Electronic Supplementary Information

Total synthesis of cynaropicrin

Tenma Nakamura, Dinda B. Pitna, Kogaku Kimura, Yukiko Yoshimoto, Tomoya Uchiyama, Takaya Mori, Ryosuke Kondo, Shihori Hara, Yuki Egoshi, Shoya Yamaguchi, Noriyuki Suzuki, Yumiko Suzuki, and Toyonobu Usuki*

Department of Materials and Life Sciences, Faculty of Science and Technology, Sophia University, 7-1 Kioicho, Chiyoda-ku, Tokyo 102-8554, Japan

E-mail: t-usuki@sophia.ac.jp

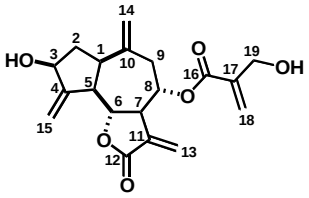
Table of Contents

General:

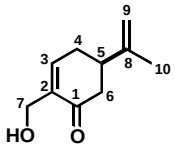
All non-aqueous reactions were conducted under an atmosphere of nitrogen with magnetic stirring unless otherwise indicated. Dichloromethane (CH_2Cl_2), methanol (MeOH), tetrahydrofuran (THF), ethanol (EtOH), and toluene were purchased from commercial suppliers and stored over activated molecular sieves. All reagents were obtained from commercial suppliers and used without further purification unless otherwise stated. Dess-Martin Periodinane (DMP) and pyridinium *p*-toluenesulfonate (PPTS) was prepared according to literature procedure. For the photo oxygenation reaction, a Shimadzu AT-100HG halogen lamp was used. Analytical thin layer chromatography (TLC) was performed on Silica gel 60 F_{254} plates produced by Merck. Column chromatography was performed with acidic Silica gel 60 (spherical, 40-50 μm) or neutral Silica gel 60N (spherical, 40-50 μm) produced by Kanto Chemicals (Tokyo, Japan). Removal of small amount of solvent was performed by Smart Evaporator CEV1-SQ-P2, CEVI-SK-P2, CEV1A-GR-P2 (Biochromato, Kanagawa, Japan).

Optical rotations were measured on a JASCO P-2200 digital polarimeter at the sodium lamp (λ = 589 nm) D line and are reported as follows: $[\alpha]_D^T$ (*c* g/100 mL, solvent). ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on a JEOL JNM-ECA 500 spectrometer (500 MHz) or BRUKER AVANCE III HD (400 MHz). ^1H NMR data are reported as follows: chemical shift (δ, ppm), integration, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constants (*J*) in Hz, assignments. ^{13}C NMR data are reported in terms of chemical shift (δ, ppm). Electrospray ionization-mass spectrometer (ESI-MS) spectra were recorded on a JEOL JMS-T100LC instrument and are reported in mass-to-charge ratio (*m*/*z*).

The carbon numberings on NMR of all compounds are corresponding with cynaropicrin **1** or (*R*)-7-hydroxycarvone **9**.

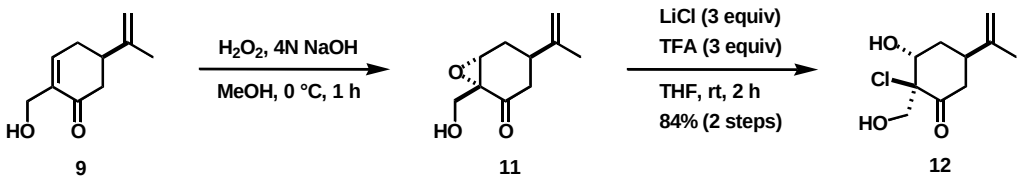


cynaropicrin (1)



(*R*)-7-hydroxycarvone (9)

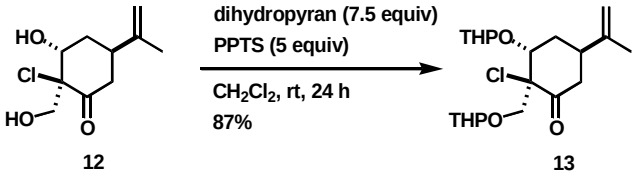
(2*R*, 3*R*, 5*R*)-2-Chloro-3-hydroxy-2-hydroxymethyl-5-isopropenyl-cyclohexanone (12):



To a solution of **9** (431.4 mg, 2.60 mmol, 1.0 equiv) and 4N NaOH solution (195 μL, 0.3 equiv), in MeOH (6.4 mL) to cooled at 0 °C was added 30% H_2O_2 (3.6 mL, large excess) dropwise. After stirring for 1 h at 0 °C, the reaction mixture was diluted with EtOAc and quenched with saturated Na_2SO_3 solution. The aqueous layer was then extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* afforded the product **11** as a yellow oil, and the residue was used for the second step without further purification; **11**: R_f 0.62 (hexane/EtOAc = 1:2).

Next, the residue **11** and LiCl (326.8 mg, 7.79 mmol, 3.0 equiv) in THF (20 mL) cooled to 0 °C was added CF_3COOH (596 μL, 7.79 mmol, 3.0 equiv) dropwise. After stirring at room temperature for 2 h, the reaction mixture was diluted with EtOAc and quenched with saturated $NaHCO_3$ solution. The aqueous layer was then extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification on silica gel column chromatography (hexane/EtOAc = 4:1) afforded **12** as a yellow oil (474.0 mg, 2.17 mmol, 84% (2 steps)); R_f 0.70 (hexane/EtOAc = 1:2); $[\alpha]_D^{25}$ +86.9 (*c* 0.1, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.82 (2H, d, J = 6.6 Hz, H9), 4.52 (1H, t, J = 2.7 Hz, H3), 4.37 (1H, d, J = 12.6 Hz, H7), 3.88 (1H, d, J = 12.6 Hz, H7), 3.07-2.92 (2H, m, H6), 2.43-2.39 (1H, m, H5), 2.33-2.23 (1H, m, H4), 2.02-1.95 (1H, m, H4), 1.78 (3H, s, H10); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.2, 146.5, 110.8, 67.1, 66.3, 41.9, 39.7, 39.5, 33.0, 20.5; ESI-HRMS (*m*/*z*) calcd for $C_{10}H_{15}ClNaO_3$ [M+Na] 241.0607, found 241.0598.

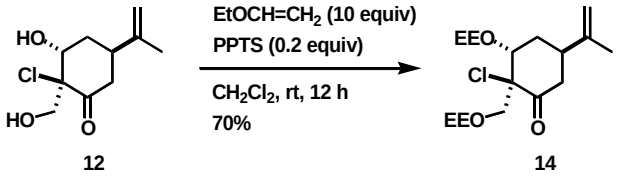
(2*S*,3*R*,5*R*)-2-Chloro-5-isopropenyl-3-(tetrahydro-pyran-2-yloxy)-2-(tetrahydro-pyran-2-yloxymethyl)-cyclohexanone (13):



To a solution of **12** (52.7 mg, 0.241 mmol, 1.0 eq) and PPTS (302.8 mg, 1.20 mmol, 5.0 eq) in CH_2Cl_2 (2.4 mL) was added dihydropyran (105.6 μL, 1.81 mmol, 7.5 eq). After stirring at rt for 24 h, the reaction mixture was diluted with EtOAc and quenched with saturated $NaHCO_3$ solution. The aqueous layer was then extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification on silica gel column chromatography (hexane/EtOAc = 10:1) afforded **13** as a colorless oil (80.7 mg, 0.210 mmol, 87%); R_f 0.67 (hexane/EtOAc = 4:1).

This compound could not be identified with ^{1}H NMR spectrrum because it contains inseparable diastereomer derived from THP group.

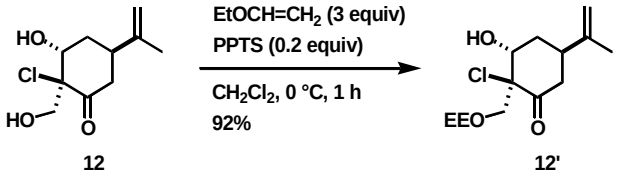
(2*R*, 3*R*, 5*R*)-2-Chloro-3-(1-ethoxy-ethoxy)-2-(1-ethoxy-ethoxymethyl)-5-isopropenyl-cyclohexanone (14):



A solution of **12** (56.9 mg, 0.260 mmol, 1.0 eq) and ethyl vinyl ether (250.2 μL, 2.601 mmol, 10.0 eq) in CH_2Cl_2 (3 mL) was stirred with PPTS (13.1 mg, 0.052 mmol, 0.2 eq) at rt for 12 h. The solution was diluted with ether and quenched with saturated $NaHCO_3$ solution. The aqueous layer was then extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification on silica gel column chromatography (hexane/EtOAc = 10:1) afforded **14** as a yellow oil (66.2 mg, 0.182 mmol, 70%); R_f 0.77 (hexane/EtOAc = 4:1).

This compound could not be identified with ^{1}H NMR spectrum because it contains inseparable diastereomer derived from EE group.

(2*R*, 3*R*, 5*R*)-2-Chloro-3-hydroxy-2-(1-ethoxy-ethoxymethyl)-5-isopropenyl-cyclohexanone (12'):

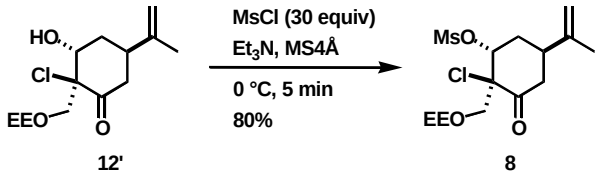


12 12'

A solution of **12** (2.8615 g, 0.01308 mol, 1.0 equiv) and ethyl vinyl ether (3.78 mL, 39.24 mmol, 3.0 equiv) in CH_2Cl_2 (137 mL) was stirred with PPTS (657.7 mg, 2.617 mmol, 0.2 equiv) at 0 °C for 1 h. The solution was diluted with CH_2Cl_2 and quenched with saturated $NaHCO_3$ solution. The aqueous layer was then extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification on silica gel column chromatography (hexane/EtOAc = 4:1) afforded **12'** as a yellow oil (3.50 g, 12.04 mmol, 92%); R_f 0.37 (hexane/EtOAc = 4:1); $[\alpha]_D^{25}$ +74.1 (*c* 0.1, CH_2Cl_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.9, 146.6, 110.4, 101.3, 72.2, 68.4, 67.9, 63.0, 41.6, 39.1, 32.0, 20.4, 20.0, 15.1; ESI-HRMS (*m*/*z*) calcd for $C_{14}H_{23}ClNaO_4$ [M+Na] 313.1183, found 313.1214.

This compound could not be identified with ^1H NMR spectrum because it contains inseparable diastereomer derived from EE group.

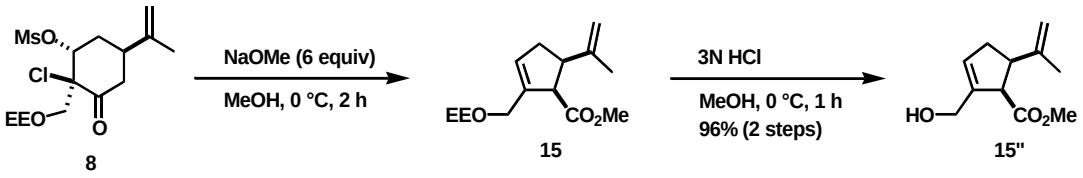
(2*R*, 3*R*, 5*R*)-2-Chloro-2-(1-ethoxy-ethoxymethyl)-5-isopropenyl-3-methanesulfonyl-cyclohexanone (8):



12' 8

To a solution of **12'** (1.2574 g, 4.4706 mmol, 1.0 equiv) and powdered MS4Å in Et_3N (100.0 mL, 0.7153 mol, 160.0 equiv) at 0 °C was added MsCl (10.4 mL, 0.1341 mol, 30.0 equiv) dropwise. After stirring for 5 min at 0 °C, the reaction mixture was diluted with CH_2Cl_2 and quenched with saturated $NaHCO_3$ solution. After that the reaction mixture was filtered through Celite. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification on silica gel column chromatography (hexane/EtOAc = 4:1) afforded compound **8** as a yellow oil (1.2712 g, 3.4462 mmol, 80%); R_f 0.30 (hexane/EtOAc = 4:1); $[\alpha]_D^{25}$ +46.0 (*c* 0.1, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.21 (1H, s, H3), 4.78 (1H, s, H9), 4.73 (1H, s, H9), 4.71-4.4.67 (1H, m, EE), 4.10 (1H, d, *J* = 12.1 Hz, EE), 3.74 (1H, d, *J* = 12.1 Hz, EE), 3.65-3.59 (1H, m, EE), 3.46-3.40 (1H, m, EE), 3.05 (3H, s, Ms), 2.96 (1H, dd, *J* = 11.5, 11.5 Hz, H5), 2.79-2.73 (1H, m, H6), 2.37-2.28 (3H, m, H4,6), 1.69 (3H, s, H10), 1.26 (3H, d, *J* = 4.12 Hz, EE), 1.11 (3H, dd, *J* = 5.96, 5.96 Hz, EE); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.7, 145.3, 111.1, 101.2, 81.1, 67.2, 65.2, 62.6, 40.9, 38.6, 38.1, 30.9, 20.3, 20.2, 15.2; ESI-HRMS (*m*/*z*) calcd for $C_{15}H_{25}ClNaO_6S$ [M+Na] 391.0958, found 391.0947.

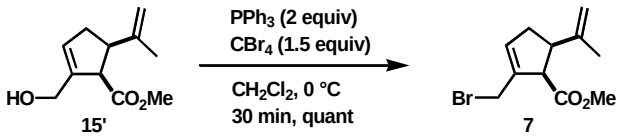
(1*R*, 5*R*)-4-Hydroxymethyl-1-isopropenyl-cyclopent-3-enecarboxylic acid methyl ester (15"):



To a solution of **8** (1.1280 g, 3.0580 mmol, 1.0 equiv) in MeOH (13 mL) was added NaOMe (0.9912 g, 18.348 mmol, 6.0 equiv) in MeOH (15 mL × 3) using a cannula at 0 °C. After stirring for 2 h at 0 °C, the product **15** was obtained as a colorless oil (0.7878 g, 2.916 mmol) in 96% yield. The product was used for the second step without further purification.

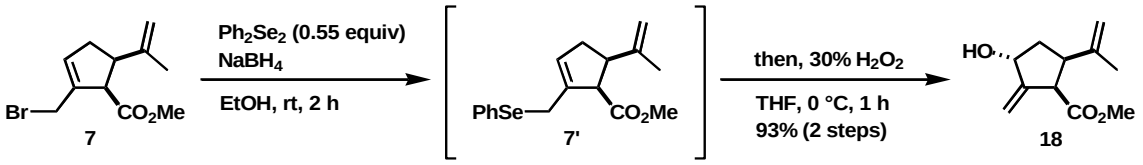
To a solution of **15** in MeOH, 3N HCl (6 mL) was added. After stirring for 1 h at 0 °C the reaction mixture was diluted with MeOH and quenched with saturated $NaHCO_3$ solution. The aqueous layer was then extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification on silica gel column chromatography (hexane/EtOAc = 4:1) afforded **15"** as a colorless oil (0.576 g, 2.9616 mmol, quant); R_f 0.62 (hexane/EtOAc = 1:1); $[\alpha]_D^{25}$ +205.9 (*c* 0.1, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.93 (1H, s, H3), 4.84 (1H, s, H14), 4.79 (1H, s, H14), 4.17 (2H, m, H15), 3.68 (1H, d, *J* = 8.0 Hz, H5), 3.61 (3H, s, Me), 3.18 (1H, q, *J* = 8.5 Hz, H1), 2.68-2.62 (1H, m, H2), 2.41-2.36 (1H, m, H2), 1.77 (3H, s, H10); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 144.8, 141.8, 131.3, 111.9, 61.7, 54.7, 51.9, 50.6, 35.2, 22.9; ESI-HRMS (*m*/*z*) calcd for $C_{11}H_{16}O_3^+$ $[M]^+$ 196.1099, found 196.1080.

(1*R*, 5*R*)-4-Bromomethyl-1-isopropenyl-cyclopent-3-enecarboxylic acid methyl ester (7):



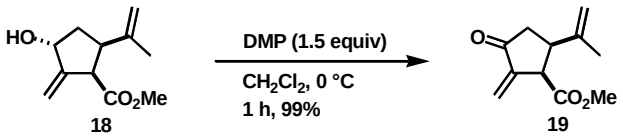
To a solution of **15'** (2.6633 g, 13.571 mmol, 1.0 equiv) and PPh_3 (7.1194 g, 27.143 mmol, 2.0 equiv) in CH_2Cl_2 (144.0 mL) was added CBr_4 (6.7511 g, 20.357 mmol, 1.5 equiv) at 0 °C. After stirring for 30 minutes at 0 °C, the reaction mixture was treated with hexane/EtOAc = 4:1 mixture and passed through short silica gel column chromatography (hexane/EtOAc = 4/1) and concentrated *in vacuo*. Purification on silica gel column chromatography (hexane/EtOAc = 9:1) afforded **7** (35273 g, 13.571 mmol, quant) as a colorless oil; R_f 0.90 (hexane/EtOAc = 1:1); $[\alpha]_D^{25}$ +62.2 (*c* 0.1, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.08 (1H, s, H3), 4.86 (1H, s, H14), 4.74 (1H, s, H14), 4.13 (1H, d, *J* = 10.7 Hz, H15), 4.02 (1H, d, *J* = 10.7 Hz, H15), 3.81 (1H, d, *J* = 8.7 Hz, H5), 3.62 (3H, s, Me), 3.21 (1H, dd, *J* = 17.1, 8.7 Hz, H1), 2.73-2.64 (1H, m, H2), 2.46-2.38 (1H, m, H2), 1.77 (3H, s, H9); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 144.1, 138.2, 134.7, 111.7, 54.2, 51.5, 50.3, 35.1, 30.2, 22.4; ESI-HRMS (*m*/*z*) calcd for $C_{11}H_{14}BrO_2^+$ $[M-H]^+$ 257.0177, found 257.0164, 259.0125.

(1*R*, 3*R*, 5*R*)-3-Hydroxy-1-isopropenyl-4-methylene-cyclopentanecarboxylic acid methyl ester (18):



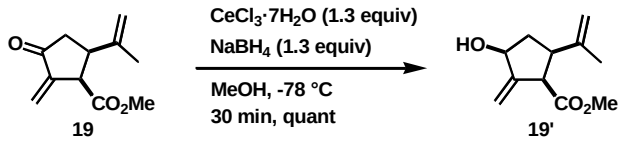
To a solution of diphenyl diselenide (4.3462 g, 13.925 mmol, 0.55 equiv) in EtOH (90.0 mL) was added enough sodium borohydride to render the yellow solution colorless. To this solution was added **7** (6.5608 g, 25.318 mmol, 1.0 equiv) in EtOH (30.0 mL × 4) using a cannula at 0 °C. The solution was stirred for 15 minutes at 0 °C, 2 h at room temperature and 1/2 of the EtOH was evaporated under a stream of N_2 gas. The reaction mixture was added THF (126.0 mL), followed by 30% H_2O_2 solution (14.54 mL, 1.74 M) at 0 °C. After stirring at 0 °C for 10 minutes, the reaction mixture was diluted with ether, quenched with saturated $NaHCO_3$ solution. The aqueous layer was then extracted with ether. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification on silica gel column chromatography (hexane/EtOAc = 4:1) afforded **18** as a colorless oil (4.452 g, 23.546 mmol, 93%); R_f 0.77 (hexane/EtOAc = 1:1); $[\alpha]_D^{25}$ -50.6 (*c* 0.2, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.40 (1H, t, *J* = 1.5 Hz, H15), 5.27 (1H, t, *J* = 1.2 Hz, H15), 4.83 (1H, s, H14), 4.72 (2H, m, H3/14), 3.79 (1H, d, *J* = 7.8 Hz, H5), 3.59 (3H, s, Me), 3.18-3.09 (1H, m, H1), 2.45-2.34 (1H, m, H2), 1.86-1.79 (4H, m, H2/9); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 153.6, 143.9, 113.6, 110.9, 73.8, 52.7, 51.6, 47.2, 37.7, 23.1; ESI-HRMS (*m*/*z*) calcd for $C_{11}H_{16}O_3^+$ $[M]^+$ 196.1099, found 196.1097.

(1*R*, 5*R*)-1-Isopropenyl-4-methylene-3-oxo-cyclopentanecarboxylic acid methyl ester (19):



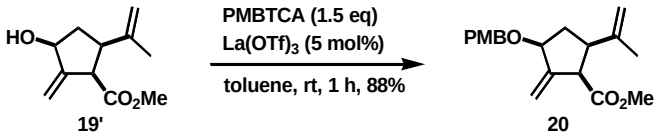
To a solution of **18** (1.8792 g, 9.5760 mmol, 1.0 equiv) in CH_2Cl_2 (94.3 mL) to cooled at 0 °C was added Dess-Martin periodinane (6.0923 g, 14.364 mmol, 1.5 equiv). After stirring for 1 h at 0 °C, the reaction mixture was diluted with CH_2Cl_2 and quenched with saturated Na_2SO_3 solution and saturated $NaHCO_3$ solution (1/1). The aqueous layer was then extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification on silica gel column chromatography (hexane/EtOAc = 4:1) afforded **19** as a colorless oil (1.8449 g, 9.5188 mmol, 99%); R_f 0.83 (hexane/EtOAc = 1:1); $[\alpha]_D^{25}$ -118.5 (*c* 0.1, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.16 (1H, d, J = 1.8 Hz, H15), 5.51 (1H, d, J = 1.5 Hz, H15), 4.92-4.91 (1H, m, H14), 4.77 (1H, s, H14), 4.00-3.97 (1H, m, H5), 3.63 (3H, s, Me), 3.05-2.96 (1H, m, H1), 2.85 (1H, dd, J = 17.7, 11.7 Hz, H2), 2.42 (1H, dd, J = 17.1, 6.9 Hz, H2), 1.80 (3H, s, H9); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.8, 171.5, 143.5, 142.7, 120.0, 111.9, 51.8, 50.6, 43.7, 40.3, 21.8; ESI-HRMS (*m*/*z*) calcd for $C_{11}H_{14}O_3^+$ $[M]^+$ 194.0943, found 194.0942.

(1*R*, 3*S*, 5*R*)-3-Hydroxy-1-isopropenyl-4-methylene-cyclopentanecarboxylic acid methyl ester (19'):



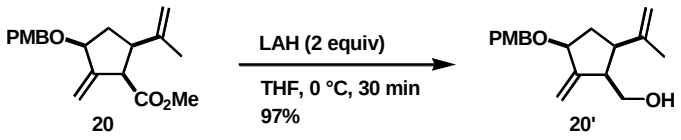
Solid $CeCl_3 \cdot 7H_2O$ (3.9585 g, 10.624 mmol, 1.3 equiv) was added in one portion to a solution of **19** (1.5874 g, 8.1727 mmol, 1.0 equiv) in MeOH (77.4 mL) at -78 °C. After stirring for 10 minutes at -78 °C, $NaBH_4$ (0.4019 g, 10.624 mmol, 1.3 equiv) was added in one portion. The reaction mixture was stirred at -78 °C for 30 minutes and then warmed to 0 °C. After stirring for 10 minutes at 0 °C, the reaction mixture was diluted with CH_2Cl_2 and quenched with saturated NH_4Cl solution. The aqueous layer was then extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification on silica gel column chromatography (hexane/EtOAc = 4:1) afforded **19'** as a yellow oil (1.4717 g, 7.4998 mmol, quant); R_f 0.67 (hexane/EtOAc = 1:1); $[\alpha]_D^{25}$ +146.4 (*c* 0.1, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.39 (1H, t, J = 1.8 Hz, H15), 5.23 (1H, t, J = 1.8 Hz, H15), 4.86-4.85 (1H, m, H14), 4.76 (1H, s, H14), 4.54-4.49 (1H, m, H3), 3.66-3.62 (4H, m, H5/Me), 2.65-2.56 (1H, m, H1), 2.35-2.26 (1H, m, H2), 2.17-2.02 (1H, m, H2), 1.78 (3H, s, H9); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 152.3, 143.2, 112.6, 111.0, 73.8, 52.3, 51.7, 45.8, 37.6, 22.7; ESI-HRMS (*m*/*z*) calcd for $C_{11}H_{16}O_3^+$ $[M]^+$ 196.1099, found 196.1097.

(1*R*, 3*S*, 5*R*)-3-(*p*-Methoxy-benzyloxy)-1-isopropenyl-4-methylene-cyclopentanecarboxylic acid methyl ester (20):



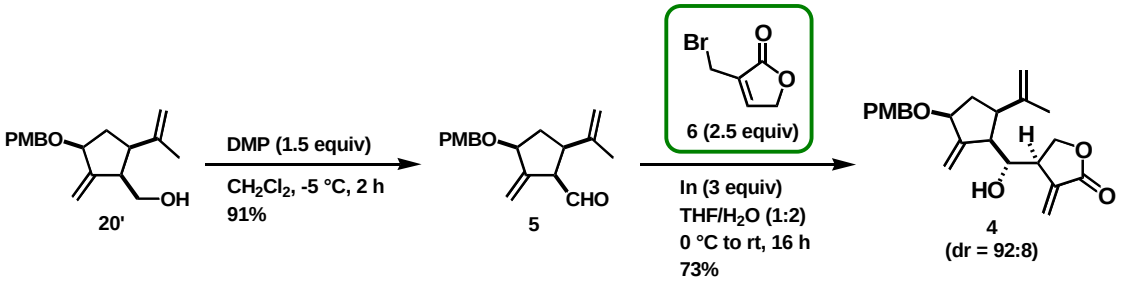
A solution of **19'** (2.2996 g, 11.72 mmol, 1.0 equiv) and *p*-methoxybenzyl trichloroacetimidate (3.649 mL, 17.58 mmol, 1.5 equiv) in toluene (276 mL) was treated with $La(OTf)_3$ (343.4 mg, 0.1611 mmol, 5 mol%) at room temperature. After stirring for 1 h at room temperature, the reaction mixture was concentrated *in vacuo*. Purification on silica gel column chromatography (hexane/EtOAc = 10:1) afforded **20** as a colorless oil (3.280 g, 10.37 mmol, 88%); R_f 0.57 (hexane/EtOAc = 4:1); $[\alpha]_D^{20}$ +80.1 (*c* 0.76, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.19 (2H, m, Bn), 6.83-6.79 (2H, m, Bn), 5.29 (1H, t, J = 1.8 Hz, H15), 5.16 (1H, t, J = 2.4 Hz, H15), 4.77 (1H, q, J = 1.8 Hz, H14), 4.69 (1H, s, H14), 4.59 (1H, d, J = 11.7 Hz, CH_2), 4.44 (1H, J = 11.7 Hz, CH_2), 4.32-4.26 (1H, m, H3), 3.82 (3H, s, Me), 3.65 (1H, d, J = 7.8 Hz, H5), 3.62 (3H, s, Me), 2.51-2.44 (1H, m, H1), 2.23-2.02 (2H, m, H2), 1.78 (3H, s, H9); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 159.3, 149.3, 143.5, 130.8, 129.5, 113.9, 112.1, 111.1, 79.4, 70.5, 55.4, 51.7, 51.5, 44.7, 33.6, 22.7; ESI-HRMS (*m*/*z*) calcd for $C_{19}H_{24}O_4^+$ $[M]^+$ 316.1675, found 316.1670.

