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Total synthesis of bi-magnolignan†

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Bi-magnolignan, isolated from the leaves of *Magnolia officinalis*, has shown excellent physiological activity against tumor cells. An efficient strategy for the first total synthesis of bi-magnolignan is reported. The bi-dibenzofuran skeleton was constructed *via* functional group interconversions of commercially available materials 1,2,4-trimethoxybenzene and 4-allylanisole. Then, the dibenzofuran skeleton was afforded by subsequent Suzuki coupling and intramolecular dehydration. The total synthesis of natural product was accomplished through FeCl₃ catalyzed oxidative coupling.

The bark of *Magnolia officinalis* Rehder & E. Wilson, known as “Houpo” or “Houpu” in Chinese, is a traditional herbal medicine that has long been used in Chinese and Japanese medicine for the treatment of anxiety, asthma, depression, gastrointestinal disorders, and headache.¹ To date, at least 255 different ingredients have been isolated from the cones, bark, flowers, and leaves of the genus *Magnolia*, such as lignans, alkaloids, coumarins, and flavonoids.² Among these ingredients, magnolol (2) and honokiol (3) are considered as the two principal compounds and the main active constituents which have been shown to possess potent anti-oxidative,³ anti-anxiety,⁴ anti-inflammatory,⁵ and anti-cancer⁶ activities (Fig. 1) widespread

interest in the ingredients of these bioactive materials led to the isolation of its ingredients.

Recently, a new lignan named bi-magnolignan (1) (Fig. 1) was isolated from the leaves of *Magnolia officinalis* by Ma and co-workers.⁷ The structure of bi-magnolignan has been characterized as a bi-dibenzofuran skeleton, formed by two identical monomers connected by a C–C bond on the benzene ring. Many dibenzofuran-containing products show a range of biological activities,⁸ such as kehokorins A(4)–C(6) and karnatakafurans A(7) and B(8).⁹ Notably, there are two hydroxyl and allyl groups on each benzene ring of bi-magnolignan, similar to honokiol and magnolol, whose potent activities are attributed to the presence of the hydroxyl and allylic groups on a biphenolic moiety.¹⁰ However, the spatial conformation of bi-magnolignan is completely different to that of honokiol and it has a larger molecular volume than honokiol. Generally, molecules with small molecular volume have more potential targets in the body, potentially causing toxic off-target side effects; however, the bi-dibenzofuran skeleton with a large molecular volume may result in fewer toxic side effects. The target of bi-magnolignan is completely different from that of *magnolia officinalis* phenols, and bi-magnolignan has better target specificity. The experimental data show that it has good anti-neoplastic effects and strong inhibitory activity against tumor cells of various tissues, with IC₅₀ values ranging from 0.4 to 7.5 μM (after 48 h), while honokiol has values ranging from 18.8 to 56.4 μM (after 72 h).⁷ Research by Ma and co-workers shows that bi-magnolignan can also induce tumor cell apoptosis, while it has little toxic side effects on normal cells. Furthermore, bi-magnolignan has active hydroxyl and allyl groups, which can be further used to link other groups or react with other reagents to obtain a new structure of *Magnolia officinalis* derivatives.

The derivatives of bi-magnolignan have diverse structures and have high potential application value. Given the potential as an antitumor drug lead candidate, we were attracted to attempt the total synthesis of bi-magnolignan.

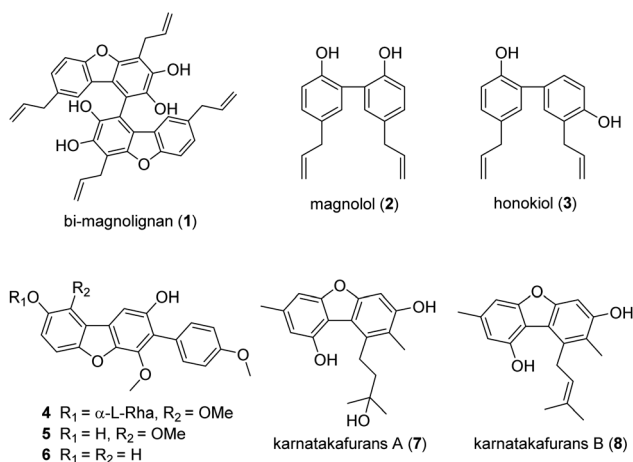
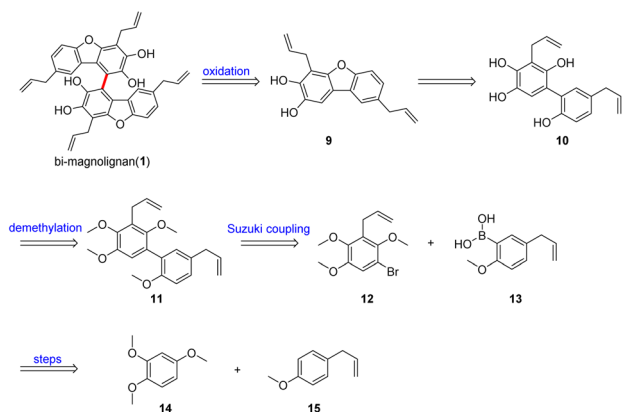


Fig. 1 Bi-magnolignan (1) and representative members of *Magnolia officinalis* and dibenzofuran-containing natural products.

