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Catalytic Asymmetric Total Synthesis of (+)- and (−)-Paeoveitol via a Hetero-Diels−Alder Reaction

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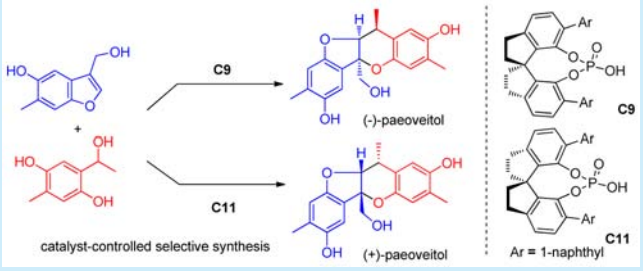
Supporting Information

ABSTRACT: The first catalytic asymmetric total synthesis of (+)- and (−)-paeoveitol has been accomplished in 42% overall yield via a biomimetic hetero-Diels−Alder reaction. The chiral phosphoric acid catalyzed hetero-Diels−Alder reaction showed excellent diastereo- and enantioselectivity (>99:1 dr and 90% ee); two rings and three stereocenters were constructed in a single step to produce (−)-paeoveitol on a scale of 452 mg. This strategy enabled us to selectively synthesize both paeoveitol enantiomers from the same substrates by simply changing the enantiomer of the catalyst.



The root of *Paeonia veitchii,* well-known as Chuan-Chi-Shao in China, is an important crude drug in traditional Chinese medicine and used as a sedative, analgesic, and cardiovascular agent.[1] Chuan-Chi-Shao is also included in the composition of many traditional formulas (such as Sini-San and Xiaoyao-Wan) used to treat mental illness.[2] To clarify the antipsychotic components of this plant, our previous chemical investigation led to the isolation of six new natural products,[3] including a pair of structurally novel norditerpene paeoveitol enantiomers (**1**) and two benzofuran constituents paeoveitols D and E (**2** and **3**) (Figure 1). Preliminary biological assays of

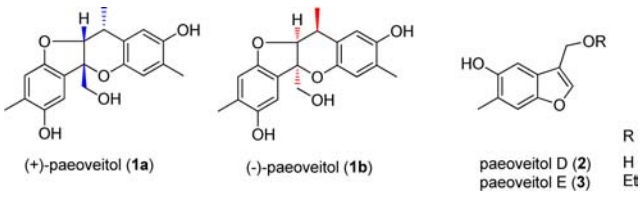
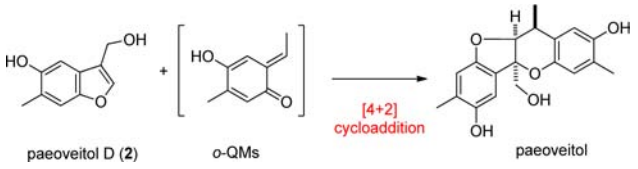


Figure 1. Structures of (+)-paeoveitol (**1a**), (−)-paeoveitol (**1b**), and paeoveitols D and E (**2** and **3**).

paeoveitol explored its interaction with 5-HT_{1A} and 5-HT_{2C} receptors in vitro, but no meaningful agonistic activities were observed.[3a] Intensive investigations of its biological activity are hampered by the limited availability of this natural product. As the chirality of a natural product is crucial to its bioactivity,[4] the development of a synthetic strategy that can provide both enantiomers in adequate amounts is clearly important for further investigation of its biological activity. Recently, Zhao and co-workers completed the first total synthesis of paeoveitol in racemic form through hetero-Diels−Alder cycloaddition from methylhydroquinone in 24% overall yield over four steps.[5] Xie's group reported a seven-step total synthesis of (±)-paeoveitol in 26% overall yield using a similar hetero-Diels−Alder cycloaddition reaction as a key step.[6] Herein, we report the first enantioselective total synthesis of (+)- and (−)-paeoveitol in six steps with 42% overall yield.

