

Total Synthesis of Ovafolinins A and B: Unique Polycyclic Benzoxepin Lignans through a Cascade Cyclization

Angew. Chem. Int. Ed. **2017**, *56*, 9483–9486

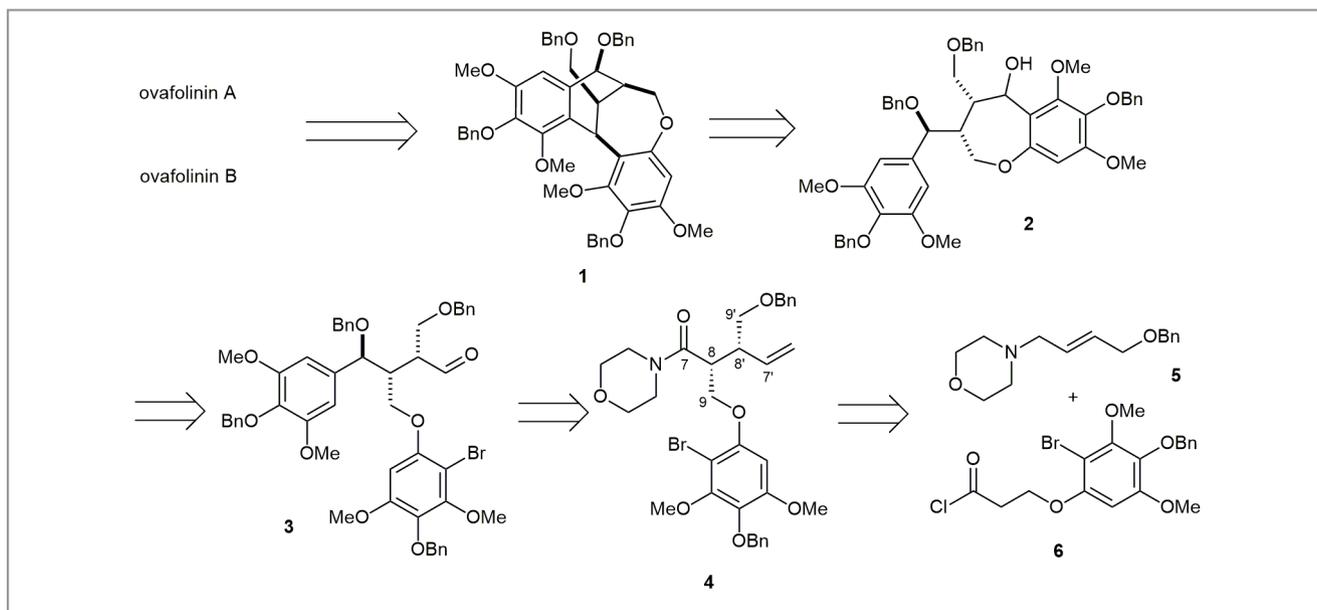
Since 2009, the research group of Professor David Barker at the University of Auckland (New Zealand) has been interested in the use of the acyl-Claisen rearrangement and its application to the synthesis of lignan natural products. Professor Barker said: “We have previously used this approach to synthesise a number of different lignan subclasses including tetrahydrofuran lignans such as galbelgin¹ and magnosalicin,² diarylbutanol lignans (kadangustin³) and aryl tetralin lignans (such as cyclogalgravin¹ and isoguaiacin⁴).”

He continued: “In this case we wished to demonstrate the utilisation of these strategies in a complex example. Ovafolinins A and B represent unique structural targets as they are the only examples of lignan natural products containing a seven-membered benzoxepin penta- or tetracyclic scaffold, respectively. This would allow us to determine the power and utility of our approach to complex natural products.” The group began the synthesis in 2014 by developing a retrosynthetic plan which aimed to form the six-membered tetrahydronaphthalene ring of the polycyclic structure **1** after the seven-membered benzoxepin ring in **2** (Scheme 1). “The rationale for this approach was that the seven-membered ring

could be formed through an intramolecular cyclisation of an open-chain precursor **3** more easily at this stage rather than trying to form it in a constrained tricyclic molecule,” explained Professor Barker. The open-chain precursor **3** would be accessed from an acyl-Claisen derived amide **4**, synthesised from a substituted allylic morpholine **5** and β -phenoxy acid chloride **6**.

