Synthesis of (±)-Nosyberkol (Isotuberculosinol, Revised Structure of Edaxadiene) and (±)-Tuberculosinol

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General Procedure. Reactions were conducted in flame- or oven-dried glassware under a nitrogen atmosphere and were stirred magnetically. The phrase "concentrated" refers to removal of solvents by means of a rotary evaporator attached to a diaphragm pump (15-60 Torr) followed by removal of residual solvents at < 1 Torr with a vacuum pump. Flash chromatography was performed on silica gel 60 (230-400 mesh). Analytical thin layer chromatography (TLC) was performed using silica gel 60 F-254 pre-coated glass plates (0.25 mm). TLC Plates were analyzed by short wave UV illumination, or by dipping in vanillin stain (27 g of vanillin in 380 mL of EtOH, 50 mL of water and 20 mL of concentrated sulfuric acid) and heating on a hot plate or by spray with permanganate spray (5 g of $KMnO_4$ in 495 mL of water). THF was dried and purified by distillation from sodium/benzophenone. DIPEA and benzene were distilled from CaH_2. ^1H and ^{13}C NMR spectra were obtained on a 400 MHz spectrometer in $CDCl_3$ with tetramethylsilane as internal standard unless otherwise indicated. Chemical shifts are reported in δ (ppm downfield from tetramethylsilane). Spectra recorded in $CDCl_3$ are referenced to residual $CHCl_3$ at δ 7.26 and the center peak of $CDCl_3$ at 77.00. Spectra in C_6D_6 are referenced to the C_6D_5H at δ 7.16 and the center peak of C_6D_6 at δ 128.06. Coupling constants are reported in Hz with multiplicities denoted as s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), m (multiplet) and br (broad). IR spectra were acquired on an FT-IR spectrometer and are reported in wave numbers (cm^{-1}). High resolution mass spectra were obtained using the following ionization techniques: chemical ionization (CI), electron impact (EI), electrospray ionization analyzed by quadrupole time of flight (QTOF). 3-[(2*E*)-2-Methyl-1-oxo-2-buten-1-yl]-2-oxazolidinone (15) was prepared by the literature procedure.[9]

1-Ethenyl-6,6-dimethyl-cyclohexene (7). Following the literature procedure,[5b] 2,2-dimethylcyclohexanone (2.0 g, 15.85 mmol) in 5 mL of THF was added over 30 min to a stirred solution of vinylmagnesium bromide (1.0 M in THF, 20.6 mL, 20.6 mmol) cooled in an ice bath under N_2. The ice bath was removed, and the solution was allowed to warm to 25 °C over 30 min and stirred for an additional 1 hr. The reaction was then quenched by slow addition of saturated aqueous NH_4Cl solution (20 mL). The layers were separated and the aqueous layer was extracted

with EtOAc (3 × 15 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to give 2.75 g (125%) of crude 1-ethenyl-2,2-dimethyl-cyclohexanol.

The entire crude 1-ethenyl-2,2-dimethyl-cyclohexanol was dissolved in 50 mL of benzene and anhydrous $CuSO_4$ (3.8 g, 23.8 mmol) was added. The suspension was heated at reflux with azeotropic removal of water using a Dean-Stark trap for 12 hr. The suspension was cooled to 25 °C, filtered through a pad of Celite (pentane) to remove $CuSO_4$, and concentrated at 50 °C and 200 Torr to give 1.9 g of crude **7**. Distillation of crude **7** (35 °C, 0.8 Torr) gave 1.36 g (63%) of pure **7** as colorless oil: ^{1}H NMR 6.30 (dd, 1, *J* = 18, 11), 5.78 (t, 1, *J* = 4), 5.27 (d, 1, *J* = 18), 4.91 (d, 1, *J* = 11), 2.10-2.00 (m, 2), 1.63-1.56 (m, 2), 1.51-1.44 (m, 2), 1.06 (s, 6). The spectral data were identical to those previously reported.[7]

3-[[(1α,2β,8aα)-)-1,2,3,5,6,7,8,8a-Octahydro-1,2,5,5-tetramethyl-1-naphthalenyl]carbonyl]-2-oxazolidinone (16) and 3-[[(1β,2α,8aα)-)-1,2,3,5,6,7,8,8a-Octahydro-1,2,5,5-tetramethyl-1-naphthalenyl]carbonyl]-2-oxazolidinone (S1). To a stirred solution of oxazolidinone **15**[9] (338.14 mg, 2 mmol) in 6 mL of CH_2Cl_2 at -78 °C under N_2 was added Me_2AlCl (2 mL, 1.9 M in hexanes, 3.8 mmol). The reaction was stirred for 10 min and diene **7** (272.4 mg, 2 mmol in 3 mL of CH_2Cl_2) was added over 5 min. The flask was sealed under N_2, transferred to a 4 °C cold room and stirred for 48 hr at which time the reaction was quenched at 0 °C by slow addition of 5 mL of aqueous 1 M HCl. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. Flash chromatography of the residue (5:1 hexanes/EtOAc) afforded 330 mg (54%) of a 10:1 mixture of **16** and the endo isomer **S1**. Careful flash chromatography gave mixtures containing ~20:1 **16** and **S1** in more polar fractions: ^{1}H NMR 5.48 (br d, 1, *J* = 5), 4.50-4.30 (m, 2), 4.20-3.96 (m, 2), 3.51 (br d, 1, *J* = 13.4, H-8a), 3.06-2.74 (m, 1, H-2), 1.93 (ddd, 1, *J* = 18, 5, 5, H-3eq), 1.72 (br dd, 1, *J* = 18, 11, H-3ax), 1.60-1.46 (m, 2), 1.44-1.28 (m, 2), 1.28-1.12 (m, 2), 1.07 (s, 3), 1.06 (s, 3), 1.02 (s, 3), 0.77 (d, 3, *J* = 7.3); ^{13}C NMR 178.6, 152.4, 144.7, 115.9, 62.0, 53.2, 45.8, 40.8, 37.5, 36.3, 30.9, 29.6 (2 C),

29.3, 28.8, 22.0, 16.5, 12.1; IR 1775, 1682, 1472, 1457, 1381, 1359, 1264, 1246, 1197; HRMS (EI) calcd for $C_{18}H_{27}NO_3$ (M^+) 305.1991, found 305.1994.

Partial data for **S1**: 5.30 (br d, 1, *J* = 5), 3.35 (br d, 1, *J* = 13.4, H-8a), 2.28-2.21 (m, 1, H-2), 0.85 (d, 3, *J* = 7.3).

The above reaction was repeated several times with identical results, but in one run, the reaction of oxazolidinone **15** (338.14 mg, 2 mmol) in 6 mL of CH_2Cl_2, Me_2AlCl (2 mL, 1.9 M in hexanes, 3.8 mmol) and diene **7** (272.4 mg, 2 mmol in 3 mL of CH_2Cl_2) for 60 hr afforded 163 mg (27%) of a 20:1 mixture of **16** and the endo isomer **S1**. The lower yield and greater selectively suggests that the endo isomer **S1** was selectively decomposed.

(1α,2β,8aα)-1,2,3,5,6,7,8,8a-Octahydro-1,2,5,5-tetramethyl-1-naphthalenemethanol (17). $LiBH_4$ (70 mg, 3.2 mmol) was added in three portions to a stirred solution of **16** (325.4 mg, 1.065 mmol) in 22 mL of 10:1 THF/MeOH cooled in an ice bath. The reaction was stirred for one hour, the ice bath was removed, and the reaction was stirred an additional hour, at which time the reaction was complete as indicated by TLC (10:1 hexanes/Et_2O). The reaction was quenched with saturated aqueous NH_4Cl solution (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. Flash chromatography of the residue (5:1 hexanes/EtOAc) afforded 194 mg (82%) of a 20:1 mixture of **17** and the endo isomer **S2** as a colorless oil: ^{1}H NMR 5.45 (br d, 1, *J* = 5), 3.51 (dd, 1, *J* = 11, 6), 3.42 (dd, 1, *J* = 11, 6), 2.37 (br d, 1, *J* = 13), 1.88 (ddd, 1, *J* = 18, 5, 5), 1.83-1.73 (m, 2), 1.73-1.62 (m, 1), 1.62-1.50 (m, 2), 1.41 (br d, 1, *J* = 12.8), 1.28-1.14 (m, 2 including OH), 1.07 (s, 3), 1.06-0.96 (m, 1), 1.02 (s, 3), 0.88 (d, 3, *J* = 6.7), 0.52 (s, 3); ^{13}C NMR 145.9, 115.9, 65.5, 40.9, 39.1, 37.8, 36.1, 31.7, 31.1, 29.7, 28.7, 27.5, 22.1, 14.9, 11.4; IR 3371, 2928, 1455, 1381, 1036; HRMS (EI) calcd for $C_{15}H_{26}O$ (M^+) 222.1984, found 222.1979.

(1α,2β,8aα)-1,2,3,5,6,7,8,8a-Octahydro-1,2,5,5-tetramethyl-1-naphthalenecarboxaldehyde (6). Dess-Martin periodinane (291 mg 0.686 mg) was added in one portion to a solution of **17** (138.5 mg, 0.623 mmol) in 6 mL of CH_2Cl_2 at 25 °C. The

solution was stirred for two hours, at which time the reaction was complete as indicated by TLC (10:1 hexanes/Et_2O). Et_2O (6 mL), saturated aqueous Na_2SO_3 solution (3 mL), and saturated aqueous $NaHCO_3$ solution (1.5 mL) were added and the reaction was stirred for five min. The layers were separated and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. Flash chromatography of the residue (hexanes) afforded 129 mg (94%) of **6** as an easily oxidized colorless oil: ^{1}H NMR 9.39 (s, 1), 5.50 (br d, 1, *J* = 5), 2.51 (br d, 1, *J* = 13), 2.03-1.92 (m, 1), 1.92-1.81 (m, 1), 1.81-1.68 (m, 1), 1.62-1.46 (m, 2), 1.46-1.37 (m, 1), 1.37-1.28 (m, 1), 1.28-1.14 (m, 1), 1.09 (s, 3), 1.09-1.01 (m, 1), 1.05 (s, 3), 0.81 (s, 3), 0.79 (d, 3, *J* = 6.1); ^{13}C NMR 207.1, 143.7, 116.4, 52.1, 40.4, 38.0, 36.1, 32.5, 30.3, 29.5, 29.0, 28.5, 21.6, 16.0, 7.3; IR 2960, 2930, 1726, 1461, 1382.

A similar sequence starting with a 9:1 mixture of **16** and **S1** was reduced with $LiBH_4$ and the resulting mixture of alcohols was oxidized with Dess-Martin periodinane to give a comparable yield of a 9:1 mixture of **6** and (1β,2α,8aα)-1,2,3,5,6,7,8,8a-octahydro-1,2,5,5-tetramethyl-1-naphthalenecarboxaldehyde (**9**). The partial spectral data of **9** as determined from the mixture are identical to those previously reported:[6] ^{1}H NMR 9.68 (s, 1), 5.40 (br d, 1, *J* = 5), 2.28-2.01 (m, 3); ^{13}C NMR 209.9, 145.2, 115.0, 50.1, 42.4, 41.8, 36.7, 30.8, 29.4, 28.9, 25.9, 22.6, 14.4, two carbons near 30.3 and 16.0 are obscured by **6**.

(1α,2β,8aα)-1,2,3,5,6,7,8,8a-Octahydro-1,2,5,5-tetramethyl-1-naphthalenyl)-but-3-en-2-one (18). NaOMe (25% in MeOH, 226μL, 1.05 mmol) was added to a stirred solution of **6** (46 mg, 0.209 mmol) in acetone (243μL, 4.18 mmol) at 25 °C. The reaction was stirred for 20 hr and H_2O (4 mL) was added. The reaction was neutralized with conc H_2SO_4 and extracted with hexanes (3 × 10 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. Flash chromatography of the residue (10:1 hexanes/Et_2O) afforded 32.5 mg (60%) of **18** as a colorless oil: ^{1}H NMR 6.62 (d, 1, *J* = 15.9), 6.03 (d, 1, *J* = 15.9), 5.51 (br d, 1, *J* = 5), 2.28 (s, 3), 2.14 (br d, 1, *J* = 14), 1.94 (ddd, 1, *J* = 18, 5, 5), 1.76 (br dd, 1, *J* = 18, 11), 1.62-1.45 (m, 4), 1.40 (br d, 1, *J* = 13), 1.28-1.14 (m, 1), 1.08 (s, 3), 1.02-0.92 (m, 1), 1.01 (s, 3), 0.79 (s, 3), 0.73 (d, 3, *J* = 6.7); ^{13}C NMR 198.5, 158.0, 144.5, 129.3, 116.2, 43.4, 42.7, 40.5, 36.4, 36.0,

30.9, 29.4, 29.0, 28.0, 27.2, 21.7, 16.2, 10.0; IR 2959, 2930, 1676 (sh), 1620, 1455, 1383, 1356, 1254; HRMS (EI) calcd for $C_{18}H_{28}O$ (M^+) 260.2140, found 260.2129.

(1α,2β,8aα)-1,2,3,5,6,7,8,8a-Octahydro-1,2,5,5-tetramethyl-1-naphthalenyl)-butan-2-one (5). A solution of **18** (90 mg, 0.346 mmol) and EtOH (637 mg, 13.8 mmol) in 3 mL of THF was added to a solution of Li (48 mg, 6.91 mmol) in 60 mL of liquid NH_3 at -78 °C. The resulting solution was stirred for 10 min, the reaction was quenched by addition of solid NH_4Cl until the blue solution turned colorless, and the NH_3 was evaporated. The residual material was partitioned between Et_2O (20 mL) and H_2O (10 mL). The two layers were separated and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated to give a 1.5:1 mixture of ketone **5** and the saturated secondary alcohol.

The entire crude mixture of **5** and saturated alcohol was dissolved in 10 mL of acetone and cooled in an ice bath. Jones reagent was added until an orange color persisted. Isopropanol was added until a green color persisted and 10 mL of H_2O was added. The reaction mixture was extracted with Et_2O (3 × 10 mL) and the organic layers were combined, washed with brine, dried ($MgSO_4$), and concentrated. Flash chromatography of the residue (20:1 hexanes/Et_2O) afforded 82 mg (90%) of **5** as a colorless oil: ^{1}H NMR 5.43 (br d, 1, J = 5), 2.44-2.26 (m, 2), 2.17 (s, 3), 2.01 (br d, 1, J = 13), 1.84 (ddd, 1, J = 18, 5, 5), 1.80-1.62 (m, 4), 1.62-1.35 (m, 4), 1.26-1.12 (m, 1), 1.08-1.02 (m, 1), 1.06 (s, 3), 1.00 (s, 3), 0.80 (d, 3, J = 6.7), 0.64 (s, 3); ^{13}C NMR 209.4, 145.7, 116.1, 40.7, 39.9, 37.5, 36.5, 36.0, 33.4, 31.4, 29.91, 29.88, 29.6, 28.9, 27.4, 22.1, 15.8, 14.9; IR 2931, 1717 (sh), 1456, 1382, 1357, 1163; HRMS (ESI) calcd for $C_{18}H_{30}ONa$ (MNa^+) 285.2194, found 285.2197.

(1α,2β,8aα)-α-Ethenyl-1,2,3,5,6,7,8,8a-octahydro-α,1,2,5,5-pentamethyl-1-naphthalenepropanol (Nosyberkol, Isotuberculosinol, Revised Structure of Edaxadiene, 4). Ketone **5** (30 mg, 0.114 mmol) in 300 μL of THF was added dropwise over 10 min to a stirred solution of vinylmagnesium bromide (1.0 M in THF, 160μL, 0.16 mmol) cooled in an ice bath under N_2. The ice bath was removed and the solution was allowed to warm to 25 °C over 30 min

and stirring was continued for an additional 1 hr. The reaction was then quenched by slow addition of saturated aqueous NH_4Cl solution (2 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 3 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. Flash chromatography of the residue (20:1 hexanes/EtOAc) afforded 29.2 mg (88%) of **4** as a colorless oil: ^{1}H NMR ($CDCl_3$) 5.92 (dd, 1, *J* = 17.3, 10.9) 5.43 (s, 1), 5.21 (d, 1, 17.3), 5.07 (d, 1, *J* = 10.9), 2.12 (br d, 1, *J* = 12.8), 1.85-1.65 (m, 3) 1.60-1.35 (m, 7), 1.35-1.15 (m, 2), 1.30 (s, 3), 1.05 (s, 3), 1.05-0.95 (m, 1), 1.00 (s, 3), 0.790 (d, 0.67 × 3, *J* = 6.7), 0.783 (d, 0.33 × 3, *J* = 6.7), 0.61 (s, 3); (C_6D_6); 5.78 (dd, 1, *J* =17.3, 10.4), 5.55 (s, 1), 5.18 (d, 1, *J* =17.3), 4.96 (d, 1, *J* =10.4), 2.25 (br d, 1, *J* = 12), 1.85-1.75 (m, 3), 1.60-1.36 (m, 7), 1.35-1.22 (m, 2), 1.17-1.02 (m, 1), 1.14 (s, 3), 1.12 (s, 3), 1.09 (s, 3), 0.839 (d, 0.67 × 3, *J* = 7.3), 0.813 (d, 0.33 × 3, *J* = 6.7), 0.71 (s, 3); ^{13}C NMR ($CDCl_3$) (major, minor) (145.98, 146.00), (145.08, 145.03), (116.18, 116.13), (111.80, 111.83), (73.47, 73.49), 40.9, 39.6, 36.6, 36.0, (35.09, 35.07), 33.3, 31.6, 30.1, 29.8, 29.1, 27.6, 27.3, 22.2, (16.17, 16.19), (15.00, 14.98); (C_6D_6) (major, minor); (146.16, 146.21), 145.7, (116.88, 116.81), 111.5, 73.0, 41.3, 40.2, 37.0, 36.3, (35.48, 35.46), (33.70, 33.68), 32.1, 30.4, 30.1, 29.3, (28.31, 28.30), (27.68, 27.66), (22.62, 22.60), 16.5, (15.30, 15.33); IR 3404, 2931, 1457, 1381, 997, 919: HRMS (EI) calcd for $C_{20}H_{32}$ (M-H_2O^+) 272.2504, found 272.2494. The ^{1}H and ^{13}C NMR data in $CDCl_3$ are identical to those previously reported for nosyberkol (see Table S1).[4] The ^{1}H and ^{13}C NMR data in C_6D_6 are identical to those previously reported for edaxadiene (see Table S2).[1a]

Ethyl (*E*)- and (*Z*)-3-Methyl-5-(1α,2β,8aα)-(1,2,3,5,6,7,8,8a-octahydro-1,2,5,5-tetramethyl-1-naphthalenyl)-2-pentenoate (19 and S3). Triethyl phosphonoacetate (43.56 mg, 0.194 mmol) in 0.5 mL of THF was added dropwise to a suspension of NaH (60% in oil, 7.6 mg, 0.191 mmol) in 0.5 mL of THF in a resealable tube cooled in an ice bath under N_2. The reaction was stirred for 30 min and ketone **5** (10 mg, 0.038 mmol) in 1 mL of THF was added over five minutes. The ice bath was removed and the reaction was allowed to warm to 25 °C over 15 min. The reaction vessel was sealed under N_2 and placed directly in a 95 °C oil bath. The reaction was heated at 95 °C for 12 hr and then cooled to 25 °C. Saturated aqueous NH_4Cl solution (2

mL) was added and the reaction mixture was extracted with EtOAc (3 × 3 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. Flash chromatography of the residue (toluene) afforded 1.5 mg, (12%) of **S3** followed by10.6 mg (84%) of **19**, both as colorless oils.

