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RESEARCH ARTICLE

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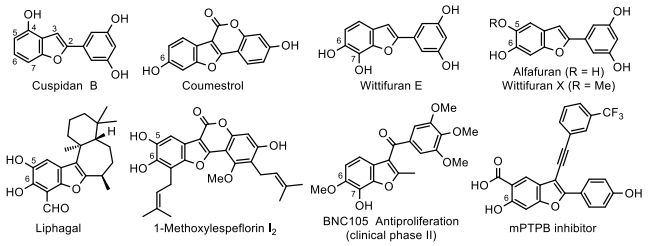
Deconstructive Reorganization: *De Novo* Synthesis of Hydroxylated Benzofuran

Ling Zhang[+], Tongxiang Cao[+], Huanfeng Jiang, and Shifa Zhu*

Abstract: An unprecedented deconstructive reorganization strategy for the *de novo* synthesis of hydroxylated benzofurans from kojic acid- or maltol-derived alkynes is reported. In this reaction, both the benzene and furan rings were simultaneously constructed, whereas the pyrone moiety of the kojic acid or maltol was deconstructed and then reorganized into the benzene ring as a six-carbon component. Through this strategy, at least one free hydroxyl group was introduced into the benzene ring in a substitution-pattern tunable fashion without protection-deprotection and redox adjustment. With this method, a large number of hydroxylated benzofuran derivatives with different substitution-patterns have been prepared efficiently. This methodology has also been shown as the key step in a collective total synthesis of hydroxylated benzofuran-containing natural products (11 examples).

Introduction

Hydroxylated benzofurans are ubiquitous structural motifs of various natural products and bioactive molecules.[1] As shown in Scheme 1, these molecules contain at least one free hydroxyl group attached to the benzene ring with different substituent patterns, which have attracted much attention owing to their wide spectrum of biological activities. For example, as a phytoestrogen, coumestrol (with one hydroxyl at C6) exhibits diverse activities against cancers, neurological disorders, and autoimmune diseases.[2] The marine natural product liphagal (with two hydroxyl groups at C5 and C6) can modulate human phosphatidylinositol-3-kinase (PI3K) signalling pathway,[3], which may have therapeutic potential in treatment of autoimmune disorders, cardiovascular disease, and cancer.[4] Furthermore, hydroxylated benzofuran is also a privileged structure in drug candidates. For instance, BNC 105 (with one methoxyl at C6 and one hydroxyl at C7) is a tubulin polymerization inhibitor with potent antiproliferative and tumor vascular disrupting properties and has been tested in phase II clinical trials.[5] The great biological potential of hydroxylated benzofurans stimulates us to exploit a platform for the practical synthesis of hydroxylated benzofuran derivatives with different substitution patterns in order to streamline the drug discovery process.[6]



Scheme 1. Hydroxylated benzofuran-containing natural products and drug candidates.

So far, there are two general strategies to assemble functionalized benzo-fused five-membered heteroarenes in the literature. The first strategy is based on transition metal-catalyzed C-H functionalization, which can directly introduce the desired functional groups to the heteroarene precursors (Scheme 2a: C-H functionalization). It has become a powerful tool to realize the selective functionalization of the challenging C4-C7 positions of indole, which is assisted by a directing group in two complementary directions (e.g. DG_1 and DG_2).[7] However, this strategy cannot be extended to the substitution-pattern tunable synthesis of benzofuran, because the oxygen atom of benzofuran cannot sever as “anchor donor” for directing group introduction, leaving the remote C6 and C7 sites almost inaccessible. The second strategy is *via* annulation, which capitalizes on individual construction of the benzene or five-membered heteroarenes (Scheme 2b: annulation). As for the synthesis of benzofuran, mostly pericyclic reactions[8] and transition metal-catalyzed cyclizations[9] were applied to forge the benzene moiety. For comparison, more studies have been devoted to the construction of the furan moiety by formal [3+2][10] cycloadditions or intramolecular ring-closure reactions[11] with prefunctionalized phenols,[10d-p, 11i-m] quinones,[10b, 10c] or phenolic ethers as starting materials.[11a-g, 11j, 11k, 12] Of all these methods, the alkyne-based benzofuran synthesis has many benefits such as easy availability and versatile reaction types, but usually it needs to sacrifice a phenolic hydroxyl group of the starting material.[10m-p, 11l, 11m, 13] Although these annulation approaches could provide a wide spectrum of substituted benzofurans, it is still challenging to incorporate free hydroxyl group into the benzene moiety due to the interference of phenolic hydroxyl groups,[10g, 10h] which usually require protection-deprotection or redox manipulation. Therefore, it is desirable for a practical and flexible avenue to free hydroxylated benzofurans with tunable substitution pattern. We thus surmised that a *de novo* synthesis strategy through formation of both benzene and furan rings could address these challenges, because there might be more possibilities for the incorporation of functional groups in the ring-forming process, which could obviate aforementioned