(1*R*, 3*S*, 5*R*)-5-(Hydroxymethyl)-1-isopropenyl-3-(*p*-methoxy-benzyloxy)-4-methylene-cyclopentanecarboxylic acid methyl ester (20'):



To a solution of lithium aluminium hydride (196.7 mg, 5.1841 mmol, 2.0 equiv) in THF (10 mL) was added dropwise **20** (820.1 mg, 2.5920 mmol, 1.0 equiv) in THF (10 mL × 3) using a cannula at 0 °C. After stirring for 30 min at 0 °C, the reaction mixture was diluted with ether, quenched with 10% KOH aqueous solution and filtered with Celite. The aqueous layer was then extracted with ether. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification on silica gel column chromatography (hexane/EtOAc = 4:1) afforded **20'** as a colorless oil (722.2 mg, 2.5044 mmol, 97%); R_f 0.43 (hexane/EtOAc = 4:1); $[\alpha]_D^{25}$ +135.9 (*c* 0.1, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30-7.26 (2H, m, Bn), 6.91-6.86 (2H, m, Bn), 5.31 (1H, s, H15), 5.22 (1H, s, H15), 4.91 (1H, s, H14), 4.82 (1H, s, H14), 4.57 (1H, d, J = 11.4 Hz, CH_2), 4.50 (1H, d, J = 11.4 Hz, CH_2), 4.31-4.25 (1H, m, H3), 3.60 (1H, dd, J = 11.7, 6.3 Hz, H6), 3.41 (1H, dd, J = 11.7, 7.2 Hz, H6), 2.81-2.76 (1H, m, H5), 2.52-2.46 (1H, m, H1), 2.20-2.12 (1H, m, H2), 1.93-1.82 (4H, m, H2/9); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 152.2, 144.4, 130.5, 129.4, 113.9, 112.0, 110.9, 79.6, 70.8, 62.6, 55.3, 47.5, 44.6, 34.0, 23.2; ESI-HRMS (*m*/*z*) calcd for $C_{18}H_{24}O_3^+$ $[M]^+$ 288.1725, found 288.1721.

7-{Hydroxy-[1-isopropenyl-3-(*p*-methoxy-benzyloxy)-4-methylene-cyclopentyl]-methyl}-11-methylene-dihydro-furan-12-one (4):

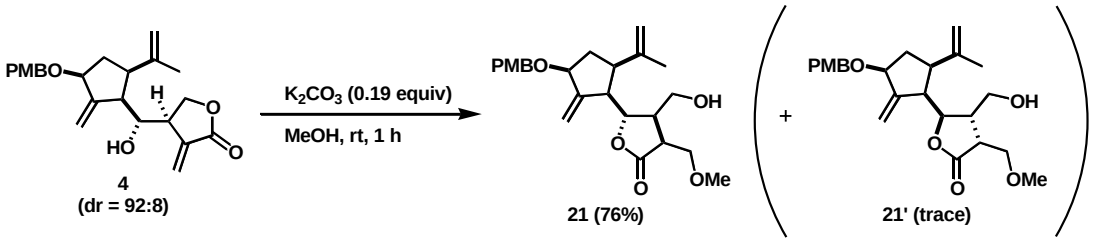


To a solution of **20'** (65.5 mg, 0.2273 mmol, 1.0 equiv) in CH_2Cl_2 (2.8 mL) to cooled at 0 °C was added Dess-Martin periodinane (152.0 mg, 0.3409 mmol, 1.5 equiv). After stirring for 2 h at -5 °C, the reaction mixture was diluted with CH_2Cl_2 and quenched with saturated Na_2SO_3 and $NaHCO_3$ solution (1/1). The aqueous layer was then extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* afforded **5** as a colorless oil (59.2 mg, 0.2068 mmol, 91%), and the residue was used for the second step without further purification; **5**: R_f 0.70 (hexane/EtOAc = 2:1).

Next, the residue **5** and bromolactone **6** (92.4 mg, 0.5682 mmol, 2.5 equiv) in THF/H_2O (1:2) (0.3 mL) was treated with In powder (72.1 mg, 0.6818mmol, 3.0 equiv) at 0 °C. After stirring for 16 h at 0 °C to room temperature, the reaction mixture wa filtered through Celite and combined. The aqueous layer was then extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification on silica gel column chromatography (hexane/EtOAc = 5:1) afforded **4** as a yellow oil (63.8 mg, 0.1659 mmol, 73% (2 steps) (dr = 92:8)); R_f 0.37 (hexane/EtOAc = 2:1); $[\alpha]_D^{25}$ -36.0 (*c* 0.032, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27-7.22 (2H, m, Bn), 6.90-6.67 (2H, m, Bn), 6.32 (1H, dd, *J* = 2.7, 0.9 Hz, H13), 5.98 (1H, dd, *J* = 2.4, 1.2 Hz, H13), 5.40 (1H, s, H15), 5.23 (1H, s, H15), 5.03 (1H, s, H14), 4.94 (1H, s, H14), 4.52-4.38 (3H, m, H8/CH_2), 4.33-4.20 (1H, m, H3), 4.01-3.97 (1H, m, H6), 3.80 (3H, s, Me), 3.53 (1H, d, *J* = 9.3 Hz, H8), 3.20-3.12 (1H, m, H7), 2.99-2.91 (1H, m, H5), 2.62-2.21 (2H, m, H1/2), 2.28-2.21 (1H, m, H2), 1.78 (3H, s, H9); ^{13}C NMR

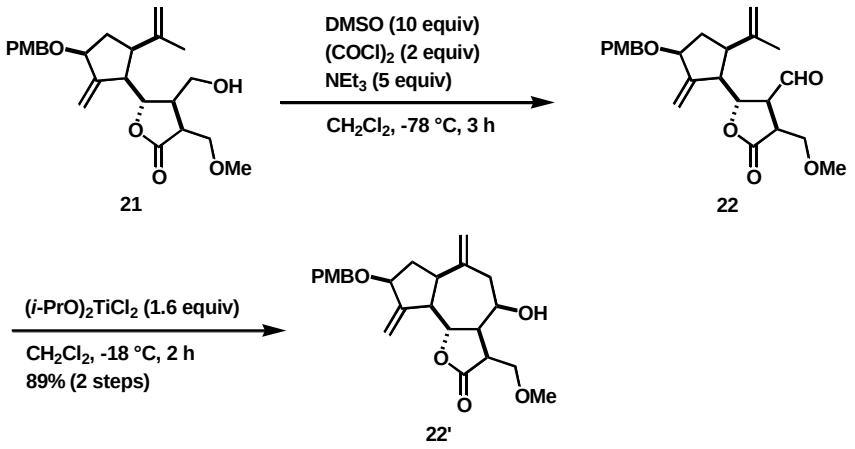
(125 MHz, $CDCl_3$) δ 171.0, 159.6, 149.1, 142.1, 135.1, 129.8, 129.3, 126.0, 117.2, 114.1, 112.8, 80.1, 71.6, 70.0, 67.8, 55.4, 49.5, 47.3, 43.2, 35.2, 23.6; ESI-HRMS (*m*/*z*) calcd for $C_{23}H_{28}O_5^+$ $[M]^+$ 384.1937, found 384.1950.

7-Hydroxymethyl-6-[1-isopropenyl-3-(*p*-methoxy-benzyloxy)-4-methylene-cyclopentyl]-11-methoxymethyl-dihydro-furan-12-one (21):



To a solution of **4** (24.7 mg, 0.0642 mmol, 1.0 equiv) in MeOH (1.0 mL) was added K_2CO_3 (1.7 mg, 0.0122 mmol, 0.19 equiv) at room temperature. After stirring for 1 h, the reaction mixture was diluted with CH_2Cl_2 and quenched with saturated NH_4Cl solution. The aqueous layer was then extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification on silica gel column chromatography (hexane/EtOAc = 2:1) afforded **21** as a colorless oil (20.6 mg, 0.0488 mmol, 76%); R_f 0.27 (hexane/EtOAc = 1:1); $[\alpha]_D^{25}$ +29.9 (*c* 0.1, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31-7.29 (2H, m, Bn), 6.88-6.86 (2H, m, Bn), 5.42 (1H, s, H15), 5.29 (1H, s, H15), 4.98 (1H, s, H14), 4.92 (1H, s, H14), 4.57 (1H, d, *J* = 6.6 Hz, CH_2), 4.46 (1H, d, *J* = 6.6 Hz, CH_2), 4.33-4.30 (1H, m, H3), 4.11-4.09 (1H, m, H6), 3.85 (1H, dd, *J* = 6.0, 2.1 Hz, H13), 3.80 (3H, s, Me), 3.74 (1H, dd, *J* = 6.6, 2.1, H8), 3.60-3.56 (1H, m, H8), 3.43-3.39 (4H, m, H13/Me), 2.83 (1H, d, *J* = 4.2 Hz, H5), 2.69-2.65 (2H, m, H7/11), 2.56-2.51 (1H, m, H1), 2.19-2.14 (1H, m, H2), 2.09-2.04 (1H, m, H2), 1.75 (3H, s, H9); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.3, 158.9, 149.3, 142.4, 130.8, 129.1, 114.4, 113.6, 112.9, 79.0, 78.8, 71.4, 69.7, 63.0, 59.1, 55.2, 46.9, 46.0, 46.0, 45.5, 33.2, 22.9.; ESI-HRMS (*m*/*z*) calcd for $C_{24}H_{32}NaO_6^+$ $[M+Na]^+$ 439.2097, found 439.2128.

8-Hydroxy-3-(*p*-methoxy-benzyloxy)-11-methoxymethyl-4,10-dimethylene-decahydro-azuleno[6,7-β]furan-12-one (22'):

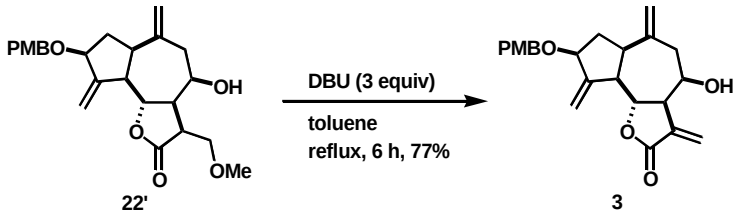


To a solution of DMSO (49.1 μL, 0.691 mmol, 10.0 equiv) in CH_2Cl_2 (0.29 mL) was added dropwise oxalic chloride (11.9 μL, 0.138 mmol, 2.0 equiv) at -78 °C. After stirring at this temperature for 30 min, a solution of **21** (28.8 mg, 0.0691 mmol, 1.0 equiv) in CH_2Cl_2 (0.58 mL) was added dropwise at the same temperature. The reaction mixture was stirred for 3 h and then Et_3N (48.3 μL, 0.346 mmol, 5.0 equiv) was added. After stirring for 1 h at -78 °C and 15 min at room temperature, the reaction mixture was diluted with CH_2Cl_2. The aqueous layer was then extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The crude aldehyde **22** was used in the next step without further purification.

To a solution of crude aldehyde **22** in CH_2Cl_2 (0.66 mL) was added (iPrO)$_2$TiCl$_2$ (26.2 mg, 0.1029 mmol, 1.6 equiv) at -18 °C. After stirring for 2 h at -18 °C, the reaction mixture was diluted with CH_2Cl_2 and quenched with saturated Na_2SO_3 solution. The aqueous layer was then extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification on silica gel column chromatography (hexane/EtOAc = 2:1) afforded **22'** as a colorless oil (25.6 mg, 0.06176 mmol, 89% (2 steps)); R_f 0.37

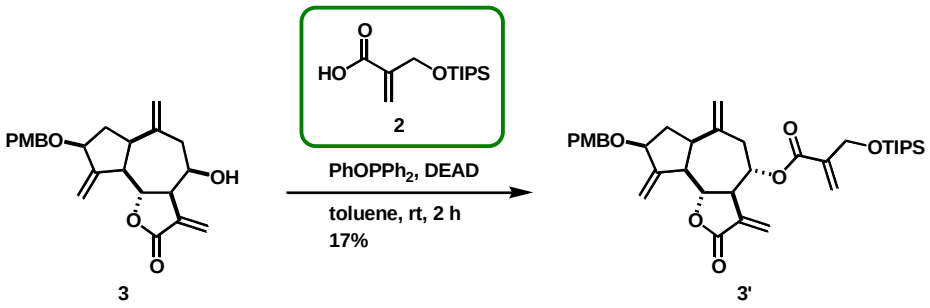
(hexane/EtOAc = 1:1); $[\alpha]_D^{25}$ +32.4 (*c* 0.1, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27-7.25 (2H, m, Bn), 6.88-6.86 (2H, m, Bn), 5.39 (1H, s, H15), 5.30 (1H, s, H15), 5.21 (1H, s, H14), 4.96 (1H, s, H14), 4.54 (1H, d, J = 6.9 Hz, CH_2), 4.43 (1H, d, J = 6.9 Hz, CH_2), 4.25-4.19 (1H, m, H3/6), 4.07-4.04 (1H, m, H8), 3.80 (3H, s, Me), 3.70 (2H, d, J = 2.4 Hz, H13), 3.37 (3H, s, Me), 3.09-3.05 (1H, m, H11), 2.96-2.90 (1H, m, H1), 2.75 (1H, t, J = 5.4 Hz, H5), 2.55-2.45 (2H, m, H9), 2.42-2.37 (1H, m, H7), 2.29-2.23 (1H, m, H2), 1.98-1.93 (1H, m, H2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.3, 159.5, 149.7, 143.9, 131.0, 129.7, 129.7, 117.4, 114.4, 114.2, 80.4, 78.0, 70.5, 69.5, 59.7, 55.7, 51.1, 51.0, 45.2, 43.6, 43.3, 36.9, 21.4; ESI-HRMS (*m*/*z*) calcd for $C_{24}H_{30}NaO_6^+$ $[M+Na]^+$ 437.1940, found 437.1939.

8-Hydroxy-3-(*p*-methoxy-benzyloxy)-13,14,15-trimethylene-decahydro-azuleno[6,7-β]furan-12-one (3):



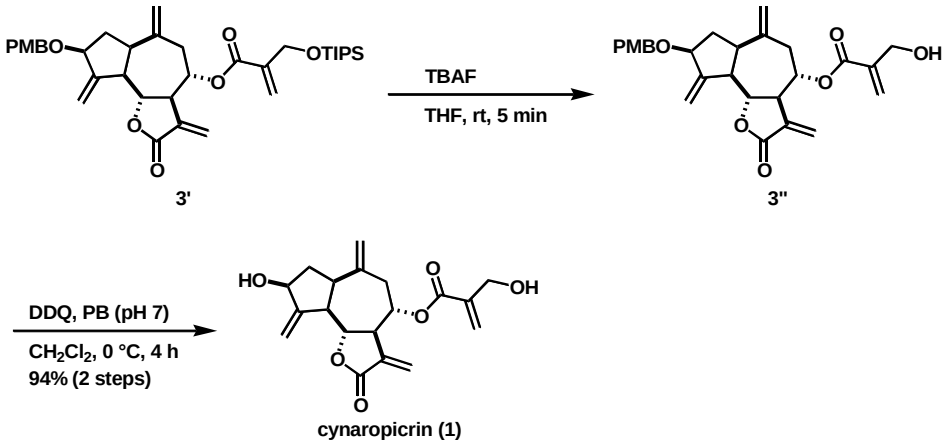
A solution of **22'** (36.5 mg, 0.0881 mmol, 1.0 equiv) and DBU (40.0 μL, 0.2642 mmol, 3.0 equiv) in toluene (12.2 mL) was reflux for 6 h, cooled to room temperature, and concentrated *in vacuo*. Purification on silica gel column chromatography (hexane/EtOAc = 2:1) afforded **3** as a colorless oil (26.4 mg, 0.0690 mmol, 77%); R_f 0.30 (hexane/EtOAc = 1:1); $[\alpha]_D^{25}$ +0.77 (*c* 0.35, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28-7.26 (2H, m, Bn), 6.88-6.87 (2H, m, Bn), 6.40 (1H, d, *J* = 2.4 Hz, H13), 5.90 (1H, d, *J* = 1.8 Hz, H13), 5.46 (1H, s, H15), 5.34 (1H, s, H15), 5.17 (1H, s, H14), 4.95 (1H, s, H14), 4.57-4.46 (3H, m, H6/CH_2), 4.34-4.32 (1H, m, H8), 4.26-4.23 (1H, m, H3), 3.80 (3H, s, Me), 2.96-2.92 (2H, m, H1/5), 2.78-2.73 (1H, m, H7), 2.58 (1H, dd, *J* = 8.1, 3.6 Hz, H9), 2.45 (1H, dd, *J* = 7.8, 3.9 Hz, H9), 2.28-2.23 (1H, m, H2), 1.95-1.90 (1H, m, H2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.0,159.5, 149.6, 143.7, 136.7, 130.9, 129.7, 129.7, 121.8, 117.8, 114.2, 114.2, 80.2, 78.3, 70.7, 66.1, 55.7, 51.5, 50.9, 45.8, 41.8, 37.2; ESI-HRMS (*m*/*z*) calcd for $C_{23}H_{26}NaO_5^+$ $[M+Na]^+$ 405.1678, found 405.1670.

(1*R*,3*S*,5*R*,6*R*,7*R*,8*S*)-3-(*p*-Methoxy-benzyloxy)-13,14,15-trimethylene-12-oxododecahydroazuleno[6,7-β]furan-8-yl-19-(triisopropylsilyloxy)acrylate (3'):



$PhOPPh_2$ (76.8 mg, 0.2761 mmol, 4.0 equiv) in toluene (605 μL) was added to **3** (26.4 mg, 0.0690 mmol, 1.0 equiv) and **2** (71.3 mg, 0.2761 mmol, 4.0 equiv) using a cannula. The mixture was cooled to 0 °C, and then added DEAD (126 μL, 0.2761 mmol, 4.0 equiv) 0 °C. After stirring for 2 h at room temperature, the mixture was diluted with ether, and quenched with a saturated $NaHCO_3$ solution. The aqueous layer was then extracted with ether. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification on silica gel column chromatography (hexane/EtOAc = 5:1) afforded **3'** as yellow oil (7.1 mg, 0.01140 mmol, 17%); R_f 0.77 (hexane/EtOAc = 2/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (2H, ddd, J = 8.4, 1.1, 0.6 Hz, Bz), 6.87 (2H, ddd, J = 8.4, 1.1, 0.6 Hz, Bz), 6.34 (1H, s, H13), 6.20 (1H, d, J = 0.1 Hz, H19), 6.09 (1H, s, H13), 5.58 (1H, d, J = 0.1 Hz, H19), 5.45 (1H, s, H15), 5.31 (1H, s, H15), 5.13 (1H, s, H14), 5.10 (1H, m, H8), 4.89 (1H, s, H14), 4.54 (1H, d, J = 1.5 Hz, H18), 4.48 (2H, s, Bz), 4.40 (1H, d, J = 1.5 Hz, H18), 4.34 (1H, m, H3), 4.21 (1H, m, H6), 3.80 (3H, s, Bz), 3.15 (1H, m, H7), 3.01 (1H, m, H1), 2.78 (1H, m, H5), 2.69 (1H, m, H9), 2.36 (1H, m, H9), 2.27 (1H, m, H2), 1.82 (1H, m, H2), 1.25-1.07 (21H, m, TIPS); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.5, 165.1, 159.3, 148.5, 142.4, 139.7, 137.9, 130.4, 129.6, 125.0, 122.5, 118.1, 115.5, 114.0, 80.2, 78.4, 77.4, 77.16, 76.9, 74.1, 70.0, 61.7, 55.4, 53.3, 47.6, 46.4, 37.2, 36.8, 29.8, 18.1, 12.1; ESI-HRMS (*m*/*z*) calcd for $C_{36}H_{50}NaO_7Si$ [M+Na] 645.3224, found 645.3216.

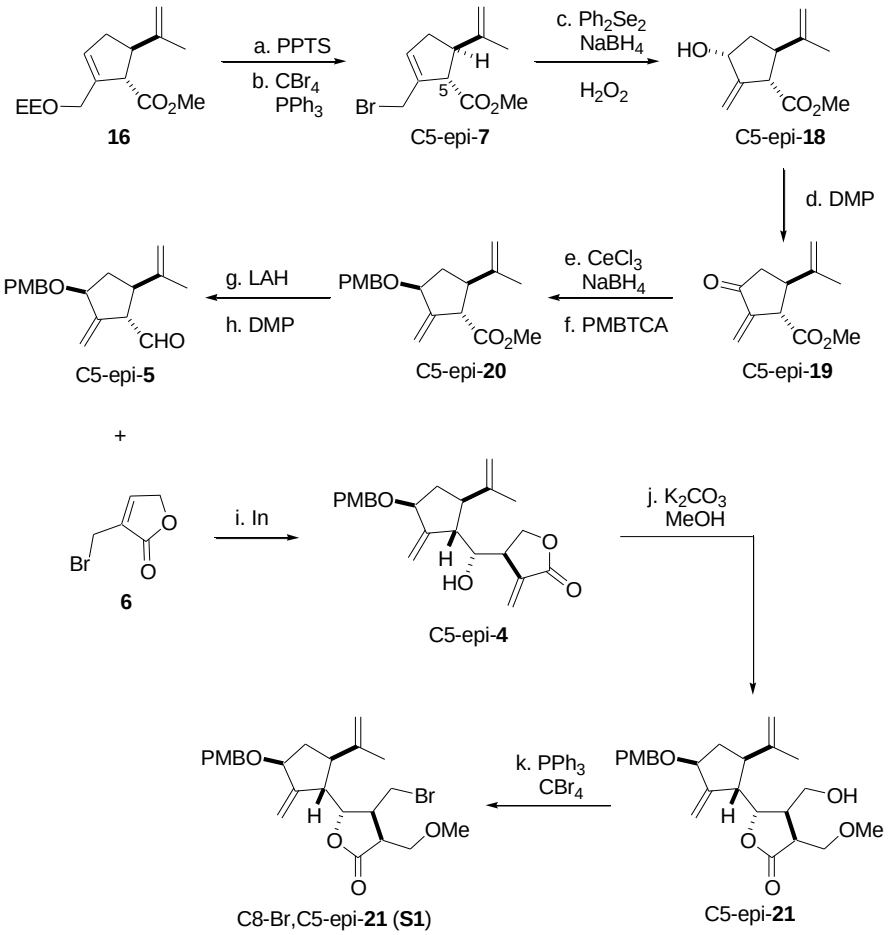
Cynaropicrin (1):



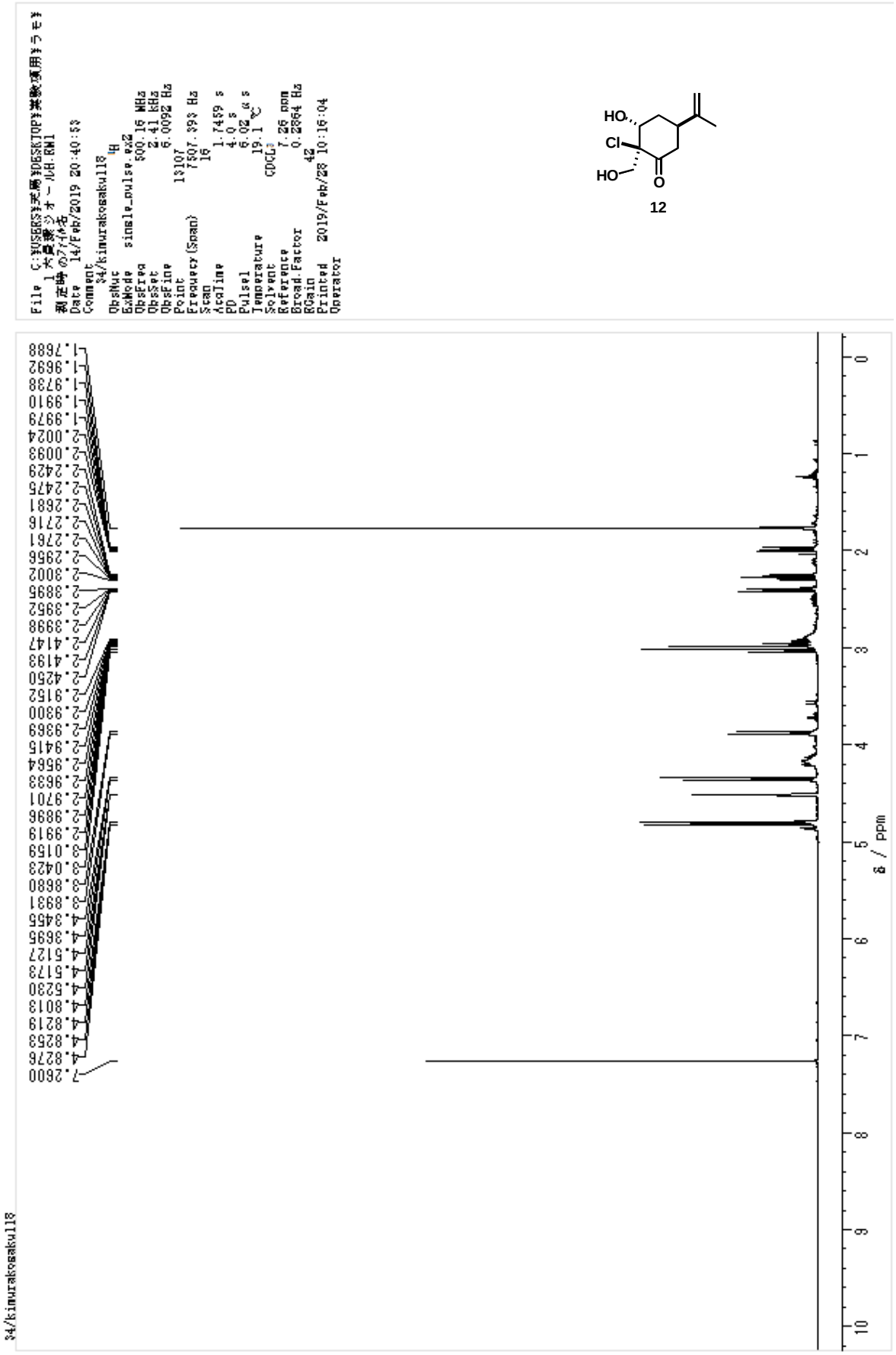
To a solution of **3'** (4.2 mg, 0.00674 mmol, 1.0 equiv) in THF (187 μL) cooled to 0 °C was added and TBAF (13.5 μL, 0.01349 mmol, 2.0 equiv). After stirring for 5 min, the reaction mixture was diluted with EtOAc and quenched with saturated NH_4Cl solution. The aqueous layer was then extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* afforded **3''** as a colorless oil, and the residue was used for the second step without further purification; **3''**: R_f 0.83 (hexane/EtOAc = 1:3); ESI-HRMS (*m*/*z*) calcd for $C_{27}H_{30}NaO_7$ [M+Na] 489.1889, found 489.1912.

