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Biomimetic Total Synthesis of Paeoveitol

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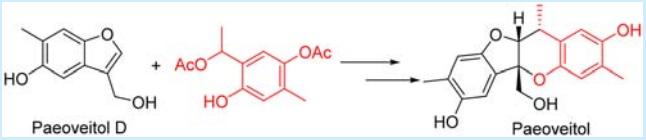
Supporting Information

ABSTRACT: A highly stereocontrolled synthesis of paeoveitol has been developed in 26% yield, in 7 steps from commercially available materials. The synthetic strategy was inspired primarily by the biogenetic hypothesis and was enabled by hetero-Diels–Alder cycloaddition to construct the target molecular framework.



The root of *Paeonia veitchii* (Chuan-Chi-Shao) has a long history of use as the composition in many traditional medicine formulas (for example Sini-San and Xiaoyao-Wan) for the treatment of depression-like disorders in China.[1] Its genus, *Paeonia* (Paeoniaceae), is gaining interest in the medicinal chemistry and drug discovery community. As the characteristic components of the genus *Paeonia*, Paeoniflorin-related monoterpene glycosides with a cagelike unit are rich and generally recognized as the active constituents including activities in immunomodulation, anti-inflammation, hypoglycemic action, antidepression, and circadian regulation.[2] The monoterpene, diterpene, and triterpenoids are also isolated from this genus. Paeoveitol, a pair of norditerpene enantiomers, were isolated from the root of *Paeonia veitchii* in 2014 by Chen et al.[3] (Figure 1). Extensive NMR spectroscopic analyses and

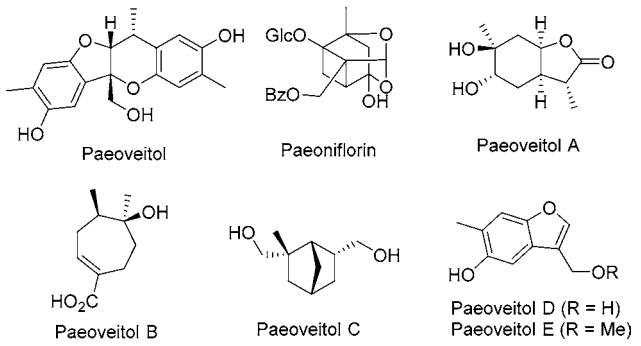


Figure 1. Paeoveitol, paeoniflorin, and paeoveitol A–E.

X-ray crystallographic analysis of this molecule revealed that its structure was featured by an unprecedented [3, 2-b] fused 2, 3-dihydrobenzofuran and chromane in a tetracyclic framework with three contiguous stereogenic centers. After being separated by chiral HPLC, the absolute configurations of (+)-paeoveitol and (−)-paeoveitol were determined on the basis of electronic circular dichroism (ECD).

Unfortunately, the bioactivity of paeoveitol was not reported in detail due to the limited supply in the original paper that isolated it. The combination of the uncharacterized bioactivity and the structural novelty prompted us to undertake synthetic studies of paeoveitol. Herein, we report a biomimetic total synthesis of paeoveitol, which was enabled by hetero-Diels–Alder cycloaddition. Very recently, Zhao and co-workers reported the first total synthesis of paeoveitol employing a similar hetero-Diels–Alder cycloaddition.[4]

In the isolation paper, Chen and co-workers postulated that paeoveitol might biosynthetically be derived from two molecules of paeoniflorin.[3] The intermediates were assumed to be obtained by hydrolysis of glucosyl, loss of benzoyl groups, cleavage of the hemiketal–acetal linkage, and the four-membered ring from paeoniflorin. The structure of paeoveitol was then established via a series of dehydration, cyclization, oxidation, and decarboxylation derived from the intermediates.[3] However, the structure of paeoniflorin is thought to be more complex than the intermediates. Generally, most biogenetic pathways always approached the natural products from simple molecules.[5] Based on this realization, the biogenesis precursor of paeoveitol may not be the paeoniflorin. Recently, Chen and co-workers have isolated five monoterpene paeoveitols A–E from the same genus plant[6] (Figure 1). Inspired by the finding that the benzofuran moiety of paeoveitol is paeoveitol D, which was isolated from the same species, we deduced that paeoveitol D would be one of the precursors of paeoveitol. With one partner (paeoveitol D) in mind, the target molecule (paeoveitol) should be the mergence of the paeoveitol D and the other partner by hetero-Diels–Alder reaction (Scheme 1). The other partner would be easily transformed to *ortho*-quinone methides (*o*-QMs) via acid catalysis, base catalysis, oxidation, thermolysis, photolysis, or tautomerization.[7] Thus, paeoveitol A was assumed to be the other precursor partner of paeoveitol. There existed two basic assumptions: one was that the paeoveitol A directly transformed to the *o*-QM intermediate via a series of dehydration, oxidation, and decarboxylation (Scheme 1, path a); the other was that the paeoveitol A was transformed to paeoniflorin A at first[8] and then to the *o*-QM intermediate in the next step (Scheme 1, path b). Technically,

