Asymmetric Formal Synthesis of (+)-Catharanthine via Desymmetrization of Isoquinuclidine

Masato Kono,[†] Shingo Harada,[*,†] Tomoyuki Nozaki,[†] Yoshinori Hashimoto,[†] Shun-ichi Murata,[†] Harald Gröger,[‡] Yusuke Kuroda,[§] Ken-ichi Yamada,[‖] Kiyosei Takasu,[§] Yasumasa Hamada,[†] Tetsuhiro Nemoto[*,†,⊥]

[†]Graduate School of Pharmaceutical Sciences, Chiba University, 1-8-1, Inohana, Chuo-ku, Chiba 260-8675, Japan

[‡]Chair of Organic Chemistry I, Faculty of Chemistry, Bielefeld University, Universitätsstraße 25, 33615 Bielefeld, Germany

[§]Graduate School of Pharmaceutical Sciences, Kyoto University, Yoshida, Sakyo-ku, Kyoto 606-8501, Japan

[‖]Graduate School of Pharmaceutical Sciences, Tokushima University, Shomachi, Tokushima 770-8505, Japan

[⊥]Molecular Chirality Research Center, Chiba University, 1-33, Yayoi-cho, Inage-ku, Chiba 263-8522, Japan

E-mail: tnemoto@faculty.chiba-u.jp, Sharada@chiba-u.jp

Tel/Fax: +81-43-226-2920.

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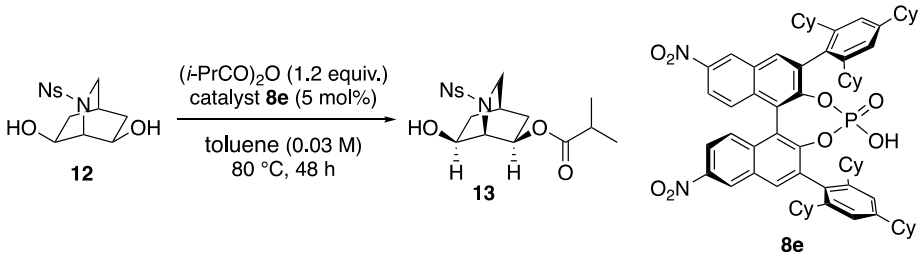
1. General Information

NMR spectra were recorded on a JEOL ecs 400 spectrometer. Chemical shifts in $CDCl_3$, were reported downfield from TMS (= 0 ppm) for ^1H NMR. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad), integration and coupling constants in Hz. For ^{13}C NMR, chemical shifts were reported in the scale relative to the solvent signal [$CHCl_3$ (77.0 ppm)] as an internal reference. ESI mass spectra were measured on JEOL AccuTOF LC-plus JMS-T100LP. Optical rotations were measured on a JASCO P-1020 polarimeter. IR spectra were recorded on a JASCO FT/IR 230 Fourier transform infrared spectrophotometer, equipped with ATR (Smiths Detection, DuraSample IR II). The enantiomeric ratio (er) was determined by HPLC analysis. HPLC was performed on JASCO HPLC systems consisting of the following: pump, PU-980; detector, UV-970; column DAICEL CHIRALPAK AS-H, mobile phase, *n*-hexane/*i*-PrOH. Melting points were measured with a SIBATA NEL-270 melting point apparatus. Analytical thin layer chromatography was performed on Kieselgel 60F254, 0.25 mm thickness plates. Column chromatography was performed with silica gel 60 N (spherical, neutral 63-210 mesh). Reactions were conducted in dry solvent. Other reagents were purified by the usual methods. Catalysts **8d** and **8e** were prepared according to the reported procedure.[1]

2. Asymmetric Desymmetrization



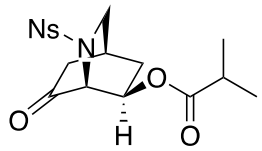
(1*S*,4*R*,6*R*,7*S*)-7-Hydroxy-2-((2-nitrophenyl)sulfonyl)-2-azabicyclo[2.2.2]octan-6-yl isobutyrate (13)

To a stirred solution of **12** (99 mg, 0.3 mmol) and (*S*)-3,3'-bis(2,4,6-tricyclohexylphenyl)-6,6'-dinitro-1,1'-binaphthyl phosphate **8e** (16.3 mg, 5 mol %, 0.015 mmol) in toluene (10 mL, 0.03 M) at room temperature was added isobutyric anhydride (6.3 μL, 1.2eq, 0.038 mmol), and the resulting mixture was stirred at 80 °C for 48 h. The reaction was quenched with H_2O and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under vacuum. The obtained residue was purified by flash chromatography on silica gel (column condition; gradient elution: *n*-hexane/EtOAc = 3/1 → 1/2) to give **13** as colorless oil in 74% yield (89 mg): R_f = 0.2 (*n*-hexane/EtOAc, 1/2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08-1.11 (m, 6H), 1.39-1.43 (m, 1H), 1.51-1.57 (m, 1H), 1.94-2.03 (m, 2H), 2.13 (t, *J*=2.8 Hz, 1H), 2.33-2.38 (m, 1H), 2.60 (d, 1.6 Hz, 1H), 3.42 (dt, *J*= 2.4, 4.8 Hz, 1H), 3.63 (dt, *J*=2.4, 4.8Hz, 1H), 4.06-4.09 (m, 2H), 4.82 (ddd, *J*= 2.0, 2.4, 4.0 Hz, 1H), 7.56-7.58 (m, 1H), 7.66-7.68 (m,

2H), 8.07-8.10 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.6, 18.9, 25.3, 31.4, 33.8, 33.9, 49.1, 56.3, 66.2, 68.2, 123.7, 130.8, 131.6, 133.1, 133.2, 147.8, 176.7; IR (ATR) v 3526, 2971, 1729, 1543, 1373, 1345, 1170, 1092, 1043, 991 cm^{-1}; HRMS (ESI-TOF) $[M + Na]^+$ calcd for $C_{17}H_{22}N_2NaO_7S^+$ m/z 421.1047, found m/z 421.1040; $[\alpha]^{23.2}{}_D$ −54.2 (*c* 1.0, $CHCl_3$).

The enantiomeric ratio was determined to be 97:3 by analytical chiral HPLC. 48 min (minor), 67 min (major) (AS-H column, 75/25 *n*-hexane/*i*-PrOH, 1 mL/min, 254 nm).

3. Asymmetric Formal Synthesis of (+)-Catharanthine (Scheme 4)

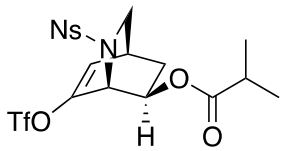


(1*R*,4*S*,6*R*)-2-((2-Nitrophenyl)sulfonyl)-7-oxo-2-azabicyclo[2.2.2]octan-6-yl isobutyrate (14)

A solution of **13** (87.2 mg, 0.22 mmol) and Ac_2O (0.31 mL, 15 eq, 3.3 mmol) in DMSO (4.4 mL, 0.05 M) was stirred for 24 h at room temperature. The reaction was quenched with saturated aqueous $NaHCO_3$, extracted with EtOAc, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (column condition; *n*-hexane/EtOAc = 1/1) to give **14** as white solid in 84% yield (72.5 mg). The optical purity was increased to 99:1 er by recrystallization from *n*-hexane/EtOAc: mp 108–110 °C; R_f = 0.2 (*n*-hexane/EtOAc, 1/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12 (dd, J = 0.8, 2.8 Hz, 6H), 1.73 (dd, J = 2.8, 12.0 Hz, 1H), 2.10-2.17 (m, 1H), 2.33-2.37 (m, 2H), 2.41-2.49 (m, 1H), 2.58 (s, 1H), 3.61-3.75 (m, 2H), 4.33 (d, J = 3.2 Hz, 1H), 5.07-5.11 (m, 1H), 7.61-7.63 (m, 1H), 7.67-7.74 (m, 2H), 7.98-8.00 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.6, 18.8, 27.7, 32.4, 33.8, 41.6, 48.1, 59.7, 67.6, 124.1, 131.1, 131.9, 132.4, 133.9, 147.8, 176.0, 202.8; IR (ATR) ν 2974, 1732, 1540, 1470, 1352, 1146, 1128, 1078, 936, 730 cm^{-1}; HRMS (ESI-TOF) $[M + Na]^+$ calcd

for $C_{17}H_{20}N_2NaO_7S^+$ m/z 419.0879, found 419.0883; $[\alpha]^{22.4}{}_D$ − 15.1 (*c* 1.0, $CHCl_3$).

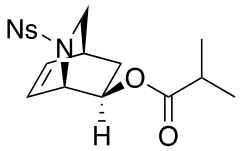
The enantiomeric ratio was determined to be 99:1 by analytical chiral HPLC. 28 min (minor), 36 min (major) (AS-H column, 70/30 *n*-hexane/*i*-PrOH, 1 mL/min, 254 nm).



(1*R*,4*S*,6*R*)-2-((2-Nitrophenyl)sulfonyl)-7-(((trifluoromethyl)sulfonyl)oxy)-2-azabicyclo[2.2.2]oct-7-en-6-yl isobutyrate (15)

To a stirred solution of **14** (92 mg, 0.23 mmol) in THF (4.6 mL, 0.05 M) was added KHMDS (0.5 M solution in toluene) (0.51 mL, 1.1 eq, 0.25 mmol) at − 78 °C, and the reaction mixture was stirred for 30 min at the same temperature. Then $PhNTf_2$ (90.4 mg, 1.1 eq, 0.25 mmol) was added, and the mixture was stirred for 1 h at − 78 °C. The reaction was quenched with saturated aqueous NH_4Cl, extracted with EtOAc, washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (column condition; gradient elution: *n*-hexane/EtOAc 3/1 → 1/1) to give **15** as white solid in 86% yield (106 mg): mp 80−82 °C; R_f = 0.5 (*n*-hexane/EtOAc, 1/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14 (d, *J* = 6.8 Hz, 6H), 1.50 (ddd, *J* = 12.0, 2.8, 2.0

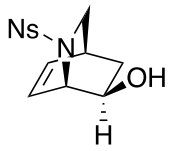
Hz, 1H), 2.12 (m, 1H), 2.50 (m, 1H), 3.07 (ddd, *J* = 7.2, 2.8, 2.8 Hz, 1H), 3.14 (m, 1H), 3.64 (dd, *J* = 9.6, 2.0 Hz, 1H), 4.87 (dd, *J* = 2.8, 2.4 Hz, 1H), 4.95 (ddd, *J* = 9.6, 3.2, 2.8 Hz, 1H), 6.22 (dd, *J* = 7.6, 2.0 Hz, 1H), 7.64 (d, *J* = 7.2 Hz, 1H), 7.66-7.74 (m, 2H), 7.98 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.6, 18.8, 29.6, 30.8, 33.8, 47.6, 54.8, 70.5, 118.4 (q, *J* = 320.4 Hz), 122.1, 124.2, 130.7, 131.8, 132.2, 133.8, 147.0, 148.1, 176.6; IR (ATR) ν 2925, 1734, 1655, 1544, 1423, 1370, 1246, 1211, 1172, 1133 cm^{-1}; HRMS (ESI-TOF) $[M + Na]^+$ calcd for $C_{18}H_{19}F_3N_2NaO_9S_2^+$ m/z 551.0382, found 551.0372; $[\alpha]^{22.1}{}_D$ −30.7 (*c* 1.0, $CHCl_3$).



(1*S*,4*S*,6*R*)-2-((2-Nitrophenyl)sulfonyl)-2-azabicyclo[2.2.2]oct-7-en-6-yl isobutyrate (16)

To a stirred solution of **15** (106 mg, 0.2 mmol) and $PdCl_2(PPh_3)_2$ (14.0 mg, 10 mol%, 0.02 mmol) in DMF (2 mL, 0.1 M) were added Et_3N (0.084 mL, 3 eq, 0.6 mmol) and HCOOH (0.015 mL, 2 eq, 0.4 mmol) at room temperature, and the reaction mixture was stirred for 2 h at 60 °C. The reaction was quenched with saturated aqueous $NaHCO_3$, extracted with EtOAc, washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (column

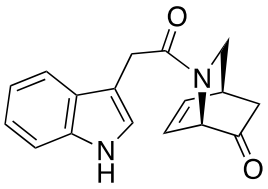
condition; gradient elution: *n*-hexane/EtOAc 3/1 → 1/1) to give **16** as pale brown oil in 85% yield (65 mg): R_f = 0.4 (*n*-hexane/EtOAc, 1/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16 (d, *J* = 6.8 Hz, 3H), 1.17 (d, *J* = 6.8 Hz, 3H), 1.44 (ddd, *J* = 14.0, 2.8, 2.4 Hz, 1H), 2.01 (m, 1H), 2.51 (qq, *J* = 6.8, 6.8 Hz, 1H), 2.82 (m, 1H), 2.96 (ddd, *J* = 9.2, 2.8, 2.4 Hz, 1H), 3.61 (dd, *J* = 9.2, 2.8 Hz, 1H), 4.68-4.74 (m, 2H), 6.37-6.42 (m, 2H), 7.58-7.69 (m, 3H), 7.96 (d, *J* = 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.77, 18.85, 28.9, 30.1, 34.0, 48.4, 52.1, 70.6, 124.1, 130.0, 130.8, 131.4, 132.8, 133.2, 135.9, 148.1, 176.9; IR (ATR) v 2925, 1727, 1541, 1469, 1348, 1260, 1170, 1129, 1098, 1008 cm^{-1}; HRMS (ESI-TOF) $[M + Na]^+$ calcd for $C_{17}H_{20}N_2NaO_6S^+$ m/z 403.0940, found 403.0935; $[\alpha]^{22.0}{}_D$ − 14.6 (*c* 1.0, $CHCl_3$).



(1*S*,4*S*,6*R*)-2-((2-Nitrophenyl)sulfonyl)-2-azabicyclo[2.2.2]oct-7-en-6-ol (17)

To a stirred solution of **16** (60.0 mg, 0.16 mmol) in 1,4-dioxane (3.2 mL, 0.05 M) was added 2.5 N aqueous NaOH (0.19 mL, 3 eq, 0.48 mmol), and the reaction mixture was stirred for 15 h at 80 °C. The reaction was quenched with saturated aqueous $NaHCO_3$, extracted with EtOAc, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (column condition;

gradient elution: *n*-hexane/EtOAc 1/1 → EtOAc) to give **17** as colorless oil in 90% yield (43.9 mg): R_f = 0.3 (*n*-hexane/EtOAc, 1/2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (ddd, *J* = 13.6, 2.8, 2.4, 1H), 1.96 (m, 1H), 2.38 (d, *J* = 8.4 Hz, 1H), 2.78 (m, 1H), 3.10 (ddd, *J* = 9.2, 2.8, 2.0 Hz, 1H), 3.54 (dd, *J* = 9.2, 2.4 Hz, 1H), 3.82 (m, 1H), 4.42 (m, 1H), 6.31-6.39 (m, 2H), 7.60 (dd, *J* = 7.2, 2.0 Hz, 1H), 7.64-7.73 (m, 2H), 8.02 (dd, *J* = 7.6, 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.3, 31.9, 48.9, 55.7, 68.9, 124.1, 130.0, 131.1, 131.5, 132.1, 133.6, 135.6, 148.1; IR (ATR) ν 3535, 2958, 1542, 1440, 1372, 1348, 1170, 1130, 1096, 1033 cm^{-1}; HRMS (ESI-TOF) $[M + Na]^+$ calcd for $C_{13}H_{14}N_2NaO_5S^+$ m/z 333.0521, found 333.0525; $[\alpha]^{23.9}{}_D$ +8.5 (*c* 1.0, $CHCl_3$).



(1*S*,4*S*)-2-(2-(1*H*-Indol-3-yl)acetyl)-2-azabicyclo[2.2.2]oct-7-en-6-one (18)

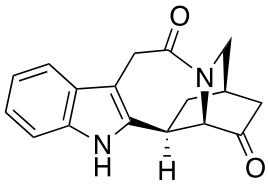
A solution of **17** (43.9 mg, 0.14 mmol) and Ac_2O (0.2 mL, 15 eq, 2.1 mmol) in DMSO (2.8 mL, 0.05 M) was stirred for 24 h at room temperature. The reaction was quenched with saturated aqueous $NaHCO_3$, extracted with EtOAc, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude ketone was used for the next step without further purification.

A solution of the crude ketone obtained above, Cs_2CO_3 (136.8 mg, 3 eq, 0.42 mmol) and MetSThiol® (1.24 mmol/g) (451.6 mg, 4 eq, 0.56 mmol) in CH_3CN (14 mL, 0.01 M) was stirred for 18 h at 80 °C. The reaction mixture was filtered through celite and concentrated under reduced pressure to give crude secondary amine which was used for the next step without further purification.