[*] L. Zhang,[+] Dr. T. Cao,[+] Prof. Dr. H. Jiang, Prof. Dr. S. Zhu[*]
Key Laboratory of Functional Molecular Engineering of Guangdong Province
School of Chemistry and Chemical Engineering, South China University of Technology
510640, Guangzhou (China);
E-mail: zhusf@scut.edu.cn

Prof. Dr. S. Zhu
State Key Laboratory of Elemento-Organic Chemistry
Nankai University
300071, Tianjing (China);

Prof. Dr. S. Zhu
Singfar Laboratories
510670, Guangzhou (China)

[+] These authors contributed equally to this work.

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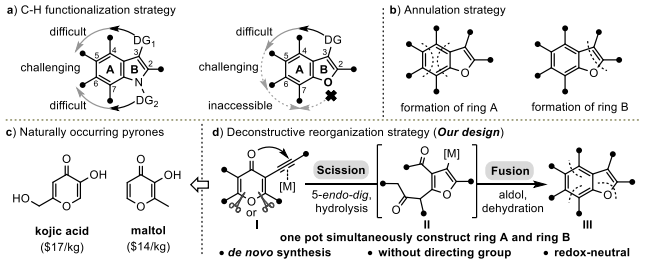
challenges of C-H functionalization and the dependence of arenes.

As two kinds of cheap and commercially available pyrone-containing compounds, kojic acid ($17/kg) and maltol ($14/kg) have been widely used in food, medicine and daily chemical industry (Scheme 2c). Furthermore, they have also been utilized as five-carbon component in oxidopyrylium-based [5+2] cycloadditions and were showcased as the key steps in the total synthesis of several complex natural products.[14] Conceptually, if the pyrone moiety of kojic acid or maltol was broken, releasing the inherent oxidation state, unlocking the embedded functional groups, awaking the dormant reactivity, and then harnessing its behaviour, it might serve as a versatile synthon for numerous transformations (Scheme 2c). In combination with these considerations and the inspiration from keto alkyne cyclization,[15] especially the cascade reaction that was initiated by π-acid activation,[16] we proposed that a suitable alkynophilic catalyst could activate the pyrone-based keto alkyne **I**, trigger the 5-*endo-dig* cyclization and then hydrolysis to give a pyrone-free furan **II**, which could then engage in an aldol cyclization and followed by dehydration process to finally deliver benzofuran **III** (Scheme 2d). As part of our continuous endeavours to develop new dearomatic cascade rearrangement of pyrones,[17] we herein would like to report an unprecedented deconstructive reorganization strategy for the *de novo* synthesis of hydroxylated benzofuran from kojic acid- or maltol-derived alkynes (Scheme 2d). In this reaction, both the benzene and furan rings were simultaneously established *via* an arene cycloisomerizaiton tandem reaction. The pyrone moiety originated from kojic acid or maltol was deconstructed and finally reorganized into the benzene ring as a six-carbon component. In this process, at least one free hydroxyl group was introduced in a substitution-pattern tunable fashion without protection-deprotection and redox adjustment.

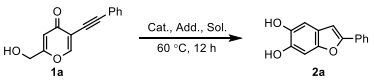


Scheme 2. Challenges and strategies in attaining benzofuran with pattern-tunable substituents.

