Skeletal and Stereochemical Diversification of Tricyclic Frameworks Inspired by Ca^{2+}-ATPase Inhibitors, Artemisinin and Transtaganolide D

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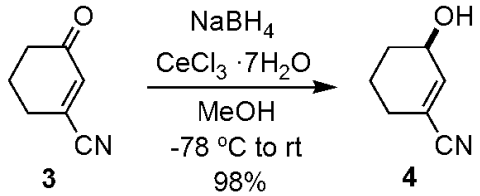
Supporting Information

S1-S15: Experimental Section

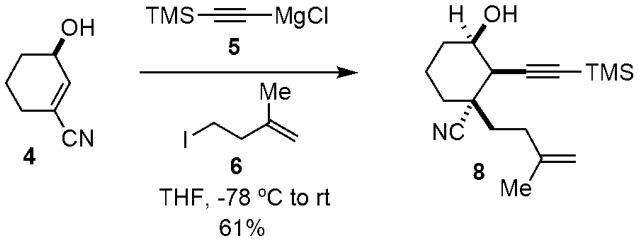
S16-S59: ^{1}H and ^{13}C-NMR Spectra

General : NMR spectra were recorded on JEOL ECP-300 (^{1}H/300 MHz, ^{13}C/75 MHz), JEOL α-400 and JNM-ECX 400 (^{1}H/400 MHz, ^{13}C/100 MHz) spectrometers. Chemical Shifts are reported in δ (ppm) using chloroform as an internal standard of δ 7.26. IR spectra were recorded on a JASCO FT/IR 660 Plus infrared spectrometer. Mass spectra were recorded on JEOL JMS-T100CS (ESI) spectrometer. The medium pressure liquid chromatography (MPLC) purifications were performed on a YAMAZEN YFLC-AI-580. Where necessary, solvents were distilled from appropriate drying agents prior to use. Flash column chromatography was performed using Kanto Silica Gel 60N.

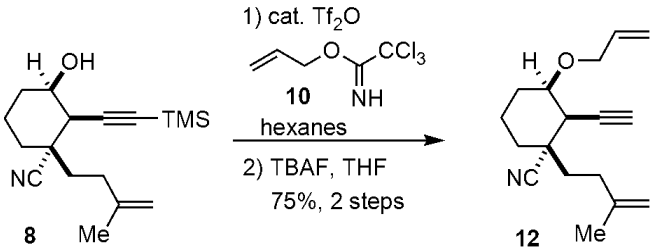
Materials : 4-Iodo-2-methyl-1-butene and 4-iodo-1-butene were prepared from corresponding alcohols by treatment with I_2, PPh_3, and imidazole in CH_2Cl_2. 4-Chloro-2-methyl-1-butene was prepared from corresponding alcohol by treatment with CCl_4 and PPh_3 in CH_2Cl_2. 4-Bromo-2-methyl-1-butene was prepared from corresponding alcohol, MsCl, Et_3N, and LiBr. 4-Chloro-1-butene was prepared from corresponding alcohol with $SOCl_2$ and pyridine. Trichloroacetimidates were prepared from corresponding alcohols with CCl_3CN and NaH in Et_2O.[1] Grignard reagents were prepared by the standard method, and the concentrations were determined by titration. Oxonitrile **3** was prepared according to the reported procedure.[2] Unless otherwise noted, all other materials were obtained from commercial suppliers and used without further purification.



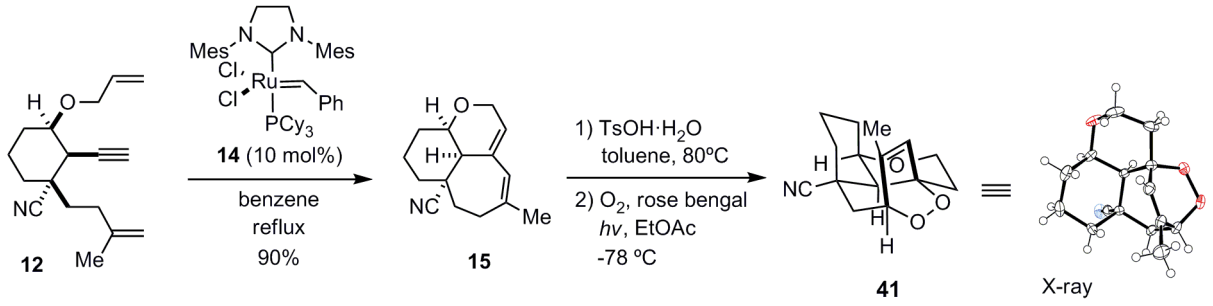
To a stirred solution of **3** (1.49 g, 12.3 mmol) in methanol (0.5 M) was added $CeCl_3$-$7H_2O$ (6.8 g, 18.5 mmol, in methanol 37 mL) at -78 °C. After 5 min at -78 °C, $NaBH_4$ (462 mg, 12.3 mmol) was added in one portion. The mixture was stirred for 20 min and then allowed to warm to room temperature. After being stirred for 1.5 h, the mixture was concentrated. The resulting residue was diluted with water and extracted with Et_2O. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated to afford **4**[3] (1.49 g, 12.1 mmol, 98%) as a colorless oil.



Trimethylsilylethynylmagnesium chloride **5** (28.4 mmol, 1.0 M in THF) was added dropwisely to a solution of **4** (1.0 g, 8.1 mmol) in THF (8.1 mL) at -78 °C. After being stirred for 1.5 h, **6** (4.1 mL, 32.4 mmol) was added. The mixture was maintained at -78 °C for 0.5 h, then warmed to room temperature and stirred for 11 h. The reaction mixture was quenched with saturated NH_4Cl at 0 °C, and the resulting mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated. The resulting residue was purified by silica-gel column chromatography to afford **8** (1.42 g, 4.91 mmol, 61%) as a pale yellow oil. IR (film) ν 3468, 2948, 2864, 2172, 1452, 1252, 1092, 1006, 892, 844, 760 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.77 (1H, m), 4.75 (1H, m), 3.94 (1H, m), 3.24 (1H, d, J = 4.6 Hz), 2.28-2.15 (2H, m), 1.98-1.53 (8H, m), 1.77 (3H, s), 0.18 (9H, s); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 144.24, 122.04, 110.88, 99.07, 93.86, 68.51, 43.43, 41.79, 36.54, 32.21, 30.92, 30.40, 22.40, 21.09, -0.089; MS (ESI) calcd. for $C_{17}H_{27}NOSiNa$ $[M+Na]^+$ 312.18, found 312.23. The ^{1}H and ^{13}C NMR spectra of **8** are shown in Figure S1 and S2.

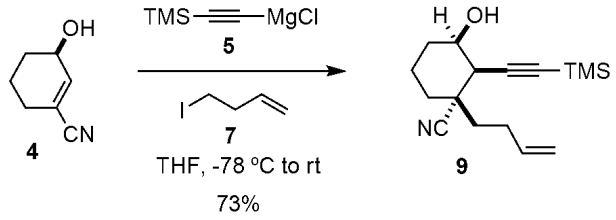


To a solution of **8** (2.67 g, 9.22 mmol) and **10** (5.60 g, 27.7 mmol) in hexanes (18.4 mL), trifluoromethanesulfonic anhydride (total 650 μL, 1.37 mmol) was added at room temperature in four portions over 34 h. The precipitates were filtered off. The filtrate was washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated. The resulting residue was purified by silica-gel column chromatography to yield 2.59 g of the allylether with some impurities. The mixture was used for the next step without further purification. A solution of crude allylether (2.55 g, ca 7.74 mmol) was treated with TBAF (9.3 mL, 1.0 M in THF, 9.29 mmol) at 0 °C. After being stirred at room temperature for 15 min, the mixture was concentrated and purified by silica-gel column chromatography to afford **12** [1.77 g, 6.89 mmol, 75% (2 steps from **8**)] as a white solid. IR (film) ν 3308, 3016, 2948, 1452, 1216, 1074, 758, 668 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.99-5.89 (1H, m), 5.32 (1H, dq, *J* = 17.1, 1.5 Hz), 5.21 (1H, dd, *J* = 10.4, 1.5 Hz), 4.77 (1H, m), 4.75 (1H, m), 4.14-4.05 (2H, m), 3.73 (1H, dt, *J* = 10.8, 4.1 Hz), 3.27 (1H, m), 2.29-2.15 (2H, m), 2.25 (1H, d, *J* = 2.4 Hz), 2.00-1.62 (8H, m), 1.77 (3H, s); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 144.25, 134.60, 122.19, 117.54, 110.77, 77.81, 75.61, 75.02, 69.78, 41.76, 39.31, 36.08, 32.17, 30.98, 27.12, 22.52, 21.07; HR-MS (ESI) calcd. for $C_{17}H_{23}NONa$ $[M+Na]^+$ 280.1677, found 280.1670. The ^{1}H and ^{13}C NMR spectra of **12** are shown in Figure S3 and S4.

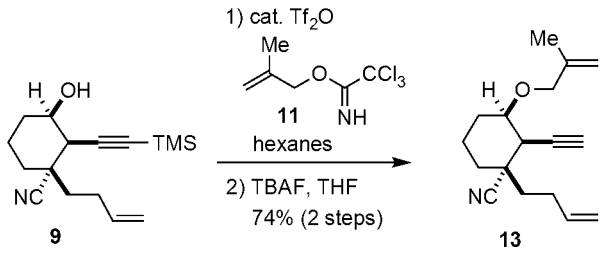


To a solution of **12** (100 mg, 0.389 mmol) in benzene (15.6 mL, 0.025 M) was added Grubbs' 2nd generation catalyst **14** (33.0 mg, 0.0389 mmol), and the resulting solution was heated to reflux for 3.5 h. The mixture was then concentrated leaving a residue which was purified by silica-gel column chromatography to afford **15** (79.9 mg, 0.349 mmol, 90%) as a white solid. IR (KBr) ν 2921, 2849, 1448, 1133 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.87 (1H, m), 5.68 (1H, m), 4.25-4.14

(2H, m), 3.94 (1H, m), 2.84 (1H, m), 2.54 (1H, dd, *J* = 19.2, 8.8 Hz), 2.24 (1H, dd, *J* = 19.2, 8.2 Hz), 2.08-1.56 (8H, m), 1.76 3H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 136.98, 130.83, 128.04, 127.79, 125.29, 71.40, 63.57, 45.17, 41.20, 37.38, 31.66, 27.77, 26.11, 23.72, 17.85; HR-MS (ESI) calcd. for $C_{15}H_{19}NONa$ $[M+Na]^+$ 252.1364, found 252.1353. The ^{1}H and ^{13}C NMR spectra of **15** are shown in Figure S5 and S6. The structure of **15** was confirmed based on X-ray analysis of crystalline endoperoxide **41** prepared by acid-mediated isomerization of the conjugate diene and subsequent photooxidation.

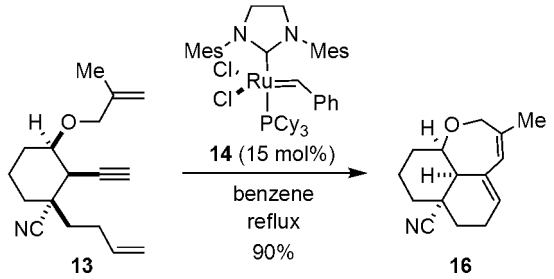


Trimethylsilylethynylmagnesium chloride **5** (32.4 mmol, 0.8 M in THF) was added dropwisely to a solution of **4** (1.0 g, 8.1 mmol) in THF (8.1 mL) at -78 °C. After being stirred for 2 h, **7** (4.1 mL, 32.4 mmol) was added. The mixture was maintained at -78 °C for 1.5 h, then warmed to room temperature and stirred for 18 h. The reaction mixture was quenched with saturated NH_4Cl at 0 °C, and the resulting mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated. The resulting residue was purified by silica-gel column chromatography to afford **9** (1.63 g, 5.92 mmol, 73%) as a pale yellow oil. IR (film) ν 3468, 2948, 2864, 2172, 1644, 1452, 1252, 1086, 1056, 1006, 914, 892, 846, 762 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.88-5.78 (1H, m), 5.13-5.07 (1H, m), 5.05-5.01 (1H, m), 3.94 (1H, m), 3.23 (1H, d, *J* = 4.8 Hz), 2.36-2.20 (2H, m), 1.91-1.53 (9H, m), 0.18 (9H, s); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 136.83, 122.04, 115.69, 99.12, 93.92, 68.50, 43.52, 41.76, 37.39, 30.84, 30.38, 28.42, 21.08, -0.073; MS (ESI) calcd. for $C_{16}H_{25}NOSiNa$ $[M+Na]^+$ 298.16, found 298.13. The ^{1}H and ^{13}C NMR spectra of **9** are shown in Figure S7 and S8.

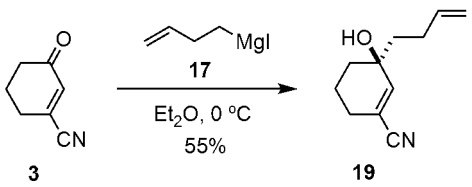


To a solution of **9** (1.49 g, 5.42 mmol) and **11** (3.45 mL, 16.2 mmol) in hexanes (10.8 mL), a catalytic amount of trifluoromethane sulfonic anhydride (0.768 mmol, 360 μL) was added, and the

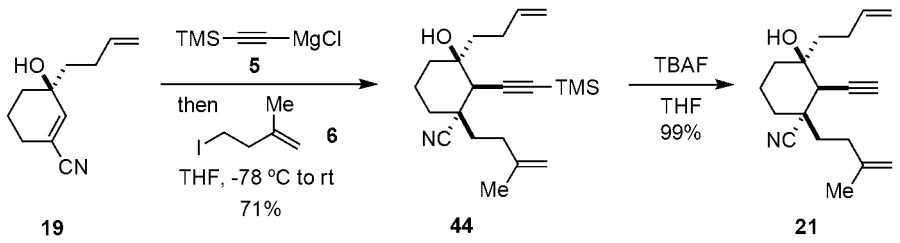
mixture was stirred for 12 h at room temperature. The precipitates were filtered off. The filtrate was washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated. The resulting residue was purified by silica-gel column chromatography to yield the crude allylether (1.37 g) with some impurities. The mixture was used without further purification. A solution of the crude allylether (1.26 g) in THF (7.64 mL) was treated with TBAF (4.58 mL, 1.0 M in THF, 4.58 mmol) at 0 °C. After being stirred at room temperature for 15 min, the mixture was concentrated and purified by silica-gel column chromatography to afford **13** (0.941 g, 3.66 mmol) in 74% yield (2 steps) as a white solid. IR (film) ν 3284, 3080, 2948, 2868, 2228, 1644, 1454, 1374, 1274, 1104, 994, 910, 652 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.89-5.79 (1H, m), 5.11 (1H, dq, *J* = 17.1, 1.5 Hz), 5.03 (1H, m), 5.01 (1H, m), 4.92 (1H, m), 4.00 (1H, d, *J* = 12.2 Hz), 3.97 (1H, d, *J* = 12.2 Hz), 3.70 (1H, dt, *J* = 10.9, 4.2 Hz), 3.25 (1H, m), 2.37-2.20 (2H, m), 2.24 (1H, d, *J* = 2.4 Hz), 1.95-1.62 (8H, m), 1.76 (3H, s); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 142.02, 136.83, 122.18, 115.70, 112.85, 77.91, 75.47, 74.98, 72.68, 41.72, 39.28, 37.01, 30.90, 28.50, 27.09, 21.07, 19.52; MS (ESI) calcd. for $C_{17}H_{23}NONa$ $[M+Na]^+$ 280.17, found 280.13. The ^{1}H and ^{13}C NMR spectra of **13** are shown in Figure S9 and S10.



To a solution of **13** (50 mg, 0.195 mmol) in benzene (7.8 mL, 0.025 M) was added Grubbs' 2nd generation catalyst **14** (24.9 mg, 0.0293 mmol), and the resulting solution was heated to reflux for 3.5 h. The mixture was then concentrated leaving a residue which was purified by silica-gel column chromatography to afford **16** (40.3 mg, 0.176 mmol, 90%) as a white solid. IR (film) ν 2952, 2863, 2825, 2225, 1435, 1176, 979 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.79 (1H, m), 5.69 (1H, m), 4.34 (1H, dt, *J* = 11.2, 4.0 Hz), 4.16 (1H, d, *J* = 18.0 Hz), 4.10 (1H, d, *J* = 18.0 Hz), 3.07 (1H, m), 2.33-2.14 (2H, m), 2.05-1.93 (2H, m), 1.88-1.71 (3H, m), 1.68 (3H, s), 1.67-1.50 (3H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 135.48, 133.00, 129.15, 128.14, 124.36, 75.77, 67.18, 46.77, 38.02, 31.54, 27.54, 24.89, 21.97, 21.90, 21.84; MS (ESI) calcd. for $C_{17}H_{19}NONa$ $[M+Na]^+$ 252.14, found 252.08. The ^{1}H and ^{13}C NMR spectra of **16** are shown in Figure S11 and S12.

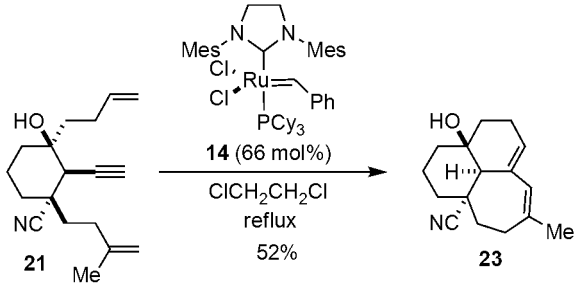


A solution of Grignard reagent **17** (28.4 mmol, 1.0 M in Et_2O) was added to a stirred solution of **3** (100 mg, 0.825 mmol, 0.5 M in Et_2O) at 0 °C. After being stirred at 0 °C for 4 h, saturated NH_4Cl was added. The resulting mixture was extracted with EtOAc, washed with brine, dried over Na_2SO_4, and concentrated. The resulting residue was purified by silica-gel column chromatography to afford **19** (82.6 mg, 0.467 mmol, 55%) as a pale yellow oil. IR (film) ν 3442, 3078, 2944, 2221, 1641, 1439, 1439 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.45 (1H, m), 5.88-5.78 (1H, m), 5.07 (1H, dq, *J* = 17.2, 2.0 Hz), 5.00 (1H, dq, *J* = 10.0, 2.0 Hz), 2.30-2.14 (4H, m), 1.81-1.61 (6H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 147.87, 137.88, 118.72, 114.89, 113.75, 69.06, 40.10, 33.73, 27.27, 26.69, 18.18; MS (ESI) calcd. for $C_{11}H_{15}NONa$ $[M+Na]^+$ 200.11, found 200.09. The ^{1}H and ^{13}C NMR spectra of **19** are shown in Figure S13 and S14.

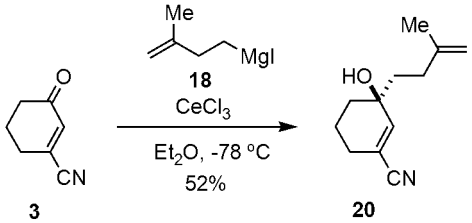


A solution of **5** (10.4 mmol, 0.5 M in THF) was added to a THF solution of **19** (610 mg, 3.45 mmol) at -78 °C. After being stirred at -78 °C for 10 min, **6** (4.3 mL, 34.5 mmol) was added. The mixture was maintained at -78 °C for 10 min, then warmed to room temperature and stirred for 40 h. The reaction mixture was quenched with saturated NH_4Cl at 0 °C, and the resulting mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated. The resulting residue was purified by silica-gel column chromatography to afford a desired dienyne **44** (840 mg, 2.45 mmol, 71%) as a white solid. The solution of **44** (346 mg, 1.01 mmol) in THF (5.0 mL) was treated with TBAF (1.11 mL, 1.0 M in THF, 1.11 mmol) at 0 °C. The mixture was stirred at room temperature for 15 min, then concentrated, and purified by silica-gel column chromatography to afford **21** (271 mg, 1.0 mmol, 99%) as a colorless oil. IR (film) ν 3492, 3293, 3077, 2941, 2870, 2233, 1642, 1452, 1378 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.90-5.80 (1H, m), 5.08 (1H, dq, *J* = 17.4, 1.6 Hz), 4.98 (1H, dq, *J* = 10.6, 1.5 Hz), 4.75 (2H, m), 2.96 (1H, d, *J* = 2.3 Hz), 2.43 (1H, d, *J* = 2.3 Hz), 2.28-1.90 (8H, m), 1.77 (3H, s), 1.82-1.47 (6H, m); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 144.46, 138.10, 123.32, 114.96, 110.67, 79.20, 76.40, 72.20, 45.23, 40.49,

39.24, 34.49, 32.97, 32.66, 31.90, 27.59, 22.58, 17.94; MS (ESI) calcd. for $C_{18}H_{25}NONa$ $[M+Na]^+$ 294.18, found 294.14. The ^1H and ^{13}C NMR spectra of **21** are shown in Figure S15 and S16.

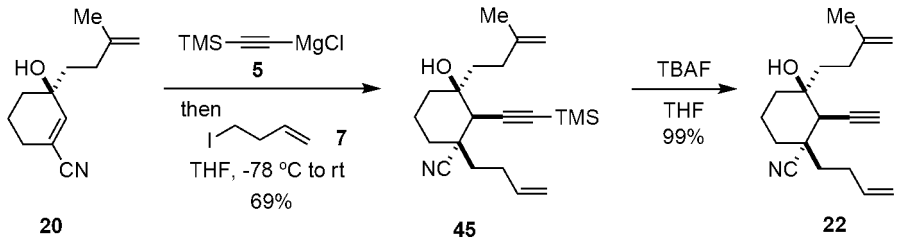


To a solution of **21** (20.0 mg, 0.0737 mmol) in 1,2-dichloroethane (3.69 mL, 0.02 M) was added catalyst **14** (41.3 mg, 0.0486 mmol), and the resulting solution was heated to reflux for 1 h. The mixture was then concentrated leaving a residue which was purified by silica-gel column chromatography to afford **23** (9.3 mg, 52%) as a white solid. IR (film) ν 3481, 2930, 2879, 2227, 1448, 1376 cm^{-1}; ^1H-NMR (400 MHz, $CDCl_3$) δ 5.99 (1H, m), 5.67 (1H, m), 2.81-2.73 (2H, m), 2.44-2.25 (4H, m), 2.12 (1H, m), 2.02 (1H, m), 1.99-1.80 (3H, m), 1.79 (3H, s), 1.70-1.50 (3H, m), 1.38 (1H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 135.65, 133.59, 128.22, 126.07, 125.37, 69.90, 50.28, 40.16, 38.09, 37.60, 37.17, 33.36, 28.52, 25.96, 22.01, 16.37; MS (ESI) calcd. for $C_{16}H_{21}NONa$ $[M+Na]^+$ 266.15, found 266.10. The ^1H and ^{13}C NMR spectra of **23** are shown in Figure S17 and S18.



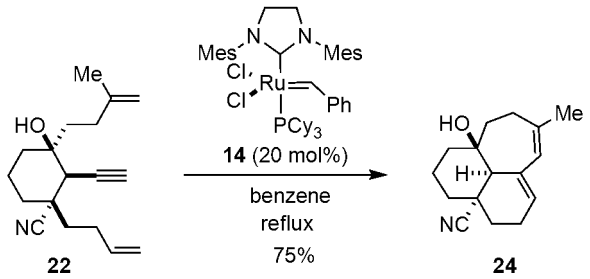
To a suspension of anhydrous $CeCl_3$ (690 mg, 2.80 mmol) in Et_2O (11 mL) was added **18** (1.53 mL of a 1.62 M THF solution, 2.48 mmol) at 0 °C, and the resulting suspension was stirred for 2 h at the same temperature. After cooling to -78 °C, **3** (150 mg, 1.24 mmol) in Et_2O (6.2 mL, 0.2 M) was added to this suspension, and the resulting mixture was stirred for 30 min at the same temperature. The reaction was quenched with 10% aqueous acetic acid, and the resulting mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated. The resulting residue was purified by silica-gel column chromatography to afford **20** (123 mg, 0.641 mmol, 52%) as a pale yellow oil. IR (film) ν 3442, 3075, 2944, 2222, 1649, 1448 cm^{-1}; ^1H-NMR (400 MHz, $CDCl_3$) δ 6.46 (1H, m), 4.75 (1H, m), 4.72 (1H, m),

2.32-2.04 (4H, m), 1.81-1.65 (6H, m), 1.75 (3H, s); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 147.71, 145.20, 118.78, 114.05, 110.23, 69.23, 39.07, 33.87, 31.06, 26.82, 22.49, 18.28; MS (ESI) calcd. for $C_{12}H_{17}NONa$ $[M+Na]^+$ 214.12, found 214.05. The ^{1}H and ^{13}C NMR spectra of **20** are shown in Figure S19 and S20.

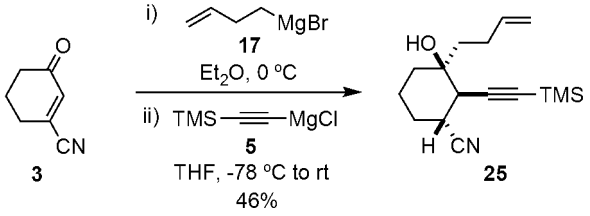


20 **45** **22**

To a solution of Grignard reagent **5** (2.1 mL of 1.0 M solution in THF, 2.1 mmol) was added to a solution of the alcohol **20** (100 mg, 0.524 mmol) in THF (1.0 mL) at -78 °C. After being stirred at -78 °C for 10 min, **7** (0.284 mL, 2.62 mmol) was added. The mixture was stirred at -78 °C for 10 min, then warmed to room temperature and stirred for 20 h. The reaction was quenched with saturated NH_4Cl at 0 °C, and the resulting mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated. The resulting residue was purified by silica-gel column chromatography to afford a desired dienyne **45** (124 mg, 0.362 mmol, 69%) as a colorless oil. The solution of **45** (330 mg, 0.959 mmol) in THF (4.8 mL) was treated with TBAF (1.15 mL, 1.0 M in THF, 1.15 mmol) at 0 °C. After being stirred for 15 min at room temperature, the mixture was concentrated and purified by silica-gel column chromatography to afford **22** (257 mg, 0.948 mmol, 99%) as a colorless oil. IR (film) ν 3488, 3289, 3076, 2945, 2866, 2233, 1643, 1376 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.89-5.79 (1H, m), 5.17 (1H, dq, *J* = 17.2, 1.6 Hz), 5.02 (1H, d, *J* = 10.0 Hz), 4.74 (2H, m), 2.95 (1H, d, *J* = 2.5 Hz), 2.43 (1H, d, *J* = 2.5 Hz), 2.33-1.94 (8H, m), 1.83-1.47 (6H, m), 1.76 (3H, s); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 145.35, 137.06, 123.31, 115.49, 110.18, 79.20, 76.31, 72.21, 45.25, 40.48, 38.40, 34.32, 33.20, 31.82, 31.27, 29.30, 22.57, 17.68; MS (ESI) calcd. for $C_{18}H_{25}NONa$ $[M+Na]^+$ 294.18, found 294.18. The ^{1}H and ^{13}C NMR spectra of **22** are shown in Figure S21 and S22.

