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

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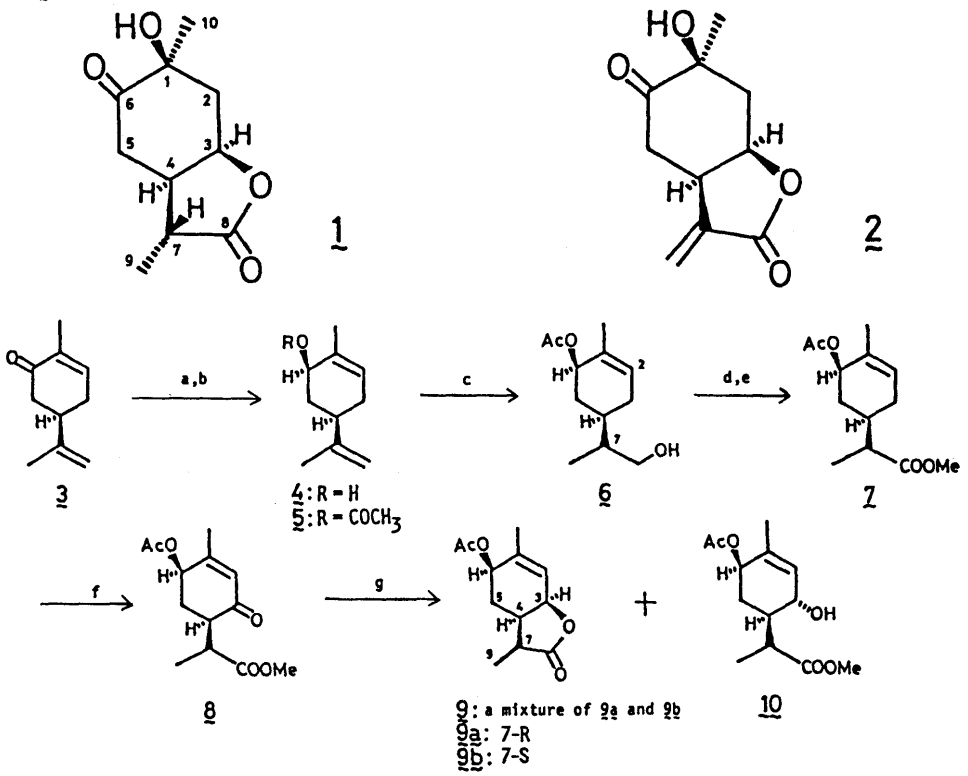
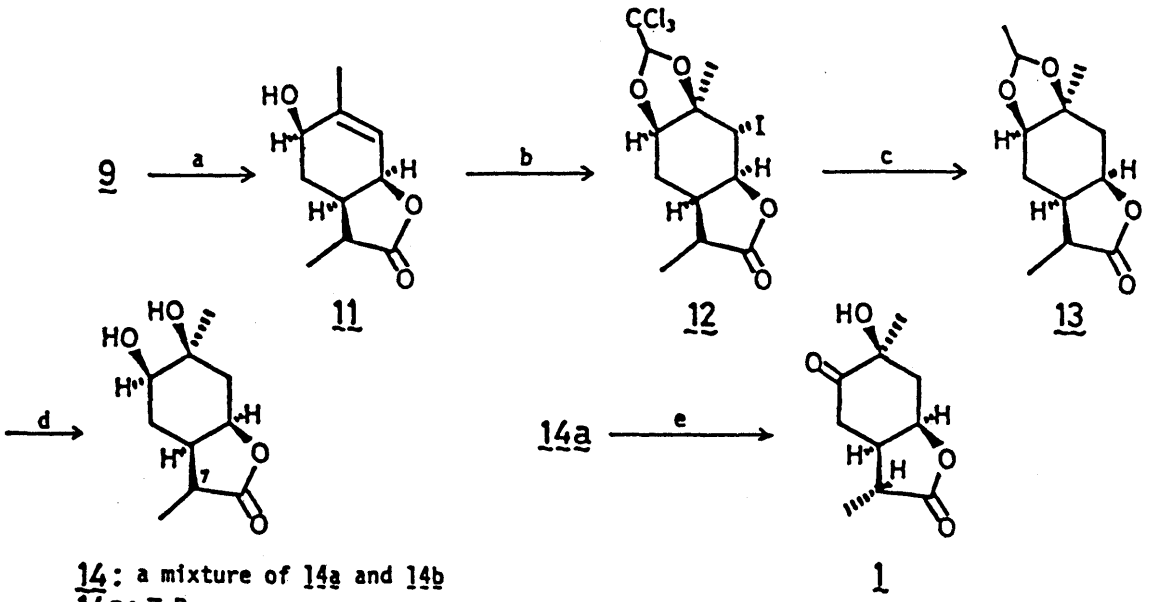
The first synthesis of paeonilactone-A and -B, minor components of Paeony root, has been completed efficiently starting from (-)-carvone.

KEYWORDS paeonilactone-A; paeonilactone-B; monoterpenoid; 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 albiflorin[3] 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-BBN[6] (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 chromate[7] gave an α,β-unsaturated ketone (8)[8] in 70% yield.



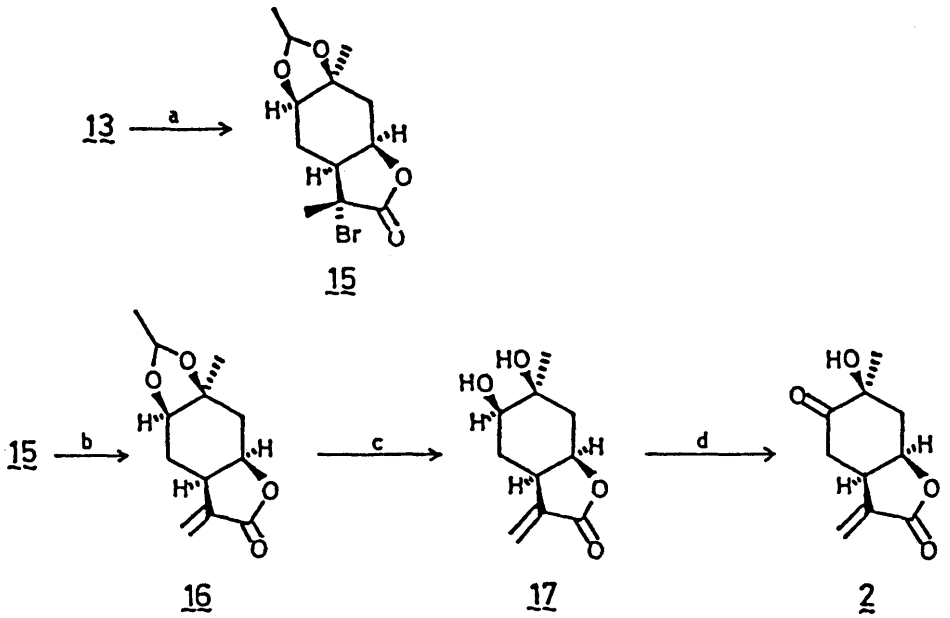


14: a mixture of 14a and 14b
14a: 7-R
14b: 7-S

a K_2CO_3/aq.MeOH, 89%; b CCl_3CHO/CH_3CN/Amberlyst-15/I_2/rt, 20h, 50%; c $[CH_3(CH_2)_3]_3SnH$/AIBN/benzene/reflux, 94%; d H_2SO_4/aq.MeOH/reflux, 96%; e DMSO/oxalyl chloride/$(Et)_3N$/-50°C, 60%

Reduction of 8 with $NaBH(OCH_3)_3$ 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 15[11] 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 LDA/CBr_4/-70°C, 52%; b DBU/benzene, 56%; c H_2SO_4/aq. MeOH/reflux, 62%; d DMSO/oxalyl chloride/$(Et)_3N$/-50°C, 47%

the presence of azobisisobutyronitrile[12] 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 PF_{254} 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 chloride[15] to give a keto-alcohol (1), mp 124 - 125°C, $[\alpha]_D$ -23.1° (MeOH), in 60% yield, which was identified as paeonilactone-A (1) by comparing its spectra (IR and ^{1}H-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 tetrabromomethane[16] 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 chloride[15] gave a keto-alcohol (2), mp 92 - 93°C, $[\alpha]_D$ +27.9° (MeOH), which was identical in all respects (IR, ^{1}H-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 $\nu_{max}^{CHCl_3}$ cm^{-1}: 1725 (ester) and 1660 (α,β-unsaturated ketone); MS m/z: 254 (M^+), 223, 212, 168, 162, 135, 134, 108, and 98; ^{1}H-NMR ($CDCl_3$) δ: 1.10 (3H, d, J = 7.0 Hz, 9-H_3), 1.92 (3H, t, J = 1.0 Hz, 10-H_3), 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, $COOCH_3$), 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-H_3), 1.93 (3H, t, J = 1.0 Hz, 10-H_3), 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, $COOCH_3$), 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 $\nu_{max}^{CHCl_3}$ cm^{-1}: 1770 (γ lactone) and 1730 (ester); MS m/z: 182 (M^+ - 42), 165, 151, 149, 135, and 122; ^{1}H-NMR ($CDCl_3$) δ, 9a: 1.27 (3H, d, J = 7.0 Hz, 9-H_3), 1.76 (3H, q, J = 1.5 Hz, 10-H_3), 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-H_3), 1.78 (3H, q, J = 1.5 Hz, 10-H_3), 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 ^{1}H-NMR signals were accomplished by means of the ^{1}H-^{1}H COSY method.
10) 10 (a mixture of 7-epimers in a ratio 35:65): oil, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500 (OH) and 1735 (ester); MS m/z: 256 (M^+), 239, 214, 165, 136, and 109; ^{1}H-NMR ($CDCl_3$) δ: 1.13 (35%), 1.14 (65%)(3H, d, J = 7.0 Hz, 9-H_3), 1.71 (35%), 1.66 (65%)(3H, br s, 10-H_3), 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, $COOCH_3$), 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, $[\alpha]_D$ +16.5° ($CHCl_3$), IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500 (OH) and 1760 (lactone); MS m/z: 200 (M^+), 182, 164, 154, 139, and 127; ^{1}H-NMR ($CDCl_3$) δ: 1.26 (3H, d, J = 7.0 Hz, 9-H_3), 1.28 (3H, s, 10-H_3), 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, $[\alpha]_D$ +15.5° ($CHCl_3$), IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3550 (OH) and 1765 (lactone); MS m/z: 200 (M^+), 182, 164, 154, and 127. ^{1}H-NMR ($CDCl_3$) δ: 1.21 (3H, d, J = 7.0 Hz, 9-H_3), 1.31 (3H, s, 10-H_3), 1.35 (1H, dt, J = 13.5, 12.0 Hz, 5β-H), 1.81 (1H, ddd, J = 13.5, 5.5, 4.0 Hz, 5α-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, $[\alpha]_D$ +31.6° ($CHCl_3$), IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3550 (OH) and 1760 (lactone); MS m/z: 198 (M^+), 180, 152, 138, and 112; ^{1}H-NMR ($CDCl_3$) δ: 1.31 (3H, s, 10-H_3), 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 = CH_2), and 6.19 (1H, d, J = 1.5 Hz, C = CH_2).

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