

Supporting Information

Total Syntheses of (-)- and (+)-Goniomitine

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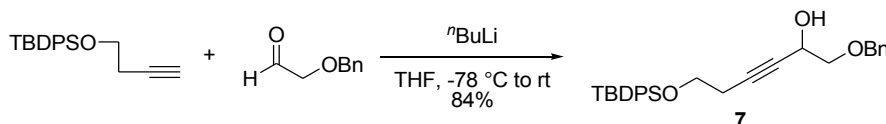
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Experimental Section

General

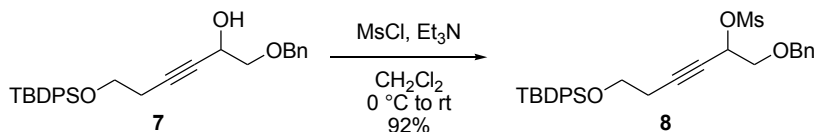
Melting points are uncorrected. IR spectra were measured in CHCl_3 . ^1H NMR spectra were taken in CDCl_3 . CHCl_3 (7.26 ppm) for silyl compounds and tetramethylsilane (0.00 ppm) for compounds without a silyl group were used as internal standards unless otherwise stated. ^{13}C NMR spectra were recorded in CDCl_3 with CDCl_3 (77.00 ppm) as an internal standard unless otherwise stated. All reactions were carried out under a nitrogen atmosphere. Silica gel (silica gel 60, 230-400 mesh) was used for chromatography. Organic extracts were dried over anhydrous Na_2SO_4 . Optical rotation ($[\alpha]_D^{25}$) of commercially available (-)-(*R*)-phenylglycinol showed -30.0 ($c = 0.75$, MeOH) and that of commercially available (+)-(*S*)-phenylglycinol showed +23.9 ($c = 0.75$, MeOH).

1-Benzyloxy-6-*tert*-butyldiphenylsilyloxyhex-3-yn-2-ol (7)



To a solution of *tert*-butyl(but-3-ynyloxy)diphenylsilane (3.59 g, 11.6 mmol) in THF (40 mL) was added $n\text{BuLi}$ (1.60 M hexane solution, 6.50 mL, 10.4 mmol) at -78°C and the reaction mixture was stirred for 1.5 h. Then, a solution of 2-(benzyloxy)acetaldehyde (1.33 g, 8.86 mmol) in THF (5 mL) was added to the mixture. After stirring for 22 h at room temperature, the reaction mixture was quenched by addition of saturated aqueous NH_4Cl , and the mixture was extracted with AcOEt . The extract was washed with water and brine, dried, and concentrated to dryness. The residue was chromatographed with hexane- AcOEt (7:1 to 5:1) to give alcohol **7** (3.40 g, 84%) as a pale yellow oil: IR 3574, 3433 cm^{-1} ; ^1H NMR δ 7.66 (dd, 4H, $J = 7.5, 1.6$ Hz), 7.45-7.25 (m, 11H), 4.62-4.48 (m, 3H), 3.75 (t, 2H, $J = 7.1$ Hz), 3.58 (dd, 1H, $J = 9.8, 3.5$ Hz), 3.52-3.45 (m, 1H), 2.48 (td, 2H, $J = 7.1, 1.9$ Hz), 2.40 (d, 1H, $J = 4.5$ Hz), 1.04 (s, 9H); ^{13}C NMR δ 137.6, 135.5, 133.5, 129.7, 128.4, 127.83, 127.77, 127.65, 83.4, 78.8, 73.8, 73.3, 62.2, 61.8, 26.7, 22.8, 19.2; FABMS m/z 459 ($\text{M}^+ + 1$, 4.1). FABHRMS calcd. for $\text{C}_{29}\text{H}_{35}\text{O}_3\text{Si}$ 459.2356, found 459.2342.

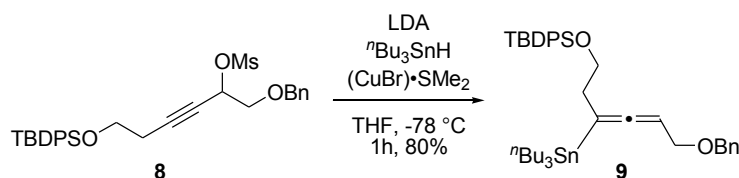
1-Benzyloxy-6-*tert*-butyldiphenylsilyloxy-2-methanesulfonyloxyhex-3-yne (8)



To a solution of alcohol **7** (4.52 g, 9.86 mmol) in CH_2Cl_2 (90 mL) were added Et_3N (2.8 mL,

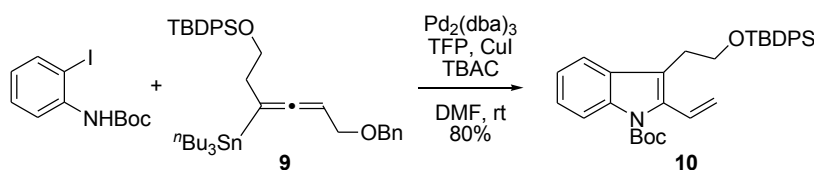
20 mmol) and MsCl (1.2 mL, 16 mmol) at 0 °C. After stirring for 20 min at room temperature, the reaction mixture was quenched by addition of saturated aqueous NaHCO₃, and the mixture was extracted with CH₂Cl₂. The extract was washed with water and brine, dried, and concentrated to dryness. The residue was chromatographed with hexane-AcOEt (3:1) to give mesylate **8** (5.14 g, 97%) as a colorless oil: IR 1364 cm⁻¹; ¹H NMR δ 7.65 (dd, 4H, *J* = 7.5, 1.7 Hz), 7.46-7.27 (m, 11H), 5.33 (m, 1H), 4.58 (s, 2H), 3.78-3.67 (m, 4H), 3.02 (s, 3H), 2.49 (td, 2H, *J* = 6.7, 2.0 Hz), 1.04 (s, 9H); ¹³C NMR δ 137.2, 135.4, 133.2, 129.7, 128.4, 127.9, 127.72, 127.69, 88.0, 74.1, 73.3, 71.5, 71.3, 61.7, 39.0, 26.7, 22.8, 19.1; FABMS *m/z* 559 (M⁺+23, 1.0). FABHRMS calcd. for C₃₀H₃₇O₅SSi 537.2131, found 537.2141.

1-Benzyloxy-6-*tert*-butyldiphenylsilyloxy-4-tributylstannylhexa-2,3-diene (**9**)



To a solution of distilled diisopropylamine (3.30 mL, 23.5 mmol) in THF (70 mL) was added ⁿBuLi (1.40 M hexane solution, 15.5 mL, 21.7 mmol) dropwise at -78 °C. After stirring for 1 h at the same temperature, ⁿBu₃SnH (5.80 mL, 21.6 mmol) was added to the mixture, which was further stirred for 1 h. Then, CuBr•SMe₂ (5.00 g, 24.3 mmol) was added and the mixture was stirred for 40 min at the same temperature. A solution of mesylate **8** (4.7g, 8.8 mmol) in THF (10 mL) was added slowly and the mixture was stirred for an additional 1 h at -78 °C. The mixture was quenched with aqueous solution of NH₄Cl/NH₄OH (9:1) and the mixture was extracted with Et₂O. The extract was washed with water, brine, dried and concentrated to dryness. The residue was chromatographed with hexane-AcOEt (50:1) to give allenylstannane **9** (5.23 g, 80%) as a colorless oil: IR 1929 cm⁻¹; ¹H NMR δ 7.69-7.64 (m, 4H), 7.41-7.24 (m, 11H), 4.78-4.65 (m, 1H), 4.46 (d, 1H, *J* = 11.9 Hz), 4.39 (d, 1H, *J* = 11.9 Hz), 4.06-3.89 (m, 2H), 3.73 (t, 2H, *J* = 7.3 Hz), 2.44-2.31 (m, 2H), 1.55-1.20 (m, 13H), 1.04 (s, 9H), 0.97-0.80 (m, 14H); ¹³C NMR δ 202.2, 138.6, 135.5, 133.9, 130.0, 128.3, 127.7, 127.6, 127.4, 89.4, 79.2, 71.1, 70.0, 64.0, 35.4, 28.9, 27.2, 26.8, 19.1, 13.7, 10.2; FABMS *m/z* 755 (M⁺+23, 4.1). FABHRMS calcd. for C₄₁H₆₁O₂SiSn 733.3463, found 733.3461.

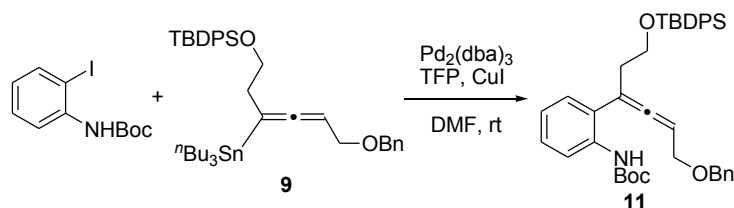
tert-Butyl 3-(2-*tert*-Butyldiphenylsiloxyethyl)-2-vinyl-1*H*-indole-1-carboxylate (**10**)



To a solution of *tert*-butyl 2-iodophenylcarbamate (134 mg, 0.420 mmol) and allenylstannane **9** (240 mg, 0.328 mmol) in DMF (3 mL) were added TBAC (300 mg, 1.08 mmol), TFP (19.4 mg, 8.4×10^{-2} mmol), $\text{Pd}_2(\text{dba})_3$ (9.7 mg, 1.0×10^{-2} mmol), and CuI (7.2 mg, 3.8×10^{-2} mmol) at room temperature. After stirring for 2 h at the same temperature, the reaction mixture was quenched by addition of 10% aqueous NH_3 solution, and the mixture was extracted with Et_2O . The extract was washed with water and brine, dried, and concentrated to dryness. The residue was chromatographed with hexane-AcOEt (30:1) to give vinylindole **10** (137 mg, 80%) as a colorless oil: IR 1724 cm^{-1} ; ^1H NMR δ 8.04 (d, 1H, $J = 8.2$ Hz), 7.62 (d, 4H, $J = 6.6$ Hz), 7.44-7.08 (m, 9H), 6.84 (dd, 1H, $J = 17.3, 11.7$ Hz), 5.37-5.30 (m, 2H), 3.88 (t, 2H, $J = 7.5$ Hz), 3.05 (t, 2H, $J = 7.5$ Hz), 1.65 (s, 9H), 1.03 (s, 9H); ^{13}C NMR δ 150.5, 135.7, 135.6, 135.4, 133.7, 130.3, 129.5, 128.8, 127.6, 124.3, 122.4, 119.1, 117.2, 116.7, 115.3, 83.8, 64.0, 28.2, 28.1, 26.8, 19.1; MS m/z 525 (M^+ , 5.7). HRMS calcd. for $\text{C}_{33}\text{H}_{39}\text{NO}_3\text{Si}$ 525.2699 found 525.2696.

tert-Butyl

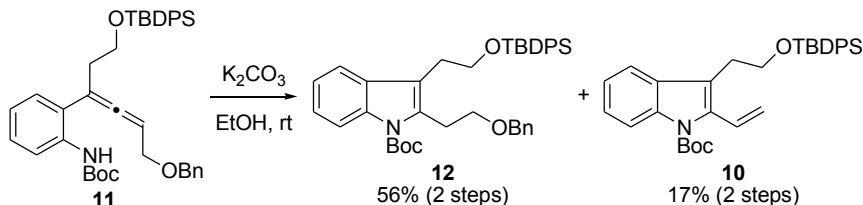
N-2-(6-Benzyloxy-1-*tert*-butyldiphenylsilyloxyhexa-3,4-dien-3-yl)phenylcarbamate (**11**).



To a solution of *tert*-butyl 2-iodophenylcarbamate (492 mg, 1.54 mmol) and allenylstannane **9** (1.13 g, 1.54 mmol) in DMF (15 mL) were added TFP (92 mg, 0.40 mmol), $\text{Pd}_2(\text{dba})_3$ (43 mg, 4.7×10^{-2} mmol), and CuI (33 mg, 0.17 mmol) at room temperature. After stirring for 15 h at the same temperature, the reaction mixture was quenched by addition of 10% aqueous NH_3 solution, and the mixture was extracted with Et_2O . The extract was washed with water and brine, dried, and concentrated to dryness. The residue was chromatographed with hexane-AcOEt (40:1) to give allenylaniline **11** (738 mg, 75%) as a colorless oil: IR 3418, 3331, 1958, 1722 cm^{-1} ; ^1H NMR δ 8.02 (d, 1H, $J = 8.1$ Hz), 7.62 (dd, 4H, $J = 7.9, 1.3$ Hz), 7.41-7.21 (13H, m), 7.11 (dd, 1H, $J = 7.7, 1.6$ Hz), 6.98 (td, 1H, $J = 7.6, 1.1$ Hz), 5.41-5.38 (m, 1H), 4.51 (ABq, 2H, $J = 12.0$ Hz), 4.08 (dd, 2H, $J = 6.0, 2.1$ Hz), 3.75 (t, 2H, $J = 6.4$ Hz), 2.60 (td, 2H, $J = 6.4, 2.1$ Hz), 1.45 (s, 9H), 1.04 (s, 9H); ^{13}C NMR δ 202.8, 153.0, 137.9, 135.8, 135.5, 133.6, 129.6, 128.4, 127.9, 127.8, 127.67, 127.65, 127.61, 126.0, 122.8, 120.4, 100.1, 90.0, 80.2, 71.9, 67.4, 61.8, 37.1, 28.4, 26.9, 19.1; MS m/z 633 (M^+ , 1.1). HRMS calcd. for $\text{C}_{40}\text{H}_{47}\text{NO}_4\text{Si}$ 633.3274 found 633.3271.

tert-Butyl

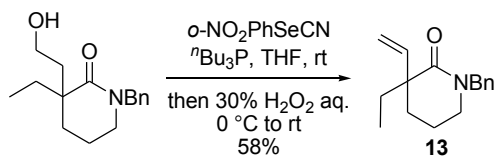
2-(2-Benzyloxyethyl)-3-(2-*tert*-butyldiphenylsilyloxyethyl)-1*H*-indole-1-carboxylate (**12**)



To a solution of crude allenylaniline **11** (464 mg) in EtOH (7 mL) was added K_2CO_3 (199 mg, 1.44 mmol) at room temperature. The mixture was stirred for 5 h at the same temperature, quenched with saturated aqueous NH_4Cl and extracted with AcOEt, washed with water and brine, dried, and concentrated to dryness. The residue was chromatographed with hexane-AcOEt (50:1) to afford indole **12** (345 mg, 56% from **9**) as a colorless oil: IR 1720 cm^{-1} ; 1H NMR δ 8.05 (d, 1H, $J = 8.2$ Hz), 7.60 (d, 4H, $J = 6.6$ Hz), 7.41-7.07 (m, 14H), 4.43 (s, 2H), 3.82 (t, 2H, $J = 7.4$ Hz), 3.59 (t, 2H, $J = 6.9$ Hz), 3.27 (t, 2H, $J = 6.9$ Hz), 2.97 (t, 2H, $J = 7.4$ Hz), 1.60 (s, 9H), 1.03 (s, 9H); ^{13}C NMR δ 150.3, 138.4, 135.9, 135.6, 134.2, 133.7, 129.9, 129.5, 128.2, 127.6, 127.4, 123.5, 122.3, 118.3, 116.7, 115.4, 83.5, 72.8, 69.7, 63.7, 28.1, 27.6, 27.5, 26.9, 19.1; FABMS m/z 634 ($M^+ + 1$, 53.1). FABHRMS calcd. for $C_{40}H_{48}NO_4Si$ 634.3353 found 634.3345.