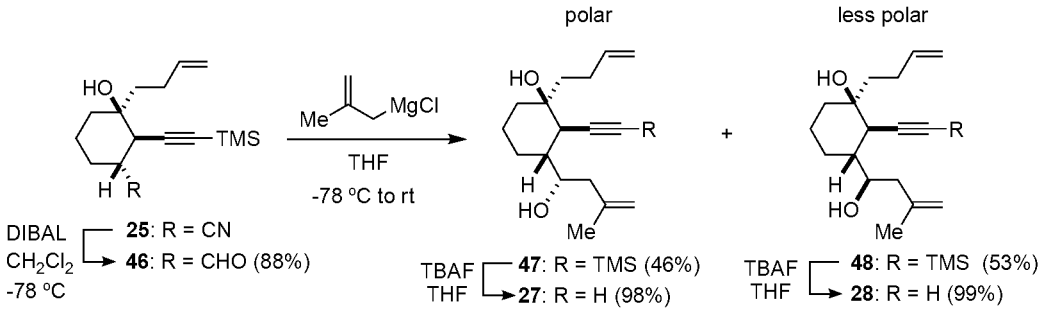


To a solution of **22** (35.0 mg, 0.129 mmol) in benzene (6.45 mL, 0.02 M) was added catalyst **14** (21.9 mg, 0.0258 mmol), and the resulting solution was heated to reflux for 3.5 h. The mixture was then concentrated leaving a residue which was purified by silica-gel column chromatography to afford **24** (23.4 mg, 0.0962 mmol, 75%) as a white solid. IR (film) ν 3485, 2925, 2229, 1446 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.98 (1H, m), 5.82 (1H, t, *J* = 3.6 Hz), 2.71 (1H, m), 2.68 (1H, m), 2.58-2.48 (1H, m), 2.37-2.26 (2H, m), 2.04-1.82 (4H, m), 1.78 (3H, s), 1.73 (1H, m), 1.69 (1H, m), 1.59-1.45 (4H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 140.01, 132.97, 128.62, 128.28, 125.10, 72.59, 46.59, 46.00, 37.52, 36.30, 35.56, 29.98, 26.59, 25.25, 23.40, 16.72; MS (ESI) calcd. for $C_{16}H_{21}NONa$ $[M+Na]^+$ 266.15, found 266.11. The ^{1}H and ^{13}C NMR spectra of **24** are shown in Figure S23 and S24.

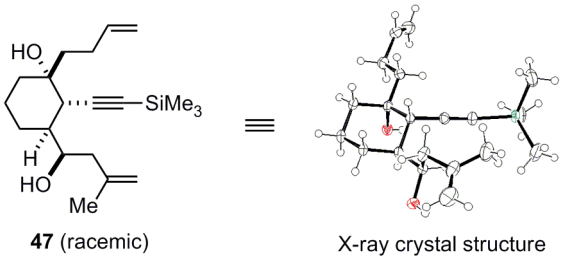


To a solution of Grignard reagent **17** (1.49 mmol, 1.0 M in Et_2O) was added to a solution of **3** (150 mg, 1.24 mmol) in Et_2O (6.2 mL) at 0 °C. The mixture was stirred for 1 h at the same temperature and the cooled to -78 °C. A solution of **5** (4.34 mmol, 4.34 mL of 1.0 M THF solution) was added, and the mixture was stirred at -78 °C for 30 min and then warmed to room temperature. After being stirred for 4 h at room temperature, the reaction was quenched with saturated NH_4Cl at 0 °C. The resulting mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated. The resulting residue was purified by silica-gel column chromatography to afford **25** (157 mg, 0.571 mmol, 46%) as a yellow oil. IR (film) ν 3492, 3078, 2954, 2866, 2243, 2174, 1641, 1449, 1251 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.87-5.77 (1H, m), 5.05 (1H, dq, *J* = 17.2. 1.6 Hz), 4.98 (1H, dq, *J* = 10.4, 1.4 Hz), 2.94 (1H, td, *J* = 11.5, 3.6 Hz), 2.97-2.90 (1H, m), 2.56 (1H, d, *J* = 11.5 Hz), 2.17-2.04 (3H, m), 1.89-1.78 (2H, m), 1.70-1.56 (3H, m), 1.47 (1H, m), 1.22 (1H, m), 0.18 (9H, s); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 138.11, 121.46,

114.81, 102.13, 92.03, 71.11, 43.40, 41.15, 32.87, 31.54, 29.28, 27.66, 19.65, -0.13; MS (ESI) calcd. for $C_{16}H_{25}NOSiNa$ $[M+Na]^+$ 298.16, found 298.12. The ^1H and ^{13}C NMR spectra of **25** are shown in Figure S25 and S26.



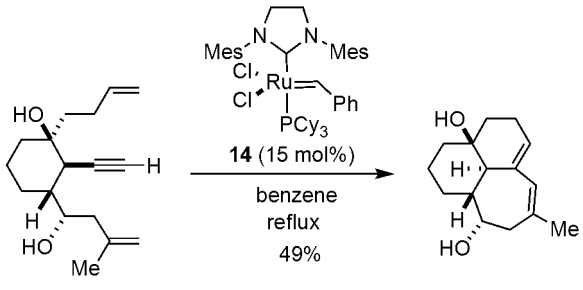
To a solution of **25** (499 mg, 1.81 mmol) in CH_2Cl_2 (36.2 mL) was added DIBAL (0.97 M *n*-hexane solution, 4.7 mL, 4.53 mmol) at -78 °C, and the mixture was stirred for 1 h at the same temperature. After additional treatment with DIBAL (0.97 M *n*-hexane solution, 1.8 mL, 1.75 mmol), the mixture was stirred for another 1 h. The reaction was quenched with EtOAc, treated with saturated NH_4Cl and Rochelle salt, and extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated. The resulting residue was purified by silica-gel column chromatography to afford an aldehyde **46** (443 mg, 1.59 mmol, 88%) as a colorless oil. To a solution of 2-methylallylmagnesium chloride in THF (0.71 M, 33.3 mL, 23.6 mmol) was added a solution of **46** (1.09 g, 3.94 mmol) in THF (19.7 mL, 0.2 M) at -78 °C. The mixture was stirred for 1 h at the same temperature, then warmed to 0 °C, and stirred for 1.5 h. The reaction was quenched at 0 °C with saturated NH_4Cl, and the resulting mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated. The resulting residue was purified by silica-gel column chromatography to afford **47** (603 mg, 1.80 mmol, 46%) and **48** (691 mg, 2.07 mmol, 53%) as a pair of diastereomers. The X-ray analysis of crystalline **47** determined its structure and stereochemistry of the diastereomeric hydroxyl group.



A solution of **47** (322 mg, 0.961 mmol) in THF (4.81 mL) was treated with TBAF (1.0 M THF solution, 1.11 mL, 1.11 mmol) at 0 °C. The mixture was stirred at room temperature for 15 min,

then concentrated, and purified by silica-gel column chromatography to afford **27** (245 mg, 0.937 mmol, 98%) as a white solid. **27**: IR (film) ν 3465, 3304, 3075, 2941, 2860, 1642, 1449 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.88-5.78 (1H, m), 5.03 (1H, dq, *J* = 17.2. 1.6 Hz), 4.95 (1H, dq, *J* = 10.0, 1.4 Hz), 4.87 (1H, m), 4.81 (1H, m), 4.14 (1H, m), 2.27 (1H, d, *J* = 2.0 Hz), 2.18-2.07 (6H, m), 1.93-1.80 (3H, m), 1.77 (3H, s), 1.74 (1H, d, *J* = 2.0 Hz), 1.66-1.56 (3H, m), 1.20 (1H, m), 0.91 (1H, m); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 143.15, 138.69, 114.39, 113.42, 82.57, 74.09, 72.15, 69.75, 42.05, 41.88, 41.36, 39.95, 34.31, 27.88, 24.71, 21.97, 20.53; MS (ESI) calcd. for $C_{17}H_{26}O_2Na$ $[M+Na]^+$ 285.1830, found 285.1459. The ^{1}H and ^{13}C NMR spectra of **27** are shown in Figure S27 and S28.

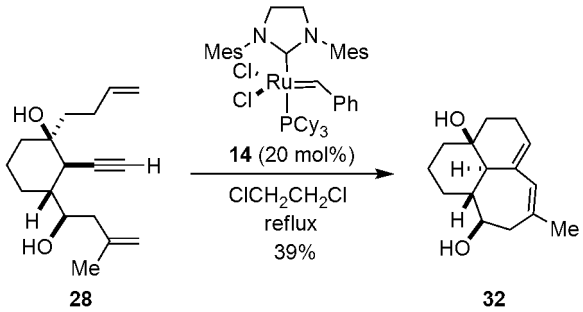
A solution of **48** (518 mg, 1.55 mmol) in THF (7.75 mL) was treated with TBAF (1.0 M THF solution, 1.78 mL, 1.78 mmol) at 0 °C. The mixture was stirred at room temperature for 15 min, then concentrated, and purified by silica-gel column chromatography to afford **28** (400 mg, 1.53 mmol, 99%) as a colorless oil. **28**: IR (film) ν 3465, 3304, 3076, 2940, 2865, 1642, 1448 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.88-5.78 (1H, m), 5.03 (1H, dq, *J* = 17.2, 1.6 Hz), 4.94 (1H, dq, J = 10.0, 1.4 Hz), 4.85 (1H, m), 4.79 (1H, m), 4.22 (1H, m), 2.52 (1H, dd, *J* = 11.4, 2.3 Hz), 2.24 (1H, dd, *J* = 13.2, 8.8 Hz), 2.23 (1H, d, *J* = 2.3 Hz), 2.16-2.07 (3H, m), 1.92-1.73 (2H, m), 1.77 (3H, s), 1.70-1.58 (5H, m), 1.26-1.11 (2H, m); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 142.89, 138.78, 114.34, 113.15, 83.58, 73.42, 72.22, 68.97, 43.70, 42.20, 42.04, 41.69, 33.86, 27.93, 22.88, 22.26, 20.21; MS (ESI) calcd. for $C_{17}H_{26}O_2Na$ $[M+Na]^+$ 285.18, found 285.15. The ^{1}H and ^{13}C NMR spectra of **28** are shown in Figure S29 and S30.



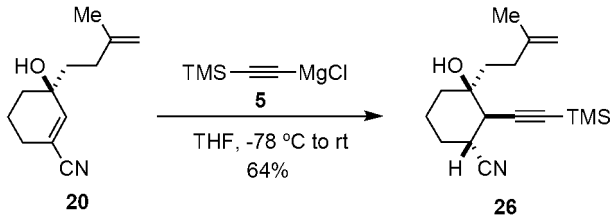
27 **31**

To a solution of **27** (50.0 mg, 0.191 mmol) in benzene (9.55 mL, 0.02 M) was added catalyst **14** (24.3 mg, 0.0286 mmol), and the resulting solution was heated to reflux for 1 h. The mixture was then concentrated, leaving a residue which was purified by silica-gel column chromatography to afford **31** (21.8 mg, 0.093 mmol, 49%) as a brown oil. IR (film) ν 3403, 2925, 1669, 1445, 1031, 915, 734 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 5.98 (1H, m), 5.78 (1H, d, *J* =3.8 Hz), 3.77 (1H, t, *J* = 3.5 Hz), 2.49-2.35 (4H, m), 2.23 (1H, m), 1.87-1.81 (2H, m), 1.78 (3H, s), 1.75-1.68 (2H, m),

1.67-1.58 (2H, m), 1.57-1.52 (2H, m), 1.34 (1H, m); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 136.05, 131.84, 131.18, 127.83, 74.53, 69.86, 44.21, 43.52, 40.69, 38.31, 35.92, 34.28, 28.10, 22.62, 20.71; MS (ESI) calcd. for $C_{15}H_{22}O_2Na$ $[M+Na]^+$ 257.15, found 257.13. The ^{1}H and ^{13}C NMR spectra of **31** are shown in Figure S31 and S32.

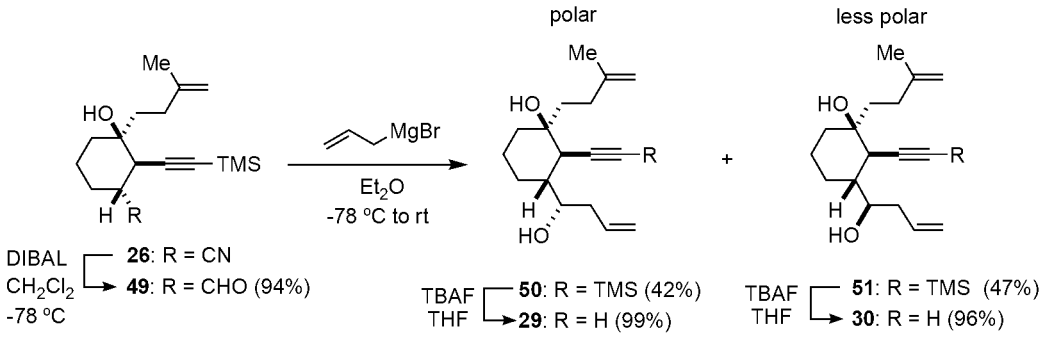


To a solution of **28** (20.0 mg, 0.0762 mmol) in 1,2-dichloroethane (3.81 mL) was added catalyst **14** (12.9 mg, 0.0152 mmol), and the resulting solution was heated to reflux for 8 h. The mixture was then concentrated, leaving a residue which was purified by silica-gel column chromatography to afford **32** (7.0 mg, 0.0299 mmol, 39%) as a brown oil. IR (film) ν 3409, 2925, 2845, 1446, 1040 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.93 (1H, m), 5.72 (1H, m), 3.62 (1H, m), 2.65 (1H, d, J = 15.6 Hz), 2.36 (1H, m), 2.23-2.08 (4H, m), 1.91-1.84 (1H, m), 1.83-1.72 (3H, m), 1.82 (3H, s), 1.65-1.50 (4H, m), 1.34 (1H, tdd, J = 13.0, 4.3, 1.7 Hz), 1.17 (1H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 137.36, 131.19, 129.65, 129.38, 76.23, 69.73, 47.96, 43.15, 39.09, 38.24, 35.75, 32.56, 27.40, 22.11, 20.44; MS (ESI) calcd. for $C_{15}H_{22}O_2Na$ $[M+Na]^+$ 257.15, found 257.12. The ^{1}H and ^{13}C NMR spectra of **32** are shown in Figure S33 and S34.



To a solution of **20** (200 mg, 1.05 mmol) in THF (2.1 mL) was added a solution of Grignard reagent **5** (4.20 mL, 1.0 M THF solution, 4.20 mol) at -78 °C. The mixture was stirred at -78 °C for 40 min and then warmed to room temperature. After being stirred for 20 h, the reaction was quenched at 0 °C with *t*-BuOH and saturated NH_4Cl. The mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated. The resulting residue was purified by silica-gel column chromatography to afford **26** (193 mg, 0.668 mmol, 64%) as a pale yellow oil. IR (film) ν 3490, 3074, 2951, 2866, 2243, 2175, 1649, 1448, 1251

cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.74 (1H, m), 4.72 (1H, m), 2.95 (1H, td, *J* = 12.0, 3.6 Hz), 2.58 (1H, d, *J* = 12.0 Hz), 2.15-1.98 (3H, m), 1.93-1.75 (2H, m), 1.75 (3H, s), 1.74-1.56 (4H, m), 1.48 (1H, m), 1.24 (1H, m), 0.19 (9H, s); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 145.37, 121.50, 110.18, 102.15, 91.98, 71.22, 43.30, 40.13, 32.87, 31.57, 31.53, 29.34, 22.50, 19.68, -0.11; MS (ESI) calcd. for $C_{17}H_{27}NOSiNa$ $[M+Na]^+$ 312.18, found 312.07. ^{1}H and ^{13}C NMR spectra of **26** are shown in Figure S35 and S36.



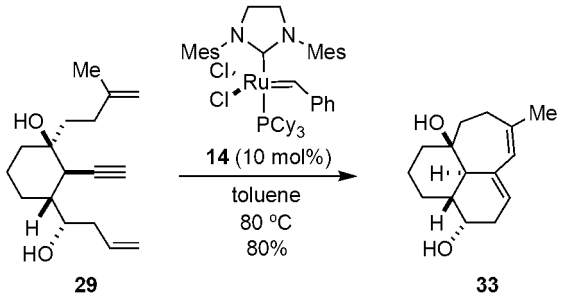
To a solution of **26** (366 mg, 1.26 mmol) in CH_2Cl_2 (12.6 mL) was added DIBAL (5.2 mL, 0.97 M *n*-hexane solution, 5.04 mmol) at -78 °C, and the mixture was stirred for 3 h at the same temperature. The reaction was quenched with EtOAc, then treated with saturated NH_4Cl and Rochelle salt, and extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated. The resulting residue was purified by silica-gel column chromatography to afford **49** (347 mg, 1.19 mmol, 94%) as a colorless oil.

To a solution of allylmagnesium bromide in Et_2O (1.03 M, 4.05 mL, 4.17 mmol) was added a solution of aldehyde **49** (122 mg, 0.417 mmol) in Et_2O (12.5 mL, 0.25 M) at -78 °C. The mixture was gradually warmed up to -25 °C over 10 h, and then quenched with saturated NH_4Cl. The resulting mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated. The resulting residue was purified by silica-gel column chromatography to afford **50** (polar diastereomer: 58.6 mg, 0.175 mmol, 42%) and **51** (less polar diastereomer: 65.9 mg, 0.197 mmol, 47%).

A solution of diol **50** (211 mg, 0.632 mmol) in THF (3.16 mL) was treated with TBAF (0.76 mL, 1.0 M THF solution, 0.76 mmol) at 0 °C. The mixture was stirred at room temperature for 15 min, then concentrated, and purified by silica-gel column chromatography to afford **29** (166 mg, 0.632 mmol, 99%) as a white solid. IR (film) ν 3354, 3309, 3072, 2929, 2858, 1645 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.94-5.83 (1H, m), 5.20-5.13 (2H, m), 4.72 (2H, m), 4.03 (1H, m), 2.28 (1H, d, *J* = 2.0 Hz), 2.27 (1H, m), 2.20-2.00 (5H, m), 1.97-1.81 (3H, m), 1.75 (3H, s), 1.73-1.59 (3H, m), 1.23 (1H, m), 0.96 (1H, m); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 145.87, 135.81, 117.75, 109.67, 82.83, 74.18,

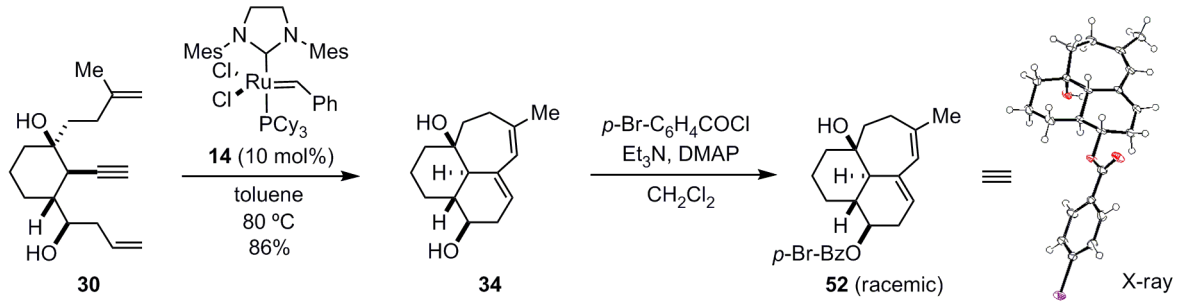
72.31, 72.20, 42.56, 41.81, 40.22, 36.32, 34.15, 31.63, 25.12, 22.62, 20.47; MS (ESI) calcd. for $C_{17}H_{26}O_2Na$ $[M+Na]^+$ 285.1830, found 285.1253. ^1H and ^{13}C NMR spectra of **29** are shown in Figure S35 and S36.

A solution of diol **51** (31.1 mg, 0.0929 mmol) in THF (1.0 mL) was treated with TBAF (0.11 mL, 1.0 M THF solution, 0.11 mmol) at 0 °C. The mixture was stirred at room temperature for 15 min, then concentrated, and purified by silica-gel column chromatography to afford **30** (23.3 mg, 0.0889 mmol, 96%) as a colorless oil. IR (film) ν 3458, 3303, 3075, 2942, 2863, 2108, 1644, 1447 cm^{-1}; ^1H-NMR (400 MHz, $CDCl_3$) δ 5.90-5.80 (1H, m), 5.18-5.12 (2H, m), 4.71 (2H, m), 4.11 (1H, m), 2.53 (1H, dd, *J* = 11.5, 2.4 Hz), 2.34-2.19 (3H, m), 2.14-2.03 (2H, m), 1.94 (1H, m), 1.84-1.53 (5H, m), 1.75 (3H, s), 1.67 (1H, d, *J* = 2.4 Hz), 1.28-1.11 (2H, m); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 145.91, 135.40, 117.59, 109.57, 83.47, 73.48, 72.24, 71.05, 41.91, 41.85, 40.53, 39.72, 33.75, 31.62, 22.87, 22.62, 20.16; MS (ESI) calcd. for $C_{17}H_{26}O_2Na$ $[M+Na]^+$ 285.18, found 285.12. ^1H and ^{13}C NMR spectra of **30** are shown in Figure S39 and S40.



29 **33**

To a solution of **29** (27.6 mg, 0.105 mmol) in toluene (4.20 mL, 0.025 M) was added catalyst **14** (8.91 mg, 0.0105 mmol), and the resulting solution was heated to 80 °C for 30 min. The mixture was then concentrated, leaving a residue which was purified by silica-gel column chromatography to afford **33** (19.6 mg, 80%) as a brown oil. IR (film) ν 3399, 2919, 1444, 1068 cm^{-1}; ^1H-NMR (400 MHz, $CDCl_3$) δ 5.85 (1H, m), 5.62 (1H, m), 3.84 (1H, m), 2.50 (1H, d, *J* = 18.0 Hz), 2.39 (1H, m), 2.32-2.10 (3H, m), 1.93-1.65 (4H, m), 1.79 (3H, s), 1.64-1.35 (5H, m); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 136.11, 135.78, 129.41, 129.32, 72.38, 69.71, 46.43, 42.77, 41.54, 39.64, 35.19, 30.01, 29.84, 27.47, 21.67; MS (ESI) calcd. for $C_{15}H_{22}O_2Na$ $[M+Na]^+$ 257.15, found 257.09. ^1H and ^{13}C NMR spectra of **33** are shown in Figure S41 and S42.



To a solution of **30** (30.0 mg, 0.114 mmol) in toluene (4.56 mL, 0.025 M) was added catalyst **14** (9.68 mg, 0.0114 mmol), and the resulting solution was heated to 80 °C for 1 h. The mixture was then concentrated, leaving a residue which was purified by silica-gel column chromatography to afford **34** (22.9 mg, 0.0977 mmol, 86%) as a brown oil. IR (film) ν 3399, 2924, 1443, 1064 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.83 (1H, m), 5.64 (1H, m), 3.54 (1H, m), 2.53 (1H, dt, J = 16.8, 5.6 Hz), 2.32-2.06 (5H, m), 1.86-1.61 (6H, m), 1.78 (3H, s), 1.45 (1H, m), 0.93 (1H, m); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 136.06, 135.68, 130.64, 129.01, 71.81, 71.53, 52.61, 42.70, 42.41, 41.32, 36.08, 29.84, 27.62, 27.39, 21.12; MS (ESI) calcd. for $C_{15}H_{22}O_2Na$ $[M+Na]^+$ 257.15, found 257.09. ^{1}H and ^{13}C NMR spectra of **34** are shown in Figure S43 and S44. The structure of **34** was unambiguously determined by X-ray analysis of crystalline *p*-bromobenzoate ester **52**.

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2) Nicolaou, K. C.; Gray, D. L. F.; Montagnon, T.; Harrison, S. T. *Angew. Chem. Int. Ed.* **2002**, *41*, 996-1000.
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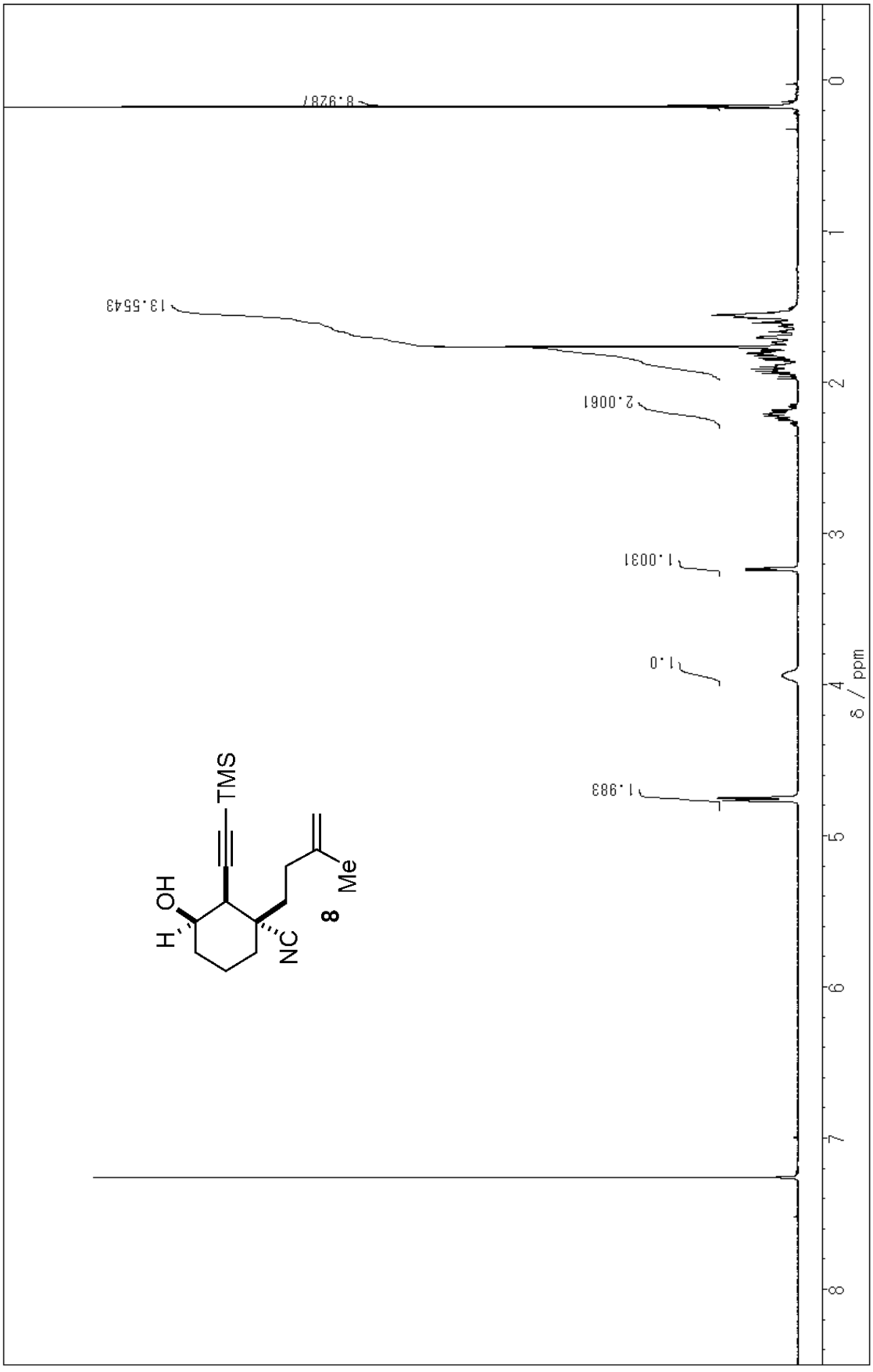

Figure S1. A ^{1}H-NMR spectrum of **8** in $CDCl_3$.

