Electronic Supplementary Material (ESI) for Chemical Communications

Supporting Information

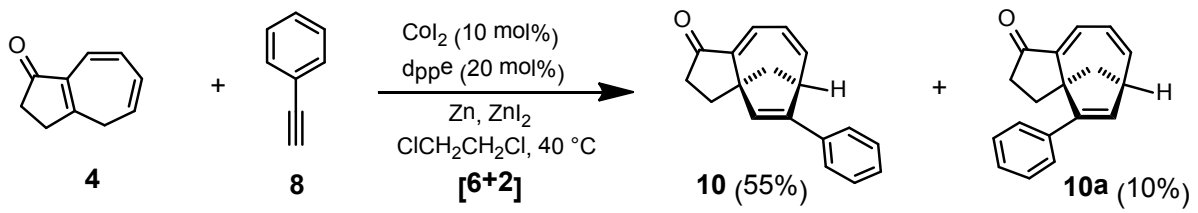
Sequential [6+2], [2+2], [3+2] Annulations for Rapid Assembly of Multiple Fragments

Velisoju Mahendar, Hideaki Oikawa and Hiroki Oguri*

Division of Chemistry, Graduate School of Science, Hokkaido University,
North 10, West 8, Kita-ku, Sapporo 060-0810, Japan
*Corresponding Author: oguri@sci.hokudai.ac.jp

General Information:

Air-sensitive and moisture-sensitive reactions were carried out under nitrogen atmosphere in dry solvents under anhydrous conditions. Reagents were used as supplied unless otherwise noted. Microwave reactions were conducted using Biotage Initiator EXP^{TM}. The medium pressure liquid chromatography (MPLC) purifications using a silica-gel column were performed on a YAMAZEN YFLC-AI-580. NMR spectra were recorded on JEOL JNM-ECX 400 (^{1}H/400 MHz, ^{13}C/100 MHz) and JNM-ECX 600 (^{1}H/600 MHz, ^{13}C/150 MHz) spectrometers. Chemical Shifts are reported in δ (ppm) and are referenced to proton and carbon resonances of the NMR solvent ($CHCl_3$: δ 7.26, and δ 77.16, DMSO: δ 2.50 and δ 39.52, C_6D_6: δ 7.16 and 128.06). Mass spectra were recorded on JEOL JMS-T100CS (ESI) spectrometer. Analytical ultra-performance liquid chromatography (UPLC) was carried out on WATERS ACQUITY™ UPLC® H-Class system.

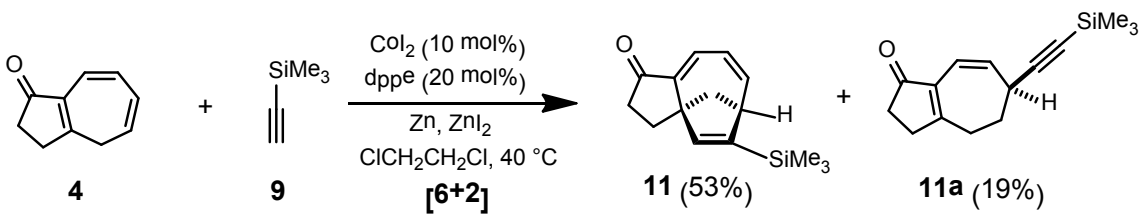


A solution of CoI_2 (31 mg, 10 mol%) and dppe (80 mg, 20 mol%) in 1,2-dichloroethane (10 ml)

was stirred at room temperature for 15 min, then zinc powder (20 mg, 30 mol%), azulenone **4** (146 mg, 1.00 mmol) in 1,2-dichloroethane (5 ml), phenyl acetylene **8** (110 µl, 1.0 equiv.) in 1,2-dichloroethane (5 ml) and zinc iodide (64.0 mg, 20 mol%) were added successively. The resulting mixture was stirred at 40 °C for 20 h and then filtered through Celite. Concentration of the filtrate and purification by MPLC to afford desired **10** (136 mg, 0.548 mmol, 55%) and regioisomer **10a** (25 mg, 0.10 mmol, 10%).

10: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.45 (2H, m), 7.30 (2H, m), 7.21 (1H, m), 6.76 (1H, d, J = 7.6 Hz), 6.69 (1H, dd, J = 11.2, 7.2 Hz), 6.11 (1H, dd, J = 11.2, 7.6 Hz), 5.85 (1H, s), 3.87 (1H, t, J = 7.2 Hz), 2.66 (1H, m), 2.54 (1H, m), 2.32 (1H, dd, J = 11.4, 7.2 Hz), 2.20 (1H, dd, J = 13.2, 9.2 Hz), 1.99 (1H, m), 1.74 (1H, d, J = 11.4 Hz); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 206.15, 148.95, 148.20, 140.24, 134.15, 128.62, 127.60, 126.69, 124.82, 124.78, 123.70, 55.05, 44.46, 38.40, 36.01, 29.37; HR-MS (ESI) calcd. for $C_{36}H_{32}NaO_2$ $[2M+Na]^+$ 519.2300, found 519.2336. The ^{1}H and ^{13}C NMR spectra of **10** are shown in Figure S1 and S2.

10a: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.23 (3H, m), 7.05 (2H, m), 6.91 (1H, d, J = 7.6 Hz), 6.65 (1H, dd, J = 11.2, 7.6 Hz), 6.15 (1H, dd, J = 11.2, 7.6 Hz), 5.46 (1H, d, J = 2.8 Hz), 3.20 (1H, m), 2.32 (3H, m), 2.06 (2H, m), 1.66 (1H, d, J = 11.4 Hz); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 206.60, 149.31, 148.01, 142.86, 136.73, 128.89, 128.27, 127.46, 126.09, 125.28, 122.91, 56.94, 42.49, 38.74, 37.35, 27.95; HR-MS (ESI) calcd. for $C_{36}H_{32}NaO_2$ $[2M+Na]^+$ 519.2300, found 519.2320. The ^{1}H and ^{13}C NMR spectra of **10a** are shown in Figure S3 and S4.



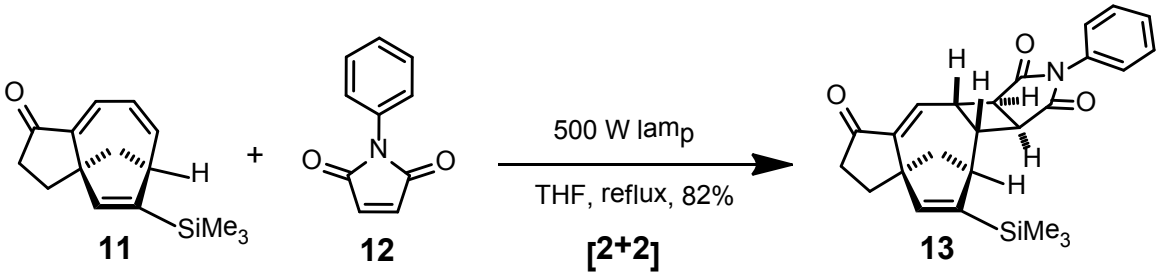
4 **9** **[6+2]** **11** (53%) **11a** (19%)

A solution of CoI_2 (157 mg, 10 mol%) and dppe (399 mg, 20 mol%) in 1,2-dichloroethane (15 ml) was stirred at room temperature for 15 min, then zinc powder (98 mg, 30 mol%), azulenone **4**

(730 mg, 5.00 mmol) in 1,2-dichloroethane (5 ml), trimethylsilyl acetylene **9** (780 µl, 1.1 equiv.) in 1,2-dichloroethane (5 ml) and zinc iodide (319 mg, 20 mol%) were added successively. The resulting mixture was stirred at 40 °C for 20 h then filtered through Celite. Concentration of the filtrate and purification by MPLC to afford desired **11** (647 mg, 2.65 mmol, 53%) and by-product **11a** (232 mg, 0.949 mmol, 19%).

11: ^{1}H-NMR (600 MHz, $CDCl_3$) δ 6.75 (1H, d, *J* = 7.2 Hz), 6.51 (1H, dd, *J* = 11.4, 7.2 Hz), 6.03 (1H, dd, *J* = 11.4, 7.2 Hz), 5.41 (1H, s), 3.28 (1H, t, *J* = 7.2 Hz), 2.61 (1H, m), 2.50 (1H, m) 2.11 (1H, dd, *J* = 12.6, 9.0 Hz), 1.95 (2H, m), 1.51 (1H, d, *J* = 11.4 Hz), 0.07 (9H, s); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 206.24, 148.29, 147.49, 141.21, 135.88, 125.04, 122.45, 56.55, 46.71, 38.44, 36.17, 28.66, -0.43; HR-MS (ESI) calcd. for $C_{30}H_{40}NaO_2Si_2$ $[2M+Na]^+$ 511.2465, found 511.2477; UV (EtOH) λ_{max} 327 nm (ε 6100). The ^{1}H and ^{13}C NMR spectra of **11** are shown in Figure S5 and S6.

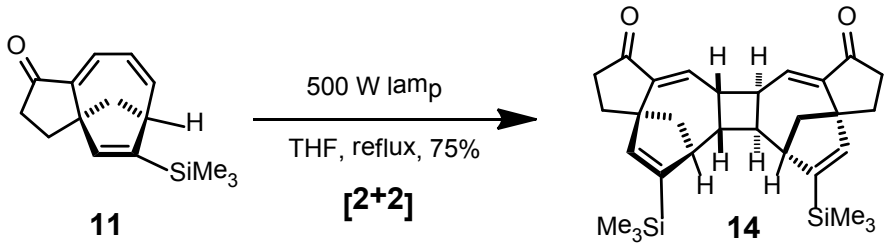
11a: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.22 (1H, d, *J* = 11.6 Hz), 5.95 (1H, dd, *J* = 11.6, 6.0 Hz), 3.50 (1H, t, *J* = 6.0 Hz), 2.91 (1H, dd, *J* = 19.6, 9.6 Hz), 2.67 (1H, m), 2.61 (2H, m), 2.44 (1H, t, *J* = 5.0 Hz), 2.08 (1H, m), 1.96 (1H, m), 0.14 (9H, s); ^{13}C-NMR (100 MHz, C_6D_6) δ 205.78, 173.63, 135.59, 133.12, 119.19, 108.84, 87.17, 34.64, 34.47, 32.00, 31.20, 28.74, 0.51; HR-MS (ESI) calcd. for $C_{30}H_{40}NaO_2Si_2$ $[2M+Na]^+$ 511.2465, found 511.2426. The ^{1}H and ^{13}C NMR spectra of **11a** are shown in Figure S7 and S8.



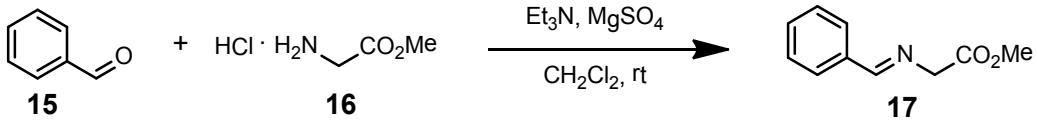
To a solution of **11** (244 mg, 1.00 mmol) in THF (20 ml) was added *N*-phenylmaleimide **12** (519 mg, 3.00 mmol). The resulting reaction mixture was irradiated with 500 W spot lamp (Iwasaki: PRS500W) for 15 h under reflux, then cooled to room temperature and concentrated. The residue was purified by MPLC to afford **13** (340 mg, 0.815 mmol, 82%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ

7.50 (2H, t, *J* = 7.6 Hz), 7.41 (1H, t, *J* = 7.6 Hz), 7.31 (2H, d, *J* = 7.6 Hz), 6.51 (1H, d, *J* = 4.8 Hz), 6.19 (1H, s), 3.55 (1H, m), 3.42 (1H, t, *J* = 6.8 Hz), 3.22 (2H, m), 3.12 (1H, m), 2.50 (2H, m), 2.34 (1H, d, *J* = 12.0 Hz), 2.22 (1H, dd, *J* = 12.0, 6.8 Hz), 2.11 (1H, m), 1.97 (1H, m), 0.1 (9H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 206.14, 178.02, 177.23, 150.38, 145.39, 145.30, 133.31, 132.31, 129.70, 129.21, 126.78, 57.29, 50.91, 47.12, 46.49, 43.79, 42.07, 38.75, 29.79, -0.55; HR-MS (ESI) calcd. for $C_{25}H_{28}NO_3Si$ $[M+H]^+$ 418.1838, found 418.1830. UPLC analysis of the crude reaction mixture including **13** is shown in Figure S21. The ^{1}H and ^{13}C NMR spectra of **13** are shown in Figure S9 and S10.

Synthesis of 18:

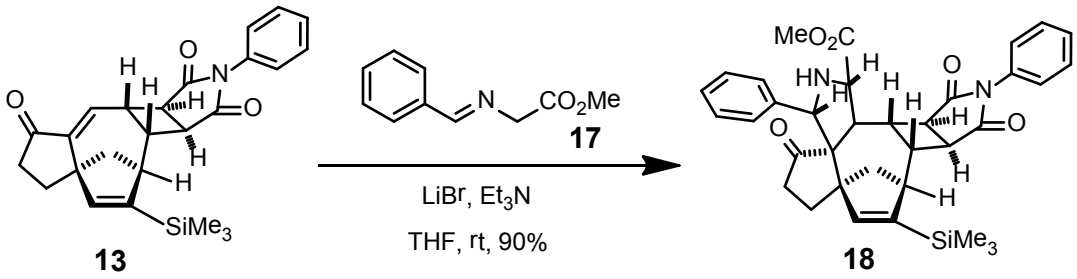


A solution of **11** (200 mg, 0.820 mmol) in THF (8 ml) was irradiated with 500 W spot lamp (Iwasaki: PRS500W) under reflux for 9 h, and then cooled down to room temparature and concentrated. The resulting residue was purified by MPLC to afford **14** (150 mg, 0.307 mmol, 75%). ^{1}H-NMR (400 MHz, C_6D_6) δ 6.60 (2H, d, *J* = 2.8 Hz), 5.92 (2H, s), 2.92 (2H, d, *J* = 7.2 Hz), 2.86 (2H, d, *J* = 7.2 Hz), 2.74 (2H, d, *J* = 7.2 Hz), 2.14 (6H, m), 1.83 (2H, dd, *J* = 12.0, 7.2 Hz), 1.62 (2H, m), 1.45 (2H, m), 0.14 (18H, s); ^{13}C-NMR (100 MHz, C_6D_6) δ 203.89, 148.77, 145.28, 142.80, 136.04, 56.91, 49.20, 46.38, 45.41, 44.55, 38.40, 29.82, -0.66; HR-MS (ESI) calcd. for $C_{30}H_{40}NaO_2Si_2$ $[M+Na]^+$ 511.2465, found 511.2493. The ^{1}H and ^{13}C-NMR spectra of **14** are shown in Figure S11 and S12. The structure of **14** was confirmed by X-ray analysis and ORTEP drawing is shown in Figure S23. The crystallographic data [CCDC-910960] can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.



