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Facile Synthesis of (±)-Paeonilide

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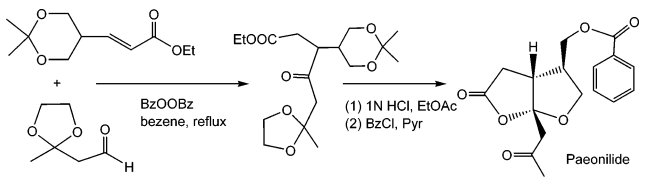
Received January 22, 2007



(±)-Paeonilide, a novel monoterpenoid metabolite from the roots of *Paeonia delavayi* showing anti-platelet activating factor activity, is convergently synthesized in five steps with 59% overall yield. The application of benzoyl peroxide-promoted radical addition of unsaturated ester to aldehyde and subsequent topologically favored cyclization greatly simplified the synthesis.

Paeony root, having a Chinese name of "mu-dan-pi" or "dan-pi", is widely used as crude drugs in several Chinese medicinal prescriptions for treatment of abdominal pain and syndromes such as stiffness of abdominal muscles.[1] Studies on the biologically active components of the paeony root have resulted in the discovery of a variety of monoterpenes, and their chemical structures have been established based on spectroscopy and/or X-ray crystallography.[2] In the year of 2000, Liu and co-workers discovered an active compound with a novel monoterpenoid skeleton from the roots of *Paeonia delavayi* and named it paeonilide.[3] The biossay indicated that paeonilide selectively inhibited platelet aggregation induced by the platelet activating factor (PAF) with an IC_{50} value of 8 μg/mL, with no inhibitory effect on adenoside diphosphate (ADP) or arachidonic acid (AA)-induced platelet aggregation. However, 1.13 kg of *Paeonia delavayi* root methanol extract afforded only 8 mg of paeonilide. The scarcity of the pure compound has become a bottleneck for the further biological investigation of paeonilide. We were attracted by its both interesting chemical structure and potential medicinal use, and initiated a project aimed at the total synthesis of paeonilide.[4]

Our approach involves the synthesis of the key intermediate ketone-ester **3** by the intermolecular radical addition of 3-(ethylenedioxy)butanal (**4**)[5] and (*E*)-2-(ethoxycarbonyl)ethenyl-2,2-dimethyl-1,3-dioxane (**5**) as shown in Scheme 1. Intermediate **5** can be prepared from 5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxane (**6**) and ethyl (triphenylphosphoranylidene)acetate through Swern oxidation and Wittig olefination.

Alcohol **6** (Scheme 2) was subjected to a one-pot sequential Swern oxidation and Wittig olefination to afford *trans*-ester *E*-**5** in a 84% overall yield from the starting triol.[6] However, the attempted two-step procedure,[7] i.e., pyridinium dichromate (PDC) oxidation of **6** followed by Wittig reaction with ethyl (triphenylphosphoranylidene)acetate in methanol, gave a separable mixture of *Z*-**8** (64%) and *E*-**5** (27%).[8] Benzoyl peroxide-promoted radical addition[9] of **4** to **5** in benzene under reflux conditions furnished the critical ketone-ester **3** in 79% yield (Scheme 3). The neat reaction of **4** (10 equiv) and **5**, and the same reaction in toluene under reflux, were sluggish. It is also worth noting that the same radical reaction of *Z*-**8** and **4** afforded **3** in only 47% yield. These results are in contrast to those observed for the addition of butanal to ethyl maleate and fumarate, but parallel the results obtained for crotonate and cinnamate.[10] Treatment of **3** with aqueous 1 N HCl in EtOAc afforded bicycliclactone **2** in a one-pot yield of 91% through the sequential *in situ* deacetalation, hemiacetal formation, and lactonization. The relative stereochemistry in compound **2,** postulated based on the Felkin−Ahn model, is supported by identical, recently published spectra data.[4a] Benzoylation of **2** with BzCl in pyridine completed the total synthesis of (±)-paeonilide **1**. Our strategy provides the efficient total synthesis of (±)-paeonilide **1** in five steps with 59% overall yield, compared to the recently reported[4a] synthesis of compound **1** in 16 steps with 15% overall yield.

