



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

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(+)-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 debenylation 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 disease⁵ 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-workers⁹ 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

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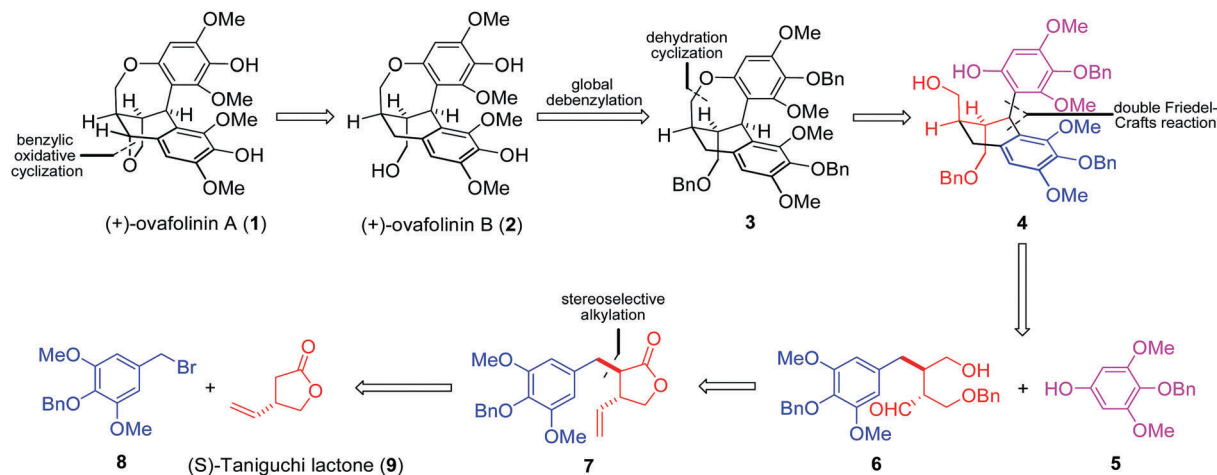
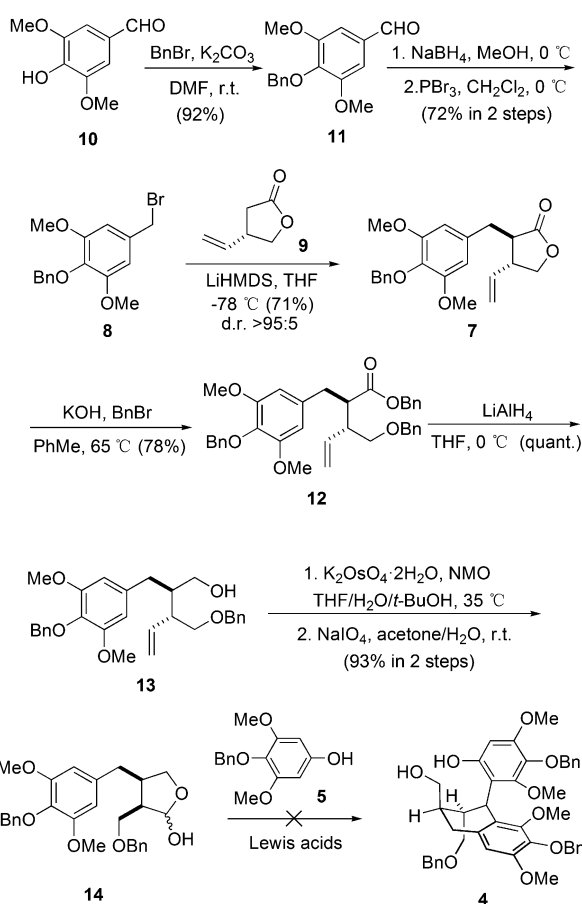


Fig. 1 Our original retrosynthetic analysis of (+)-ovafolinins A and B.

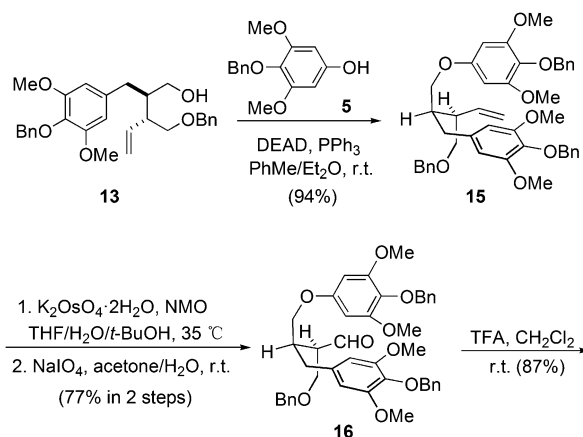


Scheme 1 The attempt on the synthesis of 4.