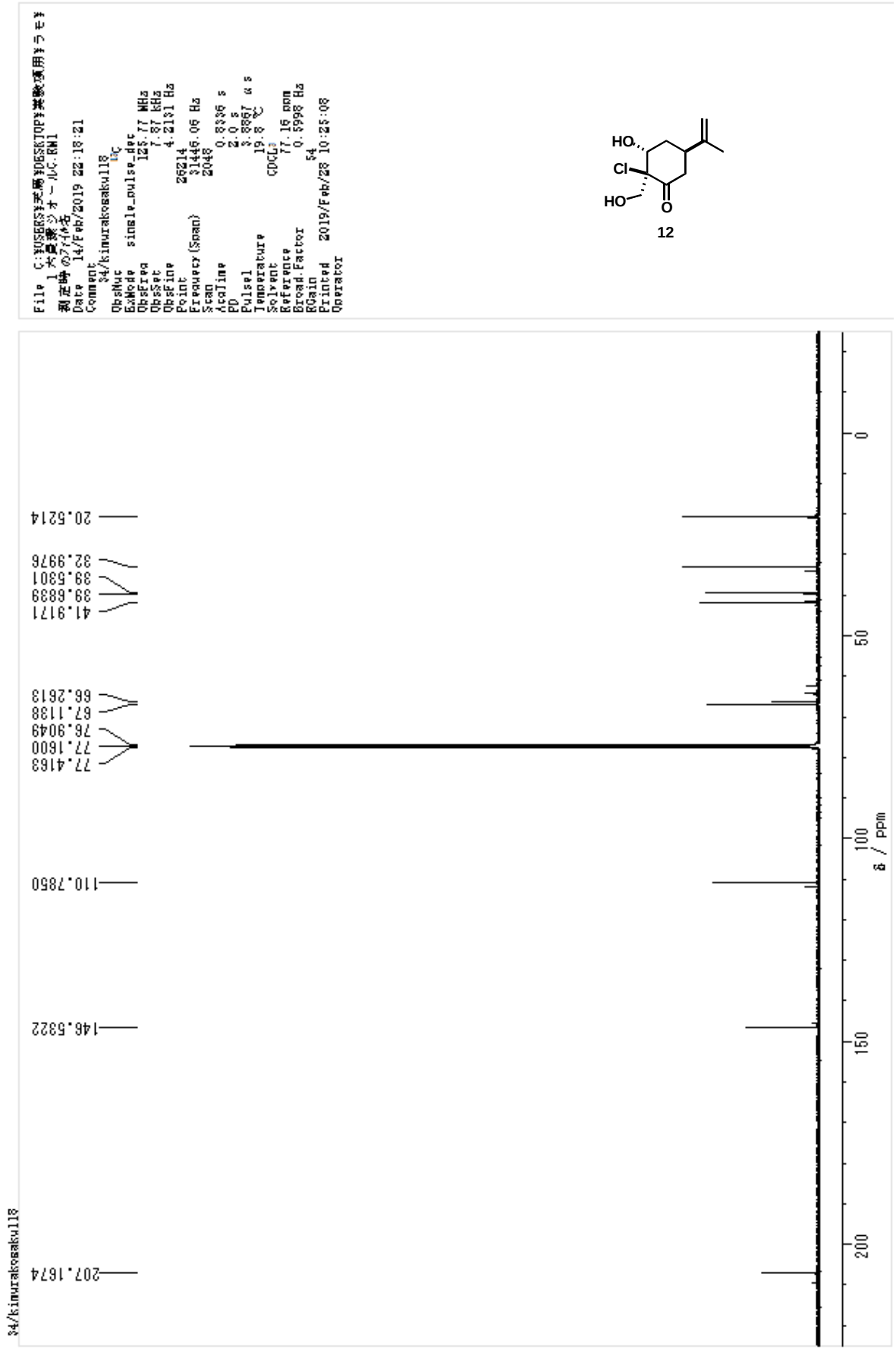
To a solution of **3''** in CH_2Cl_2 (123 μL) cooled to 0 °C was added PB (pH 7) (12.3 μL) and DDQ (3.1 mg, 0.0135 mmol, 2.0 equiv). After stirring at 0 °C for 4 h, the reaction mixture was diluted with CH_2Cl_2 and quenched with saturated Na_2SO_3 solution and saturated $NaHCO_3$ solution (1/1). The aqueous layer was then extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification on HPLC afforded cynaropicrin (**1**) as a yellow oil (2.2 mg, 0.00635mmol, 94% (2 steps)); R_f 0.50 (hexane/EtOAc = 1/3); $[\alpha]_D^{25}$ +152.2 (*c* 0.08, MeOH); ^{1}H NMR (500 MHz, CD_3Cl_3) δ6.39 (1H, s, H19), 6.23 (1H, d, *J* = 3.4 Hz, H13), 5.96 (1H, s, H19), 5.62 (1H, d, *J* = 3.1 Hz, H13), 5.51 (1H, s, H15), 5.37 (1H, s, H15), 5.12-5.18 (2H, m, H14/H8), 4.95 (1H, s, 14H), 4.57 (1H, t, *J* =

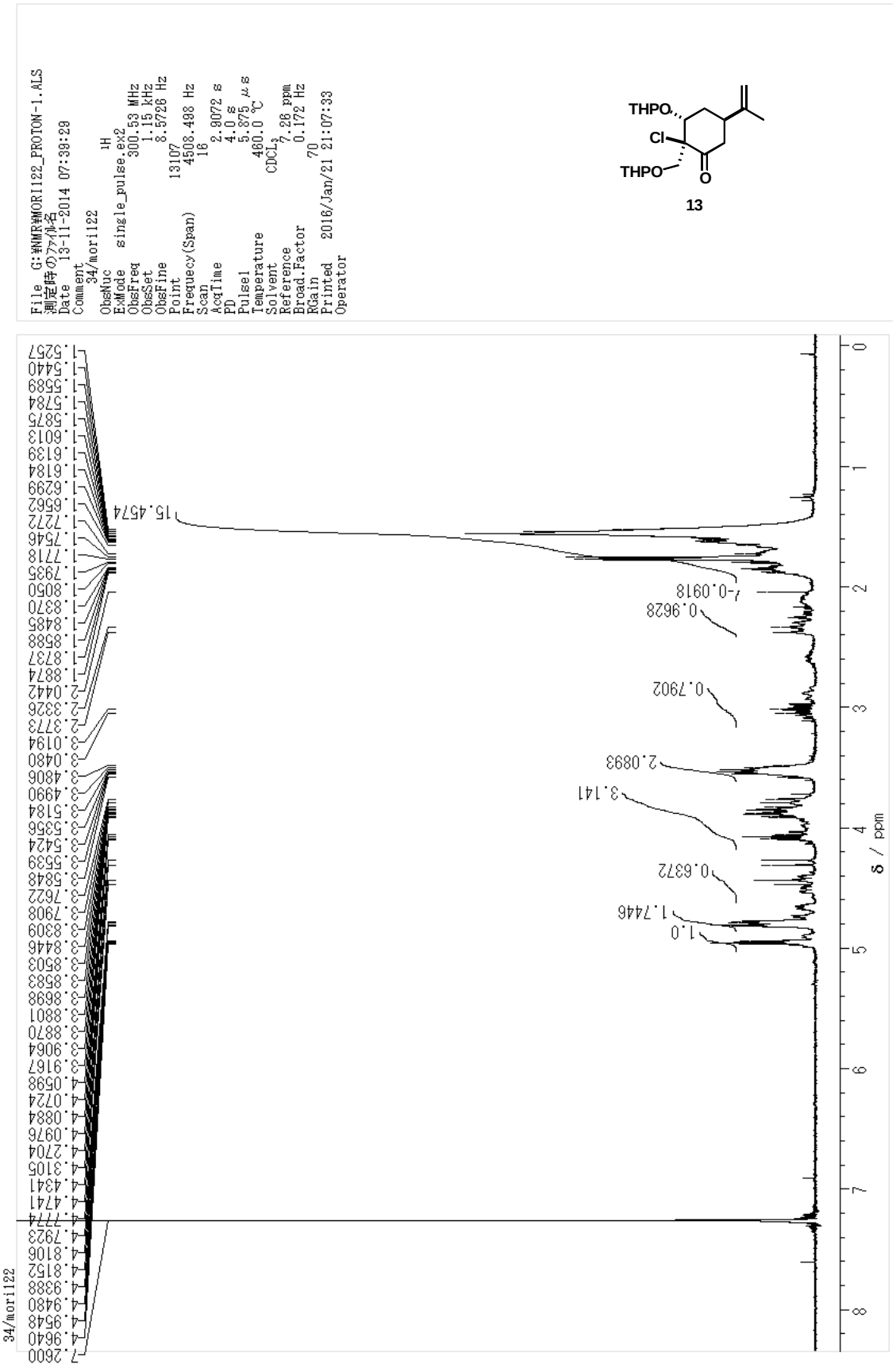
7.2 Hz, H3), 4.39 (2H, s, H18), 4.26 (1H, dd, J = 10.6 Hz, H6), 3.24-3.17 (1H, m, H7), 3.01-2.95 (1H, m, H1), 2.85 (1H, t, J = 10.3 Hz, H5) 2.72 (1H, dd, J = 14.8 Hz, H9), 2.41 (1H, dd, J = 14.4 Hz, H9), 2.30-2.20 (1H, m, H2), 1.79-1.69 (1H, m, H2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.8, 165.1, 152.0, 141.5, 139.0, 137.0, 126.6, 122.6, 118.0, 113.4, 78.2, 74.1, 73.6, 62.1, 51.1, 47.4, 45.1, 38.9, 36.8; ESI-HRMS (*m*/*z*) calcd for $C_{19}H_{22}NaO_6$ [M+Na] 369.1314, found 369.1310.

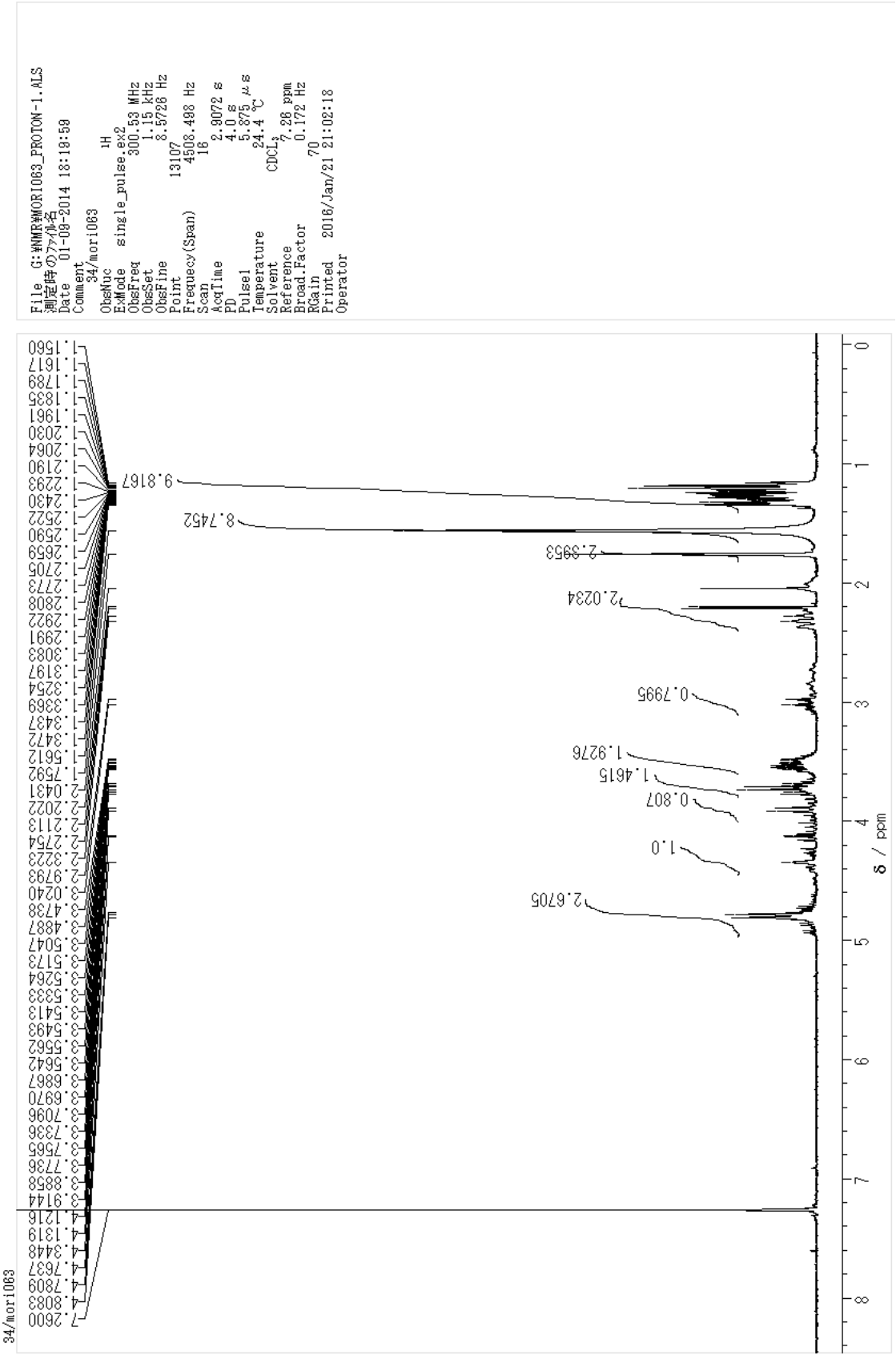


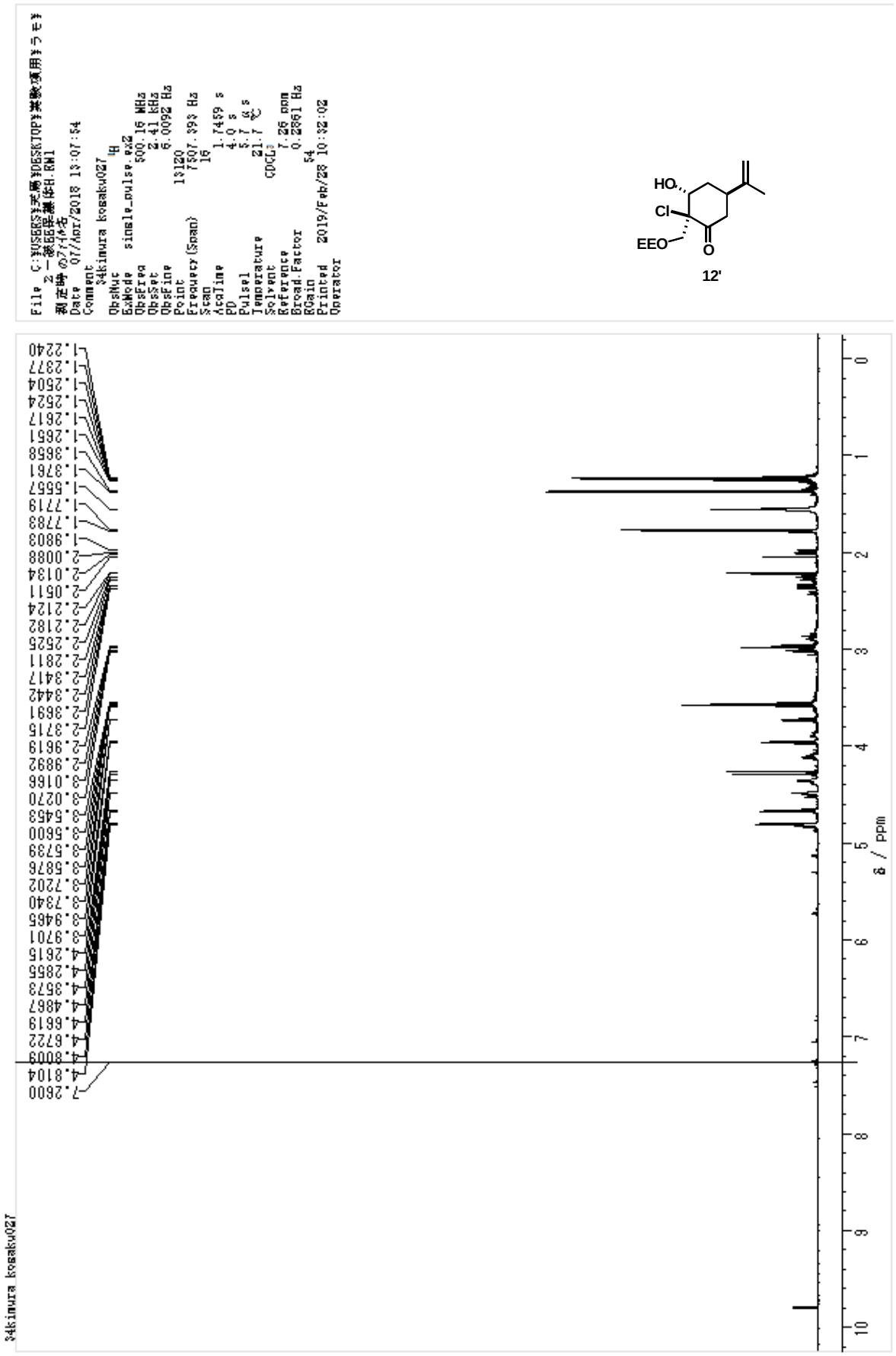
Scheme S1. Synthesis of C8-brominated C5-epimer of **21** (**S1**) prepared from compound **16**. Reagents and conditions: a) PPTS, MeOH, rt, 95%; b) CBr_4, PPh_3, CH_2Cl_2, 0 °C, 92%; c) Ph_2Se_2, $NaBH_4$, EtOH, rt, then H_2O_2, THF, 0 °C, 90%; d) DMP, CH_2Cl_2, 0 °C, 90%; e) $CeCl_3 \cdot 7H_2O$, $NaBH_4$, CH_2Cl_2, 0 °C, quant; f) PMBTCA, $La(OTf)_3$, toluene, rt, 77%; g) LAH, THF, 0 °C, 97%; h) DMP, CH_2Cl_2, 0 °C, 90%; i) Zn(0), THF/H_2O, rt, 71%; j) K_2CO_3, MeOH, rt, 66%; k) PPh_3, CBr_4, CH_2Cl_2, 0 °C, 52%.

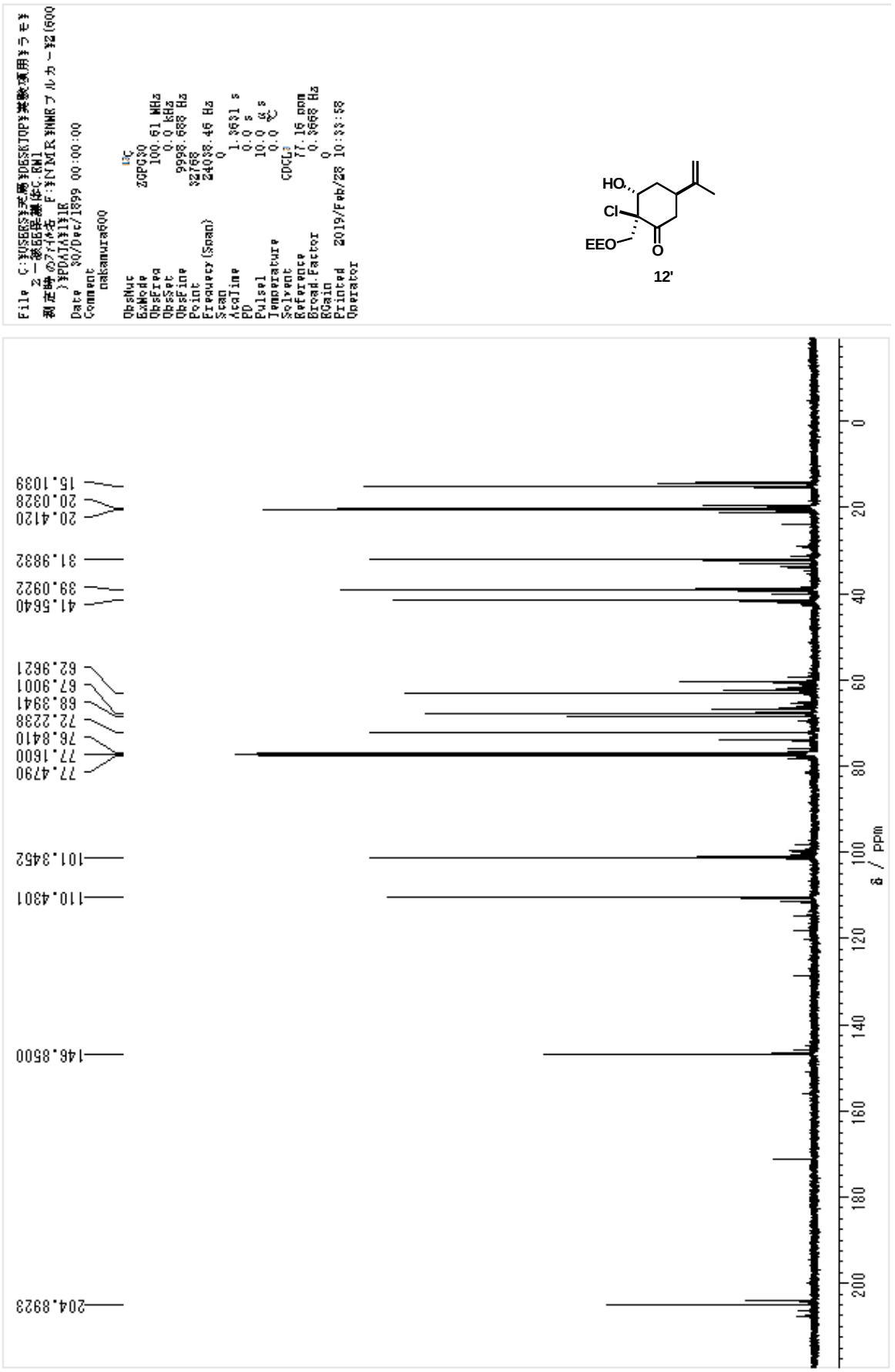

File C:¥USERS¥天馬¥DESKTOP¥実験項用¥ラモ¥
1 木曽線ジオ～ル.EM1
測定時のプロトン
Date 14/Feb/2019 20:40:53
Comment
34/kimurakosaku118
ObsNuc 1H
ExMode single_pulse.ex2
ObsFreq 500.16 MHz
ObsSpe 2.41 kHz
ObsFine 6.0092 Hz
Point 11107
Frequency(Scan) 7507.893 Hz
Scan 16
AcqTime 1.7459 s
PD 4.0 s
Pulse1 6.02 μs
Temperature 19.1 ℃
Solvent CDCl3
Reference 7.26 ppm
Broad.Factor 0.2864 Hz
RGain 42
Printed 2019/Feb/28 10:16:04
Operator
HO
Cl
HO
O
12
34/kimurakosaku118
δ / ppm

