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Efficient Enantio- and Diastereodivergent Synthesis of Poison-Frog Alkaloids 251O and *trans*-223B

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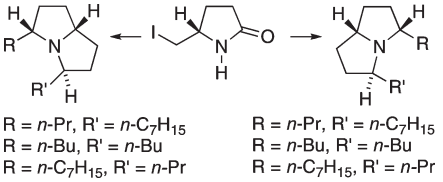

An efficient and flexible synthesis of poison-frog alkaloids **251O** and *trans*-**223B** has been achieved by using for both alkaloids an enantiodivergent process starting from the common lactam **1**. The relative stereochemistry of **251O** and *trans*-**223B** was determined to be **7** (R = *n*-C_7H_{15}, R′ = *n*-Pr) and **14** by the present enantioselective synthesis.

Introduction

A variety of lipophilic alkaloids have been detected in skin extracts of neotropical poison-frogs and over 800 alkaloids from 24 classes have been detected to date.[1] These alkaloids serve as a chemical defense against predation and some of them also exhibit significant inhibitory effects on nicotinic acetylcholine receptors (nAChRs).[2]

Very interestingly, most of these alkaloids appear to be sequestered from dietary arthropods.[3] Thus, the 3,5-disubstituted pyrrolizidine **251O**, detected in the poison-frogs *Mantella haraldmeieri*, *M. bernhardi*, and *M. baroni* of Madagascar, has also been found in Malagasy ants of the genus *Anochetus grandidieri*.[4] So far, several syntheses of trans,trans-type of 3,5-disubstituted pyrrolizidines such as xenovenine have been reported,[5] whereas no synthesis of he trans,cis-type of 3,5-disubstituted pyrrolizidine alkaloids has been reported. Natural xenovenine is found in frogs as *cis*-**223H**. It has the 3*R*,5*S*,8*S* absolute configuration as shown in Figure 1 (unpublished work, H.M.G., T.F.S., and J.W.D.). Alkaloid **251O** has a trans,cis-type of pyrrolizidine ring system; however, both the relative and absolute stereochemistry are still unknown (Figure 1). As part of a program directed at studying the synthesis of biologically

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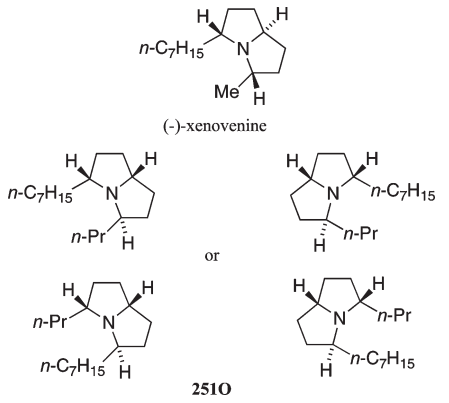

FIGURE 1. Structure of xenovenine and **251O**.

active alkaloids,[6] we report herein the efficient enantio- and diastereodivergent synthesis of **251O** starting from a common lactam, **1**.[7]

Results and Discussion

The known olefin **2**,[8] derived from **1**, was converted to a Boc-imide, which was treated with *n*-Pr or *n*-C_7H_{15} magnesium bromide according to Martin's reaction conditions[9] to provide the ketones **3** (R = *n*-Pr or *n*-C_7H_{15}) in high yield. Both ketones **3** were subjected to cyclization and subsequent reduction of the resulting iminium ion with Ph_3SiH[9] to give rise to the cis-substituted pyrrolidines **4** (R = *n*-Pr or *n*-C_7H_{15}). The cross-metathesis reaction of **4** (R = *n*-Pr or *n*-C_7H_{15}) with ethyl acrylate, using Grubbs' second-generation catalyst,[10] afforded the unsaturated esters **5** (R = *n*-Pr or *n*-C_7H_{15}). The key pyrrolizidine ring-closure reaction of **5** (R = *n*-Pr or *n*-C_7H_{15}) resulted after treatment with 2 equiv of $AlCl_3$ in CH_2Cl_2 followed by K_2CO_3 to the desired pyrrolizidines **6** (R = Et or *n*-C_6H_{13}) in excellent yield with high diastereoselectivity (>30:1). The stereochemistry of **6** (R = Et) was determined to be as shown based on an NOE experiment. In a difference NOE experiment, an NOE enhancement (ca. 2.3%) was observed on one of the methylene protons of the side chain at C-5 upon irradiation of the methine proton at C-3.

The highly selective formation of the desired **6** (R = Et or *n*-C_6H_{13}) is explained by invoking kinetic control as shown in Figure 2.[11] Finally, half-reduction of the ester moiety with diisobutylaluminum hydride, Wittig olefination of the resulting aldehyde, followed by hydrogenation of the corresponding olefin furnished **7** (R = *n*-Pr, R′ = *n*-C_7H_{15} or R = *n*-C_7H_{15}, R′ = *n*-Pr) (Scheme 1).

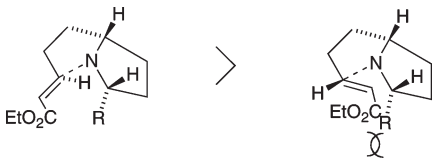

FIGURE 2. Kinetic control on pyrrolizidine formation.

ent-**7** (R = *n*-Pr, R′ = *n*-C_7H_{15} or R = *n*-C_7H_{15}, R′ = *n*-Pr) was synthesized from **1** in a similar way as shown in Scheme 2.

The enantiodivergent synthesis of *trans*-**223B** was also achieved starting from common lactam **2** as shown in Scheme 3.

The GC-MS and GC-FTIR spectra of synthetic **7** (R = *n*-C_7H_{15}, R′ = *n*-Pr) were identical with those for natural **251O** present in skin extracts of three Madagascan frogs (*Mantella haraldmeieri* collected in 2004, *M. bernhardi* collected in 1997, and *M. baroni* collected in 2004, unpublished results; see the Supporting Information). Furthermore, the GC-MS and GC-FTIR spectra of synthetic **14** were also identical with those for natural *trans*-**223B** present in a skin extract of the Argentinean frog *Melanophryniscus stelzneri*.[12] The mass spectral evidence, with a strong loss of propyl from the molecular ion to give *m*/*z* 208 (251−43), indicates a pseudoaxial position for the propyl group: a group that is trans-antiparallel to the radical ion on the N atom should cleave preferentially, all other things being equal. The heptyl group, being larger cleaves better, but the comparison of the MS in the Supporting Information, between trans-stereoisomers with a Pr-group pseudoaxial or a Pr-group pseudoequatorial clearly indicates a bigger fragmentation of the propyl group for the one in the pseudoaxial position. This MS evidence indicates that natural **251O** is (3*S*,5*S*,8*R*) or the enantiomer (3*R*,5*R*,8*S*) the same as **7** (R = *n*-C_7H_{15}, R′ = *n*-Pr) or *ent*-**7** (*R* = *n*-C_7H_{15}, R′ = *n*-Pr). Unfortunately, we could not achieve the separation of enantiomers of synthetic **7** by GC analysis using two different chiral columns. For the enantiomers of synthetic **14**, we anticipate even more difficulty in the separation since the two side chains are identical; however, this separation was not attempted.

In conclusion, we have achieved the first synthesis of alkaloids **251O** and *trans*-**223B** in enantio- and diastereodivergent fashion in 8 or 9 steps in 25−29% overall yield from the known lactam **1**, respectively. Furthermore, the relative stereochemistries of natural **251O** and *trans*-**223B** were determined to be **7** (R = *n*- C_7H_{15} R′ = *n*-Pr) and **14**, respectively, by the present efficient syntheses and comparisons with the natural compounds. It is difficult to separate the enantiomers of **7** and **14**, but further work on the GC separation of the enantiomers of **7** and **14** for the determination of the absolute stereochemistry of natural **251O** and *trans*-**223B** is in progress.[13]

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(11) Exposure of the stereoisomer at the 3-position (all *cis*-pyrrolizidine) of **6** (R = Et) to the same reaction conditions (K_2CO_3 in CH_2Cl_2 at room temperature for 48 h) recovered the starting material, and no formation of **6** (R = Et) was observed.