To a stirred solution of the crude amine, indole-3-acetic acid (49.1 mg, 2 eq, 0.28 mmol) in CH_2Cl_2 (14 mL, 0.01 M) were added Et_3N (0.098 mL, 5 eq, 0.7 mmol) and EDCI (53.7 mg, 2 eq, 0.28 mmol) at 0 °C, and the reaction mixture was stirred for 20 h at room temperature. The reaction was quenched with saturated aqueous $NaHCO_3$, extracted with $CHCl_3$, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (column condition; gradient elution: *n*-hexane/EtOAc 1/1 → 1/2) to give **18** as colorless oil in 47% yield (3 steps, 18.7 mg): R_f = 0.2 (*n*-hexane/EtOAc, 1/2); ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of rotamers) δ 2.03-2.23 (m, 4H), 3.12 (m, 1H), 3.16 (m, 1H), 3.26 (d, J = 11.6 Hz, 1H), 3.32 (ddd, J = 9.2, 2.0, 1.6 Hz, 1H), 3.53 (dd, J = 9.6, 2.8 Hz, 1H), 3.63 (dd, J = 11.2, 2.4 Hz, 1H), 3.76 (s, 2H), 3.82 (d, J = 15.6 Hz, 1H), 3.91 (d, J = 15.6 Hz, 1H), 4.75 (d, J = 6.4 Hz, 1H), 5.57 (d, J = 6.4 Hz, 1H), 6.16 (m, 1H), 6.40 (m, 1H), 6.58-6.66 (m, 2H), 6.97-7.02 (m, 2H), 7.08-7.14 (m, 2H), 7.15-7.21 (m, 2H), 7.31-7.35 (m, 2H), 7.55 (d, J = 8.0 Hz, 1H), 7.62 (d, J = 8.0 Hz, 1H), 8.34 (br s, 1H), 8.40 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$)

(mixture of rotamers) δ 31.7 (2C), 32.2, 32.5, 36.5, 36.6, 46.3, 47.0, 55.6, 60.1, 108.1, 108.6, 111.2, 111.3, 118.3, 118.8, 119.55, 119.65, 122.1, 122.2, 122.60, 122.64, 127.0, 127.1, 127.2, 128.5, 136.1, 136.2, 139.0, 140.2, 170.5, 170.7, 202.58, 202.60; IR (ATR) v 3281, 2925, 1729, 1631, 1457, 1406, 1339, 1317, 1271, 1227 cm^{-1}; HRMS (ESI-TOF) $[M + Na]^+$ calcd for $C_{17}H_{16}N_2NaO_2^+$ m/z 303.1110, found 303.1111.

At this stage, optical rotation was compared with that of the known intermediate of (+)-catharanthine, and it turned out that our compound has the same absolute configuration of (+)-catharanthine: $[\alpha]^{22.9}{}_D$ −85.4 (*c* 1.0, $CHCl_3$) (reported; $[\alpha]^{20}{}_D$ −61 (*c* 1.2, $CHCl_3$)[2]).



(6*S*,6a*R*,9*R*,11*R*)-5,6,6a,9,10,13-Hexahydro-12*H*-6,9-methanopyrido[1',2':1,2]azepino[4,5-*b*]indole-7,12(8*H*)-dione (19)

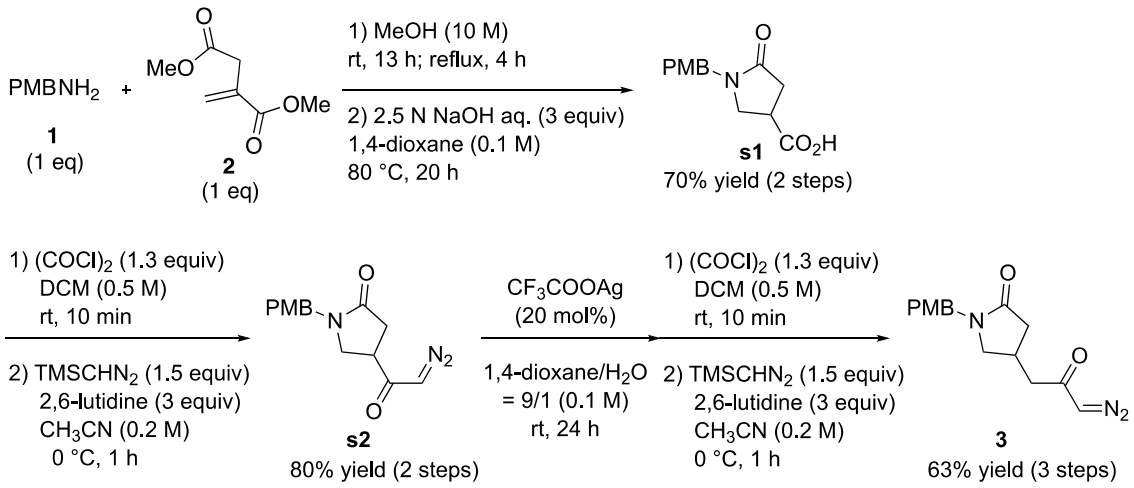
To a suspension of $(CH_3CN)_2PdCl_2$ (10.1 mg, 1.3 eq, 0.04 mmol) and $AgBF_4$ (8.2 mg, 1.4 eq, 0.042 mmol) in CH_3CN (0.5 mL) was added a solution of **18** (8.2 mg, 0.03 mmol) in CH_3CN (1 mL), and the reaction mixture was stirred for 1 h at room temperature and 18 h at 70 °C. The reaction was then cooled down to 0 °C, and MeOH (0.3 mL) was added followed by $NaBH_4$ (3.6 mg, 3.2

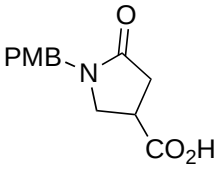
eq, 0.1 mmol). The reaction mixture was filtered through celite and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (column condition; gradient elution: *n*-hexane/EtOAc 1/1 → EtOAc) to give **19** as white solid in quantitative yield (8.2 mg).

^{1}H and ^{13}C NMR, and other data are identical to those reported[3] (NMR charts are given in the spectra section).

We found that the compound **19** is unstable under the reported measurement condition (CH_2Cl_2/MeOH mix solvent, ($[\alpha]^{25}_{D}$ −102.2 (*c* 0.59, CH_2Cl_2/MeOH = 1:1))[3]). Therefore, we measured the optical rotation of **19** in another solvent: $[\alpha]^{25}_{D}$ −55.8 (*c* 0.23, DMSO) .

4. Synthesis and Characterization of 3





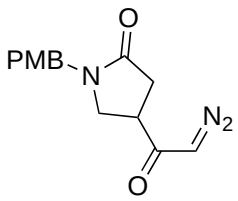
1-(4-Methoxybenzyl)-5-oxopyrrolidine-3-carboxylic acid (s1)

A solution of dimethyl itaconate (7.1 mL, 50 mmol) and $PMBNH_2$ (6.5 mL, 1 eq, 50 mmol) in MeOH (5 mL, 10 M) was stirred for 13 h at room temperature and then refluxed for 4 h. The reaction mixture was cooled down to room temperature and concentrated under reduced pressure. The crude residue was used for the next step without further purification.

To a stirred solution of the crude product obtained above in 1,4-dioxane (250 mL, 0.2 M) was added 2.5 N aqueous NaOH (60 mL, 3 eq, 150 mmol) at 0 °C, and the mixture was stirred for 24 h at 80 °C. The reaction mixture was

cooled down to room temperature, concentrated under reduced pressure to remove 1,4-dioxane. The water layer was washed with $CHCl_3$, acidified with 1 N aqueous $KHSO_4$, and extracted with EtOAc. The organic layer of EtOAc was washed with brine, dried over Na_2SO_4, concentrated under reduced pressure to give white precipitate. The precipitate was washed with Et_2O to give pure **s1** as white powder in 70% yield (2 steps, 8.7 g).

Compound data was identical to those reported.[4]

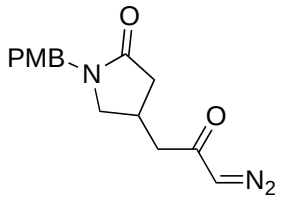


4-(2-Diazoacetyl)-1-(4-methoxybenzyl)pyrrolidin-2-one (s2)

To a stirred solution of **s1** (2.5 g, 10 mmol) in CH_2Cl_2 (20 mL, 0.5 M) was added $(COCl)_2$ (1.1 mL, 1.3 eq, 13 mmol) at room temperature. The reaction mixture was stirred for 10 min at room temperature and concentrated under reduced pressure to give crude acid chloride which was used for the next step without further purification.

To a stirred solution of the crude acid chloride in CH_3CN (50 mL, 0.2 M) were added 2,6-lutidine (3.5 mL, 3 eq, 30 mmol) and $TMSCHN_2$ (2.0 M in Et_2O) (7.5 mL, 1.5 eq, 15 mmol) at 0 °C, and the reaction mixture was stirred for 1 h at 0 °C. The reaction was quenched with saturated aqueous $NaHCO_3$, extracted with Et_2O, washed with brine, dried over Na_2SO_4, and concentrated

under reduced pressure. The crude residue was purified by flash chromatography on silica gel (column condition; gradient elution: *n*-hexane/EtOAc 1/2 → EtOAc → EtOAc/MeOH 20/1) to give **s2** as brown oil in 80% yield (2 steps, 2.2 g): R_f = 0.1 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2,58-2.77 (m, 2H), 3.12 (m, 1H), 3.36 (dd, J = 10.4, 8.4 Hz, 1H), 3.47 (dd, J = 10.4, 6.8 Hz, 1H), 3,79 (s, 3H), 4.32 (d, J = 14.8 Hz, 1H), 4.45 (d, J = 14.8 Hz, 1H), 5.28 (s, 1H), 6.86 (d, J = 8.4 Hz, 2H), 7.16 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 34.2, 40.8, 45.9, 48.1, 54.7, 55.2, 114.1, 127.9, 129.4, 159.1, 171.9, 192.9; IR (ATR) v 2933, 2103, 1678, 1634, 1585, 1511, 1419, 1373, 1318, 1302 cm^{-1}; HRMS (ESI-TOF) $[M + Na]^+$ calcd for $C_{14}H_{15}N_3NaO_3^+$ m/z 296.1011, found m/z 296.1009.



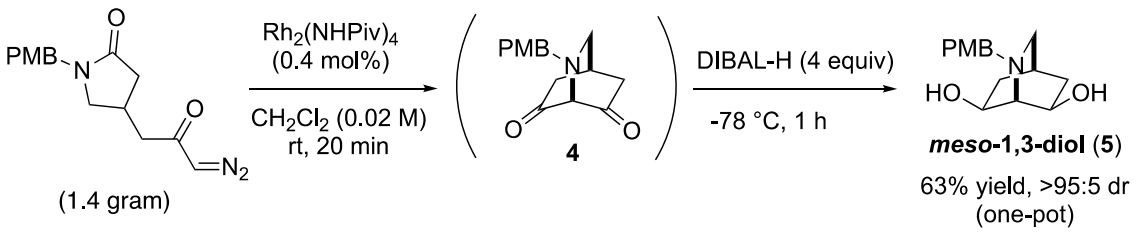
4-(2-Diazoacetyl)-1-(4-methoxybenzyl)pyrrolidin-2-one (3)

To a stirred solution of **s2** (2.2 g, 8.0 mmol) in 1,4-dioxane (72 mL) and H_2O (8 mL) was added CF_3COOAg (353 mg, 20 mol%, 1.6 mmol), and the reaction mixture was stirred for 14 h at room temperature and concentrated under reduced pressure to remove 1,4-dioxane. EtOAc and 1 N aqueous HCl were successively added to the reaction mixture, and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine,

dried over Na_2SO_4, and concentrated under reduced pressure to give crude carboxylic acid which was used for the next step without further purification. To a stirred suspension of the crude carboxylic acid (1.8 g, 6.8 mmol) in CH_2Cl_2 (14 mL, 0.5 M) was added $(COCl)_2$ (0.76 mL, 1.3 eq, 8.8 mmol) at room temperature. The reaction mixture was stirred for 10 min at room temperature and concentrated under reduced pressure to give crude acid chloride which was used for the next step without further purification.

To a stirred solution of the crude acid chloride in CH_3CN (34 mL, 0.2 M) were added 2,6-lutidine (2.4 mL, 3 eq, 20 mmol) and $TMSCHN_2$ (2.0 M in Et_2O) (5.1 mL, 1.5 eq, 10 mmol) at 0 °C, and the reaction mixture was stirred for 1 h at 0 °C. The reaction was quenched with saturated aqueous $NaHCO_3$, extracted with Et_2O, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (column condition; gradient elution: *n*-hexane/EtOAc 1/2 → EtOAc → EtOAc/MeOH 20/1) to give **3** as brown oil in 63% yield (3 steps, 1.4 g).

^1H and ^{13}C NMR, IR, and MS were identical to those reported.[5]

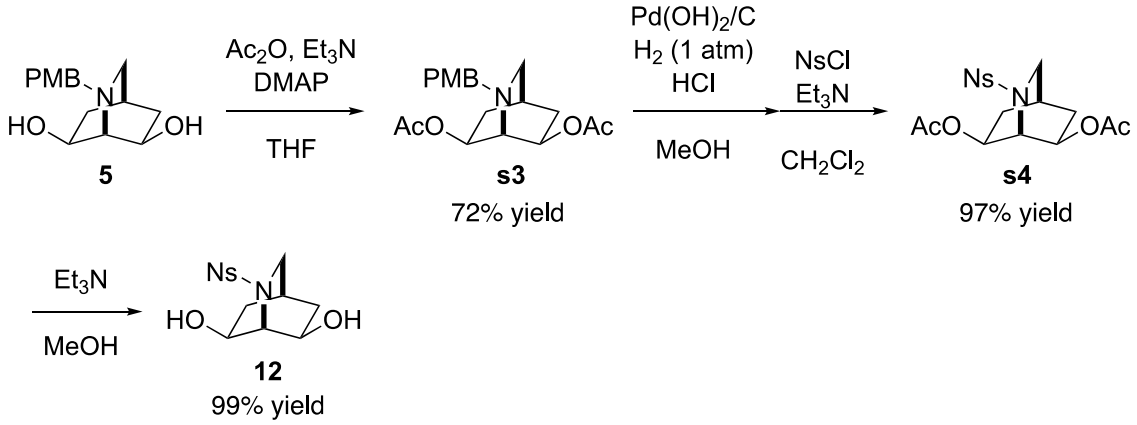


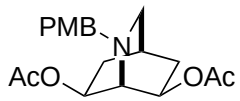
(1*S*,4*R*,6*R*,7*S*)-2-(4-Methoxybenzyl)-2-azabicyclo[2.2.2]octane-6,7-diol (5)

To a stirred solution of $Rh_2(NHPiv)_4$ (12 mg, 0.4 mol%, 0.02 mmol) in CH_2Cl_2 (240 mL) was added **3** (1.4 g, 5.0 mmol) in CH_2Cl_2 (10 mL), and the reaction mixture was stirred for 20 min at room temperature. Then the reaction mixture was cooled to −78 °C, and DIBAL-H (1.02 M in hexane) (20 mL, 4 eq, 20 mmol) was added. After being stirred for 1 h at the same temperature, the reaction was quenched with 2 M aqueous Rochelle salt, and the resulting mixture was stirred for 1 h at room temperature. The reaction mixture was filtered through Celite, extracted with CH_2Cl_2, washed with brine, dried over Na_2SO_4, concentrated under reduced pressure, and purified by flash chromatography on silica gel (column condition; gradient elution: $CHCl_3$/MeOH 15/1 → 5/1) to give **5** as pale yellow powder in 63% yield (2 steps, 822 mg).

^1H and ^{13}C NMR, IR, and MS were identical to those reported.[5]

5. Protecting-group Manipulation

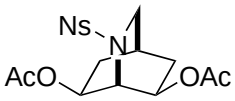




(1*S*,4*R*,6*R*,7*S*)-2-(4-Methoxybenzyl)-2-azabicyclo[2.2.2]octane-6,7-diyl diacetate (s3)

To a stirred solution of **5** (753 mg, 2.9 mmol), DMAP (35.4 mg, 10 mol%, 0.29 mmol) and triethylamine (0.9 mL, 2.2 eq, 6.4 mmol) in THF (29 mL, 0.1 M) at 0 °C was added acetic anhydride (0.6 mL, 2.2 eq, 6.4 mmol), and the resulting mixture was stirred for 3 h at room temperature. The reaction was quenched with saturated aqueous $NaHCO_3$ and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, and then concentrated under vacuum. The obtained residue was purified by flash chromatography on silica gel (column condition; *n*-hexane/EtOAc, 3/1) to give **s3** as colorless oil in 72% yield (712 mg).

