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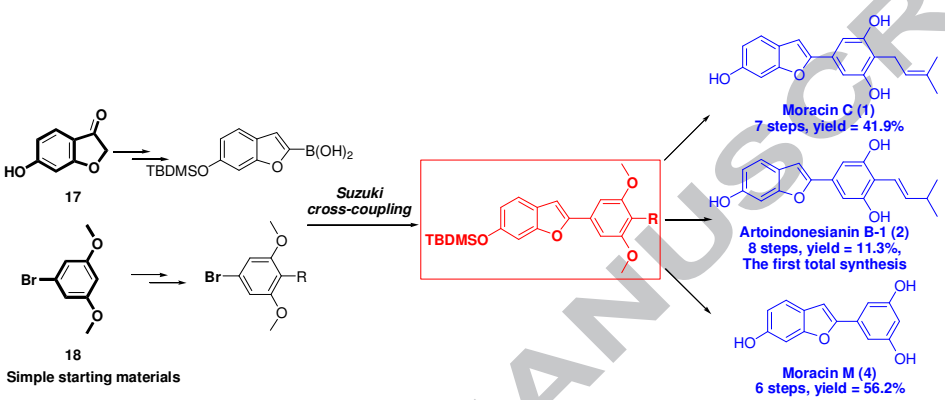

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Total Synthesis of the 2-Arylbenzo[*b*]furan-Containing Natural Products from *Artocarpus*

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ABSTRACT

In this study, 2-arylbenzo[*b*]furan-containing derivatives moracin C (**1**) and moracin M (**4**), the natural products from *Artocarpus*, have been synthesized in highest overall yield to date (**1**, 7 steps with an overall yield of 41.9%; **4**, 6 steps with an overall yield of 56.3%), and we also report the first total synthesis of artoindonesianin B-1 (**2**), another member of this family, in the same route (8 steps with an overall yield of 11.3%). This discovery provides a concise route for preparing enough amounts of **1**, **2** and **4** as well as 2-arylbenzo[*b*]furan-containing natural product-like analogs (**71-74**) to explore the biological potential.

† Deyan Wu, Hanbing Mei and Ping Tan contributed equally to this work.

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1. Introduction

Nature, especially plants, has provided a source of medicines for the treatment of a wide spectrum of diseases. The *Artocarpus* species consists of 60 genera comprising 1400 species distributed in the tropical and subtropical regions of Asia, among them the genus *Artocarpus* comprises about 50 species of evergreen and deciduous trees, mainly including breadfruit and *Artocarpus* heterophyllus trees.[1] There are rich in phenolic compounds including flavonoids, stilbenoids, arylbenzofurons and Jacalin.[2,3] Several pharmacological studies of the natural products from *Artocarpus* have found that they possessed various biological activities, such as antibacterial activity,[4,5] antiviral activity,[6,7] antifungal activity,[8,9] and antidiabetic activity.[10] As a part of our efforts on discovering novel potential anti-inflammatory compounds, we screen the natural products in our inventory, several natural products were found to have excellent inhibitory activities against LOXs and proinflammatory cytokines. Among them four natural phenolic compounds containing common 2-arylbenzo[*b*]furan scaffold draw our attention for their potent 5-LOX inhibitory activities, namely moracin C (**1**, IC_{50} (5-LOX) = 2.35 μM), artoindonesianin B-1 (**2**, IC_{50} (5-LOX) = 1.67 μM), moracin D (**3**, IC_{50} (5-LOX) = 3.50 μM), and moracin M (**4**, IC_{50} (5-LOX) = 4.95 μM) (Figure 1), which were originally isolated from *Morus alba* Linn (*Artocarpus*).[11-13] A survey of literature reveals that compounds **1**-**4** have various biological activities, including significant inhibitory activity towards the differentiation of 3T3-L1 cells and nitric oxide production in RAW 264.7 Cells,[14] and inhibitory activities against α-glucosidase and tyrosinase.[15] Moreover, some synthetic analogs, viz. 2-substituted-5-benzofuran compounds, were found to be potent estrogen receptor β (ER-β) ligands,[16-19] and 5-LOX inhibitors.[20, 21]