Vinylindole **10** (84.6 mg, 17% from **9**) was also obtained: Spectral data are shown (see S5).

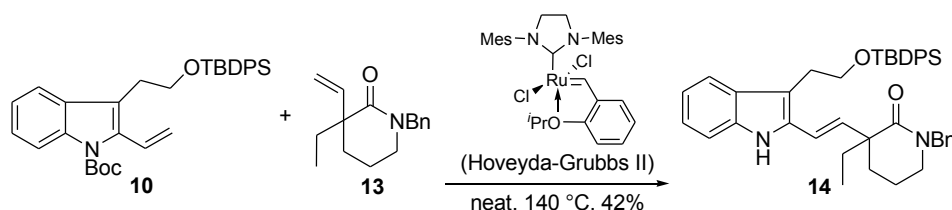
1-Benzyl-3-ethyl-3-vinylpiperidin-2-one (**13**)



To a solution of known alcohol¹ (311 mg, 1.19 mmol) in dry THF (2.5 mL) were added $o\text{-NO}_2\text{PhSeCN}$ (416 mg, 1.83 mmol) and $t\text{Bu}_3\text{P}$ (0.50 mL, 1.85 mmol) at room temperature. After stirring for 5 h at the same temperature, a solution of 30% aqueous H_2O_2 (0.8 mL) in THF (18 mL) was added to the reaction mixture at $0\text{ }^\circ\text{C}$. After the reaction mixture was stirred for 20 min at the same temperature, the reaction mixture was allowed to warm to room temperature, stirred for additional 17 h. The reaction mixture was quenched by addition of saturated aqueous $NaHCO_3$, and the mixture was extracted with Et_2O . The extract was washed with water and brine, dried, and concentrated to dryness. The residue was chromatographed with hexane-AcOEt (9:1) to give vinyl lactam **13** (167 mg, 58%) as a yellow oil: IR 1624 cm^{-1} ; 1H NMR δ 7.32-7.30 (m, 2H), 7.26-7.23 (m, 3H), 5.93 (dd, 1H, $J = 17.2, 10.3$ Hz), 5.16 (d, 1H, $J =$

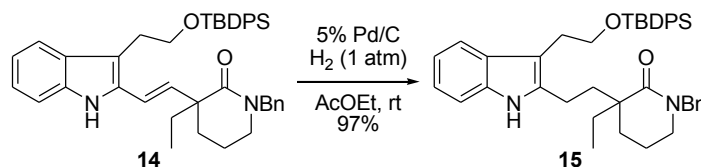
10.3 Hz), 5.08 (d, 1H, $J = 17.2$ Hz), 4.59 (ABq, 2H, $J = 14.4$ Hz), 3.23-3.14 (m, 2H), 1.92-1.79 (m, 4H), 1.74-1.64 (m, 2H), 0.86 (t, 3H, $J = 7.2$ Hz); ^{13}C NMR δ 172.9, 142.5, 137.6, 128.5, 128.0, 127.2, 114.0, 50.5, 49.2, 47.7, 31.7, 28.7, 19.2, 8.5; MS m/z 243 (M^+ , 79.4); HRMS calcd. for $\text{C}_{16}\text{H}_{21}\text{NO}$ 243.1623 found 243.1625.

1-Benzyl-3-ethyl-3-[(*E*)-2-[3-(2-*tert*-butyldiphenylsilyloxyethyl)-1*H*-indol-2-yl]vinyl]-piperidin-2-one (14)



To a mixture of indole **10** (52.3 mg, 9.96×10^{-2} mmol) and lactam **13** (228.3 mg, 0.940 mmol) was added Hoveyda-Grubbs 2nd catalyst (18.9 mg, 3.02×10^{-2} mmol) at room temperature, then the mixture was purged with nitrogen and warmed up to 140 °C. After stirring for 3 h at the same temperature, the reaction mixture was cooled and concentrated. The residue was chromatographed with hexane-AcOEt (5:1 to 3:1) to afford compound **14** (27.0 mg, 42%) as colorless needles; mp 122-124 °C (from hexane); IR 3471, 3323, 1624 cm^{-1} ; ^1H NMR δ 8.20 (bs, 1H), 7.61-7.59 (m, 4H), 7.39-7.23 (m, 12H), 7.16-7.10 (m, 2H), 6.94 (t, 1H, $J = 7.4$ Hz), 6.48 (d, 1H, $J = 16.5$ Hz), 6.20 (d, 1H, $J = 16.5$ Hz), 4.64 (d, 1H, $J = 14.4$ Hz), 4.58 (d, 1H, $J = 14.4$ Hz), 3.84 (t, 2H, $J = 7.4$ Hz), 3.26-3.15 (m, 2H), 3.05 (t, 2H, $J = 7.4$ Hz), 1.97-1.73 (m, 6H), 1.01 (s, 9H), 0.86 (t, 3H, $J = 7.4$ Hz); ^{13}C NMR δ 173.2, 137.3, 136.1, 135.6, 133.80, 133.76, 132.7, 132.2, 129.5, 128.9, 128.6, 127.9, 127.6, 127.3, 122.5, 119.2, 118.8, 117.5, 111.4, 110.3, 64.2, 50.6, 48.8, 47.7, 32.3, 28.2, 27.7, 26.8, 19.3, 19.1, 8.5; MS m/z 640 (M^+ , 9.6). Anal. Calcd for $\text{C}_{42}\text{H}_{48}\text{N}_2\text{O}_2\text{Si}$: C, 78.71; H, 7.55; N, 4.37. Found: C, 78.51, H, 7.59, N, 4.43.

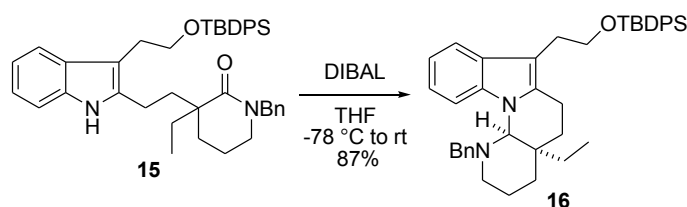
1-Benzyl-3-ethyl-3-[2-[3-(2-*tert*-butyldiphenylsilyloxyethyl)-1*H*-indol-2-yl]ethyl]piperidin-2-one (15)



To a solution of compound **14** (32.2 mg, 5.03×10^{-2} mmol) in AcOEt (4 mL) was added 5% Pd/C (12 mg) at room temperature. The mixture was stirred under H_2 atmosphere at the same temperature for 23 h, then filtered and concentrated to dryness. The residue was chromatographed with hexane-AcOEt (3:1) to afford compound **15** (31.3 mg, 97%) as a

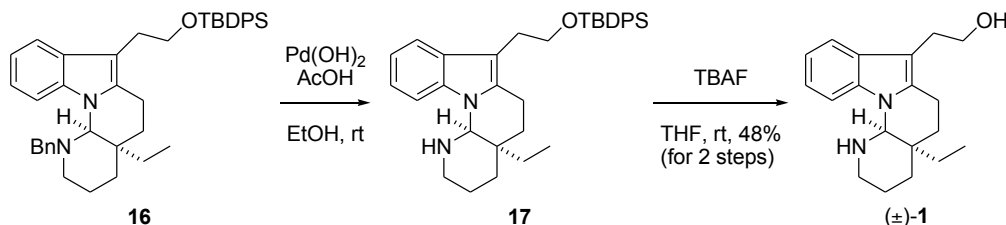
colorless oil; ^1H NMR δ 8.54 (bs, 1H), 7.65-7.61 (m, 4H), 7.41-7.17 (m, 13H), 7.04 (t, 1H, J = 7.4 Hz), 6.94 (t, 1H, J = 7.3 Hz), 4.67 (d, 1H, J = 14.7 Hz), 4.49 (d, 1H, J = 14.7 Hz), 3.81 (t, 2H, J = 7.6 Hz), 3.19 (t, 2H, J = 5.5 Hz), 2.97 (t, 2H, J = 7.6 Hz), 2.83-2.75 (m, 1H), 2.46-2.39 (m, 1H), 2.10-2.03 (m, 1H), 1.85-1.58 (m, 7H), 1.04 (s, 9H), 0.86 (t, 3H, J = 7.6 Hz); ^{13}C NMR δ 175.1, 137.4, 136.6, 135.6, 135.3, 134.0, 133.9, 129.5, 128.6, 128.4, 127.9, 127.6, 127.3, 120.7, 118.7, 118.0, 110.4, 107.0, 64.6, 50.6, 47.7, 45.8, 38.0, 31.5, 28.8, 27.8, 26.9, 21.5, 19.5, 19.1, 8.5; FABMS m/z 643 ($\text{M}^+ + 1$, 22.2); FABHRMS calcd. for $\text{C}_{42}\text{H}_{51}\text{N}_2\text{O}_2\text{Si}$ 643.3720, found 643.3717.

(4a*R,12a*S**)-1-Benzyl-7-(2-*tert*-butyldiphenylsilyloxyethyl)-4a-ethyl-1,2,3,4,4a,5,6,12a-octahydroindolo[1,2-a][1,8]naphthyridine (16)**



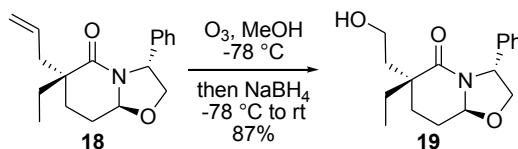
To a solution of piperidone **15** (3.8 mg, 5.9×10^{-3} mmol) in dry THF (0.5 mL) was slowly added a solution of DIBAL (1 M in hexane, 0.02 mL) at -78°C . The mixture was gradually warmed up to room temperature, then the reaction was quenched with saturated aqueous Na_2SO_4 . The mixture was filtered and extracted with Et_2O . The extract was washed with water and brine, dried, and concentrated to dryness. The residue was chromatographed with hexane-AcOEt (20:1) to afford compound **16** (3.2 mg, 87%) as a colorless oil: ^1H NMR δ 7.66-7.65 (m, 4H), 7.41-7.38 (m, 2H), 7.33-7.31 (m, 5H), 7.17 (d, 1H, J = 7.8 Hz), 7.12-7.05 (m, 4H), 7.00 (d, 2H, J = 7.3 Hz), 6.95 (t, 1H, J = 7.6 Hz), 4.26 (s, 1H), 3.81-3.75 (m, 2H), 3.53 (d, 1H, J = 13.1 Hz), 3.07-3.03 (m, 1H), 2.95-2.87 (m, 4H), 2.82-2.77 (m, 1H), 2.45-2.41 (m, 1H), 2.09 (t, 1H, J = 12.0 Hz), 1.78-1.75 (m, 1H), 1.68-1.64 (m, 1H), 1.47-1.41 (m, 2H), 1.37-1.32 (m, 1H), 1.05 (s, 9H), 0.87-0.84 (m, 1H), 0.77-0.74 (m, 1H), 0.61 (t, 3H, J = 7.2 Hz); ^{13}C NMR δ 140.2, 137.4, 135.8, 134.2, 134.1, 133.7, 129.7, 128.6, 128.5, 128.0, 127.8, 126.5, 120.1, 119.0, 118.1, 108.7, 106.3, 76.8, 64.4, 57.6, 52.2, 38.5, 33.9, 30.8, 28.1, 27.1, 24.2, 21.3, 19.3, 18.1, 7.6; MS m/z 626 (M^+ 54.3); HRMS calcd. for $\text{C}_{42}\text{H}_{50}\text{N}_2\text{OSi}$ 626.3692 found 626.3691.

2-((4a*R,12a*S**)-4a-Ethyl-1,2,3,4,4a,5,6,12a-octahydro-indolo[1,2a][1,8]naphthyridin-7-yl)ethanol (Goniomitine) {(±)-1}.**



To a solution of compound **16** (21 mg, 3.5×10^{-2} mmol) in EtOH (2 mL) and AcOH (5 mL) was added 42 mg of 20% Pd(OH)₂ at room temperature. After stirring for 2 h under H₂ atmosphere at the same temperature, the mixture was added saturated aqueous NaHCO₃, filtered, and the mixture was extracted with AcOEt. The extract was washed with water and brine, dried, and concentrated to dryness. The residue was passed through a short pad of silica gel (hexane-AcOEt = 3:1 to 2:1) to afford the crude amine **17** (8.4 mg). To a solution of the crude amine **17** (8.4 mg) in dry THF (0.5 mL) was added TBAF (1 M in THF, 0.05 mL) at room temperature. After stirring for 14 h, the mixture was quenched with water, extracted with CH₂Cl₂. The extract was washed with brine, dried and concentrated to dryness. The residue was chromatographed with alumina (hexane-AcOEt = 2:1 to 1:1) to afford (±)-**1** (4.5 mg, 48% from **16**) as colorless powders: IR 3009, 2941, 2860 cm⁻¹; ¹H NMR δ 7.52 (d, 1H, *J* = 7.6 Hz), 7.30 (d, 1H, *J* = 8.2 Hz), 7.14 (d, 1H, *J* = 7.6 Hz), 7.08 (t, 1H, *J* = 7.9 Hz), 4.79 (s, 1H), 3.83 (t, 2H, *J* = 6.5 Hz), 3.06-3.02 (m, 2H), 2.98-2.90 (m, 2H), 2.86-2.78 (m, 2H), 2.52 (td, 1H, *J* = 12.9, 6.4 Hz), 1.91-1.88 (m, 1H), 1.75-1.46 (m, 7H), 1.22-1.16 (m, 1H), 0.88 (t, 3H, *J* = 7.6 Hz); ¹³C NMR δ 135.3, 132.7, 129.0, 120.5, 119.5, 118.1, 108.2, 105.9, 71.5, 62.6, 45.6, 35.1, 34.0, 28.6, 27.7, 21.6, 21.5, 18.5, 7.1; MS *m/z* 298 (M⁺, 87.2). HRMS calcd. for C₁₉H₂₆N₂O 298.2045, found 298.2045.

