Supporting Information for the Manuscript

**Enantiopure 2,6-Disubstituted Piperidines Bearing One Alkene- or Alkyne-Containing Substituent: Preparation and Application to Total Syntheses of Indolizidine-Alkaloids**

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Page S3-S21: Experimental Procedures.

Page S22-S85: the $^1$H NMR and $^{13}$C NMR spectra for compounds 14a-e, 16, 7a-r, 8a-d, (–)-167B (1), (–)-195H (2), (–)-209D (3), (–)-223AB (4).

**List of $^1$H NMR and $^{13}$C NMR spectra for compounds.**

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Experimental Section

General Conditions: All melting points were determined on a Yanaco melting point apparatus and are uncorrected. Optical rotations were recorded on a Perkin-Elmer 343 polarimeter. IR spectra were recorded on a Nicolet FT-IR 5DX spectrometer with KBr pellets. $^1$H NMR and $^{13}$C NMR spectra were recorded on a JEOL JNM-ECA 300 spectrometer in CDCl$_3$. TMS was used as internal reference and the $J$ values are given in Hz. MS were recorded on a VG-ZAB-MS spectrometer with 70 eV. Elementary analysis data were obtained on a Perkin-Elmer-241C apparatus. PE is petroleum ether (60-90$^\circ$).

A Typical Procedure for Preparation of (7aR,11R,13S)-11-Vinyl-13-phenyl-7a,8,10,11-tetrahydro-9H,13H-naphtho[1,2-e]pyrido[2,1-b][1,3]oxazine (14a): To a cold solution (ice-water bath) of 12 (4.32 g, 10 mmol) in dry THF (70 mL) was added H$_2$C=CHMgCl (1.6 M in THF, 18.8 mL, 30 mmol) dropwise under N$_2$. After the reaction was stirred at 0 $^\circ$C for 0.5 h (monitored by TLC), a saturated aqueous solution of NH$_4$Cl (30 mL) was added to quench the reaction. Then, the resultant mixture was extracted with CH$_2$Cl$_2$ (3 x 30 mL). The combined organic layers were washed with H$_2$O, brine and dried over anhydrous Na$_2$SO$_4$. After removal of the solvent, the residue was purified by chromatography (silica gel, EtOAc:PE = 1:15) to give product 14a.
(3.14 g, 92%) as a white crystal, mp 137-138 °C (EtOAc-PE), [\( \alpha \)\( _D \)]\( ^{25} \) = +173.4° (c 0.2, CHCl\(_3\)). IR: \( \nu \) 3063, 2935, 1628 cm\(^{-1}\); \(^1\)H NMR: \( \delta \) 1.43-1.50 (m, 1H), 1.65-1.74 (m, 2H), 1.85-2.07 (m, 3H), 3.62-3.70 (m, 1H), 4.51-4.55 (m, 1H), 4.91-4.97 (m, 2H), 5.17 (s, 1H), 5.92-6.08 (m, 1H), 7.06-7.08 (m, 1H), 7.16-7.31 (m, 8H), 7.65-7.75 (m, 2H); \(^{13}\)C NMR: \( \delta \) 15.2, 29.8, 31.6, 60.2, 63.5, 81.0, 114.4, 115.3, 118.7, 122.8, 123.0, 126.1, 127.0, 128.0 (2C), 128.4, 128.6 (2C), 129.2 (2C), 131.9, 140.6, 143.1, 153.4; MS m/z (\%) : 341 (M\(^+\), 6.3), 231 (100). Anal. Calcd. For C\(_{24}\)H\(_{23}\)NO: C, 84.42; H, 6.79; N, 4.10. Found: C, 84.20; H, 6.89; N, 4.25.

By using the similar procedure, the intermediates 14b-e were prepared.

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14b
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(7aR,11R,13S)-11-(2-Methyl-propenyl)-13-phenyl-7a,8,10,11-tetrahydro-9H-naphtho[1,2-e]pyrido[2,1-b][1,3]oxazine (14b): It is a white crystal (94%), mp 142-144 °C (EtOAc-PE), [\( \alpha \)\( _D \)]\( ^{25} \) = +230.2° (c 0.2, CHCl\(_3\)). IR: \( \nu \) 3053, 2935, 1622, 1598 cm\(^{-1}\); \(^1\)H NMR: \( \delta \) 1.16 (s, 3H), 1.34-1.48 (m, 1H), 1.50 (s, 3H), 1.51-1.61 (m, 1H), 1.76-2.00 (m, 4H), 3.76-3.83 (m, 1H), 4.96 (t, \( J = 3.5 \), 1H), 5.26 (s, 1H), 5.35 (d, \( J = 10.0 \), 1H), 7.06-7.10 (m, 1H), 7.16-7.38 (m, 8H), 7.63-7.72 (m, 2H); \(^{13}\)C NMR: \( \delta \) 16.2, 17.8, 25.5, 30.3, 31.3, 56.1, 59.6, 81.5, 114.8, 118.6, 122.6 (2C), 126.0, 126.9, 127.0, 127.9 (2C), 128.3, 128.4, 128.7, 129.5 (2C), 131.6, 132.5, 142.1, 152.4; MS m/z (%):
369 (M⁺, 15.8), 231 (100). Anal. Calcd. For C₂₆H₂₇NO: C, 84.51; H, 7.37; N, 3.79.
Found: C, 84.64; H, 7.41; N, 3.70.

