Supporting Information

Nickel-Catalyzed Preparation of Bicyclic Heterocycles:

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Experimental Section

All reagents were used as received unless otherwise noted. Tetrahydrofuran (THF) was freshly distilled from sodium/benzophenone ketyl. Dichloromethane and triethylamine were distilled from calcium hydride. Ni(COD)$_2$ was stored and weighed in an inert atmosphere glovebox. All reactions were conducted in flame-dried glassware under an argon atmosphere.

General procedure for the Ni(COD)$_2$ / PBu$_3$ catalyzed cyclization of ynals:
To a solution of Ni(COD)$_2$ (0.1-0.2 equiv.) in THF was added dropwise PBu$_3$ (0.2-0.4 equiv.) at rt. After 5 min at rt, the solution was cooled to 0 °C with an ice-bath and Et$_3$SiH (5 equiv.) was added dropwise. Then a solution of ynal in THF was added dropwise. The reaction mixture was stirred at the indicated temperature until TLC analysis indicated disappearance of the ynal. The reaction mixture was quenched with saturated NaHCO$_3$ at rt and was extracted twice with Et$_2$O. The combined organic layers were washed with brine, dried over Na$_2$SO$_4$, filtered, and concentrated, and the residue was purified by column chromatography on silica gel.
(2R*, 9αS*)-3-[(E)-Benzylidene]-2-(triethylsilyloxy)octahydroquinolizine (6a).
Following the general procedure at 45 °C, 5a (241 mg, 1.0 mmol), Et₃SiH (0.80 mL, 5.0 mmol), Ni(COD)₂ (27 mg, 0.1 mmol), and PBu₃ (50 μL, 0.2 mmol) were employed to give 6a (303 mg, 85%) and 7a (25 mg, 7%) as colorless oils after chromatography (Et₂O/pet ether: 3/2). ¹H NMR (400 MHz, CDCl₃) δ 0.67 (q, J = 8.0 Hz, 6H), 1.00 (t, J = 8.0 Hz, 9H), 1.20-1.36 (m, 2H), 1.46-1.61 (m, 4H), 1.70 (br d, J = 12.0 Hz, 1H), 1.88 (ddd, J = 12.0, 5.2, 2.4 Hz, 1H), 1.93-2.00 (m, 2H), 2.48 (d, J = 12.4 Hz, 1H), 2.79 (d, J = 11.2 Hz, 1H), 3.85 (d, J = 12.4 Hz, 1H), 4.20 (ddd, J = 11.2, 5.2, 1.6 Hz, 1H), 6.69 (s, 1H), 7.17-7.22 (m, 3H), 7.28-7.32 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 4.9, 6.9, 23.9, 25.5, 32.6, 43.9, 55.7, 60.9, 71.7, 120.8, 126.1, 127.9, 129.1, 137.6, 139.6; IR (film) 2936, 2873, 2746 cm⁻¹; EIMS m/z (relative intensity) 357 (M⁺, 56), 328 (12), 266 (12), 225 (100), 199 (22); HRMS calec for C₂₂H₃₅NOSi (M⁺) 357.2488, found 357.2485. On irradiation of the C-2 proton at δ 4.20, NOEs were observed on the C-4 axial proton at δ 2.48 (2%), C-1 equatorial proton at δ 1.88 (3%), and C-9a axial proton at δ 1.97 (2%), confirming that the C-2 proton is axial, which was also in accord with ¹H NMR analysis; coupling constants of vicinal 2-H/1-Hax and 2-H/1-Heq were observed at 11.2 and 5.2 Hz, respectively, the former of which confirms a trans diaxial relationship between the two corresponding protons.
(2S*, 9aS*)-3-[(E)-Benzyldiene]-2-(triethylsilyloxy)octahydroquinolizine (7a).

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 0.62 (q, $J = 8.0$ Hz, 6H), 0.97 (t, $J = 8.0$ Hz, 9H), 1.20-1.35 (m, 2H), 1.54-1.62 (m, 4H), 1.71-1.73 (m, 1H), 1.78 (dt, $J = 13.5$, 2.8 Hz, 1H), 2.08-2.14 (m, 1H), 2.42 (m, 1H), 2.75 (d, $J = 11.0$ Hz, 1H), 3.00 (d, $J = 12.5$ Hz, 1H), 3.62 (d, $J = 12.5$ Hz, 1H), 4.33 (t, $J = 2.5$ Hz, 1H), 6.42 (s, 1H), 7.19 (d, $J = 7.5$ Hz, 2H), 7.22 (t, $J = 7.5$ Hz, 1H), 7.31 (t, $J = 7.5$ Hz, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 5.0, 6.9, 24.4, 25.7, 32.9, 42.6, 52.4, 56.0, 56.3, 72.8, 125.6, 126.6, 128.0, 129.1, 136.6, 139.7; IR (film) 2936, 2873, 2802 cm$^{-1}$. EIMS m/z (relative intensity) 357 (M$^+$, 25), 328 (4), 266 (15), 225 (67), 199 (60), 84 (100); HRMS calcd for C$_{22}$H$_{35}$NOSi (M$^+$) 357.2488, found 357.2489. On irradiation of the C-2 proton at $\delta$ 4.33, NOEs were observed on the C-10 olefinic proton at $\delta$ 6.42 (10%) and C-1 axial proton at $\delta$ 1.78 (2%), confirming that the C-2 proton is equatorial.

(2R*, 9aS*)-3-[(E)-Heptylidene]-2-(triethylsilyloxy)octahydroquinolizine (6b).

Following the general procedure at 45 °C, 5b (175 mg, 0.70 mmol), Et$_3$SiH (561 $\mu$L, 3.51 mmol), Ni(COD)$_2$ (20 mg, 0.073 mmol), and PBu$_3$ (35 $\mu$L, 0.14 mmol) were employed to give 6b (212 mg, 83%) as a colorless oil after chromatography (EtOAc/Hexanes: 1/4). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 0.60 (q, $J = 8.0$ Hz, 6H), 0.86 (t, $J = 6.8$ Hz, 3H), 0.95 (t, $J = 8.0$ Hz, 9H), 1.24-1.40 (m, 12H), 1.53-1.72 (m, 4H), 1.76 (ddd, $J = 12.0$, 7.2, 2.4 Hz, 1H), 1.84-2.10 (m,
3H), 2.31 (br d, J = 12.4 Hz, 1H), 2.87 (br d, J = 11.6 Hz, 1H), 3.57 (d, J = 12.4 Hz, 1H), 3.99 (dd, J = 11.2, 3.6 Hz, 1H), 5.54 (t, J = 7.2 Hz, 1H); 13C NMR (100 MHz, CDCl3) δ 4.9, 6.9, 14.1, 22.6, 24.0, 25.5, 26.9, 28.9, 29.9, 31.8, 32.6, 44.0, 55.3, 55.9, 61.1, 71.5, 120.9, 135.9; IR (film) 2929, 2851, 2731, 1661 cm⁻¹; ElMS m/z (relative intensity) 365 (M⁺, 36), 336 (33), 294 (11), 280 (46), 266 (14), 234 (45), 176 (37), 162 (82), 84 (100); HRMS calcd for C22H43NOSi (M⁺) 365.3114, found 365.3138.

(2R*, 9aS*)-3-(Methylidene)-2-(triethylsilyloxy)octahydroquinolizine (6c).

Following the general procedure at 45 °C, 5c (83 mg, 0.5 mmol), Et3SiH (0.40 mL, 2.5 mmol), Ni(COD)₂ (15 mg, 0.06 mmol), and PBu₃ (30 μL, 0.12 mmol) were employed to give 6c (114 mg, 81%) as a colorless oil after chromatography (CH₂Cl₂/MeOH/NH₃: 92/8/0.1). 1H NMR (500 MHz, CDCl₃) δ 0.61 (q, J = 8.0 Hz, 6H), 0.96 (t, J = 8.0 Hz, 9H), 1.19-1.42 (m, 4H), 1.56-1.62 (m, 2H), 1.70 (dt, J = 12.0, 2.5 Hz, 1H), 1.81 (ddd, J = 12.0, 5.5, 2.5 Hz, 1H), 1.90 (br t, J = 10.5 Hz, 1H), 1.94-1.99 (m, 1H), 2.60 (d, J = 12.0 Hz, 1H), 2.86 (dt, J = 11.0, 1.5 Hz, 1H), 3.26 (d, J = 12.0 Hz, 1H), 4.04 (ddt, J = 11.0, 5.5, 2.5 Hz, 1H), 4.87 (d, J = 1.0 Hz, 1H), 5.10 (t, J = 1.0 Hz, 1H); 13C NMR (125 MHz, CDCl₃) δ 4.8, 6.9, 24.0, 25.5, 32.7, 44.0, 55.7, 61.0, 61.4, 71.2, 106.9, 146.6; IR (film) 2936, 2880, 2739, 1661 cm⁻¹; ElMS m/z (relative intensity) 281 (M⁺, 19), 266 (6), 252 (22), 149 (100); HRMS calcd for C₁₆H₃₁NOSi (M⁺) 281.2175, found 281.2175.
(2R*, 9aS*)-2-(Triethylsilyloxy)-3-[(E)-trimethylsilylmethylidene]octahydroquinoline (6d). Following the general procedure at 45 °C, 5d (118 mg, 0.5 mmol), Et₃SiH (0.40 mL, 2.5 mmol), Ni(COD)₂ (14 mg, 0.05 mmol), and PBu₃ (25 μL, 0.1 mmol) were employed to give 6d (163 mg, 93%) as a colorless oil after chromatography (EtOAc/Hexanes: 1/4). ¹H NMR (500 MHz, CDCl₃) δ 0.12 (s, 9H), 0.61 (q, J = 8.0 Hz, 6H), 0.96 (t, J = 8.0 Hz, 9H), 1.21-1.44 (m, 3H), 1.56-1.61 (m, 3H), 1.69 (br d, J = 12.5 Hz, 1H), 1.79 (ddd, J =12.0, 5.0, 2.5 Hz, 1H), 1.9-2.02 (m, 2H), 2.52 (br d, J = 12.5 Hz, 1H), 2.83 (d, J = 11.0 Hz, 1H), 3.48 (d, J = 12.5 Hz, 1H), 3.98 (dd, J = 11.5, 5.0 Hz, 1H), 5.66 (s, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 0.4, 4.9, 6.9, 23.8, 25.4, 32.3, 43.6, 55.7, 59.8, 61.0, 72.5, 118.2, 154.1; IR (film) 2950, 2880, 2731, 1633 cm⁻¹; EIMS m/z (relative intensity) 353 (M⁺, 20), 338 (14), 324 (20), 280 (66), 221 (100), 148 (43), 122 (20), 84 (55); HRMS calcd for C₁₉H₃₉NOSi₂ (M⁺) 353.2570, found 353.2569.