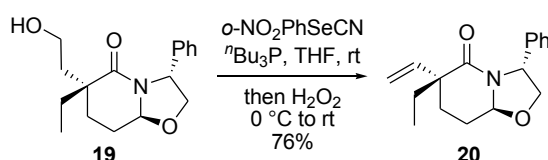
(3*R*,6*R*,8a*S*)-6-ethyl-6-(2-hydroxyethyl)-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridin-5-one (19)



A solution of alkene **18**² (1.47 g, 5.16 mmol) in methanol (70 mL) was cooled to -78 °C and treated with a stream of O₃ for 15 minutes. The ozone generator was then turned off and the reaction was sparged with nitrogen. To this solution was added NaBH₄ (300 mg, 7.89 mmol) at -78 °C and the mixture was then allowed to warm up to room temperature. After stirring for 2 h,

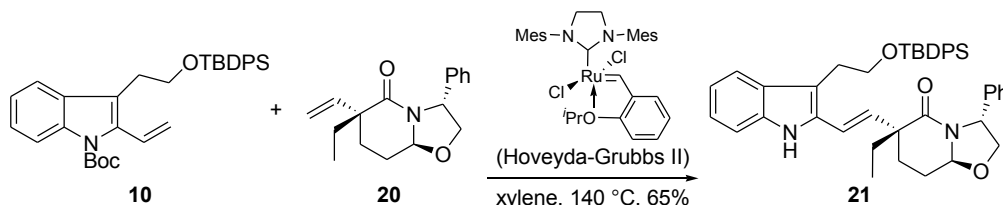
the mixture was quenched with saturated aqueous NH_4Cl and extracted with AcOEt. The extract was washed with water and brine, dried, and concentrated to dryness. The residue was chromatographed with hexane-AcOEt (1:1 to 1:2) to afford alcohol **19** (1.28 g, 86%) as a white needle: mp 79-82 °C (from AcOEt); $[\alpha]_{\text{D}}^{24} = -96.0$ ($c = 0.99$, MeOH); IR 3414, 3387, 1628 cm^{-1} ; ^1H NMR δ 7.33 (t, 2H, $J = 7.7$ Hz), 7.27-7.24 (m, 3H), 5.19 (t, 1H, $J = 8.1$ Hz), 5.04 (dd, 1H, $J = 8.9, 4.5$ Hz), 4.50 (t, 1H, $J = 8.4$ Hz), 3.75 (t, 2H, $J = 8.6$ Hz), 3.60-3.55 (m, 1H), 2.69 (bs, 1H), 2.26-2.22 (m, 1H), 1.88-1.62 (m, 7H), 0.90 (t, 3H, $J = 7.6$ Hz); ^{13}C NMR δ 174.9, 139.4, 128.6, 127.6, 126.0, 88.8, 73.1, 59.0, 58.7, 43.8, 40.2, 29.0, 26.4, 25.6, 8.4; MS m/z 289 (M^+ , 13.9); HRMS calcd. for $\text{C}_{17}\text{H}_{23}\text{NO}_3$ 289.1678 found 289.1679. *ent*-**19**; colorless plates: mp 111-114 °C (from AcOEt); $[\alpha]_{\text{D}}^{24} = +117.8$ ($c = 1.00$, MeOH).

(3*R*,6*R*,8*aS*)-6-ethyl-3-phenyl-6-vinyl-2,3,6,7,8,8*a*-hexahydro-5*H*-oxazolo[3,2-*a*]pyridin-5-one (20**)**



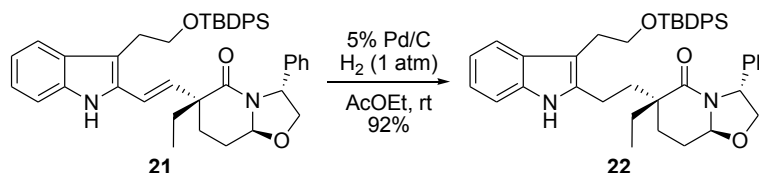
To a solution of known alcohol **19** (9.4 mg, 3.3×10^{-2} mmol) in dry THF (0.05 mL) were added *o*- NO_2PhSeCN (29 mg, 0.13 mmol) and $^n\text{Bu}_3\text{P}$ (0.05 mL, 0.2 mmol) at room temperature. After stirring for 3 h at the same temperature, a solution of 30% aqueous H_2O_2 (0.05 mL) in THF (1 mL) was added to the reaction mixture at 0 °C. After stirring for 9 h at room temperature, the reaction mixture was quenched by addition of saturated aqueous NaHCO_3 , extracted with Et_2O . The extract was washed with water and brine, dried, and concentrated to dryness. The residue was chromatographed with hexane-AcOEt (10:1 to 8:1) to give vinyl lactam **20** (6.7 mg, 76%) as colorless needles: mp 87-88 °C (from $i\text{Pr}_2\text{O}$); $[\alpha]_{\text{D}}^{25} = -89.9$ ($c = 1.00$, MeOH); IR 1647 cm^{-1} ; ^1H NMR δ 7.34-7.21 (m, 5H), 6.00 (dd, 1H, $J = 17.6, 11.0$ Hz), 5.25 (t, 1H, $J = 8.0$ Hz), 5.14 (d, 1H, $J = 11.0$ Hz), 5.04-4.97 (m, 2H), 4.48 (t, 1H, $J = 8.5$ Hz), 3.73 (t, 1H, $J = 8.5$ Hz), 2.32-2.26 (m, 1H), 1.97-1.69 (m, 5H), 0.85 (t, 3H, $J = 7.6$ Hz); ^{13}C NMR δ 172.5, 141.9, 139.8, 128.8, 127.5, 126.0, 114.1, 88.3, 72.7, 58.5, 48.4, 29.6, 25.1, 24.1, 8.3; MS m/z 271 (M^+ , 3.1). Anal. Calcd for $\text{C}_{17}\text{H}_{21}\text{NO}_2$: C, 75.25; H, 7.80; N, 5.16. Found: C, 74.96; H, 7.88; N, 5.05. *ent*-**20**; colorless needles: mp 85-86 °C (from hexane); $[\alpha]_{\text{D}}^{24} = +79.6$ ($c = 1.00$, MeOH).

(3*R*,6*R*,8*aS*)-6-ethyl-6-{(*E*)-2-[3-(2-*tert*-butyldiphenylsilyloxyethyl)-1*H*-indol-2-yl]vinyl}-3-phenyl-2,3,6,7,8,8*a*-hexahydro-5*H*-oxazolo[3,2-*a*]pyridin-5-one (21**)**



To a solution of indole **10** (23.2 mg, 4.42×10^{-2} mmol) and lactam **20** (42.0 mg, 0.155 mmol) in dry xylene (0.05 mL) was added Hoveyda-Grubbs 2nd catalyst (8.8 mg, 1.4×10^{-2} mmol) at room temperature, then the mixture was purged with nitrogen and warmed up to 140 °C. After stirring for 3 h at the same temperature, the reaction mixture was cooled and concentrated. The residue was chromatographed with hexane-AcOEt (4:1 to 3:1) to afford compound **21** (19.3 mg, 65%) as colorless needles: mp 81-85 °C (from hexane); $[\alpha]_D^{24} = -24.2$ ($c = 0.64$, CHCl₃); IR 3468, 3304, 1636 cm⁻¹; ¹H NMR δ 8.17 (s, 1H), 7.64-7.57 (m, 4H), 7.42-7.16 (m, 13H), 7.10 (t, 1H, $J = 7.3$ Hz), 6.94 (t, 1H, $J = 7.6$ Hz), 6.40 (d, 1H, $J = 16.7$ Hz), 6.22 (d, 1H, $J = 16.7$ Hz), 5.23 (t, 1H, $J = 8.0$ Hz), 4.98 (dd, 1H, $J = 8.5, 4.8$ Hz), 4.51 (t, 1H, $J = 8.5$ Hz), 3.90-3.80 (m, 2H), 3.75 (t, 1H, $J = 8.5$ Hz), 3.05 (t, 2H, $J = 7.3$ Hz), 2.35-2.32 (m, 1H), 2.06-2.01 (m, 1H), 1.92-1.71 (m, 4H), 1.01 (s, 9H), 0.82 (t, 3H, $J = 7.3$ Hz); ¹³C NMR δ 172.6, 139.4, 136.1, 135.6, 133.8, 133.7, 132.5, 131.4, 129.49, 129.48, 128.83, 128.78, 127.59, 127.55, 126.0, 122.7, 119.3, 118.8, 117.9, 111.7, 110.3, 88.5, 72.9, 64.2, 58.8, 48.0, 30.1, 27.7, 26.9, 25.0, 23.9, 19.1, 8.2; MS m/z 668 (M⁺, 59.5); Anal. Calcd for C₄₃H₄₈N₂O₃Si: C, 77.21; H, 7.23; N, 4.19. Found: C, 77.05, H, 7.43, N, 4.20. *ent*-**21**; colorless powders: mp 25-28 °C (from hexane); $[\alpha]_D^{25} = +4.8$ ($c = 0.58$, CHCl₃).

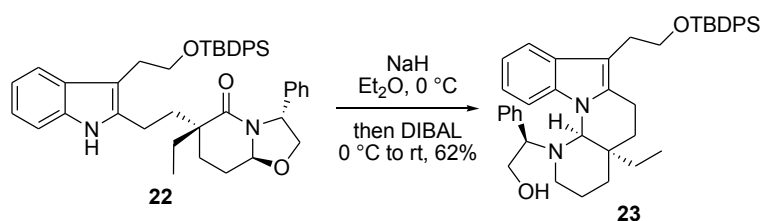
(3*R*,6*S*,8*aS*)-6-{2-[3-(2-*tert*-butyldiphenylsilyloxyethyl)-1*H*-indol-2-yl]ethyl}-6-ethyl-3-phenyl-2,3,6,7,8,8*a*-hexahydro-5*H*-oxazolo[3,2-*a*]pyridin-5-one (22**)**



To a solution of indole **21** (19.6 mg, 2.93×10^{-2} mmol) in AcOEt (3 mL) was added 5% Pd/C (5 mg) at room temperature. The mixture was stirred under H₂ atmosphere at the same temperature for 27 h and concentrated to dryness. The residue was chromatographed with hexane-AcOEt (3:1) to afford **3** (18.0 mg, 92%) as colorless powders: mp 31-35 °C (from hexane); $[\alpha]_D^{21} = -57.9$ ($c = 0.34$, CHCl₃); IR 3460, 3389, 3290, 1634 cm⁻¹; ¹H NMR δ 7.98 (s,

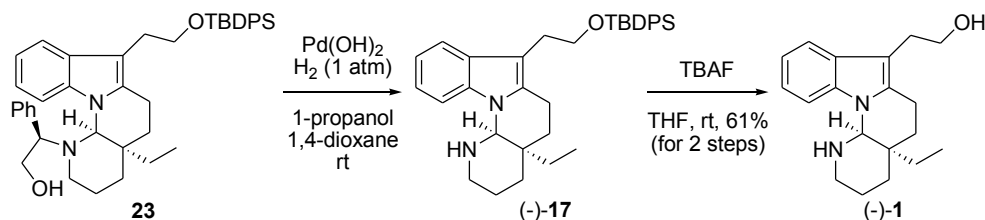
1H), 7.62 (t, 4H, $J = 6.9$ Hz), 7.40-7.15 (m, 12H), 7.08-6.99 (m, 2H), 6.92 (t, 1H, $J = 7.1$ Hz), 5.19 (t, 1H, $J = 8.0$ Hz), 5.02 (dd, 1H, $J = 8.7, 4.6$ Hz), 4.51 (t, 1H, $J = 8.5$ Hz), 3.82-3.74 (m, 3H), 2.93 (t, 2H, $J = 7.6$ Hz), 2.80-2.72 (m, 1H), 2.23-2.18 (m, 2H), 1.91-1.50 (m, 7H), 1.05 (s, 9H), 0.86 (t, 3H, $J = 7.6$ Hz); ^{13}C NMR δ 173.9, 139.6, 135.9, 135.6, 135.3, 133.97, 133.95, 129.51, 129.48, 128.9, 128.3, 127.7, 127.60, 127.57, 126.2, 120.8, 118.7, 118.0, 110.4, 107.1, 89.0, 73.1, 64.6, 59.1, 45.5, 38.4, 30.6, 27.8, 26.9, 25.8, 25.0, 21.0, 19.2, 8.7; MS m/z 670 (M^+ , 58.1), HRMS calcd. for $\text{C}_{43}\text{H}_{50}\text{N}_2\text{O}_3\text{Si}$ 670.3591 found 670.3596. *ent*-**22**; colorless powders: mp 59-60 °C (from hexane); $[\alpha]_{\text{D}}^{22} = +36.5$ ($c = 0.17$, CHCl_3).

(*R*)-2-[(4*aR*,12*aS*)-7-(2-*tert*-Butyldiphenylsilyloxyethyl)-4*a*-ethyl-1,2,3,4,4*a*,5,6,12*a*-octahydroindolo[1,2-*a*][1,8]naphthyridin-1-yl]-2-phenylethanol (23**)**



To a solution of indole **22** (9.1 mg, 1.4×10^{-2} mmol) in dry Et_2O (3 mL) was added NaH (60% in oil, 10.0 mg, 0.25 mmol) at 0 °C and stirred at the same temperature for 30 min. DIBAL (1 M in hexane, 15 μL) was added to the mixture dropwise at 0 °C then the reaction mixture was warmed to room temperature. After stirring for 10 min at the same temperature, the mixture was cooled to 0 °C again, added more 15 μL of DIBAL solution and further stirred for 10 min at room temperature. Another 15 μL of DIBAL solution was finally added to the mixture at 0 °C, then the mixture was stirred for 40 min at room temperature. The mixture was quenched with saturated aqueous Rochelle's salt at 0 °C and extracted with Et_2O . The extract was washed with water and brine, dried, and concentrated to dryness. The residue was chromatographed with hexane-AcOEt (6:1) to afford **23** (5.6 mg, 62%) as a colorless oil: $[\alpha]_{\text{D}}^{26} = -94.1$ ($c = 0.28$, CHCl_3); IR 3568, 3470 cm^{-1} ; ^1H NMR δ 7.67-7.64 (m, 4H), 7.44-7.32 (m, 7H), 7.18-6.95 (m, 8H), 4.80 (s, 1H), 4.16 (d, 1H, $J = 12.4$ Hz), 4.01-3.94 (m, 1H), 3.74 (t, 2H, $J = 7.8$ Hz), 3.16 (t, 1H, $J = 6.0$ Hz), 3.00-2.84 (m, 4H), 2.76-2.68 (m, 1H), 2.53 (t, 1H, $J = 11.9$ Hz), 2.38-2.31 (m, 1H), 1.78-1.65 (m, 2H), 1.51-1.38 (m, 2H), 1.35-1.26 (m, 2H), 1.04 (s, 9H), 0.93-0.87 (m, 1H), 0.83-0.74 (m, 1H), 0.63 (t, 3H, $J = 7.6$ Hz); ^{13}C NMR δ 140.9, 136.9, 135.6, 133.9, 133.6, 129.51, 129.49, 128.7, 127.9, 127.60, 127.58, 127.2, 126.4, 120.3, 119.1, 118.4, 107.7, 106.6, 74.2, 64.2, 61.0, 60.2, 46.1, 38.7, 33.8, 30.9, 27.8, 26.9, 24.1, 21.5, 19.1, 17.9, 7.6; MS m/z 656 (M^+ , 36.8), HRMS calcd. for $\text{C}_{43}\text{H}_{52}\text{N}_2\text{O}_2\text{Si}$ 656.3798, found 656.3795. *ent*-**23**; a colorless oil: $[\alpha]_{\text{D}}^{27} = +86.9$ ($c = 0.22$, CHCl_3).

2-((4*aR*,12*aS*)-4*a*-Ethyl-1,2,3,4,4*a*,5,6,12*a*-octahydro-indolo[1,2*a*][1,8]naphthyridin-7-yl)ethanol (Goniomitine) {(-)-1**}.**



To a solution of compound **23** (3.8 mg, 5.8×10^{-3} mmol) in 1-propanol (0.25 mL) and 1,4-dioxane (0.25 mL) was added 14.9 mg of 20% Pd(OH)₂ at room temperature. After stirring for 11 h under H₂ atmosphere at the same temperature, the mixture was filtered and concentrated to dryness. The residue was passed through short pad of alumina (hexane-AcOEt = 10:1) to afford crude amine (-)-**17** (1.9 mg). The crude (-)-**17** (1.9 mg) was converted to (-)-**1** (4.5 mg, 61% from **23**) by the same procedure described in page S9: (-)-**1** was colorless powders: mp 144-145 °C (from hexane) (lit.^{3,4} mp 149-150 °C); $[\alpha]_D^{24} = -78.1$ ($c = 0.14$, CHCl₃) {lit.³ $[\alpha]_D^{20} = -80$ ($c = 0.9$, CHCl₃), lit.⁴ $[\alpha]_D^{27} = -87.1$ ($c = 0.42$, CHCl₃)}; (+)-**1** was colorless powders: mp 140-143 °C (from hexane); $[\alpha]_D^{22} = +72.9$ ($c = 0.05$, CHCl₃).

