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Synthesis of *N*-benzyl-des-*D*-ring lamellarin K via an acyl-Claisen/Paal-Knorr approach

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ABSTRACT

Lamellarin K is a complex pyrrole natural product and member of the lamellarin family – a group of natural products known for their potent biological activities, such as, antiproliferative activity and inhibition of P-gp mediated drug efflux pumps. We herein describe the synthesis of the *N*-benzyl-des-*D* ring analogue of lamellarin K using a route that centres on an acyl-Claisen reaction to eventually prepare a highly-functionalised 1-aryl-4-methyl-1,4-diketone. Paal-Knorr pyrrole formation using this diketone undergoes auto-oxidation to give a fully-substituted 5-formyl pyrrole which was converted into the natural lactone B ring. Antiproliferative testing of the *N*-benzyl-des-*D* ring analogue gave an IC_{50} of 2.63 μM against the MDA-MB-231 breast cancer cell line.

1. Introduction

Lamellarin K (**1**), a member of the lamellarin family of marine alkaloids, is a complex pyrrole natural product (Fig. 1). First isolated in 1993 by Carroll et al. from the *Didemnum* sp. ascidian,[1] lamellarin K (**1**), like all members of the lamellarin family, contains a fused pentacyclic core (rings A-E) with a central pyrrole lactone moiety.[2,3] Differences between members of this family arise primarily as a result of the substituents around rings A, E and the un-fused ring F, as well as the degree of saturation of the C5–C6 bond.

The majority of SAR studies have thus far focused on the most cytotoxic member of the lamellarin family, lamellarin D (**2**),[1,2,4] with other examples of this class remaining largely unexplored. Of further interest, some members of the lamellarin family show *in vivo* multiple drug resistance (MDR) reversal in certain cancer cell lines at sub-cytotoxic concentrations.[2] In many cancer cells, resistance to traditional chemotherapeutic agents is achieved by the encoding of increased numbers of P-glycoprotein (P-gp) drug efflux pumps.[2] Quesada and co-workers were able to show that some members of the lamellarin family act as inhibitors of P-gp mediated drug efflux pumps, thereby maintaining a high concentration of the drug inside cells.[5] Lamellarin K (**1**) is perhaps the best example of this, reported as being one of the most potent members of its class and performing well in cytotoxicity assays in multiple cell lines.[2]

We have previously reported the extensive use of the acyl-Claisen reaction in the synthesis of a number of derivatives, particularly lignan natural products and as precursors to pyrroles.[6–14] We wished to apply this reaction to the complex pyrrole, lamellarin K (**1**), with the goal of creating a synthetic pathway to access various analogues of **1**.

We envisaged that ring B would be formed last by the deprotection of the benzyl group at C-18 and simultaneous cyclisation to give the lactol which would then be subsequently oxidised to the corresponding lactone ring in lamellarin K (**1**) (Fig. 2). Lactol formation would be possible due to the presence of the aldehyde functionality in **3**; we have previously reported the formation of pyrrole aldehydes as autooxidation products of Paal-Knorr cyclisation reactions of highly-functionalised 1,4-dicarbonyl compounds.[6] 1,4-Dicarbonyl **4** was thought to be accessed through the addition of the organolithiate formed from bromide **5** to amide **6**, itself the product of an acyl-Claisen rearrangement between cinnamyl morpholine **7** and acid chloride **8**.

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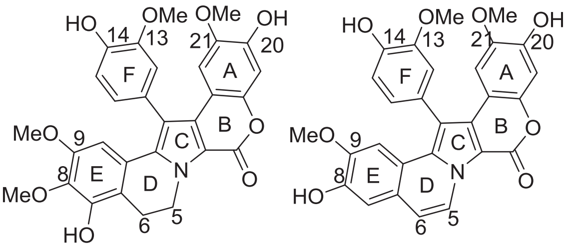

Lamellarin K (**1**) Lamellarin D (**2**)

Fig. 1. Lamellarin K (**1**) and lamellarin D (**2**).

2. Results and discussion

2.1. Synthesis of cinnamyl morpholine **7**

To begin, the first acyl-Claisen component to be synthesised was cinnamyl morpholine **7** (Scheme 1). The synthesis of **7** began from commercially-available 2,4,5-trimethoxybenzaldehyde **9**, which was selectively deprotected at the 2- and 4-positions with $AlCl_3$ to give diphenol **10**. A number of conditions were trialled for the selective isopropyl protection of the 4-hydroxy group of **10**, including bases such as KOH, K_2CO_3 and $CsCO_3$, as well as the use of additives. It was found that $NaHCO_3$,[15] using TBAI as an additive[16] allowed for the synthesis of **11** in good yield, the remaining phenol of which was benzylated in quantitative yield to give benzyl ether **12**. Benzaldehyde **12** was then reacted with vinyl magnesium bromide to give alcohol **13**, which was then converted to an acetate leaving group, giving **14**, ready for the ensuing Tsuji-Trost-type allylic displacement reaction. Cinnamyl morpholine **7** was successfully produced from acetate **14** using conditions similar to those reported by Thiel et al.,[17] reacting **14** with morpholine using $Pd(PPh_3)_4$ as the catalyst, gave **7** in quantitative yield.