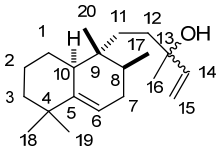
Data for **19**: ^{1}H NMR 5.68 (s, 1), 5.44 (br d, 1, *J* = 5), 4.15 (q, 2, *J* = 7), 2.18 (s, 3), 2.14 (br d, 1, *J* = 13), 2.10-1.97 (m, 2), 1.85 (ddd, 1, *J* = 18, 5, 5), 1.81-1.68 (m, 2), 1.64-1.44 (m, 4), 1.44-1.32 (m, 2), 1.28 (t, 3, *J* = 7), 1.25-1.15 (m, 1), 1.10-1.00 (m, 1), 1.06 (s, 3), 1.00 (s, 3), 0.82 (d, 3, *J* = 6.7), 0.63 (s, 3); ^{13}C NMR 166.9, 161.3, 145.9, 116.2, 115.1, 59.4, 40.8, 39.8, 37.0, 36.1, 34.54, 34.45, 33.3, 31.5, 29.7, 29.0, 27.4, 22.2, 19.1, 16.1, 15.0, 14.3; IR 2932, 1717 (sh), 1648, 1456, 1381, 1224, 1146, 1052. The ^{1}H NMR and IR spectral data are identical to those previously reported.[18]

Data for **S3**: ^{1}H NMR 5.63 (s, 1), 5.44 (br d, 1, *J* = 5), 4.14 (q, 2, *J* = 7), 2.59 (ddd, 1, *J* = 12, 5, 5), 2.54 (ddd, 1, *J* = 12, 5, 5), 2.27 (br d, 1, *J* = 13), 1.89 (s, 3), 1.88-1.70 (m, 3), 1.64-1.34 (m, 6), 1.26 (t, 3, *J* = 7), 1.27-1.15 (m, 1), 1.08-0.98 (m, 1), 1.06 (s, 3), 1.02 (s, 3), 0.89 (d, 3, *J* = 6.7), 0.64 (s, 3); ^{13}C NMR 166.2, 161.1, 146.1, 116.0, 115.8, 59.4, 41.0, 39.7, 37.3, 36.1, 34.9, 33.3, 31.6, 29.8, 29.0, 27.6, 27.0, 25.2, 22.2, 16.1, 15.1, 14.4; IR 2931, 1716 (sh), 1647, 1448, 1378, 1249, 1192, 1152, 1056.

(*E*)-3-Methyl-5-(1α,2β,8aα)-(1,2,3,5,6,7,8,8a-octahydro-1,2,5,5-tetramethyl-1-naphthalenyl)-2-penten-1-ol (Tuberculosinol, 2). DIBAL-H (1.0 M in CH_2Cl_2, 65μL, 0.065 mmol) was added dropwise over 5 min to a stirred solution of **19** (7 mg, 0.021 mmol) in 0.5 ml of CH_2Cl_2 at -78 °C under N_2. The solution was stirred for 4 hr, at which time the reaction was complete as indicated by TLC (10:1 hexanes/EtOAc). Acetic acid (200 μL, 5 M in CH_2Cl_2) was added and the reaction was allowed to warm to 25 °C. 10% Aqueous tartaric acid (400 μL) and 400 μL of H_2O were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 2 mL) and the combined organic layers were washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_3), and concentrated. Flash chromatography of the residue (10:1 hexanes/EtOAc) afforded 5.6 mg, (92%) of **2**: ^{1}H NMR ($CDCl_3$) 5.47-5.39 (m, 2), 4.15 (s, 2),

2.17 (br d, 1, *J* = 13), 2.00-1.66 (m, 5), 1.70 (s, 3), 1.64-1.29 (m, 6), 1.27-1.14 (m, 1), 1.09-1.03 (m, 1), 1.06 (s, 3), 1.01 (s, 3), 0.82 (d, 3, *J* = 6.7), 0.62 (s, 3); (C_6D_6); 5.55 (s, 1), 5.43 (br t, 1, *J* = 6.5), 3.99 (d, 2, *J* = 6.5), 2.26 (br d, 1, *J* = 12), 1.95 (ddd, 1, *J* = 13.2, 12.8, 4), 1.87 (ddd, 1, *J* = 13.2, 12.8, 4), 1.85-1.80 (m, 2), 1.78-1.70 (m, 1), 1.60-1.45 (m, 4), 1.51 (s, 3), 1.45-1.23 (m, 3), 1.15 (s, 3), 1.15-1.05 (m, 1), 1.10 (s, 3), 0.82 (d, 3, *J* = 6.7), 0.70 (s, 3); ^{13}C NMR ($CDCl_3$) 146.0, 141.0, 122.7, 116.1, 59.5, 40.9, 39.7, 36.9, 36.1, 34.9, 33.3, 32.7, 31.6, 29.8, 29.0, 27.4, 22.2, 16.5, 16.2, 15.1; (C_6D_6); 146.2, 139.2, 124.5, 116.8, 59.5, 41.3, 40.3, 37.3, 36.3, 35.3, 33.7, 33.1, 32.0, 30.1, 29.2, 27.8, 22.6, 16.50, 16.47, 15.3; IR 3346, 2930, 1455, 1381, 1000. The ^{1}H and ^{13}C NMR data in C_6D_6 are identical to those previously reported for tuberculosinol (See Table S3).[3a]

Table S1. Comparison of the Spectral Data of Natural and Synthetic Nosyberkol (Isotuberculosinol, Revised Structure of Edaxadiene, **4**) in $CDCl_3$

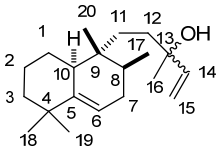


nosyberkol (isotuberculosinol, revised structure of edaxadiene, **4**)

	Natural **4**[a]		Synthetic **4** as 2:1 mixture of diastereomers (major, minor)[b]	
Atom #	^{13}C	^{1}H	^{13}C	^{1}H
1	27.6	1.68	27.3[c]	1.85-1.65
1		1.03		1.05-0.95
2	22.2	1.56	22.2	1.60-1.35
2		1.50		1.60-1.35
3	40.9	1.40	40.9	1.60-1.35
3		1.20		1.35-1.15
4	36.6		36.6	
5	146.0		(145.98, 146.00)	
6	116.2	5.43	(116.18, 116.13)	5.43
7	31.6	1.82	31.6	1.85-1.65
7		1.70		1.85-1.65
8	33.3	1.47	33.3	1.60-1.35
9	36.0		36.0	
10	39.7	2.11 (br d, 13.7)	39.6	2.12 (br d, 12.8)
11	30.6	1.35	30.1	1.60-1.35
11		1.28		1.35-1.15
12	35.1	1.45	(35.09, 35.07)	1.60-1.35
12		1.45		1.60-1.35
13	73.5		(73.47, 73.49)	
14	145.1	5.92 (dd, 17.3, 10.7)	(145.08, 145.03)	5.92 (dd, 17.3, 10.9)
15	111.8	5.20 (d, 17.3)	(111.80, 111.83)	5.21 (d, 17.3)
15		5.07 (d, 10.7)		5.07 (d, 10.9)
16	27.7	1.30 (s)	27.6[c]	1.30
17	14.9	0.79 (d, 6.7)	(15.00, 14.98)	0.790 (d, 6.7), 0.783 (d, 6.7)
18	29.7	1.06 (s)	29.8	1.05
19	29.0	1.00 (s)	29.1	1.00
20	16.2	0.62 (s)	(16.17, 16.19)	0.61

a) ^{1}H and ^{13}C NMR assignments from reference 4. b) Referenced to $CHCl_3$ at δ 7.26 and the center peak of $CDCl_3$ at δ 77.0. c) Assignments may be switched.

Table S2. Comparison of the Spectral Data of Natural and Synthetic Nosyberkol (Isotuberculosinol, Revised Structure of Edaxadiene, **4**) in C_6D_6

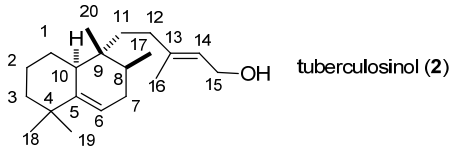


nosyberkol (isotuberculosinol, revised structure of edaxadiene, **4**)

	Natural **4**[a]		Synthetic **4** as 2:1 mixture of diastereomers (major, minor)[c]	
Atom #	^{13}C	^{1}H	^{13}C	^{1}H
1	27.53	1.894	(27.68, 27.66)	1.85-1.75
1		1.164		1.17-1.02
2	22.48	1.651	(22.62, 22.60)	1.60-1.36
2		0.957		1.35-1.22
3	41.15	1.481	41.3	1.60-1.36
3		1.359		1.35-1.22
4	36.13		37.0[d]	
5	145.80		(146.16, 146.21)	
6	116.69	5.643	(116.88, 116.81)	5.55
7	31.84	1.920	32.1	1.85-1.75
7		1.920		1.85-1.75
8	33.53	1.580	(33.70, 33.68)	1.60-1.36
9	36.14		36.3[d]	
10	40.07	2.346 (br d[b], 12.4)	40.2	2.25 (br d, 12)
11	30.24	1.561	30.4	1.60-1.36
11		1.453		1.60-1.36
12	35.35	1.549	(35.48, 35.46)	1.60-1.36
12		1.473		1.60-1.36
13	72.90		73.0	
14	145.60	5.871 (dd, 17.3, 10.8))	145.7	5.78 (dd, 17.3, 10.4)
15	111.49	5.273 (d. 17.7)	111.5	5.18 (d, 17.3)
15		5.051 (d, 10.6)		4.96 (d, 10.4)
16	28.22[b]	1.211 (s)	(28.31, 28.30)	1.12
17	15.20	0.909 (d, 7.1)	(15.30, 15.33)	0.839 (d, 7.3), 0.813 (d, 6.7)
18	29.97	1.239 (s)	30.1	1.14
19	29.22	1.186 (s)	29.3	1.09
20	16.42	0.806 (s)	16.5	0.71

[a] ^{1}H and ^{13}C NMR assignments from reference 1a. ^{1}H NMR peaks are referenced to the residual peak of C_6D_5H at 7.254. [b] Corrected from typographical errors in reference 1a. [c] Referenced to the residual peak of C_6D_5H at δ 7.16 and the center peak of C_6D_6 at 128.06. The ^{1}H NMR data correspond well except for a difference of about 0.09 due to a difference in referencing. [d] Assignments may be switched.

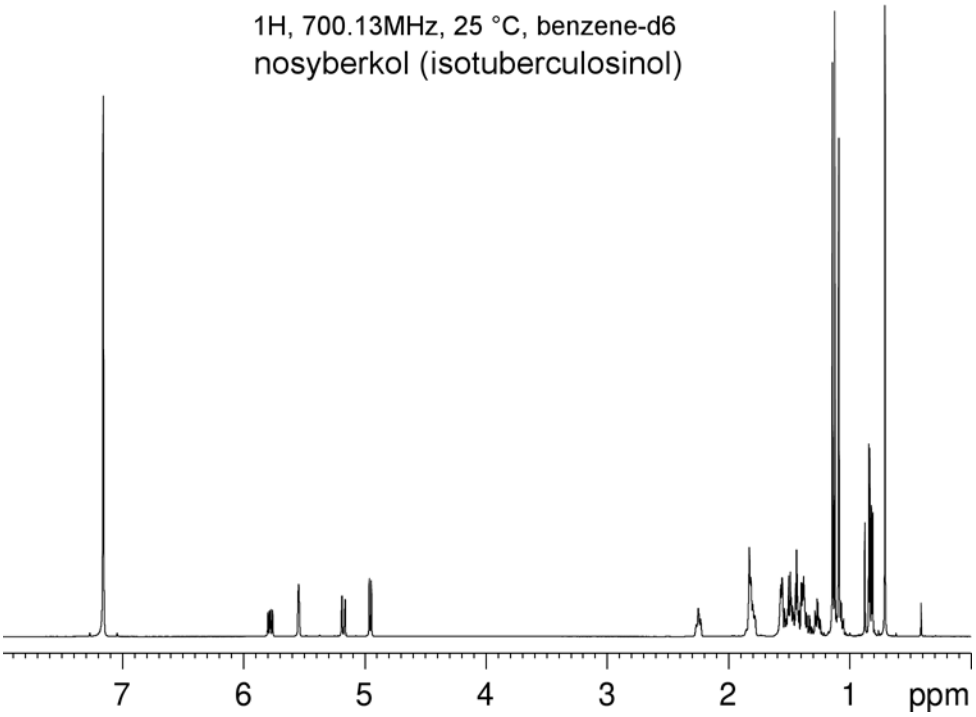
Table S3. Comparison of the Spectral Data of Natural and Synthetic Tuberculosinol (**2**) in C_6D_6



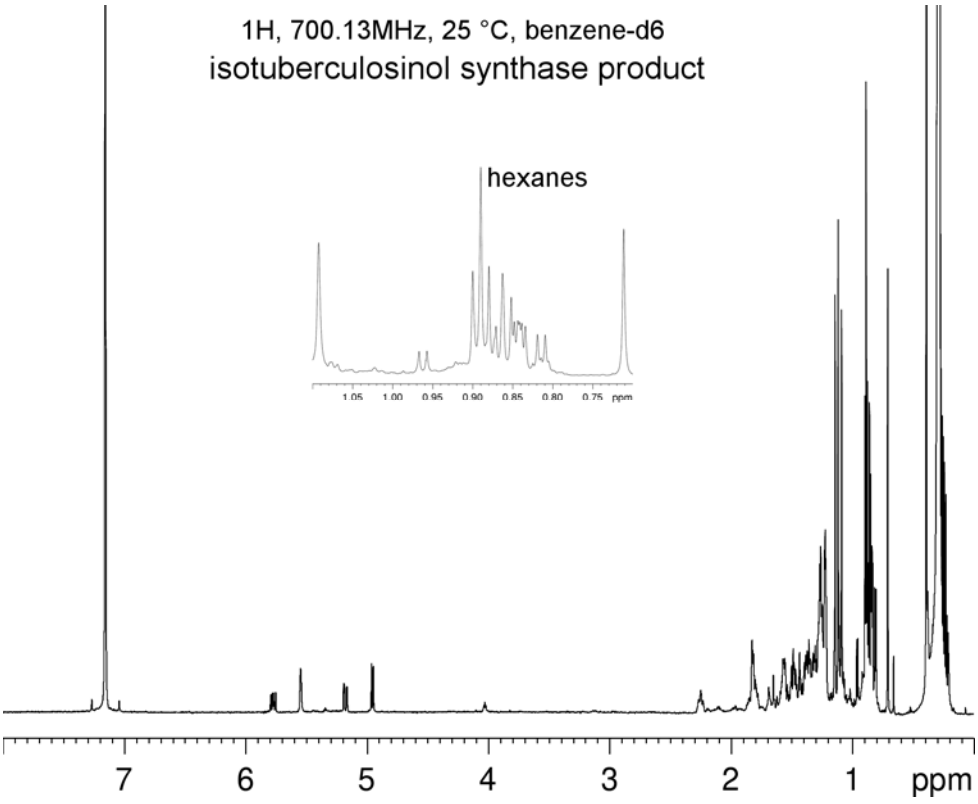
	Natural **4**[a]		Synthetic 4[b]	
Atom #	^{13}C	^{1}H	^{13}C	^{1}H
1	27.22	1.86	27.8	1.78-1.70
1		1.21		1.15-1.05
2	22.60	1.67	22.6	1.60-1.45
2		1.67		1.60-1.45
3	41.25	1.52	41.3	1.45-1.23
3		1.38		1.45-1.23
4	36.28		36.3	
5	146.2		146.2	
6	116.73	5.67	116.8	5.55
7	31.97	1.94	32.0	1.85-1.80
7		1.94		1.85-1.80
8	33.70	1.64	33.7	1.60-1.45
9	37.25		37.3	
10	40.31	2.37 (br d, 11.8)	40.3	2.26 (br d, 12)
11	35.35	1.66	35.3	1.60-1.45
11		1.50		1.45-1.23
12	33.05	2.06 (ddd, 13.2, 12.8, 4)	33.1	1.95 (ddd, 13.2, 12.8, 4)
12		1.99 (ddd, 13.2, 12.8, 4)		1.87 (ddd, 13.2, 12.8, 4)
13	139.2		139.2	
14	124.5	5.54 (br t)	124.5	5.43 (br t, 6.5)
15	59.41	4.10 (d, 6.5)	59.5	3.99 (d, 6.5)
16	16.39	1.63 (s)	16.47	1.51
17	15.28	0.92 (d, 6.8)	15.3	0.82 (d, 6.7)
18	30.04	1.27 (s)	30.1	1.15
19	29.15	1.22 (s)	29.2	1.10
20	16.43	0.81 (s)	16.50	0.70 (s)

