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Enantioselective Syntheses of (−)- and (+)-Monomorine I†

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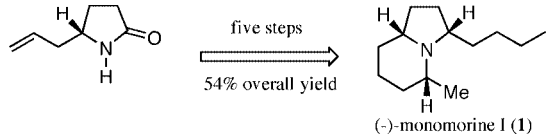

A concise enantioselective total synthesis of unnatural (−)-monomorine I has been achieved starting from lactam **2** in 54% overall yield. Natural (+)-monomorine I was also synthesized.

Introduction

(+)-Monomorine I (**1**), a trail pheromone of the widespread pharaoh's ant *Monomorium pharaonis* L.,[1] possessing a 3,5-disubstituted indolizidine skeleton, was detected in 1993, together with three other diastereomers, in amphibian skin extracts of *Melanophryniscus stelzneri*, and all are named as diastereomeric **195B**.[2] The absolute configurations of the frog **195B**s are unknown. The absolute stereochemistry of this interesting natural product was determined by the Husson's first asymmetric synthesis[4d] and was recognized as a target suitable for testing the applicability of the synthetic concept of Scheme 1.

To date several enantioselective syntheses of both natural (+)-[3] and unnatural (−)-enantiomers[4] of **1** have been reported. Among them, Blechert[5] reported the most effective seven-step enantioselective synthesis of (+)-**1** in 35% overall yield; however, the final and key step in this synthesis provided (+)-**1** and its 3-epimer in a 5:1 ratio. Here we disclose a shorter (five-step) synthesis of (−)-**1** starting from commercially available lactam **2**.[6]

Results and Discussion

Lactam **2** was converted to the corresponding Cbz-imide **3**, which was transformed into the acyclic ketone **4** using Martin's procedure.[7] Formation of the 2,5-*cis*-disubstituted pyrrolidine **5** was accomplished by the stereoselective reduction from less hindered β-face of the iminium salt, derived from **4**, with triphenylsilane.[7] Cross-metathesis reaction of **5** with methyl vinyl ketone in the presence of the Grubbs' second generation catalyst[8] afforded the unsaturated ketone **6**, which underwent a final indolizidine ring closure under catalytic hydrogenation conditions to afford (−)-monomorine I [(−)-**1**]. The spectral data (^{1}H and ^{13}C NMR) of our synthetic (−)-**1** showed no presence of the diastereomer on the 5-position and were identical with those reported.[3,4] (SCHEME 1)

This methodology can be applied to an enantiodivergent process as shown in Scheme 2. Thus, the known lactam **7**[9] was converted to ketone **9** via Cbz-imide **8**. Cyclization via an iminium ion intermediate provided the pyrrolidine **10**, which after Wacker oxidation afforded the methyl ketone **11**. By the same reaction conditions used for the synthesis of (−)-**1** from **6** described in Scheme 1, **11** was converted to (+)-**1**. The synthetic (+)-**1** is identical to (−)-**1** in all aspects except the sign of optical rotation.

† This paper is dedicated to the memory of Dr. John W. Daly, whose many contributions to the field of poison-frog alkaloids led directly to significant advances in synthetic organic chemistry and pharmacology.

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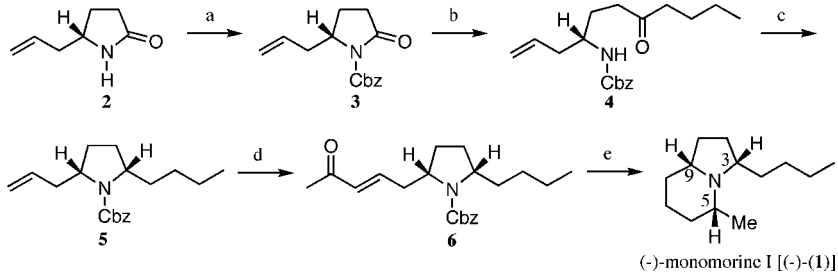
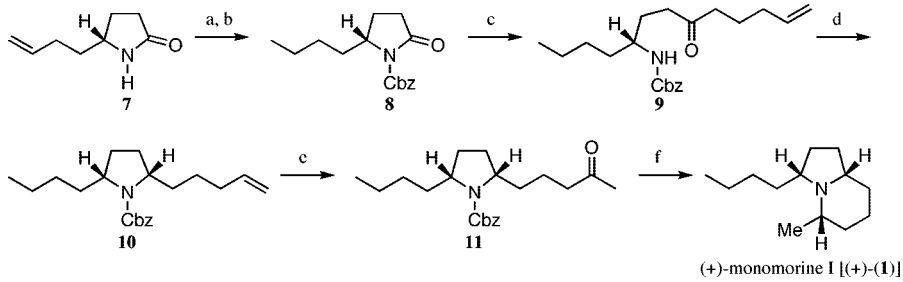
SCHEME 1. Synthesis of (−)-Monomorine I [(−)-1][a]