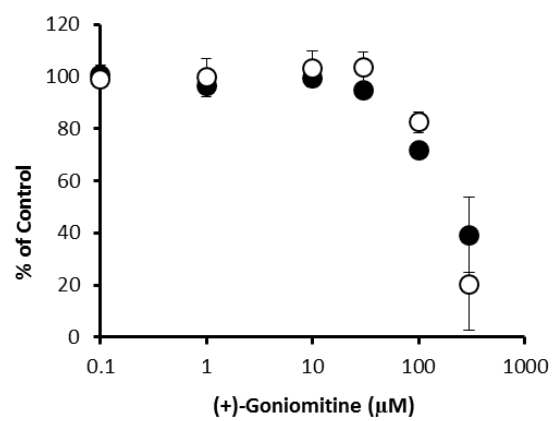
The obtained spectral data were identical with reported goniomitine.^{1,3-5}

Methods for determination of antiproliferative activity of (+)-, (-)- and (±)-goniomitine⁶

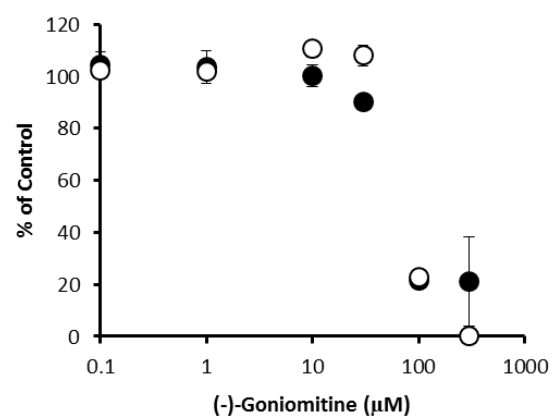
The effects of (+), (-)- and (±)-goniomitine on proliferation of adherent canine kidney MDCK II cells transfected with human MDR1 gene (MDCK/MDR1), and the empty plasmid vector (Mock) were evaluated by measuring total protein staining with sulforhodamine B (SRB assay) as described previously¹. In general, 2000 cells were plated with 0.2 mL of culture medium containing 1 % of DMSO into a 96-well tissue culture plate. The cells were cultured for 3 days at 37 °C in an atmosphere of 5% CO₂, and then fixed with 10% trichloroacetic acid and stained with 0.057% (w/v) SRB. SRB was dissolved in 0.1 mL of 10 mM Tris/HCl (pH 10), and then the absorbance of each well at 570 nm was measured using a conventional microplate reader (ARVO™ X3, PerkinElmer Japan, Osaka). To estimate the IC₅₀ values of goniomitine in MDCK cells, SRB cell proliferation assay data were fitted to the Hill equation with a slope of 2.0.

Supplemental Figure 1

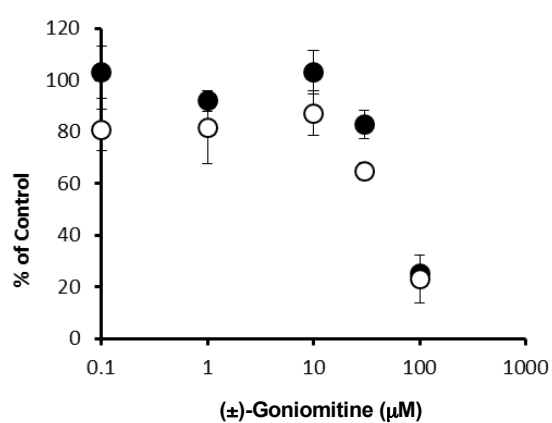
(A)



(B)

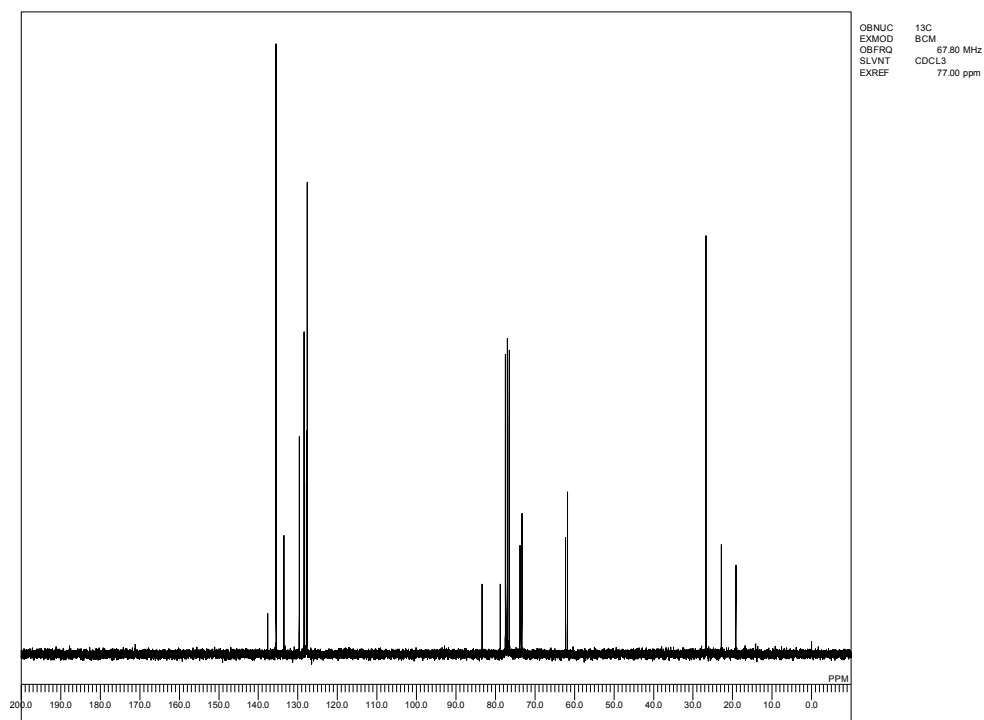
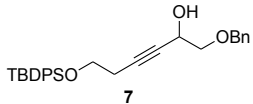


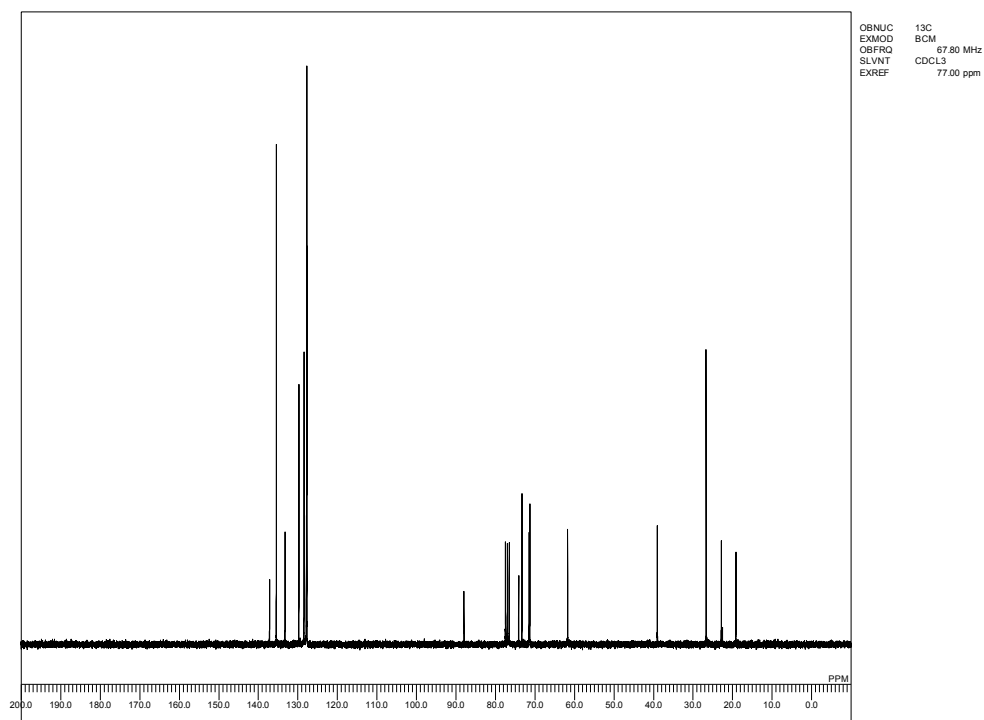
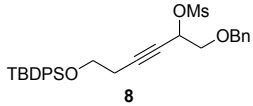
(C)

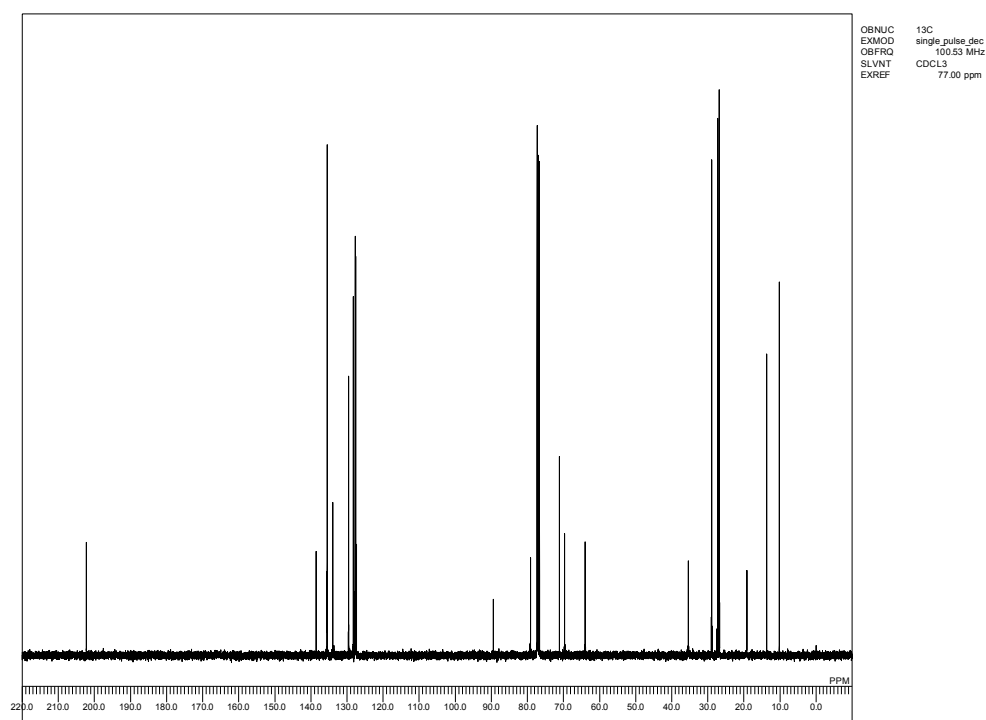
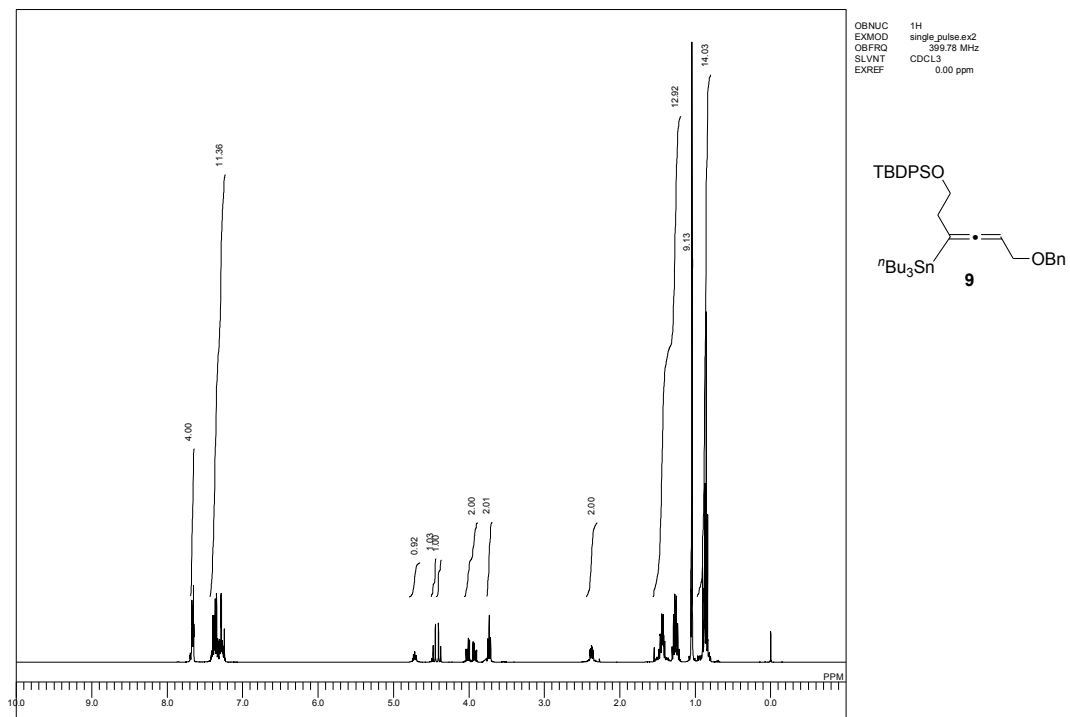