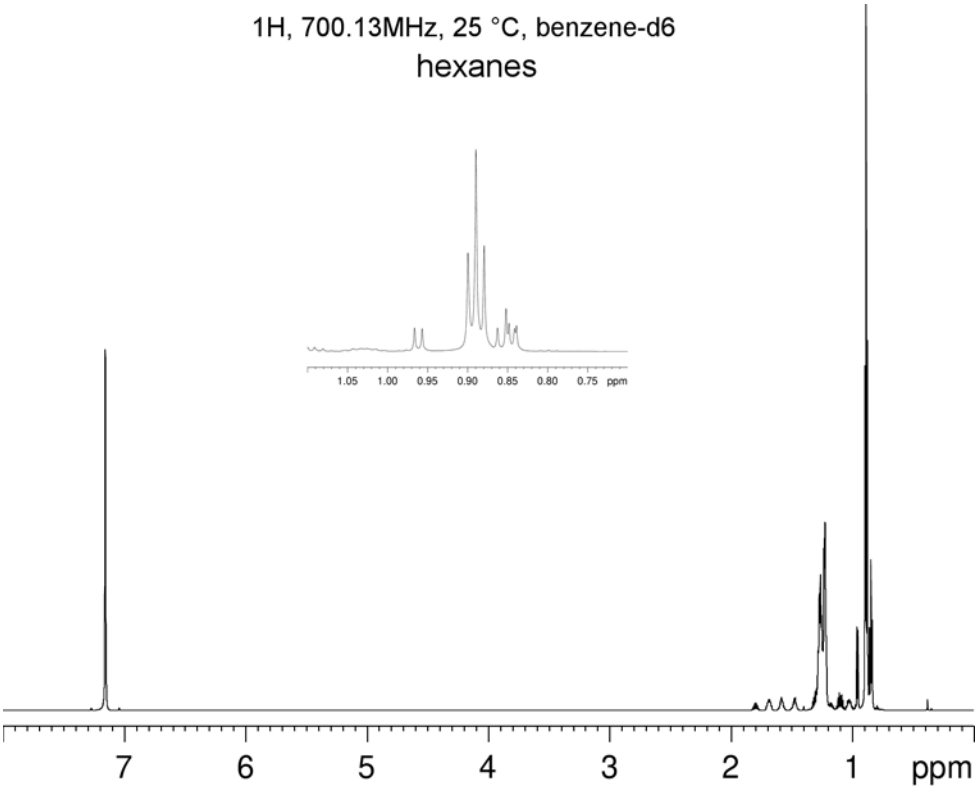
[a] ^{1}H and ^{13}C NMR assignments from reference 3a. [b] Referenced to the residual peak of C_6D_5H at δ 7.16 and the center peak of C_6D_6 at 128.06. The ^{1}H NMR data are identical except for a difference about 0.11 due to a difference in referencing.

Comparison of ^{1}H NMR Spectra of Synthetic and Natural Nosyberkol (Isotuberculosinol, Revised Structure of Edaxadiene, 4) in C_6D_6 at 700 MHz.

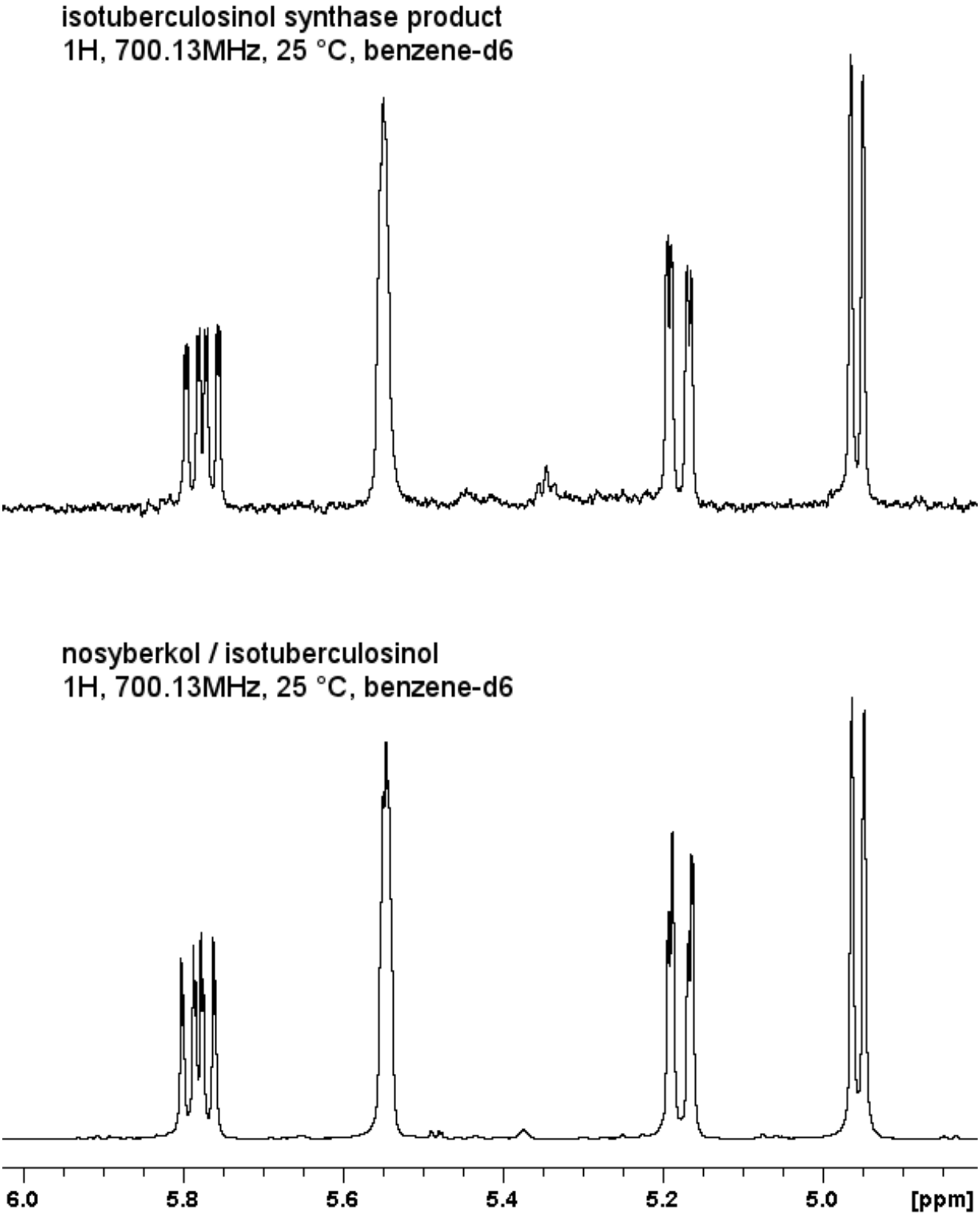


The spectrum above is pure synthetic material. The spectra on the following page shows the spectrum of natural material containing hexanes (reference spectrum provided) and silicone grease at about δ 0.3.

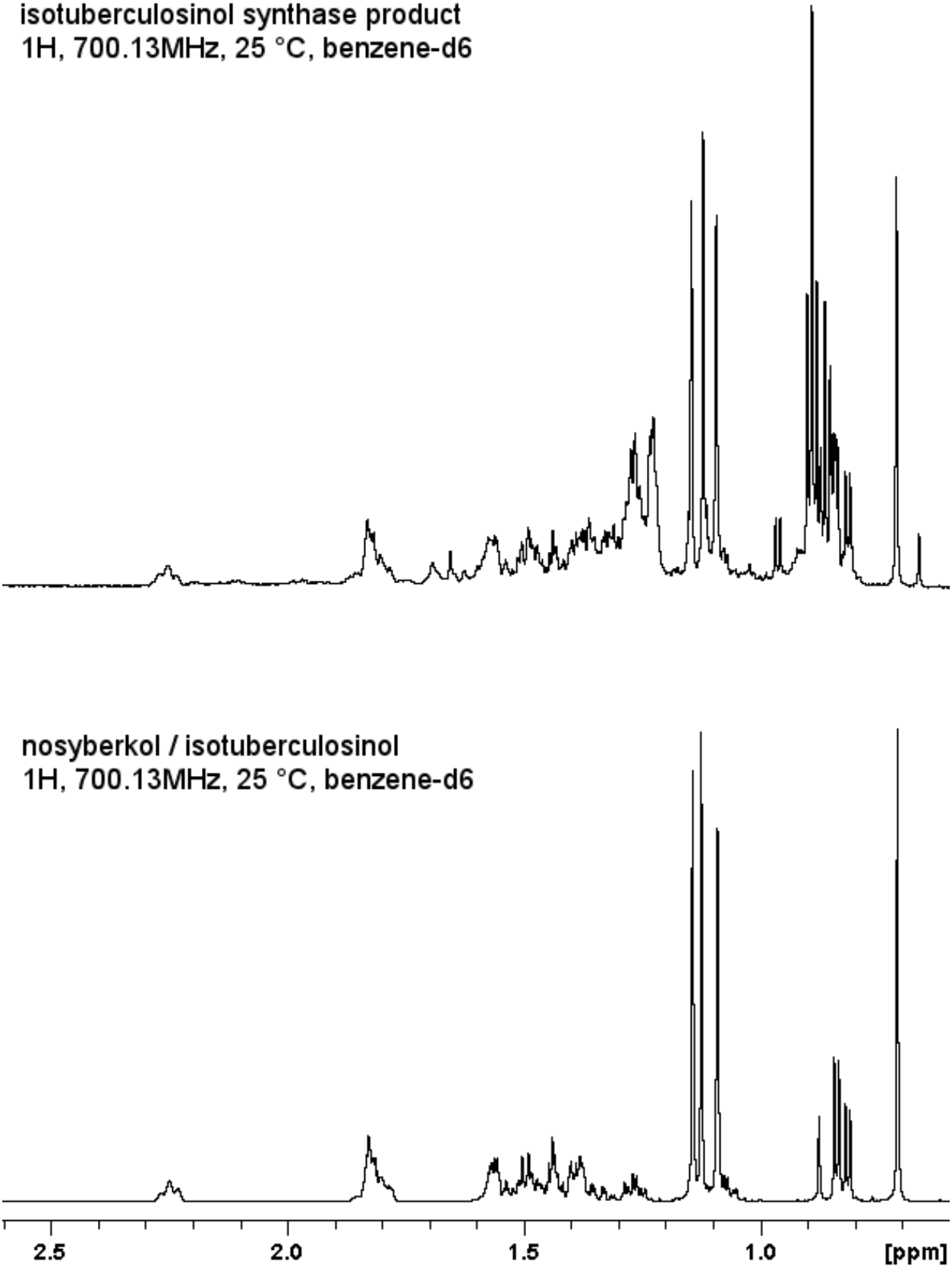

1H, 700.13MHz, 25 °C, benzene-d6
isotuberculosinol synthase product
hexanes
1.05 1.00 0.95 0.90 0.85 0.80 0.75 ppm
7 6 5 4 3 2 1 ppm


1H, 700.13MHz, 25 °C, benzene-d6
hexanes
1.05 1.00 0.95 0.90 0.85 0.80 0.75 ppm
7 6 5 4 3 2 1 ppm

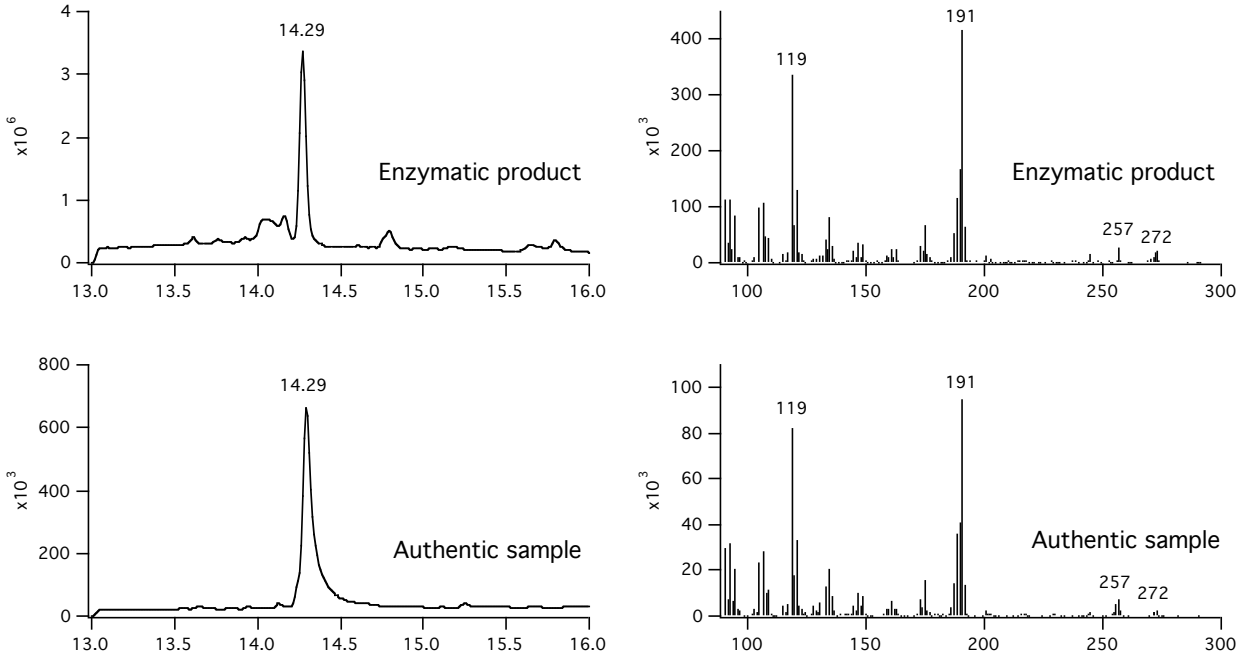
Comparison of Low Field Region of ^{1}H NMR Spectra of Synthetic and Natural Nosyberkol (Isotuberculosinol, Revised Structure of Edaxadiene, 4) in C_6D_6 at 700 MHz.



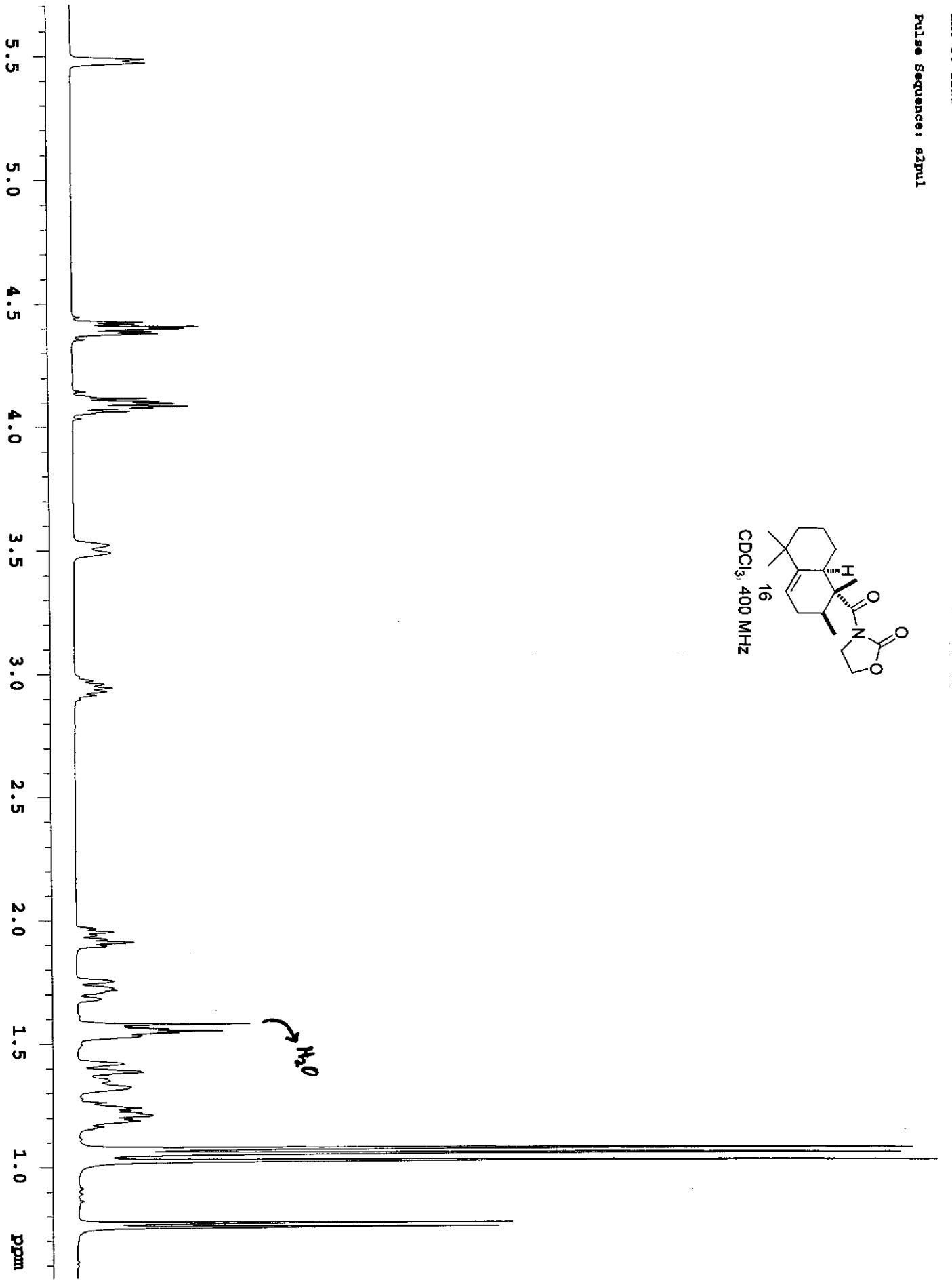
Comparison of High Field Region of ^{1}H NMR Spectra of Synthetic and Natural Nosyberkol (Isotuberculosinol, Revised Structure of Edaxadiene, 4) in C_6D_6 at 700 Hz.