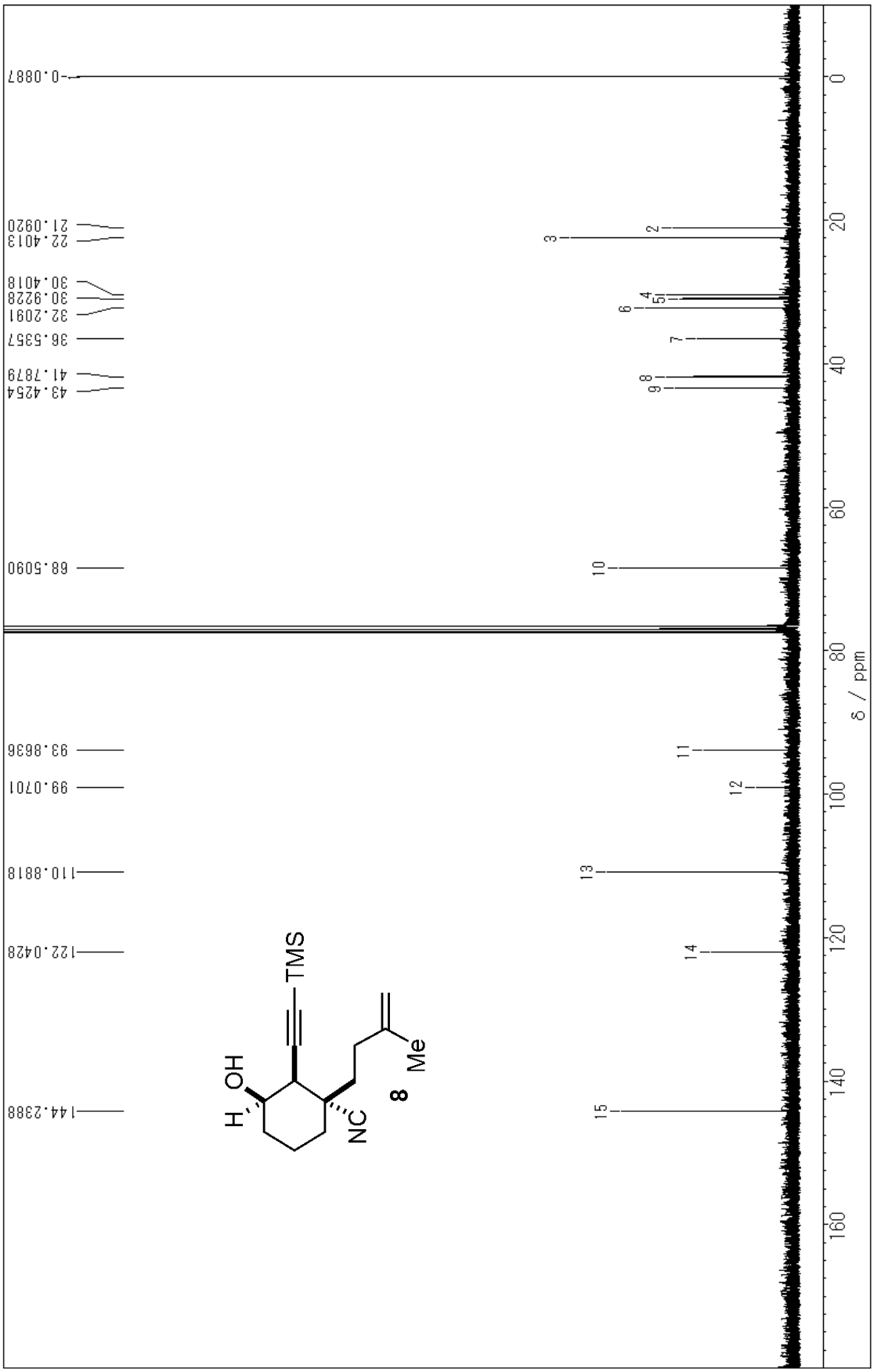

Figure S2. A ^{13}C-NMR spectrum of **8** in $CDCl_3$.

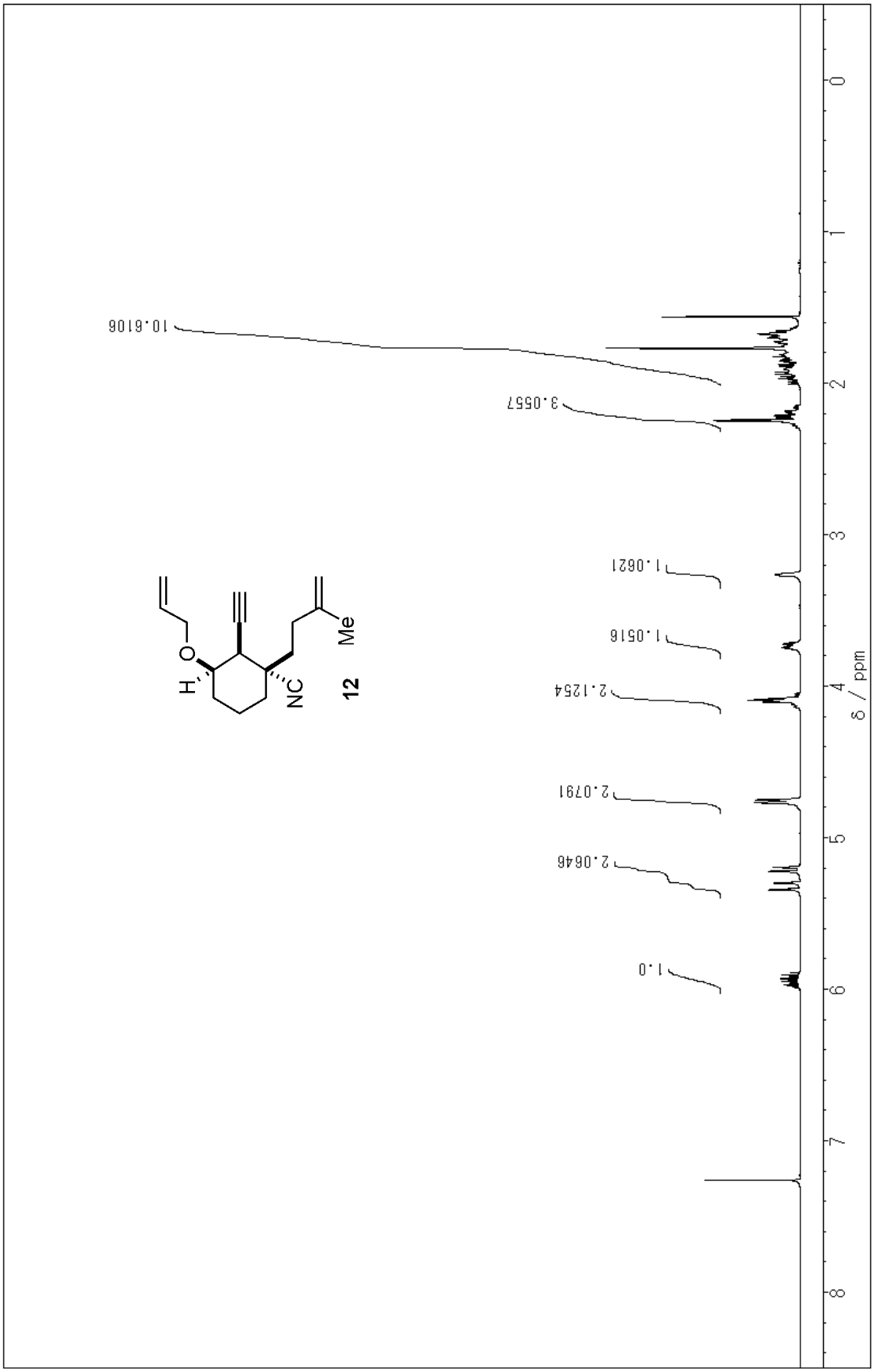

Figure S3. A ^{1}H-NMR spectrum of **12** in $CDCl_3$.

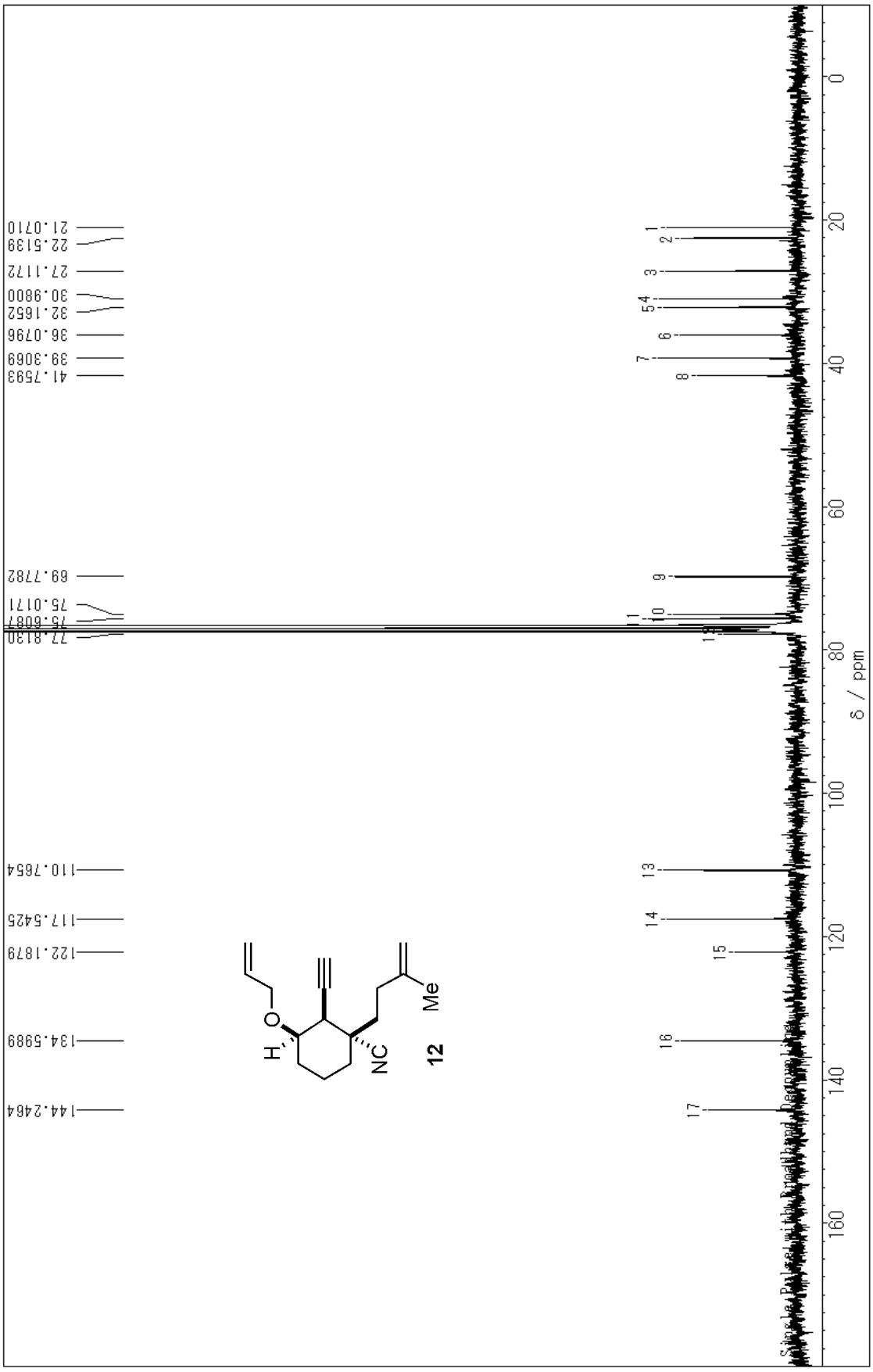

Figure S4. A ^{13}C-NMR spectrum of **12** in $CDCl_3$.

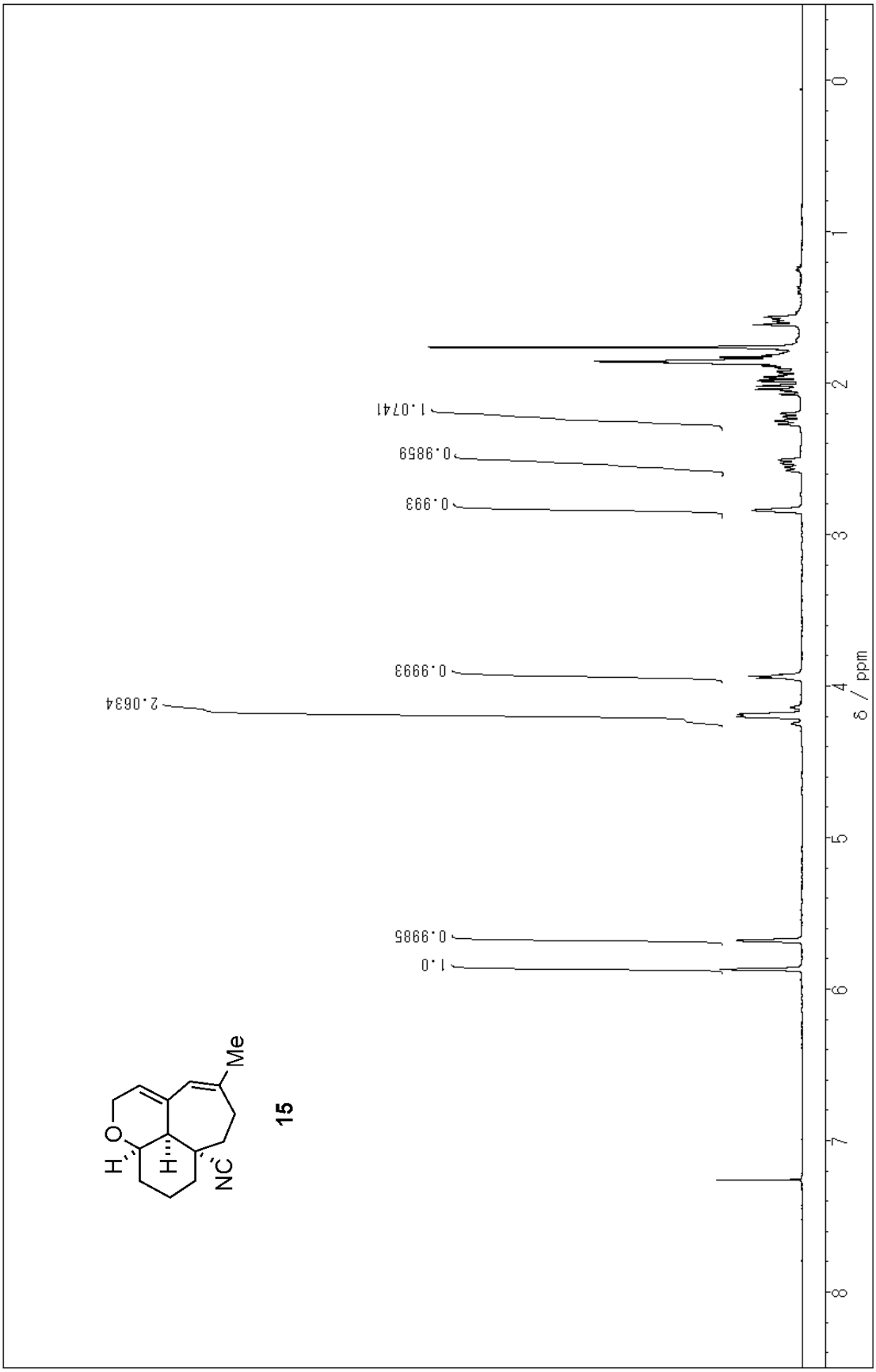

Figure S5. A ^{1}H-NMR spectrum of **15** in $CDCl_3$.

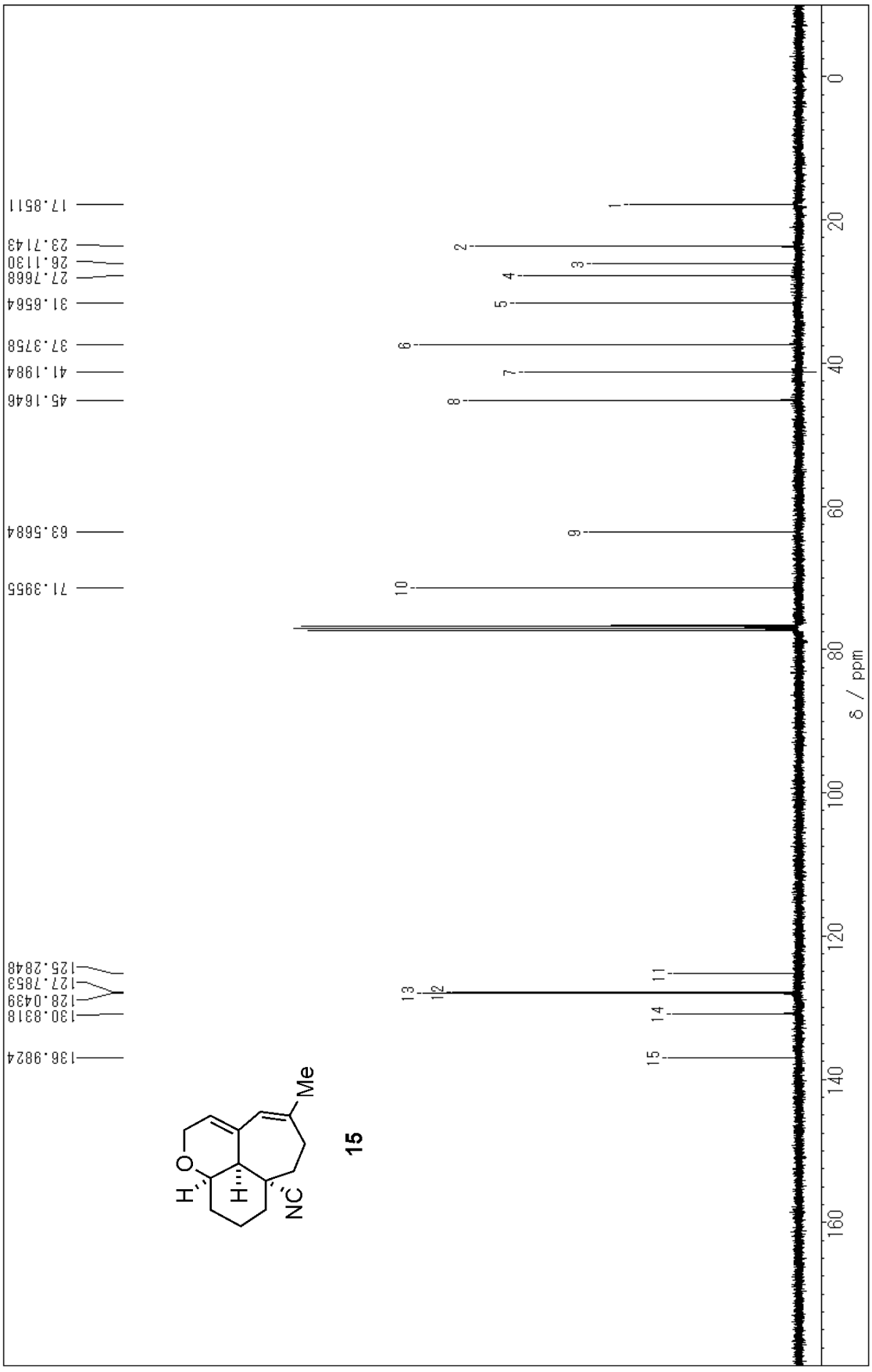

Figure S6. A ^{13}C-NMR spectrum of **15** in $CDCl_3$.

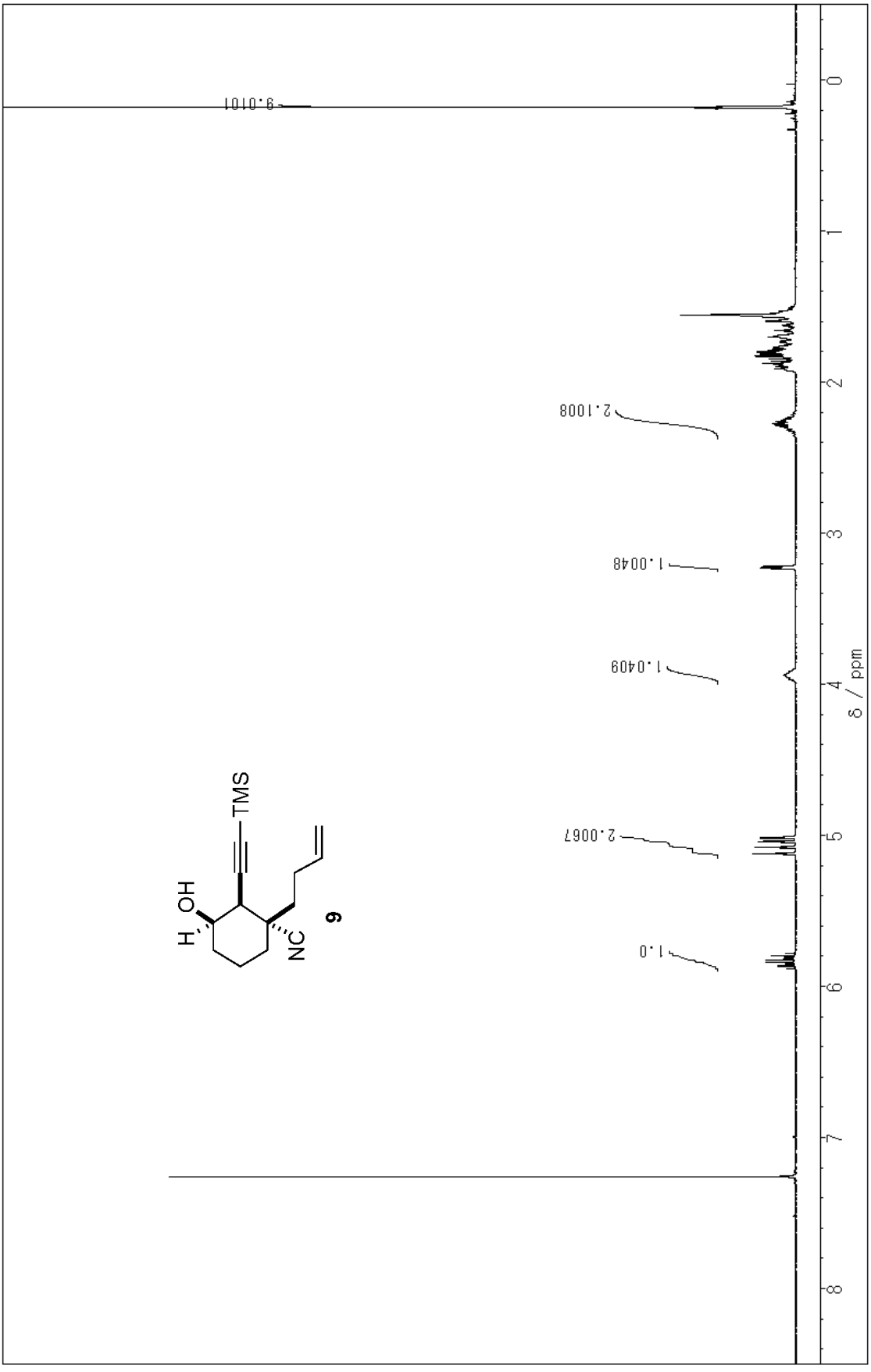

Figure S7. A ^{1}H-NMR spectrum of **9** in $CDCl_3$.

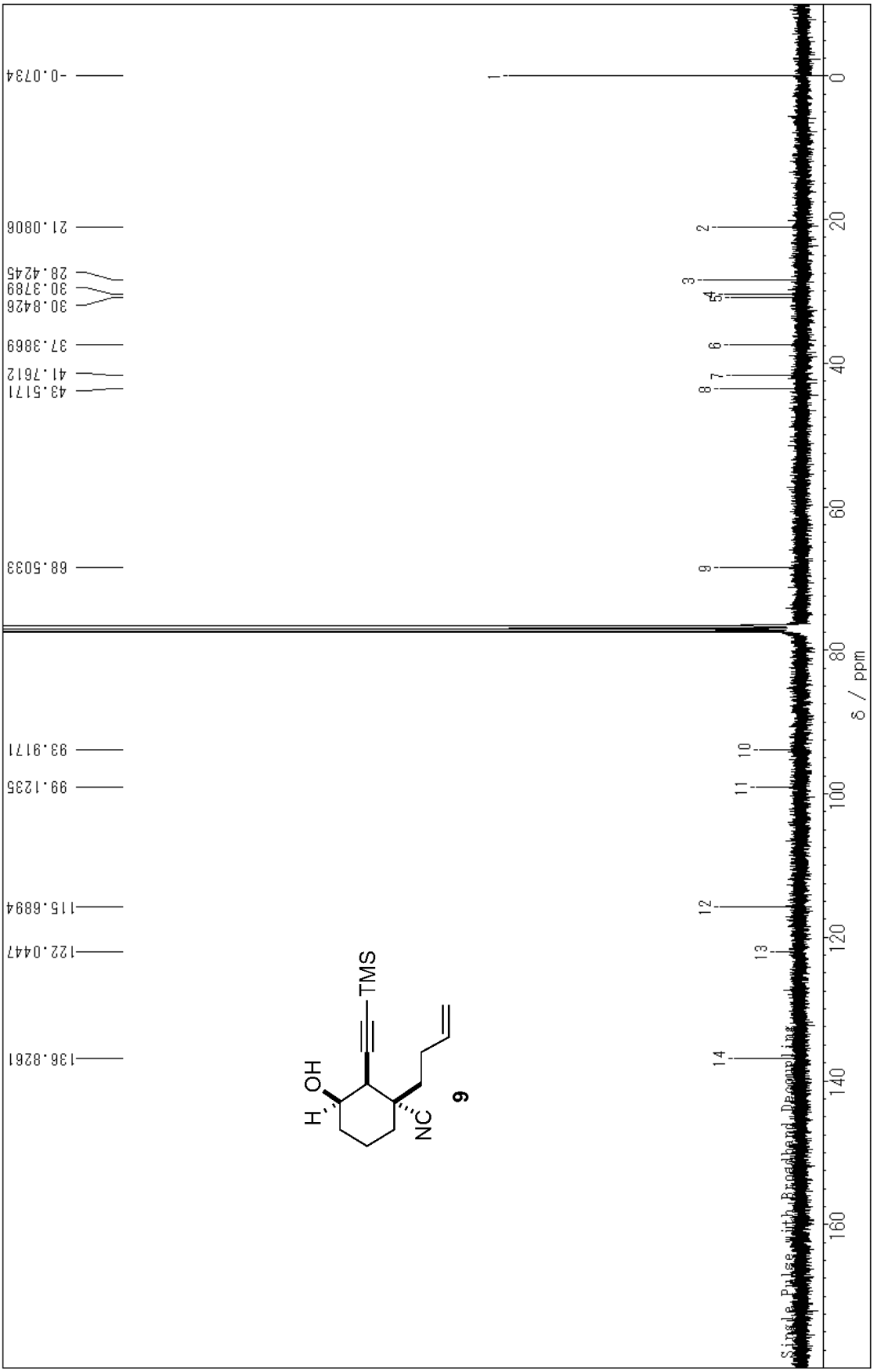

Figure S8. A ^{13}C-NMR spectrum of **9** in $CDCl_3$.