![Chemical Structure](image)

(1R, 1aS)-2-[(E)-Benzyldiene]-1-(triethylsilyloxy)hexahydropyrrolizine (9a).
Following the general procedure at 50 °C, the ynal substrate [crude, 205 mg, 0.96 mmol, obtained from Swern oxidation of 8a (217 mg, 1.0 mmol) and used without purification], Et₃SiH (0.80 mL, 5.0 mmol), Ni(COD)₂ (55 mg, 0.2 mmol), and PBu₃ (100 μL, 0.4 mmol) were employed to give 9a (181 mg, 55%) as a pale-yellow oil after chromatography (CH₂Cl₂/MeOH/NH₃: 90/10/0.1). ¹H NMR (500 MHz, CDCl₃) δ 0.69 (q, J = 8.0 Hz, 6H), 1.01 (t, J = 8.0 Hz, 9H), 1.61-1.68 (m, 1H), 1.81-1.89 (m, 2H), 2.07-2.13 (m, 1H), 2.57 (ddd, J = 10.0, 8.0, 7.0 Hz, 1H), 3.11 (ddd, J = 9.5, 7.0, 5.0 Hz, 1H), 3.31 (dd, J = 8.0, 6.0 Hz, 1H), 3.54 (dd, J = 15.7, 2.2 Hz, 1H), 4.14 (br d, J = 15.5 Hz, 1H), 4.37 (br d, J = 5.0 Hz, 1H), 6.51 (dd, J = 1.5, 0.6 Hz, 1H), 7.21 (d, J = 7.5 Hz, 2H), 7.23 (t, J = 7.5 Hz, 1H), 7.35 (t, J = 7.5 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 5.1, 6.9, 25.5, 29.3, 55.3, 55.7, 70.2, 80.3, 123.2, 126.7, 128.3, 128.6,
137.1, 145.0; IR (film) 2957, 2873, 1682 cm\(^{-1}\); EIMS \(m/z\) (relative intensity) 329 (M\(^+\), 24), 300 (9), 260 (100), 231 (26), 129 (49), 103 (40), 87 (43); HRMS calcd for C\(_{20}\)H\(_{31}\)NOSi (M\(^+\)) 329.2175, found 329.2175. On irradiation of the C-1 proton at \(\delta\) 4.39, NOEs were observed on the C-8 olefinic proton at \(\delta\) 6.51 (2%), one of the two C-3 protons at \(\delta\) 4.14 (3%), and one of the two C-7 protons at \(\delta\) 1.65 (3%); no NOE was observed on the C-7a proton at \(\delta\) 3.31, confirming the trans relationship between the C-1 proton and the C-7a proton.

(1\(R\), 1a\(S\))-2-[(\(E\)-Ethylidene)-1-(triethylsilyloxy)hexahydropyrrolizine (9b).

Following the general procedure at 45 °C, the ynal substrate [crude, 151 mg, 1.0 mmol, obtained from Swern oxidation of 8b (153 mg, 1.0 mmol) and used without purification], Et\(_3\)SiH (0.8 mL, 5.0 mmol), Ni(COD)\(_2\) (55 mg, 0.2 mmol), and Pb\(_3\) (100 \(\mu\)L, 0.4 mmol) were employed to give 9b (112 mg, 42%) as a pale-yellow oil after chromatography (CH\(_2\)Cl\(_2\)/MeOH/NH\(_3\): 90/10/0.1).

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 0.58 (q, \(J = 8.0\) Hz, 6H), 0.92 (t, \(J = 8.0\) Hz, 9H), 1.57-1.67 (m, 1H), 1.70 (br d, \(J = 7.2\) Hz, 3H), 1.95 - 2.14 (m, 2H), 2.28-2.36 (m, 1H), 2.59-2.67 (m, 1H), 3.53 (d, \(J = 14.4\) Hz, 1H), 3.86-3.93 (m, 1H), 4.04 (qd, \(J = 14.4, 2.8\) Hz, 1H), 4.23 (br s, 1H), 4.30 (br dd, \(J = 14.2, 5.6\) Hz, 1H), 5.81 (br q, \(J = 7.2\) Hz, 1H); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 4.9, 6.9, 14.8, 25.1, 29.0, 52.0, 55.6, 73.1, 77.4, 125.6, 134.6; IR (film) 2922, 2816, 2746, 1647 cm\(^{-1}\); EIMS \(m/z\) (relative intensity) 267 (\(M^+\), 43), 252 (4), 238 (21), 198 (38), 183 (65), 169 (35), 103 (100); HRMS calcd for C\(_{15}\)H\(_{29}\)NOSi (M\(^+\)) 267.2018, found 267.2018.

(1\(R\), 1a\(S\))-2-[(\(E\)-Heptylidene)-1-(triethylsilyloxy)hexahydropyrrolizine (9c).

Following the general procedure at 45 °C, the ynal substrate [crude, 120 mg, 0.54 mmol, obtained
from Swern oxidation of 8c (124 mg, 0.56 mmol) and used without purification], Et₃SiH (434 µL, 2.72 mmol), Ni(COD)₂ (30 mg, 0.11 mmol), and PBU₃ (54 µL, 0.22 mmol) were employed to give 9c (93 mg, 51%) as a colorless oil after chromatography (CH₂Cl₂/MeOH/NH₃: 90/10/0.1). ¹H NMR (400 MHz, CDCl₃) δ 0.62 (q, J = 8.0 Hz, 6H), 0.87 (t, J = 7.2 Hz, 3H), 0.96 (t, J = 8.0 Hz, 9H), 1.25-1.37 (m, 10H), 1.51-1.60 (m, 1H), 1.82-1.89 (m, 1H), 1.92-2.03 (m, 1H), 2.05-2.13 (m, 1H), 2.52 (dt, J = 10.0, 7.2 Hz, 1H), 3.23 (d, J = 12.8 Hz, 1H), 3.25 (t, J = 7.6 Hz, 1H), 3.41 (dd, J = 12.0, 6.4 Hz, 1H), 5.32 (d, J = 14.4 Hz, 1H), 4.14 (d, J = 4.8 Hz, 1H), 5.50 (tq, J = 7.2, 1.6 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 4.9, 6.7, 14.0, 22.5, 25.3, 28.9, 29.2, 31.6, 53.0, 55.5, 72.2, 78.4, 127.2, 138.4; IR (film) 2957, 2929, 2873, 1689 cm⁻¹; EIMS m/z (relative intensity) 337 (M⁺, 87), 308 (17), 278 (65), 198 (63), 103 (100); HRMS calcd for C₂₀H₃₉NO₃Si (M⁺) 337.2801, found 337.2796. On irradiation of the C-1 proton at δ 4.14, NOE's were observed on the C-8 olefinic proton at δ 5.50 (2%) and one of the two C-7 protons at δ 1.56 (4%). No NOE was observed on the C-7a proton at δ 3.41, confirming the trans relationship between the C-1 proton and the C-7a proton.

(8R,8aS)-7-[(E)-Butylidene]-8-(triethylsilyloxy)octahydroindolizine  (12).
Following the general procedure at 45 °C, the ynal substrate [crude, 197 mg, 1.0 mmol, obtained from Swern oxidation of 11 (195 mg, 1.0 mmol) and used without purification], Et₃SiH (0.4 mL, 5.0 mmol), Ni(COD)₂ (55 mg, 0.2 mmol), and PBU₃ (100 µL, 0.4 mmol) were employed to give 12 (167 mg, 54%) as a colorless oil after chromatography (CH₂Cl₂/MeOH/NH₃: 92/8/0.1). ¹H NMR (500 MHz, CDCl₃) δ 0.64 (q, J = 8.0 Hz, 6H), 0.90 (t, J = 7.5 Hz, 3H), 0.97 (t, J = 8.0 Hz, 9H), 1.38 (sextet, J = 7.5 Hz, 2H), 1.54-1.61 (m, 1H), 1.65-1.73 (m, 1H), 1.74-1.80 (m, 1H), 1.82-1.88 (m, 1H), 1.92 (td, J = 11.5, 2.5 Hz, 1H), 1.99-2.06 (m, 4H), 2.16 (q, J = 9.0 Hz, 1H), 2.64 (dt, J = 14.0, 2.5 Hz, 1H), 3.03-3.07 (ddd, J = 11.0, 4.5, 2.0 Hz, 1H), 3.09 (td, J = 9.0, 1.8 Hz, 1H), 3.83 (d, J = 9.0 Hz, 1H), 5.53 (t, J = 7.5 Hz, 1H); ¹³C NMR (125 MHz,
CDCl₃ δ 4.9, 6.9, 13.8, 21.2, 23.2, 27.4, 29.1, 29.3, 52.3, 53.9, 71.6, 76.7, 120.1, 138.1; IR (film) 2957, 2872, 2788 cm⁻¹; EIMS m/z (relative intensity) 309 (M⁺, 37), 280 (33), 266 (17), 211 (7), 178 (18), 164 (59), 84 (100); HRMS calcd for C₁₈H₃₅NOSi (M⁺) 309.2488, found 309.2488. On irradiation of the C-8 proton at δ 3.83, an NOE was observed on the C-1 axial proton at δ 1.58 (1%); no NOEs were observed on the C-8a proton at δ 1.77 and the C-9 olefinic proton at δ 5.53, confirming the trans relationship between the C-8 proton and the C-8a proton.

