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

Xianhe Fang, Lei Shen and Xiangdong Hu*

(+)-Ovafolinins 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 debenzylation and a $Cu(OAc)_2$-enabled benzylic oxidative cyclization, we present herein an efficient synthetic approach to (+)-ovafolinins 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.[1] Many important biological properties including anticancer,[2] antiviral,[3] and antioxidant activities,[4] alleviating menopausal symptoms, and reducing the risk of cardiovascular disease[5] have been disclosed from biological evaluations of this family. In 2010, ovafolinin A, ovafolinin 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.[6] Ovafolinin B was also found in Sinocalamus affinis (Rendle) McClure (Poaceae),[7] a widely cultivated traditional Chinese medicine named ''Ci Zhu Li'' and applied in treatments for diseases including cough and phlegm in China.[8] Structurally, ovafolinin A has a particular polycyclic skeleton containing an aryl tetralin unit with a tetrahydrofuran motif and a seven-membered benzoxepin bridged-ring. Ovafolinin B possesses a very similar framework except for the opening of the tetrahydrofuran ring. The first asymmetric synthesis of (+)-ovafolinins A and B was achieved by Barker and co-workers[9] employing an acyl-Claisen rearrangement developed in their laboratory.[10] 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 (+)-ovafolinins A and B. Furthermore, based on optical rotation comparisons between the synthetic compounds (+154.8 (c = 0.16, MeOH) for (+)-ovafolinin A, +150.0 (c = 0.26, MeOH) for (+)-ovafolinin B)[9] and the natural samples (−37.3 (c = 0.36, MeOH) for ovafolinin A, +52.0 (c = 0.26, MeOH)[6] and +43.3 (c = 0.12, MeOH)[7] for ovafolinin B), the exploration convincingly suggested that natural ovafolinins 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), (+)-ovafolinin A (**1**) and (+)-ovafolinin 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.[11] 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.[12] According to Kieseritzky's approach,[13] **9** was prepared in

Key Laboratory of Synthetic and Natural Functional Molecule Chemistry of Ministry of Education, College of Chemistry & Materials Science, Northwest University, Xi'an 710127, China. E-mail: Xiangdonghu@nwu.edu.cn

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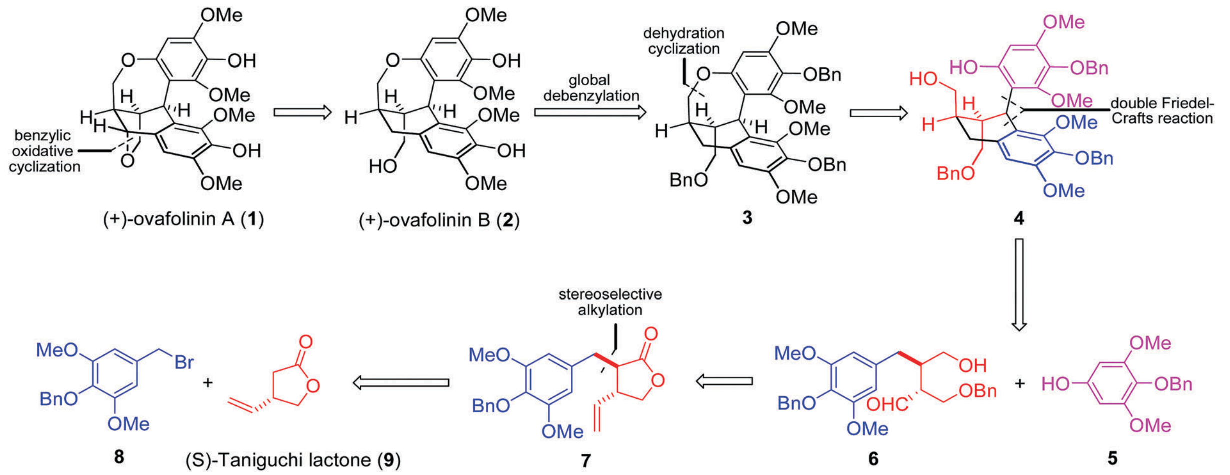
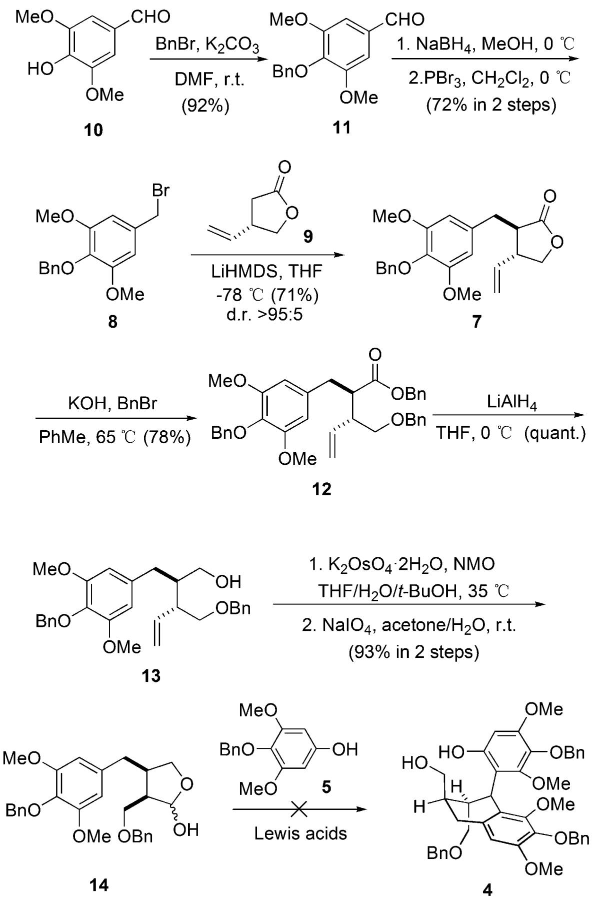