In summary, the convergent synthesis of paeonilide was achieved in five steps with 59% overall yield. The application of benzoyl peroxide-promoted radical addition of unsaturated ester to aldehyde and subsequent topologically favored cyclization greatly simplified the synthesis. The current strategy provides a suitable approach for the large-scale preparation of

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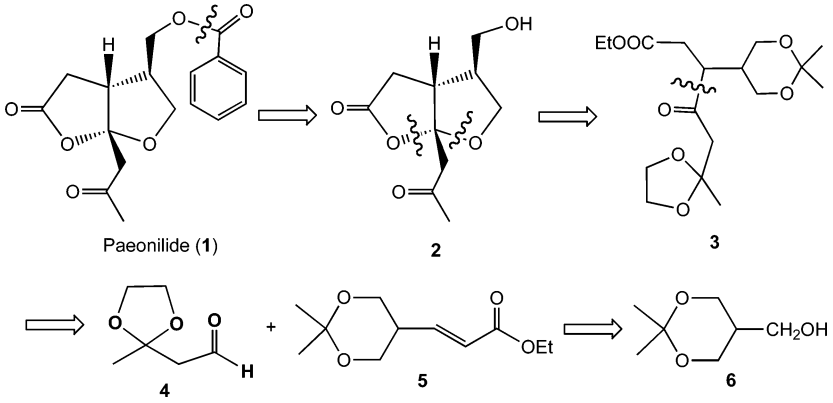
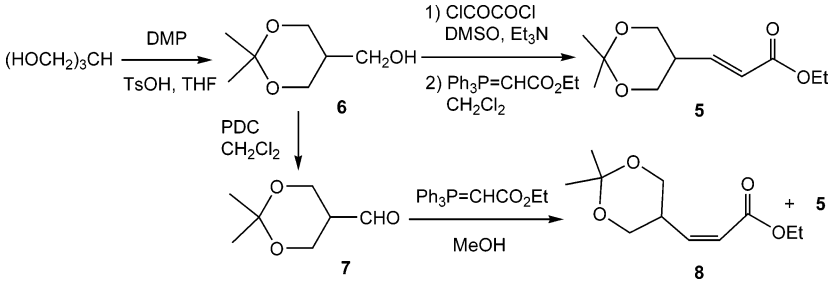
10.1021/jo0701278 CCC: $37.00
Published on Web 04/06/2007

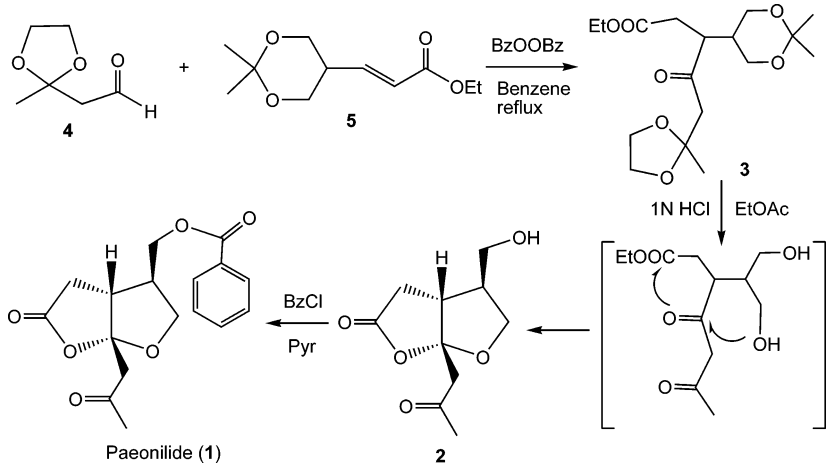
SCHEME 1. Retrosynthetic Analysis of Paeonilide



SCHEME 2. Synthesis of Intermediates



SCHEME 3. Synthesis of Paeonilide



paeonilide required for the screening of its bioactivities by our collaborators.

