De Novo Asymmetric Synthesis of Milbemycin β_3 via an Iterative Asymmetric Hydration Approach

Miaosheng Li and George A. O'Doherty*

Department of Chemistry, West Virginia University

Morgantown, WV 26506

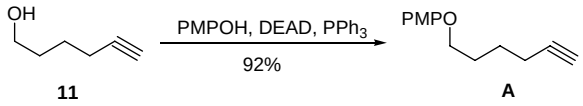
Supporting Information:

Table of Contents

General Methods and Materials:

^{1}H and ^{13}C NMR spectra were recorded on a 600 MHz or a 270 MHz spectrometer. Chemical shifts are reported relative to $CDCl_3$ (δ 7.24 ppm) for ^{1}H NMR and $CDCl_3$ (δ 77.23 ppm) for ^{13}C NMR. Infrared (IR) spectra were obtained on a FT-IR spectrometer. Optical rotations were measured with a digital polarimeter in the solvent specified. Melting points were uncorrected. Flash chromatography was performed using the indicated solvent system on silica gel 60 (60-200 mesh). Diethyl ether, tetrahydrofuran (THF), methylene chloride (CH_2Cl_2), and triethylamine (Et_3N) were dried by passing through activated alumina columns with argon gas pressure. R_f values were obtained by elution in the stated solvent (v/v). Commercial reagents were used without purification unless otherwise noted. Air- and moisture-sensitive reactions were carried out under an atmosphere of argon using oven-dried glassware and standard syringe/septa techniques.

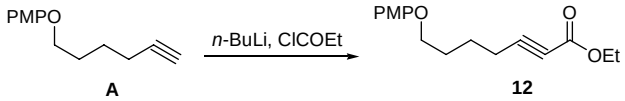
6-(4-Methoxy-phenoxy)-hex-1-yne (A).



To a solution of 5-hexyn-1-ol **11** (0.196 g, 2.00 mmol) in benzene (10 mL) at 10 ^{o}C, containing Ph_3P (0.630 g, 2.40 mmol) and *p*-methoxyphenol (0.40 g, 3.22 mmol), was added DEAD (0.418 g, 0.240 mmol) dropwise. The reaction mixture was stirred at 10 ^{o}C for 2 h before the solvent was removed *in vacuo*. The crude product was triturated with $CHCl_3$ and filtered to remove $Ph_3P=O$. After removal of the solution, the residue was purified by flash chromatography (1:19 EtOAc/hexanes) on silica gel to afford PMP ether **A** (0.38 g, 92%) as a white solid: m.p. = 56-58 ^{o}C; R_f (30 % EtOAc/hexanes) = 0.72; IR (thin film, cm^{-1}) 3293, 2952, 1508, 1230, 1039, 825; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.80 (m, 4H), 3.91 (t, J = 6 Hz, 2H), 3.74 (s, 3H), 2.24 (dt, J = 7.2, 2.4 HZ, 2H), 1.93 (t, J = 2.4 Hz, 1H), 1.86 (m, 2H), 1.69

(m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 154.0, 153.4, 115.7, 114.9, 84.4, 68.8, 68.2, 56.0, 28.6, 25.3, 18.4; ESI HRMS Calcd for $[C_{13}H_{16}O_2 + Na]^+$: 227.1048, Found: 227.1042.

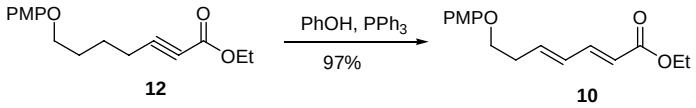
Ethyl 7-(4-methoxy-phenoxy)-hept-2-ynoate (12).



A 12

To a solution of alkyne **A** (2.4 g, 11.8 mmol) in THF (20 mL) at -78 °C was added *n*-BuLi (5.2 mL, 2.5 M in *n*-hexane, 13.0 mmol) dropwise and the mixture was stirred for 1 h. Then, ethylchloroformate (1.46 mL, 15.3 mmol) was added at −78 °C and the mixture was stirred for 1 h. The reaction mixture was warmed to 0 °C and stirred for 15 min. The reaction was quenched with saturated aqueous NH_4Cl (10 mL). The aqueous layer was extracted with ether (2 x 50 mL). The organic layer was washed with brine (20 ml) and dried with anhydrous sodium sulfate. After removal of the solvent in *in vacuo*, the residue was purified by flash chromatography (1:9 EtOAc/hexane) on silica gel to afford ethyl heptynoate **12** (3.1 g, 95%) as a light yellow oil: R_f (30 % EtOAc/hexanes) = 0.6; IR (thin film, cm^{-1}) 2943, 2872, 2234, 1706, 1508, 1249, 1230, 1070, 825; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.83 (m, 4H), 4.22 (q, *J* = 7.2 Hz, 2H), 3.93 (t, *J* = 6.0 Hz, 2H), 3.76 (s, 3H), 2.42 (t, *J* = 7.2 Hz, 2H), 1.88 (m, 2H), 1.78 (m, 2H), 1.31 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 154.0, 153.9, 153.2, 115.6, 114.8, 88.9, 73.7, 67.9, 61.9, 55.9, 28.6, 24.4, 18.6, 14.2; ESI HRMS Calcd for $[C_{16}H_{20}O_4 + Na]^+$: 299.1259, Found: 299.1258.

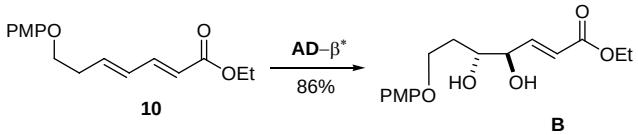
Ethyl 7-(4-methoxy-phenoxy)-hept-2,4-dienoate (10).



12 10

Into a 100 mL round bottom flask were added ynoate **12** (3.1 g, 11.2 mmol), Ph_3P (2.94 g, 11.2 mmol), phenol (1.06 g, 11.2 mmol) and benzene (20 mL). The mixture was stirred at room temperature for 12 h. The solution was diluted with ether (50 mL) and 1N NaOH (50 mL). The layer was separated and the aqueous layer was extracted with ether (2 x 50 mL). The combined organic layers were washed (water, brine), dried (Na_2SO_4), and concentrated. The residue was dissolved in ether (100 mL) and MeI (4.8 g, 33.6 mmol) was added to the solution. The reaction mixture was refluxed for 12 h. The solution was filtered, concentrated, and purified by flash chromatography (1:9 EtOAc/hexanes) on silica gel to give ethyl dienoate **10** (3.0 g, 97%) as light yellow oil: R_f (20 % EtOAc/hexanes) = 0.42; IR (thin film, cm^{-1}) 2983, 2937, 1707, 1643, 1506, 1227, 1137, 1037, 999, 824; ^1H NMR (600 MHz, $CDCl_3$) δ 7.28 (dd, *J* = 15.6, 10.8 Hz, 1H), 6.83 (m, 4H), 6.29 (dd, *J* = 15.6, 10.8 Hz, 1H), 6.20 (dt, *J* = 15.0, 7.2 Hz, 1H), 5.83 (d, *J* = 15.0 Hz, 1H), 4.21 (q, *J* = 7.2 Hz, 2H), 4.00 (t, *J* = 6.0 Hz, 2H), 3.76 (s, 3H), 2.63 (dt, *J* = 12.6, 6.6 Hz, 2H), 1.30 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.2, 154.2, 153.0, 144.6, 139.6, 130.5, 120.4, 115.8, 114.8, 67.5, 60.4, 55.8, 33.1, 14.4; ESI HRMS Calcd for $[C_{16}H_{20}O_4 + Na]^+$: 299.1259, Found: 299.1258.

Ethyl (4*R*,5*R*)-7-(4-methoxy-phenoxy)-4,5-dihydroxy-hept-2-enoate (B).

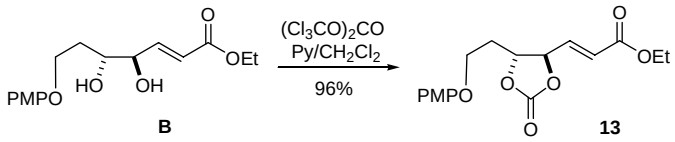


10 B

Into a 250 mL round bottom flask were added 60 mL of *t*-BuOH, 60 mL of water, $K_3Fe(CN)_6$ (11.80 g, 35.8 mmol), K_2CO_3 (4.94 g, 35.8 mmol), $MeSO_2NH_2$ (1.14 g, 11.9 mmol),

$(DHQD)_2$-PHAL (140 mg, 0.18 mmol), and OsO_4 (30.4 mg, 0.119 mmol). The mixture was stirred at room temperature for about 15 minutes and then cooled to 0°C. To this solution was added dienoate **10** (3.3 g, 11.9 mmol) and the reaction was stirred vigorously at 0 °C overnight. The reaction was quenched with saturated aqueous sodium sulfite (30 mL) at room temperature. Ethyl acetate (100 mL) was added to the reaction mixture, and after separation of the layers, the aqueous phase was further extracted with the ethyl acetate (2 x 50 mL). The combined organic layers were washed with 2N KOH (20 mL) and brine to remove the methanesulfonamide, and dried over anhydrous sodium sulfate. After removal of the solvents *in vacuo*, flash chromatography on silica gel (3:7 EtOAc/hexanes) afforded diol **B** as a white solid (3.2 g, 86%): m.p. = 80-82 ^{o}C; $[\alpha]^{25}_{D}$ +22 (*c* 1.0, CH_2Cl_2); R_f (50 % EtOAc/hexanes) = 0.32; IR (thin film, cm^{-1}) 3428, 2956, 1709, 1509, 1230, 1038, 826; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.99 (dd, *J* = 15.6, 4.8 Hz, 1H), 6.84 (m, 4H), 6.17 (dd, *J* = 15.6, 1.8 Hz, 1H), 4.24 (br, 1H), 4.21 (q, *J* = 7.2 Hz, 2H), 4.13 (m, 2H), 3.11 (m, 1H), 2.88 (s, 1H), 2.78 (s, 1H), 2.02 (m, 2H), 1.30 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.4, 154.4, 152.7, 146.7, 122.9, 115.8, 115.0, 74.2, 72.3, 66.3, 60.8, 56.0, 55.9, 32.8, 14.4; ESI HRMS Calcd for $[C_{16}H_{22}O_6 + Na]^+$: 333.1314, Found: 333.1314.

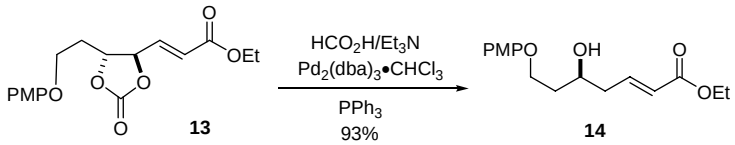
Ethyl (4*R*,5*R*)-3-{[5-(4-methoxy-phenoxy)-ethyl]-2-oxo-[1,3]dioxolan-4-yl} acrylate (13).



Into a 250 mL round-bottom flask were placed 1.84 g (5.93 mmol) of diol **B**, 50 mL of CH_2Cl_2, pyridine (2.34 g, 29.6 mmol), and DMAP (10 mg). The solution was cooled to -78 and triphosgene (1.23 g, 4.14 mmol) in 20 mL of CH_2Cl_2 was added slowly with an addition funnel. The reaction was stirred and warmed to 0 °C in 2 h and quenched with saturated aqueous NH_4Cl (40 mL). The layers were separated and the aqueous layer was extracted with ether (3 x 20 mL). The combined organic layers were washed with saturated

aqueous sodium bicarbonate (30 mL), brine (25 mL), and dried over anhydrous sodium sulfate. After removal of the solvents *in vacuo*, flash chromatography on silica gel (1:9 EtOAc/hexanes) afforded carbonate **13** as a colorless oil (1.92 g, 96%): $[\alpha]^{25}_{D}$ +47 (*c* 1.1, CH_2Cl_2); R_f (40 % EtOAc/hexanes) = 0.57; IR (thin film, cm^{-1}) 2939, 2836, 1802, 1718, 1508, 1228, 1169, 1032, 826; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.89 (dd, *J* = 15.6, 6.6 Hz, 1H), 6.83 (m, 4H), 6.20 (d, *J* = 15.6 Hz, 1H), 5.06 (dd, *J* = 6.0, 5.4 Hz, 1H), 4.66 (dd, *J* = 13.2, 6.6 Hz, 1H), 4.23 (q, *J* = 7.2 Hz, 2H), 4.06-4.13 (m, 2H), 3.76 (s, 3H), 2.26 (m, 2H), 1.29 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.1, 154.6, 153.6, 152.3, 139.3, 125.1, 115.6, 115.0, 80.1, 79.2, 63.8, 61.2, 55.9, 33.2, 14.3; ESI HRMS Calcd for $[C_{17}H_{20}O_7 + Na]^+$: 359.1107, Found: 359.1107.

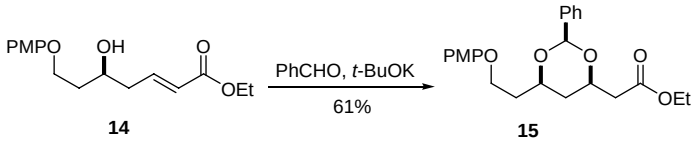
Ethyl (5*S*)-7-(4-methoxy-phenoxy)-5-hydroxy-2-heptenoate (14).



Into a 100 mL round bottomed flask maintained under argon were added $Pd_2(dba)_3{\cdot}CHCl_3$ (29 mg, 0.028 mmol), PPh_3 (7.5 mg, 0.029 mmol), THF (20 mL) and carbonate **13** (1.92 g, 5.7 mmol). Triethylamine (2 mL, 14.4 mmol) and HCO_2H (1 mL, 26.5 mmol) were added and the mixture was allowed to stir at room temperature until the color of the solution turned black. The reaction was quenched with saturated aqueous sodium bicarbonate (20 mL). The aqueous layer was extracted with ether (2 x 50 mL). The organic layers were combined, washed with brine (20 mL) and dried with anhydrous sodium sulfate. After removal of the solvents *in vacuo*, flash chromatography on silica gel (2:8 EtOAc/hexanes) provided alcohol **14** as a yellow oil (1.56 g , 93%): $[\alpha]^{25}_{D}$ -3.0 (*c* 1.2, CH_2Cl_2); R_f (40 % EtOAc/hexanes) = 0.41; IR (thin film, cm^{-1}) 3459, 2940, 2836, 1716, 1655, 1508, 1228, 1038, 825; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.00 (ddd, *J* = 15.0, 7.2, 7.2 Hz, 1H), 6.83 (m, 4H), 5.92 (dd, *J* = 15.6, 1.2 Hz, 1H), 4.19 (q, *J* = 7.2 Hz, 2H), 4.13 (m, 1H), 4.06 (m, 2H), 3.76 (s, 3H), 2.60 (d, *J* =

3.0 Hz, 1H), 2.44 (dd, *J* = 6.6, 6.6 Hz, 2H), 1.93 (m, 2H), 1.29 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.5, 154.3, 152.9, 145.0, 124.2, 115.7, 114.9, 69.0, 66.6, 60.5, 55.9, 40.4, 36.3, 14.4; ESI HRMS Calcd for $[C_{16}H_{22}O_5 + Na]^+$: 317.1365, Found: 317.1365.

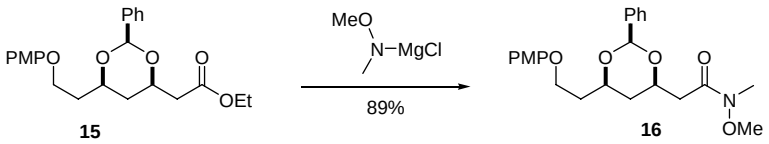
Ethyl 2-{(2*R*,4*R*,6*R*)-6-[(4-methoxy-phenoxy)-ethyl]-2-phenyl-1,3-dioxan-4-yl} acetate (15).



14 **15**

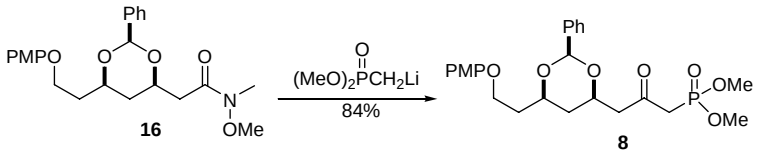
To a solution of alcohol **14** (1.56, 5.3 mmol) in THF (50 mL) at 0 °C were added benzaldehyde (0.54 ml, 5.3 mmol), followed *t*-BuOK (59.5 mg, 0.53 mmol). The solution was stirred for 15 min. The addition of benzaldehyde/*t*-BuOK was repeated 3 more times and the reaction was quenched with 50 mL of pH 7 phosphate buffer. The layers were separated, and the aqueous layer was extracted with ether (3 x 50 mL). The combined organic layers were washed, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (1:9 EtOAc/hexanes) to produce benzylidene protected diol **15** (1.29 g, 61%) as colorless oil: $[\alpha]^{25}_D$ +33 (*c* 1.2, CH_2Cl_2); R_f (30 % EtOAc/hexanes) = 0.46; IR (thin film, cm^{-1}) 2916, 1734, 1508, 1231, 1027, 826, 700; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.49 (m, 2H), 7.35 (m, 3H), 6.86 (m, 4H), 5.60 (s, 1H), 4.36 (dddd, *J* = 13.2, 6.6, 6.6, 2.4 Hz, 1H), 4.19 (q, *J* = 7.2 Hz, 2H), 4.16 (m, 2H), 4.07 (dddd, *J* = 10.8, 5.4, 5.4, 2.4 Hz, 1H), 3.78 (s, 3H), 2.75 (dd, *J* = 15.0, 6.6 Hz, 1H), 2.55 (dd, *J* = 15.0, 6.0 Hz, 1H), 2.07 (m, 2H), 1.80 (ddd, *J* = 13.2, 2.4, 2.4 Hz, 1H), 1.55 (ddd, *J* = 12.6, 12.0, 12.0 Hz, 1H), 1.29 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.9, 154.0, 153.3, 138.6, 128.8, 128.3, 126.2, 115.7, 114.9, 100.8, 73.6, 73.4, 64.6, 60.8, 55.9, 41.2, 36.8, 35.9, 14.4; ESI HRMS Calcd for $[C_{23}H_{28}O_6 + Na]^+$: 423.1784, Found: 423.1784.

***N*-Methoxy-*N*-methyl- 2-{(2*R*,4*R*,6*R*)-6-[(4-methoxy-phenoxy)-ethyl]-2-phenyl-1,3-dioxan-4-yl}acetamide (16).**



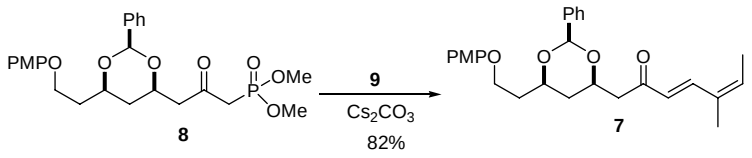
Into a 100 mL round bottomed flask maintained under argon were added ester **15** (1.29 g, 3.2 mmol), *N,O*-dimethylhydroxylamine hydrochloride (0.56 g, 5.7 mmol) and THF (30 mL). The reaction mixture was cooled to -20 °C using NaCl/ice bath. To the reaction mixture was added 2M solution of isopropylmagnesium chloride in ether (5.8 ml, 11.6 mmol) dropwise over 30 min. The reaction mixture was stirred at -20 °C for 30 min and quenched with saturated aqueous NH_4Cl (20 mL). The layers were separated and the aqueous layer was extracted with ether (2 x 50 mL). The combined organic layers were washed with brine (25 mL) and dried over anhydrous sodium sulfate. After removal of the solvents *in vacuo*, flash chromatography on silica gel (3:7 EtOAc/hexanes) afforded Weinreb amide **16** as a colorless oil (1.19 g, 89%): $[\alpha]^{25}_D$ +48 (*c* 1.4, CH_2Cl_2); R_f (60 % EtOAc/hexanes) = 0.46; IR (thin film, cm^{-1}) 2937, 1660, 1508, 1230, 1111, 1027, 826, 701; ^1H NMR (600 MHz, $CDCl_3$) δ 7.49 (m, 2H), 7.34 (m, 3H), 6.85 (m, 4H), 5.60 (s, 1H), 4.43 (dddd, *J* = 13.2, 6.6, 6.6, 2.4 Hz, 1H), 4.15 (m, 2H), 4.06 (dddd, *J* = 11.4, 5.4, 5.4, 1.8 Hz, 1H), 3.77 (s, 3H), 3.69 (s, 3H), 3.21 (s, 3H), 3.00 (dd, *J* = 15.6, 4.8 Hz, 1H), 2.58 (dd, *J* = 15.6, 6.6 Hz, 1H), 2.06 (m, 2H), 1.88 (ddd, *J* = 12.6, 2.4, 2.4 Hz, 1H), 1.55 (ddd, *J* = 12.6, 11.4, 11.4 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.5, 154.0, 153.3, 138.8, 128.8, 128.3, 126.3, 115.7, 114.9, 100.9, 73.7, 64.7, 61.6, 56.0, 38.4, 37.2, 36.0, 32.2, 31.1; ESI HRMS Calcd for $[C_{23}H_{29}NO_6 + Na]^+$: 438.1893, Found: 438.1893.

Dimethyl 3-{(2*R*,4*R*,6*R*)-6-[(4-methoxy-phenoxy)-ethyl]-2-phenyl-1,3-dioxan-4-yl}-2-oxopropyl phosphonate (8).



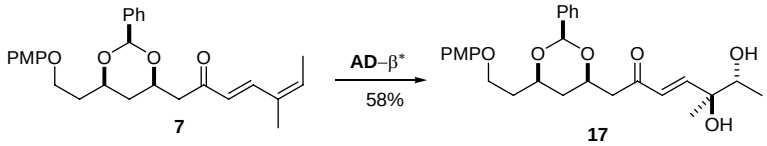
A solution of dimethyl methylphosphonate (1.42 g, 11.4 mmol) in THF (30 mL) was stirred at -78 °C under argon. To this solution was added *n*-BuLi (4.6 mL, 2.5 M in *n*-hexane, 11.5 mmol) dropwise and the mixture was stirred for 1 h. A solution of amide **16** (1.19 g, 2.86 mmol) in THF (1 mL) was added via cannula. The solution was stirred at -78 °C for 1h. The reaction was quenched by the addition of saturated aqueous NH_4Cl (20 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine (25 mL) and dried over anhydrous sodium sulfate. After removal of the solvents *in vacuo*, flash chromatography on silica gel (7:3 EtOAc/hexanes) afforded ketophosphonate **8** as a colorless oil (1.15 g, 84%): $[\alpha]^{25}_D$ +24.4 (*c* 0.75, CH_2Cl_2); R_f (100 % EtOAc) = 0.38; IR (thin film, cm^{-1}) 2955, 1717, 1508, 1231, 1025, 827, 701; ^1H NMR (600 MHz, $CDCl_3$) δ 7.46 (m, 2H), 7.34 (m, 3H), 6.84 (m, 4H), 5.57 (s, 1H), 4.40 (dddd, *J* = 12.6, 7.2, 7.2, 2.4 Hz, 1H), 4.14 (m, 2H), 4.05 (dddd, *J* = 13.2, 5.4, 5.4, 1.2 Hz, 1H), 3.78 (d, *J* = 6.6 Hz, 3H), 3.77 (s, 3H), 3.76 (d, *J* = 6.6 Hz, 3H), 3.17 (m, 2H), 3.03 (dd, *J* = 16.8, 7.2 Hz, 1H), 2.81 (dd, *J* = 16.2, 5.4 Hz, 1H), 2.04 (m, 2H), 1.77 (ddd, *J* = 13.2, 2.4, 2.4 Hz, 1H), 1.51 (ddd, *J* = 13.2, 11.4, 10.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 199.8, 199.7, 154.1, 153.2, 138.5, 128.9, 128.4, 126.2, 115.7, 114.9, 100.8, 73.6, 72.9, 64.6, 56.0, 53.3, 53.2, 53.1, 49.9, 42.9, 42.1, 36.7, 35.9; ESI HRMS Calcd for $[C_{24}H_{31}O_8P + Na]^+$: 501.1654, Found: 501.1656.

(3*E*,5*Z*)-1-{(2*R*,4*R*,6*R*)-6-[2-(4-Methoxy-phenoxy)-ethyl]-2-phenyl-1,3-dioxan-4-yl}-5-methylhepta-3,5-dien-2-one (7).



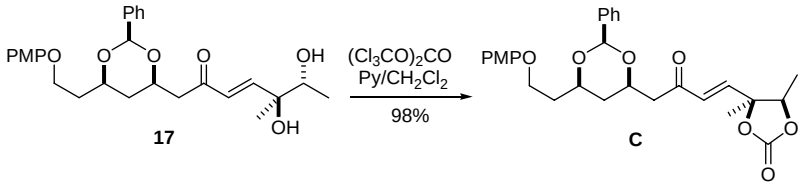
To a solution of ketophophonate **8** (3.1 g, 6.5 mmol) in 2-propanol (10 mL) at 0 °C was added Cs_2CO_3 (2.1 g, 6.4 mmol). The slurry was stirred for 5 min before angelaldehyde (1.09 g, 13.0 mmol) was added. The cloudy white reaction mixture was stirred for 3 h at room temperature. The mixture was diluted with ether (20 mL) and saturated aqueous NH_4Cl (20 mL). The layers were separated and the aqueous layer was extracted with ether (2 x 50 mL). The combined organic layers were washed with brine (25 mL), dried over anhydrous sodium sulfate, filtered and concentrated to an oil. Flash chromatography on silica gel (1:9 EtOAc/hexanes) afforded dienone **7** as a colorless oil (2.3 g, 82%): $[\alpha]^{25}_D$ +42 (*c* 0.5, CH_2Cl_2); R_f (30 % EtOAc/hexanes) = 0.55; IR (thin film, cm^{-1}) 2916, 2872, 1683, 1631, 1656, 1588, 1507, 1229, 1125, 1015, 825, 699; ^1H NMR (600 MHz, $CDCl_3$) δ 7.72 (d, *J* = 15.6 Hz, 1H), 7.49 (m, 2H), 7.35 (m, 3H), 6.86 (m, 4H), 6.24 (d, *J* = 15.6 Hz, 1H), 5.91 (q, *J* = 6.6 Hz, 1H), 5.61 (s, 1H), 4.45 (dddd, *J* = 13.2, 6.6, 6.0, 2.4 Hz, 1H), 4.16 (m, 2H), 4.07 (dddd, *J* = 10.8, 5.4, 5.4, 1.2 Hz, 1H), 3.12 (dd, *J* = 16.2, 6.6 Hz, 1H), 2.79 (dd, *J* = 16.2, 6.6 Hz, 1H), 2.06 (m, 2H), 1.87 (s, 3H), 1.86 (m, 4H), 1.55 (ddd, *J* = 12.6, 11.4, 11.4 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 198.4, 154.0, 153.2, 139.5, 138.7, 135.6, 132.0, 128.8, 128.3, 126.7, 126.2, 115.7,114.8, 100.7, 73.7, 73.6, 64.6, 55.9, 46.9, 37.2, 35.9, 20.1, 14.0; ESI HRMS Calcd for $[C_{27}H_{32}O_5 + Na]^+$: 459.2148, Found: 459.2150.

(*E*,5*S*,6*R*)-1-{(2*R*,4*R*,6*R*)-6-[2-(4-Methoxy-phenoxy)-ethyl]-2-phenyl-1,3-dioxan-4-yl}-5,6-dihydroxy-5-methylhept-3-en-2-one (17).



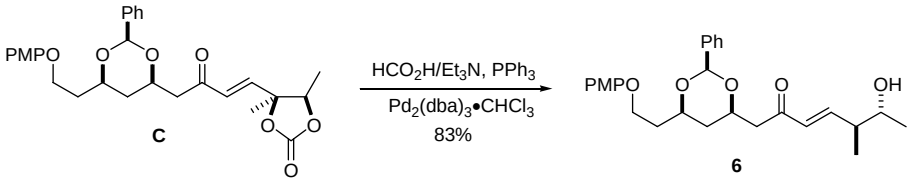
Into a 100 mL round bottom flask were added 10 mL of *t*-BuOH, 10 mL of water, $K_3Fe(CN)_6$ (1.11 g, 3.37 mmol), K_2CO_3 (0.46 g, 3.37 mmol), $NaHCO_3$ (0.3 g, 3.37 mmol), $MeSO_2NH_2$ (0.213 g, 1.12 mmol), $(DHQD)_2$-PHAL (26.2 mg, 0.036 mmol), and OsO_4 (5.7 mg, 0.024 mmol). The mixture was stirred at room temperature for about 15 minutes and then cooled to 0 °C. To this solution was added dienone **7** (0.49 g, 1.12 mmol) and the reaction was stirred vigorously at 0 °C for 5 h. The reaction was quenched with saturated aqueous sodium sulfite (10 mL). Ethyl acetate (20 mL) was added to the reaction mixture, and after separation of the layers, the aqueous phase was further extracted with ethyl acetate (2 x 20 mL). The combined organic layers were washed with brine and dried over anhydrous sodium sulfate. After removal of the solvents *in vacuo*, flash chromatography on silica gel (4:6 EtOAc/hexanes) afforded starting material dienone **7** (0.15 g, 30%) and diol **17** (0.31 g, 58%) as a colorless oil: $[\alpha]^{25}_D$ +37 (*c* 1.3, CH_2Cl_2); R_f (80 % EtOAc/hexanes) = 0.44; IR (thin film, cm^{-1}) 3452, 2934, 1665, 1628, 1508, 1230, 1017, 826, 700; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.46 (m, 2H), 7.33 (m, 3H), 6.85 (m, 5H), 6.43 (d, *J* = 16.2 Hz, 1H), 5.57 (s, 1H), 5.02 (br, 1H), 4.41 (dddd, *J* = 13.2, 6.0, 6.0, 1.8 Hz, 1H), 4.13 (m, 2H), 4.05 (dddd, *J* = 11.4, 6.0, 6.0, 2.4 Hz, 1H), 3.77 (s, 3H), 3.67 (q, *J* = 6.6 Hz, 1H), 3.07 (dd, *J* = 15.6, 6.6 Hz, 1H), 2.71 (dd, *J* = 16.2, 5.4 Hz, 1H), 2.36 (br, 1H), 2.05 (m, 2H), 1.80 (ddd, *J* = 13.2, 2.4, 2.4 Hz, 1H), 1.53 (ddd, *J* = 12.6, 11.4, 11.4 Hz, 1H), 1.29 (s, 3H), 1.12 (d, J = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 198.1, 154.0, 153.2, 149.0, 138.6, 129.4, 128.9, 128.3, 126.2, 115.7, 114.9, 100.8, 75.6, 73.9, 73.7, 73.4, 64.6, 55.9, 46.8, 37.0, 35.9, 24.4, 18.2; ESI HRMS Calcd for $[C_{27}H_{34}O_7 + Na]^+$: 493.2202, Found: 493.2204.

(4*S*,5*R*)-4-{(*E*)-4-[(2*R*,4*R*,6*R*)-6-[2-(4-Methoxy-phenoxy)-ethyl]-2-phenyl-1,3-dioxan-4-yl]-3-oxobut-1-enyl}-4,5-dimethyl-1,3-dioxolan-2-one (C).



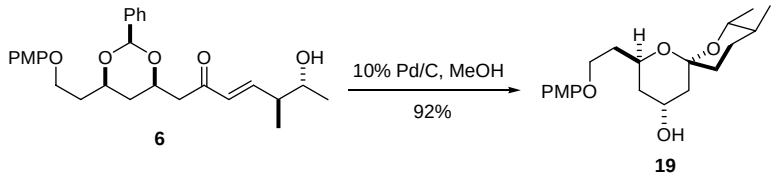
Into a 50 mL round-bottom flask were placed 0.46 g (0.98 mmol) of diol **17**, 10 mL of CH_2Cl_2, pyridine (0.39 g, 4.9 mmol), and DMAP (2 mg). The solution was cooled to -78 and triphosgene (0.2 g, 0.67 mmol) in 2 mL of CH_2Cl_2 was added dropwise. The reaction was stirred and warmed to 0 °C in 2 h and quenched with saturated aqueous NH_4Cl (10 mL). The layers were separated and the aqueous layer was extracted with ether (2 x 20 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate (10 mL), brine (20 mL), and dried over anhydrous sodium sulfate. After removal of the solvents *in vacuo*, flash chromatography on silica gel (2:8 EtOAc/hexanes) afforded carbonate **C** as a colorless oil (0.47 g, 98%): $[\alpha]^{25}_D$ +49 (*c* 1.5, CH_2Cl_2); R_f (60 % EtOAc/hexanes) = 0.65; IR (thin film, cm^{-1}) 2951, 2877, 1802, 1701, 1677, 1636, 1508, 1347, 1230, 1004, 827, 701; ^1H NMR (600 MHz, $CDCl_3$) δ 7.45 (m, 2H), 7.34 (m, 3H), 6.85 (m, 4H), 6.66 (d, *J* = 15.6 Hz, 1H), 6.63 (d, *J* = 15.6 Hz, 1H), 5.57 (s, 1H), 4.53 (q, *J* = 6.6 Hz, 1H), 4.41 (dddd, *J* = 13.2, 6.6, 6.6, 1.8 Hz, 1H), 4.15 (m, 2H), 4.06 (dddd, *J* = 10.8, 6.0, 6.0, 1.2 Hz, 1H), 3.77 (s, 3H), 3.04 (dd, *J* = 16.2, 7.8 Hz, 1H), 2.71 (dd, *J* = 16.2, 4.8 Hz, 1H), 2.05 (m, 2H), 1.80 (ddd, *J* = 12.6, 1.8, 1.8 Hz, 1H), 1.56 (s, 3H), 1.55 (ddd, *J* = 12.0, 11.4, 11.4 Hz, 1H), 1.24 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.7, 154.0, 153.3, 153.2, 140.4, 138.5, 130.1, 128.9, 128.4, 126.2, 115.7, 114.9, 100.8, 84.4, 81.9, 73.6, 73.3, 64.5, 55.9, 47.8, 37.0, 35.9, 24.4, 16.0; ESI HRMS Calcd for $[C_{28}H_{32}O_8 + Na]^+$: 519.1995, Found: 519.1997.

