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Enantiospecific Synthesis of (+)-Paeonilactone C and (+)-Paeoniflorigenone from *R*-(–)-Carvone

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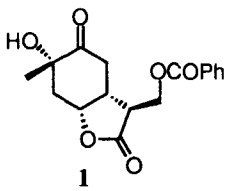
Abstract: The first total syntheses of (+)-paeonilactone C and (+)-paeoniflorigenone , representative monoterpenes of Paeoniae Radix, have been accomplished starting with *R*-(–)-carvone *via* lipase catalyzed highly diastereoselective enzymatic acetylation. The latter synthesis also means the first total synthesis of (+)-paeonisuffral, a new monoterpene recerntly isolated from Moutan Cortex.

As part of our project[1] directed toward the synthesis of pharmacologically active principles of Paeoniae Radix, the root of *Paeonia albiflora* Pallas, we are interested in the synthesis of paeonilactone C (**1**)[2] and paeoniflorigenone (**2**),[3] which have not been synthesized in their naturally occuring forms,[4] because these monoterpenes possess unique structural features and biological activities. For instance, it was reported that paeonilactone C (**1**) suppresses both directly and indirectly stimulated muscle twitching of sciatic nerve-sartorius muscle preparations from flogs[2] while paeoniflorigenone (**2**) produces a blocking effect[3] on the neuromuscular junction in pherenic nerve-diaphragm preparations from mice. We now report the first enantiospecific syntheses of (+)-paeonilactone C (**1**) and (+)-paeoniflorigenone (**2**) from *R*-(–)-carvone (**3**) on the basis of the strategy devised in our previous synthesis[1b] of structurally related other paeonilactones and paeonimetabolines.



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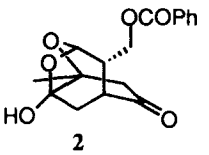
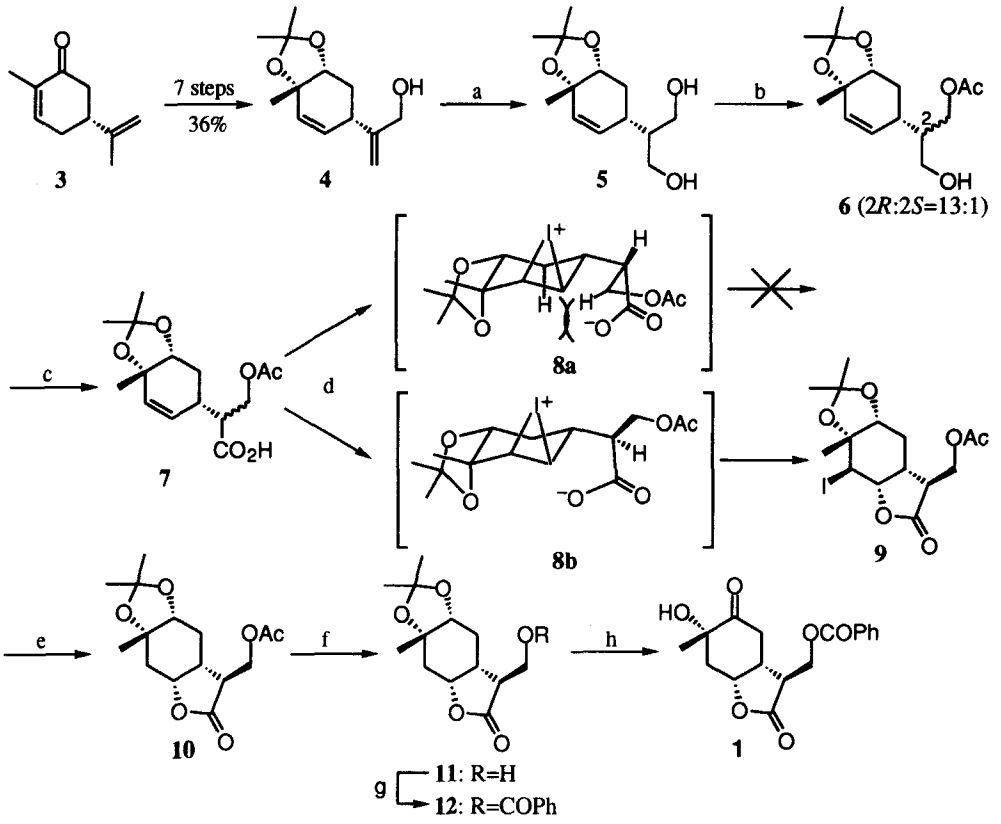