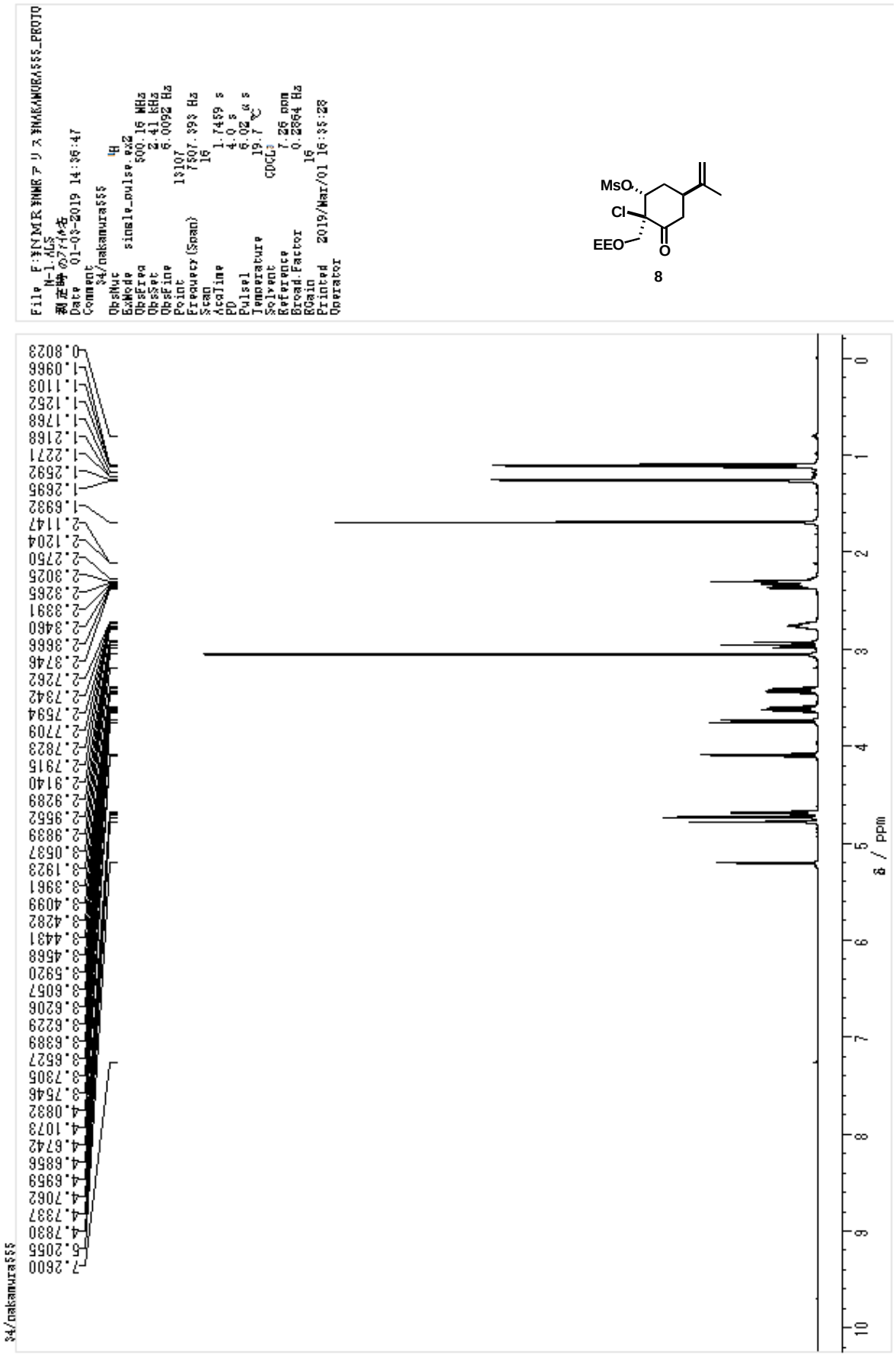

File C:¥USERS¥天馬¥DESKTOP¥実験項用ラモ¥
1
Date 14/Feb/2019 22:18:21
Comment %4/kinurakosakw118
ObsNuc 13C
ExMode single_pulse_dec
ObsFreq 125.77 MHz
ObsSet 7.87 kHz
ObsFine 4.2181 Hz
Point 26214
Frequency(Span) 31446.06 Hz
Scan 2048
AcqTime 0.8336 s
PD 2.0 s
Pulsel 3.8867 μ s
Temperature 19.8 ℃
Solvent CDCl3
Reference 77.16 ppm
Broad.Factor 0.5998 Hz
RGain 54
Printed 2019/Feb/28 10:25:08
Operator
HO
Cl
HO
O
12
%4/kinurakosakw118
207.1674
146.5822
110.7850
77.4163
77.1600
76.9049
67.1138
66.2613
41.9171
39.6839
39.5301
32.9976
20.5214
200
150
100
50
0
δ / ppm

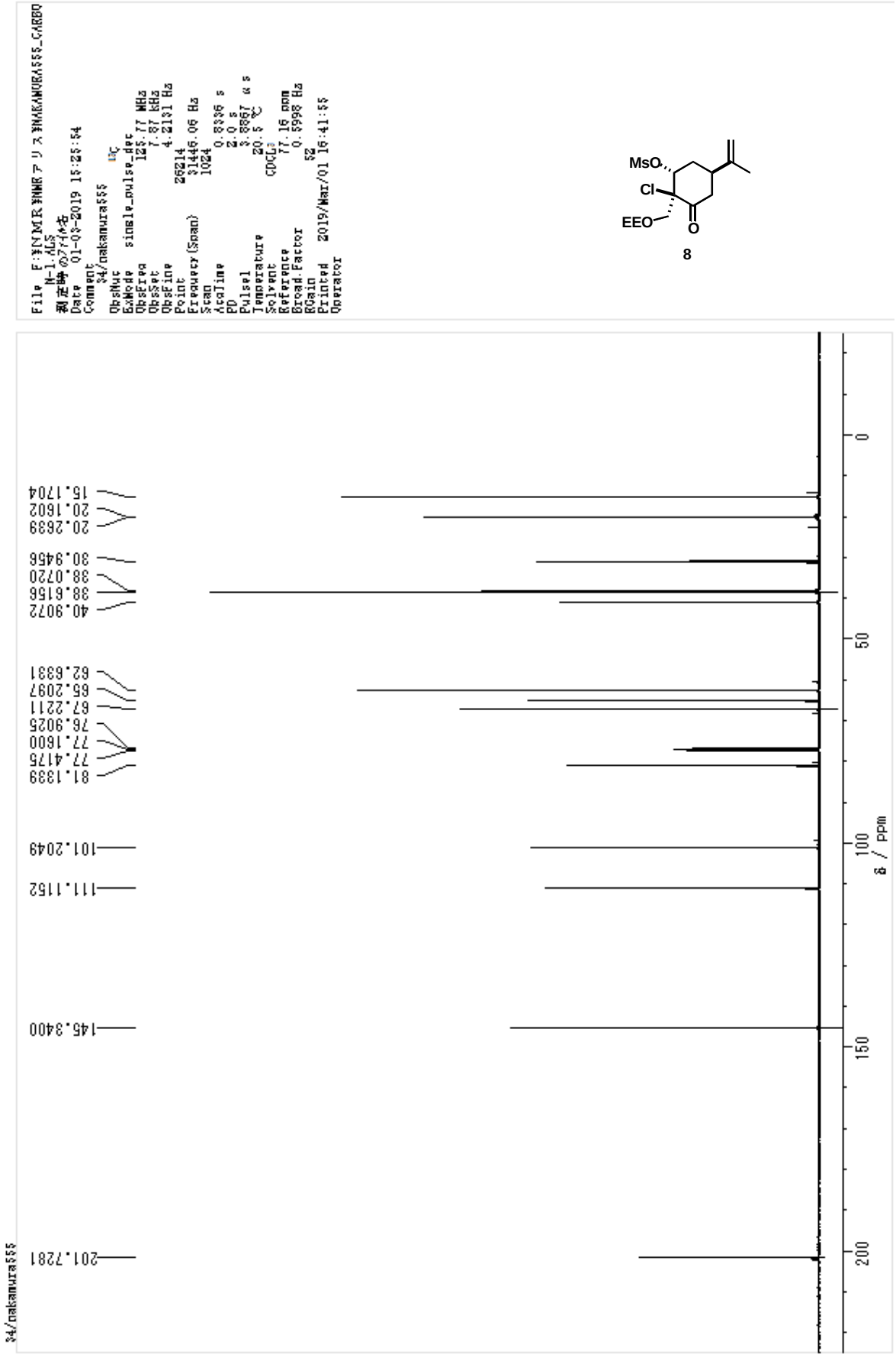

File G:¥NMR¥MOR1122_PROTON-1.ALS
測定時のファイル名
Date 13-11-2014 07:38:29
Comment 34/mori122
1H
ObsNuc
ExMode single_pulse.ex2
ObsFreq 300.53 MHz
ObsSet 1.15 kHz
ObsFine 8.5726 Hz
Point 13107
Frequecy(Span) 4508.498 Hz
Scan 16
AcqTime 2.9072 s
FD 4.0 s
Pulsel 5.875 μs
Temperature 460.0 ℃
Solvent CDCl3
Reference 7.28 ppm
Broad.Factor 0.172 Hz
RGain 70
Printed 2016/Jan/21 21:07:33
Operator
THPO
Cl
THPO
O
13
34/mori122
15.4574
0.0918
0.9628
0.7902
2.0893
3.141
0.6372
1.7446
1.0
δ / ppm

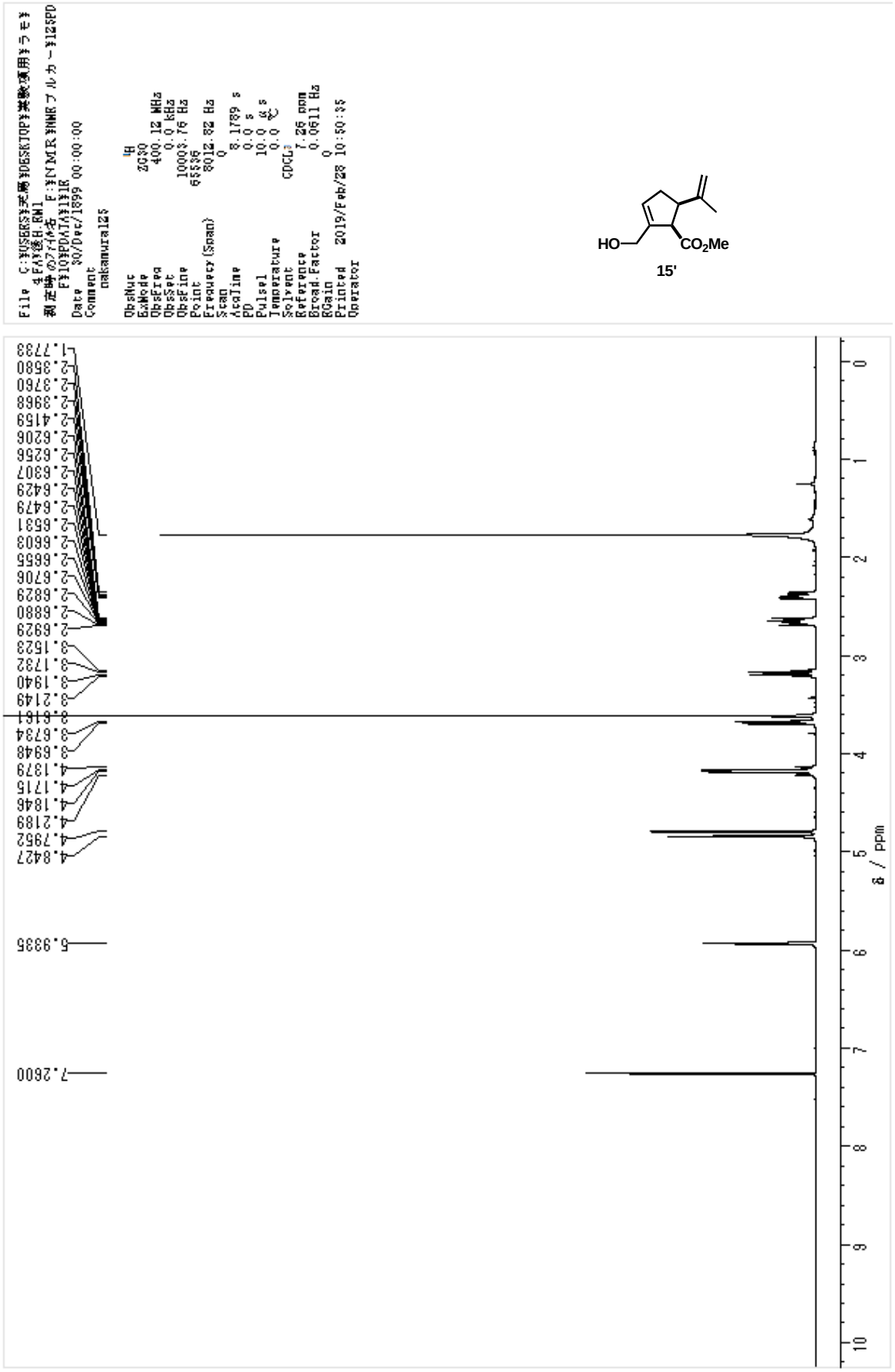

File G:¥NMR¥MORI063_PROTON-1.ALS
測定時のファイル名
Date 01-09-2014 18:19:59
Comment 34/mori063
ObsNuc 1H
ExMode single_pulse.ex2
ObsFreq 300.53 MHz
ObsSet 1.15 kHz
ObsFine 8.5728 Hz
Point 13107
Frequecy(Span) 4508.488 Hz
Scan 16
AcqTime 2.9072 s
PD 4.0 s
Pulsel 5.875 μs
Temperature 24.4 ℃
Solvent CDCl3
Reference 7.28 ppm
Broad.Factor 0.172 Hz
RGain 70
Printed 2016/Jan/21 21:02:18
Operator
34/mori063
9.8167
8.7452
2.3953
2.0234
0.7995
1.9276
1.4615
0.807
1.0
2.6705
δ / ppm

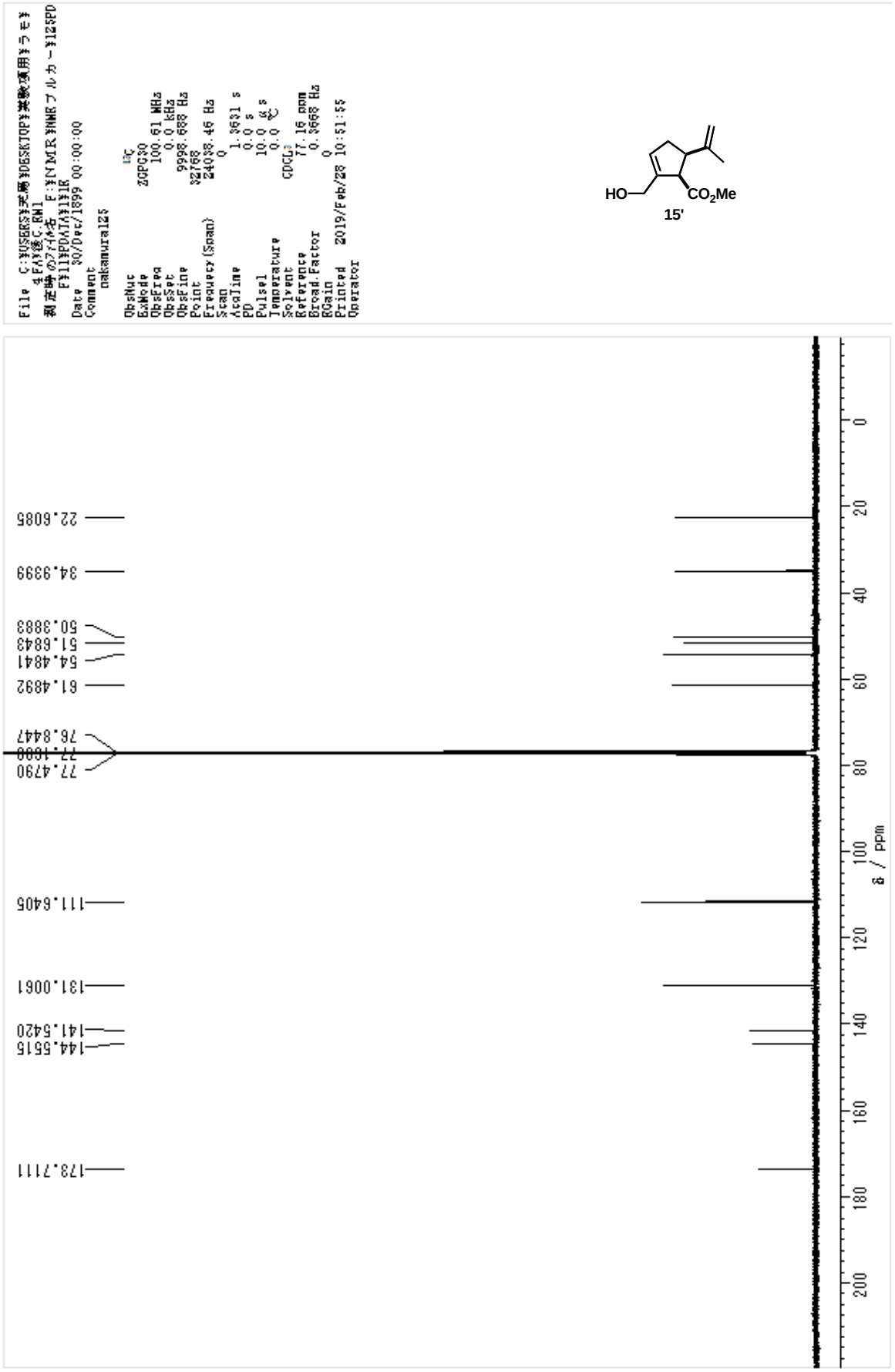

File C:¥USERS¥武馬¥DESKTOP¥実験項用¥ラモ¥
2－酸化生成物1H.RM1
Date 07/Mar/2018 13:07:54
Comment s4kimura kosaku027
1H
ExpMode single_pulse.ex2
500.16 MHz
2.41 kHz
0.0092 Hz
Point 13120
Frequency(Scan) 7507.398 Hz
Scan 16
1.7459 s
4.0 s
5.7 μs
21.7 ℃
Solvent CDCl3
Reference 7.26 ppm
Broad.Factor 0.2861 Hz
RGain 54
Printed 2019/Feb/28 10:32:02
Operator
HO
Cl
EEO
O
12'
δ / ppm
s4kimura kosaku027

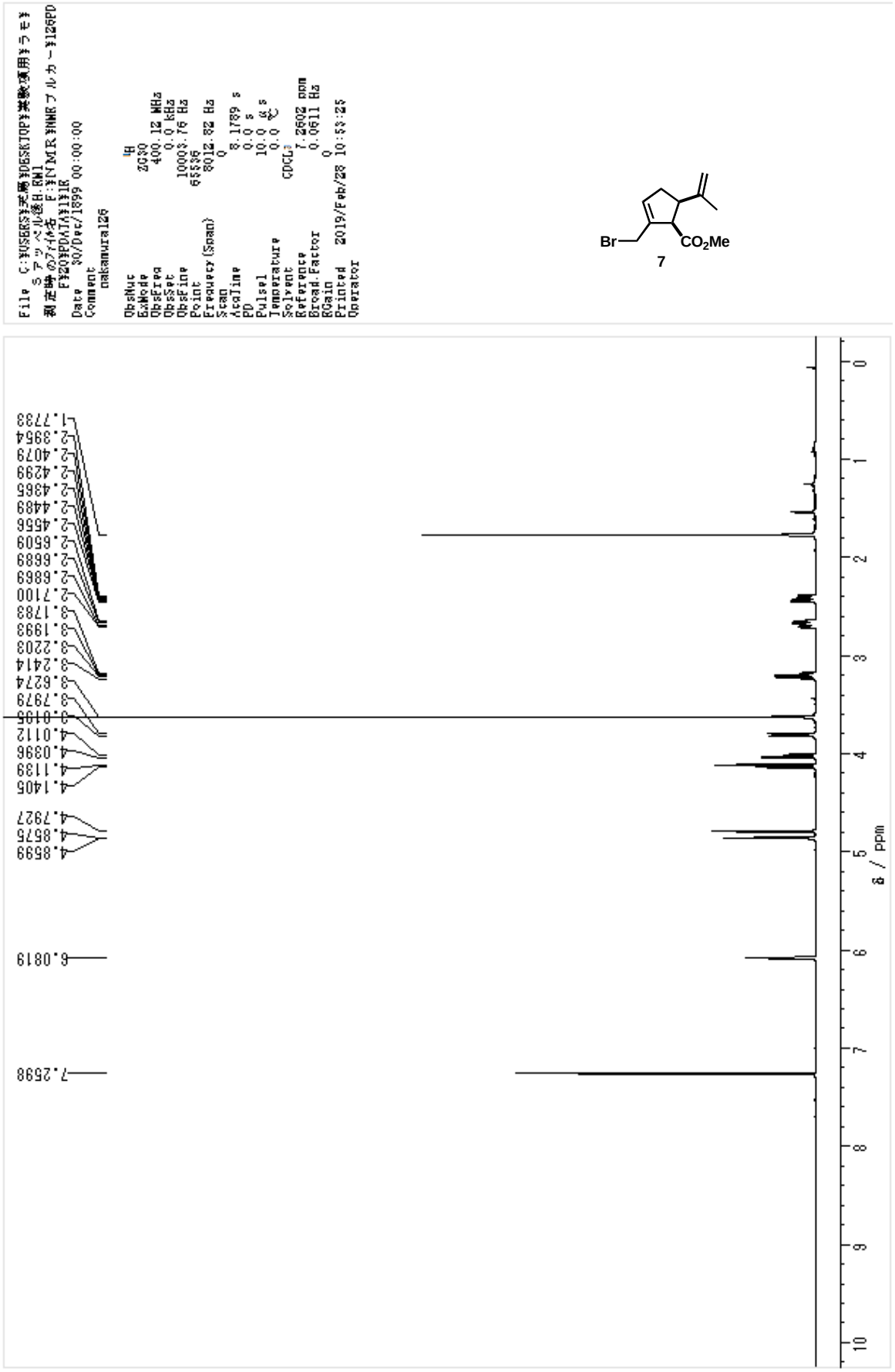

HO
Cl
EEO
O
12'
15.1089
20.0328
20.4120
31.9832
39.0922
41.5640
62.9621
67.9001
68.3941
72.2238
76.8410
77.1600
77.4790
101.3452
110.4301
146.8500
204.8928
δ / ppm