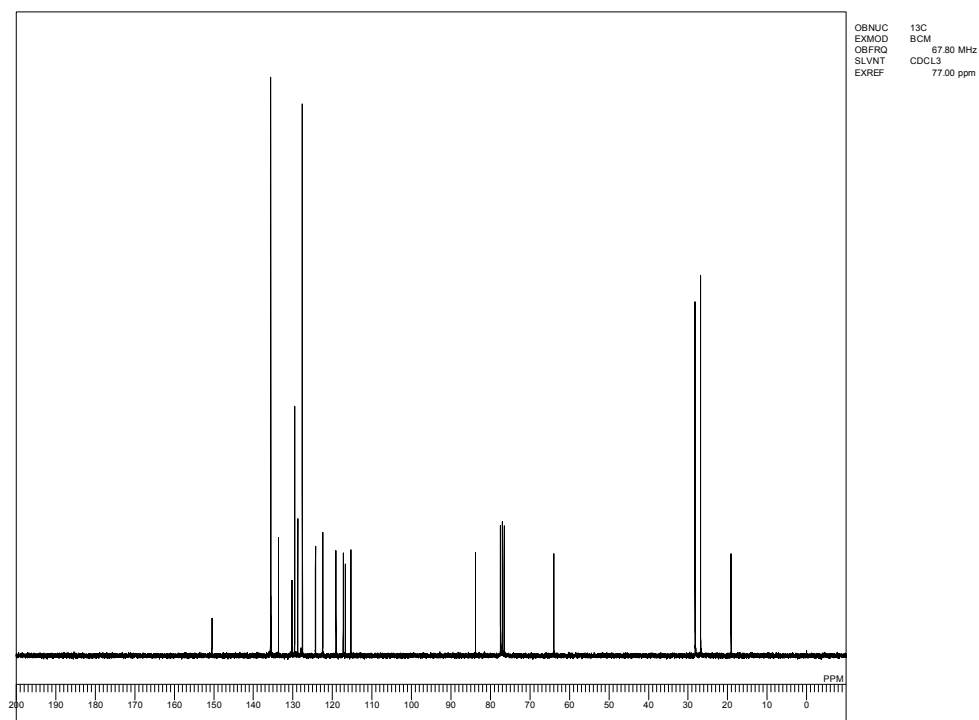
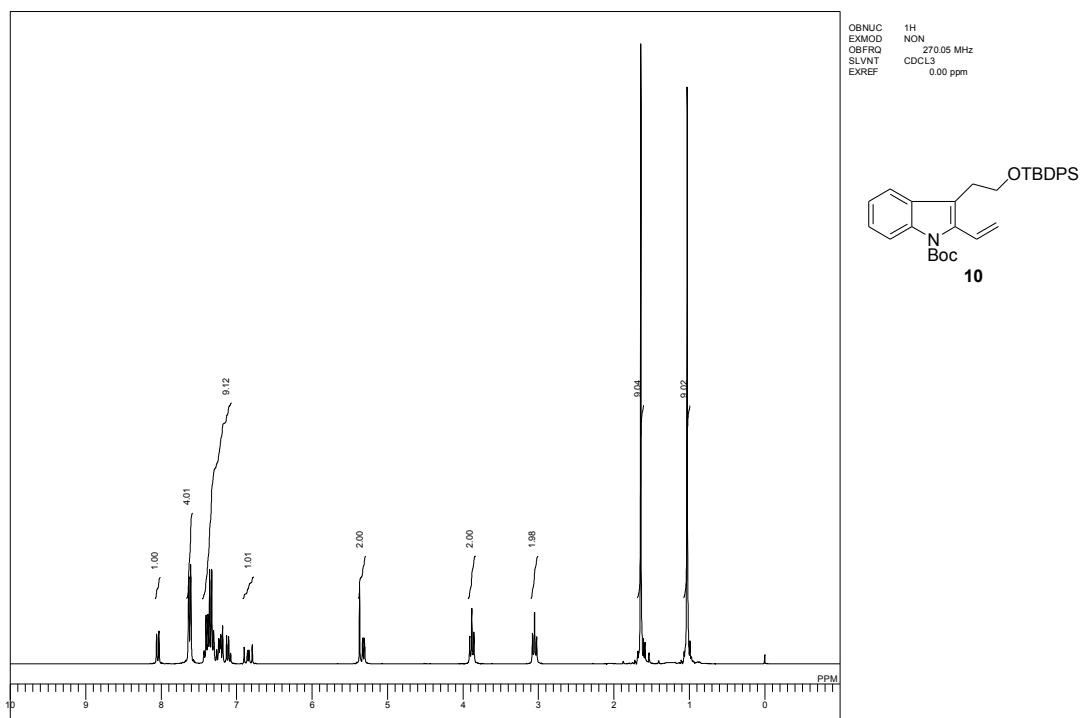
Supplemental Figure Legend

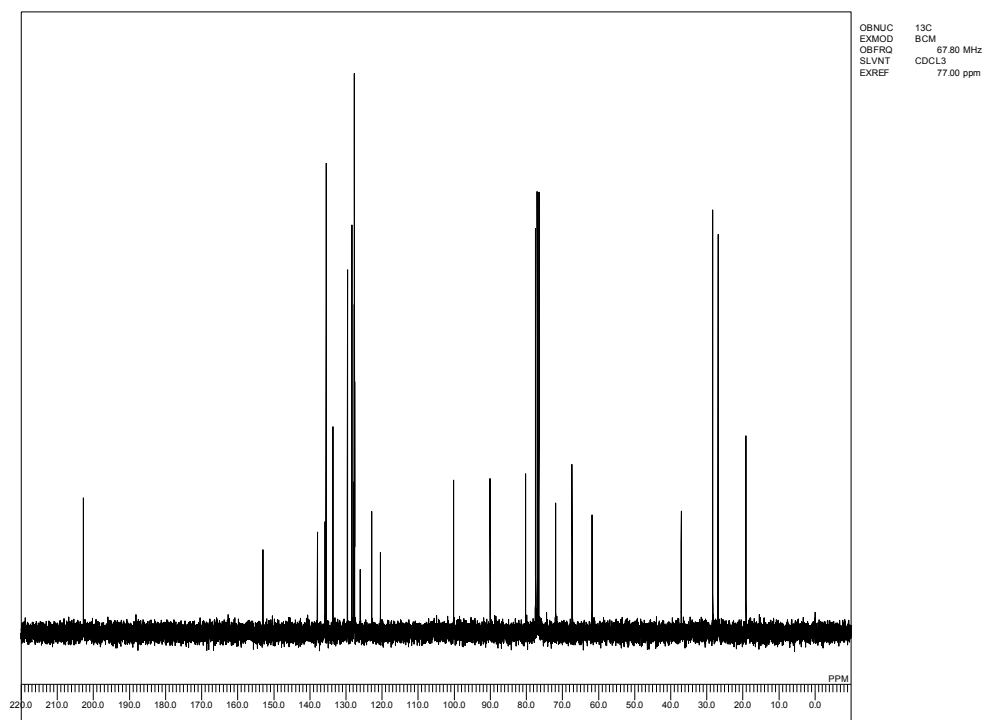
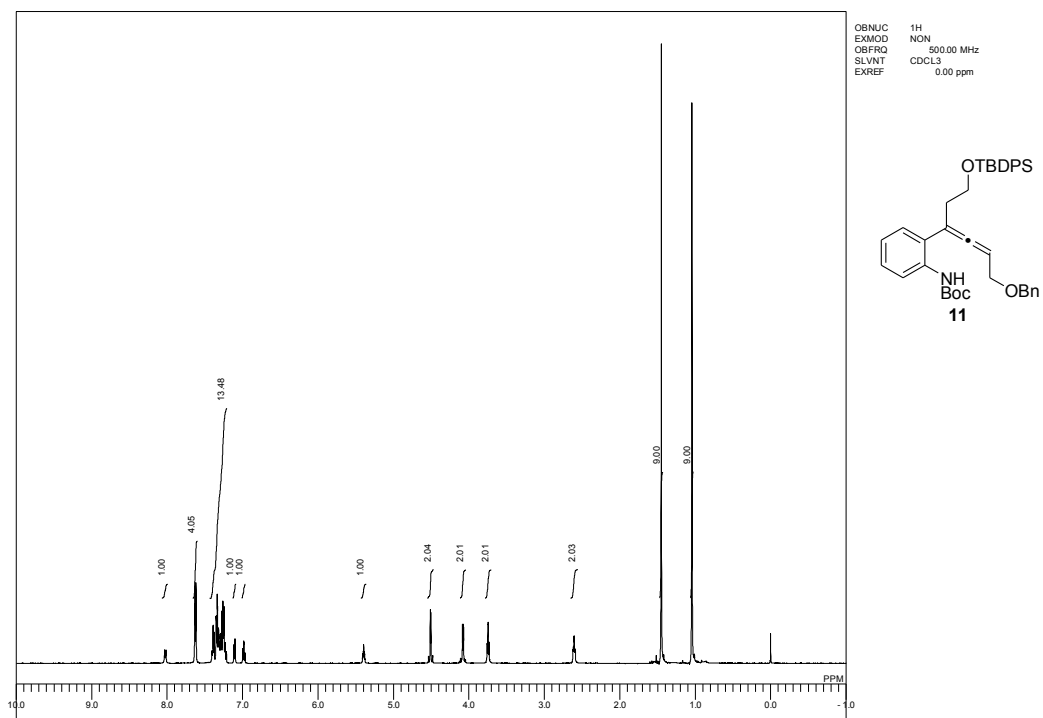
Cell proliferation was studied in presence of various concentrations of (+)- (A), (-)- (B) or (±)-goniomitine (C). Mock (open circle) and MDCK/MDR1 (closed circle) cells were seeded at a density of 2000 cells/well on Day 0. Each point (mean \pm S.E.) represents proliferation relative to the control (in the absence of goniomitine) at Day 3. Experiments were repeated at least twice in triplicate.

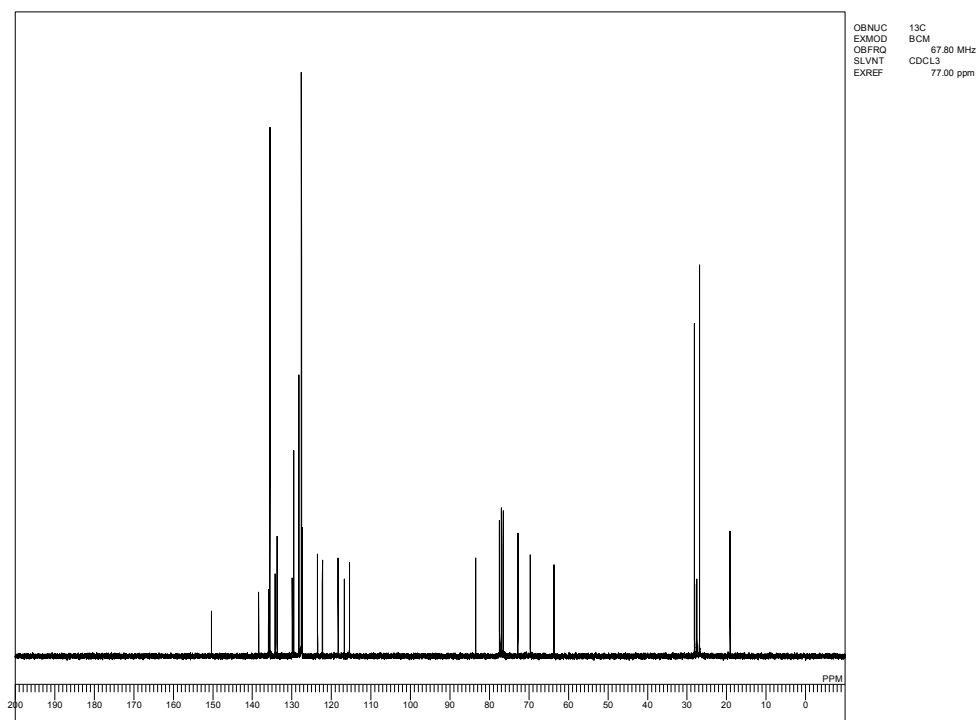
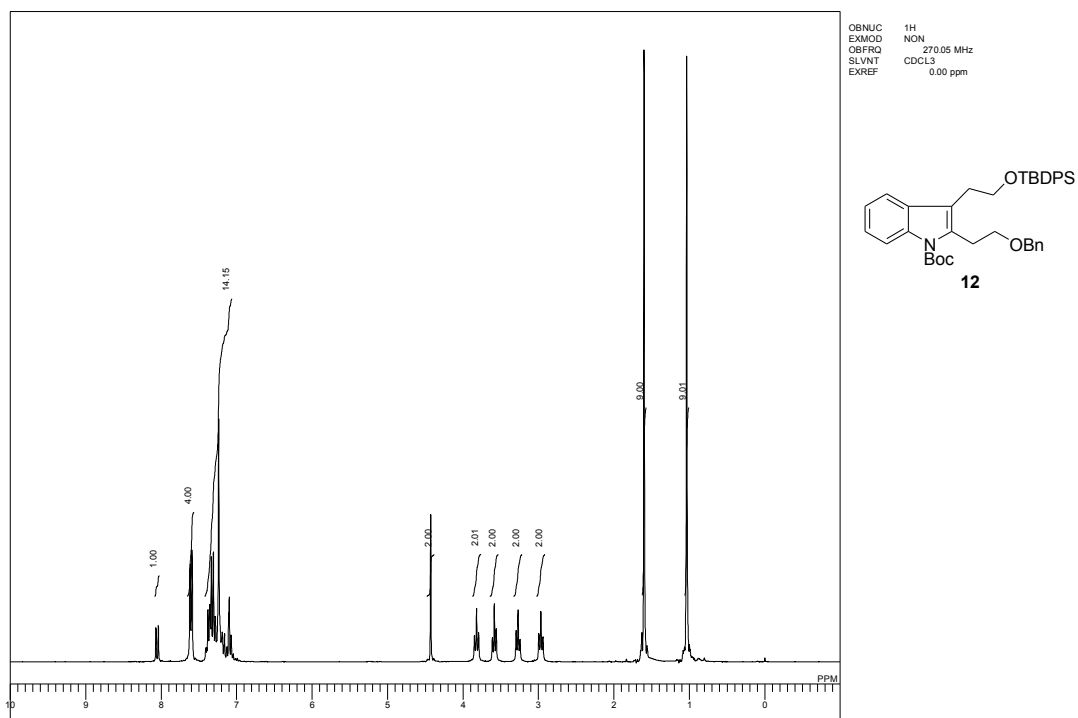


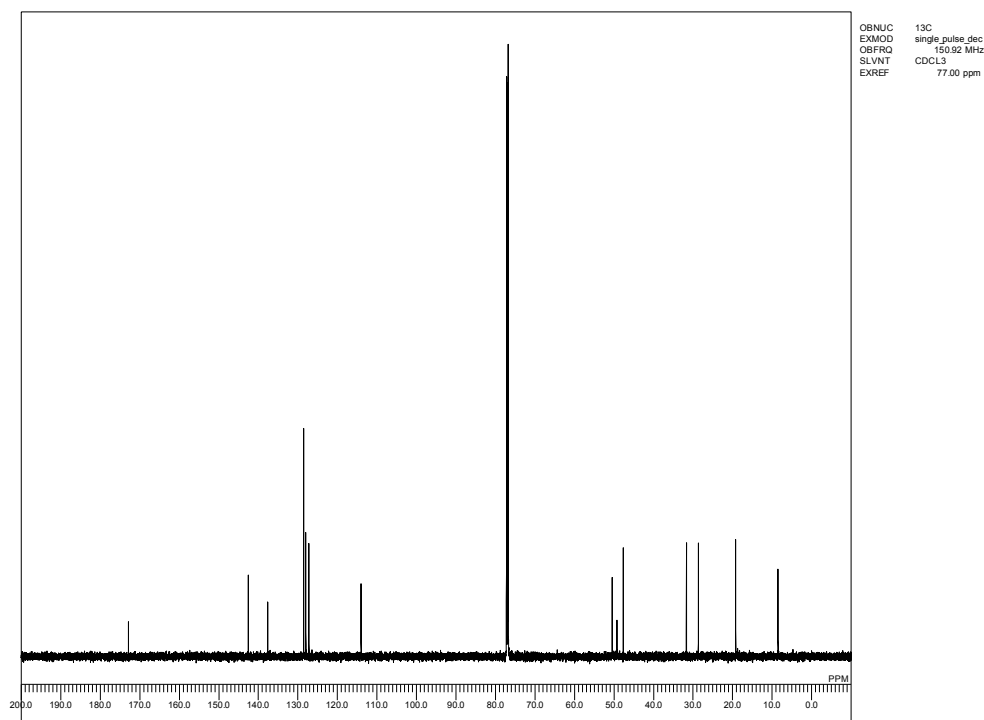
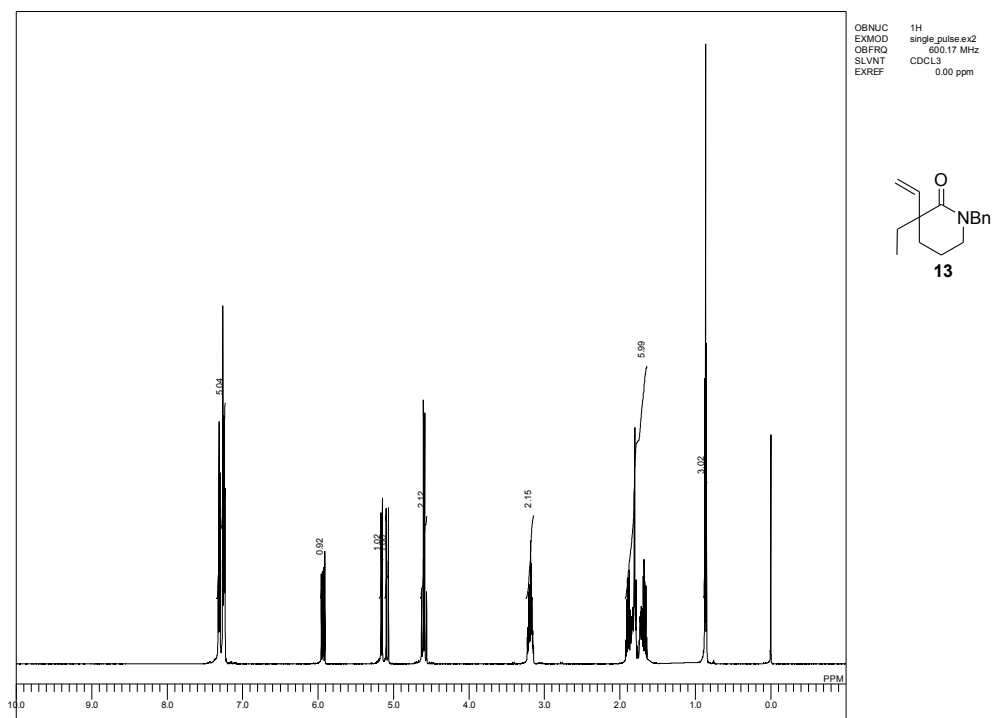