(7aR,11R,13S)-11-(3-Buten-1-yl)-13-phenyl-7a,8,10,11-tetrahydro-9H,13H-naphtho[1,2-e]pyrido[2,1-b][1,3]oxazine (14c): It is a white crystal (90%), mp 116-117 °C (EtOAc-PE), [α]D²⁵ = +223.8° (c 0.2, CHCl₃). IR: ν 3064, 2932, 1622 cm⁻¹;¹H NMR: δ 1.22-1.40 (m, 2H), 1.45-1.96 (m, 8H), 3.20-3.29 (m, 1H), 4.64-4.72 (m, 2H), 4.85-4.87 (m, 1H), 5.06 (s, 1H), 5.40-5.52 (m, 1H), 6.98-7.00 (m, 1H), 7.16-7.36 (m, 8H), 7.68-7.79 (m, 2H);¹³C NMR: δ 13.8, 27.3, 28.7, 29.4, 31.4, 58.7, 60.6, 81.5, 114.5, 119.1, 122.8, 123.2, 126.2, 126.9, 128.0 (2C), 128.4, 128.7 (2C), 128.8, 128.9 (2C), 131.7, 138.3, 144.1, 154.5; MS m/z (%): 369 (M⁺, 11.5), 231 (100). Anal. Calcd. For C₂₆H₂₇NO: C, 84.51; H, 7.37; N, 3.79. Found: C, 84.73; H, 7.21; N, 3.82.

(7aR,11R,13S)-11-Ethynyl-13-phenyl-7a,8,10,11-tetrahydro-9H,13H-naphtho[1,2-e]pyrido[2,1-b][1,3]oxazine (14d): It is a white crystal (94%), mp 164-166 °C (EtOAc-PE); [α]D²⁵ = +188.0° (c 0.2, CHCl₃); IR: ν 3274, 2951, 1622, 1597 cm⁻¹;¹H NMR: δ 1.48-1.56 (m, 1H), 1.61-1.70 (m, 2H), 1.91-2.20 (m, 4H), 4.08-4.11 (m, 1H),
4.93 (t, J = 3.1, 1H), 5.36 (s, 1H), 7.06-7.10 (m, 1H), 7.20-7.28 (m, 7H), 7.30-7.36 (m, 1H), 7.68-7.77 (m, 2H); 13C NMR: δ 15.3, 29.4, 31.6, 49.7, 61.5, 70.3, 80.1, 84.5, 112.6, 118.4, 122.7, 123.0, 126.1, 127.1, 128.1 (2C), 128.4 (2C), 128.7, 129.1 (2C), 132.0, 142.9, 153.9; MS m/z (%): 339 (M\(^+\), 1.82), 311 (3.52), 231 (100), 202 (13.6), 106 (7.39); Anal. Calcd. For C\(_{24}\)H\(_{21}\)NO: C, 84.92; H, 6.24; N, 4.13. Found: C, 84.67; H, 6.51; N, 4.25.

![Image](14e)

(7\(a\)R,11\(R\),13\(S\))-11-(Propyn-1-yl)-13-phenyl-7\(a\),8,10,11-tetrahydro-9\(H\),13\(H\)-naphtho[1,2-\(e\)]pyrido[2,1-\(b\)][1,3]oxazine (14e): It is a white crystal (90%), mp 162-163 °C (EtOAc-PE), [\(\alpha\)]\(_D\)\(^{25}\) = +203.8° (c 0.2, CHCl\(_3\)). IR: ν 2944, 2924, 1621, 1599 cm\(^{-1}\); ¹H NMR: δ 1.15 (d, J = 2.1, 3H), 1.41-1.50 (m, 1H), 1.52-1.70 (m, 1H), 1.81-2.18 (m, 4H), 3.97-4.01 (m, 1H), 4.92 (t, J = 3.4, 1H), 5.36 (s, 1H), 7.10-7.13 (m, 1H), 7.14-7.30 (m, 7H), 7.31-7.40 (m, 1H), 7.64-7.75 (m, 2H); 13C NMR: δ 2.9, 15.5, 29.6, 31.8, 50.1, 61.3, 79.0, 80.0, 80.5, 85.5, 112.7, 118.5, 122.6, 123.1, 126.0, 127.1, 128.0, 128.3 (2C), 128.4, 128.7, 129.2 (2C), 132.0, 143.0, 153.8; MS m/z (%): 353 (M\(^+\), 5.8), 231 (100). Anal. Calcd. For C\(_{25}\)H\(_{23}\)NO: C, 84.95; H, 6.56; N, 3.96. Found: C, 85.07; H, 6.64; N, 3.78.
1-(Methoxybenzyl)naphthalen-2-ol (17): It is a white crystal, mp 74-76 °C (EtOAc). IR: ν 3305, 1621, 1453, 1407, 1225 cm⁻¹; ¹H NMR: δ 3.38 (s, 3H), 6.12 (s, 1H), 7.13-7.23 (m, 5H), 7.29-7.38 (m, 3H), 7.64-7.70 (m, 3H), 9.14 (s, 1H); ¹³C NMR: δ 57.4, 83.3, 114.2, 119.5, 121.2, 122.9, 126.6, 127.4 (2C), 128.2, 128.4 (2C), 128.6, 128.7, 130.1, 132.1, 139.2, 154.0; MS m/z (%): 264 (M⁺, 3.1), 231 (100), 202 (13.7); Calcd for C₁₈H₁₆O₂: C, 81.79; H, 6.10. Found: C, 81.51; H, 6.19.

A typical procedure for preparation of (2R,6R)-benzyl 2-vinyl-6-propyl-piperidine-1-carboxylate (7a): To a stirred solution of n-PrMgBr made from Mg (1.22 g, 50 mmol) and n-PrBr (3.69 g, 30 mmol) in dry Et₂O (15 mL) was added a solution of 14a (3.41 g, 10 mmol) in dry Et₂O (70 mL) within 20 min at 0 °C under N₂. After the resultant mixture was stirred for another 10 min, it was quenched by addition of a saturated aqueous solution of NH₄Cl (40 mL). The organic layer was separated and the aqueous layer was extracted by Et₂O (3 x 30 mL). The combined organic layers were washed with brine (3 x 30 mL) and dried over NaSO₄. The solvent was removed to give crude 16a as an oil residue.

