ORGANIC LETTERS

2006
Vol. 8, No. 12
2479−2481

Total Synthesis of (±)-Paeonilide

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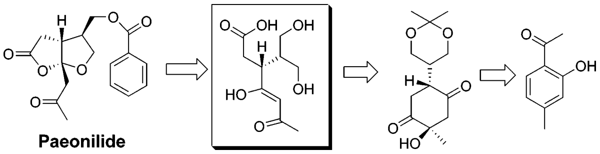
Received February 14, 2006

ABSTRACT



The total synthesis of paeonilide, a natural anti-PAF (platelet-activating factor) new skeleton monoterpenoid with an IC_{50} value of 8 μg/mL, was achieved in 16 steps with 15% overall yield from commercially available 2-hydroxy-4-methylacetophenone.

Paeonia root bark is used in traditional Chinese medicine for treatment of abdominal pain and syndromes such as stiffness of abdominal muscles.[1] Phytochemical research has generated a number of structurally related monoterpenes from paeony roots.[2] Representative compounds are shown in Figure 1. In 2000, a novel monoterpenoid, paeonilide (**4**) (Figure 1), was isolated from the roots of *Paeonia delavayi*.[3] Its new skeleton was established by a combination of spectroscopic and X-ray crystallographic analyses. Because of its ginkgolide-like ring structure, paeonilide was screened against platelet-activating factors (PAFs).[4] The bioassay indicated that paeonilide selectively inhibited the platelet aggregation induced by PAFs with an IC_{50} value of 8 μg/mL (25 μM), with no inhibitory effect on adenoside diphosphate-induced or arachidonic acid-induced platelet aggregation. Because of the scarcity of available samples, however, further biological study of this compound was suspended. Paeonilide represents a new monoterpene skeleton. Synthesis of paeonilide and its derivatives is of interest in terms of medicinal chemistry as well as synthetic chemistry. In this paper, we describe the total synthesis of paeonilide.

As shown in Figure 1, paeonilide is a highly oxygenated monoterpenoid featured with an acetonyl moiety attached to the ketal function. We drafted a synthetic plan starting from the readily available 2-hydroxy-4-methylacetophenone. The key to the synthesis of paeonilide was the construction of a disubstituted acetylacetone **6** as indicated in the retrosynthetic analysis in Scheme 1.

A synthetic study was initiated from commercially available 2-hydroxy-4-methylacetophenone.[5] The phenol group

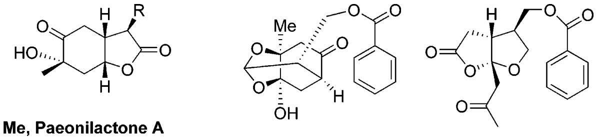


Figure 1. Paeonilactone A, C, and paeonilide.

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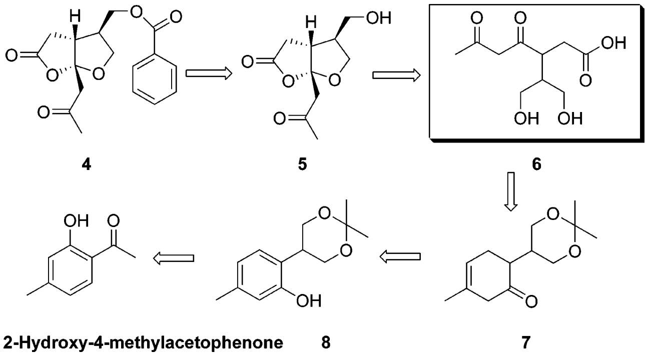
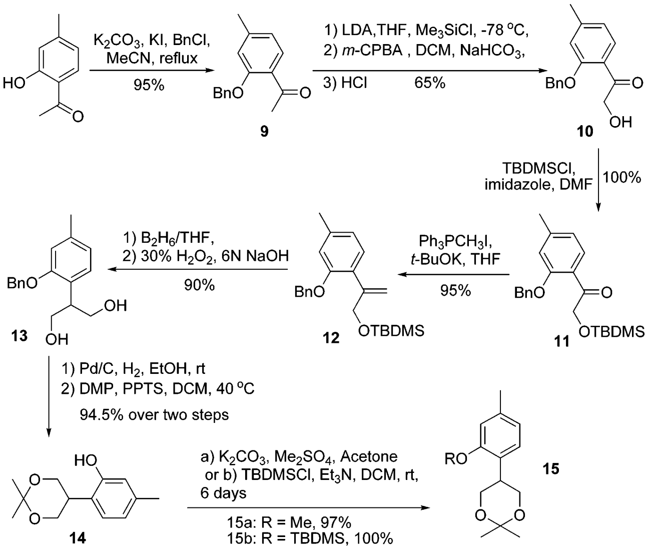
10.1021/ol060382z CCC: $33.50