[a] Reagents and conditions: (a) LiHMDS, CbzCl, THF, −78 to 0 °C (93%); (b) *n*-BuMgBr, TMEDA, THF, −78 °C (73%); (c) Ph_3SiH, $BF_3 \cdot Et_2O$ CH_2Cl_2, −78 to rt (96%); (d) methyl vinyl ketone, Grubbs' second catalyst (10 mol %), CH_2Cl_2, reflux (95%); (e) 20% $Pd(OH)_2$, H_2, 1 atm, EtOH (88%).

SCHEME 2. Synthesis of (+)-1[a]



[a] Reagents and conditions: (a) 10% Pd/C, H_2, EtOAc, 1 atm; (b) LiHMDS, CbzCl, THF, −78 to 0 °C (96% in two steps); (c) 5-pentenylMgBr, TMEDA, THF, −78 °C (57%); (d) Ph_3SiH, $BF_3 \cdot Et_2O$ CH_2Cl_2, −78 °C to rt (90%); (e) $PdCl_2$, CuCl, O_2, H_2O−DMF, rt (86%); (f) 20% $Pd(OH)_2$, H_2, 1 atm, EtOH (84%).

Conclusion

A concise, five-step enantioselective total synthesis of (−)-monomorine I (**1**) in 54% overall yield was achieved starting from the commercially available lactam **2**. An enantiodivergent process is also reported for the synthesis of (+)-monomorine I [(+)-**1**].

Experimental Section

(2*S*)-(−)-2-Allyl-5-oxopyrrolidine-1-carboxylic Acid Benzyl Ester (3). To a stirring solution of **2** (322 mg, 2.58 mmol) in THF (10 mL) was added a solution of LiHMDS, prepared from HMDS (0.59 mL, 2.83 mmol) and *n*-BuLi (1.6 M in hexane, 1.77 mL, 2.83 mmol) in THF (10 mL) at 0 °C for 30 min, at −78 °C, and then the resulting mixture was stirred at the same temperature for 30 min. To the reaction mixture was added CbzCl (0.44 mL, 3.10 mmol) at −78 °C, and the reaction mixture was stirred at −78 °C for 0.5 h and allowed to warm to 0 °C over 1 h. The reaction was quenched with saturated $NaHCO_3$, and the aqueous mixture was extracted with CH_2Cl_2 (20 mL × 4). The organic extracts were combined, dried over $MgSO_4$, filtered, and evaporated to give a residue, which was chromatographed on silica gel (25 g, hexane/acetone 25:1−10:1) to give **3** (621 mg, 93%) as a colorless oil: IR (neat) 3060, 1791, 1749, 1716, 1293 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.86 (1H, m), 2.10 (1H, m), 2.34 (1H, m), 2.47 (1H, m), 2.50 (1H, m), 2.60 (1H, m), 4.27 (1H, m), 5.10 (2H, m), 5.28 (2H, ABq, J = 12.4 Hz), 5.73 (1H, m), 7.32−7.38 (3H, m), 7.40−7.44 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.5 (t), 30.8 (t), 37.4 (t), 56.7 (d), 67.3 (t), 118.3 (t), 127.4 (d), 127.7 (d), 127.9 (d), 132.2 (d), 134.7 (s), 150.6 (s), 173.3 (s); MS 259 (M^+), 91 (100); HRMS calcd for $C_{15}H_{17}O_3N$ 259.1207, found 259.1234; $[\alpha]^{26}_D$ −76.15 (*c* 1.00, $CHCl_3$).