^1H and ^{13}C NMR, IR, and MS were identical to those reported.[5]

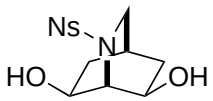


(1*S*,4*R*,6*R*,7*S*)-2-((2-Nitrophenyl)sulfonyl)-2-azabicyclo[2.2.2]octane-6,7-diyl diacetate (s4)

To a suspension of **s3** (534 mg, 1.54 mmol) and 20% $Pd(OH)_2/C$ (100 mg) in MeOH (30 mL, 0.05 M) was added 2 N HCl in MeOH (1.54 mL, 2 eq, 3.1 mmol) and the reaction mixture was stirred under H_2 atmosphere for 13 h at room temperature. The reaction mixture was filtered through a short pad of celite and concentrated under reduced pressure. The crude residue was used for the next step without further purification.

To a stirred solution of the crude product in CH_2Cl_2 (30 mL, 0.05 M) was added NEt_3 (0.86 mL, 4 eq, 6.12 mmol) at 0 °C, and the reaction mixture was stirred for 5 min at 0 °C. Then NsCl (409 mg, 1.2 eq, 1.83 mmol) was added and the resulting mixture was stirred for 5 h at room temperature. The reaction was quenched with saturated aqueous $NaHCO_3$, extracted with EtOAc, dried over Na_2SO_4, and concentrated under reduced pressure. The crude mixture was purified by flash chromatography on silica gel (column condition; *n*-hexane/EtOAc, 1/1) to give **s4** as colorless oil in 97% yield (612 mg): R_f = 0.3 (*n*-hexane/EtOAc, 1/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.57 (dd, J =2.8, 12.4 Hz, 2H), 1.81 (s, 6H), 2.05-2.11 (m, 2H), 2.18-2.20 (m, 1H), 3.60 (s, 2H), 4.16 (t, J =2.4 Hz, 1H), 4.88 (dt, J =2.0, 3.2 Hz, 2H), 7.64-7.71 (m, 3H),

8.03-8.05 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.7, 25.1, 31.3, 49.1, 52.7, 68.0, 123.6, 130.8, 131.4, 133.1, 133.8, 147.8, 170.1; IR (ATR) ν 2942, 1736, 1541, 1438, 1353, 1223, 1170, 1025, 942, 749 cm^{-1}; HRMS (ESI-TOF) [M + Na]$^+$ calcd for $C_{17}H_{20}N_2NaO_8S^+$ m/z 435.0832, found m/z 435.0833.

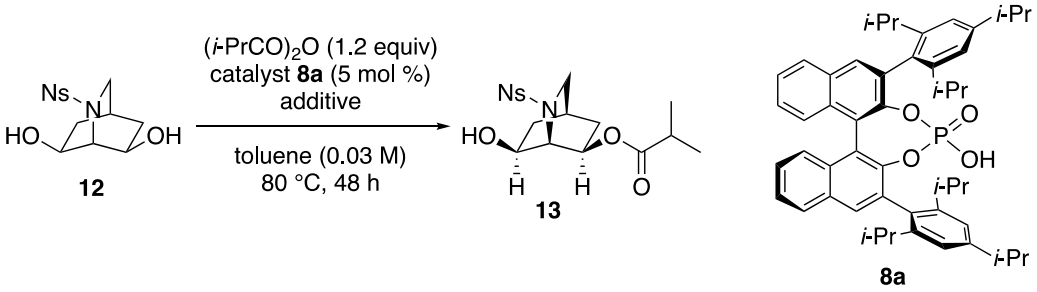


(1*S*,4*R*,6*R*,7*S*)-2-((2-Nitrophenyl)sulfonyl)-2-azabicyclo[2.2.2]octane-6,7-diol (12)

A solution of **s4** (630 mg, 1.53 mmol) and NEt_3 (1.1 mL, 5 eq, 7.6 mmol) in MeOH (30 mL, 0.05 M) was stirred at 60 °C. After 13 h, the reaction mixture was concentrated *in vacuo*. The obtained residue was purified by flash chromatography on silica gel (column condition; *n*-hexane/EtOAc, 1/2) to give **12** as white powder in 99% yield (502 mg): R_f = 0.2 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (dd, J=2.8, 12.4 Hz, 2H), 1.92-1.98 (m, 2H), 2.09-2.12 (m, 1H), 2.36 (br, 2H), 3.54 (dd, J=0.8, 1.6 Hz, 2H), 3.81 (t, 2.8 Hz, 1H), 3.93-3.96 (m, 2H), 7.58-7.61 (m, 1H), 7.68-7.73 (m, 2H), 8.08-8.11 (m, 1H); ^{13}C NMR (100 MHz, CD_3CN) δ 26.4, 34.5, 50.1, 61.1, 66.8, 124.3, 131.7, 132.4, 133.6, 134.3, 149.2; IR (ATR) ν 1539, 1367, 1337, 1167, 1130, 1044, 1009, 942, 740, 631 cm^{-1}; HRMS (ESI-TOF) [M + Na]$^+$ calcd for $C_{13}H_{16}N_2NaO_6S^+$ m/z 351.0620, found m/z 351.0621.

6. Supplementary Data for Asymmetric Desymmetrization

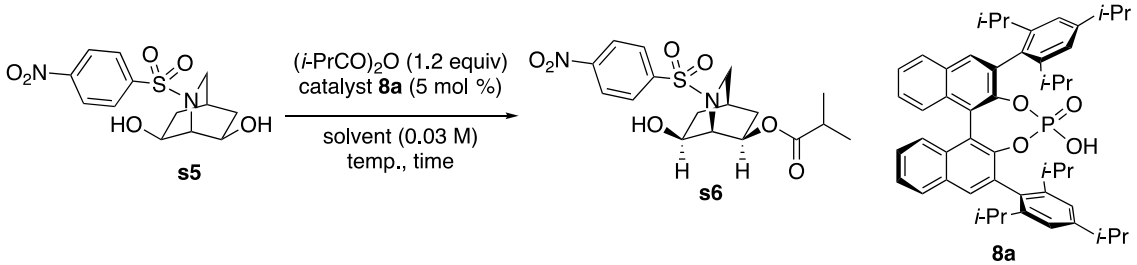
Table S1. An Additive Effect



entry	additive	yield of **13** (%)	er
1	none	51	92:8
2	MS3A	35	52:48
3	MS4A	54	50:50
4	Benzoic acid (1.1 eq)	55	79:21
5	(+)-CSA (1.1 eq)	58	50:50
6	Isobutyric acid (1.1 eq)	41	82:18

CSA : 10-Camphorsulfonic acid

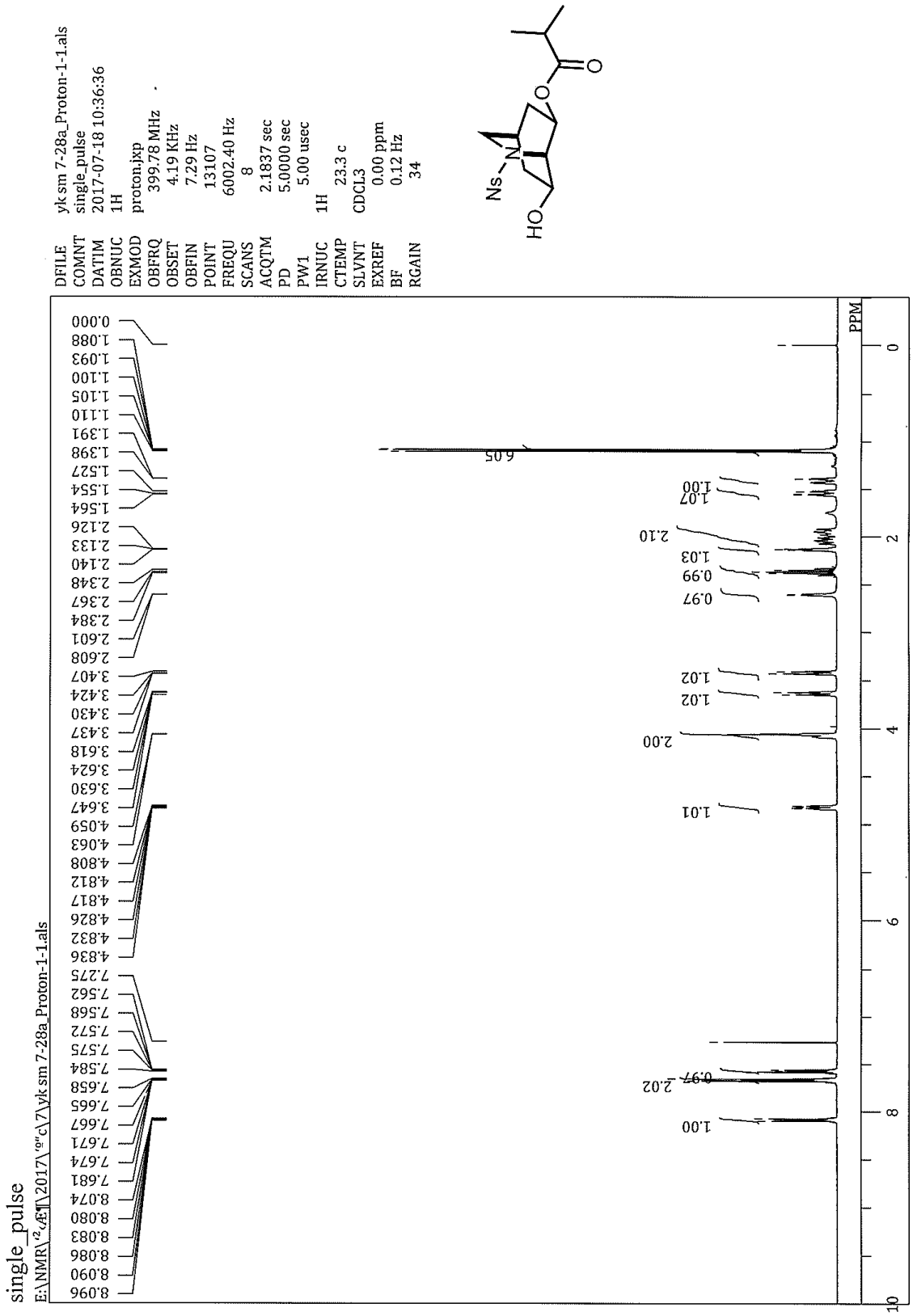
Table S2. Asymmetric Desymmetrization of s5 possessing 4-Nitrobenzenesulfonyl Group

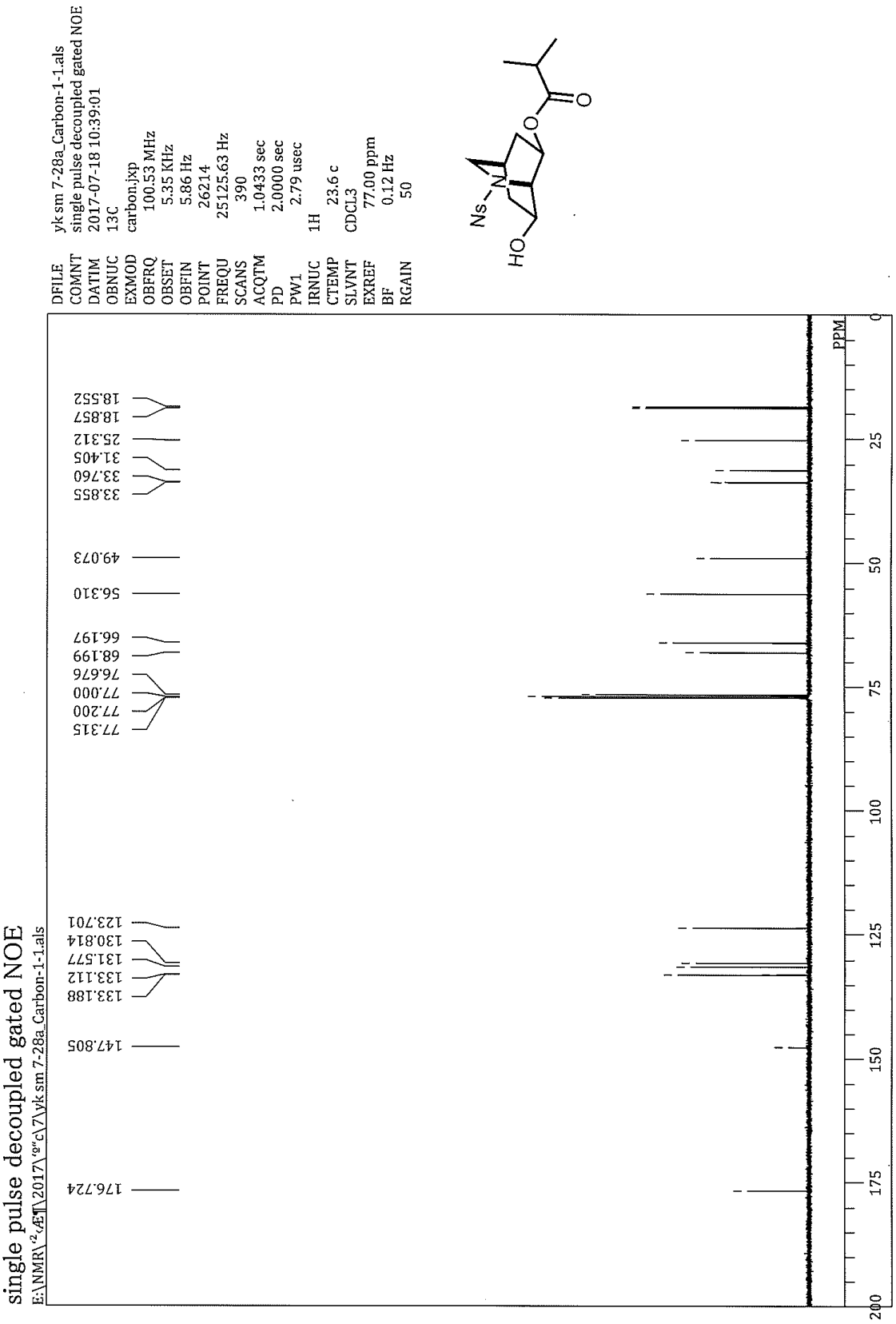


entry	solvent	temp.	time	yield of **s6** (%)	er
1	PhCl	80 °C	24 h	79	50:50
2	$CHCl_3$	50 °C	48 h	46	50:50
3	$CHCl_3$	rt	48 h	15	85:15

