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# Efficient total synthesis of dehydro- $\delta$ -viniferin through metal–halogen exchange cyclization†

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Bioactive dehydro- $\delta$ -viniferin was synthesized through an efficient and practical eight-step route, achieving an overall yield of 27%. The synthesis process involves an intramolecular cyclization and dehalogenation *via* a metal–halogen exchange, producing 3-arylbenzofuran, with the di-iodinated  $\alpha$ -aryloxyketone serving as the key intermediate. Long reaction times and the use of excess reagent *i*-PrMgCl·LiCl facilitate metal–halogen exchange cyclization and dehalogenation. This synthetic approach, scalable for the production of analogs, was successfully conducted for the first time in multigram quantities.

## Introduction

Oligostilbenes, a class of polyphenols derived from resveratrol and its analogs, have attracted considerable interest over the past three decades due to their unique structures and diverse bioactivities.<sup>1–3</sup> Stilbene dimers with a 2,3-diarylbenzofuran skeleton, such as dehydro- $\delta$ -viniferin (1), anigopreissin A (2), and amurensin H (3) (Fig. 1), display potent anti-inflammatory, antioxidant, antifungal, antibacterial, and anticancer activities.<sup>3,4</sup> Resveratrol dimers with a benzofuran skeleton have been recently identified as novel inhibitors of the T3SS (type III secretion system) in *Y. pseudotuberculosis* and *P. aeruginosa*.<sup>5</sup> Dehydro- $\delta$ -viniferin (1), a benzofuran derivative of the natural product  $\delta$ -viniferin, has shown substantial inhibitory activity against T3SS, better efficacy in rescuing eukaryotic cells from infection, and strong toxicity toward eukaryotic cells at high concentrations.<sup>5</sup> Additionally, compound 1 exhibited remarkable antibacterial activity against *S. aureus* and antioxidant properties.<sup>6,7</sup>

Considering their interesting structure and unexplored potential in medicine, several synthetic approaches to these compounds have been reported. Notable strategies include the biotransformation strategy reported by Beneventi *et al.*<sup>7</sup> and the chemically controlled approaches described by Mattio, Shaw, and, most notably, the Elofsson groups.<sup>6,8,9</sup> As described by Beneventi *et al.*,<sup>7</sup> dehydro- $\delta$ -viniferin 1 was semi-synthesized through a laccase-biocatalyzed dimerization of resveratrol, followed by a dehydrogenation reaction of  $\delta$ -viniferin. Its total

synthesis was also realized through a one-pot, two-step Sonogashira cyclization of *o*-iodophenol and 4-ethynylanisole, as reported by Mikael Elofsson *et al.*<sup>9</sup>

In previous work,<sup>10</sup> the stilbene dimer dehydro- $\delta$ -viniferin was successfully synthesized in nine steps, with the Amberlyst 15-catalyzed cyclodehydration of  $\alpha$ -aryloxyketone serving as the key step. However, the lower yield proved to be less effective to some extent. Therefore, developing a facile and practical synthetic route is necessary for further investigating compound 1. This paper reports a highly efficient and operationally convenient route to the dehydro- $\delta$ -viniferin and its analogs, using metal–halogen exchange cyclization and dehalogenation as the key step, and at a scale that addresses the demands for structure–activity relationship studies.

## Results and discussion

Previous research demonstrated that the low yield in the construction of 2-arylbenzofuran catalyzed by Amberlyst 15 led to a less efficient synthetic route for the synthesis of compound 1.<sup>10</sup> Literature and experiment reports revealed that the

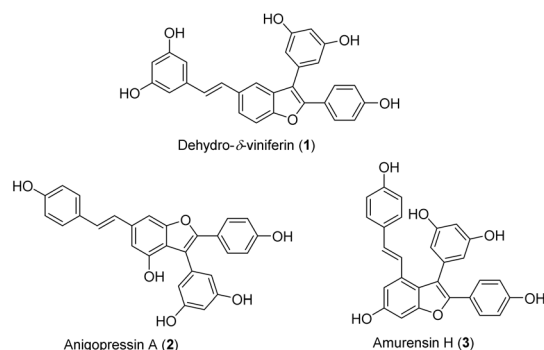


Fig. 1 Active stilbene dimers with 2,3-diarylbenzofuran skeleton.