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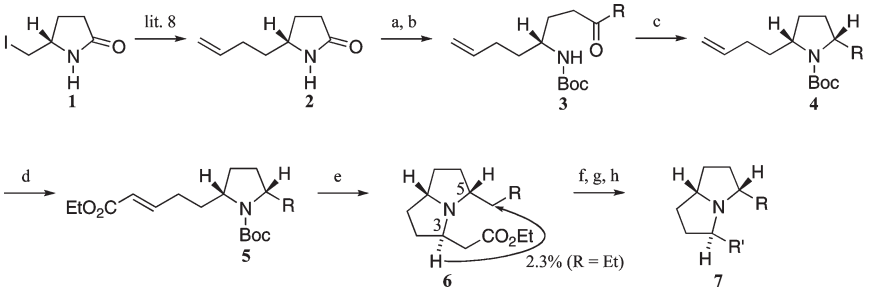
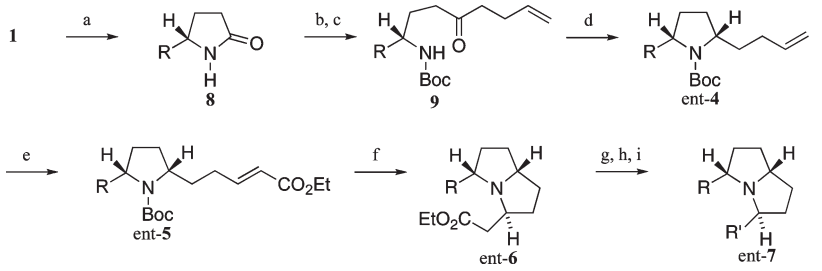
(13) No separation of a mixture of **7** and *ent*-**7** (ca. 1:1) was observed with either of two β-cyclodextrin chiral columns. One column was a 30 m × 0.25 mm i.d. (0.25 um film thickness) β Dex 120 column (Supelco); the other column was a 25 m × 0.22 mm i.d. (0.25 um film thickness) permethylated β-cyclodextrin column (SGE). Both were operated at a head pressure of 20 psi and used a gas chromatograph with flame ionization detection. A 3390A recorder integrator was used and a temperature program of 100 to 150 °C at 1 or 2 deg/min. A separation of a mixture of **14** and *ent*-**14** was not attempted.

SCHEME 1. Synthesis of 7 (R = *n*-Pr, R′ = *n*-C_7H_{15} or R = *n*-C_7H_{15}, R′ = *n*-Pr)[a]



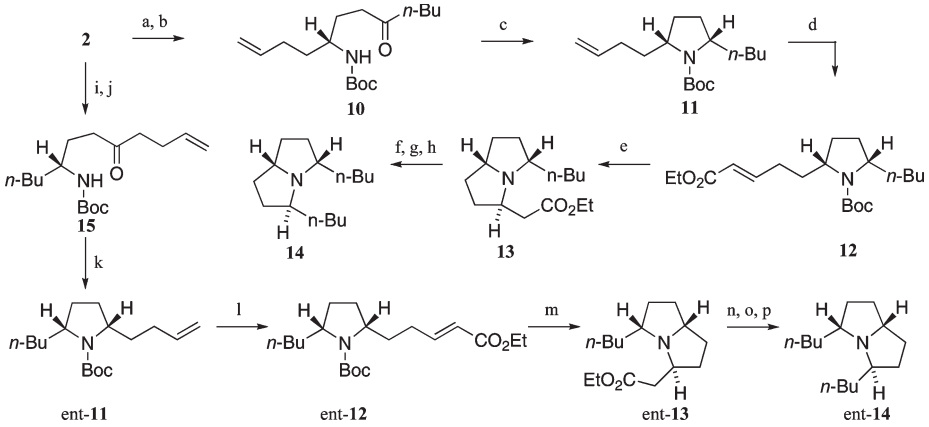
[a]Reagents and conditions: (a) Boc_2O, DMAP, MeCN, rt (95%); (b) n-C_3H_7MgBr or n-$C_7H_{15}MgBr$, TMEDA, THF, −78 °C (88% for R = n-Pr, 78% for R = n-C_7H_{15}); (c) $B(C_6F_5)_3$, Ph_3SiH, CH_2Cl_2, −78 °C to rt (85% for R = n-Pr, 89% for R = n-C_7H_{15}); (d) ethyl acrylate, Grubbs' second catalyst, CH_2Cl_2, reflux (96% for R = n-C_3H_7, 96% for R = n-C_7H_{15}); (e) $AlCl_3$, CH_2Cl_2, rt then K_2CO_3, CH_2Cl_2, rt (93% for R = Et, 88% for R = n-C_6H_{13}); (f) DIBAL, CH_2Cl_2, −78 °C; (g) n-$C_5H_{11}P^+Ph_3Br^-$, n-BuLi or $MeP^+Ph_3I^-$, n-BuLi, THF, 0 °C to rt (46% for R = n-Pr, R′ = C_7H_{13}, 49% for R = n-C_7H_{15}, R′ = allyl); (h) 10% Pd/C, H_2, EtOAc, 1 atm (quant for R = n-Pr, R′ = n-C_7H_{15}, 95% for R = n-C_7H_{15}, R′ = n-Pr).

SCHEME 2. Synthesis of *ent*-7 (R = *n*-Pr, R′ = *n*-C_7H_{15} or R = *n*-C_7H_{15}, R′ = *n*-Pr)[a]



[a]Reagents and conditions: (a) EtMgBr or n-$C^6H_{13}MgBr$, THF, −35 °C (52% for R = n-Pr, 50% for R = n-C_7H_{15}); (b) Boc_2O, DMAP, MeCN, rt (94% for R = n-Pr, 93% for R = n-C_7H_{15}); (c) 4-butenylMgBr, TMEDA, THF, −78 °C (95% for R = n-Pr, 98% for R = n-C_7H_{15}); (d) $B(C_6F_5)_3$, Ph_3SiH, CH_2Cl_2, −78 °C to rt (73% for R = n-Pr, 86% for R = n-C_7H_{15}); (e) ethyl acrylate, Grubbs' second catalyst, CH_2Cl_2, reflux (96% for R = n-Pr, 95% for R = n-C_7H_{15}); (f) $AlCl_3$, CH_2Cl_2, rt then K_2CO_3, CH_2Cl_2, rt (93% for R = n-Pr, 91% for R = n-C_7H_{15}); (g) DIBAL, CH_2Cl_2, −50 °C; (h) n-$C_5H_{11}P^+Ph_3Br^-$, n-BuLi or $MeP^+Ph_3I^-$, n-BuLi, THF, 0 °C to rt (48% for R = n-Pr, R′ = C_7H_{13}, 52% for R = n-C_7H_{15}, R′ = allyl); (h) 10% Pd/C, H_2, EtOAc, 1 atm (96% for R = n-Pr, R′ = n-C_7H_{15}, quant for R = n-C_7H_{15}, R′ = n-Pr).

SCHEME 3. Synthesis of Both Enantiomers of *trans*-223B[a]



[a]Reagents and conditions: (a) Boc_2O, DMAP, MeCN, rt (95%); (b) n-BuMgBr, TMEDA, THF, −78 °C (98%); (c) $B(C_6F_5)_3$, Ph_3SiH, CH_2Cl_2, −78 °C to rt (73%); (d) ethyl acrylate, Grubbs' second catalyst, CH_2Cl_2, reflux (96%); (e) $AlCl_3$, CH_2Cl_2, rt then K_2CO_3, CH_2Cl_2, rt (92%); (f) DIBAL, CH_2Cl_2, −50 °C; (g) $EtP^+Ph_3Br^-$, n-BuLi, THF, 0 °C to rt (50%); (h) 10% Pd/C, H_2, EtOAc, 1 atm (quant); (i) Boc_2O, DMAP, MeCN, rt (95%); (j) 10% Pd/C, H_2, EtOAc, 1 atm, then 4-butenylMgBr, TMEDA, THF, −78 °C (96%); (k) $B(C_6F_5)_3$, Ph_3SiH, CH_2Cl_2, −78 °C to rt (72%); (l) ethyl acrylate, Grubbs' second catalyst, CH_2Cl_2, reflux (84%); (m) $AlCl_3$, CH_2Cl_2, rt then K_2CO_3, CH_2Cl_2, rt (92%); (n) DIBAL, CH_2Cl_2, −50 °C; (o) $EtP^+Ph_3Br^-$, n-BuLi, THF, 0 °C to rt (53%); (p) 10% Pd/C, H_2, EtOAc, 1 atm (quant).

Experimental Section

(2*R*)-(−)-2-(But-3-enyl)-5-oxopyrrolidine-1-carboxylic Acid *tert*-Butyl Ester. To a stirred solution of **2**[8] (337 mg, 2.42 mmol) in MeCN (20 mL) was added DMAP (326 mg, 2.67 mmol) at 0 °C, and the reaction mixture was stirred at 0 °C for 30 min. To the reaction mixture was added Boc_2O (633 mg, 2.90 mmol) at 0 °C, and the resulting mixture was stirred at room temperature for 45 h. The volatiles were evaporated, and the residue was chromatographed on silica gel (20 g, hexane/acetone = 15:1) to give the Boc-imide (550 mg, 95%) as a colorless oil.