Results and Discussion

Initially, the kojic acid-derived alkyne **1a** with an unprotected hydroxyl group was selected as the model substrate for optimization of the reaction conditions. Firstly, several gold complexes in combination with different silver salts as the additives were tested as catalysts, which resulted in a complicated system (Table 1, entries 1-5). When utilizing $Fe(OTf)_3$ and $Yb(OTf)_3$ as the catalysts, a trace amount of the desired product **2a**, bearing two free phenolic hydroxyl groups, were detected (entries 6-7). Encouraged by these observations, several other metal triflates were then examined. When $Sn(OTf)_3$ and $Bi(OTf)_3$ were applied, the desire product **2a** was furnished in 32% and 45% yields, respectively (entries 8-9). Gratifyingly, the product yield increased to 82% by using $In(OTf)_3$ as the catalyst (entry 10). Control experiment showed that the reaction was completely depressed with the addition of 4Å molecular sieve (entry 11). Nevertheless, an external addition of water didn't display any beneficial effect on the reaction results (entry 12). These results indicated that the adventitiously introduced and trace amount of water might be involved in the catalytic process.

Table 1. Optimization of the reaction conditions[a,b].



Entry	Catalyst	Additive	Solvent	Conversion **1a** [%]	Yield **2a** [%]
1	PPh_3AuCl	$AgBF_4$	DCE	100	n.d.
2	PPh_3AuCl	$AgSbF_6$	DCE	100	n.d.
3	PPh_3AuCl	$AgNTf_2$	DCE	100	n.d.
4	IPrAuCl	$AgNTf_2$	DCE	100	n.d.
5	SIPrAuCl	$AgNTf_2$	DCE	100	n.d.
6	$Fe(OTf)_3$	-	THF	100	trace
7	$Yb(OTf)_3$	-	THF	100	trace
8	$Sn(OTf)_3$	-	THF	87	32
9	$Bi(OTf)_3$	-	THF	90	45
10	**$In(OTf)_3$**	**-**	**THF**	**100**	**82 (78)[c]**
11[d]	$In(OTf)_3$	4Å MS	THF	<5	n.r.
12[e]	$In(OTf)_3$	H_2O	THF	95	76%

[a] Reaction conditions: **1a** (0.2 mmol) and 10 mmol% catalyst in 2 mL solvent stirred at 60 ºC for 12 h. [b] Yields were based on ^1H NMR analysis with 4-Nitrotoluene as internal standard. [c] Isolated yield. [d] 120 mg 4 Å molecular sieves (MS) was added [e] 0.5 eq H_2O was added. DCE: 1,2-dichloroethane; THF: tetrahydrofuran; IPr: 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene; *S*IPr: 1,3-bis (2,6-diisopropylphenyl)imidazolin-2-ylidene.

With the optimized reaction conditions (Table 1, entry 10) in hand, the substrate scope was then explored. As shown in Figure 1, kojic acid-derived substrates **1** with both aryl- and alkyl-substituted alkynes could be effectively converted into the desired C5, C6-dihydroxyl benzofurans **2**. The reaction was not strongly affected by the electronic properties of group R^1. Both electron-donating and electron-withdrawing aryl groups were well-tolerated under the reaction conditions, giving rise to the products **2a-p** in 43-78% yield. The reaction wasn't noticeably affected by the position of the substituents on the aryl group R^1 either (**2j-n**). The thiophene-containing substrate could participate in this reaction to give product **2p** in 62% yield. In addition, the pyrazole- and isoxazole-substituted benzofurans **2q** and **2r** were also obtained in 65% and 68% yields, respectively, under an elevated temperature (100 ºC). The alkyl-capped substrates could be efficiently converted to the desired products **2s**-**u** in 54-72% yield. Finally, the synthesis of dihydroxyl benzofuran **2v** without substituent on furan moiety was also achievable, albeit in a relative lower yield (36%).

Having established the indium-catalyzed reaction as a reliable and efficient method to assemble dihydroxylated benzofurans, we then proceeded to evaluate the substituent of R^2, with a desire to vary the substituent-patterns of benzene moiety. When dehydroxyl kojic acid-derived alkynes **1** (R^2 = H) were used as substrates, the reactions took place smoothly under a modified condition (10 mol% catalyst, 100 ºC). A variety of C6-hydroxyl benzofuran **2w-2ah** with different aryl and alkyl groups could be furnished in 56-76% yield.

