Rearrangements

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Cascade Claisen Rearrangement: Rapid Synthesis of Polysubstituted Salicylaldehydes and Total Syntheses of Hemigossypol and Gossypol

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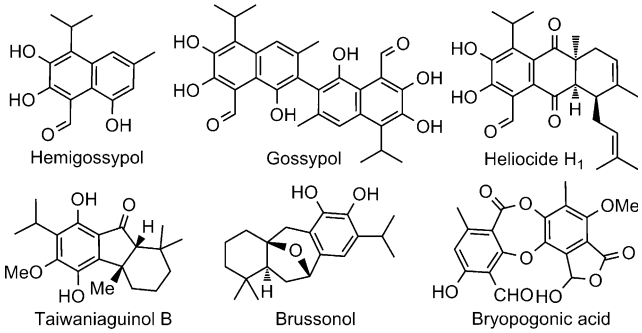
Abstract: *A cascade Claisen rearrangement of a well-organized maltol propargyl ether for the construction of polysubstituted salicylaldehydes is reported. This reaction features high atom economy (100 %), as well as catalyst-free and gram-scale conditions. Based on this novel methodology, the total synthesis of hemigossypol, gossypol, and their analogues has been realized.*

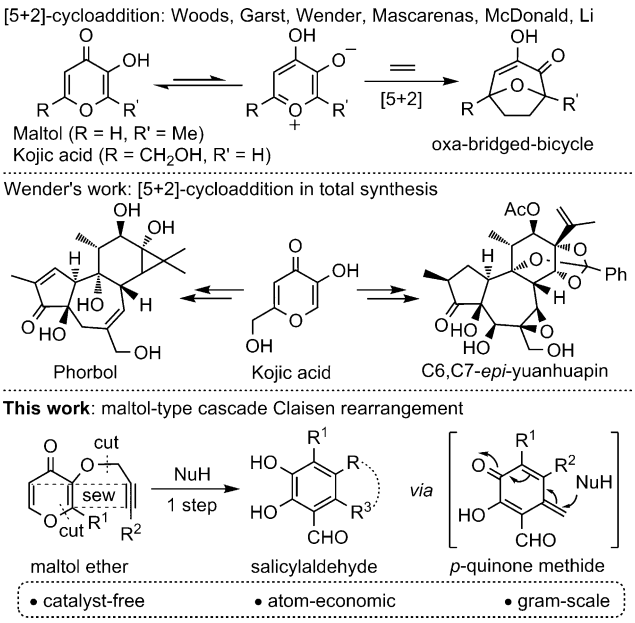
Polysubstituted salicylaldehydes and their derivatives are ubiquitous in pharmaceuticals, natural products, and agrochemicals, such as hemigossypol, gossypol, helicocide H_1, Taiwaniaguinol B, brussonol, and bryopogonic acid (Scheme 1).[1] Among them, gossypol is found in flowers, seeds, roots and foliage of cotton plants, where it serves as a defense compound against insect pests and pathogens.[2] It has attracted a lot of interest for its multiple pharmacological activities including spermicidal, antiparasitic, anticancer, and antiviral activities.[3] Hemigossypol is the biosynthetic precursor of gossypol and has shown improved antifungal activity compared to gossypol.[4] Despite the tremendous progress achieved in transition metal-catalyzed polyphenol synthesis,[5] construction of these compounds in a concise manner still remains a difficult problem because of low selectivity[6] and oxidant sensitivity (such as oxidative phenolic coupling and dearomatic reactivity),[1d,e,7] which may result in protecting-group or redox manipulation and multistep processes for the introduction of other substituents.

Traditionally, Diels–Alder[8] and 6π-electrocyclization[9] reactions can assemble the cyclohexene skeleton, but further oxidation is commonly required to access the benzene structure. Dehydro-Diels–Alder and transition metal-catalyzed [2+2+2] reactions can form the benzene skeleton, but a mixture of isomers is often obtained, and the introduction of polyphenolic hydroxy groups is difficult.[10] The complementary methods using a parent arene to introduce the desired functional groups by means of Friedel–Crafts reaction, S_NAr reaction, cross-coupling reaction, or C(sp^2)–H activation can serve as a good solution. However, these reactions usually need either pre-activation, prefunctionalization of the arene, directing-group assistance, or extensive reaction condition optimization for satisfactory selectivity and reactivity.[11] Therefore, the development of efficient and practical methods for the rapid synthesis of polysubstituted salicylaldehyde derivatives would be a challenging but promising project.