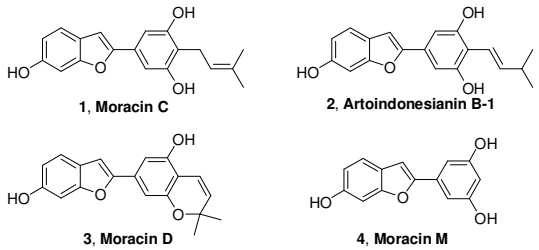
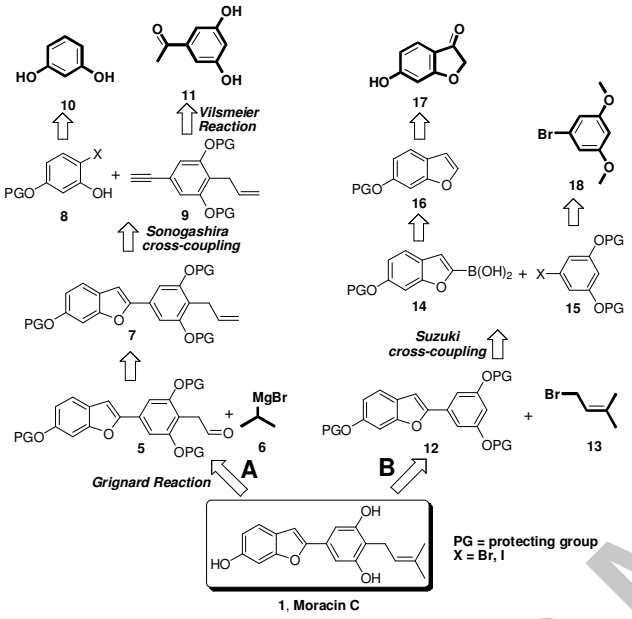


Figure 1. Four natural LOXs inhibitors containing common 2-arylbenzo[*b*]furan scaffold from *Artocarpus*.

2-Arylbenzo[*b*]furan, a privileged architecture combined with the impressive bioactivity, has attracted wide attention in the synthetic community.[22-27] In all cases, however, there is not a

convenient and universal synthetic method for preparing these compounds. Therefore, in order to probe the value of this kind of natural products found in our inventory, we need a short and high yield route first. Different from the existing synthetic method on compound **1**,[28,29] our retrosynthetic analysis of these compounds defined in Scheme 1 is based on the construction of 2-arylbenzo[*b*]furan. As indicated, our synthesis of the 2-arylbenzo[*b*]furan scaffold began with Sonogashira cross-coupling reaction (Route A) or Suzuki cross-coupling reaction (Route B), and all of the starting material is cheap and easy to get.

