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A Total Synthesis of Paeoveitol

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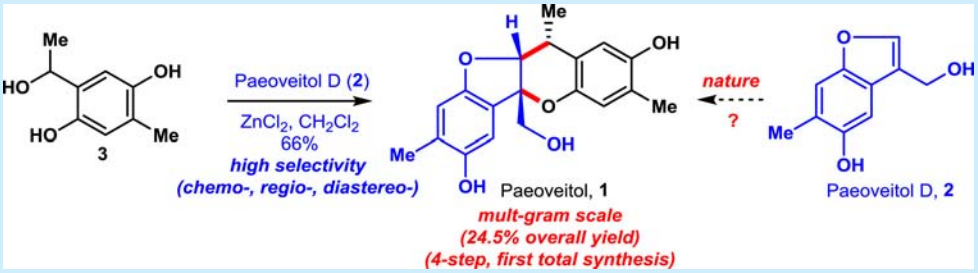
Supporting Information



ABSTRACT: A four-step total synthesis of paeoveitol (**1**), a recently disclosed norditerpene natural product from *Paeonia vetchii*, is reported. This highly concise synthetic route was guided by biosynthetic considerations and enabled by an unusual intermolecular *ortho*-quinone methide [4 + 2]-cycloaddition reaction, which proceeded with excellent regio- and diastereoselectivity. Density functional theory (DFT) calculations point to a crucial intermolecular hydrogen bond and $\pi-\pi$ stacking interaction that govern selectivity in this process.

The plant *Paeonia veitchii* has been used in many traditional Asian medicines for hundreds of years.[1] The root of this plant has been shown to have intriguing biological activity, including immunomodulation, anti-inflammation properties, and hypoglycemic action, among others.[2] In 2014, Chen and co-workers isolated a unique norditerpene natural product paeoveitol (**1**) from the root of *Paeonia veitchii* in racemic form.[3] In addition, five new natural products, paeoveitols A–E, were also isolated from *Paeonia veitchii* a year later (Figure 1).[4]

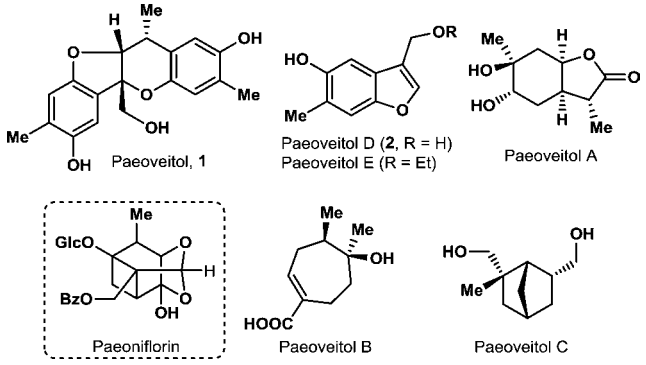


Figure 1. Paeoveitol and related natural products from *Paeonia veitchii*.

The structure of **1** was determined using X-ray crystallographic analysis, and a biosynthetic route involving two molecules of the chiral monoterpene paeoniflorin was also postulated by Chen and co-workers. Preliminary biological evaluation only studied the antidepressant abilities of **1** and showed no agitating activity.[3] However, the poor accessibility of this material (1.6 mg per 5 kg of dried plant roots) severely limited further and systemic biological screening. Further biological evaluation will become possible if greater quantities of **1** can be procured through synthesis.

Structurally, paeoveitol (**1**) features a 6/5/6/6-fused tetracyclic framework with three contiguous stereogenic centers and two free phenol subunits, rendering it a nontrivial synthetic target. Herein, we report a four-step, protecting group-free total synthesis of **1** that can be conducted on multigram scale. An unusual, yet highly selective, *ortho*-quinone methide (*o*-QM) [4 + 2]-cycloaddition reaction employing benzofuran alcohol as a coupling partner serves as the hallmark bond-forming step in this synthetic pathway.