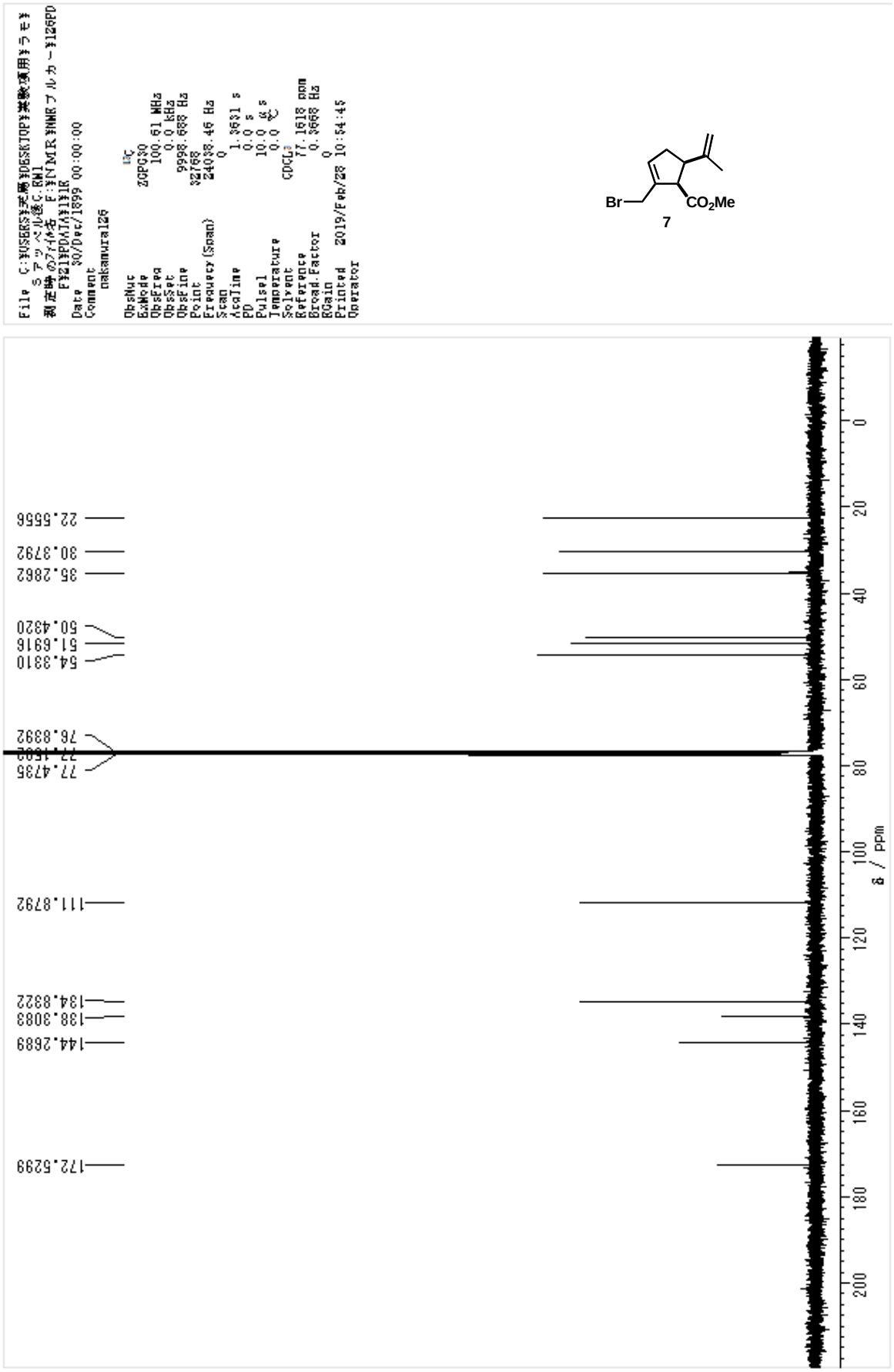

MsO
Cl
EEO
O
8
δ / ppm

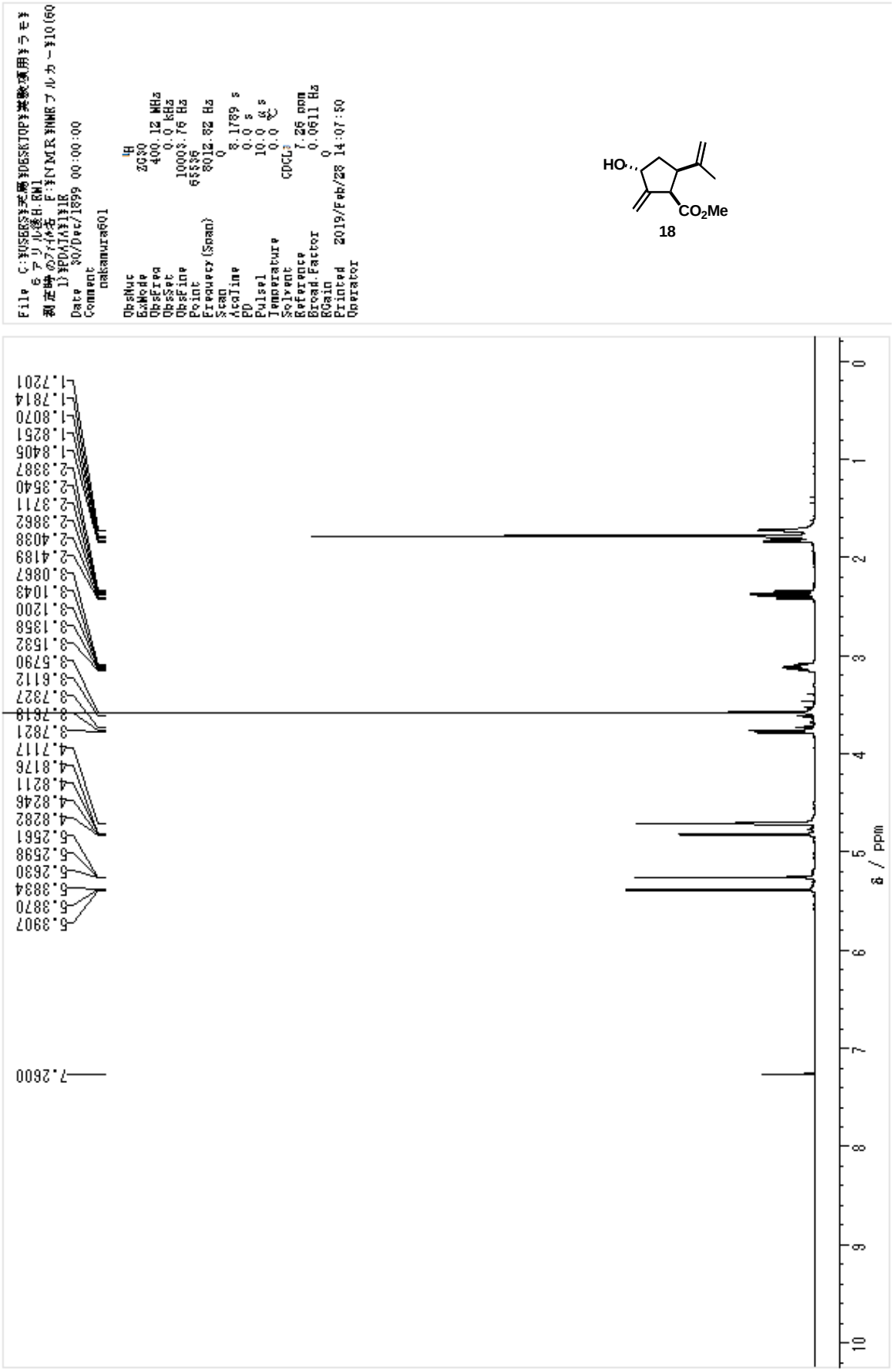

File F:¥NMR¥NMRアリス¥MAKAMURA555_CARBO
N-1.AUS
測定時 07分4秒
Date 01-03-2019 15:25:54
Comment
34/nakamura555
ObsNuc 13C
ExMode single_pulse_dec
ObsFreq 125.77 MHz
ObsSet 7.87 kHz
ObsFine 4.2131 Hz
Point 26214
Frequency(Span) 31446.06 Hz
Scan 1024
AcqTime 0.8336 s
PD 2.0 s
Pulsel 3.9861 μ s
Temperature 20.5 ℃
Solvent CDCl3
Reference 77.16 ppm
Broad.Factor 0.5998 Hz
RGain 52
Printed 2019/Mar/01 16:41:55
Operator
MsO
Cl
EEO
O
8
34/nakamura555
201.7281
145.8400
111.1152
101.2049
81.1389
77.4175
77.1600
76.9025
67.2211
65.2097
62.6381
40.9072
38.6156
38.0720
30.9456
20.2639
20.1602
15.1704
200
150
100
50
0
δ / ppm

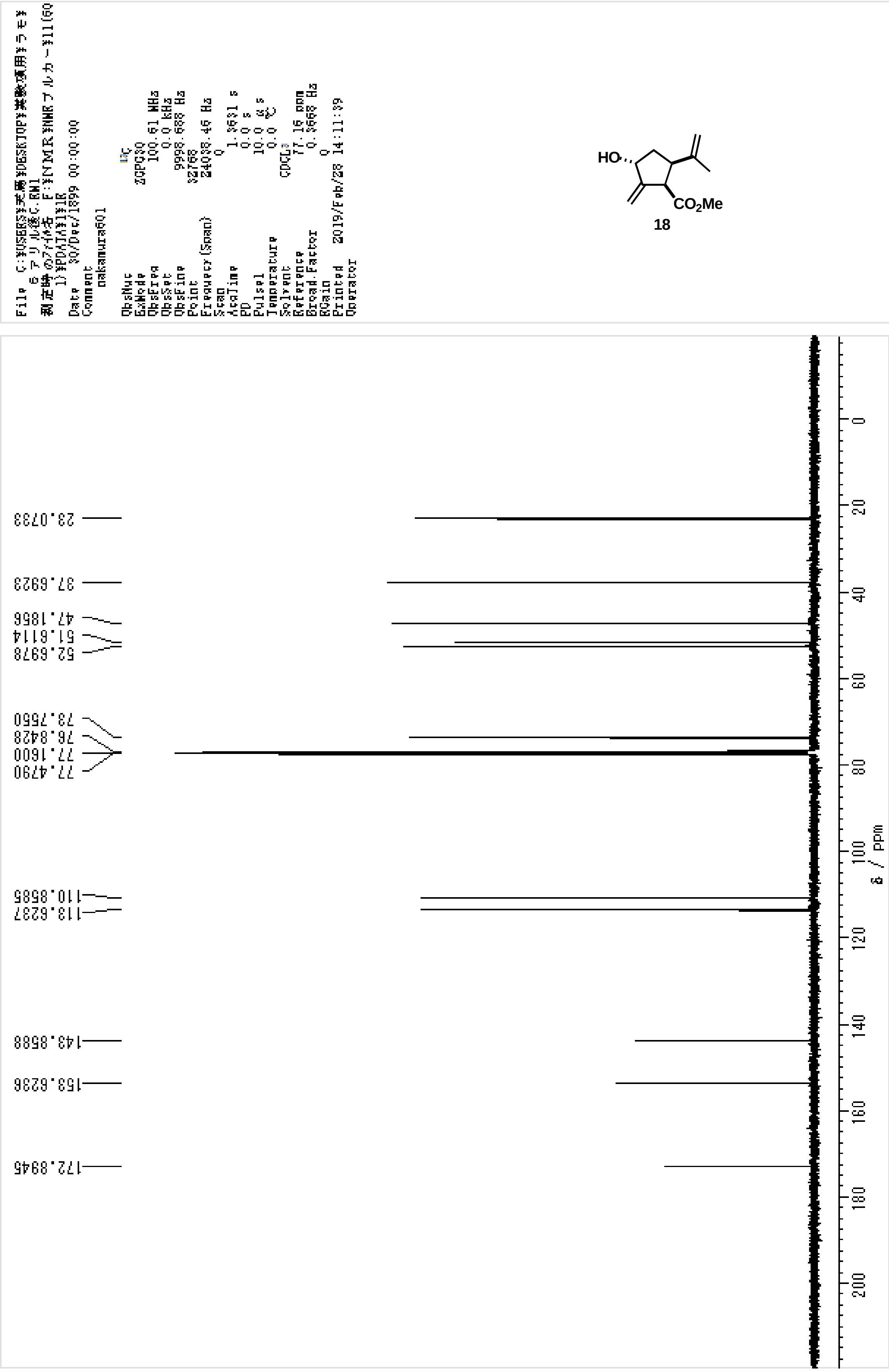

HO
CO2Me
15'
δ / ppm

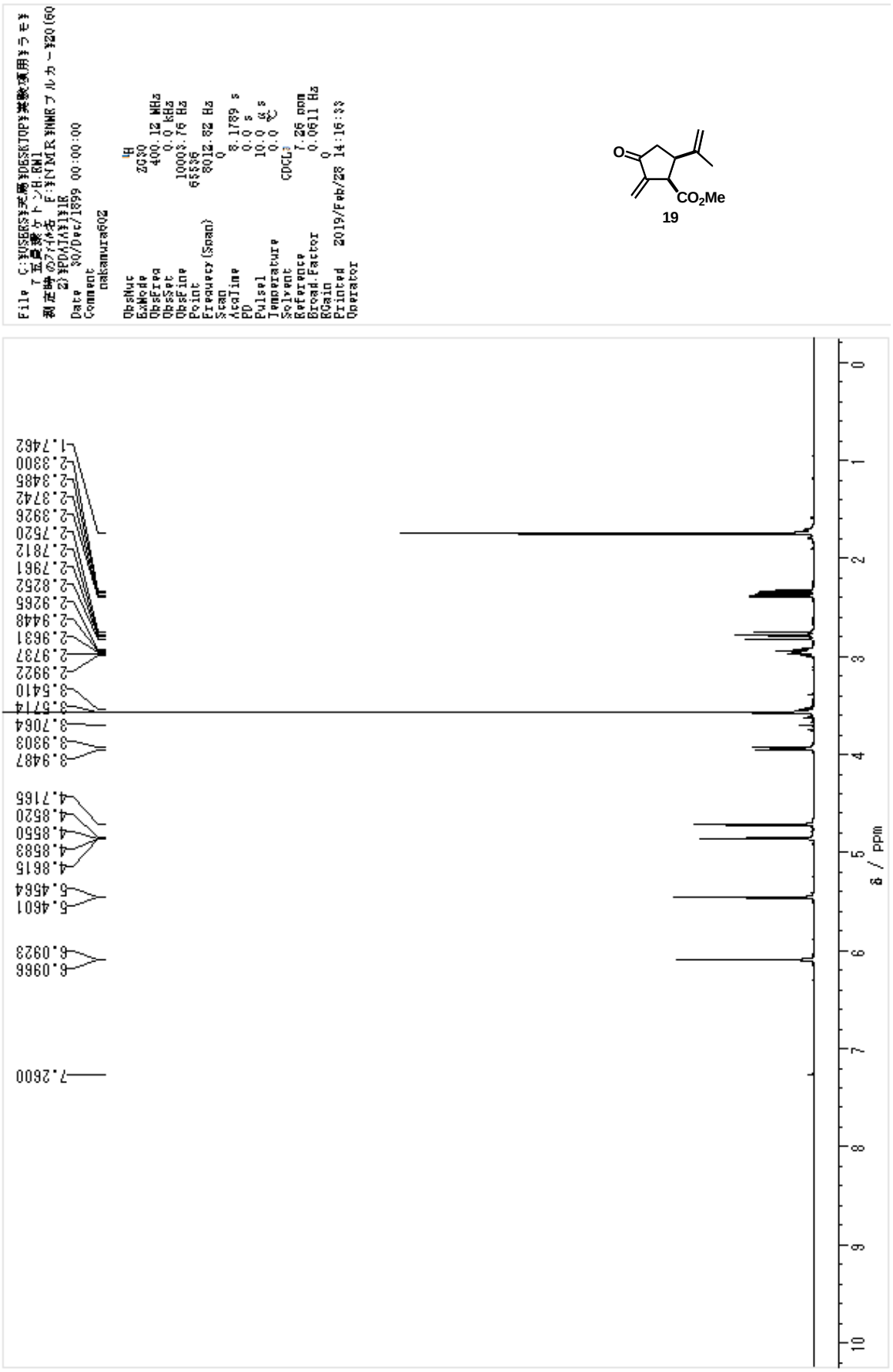

File C:¥USERS¥天馬¥DESKTOP¥実験項用¥ラモ¥
生FA¥後C.RM1
測定時のファイル名 F:¥NMR¥NMRプルカ一¥125PD
F¥111¥PDATA¥11¥1R
Date 30/Dec/1899 00:00:00
Comment
nakamura125
13C
ZGPG30
100.61 MHz
0.0 kHz
9998.688 Hz
32768
240198.46 Hz
0
1.8631 s
0.0 s
10.0 μs
0.0 ℃
CDCl3
77.16 ppm
0.3668 Hz
0
2019/Feb/23 10:51:55
HO
CO2Me
15'
22.6085
34.9399
50.3883
51.6843
54.4841
61.4892
76.8447
77.1608
77.4790
111.6405
131.0061
141.5420
144.5515
178.7111
δ / ppm

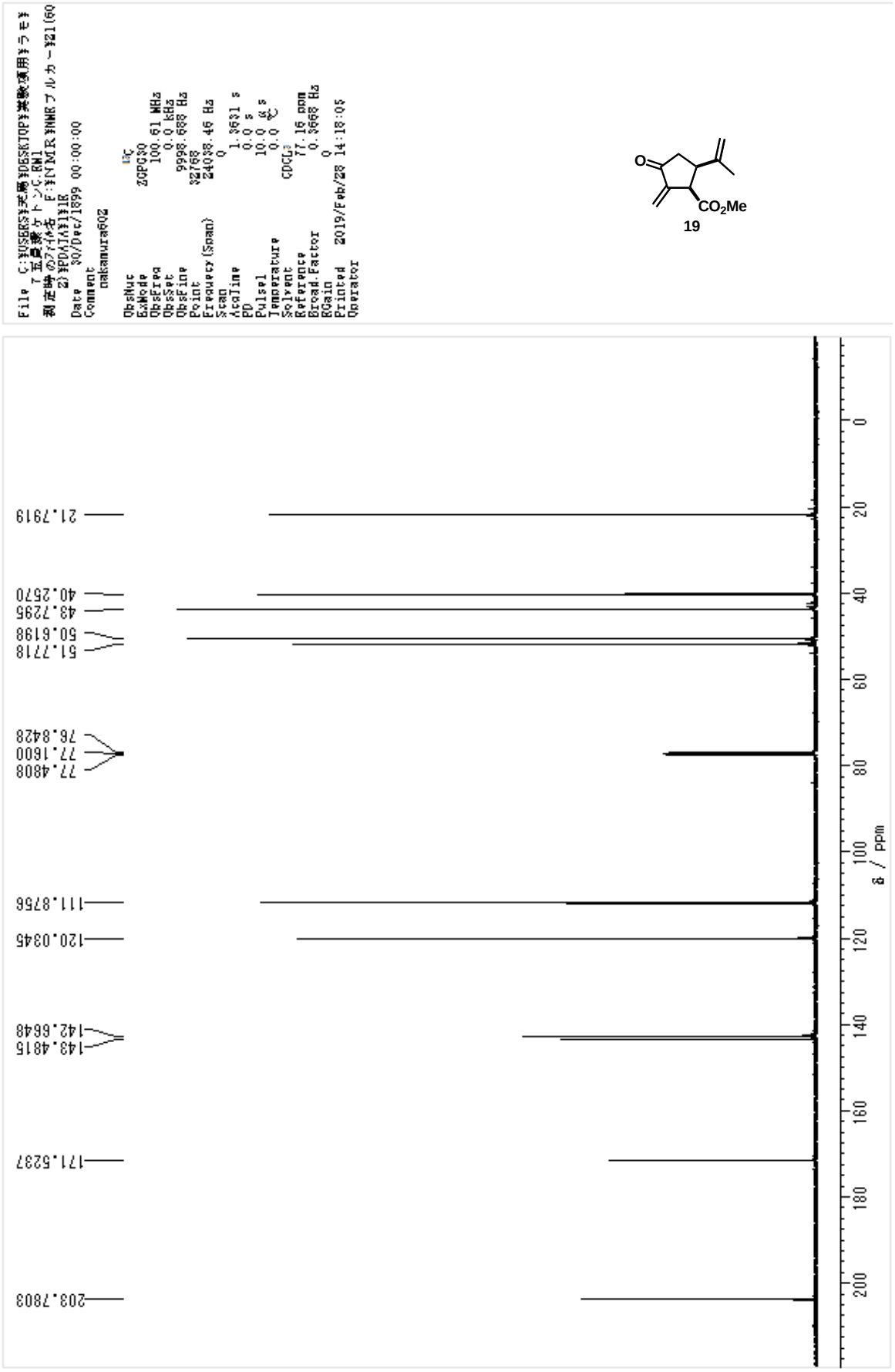

File C:¥USERS¥武原¥DESKTOP¥実験項用¥ラモ¥
SアッペルⅡ.EN1
測定時のファイル名 F:¥NMR¥NMRアルカ～¥126PD
F¥20¥PDATA¥1¥1R
Date 20/Dec/1899 00:00:00
Comment
nakamura126
1H
ZG30
400.12 MHz
0.0 kHz
10003.76 Hz
65536
8012.82 Hz
0
8.1789 s
0.0 s
10.0 μs
0.0 ℃
CDCL3
7.2602 ppm
0.0611 Hz
0
2019/Feb/28 10:53:25
Br
CO2Me
7
δ / ppm

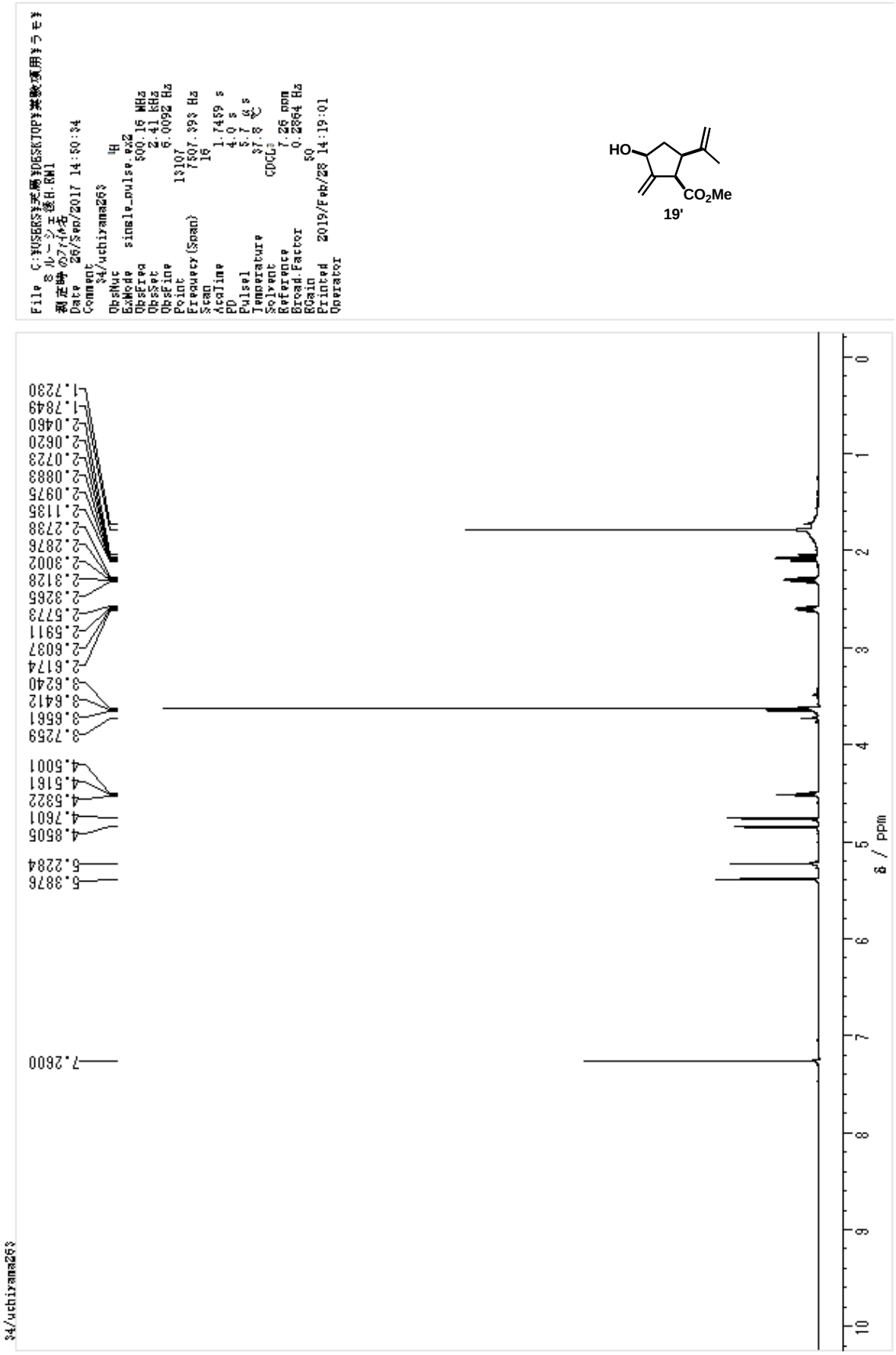

File C:¥USERS¥共用¥DESKTOP¥実験項用¥ラモ¥
SアッペルⅡ後C.EN1
測定時のファイル名 F:¥JNM-MIR¥NMRアルカ～¥126PD
FY21¥PDATA¥1¥1R
Date 30/Dec/1899 00:00:00
Comment
nakamura126
13C
ObsNuc
ExMode
ObsFreq
ObsSet
ObsFine
Point
Frequency(Scan)
Scan
AcqTime
PD
Pulse1
Temperature
Solvent
Reference
Broad.Factor
RGain
Printed 2019/Feb/28 10:54:45
Operator
ZGPG30
100.61 MHz
0.0 kHz
9998.688 Hz
32768
24038.46 Hz
0
1.3631 s
0.0 s
10.0 μs
0.0 ℃
CDCl3
77.1618 ppm
0.3668 Hz
0
Br
CO2Me
7
22.5556
30.3792
35.2862
50.4320
51.6916
54.3310
76.8992
77.1618
77.4735
111.8792
134.8822
138.3083
144.2689
172.5299
0
20
40
60
80
100
120
140
160
180
200
δ / ppm

