

EFFICIENT SYNTHESIS OF PAEONILACTONE-A AND -B FROM (-)-CARVONE

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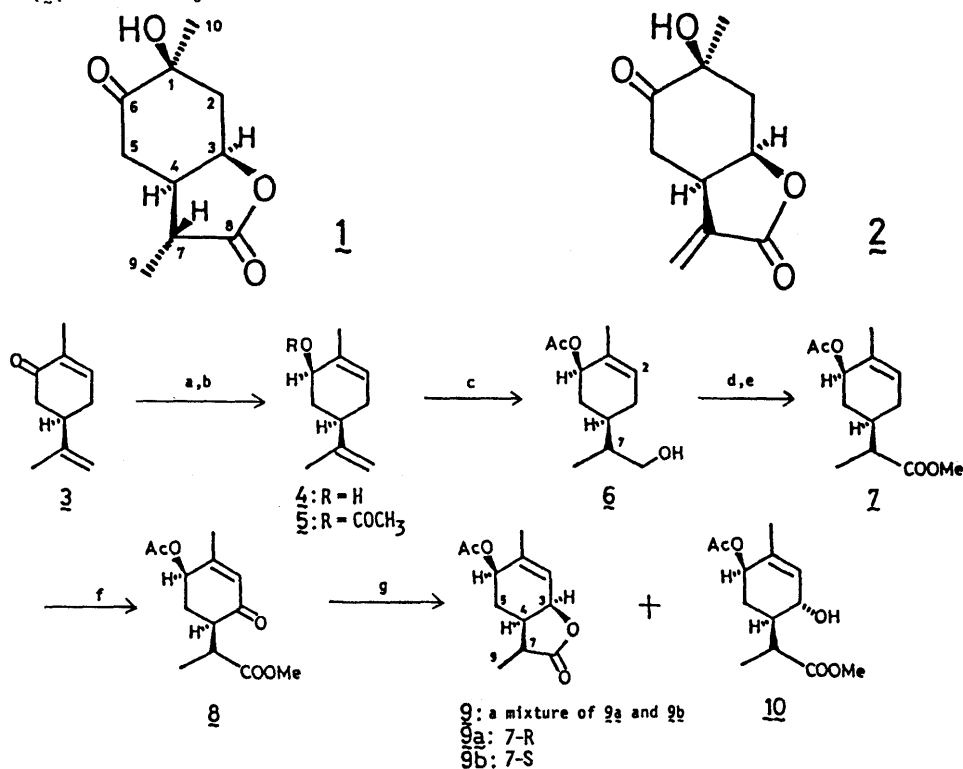
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The first synthesis of paeonilactone-A and -B, minor components of Paeony root, has been completed efficiently starting from (-)-carvone.

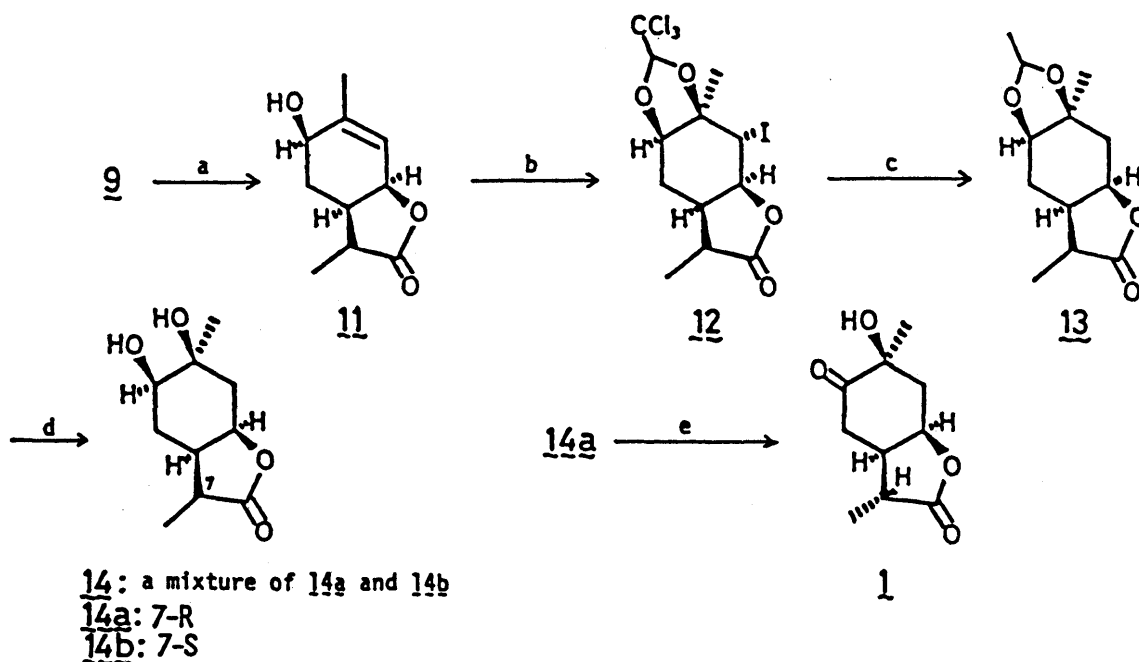
KEYWORDS paeonilactone-A; paeonilactone-B; monoterpene; *Paeonia albiflora* var. *trichocarpa*; (-)-carvone; synthesis

Paeonilactone-A (1) and -B (2)¹⁾ were recently isolated as minor components from Paeony root (roots of *Paeonia albiflora* PALLAS var. *trichocarpa* BUNGE), together with paeoniflorigenone which has a blocking effect on the neuromuscular junction in phrenic nerve diaphragm preparation of mice.²⁾ Also, 1 and 2 were reported to be identical with metabolite A1 and A2 respectively, which are metabolites of albiflorin³⁾ by intestinal bacteria.⁴⁾ Because they are available only in small quantities from natural sources, their synthesis is desired in order to study their biological activities. Now we describe the first synthesis of paeonilactone-A (1) and -B (2), starting from readily available (-)-carvone.

(-)-cis-Carveol (4),⁵⁾ obtained from (-)-carvone (3) by LiAlH_4 reduction, was acetylated with acetic anhydride in pyridine to afford an acetate (5). Hydroboration of the acetate (5) with 9-BBN⁶⁾ (9-borabicyclo[3,3,1]nonane) in hexane followed by treatment with hydrogen peroxide gave a mixture of 7-epimeric alcohols (6) (approximate ratio, 1:1), which without separation was oxidized with Jones reagent and then methylated with diazomethane to give a methyl ester (7, 7-epimeric mixture). Oxidation of 7 with t-butyl chromate⁷⁾ gave an α,β -unsaturated ketone (8)⁸⁾ in 70% yield.



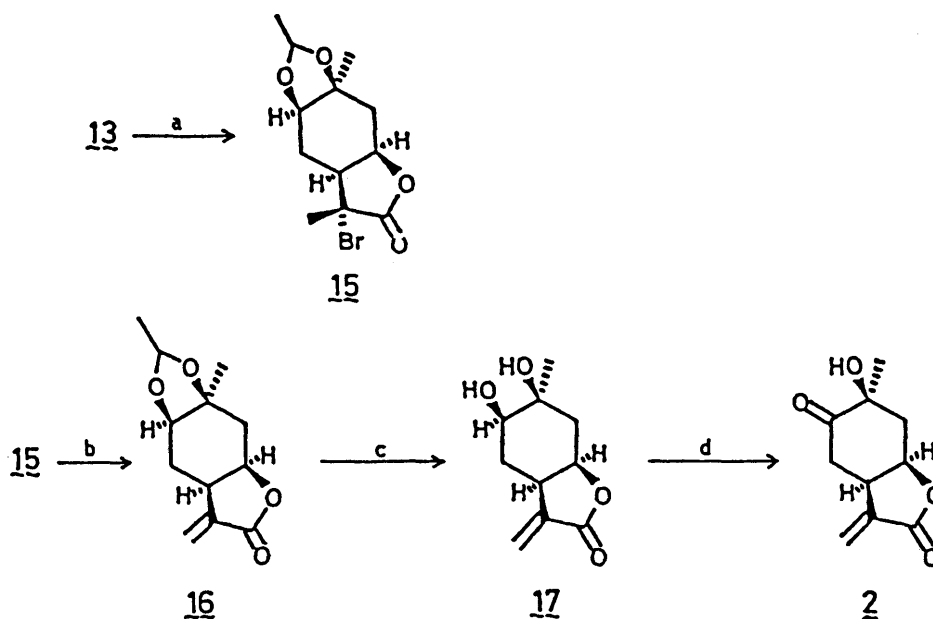
a LiAlH_4 /ether/-78°C, 96%; b $\text{Ac}_2\text{O/Py.}$, 86%; c 9-BBN/hexane/ H_2O_2 /NaOH, 60%;
d $\text{CrO}_3/\text{H}_2\text{SO}_4$ /acetone, 75%; e CH_2N_2 /ether, 89%; f $(\text{t-BuO})_2\text{CrO}_2/\text{AcOH-Ac}_2\text{O/CCl}_4$ /reflux, 73%; g $\text{NaBH}(\text{OCH}_3)_3$ /ether/reflux, 9: 53%, 10: 14%



a $\text{K}_2\text{CO}_3/\text{aq. MeOH}$, 89%; b $\text{CCl}_3\text{CHO}/\text{CH}_3\text{CN}/\text{Amberlyst-15}/\text{I}_2/\text{rt}$, 20h, 50%;
 c $[\text{CH}_3(\text{CH}_2)_3]_3\text{SnH}/\text{AIBN}/\text{benzene}/\text{reflux}$, 94%; d $\text{H}_2\text{SO}_4/\text{aq. MeOH}/\text{reflux}$, 96%; e $\text{DMSO}/\text{oxalyl chloride}/(\text{Et})_3\text{N}/-50^\circ\text{C}$, 60%

Reduction of 8 with $\text{NaBH}(\text{OCH}_3)_3$ gave a lactone (9)⁹ (a mixture of 9a and 9b in a ratio 2:1)(53%) together with an alcohol (10)¹⁰ (a mixture of 7-epimers in a ratio 1:2)(14%). The stereochemistry of 9a was determined on the basis of the coupling constants of each proton and the result of NOE experiments. Irradiation at the 9- H_3 and 4-H enhanced the signal intensity of the 7- and 4-protons and the 3-, 5-, and 9-protons, respectively. These observations surely supported the relative configuration of the lactone as depicted in 9a. The lactone (9) was then hydrolyzed with K_2CO_3 in aqueous MeOH to afford an allyl alcohol (11) in 89% yield.

The stereo-controlled introduction of an oxygen function at the C-1 position of 11 was achieved in 50% yield by hemiacetal formation with chloral catalyzed with Amberlist 15¹¹ in CH_3CN , followed by iodocyclization to afford a cyclic iodo trichloroacetal (12) as the sole product. Reduction of 12 with tributyltin hydride in



a $\text{LDA}/\text{CBr}_4/-70^\circ\text{C}$, 52%; b $\text{DBU}/\text{benzene}$, 56%; c $\text{H}_2\text{SO}_4/\text{aq. MeOH}/\text{reflux}$, 62%; d $\text{DMSO}/\text{oxalyl chloride}/(\text{Et})_3\text{N}/-50^\circ\text{C}$, 47%

the presence of azobisisobutyronitrile¹²⁾ gave an acetal (13) in 94% yield. The acetal (13) was hydrolyzed with sulfuric acid in aqueous MeOH to give a mixture of diols 14a and 14b, which was separated by repeated preparative TLC on Merck Kieselgel 60 PF₂₅₄ with AcOEt-benzene (1:1) to give the desired compound (14a)¹³⁾ and its epimer (14b)¹⁴⁾ in a ratio of 2:1.

The diol (14a) was oxidized with dimethyl sulfoxide and oxalyl chloride¹⁵⁾ to give a keto-alcohol (1), mp 124–125°C, $[\alpha]_D^{20}$ -23.1° (MeOH), in 60% yield, which was identified as paeonilactone-A (1) by comparing its spectra (IR and ¹H-NMR) and chromatographic behavior (TLC) with those of an authentic sample of natural paeonilactone-A (1).

Next, the synthesis of paeonilactone-B (2) was examined. Intermediate (13) (a mixture of 7-epimers in a ratio 3:1) was treated with LDA (lithium diisopropylamide) followed by tetrabromomethane¹⁶⁾ to afford a bromo lactone (15) (52%). The bromo lactone was treated with DBU (diazabicycloundecene) in benzene to give an α,β -unsaturated lactone (16) in 56% yield, which was hydrolyzed with sulfuric acid in aqueous MeOH to give a diol (17).¹⁷⁾

Oxidation of 17 with dimethyl sulfoxide and oxalyl chloride¹⁵⁾ gave a keto-alcohol (2), mp 92–93°C, $[\alpha]_D^{20}$ +27.9° (MeOH), which was identical in all respects (IR, ¹H-NMR, and TLC) with an authentic sample of natural paeonilactone-B (2).