7. Charts of ^{1}H- and ^{13}C-NMR spectra

13

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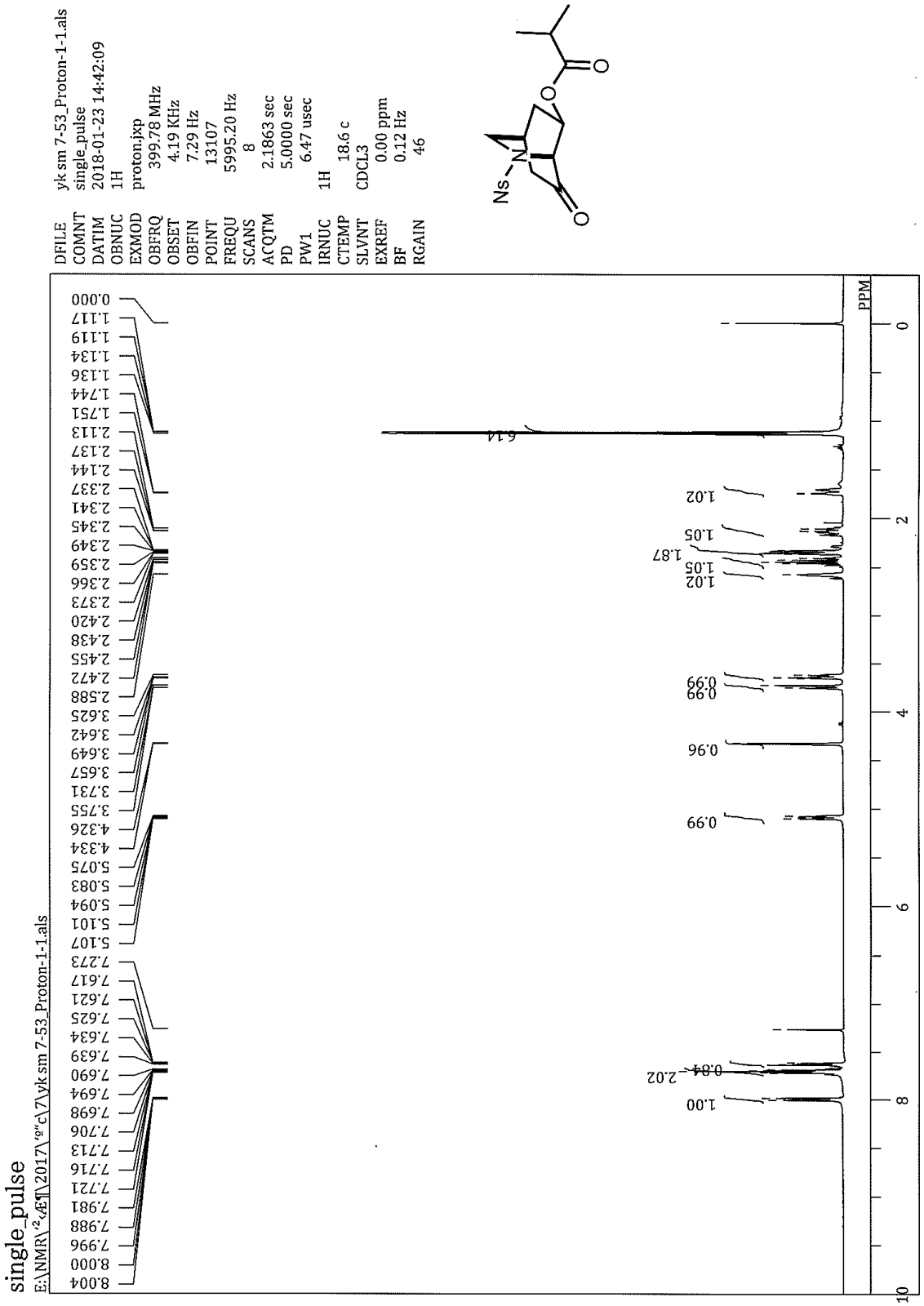
14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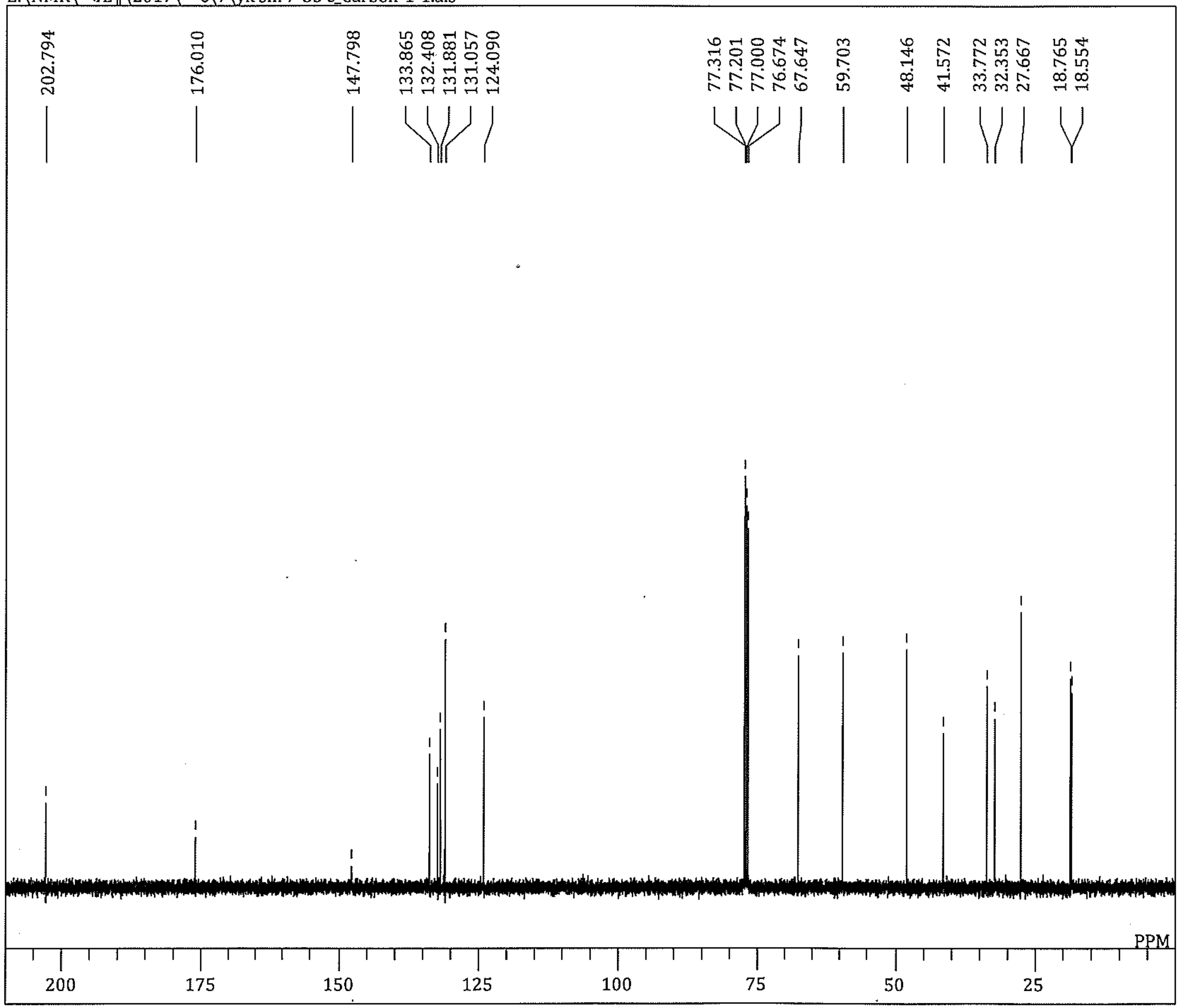

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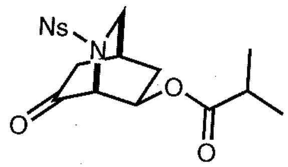