(7R,8aS)-6-[(E)-Benzylidene]-7-(triethylsilyoxy)octahydroindolizine (15). Pb₃Bu (68 μL, 0.27 mmol) was added dropwise by syringe to a solution of Ni(COD)₂ (38 mg, 0.14 mmol) in THF (20 mL) at rt under an atmosphere of argon. After 5 min, Et₃SiH (542 μL, 3.39 mmol) was added dropwise. The mixture was cooled to 0 °C with an ice-bath and a solution of 13 (154 mg, 0.68 mmol) in THF (2 mL) was added dropwise. The reaction mixture was then stirred at 0 °C for 48 h. Upon the completion of the reaction by TLC analysis, the mixture was diluted with Et₂O, washed with saturated aqueous NaHCO₃, brine, dried over Na₂SO₄, and filtered. After concentration under reduced pressure, the residue was purified by column chromatography on silica gel (CH₂Cl₂/MeOH/NH₃: 95/5/0.1) to give product 15 (208 mg, 89%) as a colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 0.68 (q, J = 8.0 Hz, 6H), 1.01 (t, J = 8.0 Hz, 9H), 1.44-1.50 (m, 2H), 1.68-1.76 (m, 1H), 1.79-1.89 (m, 2H), 2.09-2.15 (m, 2H), 2.16-2.22 (m, 1H), 2.58 (d, J = 12.0 Hz, 1H), 2.95 (dt, J = 2.5, 8.5 Hz, 1H), 4.11 (d, J = 12.5 Hz, 1H), 4.25 (ddd, J = 2.0, 5.0, 11.0 Hz, 1H), 6.78 (s, 1H), 7.20 (m, 3H), 7.31 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 4.9, 6.9, 22.0, 30.0, 41.1, 51.5, 53.1, 62.5, 72.2, 121.8, 126.2, 127.9, 129.1, 137.7, 139.2; IR (film) 2957, 2873, 2781, 1598 cm⁻¹; EIMS m/z (relative intensity) 343 (M⁺, 1), 218 (7), 189 (33), 92 (100); HRMS calcd for C₂₁H₃₃NOSi (M⁺) 343.2331, found 343.2329.
(7R,8aS)-6-[(E)-Ethylidene]-7-(triethylsiloxy)octahydroindolizine (16). PBu$_3$ (100 µL, 0.40 mmol) was added dropwise by syringe to a solution of Ni(COD)$_2$ (28 mg, 0.10 mmol) in THF (10 mL) at rt under an atmosphere of argon. After 5 min, Et$_3$SiH (400 µL, 2.50 mmol) was added dropwise. The mixture was cooled to 0 °C with an ice-bath and a solution of 14 (83 mg, 0.50 mmol) in THF (2 mL) was added dropwise. The reaction mixture was then stirred at 0 °C for 24 h. Upon the completion of the reaction by TLC analysis, the mixture was diluted with Et$_2$O, washed with saturated aqueous NaHCO$_3$, brine, dried over Na$_2$SO$_4$, and filtered. After concentration under reduced pressure, the residue was purified by column chromatography on silica gel (CH$_2$Cl$_2$/MeOH/NH$_3$: 95/5/0.1) to give product 16 (130 mg, 92%) as a colorless oil as a mixture of two diastereomers (97:3 dr). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 0.61 (q, $J = 8.0$ Hz, 6H), 0.95 (t, $J = 8.0$ Hz, 9H), 1.28 (q, $J = 17.3$ Hz, 1H), 1.39-1.47 (m, 1H), 1.66 (d, $J = 7.0$ Hz, 3H), 1.70-1.76 (m, 1H), 1.79-1.88 (m, 2H), 2.00 (ddd, $J = 2.5$, 5.0, 11.6 Hz, 1H), 2.06-2.12 (m, 1H), 2.14 (q, $J = 8.5$ Hz, 1H), 2.35 (d, $J = 12.0$ Hz, 1H), 3.03 (dt, $J = 2.5$, 8.5 Hz, 1H), 3.90 (d, $J = 12.0$ Hz, 1H), 4.02 (d, $J = 11.0$, 2.0 Hz, 1H), 5.67 (br q, $J = 7.0$ Hz, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 4.8, 6.9, 12.6, 22.0, 30.0, 41.3, 50.4, 53.1, 62.7, 72.0, 115.5, 136.5; IR (film) 2957, 2880, 2781, 1668 cm$^{-1}$; EIMS m/z (relative intensity) 281 (M$^+$, 10), 280 (13), 266 (8), 252 (21), 149 (100); HRMS calc for C$_{16}$H$_{31}$NOSi (M$^+$) 281.2175, found 281.2173. On irradiation of the C-7 proton at $\delta$ 4.02, an NOE was observed on the C-8 equatorial proton at $\delta$ 2.00 (2%). The C-8 axial proton at $\delta$ 1.28 appears as a quartet ($J = 11.5$ Hz) which confirms the axial position of 7-H.
(2S)-2-[(R)-1-(Hydroxy)-1-(trimethylsilylethoxymethoxymethyl)ethyl]-N-[2'-butynyl]pyrrolidine. A degassed solution of 273c (1.00 g, 3.32 mmol) and KOH (4.38 g, 85% purity, 66.4 mmol) in EtOH (15 mL) and H2O (3 mL) was stirred at 80 °C for 16 h under argon. Upon cooling to rt, EtOH was removed under reduced pressure, and the residue was extracted twice with THF. The combined organic layers were dried over K2CO3 and filtered. After evaporation of the solvent, the remaining residue was dried under vacuum and then was dissolved in dry THF (20 mL). To this solution was added i-Pr2NEt (1.16 mL, 6.67 mmol), followed by the addition of a solution of 1-bromo-2-butyne (320 µL, 3.65 mmol) in THF (2 mL). The reaction mixture was then stirred at rt under argon for 48 h and was quenched with saturated aqueous NaHCO3. The mixture was extracted twice with Et2O, washed with brine, and dried over Na2SO4 and filtered. After evaporation of the solvent, the residue was purified by column chromatography on silica gel (EtOAc/Hexanes: 2/3) to give the product (0.99 g, 91%) as a colorless oil. 1H NMR (400 MHz, CDCl3) δ 0.13 (s, 9H), 1.06 (m, 2H), 1.25 (s, 3H), 1.79-1.93 (m, 8H), 2.84-2.90 (m, 1H), 3.03 (m, 1H), 3.10-3.15 (m, 1H), 3.45-3.73 (m, 6H), 4.79 (s, 2H); 13C NMR (100 MHz, CDCl3) δ -1.0, 3.6, 18.0, 20.7, 24.9, 27.7, 45.1, 54.5, 65.3, 65.9, 73.6, 74.6, 75.7, 79.3, 95.3; IR (film) 3459, 2958, 2928, 2873 cm⁻¹; CIMS m/z (relative intensity) 328 (MH⁺, 70), 312 (3), 288 (6), 210 (18), 122 (100); EIMS m/z (relative intensity) 312 (M⁺-Me, 1), 210 (3), 122 (100); HRMS calcd for C17H33NO3Si (M⁺) 327.2230, found 327.2225.
(2S)-2-[(R)-1-(Benzyloxy)-1-(trimethylsilylethoxymethoxymethyl)ethyl]-N-[2'-butynyl]pyrrolidine. To a stirred cold (0 °C) suspension of KH (35% suspension in mineral oil, 525 mg, 4.59 mmol) in THF (10 mL) was added dropwise a solution of the alcohol derivative (1.00 g, 3.06 mmol) in THF (10 mL) under argon. Benzyl bromide (727 μL, 6.11 mmol) was then added dropwise via a syringe. The reaction mixture was stirred at rt for 3 h and was then carefully quenched with water at 0 °C. The mixture was extracted twice with Et₂O, washed with brine, dried over Na₂SO₄, and filtered. After evaporation of the solvent, the residue was purified by column chromatography on silica gel (EtOAc/Hexanes: 1/4) to give the product (1.09 g, 86%) as a colorless oil. [α]²³D -49.6° (c 1.05, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 0.00 (s, 9H), 0.94 (m, 2H), 1.23 (s, 3H), 1.65-1.75 (m, 4H), 1.82 (t, J = 2.2 Hz, 3H), 1.84-1.90 (m, 1H), 2.65 (dd, J = 8.0, 16.8 Hz, 1H), 3.04-3.09 (m, 2H), 3.46-3.65 (m, 3H), 3.55 and 3.69 (AB q, J = 10.8 Hz, 2H), 4.57 and 4.64 (AB q, J = 11.2 Hz, 2H), 4.66 and 4.69 (AB q, J = 6.8 Hz, 2H), 7.22-7.36 (m, 5H); ¹³C NMR (100 MHz, CDCl₃) δ -1.5, 3.6, 16.5, 18.1, 23.7, 27.9, 44.4, 54.3, 64.3, 65.15, 65.21, 71.0, 76.1, 79.3, 80.5, 95.1, 126.9, 127.1, 128.1, 139.9; IR (film) 2958, 2928, 2875 cm⁻¹; CIMS m/z (relative intensity) 418 (MH⁺, 15), 378 (2), 328 (6), 300 (7), 122 (100); EIMS m/z (relative intensity) 416 (M⁺-1, 0.2), 300 (8), 122 (100); HRMS calcd for C₂₄H₃₉NO₃Si (M⁺) 417.2699, found 417.2705.
(2S)-2-[(R)-1-(Benzyloxy)-1-(hydroxymethyl)ethyl]-N-[2'-butynyl]pyrrolidine.
Molecular sieves (4Å, crushed to powder, and flame-dried under vacuum, 2.0 g) were added in
one portion to a solution of the silyl ether derivative (1.06 g, 2.54 mmol) in THF (50 mL) at rt. To
this stirred suspension was added dropwise a solution of n-Bu₄F (1.0 M in THF, 15.0 mL, 15
mmol). The reaction mixture was then warmed to 55 °C and stirred at that temperature for 38 h.
Upon cooling to rt, the mixture was filtered and the solid residue was washed with Et₂O three
times. The filtrate was washed with saturated NaHCO₃, brine, dried over Na₂SO₄, and filtered.
After evaporation of the solvent, the residue was purified by column chromatography on silica gel
(Et₂O/pet ether: 8/2) to give the product (632 mg, 87%) as a colorless oil. [α]²³D -27.2° (c 1.16,
CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 1.31 (s, 3H), 1.77-1.91 (m, 6H), 2.06-2.12 (m, 1H),
2.77 (m, 1H), 3.06 (m, 1H), 3.21 (dd, J = 8.5, 3.5 Hz, 1H), 3.45 (q, J = 2.0 Hz, 2H), 3.57 and
3.85 (AB q, J = 11.5 Hz, 2H), 4.44 and 4.58 (AB q, J = 11.3 Hz, 2H), 5.79 (br s, 1H), 7.24-
7.27 (m, 1H), 7.31-7.35 (m, 4H); ¹³C NMR (125 MHz, CDCl₃) δ 3.5, 19.3, 24.7, 27.0, 44.9,
54.2, 63.6, 66.6, 69.5, 74.7, 76.5, 80.2, 127.10, 127.12, 128.2, 139.4; IR (film) 3389, 2966,
2929, 2873 cm⁻¹; CIMS m/z (relative intensity) 288 (MH⁺, 5), 122 (38); EIMS m/z (relative
intensity) 256 (M⁺-CH₂OH, 1.3), 220 (2), 205 (8), 122 (100); HRMS calcd for C₁₇H₂₂NO (M⁺-
CH₂OH) 256.1702, found 256.1701.
(2S)-2-[(R)-1-(Benzyloxy)-1-(formyl)ethyl]-N-[2'-butynyl]pyrrolidine (17). To a cold (-78 °C) solution of (COCl)₂ (2.0 M in CH₂Cl₂, 0.90 mL, 1.80 mmol) in CH₂Cl₂ (4 mL) was added dropwise DMSO (255 μL, 3.59 mmol). After the solution was stirred at -78 °C for 1 h, a solution of the alcohol derivative (206 mg, 0.72 mmol) in CH₂Cl₂ (3 mL) was added dropwise. The reaction mixture was stirred at -78 °C for 3 h. Et₃N (760 μL, 5.45 mmol) was then added, and the reaction mixture was allowed to warm to rt. Water was added and the mixture was extracted twice with Et₂O. The combined organic layers were washed with saturated NaHCO₃, brine, and dried over Na₂SO₄. After evaporation of the solvent, the residue was purified by column chromatography on silica gel (EtOAc/Hexanes: 1/4) to give product 17 (186 mg, 92%) as a pale-yellow liquid. [α]²³D -10.0° (c 1.11, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 1.36 (s, 3H), 1.70-1.76 (m, 3H), 1.78-1.83 (m, 1H), 1.84 (t, J = 2.3 Hz, 3H), 2.71 (tq, J = 2.5, 6.5 Hz, 1H), 3.01-3.04 (m, 1H), 3.19 (dd, J = 4.3, 8.8 Hz, 1H), 3.54 (q, J = 2.3 Hz, 2H), 4.42 and 4.55 (ABq, J = 11.5 Hz, 2H), 7.28 (m, 1H), 7.33-7.39 (m, 4H), 9.70 (s, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 3.5, 13.9, 24.4, 27.1, 44.2, 53.9, 65.3, 66.7, 75.1, 79.9, 86.1, 127.1, 127.4, 128.3, 138.6, 205.1; IR (film) 2965, 2929, 2872, 1732 cm⁻¹; CIMS m/z (relative intensity) 286 (MH⁺, 3), 256 (1), 122 (80); EIMS m/z (relative intensity) 257 (M⁺-CHO, 0.1), 182 (1), 122 (40), 91 (100); HRMS calcd for C₁₇H₂₂NO (M⁺-CHO) 256.1701, found 256.1702.
(7R,8R,8aS)-8-(Benzyloxy)-7-(triethylsilyloxy)-8-methyl-6-[(E)-ethyldene]octahydroindolizine (18). PBu₃ (59 µL, 0.24 mmol) was added dropwise by syringe to a solution of Ni(COD)₂ (17 mg, 0.06 mmol) in THF (15 mL) at rt under an atmosphere of argon. After 5 min, Et₃SiH (238 µL, 1.49 mmol) was added dropwise. The mixture was cooled to 0 °C with an ice-bath and a solution of 17 (84 mg, 0.295 mmol) in THF (2 mL) was added dropwise. The reaction mixture was then stirred at 0 °C for 28 h. Upon the completion of the reaction by TLC analysis, the mixture was diluted with Et₂O, washed with saturated aqueous NaHCO₃, brine, dried over Na₂SO₄, and filtered. After concentration under reduced pressure, the residue was purified by column chromatography on silica gel (CH₂Cl₂/MeOH/NH₃: 92/8/0.1) to give product 18 (107 mg, 91%) as a colorless oil. [α]²³⁺D +32.6° (c 1.03, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 0.57 (q, J = 8.0 Hz, 6H), 0.94 (t, J = 8.0 Hz, 9H), 1.18 (s, 3H), 1.65-1.68 (m, 2H), 1.69 (d, J = 7.0 Hz, 3H), 1.79-1.87 (m, 1H), 1.95-2.00 (m, 1H), 2.14 (m, 1H), 2.45 (m, 1H), 2.68 (d, J = 10.0 Hz, 1H), 3.14 (t, J = 8.3 Hz, 1H), 3.72 (d, J = 11.5 Hz, 1H), 4.02 (s, 1H), 4.55 and 4.58 (AB q, J = 12.8 Hz, 2H), 5.50 (q, J = 6.5 Hz, 1H), 7.21 (t, J = 7.5 Hz, 1H), 7.28 (t, J = 7.5 Hz, 2H), 7.33 (d, J = 7.5 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 5.0, 6.9, 13.1, 18.9, 20.8, 22.7, 47.6, 54.3, 64.2, 66.4, 76.6, 77.4, 123.0, 126.7, 127.0, 127.9, 136.3, 140.7; IR (film) 2957, 2908, 2873, 2788, 1612, 1457 cm⁻¹; CIMS m/z (relative intensity) 402 (MH⁺, 2), 372 (1), 310 (8); EIMS m/z (relative intensity) 372 (M⁺-Et, 3), 310 (100), 295 (8), 241 (11); HRMS calcd for C₂₂H₃₄NO₂Si (M⁺-Et) 372.2359, found 372.2358. Upon irradiation of the C-7 proton at δ 4.02, NOEs were observed on the C-10 olefinic proton at δ 5.50 (8%) and the benzylic methylene protons at δ 4.57 (6%), confirming that C-7 proton is equatorial.
(2S)-2-[(R)-1-(Hydroxy)-1-[[trimethylsilyl]ethoxymethoxymethyl]ethyl]-
N-[(R)-4'-methyl-2'-octynyl]pyrrolidine (29). A degassed solution of 273c (903 mg, 3
mmol) and KOH (3.95 g, 85%, 60 mmol) in EtOH (15 mL) and H₂O (3 mL) was stirred at 80 °C
for 16 h under argon. Upon cooling to rt, EtOH was removed under reduced pressure, and the
residue was extracted twice with THF. The combined organic layers were dried over K₂CO₃ and
filtered. After evaporation of the solvent, the remained residue was dried under vaccum and then
dissolved in THF (20 mL). To this solution was added i-Pr₂NEt (1.04 mL, 6.0 mmol), followed
by the addition of a solution of 287 (640 mg, 3.15 mmol) in THF (2 mL). The reaction mixture
was then stirred at rt under argon for 38 h and was quenched with saturated NaHCO₃. The mixture
was extracted twice with Et₂O, washed with brine, and dried over Na₂SO₄ and filtered. After
evaporation of the solvent, the residue was purified by column chromatography on silica gel
(EtOAc/Hexanes: 3/7) to give 29 (885 mg, 74%) as a colorless oil. [α]23D -57.8° (c 1.16,
CHCl₃); 1H NMR (400 MHz, CDCl₃) δ 0.01 (s, 9H), 0.89 (t, J =7.0 Hz, 3H), 0.94 (t, J = 8.0
Hz, 2H), 1.13 (d, J = 6.0 Hz, 3H), 1.14 (s, 3H), 1.28-1.42 (m, 6H), 1.69-1.80 (m, 4H), 2.38-
2.42 (m, 1H), 2.78-3.02 (m, 3H), 3.37 and 3.41 (AB q, J = 9.6 Hz, 2H), 3.45-3.55 (m, 2H),
3.60-3.64 (t, J = 8.0 Hz, 2H), 4.68 (s, 2H); 13C NMR (100 MHz, CDCl₃) δ -1.4, 14.0, 18.1,
20.8, 21.4, 22.5, 25.1, 25.9, 27.8, 29.6, 36.8, 45.1, 54.4, 65.3, 65.8, 73.7, 74.6, 76.2, 89.2,
95.3; IR (film) 3457, 2957, 2929, 2872 cm⁻¹; CIMS m/z 398 (MH⁺), 288, 280, 236, 192; EIMS
m/z (relative intensity) 397 (M⁺, 0.1), 382 (1.2), 280 (5), 236 (6), 192 (100); HRMS calcd for
C₂₁H₄₀NO₃Si (M⁺-CH₃) 382.2777, found 382.2780.
(2S)-2-[(R)-1-((Benzyloxy)-1-[(trimethylsilyl)ethoxymethoxymethyl]ethyl]-N-[(R)-4'-methyl-2'-octynyl]pyrrolidine (30). To a stirred cold (0 °C) suspension of KH (35% suspension in mineral oil, 232 mg, 2.0 mmol) in THF (8 mL) was added dropwise a solution of 29 (536 mg, 1.35 mmol) in THF (4 mL) under argon. Benzyl bromide (321 μL, 2.7 mmol) was then added dropwise via a syringe. The reaction mixture was stirred at rt for 3 h and was then carefully quenched with water. The mixture was extracted twice with Et<sub>2</sub>O, washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and filtered. After evaporation of the solvent, the residue was purified by column chromatography on silica gel (EtOAc/Hexanes: 1/4) to give 30 (550 mg, 84%) as a colorless oil. [α]<sup>23</sup><sub>D</sub> -66.1° (c 1.16, CHCl<sub>3</sub>); 1H NMR (500 MHz, CDCl<sub>3</sub>) δ 0.01 (s, 9H), 0.90 (t, J = 7.0 Hz, 3H), 0.94 (t, J = 8.0 Hz, 2H), 1.15 (d, J = 7.0 Hz, 3H), 1.24 (s, 3H), 1.25-1.47 (m, 6H), 1.66-1.75(m, 3H), 1.81-1.88 (m, 1H), 2.41-2.45 (m, 1H), 2.71-2.76 (m, 1H), 3.00-3.03 (m, 1H), 3.14-3.17 (m, 1H), 3.59 and 3.67 (AB q, J = 10.5 Hz, 2H), 3.60-3.65 (m, 4H), 4.60 and 4.66 (AB q, J = 11.5 Hz, 2H), 4.68-4.70 (m, 2H), 7.23 (t, J = 7.0 Hz, 1H), 7.31 (t, J = 7.5 Hz, 2H), 7.38 (d, J =7.0 Hz, 2H); 13C NMR (125 MHz, CDCl<sub>3</sub>) δ -1.5, 14.1, 16.8, 18.1, 21.5, 22.5, 24.0, 26.0, 28.0, 29.7, 36.9, 44.2, 54.0, 64.4, 64.5, 65.2, 71.2, 76.6, 80.5, 89.0, 95.2, 126.8, 127.1, 128.1, 139.9; CIMS m/z 488 (MH<sup>+</sup>), 370, 192; IR (film) 2957, 2929, 2872 cm<sup>-1</sup>; EIMS m/z (relative intensity) 487 (M<sup>+</sup>, 0.1), 370 (3), 246 (2), 202 (8), 192 (100); HRMS calcd for C<sub>24</sub>H<sub>36</sub>NO<sub>2</sub> (M<sup>+</sup>-OCH<sub>2</sub>CH<sub>2</sub>SiMe<sub>3</sub>) 370.2746, found 370.2745.
(2S)-2-[(R)-1-(Benzyloxy)-1-(hydroxymethyl)ethyl]-N-[(R)-4'-methyl-2'-octynyl]pyrrolidine (31). Molecular sieves (4 Å, crushed to powder, and activated with flame under vacuum, 1.2 g) was added in one portion to a solution of 30 (498 mg, 1.02 mmol) in THF (10 mL) at rt. To this stirred suspension was added dropwise a solution of n-Bu$_4$NF (1.0 M in THF, 10.0 mL, 10 mmol). The reaction mixture was then warmed to 55 °C and stirred at that temperature for 30 h. Upon cooling to rt, the mixture was filtered and the solid was washed with Et$_2$O. The filtrate was washed with saturated NaHCO$_3$, brine, dried over Na$_2$SO$_4$, and filtered. After evaporation of the solvent, the residue was purified by column chromatography on silica gel (Et$_2$O/pet ether: 7/3) to give 31 (343 mg, 94%) as a colorless oil. [α]$^\text{23D}$ -43.2° (c 1.07, CHCl$_3$)