To further investigate the generality and robustness of this methodology, other substituents of R^2 were also explored. Interestingly, when 5.0 equivalents of methanol (using as reaction reagent) were added to the reaction mixture with the bromine-substituted starting material (**1ai-1aj**, R^2 = Br), the methanol incorporated products **2ai** and **2aj** could be furnished instead in 53% and 54% yields. Furthermore, the thiol-substituted hydroxylated benzofuran **2ak** and **2al** were also obtained in good yields under the standard conditions. In addition to the substituent patterns, a series of L-shape trisubstituted hydroxylated benzofurans (C4-aryl, C5, C6-dihydroxyl benzofurans) **2am-2ap** were also prepared in 52-78% yield. The structure of the dihydroxylated benzofuran **2am** was confirmed by the X-ray diffraction analysis.

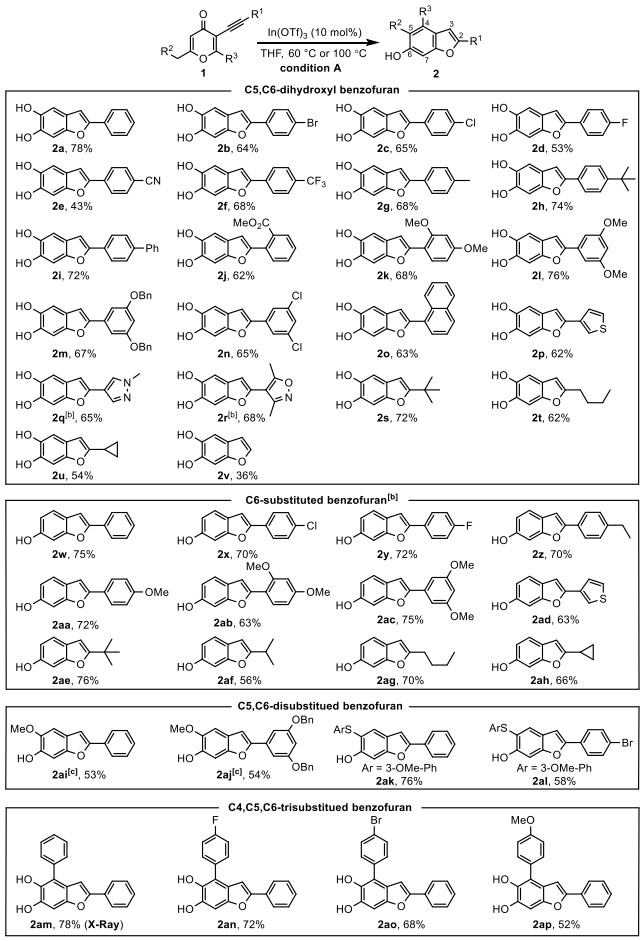


Figure 1. Substrate scope for the cycloisomerization of kojic acid-derived alkynes.[a] [a] General procedure: the reactions were stirred with **1** (0.2 mmol) and 10 mmol% $In(OTf)_3$ in 2 mL THF at 60 °C for 12 h; Isolated yields. [b] 100 °C. [c] Using **1ah** (R^2 = Br) as substrate and 5.0 equiv. MeOH was added.

Having realized four kinds of substitution patterns of hydroxylated benzofuran with kojic acid derivatives, other substitution patterns by using maltol derivatives **3** as the substrates were then exploited (Figure 2). Although the aforementioned conditions were initially found inapplicable for the maltol derivatives **3**, satisfactory results could be obtained with the addition of methanol and hydrochloric acid, which could promote the methanolysis process and the subsequent aldol cyclization, respectively. These modified conditions were also found to be robust and efficient for one-pot synthesis of C4-substituted and C4, C5-disubstituted hydroxylated benzofurans. As shown in Figure 2, both alkyl- and aryl-substituted substrates could take part in this transformation smoothly, affording the desired C4-hydroxylated benzofurans **4a**-**t** in 36-78% yield. It is noteworthy that the dimethylamino- and thiophenyl-adorned substrates were well tolerated to give **4h** and **4q** in 65% and 56% yields, respectively. In addition, when ethyl maltol-derived substrates **3** were applied, the C4, C5-disubstituted (C4-OH, C5-Me) benzofurans **4u-x** were afforded in 65-76% yield.

