Supporting Information

Nickel-Catalyzed Preparation of Bicyclic Heterocycles: Total Synthesis of (+)-Allopumiliotoxin 267A, (+)-Allopumiliotoxin 339A, and (+)-Allopumiliotoxin 339B

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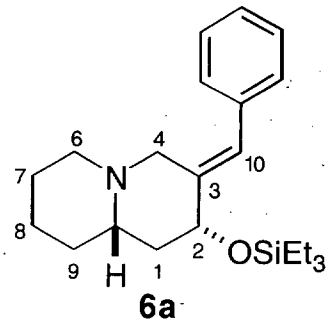
Experimental Section

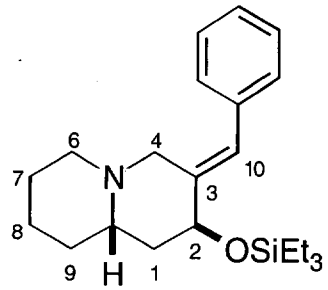
All reagents were used as received unless otherwise noted. Tetrahydrofuran (THF) was freshly distilled from sodium/benzophenone ketyl. Dichloromethane and triethylamine were distilled from calcium hydride. $Ni(COD)_2$ was stored and weighed in an inert atmosphere glovebox. All reactions were conducted 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_3SiH (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_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated, and the residue was purified by column chromatography on silica gel.



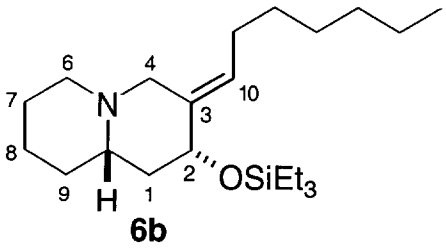
6a

(2*R, 9a*S**)-3-[(*E*)-Benzylidene]-2-(triethylsilyloxy)octahydroquinolizine (6a).** Following the general procedure at 45 °C, **5a** (241 mg, 1.0 mmol), Et_3SiH (0.80 mL, 5.0 mmol), $Ni(COD)_2$ (27 mg, 0.1 mmol), and PBu_3 (50 μL, 0.2 mmol) were employed to give **6a** (303 mg, 85%) and **7a** (25 mg, 7%) as colorless oils after chromatography (Et_2O/pet ether: 3/2). ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 calcd for $C_{22}H_{35}NOSi$ (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-H_{ax} and 2-H/1-H_{eq} were observed at 11.2 and 5.2 Hz, respectively, the former of which confirms a trans diaxial relationship between the two corresponding protons.



7a

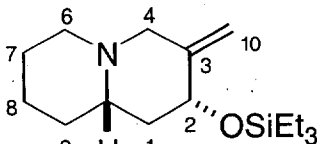
(2*S, 9a*S**)-3-[(*E*)-Benzylidene]-2-(triethylsilyloxy)octahydroquinolizine (7a).** ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.62 (q, *J* = 8.0 Hz, 6H), 0.97 (t, *J* = 8.0 Hz, 9H), 1.20-1.35 (m, 2H), 1.54-1.62 (m, 4H), 1.71-1.73 (m, 1H), 1.78 (dt, *J* = 13.5, 2.8 Hz, 1H), 2.08-2.14 (m, 1H), 2.42 (m, 1H), 2.75 (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, $CDCl_3$) δ 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 δ 4.33, NOEs were observed on the *C*-10 olefinic proton at δ 6.42 (10%) and *C*-1 axial proton at δ 1.78 (2%), confirming that the *C*-2 proton is equatorial.



6b

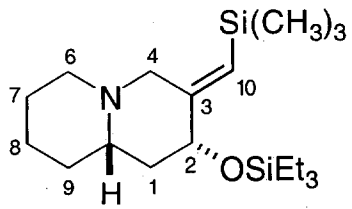
(2*R, 9a*S**)-3-[(*E*)-Heptylidene]-2-(triethylsilyloxy)octahydroquinolizine (6b).** Following the general procedure at 45 °C, **5b** (175 mg, 0.70 mmol), Et_3SiH (561 μL, 3.51 mmol), $Ni(COD)_2$ (20 mg, 0.073 mmol), and PBu_3 (35 μL, 0.14 mmol) were employed to give **6b** (212 mg, 83%) as a colorless oil after chromatography (EtOAc/Hexanes: 1/4). ^{1}H NMR (400 MHz, $CDCl_3$) δ 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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}; EIMS *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 $C_{22}H_{43}NOSi$ (M^+) 365.3114, found 365.3138.



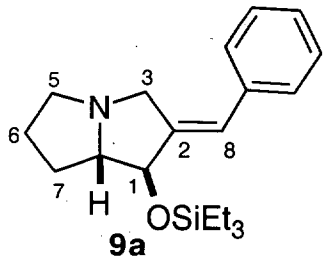
6c

(2*R, 9a*S**)-3-(Methylidene)-2-(triethylsilyloxy)octahydroquinolizine (6c).** Following the general procedure at 45 °C, **5c** (83 mg, 0.5 mmol), Et_3SiH (0.40 mL, 2.5 mmol), $Ni(COD)_2$ (15 mg, 0.06 mmol), and PBu_3 (30 μL, 0.12 mmol) were employed to give **6c** (114 mg, 81%) as a colorless oil after chromatography (CH_2Cl_2/MeOH/NH_3: 92/8/0.1). ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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}; EIMS *m/z* (relative intensity) 281 (M^+, 19), 266 (6), 252 (22), 149 (100); HRMS calcd for $C_{16}H_{31}NOSi$ (M^+) 281.2175, found 281.2175.



6d

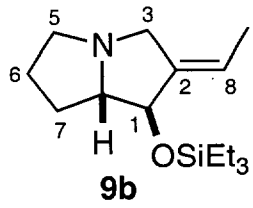
(2*R, 9a*S**)-2-(Triethylsilyloxy)-3-[(*E*)-trimethylsilylmethylidene]octahydroquinolizine (6d).** Following the general procedure at 45 °C, **5d** (118 mg, 0.5 mmol), Et_3SiH (0.40 mL, 2.5 mmol), $Ni(COD)_2$ (14 mg, 0.05 mmol), and PBu_3 (25 μL, 0.1 mmol) were employed to give **6d** (163 mg, 93%) as a colorless oil after chromatography (EtOAc/Hexanes: 1/4). ^1H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_{19}H_{39}NOSi_2$ (M^+) 353.2570, found 353.2569.



9a

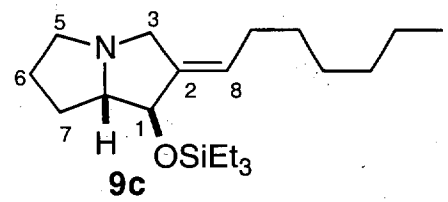
(1*R*, 1a*S*)-2-[(*E*)-Benzylidene]-1-(triethylsilyloxy)hexahydropyrrolizine (9a). Following the general procedure at 50 °C, the ynal substrate [crude, 205 mg, 0.96 mmol, obtained from Swern oxidation of **8a** (217 mg, 1.0 mmol) and used without purification], Et_3SiH (0.80 mL, 5.0 mmol), $Ni(COD)_2$ (55 mg, 0.2 mmol), and PBu_3 (100 μL, 0.4 mmol) were employed to give **9a** (181 mg, 55%) as a pale-yellow oil after chromatography (CH_2Cl_2/MeOH/NH_3: 90/10/0.1). ^1H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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 δ 4.39, NOEs were observed on the *C*-8 olefinic proton at δ 6.51 (2%), one of the two *C*-3 protons at δ 4.14 (3%), and one of the two *C*-7 protons at δ 1.65 (3%); no NOE was observed on the *C*-7a proton at δ 3.31, confirming the trans relationship between the *C*-1 proton and the *C*-7a proton.



