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Synthesis and Biological Activities of the 3,5-Disubstituted Indolizidine Poison Frog Alkaloid 239Q and Its Congeners

Xu Wang,[a] Hiroshi Tsuneki,*[b] Noriko Urata,[a] Yasuhiro Tezuka,[c] Tsutomu Wada,[b] Toshiyasu Sasaoka,[b] Hideki Sakai,[b] Ralph A. Saporito,[d] and Naoki Toyooka*[a,e]

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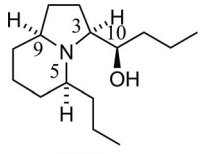
The first total synthesis of the 3,5-disubstituted indolizidine toad alkaloid **239Q** from the known pyrrolidine **1** has been achieved, in seven steps with a 35 % overall yield. The relative stereochemistry of natural **239Q** was determined unambiguously by comparison of GC-FTIR spectra of synthetic material with the skin extracts of the toad *Melanophryniscus cupreuscapularis*. The C7 congeners at the 5-position (**12** and **13**) showed strong antagonist activities on the α4β2 nicotinic acetylcholine receptors.

Introduction

The 3,5-disubstituted indolizidine alkaloid **239Q** (3,5-I, Figure 1) was isolated from methanol extracts of two species of toads (*Melanophryniscus klappenbachi* and *Melanophryniscus cupreuscapularis*) from Argentina as a major alkaloid, along with the 4,6-disubstituted quinolizidine **275I**.[1] The structure and relative stereochemistry of natural 3,5-I **239Q** were determined by mass, FTIR, and NMR spectral analysis to correspond to (5*Z*,9*Z*)-3-(1-hydroxybutyl)-5-propylindolizidine, but no total synthesis has been reported to date. In most cases, the odd-numbered carbon side chains of indolizidines present in frog skin and/or arthropods are at the C-5 position, but 3,5-I **239Q** possesses an unusual butyl side chain with a hydroxy group. From the FTIR and ^{1}H NMR spectra, the location of the hydroxy group in 3,5-I **239Q** is anticipated not to be terminal, but instead at C-10 (Figure 1), which has also previously been reported for the 3,5-disubstituted indolizidine **239AB** and the 5,8-disubstituted indolizidine **239D**.[2] As part of a program directed towards study of the synthesis and biological activities of poison frog alkaloids,[3] here we report the synthesis of 3,5-disubstituted indolizidine **239Q** and its congeners and the determination of their pharmacological activities on nicotinic acetylcholine receptors.



239Q

Figure 1. Structure of **239Q**.

Synthesis

The synthesis began with the known pyrrolidine **1** (Scheme 1).[4] Reduction of **1** with Super-Hydride, followed by oxidation of the resulting alcohol **2** with PCC, gave aldehyde **3**. Treatment of **3** with *n*PrMgBr resulted in alcohols **4a** and **4b** in 1:1 ratio and 85% combined yield. Use of $(n\text{Pr})_2\text{Zn}$ instead of the Grignard reagent resulted in a 48% yield of the single alcohol isomer **4a**. The stereochemistry at the newly formed carbinol positions of **4a** and **4b** was determined by NOE experiments with the corresponding oxazolizinone **7**.

The selectivity of the above addition reaction to **3** was not quite satisfactory, and so we next examined the reduction of ketone **5**, derived from the mixture of alcohols

[a] Graduate School of Science and Technology for Research, University of Toyama,
3190 Gofuku, Toyama 930–8555, Japan
Homepage: http://pse.eng.u-toyama.ac.jp/life/research.html#lab7a
[b] Graduate School of Medicine and Pharmaceutical Sciences, University of Toyama,
2630 Sugitani, Toyama 930–0194, Japan
Homepage: http://www.pha.u-toyama.ac.jp/clinphar/index-j.html
[c] Institute of Natural Medicine, University of Toyama,
2630 Sugitani, Toyama 930–0194, Japan
[d] Department of Biology, John Carroll University, University Heights,
Ohio 44118, USA
[e] Graduate School of Innovative Life Science, University of Toyama,
3190 Gofuku, Toyama 930–8555, Japan
Homepage: http://www.ils.u-toyama.ac.jp/index-e.html

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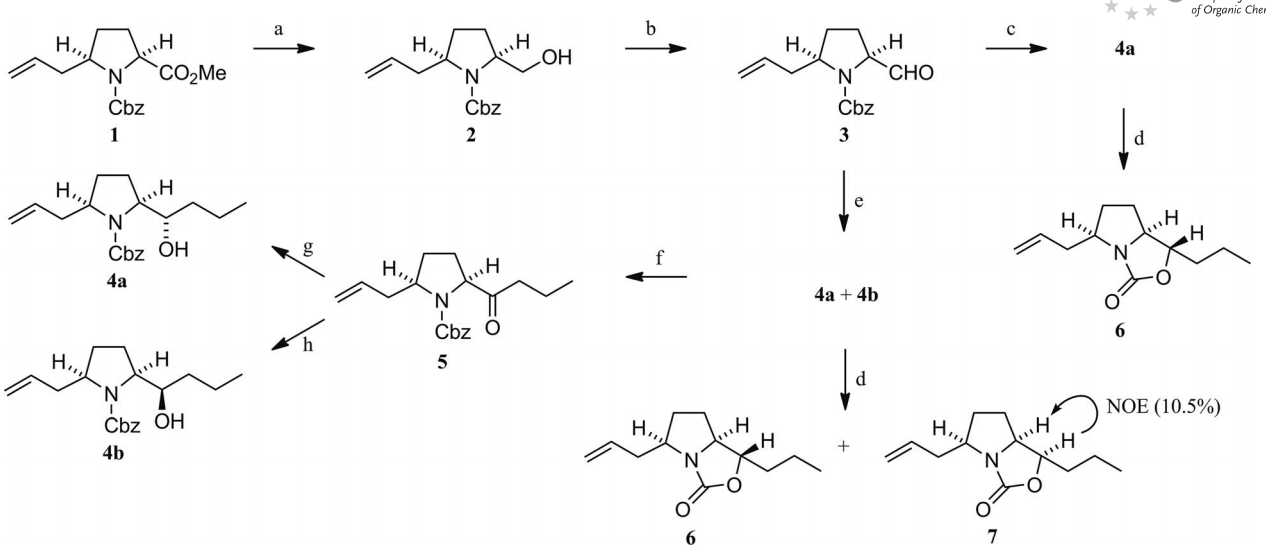


Scheme 1. Synthesis of alcohols **4a** and **4b** and determination of the orientations of their OH groups. *Reagents and conditions:* a) Super-Hydride, THF, 0 °C (99%); b) PCC, CH_2Cl_2, 0 °C to room temp. (74%); c) $(nPr)_2Zn$, THF, –78 °C to room temp. (48%); d) NaH, THF/DMF, 0 °C to room temp. [80% from **4a** to **6**, from **4a** and **4b** to **6** (45%) and **7** (43%)]; e) *n*PrMgBr, THF, 0 °C to room temp. (85%, *dr* = 1:1); f) PCC, CH_2Cl_2, 0 °C to room temp. (91%); g) $NaBH_4$, MeOH, 0 °C to room temp. (94%); h) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, 0 °C to room temp. (80%).

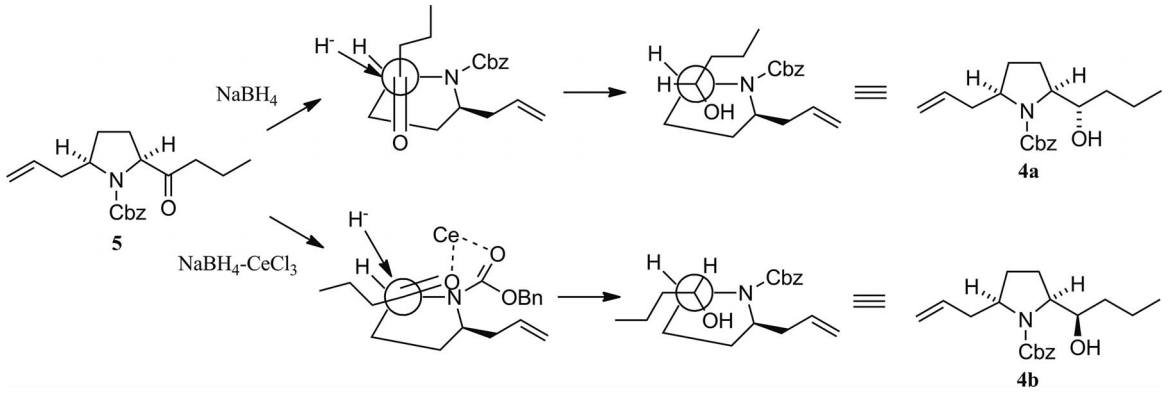
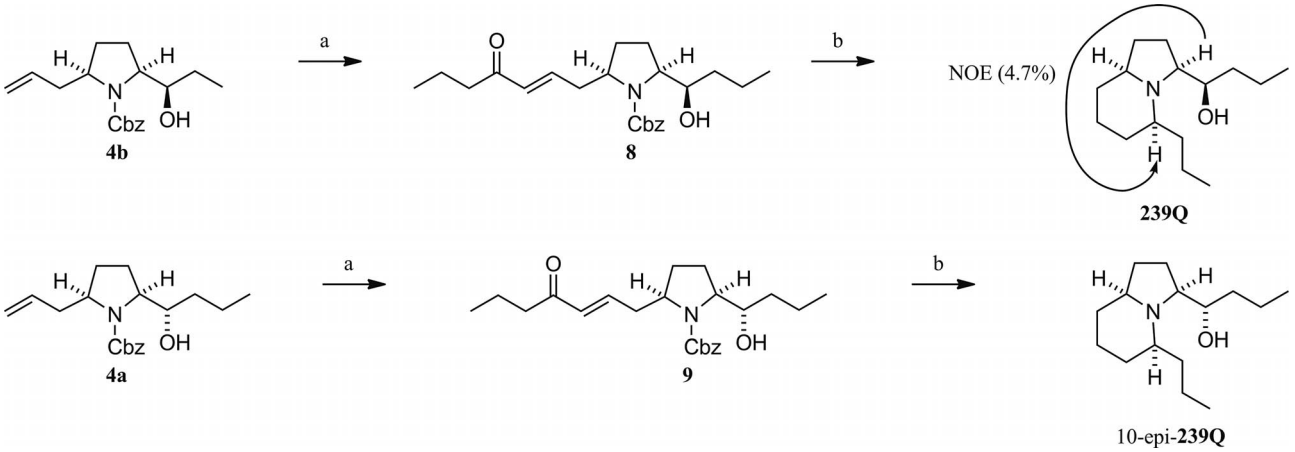


Figure 2. Stereoselectivity in the reduction of **5**.



Scheme 2. Synthesis of **239Q** and 10-*epi*-**239Q**. *Reagents and conditions:* a) Hex-1-en-3-one, second-generation Grubbs catalyst, CH_2Cl_2, reflux (94% from **4b** to **8**, 98% from **4a** to **9**); b) H_2, 20% $Pd(OH)_2$/C, MeOH (83% from **8** to **239Q**, 83% from **9** to 10-epi-**239Q**).

4a and **4b** by PCC oxidation. Reduction of **5** with DIBAL resulted in an almost 1:1 mixture of **4a** and **4b**, but under the Luche reduction conditions the alcohol **4b** was obtained as the major product (5:1, estimated from the ^{1}H NMR spectrum of crude product) with a 92% combined yield and an 80% isolated yield. The selectivity of the reduction of **5** with $NaBH_4$ in MeOH was very high, and we obtained the alcohol **4a** as the sole product in 94% yield. $NaBH_4$ reduction of **5** in the CH_2Cl_2/MeOH (10:1) solvent system, however, provided a 1:2.3 mixture of **4a** and **4b** in 95% combined yield..