15 16 17

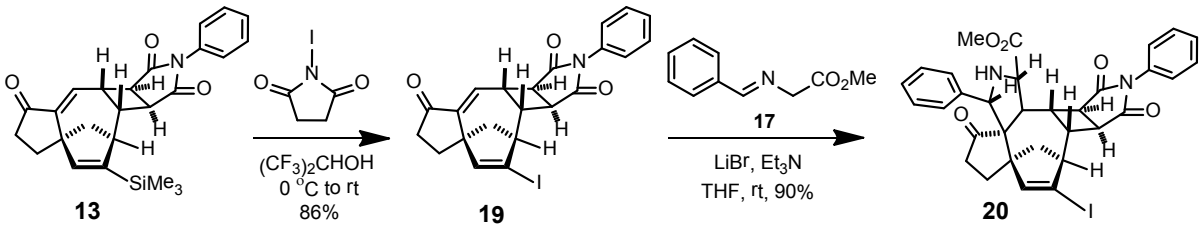
To a suspension of hydrochloride salt of glycine methylester **16** (1.88 g, 15.0 mmol) and $MgSO_4$ (1.80 g, 15.0 mmol) in CH_2Cl_2 (20 ml) was added Et_3N (2.10 ml, 15.0 mmol). After stirring the mixture at room temperature for 1 h, benzaldehyde **15** (1.06 g, 10.0 mmol) was added. The reaction was stirred at room temperature for 12 h, and the resulting precipitate was then removed by filtration. The filtrate was washed with water (5 ml), and then the separated aqueous phase was extracted with CH_2Cl_2 (30 ml). Combined organic extracts were washed with brine (three times), dried over Na_2SO_4 and concentrated. The resulting **17** was used without further purification. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.29 (1H, s), 7.77 (2H, m), 7.43 (3H, m), 4.41 (2H, s), 3.77 (3H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.87, 165.77, 135.96, 131.59, 128.97, 128.85, 62.31, 52.43. The ^{1}H and ^{13}C NMR spectra of **17** are shown in Figure S13 and S14.



13 18

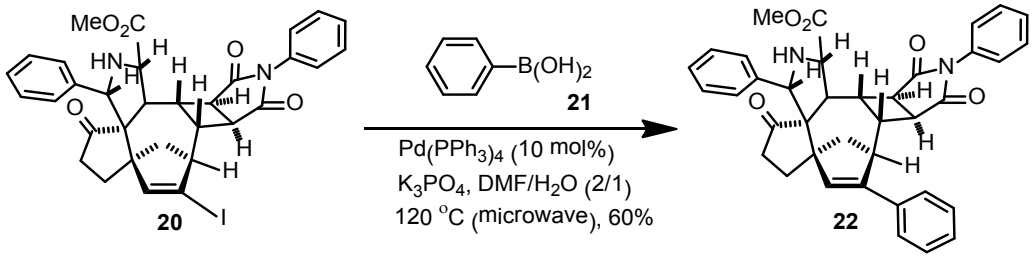
To a solution of **13** (412 mg, 1.00 mmol) in THF (20 ml) were added **17** (265 mg, 1.50 mmol), lithium bromide (194 mg, 2.26 mmol) and triethylamine (315 µl, 2.26 mmol). After stirring at room temperature for 15 h, the reaction mixture was treated with saturated solution of NH_4Cl (10 ml) followed by water (30 ml) and then extracted with CH_2Cl_2 for three times. The combined organic extracts were dried over Na_2SO_4 and concentrated. The residue was purified by MPLC to afford **18** (535 mg, 0.899 mmol, 90%) as a white solid. ^{1}H-NMR (600 MHz, CD_3CN) δ 7.32 (2H, t, J = 7.6 Hz), 7.25 (1H, t, J = 7.6 Hz), 7.15 (5H, m), 7.04 (2H, m), 6.10 (1H, s), 4.29 (1H, brs), 3.61 (3H, s), 3.27 (1H, brs), 3.24 (1H, t, J = 7.6 Hz), 3.15 (1H, dd, J = 7.6, 2.4 Hz), 2.84 (1H, dd, J = 10.8, 3.0 Hz),

2.80 (1H, dd, J = 7.2, 2.4 Hz), 2.63 (1H, m), 2.57 (1H, brs), 2.48 (1H, t, J = 7.6 Hz), 2.11 (1H, d, J = 12.6 Hz), 1.90 (1H, m), 1.46 (1H, dd, m), 1.37 (1H, dd, J = 12.6, 7.2 Hz), 1.27 (1H, m), 1.11 (1H, m), 0.03 (9H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 222.17, 177.84, 176.77, 174.15, 150.30, 145.34, 138.09, 132.24, 129.49, 129.15, 128.91, 128.86, 127.91, 126.49, 73.23, 67.91, 65.91, 58.14, 53.93, 52.85, 49.30, 48.22, 44.74, 43.68, 41.73, 41.69, 36.76, 32.96, -0.77; HR-MS (ESI) calcd. for $C_{35}H_{39}N_2O_5Si$ $[M+H]^+$ 595.2628, found 595.2644. UPLC analysis of the crude reaction mixture including **18** is shown in Figure S22. The ^{1}H and ^{13}C-NMR spectra of **18** are shown in Figure S15 and S16. The structure of **18** was confirmed by X-ray analysis and ORTEP drawing is shown in Figure S24. The crystallographic data [CCDC-910961] can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.



To a solution of **13** (417 mg, 1.00 mmol) in hexafluoroisopropanol was added *N*-iodosuccinimide (338 mg, 1.50 mmol) portion-wise at 0 °C.[2] The resulting mixture was allowed to warm up to room temperature. After stirring for 4 h, the mixture was quenched with water (30 ml) and extracted with dichloromethane (30 ml x 3). The combined organic extracts were washed with saturated aqueous sodium thiosulfate (30 ml) and water, dried over Na_2SO_4, and concentrated. The residue was purified by MPLC to afford **19** (405 mg, 0.859 mmol, 86%). To a solution of **19** (118 mg, 0.250 mmol) in THF (3 ml) were added **17** (66 mg, 0.37 mmol), lithium bromide (65.0 mg, 0.75 mmol) and triethylamine (105 µl, 0.75 mmol). The reaction mixture was stirred at room temperature for overnight. The reaction mixture was quenched with saturated aqueous solution of NH_4Cl (10 ml) and extracted with $CHCl_3$ (30 ml x 3). The combined extracts were washed with brine, water, dried over Na_2SO_4 and concentrated. The residue was purified by MPLC to afford **20** (146 mg, 0.225

mmol, 90%) as a white solid. ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.52 (2H, t, *J* = 7.2 Hz), 7.43 (1H, t, *J* = 7.2 Hz), 7.34 (3H, m), 7.31 (4H, m), 6.43 (1H, s), 4.43 (1H, s), 3.94 (3H, s), 3.67 (1H, s), 3.52 (2H, m), 3.02 (2H, m), 2.94 (1H, dd, *J* = 7.2, 2.4 Hz), 2.90 (1H, t, *J* = 7.2 Hz), 2.87 (1H, brs), 2.27 (1H, d, *J* = 12.0 Hz), 2.12 (1H, m), 1.82 (2H, m), 1.35 (2H, m); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 220.93, 177.46, 176.51, 173.94, 144.58, 137.60, 132.08, 129.48, 129.22, 129.10, 128.93, 127.77, 126.60, 100.06, 72.96, 67.73, 65.88, 58.47, 55.02, 54.28, 52.92, 46.36, 43.95, 43.64, 40.97, 40.43, 36.42, 32.33; HR-MS (ESI) calcd. for $C_{32}H_{30}IN_2O_5$ $[M+H]^+$ 649.1199, found 649.1239. The ^{1}H and ^{13}C NMR spectra of **20** are shown in Figure S17 and S18.



Vinyl iodide **20** (130 mg, 0.20 mmol), phenylboronic acid **21** (27 mg, 0.22 mmol), K_3PO_4 (64 mg, 0.30 mmol), and $Pd(PPh_3)_4$ (23 mg, 10 mol%) were suspended in 3 ml of DMF/H_2O (2/1) using a microwave reaction glass vial (5 ml) containing a stirring magnet. The vial was sealed tightly with an aluminium-Teflon crimp top. After bubbling of N_2 gas for 15 min, the mixture was irradiated at 120 °C for 20 min. The resulting mixture was poured into water (30 ml) and extracted with EtOAc (50 ml x 3). The combine organic layers were washed with brine and water, dried over Na_2SO_4 and concentrated. The residue was purified by MPLC to afford **22** (73 mg, 0.12 mmol, 60%). ^{1}H-NMR (600 MHz, DMSO-d_6) δ 7.74 (2H, d, *J* = 7.2 Hz), 7.52 (2H, d, *J* = 7.8 Hz), 7.49 (2H, d, *J* = 7.2 Hz), 7.43 (2H, t, *J* = 7.2 Hz), 7.38 (2H, t, *J* = 7.2 Hz), 7.33 (2H, t, *J* = 7.2 Hz), 7.22 (2H, t, *J* = 7.8 Hz), 6.99 (1H, t, *J* = 7.2 Hz), 6.50 (1H, s), 4.53 (1H, s), 3.84 (3H, s), 3.53 (1H, dd, *J* = 12.0, 9.0 Hz), 3.40 (1H, t, *J* = 9.8 Hz), 3.27 (2H, m), 3.19 (1H, d, *J* = 9.0 Hz), 3.17 (1H, d, *J* = 4.8 Hz), 3.10 (1H, d, *J* = 12.0 Hz), 2.61 (1H, m), 2.45 (1H, d, *J* = 12.6 Hz), 2.10 (1H, m), 1.63 (1H, dd, *J* = 12.6, 7.2 Hz), 1.49 (1H, q, *J* = 9.3 Hz), 1.34 (2H, m); ^{13}C-NMR (150 MHz, DMSO-d_6) δ 220.97, 174.22, 174.00, 170.45,

146.77, 139.73, 139.16, 133.86, 128.76, 128.56, 128.47, 128.23, 128.16, 127.82, 126.34, 123.23, 119.81, 72.51, 66.55, 65.20, 56.48, 52.09, 51.97, 48.67, 46.42, 44.98, 42.51, 41.91, 40.70, 40.20, 40.06, 35.98, 33.12; HR-MS (ESI) calcd. for $C_{38}H_{35}N_2O_5$ $[M+H]^+$ 599.2546, found 599.2487. The ^1H and ^{13}C NMR spectra of **22** are shown in Figure S19 and S20.

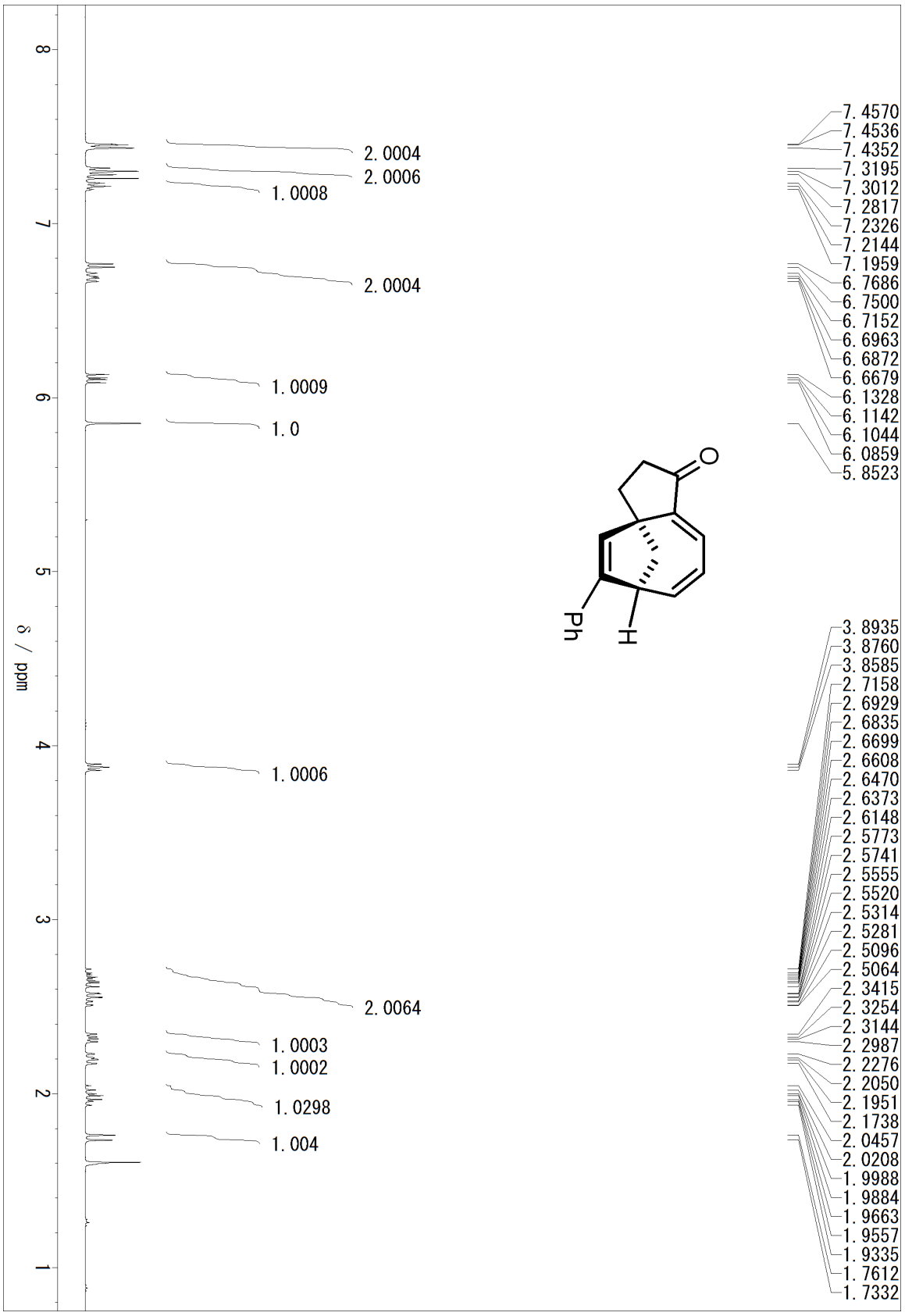


Figure S1. A ^{1}H-NMR spectrum of **10** in $CDCl_3$.

