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The First Total Synthesis of Ovafolinin A and B: Unique Polycyclic Benzoxepin Lignans *via* a Cascade Cyclization

Samuel J. Davidson and David Barker*[a]

Abstract: Ovafolinins A and B, isolated from *Lyonia ovalifolia* var. elliptica, are lignans which contain a unique penta- and tetracyclic benzoxepin bridged aryl tetralin structure. We report the first total synthesis of these natural products initially utilizing an acyl-Claisen rearrangement to construct the lignan backbone with correct relative stereochemistry. Judicious use of a bulky protecting group placed reactive moieties in the correct orientation resulting in a cascade reaction forming the benzoxepin bridged aryl tetralin from a linear precursor in a single step. Modification of this route allowed an enantioselective synthesis of (+)-ovafolinin A and B which confirmed the absolute stereochemistry and comparison of optical rotation suggests these compounds are found as scalemic mixtures in nature.

Ovafolinins A–C (**1**–**3**) isolated from *Lyonia ovalifolia* var. elliptica; a deciduous tree found in areas of Taiwan, China and Japan, are classical lignans that have a unique 7 membered benzoxepin bridged aryl tetralin structure (Figure 1).[1] Ovafolinin B (**2**) has also been isolated from *Sinocalamus affinis* (Rendle) McClure (Poaceae)[2] which is found and cultivated in the southwest of China and much of the plant has been used as a traditional Chinese medicine.[2,3] We have previously shown[4–6] that the acyl-Claisen rearrangement,[7,8] which has excellent diastereoselectivity when compared to many other Claisen variants, is a useful transformation to construct the 8–8′ linkage present in classical lignans (Figure 2).[4,5]

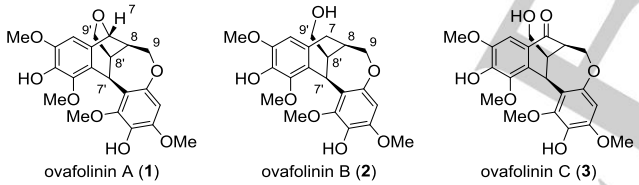

Figure 1: Structures of ovafolinins A–C (**1**–**3**)

We now report the use of acyl-Claisen methodology to prepare the unique lignan scaffolds found in ovafolinin A–C (**1**–**3**). It was envisaged that this could be accomplished through the acyl-Claisen rearrangement of oxygenated allylic morpholine **4** and acid chloride **5** to give an oxymethylene disubstituted amide **6**. Stereoselective addition of the appropriately substituted aryl groups, directed by the defined stereochemistry of amide **6**, and cyclizations therein would allow for a convenient approach to the synthesis of ovafolinin A–C (**1**–**3**) (Figure 3).

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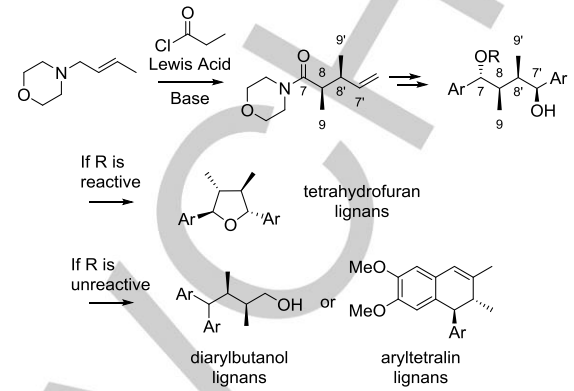

Figure 2: Acyl-Claisen approach to the synthesis of lignan subclasses.

Our initial approach involved the reaction of allylic morpholine **4** and acid chloride **5** (see Scheme SI1 and SI2 for synthesis) to give morpholine amide **6** (Figure 3). However, this resulted in the formation of acrylate **7** when using $AlCl_3$ or phenol **8** when using $TiCl_4{\cdot}2THF$ which is likely due to the reactivity of the formed ketene with the very electron rich aryl group promoting rearrangement (Table 1). A screen of various acid chlorides showed oxygenation at the β–position gave only trace amounts of amide products however alkyl (**9**–**10**), vinyl (**11**), and aryl (**12**) groups as well as oxygenated allylic morpholine **4** were well tolerated in the acyl-Claisen rearrangement (Table 1).