The stereoselectivity of the reduction of **5** under the two sets of reaction conditions above was explained by the Felkin–Anh or chelation-controlled model as shown in Figure 2.

After the synthesis of alcohol **4b**, our attention was focused on the conversion of **4b** into the indolizidine **239Q**. A cross-metathesis reaction between **4b** and hex-1-en-3-one in the presence of the second-generation Grubbs catalysis[5] proceeded smoothly to afford the unsaturated ketone **8** (Scheme 2), which was subjected to a catalytic hydrogenation reaction to furnish the indolizidine **239Q** as a single stereoisomer in 85% yield. The stereochemistry of the synthetic indolizidine **239Q** was determined by the NOE experiments as shown in Scheme 2. The isomer 10-*epi*-**239Q** was also synthesized from **4a** via the corresponding unsaturated ketone **9** in a similar way.

Comparison of Synthetic 3,5-I 239Q and 3,5-I 10-*epi*-239Q with Natural 3,5-I 239Q

The newly synthesized 3,5-I **239Q** and 3,5-I 10-*epi*-**239Q** (see Scheme 2) were compared with the naturally occurring 3,5-I **239Q** present in the skin of the toad *Melanophrynsicus cupreuscapularis* by GC–MS and GC-FTIR. The GC–MS retention times and mass spectral properties of the synthetic **239Q**, the 10-epimer 10-*epi*-**239Q**, and natural **239Q** were identical. This was determined by analyzing each alkaloid individually, as well as by co-injection of all three alkaloids. The major GC peak for the co-injection of all three alkaloids had a retention time of 10.82, an EI base peak at *m*/*z* 166 accompanied by a peak at *m*/*z* 124 (ca. 15%), and a molecular weight of 239 as determined by CIMS (CH_3OH).

GC-FTIR vapor-phase infrared spectra indicated that the synthetic and natural **239Q** were indistinguishable from one another. Co-injection of both compounds resulted in a very broad absorption at 3528 cm^{-1}, a moderate Bohlmann band at 2798 cm^{-1}, and identical fingerprint regions (Figure 3a). Compound 10-*epi*-**239Q** showed a moderate Bohlmann band at 2798 cm^{-1}, but had a different absorption in the OH region (3649 cm^{-1}) and fingerprint region (Figure 3b). Therefore, from the retention times and the mass and FTIR spectral properties, the relative stereochemistries of the synthetic and natural **239Q** are considered identical.

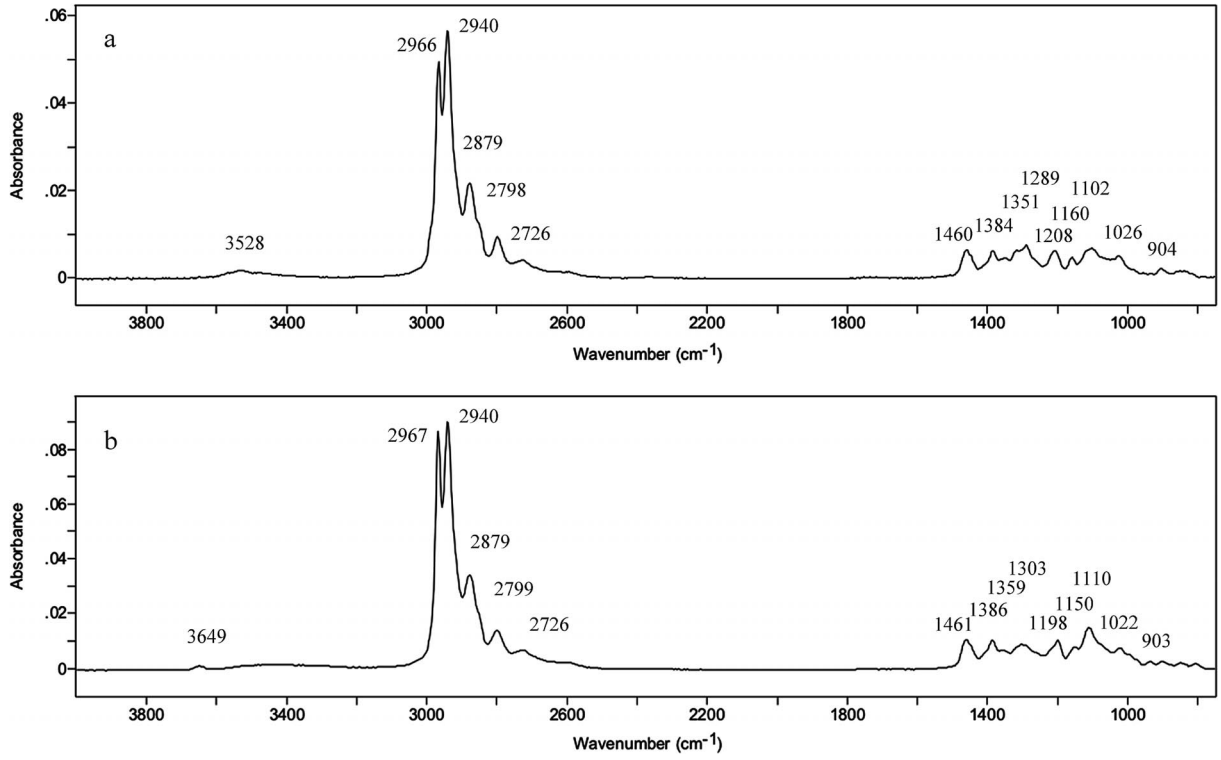


Figure 3. a) FTIR spectrum obtained after co-injection of *natural* and *synthetic* 3,5-disubstituted indolizidine **239Q**. b) FTIR of *synthetic* 3,5-disubstituted indolizidine 10-epimer 10-*epi*-**239Q**.

Our previous results on the pharmacological activities of synthetic poison frog alkaloids on nicotinic acetylcholine receptors showed that 5,8-disubstituted indolizidine (–)-**235B′** (Figure 4) displayed strong and selective antagonist activity for α4β2 nicotinic acetylcholine receptors,[6] and that the 5,8-disubstituted indolizidine (–)-**237D** also inhibited nicotine-evoked [^{3}H]dopamine release.[7] Alkaloids **235B′** and **237D** each possess a C7 side chain at the 5-positions in their indolizidine nuclei.

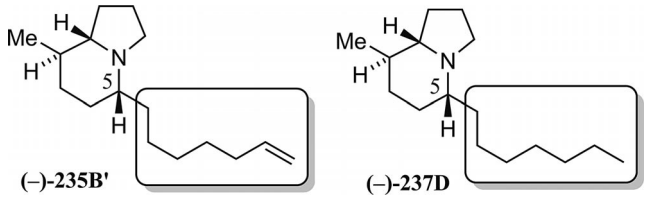
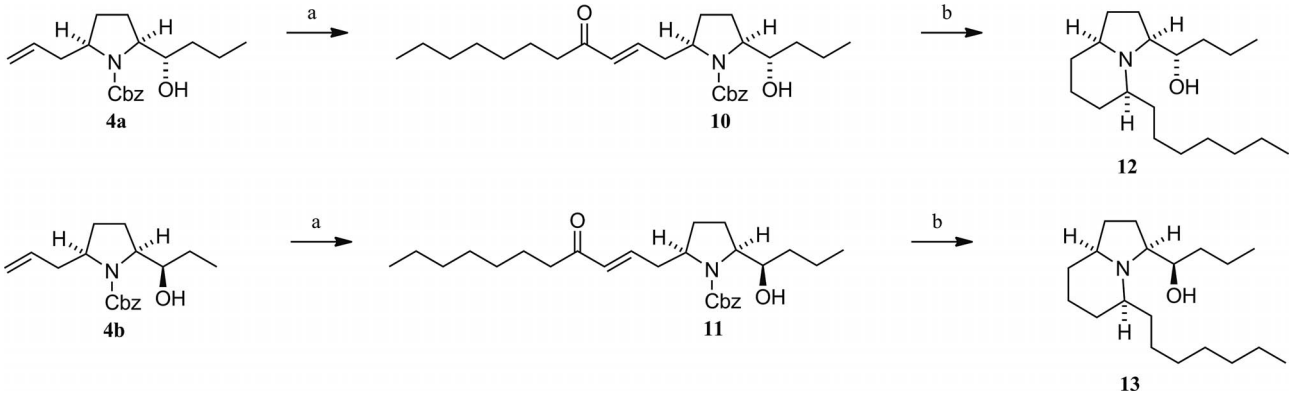


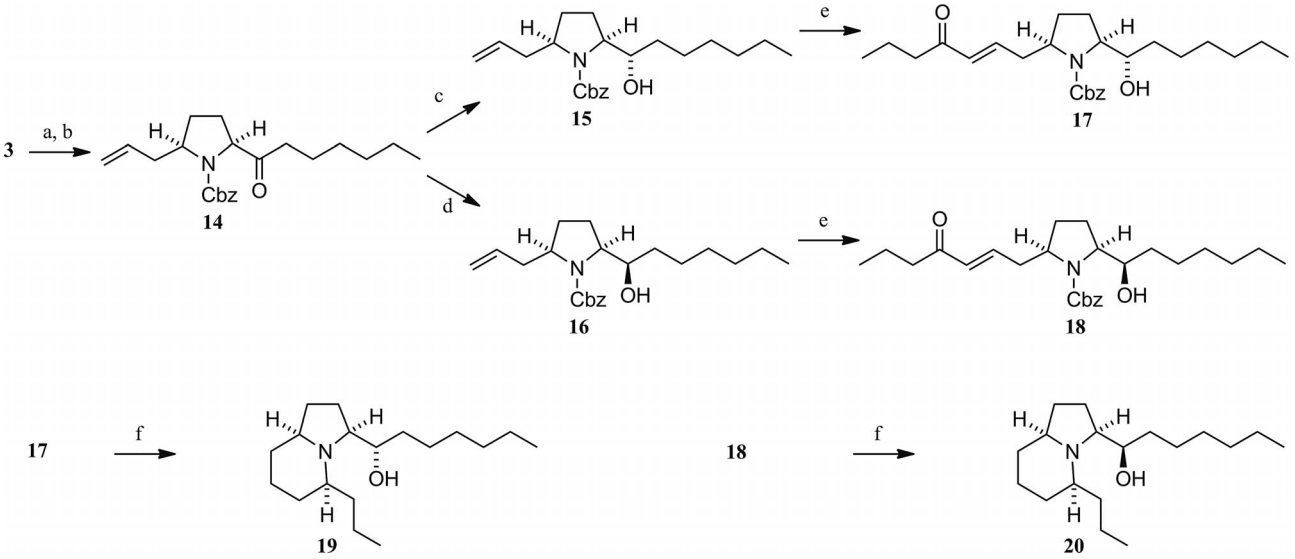
Figure 4. Structures of (–)-**235B′** and (–)-**237D**.

In view of these results, we planned the synthesis of C7 congeners **12** and **13** (Scheme 3), **19** and **20** (Scheme 4, below), and **21** and **22** (Scheme 5, below) of 3,5-I **239Q** to test their biological activities on nicotinic acetylcholine receptors. The alcohols **4a** and **4b** were converted into the unsaturated ketones **10** and **11**, which were subjected to hydrogenation to provide the congeners **12** and **13**.