2

R-(–)-Carvone (**3**) was first converted to the allyl alcohol **4** according to the previously developed method.[1b] Upon rhodium(I) catalyzed hydroboration[5, 6] using catecholborane followed by oxidation, **4** afforded the diol **5**,[7] mp 84-85 °C (hexane-benzene), $[\alpha]_D^{26}$ –103° (*c* 0.94, $CHCl_3$), regioselectively in 77% yield. Treatment of **5** with vinyl acetate in the presence of lipase PS brought about highly diastereoselective enzymatic acetylation[8] to give the monoacetate **6** as a 13:1[9] epimeric mixture in 87% yield. Without separation, Swern oxidation of **6** followed by $NaClO_2$ oxidation[10] gave the carboxylic acid **7** which was directly subjected to iodolactonization. Interestingly, in this particular case, the iodolactone **9**, $[\alpha]_D^{28}$ +21.8° (*c* 1.08, $CHCl_3$), was obtained as the sole product in 88% overall yield from **6**. This result suggests that the major isomer

smoothly underwent cyclization *via* **8b** whereas the minor isomer cyclized *via* **8a** with extreme difficulty by steric reasons. Reductive dehalogenation of **9** with tri-*n*-butyltin hydride afforded the lactone **10**,[11] $[\alpha]_D^{30}$ +27.1° (*c* 1.09, $CHCl_3$), in 93% yield.

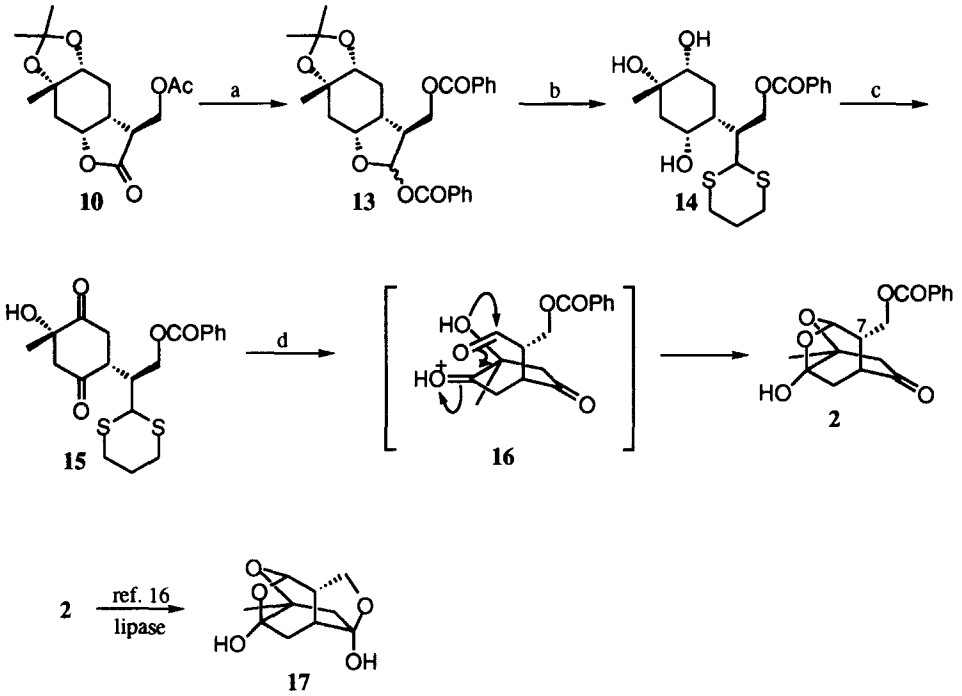
From this lactone **10**, paeonilactone C (**1**) was first synthesized. Thus, treatment of **10** with lipase PS in aqueous acetone under buffered conditions allowed chemoselective enzymatic hydrolysis[8] to give the alcohol **11**, mp 104-105 °C (hexane-Et_2O), $[\alpha]_D^{27}$ +33.0° (*c* 1.17, $CHCl_3$), in 83% yield. After benzoylation of **11**, the benzoate **12**, mp 87-88 °C (hexane), $[\alpha]_D^{26}$ +38.1° (*c* 1.30, $CHCl_3$), was successively subjected to acid hydrolysis, Swern oxidation, and cleavage of the methyl thiomethyl ether[12] concomitantly formed during oxidation to furnish (+)-paeonilactone C (**1**) in 42% overall yield from **11**. The synthetic substance, mp 130-132 °C (MeOH), $[\alpha]_D^{27}$ +27.4° (*c* 1.30, MeOH), was identical with natural paeonilactone C,[2] mp 132-133 °C (MeOH), $[\alpha]_D^{27}$ +23.5° (*c* 0.31, MeOH),[13] by spectroscopic (^1H and ^{13}C NMR) comparison. As a result, our accomplishment of the synthesis of (+)-paeonilactone C (**1**) from *R*-(−)-carvone (**3**) made the absolute structure[14] of natural paeonilactone C unambiguous.