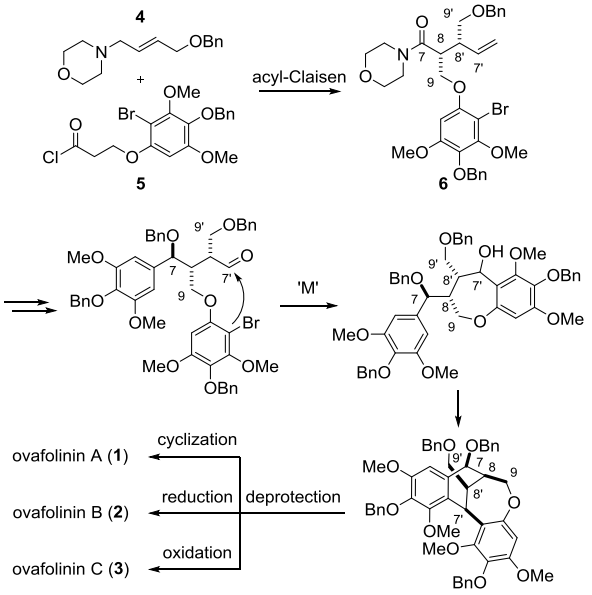

Figure 3: Initial synthetic approach to ovafolinin A–C (**1**–**3**).

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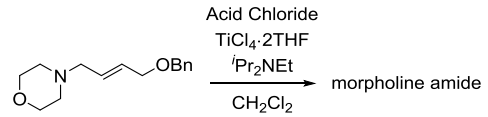
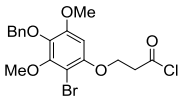
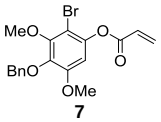
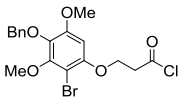
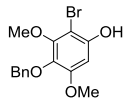
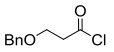
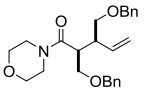
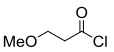
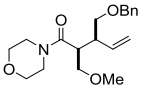
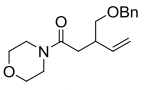
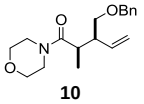
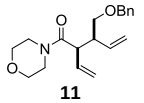
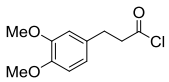
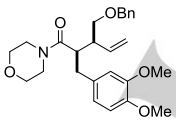


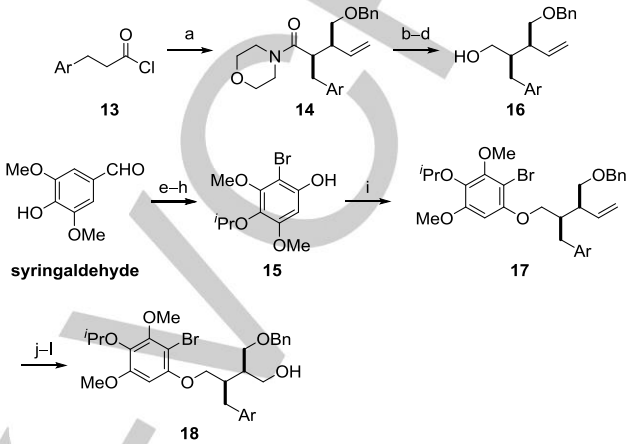
Table 1: Acyl-Claisen attempts towards ovafolinin B.

Acid Chloride	Product	Yield
	 **7**	24%[a,c]
	 **8**	n.d.[b]
		trace[b]
		trace[b]
	 **9**	95%[c]
	 **10**	>99%[c]
	 **11**	91%[c]
	 **12**	90%[c]

a) $AlCl_3$ was used in place of $TiCl_4$·2THF
b) Identified by ^1H NMR spectroscopy
c) Isolated yields
n.d. - yield not determined

Based on the results of this acyl-Claisen study, a new synthetic method towards the synthesis of ovafolinin B was investigated utilizing acid chloride **13** which was synthesized over five high yielding steps (Scheme SI3) and reacted with allylic morpholine **4** to give morpholine amide **14** as a single diastereoisomer, in excellent yield, (Scheme 1). An isopropyl protecting group was used on phenol **15** as opposed to the previous benzyl protecting group strategy which would need to be selectively removed to form the reactive aldehyde site.

Following synthesis of morpholine amide **14**, the amide functionality was converted to alcohol **16**, over three steps, then coupled to phenol **15** – synthesised from syringaldehyde in four steps – in a Mitsunobu reaction to give aryl ether **17**. The olefin was then converted to alcohol **18** in 84% over three steps *via* alkene oxidation followed by reduction.