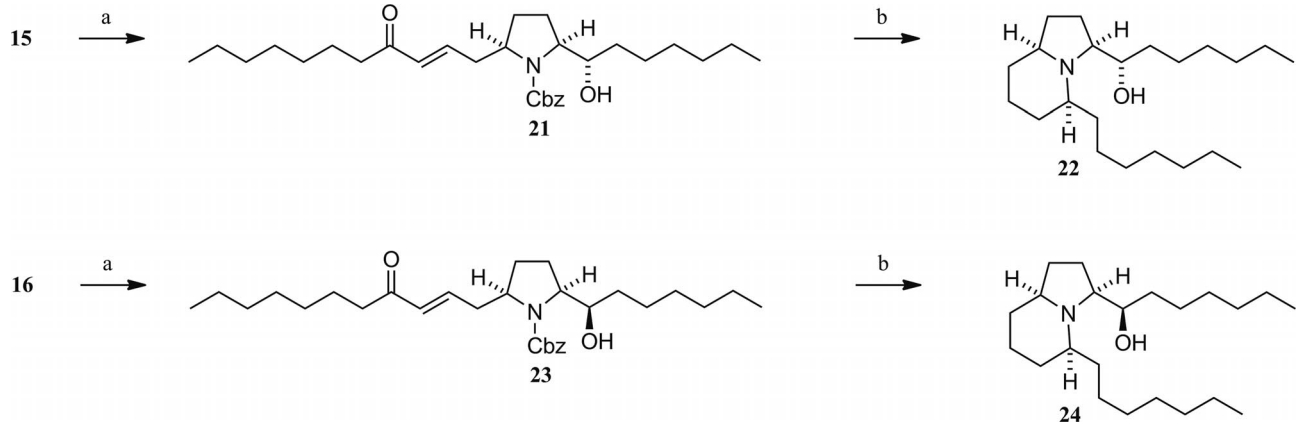
The ketone **14** (Scheme 4), derived from the aldehyde **3**, was transformed into the alcohols **15** and **16**, which were converted into the congeners **19** and **20** (Scheme 4) and **22** and **24** (Scheme 5), via the unsaturated ketones **17**, **18**, **21**, and **23**, by the same procedure.



Scheme 3. Synthesis of the **239Q** analogues **12** and **13**. *Reagents and conditions:* a) Dec-1-en-3-one,[8] second-generation Grubbs catalyst, CH_2Cl_2, reflux (80% from **4a** to **10**, 96% from **4b** to **11**); b) H_2, 20% $Pd(OH)_2$/C, MeOH (79% from **10** to **12**, 90% from **11** to **13**).



Scheme 4. Synthesis of the **239Q** analogues **19** and **20**. *Reagents and conditions:* a) *n*-HexylMgBr, THF, 0 °C to room temp. (75%); b) PCC, CH_2Cl_2, 0 °C to room temp. (89%); c) $NaBH_4$, MeOH, 0 °C to room temp. (90%, *dr* = 14:1); d) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, 0 °C to room temp. (80%, *dr* = 6:1); e) hex-1-en-3-one, second-generation Grubbs catalyst, CH_2Cl_2, reflux (94% from **15** to **17**, 99% from **16** to **18**); f) H_2, 20% $Pd(OH)_2$/C, MeOH (71% from **17** to **19**, 88% from **18** to **20**).



Scheme 5. Synthesis of the **239Q** analogues **22** and **24**. *Reagents and conditions:* a) Dec-1-en-3-one,[8] second-generation Grubbs catalyst, CH_2Cl_2, reflux (99% from **15** to **21**, 79% from **16** to **23**); b) H_2, 20% $Pd(OH)_2$/C, MeOH (66% from **21** to **22**, 62% from **23** to **24**).

Pharmacological Activities of Synthesized Alkaloids

To investigate the pharmacological activities of the synthesized alkaloids on nicotinic acetylcholine receptors, we conducted electrophysiological recordings from *Xenopus laevis* oocytes ectopically expressing nicotinic receptors by the methods described previously.[6] In brief, either the mixture of mouse α4 and β2 subunit cDNA in a ratio of 1:1 or the mouse α7 subunit cDNA alone was injected into *Xenopus* oocytes. The oocytes were then cultured for 4–8 days. An oocyte was placed in a recording chamber in which Ringer's solution [NaCl (82.5 mM), KCl (2.5 mM), $CaCl_2$ (2.5 mM), $MgCl_2$ (1 mM), and HEPES (5 mM), pH 7.4] containing atropine (1 μM, Sigma, MO) to block endogenous muscarinic receptors was perfused. Current responses were recorded in the two-electrode voltage-clamp mode at a holding potential of –60 mV, with a GeneClamp 500 amplifier and pClamp7 software (Axon Instruments, CA). After treatment with the synthetic alkaloid for 3 min, acetylcholine (ACh, Sigma, 1 μM for α4β2 nicotinic receptors, 1 mM for α7 nicotinic receptors) was applied in combination with the alkaloid for 5 s through a computer-controlled valve. Fittings of sigmoid concentration/inhibition curves were carried out with the aid of Prism software (GraphPad Software, Inc., CA) to calculate the half-maximum inhibitory concentration (IC_{50}) with 95% confidence interval (95% CI).

When the oocytes expressing recombinant α4β2 nicotinic receptors were treated with the alkaloid **239Q**, the peak amplitudes of the ACh-elicited currents were greatly decreased (Figure 5, a). The blocking effects of **239Q** were concentration-dependent, and the IC_{50} value was 11.0 μM (95% CI: 7.2–16.7). The **239Q** analogues **13**, possessing a C7 side chain at the 5-position, and **20**, possessing it at the 3-position, also showed concentration-dependent blocking effects on the α4β2-receptor-mediated currents (Figure 5, b and c). Analogue **13** was 22.0 times more potent than **239Q** in inhibiting α4β2 nicotinic receptors, whereas analogue **20** was 5.8 times more potent than **239Q**: the IC_{50} value of **13** was 0.5 μM (95% CI: 0.4–0.6) and that of **20** was 1.9 μM (95% CI: 1.3–2.7). In addition, **239Q** blocked the currents mediated by the α7 nicotinic receptor in a concentration-dependent manner, with an IC_{50} value of 5.7 μM (95% CI: 2.7–11.8), and **13** was 4.1 times more potent (IC_{50}: 1.4 μM, 95% CI: 0.8–2.3) than **239Q** (data not shown).

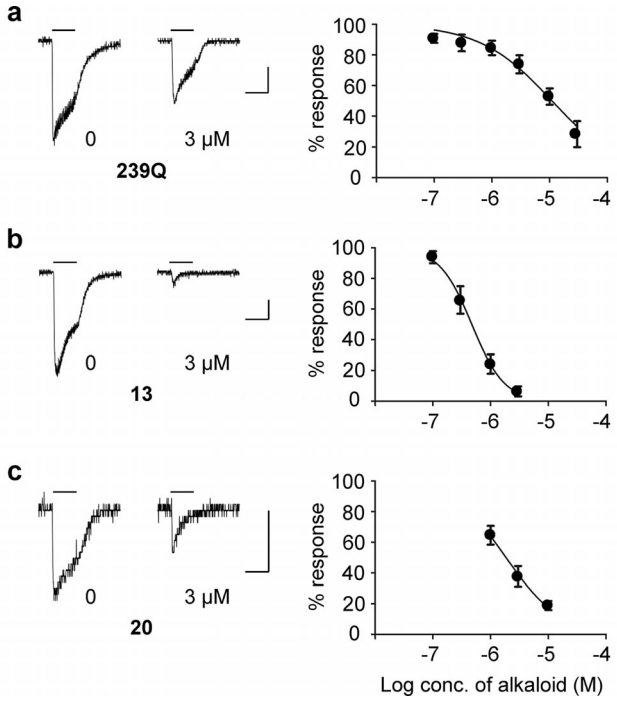


Figure 5. Inhibitory effects a) of the alkaloid **239Q**, and of its synthetic analogues b) **13**, and c) **20** on ACh-induced currents in *Xenopus* oocytes expressing α4β2 nicotinic acetylcholine receptors. Left. Typical traces showing the ACh-elicited (1 μM) currents through α4β2 nicotinic receptors in the absence or presence of the alkaloids (3 μM). Horizontal bars indicate the period of perfusion with ACh for 5 s. Vertical scale bars represent 500 nA. Right. Concentration/response curves for the alkaloids on α4β2 nicotinic receptors. The current responses to ACh in the presence of alkaloids in each oocyte were normalized to the ACh response in the presence of vehicle alone (0.1% dimethyl sulfoxide) in the same oocyte. Values represents the means ±S.E.M.s for three to six separate experiments.

To investigate the influence of C7 side chain addition to the 5- and/or 3-position(s) of the indolizidine nuclei on pharmacological activities further, the blocking effects of 10-*epi*-**239Q**, **12**, **19**, and **22** were compared. The analogue 10-*epi*-**239Q** blocked the currents mediated by the α4β2 nicotinic receptor in concentration-dependent manner (Figure 6, a) with an IC_{50} value of 2.7 μM (95% CI: 1.9–3.9). The analogue **12** (Figure 6, b), possessing a C7 side chain at the 5-position, was 3.9 times more potent than 10-*epi*-**239Q** in blocking the ACh-elicited currents through α4β2 nicotinic receptors, and its IC_{50} value was 0.7 μM (95% CI: 0.4–1.2). However, the effects of **19** (Figure 6, c), possessing a C7 side chain at the 3-position, were comparable to those of 10-*epi*-**239Q** (IC_{50}: 2.6 μM, 95% CI: 1.ng C7 side chains at both the 5- and the 3-positions, was 2.4 times less potent than 10-*epi*-**239Q** in inhibiting α4β2 nicotinic receptors (IC_{50}: 6.4 μM, 95% CI: 5.4–7.6). The blocking effects of all alkaloids tested on α4β2 and α7 nicotinic receptors were reversible, with the ACh responses being recovered 3–6 min after removal of the alkaloids (data not shown).

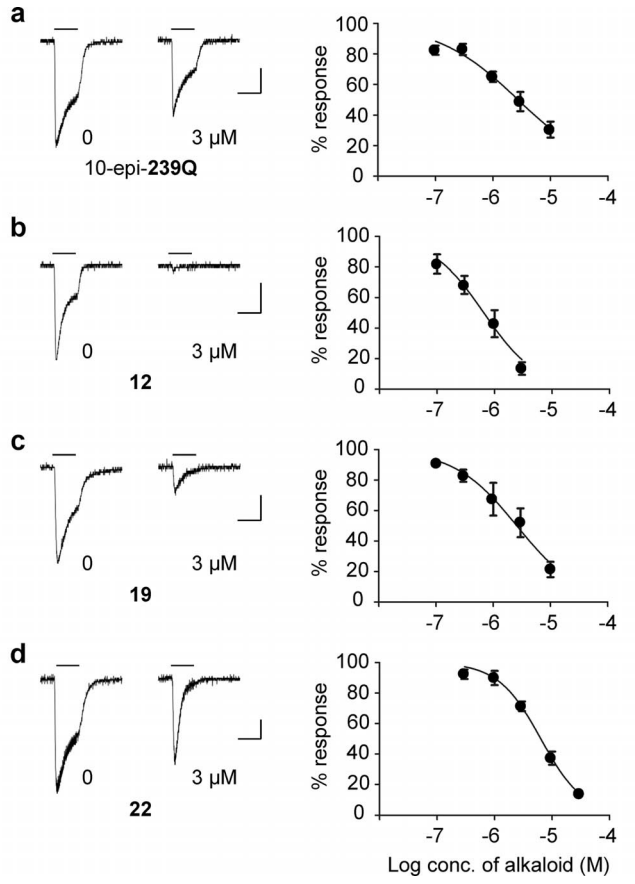


Figure 6. Inhibitory effects a) of the alkaloid 10-*epi*-**239Q**, and of its synthetic analogues b) **12**, c) **19**, and d) **22** on ACh-induced currents in *Xenopus* oocytes expressing α4β2 nicotinic acetylcholine receptors. Left. Typical traces showing the ACh (1 μM) elicited currents through α4β2 nicotinic receptors in the absence or presence of the alkaloids (3 μM). Horizontal bars indicate the period of perfusion with ACh for 5 s. Vertical scale bars represent 500 nA. Right. Concentration/response curves for the alkaloids on α4β2 nicotinic receptors. The current responses to ACh in the presence of alkaloids in each oocyte were normalized to the ACh response in the presence of vehicle alone (0.1% dimethyl sulfoxide) in the same oocyte. Values represents the means ±S.E.M.s for three to seven separate experiments.

