ALTERNATIVE SYNTHESIS OF A PYRIDONE ALKALOID, CERPEGIN

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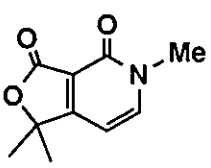
Abstract - A new pyridone alkaloid, cerpegin was synthesized starting from (-)-carvone.

A new pyridone alkaloid, cerpegin was isolated from *Ceropegia juncea*, and its structure was elucidated as 1,1,5-trimethylfuro[3,4-*c*]pyridine-3,4(1*H*,5*H*)-dione (**1**).[1] *Ceropegia juncea* Roxb. is reported to be the source of "Soma," a plant drug of the Ayurvedic system of medicine with a wide variety of uses.[2] Although the total alkaloidal fraction of the 90% ethanol extracts of this plant exhibited promising tranquilizing, anti-inflammatory, anti-ulcer, hypotensive, antipyretic, analgesic, mast-cell stabilizing, hepato-protective and local anesthetic activities in experimental animals,[1] it is not clear whether **1** itself has those activities or not. Because of the novelty of its structure and our continuing interest in the synthesis of heterocyclic compounds possessing fused furanone moieties,[3] we undertook the synthesis of **1**. Four total syntheses of **1** have appeared so far. The first total synthesis of **1** was reported by Godard *et al.*[4] They selected 2-methoxynicotinic acid diisopropylamide as the starting material. Kelly and Walsh[5] synthesized **1** in five steps starting from 2-chloronicotinic acid. The third one reported by us[6] used the Michael reaction of phenylthioacetonitrile to 2-methoxycarbonyl-4-methyl-2-penten-4-olide as the key reaction. Recently, Hong and Comins synthesized **1** starting from 2-methoxypyridine.[7]



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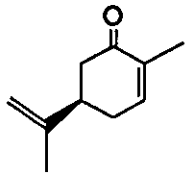
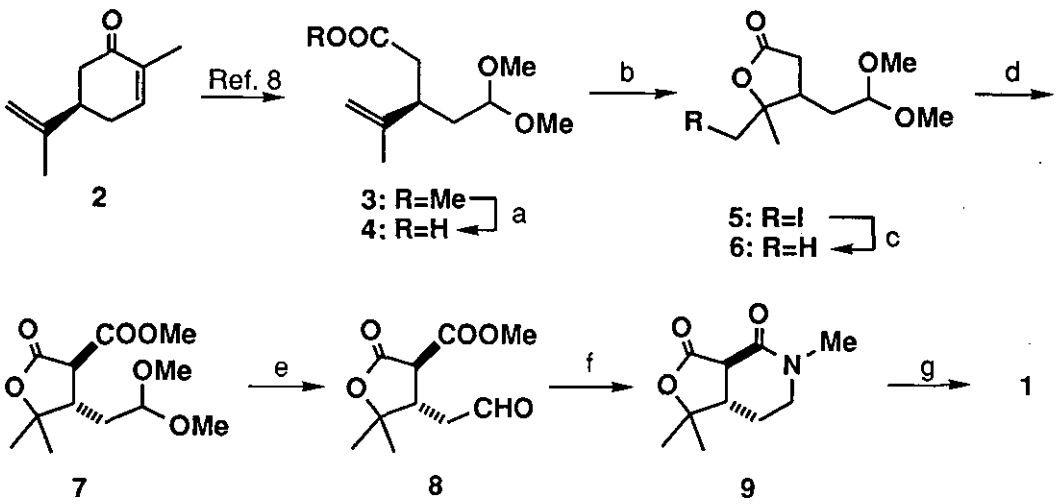


(-)-Carvone (2)

The starting material of our alternative synthesis of **1** was methyl 3-(2,2-dimethoxyethyl)-4-methyl-4-pentenoate (**3**), which was prepared from (-)-carvone (**2**) by Mori and Fukamatsu.[8] In order to get 3-substituted 4-methyl-4-pentanolide (**6**), **3** was hydrolyzed first with lithium hydroxide in THF-H_2O to give **4** in 80% yield,[9] which was iodolactonized with I_2-KI-$NaHCO_3$ in CH_2Cl_2-H_2O to form **5** in 78%

yield.[8] Reduction of **5** with tri-*n*-butyltin hydride in the presence of azobisisobutyronitrile (AIBN) in benzene at refluxing temperature furnished **6** in quantitative yield.[10] Introduction of a methoxycarbonyl group at 2-position of **6** was performed by its treatment with lithium diisopropylamide (LDA) and methyl chloroformate in quantitative yield.[11] Hydrolysis of the dimethyl acetal group of **7** with AcOH-H_2O gave the aldehyde **8** in 52% yield.[8] Reductive amination of **8** with methylamine and sodium cyanoborohydride furnished directly the lactam **9** in 63% yield.[12] Finally, heating of **9** with 10% Pd/C in decalin gave cerpegin (**1**) in 81% yield.[13] Thus, cerpegin (**1**) was synthesized from the known compound **3**, which was prepared in good yield from inexpensive (-)-carvone (**2**), in 7 steps and 17% overall yield. The IR, ^{1}H-NMR, and MS spectral data of synthesized **1** are identical to those of the reported one.[1]