Scheme 1: Reagents and conditions: (a) $TiCl_4$·2THF (100 mol%), **4**, $^iPr_2NEt$, CH_2Cl_2, 3 h, 99%; (b) I_2, THF/H_2O (1:1), 16 h; (c) Zinc dust, AcOH, 80 °C, 19 h 96% (2 steps); (d) $LiAlH_4$, THF, reflux, 3 h, 97%; (e) K_2CO_3, ^{i}PrBr, DMF, 80 °C, 17 h, 99%; (f) *m*-CPBA, CH_2Cl_2, 0 °C, 22 h; (g) KOH, MeOH, 10 min, 57% (2 steps); (h) NBS, CH_2Cl_2, -78 °C, 1 h, 73% (3 steps); (i) Ph_3P, DIAD, **16**, toluene, 18 h, 82%; (j) OsO_4 (2.5 mol%), NMO, ^{t}BuOH/H_2O (1:1), 5 d, 94%; (k) $NaIO_4$, MeOH/H_2O (3:1), 30 min, 92%; (l), $NaBH_4$, MeOH, 2 h, 97%.

Initial attempts at the synthesis of ovafolinin B from alcohol **18** involved the use of a methoxymethyl protecting group, however these compounds were unstable and lead to decomposition products (scheme SI4). The more stable and bulky *tert*-butyldiphenylsilyl (TBDPS) group was trialed in order to avoid decomposition, while simple modelling also suggested that a TBDPS group at C-9′ should result in the aldehyde being closer in proximity to the two aromatic rings which we believed should increase subsequent reactivity (Figure 4).

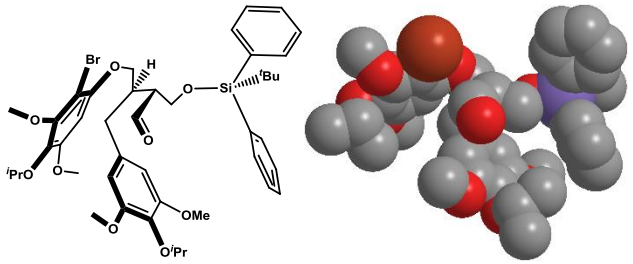


Figure 4: 3D stick and space filling models of TBDPS derivative structure of **17** showing proximity of aldehyde to the two highly oxygenated aromatic rings: C = gray, O = red, Si = purple, Br = brown, hydrogen atoms not shown.

Therefore, alcohol **18** was protected as TBDPS ether **19** and hydrogenation gave an inseparable mixture of brominated and debrominated alcohol **20**. Dess-Martin periodinane oxidation of

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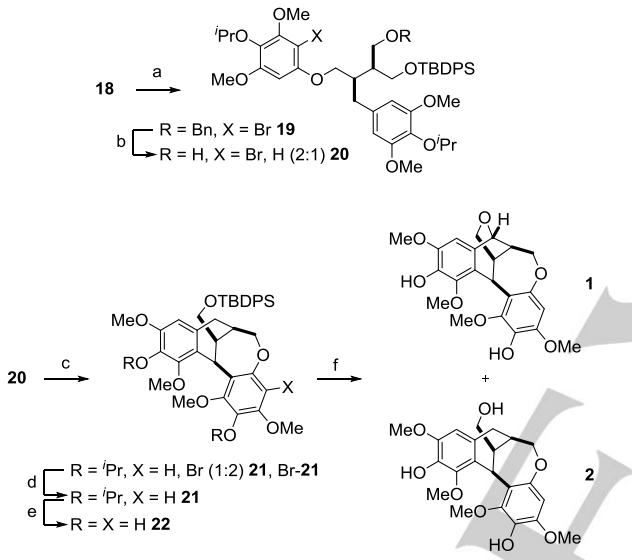
20 then resulted in formation of the aldehyde which underwent a cascade cyclization (Figure SI1) during workup to give protected ovafolinin B (**21**) and bromo-**21** which were easily separable. We propose that the mildly acidic conditions following the periodinane oxidation combined with the proximity of the aldehyde to both aromatic rings due to the steric effects of the TBDPS group enabled a cascade cyclization to give the tetracyclic ovafolinin B skeleton (Scheme 2). Benzylic oxidation of **21** was attempted using PCC-Celite which has been shown to oxidize other tetralin lignans.[9] However, in this case the highly oxygenated aromatic ring was instead oxidized to give a ring opened diester (scheme SI5). To our knowledge this is the first example of a chromium-based oxidant leading to the oxidative ring-opening of an aryl ring and opens up synthetic routes towards lignans containing similar oxidatively opened rings.[10–13]

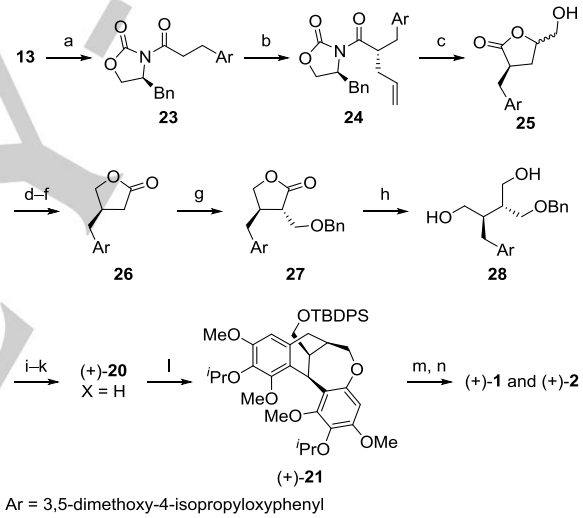


Scheme 2: Reagents and conditions: (a) TBDPSCl, imidazole, DMF, 0 °C, 4 d, 92%; (b) H_2, Pd/C, MeOH, 4 h, 99%; (c) DMP, CH_2Cl_2, 1 h, Br-61%, H-28%; (d) HCO_2NH_4, Pd/C, MeOH, reflux, 5 h, 99%; (e) $AlCl_3$, CH_2Cl_2, 10 min, 88%; (f) TBAF, THF, 0 °C, 5 h, (**1**) 19%, (**2**) 25%.

Debromination of **21** and deprotection gave phenol **22**. Removal of the TBDPS ether in **22** surprisingly gave not only ovafolinin B (**2**) but also ovafolinin A (**1**). It was unanticipated that TBAF would result in the oxidative-cyclization to give pentacyclic ovafolinin A (**1**) alongside ovafolinin B (**2**) and suggests the highly electron-rich **2** can undergo aerial oxidation to form **1**. Comparison of NMR data (table SI1) of synthetic **1** and **2** to that of isolated **1** and **2** confirmed the reported structures of these polycyclic natural products.[1,2] Ovafolinin B (**2**) has been isolated from two different plant sources with similar reported optical rotations.[1,2] Whilst the initial report proposed only relative stereochemistry further analysis by Xiong *et al.*[2] proposed the absolute stereochemistry through the use of circular dichroism (CD).

Following the successful racemic synthesis of **1** and **2** an enantioselective synthesis was then attempted to determine the absolute stereochemistry of these natural products. Initial attempts at an enantioselective aza-Claisen rearrangement[4,14] were unsuccessful (see Scheme SI6). Coupling of the carboxylic acid, formed from the hydrolysis of racemic amide **14**, to chiral amine (*S*)-(–)-α-methyl-benzylamine gave an inseparable mixture of diastereomers confirming that had the chiral aza-Claisen been successful the diastereomers formed would not have been separable, which is in contrast to previous aza-Claisen derived amides.[4,14] Therefore, a new strategy was designed using an Evan's chiral auxiliary to which a stereoselective allylation would allow for the induction of the desired stereocenters (Scheme 3).

Synthesis began using acid chloride **13** with acylation of (*S*)-4-benzyloxazolidin-2-one giving **23**, followed by a stereoselective allylation,[15,16] giving (+)-(*S,S*)-**24** in 78% yield with >97:3 d.r.. Dihydroxylation of olefin **24** then gave lactone **25**, with concomitant removal of the chiral auxiliary, followed by a reduction and two oxidative steps gave lactone **26** in 52% yield over 4 steps.



Scheme 3: Reagents and conditions: (a) (*S*)-4-benzyloxazolidin-2-one, ^{n}BuLi, THF, -78 °C, 1 h, 74%; (b) LiHMDS, THF, -78 °C, 4 h, 78%; (c) OsO_4 (1 mol%) NMO, ^{t}BuOH/THF/H_2O (1:1:1), 44 h, 86%; (d) $LiAlH_4$, THF, 3 h; (e) $NaIO_4$, MeOH/H_2O (3:1), 1 h; (f) Fétizon's reagent, toluene, reflux, 5 h, 61% (3 steps); (g) BOMCl, LDA, THF, -78 °C, 18 h, 47%; (h) $LiAlH_4$, THF, 0 °C, 9 h, 94%; (i) TBDPSCl, imidazole, CH_2Cl_2, 19 h; (j) Ph_3P, DIAD, 4-isopropoxy-3,5-dimethoxyphenol, 0 °C, 17 h; (k) H_2, Pd/C, MeOH, 16 h, 20% (3 steps); (l), DMP, CH_2Cl_2, 1 h, 87%; (m) $AlCl_3$, CH_2Cl_2, 0 °C, 20 min, 79%; (n) TBAF, THF, 0 °C, 2 h, (**1**) 17%, (**2**) 17%.

The desired benzyloxymethyl group was then introduced to lactone **26** through stereoselective alkylation to give lactone **27** which followed by reduction gave diol **28** in 44% yield over two steps with a >95:5 d.r.. Mono-TBDPS protection of diol **28** gave a 1:1 inseparable mixture of regioisomers. However, a subsequent Mitsunobu reaction with 4-isopropoxy-3,5-dimethoxyphenol and hydrogenolysis of the benzyl protecting group gave (+)-debromo-**20** in 20% yield over three steps, easily separable from the regioisomer. With (+)-**20** in hand, oxidation

with Dess-Martin periodinane facilitated the cascade cyclization to give tetracyclic **21** in 87% yield. Subsequent deprotections gave (+)-ovafolinin A (**1**) and (+)-ovafolinin B (**2**) over two steps both with >99:1 d.r.. The sign of the optical rotation of synthetic-**1** was found to be opposite to that of natural-**1**, with the magnitude being approximately three times greater: synthetic-**1** +154.8 (c 0.16, MeOH), natural-**1** –37.3 (c 0.36, MeOH).[1] Synthetic-**2** has the same sign of rotation as natural-**2** but again the magnitude of rotation was three times greater: synthetic-**2** +150.0 (c 0.26, MeOH), natural-**2** +52.0 (c 0.26, MeOH)[1] and +43.3 (c 0.12, MeOH).[2]

The absolute stereochemistry of synthetic **1** and **2** is *7R,8R,7'R,8'R* and *8R,7'R,8'R* respectively. Based on the optical rotation data we propose that these natural products were actually isolated as scalemic mixtures with natural-**1** being found predominantly as the *7S,8S,7'S,8'S* enantiomer whilst natural-**2** is predominantly found with the same absolute stereochemistry as that synthesized. It is possible that racemic **2** is the first formed natural product and that the *8S,7'S,8'S* enantiomer is preferentially oxidized to give **1** enriched in the *7S,8S,7'S,8'S* enantiomer, i.e. (–)-**1**, thus leaving **2** to be enriched in the opposite enantiomer, (+)-**2**. The absolute stereochemistry of (+)-**2** was proposed using CD analysis to be *8S,7'S,8'S* however this has been shown to be incorrect, with this synthesis determining the absolute stereochemistry of natural (+)-**2** to be *8R,7'R,8'R*. This is a further example where the use of CD as the sole determining method for the absolute stereochemistry in complex lignans has been shown to give incorrect assignments.[17]

In summary the unique polycyclic structures of both ovafolinin A (**1**) and B (**2**) have been confirmed through the use of a high yielding synthesis resulting in 9% and 11% overall yield from allylic morpholine **4** over 14 linear steps respectively and utilizes a spontaneous cascade cyclization giving the tetracyclic structure in a single step. Following the confirmation of the relative stereochemistry of **1** and **2** an enantioselective synthesis was used to determine the absolute stereochemistry of these complex natural products. This synthesis was also achieved in 14 steps with an overall yield (0.3% each of **1** and **2**) with the reduced yield being due to the difficulty transforming **28** to (+)-**20**. From these findings it is proposed that natural-**1** and **2** are present as scalemic mixtures and may be formed through the preferential oxidation of one enantiomer *in vivo*. Furthermore, the original stereochemical assignment of ovafolinin B (**2**) using CD spectra was shown to be incorrect highlighting the use of synthesis in conclusively determining absolute stereochemistry in complex natural products.

Acknowledgements

We acknowledge the University of Auckland for funding and a Doctoral Scholarship (S.D.).

Keywords: lignan • tetralin • benzoxepin • acyl-Claisen • cascade cyclization

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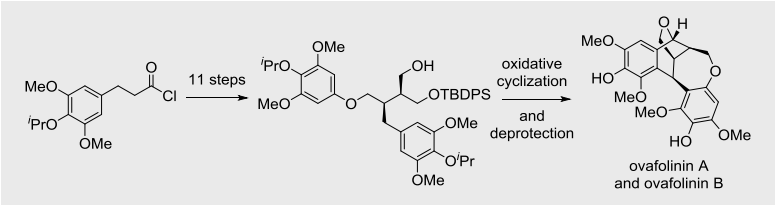

Ovafolinins A and B, isolated from *Lyonia ovalifolia* var. elliptica, contain a unique penta- and tetracyclic benzoxepin bridged aryl tetralin structure. These natural products have been synthesized utilizing an acyl-Claisen rearrangement and a cascade cyclization forming the benzoxepin bridged aryl tetralin and a subsequent enantioselective synthesis of ovafolinin A and B has assigned the absolute stereochemistry of these natural products.

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