IR (neat) 3078, 1785, 1750, 1714, 1308, 1153 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.52 (9H, s), 1.59 (1H, m), 1.78 (1H, m), 1.90 (1H, m), 2.03−2.19 (3H, br m), 2.43 (1H, ddd, J = 9.0, 8.5,

2.1 Hz), 2.57 (1H, dd, J = 9.0, 8.5 Hz), 4.12 (1H, m), 5.01 (1H, d, J = 10.7 Hz), 5.04 (1H, d, J = 15.0 Hz), 5.80 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.9 (t), 27.7 (q), 29.6 (t), 31.0 (t), 32.4 (t), 57.1 (d), 82.2 (s), 115.0 (t), 136.7 (d), 149.3 (s), 173.7 (s); MS 182 ($M^+ - 57$), 84 (100); HRMS calcd for $C_9H_{12}O_3N$ 182.0817, found 182.0830; $[\alpha]^{26}_D$ −56.68 (c 2.34, $CHCl_3$).

(1*R*)-(+)-[1-(3-Oxohexyl)pent-4-enyl]carbamic Acid *tert*-Butyl Ester (3, R = *n*-Pr). To a stirred solution of the above Boc-imide (239 mg, 1.00 mmol) in THF (5 mL) was added a solution of *n*-PrMgBr, prepared from *n*-PrBr (0.27 mL, 3.00 mmol) and Mg (72 mg, 3.00 mmol) in THF (10 mL) at reflux, and TMEDA (0.48 mL, 3.00 mmol) at −78 °C, and the resulting mixture was stirred at the same temperature for 1.5 h. The reaction was quenched with *i*-PrOH (5 mL), and the reaction mixture was diluted with Et_2O. The organic layer was washed with 10% HCl (aq) solution, dried over $MgSO_4$, and evaporated to give pale yellow oil, which was chromatographed on silica gel (20 g, hexane/acetone = 50:1−30:1) to give **3** (R = *n*-Pr, 250 mg, 88%) as a colorless solid (mp 41−43 °C).

IR (KBr) 3349, 3081, 1708, 1689, 1528, 1175 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.90 (3H, t, J = 7.2 Hz), 1.42 (9H, s), 1.48−1.63 (5H, br m), 1.79 (1H, m), 2.08 (2H, q-like, J = 7.2 Hz), 2.37 (2H, t, J = 7.2 Hz), 2.46 (2H, t, J = 7.2 Hz), 3.53 (1H, br), 4.25 (1H, br d, J = 10.2 Hz), 4.95 (1H, d, J = 9.4 Hz), 5.01 (1H, d, J = 14.8 Hz), 5.78 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.6 (q), 17.1 (t), 28.2 (q), 29.0 (t), 30.1 (t), 35.1 (t), 39.1 (t), 44.6 (t), 49.9 (d), 78.5 (s), 114.5 (t), 137.6 (d), 155.4 (s), 210.3 (s); MS 226 ($M^+ - 57$), 57 (100); HRMS calcd for $C_{12}H_{20}O_3N$ 226.1443, found 226.1457; $[\alpha]^{26}_D$ +1.17 (c 1.21, $CHCl_3$).

(1*R*)-(−)-[1-(3-Oxodecyl)pent-4-enyl]carbamic Acid *tert*-Butyl Ester (3, R = *n*-C_7H_{15}). To a stirred solution of the above Boc-imide (239 mg, 1.00 mmol) in THF (5 mL) was added a solution of *n*-C_7H_{15}MgBr, prepared from *n*-C_7H_{15}Br (0.47 mL, 3.00 mmol) and Mg (72 mg, 3.00 mmol) in THF (10 mL) at reflux, and TMEDA (0.48 mL, 3.00 mmol) at −78 °C, and the resulting mixture was stirred at the same temperature for 1.5 h. The reaction was quenched with *i*-PrOH (5 mL), and the reaction mixture was diluted with Et_2O. The organic layer was washed with 10% HCl (aq) solution, dried over $MgSO_4$, and evaporated to give a pale yellow oil, which was chromatographed on silica gel (20 g, hexane/acetone = 50:1−30:1) to give **3** (R = *n*-C_7H_{15}, 265 mg, 78%) as a colorless solid (mp 60−62 °C).

IR (KBr) 3347, 3080, 1709, 1684, 1525, 1173 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85 (3H, t, J = 7.2 Hz), 1.26 (8H, br), 1.43 (9H, s), 1.46−1.61 (5H, br m), 1.81 (1H, m), 2.13 (2H, m), 2.39 (2H, t, J = 7.2 Hz), 2.47 (2H, t, J = 7.2 Hz), 3.53 (1H, br), 4.24 (1H, br d, J = 9.6 Hz), 4.95 (1H, d, J = 9.6 Hz), 5.01 (1H, d, J = 15.0 Hz), 5.78 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0 (q), 22.5 (t), 23.7 (t), 28.3 (q), 29.0 (t), 29.1 (t), 30.1 (t), 31.6 (t), 35.2 (t), 39.2 (t), 42.9 (t), 50.0 (d), 78.7 (s), 114.6 (t), 137.7 (d), 155.4 (s), 210.6 (s); MS 282 ($M^+ - 57$), 57 (100); HRMS calcd for $C_{16}H_{28}O_3N$ 282.2069, found 282.2091; $[\alpha]^{26}_D$ −1.56 (c 0.74, $CHCl_3$).

(2*R*,5*S*)-(−)-2-But-3-enyl-5-propylpyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (4, R = *n*-Pr). To a stirred solution of **3** (R = *n*-Pr, 226 mg, 0.80 mmol) in CH_2Cl_2 (5 mL) was added a solution of $(C_6F_5)_3B$ (82 mg, 0.16 mmol) and Ph_3SiH (415 mg, 1.59 mmol) in CH_2Cl_2 (5 mL) at −78 °C, and the reaction mixture was stirred at −78 °C for 30 min, and then at room temperature for 20 h. The reaction was quenched with Et_3N (0.6 mL), and the resulting mixture was stirred at room temperature for 20 min. The mixture was diluted with Et_2O, and the organic layer was washed successively with 10% AcOH (aq) solution and satd $NaHCO_3$ (aq) solution, dried over $MgSO_4$, and evaporated to give a pale yellow oil, which was chromatographed on silica gel (20 g, hexane/acetone = 200:1−150:1) to give **4** (R = *n*-Pr, 182 mg, 85%) as a colorless oil.

IR (neat) 3073, 1694, 1389 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.92 (3H, t, J = 7.2 Hz), 1.28 (6H, br m), 1.46 (9H, s), 1.61 (2H, m), 1.90 (2H, m), 2.04 (2H, m), 3.76 (2H, br), 4.94 (1H, d, J = 9.6 Hz), 5.03 (1H, d, J = 15.6 Hz), 5.81 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2 (q), 19.6 (t), 28.5 (q), 29.4 (t), 30.7 (t), 35.1 (t), 38.2 (t), 57.8 (d), 58.1 (d), 78.7 (s), 114.2 (t), 138.3 (d), 154.7 (s); MS 267 (M^+), 57 (100); HRMS calcd for $C_{16}H_{29}O_2N$ 267.2198, found 267.2215; $[\alpha]^{26}_D$ −3.23 (c 1.10, $CHCl_3$).

(2*R*,5*S*)-(−)-2-But-3-enyl-5-heptylpyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (4, R = *n*-C_7H_{15}). To a stirred solution of **3** (R = *n*-C_7H_{15}, 250 mg, 0.77 mmol) in CH_2Cl_2 (5 mL) was added a solution of $(C_6F_5)_3B$ (78 mg, 0.15 mmol) and Ph_3SiH (401 mg, 1.54 mmol) in CH_2Cl_2 (5 mL) at −78 °C, and the reaction mixture was stirred at −78 °C for 30 min, and then at room temperature for 20 h. The reaction was quenched with Et_3N (0.6 mL), and the resulting mixture was stirred at room temperature for 20 min. The mixture was diluted with Et_2O, and the organic layer was washed successively with 10% AcOH (aq) solution and satd $NaHCO_3$ (aq) solution, dried over $MgSO_4$, and evaporated to give a pale yellow oil, which was chromatographed on silica gel (20 g, hexane/acetone = 200:1−150:1) to give **4** (R = *n*-C_7H_{15}, 222 mg, 89%) as a colorless oil.