GC-MS comparison



Synthetic **4**


NM8-36-1Lia
Pulse Sequence: s2pul
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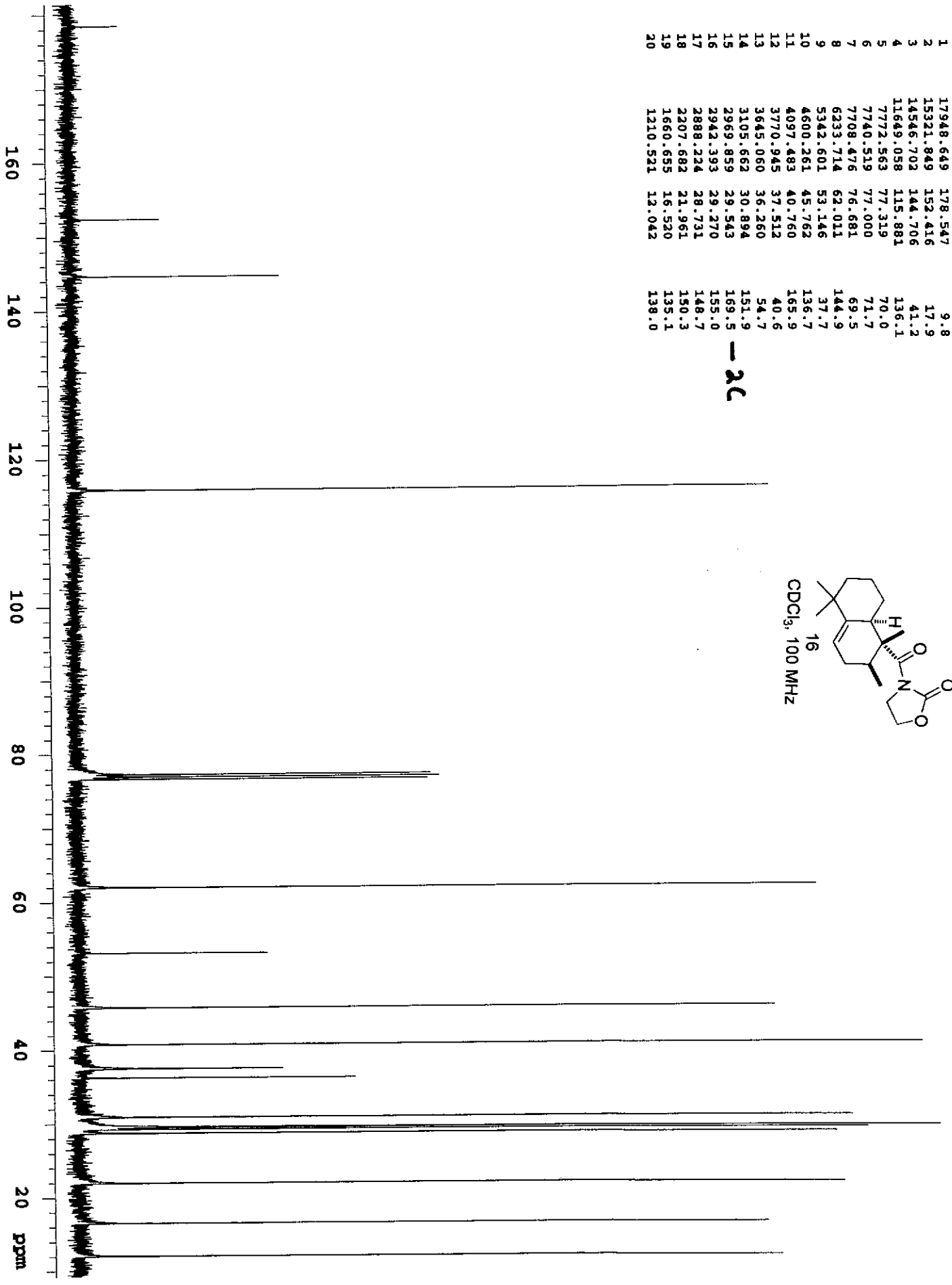
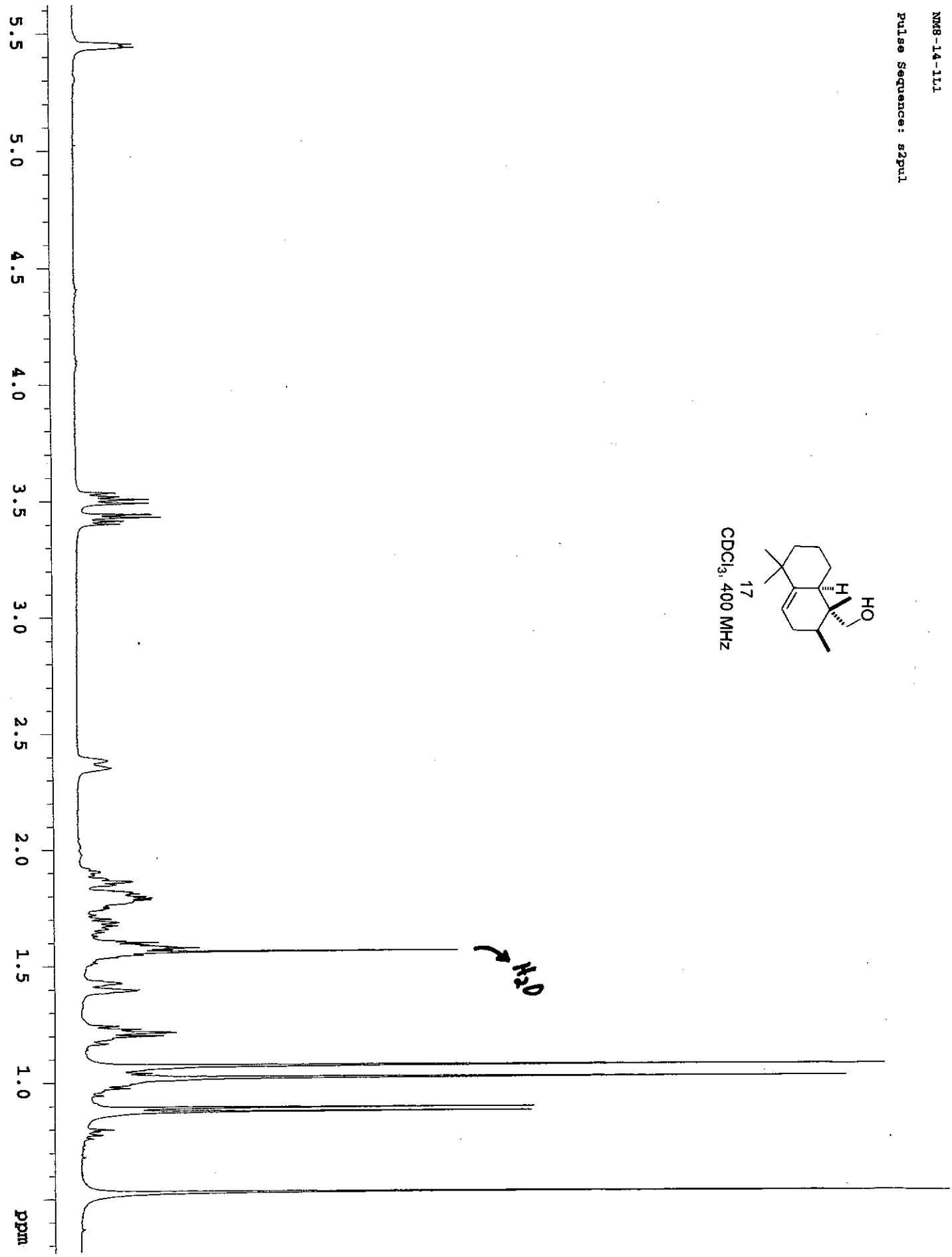
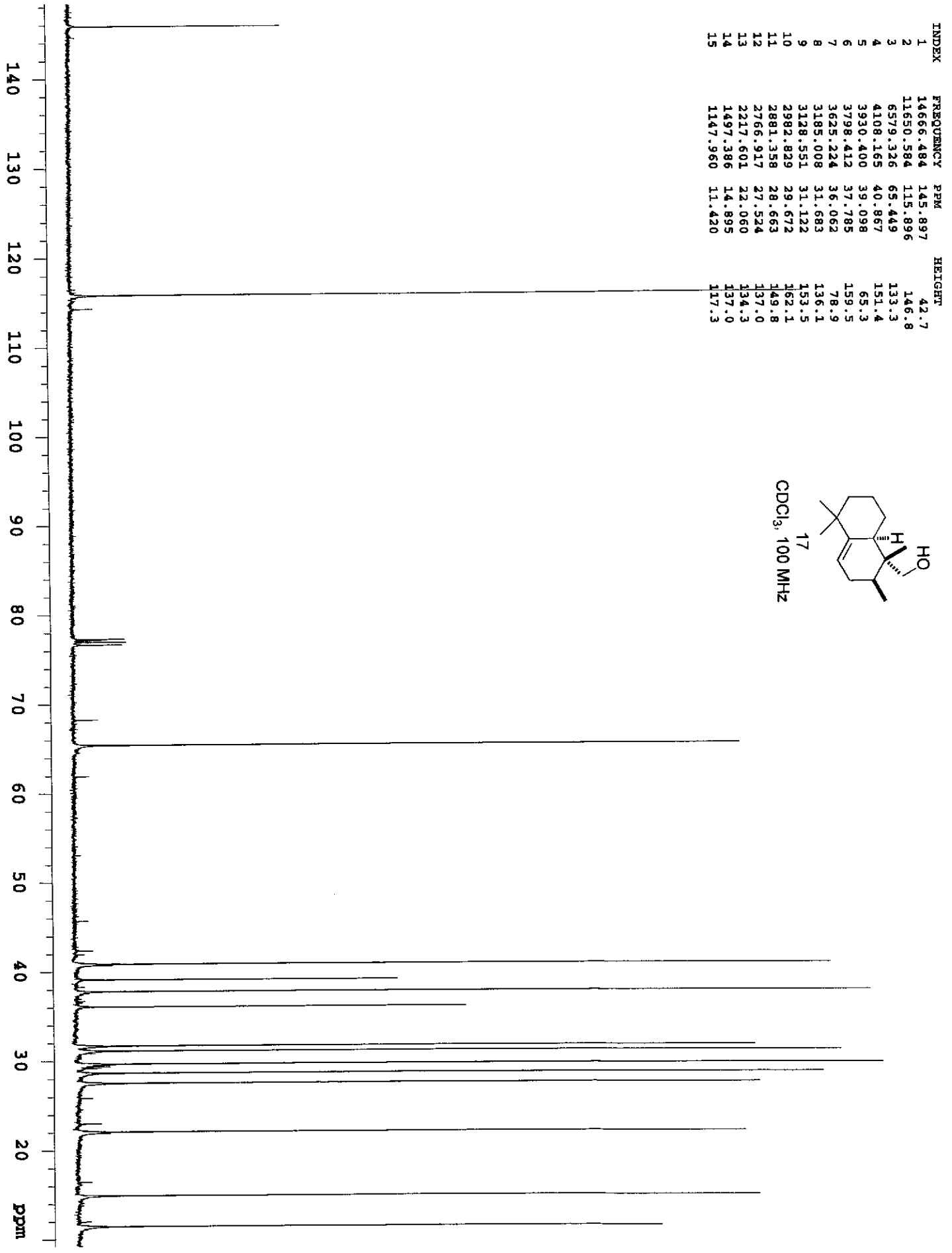
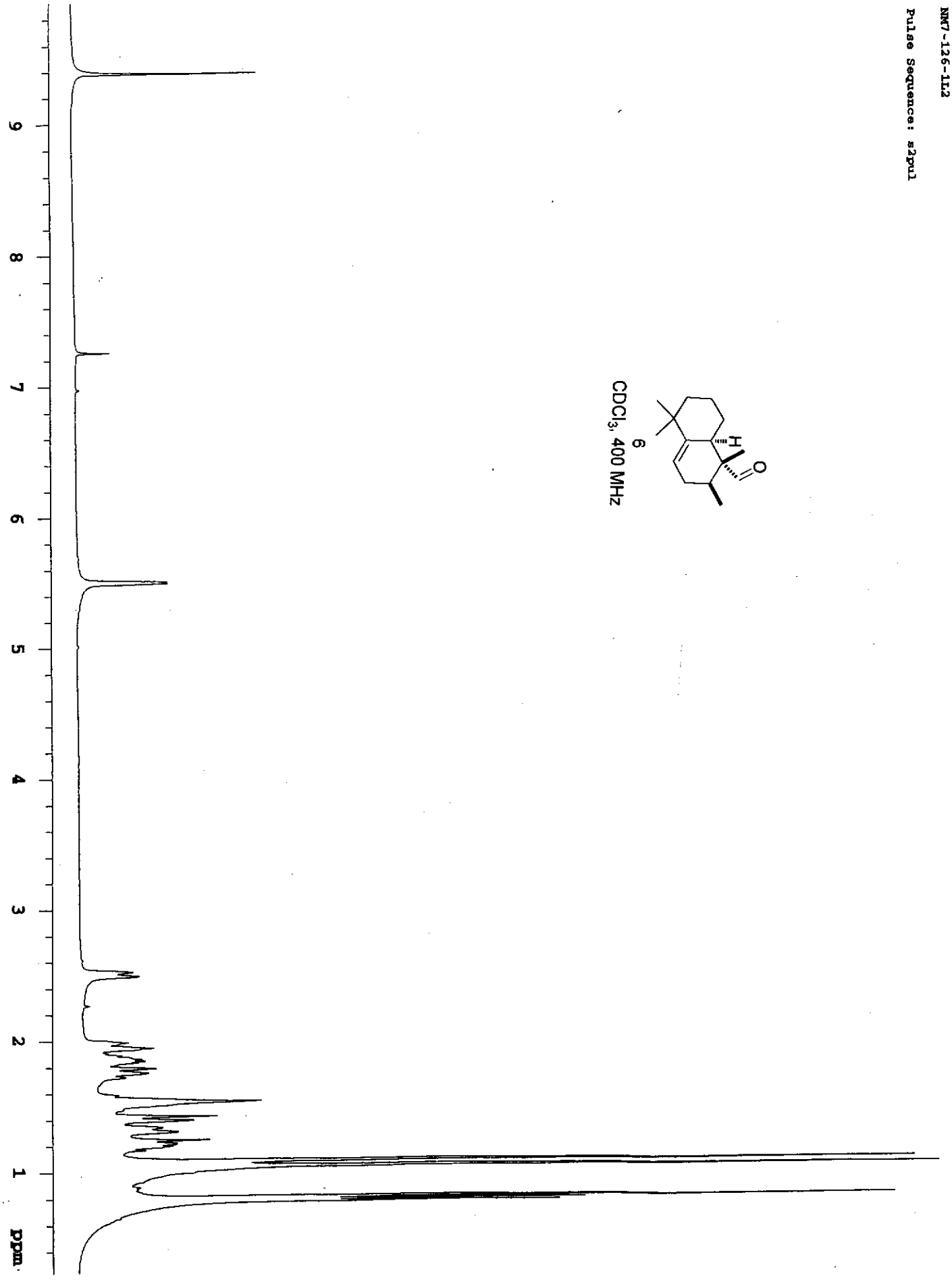
CDCl3, 400 MHz
H2O
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

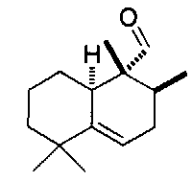

INDEX FREQUENCY PPM HEIGHT
1 17948.649 178.547 9.8
2 15321.849 152.416 17.9
3 14546.702 144.706 41.2
4 11649.058 115.881 136.1
5 7772.563 77.319 70.0
6 7740.519 77.000 71.7
7 7708.476 76.681 69.5
8 6233.714 62.011 144.9
9 5342.601 53.146 37.7
10 4600.261 45.762 136.7
11 4097.483 40.760 165.9
12 3770.945 37.512 40.6
13 3645.060 36.260 54.7
14 3105.662 30.894 151.9
15 2969.859 29.543 169.5
16 2942.393 29.270 155.0
17 2888.224 28.731 148.7
18 2207.682 21.961 150.3
19 1660.655 16.520 135.1
20 1210.521 12.042 138.0
— 2C
CDCl3, 100 MHz
16
160
140
120
100
80
60
40
20
ppm


NMS-14-1Ll
Pulse Sequence: s2pul
HO
H
17
CDCl3, 400 MHz
H2O
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm


INDEX FREQUENCY PPM HEIGHT
1 14666.484 145.897 42.7
2 11650.584 115.896 146.8
3 6579.326 65.449 133.3
4 4108.165 40.867 151.4
5 3930.400 39.098 65.3
6 3798.412 37.785 159.5
7 3625.224 36.062 78.9
8 3185.008 31.683 136.1
9 3128.551 31.122 153.5
10 2982.829 29.672 162.1
11 2881.358 28.663 149.8
12 2766.917 27.524 137.0
13 2217.601 22.060 134.3
14 1497.386 14.895 137.0
15 1147.960 11.420 117.3
H
HO
17
CDCl3, 100 MHz
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