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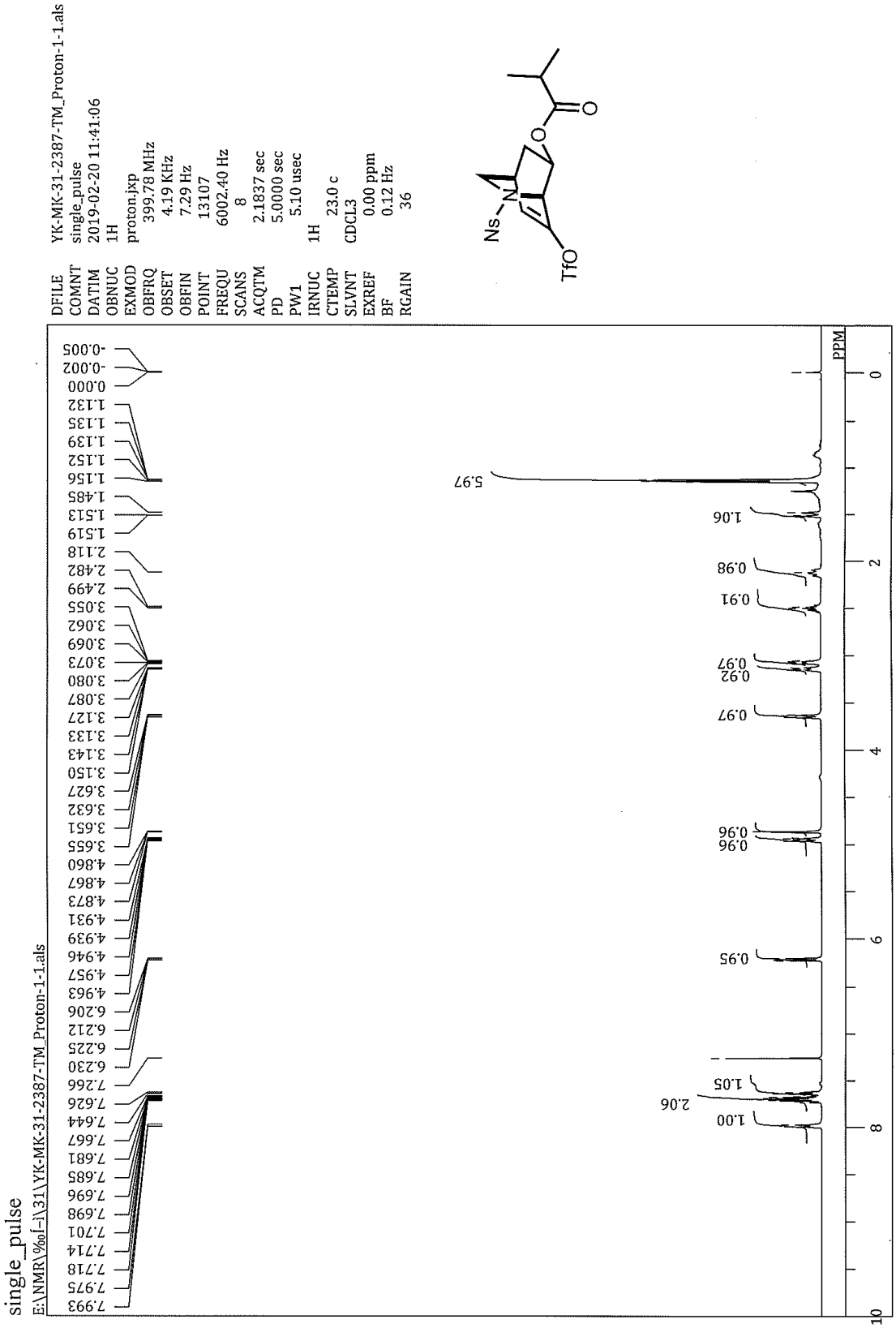
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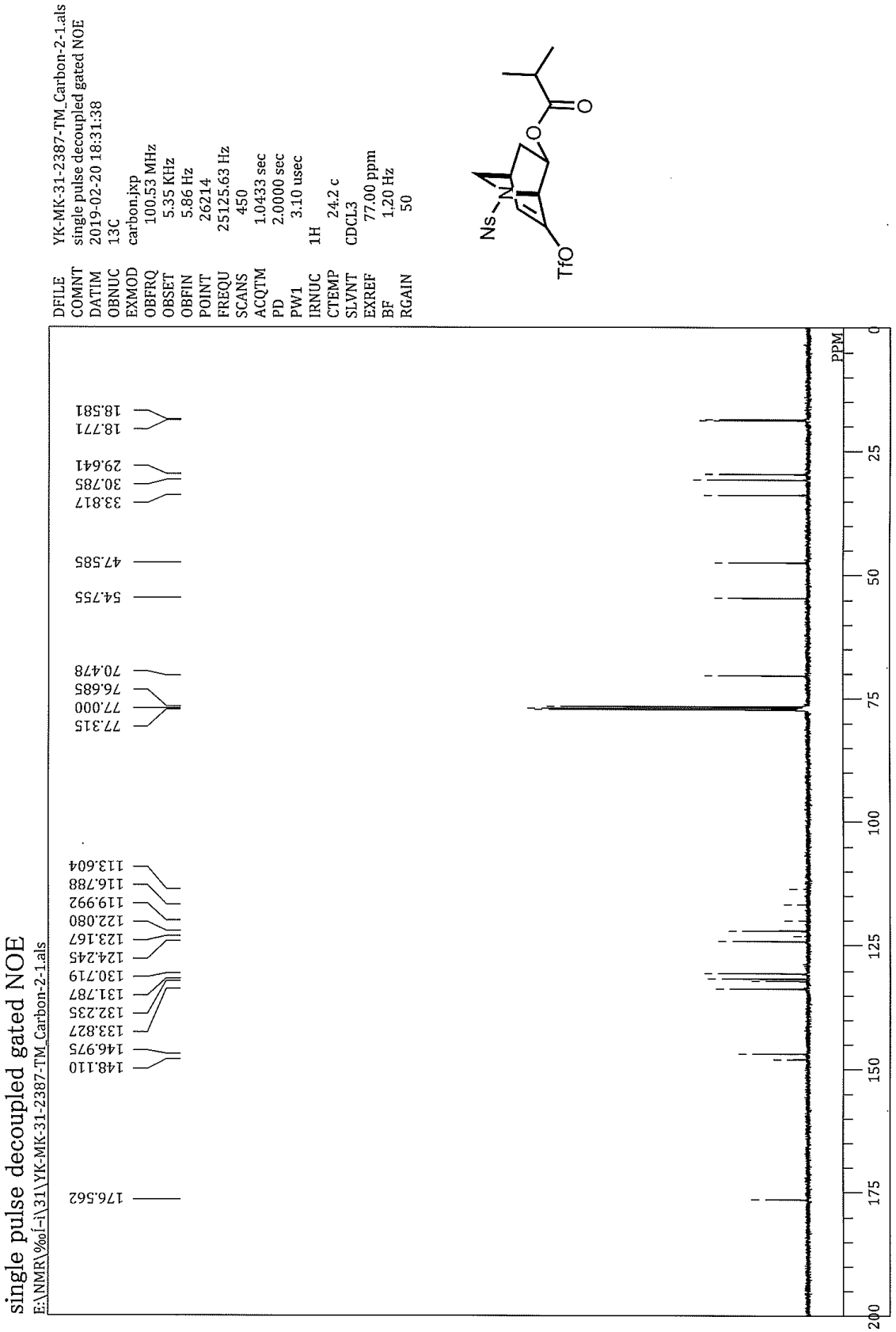
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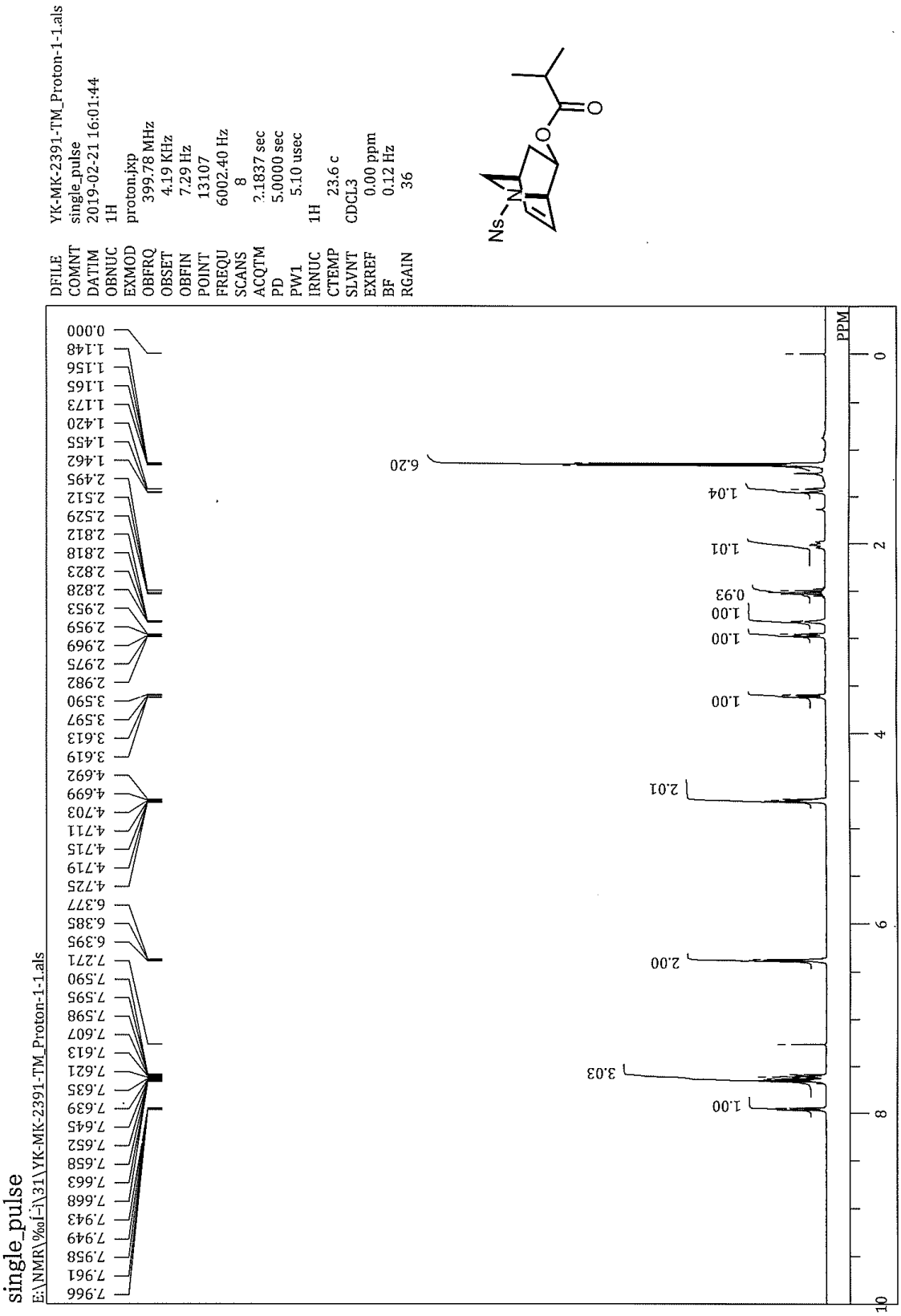
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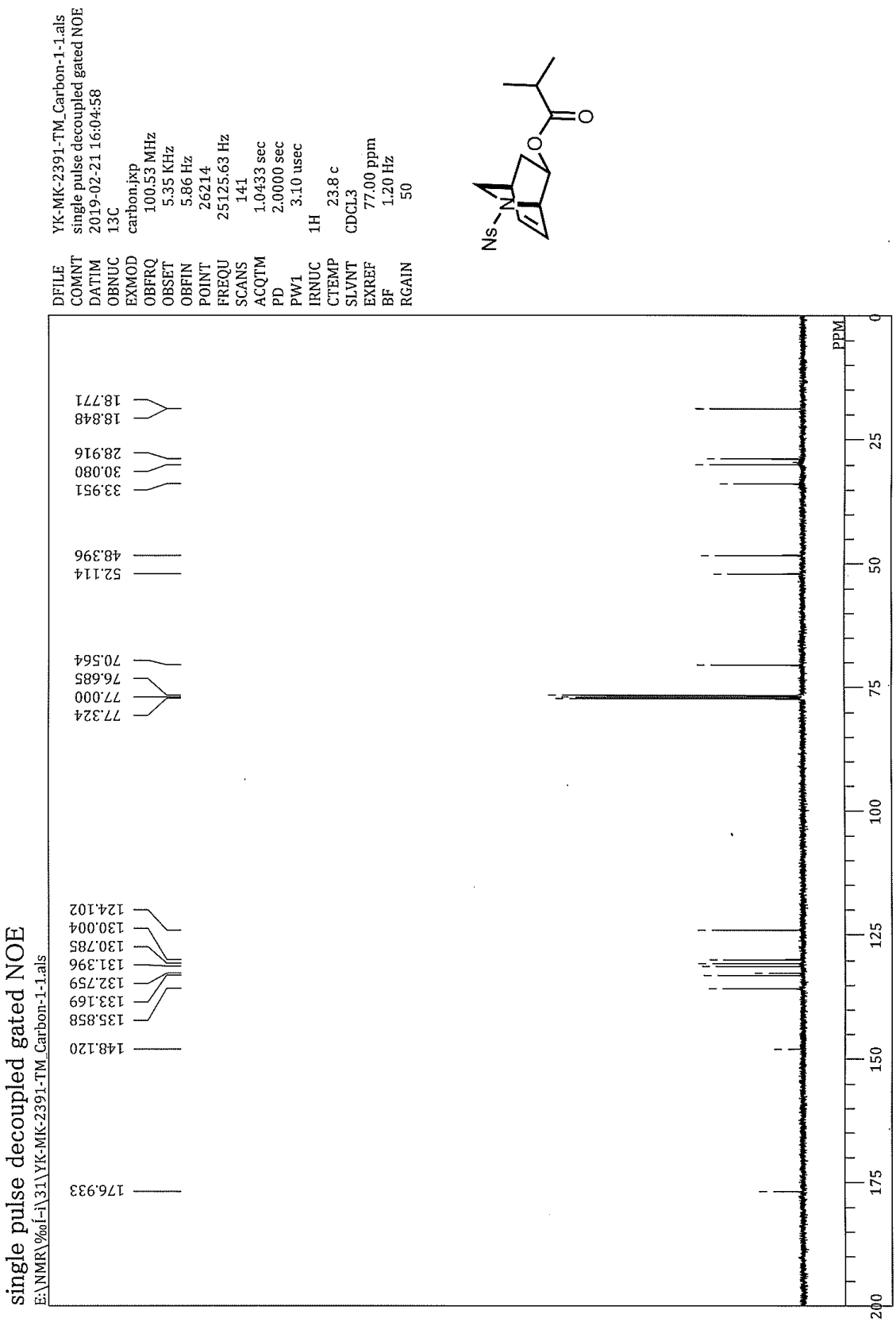
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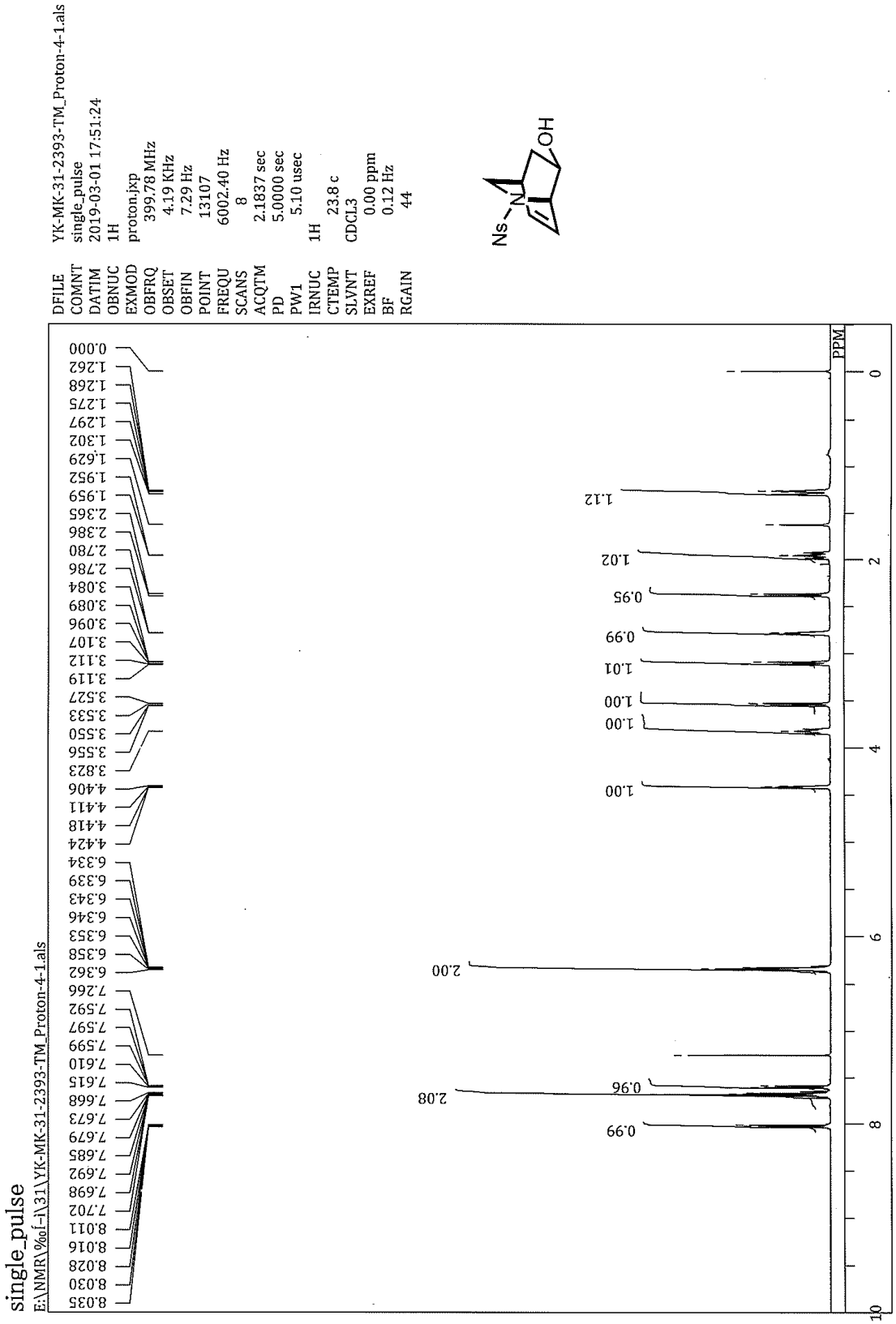
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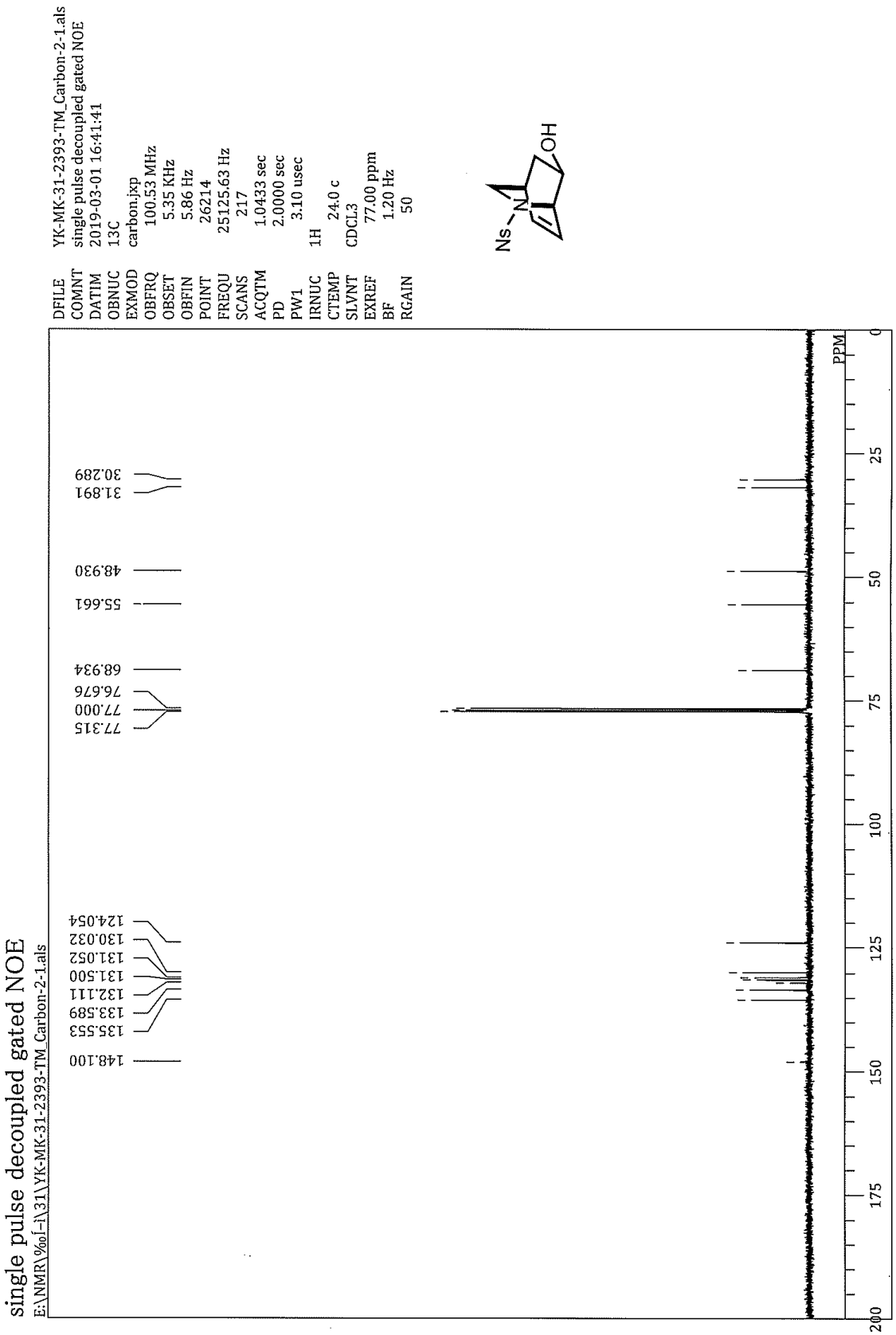
1.302
1.297
1.275
1.268
1.262
0.000
2.00
2.08
0.96
0.99
1.00
1.00
1.00
1.01
0.99
0.95
1.02
1.12
PPM
0
2
4
6
8
10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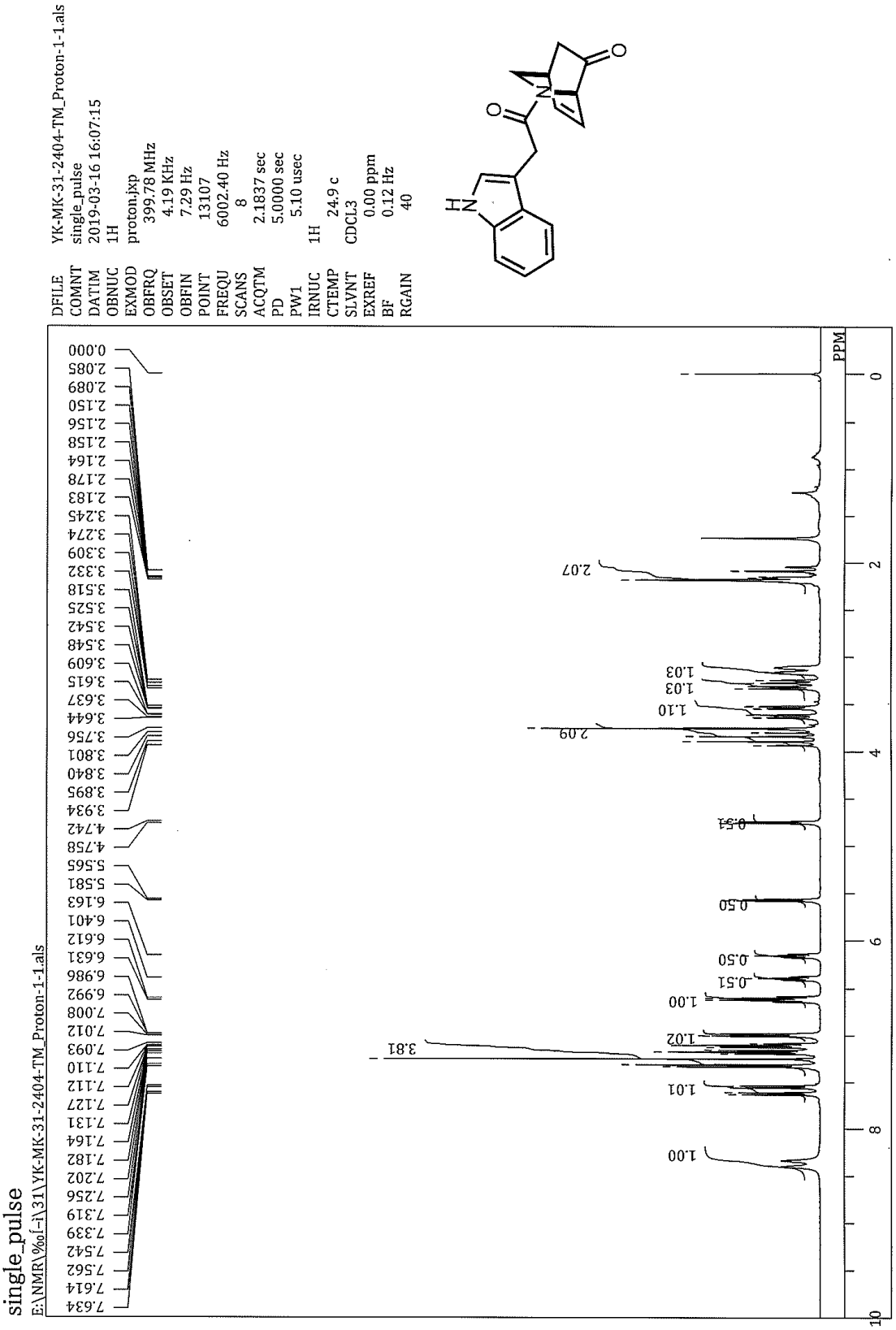
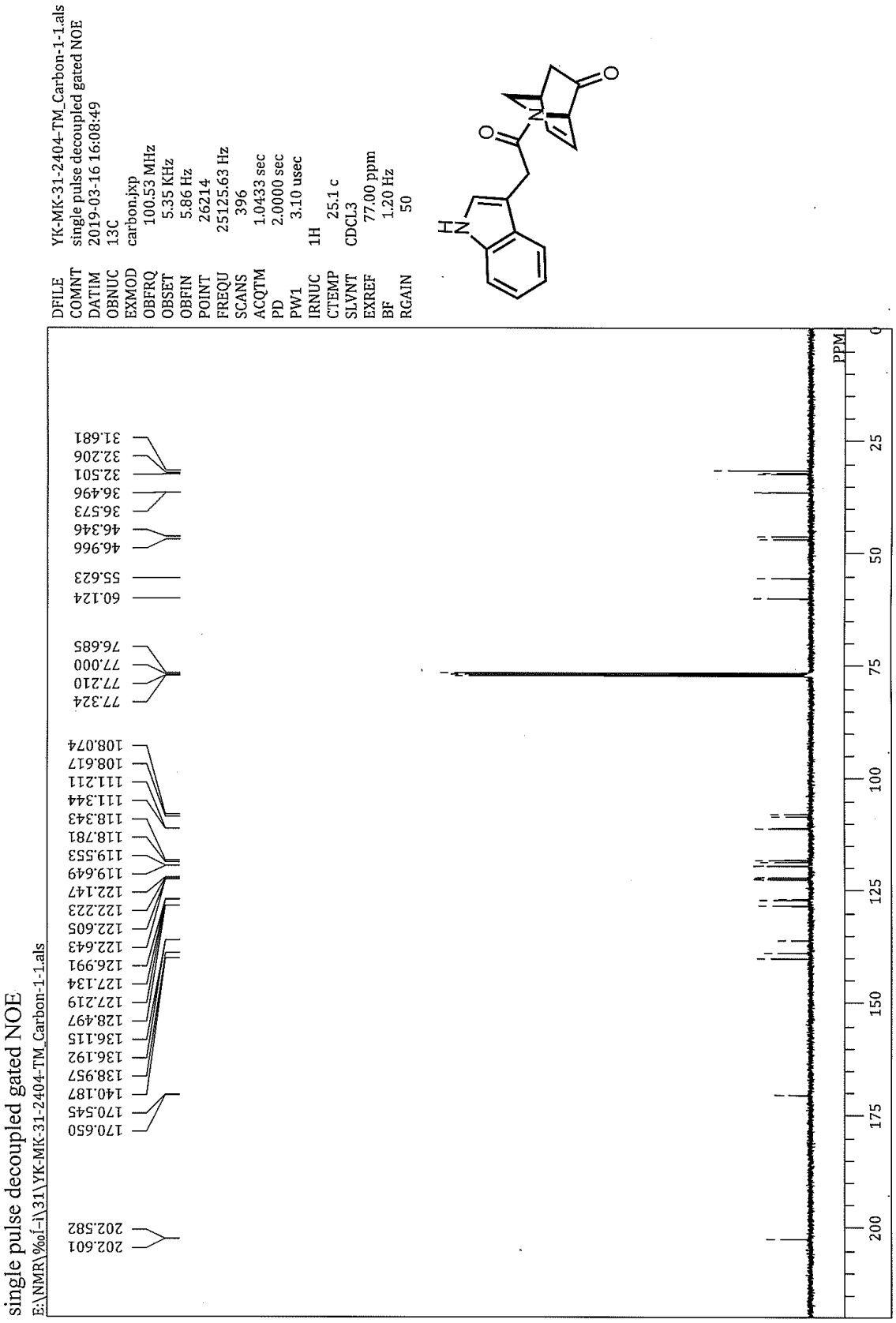
E:\NMR\%o[-i\31\YK-MK-31-2393-TM_Carbon-2-1.als
DFILE YK-MK-31-2393-TM_Carbon-2-1.als
COMNT single pulse decoupled gated NOE
DATIM 2019-03-01 16:41:41
OBNUC 13C
EXMOD carbon.jxp
OBFRQ 100.53 MHz
OBSET 5.35 KHz
OBFIN 5.86 Hz
POINT 26214
FREQU 25125.63 Hz
SCANS 217
ACQTM 1.0433 sec
PD 2.0000 sec
PW1 3.10 usec
IRNUC 1H
CTEMP 24.0 c
SLVNT CDCL3
EXREF 77.00 ppm
BF 1.20 Hz
RGAIN 50
Ns
N
OH
148.100
135.553
133.589
132.111
131.500
131.052
130.032
124.054
77.315
77.000
76.676
68.934
55.661
48.930
31.891
30.289
PPM
200
175
150
125
100
75
50
25
0