The synthetic steps to prepare **5** and **6** worked very well, as the group expected, giving them the required starting materials to attempt the acyl-Claisen rearrangement. “Unfortunately, we were to discover that the main isolated product from this reaction was a substituted acrylate, which we thought was a very complicated and redundant way to form such compounds,” commented Professor Barker. He continued: “Further model studies showed that all acid chlorides containing a β -alkoxy group underwent the same unwanted reactions and did not undergo the acyl-Claisen reaction. This led us to redesign our synthesis, still utilising the acyl-Claisen rearrangement but altering the reaction substrates.”

In the group’s initial approach, the mapping of carbons of the final structures onto amide **4** would be as shown in

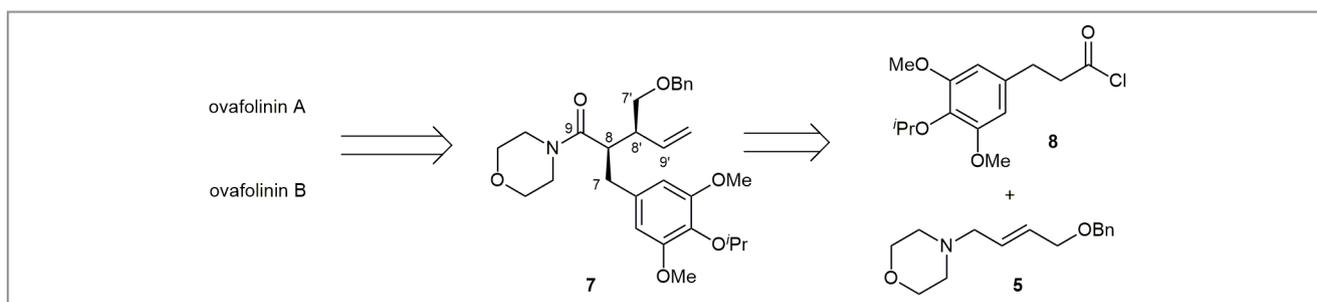


Scheme 1 Initial retrosynthetic approach to ovafolinins A and B

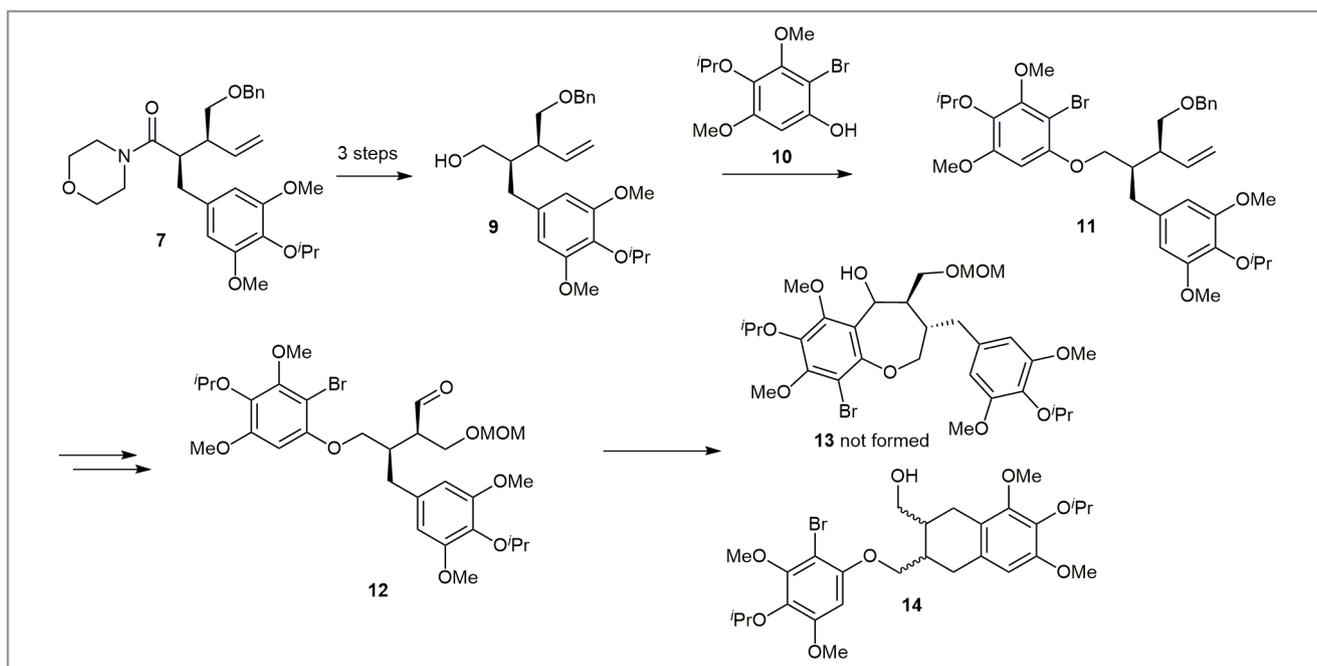
Scheme 1. “We envisaged that it would be possible to remove the troublesome β -alkoxy fragment (C-8 to C-9) and instead form amide **7** (Scheme 2), which contains a substituted benzyl group at C-8,” said Professor Barker. “This would require that the amide would eventually become C-9 in the final compounds. Additionally, because of this interconversion, the original mapping of C-7' and C-9' would be swapped to retain the same relative stereochemistry. We envisaged, based on our previous experience with this reaction,^{5,6} that it would be much easier to form amide **7** from **5** and newly prepared acid chloride **8**.”