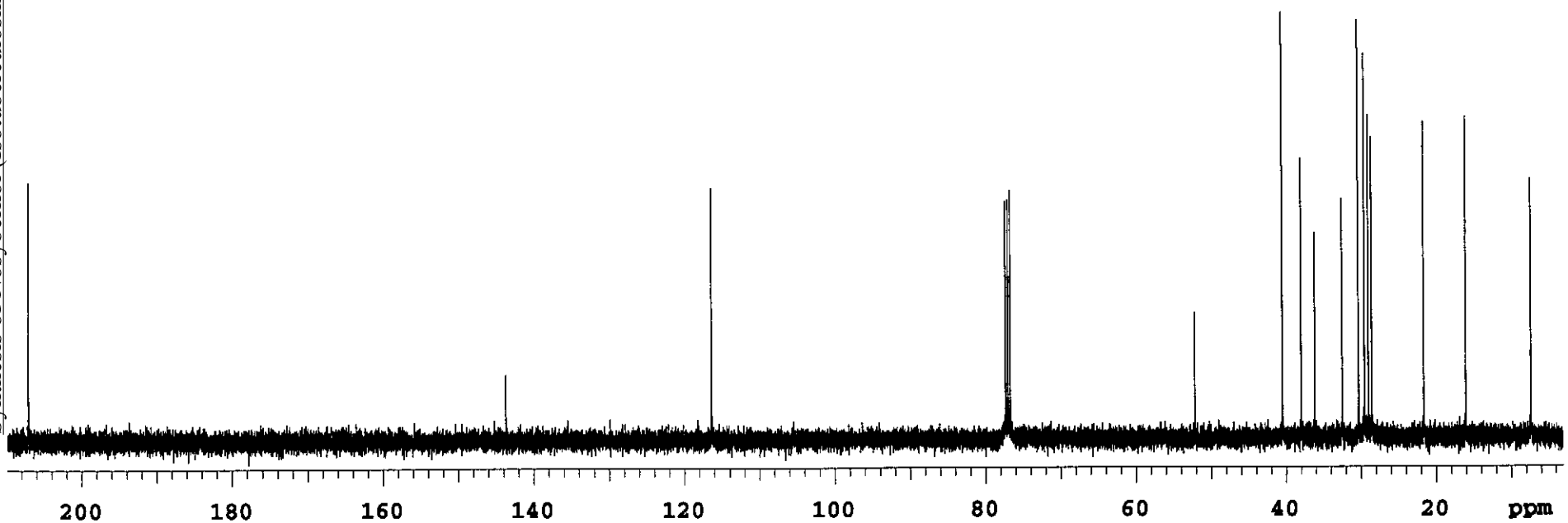

NM7-126-1L2
Pulse Sequence: s2pul
6
CDCl3, 400 MHz
H
O
9
8
7
6
5
4
3
2
1
ppm

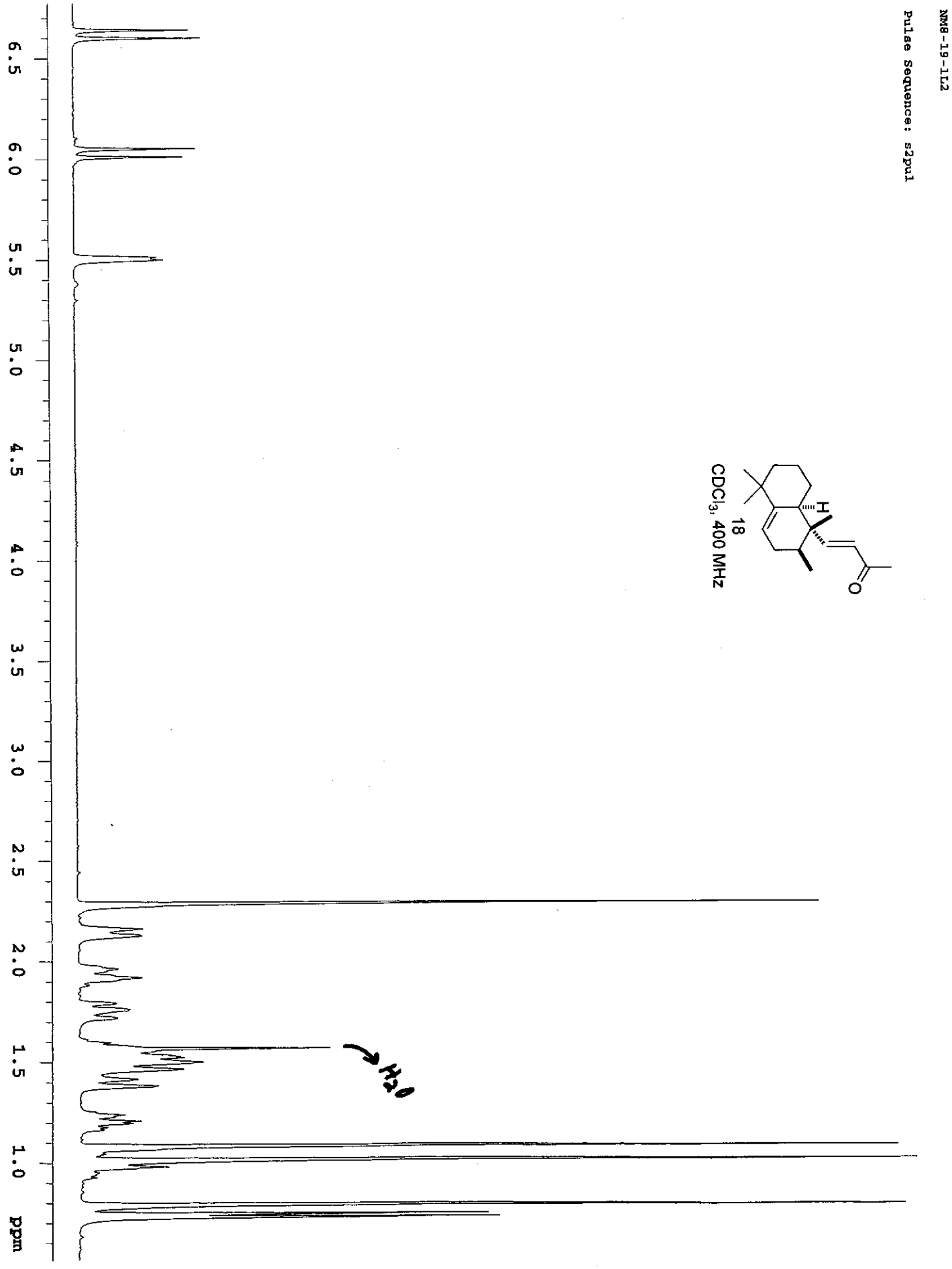
INDEX	FREQUENCY	PPM	HEIGHT
1	20823.041	207.140	42.0
2	14450.014	143.744	10.8
3	11702.585	116.413	41.0
4	7772.564	77.319	38.7
5	7740.519	77.000	39.0
6	7708.475	76.681	40.4
7	5241.053	52.136	20.7
8	4065.328	40.440	69.2
9	3815.076	37.951	45.5
10	3631.965	36.130	33.7
11	3264.217	32.471	39.0
12	3044.484	30.285	68.0
13	2965.898	29.504	62.5
14	2912.491	28.972	52.5
15	2867.476	28.525	49.0
16	2172.417	21.610	51.4
17	1608.588	16.002	52.3
18	734.995	7.311	42.2