The residue (crude 16a) was diluted by a solution of THF (10 mL), CH₃OH (10 mL) and aq. NaOH (6.0 M, 5 mL) and was refluxed for 1 h. Then it was cooled to room
temperature and quenched by addition of CH$_2$Cl$_2$ (50 mL). The resultant mixture was extracted by aq. HCl (6.0 M, 3 x 20 mL) and the combined aqueous layers were neutralized by aq. NaOH (6.0 M). The alkaline solution was extracted with CH$_2$Cl$_2$ (3 x 20 mL) again and the combined organic layers were washed with brine (20 mL) and dried over Na$_2$SO$_4$.

After the Na$_2$SO$_4$ was filtrated off, the filtrate containing free amine $11a$ was treated with CbzCl (3.41 g, 20 mmol) and Na$_2$CO$_3$ (5.3 g, 50 mmol). Then the mixture was stirred for 4 h at room temperature and the solid was filtrated off. The solvent was evaporated in vacuum and the residue was purified by chromatography (silica gel, EtOAc:PE = 1:30) to give product $7a$ (2.45 g, 84%) as a colorless oil, $[\alpha]_{D}^{25} = +24.7^\circ$ (c 1.8, CHCl$_3$). IR: $\nu$ 2939, 1691, 1408 cm$^{-1}$; $^1$H NMR: $\delta$ 0.87 (t, $J = 7.2$, 3H), 1.15-1.92 (m, 10H), 4.15-4.30 (m, 1H), 4.75-4.85 (m, 1H), 5.02-5.20 (m, 4H), 5.85-6.05 (m, 1H), 7.25-7.41 (m, 5H); $^{13}$C NMR: $\delta$ 14.0, 14.5, 202, 27.7, 27.8, 36.3, 50.9, 51.7, 66.9, 114.8, 127.8 (3C), 128.4 (2C), 137.0, 139.7, 156.0; MS m/z (%): 287 (M$^+$, 4.58), 200 (100). Anal. Calcd. For C$_{18}$H$_{25}$NO$_2$: C, 75.22; H, 8.77; N, 4.87. Found: C, 75.50; H, 8.72; N, 4.85.

By the similar procedure, the compounds $7a$-$r$ were prepared from $14a$-$e$ and different $R^1$MgBr ($15a$-$h$).

(2R,6R)-Benzyl 2-vinyl-6-pentylpiperidine-1-carboxylate ($7b$): It is a colorless oil
(82%) from 14a and CH$_3$(CH$_2$)$_n$MgBr (15b), $[\alpha]_D^{25} = +25.8^\circ$ (c 1.5, CHCl$_3$). IR: $\nu$ 2934, 1686, 1408 cm$^{-1}$. $^1$H NMR: $\delta$ 0.85 (t, $J = 7.2$, 3H), 1.15-1.92 (m, 14H), 4.15-4.30 (m, 1H), 4.75-4.85 (m, 1H), 5.02-5.20 (m, 4H), 5.85-6.02 (m, 1H), 7.23-7.40 (m, 5H); $^{13}$C NMR: $\delta$ 14.0, 14.5, 22.5, 26.7, 27.6, 27.8, 31.7, 34.0, 51.1, 51.7, 66.9, 114.8, 127.8 (3C), 128.3 (2C), 137.0, 139.6, 156.0; MS $m/z$ (%): 315 (M$^+$, 2.28), 200 (100). Anal. Calcd. For C$_{20}$H$_{29}$NO$_2$: C, 76.15; H, 9.27; N, 4.44. Found: C, 75.70; H, 8.87; N, 4.30.

(2R,6R)-Benzyl 2-vinyl-6-hexylpiperidine-1-carboxylate (7c). It is a colorless oil (80%) from 14a and CH$_3$(CH$_2$)$_5$MgBr (15c), $[\alpha]_D^{25} = +28.3^\circ$ (c 1.4, CHCl$_3$). IR: $\nu$ 2932, 1691, 1409 cm$^{-1}$; $^1$H NMR: $\delta$ 0.87 (t, $J = 7.2$, 3H), 1.15-1.92 (m, 16H), 4.15-4.30 (m, 1H), 4.75-4.85 (m, 1H), 5.02-5.20 (m, 4H), 5.85-6.02 (m, 1H), 7.23-7.41 (m, 5H); $^{13}$C NMR: $\delta$ 14.1, 14.5, 22.6, 27.1, 27.7, 27.8, 29.2, 31.8, 34.1, 51.1, 51.7, 66.9, 114.8, 127.8 (3C), 128.4 (2C), 137.0, 139.7, 156.0; MS $m/z$ (%): 329 (M$^+$, 1.63), 200 (100). Anal. Calcd. For C$_{21}$H$_{31}$NO$_2$: C, 76.15; H, 9.48; N, 4.25. Found: C, 77.02; H, 9.41; N, 4.20.

(2R,6R)-Benzyl 2-cyclopropyl-6-vinylpiperidine-1-carboxylate (7d): It is a
yellowish oil (82%) from 14a and (CH$_2$)$_2$CHMgBr (15d), $[\alpha]_D^{25} = +33.7^\circ$ (c 0.9, CHCl$_3$). IR: $\nu$ 2941, 1691, 1410 cm$^{-1}$; $^1$H NMR: $\delta$ 0.05-0.17 (m, 1H), 0.19-0.61 (m, 3H), 1.09-1.28 (m, 1H), 1.40-2.05 (m, 6H), 3.42-3.55 (m, 1H), 4.82-4.92 (m, 1H), 5.02-5.34 (m, 4H), 5.95-6.12 (m, 1H), 7.20-7.42 (m, 5H); $^{13}$C NMR: $\delta$ 3.9, 5.4, 15.2, 16.0, 27.8, 29.3, 51.7, 56.0, 67.0, 114.5, 127.8 (2C), 127.9, 128.4 (2C), 136.9, 140.0, 156.1; MS $m/z$ (%): 285 (M$^+$, 4.54), 91 (100). Anal. Calcd. For C$_{18}$H$_{23}$NO$_2$: C, 75.76; H, 8.12; N, 4.91. Found: C, 75.21; H, 7.85; N, 4.83.