(*E*,5*S*,6*R*)-1-{(2*R*,4*R*,6*R*)-6-[2-(4-Methoxy-phenoxy)-ethyl]-2-phenyl-1,3-dioxan-4-yl}-6-dihydroxy-5-methylhept-3-en-2-one (6).



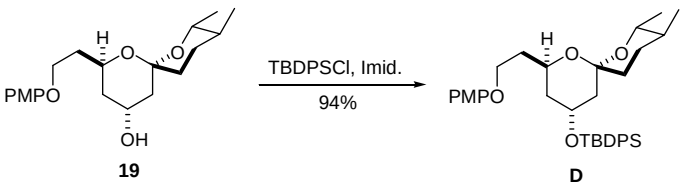
Into a 10 mL round bottomed flask maintained under argon were added $Pd_2(dba)_3{\cdot}CHCl_3$ (2.48 mg, 0.0024 mmol), PPh_3 (0.63 mg, 0.0024 mmol), THF (3 mL) and carbonate **C (**0.12 g, 0.24 mmol). Triethylamine (167 μL, 1.2 mmol) and HCO_2H (45 μL, 1.2 mmol) were added and the mixture was allowed to stir at room temperature until the color of the solution turned black. The reaction was quenched with saturated aqueous sodium bicarbonate (20 mL). The aqueous layer was extracted with ether (2 x 20 mL). The organic layers were combined, washed with brine (20 mL) and dried with anhydrous sodium sulfate. After removal of the solvents *in vacuo*, flash chromatography on silica gel (2:8 EtOAc/hexanes) provided alcohol **6** as a yellow oil (90 mg, 83%): $[\alpha]^{25}_D$ +8 (*c* 1.0, CH_3OH); R_f (60 % EtOAc/hexanes) = 0.53; IR (thin film, cm^{-1}) 3448, 2963, 2931, 1665, 1624, 1508, 1230, 1027, 826, 700; ^1H NMR (600 MHz, $CDCl_3$) δ 7.47 (m, 2H), 7.34 (m, 3H), 6.85 (m, 5H), 6.18 (d, *J* = 16.2 Hz, 1H), 5.58 (s, 1H), 4.41 (dddd, *J* = 13.2, 8.4, 6.6, 2.4 Hz, 1H), 4.15 (m, 2H), 4.06 (dddd, *J* = 10.8, 6.0, 6.0, 1.2 Hz, 1H), 3.77 (s, 3H), 3.72 (dq, *J* = 6.0, 6.0 Hz, 1H), 3.08 (dd, *J* = 16.2, 7.2 Hz, 1H), 2.71 (dd, *J* = 16.2, 6.0 Hz, 1H), 2.34 (m, 1H), 2.05 (m, 2H), 1.82 (ddd, *J* = 13.2, 2.4, 1.8 Hz, 1H), 1.53 (ddd, *J* = 13.2, 11.4, 10.8 Hz, 1H), 1.48 (br, 1H), 1.16 (d, *J* = 6.6 Hz, 3H), 1.09 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 198.0, 154.0, 153.3, 149.8, 138.7, 131.7, 128.9, 128.3, 126.3, 115.7, 114.9, 100.8, 73.7, 73.5, 71.0, 64.6, 56.0, 55.9, 64.2, 44.5, 37.2, 36.0, 21.0, 15.8; ESI HRMS Calcd for $[C_{27}H_{34}O_6 + Na]^+$: 477.2253, Found: 477.2255.

(2*S*,4*R*,6*R*,8*R*,9*S*)-4-Hydroxy-8,9-dimethyl-2-[2-(4-methoxy-phenoxy)-ethyl]-1,7-dioxaspiro[5.5]undecane (19).



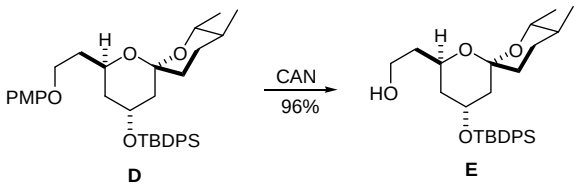
To a solution of alcohol **6** (0.63 g, 1.38 mmol) in methanol (15 mL) was added palladium on carbon (10%, 0.15 g, 0.14 mmol). The reaction mixture was stirred under H_2 (1 atm) for 12 h. Ethyl ether (20 ml) was added and the mixture was filtered through a pad of celite. After removal of the solvents *in vacuo*, flash chromatography on silica gel (2:8 EtOAc/hexanes) provided spiroketal **19** as a colorless solid (0.45 g, 92%): m.p. = 86-88 ^{o}C; $[\alpha]^{25}_{D}$ +67 (*c* 0.8, CH_2Cl_2); R_f (40 % EtOAc/hexanes) = 0.5; IR (thin film, cm^{-1}) 3510, 2930, 1509, 1231, 1086, 1041; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.83 (m, 4H), 4.26 (d, *J* = 10.2 Hz, 1H), 4.25 (dddd, *J* = 12.0, 9.6, 3.0, 2.4 Hz, 1H), 4.16 (dddd, *J* = 13.8, 10.2, 9.6, 4.8 Hz, 1H), 4.08 (ddd, *J* = 9.0, 3.0, 3.0 Hz, 1H), 4.02 (ddd, *J* = 9.0, 5.4, 3.6 Hz, 1H), 3.77 (s, 3H), 3.25 (dq, *J* = 10.2, 6.0 Hz, 1H), 2.00 (m, 1H), 1.85 (m, 3H), 1.60 (m, 2H), 1.49 (m, 4H), 1.17 (m, 1H), 1.06 (d, *J* = 6.0 Hz, 3H), 1.05 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 154.0, 153.4, 115.3, 114.9, 98.2, 72.0, 65.6, 64.1, 60.1, 56.0, 40.4, 38.7, 36.3, 35.8, 35.6, 27.6, 19.7, 17.6; ESI HRMS Calcd for $[C_{20}H_{30}O_5 + Na]^{+}$: 373.1992, Found: 373.1991.

(2*S*,4*R*,6*R*,8*R*,9*S*)-4-[(*tert*-Butyldiphenylsilyl)-oxy]-8,9-dimethyl-2-[2-(4-methoxy-phenoxy)-ethyl]-1,7-dioxaspiro[5.5]undecane (D).



Imidazole (0.12 g, 1.76 mmol) and TBDPSCl (0.22 g, 0.80 mmol) were added to a solution of alcohol **19** (0.20 g, 0.57 mmol) in DMF (6 ml). After stirring at 50 °C for 12 h, the mixture was cooled to room temperature and diluted with ether (20 mL) and water (10 mL). The organic layer was separated, washed with brine and dried (Na_2SO_4). After removal of the solvents *in vacuo*, flash chromatography on silica gel (1:19 EtOAc/hexanes) yielded TBDPS ether **D** (0.32 g, 94%) as a colorless oil: $[\alpha]^{25}_D$ +32 (*c* 2.4, CH_2Cl_2); R_f (10 % EtOAc/hexanes) = 0.42; IR (thin film, cm^{-1}) 3049, 2951, 2928, 1508, 1230, 1089, 822, 701; ^1H NMR (600 MHz, $CDCl_3$) δ 7.80 (m, 2H), 7.72 (m, 2H), 7.44 (m, 2H), 7.38 (m, 4H), 6.87 (m, 4H), 4.52 (m, 1H), 4.16 (m, 2H), 4.05 (ddd, *J* = 11.2, 5.4, 5.4 Hz, 1H), 3.80 (s, 3H), 3.31 (dq, *J* = 10.2, 6.6 Hz, 1H), 1.88 (m, 3H), 1.61 (m, 1H), 1.42-1.55 (m, 4H), 1.36 (ddd, *J* = 14.4, 12.0, 4.8 Hz, 1H), 1.29 (dd, *J* = 7.2, 7.2 Hz, 1H), 1.22 (m, 1H), 1.13 (d, *J* = 7.8 Hz, 3H), 1.12 (s, 9H), 0.64 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.9, 153.5, 136.3, 136.1, 134.9, 134.8, 129.7, 129.6, 127.7, 127.5, 115.4, 114.8, 96.3, 71.3, 66.1 64.6, 60.2, 56.0, 41.8, 38.9, 36.8, 36.5, 35.7, 28.2, 27.2, 19.8, 19.5, 18.0; ESI HRMS Calcd for $[C_{36}H_{48}O_5Si + Na]^+$: 611.3169, Found: 611.3172.

(2*R*,4*R*,6*R*,8*R*,9*S*)-4-[(*tert*-Butyldiphenylsilyl)-oxy]- 2-(2-hydroxyethyl)-8,9-dimethyl-1,7-dioxaspiro[5.5]undecane (E).



To a solution of **D** (0.32 g, 0.54 mmol) in CH_3CN-H_2O (5:1) (10 mL) at 0 °C was added ceric ammonium nitrate (0.60 g, 1.09 mmol). After 10 min the mixture was diluted with EtOAc (50 mL), washed with brine (20 mL), dried over Na_2SO_4, filtered, and evaporated. The residue was purified by flash chromatography (1:9 EtOAc/hexanes) on silica gel to give the expected product alcohol **E** (0.25 g, 96%) as a yellow oil: $[\alpha]^{25}_D$ +28 (*c* 2.4, CH_2Cl_2); R_f (30 %

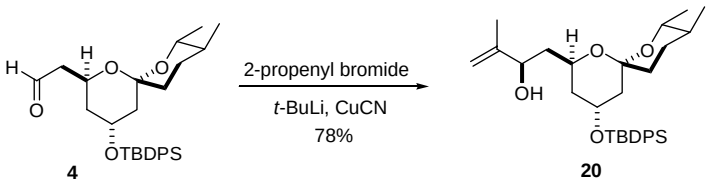
EtOAc/hexanes) = 0.54; IR (thin film, cm^{-1}) 3452, 3072, 2929, 2858, 1428, 1073, 701; ^1H NMR (600 MHz, $CDCl_3$) δ 7.77 (m, 2H), 7.68 (m, 2H), 7.43 (m, 2H), 7.37 (m, 4H), 4.43 (m, 1H), 4.10 (m, 1H), 3.83 (m, 2H), 3.43 (dq, *J* = 9.6, 6.0 Hz, 1H), 2.92 (br, 1H), 1.86 (ddd, *J* = 13.8, 2.4, 2.4 Hz, 1H), 1.70 (m, 2H), 1.38-1.55 (m, 7H), 1.27 (m, 1H), 1.26 (d, *J* = 6.0 Hz, 3H), 1.09 (s, 9H), 0.88 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 136.3, 136.0, 134.7, 134.6, 129.7, 129.6, 127.7, 127.6, 96.7, 71.8, 65.7, 65.4, 62.1, 41.6, 38.7, 37.7, 36.5 (2*C*), 28.3, 27.2, 19.9, 19.5, 18.2; ESI HRMS Calcd for $[C_{29}H_{42}O_4Si + Na]^+$: 505.2750, Found: 505.2752.

2-{(2*S*,4*R*,6*R*,8*R*,9*S*)-4-[(*tert*-Butyldiphenylsilyl)-oxy]-8,9-dimethyl-1,7-dioxaspiro [5.5]undecyl}-ethanal (4).

To a solution of alcohol **E** (0.25 g, 0.52 mmol) in CH_2Cl_2 (5 mL) at room temperature was added Dess-Martin periodinane (0.44 g, 1.04 mmol). The resulting mixture was stirred for 3 h before being quenched with saturated $Na_2S_2O_3 \cdot NaHCO_3$ (10 mL). The mixture was extracted with ether (2 x 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and evaporated. The residue was purified by flash chromatography (1:19 EtOAc/hexanes) on silica gel to give the expected product aldehyde **4** (0.23 g, 92%) as a colorless oil: $[\alpha]^{25}_D$ +43 (*c* 1.3, CH_2Cl_2); R_f (20 % EtOAc/hexanes) = 0.62; IR (thin film, cm^{-1}) 3048, 2956, 2929, 2858, 1729, 1428, 1083, 702; ^1H NMR (600 MHz, $CDCl_3$) δ 9.85 (dd, *J* = 3.0, 1.8 Hz, 1H), 7.76 (m, 2H), 7.67 (m, 2H), 7.41 (m, 2H), 7.35 (m, 4H), 4.72 (dddd, *J* = 13.2, 9.0, 4.2, 1.8 Hz, 1H), 4.10 (dddd, *J* = 6.6, 6.0, 3.0, 3.0 Hz, 1H), 3.37 (dq, *J* = 10.2, 6.6 Hz, 1H), 2.50 (ddd, *J* = 15.6, 9.0, 3.0 Hz, 1H), 2.40 (ddd, *J* = 15.6, 4.2, 1.8 Hz, 1H), 1.85 (ddd, *J* = 14.4, 2.4, 1.8 Hz, 1H), 1.59 (m, 1H), 1.47 (m, 4H), 1.38 (m, 2H), 1.26 (m, 1H), 1.23

(d, J = 6.0 Hz, 3H), 1.08 (s, 9H), 0.83 (d, J = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 201.8, 136.3, 136.0, 134.6, 134.5, 129.8, 129.6, 127.8, 127.6, 96.6, 71.9, 65.6, 60.2, 49.6, 41.4, 38.5, 36.7, 36.6, 27.9, 27.1, 19.9, 19.4, 18.2; ESI HRMS Calcd for $[C_{29}H_{40}O_4Si + Na]^+$: 503.2594, Found: 503.2586.

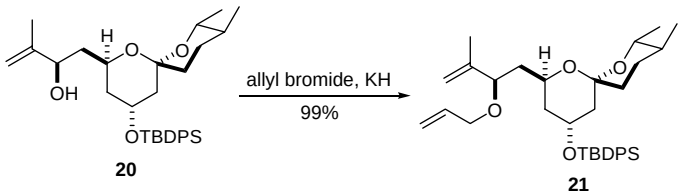
(2*R*)-1-{(2*R*,4*R*,6*R*,8*R*,9*S*)-4-[(*tert*-Butyldiphenylsilyl)-oxy]-8,9-dimethyl-1,7-dioxaspiro[5.5]undecyl}-3-methylbut-3-en-2-ol (20).



To 20 mL of ether at -78 °C under argon was added *t*-BuLi (1.5 M in pentane, 15.6 mL, 23.4 mmol) followed by addition of neat 2-propenyl bromide (1.04 ml, 11.76 mmol). The reaction mixture was stirred at -78 °C for 1 h before being transferred via cannula to another flask which was charged with CuCN (0.525g, 5.86 mmol) in ether (50 mL) at -78 °C under argon. The resulting mixture was stirred for 20 min at -78 °C and then warmed to 0 °C and stirred until all the CuCN dissolved. The solution was recooled to -78 °C and neat benzaldehyde (100 μL, 1 mmol) was added. After 10 min, aldehyde **4** (0.94 g, 1.96 mmol) in ether (3 mL) was added dropwise. After 10 min, the solution was warmed to 0 °C and quenched with saturated aqueous NH_4Cl (30 mL). The aqueous layer was extracted with ether (2 x 100 mL), and the combined organic layers were washed with NH_4OH and brine, dried over Na_2SO_4, filtered, and evaporated. The residue was purified by flash chromatography (1:19 EtOAc/hexanes) on silica gel to give the expected product alcohol **20** (0.80 g, 78%) as a colorless oil: $[\alpha]^{25}_D$ +31 (*c* 1.5, CH_2Cl_2); R_f (20 % EtOAc/hexanes) = 0.59; IR (thin film, cm^{-1}) 3436, 3071, 2928, 2858, 1450, 1428, 1378, 1111, 1076, 701; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.75 (m, 2H), 7.66 (m, 2H), 7.40 (m, 2H), 7.35 (m, 4H), 5.08 (s, 1H), 4.89 (s, 1H), 4.50 (dddd, J = 13.2, 10.8, 9.0, 4.2 Hz, 1H), 4.30 (m, 1H), 4.09 (dddd, J = 6.6, 6.6, 4.8, 4.8 Hz, 1H), 3.52

(dq, *J* = 9.6, 6.0 Hz, 1H), 3.14 (d, *J* = 4.2 Hz, 1H), 1.84 (m, 1H), 1.74 (m, 2H), 1.73 (s, 3H), 1.45-1.54 (m, 6H), 1.40 (dd, *J* = 13.8, 4.8 Hz, 1H), 1.26 (m, 1H), 1.19 (d, *J* = 6.0 Hz, 3H), 1.06 (s, 9H), 0.85 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 147.4, 136.3, 136.0, 134.7, 134.6, 129.7, 129.6, 127.7, 127.6, 110.7, 96.8, 72.9, 71.7, 65.8, 62.3, 41.7, 40.0, 38.4, 36.7, 36.6, 28.3, 27.1, 19.7, 19.4, 18.9, 18.3; ESI HRMS Calcd for $[C_{32}H_{46}O_4Si + Na]^+$: 545.3063, Found: 545.3065.

(2*R*) -2-(Allyloxy)-1-{(2*R*,4*R*,6*R*,8*R*,9*S*)-4-[(*tert*-butyldiphenylsilyl)-oxy]-8,9-dimethyl-1,7-dioxaspiro[5.5]undecyl}-3-methylbut-3-ene (21).

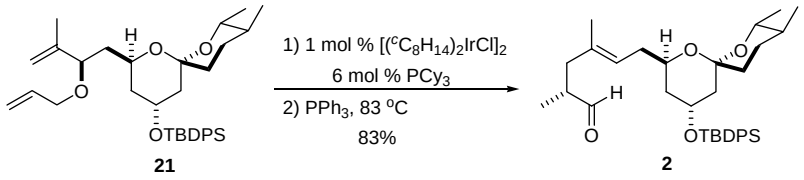


20 **21**

A 30 % suspension of KH in mineral oil (77 mg, equivalent to ca. 0.58 mmol of active hydride) was washed three times under argon with dry ether. Dry THF (2 mL) was then added, followed by addition of 18-crown-6 (1 mg) and a solution of alcohol **20** (0.15 g, 0.29 mmol) in dry THF (1 mL). The solution was stirred at room temperature for 10 min. Allyl bromide (52 μL, 0.58 mmol) was then added dropwise, followed by tetrabutylammonium iodide (1 mg). The reaction mixture was stirred for 3 h before being quenched with careful addition of water (5 mL). The aqueous layer was extracted with ether (2 x 20 mL), and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and evaporated. The residue was purified by flash chromatography (1:19 EtOAc/hexanes) on silica gel to give the allyl etherl **21** (0.16 g, 99%) as a colorless oil: $[\alpha]^{25}_D$ +40 (*c* 1.0, CH_2Cl_2); R_f (10 % EtOAc/hexanes) = 0.56; IR (thin film, cm^{-1}) 3072, 2951, 2927, 1428, 1106, 1071, 701; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.75 (m, 2H), 7.66 (m, 2H), 7.38 (m, 2H), 7.34 (m, 4H), 5.92 (dddd, *J* = 17.4, 16.2, 10.8, 5.4 Hz, 1H), 5.28 (ddd, *J* = 17.4, 3.0, 1.8 Hz, 1H), 5.13 (ddd, *J* = 10.2, 3.0, 1.8 Hz, 1H), 4.92 (s, 1H), 4.88 (dd, *J* = 1.8, 1.2 Hz, 1H), 4.39 (dddd, *J* = 13.2, 12.0,

3.0, 3.0 Hz, 1H), 4.06 (dddd, *J* = 6.6, 6.6, 3.0, 3.0 Hz, 1H), 3.98 (dd, *J* = 10.2, 3.0 Hz, 1H), 3.94 (dddd, *J* = 12.6, 5.4, 1.8, 1.2 Hz, 1H), 3.69 (dddd, *J* = 12.0, 5.4, 1.8, 1.2 Hz, 1H), 3.43 (dq, *J* = 9.6, 6.0 Hz, 1H), 1.80 (ddd, *J* = 13.8, 2.4, 2.4 Hz, 1H), 1.69 (m, 1H), 1,67 (s, 3H), 1.42-1.57 (m, 7H), 1.35 (dd, *J* = 13.8, 3.6 Hz, 1H), 1.26 (m, 1H), 1.18 (d, *J* = 6.6 Hz, 3H), 1.06 (s, 9H), 0.83 (d, *J* = 6.6 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 145.5, 136.4, 136.1, 135.2, 135.0, 134.8, 129.6, 129.5, 127.7, 127.5, 116.4, 113.2, 96.2, 80.1, 71.3, 69.4, 66.1, 60.5, 41.8, 41.5, 39.3, 36.9, 36.7, 28.3, 27.2, 19.9, 19.5, 18.4, 16.9; ESI HRMS Calcd for $[C_{35}H_{50}O_4Si + Na]^+$: 585.3376, Found: 585.3380.

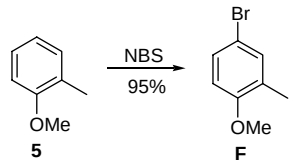
(5*R*)-1-{(2*R*,4*R*,6*R*,8*R*,9*S*)-4-[(*tert*-Butyldiphenylsilyl)-oxy]-8,9-dimethyl-1,7-dioxaspiro[5.5]undecan-2-yl}-3,5-dimethyl-2(*E*)-hexen-6-al (2).



A solution of $[(^cC_8H_{14})_2IrCl]_2$ (1.27 mg, 1.4 μmol) and PCy_3 (2.39 mg, 8.5 μmol) in CH_2Cl_2 (0.1 mL) was added to a solution of $NaBPh_4$ (0.97 mg, 2.8 μmol) in 1,2-DCE/acetone (25:1) (2 mL). The resulting yellow solution was stirred for 5 min at room temperature. Allyl ether **21** (80 mg, 0.14 mmol) in 1,2-DCE (1 mL) was added and the reaction mixture was stirred for 30 min before the addition of PPh_3 (2.23 mg, 8.5 μmol). The resulting solution was heated at reflux (83 °C) for 24 h. Evaporating the solvent provided the crude aldehyde product that was used in the subsequent reaction without purification. For characterization purposes, the solvent was removed in vacuo and the residue was purified by flash chromatography (1:19 ether/hexanes) on florisil to give the aldehyde **2** (66 mg, 83%) as a yellow oil: $[\alpha]^{25}_D$ +24 (*c* 0.9, CH_2Cl_2); R_f (15 % EtOAc/hexanes) = 0.66; IR (thin film, cm^{-1}) 3071, 2928, 1728, 1428, 1377, 1105, 1073, 991, 701; ^{1}H NMR (600 MHz, Acetone-d_6) δ 9.61 (d, *J* = 1.8 Hz, 1H), 7.79 (m, 2H), 7.70 (m, 2H), 7.44 (m, 2H), 7.41 (m, 4H), 5.36 (dd, *J* = 7.8, 6.6 Hz, 1H), 4.20 (dddd,

J = 12.6, 9.0, 6.6, 1.8 Hz, 1H), 4.15 (dddd, *J* = 6.0, 6.0, 3.0, 3.0 Hz, 1H), 3.48 (dq, *J* = 9.6, 6.0 Hz, 1H), 1.21 (d, *J* = 6.6 Hz, 3H), 1.08 (s, 9H), 1.02 (d, *J* = 7.2 Hz, 3H), 0.84 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, Acetone-d_6) δ 206.7, 137.5, 137.3, 136.0, 135.9, 134.9, 131.2, 131.0, 129.1, 129.0, 125.1, 97.5, 72.5, 67.7, 65.3, 45.9, 45.6, 42.8, 42.2, 39.6, 38.1, 35.8, 29.4, 28.1, 20.8, 20.5, 19.0, 17.0, 14.2; ESI HRMS Calcd for $[C_{35}H_{50}O_4Si + Na]^+$: 585.3376, Found: 585.3368.

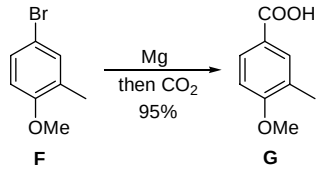
1-Bromo-4-methoxy-3-methylbenzene (F).[1]



5 **F**

To a stirred solution of 2-methylanisol **5** (3.67 g, 30.0 mmol) in CH_3CN at rt was added NBS (5.87 g, 33.0 mmol). After 1 h, the solvent was removed and the residue was dissolved in ether (100 mL). The organic layer was washed with water (100 mL), brine (20 mL) and dried with anhydrous sodium sulfate. After removal of the solvent *in vacuo*, the residue was recrystallized from hexane/ether to give bromide **F** (5.7 g, 95%) as a white solid: m.p. = 66-68 ^{o}C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.25 (m, 2H), 6.67 (m, 1H), 3.79 (s, 3H), 2.18 (s, 3H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 156.9, 133.2, 129.4, 129.0, 112.4, 111.5, 55.5, 16.2.

4-Methoxy-3-methylbenzoic acid (G).[2]



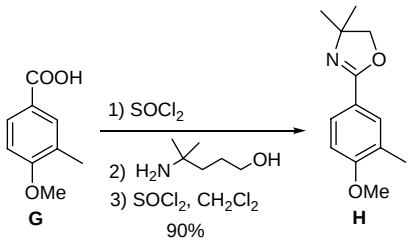
F **G**

[1] Carreno, M. C.; Ruano, J. L. G.; Sanz, G.; Toledo, M. A.; Urbano, A. *J. Org. Chem.* **1995**, *60*, 5328-5331.

[2] Tietze, L. F.; Stewart, S. G.; Polomska, M. E.; Modi, A.; Zeeck, A. *Chem. Eur. J.* **2004**, *10*, 5233-5242.

To a mixture of magnesium turnings (6.7 g, 0.28 mol), THF (300 mL), 1,2-dibromoethane (0.5 mL) was added a solution of bromide **F** (50 g, 0.25 mol) in THF (100 mL) slowly. The resulting mixture was refluxed for 5 h under argon. Then the Grignard reagent was added to dry ice (~500 g) over 1 h. When the addition was completed, the mixture was warmed to rt and water (500 mL) was added. The solution was acidified with H_2SO_4 (2M) to pH = 2. The solution was extracted with AcOEt (500 mL x 2). The organic layers were washed with water (200 mL), brine (200 mL) and dried with anhydrous sodium sulfate. After removal of the solvent *in vacuo*, the residue was recrystallized from AcOEt/hexane (1:1) to give acid **G** (39.2 g, 95%) as a white solid: m.p. = 194-196 ^oC; ^1H NMR (270 MHz, DMSO-d_6) δ 7.80 (dd, J = 8.7, 2.2 Hz, 1H), 7.73 (d, J = 2.2 Hz, 1H), 7.02 (d, J = 8.7 Hz, 1H), 3.84 (s, 3H), 3.45 (br, 1H), 2.17 (s, 3H); ^{13}C NMR (68 MHz, DMSO-d_6) δ 167.8, 161.5, 132.0, 129.8, 126.2, 122.9, 110.4, 56.1, 16.5.

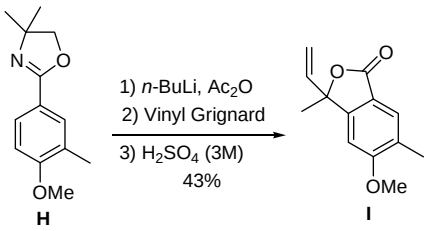
4,5-Dihydro-2-(4-methoxy-3-methylphenyl)-4,4-dimethyloxazole (H).[3]



Following the procedure reported by Smith et al., acid **G** (121 g, 0.73 mol) was converted into oxazoline **H** (144 g, 90%): ^1H NMR (600 MHz, $CDCl_3$) δ 7.72 (d, J = 1.8 Hz, 1H), 7.70 (dd, J = 8.4, 1.8 Hz, 1H), 7.76 (d, J = 8.4 Hz, 1H), 4.03 (s, 3H), 3.81 (s, 3H), 2.18 (s, 3H), 1.33 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.2, 160.3, 130.7, 127.5, 126.8, 120.1, 109.4, 79.1, 67.5, 55.5, 28.6, 16.1.

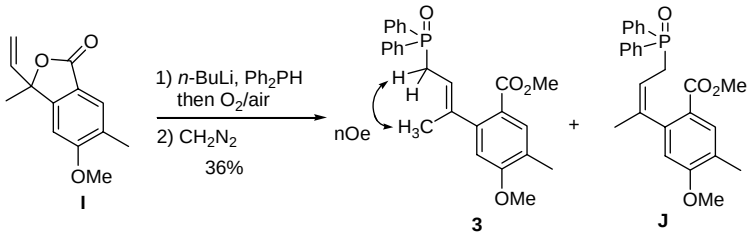
[3] Schow, S. R.; Bloom J. D.; Thompson, A. S.; Winzenberg, K. N.; Smith, A. B., III. *J. Am. Chem. Soc.* **1986**, *108*, 2662-2674.

3-Ethenyl-5-methoxy-3,6-dimethyl-1(3*H*)-isobenzofuranone (I).



Following the procedure reported by Smith et al., oxazoline **H** was transformed to lactone **I** (43%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.56 (s, 1H), 6.67 (s, 1H), 5.99 (dd, *J* = 16.8, 10.8 Hz, 1H), 5.37 (d, *J* = 17.4 Hz, 1H), 5.16 (d, *J* = 10.8 Hz, 1H), 3.90 (s, 3H), 2.22 (s, 3H), 1.68 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.9, 163.3, 153.8, 138.5, 129.3, 127.2, 117.0, 115.4, 102.0, 85.8, 56.0, 25.4, 16.7.

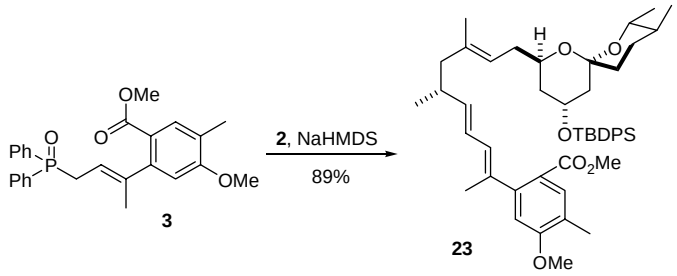
Methyl 2-[3-(diphenylphosphinyl)-1-propenyl]-4-methoxy-5-methyl-(*E*)-benzoate (3).



Following the procedure reported by Smith et al., lactone **I** was converted into phosphine oxide **3**[4] (36%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.78 (m, 4H), 7.62 (s, 1H), 7.49 (m, 6H), 6.30 (s, 1H), 5.34 (dd, *J* = 14.4, 6.6 Hz, 1H), 3.75 (s, 6H), 3.25 (dd, *J* = 15.0, 7.8 Hz, 2H), 2.14 (s, 3H), 1.84 (d, *J* = 1.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.3, 160.4, 147.0, 146.9, 143.4, 143.3, 133.6, 132.9, 132.9, 132.0, 131.9, 131.3, 131.2, 128.8, 128.7, 125.3, 120.0, 115.8, 115.8, 111.6, 111.6, 55.6, 51.8, 31.7, 31.2, 19.2, 19.2, 15.8.

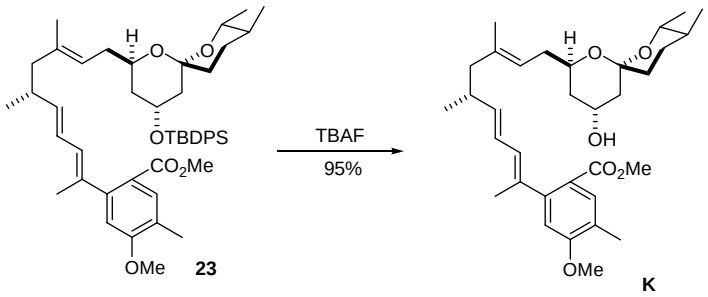
[4] In the paper by Smith (ref. 3) the data for phosphine oxides **3** and **J** were switched. This assignment was confirmed by an nOe experiment on phosphine oxide **3**.

Methyl 2-{(5*R*)-9-[(2*R*,4*R*,6*R*,8*R*,9*S*)-4-[(*tert*-butyldiphenylsilyl)-oxy]-8,9-dimethyl-1,7-dioxaspiro[5.5]undecan-2-yl]-1,5,7-trimethyl-1(*E*),3(*E*),7(*E*)-nonatrien-1-yl}-4-methoxy-5-methylbenzoate (23).