9b

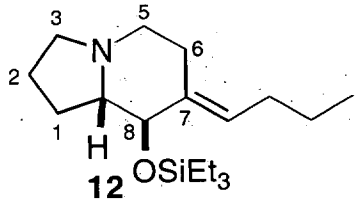
(1*R*, 1a*S*)-2-[(*E*)-Ethylidene]-1-(triethylsilyloxy)hexahydropyrrolizine (9b). Following the general procedure at 45 °C, the ynal substrate [crude, 151 mg, 1.0 mmol, obtained from Swern oxidation of **8b** (153 mg, 1.0 mmol) and used without purification], Et_3SiH (0.8 mL, 5.0 mmol), $Ni(COD)_2$ (55 mg, 0.2 mmol), and PBu_3 (100 μL, 0.4 mmol) were employed to give **9b** (112 mg, 42%) as a pale-yellow oil after chromatography (CH_2Cl_2/MeOH/NH_3: 90/10/0.1). ^1H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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.



9c

(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

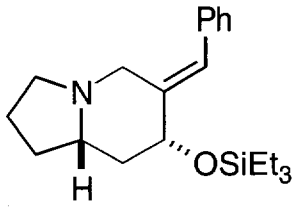
from Swern oxidation of **8c** (124 mg, 0.56 mmol) and used without purification], Et_3SiH (434 μL, 2.72 mmol), $Ni(COD)_2$ (30 mg, 0.11 mmol), and PBu_3 (54 μL, 0.22 mmol) were employed to give **9c** (93 mg, 51%) as a colorless oil after chromatography (CH_2Cl_2/MeOH/NH_3: 90/10/0.1). ^1H NMR (400 MHz, $CDCl_3$) 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), 3.92 (d, J = 14.4 Hz, 1H), 4.14 (d, J = 4.8 Hz, 1H), 5.50 (tq, J = 7.2, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{20}H_{39}NOSi$ (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.



12

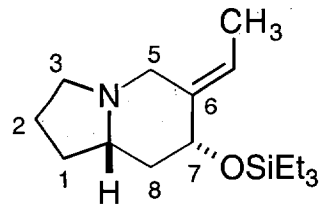
(8*R*,8a*S*)-7-[(*E*)-Butylidene]-8-(triethylsilyloxy)octahydroindolizine (12). Following the general procedure at 45 °C, the ynal substrate [crude, 197 mg, 1.0 mmol, obtained from Swern oxidation of **11** (195 mg, 1.0 mmol) and used without purification], Et_3SiH (0.4 mL, 5.0 mmol), $Ni(COD)_2$ (55 mg, 0.2 mmol), and PBu_3 (100 μL, 0.4 mmol) were employed to give **12** (167 mg, 54%) as a corlorless oil after chromatography (CH_2Cl_2/MeOH/NH_3: 92/8/0.1). ^1H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz,

$CDCl_3$) 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 $C_{18}H_{35}NOSi$ (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.



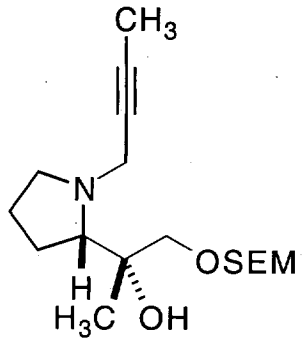
15

(7R,8aS)-6-[(*E*)-Benzylidene]-7-(triethylsilyoxy)octahydroindolizine (15). PBu_3 (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, Et_3SiH (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 Et_2O, washed with saturated aqueous $NaHCO_3$, brine, dried over Na_2SO_4, and filtered. After concentration under reduced pressure, the residue was purified by column chromatography on silica gel (CH_2Cl_2/MeOH/NH_3: 95/5/0.1) to give product **15** (208 mg, 89%) as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_{21}H_{33}NOSi$ (M^+) 343.2331, found 343.2329.

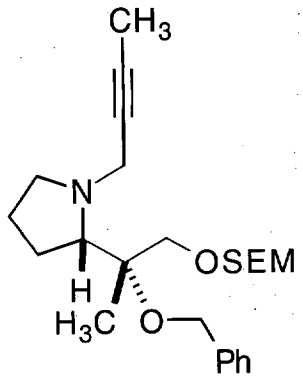


16

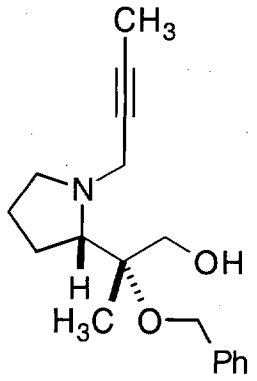
(7R,8aS)-6-[(*E*)-Ethylidene]-7-(triethylsilyoxy)octahydroindolizine (16). PBu_3 (100 μL, 0.40 mmol) was added dropwise by syringe to a solution of $Ni(COD)_2$ (28 mg, 0.10 mmol) in THF (10 mL) at rt under an atmosphere of argon. After 5 min, Et_3SiH (400 μL, 2.50 mmol) was added dropwise. The mixture 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_2O, washed with saturated aqueous $NaHCO_3$, brine, dried over Na_2SO_4, and filtered. After concentration under reduced pressure, the residue was purified by column chromatography on silica gel (CH_2Cl_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). ^1H NMR (500 MHz, $CDCl_3$) δ 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 (dquint, J = 11.0, 2.0 Hz, 1H), 5.67 (br q, J = 7.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 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 calcd for $C_{16}H_{31}NOSi$ (M^+) 281.2175, found 281.2173. On irradiation of the *C*-7 proton at δ 4.02, an NOE was observed on the *C*-8 equatorial proton at δ 2.00 (2%). The *C*-8 axial proton at δ 1.28 appears as a quartet (J = 11.5 Hz) which confirms the axial position of 7-H.



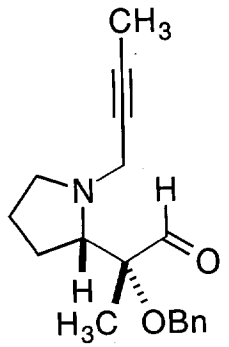
(2*S*)-2-[(*R*)-1-(Hydroxy)-1-(trimethylsilylethoxymethoxymethyl)ethyl]-*N*-[2'-butynyl]pyrrolidine. A degassed solution of **27**[3c] (1.00 g, 3.32 mmol) and KOH (4.38 g, 85% purity, 66.4 mmol) in EtOH (15 mL) and H_2O (3 mL) was stirred at 80 °C for 16 h under argon. Upon cooling to rt, EtOH was removed under reduced pressure, and the residue was extracted twice with THF. The combined organic layers were dried over K_2CO_3 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*-Pr_2NEt (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 $NaHCO_3$. The mixture was extracted twice with Et_2O, washed with brine, and dried over Na_2SO_4 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, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{17}H_{33}NO_3Si$ (M^+) 327.2230, found 327.2225.



(2*S*)-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 Et_2O, washed with brine, dried over Na_2SO_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 (1.09 g, 86%) as a colorless oil. $[\alpha]^{23}_D$ -49.6° (*c* 1.05, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{24}H_{39}NO_3Si$ (M^+) 417.2699, found 417.2705.

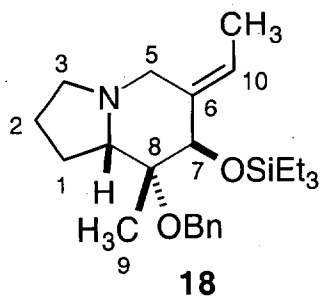


(2*S*)-2-[(*R*)-1-(Benzyloxy)-1-(hydroxymethyl)ethyl]-*N*-[2'-butynyl]pyrrolidine. Molecular sieves (4Å, crushed to powder, and flame-dried under vacuum, 2.0 g) were added in one portion to a solution of the silyl ether derivative (1.06 g, 2.54 mmol) in THF (50 mL) at rt. To this stirred suspension was added dropwise a solution of *n*-Bu_4F (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 Et_2O three times. The filtrate was washed with saturated $NaHCO_3$, brine, dried over Na_2SO_4, and filtered. After evaporation of the solvent, the residue was purified by column chromatography on silica gel (Et_2O/pet ether: 8/2) to give the product (632 mg, 87%) as a colorless oil. $[\alpha]^{23}_D$ -27.2° (*c* 1.16, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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^+-CH_2OH, 1.3), 220 (2), 205 (8), 122 (100); HRMS calcd for $C_{17}H_{22}NO$ (M^+-CH_2OH) 256.1702, found 256.1701.