(1*S*)-(−)-[1-(3-Oxo-*n*-heptyl)but-3-enyl]carbamic Acid Benzyl Ester (4). To a stirring solution of **3** (259 mg, 1.00 mmol) in THF (5 mL) was added a solution of *n*-BuMgBr, prepared from *n*-BuBr (0.32 mL, 3.00 mmol) and Mg (72 mg, 3.00 mmol) in THF (10 mL) at reflux, and TMEDA (0.48 mL, 3.00 mmol) in THF at −78 °C, and the reaction mixture was stirred at the same temperature for 1.5 h. The reaction was quenched with *i*-PrOH (1 mL), and diluted with Et_2O. The ethereal layer was washed with 10% HCl aqueous solution, dried over $MgSO_4$, filtered, and evaporated to give a residue, which was chromatographed on silica gel (20 g, hexane/acetone 20:1−10:1) to give **4** (231 mg, 73%) as a colorless solid (mp 90−92 °C): IR (KBr) 3306, 1704, 1686, 1546, 1262 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.89 (3H, t, J = 7.2 Hz), 1.28 (2H, sext, J = 7.2 Hz), 1.52 (2H, quint, J = 7.2 Hz), 1.63 (1H, m), 1.81 (1H, m), 2.22 (2H, m), 2.36 (2H, t-like, J = 6.4 Hz), 2.47 (2H, m), 3.68 (1H, br m), 4.60 (1H, br d, J = 8.5 Hz), 5.08 (4H, m), 5.75 (1H, m), 7.30−7.37 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8 (q), 22.2 (t), 25.8 (t), 28.2 (t), 39.2 (t), 39.9 (t), 42.5 (t), 50.5 (d), 66.3 (t), 117.7 (t), 127.7 (d), 127.7 (d), 128.2 (d), 133.7 (d), 136.3 (s), 155.8 (s), 210.5 (s); MS 317 (M^+), 276 (100); HRMS calcd for $C_{19}H_{27}O_3N$ 317.1989, found 317.1982; $[\alpha]^{26}_D$ −16.86 (*c* 0.57, $CHCl_3$).

(2*S*,5*S*)-(−)-2-Allyl-5-*n*-butylpyrrolidine-1-carboxylic Acid Benzyl Ester (5). To a stirring solution of **4** (171 mg, 0.54 mmol) in CH_2Cl_2 (5 mL) was added a solution of $BF_3 \cdot Et_2O$ (0.27 mL, 2.16 mmol) and Ph_3SiH (280 mg, 1.08 mmol) in CH_2Cl_2 (5 mL) at −78 °C, and the resulting mixture was stirred at the same temperature for 0.5 h, and then at room temperature for 2 h. The reaction was quenched with saturated $NaHCO_3$ aqueous solution at 0 °C, and the mixture was diluted with Et_2O. The organic layer was separated, and the aqueous layer was extracted with Et_2O (10 mL × 3). The organic extracts were combined, dried over $MgSO_4$, filtered, and evaporated to give a residue, which was chromatographed on silica gel (20 g, hexane/acetone 100:1−60:1) to give **5** (156 mg, 96%) as a colorless oil: IR (neat) 3079, 3029, 1698, 1405 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (3H, br), 1.27 (5H, br), 1.38−1.80 (3H, m), 1.81−1.99 (2H, m), 2.16 (1H, m), 2.59 (1H, br), 3.87 (2H, br), 4.99−5.09 (4H, m), 5.74 (1H, br), 7.24−7.40 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1 (q), 22.6 (t), 28.5 (t), 29.2 (t), 35.1 (t), 39.4 (t), 40.0 (t), 57.7 and 58.1 (each d), 59.0 (d), 66.4 (t), 116.8 (t), 127.5 (d), 127.5 (d), 128.1 (d), 134.8 (d), 136.8 (s), 155.0 (s); MS 301 (M^+), 216 (100); HRMS calcd for $C_{19}H_{27}O_2N$ 301.2040, found 301.2027; $[\alpha]^{26}_D$ −7.83 (*c* 0.64, $CHCl_3$).