Structurally, paeoveitol consists of a unique 6,5,6,6-fused tetracyclic ring system with three contiguous stereogenic centers, one of which is a quaternary carbon. The structural correlation between paeoveitol and **2** inspired us to develop a biomimetic strategy for the synthesis of paeoveitol. Biogenetically, paeoveitol may arise from **2** via an oxo-Diels−Alder reaction with in situ generated *o*-quinone methides (*o*-QMs) (Scheme 1). *o*-QMs are highly efficient intermediates in organic

Scheme 1. Proposed Biosynthesis of Paeoveitol



chemistry that are widely used in the key step of the synthesis of various natural products.[7] However, the fleeting nature of *o*-QMs leads to difficulties in the stereocontrol of reactions, and only one example of the utilization of *o*-QMs in the catalytic asymmetric total synthesis of natural products has been documented.[8] With the development of asymmetric Brønsted acid catalysis, enantioselective reactions that involve *o*-QMs have been reported in the recent literature.[9] Inspired by this, we

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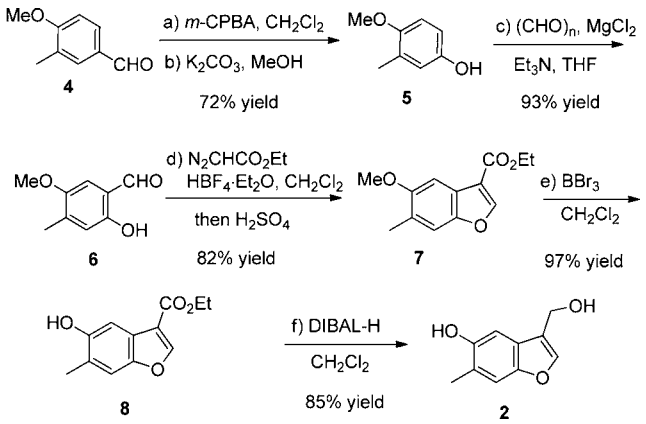
envisioned that the enantioselective total synthesis of paeoveitol could be realized if chiral phosphoric acid could promote the asymmetric hetero-Diels–Alder reaction between paeoveitol D and *o*-QMs. In this design, three stereocenters could be constructed in a single step, and by changing only the enantiomer of the catalyst, both paeoveitol enantiomers could be synthesized from the same prochiral substrates.

Our synthesis commenced with the preparation of paeoveitol D from commercially available 4-methoxy-3-methylbenzaldehyde (Scheme 2). According to the reported procedure, **4** was converted into the phenol **5** through Baeyer–Villiger oxidation/saponification in 72% yield.[10] Substituted salicylaldehyde **6** was easily obtained by the magnesium chloride mediated *ortho*-specific formylation of **5** in good yield.[11] Treatment of **6** with ethyl diazoacetate produced **7** in 82% yield.[12] Removal of the methoxyl group with BBr_3, followed by DIBAL-H reduction furnished paeoveitol D in 45% overall yield.

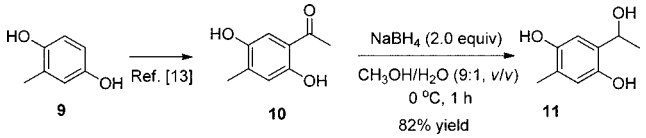
Scheme 2. Synthesis of Paeoveitol D[a]



[a]Reagents and conditions: (a) *m*-CPBA (1.7 equiv), CH_2Cl_2, 0 °C to rt, 2 h; (b) K_2CO_3 (2.0 equiv), MeOH, 0 °C, 15 min, 72% (two steps); (c) $(CHO)_n$ (5.0 equiv), $MgCl_2$ (1.5 equiv), Et_3N (4.0 equiv), THF, reflux, 8 h, 93%; (d) N_2CHCO_2Et (3.0 equiv), $HBF_4{\cdot}Et_2O$ (0.1 equiv), 0 °C to rt, 30 min, then H_2SO_4 (1 mL), rt, 30 min, 82%; (e) BBr_3 (1.5 equiv), CH_2Cl_2, − 78 to 0 °C, 1 h, 97%; (f) DIBAL-H (3.0 equiv), CH_2Cl_2, − 78 to 0 °C, 1 h, 85%.