Scheme 1. Retrosynthetic Analysis of **1**



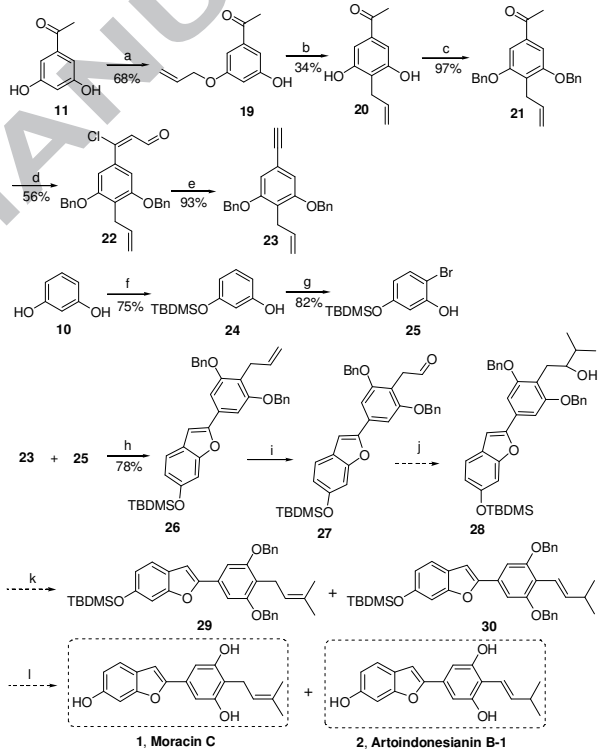
2. Results and Discussion

The retrosynthetic analysis of moracin C (**1**) suggested the compounds **6**, **10**, **11**, **13**, **17**, and **18** (bold structures, scheme 1) as suitable building blocks by two synthetic strategies (scheme 1, routes A-B). To demonstrate the feasibility of the proposed synthetic strategies, we carried out two parts of the synthetic work on the basis of two synthetic strategies. The key intermediates, 2-arylbenzo[*b*]furan moiety **7** or **12**, were constructed by Sonogashira cross-coupling between alkyne **9** or **14** with a suitably substituted aryl halide **8** (scheme 1, routes A-B) or by Suzuki cross-coupling between suitably substituted indole-2-boronic acid **14** with aryl halide **15** (scheme 1, route B).

Our initial efforts focused on use the compounds **10** and **11** as building blocks (scheme 1, route A). The alkyne **24** was obtained from 3,5-dihydroxyacetophenone **11** by using the Claisen rearrangement reaction followed by Vilsmeier reaction.[30,31] Then, we use the Sonogashira cross-coupling reaction to synthesize 2-arylbenzo[*b*]furan **27** (scheme 2). All the designed steps have a moderate to good yield (34%-97%) except the synthesis of compound **28**, and all the attempts to improve the yield ended in failure (e.g. O_3/DMS, $RuCl_3$/$NaIO_4$/$PhEt_3N^+Cl^-$).[32,33]

Therefore, we apply the route B (schemes 1 and 3) for the synthesis of moracin C by using 6-hydroxy-2,3-dihydrobenzo[*b*]furan-3-one **17** as the starting material. Reaction of **17** with tert-butyldimethylsilyl chloride in the presence of imidazole in THF at room temperature overnight afforded the protected 2,3-dihydrobenzo[*b*]furan-3-one **31**. Reduction of **31** get the 6-(*tert*-butyl-dimethylsilanyloxy)benzofuran **32**. The benzofuran **32** was then treated with n-BuLi in anhydrous THF at -78 °C for 1 h followed by addition of triisopropyl borate and stirred at -30 °C for 2 h under a nitrogen atmosphere to afford 6-(*tert*-butyl-dimethylsilanyloxy)benzofuran-2-boronic acid **33**. Coupling of **33** with 1-bromo-3,5-dimethoxybenzene **18** in the presence of $Pd(OAc)_2$ and K_2CO_3 yielded the 2-arylbenzo[*b*]furan **34** (two steps). Regioselectively lithiated of **34** with n-butyllithium in cyclohexane followed by addition of 3, 3-dimethylallyl bromide to result **35** as a yellow oil. And removal of the protected groups by Ph_2PLi in anhydrous THF under reflux for 2 h afforded the benzene-1,3-diol **36** or reflux for 36 h afforded the desired product moracin C (**1**). Uniformly all the designed steps have a good to excellent yield (57%-99%, Scheme 3). Finally, moracin C (**1**) was achieved in 7 steps with an overall yield of 41.9% from commercially available benzo[*b*]furan-3-one derivative **17**, the efficiency of our method was better than that of the pioneering synthetic study (10 steps in 12.3% total yield) by Hartley and co-workers in 1998.[29] Global deprotection of intermediate **34** conveniently completed the total synthesis of another natural product moracin M (**4**) with an overall yield of 56.2% (6 steps), which was higher yields than recent synthetic method (2 steps in 6.5% total yield) by Cossío and co-workers in 2012.[27] Moracin D (**3**) can be obtained from moracin C (**1**) by using the published procedures,[34] but in view of weaker LOXs inhibitory activities of moracin D, we haven't carry out this reaction in our laboratory.

