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Regioselective biomimetic oxidation of halogenated resveratrol for the synthesis of (±)-ε-viniferin and its analogues

Meijie Liu, Tao Dong, Xingchao Guan, Zhibo Shao, Wenling Li*

School of Chemical and Biological Engineering, Lanzhou Jiaotong University, Lanzhou, 730070, China

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ABSTRACT

$FeCl_3 \cdot 6H_2O$-promoted biomimetic oxidations of 3,5-dihalogeno-resveratrol in different acetone systems produced several coupling intermediates bearing distinct dimeric skeletons with moderate yields. The subsequent deprotection reactions of brominated coupling products achieved the efficient synthesis of natural products (±)-ε-viniferin, (±)-ampelosin B, and (±)-gnetins F, as well as an unnatural oligostilbene. The coupling mechanisms for the formation of different dimeric structures were also proposed.

1. Introduction

Since ε-viniferin (**2**), a dehydrodimer of resveratrol (**1**), was first discovered by Langcake and Pryce in 1977,[1] more than three hundred natural oligostilbenes with complicated structures and diverse biological activities have been isolated and studied in the past four decades (Fig. 1).[2] Some resveratrol oligomers, such as dimers **3**–**7**, have been prepared through efficient chemical synthesis or various biomimetic oxidations.[3] However, the exploration on the preparation of **2** has rarely succeeded except in a few biosynthetic reports because of its structural instability.[4] In 1999, Lin et al. successfully synthesized (±)-**2** from **1** with 30.5% yield under the $FeCl_3$-MeOH oxidative condition and Yao' team in 2017 conducted the $FeCl_3 \cdot 6H_2O$-promoted oxidation of **1** in aqueous methanol to form (±)-**2** with 13.5% yield.[5] Niwa's group synthesized **2** as the sole coupling product of **1** with 30% yield by using $Ti(NO_3)_3$ as a catalyst at −50 °C and prepared the dimeric mixture including **2**, with 22% overall yield in the $K_3Fe(CN)_6$-oxidized alkaline methanol solution.[6]

Considering the importance of **2** as the biogenic precursor for a majority of the natural resveratrol oligomers and existing synthetic challenge, our group has been devoted to the regioselective biomimetic synthesis of oligostilbenes under a variety of oxidative conditions by using *tert*-butyl-protected stilbenes, such as **8**, as the coupling precursor.[7] However, dihydrobenzofuran-type dimeric stilbenes, such as **2**–**4**, were rarely observed in coupling products. In view of the adverse effects of acidic debutylation conditions on the structural stability of dimeric products, we recently used brominated resveratrol **9** as an alternative precursor. The different enzyme-catalyzed oxidation of **9** followed by the debromination reactions facilitated the total synthesis of several novel resveratrol dimers in addition to the natural products **5**–**7**.[8] Encouraged by this finding, we intended to further investigate the regioselective coupling reactions of halogenated resveratrol precursors oxidized by $FeCl_3 \cdot 6H_2O$ in various solvent systems to finally synthesize natural dimer **2**.

2. Results and discussion

We first studied the oxidative coupling reactions of brominated resveratrol (**9**) promoted by $FeCl_3 \cdot 6H_2O$ in different solvent systems. As illustrated in Scheme 1 and Table 1, the treatment of precursor **9** with 6.5 equimolar amount of $FeCl_3 \cdot 6H_2O$ in acetone for 24 h generated the dihydrobenzofuran-type product **10** with 38% yield and another unexpected dimer **11** with 32% yield. Increasing the amount of $FeCl_3 \cdot 6H_2O$ or prolonging the reaction time resulted in considerably decrease in the isolated yields of **10** and **11** owing to the formation of complex polar products. When the same oxidative condition and reaction time were applied in the

* Corresponding author.
E-mail address: liwl@mail.lzjtu.cn (W. Li).

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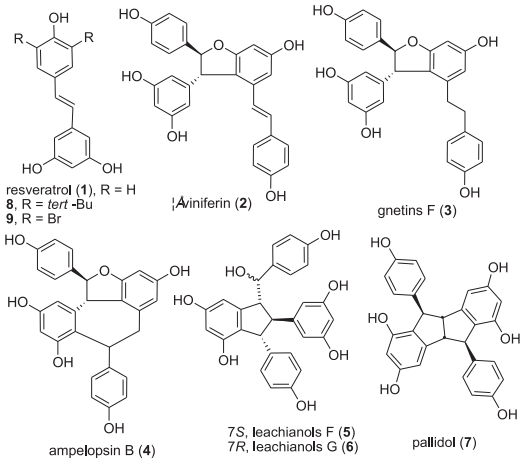