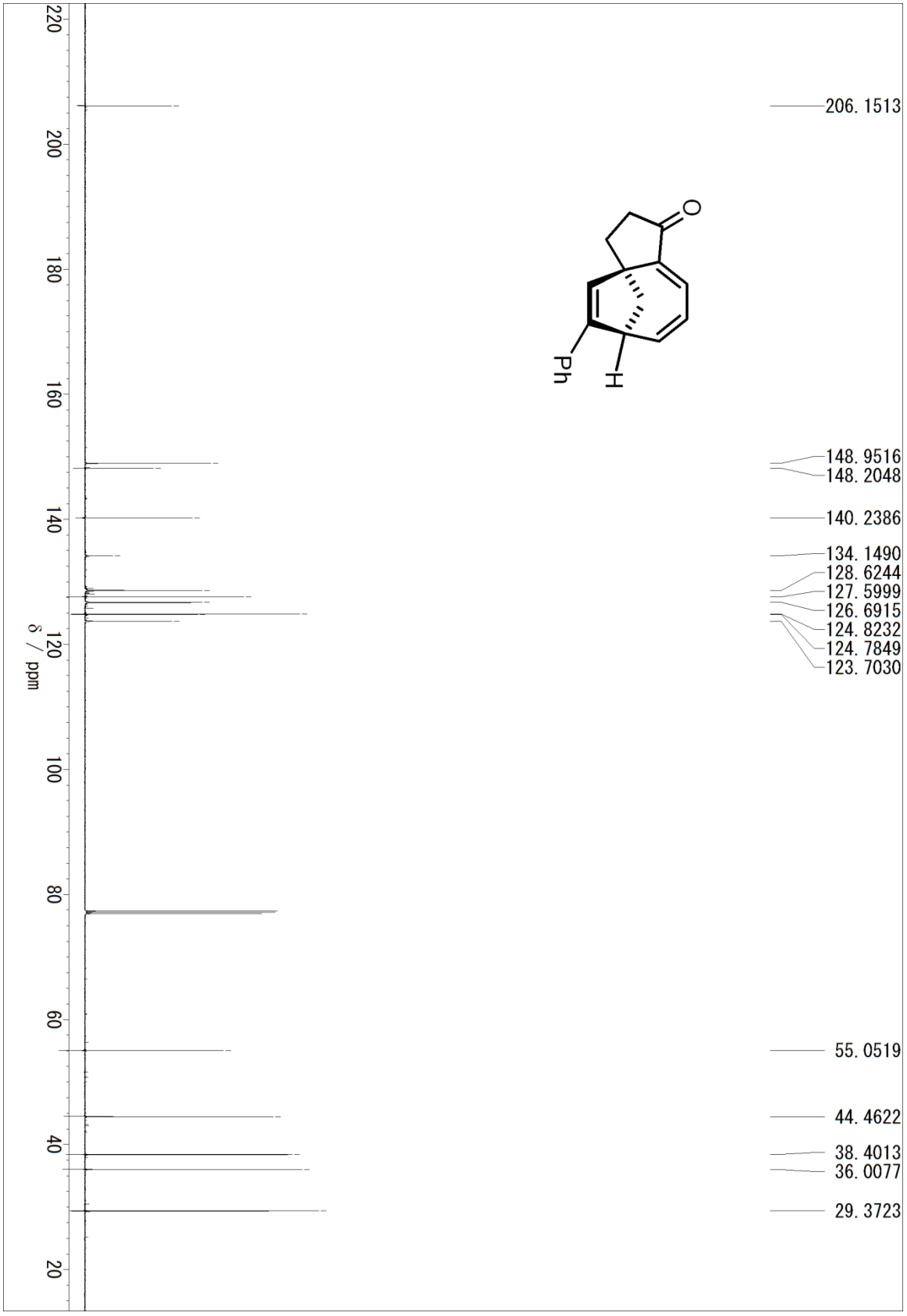


Figure S2. A ^{13}C-NMR spectrum of **10** in $CDCl_3$.

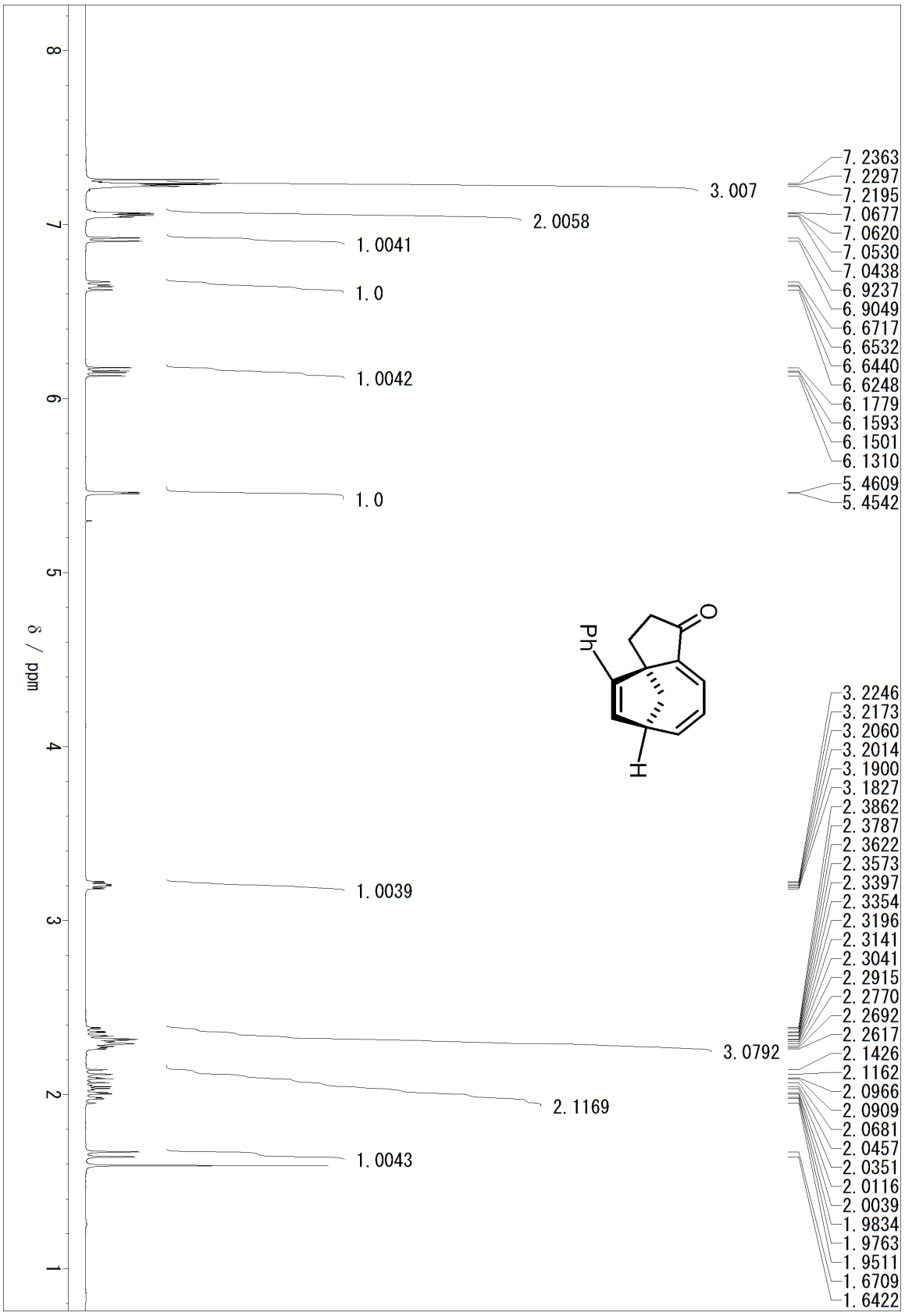


Figure S3. A ^{1}H-NMR spectrum of **10a** in $CDCl_3$.

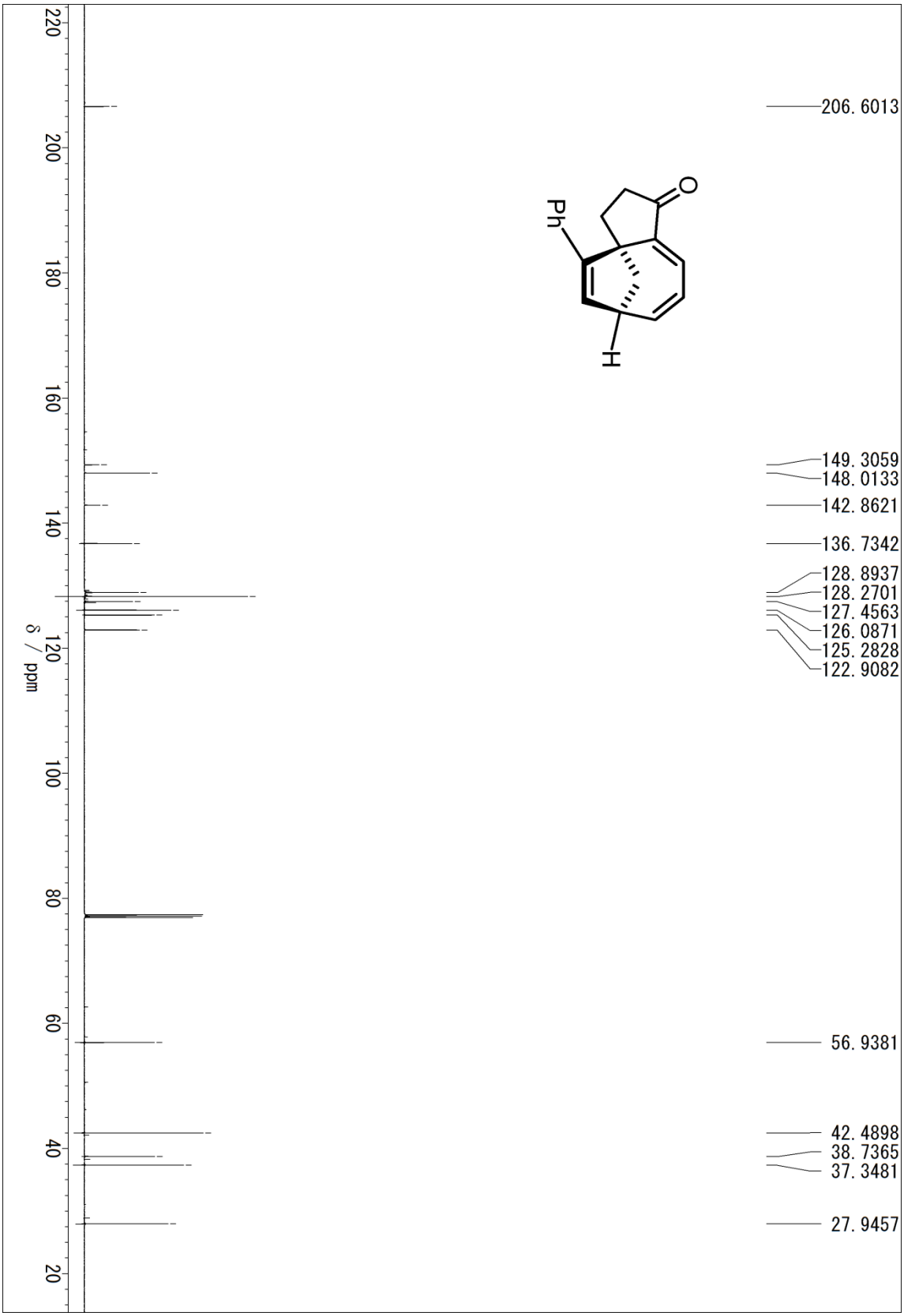


Figure S4. A ^{13}C-NMR spectrum of **10a** in $CDCl_3$.

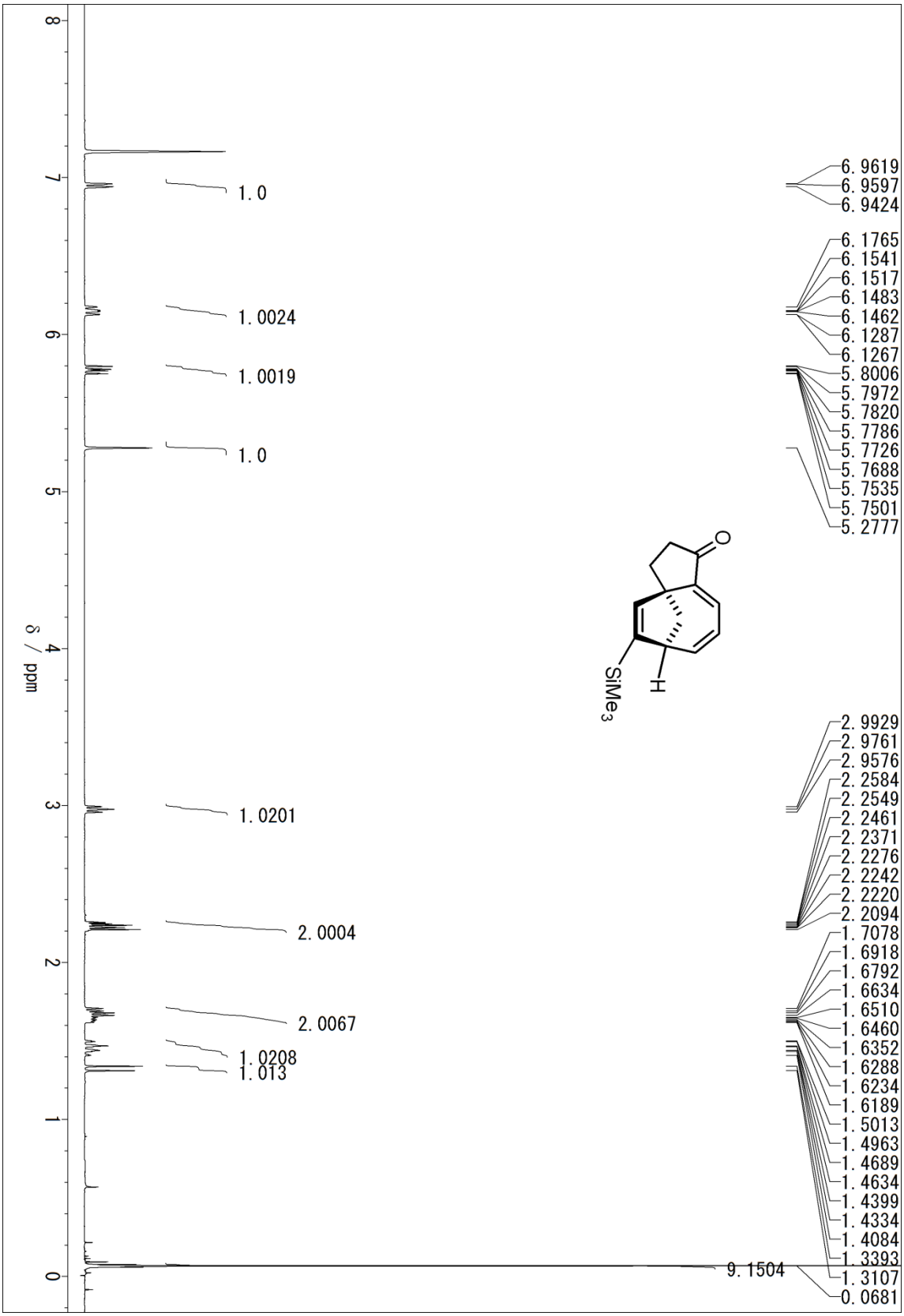


Figure S5. A ^{1}H-NMR spectrum of **11** in $CDCl_3$.

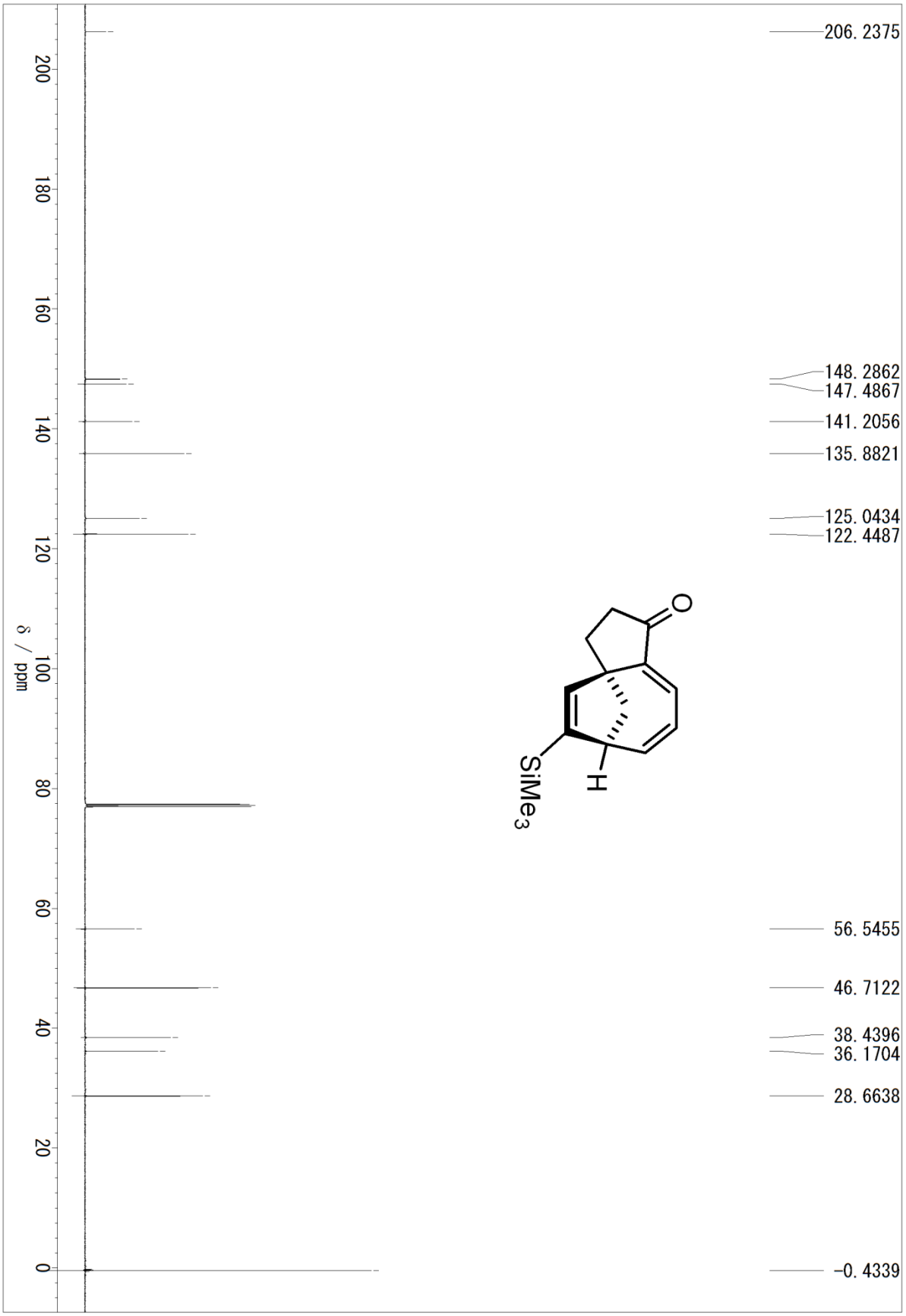


Figure S6. A ^{13}C-NMR spectrum of **11** in $CDCl_3$.

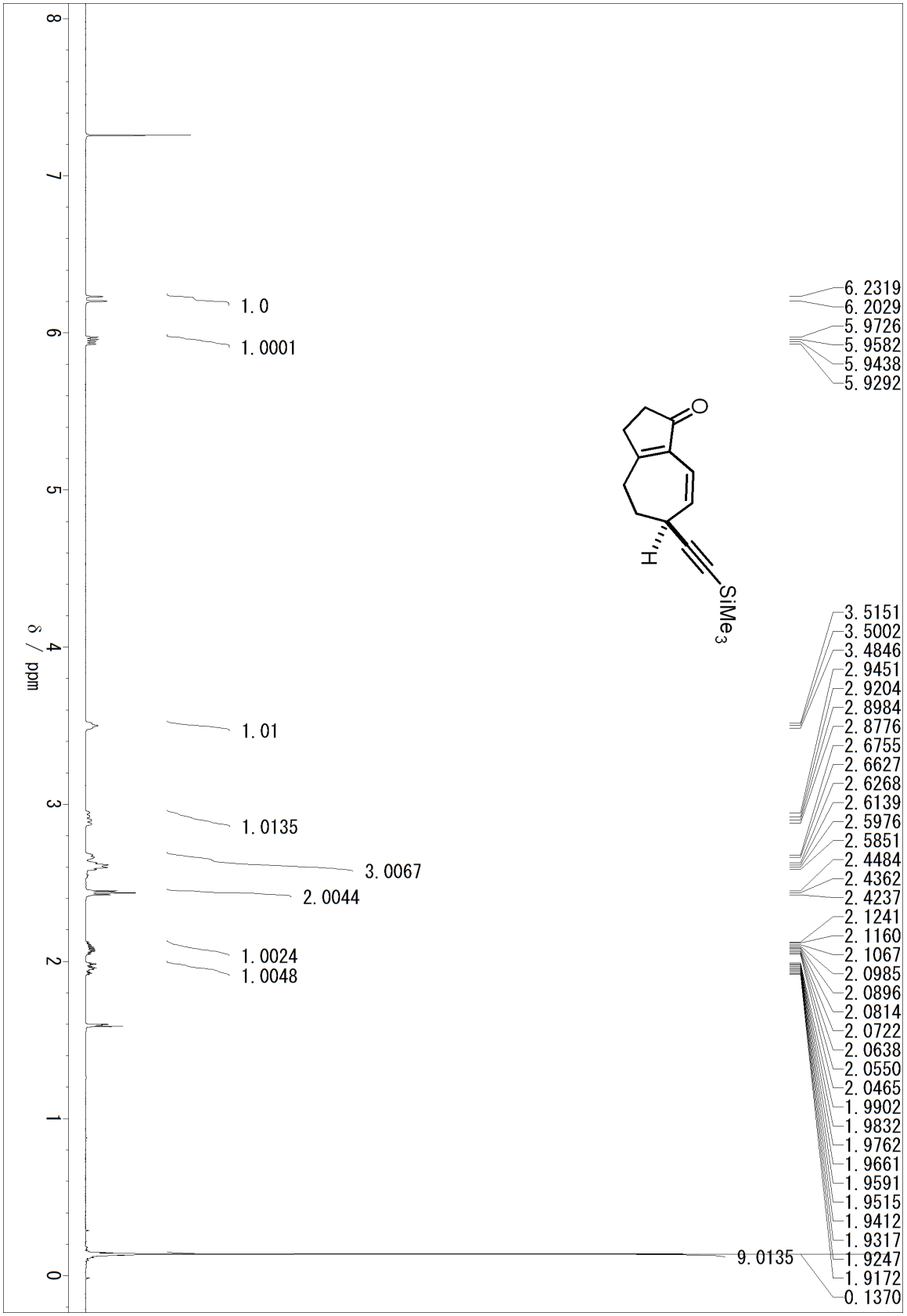


Figure S7. A ^{1}H-NMR spectrum of **11a** in $CDCl_3$.

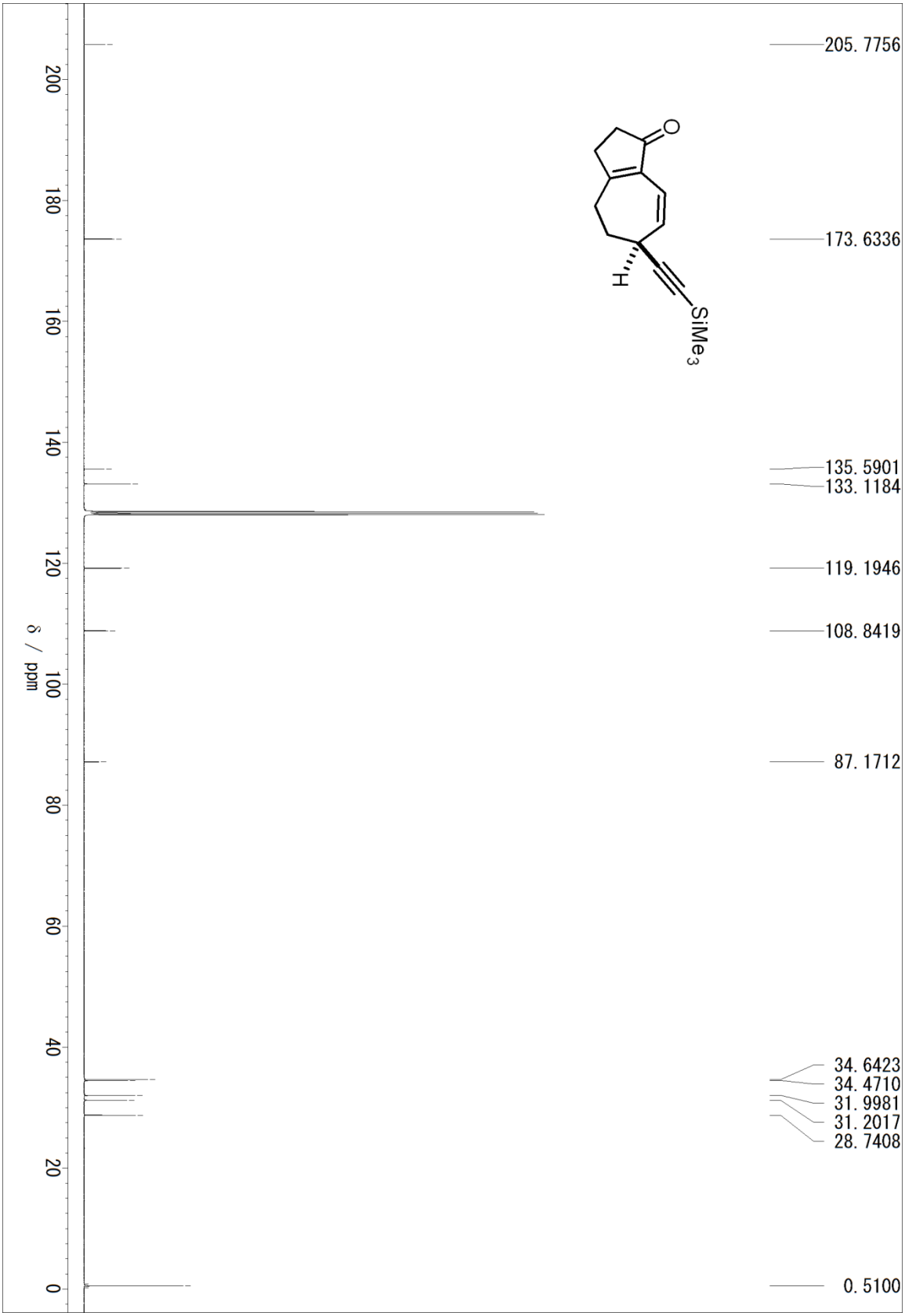


Figure S8. A ^{13}C-NMR spectrum of **11a** in C_6D_6.

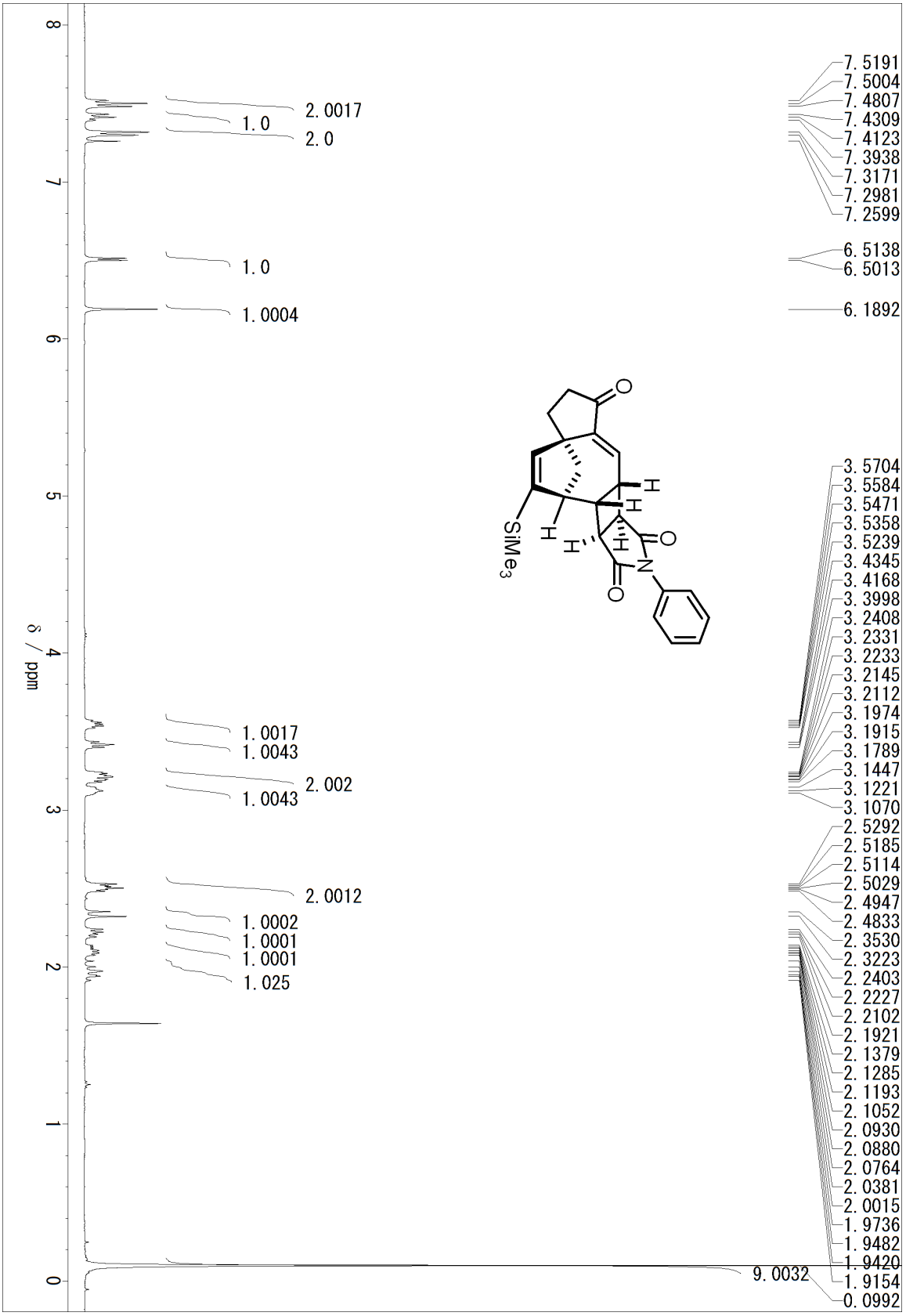


Figure S9. A ^{1}H-NMR spectrum of **13** in $CDCl_3$.

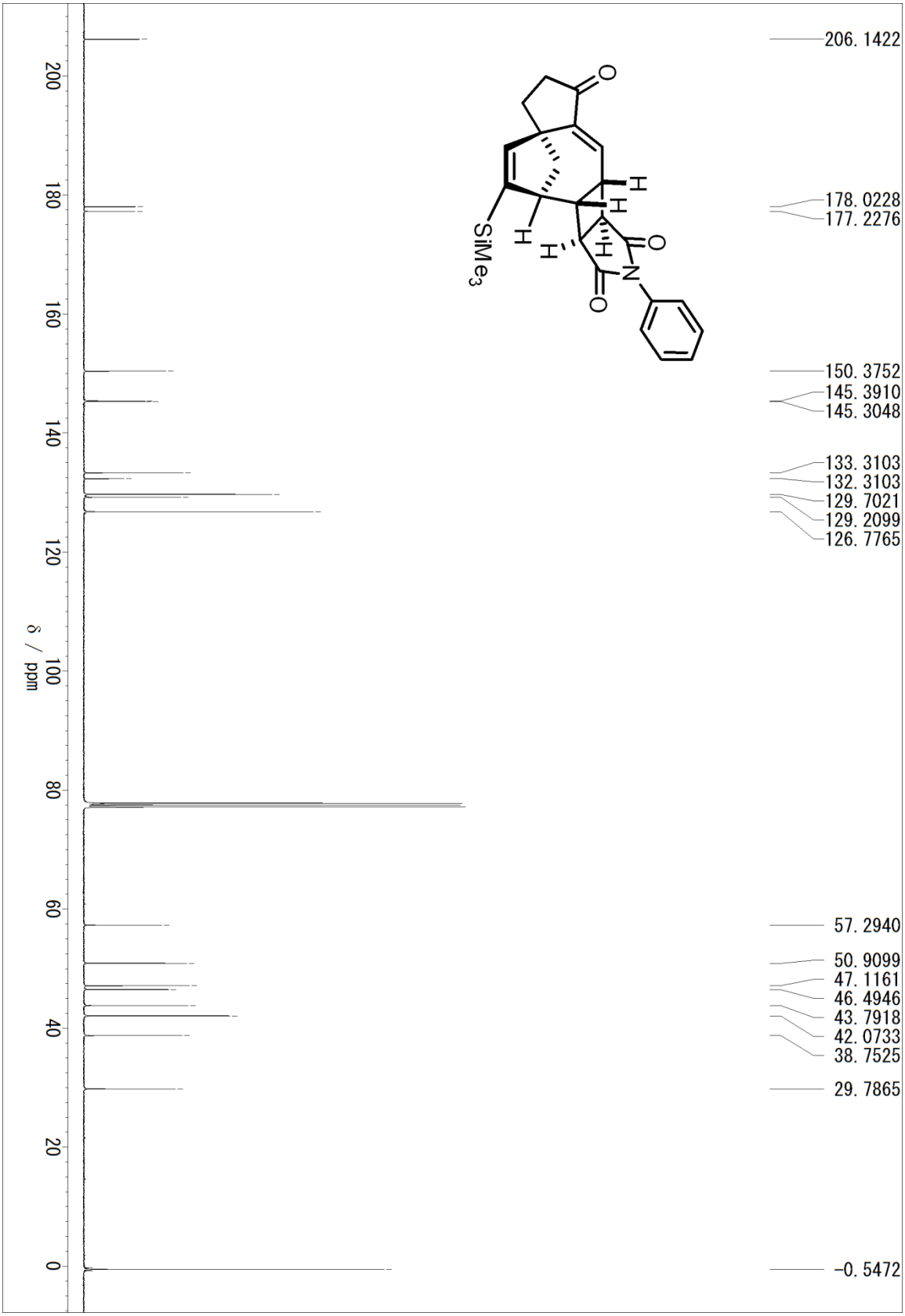


Figure S10. A ^{13}C-NMR spectrum of **13** in $CDCl_3$.

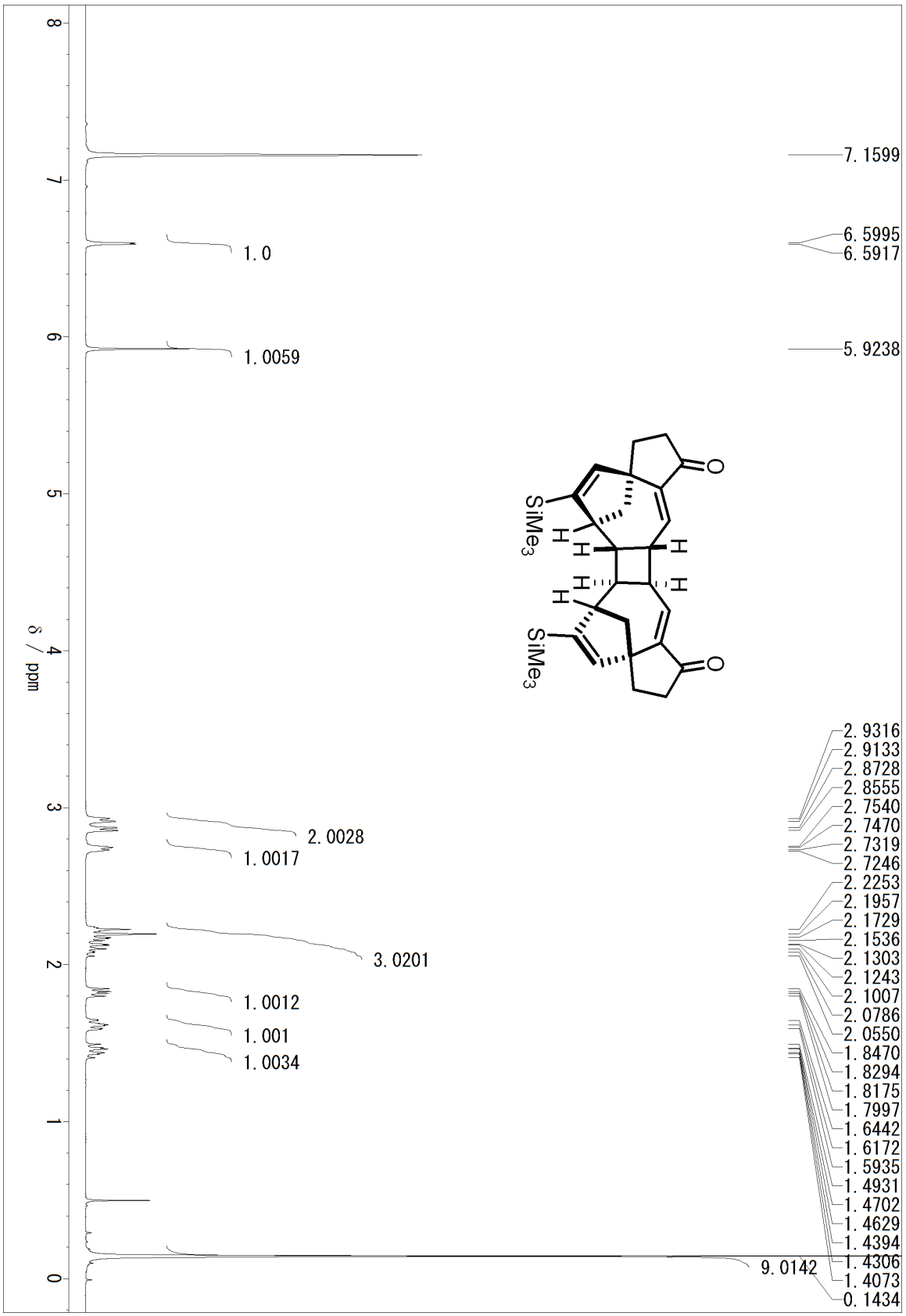


Figure S11. A ^{1}H-NMR spectrum of **14** in C_6D_6.

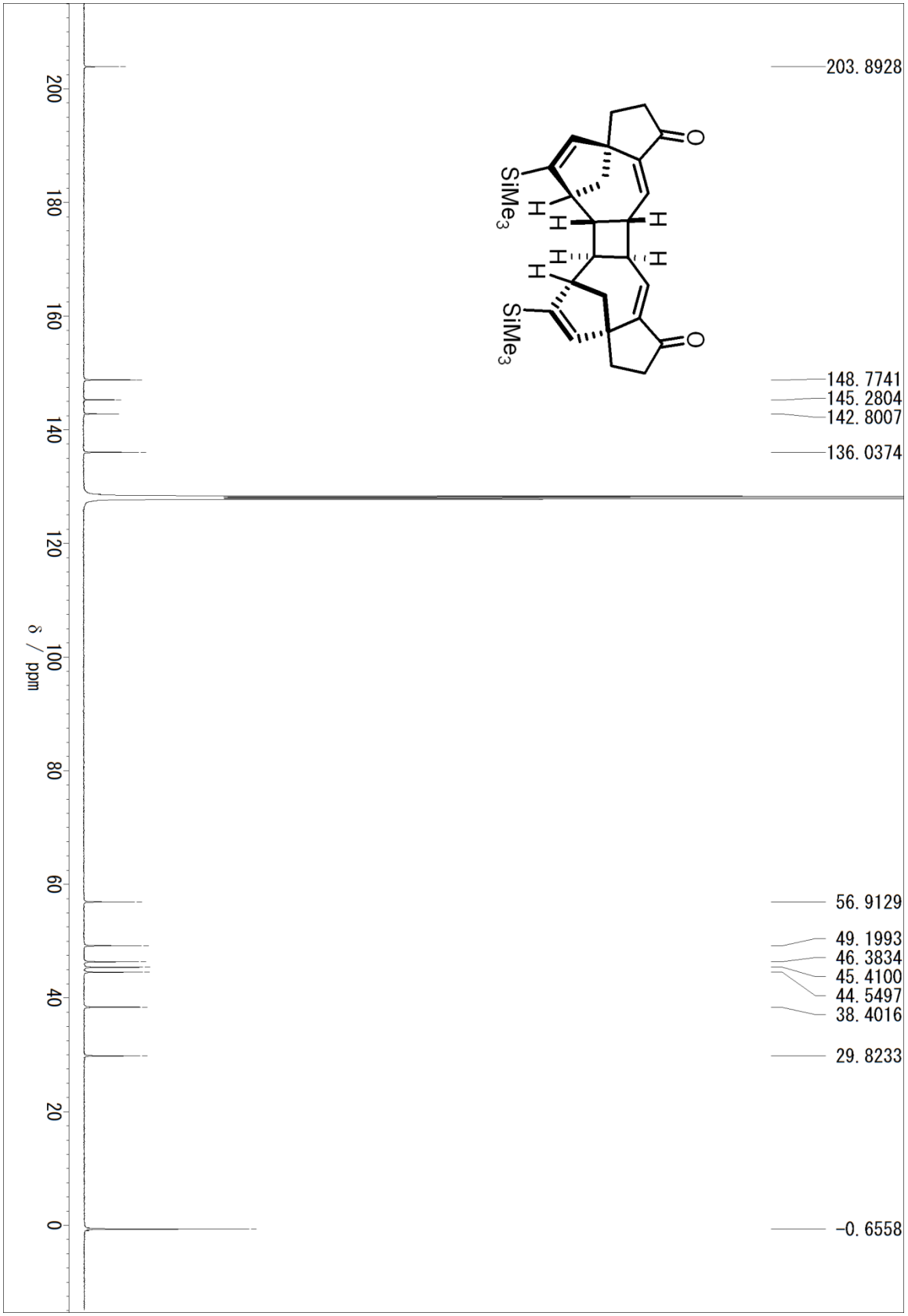


Figure S12. A ^{13}C-NMR spectrum of **14** in C_6D_6.

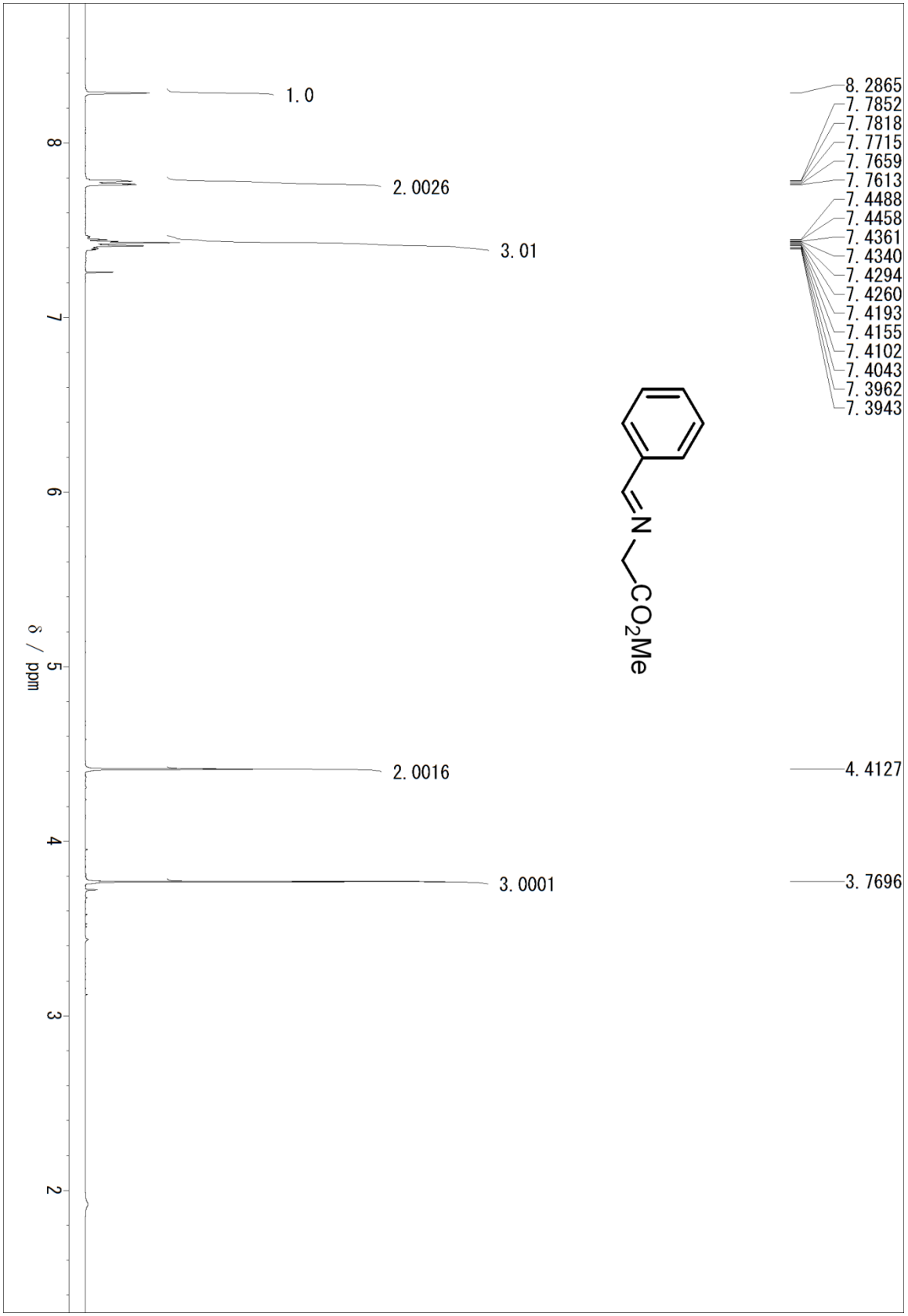


Figure S13. A ^{1}H-NMR spectrum of **17** in $CDCl_3$.

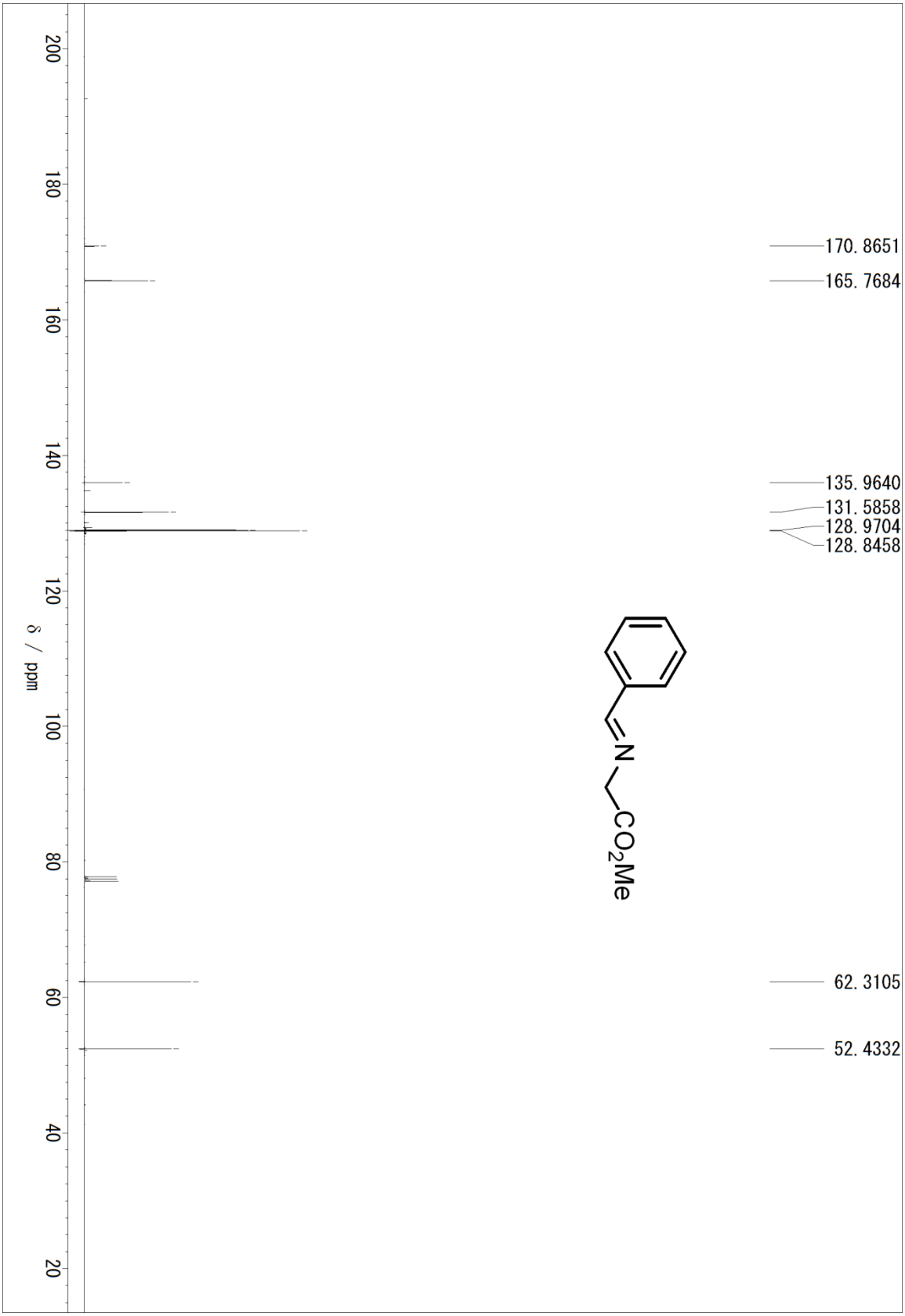


Figure S14. A ^{13}C-NMR spectrum of **17** in $CDCl_3$.

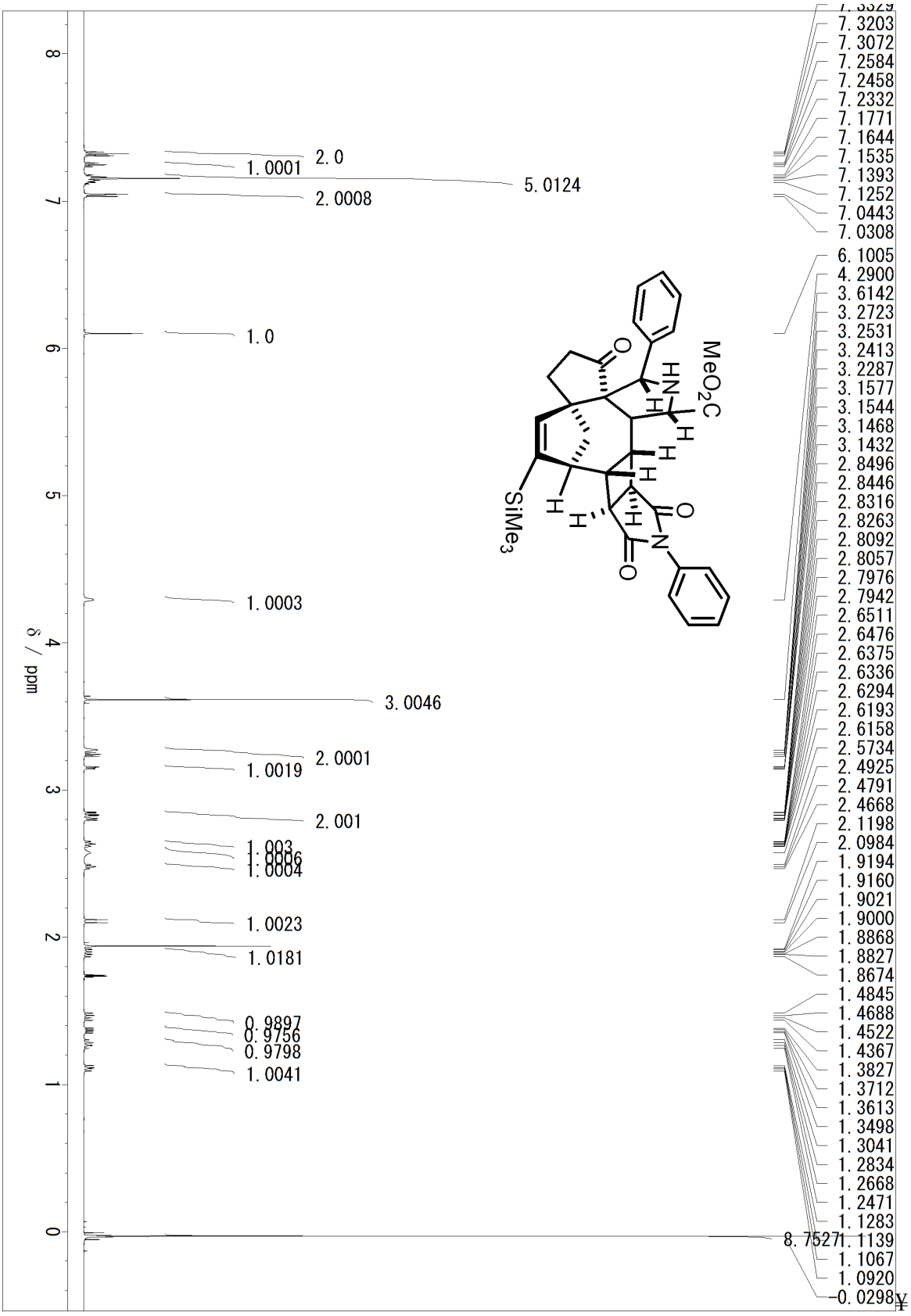


Figure S15. A ^{1}H-NMR spectrum of **18** in CD_3CN.

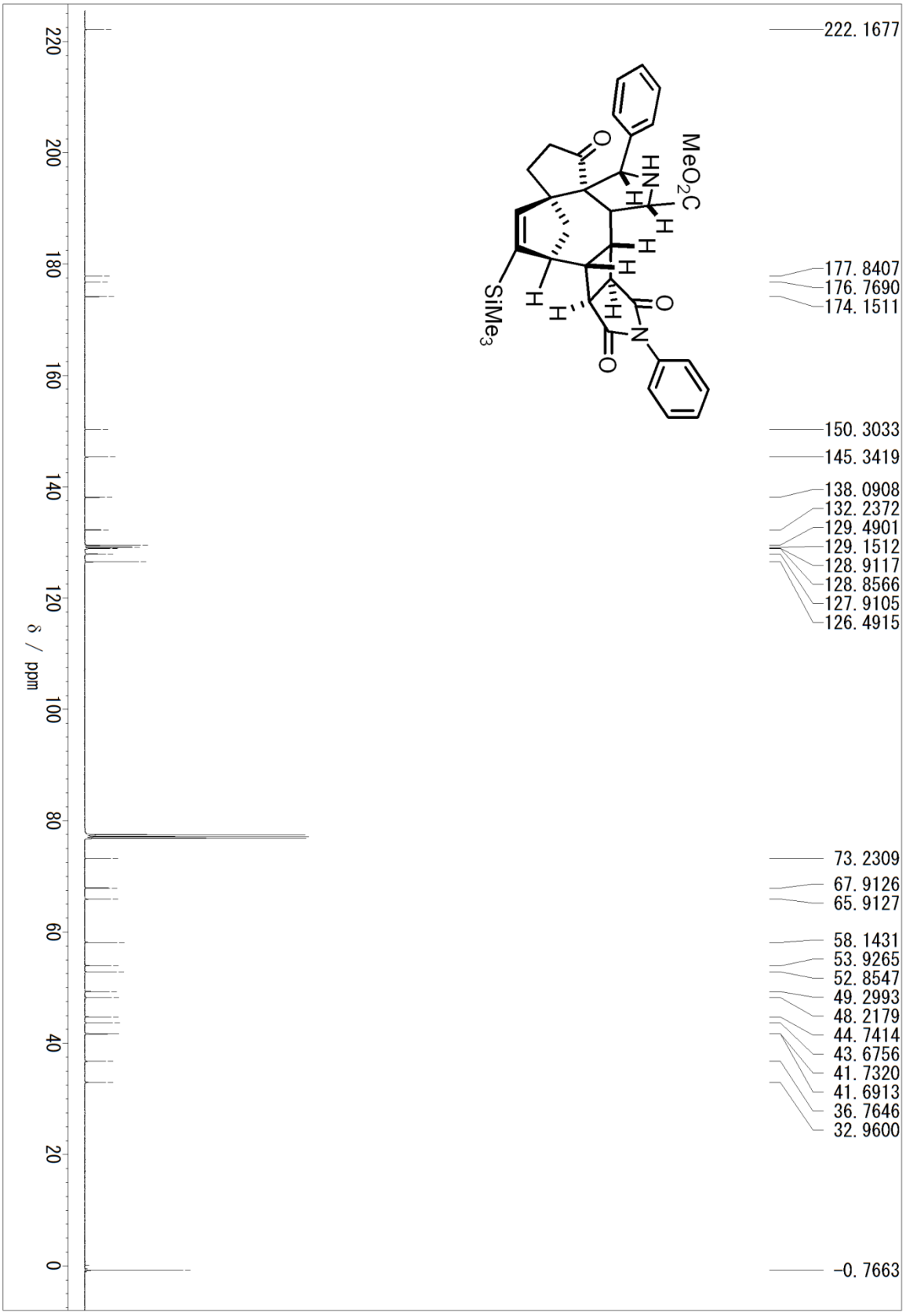


Figure S16. A ^{13}C-NMR spectrum of **18** in $CDCl_3$.

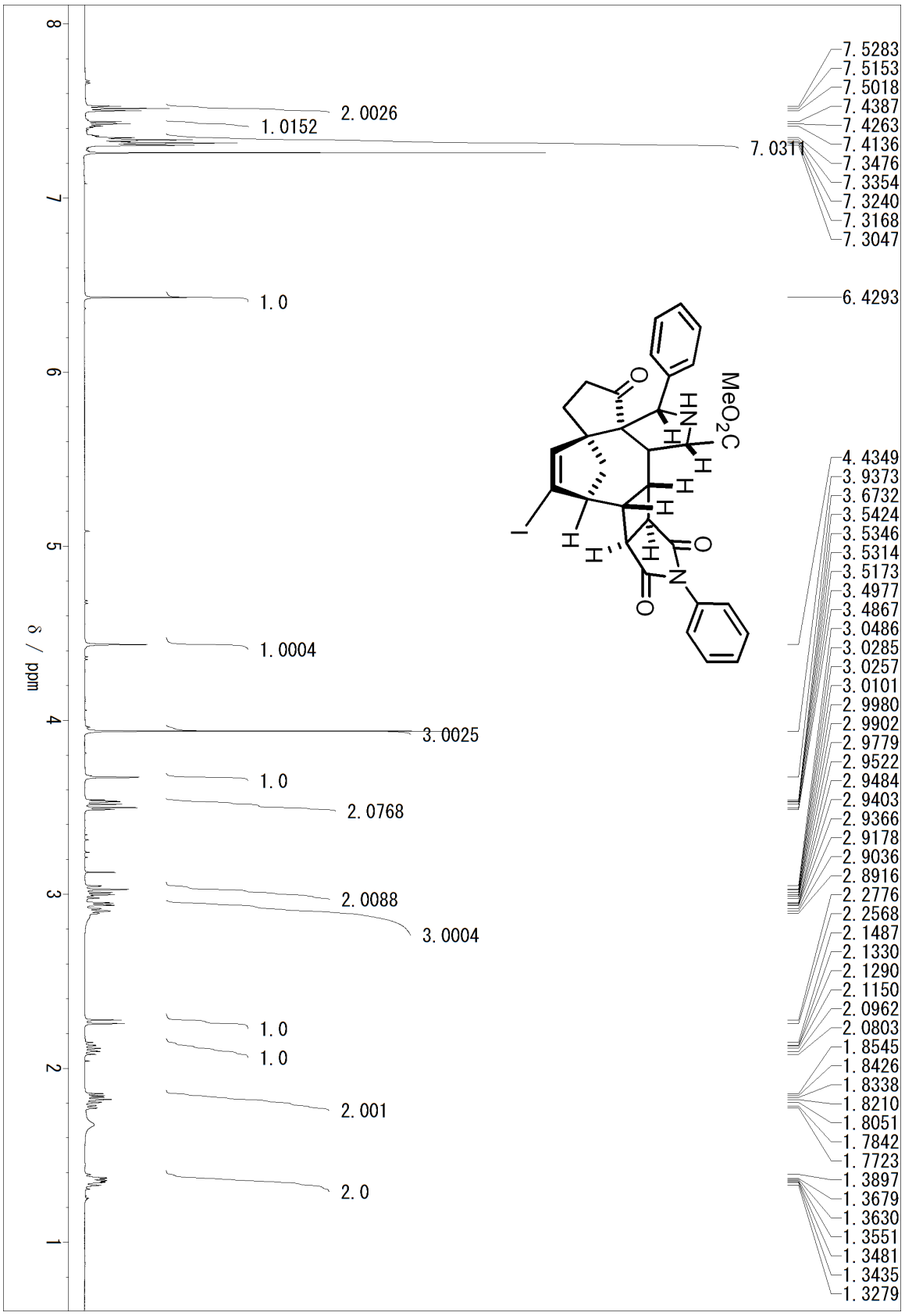


Figure S17. A ^{1}H-NMR spectrum of **20** in $CDCl_3$.

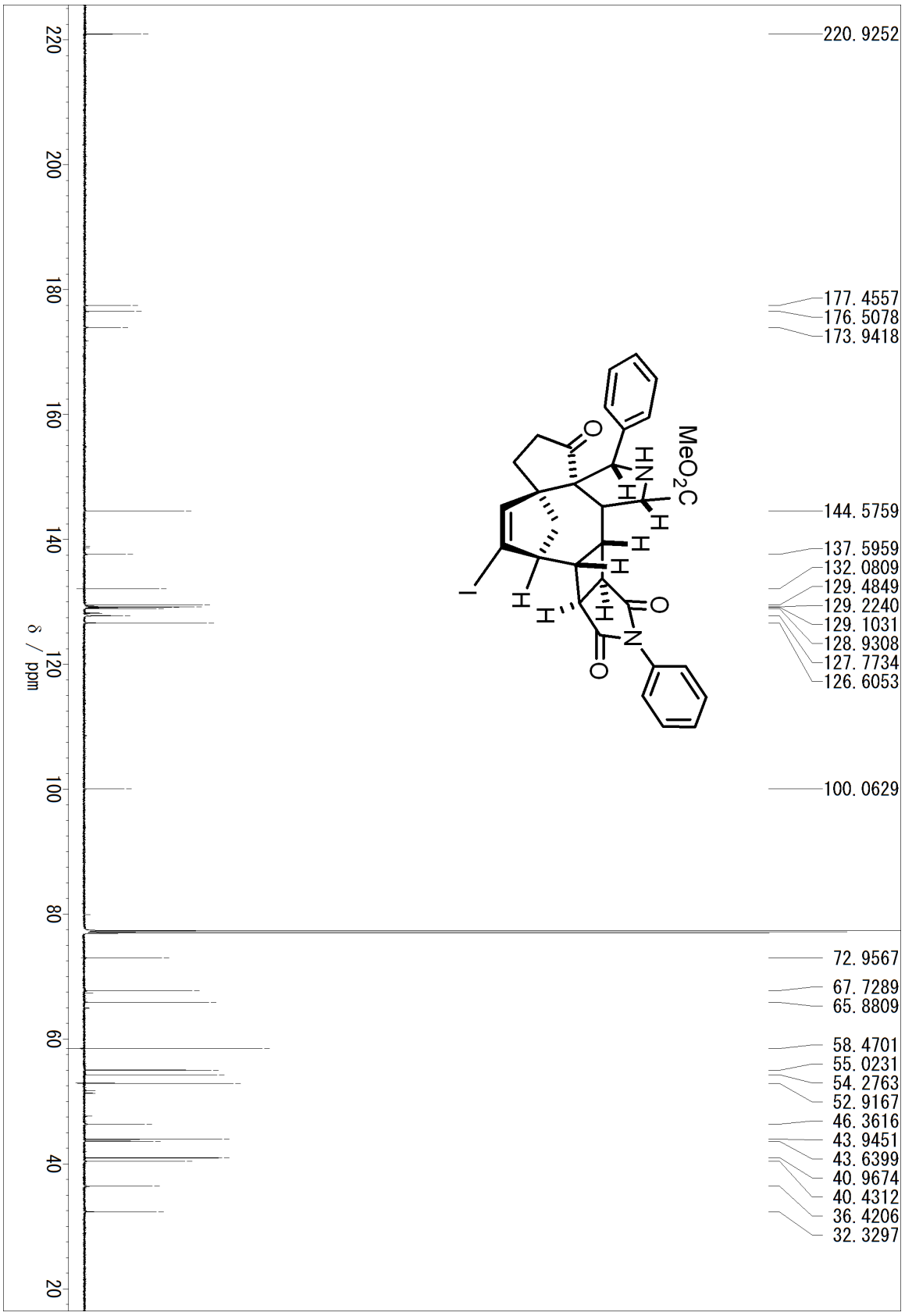


Figure S18. A ^{13}C-NMR spectrum of **20** in $CDCl_3$.

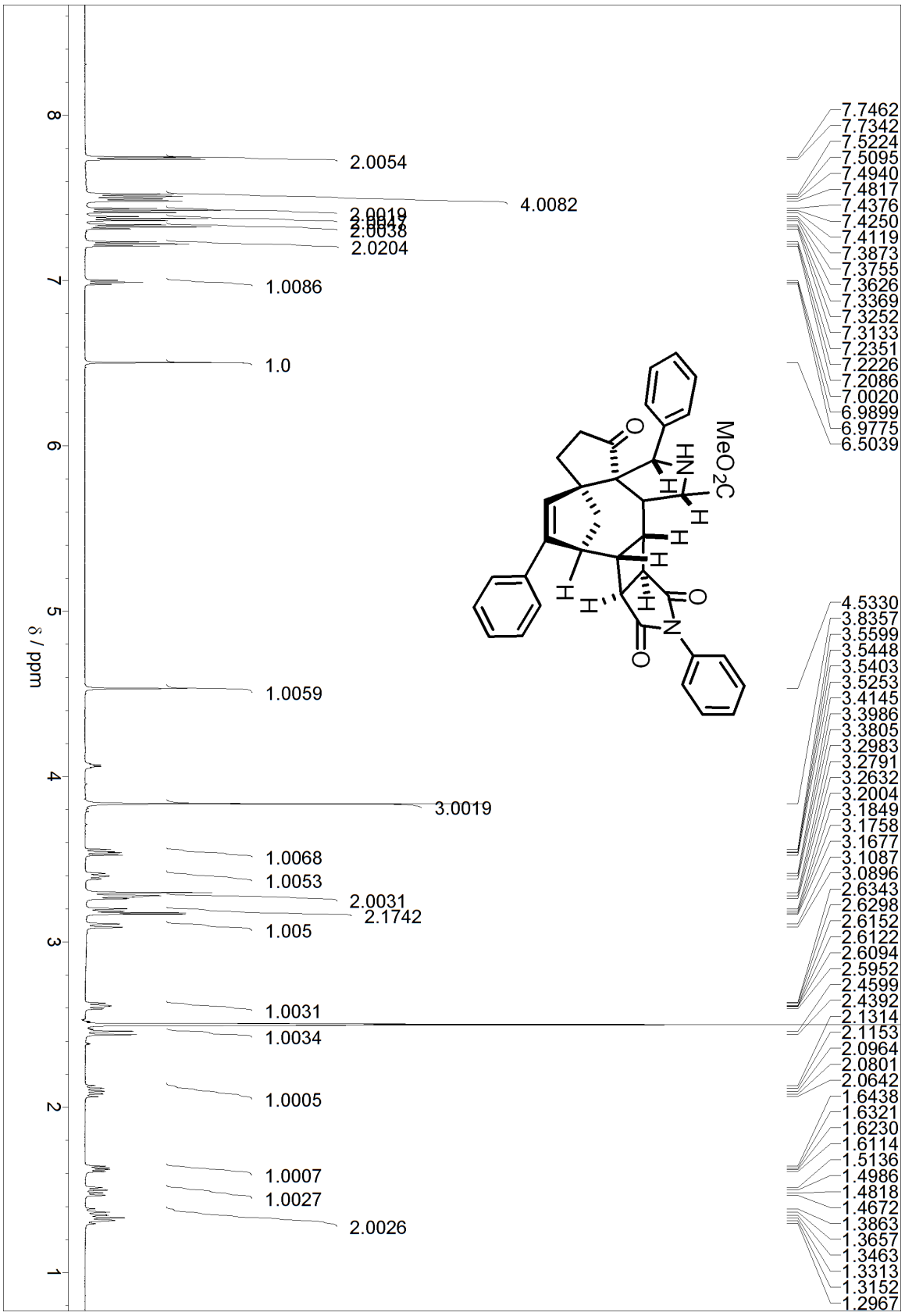


Figure S19. A ^{1}H-NMR spectrum of **22** in DMSO-d_6.

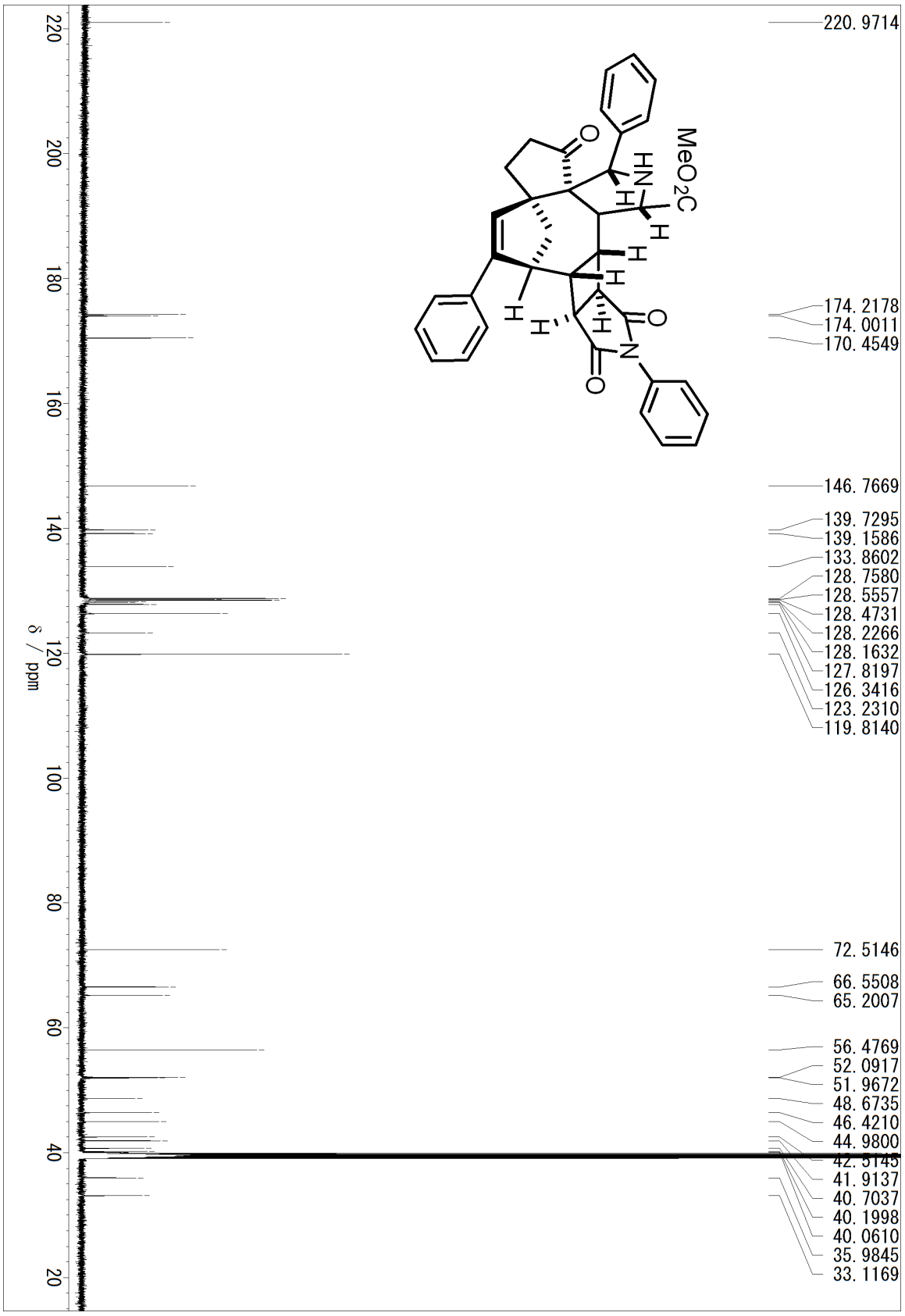


Figure S20. A ^{13}C-NMR spectrum of **22** in DMSO-d_6.