$^1$H NMR (500 MHz, CDCl$_3$) δ 0.91 (t, J = 7.0 Hz, 3H), 1.16 (d, J = 7.0 Hz, 3H), 1.31 (s, 3H), 1.30-1.45 (m, 6H), 1.79-1.89 (m, 3H), 2.08-2.13 (m, 1H), 2.42-2.46 (m, 1H), 2.77-2.82 (m, 1H), 3.03-3.07 (m, 1H), 3.27 (dd, J = 9.0, 3.8 Hz, 1H), 3.46 (dd, J = 17.0, 2.0 Hz, 1H), 3.52 (dd, J = 17.0, 2.0 Hz, 1H), 3.59 and 3.84 (AB q, J = 11.0 Hz, 2H), 4.44 and 4.58 (AB q, J = 11.0 Hz, 2H), 5.88 (br s, 1H, OH), 7.24-7.28 (m, 1H), 7.31-7.35 (m, 4H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 14.1, 19.4, 21.4, 22.5, 24.8, 25.9, 27.0, 29.7, 36.8, 44.8, 54.1, 63.6, 66.7, 69.3, 75.4, 76.4, 89.8, 127.1, 128.2, 139.5; IR (film) 3387, 3239, 2964, 2929, 2872 cm$^{-1}$; CIMS m/z 358 (MH$^+$), 250, 192, 107, 91, 81, 70; EIMS m/z (relative intensity) 326 (M$^+$-CH$_2$OH, 0.3), 236 (1), 192 (100), 91 (7), 70 (14); HRMS calcd for C$_{22}$H$_{32}$NO (M$^+$-CH$_2$OH) 326.2484, found 326.2481.
(2S)-2-[(R)-1-(Benzyloxy)-1-formylethyl]-N-[(R)-4'-methyl-2'-octynyl]-pyrrolidine (32). To a cold (-78 °C) solution of (COCl)$_2$ (2.0 M in CH$_2$Cl$_2$, 1.16 mL, 2.32 mmol) in CH$_2$Cl$_2$ (5 mL) was added dropwise DMSO (329 μL, 4.64 mmol). After the solution was stirred at -78 °C for 1 h, a solution of 31 (236 mg, 0.66 mmol) in CH$_2$Cl$_2$ (3 mL) was added dropwise. The reaction mixture was stirred at -78 °C for 3 h. Et$_3$N (968 μL, 6.96 mmol) was then added, and the reaction mixture was allowed to warm to rt. Water was added and the mixture was extracted twice with Et$_2$O. The combined organic layers were washed with saturated NaHCO$_3$, brine, and dried over Na$_2$SO$_4$. After evaporation of the solvent, the residue was purified by column chromatography on silica gel (EtOAc/Hexanes: 1/4) to give 32 (216 mg, 92%) as a pale-yellow liquid. $\alpha$$_{D}^{23}$ -31.2° (c 1.0, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 0.90 (t, $J$ =7.0 Hz, 3H), 1.16 (d, $J$ = 7.0 Hz, 3H), 1.36 (s, 3H), 1.25-1.45 (m, 6H), 1.71-1.81 (m, 4H), 2.41-2.45 (m, 1H), 2.75-2.80 (m, 1H), 2.98-3.01 (m, 1H), 3.24 (dd, $J$ =8.5, 4.5 Hz, 1H), 3.53 (dd, $J$ =17.5, 1.8 Hz, 1H), 3.61 (dd, $J$ = 17.5, 1.8 Hz, 1H), 4.44 and 4.56 (AB q, $J$ = 11.8 Hz, 2H), 7.27-7.29 (m, 1H), 7.33-7.39 (m, 4H), 9.70 (s, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 14.0, 14.2, 21.5, 22.5, 24.6, 26.0, 27.3, 29.7, 36.9, 44.1, 53.7, 65.2, 66.6, 75.7, 86.0, 89.5, 127.0, 127.4, 128.3, 138.8, 205.1; CIMS $m/z$ 356 (MH$^+$), 248, 234, 192; IR (film) 2964, 2929, 2873, 2239, 1732 cm$^{-1}$; EIMS $m/z$ (relative intensity) 326 (M$^{+}$-CH$_2$CH$_3$, 2), 192 (100), 135 (6), 91 (70); HRMS calcd for C$_{21}$H$_{28}$NO$_2$ (M$^{+}$-CH$_2$CH$_3$) 326.2120, found 326.2117.
(7R,8R,8aS)-8-(Benzyl oxy)-7-(triethylsilyloxy)-8-methyl-6-[(E)-(R)-2-methylhexylidene]octahydroindolizine (33). PBu$_3$ (63 µL, 0.25 mmol) was added dropwise by syringe to a solution of Ni(COD)$_2$ (34 mg, 0.12 mmol) in THF (20 mL) at rt under an atmosphere of argon. After 5 min, Et$_3$SiH (500 µL, 3.13 mmol) was added dropwise. The mixture was cooled to 0 °C with an ice-bath and a solution of 32 (222 mg, 0.63 mmol) in THF (5 mL) was added dropwise. The reaction mixture was then stirred at 0 °C for 20 h. Upon the completion of the reaction by TLC analysis, the mixture was diluted with Et$_2$O, washed with saturated NaHCO$_3$, brine, dried over Na$_2$SO$_4$, and filtered. After concentration under reduced pressure, the residue was purified by column chromatography on silica gel (CH$_2$Cl$_2$/MeOH/NH$_3$: 92/8/0.1) to give 33 (280 mg, 95%) as a colorless oil. [α]$^{23}_D$ +23.6° (c 1.02, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) δ 0.59 (q, J = 8.0 Hz, 6H), 0.89 (t, J = 7.0 Hz, 3H), 0.95 (t, J = 8.0 Hz, 9H), 1.00 (d, J = 6.5 Hz, 3H), 1.20 (s, 3H), 1.21-1.31 (m, 6H), 1.64-1.71 (m, 2H), 1.79-1.87 (m, 1H), 1.90-1.98 (m, 1H), 2.16 (q, J = 8.5 Hz, 1H), 2.46-2.53 (m, 2H), 2.75 (d, J = 12.0 Hz, 1H), 3.12 (t, J = 8.5 Hz, 1H), 3.66 (d, J = 12.0 Hz, 1H), 4.00 (s, 1H, 7-H), 4.547 and 4.551 (AB q, J = 13.0 Hz, 2H, CH$_2$Ph), 5.19 (d, J = 9.5 Hz, 1H, 10-H), 7.19-7.23 (m, 1H), 7.26-7.29 (m, 2H), 7.32-7.34 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 5.0, 7.0, 14.0, 19.0, 20.8, 21.0, 22.8, 22.9, 29.4, 31.6, 37.3, 48.3, 54.1, 64.2, 66.0, 76.7, 77.4, 126.8, 127.2, 128.0, 133.9, 135.6, 140.5; IR (film) 2957, 2936, 2873, 2774, 1710, 1605 cm$^{-1}$; CIMS m/z 472 (MH$^+$), 442, 380, 365, 233; EIMS m/z (relative intensity) 471 (M$^+$, 0.3), 380 (M$^+$-CH$_2$Ph, 100), 365 (6), 336 (4), 311 (2), 267 (3), 233 (8), 115 (14), 91 (24); HRMS calcd for C$_{22}$H$_{42}$NO$_2$Si (M$^+$-CH$_2$Ph) 380.2985, found 380.2985. On irradiation of the C-7 proton at δ 4.00, NOEs were observed on the C-10
olefinic proton at δ 5.19 (10%) and the benzilic methylene protons at δ 4.55 (7%), confirming that
C-7 proton is equatorial.