Conclusions

We have achieved the first synthesis of the 3,5-disubstituted indolizidine poison frog alkaloid **239Q**, from the known pyrrolidine **1** in seven steps with 35% overall yield. The relative stereochemistry of natural **239Q** was determined by comparison of the GC-FTIR spectra of synthetic material with extracts of the skin of the toad *Melanophrynsicus cupreuscapularis*. Taken together, we found that **239Q** is a natural alkaloid that possesses antagonistic activities on α4β2 and α7 nicotinic acetylcholine receptors. In addition, a single C7 side chain added to the 5-position of **239Q**-related structure **13**, designed from the structure of (–)-**237D**, appears to serve as a moiety to enhance the blocking (antagonistic) activities against nicotinic acetylcholine receptors.

Experimental Section

General Information: Flash chromatography was performed with Kanto Kagaku silica gel (60N, 63–210 μm). NMR spectra were recorded with a JEOL a-GX 400 or ECP-NMR 600 spectrometer in the solvents indicated. Chemical shifts (δ) are given in ppm downfield from TMS and referenced to $CHCl_3$ (δ = 7.26 ppm) as an internal standard. Peak multiplicities are designated by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad and coupling constants (J) are given in Hz. High-resolution mass spectroscopic data were obtained with a JEOL MStation JMS-700 instrument. All commercial reagents were used as received unless otherwise noted.

Benzyl (2*S*,5*R*)-(–)-5-Allyl-2-(hydroxymethyl)pyrrolidine-1-carboxylate (2): A solution of Super-Hydride (1.02 M in THF, 4.56 mL, 4.65 mmol) was added at 0 °C to a stirred solution of ester **1**[4] (641 mg, 2.11 mmol) in THF (20 mL), and the resulting solution was stirred at 0 °C for 2 h. The reaction was quenched with ice/water, and the aqueous mixture was extracted with CH_2Cl_2 (10 mL × 4). The extracts were combined, dried with Na_2SO_4, and concentrated to afford the residue, which was chromatographed on silica gel (25 g, hexane/acetone 15:1 to 8:1) to give **2** (574 mg, 99%) as a colorless oil. $[\alpha]_D^{26}$ = –2.4 (c = 1.10, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.64–1.70 (m, 1 H), 1.74–1.78 (m, 1 H), 1.86–1.93 (m, 1 H), 1.99–2.09 (m, 1 H), 2.12–2.25 (m, 1 H), 2.30–2.41 (m, 1 H), 3.55–3.62 (m, 1 H), 3.70–3.73 (m, 1 H), 3.91–3.94 (m, 2 H), 4.45–4.53 (m, 1 H), 5.03 (d-like, J = 10.2 Hz, 2 H), 5.16 (ABq-like, J = 12.2 Hz, 2 H), 5.68–5.81 (m, 1 H), 7.26–7.38 (m, 5 H) ppm. ^{13}C NMR (100 MHz): δ = 26.61, 28.19, 39.47, 58.66, 61.95, 67.39, 67.71, 117.48, 127.90, 128.09, 128.50, 134.65, 136.30, 157.46 ppm. IR (neat): $\tilde{\nu}$ = 3427, 2950, 1682, 1412, 1354, 1111 cm^{-1}. MS (EI): m/z = 234 [M – C_3H_5]$^+$. HRMS calcd. for $C_{13}H_{16}NO_3$ [M – C_3H_5]$^+$ 234.1130; found 234.1125.

Benzyl (2*S*,5*R*)-5-Allyl-2-formylpyrrolidine-1-carboxylate (3): PCC (127 mg, 0.59 mmol) was added at 0 °C to a stirred solution of alcohol **2** (108 mg, 0.39 mmol) in CH_2Cl_2 (5 mL). The resulting suspension was stirred at room temperature for 20 h. The solvent was evaporated, and the residue was chromatographed on silica gel

(13 g, hexane/acetone 20:1 to 15:1) to give **3** (79 mg, 74%) as a colorless oil. The aldehyde was used immediately in the next step. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.73–1.80 (m, 1 H), 1.96–2.07 (m, 3 H), 2.11–2.25 (m, 1 H), 2.50 and 2.63 (m, 1 H), 4.02 and 4.10 (each br, 1 H), 4.19 and 4.28 (each br, 1 H), 5.01–5.09 (m, 2 H), 5.13–5.21 (m, 2 H), 5.68–5.81 (m, 1 H), 7.31–7.37 (m, 5 H), 9.46 and 9.55 (each s, 1 H) ppm.

Benzyl (2*S*,2α*S*,5*R*)-(–)-5-Allyl-2-(1-hydroxybutyl)pyrrolidine-1-carboxylate (4a) and Benzyl (2*S*,2α*R*,5*R*)-(–)-5-Allyl-2-(1-hydroxybutyl)pyrrolidine-1-carboxylate (4b): A solution of *n*PrMgBr (1.05 M in THF, 1.27 mL, 1.34 mmol) was added at 0 °C to a stirred solution of aldehyde **3** (73 mg, 0.27 mmol) in THF (5 mL) and the reaction mixture was stirred at room temperature for 20 h. The reaction was quenched with satd. NH_4Cl soln. and the aqueous mixture was extracted with CH_2Cl_2 (10 mL × 3). The extracts were combined, dried with Na_2SO_4, and concentrated to afford the residue, which was chromatographed on silica gel (20 g, hexane/acetone 30:1 to 25:1) to give **4a** and **4b** (73 mg, 85%) as a 1:1 mixture of diastereoisomers and as a colorless oil.

Benzyl (2*S*,5*R*)-(–)-5-Allyl-2-butyrylpyrrolidine-1-carboxylate (5): PCC (127 mg, 0.59 mmol) was added to a stirred solution of alcohols **4a** and **4b** (125 mg, 0.39 mmol) in CH_2Cl_2 (5 mL) and the resulting mixture was stirred at room temperature for 24 h. The solvent was evaporated and the residue was chromatographed on silica gel (20 g, hexane/EtOAc 20:1 to 10:1) to give **5** (113 mg, 91%) as a colorless oil. $[\alpha]_D^{20}$ = –20.2 (c = 0.95, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.80 and 0.92 (each t, J = 7.4 Hz, 3 H), 1.45–1.52 (m, 1 H), 1.60–1.67 (m, 2 H), 1.76–1.94 (m, 3 H), 2.05–2.19 (m, 2 H), 2.32–2.48 (m, 2 H), 4.05 and 3.98 (each br, 1 H), 4.33 and 4.42 (each t, J = 7.8 Hz, 1 H), 5.02 (d, J = 9.0 Hz, 2 H), 5.14 (d, J = 10.3 Hz, 2 H), 5.71–5.85 (m, 1 H), 7.27–7.37 (m, 5 H) ppm. ^{13}C NMR (100 MHz): δ = 13.62 and 13.72, 16.61 and 16.68, 27.05 and 28.04, 28.57 and 29.41, 38.46 and 39.10, 40.60 and 41.38, 58.22 and 58.88, 66.10 and 66.24, 67.11, 117.24, 127.75, 128.07, 128.44, 134.91 and 134.99, 136.31 and 136.55, 154.37 and 155.16, 209.37 and 209.57 ppm. IR (neat): $\tilde{\nu}$ = 2956, 1701, 1508, 1458, 1208 cm^{-1}. MS (EI): m/z = 274 [M – C_3H_5]$^+$. HRMS (EI): calcd. for $C_{16}H_{20}O_3N$ [M – C_3H_5]$^+$ 274.1444; found 274.1425.

Benzyl (2*S*,2α*S*,5*R*)-(–)-5-Allyl-2-(1-hydroxybutyl)pyrrolidine-1-carboxylate (4a) from 5: $NaBH_4$ (15 mg, 0.39 mmol) was added at 0 °C to a stirred solution of ketone **5** (51 mg, 0.16 mmol) in MeOH (2 mL) and the reaction mixture was stirred at room temperature for 22 h. The reaction was quenched with HCl (10%) and the aqueous mixture was extracted with CH_2Cl_2 (5 mL × 3). The organic extracts were combined, dried with Na_2SO_4, and concentrated to afford a residue, which was chromatographed on silica gel (15 g, hexane/acetone 30:1 to 25:1) to give **4a** (48 mg, 94%) as a colorless oil. $[\alpha]_D^{17}$ = –23.4 (c = 2.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.93 (t, J = 7.1 Hz, 3 H), 1.39–1.47 (m, 3 H), 1.50–1.59 (m, 1 H), 1.68–1.75 (m, 2 H), 1.76–1.90 (m, 1 H), 1.93–2.01 (m, 1 H), 2.13–2.20 (m, 1 H), 2.44 (br, 1 H), 3.48 (m, 1 H), 3.87 (m, 1 H), 4.04 (m, 1 H), 5.03 (m, 2 H), 5.12 and 5.19 (ABq, J = 12.2 Hz, 2 H), 5.71 (m, 1 H), 7.29–7.39 (m, 5 H) ppm. ^{13}C NMR (100 MHz): δ = 14.24, 18.32, 27.20, 28.75, 36.96, 39.53, 58.68, 64.57, 67.54, 76.41, 117.49, 127.93, 128.10, 128.53, 134.66, 136.56, 158.36 ppm. IR (neat): $\tilde{\nu}$ = 3442, 2961, 1670, 1508, 1406, 1113 cm^{-1}. MS (EI): m/z = 276 [M – C_3H_5]$^+$. HRMS (EI): calcd. for $C_{16}H_{22}O_3N$ [M – C_3H_5]$^+$ 276.1599; found 276.1577.

Benzyl (2*S*,2α*S*,5*R*)-(–)-5-Allyl-2-(1-hydroxybutyl)pyrrolidine-1-carboxylate (4a) from 3: A solution of (nPr)$_2$Zn [prepared from $ZnCl_2$ (334 mg, 2.45 mmol) and *n*PrMgBr (1.05 M in THF, 4.67 mL, 4.90 mmol) at room temperature for 0.5 h] was added at –78 °C to a stirred solution of aldehyde **3** (134 mg, 0.49 mmol) in THF (3 mL) and the reaction mixture was stirred at –78 °C to room temperature for 3 h. The reaction was quenched with aq. NH_4Cl and the aqueous mixture was extracted with CH_2Cl_2 (10 mL × 3). The organic extracts were combined, dried with Na_2SO_4, and concentrated to afford a residue, which was chromatographed on silica gel (15 g, hexane/acetone 30:1 to 25:1) to give **4a** (65 mg, 48%) as a colorless oil.

Benzyl (2*S*,2α*R*,5*R*)-(–)-5-Allyl-2-(1-hydroxybutyl)pyrrolidine-1-carboxylate (4b) from 5: $CeCl_3 \cdot 7H_2O$ (295 mg, 0.79 mmol) was added at 0 °C to a stirred solution of ketone **5** (100 mg, 0.32 mmol) in MeOH (4 mL), and the resulting mixture was stirred for 10 min. $NaBH_4$ (29 mg, 0.76 mmol) was added to the mixture at 0 °C and the reaction mixture was then stirred at room temperature for 17 h. The reaction was quenched with H_2O and the aqueous mixture was extracted with EtOAc (5 mL × 3). The extracts were combined, dried with Na_2SO_4, and concentrated to afford a residue, which was chromatographed on silica gel (15 g, hexane/acetone 30:1 to 25:1) to give **4a** (80 mg, 80%) as a colorless oil. $[\alpha]_D^{17}$ = –5.5 (c = 1.30, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.86–0.98 (m, 3 H), 1.26–1.34 (m, 3 H), 1.59–1.60 (m, 1 H), 1.68–1.78 (m, 2 H), 1.79–1.82 (m, 1 H), 1.84–1.89 (m, 1 H), 2.17–2.23 (m, 1 H), 2.43 (br, 1 H), 3.88–3.90 (m, 1 H), 3.96–3.98 (m, 1 H), 4.03–4.04 (m, 1 H), 5.05 (m, 2 H), 5.13 (s, 2 H), 5.63–5.76 (m, 1 H), 7.26–7.38 (m, 5 H) ppm. ^{13}C NMR (100 MHz): δ = 14.10, 19.44, 24.37, 28.54, 34.53, 39.56, 58.63, 60.35, 67.09, 70.75, 117.28, 127.86, 128.04, 128.51, 135.40, 136.55, 156.49 ppm. IR (neat): $\tilde{\nu}$ = 3421, 2934, 1684, 1412, 1354, 1103 cm^{-1}. MS (EI): m/z = 276 [M – C_3H_5]$^+$. HRMS (EI): calcd. for $C_{16}H_{22}O_3N$ [M – C_3H_5]$^+$ 276.1600; found 276.1590.

(1*S*,5*R*,8*S*)-5-Allyl-1-propyltetrahydropyrrolo[1,2-*c*]oxazol-3-one (6) from 4a: NaH (60%, 15 mg, 0.38 mmol) was added at 0 °C to a stirred solution of alcohol **4a** (78 mg, 0.25 mmol) in THF (3 mL) and DMF (1 mL) and the resulting solution was stirred at room temperature for 24 h. The reaction was quenched with H_2O and the aqueous mixture was extracted with CH_2Cl_2 (10 mL × 2). The organic extracts were combined, dried with Na_2SO_4, and concentrated to afford a residue, which was chromatographed on silica gel (10 g, hexane/acetone 30:1 to 25:1) to give **6** (42 mg, 80%) as a solid. M.p. 48–50 °C. $[\alpha]_D^{16}$ = +9.3 (c = 0.75, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (t, J = 7.4 Hz, 3 H), 1.27–1.43 (m, 2 H), 1.47–1.60 (m, 2 H), 1.69–1.78 (m, 1 H), 1.79–1.86 (m, 1 H), 1.93–1.99 (m, 1 H), 2.05–2.15 (m, 1 H), 2.29 (dt, J = 13.8, 8.4 Hz, 1 H), 2.85 (dm, J = 13.8 Hz, 1 H), 3.58 (tt, J = 3.1, 8.4 Hz, 1 H), 3.69 (ddd, J = 6.3, 8.6, 6.8 Hz, 1 H), 4.12 (dt, J = 6.3, 7.6 Hz, 1 H), 5.04 (d, J = 10.2 Hz, 1 H), 5.08 (d, J = 15.9 Hz, 1 H), 5.64–5.74 (m, 1 H) ppm. ^{13}C NMR (100 MHz): δ = 13.80, 18.14, 28.44, 33.13, 34.91, 36.13, 54.72, 66.75, 82.38, 118.22, 134.161, 155.93 ppm. IR (KBr): $\tilde{\nu}$ = 2959, 1740, 1398, 1069 cm^{-1}. MS (EI): m/z = 168 [M – C_3H_5]$^+$. HRMS (EI): calcd. for $C_9H_{14}O_2N$ [M – C_3H_5]$^+$ 168.1024; found 168.1008.

(1*S*,5*R*,8*S*)-5-Allyl-1-propyltetrahydropyrrolo[1,2-*c*]oxazol-3-one (6) and (1*R*,5*R*,8*S*)-5-Allyl-1-propyltetrahydropyrrolo[1,2-*c*]oxazol-3-one (7) from 4a and 4b: NaH (60%, 10 mg, 0.25 mmol) was added at 0 °C to a stirred solution of alcohols **4a** and **4b** (53 mg, 0.17 mmol) in THF (3 mL) and DMF (1 mL) and the resulting solution was stirred at room temperature for 20 h. The reaction was quenched with H_2O and the aqueous mixture was extracted with CH_2Cl_2 (10 mL × 2). The organic extracts were combined, dried with Na_2SO_4, and concentrated to afford a residue, which was chromatographed on silica gel (10 g, hexane/acetone 30:1 to 25:1) to give **6** (16 mg, 45%) and **7** (15 mg, 43%), both as solids.

(1*R*,5*R*,8*S*)-5-Allyl-1-propyltetrahydropyrrolo[1,2-*c*]oxazol-3-one (7): M.p. 42–44 °C. $[\alpha]_D^{17}$ = +45.7 (*c* = 0.40, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 7.4 Hz, 3 H), 1.24–1.45 (m, 2 H), 1.47–1.60 (m, 1 H), 1.61–1.71 (m, 3 H), 1.90–1.97 (m, 1 H), 2.03–2.13 (m, 1 H), 2.24 (dt, *J* = 13.9, 8.4 Hz, 1 H), 2.93 (dm, *J* = 13.9 Hz, 1 H), 3.55 (tt, *J* = 3.4, 8.4 Hz, 1 H), 4.13 (ddd, *J* = 6.0, 8.0, 8.5 Hz, 1 H), 4.44 (dt, *J* = 4.5, 8.5 Hz, 1 H), 5.04 (d, *J* = 11.2 Hz, 1 H), 5.08 (d, *J* = 17.3 Hz, 1 H), 5.65–5.75 (m, 1 H) ppm. ^{13}C NMR (100 MHz): δ = 13.80, 18.74, 23.34, 32.60, 33.23, 34.88, 54.79, 63.60, 76.30, 118.07, 134.41, 155.70 ppm. IR (KBr): $\tilde{\nu}$ = 2934, 1747, 1404, 1063 cm^{-1}. MS (EI): *m*/*z* = 168 $[M - C_3H_5]^+$. HRMS (EI): calcd. for $C_9H_{14}O_2N$ $[M - C_3H_5]^+$ 168.1024; found 168.1006.

Benzyl (2*S*,2α*R*,5*R*)-(+)-2-(1-Hydroxybutyl)-5-[(*E*)-4-oxohept-2-enyl]pyrrolidine-1-carboxylate (8): Hex-1-en-3-one (0.11 mL, 1.00 mmol) and the second-generation Grubbs catalyst (16 mg, 0.02 mmol) were added to a stirred solution of alcohol **4b** (62 mg, 0.20 mmol) in CH_2Cl_2 (3 mL), and the reaction mixture was heated at reflux for 23 h. After the mixture had cooled, the solvent was evaporated, and the residue was chromatographed on silica gel (15 g, hexane/acetone 15:1 to 10:1) to give **8** (71 mg, 94%) as a pale yellow oil. $[\alpha]_D^{26}$ = +8.4 (*c* = 1.35, $CHCl_3$).^1H NMR (400 MHz, $CDCl_3$): δ = 0.91 (t, *J* = 7.3 Hz, 6 H), 1.26–1.41 (m, 3 H), 1.56–1.65 (m, 4 H), 1.70 (br, 1 H), 1.87–2.01 (m, 2 H), 2.33 (br, 1 H), 2.40–2.44 (m, 2 H), 2.60–2.68 (br, 1 H), 3.82–3.92 (m, 1 H), 3.97 (br, 1 H), 4.10 (br, 1 H), 5.10 and 5.16 (ABq, *J* = 12.2 Hz, 2 H), 6.07 (d, *J* = 15.6 Hz, 1 H), 6.78 (br, 1 H), 7.32–7.35 (m, 5 H) ppm. ^{13}C NMR (100 MHz): δ = 13.69, 14.09, 17.49, 19.31, 23.94, 28.99, 34.85, 38.02, 42.03, 58.02, 64.88, 67.12, 70.43, 127.83, 128.05, 128.47, 131.97, 136.32, 143.04, 156.00, 200.39 ppm. IR (neat): $\tilde{\nu}$ = 3447, 2959, 1696, 1676, 1409, 1319, 1103 cm^{-1}. MS (EI): *m*/*z* = 387 $[M]^+$. HRMS (EI): calcd. for $C_{23}H_{33}NO_4$ $[M]^+$ 387.2409; found 387.2379.

239Q: $Pd(OH)_2$/C (20%, 5 mg) was added to a stirred solution of **8** (132 mg, 0.34 mmol) in MeOH (5 mL), and the resulting suspension was stirred under hydrogen at 1 atm for 24 h. The catalyst was removed by filtration and the filtrate was concentrated to afford a residue, which was chromatographed on silica gel (7 g, hexane/acetone 25:1 to 15:1) to give **239Q** (67 mg, 83%) as a pale yellow oil. $[\alpha]_D^{26}$ = +50.9 (*c* = 1.35, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 7.6 Hz, 3 H), 0.92 (t, *J* = 7.4 Hz, 3 H) 1.02–1.16 (m, 2 H), 1.17–1.42 (m, 7 H), 1.43–1.60 (m, 4 H), 1.63–1.68 (m, 1 H), 1.69–1.84 (m, 4 H), 2.20–2.35 (m, 2 H), 2.85 (d-like, *J* = 10.0 Hz, 1 H), 3.58 (br, 1 H) ppm. ^{13}C NMR (100 MHz): δ = 14.36, 14.41, 19.03, 19.59, 22.92, 24.85, 31.63, 32.07, 32.16, 35.58, 37.72, 64.25, 64.51, 67.10, 72.44 ppm. IR (neat): $\tilde{\nu}$ = 3452, 2957, 2932, 2870, 2795, 1456 cm^{-1}. MS (EI): *m*/*z* = 239 $[M]^+$. HRMS (EI): calcd. for $C_{15}H_{29}NO$ $[M]^+$ 239.2249; found 239.2251.

Benzyl (2*S*,2α*S*,5*R*)-(+)-2-(1-Hydroxybutyl)-5-[(*E*)-4-oxohept-2-enyl]pyrrolidine-1-carboxylate (9): Hex-1-en-3-one (0.09 mL, 0.79 mmol) and the second-generation Grubbs catalyst (13 mg, 0.016 mmol) were added to a stirred solution of alcohol **4a** (50 mg, 0.16 mmol) in CH_2Cl_2 (3 mL), and the reaction mixture was heated at reflux for 20 h. After the mixture had cooled, the solvent was evaporated, and the residue was chromatographed on silica gel (10 g, hexane/acetone 20:1 to 10:1) to give **9** (60 mg, 98%) as a pale yellow oil. $[\alpha]_D^{26}$ = +16.0 (*c* = 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.90 (t, *J* = 7.3 Hz, 6 H), 1.33–1.44 (m, 3 H), 1.53–1.60 (m, 3 H), 1.62–1.67 (m, 2 H), 1.91–1.95 (m, 2 H), 2.36 (br, 1 H), 2.43 (t-like, *J* = 7.2 Hz, 2 H), 2.53 (br, 1 H), 3.41–3.45 (m, 1 H), 3.86–3.87 (m, 1 H), 4.09 (br, 1 H), 5.12 (s, 2 H), 6.05 (d, *J* = 15.6 Hz, 1 H), 6.69–6.72 (m, 1 H), 7.28–7.36 (m, 5 H) ppm. ^{13}C NMR (100 MHz): δ = 13.60, 14.01, 17.37, 18.21, 27.03, 29.09, 36.75, 37.98, 41.75, 57.92, 64.43, 67.53, 75.87, 127.86, 128.07, 128.43, 132.40, 135.97, 142.25, 156.12, 200.25 ppm. IR (neat): $\tilde{\nu}$ = 3466, 2960, 1699, 1670, 1410, 1313, 1113 cm^{-1}. MS (EI): *m*/*z* = 387 $[M]^+$. HRMS (EI): calcd. for $C_{23}H_{34}NO_4$ $[M + H]^+$ 388.2488; found 388.2515.