Given the fact that many complex yet racemic natural products are often associated with nonenzymatic pericyclic reactions,[5] as well as the structural similarity between **1** and **2**, we speculated that **1** might be formed in nature from **2** via the concerted *o*-QM [4 + 2]-cycloaddition reaction shown (Scheme 1).[6] Executing this potentially biomimetic cycloaddition, however, requires addressing several challenges in chemo- and regioselectivity. As a reactive intermediate, *o*-QM can also react with the nucleophilic hydroxyl group of **2** to form an ether linkage.[7] In addition, the regioselectivity of an intermolecular concerted [4 + 2]-cycloaddition reaction between an *o*-QM and **2** has two chemically feasible possibilities given the nucleophilicity of both the 2- and 3-positions of a benzofuran. To the best of our knowledge, currently disclosed intermolecular [4 + 2]-cycloaddition reactions between *o*-QMs and electron-rich enol ethers only

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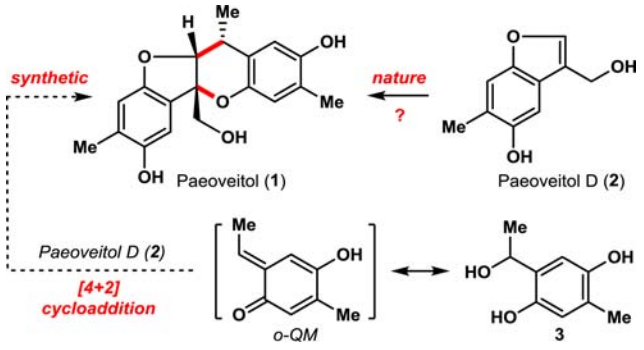
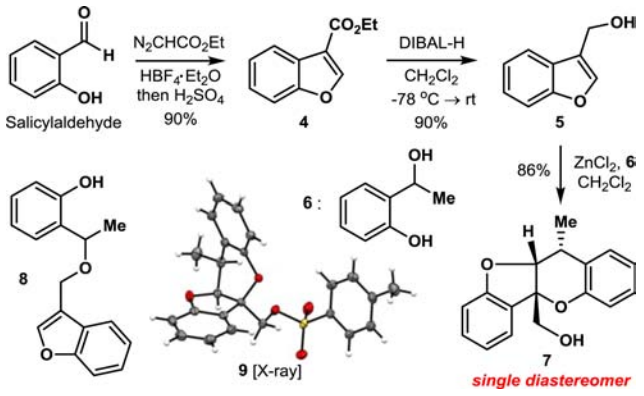
Scheme 1. Nature-Inspired Synthetic Design



afforded α-oxygen-substituent benzannulated tetrahydropyran analogues, which if extrapolated to the system at hand, corresponds to the undesired regioisomer.[8]

Seeking to evaluate the aforementioned strategy, we initially conducted a model study for the proposed intermolecular [4 + 2]-cycloaddition reaction (Scheme 2). Using the method

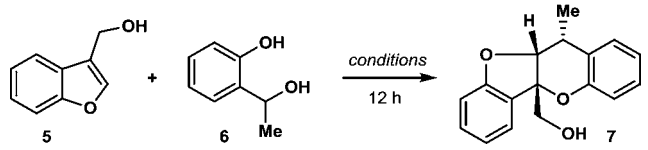
Scheme 2. Model Study for the Desired [4 + 2]-Cycloaddition Reaction



reported by Hossain and co-workers,[9] benzofuran ester **4** could be prepared easily from salicylaldehyde and ethyl diazoacetate in 90% yield. Reduction of both **4** and 2′-hydroxyacetophenone (not shown) afforded the desired model alcohols **5** and **6** and set the stage for the key coupling event. After significant experimentation, it was discovered that reacting **5** and **6** with zinc chloride in CH_2Cl_2 produced the desired cycloaddition product (**7**) in 86% yield and as a single isomer. To our delight, X-ray crystallographic analysis of tosyl-protected **7** confirmed its relative configuration, which was identical to that found in paeoveitol **1**. High yields of **7** only became possible after exploring a number of conditions and Lewis acid promoters (Table 1). Although initial evaluation showed that Lewis acids based on Al, Ti, and Sn were competent (Table 1, entries 1−3), $ZnCl_2$ exhibited the best performance (Table 1, entry 5). Further optimization indicated that the use of 4 Å molecular sieves and a lower catalyst loading did not affect the efficiency (Table 1, entries 7 and 8).[10] It is noteworthy that the oxa-Michael addition product **8** (Scheme 2) and any other diastereomers were not observed under any of these conditions.