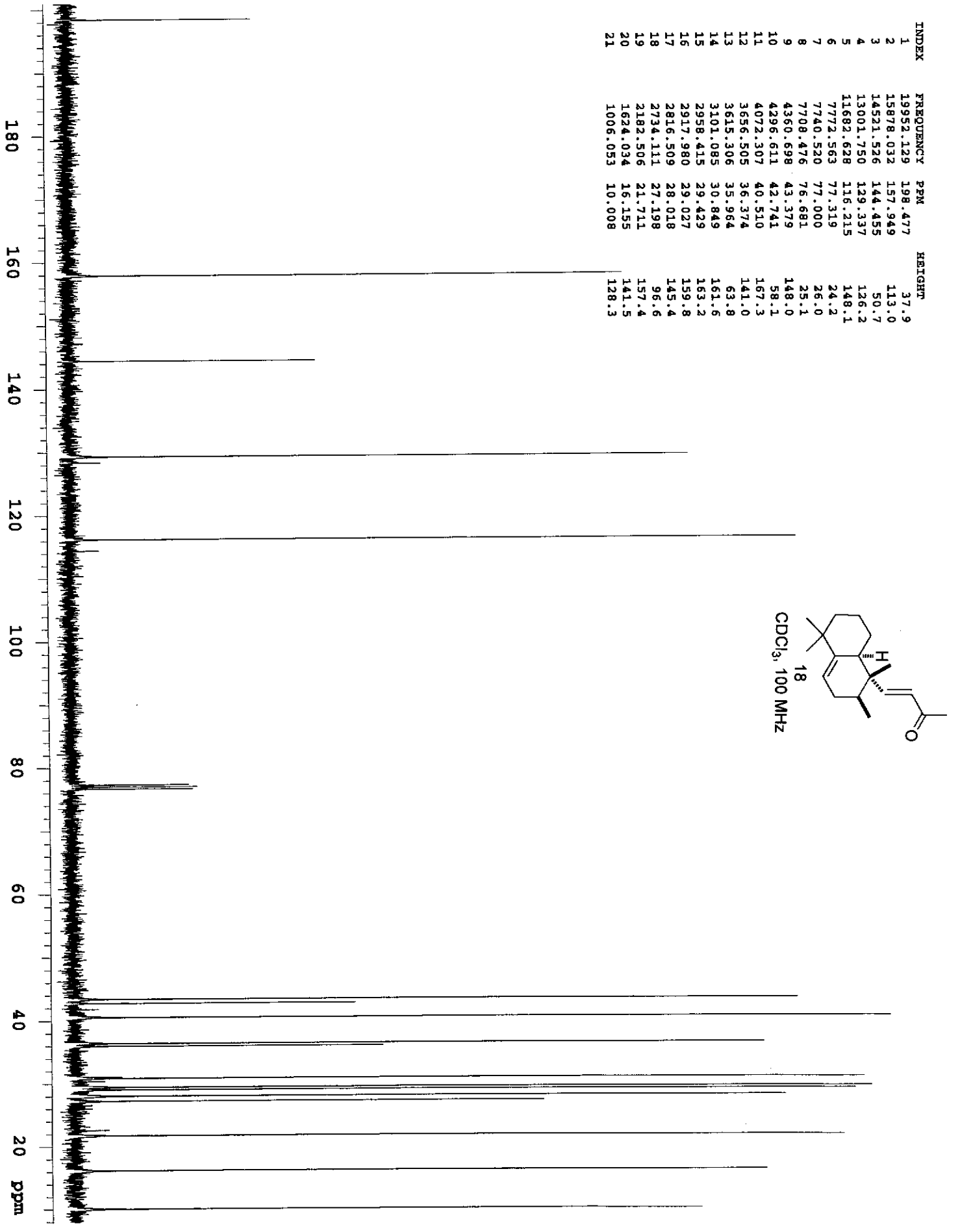


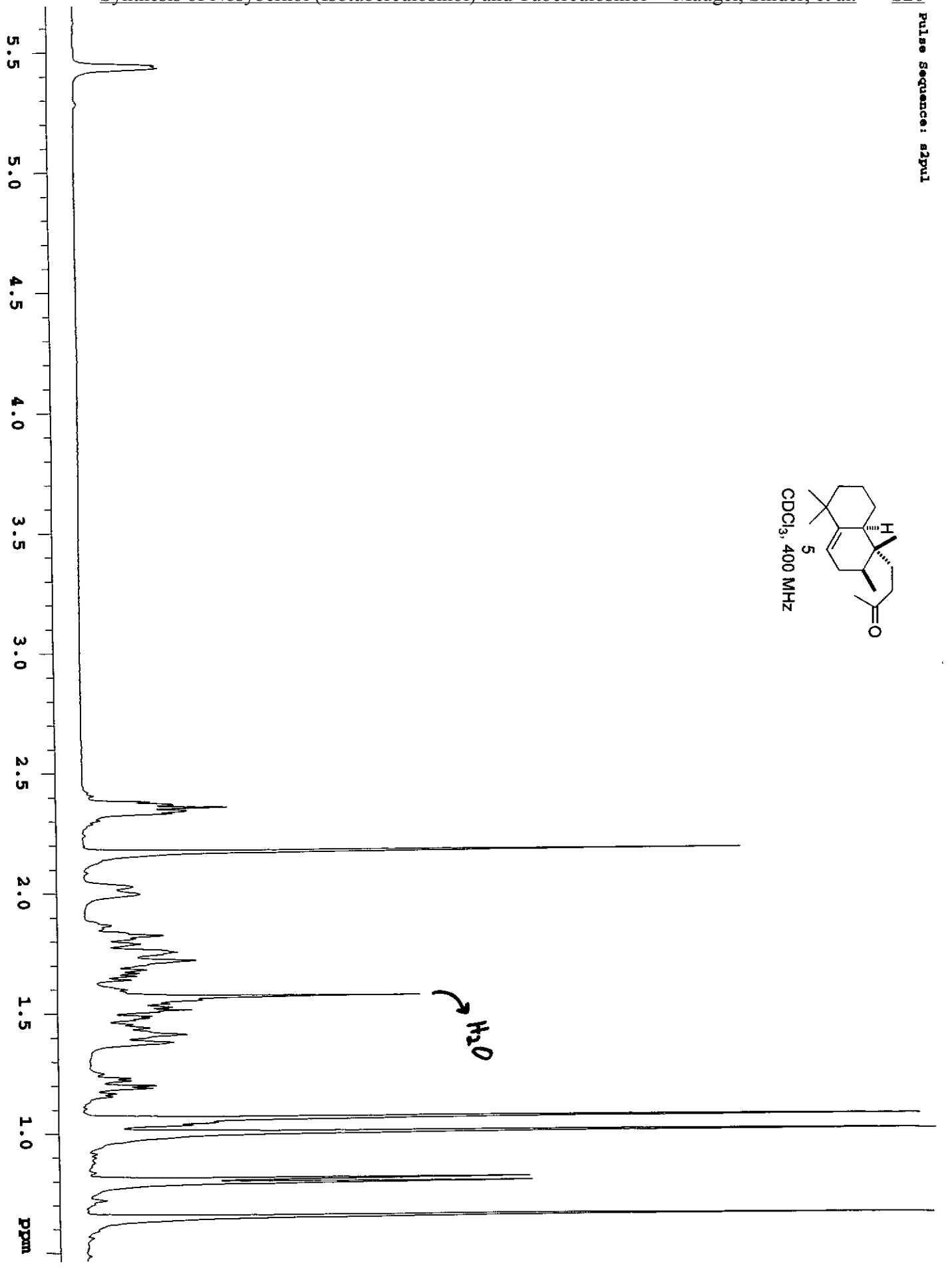
6

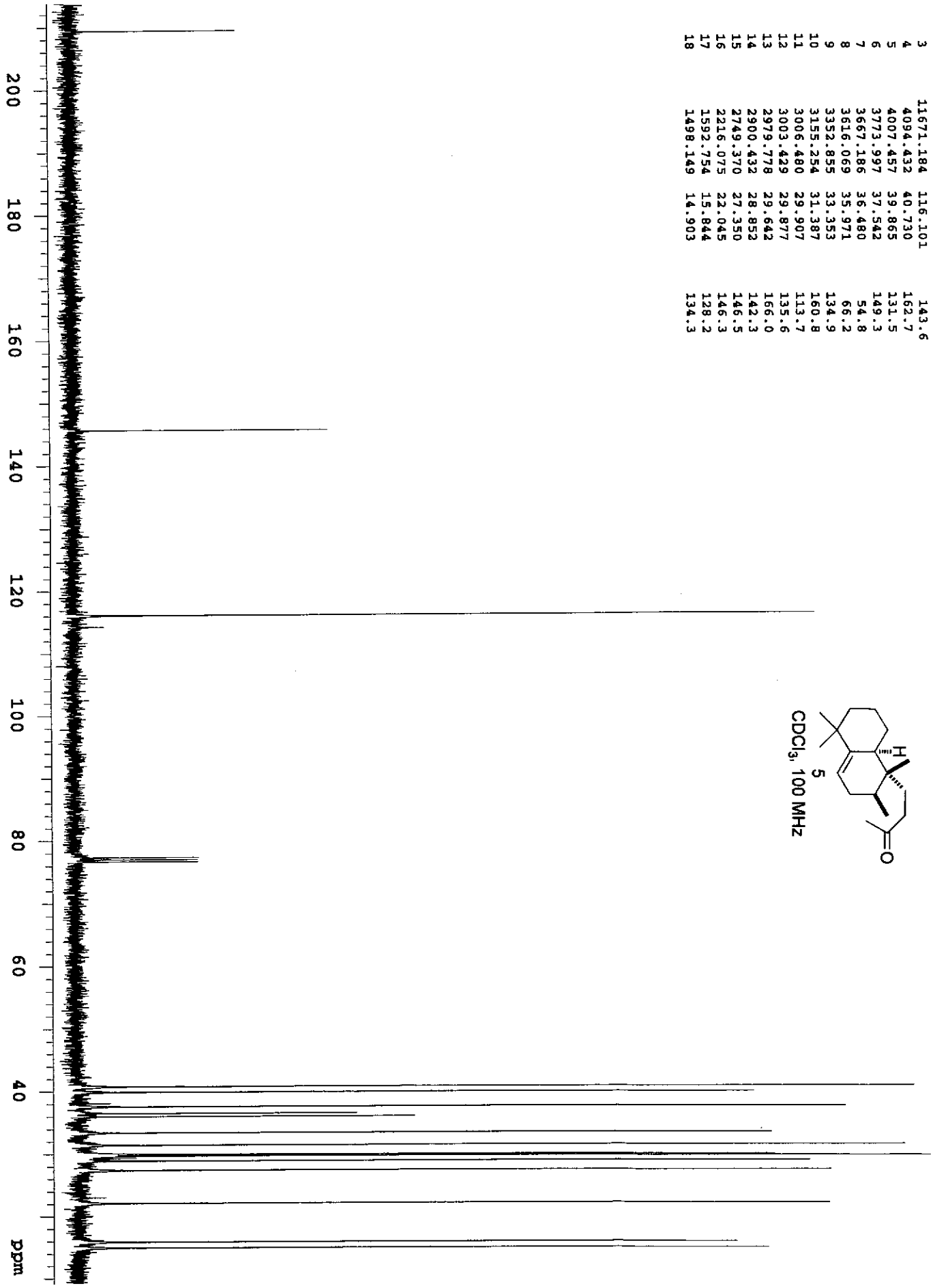
$CDCl_3$, 100 MHz

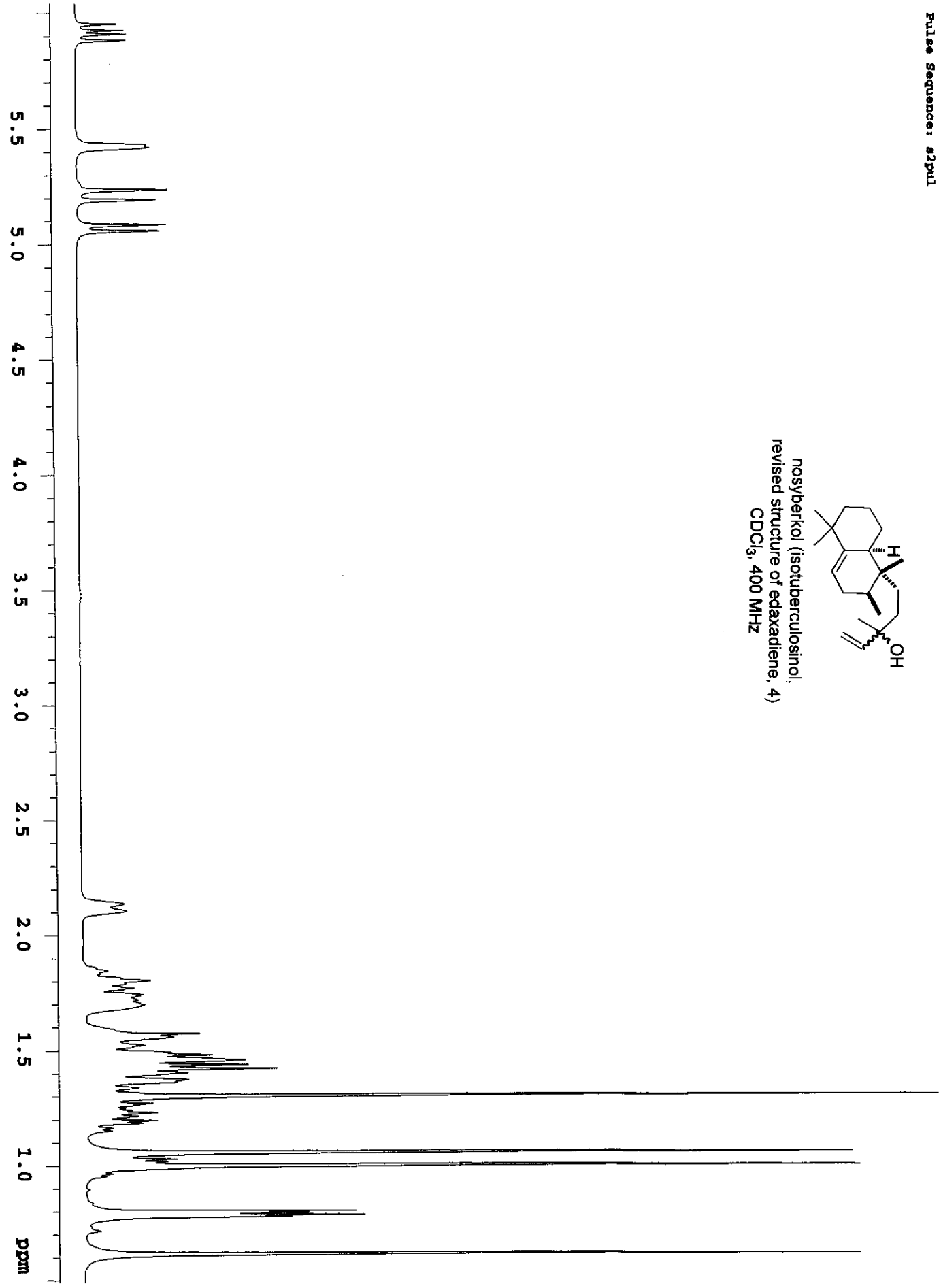


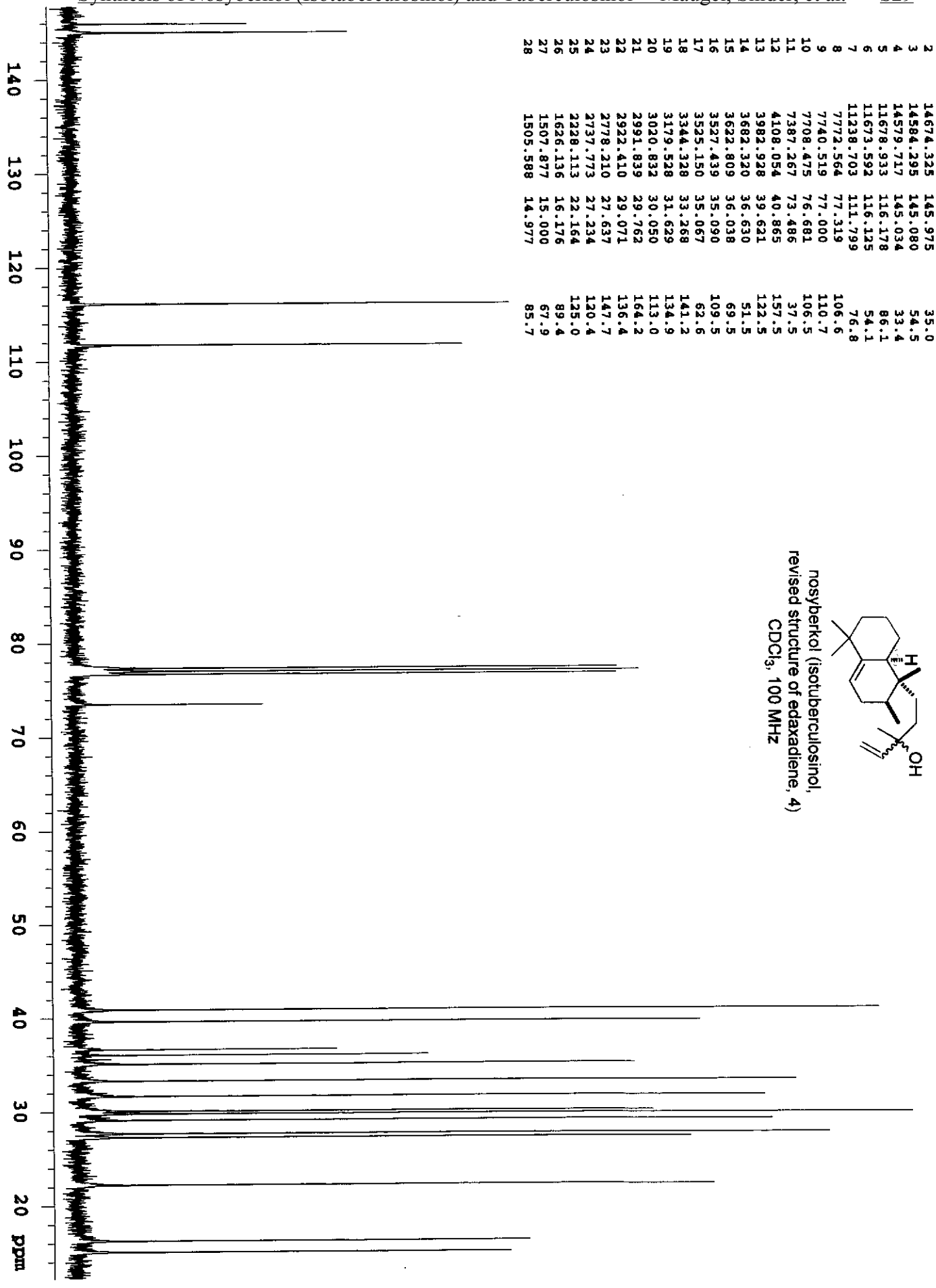

NMR-19-1L2
Pulse Sequence: s2pul
18
CDCl3, 400 MHz
H2O
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

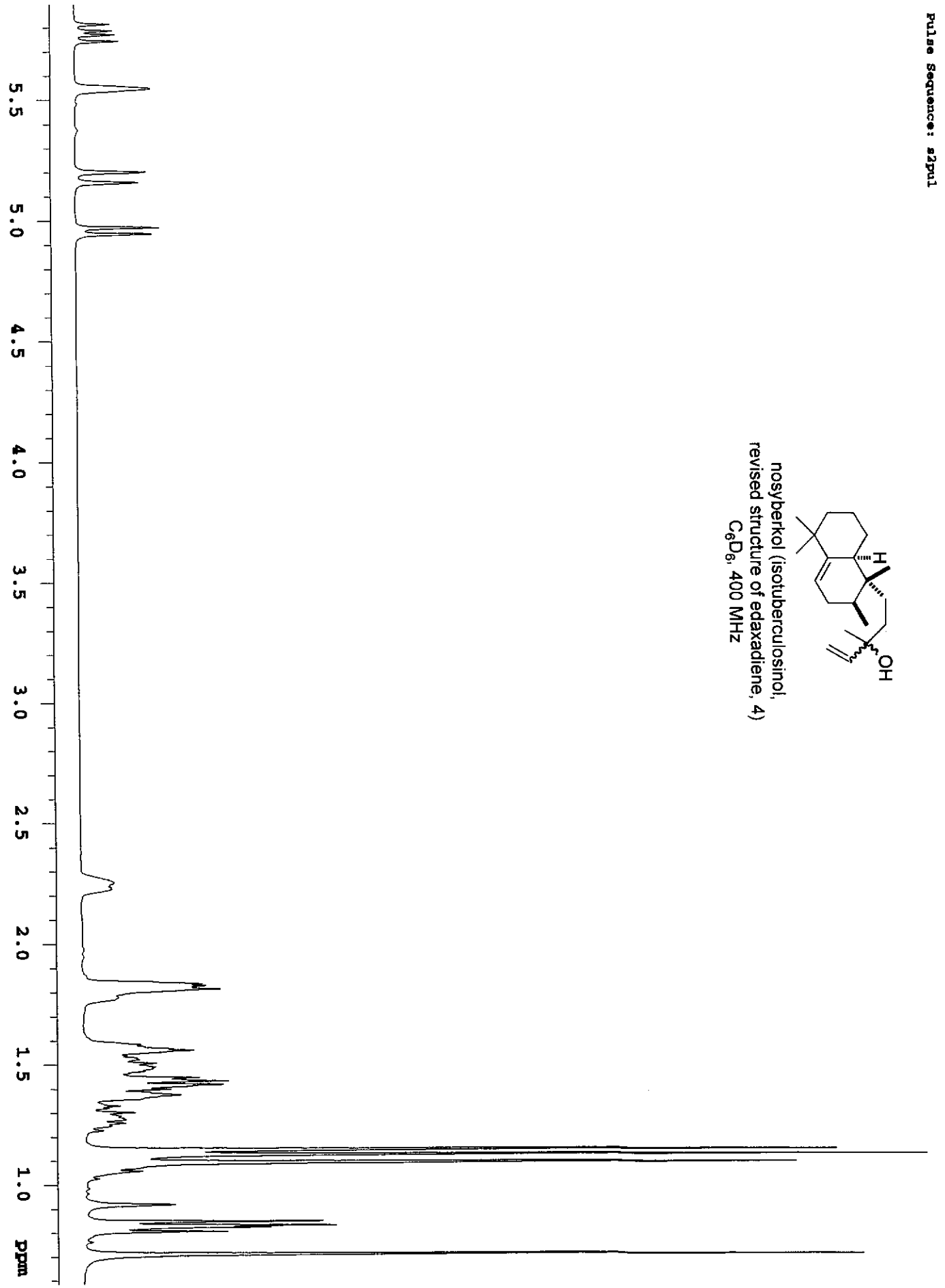

INDEX FREQUENCY PPM HEIGHT
1 19952.129 198.477 37.9
2 15878.032 157.949 113.0
3 14521.526 144.455 50.7
4 13001.750 129.337 126.2
5 11682.628 116.215 148.1
6 7772.563 77.319 24.2
7 7740.520 77.000 26.0
8 7708.476 76.681 25.1
9 4360.698 43.379 148.0
10 4296.611 42.741 58.1
11 4072.307 40.510 167.3
12 3656.505 36.374 141.0
13 3615.306 35.964 63.8
14 3101.085 30.849 161.6
15 2958.415 29.429 163.2
16 2917.980 29.027 159.8
17 2816.509 28.018 145.4
18 2734.111 27.198 96.6
19 2182.506 21.711 157.4
20 1624.034 16.155 141.5
21 1006.053 10.008 128.3
H
O
18
CDCl3, 100 MHz
180
160
140
120
100
80
60
40
20
ppm


NM8-27-1L1
Pulse Sequence: s2pul
5
CDCl3, 400 MHz
H
O
H2O
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

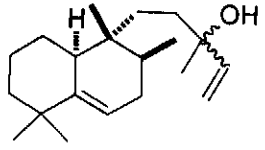

INDEX FREQUENCY PPM HEIGHT
1 21054.576 209.444 32.1
2 14645.122 145.685 49.7
3 11671.184 116.101 143.6
4 4094.432 40.730 162.7
5 4007.457 39.865 131.5
6 3773.997 37.542 149.3
7 3667.186 36.480 54.8
8 3616.069 35.971 66.2
9 3352.855 33.353 134.9
10 3155.254 31.387 160.8
11 3006.480 29.907 113.7
12 3003.429 29.877 135.6
13 2979.778 29.642 166.0
14 2900.432 28.852 142.3
15 2749.370 27.350 146.5
16 2216.075 22.045 146.3
17 1592.754 15.844 128.2
18 1498.149 14.903 134.3
H
O
5
CDCl3, 100 MHz
200
180
160
140
120
100
80
60
40
ppm


NM8-32-1L2
Pulse Sequence: s2pul
nosyberkol (isotuberculosinol,
revised structure of edaxadiene, 4)
$CDCl_3$, 400 MHz
H
OH
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

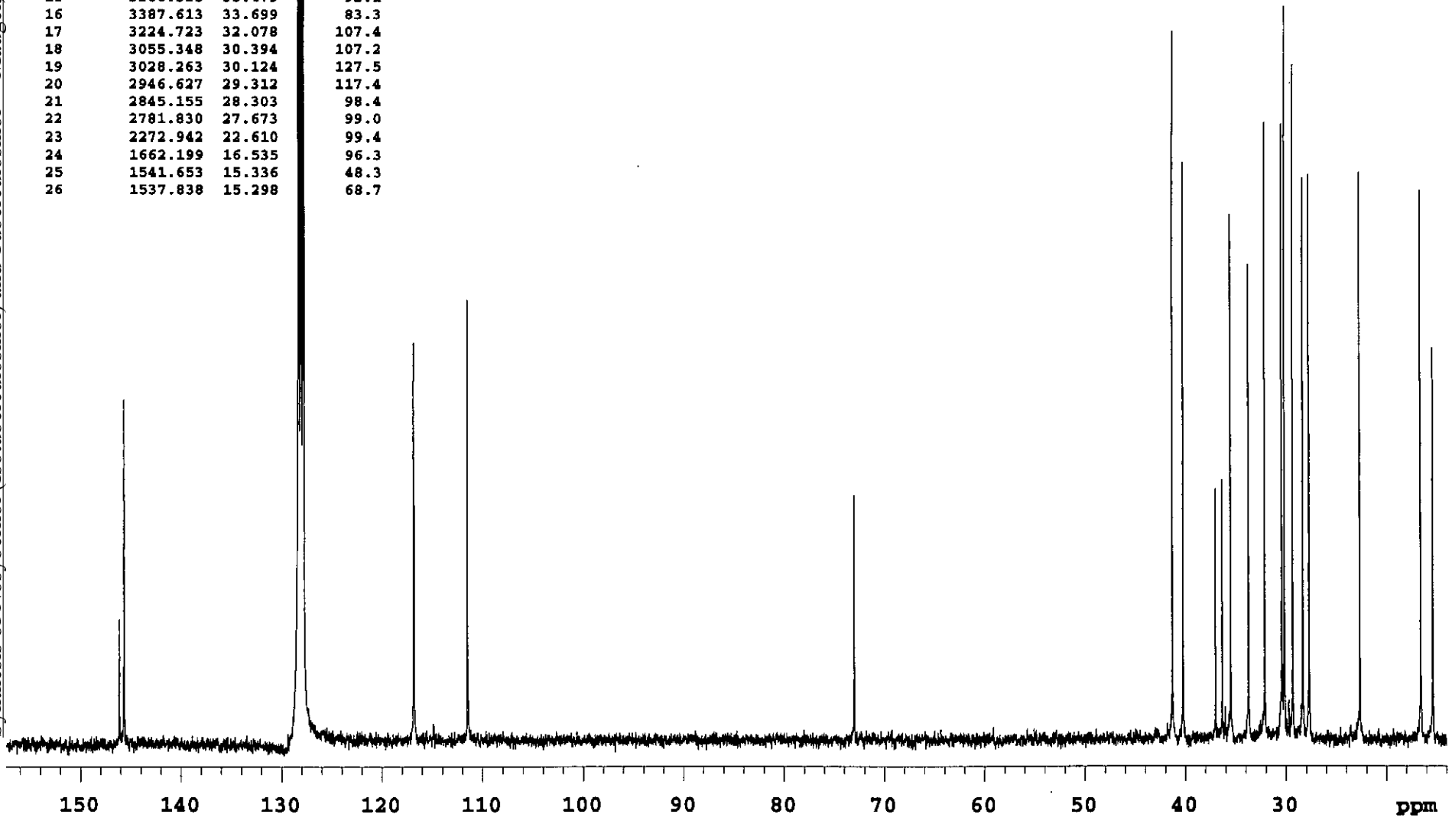

INDEX FREQUENCY PPM HEIGHT
1 14677.376 146.005 21.4
2 14674.325 145.975 35.0
3 14584.295 145.080 54.5
4 14579.717 145.034 33.4
5 11678.933 116.178 86.1
6 11673.592 116.125 54.1
7 11238.703 111.799 76.8
8 7772.564 77.319 106.6
9 7740.519 77.000 110.7
10 7708.475 76.681 106.5
11 7387.267 73.486 37.5
12 4108.054 40.865 157.5
13 3982.928 39.621 122.5
14 3682.320 36.630 51.5
15 3622.809 36.038 69.5
16 3527.439 35.090 109.5
17 3525.150 35.067 62.6
18 3344.328 33.268 141.2
19 3179.528 31.629 134.9
20 3020.832 30.050 113.0
21 2991.839 29.762 164.2
22 2922.410 29.071 136.4
23 2778.210 27.637 147.7
24 2737.773 27.234 120.4
25 2228.113 22.164 125.0
26 1626.136 16.176 89.4
27 1507.877 15.000 67.9
28 1505.588 14.977 85.7
H
OH
nosyberkol (isotuberculosinol,
revised structure of edaxadiene, 4)
CDCl3, 100 MHz
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