10-*epi*-239Q: $Pd(OH)_2$/C (20%, 5 mg) was added to a stirred solution of **9** (111 mg, 0.29 mmol) in MeOH (5 mL), and the resulting suspension was stirred under hydrogen at 1 atm for 28 h. The catalyst was removed by filtration and the filtrate was concentrated to afford a residue, which was chromatographed on silica gel (10 g, hexane/acetone 25:1 to 15:1) to give 10-*epi*-**239Q** (57 mg, 83%) as a pale yellow oil. $[\alpha]_D^{26}$ = +84.5 (*c* = 1.25, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.90 (t, *J* = 7.1 Hz, 3 H), 0.93 (t, *J* = 6.8 Hz, 3 H), 1.01–1.10 (m, 1 H), 1.17–1.25 (m, 4 H), 1.28–1.38 (m, 4 H), 1.42–1.47 (m, 2 H), 1.51–1.57 (m, 2 H), 1.64–1.70 (m, 2 H),1.72–1.85 (m, 3 H), 2.28 (t-like, *J* = 9.7 Hz, 1 H), 2.35 (t-like, *J* = 10.2 Hz, 1 H), 2.83 (t, *J* = 7.3 Hz, 1 H), 2.96 (br, 1 H) ppm. ^{13}C NMR (100 MHz): δ = 14.29, 14.39, 19.67, 19.80, 25.28, 29.53, 30.60, 31.11, 33.15, 36.91, 38.19, 62.66, 63.78, 67.99, 74.30 ppm. IR (neat): $\tilde{\nu}$ = 3433, 2957, 2870, 2761, 1456, 1119 cm^{-1}. MS (EI): *m*/*z* = 239 $[M]^+$. HRMS (EI): calcd. for $C_{15}H_{30}NO$ $[M + H]^+$ 240.2328; found 240.2315.

Benzyl (2*S*,2α*S*,5*R*)-2-(1-Hydroxybutyl)-5-[(*E*)-4-oxoundec-2-enyl]pyrrolidine-1-carboxylate (10): Dec-1-en-3-one (95 mg, 0.61 mmol) and the second-generation Grubbs catalyst (16 mg, 0.02 mmol) were added to a stirred solution of alcohol **4a** (65 mg, 0.21 mmol) in CH_2Cl_2 (3 mL) and the reaction mixture was heated at reflux for 21 h. After the mixture had cooled, the solvent was evaporated and the residue was chromatographed on silica gel (15 g, hexane/acetone 15:1 to 10:1) to give **10** (73 mg, 80%) as a pale yellow oil. $[\alpha]_D^{26}$ = +6.1 (*c* = 0.80, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.8 Hz, 3 H), 0.92 (t, *J* = 6.8 Hz, 3 H), 1.21–1.32 (m, 9 H), 1.35–1.48 (m, 2 H), 1.53–1.63 (m, 3 H), 1.65–1.72 (m, 2 H), 1.86–2.03 (m, 2 H), 2.36 (br, 1 H), 2.47 (t, *J* = 7.4 Hz, 2 H), 2.57 (br, 1 H), 3.39–3.49 (m, 1 H), 3.85–3.93 (m, 1 H), 4.06–4.16 (m, 1 H), 5.16 (s, 2 H), 6.07 (d, *J* = 16.1 Hz, 1 H), 6.66–6.78 (m, 1 H), 7.29–7.39 (m, 5 H) ppm. ^{13}C NMR (100 MHz): δ = 14.00, 14.10, 18.32, 22.52, 22.53, 24.06, 27.16, 29.02, 29.17, 31.62, 36.92, 38.09, 40.09, 58.03, 64.44, 67.65, 76.68, 127.97, 128.18, 128.53, 132.48, 136.08, 142.24, 157.98, 200.50 ppm. IR (neat): $\tilde{\nu}$ = 3495, 2951, 1697, 1670, 1413, 1356, 1113 cm^{-1}. MS (EI): *m*/*z* = 443 $[M]^+$. HRMS (EI): calcd. for $C_{27}H_{41}NO_4$ $[M]^+$ 443.3036; found 443.3040.

(3*S*,3α*S*,5*S*,9*S*)-5-Heptyl-3-(1-hydroxybutyl)octahydroindolizine (12): $Pd(OH)_2$/C (20%, 5 mg) was added to a stirred solution of **10** (120 mg, 0.27 mmol) in MeOH (5 mL), and the resulting suspension was stirred under hydrogen at 1 atm for 23 h. The catalyst was removed by filtration and the filtrate was concentrated to give a residue, which was chromatographed on silica gel (10 g, hexane/acetone 40:1 to 30:1) to give **12** (63 mg, 79%) as a pale yellow oil. $[\alpha]_D^{26}$ = +63.4 (*c* = 1.10, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.8 Hz, 3 H), 0.94 (t, *J* = 6.9 Hz, 3 H), 1.01–1.11 (m, 1 H), 1.13–1.19 (m, 2 H), 1.20–1.31 (m, 9 H), 1.32–1.39 (m, 4 H), 1.42–1.47 (m, 2 H), 1.52–1.62 (m, 3 H), 1.64–1.71 (m, 2 H), 1.73–1.78 (m, 2 H), 1.83–1.87 (m, 1 H), 2.27 (t-like, *J* = 10.5 Hz, 1 H), 2.35 (t-like, *J* = 10.5 Hz, 1 H), 2.83 (t-like, *J* = 7.4 Hz, 1 H), 2.94–2.99 (m, 1 H) ppm. ^{13}C NMR (100 MHz): δ = 14.04, 14.27, 19.61, 22.61, 25.25, 26.68, 29.33, 29.51, 29.83, 30.60, 31.11, 31.78, 33.16, 34.75, 35.97, 62.68, 64.02, 67.96, 74.29 ppm. IR (neat): $\tilde{\nu}$ = 3368, 2928, 2858, 2793, 1456, 1302, 1109 cm^{-1}. MS (EI): *m*/*z* = 295 $[M]^+$. HRMS (EI): calcd. for $C_{19}H_{37}NO$ 295.2875; found 295.2861.

Benzyl (2*S*,2α*R*,5*R*)-2-(1-Hydroxybutyl)-5-[(*E*)-4-oxoundec-2-enyl]pyrrolidine-1-carboxylate (11): Dec-1-en-3-one (95 mg, 0.61 mmol)

and the second-generation Grubbs catalyst (16 mg, 0.02 mmol) were added to a stirred solution of alcohol **4b** (65 mg, 0.21 mmol) in CH_2Cl_2 (4 mL), and the reaction mixture was heated at reflux for 20 h. After the mixture had cooled, the solvent was evaporated, and the residue was chromatographed on silica gel (15 g, hexane/acetone 20:1 to 10:1) to give **11** (87 mg, 96%) as a pale yellow oil. $[\alpha]_D^{26}$ = +21.9 (*c* = 0.60, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.9 Hz, 3 H), 0.92 (br, 3 H), 1.21–1.37 (m, 11 H), 1.51–1.62 (m, 3 H), 1.70 (br, 1 H), 1.81–1.93 (m, 3 H), 2.34 (br, 1 H), 2.40–2.49 (m, 2 H), 2.60 (br, 1 H), 3.88 (br, 1 H), 3.94–4.01 (m, 1 H), 4.06–4.14 (m, 1 H), 5.10 and 5.17 (ABq, *J* = 12.3 Hz, 2 H), 6.08 (d, *J* = 15.9 Hz, 1 H), 6.76 (br, 1 H), 7.31–7.39 (m, 5 H) ppm. ^{13}C NMR (100 MHz): δ = 13.95, 14.05, 19.29, 22.49, 23.83, 24.05, 28.97, 29.12, 31.56, 34.91, 37.96, 40.01, 40.18, 57.99, 64.79, 67.06, 70.38, 127.78, 128.00, 128.43, 131.91, 136.31, 143.04, 155.92, 200.47 ppm. IR (neat): $\tilde{\nu}$ = 3485, 2930, 1699, 1682, 1409, 1350, 1101 cm^{-1}. MS (EI): *m*/*z* = 443 $[M]^+$. HRMS (EI): calcd. for $C_{27}H_{41}NO_4$ 443.3036 $[M]^+$; found 443.3041.

(3*S*,3a*R*,5*S*,9*S*)-5-Heptyl-3-(1-hydroxybutyl)octahydroindolizine (13): $Pd(OH)_2$/C (20%, 5 mg) was added to a stirred solution of **11** (161 mg, 0.36 mmol) in MeOH (5 mL), and the resulting suspension was stirred under hydrogen at 1 atm for 26 h. The catalyst was removed by filtration and the filtrate was concentrated to give a residue, which was chromatographed on silica gel (10 g, hexane/acetone 30:1 to 20:1) to give **13** (97 mg, 90%) as a pale yellow oil. $[\alpha]_D^{26}$ = +48.2 (*c* = 1.50, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.86 (t, *J* = 6.5 Hz, 3 H), 0.92 (t, *J* = 7.0 Hz, 3 H), 1.01–1.11 (m, 1 H), 1.13–1.19 (m, 2 H), 1.20–1.38 (m, 13 H), 1.41–1.54 (m, 3 H), 1.57–1.68 (m, 3 H), 1.71–1.82 (m, 4 H), 2.21–2.34 (m, 2 H), 2.84 (d-like, *J* = 10.2 Hz, 1 H), 3.58 (br, 1 H) ppm. ^{13}C NMR (100 MHz): δ = 14.02, 14.33, 19.55, 22.60, 22.90, 24.84, 25.96, 29.26, 29.96, 31.61, 31.78, 32.06, 32.20, 35.51, 35.54, 64.51, 64.52, 67.08, 72.48 ppm. IR (neat): $\tilde{\nu}$ = 3456, 2930, 2858, 2794, 1456, 1379, 1103 cm^{-1}. MS (EI): *m*/*z* = 295 $[M]^+$. HRMS (EI): calcd. for $C_{19}H_{37}NO$ 295.2875 $[M]^+$; found 295.2849.

Benzyl (2*S*,5*R*)-(–)-5-Allyl-2-heptanoylpyrrolidine-1-carboxylate (14): A solution of *n*-hexylMgBr (2.0 M in THF, 2.60 mL, 5.20 mmol) was added at 0 °C to a stirred solution of aldehyde **3** (284 mg, 1.04 mmol) in THF (10 mL), and the reaction mixture was stirred at room temperature for 24 h. The reaction was quenched with satd. NH_4Cl soln. and the aqueous mixture was extracted with CH_2Cl_2 (10 mL × 3). The extracts were combined, dried with Na_2SO_4, and concentrated to afford the residue, which was chromatographed on silica gel (25 g, hexane/acetone 30:1 to 25:1) to give **10** (280 mg, 75%) as a 1:1 mixture of diastereomers and as a colorless oil.