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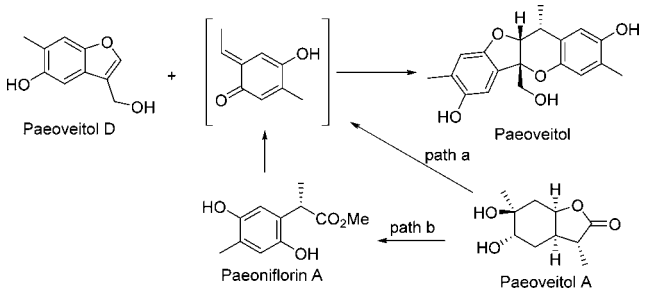
Scheme 1. Biogenetic Pathway Proposed for Paeoveitol

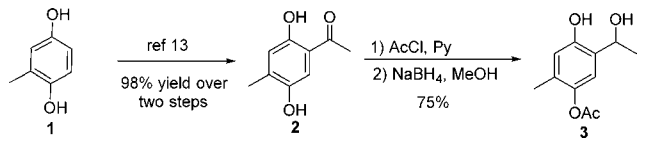


paeoniflorin A has a very similar structure with the *o*-QM intermediate and successfully been isolated from *Paeonia suffruticosa*,[8] belonging to the same genus of paeoveitol. Thus, the paeoveitol A or the related compounds that might be transformed to *o*-QMs, together with paeoveitol D, were used to build paeoveitol via hetero-Diels–Alder reaction (Scheme 1).

Hetero-Diels–Alder reaction of *o*-QMs has been proven to be an efficient method for the preparation of a wide variety of chromane motifs (benzopyrans) based on the dienophile with high chemo-, regio-, diastereo-, and enantioselectivity.[7,9] This powerful reaction has also been used in linchpin reactions for the construction of complex natural products.[10] As shown in Scheme 1, we envisioned that if the dienophile simple natural product paeoveitol D and *o*-QM could be merged together by hetero-Diels–Alder reaction, a short and biomimetic synthesis of paeoveitol could be realized. However, benzofuran as the dienophile occurring in a hetero-Diels–Alder reaction is rarely reported. Pioneering work for benzofuran as the dienophile with *o*-naphthoquinone methides was reported by Sajiki and co-workers.[11] There are two challenges in this reaction: first, the paeoveitol D has a benzofuran motif, which is inactive due to aromaticity; second, the regioselectivity is unpredictable in the hetero-Diels–Alder reaction when using the benzofuran motif as the dienophile to react with *o*-QM.

Efficient methods for *o*-QM intermediate generation from 2-(hydroxymethyl)phenol or *o*-methylene-acetoxy-phenols have been developed and applied.[12] Based on these methodologies, an *o*-QM precursor was designed and prepared. As illustrated in Scheme 2, the synthesis of the precursor of *o*-QM was started

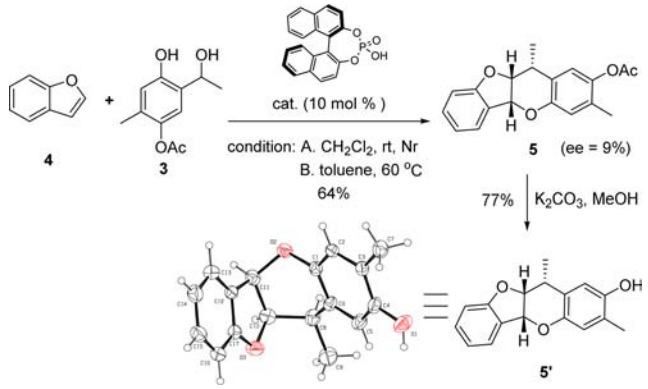
Scheme 2. Synthesis the Precursor of the *o*-Quinone Methide



from commercially available 2-methylhydroquinone **1**. The compound **2** was prepared in 98% over two steps using the known method.[13] To avoid forming *p*-quinone, compound **2** was selectively protected by acetate and then reduced the ketone to the corresponding alcohol by $NaBH_4$ to obtain the compound **3**.

With the precursor of the *o*-QM **3** in hand, we started our initial investigation to utilize benzofuran **4** and compound **3** as a model reaction. According to the literature, BINOL-based phosphoric acids as a Brønsted acid can catalyze *ortho*-hydroxy benzhydryl alcohol transferred to *o*-QMs which generated *in situ* followed by addition of the dienophile to form benzopyrane in high yields and excellent stereoselectivities.[14] This strategy happened to coincide with the idea of asymmetric synthesis of paeoveitol. Reaction setups were referred to by Schneider.[14a] However, it did not work (Scheme 3, condition A). The reason

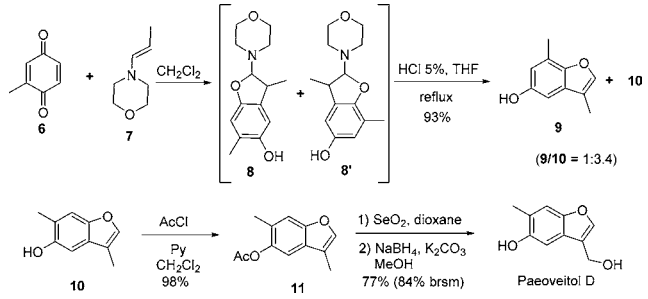
Scheme 3. Model Reaction between Benzofuran and Compound 3



might be that the benzofuran is an aromatic ring and inactive as a dienophile. In order to make the reaction occur, the reaction temperature was elevated. After careful consideration, dichloromethane as solvent is not suitable for increasing the temperature of reaction. The solvent was changed from dichloromethane to toluene. Using toluene as solvent with 10% BINOL-based phosphoric acid catalyst, the cycloaddition product **5** was obtained as a single diastereoisomer in good yield with excellent regio- and diastereoselectivity at 60 °C. However, the enantioselectivity is poor. The relative configuration of **5** was determined on the nuclear overhauser effect (NOE) and confirmed by transforming **5** to compound **5′**, which was determined by X-ray crystallography analysis. The success of the model study made us more confident to pursue further exploration.

With the success of our model study, our efforts were focused on synthesis of the paeoveitol D (Scheme 4). The

Scheme 4. Synthesis of Paeoveitol D



synthesis commenced from the commercially available *p*-toluquinone **6**. Treatment of *p*-toluquinone **6** with enamine **7**, which was prepared from propionaldehyde and morpholine, provided the addition products **8** and **8′** in a red color. The compound **8** and **8′** were directly used without further purification. After evaporation of the dichloromethane, the residue was refluxed in THF in the presence of diluted hydrochloric acid. Compounds **9** and **10** were obtained in 21% and 72% yield, respectively.[15] Selective allylic oxidation of

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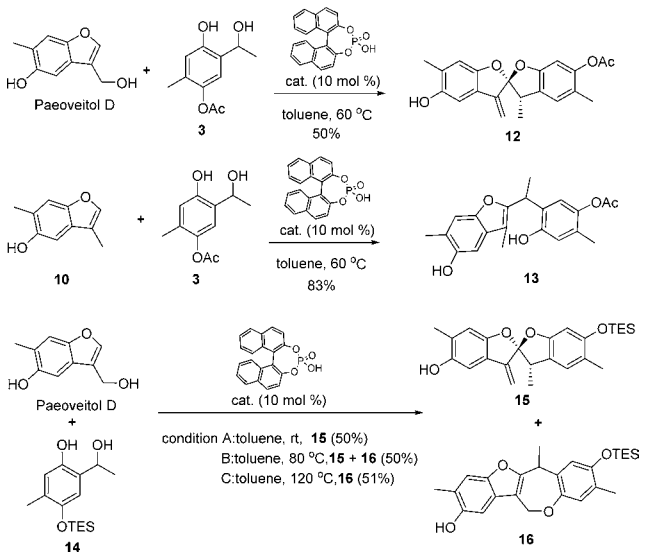
methyl at the furan of **10** was performed with 1.2 equiv of SeO_2 in 1,4-dioxane under reflux conditions. This attempt resulted in a complex mixture.[16] Presumably this result was due to the free phenol function group, which could be oxidized under the same conditions.[17] Notably, when acetyl derivative **11** was performed under the same conditions, only two components were achieved: the corresponding allylic alcohol and allylic aldehyde. Fortunately when the crude mixture was treated with $NaBH_4$ and K_2CO_3 via reduction and deacetylization, paeoveitol D was obtained as a single product.

With paeoveitol D in hand, the biomimetic synthesis of paeoveitol was investigated via hetero-Diels–Alder reaction (Scheme 5). Using model study conditions, paeoveitol D was

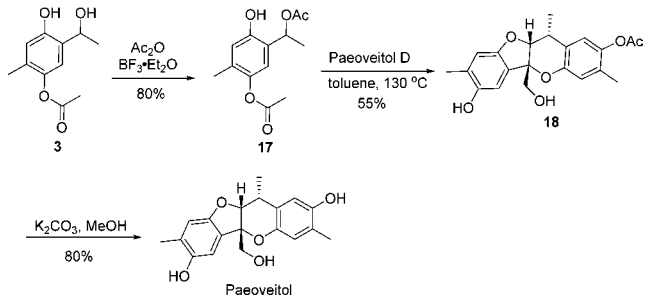
Scheme 5. Attempt to Synthesize Paeoveitol via BINOL-Based Phosphoric Acid Catalyst



treated with compound **3** in the presence of a BINOL-based phosphoric acid catalyst. Compound **12** was obtained as a single product in 50% yield. The formation of **12** suggested that the conjugated addition of the benzofuran to the *o*-QM, followed by rearomatization of the benzofuran, dehydration, and trapping of the resulting cationic species by the phenol oxygen (in a S_N2-like reaction). In order to resist the dehydration, compound **10** was replaced with paeoveitol D. However, it still did not work. Only compound **13** was produced to undergo conjugate addition to the *o*-QM and rearomatization in good yield. Presumably compound **5** derives from the stepwise electrophilic addition of a resonance-stabilized benzylic carbocation to nucleophilic benzofuran, followed by capture of the benzylic carbocation intermediate by a phenoxide ion.[18] In those cases, the C–O bond is not formed due to the electron-withdrawing group factors of acetate, which may decrease the nucleophilicity of the phenol (phenoxide ion).[19] Elimination of the electron-withdrawing mesomeric effect on the acetate fragment of the precursor **3** was expected to increase the nucleophilicity of the phenol, thus encouraging the key acid mediated cyclization to form the benzopyran ring. So we changed the –Ac group to the more electron-donating triethylsilyl group for further investigation. The compound **14** was prepared from compound **2** via TES protection and reduction. And our results revealed that the reaction between paeoveitol D and compound **14** produced compound **15**, **16**, or both depending on the reaction conditions. As shown in Scheme 5, compound **15** was the sole product at room temperature (~25 °C) and compound **16** was the sole product at 120 °C. By running the reaction at 80 °C, both compound **15** and **16** were obtained in an about 1:1 ratio, respectively. Notably, the compound **15** may convert to thermodynamically more stable **16** via a [2,3]-sigmatropic-type rearrangement under the same conditions, and without BINOL-based phosphoric acid, the compound **15** is stable even at 120 °C. As this kind of reaction did not work, we gave up this methodology and sought other possible solutions. The *o*-naphthoquinone methides which are formed from $FeCl_3$-catalyzed ring opening through a Diels–Alder reaction between benzynes and furans provided the highly functionalized naphthalene derivatives.[11] However, using $FeCl_3$ as the Lewis acid catalyst, the hetero-Diels–Alder reaction of paeoveitol D with compound **3** caused a complex product and no main product. When paeoveitol D was replaced with compound **10**, the reaction did not work. Unfortunately, we did not try other Lewis acids; very recently Zhao reported $ZnCl_2$ as catalyst successfully promoted cycloaddition which also is a Lewis acid.[4] Following Zhao's procedure, we obtained the desired cycloaddition products in 65% yield between **3** and paeoveitol D, so the failure of the approaches is due to the wrong Lewis acid promoter.

The final [4 + 2]-cycloaddition turned out to be the most difficult task. $FeCl_3$ as the Lewis acid and BINOL-based phosphoric acid as the Brønsted acid catalyzed *o*-QMs, which generated *in situ*, would not react with paeoveitol D to obtain the desired [4 + 2]-cycloaddition product. Those results can be understood as the BINOL-based phosphoric acid catalyzed to produce the *o*-QMs in the zwitterionic aromatic resonance structures rather than in neutral molecules.[9] Thermolysis, the most common method for *o*-QMs generation in neutral molecules, led to the elimination of a stable molecule, such as water, acetic acid, etc.[20] Our group has found a series of efficient methods of *o*-QMs generation for the syntheses of racemic spiroketals thermally.[21] Using compound **3** as the precursor of *o*-QM, the result is unsatisfactory. We then turned to prepare *o*-QM via elimination of acetic acid. Compound **17** was designed and prepared for the precursor of *o*-QM. Using acetic anhydride in the presence of $BF_3{\cdot}Et_2O$, the alcoholic hydroxyl groups of compound **3** were selectively acetylated to afford compound **17** (Scheme 6).[22] Following our procedure,[21] the paeoveitol D and compound **17** reacted in analytical toluene at 130 °C in a sealed tube, giving the [4 + 2]-cycloaddition product **18** as a single diastereoisomer in 55% yield. The final step of deprotection was achieved by adding K_2CO_3 in MeOH, from which we successfully obtained the

Scheme 6. Total Synthesis of Paeoveitol



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paeoveitol. The ^{1}H and ^{13}C NMR spectra were in agreement with literature data.[3]

In summary, we achieved total synthesis of the new norditerpene paeoveitol in 7 steps in 26% yield. The key step in the total synthesis is the final hetero-Diels–Alder cycloaddition to construct the target molecular framework.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02228.

Copies of ^{1}H, ^{13}C spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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