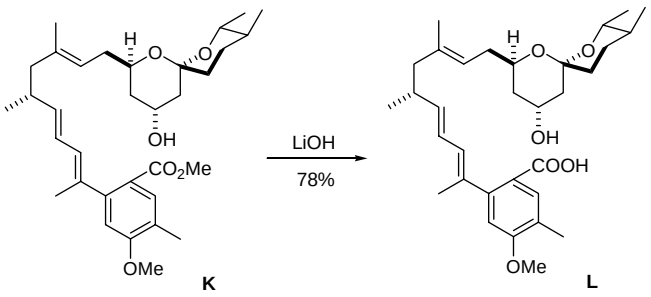
To a solution of phosphine oxide **3** (158 mg, 364 μmol) in THF (2 mL) under argon at -78 °C was added sodium hexamethyldisilazide in THF (2 M, 0.16 mL, 320 μmol). After 10 min, aldehyde **2** (66 mg, 117 μmol) in THF (1 mL) was added dropwise. The resulting mixture was stirred at -78 °C for 20 min before warmed to room temperature and stirred for 1 h. The reaction was quenched with saturated aqueous NH_4Cl (10 mL). The aqueous layer was extracted with ether (2 x 20 mL), and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and evaporated. The residue was purified by flash chromatography (1:9 EtOAc/hexanes) on silica gel to give the expected product dien **23** (81 mg, 89%) as a colorless oil: $[\alpha]^{25}_D$ +19 (*c* 0.8, CH_2Cl_2); R_f (15 % EtOAc/hexanes) = 0.55; IR (thin film, cm^{-1}) 2954, 2928, 1718, 1607, 1560, 1428, 1257, 1152, 1104, 907, 730. 701; ^1H NMR (600 MHz, $CDCl_3$) δ 7.74 (m, 2H), 7.65 (s, 1H), 7.64 (m, 2H), 7.39 (m, 2H), 7.32 (m, 4H), 6.60 (s, 1H), 6.34 (dd, *J* = 15.0, 10.8 Hz, 1H), 5.92 (d, *J* = 10.8 Hz, 1H), 5.66 (dd, *J* = 15.0, 7.2 Hz, 1H), 5.24 (dd, *J* = 7.2, 6.6 Hz, 1H), 4.15 (m, 1H), 4.06 (m, 1H), 3.83 (s, 3H), 3.79 (s, 3H), 3.43 (dq, *J* = 10.8, 6.0 Hz, 1H), 2.43 (m, 1H), 2.19 (s, 3H), 2.18 (m, 2H), 2.08 (ddd, *J* = 13.8, 4.8, 4.8 Hz, 1H), 2.05 (s, 3H), 1.90 (dd, *J* = 12.6, 8.4 Hz, 1H), 1.81 (m, 1H), 1.61 (s, 3H), 1.34-1.59 (m, 7H), 1.25 (m, 3H), 1.19 (d, *J* = 6.0 Hz, 3H), 1.05 (s, 9H), 0.98 (d, *J* = 6.6 Hz, 3H), 0.83 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.0, 160.4, 147.5, 141.1, 137.5, 136.3, 136.1, 135.1, 134.9, 134.8, 132.9, 129.6, 129.5, 127.7, 127.6, 127.5, 125.1, 124.6, 123.0, 120.8, 111.2, 96.4, 71.3, 66.2, 64.3, 55.7, 51.9, 47.7, 41.8, 38.5, 36.8, 36.7, 35.2, 34.7, 28.1, 27.1, 19.9, 19.8, 19.5, 19.0, 18.3, 16.6, 15.9; ESI HRMS Calcd for $[C_{49}H_{66}O_6Si + Na]^+$: 801.4526, Found: 801.4517.

Methyl 2-{(5*R*)-9-[(2*R*,4*R*,6*R*,8*R*,9*S*)-4-hydroxy-8,9-dimethyl-1,7-dioxaspiro [5.5]undecan-2-yl]-1,5,7-trimethyl-1(*E*),3(*E*),7(*E*)-nonatrien-1-yl}-4-methoxy-5-methylbenzoate (K).



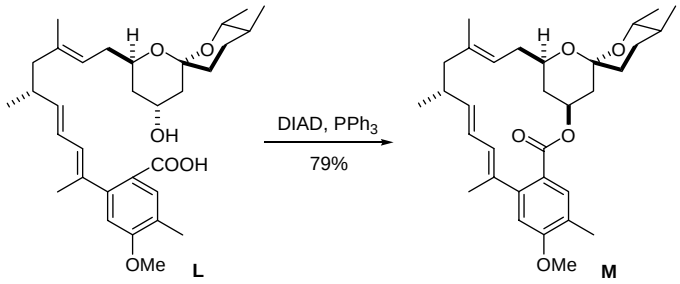
To a solution of TBDPS ether **23** (81 mg, 104 μmol) in THF (5 mL) under argon was added TBAF (1 M in THF, 1 ml). The mixture was warmed to 50 °C and stirred for 24 h. The reaction was cooled to room temperature and quenched with saturated aqueous $NaHCO_3$ (10 mL). The aqueous layer was extracted with ether (2 x 30 mL), and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and evaporated. The residue was purified by flash chromatography (15:85 EtOAc/hexanes) on silica gel to give the expected product alcohol **K** (53 mg, 95%) as a colorless oil: $[\alpha]^{25}_D$ +19 (*c* 0.95, CH_2Cl_2); R_f (30 % EtOAc/hexanes) = 0.58; IR (thin film, cm^{-1}) 3510, 2953, 2926, 1721, 1607, 1561, 1500, 1435, 1327, 1556, 1151, 1039, 965; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.62 (s, 1H), 6.60 (s, 1H), 6.31 (dd, *J* = 15.0, 10.8 Hz, 1H), 5.89 (d, *J* = 10.8 Hz, 1H), 5.62 (dd, *J* = 15.0, 7.2 Hz, 1H), 5.21 (dd, *J* = 7.2, 6.6 Hz, 1H), 4.19 (d, *J* = 1.8 Hz, 1H), 4.00 (dddd, *J* = 9.6, 9.6, 3.0, 3.0 Hz, 1H), 3.84 (m, 1H), 3.83 (s, 3H), 3.77 (s, 3H), 3.37 (dq, *J* = 9.6, 6.0 Hz, 1H), 2.41 (m, 1H), 2.23 (m, 1H), 2.17 (s, 3H), 2.11 (dd, *J* = 13.2, 6.0 Hz, 1H), 1.90 (dd, *J* = 13.2, 8.4 Hz, 1H), 1.78 (m, 1H), 1.60 (s, 3H), 1.35-1.59 (m, 7H), 1.22 (m, 1H), 1.11 (d, *J* = 6.0 Hz, 1H), 0.96 (d, *J* = 6.6 Hz, 3H), 0.80 (d, *J* = 6.6 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.0, 160.4, 147.5, 140.9, 137.5, 135.4, 132.9, 127.6, 125.1, 124.7, 122.4, 122.4, 120.7, 111.2, 98.3, 71.1, 65.6, 64.4, 55.7, 51.9, 47.8, 40.4, 38.2, 36.5, 35.9, 35.2, 34.6, 27.5, 20.0, 19.8, 19.0, 18.1, 16.6, 15.9; ESI HRMS Calcd for $[C_{33}H_{49}O_6 + Na]^+$: 563.3349, Found: 563.3340.

2-{(5*R*)-9-[(2*R*,4*R*,6*R*,8*R*,9*S*)-4-Hydroxy-8,9-dimethyl-1,7-dioxaspiro [5.5]undecan-2-yl]-1,5,7-trimethyl-1(*E*),3(*E*),7(*E*)-nonatrien-1-yl}-4-methoxy-5-methylbenzoic acid (L).



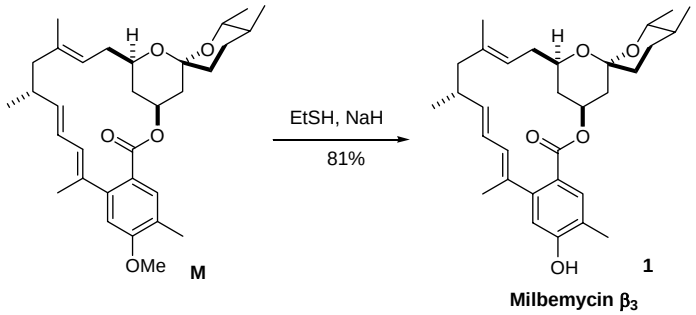
To a solution of ester **K** (53 mg, 98 μmol) in THF (1 mL) under argon was added methanol (2 mL) and LiOH (1.5 M, 1mL). The mixture was heated to 70 °C and stirred for 24 h. The resulting solution was cooled to room temperature and acidified to PH 2 by using HCl (1 M) solution. The solution was extracted with EtOAc (2 x 50 mL), and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and evaporated. The residue was purified by flash chromatography (4:6 EtOAc/hexanes) on silica gel to give the expected product acid **L** (40 mg, 78%) as a colorless oil: $[\alpha]^{25}_D$ +28 (*c* 1.3, CH_2Cl_2); R_f (40 % EtOAc/hexanes) = 0.37; IR (thin film, cm^{-1}) 3478, 3100 (br), 2928, 1686, 1606, 1560, 1446, 1381, 1249, 1154, 1039, 908, 730; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.70 (s, 1H), 6.60 (s, 1H), 6.29 (dd, *J* = 15.0, 10.8 Hz, 1H), 5.90 (d, *J* = 10.8 Hz, 1H), 5.57 (dd, *J* = 15.0, 7.8 Hz, 1H), 5.18 (dd, *J* = 7.2, 7.2 Hz, 1H), 4.09 (m, 1H), 3.80 (m, 1H), 3.84 (s, 3H), 3.38 (dq, *J* = 9.0, 6.0 Hz, 1H), 2.44 (m, 1H), 2.24 (m, 1H), 2.18 (s, 3H), 2.06 (s, 3H), 2.05 (m, 1H), 1.96 (dd, *J* = 13.2, 6.6 Hz, 1H), 1.81 (m, 2H), 1.61 (s, 3H), 1.50-1.59 (m, 5H), 1.44 (m, 1H), 1.35 (m, 1H), 1.23 (m, 2H), 1.33 (d, *J* = 6.0 Hz, 3H), 0.99 (d, *J* = 6.6 Hz, 3H), 0.81 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 160.4, 147.5, 140.6, 136.9, 135.5, 133.2, 127.6, 124.9, 124.8, 121.8, 120.3, 110.8, 98.1, 72.0, 65.4, 64.3, 64.2, 55.4, 47.7, 39.9, 37.6, 36.3, 35.6, 35.0, 34.6, 30.6, 27.2, 20.6, 19.6, 19.1, 18.8, 17.8, 16.3, 15.6, 13.6; ESI HRMS Calcd for $[C_{32}H_{46}O_6 + Na]^+$: 549.3192, Found: 549.3195.

5-*O*-Methylmilbemycin β_3 (M).



To a solution of hydroxy acid **L** (40 mg, 76 μmol) in benzene (20 mL) under argon was added PPh_3 (60 mg, 229 μmol). The solution was cooled to 8 °C and diisopropyl azodicarboxylate (30 μL, 152 μmol) in benzene (2mL) was added dropwise. The resulting mixture was stirred for 2 h and the solvent was removed *in vacuo*. The residue was purified by flash chromatography (1:29 EtOAc/hexanes) on silica gel to give the expected product macrolactone **M** (30 mg, 79%) as a colorless oil: $[\alpha]^{25}_D$ +84 (*c* 1.1, CH_2Cl_2); R_f (5 % EtOAc/hexanes) = 0.31; IR (thin film, cm^{-1}) 2958, 2927, 1706, 1608, 1501, 1447, 1378, 1257, 1163, 997, 731; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33 (d, *J* = 0.6 Hz, 1H), 6.60 (s, 1H), 6.12 (dd, *J* = 15.0, 10.8 Hz, 1H), 5.70 (d, *J* = 10.8 Hz, 1H), 5.48 (dddd, *J* = 16.2, 11.4, 9.6, 4.8 Hz, 1H), 5.25 (dd, *J* = 15.0, 9.6 Hz, 1H), 4.88 (dd, *J* = 10.8, 1.8 Hz, 1H), 3.80 (s, 3H), 3.67 (m, 1H), 3.27 (dq, *J* = 9.6, 6.0 Hz, 1H), 2.47 (m, 1H), 2.30 (m, 1H), 2.20 (m, 1H), 1.91-2.02 (m, 2H), 1.84 (dd, *J* = 7.2, 6.0 Hz, 1H), 1.64 (m, 1H), 1.62 (s, 3H), 1.44-1.56 (m, 3H), 1.37 (dd, *J* = 12.0, 12.0 Hz, 1H), 1.24 (m, 2H), 1.12 (d, *J* = 6.0 Hz, 3H), 1.01 (d, *J* = 6.6 Hz, 3H), 0.78 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.3, 159.1, 144.0, 140.2, 135.8, 134.8, 131.2, 128.6, 125.4, 125.2, 123.4, 121.5, 109.0, 97.7, 71.2, 68.0, 67.6, 55.4, 48.7, 41.2, 36.6 (2*C*), 36.3, 35.8, 33.9, 27.8, 21.6, 19.4, 18.2, 17.9, 16.1, 15.7; ESI HRMS Calcd for $[C_{32}H_{44}O_5 + Na]^+$: 531.3086, Found: 531.3089.

Milbemycin β_3 (1).



Sodium hydride (400 mg, 60% in mineral oil, 6 mmol) was washed with ether (2 x 3 mL) and dried under argon. DMF (2 mL) was added followed by the addition of 1:1 EtSH-DMF solution to consume all of the NaH. Methyl ether **M** (30 mg, 59 μmol) in DMF was added and the mixture heated to reflux for 1 h. The reaction mixture was cooled and quenched with saturated aqueous NH_4Cl (20 mL). The aqueous layer was extracted with ether (2 x 20 mL), and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and evaporated. The residue was purified by flash chromatography (1:9 EtOAc/hexanes) on silica gel to give the expected product milbemycin β_3 (**1**) (24 mg, 81%) as a light yellow solid, crystallization from CH_2Cl_2-hexane gave 22 mg of crystalline solid: m.p. = 182-184 °C (lit.[5] 181-183 °C); $[\alpha]^{25}_D$ +99 (*c* 0.25, MeOH) [lit. value[5] +102 (*c* 0.17, MeOH)]; R_f (30 % EtOAc/hexanes) = 0.59; IR (thin film, cm^{-1}) 3378, 2968, 2928, 1682, 1612, 1577, 1449, 1381, 1311, 1282, 1164, 1096, 1054, 998, 909; ^1H NMR (600 MHz, $CDCl_3$) δ 7.32 (s, 1H), 6.60 (s, 1H), 6.11 (dd, *J* = 15.0, 10.8 Hz, 5.70 (d, *J* = 10.8 Hz, 1H), 5.49 (m, 1H), 5.25 (dd, *J* = 14.4, 9.0 Hz, 1H), 5.05 (s, 1H), 4.88 (d, *J* = 5.6 Hz, 1H), 3.67 (m, 1H), 3.27 (dq, *J* = 9.6, 6.6 Hz,1H), 2.46 (m, 1H), 2.30 (m, 1H), 2.20 (s, 3H), 2.18 (m, 1H), 2.05 (s, 3H), 1.95 (m, 2H), 1.83 (dd, *J* = 12.6, 12.6 Hz, 1H), 1.62 (s, 3H), 1.52 (m, 3H), 1.38 (dd, *J* = 12.6, 12.0 Hz, 1H), 1.25 (m, 2H), 1.12 (d, *J* = 6.6 Hz, 3H), 1.01 (d, *J* = 6.6 Hz, 3H), 0.86 (m, 1H), 0.81 (d, *J* = 6.6 Hz, 3H), 0.76 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.4, 155.3, 144.1, 140.3, 135.8,

[5] Barrett, A. G. M.; Carr, R. A. E.; Attwood, S. V.; Richardson, G.; Walshe, N. D. A. *J. Org. Chem.* **1986**, *51*, 4840-4856.

134.0, 131.9, 128.8, 125.4, 124.2, 122.2, 121.4, 114.1, 97.7, 71.2, 68.1, 67.6, 48.7, 41.2, 36.6 (2*C*), 36.3, 35.8, 33.9, 27.8, 21.6, 19.4, 18.0, 17.9, 16.1, 15.2; ESI HRMS Calcd for $[C_{31}H_{42}O_5 + Na]^+$: 517.2930, Found: 517.2922.

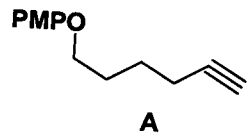
STANDARD PROTON PARAMETERS

Archive directory: /export/home/vnmr1/vnmrsys/data
Sample directory:
File: PROTON

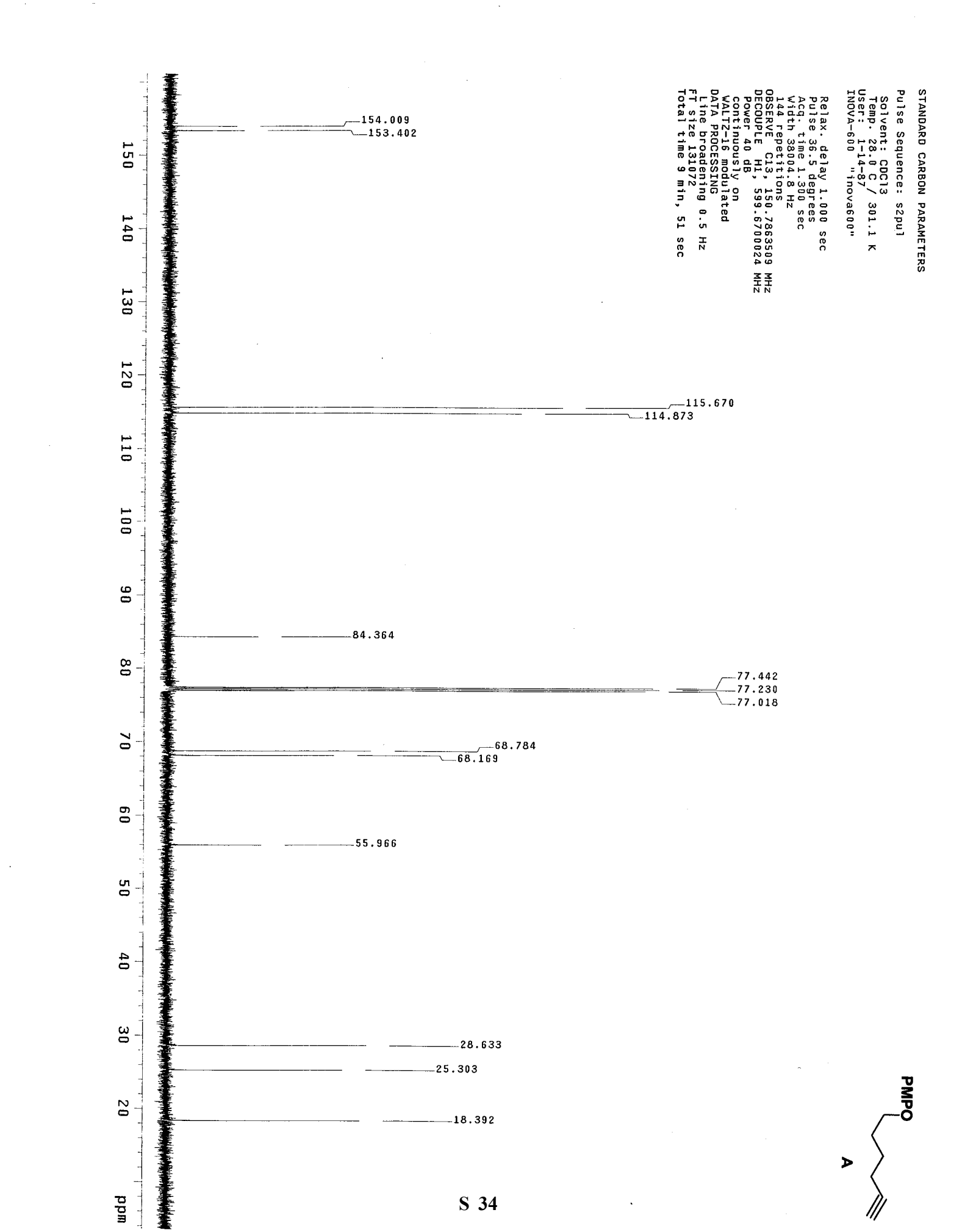
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 28.0 C / 301.1 K
INOVA-600 "inova600"

Relax. delay 1.000 sec
Pulse 26.9 degrees
Acq. time 1.892 sec
Width 9594.6 Hz
16 repetitions
OBSERVE H1, 599.6670139 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min, 46 sec



A


STANDARD CARBON PARAMETERS
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 28.0 C / 301.1 K
User: 1-14-87
INOVA-600 "inova600"
Relax. delay 1.000 sec
Pulse 36.5 degrees
Acq. time 1.300 sec
width 38004.8 Hz
144 repetitions
OBSERVE C13, 150.7863589 MHz
DECOUPLE H1, 599.6700024 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 131072
Total time 9 min, 51 sec
154.009
153.402
115.670
114.873
84.364
77.442
77.230
77.018
68.784
68.169
55.966
28.633
25.303
18.392
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm
PMPO
A

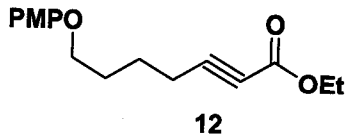
STANDARD PROTON PARAMETERS

Archive directory: /export/home/vnmr1/vnmrsys/data
Sample directory:
File: PROTON

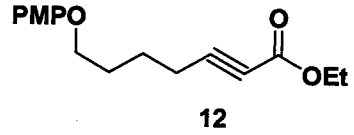
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 28.0 C / 301.1 K
INOVA-600 "inova600"

Relax. delay 1.000 sec
Pulse 26.9 degrees
Acq. time 1.892 sec
Width 9594.6 Hz
16 repetitions
OBSERVE H1, 599.6669894 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min, 46 sec



12



12

STANDARD CARBON PARAMETERS

Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 28.0 C / 301.1 K
User: 1-14-87
INOVA-600 "inova600"

Relax. delay 1.000 sec
Pulse 36.5 degrees
Acq. time 1.300 sec
Width 38004.8 Hz
328 repetitions
OBSERVE C13, 150.7863607 MHz
DECOUPLE H1, 599.6700024 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 131072
Total time 6 hr, 24 min, 53 sec

154.001
153.905
153.209
115.570
114.812
88.887
77.442
77.230
77.018
73.715
67.850
61.923
55.862
28.614
24.449
18.584
14.181

160 140 120 100 80 60 40 20 ppm

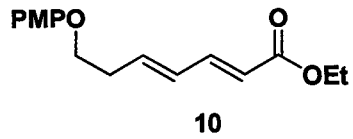
STANDARD PROTON PARAMETERS

Archive directory: /export/home/vnmr1/vnmrsys/data
Sample directory:
File: PROTON

Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 28.0 C / 301.1 K
INOVA-600 "inova600"

Relax. delay 1.000 sec
Pulse 26.9 degrees
Acq. time 1.892 sec
Width 9594.6 Hz
16 repetitions
OBSERVE H1, 599.6669888 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min, 46 sec



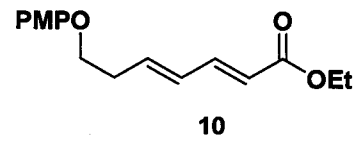
10

STANDARD CARBON PARAMETERS

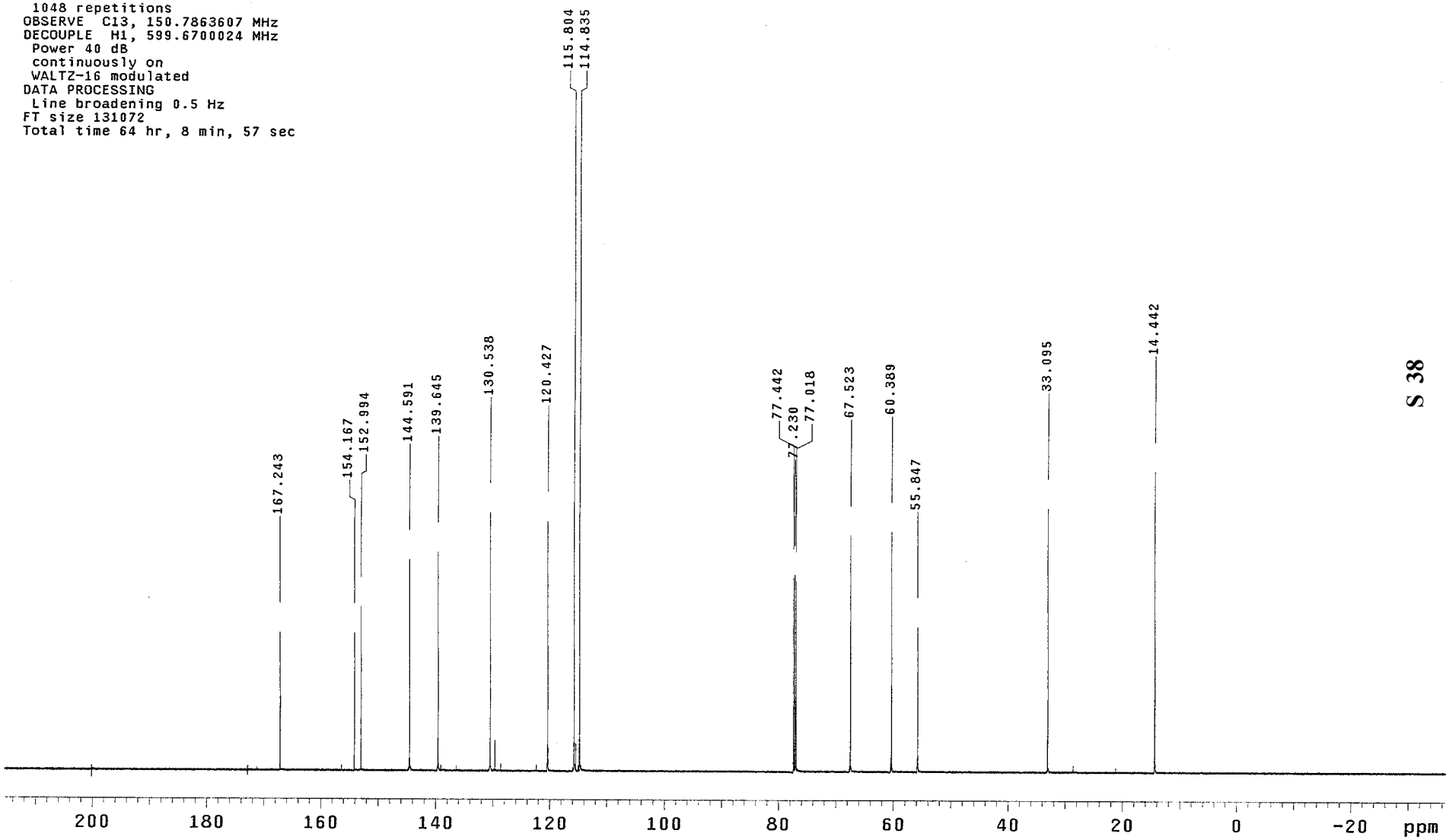
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 28.0 C / 301.1 K
User: 1-14-87
INOVA-600 "inova600"

Relax. delay 1.000 sec
Pulse 36.5 degrees
Acq. time 1.300 sec
Width 38004.8 Hz
1048 repetitions
OBSERVE C13, 150.7863607 MHz
DECOUPLE H1, 599.6700024 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 131072
Total time 64 hr, 8 min, 57 sec



10



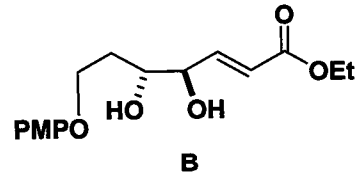
STANDARD PROTON PARAMETERS

Archive directory: /export/home/vnmr1/vnmrsys/data
Sample directory:
File: PROTON

Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 28.0 C / 301.1 K
INOVA-600 "inova600"

Relax. delay 1.000 sec
Pulse 26.9 degrees
Acq. time 1.892 sec
Width 9594.6 Hz
16 repetitions
OBSERVE H1, 599.6669897 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min, 46 sec



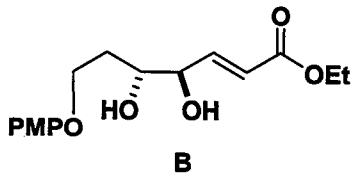
B

STANDARD CARBON PARAMETERS

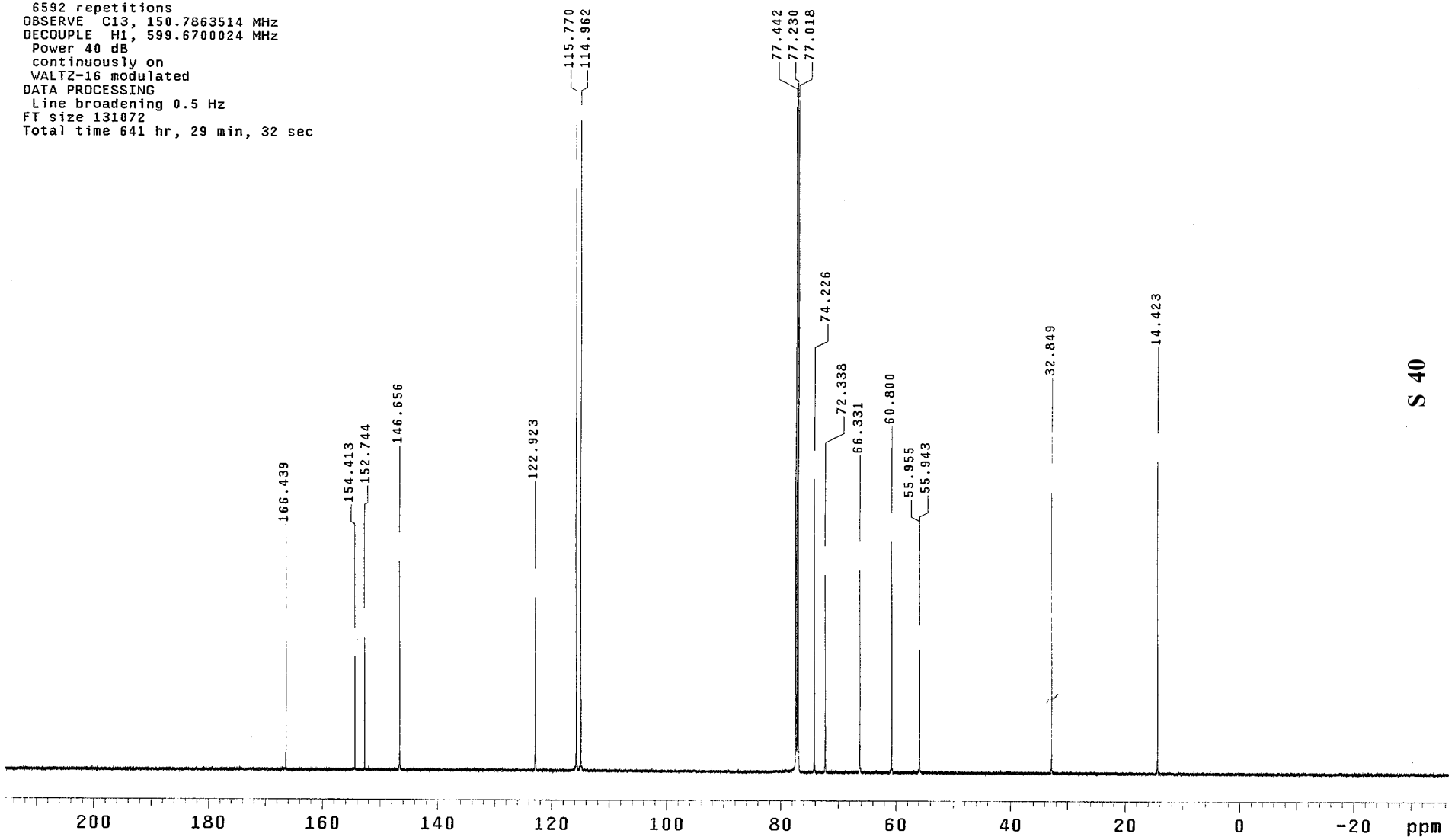
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 28.0 C / 301.1 K
User: 1-14-87
INOVA-600 "inova600"

Relax. delay 1.000 sec
Pulse 36.5 degrees
Acq. time 1.300 sec
Width 38004.8 Hz
6592 repetitions
OBSERVE C13, 150.7863514 MHz
DECOUPLE H1, 599.6700024 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 131072
Total time 641 hr, 29 min, 32 sec



B



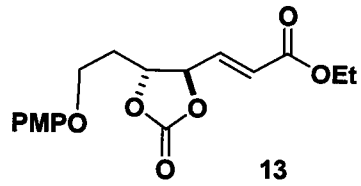
STANDARD PROTON PARAMETERS

Archive directory: /export/home/vnmr1/vnmrsys/data
Sample directory:
File: PROTON