18 (~1 : 1 rotamers)




single pulse decoupled gated NOE
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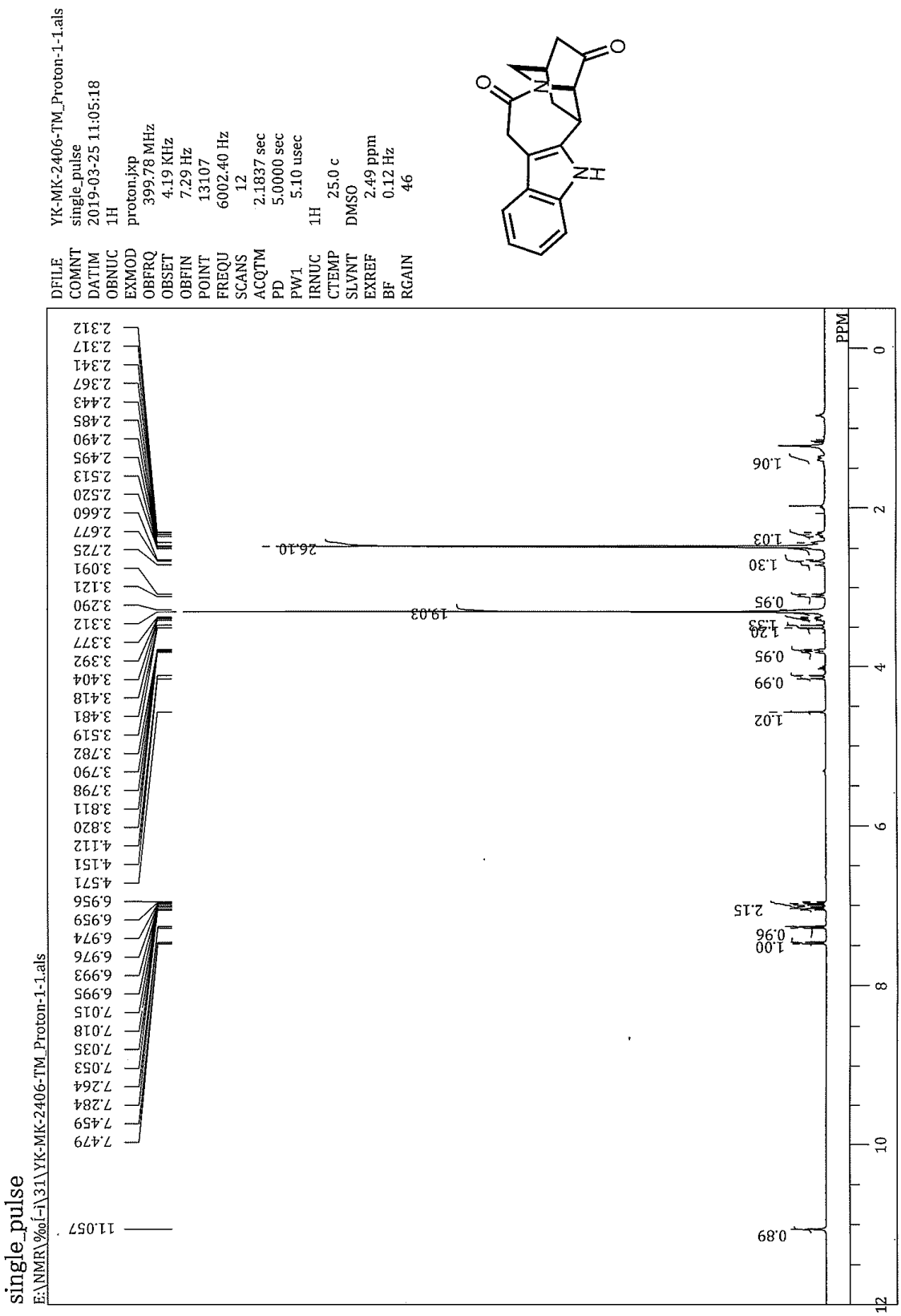
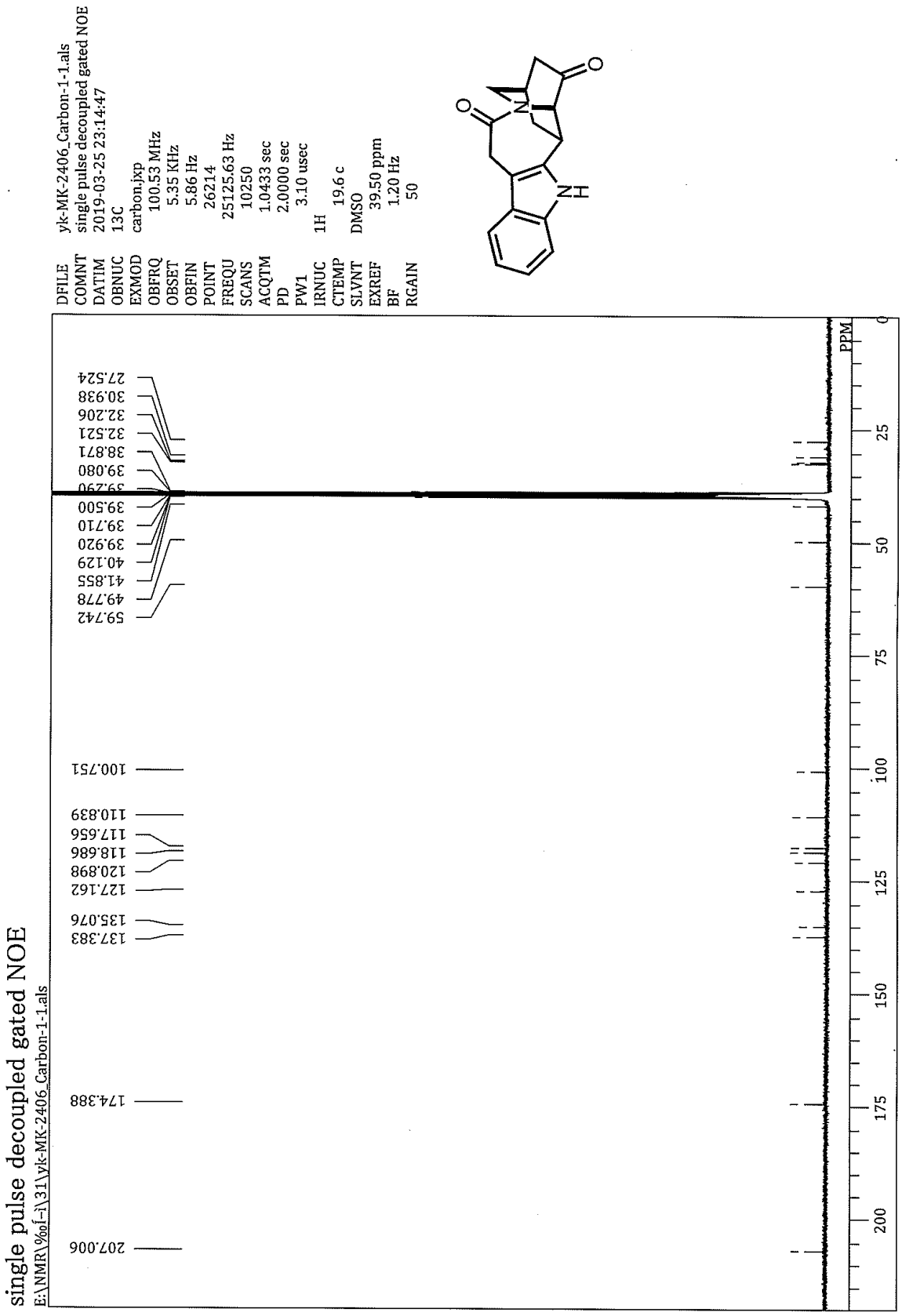
DFILE YK-MK-31-2404-TM_Carbon-1-1.als
COMNT single pulse decoupled gated NOE
DATIM 2019-03-16 16:08:49
OBNUC 13C
EXMOD carbon.jxp
OBFRQ 100.53 MHz
OBSET 5.35 KHz
OBFIN 5.86 Hz
POINT 26214
FREQU 25125.63 Hz
SCANS 396
ACQTM 1.0433 sec
PD 2.0000 sec
PW1 3.10 usec
IRNUC 1H
CTEMP 25.1 c
SLVNT CDCL3
EXREF 77.00 ppm
BF 1.20 Hz
RGAIN 50
202.601
202.582
170.650
170.545
140.187
138.957
136.192
136.115
128.497
127.219
127.134
126.991
122.643
122.605
122.223
122.147
119.649
119.553
118.781
118.343
111.344
111.211
108.617
108.074
77.324
77.210
77.000
76.685
60.124
55.623
46.966
46.346
36.573
36.496
32.501
32.206
31.681
PPM
200
175
150
125
100
75
50
25
0

19 (DMSO-d6)