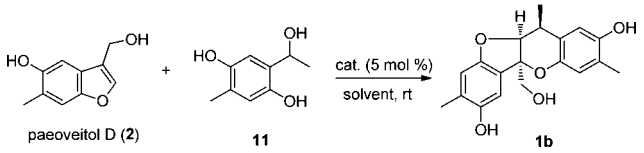
As depicted in Scheme 3 for the construction of coupling partner **11**, the ketone **10** was prepared from the commercially available 2-methylhydroquinone **9** in a reported two-step process[13] and was then reduced with $NaBH_4$ to provide the *o*-QM precursor **11** in 82% yield.

Scheme 3. Synthesis of the *o*-QM Precursor



With paeoveitol D and **11** in hand, attention was turned to the crucial asymmetric [4 + 2] cycloaddition. The initial experiment to test our hypothesis commenced with the reaction of paeoveitol D and **11** in CH_3CN catalyzed by 5 mol % of **C1**. The desired natural product could be obtained in 72% yield with 34% ee as a single diastereomer. The reaction conditions were investigated to improve the yield and enantiomeric excess of the asymmetric [4 + 2] addition. The subsequent screening of different BINOL-derived CPAs (Table 1, entries 1–5) revealed that catalyst **C2** bearing a bulky $SiPh_3$ substituent slightly improved the ee value to 57%, albeit with a minor decrease in yield (47%). We resorted to the chiral acids **C7–C10** with a spirocyclic backbone that were structurally more rigid (Figure 2).[14] The highest selectivity was eventually obtained with phosphoric acid **C9**, which delivered (−)-paeoveitol in 66% yield and 92% ee. Next, the solvent effect was investigated. The reaction became sluggish in EtOH, THF, and EtOAc (Table 1, entries 11–13). The stereoselectivity decreased when toluene was used as the solvent (Table 1, entry 14). The reaction proceeded well in chlorinated solvents such as CH_2Cl_2, CH_3Cl_3, and $ClCH_2CH_2Cl$ (Table 1, entries 15–17). Using CH_2Cl_2 as the solvent, the reaction yield was enhanced to 95% while maintaining excellent enantioselectivity (90% ee). Reducing the catalyst loading from 5 to 2 mol % led to a significant decrease in the yield with retained enantioselectivity, and only 67% yield was achieved after stirring for 6 d (Table 1, entry 18 vs 15).

Table 1. Optimization of the Brønsted Acid Catalyzed [4 + 2] Hetero-Diels–Alder Reaction[a]



entry	solvent	cat.	time (d)	yield[b] (%)	ee[c] (%)
1	CH_3CN	**C1**	2	72	34
2	CH_3CN	**C2**	4	51	57
3	CH_3CN	**C3**	4	59	52
4	CH_3CN	**C4**	3	72	14
5	CH_3CN	**C5**	3.5	68	27
6	CH_3CN	**C6**	4	58	48
7	CH_3CN	**C7**	3.5	62	80
8	CH_3CN	**C8**	4	74	63
9	CH_3CN	**C9**	3	66	92
10	CH_3CN	**C10**	3	67	68
11	EtOH	**C9**	5	trace	
12	THF	**C9**	5	trace	
13	EtOAc	**C9**	5	trace	
14	toluene	**C9**	2.5	85	68
15	CH_2Cl_2	**C9**	3	95	90
16	$CHCl_3$	**C9**	3	93	90
17	$ClCH_2CH_2Cl$	**C9**	3	92	90
18[d]	CH_2Cl_2	**C9**	6	67	90
19[e]	CH_2Cl_2	**C9**	3	92	90 (96)[f]
20[e]	CH_2Cl_2	**C11**	3	93	89[g]