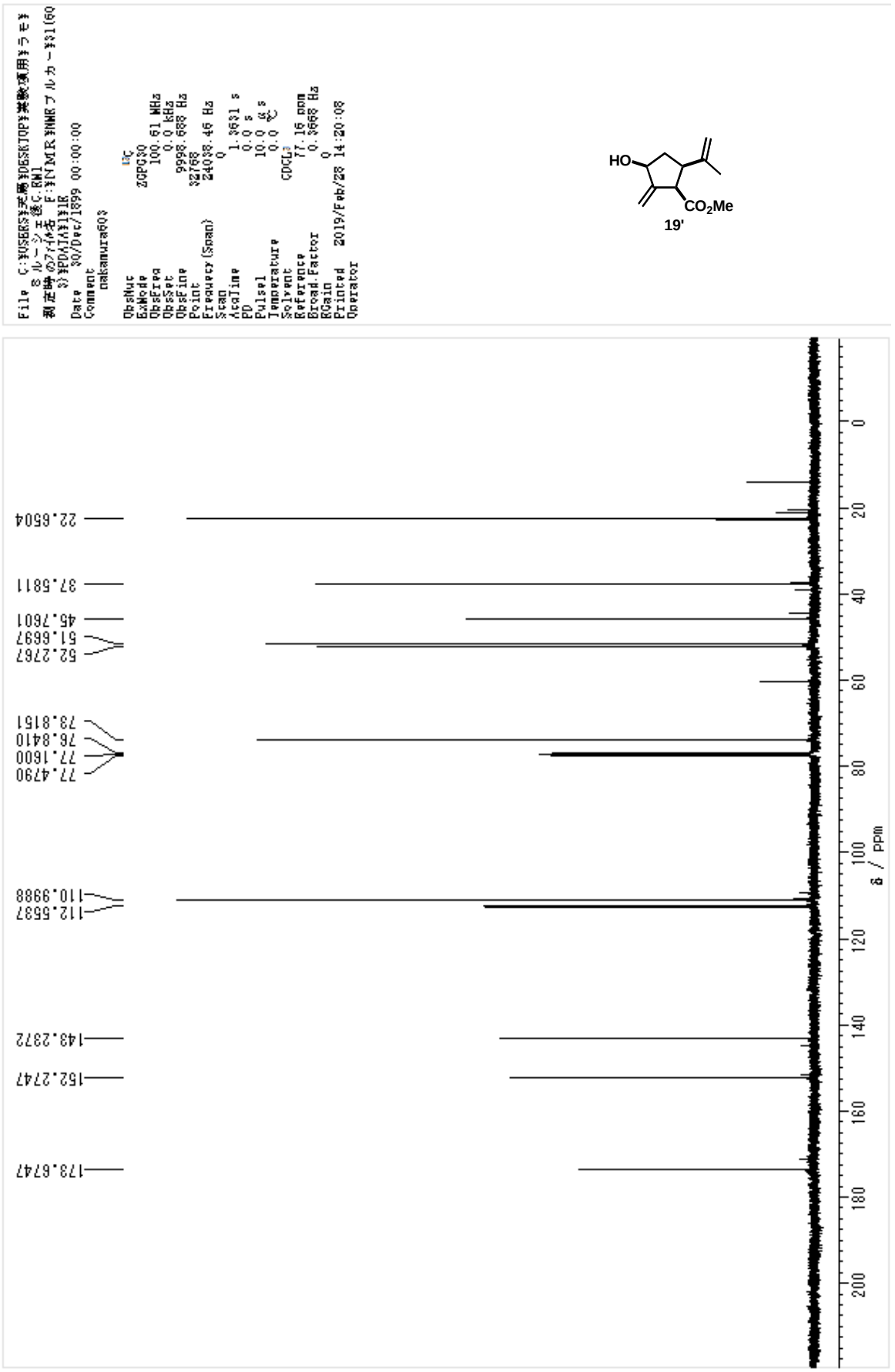

HO
CO2Me
18
δ / ppm

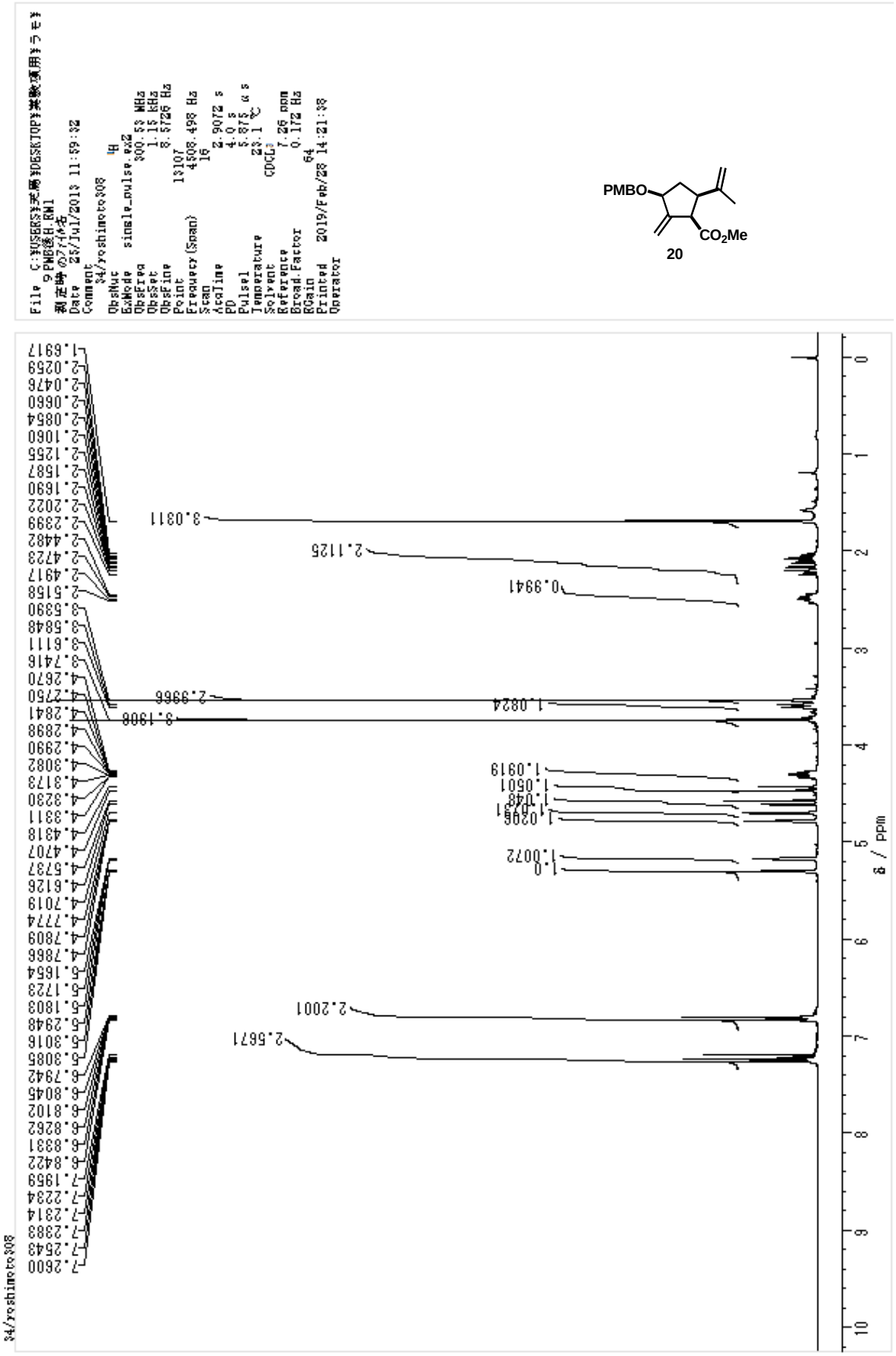

HO
CO2Me
18

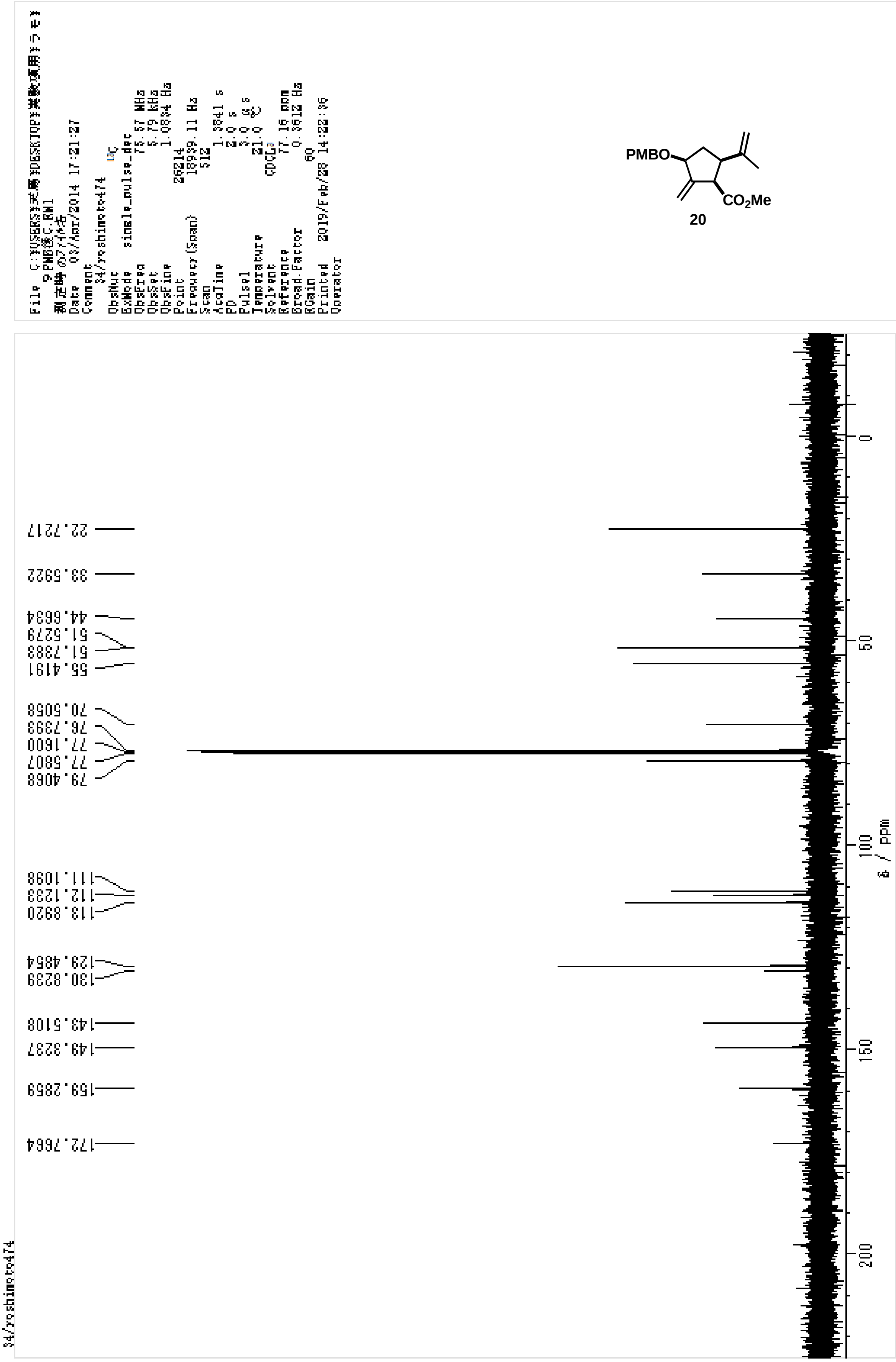

File C:¥USERS¥天馬¥DESKTOP¥実験項用¥ラモ¥
7_五員環ケトン_H.RM1
測定時のファイル名 F:¥NMR¥NMRプルカ～¥20(60
2)¥PDATA¥1¥1R
Date 30/Dec/1899 00:00:00
Comment
nakamura602
1H
ZG30
400.13 MHz
0.0 kHz
10003.76 Hz
65536
8012.82 Hz
0
8.1789 s
0.0 s
10.0 μs
0.0 ℃
CDCl3
7.26 ppm
0.0611 Hz
0
2019/Feb/23 14:16:33
Operator
O
CO2Me
19
δ / ppm

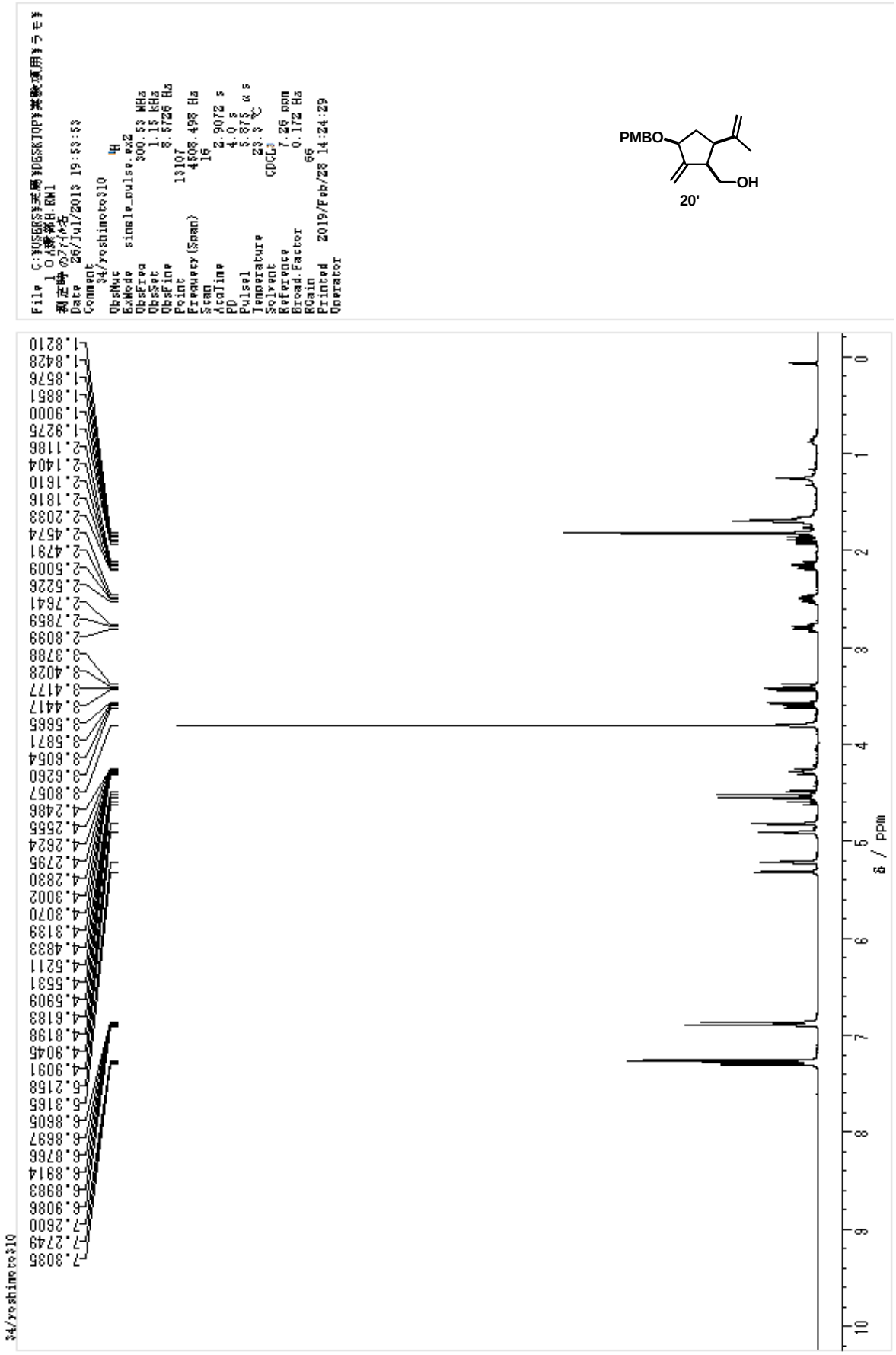

File C:¥USERS¥天馬¥DESKTOP¥実験項用¥ラモ¥
7五員環ケトン(C.RWI
測定時のファイル名 F:¥NMR¥NMRプルカ一¥21(60
2)¥PDATA¥1¥1R
Date 30/Dec/1899 00:00:00
Comment
nakamura602
13C
ObsNuc
ExMode
ObsFreq
ObsSet
ObsFine
Point
Frequency(Snum)
Scan
AcqTime
PD
Pulsel
Temperature
Solvent
Reference
Broad.Factor
RGain
Printed 2019/Feb/23 14:18:05
Operator
O
CO2Me
19
21.7919
40.2570
43.7295
50.6198
51.7718
76.8428
77.1600
77.4808
111.8756
120.0845
142.6648
143.4815
171.5237
208.7803
δ / ppm

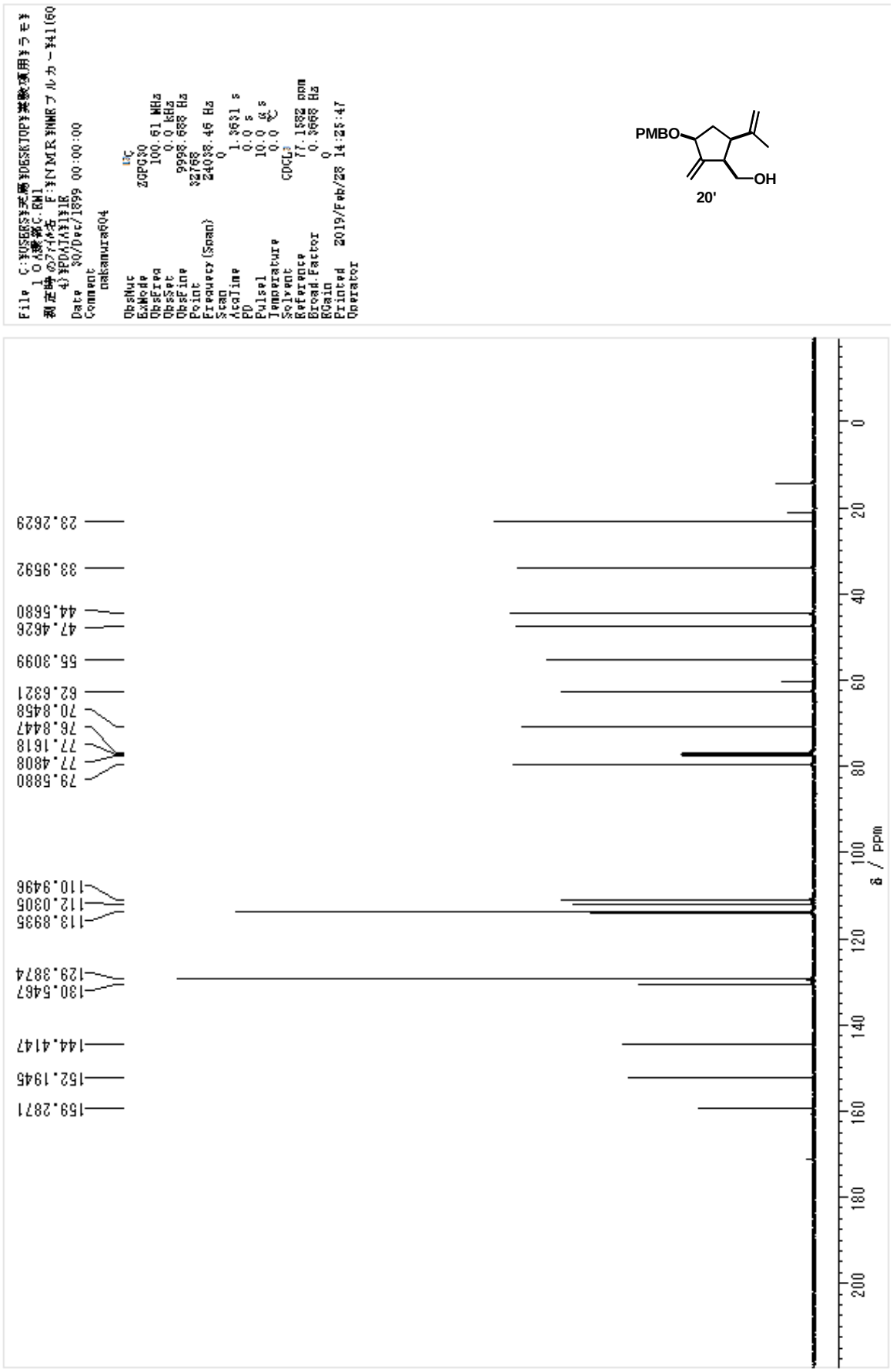

HO
CO2Me
19'
δ / PPM

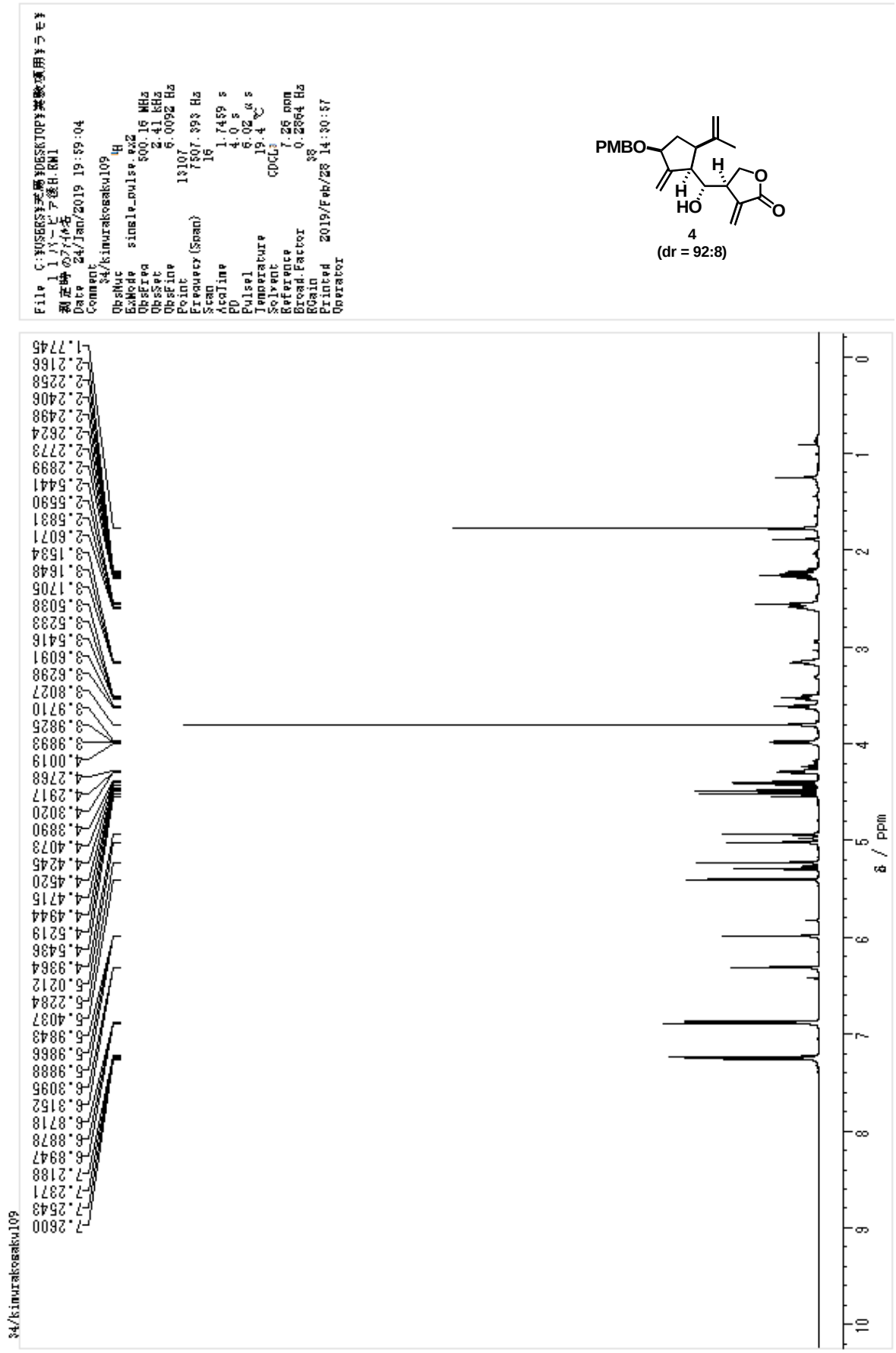

HO
CO2Me
19'
22.6504
37.5811
45.7601
51.6697
52.2767
78.8151
76.8410
77.1600
77.4790
110.9988
112.5587
143.2372
152.2747
178.6747
δ / ppm

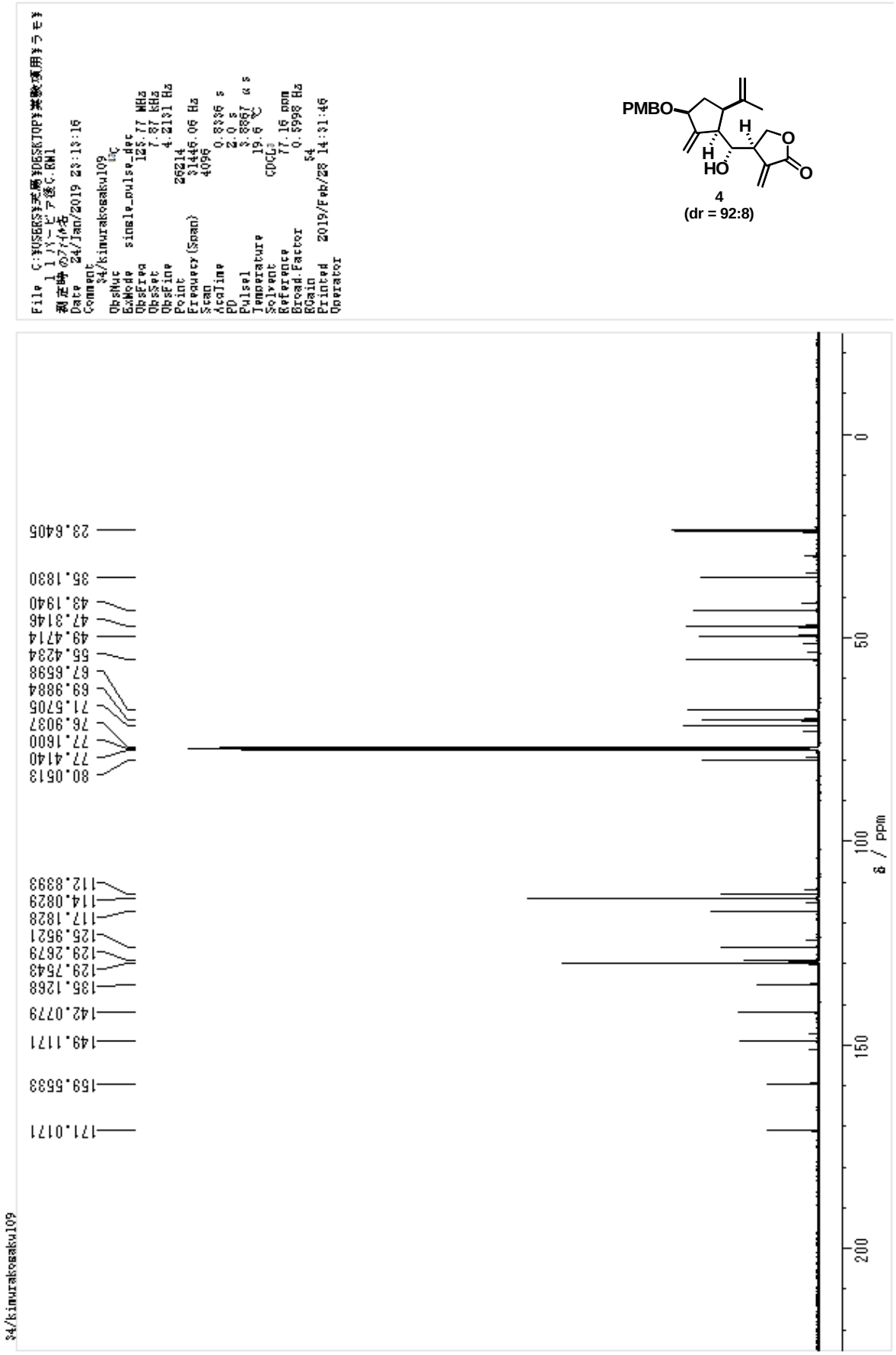

PMBO
CO2Me
20
δ / ppm

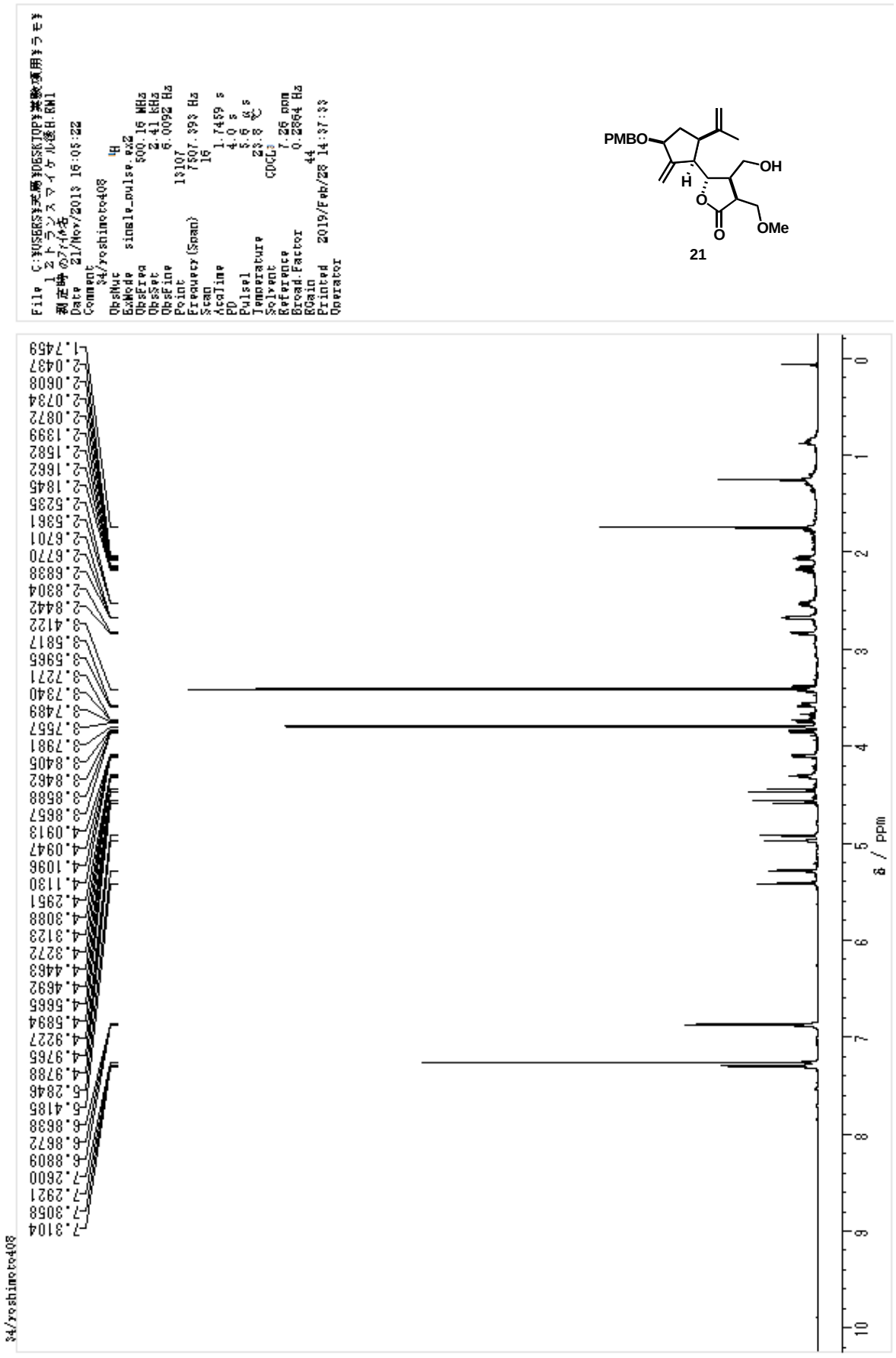

PMBO
CO2Me
20
22.7217
38.5922
44.6634
51.5279
51.7383
55.4191
70.5058
76.7393
77.1600
77.5807
79.4068
111.1098
112.1233
113.8920
129.4864
130.8239
143.5108
149.3237
159.2859
172.7664
δ / ppm
34/yoshimoto474