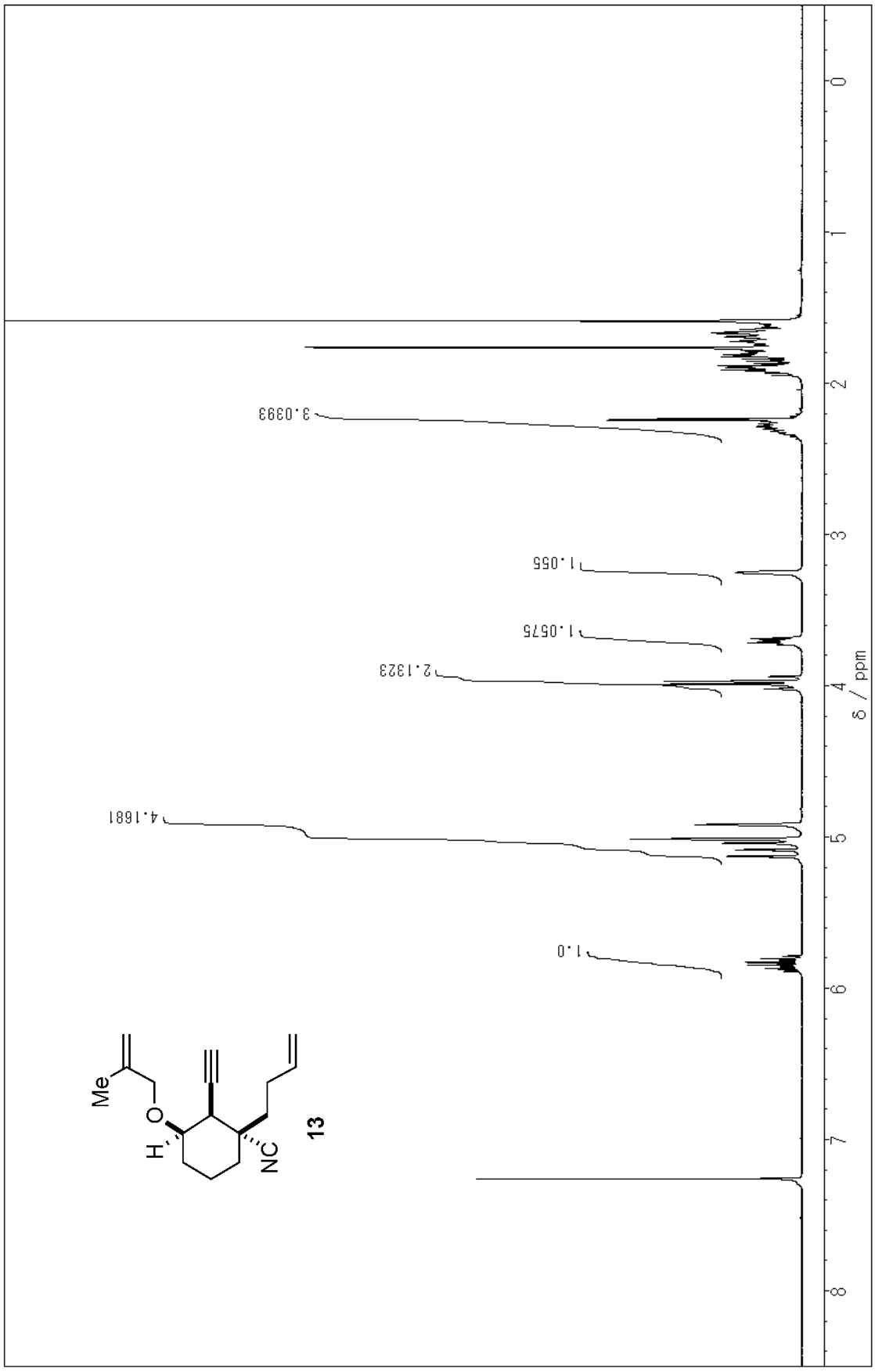

Figure S9. A ^{1}H-NMR spectrum of **13** in $CDCl_3$.

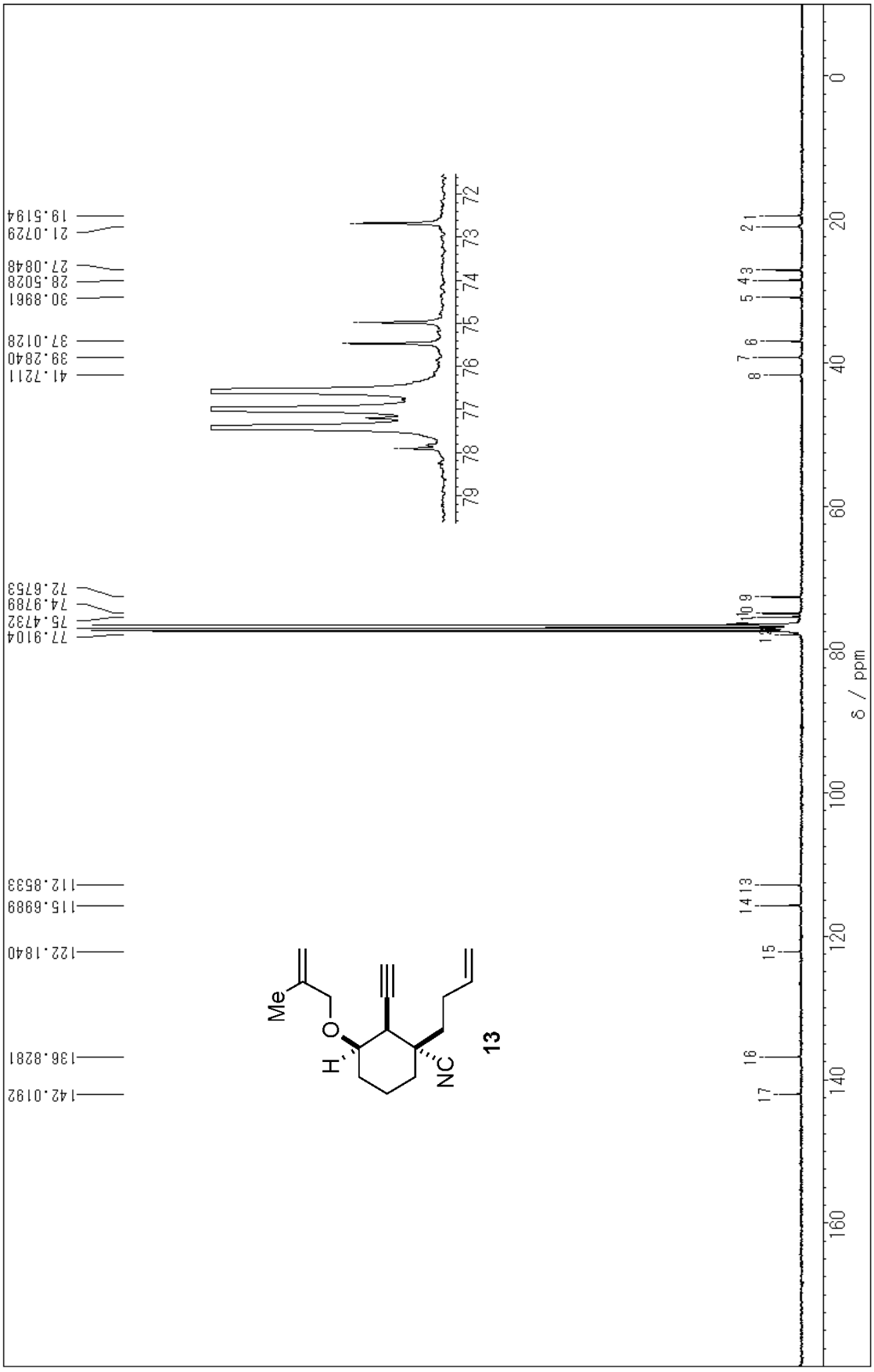

Figure S10. A ^{13}C-NMR spectrum of **13** in $CDCl_3$.

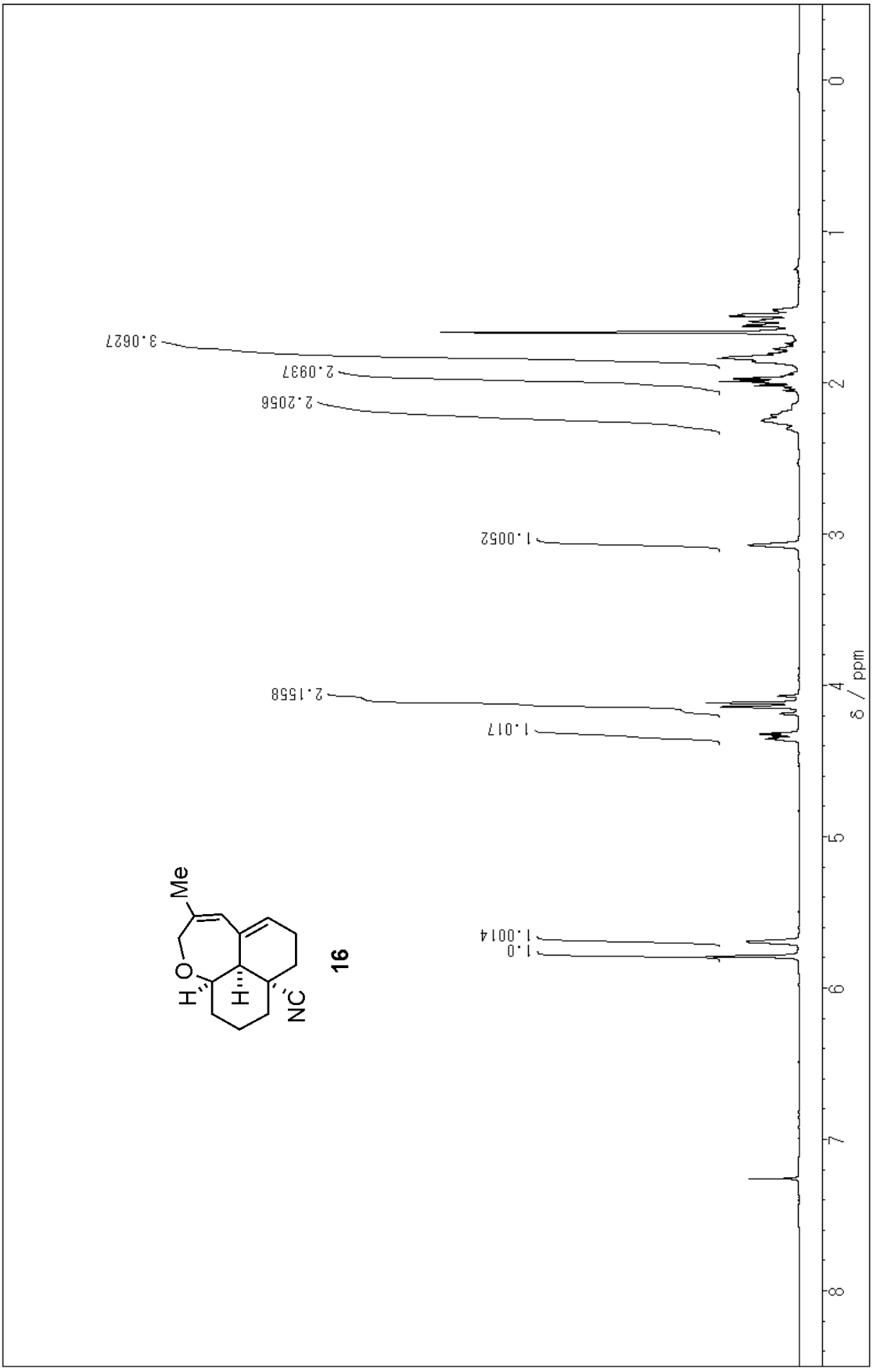

Figure S11. A ^{1}H-NMR spectrum of **16** in $CDCl_3$.

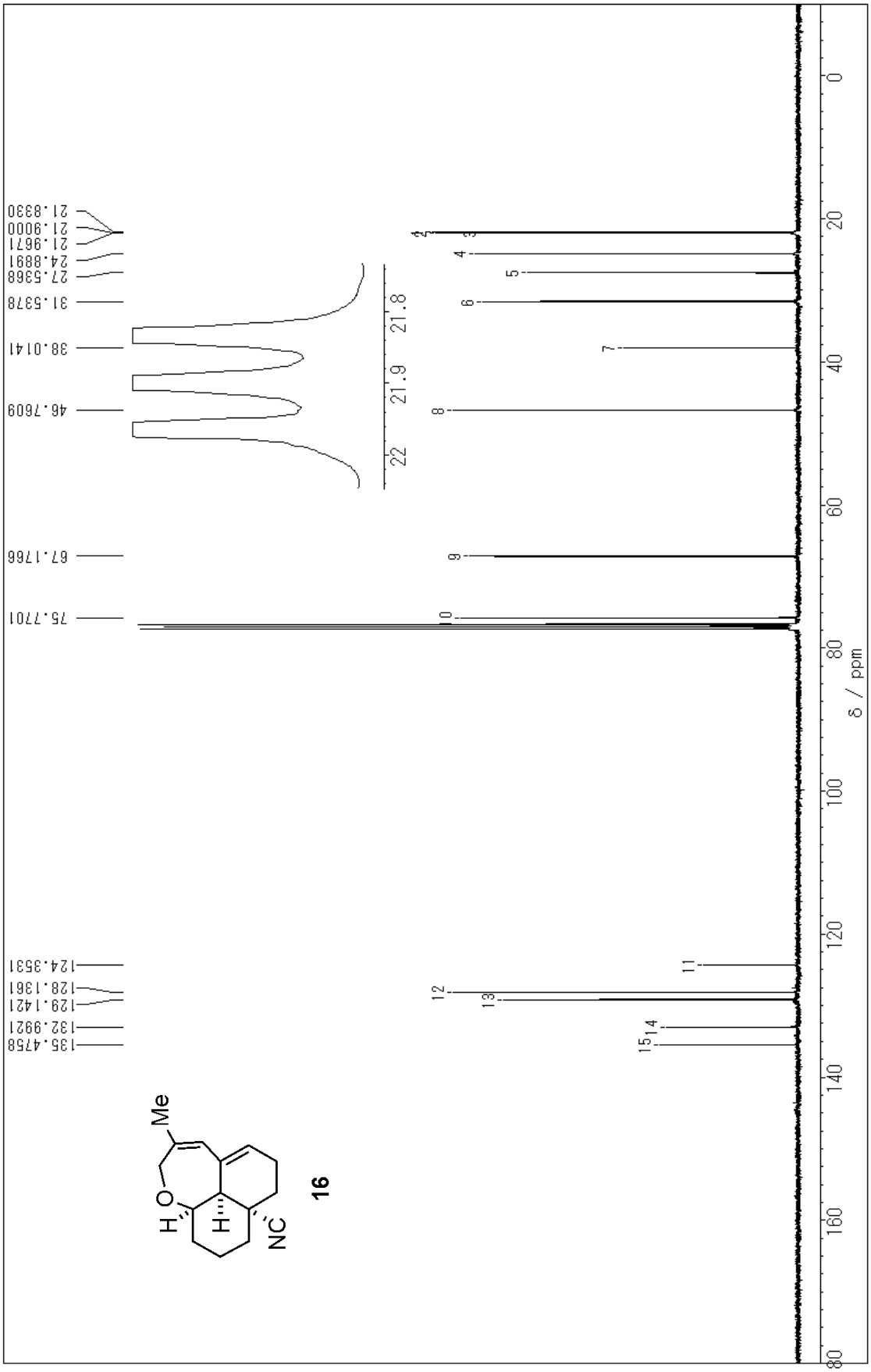

Figure S12. A ^{13}C-NMR spectrum of **16** in $CDCl_3$.

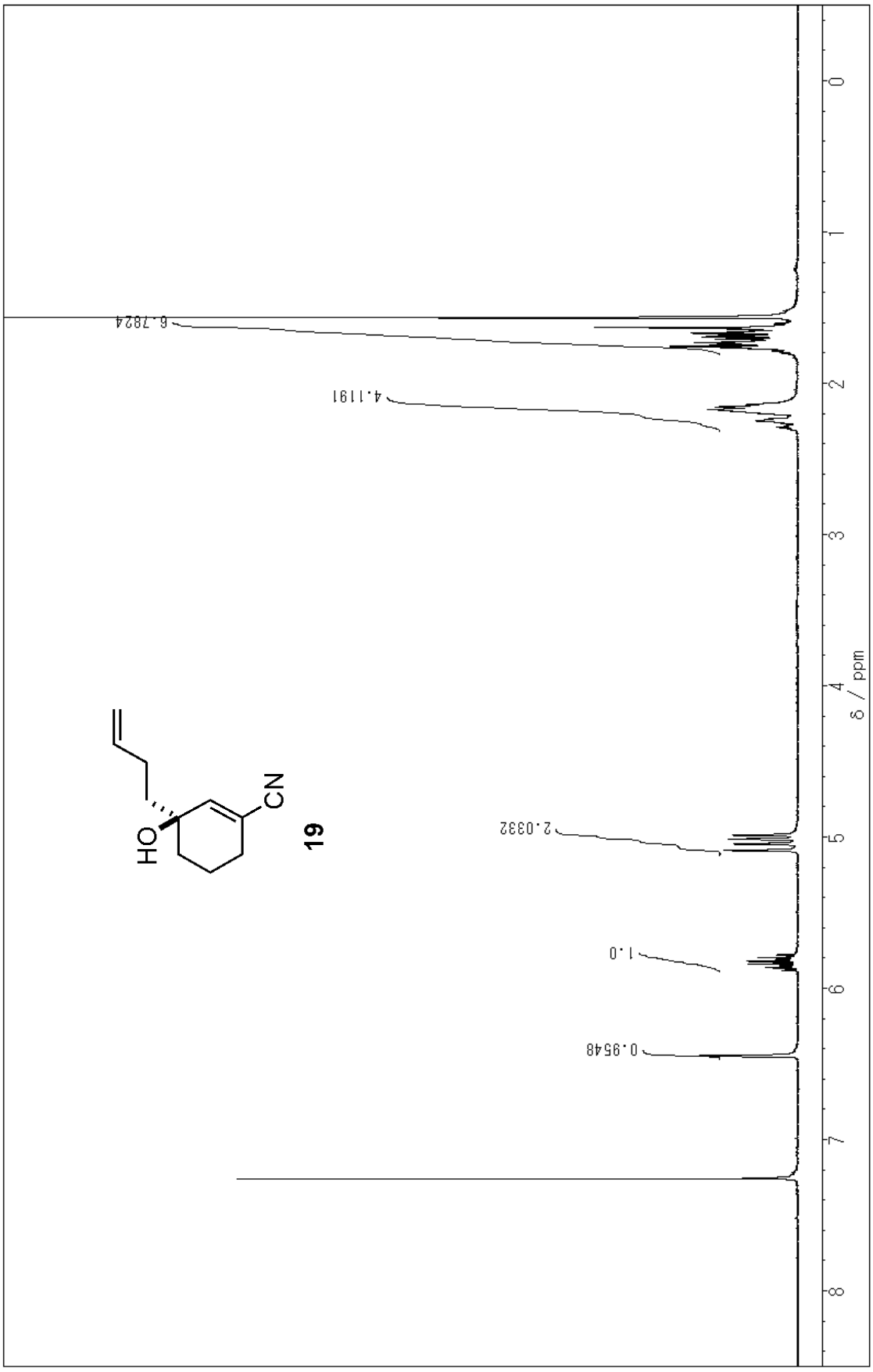

Figure S13. A ^{1}H-NMR spectrum of **19** in $CDCl_3$.

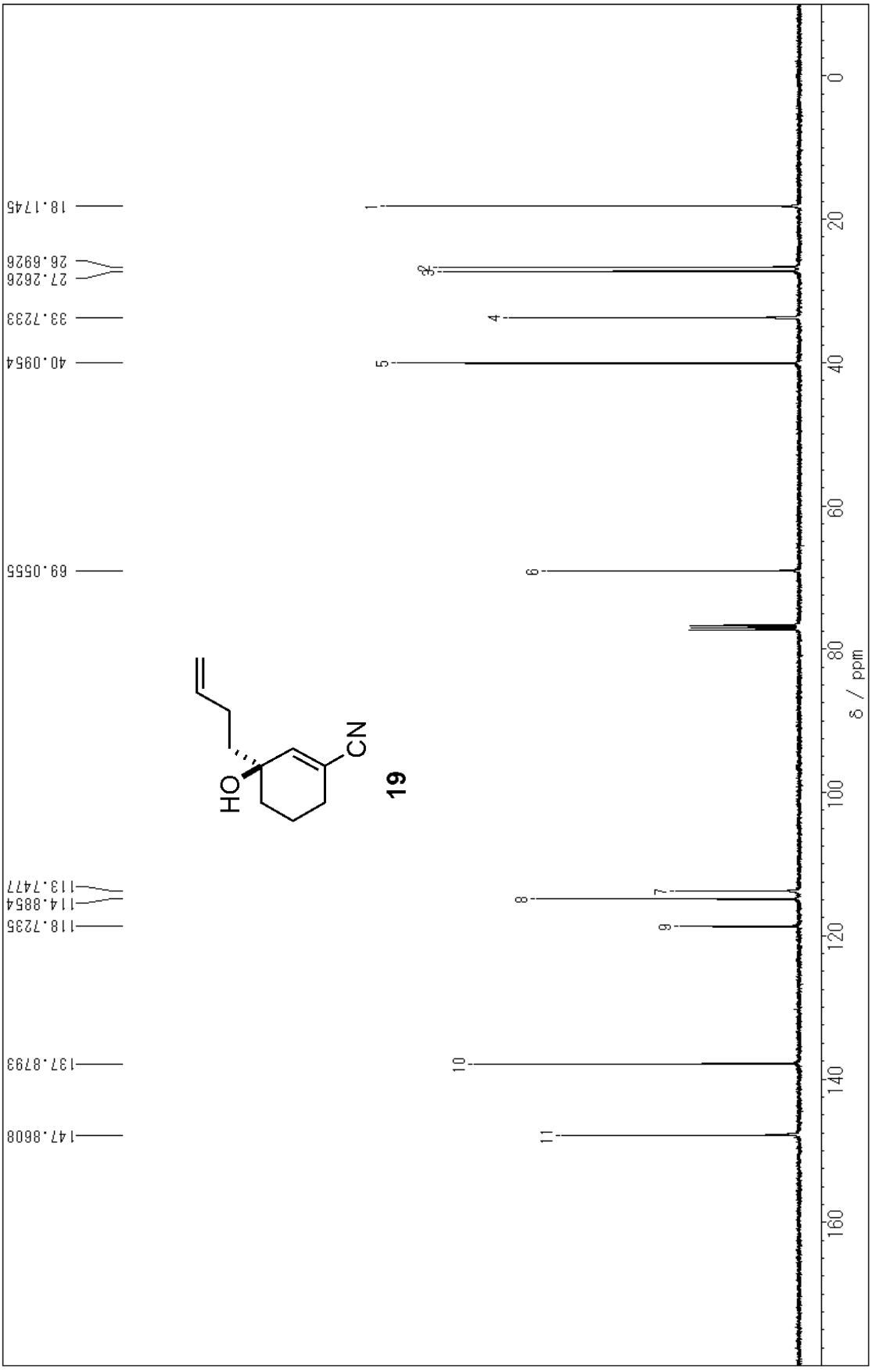

Figure S14. A ^{13}C-NMR spectrum of **19** in $CDCl_3$.

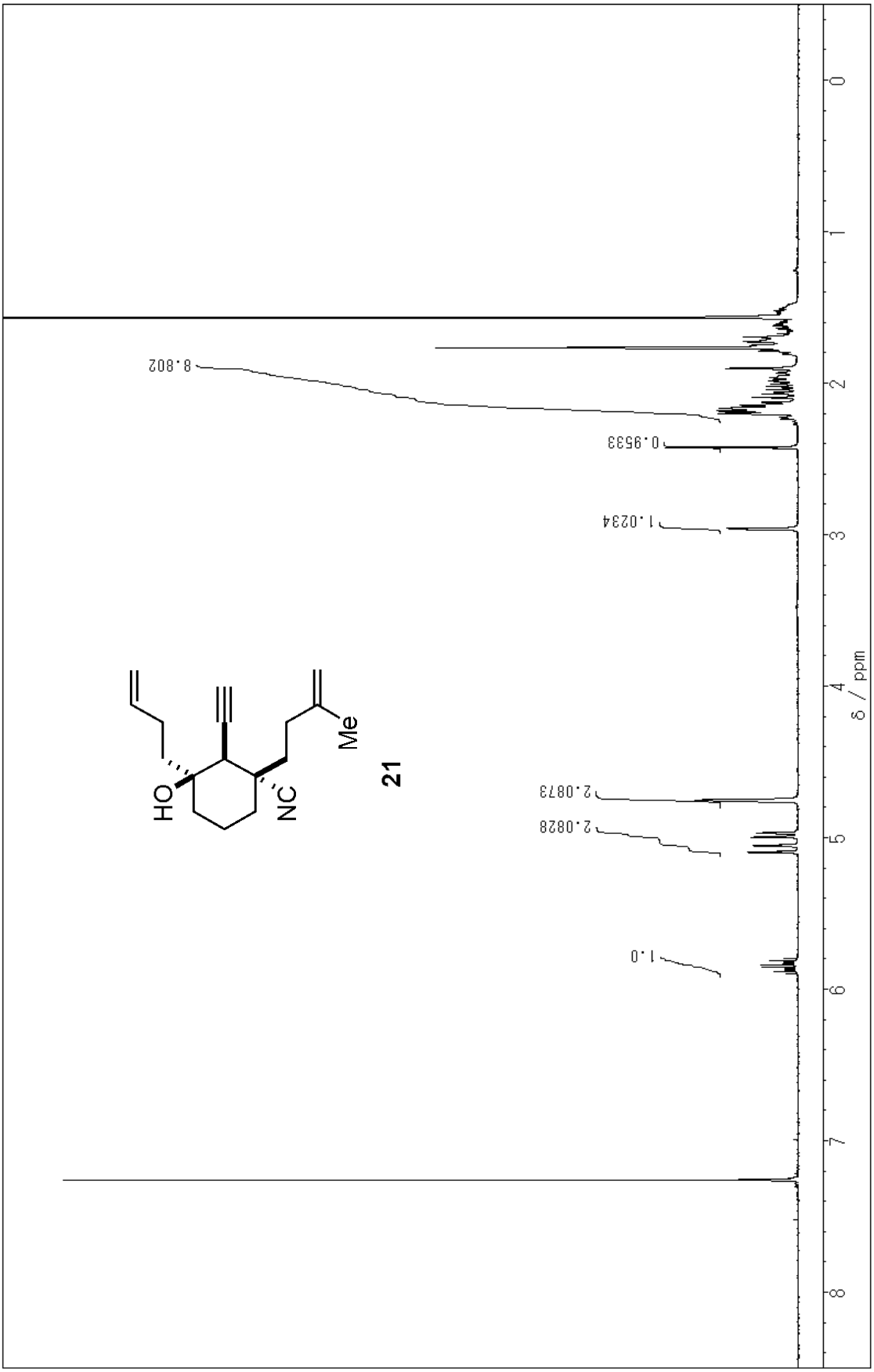

Figure S15. A ^{1}H-NMR spectrum of **21** in $CDCl_3$.