Scheme 1. *Reagents and conditions*: a) LiOH in THF-H_2O (80%) b) I_2-KI, $NaHCO_3$ in CH_2Cl_2-H_2O (78%) c) (n-Bu)$_3$SnH, AIBN in benzene d) LDA, ClCOOMe in THF (quant. from **5**) e) AcOH-H_2O (52%) f) $MeNH_2$ in MeOH, $MeNH_2$-HCl, $NaBH_3CN$ in MeOH (63%) g) 10% Pd/C in decalin (81%)

EXPERIMENTAL SECTION

Melting points were determined using a Yanagimoto micro-melting point apparatus, model MP-S3, and are uncorrected. IR spectra were measured with a Hitachi 260-30 infrared spectrophotometer. ^{1}H-NMR spectra were recorded on a JEOL JNM-GSX270 (270 MHz) spectrometer using tetramethylsilane as the internal standard. High-resolution MS spectra (HRMS) were measured with a JEOL JMS-HX100 instrument at 70 eV.

3-(2,2-Dimethoxyethyl)-4-methyl-4-pentenoic acid (4)

Lithium hydroxide monohydrate (9.01 g, 214.7 mmol) was added to a solution of **3**[8] (18.49 g, 85.5 mmol) in THF (1960 mL) and H_2O (245 mL) and the mixture was stirred at rt for 16 h . The mixture was

concentrated under reduced pressure and the residue was acidified with 5% HCl. After salting out, the solution was extracted with CH_2Cl_2 and the combined extract was washed with brine and then dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure gave an oil, which was purified over SiO_2 column chromatography (acetone-*n*-hexane=2:3) to afford **4** (13.79 g, 80%) as a pale yellow oil . IR (neat): 3160, 1730, 1710, 1645 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.70 (3H, s, CCH_3), 1.61-1.82 (2H, m, $C\underline{H}_2CH(OCH_3)_2$), 2.40-2.46 (2H, m, $C\underline{H}_2COOH$), 2.74 (1H, quint. *J*=7.3 Hz, $CH_2C\underline{H}CH_2$), 3.30 and 3.31 (each 3H, s, 2 X OCH_3), 4.34 (1H, dd, *J*=7.0, 4.0 Hz, $C\underline{H}(OCH_3)_2$), 4.82 (2H, d, *J*=1.0 Hz, C=CH), 7.40 (1H, br s, COOH).

3-(2,2-Dimethoxyethyl)-5-iodo-4-methyl-4-pentanolide (5)

A solution of $NaHCO_3$ (15.00 g, 178.6 mmol) in H_2O (250 mL) was added to a solution of **4** (14.50 g, 71.7 mmol) in CH_2Cl_2 (65 mL). A solution of I_2 (13.50 g, 53.2 mmol) and KI (27.00 g, 162.7 mmol) in H_2O (160 mL) was added to the above reaction mixture with stirring under ice-cooling and the whole was stirred at rt for 1 h . The reaction mixture was extracted with ether and the combined organic layer was washed with 5% aqueous $Na_2S_2O_3$ solution and brine, respectively. The organic layer was dried over anhydrous Na_2SO_4 and removal of the solvent under reduced pressure gave a brown oil, which was purified by SiO_2 column chromatography (acetone-*n*-hexane=1:3) to give **5** (18.37 g, 78%) as a brown oil. IR (neat): 1780 cm^{-1}. ^{1}H-NMR showed that this oil was a mixture of stereoisomers. This compound was used for the next reaction immediately.

3-(2,2-Dimethoxyethyl)-2-methoxycarbonyl-4-methyl-4-pentanolide (7)

To a solution of **5** (18.60 g, 56.7 mmol) in dry benzene (300 mL) were added tri-*n*-butyltin hydride (19.80 g, 68.0 mmol) and AIBN (0.90 g, 3.1 mmol) and the whole was refluxed for 30 min. After the reaction mixture was cooled to rt, a solution of KF (23.0 g, 395.9 mmol) in H_2O (230 mL) was added to the mixture and the whole was stirred at rt for 30 min . The mixture was extracted with ether and the organic layer was washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure gave an oil which was purified by SiO_2 column chromatography (acetone:*n*-hexane=2:3) to afford **6** (14.56 g) as a pale yellow oil. To a solution of diisopropylamine (12.0 ml, 85.9 mmol) in dry THF (290 mL) was added *n*-BuLi (1.6 M *n*-hexane solution, 54.0 mL, 86.4 mmol) under N_2 atmosphere and stirring at -78 °C. After 5 min, a solution of **6** (11.263 g) in dry THF (45 mL) was added and the mixture was stirred at rt for 30 min. Methyl chloroformate (4.8 mL, 61.5 mmol) was added and the mixture was stirred at rt for 2 h. A saturated solution of NH_4Cl (17 mL), H_2O (145 mL), and CH_2Cl_2 (170 mL) were added successively to the reaction mixture and the whole was extracted with CH_2Cl_2. The organic layer was washed with H_2O and brine, respectively and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure gave an oil which was purified by SiO_2 column chromatography (acetone:*n*-hexane=1:1) to afford **7** (12.269 g, quantitative yield from **5**) as a pale yellow oil. IR (neat): 1770, 1735 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.26 and 1.51 (each 3H, s, 2 X CH_3), 1.65-1.80 (2H, m, $C\underline{H}_2CH(OCH_3)_2$), 2.86 (1H, ddd, *J*=12.0, 10.0, 4.5 Hz, $CH_2C\underline{H}CH$), 3.24 and 3.31 (each 3H, s, 2 X OCH_3), 3.47 (1H, d, *J*=12.0 Hz, $C\underline{H}COOCH_3$), 3.84 (3H, s, $COOCH_3$), 4.33 (1H, dd, *J*=7.0, 4.0 Hz, $C\underline{H}(OCH_3)_2$).