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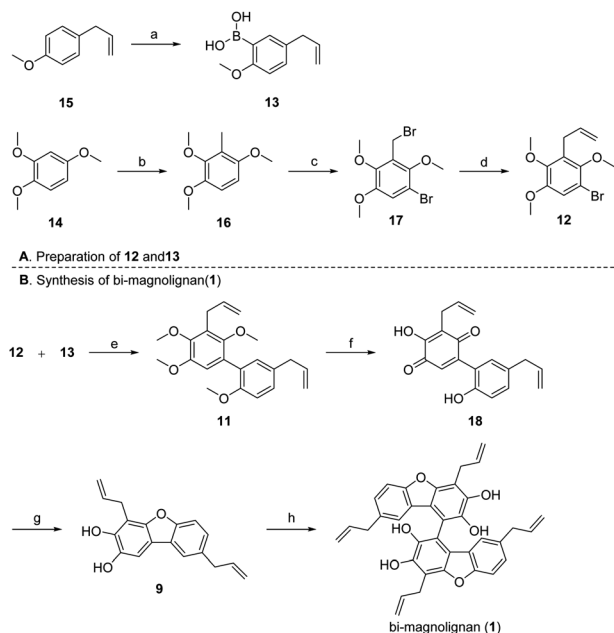




Scheme 1 Retrosynthetic analysis of bi-magnolignan (1).

A retrosynthetic analysis of bi-magnolignan is shown in Scheme 1. Considering its symmetry, we envisioned that it should be accessible *via* oxidative coupling of its monomer **9**, which could be generated through intramolecular dehydration of **10** to construct the dibenzofuran framework. Further disconnection led to compound **11** *via* a Suzuki coupling of **12** and **13** followed by demethylation. In turn, **12** and **13** are accessible from commercially available 1,2,4-trimethoxybenzene (**14**) and 4-allylanisole (**15**) in few steps.

As outlined in Scheme 2, our strategy for the total synthesis began with the preparation of **12** and **13**. According to Denton's



Scheme 2 Total Synthesis of bi-magnolignan (**1**). Reagents and conditions: (a) (i) *s*-BuLi, TMEDA, THF, -78°C to rt, 1 h, (ii) B(OMe)₃, 24 h, (iii) 1 M HCl, 1 h, 63%; (b) (i) *n*-BuLi, THF, -78°C , 15 min, then rt, 1 h, (ii) MeI, THF, -78°C to rt, 99%, 1 h; (c) AIBN, NBS, CCl₄, 80 $^{\circ}\text{C}$, 8 h, 91%; (d) CuI, BIPY, vinylmagnesium bromide, THF, -20°C to rt, 8 h, 83%; (e) K₂CO₃, Pd(PPh₃)₄, 1,4-dioxane, H₂O, 100 $^{\circ}\text{C}$, 10 h, 84%; (f) BBr₃, DCM, -78°C to rt, 3 h, 89%; (g) hydroquinone, 2 M sulfuric acid, AcOH, 115 $^{\circ}\text{C}$, 20 min, 55%; (h) *m*-CPBA, FeCl₃, DCM, rt, 1 h, 56%.

protocol,¹¹ directed ortho lithiation of **15** followed by trimethylborate and hydrolysis of the resulting arylboronate ester with aqueous hydrochloric acid afforded **13** in 63% isolated yield. The methylation of **14** with MeI afforded **16** in excellent yield (99%) on a decagram scale. Subsequently, we envisioned bromination of both the benzyl and the benzene in one pot. Fortunately, we were delighted to find that the reaction performed with NBS and AIBN afforded **17** in 91% yield after refluxing for 8 h in CCl₄. Benzyl bromide **17** was then reacted with vinylmagnesium bromide in THF at -20°C to afford **12** in good yield (83%).

With **12** and **13** in hand, we turned our attention to the construction of the desired C–C bond. Suzuki coupling between **12** and **13** using Pd(PPh₃)₄ and K₂CO₃ afforded **11** in 84% yield on a gram scale. However, subsequent demethylation with BBr₃ failed to afford the desired compound **10**, giving benzoquinone **18** instead with a yield of 89%. This may be due to the instability of **10**, which contains many hydroxyl groups on the same benzene meaning that it is easily oxidized. Fortunately, we were delighted to find that the original conditions developed by Högborg¹² and co-workers under sulfuric acid and hydroquinone provided the desired product **9** in an acceptable yield (55%), thus we successfully furnished the dibenzofuran skeleton. After screening various conditions for oxidative coupling of phenols, such as Koga's copper–amine complex CuCl(OH)·TMEDA, CuCl, DDQ, MnO₂ and FeCl₃, we found that the FeCl₃ catalyzed oxidative coupling of aromatic nuclei, developed by Wang and co-workers,¹³ was suitable for the last step, however, the yield is low or no reaction under other conditions. Finally, the synthesis of the natural product was completed using FeCl₃ and *m*-CPBA with a yield of 56%. The NMR data of the synthetic sample of bi-magnolignan were consistent with those reported in the literature.

Conclusions

In summary, we have developed the first total synthesis of bi-magnolignan in eight steps from commercially available starting materials. This provides a synthetic strategy for the oxidative coupling of natural products in dimer form, especially those lignans who share analogous structural frameworks. In addition, the salt of bi-magnolignan and its derivatives have shown considerable antitumor activity. The present work may facilitate larger-scale preparation and further biological studies of bi-magnolignan.

Author contributions

A.-J. M. conceived and directed the project. S.-Y. L. performed the experiments. H.-M. W. and N. F. participated in substrate synthesis and discussions. S.-Y. L. and A.-J. M. wrote the manuscript and ESI.[†]

Conflicts of interest

There are no conflicts to declare.



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