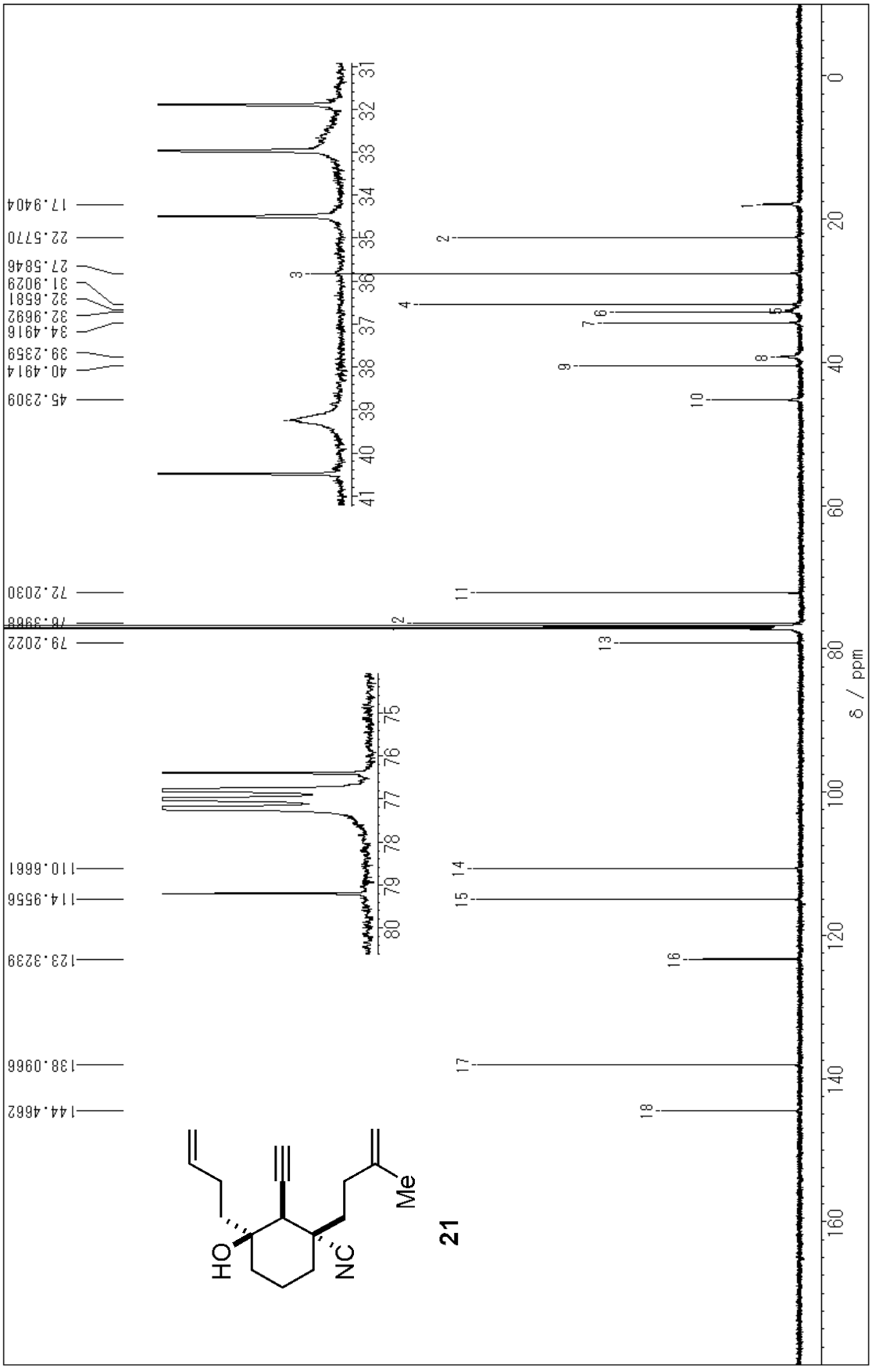

Figure S16. A ^{13}C-NMR spectrum of **21** in $CDCl_3$.

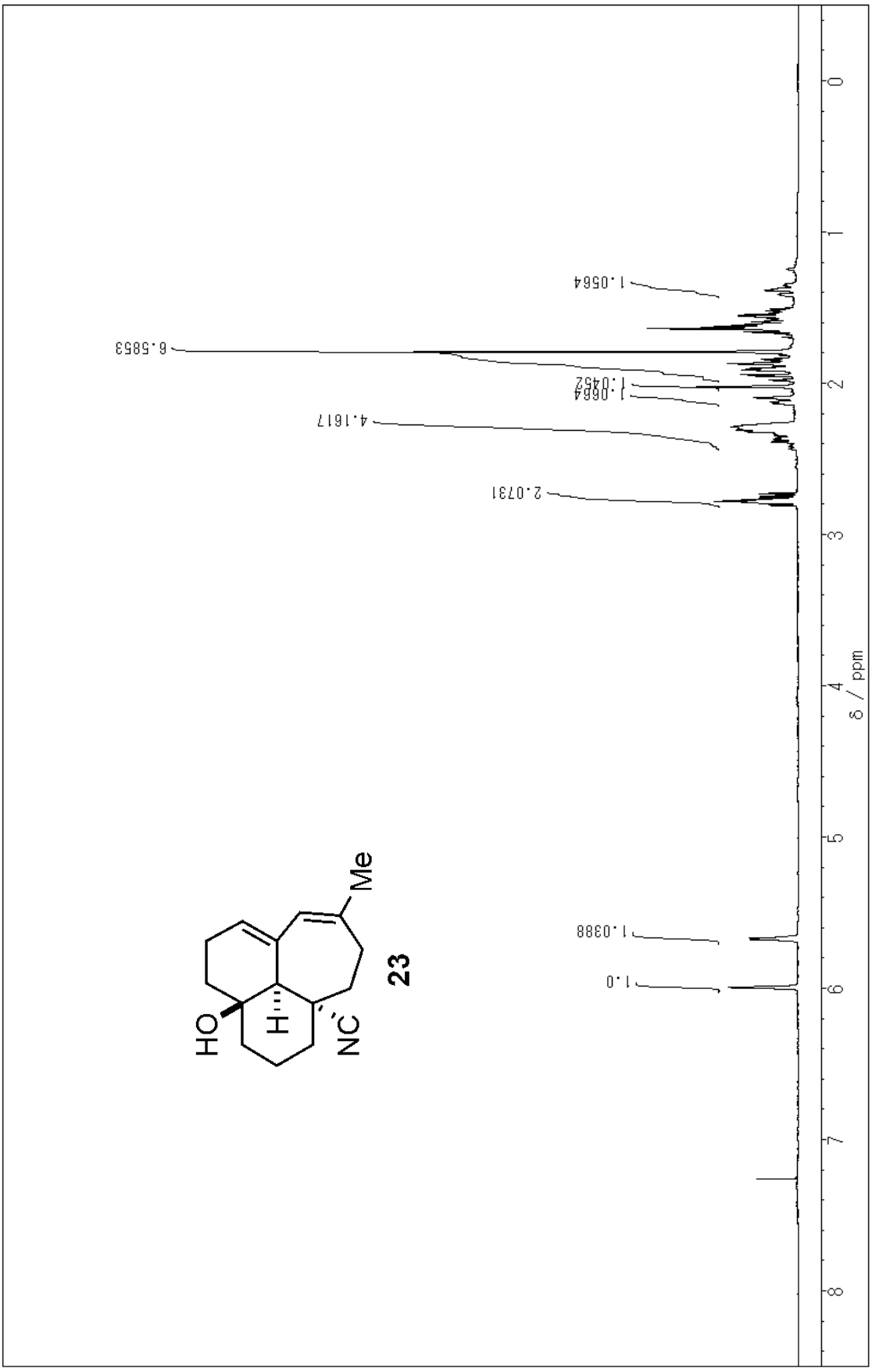

Figure S17. A ^{1}H-NMR spectrum of **23** in $CDCl_3$.

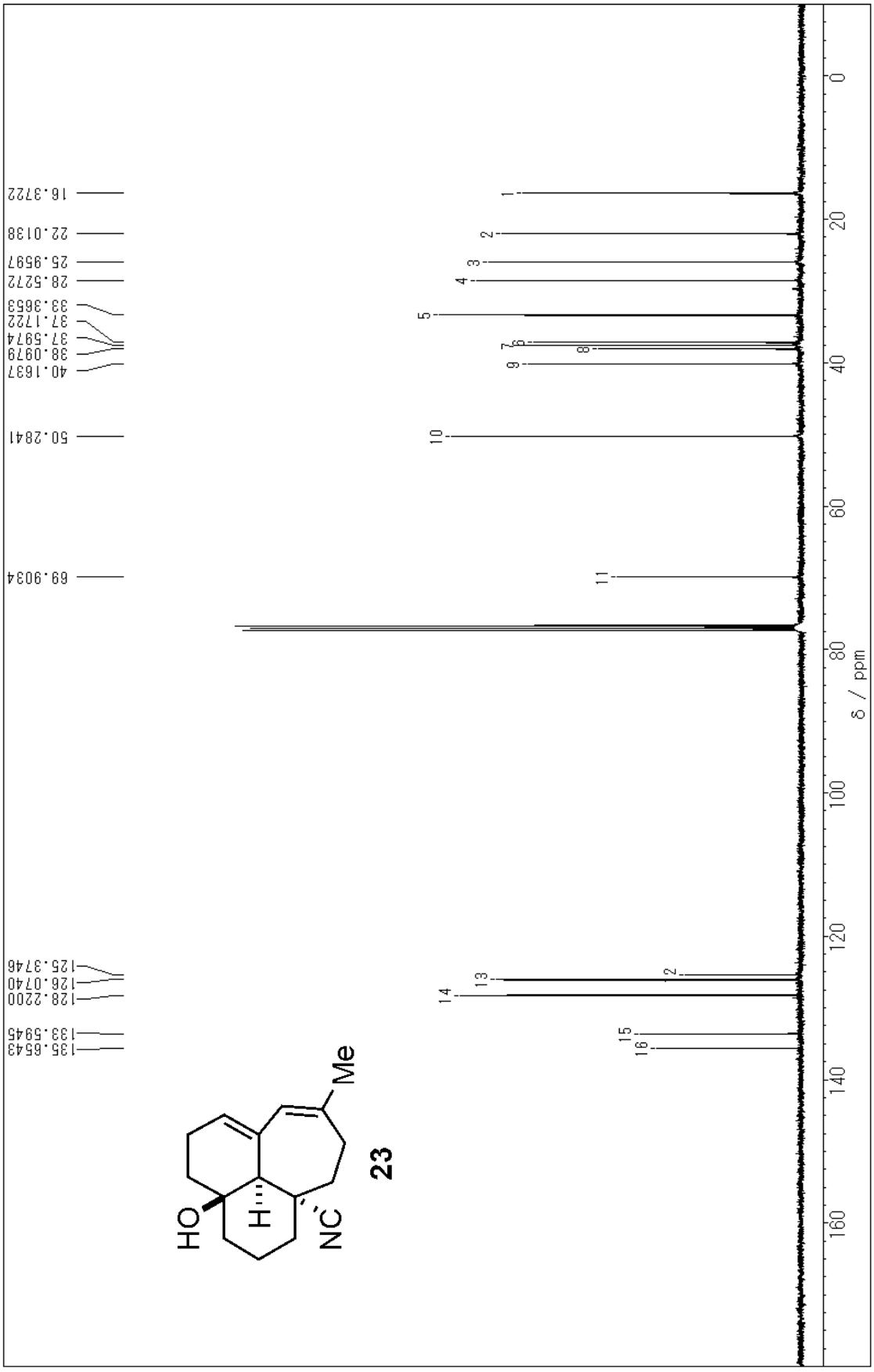

Figure S18. A ^{13}C-NMR spectrum of **23** in $CDCl_3$.

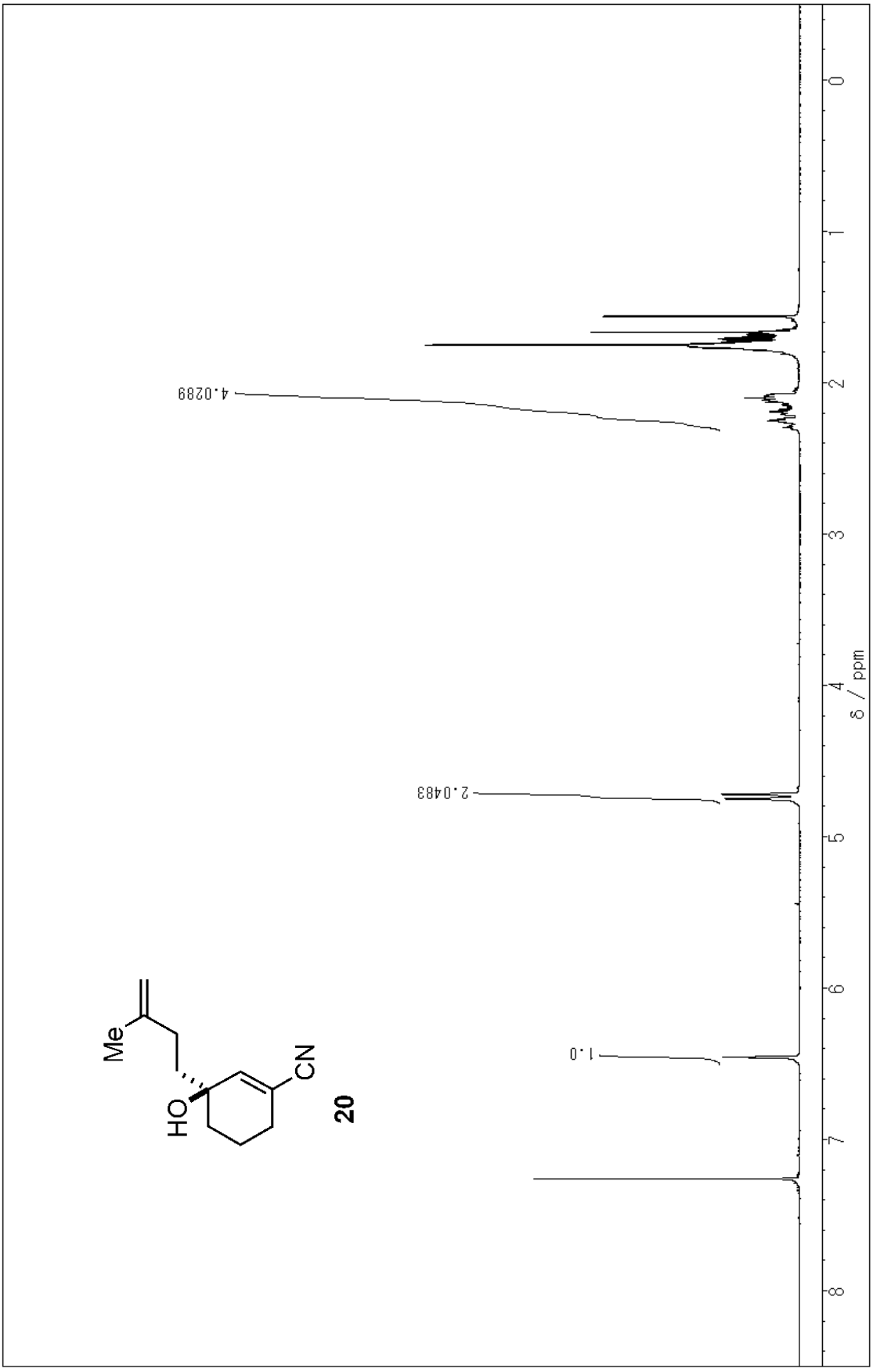

Figure S19. A ^{1}H-NMR spectrum of **20** in $CDCl_3$.

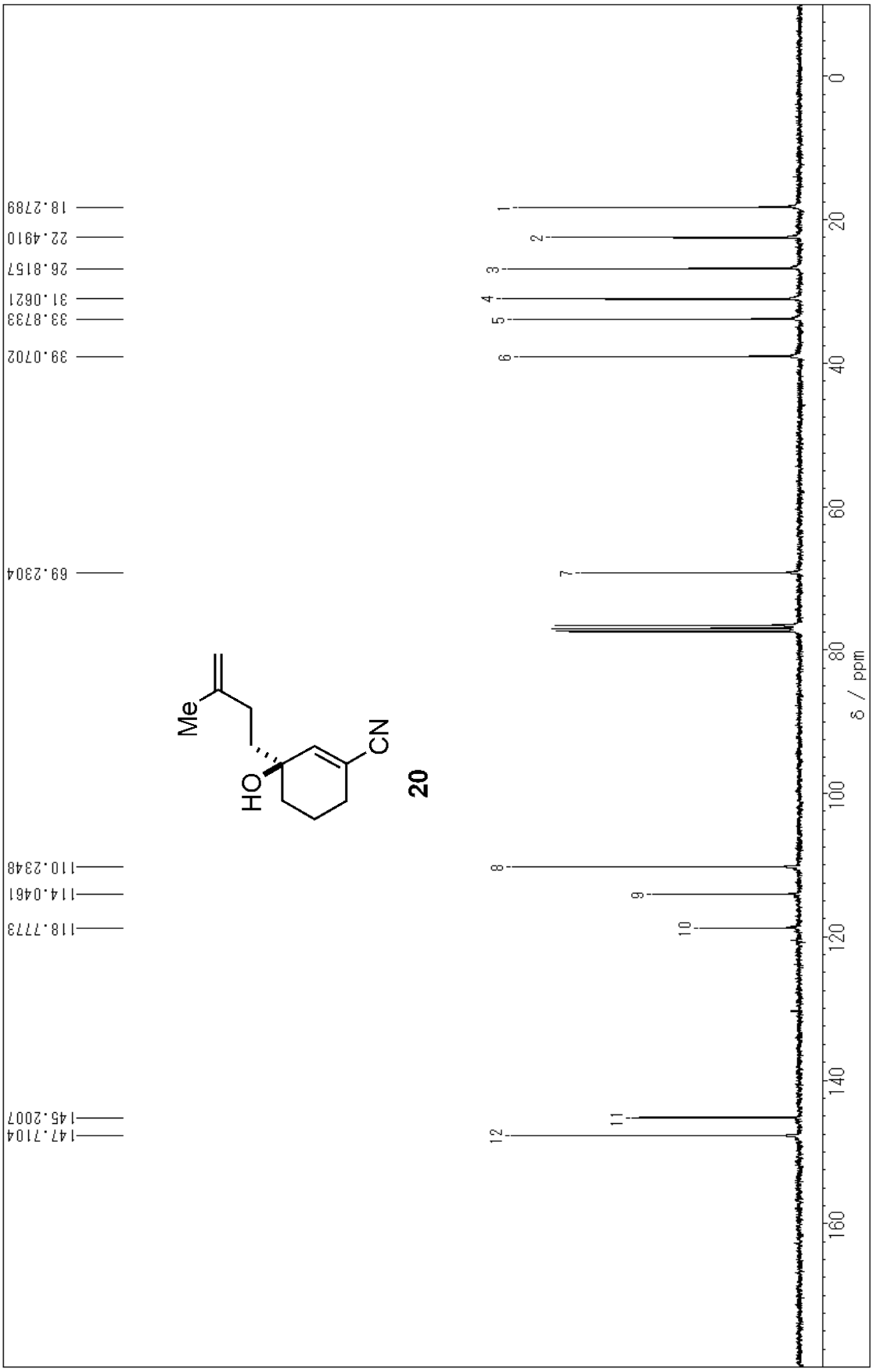

Figure S20. A ^{13}C-NMR spectrum of **20** in $CDCl_3$.

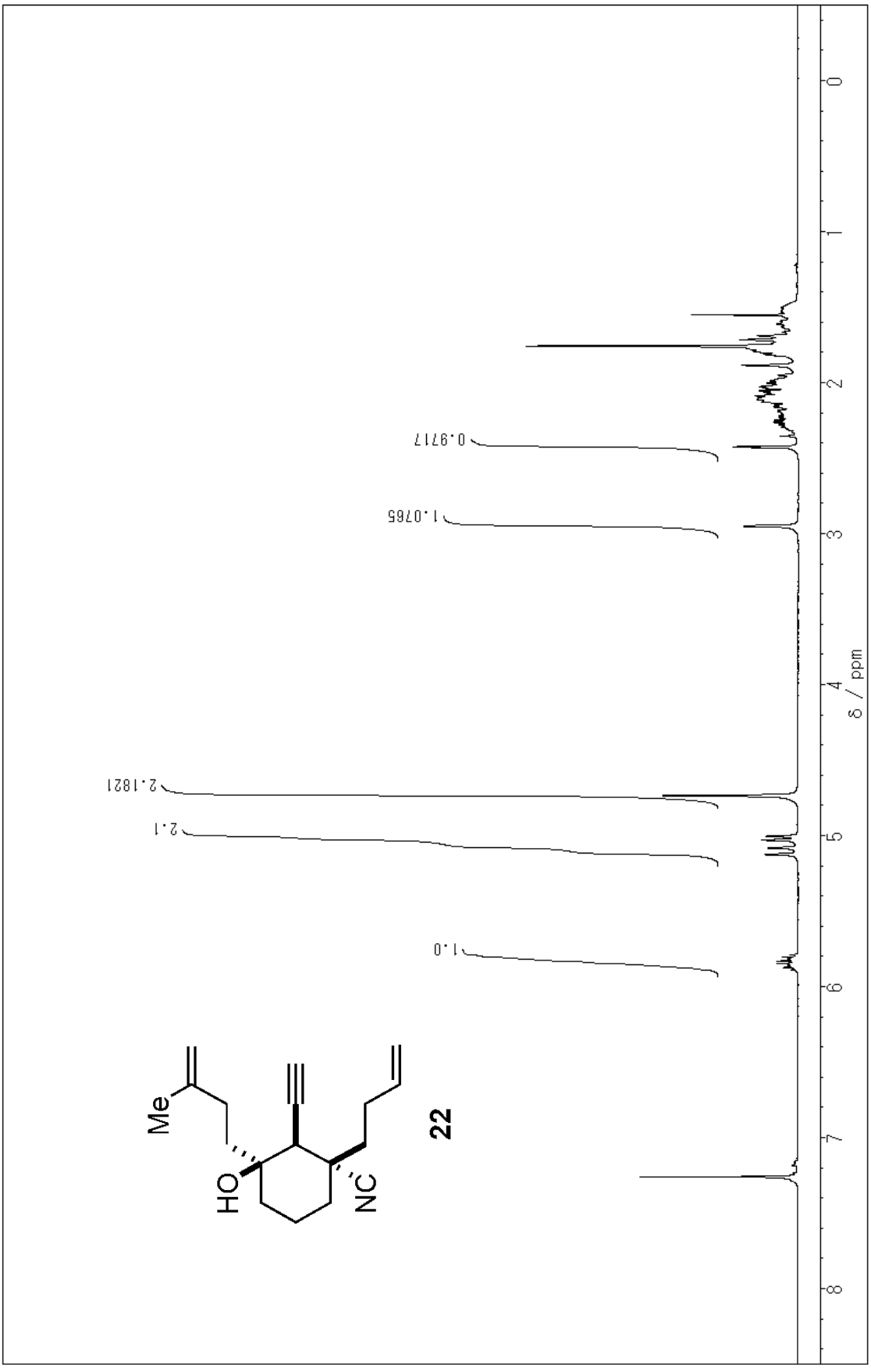

Figure S21. A ^{1}H-NMR spectrum of **22** in $CDCl_3$.

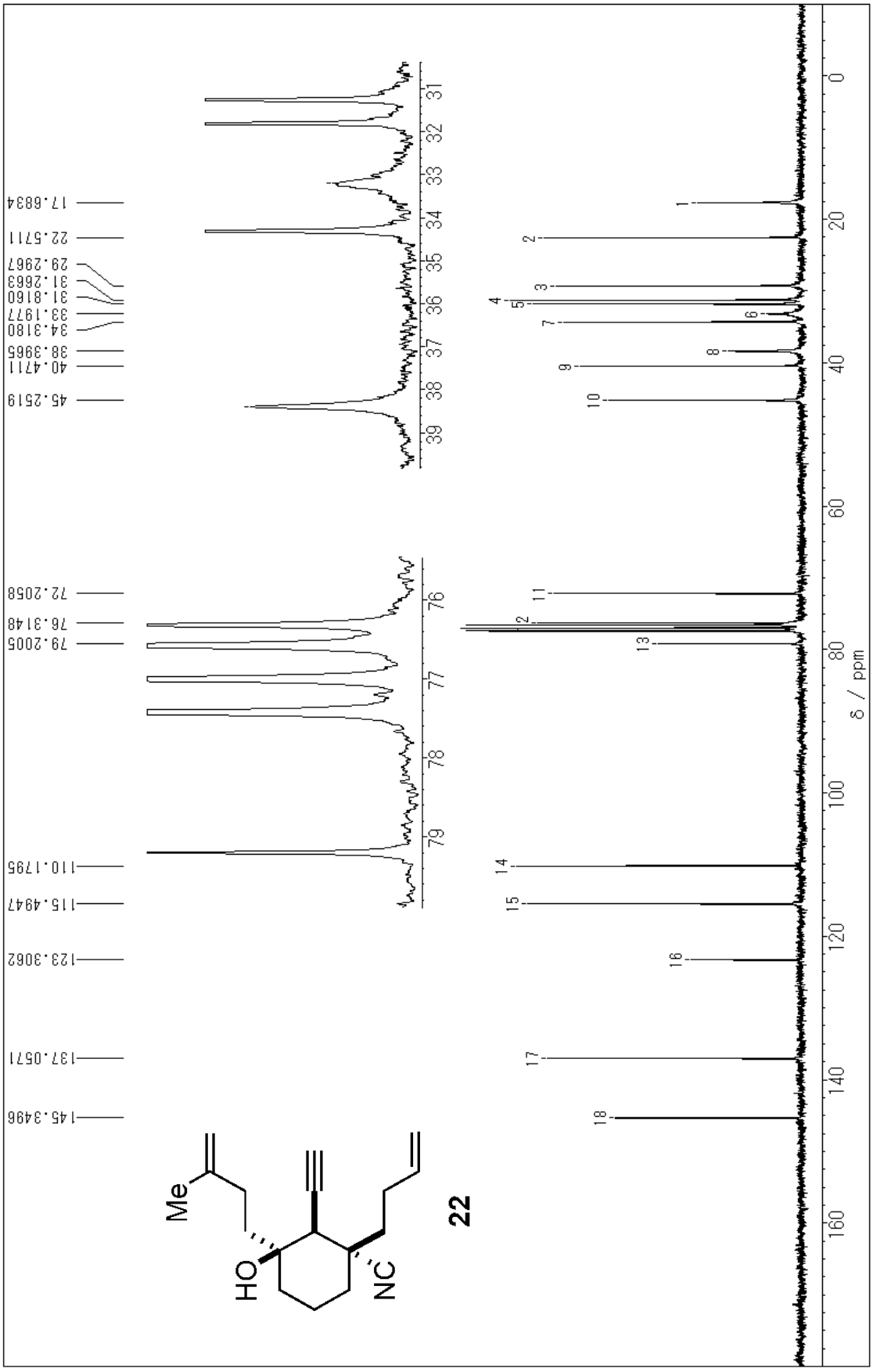

Figure S22. A ^{13}C-NMR spectrum of **22** in $CDCl_3$.

