Supplementary Information

Second-generation total synthesis of aplyronine A featuring Ni/Cr-mediated coupling reaction

Ichiro Hayakawa,*[a] Keita Saito,[b] Sachiko Matsumoto,[b] Shinichi Kobayashi,[b] Ayaka Taniguchi,[b] Kenichi Kobayashi,[b] Yusuke Fujii,[b] Takahiro Kaneko[b] and Hideo Kigoshi*[b]

[a]Division of Applied Chemistry, Graduate School of Natural Science and Technology, Okayama University, 3-1-1 Tsushima-naka, Kita-ku, Okayama 700-8530, Japan

[b]Department of Chemistry, Graduate School of Pure and Applied Sciences, University of Tsukuba, 1-1-1 Tennodai, Tsukuba 305-8571, Japan

Contents

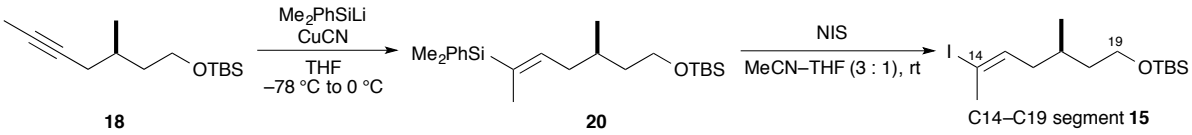
Experimental Procedures and Spectral Data for All New Compounds.

Experimental.

General: All moisture-sensitive reactions were performed under an atmosphere of argon or nitrogen, and the starting materials were azeotropically dried with benzene before use. Anhydrous MeCN, MeOH, EtOH, CH_2Cl_2, THF, Et_2O, toluene, DMF, DMSO, and pyridine were purchased from Kanto Chemical Co., Inc. or Wako Pure Chemical Industries Ltd. and used without further drying. Anhydrous THF for silylcupration was distilled from Na–benzophenone ketyl. TLC analysis were conducted on E. Merck precoated silica gel 60 F_{254} (0.25 mm layer thickness). Fuji Silysia silica gel BW-820MH (75–200 μm) and FL-60D (45–75 μm) were used for column chromatography. Optical rotations were measured with a JASCO DIP-370 polarimeter. Infrared (IR) spectra were recorded on a JASCO FT/IR-4100 instrument and only selected peaks are reported in wavenumbers (cm^{-1}). ^1H and ^{13}C NMR spectra were recorded on a Bruker AVANCE 600, a Bruker AVANCE 400, or a Bruker DPX 400 spectrometer. The ^1H and ^{13}C chemical shifts (δ) were reported in parts per million (ppm) downfield relative to $CDCl_3$ (δ_H = 7.26 and δ_C = 77.0), CD_3OD (δ_H = 3.33), and acetone-d_6 (δ_H = 2.04), respectively. *J* values are given in Hz. The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad. High resolution ESI/TOF mass spectra were recorded on a JEOL AccuTOFCS JMS-T100CS spectrometer.

Procedures and spectroscopic data for the compounds

Synthesis of C14–C19 segment **15**



18 **20** C14–C19 segment **15**

(preparation of $Me_2PhSiLi$)

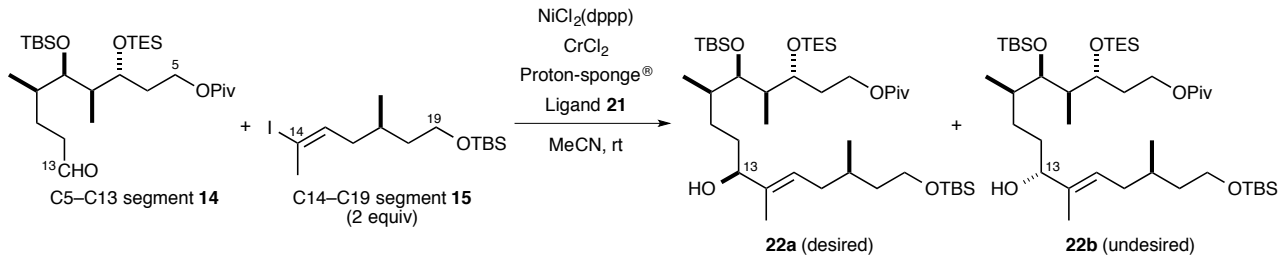
To a stirred solution of $Me_2PhSiCl$ (4.60 mL, 27.8 mmol) in THF (28 mL) was added Li (734 mg,

106 mmol) at 0 ºC. The resultant mixture was stirred at –8 ºC for 14 h to afford $Me_2PhSiLi$ solution.

The above-mentioned solution of $Me_2PhSiLi$ was added to a stirred solution of CuCN (1.26 g, 14.1 mmol) in THF (10 mL) at 0 ºC. After being stirred for 30 min, the mixture was cooled to –78 ºC. A solution of **18** (998 mg, 4.15 mmol) in THF (20 mL) was added dropwise, and stirring was continued for 2 h. The mixture was allowed to warm to 0 ºC, and stirring was continued for another 30 min. The mixture was then diluted with a 9 : 1 mixture of saturated aqueous NH_4Cl and 25% NH_3 aq. (20 mL), and extracted with Et_2O (3 × 30 mL). The combined extracts were washed with H_2O (20 mL) and brine (20 mL) successively; dried (Na_2SO_4); filtered; and concentrated. The crude product was purified by column chromatography on silica gel (50 g, hexane–EtOAc 30 : 1 → 10 : 1) to give vinylsilane **20** (1.97 g, containing a small quantity of impurity). Vinylsilane **20** was used for the next reaction without further purification.

To a stirred solution of vinylsilane **20** (1.97 g, containing a small quantity of impurity) in MeCN (18 mL) and THF (6 mL) was added NIS (2.32 g, 10.3 mmol) at 0 ºC. After being stirred at room temperature for 1.5 h in the dark, the mixture was diluted with saturated aqueous $Na_2S_2O_3$ (20 mL) at 0 ºC and extracted with Et_2O (3 × 25 mL). The combined extracts were washed with brine (20 mL), dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by column chromatography on silica gel (60 g, hexane–EtOAc 30 : 1 → 10 : 1) to give C14–C19 segment **15** (1.47 g, 96% in 2 steps) as a colorless oil: R_f = 0.51 (hexane : benzene = 9 : 1); The ^{1}H NMR and ^{13}C NMR spectroscopy and optical rotation were full agreement with those of our authentic sample.[1] $[\alpha]^{22}_D$ +2.2 (*c* 0.42, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.16 (tq, *J* = 7.5, 1.6 Hz, 1H), 3.57–3.48 (m, 2H), 2.36 (d, *J* = 1.6 Hz, 3H), 2.04 (dt, *J* = 14.0, 7.5 Hz, 1H), 1.88 (dt, *J* = 14.0, 7.5 Hz, 1H), 1.72–1.65 (m, 1H), 1.59–1.49 (m, 1H), 1.40–1.29 (m, 1H), 0.89 (s, 9H), 0.89 (d, *J* = 6.5 Hz, 3H), 0.05 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 140.1, 94.1, 61.2, 39.3, 37.9, 29.8, 27.6, 26.0 (3C), 19.4, 18.3, 5.3 (2C).

Optimization of asymmetric Ni/Cr-mediated coupling for preparation of alcohol **22a**



Alcohol 22a

(preparation of a MeCN solution of $CrCl_2$–ligand **21** complex)

MeCN was degassed by freeze-thawing. To a stirred solution of ligand **21** (639 mg, 1.65 mmol) in MeCN (12.5 mL) were added $CrCl_2$ (178 mg, 1.45 mmol) and Proton-sponge® (305 mg, 1.42 mmol) at room temperature in a glove box. The mixture was stirred at room temperature for 2 h in a glove box to give a MeCN solution of $CrCl_2$–ligand **21** complex.

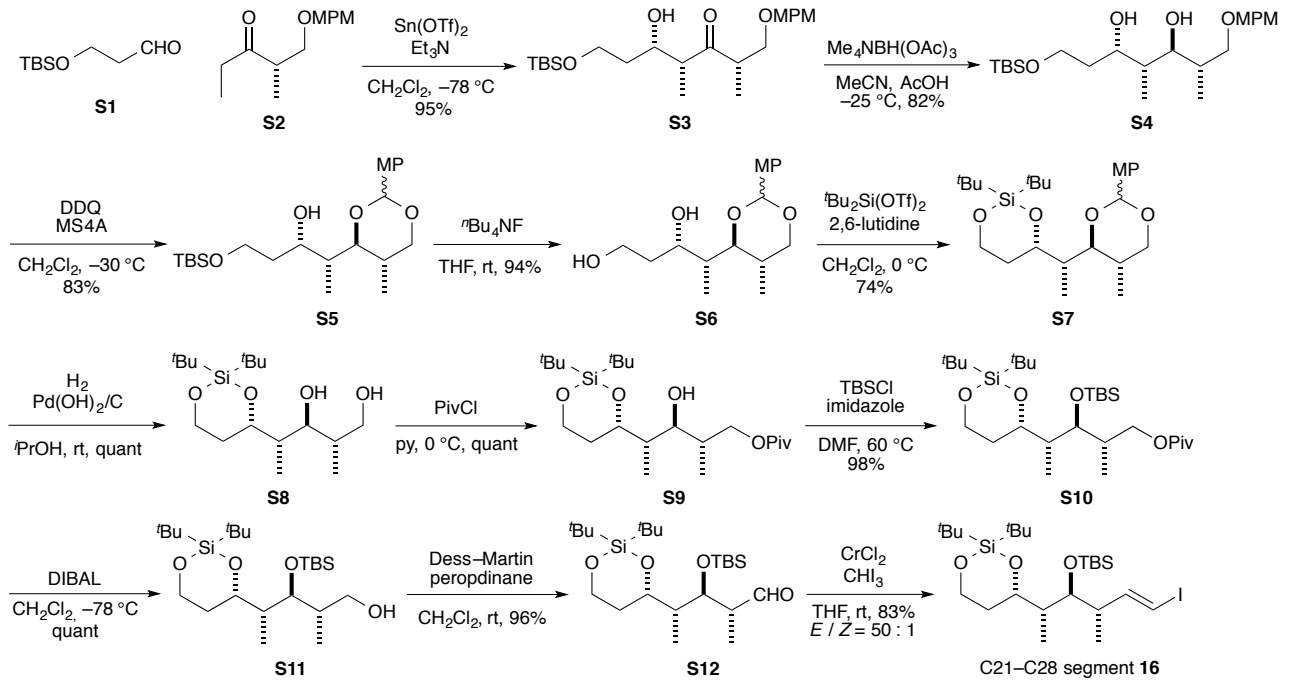
The above–mentioned solution of $CrCl_2$–ligand **21** complex was added to a mixture of the C5–C13 segment **14** (249 mg, 0.469 mmol), the C14–C19 segment **15** (341 mg, 0.926 mmol), and $NiCl_2$(dppp) (38.2 mg, 0.0705 mmol) at room temperature in a glove box. After being stirred at room temperature for 1.5 h in a glove box, the mixture was filtered through a column of florisil – silica gel (8.0 g / 8.0 g), and the residue was washed with hexane–EtOAc (1 : 1). The filtrate and the washings were combined and concentrated. The crude product was purified by column chromatography on silica gel (10 g, hexane–EtOAc 50 : 1 → 30 : 1 → 10 : 1) to afford a mixture of allylic alcohols **22a** and **22b** (7.3 : 1, 319 mg, 88%) as a colorless oil. The diastereomeric ratio of this product was determined from ^{1}H NMR (600 MHz) analysis.

Diastereomeric mixture of allylic alcohols **22a** and **22b** (7.3 : 1, 692 mg) was separated by column chromatography on FL-60D (35g, benzene–Et_2O 200 : 1, four times) to give alcohol **22a** (537 mg) and a mixture of allylic alcohols **22a** and **22b** (1 : 1.1, 122 mg).

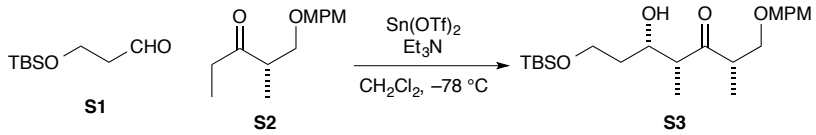
Allylic alcohol **22a**: R_f = 0.40 (benzene : Et_2O = 40 : 1); The ^1H and ^{13}C NMR spectroscopy was full agreement with those of our authentic sample.[1] ^1H NMR (400 MHz, $CDCl_3$) δ 5.38 (t, *J* = 7.0 Hz, 1H), 4.22 (dt, *J* = 10.8, 5.3 Hz, 1H), 4.04 (dt, *J* = 10.8, 7.5 Hz, 1H), 3.95 (t, *J* = 6.8 Hz, 1H), 3.75–3.55 (m, 3H), 3.40 (dd, *J* = 4.7, 2.8 Hz, 1H), 2.05 (dt, *J* = 14.1, 7.4 Hz, 1H), 1.86 (dt, *J* = 14.1, 7.4 Hz, 1H), 1.82–1.74 (m, 1H), 1.69–1.51 (m, 5H), 1.59 (s, 3H), 1.51–1.27 (m, 4H), 1.26–1.22 (m, 1H), 1.19 (s, 9H), 0.95 (t, *J* = 7.8 Hz, 9H), 0.92–0.84 (m, 9H), 0.89 (s, 9H), 0.88 (s, 9H), 0.59 (q, *J* = 7.8 Hz, 6H), 0.04 (s, 6H), 0.04 (s, 3H), 0.03 (s, 3H) A signal due to one proton (OH) was not observed; ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.5, 137.8, 126.1, 78.9, 77.1, 71.5, 61.7, 61.4, 41.2, 39.7, 38.9, 38.7, 34.9, 33.1, 31.0, 30.1, 27.9, 27.2 (3C), 26.1 (3C), 26.0 (3C), 19.6, 18.5, 18.3, 16.0, 11.0, 10.1, 7.0 (3C), 5.1 (3C), –3.4, –4.0, –5.3, –5.3.

Synthesis of the C21–C28 segment **16**

The synthesis of the C21–C28 segment **16** started from the known aldehyde **S1** (Scheme S1).[2] The Mukaiyama–Paterson Sn(II)-promoted aldol reaction[3] between aldehyde **S1** and ketone **S2**[4] gave aldol adduct **S3** as a single diastereomer. The stereochemistry of the newly generated secondary hydroxy group in **S3** was confirmed by modified Mosher's method.[5] 1,3-Anti-selective reduction of aldol adduct **S3** with $Me_4NBH(OAc)_3$[6] afforded diol **S4**. The stereochemistry of **S4** was determined by NMR analysis. ^{13}C chemical shifts[7] and ^1H–^1H coupling constants of the corresponding acetonide derivative.[8] Oxidative acetalization of **S4** with DDQ gave anisylidene acetal **S5**. Removal of the TBS group in **S6** afforded a 1,3-diol, which was converted into silylene acetal **S7**. Hydrogenolysis of anisylidene acetal **S7** and subsequent selective protection of the primary and secondary hydroxy groups afforded **S10**. Reduction of the pivaloyl group in **S10** and oxidation of the resultant primary hydroxy group gave aldehyde **S12**, which was transformed into vinyl iodide **16** as a C21–C28 segment by using Takai olefination.[9]



Scheme S1. Synthesis of C21–C28 segment **16**

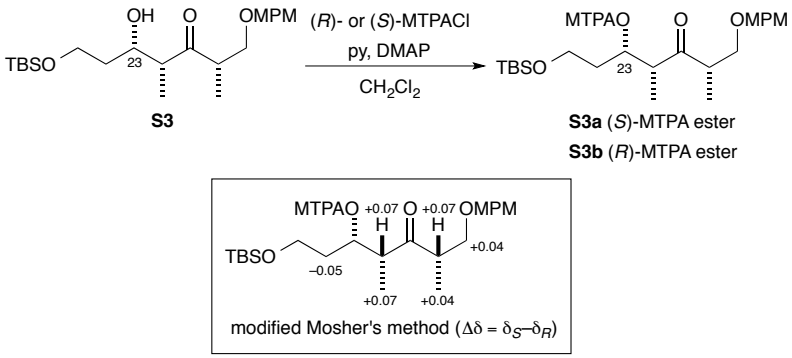


To a stirred solution of $Sn(OTf)_2$ (2.64 g, 6.34 mmol) in CH_2Cl_2 (32 mL) were added Et_3N (0.950 mL, 6.80 mmol) and a solution of ketone **S2** (1.01 g, 4.28 mmol) in CH_2Cl_2 (13 mL) at –78 °C, and the mixture was stirred at –78 °C for 2 h. After a solution of aldehyde **S1** (2.40 g, 12.8 mmol) in CH_2Cl_2 (13 mL) was added, the reaction mixture was stirred at –78 °C for 2 h. The resultant mixture was warmed to –50 °C and stirred for 30 min. The mixture was diluted with 0.2 M phosphate buffer (pH 7.0, 120 mL) and filtered through a pad of Celite, and the Celite was washed with Et_2O. The filtrate and washings were combined, and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layer and extracts were dried ($MgSO_4$), filtered, and concentrated. The residual oil was purified by column chromatography on silica gel (86 g, hexane–EtOAc 9 : 1) to give aldol **S3** (1.71 g, 95%) as a colorless oil: R_f = 0.40 (hexane : EtOAc = 4 : 1); $[\alpha]^{24}_D$ –6.51 (*c* 1.40, $CHCl_3$); IR ($CHCl_3$) 3462, 3006, 2957, 2931, 2858, 1708, 1613, 1513, 1464, 1251, 1084, 837 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.19 (d, J = 8.5 Hz,

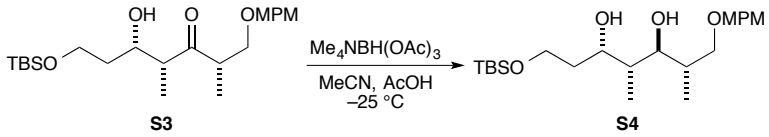
2H), 6.86 (d, J = 8.5 Hz, 2H), 4.40 (d, J = 11.4 Hz, 1H), 4.36 (d, J = 11.4 Hz, 1H), 4.15 (m, 1H), 3.80 (s, 3H), 3.75–3.68 (m, 2H), 3.62 (dd, J = 8.8, 8.8 Hz, 1H), 3.41 (dd, J = 8.8, 5.0 Hz, 1H), 3.39 (d, J = 2.6 Hz, 1H), 3.18 (ddq, J = 8.8, 5.0, 7.0 Hz, 1H), 2.78 (dq, J = 4.6, 7.0 Hz, 1H), 1.63–1.54 (m, 2H), 1.11 (d, J = 7.0 Hz, 3H), 1.02 (d, J = 7.0 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 217.1, 159.2, 129.8, 129.3 (2C), 113.8 (2C), 73.0, 72.6, 70.2, 61.5, 55.2, 51.4, 45.2, 36.1, 25.9 (3C), 18.2, 13.7, 10.5, –5.5 (2C); HRMS (ESI) m/z 447.2551, calcd for $C_{23}H_{40}NaO_5Si$ $[M+Na]^+$ 477.2543.

Determination of the absolute configuration of C23 in **S3**

For the determination of the absolute configuration of C23 in **S3**, aldol **S3** was converted into (*S*)- and (*R*)-MTPA esters **S3a** and **S3b**.[5] The Δδ values for these MTPA esters are described below:



Δδ values (δ_S–δ_R) for these MTPA esters in ppm (400 MHz).

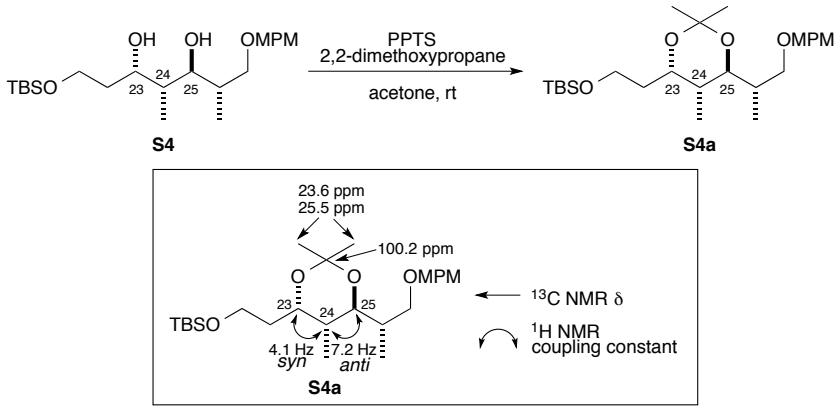


To a stirred solution of $Me_4NBH(OAc)_3$ (342 mg, 1.30 mmol) in MeCN (1.25 mL) and AcOH (1.25 mL) was added a solution of aldol **S3** (106 mg, 0.250 mmol) in MeCN (0.4 mL) at –25 °C. After stirring for 46 h at same temperature, the mixture was diluted with saturated aqueous Na/K tartrate (5 mL), allowed to warm to room temperature, and stirred for 30 min. The resultant mixture was diluted saturated aqueous $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2 (3 × 5.0 mL). The combined

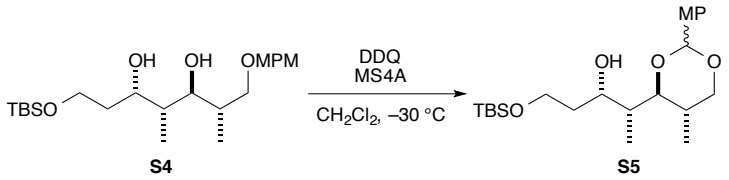
extracts were washed with saturated aqueous $NaHCO_3$ (10 mL), dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by column chromatography on silica gel (8.8 g, hexane–EtOAc 5 : 1 → 3 : 1) to give diol **S4** (87.1 mg, 82%) as a colorless oil: R_f = 0.27 (hexane : EtOAc = 4 : 1); $[\alpha]^{24}_D$ –0.483 (*c* 1.55, $CHCl_3$); IR ($CHCl_3$) 3433, 2958, 2930, 2859, 1613, 1513, 1464, 1252, 1111, 1082, 837 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.5 Hz, 2H), 6.89 (d, *J* = 8.5 Hz, 2H), 4.45 (s, 2H), 4.29 (d, *J* = 3.4 Hz, 1H), 4.16 (m, 1H), 3.97 (d, *J* = 1.1 Hz, 1H), 3.85–3.74 (m, 2H), 3.81 (s, 3H), 3.60–3.51 (m, 3H), 2.09 (m, 1H), 1.81 (m, 1H), 1.74 (m, 1H), 1.50 (m,1H), 1.00 (d, *J* = 7.1 Hz, 3H), 0.891 (s, 9H), 0.890 (d, *J* = 6.1 Hz, 3H), 0.06 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 129.8, 129.3 (2C), 113.8 (2C), 81.1, 74.7, 73.1, 70.3, 61.6, 55.2, 38.3, 36.5, 35.9, 25.8 (3C), 18.1, 14.1, 11.5, –5.5 (2C); HRMS (ESI) *m*/*z* 449.2702, calcd for $C_{23}H_{42}NaO_5Si$ $[M+Na]^+$ 449.2700.

Determination of the absolute configurations of C24 and C25 in **S4**

The stereochemistry of **S4** was determined as follows. Diol **S4** was converted into 1,3-acetonide **S4a**, the stereochemistry of which was confirmed to be *anti* by the ^{13}C chemical shifts of two acetonide methyls (δ_C 23.6 and 25.5).[7] Also, stereochemistry of C24 in **S4** was determined by a comparison of all possible stereoisomers of 1,3-acetonide derivatives.[8] Thus, ^1H-^1H coupling constants of 1,3-acetonide **S4a** was similar to that of *syn–anti* compound.



Determination of the absolute configurations of C24 and C25 in **S4**



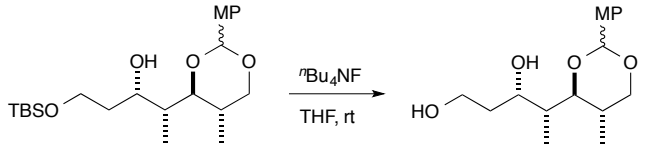
S4 S5

To a stirred solution of DDQ (46.4 mg, 0.204 mmol) and MS4A (106 mg) in CH_2Cl_2 (1.0 mL) was added a solution of diol **S4** (87.1 mg, 0.204 mmol) in CH_2Cl_2 (1.0 mL) at –30 °C. After stirring for 15 h at same temperature, the mixture was filtered through a pad of Celite, and the pad was washed with Et_2O. The filtrate and washings were combined, washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL) successively; dried (Na_2SO_4); filtered; and concentrated. The crude product was purified by column chromatography on silica gel (FL-60D 2.0 g, hexane–EtOAc 20 : 1 → 10 : 1) to give anisylidene acetal **S5** (57.3 mg, 66%) and its isomer (14.6 mg, 17%) as colorless oils, respectively.

Anisylidene acetal **S5**: R_f = 0.56 (hexane : EtOAc = 3 : 1); $[\alpha]^{24}_D$ –13.7 (*c* 1.03, $CHCl_3$); IR ($CHCl_3$) 3519, 3009, 2958, 2931, 2856, 1615, 1518, 1463, 1390, 1252, 1173, 1122, 1094, 836 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 5.38 (s, 1H), 4.28 (dd, *J* = 8.4, 4.5 Hz, 1H), 4.14 (dd, *J* = 11.2, 4.6 Hz, 1H), 3.79 (s, 3H), 3.74 (t, *J* = 5.8 Hz, 2H), 3.54–3.67 (m, 2H), 3.12 (brs, 1H), 2.24 (m, 1H), 1.88 (m, 1H), 1.80 (m, 1H), 1.54 (ddq *J* = 4.5, 6.8, 6.8 Hz, 1H), 1.11 (d, *J* = 7.1 Hz, 3H), 0.90 (s, 9H), 0.78 (d, *J* = 6.8 Hz, 3H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 130.8, 127.1 (2C), 113.6 (2C), 101.9, 89.2, 73.0, 67.0, 60.4, 55.2, 37.9, 36.9, 31.0, 25.9 (3C), 18.2, 12.1, 11.0, –5.3 (2C); HRMS (ESI) *m*/*z* 447.2551, calcd for $C_{23}H_{40}NaO_5Si$ $[M+Na]^+$ 447.2543.

Isomer of **S5**: R_f = 0.49 (hexane : EtOAc = 3 : 1); $[\alpha]^{24}_D$ –5.50 (*c* 1.08, $CHCl_3$); IR ($CHCl_3$) 3511, 3007, 2958, 2930, 2858, 1613, 1510, 1463, 1252, 1170, 1096, 1027, 837 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.6 Hz, 2H), 6.92 (d, *J* = 8.6 Hz, 2H), 5.96 (s, 1H), 4.28 (m, 1H), 3.92 (dd, *J* = 11.3, 3.9 Hz, 1H), 3.82 (s, 3H), 3.80–3.72 (m, 2H), 3.59 (dd, *J* = 6.1, 7.0 Hz, 1H), 3.58 (dd, *J* = 7.4, 11.3 Hz, 1H), 3.06 (d, *J* = 1.3 Hz, 1H), 2.08 (m, 1H), 2.02 (ddt, *J* = 12.6, 1.6, 5.7 Hz, 1H) , 1.82 (m, 1H), 1.56 (m, 1H), 1.06 (d, *J* = 7.0 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.89 (s, 9H), 0.060 (s, 3H),

0.056 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 129.9, 127.9 (2C), 113.9 (2C), 96.1, 80.7, 67.6, 66.7, 60.9, 55.3, 37.3, 36.5, 30.5, 25.9 (3C), 18.2, 14.8, 10.7, –5.38, –5.40; HRMS (ESI) *m*/*z* 447.2514, calcd for $C_{23}H_{40}NaO_5Si$ $[M+Na]^+$ 447.2543.



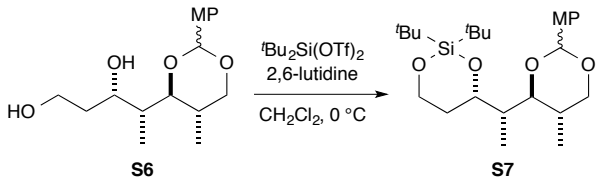
S5 **S6**

To a stirred solution of the mixture of anisylidene acetal **S5** and its isomer (1.46 g, 3.44 mmol) in THF (35 mL) was added ^{n}Bu$_4$NF (1.0 M THF solution, 6.8 mL, 6.8 mmol) at 0 °C. After stirring for 3.5 h at room temperature, the mixture was concentrated. The crude product was purified by column chromatography on silica gel (36 g, hexane–EtOAc 3 : 7) to give a diastereomeric mixture (4 : 1) of diol **S6** (1.16 g, 94%) as a colorless oil.

Diol **S6**: R_f = 0.32 (hexane : EtOAc = 3 : 7); $[\alpha]^{24}_D$ +0.245 (*c* 1.63, $CHCl_3$); IR ($CHCl_3$) 3501, 3010, 2969, 2931, 2842, 1616, 1519, 1462, 1252, 1113, 1034, 833, 666 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 5.37 (s, 1H), 4.35 (dd, *J* = 10.3, 2.3 Hz, 1H), 4.15 (dd, *J* = 11.3, 4.7 Hz, 1H), 3.88–3.82 (m, 2H), 3.80 (s, 3H), 3.54 (dd, *J* = 10.3, 1.5 Hz, 1H), 3.49 (dd, *J* = 11.3, 11.3 Hz, 1H), 3.36 (brs, 1H), 2.82 (brs, 1H), 2.25 (m, 1H), 1.92 (m, 1H), 1.81 (m, 1H), 1.44 (m, 1H), 1.14 (d, *J* = 7.2 Hz, 3H), 0.77 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 130.6, 127.1 (2C), 113.7 (2C), 101.9, 89.3, 72.9, 70.5, 62.0, 55.3, 37.3, 36.6, 30.9, 12.2, 11.3; HRMS (ESI) *m*/*z* 333.1680, calcd for $C_{17}H_{26}NaO_5$ $[M+Na]^+$ 333.1678.

Isomer of **S6**: R_f = 0.16 (hexane : EtOAc = 3 : 7); $[\alpha]^{24}_D$ –5.00 (*c* 1.57, $CHCl_3$); IR ($CHCl_3$) 3498, 3011, 2965, 2934, 2877, 1613, 1510, 1463, 1251, 1116, 1035, 666 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.8 Hz, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 6.03 (s, 1H), 4.36 (m, 1H), 3.88–3.80 (m, 2H), 3.86 (dd, *J* = 11.3, 4.7 Hz, 1H), 3.83 (s, 3H), 3.55 (dd, *J* = 8.2, 4.7 Hz, 1H), 3.54 (dd, *J* = 11.6, 8.2 Hz, 1H), 3.33 (brs, 1H), 2.76 (brs, 1H), 2.18 (m, 1H), 1.99–1.87 (m, 2H), 1.47 (m, 1H), 1.13 (d, *J* = 7.1 Hz, 3H), 0.80 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 129.3,

127.9 (2C), 114.0 (2C), 96.3, 80.9, 70.3, 66.3, 61.9, 55.2, 36.8, 36.3, 30.8, 14.1, 11.0; HRMS (ESI) *m*/*z* 333.1664, calcd for $C_{17}H_{26}NaO_5$ $[M+Na]^+$ 333.1678.

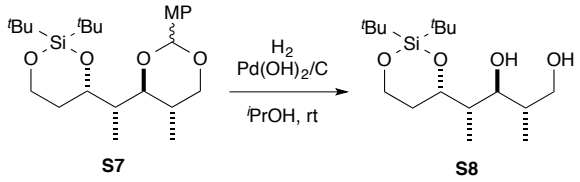


To a stirred solution of a mixture of diol **S6** and its isomer (1.53 g, 4.92 mmol) in CH_2Cl_2 (22 mL) were added 2,6-lutidine (3.80 mL, 32.7 mmol) and $^tBu_2Si(OTf)_2$ (2.20 mL, 6.74 mmol) at 0 °C. After stirring for 30 min at same temperature, the mixture was diluted with CH_2Cl_2 (10 mL) and saturated aqueous $NaHCO_3$ (20 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The organic layer and extracts were combined, dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by column chromatography on silica gel (70 g, hexane–EtOAc 5 : 1 → 2 : 1 → 1 : 1) to give a diastereomeric mixture (3 : 5) of **S7** (1.63 g, 74%) as a colorless oil.

S7: R_f = 0.71 (hexane : EtOAc = 3 : 7); $[\alpha]^{24}_D$ +40.1 (*c* 0.667, $CHCl_3$); IR ($CHCl_3$) 3008, 2965, 2934, 2859, 1616, 1518, 1473, 1394, 1303, 1115, 1034, 973, 892, 652 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 5.38 (s, 1H), 4.37 (ddd, *J* = 11.3, 3.9, 1.8 Hz, 1H), 4.13–4.09 (m, 2H), 4.07 (dd, *J* = 11.3, 4.8 Hz, 1H), 3.80 (s, 3H), 3.51–3.43 (m, 2H), 2.13 (m, 1H), 2.03 (m, 1H), 1.86 (m, 1H), 1.57 (dd, *J* = 13.9, 2.0 Hz, 1H), 1.11 (d, *J* =7.1 Hz, 3H), 1.00 (s, 18H), 0.84 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 131.5, 127.3 (2C),116.8 (2C), 94.7, 78.9, 72.0, 67.8, 65.1, 55.3, 38.0, 34.5, 28.9, 27.5 (3C), 27.2 (3C), 22.9, 20.1, 28.1, 10.3; HRMS (ESI) *m*/*z* 473.2682, calcd for $C_{25}H_{42}NaO_5$ $[M+Na]^+$ 473.2699.

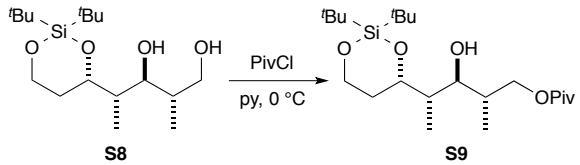
Isomer of **S7**: R_f = 0.68 (hexane : EtOAc = 3 : 7); $[\alpha]^{24}_D$ +44.6 (*c* 0.707, $CHCl_3$); IR ($CHCl_3$) 3026, 2966, 2934, 2859, 1615, 1517, 1466, 1387, 1250, 1118, 972, 894, 828, 651 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 5.66 (s, 1H), 4.51 (dt, *J* = 11.6, 1.7 Hz, 1H), 4.15–4.09 (m, 3H), 3.81 (s, 3H), 3.75 (dd, *J* = 11.2, 2.0 Hz, 2H), 2.24 (m, 1H), 2.09 (m,

1H), 1.78 (m, 1H), 1.40 (dd, J = 13.9, 1.9 Hz, 1H), 1.35 (d, J = 7.0 Hz, 3H), 1.00 (s, 9H), 0.97 (s, 9H), 0.95 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 131.5, 127.3 (2C), 113.5 (2C), 94.7, 78.9, 72.0, 67.8, 65.1, 55.3, 38.0, 34.5, 28.9, 27.5 (3C), 27.2 (3C), 22.9, 20.1, 18.2, 10.3; HRMS (ESI) *m/z* 473.2670, calcd for $C_{25}H_{42}NaO_5$ $[M+Na]^+$ 473.2699.



S7 **S8**

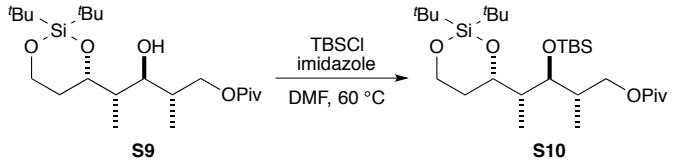
A mixture of a diastereomeric mixture of **S7** (61.8 mg, 137 μmol) and 20% $Pd(OH)_2$/C (ca. 50% wetted with water, 12.6 mg) in ^{i}PrOH (1.3 mL) was stirred under a hydrogen atmosphere at room temperature for 1.5 h. The mixture was filtered through a pad of Celite, and the residue was washed with EtOAc. The filtrate and the washings were combined and concentrated. The residual oil was purified by column chromatography on silica gel (1.5 g, hexane–EtOAc 2 : 1) to give diol **S8** (46.4 mg, quant) as a colorless oil: R_f = 0.25 (hexane : EtOAc = 2 : 1); $[\alpha]^{24}_D$ +24.0 (*c* 0.902, $CHCl_3$); IR ($CHCl_3$) 3433, 3009, 2966, 2934, 2879, 2861, 1472, 1252, 1112, 957, 887, 827, 653 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.63 (dt, J = 11.4, 1.9 Hz, 1H), 4.26 (d, J = 7.9 Hz, 1H), 4.17 (t, J = 2.1 Hz, 1H), 4.15 (d, J = 2.1 Hz, 1H), 3.86 (m, 1H), 3.72–3.69 (m, 2H), 3.49 (m, 1H), 2.15 (m, 1H), 2.04 (m, 1H), 1.74 (m, 1H), 1.37 (m, 1H), 1.15 (d, J = 7.1 Hz, 3H), 1.06 (s, 9H), 1.01 (s, 9H), 0.80 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz) δ 83.8, 75.4, 69.0, 64.8, 38.5, 38.3, 33.7, 27.4 (3C), 27.1 (3C), 22.8, 20.1, 13.9, 11.7; HRMS (ESI) *m/z* 355.2276, calcd for $C_{17}H_{36}NaO_4Si$ $[M+Na]^+$ 355.2275.



S8 **S9**

To a stirred solution of diol **S8** (345 mg, 1.05 mmol) in pyridine (10 mL) was added PivCl (0.39 mL, 3.2 mmol) at 0 °C. After stirring for 1 h at same temperature, the mixture was diluted with

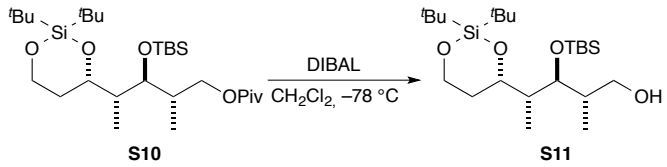
saturated aqueous $NaHCO_3$ (10 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 8.0 mL). The organic layer and extracts were combined, washed with brine (10 mL), dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by column chromatography on silica gel (15 g, hexane–EtOAc 10 : 1) to give **S9** (439 mg, quant) as a yellow oil: R_f = 0.28 (hexane : EtOAc = 9 : 1); $[\alpha]^{25}_D$ +0.146 (*c* 1.72, $CHCl_3$); IR ($CHCl_3$) 3485, 3022, 2970, 2932, 2864, 1720, 1480, 1365, 1288, 1172, 1106, 1018, 960, 890, 827 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.55 (dt, *J* = 11.3, 1.7 Hz, 1H), 4.37 (dd, *J* = 10.7, 3.8 Hz, 1H), 4.17–4.09 (m, 3H), 3.49–3.41 (m, 2H), 2.20–2.06 (m, 2H), 1.75 (m, 1H), 1.37 (m, 1H), 1.21 (s, 9H), 1.13 (d, *J* = 7.0 Hz, 3H), 1.04 (s, 9H), 1.01 (s, 9H), 0.96 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.6, 77.6, 75.3, 66.5, 64.9, 38.9, 38.6, 37.0, 33.6, 27.2 (3C), 27.0 (3C), 26.5 (3C), 22.8, 20.1, 14.5, 11.9; HRMS (ESI) *m*/*z* 439.2842, calcd for $C_{22}H_{44}NaO_5Si$ $[M+Na]^+$ 439.2856.



S9 **S10**

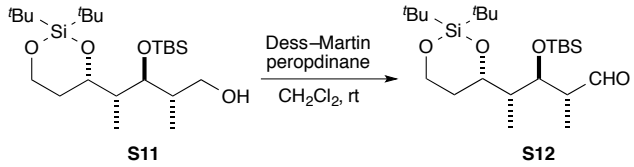
A solution of **S9** (347 mg, 0.833 mmol), imidazole (1.70 g, 25.0 mmol), and TBSCl (1.89 g, 12.5 mmol) in DMF (1.7 mL) was heated to 60 °C for 22 h. The mixture was cooled to room temperature and diluted with Et_2O (7.0 mL) and H_2O (5.0 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (2 × 10 mL). The organic layer and extracts were combined; washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL) successively; dried (Na_2SO_4); filtered; and concentrated. The crude product was purified by column chromatography on silica gel (15 g, hexane–EtOAc 60 : 1) to give TBS ether **S10** (436 mg, 98%) as a colorless oil: R_f = 0.58 (hexane : EtOAc = 9 : 1); $[\alpha]^{25}_D$ –7.46 (*c* 0.650, $CHCl_3$); IR ($CHCl_3$) 2956, 2932, 2859, 1718, 1472, 1364, 1288, 1259, 1259, 1162, 1109, 1021, 973, 827, 651 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.32 (dd, *J* = 10.9, 4.2 Hz, 1H), 4.12 (m, 1H), 4.11 (d, *J* = 7.1 Hz, 2H), 3.85 (dd, *J* = 10.9, 9.0 Hz, 1H), 3.70 (dd, *J* = 3.5, 3.5 Hz, 1H), 2.26 (m, 1H), 1.98 (m, 1H), 1.66 (m, 1H), 1.51 (dd, *J* = 14.0, 2.0 Hz,

1H), 1.18 (s, 9H), 1.07 (d, J = 7.1 Hz, 3H), 1.03 (s, 9H), 1.01 (d, J = 7.3 Hz, 3H), 0.99 (s, 9H), 0.89 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5, 77.9, 75.4, 67.0, 64.7, 46.6, 38.8, 35.8, 35.3, 27.5 (3C), 27.2 (3C), 27.1 (3C), 25.9 (3C), 22.8, 20.0, 18.2, 16.6, 9.8, –4.2, –4.5. HRMS (ESI) m/z 553.3698, calcd for $C_{28}H_{58}NaO_5Si_2$ $[M+Na]^+$ 553.3720.



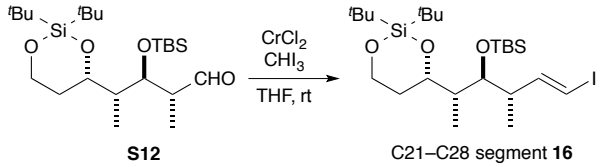
S10 **S11**

To a stirred solution of **S10** (640 mg, 1.21 mmol) in CH_2Cl_2 (12 mL) was added DIBAL (1.04 M solution in hexane, 2.40 mL, 2.50 mmol) at –78 °C. After stirring for 1 h at same temperature, the mixture was diluted with MeOH (2.5 mL) and saturated aqueous Na/K tartrate (10 mL) and stirred at room temperature for 1 h. The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 5.0 mL). The organic layer and extracts were combined, washed with brine (5.0 mL), dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by column chromatography on silica gel (10 g, hexane–EtOAc 10 : 1) to give **S11** (540 mg, quant) as a colorless oil: R_f = 0.28 (hexane : EtOAc = 9 : 1); $[\alpha]^{25}_D$ +5.79 (c 1.12, $CHCl_3$); IR ($CHCl_3$) 3497, 3003, 2956, 2932, 2859, 1472, 1387, 1364, 1256, 1128, 1020, 985, 886, 838, 827, 651 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.12–4.05 (m, 3H), 3.82 (dt, J = 10.9, 3.9 Hz, 1H), 3.77 (dd, J = 4.2, 3.6 Hz, 1H), 3.57 (dt, J = 10.9, 5.4 Hz, 1H), 2.76 (dd, J = 6.0, 5.1 Hz, 1H), 2.08 (m, 1H), 1.98 (m, 1H) 1.73 (m, 1H), 1.51 (m, 1H), 1.12 (d, J = 7.1 Hz, 3H), 1.06 (d, J = 7.1 Hz, 3H), 1.02 (s, 9H), 1.00 (s, 9H), 0.92 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 80.7, 75.4, 66.4, 64.6, 47.2, 36.4, 35.4, 27.5 (3C), 27.2 (3C), 25.9 (3C), 22.8, 20.0, 18.1, 17.4, 9.1, –4.3, –4.7; HRMS (ESI) m/z 469.3172, calcd for $C_{23}H_{50}NaO_4Si_2$ $[M+Na]^+$ 469.3145.



S11 **S12**

To a stirred solution of alcohol **S11** (472 mg, 1.04 mmol) in CH_2Cl_2 (10 mL) was added Dess–Martin periodinane (1.32 g, 3.12 mmol) at room temperature. After stirring for 35 min at room temperature, the mixture was diluted with a 1 : 1 : 1 mixture of saturated aqueous $Na_2S_2O_3$, saturated aqueous $NaHCO_3$, and H_2O (15 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 15 mL). The organic layer and extracts were combined; washed with saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL) successively; dried (Na_2SO_4); filtered; and concentrated. The crude product was purified by column chromatography on silica gel (6.0 g, hexane–EtOAc 20 : 1) to give aldehyde **S12** (444 mg, 96%) as a colorless oil: R_f = 0.29 (hexane : EtOAc = 19 : 1); $[\alpha]^{25}_D$ –11.0 (*c* 0.894, $CHCl_3$); IR ($CHCl_3$) 3009, 2956, 2932, 2859, 1718, 1472, 1387, 1364, 1254, 1163, 1126, 984, 886 827, 653 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.87 (d, *J* = 2.2 Hz, 1H), 4.20–4.11 (m, 3H), 3.95 (dd, *J* = 4.3, 2.0 Hz, 1H), 2.88 (m, 1H), 1.97 (m, 1H), 1.72 (m, 1H), 1.45 (m, 1H), 1.14 (d, *J* = 7.0 Hz, 3H), 1.03 (s, 9H), 1.02 (d, *J* = 7.0 Hz, 3H), 1.00 (s, 9H), 0.89 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.2, 78.3, 75.4, 64.6, 49.1, 46.7, 34.9, 27.5 (3C), 27.1 (3C), 25.8 (3C), 22.8, 20.0, 18.0, 13.3, 9.1, –4.3, –4.7; HRMS (ESI) *m*/*z* 467.3011, calcd for $C_{23}H_{48}NaO_4Si_2$ $[M+Na]^+$ 467.2989.

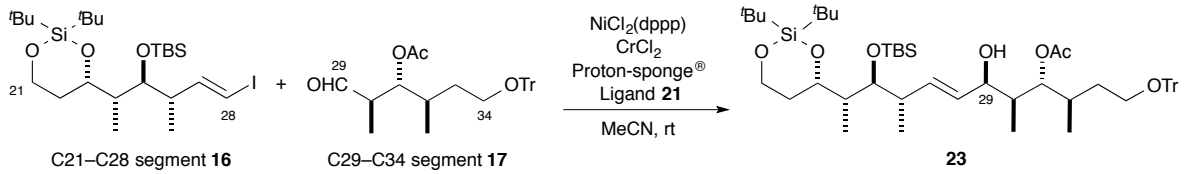


S12 C21–C28 segment **16**

THF was degassed by freeze-thawing. To a stirred solution of aldehyde **S12** (444 mg, 0.998 mmol) in THF (10 mL) were added $CrCl_2$ (735 mg, 5.99 mmol) and CHI_3 (785 mg, 1.99 mmol) at room temperature in a glove box. After stirring for 1.5 h at room temperature in a glove box, the resultant mixture was diluted with H_2O (10 mL). The layers were separated, and the aqueous layer was

extracted with Et_2O (4 × 20 mL). The organic layer and extracts were combined, washed with brine (25 mL), dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by column chromatography on silica gel (15 g, hexane–EtOAc 100 : 1) to give C21–C28 segment **16** (*E* / *Z* = 50 : 1) (469 mg, 83%) as a colorless oil: R_f = 0.35 (hexane : EtOAc = 19 : 1); $[\alpha]^{25}_{D}$ –17.6 (*c* 1.20, $CHCl_3$); IR ($CHCl_3$) 2959, 2889, 2858, 1472, 1364, 1252, 1161, 1128, 1076, 1021, 889, 827, 651 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.68 (dd, *J* = 14.5, 8.8 Hz, 1H), 5.91 (d, *J* = 14.5 Hz, 1H), 4.12–4.06 (m, 3H), 3.60 (dd, *J* = 4.3, 2.4 Hz, 1H), 2.71 (m, 1H), 1.99 (m, 1H), 1.63 (m, 1H), 1.45 (m, 1H), 1.03 (d, *J* = 7.2 Hz, 3H), 1.03 (s, 9H), 1.00 (s, 9H), 0.96 (d, *J* = 7.2 Hz, 3H), 0.92 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.8, 78.8, 75.6, 73.9, 64.7, 47.0, 43.5, 35.4, 27.6 (3C), 27.2 (3C), 26.0 (3C), 22.9, 20.1, 19.8, 18.2, 9.4, –4.1, –4.5; HRMS (ESI) *m*/*z* 591.2140, calcd for $C_{24}H_{49}INaO_3Si_2$ $[M+Na]^+$ 591.2163.

Synthesis of C20–C34 segment **13**



C21–C28 segment **16** C29–C34 segment **17** **23**

(preparation of a MeCN solution of $CrCl_2$–ligand **21** complex)

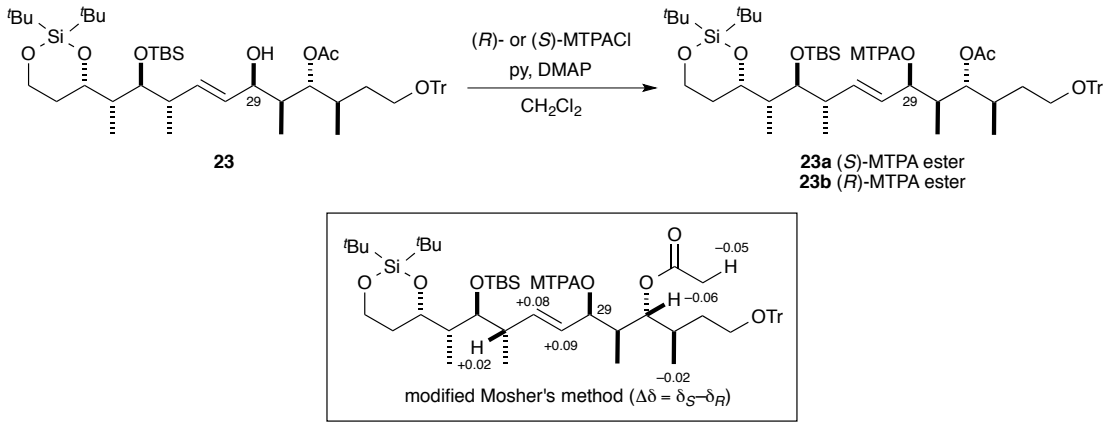
MeCN was degassed by freeze-thawing. To a stirred solution of ligand **21** (77.3 mg, 0.200 mmol) in MeCN (1.3 mL) were added $CrCl_2$ (24.6 mg, 0.200 mmol) and Proton-sponge® (42.9 mg, 0.200 mmol) at room temperature in a glove box. The mixture was stirred at room temperature for 2 h in a glove box to give a MeCN solution of $CrCl_2$–ligand **21** complex.

The above–mentioned solution of $CrCl_2$–ligand **21** complex was added to a mixture of the C21–C28 segment **16** (23.9 mg, 0.040 mmol), the C29–C34 segment **17** (17.8 mg, 0.040 mmol), and $NiCl_2$(dppp) (4.4 mg, 8.1 μmol) at room temperature in a glove box. After being stirred at room temperature for 3 h in a glove box, the mixture was filtered through a pad of florisil, and the residue

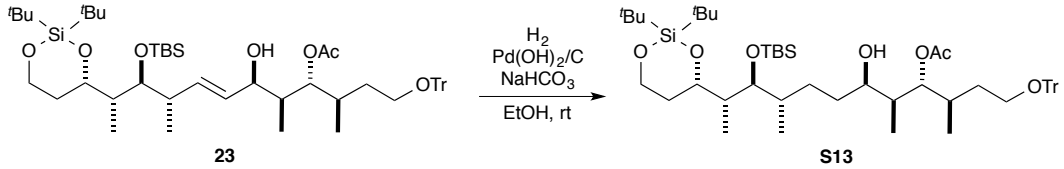
was washed with hexane–EtOAc (1 : 1). The filtrate and the washings were combined and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (FL-60D 3.1 g, hexane–EtOAc 50 : 1 → 20 : 1 → 1 : 1) to afford allylic alcohol **23** (22.8 mg, 64%) as a colorless oil: R_f = 0.56 (benzene : EtOAc = 20 : 1); $[\alpha]^{22}_{D}$ +5.75 (*c* 1.01, $CHCl_3$); IR ($CHCl_3$) 3449, 2958, 2931, 2858, 1712, 1471, 1375, 1255, 1220, 1075 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45–7.43 (m, 6H), 7.31–7.27 (m, 6H), 7.24–7.21 (m, 3H), 5.88 (ddd, *J* = 15.5, 7.1, 1.3 Hz, 1H), 5.40 (dd, *J* = 15.5, 5.2 Hz, 1H), 4.85 (dd, *J* = 9.8, 2.8 Hz, 1H), 4.16–4.05 (m, 3H), 4.05 (br s, 1H), 3.67 (dd, *J* = 5.0, 2.2 Hz, 1H), 3.22 (m, 1H), 3.00 (td, *J* = 8.7, 6.0 Hz, 1H), 2.62 (m, 1H), 2.36 (d, *J* = 3.6 Hz, 1H), 2.07 (s, 3H), 2.04 (m, 1H), 1.96 (m, 1H), 1.91–1.77 (m, 2H), 1.62 (m, 1H), 1.50 (m, 1H), 1.35 (m, 1H), 1.07 (d, *J* = 7.2 Hz, 3H), 1.04 (s, 9H), 1.00 (s, 9H), 0.99 (d, *J* = 7.3 Hz, 3H), 0.91 (s, 9H), 0.90 (d, *J* = 7.0 Hz, 3H), 0.73 (d, *J* = 6.8 Hz, 3H), 0.08 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 144.4 (3C), 134.2, 129.6, 128.6 (6C), 127.7 (6C), 126.9 (3C), 86.5, 80.0, 78.6, 75.5, 70.7, 64.7, 61.4, 46.8, 40.1, 39.7, 35.4, 30.5, 29.6, 27.6 (3C), 27.2 (3C), 26.1 (3C), 22.8, 20.9, 20.1, 19.7, 18.3, 16.9, 10.5, 9.3, –4.0, –4.3; HRMS (ESI) *m*/*z* 909.5501, calcd for $C_{53}H_{82}NaO_7Si_2$ $[M+Na]^+$ 909.5497.