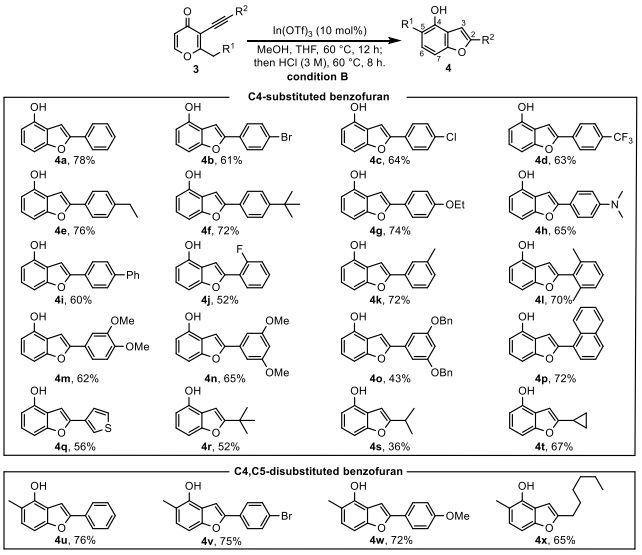


Figure 2. Substrate scope for the cycloisomerization of maltol-derived alkynes.[a] [a] General procedure: the reactions were stirred with **3** (0.2 mmol) and 10 mmol% $In(OTf)_3$ in 2 mL THF at 60 °C for 12 h, then 2 mL 3M HCl (aqueous) was added and stirred at 60 °C for another 8 h; Isolated yields;

Encouraged by the above achievements, we further advanced to address the unmet challenges of different substitution-patterns, especially for those difficult accessible C6, C7-disubstituted pattern (Figure 3). For this purpose, two new maltol-derived alkynes **5** and **7** were prepared from maltol through a three-step transformation (see details in SI). Under the condition B (See Figure 2), the C6, C7-disubstituted hydroxylated **6a** and **6b** were obtained in 76% and 53% yields, respectively, from maltol-derived alkynes **5**. Similarly, the C5, C6, C7-trisubstituted hydroxylated benzofuran **8** could also be afforded in 72% yield from the ethyl maltol-derived alkyne **7**. For the molecules **6** and **8**, there are one free hydroxyl group at C6-position and one methoxyl group (hidden hydroxyl) at C7-position, which make it possible to differentiate the C6 and C7 positions for further selective transformations or modifications. After the realization of C6, C7 substitution-pattern, endeavors were made to attain C4, C7 substitution-pattern by leveraging the C4-phenolic hydroxyl group. After the indium-acid mediated deconstructive ring-isomerization and followed by a salcomine-catalyzed oxidation, the benzofuran C4, C7-dione **9** was obtained in 38% yield from **3a**. Similarly, C4, C5, C7-trisubstituted product **11** was also achieved in 60% yield from ethyl maltol-derived starting material **3u**. The desired C4,C7-diphenols **10** and **12** could be formed in quantitative yields (disclosed by the NMR spectra of the crude reaction mixture) from *p*-quinones **9** and **11** by the $NaBH_4$ reduction, but both diphenols **10** and **12** are oxygen-sensitive and easily reoxidized to the corresponding *p*-quinones **9** and **11** automatically under

an air atmosphere. After a flash chromatograph process (about 5 min's elution), C4,C7-diphenols **10** and **12** could be obtained in 75% and 33% yields, respectively. The unsatisfactory yields could be caused by their high sensitivity to oxygen. It is noted that the quinone-type dione could serve as a versatile intermediate for scaffold diversification,[10b, 10c, 18] and the redox-shuttle effect between the *p*-quinone and diphenol might play a critical role in many bioactive molecule.[19]

