Atmospheric Nitrogen Fixation. Short-Step Synthesis of Monomorine I

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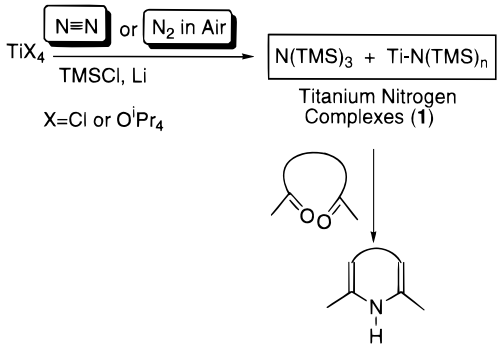
Molecular nitrogen fixation is a very fascinating process,[1] and we succeeded in molecular nitrogen fixation[2] and in atmospheric nitrogen fixation[2f] using a TiX_4−Li−TMSCl system (Scheme 1). Recently, we achieved the synthesis of nitrogen heterocycles and a formal total synthesis of (±)-lycopodine using this nitrogen fixation method.[2e,f] Here, we report a short total synthesis of indolizidine alkaloids, monomorine I and indolizidine 195B, from dry air.[2f]

Since isolation of monomorine I (**2**) from *Monomorium pharaonis* L. by Ritter,[3] many total syntheses of racemic and optically active monomorine I have been reported.[4] Our retrosynthetic analysis is shown in Scheme 2. To synthesize monomorine I (**2**) from indolizine derivative **3** using our atmospheric nitrogen fixation method, triketone **4** is required, and the hydrogenation of **3** would afford monomorine I (**2**) as a main product because hydrogen on the catalyst approaches from the backside of the methyl group to the pyrrole ring of **5**, which would be obtained as a product on the initial stage of hydrogenation of **3**.

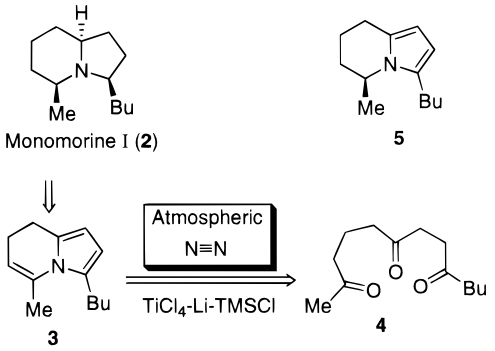
Ozonolysis of **6**[5] followed by treatment with Me_2S gave triketone **4** in 85% yield. A THF solution of triketone **4** and titanium nitrogen complexes **1** (2 equiv), prepared from $TiCl_4$, Li, and TMSCl under *dry air*,[2f] was refluxed for 24 h (Scheme 3). After the usual workup, the desired indolizine derivative **3** was obtained in 22% yield.[6] As expected, hydrogenation of **3** by PtO_2 (1 atm) gave **5** in good yield as a sole product. The use of Rh on alumina (20 atm) as a hydrogenation catalyst afforded monomorine I (**2**) as a main product in 32% yield along with indolizidines **7** and **8**[7] in 4% and 16% yields, respectively.

The ^{1}H NMR[8] and ^{13}C NMR[9] spectra of **2** were in complete agreement with those reported in the literature. From the spectral data of indolizidine **7**, it was clear that this is indolizidine 195B.[10] Thus, a short-step synthesis of monomorine I and indolizidine 195B was achieved using titanium nitrogen complexes **1** prepared from *atmospheric nitrogen*.