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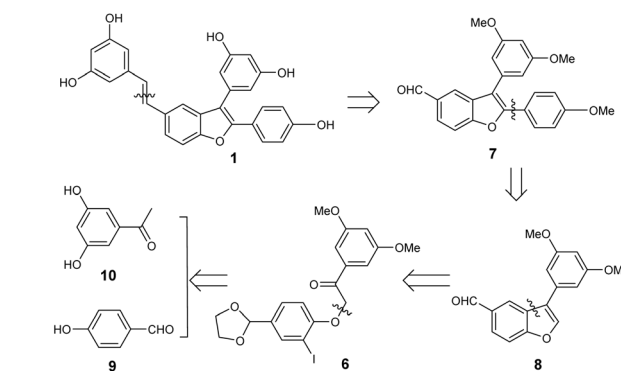
‡ Jinfang Cao and Qibin Zhu contributed equally to this work.



cyclodehydration reaction of  $\alpha$ -aryloxyketone (**4**) was possible,<sup>10–13</sup> but the cyclodehydration reaction of  $\alpha$ -aryloxyketone (**5**) proved to be challenging in the same manner (Scheme 1). The lower reactivity of intermediate (**5**), which lacks methoxy groups on the aromatic rings, combined with the instability of the ether linkage, resulted in a lower yield during cyclodehydration. Constructing the 2-arylbenzofuran intermediate **5a** using the cyclodehydration reaction in this procedure is impractical. Thus, the critical issue that must be addressed lies in achieving the installation of the 2-arylbenzofuran intermediate with a higher yield.

As reported in the literature,<sup>14,15</sup> benzofuran carboxaldehyde can be generated in high yield *via* a metal–halogen exchange between iodo ketone and methyl lithium, followed by treatment with PTSA. Based on these results, this study assumed that metal–halogen exchange using alkyllithium reagents, followed by treatment with PTSA in dichloromethane, could provide a simple and convenient method for synthesizing dehydro- $\delta$ -viniferin. Accordingly, iodo ketone **6** has been selected as the key synthetic precursor for compound **1**, and the retrosynthetic route is designed and outlined in Scheme 2. The target compound **1** could be prepared through the olefination of benzofuran aldehyde **7**. This aldehyde could be prepared *via* a transition-metal-catalyzed direct C–H activation of benzofuran **8**, followed by intermolecular coupling with an appropriate aryl bromide. The requisite **8** is expected to be derived from iodo ketone **6**, which can be conveniently prepared from commercially available 4-hydroxybenzaldehyde (**9**) and 3,5-dihydroxyacetophenone (**10**).

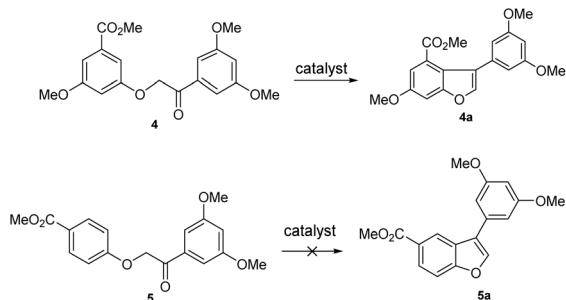
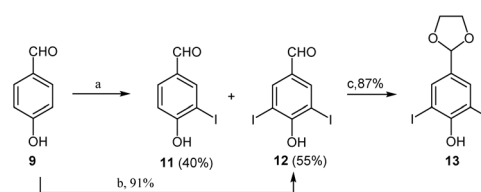
As outlined in Scheme 3, the synthesis began with the preparation of the required 3-iodo-4-hydroxyaldehyde (**11**). Following the iodination reaction described by Castanet *et al.*,<sup>16,17</sup> iodination of 4-hydroxybenzaldehyde (**9**) was conducted in the presence of NIS (1.2 eq.) and trifluoroacetic acid. However, the reaction produced an inseparable mixture of the monoiodinated benzaldehyde **11** and diiodinated benzaldehyde (**12**) in a 43 : 57 ratio, instead of the target product **11**. Thus, the molar ratio of the substrate to reagent was altered from 1 : 1.2 to 1 : 1.8, or 1 : 2.2, to improve the reaction efficiency. As a result, the diiodinated product **12** was obtained in 91% yield at a ratio of 1 : 2.2, though the monoiodinated product **11** was still unsuccessfully isolated in higher yield. Theoretically, subsequent dehalogenation reactions at the benzofuran ring after cyclization can be easily conducted; thus,

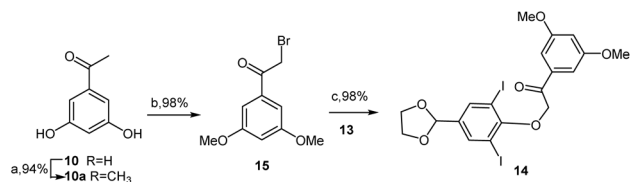
Scheme 2 Retrosynthetic analysis of dehydro- $\delta$ -viniferin (**1**).

di-iodinated product **12** remains a viable intermediate for the designed synthetic route. Therefore, this strategy is advantageous compared to using the monoiodinated product as the key intermediate.<sup>15,18</sup> Afterward, protection of the aldehyde **12** using TMSCl and ethylene glycol under refluxing dichloromethane conditions successfully yielded the glycol acetal **13** in 87% yield.<sup>19</sup>

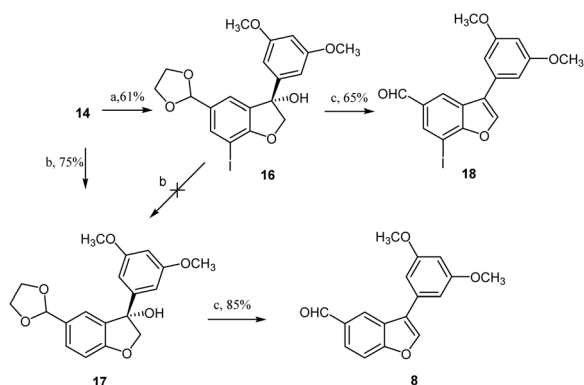
Using prepared glycol acetal **13**, this study focused on constructing the di-iodinated  $\alpha$ -aryloxyketone **14**, which was achieved through the etherification of phenol **13** with 2-bromo-3,5-dimethoxyacetophenone (**15**) in boiling acetone in the presence of potassium carbonate, which resulted in a 98% yield. Compound **15** was easily synthesized from commercially available 3,5-dihydroxyacetophenone **10** *via* methylation with methyl iodide in acetone, followed by  $\alpha$ -bromination with  $\text{TBABr}_3$  in THF and methanol (Scheme 4).<sup>11–13</sup>

After preparing the di-iodinated  $\alpha$ -aryloxyketone **14**, the installation of the key intermediate 3-arylbenzofuran **8** *via* a metal–halogen exchange reaction commenced (Scheme 5). Previous reports indicated that metal–halogen exchange with alkyllithium is faster than with a carbonyl group.<sup>20,21</sup> Hence, the approach described by Kraus and Kim was initially explored, and compound **14** was treated with three equivalents of methyl lithium at  $-78$  °C in THF.<sup>14,15</sup> Unfortunately, this reaction resulted in a complex mixture, with no detection of the expected monoiodinated benzofuran **16**, as indicated by TLC. Furthermore, using butyllithium instead of methyl lithium, the metal–halogen exchange reaction of **14** in THF generated only the dehalogenated starting compound, rather than the target

Scheme 1 Cyclodehydration of  $\alpha$ -aryloxyketones **4** and **5**.Scheme 3 Iodination and protection of 4-hydroxybenzaldehyde **9**. Reagents and conditions: (a) NIS (1.2 eq.), TFA, r.t., 6 h, 40% (**11**), 55% (**12**); (b) NIS (2.2 eq.), TFA, r.t., 6 h, 91%; (c) TMSCl, DCM, ethylene glycol, reflux, 18 h, 87%.



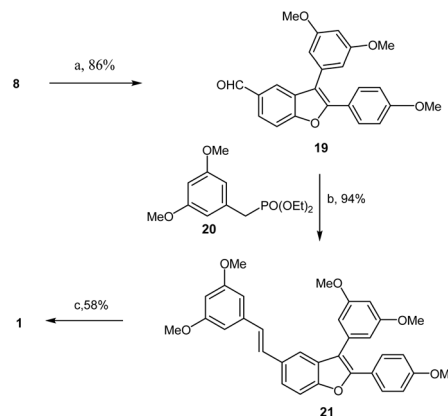
**Scheme 4** Synthesis of di-iodinated  $\alpha$ -aryloxyketone **14**. Reagents and conditions: (a)  $\text{CH}_3\text{I}$ ,  $\text{K}_2\text{CO}_3$ , acetone, r.t., 24 h, 94%; (b)  $\text{TBABr}_3$ , THF-methanol, reflux, 3 h, 98%; (c)  $\text{K}_2\text{CO}_3$ , acetone, reflux, 3 h, 98%.



**Scheme 5** Metal-halogen exchange cyclization, dehalogenation and dehydration reaction of di-iodinated  $\alpha$ -aryloxyketone **14**. Reagents and conditions: (a)  $i\text{-PrMgCl}\cdot\text{LiCl}$  (3.5 eq.), THF,  $-78^\circ\text{C}$ , 0.5 h, 61%; (b)  $i\text{-PrMgCl}\cdot\text{LiCl}$  (3.5 eq.), THF,  $-78^\circ\text{C}$ , 2 h, 75%; (c)  $p\text{-TsOH}$ , DCM, r.t., 2 h, 65% or 85%.

compound **16**. Intensive exploration of the reaction conditions surprisingly revealed that exposure of **14** to 3.5 equivalents  $i\text{-PrMgCl}\cdot\text{LiCl}$  in THF at  $-78^\circ\text{C}$  for 0.5 h, following the reported procedure,<sup>22,23</sup> generated the desired monoiodinated benzofuran **16** in 61% yield. However, when the reaction time was extended to 2 h, intermediate **14** was unexpectedly directly converted into the dehalogenated alcohol **17** in 75% yield, instead of the expected monoiodinated product **16**. This finding indicates that a longer reaction time facilitates the intramolecular cyclization and dehalogenation simultaneously. Further exploration indicates that the longer reaction time and using more than 3.5 equivalent reagents ( $i\text{-PrMgCl}\cdot\text{LiCl}$ ) were crucial for generating dehalogenated product **17**. By contrast, when monoiodinated alcohol **16** was treated under the same conditions, the expected dehalogenated product **17** remained undetected in the product mixture, as indicated by TLC.

With the efficient construction of alcohol **17** realized, the path was cleared for completing the synthesis of aldehyde **8**, as illustrated in Scheme 5. Based on previous work reported in the literature,<sup>14,15,24</sup> treatment of alcohol **17** or monoiodinated alcohol **16** in dichloromethane with PTSA (15% mol) at room temperature resulted not only in dehydration but also in the deprotection of the dioxolane, generating the desired aldehyde **8** or monoiodinated aldehyde **18** in 85% and 65% yields, respectively. Subsequently, aldehyde **8** was reacted with 4-bromoanisole in the presence of  $\text{Pd}(\text{OAc})_2$  (0.2 equiv.) and  $\text{Cs}_2\text{CO}_3$  (2 equiv.) at  $140^\circ\text{C}$  in DMA, producing aldehyde **19** in 86%



**Scheme 6** Synthesis of dehydro- $\delta$ -viniferin **1**. Reagents and conditions: (a) 4-bromoanisole,  $\text{Pd}(\text{OAc})_2$ ,  $\text{Cs}_2\text{CO}_3$ ,  $\text{PCy}_3\cdot\text{HBF}_4$ , DMA,  $140^\circ\text{C}$ , 86%; (b)  $t\text{-BuOK}$ , THF,  $0^\circ\text{C}$  – r.t., 94%; (c)  $\text{BBr}_3$ , DCM,  $-45^\circ\text{C}$ , 58%.

yield. The Horner–Wadsworth–Emmons-type olefination of **19** with diethyl 3,5-dimethoxybenzylphosphonate (**20**) in THF at  $0^\circ\text{C}$  to room temperature resulted in the formation of permethylated dehydro- $\delta$ -viniferin (**21**) in 94% yield. Finally, treatment **21** with  $\text{BBr}_3$  in dichloromethane at  $-45^\circ\text{C}$  to room temperature for 15 h successfully yielded the target compound, dehydro- $\delta$ -viniferin, in 58% yield (Scheme 6).

## Conclusions

Overall, this study developed an efficient, concise, and practical total synthetic route to the active resveratrol dimer, dehydro- $\delta$ -viniferin, in eight steps, with an overall yield of 27% from 3,5-dihydroxyacetophenone. A metal-halogen exchange and dehalogenation was used to construct the key intermediate, 3-arylbenzofuran, with the di-iodinated  $\alpha$ -aryloxyketone serving as the key intermediate. Extended reaction times and excess reagent  $i\text{-PrMgCl}\cdot\text{LiCl}$  facilitate metal-halogen exchange cyclization and dehalogenation. The starting materials are readily available, and the reaction is operationally convenient. This synthetic approach, which is scalable for analogs, was successfully applied to multi-gram quantities for the first time, providing the necessary amounts for further studies on the bioactivity of dehydro- $\delta$ -viniferin. With sufficient quantities currently available, modifications of dehydro- $\delta$ -viniferin are presently underway.

## Experimental

Synthetic procedures and full characterization data are provided in the ESI.†

## Data availability

The data supporting this article have been included as a part of the ESI.† ESI† includes synthetic procedures, compound characterization,  $^1\text{H}$ , and  $^{13}\text{C}$  NMR, and HRMS spectra (PDF).



## Author contributions

Jinfang Cao and Qibin Zhu performed chemical synthesis and characterization data of all compounds. Chunsuo Yao designed and supervised the study. Qibin Zhu, Jinfang Cao and Chunsuo Yao wrote the original draft of the manuscript. Zhen Sha, Xiaoxuan Zhou and Ruitong Zhu reviewed and edited the manuscript. All authors have read and agreed to the published version of the manuscript.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

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