Experimental Section

(*E*)-2-(Ethoxycarbonyl)ethenyl-2,2-dimethyl-1,3-dioxane (5). A solution of oxalyl chloride (1.55 mL, 18 mmol) in dry dichloromethane (20 mL) was mixed with dimethyl sulfoxide (2.55 mL, 36 mmol) at −78 °C with stirring, and then a solution of crude alcohol **6** (1.31 g, 9 mmol) in dry dichloromethane (5 mL) was added dropwise to the mixture in 10 min. The mixture was stirred under these conditions for 10 min, triethylamine (3 mL) was then added, and the reaction was allowed to warm up to 0 °C. A solution of ethyl (triphenylphosphoranylidene)acetate (4.38 g, 12.6 mmol) in 10 mL of dichloromethane was added to the above mixture, stirred at room temperature for 2 h, and then poured into saturated aqueous NaCl. The aqueous layer was extracted with ether (3 × 50 mL), and the combined organic phase was washed with brine, dried over Na_2SO_4, and concentrated under vacuum. Purification of the residue on silica gel column chromatography (4:1 petroleum ether−ethyl acetate) gave **5** as a white solid (1.62 g, 84% for two steps): mp 40−42 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26 (t, 3H, J = 7.3 Hz), 1.39, 1.42 (2s, 2 × 3H), 2.63−2.68 (m, 1H), 3.75 (dd, 2H, J = 9.0, 12.0 Hz), 3.88 (dd, 2H, J = 4.7, 12.1 Hz), 4.15 (q, 2H, J = 7.3 Hz), 5.86 (dd, 1H, J = 1.1, 15.9 Hz), 6.77 (dd, 1H, J = 7.9, 15.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 20.7, 26.8, 37.7, 60.4, 63.0, 97.8, 123.4, 144.4, 165.9. Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.43; H, 8.41.

(*Z*)-2-(Ethoxycarbonyl)ethenyl-2,2-dimethyl-1,3-dioxane (8). A mixture of crude alcohol **6** (1.022 g, 7 mmol) and PDC (3.76 g, 10 mol) in dry dichloromethane (30 mL) was refluxed overnight under N_2 protection. The solution was cooled to room temperature and filtered through a Celite. The filtrate was concentrated under vacuum to give **7**, which was directly added into a solution of ethyl (triphenylphosphoranylidene)acetate (2.95 g, 8.5 mmol) in anhydrous MeOH (20 mL) in one portion at 0 °C. The mixture was

stirred at room temperature until **7** was consumed based on TLC monitoring and concentrated under vacuum, and the residue was subjected to the silica gel column chromatography (5:1 petroleum ether−ethyl acetate) to give amorphous solid (*Z*)-**8** (958 mg, 64%) and white solid (*E*)-**5** (404 mg, 27%). For **8**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.27 (t, 3H, J = 7.1 Hz), 1.39, 1.42 (2s, 2 × 3H), 3.61−3.63 (m, 1H), 3.71 (dd, 2H, J = 5.9, 11.6 Hz), 4.06 (dd, 2H, J = 4.0, 11.7 Hz), 4.15 (q, 2H, J = 7.2 Hz), 5.89 (dd, 1H, J = 1.1, 11.5 Hz), 6.41 (dd, 1H, J = 9.5, 11.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 23.4, 24.4, 34.5, 60.1, 63.5, 97.9, 121.6, 147.0, 166.8. Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.38; H, 8.39.

Synthesis of 3. Benzoyl peroxide (303 mg, 1.25 mmol) was added to a mixture of **5** (321 mg, 1.50 mmol) and **4** (650 mg, 5 mmol) in benzene (10 mL). The reaction was vigorously stirred under reflux with N_2 protection. More benzoyl peroxide (303 mg, 1.25 mmol) was added twice, at 2 h intervals, and the reaction was monitored by TLC (1:2 ethyl acetate−petroleum ether) until ester **5** was completely consumed. The reaction mixture was concentrated to dryness, and the residue was subjected to the silica gel column chromatography (2:1 petroleum ether−ethyl acetate) to give **3** (390 mg, 79%) as a white foam: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.24 (t, 3H, J = 7.1 Hz), 1.40, 1.41 (2s, 2 × 3H), 1.48 (s, 3H), 1.95−1.99 (m, 1H), 2.47 (dd, 1H, J = 4.0, 16.9 Hz), 2.80 (dd, 1H, J = 10.0, 16.9 Hz), 3.05 (dd, 2H, J = 16.4, 26.8 Hz), 3.21−3.23 (m, 1H), 3.70−3.74 (m, 2H), 3.84−3.89 (m, 2H), 3.96 (s, 4H), 4.10 (q, 2H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 23.7, 24.1, 24.3, 33.6, 35.6, 46.9, 51.8, 60.9, 61.6, 62.4, 64.5, 64.6, 98.3, 107.8, 172.1, 208.8. HR-ESI(+)MS calcd. for $C_{17}H_{28}O_7Na$: 367.1733; found: 367.1719 $(M + Na)^+$.

Synthesis of 2. To a solution of ketone **3** (50 mg, 0.15 mmol) in ethyl acetate (5 mL) was added 1 N HCl (2 drops). The resulting mixture was stirred at room temperature until all starting material was consumed. The mixture was diluted with ethyl acetate (10 mL), and saturated aqueous sodium carbonate (1 mL) was added. The organic phase was dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was subjected to the silica gel column chromatography (1:4 petroleum ether−ethyl acetate) to give compound **2** (29.5 mg, 91%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.84 (br s, 1H), 2.20 (s, 3H), 2.21−2.26 (m, 1H), 2.50 (dd, 1H, J = 2.8, 18.5 Hz), 2.94−2.97 (m, 1H), 2.98 (d, 1H, J = 17.5 Hz), 3.26 (dd, 1H, J = 10.5, 18.5 Hz), 3.33 (d, 1H, J = 17.6 Hz), 3.58 (d, 2H, J = 6.9 Hz), 3.94 (dd, 1H, J = 1.8, 9.8 Hz), 4.00 (dd, 1H, J = 5.5, 9.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 31.0, 36.8, 44.0, 49.3, 49.5, 63.8, 68.3, 115.4, 174.8, 204.5. HR-ESI-(+)MS calcd. for $C_{10}H_{14}O_5Na$: 237.0739; found: 237.0782 $(M + Na)^+$.

Synthesis of Paeonilide (1). Crude compound **2** was used directly without purification. Benzoyl chloride (12 μL, 0.1 mmol) was added to a solution of **2** (11 mg, 0.05 mmol) in pyridine (1 mL). The mixture was stirred at room temperature for 1 h and coevaporated with toluene for twice. The residue was subjected to silica gel column chromatography (2:1 petroleum ether−ethyl acetate) to give compound **1** (16 mg, 98%) as a white needles: mp 162−164 °C (lit.[4a] mp 168−170 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.20 (s, 3H), 2.52−2.55 (m, 1H), 2.57 (dd, 1H, J = 2.8, 18.5 Hz), 2.94 (d, 1H, J = 17.7 Hz), 2.95−3.01 (m, 1H), 3.34 (dd, 1H, J = 10.6, 18.6 Hz), 3.40 (d, 1H, J = 17.9 Hz), 4.00−4.07 (m, 2H), 4.19 (dd, 1H, J = 8.0, 11.0 Hz), 4.30 (dd, 1H, J = 7.3, 11.0 Hz), 7.47−7.53 (m, 2H), 7.57−7.62 (m, 1H), 8.02 (dd, 2H, J = 1.1, 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 30.9, 36.6, 44.4, 46.7, 49.5, 64.9, 67.9, 115.0, 128.5, 129.2, 129.5, 129.6, 133.4, 166.3, 174.5, 204.4. HR-ESI(+)MS calcd. for $C_{17}H_{18}O_6Na$: 341.1001; found: 341.1027 $(M + Na)^+$.

Acknowledgment. This work was supported by National Basic Research Program of China (2003CB415001) and NNSF of China (Projects 20621703 and 20572128).

Supporting Information Available: Spectral data for compounds **1**−**3**, **5**, and **8** are available free of charge via the Internet at http://pubs.acs.org.

JO0701278