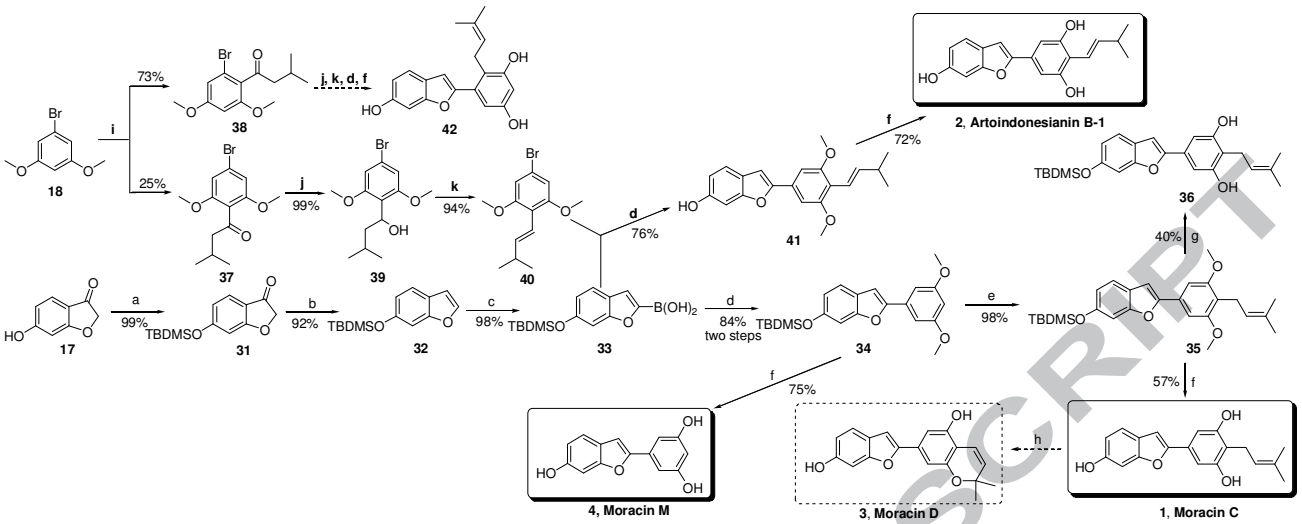
Scheme 2. Synthetic Route for **1** and **2** [a]



[a]*Reagents and conditions:* (a) Allyl bromide, K_2CO_3, DMF, rt, 12h; (b) N,N-diethylaniline, 210°C, 6h; (c) Benzyl bromide, K_2CO_3, DMF, rt, 12h; (d) (Chloromethylene)dimethyliminium chloride, DMF, 0°C to 50°C, 2h; (e) NaOH, dioxane, H_2O, 80°C, 1h; (f) TBDMSCl, imidazole, THF, rt, 4h; (g) Br_2, CH_2Cl_2, 0°C, 30min; (h) $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, DMF, rt, 24h; (i) $RuCl_3$, $NaIO_4$, $PhEt_3N^+Cl^-$, EtOAc, rt, 2h; (j) Isopropylmagnesium bromide, THF, 0°C; (k) *p*-TSA, $PhCH_3$, reflux; (l) Ph_2PLi, THF, reflux.

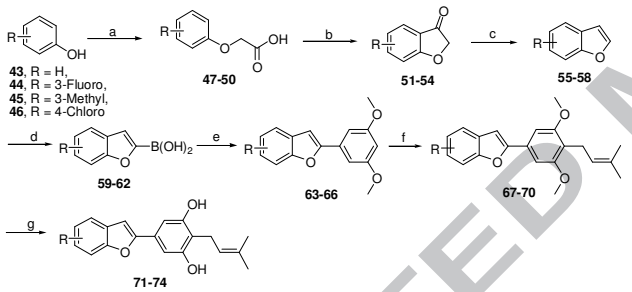
Besides, the reuse of the starting material **18** and the intermediate **33** can get another natural product artoindonesianin B-1 (**2**) with an overall yield of 11.3% (8 steps, Scheme 3). Acylation of **18** with isovaleryl chloride afforded two isomers **37** and **38**, owing to steric hindrance of two methoxy groups, isomer **37** we needed was separated in low yield (25%), that was a direct result of low overall yield of **2**. Still, it's worth mentioning that this is the first time reported the synthesis method about artoindonesianin B-1 (**2**).

