Synthesis of Poison-Frog Alkaloids 237D, 207A, and Two Congeners of 235B′ for Evaluation to Inhibitory Effect of Nicotinic Acetylcholine Receptors

Naoki TOYOOKA,*[,a] Masashi KAWASAKI,[b] and Hideo NEMOTO*[,a]

[a] *Faculty of Pharmaceutical Sciences, Toyama Medical and Pharmaceutical University; 2630 Sugitani, Toyama 930–0194, Japan:* [b] *Department of Liberal Arts and Sciences, Faculty of Engineering, Toyama Prefectural University; 5180 Kurokawa, Kosugi-machi, Toyama 939–0398, Japan.*

Received January 26, 2005; accepted March 7, 2005; published online March 10, 2005

Enantioselective synthesis of the poison-frog alkaloids 237D, 207A, and two congeners of 235B′ has been achieved. The absolute stereochemistry of 237D was determined to be 5*S*, 8*S*, 9*R* by the present synthesis.

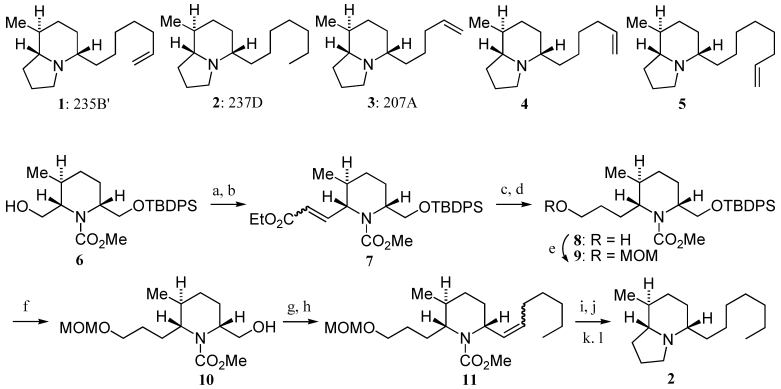
Key words poison-frog alkaloid; 237D; 207A; 235B′; 5,8-disubstituted indolizidine

A large number of biologically active alkaloids have been found in amphibian skin, and the 5,8-disubstituted indolizidines, one of the largest subclass of these alkaloids, were detected from skin extracts of the poison-frog.[1—3] Quite recently, we have found the synthetic 5,8-disubstituted indolizidine **235B′** (**1**), isolated from *Dendrobates* pumilio, acted as a potent noncompetitive and selective blocker of $\alpha4\beta2$ nicotinic receptor ($IC_{50}=74$ nM).[4] The sensitivity of **235B′** for $\alpha4\beta2$ receptors was comparable with that of the best characterized antagonist of $\alpha4\beta2$ nicotinic acetylcholine reseptors (nAChRs), dihydro-β-erythroidine (DHβE) ($IC_{50}=0.11$ μM).[5] This result shows that poison-frog alkaloids such as indolizidine **235B′** alter the function of nicotinic receptors in a subtype-selective manner, suggesting that an analysis of these alkaloids may aid in the development of selective drugs to alter nicotinic cholinergic functions. As part of our ongoing program at directing the synthesis of biologically active alkaloids,[6—8] we planned the synthesis of **237D** (**2**, saturated congener of **1**), **207A** (**3**, bis-nor congener of **1**), nor congener of **235B′** (**4**), and homo congener of **1** (**5**) as potent blockers for nAChRs. This paper describes a full account of the experiments, some of which were reported in a preliminary communication.[9]

The synthesis of **2** began with trisubstituted piperidine **6**,[10,11] which was converted to the α,β-unsaturated ester **7** in 2-step sequence. Hydrogenation of **7** over Pd–C under medium pressure followed by reduction of the ester moiety with Super-Hydride gave rise to the alcohol **8**. Treatment of **8** with MOMCl in the presence of Hünig base provided the MOM ether **9**, which was treated with TBAF to afford the alcohol **10**. Swern oxidation of **10** followed by Wittig olefination of the resulting aldehyde provided the olefin, which was hydrogenated over Pd–C to give rise to the alkaloid **237D** (**2**). The absolute stereochemistry of natural **237D** was determined to be 5*S*, 8*S*, 9*R* by the present synthesis (see Experimental and reference 9).

Swern oxidation of **10** followed by the Wittig reaction of the resulting aldehyde provided the olefin **12**, which was converted to the alcohol **13**. Swern oxidation of **13** and Wittig reaction of the resulting aldehyde afforded the terminal olefin **14**. Deprotection of the urethane moiety in **14** using Corey's procedure,[12] and cleavage of the MOM ether with acid followed by indolizidine formation under the bromination reaction condition[13] provided the alkaloid **207A** (**3**), whose spectral data were identical with those of reported values.[13,14] On the other hand, the alcohol **13** was converted to the iodide **15**, and the cross coupling reaction of **15** using the dibutenyl cuprate gave rise to the homologated olefin **16**. Indolizidine formation reaction of **16** furnished **5**.

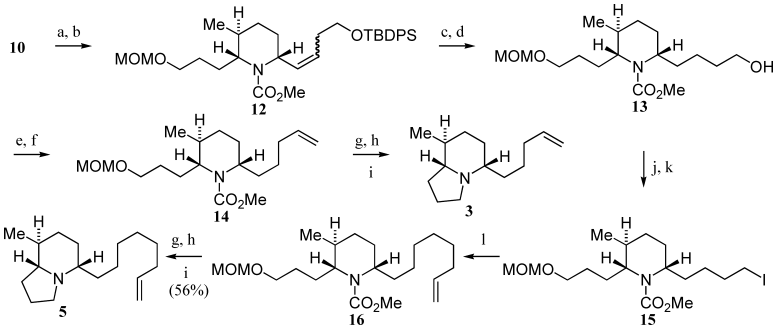
Finally, the nor-congener of **1** (**4**) was synthesized from the



Reagents and conditions: a: Swern ox.; b: $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, 0 °C—rt (95%); c: 10% Pd–C, H_2, EtOAc, 4 atm; d: Super-Hydride, THF, 0 °C (93%); e: MOMCl, Hünig base CH_2Cl_2, 0 °C—rt (85%); f: TBAF, THF, 0 °C—rt (95%); g: Swern ox.; h: $Me(CH_2)_5P^+Ph_3Br^-$, *n*-BuLi, THF, 0 °C—rt (66%); i: 10% Pd–C, H_2, EtOAc, 1 atm; j: *n*-PrSLi, HMPA, THF, 0 °C—rt; k: conc. HCl, MeOH, reflux; l: CBr_4, Ph_3P, Et_3N, CH_2Cl_2, 0 °C—rt (42%).

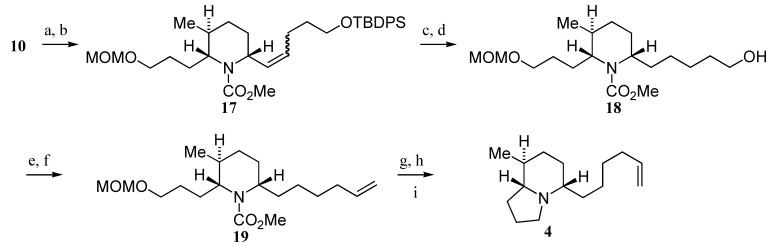
Chart 1

* To whom correspondence should be addressed. e-mail: toyooka@ms.toyama-mpu.ac.jp



Reagents and conditions: a: Swern ox.; b: $TBDPSO(CH_2)_3P^+Ph_3Br^-$, *n*-BuLi, THF, 0 °C—rt (87%); c: 10% Pd–C, H_2, EtOAc, 1 atm; d: TBAF, THF, 0 °C—rt (87%); e: Swern ox.; f: $CH_3P^+Ph_3I^-$, *n*-BuLi, THF, 0 °C—rt (89%); g: *n*-PrSLi, HMPA, THF, 0 °C—rt; h: conc. HCl, MeOH, reflux; i: CBr_4, Ph_3P, Et_3N, CH_2Cl_2, 0 °C—rt (63%); j: MsCl, Et_3N, CH_2Cl_2, 0 °C; k: NaI, acetone, 50 °C (96%); l: butenylmagnesium bromide, CuI, THF, −40—−30 °C (91%).

Chart 2



Reagents and conditions: a: Swern ox.; b: $TBDPSO(CH_2)_4P^+Ph_3Br^-$, *n*-BuLi, THF, 0 °C—rt (97%); c: 10% Pd–C, H_2, EtOAc, 1 atm; d: TBAF, THF, 0 °C—rt (74%); e: Swern ox.; f: $CH_3P^+Ph_3I^-$, *n*-BuLi, THF, 0 °C—rt (88%); g: *n*-PrSLi, HMPA, THF, 0 °C—rt; h: conc. HCl, MeOH, reflux; i: CBr_4, Ph_3P, Et_3N, CH_2Cl_2, 0 °C—rt (51%).

Chart 3

common alcohol **10** as shown in Chart 3. The alcohol **10** was converted to the olefin **17**, which was hydrogenated over 10% Pd–C in EtOAc followed by cleavage of silyl ether with TBAF to afford the alcohol **18**. Swern oxidation of **18** and Wittig olefination reaction of the resulting aldehyde provided the terminal olefin **19**. Indolizidine formation reaction of **19** in 3-step sequence furnished **4**.

Pharmacological studies on the nicotinic acetylcholine receptors of these synthesized indolizidines are now being conducted, and the results will be described in due course.

Experimental

General ^{1}H- and ^{13}C-NMR spectra were taken on a Varian Gemini 300 or Unity Plus 500 spectrometer. ^{1}H-NMR spectra were recorded at the indicated field strength as solutions in $CDCl_3$ unless otherwise indicated. Chemical shifts are given in parts per million (ppm, δ) downfield from TMS and are referenced to $CHCl_3$ (7.26 ppm) as internal standard. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. ^{13}C-NMR spectra were recorded at the indicated field strength as solutions in $CDCl_3$ unless otherwise indicated. Chemical shifts are given in parts per million (ppm, δ) downfield from TMS and are referenced to the center line of $CDCl_3$ (77.0 ppm) as internal standard. Carbon signals were assigned by a DEPT pulse sequence, q=methyl, t=methylene, d=methyne, and s=quaternary carbons. Infrared spectra (IR) were measured with a Perkin-Elmer 1600 series FT-IR spectrophotometer. Mass spectra (MS) and high-resolution mass spectra (HR-MS) were measured on a JEOL JMS-AX505HAD mass spectrometer. Optical rotations were measured on a JASCO DIP-1000 digital polarimeter. Column chromatography was performed on Merck silica gel 60 (No. 7734-5B) or (No. 9385).

Methyl 6-(*tert*-Butyldiphenylsilyloxymethyl)-2-(2-ethoxycarbonylvinyl)-3-methylpiperidine-1-carboxylate (7) To a stirred solution of $(COCl)_2$ (1.15 ml, 13.19 mmol) in CH_2Cl_2 (30 ml) was added DMSO (1.87 ml, 26.37 mmol) at −78 °C, and the resulting solution was stirred at −78 °C for 5 min. To the mixture was added dropwise a solution of **6** (4 g, 8.79 mmol) in CH_2Cl_2 (6 ml) *via* a double-tipped stainless steel needle. After the reaction mixture was stirred for 30 min at −78 °C, triethylamine (5.47 ml, 39.56 mmol) was added to the reaction mixture. The reaction mixture was warmed to 0 °C for 1 h, and quenched with H_2O. The aqueous mixture was extracted with Et_2O (20 ml×3). The organic extracts were combined, dried, and evaporated to give pale yellow oil, which was used directly in the next step.

To a stirred suspension of NaH (60%, 386 mg, 9.67 mmol) in THF (20 ml) was added $(EtO)_2P(O)CH_2CO_2Et$ (1.94 ml, 9.67 mmol) at 0 °C, and the reaction mixture was stirred for 30 min at 0 °C. To the mixture was added dropwise a solution of the above aldehyde in THF (6 ml) *via* a double-tipped stainless needle. The reaction mixture was stirred at room temperature for 20 h, and quenched with H_2O. The aqueous mixture was extracted with CH_2Cl_2 (20 ml×3). The organic extracts were combined, dried, and evaporated to give pale yellow oil, which was chromatographed on SiO_2 (80 g, hexane : acetone=100 : 1—10 : 1) to afford **7** (4.29 g, 95%) as a 2 : 1 mixture of *E*- and *Z*-isomers.

IR (neat) 2955, 1759, 1698 cm^{-1}; ^{1}H-NMR (500 MHz) δ 0.90, 1.11 (3H, each d, J=6.9 Hz), 1.05 (9H, s), 1.23, 1.31 (3H, each t, J=7.2 Hz), 1.44—2.08 (5H, br m), 3.11—3.21 (1H, br m), 3.48—3.58 (1H, br m), 3.61, 3.71 (3H, each s), 4.14—4.22 (2H m), 4.33—4.53 (2H br), 5.65, 5.93 (1H, each d, each J=10.3, 14.1 Hz), 6.19, 6.89 (1H, each dd, J=10.3, 8.5, 14.1, 5.5 Hz), 7.39—7.48 (6H, m), 7.66—7.74 (4H, m); MS *m/z*: 523 (M^+).

Methyl 6-(*tert*-Butyldiphenylsilyloxymethyl)-2-(3-hydroxypropyl)-3-methylpiperidine-1-carboxylate (8) To a stirred solution of **7** (1.2 g, 2.29 mmol) in EtOAc (20 ml) was added 10% Pd–C (50 mg), and the resulting suspension was hydrogenated under hydrogen atmosphere at 4 atm for 40 h. The catalyst was removed by filtration and the filtrate was evaporated to give colorless oil, which was used directly in the next step.

To a stirred solution of the above oil in THF (10 ml) was added a solution of Super-Hydride (1 M in THF, 5 ml, 5 mmol) at 0 °C, and the resulting solution was stirred at 0 °C for 1.5 h. The reaction was quenched with ice-water, and the aqueous mixture was extracted with CH_2Cl_2 (10 ml×5). The organic extracts were combined, dried, and evaporated to give colorless oil, which was chromatographed on SiO_2 (20 g, hexane : acetone=30 : 1—10 : 1) to afford **8** (1.02 g, 93%) as colorless oil.

IR (neat) 3471, 1688 cm^{-1}; ^{1}H-NMR (500 MHz) δ 0.90 (3H, br), 1.06 (12H, br s), 1.14—1.79 (6H, br m), 3.38—4.66 (9H, br m), 7.43 (6H, br),

7.72—7.87 (4H, br m); ^{13}C-NMR (75 MHz) δ 18.87, 19.03 (each t), 19.22, 19.37 (each t), 20.89, 21.46 (each q), 22.33, 22.57 (each t), 26.65 (q), 31.49 (t), 50.26 (d), 51.13 (d), 52.65, 52.81 (each q), 63.04, 63.56 (each d), 64.90, 65.37 (each t), 68.18, 69.40 (each d), 127.50 (d), 127.55 (d), 129.57 (d), 132.71 (s), 135.23 (d), 158.43, 158.79 (each s); MS *m/z*: 483 (M^+); HR-MS Calcd for $C_{28}H_{41}NO_4Si$ 483.2802, Found 483.2822; $[\alpha]_D^{26}$ +9.7° (*c*=1.75, $CHCl_3$).

Methyl 6-(*tert*-Butyldiphenylsilyloxymethyl)-2-(3-methoxymethoxypropyl)-3-methylpiperidine-1-carboxylate (9) To a stirred solution of **8** (785 mg, 1.63 mmol) in CH_2Cl_2 (8 ml) were added MOMCl (0.49 ml, 6.50 mmol) and Hünig base (1.42 ml, 8.13 mmol) at 0 °C, and the resulting mixture was stirred at room temperature for 45 h. The solvent was evaporated and the residue was chromatographed on SiO_2 (20 g, hexane : acetone=30 : 1—15 : 1) to afford **9** (730 mg, 85%) as colorless oil.

IR (neat) 2953, 1695 cm^{-1}; ^{1}H-NMR (500 MHz) δ 1.05—1.18 (15H, br), 1.40—1.95 (6H, br m), 3.29 (3H, br), 3.44—4.58 (8H, br), 3.66 (3H, s), 7.39—7.42 (6H, br), 7.70—7.72 (4H, m); ^{13}C-NMR (75 MHz) δ 19.24 (q), 20.73, 21.08 (each t), 24.04 (t), 26.59 (t), 26.83 (q), 29.69, 30.32 (each t), 52.46 (q), 55.38 (q), 60.79 (d), 63.72, 64.96 (each t), 67.37 (t), 77.21 (d), 95.32 (t), 127.38 (d), 129.34 (d), 133.53, 133.69 (each s), 135.34 (d), 158.06 (s); MS *m/z*: 527 (M^+); HR-MS Calcd for $C_{30}H_{45}NO_5Si$ 527.3064, Found 527.3059; $[\alpha]_D^{26}$ −20.1° (*c*=3.36, $CHCl_3$).

Methyl 6-Hydroxymethyl-2-(3-methoxymethoxypropyl)-3-methylpiperidine-1-carboxylate (10) To a stirred solution of **9** (730 mg, 1.39 mmol) in THF (6 ml) was added a solution of TBAF (1 M in THF, 1.56 ml, 1.56 mmol) at 0 °C, and the resulting solution was stirred at room temperature for 2 h. The reaction was quenched with satd. NH_4Cl (aq.), and the aqueous mixture was extracted with $CHCl_3$ (10 ml×6). The organic extracts were combined, dried, and evaporated to give colorless oil, which was chromatographed on SiO_2 (20 g, hexane : acetone=10 : 1—2 : 1) to afford **10** (380 mg, 95%) as colorless oil.

IR (neat) 3475, 2951, 1692 cm^{-1}; ^{1}H-NMR (500 MHz) δ 1.03 (3H, d, *J*=6 Hz), 1.07—1.86 (9H, br m), 3.35 (3H, s), 3.54—3.91 (4H, br m), 4.04—4.23 (2H, br), 4.59, 4.72 (2H, each br); ^{13}C-NMR (75 MHz) δ 18.03 (q), 21.25 (t), 21.36 (t), 25.06 (t), 29.82 (d), 32.07 (t), 52.78 (q), 55.87 (q), 61.74 (d), 65.55 (t), 69.19 (t), 76.09 (d), 76.24 (d), 95.32 (t), 159.71 (s); MS *m/z*: 289 (M^+); HR-MS Calcd for $C_{14}H_{27}NO_5$ 289.1888, Found 289.1869; $[\alpha]_D^{26}$ −39.0° (*c*=3.04, $CHCl_3$).

Methyl 6-Hept-1-enyl-2-(3-methoxymethoxypropyl)-3-methylpiperidine-1-carboxylate (11) To a stirred solution of $(COCl)_2$ (0.25 ml, 1.95 mmol) in CH_2Cl_2 (5 ml) was added DMSO (0.43 ml, 3.90 mmol) at −78 °C, and the resulting solution was stirred at −78 °C for 5 min. To the mixture was added dropwise a solution of **10** (380 mg, 1.31 mmol) in CH_2Cl_2 (3 ml) *via* a double-tipped stainless steel needle. After the reaction mixture was stirred for 30 min at −78 °C, triethylamine (1.3 ml, 5.85 mmol) was added to the reaction mixture. The reaction mixture was warmed to 0 °C for 1 h, and quenched with H_2O. The aqueous mixture was extracted with Et_2O (10 ml×3). The organic extracts were combined, dried, and evaporated to give pale yellow oil, which was used directly in the next step.

To a stirred suspension of hexyltriphenylphsphoniumbromide (2.8 g, 6.56 mmol) in THF (10 ml) was added a solution of *n*-BuLi (1.6 M in hexane, 3.7 ml, 5.92 mmol) at 0 °C, and the resulting orange solution was stirred for 10 min at 0 °C. To the mixture was added dropwise a solution of the above aldehyde in THF (4 ml) *via* a double-tipped stainless steel needle. After the reaction mixture was stirred for 14 h at room temperature, the reaction was quenched with H_2O. The aqueous mixture was extracted with Et_2O (10 ml×3), and the organic extracts were combined, dried, and evaporated to give pale yellow oil, which was chromatographed on SiO_2 (20 g, hexane : acetone=100 : 1—15 : 1) to afford **11** (310 mg, 66%) as pale yellow oil.

IR (neat) 2953, 1694 cm^{-1}; ^{1}H-NMR (500 MHz) δ 0.86—0.93 (6H, m), 1.02—1.43 (10H, br m), 1.53—2.18 (7H, br m), 3.36 (3H, s), 3.67 (3H, s), 3.65—3.79 (2H, br), 3.90 (1H, br), 4.60 (2H, s), 4.83 (1H, br), 5.38 (1H, m), 5.68 (1H, m); MS *m/z*: 355 (M^+).

5-Heptyl-8-methyloctahydroindolizine (Indolizidine 237D, 2) To a stirred solution of **11** (200 mg, 0.56 mmol) in EtOAc (10 ml) was added 10% Pd–C (30 mg), and the resulting suspension was hydrogenated under hydrogen atmosphere at 1 atm for 48 h. The catalyst was removed by filtration and the filtrate was evaporated to give colorless oil, which was used directly in the next step.

To a stirred solution of *n*-PrSH (0.51 ml, 5.63 mmol) in HMPA (2.5 ml) was added a solution of *n*-BuLi (1.6 M in hexane, 3.3 ml, 5.35 mmol) at 0 °C, and the reaction mixture was stirred at 0 °C for 30 min. To the reaction mixture was added dropwise a solution of the above oil in THF (3 ml) *via* a double-tipped stainless needle. The reaction was stirred at room temperature for 54 h, and quenched with 28% NH_3 (aq.). The aqueous mixture was extracted with Et_2O (10 ml×10), and the organic extracts were combined, dried over K_2CO_3, and evaporated to give pale yellow oil, which was used directly in the next step.

To a solution of the above oil in MeOH (5 ml) was added conc. HCl (8 drops), and the reaction mixture was heated at reflux for 1 h. After cooling, the solvent was evaporated, and the residue was washed with Et_2O. To the residue was added 28% NH_3 (aq.), and the aqueous mixture was extracted with $CHCl_3$ (10 ml×10). The organic extracts were combined, dried over K_2CO_3, and evaporated to give pale yellow oil, which was used directly in the next step.

To a stirred solution of the above oil in CH_2Cl_2 (5 ml) were added CBr_4 (262 mg, 0.79 mmol) and Ph_3P (221 mg, 0.85 mmol) at 0 °C, and the resulting mixture was stirred at 0 °C for 1 h. To the reaction mixture was added triethylamine (1.25 ml, 9.01 mmol), and the stirring was continued for 30 min at room temperature. The volatiles were removed, and the residue was extracted with pentane (5 ml×4). The solvent was evaporated to give pale orange solid, which was chromatographed on SiO_2 (20 g, hexane : acetone=20 : 1) to afford **2** (56 mg, 42%) as pale yellow oil.

Determination of absolute stereochemistry of natural 237D was as follows: Both (+)- and (−)-237D were prepared by the catalytic hydrogenation of natural (+)-235B, isolated from *D. pumilio* or (−)-235B, present in an extract of *D. speciosus*. Gas chromatography using flame-ionization detection and a chiral column, permethylated β-cycldextrin (SGE, 30 m×0.25 mm; 130 °C at 0.5 °C/min), resulted in a baseline separation of (+)- and (−)-237D as previously reported. The retention times were 31.9 and 32.4 min respectively. Natural 237D present in *D. pumilio* or *D. speciosus* was co-chromatographed with (−)-**7** on the chiral column using the above conditions. The synthetic (−)-**7** and (−)-**7**, prepared from the hydrogenation of 235B, were co-chromatographed on GC-MS with a non-chiral column (Zebron-5 (Phenomenex) 100—280 °C at 5 °C/min) and had identical GC-EI-MS and GC-FT-IR spectra providing that they had the same relative and absolute stereochemistry.

IR (neat) 2926, 2855, 2777, 1457, 1376, 1164, 1131, 908, 733, 640 cm^{-1}; ^{1}H-NMR (500 MHz) δ 0.88 (3H, d, *J*=6.8 Hz), 0.89 (3H, t, *J*=6.8 Hz), 0.97 (1H, q-like, *J*=11.5 Hz), 1.27—1.38 (13H, br m), 1.51—2.18 (10H, br m), 3.31 (1H, br); ^{13}C-NMR (75 MHz) δ 14.16 (q), 18.93 (q), 20.36 (t), 22.72 (t), 25.89 (t), 29.03 (t), 29.32 (t), 30.05 (t), 31.15 (t), 31.88 (t), 33.67 (t), 34.53 (t), 36.44 (d), 51.78 (t), 63.60 (d), 71.37 (d); MS *m/z*: 237 (M^+); HR-MS Calcd for $C_{16}H_{31}N$ 237.2455, Found 237.2452; $[\alpha]_D^{26}$ −98.9° (*c*=1.59, $CHCl_3$).

Methyl 6-[4-(*tert*-Butyldiphenylsilyloxy)but-1-enyl]-2-(3-methoxymethoxypropyl)-3-methylpiperidine-1-carboxylate (12) To a stirred solution of $(COCl)_2$ (0.32 ml, 3.63 mmol) in CH_2Cl_2 (10 ml) was added DMSO (0.52 ml, 7.27 mmol) at −78 °C, and the resulting solution was stirred at −78 °C for 5 min. To the mixture was added dropwise a solution of **10** (700 mg, 2.42 mmol) in CH_2Cl_2 (6 ml) *via* a double-tipped stainless steel needle. After the reaction mixture was stirred for 30 min at −78 °C, triethylamine (1.5 ml, 10.90 mmol) was added to the reaction mixture. The reaction mixture was warmed to 0 °C for 1 h, and quenched with H_2O. The aqueous mixture was extracted with Et_2O (15 ml×3). The organic extracts were combined, dried, and evaporated to give pale yellow oil, which was used directly in the next step.

To a stirred suspension of $TBDPSO(CH_2)_3P^+Ph_3Br^-$ (6.96 g, 10.90 mmol) in THF (18 ml) was added a solution of *n*-BuLi (1.6 M in hexane, 6 ml, 9.69 mmol) at 0 °C, and the resulting orange solution was stirred at 0 °C for 10 min. To the mixture was added dropwise a solution of the above aldehyde in THF (4 ml) *via* a double-tipped stainless needle. The reaction was stirred at room temperature for 21 h, and quenched with H_2O. The aqueous mixture was extracted with Et_2O (15 ml×3). The organic extracts were combined, dried, and evaporated to give pale yellow oil, which was chromatographed on SiO_2 (40 g, hexane : acetone=100 : 1—40 : 1) to afford **12** (1.19 g, 87%) as pale yellow oil.

IR (neat) 2956, 1691 cm^{-1}; ^{1}H-NMR (500 MHz) δ 1.03 (3H, d, *J*=7.4 Hz), 1.06 (9H, s), 1.18—1.24 (1H, m), 1.28—1.30 (1H, m), 1.56—1.93 (7H, br m), 2.38—2.42 (1H, m), 2.52—2.55 (1H, m), 3.37 (3H, s), 3.52—3.59 (2H, m), 3.63 (3H, s), 3.62—3.73 (2H, m), 3.92, 4.06 (1H, each br), 4.61 (2H, s), 4.87—4.92 (1H, br), 5.46—5.50 (1H, m), 5.61—5.68 (1H, m), 7.37—7.45 (6H, m), 7.67—7.74 (4H, m); MS *m/z*: 567 (M^+).

Methyl 6-(4-Hydroxybutyl)-2-(3-methoxymethoxypropyl)-3-methylpiperidine-1-carboxylate (13) To a stirred solution of **12** (1.08 g, 1.90 mmol) in EtOAc (20 ml) was added 10% Pd–C (100 mg), and the resulting suspension was hydrogenated under hydrogen atmosphere at 1 atm

for 48 h. The catalyst was removed by filtration and the filtrate was evaporated to give colorless oil, which was used directly in the next step.

To a stirred solution of the above oil in THF (8 ml) was added a solution of TBAF (1 M in THF, 2.1 ml, 2.1 mmol) at 0 °C, and the mixture was stirred at room temperature for 2 h. The reaction was quenched with satd. NH_4Cl (aq.), and the aqueous mixture was extracted with $CHCl_3$ (10 ml×7). The organic extracts were combined, dried, and evaporated to give colorless oil, which was chromatographed on SiO_2 (20 g, hexane : acetone=15 : 1—2 : 1) to afford **13** (548 mg, 87%) as colorless oil.

IR (neat) 3442, 2941, 1672 cm^{-1}; ^{1}H-NMR (500 MHz) δ 0.91—0.93 (3H, br), 1.09—1.87 (15H, br m), 2.86 (1H, br), 3.27 (3H, s), 3.43 (2H, br s), 3.50 (2H, br s), 3.58 (3H, s), 3.72—4.02 (2H, br), 4.52 (2H, s); ^{13}C-NMR (75 MHz) δ 18.88 (q), 19.21 (t), 21.55 (t), 22.02 (t), 23.20 (t), 27.33 (t), 30.63 (d), 32.30 (t), 32.83 (t), 34.87 (t), 50.63 (d), 52.25 (q), 54.87 (d), 56.52 (d), 62.10 (t), 67.36 (t), 96.03 (t), 157.27 (s); MS *m/z*: 331 (M^+); HR-MS Calcd for $C_{17}H_{33}NO_5$ 331.2357, Found 331.2370; $[\alpha]_D^{26}$ −11.2° (*c*=0.82, $CHCl_3$).

Methyl 2-(3-Methoxymethoxypropyl)-3-methyl-6-pent-4-enylpiperidine-1-carboxylate (14) To a stirred solution of $(COCl)_2$ (0.1 ml, 1.15 mmol) in CH_2Cl_2 (2 ml) was added DMSO (0.17 ml, 2.30 mmol) at −78 °C, and the resulting solution was stirred at −78 °C for 5 min. To the mixture was added dropwise a solution of **13** (150 mg, 0.45 mmol) in CH_2Cl_2 (2 ml) *via* a double-tipped stainless steel needle. After the reaction mixture was stirred for 30 min at −78 °C, triethylamine (0.5 ml, 3.45 mmol) was added to the reaction mixture. The reaction mixture was warmed to 0 °C for 1 h, and quenched with H_2O. The aqueous mixture was extracted with Et_2O (10 ml×3). The organic extracts were combined, dried, and evaporated to give pale yellow oil, which was used directly in the next step.

To a stirred suspension of $MeP^+Ph_3I^-$ (915 mg, 2.27 mmol) in THF (8 ml) was added a solution of *n*-BuLi (1.6 M in hexane, 1.27 ml, 2.04 mmol) at 0 °C, and the resulting orange solution was stirred at 0 °C for 10 min. To the mixture was added dropwise a solution of the above aldehyde in THF (4 ml) *via* a double-tipped stainless needle. The reaction was stirred at room temperature for 17 h, and quenched with H_2O. The aqueous mixture was extracted with Et_2O (15 ml×3). The organic extracts were combined, dried, and evaporated to give pale yellow oil, which was chromatographed on SiO_2 (20 g, hexane : acetone=100 : 1—20 : 1) to afford **14** (132 mg, 89%) as pale yellow oil.

IR (neat) 3071, 2940, 1694 cm^{-1}; ^{1}H-NMR (500 MHz) δ 1.00 (3, d, *J*=7 Hz), 1.12—1.19 (1H, m), 1.30—1.44 (3H, m), 1.45—1.63 (5H, br m), 1.71—1.89 (4H, m), 1.98—2.09 (2H, m), 3.34 (3H, s), 3.47—3.55 (2H, m), 3.66 (3H, s), 3.72—3.92 (1H, br), 4.03—4.13 (1H, br), 4.60 (2H, s), 4.93 (1H, dq-like, *J*=9.9, 1 Hz), 4.98 (1H, dq-like, *J*=16.1, 1.7 Hz), 5.78 (1H, ddt, *J*=16.1, 9.9, 6.5 Hz); ^{13}C-NMR (75 MHz) δ 19.32 (q), 21.67 (t), 22.18 (t), 26.46 (t), 27.48 (t), 30.72 (d), 32.94 (t), 33.61 (t), 34.83 (t), 50.76 (d), 52.38 (q), 55.07 (q), 56.66 (d), 67.57 (t), 96.32 (t), 114.48 (t), 138.68 (d), 157.57 (s); MS *m/z*: 327 (M^+); HR-MS Calcd for $C_{18}H_{33}NO_4$ 327.2408, Found 327.2441; $[\alpha]_D^{26}$ −10.9° (*c*=0.95, $CHCl_3$).

8-Methyl-5-pent-4-enyloctahydro-indolizine (Indolizidine 207A, 3) To a stirred solution of *n*-PrSH (0.38 ml, 4.20 mmol) in HMPA (2.5 ml) was added a solution of *n*-BuLi (1.6 M in hexane, 2.5 ml, 4.02 mmol) at 0 °C, and the reaction mixture was stirred at 0 °C for 30 min. To the reaction mixture was added dropwise a solution of **14** (138 mg, 0.42 mmol) in THF (3 ml) *via* a double-tipped stainless needle. The reaction was stirred at room temperature for 49 h, and quenched with 28% NH_3 (aq.). The aqueous mixture was extracted with Et_2O (10 ml×10), and the organic extracts were combined, dried over K_2CO_3, and evaporated to give pale yellow oil, which was used directly in the next step.

To a solution of the above oil in MeOH (5 ml) was added conc. HCl (5 drops), and the reaction mixture was heated at reflux for 1 h. After cooling, the solvent was evaporated, and the residue was washed with Et_2O. To the residue was added 28% NH_3 (aq.), and the aqueous mixture was extracted with $CHCl_3$ (10 ml×10). The organic extracts were combined, dried over K_2CO_3, and evaporated to give pale yellow oil, which was used directly in the next step.

To a stirred solution of the above oil in CH_2Cl_2 (7 ml) were added CBr_4 (195 mg, 0.59 mmol) and Ph_3P (166 mg, 0.63 mmol) at 0 °C, and the resulting mixture was stirred at 0 °C for 1 h. To the reaction mixture was added triethylamine (0.9 ml, 6.47 mmol), and the stirring was continued for 30 min at room temperature. The volatiles were removed, and the residue was extracted with pentane (5 ml×4). The solvent was evaporated to give pale orange solid, which was chromatographed on SiO_2 (20 g, hexane : acetone=20 : 1) to afford **3** (55 mg, 63%) as pale yellow oil.

IR (neat) 3074, 2933, 2872, 2775, 2701, 1642, 1455, 1336, 1242, 1165, 1088, 909 cm^{-1}; ^{1}H-NMR (500 MHz) δ 0.86 (3H, d, *J*=6.4 Hz), 0.98 (1H, qd-like, *J*=14.1, 4.7 Hz), 1.20—2.09 (17H, br m), 3.26 (1H, t-like, *J*=8.7 Hz), 4.93 (1H, dd, *J*=10.1, 2.2 Hz), 4.99 (1H, dd, *J*=17.1, 2.2 Hz), 5.76—5.84 (1H, m); ^{13}C-NMR (75 MHz) δ 18.96 (q), 20.42 (t), 25.21 (t), 29.13 (t), 31.29 (t), 33.72 (t), 34.12 (t), 34.16 (t), 36.60 (d), 51.87 (t), 63.36 (d), 71.32 (d), 114.31 (t), 138.69 (d); MS *m/z*: 207 (M^+); $[\alpha]_D^{26}$ −86.7° (*c*=2.64, $CHCl_3$); lit.[13] $[\alpha]_D^{28}$ −86.5° (*c*=0.95, $CHCl_3$); lit.[14] $[\alpha]_D^{22.5}$ −103.2° (*c*=0.47, $CHCl_3$).

Methyl 6-(4-Iodobutyl)-2-(3-methoxymethoxypropyl)-3-methylpiperidine-1-carboxylate (15) To a stirred solution of **13** (257 mg, 0.78 mmol) in CH_2Cl_2 (3 ml) were added triethylamine (0.41 ml, 2.95 mmol) and MsCl (0.17 ml, 2.18 mmol) at 0 °C, and the reaction mixture was stirred at 0 °C for 30 min. The reaction was quenched with satd. $NaHCO_3$ (aq.), and the aqueous mixture was extracted with CH_2Cl_2 (10 ml×3). The organic extracts were combined, dried, and evaporated to give pale yellow oil, which was used directly in the next step.

To a stirred solution of the above oil in acetone (10 ml) was added NaI (582 mg, 3.88 mmol), and the resulting mixture was heated at 50 °C for 2 h. After cooling, the reaction was quenched with 10% $Na_2S_2O_3$ in satd. $NaHCO_3$ (aq.), and the aqueous mixture was extracted with CH_2Cl_2 (15 ml×3). The organic extracts were combined, dried, and evaporated to give pale yellow oil, which was chromatographed on SiO_2 (20 g, hexane : acetone=30 : 1) to afford **15** (330 mg, 96%) as colorless oil.

IR (neat) 2944, 1701 cm^{-1}; ^{1}H-NMR (500 MHz) δ 0.99 (3H, d, *J*=7.2 Hz), 1.15—1.17 (1H, m), 1.32—1.89 (14H, br m), 3.17 (2H, t-like, *J*=6.9 Hz), 3.34 (3H, s), 3.49—3.52 (2H, m), 3.66 (3H, s), 3.80 (1H, br), 4.08 (1H, br), 4.60 (2H, s); ^{13}C-NMR (75 MHz) δ 6.94 (t), 19.42 (q), 21.76 (t), 22.20 (t), 27.52 (t), 28.01 (t), 30.78 (d), 33.09 (t), 33.19 (t), 34.14 (t), 50.53 (d), 52.42 (q), 55.09 (q), 56.65 (d), 67.52 (t), 96.27 (t), 157.28 (s); MS *m/z*: 441 (M^+); HR-MS Calcd for $C_{17}H_{32}INO_4$ 441.1375, Found 441.1387; $[\alpha]_D^{26}$ −8.60° (*c*=5.31, $CHCl_3$).

Methyl 2-(3-Methoxymethoxypropyl)-3-methyl-6-oct-7-enylpiperidine-1-carboxylate (16) To a stirred suspension of CuI (501 mg, 2.63 mmol) in THF (5 ml) was added a solution 1-butenylmagnesium bromide in THF (prepared from 4-bromo-1-butene (0.53 ml, 5.26 mmol) and magnesium (126 mg, 5.26 mmol) in THF (3 ml), reflux) at −40 °C, and the reaction was stirred at −40—35 °C for 15 min. To the reaction mixture was added **15** (290 mg, 0.66 mmol) in THF (4 ml) at the same temperature, and the stirring was continued for 5 h. The reaction was quenched with satd. NH_4Cl (aq.), and the insoluble materials were filtered off. The filtrate was extracted with CH_2Cl_2 (15 ml×4). The organic extracts were combined, dried, and evaporated to give pale yellow oil, which was chromatographed on SiO_2 (20 g, hexane : acetone=50 : 1—20 : 1) to afford **16** (220 mg, 91%) as colorless oil.

IR (neat) 3073, 2941, 1696 cm^{-1}; ^{1}H-NMR (500 MHz) δ 0.97 (3H, d, *J*=6.8 Hz), 1.11—1.58 (16H, br m), 1.72—1.84 (3H, m), 1.97—2.00 (2H, m), 3.31 (3H, s), 3.45—3.51 (2H, m), 3.63 (3H, s), 3.80 (1H, br), 4.04 (1H, br), 4.56 (2H, s), 4.88 (1H, dm, *J*=9.8 Hz), 4.94 (1H, dm, *J*=17 Hz), 5.71—5.80 (1H, m); ^{13}C-NMR (75 MHz) δ 19.35 (q), 21.73 (t), 22.12 (t), 27.15 (t), 27.47 (t), 28.83 (t), 29.03 (t), 29.37 (t), 30.78 (d), 32.96 (t), 33.70 (t), 35.34 (t), 50.84 (d), 52.25 (q), 54.96 (q), 56.58 (d), 67.47 (t), 96.16 (t), 113.95 (t), 138.82 (d), 157.27 (s); MS *m/z*: 369 (M^+); HR-MS Calcd for $C_{21}H_{39}NO_4$ 369.2877, Found 369.2871; $[\alpha]_D^{26}$ −5.20° (*c*=11.0, $CHCl_3$).

8-Methyl-5-oct-7-enyloctahydroindolizine (5) To a stirred solution of *n*-PrSH (0.55 ml, 5.99 mmol) in HMPA (4 ml) was added a solution of *n*-BuLi (1.6 M in hexane, 3.6 ml, 5.77 mmol) at 0 °C, and the reaction mixture was stirred at 0 °C for 30 min. To the reaction mixture was added dropwise a solution of **16** (220 mg, 0.60 mmol) in THF (6 ml) *via* a double-tipped stainless needle. The reaction was stirred at room temperature for 49 h, and quenched with 28% NH_3 (aq.). The aqueous mixture was extracted with Et_2O (10 ml×10), and the organic extracts were combined, dried over K_2CO_3, and evaporated to give pale yellow oil, which was used directly in the next step.

To a solution of the above oil in MeOH (15 ml) was added conc. HCl (10 drops), and the reaction mixture was heated at reflux for 1 h. After cooling, the solvent was evaporated, and the residue was washed with Et_2O. To the residue was added 28% NH_3 (aq.), and the aqueous mixture was extracted with $CHCl_3$ (10 ml×10). The organic extracts were combined, dried over K_2CO_3, and evaporated to give pale yellow oil, which was used directly in the next step.

To a stirred solution of the above oil in CH_2Cl_2 (10 ml) were added CBr_4 (280 mg, 0.84 mmol) and Ph_3P (237 mg, 0.90 mmol) at 0 °C, and the resulting mixture was stirred at 0 °C for 1 h. To the reaction mixture was added triethylamine (1.33 ml, 9.66 mmol), and the stirring was continued for

30 min at room temperature. The volatiles were removed, and the residue was extracted with pentane (10 ml×4). The solvent was evaporated to give pale orange solid, which was chromatographed on SiO_2 (20 g, hexane : acetone=20 : 1) to afford **5** (83 mg, 56%) as pale yellow oil.

IR (neat) 3077, 2936, 2870, 2779, 2702, 1640, 1455, 1332, 1243, 1166, 1133, 1109, 992, 907 cm^{-1}; ^{1}H-NMR (500 MHz) δ 0.85 (3H, d, J=6.4 Hz), 0.87—0.98 (1H, m), 1.17—1.54 (13H, br m), 1.58—1.66 (2H, m), 1.70—1.85 (3H, br m), 1.84 (1H, m), 1.90—1.98 (2H, m), 2.01—2.05 (2H, m), 3.25 (1H, t-like, J=8.0 Hz), 4.91 (1H, dd, J=10.2, 2.2 Hz), 5.00 (1H, dd, J=16.8, 2.2 Hz), 5.80 (1H, m); ^{13}C-NMR (75 MHz) δ 18.96 (q), 20.42 (t), 25.82 (t), 28.93 (t), 29.13 (two t), 29.95 (t), 31.29 (t), 33.74 (t), 33.83 (t), 34.66 (t), 36.62 (d), 51.86 (t), 63.51 (d), 71.31 (d), 114.00 (t), 138.98 (d); MS m/z: 249 (M^+); HR-MS Calcd for $C_{17}H_{31}N$ 249.2455; Found 249.2450; $[\alpha]_D^{26}$ −73.1° (c=3.44, $CHCl_3$).

Methyl 6-[5-(*tert*-Butyldiphenylsilyloxy)pent-1-enyl]-2-(3-methoxymethoxypropyl)-3-methylpiperidine-1-carboxylate (17) To a stirred solution of $(COCl)_2$ (0.14 ml, 1.59 mmol) in CH_2Cl_2 (2 ml) was added DMSO (0.22 ml, 3.18 mmol) at −78 °C, and the resulting solution was stirred at −78 °C for 5 min. To the mixture was added dropwise a solution of **10** (300 mg, 1.04 mmol) in CH_2Cl_2 (2 ml) *via* a double-tipped stainless steel needle. After the reaction mixture was stirred for 30 min at −78 °C, triethylamine (0.64 ml, 4.77 mmol) was added to the reaction mixture. The reaction mixture was warmed to 0 °C for 1 h, and quenched with H_2O. The aqueous mixture was extracted with Et_2O (10 ml×3). The organic extracts were combined, dried, and evaporated to give pale yellow oil, which was used directly in the next step.

To a stirred suspension of $TBDPSO(CH_2)_4P^+Ph_3Br^-$ (2.72 g, 4.16 mmol) in THF (18 ml) was added a solution of *n*-BuLi (1.6 M in hexane, 2.5 ml, 3.95 mmol) at 0 °C, and the resulting orange solution was stirred at 0 °C for 10 min. To the mixture was added dropwise a solution of the above aldehyde in THF (4 ml) *via* a double-tipped stainless needle. The reaction was stirred at room temperature for 21 h, and quenched with H_2O. The aqueous mixture was extracted with Et_2O (15 ml×3). The organic extracts were combined, dried, and evaporated to give pale yellow oil, which was chromatographed on SiO_2 (20 g, hexane : acetone=60 : 1—20 : 1) to afford **17** (584 mg, 97%) as pale yellow oil.

IR (neat) 2952, 1692 cm^{-1}; ^{1}H-NMR (500 MHz) δ 1.03 (3H, d, J=7.3 Hz), 1.07 (9H, s), 1.17—1.22 (1H, m), 1.27—1.33 (1H, m), 1.55—1.93 (9H, br m), 2.17—2.23 (1H, m), 2.29—2.35 (1H, m), 3.37 (3H, s), 3.49—3.57 (2h, m), 3.63 (3H, s), 3.69 (2H, t-like, J=6.4 Hz), 3.92 (1H, br), 4.62 (2H, s), 4.96 (1h, br), 5.35—5.40 (1H, m), 5.56—5.60 (1H, m), 7.38—7.45 (6H, m), 7.68—7.74 (4H, m); MS m/z: 581 (M^+).

Methyl 6-(5-Hydroxypentyl)-2-(3-methoxymethoxypropyl)-3-methylpiperidine-1-carboxylate (18) To a stirred solution of **17** (581 mg, 1 mmol) in EtOAc (20 ml) was added 10% Pd–C (100 mg), and the resulting suspension was hydrogenated under hydrogen atmosphere at 1 atm for 48 h. The catalyst was removed by filtration and the filtrate was evaporated to give colorless oil, which was used directly in the next step.

To a stirred solution of the above oil in THF (8 ml) was added a solution of TBAF (1 M in THF, 1.1 ml, 1.1 mmol) at 0 °C, and the mixture was stirred at room temperature for 2 h. The reaction was quenched with satd. NH_4Cl (aq.), and the aqueous mixture was extracted with $CHCl_3$ (10 ml×7). The organic extracts were combined, dried, and evaporated to give colorless oil, which was chromatographed on SiO_2 (20 g, hexane : acetone=15 : 1—2 : 1) to afford **18** (246 mg, 74%) as colorless oil.

IR (neat) 3444, 2945, 1678 cm^{-1}; ^{1}H-NMR (500 MHz) δ 0.96 (3H, d, J=6.9 Hz), 1.12—1.83 (16H, br m), 2.43 (1H, br), 3.31 (3H, s), 3.47 (2H, m), 3.56 (2H, t-like, J=6.6 Hz), 3.62 (3H, s), 3.80 (1H, br), 4.06 (1H, br), 4.56 (2H, s); ^{13}C-NMR (75 MHz) δ 19.35 (q), 21.70 (t), 22.22 (t), 25.47 (t), 26.75 (t), 27.47 (t), 30.78 (d), 32.54 (t), 32.96 (t), 35.26 (t), 50.64 (d), 52.38 (q), 55.03 (q), 56.65 (d), 62.46 (t), 67.52 (t), 96.19 (t), 157.40 (s); MS m/z: 345 (M^+); HR-MS Calcd for $C_{18}H_{35}NO_5$ 345.2513; Found 345.2533; $[\alpha]_D^{26}$ −9.0° (c=4.71, $CHCl_3$).

Methyl 6-Hex-5-enyl-2-(3-methoxymethoxypropyl)-3-methylpiperidine-1-carboxylate (19) To a stirred solution of $(COCl)_2$ (0.1 ml, 1.15 mmol) in CH_2Cl_2 (2 ml) was added DMSO (0.17 ml, 2.30 mmol) at −78 °C, and the resulting solution was stirred at −78 °C for 5 min. To the mixture was added dropwise a solution of **18** (120 mg, 0.35 mmol) in CH_2Cl_2 (2 ml) *via* a double-tipped stainless steel needle. After the reaction mixture was stirred for 30 min at −78 °C, triethylamine (0.5 ml, 3.45 mmol) was added to the reaction mixture. The reaction mixture was warmed to 0 °C for 1 h, and quenched with H_2O. The aqueous mixture was extracted with Et_2O (10 ml×3). The organic extracts were combined, dried, and evaporated to give pale yellow oil, which was used directly in the next step.