(7R,8R,8aR)-8-(Benzyloxy)-7-hydroxy-8-methyl-6-[(E)-(R)-2-methylhexylidene]octahydroindolizine (34). To a cold (0 °C) solution of 33 (178 mg, 0.38 mmol) in THF (10 mL) was added dropwise HF-pyridine (6 M in pyridine, 1.5 mL). The reaction mixture was then stirred at 0 °C - rt overnight. The mixture was quenched with saturated NaHCO₃, and was extracted twice with CH₂Cl₂. The combined organic layers were washed with saturated NaHCO₃, brine, dried over Na₂SO₄, and filtered. After evaporation of the solvent, the residue was purified by column chromatography on silica gel (CH₂Cl₂/MeOH/NH₃: 91/9/0.1) to give 34 (124 mg, 92%) as a white solid: mp 126-127 °C (lit.⁶a mp 126-127 °C); [α]²³D +16.6° (c 0.48, CHCl₃) (lit.⁶a [α]²₅D +15.8° (c 0.41, CHCl₃)). Synthetic 34 showed TLC mobility and 500 MHz ¹H NMR, 125 MHz ¹³C NMR, MS, and IR spectra that were indistinguishable from those of the synthetic sample kindly provided by Overman.

(allopumilioxin 267A, 1)

(+) Allopumilioxin 267A (1). A solution of 34 (55 mg, 0.15 mmol) in THF (5 mL) was added dropwise to liquid NH₃ (10 mL) at -78 °C with stirring. To this mixture was added
Li (11 mg, 1.6 mmol) in small portions. After 10 min at -78 °C, the cooling bath was removed, and the reaction mixture was continued to stir for another 15 min. The resulting deep-blue mixture was carefully quenched by addition of solid NH₄Cl in small portions until the color disappeared and then allowed to warm to rt to evaporate the ammonia. To the residue was added saturated NaHCO₃, the mixture was extracted twice with CH₂Cl₂. The extract was washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (CH₂Cl₂-MeOH-NH₃, 92-8-0.1) to give 1 (36 mg, 88%) as a colorless oil which was solidified on storage: mp 46-47 °C (lit.⁶a mp 45-47 °C); [α]²³_D +31.4° (c 0.32, MeOH) (lit.³c [α]²⁰_D +31° (c 0.22, MeOH), lit.¹b [α]²⁵_D +24.7° (c 0.17, MeOH)). Synthetic 1 showed TLC mobility and 500 MHz ¹H NMR, 125 MHz ¹³C NMR, MS, and IR spectra that were indistinguishable from those of the synthetic sample kindly provided by Overman.

(E)-(4R,8R,9R)-1-Bromo-8,9-(isopropylidenedioxy)-4,7-dimethyl-6-decen-2-yne (35). To a cold (0 °C) solution of the propargyl alcohol⁶a (2.28 g, 9.05 mmol) and PPh₃ (4.74 g, 18.1 mmol) in CH₂Cl₂ (50 mL) was added CBr₄ (6.01 g, 18.1 mmol) in small portions over a period of 15 min. under argon. The resultant bright-yellow solution was stirred at 0 °C for 0.5 h. The reaction mixture was then diluted with hexanes (50 mL) while it was vigorously stirred, and filtered. The solid residue was washed three times with Et₂O, and the filtrate was concentrated under reduced pressure to leave a yellow oil residue which was purified by column chromatography on silica gel (EtOAc/hexanes: 5/95) to give product 35 (2.64 g, 93%) as a 95:5 mixture of E and Z isomers as a colorless liquid. [α]²³_D -15.1° (c 1.36, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 1.14 (m, 3H), 1.22 (m, 3H), 1.41 (s, 3H), 1.42 (s, 3H), 1.66 (s, 3H), 2.22 (m, 2H), 2.53-2.58 (m, 1H), 3.83-3.89 (m, 2H), 3.90 (t, J = 2.5 Hz, 2H), 5.56 (t, J = 7.0 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 11.7, 15.6, 17.0, 20.0, 26.1, 26.9, 27.5, 34.4, 74.5, 75.7,
88.3, 91.7, 108.0, 126.4, 133.1; IR (film) 2985, 2873, 2232, 1739 cm\(^{-1}\); EIMS \(m/z\) (relative intensity) 315 (M\(^{+}\)+1, 7), 317 (2), 301 (3), 299 (3), 272 (4), 270 (4); HRMS calc for C\(_{14}\)H\(_{20}\)BrO\(_{2}\) (M\(^{+}\)-CH\(_{3}\)) 299.0647, found 299.0653.