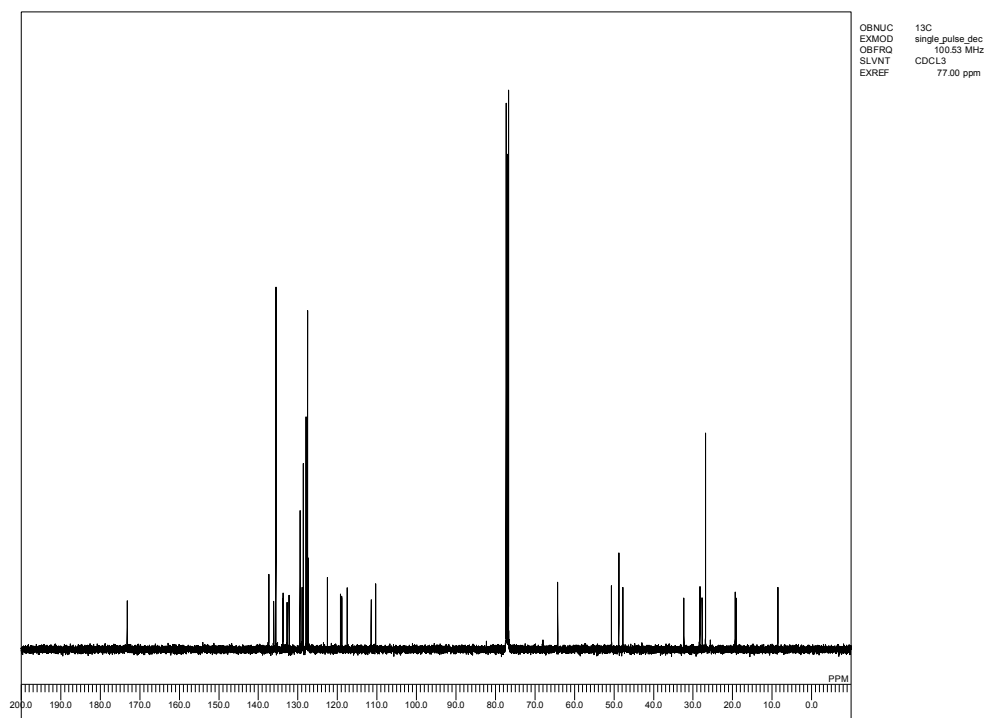
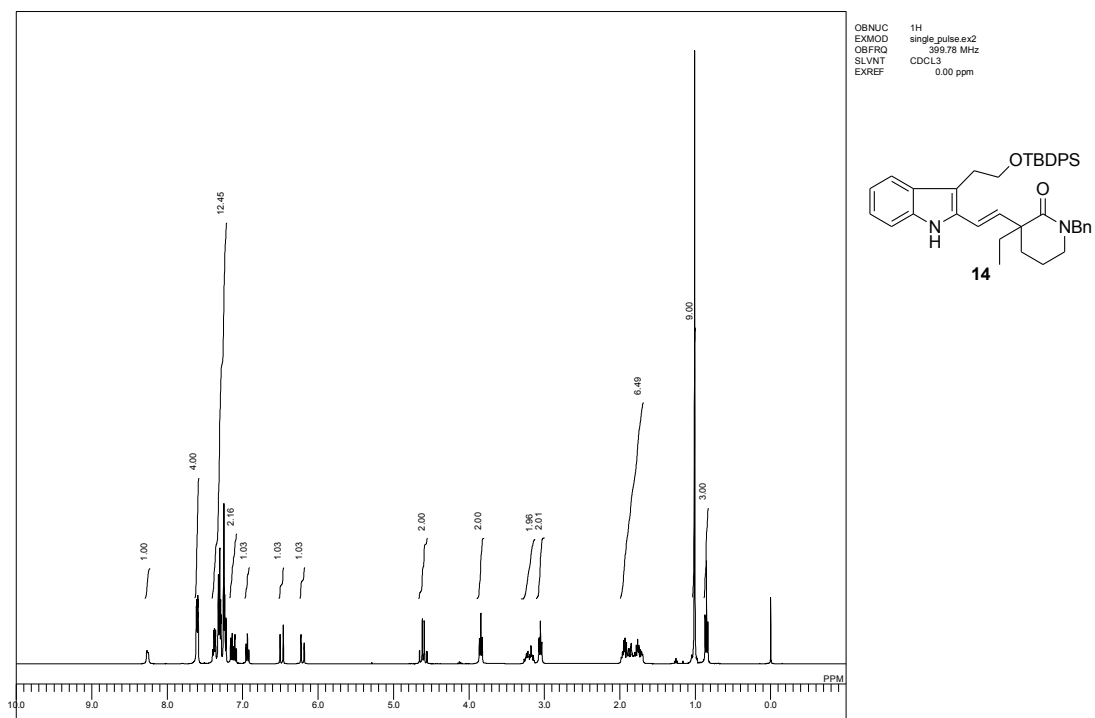


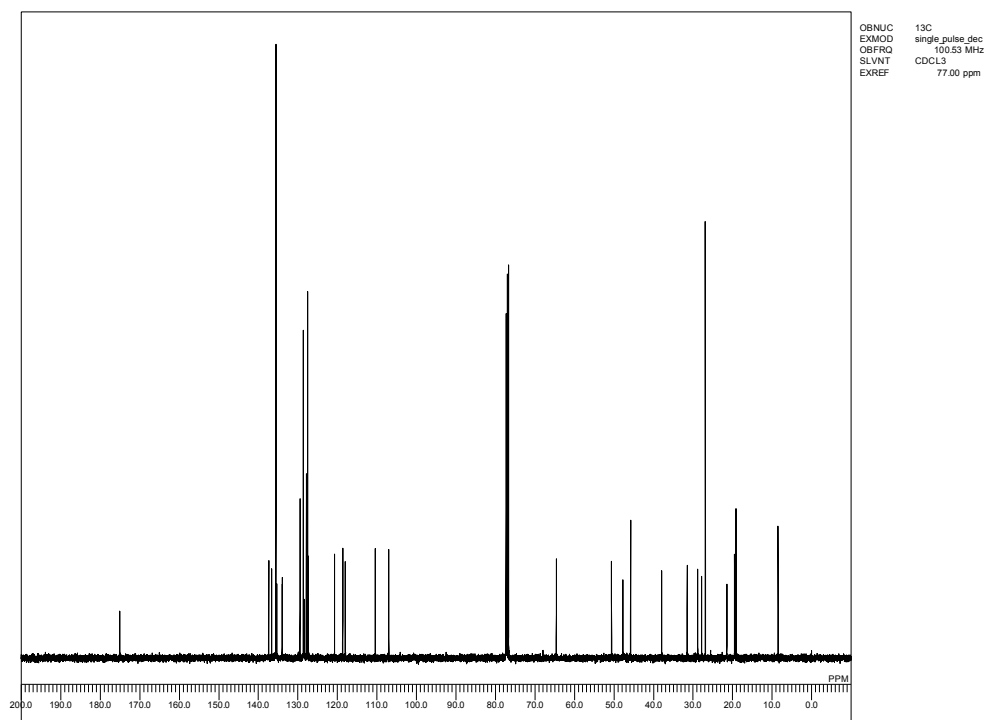
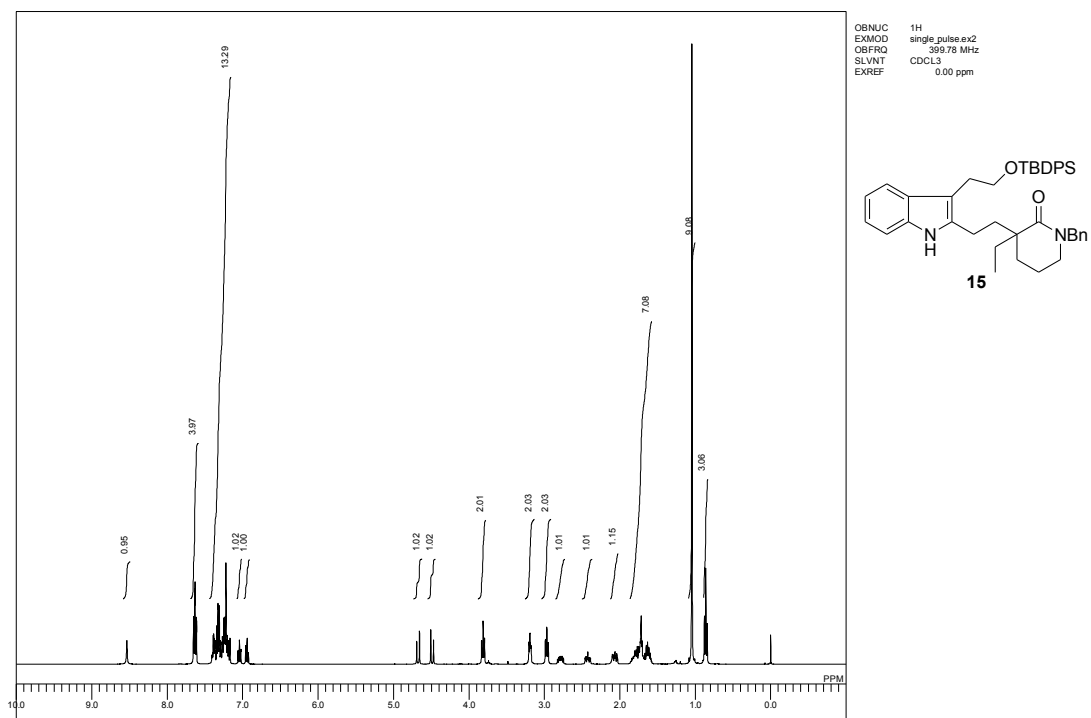


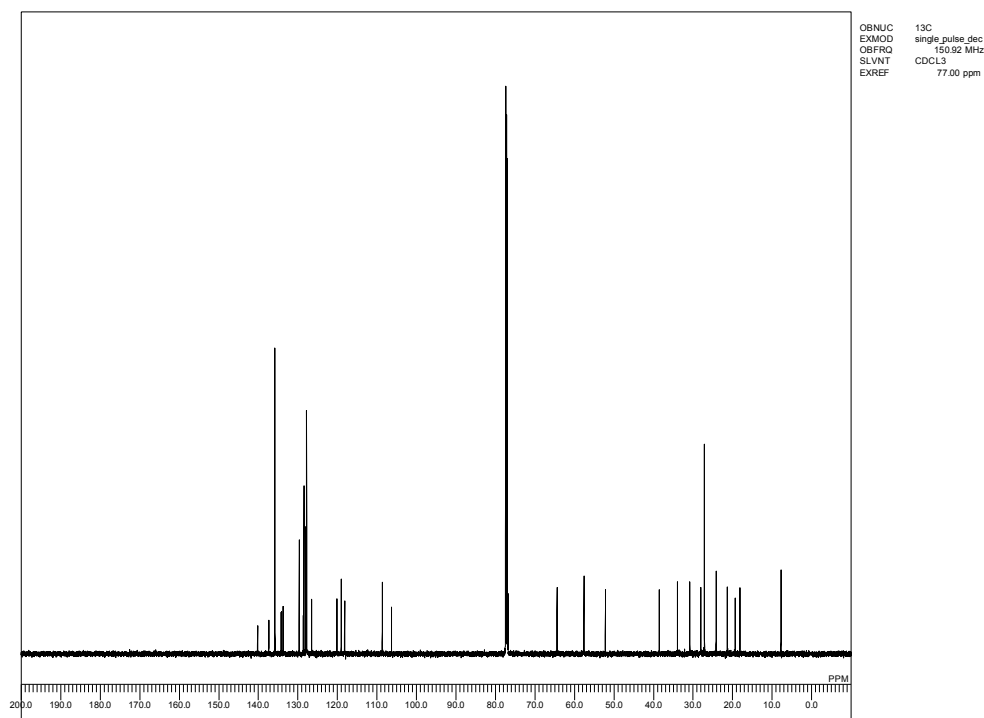
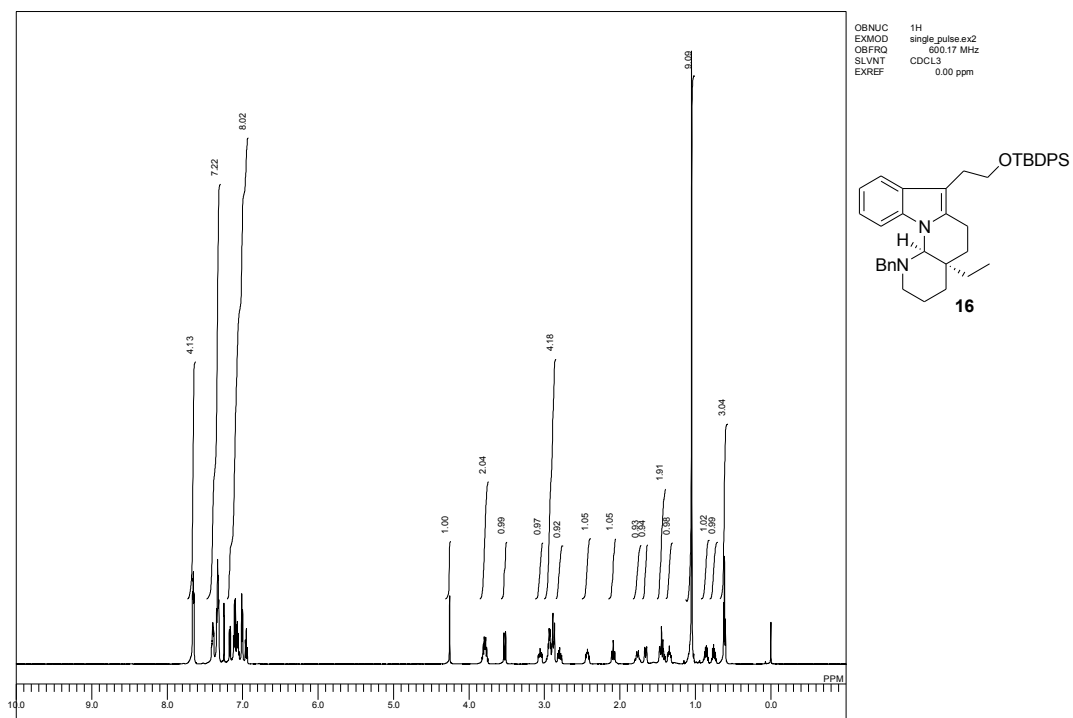