Maltol and kojic acid, pyrone-containing natural products, have been widely used in oxidopyrylium-based [5+2] cycloadditions (Scheme 2).[12] In addition to the synthetic methodology, Wender and co-workers also applied this method to the landmark total syntheses of phorbol and C6,C7-epi-yuanhuapin.[13] In these [5+2] cycloaddition reactions, the pyrone moiety served as a five-carbon synthon to assemble the oxa-bridged bicyclic system. Herein we disclose an entirely new reaction type for pyrone, a cascade Claisen rearrangement of the well-organized maltol propargyl ether for rapid synthesis



Scheme 1. Natural products containing polysubstituted phenols.



Scheme 2. Pyrone-based transformations.

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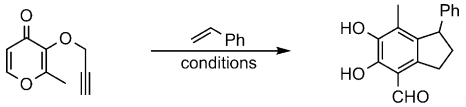
of polysubstituted salicylaldehyde by a cut-and-sew strategy,[14] where the aromatic pyrone is taken apart and then incorporated into the benzene ring (Scheme 2). The reaction is a catalyst-free process and proposed to occur through 1,6-Michael addition to the *p*-quinone-methide (*p*-QM) intermediate. This protocol features high atom economy (100%) and gram-scale conditions.

First, the maltol propargyl ether **1a** (Table 1), which can easily be prepared from naturally occurring maltol and propargyl bromide in only one step with a 94% yield, was chosen as the model substrate for this investigation. Styrene was used as the nucleophile to trap the proposed *p*-QM intermediate (Scheme 2).[15] As shown in Table 1, gold salts were initially utilized as the catalyst owing to their high efficiency in promoting the transformation of alkynes through activating the C≡C bond.[16] However, no product was detected at 60 °C, and the reaction did not work even at an elevated temperature of 120 °C with either $Ph_3PAuCl/AgBF_4$ or Ph_3PAuCl/NaBArF as the catalyst (entries 1–3). Encouragingly, the 1,6-Michael addition/Friedel–Crafts product **2a** was detected in 53% yield when the temperature was raised to 150 °C with CH_3CN as the solvent (entry 4). However, the control reaction without the gold salt proceeded equally well, which indicated that this reaction is a noncatalytic thermolysis process (entry 5). In the absence of catalysts and additives, the yield of **2a** was enhanced to 75% by variation of the solvent (entries 6–8; see the Supporting Information for more details).

Table 1: Optimization of the reaction conditions.[a]



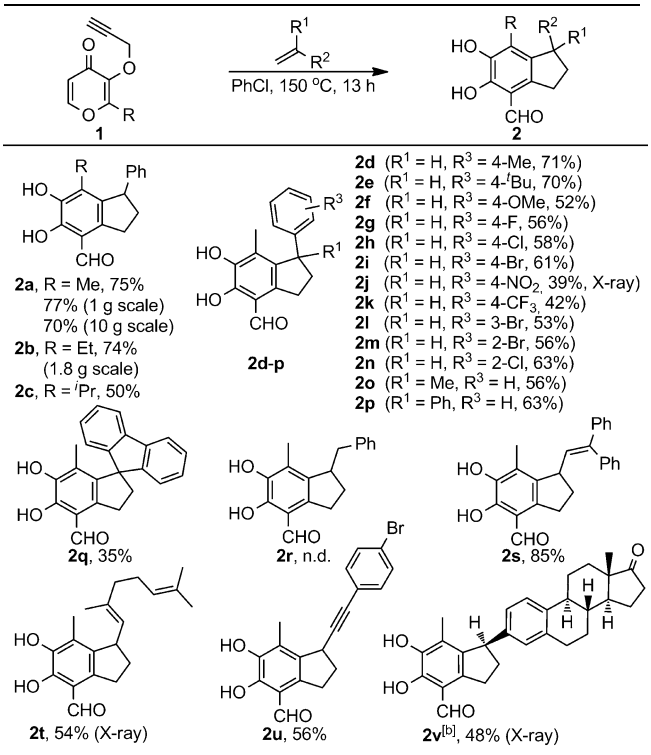
1a **2a**

Entry	Cat.	Add.	Sol.	*T* [°C]	Yield [%]
1	Ph_3PAuCl	$AgBF_4$	DCE	60	n.d.
2	Ph_3PAuCl	$AgBF_4$	DCE	120	n.d.
3	Ph_3PAuCl	NaBArF	DCE	120	n.d.
4	Ph_3PAuCl	NaBArF	MeCN	150	53
5	–	–	MeCN	150	59
6	–	–	DCE	150	67[b]
7	–	–	PhMe	150	64[b]
8	–	–	PhCl	150	75[b]

[a] Unless otherwise noted, the reaction was performed with **1a** (0.25 mmol) and styrene (0.88 mmol) for 13 h under a N_2 atmosphere. The yield was determined by ^1H NMR analysis. NaBArF = Na[B-(3,5-$(CF_3)_2C_6H_3)_4$]. [b] Yield of isolated product. DCE = 1,2-dichloroethane, n.d. = not determined.

With the optimized reaction conditions (Table 1, entry 8) in hand, the substrate scope was then explored. As shown in Table 2, this cascade reaction was successfully extended to propargyl ethers (**1**) derived from different maltols. For example, the propargyl ethers from ethyl maltol and isopropyl maltol were transformed into the corresponding products **2b** and **2c** in 74 and 50% yield, respectively. It is noted that the gram-scale reactions proceeded smoothly as well, thus giving the desired products in good yields (**2a**,**b**: 1–10 gram scale).

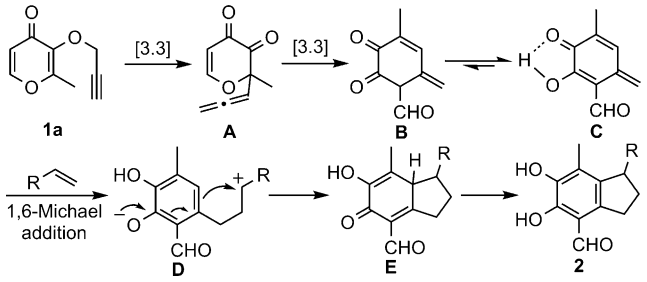
Table 2: Evaluation of various alkenes and maltol ethers.[a]



[a] Reaction conditions: **1** (0.25 mmol) and alkene (0.88 mmol), under N_2. [b] Estrone-derived styrene (0.2 mmol) and **1a** (0.7 mmol). For X-ray data[20] please see the Supporting Information.

Furthermore, the reactions of **1a** with a variety of alkene substrates as nucleophiles were carried out (**2d–v**). In addition to styrene, various styrene derivatives effectively reacted with **1a**, thus furnishing **2d–n** in 39–71% yields. Both electron-rich and electron-poor styrene derivatives functioned well to afford the desired fully substituted salicylaldehydes. The results indicated that electron-rich styrenes were better substrates and gave the products in higher yields. When gem-substituted styrenes were used, products with a quaternary carbon center were formed in moderate yields (**2o**,**p**). A sterically congested spirocompound was tolerated as well, albeit with a lower yield (**2q**). However, a simple aliphatic alkene did not work (**2r**). The more electron-rich conjugated diene and enyne were investigated as well, thus furnishing the corresponding products in good yields (**2s–u**). It is worth mentioning that estrone-derived styrene was also a good substrate for this reaction, thus delivering the desired product **2v** in 48% yield. In addition, we have tried both allyl trimethylsilane and allyl boronic acid pinacol for this reaction, but no desired products were observed. Internal alkyne ethers were also treated with styrene under the standard reaction conditions, however, it only led to complex mixtures (see details in the Supporting Information). The structures of compounds **2j**, **2t**, and **2v** were confirmed by X-ray diffraction analysis.

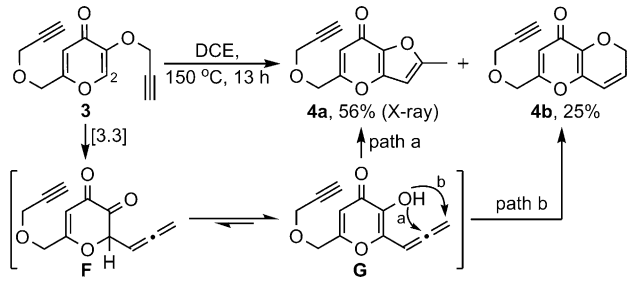
A plausible mechanism is proposed in Scheme 3. The initial dearomatization through the propargylic-Claisen rearrangement establishes a well-organized 1,5-ene-allene inter-



Scheme 3. Proposed mechanism.

mediate (**A**), which then undergoes a second allenylic-Claisen rearrangement to furnish the aldehyde **B**. After tautomerization, the key intermediate *p*-QM **C** is formed and trapped by the intermolecular 1,6-Michael addition of an alkene to give **D**, followed by an intramolecular Friedel–Crafts reaction and 1,5-hydrogen shift to deliver the desired product **2**.

To investigate the necessity of the substituent at the C2-position, a progargyl ether of kojic acid (**3**) was then synthesized (Scheme 4). Consistent with the report of

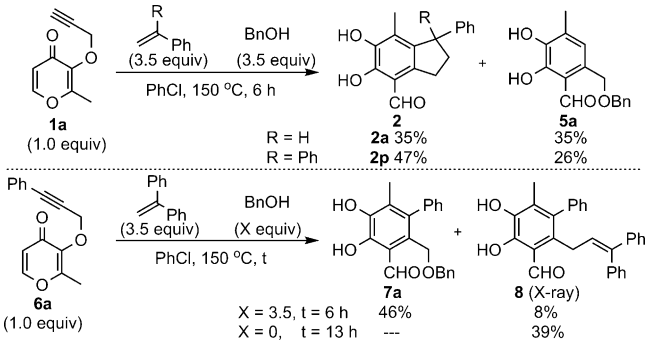


Scheme 4. Investigation of the substituent effect at C2-position. For X-ray data[20] please see the Supporting Information.

Elmore and co-workers,[17] the furo[3,2-*b*]pyrone **4a** was formed in 56% yield when the reaction was conducted in the absence of a trapping reagent. At the same time, the unexpected product chromone **4b** was also obtained in 25% yield. Compounds **4a** and **4b** might come from the cyclization of the rearomatized allene intermediate **G**. These results demonstrated the importance of the anchor group at the C2-position, which might block the rearomatization pathway.

To trap the cationic intermediate **D**, benzyl alcohol, which might act as a nucleophile, was added to the reaction mixture of **1a** and styrene (Scheme 5). A mixture of **2** and **5a** was ultimately furnished rather than the desired three-component adducts. Fortunately, when the internal alkyne ether **6a** was used, **7a** and **8** were obtained in 46 and 8% yield, respectively. The yield of **8** was increased to 39% when no alcohol was added. **8** might come from the trapping of the **6a**-derived *p*-QM intermediate by 1,1-diphenylethylene to form a relatively stable cationic intermediate, followed by an elimination process. Although we failed to directly trap **D**, the generation of **8** demonstrated that a **D**-like cationic intermediate was involved in the cascade process.

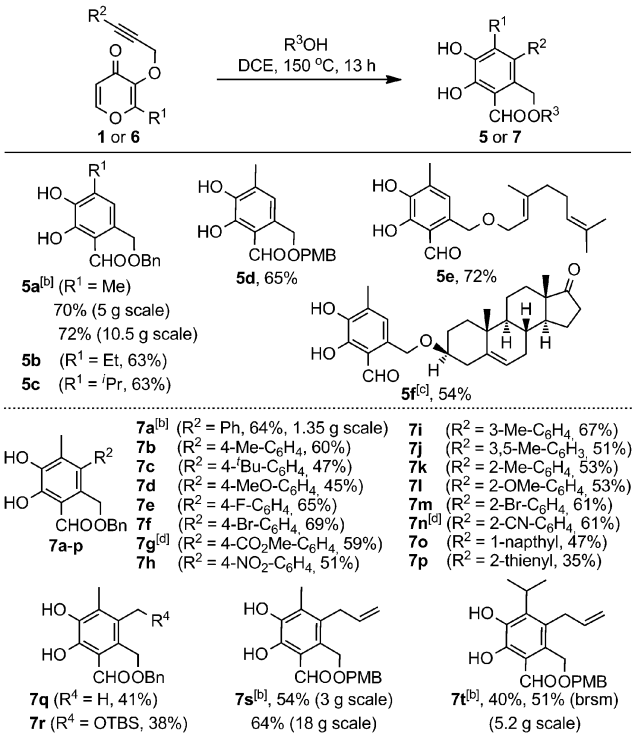
Based on the above observation, we then moved to trap the proposed *p*-QM intermediate with different alcohols



Scheme 5. Attempts to trap the cationic intermediate. For X-ray data[20] please see the Supporting Information.

(Table 3), aiming for penta- and hexasubstituted salicylaldehyde derivatives, which might be used as a key precursor for the total synthesis of hemigossypol and gossypol. Considering the benzyl ether could be easily removed, benzyl alcohol (BnOH) was initially tested as the nucleophile. As expected, the desired pentasubstituted salicylaldehyde products **5a–c** were produced in 63–72% yields by using terminal propargyl ethers (**1**) derived from different maltols. The reaction was easily scaled up to 10-gram quantities without loss of yield (**5a**). *p*-Methoxybenzyl alcohol (PMBOH) was also a good nucleophile for this reaction, thus affording the desired PMB-protected ether **5d** in 65% yield. Naturally occurring alcohols geraniol and prasterone were also employed to trap the

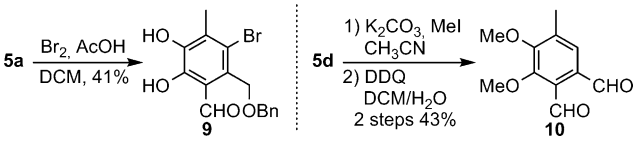
Table 3: Evaluation of various alcohols and maltol ethers.[a]



[a] Reaction conditions: **1** or **6** (0.2 mmol) and alcohol (0.7 mmol), DCE, 150 °C, 13 h, under N_2. [b] PhCl as solvent. [c] Prasterone (0.2 mmol) and **1a** (0.7 mmol). [d] 140 °C, 24 h. Bn = benzyl group, PMB = *p*-methoxybenzyl.

transient Michael acceptor, thus leading to the corresponding products **5e** and **5f** in 72 and 54% yield, respectively. In addition, the fully substituted salicylaldehyde products **7a–t** were furnished with internal propargyl maltol ethers (**6**) as the substrates and either BnOH or PMBOH as the nucleophile. As shown in Table 3, the reactions proceeded smoothly when the propargyl group was capped with different aryl groups (**7a–p**). It seems that the reaction was not very sensitive to the electronic properties of the aryl groups (**7a–n**), with the product yields ranging from 45 to 69%. The structure of **7g** was unambiguously confirmed by X-ray diffraction analysis. The naphthyl-, thienyl-, and alkyl-substituted alkynes were tolerated as well, giving the desired products **7o–r** in slightly lower yields. The allylic handle group containing products **7s** and **7t**, aimed at the total synthesis of gossypol and its analogues, were obtained on a large scale in an acceptable yield.

In the effort to demonstrate the synthetic utility of this procedure, we took advantage of the highly substituted parent benzene for further transformations. As shown in Scheme 6, **5a** was transformed into the bromo-salicylaldehyde **9** in 41% yield with Br_2/HOAc as the brominating reagent. Furthermore, the deprotection and oxidation of **5d** gave rise to the aldehyde **10** in 43% yield.

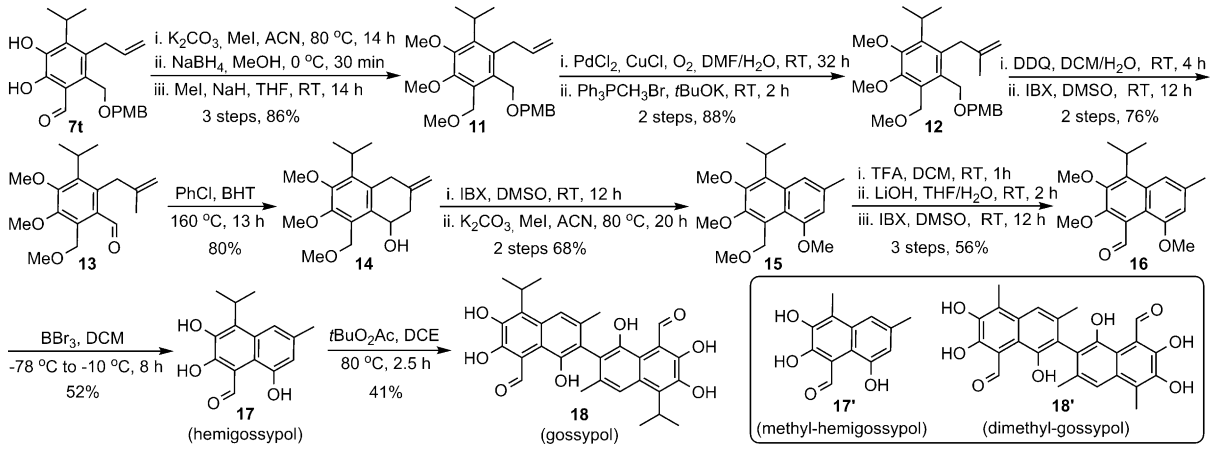


Scheme 6. Further transformation of products **5**. DCM = dichloromethane, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

To further illustrate the utility of this unique methodology, we began the total synthesis of hemigossypol, gossypol, and their analogues (Scheme 7). The synthesis started with methylation and reduction of the fully substituted salicylaldehyde **7t** to furnish **11** in 86% yield over three steps. After Wacker oxidation and a Wittig reaction of **11**, the alkene **12** was obtained in 88% yield. Deprotection of **12** with DDQ and subsequent oxidation with IBX gave the aldehyde **13** in 76% yield. An efficient intramolecular Alder-ene reaction occurred using **13** for assembly of the bicyclic tetrahydronaphthol **14** in 80% yield, which differed from the previous synthetic strategy employing a Friedel–Crafts reaction[18,19] to construct the naphthalene skeleton. Afterward, oxidation and methylation took place to generate the naphthalene **15** in 68% total yield. According to the reported protocol,[18c] **15** was selectively deprotected, followed by IBX oxidation to provide **16**, which was then globally demethylated by BBr_3 to deliver hemigossypol (**17**) in 52% yield. The endgame to complete the total synthesis of gossypol (**18**) was achieved by treating **17** with $tBuO_2Ac$ under nitrogen at 80°C for 2.5 hours; **18** was obtained in 41% yield. The spectral data of synthetic **17** and **18** were in full agreement with those reported for these natural products. It is worth mentioning that the methyl analogues of hemigossypol (**17′**) and gossypol (**18′**) were also obtained from the polysubstituted salicylaldehyde **7s** following a similar procedure (see the Supporting Information for details).

Previously, several groups realized the total synthesis of gossypol. In 1958, Edwards reported the first synthesis using a late-stage formylation strategy (9 steps).[18a,19a] In 1997, Meyers achieved the first asymmetric total synthesis of (*S*)-(+)-gossypol (23 steps and 8.71% yield), which highlighted a chiral oxazoline-induced diastereoselective Ullmann coupling.[18b] Recently, Wang developed a practical route to gossypol from commercially available carvacrol (19 steps and 6.67% yield), and it featured an oxidative phenolic dimerization.[18c] Our synthesis using **7t** as the starting material successfully preinstalled all the required functional groups on the phenyl ring, which is otherwise difficult to access.[18c,19h] Although the inevitable protection/deprotection of these groups resulted in a slightly lengthy procedure (15 steps and 3.73% yield), the intramolecular carbonyl-ene reaction for the rapid synthesis of the polysubstituted naphthol skeleton marks another highlight to this total synthesis.

In summary, we have disclosed a novel reaction type for pyrone, the cascade Claisen rearrangement of a well-organ-



Scheme 7. Total synthesis of hemigossypol, gossypol, and their analogues. ACN = acetonitrile, BHT = 2,6-di-*tert*-butyl-4-methylphenol, DMF = *N*,*N*-dimethylformamide, DMSO = dimethylsulfoxide, IBX = 2-iodoxybenzoic acid, TFA = trifluoroacetic acid.

ized maltol propargyl ether for the rapid synthesis of polysubstituted salicylaldehyde through a cut-and-sew strategy, where the aromatic pyrone is taken apart and then incorporated into a benzene ring. This reaction is a catalyst-free process and proposed to go through the cascade dearomatic propargylic-Claisen rearrangement/allenylic-Claisen rearrangement/1,6-Michael addition. It features high atom economy (100%) and easy scale-up (up to 18-gram quantities). Based on this methodology, we also realized the total synthesis of hemigossypol, gossypol, and their analogues, and highlighted the maltol-type cascade Claisen rearrangement and an intramolecular Alder-ene reaction. Given the obvious advantages, this method holds great potential for the synthesis of polyphenolic natural products.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: arenes · natural products · rearrangements · synthetic methods · total synthesis

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