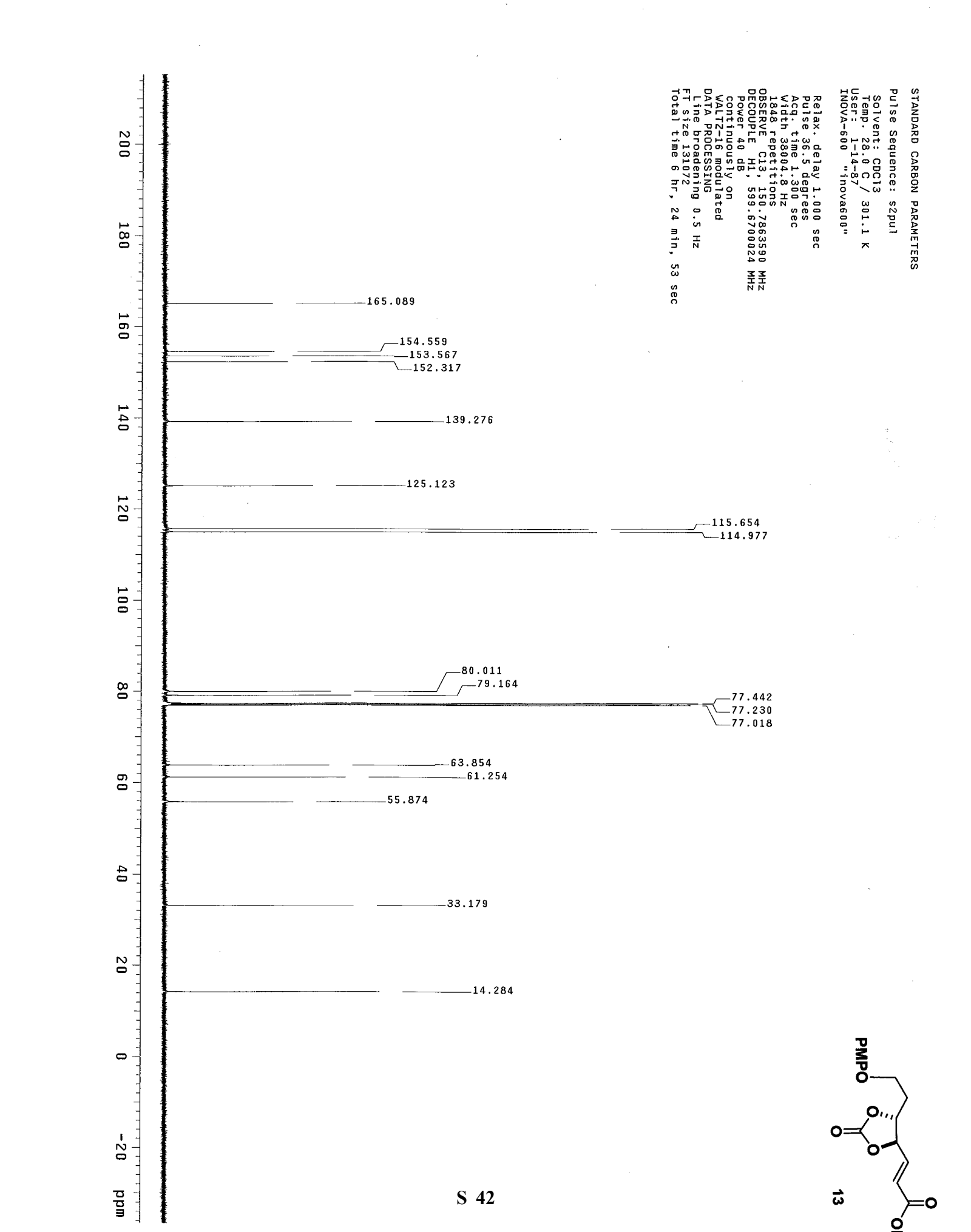
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 28.0 C / 301.1 K
INOVA-600 "inova600"

Relax. delay 1.000 sec
Pulse 26.9 degrees
Acq. time 1.892 sec
Width 9594.6 Hz
16 repetitions
OBSERVE H1, 599.6669885 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min, 46 sec



13


STANDARD CARBON PARAMETERS
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 28.0 C / 301.1 K
User: 1-14-87
INOVA-600 "inova600"
Relax. delay 1.000 sec
Pulse 36.5 degrees
Acq. time 1.300 sec
Width 38004.8 Hz
1848 repetitions
OBSERVE C13, 150.7863590 MHz
DECOUPLE H1, 599.6700024 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 131072
Total time 6 hr, 24 min, 53 sec
165.089
154.559
153.567
152.317
139.276
125.123
115.654
114.977
80.011
79.164
77.442
77.230
77.018
63.854
61.254
55.874
33.179
14.284
200
180
160
140
120
100
80
60
40
20
0
-20
ppm
PMPO
O
O
O
O
OEt
13

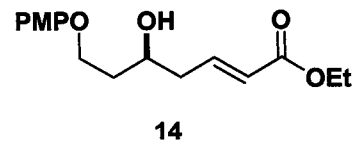
STANDARD PROTON PARAMETERS

Archive directory: /export/home/vnmr1/vnmrsys/data
Sample directory:
File: PROTON

Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 28.0 C / 301.1 K
INOVA-600 "inova600"

Relax. delay 1.000 sec
Pulse 26.9 degrees
Acq. time 1.892 sec
Width 9594.6 Hz
16 repetitions
OBSERVE H1, 599.6669888 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min, 46 sec



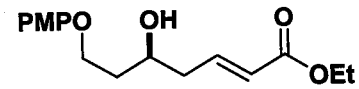
14

STANDARD CARBON PARAMETERS

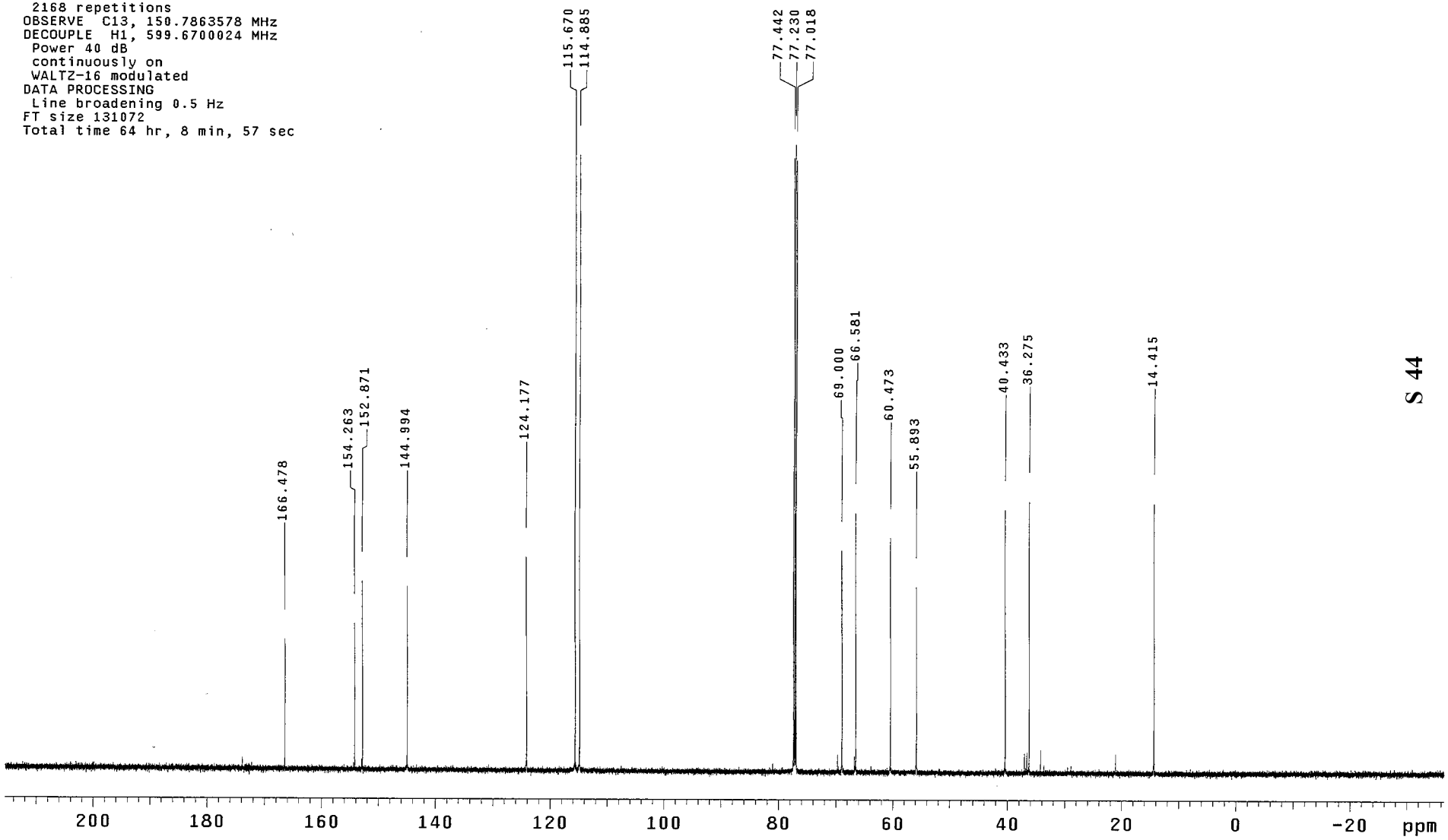
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 28.0 C / 301.1 K
User: 1-14-87
INOVA-600 "inova600"

Relax. delay 1.000 sec
Pulse 36.5 degrees
Acq. time 1.300 sec
Width 38004.8 Hz
2168 repetitions
OBSERVE C13, 150.7863578 MHz
DECOUPLE H1, 599.6700024 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 131072
Total time 64 hr, 8 min, 57 sec



14

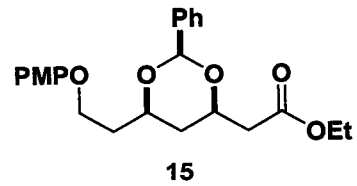


STANDARD PROTON PARAMETERS

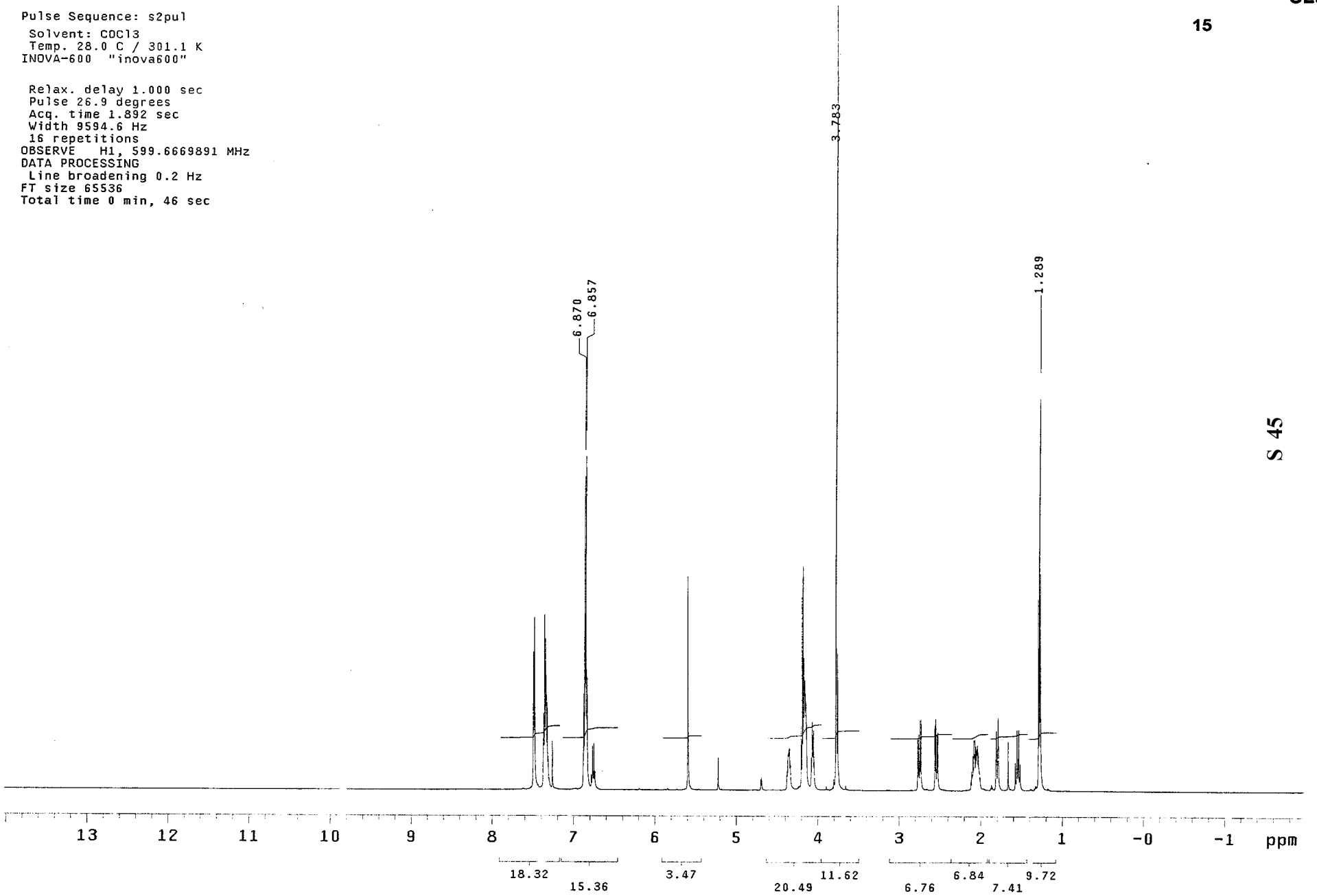
Archive directory: /export/home/vnmr1/vnmrsys/data
Sample directory:
File: PROTON

Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 28.0 C / 301.1 K
INOVA-600 "inova600"

Relax. delay 1.000 sec
Pulse 26.9 degrees
Acq. time 1.892 sec
Width 9594.6 Hz
16 repetitions
OBSERVE H1, 599.6669891 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min, 46 sec



15

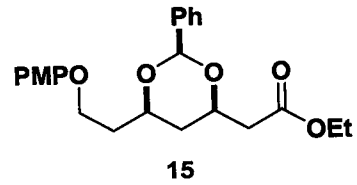


STANDARD CARBON PARAMETERS

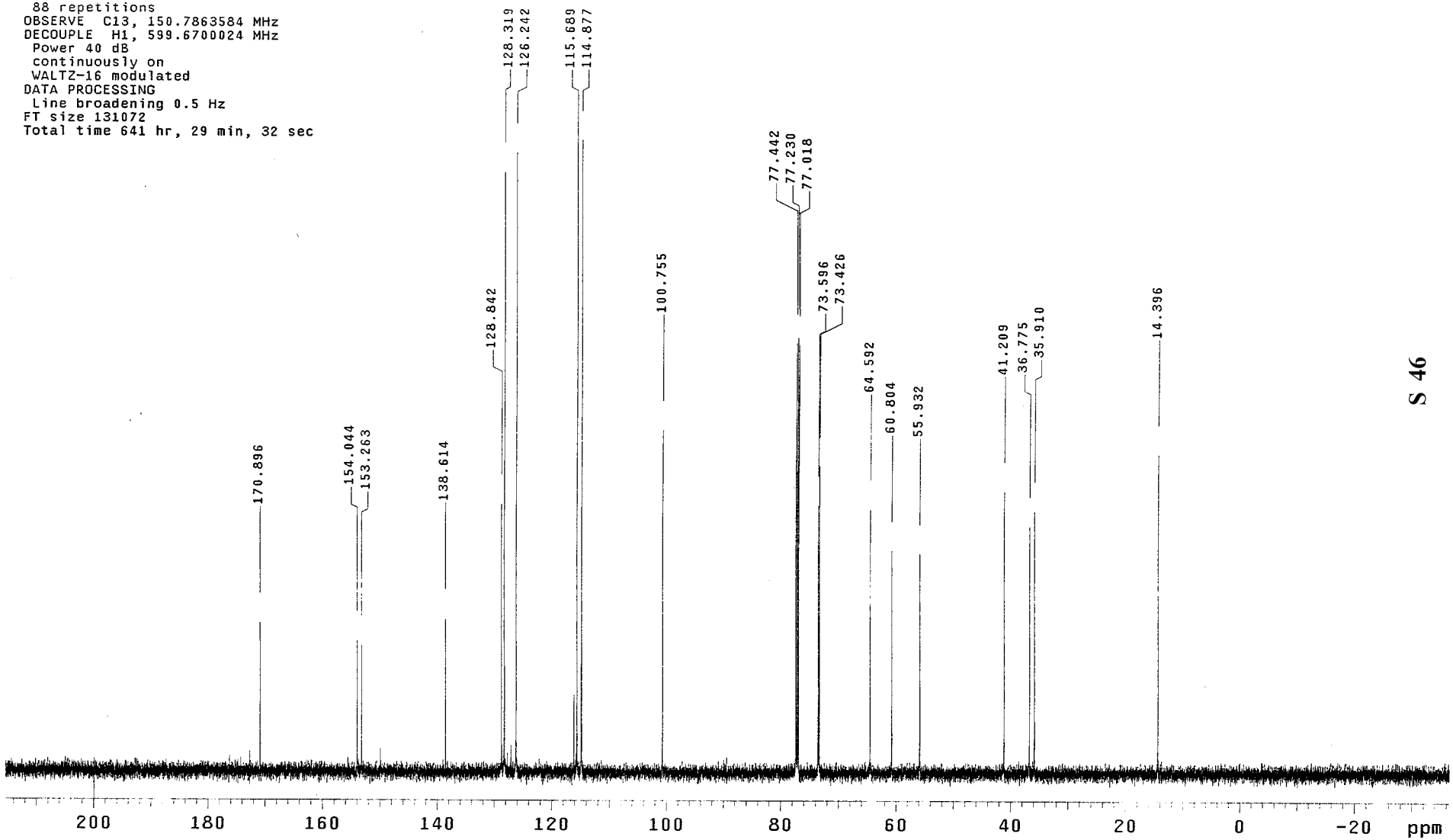
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 28.0 C / 301.1 K
User: 1-14-87
INOVA-600 "inova600"

Relax. delay 1.000 sec
Pulse 36.5 degrees
Acq. time 1.300 sec
Width 38004.8 Hz
88 repetitions
OBSERVE C13, 150.7863584 MHz
DECOUPLE H1, 599.6700024 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 131072
Total time 641 hr, 29 min, 32 sec



15



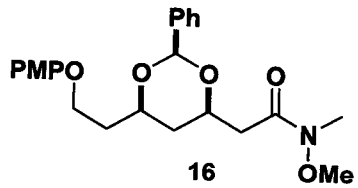
STANDARD PROTON PARAMETERS

Archive directory: /export/home/vnmr1/vnmrsys/data
Sample directory:
File: PROTON

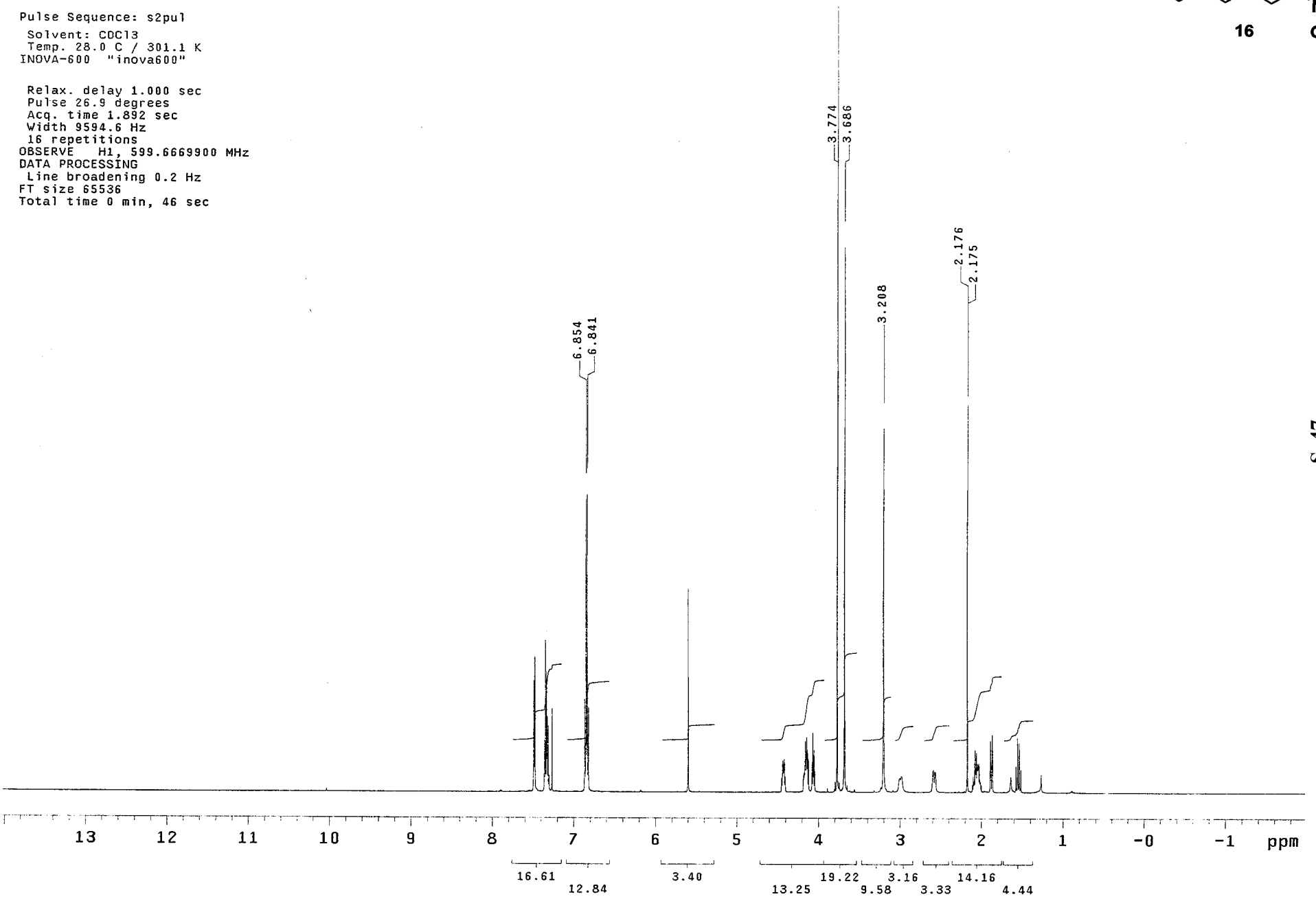
Pulse Sequence: s2pul

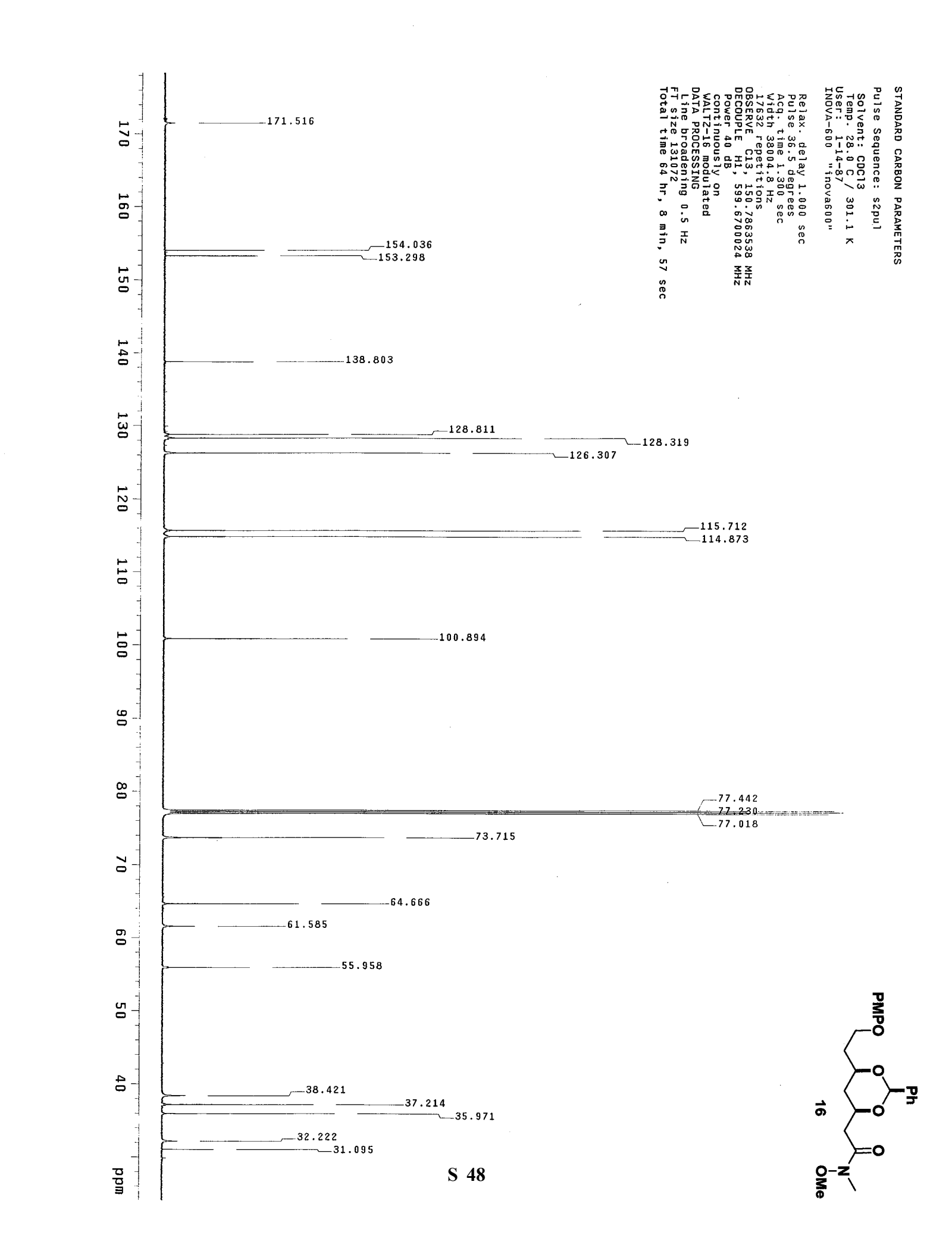
Solvent: CDCl3
Temp. 28.0 C / 301.1 K
INOVA-600 "inova600"

Relax. delay 1.000 sec
Pulse 26.9 degrees
Acq. time 1.892 sec
Width 9594.6 Hz
16 repetitions
OBSERVE H1, 599.6669900 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min, 46 sec



16




STANDARD CARBON PARAMETERS
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 28.0 C / 301.1 K
User: 1-14-87
INOVA-600 "inova600"
Relax. delay 1.000 sec
Pulse 36.5 degrees
Acq. time 1.300 sec
Width 38004.8 Hz
17632 repetitions
OBSERVE C13, 150.7863538 MHz
DECOUPLE H1, 599.6700024 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 131072
Total time 64 hr, 8 min, 57 sec
171.516
154.036
153.298
138.803
128.811
128.319
126.307
115.712
114.873
100.894
77.442
77.230
77.018
73.715
64.666
61.585
55.958
38.421
37.214
35.971
32.222
31.095
ppm
PMPO
Ph
16
OMe

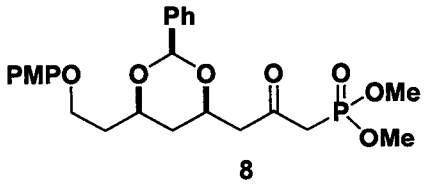
STANDARD PROTON PARAMETERS

Archive directory: /export/home/vnmr1/vnmrsys/data
Sample directory:
File: PROTON

Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 28.0 C / 301.1 K
INOVA-600 "inova600"

Relax. delay 1.000 sec
Pulse 26.9 degrees
Acq. time 1.892 sec
Width 9594.6 Hz
16 repetitions
OBSERVE H1, 599.6669897 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min, 46 sec



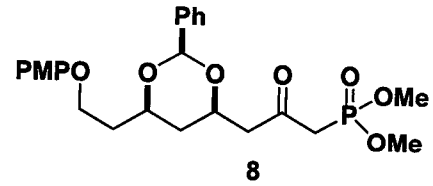
8

STANDARD CARBON PARAMETERS

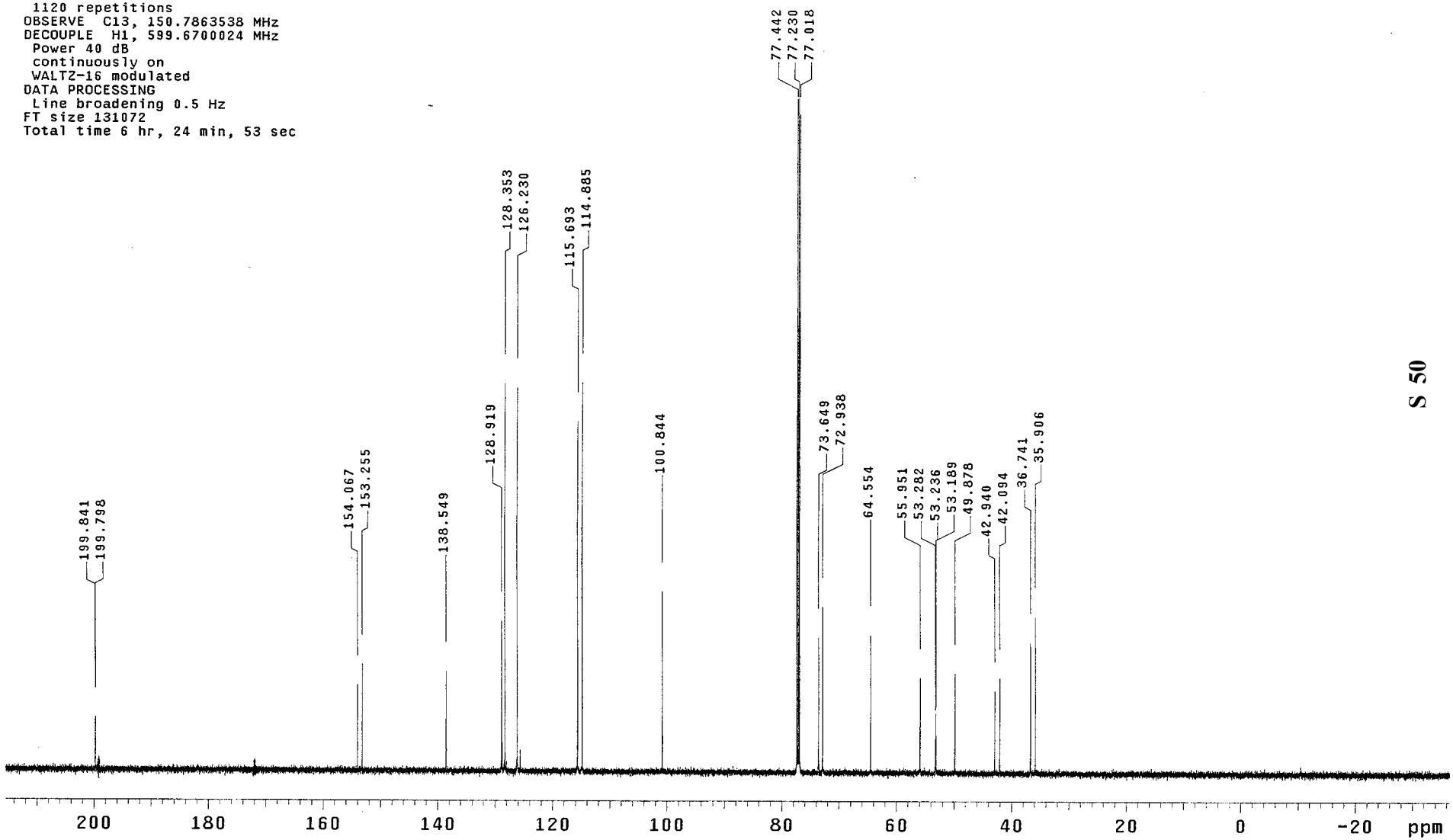
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 28.0 C / 301.1 K
User: 1-14-87
INOVA-600 "inova600"

Relax. delay 1.000 sec
Pulse 36.5 degrees
Acq. time 1.300 sec
Width 38004.8 Hz
1120 repetitions
OBSERVE C13, 150.7863538 MHz
DECOUPLE H1, 599.6700024 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 131072
Total time 6 hr, 24 min, 53 sec



8



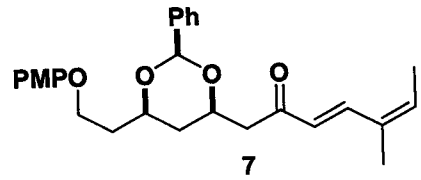
STANDARD PROTON PARAMETERS

Archive directory: /export/home/vnmr1/vnmrsys/data
Sample directory:
File: PROTON