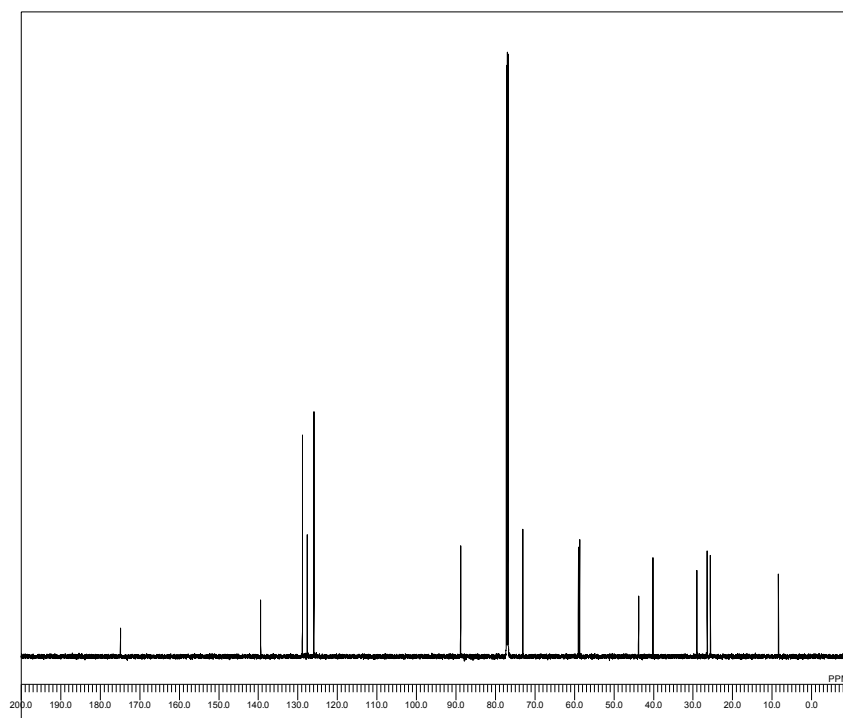
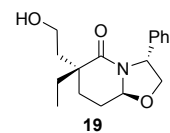
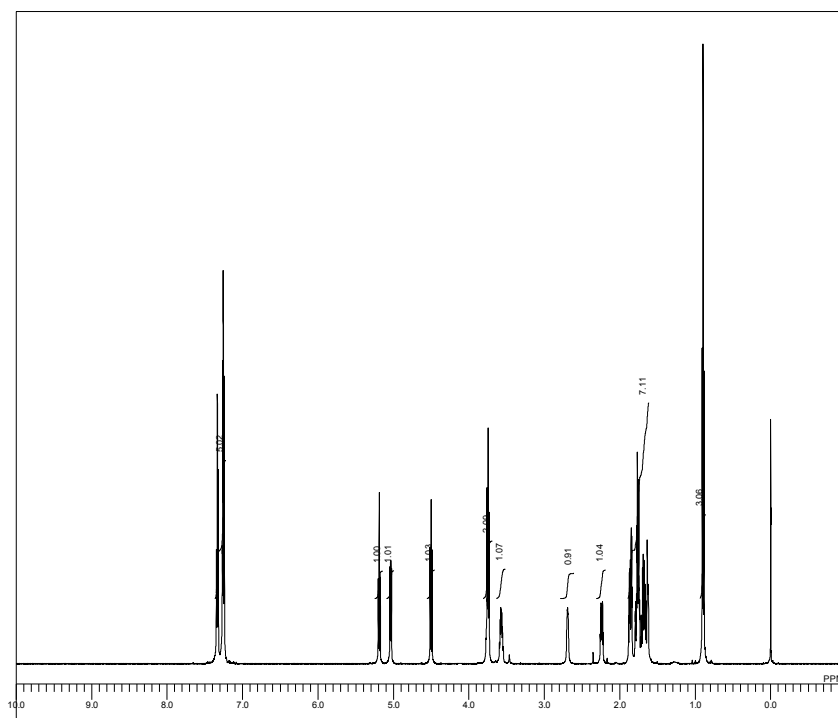


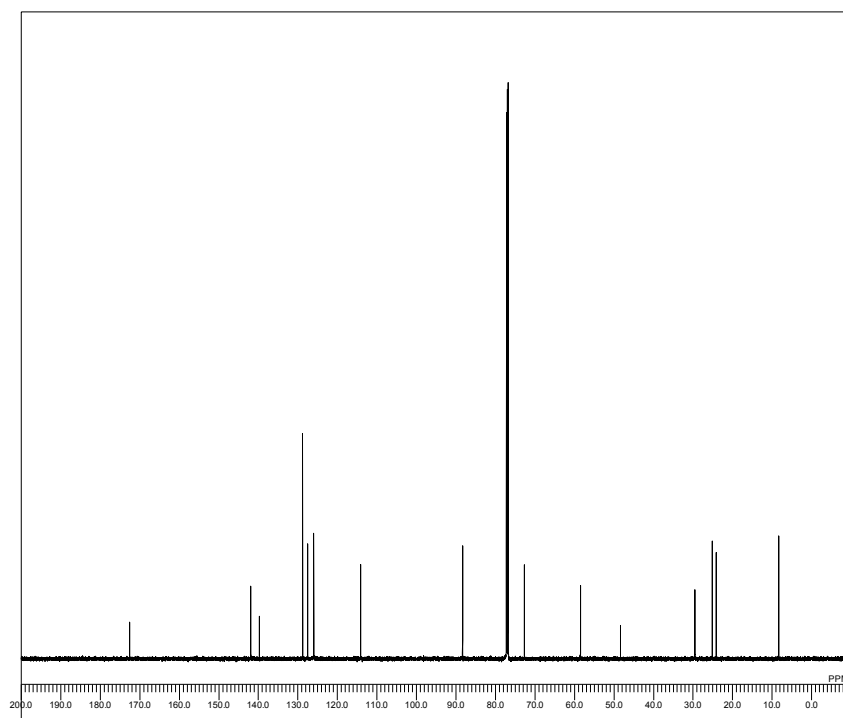
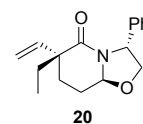
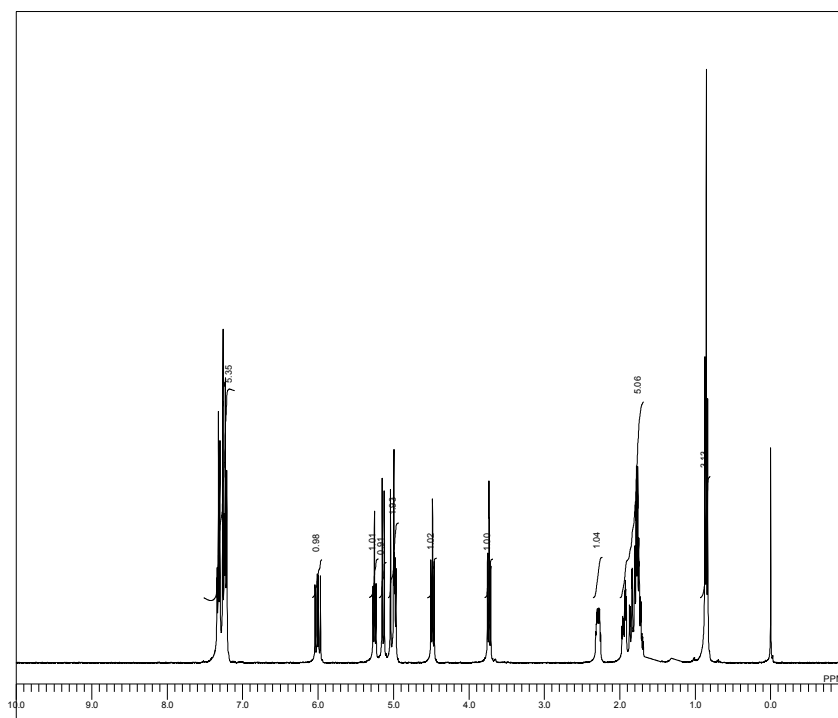


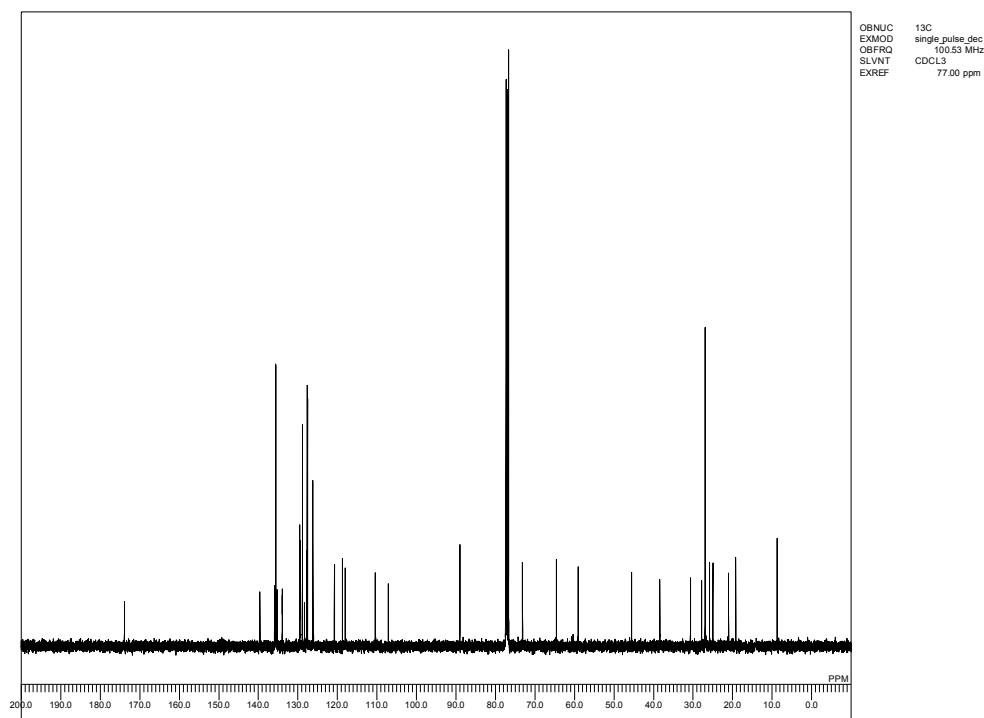
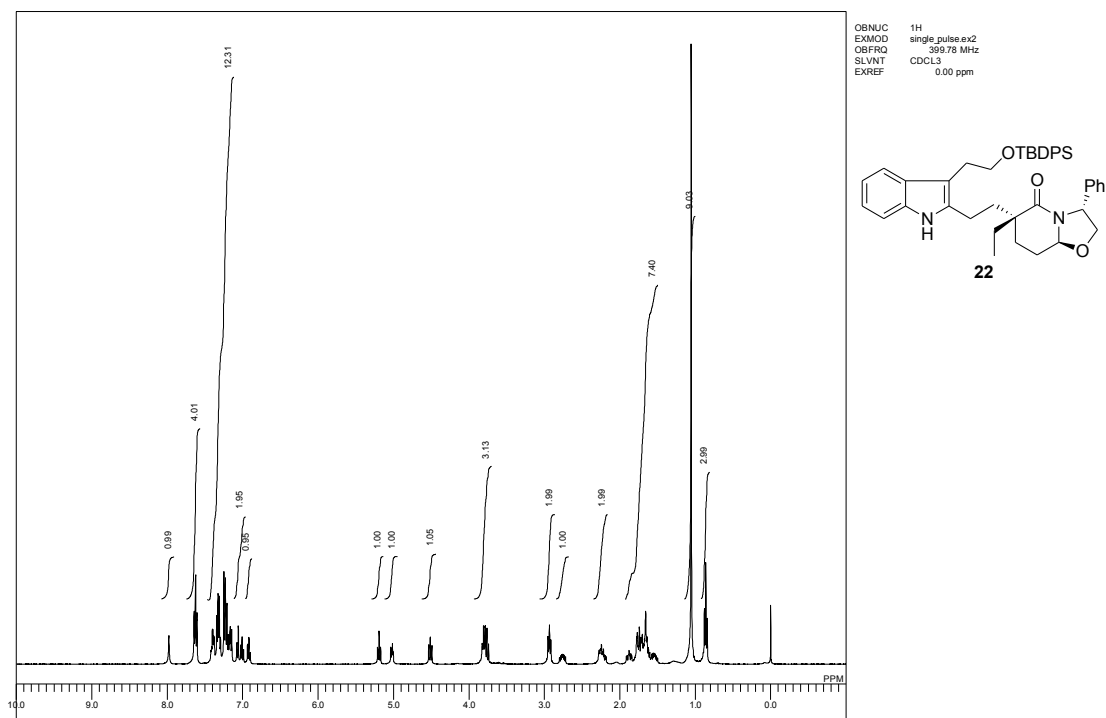


