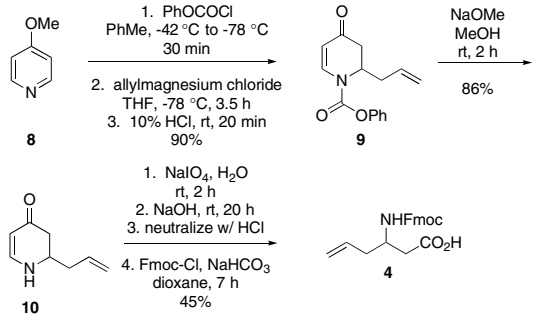
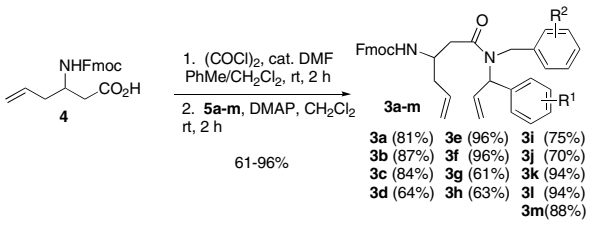


Scheme 2. Synthesis of amine sublibrary **5a–m**.



Scheme 3. Synthesis of Fmoc-protected 3-amino-2-hexenoic acid **4**.



Scheme 4. Diene amide formation via the acid chloride.

The unsaturated lactam scaffold **2** would be constructed by means of RCM. The diene amides **3** would result from the condensation of the racemic Fmoc-protected 3-amino-5-hexenoic acid **4** and the sublibrary of various racemic secondary allylic amines **5**. The allylic amines in turn would be derived from vinyl Grignard addition to the Schiff bases. By using readily prepared racemic components, a mixture of diastereomers **2** would be obtained resulting in a larger library with a relative minimum of effort and cost. Separation of the diastereomeric scaffolds would precede derivitization of the primary amines, thus generating the desired lactam library.

The allylic amine sublibrary was prepared as shown in Scheme 2. Reaction of a series of commercially available benzaldehydes **6a-h** and benzyl amines **7a-f** in ether at room temperature in the presence of magnesium sulfate[10] gave after filtration the Schiff bases in nearly quantitative yield in all cases.

Addition of vinyl Grignard with $BF_3{\cdot}OEt_2$ at −78 °C for 12 h gave a representative 13-member sublibrary in 67–87% yield (Fig. 2).

Synthesis of the racemic Fmoc-protected aminohexenoic acid component **4** was achieved using a modified literature procedure (Scheme 3).[11,12] Addition of allylmagnesium chloride to the acylpyridinium salt formed between 4-methoxypyridine and phenylchloroformate gave the allyl-substituted dihydropyridone carbamate **9** in 90% isolated yield.

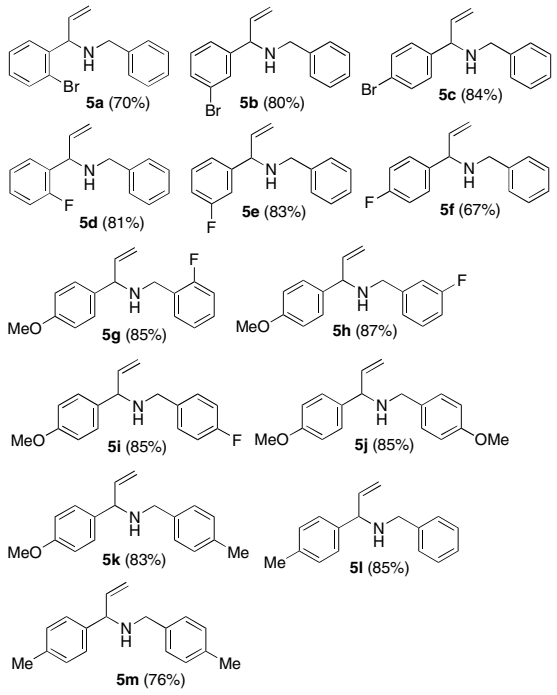
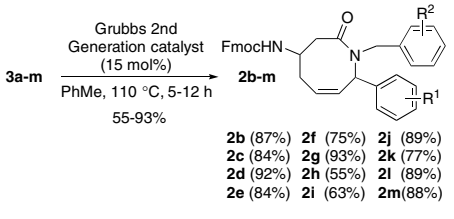


Figure 2. Allylic amines **5a–m**.

Methanolysis of the carbamate to give **10** was achieved in 86% yield. Oxidative cleavage with sodium periodate, followed by basic hydrolysis of the intermediate formamide, and finally Fmoc protection of the resulting primary amine gave **4** in 45% overall yield from **10** on a 5-g scale.

Several methods for the condensation of **4** and **5** were attempted, including DCC coupling,[13] HATU-mediated coupling,[14] activation of the carboxylic acid as its pentafluorophenyl (Pfp) ester,[15] and the in situ generated acid chloride with oxalyl chloride and catalytic DMF.[16] Of these attempts, only the last method (Scheme 4) gave consistent and reliable yields (61–96%) of the amides with our components.

Construction of the eight-membered lactam scaffolds via RCM was investigated next. Although we previously showed that the monocyclic oxocenes in the octalactin series could be obtained via RCM at only 40 °C,[9] no ring closure with the amides **3a–m** was observed at temperatures up to 80 °C. We attribute this observation to an unfavorable amide rotamer population present at these temperatures. Gratifyingly, RCM was eventually effected with 15 mol% of the Grubbs' second-generation catalyst in refluxing toluene for 5–12 h to give a diastereomeric 1:1 separable mixture of lactams **2** in yields ranging from 55% to 93% (Scheme 5). There was no observed cyclization preference for either amide diastereomer, except in the case of **3a** which failed to cyclize, presumably due to the sterically hindered *o*-bromobenzaldehyde moiety. In this manner 24 diastereomerically pure eight-membered lactam scaffolds were obtained on a 20–50 mg scale.



Scheme 5. RCM reaction to give lactam library **2b–m**.

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