(2R,6R)-Benzyl 2-vinyl-6-methylpiperidine-1-carboxylate (7e): It is a yellowish oil (83%) from 14a and MeMgBr (15e), $[\alpha]_D^{25} = +19.1^\circ$ (c 1.6, CHCl$_3$). IR: $\nu$ 2940, 1697, 1405 cm$^{-1}$; $^1$H NMR: $\delta$ 1.18 (d, $J$ = 7.2, 3H), 1.38-2.00 (m, 6H), 4.38-4.52 (m, 1H), 4.70-4.90 (m, 1H), 5.00-5.25 (m, 4H), 5.83-6.06 (m, 1H), 7.20-7.42 (m, 5H); $^{13}$C NMR: $\delta$ 14.2, 20.4, 27.9, 30.1, 46.5, 51.7, 66.9, 114.8, 127.7 (2C), 127.8, 128.4 (2C), 137.0, 139.9, 155.8; MS: $m/z$ (%): 259 (M$^+$, 4.99), 91 (100). Anal. Calcd. For C$_{16}$H$_{21}$NO$_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 74.32; H, 8.23; N, 5.29.

(2R,6R)-Benzyl 2-vinyl-2-benzylpiperidine-1-carboxylate (7f): It is a yellowish oil (83%) from 14a and BnMgBr (15f), $[\alpha]_D^{25} = +45.9^\circ$ (c 1.8, CHCl$_3$). IR: $\nu$ 2941,
1690, 1404 cm\(^{-1}\); \(^1\)H NMR: \(\delta\) 1.15-2.00 (m, 6H), 2.86-2.92 (m, 2H), 4.26-4.40 (m, 1H), 4.70-4.90 (m, 1H), 5.02-5.30 (m, 4H), 5.92-6.09 (m, 1H), 7.23-7.45 (m, 10H); \(^{13}\)C NMR: \(\delta\) 14.2, 25.3, 27.8, 40.3, 51.8, 53.2, 67.2, 115.3, 126.1, 128.0 (3C), 128.3 (2C), 128.5 (2C), 129.3 (2C), 136.8, 139.5, 139.7, 155.9; MS m/z (%): 335 (M\(^+\), 0.17), 91 (100). Anal. Calcd. For C\(_{22}\)H\(_{25}\)NO\(_2\): C, 78.77; H, 7.51; N, 4.18. Found: C, 78.57; H, 7.55; N, 4.21.

\[7g\]

\((2R,6R)\)-Benzyl 2-(2-methylprop-1-enyl)-6-pentylpiperidine-1-carboxylate (7g): It is a yellowish oil (85%) from 24b and Me(CH\(_2\))\(_4\)MgBr (15b), [\(\alpha\)]\(_{D}^{25}\) = +23.9\(^o\) (c 1.9, CHCl\(_3\)). IR: \(\nu\) 2931, 1690 cm\(^{-1}\); \(^1\)H NMR: \(\delta\) 0.86 (t, \(J = 7.2\), 3H), 1.25 (s, 6H), 1.40-1.80 (m, 14H), 4.13-4.25 (m, 1H), 4.90-5.00 (m, 1H), 5.15 (s, 2H), 5.41 (d, \(J = 9.2\), 1H), 7.25-7.39 (m, 5H); \(^{13}\)C NMR: \(\delta\) 14.0, 14.8, 17.8, 22.6, 26.0, 26.7, 28.0, 30.6, 31.8, 34.8, 48.5, 50.9, 66.8, 125.5, 127.7 (2C), 127.8, 128.3 (2C), 133.2, 137.1, 155.9; MS m/z (%): 343 (M\(^+\), 4.79), 91 (100). Anal. Calcd. For C\(_{22}\)H\(_{33}\)NO\(_2\): C, 76.92; H, 9.68; N, 4.08. Found: C, 76.87; H, 9.74; N, 4.13.

\[7h\]

\((2R,6R)\)-Benzyl (2-methylprop-1-enyl)-6-methylpiperidine-1-carboxylate (7h):

It is a yellowish oil (82%) from 14b and MeMgBr (15e), [\(\alpha\)]\(_{D}^{25}\) = +45.6\(^o\) (c 2.9,
CHCl₃). IR: ν2935, 1693, 1407 cm⁻¹; ¹H NMR: δ 1.19-1.80 (m, 15H), 4.33-4.45 (m, 1H), 4.85-4.96 (m, 1H), 5.05-5.18 (m, 2H), 5.46 (d, J = 9.2, 1H), 7.25-7.39 (m, 5H); ¹³C NMR: δ 14.5, 17.6, 20.9, 26.1, 30.0, 30.6, 46.3, 48.8, 66.7, 126.0, 127.7 (3C), 128.3 (2C), 132.9, 137.1, 156.7; MS m/z (%): 287 (M⁺, 4.21), 91 (100). Anal. Calcd. For C₁₈H₂₅NO₂: C, 75.22; H, 8.77; N, 4.87. Found: C, 75.32; H, 8.95; N, 4.92.