With the success of our model study, we returned to the total synthesis of **1** (Scheme 3). Direct Vilsmeier−Haack formylation of commercially available methylhydroquinone, which was demonstrated to be difficult previously, produced **11** in

Table 1. Desired [4 + 2]-Cycloaddition: Selected Optimization[a]



entry	conditions	yield (%)[b]
1	Et_2AlCl (0.2 equiv), CH_2Cl_2, −78 °C → rt	43
2	$TiCl_4$ (0.2 equiv), CH_2Cl_2, −78 °C → rt	32
3	$SnCl_4$ (0.2 equiv), CH_2Cl_2, −78 °C → rt	<5
4	$ZnBr_2$ (0.2 equiv), CH_2Cl_2, rt	51
5	$ZnCl_2$ (0.2 equiv), CH_2Cl_2, rt	86
6	*p*-TsOH (0.2 equiv), CH_2Cl_2, rt	42[c]
7	$ZnCl_2$ (0.2 equiv), CH_2Cl_2, rt	87[d]
8	**$ZnCl_2$ (0.1 equiv), CH_2Cl_2, rt**	**84**

[a]Conditions: **5** (0.20 mmol), **6** (0.24 mmol), acid catalyst, solvent (0.1 M). [b]Isolated yield. [c]*p*-TsOH·H_2O was used. [d]Conducted with 4 Å molecular sieves (30 mg) as an additive.

62% yield.[11] Following a similar route as the model study, paeoveitol D **2** was synthesized in three-steps and on gram-scale (37% overall yield from inexpensive methylhydroquinone). With building block **2** in hand, we then focused on coupling partner **3**. Ketone **13** was easily prepared according to the reported procedure in two steps.[12] Reduction of **13** with BH_3 in THF afforded desired alcohol **3** in 86% yield. In our hands, it was found that **3** was somewhat unstable in air and difficult to purify on a larger scale. Thus, the crude reduction product from **13** was used directly in the key intermolecular [4 + 2]-cycloaddition reaction without further purification. To our delight, the desired cycloaddition product paeoveitol **1** was obtained in 66% yield as a single diastereomer. After a number of attempts, single crystals of **1** could be obtained from an acetone/aqueous ammonia solvent mixture. Utilizing this four-step synthetic sequence, over 2 g of paeoveitol **1** has been prepared to date.

For probing the high selectivity of the intermolecular reaction between *o*-QM and benzofuran alcohols, with an emphasis on understanding why only one isomer was afforded in this reaction, density functional theory (DFT) calculations with M06-2X functional and polarized triple-ζ 6-311+G(d,p) basis sets were performed (Figure 2, more stable *trans-o*-QM (**I**) was used here as a starting point to discuss the reaction; for the *cis-o*-QM case, see the Supporting Information). Intrinsic reaction coordinate (IRC) calculations were used to confirm the connection between the reactant, product, and transition state. The polarizable continuum model (PCM) was employed to consider the solvent (CH_2Cl_2) contribution to both energy and geometry.

Starting with the reactant benzofuran alcohol **5** and *trans-o*-QM (**I**), the reaction processes through either an oxa-Michael addition or a concerted [4 + 2]-cycloaddition pathway. In the former case, the benzylidene carbon in **I** and hydroxyl oxygen in **5** approach each other in two different orientations to reach two transition states **TS0** and **TS0′** with activation free energies of 20.1 and 21.6 kcal/mol. Once the barrier was conquered, the oxa-Michael addition products **MP0** and **MP0′** are finally generated with 12.7 and 12.4 kcal/mol of exergonicity, respectively. Compared to the oxa-Michael addition pathway, the concerted [4 + 2]-cycloaddition pathway is more complex due to the regioselectivity as well as the endo/exo selectivity. In

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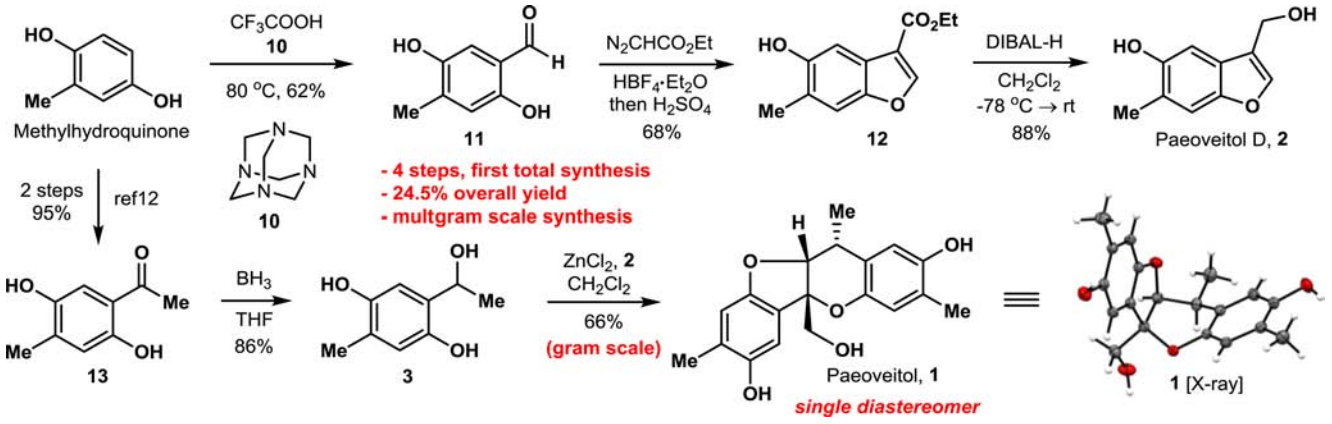
Scheme 3. Four Step Total Synthesis of Paeoveitol (1)