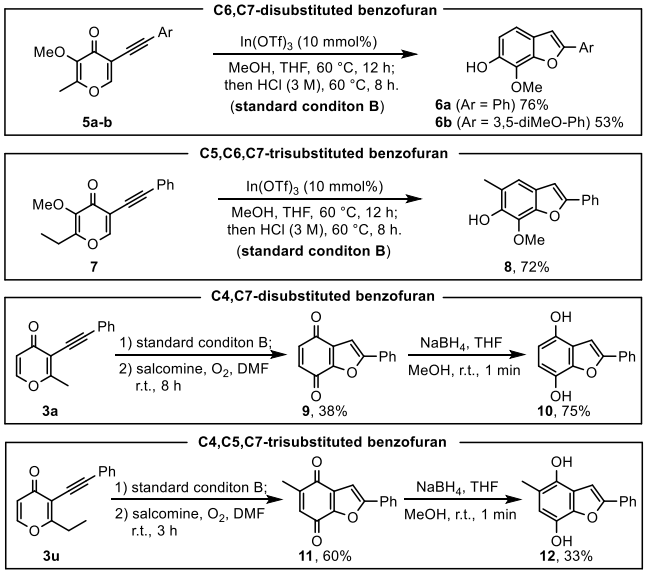
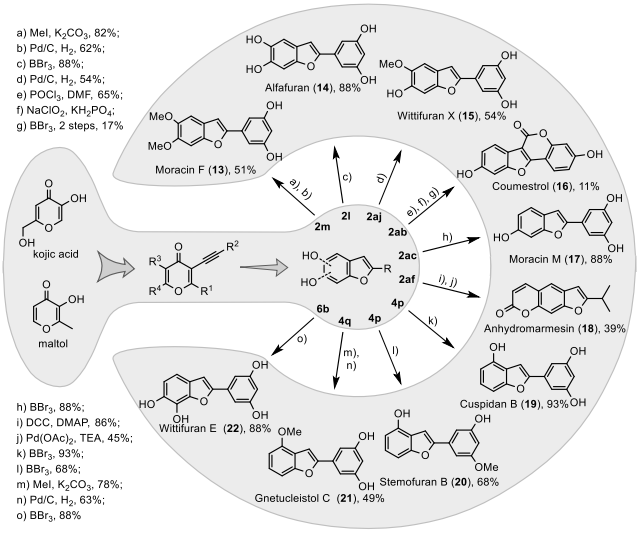


Figure 3. Avenue for different substitution patterns of hydroxylated benzofuran.

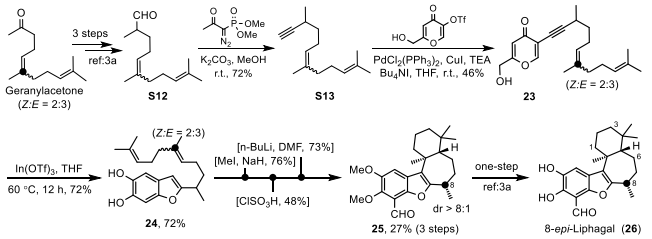
As aforementioned, a myriad of bioactive natural products and drug candidates shared a hydroxylated benzofuran motif. Herein we exhibited a collective synthesis of these compounds to demonstrate the utility of this methodology (Scheme 3). Moracin family contains a plethora of pharmacological important benzofuran, which exhibits a broad scope of biological activity, including anticancer, antimicrobial, antioxidant, anti-inflammatory and immunomodulatory.[20] Moracin F (**13**) could be obtained in 51% yield from **2m** through methylation and then hydrogenation. After the deprotection of **2l** and **2aj**, the tetraphenolic Alfafuran[21] (**14**) and triphenolic Wittifuran X[22] (**15**) were afforded in 86% and 54% yields, respectively. Coumestrol (**16**), a proliferate inhibitor of ovarian and breast cancer,[2] which could be obtained in 17% total yield from **2ab** *via* a sequence of formylation, Pinnick oxidation, demethylation and automatic esterification. Moracin M[23] (**17**), a phosphodiesterase-4 inhibitor, was also accessible from **2ac** after simple transformation[24] in 88% yield. Through esterification with propargylic acid and palladium-catalyzed cyclization,[25] **2af** could advance to anhydromarmesin (**18**) in 39% yield. Global or partial demethylation of **4p** gave the corresponding Cuspidan B (**19**, inhibit HL-60 cells)[26] and Stemofuran B (**20**, anti-inflammatory activity)[27] in 93% and 68% yields, respectively. After protecting group manipulation, **4q** was transferred to Gnetucleistol C[28] (**21**) in 49% yield. Global demethylation of **6b** could afford Wittifuran E (**22**, pancreatic lipase inhibitor)[29] in 88% yield.



Scheme 3. Application in collective total synthesis of hydroxylated benzofuran-containing natural products.