(2R,6R)-Benzyl 2-(2-methylprop-1-enyl)-6-benzylpiperidine-1-carboxylate (7i): It is a yellowish oil (75%) from 14b and BnMgBr (15f), [α]D²⁵ = +24.3° (c 0.7, CHCl₃). IR: ν2933, 1686 cm⁻¹; ¹H NMR: δ 1.26-1.90 (m, 12H), 2.77-2.97 (m, 2H), 4.28-4.40 (m, 1H), 4.93-5.03 (m, 1H), 5.15-5.20 (m, 2H), 5.52 (d, J = 9.6, 1H), 7.01-7.42 (m, 10H); ¹³C NMR: δ 14.4, 17.8, 25.6, 26.1, 30.6, 41.0, 48.8, 53.2, 67.1, 125.5, 126.1, 127.9 (2C), 128.1 (2C), 128.3, 128.4 (2C), 129.3 (2C), 133.2, 136.9, 140.0, 155.8; MS m/z (%): 363 (M⁺, 0.11), 91 (100). Anal. Calcd. For C₂₄H₂₉NO₂: C, 79.30; H, 8.04; N, 3.85. Found: C, 79.08; H, 7.87; N, 3.69.

(2R,6R)-Benzyl 2-(but-3-enyl)-6-butylpiperidine-1-carboxylate (7j): It is a yellowish oil (81%) from 14c and n-BuMgBr (15g), [α]D²⁵ = +3.8° (c 0.47, CHCl₃). IR: ν2934, 1697, 1413 cm⁻¹; ¹H NMR: δ 0.86 (t, J = 7.2, 3H), 1.16-1.72 (m, 14H),
1.91-2.16 (m, 2H), 4.10-4.25 (m, 2H), 4.85-5.02 (m, 2H), 5.12 (s, 2H), 5.65-5.87 (m, 1H), 7.23-7.35 (m, 5H); $^{13}$C NMR: $\delta$ 14.0, 14.3, 22.6, 27.5, 27.6, 29.6, 31.7, 33.9, 34.4, 50.3, 50.7, 66.9, 114.5, 127.8 (2C), 127.9, 128.4 (2C), 137.0, 138.2, 156.0; MS m/z (%): 329 (M$^+$, 3.27), 91 (100). Anal. Calcd. For C$_{21}$H$_{31}$NO$_2$: C, 76.55; H, 9.48; N, 4.25. Found: C, 77.29; H, 9.70; N, 4.34.

(2R,6R)-Benzyl 2-(but-3-enyl)-6-isobutylpiperidine-1-carboxylate (7k): It is a yellowish oil (80%) from 14c and Me$_2$CHCH$_2$MgBr (15h), $[\alpha]_D^{25}$ = +2.9$^\circ$ (c 1.7, CHCl$_3$). IR: $\nu$ 2950, 1686, 1413 cm$^{-1}$; $^1$H NMR: $\delta$ 0.70-1.00 (m, 6H), 1.16-1.72 (m, 10H), 1.91-2.16 (m, 2H), 4.10-4.35 (m, 2H), 4.85-5.02 (m, 2H), 5.12 (s, 2H), 5.65-5.88 (m, 1H), 7.26-7.37 (m, 5H); $^{13}$C NMR: $\delta$ 14.2, 21.8, 23.6, 25.6, 27.5, 27.8, 31.6, 34.0, 43.6, 48.7, 50.3, 66.9, 114.5, 127.8 (2C), 128.0, 128.3 (2C), 137.0, 138.3, 156.0; MS m/z (%): 329 (M$^+$, 2.04), 91 (100). Anal. Calcd. For C$_{21}$H$_{31}$NO$_2$: C, 76.55; H, 9.48; N, 4.25. Found: C, 76.50; H, 9.47; N, 4.24.

(2R,6R)-Benzyl 2-(but-3-enyl)-6-cyclopropylpiperidine-1-carboxylate (7l): It is a yellowish oil (79%) from 14c and (CH$_2$)$_2$CHMgBr (15d), $[\alpha]_D^{25}$ = +6.9$^\circ$ (c 1.3, CHCl$_3$). IR: $\nu$ 2938, 1686, 1415 cm$^{-1}$; $^1$H NMR: $\delta$ 0.09-0.20 (m, 1H), 0.31-0.72 (m, 3H),
1.07-1.24 (m, 1H), 1.46-1.96 (m, 8H), 2.03-2.21 (m, 2H), 3.45-3.68 (m, 1H), 4.24-4.39 (m, 1H), 4.85-5.05 (m, 2H), 5.12 (s, 2H), 5.71-5.90 (m, 1H), 7.26-7.48 (m, 5H); $^{13}$C NMR: $\delta$ 3.7, 5.4, 15.0, 16.2, 28.2, 29.3, 31.4, 33.9, 50.2, 55.5, 66.9, 114.3, 127.8 (2C), 127.9, 128.4 (2C), 136.9, 138.6, 156.2; MS $m/z$ (%): 313 (M$^+$, 2.52), 91 (100). Anal. Calcd. For C$_{20}$H$_{27}$NO$_2$: C, 76.64; H, 8.68; N, 4.47. Found: C, 76.36; H, 8.52; N, 4.32.

(2R,6R)-Benzyl 2-ethynyl-6-hexylpiperidine-1-carboxylate (7m): It is a yellowish oil (84%) from 14d and Me(CH$_2$)$_5$MgBr (15c), $[\alpha]_D^{25}$ = +50.9° (c 1.3, CHCl$_3$). IR: $\nu$ 3307, 2932, 2109, 1701, 1409 cm$^{-1}$; $^1$H NMR: $\delta$ 0.86 (d, $J = 7.2$, 3H), 1.12-1.32 (m, 8H), 1.46-1.75 (m, 5H), 1.79-2.02 (m, 3H), 2.19 (d, $J = 2.4$, 1H), 4.12-4.26 (m, 1H), 5.08-5.23 (m, 3H), 7.25-7.41 (m, 5H); $^{13}$C NMR: $\delta$ 14.1, 15.0, 22.6, 26.9, 27.8, 29.2, 30.8, 31.8, 32.5, 41.4, 51.6, 67.2, 70.2, 84.6, 127.9 (2C), 128.4 (3C), 136.7, 155.7; MS $m/z$ (%): 327 (M$^+$, 1.14), 198 (100). Anal. Calcd. For C$_{21}$H$_{29}$NO$_2$: C, 77.02; H, 8.93; N, 4.28. Found: C, 77.03; H, 8.92; N, 4.23.