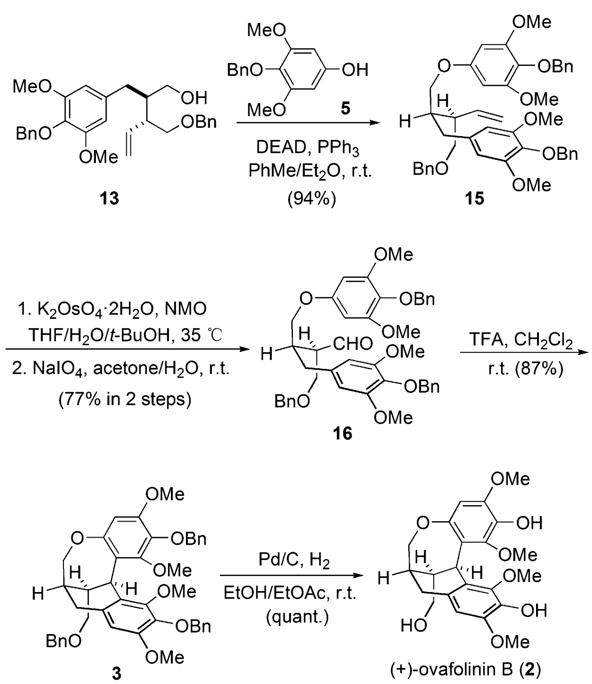
Fig. 1 Our original retrosynthetic analysis of (+)-ovafolinins A and B.



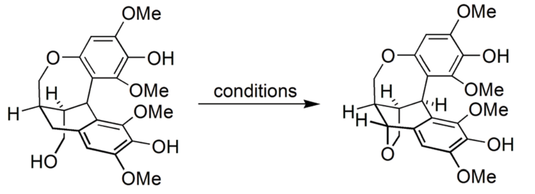
Scheme 1 The attempt on the synthesis of **4**.

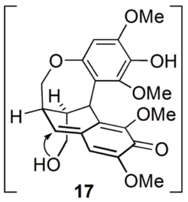
enantiomerically pure form over three steps. The alkylation process between **8** and **9** successfully afforded **7** in excellent stereoselectivity. The treatment of **7** with an excess amount of benzyl bromide under basic conditions opened the lactone unit smoothly,[14] generating ester **12** in 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**[15] and **14** was then examined with various Lewis acids. However, no consumption of **5** was observed in all cases.[16] 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**).





conditions	yields of **1**
$PhI(OAc)_2$, DCM, r.t.	28%
Ag_2O, DCM, r.t.	55%
DDQ, 1,4-dioxane, r.t.	76%
$Cu(OAc)_2$, MeCN, 65 ℃	91%
TBAF, air, THF, r.t.	52%
air, neat, r.t.	< 5%

Scheme 3 Synthesis of (+)-ovafolinin A.

the expected cyclization. However, methoxymethyl protection will lead to decomposition products.[9] 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 $PhI(OAc)_2$[17] resulted in the generation of **1** but in poor yield. Oxidation with Ag_2O[18] and DDQ[19] could significantly improve the formation of **1**, respectively. The best result was obtained from the treatment with $Cu(OAc)_2$,[20] 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.[9]

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 $Cu(OAc)_2$-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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