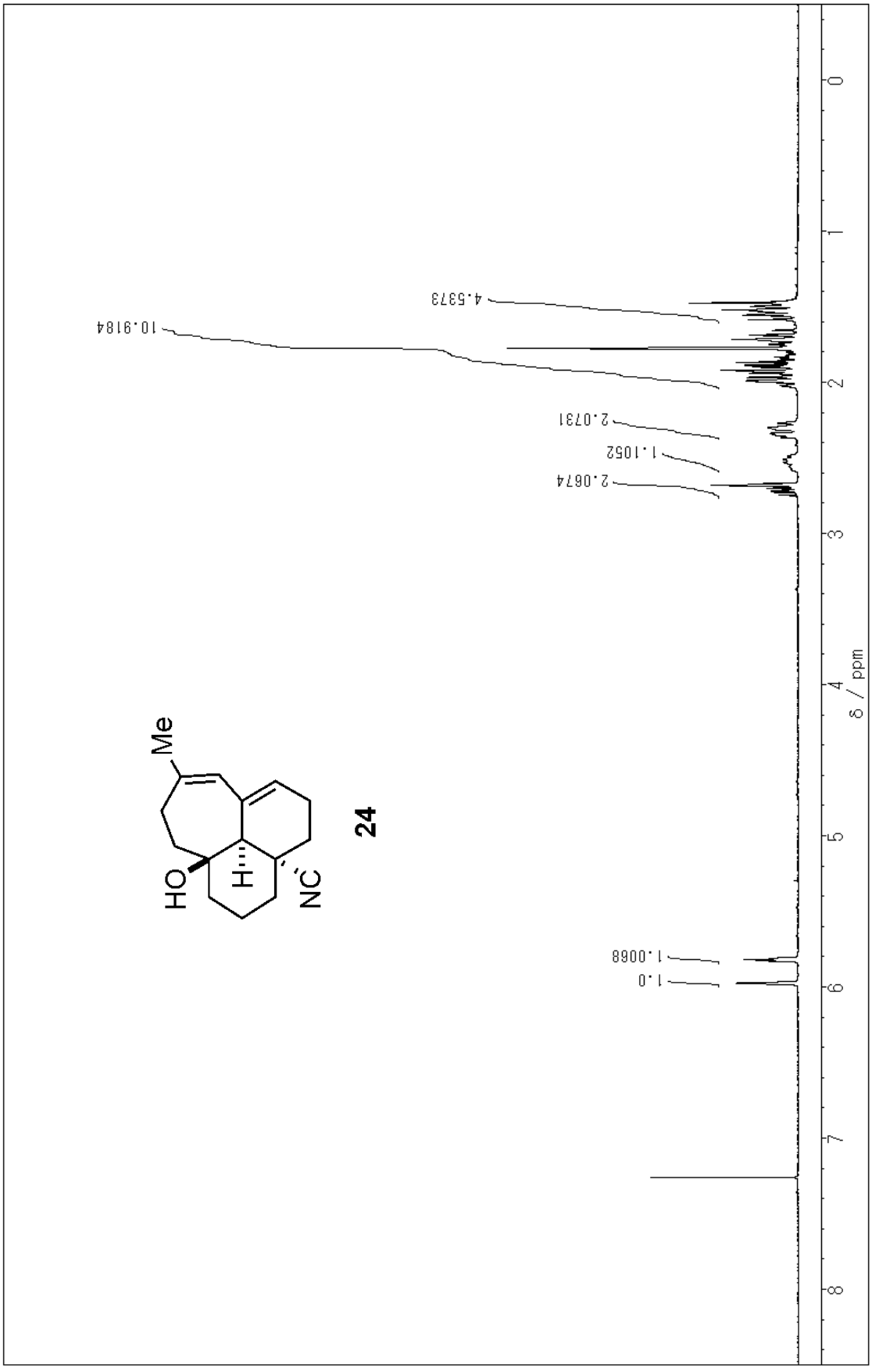

Figure S23. A ^{1}H-NMR spectrum of **24** in $CDCl_3$.

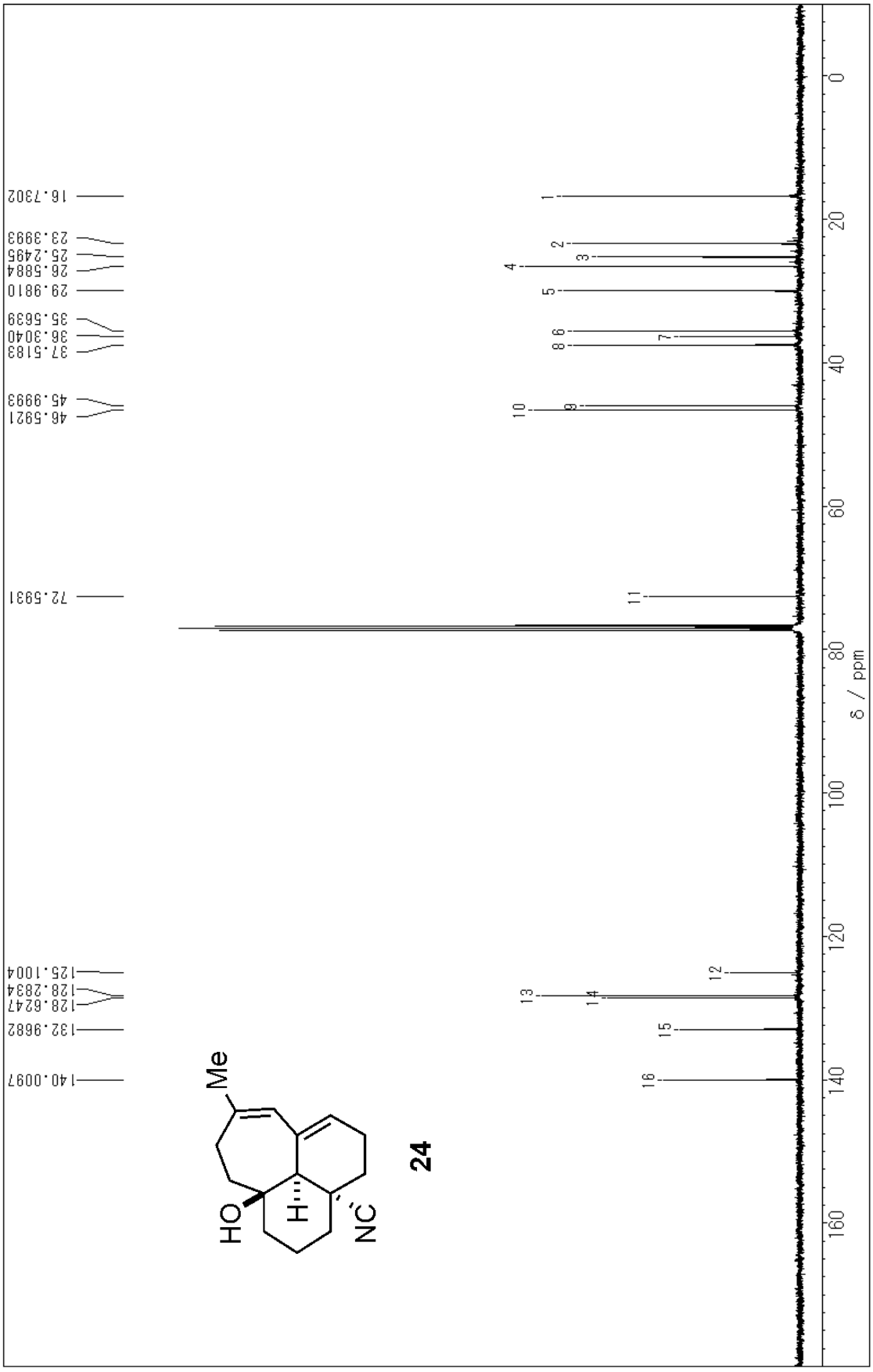

Figure S24. A ^{13}C-NMR spectrum of **24** in $CDCl_3$.

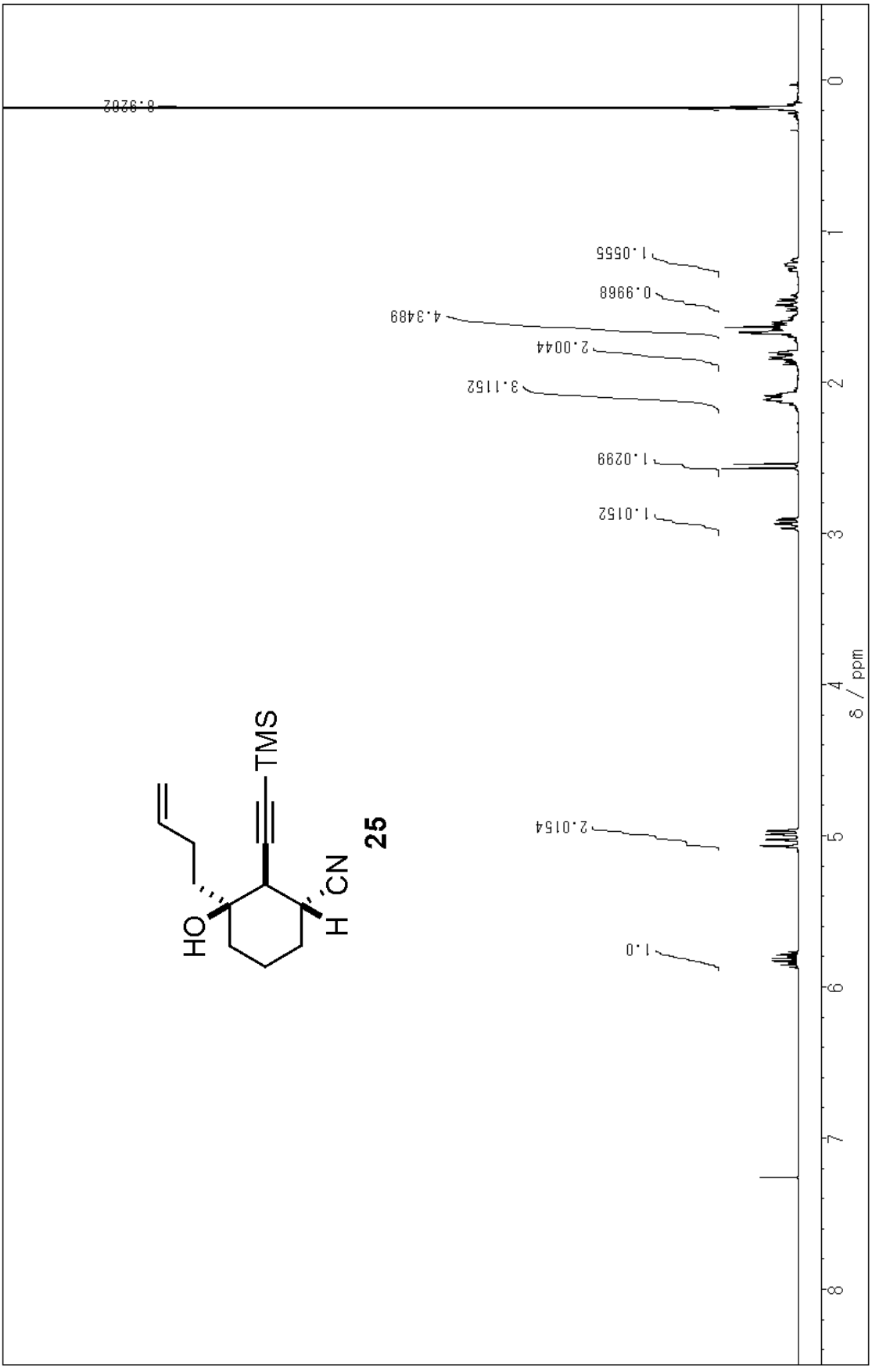

Figure S25. A ^{1}H-NMR spectrum of **25** in $CDCl_3$.

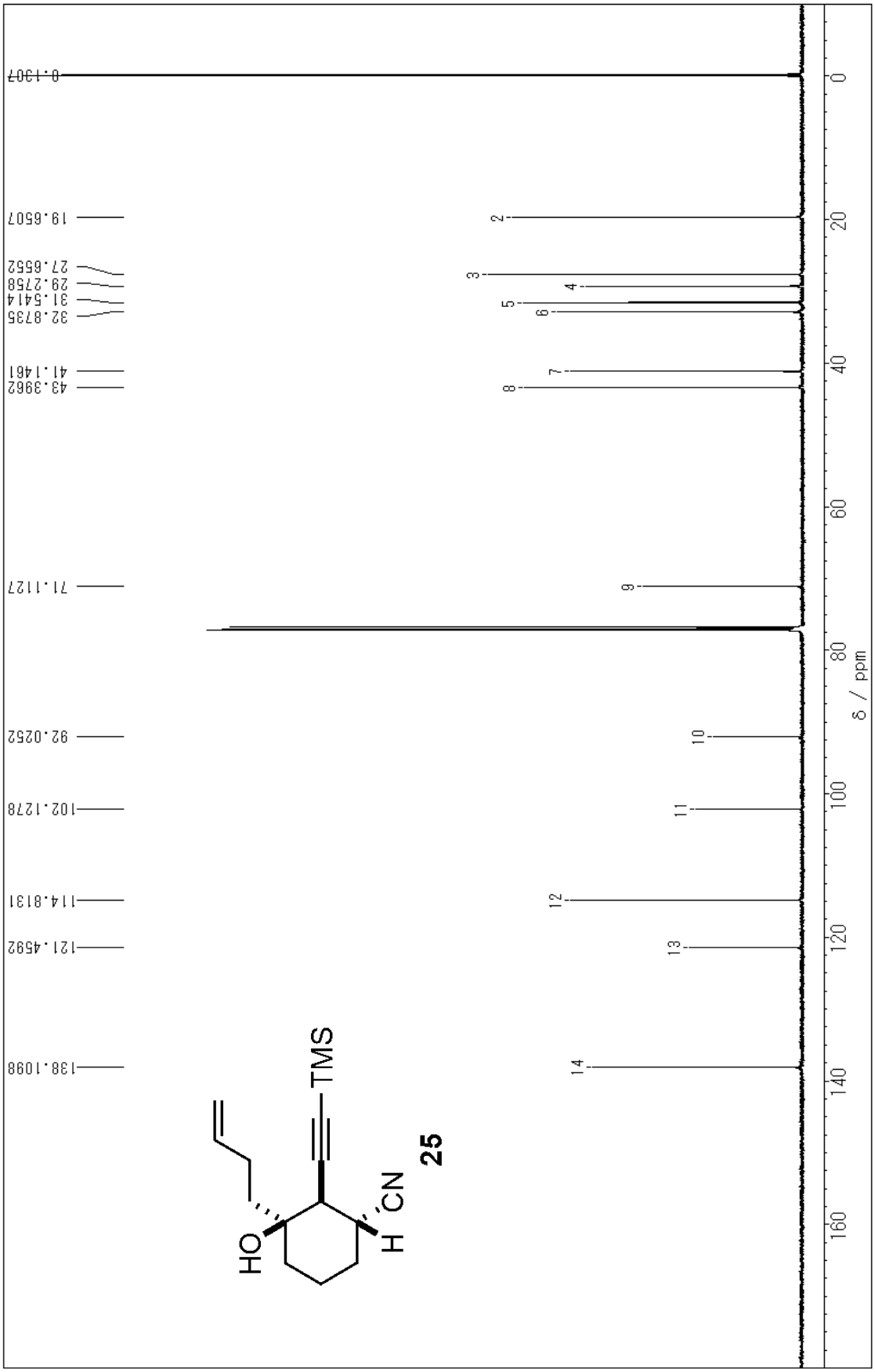

Figure S26. A ^{13}C-NMR spectrum of **25** in $CDCl_3$.

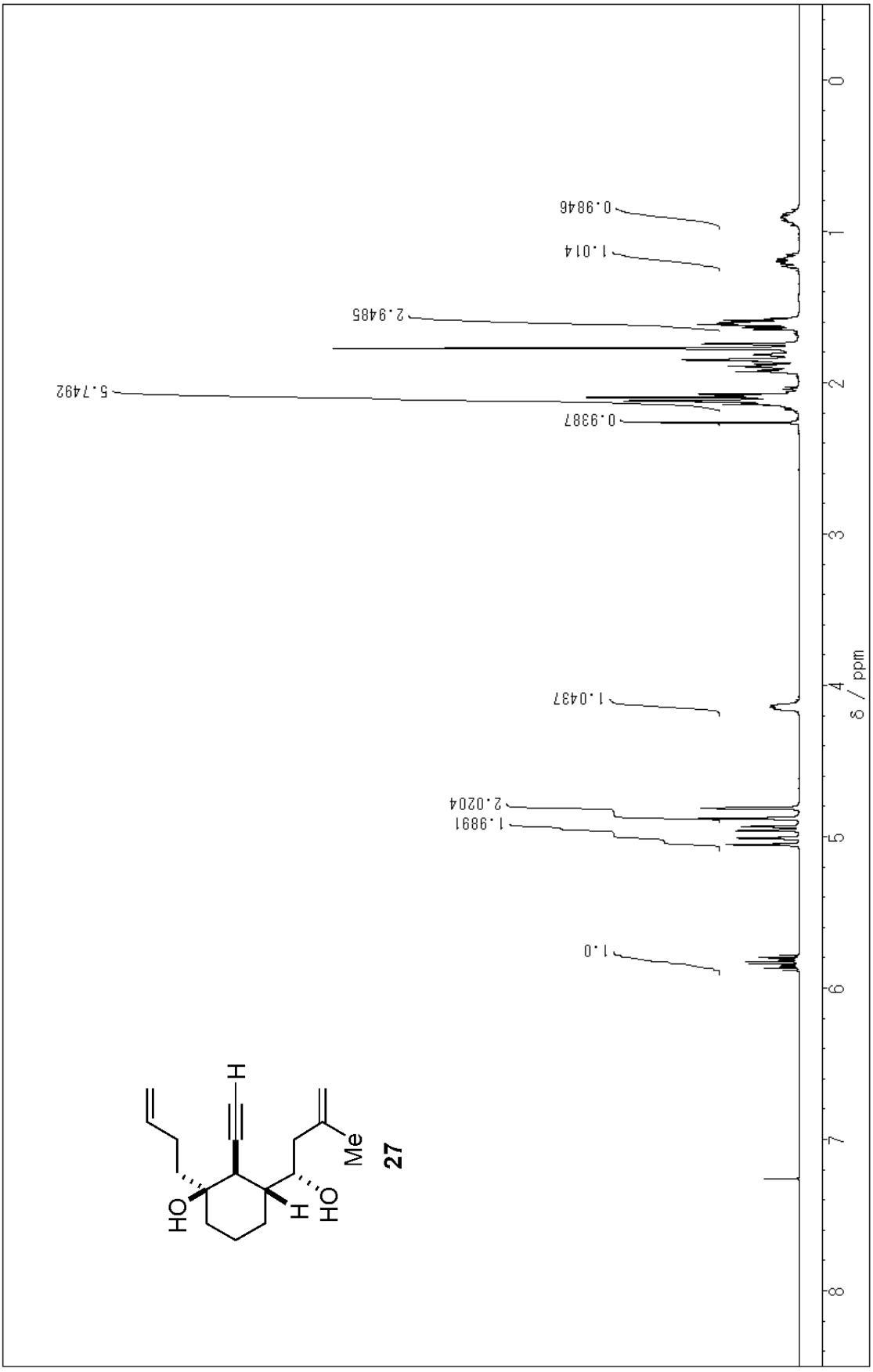

Figure S27. A ^{1}H-NMR spectrum of **27** in $CDCl_3$.

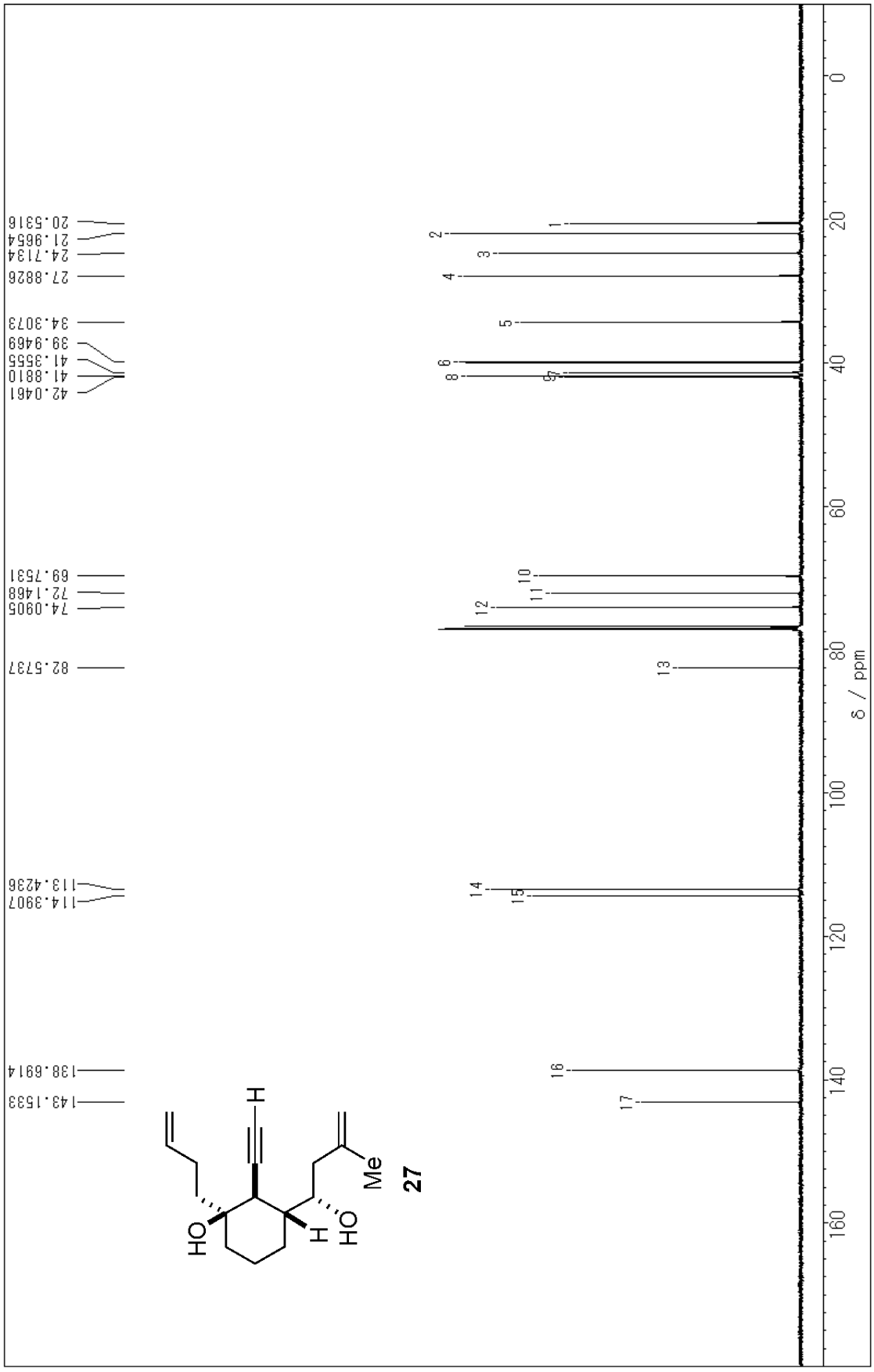

Figure S28. A ^{13}C-NMR spectrum of **27** in $CDCl_3$.

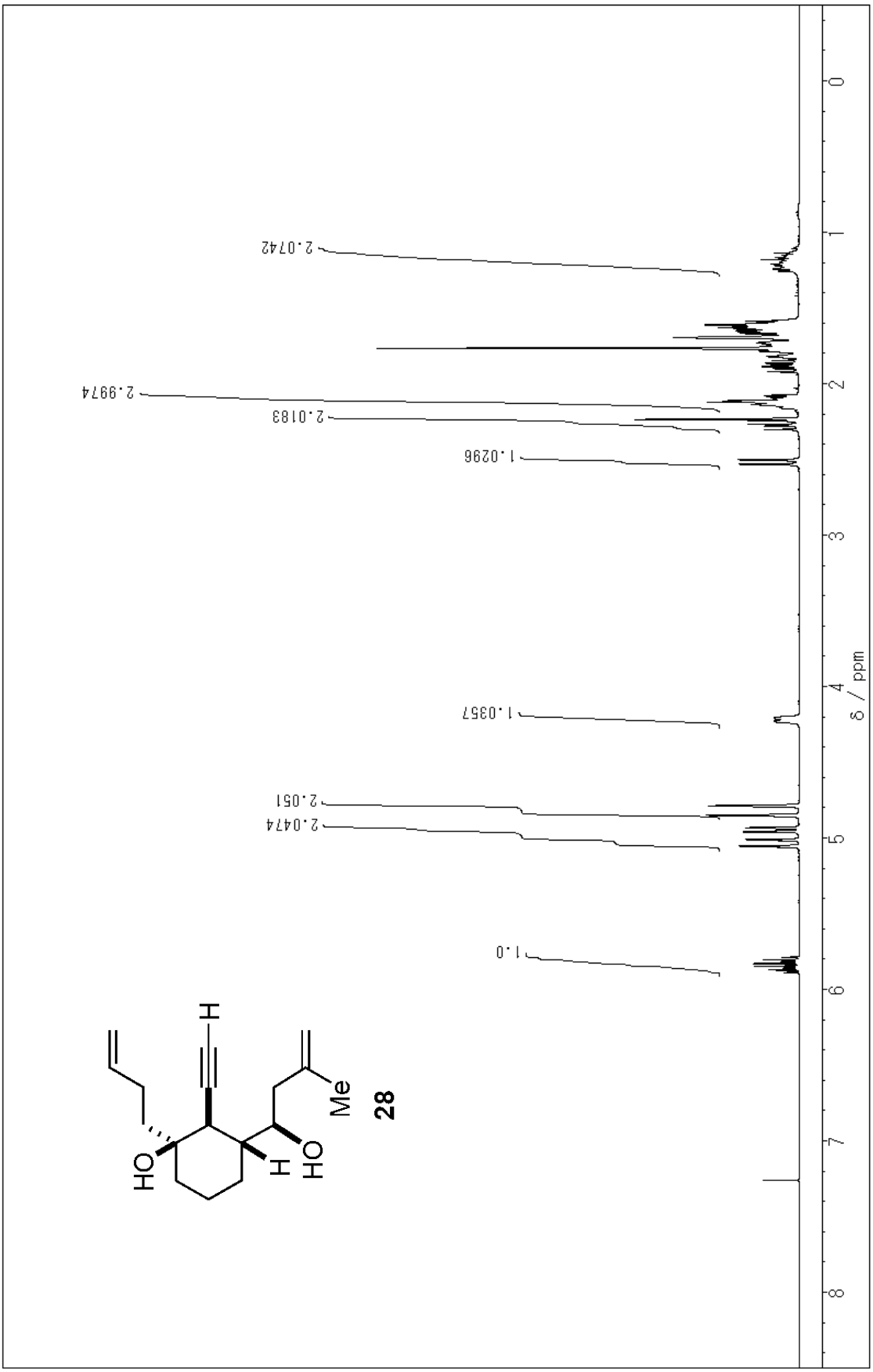

Figure S29. A ^{1}H-NMR spectrum of **28** in $CDCl_3$.