(2R,6R)-Benzyl 2-ethynyl-6-methylpiperidine-1-carboxylate (7n): It is a yellowish oil (83%) from 14d and MeMgBr (15e), $[\alpha]_D^{25}$ = +64.1° (c 3.2, CHCl$_3$).
IR: \(\nu\) 3292, 2945, 2109, 1701, 1603, 1585 cm\(^{-1}\); \(^1\)H NMR: \(\delta\) 1.38 (d, \(J = 7.2\), 3H), 1.50-1.73 (m, 4H), 1.82-2.18 (m, 2H), 2.21 (d, \(J = 2.4\), 1H), 4.33-4.45 (m, 1H), 5.02-5.10 (m, 1H), 5.18 (s, 2H), 7.25-7.41 (m, 5H); \(^{13}\)C NMR: \(\delta\) 14.8, 18.7, 29.9, 30.6, 41.5, 47.3, 67.2, 70.5, 85.1, 127.7, 127.9 (2C), 128.4 (2C), 136.7, 155.4; MS \(m/z\) (%): 257 (M\(^+\), 1.67), 91 (100). Anal. Calcd. For C\(_{16}\)H\(_{19}\)NO\(_2\): C, 74.68; H, 7.44; N, 5.44. Found: C, 74.55; H, 7.57; N, 5.46.

\(\textbf{N}^{\text{Cbz}}\)\(\text{7o}\) (2\(R,6R\))-benzyl 2-ethyl-6-benzylpiperidine-1-carboxylate (7o): It is a yellowish oil (82%) from 14d and BnMgBr (15f), \([\alpha]_D^{25} = +114^\circ\) (c 2.9, CHCl\(_3\)).

IR: \(\nu\) 3292, 2945, 2109, 1701, 1603, 1585 cm\(^{-1}\); \(^1\)H NMR: \(\delta\) 1.30-1.45 (m, 1H), 1.50-1.75 (m, 3H), 1.89-2.16 (m, 2H), 2.31 (d, \(J = 2.4\), 1H), 3.00-3.29 (m, 2H), 4.27-4.41 (m, 1H), 5.01-5.23 (m, 3H), 7.25-7.41 (m, 10H); \(^{13}\)C NMR: \(\delta\) 14.8, 25.6, 30.6, 38.7, 41.8, 53.8, 67.4, 71.1, 84.8, 126.1 (2C), 128.0 (2C), 128.3 (2C), 128.4 (2C), 129.3 (2C), 136.4, 139.9, 155.6; MS \(m/z\) (%): 333 (M\(^+\), 0.10), 91 (100). Anal. Calcd. For C\(_{22}\)H\(_{23}\)NO\(_2\): C, 79.25; H, 6.95; N, 4.20. Found: C, 79.33; H, 6.77; N, 4.15.

\(\textbf{N}^{\text{Cbz}}\)\(\text{7p}\) (2\(R,6R\))-Benzyl 2-(prop-1-ynyl)-6-pentylpiperidine-1-carboxylate (7p): It is a yellowish oil (78%) from 14e and Me(CH\(_2\))\(_4\)MgBr (15b), \([\alpha]_D^{25} = +38.9^\circ\) (c 0.35, CHCl\(_3\)).
(2R,6R)-Benzyl 2-(prop-1-ynyl)-2-isobutylpiperidine-1-carboxylate (7q): It is a colorless oil (76%) from 14e and Me₂CHCH₂MgBr (15h), [α]D²⁵ = +66.1° (c 0.85, CHCl₃). IR: ν 2951, 2238, 1693, 1411 cm⁻¹; ¹H NMR: δ 0.75-0.95 (m, 6H), 1.39-1.68 (m, 6H), 1.76-1.85 (m, 4H), 1.86-2.02 (m, 2H), 4.22-4.39 (m, 1H), 5.03-5.19 (m, 3H), 7.25-7.40 (m, 5H); ¹³C NMR: δ 3.6, 15.2, 22.6, 22.9, 25.1, 28.5, 31.3, 41.5, 41.8, 49.4, 67.1, 77.8, 79.9, 127.8 (2C), 128.3 (3C), 136.8, 155.6; MS m/z (%): 313 (M⁺, 3.15), 91 (100). Anal. Calcd. For C₂₁H₂₉NO₂: C, 77.02; H, 8.93; N, 4.28. Found: C, 77.05; H, 8.90; N, 4.27.

(2R,6R)-Benzyl 2-(prop-1-ynyl)-6-cyclopropyl-piperidine-1-carboxylate (7r): It is a colorless oil (79%) from 14e and (CH₂)₂CHMgBr (15d), [α]D²⁵ = +55.7° (c 1.1,
CHCl₃). IR: ν 2941, 2238, 1696, 1398 cm⁻¹; ¹H NMR: δ 0.00-0.15 (m, 1H), 0.32-0.75 (m, 3H), 1.20-2.20 (m, 10H), 3.35-3.50 (m, 1H), 5.00-5.19 (m, 3H), 7.25-7.47 (m, 5H); ¹³C NMR: δ 3.6, 4.1, 4.8, 14.7, 15.8, 29.2, 31.3, 42.1, 56.5, 67.1, 78.3, 79.9, 127.8 (2C), 128.3, 128.4 (2C), 136.8, 155.6; MS m/z (%): 297 (M⁺, 5.18), 91 (100). Anal. Calcd.

For C₁₉H₂₃NO₂: C, 76.73; H, 7.80; N, 4.71. Found: C, 76.73; H, 7.50; N, 4.66.