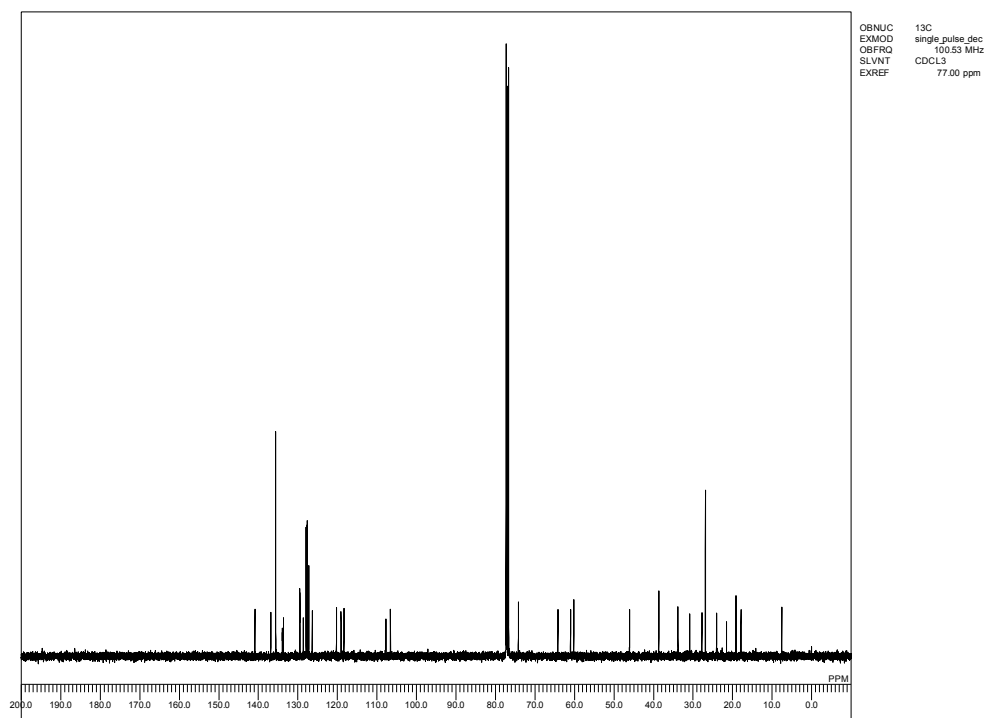
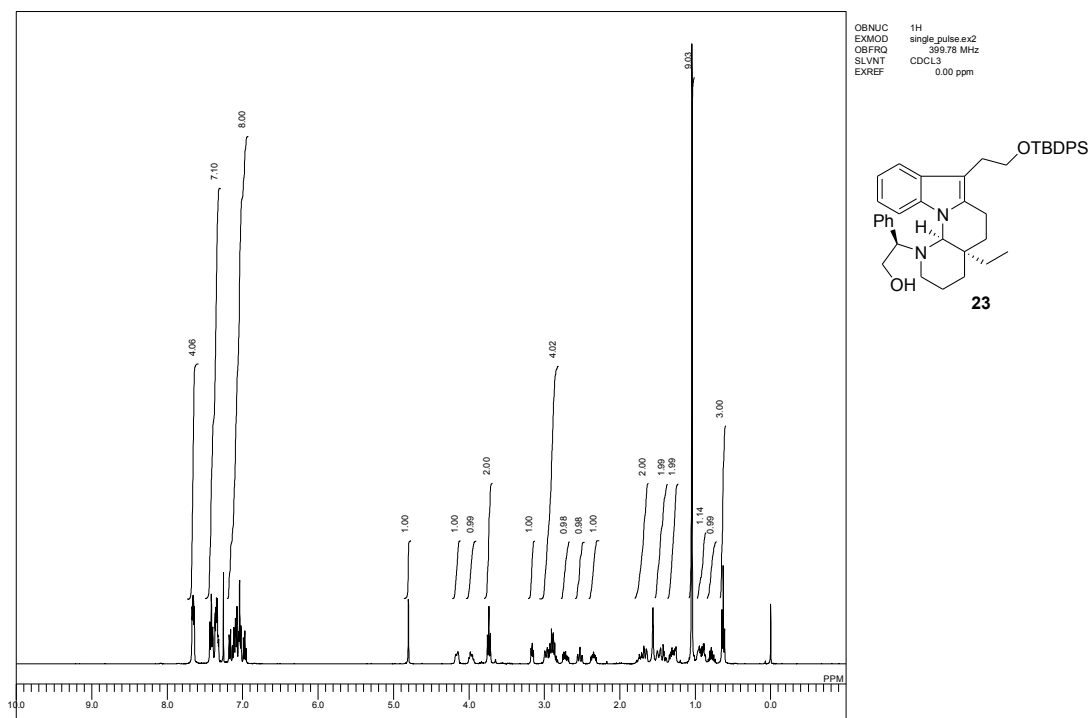


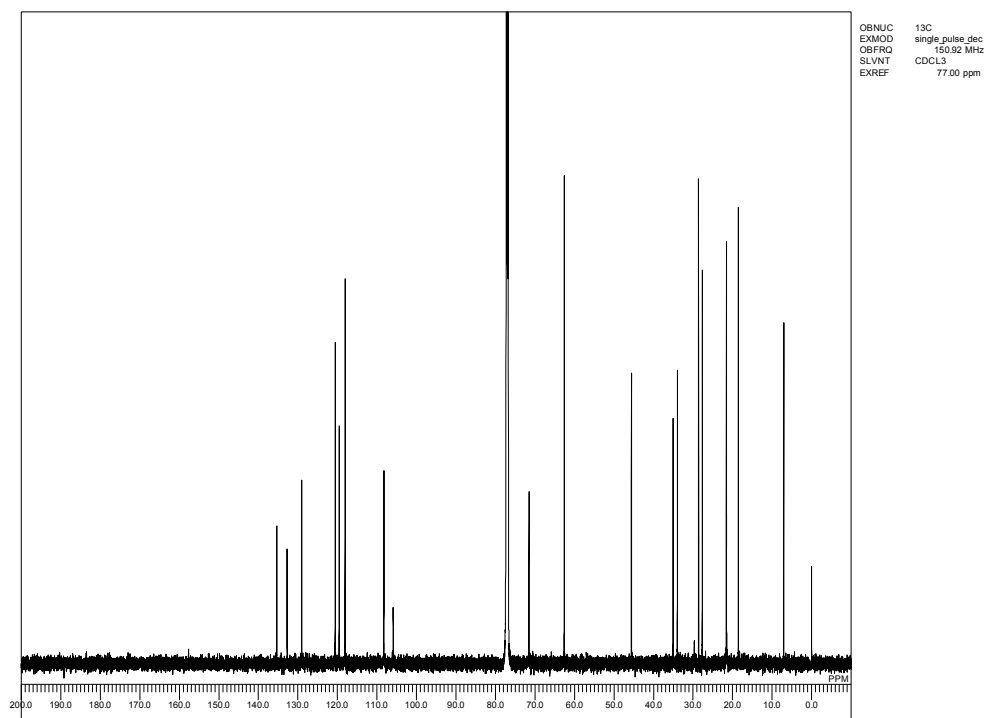
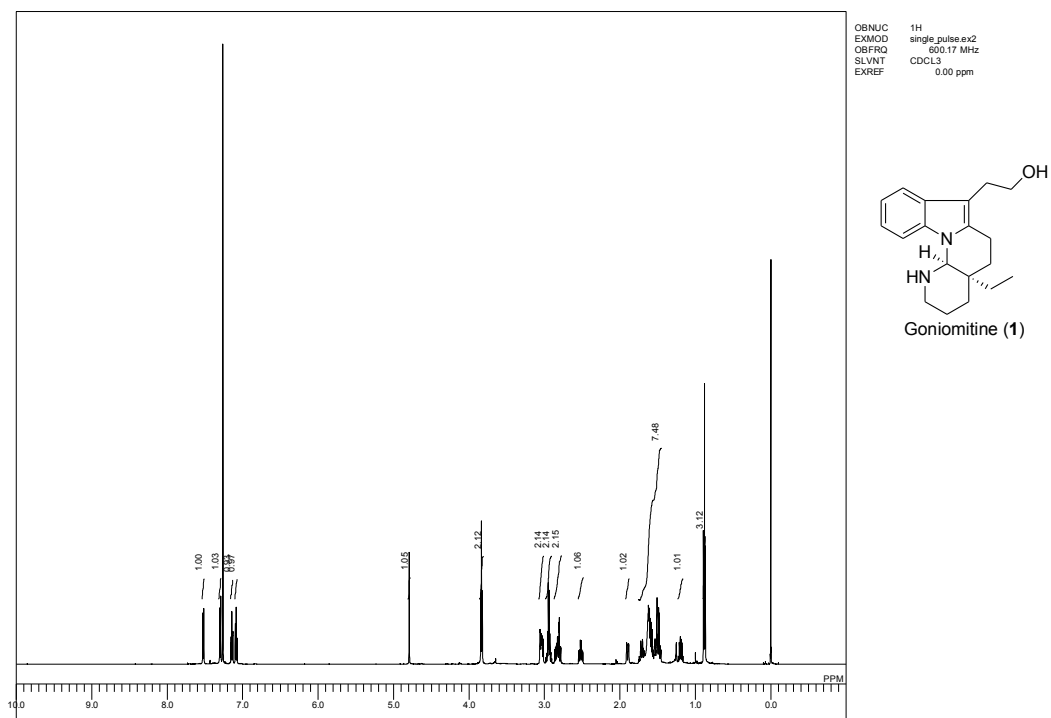




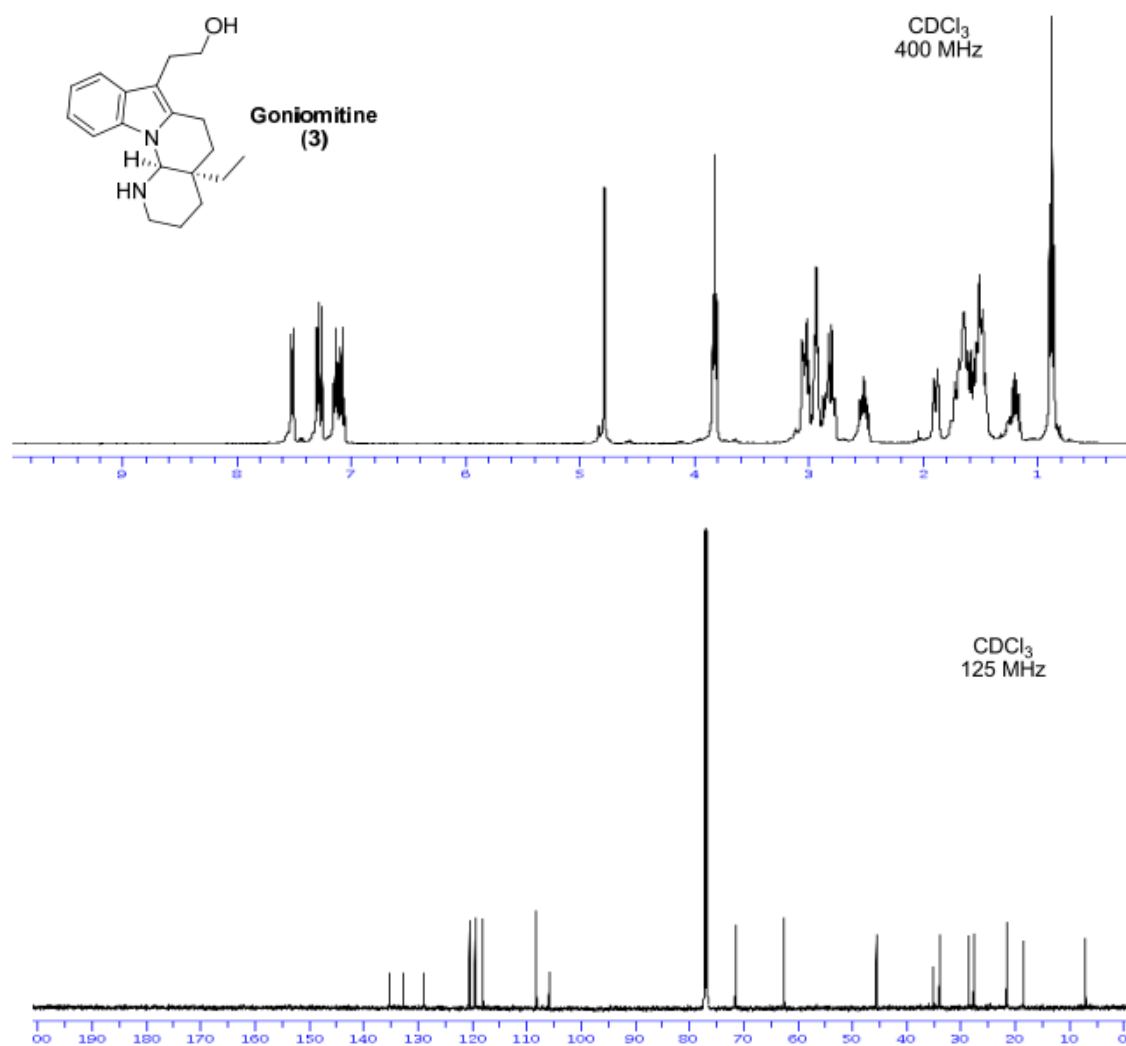




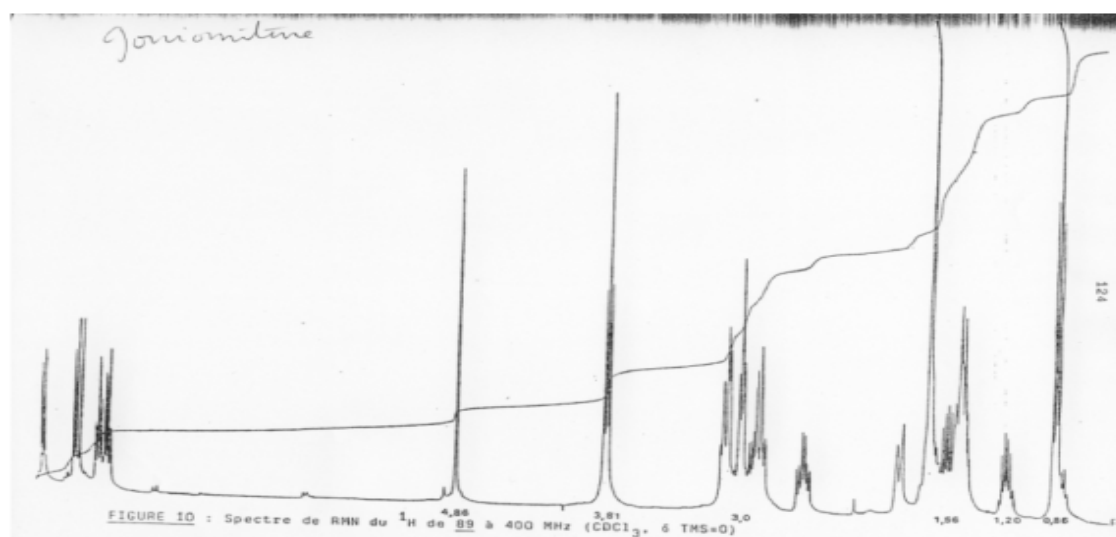




Copy of spectra from Waser⁵



Copy of Spectra from Husson³



References

- 1) Morales, C. L.; Pagenkopf, B. L. *Org. Lett.* **2008**, *10*, 157-159.
- 2) (a) Amat, M.; Bosch, J.; Hidalgo, J.; Cantó M.; Pérez, M.; Llor, N.; Molins, E.; Miravittles, C.; Orozco, M.; Luque, J. *J. Org. Chem.* **2000**, *65*, 3074-3084. (b) Amat, M.; Lozano, O.; Escolano, C.; Molins, E.; Bosch, J. *J. Org. Chem.* **2007**, *72*, 4431-4439.
- 3) Randriambola, L.; Quirion, J.-C.; Kan-Fan, C.; Husson, H.-P. *Tetrahedron Lett.* **1987**, *28*, 2123-2126.
- 4) Takano, S.; Sato, T.; Inomata, K.; Ogasawara, K. *J. Chem. Soc. Chem. Commun.* **1991**, 462-464.
- 5) Simone, F. D.; Gertsch, J.; Waser, J. *Angew. Chem. Int. Ed.* **2010**, *49*, 5767-5770.
- 6) Sulforhodamine B colorimetric assay for cytotoxicity screening, Vichai, V.; Kirtikara, K. *Nat. Protoc.* **2006**, *1*, 1112-1116.