(2*S*,5*S*)-(−)-2-*n*-Butyl-5-(4-oxopent-2*E*-enyl)pyrrolidine-1-carboxylic Acid Benzyl Ester (6). To a stirring solution of **5** (47 mg, 0.16 mmol) in CH_2Cl_2 (5 mL) were added methyl vinyl ketone (0.07 mL, 0.78 mmol) and Grubbs' second catalyst (14 mg, 0.016 mmol),

and the resulting mixture was refluxed for 6 h. After cooling, the solvent was evaporated, and the residue was chromatographed on silica gel (20 g, hexane/acetone 80:1−15:1) to give **6** (51 mg, 95%) as a colorless oil: IR (neat) 3048, 1697, 1405 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.86 (3H, br), 1.26 (5H, br), 1.66 (3H, br), 1.95 (2H, br), 2.16 and 2.21 (3H, br), 2.40 (1H, br), 2.59 and 2.72 (1H, br), 3.85 (1H, br), 4.02 (1H, br), 5.12 (2H, ABq, J = 11.5 Hz), 6.05 (1H, br), 6.75 (1H, br), 7.29−7.37 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1 (q), 22.6 (t), 26.7 (q), 28.5 (t), 29.3 (t), 29.5 (t), 35.5 (t), 38.2 (t), 57.6 (d), 58.6 and 59.2 (each d), 66.7 (t), 127.6 and 127.8 (each d), 128.3 (d), 133.0 (d), 136.6 (s), 144.2 (d), 144.4 (d), 155.1 (s), 198.1 (s); MS 343 (M^+), 216 (100); HRMS calcd for $C_{21}H_{29}O_3N$ 343.2148, found 343.2113; $[\alpha]^{26}_D$ −34.99 (*c* 0.90, $CHCl_3$).

(3*S*,5*R*,9*R*)-(−)-3-*n*-Butyl-5-methyloctahydroindolizine ((−)-Monomorine I, 1). To a stirring solution of **6** (125 mg, 0.36 mmol) in EtOH (10 mL) was added 20% $Pd(OH)_2$ (50 mg), and the resulting suspension was hydrogenated at 1 atm for 48 h. The catalyst was removed by filtration, and the filtrate was evaporated to give (−)-**1** (62.2 mg, 88%) as a pale pinkish oil: IR (neat) 2956, 2929, 2859, 1456, 1378, 1319, 1206, 1130 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.86 (3H, t, J = 7.1 Hz), 1.12 (3H, d, J = 6.3 Hz), 1.18−1.38 (6H, m), 1.40−1.85 (6H, br m), 2.07 (1H, br), 2.22 (1H, m), 2.47 (1H, br t-like, J = 9.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2 (q), 22.7 (q), 22.9 (t), 24.9 (t), 29.5 (t), 29.7 (t), 30.2 (t), 30.7 (t), 35.6 (t), 39.4 (t), 60.4 (d), 63.1 (d), 67.3 (d); MS 195 (M^+), 138 (100); $[\alpha]^{26}_D$ −33.14 (*c* 0.87, *n*-hexane), lit.[4b] $[\alpha]^{26}_D$ −35.6 (*c* 0.5, *n*-hexane).