**A typical procedure for the preparation of (2R,6R,E)-benzyl 2-(3-oxoprop-1-enyl)-6-propylpiperidine-1-carboxylate (8a):** To a boiling solution of 7a (500 mg, 1.75 mmol) and crotonaldehyde (19, 370 mg, 5.25 mmol) in CH₂Cl₂ was added Hoveyda-Grubbs catalyst [2nd Generation (HG2), 110 mg, 0.525 mmol] with bubble of N₂ at the bottom of solution. After the reaction system was refluxed for 18 h, the solvent was evaporated in vacuum. The residue was purified by a chromatography (silica gel, EtOAc:PE = 1:5) to give product 8a (460 mg, 85%) as a yellowish oil, [α]D²⁵ = +92.9° (c 0.4, CHCl₃). IR: ν 2954, 1686, 1406 cm⁻¹; ¹H NMR: δ 0.86 (t, J = 7.2, 3H), 1.15-2.05 (m, 10H), 4.15-4.30 (m, 1H), 5.03-5.22 (m, 3H), 6.18 (qd, J = 7.6 and 1.8, 1H), 6.83 (dd, J = 14.5 and 7.8, 1H), 7.25-7.41 (m, 5H), 9.53 (d, J = 7.8, 1H); ¹³C NMR: δ 13.9, 14.5, 20.1, 27.3, 36.1, 50.7, 50.9, 67.4, 128.0 (2C), 128.1 (2C), 128.5 (2C), 131.7, 136.4, 155.8, 158.8, 193.6; MS m/z (%): 315 (M⁺, 1.83), 91 (100). Anal. Calcd. For C₁₉H₂₅NO₃: C, 72.35; H, 7.99; N, 4.44. Found: C, 72.27; H, 8.05; N, 4.38.
By using the similar procedure, the products 8b-d were prepared.

\[ \text{8b} \]

\((2R,6R,E)\)-Benzyl 2-(3-oxoprop-1-enyl)-6-pentylpiperidine-1-carboxylate (8b):
It is a yellowish oil (88%), \([\alpha]_D^{25} = +88.3^\circ \) (c 0.2, CHCl₃). IR: \( v \) 2933, 1684, 1406 cm\(^{-1}\). \(^1\)H NMR: \( \delta 0.84 \) (t, \( J = 7.2 \), 3H), 1.15-2.05 (m, 14H), 4.15-4.30 (m, 1H), 5.03-5.22 (m, 3H), 6.17 (dq, \( J = 1.8 \) and 7.6, 1H), 6.83 (dd, \( J = 14.5 \) and 7.8, 1H), 7.25-7.45 (m, 5H), 9.53 (d, \( J = 7.8 \), 1H); \(^{13}\)C NMR: \( \delta 14.0, 14.5, 22.5, 26.5, 27.3, 31.5, 33.9, 50.6, 51.1, 67.4, 128.0 (2C), 128.1 (2C), 128.5 (2C), 131.6, 136.4, 155.8, 158.8, 193.5; MS \( m/z \) (%): 343 (M+, 2.84), 91 (100). Anal. Calcd. For C\(_{21}\)H\(_{29}\)NO\(_3\): C, 73.44; H, 8.51; N, 4.08. Found: C, 73.05; H, 8.48; N, 4.00.

\[ \text{8c} \]

\((2R,6R,E)\)-Benzyl 2-(3-oxoprop-1-enyl)-6-hexylpiperidine-1-carboxylate (8c):
It is a yellowish oil (81%), \([\alpha]_D^{25} = +101.2^\circ \) (c 0.5, CHCl₃). IR: \( v \) 2931, 1686, 1408 cm\(^{-1}\). \(^1\)H NMR: \( \delta 0.86 \) (t, \( J = 7.2 \), 3H), 1.15-2.05 (m, 16H), 4.15-4.30 (m, 1H), 5.03-5.22 (m, 3H), 6.17 (dq, \( J = 1.8 \) and 7.6, 1H), 6.83 (dd, \( J = 14.5 \) and 7.8, 1H), 7.25-7.45 (m, 5H), 9.53 (d, \( J = 7.8 \), 1H); \(^{13}\)C NMR: \( \delta 14.0, 14.5, 22.5, 26.9, 27.3, 27.4, 29.1, 31.7, 33.9, 50.6, 51.1, 67.4, 128.0 (2C), 128.1, 128.5 (2C), 131.6, 136.4, 155.8, 158.8, 193.5; MS \( m/z \) (%): 357 (M+, 2.70), 91 (100). Anal. Calcd. For
C$_{22}$H$_{31}$NO$_{3}$: C, 73.91; H, 8.74; N, 3.92. Found: C, 73.87; H, 8.95; N, 4.02.

(2R,6R,E)-Benzyl 2-(3-oxohept-1-enyl)-6-propylpiperidine-1-carboxylate (8d): It is a yellowish oil (92%), $[\alpha]_D^{25} = +67.9^\circ$ (c 0.48, CHCl$_3$). IR: $\nu$ 2936, 1951, 1686, 1408 cm$^{-1}$; $^1$H NMR: $\delta$ 0.78-0.95 (m, 6H), 1.15-2.00 (m, 13H), 2.50 (t, $J = 7.2$, 3H), 4.15-4.30 (m, 1H), 4.90-5.00 (m, 1H), 5.15 (s, 2H), 6.15 (dd, $J = 14.5$ and 1.8, 1H), 6.81 (dd, $J = 14.5$ and 7.8, 1H), 7.25-7.45 (m, 5H); $^{13}$C NMR: $\delta$ 13.8, 13.9, 14.5, 20.1, 22.3, 26.1, 27.5, 27.7, 36.2, 40.1, 50.4, 50.8, 67.2, 127.9 (2C), 128.0, 128.4 (2C), 129.4, 136.6, 146.7, 155.8, 200.5. MS $m/z$ (%): 371 (M$^+$, 13.65), 284 (100). Anal. Calcd. For C$_{23}$H$_{33}$NO$_{3}$: C, 74.36; H, 8.95; N, 3.77. Found: C, 74.45; H, 8.95; N, 3.61.

A typical procedure for the preparation of (–)-(5R,9R)-Indolizidine 167B (1): The suspension of 8a (420 mg, 1.33 mmol) and 10% Pd-C (105 mg, 25 wt%) in anhydrous MeOH (20 mL) was stirred under hydrogen atmosphere (55 psi) at room temperature for 12 h. After the Pd-C catalyst was filtered off, solvent was removed on a rotary evaporator. The residue was purified by chromatography (silica gel,
EtOAc:MeOH = 10:1) to give 184 mg (83%) of product 5a as a yellowish oil, 
$\alpha^{D}_{D25} = -104.4^\circ$ (c 0.44, CH$_2$Cl$_2$) [lit.$^3d$ $\alpha^{D}_{D22} = -109^\circ$ (c 1.32, CH$_2$Cl$_2$); lit.$^5c$ $\alpha^{D}_{D20} = -106.9^\circ$ (c 1.10, CH$_2$Cl$_2$)]. $^1$H NMR: $\delta$ 0.91 (t, $J = 7.0$, 3H), 1.10-2.05 (m, 16H), 2.05 (q, $J = 8.6$, 1H), 3.31 (dt, $J = 2.1$ and 8.6, 1H); $^{13}$C NMR: $\delta$ 14.4, 19.0, 20.2, 24.4, 30.3, 30.4, 30.5, 36.5, 51.2, 63.7, 65.2.

By using the similar procedure, the target products 2-4 were prepared (see ESI).

(–)-(5R,9R)-Indolizidine 195H (2)

(–)-(5R,9R)-Indolizidine 195H (2)$^5$. It is a yellowish oil (86%), $\alpha^{D}_{D25} = -95.6^\circ$ (c 1.1, CH$_2$Cl$_2$). $^1$H NMR: $\delta$ 0.89 (t, $J = 6.8$, 3H), 1.05-1.95 (m, 20H), 1.97 (q, $J = 8.8$, 1H), 3.25 (dt, $J = 2.1$ and 8.6, 1H); $^{13}$C NMR: $\delta$ 14.0, 20.4, 22.6, 24.7, 25.5, 30.5, 30.8, 31.0, 32.3, 34.6, 51.5, 63.9, 65.0.

(–)-(5R,9R)-Indolizidine 209D (3)

(–)-(5R,9R)-Indolizidine 209D (3): It is a yellowish oil (85%), $\alpha^{D}_{D25} = -77.1^\circ$ (c 0.34, CH$_2$Cl$_2$) [lit.$^5c$ $\alpha^{D}_{D19} = -84.9^\circ$ (c 0.98, CH$_2$Cl$_2$); lit.$^5f$ $\alpha^{D}_{D25} = -80.4^\circ$ (c 1.0, CH$_2$Cl$_2$)]. $^1$H NMR: $\delta$ 0.88 (t, $J = 6.6$, 3H), 1.05-1.95 (m, 22H), 1.97 (q, $J = 8.6$, 1H), 3.26 (dt, $J = 2.1$ and 8.6, 1H); $^{13}$C NMR: $\delta$ 14.1, 20.4, 22.6, 24.7, 25.8, 29.7, 30.5, 30.8,
31.0, 31.8, 34.6, 51.5, 63.9, 65.0.

(-)-(3S,5R,9R)-Indolizine 223AB (4)

(-)-(3S,5R,9R)-Indolizine 223AB (4): It is a yellowish oil (91%), $[\alpha]_D^{25} = -82.0^\circ$ (c 0.8, MeOH), $[\text{lit.}\, 3c\, [\alpha]_D^{25} = -11.1^\circ$ (c 0.2, MeOH)]. $^1$H NMR: $\delta$ 0.80-0.95 (m, 6H), 1.05-1.50 (m, 16H), 1.50-1.85 (m, 4H), 2.16-2.00 (m, 2H), 2.45-2.57 (m, 1H); $^{13}$C NMR: $\delta$ 14.1, 14.5, 19.3, 22.8, 24.9, 29.3, 29.8, 30.5, 31.0, 31.8, 38.0, 39.9, 62.1, 65.1, 67.4.
X: parts per Million : 1H
Supplementary Material (ESI) for Organic and Biomolecular Chemistry
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14e

X: parts per Million: 1H
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X : parts per Million : 13C
Supplementary Material (ESI) for Organic and Biomolecular Chemistry

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X : parts per Million : 1H
X : parts per Million : 1H
\text{Ph} \quad \text{N} \quad \text{Cbz} \\
\text{7f}

X: \text{parts per Million: } 13C
X: parts per Million: 13C
Ph
N
Cbz
7i

X: parts per Million: 1H
Supplementary Material (ESI) for Organic and Biomolecular Chemistry
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$\text{Cbz}$

$\text{7j}$
X: parts per Million: 1H
X : parts per Million : 13C
Supplementary Material (ESI) for Organic and Biomolecular Chemistry
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X: parts per Million : 1H
Figure 1: NMR spectrum for compound 7m.
Ph
N
Cbz

7o

X : parts per Million \times 10^3
X: parts per Million: 13C
X: parts per Million : 1H
\[
\text{Cbz} \\
7q
\]
Supplementary Material (ESI) for Organic and Biomolecular Chemistry
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\[ (-)-195H \ (2) \]

X : parts per Million : 13C
(-)-(3S,5R,9R)-Indolizine 223AB (4)
(-)-(3S,5R,9R)-Indolizine 223AB (4)