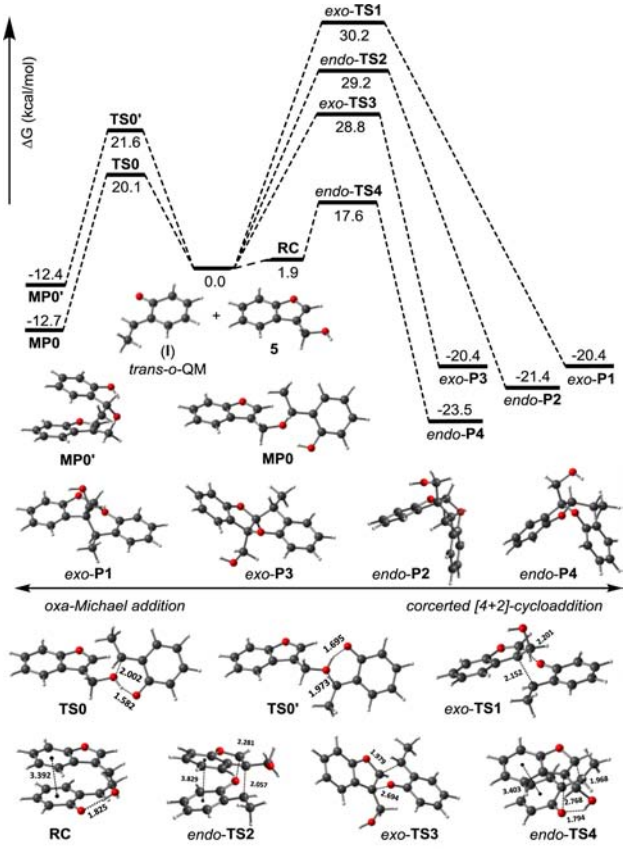


Figure 2. DFT computed energy surface and transition state structures.

total, four reach paths are found, including two endo- and two exo-type additions. Among them, the energetically most favorable channel corresponds to transition state *endo*-**TS4**, which is stabilized by both a hydrogen bond and $\pi-\pi$ stacking of the benzyl moieties. The free energy barrier height with respect to reactant complex **RC** is 15.7 kcal/mol, which is lower than that of the most feasible oxa-Michael addition channel (**TS0**, $\Delta G^{\ddagger}$ = 20.1 kcal/mol). Furthermore, the product of *endo*-**TS4** channel, *endo*-**P4**, is also lower in free energy than oxa-Michael addition product by ~10 kcal/mol and is actually thermodynamically the most favorable product. The M06-2X predicted structure for *endo*-**P4** is in good agreement with the experimentally obtained crystal structure, further confirming the validation of computational results. Therefore, the concerted [4 + 2]-cycloaddition reaction (more specifically, via *endo*-**TS4**) is the most favorable pathway both kinetically and thermodynamically.

In conclusion, we have achieved the first total synthesis of unique norditerpene natural product paeoveitol (**1**) with a high level of efficiency and scalability. The synthesis featured a Lewis acid-catalyzed biomimetic intermolecular [4 + 2]-cycloaddition reaction. The selectivities in the key step of the synthesis have also been studied by DFT calculations. Further application of the strategy reported herein are underway and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications Web site. (PDF) and **1** (CIF) The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01736.

Experimental procedures, spectroscopic data, and images of ^{1}H and ^{13}C NMR spectra for all new compounds (PDF)

Single crystal X-ray data for compound **9** (CIF)

Single crystal X-ray data for compound **1** (CIF)

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Notes

The authors declare no competing financial interest.

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