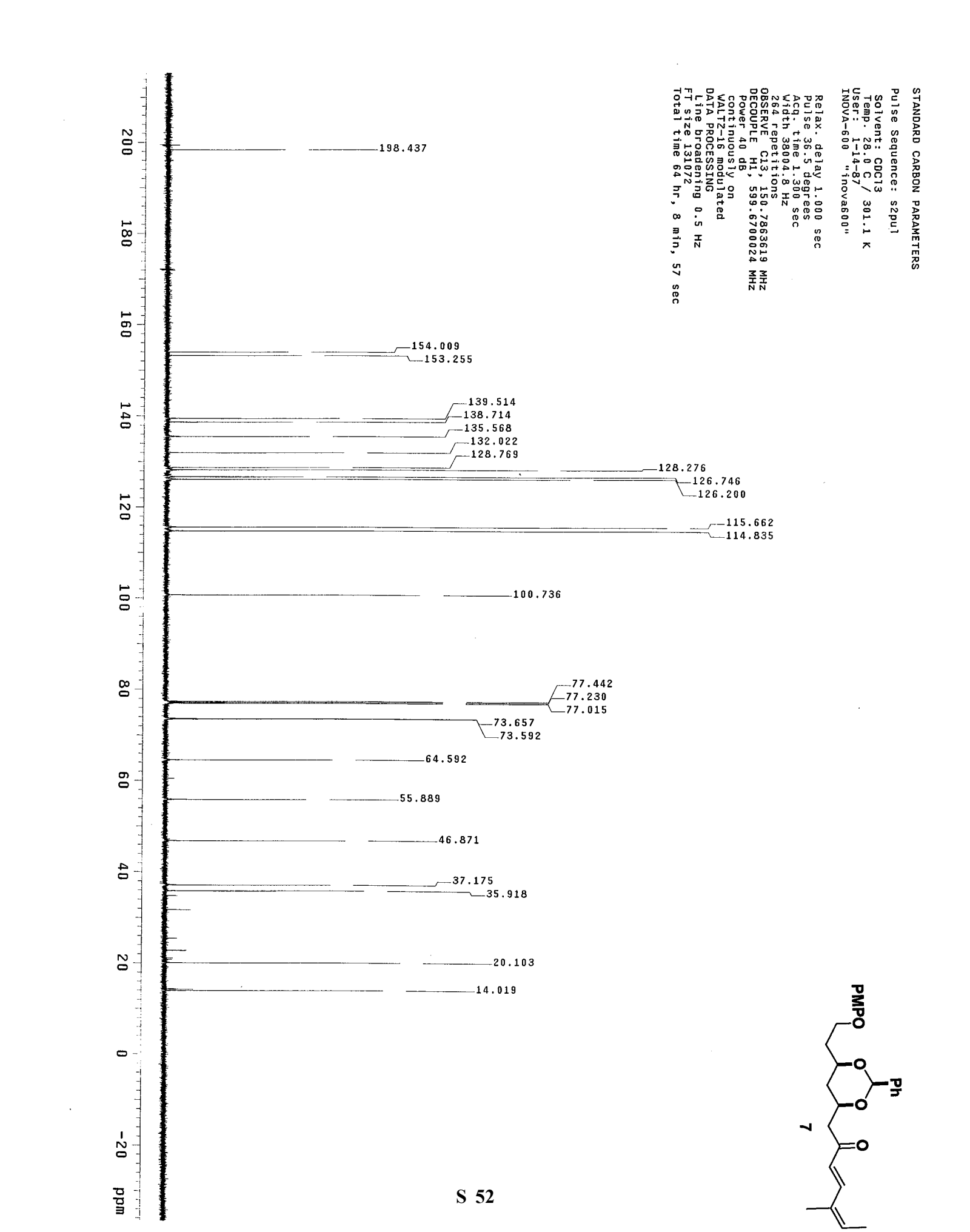
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 28.0 C / 301.1 K
INOVA-600 "inova600"

Relax. delay 1.000 sec
Pulse 26.9 degrees
Acq. time 1.892 sec
Width 9594.6 Hz
16 repetitions
OBSERVE H1, 599.6669891 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min, 46 sec



7


STANDARD CARBON PARAMETERS
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 28.0 C / 301.1 K
User: 1-14-87
INOVA-600 "inova600"
Relax. delay 1.000 sec
Pulse 36.5 degrees
Acq. time 1.300 sec
width 38004.8 Hz
264 repetitions
OBSERVE C13, 150.7863619 MHz
DECOUPLE H1, 599.6700024 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 131072
Total time 64 hr, 8 min, 57 sec
198.437
154.009
153.255
139.514
138.714
135.568
132.022
128.769
128.276
126.746
126.200
115.662
114.835
100.736
77.442
77.230
77.015
73.657
73.592
64.592
55.889
46.871
37.175
35.918
20.103
14.019
200
180
160
140
120
100
80
60
40
20
0
-20
ppm
PMPO
O
Ph
O
7
O

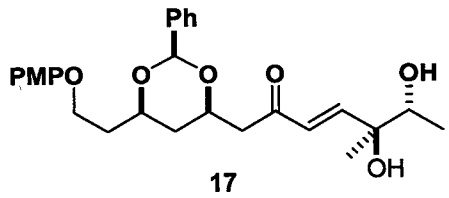
STANDARD PROTON PARAMETERS

Archive directory: /export/home/vnmr1/vnmrsys/data
Sample directory:
File: PROTON

Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 28.0 C / 301.1 K
INOVA-600 "inova600"

Relax. delay 1.000 sec
Pulse 26.9 degrees
Acq. time 1.892 sec
Width 9594.6 Hz
16 repetitions
OBSERVE H1, 599.6669897 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min, 46 sec

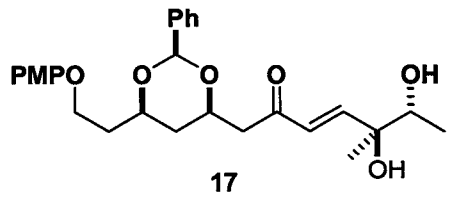


17

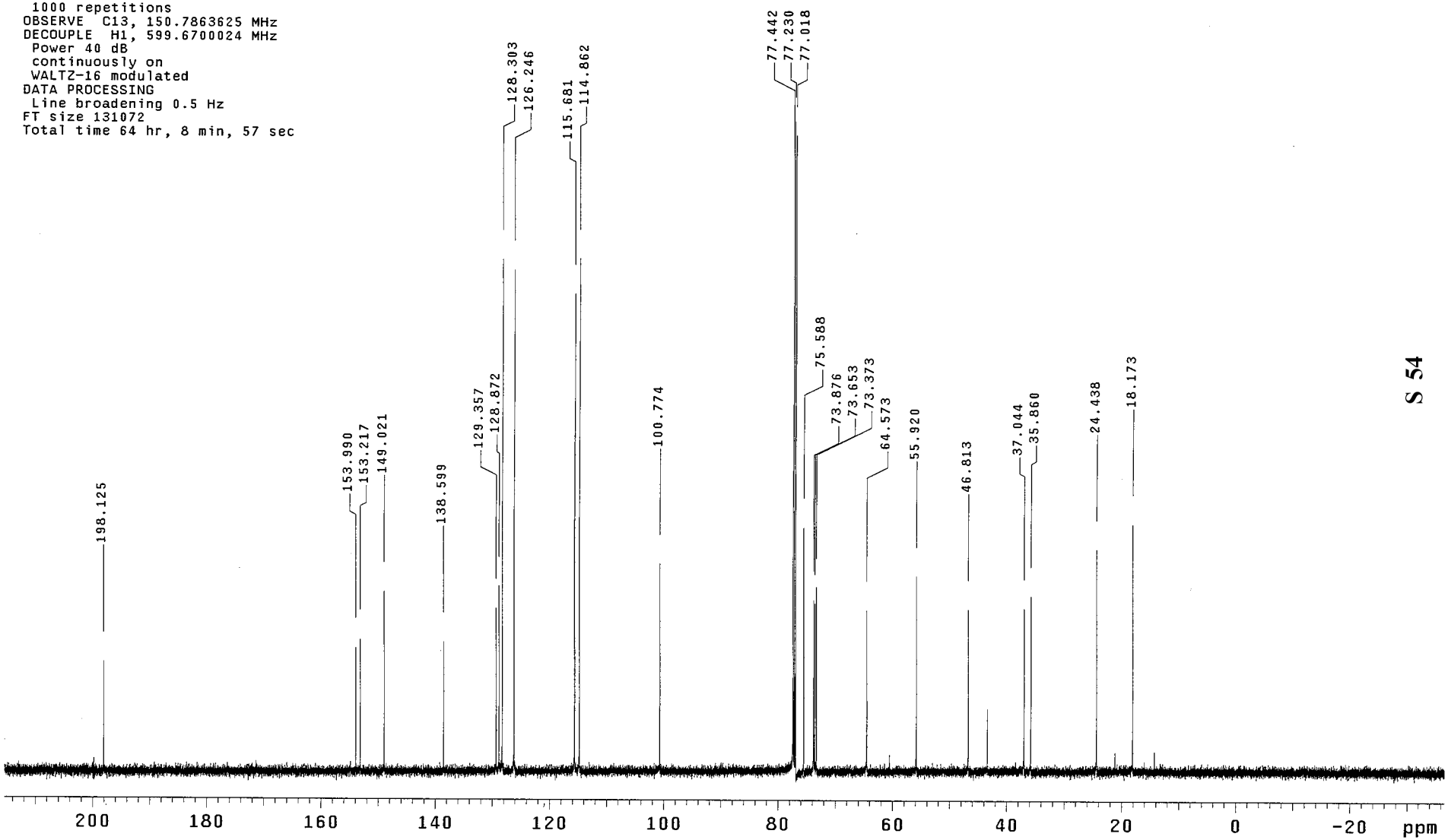
STANDARD CARBON PARAMETERS

Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 28.0 C / 301.1 K
User: 1-14-87
INOVA-600 "inova600"

Relax. delay 1.000 sec
Pulse 36.5 degrees
Acq. time 1.300 sec
Width 38004.8 Hz
1000 repetitions
OBSERVE C13, 150.7863625 MHz
DECOUPLE H1, 599.6700024 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 131072
Total time 64 hr, 8 min, 57 sec



17



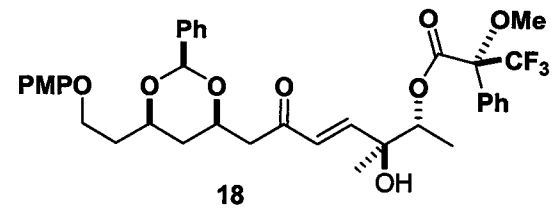
STANDARD PROTON PARAMETERS

Archive directory: /export/home/vnmr1/vnmrsys/data
Sample directory:
File: PROTON

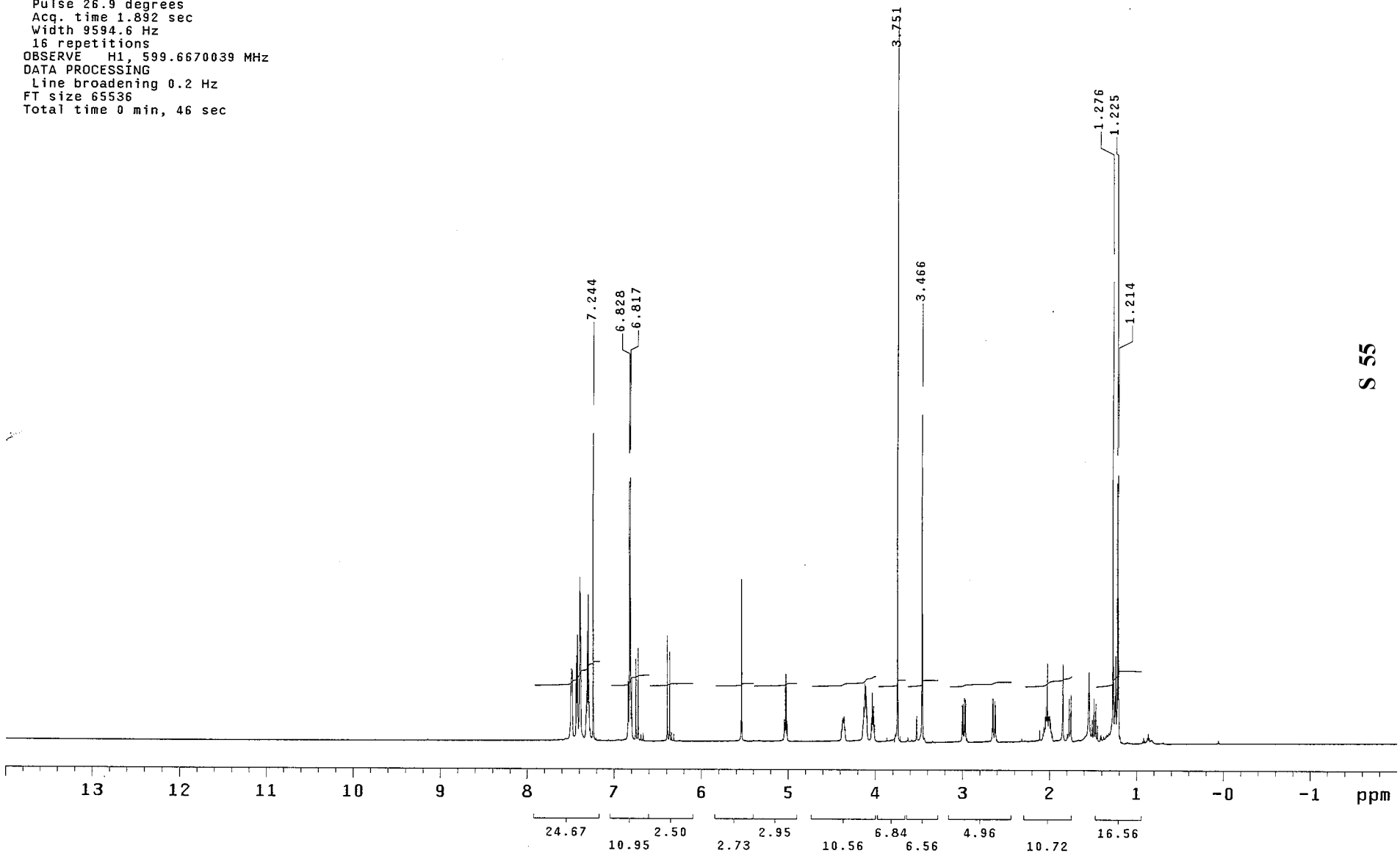
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 28.0 C / 301.1 K
INOVA-600 "inova600"

Relax. delay 1.000 sec
Pulse 26.9 degrees
Acq. time 1.892 sec
Width 9594.6 Hz
16 repetitions
OBSERVE H1, 599.6670039 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min, 46 sec



18

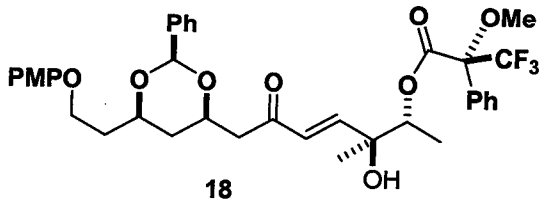


STANDARD PROTON PARAMETERS

Archive directory: /export/home/vnmr1/vnmrsys/data
Sample directory:
File: PROTON

Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 28.0 C / 301.1 K
INOVA-600 "inova600"

Relax. delay 1.000 sec
Pulse 26.9 degrees
Acq. time 1.892 sec
Width 9594.6 Hz
16 repetitions
OBSERVE H1, 599.6670039 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min, 46 sec



18

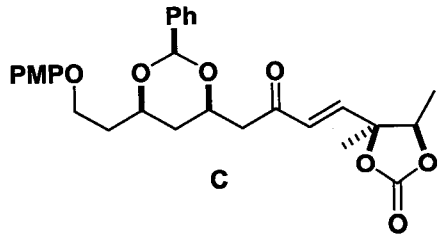
STANDARD PROTON PARAMETERS

Archive directory: /export/home/vnmr1/vnmrsys/data
Sample directory:
File: PROTON

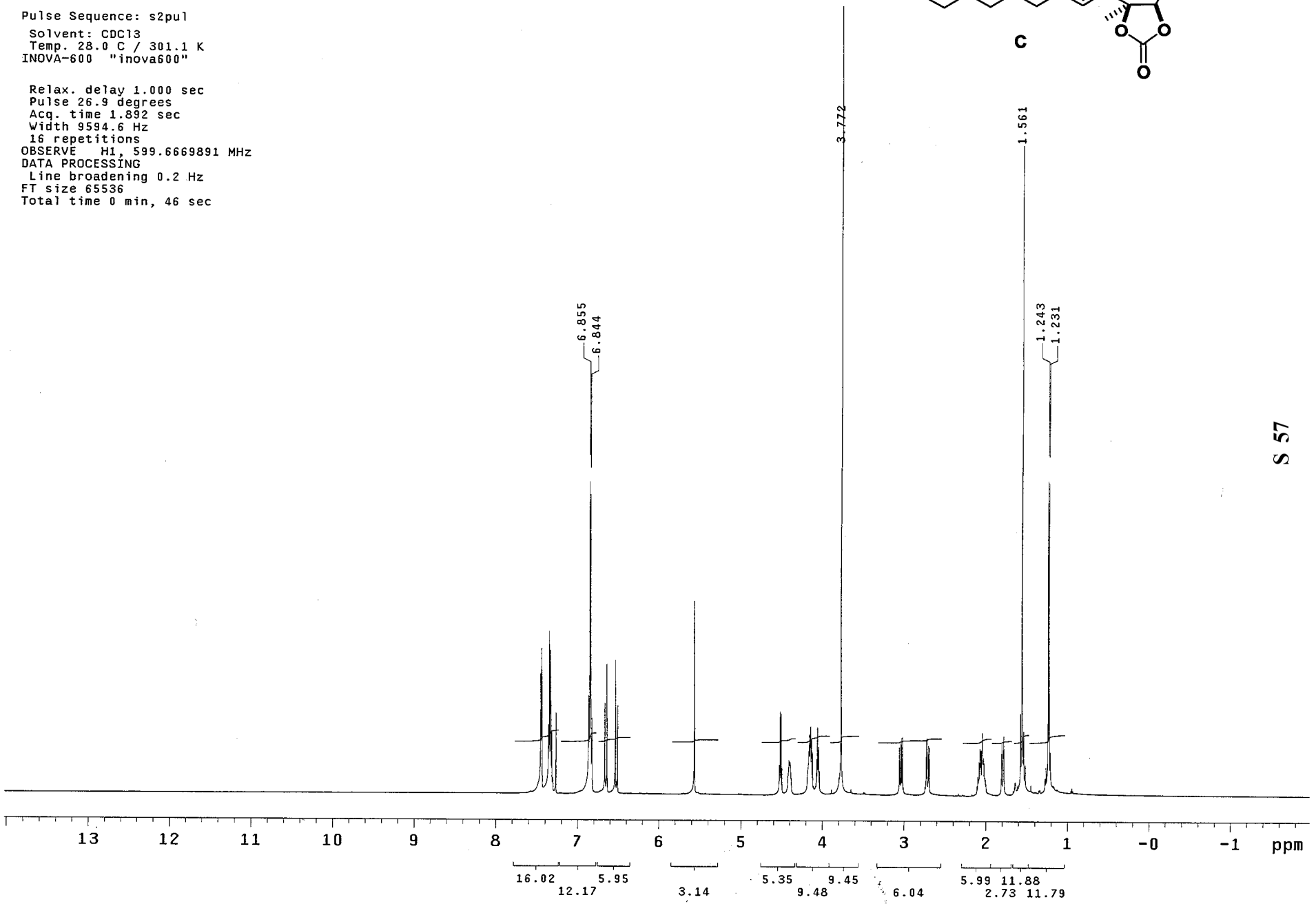
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 28.0 C / 301.1 K
INOVA-600 "inova600"

Relax. delay 1.000 sec
Pulse 26.9 degrees
Acq. time 1.892 sec
Width 9594.6 Hz
16 repetitions
OBSERVE H1, 599.6669891 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min, 46 sec



C

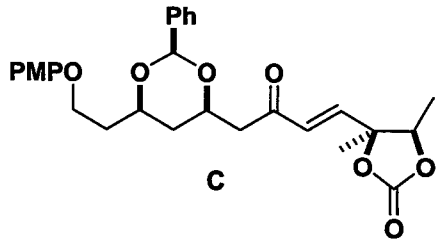


STANDARD CARBON PARAMETERS

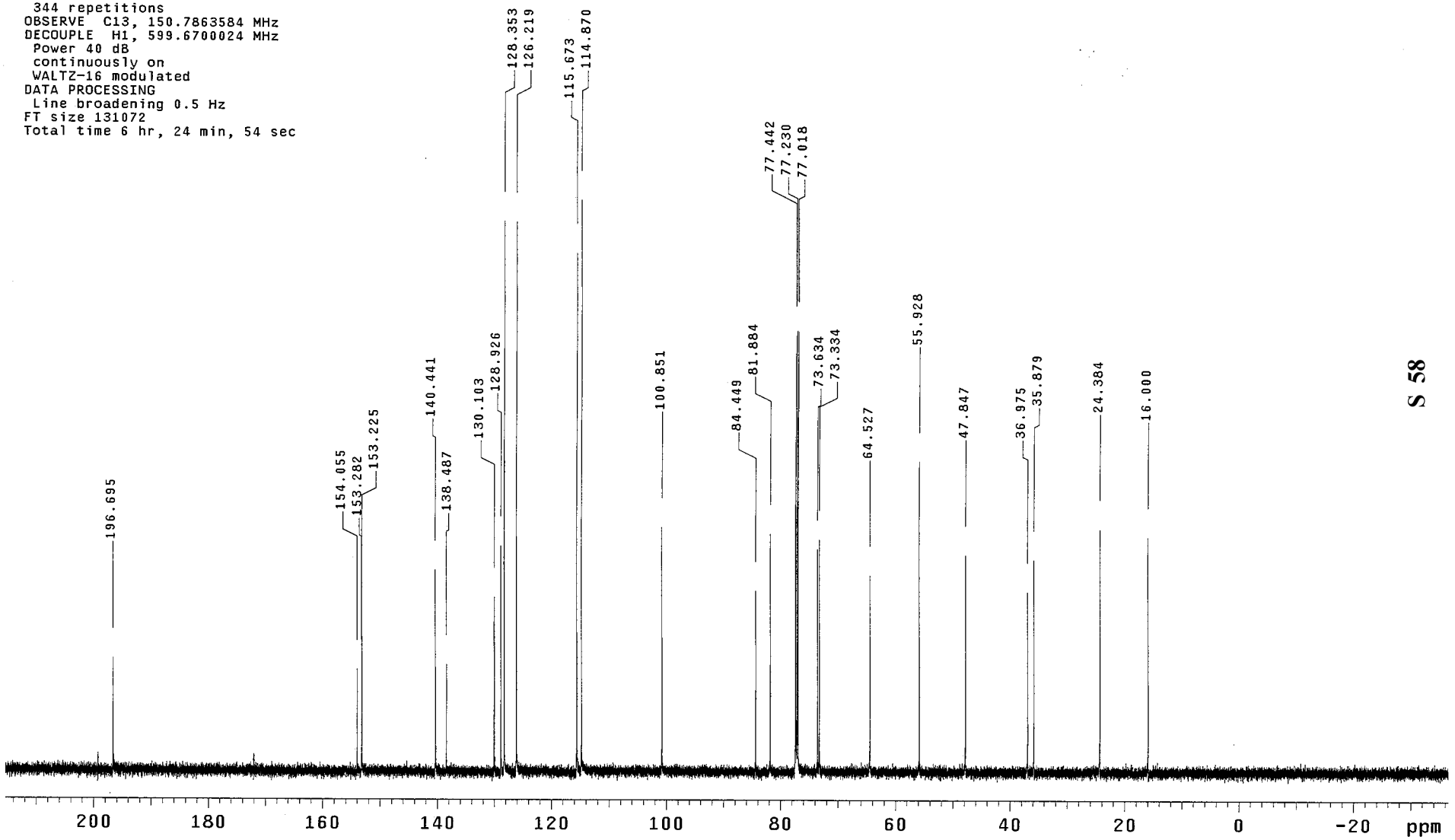
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 28.0 C / 301.1 K
User: 1-14-87
INOVA-600 "inova600"

Relax. delay 1.000 sec
Pulse 36.5 degrees
Acq. time 1.301 sec
Width 38004.8 Hz
344 repetitions
OBSERVE C13, 150.7863584 MHz
DECOUPLE H1, 599.6700024 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 131072
Total time 6 hr, 24 min, 54 sec



C



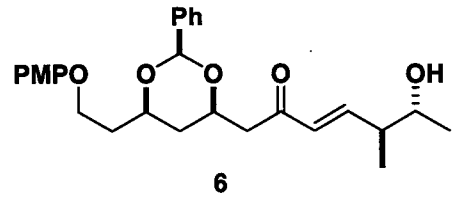
STANDARD PROTON PARAMETERS

Archive directory: /export/home/vnmr1/vnmrsys/data
Sample directory:
File: PROTON

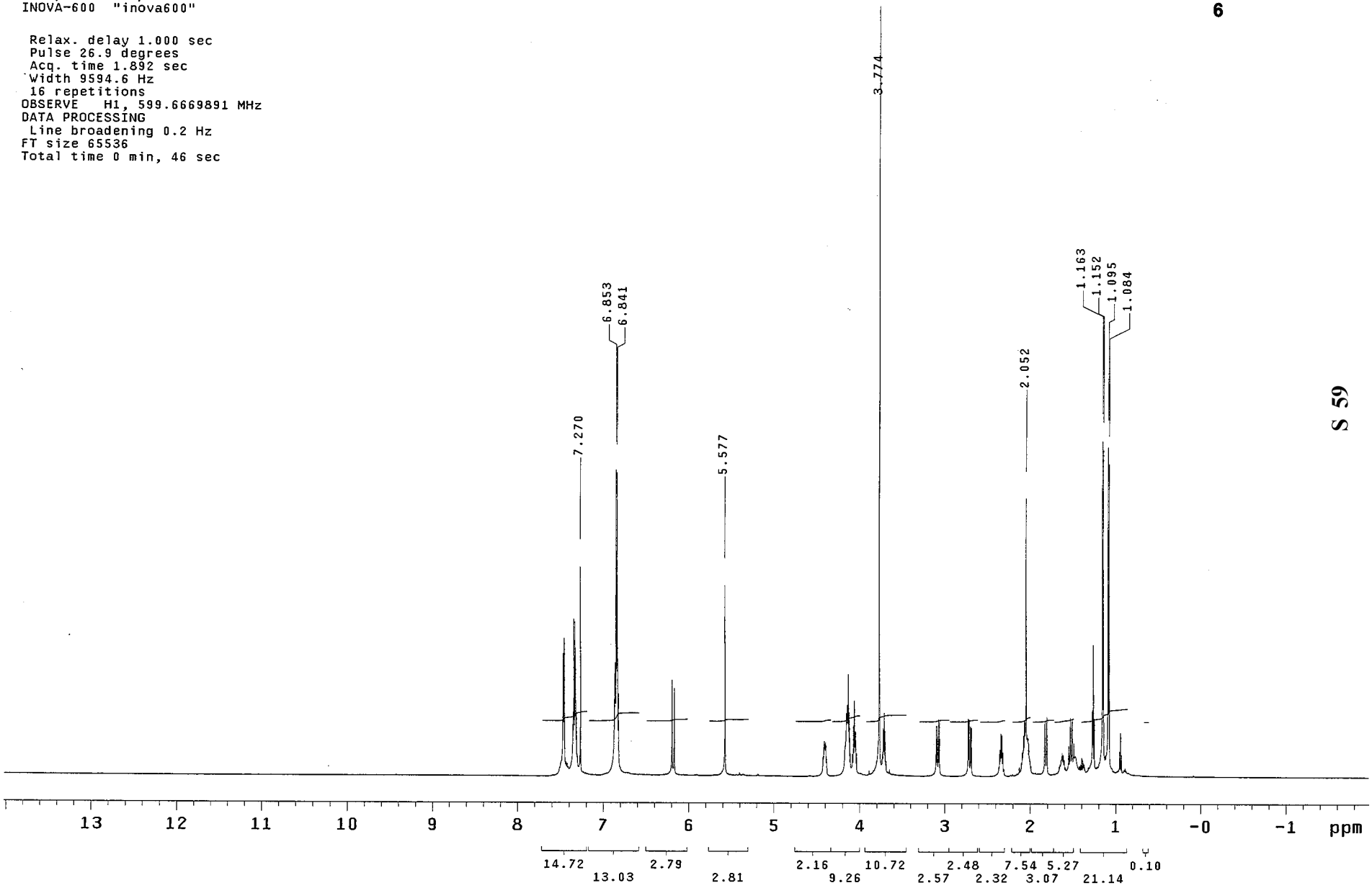
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 28.0 C / 301.1 K
INOVA-600 "inova600"

Relax. delay 1.000 sec
Pulse 26.9 degrees
Acq. time 1.892 sec
Width 9594.6 Hz
16 repetitions
OBSERVE H1, 599.6669891 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min, 46 sec



6

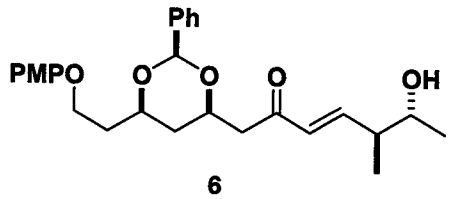


STANDARD CARBON PARAMETERS

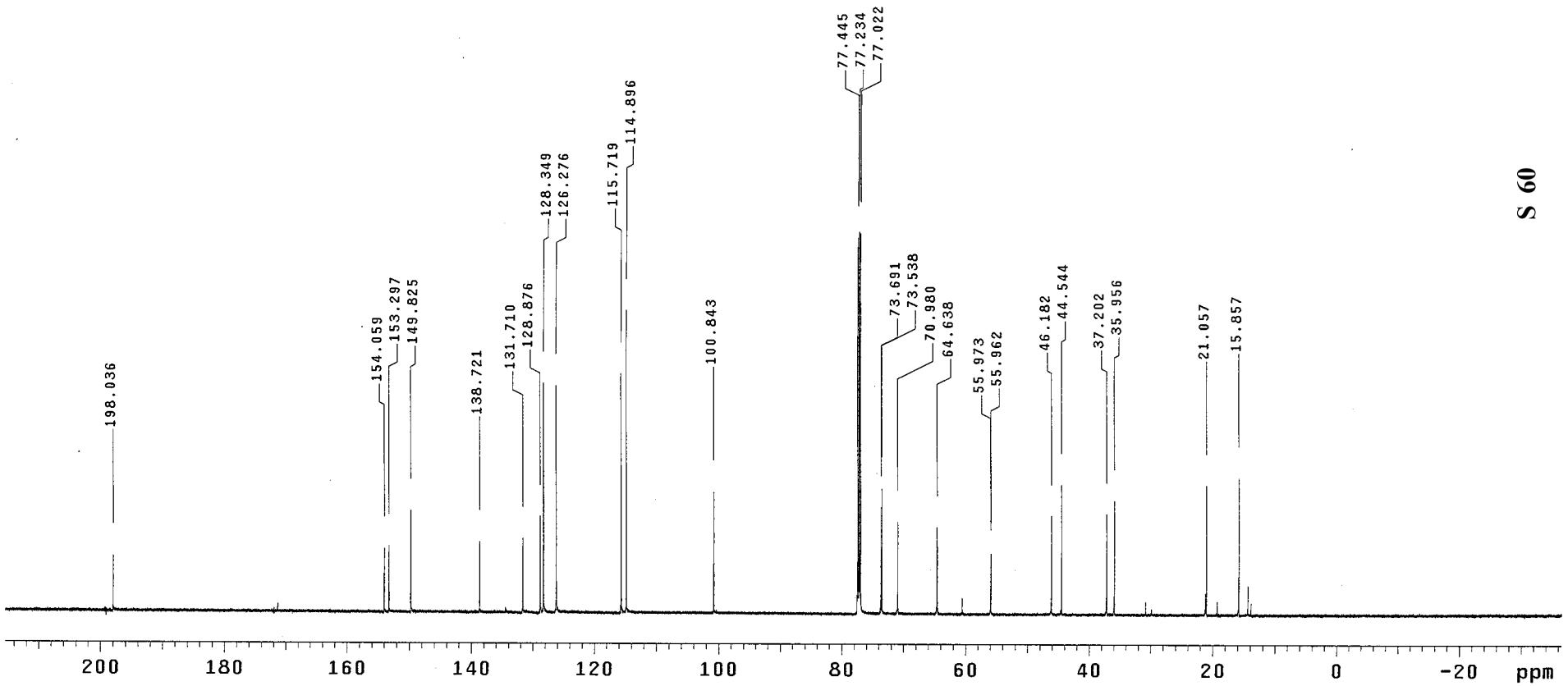
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 28.0 C / 301.1 K
User: 1-14-87
INOVA-600 "inova600"

Relax. delay 1.000 sec
Pulse 36.5 degrees
Acq. time 1.300 sec
Width 38004.8 Hz
4456 repetitions
OBSERVE C13, 150.7863521 MHz
DECOUPLE H1, 599.6700024 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 131072
Total time 641 hr, 29 min, 32 sec



6



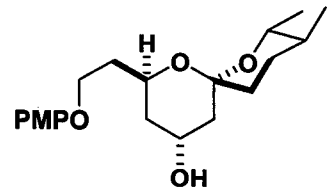
STANDARD PROTON PARAMETERS

Archive directory: /export/home/vnmr1/vnmrsys/data
Sample directory:
File: PROTON

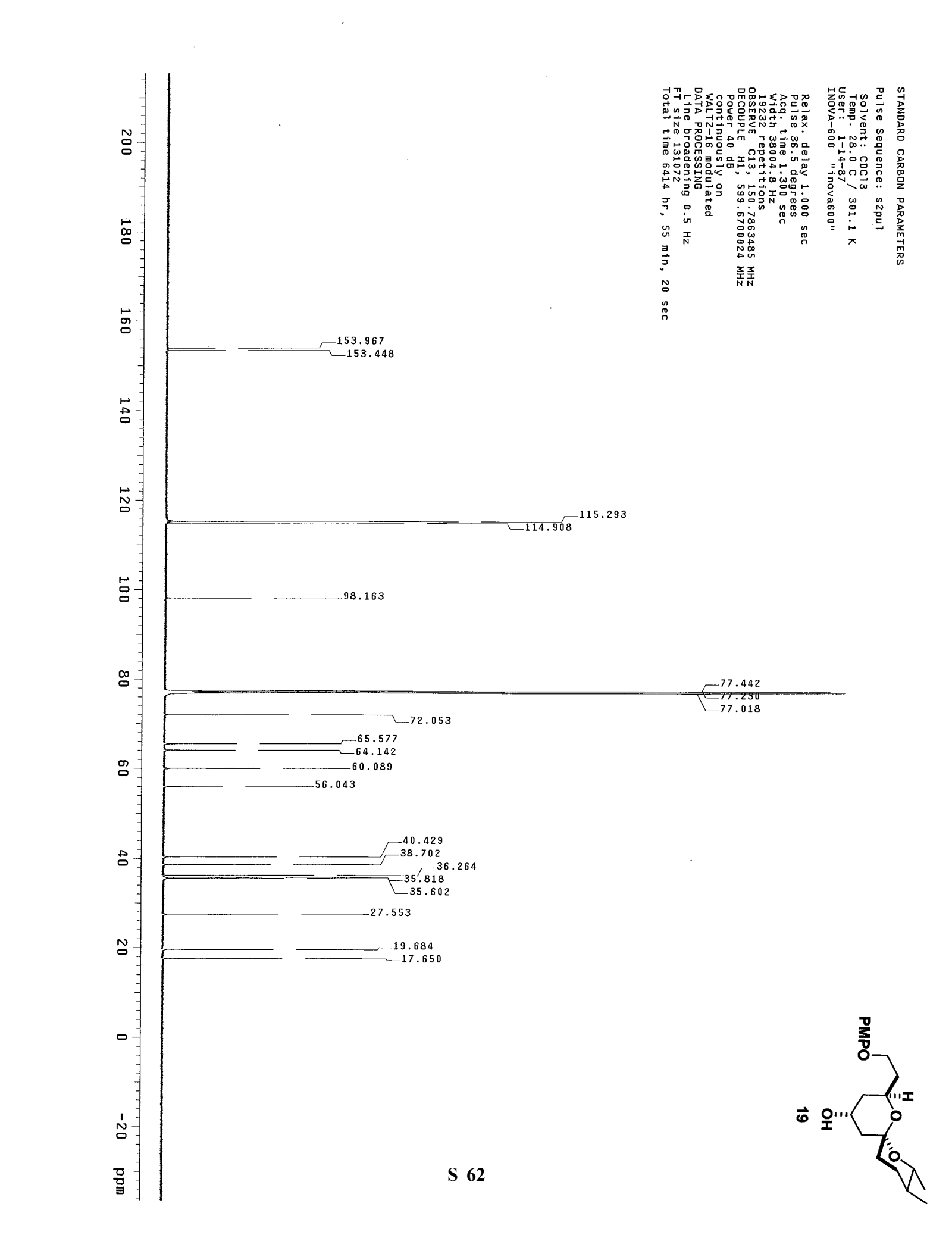
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 28.0 C / 301.1 K
INOVA-600 "inova600"

Relax. delay 1.000 sec
Pulse 26.9 degrees
Acq. time 1.892 sec
Width 9594.6 Hz
16 repetitions
OBSERVE H1, 599.6669882 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min, 46 sec



19


STANDARD CARBON PARAMETERS
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 28.0 C / 301.1 K
User: 1-14-87
INOVA-600 "inova600"
Relax. delay 1.000 sec
Pulse 36.5 degrees
Acq. time 1.300 sec
width 38004.8 Hz
19232 repetitions
OBSERVE C13, 150.7863485 MHz
DECOUPLE H1, 599.6700024 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 131072
Total time 6414 hr, 55 min, 20 sec
153.967
153.448
115.293
114.908
98.163
77.442
77.230
77.018
72.053
65.577
64.142
60.089
56.043
40.429
38.702
36.264
35.818
35.602
27.553
19.684
17.650
200
180
160
140
120
100
80
60
40
20
0
-20
ppm
PMPO
H
O
OH
O
19

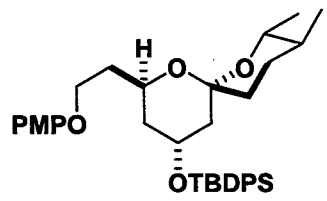
STANDARD PROTON PARAMETERS

Archive directory: /export/home/vnmr1/vnmrsys/data
Sample directory:
File: PROTON

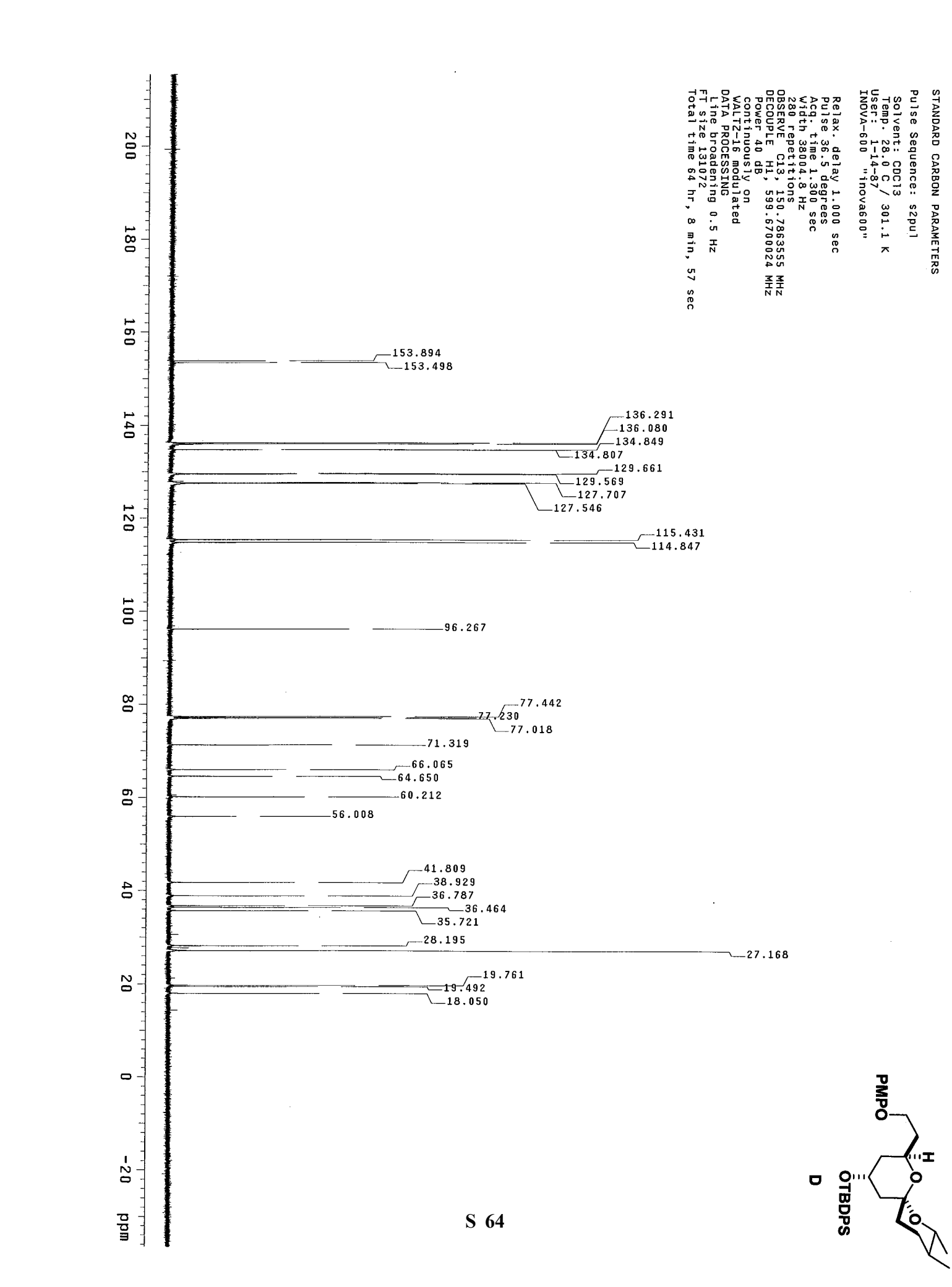
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 28.0 C / 301.1 K
INOVA-600 "inova600"

Relax. delay 1.000 sec
Pulse 26.9 degrees
Acq. time 1.892 sec
Width 9594.6 Hz
16 repetitions
OBSERVE H1, 599.6669888 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min, 46 sec



D


STANDARD CARBON PARAMETERS
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 28.0 C / 301.1 K
User: 1-14-87
INOVA-600 "inova600"
Relax. delay 1.000 sec
Pulse 36.5 degrees
Acq. time 1.300 sec
width 38004.8 Hz
280 repetitions
OBSERVE C13, 150.7863555 MHz
DECOUPLE H1, 599.6700024 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 131072
Total time 64 hr, 8 min, 57 sec
153.894
153.498
136.291
136.080
134.849
134.807
129.661
129.569
127.707
127.546
115.431
114.847
96.267
77.442
77.230
77.018
71.319
66.065
64.650
60.212
56.008
41.809
38.929
36.787
36.464
35.721
28.195
27.168
19.761
19.492
18.050
200
180
160
140
120
100
80
60
40
20
0
-20
ppm
PMPO
H
O
O
OTBDPS
D

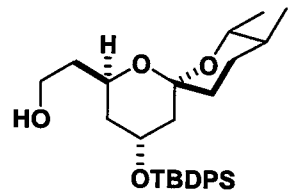
STANDARD PROTON PARAMETERS

Archive directory: /export/home/vnmr1/vnmrsys/data
Sample directory:
File: PROTON

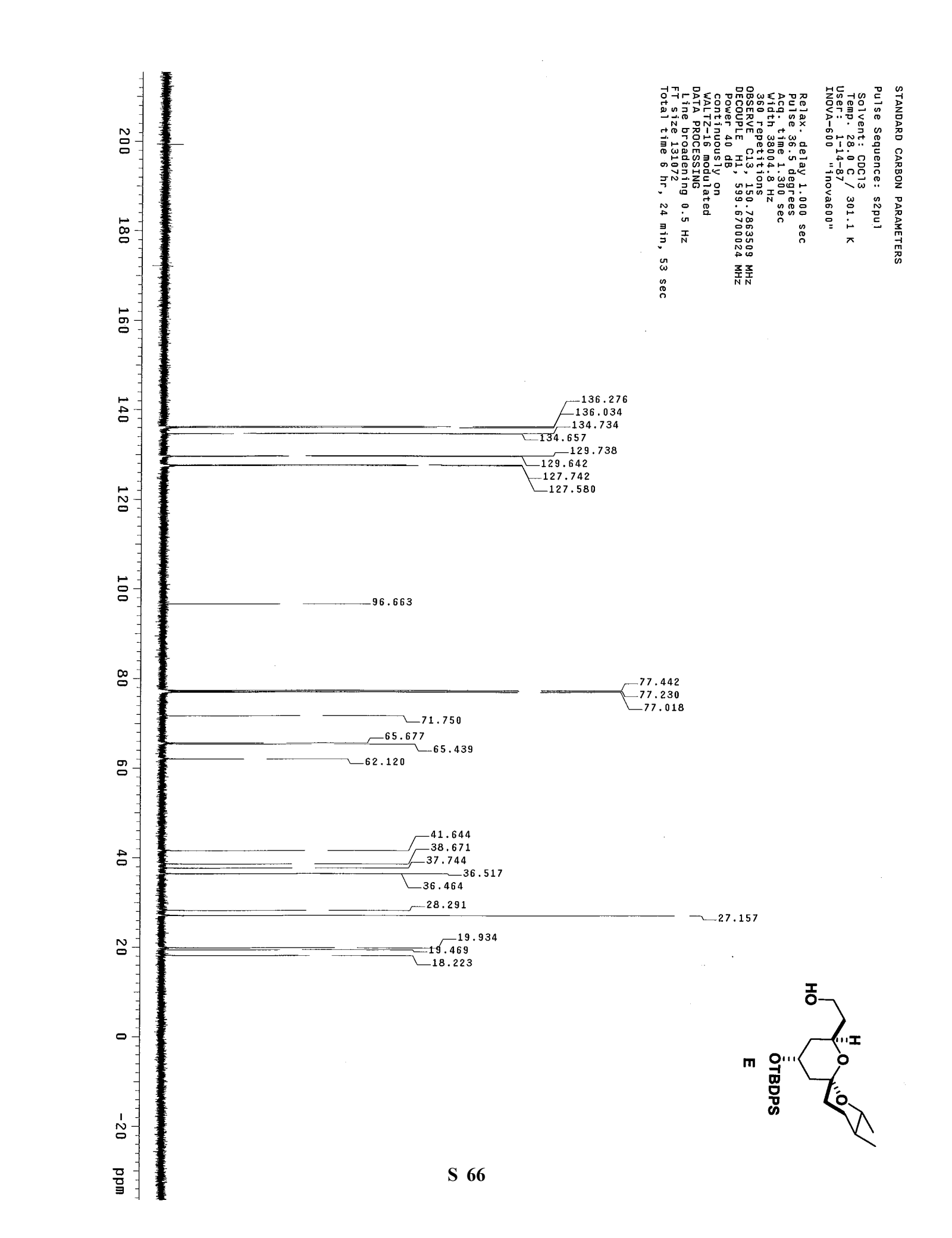
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 28.0 C / 301.1 K
INOVA-600 "inova600"

Relax. delay 1.000 sec
Pulse 26.9 degrees
Acq. time 1.892 sec
Width 9594.6 Hz
16 repetitions
OBSERVE H1, 599.6669891 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min, 46 sec



E


STANDARD CARBON PARAMETERS
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 28.0 C / 301.1 K
User: 1-14-87
INOVA-600 "inova600"
Relax. delay 1.000 sec
Pulse 36.5 degrees
Acq. time 1.300 sec
width 38004.8 Hz
360 repetitions
OBSERVE C13, 150.7863509 MHz
DECOUPLE H1, 599.6700024 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 131072
Total time 6 hr, 24 min, 53 sec
136.276
136.034
134.734
134.657
129.738
129.642
127.742
127.580
96.663
77.442
77.230
77.018
71.750
65.677
65.439
62.120
41.644
38.671
37.744
36.517
36.464
28.291
27.157
19.934
19.469
18.223
200
180
160
140
120
100
80
60
40
20
0
-20
ppm
HO
H
O
O
OTBDPS
E

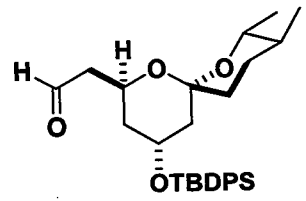
STANDARD PROTON PARAMETERS

Archive directory: /export/home/vnmr1/vnmrsys/data
Sample directory:
File: PROTON

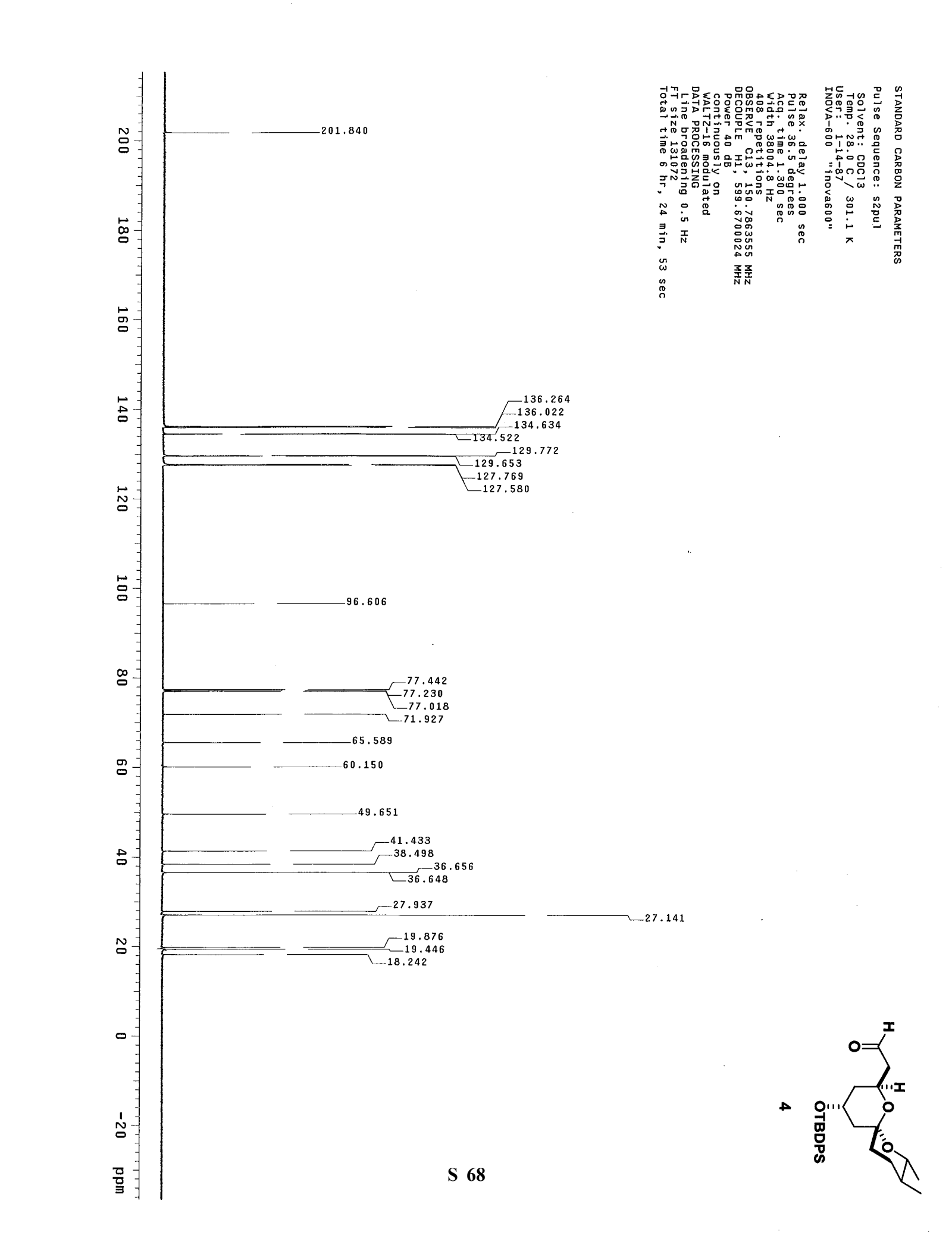
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 28.0 C / 301.1 K
INOVA-600 "inova600"

Relax. delay 1.000 sec
Pulse 30.0 degrees
Acq. time 4.000 sec
Width 9594.6 Hz
16 repetitions
OBSERVE H1, 599.6670075 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 131072
Total time 1 min, 20 sec



4


STANDARD CARBON PARAMETERS
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 28.0 C / 301.1 K
User: 1-14-87
INOVA-600 "inova600"
Relax. delay 1.000 sec
Pulse 36.5 degrees
Acq. time 1.300 sec
width 38004.8 Hz
408 repetitions
OBSERVE C13, 150.7863555 MHz
DECOUPLE H1, 599.6700024 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 131072
Total time 6 hr, 24 min, 53 sec
201.840
136.264
136.022
134.634
134.522
129.772
129.653
127.769
127.580
96.606
77.442
77.230
77.018
71.927
65.589
60.150
49.651
41.433
38.498
36.656
36.648
27.937
27.141
19.876
19.446
18.242
200
180
160
140
120
100
80
60
40
20
0
-20
ppm
H
O
H
O
O
OTBDPS
4

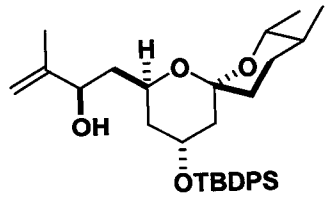
STANDARD PROTON PARAMETERS

Archive directory: /export/home/vnmr1/vnmrsys/data
Sample directory:
File: PROTON

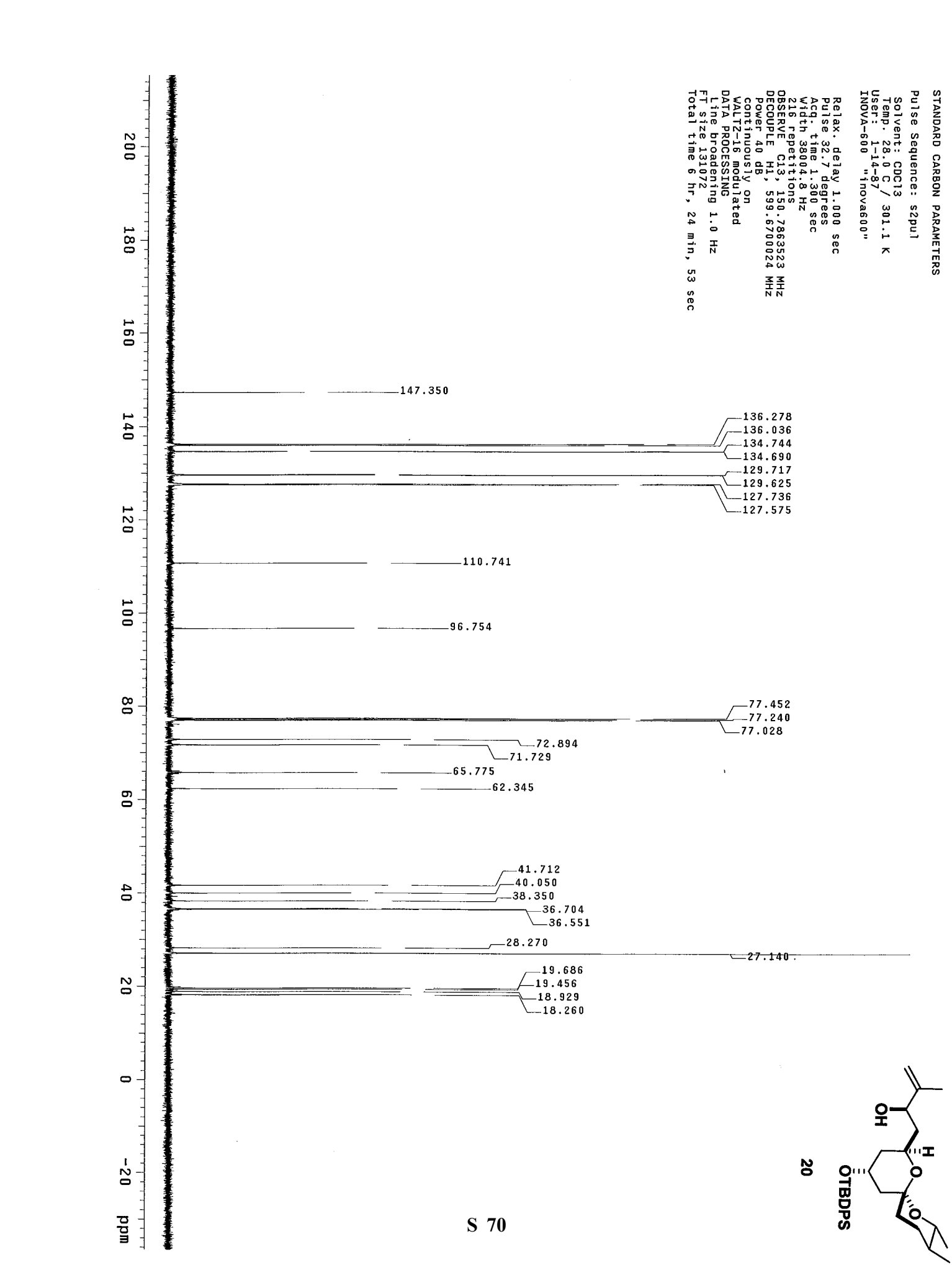
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 28.0 C / 301.1 K
INOVA-600 "inova600"

Relax. delay 1.000 sec
Pulse 30.0 degrees
Acq. time 4.000 sec
Width 9594.6 Hz
16 repetitions
OBSERVE H1, 599.6670075 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 131072
Total time 1 min, 20 sec



20


STANDARD CARBON PARAMETERS
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 28.0 C/ 301.1 K
User: 1-14-87
INOVA-600 "inova600"
Relax. delay 1.000 sec
Pulse 32.7 degrees
Acq. time 1.300 sec
width 38004.8 Hz
216 repetitions
OBSERVE C13, 150.7863523 MHz
DECOUPLE H1, 599.6700024 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 6 hr, 24 min, 53 sec
147.350
136.278
136.036
134.744
134.690
129.717
129.625
127.736
127.575
110.741
96.754
77.452
77.240
77.028
72.894
71.729
65.775
62.345
41.712
40.050
38.350
36.704
36.551
28.270
27.140
19.686
19.456
18.929
18.260
200
180
160
140
120
100
80
60
40
20
0
-20
ppm
OH
H
O
O
OTBDPS
20

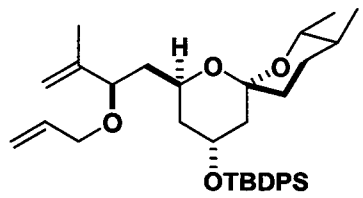
STANDARD PROTON PARAMETERS

Archive directory: /export/home/vnmr1/vnmrsys/data
Sample directory:
File: PROTON

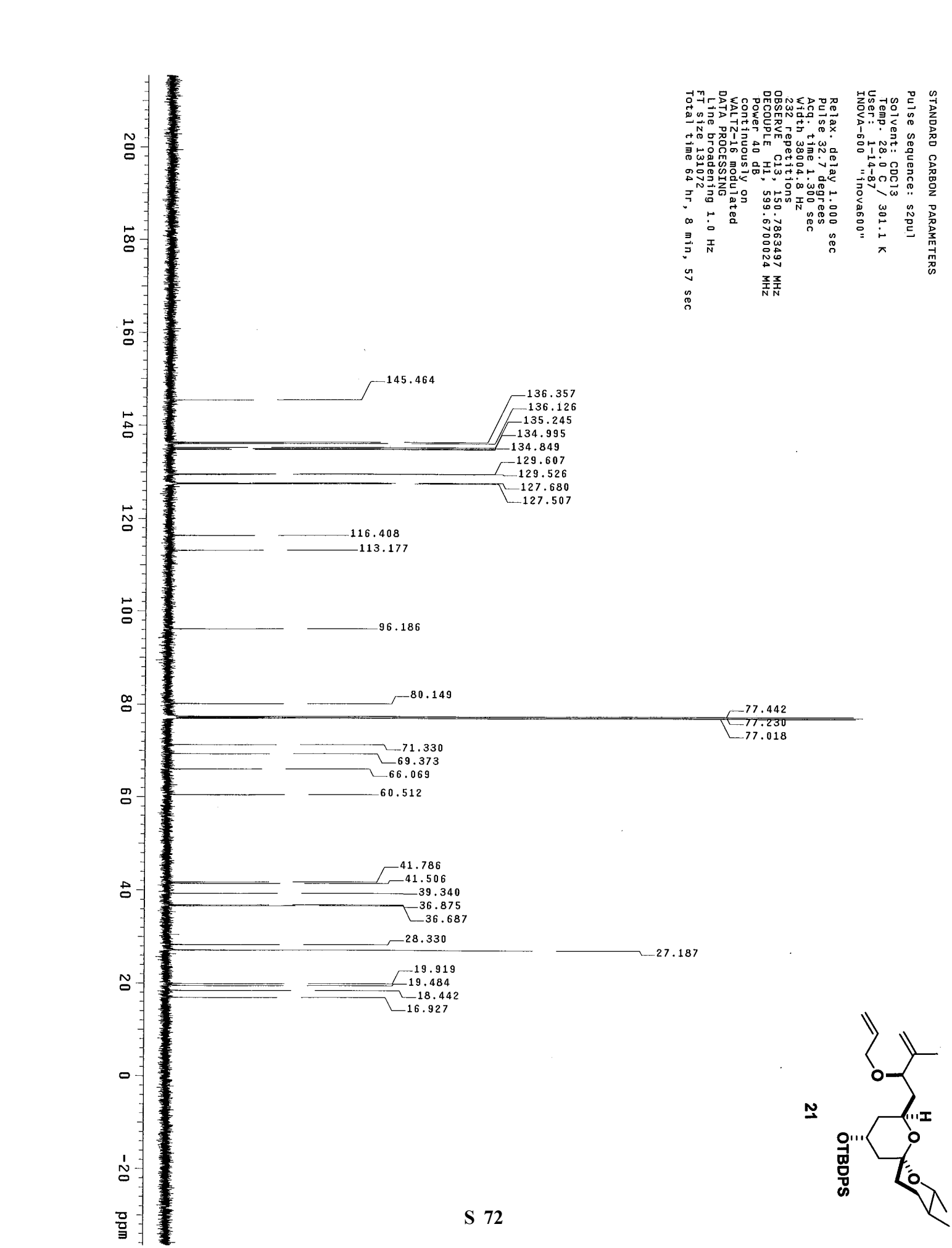
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 28.0 C / 301.1 K
INOVA-600 "inova600"

Relax. delay 1.000 sec
Pulse 30.0 degrees
Acq. time 4.000 sec
Width 9594.6 Hz
8 repetitions
OBSERVE H1, 599.6670072 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 131072
Total time 0 min, 40 sec



21


STANDARD CARBON PARAMETERS
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 28.0 C / 301.1 K
User: 1-14-87
INOVA-600 "inova600"
Relax. delay 1.000 sec
Pulse 32.7 degrees
Acq. time 1.300 sec
width 38004.8 Hz
232 repetitions
OBSERVE C13, 150.7863497 MHz
DECOUPLE H1, 599.6700024 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 64 hr, 8 min, 57 sec
145.464
136.357
136.126
135.245
134.995
134.849
129.607
129.526
127.680
127.507
116.408
113.177
96.186
80.149
77.442
77.230
77.018
71.330
69.373
66.069
60.512
41.786
41.506
39.340
36.875
36.687
28.330
27.187
19.919
19.484
18.442
16.927
200
180
160
140
120
100
80
60
40
20
0
-20
ppm
21
OTBDPS

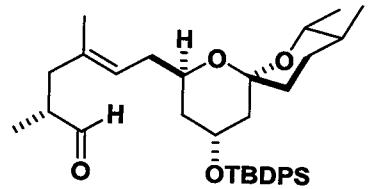
STANDARD PROTON PARAMETERS

Archive directory: /export/home/vnmr1/vnmrsys/data
Sample directory:
File: PROTON

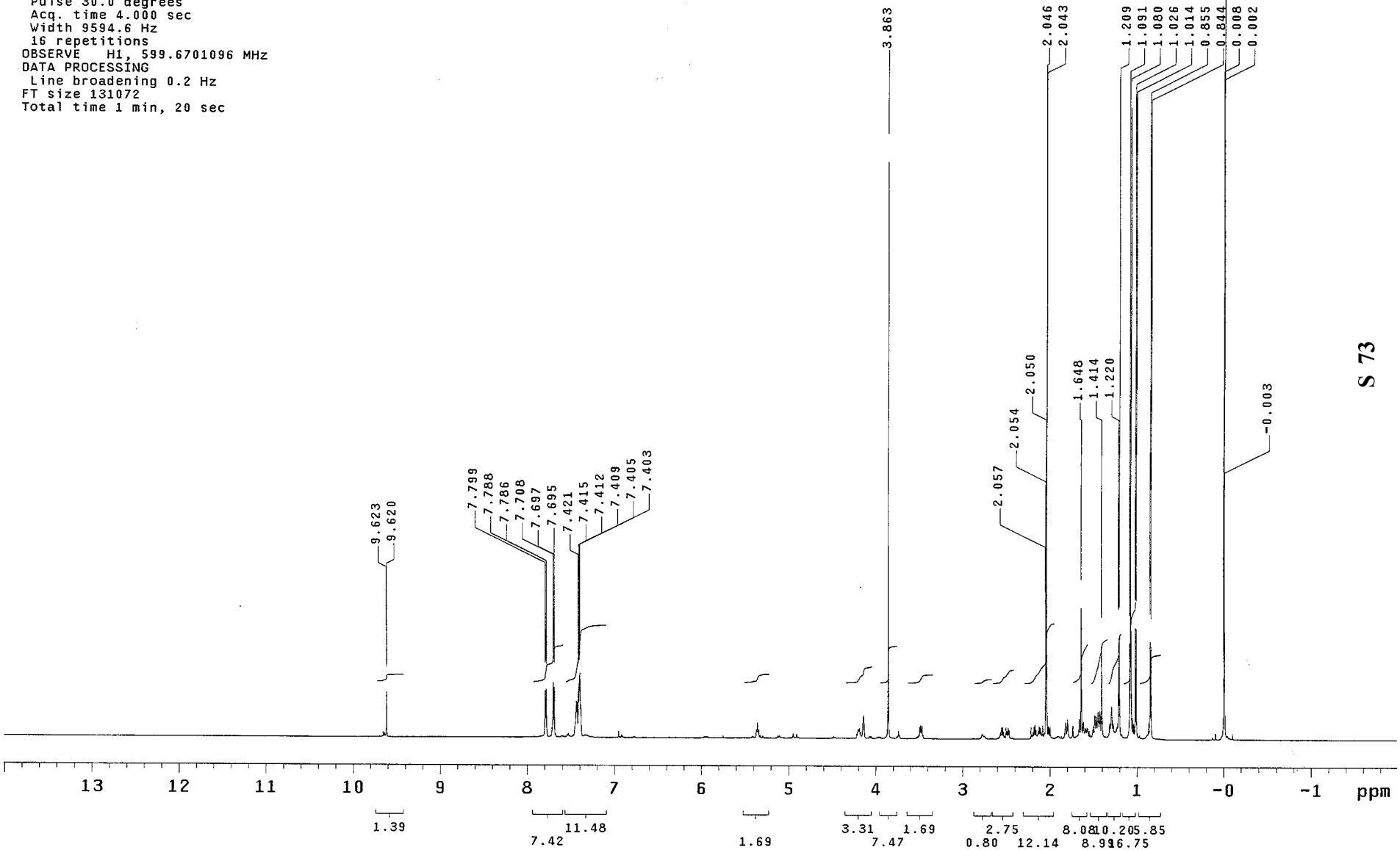
Pulse Sequence: s2pul

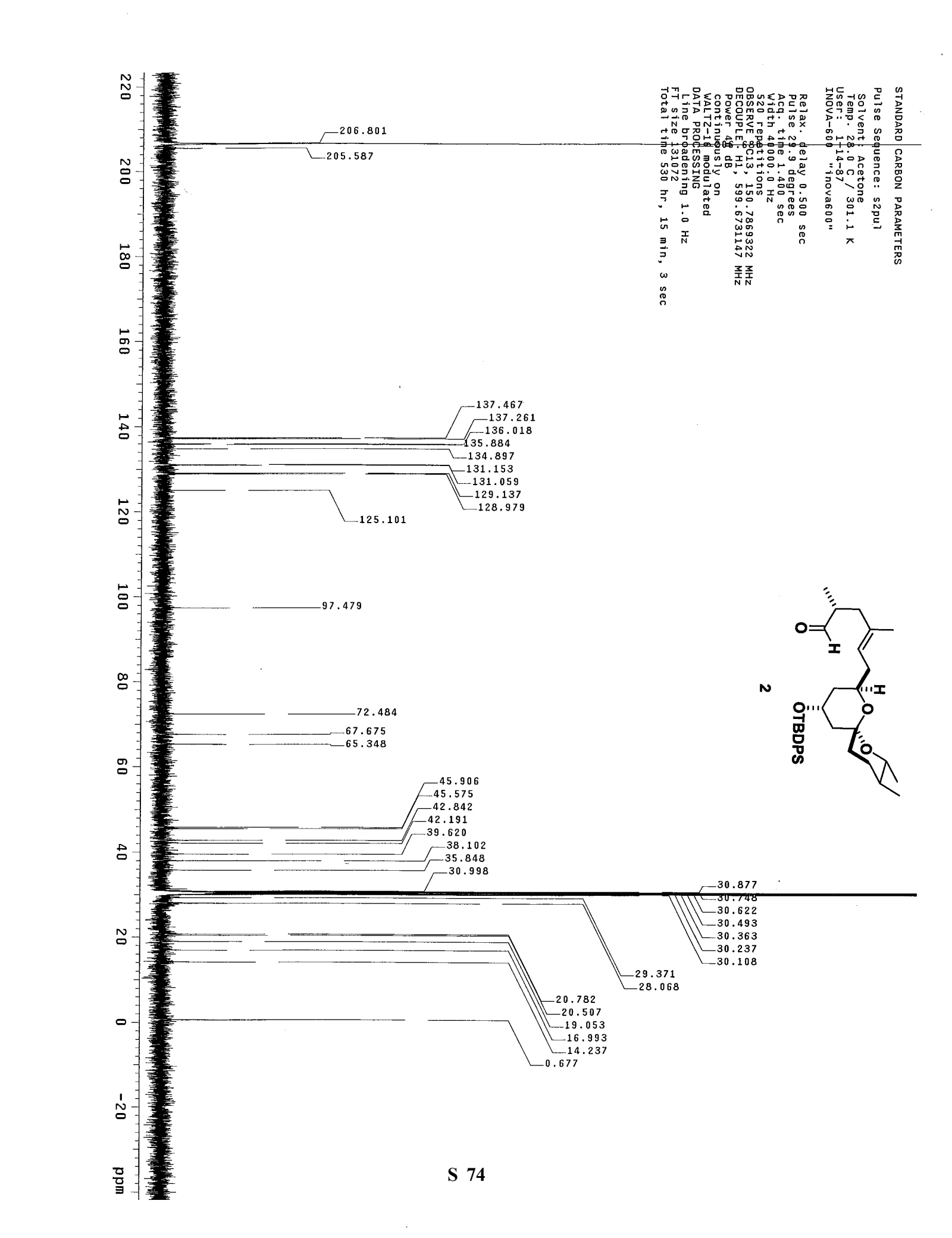
Solvent: Acetone
Temp. 28.0 C / 301.1 K
INOVA-600 "inova600"

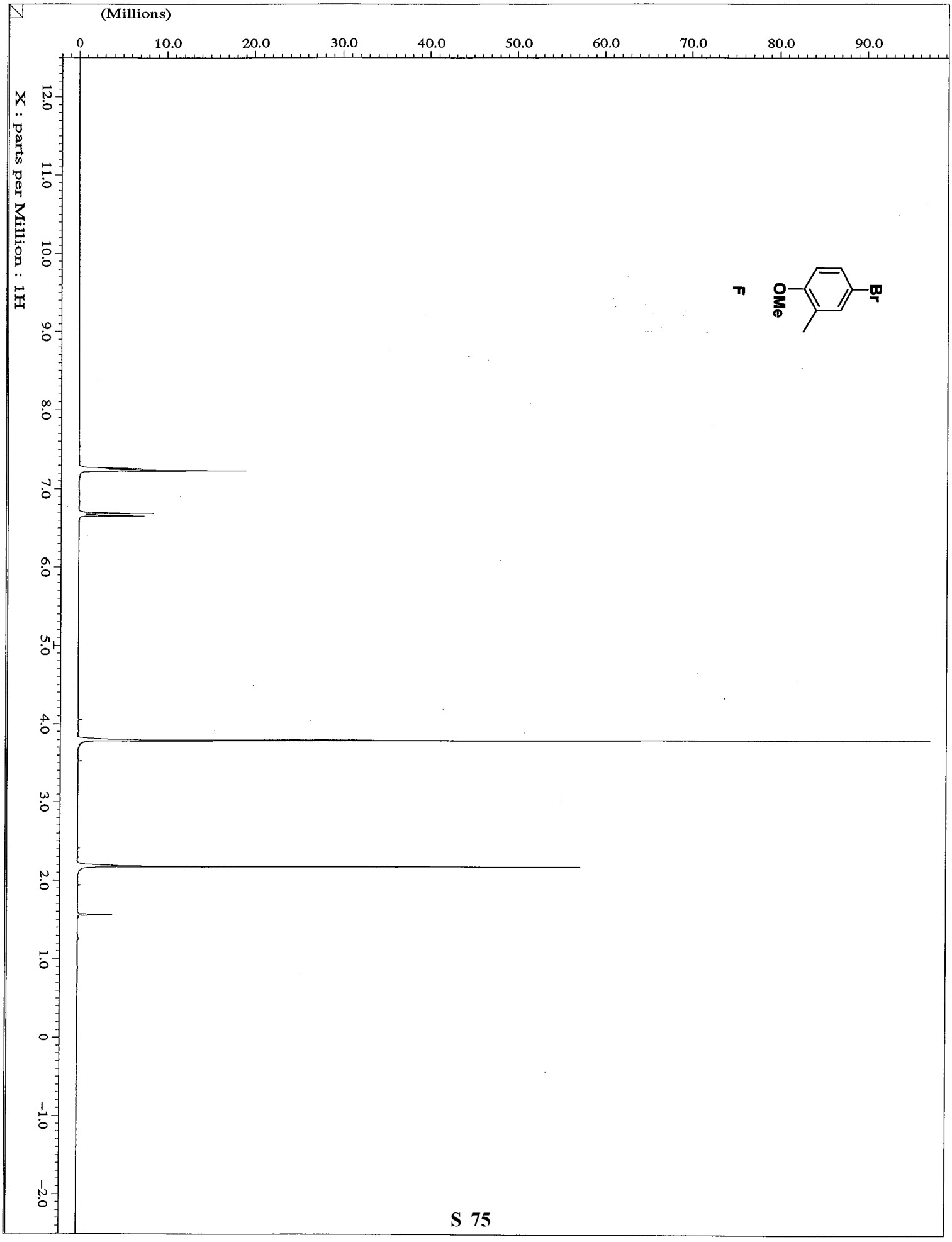
Relax. delay 1.000 sec
Pulse 30.0 degrees
Acq. time 4.000 sec
Width 9594.6 Hz
16 repetitions
OBSERVE H1, 599.6701096 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 131072
Total time 1 min, 20 sec

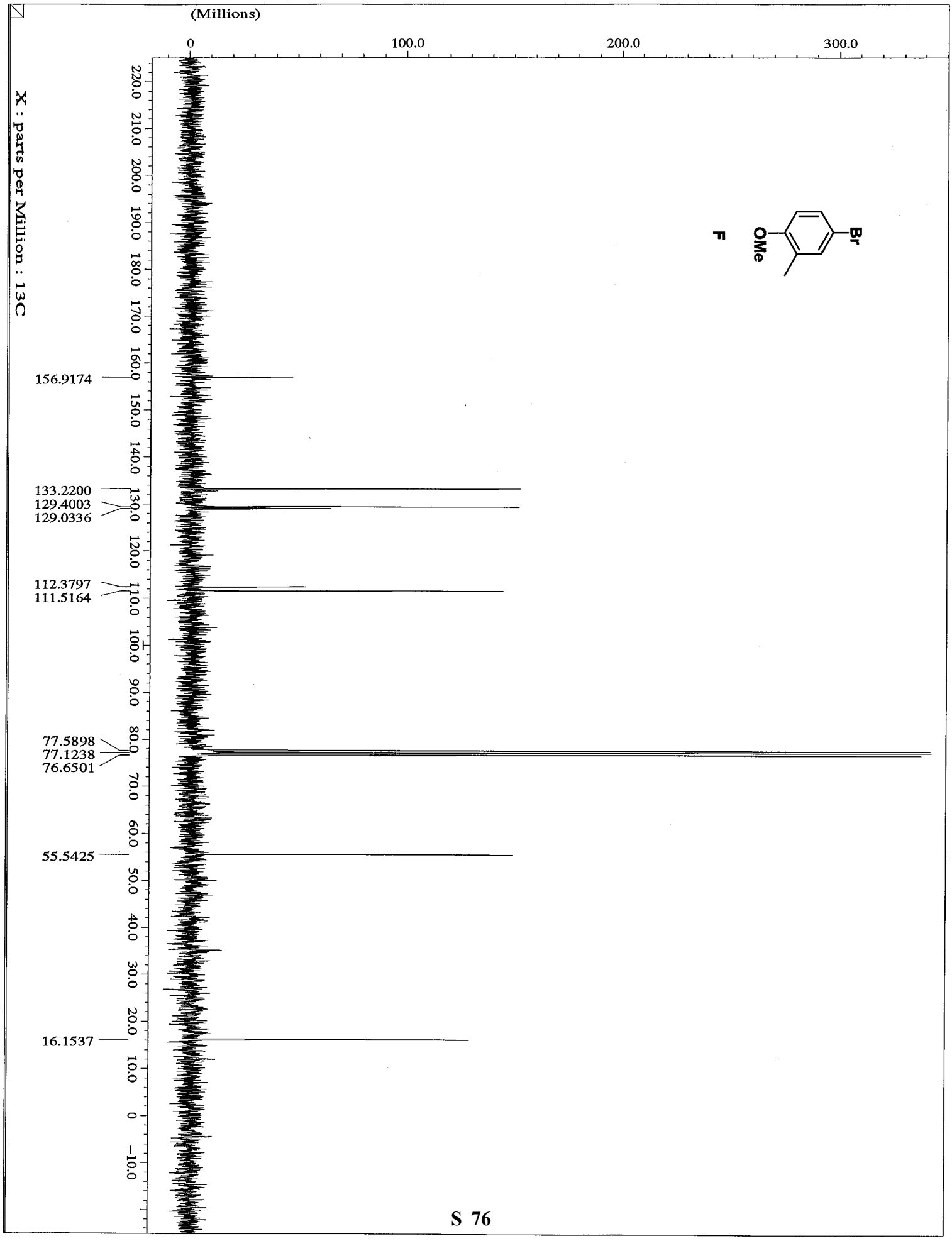


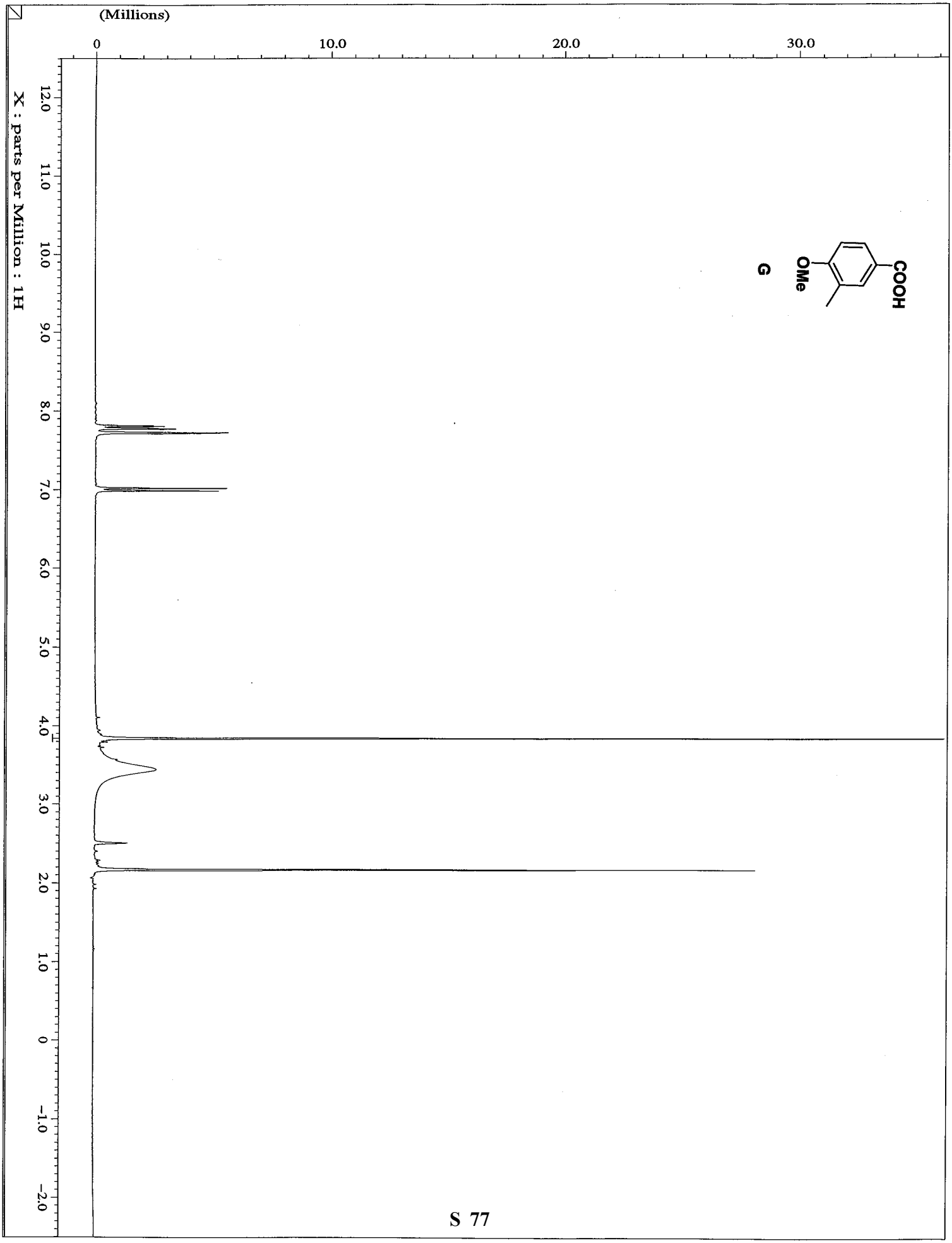
2

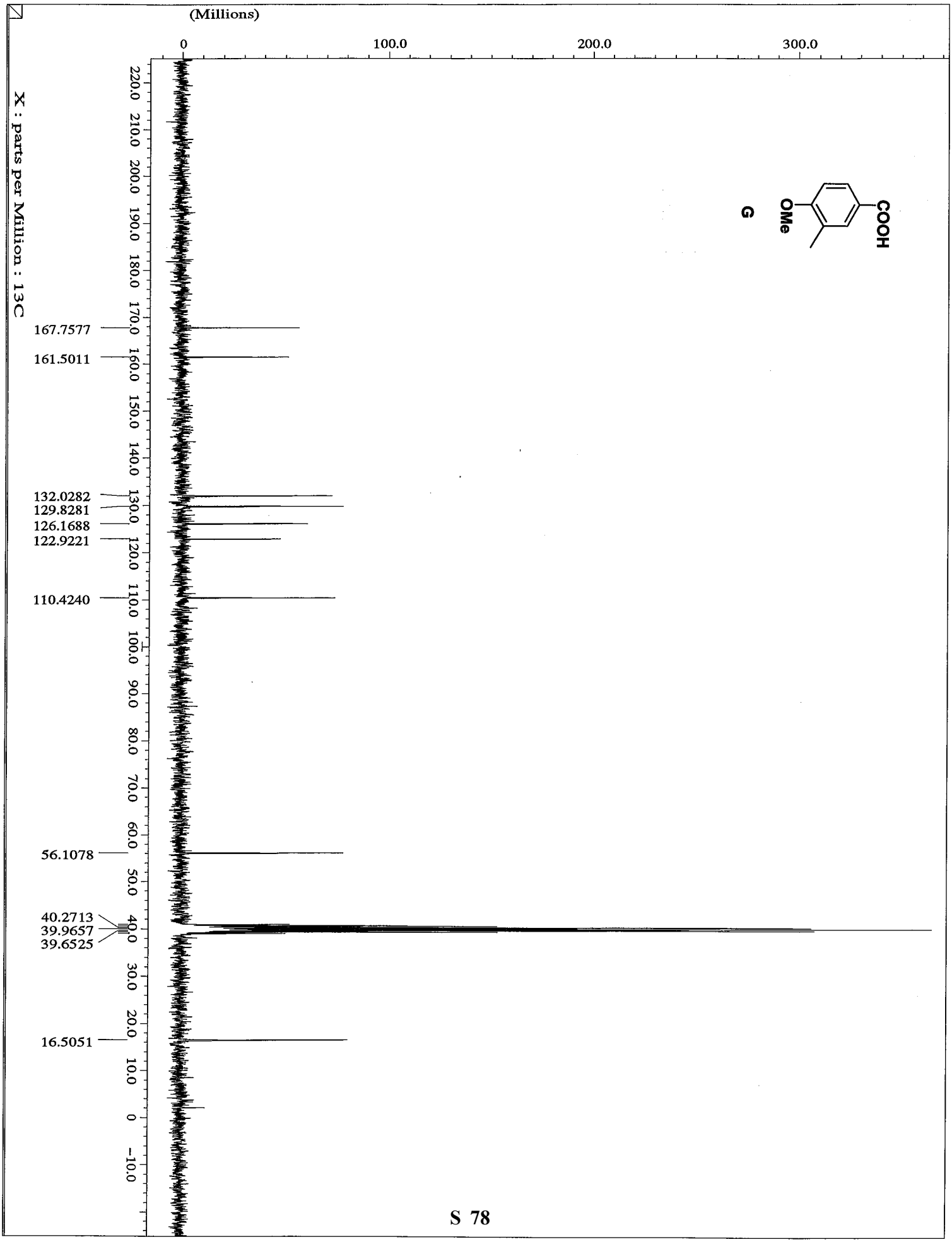



STANDARD CARBON PARAMETERS
Pulse Sequence: s2pul
Solvent: Acetone
Temp. 28.0 C / 301.1 K
User: 1-14-87
INOVA-600 "inova600"
Relax. delay 0.500 sec
Pulse 29.9 degrees
Acq. time 1.400 sec
width 40000.0 Hz
520 repetitions
OBSERVE C13, 150.7869322 MHz
DECOUPLE H1, 599.6731147 MHz
Power 42 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 530 hr, 15 min, 3 sec
206.801
205.587
137.467
137.261
136.018
135.884
134.897
131.153
131.059
129.137
128.979
125.101
97.479
72.484
67.675
65.348
45.906
45.575
42.842
42.191
39.620
38.102
35.848
30.998
30.877
30.748
30.622
30.493
30.363
30.237
30.108
29.371
28.068
20.782
20.507
19.053
16.993
14.237
0.677
ppm
220
200
180
160
140
120
100
80
60
40
20
0
-20
O
H
H
O
O
OTBDPS
2


(Millions)
0
10.0
20.0
30.0
40.0
50.0
60.0
70.0
80.0
90.0
X : parts per Million : 1H
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
-1.0
-2.0
F
OMe
Br


(Millions)
0
100.0
200.0
300.0
X : parts per Million : 13C
220.0 210.0 200.0 190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0 -10.0
156.9174
133.2200
129.4003
129.0336
112.3797
111.5164
77.5898
77.1238
76.6501
55.5425
16.1537
F
OMe
Br


(Millions)
0
10.0
20.0
30.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
-1.0
-2.0
X : parts per Million : 1H
G
OMe
COOH


(Millions)
0
100.0
200.0
300.0
X : parts per Million : 13C
220.0 210.0 200.0 190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0 -10.0
167.7577
161.5011
132.0282
129.8281
126.1688
122.9221
110.4240
56.1078
40.2713
39.9657
39.6525
16.5051
G
OMe
COOH

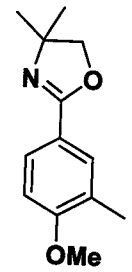
STANDARD PROTON PARAMETERS

Archive directory: /export/home/vnmr1/vnmrsys/data
Sample directory:
File: PROTON

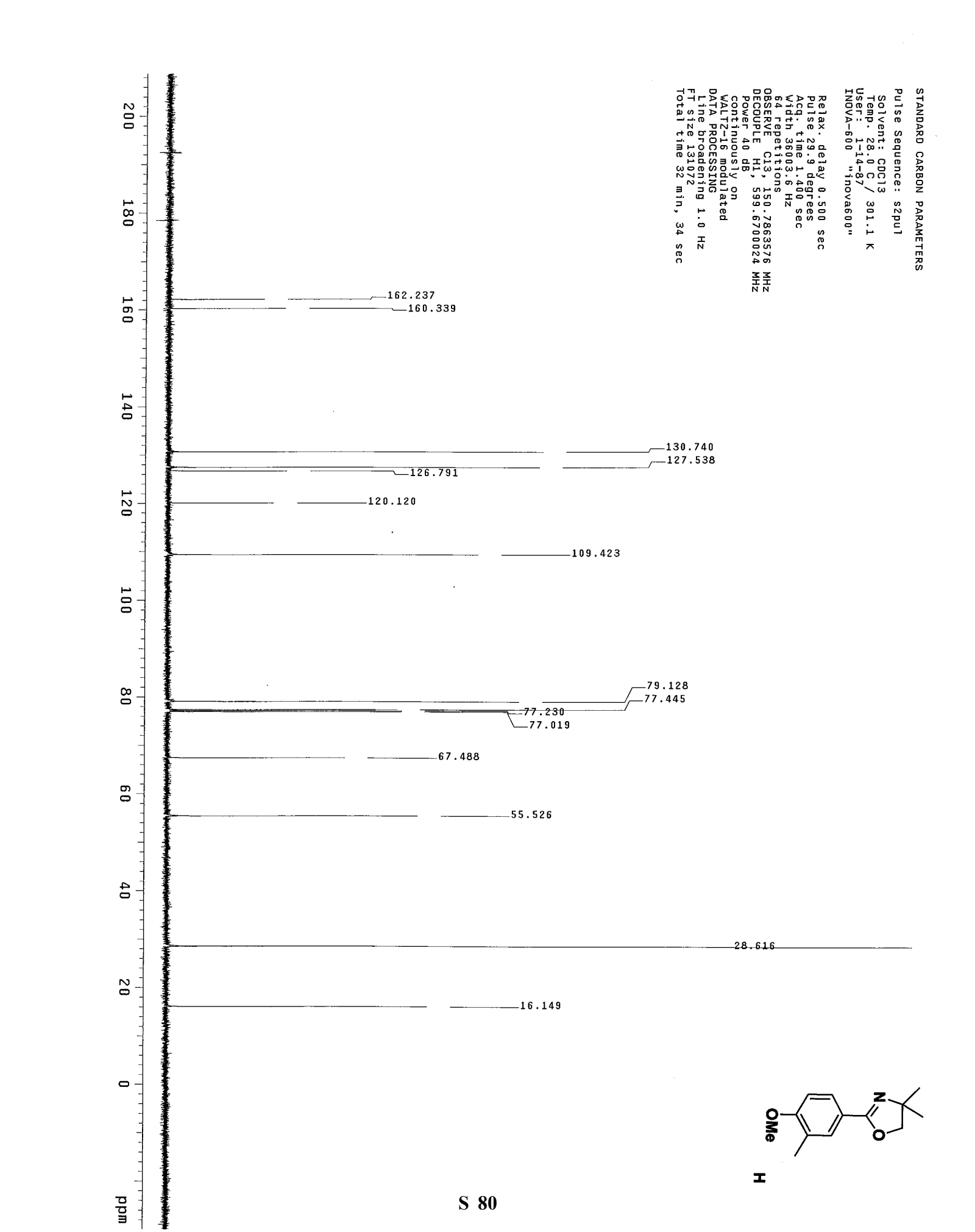
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 28.0 C / 301.1 K
INOVA-600 "inova600"

Relax. delay 1.000 sec
Pulse 30.0 degrees
Acq. time 4.000 sec
Width 9594.6 Hz
10 repetitions
OBSERVE H1, 599.6670079 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 131072
Total time 0 min, 50 sec



H


STANDARD CARBON PARAMETERS
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 28.0 C / 301.1 K
User: 1-14-87
INOVA-600 "inova600"
Relax. delay 0.500 sec
Pulse 29.9 degrees
Acq. time 1.400 sec
width 36003.6 Hz
64 repetitions
OBSERVE C13, 150.7863576 MHz
DECOUPLE H1, 599.6700024 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 32 min, 34 sec
162.237
160.339
130.740
127.538
126.791
120.120
109.423
79.128
77.445
77.230
77.019
67.488
55.526
28.616
16.149
200
180
160
140
120
100
80
60
40
20
0
ppm
OMe
N
O
H

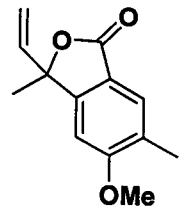
STANDARD PROTON PARAMETERS

Archive directory: /export/home/vnmr1/vnmrsys/data
Sample directory:
File: PROTON

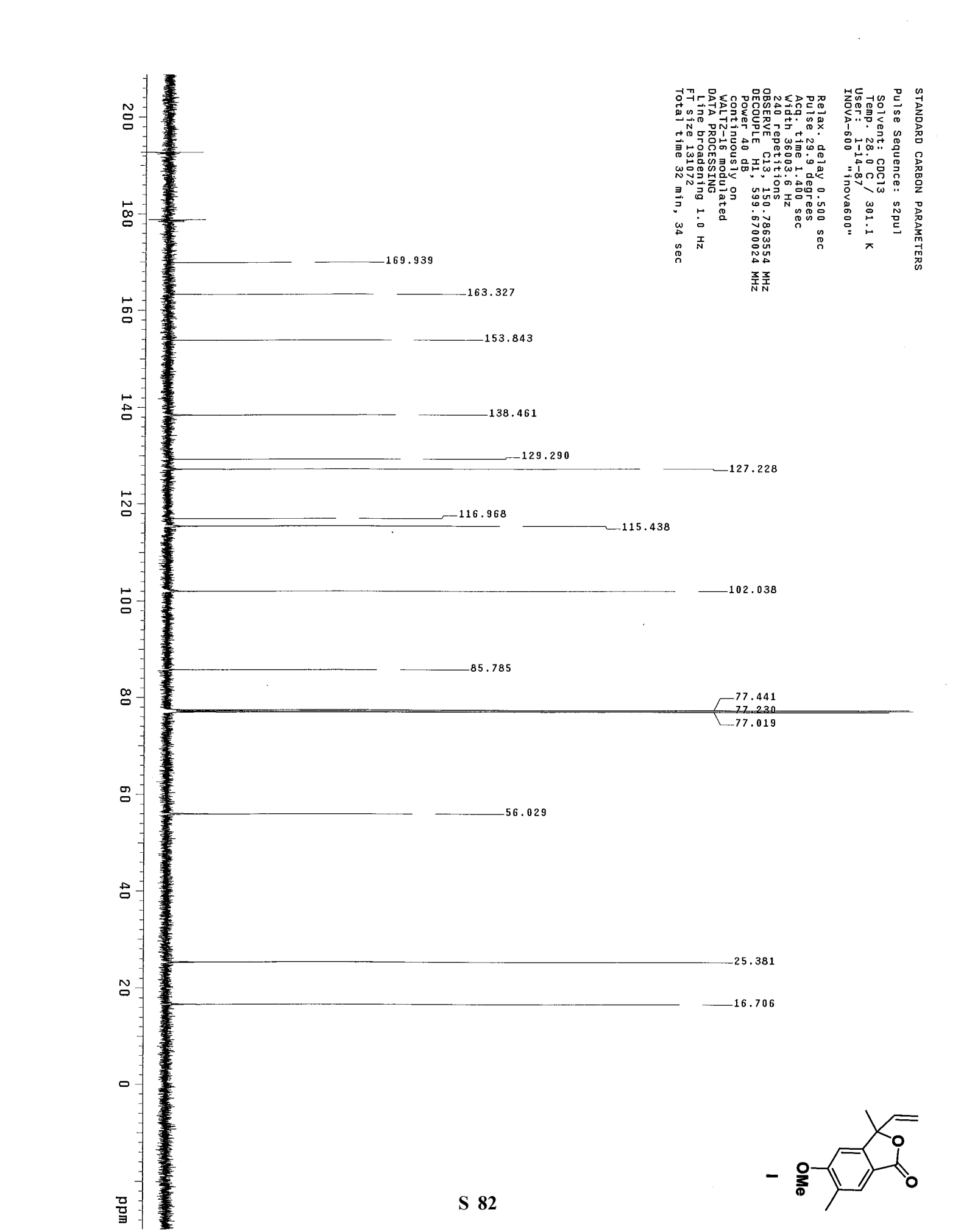
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 28.0 C / 301.1 K
INOVA-600 "inova600"

Relax. delay 1.000 sec
Pulse 30.0 degrees
Acq. time 4.000 sec
Width 9594.6 Hz
12 repetitions
OBSERVE H1, 599.6670076 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 131072
Total time 1 min, 0 sec



I


STANDARD CARBON PARAMETERS
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 28.0 C / 301.1 K
User: 1-14-87
INOVA-600 "inova600"
Relax. delay 0.500 sec
Pulse 29.9 degrees
Acq. time 1.400 sec
width 36003.6 Hz
240 repetitions
OBSERVE C13, 150.7863554 MHz
DECOUPLE H1, 599.6700024 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 32 min, 34 sec
169.939
163.327
153.843
138.461
129.290
127.228
116.968
115.438
102.038
85.785
77.441
77.230
77.019
56.029
25.381
16.706
200
180
160
140
120
100
80
60
40
20
0
ppm
OMe
O
O

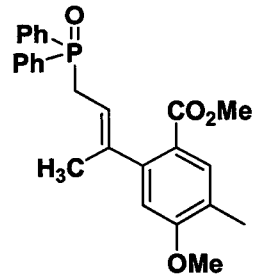
STANDARD PROTON PARAMETERS

Archive directory: /export/home/vnmr1/vnmrsys/data
Sample directory:
File: PROTON

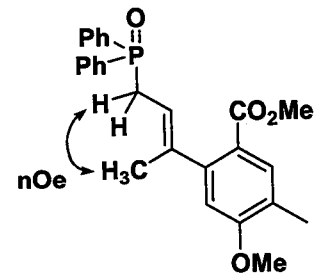
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 28.0 C / 301.1 K
INOVA-600 "inova600"

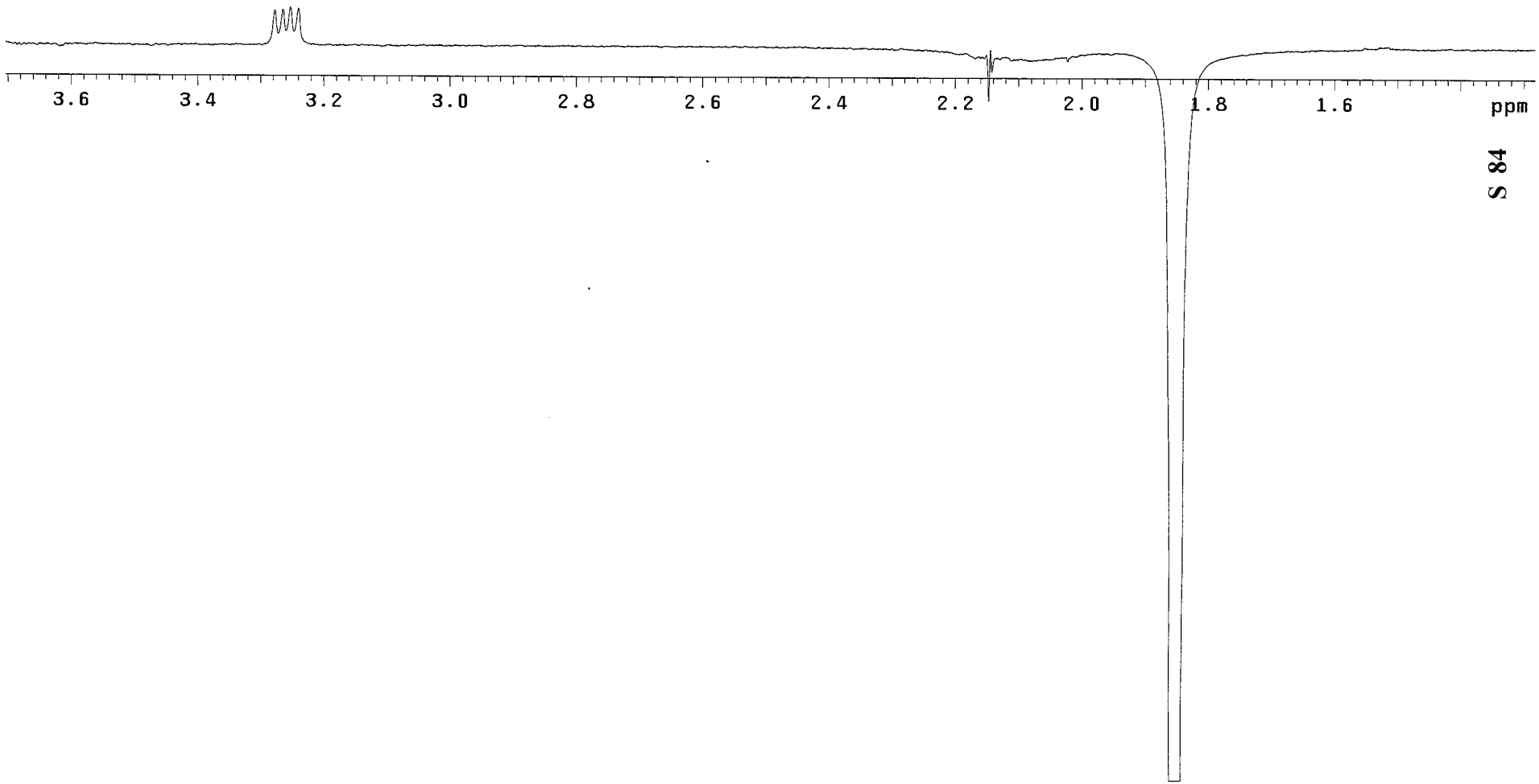
Relax. delay 1.000 sec
Pulse 30.0 degrees
Acq. time 4.000 sec
Width 9594.6 Hz
12 repetitions
OBSERVE H1, 599.6670079 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 131072
Total time 1 min, 0 sec



3



3

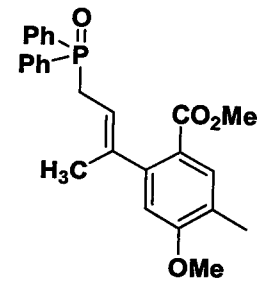


STANDARD CARBON PARAMETERS

Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 28.0 C / 301.1 K
User: 1-14-87
INOVA-600 "inova600"

Relax. delay 0.500 sec
Pulse 29.9 degrees
Acq. time 1.400 sec
Width 38004.8 Hz
528 repetitions
OBSERVE C13, 150.7863532 MHz
DECOUPLE H1, 599.6700024 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 53 hr, 1 min, 31 sec



3

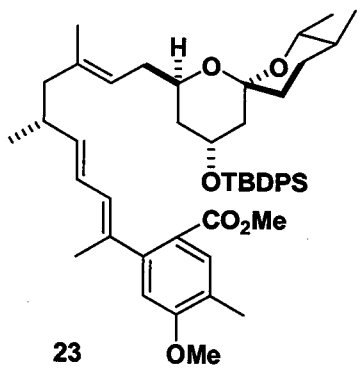
STANDARD PROTON PARAMETERS

Archive directory: /export/home/vnmr1/vnmrsys/data
Sample directory:
File: PROTON

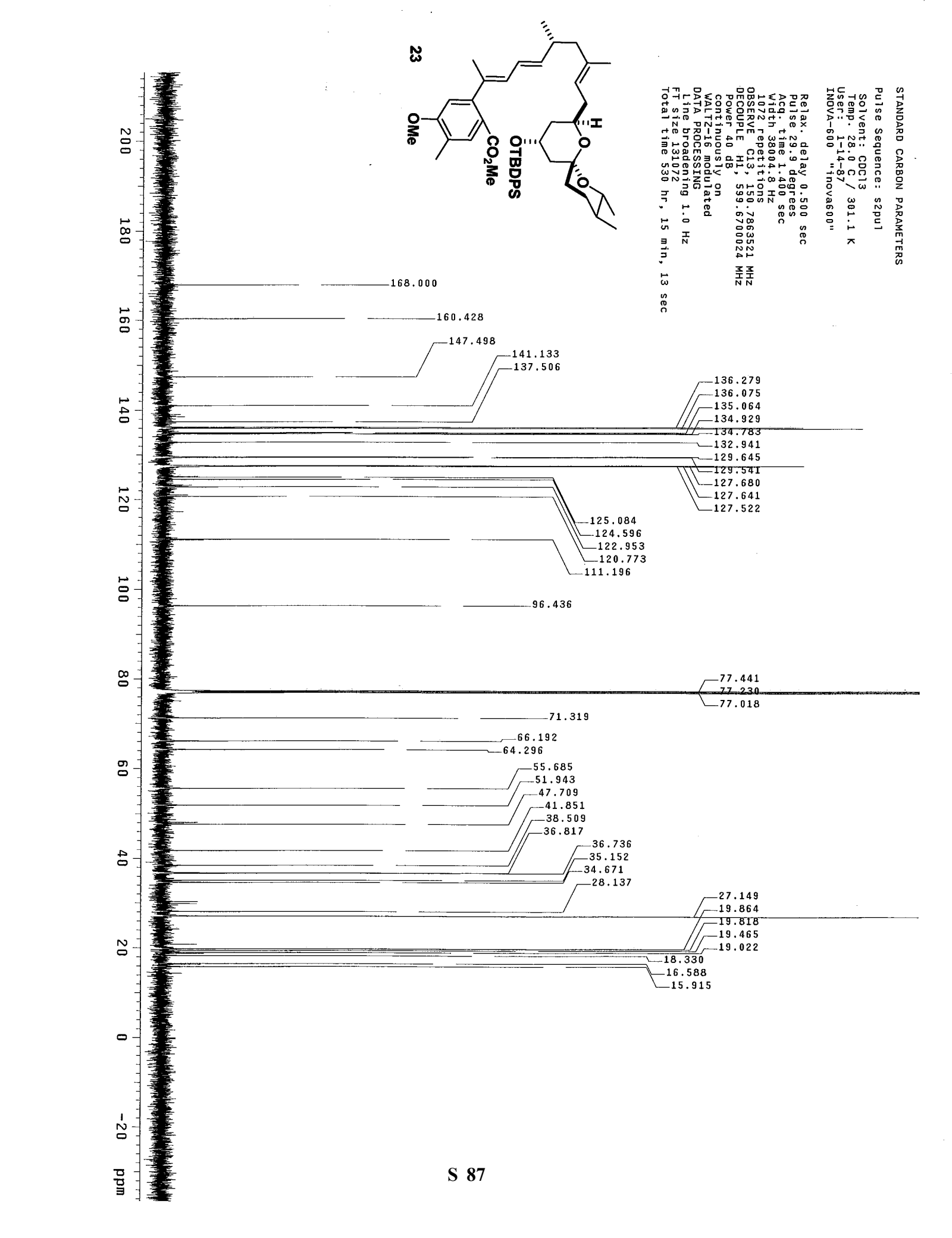
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 28.0 C / 301.1 K
INOVA-600 "inova600"

Relax. delay 1.000 sec
Pulse 30.0 degrees
Acq. time 4.000 sec
Width 9594.6 Hz
16 repetitions
OBSERVE H1, 599.6670085 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 131072
Total time 1 min, 20 sec



23


23
OMe
CO2Me
OTBDPS
H
O
O
STANDARD CARBON PARAMETERS
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 28.0 C / 301.1 K
User: 1-14-87
INOVA-600 "inova600"
Relax. delay 0.500 sec
Pulse 29.9 degrees
Acq. time 1.400 sec
width 38004.8 Hz
1072 repetitions
OBSERVE C13, 150.7863521 MHz
DECOUPLE H1, 599.6700024 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 530 hr, 15 min, 13 sec
168.000
160.428
147.498
141.133
137.506
136.279
136.075
135.064
134.929
134.783
132.941
129.645
129.541
127.680
127.641
127.522
125.084
124.596
122.953
120.773
111.196
96.436
77.441
77.230
77.018
71.319
66.192
64.296
55.685
51.943
47.709
41.851
38.509
36.817
36.736
35.152
34.671
28.137
27.149
19.864
19.818
19.465
19.022
18.330
16.588
15.915
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

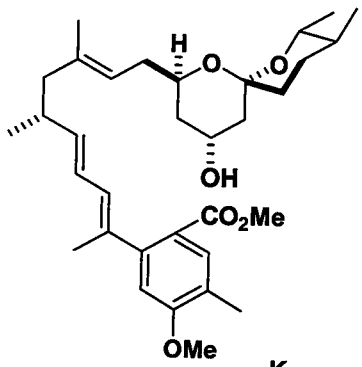
STANDARD PROTON PARAMETERS

Archive directory: /export/home/vnmr1/vnmrsys/data
Sample directory:
File: PROTON

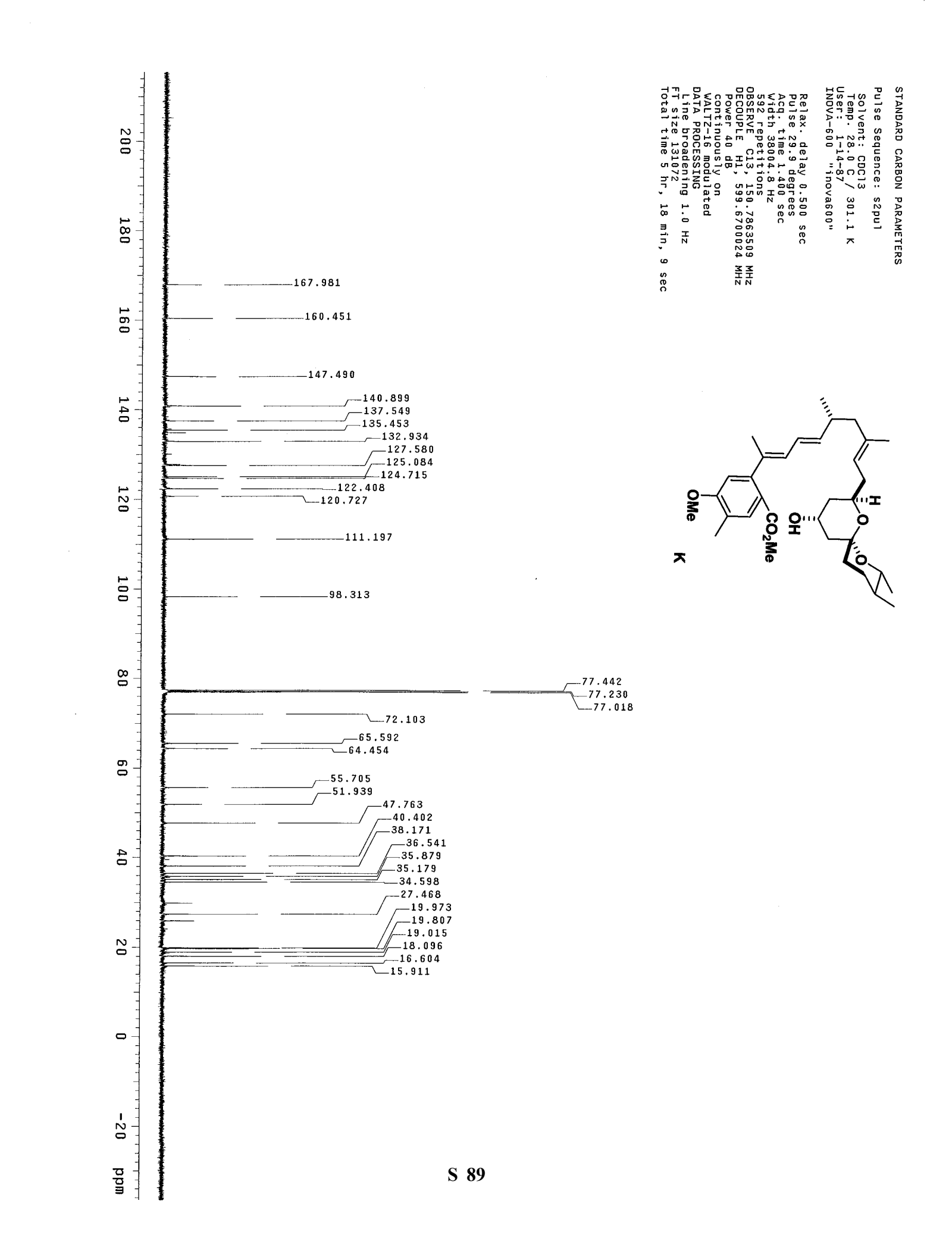
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 28.0 C / 301.1 K
INOVA-600 "inova600"

Relax. delay 1.000 sec
Pulse 30.0 degrees
Acq. time 4.000 sec
Width 9594.6 Hz
15 repetitions
OBSERVE H1, 599.6670141 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 131072
Total time 1 min, 15 sec



K


STANDARD CARBON PARAMETERS
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 28.0 C / 301.1 K
User: 1-14-87
INOVA-600 "inova600"
Relax. delay 0.500 sec
Pulse 29.9 degrees
Acq. time 1.400 sec
width 38004.8 Hz
592 repetitions
OBSERVE C13, 150.7863509 MHz
DECOUPLE H1, 599.6700024 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 5 hr, 18 min, 9 sec
OMe
OH
CO2Me
K
167.981
160.451
147.490
140.899
137.549
135.453
132.934
127.580
125.084
124.715
122.408
120.727
111.197
98.313
77.442
77.230
77.018
72.103
65.592
64.454
55.705
51.939
47.763
40.402
38.171
36.541
35.879
35.179
34.598
27.468
19.973
19.807
19.015
18.096
16.604
15.911
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

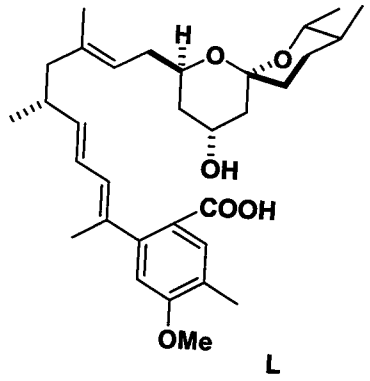
STANDARD PROTON PARAMETERS

Archive directory: /export/home/vnmr1/vnmrsys/data
Sample directory:
File: PROTON

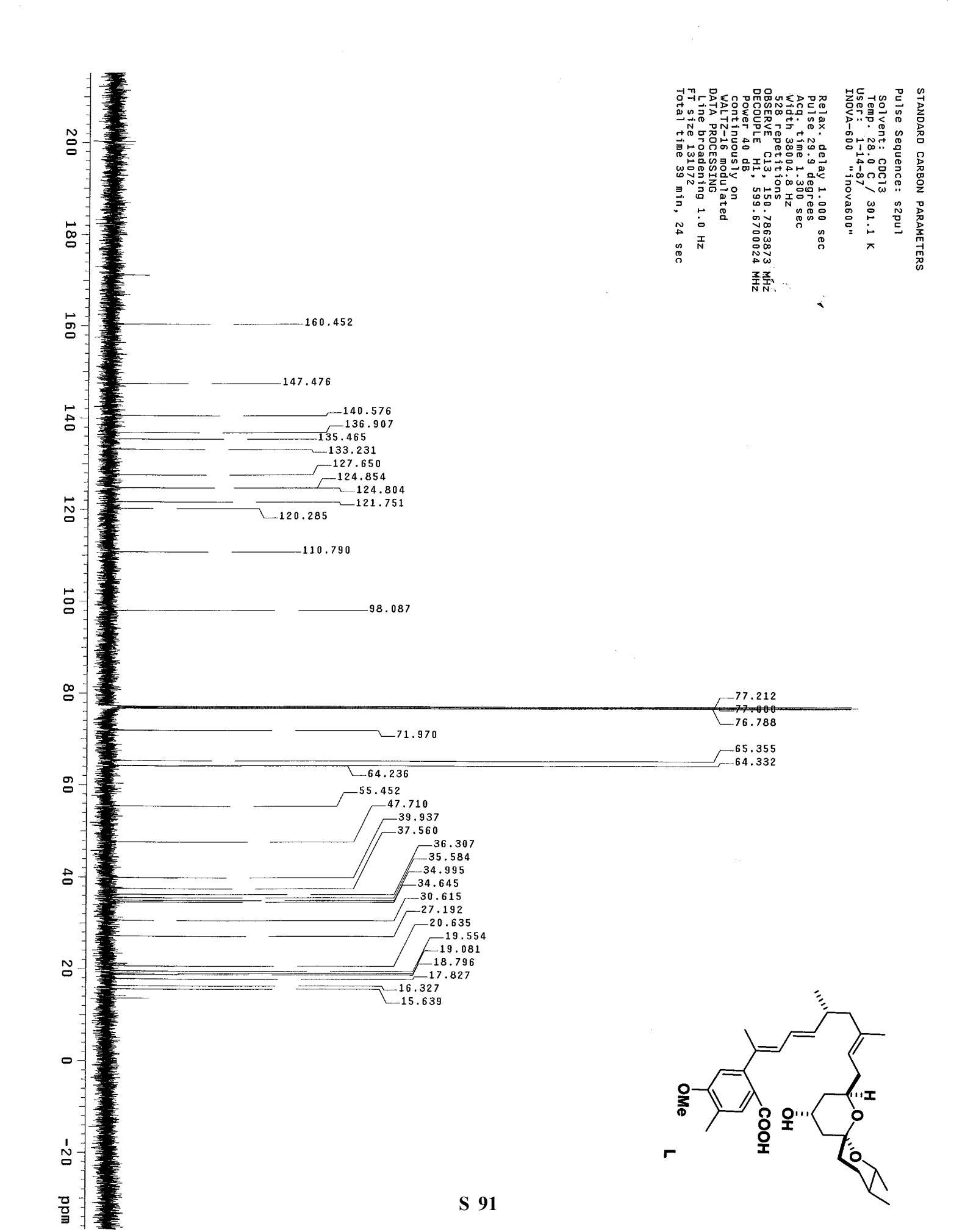
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 28.0 C / 301.1 K
INOVA-600 "inova600"

Relax. delay 1.000 sec
Pulse 30.0 degrees
Acq. time 4.000 sec
Width 9594.6 Hz
2 repetitions
OBSERVE H1, 599.6670039 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 131072
Total time 0 min, 10 sec



L


STANDARD CARBON PARAMETERS
Pulse Sequence: s2pul
Solvent: CDCl3
Temp: 28.0 C/ 301.1 K
User: 1-14-87
INOVA-600 "inova600"
Relax. delay 1.000 sec
Pulse 29.9 degrees
Acq. time 1.300 sec
Width 38004.8 Hz
528 repetitions
OBSERVE C13, 150.7863873 MHz
DECOUPLE H1, 599.6700024 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 39 min, 24 sec
160.452
147.476
140.576
136.907
135.465
133.231
127.650
124.854
124.804
121.751
120.285
110.790
98.087
77.212
77.000
76.788
71.970
65.355
64.332
64.236
55.452
47.710
39.937
37.560
36.307
35.584
34.995
34.645
30.615
27.192
20.635
19.554
19.081
18.796
17.827
16.327
15.639
200
180
160
140
120
100
80
60
40
20
0
-20
ppm
OMe
COOH
OH
H
O
O
L

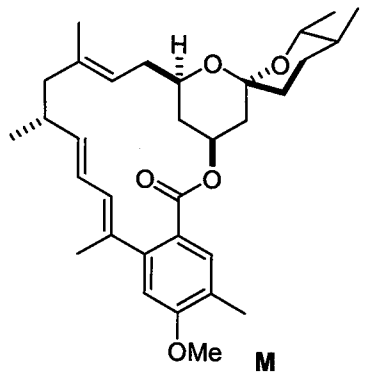
STANDARD PROTON PARAMETERS

Archive directory: /export/home/vnmr1/vnmrsys/data
Sample directory:
File: PROTON

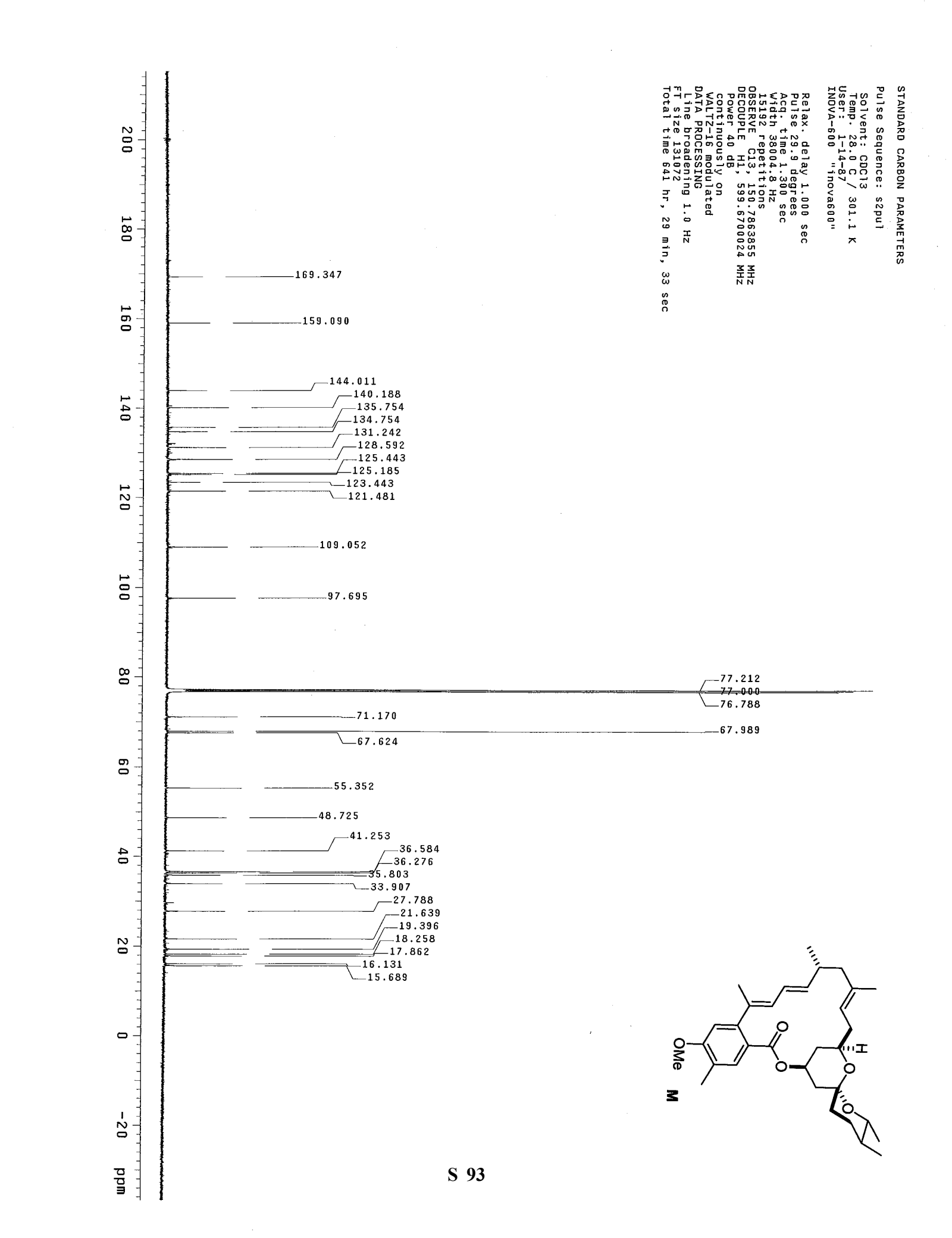
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 28.0 C / 301.1 K
INOVA-600 "inova600"

Relax. delay 1.000 sec
Pulse 30.0 degrees
Acq. time 4.000 sec
Width 9594.6 Hz
10 repetitions
OBSERVE H1, 599.6670068 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 131072
Total time 0 min, 50 sec



M


STANDARD CARBON PARAMETERS
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 28.0 C / 301.1 K
User: 1-14-87
INOVA-600 "inova600"
Relax. delay 1.000 sec
Pulse 29.9 degrees
Acq. time 1.300 sec
Width 38004.8 Hz
15192 repetitions
OBSERVE C13, 150.7863855 MHz
DECOUPLE H1, 599.6700024 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 641 hr, 29 min, 33 sec
169.347
159.090
144.011
140.188
135.754
134.754
131.242
128.592
125.443
125.185
123.443
121.481
109.052
97.695
77.212
77.000
76.788
71.170
67.989
67.624
55.352
48.725
41.253
36.584
36.276
35.803
33.907
27.788
21.639
19.396
18.258
17.862
16.131
15.689
200
180
160
140
120
100
80
60
40
20
0
-20
ppm
OMe
M

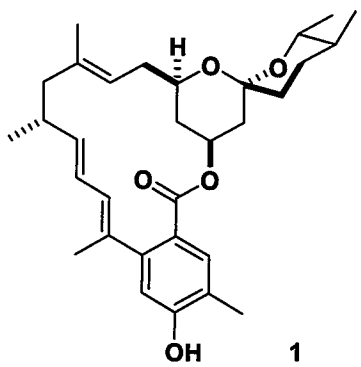
STANDARD PROTON PARAMETERS

Archive directory: /export/home/vnmr1/vnmrsys/data
Sample directory:
File: PROTON

Pulse Sequence: s2pul

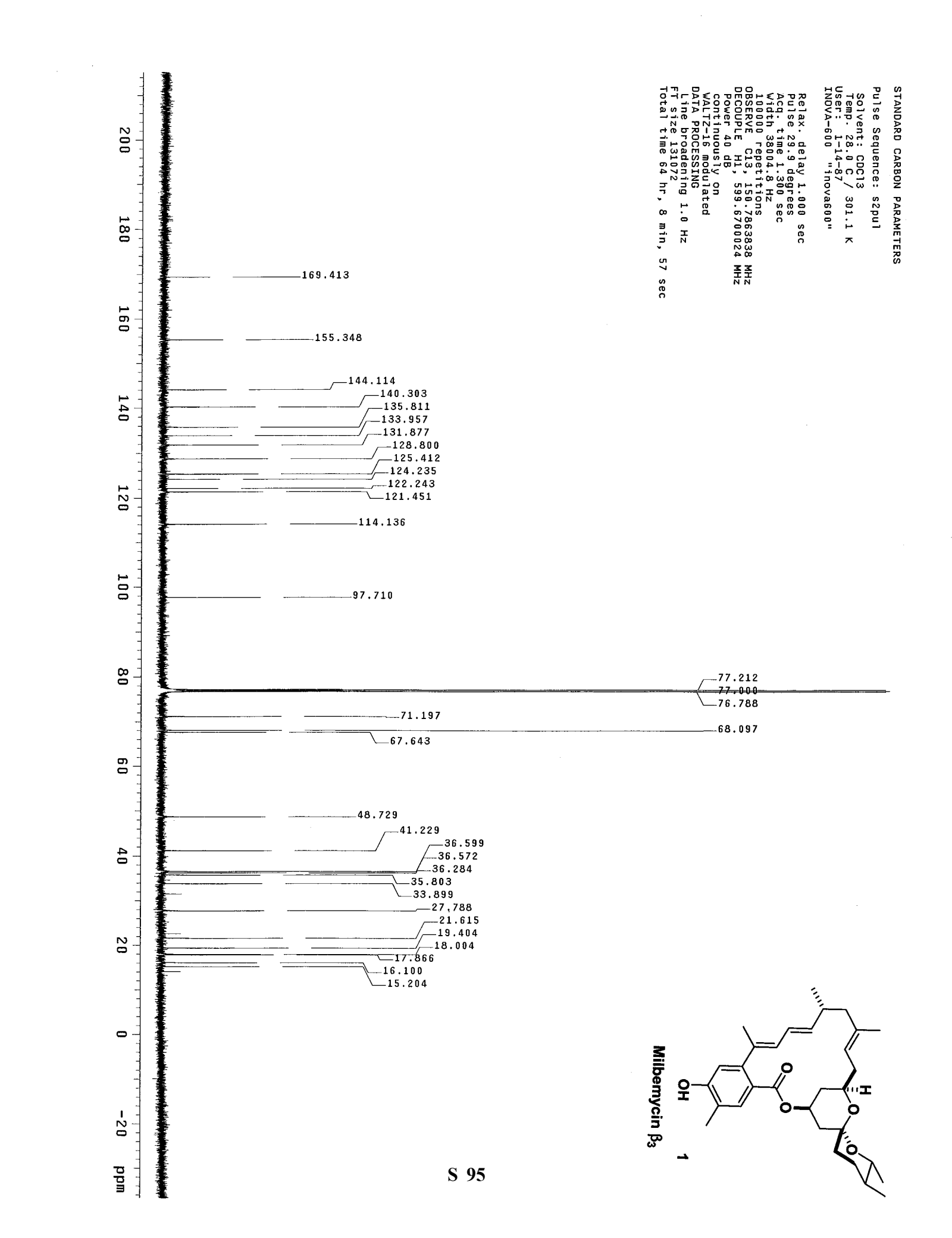
Solvent: CDCl3
Temp. 28.0 C / 301.1 K
INOVA-600 "inova600"

Relax. delay 1.000 sec
Pulse 30.0 degrees
Acq. time 4.000 sec
Width 9594.6 Hz
30 repetitions
OBSERVE H1, 599.6670039 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 131072
Total time 2 min, 30 sec



1

Milbemycin β_3


STANDARD CARBON PARAMETERS
Pulse Sequence: s2pul
Solvent: CDCl3
Temp: 28.0 C / 301.1 K
User: 1-14-87
INOVA-600 "inova600"
Relax. delay 1.000 sec
Pulse 29.9 degrees
Acq. time 1.300 sec
width 38004.8 Hz
100000 repetitions
OBSERVE C13, 150.7863838 MHz
DECOUPLE H1, 599.6700024 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 64 hr, 8 min, 57 sec
169.413
155.348
144.114
140.303
135.811
133.957
131.877
128.800
125.412
124.235
122.243
121.451
114.136
97.710
77.212
77.000
76.788
71.197
68.097
67.643
48.729
41.229
36.599
36.572
36.284
35.803
33.899
27.788
21.615
19.404
18.004
17.866
16.100
15.204
200
180
160
140
120
100
80
60
40
20
0
-20
ppm
OH
O
O
H
O
O
Milbemycin β3
1