PCC (50 mg, 0.23 mmol) was added to a stirred solution of the alcohols obtained above (55 mg, 0.15 mmol) in CH_2Cl_2 (2 mL), and the resulting mixture was stirred at room temperature for 23 h. The solvent was evaporated and the residue was chromatographed on silica gel (13 g, hexane/EtOAc 20:1 to 10:1) to give **14** (48 mg, 89%) as a colorless oil. $[\alpha]_D^{26}$ = –22.9 (*c* = 0.70, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.84 (t, *J* = 6.5 Hz, 3 H), 1.06–1.32 (m, 7 H), 1.50–1.63 (m, 3 H), 1.69–1.95 (m, 3 H), 2.05–2.22 (m, 2 H), 2.40–2.64 (m, 1 H), 3.96 and 4.02 (each br, 1 H), 4.31 and 4.40 (each t, *J* = 7.6 Hz, 1 H), 4.97–5.15 (m, 4 H), 5.65–5.85 (m, 1 H), 7.27–7.33 (m, 5 H) ppm. ^{13}C NMR (100 MHz): δ = 13.99, 22.42, 23.14, 27.07 and 28.06, 28.55 and 28.84, 28.79 and 29.64, 31.54, 38.43 and 38.74, 39.07 and 39.46, 58.18 and 58.84, 66.06 and 66.21, 67.07, 117.21, 127.72, 128.03, 128.41, 134.89 and 134.98, 136.26 and 136.52, 154.34 and 155.12, 209.50 and 209.70 ppm. IR (neat): $\tilde{\nu}$ = 2930, 1703, 1410, 1352, 1111 cm^{-1}. MS (EI): *m*/*z* = 316 $[M - C_3H_5]^+$. HRMS: calcd. for $C_{19}H_{26}NO_3$ $[M - C_3H_5]^+$ 316.1913; found 316.1914.

Benzyl (2*S*,2a*S*,5*R*)-5-Allyl-2-(1-hydroxyheptyl)pyrrolidine-1-carboxylate (15): $NaBH_4$ (44 mg, 1.15 mmol) was added at 0 °C to a stirred solution of ketone **14** (170 mg, 0.48 mmol) in MeOH (5 mL), and the reaction mixture was stirred at room temperature for 24 h. The reaction was quenched with HCl (10%) and the aqueous mixture was extracted with CH_2Cl_2 (5 mL × 3). The organic extracts were combined, dried with Na_2SO_4, and concentrated to afford a residue, which was chromatographed on silica gel (15 g, hexane/acetone 30:1 to 25:1) to give **15** (155 mg, 90%) as a colorless oil. $[\alpha]_D^{22}$ = –26.4 (*c* = 0.75, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.8 Hz, 3 H), 1.22–1.35 (m, 8 H), 1.42–1.54 (m, 2 H), 1.64–1.75 (m, 2 H), 1.80–1.88 (m, 1 H), 1.91–1.99 (m, 1 H), 2.12–2.21 (m, 1 H), 2.44 (br, 1 H), 3.47 (t-like, *J* = 8.1 Hz, 1 H), 3.84–3.89 (m, 1 H), 4.00–4.07 (m, 1 H), 4.98–5.07 (m, 2 H), 5.12 and 5.19 (ABq, *J* = 12.3 Hz, 2 H), 5.66–5.78 (m, 1 H), 7.29–7.34 (m, 5 H) ppm. ^{13}C NMR (100 MHz): δ = 14.06, 22.60, 25.03, 27.16, 28.73, 29.46, 31.83, 34.74, 39.49, 58.65, 64.52, 67.49, 76.51, 117.44, 127.89, 128.06, 128.49, 134.62, 136.31, 158.25 ppm. IR (neat): $\tilde{\nu}$ = 3437, 2930, 1682, 1418, 1101 cm^{-1}. MS (EI): *m*/*z* = 318 $[M - C_3H_5]^+$. HRMS: calcd. for $C_{19}H_{28}NO_3$ $[M - C_3H_5]^+$ 318.2070; found 318.2061.

Benzyl (2*S*,2a*R*,5*R*)-(+)-5-Allyl-2-(1-hydroxyheptyl)pyrrolidine-1-carboxylate (16): $CeCl_3 \cdot 7H_2O$ (391 mg, 1.05 mmol) was added at 0 °C to a stirred solution of ketone **14** (150 mg, 0.42 mmol) in MeOH (4 mL) and the resulting mixture was stirred for 10 min. $NaBH_4$ (38 mg, 1.01 mmol) was added to the mixture at 0 °C, and the mixture was then stirred at room temperature for 21 h. The reaction was quenched with H_2O, and the aqueous mixture was extracted with EtOAc (10 mL × 3). The extracts were combined, dried with Na_2SO_4, and concentrated to afford a residue, which was chromatographed on silica gel (20 g, hexane/acetone 30:1 to 20:1) to give **16** (120 mg, 80%) as a colorless oil. $[\alpha]_D^{22}$ = +2.1 (*c* = 0.75, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.86 (t, *J* = 6.8 Hz, 3 H), 1.20–1.27 (m, 7 H), 1.29–1.35 (m, 2 H), 1.43–1.48 (m, 1 H), 1.66–1.73 (m, 1 H), 1.75–1.87 (m, 3 H), 2.10–2.21 (m, 1 H), 2.41 (br, 1 H), 3.82–3.87 (m, 1 H), 3.89–3.95 (m, 1 H), 3.96–4.05 (m, 1 H), 4.98–5.03 (m, 2 H), 5.12 (s, 2 H), 5.63–5.72 (m, 1 H), 7.27–7.37 (m, 5 H) ppm. ^{13}C NMR (100 MHz): δ = 14.05, 22.56, 24.26, 26.21, 28.52, 29.30, 31.78, 32.50, 39.41, 58.59, 65.07, 67.02, 71.02, 117.20, 127.79, 127.98, 128.45, 135.35, 136.52, 156.33 ppm. IR (neat): $\tilde{\nu}$ = 3437, 2930, 1682, 1418, 1107 cm^{-1}. MS (EI): *m*/*z* = 318 $[M - C_3H_5]^+$. HRMS: calcd. for $C_{19}H_{28}NO_3$ $[M - C_3H_5]^+$ 318.2070; found 318.2071.

Benzyl (2*S*,2a*S*,5*R*)-2-(1-Hydroxyheptyl)-5-[(*E*)-4-oxohept-2-enyl]-pyrrolidine-1-carboxylate (17): Hex-1-en-3-one (0.09 mL, 0.73 mmol) and the second-generation Grubbs catalyst (12 mg, 0.014 mmol) were added to a stirred solution of alcohol **15** (52 mg, 0.15 mmol) in CH_2Cl_2 (3 mL), and the reaction mixture was heated at reflux for 23 h. After the mixture had cooled, the solvent was evaporated, and the residue was chromatographed on silica gel (12 g, hexane/acetone 20:1 to 10:1) to give **17** (58 mg, 94%) as a pale yellow oil. $[\alpha]_D^{26}$ = +2.0 (*c* = 0.50, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.7 Hz, 3 H), 0.91 (t, *J* = 7.4 Hz, 3 H), 1.22–1.40 (m, 7 H), 1.43–1.54 (m, 2 H), 1.56–1.73 (m, 5 H), 1.88–2.03 (m, 2 H), 2.31–2.40 (m, 1 H), 2.46 (t-like, *J* = 7.2 Hz, 2 H), 2.52–2.68 (m, 1 H), 3.38–3.47 (m, 1 H), 3.85–3.93 (m, 1 H), 4.06–4.14 (m, 1 H), 5.15 (s, 2 H), 6.07 (d, *J* = 15.6 Hz, 1 H), 6.67–6.77 (m, 1 H), 7.29–7.39 (m, 5 H) ppm. ^{13}C NMR (100 MHz): δ = 13.68, 13.99, 17.45, 22.52, 25.02, 27.12, 29.17, 29.35, 31.74, 34.73, 38.06, 41.85, 58.00, 64.28, 67.62, 76.24, 127.94, 128.16, 128.50, 132.49,

136.04, 142.26, 158.02, 200.34 ppm. IR (neat): $\tilde{\nu}$ = 3418, 2930, 1693, 1666, 1408, 1103 cm^{-1}. MS (EI): *m*/*z* = 429 $[M]^+$. HRMS (EI): calcd. for $C_{26}H_{40}NO_4$ $[M + H]^+$ 430.2957; found 430.2952.

Benzyl (2*S*,2α*R*,5*R*)-2-(1-Hydroxyheptyl)-5-[(*E*)-4-oxohept-2-enyl]-pyrrolidine-1-carboxylate (18): Hex-1-en-3-one (0.12 mL, 1.02 mmol) and the second-generation Grubbs catalyst (17 mg, 0.02 mmol) were added to a stirred solution of alcohol **16** (73 mg, 0.20 mmol) in CH_2Cl_2 (4 mL), and the reaction mixture was heated at reflux for 27 h. After the mixture had cooled, the solvent was evaporated and the residue was chromatographed on silica gel (13 g, hexane/acetone 20:1 to 10:1) to give **18** (86 mg, 99%) as a pale yellow oil. $[\alpha]_D^{26}$ = +3.0 (*c* = 0.55, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.2 Hz, 3 H), 0.91 (t, *J* = 7.4 Hz, 3 H), 1.21–1.32 (m, 7 H), 1.33–1.58 (m, 4 H), 1.58–1.64 (m, 2 H), 1.65–1.74 (m, 1 H), 1.82–1.93 (m, 2 H), 2.26–2.33 (m, 1 H), 2.34–2.48 (m, 2 H), 2.52–2.70 (m, 1 H), 3.80–3.92 (m, 1 H), 3.93–3.99 (m, 1 H), 4.05–4.15 (m, 1 H), 5.10 and 5.16 (ABq, *J* = 12.3 Hz, 2 H), 6.08 (d, *J* = 16.1 Hz, 1 H), 6.69–6.84 (m, 1 H), 7.27–7.38 (m, 5 H) ppm. ^{13}C NMR (100 MHz): δ = 13.68, 13.99, 17.48, 22.50, 23.88, 26.12, 29.00, 29.23, 31.72, 32.78, 38.00, 42.02, 58.02, 64.81, 67.10, 70.72, 127.80, 128.03, 128.45, 132.34, 136.33, 143.10, 155.98, 200.37 ppm. IR (neat): $\tilde{\nu}$ = 3452, 2930, 1692, 1678, 1408, 1352, 1105 cm^{-1}. MS (EI): *m*/*z* = 429 $[M]^+$. HRMS (EI): calcd. for $C_{26}H_{40}NO_4$ $[M + H]^+$ 430.2957; found 430.2965.

(3*S*,3α*S*,5*S*,9*S*)-3-(1-Hydroxyheptyl)-5-propyloctahydroindolizine (19): $Pd(OH)_2$/C (20%, 5 mg) was added to a stirred solution of **17** (100 mg, 0.23 mmol) in MeOH (5 mL), and the resulting suspension was stirred under hydrogen at 1 atm for 23 h. The catalyst was removed by filtration and the filtrate was concentrated to give a residue, which was chromatographed on silica gel (7 g, hexane/acetone 50:1 to 40:1) to give **19** (46 mg, 71%) as a pale yellow oil. $[\alpha]_D^{26}$ = +72.9 (*c* = 0.70, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 7.1 Hz, 3 H), 0.91 (t, *J* = 7.2 Hz, 3 H), 1.00–1.12 (m, 1 H), 1.14–1.27 (m, 4 H), 1.28–1.42 (m, 9 H), 1.44–1.47 (m, 2 H), 1.48–1.58 (m, 1 H), 1.59–1.62 (m, 2 H), 1.63–1.72 (m, 2 H), 1.73–1.81 (m, 2 H), 1.82–1.86 (m, 1 H),2.25–2.39 (m, 2 H), 2.84 (t-like, *J* = 7.3 Hz, 1 H), 2.93–2.97 (m, 1 H) ppm. ^{13}C NMR (100 MHz): δ = 14.07, 14.37, 19.79, 22.61, 25.26, 26.45, 29.52, 29.45, 30.60, 31.11, 31.89, 33.13, 34.68, 38.19, 62.69, 63.79, 67.98, 74.53 ppm. IR (neat): $\tilde{\nu}$ = 3375, 2930, 2858, 2793, 1468 cm^{-1}. MS (EI): *m*/*z* = 281 $[M]^+$. HRMS (EI): calcd. for $C_{18}H_{35}NO$ $[M]^+$ 281.2719; found 281.2710.