3-Formylmethyl-2-methoxycarbonyl-4-methyl-4-pentanolide (8)

A mixture of **7** (25.0 g, 96.0 mmol), acetic acid (256 mL) and H_2O (128 mL) was stirred at 60 °C for 2 h. The mixture was poured into H_2O and the whole was extracted with CH_2Cl_2. The organic extract was washed with H_2O, saturated $NaHCO_3$ solution and brine, respectively and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure gave a residue which was crystallized from $CHCl_3$-*n*-hexane to furnish **8** (10.70 g, 52%) as colorless needles. mp 138-140 °C. IR (nujol): 1755, 1725 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.29 and 1.54 (each 3H, s, 2 X CH_3), 2.615 (1H, ddd, *J*=17.5, 8.5, 1.5 Hz, C$\underline{H}_2$CHO), 2.725 (1H, ddd, *J*=17.5, 5.0, 1.5 Hz, C$\underline{H}_2$CHO), 3.21 (1H, ddd, *J*=12.0, 8.0, 5.5 Hz, C$\underline{H}$CH$_2$CHO), 3.425 (1H, d, *J*=12.0 Hz, C$\underline{H}$COOCH$_3$), 3.83 (3H, s, $COOCH_3$), 9.75 (1H, t, *J*=1.5 Hz, CHO). *Anal.* Calcd for $C_{10}H_{14}O_5$•1/10 H_2O: C, 55.59; H, 6.64. Found: C, 55.57; H, 6.42.

Tetrahydro-1,1,5-trimethylfuro[3,4-*c*]pyridine-3,4(1*H*,5*H*)-dione (9)

Dry methylamine hydrochloride (0.63 g, 9.3 mmol) was added to a 40% methylamine methanol solution (1.5 mL, 18.7 mmol). $NaBH_3CN$ (0.36 g, 5.7 mmol) was added to the above mixture. To the obtained mixture was added a solution of **8** (2.00 g, 9.3 mmol) in dry methanol (40 mL) and the whole was stirred at rt for 4 h. 18% HCl aqueous solution was added to the reaction mixture under ice-cooling (pH 2). Methanol was evaporated under reduced pressure and the mixture was made basic with 28% NH_4OH solution (pH 10). After salting out, the mixture was extracted with $CHCl_3$ and the organic layer was washed with brine. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure to give **9** (1.167 g, 63%) as colorless powder. IR (neat): 1758, 1660 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.41 and 1.42 (each 3H, s, 2 X CH_3), 1.75-2.20 (2H, m, CHC$\underline{H}_2$CH$_2$N), 2.53 (1H, ddd, *J*=12.0, 7.0, 4.5 Hz, CH$_2$C$\underline{H}$CH), 3.00 (3H, s, NCH_3), 3.25-3.42 (2H, m, CH$_2$C$\underline{H}_2$N), 3.71 (1H, dd, *J*=7.0, 1.4 Hz, COCHCO). HRMS (*m/z*): Calcd for $C_{10}H_{15}NO_3$ (M^+): 197.1052. Found: 197.1049.

Cerpegin (1)

To a solution of **9** (180 mg, 0.9 mmol) in decalin (20 mL) was added 10% Pd/C (180 mg) and the whole was refluxed for 10 h. After removal of the catalyst by filtration, the filtrate was concentrated under reduced pressure to give a residue which was crystallized from $CHCl_3$-MeOH to afford **1** (143 mg, 81%) as colorless prisms. mp 268-272 °C (lit., 268-270 °C,[1b] 268-271 °C,[5] 267-271 °C[6]). IR (nujol): 1750, 1660, 1600, 1550 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.59 (6H, s, 2 X CH_3), 3.64 (3H, s, NCH_3), 6.23 (1H, d, *J*=7.0 Hz, CCH), 7.68 (1H, d, *J*=7.0 Hz, CHN). HRMS (*m/z*): Calcd for $C_{10}H_{11}NO_3$ (M^+): 193.0739. Found: 193.0711.

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