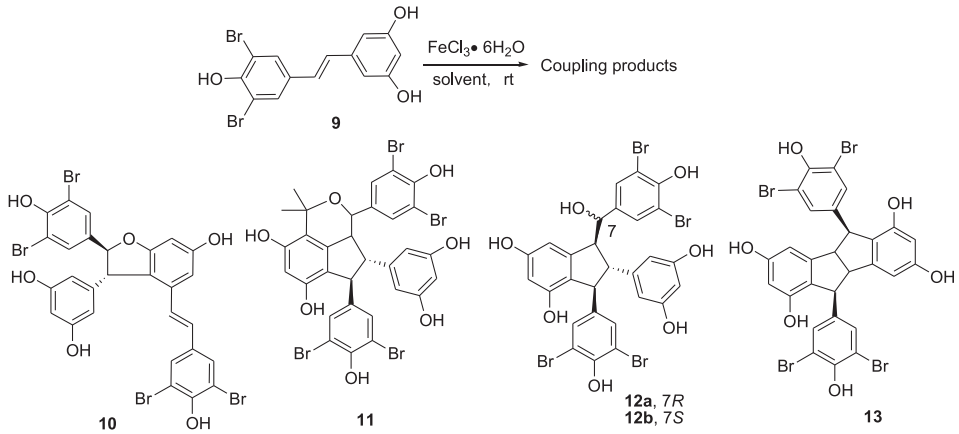
Fig. 1. Resveratrol and several representative natural dimers.

coupling reaction of **9** in acetone–benzene system, dimeric products **10** and **11** were still dominant, but their yields decreased to 28%. Large volume ratio of acetone–benzene (from 1:1 to 1:4) led to decreased total yields of **10** and **11**. Next, we investigated the effect of the acetone–H_2O solvent system on the coupling reaction of **9**. As shown in entry 3, the isomeric mixture of **12a** and **12b** with nearly 1:1 molar ratio was obtained with 41% yield, and dimer **13** was also generated with 25% yield. When the same oxidation reaction was conducted in acetone–buffer system, only the isomers **12a** and **12b** were isolated with 31% yield in the reaction mixture.

The reaction mechanisms of coupling dimers **10** and **11** were proposed as shown in Scheme 2. Precursor **9** mediated by one-electron oxidation using $FeCl_3 \cdot 6H_2O$ primarily resulted in the semiquinone radical M_8. The radical M_8 reacted directly with monomer **9** to form 8-10-coupled intermediate, which underwent sequential intramolecular cyclization rearrangement leading to the dihydrobenzofuran skeleton **10**.[9] The 8–8-coupled bis-quinone methide underwent further nucleophilic cyclization to form the dimeric structure **14**. Electron-rich C10 of the intermediate **14** attacked the electrophilic carbonyl group of acetone solvent, which further nucleophilic attacked C7 of quinone methide to construct the bicyclic dimer **11**. The indanes **12a/12b** and **13** were formed through different intramolecular cyclization paths of the initial 8–8-coupled bis-quinone methide, as hypothesized in our previous report.[8]

On the basis of the above research results, we continued to examine the oxidative coupling reactions of another halogenated stilbene precursor, 3,5-diiodo-resveratrol (**18**), which was prepared through the key Wittig reaction of phosphonium salt **15** with 3,5-diiodo-4-hydroxyl-benzaldehyde (**16**) followed by the debenzylation reaction of stilbene **17** (Scheme 3). The coupling reactions of stilbene **18** were carried out under similar oxidative conditions as those of precursor **9**, but the catalyst amount and reaction time were optimized to achieve increased product yields. As shown in Scheme 3 and Table 2, **18** was oxidized by 3 equiv. $FeCl_3 \cdot 6H_2O$ for 18 h, which resulted in the 8–10-coupled dimer **19** and 8–8-coupled intermediate **20** either in acetone or acetone–benzene system with 65%–72% total yield. However, the coupling reaction of **18** in acetone–H_2O or acetone–buffer system only formed the 8–8-coupled indane **21a** in 45% or 35% yield, and its isomer **21b** was rarely isolated from the product mixture. After the catalyst amount was increased and the reaction time was prolonged, the mixture of **21a** and **21b** with 1:2 molar ratio with 32% yield and pallidol-type dimer **22** with 10% yield were finally produced (entry 5). This result indicated the increased stereoselectivity of iodine atoms as positional protecting groups compared with bromine in $FeCl_3 \cdot 6H_2O$–mediated coupling reactions.[10]

With these coupling products, we carried out the reductive debromination reactions of **10** and **11** to prepare several natural resveratrol dimers. As shown in Scheme 4, **10** was subjected to 70



Scheme 1. Structures of coupling products from the oxidation of **9**.

Table 1
Coupling products of precursor **9** in different oxidative systems.

Entry	$FeCl_3 \cdot 6H_2O$ (Equiv.)	Solvents (Volume ratio)	Time (h)	Coupling products (isolated yield %)			
				10	11	12a/12b (molar ratio)[a]	13
1	6.5	acetone	24	36	32	–	–
2	6.5	acetone–benzene (2:1)	24	28	28	–	–
3	6.0	acetone–H_2O (2:1)	30	–	–	41 (1:1)	25
4	6.0	acetone–buffer (pH = 5.4) (2:1)	30	–	–	31 (1:1)	–

[a] Determined by a crude ^1H NMR spectrum.