(2S)-2-[(R)-1-(Hydroxy)-1-(trimethylsilylethoxymethoxymethyl)ethyl]-N-[(E)-(4R,8R,9R)-4,7-dimethyl-8,9-(isopropylidenedioxy)-6-decen-2-ynyl]pyrrolidine (36). A degassed solution of 27\(^{3}\)c (1.33 g, 4.42 mmol) and KOH (5.82 g, 85% purity, 88.3 mmol) in EtOH (20 mL) and H\(_{2}\)O (4 mL) was stirred at 80 °C for 18 h under argon. Upon cooling to rt, EtOH was removed under reduced pressure, and the residue was extracted twice with THF. The combined organic layers were dried over K\(_{2}\)CO\(_{3}\) and filtered. After evaporation of the solvent, the remained residue was dried under vaccum for 2 h and then dissolved in dry THF (40 mL). To this solution was added i-Pr\(_{2}\)NEt (1.54 mL, 8.86 mmol), followed by the addition of a solution of 35 (1.42 g, 4.51 mmol) in THF (8 mL). The reaction mixture was then stirred at rt under argon for 48 h and was quenched with saturated aqueous NaHCO\(_{3}\). The mixture was extracted twice with Et\(_{2}\)O, washed with brine, and dried over Na\(_{2}\)SO\(_{4}\) and filtered. After evaporation of the solvent, the residue was purified by column chromatography on silica gel (EtOAc/Hexanes: 1/4) to give the product 36 (2.06 g, 92%) as a colorless oil. \([\alpha]^{23}\)D -48.0° (c 1.65, CHCl\(_{3}\)); \(^1\)H NMR (500 MHz, CDCl\(_{3}\)) \(\delta\) 0.00 (s, 9H), 0.92 (t, \(J = 7.0\) Hz, 2H), 1.12-1.13 (m, 6H), 1.20 (d, \(J = 5.0\) Hz, 3H), 1.40 (s, 6H), 1.66 (s, 3H), 1.68-1.80 (m, 4H), 2.20 (m, 2H), 2.49 (q, \(J = 7.0\) Hz, 1H), 2.74-2.98 (m, 4H), 3.33-3.56 (m, 4H), 3.61 (t, \(J = 7.5\) Hz, 2H), 3.81-3.88 (m, 2H), 4.67 (s, 2H), 5.58 (t, \(J = 7.0\) Hz, 1H); \(^13\)C NMR (125 MHz, CDCl\(_{3}\)) \(\delta\) -0.9, 11.6, 17.0, 18.0, 20.7, 20.8, 25.0, 26.0, 26.9, 27.4, 27.8, 35.0, 45.0, 54.4, 65.2, 65.8, 73.7, 74.3, 74.6, 76.8, 88.5,
95.3, 107.9, 127.3, 132.5; IR (film) 3414-3239, 2977, 2879, 1455, 1377 cm⁻¹; EIMS m/z (relative intensity) 509 (M⁺, 0.1), 494 (4), 392 (5), 304 (100), 246 (5); HRMS calcd for C₂₇H₄₈NO₅Si (M⁺-CH₃) 494.3302, found 494.3300.

(2S)-2-[(R)-1-(Benzyloxy)-1-(trimethylsilylethoxymethoxymethyl)ethyl]-N-[(E)-(4R,8R,9R)-8,9-(isopropylidenedioxy)-4,7-dimethyl-6-decen-2-ynyl]pyrrolidine (37). To a stirred cold (0 °C) suspension of KH (35% suspension in mineral oil, 687 mg, 6.0 mmol) in THF (40 mL) was added dropwise a solution of 36 (2.04 g, 4.0 mmol) in THF (10 mL) under argon. Benzyl bromide (715 μL, 6.0 mmol) was then added dropwise via a syringe. The reaction mixture was stirred at rt for 2 h and was then carefully quenched with water at 0 °C. The mixture was extracted twice with Et₂O. The combined extracts were washed with saturated aqueous NaHCO₃, brine, dried over Na₂SO₄, and filtered. After evaporation of the solvent, the residue was purified by column chromatography on silica gel (EtOAc/Hexanes: 1/9) to give product 37 (1.97 g, 82%) as a colorless oil. [α]²²_D -56.1° (c 1.78, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ -0.01 (s, 9H), 0.93 (m, 2H), 1.14 (d, J = 7.0 Hz, 3H), 1.20 (d, J = 5.5 Hz, 3H), 1.23 (s, 3H), 1.41 (s, 3H), 1.42 (s, 3H), 1.65 (s, 3H), 1.66-1.74 (m, 3H), 1.81-1.86 (m, 1H), 2.15-2.26 (m, 2H), 2.50 (q, J = 6.5 Hz, 1H), 2.68 (q, J = 8.0 Hz, 1H), 3.00-3.03 (m, 1H), 3.07-3.10 (m, 1H), 3.55 and 3.67 (AB q, J = 11.0 Hz, 2H), 3.57-3.65 (m, 4H), 3.81-3.88 (m, 2H), 4.57 and 4.65 (AB q, J = 11.0 Hz, 2H), 4.66 and 4.68 (AB q, J = 7.0 Hz, 2H), 5.60 (t, J = 7.0 Hz, 1H), 7.22 (t, J = 7.5 Hz, 1H), 7.29 (t, J = 7.5 Hz, 2H), 7.36 (d, J = 7.5 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ -1.0, 11.6, 16.6, 17.0, 18.0, 20.8, 23.8, 26.0, 26.9, 27.5, 27.9, 35.1,
(2S)-2-[(R)-1-(Benzyloxy)-1-(hydroxymethyl)ethyl]-N-[(E)-(4R,8R,9R)-4,7-dimethyl-8,9-(isopropylidenedioxo)-6-decen-2-ynyl]pyrroolidine (38). Molecular sieves (4 Å, crushed to powder, and flame-dried under vacuum, 1.0 g) were added in one portion to a solution of 37 (326 mg, 0.54 mmol) in THF (15 mL) at rt. To this stirred suspension was added dropwise a solution of n-Bu₄NF (1.0 M in THF, 5.4 mL, 5.4 mmol). The reaction mixture was then warmed to 55 °C and stirred at that temperature for 36 h. Upon cooling to rt, the mixture was filtered and the solid was washed with Et₂O for three times. The filtrate was washed with saturated aqueous NaHCO₃, brine, dried over Na₂SO₄, and filtered. After evaporation of the solvent, the residue was purified by column chromatography on silica gel (EtOAc/hexanes: 1/4) to give product 38 (236 mg, 92%) as a colorless oil. [α]²³ D -33.6° (c 1.21, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 1.16 (d, J = 7.0 Hz, 3H), 1.21 (d, J = 5.5 Hz, 3H), 1.28 (s, 3H), 1.41 (s, 3H), 1.42 (s, 3H), 1.66 (s, 3H), 1.75-1.89 (m, 3H), 2.04-2.10 (m, 1H), 2.16-2.28 (m, 2H), 2.52 (tq, J = 2.0, 7.0 Hz, 1H), 2.76 (q, J = 8.3 Hz, 1H), 3.04 (m, 1H), 3.20 (dd, J = 3.8, 8.3 Hz, 1H), 3.45 and 3.49 (d AB q, J = 2.0, 16.5 Hz, 2H), 3.56 (d, J = 11.0 Hz, 1H), 3.82-3.89 (m, 4H), 4.42 and 4.57 (AB q, J = 11.0 Hz, 2H), 5.59 (t, J = 7.0 Hz, 1H), 7.23-7.26 (m, 1H), 7.30-7.34 (m, 4H); ¹³C NMR (125 MHz, CDCl₃) δ 11.7, 17.0, 19.2, 20.7, 24.8, 26.0, 26.9, 27.0, 27.5, 35.0, 44.9, 54.1, 63.6, 66.6, 69.5, 74.4, 75.9, 76.6, 88.5, 89.0, 108.0, 127.1, 128.2, 132.7,
139.5; IR (film) 3413-3244, 2976, 2878, 1455, 1377 cm\(^{-1}\); EIMS m/z (relative intensity) 469 (M\(^+\), 0.2), 454 (3), 304 (100), 246 (6); HRMS calc'd for C\(_{28}\)H\(_{40}\)NO\(_4\) (M\(^+\)-CH\(_3\)) 454.2957, found 454.2955.

(2S)-2-[(R)-1-(Benzyloxy)-1-(formyl)ethyl]-N-[(E)-(4R,8R,9R)-4,7-dimethyl-8,9-(isopropylidenedioxy)-6-decen-2-ynyl]pyrrolidine (39). To a cold (−78 °C) solution of (COCl\(_2\)) \(2\) (2.0 M in CH\(_2\)Cl\(_2\), 633 μL, 1.27 mmol) in CH\(_2\)Cl\(_2\) (5 mL) was added dropwise DMSO (180 μL, 2.54 mmol). After the solution was stirred at −78 °C for 1 h, a solution of 38 (198 mg, 0.422 mmol) in CH\(_2\)Cl\(_2\) (2 mL) was added dropwise. The reaction mixture was stirred at −78 °C for 3 h. Et\(_3\)N (530 μL, 3.80 mmol) was then added, and the reaction mixture was allowed to warm to rt. Water was added and the mixture was extracted twice with Et\(_2\)O. The combined organic layers were washed with saturated aqueous NaHCO\(_3\), brine, and dried over Na\(_2\)SO\(_4\). After evaporation of the solvent, the residue was purified by column chromatography on silica gel (EtOAc/Hexanes: 1/4) to give product 39 (175 mg, 89%) as a colorless oil. [\(\alpha\)]\(^{23}\)_D

-23.9° (c 1.05, CHCl\(_3\)); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 1.15 (d, \(J = 6.5\) Hz, 3H), 1.21 (d, \(J = 5.5\) Hz, 3H), 1.34 (s, 3H), 1.408 (s, 3H), 1.414 (s, 3H), 1.66 (s, 3H), 1.68-1.80 (m, 4H), 2.15-2.27 (m, 2H), 2.51 (tq, \(J = 2.0, 7.0\) Hz, 1H), 2.72 (dt, \(J = 6.5, 9.0\) Hz, 1H), 2.96-3.00 (m, 1H), 3.19 (dd, \(J = 4.3, 8.3\) Hz, 1H), 3.52 and 3.58 (d AB q, \(J = 2.0, 17.0\) Hz, 2H), 3.81-3.88 (m, 2H), 4.41 and 4.54 (AB q, \(J = 11.8\) Hz, 2H), 5.59 (br t, \(J = 7.3\) Hz, 1H), 7.27 (tt, \(J = 1.8, 7.3\) Hz, 1H), 7.32-7.38 (m, 4H), 9.68 (s, 1H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 11.7, 14.0, 17.0, 20.9, 24.4, 26.0, 26.9, 27.2, 27.5, 35.1, 44.0, 53.7, 65.2, 66.6, 74.4, 76.1, 86.1, 88.5, 88.7, 107.9, 127.0, 127.3, 127.4, 128.3, 132.6, 138.7, 205.1;
IR (film) 2976, 2934, 2878, 2244, 1730 cm⁻¹; CIMS m/z (relative intensity) 468 (MH⁺, 5), 410 (2), 346 (6), 304 (71), 246 (25), 91 (100); EIMS m/z (relative intensity) 468 (M⁺+1, 0.3), 452 (3), 304 (100); HRMS calcd for C₂₈H₃₈NO₄ (M⁺-CH₃) 452.2801, found 452.2808.

(7R,8R,8aS)-8-(Benzyloxy)-7-(triethylsilyloxy)-6(E)-[6(R),7(R)-(isopropylidenedioxy)-2(R),5-dimethyl-4(E)-octenyldiene]-8-methyloctahydroindolizine (40). PBu₃ (75 µL, 0.30 mmol) was added dropwise by syringe to a solution of Ni(COD)₂ (21 mg, 0.076 mmol) in THF (15 mL) at rt under an atmosphere of argon. After 5 min at rt, the solution was cooled to -12 °C with an ice-salt bath and Et₃SiH (300 µL, 1.88 mmol) was added dropwise, followed by dropwise addition of a solution of 39 (175 mg, 0.37 mmol) in THF (2 mL). The reaction mixture was then stirred at -12 - 0 °C for 18 h. Upon the completion of the reaction by TLC analysis, the mixture was diluted with Et₂O, washed with saturated NaHCO₃, brine, dried over Na₂SO₄, and filtered. After concentration under reduced pressure, the residue was purified by column chromatography on silica gel (CH₂Cl₂/MeOH/NH₃: 95/5/0.1) to give product 40 (203 mg, 93%) as a colorless oil as a 95:5 mixture of two diastereomers (resulting from an E/Z mixture of C-13 alkenes carried through from compound 35. [α]²³° +2.7° (c 1.58, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 0.58 (q, J = 8.0 Hz, 6H), 0.94 (t, J = 8.0 Hz, 9H), 0.99 (d, J = 6.5 Hz, 3H), 1.20 (m, 6H), 1.42 (s, 3H), 1.65 (s, 3H), 1.74 (m, 1H), 1.81-1.86 (m, 1H), 1.93 (m, 1H), 1.96-2.08 (m, 3H), 2.14 (m, 1H), 2.50 (m, 1H), 2.57 (quint, J = 7.5 Hz, 1H), 2.76 (m, 1H), 3.10 (br t, J = 7.5 Hz, 1H), 3.65 (d, J = 11.5 Hz, 1H), 3.82-3.89 (m, 2H), 3.99 (s, 1H), 4.51 and 4.55 (AB q, J = 12.3 Hz, 2H), 5.24 (d, J = 9.0 Hz, 1H), 5.50 (t, J = 6.5 Hz, 1H), 7.21 (br t, J = 7.3 Hz, 1H), 7.27 (t, J = 7.3 Hz, 2H), 7.32 (d, J = 7.3 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 5.0, 7.0, 11.4, 17.0, 18.9, 20.2,
20.9, 22.9, 26.9, 27.4, 31.9, 35.2, 48.0, 53.9, 64.3, 65.8, 74.1, 76.4, 77.5, 88.7, 107.8, 127.0, 127.2, 128.0, 128.3, 131.9, 134.9, 140.1; IR (film) 2957, 2873, 1640 cm⁻¹; EIMS m/z (relative intensity) 584 (M⁺+1, 5), 583 (M⁺, 4), 568 (6), 554 (2), 492 (100); HRMS calcd for C₃₅H₇₇NO₄Si (M⁺) 583.4057, found 583.4054.

![Chemical Structure](image)

**(7R,8R,8aS)-8-(Benzylxoy)-7-hydroxy-6(E)-[6(R),7(R)-(isopropylidenedioxy)-2(R),5-dimethyl-4(E)-octenylidene]-8-methyloctahydroindolizine** (41). To a cold (0 °C) solution of 40 (207 mg, 0.358 mmol) in THF (10 mL) was added dropwise HF-pyridine (6 M in pyridine, 2.0 mL). The reaction mixture was then stirred at 0 °C - rt overnight. The mixture was quenched with saturated aqueous NaHCO₃, and was extracted twice with CH₂Cl₂. The combined organic layers were washed with saturated aqueous NaHCO₃, brine, dried over Na₂SO₄, and filtered. After evaporation of the solvent, the residue was purified by column chromatography on silica gel (CH₂Cl₂/MEOH/NH₃: 92/8/0.1) to give product 41 (149 mg, 87%) as a colorless oil. [α]D²³ +27.9° (c 1.45, CHCl₃) (lit.⁶α [α]D²⁷ +27.5° (c 1.4, CHCl₃)); ¹H NMR (500 MHz, CDCl₃) δ 1.05 (d, J = 6.5 Hz, 3H), 1.20 (d, J = 6.0 Hz, 3H), 1.24 (s, 3H), 1.395 (s, 3H), 1.401 (s, 3H), 1.59 (s, 3H), 1.63-1.73 (m, 2H), 1.80-1.86 (m, 1H), 1.94-2.16 (m, 5H), 2.41 (dd, J = 6.0, 10.0 Hz, 1H), 2.54-2.60 (m, 1H), 2.68 (d, J = 12.5 Hz, 1H), 3.10 (t, J = 8.3 Hz, 1H), 3.65 (d, J = 12.0 Hz, 1H), 3.82 (d, J = 8.5 Hz, 1H), 3.87-3.92 (m, 1H), 4.01 (s, 1H), 4.54 and 4.58 (AB q, J = 12.5 Hz, 2H), 5.23 (d, J = 9.5 Hz, 1H), 5.41 (br t, J = 7.5 Hz, 1H), 7.19 (t, J = 7.5 Hz, 1H), 7.26 (t, J = 7.5 Hz, 2H), 7.31 (d, J = 7.5 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 11.5, 16.8, 18.5, 20.7, 22.7, 26.8, 27.4, 32.3, 35.7, 48.7, 54.4, 64.4, 66.3, 73.7, 75.9, 76.5, 89.1, 107.8, 126.8, 127.1, 128.0, 130.0, 131.2, 134.8, 135.0, 140.4; IR (film) 3274, 2978,
2929, 2873 cm⁻¹; EIMS m/z (relative intensity) 469 (M⁺, 0.4), 454 (3), 378 (66), 84(100); HRMS calcd for C₂₉H₄₃NO₄ (M⁺) 469.3192, found 469.3196.

(7R,8R,8aS)-8-(Benzyloxy)-7-hydroxy-6(E)-[6(R),7(R)-(dihydroxy)-2(R),5-dimethyl-4(E)-octenylidene]-8-methyloctahydroindolizine. To a solution of 41 (75 mg, 0.16 mmol) in THF (1 mL) was added 3 N HCl (1.0 mL). The reaction mixture was then stirred at rt for 0.5 h. Saturated aqueous NaHCO₃ was added, and the mixture was extracted twice with CH₂Cl₂. The combined extracts were washed with saturated aqueous NaHCO₃, brine, dried over Na₂SO₄, and filtered. After concentration under reduced pressure, the residue was purified by column chromatography on silica gel (CH₂Cl₂/MeOH/NH₃: 90/10/0.1) to give the product (63 mg, 92%) as a colorless oil. [α]°²³ +28.1° (c 1.21, CHCl₃) (lit.⁶α [α]°²³ +28.8° (c 1.9, CHCl₃)); ¹H NMR (400 MHz, CDCl₃) δ 1.07 (d, J = 6.4 Hz, 3H), 1.12 (d, J = 6.4 Hz, 3H), 1.30 (s, 3H), 1.56 (s, 3H), 1.69-1.93 (m, 3H), 1.95-2.10 (m, 3H), 2.45-2.59 (m, 2H), 2.80 (dd, J = 6.8, 8.4 Hz, 1H), 2.96-3.03 (m, 5H), 3.54 (d, J = 12.8 Hz, 1H), 3.67 (d, J = 6.4 Hz, 1H), 3.77 (quint, J = 6.4 Hz, 1H), 4.10 (s, 1H), 4.50 and 4.54 (AB q, J = 12.0 Hz, 2H), 5.25 (d, J = 10.0 Hz, 1H), 5.37 (dd, J = 6.0, 10.0 Hz, 1H), 7.21-7.25 (m, 1H), 7.26-7.31 (m, 4H); ¹³C NMR (100 MHz, CDCl₃) δ 12.5, 18.5, 19.2, 21.16, 21.23, 22.9, 32.6, 35.5, 48.5, 54.5, 64.4, 66.0, 68.4, 74.9, 76.9, 82.1, 127.06, 127.12, 127.2, 128.1, 133.2, 134.9, 135.2, 139.7; IR (film) 3393, 2874, 2801, 1653 cm⁻¹.
(+)-Allopumiliotoxin 339A (2). A solution of the benzyl ether derivative (46 mg, 0.107 mmol) in THF (2 mL) was added dropwise to liquid NH₃ (5 mL) at -78 °C with stirring. To this mixture was added Li⁺ (9 mg, 1.29 mmol) in small portions. After 10 min at -78 °C, the cooling bath was removed, and stirring was continued 15 min. The resulting deep blue mixture was carefully quenched carefully by addition of solid NH₄Cl in small portions until the color disappeared and then allowed to gradually warm to rt to evaporate the ammonia. To the residue was added saturated aqueous NaHCO₃, the mixture was extracted twice with CH₂Cl₂. The extract was washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (CH₂Cl₂/MeOH/NH₃, 90/10/0.1) to give product 2 (29 mg, 80%) as a white solid: mp 55-57 °C (lit.⁶a mp 53-56 °C; [α]²³D +70.4° (c 0.71, CHCl₃) (lit.⁶a [α]²³D +72.4° (c 0.66, CHCl₃), lit.³c [α]²³D +68.2° (c 1.0, CHCl₃)); ¹H NMR (500 MHz, CDCl₃) δ 1.05 (d, J = 7.0 Hz, 3H), 1.11 (d, J = 6.0 Hz, 3H), 1.18 (s, 3H), 1.54 (s, 3H), 1.72 (m, 4H), 1.96-2.08 (m, 2H), 2.29 (m, 1H), 2.50-2.56 (m, 2H), 2.69-3.04 (m, 6H), 3.57 (d, J = 12.0 Hz, 1H), 3.66 (s, 1H), 3.68 (d, J = 6.5 Hz, 1H), 3.77 (quint, J = 6.5 Hz, 1H), 5.24 (d, J = 9.5 Hz, 1H), 5.30 (dd J = 7.5, 8.5 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 12.4, 19.2, 20.6, 21.1, 22.6, 32.7, 35.4, 49.1, 54.2, 65.2, 68.2, 70.4, 80.6, 82.1, 127.2, 133.5, 135.0, 137.2; IR (film) 3408, 2971, 2929, 2873, 2795 cm⁻¹; EIMS m/z (relative intensity) 339 (M⁺, 33), 322 (18), 294 (34), 276 (40), 182 (100); HRMS calcd for C₁₉H₃₃NO₄ (M⁺) 339.2409, found 339.2409.
(8R,8aS)-8-(Benzyloxy)-6(E)-[6(R),7(R)-(isopropylidenedioxy)-2(R),5-
dimethyl-4(E)-octenylidene]-8-methyloctahydroindolizin-7-one (42). To a cold (-78 °C) solution of (COCl)$_2$ (2.0 M in CH$_2$Cl$_2$, 653 μL, 1.31 mmol) in CH$_2$Cl$_2$ (4 mL) was added dropwise DMSO (186 μL, 2.62 mmol) via syringe. After the solution was stirred at -78 °C for 1 h, a solution of 41 (175 mg, 0.37 mmol) in CH$_2$Cl$_2$ (1 mL) was added dropwise. The reaction mixture was stirred at -78 °C for 4 h. Et$_3$N (546 μL, 3.92 mmol) was then added, and the reaction mixture was allowed to warm gradually to rt. Water was added, and the mixture was extracted twice with Et$_2$O. The combined organic layers were washed with saturated aqueous NaHCO$_3$, brine, and dried over Na$_2$SO$_4$. After evaporation of the solvent, the residue was purified by column chromatography on silica gel (EtOAc/Hexanes: 3/7) to give product 42 (150 mg, 86%) as a colorless oil. $[\alpha]^{23}_D -7.7^\circ$ (c 1.48, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) δ 1.04 (d, $J = 6.5$ Hz, 3H), 1.21 (d, $J = 5.0$ Hz, 3H), 1.25 (s, 3H), 1.41 (s, 6H), 1.63 (s, 3H), 1.79-1.89 (m, 3H), 1.90-1.96 (m, 1H), 2.12 (dt, $J = 3.0$, 6.5 Hz, 2H), 2.21-2.28 (m, 2H), 2.45-2.51 (m, 2H), 2.99 (d, $J = 14.0$ Hz, 1H), 3.19 (dt, $J = 2.3$, 7.8 Hz, 1H), 3.81-3.86 (m, 2H), 4.07 (d, $J = 14.0$ Hz, 1H), 4.42 and 4.53 (AB q, $J = 12.8$ Hz, 2H), 5.46 (t, $J = 7.0$ Hz, 1H), 6.53 (d, $J = 10.5$ Hz, 1H), 7.19-7.22 (m, 1H), 7.25-7.29 (m, 4H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 11.7, 17.1, 17.4, 19.4, 22.6, 23.9, 26.9, 27.5, 33.0, 34.3, 52.2, 55.8, 66.0, 70.5, 74.4, 78.3, 88.4, 107.9, 126.9, 127.0, 127.2, 128.1, 131.3, 132.8, 139.5, 146.0, 196.6; IR (film) 2976, 2871, 1694, 1617, 1377, 1237 cm$^{-1}$; EIMS m/z (relative intensity) 467 (M$^+$, 0.1), 452 (1), 376 (46), 323 (6), 270 (5), 233 (10), 91 (100); HRMS calcd for C$_{22}$H$_{34}$NO$_4$ (M$^+$-Bn) 376.2488, found 376.2490.
(7S,8R,8aS)-8-(Benzyloxy)-7-hydroxy-6(E)-[6(R),7(R)-(isopropylidenedioxymethyl)octahydroindolizine (43). To a cold (0 °C) solution of 42 (130 mg, 0.28 mmol) and CeCl₃·7H₂O (207 mg, 0.56 mmol) in methanol (8 mL) was added NaBH₄ (22 mg, 0.56 mmol) in small portions under argon. The reaction mixture was then stirred at 0 °C for 1 h. Water was added to quench the reaction, and the mixture was extracted twice with methylene chloride. The combined extracts were washed with saturated aqueous NaHCO₃, brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (MeOH/CH₂Cl₂/NH₃: 8/92/0.1) to give product 43 (124 mg, 95%) as a colorless oil. [α]²³D -14.2° (c 1.57, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 1.02 (d, J = 6.5 Hz, 3H), 1.20 (m, 3H), 1.34 (s, 3H), 1.41 (s, 6H), 1.62 (s, 3H), 1.73 (m, 1H), 1.81-1.88 (m, 2H), 1.94-2.20 (m, 6H), 2.49 (m, 1H), 2.52-2.58 (m, 1H), 3.11 (dt, J = 1.5, 6.5 Hz, 1H), 3.78 (s, 1H), 3.83 and 3.85 (AB q, J = 5.5 Hz, 2H), 3.91 (d, J = 7.0 Hz, 1H), 4.77 and 4.80 (AB q, J = 12.5 Hz, 2H), 5.40-5.46 (m, 2H), 7.21-7.25 (m, 1H), 7.28-7.32 (m, 4H); ¹³C NMR (125 MHz, CDCl₃) δ 11.5, 17.0, 20.3, 20.7, 21.4, 24.3, 26.9, 27.4, 32.3, 35.6, 51.8, 54.3, 67.1, 71.6, 74.3, 77.1, 77.6, 88.6, 107.8, 127.1, 128.3, 128.4, 128.9, 131.5, 133.3, 140.4; IR (film) 3295, 2978, 2873, 1457, 1379 cm⁻¹; EIMS m/z (relative intensity) 469 (M⁺, 1), 454 (5), 378 (100); HRMS calcd for C₂₉H₄₃NO₄ (M⁺) 469.3192, found 469.3179.
(7S,8R,8aS)-8-(Benzyloxy)-7-hydroxy-6(E)-[6(R),7(R)-(dihydroxy)-2(R),5-dimethyl-4(E)-octenylidene]-8-methyloctahydroindolizine. To a solution of 43 (59 mg, 0.126 mmol) in THF (1 mL) was added 3 N HCl (1.0 mL). The reaction mixture was then stirred at rt for 0.5 h. Saturated aqueous NaHCO₃ was added. The mixture was extracted twice with CH₂Cl₂. The combined extracts were washed with saturated aqueous NaHCO₃, brine, dried over Na₂SO₄, and filtered. After concentration under reduced pressure, the residue was purified by column chromatography on silica gel (CH₂Cl₂/MeOH/NH₃: 90/10/0.1) to give the product (49 mg, 91%) as a colorless oil. [α]²³D -22.0° (c 1.95, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 1.04 (d, J = 7.0 Hz, 3H), 1.08 (d, J = 6.5 Hz, 3H), 1.40 (s, 3H), 1.56 (s, 3H), 1.76 (m, 1H), 1.88-1.99 (m, 3H), 2.08 (td, J = 5.5, 14.0 Hz, 1H), 2.13-2.21 (m, 1H), 2.48-2.54 (m, 1H), 2.65-3.08 (m, 7H), 3.64-3.68 (m, 2H), 3.73 (quint, J = 6.5 Hz, 1H), 3.92 (br s, 1H), 4.67 and 4.72 (AB q, J = 11.8 Hz, 2H), 5.41-5.43 (m, 2H), 7.23-7.27 (m, 1H), 7.29-7.33 (m, 4H); ¹³C NMR (125 MHz, CDCl₃) δ 12.3, 18.8, 20.7, 21.3, 21.5, 24.0, 32.5, 35.3, 48.9, 54.4, 66.2, 68.7, 69.6, 76.8, 77.4, 82.3, 126.8, 127.2, 127.3, 128.3, 132.6, 135.8, 139.5; IR (film) 3380, 2971, 2873 cm⁻¹; CIMS m/z (relative intensity) 430 (MH⁺, 54), 412 (31), 378 (27), 338 (100); EIMS m/z (relative intensity) 429 (M⁺, 0.1), 384 (6), 378 (28), 338 (100); HRMS calcd for C₂₆H₃₉NO₄ (M⁺) 429.2879, found 429.2874.

(+)-Allopumiliotoxin 339B (3). A solution of the corresponding benzyl ether (43 mg, 0.10 mmol) in THF (2 mL) was added dropwise to liquid NH₃ (5 mL) at -78 °C with stirring. To this mixture was added Li⁻ (7 mg, 1.0 mmol) in small portions. After 10 min at -78 °C, the cooling bath was removed, and the reaction mixture was continued to stir for another 15 min. The resulting deep-blue mixture was carefully quenched by addition of solid NH₄Cl in small portions until the color disappeared and then allowed to gradually warm to rt to evaporate the ammonia. To the
residue was added saturated aqueous NaHCO₃, and the mixture was extracted twice with CH₂Cl₂. The extract was washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (CH₂Cl₂/MeOH/NH₃, 90/10/0.1) to give product 3 (28 mg, 82%) as a colorless solid: mp 129-131 °C; [α]²⁾D +8.7° (c 1.2, MeOH) (lit.³⁾ [α]²⁾D +8.8° (c 1.0, MeOH), lit.⁴⁾ [α]²⁾D +7.0° (c 0.20, MeOH)); ¹H NMR (500 MHz, CDCl₃) δ 1.00 (d, J = 6.5 Hz, 3H), 1.08 (d, J = 6.0 Hz, 3H), 1.21 (s, 3H), 1.57 (s, 3H), 1.77 (m, 4H), 1.92-2.81 (m, 10H), 3.07 (br s, 1H), 3.67-3.68 (m, 2H), 3.74 (quint, J = 6.8 Hz, 1H), 3.80 (d, J = 12.0 Hz, 1H), 5.36 (br t, J = 7.3 Hz, 1H), 5.51 (d, J = 9.5 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 12.2, 18.9, 20.4, 21.3, 21.6, 23.5, 32.2, 35.3, 51.5, 54.2, 68.7, 70.5, 71.6, 76.3, 82.6, 127.1, 131.1, 132.7, 135.4; IR (film) 3415, 2971, 2929, 2873, 2795 cm⁻¹; EIMS m/z (relative intensity) 339 (M⁺, 41), 322 (15), 304 (11), 294 (40), 276 (28), 182 (100); HRMS calcd for C₁₉H₃₃NO₄ (M⁺) 339.2409, found 339.2406.

Reference numbers are consistent with the journal text.