(3*S*,3α*R*,5*S*,9*S*)-3-(1-Hydroxyheptyl)-5-propyloctahydroindolizine (20): $Pd(OH)_2$/C (20%, 5 mg) was added to a stirred solution of **18** (145 mg, 0.34 mmol) in MeOH (5 mL), and the resulting suspension was stirred under hydrogen at 1 atm for 25 h. The catalyst was removed by filtration and the filtrate was concentrated to give a residue, which was chromatographed on silica gel (10 g, hexane/acetone 50:1 to 40:1) to give **20** (84 mg, 88%) as a pale yellow oil. $[\alpha]_D^{26}$ = +51.8 (*c* = 0.80, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 7.0 Hz, 3 H), 0.91 (t, *J* = 7.2 Hz, 3 H), 1.02–1.12 (m, 1 H), 1.13–1.17 (m, 1 H), 1.18–1.23 (m, 2 H), 1.24–1.34 (m, 9 H), 1.37–1.54 (m, 4 H), 1.55–1.62 (m, 1 H), 1.63–1.71 (m, 2 H), 1.72–1.74 (m, 1 H), 1.75–1.84 (m, 3 H),2.23–2.37 (m, 2 H), 2.83–2.89 (m, 1 H), 4.54–4.60 (m, 1 H) ppm. ^{13}C NMR (100 MHz): δ = 14.05, 14.42, 19.03, 22.60, 22.90, 24.84, 26.30, 29.58, 31.62, 31.79, 32.06, 32.15, 33.37, 37.72, 64.26, 64.40, 67.11, 72.64 ppm. IR (neat): $\tilde{\nu}$ = 3452, 2930, 2858, 2795, 1456 cm^{-1}. MS (EI): *m*/*z* = 281 $[M]^+$. HRMS: calcd. for $C_{18}H_{35}NO$ $[M]^+$ 281.2719; found 281.2698.

Benzyl (2*S*,2α*S*,5*R*)-2-(1-Hydroxyheptyl)-5-[(*E*)-4-oxoundec-2-enyl]-pyrrolidine-1-carboxylate (21): Dec-1-en-3-one (141 mg, 0.92 mmol) and the second-generation Grubbs catalyst (26 mg, 0.03 mmol) were added to a stirred solution of alcohol **15** (110 mg, 0.31 mmol) in CH_2Cl_2 (5 mL), and the reaction mixture was heated at reflux for 23 h. After the mixture had cooled, the solvent was evaporated and the residue was chromatographed on silica gel (15 g, hexane/acetone 20:1 to 10:1) to give **21** (147 mg, 99%) as a pale yellow oil. $[\alpha]_D^{26}$ = +4.5 (*c* = 1.05, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 7.0 Hz, 3 H), 0.88 (t, *J* = 6.8 Hz, 3 H), 1.20–1.34 (m, 16 H), 1.42–1.49 (m, 2 H), 1.53–1.58 (m, 2 H), 1.64–1.71 (m, 2 H), 1.87–2.03 (m, 2 H), 2.35 (br, 1 H), 2.47 (t, *J* = 7.4 Hz, 2 H), 2.59 (br, 1 H), 3.38–3.46 (m, 1 H), 3.86–3.92 (m, 1 H), 4.06–4.14 (m, 1 H), 5.15 (s, 2 H), 6.07 (d, *J* = 15.6 Hz, 1 H), 6.67–6.78 (m, 1 H), 7.30–7.39 (m, 5 H) ppm. ^{13}C NMR (100 MHz): δ = 13.90, 13.92, 22.44, 23.96, 25.00, 27.04, 28.94, 29.07, 29.10, 29.29, 31.52, 31.69, 34.62, 37.98, 39.91, 53.30, 57.95, 64.32, 67.51, 76.09, 127.84, 128.06, 128.42, 132.39, 136.01, 142.18, 157.93, 200.35 ppm. IR (neat): $\tilde{\nu}$ = 3456, 2927, 1699, 1674, 1410, 1101 cm^{-1}. MS (EI): *m*/*z* = 485 $[M]^+$. HRMS (EI): calcd. for $C_{30}H_{47}NO_4$ $[M]^+$ 485.3505; found 485.3498.

(3*S*,3α*S*,5*S*,9*S*)-5-Heptyl-3-(1-hydroxyheptyl)octahydroindolizine (22): $Pd(OH)_2$/C (20%, 5 mg) was added to a stirred solution of **21** (146 mg, 0.30 mmol) in MeOH (5 mL), and the resulting suspension was stirred under hydrogen at 1 atm for 22 h. The catalyst was removed by filtration and the filtrate was concentrated to give a residue, which was chromatographed on silica gel (10 g, hexane/acetone 40:1 to 30:1) to give **22** (67 mg, 66%) as a pale yellow oil. $[\alpha]_D^{26}$ = +53.4 (*c* = 1.50, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.86–0.90 (m, 6 H), 1.01–1.10 (m, 1 H), 1.16–1.19 (m, 2 H), 1.20–1.36 (m, 18 H), 1.39–1.47 (m, 3 H), 1.51–1.73 (m, 5 H), 1.75–1.79 (m, 2 H), 1.82–1.86 (m, 1 H), 2.27 (t-like, *J* = 9.8 Hz, 1 H), 2.35 (t-like, *J* = 9.8 Hz, 1 H), 2.84 (t-like, *J* = 7.3 Hz, 1 H), 2.95 (br, 1 H) ppm. ^{13}C NMR (100 MHz): δ = 14.07, 14.08, 22.63, 22.64, 25.28, 26.44, 26.71, 29.35, 29.55, 29.68, 29.85, 30.62, 31.13, 31.82, 31.90, 33.20, 34.75, 36.00, 62.66, 64.03, 67.78, 74.56 ppm. IR (neat): $\tilde{\nu}$ = 3408, 2926, 2856, 2797, 1456, 1379, 1142 cm^{-1}. MS (EI): *m*/*z* = 337 $[M]^+$. HRMS (EI): calcd. for $C_{22}H_{43}NO$ $[M]^+$ 337.3344; found 337.3319.

Benzyl (2*S*,2α*S*,5*R*)-2-(1-Hydroxyheptyl)-5-[(*E*)-4-oxoundec-2-enyl]-pyrrolidine-1-carboxylate (23): Dec-1-en-3-one (134 mg, 0.87 mmol) and the second-generation Grubbs catalyst (25 mg, 0.029 mmol) were added to a stirred solution of alcohol **16** (104 mg, 0.29 mmol) in CH_2Cl_2 (5 mL) and the reaction mixture was heated at reflux for 22 h. After the mixture had cooled, the solvent was evaporated, and the residue was chromatographed on silica gel (20 g, hexane/acetone 20:1 to 10:1) to give **23** (110 mg, 79%) as a pale yellow oil. $[\alpha]_D^{26}$ = +4.5 (*c* = 1.05, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 7.0 Hz, 3 H), 0.88 (t, *J* = 6.8 Hz, 3 H), 1.20–1.34 (m, 16 H), 1.42–1.49 (m, 2 H), 1.53–1.58 (m, 2 H), 1.64–1.71 (m, 2 H), 1.87–2.03 (m, 2 H), 2.35 (br, 1 H), 2.47 (t, *J* = 7.4 Hz, 2 H), 2.59 (br, 1 H), 3.38–3.46 (m, 1 H), 3.86–3.92 (m, 1 H), 4.06–4.14 (m, 1 H), 5.15 (s, 2 H), 6.07 (d, *J* = 15.6 Hz, 1 H), 6.67–6.78 (m, 1 H), 7.30–7.39 (m, 5 H) ppm. ^{13}C NMR (100 MHz): δ = 13.90, 13.92, 22.44, 23.96, 25.00, 27.04, 28.94, 29.07, 29.10, 29.29, 31.52, 31.69, 34.62, 37.98, 39.91, 53.30, 57.95, 64.32, 67.51, 76.09, 127.84, 128.06, 128.42, 132.39, 136.01, 142.18, 157.93, 200.35 ppm. IR (neat): $\tilde{\nu}$ = 3456, 2927, 1699, 1674, 1410, 1101 cm^{-1}. MS (EI): *m*/*z* = 485 $[M]^+$. HRMS (EI): calcd. for $C_{30}H_{47}NO_4$ $[M + H]^+$ 486.3583; found 486.3592.

(3*S*,3α*R*,5*S*,9*S*)-5-Heptyl-3-(1-hydroxyheptyl)octahydroindolizine (24): $Pd(OH)_2$/C (20%, 5 mg) was added to a stirred solution of **23** (110 mg, 0.23 mmol) in MeOH (5 mL), and the resulting suspension was stirred under hydrogen at 1 atm for 24 h. The catalyst was removed by filtration and the filtrate was concentrated to give a

residue, which was chromatographed on silica gel (10 g, hexane/acetone 40:1 to 30:1) to give **24** (47 mg, 62%) as a pale yellow oil. $[\alpha]_D^{26}$ = +32.3 (*c* = 1.10, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.8 Hz, 6 H), 1.02–1.07 (m, 1 H), 1.08–1.14 (m, 1 H), 1.15–1.20 (m, 1 H), 1.23–1.36 (m, 18 H), 1.40–1.46 (m, 1 H), 1.47–1.53 (m, 1 H), 1.54–1.63 (m, 5 H), 1.64–1.71 (m, 1 H), 1.72–1.78 (m, 2 H),1.79–1.84 (m, 1 H), 2.22–2.34 (m, 2 H), 2.83–3.61 (m, 1 H), 3.54–3.61 (m, 1 H) ppm. ^{13}C NMR (100 MHz): δ = 14.06, 14.40, 22.62, 22.91, 24.86, 25.99, 26.29, 29.19, 29.28, 29.58, 29.99, 31.64, 31.81, 31.91, 32.09, 32.24, 33.36, 35.53, 64.50, 64.55, 67.13, 72.69 ppm. IR (neat): $\tilde{\nu}$ = 3447, 2928, 2856, 2795, 1458 cm^{-1}. MS (EI): *m*/*z* = 337 $[M]^+$. HRMS (EI): calcd. for $C_{22}H_{43}NO$ $[M + H]^+$ 338.3423; found 338.3416.

Spectral Analyses: GC–MS was performed with a Varian Saturn 2100 T ion trap MS instrument coupled to a Varian 3900 GC with a 30 m × 0.25 mm i.d. Varian Factor Four VF-5ms fused silica column. GC separation of alkaloids was achieved by use of a temperature program from 100 to 280 °C at a rate of 10 °C per minute with He as the carrier gas (1 mL min^{-1}). Alkaloids were analyzed both by electron impact MS and by chemical ionization MS with MeOH as the reagent.

Vapor-phase FTIR spectroscopic data (GC-FTIR) were obtained with a Hewlett–Packard model 5890 gas chromatograph and a Phenomenex Zebron ZB-5 capillary column (30 m, 0.32 mm i.d., 0.25 μm), with use of the same temperature program as above, coupled with a model 5965B (IRD) narrow band (4000–750 cm^{-1}) infrared detector. A Hewlett–Packard ChemStation was used to generate FTIR spectra.

Supporting Information (see footnote on the first page of this article): ^1H NMR and ^{13}C NMR spectra of compounds **2**, **4a**, **4b**, **5**–**8**, **239Q**, **9**, 10-*epi*-**239Q**, and **10**–**24**, ^1H NMR spectrum of compound **3**, and NOE data for compounds **7** and **239Q**.

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