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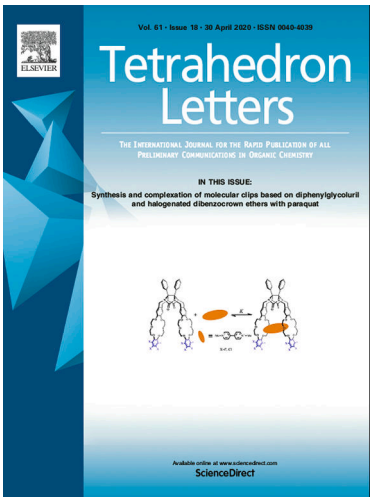

Oxidative cross-coupling approach to the biomimetic synthesis of the heterodimers of resveratrol and isorhapontigenin

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Graphical Abstract

Oxidative Cross-Coupling Approach to the Biomimetic Synthesis of the Heterodimers of Resveratrol and Isorhapontigenin

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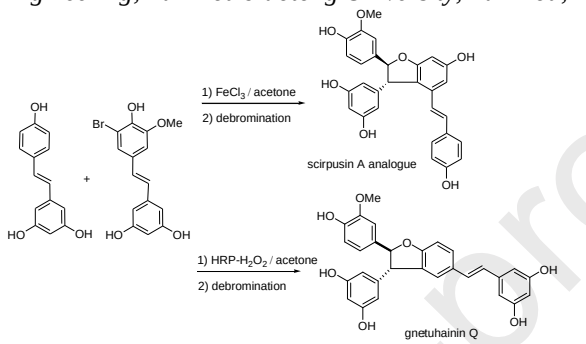

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ABSTRACT

The regioselective oxidative cross-coupling reactions of two different stilbene precursors catalyzed by $FeCl_3$ or horseradish peroxidase-H_2O_2 in acetone solvent produced three dihydrobenzofuran-type heterodimers. The reductive debrominations of these cross-coupled dimers synthesized two heterodimers of resveratrol and isorhapontigenin, an analogue of (±)-scirpusin A and (±)-gnetuhainin Q.

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1.

Natural oligostilbenes are a special group of plant polyphenols possessing complex structures and diverse biological activities.[1] Among them are more than 300 homooligomers of stilbene units including resveratrol (**1**), isorhapontigenin (**2**), piceatannol (**3**) and oxyresveratrol (**4**); and tens of novel oligomers polymerized from the different monomers, such as the heterodimer **5**–**7** (Figure 1).[2] Many chemists have focused on synthesizing these natural polyphenolic products over the past four decades.[3] Notably, the resveratrol oligomers with diverse skeletons were efficiently constructed via traditional biomimetic oxidations or well-designed chemical transformations.[4] However, little attention has been given to the heterooligomers of different stilbenes, and few synthetic efforts toward them have been reported thus far. Although the oxidative coupling reactions of the hetero-monomers were known the most concise approach to the diverse structures of heterooligomers, this strategy was mostly applied in the biomimetic synthesis of lignans and stilbenolignans.[5] Only Lin et al. in 2006 conducted the $FeCl_3 \cdot 6H_2O$-catalyzed oxidative cross-coupling reaction of stilbenes **1** and **2** in acetone and identified nine oligomeric products, including two homodimers and seven heterooligomers without definite isolated yields indicated.[1b] In addition, Queiroz's team investigated the enzyme-mediated biotransformation of the mixture of **1** and pterostilbene and isolated five homodimers and four heterodimers.[6] These findings revealed the considerable challenge in the efficient synthesis of heterodimers, such as **5**–**7**, due to the lack of regioselective control in the oxidative cross-coupling reactions of stilbenes.