Synthesis of acid chloride **8** was easily achieved from syringaldehyde and the authors of this study were pleased to find that its acyl-Claisen rearrangement with amine **5**

proceeded to give the desired amide **7** in almost quantitative yields as a single diastereoisomer. Professor Barker said: “Conversion of the amide group in **7** into the desired primary alcohol **9** was achieved over three steps (iodolactonisation, reductive ring opening and finally reduction of the carboxylic acid) using a strategy we have previously used (Scheme 3).⁷ Mitsunobu reaction of phenol **10** (which was also prepared from syringaldehyde) and alcohol **9** gave ether **11**, which had then effectively added the phenoxyethyl moiety which could not be accessed via our original acyl-Claisen route. Oxidation/periodate cleavage followed by reduction of the alkene in **11** gave a primary alcohol, which was initially protected as a MOM ether. We chose this protecting group as we have previously found it to be highly compatible with our lignan



Scheme 2 Revised retrosynthetic approach to ovafolinins A and B



Scheme 3 Attempted synthesis of benzoxepin **13**

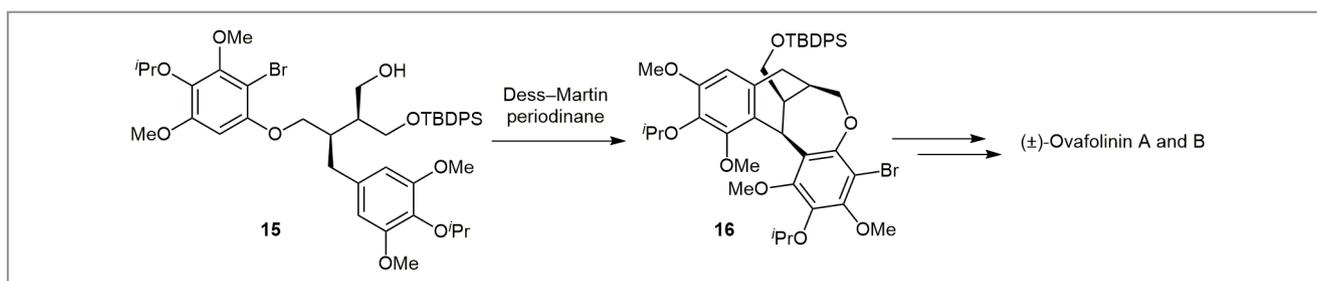
syntheses, as generally there is an acid-catalysed step during which the MOM group is removed, effectively reducing the synthesis by one step. Unfortunately we were to discover that in this case the MOM group in aldehyde **12** was incompatible with the intramolecular cyclisation step to form the seven-membered benzoxepin **13**, with tetrahydronaphthalene **14** being the only compound obtained in appreciable amounts. This led us to investigate this process using molecular modelling where we found that if a protecting group larger than a MOM was used, it appeared that the aryl bromide and aldehyde functionalities would be in very close proximity which we believed would help facilitate the desired cyclisation.”