IR (neat) 3075, 1695, 1390, 1174, 1107 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (3H, t, J = 7.2 Hz), 1.27 (14H, br), 1.46 (9H, s), 1.62 (2H, m), 1.90 (2H, m), 2.07 (2H, br), 3.75 (2H, br), 4.95 (1H, d, J = 10.2 Hz), 5.02 (1H, d, J = 15.8 Hz), 5.84 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1 (q), 22.7 (t), 26.4 (t), 28.5 (q), 29.3 (t), 29.6 (t), 30.8 (t), 31.8 (t), 35.1 (t), 35.9 (t), 57.8 (d), 58.4 (d), 78.7 (s), 114.2 (t), 138.3 (d), 154.7 (s); MS 323 (M^+), 168 (100); HRMS calcd for $C_{20}H_{37}O_2N$ 323.2824, found 323.2847; $[\alpha]^{26}_D$ −0.97 (c 0.55, $CHCl_3$).

(2*R*,5*S*)-(−)-2-(4-Ethoxycarbonylbut-3-enyl)-5-propylpyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (5, R = *n*-Pr). To a stirred solution of **4** (R = *n*-Pr, 117 mg, 0.44 mmol) in CH_2Cl_2 (8 mL) were added Grubbs' second catalyst (15 mg, 0.018 mmol) and ethyl acrylate (0.24 mL, 2.20 mmol), and the resulting mixture was refluxed for 5.5 h. After cooling, the solvent was removed under reduced pressure, and the residue was chromatographed on silica gel (20 g, hexane/acetone = 100:1−60:1) to give **5** (R = *n*-Pr, 143 mg, 96%) as a pale yellow oil.

IR (neat) 1721, 1693, 1390, 1174 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (3H, t, J = 7.2 Hz), 1.20−1.30 (8H, br, including at δ 1.27, 3H, t, J = 7.2 Hz), 1.45 (9H, s), 1.61 (2H, m), 1.90 (3H, m), 2.19 (2H, br), 3.76 (2H, br), 4.16 (2H, q, J = 7.2 Hz), 5.85 (1H, d, J = 15.8 Hz), 6.96 (1H, dt, J = 15.8, 6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1 (q), 14.2 (q), 19.5 (t), 28.5 (q), 29.1 (t), 29.5 (t), 34.2 (t), 38.2 (t), 57.6 (d), 58.1 (d), 60.0 (t), 78.8 (s), 121.1 (d), 148.4 (d), 154.6 (s), 166.2 (s); MS 339 (M^+), 196 (100); HRMS calcd for $C_{19}H_{33}O_4N$ 339.2410, found 339.2392; $[\alpha]^{26}_D$ −6.81 (c 0.66, $CHCl_3$).

(2*R*,5*S*)-(−)-2-(4-Ethoxycarbonylbut-3-enyl)-5-heptylpyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (5, R = *n*-C_7H_{15}). To a stirred solution of **4** (R = *n*-C_7H_{15}, 134 mg, 0.41 mmol) in CH_2Cl_2 (7 mL) were added Grubbs' second catalyst (14 mg, 0.016 mmol) and ethyl acrylate (0.23 mL, 2.07 mmol), and the resulting mixture was refluxed for 5.5 h. After cooling, the solvent was removed under reduced pressure, and the residue was chromatographed on silica gel (20 g, hexane/acetone = 100:1−60:1) to give **5** (R = *n*-C_7H_{15}, 157 mg, 96%) as a pale yellow oil.

IR (neat) 1716, 1696, 1387, 1174 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87 (3H, t, J = 7.2 Hz), 1.17−1.33 (13H, br, including at δ 1.27, 3H, t, J = 7.2 Hz), 1.45 (9H, s), 1.60 (2H, m), 1.92 (2H, m), 2.20 (2H, m), 3.76 (2H, br), 4.16 (2H, q, J = 7.2 Hz), 5.81 (1H, d, J = 15.6 Hz), 6.97 (1H, dt, J = 15.6, 6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9 (q), 14.1 (q), 22.4 (t), 26.2 (t), 28.3 (q), 29.0 (t), 29.1 (t), 29.4 (t), 31.6 (t), 34.1 (t), 35.8 (t), 57.4 (d), 58.2 (d),

59.7 (t), 78.6 (s), 121.0 (d), 148.2 (d), 154.4 (s), 165.9 (s); MS 338 ($M^+ - 57$), 57 (100); HRMS calcd for $C_{19}H_{32}O_4N$ 338.2331, found 338.2338; $[\alpha]^{26}_D$ −1.75 (*c* 0.88, $CHCl_3$).

(3*R*,5*S*,8*S*)-(+)-(5-Propylhexahydropyrrolizin-3-yl)acetic Acid Ethyl Ester (6, R = Et). To a stirred solution of **5** (R = *n*-Pr, 123 mg, 0.36 mmol) in CH_2Cl_2 (10 mL) was added $AlCl_3$ (106 mg, 0.80 mmol) at 0 °C, and the resulting suspension was stirred at room temperature for 24 h. The reaction was quenched with satd $NaHCO_3$ (aq) solution, and the organic layer was separated. The aqueous layer was extracted with $CHCl_3$ (5 × 10 mL), and the organic layer and extracts were combined, dried over K_2CO_3, and evaporated to give the residue. To a stirred solution of this residue in CH_2Cl_2 (10 mL) was added K_2CO_3 (100 mg, 0.72 mmol), and the resulting suspension was stirred at room temperature for 48 h. The insoluble material was filtered off and washed with CH_2Cl_2. The filtrate was evaporated to afford the residue, which was chromatographed on silica gel (20 g, hexane/acetone = 20:1−12:1) to give **6** (R = Et, 80 mg, 93%) as a pale yellow oil, and the stereoisomer at the 3-position (all *cis*-pyrrolizidine, 2.5 mg, 3%) also as a pale yellow oil.

IR (neat) 1732, 1178 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.94 (3H, t, *J* = 7.2 Hz), 1.26 (3H, t, *J* = 7.2 Hz), 1.31 (1H, m), 1.33−1.44 (4H, br m), 1.52 (1H, m), 1.74−1.81 (4H, br m), 2.03 (2H, m), 2.28 (1H, dd, *J* = 15.1, 9.8 Hz), 2.57 (1H, dd, *J* = 15.1, 3.9 Hz), 3.01 (1H, br), 3.40 (1H, m), 3.57 (1H, br), 4.12 (2H, q, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2 (q), 14.4 (q), 21.4 (t), 30.1 (t), 30.8 (t), 31.3 (t), 32.4 (t), 33.5 (t), 43.2 (t), 54.2 (d), 60.0 (t), 63.5 (d), 65.6 (d), 172.1 (s); MS 239 (M^+), 196 (100); HRMS calcd for $C_{14}H_{25}O_2N$ 239.1885, found 239.1869; $[\alpha]^{26}_D$ +25.94 (*c* 1.95, $CHCl_3$).

Stereoisomer at the 3-position: IR (neat) 1736, 1174 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.90 (3H, t, *J* = 7.2 Hz), 1.26 (3H, t, *J* = 7.2 Hz), 1.22−1.37 (2H, m), 1.38−1.52 (5H, m), 1.91−1.98 (2H, m), 2.01−2.04 (2H, m), 2.28 (1H, dd, *J* = 15.0, 8.6 Hz), 2.53 (1H, dd, *J* = 15.0, 3.6 Hz), 2.67 (1H, m), 3.15 (1H, m), 3.57 (1H, br), 4.12 (2H, q, *J* = 7.2 Hz); MS 239 (M^+), 83 (100).

(3*R*,5*S*,8*S*)-(+)-(5-Heptylhexahydropyrrolizin-3-yl)acetic Acid Ethyl Ester (6, R = *n*-C_6H_{13}). To a stirred solution of **5** (R = *n*-C_7H_{15}, 270 mg, 0.68 mmol) in CH_2Cl_2 (20 mL) was added $AlCl_3$ (200 mg, 1.50 mmol) at 0 °C, and the resulting suspension was stirred at room temperature for 24 h. The reaction was quenched with satd $NaHCO_3$ (aq) solution, and the organic layer was separated. The aqueous layer was extracted with $CHCl_3$ (5 × 20 mL), and the organic layer and extracts were combined, dried over K_2CO_3, and evaporated to give the residue. To a stirred solution of this residue in CH_2Cl_2 (20 mL) was added K_2CO_3 (189 mg, 1.37 mmol), and the resulting suspension was stirred at room temperature for 48 h. The insoluble material was filtered off and washed with CH_2Cl_2. The filtrate was evaporated to afford the residue, which was chromatographed on silica gel (30 g, hexane/acetone = 20:1−12:1) to give **6** (R = *n*-C_6H_{13}, 178 mg, 88%) as a pale yellow oil.