UPLC analysis of the crude reaction mixtures: Analytical ultra-performance liquid chromatography (UPLC) was carried out on WATERS ACQUITY™ UPLC® H-Class system equipped with a PDA detector (210–400 nm). ACQUITY UPLC® BEH C18 1.7 μm 2.1 × 150 mm column was used. Sample was dissolved in CH_3CN and eluted with CH_3CN:H_2O [0-5 min. (a linear gradient: CH_3CN 60% → 40%); 5-9 min. (a linear gradient: CH_3CN 40% → 100%); 9-13 min (CH_3CN 100%); 13-15 min. (a convex gradient back: CH_3CN 100% → 60%). Compounds were detected by UV absorption at 254 nm.

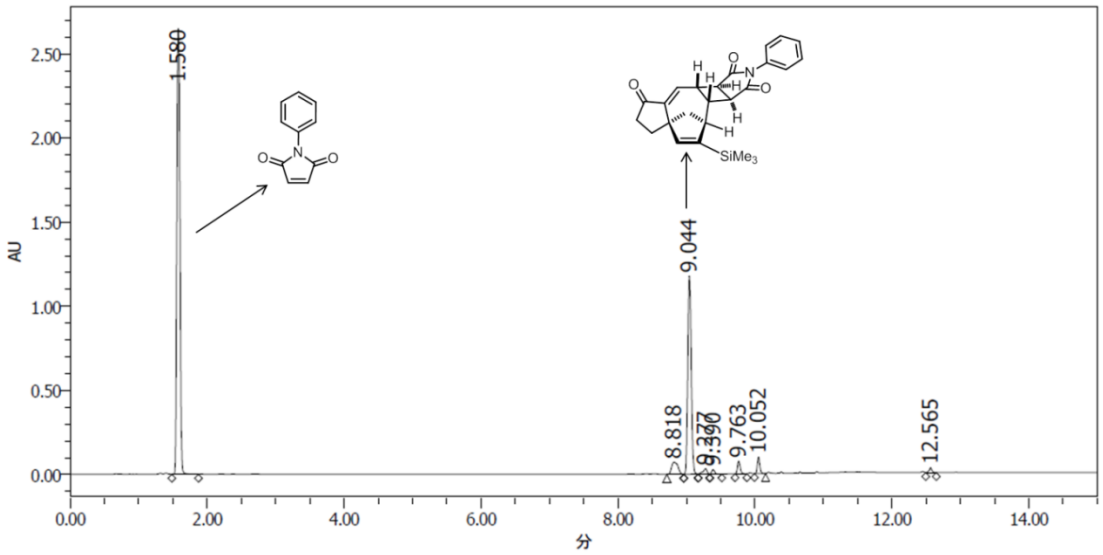


Figure S21. UPLC chromatogram for the crude reaction mixture **(11 + 12 → 13)**.

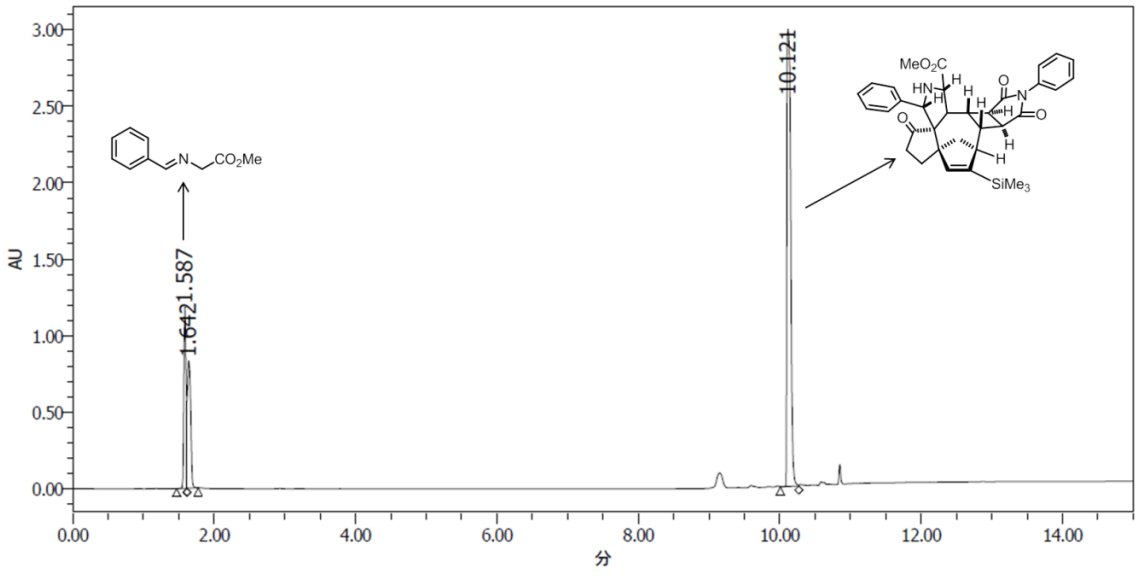


Figure S22. UPLC chromatograph for the crude reaction mixture **(20 + 21 → 22)**.

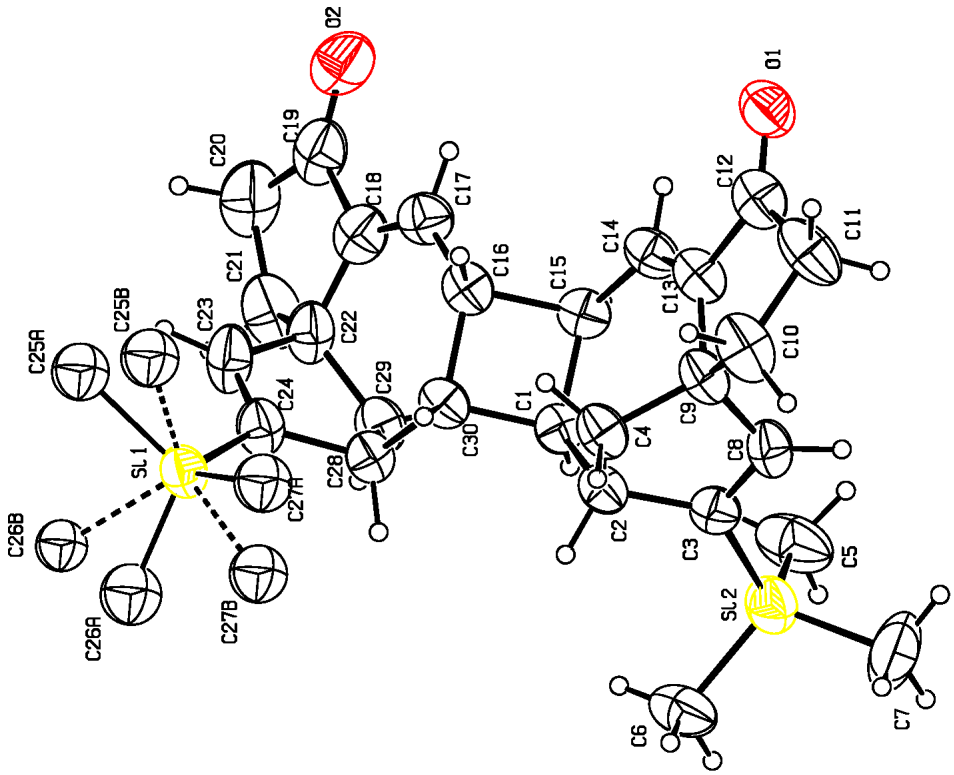


Figure S23. ORTEP drawing of **14**. Ellipsoids are drawn at the 50% probability level.

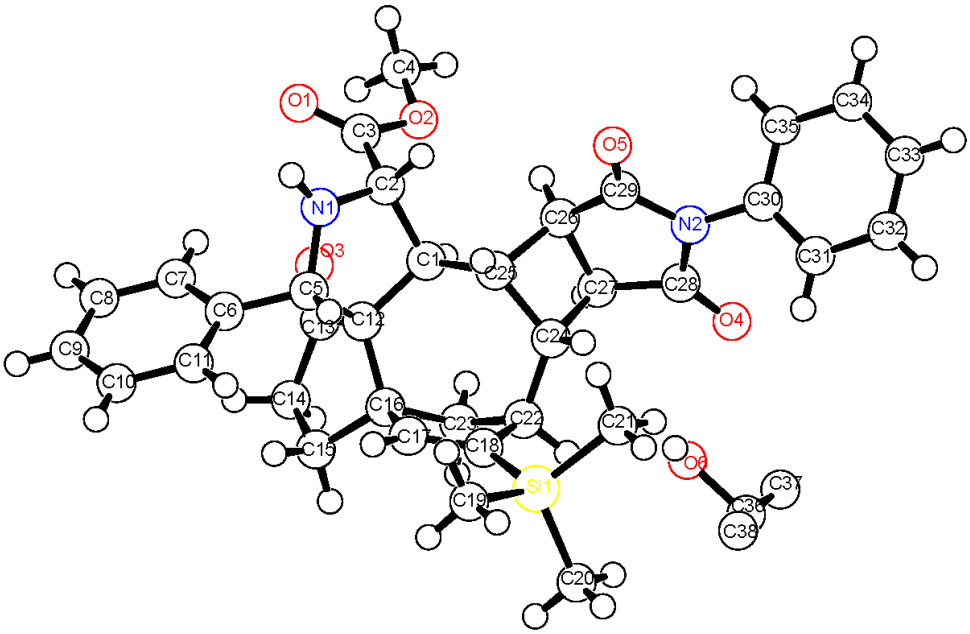


Figure S24. A plot showing the relative stereochemistry of compound **18** as an isopropanol solvate.

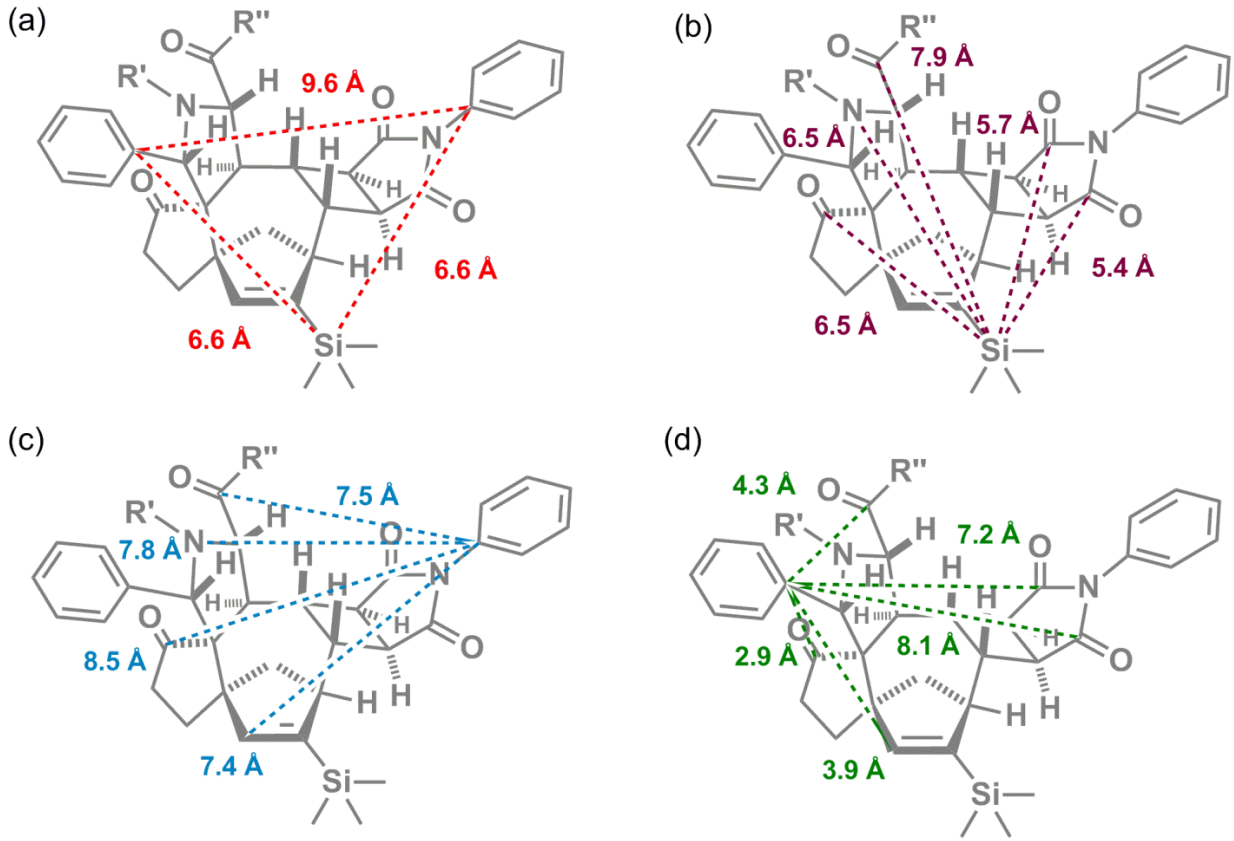


Figure S25. Spatial arrangement of the hexacyclic scaffold **18**. (a) Distances between three sites for installing aromatic fragments; (b) Distances between site 1 with five functional groups; (c) Distances between site 2 and four functional groups; (d) distances between site 3 with four functional groups.