It was then decided to use a large TBDPS protecting group, which gave the theoretical best geometry between the two reactive sites. After preparation of the TBDPS-protected cyclisation precursor, alcohol **15**, the group expected that its oxidation would give the corresponding aldehyde, ready to test their cyclisation theory (Scheme 4). Professor Barker revealed: “However, we were delighted to find that under the oxidation conditions we did not obtain the aldehyde but instead, fortuitously, the tetracyclic framework of ovafolinin B (**16**). This was a pleasant surprise but highlights the highly electron-rich nature of these compounds and shows that if the reactive groups are placed in the correct orientation then these lignan-like molecules are formed in a biosynthetic-like manner. This was further seen when, upon removal of the protecting groups from **16**, not only was ovafolinin B formed, but also the formation of the final tetrahydrofuran ring was induced to give ovafolinin A. After all the challenges of setting up the linear precursors for these compounds, we were very happy to have these key ring-forming steps occurring so readily and under such mild conditions.”

Following this, the group embarked on an enantioselective synthesis of ovafolinins A and B. Professor Barker explained that there are no existing relevant examples of asymmetric acyl-Claisen reactions, with the only well-studied examples requiring α -alkoxy groups which unfortunately were not ap-

plicable to this synthesis.⁸ “We tried a number of different approaches to asymmetrically prepare the debromo analogue of linear precursor **15**, many of which were unsuccessful. Finally, we resolved this by using a route based on an Evans asymmetric alkylation,” said Professor Barker. He continued: “Luckily, the approach worked well, with the only problem being the selective functionalisation of the diol (compound **28** in the paper) where all efforts to efficiently monosilylate it gave an inseparable mixture of regioisomers.” Fortunately, the Auckland-based researchers were able to separate the desired isomer after the Mitsunobu reaction. “This gave us our linear precursor as a single enantiomer which was then successfully converted into (+)-ovafolinins A and B,” said Professor Barker. The natural products had originally been assigned their absolute stereochemistry based on their CD (circular dichroism)^{9,10} spectra; however, the synthesis showed that the assignment was incorrect. “This is not the first time we have discovered that the use of CD to assign absolute stereochemistry in lignan natural products has led to an incorrect assignment,¹¹” remarked Professor Barker. “We believe that in many cases it is the fact that the CD spectra of these natural products are compared to those of highly simplified compounds that leads to these incorrect assignments, which unfortunately is routinely used on this class of natural products.”

When the optical rotation values of the synthetic compounds were analysed and compared to the natural ones, the group was intrigued to see that their compounds had a significantly higher magnitude of rotation and that the natural compounds had been reported with opposite signs. “As our synthesis showed that these natural products are easily interconverted, we would have expected them to have the same sign of rotation like our synthetic samples,” explained Professor Barker. The NMR spectra of the originally isolated natural products did not suggest the presence of other impurities which could have altered the optical rotation. Therefore, to account for the differences in rotation, the group postulated that the natural compounds are derived from a racemic pre-



Scheme 4 Final steps to (±)-ovafolinins A and B

cursor, potentially ovafolinin B, one enantiomer of which may have been preferentially oxidised to ovafolinin A. This could account for the apparently scalemic nature of the natural products and their opposite signs.

“This work has highlighted the acyl-Claisen rearrangement as a powerful synthetic tool to prepare complex structures with its high level of diastereoselectivity combined with its ease of modifying the substituents being key advantages,” said Professor Barker, continuing: “In the end it was our insightful analysis of the products during the MOM-protected synthesis that led us to the critical finding that the linear precursor could be coaxed into a reactive conformation by use of an alternate protecting group. Without the molecular modelling we may just have easily embarked on a different synthetic route which may or may not have eventually been successful.” He concluded: “We aim now to use this approach to form other members and analogues of the ovafolinin family as well utilising these methods for the synthesis of other complex natural products.”

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About the authors



Prof. D. Barker

David Barker was born in Altrincham (UK). After moving to Australia, he graduated from the University of Sydney (Australia) with a BSc degree (Honours, First Class) and then completed his PhD in 2002 at the same university. After postdoctoral research at the School of Medical Sciences at the University of New South Wales (Australia), he joined the University of Auckland (New Zealand) as a lecturer. He is currently an Associate Professor in Organic and Medicinal Chemistry and he has a diverse range of synthetic interests including biologically active natural products, drug discovery, and development of novel polymeric scaffolds.



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Samuel J. Davidson was born in Auckland (New Zealand). He graduated in 2012 from the University of Auckland (New Zealand) with a BSc in medicinal chemistry. Samuel then went on to graduate with a BSc (Honours, First Class) in 2013. He is currently completing his PhD at the same university under the supervision of Associate Professor David Barker.