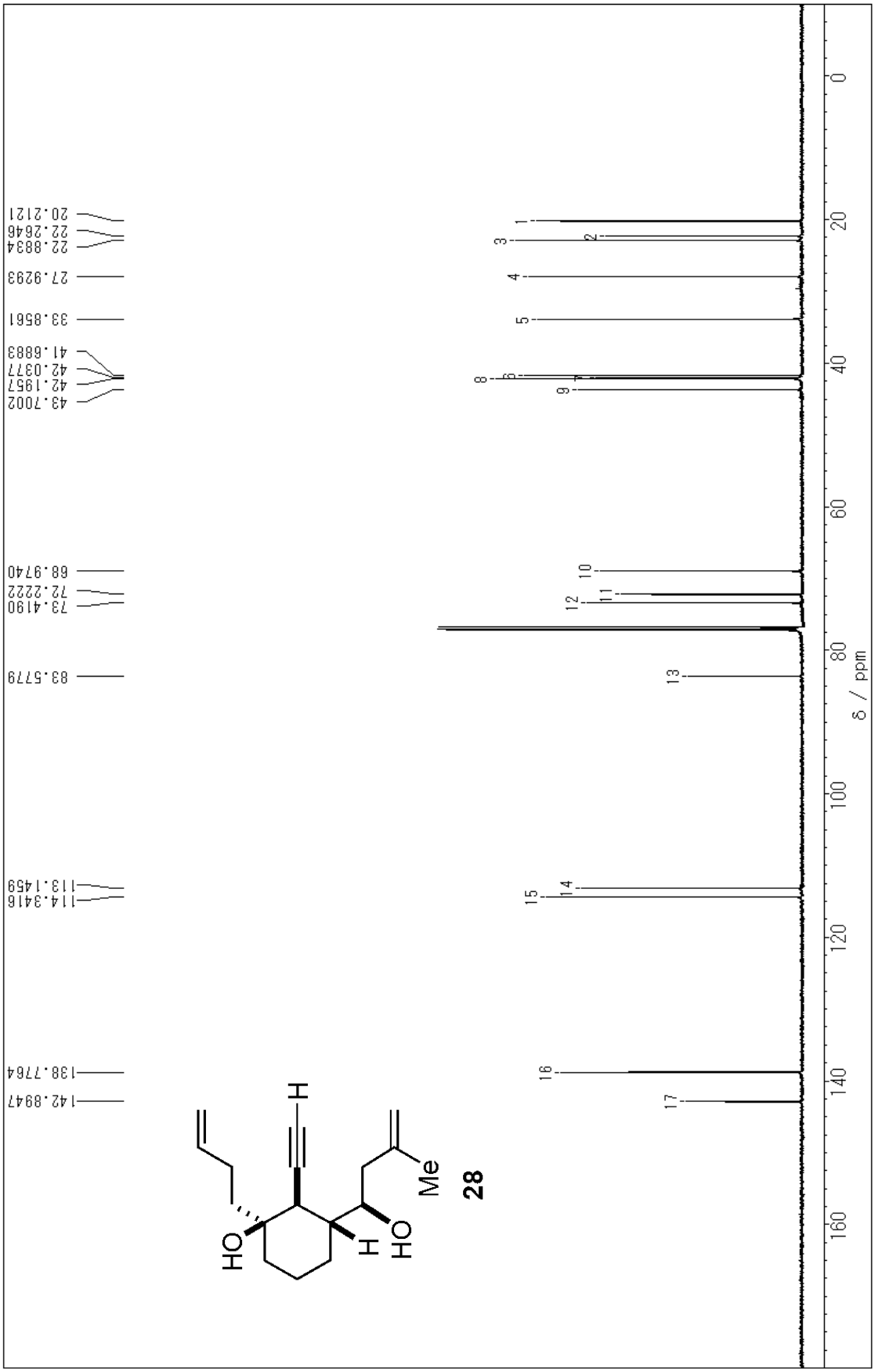

Figure S30. A ^{13}C-NMR spectrum of **28** in $CDCl_3$.

Figure S31. A ^{1}H-NMR spectrum of **31** in $CDCl_3$.

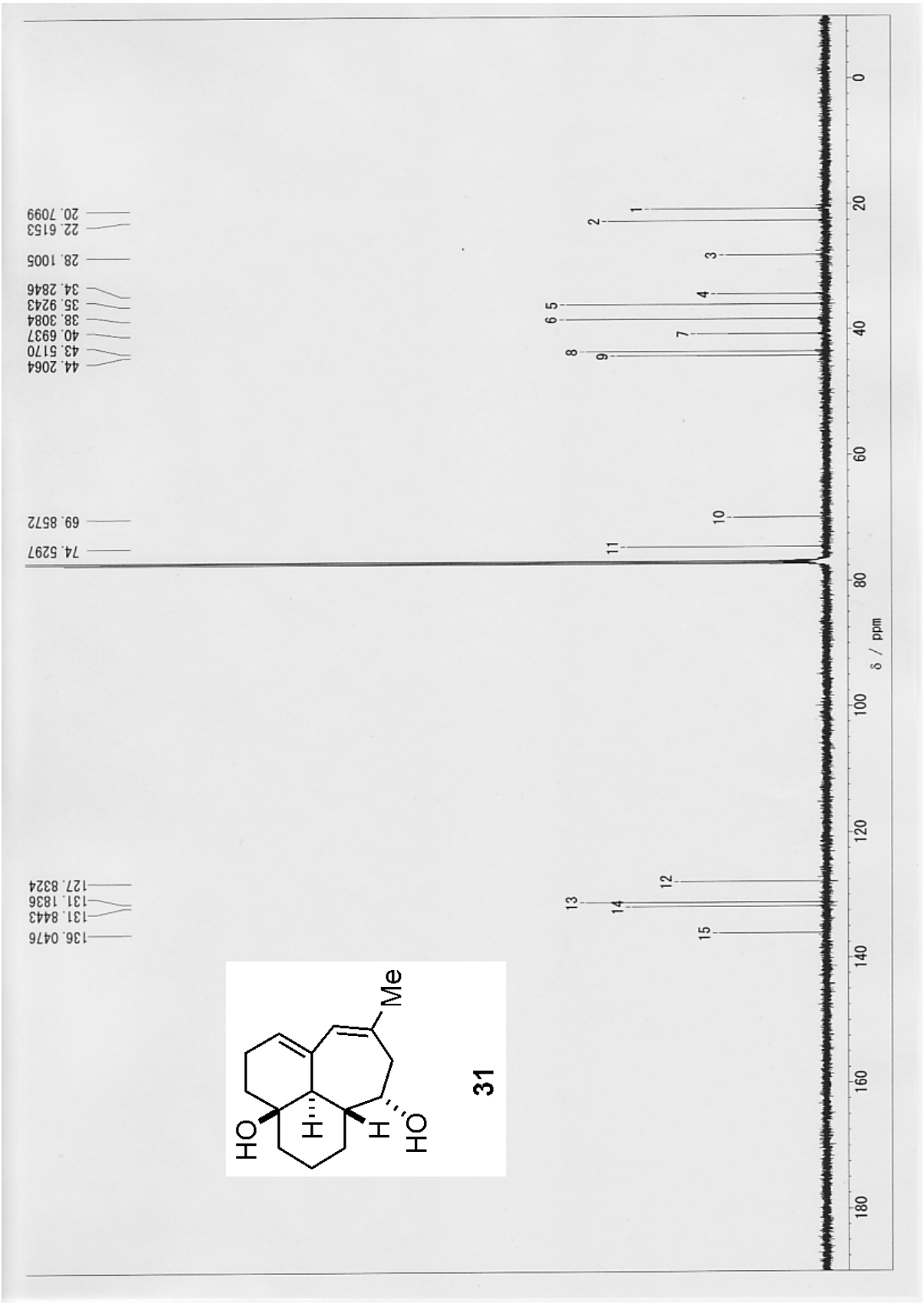

Figure S32. A ^{13}C-NMR spectrum of **31** in $CDCl_3$.

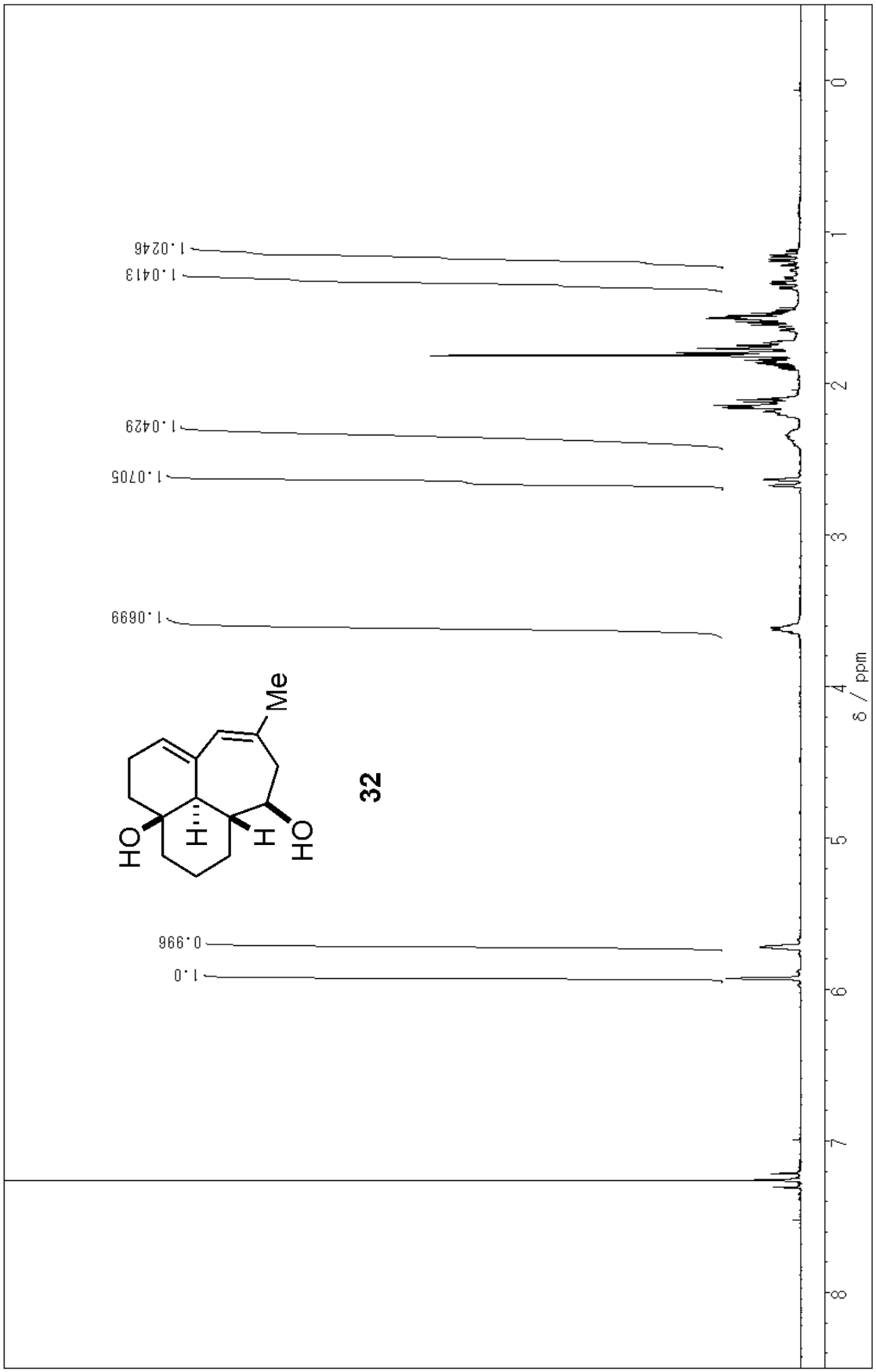

Figure S33. A ^{1}H-NMR spectrum of **32** in $CDCl_3$.

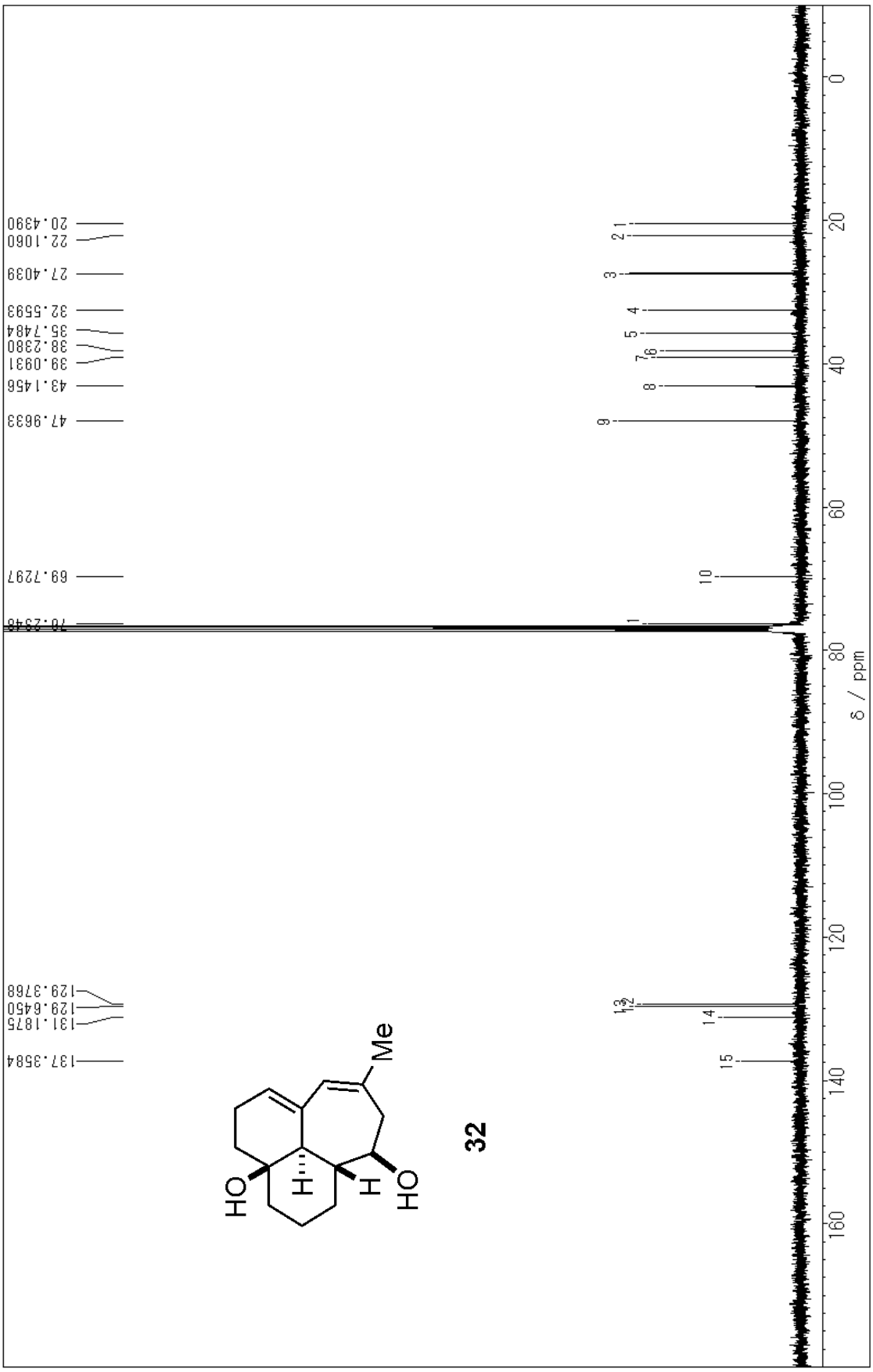

Figure S34. A ^{13}C-NMR spectrum of **32** in $CDCl_3$.

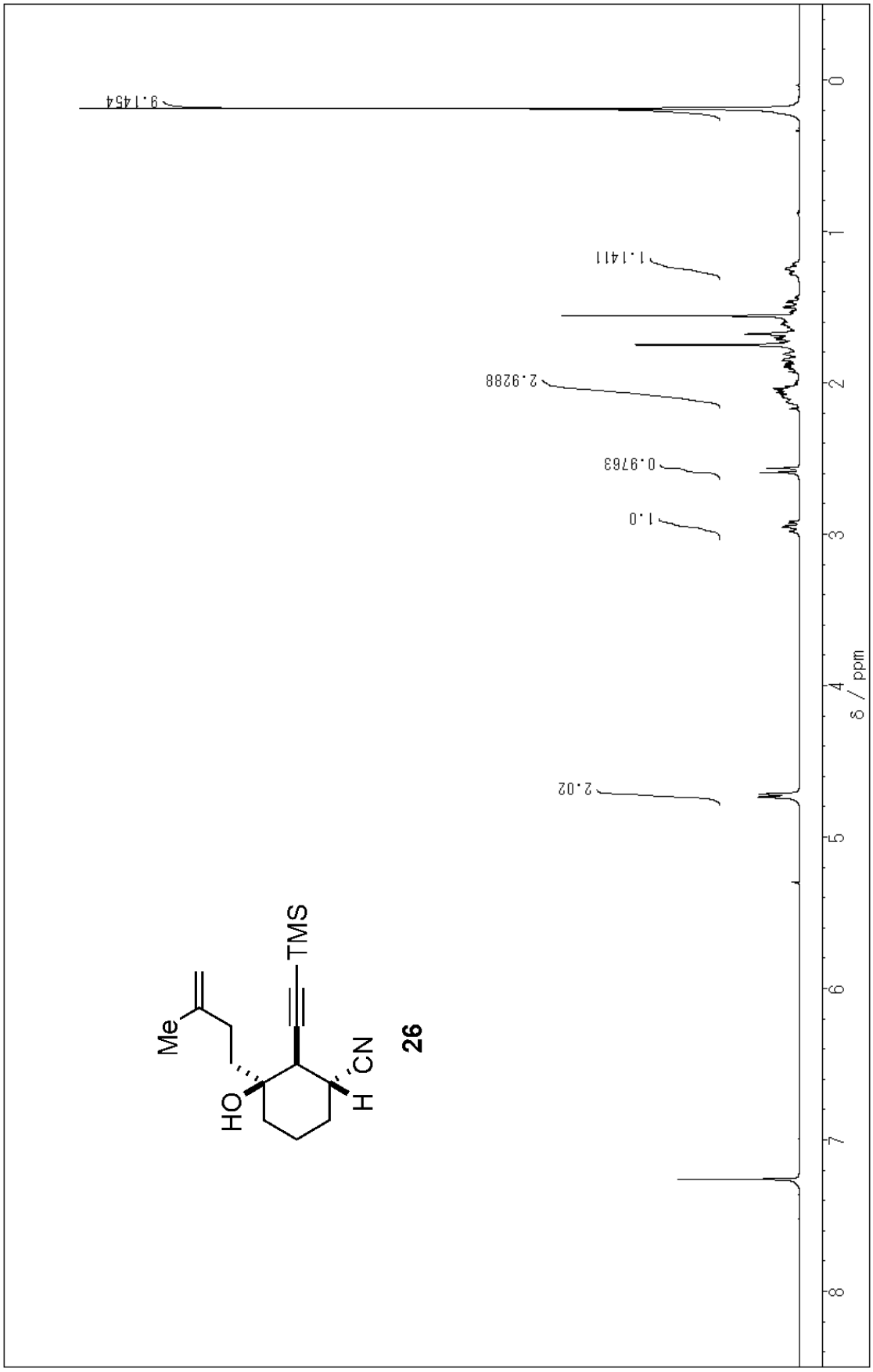

Figure S35. A ^{1}H-NMR spectrum of **26** in $CDCl_3$.

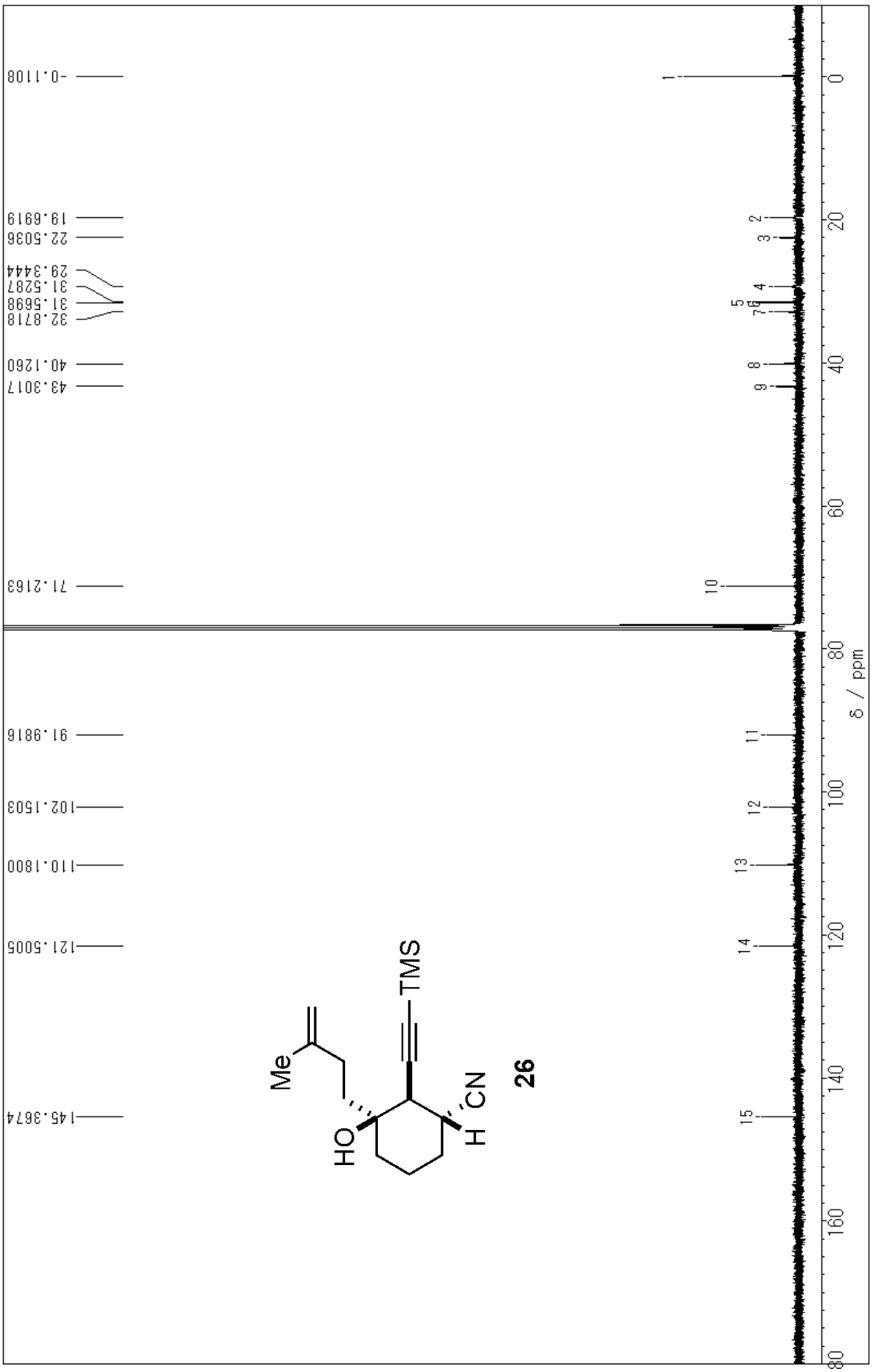

Figure S36. A ^{13}C-NMR spectrum of **26** in $CDCl_3$.

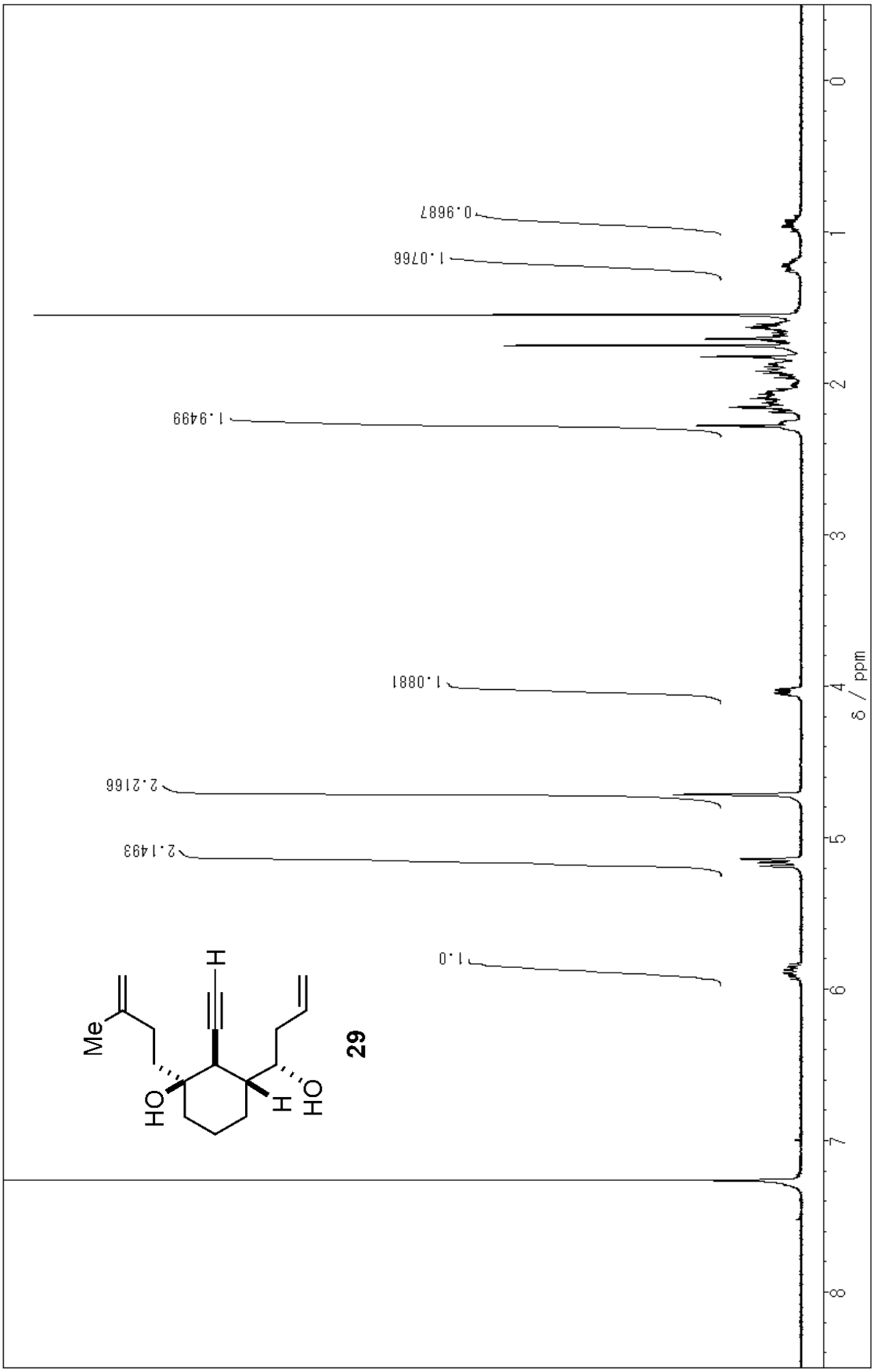

Figure S37. A ^{1}H-NMR spectrum of **29** in $CDCl_3$.