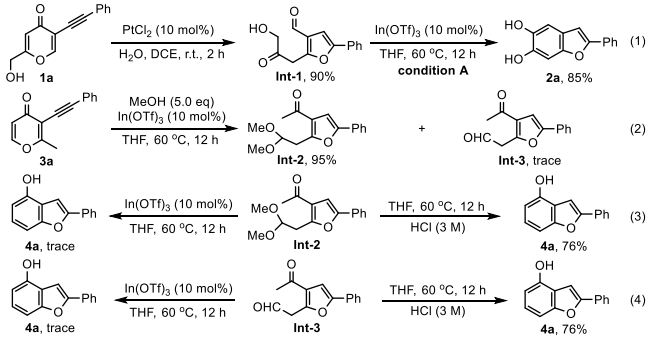
To further demonstrate the power of this methodology, Liphagal (Scheme 1), a densely functionalized hydroxylated benzofuran-containing natural product, was chose as a showcase. The interesting [6-5-7-6] tetracyclic architecture coupled with a human phosphatidylinositol-3-kinase α (PI3Kα) selective inhibitory activity[3] has attracted much attention from both pharmaceutical and synthetic community, and accumulated several elegant synthetic studies.[3, 30] For example, Andersen and co-workers firstly isolated it and determined its structure through an elegant biomimetic synthesis (11 linear steps).[3a] Subsequently, George[30a] and Alvarez-Manzaneda[30b] exploited another biomimetic synthesis independently (13 steps and 11 steps, respectively), which features a pinacol ring-expansion rearrangement. In addition, Stoltz and co-worker reported a catalytic enantioselectivity synthesis (15 steps),[30c] highlighting a combination of enantioselective α-alkylation,[31] ring expansion, and an intramolecular aryne cyclization. Lately, Winne and co-workers have realized a convergent synthesis of 5-*epi*-Liphagal (8 steps) by using an acid-catalyzed intermolecular [4+3] cycloaddition.[30d] Ferreira and co-workers accomplished the formal synthesis of Liphagal (9 steps) by using a carbenoid mediate conjugate addition as the key strategy.[30e] Herein, we would like to report a *de novo* synthetic route for the synthesis of Liphagal with the indium-triggered arene cycloisomerization as the key step. As shown in Scheme 4, the key intermediate diphenolic benzofuran **24** could be synthesized in 72% yield from the kojic acid-derived precursor **23** under the indium catalysis. The precursor **23** was prepared from Geranylacetone through a sequence of Wittig olefination, hydrolysis, Seyferth-Gilbert Homologation and Sonogashira coupling in 5 steps. By using Andersen's insightful acid-catalyzed cationic polyene cyclization conditons,[3a] the dimethylation product of **24** was smoothly evolved to an intricate tetracyclic intermediate, which, after formylation, could advance to dimethyl-8-*epi*-Liphagal (**25**) in 27% yield over 3 steps. Interestingly, the diastereoselectivity is very good (dr > 8:1) compared with Andersen's results (dr = 2.5:1). The stereochemical outcome of **25** indicated that a cationic-triggered C8 epimerization might be involved during this cyclization. The spectra of **25** were identical in all respects to the

data reported in the literatures,[3a, 30b, 30c] which represents a formal total synthesis of 8-*epi*-Liphagal (**26**).



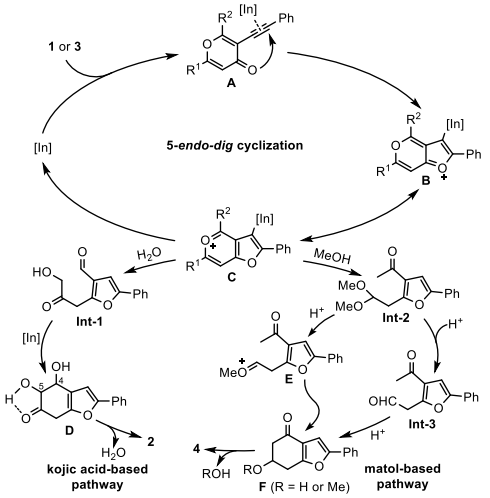
Scheme 4. Formal total synthesis of 8-*epi*-Liphagal.