Scheme 1. Retrosynthetic Analysis of Paeonilide



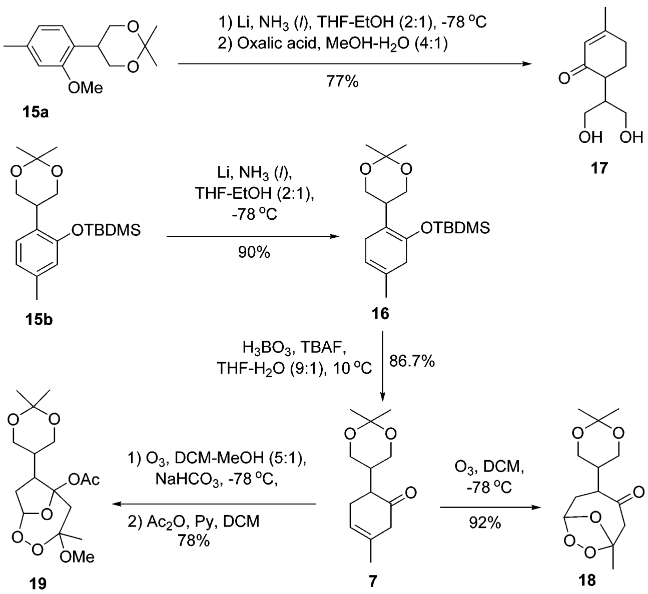
was protected by reaction with benzyl chloride in the presence of base. Rubutom oxidation[6] followed by protection of the hydroxyl group provided compound **11** in 65% yield over two steps.

Scheme 2. Synthesis of an Intermediate for Paeonilide



A Wittig reaction followed by hydroboration led to 1,3-diol **13** (Scheme 2). The benzyl protecting group was removed by hydrogenolysis with palladium on carbon. After protection of the 1,3-diol systems, phenol **14** was protected initially by formation of the corresponding methyl ether. The next Birch reaction gave the diene intermediate in good isolated yield; unfortunately, we failed to effect the conversion of methyl enol ether to β,γ-unsaturated ketone **7**. An α,β-unsaturated ketone was formed instead, upon treatment of diene **15a** with oxalic acid or a Lewis acid such as $ZnBr_2$ or $ZnCl_2$. Careful survey of the literature revealed that a TBDMS ether-protected diene system could be converted to a nonconjugated ketone system with high selectivity.[7] Phenol **14** was thus protected with TBDMS chloride. After Birch reduction, the resulting diene was treated with boric acid in the presence of n-Bu_4NF in THF at 10 °C. To our delight, the desired nonconjugated enone was isolated in 87% yield (Scheme 3).

Scheme 3. Synthesis of β,γ-Unsaturated Ketone **7** and Its Related Reactions



With the ketone in hand, oxidative cleavage of the double bond was conducted. It was expected that an ozonolysis followed by further oxidation of the resultant aldehyde would lead to disubstituted acetylacetone **6**, which was expected to undergo cyclization and provide the target compound **5**. To our surprise, ozonolysis of ketone **7** in dichloromethane at −78 °C led to ozonide **18** which could not be decomposed by a usual workup procedure such as dimethyl sulfide and triphenyl phosphine. Treatment of the ozonide with zinc powder in acetic acid resulted in a complex mixture. When ozonolysis was carried out in the presence of methanol at −78 °C, peroxide **19** was obtained in high yield. The peroxide structure was confirmed by COSY, HMBC, HMQC, and HRMS spectra.

To access the key intermediate, we decided to conduct a cis dihydroxylation using osmium tetroxide on β,γ-unsaturated ketone **7**. To our delight, only one diastereomer was isolated in 92% yield. The relative stereochemistry of compound **20** was initially deduced by small coupling constants observed for proton H−C(4) (3.84 ppm, brs) toward the two adjacent protons at C(3). If the H−C(4) was in an axial position, a large (10∼12 Hz) coupling constant between the axial H−C(4) and the axial H−C(3) would be expected. The relative stereochemistry of diol **20** was finally established by ROESY spectrum, in which significant NOE correlation peaks between H_e−C(4) and Me−C(5) (1.16

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(5) Hydroxy-4-methylacetophenone can also be prepared by Fries rearrangement: Bensari, A.; Zaveri, N. T. *Synthesis* **2003**, 267.