Determination of the absolute configuration of C29 in **23**

For the determination of the absolute configuration of C29 in **23**, allylic alcohol **23** was converted into (*S*)- and (*R*)-MTPA esters **23a** and **23b**.[5] The Δδ values for these MTPA esters are described below:

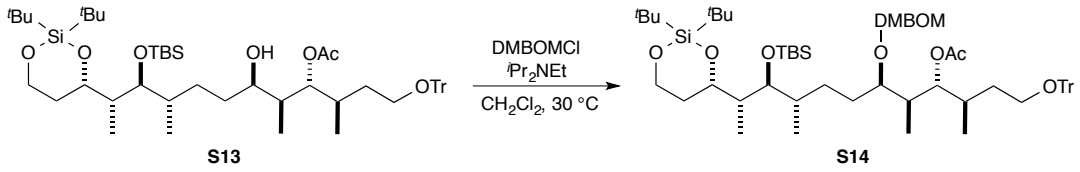


Δδ values (δ_S–δ_R) for these MTPA esters in ppm (400 MHz).



A mixture of allylic alcohol **23** (92.7 mg, 0.104 mmol), 20% $Pd(OH)_2$/C (ca. 60% wetted with water, 18.4 mg), and $NaHCO_3$ (17.5 mg, 0.208 mmol) in EtOH (9.4 mL) was stirred under a hydrogen atmosphere at room temperature for 1.5 h. The mixture was filtered through a pad of Celite, and the residue was washed with EtOAc. The filtrate and the washings were combined and concentrated. The residual oil was purified by column chromatography on silica gel (2.9 g, hexane–EtOAc 20 : 1 → 10 : 1) to give alcohol **S13** (85.2 mg, 92%) as a colorless oil: R_f = 0.49 (benzene : EtOAc = 19 : 1); $[\alpha]^{24}_D$ +4.62 (*c* 0.943, $CHCl_3$); IR ($CHCl_3$) 3524, 3007, 2957, 2933, 2858, 1709, 1472, 1258, 1071, 1022, 827, 707 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45–7.43 (m, 6H), 7.31–7.28 (m, 6H), 7.25–7.21 (m, 3H), 4.80 (dd, *J* = 9.9, 2.9 Hz, 1H), 4.15–4.09 (m, 3H), 3.56 (m, 1H), 3.42 (m, 1H), 3.23 (m, 1H), 3.00 (m, 1H), 2.55 (d, *J* = 3.4 Hz, 1H), 2.08 (s, 3H), 2.05 (m, 1H), 1.96–1.83 (m, 2H), 1.75–1.59 (m, 5H), 1.48–1.42 (m, 2H), 1.38–1.31 (m, 2H), 1.04–1.02 (m, 3H), 1.03 (s, 9H), 1.00 (s, 9H), 0.94 (d, *J* = 6.9 Hz, 3H), 0.90 (s, 9H), 0.88 (d, *J* = 6.2 Hz, 3H), 0.72 (d, *J* = 6.8 Hz, 3H), 0.07 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 144.3 (3C), 128.6 (6C), 127.7 (6C), 126.9 (3C), 86.5, 80.4, 79.4, 75.4, 70.1, 64.7, 61.3, 46.0, 38.3, 37.0, 35.7, 32.3, 30.3, 29.5, 28.7, 27.6 (3C), 27.2 (3C), 26.1 (3C), 22.8, 20.8, 20.0, 18.4, 17.7, 16.9, 11.7, 8.4, –3.9, –4.2; HRMS (ESI) *m*/*z* 911.5661, calcd

for $C_{53}H_{84}NaO_7Si_2$ $[M+Na]^+$ 911.5653.



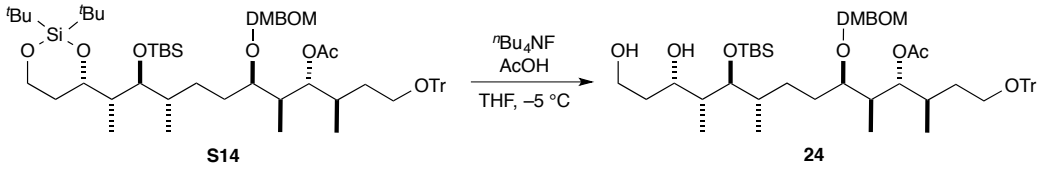
S13 **S14**

(preparation of DMBOMCl)

To a stirred solution of 3,4-dimethoxybenzyl (methylthio)methyl ether (519 mg, 2.27 mmol) in CH_2Cl_2 (3.8 mL) was added SO_2Cl_2 (0.20 mL, 2.5 mmol) at –78 °C. The mixture was stirred at –78 °C for 50 min and concentrated at 0 °C to give DMBOMCl.

To a stirred solution of alcohol **S13** (100 mg, 0.113 mmol) in CH_2Cl_2 (3.0 mL) were added $^iPr_2NEt$ (1.50 mL, 8.61 mmol) and the above–mentioned solution of DMBOMCl in CH_2Cl_2 (1.5 mL) at 0 °C. After being stirred at 30 °C for 22 h, the mixture was cooled to 0 °C, and diluted H_2O (10 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 10 mL). The organic layer and extracts were combined; washed with 0.5 M aqueous HCl (20 mL), saturated aqueous $NaHCO_3$ (10 mL) and brine (20 mL) successively; dried (Na_2SO_4); filtered; and concentrated. The crude product was purified by column chromatography on silica gel (4.0 g, hexane–EtOAc 20 : 1 → 10 : 1 → 4 : 1) to give DMBOM ether **S14** (114 mg, 94%) as a colorless oil: R_f = 0.20 (hexane: EtOAc = 17 : 3); $[\alpha]^{25}_D$ +9.96 (*c* 1.36, $CHCl_3$); IR ($CHCl_3$) 3010, 2960, 2934, 2858, 1724, 1517, 1465, 1253, 1106, 1030, 827, 707 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45–7.43 (m, 6H), 7.31–7.27 (m, 6H), 7.24–7.21 (m, 3H), 6.90–6.85 (m, 2H), 6.80 (d, *J* = 8.0 Hz, 1H), 4.98 (dd, *J* = 9.7, 2.3 Hz, 1H), 4.76 (d, *J* = 6.9 Hz, 1H), 4.67 (d, *J* = 6.9 Hz, 1H), 4.61 (d, *J* = 11.7 Hz, 1H), 4.49 (d, *J* = 11.7 Hz, 1H), 4.12–4.08 (m, 3H), 3.87 (s, 3H), 3.86, (s, 3H), 3.51 (dd, *J* = 4.3, 4.3 Hz, 1H), 3.40 (dt, *J* = 1.6, 6.8 Hz, 1H), 3.19 (m, 1H), 2.98 (m, 1H), 2.02 (m, 1H), 2.00 (s, 3H), 1.94–1.84 (m, 3H), 1.71–1.61 (m, 5H), 1.55–1.49 (m, 2H), 1.31 (m, 1H), 1.04–0.87 (m, 9H), 1.02 (s, 9H), 0.99 (s, 9H), 0.90 (s, 9H), 0.70 (d, *J* = 6.8 Hz, 3H), 0.071 (s, 3H), 0.066 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ

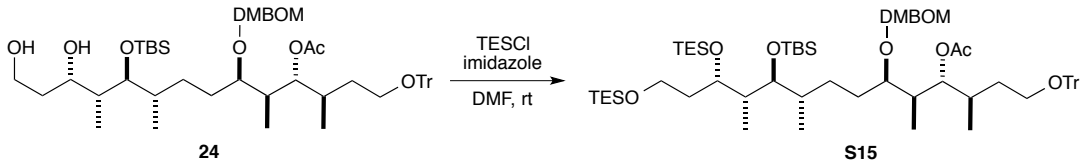
170.8, 149.0, 148.5, 144.4 (3C), 130.8, 128.7 (6C), 127.7 (6C), 126.9 (3C), 120.4, 111.2, 110.9, 95.2, 86.5, 79.5, 78.8, 78.6, 75.4, 69.5, 64.6, 61.3, 55.9, 55.8, 46.3, 36.64, 36.58, 35.7, 31.0, 30.5, 29.4, 28.1, 27.5 (3C), 27.2 (3C), 26.1 (3C), 22.8, 21.0, 20.0, 18.4, 17.7, 16.9, 11.7, 9.3, –3.8, –4.2; HRMS (ESI) *m*/*z* 1091.6412, calcd for $C_{63}H_{96}NaO_{10}Si_2$ $[M+Na]^+$ 1091.6440.



S14 **24**

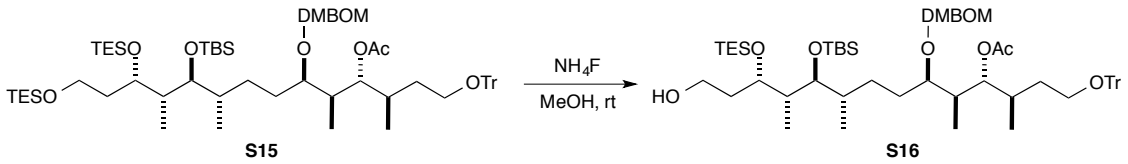
To a stirred solution of DMBOM ether **S14** (238 mg, 0.222 mmol) in THF (2.2 mL) were added AcOH (1.0 M THF solution, 1.1 mL, 1.1 mmol) and ^{n}Bu$_4$NF (1.0 M THF solution, 1.1 mL, 1.1 mmol) at –20 °C. After being stirred at –5 °C for 23 h, the mixture was diluted with saturated aqueous NH_4Cl (2.0 mL) and H_2O (2.0 mL) at –5 °C. The layers were separated, and the aqueous layer was extracted with EtOAc (4 × 4.0 mL). The organic layer and extracts were combined; washed with saturated aqueous $NaHCO_3$ (15 mL) and brine (15 mL) successively; dried (Na_2SO_4); filtered; and concentrated. The crude product was purified by column chromatography on silica gel (7.0 g, hexane–EtOAc 1 : 1) to afford diol **24** (189 mg, 91%) as a colorless oil: R_f = 0.38 (hexane: EtOAc = 1 : 1); $[\alpha]^{25}_D$ +9.69 (*c* 0.537, $CHCl_3$); IR ($CHCl_3$) 3466, 3010, 2956, 2936, 2859, 1724, 1672, 1517, 1465, 1255, 1094, 1029, 836 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.42 (m, 6H), 7.31–7.27 (m, 6H), 7.24–7.21 (m, 3H), 6.89–6.86 (m, 2H), 6.82 (d, *J* = 7.9 Hz, 1H), 4.99 (dd, *J* = 9.7, 2.2 Hz, 1H), 4.77 (d, *J* = 7.0 Hz, 1H), 4.68 (d, *J* = 7.0 Hz, 1H), 4.62 (d, *J* = 11.6 Hz, 1H), 4.49 (d, *J* = 11.6 Hz, 1H), 4.31 (m, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.80–3.78 (m, 2H), 3.63 (brs, 1H), 3.52 (dd, *J* = 6.7, 2.1 Hz, 1H), 3.42 (m, 1H), 3.20 (m, 1H), 3.00 (dt, *J* = 6.1, 8.9 Hz, 1H), 2.71 (brs, 1H), 2.03 (m, 1H), 2.01 (s, 3H), 1.96–1.80 (m, 3H), 1.76–1.52 (m, 6H), 1.37 (m, 1H), 1.28 (m, 1H), 1.01 (d, *J* = 7.1 Hz, 3H), 0.96–0.92 (m, 6H), 0.92 (s, 9H), 0.72 (d, *J* = 6.8 Hz, 3H), 0.13 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 149.0, 148.6, 144.4 (3C), 130.7, 128.6 (6C), 127.7 (6C), 126.9 (3C), 120.3, 111.2, 110.9, 95.4, 86.5, 83.4, 79.0, 78.4, 71.4, 69.6, 62.1, 61.3, 55.9,

55.8, 38.5, 38.2, 36.8, 36.7, 31.0, 30.7, 29.6, 29.5, 26.2 (3C), 21.0, 18.3, 16.9, 15.8, 12.9, 9.6, –3.77, –3.82; HRMS (ESI) *m/z* 951.5411, calcd for $C_{55}H_{80}NaO_{10}Si$ $[M+Na]^+$ 951.5418.

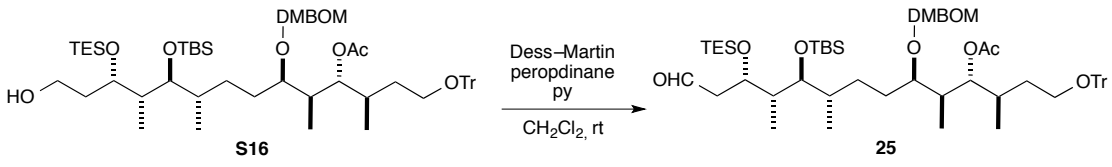


24 S15

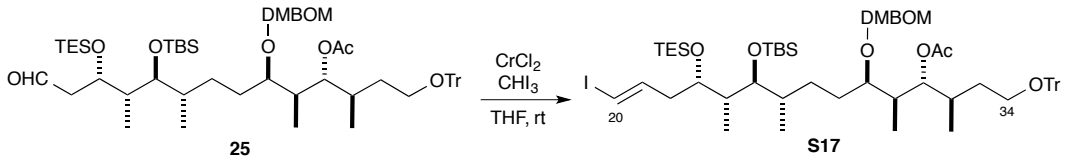
To a stirred solution of diol **24** (225 mg, 0.242 mmol) in DMF (2.4 mL) were added imidazole (165 mg, 2.42 mmol) and TESCl (0.20 mL, 1.2 mmol) at room temperature. After being stirred at room temperature for 1.5 h, the mixture was diluted with saturated aqueous NH_4Cl (2.0 mL) and H_2O (2.0 mL) at 0 °C. The layers were separated, and the aqueous layer was extracted with EtOAc (4 × 3.0 mL). The organic layer and extracts were combined, washed with brine (10 mL), dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by column chromatography on silica gel (7.9 g, hexane–EtOAc 5 : 1) to afford di-TES ether **S15** (298 mg, quant) as a colorless oil: R_f = 0.40 (hexane: EtOAc = 4 : 1), $[\alpha]^{25}_D$ +4.26 (*c* 1.62, $CHCl_3$), IR ($CHCl_3$) 3005, 2957, 2877, 1724, 1517, 1465, 1384, 1252, 1139, 1068, 1030, 836 cm^{-1}, ^1H NMR (400 MHz, $CDCl_3$) δ 7.45–7.43 (m, 6H), 7.31–7.27 (m, 6H), 7.24–7.20 (m, 3H), 6.89–6.87 (m, 2H), 6.81 (d, *J* = 8.0 Hz, 1H), 4.99 (dd, *J* = 9.6, 2.4 Hz, 1H), 4.76 (d, *J* = 6.9 Hz, 1H), 4.67 (d, *J* = 6.9 Hz, 1H), 4.61 (d, *J* = 11.7 Hz, 1H), 4.49 (d, *J* = 11.7 Hz, 1H), 3.89 (m, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.62 (t, *J* = 7.1 Hz, 2H), 3.65 (dd, *J* = 6.1, 2.7 Hz, 1H), 3.40 (m, 1H), 3.20 (m, 1H), 2.98 (m, 1H), 2.03 (m, 1H), 2.02 (s, 3H), 2.00–1.59 (m, 7H), 1.47 (m, 1H), 1.34–1.25 (m, 3H), 0.97–0.87 (m, 24H), 0.90 (s, 9H), 0.86 (d, *J* = 7.0 Hz, 3H), 0.70 (d, *J* = 6.8 Hz, 3H), 0.63–0.55 (m, 12H), 0.07 (s, 6H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 149.0, 148.5, 144.4 (3C), 130.8, 128.6 (6C), 127.7 (6C), 126.9 (3C), 120.4, 111.2, 110.9, 95.1, 86.4, 78.8, 78.6, 78.5, 71.0, 69.5, 61.3, 59.7, 55.9, 55.8, 44.1, 39.1, 36.7, 36.0, 31.0, 30.6, 29.7, 29.4, 26.2 (3C), 21.0, 18.5, 18.0, 16.8, 10.8, 9.4, 7.1 (3C), 6.8 (3C), 5.7 (3C), 4.4 (3C), –3.6, –4.0, HRMS (ESI) *m/z* 1179.7176, calcd for $C_{67}H_{108}NaO_{10}Si_3$ $[M+Na]^+$ 1179.7148.



To a stirred solution of di-TES ether **S15** (15.2 mg, 0.0131 mmol) in MeOH (0.30 mL) was added NH_4F (4.0 mg, 0.11 mmol) at room temperature. After being stirred at room temperature for 2.5 h, the mixture was diluted with saturated aqueous NH_4Cl (2.0 mL) and H_2O (1.0 mL) at 0 °C. The resultant reaction mixture was extracted with Et_2O (3 × 8.0 mL). The extracts were combined, washed with brine (8.0 mL), dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by column chromatography on silica gel (1.5 g, hexane–EtOAc 5 : 1 → 4 : 1 → 3 : 1) to afford alcohol **S16** (14.1 mg, quant) as a colorless amorphous solid: R_f = 0.50 (hexane : EtOAc = 2 : 1); $[\alpha]^{24}_D$ +7.65 (*c* 0.902 , $CHCl_3$); IR ($CHCl_3$) 3486, 3010, 2958, 2937, 2879, 1724, 1517, 1465, 1252, 1030, 837 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45–7.43 (m, 6H), 7.31–7.21 (m, 9H), 6.90–6.87 (m, 2H), 6.81 (d, *J* = 8.0 Hz, 1H), 4.99 (dd, *J* = 9.7, 2.3 Hz, 1H), 4.76 (d, *J* = 7.0 Hz, 1H), 4.68 (d, *J* = 7.0 Hz, 1H), 4.61 (d, *J* = 11.6 Hz, 1H), 4.49 (d, *J* = 11.6 Hz, 1H), 3.94 (m, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.80 (m, 1H), 3.69 (m, 1H), 3.50 (dd, *J* = 5.5, 3.4 Hz, 1H), 3.40 (m, 1H), 3.20 (m, 1H), 2.99 (td, *J* = 8.8, 6.9 Hz, 1H), 2.11 (m, 1H), 2.02 (m, 1H), 2.00 (s, 3H), 1.95–1.84 (m, 3H), 1.81–1.72 (m, 2H), 1.68–1.62 (m, 2H), 1.54–1.47 (m, 2H), 1.30 (m, 1H), 0.99–0.88 (m, 9H), 0.97 (t, *J* = 7.8 Hz, 9H), 0.90 (s, 9H), 0.70 (d, *J* = 6.8 Hz, 3H), 0.63 (q, *J* = 7.8 Hz, 6H), 0.08 (s, 3H), 0.08 (s, 3H). A signal due to one proton (OH) was not observed; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 149.0, 148.5, 144.4 (3C), 130.7, 128.6 (6C), 127.7 (6C), 126.9 (3C), 120.4, 111.2, 110.9, 95.1, 86.5, 79.0, 78.6, 72.6, 69.5, 61.3, 60.1, 55.9, 55.9, 43.1, 37.5, 36.7, 36.5, 31.0, 30.6, 29.7, 29.4, 27.8, 26.1 (3C), 21.0, 18.4, 17.8, 16.9, 12.3, 9.5, 7.1 (3C), 5.5 (3C), –3.6, –4.9; HRMS (ESI) *m*/*z* 1065.6283, calcd for $C_{61}H_{94}NaO_{10}Si_2$ $[M+Na]^+$ 1065.6278.

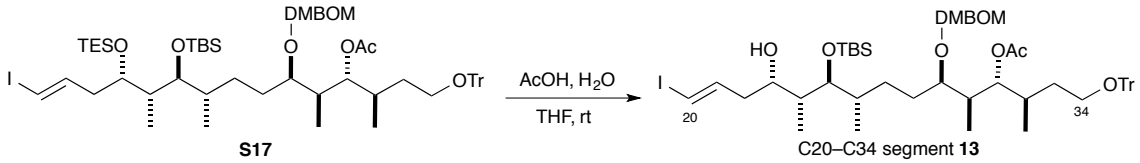


To a stirred solution of alcohol **S16** (83.1 mg, 0.0796 mmol) in CH_2Cl_2 (0.80 mL) and pyridine (45.0 μL) was added Dess–Martin periodinane (84.8 mg, 0.200 mmol) at 0 °C. After stirring for 3 h at room temperature, the mixture was diluted with a 1 : 1 : 1 mixture of saturated aqueous $Na_2S_2O_3$, saturated aqueous $NaHCO_3$, and H_2O (3.0 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 5.0 mL). The organic layer and extracts were combined, washed with brine (20 mL), dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by column chromatography on silica gel (3.2 g, hexane–EtOAc 5 : 1 → 3 : 1) to give aldehyde **25** (77.5 mg, 93%) as a colorless oil: R_f = 0.33 (hexane: EtOAc = 4 : 1); $[\alpha]^{24}_D$ +9.18 (*c* 0.561, $CHCl_3$); IR ($CHCl_3$) 3010, 2958, 2937, 2878, 1723, 1517, 1465, 1253, 1158, 1030, 837, 707, 633 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.82 (t, *J* = 2.2 Hz, 1H), 7.44–7.43 (m, 6H), 7.31–7.21 (m, 9H), 6.89–6.87 (m, 2H), 6.82 (d, *J* = 8.0 Hz, 1H), 4.99 (dd, *J* = 9.8, 2.4 Hz, 1H), 4.76 (d, *J* = 7.0 Hz, 1H), 4.67 (d, *J* = 7.0 Hz, 1H), 4.61 (d, *J* = 11.6 Hz, 1H), 4.49 (d, *J* = 11.6 Hz, 1H), 4.24 (m, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.49 (dd, *J* = 5.2, 4.1 Hz, 1H), 3.40 (m, 1H), 3.20 (m, 1H), 2.99 (dt, *J* = 6.0, 8.8 Hz, 1H), 2.70–2.58 (m, 2H), 2.01 (m, 1H), 2.00 (s, 3H), 1.93–1.84 (m, 2H), 1.76 (m, 1H), 1.68–1.62 (m, 2H), 1.46 (m, 1H), 1.32–1.26 (m, 3H), 0.97–0.88 (m, 9H), 0.95 (t, *J* = 8.0 Hz, 9H), 0.90 (s, 9H), 0.70 (d, *J* = 6.8 Hz, 3H), 0.60 (q, *J* = 8.0 Hz, 6H), 0.08 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.1, 170.8, 149.0, 148.5, 144.4 (3C), 130.7, 128.6 (6C), 127.7 (6C), 126.9 (3C), 120.4, 111.2, 110.9, 95.2, 86.5, 79.0, 78.9, 78.5, 69.7, 69.5, 61.3, 55.9, 55.8, 50.5, 44.0, 37.3, 36.7, 31.0, 30.6, 29.4, 28.0, 26.1 (3C), 21.0, 18.4, 17.2, 16.8, 13.4, 9.4, 7.0 (3C), 5.4 (3C), –3.6, –4.1; HRMS (ESI) *m*/*z* 1063.6111, calcd for $C_{61}H_{92}NaO_{10}Si_2$ $[M+Na]^+$ 1063.6121.



THF was degassed by freeze-thawing. To a stirred solution of aldehyde **25** (151 mg, 0.145 mmol) in THF (0.22 mL) were added $CrCl_2$ (103 mg, 0.838 mmol) and CHI_3 (117 mg, 0.297 mmol) at room

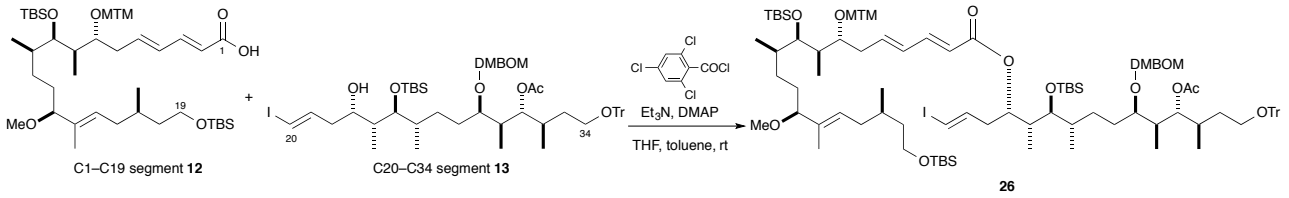
temperature in a glove box. The mixture was stirred at room temperature for 1.5 h, diluted with brine (5.0 mL) and H_2O (1.0 mL), and extracted with Et_2O (5 × 15 mL). The combined extracts was washed with brine (20 mL), dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by column chromatography on silica gel (4.0 g, hexane–EtOAc 1 : 0 → 10 : 1 → 5 : 1) to give **S17** (153 mg, 91%, *E* : *Z* = 4.5 : 1) as a colorless amorphous solid: R_f = 0.57 (hexane : EtOAc = 3 : 1); $[\alpha]^{25}_D$ +7.25 (*c* 1.09, $CHCl_3$); IR ($CHCl_3$) 3010, 2957, 2937, 2878, 1724, 1517, 1465, 1253, 1030, 836, 707 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47–7.45 (m, 6H), 7.33–7.23 (m, 9H), 6.92–6.90 (m, 2H), 6.84 (d, *J* = 8.0 Hz, 1H), 6.51 (dt, *J* = 14.4, 7.8 Hz, 1H), 6.06 (d, *J* = 14.4 Hz, 1H), 5.01 (dd, *J* = 9.8, 2.3 Hz, 1H), 4.79 (d, *J* = 7.0 Hz, 1H), 4.71 (d, *J* = 7.0 Hz, 1H), 4.64 (d, *J* = 11.6 Hz, 1H), 4.52 (d, *J* = 11.6 Hz, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 3.83 (m, 1H), 3.49 (m, 1H), 3.43 (m, 1H), 3.22 (m, 1H), 3.01 (td, *J* = 8.7, 5.7 Hz, 1H), 2.34–2.22 (m, 2H), 2.04 (m,1H), 2.02 (s, 3H), 1.97–1.86 (m, 2H), 1.71–1.66 (m, 3H), 1.47 (m, 1H), 1.33 (m, 1H), 1.13–1.03 (m, 2H), 1.00–0.89 (m, 9H), 0.95 (t, *J* = 7.8 Hz, 9H), 0.93 (s, 9H), 0.70 (d, *J* = 6.8 Hz, 3H), 0.61 (q, *J* = 7.8 Hz, 6H), 0.09 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 149.0, 148.5, 144.4 (3C), 143.1, 137.7, 130.8, 128.6 (6C), 128.3, 127.7 (6C), 126.9 (3C), 120.4, 111.2, 110.9, 95.2, 86.5, 79.0, 78.6, 72.5, 69.5, 61.3, 55.9, 55.8, 43.2, 42.6, 36.7, 36.4, 31.0, 30.6, 29.4, 27.6, 26.2 (3C), 21.1, 18.5, 17.9, 16.9, 11.8, 9.5, 7.1 (3C), 5.5 (3C), –3.5, –4.0; HRMS (ESI) *m*/*z* 1187.5299, calcd for $C_{62}H_{93}INaO_9Si_2$ $[M+Na]^+$ 1187.5295.



To a stirred solution of **S17** (135 mg, 0.116 mmol) in THF (2.1 mL) was added a 4 : 1 mixture of acetic acid and H_2O (2.8 mL) at room temperature. After stirring for 15 h at room temperature, the mixture was poured into saturated aqueous $NaHCO_3$ (20 mL) at 0 °C and stirred for 10 min. The resultant mixture was extracted with Et_2O (3 × 20 mL). The combined extracts were washed with

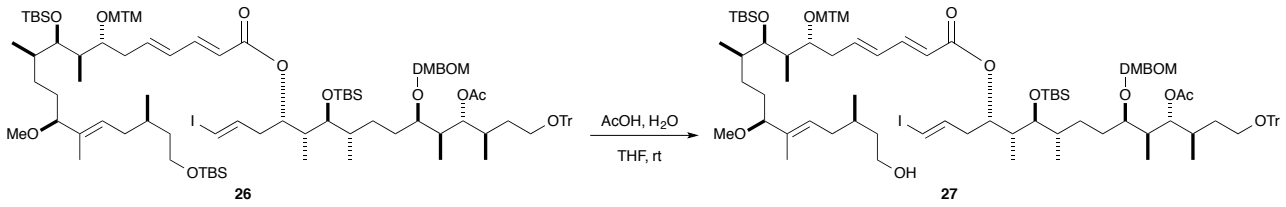
saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL) successively; dried (Na_2SO_4); filtered; and concentrated. The crude product was purified by column chromatography on silica gel (4.0 g, hexane–EtOAc 5 : 1 → 3 : 1) to give C20–C34 segment **13** (105 mg, 86%) as a colorless amorphous solid: R_f = 0.42 (benzene : EtOAc = 3 : 1); $[\alpha]^{15}_{D}$ +2.6 (*c* 0.80, $CHCl_3$); IR ($CHCl_3$) 3470, 2958, 2936, 1725, 1594, 1515, 1464, 1372, 1257, 1028, 836, 706 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.46–7.42 (m, 6H), 7.32–7.28 (m, 6H), 7.25–7.21 (m, 3H), 6.92–6.87 (m, 2H), 6.82 (d, *J* = 8.1 Hz, 1H), 6.53 (dt, *J* = 14.6, 4.9 Hz, 1H), 6.10 (d, *J* = 14.6 Hz, 1H), 5.00 (dd, *J* = 9.8, 2.3 Hz, 1H), 4.77 (d, *J* = 7.0 Hz, 1H), 4.68 (d, *J* = 7.0 Hz, 1H), 4.62 (d, *J* = 11.6 Hz, 1H), 4.48 (d, *J* = 11.6 Hz, 1H), 4.10 (m, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.51 (dd, *J* = 5.6, 3.0 Hz, 1H), 3.42 (m, 1H), 3.21 (m, 1H), 3.00 (td, *J* = 8.9, 5.8 Hz, 1H), 2.32–2.28 (m, 1H), 2.06–2.00 (m, 2H), 2.02 (s, 3H), 1.97–1.86 (m, 3H), 1.71–1.66 (m, 4H), 1.56–1.52 (m, 1H), 1.33–1.27 (m, 1H), 0.98 (d, *J* = 7.8 Hz, 3H), 0.95–0.89 (m, 6H), 0.92 (s, 9H), 0.72 (d, *J* = 6.8 Hz, 3H), 0.12 (s, 3H), 0.11 (s, 3H). A signal due to one proton (OH) was not observed; ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.7, 149.0, 148.6, 144.3 (3C), 143.3, 130.7, 128.6 (6C), 127.7 (6C), 126.9 (3C), 120.3, 111.2, 111.0, 95.5, 86.5, 83.2, 79.0, 78.4, 76.6, 69.4, 69.6, 61.3, 55.9, 55.8, 41.3, 38.4, 36.9, 36.8, 31.0, 30.7, 29.6, 29.5, 26.2 (3C), 21.1, 18.3, 16.9, 15.8, 12.3, 9.6, –3.7, –3.8; HRMS (ESI) *m*/*z* 1073.4420, calcd for $C_{56}H_{79}INaO_9Si$ $[M+Na]^+$ 1073.4436.

<u>Formal synthesis of aplyronine A (**1**) (Synthesis of intermediate **10** of our first-generation synthesis)</u>



To a stirred solution of the C1–C19 segment **12** (22.0 mg, 0.0301 mmol) in THF (0.30 mL) were added Et_3N (0.20 M solution in THF, 0.31 mL, 0.062 mmol) and 2,4,6-$Cl_3C_6H_2COCl$ (0.20 M solution in THF, 0.22 mL, 0.044 mmol) at 0 °C. After being stirred at room temperature for 1 h, Et_3N (0.20 M solution in THF, 0.31 mL, 0.062 mmol) and 2,4,6-$Cl_3C_6H_2COCl$ (0.20 M solution in

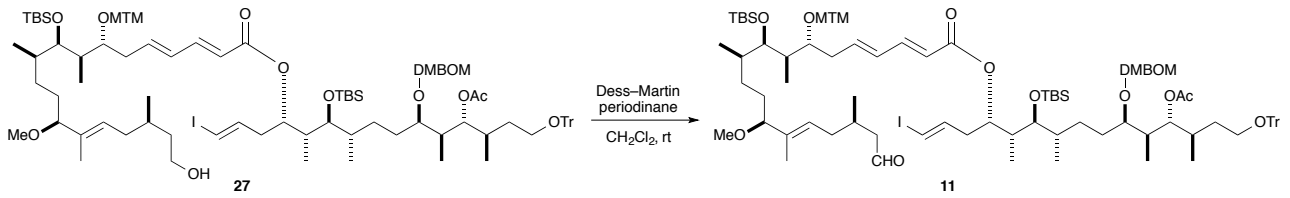
THF, 0.22 mL, 0.044 mmol) were added. After being stirred at room temperature for 45 min, a solution of the C20–C34 segment **13** (85.1 mg, 0.0810 mmol) in toluene (0.80 mL) and DMAP (12.2 mg, 0.0999 mmol) were added. The resulting mixture was stirred at room temperature for 4 h, poured into saturated aqueous $NaHCO_3$ (5.0 mL), and extracted with Et_2O (3 × 15 mL). The combined extracts were washed with brine (10 mL), dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by column chromatography on silica gel (6.0 g, hexane–EtOAc 6 : 1 → 5 : 1 → 3 : 1) to afford ester **26** (51.3 mg, 95%) as a colorless amorphous solid: R_f = 0.54 (hexane : EtOAc = 3 : 1); $[\alpha]^{15}_D$ –1.5 (*c* 1.02, $CHCl_3$); IR ($CHCl_3$) 3008, 2956, 2930, 2857, 1723, 1708, 1641, 1515, 1463, 1383, 1361, 1255, 1214, 1089, 1030, 836 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.43 (m, 6H), 7.29 (m, 6H), 7.247.21 (m, 4H), 6.90–6.87 (m, 2H), 6.82 (d, *J* = 8.0 Hz, 1H), 6.45 (dt, *J* = 14.4, 7.3 Hz, 1H), 6.29–6.15 (m, 2H), 6.08 (d, *J* = 14.4 Hz, 1H), 5.78 (d, *J* = 15.4 Hz, 1H), 5.35 (t , *J* = 6.7 Hz, 1H), 5.12 (dd, *J* = 10.6, 6.2 Hz, 1H), 4.98 (dd, *J* = 9.7, 2.2 Hz, 1H), 4.76 (d, *J* = 7.0 Hz, 1H), 4.68 (d, *J* = 7.0 Hz, 1H), 4.62–4.58 (m, 3H), 4.49 (d, *J* = 11.6 Hz, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.69–3.55 (m, 4H), 3.42–3.37 (m, 3H), 3.20 (m, 1H), 3.16 (s, 3H), 2.99 (td, *J* = 8.8, 5.7 Hz, 1H), 2.47–2.42 (m, 1H), 2.38–2.35 (m, 2H), 2.32–2.28 (m, 1H), 2.14 (s, 3H), 2.13–2.08 (m, 1H), 2.06–2.00 (m,1H), 2.01 (s, 3H), 1.97–1.80 (m, 6H), 1.71–1.66 (m, 3H), 1.60–1.50 (m, 5H), 1.50 (s, 3H), 1.49–1.34 (m, 2H), 1.33–1.28 (m, 3H), 0.96 (d, *J* = 7.0 Hz, 3H) 0.96 (d, *J* = 6.8 Hz, 3H), 0.89–0.86 (m, 9H) 0.88 (s, 9H), 0.88 (s, 9H), 0.88 (s, 9H), 0.84 (d, *J* = 7.0 Hz, 3H), 0.70 (d, *J* = 6.8 Hz, 3H), 0.07 (s, 3H), 0.06 (s, 6H), 0.05 (s, 3H) 0.04 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.8, 166.6, 149.0, 148.5, 144.8, 144.4 (3C), 141.7, 140.8, 134.9, 130.7, 130.4, 128.6 (6C), 127.9, 127.7 (6C), 126.9 (3C), 120.4, 119.8, 111.3, 111.0, 95.2, 88.2, 86.5, 79.0, 78.9, 78.6, 78.6, 77.4, 75.9, 73.3, 72.4, 69.5, 61.4, 55.9, 55.8, 55.6, 40.2, 39.7, 39.5, 37.6, 36.9, 36.8, 34.9, 33.6, 31.8, 31.0, 30.6, 30.2, 29.5, 27.6, 26.2 (3C), 26.1 (3C), 26.0 (6C), 21.1, 19.7, 18.5, 18.4, 18.3, 17.2, 16.9, 15.6, 14.4, 12.0, 10.9, 10.4, 9.6, –3.6, –3.8, –3.9 (2C), –5.3, –5.3; HRMS (ESI) *m*/*z* 1769.9062, calcd for $C_{94}H_{151}INaO_{14}SSi_3$ $[M+Na]^+$ 1769.9075.



26 **27**

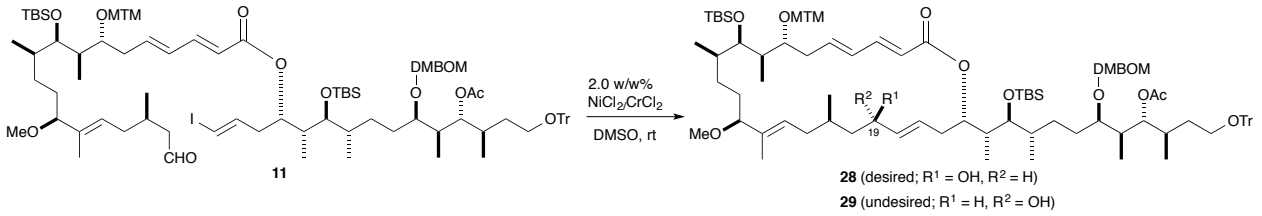
To a stirred solution of ester **26** (120 mg, 0.0690 mmol) in THF (3.6 mL) was added a 4 : 1 mixture of acetic acid and H_2O (4.8 mL) at room temperature. After stirring for 24 h at same temperature, the mixture was poured into saturated aqueous $NaHCO_3$ (45 mL) at 0 °C and stirred for 10 min. The resultant mixture was extracted with Et_2O (3 × 40 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ (2 × 40 mL) and brine (40 mL) successively; dried (Na_2SO_4); filtered; and concentrated. The crude product was purified by column chromatography on silica gel (8.0 g, hexane–EtOAc 4 : 1) to give alcohol **27** (108 mg, 96%) as a colorless amorphous solid: R_f = 0.22 (hexane : EtOAc = 3 : 1); $[\alpha]^{16}_D$ –2.7 (*c* 0.84, $CHCl_3$); IR ($CHCl_3$) 3010, 2957, 2931, 1724, 1709, 1641, 1515, 1463, 1382, 1255, 1213, 1031, 836 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.44–7.42 (m, 6H), 7.30–7.27 (m, 6H), 7.24–7.21 (m, 4H), 6.90–6.87 (m, 2H), 6.82 (d, *J* = 7.9 Hz, 1H), 6.45 (dt, *J* = 14.4, 7.3 Hz, 1H), 6.30–6.14 (m, 2H), 6.08 (d, *J* = 14.5 Hz, 1H), 5.78 (d, *J* = 15.3 Hz, 1H), 5.35 (t, *J* = 7.2 Hz, 1H), 5.12 (dd, *J* = 10.6, 5.4 Hz, 1H), 4.98 (d, *J* = 9.4 Hz, 1H), 4.76 (d, *J* = 6.8 Hz, 1H), 4.68 (d, *J* = 7.0 Hz, 1H), 4.62–4.58 (m, 3H), 4.49 (d, *J* = 11.6 Hz, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.69–3.66 (m, 2H), 3.61 (m, 1H), 3.56 (m, 1H), 3.42–3.38 (m, 3H), 3.20 (m, 1H), 3.16 (s, 3H), 2.98 (td, *J* = 8.8, 5.7 Hz, 1H), 2.47–2.42 (m, 1H), 2.38–2.35 (m, 2H), 2.32–2.26 (m, 1H), 2.14 (s, 3H), 2.13–2.08 (m, 1H), 2.06–2.00 (m, 1H), 2.01 (s, 3H), 1.95–1.80 (m, 5H), 1.71–1.50 (m, 7H), 1.50 (s, 3H), 1.48–1.25 (m, 7H), 0.96–0.86 (m, 15H), 0.90 (s, 9H), 0.89 (s, 9H), 0.84 (d, *J* = 6.8 Hz, 3H), 0.70 (d, *J* = 6.7 Hz, 3H), 0.07 (s, 3H), 0.06 (s, 6H), 0.05 (s, 3H). A signal due to one proton (OH) was not observed; ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.8, 166.6, 149.0, 148.5, 144.9, 144.4 (3C), 141.7, 140.8, 135.0, 130.8, 130.4, 128.6 (6C), 127.7, 127.6 (6C), 126.9 (3C), 120.4, 119.8, 111.3, 111.0, 95.2, 88.1, 86.5, 79.0, 78.9, 78.6, 78.5, 77.4, 75.8, 73.3, 72.5, 69.5, 61.3, 61.1, 55.9, 55.8, 55.7, 40.2, 39.6, 39.6, 37.5, 36.9, 36.8, 34.9, 33.5, 31.7, 31.0, 30.6, 30.2, 29.5, 28.7, 27.6, 26.2 (3C), 26.1 (3C), 21.1, 19.7, 18.5, 18.4, 18.3, 17.2, 16.9, 15.5, 14.4, 12.0, 11.0, 10.4, 9.5, –3.7, –3.8, –3.9,

–3.9; HRMS (ESI) *m*/*z* 1655.8225, calcd for $C_{88}H_{137}INaO_{14}SSi_2$ $[M+Na]^+$ 1655.8210.



To a stirred solution of alcohol **27** (40.2 mg, 0.0246 mmol) in CH_2Cl_2 (0.70 mL) was added Dess–Martin periodinane (14.2 mg, 0.0586 mmol) at room temperature. After stirring for 30 min at room temperature, the mixture was diluted with a 1 : 1 : 1 mixture of saturated aqueous $Na_2S_2O_3$, saturated aqueous $NaHCO_3$, and H_2O (3.0 mL) at 0 °C. The resultant reaction mixture was extracted with Et_2O (3 × 6.0 mL). The combined extracts were washed with brine (10 mL), dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by column chromatography on silica gel (6.0 g, hexane–EtOAc 4 : 1) to give aldehyde **11** (37.4 mg, 93%) as a colorless amorphous solid: R_f = 0.59 (hexane : EtOAc = 2 : 1); $[\alpha]^{16}_D$ –1.0 (*c* 0.97, $CHCl_3$); IR ($CHCl_3$) 3009, 2957, 2931, 2727, 1723, 1641, 1612, 1515, 1463, 1254, 1217, 1212, 1138, 1030, 836 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 9.76 (t, *J* = 2.1 Hz, 1H), 7.44–7.42 (m, 6H), 7.30–7.26 (m, 6H), 7.24–7.21 (m, 4H), 6.90–6.87 (m, 2H), 6.82 (d, *J* = 8.1 Hz, 1H), 6.45 (dt, *J* = 14.4, 7.3 Hz, 1H), 6.29–6.15 (m, 2H), 6.08 (t, *J* = 6.8 Hz, 1H), 5.79 (d, *J* = 15.4 Hz, 1H), 5.33 (t, *J* = 6.8 Hz, 1H), 5.12 (dd, *J* = 10.6, 6.2 Hz, 1H), 4.99 (dd, *J* = 9.7, 2.4 Hz, 1H), 4.76 (d, *J* = 6.9 Hz, 1H), 4.68 (d, *J* = 7.0 Hz, 1H), 4.62–4.58 (m, 3H), 4.49 (d, *J* = 11.6 Hz, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.62–3.59 (m, 1H), 3.58–3.52 (m, 1H), 3.42–3.37 (m, 3H), 3.20 (m, 1H), 3.16 (s, 3H), 2.99 (dt, *J* = 6.0, 8.9 Hz, 1H), 2.47–2.42 (m, 2H), 2.34–2.26 (m, 2H), 2.18–2.09 (m, 2H), 2.14 (s, 3H), 2.13–2.08 (m, 1H), 2.06–2.98 (m, 2H), 2.01 (s, 3H), 1.94–1.80 (m, 4H), 1.71–1.62 (m, 2H), 1.60–1.50 (m, 5H), 1.50 (s, 3H), 1.49–1.34 (m, 2H), 1.33–1.24 (m, 3H), 0.99–0.97 (d, *J* = 6.5 Hz, 3H), 0.96–0.94 (m, 6H), 0.92 (d, *J* = 7.0 Hz, 3H), 0.90 (s, 9H), 0.89 (s, 9H), 0.88 (d, *J* = 6.7 Hz, 3H), 0.84 (d, *J* = 7.0 Hz, 3H), 0.70 (d, *J* = 6.8 Hz, 3H), 0.07 (s, 3H), 0.06 (s, 6H), 0.05 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 202.5, 170.8, 166.6, 149.0, 148.5, 144.8, 144.4 (3C), 141.7, 140.7, 135.0, 130.8, 130.4, 128.6 (6C), 127.7 (6C), 127.6 (3C), 126.3,

120.4, 119.8, 111.3, 111.0, 95.2, 88.0, 86.5, 78.9, 78.9, 78.6, 78.5, 77.4, 75.8, 73.3, 72.4, 69.5, 61.3, 55.9, 55.8, 55.8, 50.6, 40.2, 39.7, 39.6, 37.6, 36.9, 36.8, 34.7, 33.5, 31.8, 31.0, 30.6, 29.5, 28.7, 28.6, 27.6, 26.2 (3C), 26.1 (3C), 21.1, 20.0, 18.5, 18.4, 17.2, 16.9, 15.7, 14.4, 12.0, 11.0, 10.6, 9.5, –3.7, –3.8 (2C), –3.9; HRMS (ESI) *m*/*z* 1653.8062, calcd for $C_{88}H_{135}INaO_{14}SSi_2$ $[M+Na]^+$ 1653.8053.



DMSO was degassed by freeze-thawing. To a stirred solution of aldehyde **11** (46.0 mg, 0.0282 mmol) in DMSO (2.8 mL) was added $CrCl_2$ doped with $NiCl_2$ (2.0 w/w%) (18.5 mg, $CrCl_2$ 0.128 mmol, $NiCl_2$ 0.00280 mmol) at room temperature in a glove box. The mixture was stirred at room temperature for 4 h in a glove box. The resultant reaction mixture was diluted with brine (25 mL) and extracted with Et_2O (4 × 20 mL). The combined extracts were washed with brine (20 mL), dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by column chromatography on silica gel (2.0 g, hexane–EtOAc 3.5 : 1 → 3 : 1 → 2 : 1) to afford desired allylic alcohol **28** (22.8 mg, 54%) and undesired allylic alcohol **29** (15.1 mg, 36%) as colorless amorphous solids, respectively.

Desired allylic alcohol **28**: R_f = 0.33 (hexane : EtOAc = 2 : 1); $[\alpha]^{16}_D$ +33.8 (*c* 0.78, $CHCl_3$); IR ($CHCl_3$) 3009, 2957, 2930, 2857, 1722, 1643, 1516, 1463, 1382, 1257, 1138, 1031, 836 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.44–7.42 (m, 6H), 7.31–7.26 (m, 6H), 7.24–7.20 (m, 4H), 6.89–6.87 (m, 2H), 6.82 (d, *J* = 8.1 Hz, 1H), 6.23–6.15 (m, 2H), 5.82 (d, *J* = 15.4 Hz, 1H), 5.54 (ddd, *J* = 15.0, 10.5, 4.3 Hz, 1H), 5.27–5.21 (m, 2H), 5.06 (m, 1H), 4.99 (dd, *J* = 9.8, 2.3 Hz, 1H), 4.76 (d, *J* = 7.0 Hz, 1H), 4.67 (d, *J* = 7.0 Hz, 1H), 4.61 (d, *J* = 11.7 Hz, 1H), 4.59 (d, *J* = 11.7 Hz, 1H), 4.53 (d, *J* = 11.7 Hz, 1H), 4.48 (d, *J* = 11.7 Hz, 1H), 4.09 (m, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.60 (m, 1H), 3.51 (br s, 1H), 3.41–3.36 (m, 3H), 3.21–3.14 (m, 1H), 3.18 (s, 3H), 2.98 (td, *J* = 8.8, 6.1 Hz, 1H), 2.45 (m, 1H), 2.35 (m, 1H), 2.24–2.12 (m, 2H), 2.16 (s, 3H), 2.07–1.96 (m, 2H), 2.00 (s, 3H), 1.95–1.77

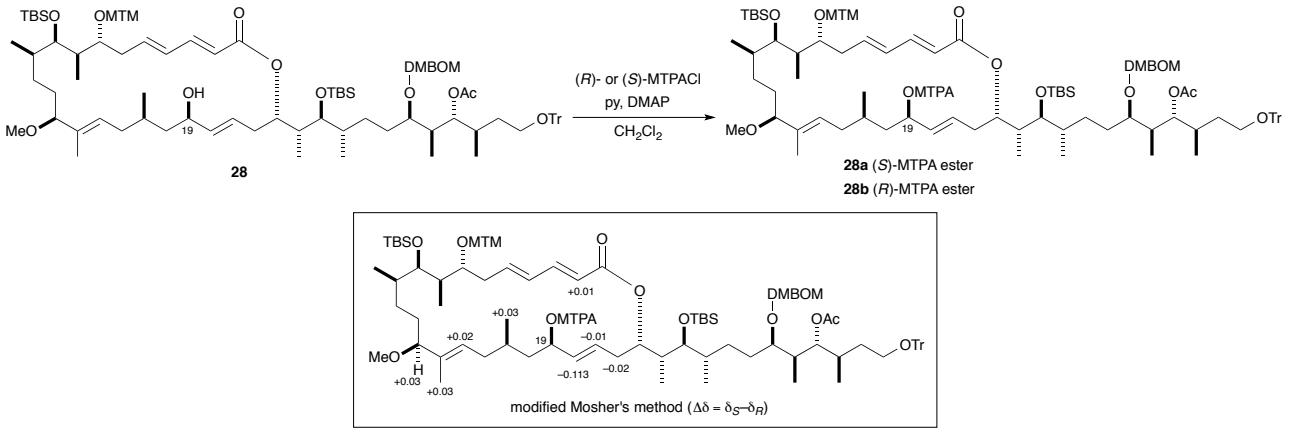
(m, 4H), 1.71–1.37 (m, 10H), 1.45 (s, 3H), 1.35–1.21 (m, 4H), 1.09 (m, 1H), 0.95–0.85(m, 15H) 0.91 (s, 9H), 0.89 (s, 9H), 0.81 (d, J = 6.2 Hz, 3H), 0.70 (d, J = 6.8 Hz, 3H), 0.13 (s, 3H), 0.07 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H). A signal due to one proton (OH) was not observed; ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.8, 166.2, 149.0, 148.5, 144.4, 144.3 (3C), 140.5, 135.3, 134.3, 130.8, 130.0, 129.6, 129.4, 128.6 (6C), 127.7 (6C), 126.9 (3C), 120.4, 120.3, 111.2, 111.0, 95.3, 87.6, 86.5, 82.0, 79.2, 78.6, 78.5, 77.0, 72.9, 72.8, 72.2, 69.5, 61.4, 55.9, 55.8, 55.6, 42.7, 42.7, 42.6, 38.5, 38.1, 37.4, 37.2, 36.7, 36.3, 33.0, 31.0, 30.5, 29.9, 29.7, 29.4, 28.0, 26.2 (3C), 26.0 (3C), 21.0, 20.1, 18.5, 18.3, 17.0, 16.9, 14.5, 14.1, 13.0, 12.0, 9.8, 9.4, –3.7, –4.0 (2C), –4.2; HRMS (ESI) *m*/*z* 1527.9102, calcd for $C_{88}H_{136}NaO_{14}SSi_2$ $[M+Na]^+$ 1527.9087.

Undesired allylic alcohol **29**: R_f = 0.43 (hexane : EtOAc = 2 : 1); $[\alpha]^{17}_D$ +8.8 (*c* 0.76, $CHCl_3$); IR ($CHCl_3$) 3009, 2957, 2930, 2857, 1723, 1642, 1516, 1463, 1383, 1254, 1219, 1138, 1089, 836 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.44–7.42 (m, 6H), 7.30–7.26 (m, 6H), 7.24–7.20 (m, 4H) 6.89–6.87 (m, 2H), 6.82 (d, J = 8.0 Hz, 1H), 6.24–6.19 (m, 1H), 6.19–6.11 (m, 1H) 5.78 (d, J = 15.4 Hz, 1H), 5.61 (ddd, J = 14.9, 8.4, 6.0 Hz, 1H), 5.49 (dd, J = 15.5, 5.1 Hz, 1H), 5.25–5.20 (m, 2H), 4.99 (dd, J = 9.8, 2.2 Hz, 1H), 4.77 (d, J = 7.0 Hz, 1H), 4.67 (d, J = 7.0 Hz, 1H), 4.63–4.56 (m, 3H), 4.47 (d, J = 11.7 Hz, 1H), 4.10 (m, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.67–3.63 (m, 1H), 3.54–3.53 (m, 1H), 3.46–3.36 (m, 3H), 3.21–3.19 (m, 1H), 3.14 (s, 3H), 2.99 (dt, J = 5.9, 8.9 Hz, 1H), 2.46–2.44 (m, 1H), 2.35 (m, 2H), 2.23 (m, 1H), 2.20–2.12 (m, 1H), 2.18 (s, 3H), 2.08–1.97 (m, 2H), 2.01 (s, 3H), 1.94–1.73 (m, 5H), 1.69–1.46 (m, 8H), 1.46 (s, 3H), 1.40 (m, 1H) 1.33–1.22 (m, 3H), 1.13 (m, 1H), 1.0–0.78 (m, 12H), 0.92 (s, 9H), 0.90 (s, 9H), 0.85 (d, J = 7.0 Hz, 3H), 0.81 (d, J = 6.6 Hz, 3H), 0.70 (d, J = 6.8 Hz, 3H), 0.12 (s, 3H), 0.09 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H). A signal due to one proton (OH) was not observed; ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.8, 166.7, 149.0, 148.5, 144.8, 144.4 (3C), 140.1, 135.9, 134.5, 130.7, 130.3, 128.6 (6C), 128.2, 127.7 (6C), 126.9 (3C), 125.8, 120.4, 120.0, 111.2, 111.0, 95.3, 87.9, 86.5, 79.0, 78.9, 78.5, 77.3, 73.4, 73.1, 69.8, 69.5, 61.3, 55.9 (2C), 55.8 (2C), 55.6, 44.5, 42.4, 40.0, 37.4, 37.0, 36.7, 34.8, 31.0, 31.0, 30.5, 29.5, 29.4, 26.2 (3C), 26.2, 26.0 (3C), 21.0, 19.8, 18.5, 18.3, 17.2, 16.9, 14.6, 14.4, 12.9, 12.1, 10.1, 9.5, –3.7, –4.0, –4.1,

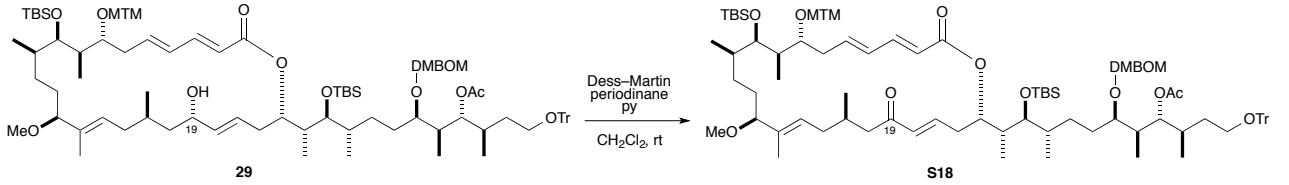
–4.2, –4.2, –4.3; HRMS (ESI) *m*/*z* 1527.9073, calcd for $C_{88}H_{136}NaO_{14}SSi_2$ $[M+Na]^+$ 1527.9087.

