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Deyan Wu, Hanbing Mei, Ping Tan, Weiqiang Lu, Jin Zhu, Wei Wang, Jin Huang, Jian Li

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Total Synthesis of the 2-Arylbenzo[b]furan-Containing Natural Products from Artocarpus
Deyan Wu\textsuperscript{a,†}, Hanbing Mei\textsuperscript{a,†}, Ping Tan\textsuperscript{a,†}, Weiqiang Lu\textsuperscript{b}, Jin Zhu\textsuperscript{a}, Wei Wang\textsuperscript{a,c}, Jin Huang\textsuperscript{a}, Jian Li\textsuperscript{a,*}

[Diagram of synthesis process]

Moracin C (1)
7 steps, yield = 41.9%

Artoindonesianin B-1 (2)
8 steps, yield = 11.3%
The first total synthesis

Moracin M (4)
6 steps, yield = 56.2%
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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.

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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. There are rich in phenolic compounds including flavonoids, stilbenoids, arylbenzofurans and Jacalin. Several pharmacological studies of the natural products from Artocarpus have found that they possessed various biological activities, such as antibacterial activity, antiviral activity, antifungal activity, and antidiabetic activity. 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, IC50 (5-LOX) = 2.35 µM), artoindonesianin B-1 (2, IC50 (5-LOX) = 1.67 µM), moracin D (3, IC50 (5-LOX) = 3.50 µM), and moracin M (4, IC50 (5-LOX) = 4.95 µM) (Figure 1), which were originally isolated from Morus alba Linn (Artocarpus). 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, and inhibitory activities against α-glucosidase and tyrosinase. Moreover, some synthetic analogs, viz. 2-substituted-5-benzofuran compounds, were found to be potent estrogen receptor β (ER-β) ligands, and 5-LOX inhibitors.
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, route 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 Ullmann rearrangement reaction followed by Vilsmeier reaction. 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/DMS, RuCl₃/NaIO₃/PhEt₃NCl). 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-(terti-butyl-dimethylsilyl)oxybenzofuran 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-(terti-butyl-dimethylsilyl)oxybenzofuran-2-boronic acid 33.

Coupling of 33 with 1-bromo-3,5-dimethoxybenzene 18 in the presence of Pd(OAc)₂ and K₂CO₃ yield the 2-arylfuran 34 (two steps). Regioselectively lithiated 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 Ph₃P=Li 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 benzofuran-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. Still, 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 Cossio and co-workers in 2012. Moreover, moracin D (3) can be obtained from moracin C (1) by using the published procedures, but in view of weaker LOX inhibitory activities of moracin D, we haven’t carry out this reaction in our laboratory.

Scheme 2. Synthetic Route for 1 and 2

“Reagents and conditions: (a) Allyl bromide, K₂CO₃, DMF, rt, 12h; (b) N,N-diethylaniline, 210°C, 6h; (c) Benzyl bromide, K₂CO₃, DMF, rt, 12h; (d) (Chloromethylene)dimethylaminochloride, DMF, 0°C to 50°C, 2h; (e) NaOH, dioxane, H₂O, 80°C, 1h; (f) TBDMSCl, imidazole, THF, rt, 4h; (g) Br₂, CHCl₃, 0°C, 30min; (h) Pd(PPh₃)₄Cl₂, Cul, Et₃N, DMF, rt, 24h; (i) RuCl₃, NaIO₃, PhEt₃NCl, EtOAc, rt, 2h; (j) Isopropylimagnesium bromide, THF, 0°C; (k) p-TSA, PhCH₃, reflux; (l) Ph₃P=Li, THF, reflux.

Besides, the reuse of the starting material 18 and the intermediate 33 can get another natural product artoindonesin 2-1 (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 artoindonesin 2-1 (2).
Scheme 3. Synthetic Route for 1, 2, 3 and 4a

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Reagents and conditions: (a) TBDMSCI, imidazole, THF, rt, 4h; (b) NaBH4, MeOH, rt, 1h; (c) i. n-BuLi, THF, -78°C, 1h; ii. Trisopropyl 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, K2CO3, DME, H2O, 80°C, 2h; ii. TBDMSCI, imidazole, THF, rt, 2h; (e) i. n-BuLi, THF, 0°C to reflux, 30min; ii. 3,3-Dimethylallyl bromide, reflux, 2h; (f) n-BuLi, Ph3P, THF, 0°C to reflux, 36h; (g) n-BuLi, Ph3P, THF, 0°C to reflux, 16h; (h) DDQ, benzene, dioxane, reflux 2h; (i) Isovaleryl chloride, AlCl3, CH2Cl2, -5°C 2h; (j) LiAlH4, THF, 0°C, 2h; (k) p-TSA, PhCH3, reflux, 2h.
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Scheme 4. Synthetic Route for Substituted 2-Arylbenzo[b]furansa

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Reagents and conditions: (a) i. Br2(CH2)2COOMe, K2CO3, DMF, r.t. 12h; ii. NaOH, MeOH, 2h; (b) i. SOCl2, reflux 4h; ii. AlCl3, CH2Cl2, 0°C to r.t. 30min; (c) NaBH4, MeOH, r.t. 1h; (d) i. n-BuLi, THF, -78°C 1h; ii. Trisopropyl borate, -78°C to -30°C 2h; iii. 2M HCl, pH=5.0; (e) i. 1-Bromo-3,5-dimethoxybenzene, Pd(OAc)2, Tricyclohexyl phosphine, K2CO3, DME, H2O, 80°C 2h; (f) Ph3P, LiAlH4, THF, reflux 12h.
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Consequently, the synthetic route of moracin C (1) in Scheme 3 provided the best way for preparing enough amounts of I as well as designed 2-arylfuran analogs of I to explore the biological potential. And four 2-arylfuran-containing natural product-like compounds (71–74, Scheme 4) were prepared to determine the significance of substituent on phenyl ring of benzo[b]furans 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 analogs are underway in our group.

3. Conclusion

In summary, we successfully completed a concise route for the synthesis of 2-arylfurans. 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.

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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://.

References and notes