To figure out the reaction mechanism, several control reactions were then performed. As shown in Scheme 5, 3-furanaldehyde (**Int-1**) could be isolated in 90% yield when kojic acid-derived alkyne **1a** was subject to a $PtCl_2$ catalysis in the presence of moisture (eq. 1). With **Int-1** as the substrate under condition A, the reaction afforded the desired hydroxylated benzofuran **2a** in excellent yield (eq. 1), which indicated that **Int-1** might be the reaction intermediate for the kojic acid-based system. Furthermore, when only 5.0 equivalents of methanol (without HCl compared with the standard condition B) were added to the reaction of maltol-derived alkyne **3a**, the acetal **Int-2** (95%) and its hydrolyzed aldehyde **Int-3** (less than 5 %) were accumulated (eq. 2). Interestingly, neither **Int-2** nor **Int-3** was converted to the desired product **4a** under the catalysis of $In(OTf)_3$, which was different with the kojic acid-based system. Further reactions showed that the aqueous HCl alone was able to promote the transformations, with the desired product **4a** was obtained in 76% yield (eqs. 3 and 4). These reactions indicated that both **Int-2** and **Int-3** might be the reaction intermediates for the maltol-based system.



Scheme 5. Mechanistic investigation.

On the basis of the above investigations, a tentative mechanism was then proposed (Scheme 6). The carbon-carbon triple bond of starting material in **1** or **3** was initially activated by the indium salt to form a π-complex **A**, which was followed by the *5-endo-dig* cyclization to generate the furanium **B** and its resonance structure pyrylium **C**. Starting from intermediate **C**, two different pathways might be expected for kojic acid-based and maltol-based systems. For the former one, the pyrylium **C** was trapped by water to give the 1, 5-dicarbonyl intermediate **Int-1**, followed by intramolecular aldol cyclization to give ketol **D**. And then selective elimination of C4-OH and aromatization led to the desired dihydroxylated benzofuran **2**. As for the maltol-based system, the pyrylium **C** was attacked by methanol to produce the acetal **Int-2**. In the presence of aqueous HCl, an intramolecular (formal) aldol cyclization occurred to deliver the furan-fused cyclohexanone **F**, which might proceed through the aldehyde **Int-3** or oxonium **E**. A sequential elimination and aromatization eventually produced the final benzofuran **4**.



Scheme 6. Proposed deconstructive arene cycloisomerization mechanism.

Conclusion

In summary, we have established a deconstructive reorganization process for a pattern-tunable synthesis of hydroxylated benzofuran in an easy handled one-pot manner by utilizing kojic acid and maltol type pyrone derived alkynes. Based on this platform, a range of substitution patterns were achieved and a large number of hydroxylated benzofurans were prepared in one-step with 100% atom economy, which enabled a collective total synthesis of different kinds of natural products (11 examples). It is note-worthy that a C8 epimer of Liphagal, containing an interesting [6-5-7-6] tetracyclic architecture, could be assembled in 10 steps from commercially available Geranylacetone, which makes it to be distinguished from previous reports. With the above advantages, we believe such a new deconstructive reorganization strategy for the *de novo* synthesis of hydroxylated benzofurans could not only inspire the chemists to design new synthetic routes for the total synthesis of benzofuran-containing complex natural products, but also help streamline the drug discovery process.

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Conflict of interest

The authors declare no competing financial interests.

Keywords: benzofuran • deconstructive reorganization • arene cycloisomerization • total synthesis • Liphagal

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Entry for the Table of Contents

Arene Cycloisomerization

Ling Zhang[+], Tongxiang Cao[+], Huanfeng Jiang, and Shifa Zhu*

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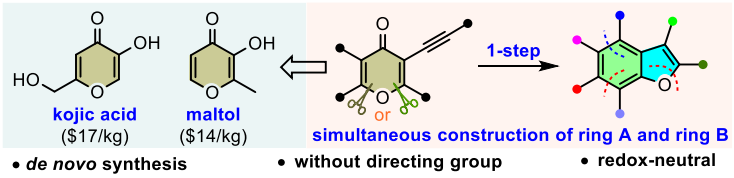
Deconstructive Reorganization: *De Novo* Synthesis of Hydroxylated Benzofuran



An unprecedented *de novo* synthesis of hydroxylated benzofuran was reported through a deconstructive arene cycloisomerization process by using kojic acid- or maltol-derived alkynes, which furnished several types of free hydroxyl group-adorned benezofurans with different substitution patterns. To showcase the utility of this methodology, a collective total synthesis of hydroxylated benzofuran-containing natural products (11 examples) was realized efficiently.