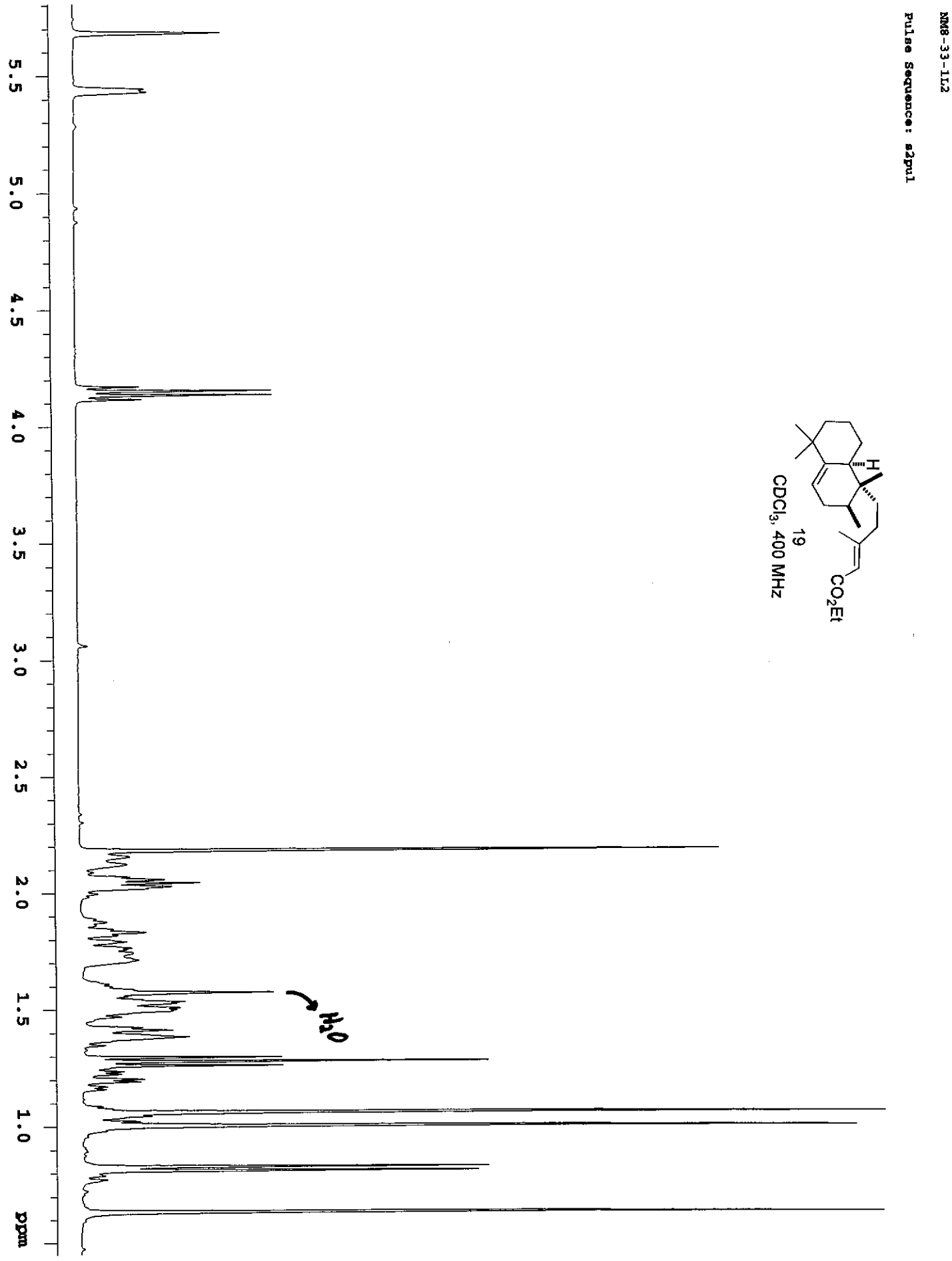

NM8-32-1L2-C6D6
Pulse Sequence: s2pul
nosyberkol (isotuberculosinol,
revised structure of edaxadiene, 4)
C_6D_6, 400 MHz
H
OH
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

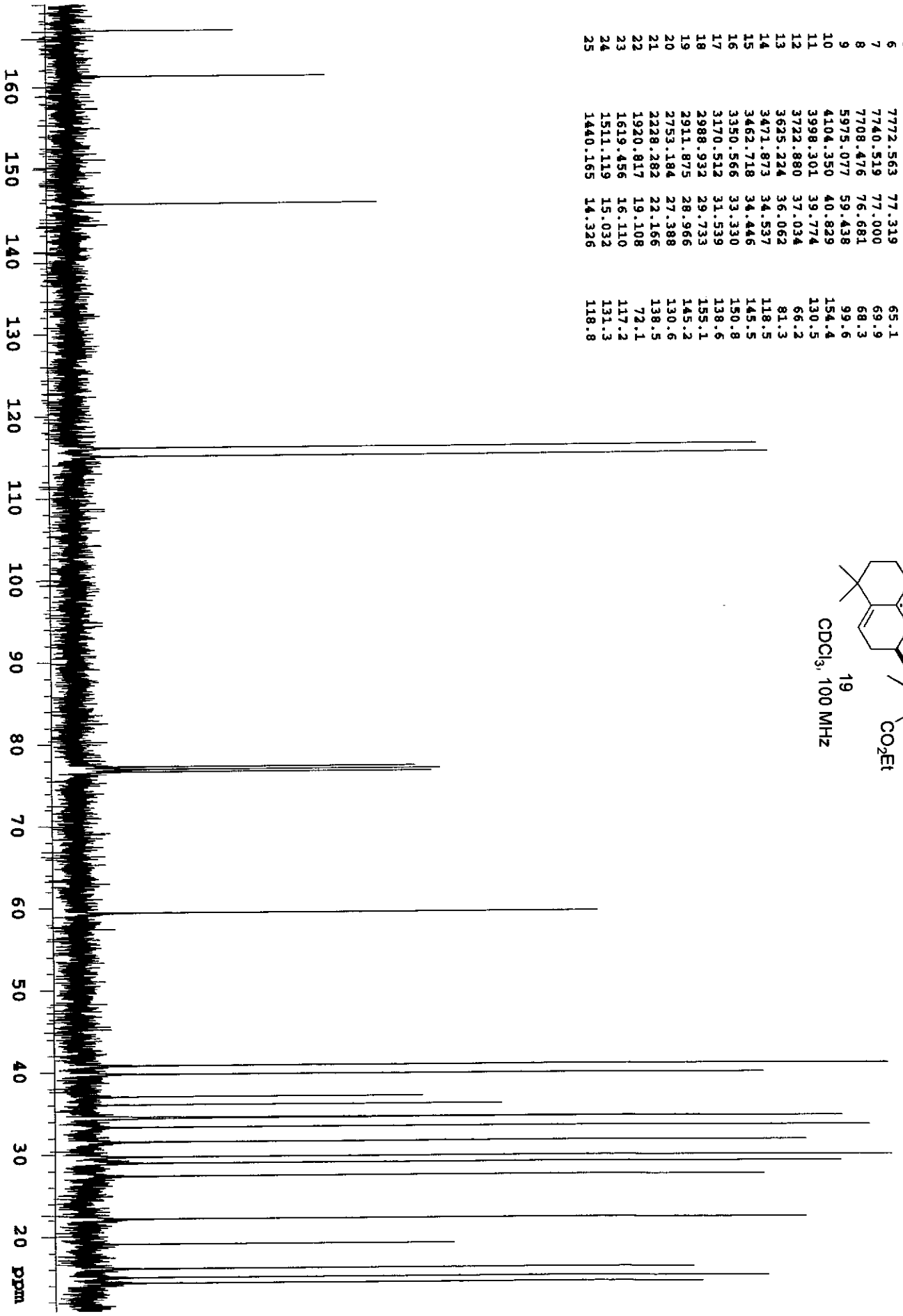
INDEX	FREQUENCY	PPM	HEIGHT
1	14698.363	146.214	14.3
2	14692.641	146.157	21.4
3	14647.245	145.706	59.4
4	12897.417	128.299	493.5
5	12873.384	128.060	520.5
6	12848.970	127.817	525.9
7	11749.939	116.884	69.5
8	11742.691	116.812	41.2
9	11212.058	111.534	76.9
10	7340.081	73.017	43.0
11	4148.275	41.266	123.1
12	4041.462	40.203	101.0
13	3717.208	36.978	44.1
14	3650.450	36.313	45.7
15	3566.525	35.479	92.1
16	3387.613	33.699	83.3
17	3224.723	32.078	107.4
18	3055.348	30.394	107.2
19	3028.263	30.124	127.5
20	2946.627	29.312	117.4
21	2845.155	28.303	98.4
22	2781.830	27.673	99.0
23	2272.942	22.610	99.4
24	1662.199	16.535	96.3
25	1541.653	15.336	48.3
26	1537.838	15.298	68.7



nosyberkol (isotuberculosinol,
revised structure of edaxadiene, 4)
C_6D_6, 100 MHz

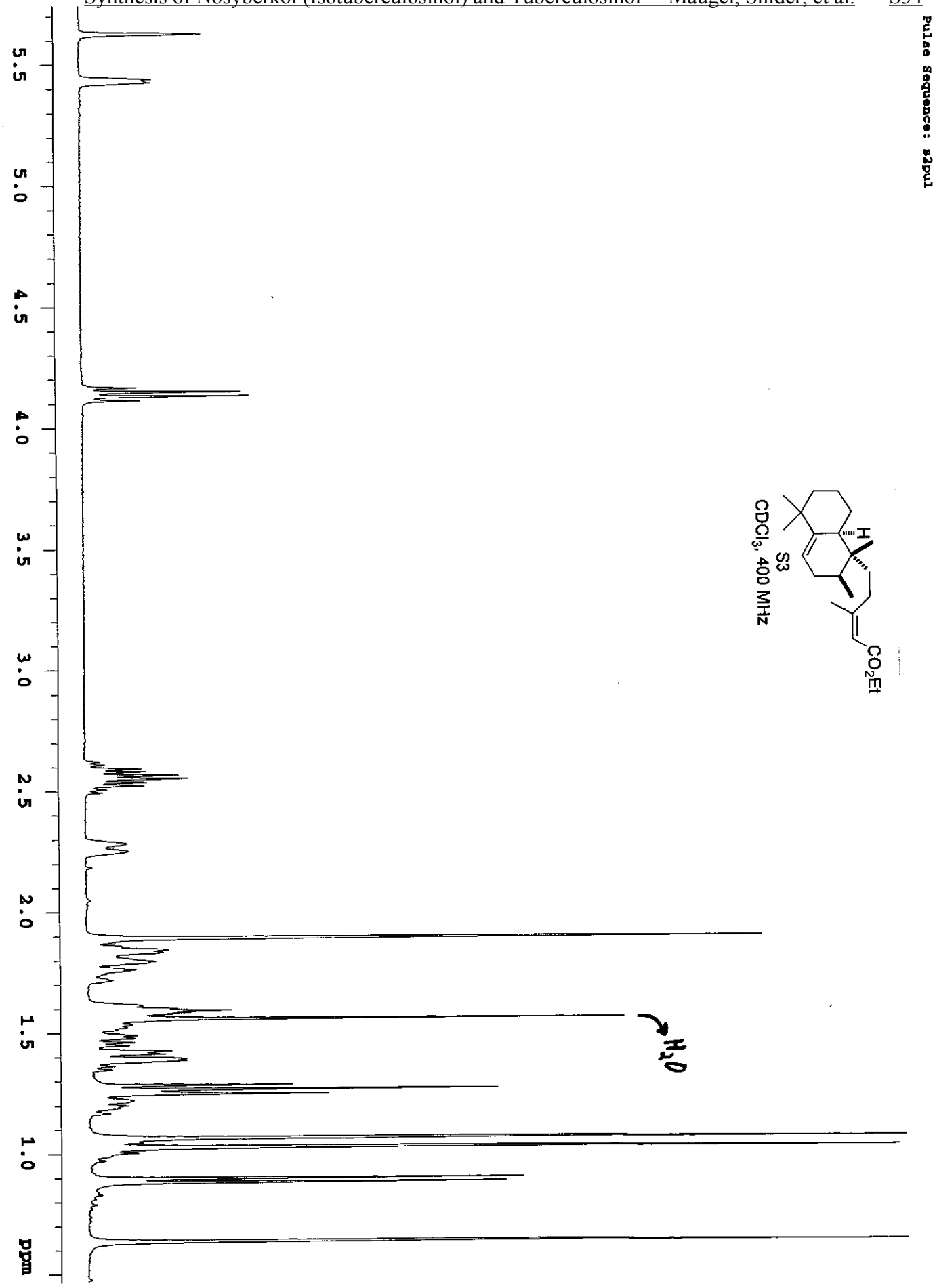


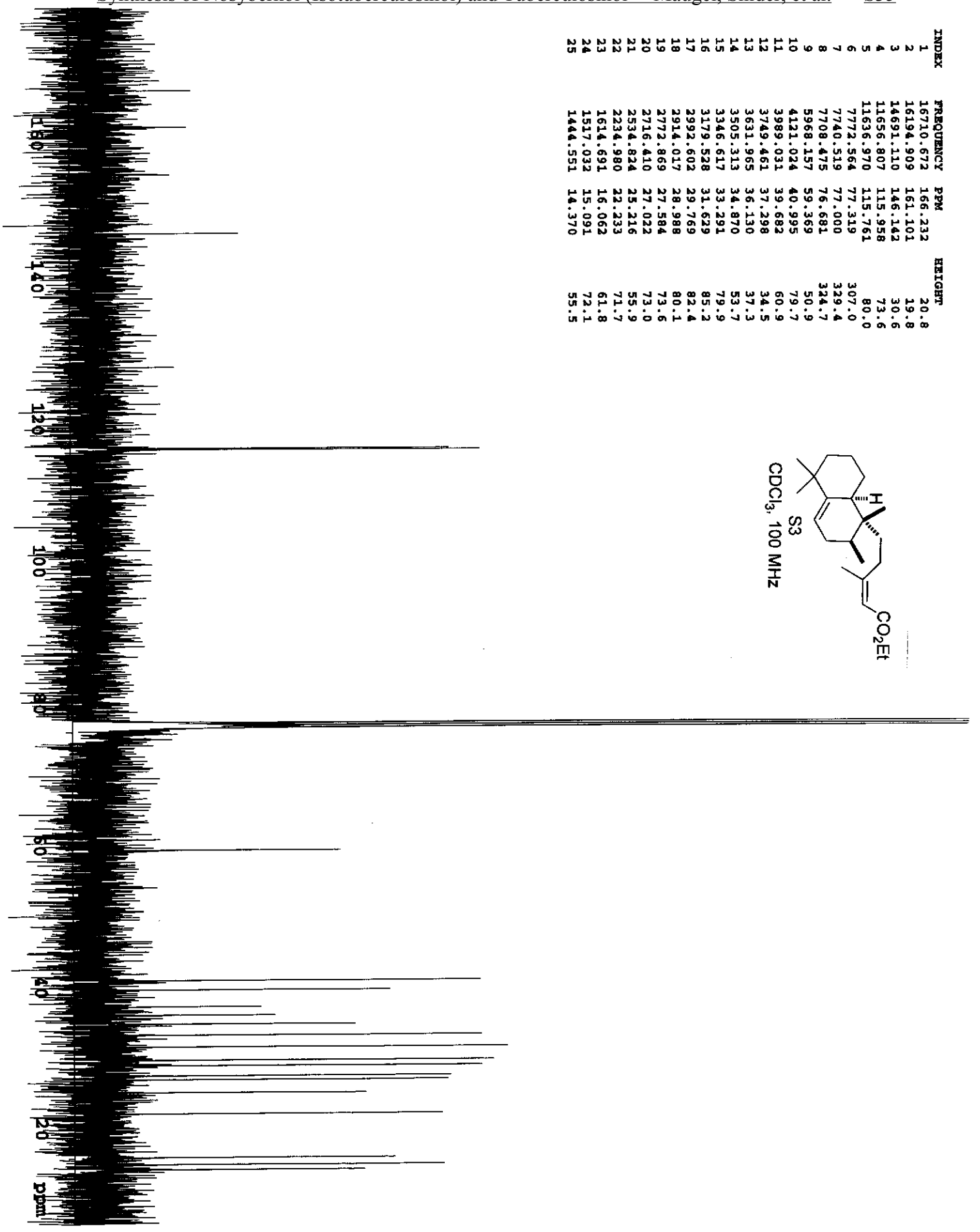

MM8-33-1L2
Pulse Sequence: s2pul
19
CDCl3, 400 MHz
CO2Et
H
H2O
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