IR (neat) 1731, 1176 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.87 (3H, t, *J* = 7.2 Hz), 1.25 (3H, t, *J* = 7.2 Hz), 1.17−2.41 (14H, br m), 1.51 (1H, m), 1.76 (3H, m), 2.01 (2H, m), 2.27 (1H, dd, *J* = 14.8, 9.6 Hz), 2.56 (1H, dd, *J* = 14.8, 4.1 Hz), 2.99 (1H, br), 3.38 (1H, m), 3.56 (1H, m), 4.10 (2H, *q* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9 (q), 14.1 (q), 22.5 (t), 28.1 (t), 29.1 (t), 29.7 (t), 30.1 (t), 30.6 (t), 31.1 (t), 31.2 (t), 31.6 (t), 32.2 (t), 43.1 (t), 54.0 (d), 59.8 (t), 63.6 (d), 65.5 (d), 171.8 (s); MS 295 (M^+), 196 (100); HRMS calcd for $C_{18}H_{33}O_2N$ 295.2510, found 295.2501; $[\alpha]^{26}_D$ +18.82 (*c* 1.14, $CHCl_3$).

(3*S*,5*S*,8*S*)-(+)-3-Heptyl-5-propylhexahydropyrrolizine (7, R = *n*-Pr, R′ = *n*-C_7H_{15}). To a stirred solution of **6** (R = Et, 79 mg, 0.32 mmol) in CH_2Cl_2 (7 mL) was added a solution of DIBAL (0.98 M in hexane, 0.36 mL, 0.35 mmol) at −50 °C, and the reaction mixture was stirred at −50 °C for 30 min. The reaction was quenched with MeOH, and satd Rochelle (aq) solution, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), and the organic layer and extracts were combined, dried over K_2CO_3, and evaporated to give a pale yellow oil, which was used directly in the next step.

To a stirred suspension of *n*-$C_5H_{11}P^+Ph_3Br^-$ (529 mg, 1.28 mmol) in THF (10 mL) was added a solution of *n*-BuLi (1.6 M in hexane, 0.7 mL, 1.12 mmol) at 0 °C, and the resulting orange suspension was stirred at 0 °C for 10 min. To the suspension was added a solution of the above aldehyde in THF (3 mL) at 0 °C, and the resulting suspension was stirred at room temperature for 22 h. The reaction was quenched with H_2O, and the aqueous mixture was extracted with Et_2O (4 × 15 mL). The organic extracts were combined, dried over K_2CO_3, and evaporated to give a residue, which was chromatographed on silica gel (20 g, hexane/acetone = 25:1−10:1) to give the corresponding olefin (37 mg, 46%) as a mixture of *E*- and *Z*-isomers.

^1H NMR (500 MHz, $CDCl_3$) δ 0.89 (3H, t, *J* = 7.2 Hz), 0.94 (3H, t, *J* = 7.1 Hz), 1.21−1.53 (12H, br m), 1.72−1.88 (3H, m), 1.89−1.94 (1H, m), 1.96−2.07 (3H, m), 2.30−2.41 (1H, m), 2.93−3.00 (1H, m), 3.02−3.16 (1H, m), 3.62 (1H, br), 5.32−5.47 (2H, m).

To a stirred solution of the above olefin (20 mg, 0.08 mmol) in EtOAc (3 mL) was added 10% Pd/C (10 mg), and the resulting suspension was stirred under a hydrogen atmosphere at 1 atm for 40 h. The catalyst was removed by filtration and the filtrate was evaporated to give **7** (R = *n*-Pr, R′ = *n*-C_7H_{15}, 20 mg, quant) as a pale yellow oil.

IR (neat) 2926, 2869, 1457 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.88 (3H, t, *J* = 7.1 Hz), 0.94 (3H, t, *J* = 7.1 Hz), 1.27−1.43 (17H, br m), 1.54 (1H, br), 1.77 (3H, m), 1.97 (3H, m), 2.90 (1H, br), 3.05 (1H, br), 3.57 (1H, br); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2 (q), 14.6 (q), 21.6 (t), 22.8 (t), 27.2 (t), 29.4 (t), 29.9 (t), 30.2 (t), 30.9 (t), 31.7 (t), 31.9 (t), 32.1 (t), 33.8 (t), 38.6 (t), 57.7 (d), 63.8 (d), 65.8 (d); MS 251 (M^+), 208 (100); HRMS calcd for $C_{17}H_{33}N$ 251.2613, found 251.2601; $[\alpha]^{26}_D$ +36.81 (*c* 0.44, $CHCl_3$).

(3*R*,5*S*,8*S*)-(+)-3-Allyl-5-heptylhexahydropyrrolizine. To a stirred solution of **6** (R = *n*-C_6H_{13}, 91 mg, 0.31 mmol) in CH_2Cl_2 (7 mL) was added a solution of DIBAL (0.98 M in hexane, 0.35 mL, 0.34 mmol) at −50 °C, and the reaction mixture was stirred at −50 °C for 30 min. The reaction was quenched with MeOH, and then satd Rochelle (aq) solution, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), and the organic layer and extracts were combined, dried over K_2CO_3, and evaporated to give a pale yellow oil, which was used directly in the next step.

To a stirred suspension of $MeP^+Ph_3I^-$ (501 mg, 1.24 mmol) in THF (10 mL) was added a solution of *n*-BuLi (1.6 M in hexane, 0.68 mL, 1.09 mmol) at 0 °C, and the resulting orange suspension was stirred at 0 °C for 10 min. To the suspension was added a solution of the above aldehyde in THF (3 mL) at 0 °C, and the resulting suspension was stirred at room temperature for 27 h. The reaction was quenched with H_2O, and the aqueous mixture was extracted with Et_2O (4 × 15 mL). The organic extracts were combined, dried over K_2CO_3, and evaporated to give a residue, which was chromatographed on silica gel (20 g, hexane/acetone = 20:1−10:1) to give the corresponding olefin (38 mg, 49%) as a pale yellow oil.

IR (neat) 3074, 2953, 2927, 2857, 1465, 909 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.87 (3H, t, *J* = 7.2 Hz), 1.20−1.41 (14H, br m), 1.50 (1H, m), 1.73−1.83 (3H, m), 1.91 (1H, m), 1.97−2.04 (2H, m), 2.36 (1H, m), 2.95−3.03 (2H, m), 3.57 (1H, m), 4.98 (1H, d, *J* = 10.2 Hz), 5.02 (1H, d, *J* = 15.0 Hz), 5.98 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2 (q), 22.8 (t), 28.4 (t), 29.3 (t), 30.0 (t), 30.2 (t), 31.0 (t), 31.4 (t), 31.5 (t), 31.6 (t), 31.9 (t), 43.0 (t), 57.1 (d), 64.0 (d), 66.0 (d), 115.8 (t), 136.6 (d); MS 249 (M^+),

208 (100); HRMS calcd for $C_{17}H_{31}N$ 249.2455, found 249.2473; $[\alpha]^{26}_D$ +36.81 (*c* 0.44, $CHCl_3$).

(3*S*,5*S*,8*R*)-(+)-3-Heptyl-5-propylhexahydropyrrolizine (7, R = *n*-C_7H_{15}, R′ = *n*-Pr). To a stirred solution of the above olefin (25 mg, 0.10 mmol) in EtOAc (3 mL) was added 10% Pd/C (13 mg), and the resulting suspension was stirred under a hydrogen atmosphere at 1 atm for 44 h. The catalyst was removed by filtration and the filtrate was evaporated to give **7** (R = *n*-C_7H_{15}, R′ = *n*-Pr, 24 mg, 95%) as a pale yellow oil.

IR (neat) 2966, 2927, 2851, 1458 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.87 (3H, t, *J* = 7.1 Hz), 0.90 (3H, t, *J* = 6.9 Hz), 1.40−1.50 (19H, br m), 1.56 (1H, m), 1.79 (2H, m), 1.98 (2H, m), 2.92 (1H, m), 3.08 (1H, br), 3.64 (1H, br); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2 (q), 14.4 (q), 20.4 (t), 22.7 (t), 28.3 (t), 29.3 (t), 30.0 (t), 30.1 (t), 30.7 (t), 31.3 (t), 31.7 (t), 31.9 (t), 32.1 (t), 40.4 (t), 57.8 (d), 64.0 (d), 66.0 (d); MS 251 (M^+), 208 (100); HRMS calcd for $C_{17}H_{33}N$ 251.2613, found 251.2620; $[\alpha]^{26}_D$ +25.48 (*c* 0.47, $CHCl_3$).