single_pulse
E:\NMR\%of-i\31\YK-MK-2406-TM_Proton-1-1.als
DFILE YK-MK-2406-TM_Proton-1-1.als
COMNT single_pulse
DATIM 2019-03-25 11:05:18
OBNUC 1H
EXMOD proton.jxp
OBFRQ 399.78 MHz
OBSET 4.19 KHz
OBFIN 7.29 Hz
POINT 13107
FREQU 6002.40 Hz
SCANS 12
ACQTM 2.1837 sec
PD 5.0000 sec
PW1 5.10 usec
IRNUC 1H
CTEMP 25.0 c
SLVNT DMSO
EXREF 2.49 ppm
BF 0.12 Hz
RGAIN 46
PPM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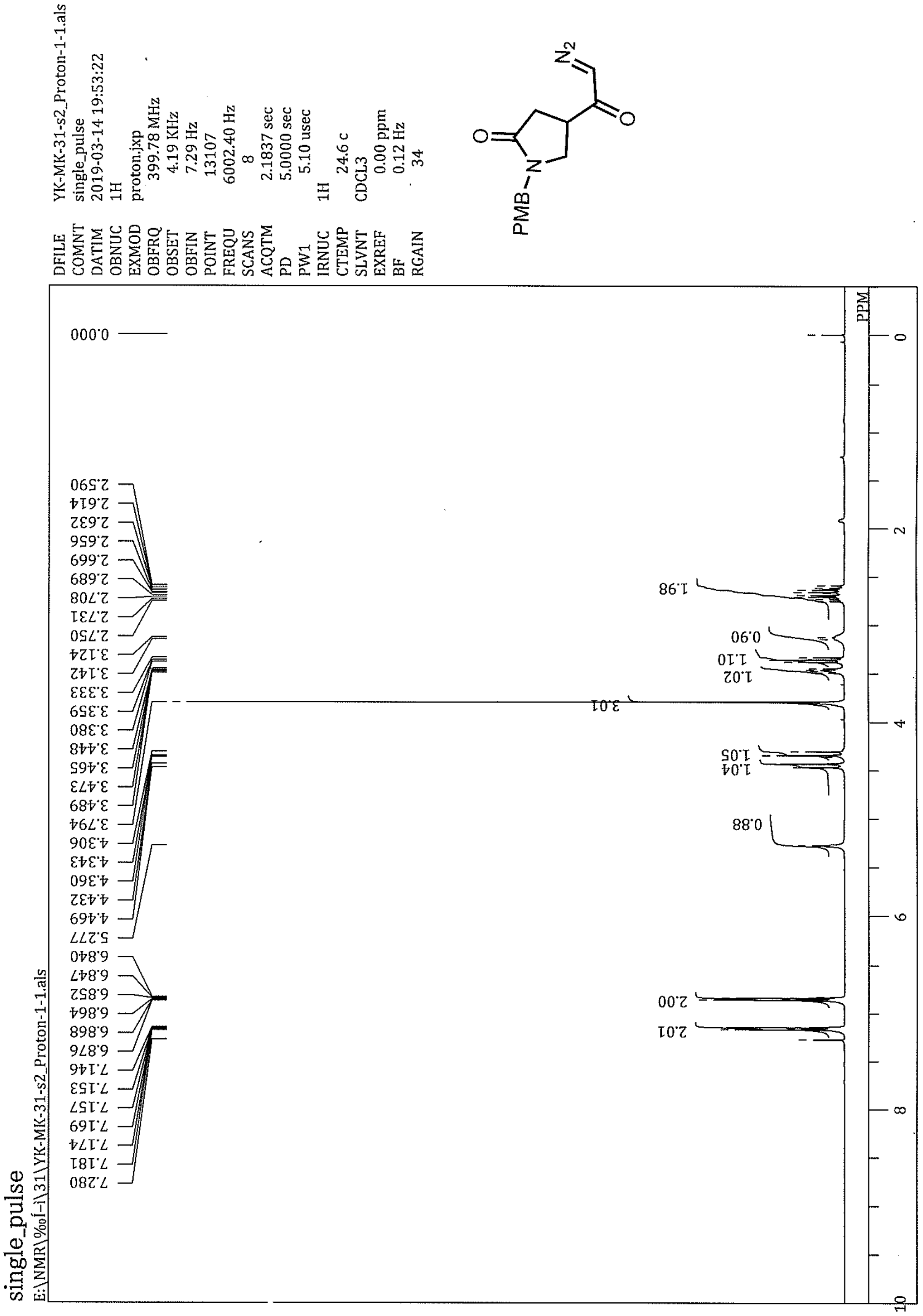
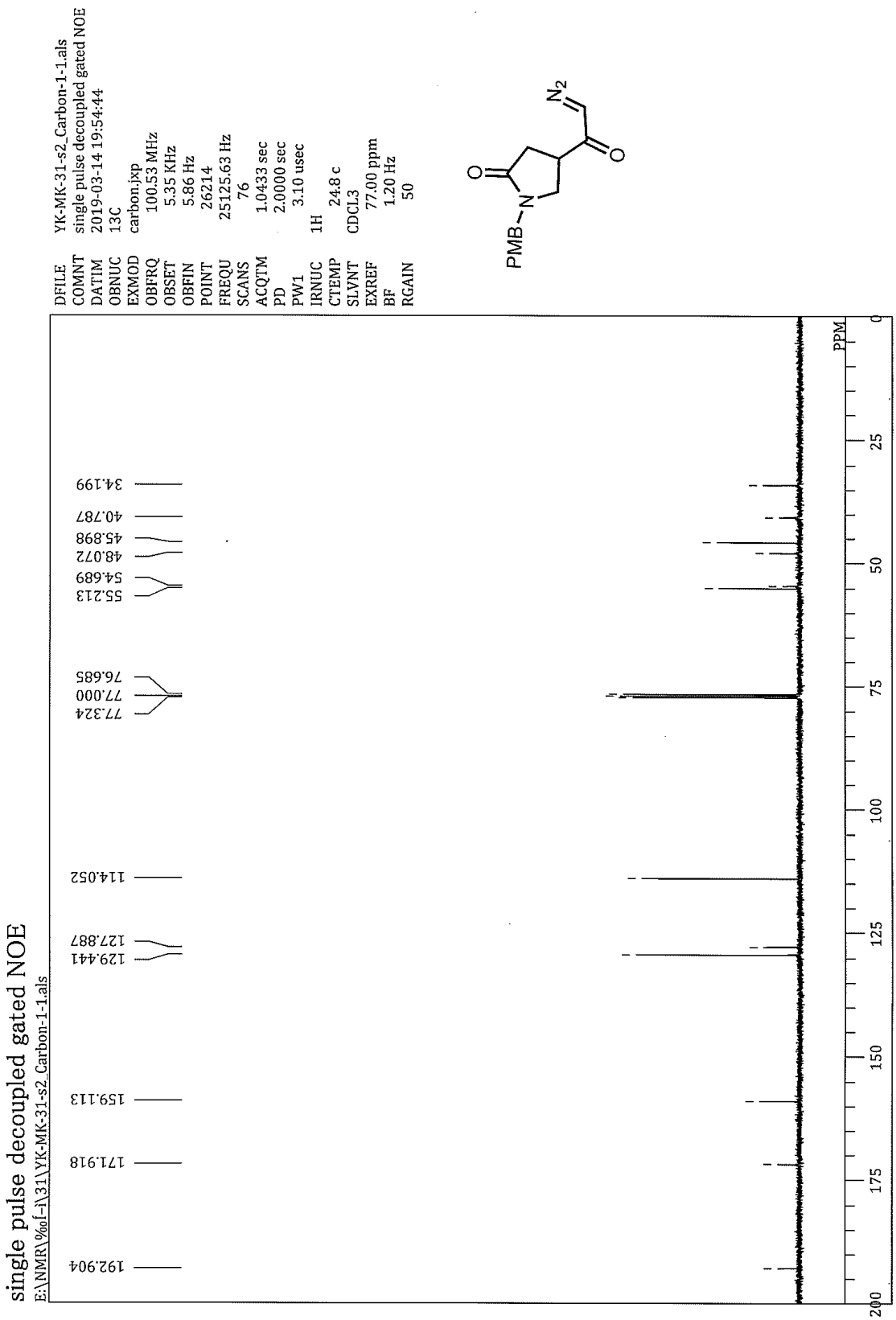
DFILE yk-MK-2406_Carbon-1-1.als
COMNT single pulse decoupled gated NOE
DATIM 2019-03-25 23:14:47
OBNUC 13C
EXMOD carbon.jxp
OBFRQ 100.53 MHz
OBSET 5.35 KHz
OBFIN 5.86 Hz
POINT 26214
FREQU 25125.63 Hz
SCANS 10250
ACQTM 1.0433 sec
PD 2.0000 sec
PW1 3.10 usec
IRNUC 1H
CTEMP 19.6 c
SLVNT DMSO
EXREF 39.50 ppm
BF 1.20 Hz
RGAIN 50
207.006
174.388
137.383
135.076
127.162
120.898
118.686
117.656
110.839
100.751
59.742
49.778
41.855
40.129
39.920
39.710
39.500
39.290
39.080
38.871
32.521
32.206
30.938
27.524
PPM
0
25
50
75
100
125
150
175
200

s2



DFILE YK-MK-31-s2_Proton-1-1.als
COMNT single_pulse
DATIM 2019-03-14 19:53:22
OBNUC 1H
EXMOD proton.jxp
OBFRQ 399.78 MHz
OBSET 4.19 KHz
OBFIN 7.29 Hz
POINT 13107
FREQU 6002.40 Hz
SCANS 8
ACQTM 2.1837 sec
PD 5.0000 sec
PW1 5.10 usec
IRNUC 1H
CTEMP 24.6 c
SLVNT CDCL3
EXREF 0.00 ppm
BF 0.12 Hz
RGAIN 34
PMB
N
O
N2
single_pulse
E:\NMR\‰[-i\31\YK-MK-31-s2_Proton-1-1.als
PPM


single pulse decoupled gated NOE
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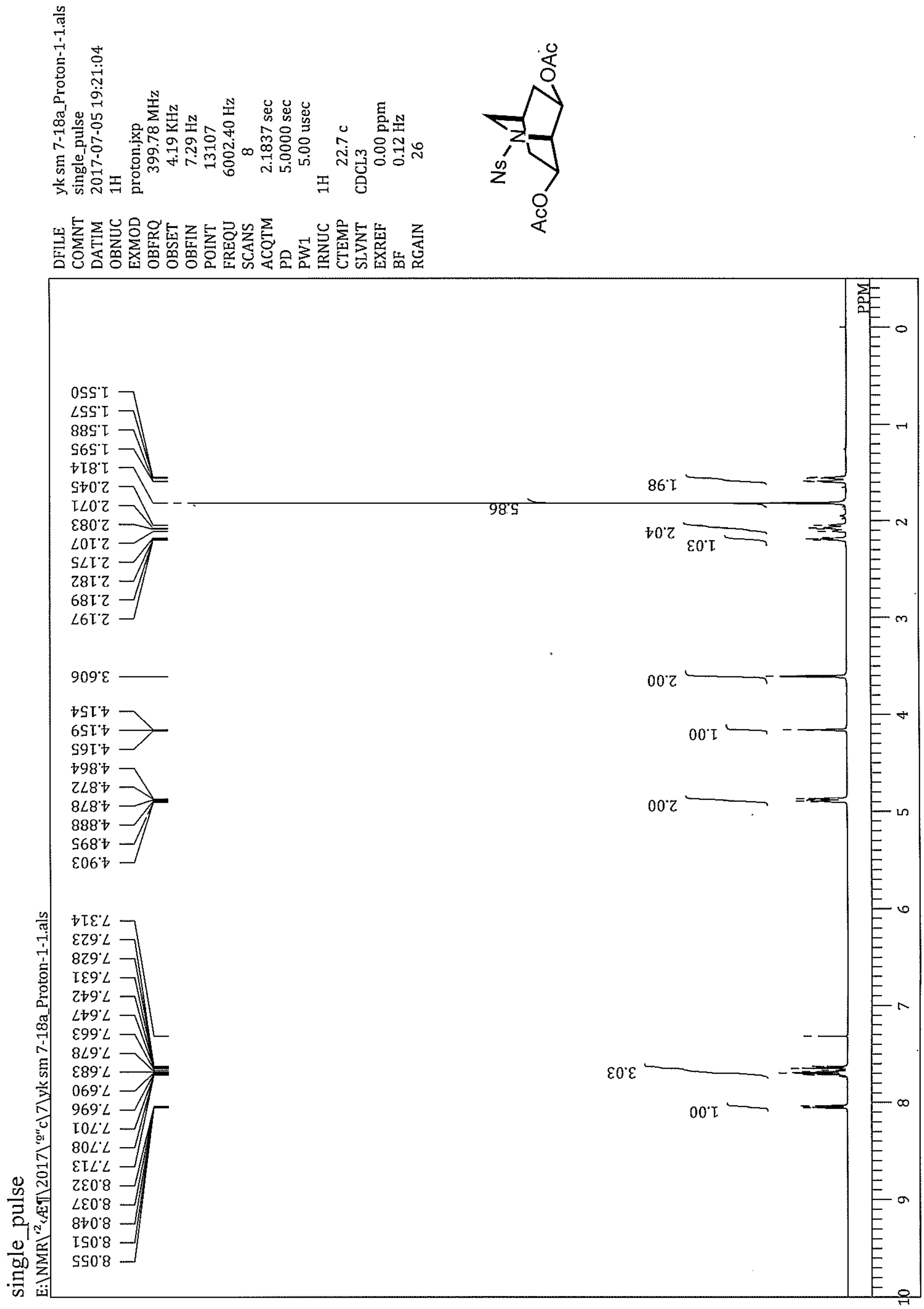
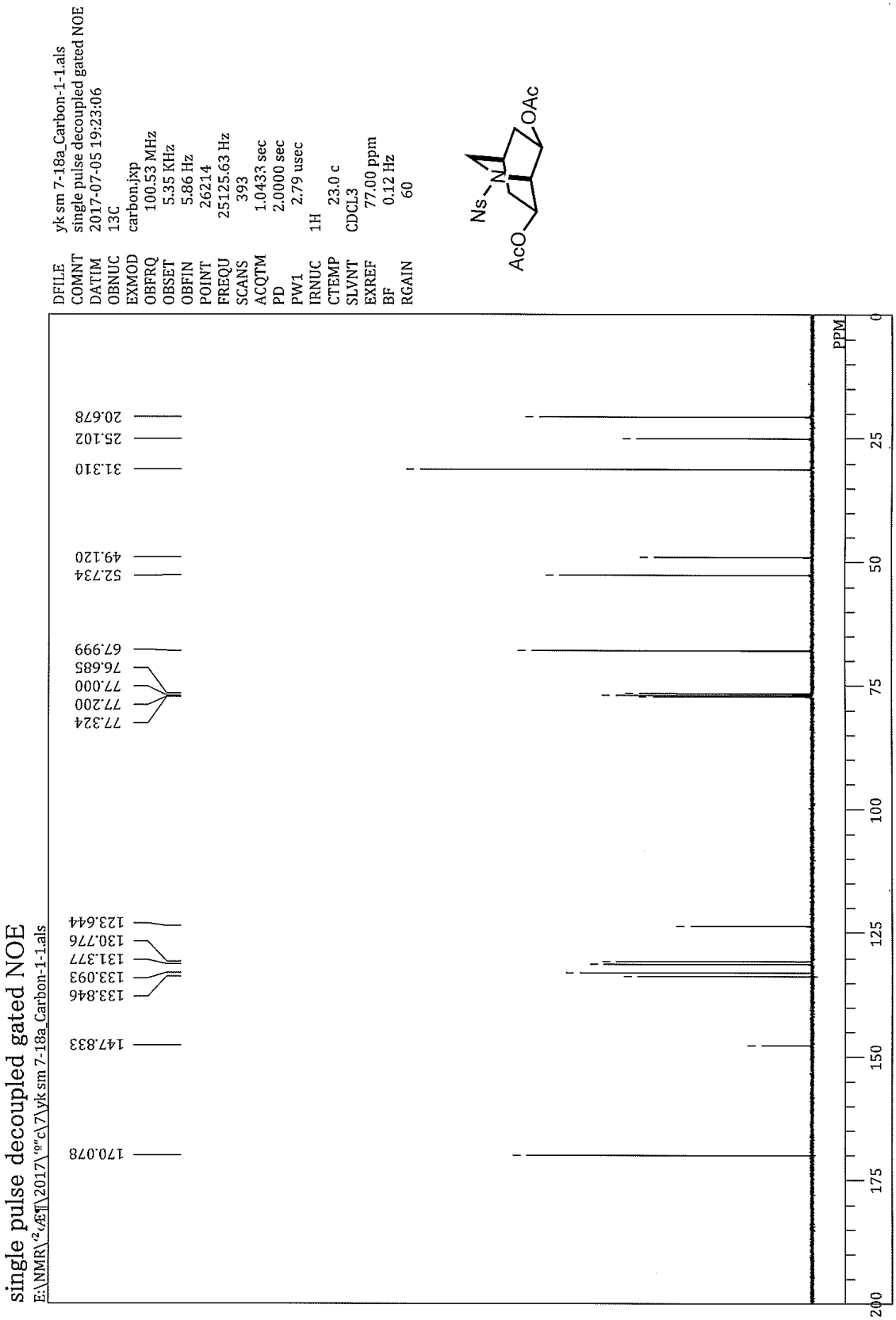
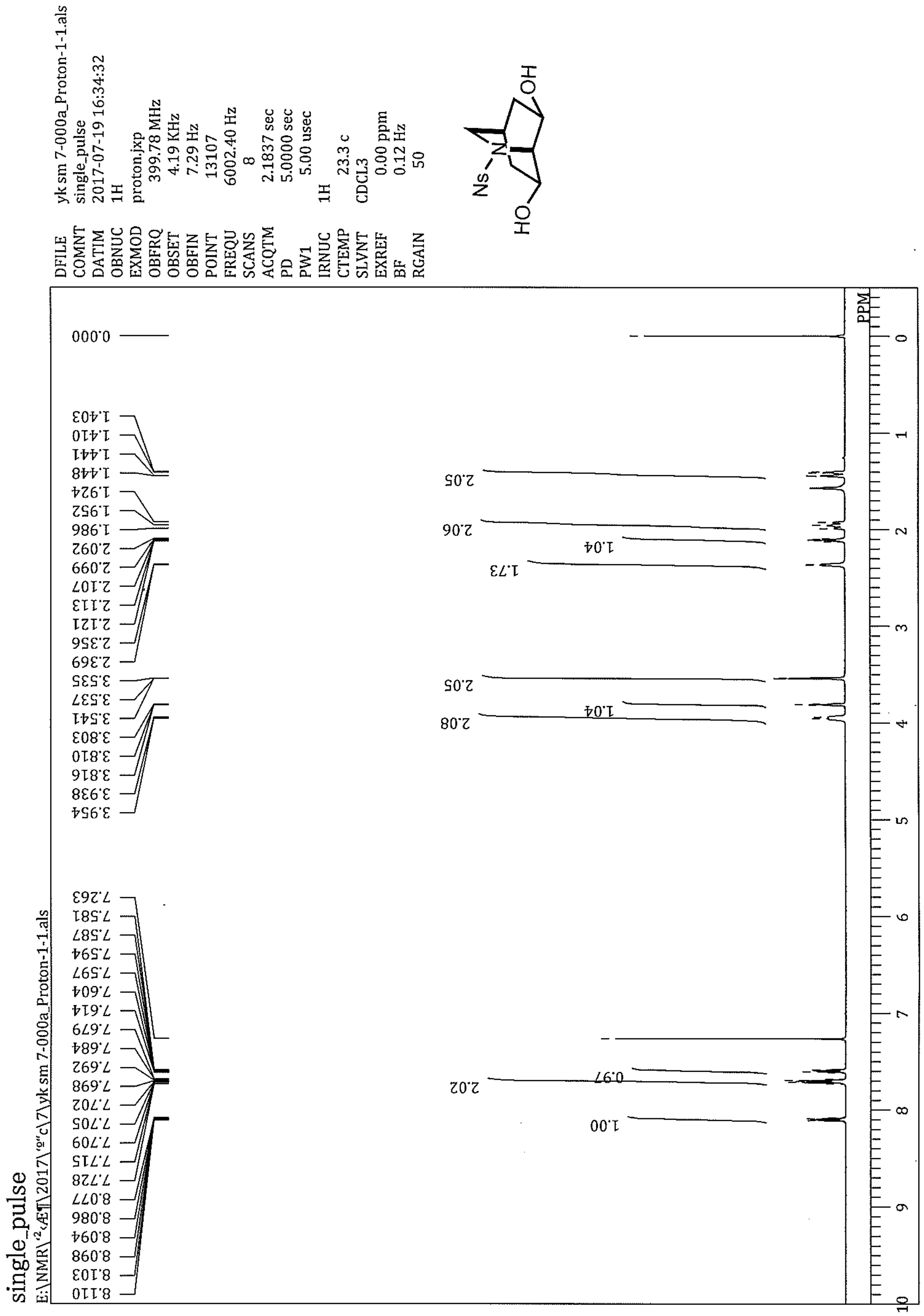
DFILE YK-MK-31-s2_Carbon-1-1.als
COMNT single pulse decoupled gated NOE
DATIM 2019-03-14 19:54:44
OBNUC 13C
EXMOD carbon.jxp
OBFRQ 100.53 MHz
OBSET 5.35 KHz
OBFIN 5.86 Hz
POINT 26214
FREQU 25125.63 Hz
SCANS 76
ACQTM 1.0433 sec
PD 2.0000 sec
PW1 3.10 usec
IRNUC 1H
CTEMP 24.8 c
SLVNT CDCL3
EXREF 77.00 ppm
BF 1.20 Hz
RGAIN 50
PMB
N2
34.199
40.787
45.898
48.072
54.689
55.213
76.685
77.000
77.324
114.052
127.887
129.441
159.113
171.918
192.904
PPM
0
25
50
75
100
125
150
175
200