(2*R*)-(−)-2-*n*-Butyl-5-oxopyrrolidine-1-carboxylic Acid Benzyl Ester (8). To a stirring solution of **7** (264 mg, 1.90 mmol) in EtOAc (15 mL) was added 10% Pd/C (50 mg), and the resulting suspension was hydrogenated under a hydrogen atmosphere at 1 atm for 45 h. The catalyst was removed by filtration, and the fitrate was evaporated to give a colorless oil, which was used directly in the next step. To a stirring solution of this oil in THF (5 mL) was added a solution of LiHMDS, prepared from HMDS (0.44 mL, 2.10 mmol) and *n*-BuLi (1.6 M in hexane, 1.31 mL, 2.10 mmol) in THF (10 mL) at 0 °C for 30 min, at −78 °C, and then the resulting mixture was stirred at the same temperature for 30 min. To the reaction mixture was added CbzCl (0.33 mL, 2.28 mmol) at −78 °C, and the reaction mixture was stirred at −78 °C for 0.5 h and allowed to warm to 0 °C over 1 h. The reaction was quenched with saturated $NaHCO_3$, and the aqueous mixture was extracted with CH_2Cl_2 (15 mL × 4). The organic extracts were combined, dried over $MgSO_4$, filtered, and evaporated to give a residue, which was chromatographed on silica gel (25 g, hexane/acetone 25:1−10:1) to give **8** (500 mg, 96%) as a colorless oil: IR (neat) 3058, 1790, 1749, 1715, 1292 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.87 (3H, t, J = 6.9 Hz), 1.19−1.37 (4H, m), 1.42−1.56 (1H, m), 1.71−1.83 (2H, m), 2.10 (1H, quint-like, J = 8.5 Hz), 2.42 (1H, ddd, J = 17.9, 9.4, 2.8 Hz), 2.60 (1H, ddd, J = 17.9, 11.2, 9.3 Hz), 4.15−4.21 (1H, m), 5.28 (2H, ABq, J = 12.4 Hz), 7.29−7.43 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.5 (q), 21.9 (t), 22.0 (t), 27.0 (t), 30.7 (t), 32.6 (t), 57.5 (d), 67.1 (t), 126.0 (d), 127.4 and 127.6 (each d), 127.8 (d), 134.7 (s), 150.6 (s), 173.2 (s); MS 275 (M^+), 91 (100); HRMS calcd for $C_{16}H_{21}O_3N$ 275.1520, found 275.1549; $[\alpha]^{26}_D$ −67.43 (*c* 0.60, $CHCl_3$).

(1*R*)-(−)-(1-*n*-Butyl-4-oxonon-8-enyl)carbamic Acid Benzyl Ester (9). To a stirring solution of **8** (350 mg, 1.27 mmol) in THF (10 mL) was added a solution of 5-pentenyl-MgBr, prepared from 5-bromo-1-pentene (0.45 mL, 3.81 mmol) and Mg (92 mg, 3.81 mmol) in THF (20 mL) at reflux, and TMEDA (0.61 mL, 3.81 mmol) in THF at −78 °C, and the reaction mixture was stirred at the same temperature for 1.5 h. The reaction was quenched with *i*-PrOH (3 mL) and diluted with Et_2O. The ethereal layer was washed with 10% HCl aqueous solution, dried over $MgSO_4$, filtered, and evaporated to give a residue, which was chromatographed on silica gel (20 g, hexane/acetone 50:1−30:1) to give **9** (250 mg, 57%) as a colorless solid (mp 75−76 °C): IR (KBr) 3316, 3038, 1707, 1687, 1540, 1253 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.88 (3H, br t-like, J = 7.2 Hz), 1.22−1.53 (6H, br m), 1.54−1.71 (3H, m), 1.80 (1H, m), 2.03 (2H, q-like, J = 8.0 Hz), 2.37 (2H, t-like, J = 6.9 Hz), 2.46 (2H, t-like, J = 6.9 Hz), 3.58 (1H, br), 4.48 (1H, br d, J = 10.5 Hz), 4.94−5.08 (4H, m), 5.75 (1H, m), 7.30−7.37 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1 (q), 22.6 (t), 22.8 (t), 28.0 (t), 29.1 (t), 33.1 (t), 35.7 (t), 39.5 (t), 42.1 (t), 51.2 (d), 66.5 (t), 115.1 (t), 127.7 (d), 127.9 (d), 128.4 (d), 136.5 (s), 137.8 (d), 156.1 (s), 210.4 (s); MS 345 (M^+), 244 (100); HRMS calcd for $C_{21}H_{31}O_3N$ 345.2302, found 345.2315; $[\alpha]^{26}_D$ −2.32 (*c* 0.60, $CHCl_3$).