To a stirred suspension of $MeP^+Ph_3I^-$ (700 mg, 1.74 mmol) in THF (8 ml) was added a solution of *n*-BuLi (1.6 M in hexane, 1.04 ml, 1.67 mmol) at 0 °C, and the resulting orange solution was stirred at 0 °C for 10 min. To the mixture was added dropwise a solution of the above aldehyde in THF (4 ml) *via* a double-tipped stainless needle. The reaction was stirred at room temperature for 22 h, and quenched with H_2O. The aqueous mixture was extracted with Et_2O (15 ml×3). The organic extracts were combined, dried, and evaporated to give pale yellow oil, which was chromatographed on SiO_2 (20 g, hexane : acetone=60 : 1—20 : 1) to afford **19** (104 mg, 88%) as pale yellow oil.

IR (neat) 3071, 2942, 1692 cm^{-1}; ^{1}H-NMR (500 MHz) δ 1.00 (3H, d, J=6.8 Hz), 1.13—1.85 (15H, br m), 2.03 (2H, q-like, J=7.3 Hz), 3.34 (3H, s), 3.48—3.54 (2H, m), 3.66 (3H, s), 3.80 (1H, br), 4.07 (1H, br), 4.60 (2H, s), 4.91 (1H, d-like, J=10.3 Hz), 4.99 (1H, d-like, J=15 Hz), 5.74—5.82 (1H, m); ^{13}C-NMR (75 MHz) δ 19.42 (q), 21.78 (t), 22.17 (t), 26.71 (t), 27.54 (t), 28.80 (t), 30.81 (d), 33.04 (t), 33.70 (t), 35.19 (t), 50.87 (d), 52.34 (q), 55.06 (q), 56.66 (t), 96.24 (t), 114.18 (t), 138.71 (d), 157.35 (s); MS m/z: 341 (M^+); HR-MS Calcd for $C_{19}H_{35}NO_4$ 341.2564, Found 341.2573; $[\alpha]_D^{26}$ −5.2° (c=3.93, $CHCl_3$).

5-Hex-5-enyl-8-methyloctahydroindolizine (4) To a stirred solution of *n*-PrSH (0.35 ml, 3.81 mmol) in HMPA (2.5 ml) was added a solution of *n*-BuLi (1.6 M in hexane, 2.3 ml, 3.63 mmol) at 0 °C, and the reaction mixture was stirred at 0 °C for 30 min. To the reaction mixture was added dropwise a solution of **19** (130 mg, 0.38 mmol) in THF (3 ml) *via* a double-tipped stainless needle. The reaction was stirred at room temperature for 49 h, and quenched with 28% NH_3 (aq.). The aqueous mixture was extracted with Et_2O (10 ml×10), and the organic extracts were combined, dried over K_2CO_3, and evaporated to give pale yellow oil, which was used directly in the next step.

To a solution of the above oil in MeOH (6 ml) was added conc. HCl (8 drops), and the reaction mixture was heated at reflux for 1 h. After cooling, the solvent was evaporated, and the residue was washed with Et_2O. To the residue was added 28% NH_3 (aq.), and the aqueous mixture was extracted with $CHCl_3$ (10 ml×10). The organic extracts were combined, dried over K_2CO_3, and evaporated to give pale yellow oil, which was used directly in the next step.

To a stirred solution of the above oil in CH_2Cl_2 (6 ml) were added CBr_4 (177 mg, 0.53 mmol) and Ph_3P (150 mg, 0.57 mmol) at 0 °C, and the resulting mixture was stirred at 0 °C for 1 h. To the reaction mixture was added triethylamine (0.84 ml, 6.10 mmol), and the stirring was continued for 30 min at room temperature. The volatiles were removed, and the residue was extracted with pentane (5 ml×4). The solvent was evaporated to give pale orange solid, which was chromatographed on SiO_2 (20 g, hexane : acetone=20 : 1) to afford **4** (43 mg, 51%) as pale yellow oil.

IR (neat) 3076, 2935, 2871, 2776, 2702, 1642, 1458, 1334, 1243, 1165, 1132, 1108, 1088, 992, 909 cm^{-1}; ^{1}H-NMR (500 MHz) δ 0.86 (3H, d, J=6.3 Hz), 0.93—0.98 (1H, m), 1.20—2.08 (19H, br m), 3.30 (1H, t-like, J=8.8 Hz), 4.91 (1H, dm, J=10.1 Hz), 4.99 (1H, dm, J=17.1 Hz), 5.73—5.86 (1H, m); ^{13}C-NMR (75 MHz) δ 18.95 (q), 20.36 (t), 25.39 (t), 28.98 (t), 29.32 (t), 31.05 (t), 33.62 (t), 33.78 (t), 34.27 (d), 51.78 (t), 63.67 (d), 71.48 (d), 114.25 (t), 138.84 (d); MS m/z: 221 (M^+); HR-MS Calcd for $C_{15}H_{27}N$ 221.2142; Found 221.2157; $[\alpha]_D^{26}$ −103.9° (c=0.60, $CHCl_3$).

Acknowledgments We are grateful to Drs. Jhon W. Daly, Thomas F. Spande, and H. Martin Garraffo, NIH, for comparison of synthetic **237D** with natural product. This work was supported in part by The Research Foundation for Pharmaceutical Sciences.

References and Notes

1) Daly J. W., *J. Med. Chem.*, **46**, 445—452 (2003).
2) Daly J. W., Garraffo H. M., Spande T. F., "Alkaloids: Chemical and Biological Perspective," Vol. 13, ed. by Pelletier S. W., Pergamon Press, New York, 1999, pp. 1—161.
3) Daly J. W., "The Alkaloids," Vol. 50, ed. by Cordell G. A., Academic Press, New York, 1998, pp. 141—169.
4) Tsuneki H., You Y., Toyooka N., Kagawa S., Kobayashi S., Sasaoka T., Nemoto H., Kimura I., Dani J. A., *Mol. Pharmacol.*, **66**, 1061—1069 (2004).
5) Chavez-Noriega L. E., Crona J. H., Washburn M. S., Urrutia A., Elliott K. L., Johnson E. C., *J. Pharmacol. Exp. Ther.*, **280**, 346—356 (1997).
6) Toyooka N., Nemoto H., "Studies in Natural Products Chemistry," Vol. 29, ed. by Atta-ur-Rahman, Elsevier, Amsterdam, 2003, pp. 419—448.
7) Toyooka N., Nemoto H., *Recent Res. Devel. Organic Chem.*, **6**, 611—624 (2002).

8) Toyooka N., Nemoto H., *Trends in Heterocyclic Chemistry*, **8**, 145—154 (2002).
9) Toyooka N., Kawasaki M., Nemoto H., Daly J. W., Spande T. F., Garraffo H. M., *Heterocycles*, **65**, 5—8 (2005).
10) Toyooka N., Fukutome A., Shinoda H., Nemoto H., *Angew. Chem. Int. Ed.*, **42**, 3808—3810 (2003).
11) Toyooka N., Fukutome A., Shinoda H., Nemoto H., *Tetrahedron*, **60**, 6197—6216 (2004).
12) Corey E. J., Yuen P., *Tetrahedron Lett.*, **30**, 5825—5828 (1989).
13) Shishido Y., Kibayashi C., *J. Org. Chem.*, **57**, 2876—2883 (1992).
14) Comins D. L., LaMunyon D. H., Chen X., *J. Org. Chem.*, **62**, 8182—8187 (1997).