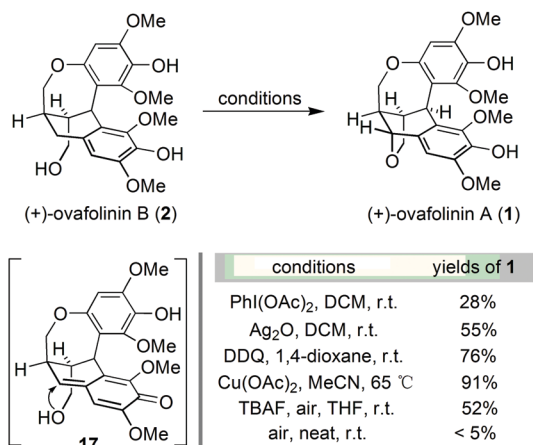
enantiomerically pure form over three steps. The alkylation process between 8 and 9 successfully afforded 7 in excellent stereoselectivity. The treatment of 7 with an excess amount of benzyl bromide under basic conditions opened the lactone unit smoothly,¹⁴ generating ester 12 in 78% yield. After subsequent 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 5¹⁵ 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).



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)₂¹⁷ resulted in the generation of **1** but in poor yield. Oxidation with Ag₂O¹⁸ and DDQ¹⁹ 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.

Notes and references

- (a) J. Chang, J. Reiner and J. Xie, *Chem. Rev.*, 2005, **105**, 4581–4609; (b) R. B. Teponno, S. Kusari and M. Spiteller, *Nat. Prod. Rep.*, 2016, **33**, 1044–1092.
- T. F. Imbert, *Biochimie*, 1998, **80**, 207–222.
- J. L. Charlton, *J. Nat. Prod.*, 1998, **61**, 1447–1451.
- M. Fauré, E. Lissi, R. Torres and L. A. Videla, *Phytochemistry*, 1990, **29**, 3773–3775.
- P. C. Li, D. H. F. Mark, M. K. T. Poon, S. P. Ip and K. M. Ko, *Phytomedicine*, 1996, **3**, 217–221.
- K. Kashima, K. Sano, Y. S. Yun, H. Ina, A. Kunugi and H. Inoue, *Chem. Pharm. Bull.*, 2010, **58**, 191–194.
- L. Xiong, C. Zhu, Y. Li, Y. Tian, S. Lin, S. Yuan, J. Hu, Q. Hou, N. Chen, Y. Yang and J. Shi, *J. Nat. Prod.*, 2011, **74**, 1188–1200.
- H. H. Jia and X. D. Wu, *Zhongyao*, 1992, **15**, 35–36.
- S. J. Davidson and D. Barker, *Angew. Chem., Int. Ed.*, 2017, **56**, 9483–9486.
- (a) C. E. Rye and D. Barker, *J. Org. Chem.*, 2011, **76**, 6636–6648; (b) S. J. Davidson and D. Barker, *Tetrahedron Lett.*, 2015, **56**, 4549–4553; (c) C. E. Rye and D. Barker, *Synlett*, 2009, 3315–3319.
- T. Suzuki, M. Takamoto, T. Okamoto and H. Takayama, *Chem. Pharm. Bull.*, 1986, **34**, 1888–1900.
- (a) F. Ishibashi and E. Taniguchi, *Chem. Lett.*, 1986, 1771–1774; (b) F. Ishibashi and E. Taniguchi, *Bull. Chem. Soc. Jpn.*, 1988, **61**, 4361–4366; (c) F. Ishibashi and E. Taniguchi, *Phytochemistry*, 1998, **49**, 613–622; (d) G. Stork, D. Niu, A. Fujimoto, E. R. Koft, J. M. Balkovec, J. R. Tata and G. R. J. Dake, *J. Am. Chem. Soc.*, 2001, **123**, 3239–3242; (e) H. Miyaoka, Y. Hara, I. Shinohara, T. Kurokawa and Y. Yamada, *Tetrahedron Lett.*, 2005, **46**, 7945–7949; (f) D. Stadler and T. Bach, *Angew. Chem., Int. Ed.*, 2008, **47**, 7557–7559; (g) K. Ota, N. Sugata, Y. Ohshiro, E. Kawashima and H. Miyaoka, *Chem. – Eur. J.*, 2012, **18**, 13531–13537.
- F. Kieseritzky, Y. Wang and M. Axelson, *Org. Process Res. Dev.*, 2014, **18**, 643–645.
- (a) J. Rath, S. Kinast and M. E. Maier, *Org. Lett.*, 2005, **7**, 3089–3092; (b) J. Quancard, A. Labonne, Y. Jacquot, G. Chassaing, S. Lavielle and P. Karoyan, *J. Org. Chem.*, 2004, **69**, 7940–7948.
- 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.
- B. Fang, X. Xie, C. Zhao, P. Jing, H. Li, Z. Wang, J. Gu and X. She, *J. Org. Chem.*, 2013, **78**, 6338–6343.
- (a) F. D. Ramdayal, D. J. Kiemle and R. T. LaLonde, *J. Org. Chem.*, 1999, **64**, 4607–4609; (b) K. C. Rice, W. C. Ripka, J. Reden and A. Brossi, *J. Org. Chem.*, 1980, **45**, 601–607.
- T. Sengoku, S. Xu, K. Ogura, Y. Emori, K. Kitada, D. Uemura and H. Arimoto, *Angew. Chem., Int. Ed.*, 2014, **53**, 4213–4216.
- J.-A. Jiang, C. Chen, J.-G. Huang, H.-W. Liu, S. Cao and Y.-F. Ji, *Green Chem.*, 2014, **16**, 1248–1254.