2.2. Synthesis of acid chloride **8** and amide **6**

The second acyl-Claisen component to be synthesised was acid chloride **8** and we envisioned commercially-available 3-methoxy-4-hydroxybenzaldehyde **15**, having an appropriate aromatic substitution pattern, would be a suitable starting material. After reduction of the aldehyde functionality of **15**, alcohol **16** was converted to nitrile **17** which was then hydrolysed to **18** under basic conditions (see Scheme 2).[18] The isopropyl protection of the phenolic acid **18** gave ester **19**, which was hydrolysed with LiOH to give carboxylic acid **20** in quantitative yield. Reaction of **20** with $SOCl_2$ provided acid chloride **8** which was used immediately in the acyl-Claisen reaction.

To catalyse the acyl-Claisen reaction between **7** and **8**, a number of Lewis acids were trialed, including $AlCl_3$, $Ti(O\textit{i}Pr)_4$, $Yb(OTf)_3 \cdot xH_2O$ and $Er(OTf)_3$, all of which failed to produce any of the desired product.[12–14] Fortunately, when using $MgBr_2 \cdot OEt_2$, **6** was produced in 93% yield as a single *syn* diastereoisomer. The reactants in this acyl-Claisen rearrangement have more alkoxy group substituents than all previous examples of this reaction. The highly coordinating $MgBr_2 \cdot OEt_2$ appears to be favoured for reactions containing these groups.[11] *Syn*-diastereoisomers are formed preferentially in acyl-Claisen reactions due to the formation, and rearrangement, of zwitterionic *Z*-enolates; generally less than 5% of the *anti* product is formed when *trans* allylic amines are used.[12]

2.3. Synthesis of arylbromide **5**

The last aryl component to be synthesised was aryl bromide **5** (Scheme 3). Beginning with *o*-vanillin **21**, selective bromination using activated silica, CAN and Br_2 in CCl_4[19] gave bromide **22** in 81% yield. Methylation of phenol **22**, giving **23**, allowed for the Dakin oxidation of the aldehyde moiety of **23** to give phenol **24** which was then allylated to give **25** in 67% yield over the five steps. Allyl ether **25** then underwent a Claisen rearrangement to provide allyl phenol **26** which was converted to isopropyl ether **27**. Dihydroxylation of the allyl group in **27** provided diol **28** which then underwent

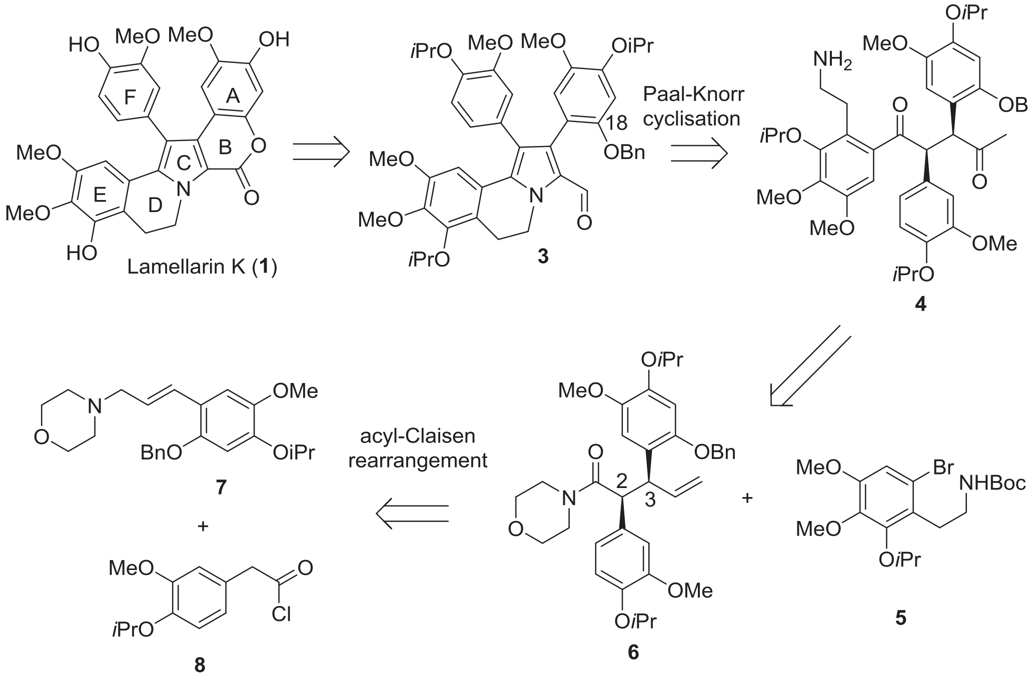

Fig. 2. Retrosynthetic plan to lamellarin K (**1**).

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