(5*S*)-(−)-5-Propyl-2-oxopyrrolidine (8, R = *n*-Pr). To a stirred suspension of CuI (3.8 g, 20 mmol) in THF (30 mL) was added a solution of EtMgBr (0.96 M in THF, 42 mL, 40 mmol) at −35 °C, and the resulting suspension was stirred at the same temperature for 30 min. To the suspension was added a solution of **1** (1.8 g, 8 mmol) in THF (15 mL) at −35 °C, and then the reaction mixture was stirred at −35 °C for 18 h. The reaction was quenched with satd NH_4Cl (aq) solution, and the insoluble material was filtered off and washed with $CHCl_3$. The organic layer was separated, and the aqueous layer was extracted with $CHCl_3$ (2 × 30 mL). The organic layer and extracts were combined, dried over $MgSO_4$, and evaporated to give a residue, which was chromatographed on silica gel (50 g, hexane/acetone = 20:1−2:1) to give **8** (R = *n*-Pr, 525 mg, 52%) as a pale yellow oil.

IR (neat) 3193, 1699, 1286 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.93 (3H, t, *J* = 7.2 Hz), 1.36 (2H, m), 1.44 (1H, m), 1.51 (1H, m), 1.69 (1H, m), 2.25 (1H, m), 2.32 (2H, m), 3.63 (1H, quint, *J* = 6.8 Hz), 6.42 (1H, br); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.6 (q), 18.7 (t), 26.8 (t), 30.2 (t), 38.6 (t), 54.3 (d), 178.3 (s); MS 127 (M^+), 84 (100); HRMS calcd for $C_7H_{13}ON$ 127.0997, found 127.1001; $[\alpha]^{26}_D$ −9.20 (*c* 1.19, $CHCl_3$).

(2*S*)-(+)-2-Heptyl-5-oxopyrrolidine (8, R = *n*-C_7H_{15}). To a stirred suspension of CuI (4.52 g, 23.8 mmol) in THF (30 mL) was added a solution of *n*-$C_7H_{15}MgBr$, prepared from *n*-$C_7H_{15}Br$ (7.34 mL, 52.31 mmol) and Mg (1.26 g, 52.31 mmol) in THF (50 mL) at reflux, at −35 °C, and the resulting suspension was stirred at the same temperature for 30 min. To the suspension was added a solution of **1** (2.14 g, 9.51 mmol) in THF (15 mL) at −35 °C, and then the reaction mixture was stirred at −35 °C for 18 h. The reaction was quenched with satd NH_4Cl (aq) solution, and the insoluble material was filtered off and washed with $CHCl_3$. The organic layer was separated, and the aqueous layer was extracted with $CHCl_3$ (2 × 30 mL). The organic layer and extracts were combined, dried over $MgSO_4$, and evaporated to give the residue, which was chromatographed on silica gel (50 g, hexane/acetone = 20:1−5:1) to give **8** (R = *n*-C_7H_{15}, 870 mg, 50%) as a pale yellow oil.

IR (neat) 3209, 1698, 1284 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.88 (3H, t, *J* = 7.2 Hz), 1.30 (9H, m), 1.43−1.54 (2H, m), 1.68−1.76 (2H, m), 2.23 (1H, m), 2.33 (2H, m), 3.62 (1H, quint, *J* = 6.9 Hz), 5.77 (1H, br); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.84 (q), 22.4 (t), 25.5 (t), 26.9 (t), 28.9 (t), 29.2 (t), 30.3 (t), 31.5 (t), 36.5 (t), 54.6 (d), 178.3 (s); MS 183 (M^+), 84 (100); HRMS calcd for $C_{11}H_{21}ON$ 183.1623, found 183.1608; $[\alpha]^{26}_D$ +8.30 (*c* 0.89, CH_2Cl_2) {lit. $[\alpha]^{26}_D$ +9.0 (*c* 2.0, CH_2Cl_2)}.

(2*R*)-(−)-5-Propyl-2-oxopyrrolidine-1-carboxylic Acid *tert*-Butyl Ester. To a stirred solution of **8** (R = *n*-Pr, 247 mg, 1.94 mmol) in MeCN (10 mL) was added DMAP (261 mg, 2.14 mmol) at 0 °C, and the reaction mixture was stirred at 0 °C for 30 min. To the reaction mixture was added Boc_2O (508 mg, 2.33 mmol) at 0 °C, and then the resulting mixture was stirred at room temperature for 43 h. The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel (20 g, hexane/acetone = 30:1−15:1) to give the title Boc-imide (414 mg, 94%) as a pale yellow oil.

IR (neat) 1786, 1749, 1714, 1306, 1153 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.95 (3H, t, *J* = 7.2 Hz), 1.34 (1H, m), 1.39 (1H, m), 1.52 (9H, s), 1.69−1.78 (2H, m), 2.42 (1H, m), 2.57 (1H, m), 4.10 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.6 (q), 18.5 (t), 22.1 (t), 27.6 (q), 31.0 (t), 31.5 (t), 35.4 (t), 57.4 (d), 82.0 (s), 149.3 (s), 173.8 (s); MS 227 (M^+), 84 (100); HRMS calcd for $C_{12}H_{21}O_3N$ 227.1522, found 227.1527; $[\alpha]^{26}_D$ −62.86 (*c* 0.87, $CHCl_3$).

(2*R*)-(−)-2-Heptyl-5-oxopyrrolidine-1-carboxylic Acid *tert*-Butyl Ester. To a stirred solution of **8** (R = *n*-C_7H_{15}, 602 mg, 3.29 mmol) in MeCN (20 mL) was added DMAP (442 mg, 3.62 mmol) at 0 °C, and the reaction mixture was stirred at 0 °C for 30 min. To the reaction mixture was added Boc_2O (862 mg, 3.95 mmol) at 0 °C, and then the resulting mixture was stirred at room temperature for 48 h. The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel (40 g, hexane/acetone = 30:1−15:1) to give the desired Boc-imide (866 mg, 93%) as a pale yellow oil.

IR (neat) 1788, 1750, 1714, 1308, 1153 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.88 (3H, t, *J* = 7.2 Hz), 1.28 (10H, m), 1.46 (1H, br), 1.52 (9H, s), 1.76 (2H, m), 2.08 (1H, m), 2.41 (1H, m), 2.53 (1H, m), 4.09 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9 (q), 22.3 (t), 22.4 (t), 25.4 (t), 27.8 (q), 29.0 (t), 31.2 (t), 31.5 (t), 33.5 (t), 57.8 (d), 82.2 (s), 149.5 (s), 174.0 (s); MS 283 (M^+), 57 (100); HRMS calcd for $C_{16}H_{29}O_3N$ 283.2148, found 283.2128; $[\alpha]^{26}_D$ −57.34 (*c* 1.21, $CHCl_3$).

(1*R*)-(+)-[1-(3-Oxohept-7-enyl)butyl]carbamic Acid *tert*-Butyl Ester (9, R = *n*-Pr). To a stirred solution of the above Boc-imide (1.08 g, 4.75 mmol) in THF (15 mL) was added a solution of 4-butenylMgBr, prepared from 1-bromo-4-butene (1.45 mL, 14.27 mmol) and Mg (342 mg, 14.27 mmol) in THF (60 mL) at reflux, and TMEDA (2.27 mL, 14.27 mmol) at −78 °C, and the resulting mixture was stirred at the same temperature for 1.5 h. The reaction was quenched with *i*-PrOH (5 mL), and the reaction mixture was diluted with Et_2O. The organic layer was washed with 10% HCl (aq) solution, dried over $MgSO_4$, and evaporated to give a pale yellow oil, which was chromatographed on silica gel (40 g, hexane/acetone = 50:1−40:1) to give **9** (R = *n*-Pr, 1.28 g, 95%) as a colorless solid (mp 64−66 °C).

IR (KBr) 3349, 3083, 1707, 1685, 1528, 1174 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.89 (3H, t, *J* = 7.2 Hz), 1.26−1.38 (5H, br m), 1.42 (9H, s), 1.50 (1H, m), 1.72 (1H, m), 2.30 (2H, q, *J* = 7.2 Hz), 2.48 (3H, q, *J* = 7.2 Hz), 3.51 (1H, br), 4.23 (1H, br d, *J* = 9.1 Hz), 4.94 (1H, d, *J* = 9.5 Hz), 5.01 (1H, d, *J* = 15.0 Hz), 5.79 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.7 (q), 18.9 (t), 27.5 (t), 28.1 (q), 29.0 (t), 37.9 (t), 39.1 (t), 41.6 (t), 49.8 (d), 78.3 (s), 114.7 (t), 136.6 (d), 155.4 (s), 209.2 (s); MS 283 (M^+), 57 (100); HRMS calcd for $C_{16}H_{29}O_3N$ 283.2148, found 283.2142; $[\alpha]^{26}_D$ +5.10 (*c* 1.15, $CHCl_3$).