Scheme 3. Synthetic Route for **1**, **2**, **3** and **4**[a]



[a]*Reagents and conditions:* (a) TBDMSCl, imidazole, THF, rt, 4h; (b) $NaBH_4$, MeOH, rt, 1h; (c) i. n-BuLi, THF, -78°C, 1h; ii. Triisopropyl borate, -78°C to -30°C, 2h; iii. 2M HCl, pH=5.0; (d) i. 1-Bromo-3,5-dimethoxybenzene, $Pd(OAc)_2$, Tricyclohexyl phosphine, K_2CO_3, DME, H_2O, 80°C, 2h; ii. TBDMSCl, imidazole, THF, rt, 2h; (e) i. n-BuLi, THF, 0°C to reflux, 30min; ii. 3,3-Dimethylallyl bromide, reflux, 2h; (f) n-BuLi, Ph_2PH, THF, 0°C to reflux, 36h; (g) n-BuLi, Ph_2PH, THF, 0°C to reflux, 16h; (h) DDQ, benzene, dioxane, reflux 2h; (i) Isovaleryl chloride, $AlCl_3$, CH_2Cl_2, -5°C 2h; (j) $LiAlH_4$, THF, 0°C, 2h; (k) *p*-TSA, $PhCH_3$, reflux, 2h.

Scheme 4. Synthetic Route for Substituted 2-Arylbenzo[*b*]furans[a]



[a]*Reagents and conditions:* (a) i. $BrCH_2COOMe$, K_2CO_3, DMF, r.t. 12h; ii. NaOH, MeOH, 2h; (b) i. $SOCl_2$, reflux 4h; ii. $AlCl_3$, CH_2Cl_2, 0°C to r.t. 30min; (c) $NaBH_4$, MeOH, r.t. 1h; (d) i. n-BuLi, THF, -78°C 1h; ii. Triisopropyl borate, -78°C to -30°C 2h; iii. 2M HCl, pH=5.0; (e) 1-Bromo-3,5-dimethoxybenzene, $Pd(OAc)_2$, Tricyclohexyl phosphine, K_2CO_3, DME, H_2O, 80°C 2h; (f) Ph_2PLi, THF, reflux 12h.

Consequently, the synthetic route of moracin C (**1**) in Scheme 3 provided the best way for preparing enough amounts of **1** as well as designed 2-arylbenzo[*b*]furan analogs of **1** to explore the biological potential. And four 2-arylbenzo[*b*]furan-containing natural product-like compounds (**71–74**, Scheme 4) were prepared to determine the significance of substituent on phenyl ring of benzo[*b*]furan for anti-inflammatory activities. The detailed synthetic procedure and spectroscopic data for all the compounds (**1**, **2**, **4**, and **71-74**) are given in *Supplementary information*. Further investigations for biological applications of these natural products and anologs are underway in our group.

3. Conclusion

In summary, we successfully completed a concise route for the synthesis of 2-arylbenzo[*b*]furans. Moracin C (**1**) and moracin M (**4**), the natural products from *Artocarpus*, have been synthesized in highest overall yield to date (**1**, 7 steps with an overall yield of 41.9%; **4**, 6 steps with an overall yield of 56.2%). Artoindonesianin B-1 (**2**) has also been prepared in 8 steps with an overall yield of 11.3%, which represents the first total synthesis of the member of this family.

Acknowledgments

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Supplementary data

General information for chemical agents and analytical measurements, detailed synthetic procedures and related spectroscopic data for the compounds **1**, **2**, **4**, and **71–74**, HPLC reports for the purity check of the compounds **1**, **2**, **4**, and **71–74**. This material is available free of charge via the Internet at http://.

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