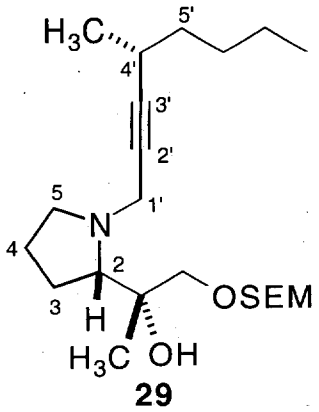
17

(2*S*)-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 CH_2Cl_2, 0.90 mL, 1.80 mmol) in CH_2Cl_2 (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 CH_2Cl_2 (3 mL) was added dropwise. The reaction mixture was stirred at -78 °C for 3 h. Et_3N (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 Et_2O. The combined organic layers were washed with saturated $NaHCO_3$, brine, and dried over Na_2SO_4. 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. $[\alpha]^{23}_D$ -10.0° (*c* 1.11, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) 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 (AB q, *J* = 11.5 Hz, 2H), 7.28 (m, 1H), 7.33-7.39 (m, 4H), 9.70 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_{17}H_{22}NO$ (M^+-CHO) 256.1701, found 256.1702.



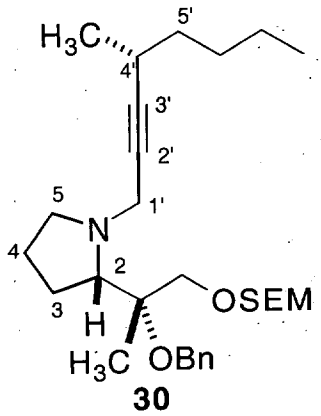
18

(7*R*,8*R*,8a*S*)-8-(Benzyloxy)-7-(triethylsilyloxy)-8-methyl-6-[(*E*)-ethylidene]octahydroindolizine (18). PBu_3 (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, Et_3SiH (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 Et_2O, washed with saturated aqueous $NaHCO_3$, brine, dried over Na_2SO_4, and filtered. After concentration under reduced pressure, the residue was purified by column chromatography on silica gel (CH_2Cl_2/MeOH/NH_3: 92/8/0.1) to give product **18** (107 mg, 91%) as a colorless oil. $[\alpha]^{23}_D$ +32.6° (*c* 1.03, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_{22}H_{34}NO_2Si$ (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.



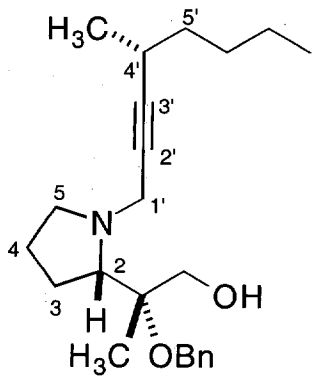
29

(2*S*)-2-[(*R*)-1-(Hydroxy)-1-[(trimethylsilyl)ethoxymethoxymethyl]ethyl]-*N*-[(*R*)-4'-methyl-2'-octynyl]pyrrolidine (29). A degassed solution of **27**[3c] (903 mg, 3 mmol) and KOH (3.95 g, 85%, 60 mmol) in EtOH (15 mL) and H_2O (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 K_2CO_3 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*-Pr_2NEt (1.04 mL, 6.0 mmol), followed by the addition of a solution of **28**[7] (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 $NaHCO_3$. The mixture was extracted twice with Et_2O, washed with brine, and dried over Na_2SO_4 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. $[\alpha]^{23}_D$ -57.8° (*c* 1.16, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{21}H_{40}NO_3Si$ (M^+-CH_3) 382.2777, found 382.2780.



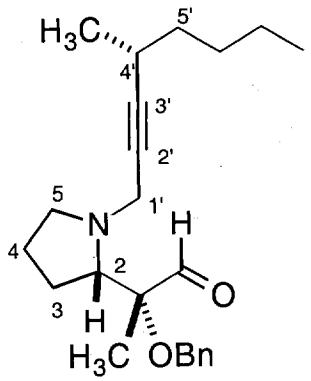
30

(2*S*)-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_2O, washed with brine, dried over Na_2SO_4, 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. $[\alpha]^{23}_D$ -66.1° (*c* 1.16, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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^+), 370, 192; IR (film) 2957, 2929, 2872 cm^{-1}; EIMS *m/z* (relative intensity) 487 (M^+, 0.1), 370 (3), 246 (2), 202 (8), 192 (100); HRMS calcd for $C_{24}H_{36}NO_2$ (M^+-$OCH_2CH_2SiMe_3$) 370.2746, found 370.2745.



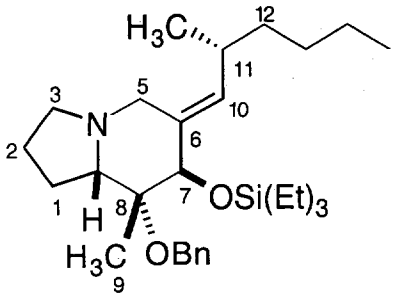
31

(2*S*)-2-[(*R*)-1-(Benzyloxy)-1-(hydroxymethyl)ethyl]-*N*-[(*R*)-4'-methyl-2'-octynyl]pyrrolidine (31). Molecular sieves (4Å, 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_4NF (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_2O. The filtrate was washed with saturated $NaHCO_3$, brine, dried over Na_2SO_4, and filtered. After evaporation of the solvent, the residue was purified by column chromatography on silica gel (Et_2O/pet ether: 7/3) to give **31** (343 mg, 94%) as a colorless oil. $[\alpha]^{23}_D$ -43.2° (*c* 1.07, $CHCl_3$); ^1H 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_2OH, 0.3), 236 (1), 192 (100), 91 (7), 70 (14); HRMS calcd for $C_{22}H_{32}NO$ (M^+-CH_2OH) 326.2484, found 326.2481.



32

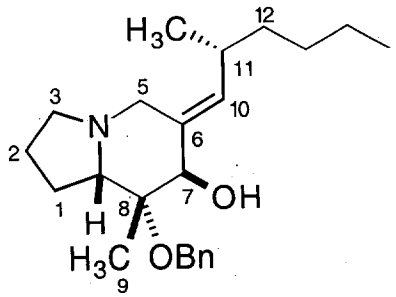
(2*S*)-2-[(*R*)-1-(Benzyloxy)-1-formylethyl]-*N*-[(*R*)-4'-methyl-2'-octynyl]-pyrrolidine (32). To a cold (-78 °C) solution of $(COCl)_2$ (2.0 M in CH_2Cl_2, 1.16 mL, 2.32 mmol) in CH_2Cl_2 (5 mL) was added dropwise DMSO (329 μL, 4.64 mmol). After the solution was stirred at -78 °C for 1 h, a solution of **31** (236 mg, 0.66 mmol) in CH_2Cl_2 (3 mL) was added dropwise. The reaction mixture was stirred at -78 °C for 3 h. Et_3N (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_2O. The combined organic layers were washed with saturated $NaHCO_3$, brine, and dried over Na_2SO_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. $[\alpha]^{23}_D$ -31.2° (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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_2CH_3, 2), 192 (100), 135 (6), 91 (70); HRMS calcd for $C_{21}H_{28}NO_2$ (M^+-CH_2CH_3) 326.2120, found 326.2117.



33

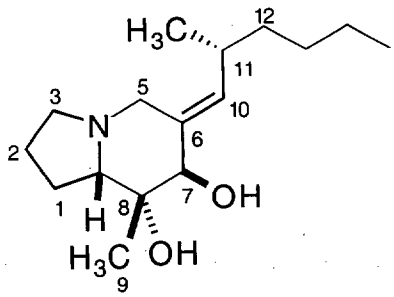
(7*R*,8*R*,8a*S*)-8-(Benzyloxy)-7-(triethylsilyoxy)-8-methyl-6-[(*E*)-(*R*)-2-methylhexylidene]octahydroindolizine (33). PBu_3 (63 μL, 0.25 mmol) was added dropwise by syringe to a solution of $Ni(COD)_2$ (34 mg, 0.12 mmol) in THF (20 mL) at rt under an atmosphere of argon. After 5 min, Et_3SiH (500 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_2O, washed with saturated $NaHCO_3$, brine, dried over Na_2SO_4, and filtered. After concentration under reduced pressure, the residue was purified by column chromatography on silica gel (CH_2Cl_2/MeOH/NH_3: 92/8/0.1) to give **33** (280 mg, 95%) as a colorless oil. $[\alpha]^{23}_D$ +23.6° (*c* 1.02, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.59 (q, *J* = 8.0Hz, 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_2Ph, 100), 365 (6), 336 (4), 311 (2), 267 (3), 233 (8), 115 (14), 91 (24); HRMS calcd for $C_{22}H_{42}NO_2Si$ (M^+-CH_2Ph) 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.



34

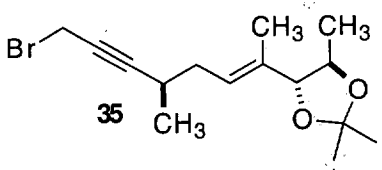
(7*R*,8*R*,8a*S*)-8-(Benzyloxy)-7-hydroxy-8-methyl-6-[(*E*)-(*R*)-2-methylhexylidene]octahydroindolizine (34). To a cold (0 °C) solution of **33** (178 mg, 0.38 mmol) in THF (10 mL) was added dropwise HF·pyridine (6 M in pyridine, 1.5 mL). The reaction mixture was then stirred at 0 °C - rt overnight. The mixture was quenched with saturated $NaHCO_3$, and was extracted twice with CH_2Cl_2. The combined organic layers were washed with saturated $NaHCO_3$, brine, dried over Na_2SO_4, and filtered. After evaporation of the solvent, the residue was purified by column chromatography on silica gel (CH_2Cl_2/MeOH/NH_3: 91/9/0.1) to give **34** (124 mg, 92%) as a white solid: mp 126-127 °C (lit.[6a] mp 126-127 °C); $[\alpha]^{23}_D$ +16.6° (*c* 0.48, $CHCl_3$) (lit.[6a] $[\alpha]^{25}_D$ +15.8° (*c* 0.41, $CHCl_3$)). Synthetic **34** showed TLC mobility and 500 MHz ^1H NMR, 125 MHz ^{13}C NMR, MS, and IR spectra that were indistinguishable from those of the synthetic sample kindly provided by Overman.



allopumiliotoxin 267A, **1**

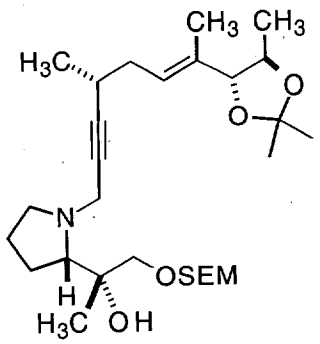
(+)-Allopumiliotoxin 267A (1). A solution of **34** (55 mg, 0.15 mmol) in THF (5 mL) was added dropwise to liquid NH_3 (10 mL) at -78 °C with stirring. To this mixture was added

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 stirr for another 15 min. The resulting deep-blue mixture was carefully quenched by addition of solid NH_4Cl in small portions until the color disapperared and then allowed to warm to rt to evaporate the ammonia. To the residue was added saturated $NaHCO_3$, the mixture was extracted twice with CH_2Cl_2. The extract was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (CH_2Cl_2-MeOH-NH_3, 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); $[\alpha]^{23}_D$ +31.4° (*c* 0.32, MeOH) (lit.[3c] $[\alpha]^{20}_D$ +31° (*c* 0.22, MeOH), lit.[1b] $[\alpha]^{25}_D$ +24.7° (*c* 0.17, MeOH)). Synthetic **1** showed TLC mobility and 500 MHz ^1H NMR, 125 MHz ^{13}C 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 alcohol[6a] (2.28 g, 9.05 mmol) and PPh_3 (4.74 g, 18.1 mmol) in CH_2Cl_2 (50 mL) was added CBr_4 (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 Et_2O, 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. $[\alpha]^{23}_D$ -15.1° (*c* 1.36, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.7, 15.6, 17.0, 20.0, 26.1, 26.9, 27.5, 34.4, 74.5, 75.7,

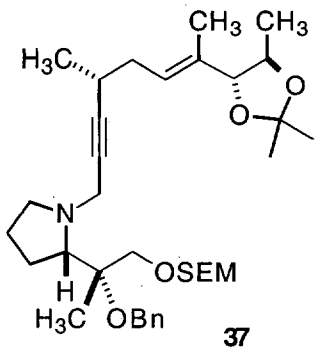
88.3, 91.7, 108.0, 126.4, 133.1; IR (film) 2985, 2873, 2232, 1739 cm^{-1}; EIMS *m/z* (relative intensity) 315 (M^++1, 7), 317 (2), 301 (3), 299 (3), 272 (4), 270 (4), ; HRMS calcd for $C_{14}H_{20}BrO_2$ (M^+-CH_3) 299.0647, found 299.0653.



36

(2*S*)-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**[3c] (1.33 g, 4.42 mmol) and KOH (5.82 g, 85% purity, 88.3 mmol) in EtOH (20 mL) and H_2O (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_2CO_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_2NEt (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_2O, washed with brine, and dried over Na_2SO_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, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ -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,

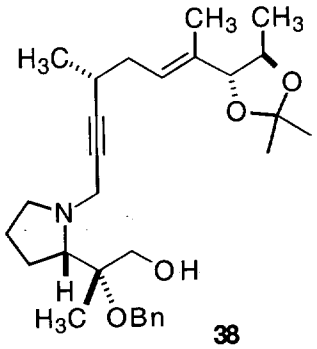
95.3, 107.9, 127.3, 132.5; IR (film) 3414-3239, 2977, 2879, 1455, 1377 cm^{-1}; EIMS *m/z* (relative intensity) 509 (M^+, 0.1), 494 (4), 392 (5), 304 (100), 246 (5); HRMS calcd for $C_{27}H_{48}NO_5Si$ (M^+-CH_3) 494.3302, found 494.3300.



37

(2*S*)-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 Et_2O. The combined extracts were washed with saturated aqueous $NaHCO_3$, brine, dried over Na_2SO_4, 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. $[\alpha]^{23}_D$ -56.1° (*c* 1.78, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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,

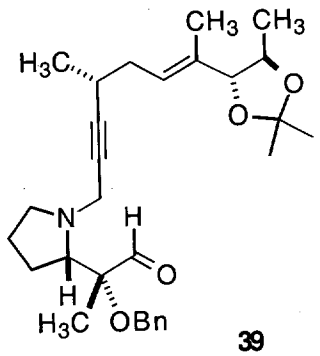
44.2, 54.0, 64.3, 64.9, 65.2, 71.1, 74.3, 77.1, 80.5, 88.2, 88.5, 95.2, 107.9, 126.8, 127.1, 127.5, 128.1, 132.4, 139.9; IR (film) 2977, 2878, 1455, 1378 cm^{-1}; EIMS *m/z* (relative intensity) 599 (M^+, 0.3), 584 (2), 482 (4), 304 (100), 246 (7), 202 (10); HRMS calcd for $C_{35}H_{57}NO_5Si$ (M^+) 599.4006, found 599.4005.



38

(2*S*)-2-[(*R*)-1-(Benzyloxy)-1-(hydroxymethyl)ethyl]-*N*-[(*E*)-(4R,8R,9R)-4,7-dimethyl-8,9-(isopropylidenedioxy)-6-decen-2-ynyl]pyrrolidine (38). Molecular sieves (4Å, 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-Bu_4NF (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 Et_2O for three times. The filtrate was washed with saturated aqueous $NaHCO_3$, brine, dried over Na_2SO_4, 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. $[\alpha]^{23}_D$ -33.6° (*c* 1.21, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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,

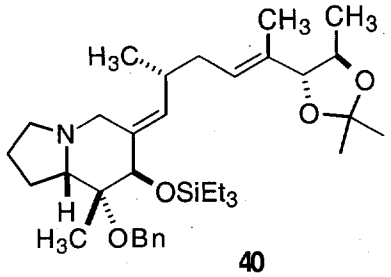
139.5; IR (film) 3413-3244, 2976, 2878, 1455, 1377 cm^{-1}; EIMS *m/z* (relative intensity) 469 (M^+, 0.2), 454 (3), 304 (100), 246 (6); HRMS calcd for $C_{28}H_{40}NO_4$ (M^+-CH_3) 454.2957, found 454.2955.



39

(2*S*)-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 $(COCl)_2$ (2.0 M in CH_2Cl_2, 633 μL, 1.27 mmol) in CH_2Cl_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_2Cl_2 (2 mL) was added dropwise. The reaction mixture was stirred at -78 °C for 3 h. Et_3N (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_2O. The combined organic layers were washed with saturated aqueous $NaHCO_3$, brine, and dried over Na_2SO_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, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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;

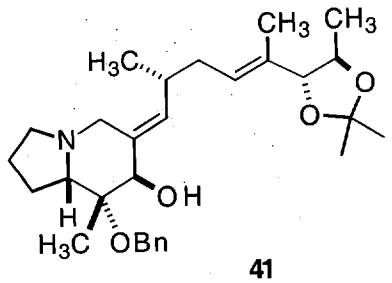
IR (film) 2976, 2934, 2878, 2244, 1730 cm^{-1}; CIMS *m/z* (relative intensity) 468 (MH^+, 5), 410 (2), 346 (6), 304 (71), 246 (25), 91 (100); EIMS *m/z* (relative intensity) 468 (M^++1, 0.3), 452 (3), 304 (100); HRMS calcd for $C_{28}H_{38}NO_4$ (M^+-CH_3) 452.2801, found 452.2808.



40

(7R,8R,8aS)-8-(Benzyloxy)-7-(triethylsilyloxy-6(*E*)-[6(R),7(R)-(isopropylidenedioxy)-2(R),5-dimethyl-4(*E*)-octenylidene]-8-methyloctahydroindolizine (40). PBu_3 (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 Et_3SiH (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 Et_2O, washed with saturated $NaHCO_3$, brine, dried over Na_2SO_4, and filtered. After concentration under reduced pressure, the residue was purified by column chromatography on silica gel (CH_2Cl_2/MeOH/NH_3: 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**. $[\alpha]^{23}_D$ +2.7° (*c* 1.58, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) 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), 1.43 (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); ^{13}C NMR (125 MHz, $CDCl_3$) δ 5.0, 7.0, 11.4, 17.0, 18.9, 20.2,

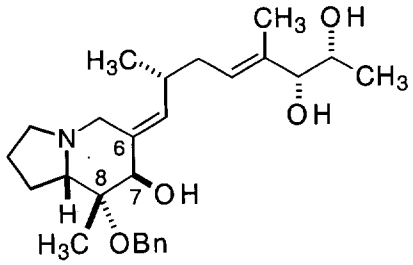
20.9, 22.9, 26.9, 27.4, 31.9, 35.2, 48.0, 53.9, 64.3, 65.8, 74.1, 76.4, 77.5, 88.7, 107.8, 127.0, 127.2, 128.0, 128.3, 131.9, 134.9, 140.1; IR (film) 2957, 2873, 1640 cm^{-1}; EIMS *m/z* (relative intensity) 584 (M^++1, 5), 583 (M^+, 4), 568 (6), 554 (2), 492 (100); HRMS calcd for $C_{35}H_{57}NO_4Si$ (M^+) 583.4057, found 583.4054.



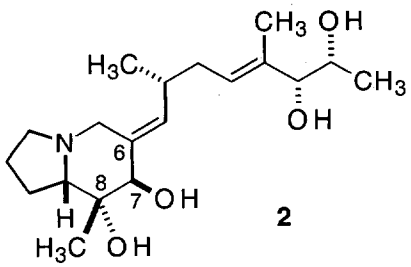
41

(7R,8R,8aS)-8-(Benzyloxy)-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 $NaHCO_3$, and was extracted twice with CH_2Cl_2. The combined organic layers were washed with saturated aqueous $NaHCO_3$, brine, dried over Na_2SO_4, and filtered. After evaporation of the solvent, the residue was purified by column chromatography on silica gel (CH_2Cl_2/MeOH/NH_3: 92/8/0.1) to give product **41** (149 mg, 87%) as a colorless oil. $[\alpha]^{23}_D$ +27.9° (*c* 1.45, $CHCl_3$) (lit.[6a] $[\alpha]^{27}_D$ +27.5° (*c* 1.4, $CHCl_3$)); ^1H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{29}H_{43}NO_4$ (M^+) 469.3192, found 469.3196.

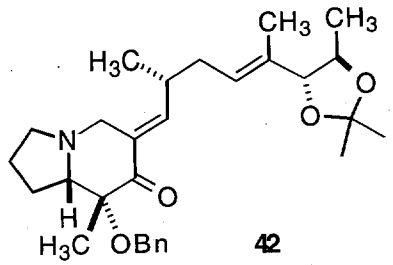


(7R,8R,8aS)-8-(Benzyloxy)-7-hydroxy-6(*E*)-[6(R),7(R)-(dihydroxy)-2(R),5-dimethyl-4(*E*)-octenylidene]-8-methyloctahydroindolizine. To a solution of **41** (75 mg, 0.16 mmol) in THF (1 mL) was added 3 N HCl (1.0 mL). The reaction mixture was then stirred at rt for 0.5 h. Saturated aqueous $NaHCO_3$ was added, and the mixture was extracted twice with CH_2Cl_2. The combined extracts were washed with saturated aqueous $NaHCO_3$, brine, dried over Na_2SO_4, and filtered. After concentration under reduced pressure, the residue was purified by column chromatography on silica gel (CH_2Cl_2/MeOH/NH_3: 90/10/0.1) to give the product (63 mg, 92%) as a colorless oil. $[\alpha]^{23}_D$ +28.1° (*c* 1.21, $CHCl_3$) (lit.[6a] $[\alpha]^{28}_D$ +28.8° (*c* 1.9, $CHCl_3$)); ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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}.



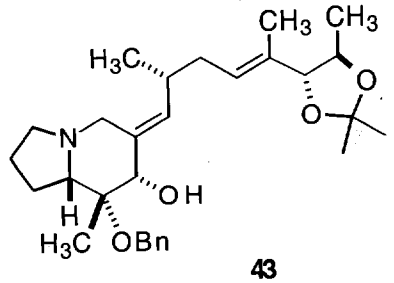
2

(+)-Allopumiliotoxin 339A (2). A solution of the benzyl ether derivative (46 mg, 0.107 mmol) in THF (2 mL) was added dropwise to liquid NH_3 (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 NH_4Cl 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 $NaHCO_3$, the mixture was extracted twice with CH_2Cl_2. The extract was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (CH_2Cl_2/MeOH/NH_3, 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); $[\alpha]^{23}_D$ +70.4° (*c* 0.71, $CHCl_3$) (lit.[6a] $[\alpha]^{28}_D$ +72.4° (*c* 0.66, $CHCl_3$), lit.[3c] $[\alpha]^{22}_D$ +68.2° (*c* 1.0, $CHCl_3$)); ^1H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{19}H_{33}NO_4$ (M^+) 339.2409, found 339.2409.



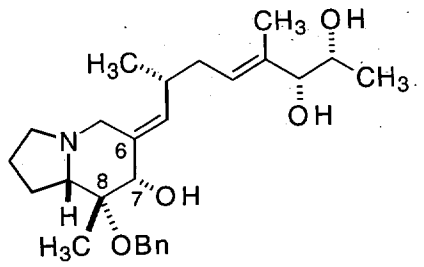
42

(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_2Cl_2, 653 μL, 1.31 mmol) in CH_2Cl_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_2Cl_2 (1 mL) was added dropwise. The reaction mixture was stirred at -78 °C for 4 h. Et_3N (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_2O. The combined organic layers were washed with saturated aqueous $NaHCO_3$, brine, and dried over Na_2SO_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° (*c* 1.48, $CHCl_3$); ^1H 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.

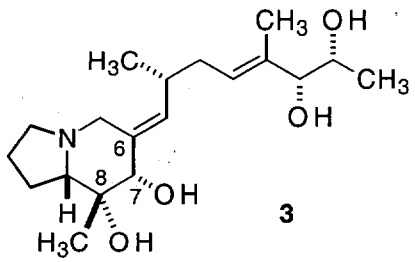


43

(7S,8R,8aS)-8-(Benzyloxy)-7-hydroxy-6(*E*)-[6(R),7(R)-(isopropylidenedioxy)-2(R),5-dimethyl-4(*E*)-octenylidene]-8-methyloctahydroindolizine (43). To a cold (0 °C) solution of **42** (130 mg, 0.28 mmol) and $CeCl_3 \cdot 7H_2O$ (207 mg, 0.56 mmol) in methanol (8 mL) was added $NaBH_4$ (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 $NaHCO_3$, brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel ($MeOH/CH_2Cl_2/NH_3$: 8/92/0.1) to give product **43** (124 mg, 95%) as a colorless oil. $[\alpha]^{23}_D$ -14.2° (*c* 1.57, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_{29}H_{43}NO_4$ (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 $NaHCO_3$ was added. The mixture was extracted twice with CH_2Cl_2. The combined extracts were washed with saturated aqueous $NaHCO_3$, brine, dried over Na_2SO_4, and filtered. After concentration under reduced pressure, the residue was purified by column chromatography on silica gel (CH_2Cl_2/MeOH/NH_3: 90/10/0.1) to give the product (49 mg, 91%) as a colorless oil. $[\alpha]^{23}_D$ -22.0° (*c* 1.95, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_{26}H_{39}NO_4$ (M^+) 429.2879, found 429.2874.



3

(+)-Allopumiliotoxin 339B (3). A solution of the corresponding benzyl ether (43 mg, 0.10 mmol) in THF (2 mL) was added dropwise to liquid NH_3 (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 NH_4Cl in small portions until the color disapperared and then allowed to gradually warm to rt to evaporate the ammonia. To the

residue was added saturated aqueous $NaHCO_3$, and the mixture was extracted twice with CH_2Cl_2. The extract was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (CH_2Cl_2/MeOH/NH_3, 90/10/0.1) to give product **3** (28 mg, 82%) as a colorless solid: mp 129-131 °C; $[\alpha]^{23}_D$ +8.7° (*c* 1.2, MeOH) (lit.[3a] $[\alpha]^{25}_D$ +8.8° (*c* 1.0, MeOH), lit.[4] $[\alpha]^{26}_D$ +7.0° (*c* 0.20, MeOH)); ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{19}H_{33}NO_4$ (M^+) 339.2409, found 339.2406.

Reference numbers are consistent with the journal text.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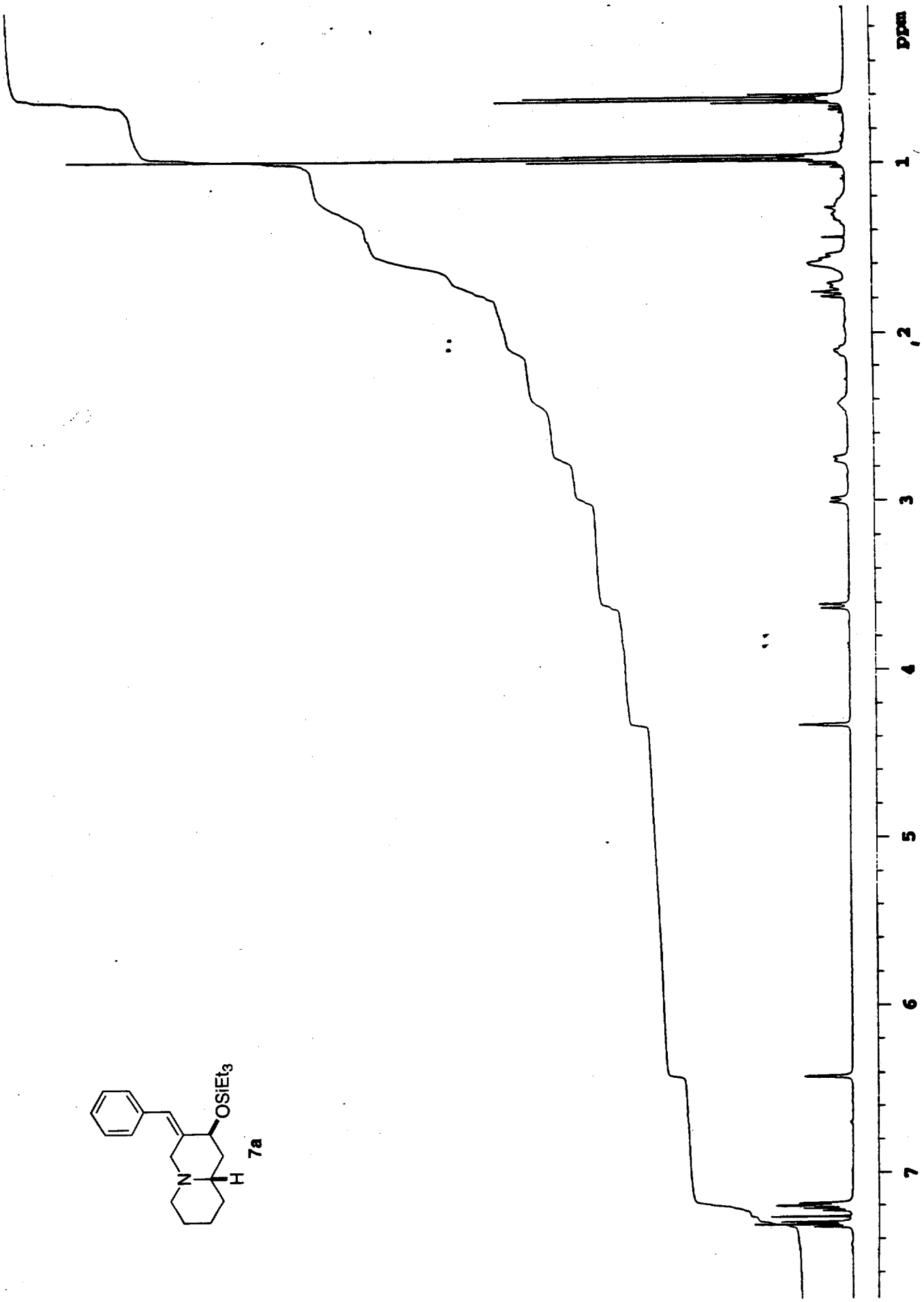
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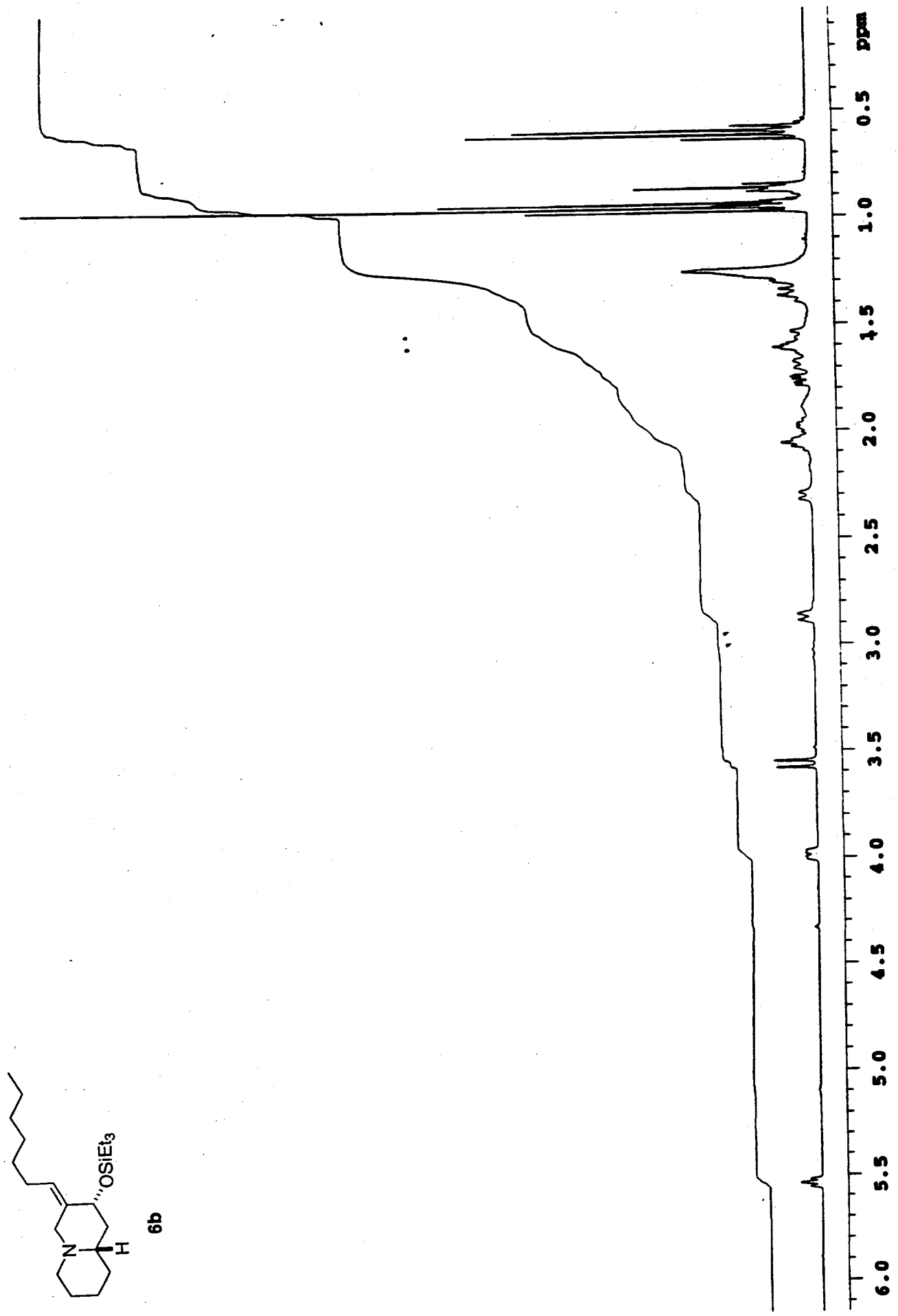
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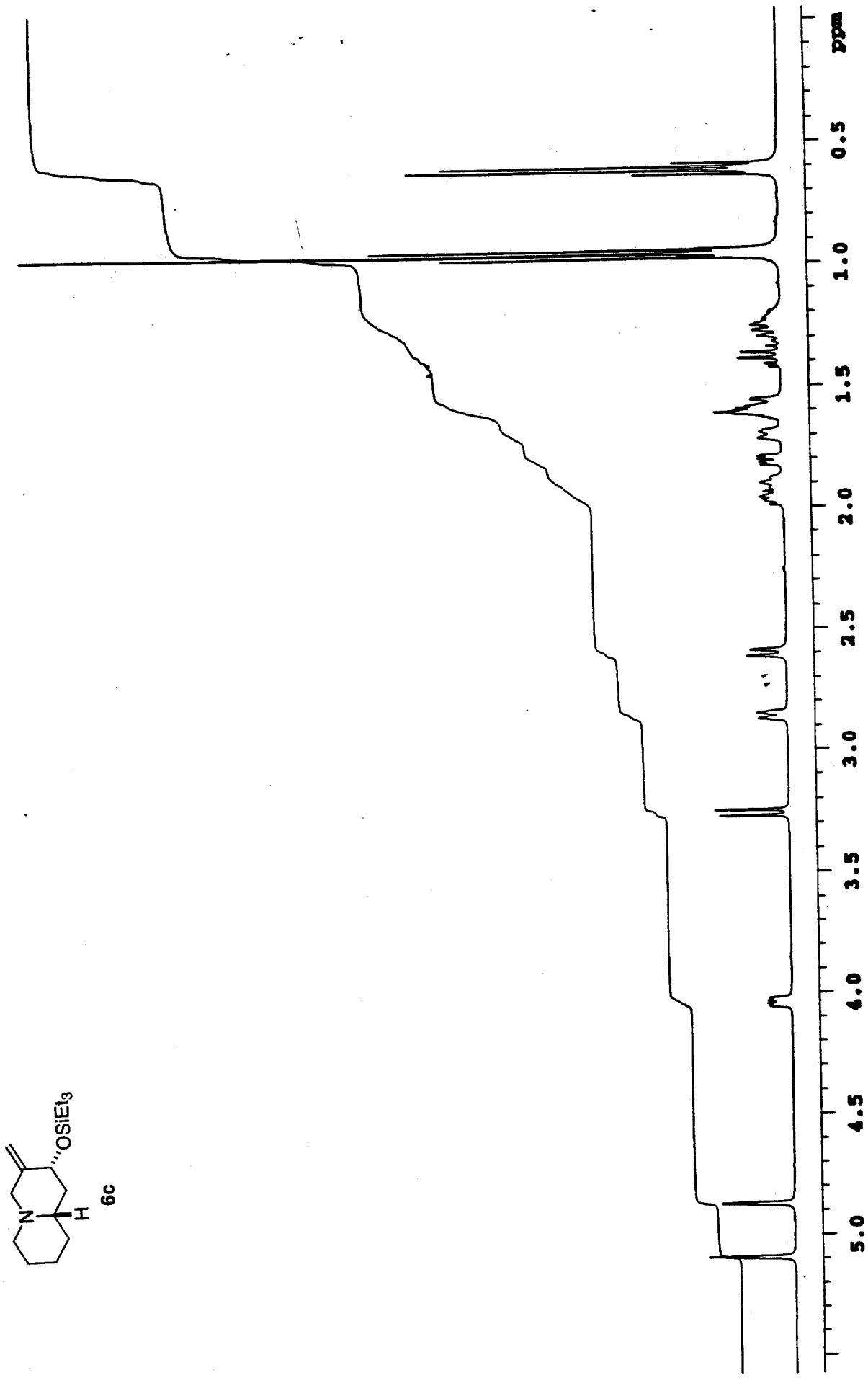

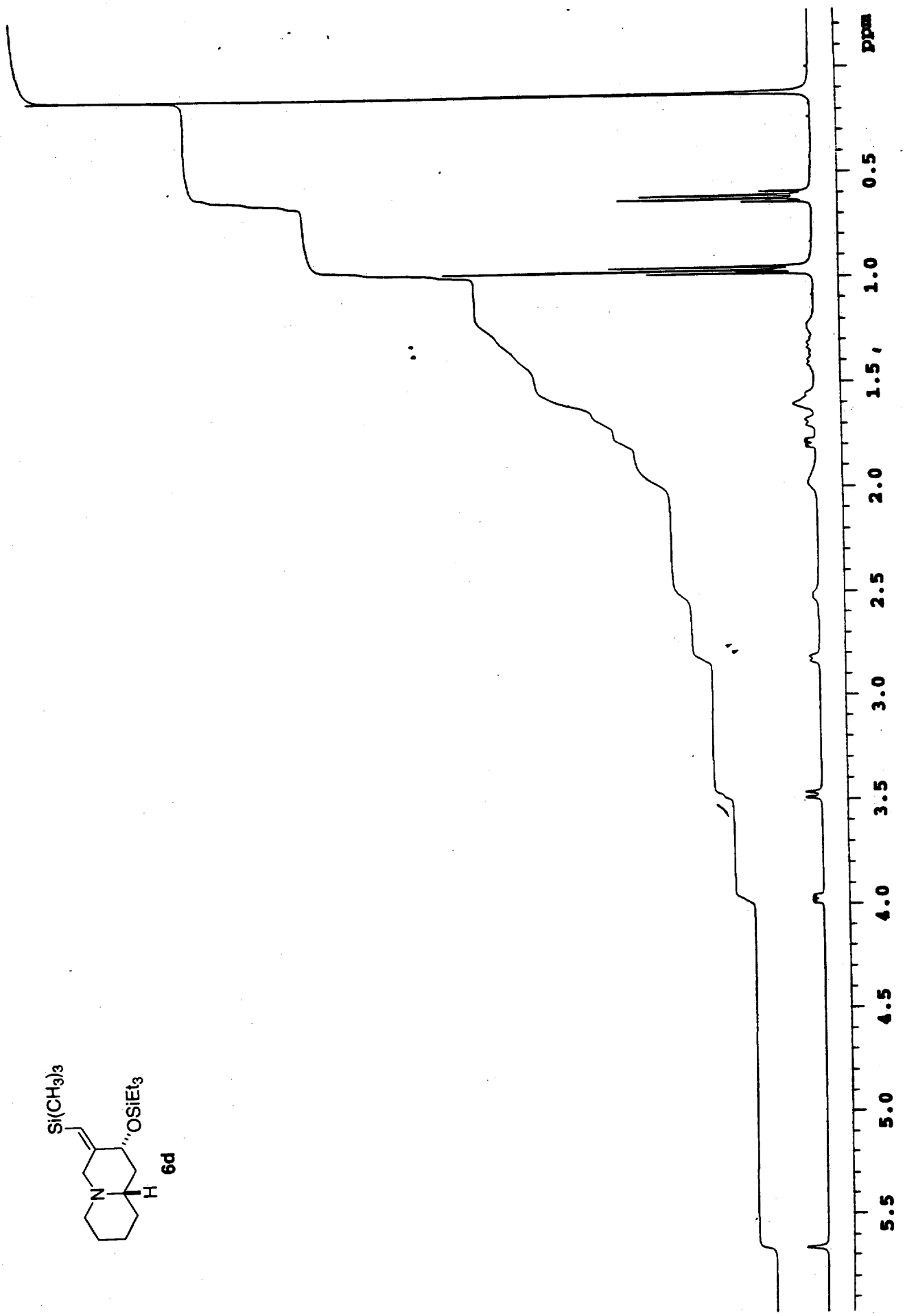
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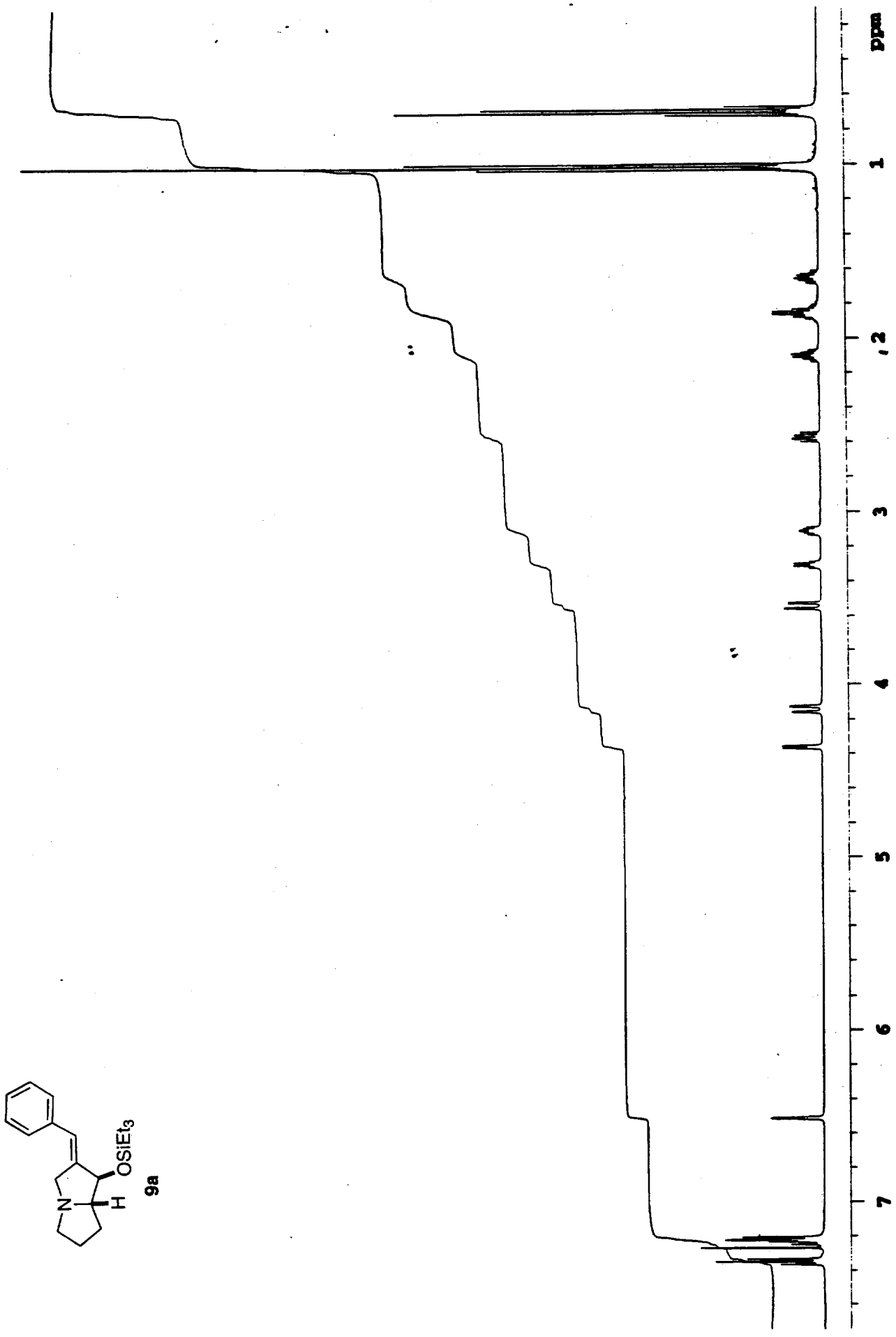
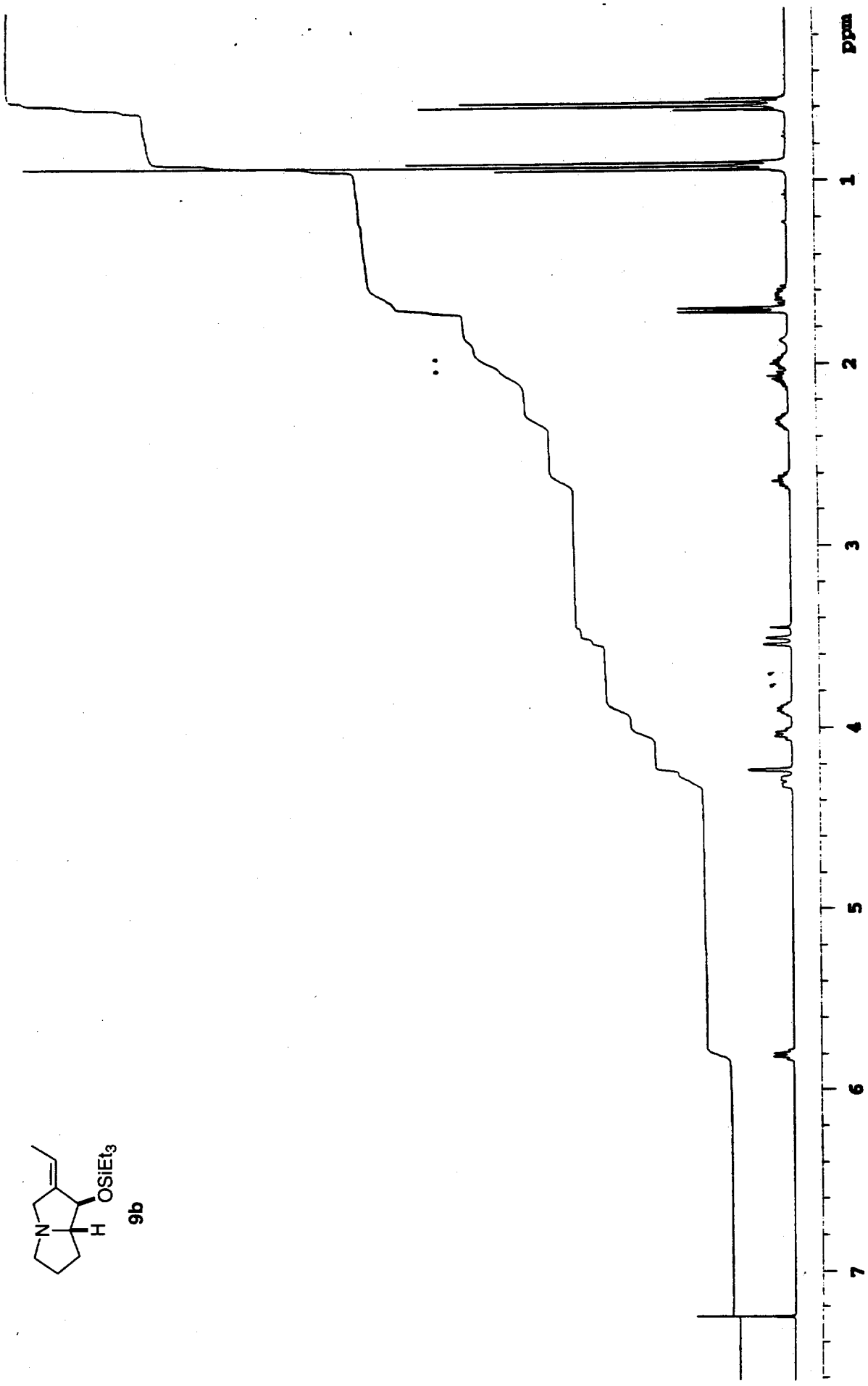


9a



9b