(1*R*)-(−)-[1-(3-Oxohept-7-enyl)octyl]carbamic Acid *tert*-Butyl Ester (9, R = *n*-C_7H_{15}). To a stirred solution of the above Boc-imide (724 mg, 2.56 mmol) in THF (10 mL) was added a solution of 4-butenylMgBr, prepared from 1-bromo-4-butene (0.78 mL, 7.68 mmol) and Mg (185 mg, 7.68 mmol) in THF (40 mL) at reflux, and TMEDA (1.16 mL, 7.68 mmol) at −78 °C, and the resulting mixture was stirred at the same temperature for 1.5 h. The reaction was quenched with *i*-PrOH (5 mL), and the reaction mixture was diluted with Et_2O. The organic layer was washed with 10% HCl (aq) solution, dried over $MgSO_4$, and evaporated to give a pale yellow oil, which was

chromatographed on silica gel (30 g, hexane/acetone = 50:1−30:1) to give **9** (R = *n*-C_7H_{15}, 850 mg, 98%) as a colorless solid (mp 48−50 °C).

IR (KBr) 3348, 3080, 1707, 1685, 1531, 1173 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.87 (3H, t, J = 7.2 Hz), 1.25 (12H, br), 1.43 (9H, s), 1.49 (1H, br), 1.77 (1H, m), 2.31 (2H, q-like, J = 7.2 Hz), 2.49 (4H, m), 3.50 (1H, br), 4.20 (1H, br d, J = 9.4 Hz), 4.95 (1H, d, J = 9.6 Hz), 5.01 (1H, d, J = 15.0 Hz), 5.79 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0 (q), 22.5 (t), 25.8 (t), 27.6 (t), 28.3 (q), 29.1 (t), 29.2 (t), 29.3 (t), 31.6 (t), 35.9 (t), 39.3 (t), 41.8 (t), 50.3 (d), 78.6 (s), 114.8 (t), 136.8 (d), 155.5 (s), 209.5 (s); MS 339 (M^+), 57 (100); HRMS calcd for $C_{16}H_{28}O_3N$ 282.2068, found 282.2091; $[\alpha]^{26}_D$ −1.04 (*c* 1.05, $CHCl_3$).

(1*R*)-(−)-[1-(3-Oxoheptyl)pent-4-enyl]carbamic Acid *tert*-Butyl Ester (10). To a stirred solution of the Boc-imide (239 mg, 1.00 mmol), prepared from **2** (as described in the preparation of **3**), in THF (10 mL) was added a solution of *n*-PrMgBr, prepared from *n*-BuBr (0.32 mL, 3.00 mmol) and Mg (72 mg, 3.00 mmol) in THF (10 mL) at reflux, and TMEDA (0.48 mL, 3.00 mmol) at −78 °C, and the resulting mixture was stirred at the same temperature for 1.5 h. The reaction was quenched with *i*-PrOH (5 mL), and the reaction mixture was diluted with Et_2O. The organic layer was washed with 10% HCl (aq) solution, dried over $MgSO_4$, and evaporated to give a pale yellow oil, which was chromatographed on silica gel (20 g, hexane/acetone = 50:1−30:1) to give **10** (292 mg, 98%) as a colorless solid (mp 42−43 °C).

IR (KBr) 3351, 3080, 1688, 1530, 1174 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.88 (3H, t, J = 7.2 Hz), 1.28 (2H, sext, J = 7.2 Hz), 1.42 (9H, s), 1.47−1.61 (5H, br m), 1.77 (1H, m), 2.08 (2H, q-like, J = 7.2 Hz), 2.38 (2H, t, J = 7.2 Hz), 2.46 (2H, t, J = 7.2 Hz), 3.50 (1H, br), 4.26 (1H, br d, J = 9.1 Hz), 4.94 (1H, d, J = 10.2 Hz), 5.00 (1H, d, J = 15.0 Hz), 5.78 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.7 (q), 22.1 (t), 25.7 (t), 28.2 (q), 29.0 (t), 30.0 (t), 35.0 (t), 39.1 (t), 42.4 (t), 49.8 (d), 78.4 (s), 114.5 (t), 137.6 (d), 155.4 (s), 210.4 (s); MS 240 (M^+ − 57), 57 (100); HRMS calcd for $C_{13}H_{22}O_3N$ 240.1600, found 240.1616; $[\alpha]^{26}_D$ −0.47 (*c* 1.20, $CHCl_3$).

(2*R*,5*S*)-(−)-2-But-3-enyl-5-butylpyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (11). To a stirred solution of **10** (279 mg, 0.94 mmol) in CH_2Cl_2 (7 mL) was added a solution of $(C_6F_5)_3B$ (96 mg, 0.19 mmol) and Ph_3SiH (490 mg, 1.88 mmol) in CH_2Cl_2 (10 mL) at −78 °C, and the reaction mixture was stirred at −78 °C for 30 min, and then at room temperature for 24 h. The reaction was quenched with Et_3N (1.0 mL), and the resulting mixture was stirred at room temperature for 20 min. The mixture was diluted with Et_2O, and the organic layer was washed successively with 10% AcOH (aq) solution and satd $NaHCO_3$ (aq) solution, dried over $MgSO_4$, and evaporated to give a pale yellow oil, which was chromatographed on silica gel (20 g, hexane/acetone = 200:1−150:1) to give **11** (194 mg, 73%) as a colorless oil.

IR (neat) 3080, 1696, 1388 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.90 (3H, t, J = 7.2 Hz), 1.24−1.40 (6H, br m), 1.46 (9H, s), 1.61 (2H, br), 1.93 (4H, br m), 2.05 (2H, br m), 3,75 (2H, br), 4.80 (1H, d, J = 10.5 Hz), 5.03 (1H, d, J = 16.0 Hz), 5.82 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1 (q), 22.7 (t), 28.5 (q), 28.6 (t), 29.4 (t), 30.7 (t), 35.1 (t), 35.6 (t), 57.8 (d), 58.3 (d), 78.6 (s), 114.2 (t), 138.2 (d), 154.6 (s); MS 281 (M^+), 170 (100); HRMS calcd for $C_{17}H_{31}O_2N$ 281.2355, found 281.2355; $[\alpha]^{26}_D$ −2.72 (*c* 1.15, $CHCl_3$).

(2*R*,5*S*)-(−)-2-(4-Ethoxycarbonylbut-3-enyl)-5-butylpyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (12). To a stirred solution of **11** (155 mg, 0.55 mmol) in CH_2Cl_2 (10 mL) were added Grubbs' second catalyst (19 mg, 0.022 mmol) and ethyl acrylate (0.30 mL, 2.76 mmol), and the resulting mixture was refluxed for 5 h. After cooling, the solvent was removed under reduced pressure, and the residue was chromatographed on silica gel (20 g, hexane/acetone = 100:1−60:1) to give **12** (186 mg, 96%) as a pale yellow oil.

IR (neat) 1718, 1696, 1389, 1174 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.89 (3H, t, J = 7.2 Hz), 1.20−1.37 (10H, br, including at δ 1.28, 3H, t, J = 7.2 Hz), 1.45 (9H, s), 1.60 (2H, br), 1.91 (3H, br), 2.20 (2H, br), 3.77 (2H, br), 4.17 (2H, q, J = 7.2 Hz), 5.82 (1H, d, J = 15.7 Hz), 6.96 (1H, dt, J = 15.7, 6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0 (q), 14.1 (q), 22.6 (t), 28.4 (q), 28.5 (t), 29.1 (t), 29.4 (t), 34.2 (t), 35.6 (t), 57.6 (d), 58.3 (d), 59.9 (t), 78.8 (s), 121.1 (d), 148.3 (d), 154.6 (s), 166.1 (s); MS 353 (M^+), 252 (100); HRMS calcd for $C_{20}H_{35}O_4N$ 353.2564, found 353.2544; $[\alpha]^{26}_D$ −2.89 (*c* 0.75, $CHCl_3$).

(3*R*,5*S*,8*S*)-(+)-(5-Butylhexahydropyrrolizin-3-yl)acetic Acid Ethyl Ester (13). To a stirred solution of **12** (100 mg, 0.28 mmol) in CH_2Cl_2 (7 mL) was added $AlCl_3$ (83 mg, 0.62 mmol) at 0 °C, and the resulting suspension was stirred at room temperature for 24 h. The reaction was quenched with satd $NaHCO_3$ (aq) solution, and the organic layer was separated. The aqueous layer was extracted with $CHCl_3$ (5 × 10 mL), and the organic layer and extracts were combined, dried over K_2CO_3, and evaporated to give a residue. To a stirred solution of this residue in CH_2Cl_2 (7 mL) was added K_2CO_3 (78 mg, 0.57 mmol), and the resulting suspension was stirred at room temperature for 48 h. The insoluble material was filtered off and washed with CH_2Cl_2. The filtrate was evaporated to afford a residue, which was chromatographed on silica gel (20 g, hexane/acetone = 20:1−8:1) to give **13** (66 mg, 92%) as a pale yellow oil.