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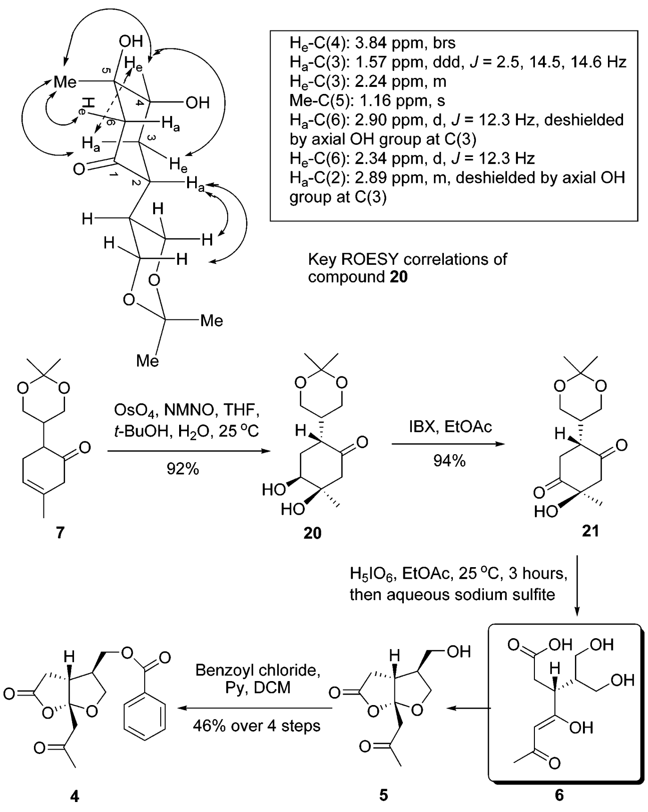
ppm); $H_e-C(4)$ and $H_a-C(3)$ (1.57 ppm, ddd, $J = 2.5$, 14.5, 14.6 Hz); $H_e-C(4)$ and $H_e-C(3)$ (2.24 ppm, m); $H_a-C(3)$ and $Me-C(5)$; and $H_e-C(6)$ (2.34 ppm, d, $J = 12.3$ Hz) and $Me-C(5)$ were observed (see Scheme 4). The diol compound **20** was then oxidized with IBX[8] in ethyl acetate to afford diketone **21** in 94% yield (see Scheme 4).

At the final stage of our journey, diketone **21** was deprotected and cleaved with periodic acid in ethyl acetate to give the key intermediate **6**. No attempt was made to isolate the UV active key intermediate, which underwent intramolecular cyclization in ethyl acetate to afford alcohol **5** as the only isolated product. The two hydroxyl groups in compound **6** are constitutionally identical but topologically different groups (diastereotopic groups). We obtained the required relative stereochemistry which might be a consequence of a diastereotopic group differentiation reaction.[9] After esterification with benzoyl chloride in the presence of triethylamine in dichloromethane, paeonilide was obtained in 46% yield over four steps (see Scheme 4). Spectroscopic data of synthetic paeonilide were completely identical to those of authentic samples isolated from the roots of *Paeonia delavayi*.[10]

Scheme 4. Total Synthesis of (±)-Paeonilide



In summary, the first total synthesis of paeonilide was achieved in 16 steps with 15% overall yield. Flexibility is a notable feature of our synthetic strategy, and synthesis of representative monoterpenes isolated from paeony roots could be expected by this strategy. Assembly of a chiral center in a later stage is also a good tactic that greatly facilitates experimental practice. Synthesis of analogues as well as other highly oxygenated monoterpenes from paeony roots is currently underway in our laboratory.

Acknowledgment. This work was supported by a grant (20272049) from the National Natural Science Foundation of China and a grant from the foundation of the Chinese Ministry of Education for the promotion of Excellent Young Scholars. We would like to thank the International Cooperation Division of Yunnan Provincial Science & Technology Department for partial financial support (2002GH04).

Supporting Information Available: ^1H NMR, ^{13}C NMR, MS, as well as HRMS spectra of all key intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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[9] (a) Hoffmann, R. W. *Synthesis* **2004**, 2075. (b) Studer, A.; Schleth, F. *Synlett* **2005**, 3033.

[10] Authentic natural paeonilide was provided by Professor Liu Ji-Kai. A few typing errors were found for the assignment of protons at the C_{13} position in the original paper published in *Biosci. Biotechnol. Biochem.* (see ref 3). It should be corrected to 3.34 (1H, dd, $J = 10.5$, 18.5 Hz) and 2.55 (1H, dd, $J = 2.8$, 18.5 Hz).