The Synthesis of (±)-Monomorine I Starting with the Palladium-Catalyzed Carbonylative 1,4-Acylation of an Organozinc Chloride

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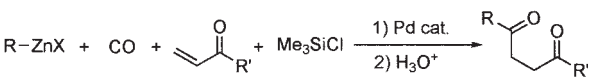
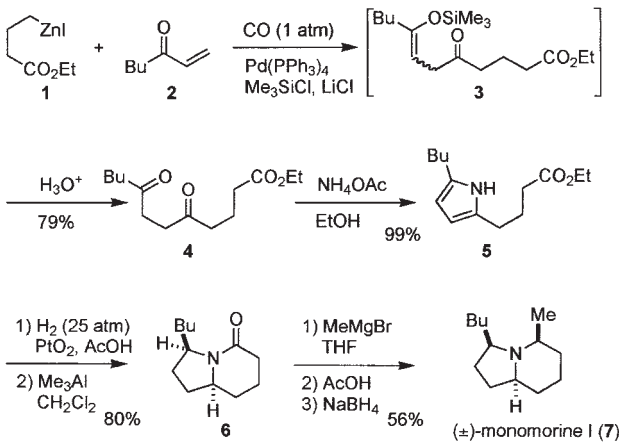
The synthesis of the indolizidine alkaloid (±)-monomorine I has successfully been achieved by a new route starting with a one-pot four-component connecting reaction based on a palladium-catalyzed carbonylative 1,4-addition of an organozinc halide to a α,β-enone in an atmosphere of carbon monoxide.

Many methods for the conjugate addition of acyl anions[1] or masked acyl anions[2] to α,β-enones or related compounds have been developed[3] because their products, 1,4-dicarbonyl compounds, are useful synthetic precursors of substituted cyclopentenones[4] and heterocyclic compounds.[5] Recently, we have developed a one-pot method for the synthesis of 1,4-diketones by the palladium-catalyzed carbonylative conjugate addition of an organozinc halide to α,β-enones in the presence of carbon monoxide (Scheme 1),[6] and applied it to the preparation of various five-membered heterocyclic compounds having a furan, thiophene or pyrrole skeleton. Monomorine I, a trail pheromone of the Pharaoh ant *Monomorium pharaonis* L.,[7] is a representative indolizidine alkaloid[8] with interesting biological activities.[9] Here, we report a new synthesis of (±)-monomorine I starting with the one-pot palladium-catalyzed 1,4-acylation.

As shown in Scheme 2, ethyl 5,8-dioxododecanoate **4** was first prepared by carbonylative addition: 3-(ethoxycarbonyl)-prop-1-ylzinc iodide **1** was treated with butyl vinyl ketone **2**[10] using $Pd(PPh_3)_4$ (5 mol%), chlorotrimethylsilane, and lithium chloride in THF at 30 °C under CO (1 atm) to afford the silyl enolate **3**. The successive acidic work-up resulted in the formation of 1,4-diketone, ethyl 5,8-dioxododecanoate **4**, in 79% yield. The amino-cyclization of **4** with ammonium acetate, a Paal–Knorr reaction,[11] produced the 2,5-disubstituted pyrrole **5** in 99% yield. The catalytic hydrogenation of the pyrrole ring of **5** with PtO_2 was followed by a cyclization using trimethyl-



Scheme 1.



Scheme 2.

aluminum[12] to afford the indolizidinone **6** in 80% yield, which has been used in the syntheses of dialkylated indolizidine alkaloid, such as (3*S*,5*S*,8a*R*)-3-butyl-5-(4-penten-1-yl)indolizidine from the venom of the New Zealand ant *Monomorium smithii*.[12b,13] Finally, a methyl group was introduced by a Grignard reaction/$NaBH_4$ reduction sequence on an amide moiety[14] of **6** to give the desired (±)-monomorine I (**7**) as a single isomer in 56% yield.

Thus, the representative indolizidine alkaloid (±)-monomorine I (**7**) has been synthesized by a simple route starting from a four-component connecting reaction based on a palladium-catalyzed 1,4-acylation in an atmosphere of carbon monoxide.