IR (neat) 1733, 1181 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.90 (3H, t, J = 7.2 Hz), 1.26 (3H, t, J = 7.2 Hz), 1.28−1.43 (7H, br m), 1.52 (1H, m), 1.69 (1H, br), 1.78 (3H, m), 2.28 (1H, dd, J = 15.0, 9.8 Hz), 2.57 (1H, dd, J = 15.0, 4.3 Hz), 3.00 (1H, br), 3.40 (1H, m), 3.57 (1H, br), 4.11 (2H, q, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1 (q), 14.2 (q), 22.9 (t), 30.2 (t), 30.4 (t), 30.8 (t), 31.0 (t), 31.3 (t), 32.4 (t), 43.2 (t), 54.2 (d), 60.0 (t), 63.7 (d), 65.6 (d), 172.1 (s); MS 253 (M^+), 196 (100); HRMS calcd for $C_{15}H_{27}O_2N$ 253.2042, found 253.2058; $[\alpha]^{26}_D$ +21.06 (*c* 0.83, $CHCl_3$).

(3*S*,5*S*,8*S*)-(+)-3,5-Dibutylhexahydropyrrolizine (14). To a stirred solution of **13** (70 mg, 0.28 mmol) in CH_2Cl_2 (7 mL) was added a solution of DIBAL (0.98 M in hexane, 0.31 mL, 0.31 mmol) at −50 °C, and the reaction mixture was stirred at −50 °C for 30 min. The reaction was quenched with MeOH, and satd Rochelle (aq) solution, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), and the organic layer and extracts were combined, dried over K_2CO_3, and evaporated to give a pale yellow oil, which was used directly in the next step.

To a stirred suspension of $EtP^+Ph_3Br^-$ (410 mg, 1.12 mmol) in THF (7 mL) was added a solution of *n*-BuLi (1.6 M in hexane, 0.6 mL, 0.98 mmol) at 0 °C, and the resulting orange suspension was stirred at 0 °C for 10 min. To the suspension was added a solution of the above aldehyde in THF (3 mL) at 0 °C, and the resulting suspension was stirred at room temperature for 27 h. The reaction was quenched with H_2O, and the aqueous mixture was extracted with Et_2O (4 × 15 mL). The organic extracts were combined, dried over K_2CO_3, and evaporated to give a residue, which was chromatographed on silica gel (20 g, hexane/acetone = 25:1−10:1) to give the corresponding olefin (31 mg, 50%) as a mixture of *E*- and *Z*-isomers.

^1H NMR (500 MHz, $CDCl_3$) δ 0.90 (3H, t, J = 6.8 Hz), 1.24−1.41 (8H, br m), 1.48 (1H, m), 1.62 (3H, d, J = 6.8 Hz), 1.72−1.93 (4H, br m), 1.95−2.08 (2H, m), 2.31 (1H, br), 2.96 (1H, m), 3.04 (1H, br), 3.60 (1H, br), 5.36−5.51 (2H, br m).

To a stirred solution of the above olefin (20 mg, 0.09 mmol) in EtOAc (3 mL) was added 10% Pd/C (10 mg), and the resulting suspension was stirred under a hydrogen atmosphere at 1 atm for 45 h. The catalyst was removed by filtration and the filtrate was evaporated to give **14** (20 mg, quant) as a pale yellow oil.

IR (neat) 2928, 2858, 1457, 1099 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (3H, t, $J = 7.2$ Hz), 0.90 (3H, t, $J = 6.8$ Hz), 1.20−1.51 (15H, br m), 1.60 (1H, m), 1.81 (2H, m), 1.98 (2H, m), 2.91 (1H, m), 3.10 (1H, br), 3.68 (1H, br); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1 (q), 14.2 (q), 22.9 (t), 23.0 (t), 29.4 (t), 30.1 (t), 30.4 (t), 30.7 (t), 30.9 (t), 31.6 (t), 32.1 (t), 37.6 (t), 58.2 (d), 64.0 (d), 66.0 (d); MS 223 (M^+), 55 (100); HRMS calcd for $C_{15}H_{29}N$ 223.2300, found 223.2312; $[\alpha]^{26}_D$ +29.77 (*c* 0.40, $CHCl_3$).

(1*R*)-(+)-[1-(3-Oxohept-7-enyl)pentyl]carbamic Acid *tert*-Butyl Ester (15). To a stirred solution of **2**[8] (337 mg, 2.42 mmol) in MeCN (20 mL) was added DMAP (326 mg, 2.67 mmol) at 0 °C, and the reaction mixture was stirred at 0 °C for 30 min. To the reaction mixture was added Boc_2O (633 mg, 2.90 mmol) at 0 °C, and the resulting mixture was stirred at room temperature for 45 h. The volatiles were evaporated, and the residue was chromatographed on silica gel (20 g, hexane/acetone = 15:1) to give the Boc-imide (550 mg, 95%) as a colorless oil.

IR (neat) 3078, 1785, 1750, 1714, 1308, 1153 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.52 (9H, s), 1.59 (1H, m), 1.78 (1H, m), 1.90 (1H, m), 2.03−2.19 (3H, br m), 2.43 (1H, ddd, $J = 9.0$, 8.5, 2.1 Hz), 2.57 (1H, dd, $J = 9.0$, 8.5 Hz), 4.12 (1H, m), 5.01 (1H, d, $J = 10.7$ Hz), 5.04 (1H, d, $J = 15.0$ Hz), 5.80 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.9 (t), 27.7 (q), 29.6 (t), 31.0 (t), 32.4 (t), 57.1 (d), 82.2 (s), 115.0 (t), 136.7 (d), 149.3 (s), 173.7 (s); MS 182 ($M^+ - 57$), 84 (100); HRMS calcd for $C_{13}H_{21}O_3N$ 239.1520, found 239.1534; $[\alpha]^{26}_D$ −56.68 (*c* 2.34, $CHCl_3$).

To a stirred solution of the above Boc-imide (239 mg, 1 mmol) in EtOAc (10 mL) was added 10% Pd/C (50 mg), and the resulting suspension was stirred under a hydrogen atmosphere at 1 atm for 48 h. The catalyst was removed by filtration and the filtrate was evaporated to give the corresponding imide as a pale yellow oil, which was used directly in the next step.

To a stirred solution of the imide prepared above in THF (5 mL) was added a solution of 4-butenylMgBr, prepared from 4-bromo-1-butene (0.30 mL, 3.00 mmol) and Mg (72 mg, 3.00 mmol) in THF (8 mL) at reflux, and TMEDA (0.48 mL, 3.00 mmol) at −78 °C, and the resulting mixture was stirred at the same temperature for 1.5 h. The reaction was quenched with *i*-PrOH (5 mL), and the reaction mixture was diluted with Et_2O. The organic layer was washed with 10% HCl (aq) solution, dried over $MgSO_4$, and evaporated to give a pale yellow oil, which was chromatographed on silica gel (20 g, hexane/acetone = 50:1−30:1) to give **15** (284 mg, 96%) as a colorless solid (mp 38−39 °C).

IR (KBr) 3355, 3070, 1709, 1685, 1530, 1174 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.88 (3H, t, $J = 7.2$ Hz), 1.30 (6H, br m), 1.43 (9H, s), 1.51 (1H, br), 1.78 (1H, m), 2.31 (2H, q-like, $J = 6.9$ Hz), 2.49 (4H, m), 3.50 (1H, br), 4.21 (1H, br d, $J = 9.0$ Hz), 4.96 (1H, d, $J = 10.2$ Hz), 5.00 (1H, d, $J = 16.0$ Hz), 5.82 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.6 (q), 22.2 (t), 27.3 (t), 27.7 (t), 28.0 (q), 28.9 (t), 35.2 (t), 39.0 (t), 41.4 (t), 49.9 (d), 78.0 (s), 114.5 (t), 136.5 (d), 155.3 (s), 209.0 (s); MS 297 (M^+), 57 (100); HRMS calcd for $C_{17}H_{31}O_3N$ 297.2304, found 297.2315; $[\alpha]^{26}_D$ +2.76 (*c* 1.04, $CHCl_3$).

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Supporting Information Available: Experimental details for compounds *ent*-**4**, **-5**, **-6**, **-7**, **-11**, **-12**, **-13**, and **-14**, characterization data for all new synthetic compounds, including ^1H and ^{13}C NMR spectra, the GC-MS of coinjection data, and FTIR spectra of synthetic stereoisomers of **251O** and natural **251O**. This material is available free of charge via the Internet at http://pubs.acs.org.