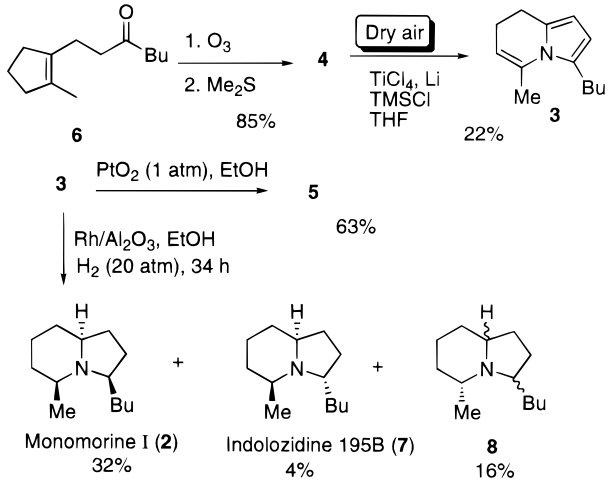
Scheme 1



Scheme 2. Retrosynthesis of Monomorine I



Scheme 3



Experimental Section

All manipulation for nitrogen fixation was performed under dry air passed through a tube of $CaCl_2$. Solvents and TMSCl were distilled under an argon atmosphere from sodium benzophenone (THF) and CaH_2 (TMSCl). All other reagents and solvents were purified when necessary using standard procedures.

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(6) By using molecular nitrogen instead of dry air for this reaction, the desired indolizine derivative **3** was obtained in 30% yield.

(7) The stereochemistry of compound **8** was not determined.

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Tetradecane-2,6,9-trione (4). A solution of **6** (2.6 g, 13.4 mmol) in MeOH (100 mL) was cooled to −78 °C, and O_3 was bubbled in the solution. To this solution was added Me_2S (4.9 mL, 67 mmol) at the same temperature. After the solution was stirred at room temperature for 1 h, the solvent was evaporated and the residue was purified by column chromatography on silica gel (hexane/ethyl acetate, 2/1) to give colorless crystals of **4** (2.57 g, 85%): mp 72.0−73.0 °C (from hexanes−Et_2O); IR (Nujol) ν 1712, 1702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.90 (t, J = 7.8 Hz, 3 H), 1.27−1.34 (m, 2 H), 1.52−1.69 (m, 2 H), 1.81−1.87 (m, 2 H), 2.13 (s, 3 H), 2.44 (t, J = 7.2 Hz, 2 H), 2.46 (t, J = 7.2 Hz, 2 H), 2.50 (t, J = 7.8 Hz, 2 H), 2.63 (dd, J = 1.9, 6.8 Hz, 1 H), 2.66 (dd, J = 6.0, 15.4 Hz, 2 H), 2.69 (dd, J = 1.9, 6.8 Hz, 1 H); EI-MS m/z 226 (M^+), 208, 184, 166, 151, 141, 123, 113, 108, 85, 71, 57, 43 (bp); El-HRMS m/z for $C_{13}H_{22}O_3$, calcd 226.1569, found 226.1570. Anal. Calcd for $C_{33}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 69.00; H, 9.85.

1-Butyl-7-methyl-4,5-dihydrohydroindolizine (3). A suspension of Li (77.4 mg, 10 mmol), $TiCl_4$ (0.11 mL, 1.0 mmol), and TMSCl (1.26 mL, 10 mmol) in THF (7.5 mL) was stirred under dry air for 24 h. To the solution of **4** (113.2 mg, 0.5 mmol) and CsF (377.6 mg, 2.5 mmol) in THF (1 mL) was added a THF solution of nitrogen fixation complexes **2** at 0 °C, and the solution was refluxed for 24 h. Saturated aqueous $NaHCO_3$ solution was added at 0 °C, and the whole solution was stirred until the solution became colorless. The aqueous layer was extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography on silica gel (hexane containing 3% of NEt_3) to give a colorless oil of **3** (21 mg, 22%): IR (neat) ν 1655, 1516 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.94 (t, J = 7.2 Hz, 3 H), 1.38−1.43 (m, 2 H), 1.58−1.65 (m, 2 H), 2.09−2.13 (m, 2 H), 2.24 (d, J = 1.3 Hz, 3 H), 2.67 (t, J = 7.3 Hz, 2 H), 2.71 (t, J = 7.9 Hz, 2 H), 5.15(t, J = 4.5 Hz, 1 H), 5.79 (d, J = 3.2 Hz, 1 H), 5.83 (d, J = 3.2 Hz, 1 H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 14.45, 21.58, 22.03, 23.20, 23.60, 29.62, 31.99, 103.88, 106.70, 113.30, 131.07, 132.31, 135.02; EI-MS m/z 189 (M^+), 174, 146, 131, 106, 77, 44; El-HRMS m/z for $C_{13}H_{19}N$, calcd 189.1518, found 189.1499.