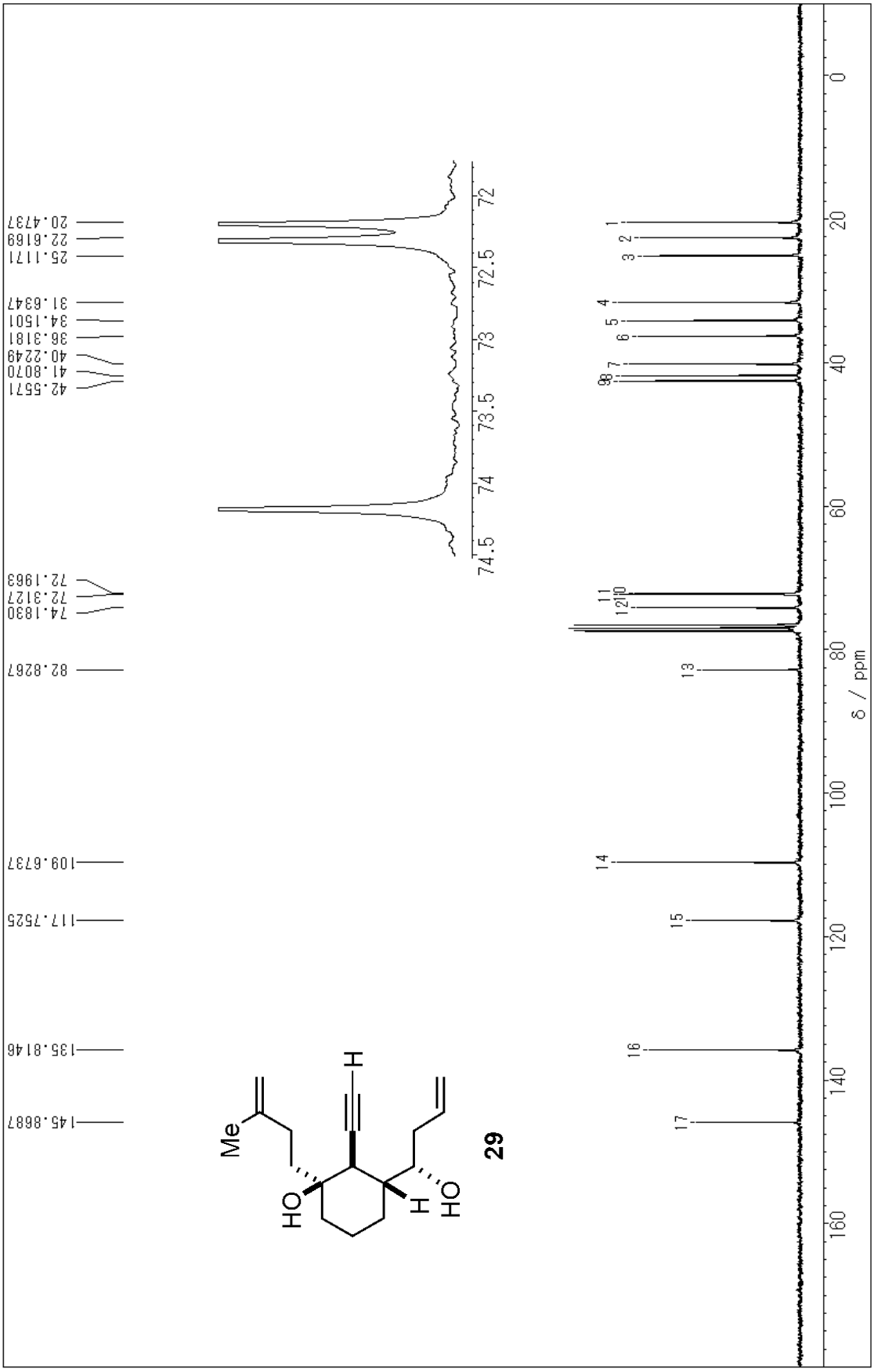

Figure S38. A ^{13}C-NMR spectrum of **29** in $CDCl_3$.

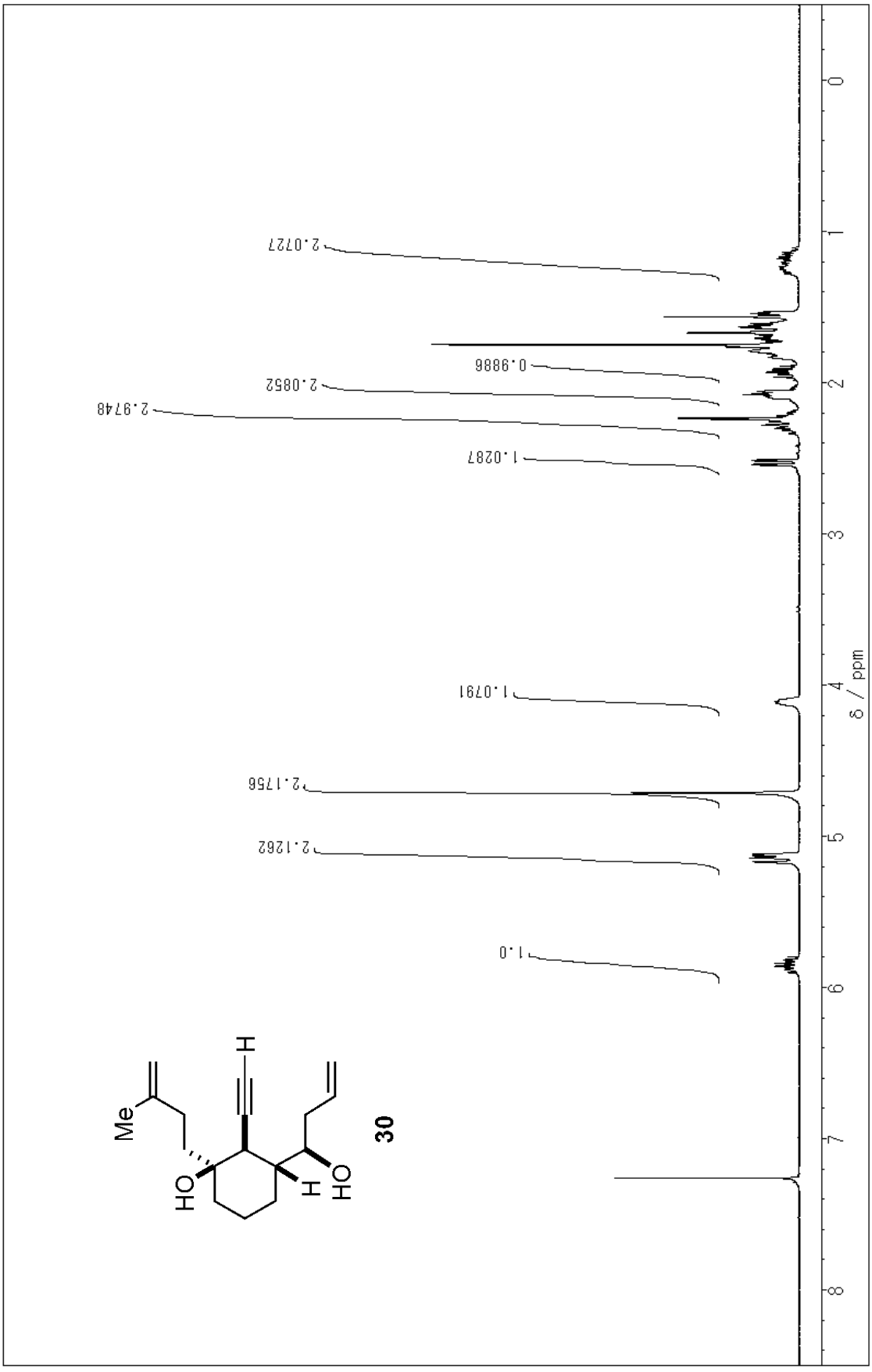

Figure S39. A ^{1}H-NMR spectrum of **30** in $CDCl_3$.

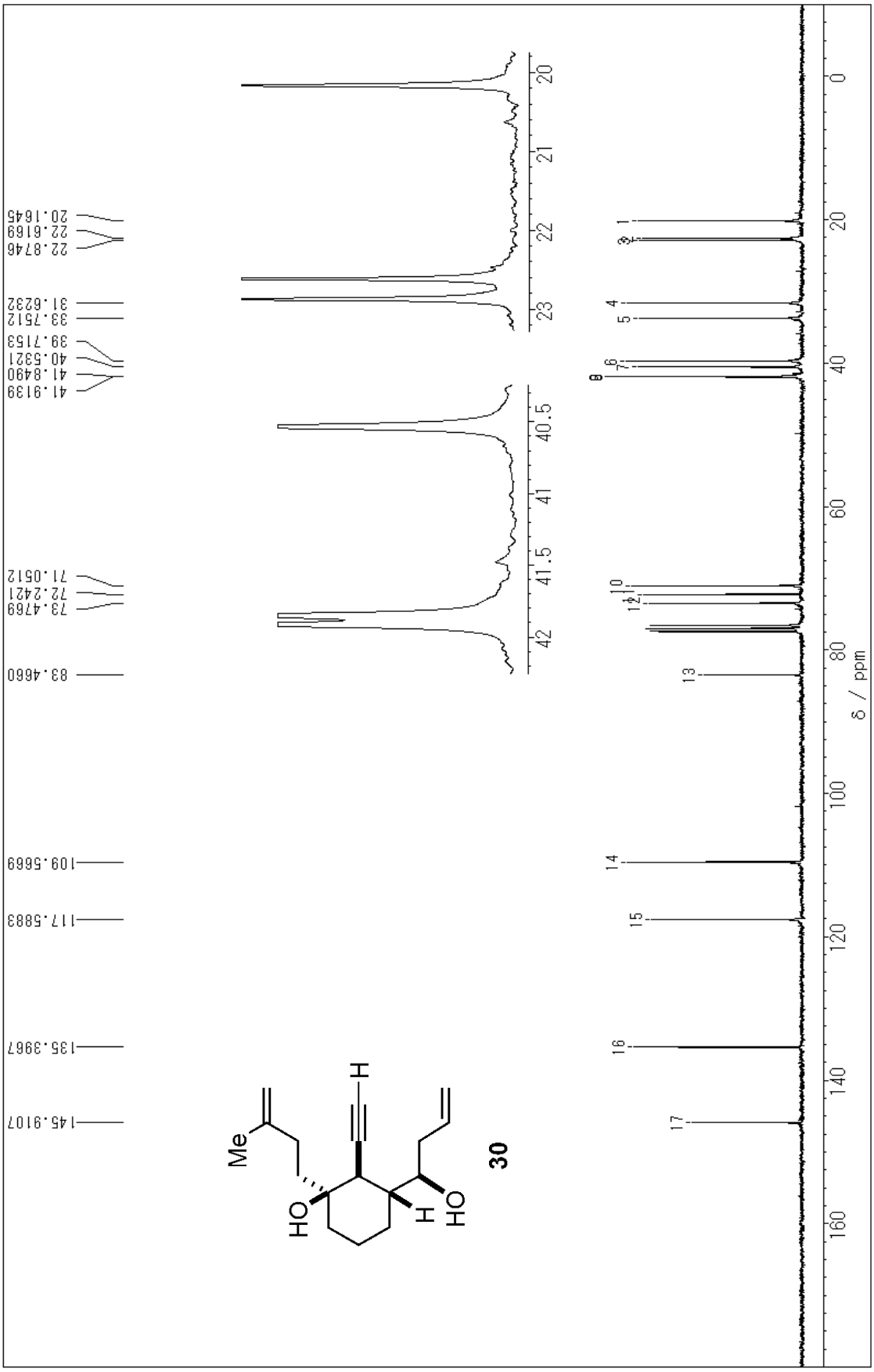

Figure S40. A ^{13}C-NMR spectrum of **30** in $CDCl_3$.

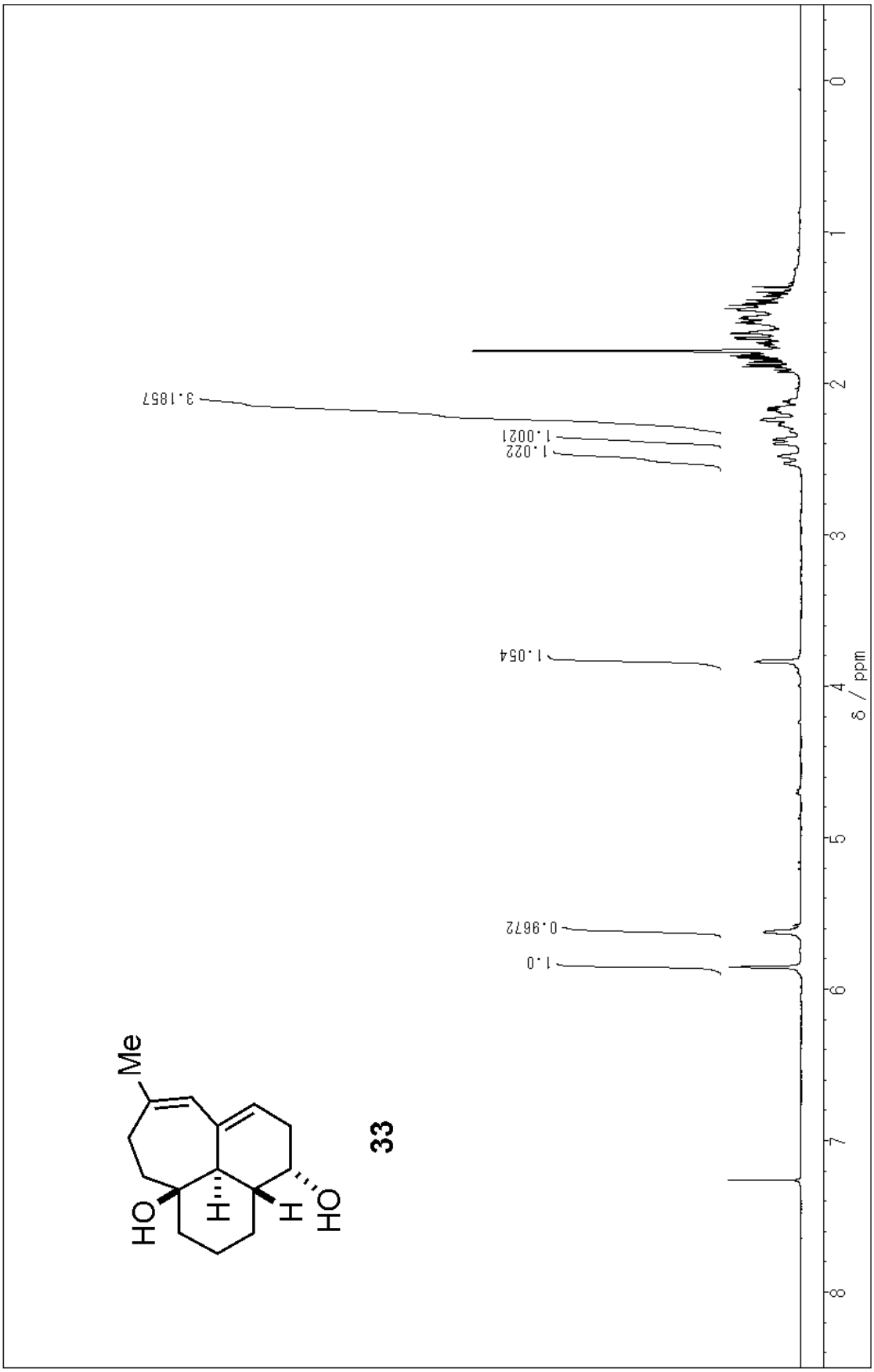

Figure S41. A ^{1}H-NMR spectrum of **33** in $CDCl_3$.

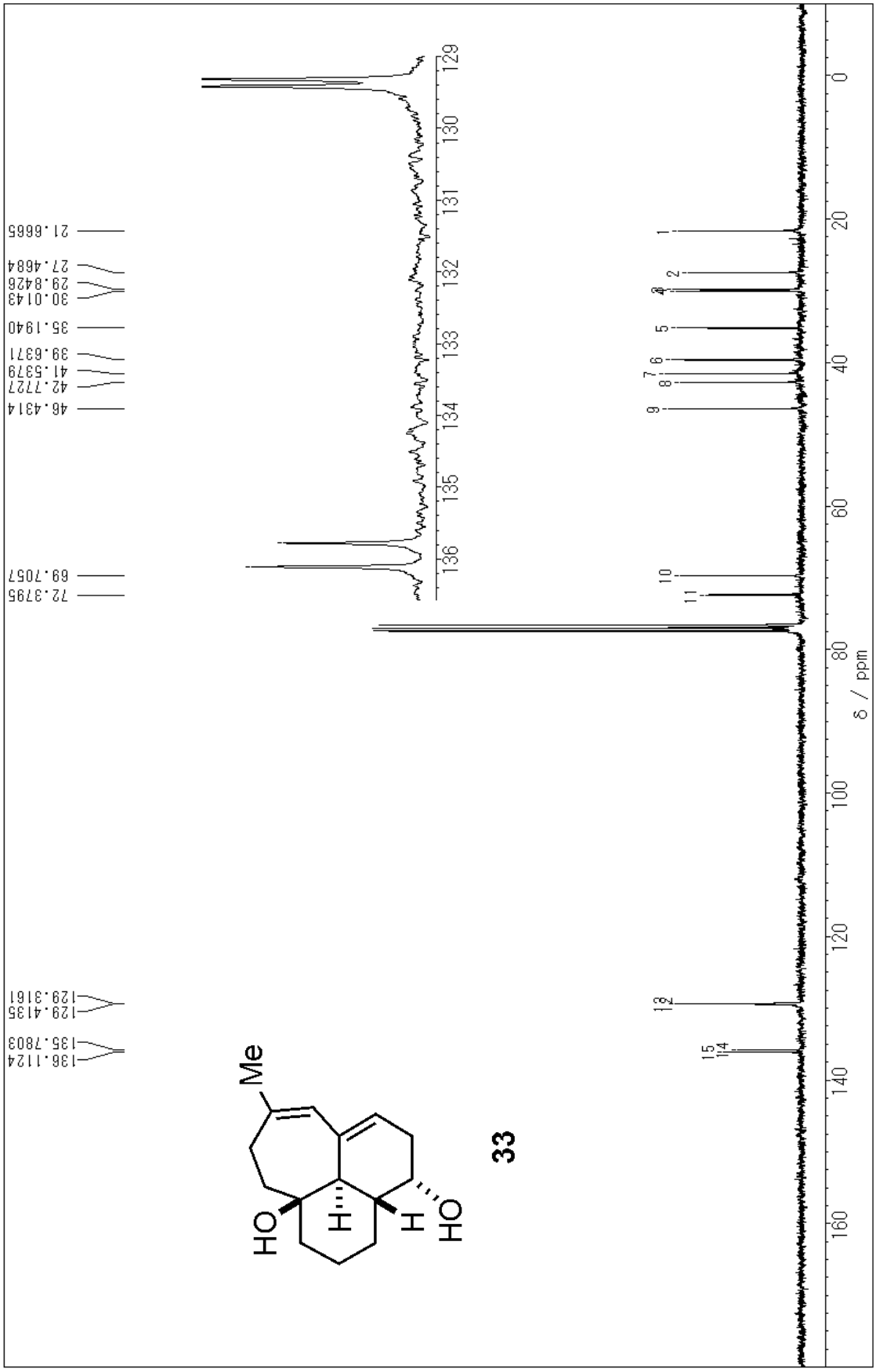

Figure S42. A ^{13}C-NMR spectrum of **33** in $CDCl_3$.

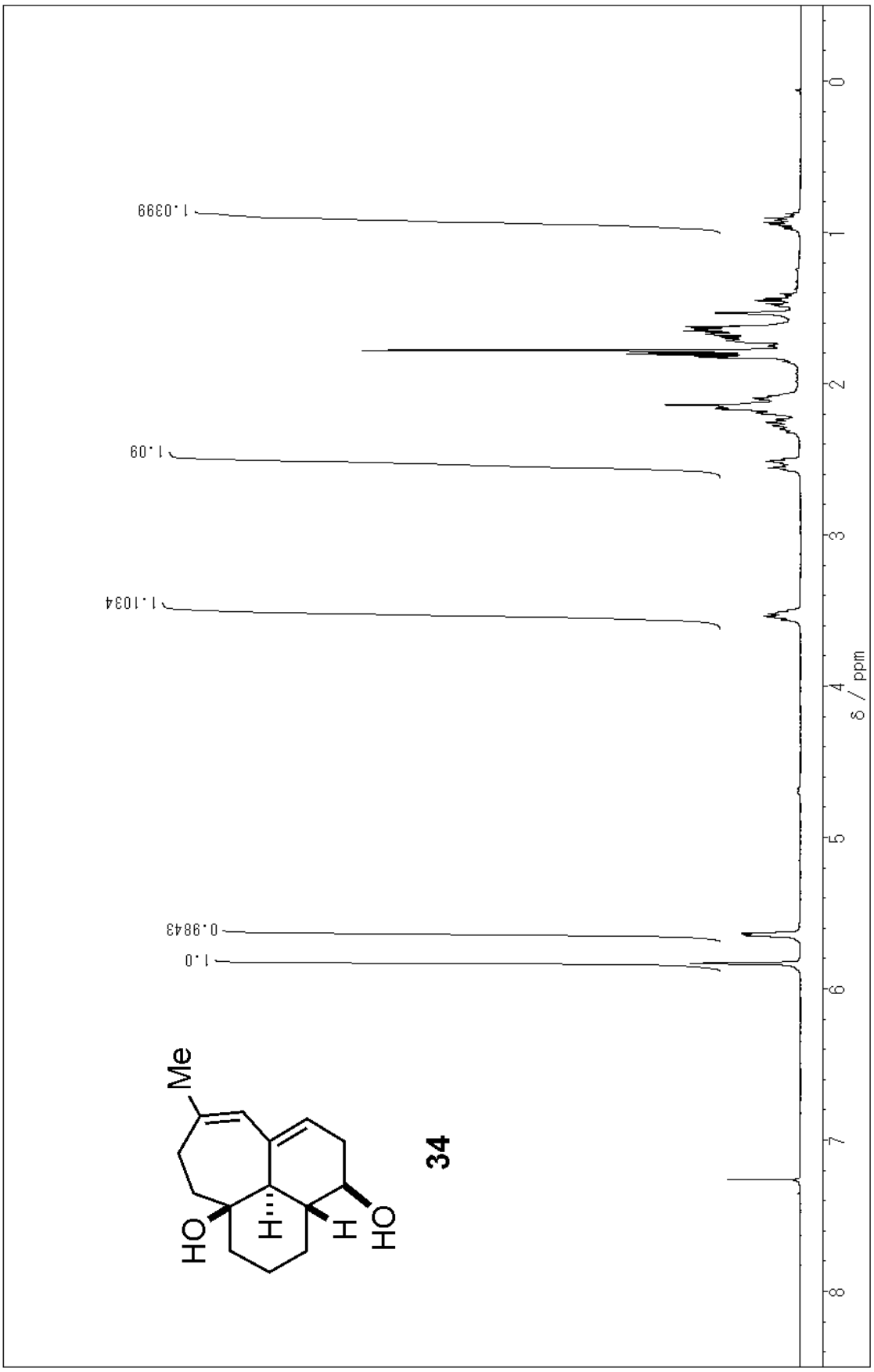

Figure S43. A ^{1}H-NMR spectrum of **34** in $CDCl_3$.

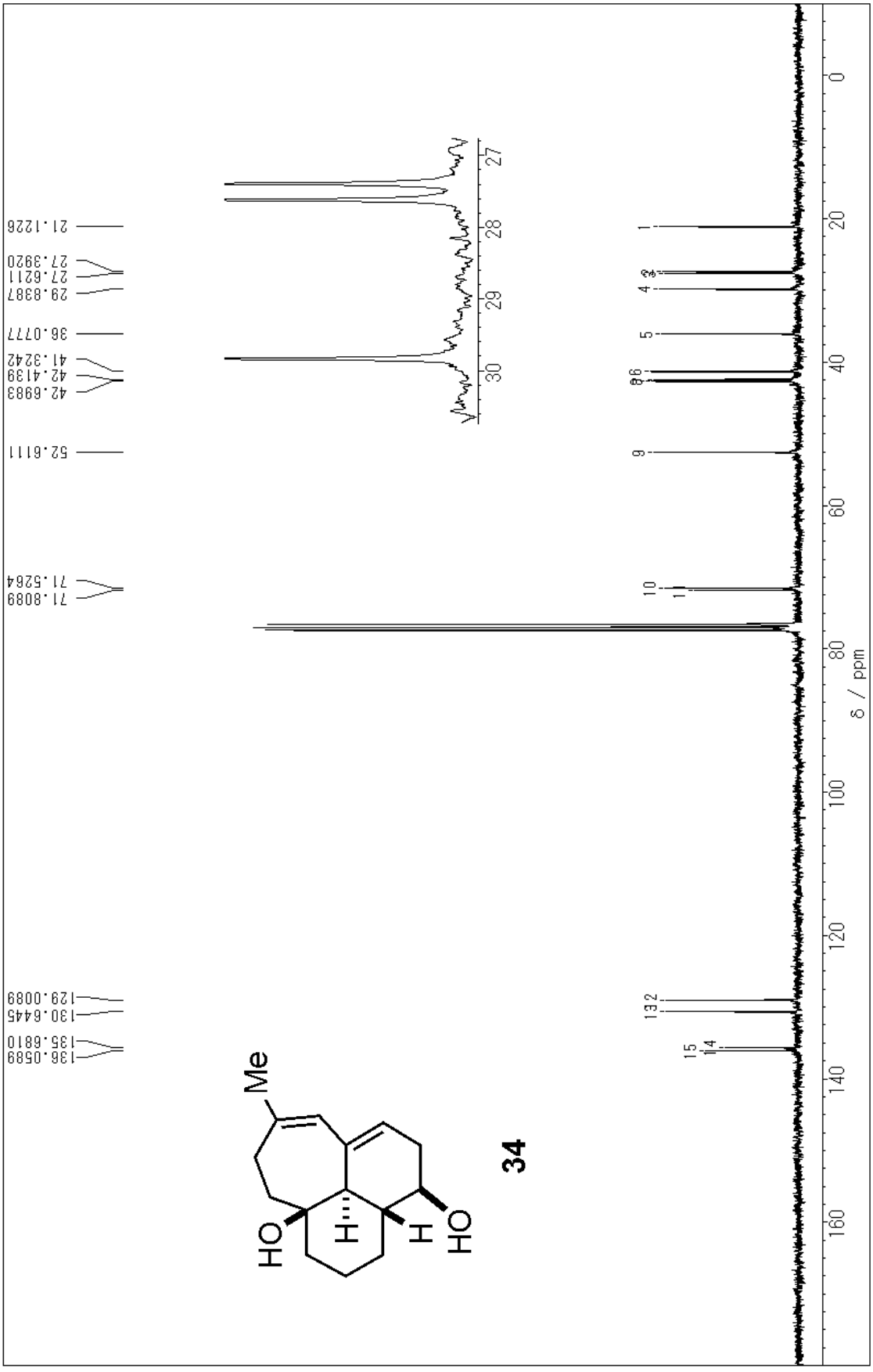

Figure S44. A ^{13}C-NMR spectrum of **34** in $CDCl_3$.