Experimental

3-(Ethoxycarbonyl)prop-1-ylzinc Iodide (1). A flask containing zinc dust (1.95 g, 30 mmol, activated by washing with dilute HCl solution[15]) was purged with Ar gas, and THF (10 mL) and TMSCl (0.05 mL) were added. After the mixture was stirred for 15 min, ethyl 4-iodobutyrate (4.83 g, 20 mmol) was added dropwise. The mixture was warmed at 40 °C for 4 h and then cooled to room temperature. The resulting clear solution of **1** (11.5 mL, 1.74 M) can be stored under Ar gas for a few months.

Ethyl 5,8-Dioxododecanoate (4). To a stirred mixture of LiCl (339 mg, 8.0 mmol) and $Pd(PPh_3)_4$ (92 mg, 0.08 mmol) in THF (15 mL) was added TMSCl (0.71 mL, 5.6 mmol) and butyl vinyl ketone **2**[10] (280 mg, 2.5 mmol) under CO gas (1 atm). After 10 min, the above-mentioned solution of **1** (0.92 mL, 1.6 mmol) was added dropwise to the mixture over a period of 30 min with vigorous stirring at 30 °C. After 20 min, the reaction was quenched with a 2 M HCl solution (4 mL), diluted with water (20 mL), and extracted with Et_2O (20 mL × 2). The combined organic layers were washed with water (20 mL) and brine (20 mL) and then dried over $MgSO_4$. The extract was concentrated, and the residue was subjected to column chromatography on silica gel eluted with 4:1 hexane/AcOEt to afford **4** (324 mg, 79%) as a colorless oil, bp 118 °C/0.2 mmHg; IR (neat) 1736, 1713 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.90 (t, $J = 7.3$ Hz, 3H), 1.25 (t, $J = 7.3$ Hz, 3H), 1.29 (m, 4H), 1.90 (quint, $J = 7.6$ Hz, 2H), 2.32 (t, $J = 7.3$ Hz, 2H), 2.45 (t, $J = 7.3$ Hz, 2H), 2.55 (t, $J = 7.3$ Hz, 2H), 2.68 (s, 2H), 4.13 (q, $J = 7.3$ Hz, 2H); ^{13}C NMR (68 MHz) δ 13.8 (q), 14.2 (q), 18.81 (t), 18.85 (t), 25.9 (t), 33.2 (t), 36.0 (t), 41.5 (t), 41.6 (t), 42.6 (t), 60.3 (t), 173.1 (s), 208.7 (s), 209.6 (s); EI-MS *m/z* (rel. int.) 256 (M^+, 3.6), 211 (81), 199 (12), 196 (41), 171 (47), 168 (25), 143 (100), 141 (100), 125 (99), 115

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(84), 113 (15), 85 (94), 57 (99). Anal. Calcd for $C_{11}H_{12}O_2$: C, 65.60; H, 9.44%. Found: C, 65.36; H, 9.18%.

2-(3-Ethoxycarbonylpropyl)-5-butylpyrrole (5). To a stirred solution of **4** (90 mg, 0.35 mmol) in EtOH (3 mL) was added NH_4OAc (270 mg, 3.5 mmol) at room temperature. After 24 h, the mixture was diluted with H_2O (10 mL), extracted with CH_2Cl_2 (10 mL × 3), and dried over Na_2SO_4. Purification by preparative TLC (5:1 hexane/AcOEt) gave **5** (R_f 0.38, 82 mg, 99%). IR (neat) 3386, 1736 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.92 (t, $J = 7.3$ Hz, 3H), 1.26 (t, $J = 7.3$ Hz, 3H), 1.38 (m, 2H), 1.59 (quint, $J = 7.3$ Hz, 2H), 1.92 (quint, $J = 7.3$ Hz, 2H), 2.35 (t, $J = 7.3$ Hz, 2H), 2.44–2.65 (m, 4H), 4.14 (q, $J = 7.3$ Hz, 2H), 5.78 (t, $J = 2.8$ Hz, 2H), 7.78 (br. s, 1H); ^{13}C NMR (68 MHz) δ 13.9 (q), 14.2 (q), 22.4 (t), 25.2 (t), 26.9 (t), 27.5 (t), 31.8 (t), 33.6 (t), 60.3 (t), 104.6 (d), 105.1 (d), 129.6 (s), 131.7 (s), 173.7 (s); EI-MS m/z (rel. int.) 237 (M^+, 32), 194 (65), 192 (22), 148 (41), 136 (100), 93 (22); HR-EI-MS calcd for $C_{14}H_{23}NO_2$ 237.1729, found 237.1726.