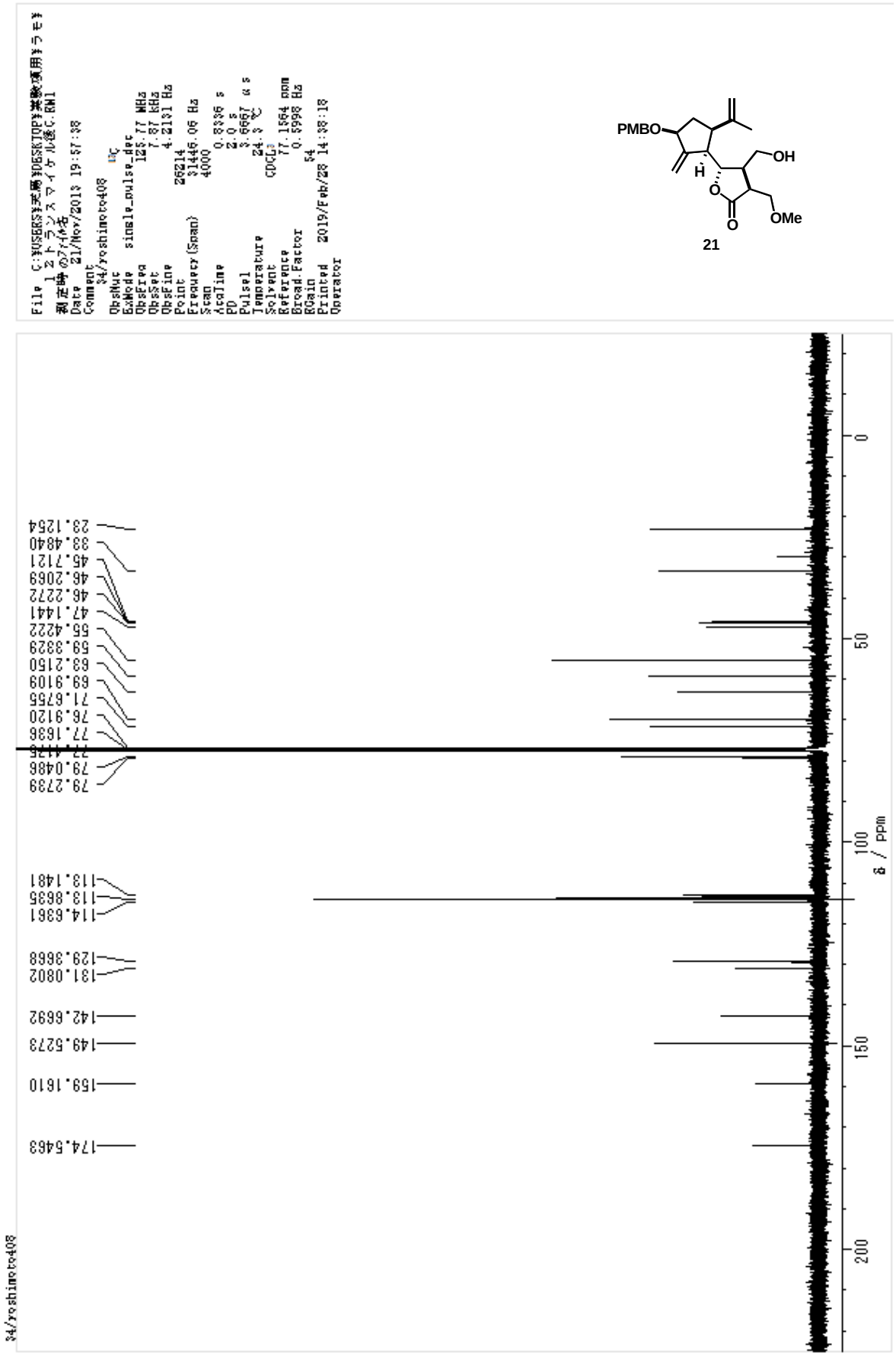

PMBO
OH
20'
δ / ppm

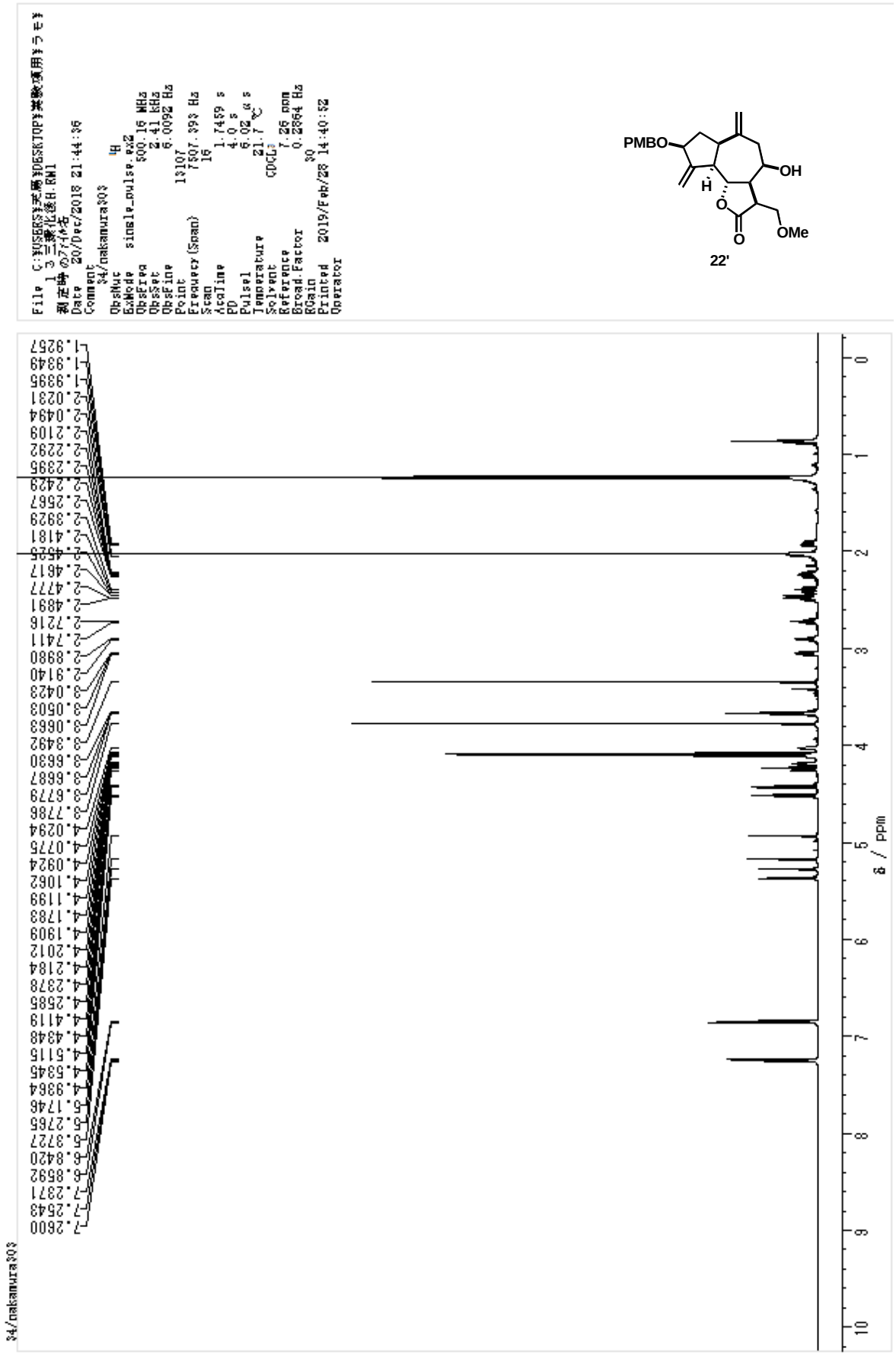

PMBO
OH
20'
28.2629
33.9592
44.5680
47.4626
55.3099
62.6321
70.8458
76.8447
77.1618
77.4808
79.5880
110.9496
112.0305
118.8935
129.3874
130.5467
144.4147
152.1945
159.2871
δ / ppm

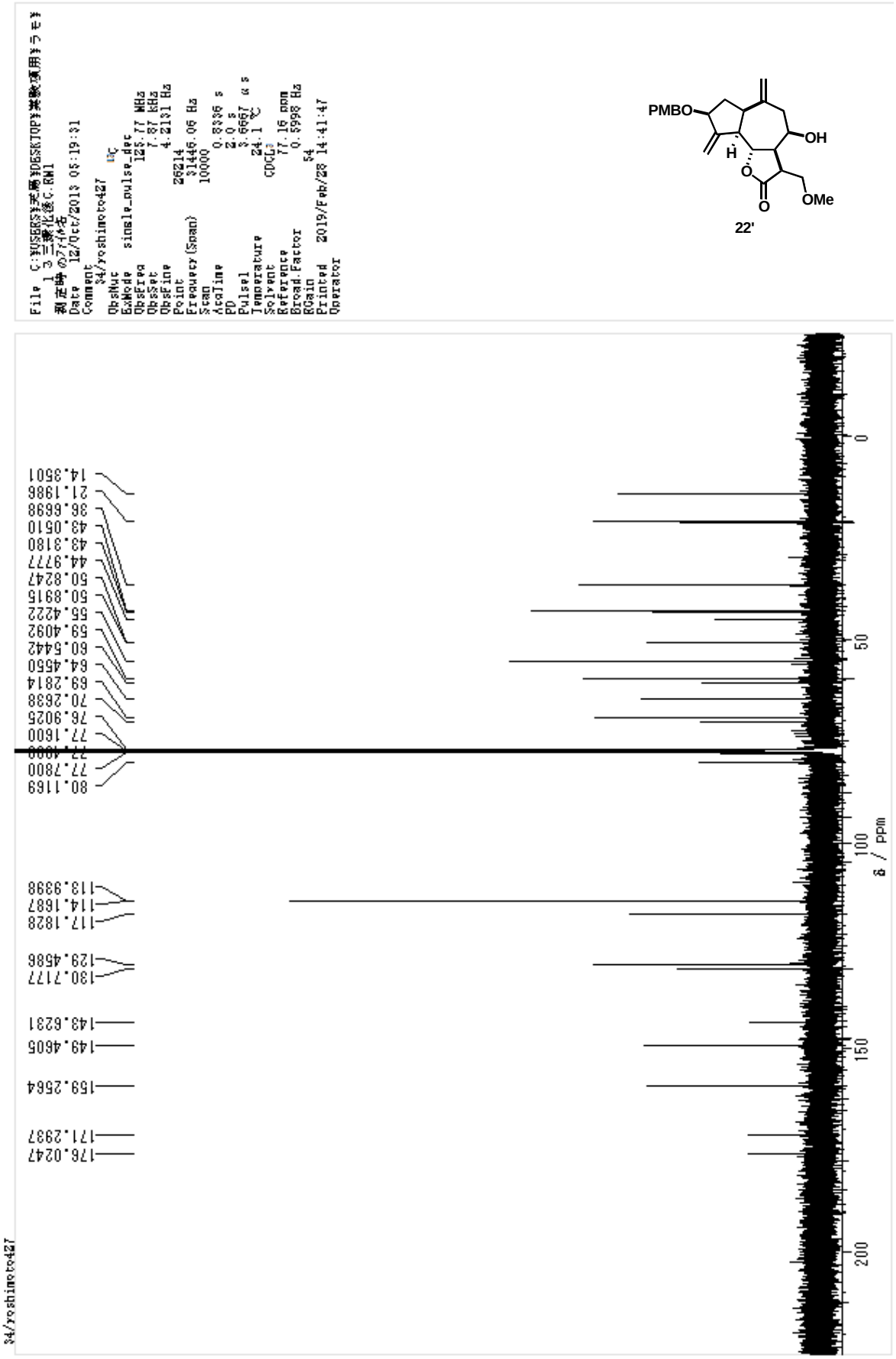

PMBO
H
O
H
HO
O
4
(dr = 92:8)
δ / ppm

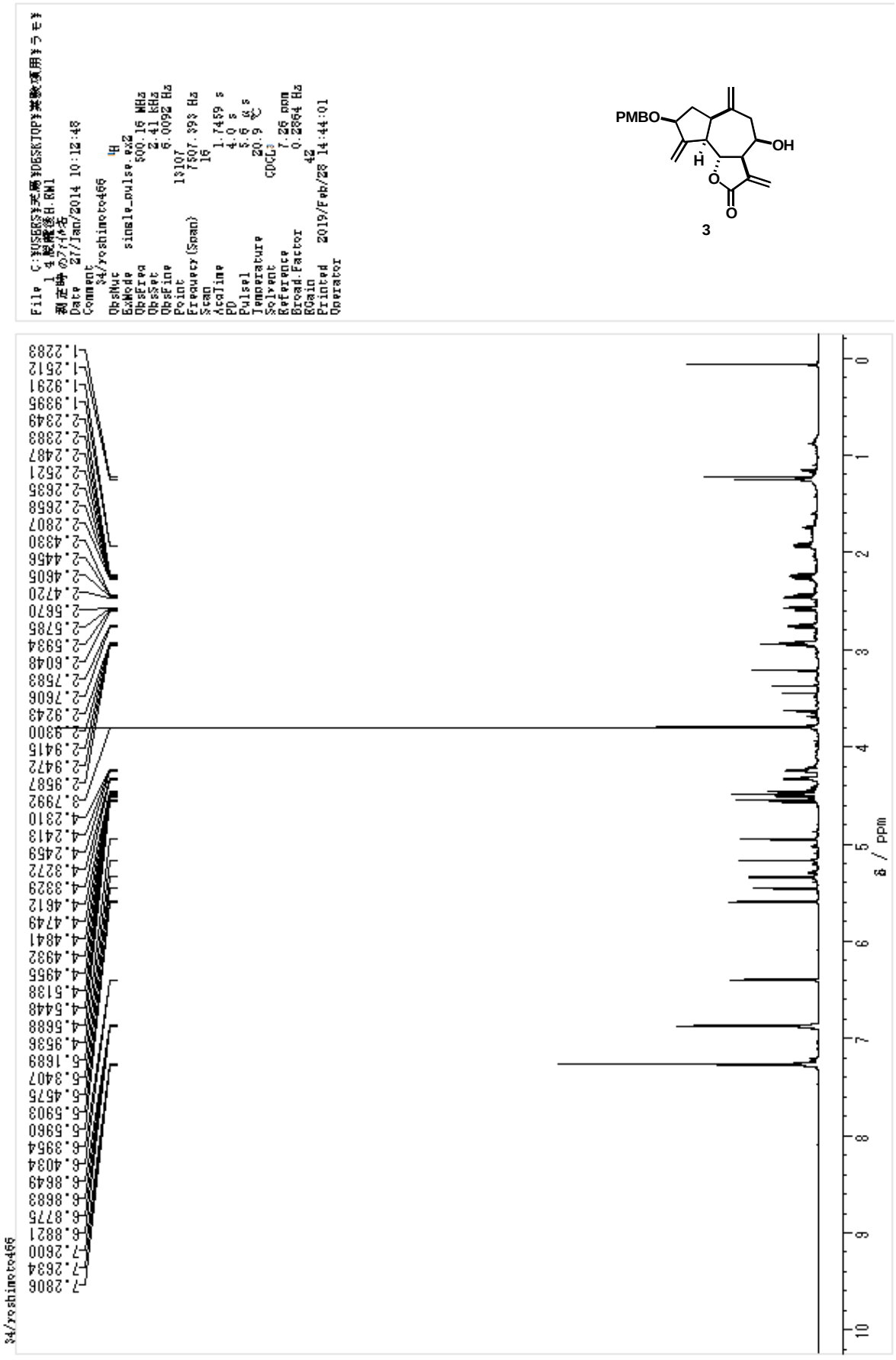

PMBO
H
O
H
HO
O
4
(dr = 92:8)
δ / ppm
0
50
100
150
200
28.6405
35.1830
43.1940
47.3146
49.4714
55.4234
67.6598
69.9884
71.5705
76.9037
77.1600
77.4140
80.0613
112.8398
114.0829
117.1828
125.9521
129.2679
129.7543
135.1268
142.0779
149.1171
159.5538
171.0171
34/kinurakosaku109

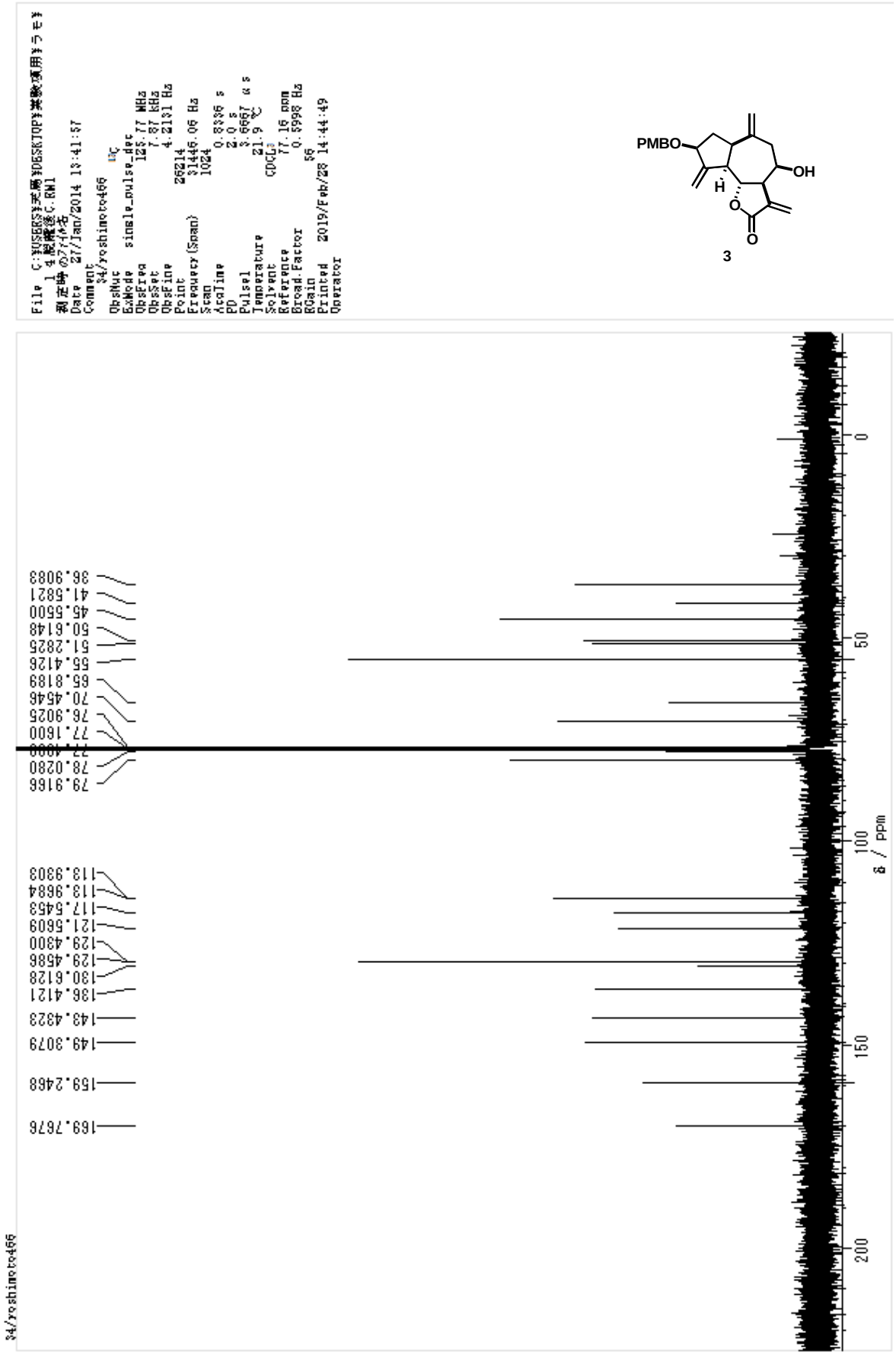

PMBO
OH
H
O
O
OMe
21
δ / ppm

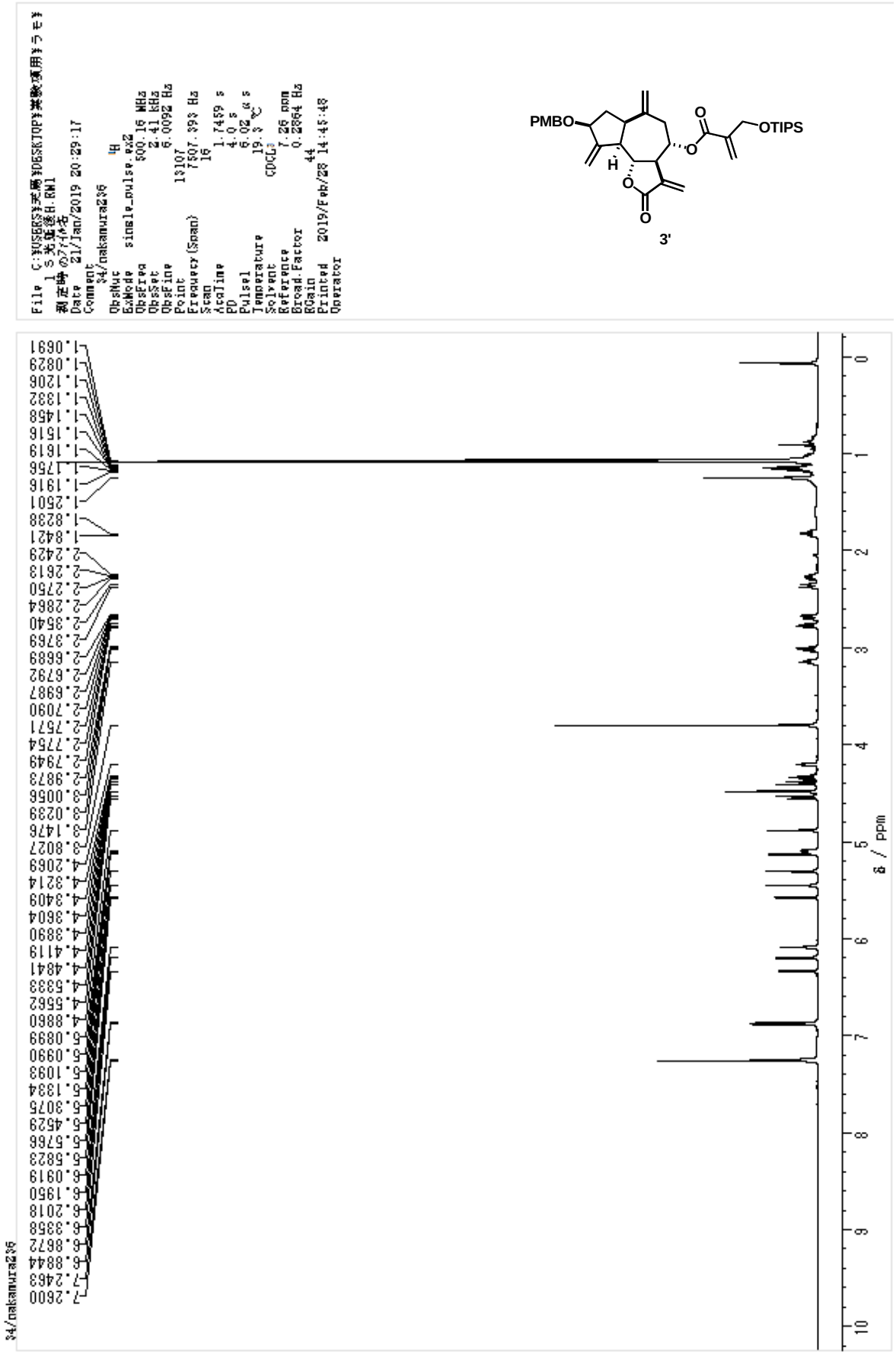

PMBO
OH
H
O
O
OMe
21
28.1254
38.4840
45.7121
46.2069
46.2272
47.1441
55.4222
59.3329
68.2150
69.9109
71.6755
76.9120
77.1636
79.0486
79.2739
114.6361
118.8635
118.1481
129.3668
131.0802
142.6692
149.5278
159.1610
174.5463
δ / ppm
0
50
100
150
200
34/yoshimoto408