Scheme 1. (a) catecholborane, $Rh(PPh_3)_3Cl$ (2.5 mol%), THF and then 30% H_2O_2, 10% NaOH; (b) vinyl acetate, lipase PS, *t*-butyl methyl ether; (c) (i) $(COCl)_2$, DMSO, CH_2Cl_2, −60 °C and then Et_3N, (ii) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH-H_2O; (d) I_2, sat. $NaHCO_3$-CH_2Cl_2 (1:1); (e) *n*-Bu_3SnH, AIBN, benzene, reflux; (f) lipase PS, acetone-0.1 M phosphate buffer (1:10), 35 °C; (g) PhCOCl, Et_3N, DMAP (catalyst), CH_2Cl_2; (h) (i) AcOH-H_2O-THF (1:1:1), reflux, (ii) $(COCl)_2$, DMSO, CH_2Cl_2, −60 °C and then Et_3N, (iii) Ph_3CBF_4, CH_2Cl_2.

The synthesis of paeoniflorigenone (**2**) was also achieved from the lactone **10** as follows. Reduction of **10** with DIBAH followed by benzoylation gave the dibenzoate **13** as a 2:3 epimeric mixture[9] in 86% yield. Exposure of **13** to $TiCl_4$ catalyzed thioacetalization conditions[15] using 1,3-propanedithiol afforded the triol **14**,[16] $[\alpha]_D^{26}$ –5.6° (*c* 1.47, $CHCl_3$), in 77% yield. After oxidation of **14**, treatment of the resulting diketone **15** with methyliodide in boiling aqueous acetonitrile[17] caused dethioacetalization followed by intramolecular acetalization as in **16** to produce (+)-paeoniflorigenone (**2**) directly in 49% overall yield from **14**. The synthetic substance, $[\alpha]_D^{29}$ +3.7° (*c* 0.90, MeOH), exhibited spectral properties (^1H and ^{13}C NMR, IR, MS) in accord with those reported for natural paeoniflorigenone,[3b] $[\alpha]_D^{25}$ +4.3° (*c* 0.69, MeOH). It is important to note that no epimerization took place at the C-7 position under these conditions. The corresponding 7-epi-paeoniflorigenone was not detected at all.

Since natural paeoniflorigenone has already been converted to (+)-paeonisuffral (**17**), a new monoterpene isolated from Moutan Cortex, the root of *Paeonia suffruticosa* Andrews (Botanpi in Japanese), by Yoshikawa and co-workers in their structure determination study,[18] the synthesis of **2** means the first total synthesis of (+)-paeonisuffral (**17**) as well.



Scheme 2. (a) (i) DIBAH, CH_2Cl_2, –78 °C, (ii) PhCOCl, Et_3N, DMAP (catalyst), CH_2Cl_2; (b) 1,3-propanedithiol, $TiCl_4$, CH_2Cl_2, 0 °C; (c) SO_3·pyridine, Et_3N, DMSO, CH_2Cl_2; (d) CH_3I, H_2O-CH_3CN (1:1), reflux.

Acknowledgment. We are grateful to professor Toshimitsu Hayashi, Toyama Medical and Pharmaceutical University, for providing ^1H and ^{13}C NMR spectra of natural paeonilactone C.

References and Notes

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6. Hydroboration of **4** proceeded very sluggishly with poor regioselectivity under uncatalyzed conditions.
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9. Determined by ^{1}H NMR (500 MHz) spectroscopic analysis.
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11. Spectral data of **10**: IR (neat) 1745 cm^{-1}; ^{1}H NMR (300MHz,$CDCl_3$) δ: 1.33 (s, 3H), 1.36 (s, 3H), 1.45 (s, 3H), 1.88-2.14 (m, 4H), 2.07 (s, 3H), 2.49 (m, 1H), 2.90 (dt, *J*=6.2 and 4.1 Hz, 1H), 4.00 (t, *J*=4.4 Hz, 1H), 4.34 (dd, *J*=4.1 and 11.4 Hz, 1H), 4.41 (dd, *J*=4.1 and 11.4 Hz, 1H), 4.61 (dt, *J*=5.5 and 7.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 20.6 (q), 26.2 (q), 26.4 (q), 27.5 (q), 28.1 (t), 33.5 (d), 37.3 (t), 46.8 (d), 62.9 (t), 75.9 (d), 77.3 (s), 77.7 (d), 108.2 (s), 170.3 (s), 175.6 (s).
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13. The reported specific rotation, $[\alpha]_D^{27}$ –31.6° (MeOH),[2] should be corrected to this value which was kindly informed by Prof. Hayashi.
14. The absolute structure of natural paeonilactone C has been tentatively determined[2] based on its CD spectrum showing the negative Cotton effect.
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16. Spectral data of **14**: IR (neat) 3436, 1719 cm^{-1}; ^{1}H NMR (300MHz,$CDCl_3$) δ: 1.25 (s, 3H), 1.54-2.10 (m, 6H), 2.17 (dd, *J*=3.3 and 15.0 Hz, 1H), 2.37 (m, 1H), 2.82-2.98 (m, 4H), 3.20 (s, 1H), 3.41-3.45 (m, 1H), 3.83 (d, J=7.7 Hz, 1H), 4.13-4.15 (m, 1H), 4.54 (dd, *J*=6.2 and 11.7 Hz, 1H), 4.56 (d, *J*=3.3 Hz, 1H), 4.66 (dd, *J*=3.3 and 11.7 Hz, 1H), 7.45 (t, *J*=7.3 Hz, 2H), 7.57 (t, *J*=7.3 Hz, 1H), 8.08 (d, *J*=7.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 26.3 (t), 26.5 (q), 26.6 (t), 29.0 (t), 39.7 (d), 41.7 (t), 45.2 (d), 51.1 (d), 63.8 (t), 68.8 (d), 73.0 (s), 74.5 (d), 77.3 (t), 128.4 (d), 129.9 (d), 130.3 (s), 133.0 (d), 166.6 (s).
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