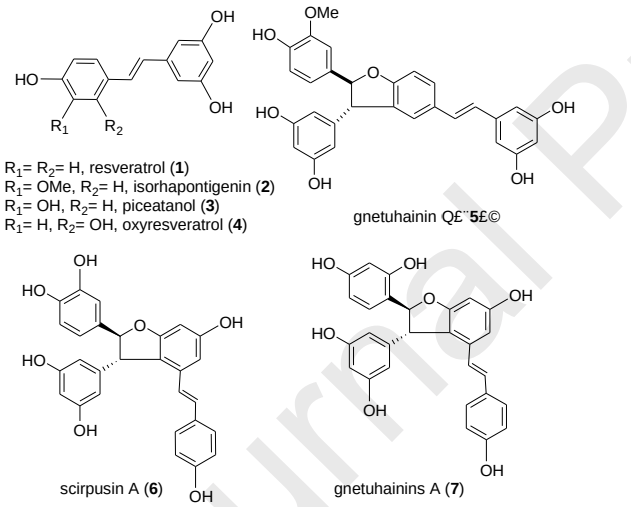
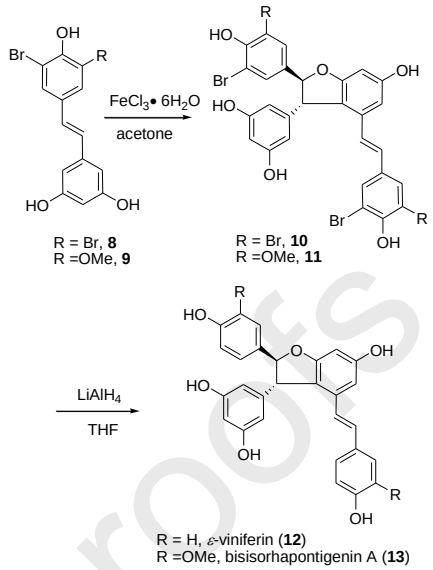


Figure 1. Natural stilbenes and several representative heterodimers

Given the high interest in the biomimetic synthesis of oligostilbenes, our group have efficiently prepared tens of homodimers of **1** and **2** through their regioselective oxidative coupling reactions under varied oxidative conditions.[7] The introduction of the positional protecting groups such as *tert*-butyl group or halogen atoms into the stilbene precursors significantly improved the coupling yields of 8-8-coupled or 8-10-coupled products. Based on this efficient synthetic strategy, this work aimed to explore the oxidative cross-coupling reactions of two different stilbenes to synthesize several heterooligomers of **1** and **2**.

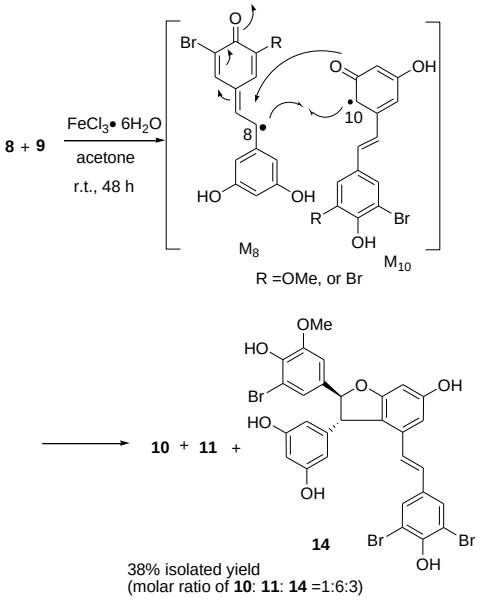
2. Results and Discussion

We recently synthesized natural (±)-*ε*-viniferin (**12**) and (±)-bisisorhapontigenin A (**13**) through the $FeCl_3 \cdot 6H_2O$-catalyzed regioselective oxidative coupling reaction of 3,5-dibromo-



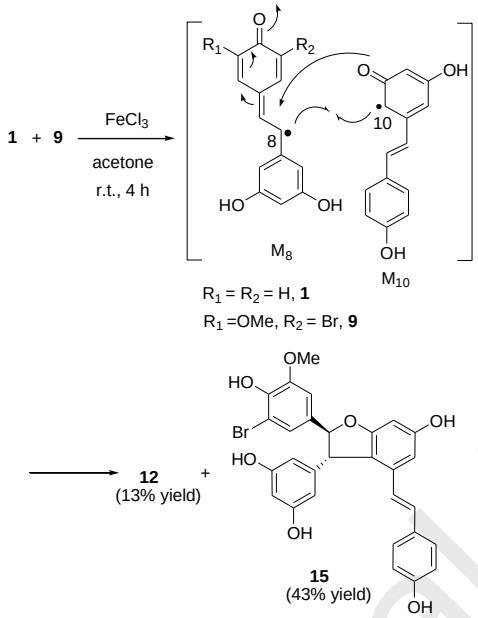
Scheme 1. Synthesis of oligostilbenes from the oxidative coupling of precursor **8** or **9**