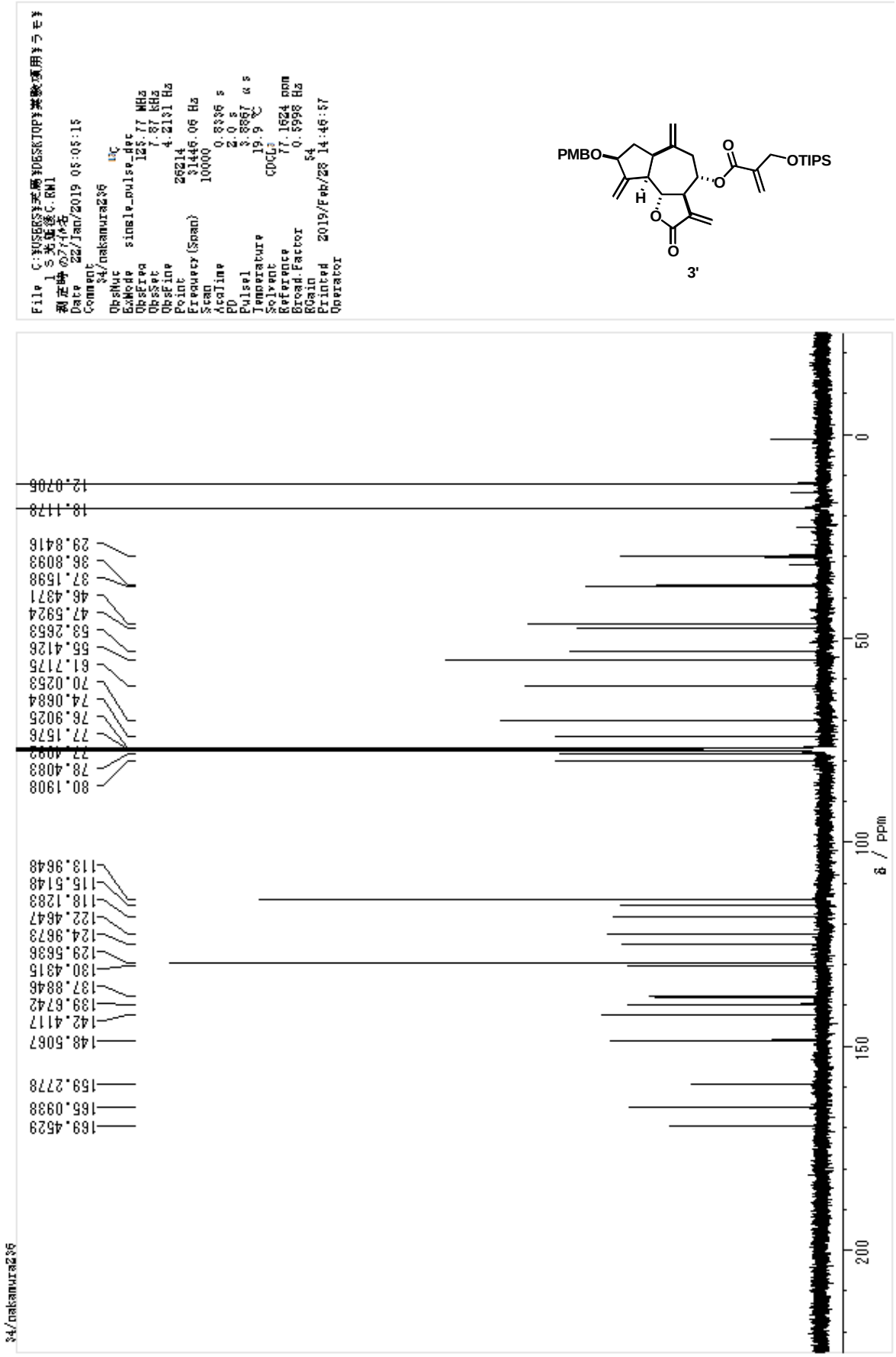

PMBO
OH
H
O
O
OMe
22'
δ / ppm

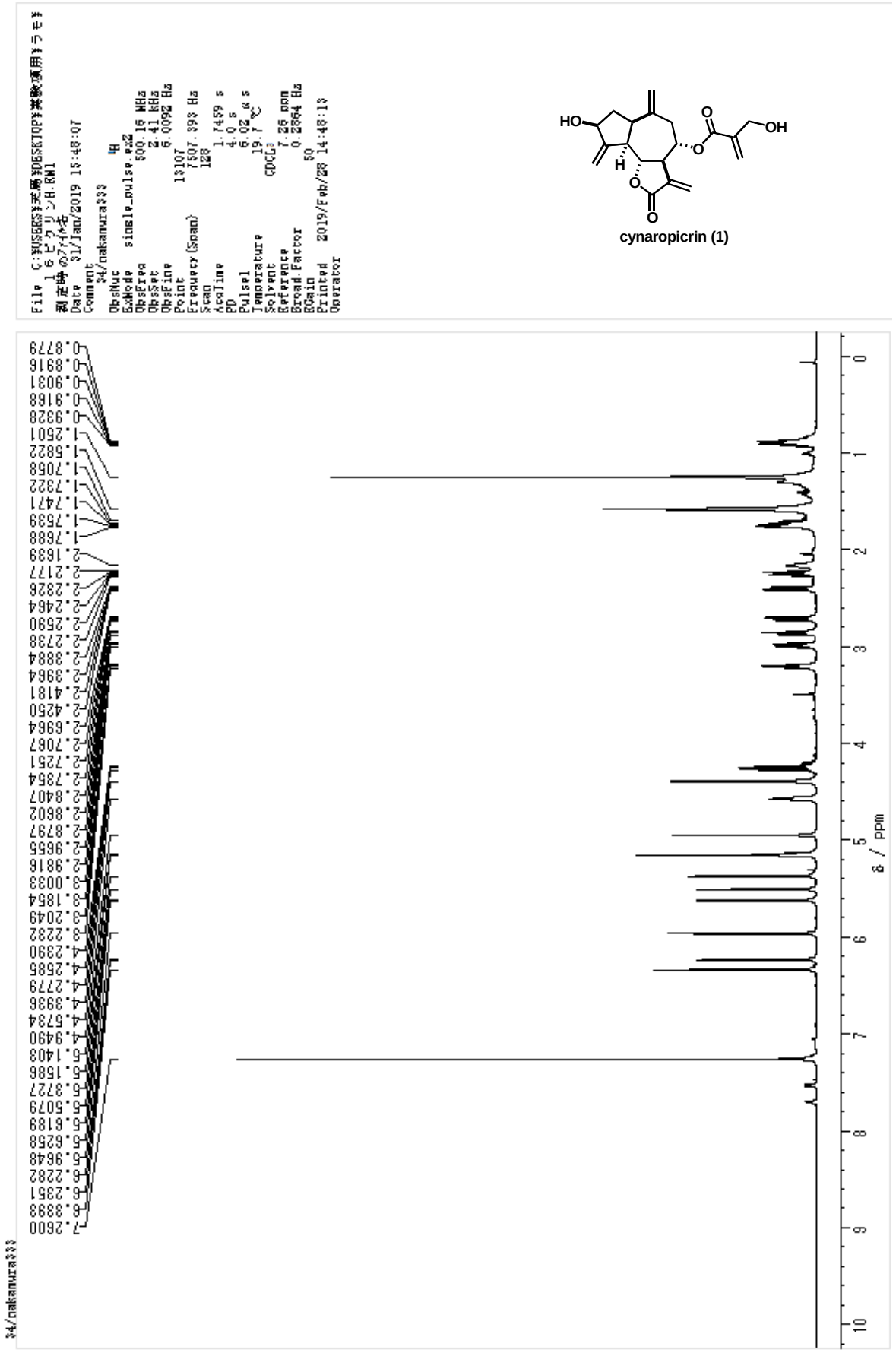

PMBO
OH
H
O
O
OMe
22'
δ / ppm
0
50
100
150
200
14.3501
21.1986
36.6698
43.0510
43.3180
44.9777
50.8247
50.8915
55.4222
59.4092
60.5442
64.4550
69.2814
70.2638
76.9025
77.1600
77.4800
77.7800
80.1169
117.1828
114.1687
118.9398
129.4586
130.7177
143.6231
149.4805
159.2564
171.2937
176.0247

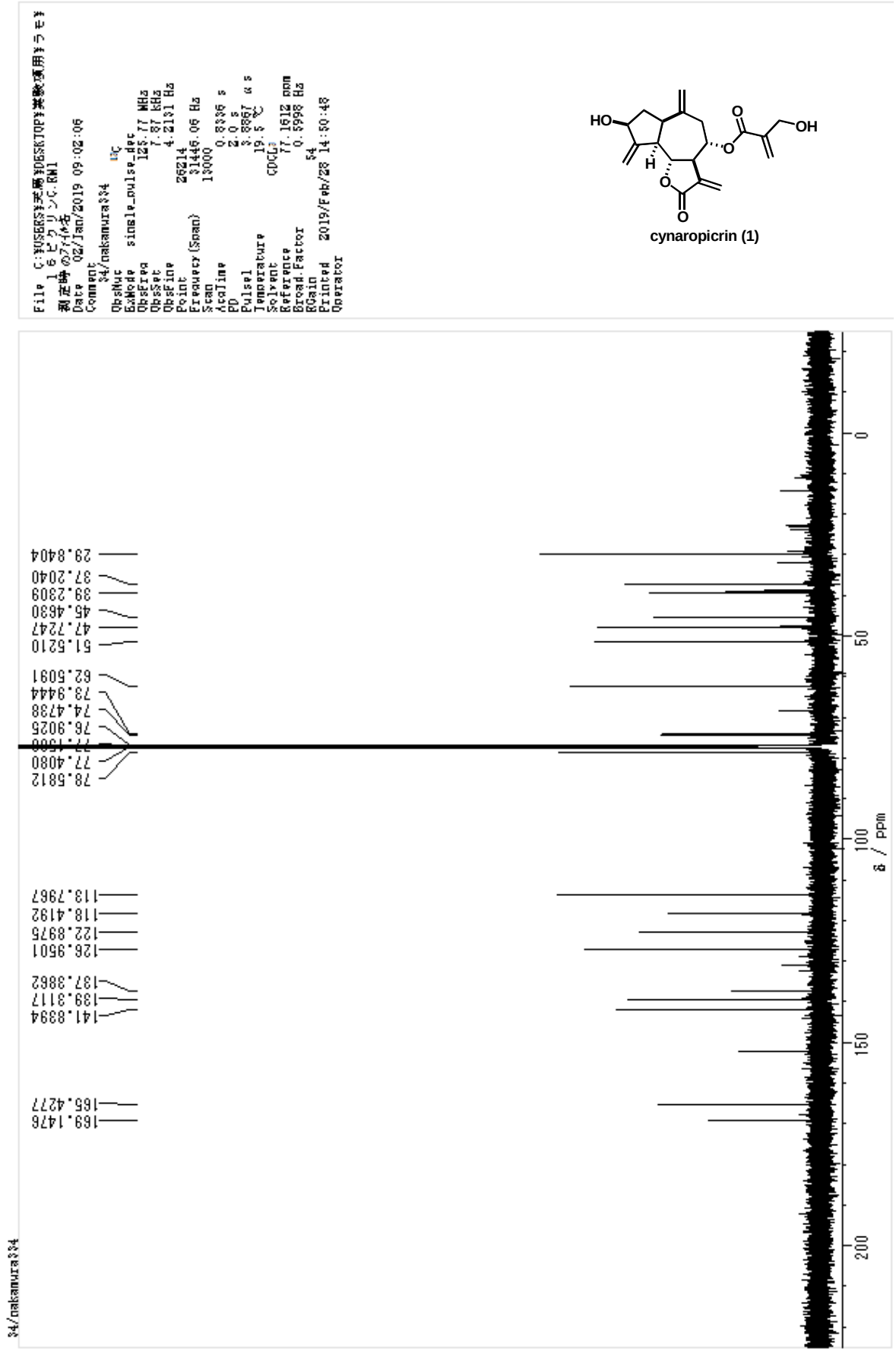

PMBO
OH
H
O
O
3
δ / ppm
34/yoshinoto466

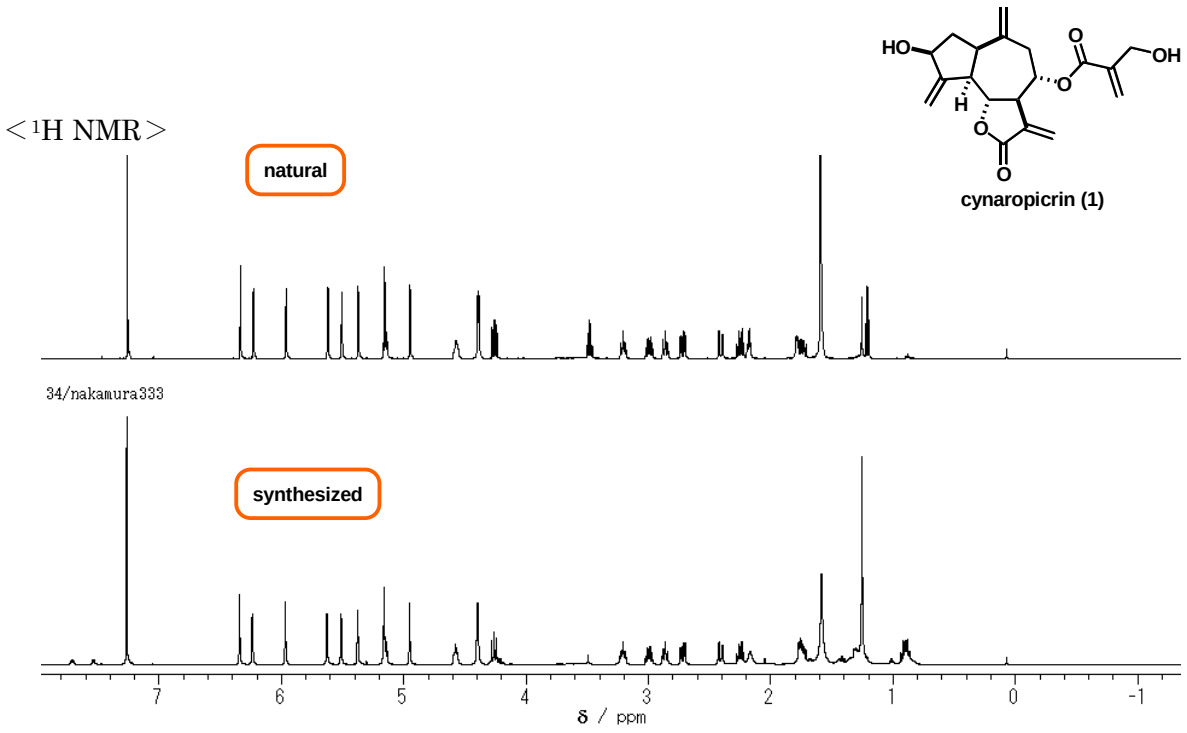

PMBO
OH
H
O
O
3
δ / ppm
34/yoshimoto466

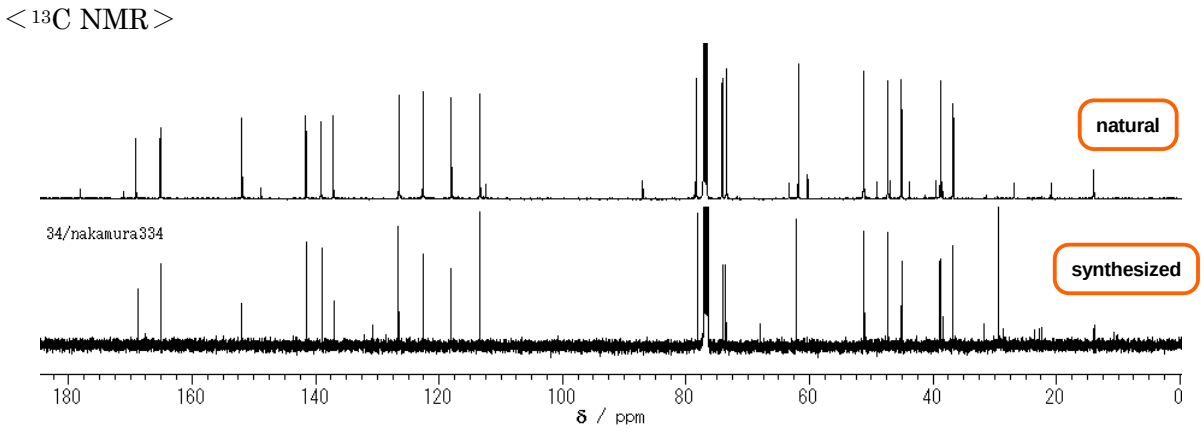

PMBO
OTIPS
H
O
3'
δ / ppm


PMBO
OTIPS
H
O
O
O
O
3'
δ / ppm
0
50
100
150
200
12.0706
18.1178
29.8416
36.8093
37.1598
46.4871
47.5924
53.2653
55.4126
61.7175
70.0253
74.0684
76.9025
77.1576
77.4093
78.4083
80.1908
113.9648
115.5148
118.1283
122.4647
124.9673
129.5636
130.4815
137.8846
139.6742
142.4117
148.5067
159.2778
165.0938
169.4529


File C:¥USERS¥武藤¥DESKTOP¥実験項用¥ラモ¥
1 6 ヒクリン/H.EM1
測定時のファイル名
Date 31/Jan/2019 15:48:07
Comment
34/nakamura¥¥¥
1H
QbsNuc
ExMode single_pulse.ex2
QbsFreq 500.16 MHz
QbsSwt 2.41 kHz
QbsFine 6.0092 Hz
Point 19107
Frequency(Sman) 7507.893 Hz
Scan 128
acqTime 1.7459 s
PD 4.0 s
Pulsel 6.02 μs
Temperature 19.7 ℃
Solvent CDCl3
Reference 7.26 ppm
Broad.Factor 0.2864 Hz
RGain 50
Printed 2019/Feb/28 14:48:13
Operator
HO
O
OH
H
O
O
O
cynaropicrin (1)
δ / ppm
34/nakamura¥¥¥


File C:¥USERS¥美樹¥DESKTOP¥実験項用¥ラモ¥
1 6ヒクリンC.RN1
測定時のファイル名
Date 02/Jan/2019 09:02:06
Comment
34/nakamura¥34
ObsNuc 13C
ExMode single_pulse_dec
ObsFreq 125.77 MHz
ObsSet 7.87 kHz
ObsFine 4.2181 Hz
Point 26214
Frequency(Span) 31446.06 Hz
Scan 13000
AcqTime 0.8336 s
PD 2.0 s
Pulsel 3.9867 u s
Temperature 19.5 ℃
Solvent CDCl3
Reference 77.1612 ppm
Broad.Factor 0.5998 Hz
RGain 54
Printed 2019/Feb/28 14:50:48
Operator
HO
O
OH
H
O
O
O
cynaropicrin (1)
29.8404
37.2040
39.2309
45.4630
47.7247
51.5210
62.5091
73.9444
74.4738
76.9025
77.4080
78.5812
118.7967
118.4192
122.8975
126.9501
137.3862
139.3117
141.8894
165.4277
169.1476
34/nakamura¥34
0
50
100
150
200
δ / ppm


HO
O
OH
O
H
O
O
cynaropicrin (1)
＜^{1}H NMR＞
natural
34/nakamura333
synthesized
7
6
5
4
3
2
1
0
-1
δ / ppm


＜^{13}C NMR＞
natural
34/nakamura334
synthesized
180
160
140
120
100
80
60
40
20
0
δ / ppm

X-ray diffraction analysis of S1:

Crystals were obtained from a hexane solution by slow evaporation of the solvent. A colorless platelet crystal (0.35 × 0.30 × 0.03 mm) was mounted on a polyimide film, MicroMounts^{TM} (MiTegen), and coated with paraffin. All measurements were made on a Rigaku Mercury70 diffractometer using graphite monochromated Mo-*Kα* radiation at 223K. Data were collected and processed using CrystalClear (Rigaku).[1] The structure was solved by direct methods[2] and expanded using Fourier techniques. A unit cell contained two independent molecules whose structures are almost identical. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined using the riding model. The final cycle of full-matrix least-squares refinement on F^2 was based on 7316 observed reflections and 547 variable parameters. All calculations were performed using the CrystalStructure[3] crystallographic software package except for refinement, which was performed using SHELXL97.[4] Crystallographic data are summarized in table S1. CIF data were deposited in Cambridge Structural Database (CCDC-2038598).

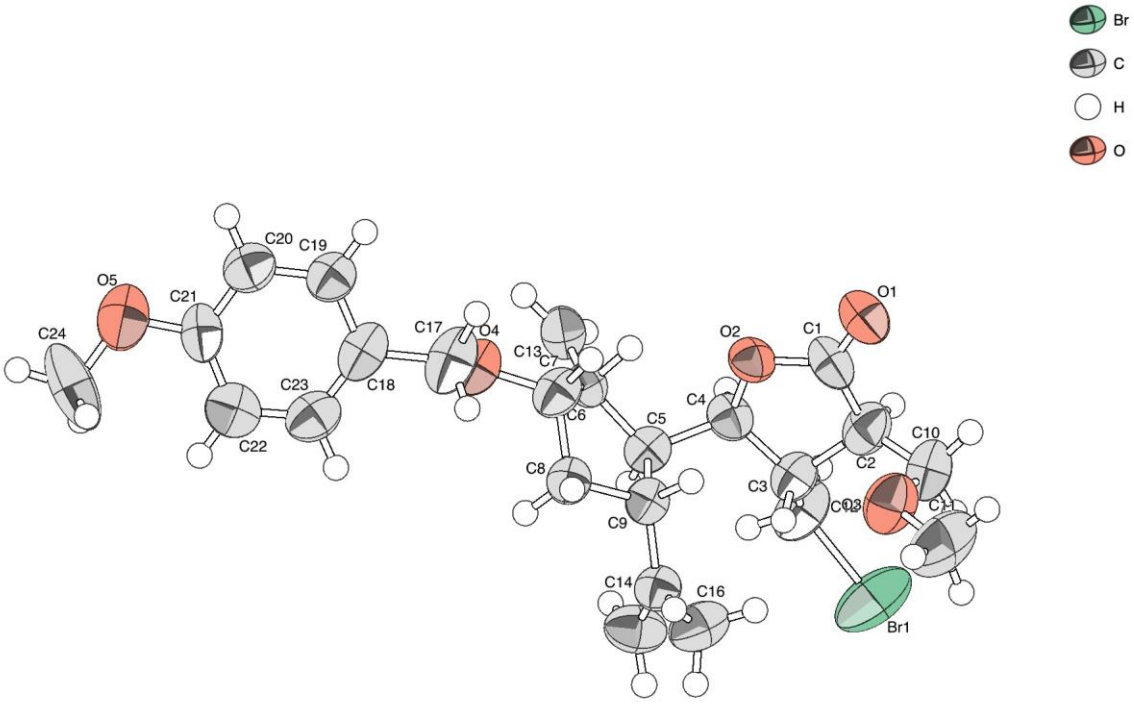


Figure S1. Molecular structure of **S1**. Draws with 50% probability.

Table S1. Crystal data and structure refinement for **S1**.

Empirical Formula	$C_{24}H_{31}BrO_5$
Formula Weight	479.41
Crystal Color, Habit	colorless, platelet
Crystal Dimensions	0.35 × 0.30 × 0.03 mm
Crystal System	triclinic
Lattice Type	Primitive
Space Group	P1 (#1)
Lattice Parameters	a = 8.703(13) Å
	b = 9.329(14) Å
	c = 14.17(2) Å
	α = 94.13(3) °
	β = 91.26(3) °
	γ = 90.13(2) °
	V = 1147(3)Å^3
Z value	2
Absorption coefficient	18.284 cm^{-1}
Radiation	MoKα (λ = 0.71073 Å)
	graphite monochromated
Temperature	223 K
No. of Reflections Measured	Total: 10727
	Unique: 7316
	(R_{int} = 0.0358)
Corrections	Lorentz-polarization Absorption
	(trans. factors: 0.737 – 0.947)

No. of Reflections	10727
No. Variables	547
Reflection/Parameter Ratio	13.37
Residuals: *R*; *wR* (All data)	0.1182; 0.2234
Residuals: R_1	0.0737
No. of Reflections to calc R_1	3598
Goodness of Fit Indicator	0.935
Flack Parameter	–0.032 (Friedel pairs = 3296)
Max Shift/Error in Final Cycle	0.000
Maximum peak in Final Diff. Map (e Å^3)	0.34
Minimum peak in Final Diff. Map (e Å^3)	–0.73
CCDC#	2038598

References:

1. CrystalClear: Data Collection and Processing Software, Rigaku Corporation (1998-2015). Tokyo 196-8666, Japan.
2. SIR2008: Burla, M. C., Caliandro, R., Camalli, M., Carrozzini, B., Cascarano, G. L., De Caro, L., Giacovazzo, C., Polidori, G. Siliqi, D. and Spagna R. (2007). *J. Appl. Cryst.* **40**, 609-613.
3. CrystalStructure 4.2.5: Crystal Structure Analysis Package, Rigaku Corporation (2000-2017). Tokyo 196-8666, Japan.
4. SHELXL97: Sheldrick, G. M. (2008). Acta Cryst. A64, 112-122.

DFT calculation with B3LYP/6-31G* for compound **S2**: