



## Asymmetric total synthesis of (+)-ovafofinins A and B†

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**(+)-Ovafofinins A and B are two homologous lignans containing unique polycyclic skeletons. Benefiting from a highly diastereoselective alkylation of (S)-Taniguchi lactone, a double Friedel–Crafts reaction, a global debenzoylation and a Cu(OAc)<sub>2</sub>-enabled benzylic oxidative cyclization, we present herein an efficient synthetic approach to (+)-ovafofinins A and B.**

Lignans are a large family of natural products widely existing in plants and our food sources, such as wheat, soybeans, broccoli and strawberry.<sup>1</sup> Many important biological properties including anticancer,<sup>2</sup> antiviral,<sup>3</sup> and antioxidant activities,<sup>4</sup> alleviating menopausal symptoms, and reducing the risk of cardiovascular disease<sup>5</sup> have been disclosed from biological evaluations of this family. In 2010, ovafofinin A, ovafofinin B and other three lignans were discovered during Yun and coworkers' explorations on *Lyonia ovalifolia* var. *elliptica*, a deciduous tree growing in China and Japan.<sup>6</sup> Ovafofinin B was also found in *Sinocalamus affinis* (Rendle) McClure (Poaceae),<sup>7</sup> a widely cultivated traditional Chinese medicine named "Ci Zhu Li" and applied in treatments for diseases including cough and phlegm in China.<sup>8</sup> Structurally, ovafofinin A has a particular polycyclic skeleton containing an aryl tetralin unit with a tetrahydrofuran motif and a seven-membered benzoxepin bridged-ring. Ovafofinin B possesses a very similar framework except for the opening of the tetrahydrofuran ring. The first asymmetric synthesis of (+)-ovafofinins A and B was achieved by Barker and co-workers<sup>9</sup> employing an acyl-Claisen rearrangement developed in their laboratory.<sup>10</sup> The unique polycyclic skeleton was achieved through an interesting cascade cyclization enabled by a bulky protecting group. As a pioneering work, Barker and coworkers' synthesis demonstrated an expedient pathway to the unique skeleton of (+)-ovafofinins A and B. Furthermore, based on optical rotation comparisons between the synthetic

compounds (+154.8 ( $c = 0.16$ , MeOH) for (+)-ovafofinin A, +150.0 ( $c = 0.26$ , MeOH) for (+)-ovafofinin B)<sup>9</sup> and the natural samples (−37.3 ( $c = 0.36$ , MeOH) for ovafofinin A, +52.0 ( $c = 0.26$ , MeOH)<sup>6</sup> and +43.3 ( $c = 0.12$ , MeOH)<sup>7</sup> for ovafofinin B), the exploration convincingly suggested that natural ovafofinins A and B were both isolated in scalemic mixtures. Attracted by their architectural complexity, we started our synthesis with the purpose of devising a new, efficient, and asymmetric route to these lignans.

Based on our retrosynthetic analysis (Fig. 1), (+)-ovafofinin A (1) and (+)-ovafofinin B (2) could be constructed from three building blocks: phenol 5, bromide 8 and (S)-Taniguchi lactone 9. Diastereoselective alkylation between 9 and 8 will be a feasible strategy to set up initially two stereogenic centers of 1 and 2. For introduction of the top-right aromatic ring and formation of the central six-membered ring, a double Friedel–Crafts reaction process between 5 and 6 was originally proposed. Intramolecular Friedel–Crafts hydroxyalkylation of 6 could furnish the central six-membered ring first. Subsequently, intermediate 4 could be formed from a diastereoselective intermolecular Friedel–Crafts alkylation with 5. As a related precedent, Takayama and coworkers reported an expedient construction of complex bridged ring frames through a double Friedel–Crafts reaction between acetal and two different aromatic rings.<sup>11</sup> Regarding the construction of the seven-membered benzoxepin bridged-ring unit, we imagined that dehydration cyclization in 4 could be a reasonable solution. Three benzyl protecting groups were designed in 3 for the convenience of synthesis. In light of the close structural relationship of 1 and 2 and their simultaneous generation in the synthesis by Barker and coworkers, we envisaged that 1 could be obtained through benzylic oxidative cyclization of 2.

Our synthesis started with the preparation of bromide 8 (Scheme 1). The starting material was the commercially available syringaldehyde (10). After benzyl protection, reduction and bromination, 8 was obtained in 66% overall yield. The diastereoselective alkylation of (S)-Taniguchi lactone (9) is a reliable strategy to introduce two adjacent stereogenic centers with defined absolute and relative configurations in the synthesis of natural products.<sup>12</sup> According to Kieseritzky's approach,<sup>13</sup> 9 was prepared in

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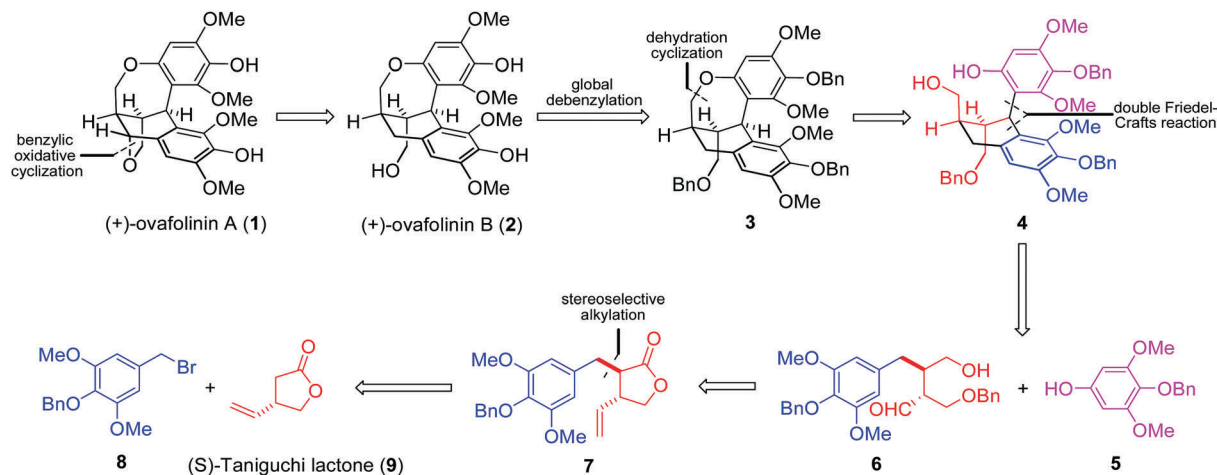
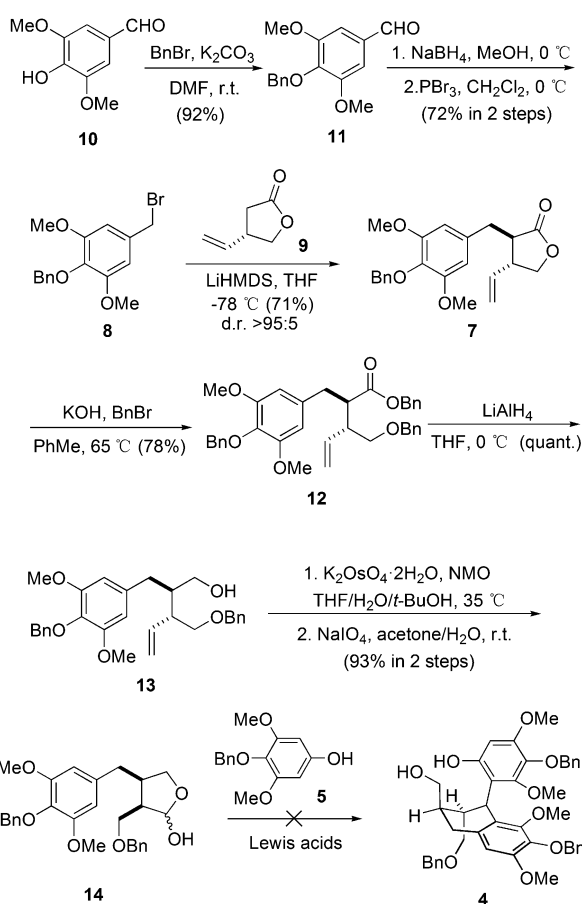


Fig. 1 Our original retrosynthetic analysis of (+)-ovafolinins A and B.

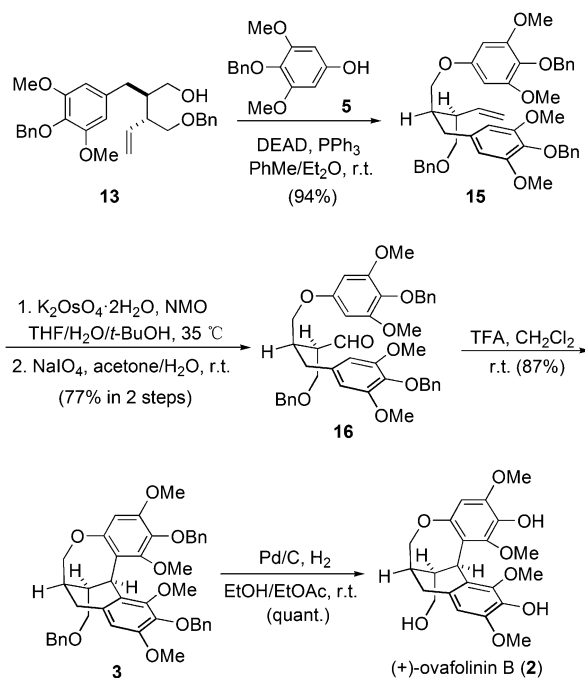


Scheme 1 The attempt on the synthesis of 4.

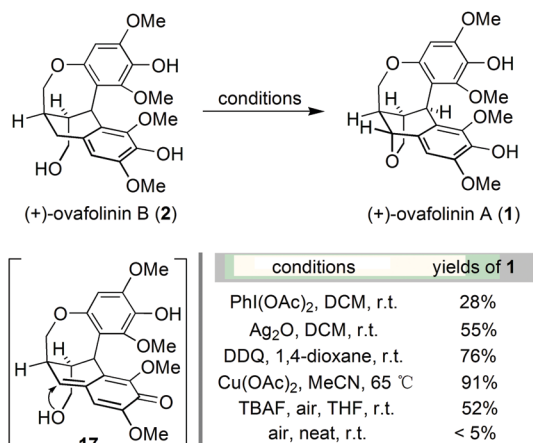
enantiomerically pure form over three steps. The alkylation process between 8 and 9 successfully afforded 7 in excellent stereoselectivity. The treatment of 7 with an excess amount of benzyl bromide under basic conditions opened the lactone unit smoothly,<sup>14</sup> generating ester 12 in 78% yield. After subsequent reduction, product 13 was subjected to vinyl oxidation. The product was hemiacetal 14 generated from the addition of

hydroxy to the aldehyde group. The originally proposed double Friedel-Crafts reaction between 5<sup>15</sup> and 14 was then examined with various Lewis acids. However, no consumption of 5 was observed in all cases.<sup>16</sup> As a result, intermolecular Friedel-Crafts reaction seems not a feasible method to couple fragment 5 with 14.

Therefore, we moved our attention to introduce motif 5 into the molecule before the construction of the carbon skeleton. Starting again from 13, motif 5 was readily connected with 13 through a Mitsunobu transformation (Scheme 2). Subsequent vinyl oxidation treatments established the aldehyde group in 16. Notably, during the construction of the unique polycyclic skeletons of 1 and 2, Barker and coworkers explored the cascade cyclization of compounds similar to 16. The bulky *tert*-butyldiphenylsilyl protecting group on the bottom-left hydroxy was found to be pivotal to enable



Scheme 2 Total synthesis of (+)-ovafolinin B (2).



Scheme 3 Synthesis of (+)-ovafolinin A.

the expected cyclization. However, methoxymethyl protection will lead to decomposition products.<sup>9</sup> In our case, the protecting groups of the three hydroxyl groups in **16** are all benzyl groups. To our delight, treatment of **16** with trifluoroacetic acid established successfully the expected polycyclic skeleton through a double Friedel–Crafts reaction process, affording **3** in 87% yield. The subsequent hydrogenation removed all three benzyl protections and gave (+)-ovafolinin B (**2**) in quantitative yield. Noteworthily, the final de-protection process in Barker's synthesis led to the formation of not only **2** but also **1**, both in poor yields. In our synthesis, there was no formation of **1** observed during the debenzylation process of **2**.

With the successful development of an asymmetric route to **2**, we focused on the synthesis of **1**. We envisaged that the benzylic oxidation cyclization of **2** could lead to the formation of *p*-benzoquinone methide intermediate **17**. And the subsequent conjugated addition from the vicinal hydroxy group will furnish **1** in the end. Therefore, **2** was subjected to various conditions reported for the formation of benzoquinone methide intermediates (Scheme 3). The employment of PhI(OAc)<sub>2</sub><sup>17</sup> resulted in the generation of **1** but in poor yield. Oxidation with Ag<sub>2</sub>O<sup>18</sup> and DDQ<sup>19</sup> could significantly improve the formation of **1**, respectively. The best result was obtained from the treatment with Cu(OAc)<sub>2</sub>,<sup>20</sup> affording **1** in 91% yield. Barker's synthesis conditions were also investigated, which led to the formation of **1** in moderate yield after complete consumption of **2**. Out of curiosity, we carried out the aerial oxidation of **2** under neat conditions. Only trace amounts of **1** were formed after three days.

After the synthesis of **1** and **2** was complete, the optical rotation properties of our synthetic (+)-ovafolinins A and B were investigated. The data (+159.5, (*c* = 0.36, MeOH) for **1** and +166.0 (*c* = 0.16, MeOH) for **2**) obtained are close to those observed by Baker and coworkers, which supports Barker's conclusion that natural ovafolinins A and B were both isolated in scalemic mixtures.<sup>9</sup>

In summary, an asymmetric synthetic approach to (+)-ovafolinins A and B has been developed. The entire synthetic route features a highly stereoselective alkylation of (*S*)-Taniguchi lactone, a double

Friedel–Crafts reaction process, a global debenzylation and a Cu(OAc)<sub>2</sub>-enabled benzylic oxidative cyclization. As a result, the synthesis of (+)-ovafolinin B has been completed in 11 linear steps and 23% total yield. And the synthesis of (+)-ovafolinin A has been achieved in 12 linear steps and 21% total yield.

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## Conflicts of interest

There are no conflicts to declare.

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- Compound **5** was prepared in three steps from syringaldehyde. Please see the ESI† file for experimental details.
- For attempts on the originally proposed double Friedel–Crafts reaction between **5** and **14**, please see the ESI† for detail.
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