1-Butyl-7-methyl-4,5,6,7-tetrahydroindolizine (**5**). A solution of **3** (16 mg, 0.085 mmol) in EtOH (1 mL) was stirred at room temperature under H_2 (1 atm) in the presence of PtO_2 (1.6 mg) for 1 h. The catalyst was filtered off, and the filtrtate was concentrated. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate containing 1% of NEt_3, 15/1) to give a colorless oil of **5** (10.2 mg, 63%): IR (neat) ν 1506 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.96 (t, J = 7.4 Hz, 3 H), 1.32 (d, J = 6.5 Hz, 3 H), 1.41−1.48 (m, 2 H), 1.61−1.71 (m, 2 H), 1.75−1.82 (m, 2 H), 1.85−1.94 (m, 1 H), 1.97−2.04 (m, 1 H), 2.52 (t, J = 7.8 Hz, 2 H), 2.70−2.73 (m, 1 H), 2.83−2.87 (m, 1 H), 4.25−4.30 (m, 1 H), 5.76 (d, J = 2.6 Hz, 1 H), 5.85 (d, J = 2.6 Hz, 1 H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ14.49, 16.68, 21.93, 23.27, 23.87, 26.17, 29.85, 30.68, 31.47, 47.30, 103.47, 104.94, 127.67, 131.55; EI-MS m/z 191 (M^+), 176, 148, 132, 118, 106, 93, 55, 41; El-HRMS m/z for $C_{13}H_{21}N$, calcd 191.1674, found 191.1660.

Synthesis of Monomorine I (2), Indolizine 195B (7), and Indolizine 8. A solution of **3** (59.8 mg, 0.316 mmol) was stirred in the presence of Rh/Al_2O_3 (59.8 mg, 0.016 mmol) in EtOH (10 mL) under H_2 (20 atm) at room temperature for 34 h. The catalyst was filtered off, and the filtrate was evaporated. The residue was purified by column chromatography on silica gel (pentane/Et_2O, 10/1, 5/1 to 2/1) to give **2** (19.6 mg, 32%), **7** (2.5 mg, 4%), and **8** (9.9 mg, 16%). **Monomorine I** (**2**): ^1H NMR (500 MHz, $CDCl_3$) δ 0.89 (t, J = 7.2 Hz, 3 H), 1.23 (d, J = 6.4 Hz, 3 H), 1.18−1.84 (m, 16 H), 2.05−2.07 (m, 1 H), 2.17−2.27 (m, 1 H), 2.43−2.49 (m, 1 H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 14.14, 22.90, 23.00, 24.91, 29.38, 29.76, 30.33, 30.93, 35.85, 39.73, 60.25, 62.89, 67.17; EI-MS m/z 195 (M^+), 194, 180, 138, 95, 70, 67, 55, 41. **Indolizine 195 B (7):** ^1H NMR (500 MHz, $CDCl_3$) δ 0.90 (t, J = 7.2 Hz, 3 H), 1.00−1.94 (m, 16 H), 1.10 (d, J = 6.4 Hz, 3 H), 2.36−2.42 (m, 1 H), 2.49−2.58 (m, 1 H), 3.26−3.31 (m, 1 H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 14.20, 20.42, 23.00, 24.71, 24.87, 26.31, 29.17, 30.01, 32.37, 34.50, 51.97, 58.78, 58.94; EI-MS m/z 195 (M^+), 194, 180, 138, 122, 95, 82, 70, 67, 55, 41. **Indolizine (8):** ^1H NMR (500 MHz, $CDCl_3$) δ 0.89 (d, J = 6.7 Hz, 3 H), 0.90 (t, J = 7.2 Hz, 3 H), 1.09−1.57 (m, 10 H), 1.65−1.80 (m, 6 H), 2.35−2.45 (m, 2 H), 3.32−3.38 (m, 1 H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 7.55, 14.11, 19.32, 23.11, 28.20, 28.81, 29.24, 31.57, 32.37, 32.44, 47.33, 55.40, 59.14; EI-MS m/z 195 (M^+), 194, 180, 138, 122, 95, 82, 70, 67, 55, 41.

Supporting Information Available: Additional experimental details for compounds prepared (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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