When the $FeCl_3 \cdot 6H_2O$-oxidized cross-coupling reaction of monomer **8** and **9** (molar ratio 1:1) was performed in acetone, **9** was quickly consumed, and the 8-10-coupled homodimer **11** was formed as major product. The amount of dimer **10** was gradually increased with prolonged time, and almost no heterodimer was found in the reaction mixture. As such, the reactivity of **9** is higher than that of **8** in the same oxidative system. The coupling reaction condition was constantly optimized to enhance the possibility of cross-coupling pattern. A small amount of 8-10-coupled heterodimer **14** was finally found in the product mixture when twice equivalent amount of **9** was slowly added in batch to the acetone solution of $FeCl_3 \cdot 6H_2O$ and **8** (Scheme 2). Although the low yield of **14** (<11%) and the difficulty in the isolation and purification because of the similar polarity of **14** with **11** restricted its further application, the formation of **14** implied the potential of the oxidative cross-coupling strategy for the synthesis of the heterodimers.



Scheme 2. $FeCl_3$▪$6H_2O$-oxidized cross-coupling reaction of stilbenes **8** and **9**

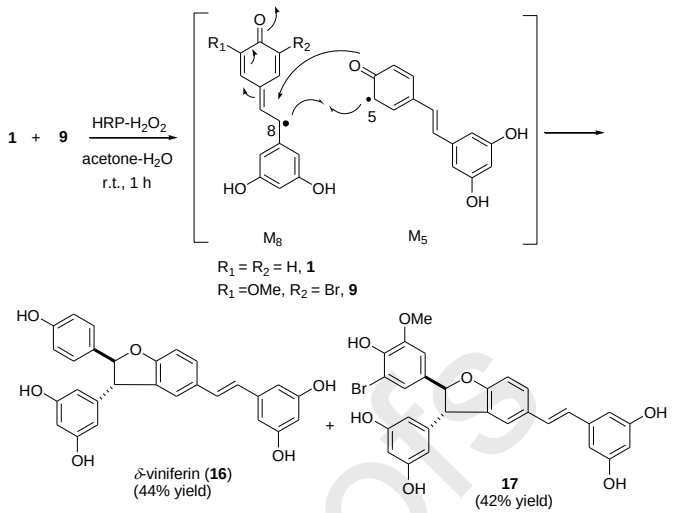
In structure and reactivity, they were used as the coupling precursors to perform the cross-coupling reaction (Scheme 3). However, the coupling dimerization of **9** to **11** was achieved under $FeCl_3$-promoted or $FeCl_3 \cdot 6H_2O$-catalyzed condition; the oxidation of **1** to **12** proceeded smoothly only in $FeCl_3$-acetone system. Thus, the $FeCl_3$-catalyzed cross-coupling reaction of **1** and **9** was conducted in anhydrous acetone solvent. The yield of the expected 8-10-coupled heterodimer **15** was largely influenced by the molar ratio and the addition sequence of two precursors, as well as the amount of $FeCl_3$ oxidant. We continuously optimized the reaction condition to increase the coupling yield of heterodimer **15**. We found when six equivalents of $FeCl_3$ was added to acetone solution of **1** and **9** (molar ratio 1.5:1) and the reaction continued for 4 hr until **9** was completely consumed, the heterodimer **15** with 43% maximum yield and the homodimer **12** with 13% yield were isolated. Only a trace amount of **11** was formed in the reaction mixture.



