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Concise total syntheses of (±)isopaucifloral F, (±)quadrangularin A, and (±)pallidol

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ABSTRACT

Concise total syntheses of (±)isopaucifloral F, (±)quadrangularin A, and (±)pallidol, starting from commercially available 3,5-dimethoxybenzoic acid, have been achieved by a sequential process. The overall synthetic strategy involves Nazarov cyclization, Ramberg–Backlund olefination, and Friedel–Crafts alkylation.

Natural polyphenols, such as resveratrol (**1**), (±)isopaucifloral F (**2**), (±)quadrangularin A (**3**), and (±)pallidol (**4**) as members of the resveratrol family (Fig. 1), have been isolated in different plants, and some of which commonly occur even in red wine. These natural products have been demonstrated to possess a variety of biological activities, such as anti-cancer, anti-fungal, anti-bacterial, and anti-oxidant.[1–8] Particularly, (±)pallidol (**4**) has been found to enable the modulation of the function of the estrogen receptor[9] and thus exerts estrogen-like activity. The intriguing structures coupled with their largely unexplored potential in medicine or as tools for biological studies, rendered these natural products as attractive targets for total synthesis.

Recently, Hou and co-workers reported an elegant approach for the synthesis of (±)quadrangularin A via an indirect radical dimerization of a *cis*-stilbene derivative.[10] Subsequently, Snyder et al. also described a general method by using a stilbene derivative as the common building block and applying a variety of highly selective and reagent-control reaction cascades to accomplish the syntheses of up to 25 diverse natural products and analogues in the resveratrol family.[11] And Sarpong and co-workers also reported an approach to the synthesis of the precursors of these dimeric resveratrol natural products via a palladium-catalyzed domino reaction.[12] Although the reported synthetic strategies for those natural products have their individual advantages, we would like to explore a novel approach to synthesize these types of natural products and analogues by our early reported Nazarov cyclization

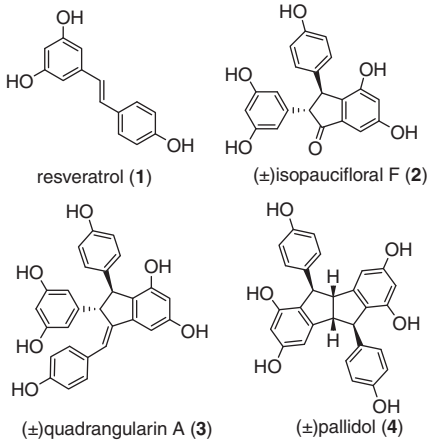

Figure 1. Some representative examples of polyphenol.

incorporated with Ramberg–Backlund olefination, and Friedel–Crafts alkylation. Herein we present our efforts to the synthesis of (±)isopaucifloral F (**2**), (±)quadrangularin A (**3**), and (±)pallidol (**4**).

Our retrosynthetic route to these natural products is outlined (Scheme 1). From the biogenetic viewpoint, (±)pallidol may have evolved from (±)quadrangularin A via a cation-based rearrangement, in other words, by intramolecular electrophilic attack of carbonium ion on benzyl position to another electron-richer and

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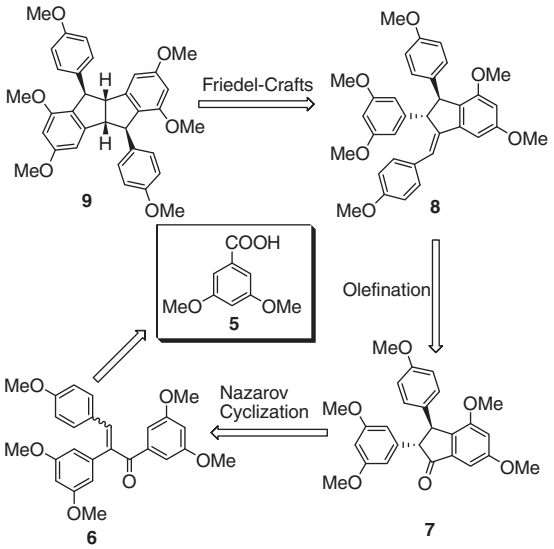


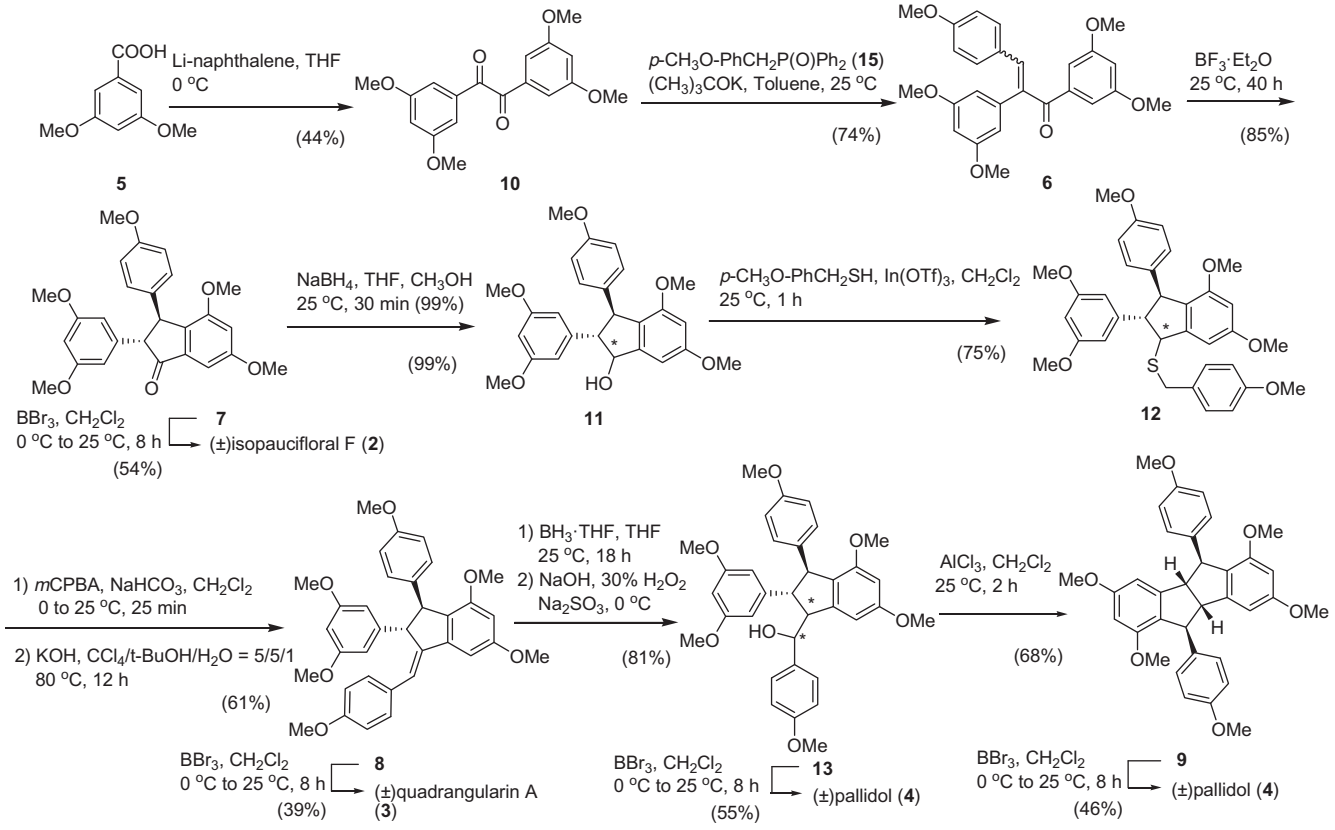
Scheme 1. Retrosynthetic route to the target natural products.

space-favorable aryl ring. Thus, **4** or its precursor **9** could be produced by intramolecular Friedel–Crafts alkylation if the desired carbonium ion successfully generated from **8**, and this strategy for synthesis of **4** is unprecedented. Intermediate **8**, a precursor of (±)quadrangularin A (**3**), could be hypothesized to be available via a simple olefination of **7**, the precursor of (±)isopaucifloral F (**2**). Although the outcome is uncertain for the steric configuration of the olefin produced, intermediate **7** could be obtained from the suitable 2-arylchalcone **6** through Nazarov cyclization based on the results from Marco[13], Flynn[14] and our previous work on the total synthesis of caraphenol C,[15] another resveratrol-type natural product. 2-Arylchalcone **6** could be conveniently prepared from the commercially available 3,5-dimethoxybenzoic acid (**5**).

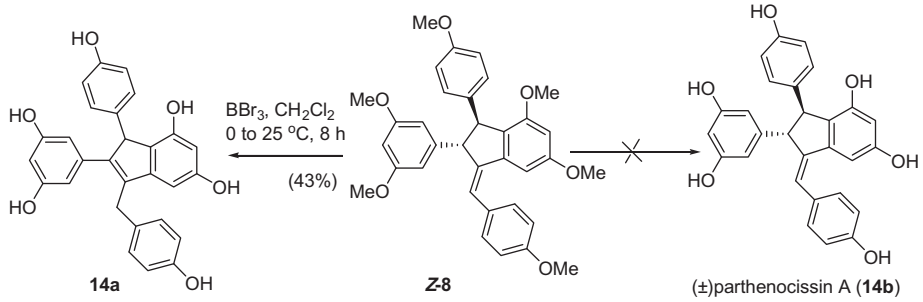
As shown in Scheme 2, our synthesis commenced with the acid **5**. The acid **5** was rapidly dimerized to give diaryl ketone **10** in 55% yield by the treatment with Li-naphthalene reagent, as the modified method.[16] Then the ketone **10** was subjected to the Wittig–Horner reaction condition to provide α,β-unsaturated ketone intermediate **6** in 78% yield as a mixture of *E*- and *Z*-isomer. It is noteworthy that such obtained mixture could be used directly and have no influence on the next Nazarov cyclization step.

Based on our experience on the Nazarov cyclization reaction,[14] *trans*-2,3-aryl indanone **7** (*trans* stereochemistry was supported by vicinal coupling constant 2.6 Hz), as a more thermodynamic stabilized conformation than its *cis* isomer, which could be offered in 85% yield after treating α,β-unsaturated ketone **6** with $BF_3{\cdot}Et_2O$ at room temperature in dichloromethane for 40 h. With **7** in hand, (±)isopaucifloral F (**2**) was conveniently obtained in 54% after removal of the protective methyl of **7** with BBr_3 at 0 °C in dichloromethane for 8 h.

Meanwhile, we aimed at the second natural product, (±)quadrangularin A (**3**), and envisaged to achieve its precursor **8** from **7** in one step through straightforward olefination. However, in our hands, tremendous efforts to this transformation were unsuccessful by the routine methods such as Wittig, Tebbe, or Peterson olefination reaction. Fortunately, Ramberg–Backlund olefination for the aim was disclosed during this period.[11] Thus, **7** was first reduced to **11** in an almost quantitative yield (>99%) by using sodium borohydride in the mixed solvents of THF and MeOH for 30 min, though **11** was obtained as a mixture of two isomers due to the lack of the selectivity of the reductive reagent. However, this will



Scheme 2. Total syntheses of (±)isopaucifloral F (**2**), (±)quadrangularin A (**3**), and (±)pallidol (**4**).



Scheme 3. An unexpected reaction of *Z*-isomer of **8** aiming at (±)parthenocissin A.

not be problematic since the new-formed chiral center will be abolished at the later stage. Subsequently introduction of the fourth suitable aryl ring into compound **11** through the $In(OTf)_3$-catalyzed nucleophilic substitution under dark in CH_2Cl_2 at room temperature for 1 h, the sulfide **12** was obtained in 75% yield. The sulfide **12** was further oxidized by *m*CPBA for 0.5 h in basic aqueous solution and dichloromethane, the crude product obtained without purification was used directly for Ramberg–Backlund reaction as the described protocol,[11] to furnish **8**, which was identified as *E*-isomer, in 61% yield. Meanwhile, we can also get the *Z*-isomer of **8** in 7% yield (*Z*-**8**), which is a potential precursor for the synthesis of another natural product (±)parthenocissin A (**14b**) (Scheme 3). After demethylation of **8** by the above-mentioned method for **2**, we could smoothly get (±)quadrangularin A (**3**) in 39% yield. Unexpectedly, when the corresponding *Z*-isomer (*Z*-**8**) was performed under the same de-protective condition, it was converted to **14a** rather than the desired (±)parthenocissin A (**14b**). Possibly, the resulting *exo* double bond preferrly shifts to form a more stable *endo* form due to bulky hindrance of its neighboring aryl rings.

Having completed the preparation of (±)quadrangularin A, our attention was turned to the more complicated compound, (±)pallidol (**4**). According to the retrosynthetic approach, the desired benzyl carbonium ion generated from **8** is required to undergo intramolecular Friedel–Crafts alkylation in order to produce **9**. Although it would in principle be accomplished by straightforward protonation of the olefin under appropriate Lewis or Brϕnsted acidic medium, we failed to complete this concise transformtion after several attempts. Thus, an indirect transformation had to be executed. Intermediate **8** was regio-selectively converted into the alcohol **13** in 75% yield according to the standard hydroboration/oxidation procedure, but it was very difficult to characterize the alcohol **13** by NMR spectra data due to the existence of its three other inseparable isomers. Then the mixed **13** was investigated for the next step under various acidic conditions. It was found that **13** was successfully converted to the precursor of (±)pallidol (**9**) in 68% yield by being subjected to $AlCl_3$ in CH_2Cl_2 at room temperature for 2 h, which was further being transformed into (±)pallidol (**4**) in 46% yield by treating with BBr_3. Interestingly, (±)pallidol (**4**) could be efficiently obtained in one step from **13** in 55% yield when BBr_3 was used in our later detailed study, probably BBr_3 is strong enough to enable the alkylation and de-protection to occur simultaneously.

In summary, concise total syntheses of (±)isopaucifloral F (**2**) (four steps, 15% overall yield), (±)quadrangularin A (**3**) (seven steps, 5% overall yield), and (±)pallidol (**4**) (eight steps, 5% overall yield) have been achieved in a straightforward fashion, starting from commercially available simple 3,5-dimethoxy benzoic acid. The ^1H and ^{13}C NMR spectra of compounds **3** and **4** are in great agreement with the respective reported data.[11,17] Combined with our previous work on the synthesis of caraphenol C, four members of reservatrol family have been synthesized through the intermediate 2-arylchalone (**6**), which demonstrated that 2-arylchalone could also serve as a common building block for the synthesis of other resveratrol-type natural products.

Acknowledgments

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Supplementary data

Supplementary data (The material of experimental procedure (Compound **2**, **3**, **4**, **6**, **7**, **8**, **Z-8**, **9**, **10**, **11**, **12**, **13**, **14a**, **15**) and full spectroscopic data for all the compounds is availble free of charge via the Internet at http://www.sciencedirect.com/science/journal/00404039) associated with this Letter can be found, in the online version, at doi:10.1016/j.tetlet.2011.03.002.

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