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- 6) When diborane was used instead of 9-BBN, no regioselective introduction of the hydroxyl group was admitted and 2,8-dihydroxy products were obtained as a mixture of stereoisomers in 90% yield.
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- 8) 8 (a mixture of 7-epimers in a ratio 1:1): colorless oil, IR $\nu_{\max}^{\text{CHCl}_3}$ cm^{-1} : 1725 (ester) and 1660 (α,β -unsaturated ketone); MS m/z : 254 (M^+), 223, 212, 168, 162, 135, 134, 108, and 98; ¹H-NMR (CDCl_3) δ : 1.10 (3H, d, $J=7.0$ Hz, 9-H₃), 1.92 (3H, t, $J=1.0$ Hz, 10-H₃), 2.14 (3H, s, OAc), 2.92 (1H, dt, $J=14.5, 5.0$ Hz, 4-H), 3.09 (1H, m, 7-H), 3.71 (3H, s, COOCH₃), 5.77 (1H, ddq, $J=11.0, 5.0, 1.0$ Hz, 6-H), and 5.94 (1H, br s, 2-H); 1.21 (3H, d, $J=7.0$ Hz, 9-H₃), 1.93 (3H, t, $J=1.0$ Hz, 10-H₃), 2.14 (3H, s, OAc), 2.71 (1H, dt, $J=13.5, 4.5$ Hz, 4-H), 3.09 (1H, m, 7-H), 3.66 (3H, s, COOCH₃), 5.69 (1H, ddq, $J=11.0, 5.0, 1.0$ Hz, 6-H), and 5.94 (1H, br s, 2-H).
- 9) 9 (a mixture of 9a and 9b) (approximate ratio, 2:1): colorless oil, IR $\nu_{\max}^{\text{CHCl}_3}$ cm^{-1} : 1770 (γ lactone) and 1730 (ester); MS m/z : 182 (M^+ - 42), 165, 151, 149, 135, and 122; ¹H-NMR (CDCl_3) δ , 9a: 1.27 (3H, d, $J=7.0$ Hz, 9-H₃), 1.76 (3H, q, $J=1.5$ Hz, 10-H₃), 2.08 (3H, s, OAc), 2.75 (1H, dq, $J=8.0, 7.0$ Hz, 7-H), 4.88 (1H, doublet quintet, $J=7.0, 1.5$ Hz, 3-H), 5.28 (1H, t, $J=5.0$ Hz, 6-H), and 5.71 (1H, quintet, $J=1.5$ Hz, 2-H); 9b: 1.19 (3H, d, $J=7.0$ Hz, 9-H₃), 1.78 (3H, q, $J=1.5$ Hz, 10-H₃), 2.11 (3H, s, OAc), 2.91 (1H, quintet, $J=7.0$ Hz, 7-H), 4.61 (1H, br t, $J=5.0$ Hz, 3-H), 5.37 (1H, dd, $J=11.0, 5.0$ Hz, 6-H), and 5.78 (1H, doublet quintet, $J=4.5, 1.5$ Hz, 2-H). Assignments of ¹H-NMR signals were accomplished by means of the ¹H-¹H COSY method.
- 10) 10 (a mixture of 7-epimers in a ratio 35:65): oil, IR $\nu_{\max}^{\text{CHCl}_3}$ cm^{-1} : 3500 (OH) and 1735 (ester); MS m/z : 256 (M^+), 239, 214, 165, 136, and 109; ¹H-NMR (CDCl_3) δ : 1.13 (35%), 1.14 (65%) (3H, d, $J=7.0$ Hz, 9-H₃), 1.71 (35%), 1.66 (65%) (3H, br s, 10-H₃), 2.08 (35%), 2.07 (65%) (3H, s, OAc), 2.76 (35%) (1H, qd, $J=7.0, 5.5$ Hz, 7-H), 2.83 (65%) (1H, qd, $J=7.0, 5.0$ Hz, 7-H), 3.68 (35%), 3.70 (65%) (3H, s, COOCH₃), 3.92 (35%) (1H, br s, 3-H), 4.05 (65%) (1H, br d, $J=8.0$ Hz, 3-H), 5.15 (35%) (1H, t, $J=3.5$ Hz, 6-H), 5.44 (65%) (1H, br t, $J=6.5$ Hz, 6-H), 5.65 (35%) (1H, br s, 2-H), and 5.56 (65%) (1H, q, $J=1.0$ Hz, 2-H).
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- 13) 14a: mp 144–145°C, $[\alpha]_D^{20}$ +16.5° (CHCl_3), IR $\nu_{\max}^{\text{CHCl}_3}$ cm^{-1} : 3500 (OH) and 1760 (lactone); MS m/z : 200 (M^+), 182, 164, 154, 139, and 127; ¹H-NMR (CDCl_3) δ : 1.26 (3H, d, $J=7.0$ Hz, 9-H₃), 1.28 (3H, s, 10-H₃), 2.88 (1H, quintet, $J=7.0$ Hz, 7-H), 3.57 (1H, t, $J=5.0$ Hz, 6-H), and 4.58 (1H, dt, $J=8.0, 6.0$ Hz, 3-H).
- 14) 14b: mp 104–105°C, $[\alpha]_D^{20}$ +15.5° (CHCl_3), IR $\nu_{\max}^{\text{CHCl}_3}$ cm^{-1} : 3550 (OH) and 1765 (lactone); MS m/z : 200 (M^+), 182, 164, 154, and 127; ¹H-NMR (CDCl_3) δ : 1.21 (3H, d, $J=7.0$ Hz, 9-H₃), 1.31 (3H, s, 10-H₃), 1.35 (1H, dt, $J=13.5, 12.0$ Hz, 5 β -H), 1.81 (1H, ddd, $J=13.5, 5.5, 4.0$ Hz, 5 α -H), 2.50 (1H, m, 4-H), 2.85 (1H, quintet, $J=7.0$ Hz, 7-H), 3.41 (1H, dd, $J=12.0, 4.0$ Hz, 6-H), and 4.40 (1H, td, $J=4.0, 2.0$ Hz, 3-H).
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- 17) 17: mp 134–135°C, $[\alpha]_D^{20}$ +31.6° (CHCl_3), IR $\nu_{\max}^{\text{CHCl}_3}$ cm^{-1} : 3550 (OH) and 1760 (lactone); MS m/z : 198 (M^+), 180, 152, 138, and 112; ¹H-NMR (CDCl_3) δ : 1.31 (3H, s, 10-H₃), 3.09 (1H, m, 4-H), 3.49 (1H, br s, 6-H), 4.49 (1H, dt, $J=5.5, 4.5$ Hz, 3-H), 5.64 (1H, d, $J=1.5$ Hz, C=CH₂), and 6.19 (1H, d, $J=1.5$ Hz, C=CH₂).

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