(2*R*,5*S*)-(+)-2-*n*-Butyl-5-(4-pentenyl)pyrrolidine-1-carboxylic Acid Benzyl Ester (10). To a stirring solution of **9** (440 mg, 1.27 mmol) in CH_2Cl_2 (10 mL) was added a solution of $BF_3 \cdot Et_2O$ (0.65 mL, 5.10 mmol) and Ph_3SiH (664 mg, 2.55 mmol) in CH_2Cl_2 (20 mL) at −78 °C, and the resulting mixture was stirred at the same temperature for 0.5 h and then at room temperature for 2 h. The reaction was quenched with saturated $NaHCO_3$ at 0 °C, and the mixture was diluted with Et_2O. The organic layer was separated, and the aqueous layer was extracted with Et_2O (15 mL × 3). The organic extracts were combined, dried over $MgSO_4$, filtered, and evaporated to give a residue, which was chromatographed on silica gel (40 g, hexane/acetone 100:1) to give **10** (376 mg, 90%) as a colorless oil: IR (neat) 3036, 1698, 1405, 1100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (3H, br), 1.20−1.42 (8H, br m), 1.54−2.14 (8H, br m), 3.83 (2H, br), 4.92−5.12 (4H, m), 5.77 (1H, br), 7.24−7.40 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1 (q), 22.6 (t), 25.6 (t), 28.5 (t), 29.4 (t), 29.6 (t), 33.6 (t), 35.3 (t), 58.3 (d), 58.8 (d), 66.3 (t), 114.3 (t), 127.5 (d), 128.1 (d), 136.9 (s), 138.4 (d), 155.1 (s); MS 329 (M^+), 228 (100); HRMS calcd for $C_{21}H_{31}O_2N$ 329.2353, found 329.2371; $[\alpha]^{26}_D$ +3.53 (*c* 1.69, $CHCl_3$).

(2*R*,5*S*)-(+)-2-*n*-Butyl-5-(4-oxopentyl)pyrrolidine-1-carboxylic Acid Benzyl Ester (11). To a stirring solution of **10** (98 mg, 0.30 mmol) in DMF (4.5 mL) and H_2O (1.5 mL) were added CuCl (31 mg, 0.30 mmol) and $PdCl_2$ (16 mg, 0.09 mmol), and the resulting suspension was stirred under oxygen atmosphere at 1 atm at room temperature for 18 h. The insoluble materials were removed by filtration, and washed with CH_2Cl_2. The filtrate was dried over $MgSO_4$, filtered and evaporated to give a residue, which was chromatographed on silica gel (20 g, hexane/acetone 30:1−15:1) to give **11** (88 mg, 86%) as a colorless oil: IR (neat) 1720, 1698, 1406, 1096 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (3H, br), 1.19−1.39 (6H, br m), 1.43−1.69 (5H, br m), 1.93 (3H, br), 2.07 (3H, br), 2.32−2.53 (2H, br), 3.82 (2H, br), 5.11 (2H, s), 7.24−7.39 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1 (q), 20.4 (t), 22.6 (t), 28.5 (t), 29.2 (t), 29.8 (q), 35.4 (t), 43.4 (t), 58.4 (d), 66.4 (t), 127.6 (d), 128.2 (d), 136.8 (s), 155.1 (s); MS 345 (M^+), 244 (100); HRMS calcd for $C_{21}H_{31}O_3N$ 345.2302, found 345.2298; $[\alpha]^{26}_D$ +2.35 (*c* 0.45, $CHCl_3$).

(3*R*,5*S*,9*S*)-(+)-3-*n*-Butyl-5-methyloctahydroindolizine ((+)-Monomorine I, 1). To a stirring solution of **11** (88 mg, 0.26 mmol) in EtOH (10 mL) was added 20% $Pd(OH)_2$ (30 mg), and the resulting suspension was hydrogenated at 1 atm for 48 h. The catalyst was removed by filtration, and the filtrate was evaporated to give (+)-**1** (42 mg, 84%) as a pale pinkish oil. The spectral data for synthetic (+)-**1** were identical with those reported. $[\alpha]^{26}_D$ +33.32 (*c* 1.40, *n*-hexane), lit.[5] $[\alpha]^{26}_D$ +34.0 (*c* 1.09, *n*-hexane).

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Supporting Information Available: General experimental procedures and ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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