3-Butylhexahydro-5(1*H*)-indolizidinone (6). Into an autoclave tube was added AcOH (3 mL), **5** (142 mg, 0.60 mmol), and PtO_2 (27 mg, 0.12 mmol). The mixture was stirred under H_2 gas (25 kg/cm^2) for 2 h at room temperature then poured into a 6 M NaOH solution (15 mL) containing ice (20 g), and extracted with CH_2Cl_2 (10 mL × 3). The combined organic layers were dried over $MgSO_4$, and filtered through a Celite pad. The filtrate was concentrated, and the residue was dissolved in CH_2Cl_2 (10 mL). To the solution was added Me_3Al (1.0 M hexane solution, 0.78 mL, 0.78 mmol), and then the solution was refluxed with stirring for 14 h under nitrogen. The reaction was quenched with 2 M HCl (2 mL), extracted with CH_2Cl_2 (10 mL × 3), and dried over Na_2SO_4. Purification by preparative TLC (2:3 hexane/AcOEt) afforded **6** (R_f 0.17, 94 mg, 80%) as a colorless oil, IR (neat) 1644 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.89 (t, $J = 7.3$ Hz, 3H), 1.19–1.34 (m, 6H), 1.47–2.05 (m, 8H), 2.29–2.35 (m, 2H), 3.37 (tdd, $J = 11.2$, 4.9, 3.0 Hz, 1H), 3.92–4.00 (m, 1H); ^{13}C NMR (68 MHz) δ 14.1 (q), 21.2 (t), 22.7 (t), 27.5 (t), 28.8 (t), 29.3 (t), 31.0 (t), 31.4 (t), 32.4 (t), 57.2 (d), 59.9 (d), 169.4 (s); EI-MS m/z (rel. int.) 195 (M^+, 8), 166 (7), 138 (100), 110 (14); HR-EI-MS calcd for $C_{12}H_{21}NO$ 195.1623, found 195.1611. These spectral data were essentially identical with the reported data.[13]

Monomorine I (7). To a stirred solution of **6** (19.5 mg, 0.10 mmol) in THF (2 mL) was added MeMgBr (0.93 M THF solution, 0.32 mL, 0.30 mmol) dropwise at room temperature under argon, followed by refluxing with stirring. After 5 h, the reaction was quenched with AcOH (0.20 mL) at 0 °C, and MeOH (2 mL) and $NaBH_4$ (38 mg, 1.0 mmol) were then added with stirring. After 2 h, the mixture was diluted with H_2O (20 mL), made alkaline with saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2 (10 mL × 3). The combined organic layers were dried over Na_2SO_4. Purification by a preparative TLC (5:1 hexane/Et_2O) afforded **7** (R_f 0.23, 11.0 mg, 56%) as a colorless oil; ^1H NMR (270 MHz, $CDCl_3$) δ 0.89 (t, $J = 6.9$ Hz, 3H), 1.14 (d, $J = 6.6$ Hz, 3H), 1.18–1.88 (m, 16H), 2.03–2.15 (m, 1H), 2.16–2.27 (m, 1H), 2.43–2.52 (m, 1H); ^{13}C NMR (68 MHz) δ 14.1 (q), 22.6 (t), 22.8 (t), 24.8 (t), 29.2 (t), 29.4 (t), 29.7 (t), 30.2 (t), 30.7 (t), 35.6 (t), 39.5 (t), 60.4 (d), 63.1 (d), 67.3 (d). These spectral data were essentially identical with the reported data.[8c]

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