Determination of the absolute configuration of C19 in **28**

For the determination of the absolute configuration of C19 in **28**, allylic alcohol **28** was converted into (*S*)- and (*R*)-MTPA esters **28a** and **28b**.[5] The Δδ values for these MTPA esters are described below:

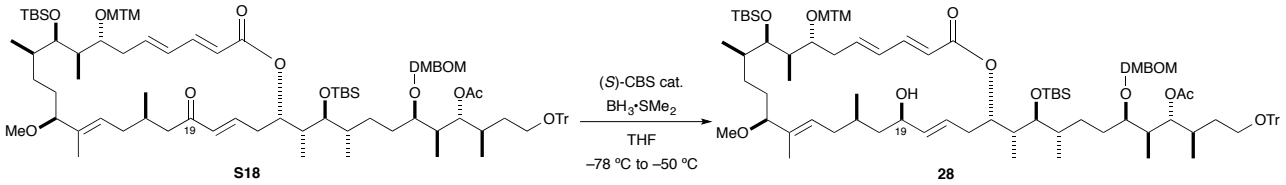


Δδ values (δ_S–δ_R) for these MTPA esters in ppm (600 MHz).



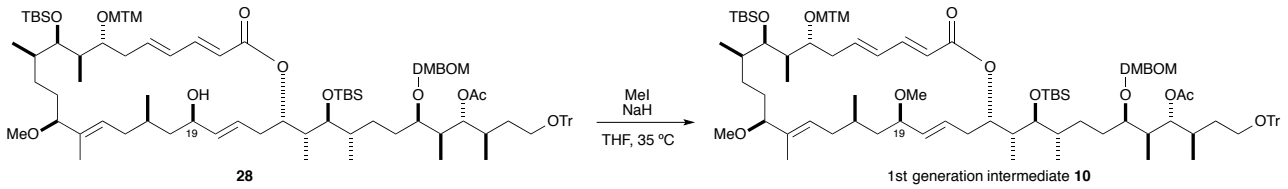
To a stirred solution of undesired allylic alcohol **29** (15.2 mg, 10.1 μmol) in CH_2Cl_2 (0.60 mL) and pyridine (0.060 mL) was added Dess–Martin periodinane (6.2 mg, 15 μmol) at room temperature. After stirring for 30 min at room temperature, the mixture was diluted with a 1 : 1 : 1 mixture of saturated aqueous $Na_2S_2O_3$, saturated aqueous $NaHCO_3$, and H_2O (3.0 mL) at 0 °C. The resultant reaction mixture was extracted with Et_2O (3 × 8.0 mL). The combined extracts were washed with brine (5.0 mL), dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by column chromatography on silica gel (0.80 g, hexane–EtOAc 6 : 1 → 2 : 1) to give enone **S18** (13.7 mg, 90%) as a colorless amorphous solid: R_f = 0.50 (hexane : EtOAc = 2 : 1); $[\alpha]^{17}_D$ +4.8 (*c* 0.29,

$CHCl_3$); IR ($CHCl_3$) 2957, 2931, 1723, 1516, 1463, 1254, 1212, 1030, 836 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.46–7.43 (m, 6H), 7.31–7.26 (m, 6H), 7.25–7.22 (m, 4H), 6.89 (m, 2H), 6.82 (d, *J* = 8.4 Hz, 1H), 6.63 (ddd, *J* = 15.7, 9.2, 6.2 Hz, 1H), 6.20 (dd, *J* = 15.0, 11.1, Hz, 1H), 6.13–6.08 (m, 1H), 5.97 (d, *J* = 16.1 Hz, 1H), 5.71 (d, *J* = 15.2 Hz, 1H), 5.37 (m, 1H), 5.19 (m, 1H), 5.00 (dd, *J* = 9.8, 2.2 Hz, 1H), 4.78 (d, *J* = 7.0 Hz, 1H), 4.68 (d, *J* = 7.0 Hz, 1H), 4.62 (d, *J* = 11.6 Hz, 1H), 4.57 (s, 2H), 4.49 (d, *J* = 11.6 Hz, 1H), 3.89 (s, 3H), 3.86 (s, 3H), 3.75 (br s, 1H), 3.54 (m, 1H), 3.45–3.41 (m, 2H), 3.37 (dd, *J* = 9.6, 5.1 Hz, 1H), 3.21 (m, 1H), 3.16 (s, 3H), 3.00 (td, *J* = 8.9, 6.0 Hz, 1H), 2.60 (m, 1H), 2.42–2.35 (m, 4H), 2.17 (s, 3H), 2.06–2.00 (m, 3H), 2.01 (s, 3H), 1.97–1.83 (m, 5H), 1.75–1.55 (m, 4H), 1.52–1.48 (m, 2H), 1.48 (s, 3H), 1.34–1.25 (m, 3H), 1.10–0.95 (m, 3H), 0.97–0.91 (m, 12H), 0.92 (s, 9H), 0.90 (s, 9H), 0.86 (d, *J* = 6.9 Hz, 3H), 0.73–0.70 (m, 6H), 0.09 (s, 3H), 0.08 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 200.6, 170.7, 166.8, 149.0, 148.6, 145.8, 144.4 (3C), 142.9, 140.5, 134.9, 133.8, 130.6, 130.4, 128.6 (6C), 127.7 (6C), 126.9 (3C), 120.4, 119.0, 111.3, 111.0, 95.3, 88.2, 86.5, 79.1, 78.9, 78.5, 73.0, 72.5, 69.6, 61.3, 55.9, 55.8, 55.5, 46.1, 42.0, 41.0, 38.3, 37.4, 36.8, 35.2, 32.3, 31.6, 31.3, 31.0, 30.6, 30.5, 29.7, 29.5, 29.2, 28.1, 26.2 (3C), 25.9 (3C), 22.7, 21.0, 19.6, 18.5, 18.3, 16.9, 16.9, 14.6, 14.1, 14.0, 13.1, 12.2, 10.0, 9.5, –3.7, –4.1, –4.2, –4.3; HRMS (ESI) *m*/*z* 1525.8953, calcd for $C_{88}H_{134}NaO_{14}SSi_2$ $[M+Na]^+$ 1525.8931.



To a stirred solution of (*S*)-CBS catalyst (1.0 M solution in toluene, 0.050 mL, 50 μmol) in THF (0.2 mL) was added $BH_3 \cdot SMe_2$ (2.0 M solution in THF, 0.022 mL, 0.044 mmol) at 0 °C. After being stirred for 30 min, the mixture was cooled –78 °C. A solution of enone **S18** (12.6 mg, 8.50 μmol) in THF (0.40 mL) was added, and the mixture was stirred for 1 h. The resultant mixture was allowed to warm to –50 °C, and stirring was continued for 30 min. The reaction was quenched by

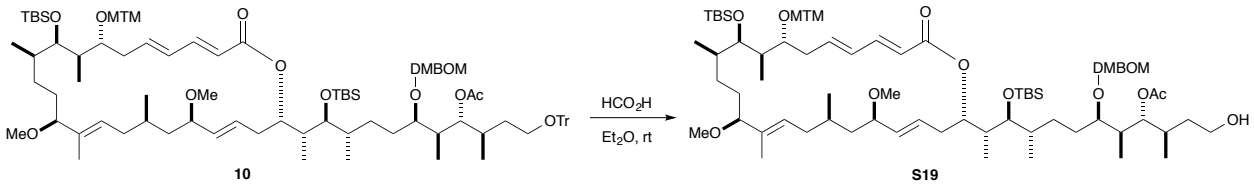
addition of MeOH (0.25 mL), and the resultant mixture was allowed to warm to 0 °C. After being stirred for 10 min, the mixture was diluted with brine (3.0 mL) at 0 °C and extracted with Et_2O (3 × 8.0 mL). The combined extracts were washed with brine (8.0 mL), dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by column chromatography on silica gel (0.80 g, hexane–EtOAc 3 : 1) to give desired allylic alcohol **28** (7.1 mg, 55%) and undesired allylic alcohol **29** (2.1 mg, 17%) as colorless amorphous solids, respectively.



A mixture of allylic alcohol **28** (21.0 mg, 0.0139 mmol), MeI (0.14 M THF solution, 1.0 mL, 0.14 mmol), and NaH (60% in mineral oil, 7.2 mg, 0.18 mmol) was stirred at 35 °C for 3.5 h. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ (10 mL) at 0 °C, and extracted with Et_2O (3 × 8.0 mL). The combined extracts were washed with brine (8.0 mL), dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by column chromatography on silica gel (0.80 g, hexane–EtOAc 4 : 1) to give methyl ether **10** (18.7 mg, 90%) as a colorless amorphous solid: R_f = 0.47 (hexane : EtOAc = 2 : 1); $[\alpha]^{18}_D$ +37.4 (*c* 0.88, $CHCl_3$); IR ($CHCl_3$) 3010, 2957, 2931, 2857, 1723, 1662, 1641, 1516, 1463, 1383, 1254, 1219, 1212, 1157, 1030, 836 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.44–7.43 (m, 6H), 7.30–7.28 (m, 6H), 7.24–7.21 (m, 4H), 6.90–6.87 (m, 2H), 6.82 (d, *J* = 8.1 Hz, 1H), 6.23–6.14 (m, 2H), 5.82 (d, *J* = 15.3 Hz, 1H), 5.54 (ddd, *J* = 15.0, 10.7, 4.2 Hz, 1H), 5.27 (m, 1H), 5.11–5.03 (m, 2H), 4.99 (dd, *J* = 9.8, 2.3 Hz, 1H), 4.76 (d, *J* = 7.0 Hz, 1H), 4.67 (d, *J* = 7.0 Hz, 1H), 4.61 (d, *J* = 11.6 Hz, 1H), 4.59 (d, *J* = 11.6 Hz, 1H), 4.53 (d, *J* = 11.6 Hz, 1H), 4.49 (d, *J* = 11.6 Hz, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.59 (br s, 1H), 3.52–3.46 (m, 2H), 3.43–3.36 (m, 3H), 3.21–3.15 (m, 1H), 3.18 (s, 3H), 3.16 (s, 3H), 2.98 (m, 1H), 2.48 (m, 1H), 2.33 (m, 1H), 2.25 (m, 1H), 2.16 (s, 3H), 2.08–1.97 (m, 3H), 2.00 (s, 3H), 1.95–1.77 (m, 4H), 1.71–1.37 (m, 10H), 1.45 (s, 3H), 1.35–1.19 (m, 4H), 1.09 (m, 1H), 0.95–0.86 (m, 15H), 0.92 (s, 9H),

0.89 (s, 9H), 0.79 (d, J = 6.2 Hz, 3H), 0.70 (d, J = 6.8 Hz, 3H), 0.14 (s, 3H), 0.08 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.7, 166.3, 149.0, 148.5, 144.4, 144.4 (3C), 140.8, 134.1, 133.0, 130.8, 130.0, 129.5, 128.6 (6C), 127.7 (6C), 126.9 (3C), 120.4, 120.3, 111.2, 111.0, 95.2, 87.6, 86.5, 81.4, 79.2, 78.8, 78.5, 77.3, 72.9, 72.8, 69.5, 61.3, 55.9, 55.8, 55.6, 55.6, 42.8, 40.8, 40.8, 38.5, 37.4, 37.1, 36.7, 36.3, 32.5, 31.0, 30.5, 30.4, 29.5, 29.4, 28.1, 28.0, 26.2 (3C), 26.0 (3C), 25.9, 21.0, 20.1, 18.5, 18.3, 17.0, 16.9, 14.5, 14.1, 12.8, 12.0, 9.7, 9.4 (2C), –3.6, –4.0 (2C), –4.3; HRMS (ESI) m/z 1541.9237, calcd for $C_{89}H_{138}NaO_{14}SSi_2$ $[M+Na]^+$ 1541.9244.

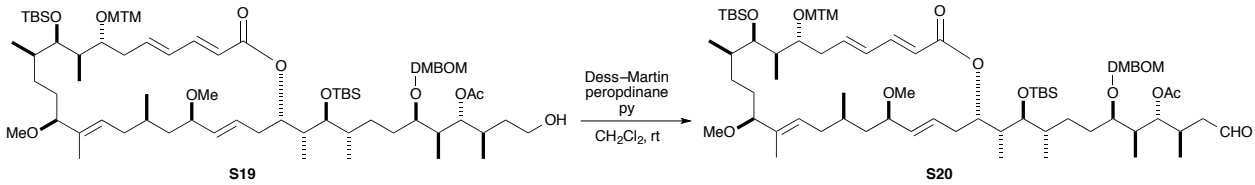
Total synthesis of aplyronine A (**1**)



10 **S19**

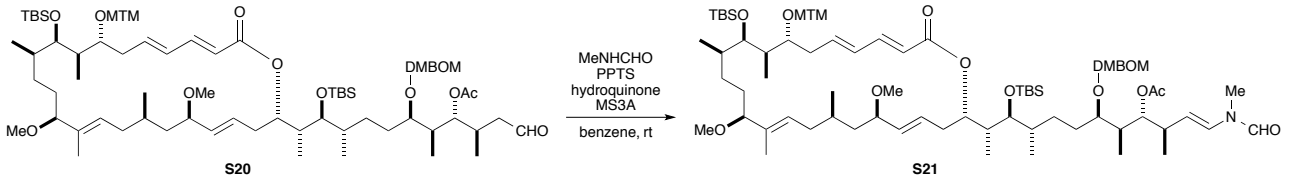
To a stirred solution of methyl ether **10** (7.0 mg, 4.6 μmol) in Et_2O (0.60 mL) was added HCO_2H (0.40 mL) at room temperature. The mixture was stirred at room temperature for 1 h, poured into saturated aqueous $NaHCO_3$ (10 mL) at 0 °C, and extracted with Et_2O (3 × 8.0 mL). The combined extracts were washed with brine (8.0 mL), dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by column chromatography on silica gel (0.80 g, hexane–EtOAc 2 : 1 → 1 : 1) to afford alcohol **S19** (5.6 mg, 95%) as a colorless amorphous solid: R_f = 0.26 (hexane : EtOAc = 2 : 1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.22 (dd, J = 15.4, 10.2 Hz, 1H), 6.89–6.83 (m, 2H), 6.82 (d, J = 8.1 Hz, 1H), 6.21–6.17 (m, 2H), 5.82 (d, J = 15.3 Hz, 1H), 5.54 (ddd, J = 14.8, 10.4, 4.1 Hz, 1H), 5.25 (ddd, J = 11.0, 5.6, 1.8 Hz, 1H), 5.09–5.01 (m, 2H), 4.99 (dd, J = 9.7, 2.6 Hz, 1H), 4.76 (d, J = 7.0 Hz, 1H), 4.66 (d, J = 7.0 Hz, 1H), 4.60 (d, J = 11.7 Hz, 1H), 4.59 (d, J = 11.7 Hz, 1H), 4.53 (d, J = 11.7 Hz, 1H), 4.49 (d, J = 11.7 Hz, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 3.80–3.71 (m, 2H), 3.67–3.58 (m, 2H), 3.52–3.45 (m, 2H), 3.42 (t, J = 4.6 Hz, 1H), 3.38 (dd, J = 10.7, 4.4 Hz, 1H), 3.19 (s, 3H), 3.16 (s, 3H), 2.48 (m, 1H), 2.38–2.29 (m, 2H), 2.24 (m, 1H), 2.16 (s, 3H), 2.04 (s, 3H), 2.04–1.96 (m, 2H), 1.90 (m, 1H), 1.81 (m, 1H), 1.74 (m, 1H), 1.69–1.04 (m, 15H), 1.02–0.84 (m, 20H),

1.45 (s, 3H), 0.91 (s, 9H), 0.89 (s, 9H), 0.79 (d, J = 6.2 Hz, 3H), 0.13 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H); HRMS (ESI) m/z 1541.9237, calcd for $C_{70}H_{124}NaO_{14}SSi_2$ $[M+Na]^+$ 1299.8149.



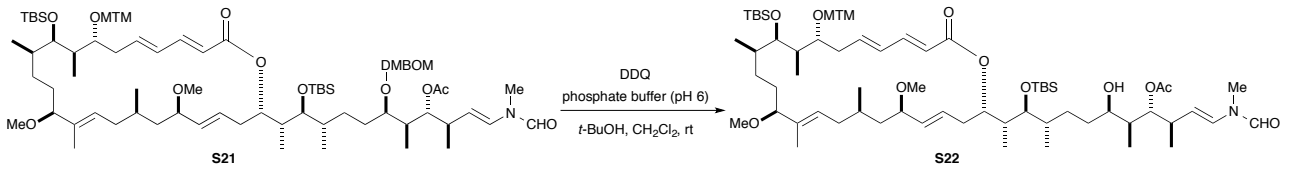
S19 **S20**

To a stirred solution of alcohol **S19** (5.6 mg, 4.4 μmol) in CH_2Cl_2 (0.25 mL) and pyridine (0.025 mL) was added Dess–Martin periodinane (2.6 mg, 3.3 μmol) at room temperature. After stirring for 30 min at room temperature, the mixture was diluted with a 1 : 1 : 1 mixture of saturated aqueous $Na_2S_2O_3$, saturated aqueous $NaHCO_3$, and H_2O (3.0 mL) at 0 °C. The resultant reaction mixture was extracted with Et_2O (3 × 8.0 mL). The combined extracts were washed with brine (8.0 mL), dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by column chromatography on silica gel (0.80 g, hexane–EtOAc 2 : 1) to give aldehyde **S20** (4.2 mg, 75%) as a colorless amorphous solid: R_f = 0.46 (hexane : EtOAc = 2 : 1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.77 (m, 1H), 7.22 (dd, J = 15.3, 10.1 Hz, 1H), 6.89–6.87 (m, 2H), 6.82 (d, J = 8.1 Hz, 1H), 6.21–6.17 (m, 2H), 5.82 (d, J = 15.3 Hz, 1H), 5.54 (ddd, J = 14.8, 10.4, 4.1 Hz, 1H), 5.26 (ddd, J = 11.0, 5.5, 1.8 Hz, 1H), 5.09–5.01 (m, 2H), 5.01 (dd, J = 9.3, 2.8 Hz, 1H), 4.76 (d, J = 7.0 Hz, 1H), 4.66 (d, J = 7.0 Hz, 1H), 4.60 (d, J = 11.7 Hz, 1H), 4.59 (d, J = 11.7 Hz, 1H), 4.53 (d, J = 11.7 Hz, 1H), 4.49 (d, J = 11.7 Hz, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 3.60 (br s, 1H), 3.49 (td, J = 9.4, 4.7 Hz, 1H), 3.45 (m, 1H), 3.40 (t, J = 4.7 Hz, 1H), 3.38 (dd, J = 10.8, 4.4 Hz, 1H), 3.19 (s, 3H), 3.18 (m, 1H), 3.16 (s, 3H), 2.50–2.44 (m, 3H), 2.37–2.20 (m, 4H), 2.16 (s, 3H), 2.04 (s, 3H), 2.03–1.97 (m, 1H), 1.83–1.76 (m, 2H), 1.70–1.18 (m, 14H), 1.45 (s, 3H), 1.09 (m, 1H), 1.03–0.86 (m, 12H), 0.97 (d, J = 6.9 Hz, 3H), 0.90 (s, 9H), 0.88 (s, 9H), 0.87 (d, J = 6.9 Hz, 3H), 0.78 (d, J = 6.1 Hz, 3H), 0.13 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), 0.04 (s, 3H); HRMS (ESI) m/z 1297.8012, calcd for $C_{70}H_{122}NaO_{14}SSi_2$ $[M+Na]^+$ 1297.7992.



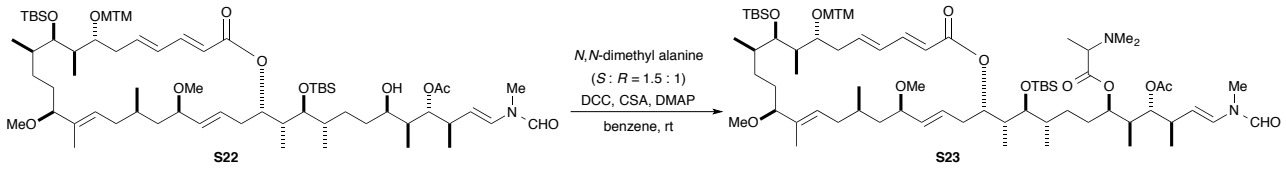
S20 S21

To a stirred solution of aldehyde **S20** (8.0 mg, 6.3 μmol) in benzene (9.0 mL) were added *N*-methylformamide (0.110 mL, 1.87 mmol), PPTS (10.2 mg, 40.6 μmol), and hydroquinone (4.6 mg, 42 μmol) at room temperature. The reaction mixture was heated to reflux for 12 h under a stream of N_2 with continuous removal of water by means of molecular sieves 3Å. The mixture was cooled to room temperature, poured into saturated aqueous $NaHCO_3$ (10 mL) at 0 °C, and extracted with Et_2O (3 × 10 mL). The combined extracts were washed with brine (10 mL), dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by column chromatography on silica gel (0.80 g, hexane–EtOAc 4 : 1 → 3 : 1 → 2 : 1) to afford enamide **S21** (5.3 mg, 64%) as a colorless amorphous solid: R_f = 0.32 (hexane : EtOAc = 2 : 1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.27 [8.06] (s, 1H), 7.22 (dd, *J* = 15.2, 9.8 Hz, 1H), 6.90–6.86 (m, 2H), 6.82 (d, *J* = 8.0 Hz, 1H), 6.48 [7.17] (d, *J* = 14.1 Hz, 1H), 6.24–6.17 (m, 2H), 5.82 (d, *J* = 15.2 Hz, 1H), 5.53 (ddd, *J* = 14.8, 10.4, 4.1 Hz, 1H), 5.23 (m, 1H), 5.15–4.98 (m, 4H), 4.76 [4.75] (d, *J* = 7.0 Hz, 1H), 4.64 (d, *J* = 7.0 Hz, 1H), 4.61 (d, *J* = 11.7 Hz, 1H), 4.60 (d, *J* = 11.7 Hz, 1H), 4.53 (d, *J* = 11.7 Hz, 1H), 4.49 (d, *J* = 11.7 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.60 (m, 1H), 3.52–3.43 (m, 3H), 3.41–3.36 (m, 2H), 3.19 (s, 3H), 3.16 (s, 3H), 2.99 [3.02] (s, 3H), 2.55 (m, 1H), 2.46 (m, 1H), 2.36–2.16 (m, 3H), 2.16 (s, 3H), 2.07 [2.06] (s, 3H), 2.01 (m, 1H), 1.85–1.17 (m, 16H), 1.44 (s, 3H), 1.12–0.84 (m, 16H), 1.03 [1.02] (d, *J* = 6.9 Hz, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.78 (d, *J* = 6.1 Hz, 3H), 0.12 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H) (the minor counterparts of doubled signals in the ratio of 2 : 1 are in brackets); HRMS (ESI) *m*/*z* 1338.8242, calcd for $C_{72}H_{125}NNaO_{14}SSi_2$ $[M+Na]^+$ 1338.8258.



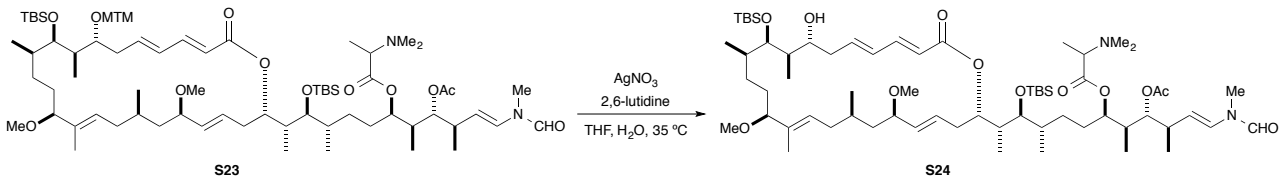
S21 S22

To a stirred solution of enamide **S21** (1.7 mg, 1.3 μmol) in CH_2Cl_2 (0.50 mL), *t*-BuOH (0.025 mL, 0.26 mmol), and 1 M phosphate buffer (pH 6.0, 0.025 mL) was added DDQ (1.2 mg, 5.3 μmol) at 0 °C. The mixture was warmed to room temperature and stirred for 30 min. The mixture was cooled to 0 °C, and DDQ (1.1 mg, 4.2 μmol) was added. After the mixture was stirred at room temperature for 30 min, 1 M phosphate buffer (pH 6.0, 1.0 mL) was added. The mixture was stirred at room temperature for 1 h, and extracted with Et_2O (3 × 6.0 mL). The combined extracts were washed with 1.0 M phosphate buffer (pH 6, 4.0 mL), saturated aqueous $NaHCO_3$ (4.0 mL), H_2O (4.0 mL) and brine (4.0 mL) successively; dried (Na_2SO_4); filtered; and concentrated. The crude product was purified by column chromatography on silica gel (0.80 g, hexane–EtOAc 2 : 1) to afford alcohol **S22** (1.3 mg, 89%) as a colorless amorphous solid: R_f = 0.59 (toluene : EtOAc = 2 : 1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.29 [8.07] (s, 1H), 7.21 (m, 1H), 6.51 [7.18] (d, *J* = 14.1 Hz, 1H), 6.24–6.15 (m, 2H), 5.82 (d, *J* = 15.3 Hz, 1H), 5.54 (ddd, *J* = 14.8, 10.4, 4.1 Hz, 1H), 5.27 (m, 1H), 5.09–4.98 (m, 3H), 4.82 [4.81] (dd, *J* = 9.8, 3.1 Hz, 1H), 4.59 (d, *J* = 11.6 Hz, 1H), 4.53 (d, *J* = 11.6 Hz, 1H), 3.62–3.38 (m, 1H), 3.60 (br s, 1H), 3.51–3.47 (m, 2H), 3.45–3.41 (m, 2H), 3.38 (dd, *J* = 10.7, 4.4 Hz, 1H), 3.19 (s, 3H), 3.16 (s, 3H), 3.02 [3.05] (s, 3H), 2.65–2.52 (m, 3H), 2.45 (m, 2H), 2.36–2.25 (m, 3H), 2.16 (s, 3H), 2.16 [2.15] (s, 3H), 2.00 (m, 1H), 1.80 (m, 1H), 1.70–1.20 (m, 12H), 1.44 (s, 3H), 1.11–0.84 (m, 7H), 1.06 [1.05] (d, *J* = 6.8 Hz, 3H), 0.95 (d, *J* = 7.1 Hz, 3H), 0.92 (d, *J* = 6.9 Hz, 3H), 0.92 (d, *J* = 6.9 Hz, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.78 (d, *J* = 6.2 Hz, 3H), 0.11 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H) (the minor counterparts of doubled signals in the ratio of 2 : 1 are in brackets); HRMS (ESI) *m*/*z* 1158.7489, calcd for $C_{62}H_{113}NNaO_{11}SSi_2$ $[M+Na]^+$ 1158.7470.



To a mixture of alcohol **S22** (4.2 mg, 3.7 μmol), L-*N*,*N*-dimethylalanine (4.6 mg, 39 μmol), D-*N*,*N*-dimethylalanine (3.1 mg, 26 μmol), DMAP (23.2 mg, 190 μmol), and CSA (15.4 mg, 66.3

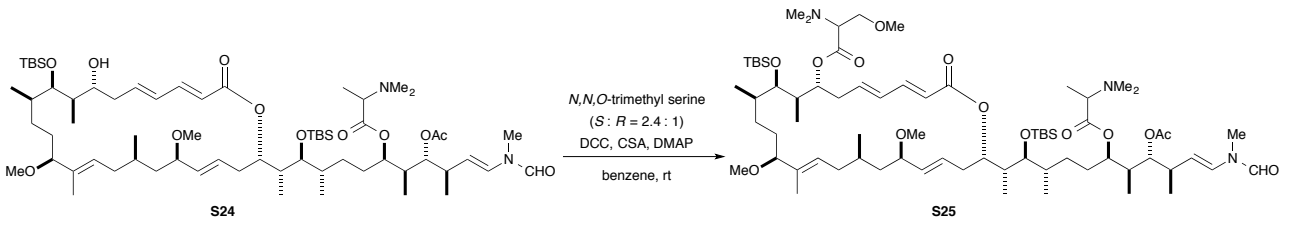
μmol) in benzene (1.5 mL) was added DCC (0.10 M CH_2Cl_2 solution, 0.66 mL, 66 μmol) at room temperature. The mixture was stirred at room temperature for 15 h, and saturated aqueous $NaHCO_3$ (4.0 mL) was added at 0 °C. The mixture was stirred at room temperature for 20 min and extracted with EtOAc (3 × 8.0 mL). The combined extracts were washed with brine (8.0 mL), dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by column chromatography on silica gel (0.50 g, hexane–EtOAc 3 : 1) to afford a diastereomeric mixture of dimethylalanine esters **S23** (*S* : *R* = 3.5 : 1) (3.8 mg, 84%) as a colorless amorphous solid: R_f = 0.34 (hexane : EtOAc = 1 : 1); ^{1}H NMR (600 MHz, acetone-d_6) δ 8.36 [8.10][a] (s, 1H), 7.24 (dd, *J* = 15.2, 10.8 Hz, 1H), 6.84 [7.15][a] (d, *J* = 14.1 Hz, 1H), 6.40 (dd, *J* = 15.2, 10.9 Hz, 1H), 6.31 (m, 1H), 5.93 (d, *J* = 15.2 Hz, 1H) 5.56 (ddd, *J* = 15.0, 10.5, 4.1 Hz, 1H), 5.30 (m, 1H), 5.15 (m, 1H), 5.10–4.98 (m, 3H), 4.80 (dd, *J* = 10.2, 2.5 Hz, 1H), 4.67 (d, *J* = 11.6 Hz, 1H), 4.63 (d, *J* = 11.6 Hz, 1H), 3.72–3.57 (m, 2H), 3.54 (m, 1H), 3.48 (td, *J* = 9.4, 4.9 Hz, 1H), 3.43 (dd, *J* = 10.7, 4.5 Hz, 1H), 3.21–3.16 (m, 1H), 3.11 (s, 3H), 3.11 (s, 3H), 2.95 [3.08][a] (s, 3H), 2.64 (m, 1H), 2.48 (br d, *J* = 12.2 Hz, 1H), 2.38–2.25 (m, 3H), 2.32 [2.30][b] (s, 6H), 2.17 (s, 3H), 2.15–1.90 (m, 2H), 1.86 (m, 1H), 1.76–1.04 (m, 15H), 1.46 (s, 3H), 1.25 [1.21][b] (d, *J* = 7.2 Hz, 3H), 1.03–0.95 (m, 18H), 0.91 [0.92][b] (s, 9H), 0.91 (s, 9H), 0.80 (d, *J* = 6.5 Hz, 3H), 0.15 (s, 3H), 0.10 (s, 3H), 0.09 (s, 3H), 0.09 (s, 3H) (signals of three protons (CH_3COO) were overlapped with the solvent signals; the minor counterparts of doubled signals in the ratios of 2 : 1 (superscript a) and 2.4 : 1 (superscript b) are in brackets); HRMS (ESI) *m*/*z* 1235.8348, calcd for $C_{67}H_{123}N_2O_{12}SSi_2$ $[M+H]^+$ 1235.8336.



S23 **S24**

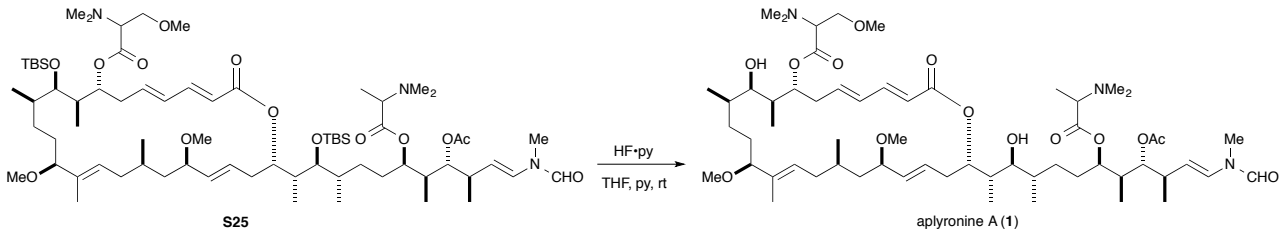
To a stirred solution of dimethylalanine esters **S23** (*S* : *R* = 3.5 : 1) (1.2 mg, 0.97 μmol) in THF (0.28 mL) and H_2O (0.070 mL) were added 2,6-lutidine (50.0 μL, 430 μmol) and $AgNO_3$ (75.0 mg, 442 μmol) at room temperature. The mixture was stirred at 35 °C for 17 h in the dark. The resultant

mixture was filtered through a pad of Celite, and the residue was washed with EtOAc (20 mL). The filtrate and the washings were combined; washed with H_2O (4.0 mL) and brine (4.0 mL) successively; dried (Na_2SO_4); filtered; and concentrated. The crude product was purified by column chromatography on silica gel (0.50 g, benzene–acetone 4 : 1 → 3 : 1 → 1 : 1) to afford alcohol **S24** (*S* : *R* = 3.5 : 1) (1.2 mg, quant) as a colorless amorphous solid: R_f = 0.32 (benzene : acetone = 3 : 1); ^{1}H NMR (600 MHz, acetone-d_6) δ 8.36 [8.10][a] (s, 1H), 7.23 (dd, *J* = 15.3 Hz, 10.1 Hz, 1H), 6.84 [7.15][a] (d, *J* = 14.1 Hz, 1H), 6.39–6.33 (m, 2H), 5.87 (d, *J* = 15.3 Hz, 1H), 5.56 (ddd, *J* = 14.9. 10.2, 4.2 Hz, 1H), 5.30 (m, 1H), 5.17 (dd, *J* = 9.6, 5.3 Hz, 1H), 5.11–4.98 (m, 3H), 4.80 (m, 2H), 3.82 (dd, *J* = 5.2, 2.6 Hz, 1H), 3.68–3.62 (m, 2H), 3.54 (m, 1H), 3.48 (m, 1H), 3.42 (dd, *J* = 10.2, 5.2 Hz, 1H), 3.21–3.15 (m, 1H), 3.11 (s, 3H), 3.10 (s, 3H), 2.95 [3.08][a] (s, 3H), 2.64 (m, 1H), 2.49 (br d, *J* = 14.5 Hz, 1H), 2.36–2.24 (m, 3H), 2.32 [2.30][b] (s, 6H), 2.15–1.81 (m, 3H), 1.78–1.05 (m, 14H), 1.43 (s, 3H), 1.25 [1.24][b] (d, *J* = 7.2 Hz, 3H), 1.01–0.83 (m, 18H), 0.91 [0.92][a] (s, 9H), 0.90 (s, 9H), 0.79 (d, *J* = 6.5 Hz, 3H), 0.15 (s, 3H), 0.09 (s, 3H), 0.08 (s, 6H) (signals of three protons (CH_3COO) were overlapped with the solvent signals; the minor counterparts of doubled signals in the ratios of 2 : 1 (superscript a) and 2.4 : 1 (superscript b) are in brackets); HRMS (ESI) *m*/*z* 1175.8306, calcd for $C_{65}H_{119}N_2O_{12}Si_2$ $[M+H]^+$ 1175.8302.



To a mixture of alcohol **S24** (*S* : *R* = 3.5 : 1) (1.1 mg, 0.94 μmol), L-*N*,*N*,*O*-trimethylserine (2.4 mg, 16 μmol), D-*N*,*N*,*O*-trimethylserine (1.0 mg, 6.8 μmol), DMAP (7.5 mg, 61 μmol), and CSA (4.7 mg, 20 μmol) in benzene (2.0 mL) was added DCC (0.050 M CH_2Cl_2 solution, 0.40 mL, 20 μmol) at room temperature. The mixture was stirred at 35 °C for 4 h, and saturated aqueous $NaHCO_3$ (2.0 mL) was added at 0 °C. The mixture was stirred at room temperature for 20 min, and extracted with

EtOAc (3 × 8.0 mL). The combined extracts were washed with brine (8.0 mL), dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by column chromatography on silica gel (0.50 g, hexane–EtOAc–MeOH 10 : 10 : 1, twice) to give a diastereomeric mixture of trimethylserine esters **S25** (*S* : *R* = 1 : 1.1 as to the trimethylserine part, *S* : *R* = 3.5 : 1 as to the dimethylalanine part) (1.0 mg, 82%) as a colorless amorphous solid: R_f = 0.58 (benzene : acetone = 2 : 1); ^{1}H NMR (600 MHz, acetone-d_6) δ 8.36 [8.10][a] (s, 1H), 7.21 (m, 1H), 6.84 [7.15][a] (d, *J* = 14.1 Hz, 1H), 6.41 [6.42][c] (m, 1H), 6.24 (m, 1H), 5.92 [5.93][c] (d, *J* = 15.4 Hz, 1H), 5.55 (ddd, *J* = 15.0, 9.1, 5.2 Hz, 1H), 5.30 (m, 1H), 5.16 (m, 1H), 5.11–4.95 (m, 3H), 4.84 (br s, 1H), 4.80 [4.80][c] (d, *J* = 10.2 Hz, 1H), 3.69 [3.68][c] (m, 1H), 3.61 (m, 1H), 3.60 [3.58][c] (m, 1H), 3.53 (m, 1H), 3.50–3.42 (m, 2H), 3.38 (dd, *J* = 7.8, 5.5 Hz, 1H), 3.33 [3.35][c] (s, 3H), 3.18 (m, 1H), 3.11 (s, 6H), 2.95 [3.07][a] (s, 3H), 2.66 (m, 1H), 2.55–2.43 (m, 3H), 2.36 [2.36][c] (s, 6H), 2.32 [2.32][b] (s, 6H), 2.17–1.87 (m, 3H), 1.83 (m, 1H), 1.72–1.45 (m, 9H), 1.47 (s, 3H), 1.42–1.07 (m, 6H), 1.24 [1.19][b] (d, *J* = 7.2 Hz, 3H), 1.00–0.94 (m, 18H), 0.91 [0.92][b] (s, 9H), 0.90 (s, 9H), 0.78 [0.78][c] (d, *J* = 6.4 Hz, 3H), 0.14 (s, 3H), 0.08 (s, 3H), 0.08 (s, 6H) (signals of three protons (CH_3COO) were overlapped with the solvent signals; the minor counterparts of doubled signals in the ratios of 2 : 1 (superscript a), 2.4 : 1 (superscript b) are in brackets), and 1 : 1.1 (superscript c) are in brackets); HRMS (ESI) *m*/*z* 1304.9079, calcd for $C_{71}H_{130}N_3O_{14}Si_2$ $[M+H]^+$ 1304.9092.



A solution of trimethylserine esters **S25** (*S* : *R* = 1 : 1.1 as to the trimethylserine part, *S* : *R* = 3.5 : 1 as to the dimethylalanine part) (0.70 mg, 0.54 μmol) in a 5 : 3 : 7 mixture of HF·py, py, and THF (500 μL) was stirred at room temperature for 14 h. The mixture was diluted with EtOAc (2.0 mL) at room temperature and poured into saturated aqueous $NaHCO_3$ (10 mL) at 0 °C. The resultant

mixture was extracted with EtOAc (5 × 8.0 mL). The combined extracts were washed with brine (6.0 mL), dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by column chromatography on silica gel (0.50 g, hexane–EtOAc–MeOH 3 : 3 : 1 → 2 : 2 : 1) and HPLC [ODS HG-5 (ϕ 20 × 250 mm); flow rate 5.0 mL/min; detection UV 215 nm; solvent MeOH–0.02 M NH_4Ac (77 : 23)] to afford aplyronine A (**1**) (*S* : *R* = 1 : 1.1 as to the trimethylserine part, *S* : *R* = 3.5 : 1 as to the dimethylalanine part) (0.4 mg, 69%) as a colorless amorphous solid: R_f = 0.49 ($CHCl_3$: MeOH = 9 : 1); ^{1}H NMR (600 MHz, CD_3OD) δ 8.33 [8.11][a] (s, 1H), 7.20 (dd, *J* = 15.2, 11.0 Hz, 1H), 6.77 [7.14][a] (d, *J* = 14.1 Hz, 1H), 6.38 (ddd, *J* = 15.5, 11.1, 4.6 Hz, 1H), 6.22 (ddd, *J* = 15.1, 9.9, 4.6 Hz, 1H), 5.97 (d, *J* = 15.2 Hz, 1H), 5.63 (ddd, *J* = 14.9, 10.7, 4.0 Hz, 1H), 5.53 (br d, *J* = 10.9 Hz, 1H), 5.09 [5.16][b] (dd, *J* = 14.1, 9.5 Hz, 1H), 5.10 (m, 1H), 4.99 (m, 1H), 4.94–4.88 (m, 1H), 4.68 (m, 1H), 3.69 (m, 2H), 3.54 (m, 2H), 3.38 [3.33][c] (s, 3H), 3.37–3.20 (m, 3H), 3.18 (s, 3H), 3.16 (s, 3H), 3.01 [3.10][a] (s, 3H), 3.07 (dd, *J* = 9.4, 2.3 Hz, 1H), 2.64 (m, 1H), 2.51–2.40 (m, 2H), 2.38 [2.39][c] (s, 6H), 2.35 [2.33][b] (s, 6H), 2.26 (m, 1H), 2.06 [2.06][b] [2.05][a] (s, 3H), 2.09–1.89 (m, 4H), 1.75–1.46 (m, 9H), 1.51 [1.52][c] (s, 3H), 1.35–1.24 (m, 2H), 1.30 [1.29][b] (d, *J* = 7.1 Hz, 3H), 1.18–1.06 (m, 3H), 1.04–0.94 (m, 15H), 0.89 [0.90][b] (d, *J* = 6.9 Hz, 3H), 0.76 [0.77][c] (d, *J* = 5.8 Hz, 3H) (signals of three protons (CH_3COO) were overlapped with the solvent signals; Signals due to two proton (OH at C7 and C31) were not observed; the minor counterparts of doubled signals in the ratios of 2 : 1 (superscript a), 2.4 : 1 (superscript b) are in brackets), and 1 : 1.1 (superscript c) are in brackets); HRMS (ESI) *m*/*z* 1076.7357, calcd for $C_{59}H_{102}N_3O_{14}$ $[M+H]^+$ 1076.7362.

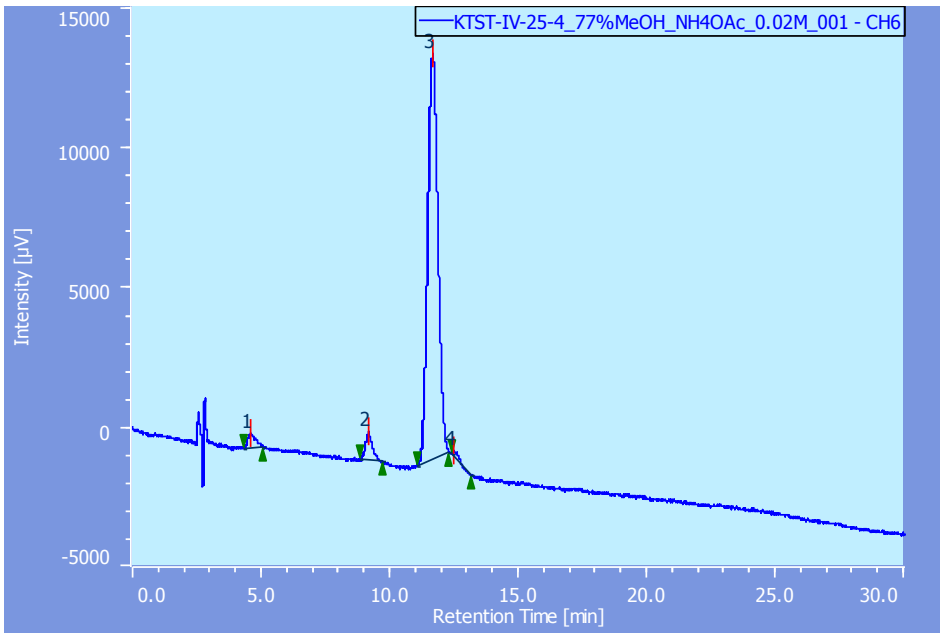


Fig S1. HPLC analysis of synthetic aplyronine A (**1**). Column: Develosil ODS HG-5 (ϕ 4.6 × 250 mm), Flow rate: 1.0 mL/min, Detection: UV 215 nm, Solvent: MeOH–0.02 M NH_4Ac (77 : 23).

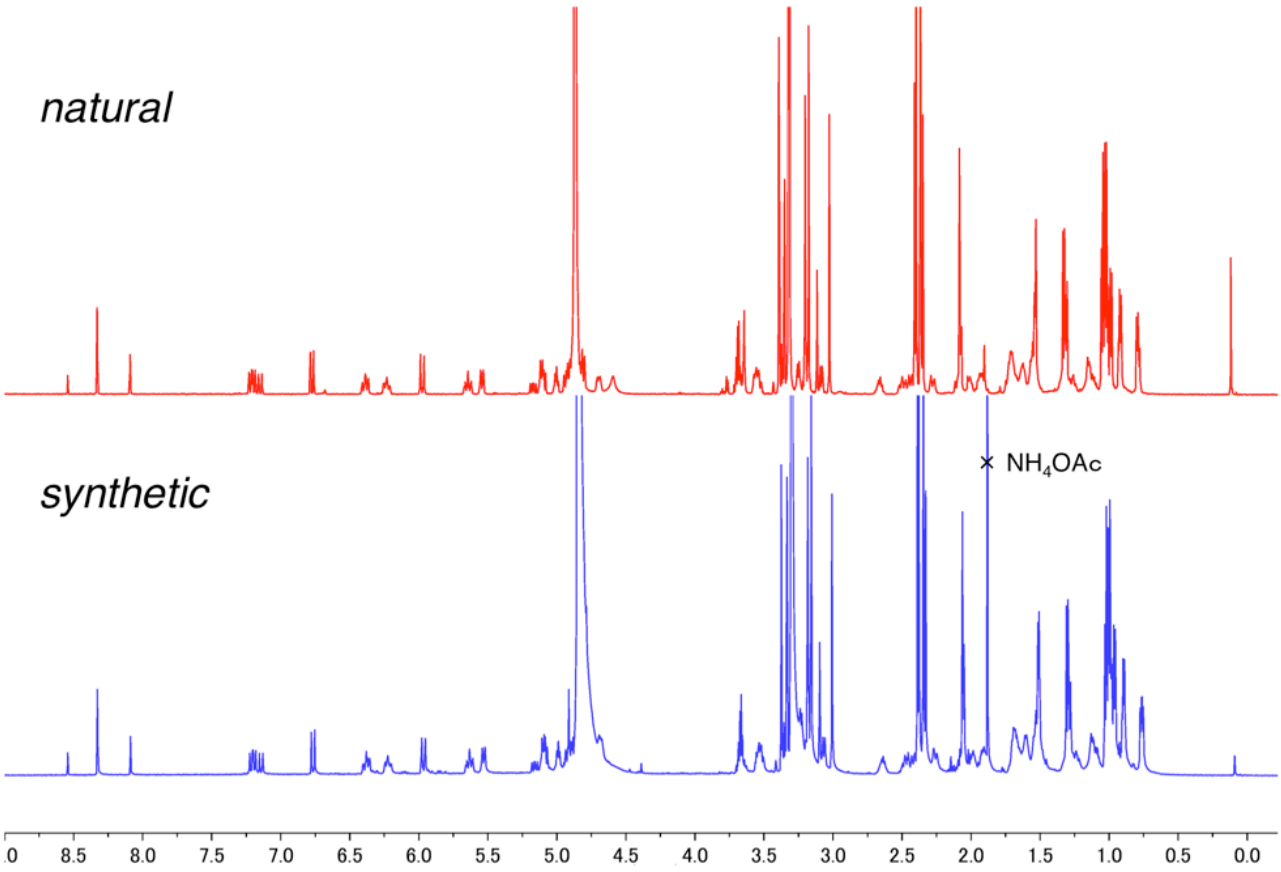


Fig. S2 ^{1}H NMR (600 MHz, CD_3OD) spectra of aplyronine A (**1**).

References

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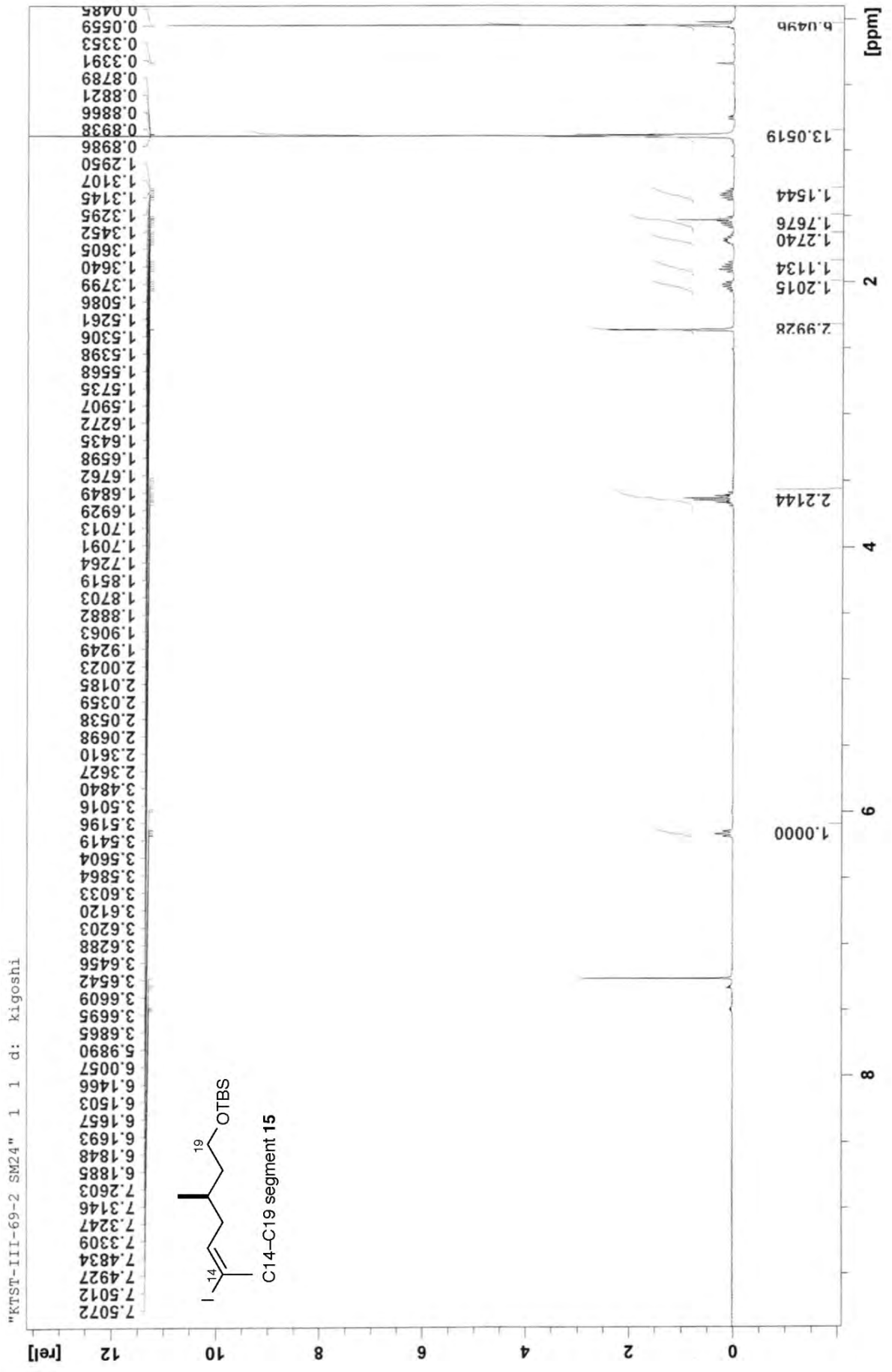
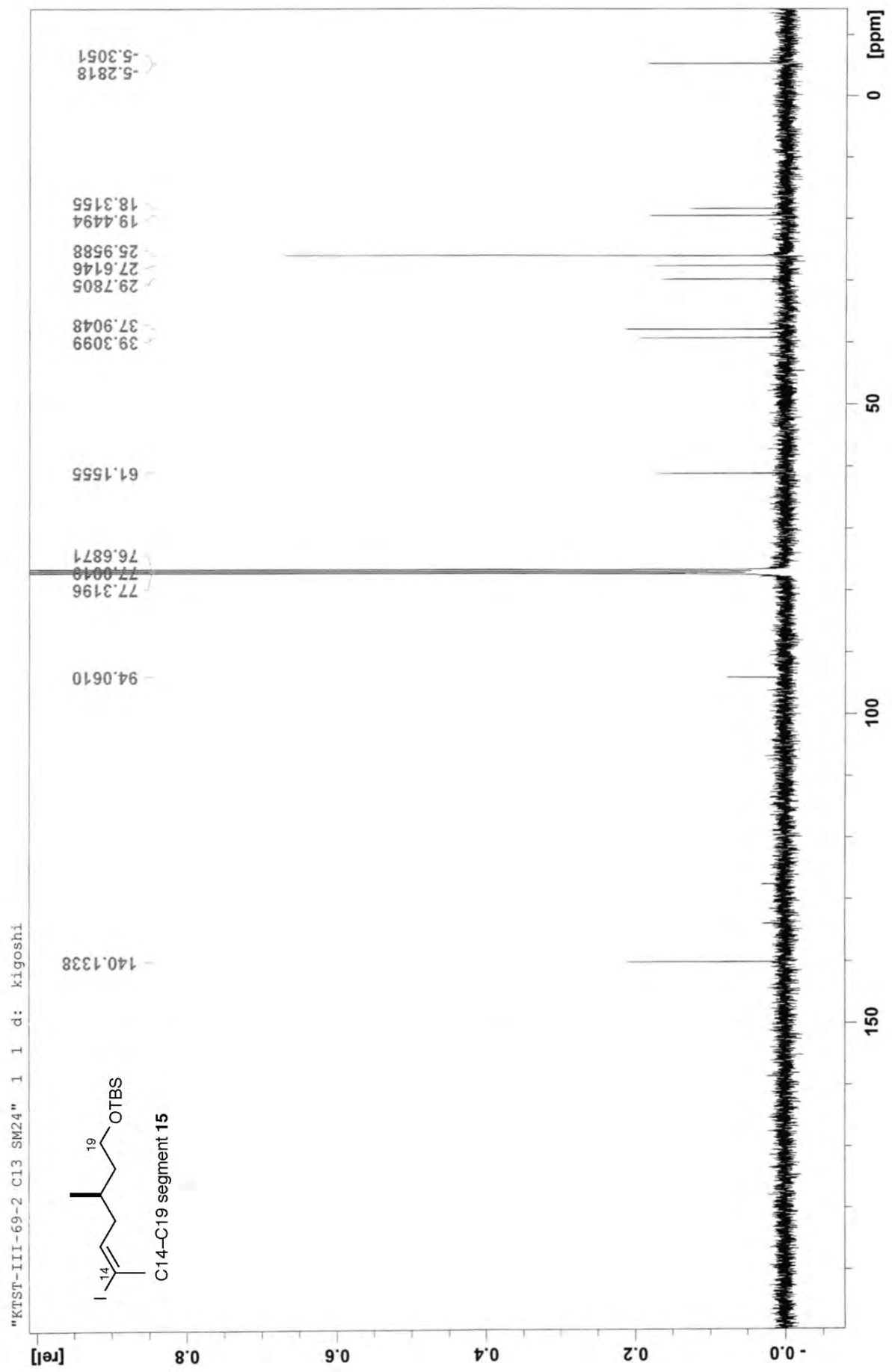
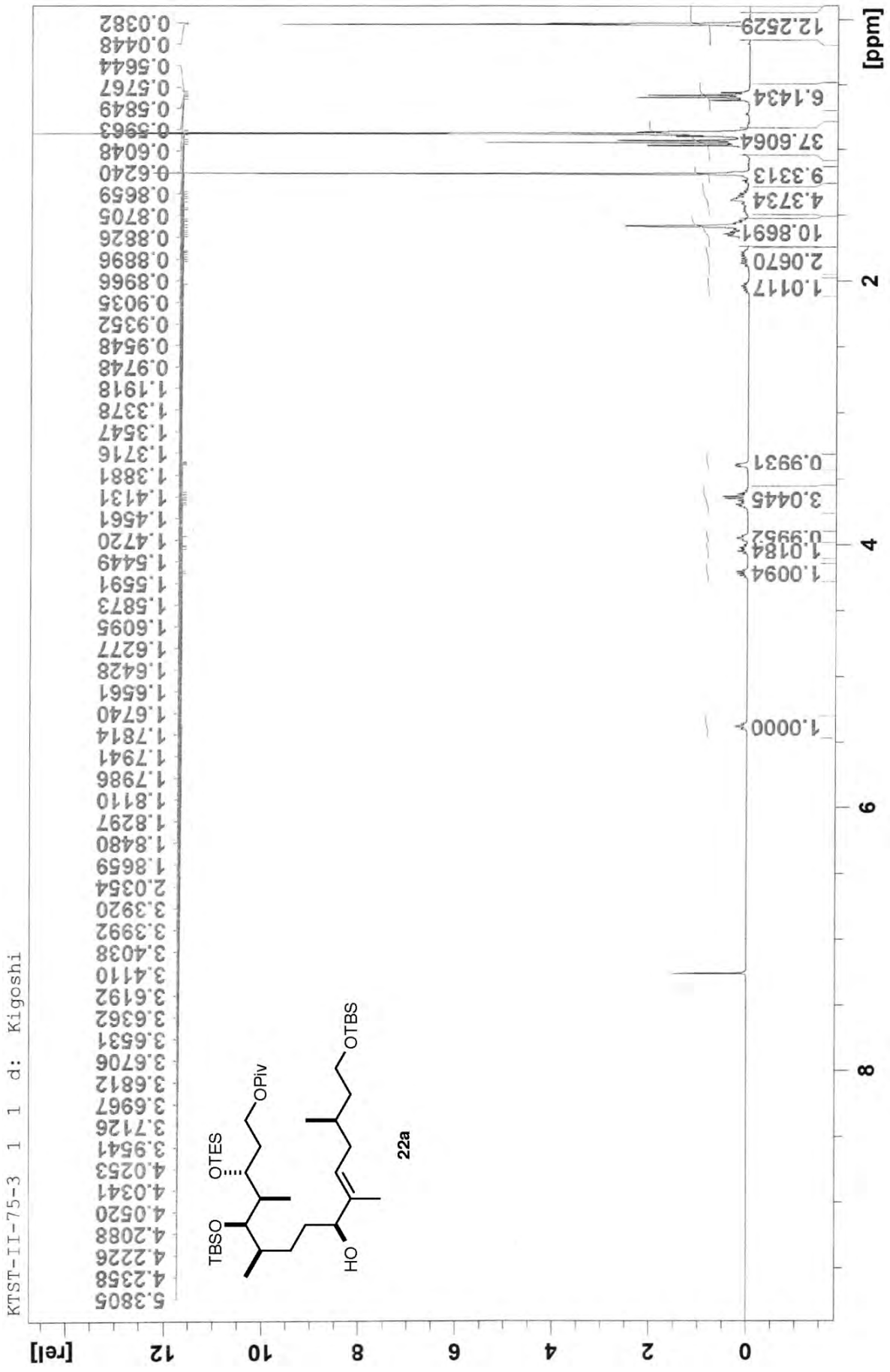


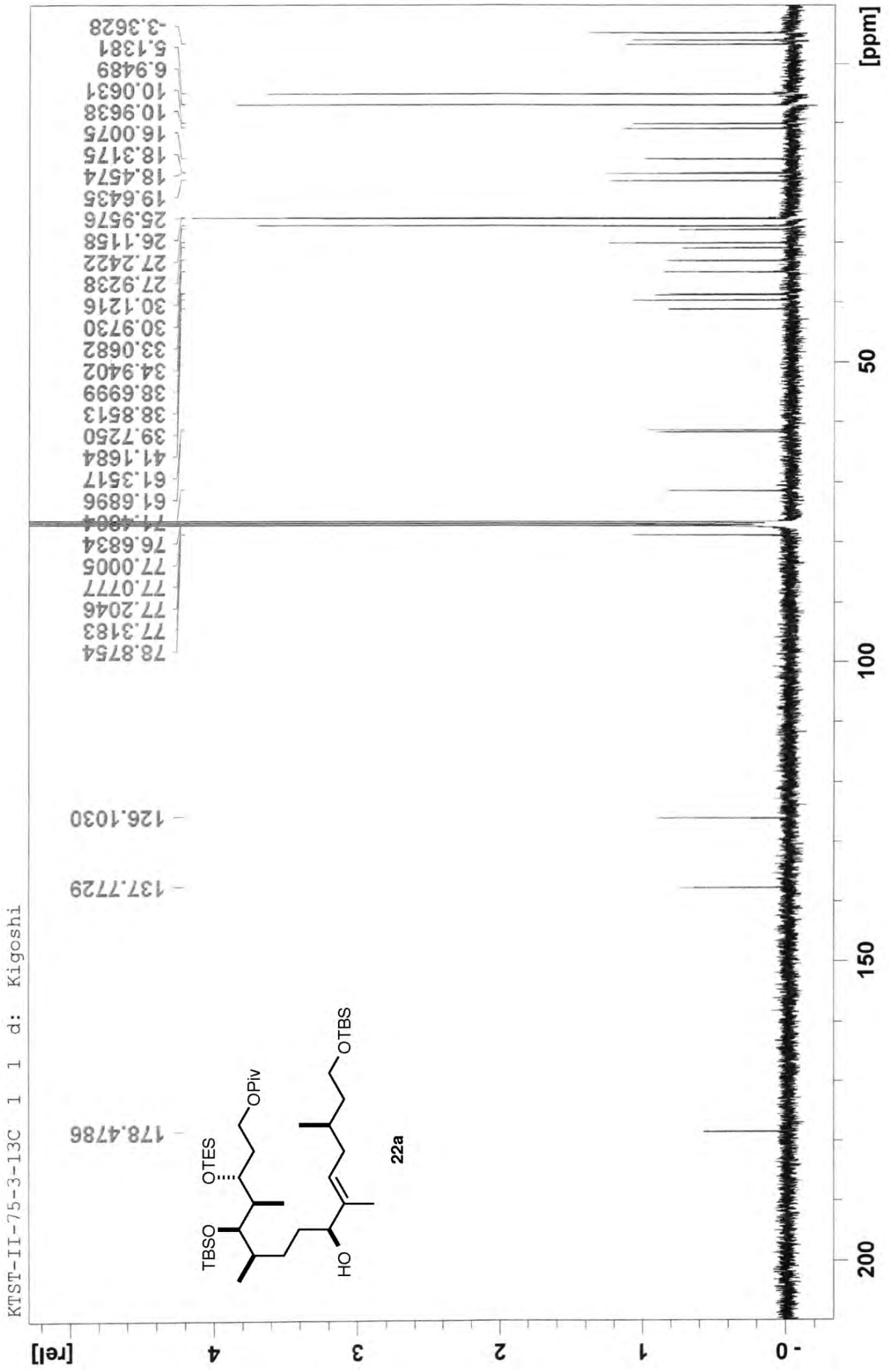
^{1}H NMR spectra of C14–C19 segment **15** (400 MHz, $CDCl_3$)



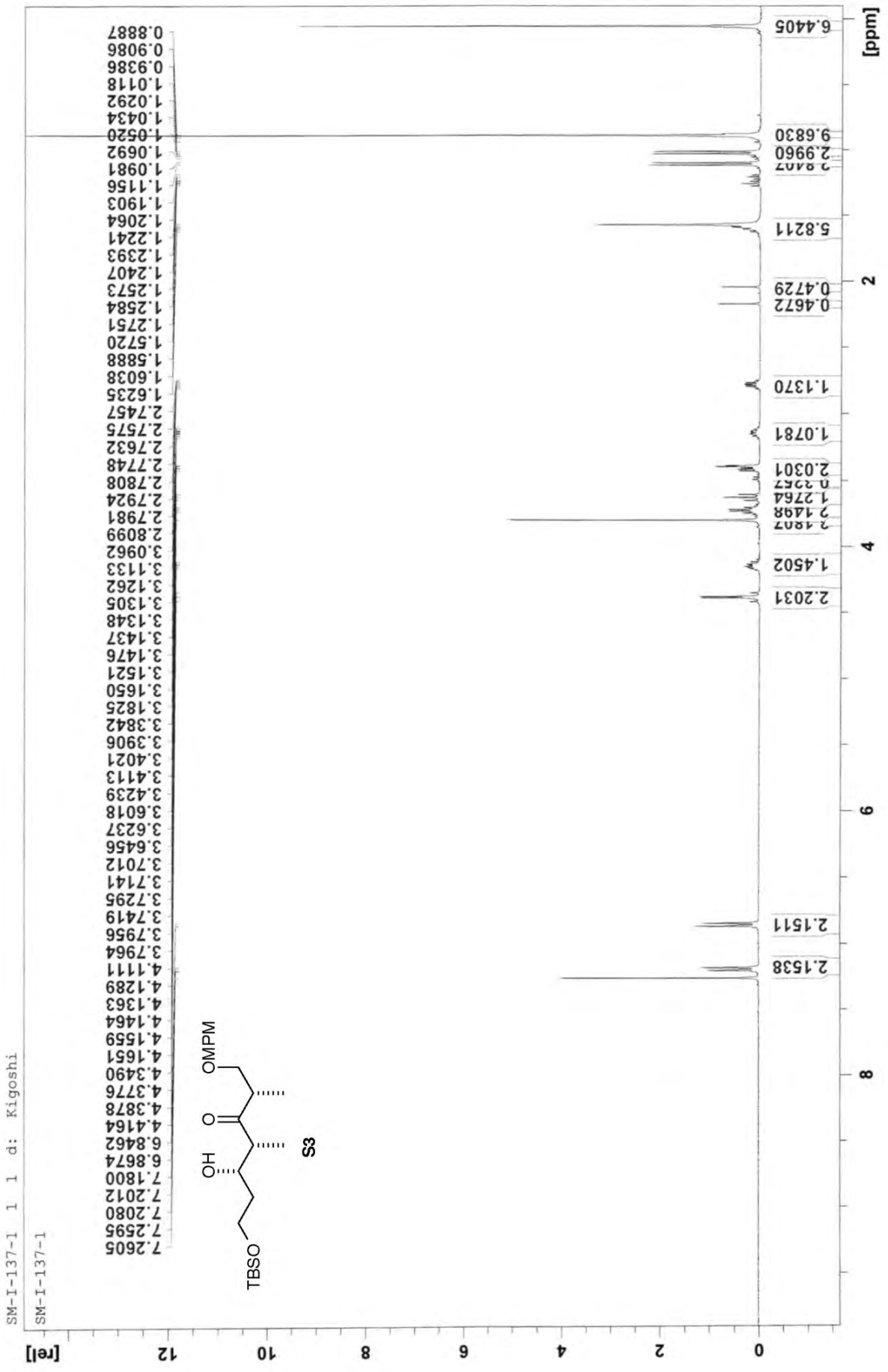
^{13}C NMR spectra of C14–C19 segment **15** (150 MHz, $CDCl_3$)



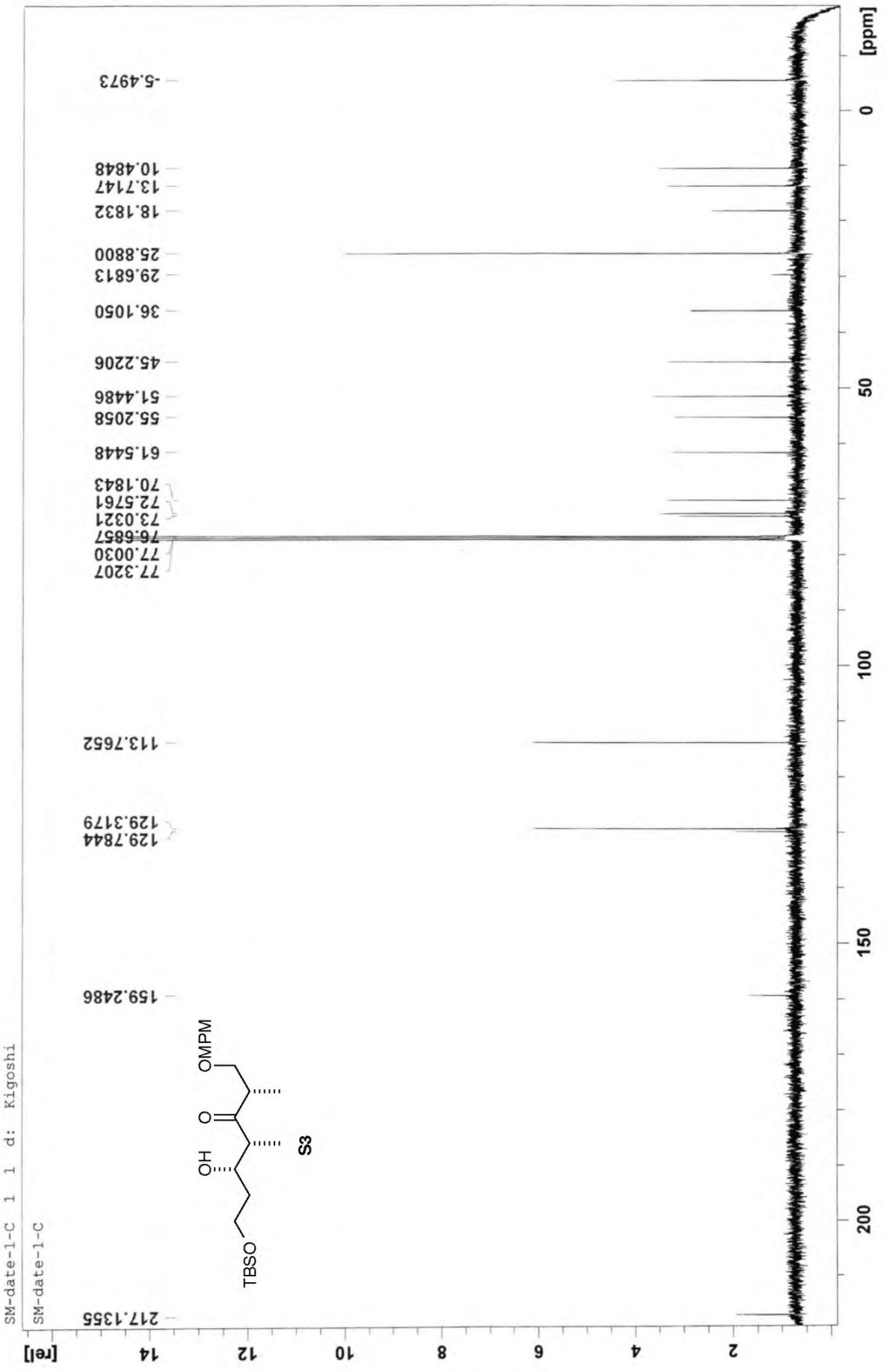
^{1}H NMR spectra of **22a** (400 MHz, $CDCl_3$)



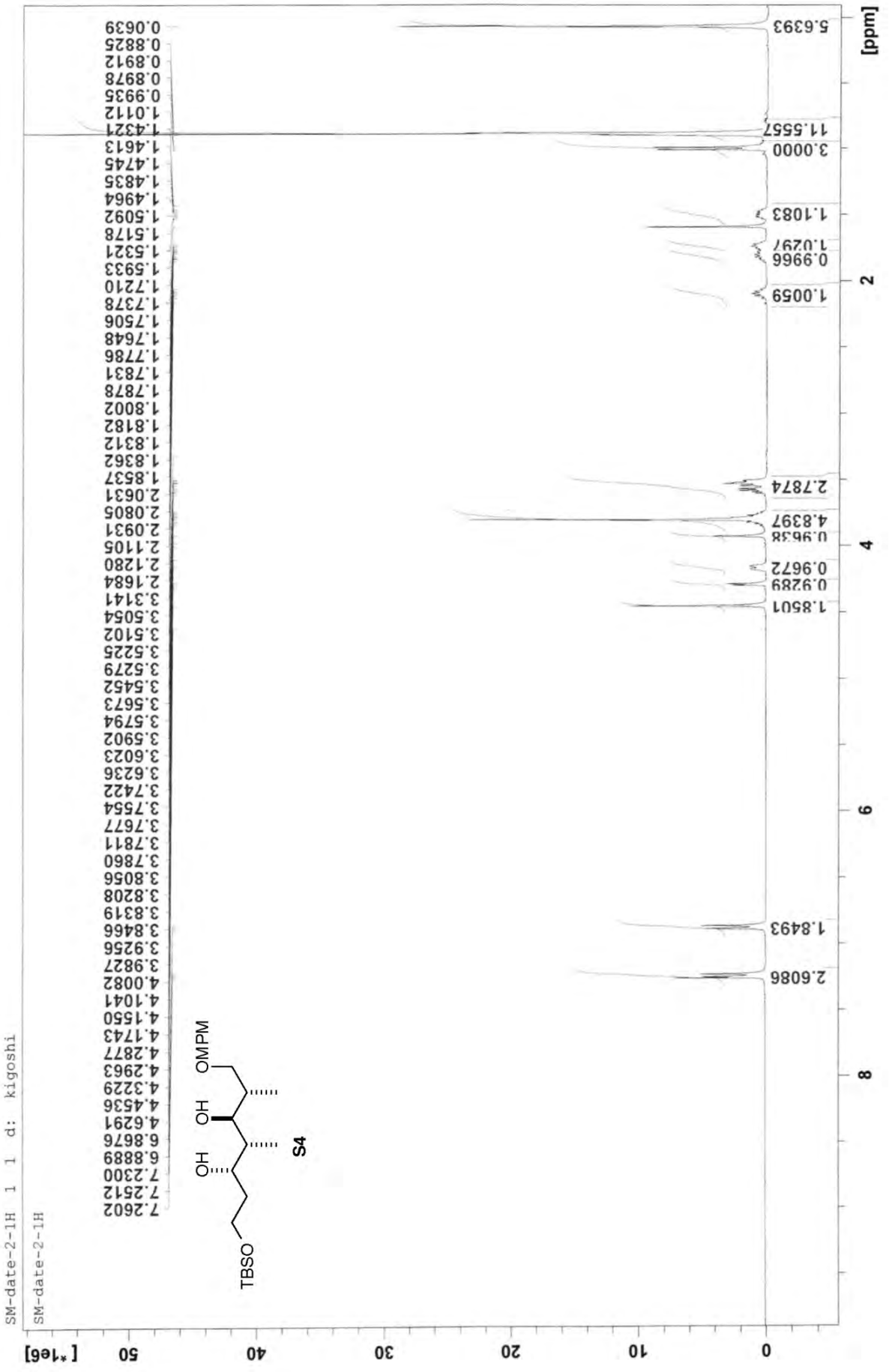
^{13}C NMR spectra of **22a** (100 MHz, $CDCl_3$)



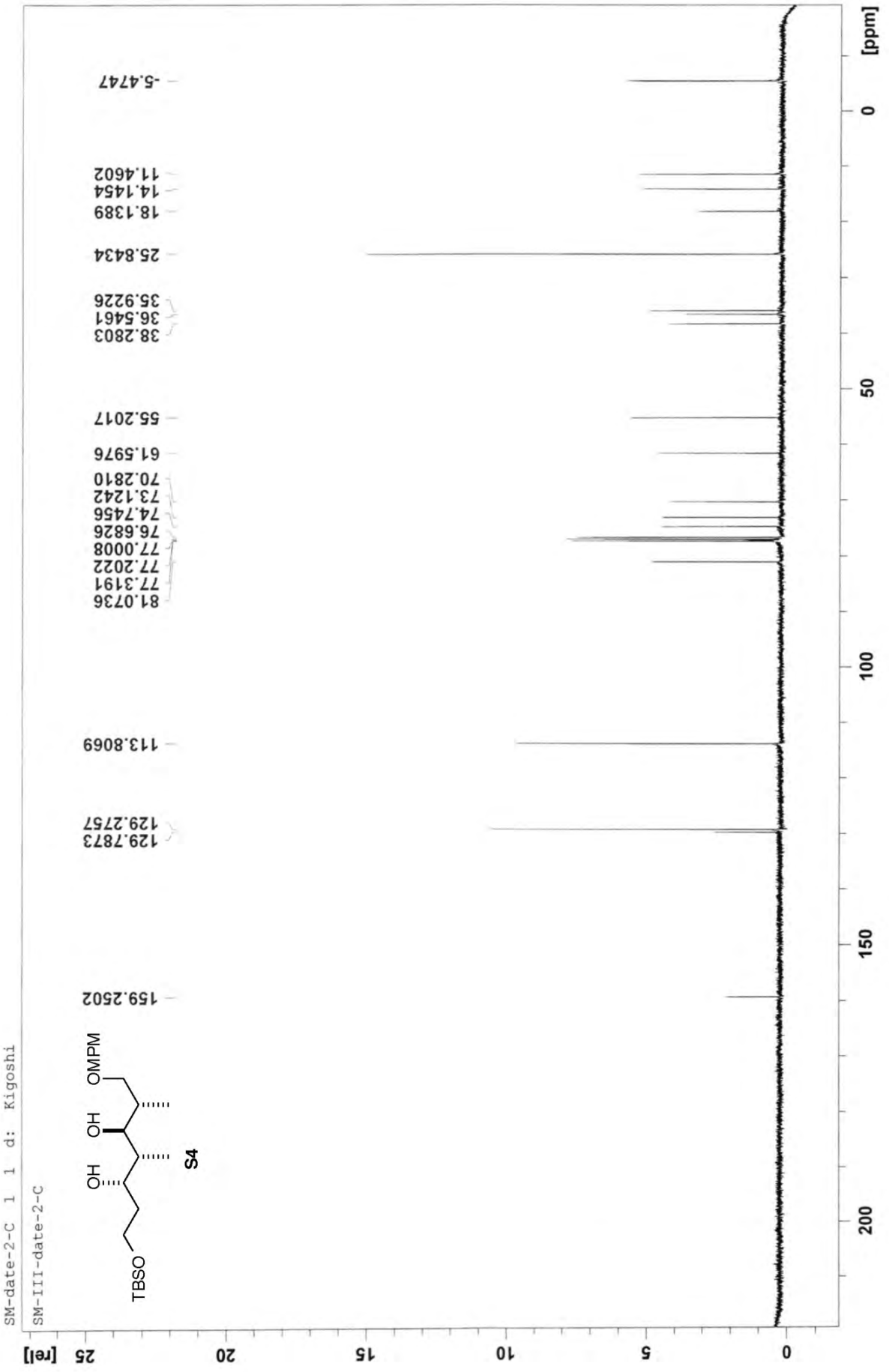
^{1}H NMR spectra of **S3** (400 MHz, $CDCl_3$)



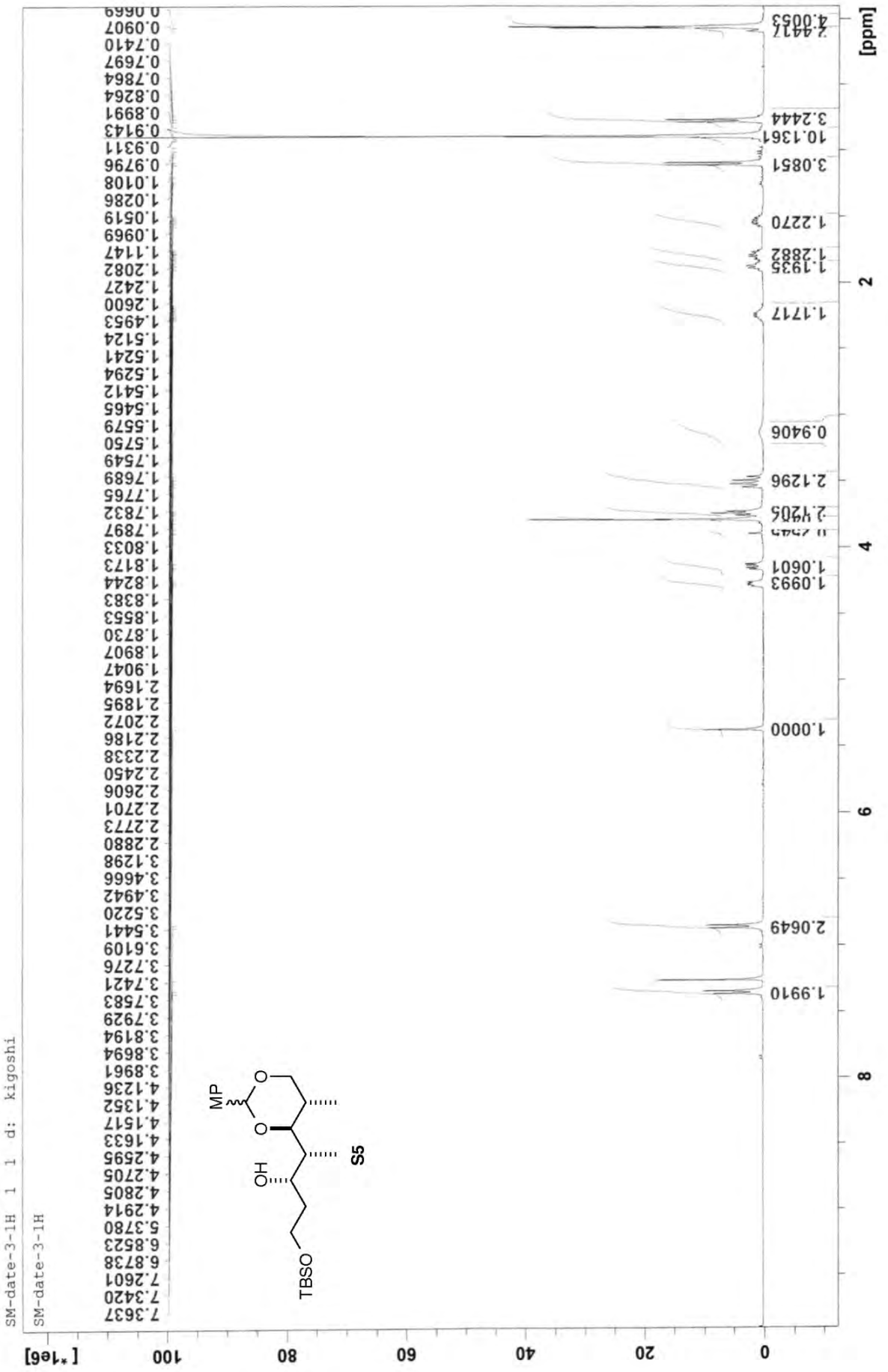
^{13}C NMR spectra of **S3** (100 MHz, $CDCl_3$)



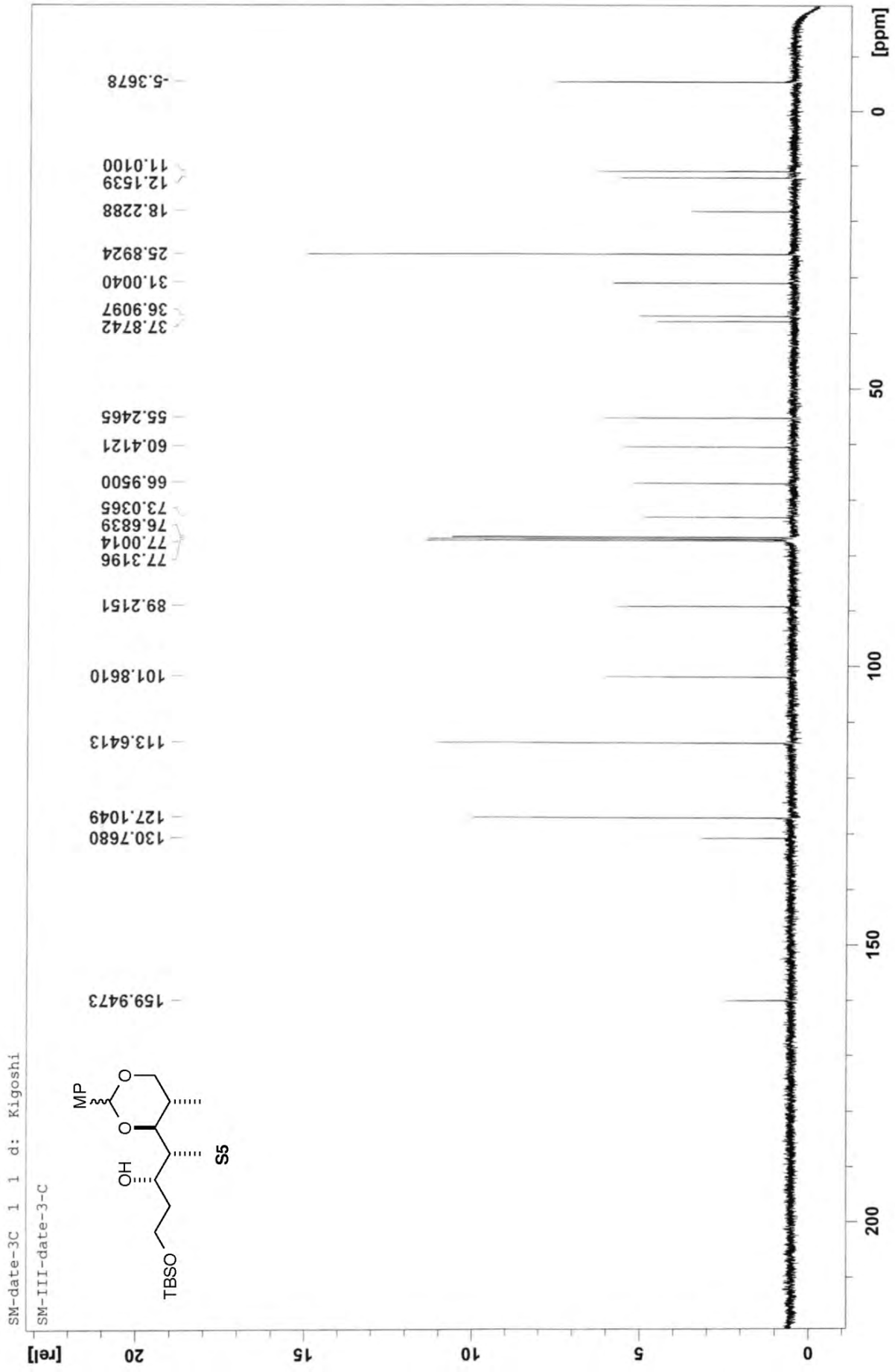
^{1}H NMR spectra of **S4** (400 MHz, $CDCl_3$)



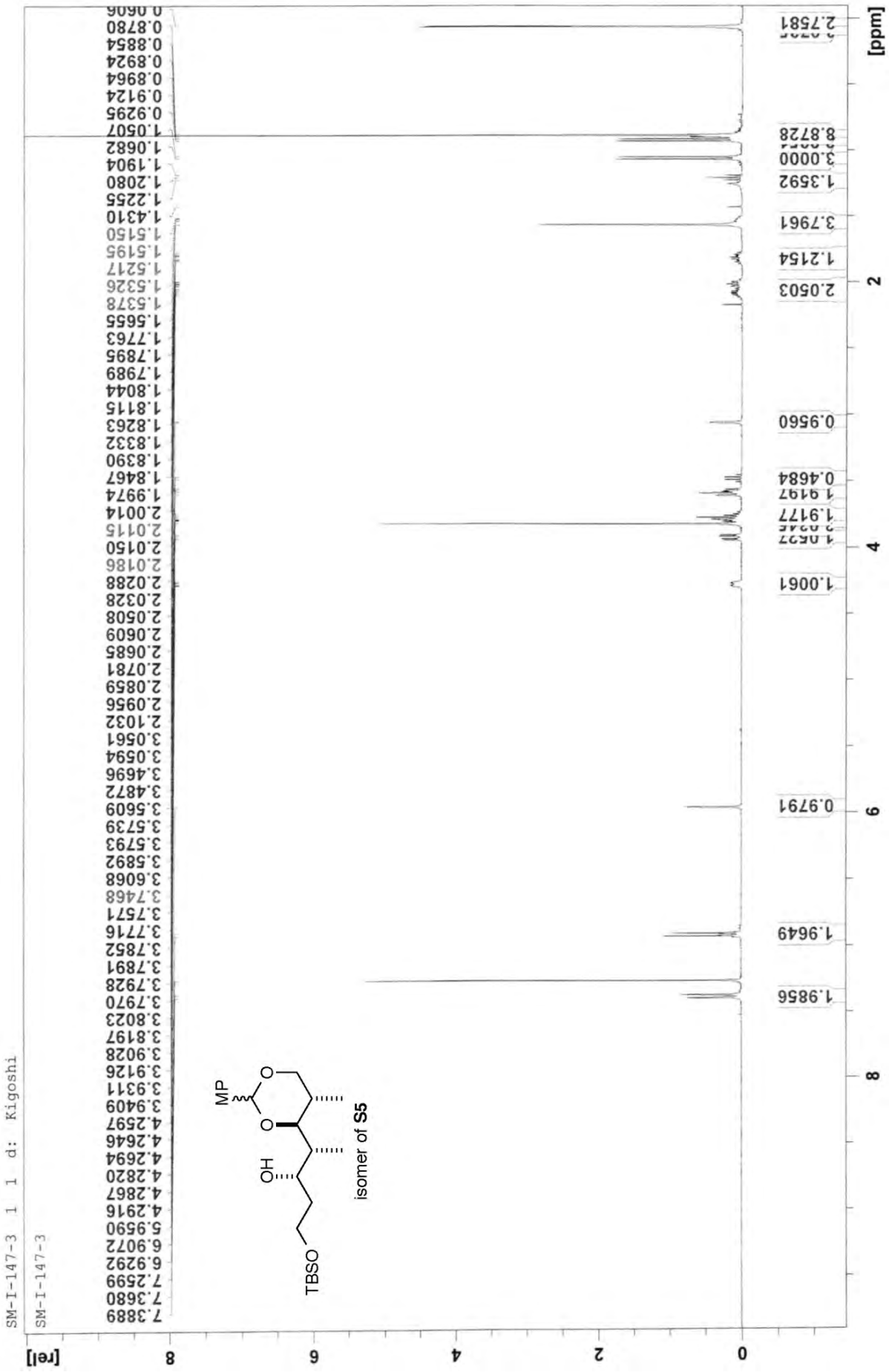
^{13}C NMR spectra of **S4** (100 MHz, $CDCl_3$)



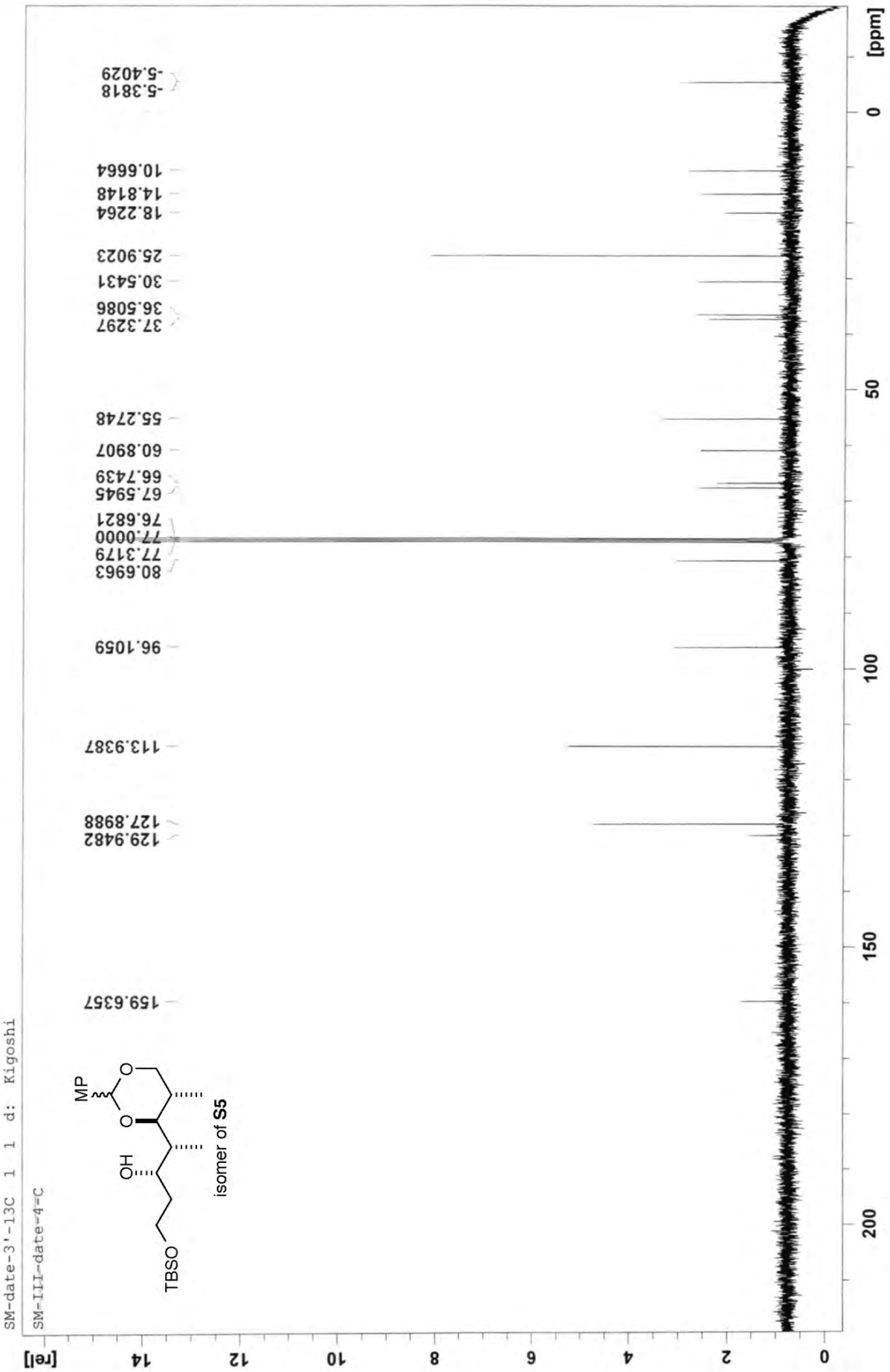
^{1}H NMR spectra of **S5** (400 MHz, $CDCl_3$)



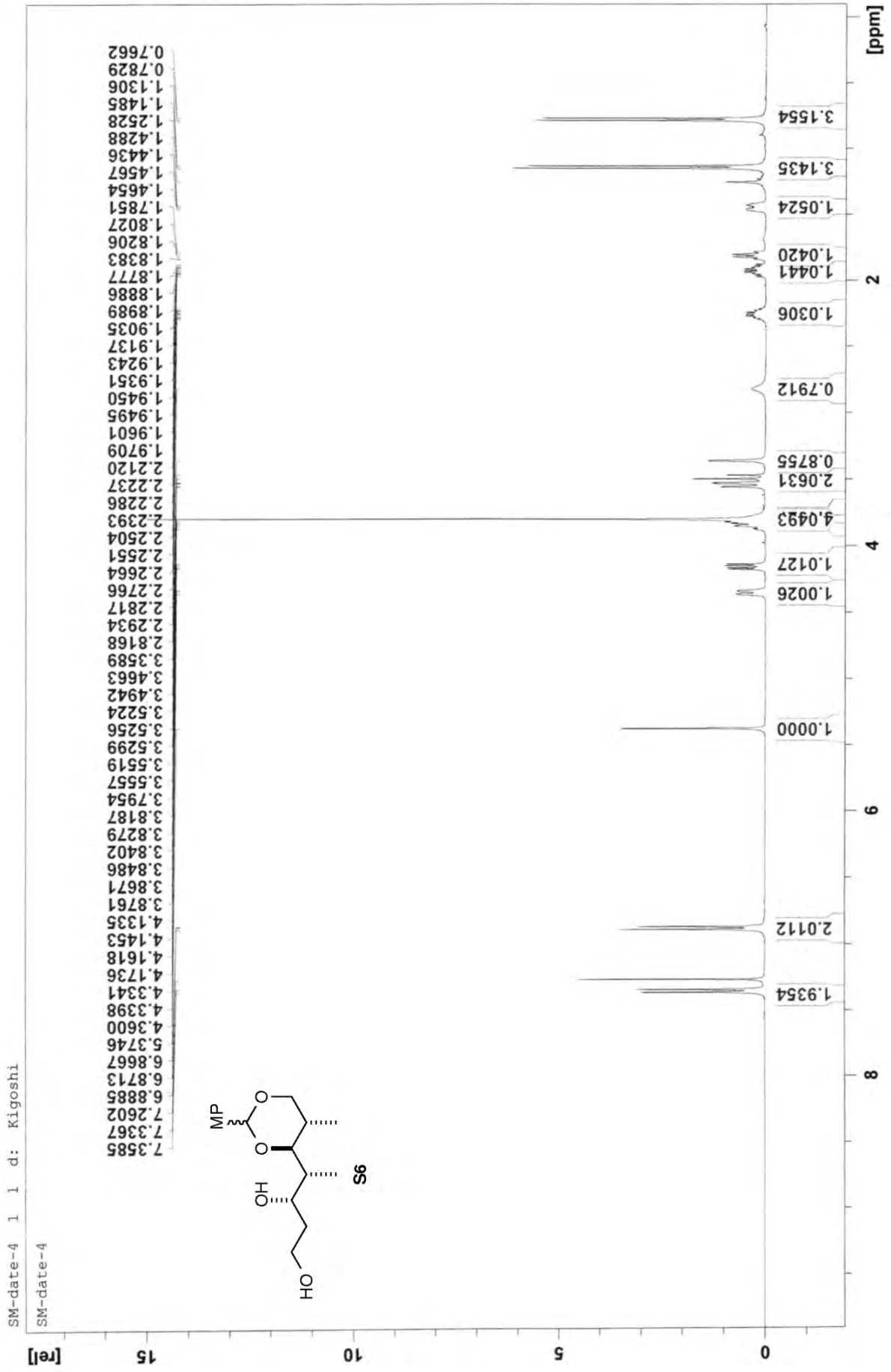
^{13}C NMR spectra of **S5** (100 MHz, $CDCl_3$)



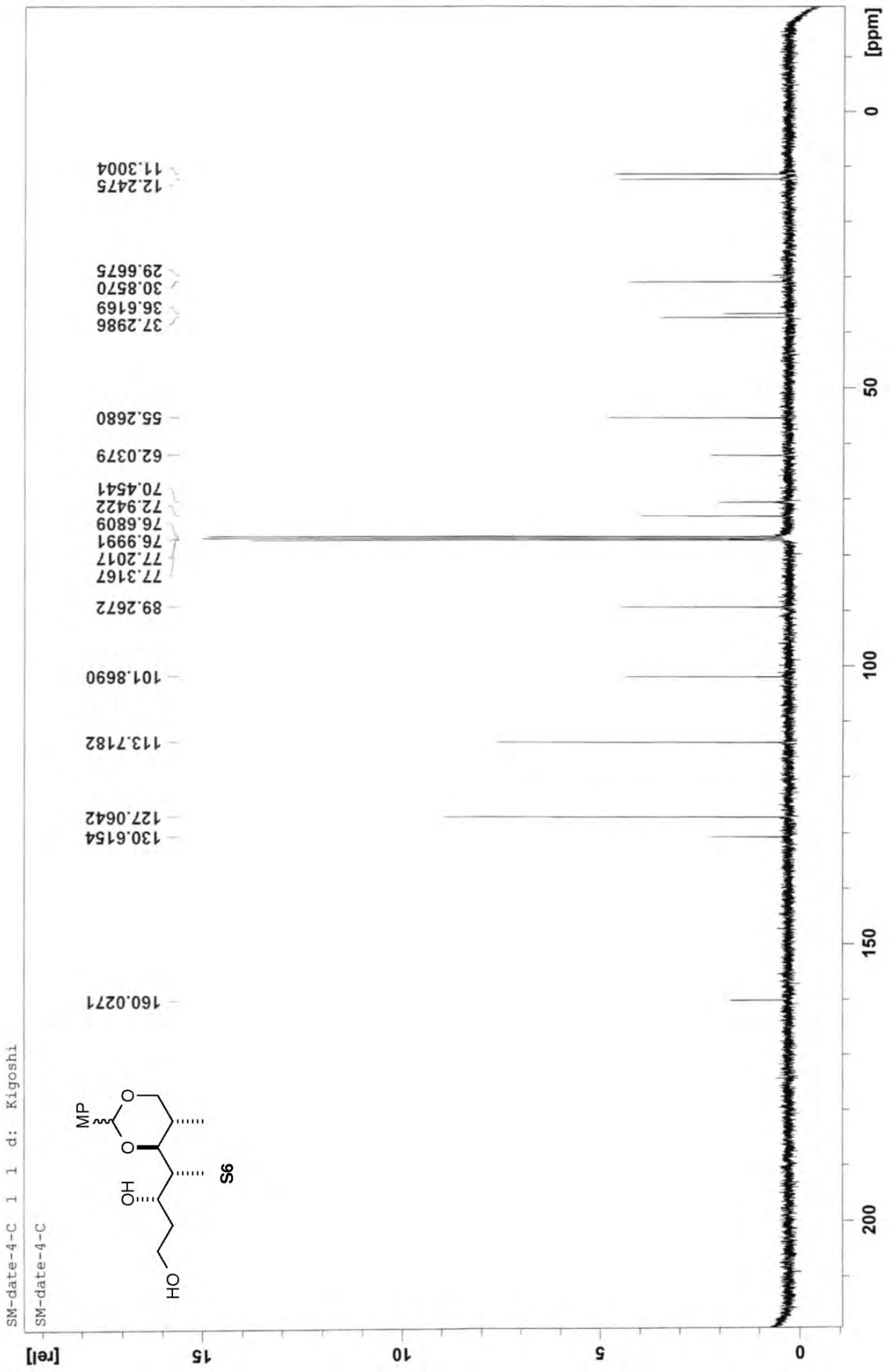
^{1}H NMR spectra of isomer of **S5** (400 MHz, $CDCl_3$)



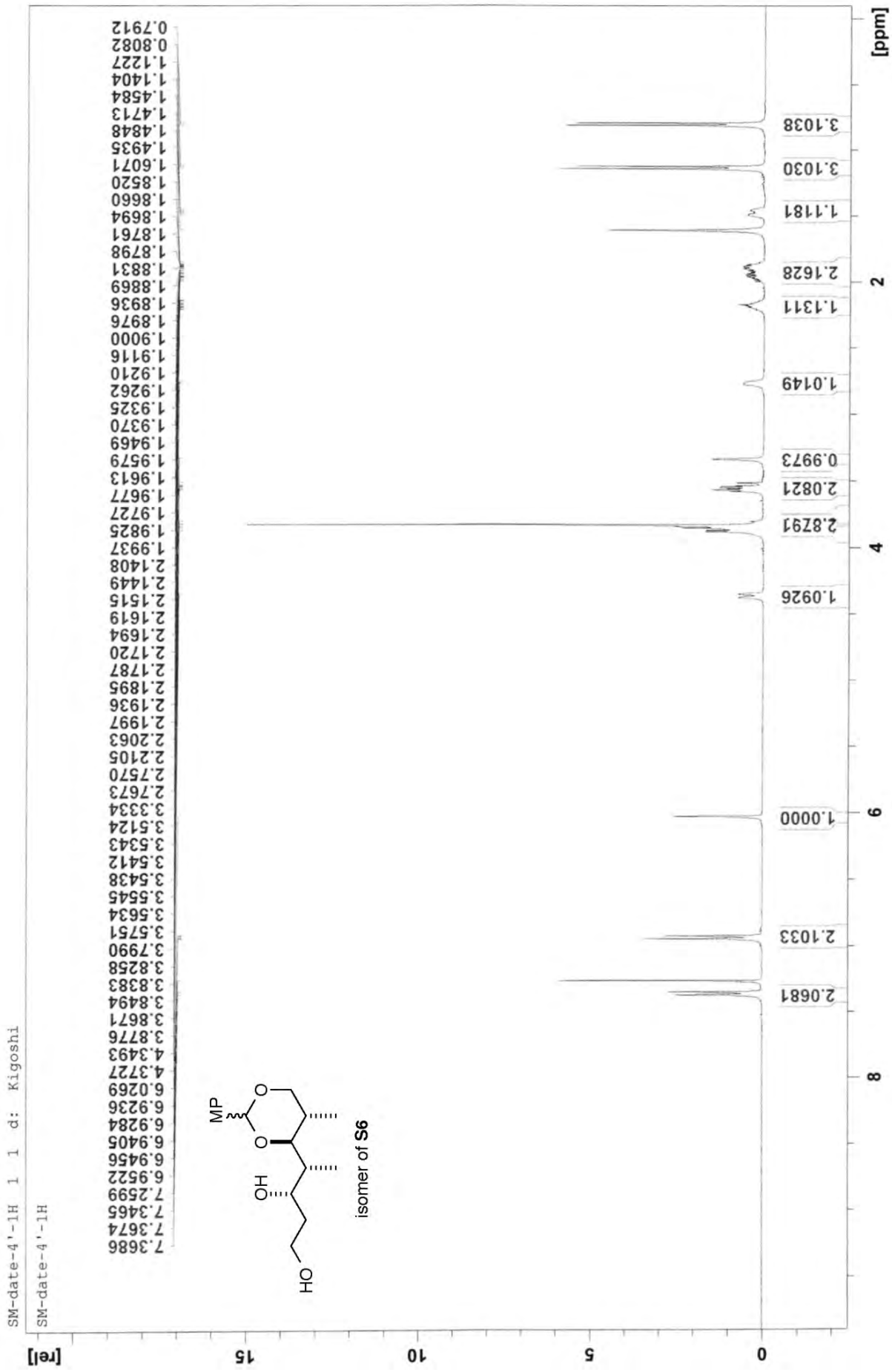
^{13}C NMR spectra of isomer of **S5** (100 MHz, $CDCl_3$)



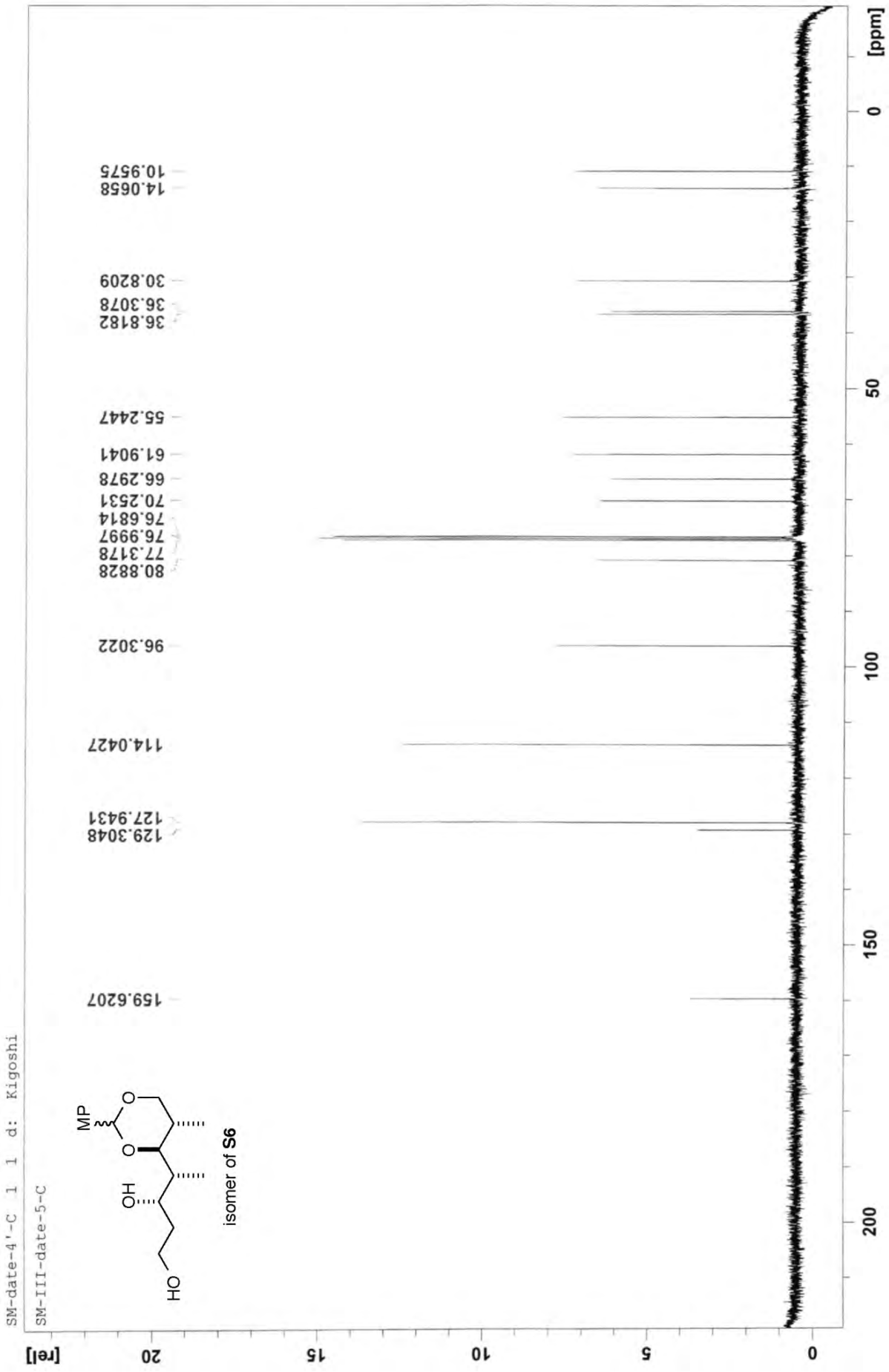
^{1}H NMR spectra of **S6** (400 MHz, $CDCl_3$)



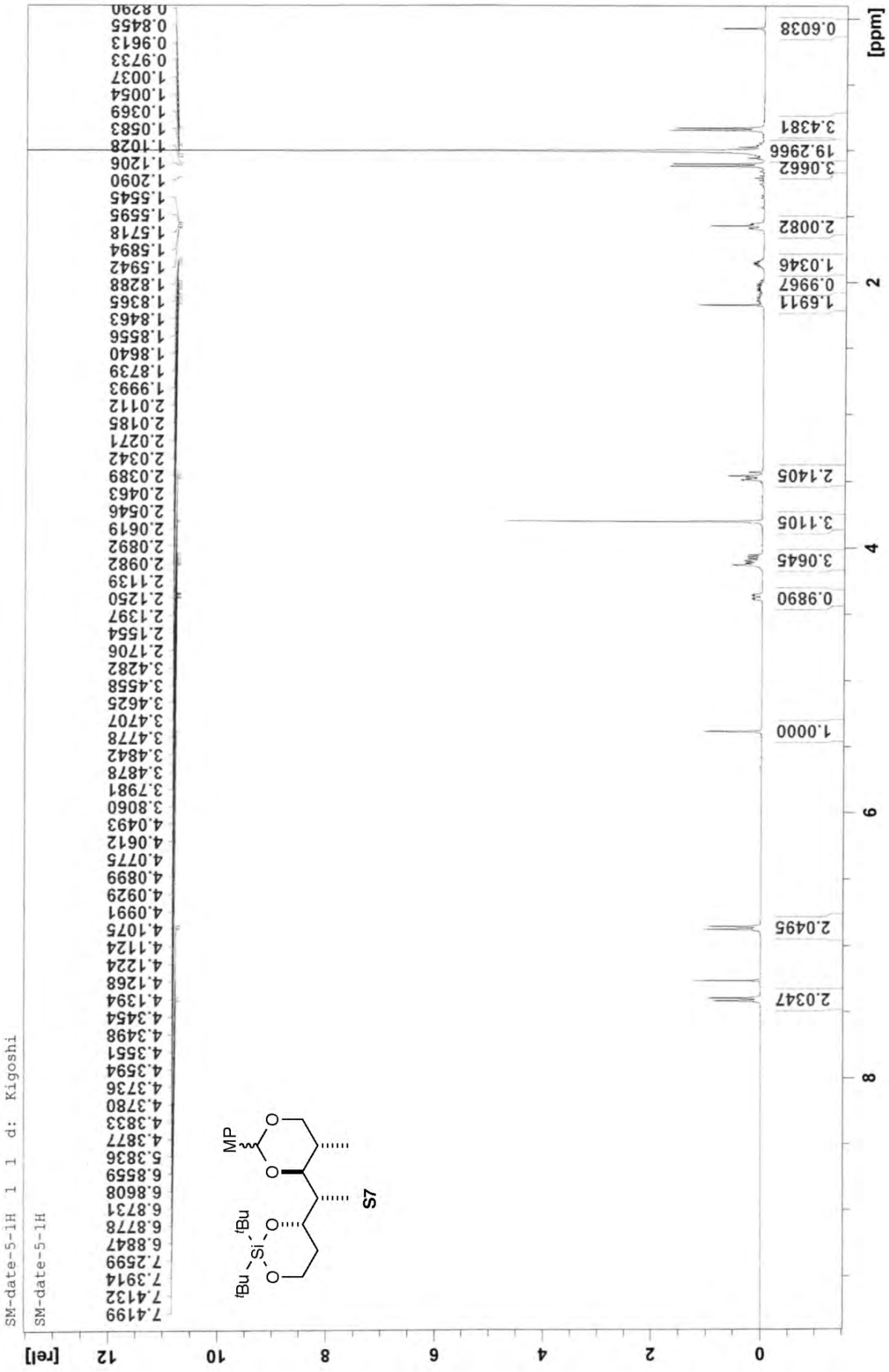
^{13}C NMR spectra of **S6** (100 MHz, $CDCl_3$)



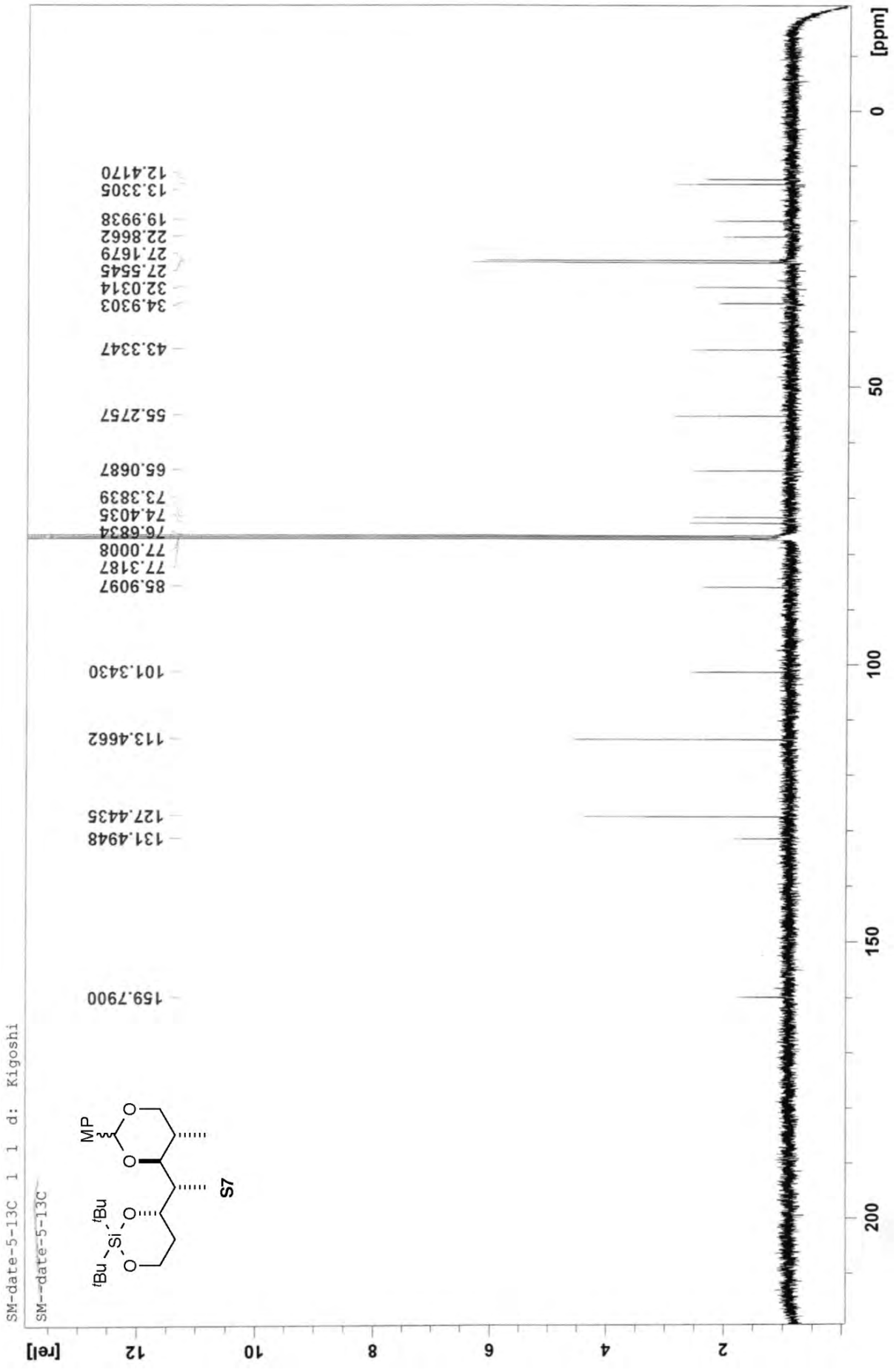
^{1}H NMR spectra of isomer of **S6** (400 MHz, $CDCl_3$)



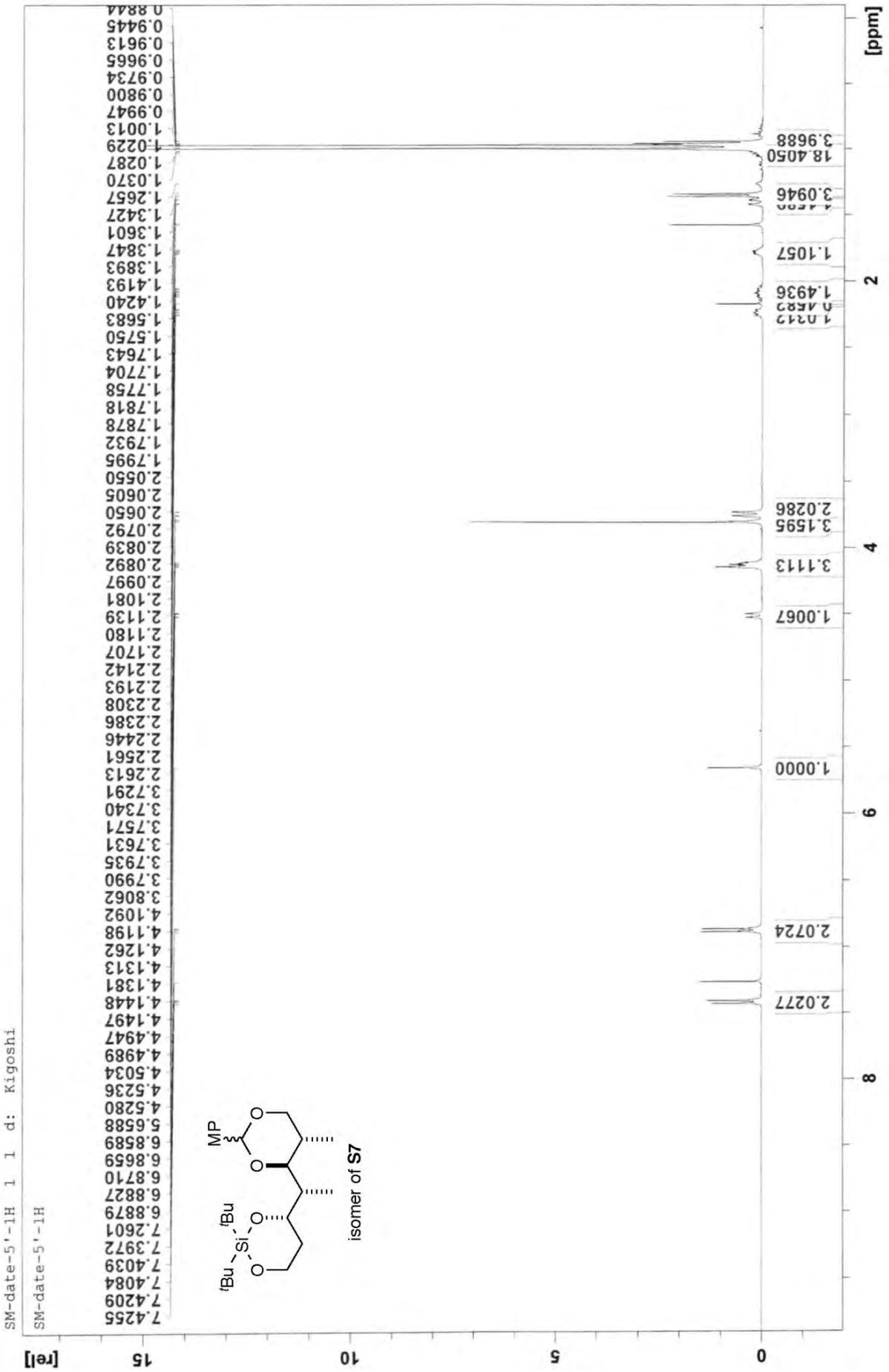
^{13}C NMR spectra of isomer of **S6** (100 MHz, $CDCl_3$)



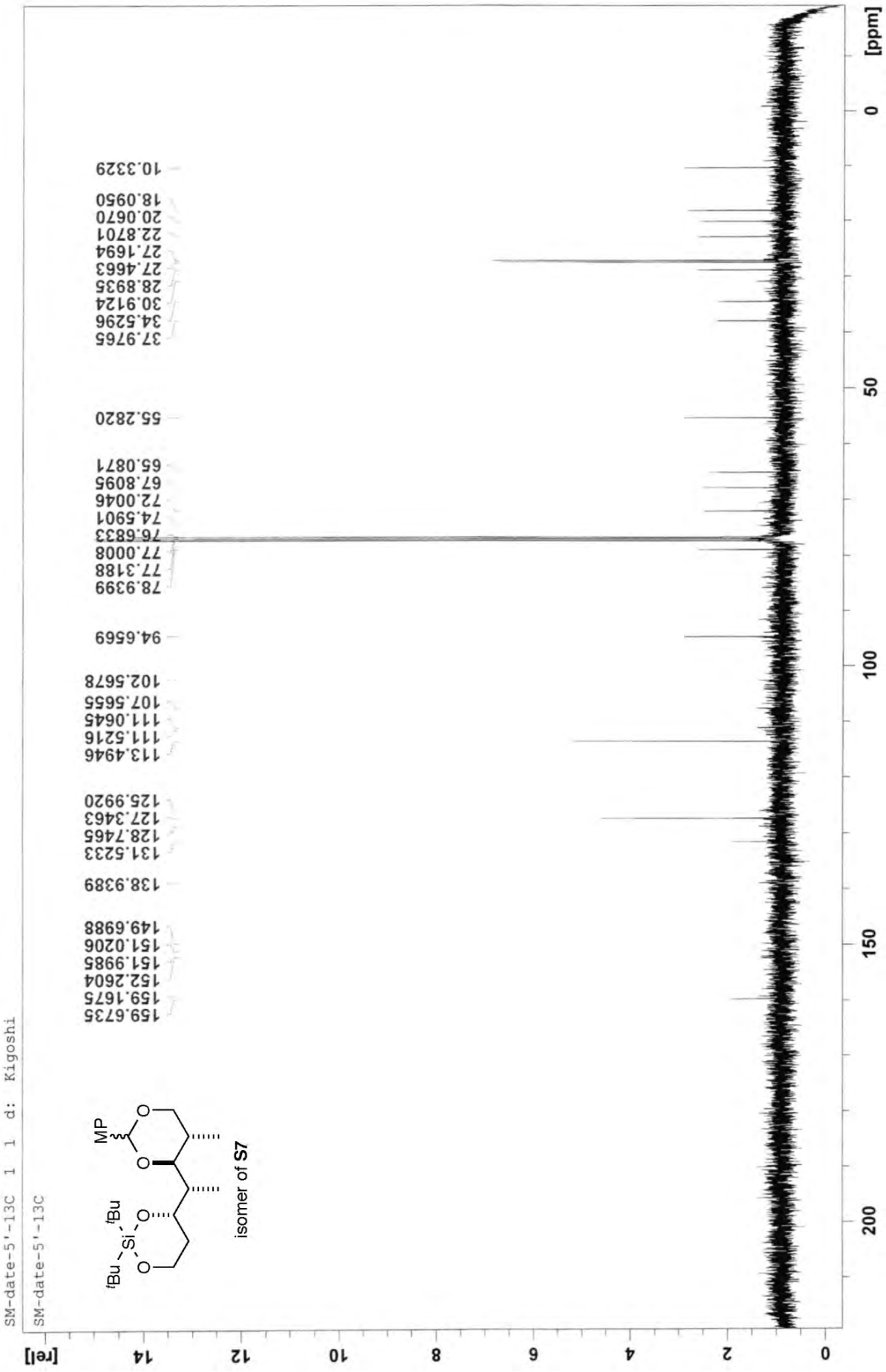
^{1}H NMR spectra of **S7** (400 MHz, $CDCl_3$)



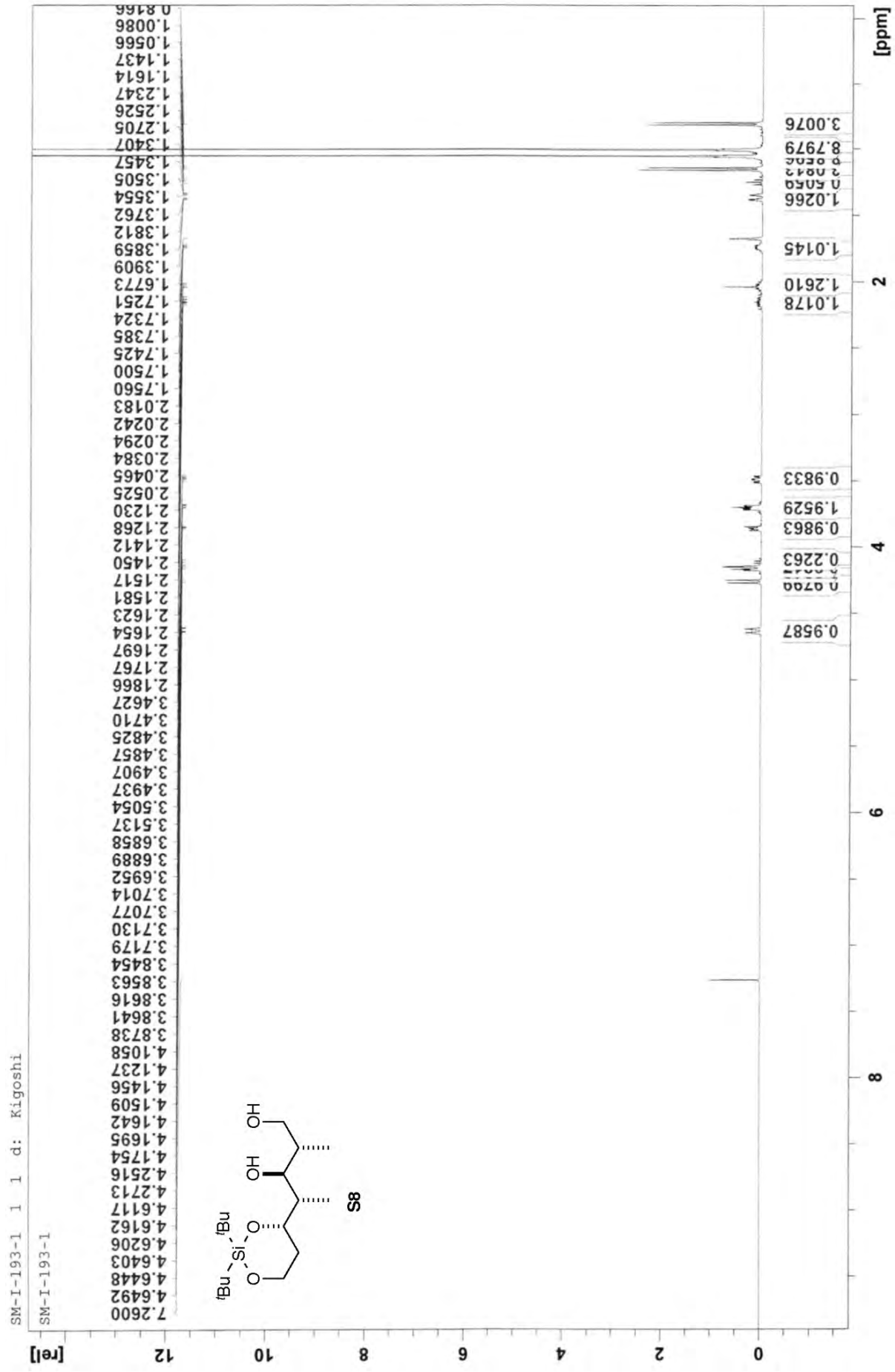
^{13}C NMR spectra of **S7** (100 MHz, $CDCl_3$)



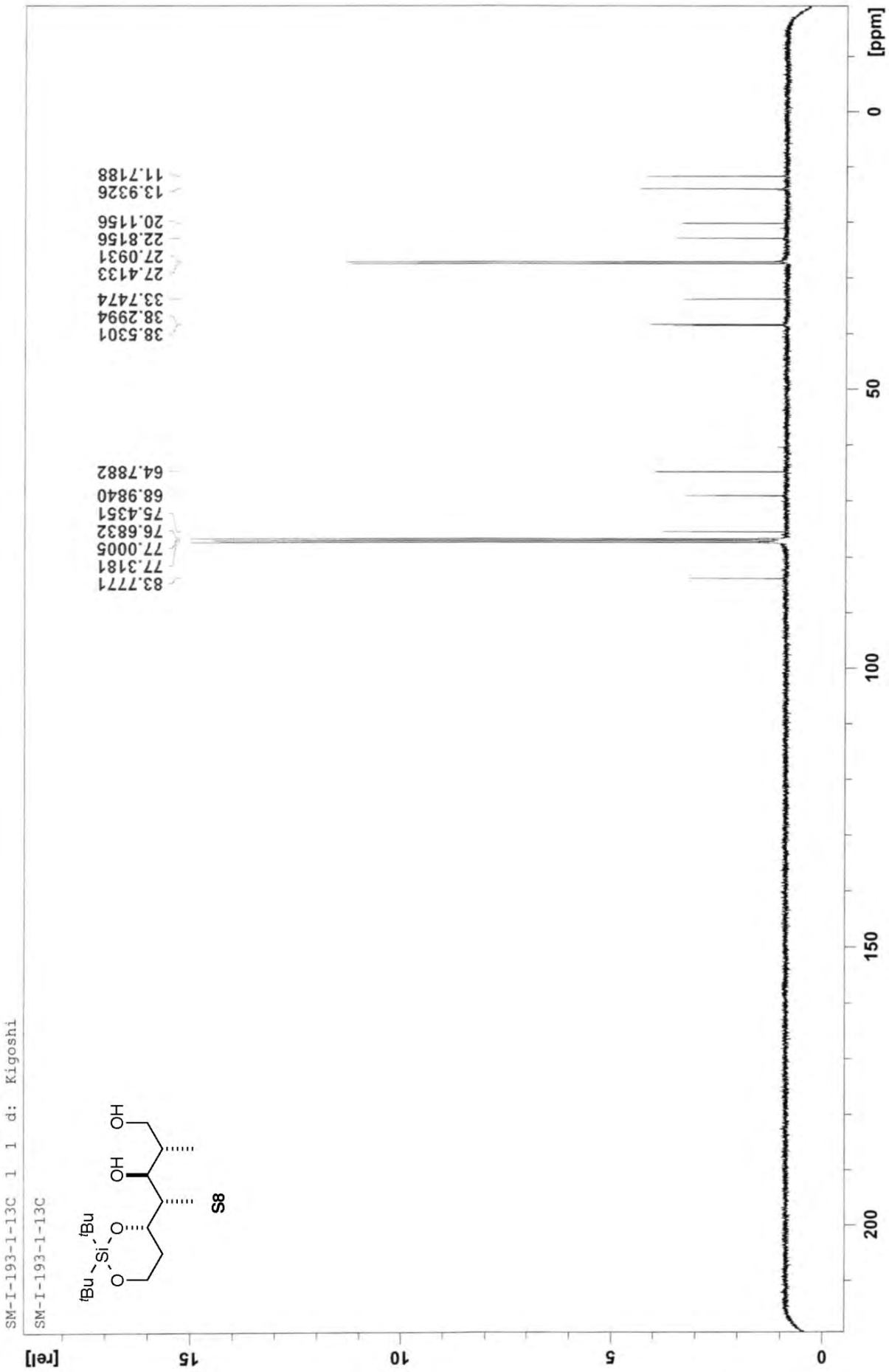
^{1}H NMR spectra of isomer of **S7** (400 MHz, $CDCl_3$)



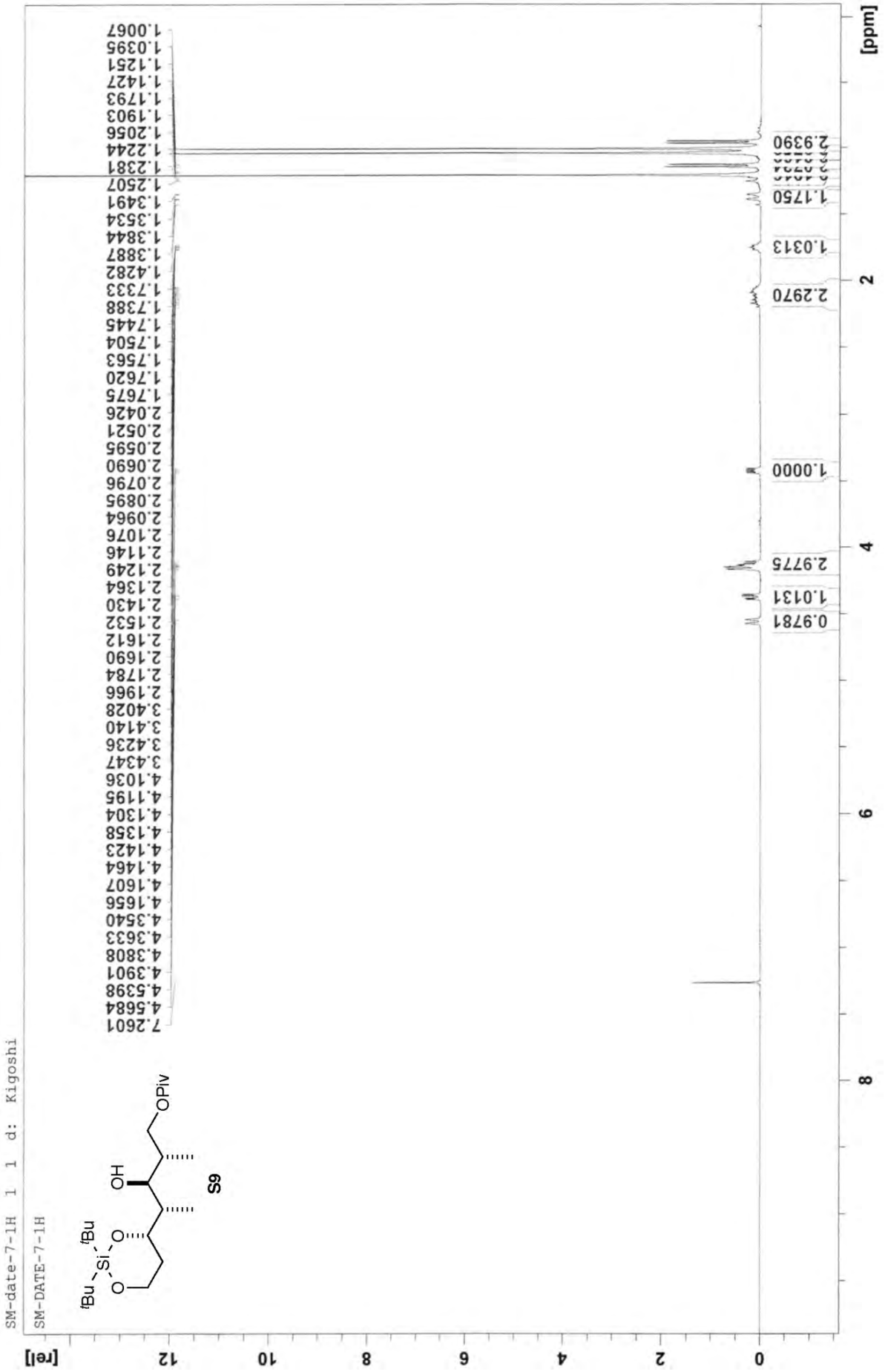
^{13}C NMR spectra of isomer of **S7** (100 MHz, $CDCl_3$)



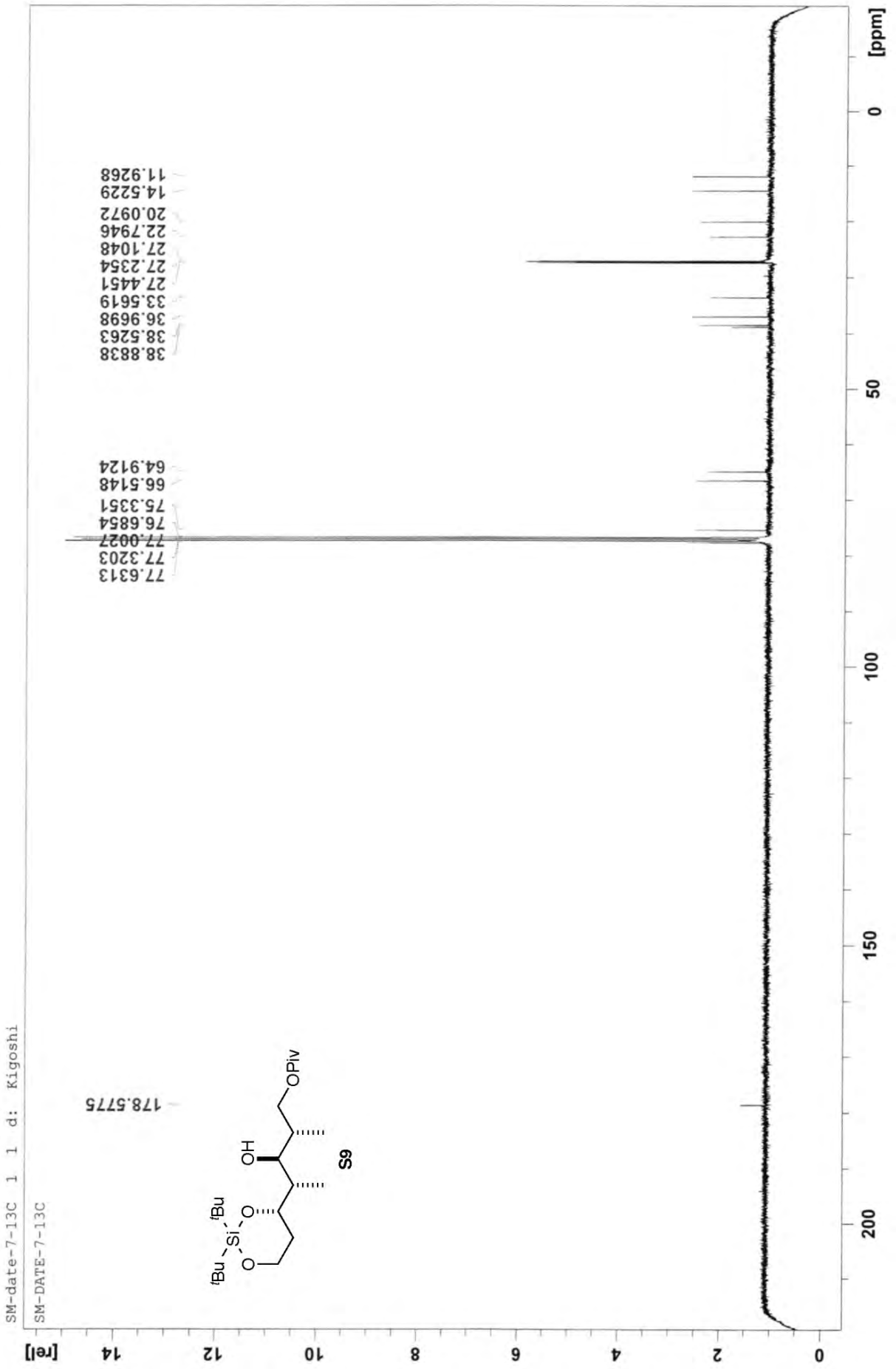
^{1}H NMR spectra of **S8** (400 MHz, $CDCl_3$)



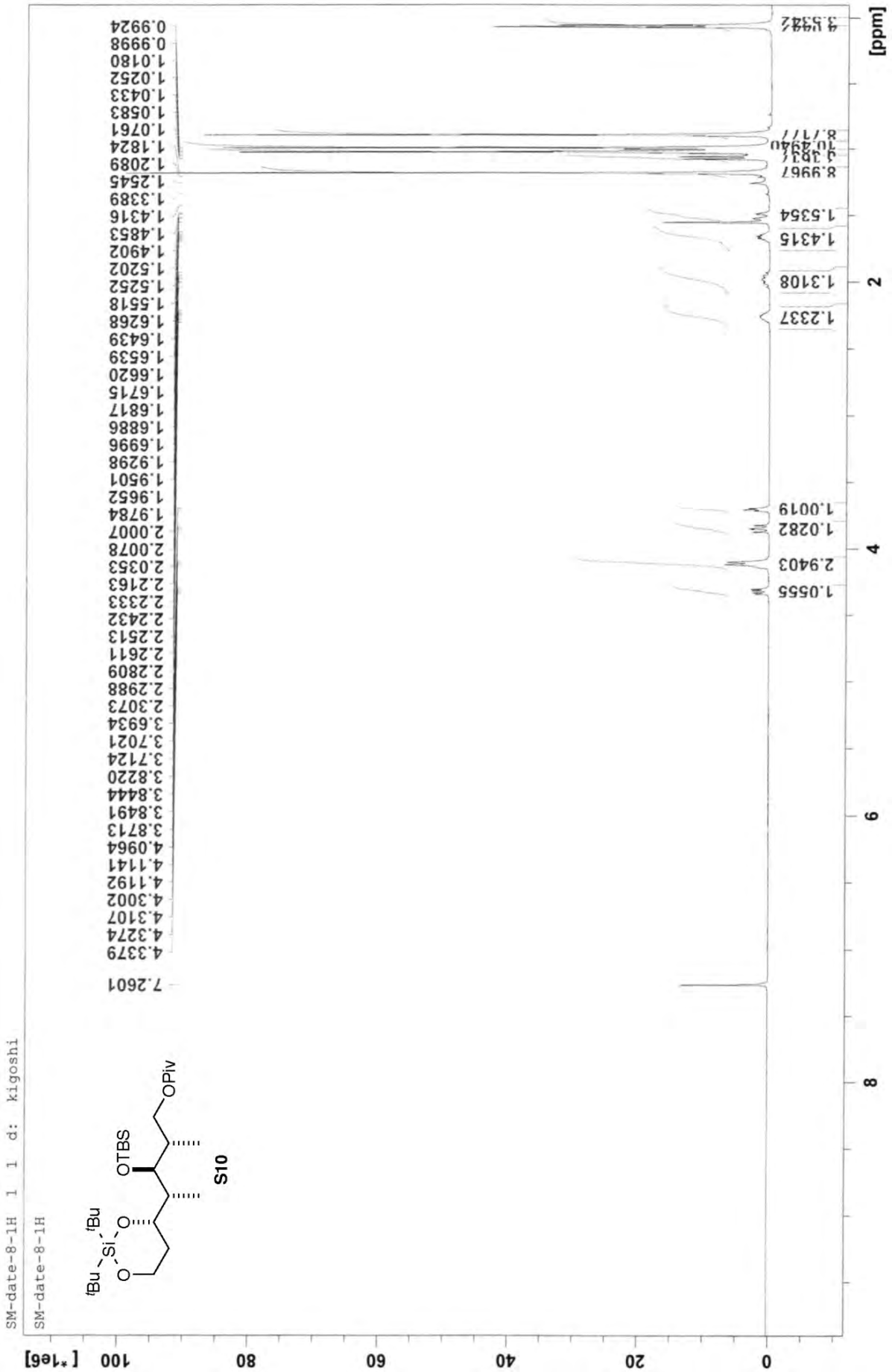
^{13}C NMR spectra of **S8** (100 MHz, $CDCl_3$)



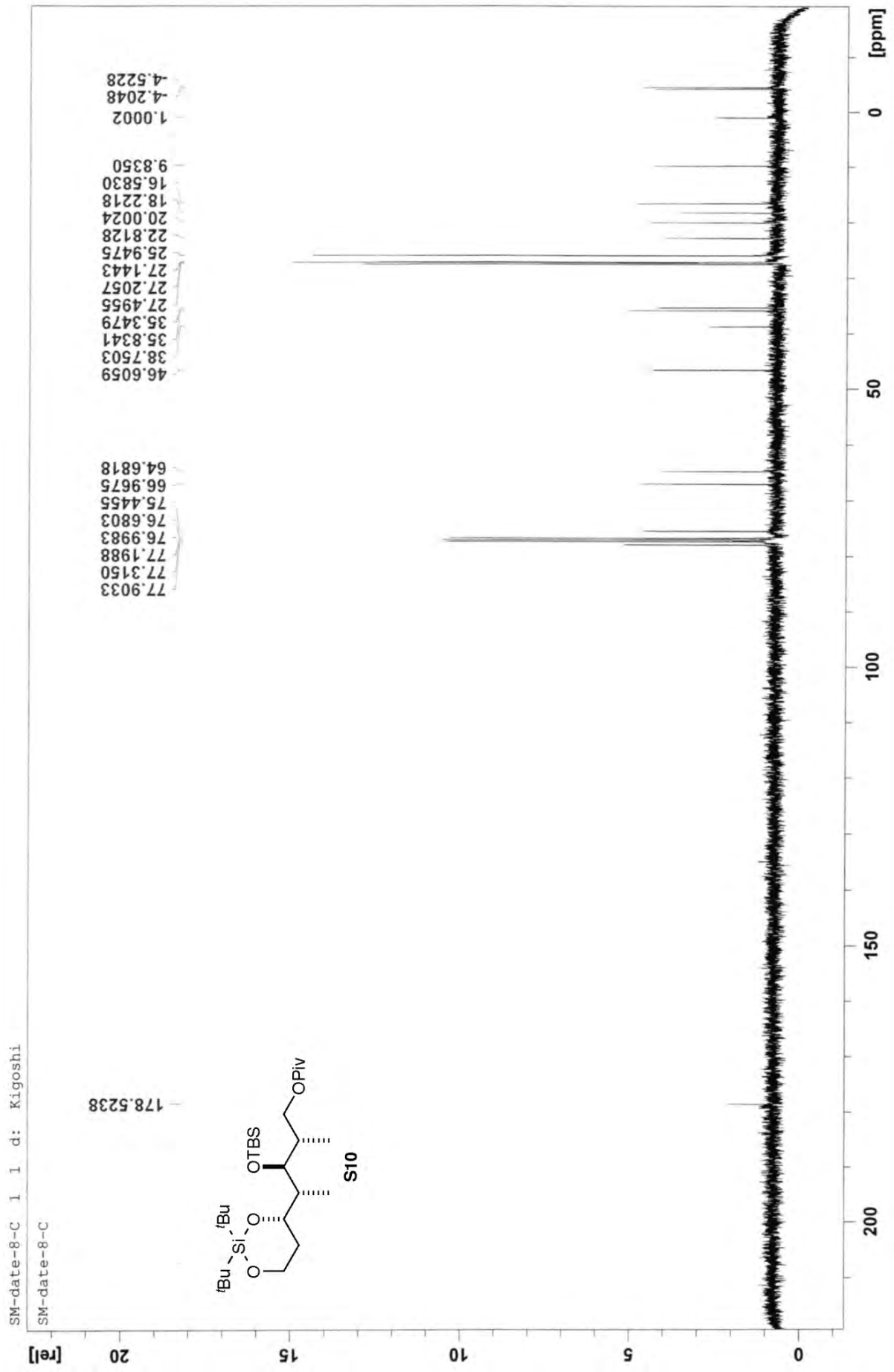
^{1}H NMR spectra of **S9** (400 MHz, $CDCl_3$)



^{13}C NMR spectra of **S9** (100 MHz, $CDCl_3$)



^{1}H NMR spectra of **S10** (400 MHz, $CDCl_3$)



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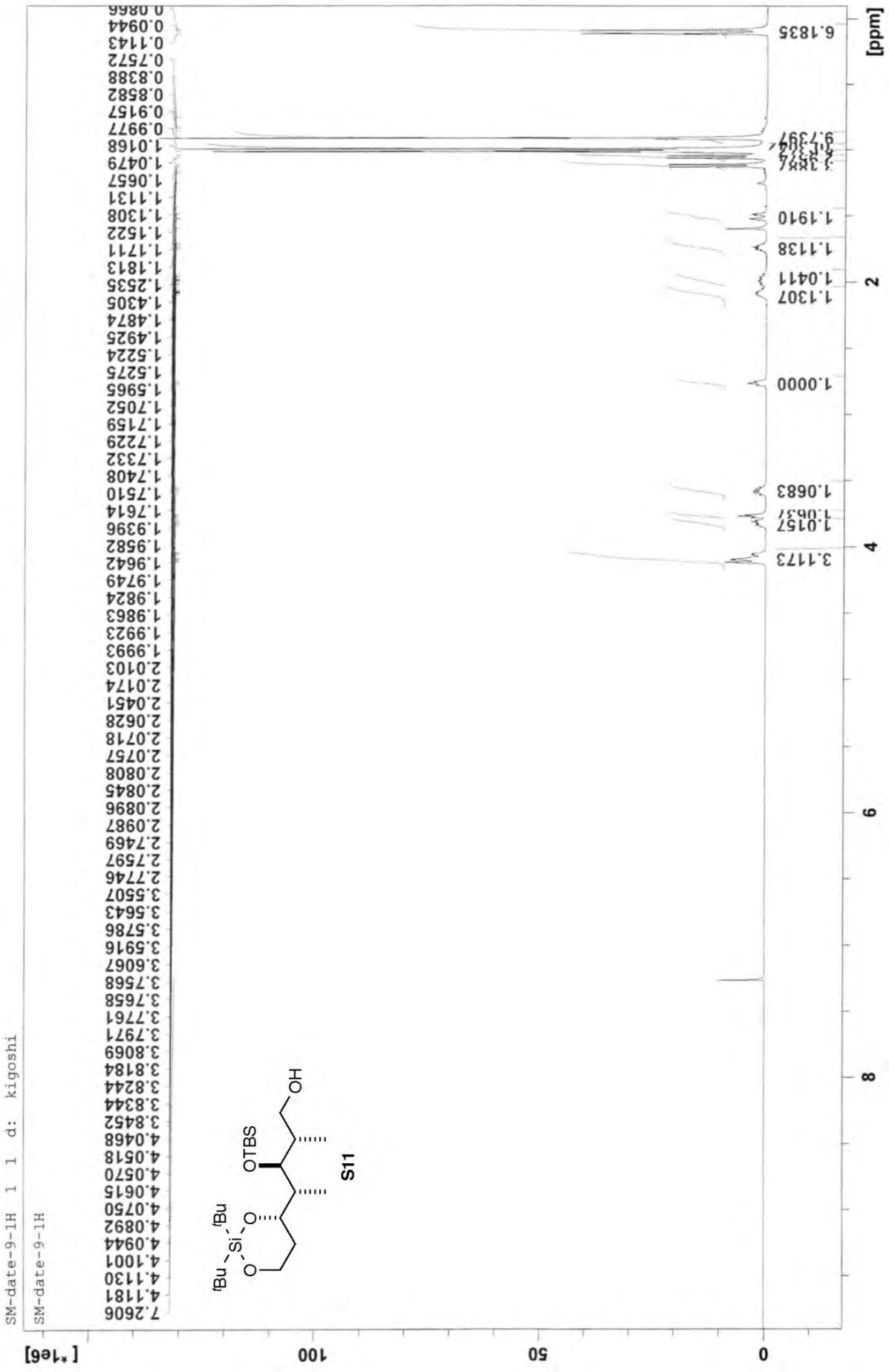
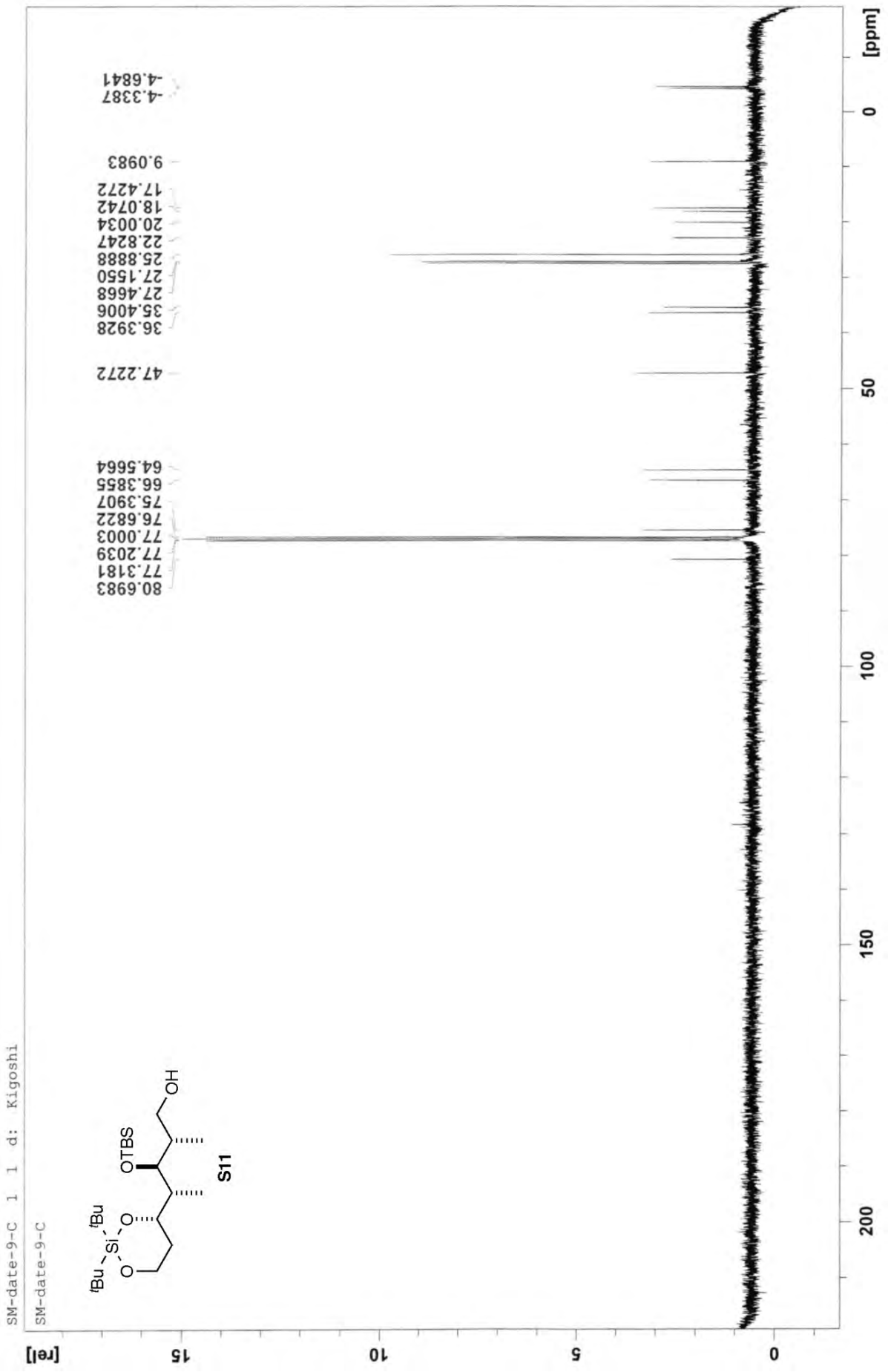
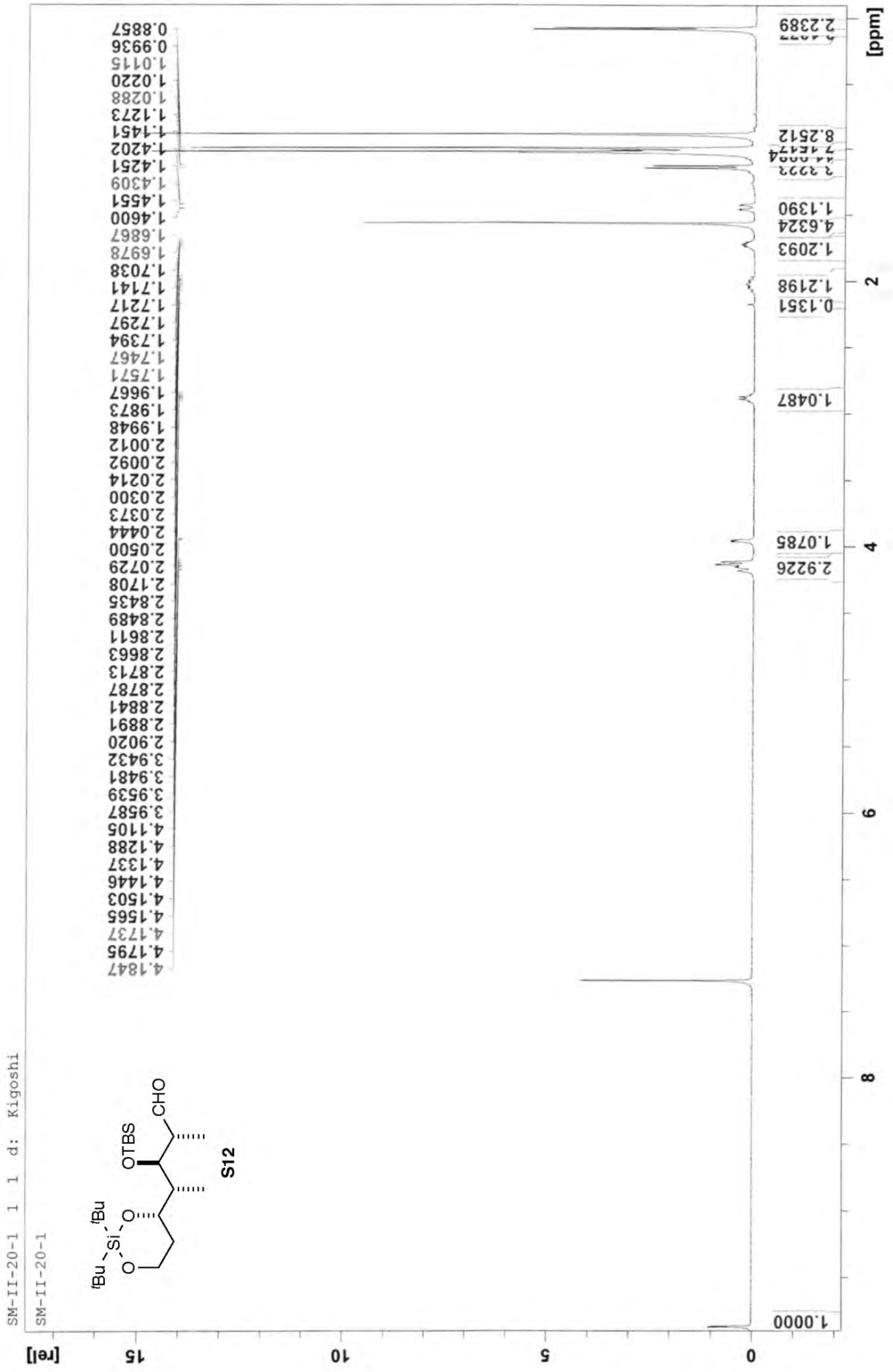


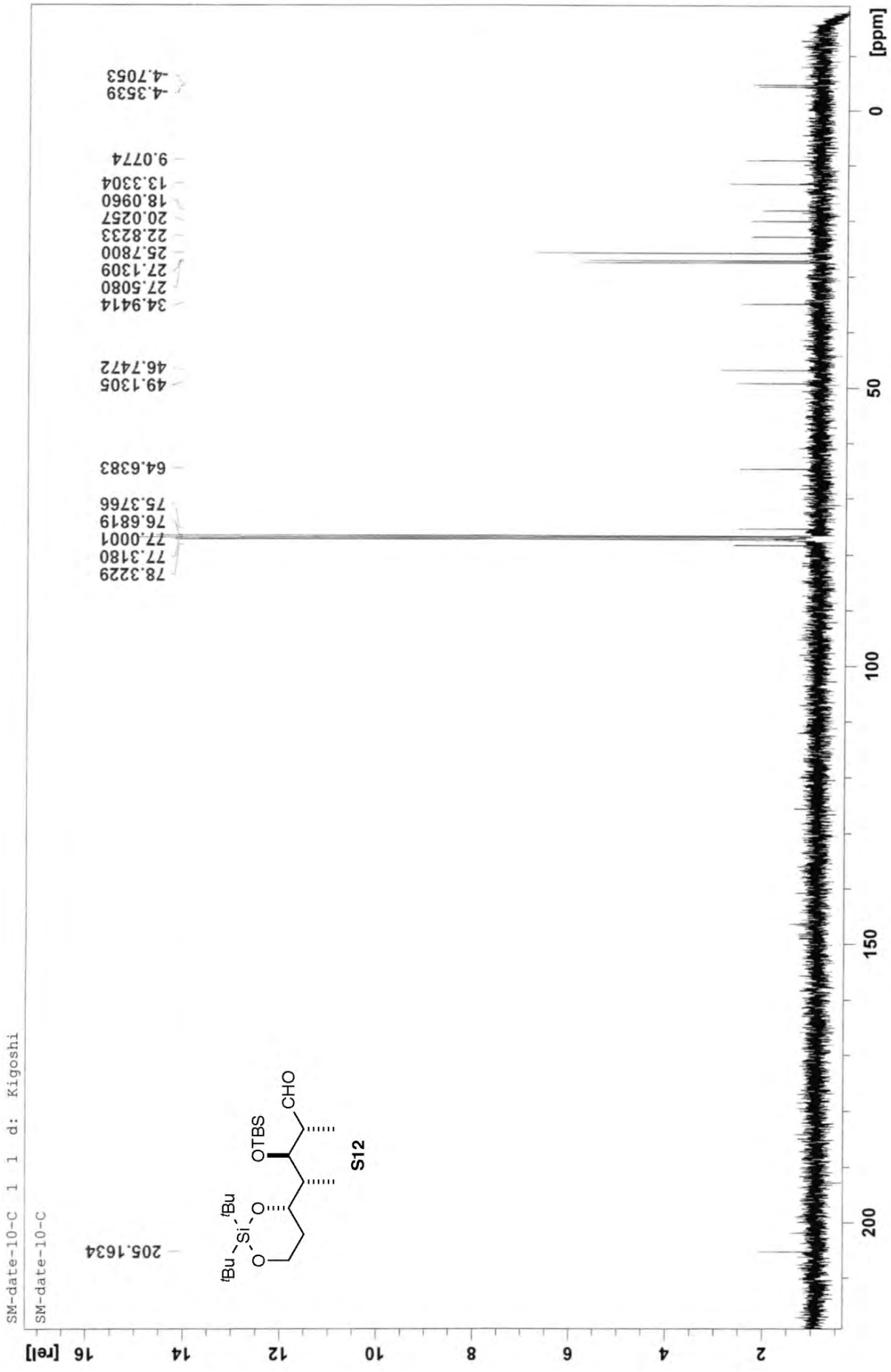
^{1}H NMR spectra of **S11** (400 MHz, $CDCl_3$)



^{13}C NMR spectra of **S11** (100 MHz, $CDCl_3$)



^{1}H NMR spectra of **S12** (400 MHz, $CDCl_3$)



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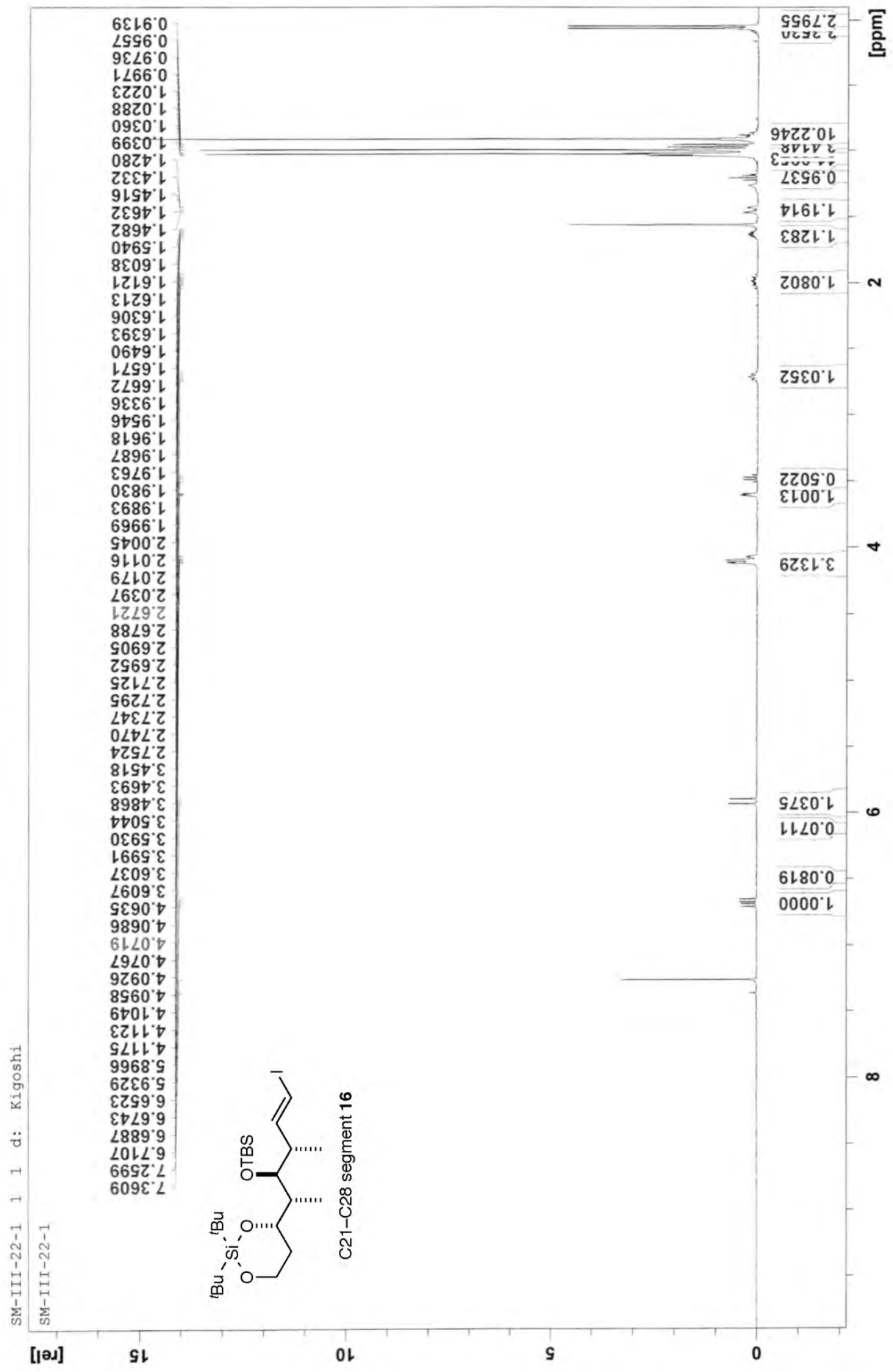
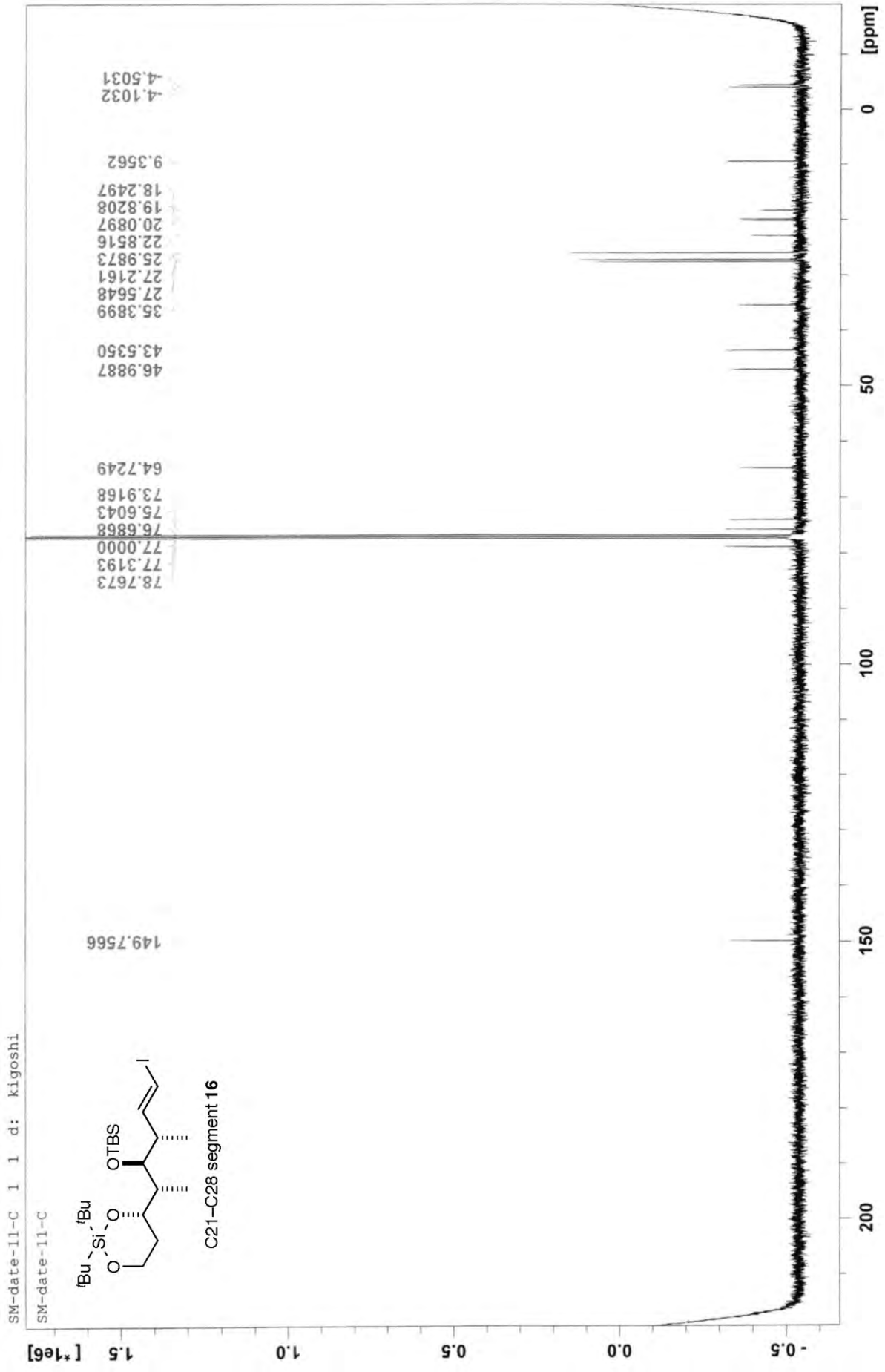
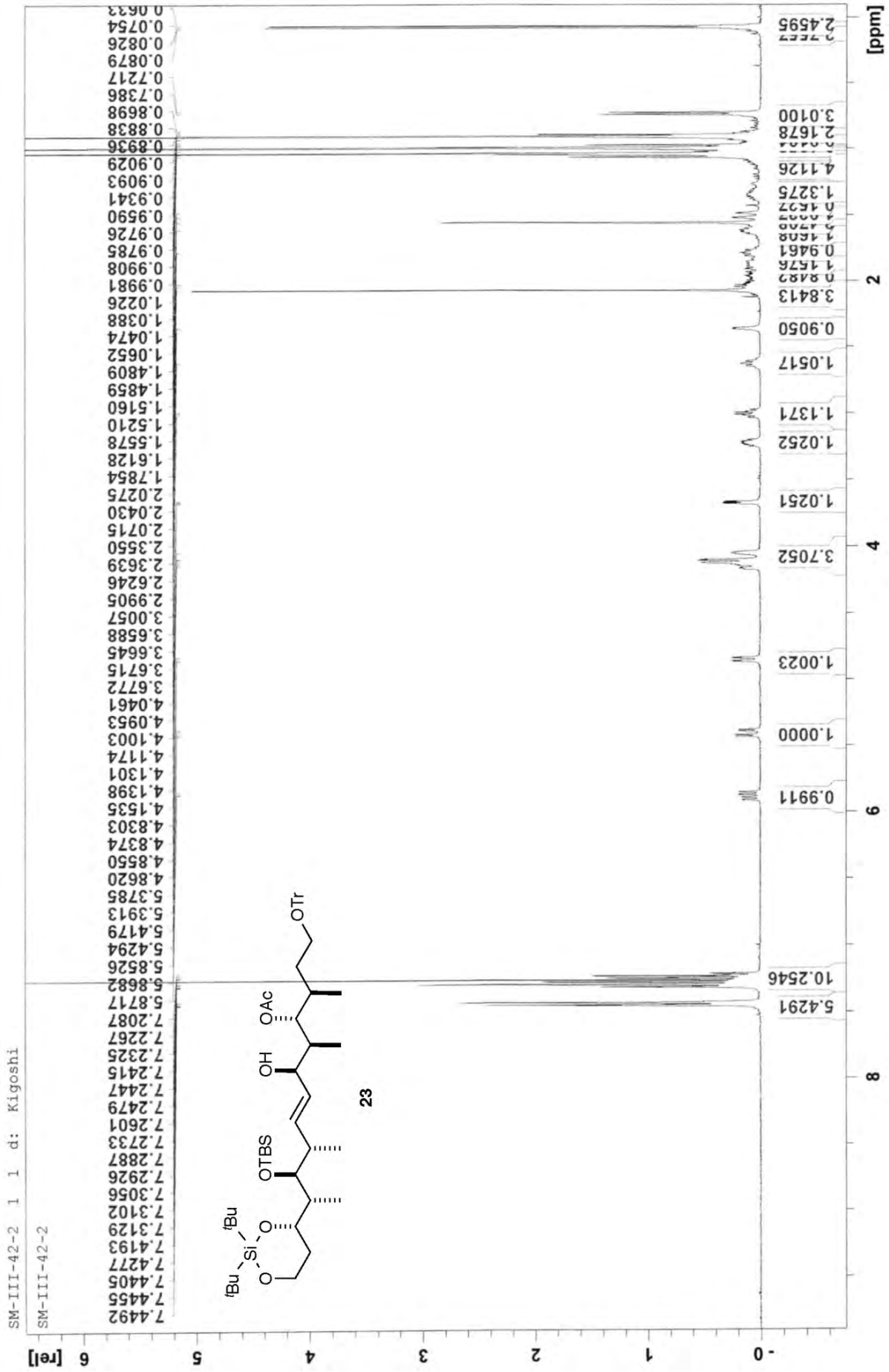


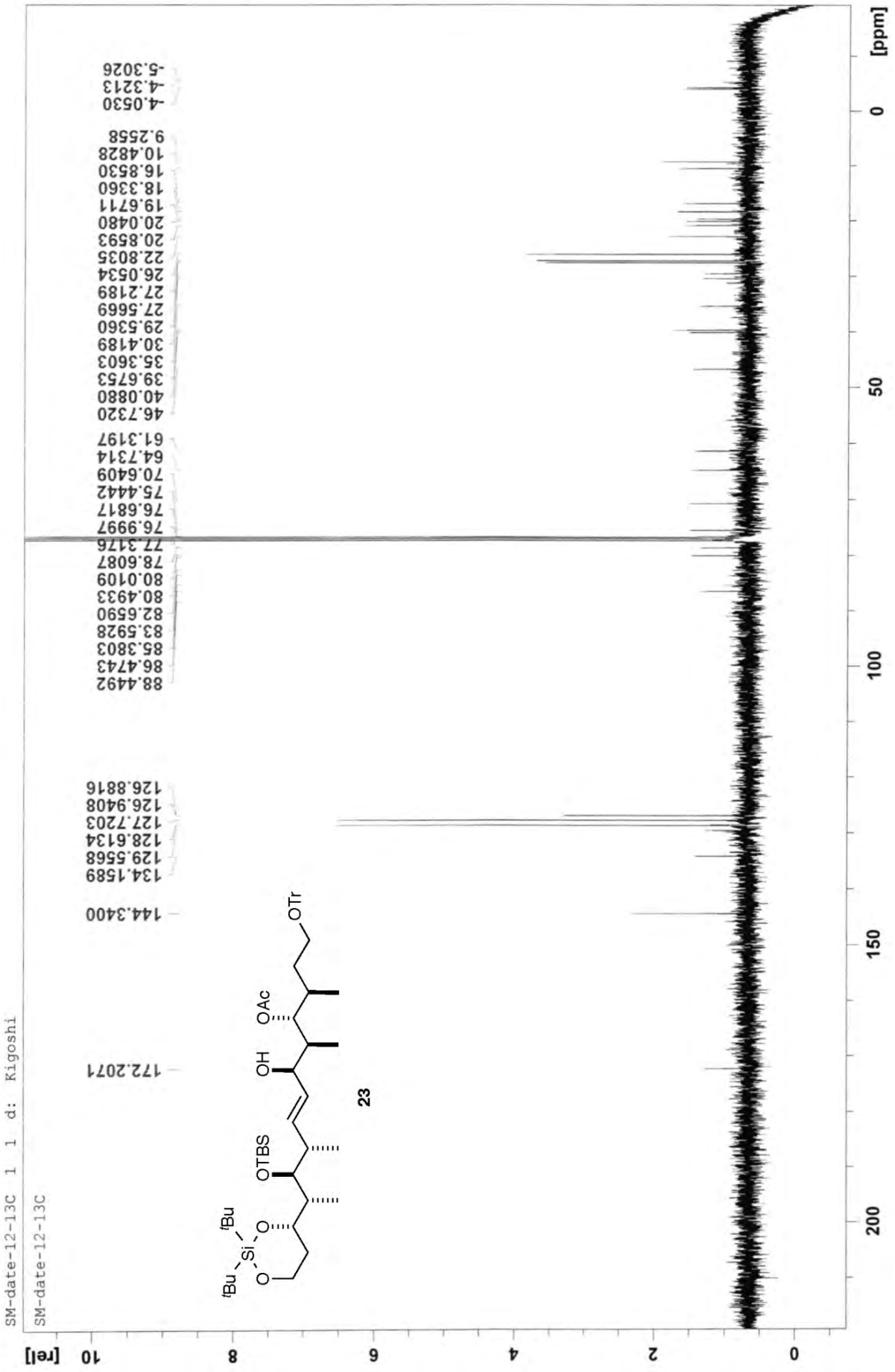
^{1}H NMR spectra of C21–C28 segment **16** (400 MHz, $CDCl_3$)



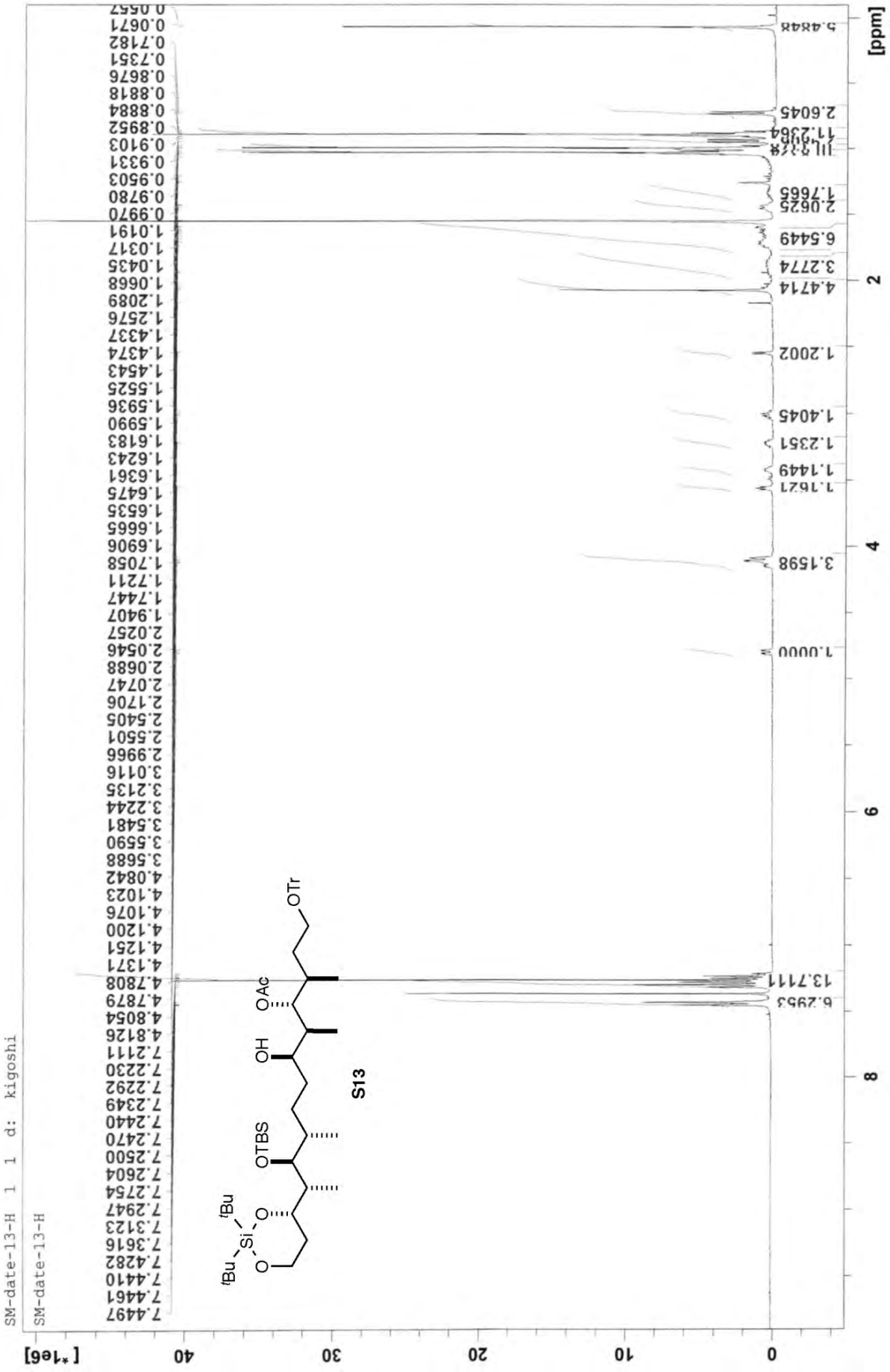
^{13}C NMR spectra of C21–C28 segment **16** (100 MHz, $CDCl_3$)



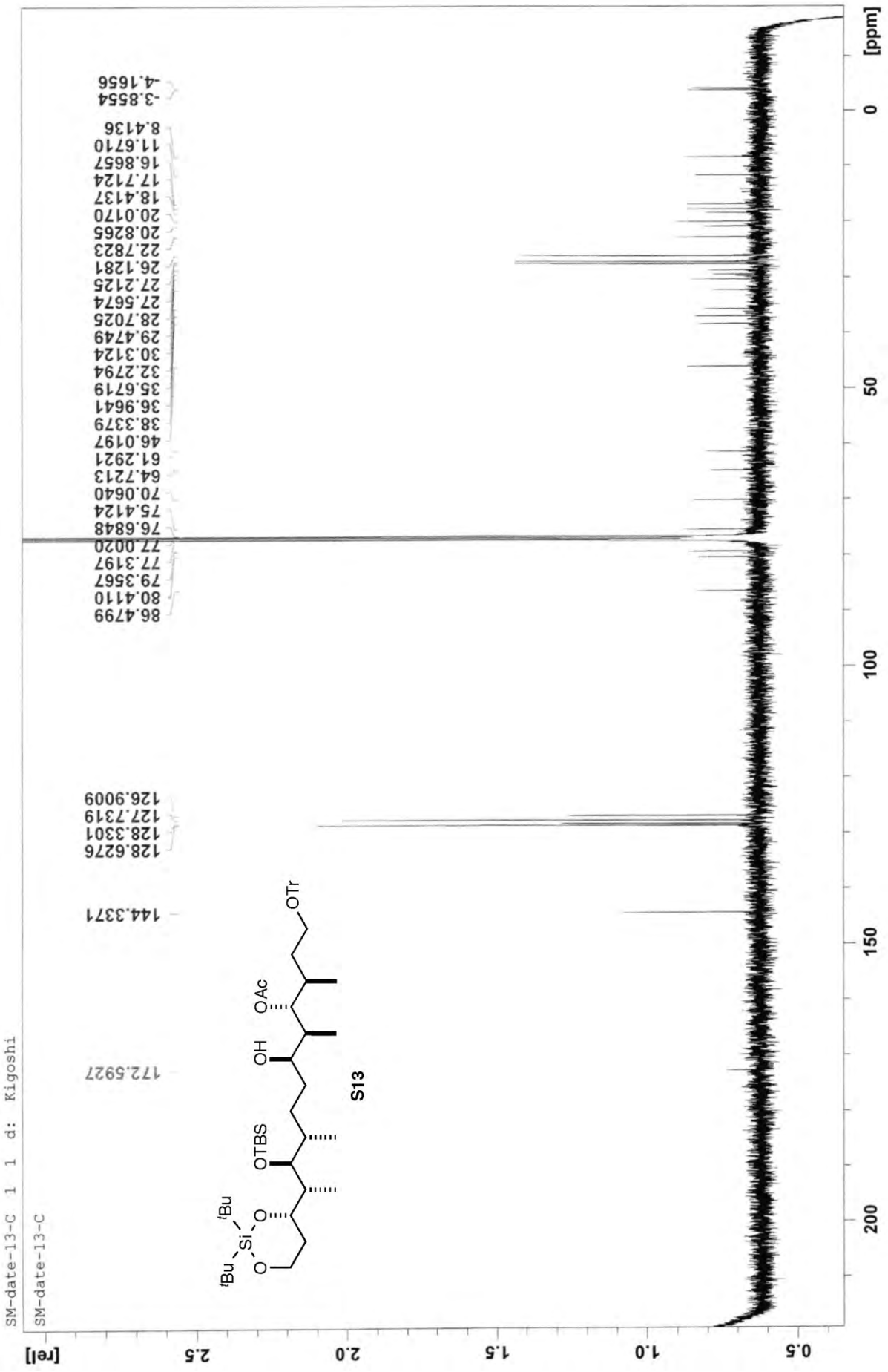
^{1}H NMR spectra of **23** (400 MHz, $CDCl_3$)



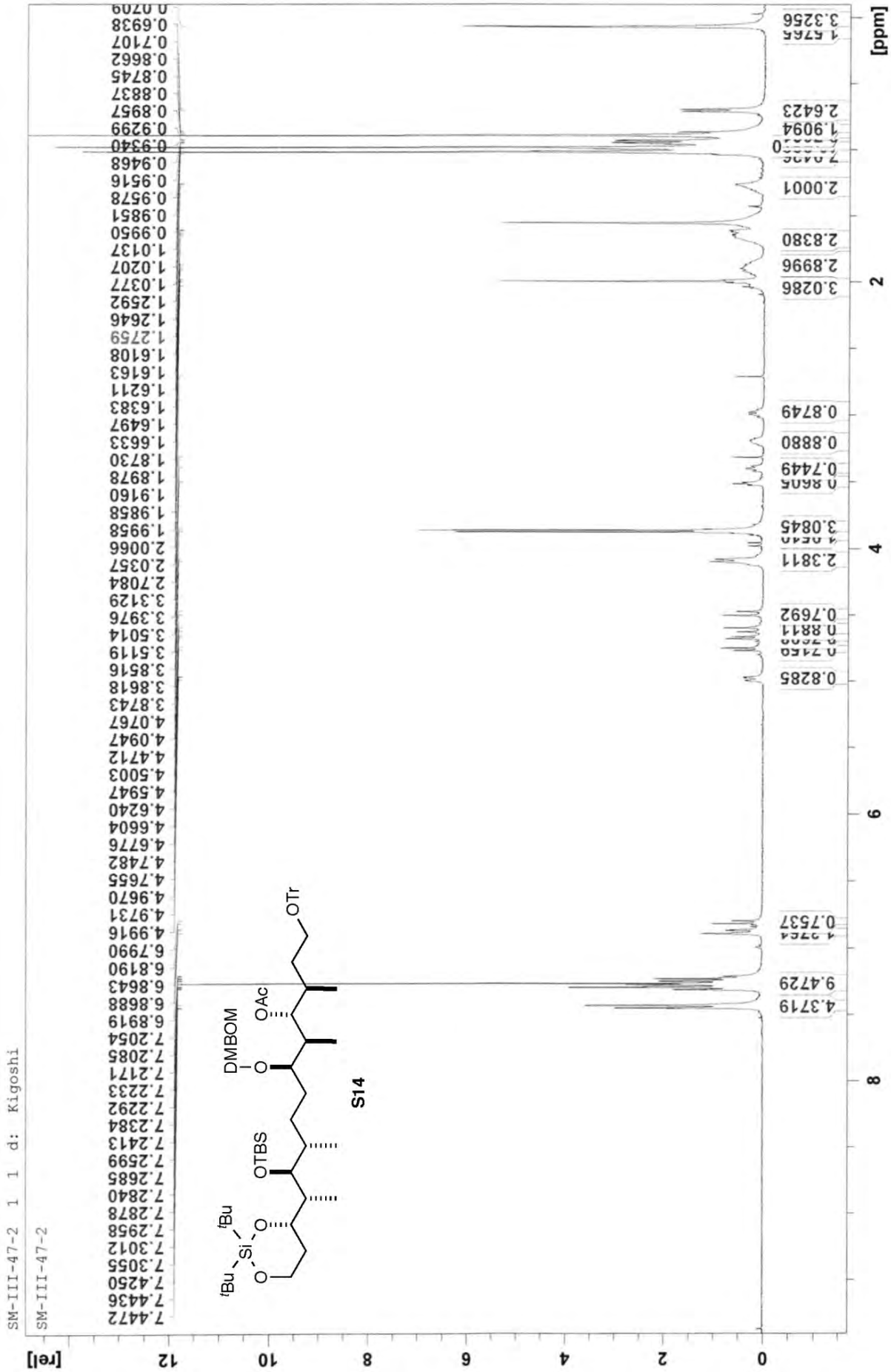
^{13}C NMR spectra of **23** (100 MHz, $CDCl_3$)



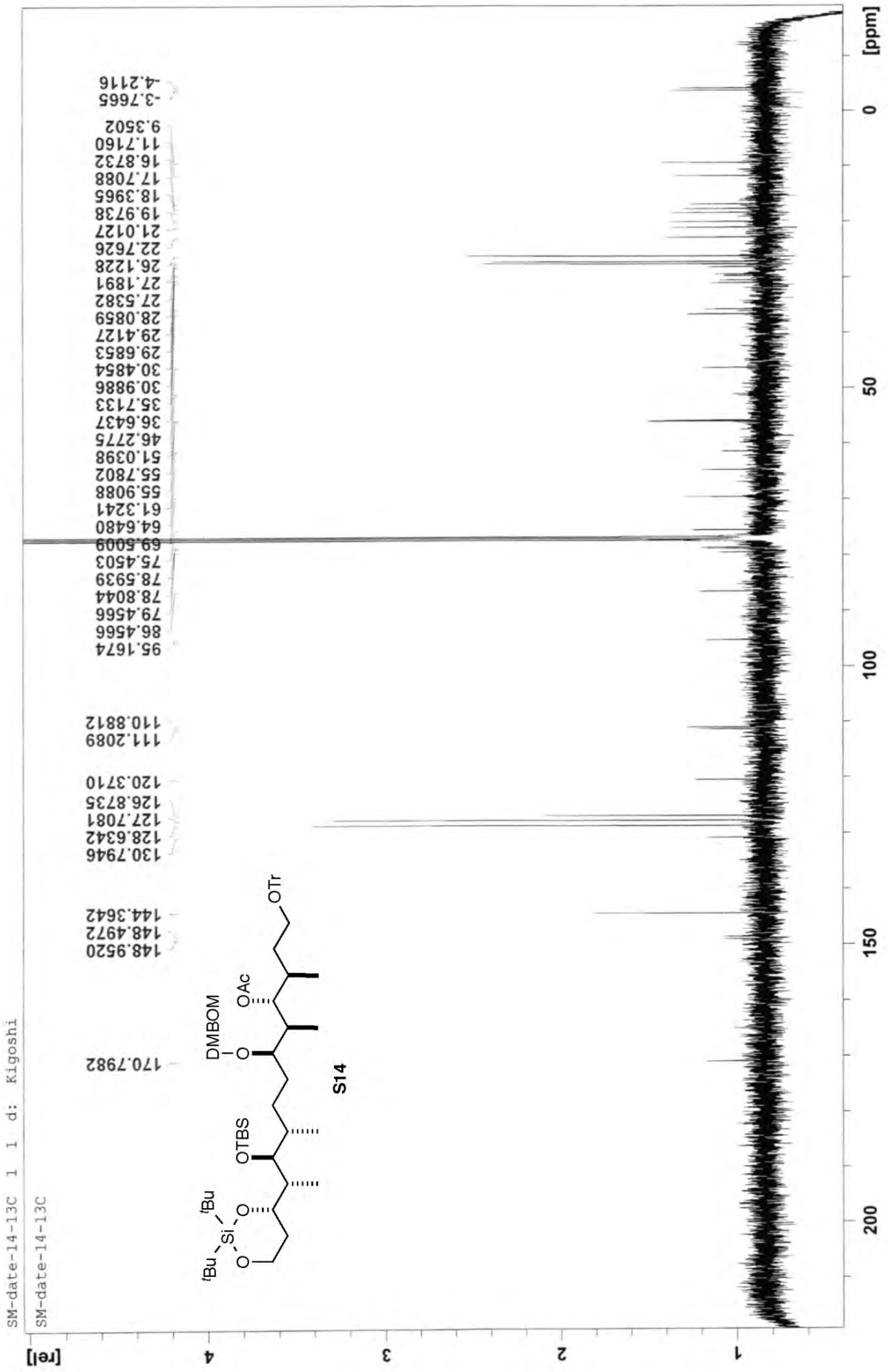
^{1}H NMR spectra of **S13** (400 MHz, $CDCl_3$)



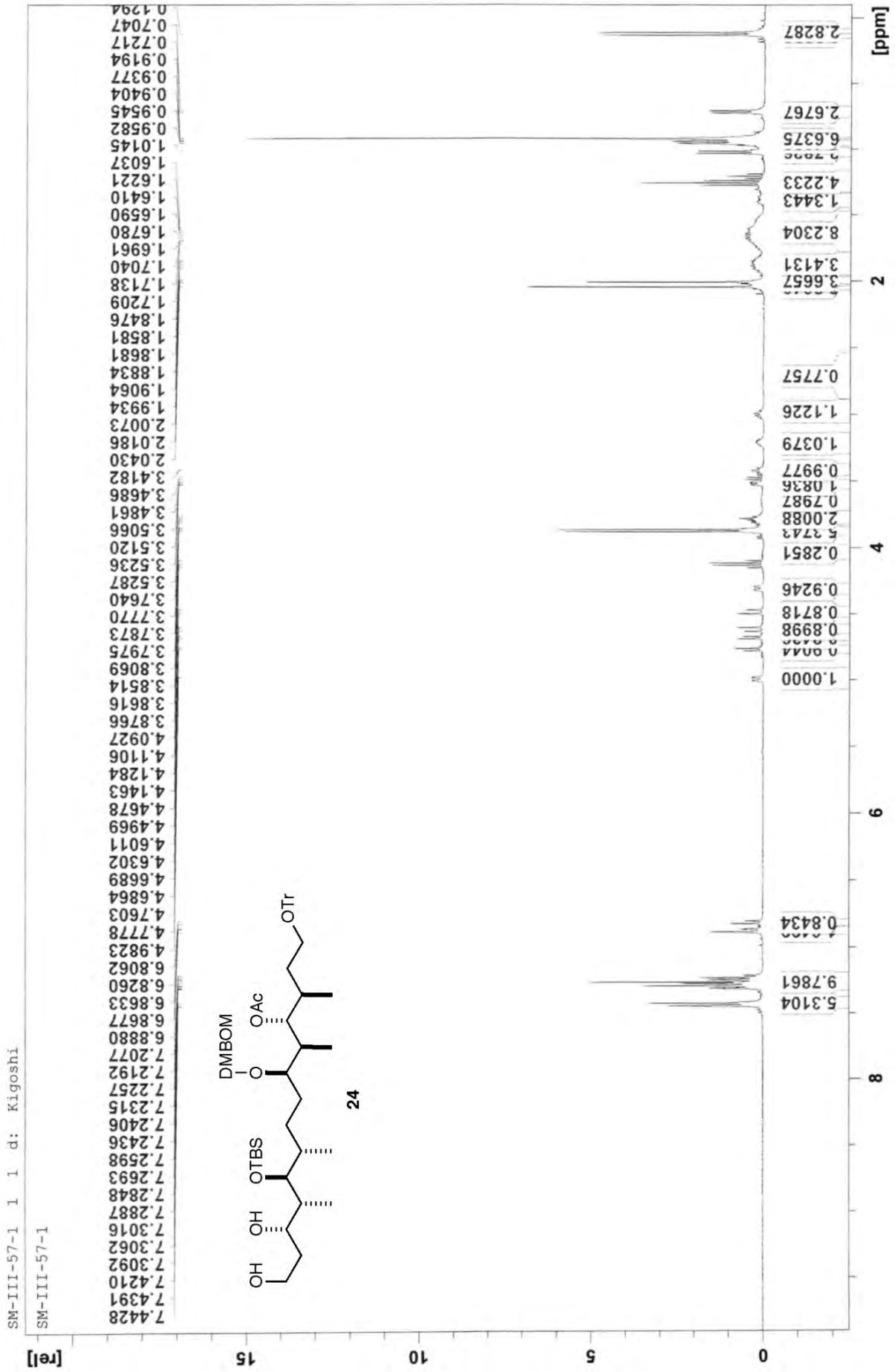
^{13}C NMR spectra of **S13** (100 MHz, $CDCl_3$)



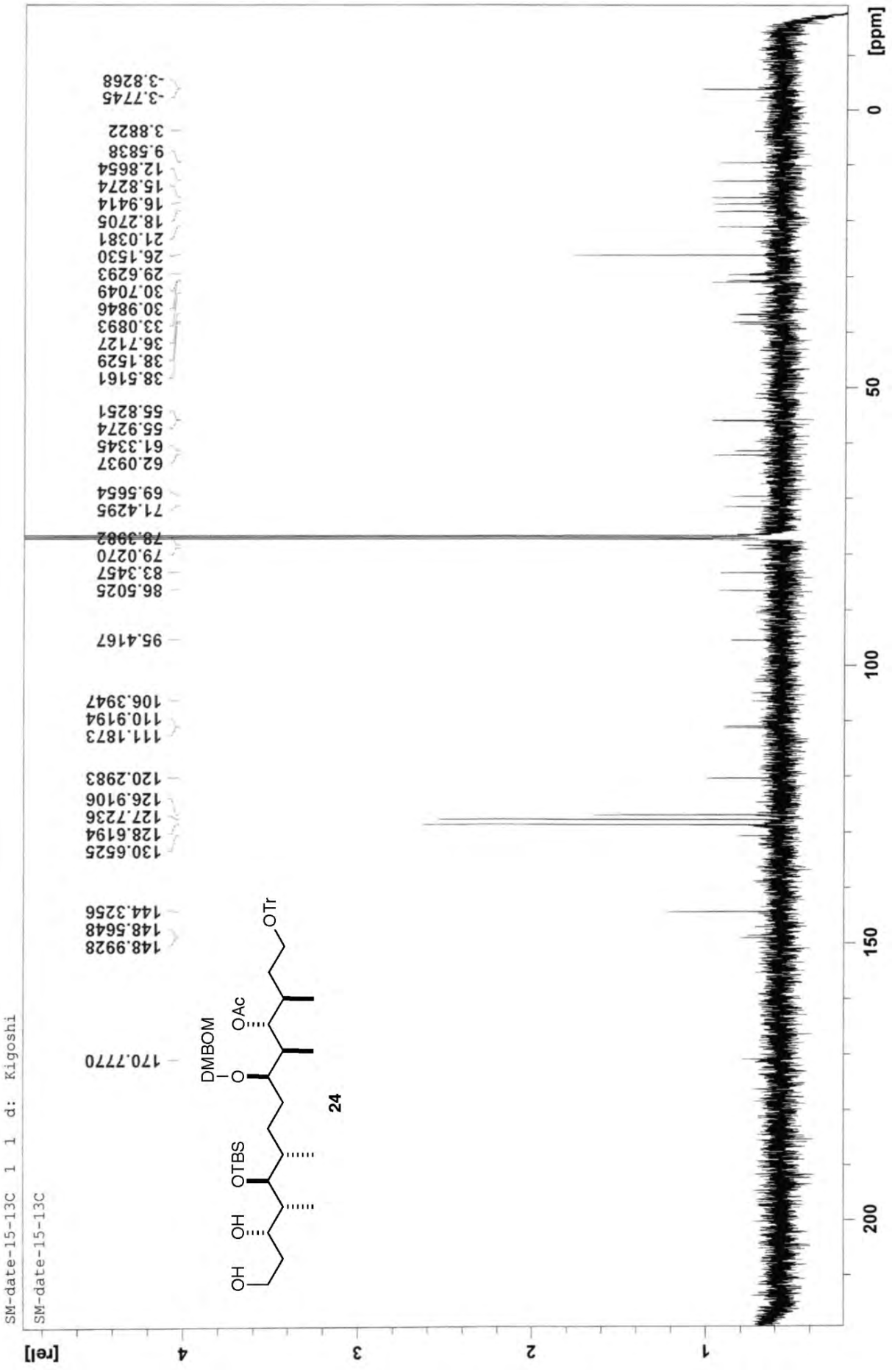
^{1}H NMR spectra of **S14** (400 MHz, $CDCl_3$)



^{13}C NMR spectra of **S14** (100 MHz, $CDCl_3$)



^{1}H NMR spectra of **24** (400 MHz, $CDCl_3$)



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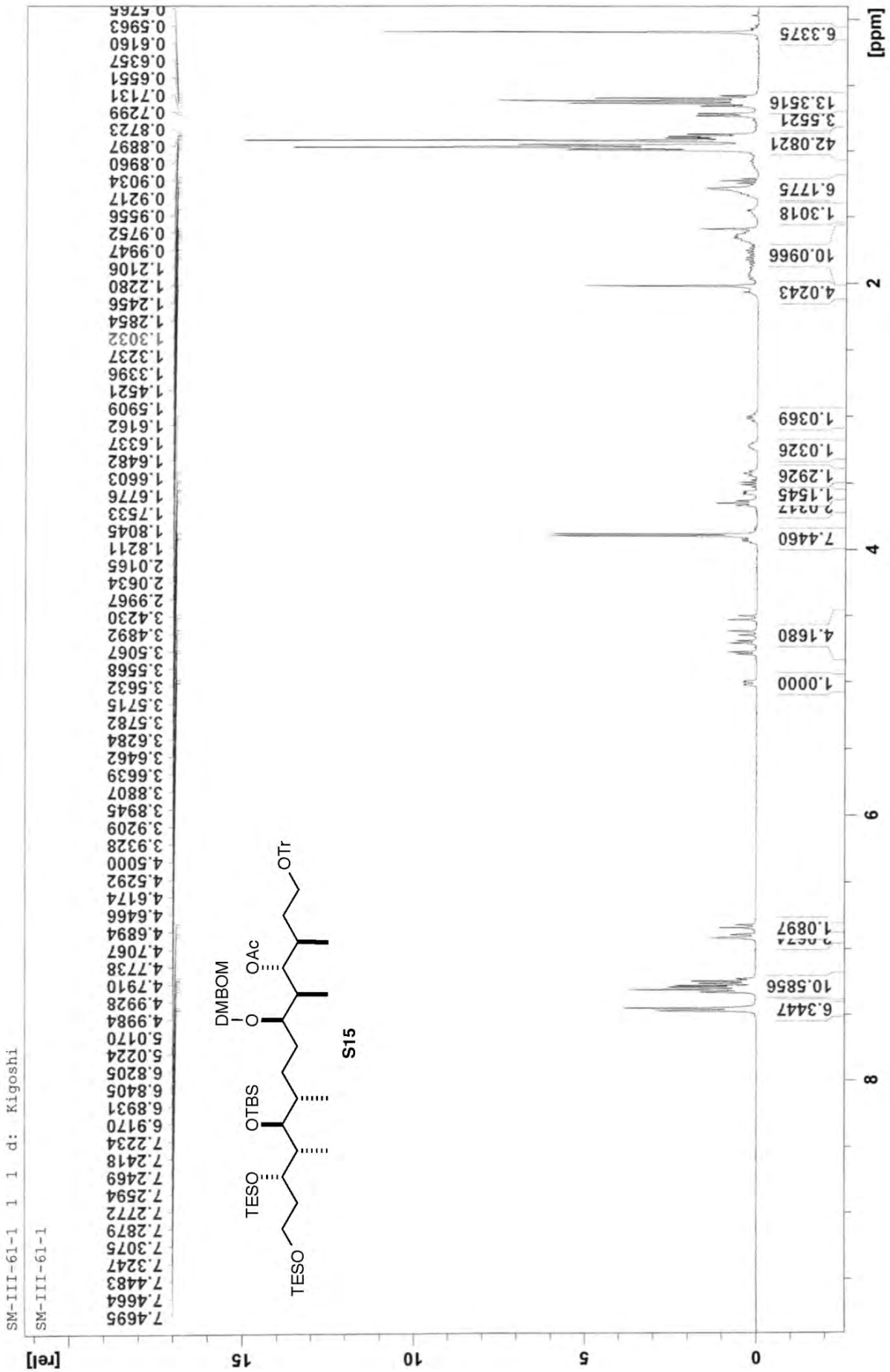
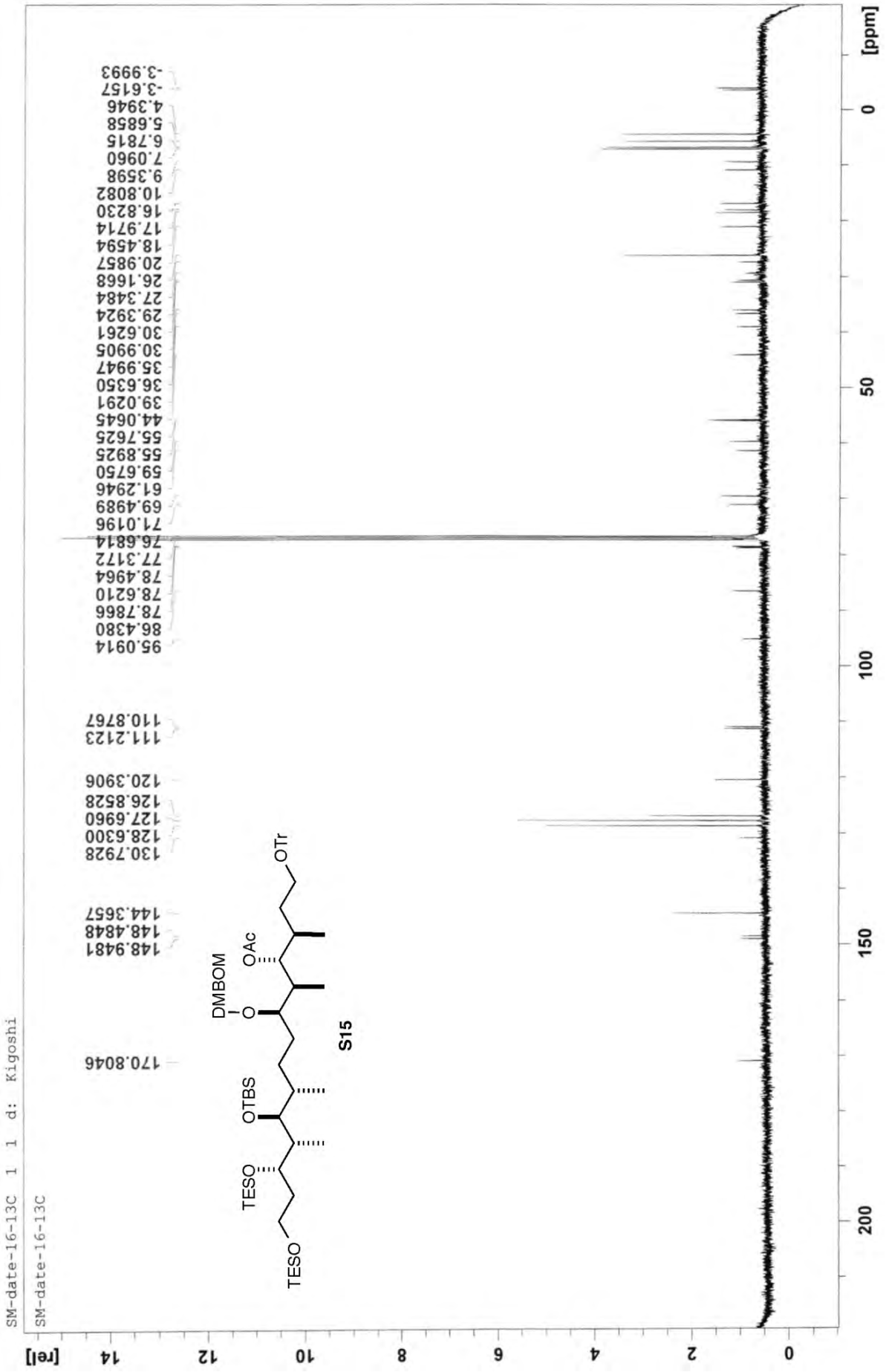


^{1}H NMR spectra of **S15** (400 MHz, $CDCl_3$)



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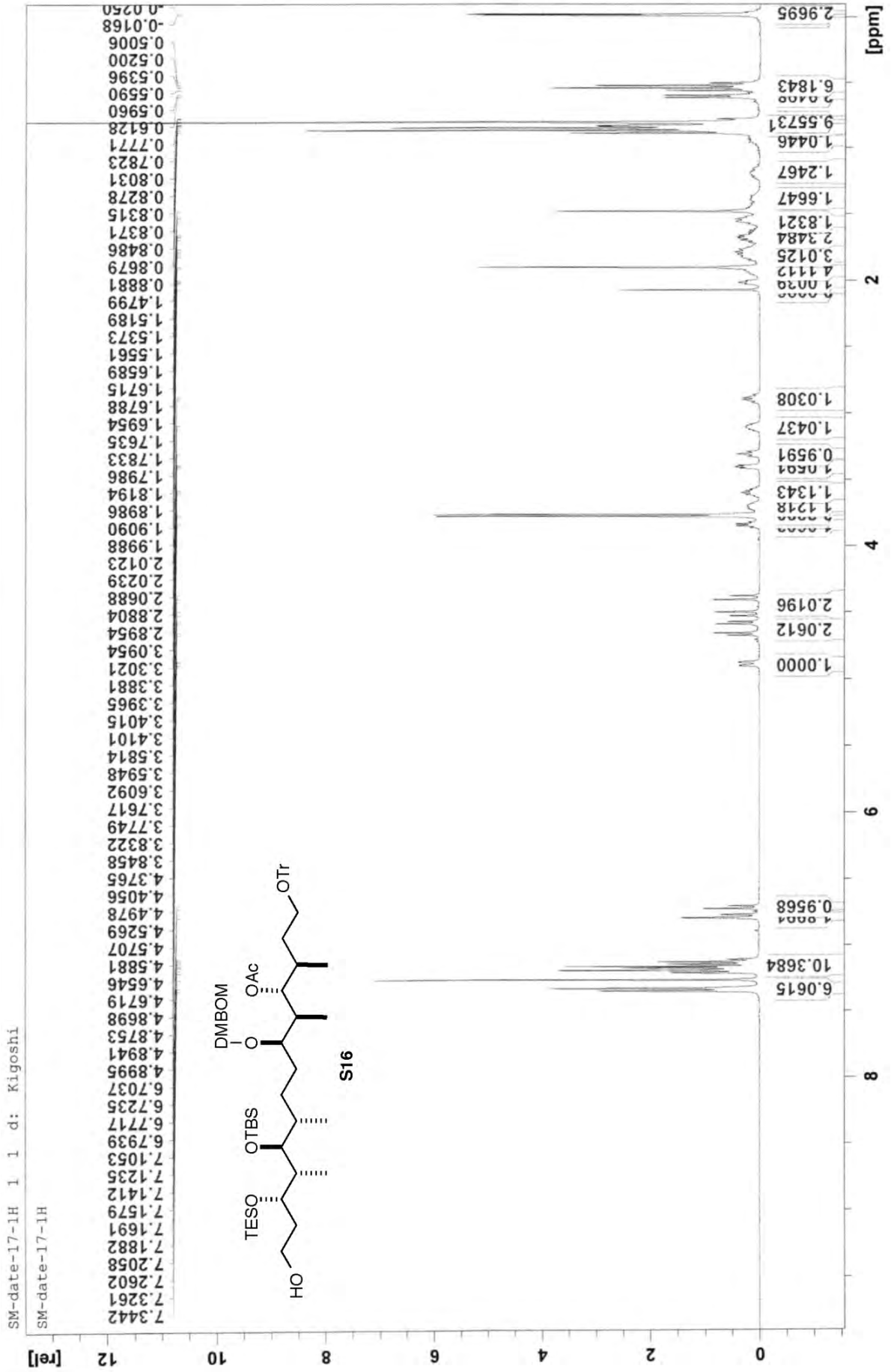
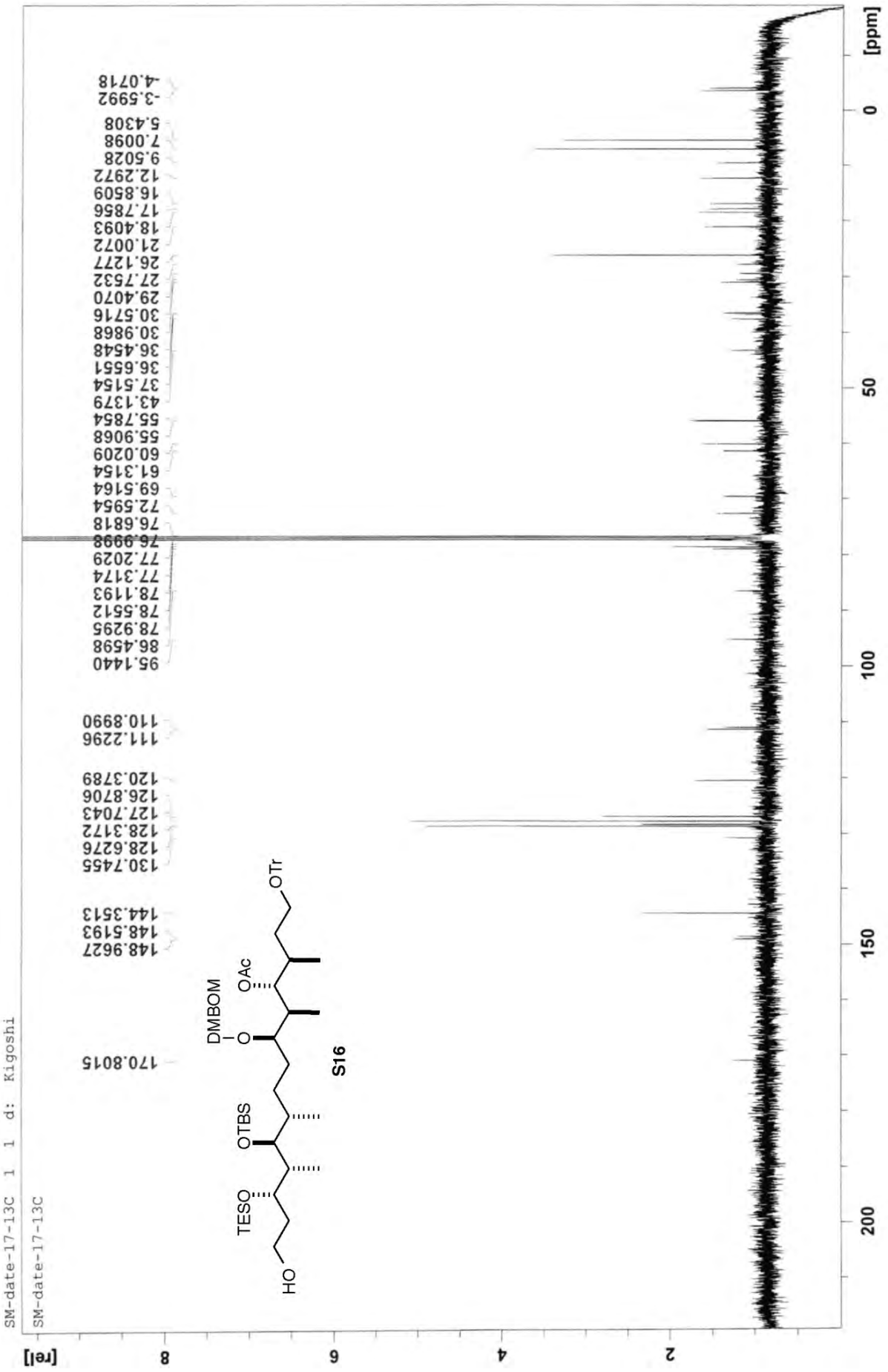
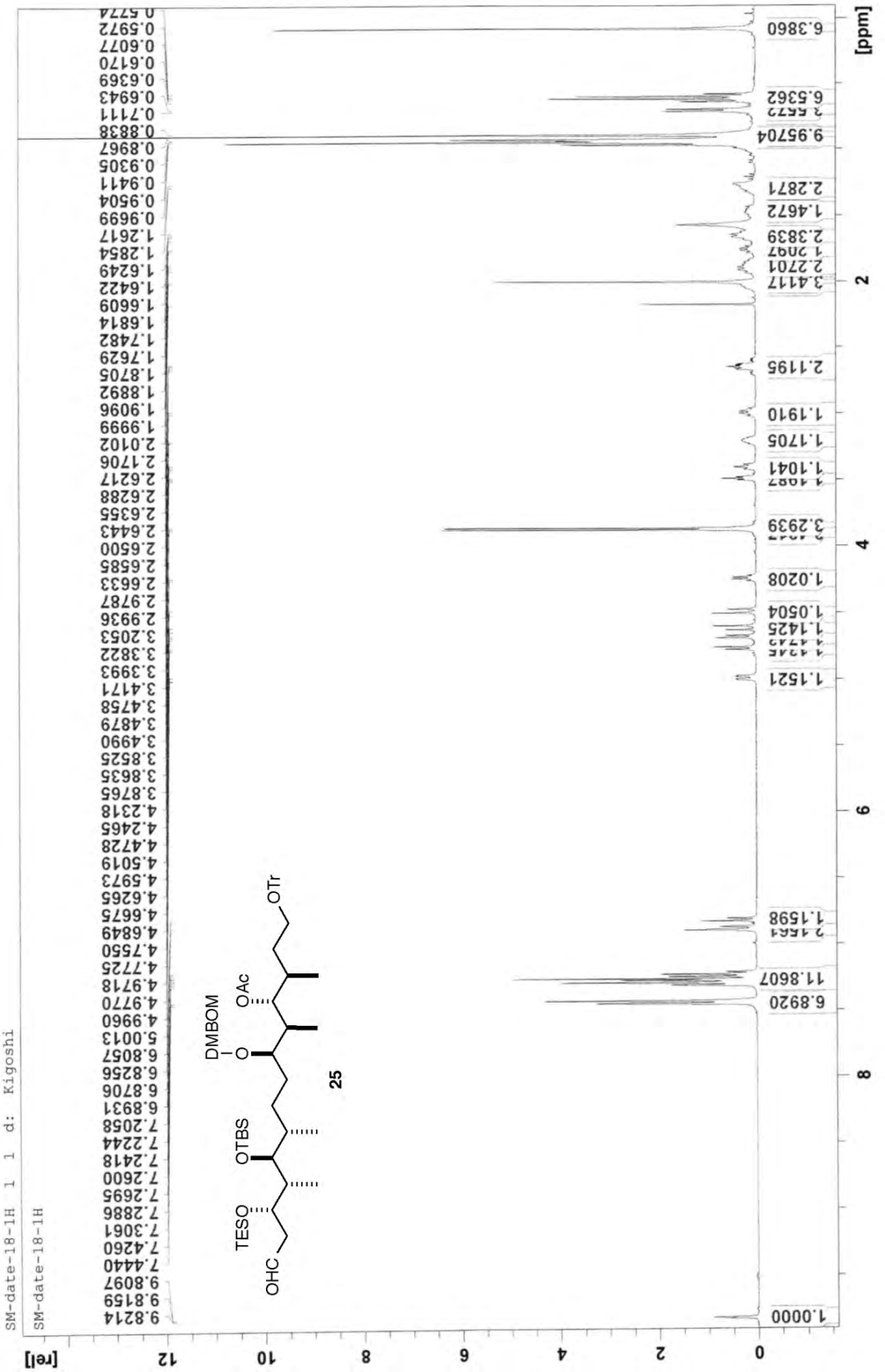


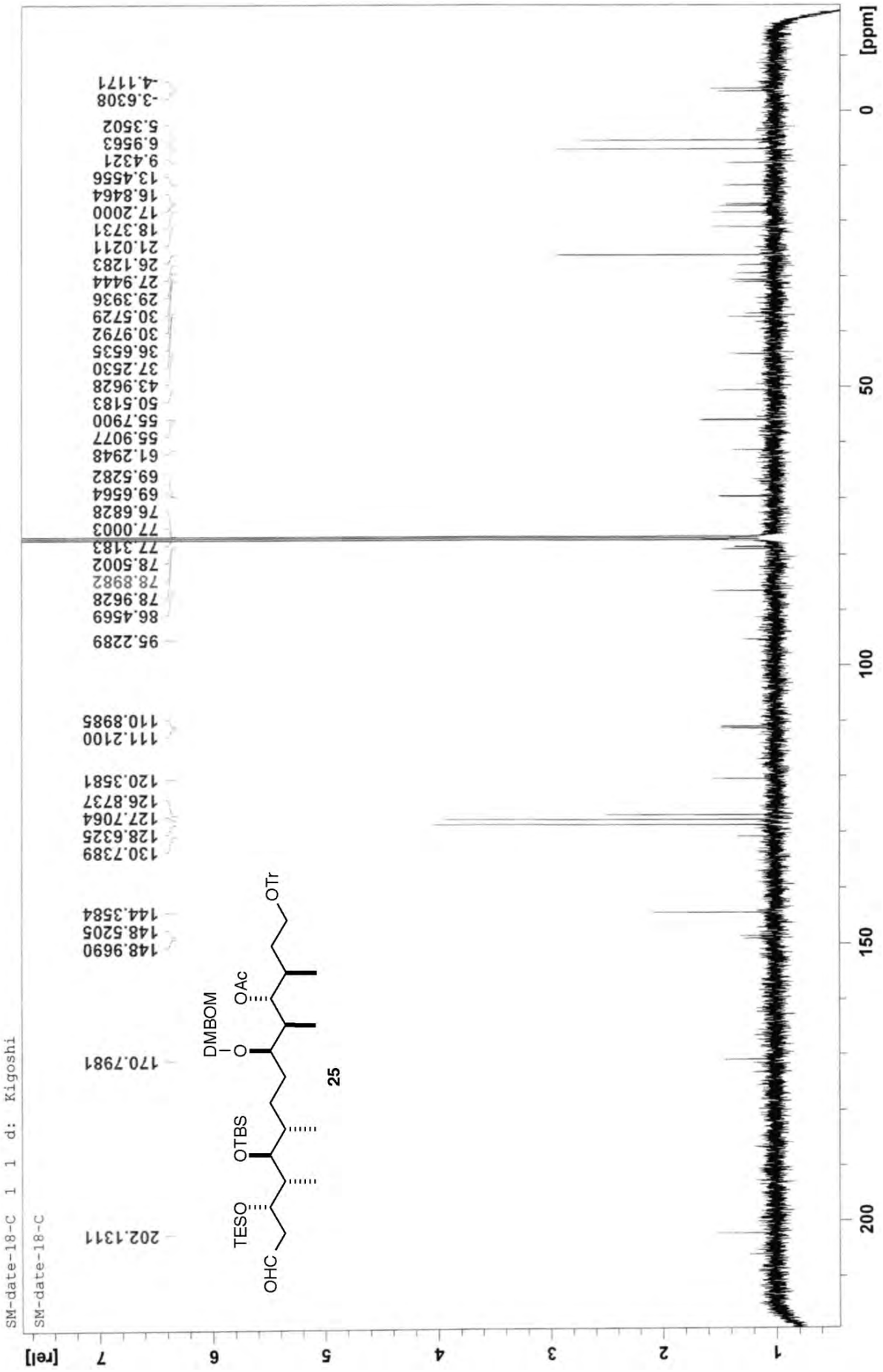
^{1}H NMR spectra of **S16** (400 MHz, $CDCl_3$)



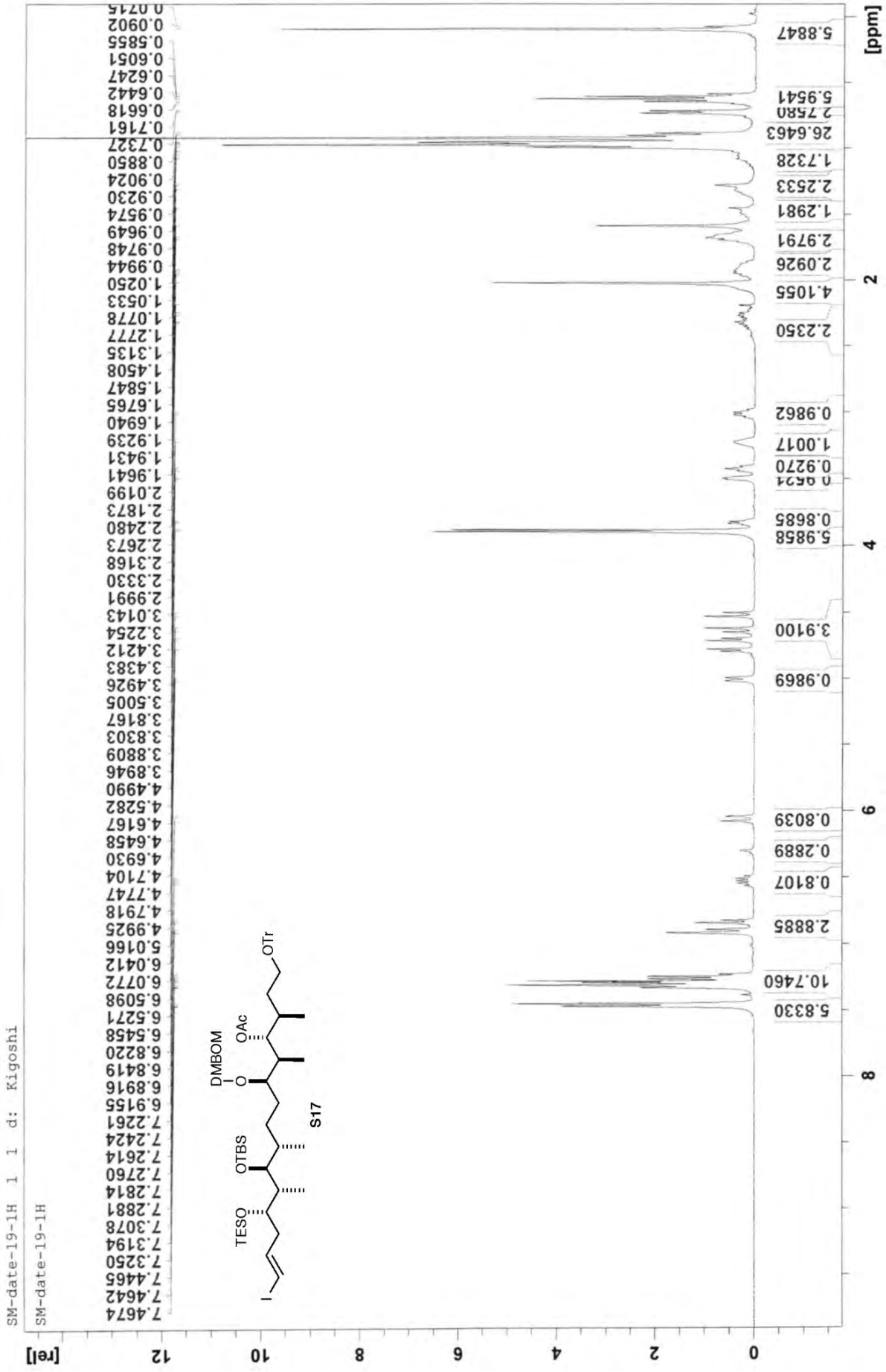
^{13}C NMR spectra of **S16** (100 MHz, $CDCl_3$)



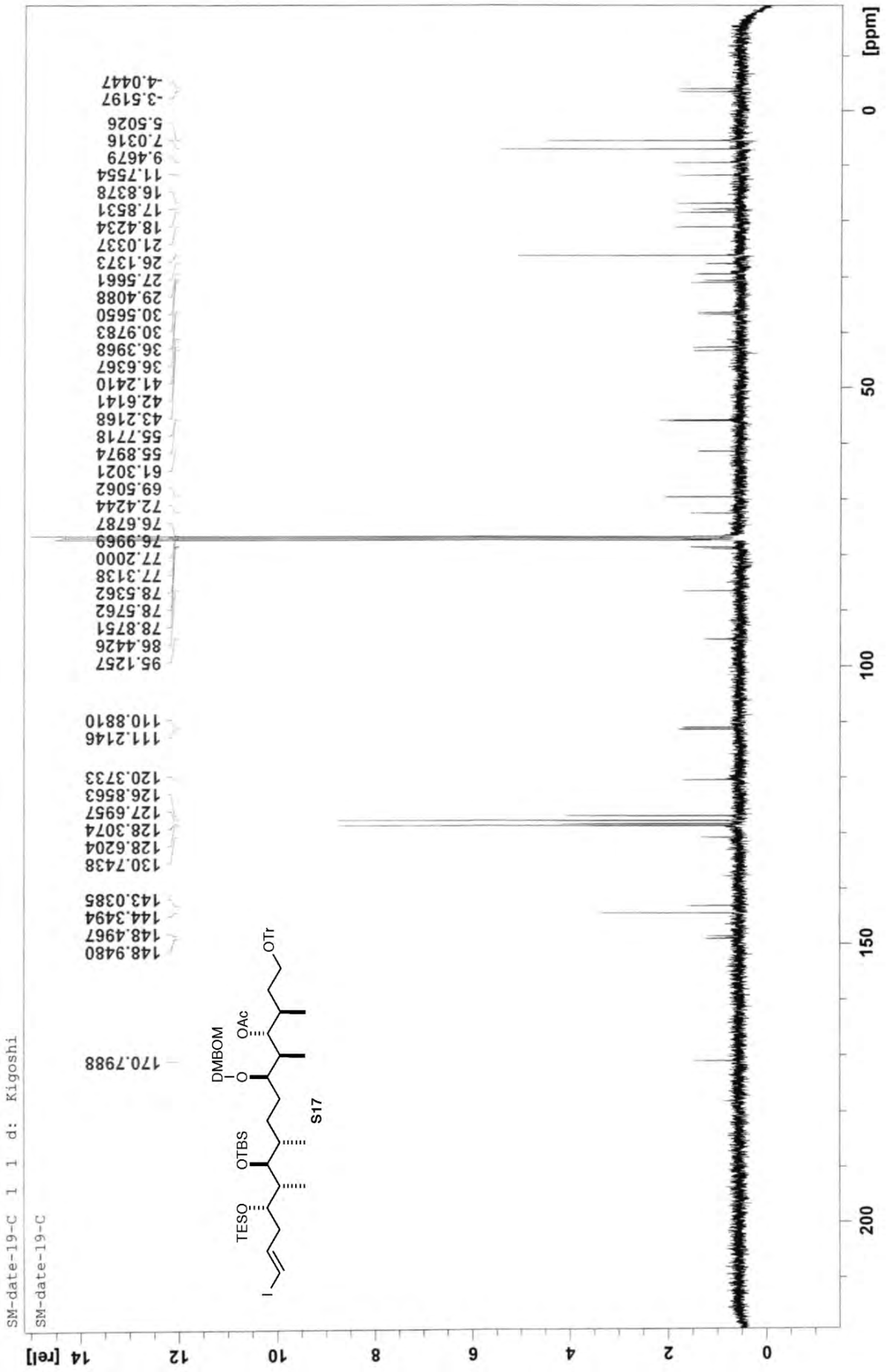
^{1}H NMR spectra of **25** (400 MHz, $CDCl_3$)



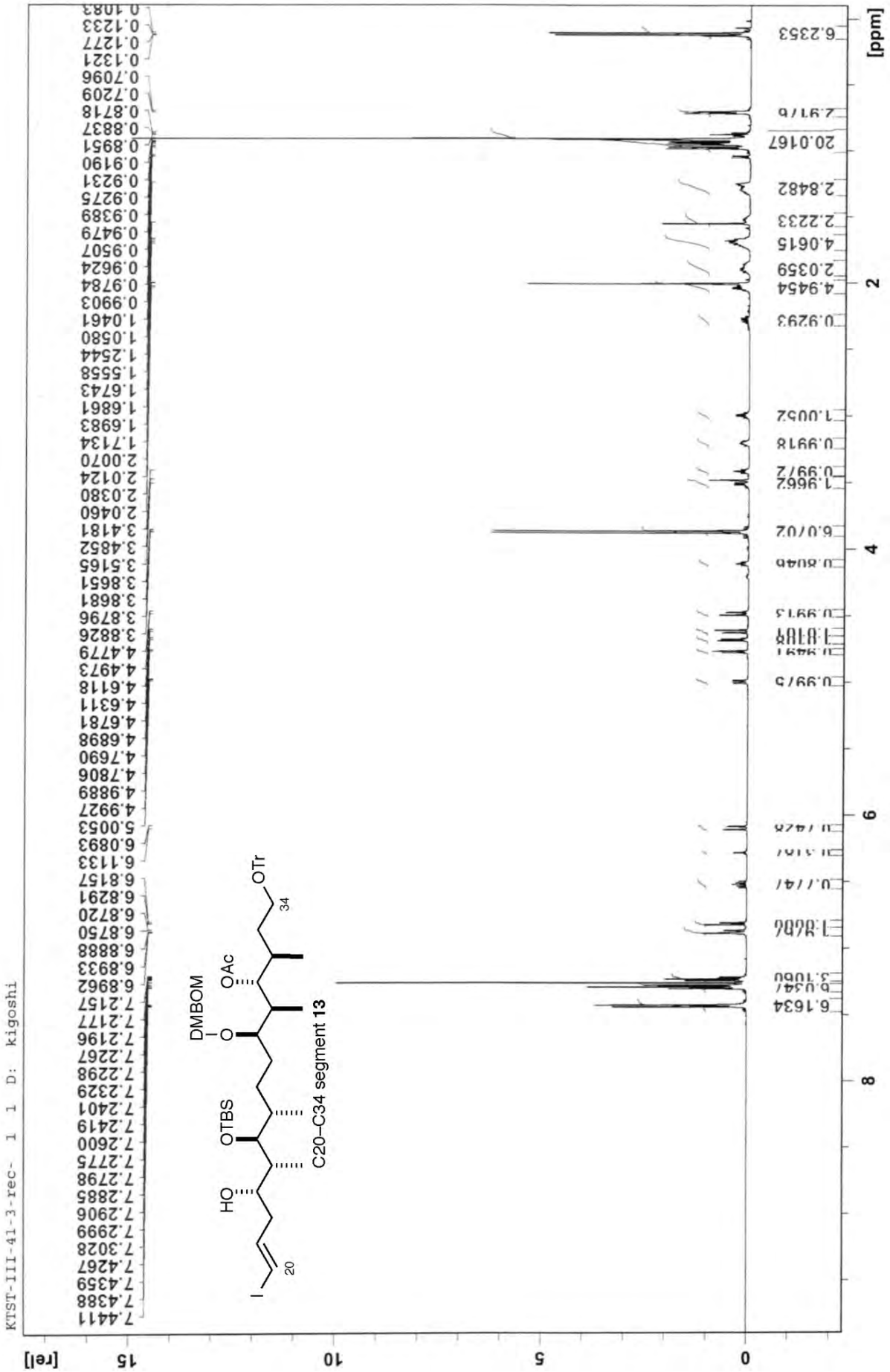
^{13}C NMR spectra of **25** (100 MHz, $CDCl_3$)



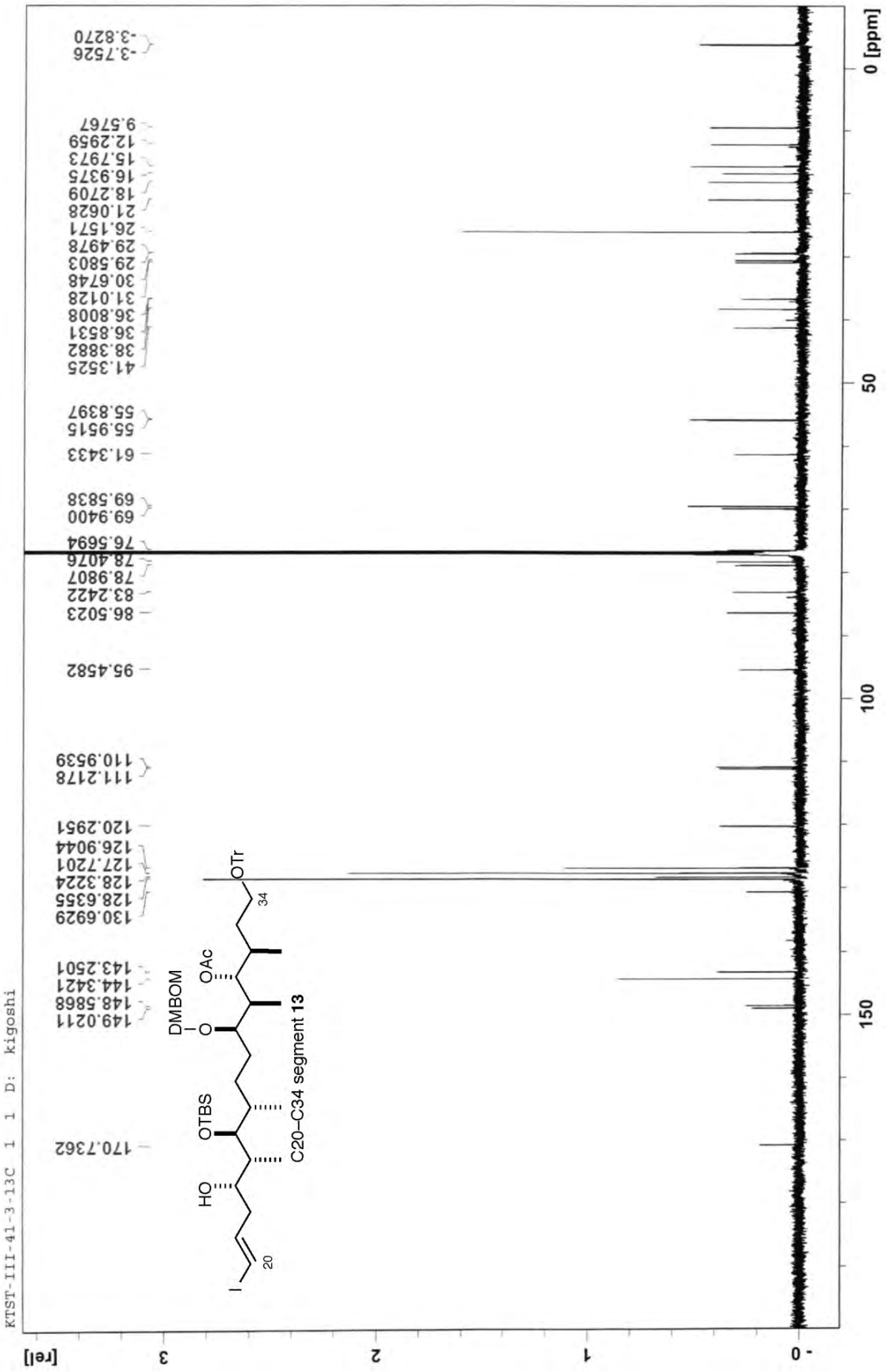
^{1}H NMR spectra of **S17** (400 MHz, $CDCl_3$)



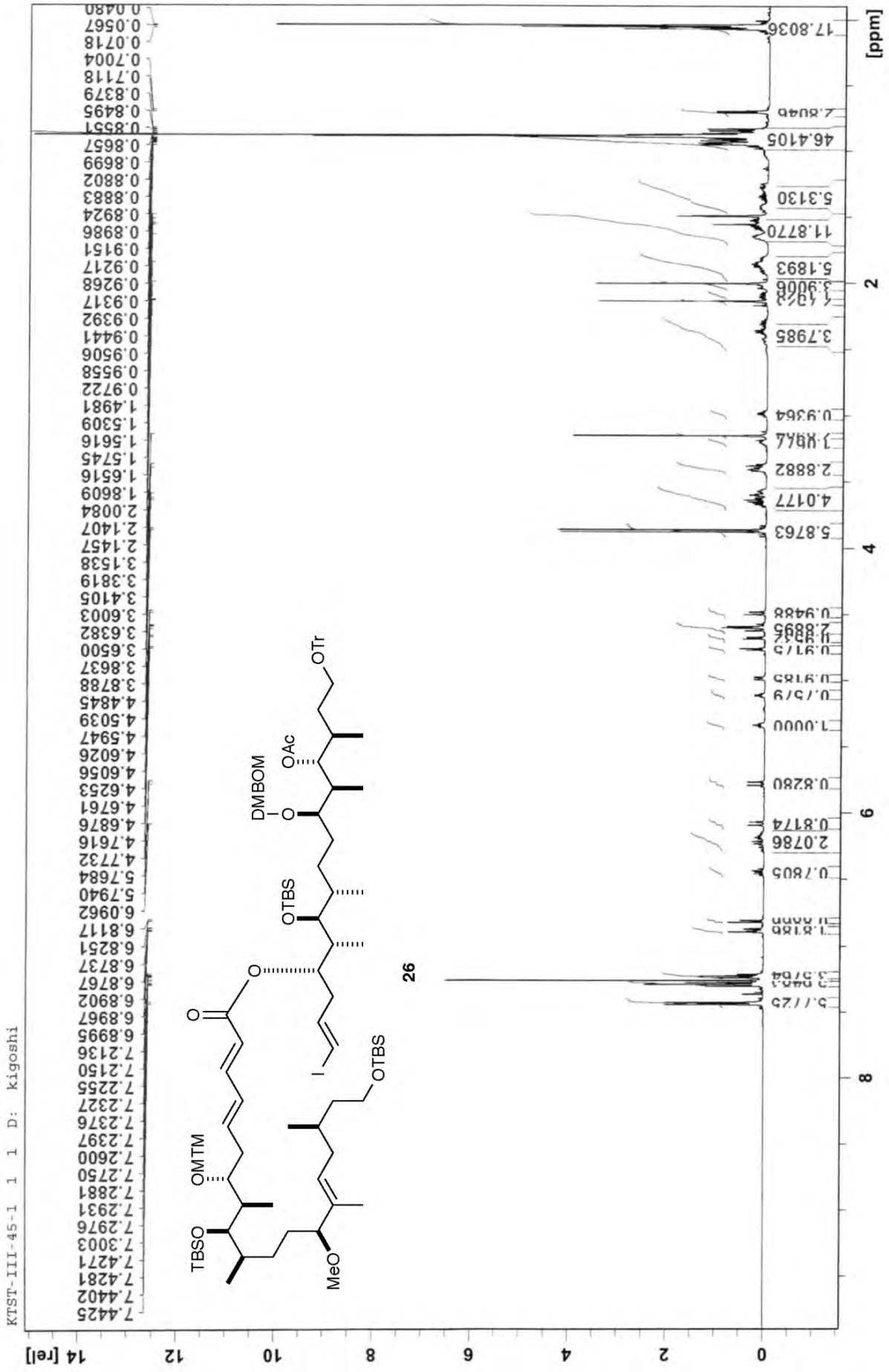
^{13}C NMR spectra of **S17** (100 MHz, $CDCl_3$)



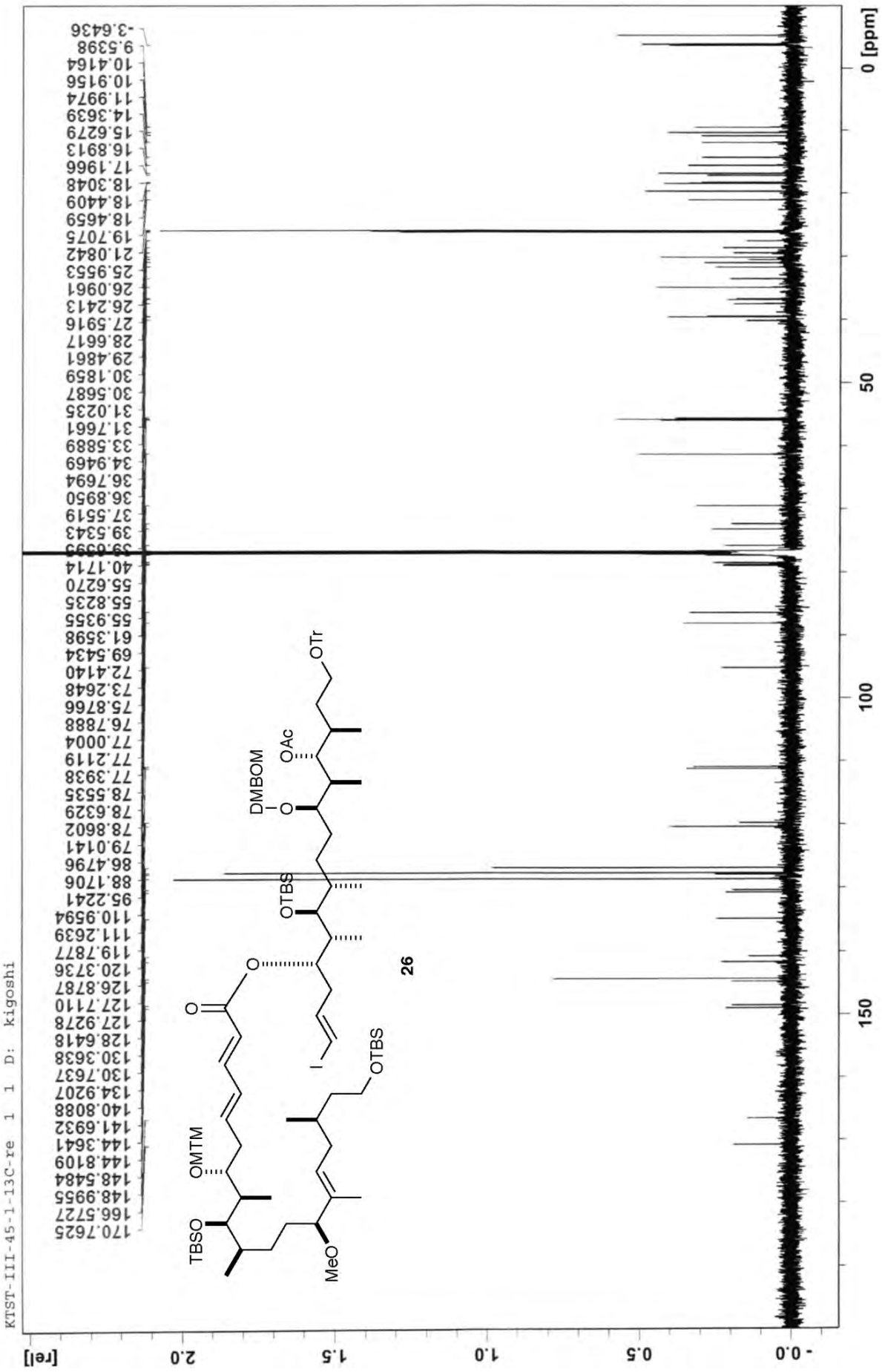
^{1}H NMR spectra of C20–C34 segment **13** (600 MHz, $CDCl_3$)



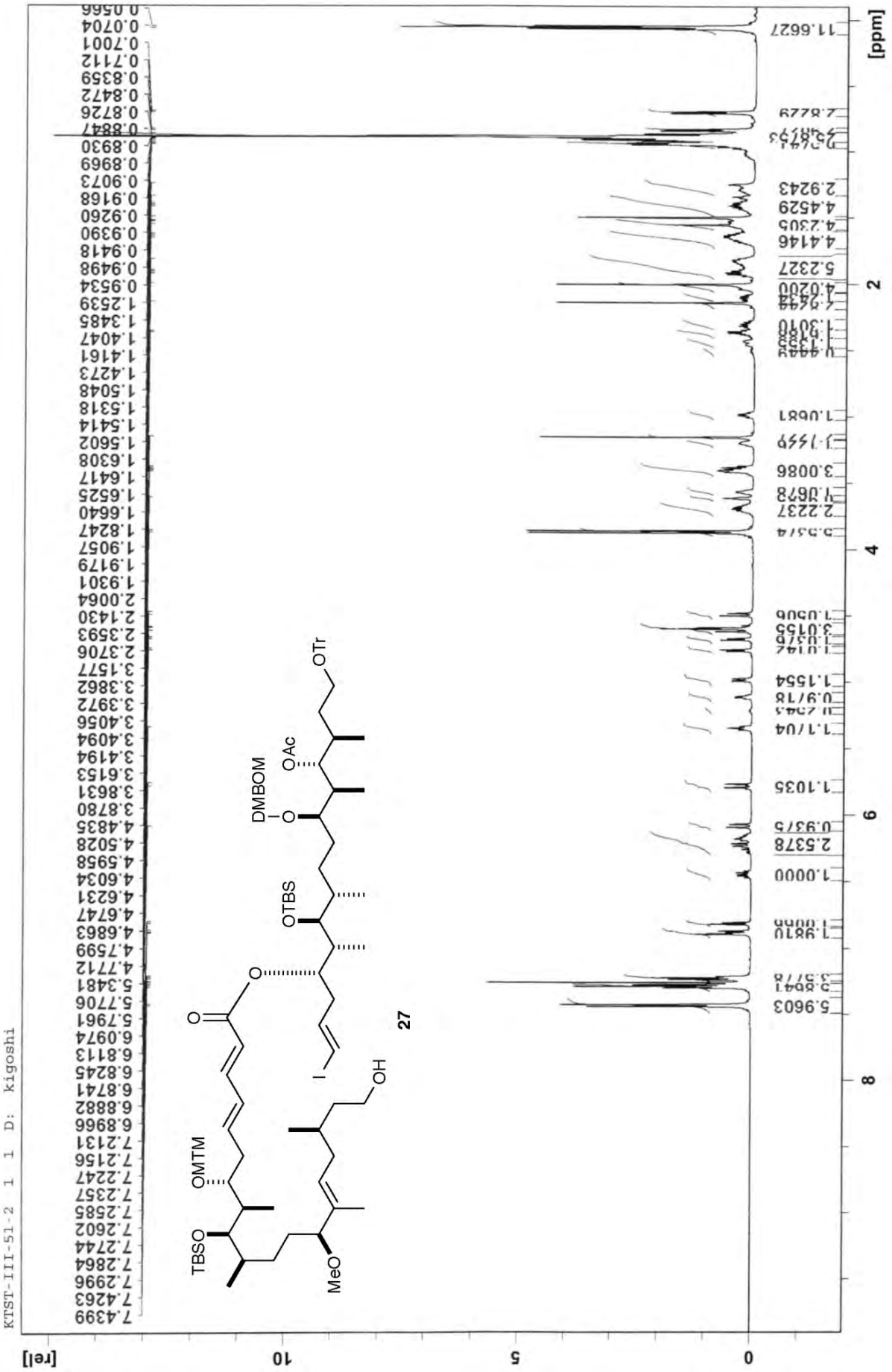
^{13}C NMR spectra of C20–C34 segment **13** (150 MHz, $CDCl_3$)



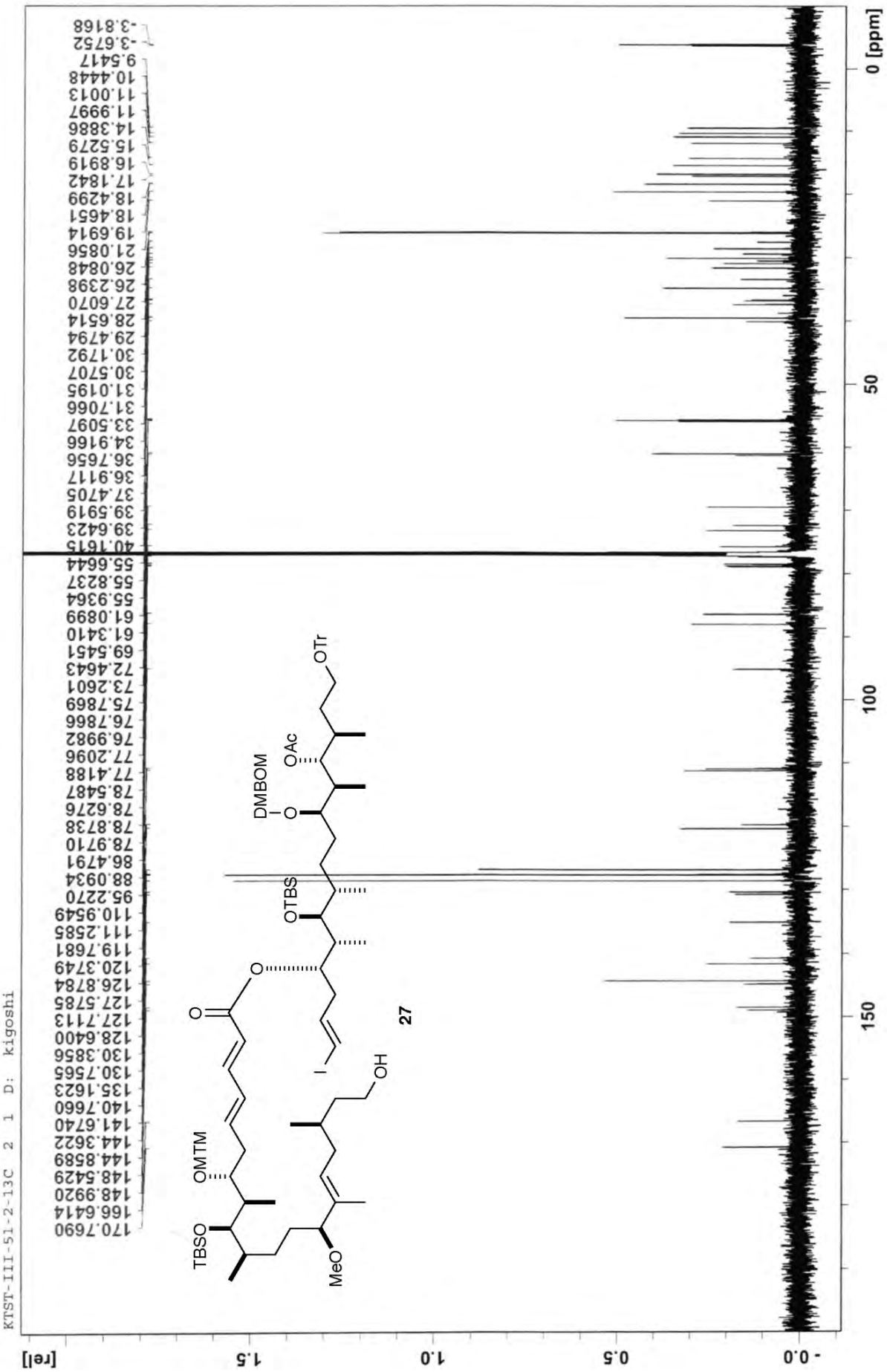
^{1}H NMR spectra of **26** (600 MHz, $CDCl_3$)



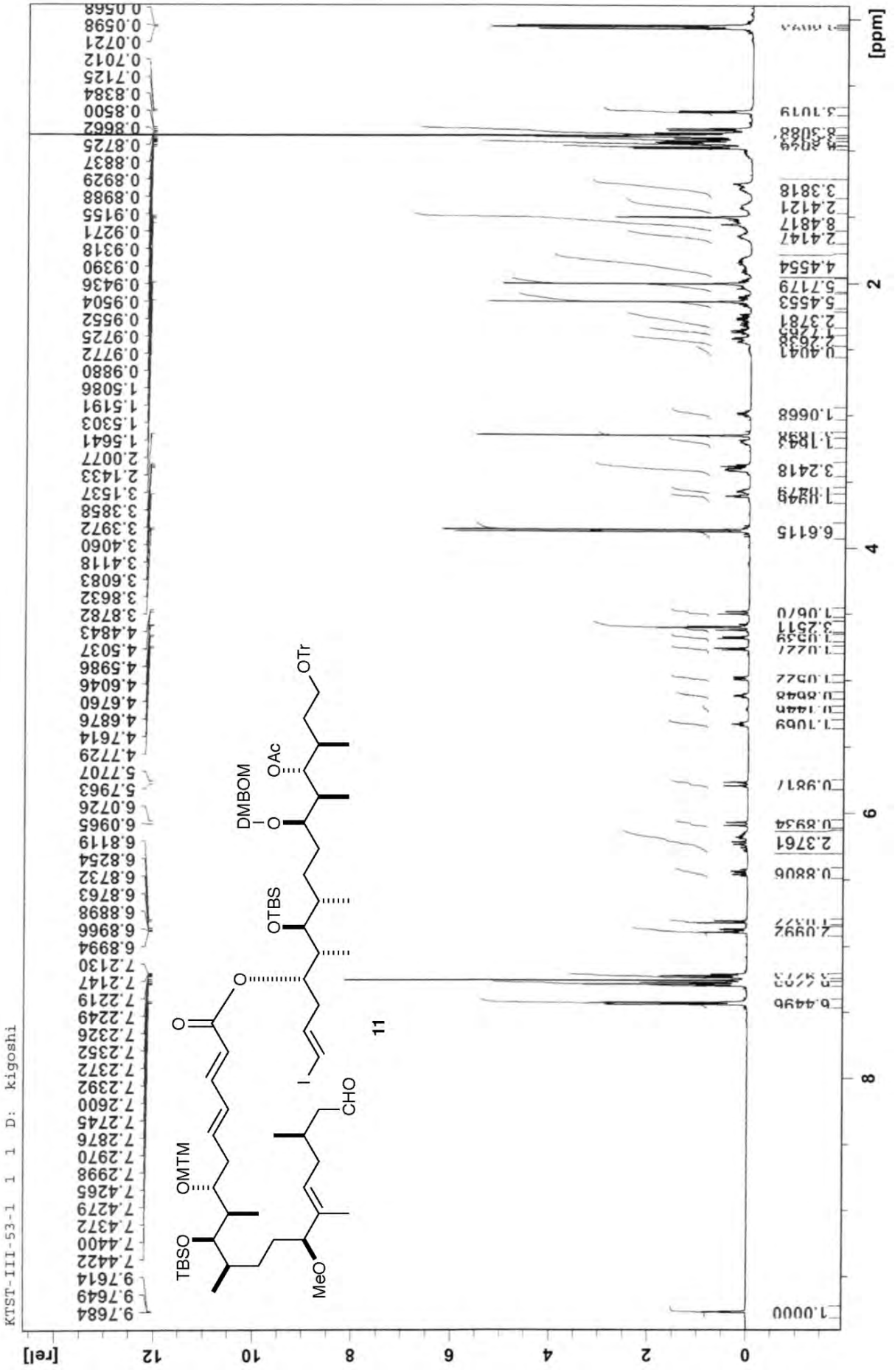
^{13}C NMR spectra of **26** (150 MHz, $CDCl_3$)



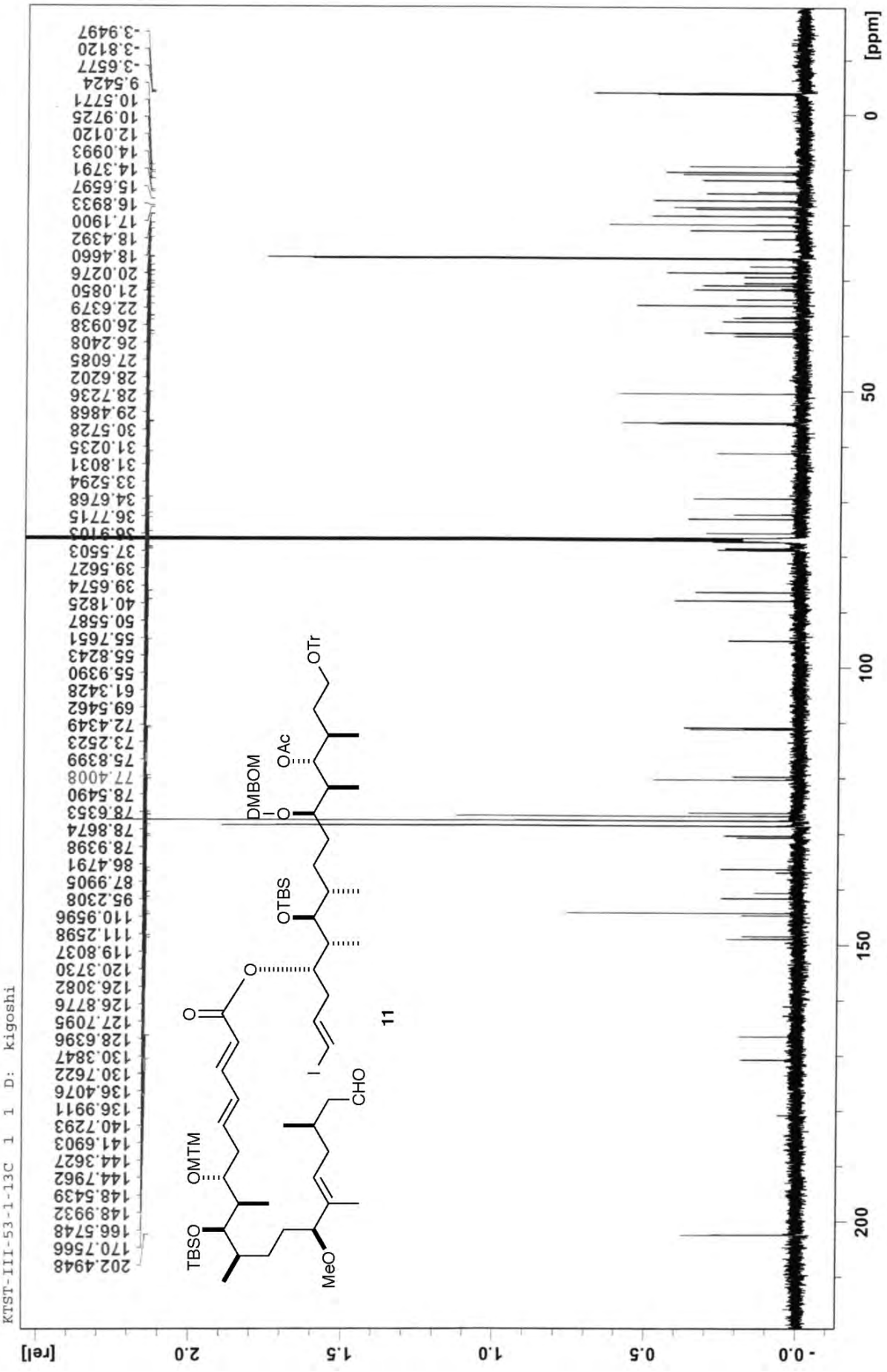
^{1}H NMR spectra of **27** (600 MHz, $CDCl_3$)



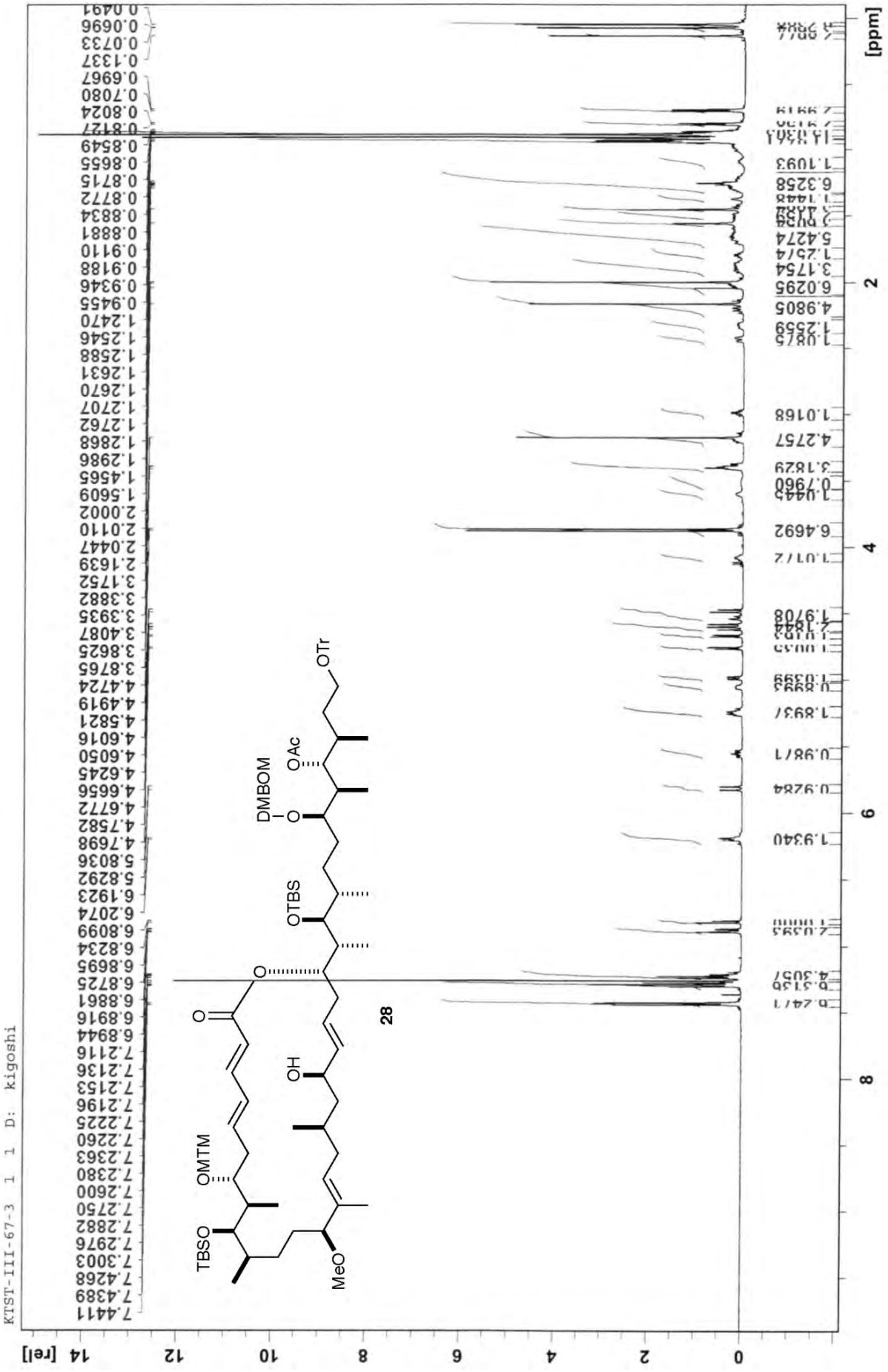
^{13}C NMR spectra of **27** (150 MHz, $CDCl_3$)



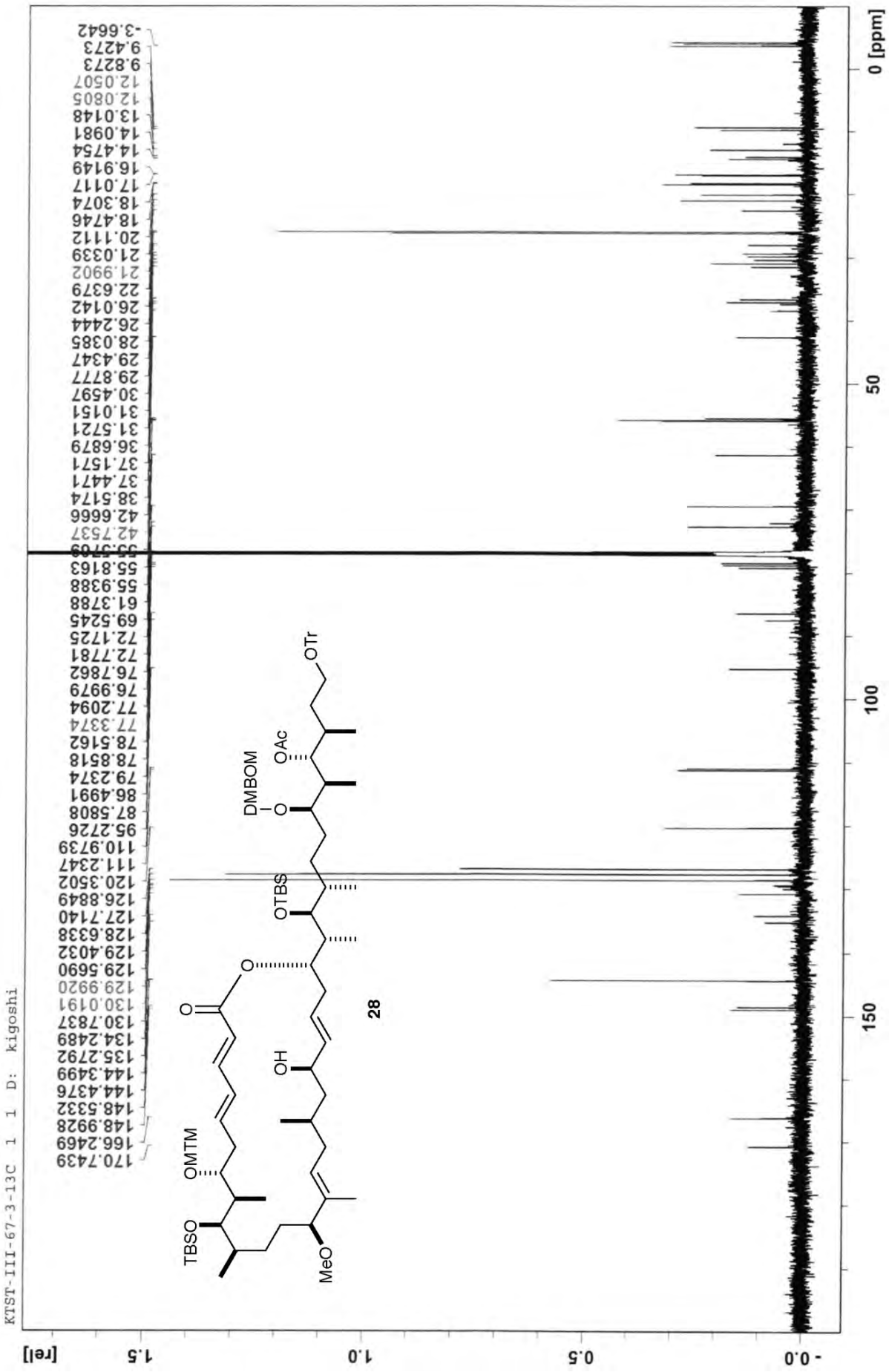
^{1}H NMR spectra of **11** (600 MHz, $CDCl_3$)



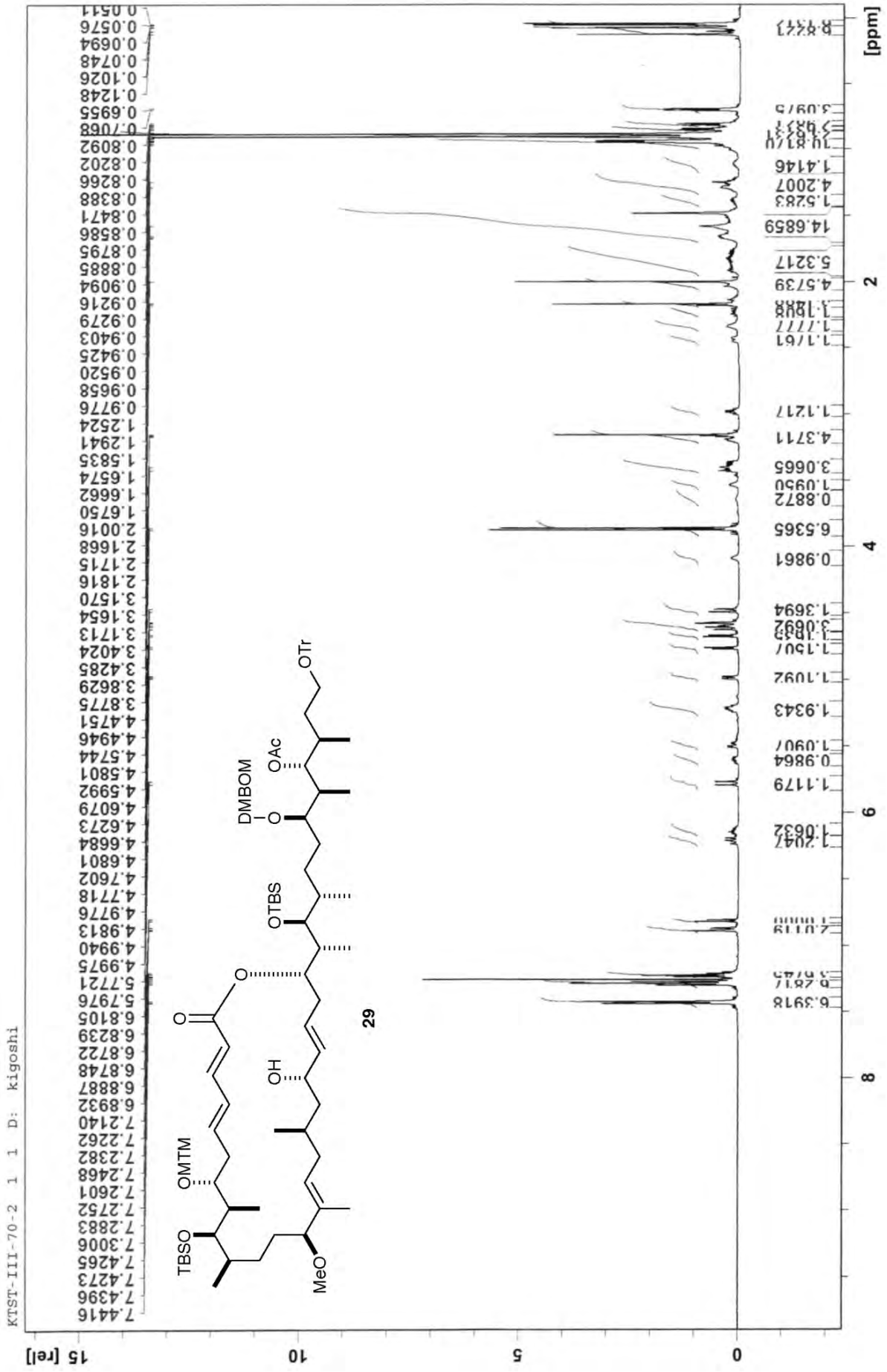
^{13}C NMR spectra of **11** (150 MHz, $CDCl_3$)



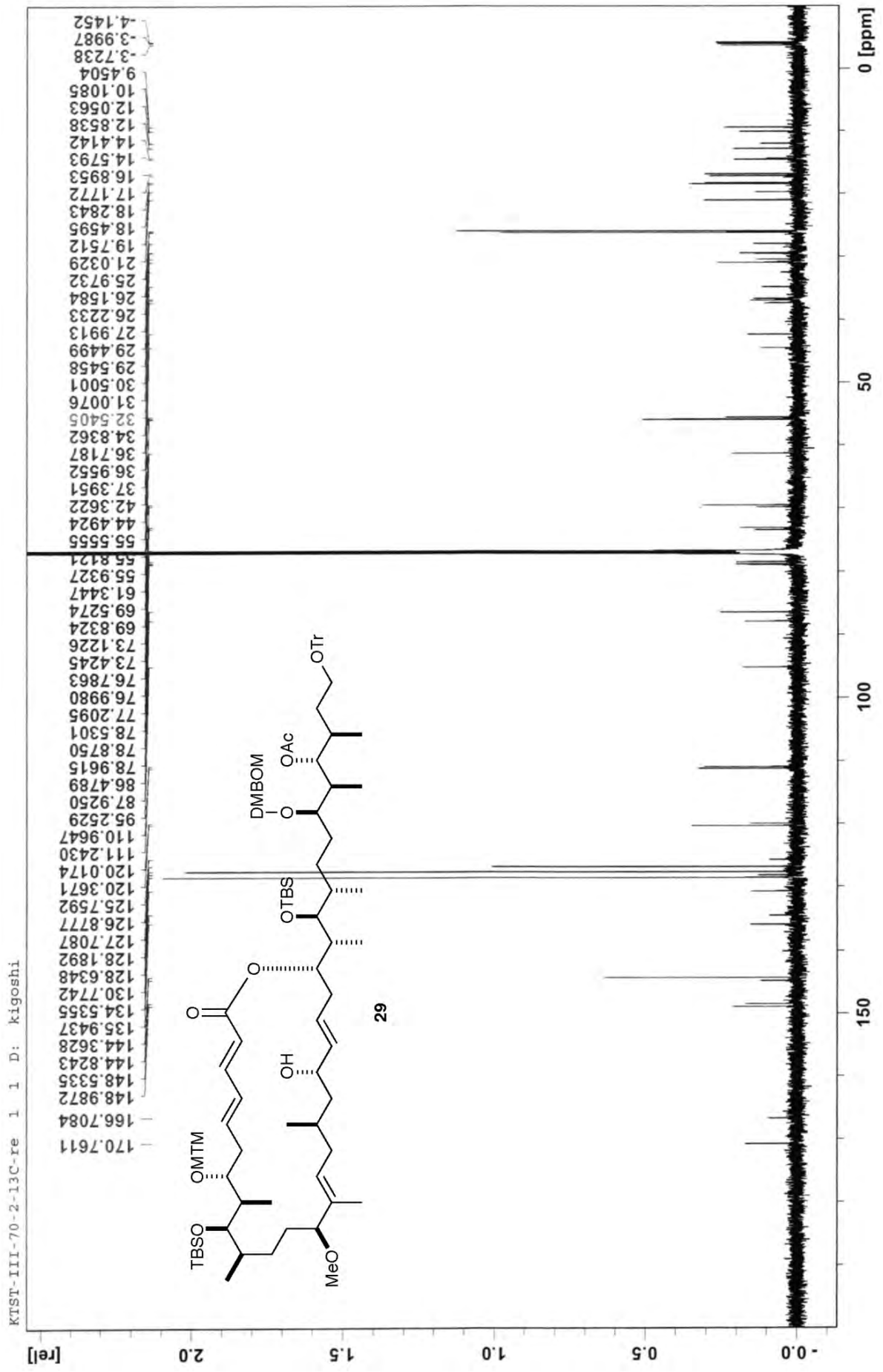
^{1}H NMR spectra of **28** (600 MHz, $CDCl_3$)



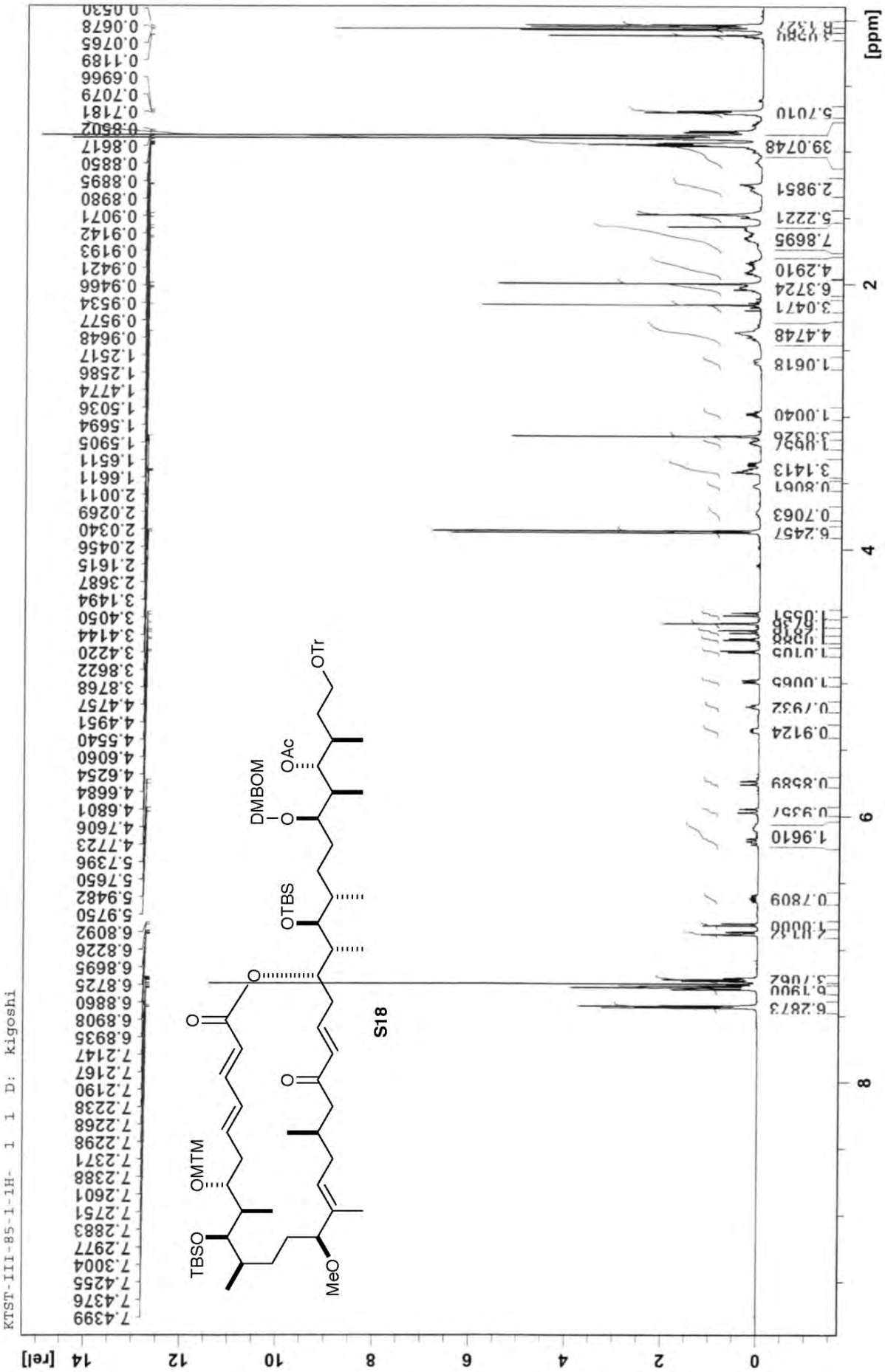
^{13}C NMR spectra of **28** (150 MHz, $CDCl_3$)



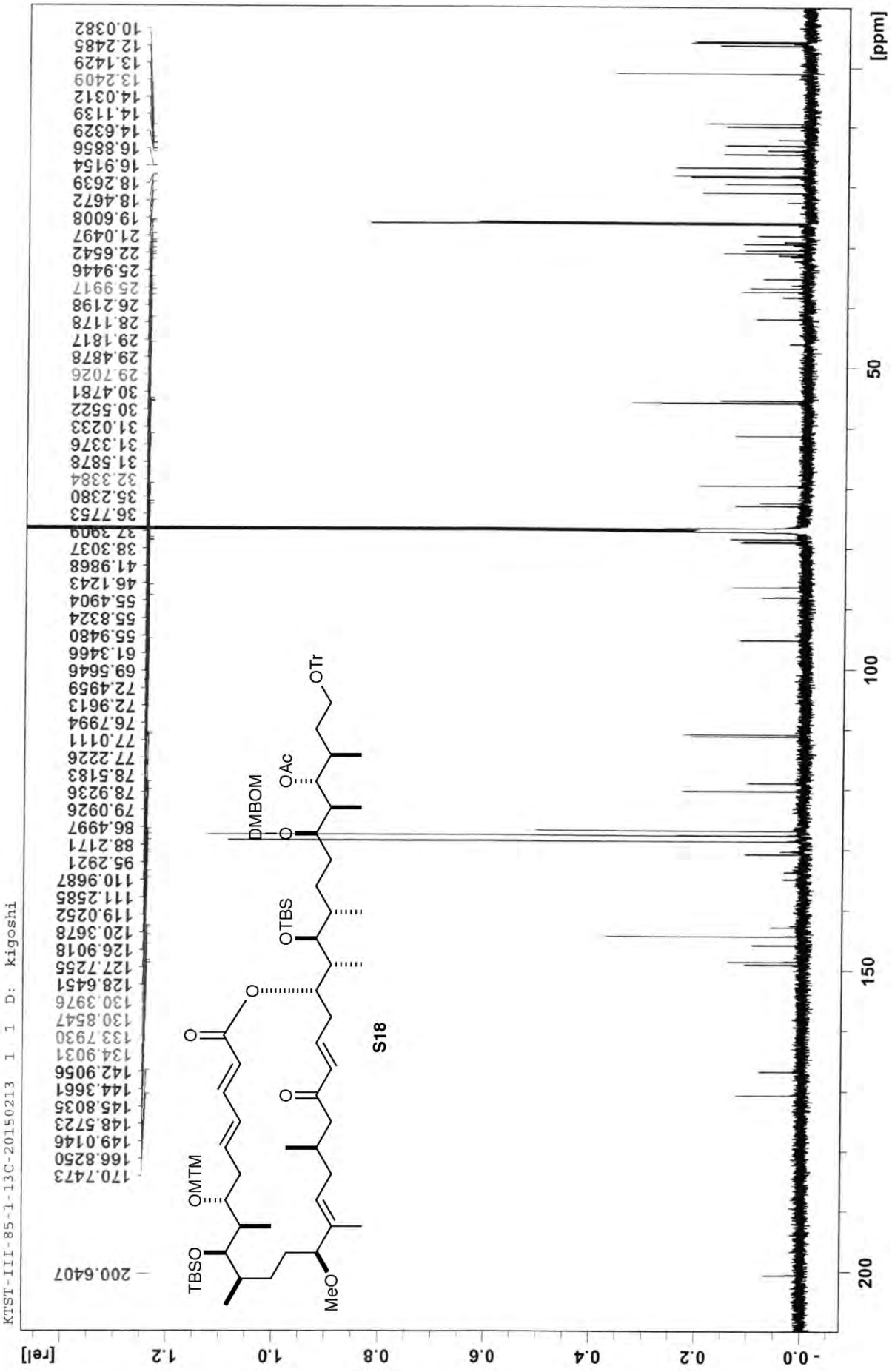
^{1}H NMR spectra of **29** (600 MHz, $CDCl_3$)



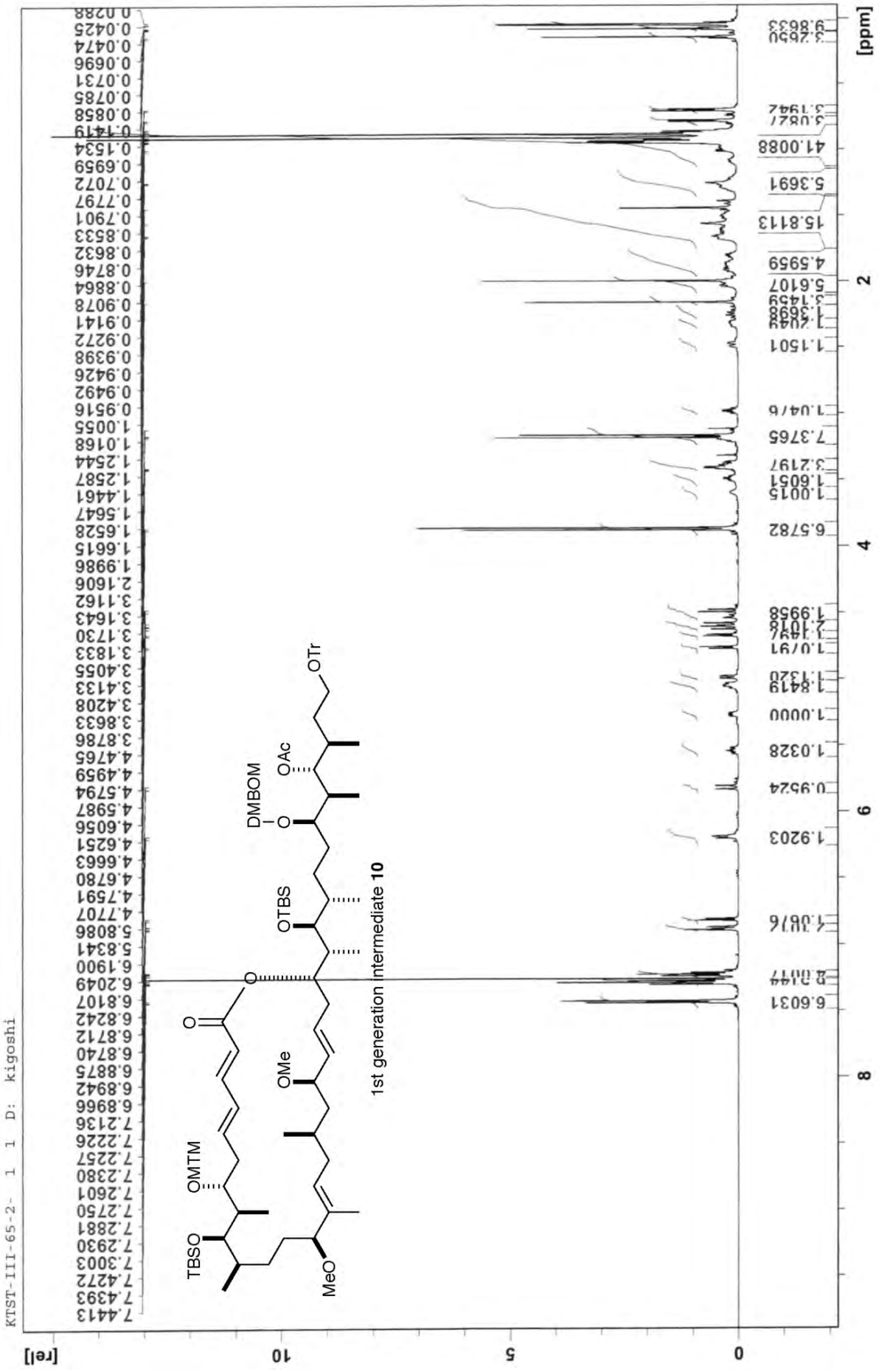
^{13}C NMR spectra of **29** (150 MHz, $CDCl_3$)



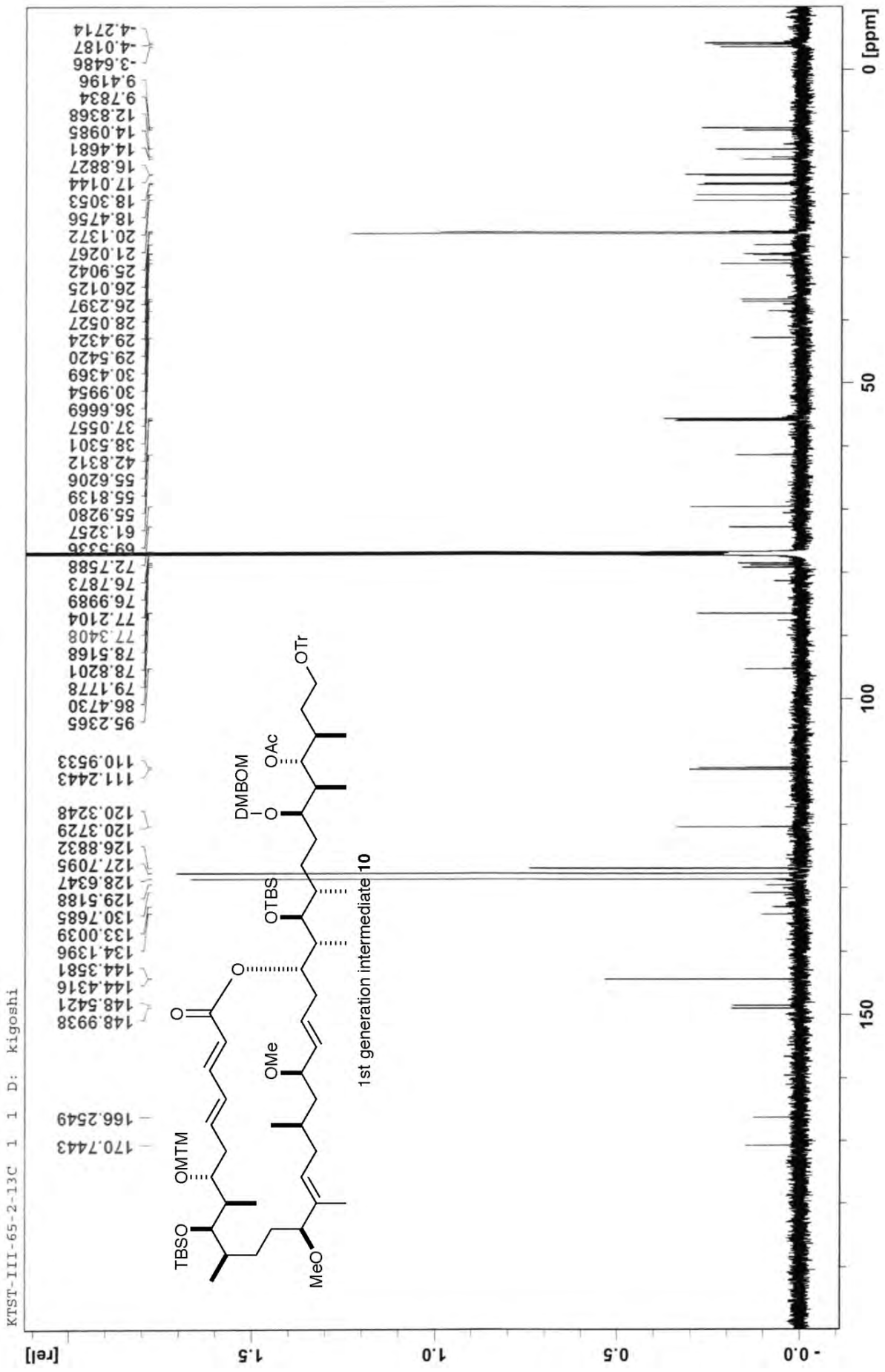
^{1}H NMR spectra of **S18** (600 MHz, $CDCl_3$)



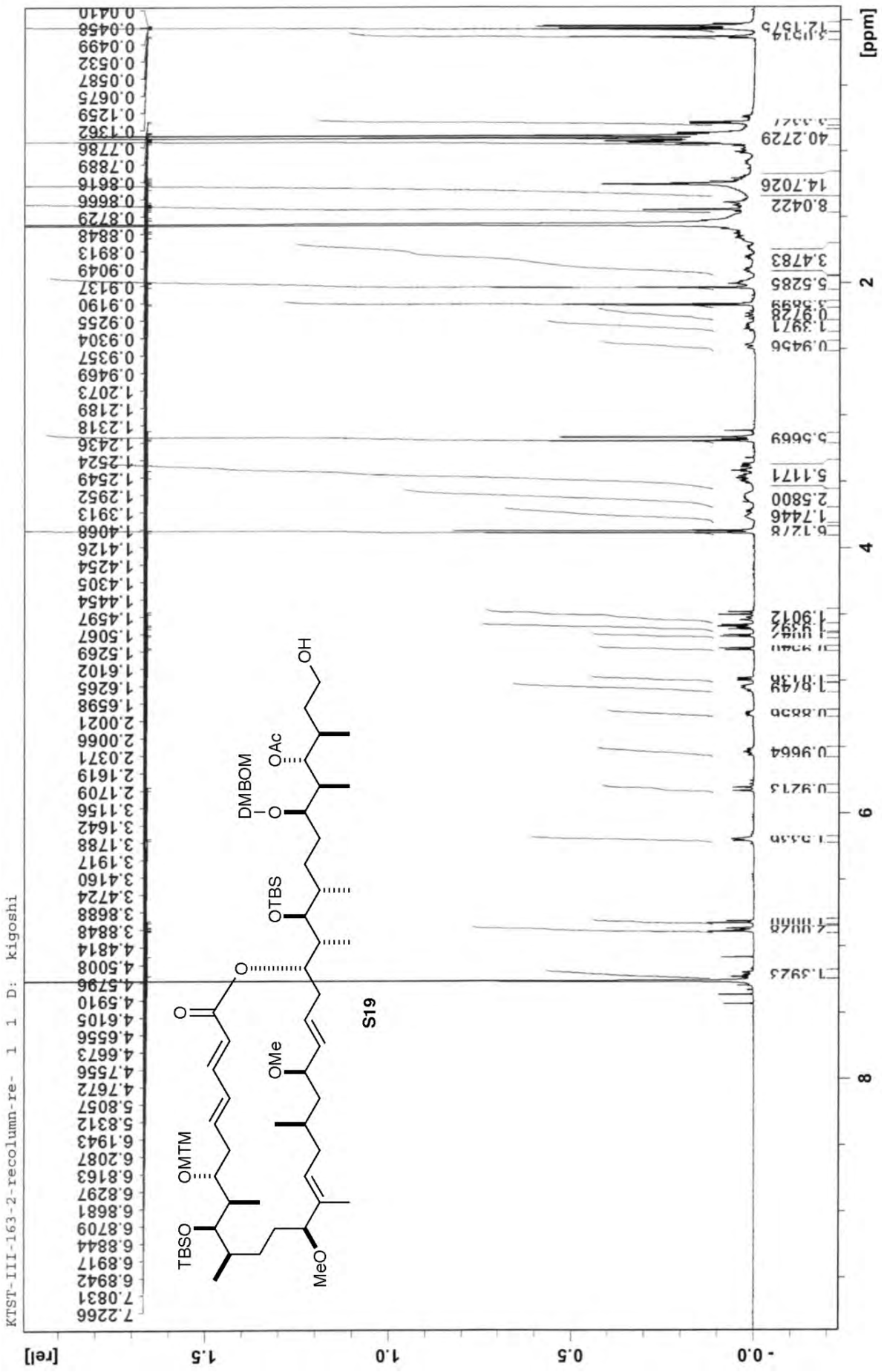
^{13}C NMR spectra of **S18** (150 MHz, $CDCl_3$)



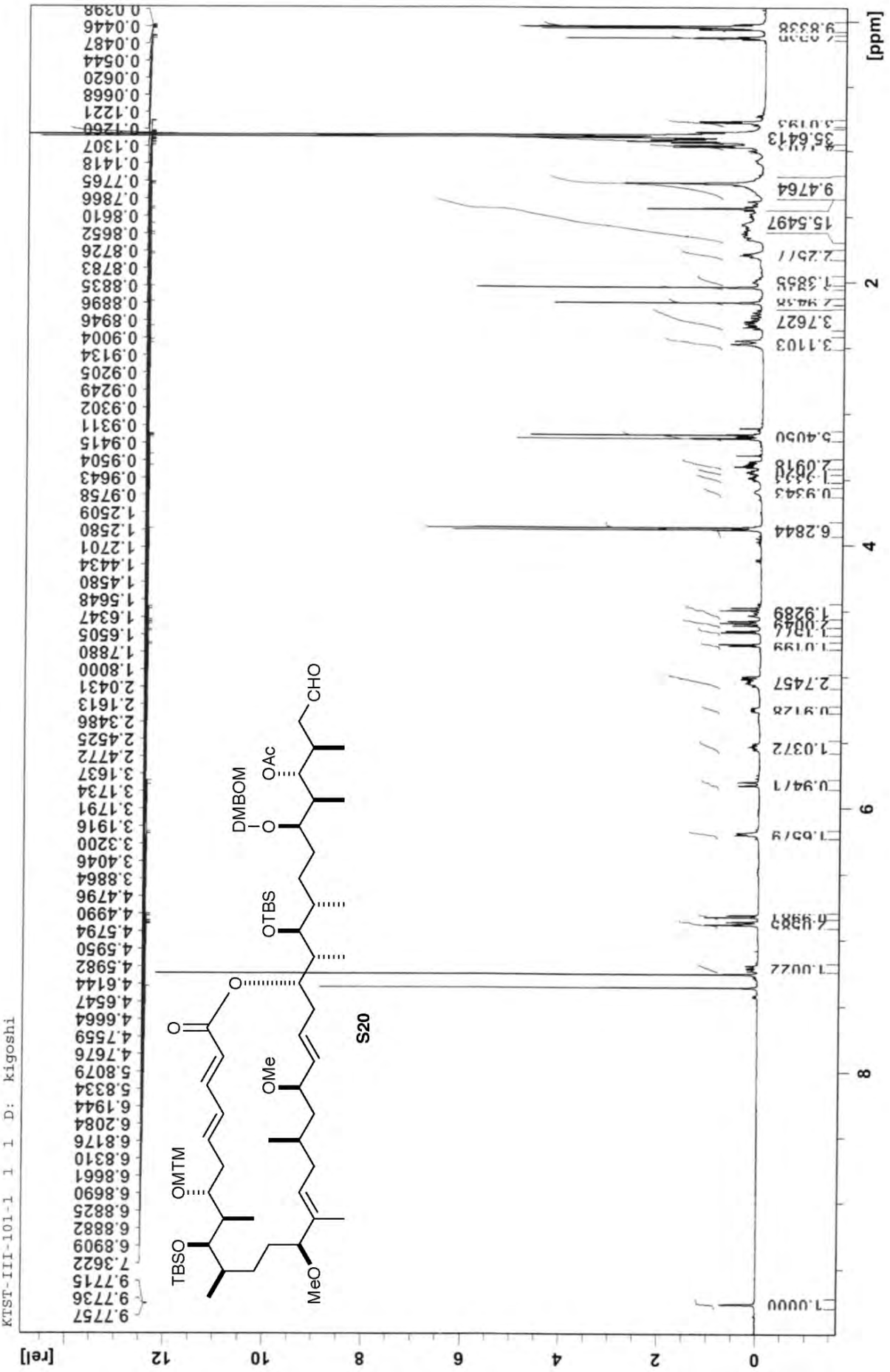
^{1}H NMR spectra of 1st generation intermediate **10** (600 MHz, $CDCl_3$)



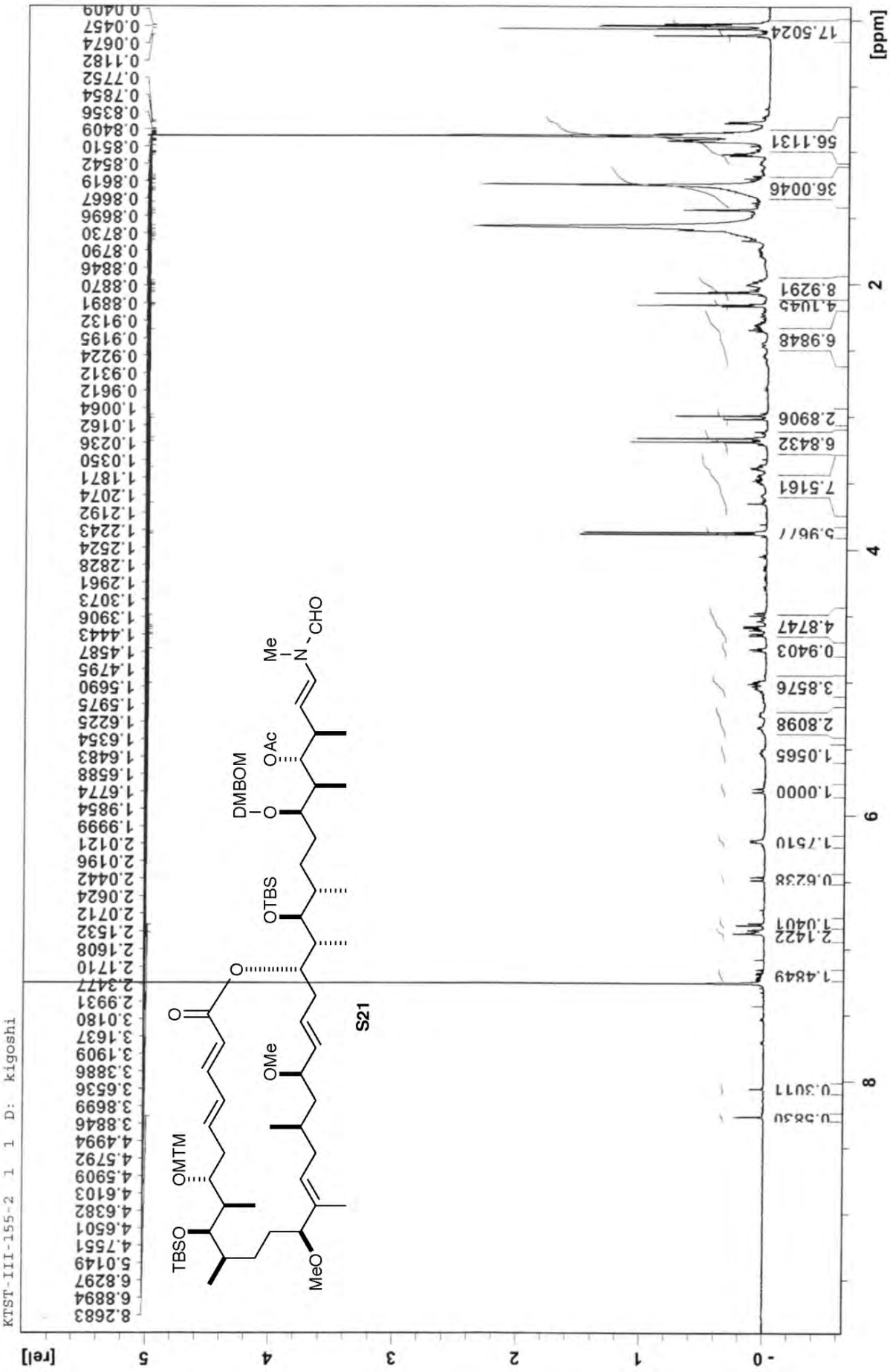
^{13}C NMR spectra of 1st generation intermediate **10** (150 MHz, $CDCl_3$)



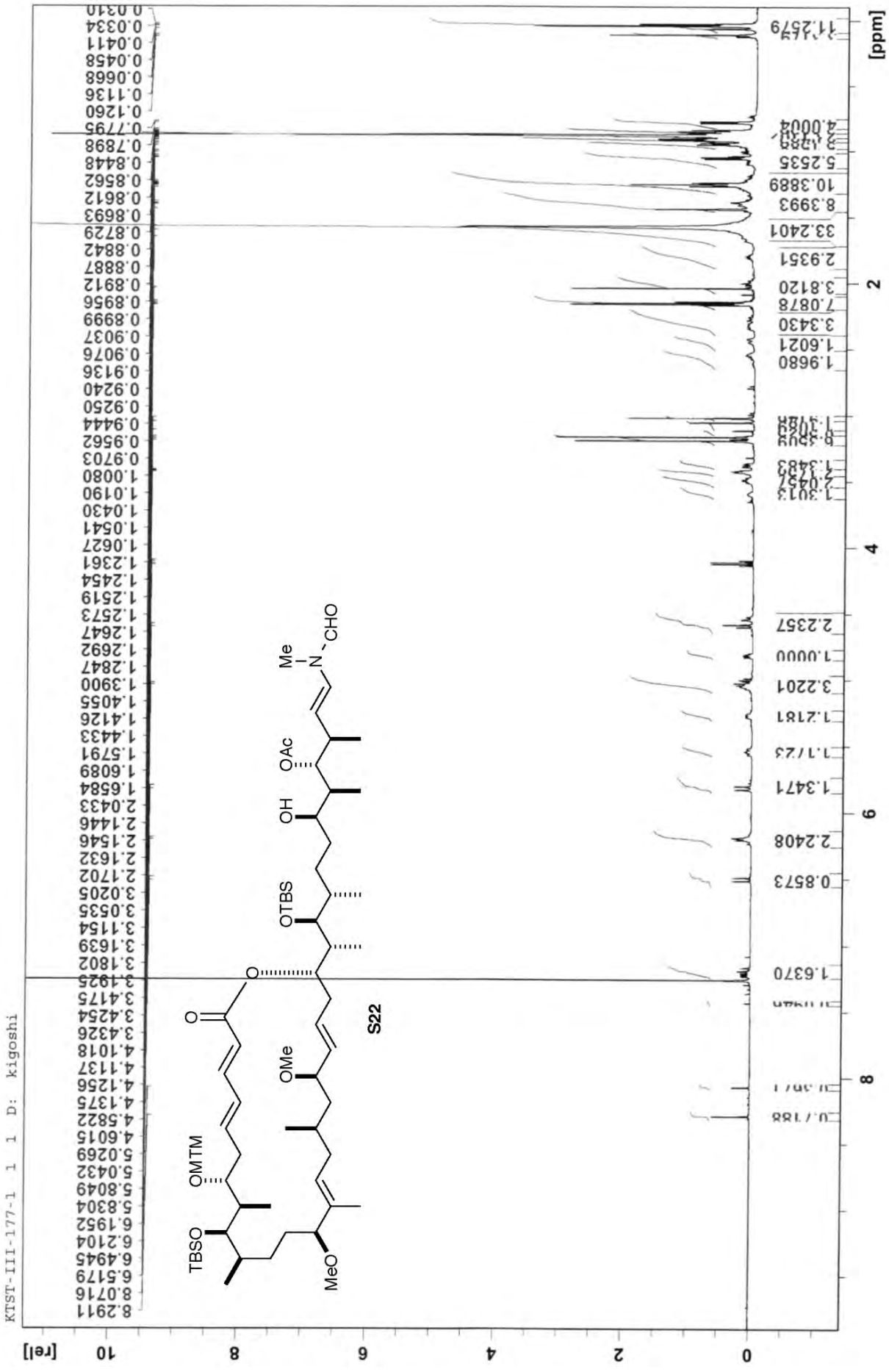
^{1}H NMR spectra of **S19** (600 MHz, $CDCl_3$)



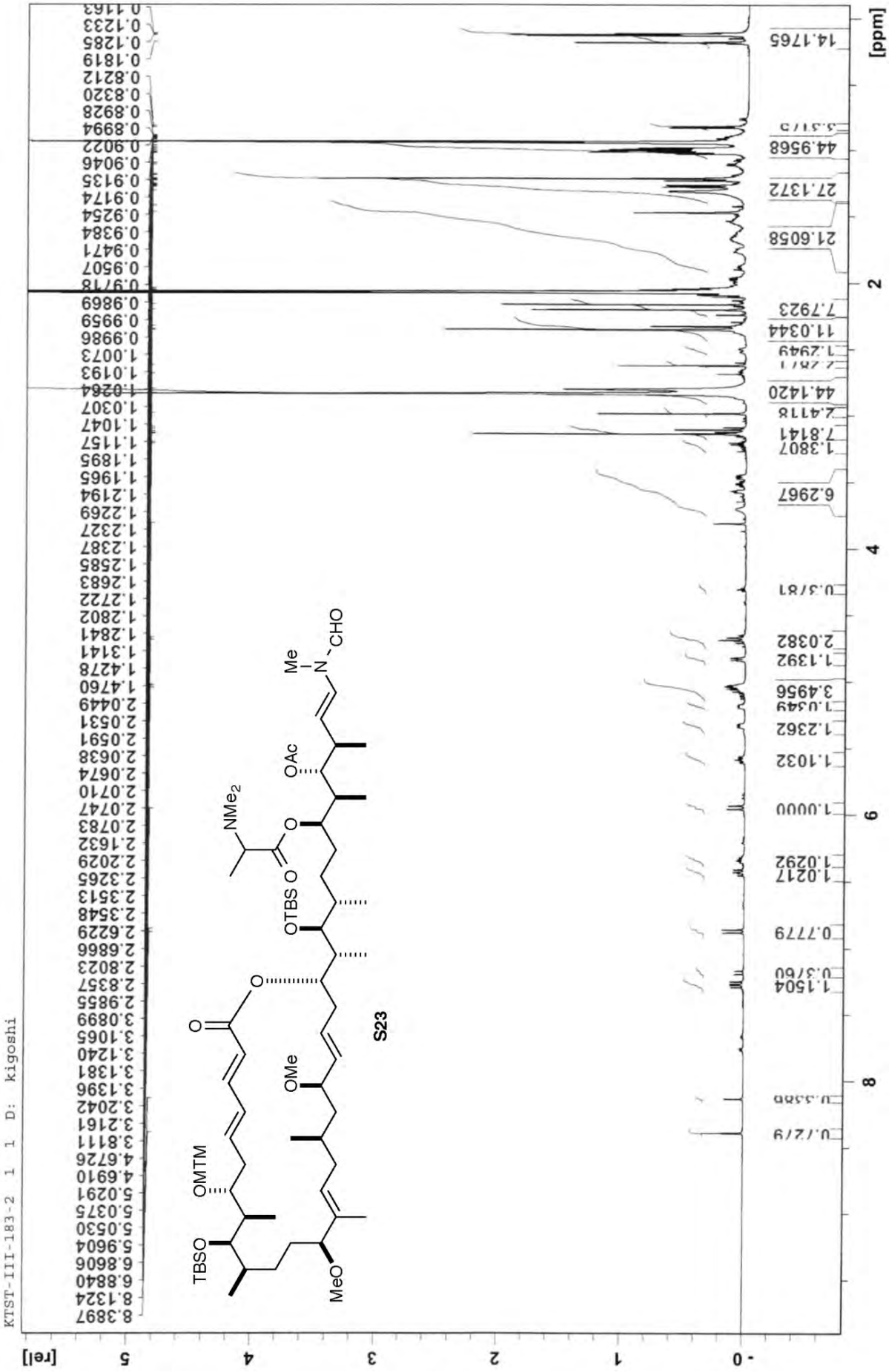
^{1}H NMR spectra of **S20** (600 MHz, $CDCl_3$)



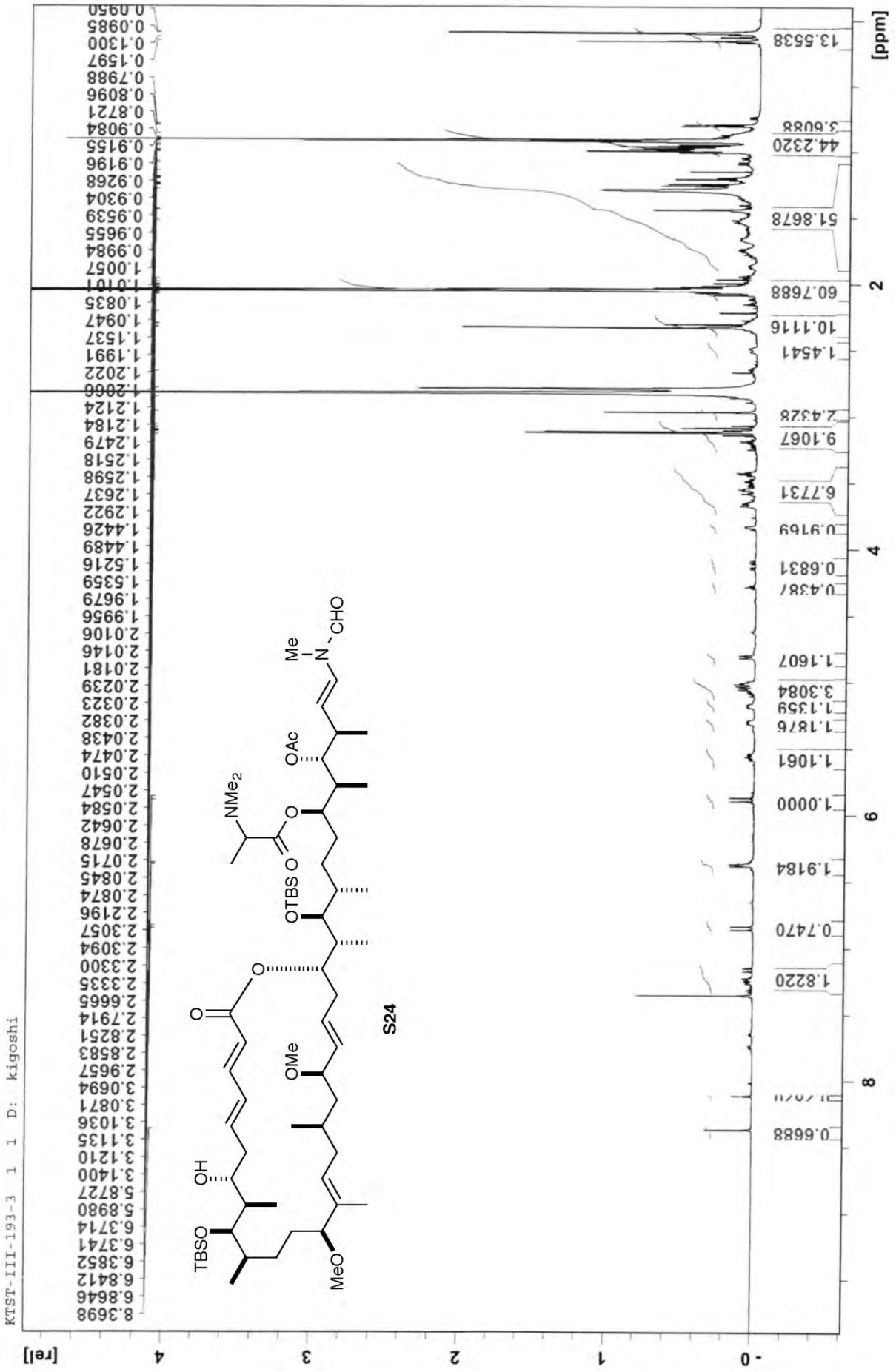
^{1}H NMR spectra of **S21** (600 MHz, $CDCl_3$)



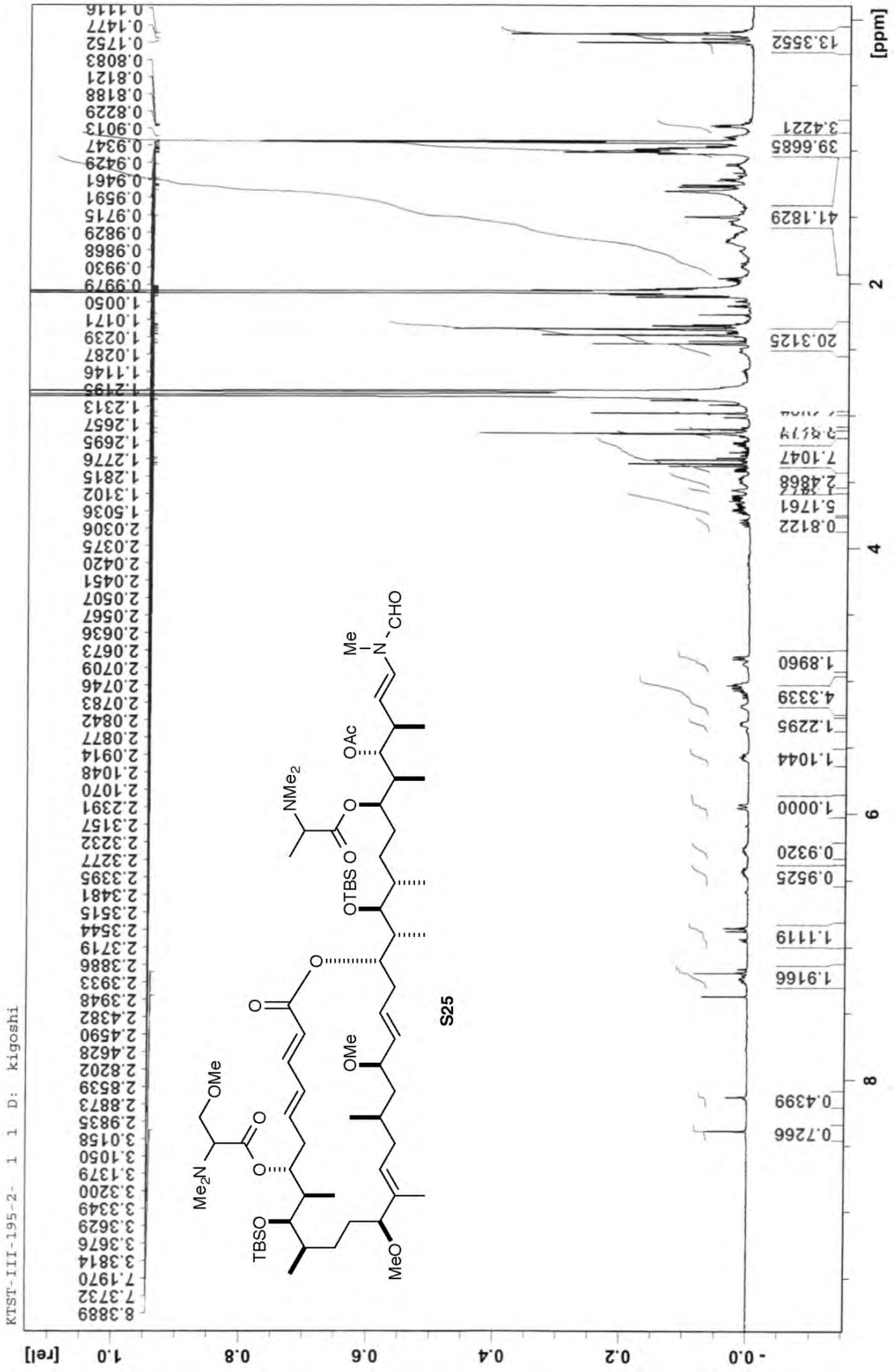
^{1}H NMR spectra of **S22** (600 MHz, $CDCl_3$)



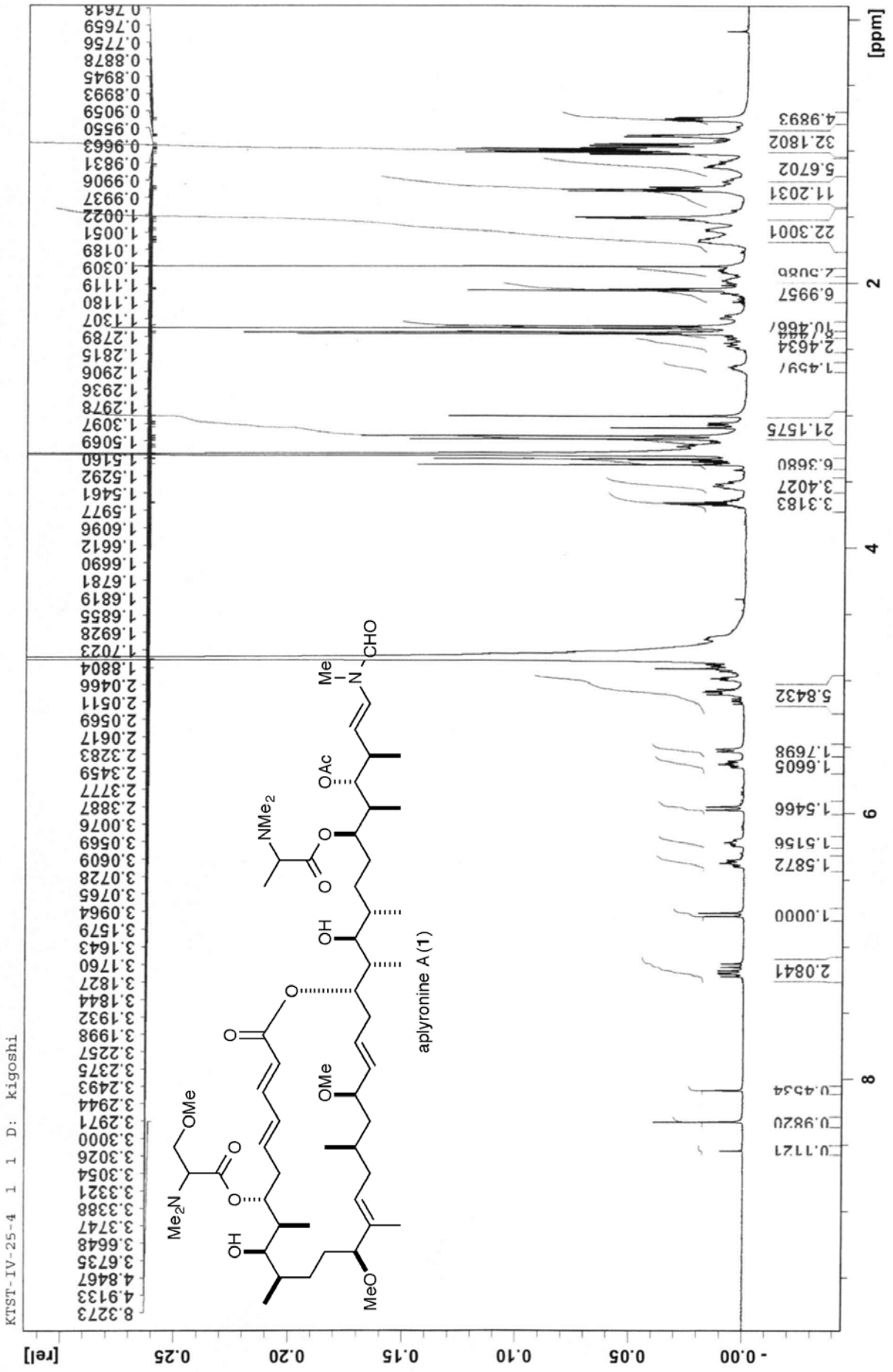
^{1}H NMR spectra of **S23** (600 MHz, acetone-d_6)



^{1}H NMR spectra of **S24** (600 MHz, acetone-d_6)



^{1}H NMR spectra of **S25** (600 MHz, acetone-d_6)



^{1}H NMR spectra of aplyronine A (**1**) (600 MHz, CD_3OD)