[a]Unless stated otherwise, the reactions were performed with 5 mol % of catalyst, 0.1 mmol of paeoveitol D, and 0.11 mmol of **11** (1.1 equiv) in 2 mL of solvent at room temperature. [b]Yield of the isolated product. [c]The enantiomeric ratio (ee) was determined by HPLC analysis on a Daicel Chiralpak AD-H column (*n*-hexane/EtOH = 85/15, 1.0 mL/min. [d]The catalyst loading of **C9** was 2 mol %. [e]The reaction was performed on a 1.5 mmol scale. [f]The data in parentheses were obtained after one recrystallization from a mixture of acetone–hexane (1:4, v/v). [g]The opposite enantiomer of **1b** was obtained.

Under the optimal reaction conditions, a large-scale synthesis using 1.5 mmol of paeoveitol D also provided excellent yield (92%, 452 mg) and enantioselectivity (90% ee, entry 19). The

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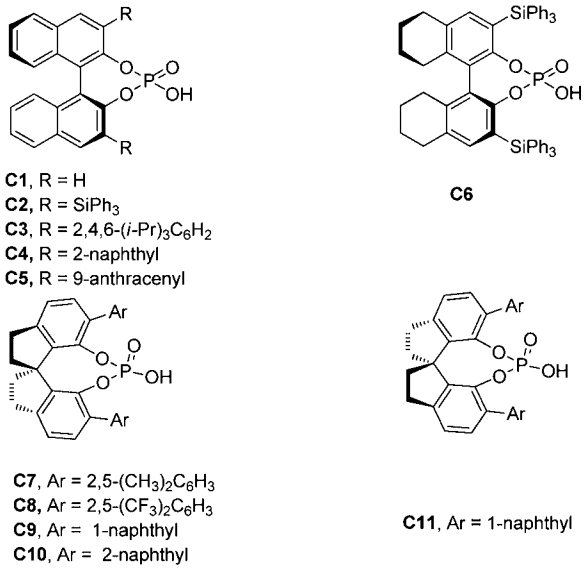

Figure 2. Structures of the chiral phosphoric acid compounds.

ee values reached 96% after a simple recrystallization from acetone−hexane (1:4, v/v), and the synthetic sample had a rotation of −320.3 (*c* 0.23, MeOH). In addition, 457 mg of (+)-paeoveitol was synthesized with 89% ee using the enantiomer of **C9** as a chiral catalyst ($[\alpha]^{22}_{D}$ +272.4 (*c* 0.22, MeOH)). A single crystal of **1b** was obtained by recrystallization from CH_3OH; X-ray crystallographic analysis with copper radiation unambiguously determined the configuration of the three contiguous stereocenters as 7*S*,8*S*,9*R* (Figure 3).

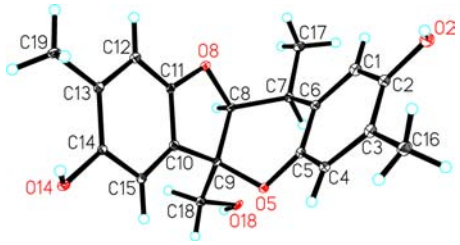

Figure 3. X-ray crystal structure of **1b**.

In summary, the enantioselective total synthesis of (+)- and (−)-paeoveitol was completed in six steps and 42% overall yield. The most significant tactical feature of this synthesis involves the chiral acid-catalyzed asymmetric hetero-Diels−Alder reaction, which enabled us to selectively synthesize both paeoveitol enantiomers from the same substrates by simply changing the catalyst's stereochemistry. Efforts to expand the application of this key transformation in the asymmetric total synthesis of other benzopyran-containing natural products are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03801.

Experimental details of chemical synthesis, compound characterizations (PDF)

X-ray crystallographic data for compound **1b** (CIF)

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Notes

The authors declare no competing financial interest.

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