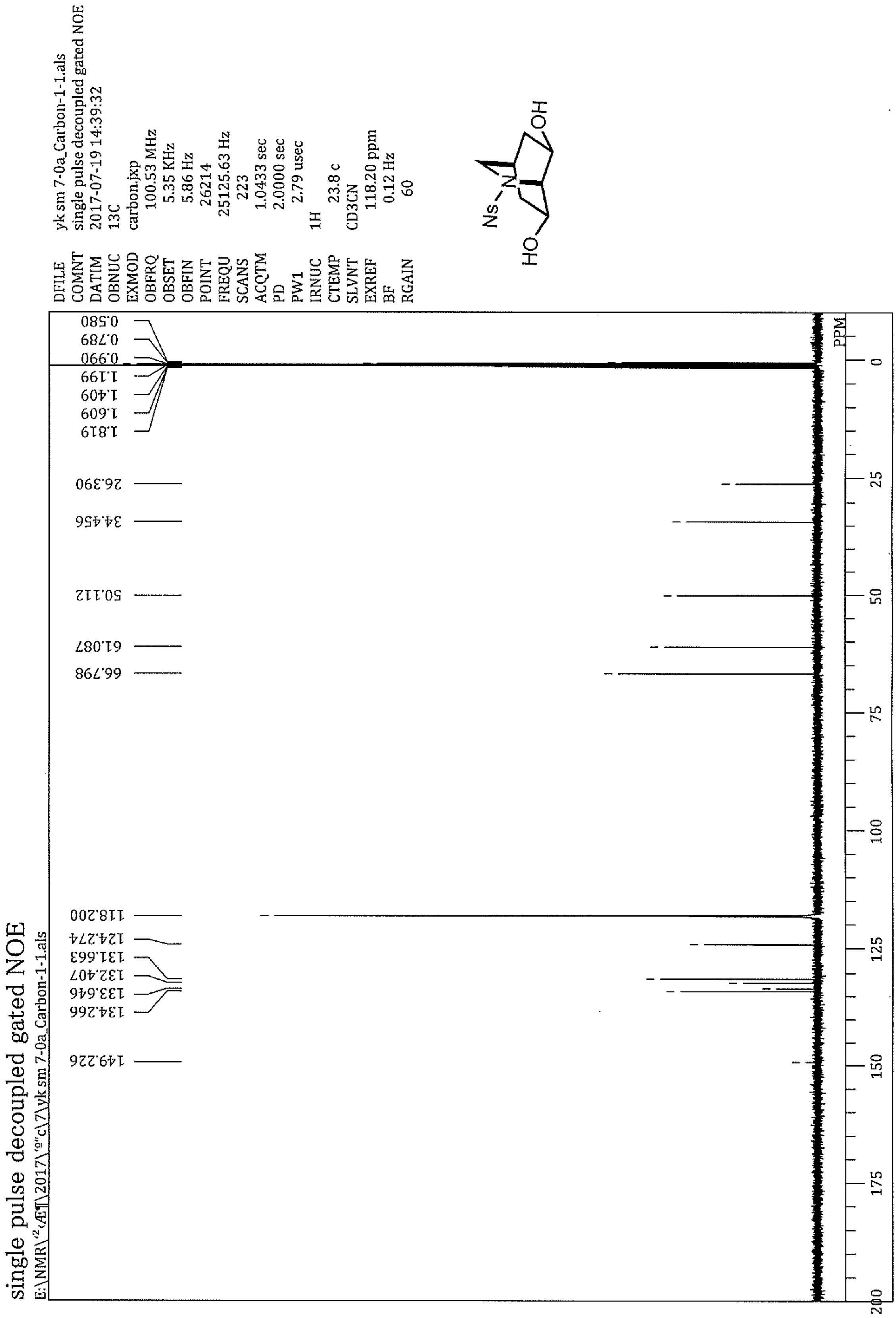
s4


DFILE yk sm 7-18a_Proton-1-1.als
COMNT single_pulse
DATIM 2017-07-05 19:21:04
OBNUC 1H
EXMOD proton.jxp
OBFRQ 399.78 MHz
OBSET 4.19 KHz
OBFIN 7.29 Hz
POINT 13107
FREQU 6002.40 Hz
SCANS 8
ACQTM 2.1837 sec
PD 5.0000 sec
PW1 5.00 usec
IRNUC 1H
CTEMP 22.7 c
SLVNT CDCL3
EXREF 0.00 ppm
BF 0.12 Hz
RGAIN 26
AcO
Ns
N
OAc
single_pulse
PPM


single pulse decoupled gated NOE
E:\NMR\²Æ¶\2017\°ë°c\7\yk sm 7-18a_Carbon-1-1.als
DFILE yk sm 7-18a_Carbon-1-1.als
COMNT single pulse decoupled gated NOE
DATIM 2017-07-05 19:23:06
OBNUC 13C
EXMOD carbon.jxp
OBFRQ 100.53 MHz
OBSET 5.35 KHz
OBFIN 5.86 Hz
POINT 26214
FREQU 25125.63 Hz
SCANS 393
ACQTM 1.0433 sec
PD 2.0000 sec
PW1 2.79 usec
IRNUC 1H
CTEMP 23.0 c
SLVNT CDCL3
EXREF 77.00 ppm
BF 0.12 Hz
RGAIN 60
Ns
N
OAc
AcO
20.678
25.102
31.310
49.120
52.734
67.999
76.685
77.000
77.200
77.324
123.644
130.776
131.377
133.093
133.846
147.833
170.078
PPM
200
175
150
125
100
75
50
25
0

12

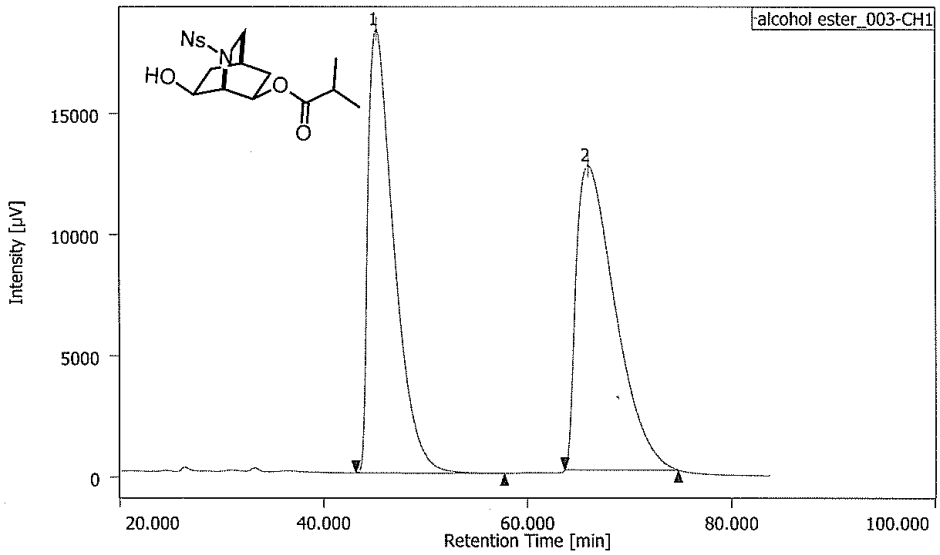

single_pulse
E:\NMR\'²‹Æ¶\2017\'º"c\7\yk sm 7-000a_Proton-1-1.als
DFILE yk sm 7-000a_Proton-1-1.als
COMNT single_pulse
DATIM 2017-07-19 16:34:32
OBNUC 1H
EXMOD proton.jxp
OBFRQ 399.78 MHz
OBSET 4.19 KHz
OBFIN 7.29 Hz
POINT 13107
FREQU 6002.40 Hz
SCANS 8
ACQTM 2.1837 sec
PD 5.0000 sec
PW1 5.00 usec
IRNUC 1H
CTEMP 23.3 c
SLVNT CDCL3
EXREF 0.00 ppm
BF 0.12 Hz
RGAIN 50
Ns
N
HO
OH
PPM


single pulse decoupled gated NOE
DFILE yk sm 7-0a_Carbon-1-1.als
COMNT single pulse decoupled gated NOE
DATIM 2017-07-19 14:39:32
OBNUC 13C
EXMOD carbon.jxp
OBFRQ 100.53 MHz
OBSET 5.35 KHz
OBFIN 5.86 Hz
POINT 26214
FREQU 25125.63 Hz
SCANS 223
ACQTM 1.0433 sec
PD 2.0000 sec
PW1 2.79 usec
IRNUC 1H
CTEMP 23.8 c
SLVNT CD3CN
EXREF 118.20 ppm
BF 0.12 Hz
RGAIN 60
Ns
N
HO
OH
0.580
0.789
0.990
1.199
1.409
1.609
1.819
26.390
34.456
50.112
61.087
66.798
118.200
124.274
131.663
132.407
133.646
134.266
149.226
PPM
0
25
50
75
100
125
150
175
200

8. Chiral and Racemic HPLC Traces

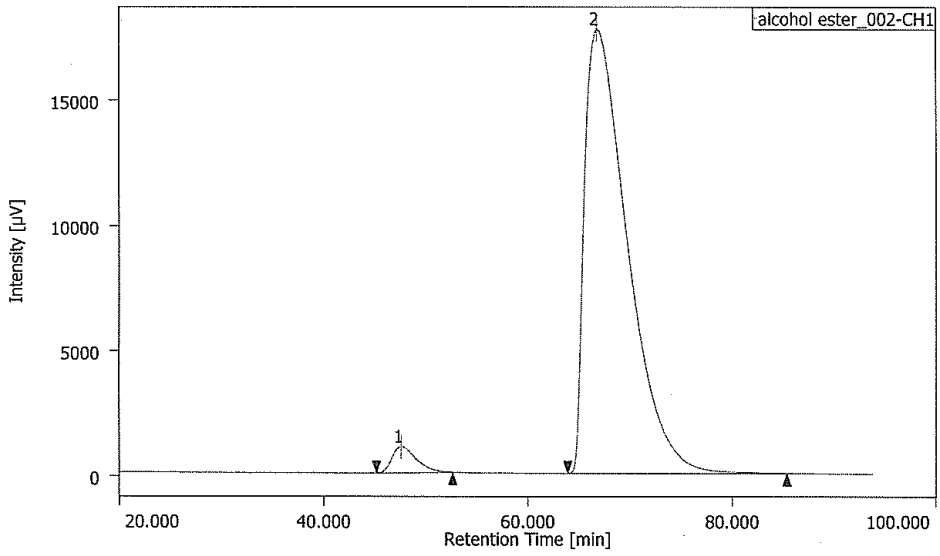
13

alcohol ester_0222 alcohol ester_003 2019/03/28 18:15:40



#	tR [min]	Area [μV·sec]	Area%	Height [μV]	Height%
1	45.250	3225199	49.073	18285	59.264
2	65.967	3347112	50.927	12568	40.736

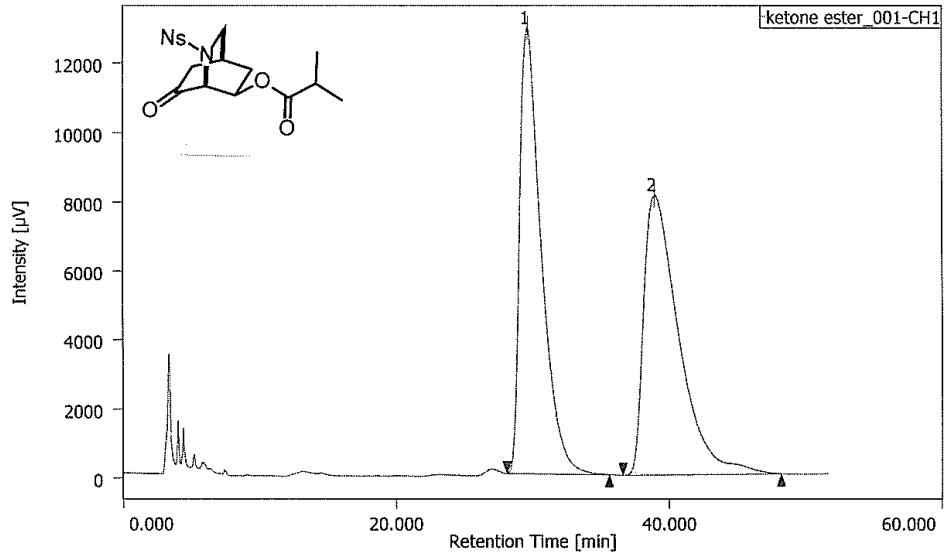
alcohol ester_0222 alcohol ester_002 2019/03/28 18:12:54



#	tR [min]	Area [μV·sec]	Area%	Height [μV]	Height%
1	47.608	173587	3.250	1045	5.573
2	66.750	5167497	96.750	17711	94.427

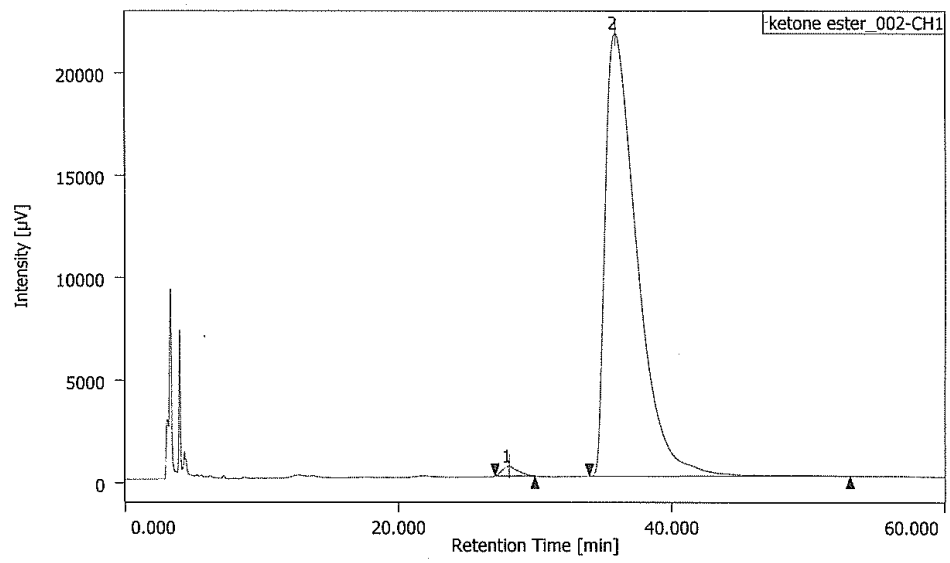
14

ketone ester_0221 ketone ester_001 2019/03/28 18:37:46



#	tR [min]	Area [μV·sec]	Area%	Height [μV]	Height%
1	29.642	1409673	49.318	12902	61.405
2	38.933	1448656	50.682	8110	38.595

ketone ester_0221 ketone ester_002 2019/03/30 12:02:32



#	tR [min]	Area [μV·sec]	Area%	Height [μV]	Height%
1	28.092	37250	1.057	472	2.138
2	35.858	3486995	98.943	21584	97.862

9. References

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