Scheme 3. $FeCl_3$-catalyzed cross-coupling products of monomers **1** and **9**

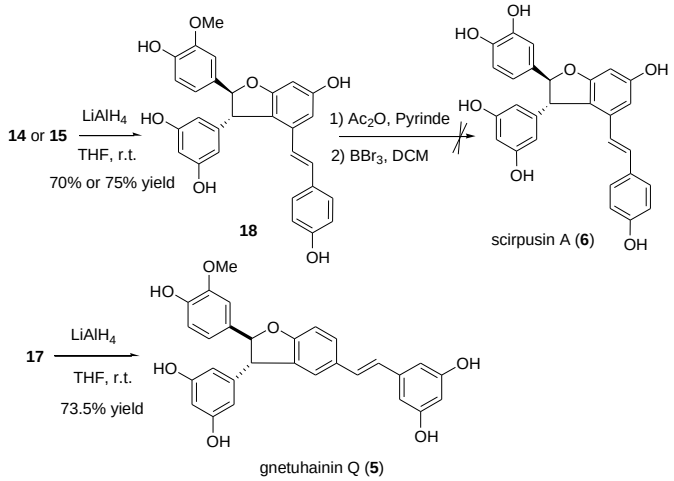
The formation of the 8-10-coupled heterodimer **14** or **15** in the ferric chloride-oxidized cross-coupling reactions verified the higher reactivity of the M_8 radical mesomer of stilbene **9** in comparison to that of **1** or **8**, which preferentially participated in the cross-coupling dimerizations under the optimized reaction conditions. Based on the above results and our previous achievements on the enzyme-mediated coupling reactions of **1** or **9**,[7e,7g] we explored the oxidative cross-coupling reaction of **1** and **9** under the horseradish peroxidase (HRP)-H_2O_2-catalyzed condition (Scheme 4).

In the aqueous acetone solution of HRP-H_2O_2 and equivalent amounts of coupling precursors, the oxidation of **1** was obviously faster than that of **9** and mostly produced the homodimer of **1**, *δ*-viniferin (**16**) and small amount of 8-5-coupled heterodimer **17**. Under the most optimum reaction condition, 1.5 equivalents of **1** and 3% H_2O_2 was added dropwise into the reaction mixture within 40 min and the reaction continued for 1 hr at room temperature utill two precursors disappeared, the homodimer **16** with 44% yield, heterodimer **17** with 42% maximum yield, and a small quantity of the homodimer **11** were isolated from the product mixture. The results confirmed that the yield of heterodimer **17** can be effectively increased by the optimization of the molar ratio and addition sequence of precursors **1** and **9**.



Scheme 4. HRP-H_2O_2-promoted cross-coupling products of stilbenes **1** and **9**

With the heterodimeric intermediates **14**, **15** and **17** in hand, we attempted to remove their protecting groups for the synthesis of several natural oligostilbenes. As shown in scheme 5, the $LiAlH_4$-catalyzed reductive debromination reactions of dimer **14** or **15** smoothly gave rise to unnatural product **18** with 70% or 75% yields. The subsequent direct demethylation of **18** for the synthesis of natural scirpusin A (**6**) did not proceed because of the insolubility of **18** in the BBr_3-dichloromethane system.[2d] The global acetylation of **18** followed by the deacetylation and demethylation in one-pot finally led to the complex and inseparable product mixture. The natural (±)-gnetuhainin Q (**5**) was firstly synthesized by the debromination of **17** under the $LiAlH_4$-THF reductive condition.[2e]



Scheme 5. Reductive debromination products of heterodimers **14**, **15** or **17**

In summary, we explored the biomimetic cross-coupling reactions of two different stilbene monomers under several oxidative conditions. The key to the regioselective synthesis of heterodimers **14**, **15** or **17** lies in the significant difference in the reactivity of brominated isorhapontigenin **9** and resveratrol (**1**) or brominated resveratrol **8** in the same oxidative system and the appropriate molar ratios and addition sequences of two coupling precursors. The formation of 8-10-coupled dimer **15** or 8-5-coupled product **17** with moderate yield under the optimized

that this strategy is practicable for the regioselective synthesis of the heterodimeric stilbenes. The scirpusin A (**6**) analogue, **18**, and (±)-gnetuhainin Q (**5**) were firstly synthesized by the reductive debromination reactions of heterodimers **14**, **15** or **17**. The application of this regioselective biomimetic strategy for the preparation of other natural stilbene heterooligomers is ongoing in our laboratory.

Acknowledgements

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