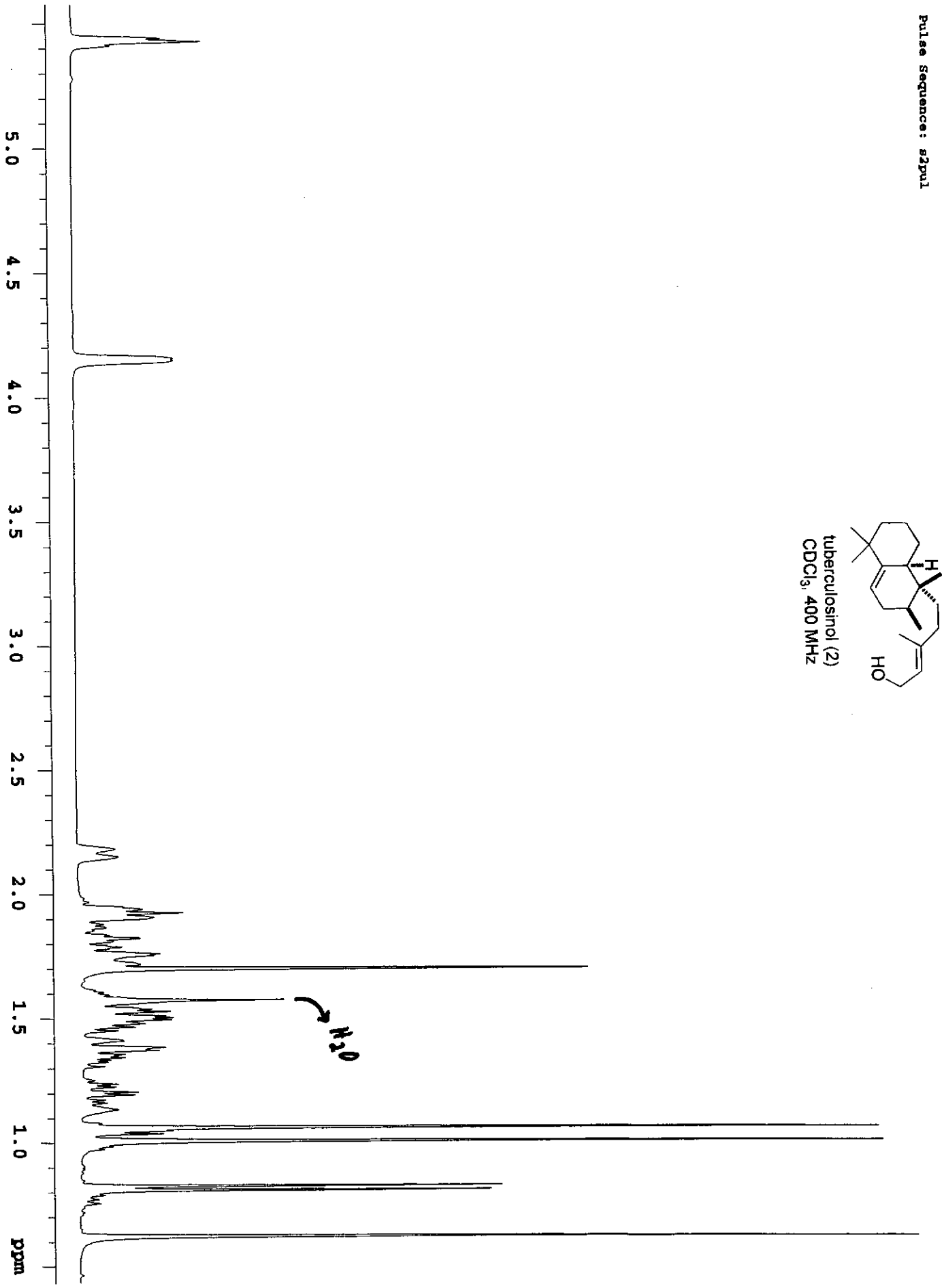


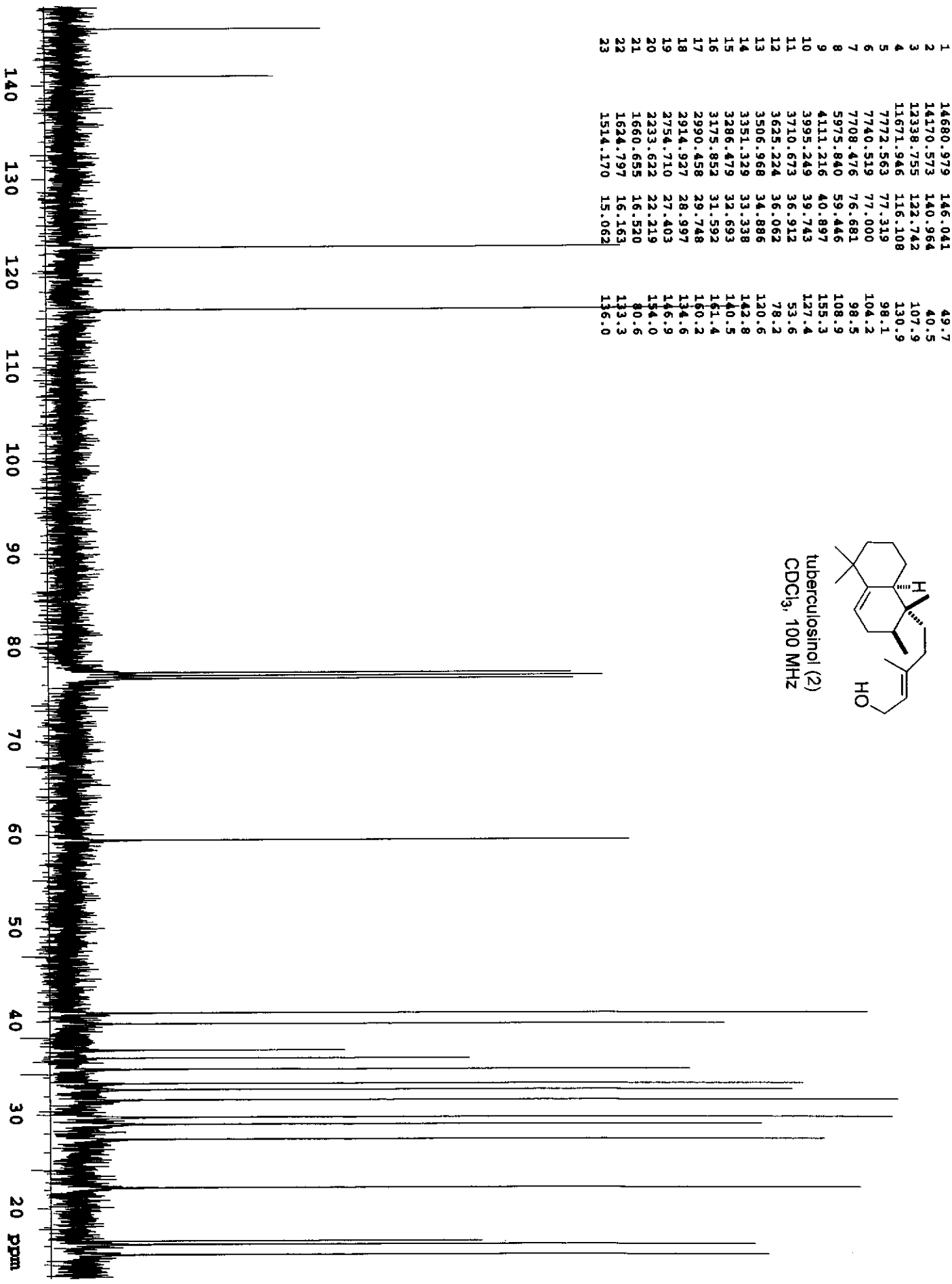
INDEX	FREQUENCY	PPM	HEIGHT
1	16776.011	166.882	31.5
2	16218.302	161.334	48.9
3	14662.669	145.859	58.5
4	11676.524	116.154	129.9
5	11572.764	115.122	132.0
6	7772.563	77.319	65.1
7	7740.519	77.000	69.9
8	7708.476	76.681	68.3
9	5975.077	59.438	99.6
10	4104.350	40.829	154.4
11	3998.301	39.774	130.5
12	3722.880	37.034	66.2
13	3625.224	36.062	81.3
14	3471.873	34.537	118.5
15	3462.718	34.446	145.5
16	3350.566	33.330	150.8
17	3170.512	31.539	138.6
18	2988.932	29.733	155.1
19	2911.875	28.966	145.2
20	2753.184	27.388	130.6
21	2228.282	22.166	138.5
22	1920.817	19.108	72.1
23	1619.456	16.110	117.2
24	1511.119	15.032	131.3
25	1440.165	14.326	118.8

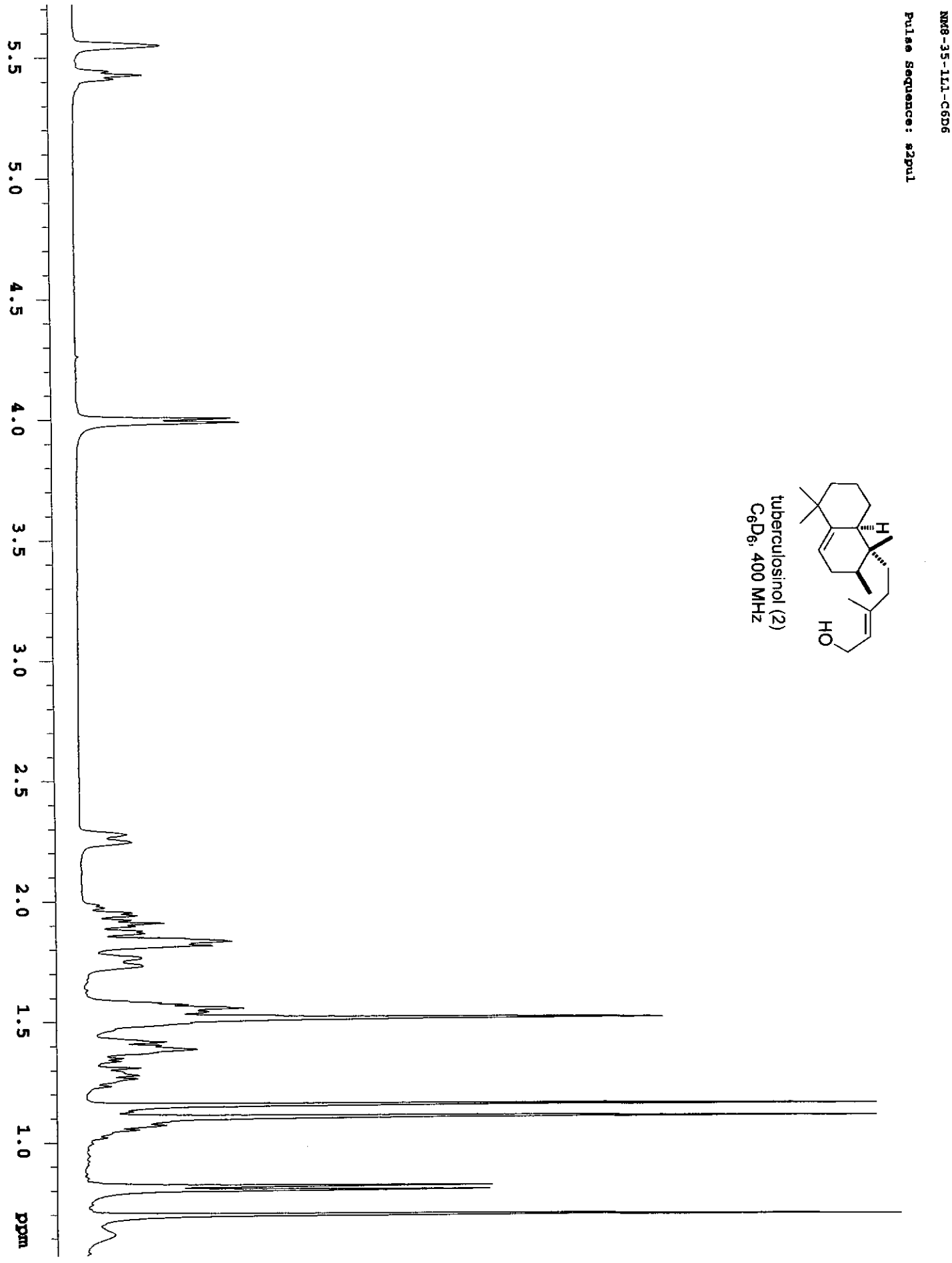
19
$CDCl_3$, 100 MHz

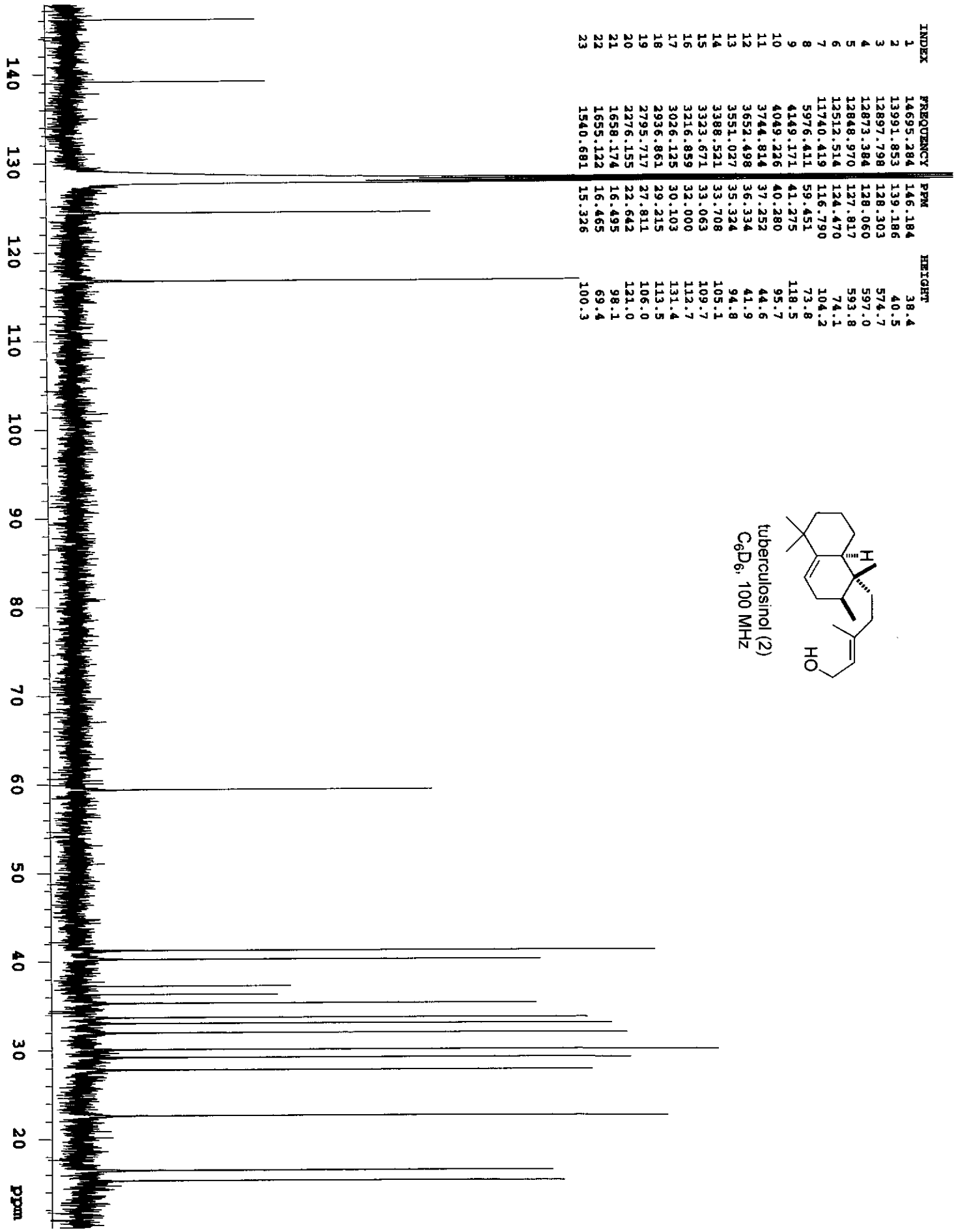

NMR-33-1L1
Pulse Sequence: s2pul
S3
CDCl3, 400 MHz
CO2Et
H
H2O
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm


INDEX FREQUENCY PPM HEIGHT
1 16710.672 166.232 20.8
2 16194.909 161.101 19.8
3 14691.110 146.142 30.6
4 11656.807 115.958 73.6
5 11636.970 115.761 80.0
6 7772.564 77.319 307.0
7 7740.519 77.000 329.4
8 7708.475 76.681 324.7
9 5968.157 59.369 50.9
10 4121.024 40.995 79.7
11 3989.031 39.682 60.9
12 3749.461 37.298 34.5
13 3631.965 36.130 37.3
14 3505.313 34.870 53.7
15 3346.617 33.291 79.9
16 3179.528 31.629 85.2
17 2992.602 29.769 82.4
18 2914.017 28.988 80.1
19 2772.869 27.584 73.6
20 2716.410 27.022 73.0
21 2534.824 25.216 55.9
22 2234.980 22.233 71.7
23 1614.691 16.062 61.8
24 1517.032 15.091 72.1
25 1444.551 14.370 55.5
H
CO2Et
S3
CDCl3, 100 MHz
160
140
120
100
80
60
40
20
ppm


NMR-35-1L1
Pulse Sequence: s2pul
tuberculosinol (2)
CDCl3, 400 MHz
H
HO
H2O
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm


INDEX FREQUENCY PPM HEIGHT
1 14680.979 146.041 49.7
2 14170.573 140.964 40.5
3 12338.755 122.742 107.9
4 11671.946 116.108 130.9
5 7772.563 77.319 98.1
6 7740.519 77.000 104.2
7 7708.476 76.681 98.5
8 5975.840 59.446 108.9
9 4111.216 40.897 155.3
10 3995.249 39.743 127.4
11 3710.673 36.912 53.6
12 3625.224 36.062 78.2
13 3506.968 34.886 120.6
14 3351.329 33.338 142.8
15 3286.479 32.693 140.5
16 3175.852 31.592 161.4
17 2990.458 29.748 160.2
18 2914.927 28.997 134.6
19 2754.710 27.403 146.9
20 2233.622 22.219 154.0
21 1660.655 16.520 80.6
22 1624.797 16.163 133.3
23 1514.170 15.062 136.0
H
HO
tuberculosinol (2)
CDCl3, 100 MHz
140
130
120
110
100
90
80
70
60
50
40
30
20 ppm


NM8-35-1Ll-C6D6
Pulse Sequence: s2pul
tuberculosinol (2)
C6D6, 400 MHz
H
HO
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm


INDEX FREQUENCY PPM HEIGHT
1 14695.284 146.184 38.4
2 13991.853 139.186 40.5
3 12897.798 128.303 574.7
4 12873.384 128.060 597.0
5 12848.970 127.817 593.8
6 12512.514 124.470 74.1
7 11740.419 116.790 104.2
8 5976.411 59.451 73.8
9 4149.171 41.275 118.5
10 4049.226 40.280 95.7
11 3744.814 37.252 44.6
12 3652.498 36.334 41.9
13 3551.027 35.324 94.8
14 3388.521 33.708 105.1
15 3323.671 33.063 109.7
16 3216.859 32.000 112.7
17 3026.125 30.103 131.4
18 2936.861 29.215 113.5
19 2795.717 27.811 106.0
20 2276.155 22.642 121.0
21 1658.174 16.495 98.1
22 1655.122 16.465 69.4
23 1540.681 15.326 100.3
H
HO
tuberculosinol (2)
C6D6, 100 MHz
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm