Supporting Information

The synthesis and antibacterial activity of doxycycline neoglycosides

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Figure S1. Doxycycline neoglycoside library (Grey colored neoglycosides represent failed reactions)

Table S1. Key characterization data for doxycycline neoglycosides.

Neoglycoside (see Figure 1)	α anomeric H1		β anomeric H1		α/β ration	H 2[a]	HRESI [M+H] m/z	
	Δ (ppm)	*J* (Hz)	Δ (ppm)	*J* (Hz)		Δ (ppm)	Measured	Calculated
Dx01	n.d [b]	n.d [b]	4.26 ppm	8.7 Hz	β only	3.38 ppm	709.25484	709.2563
Dx02	n.d [b]	n.d [b]	4.19 ppm	8.8 Hz	β only	3.36 ppm	679.24703	679.2457
Dx03	n.d [b]	n.d [b]	4.44 ppm	1.0 Hz	β only	3.59 ppm	693.26213	693.2614
Dx04	n.d [b]	n.d [b]	4.26 ppm	9.0 Hz	β only	3.55 ppm	709.25597	709.2563
Dx05	n.d [b]	n.d [b]	4.42 ppm	10.0 Hz	β only	3.72 ppm	750.28313	750.2828
Dx06	n.d [b]	n.d [b]	4.22 ppm	8.6 Hz	β only	n.d [b]	693.26212	693.2641
Dx07	4.73 ppm	3.9 Hz	4.54 ppm	8.8 Hz	α/β=1/4	n.d [b]	679.24632	679.2457
Dx09	n.d [b]	n.d [b]	4.56 ppm	6.1 Hz	β only	3.43 ppm	737.24934	737.2512
Dx10	n.d [b]	n.d [b]	4.27 ppm	9.3 Hz	β only	3.39 ppm	723.27208	723.2719
Dx11	n.d [b]	n.d [b]	4.26 ppm	8.2 Hz	β only	3.37 ppm	709.25706	709.2563
Dx12	4.61 ppm	5.2 Hz	4.18 ppm	9.0 Hz	α/β=1/5	n.d [b]	679.24591	679.2457
Dx13	4.22 ppm	4.5 Hz	4.05 ppm	5.2 Hz	α/β=3/1	n.d [b]	649.23770	649.2352
Dx14	n.d [b]	n.d [b]	4.50 ppm	9.9 Hz	β only	1.86 ppm	688.31860	688.3188
Dx15	4.69 ppm	4.5 Hz	4.46 ppm	9.4 Hz	α/β=1/1	3.33 ppm/ 3.40 ppm	792.29846	792.2934
Dx16	n.d [b]	n.d [b]	4.36 ppm	8.5 Hz	β only	3.34 ppm	734.26611	734.2628
Dx17	4.80 ppm	singlet	4.27 ppm	9.5 Hz	α/β=1/1	3.42 ppm	734.26129	734.2628
Dx18	n.d [b]	n.d [b]	4.29 ppm	9.3 Hz	β only	3.65 ppm	711.25146	711.2520
Dx19	n.d [b]	n.d [b]	4.26 ppm	9.3 Hz	β only	3.62 ppm	709.25671	709.2563
Dx20	n.d [b]	n.d [b]	4.30 ppm	9.2 Hz	β only	3.48 ppm	871.31004	871.3091
Dx21	4.79	singlet	4.65 ppm	10.0 Hz	α/β=1/1	n.d [b]	794.28488	794.2839
Dx22	n.d [b]	n.d [b]	4.00 ppm	6.1 Hz /2.2 Hz	β only	2.61 ppm/ 2.79 ppm	677.26693	677.2665
Dx23	4.74 ppm	3.2Hz	4.56 ppm	9.7 Hz	α/β=1/1	n.d [b]	822.30525	822.3040
Dx25	n.d [b]	n.d [b]	4.26 ppm	8.8 Hz	β only	3.39 ppm	862.41238	862.4080
Dx26a	5.30 ppm	3.5 Hz	n.d.	n.d.	α only	3.05 ppm	708.27445	708.2723
Dx26b	n.d [b]	n.d [b]	4.55 ppm	10.0 Hz	β only	3.08 ppm	708.27352	708.2723
Dx27	n.d [b]	n.d [b]	4.37 ppm	8.8 Hz	β only	3.41 ppm	708.27284	708.2723
Dx29	n.d [b]	n.d [b]	4.40 ppm	9.0 Hz	β only	3.68 ppm	711.25609	711.2520
Dx30	4.68 ppm	0.5 Hz	4.34 ppm	2.3 Hz	α/β=1/2	n.d [b]	709.25859	709.2563
Dx31	4.77 ppm	0.5 Hz	4.44 ppm	2.9 Hz	α/β=1/1	n.d [b]	734.26404	734.2638
Dx32	4.96 ppm	0.5 Hz	4.65 ppm	3.5 Hz	α/β=1/1	n.d [b]	708.27411	708.2723
Dx33	n.d [b]	n.d [b]	4.24 ppm	9.3 Hz	β only	3.62 ppm	734.26589	734.2628
Dx34	n.d [b]	n.d [b]	4.50 ppm	9.9 Hz	β only	3.34 ppm	708.27445	708.2723
Dx37	n.d [b]	n.d [b]	4.73 ppm	7.9 Hz	β only	4.15 ppm	804.25463	804.2546
Dx38	5.20 ppm	6.3 Hz	4.63 ppm	4.8 Hz	α/β=1/1	n.d [b]	693.26248	693.2641
Dx39	n.d [b]	n.d [b]	4.19 ppm	9.0 Hz	β only	3.28 ppm	704.25084	704.2522
Dx40	n.d [b]	n.d [b]	4.47 ppm	10.0 Hz	β only	3.08 ppm	678.25815	678.2617
Dx41	n.d [b]	n.d [b]	4.22 ppm	4.4 Hz	β only	3.47 ppm	704.25589	704.2522

[a] Identification based upon gCOSY coupling with anomeric proton. [b] Not determined

Table S2. Neoglycoside antibacterial assays (MIC in μg/mL).

Neoglycoside (Fig. 1)	Sugar Utilized	*E. coli* 25922	*E. coli* 1-849	*S. aureus* R2507
1	none	**1**	**8**	**2**
2	none	**1**	**2**	**4**
4	none	**4**	**8**	**4**
Dx01	D-glucose (**5**)	**64**	**>128**	**64**
Dx02	D-xylose (**6**)	**8**	**64**	**32**
Dx03	L-rhamnose (**7**)	**32**	**>128**	**64**
Dx04	D-galactose (**8**)	**4**	**>128**	**64**
Dx05	*N*-acetyl-D-glucosamine (**9**)	**8**	**64**	**64**
Dx06	D-fucose (**10**)	**16**	**>128**	**>128**
Dx07	D-ribose (**11**)	**4**	**>128**	**64**
Dx09	D-glucuronic acid (**13**)	**16**	**>128**	**64**
Dx10	3-*O*-methyl-D-glucose (**14**)	**>128**	**>128**	**>128**
Dx11	L-glucose (**15**)	**8**	**>128**	**64**
Dx12	D-arabinose (**16**)	**8**	**64**	**32**
Dx13	D-erythrose (**17**)	**4**	**64**	**32**
Dx14	forosamine (**18**)	**4**	**32**	**16**
Dx15	2-deoxy-2-*N*-alloc-D-glucosamine (**19**)	**8**	**16**	**8**
Dx16	6-deoxy-6-azido-D-glucose (**20**)	**8**	**64**	**64**
Dx17	2-deoxy-2-azido-D-glucose (**21**)	**16**	**8**	**8**
Dx18	3-deoxy-3-fluoro-D-glucose (**22**)	**32**	**>64**	**>64**
Dx19	L-galactose (**23**)	**8**	**64**	**32**
Dx20	D-cellobiose (**24**)	**16**	**64**	**64**
Dx21	streptozocin (**25**)	**16**	**64**	**32**
Dx22	digitoxose (**26**)	**8**	**32**	**32**
Dx23	*N*-acetylmuramic acid (**27**)	**8**	**32**	**16**
Dx25	6-deoxy-6-*N*-decanoyl-D-glucosamine (**29**)	**>128**	**>128**	**>128**
Dx26a	2-deoxy-2-azido-D-glucose (**21**)	**4**	**4**	**4**
Dx26b	2-deoxy-2-azido-D-glucose (**21**)	**8**	**32**	**32**
Dx27	6-deoxy-6-azido-D-glucose (**20**)	**8**	**32**	**32**
Dx29	2-deoxy-2-fluoro-D-glucose (**31**)	**8**	**64**	**8**
Dx30	D-mannose (**32**)	**4**	**>128**	**32**
Dx31	2-deoxy-2-azido-D-mannose (**33**)	**32**	**>128**	**32**
Dx32	2-deoxy-2-azido-D-mannose (**33**)	**4**	**32**	**32**
Dx33	2-deoxy-2-azido-D-galactose (**34**)	**16**	**>128**	**8**
Dx34	2-deoxy-2-azido-D-galactose (**34**)	**8**	**64**	**32**
Dx37	2-deoxy-2-*N*-trifluoroacetyl-D-glucosamine (**37**)	**4**	**32**	**16**
Dx38	2-deoxy-D-glucose (**38**)	**16**	**>128**	**32**
Dx39	2-deoxy-2-azido-D-xylose (**39**)	**16**	**64**	**32**
Dx40	2-deoxy-2-azido-D-xylose (**39**)	**8**	**64**	**32**
Dx41	4-deoxy-4-azido-L-ribose (**40**)	**16**	**64**	**32**

Table S3. Neoglycoside single dose (10 μM) cytotoxicity assays.

Neoglycoside (see Figure 1)	Sugar utilized	A549 viability (%)	IMR 90 viability (%)
1	none	**97.6**	**98.3**
2	none	**99.3**	**103.3**
4	none	**95.9**	**99.2**
Dx01	D-glucose (**5**)	**96.6**	**98.5**
Dx02	D-xylose (**6**)	**101**	**104.1**
Dx03	L-rhamnose (**7**)	**98**	**106.8**
Dx09	D-glucuronic acid (**13**)	**98.9**	**98.8**
Dx12	D-arabinose (**16**)	**97.2**	**101.7**
Dx13	D-erythrose (**17**)	**98.2**	**99.3**
Dx14	forosamine (**18**)	**96.9**	**100.7**
Dx15	2-deoxy-2-*N*-alloc-D-glucosamine (**19**)	**98.8**	**97.6**
Dx23	*N*-acetylmuramic acid (**27**)	**97.7**	**104.4**
Dx26a	2-deoxy-2-azido-D-glucose (**21**)	**99.1**	**94.6**
Dx26b	2-deoxy-2- azido-D-glucose (**21**)	**95.6**	**101.7**
Dx32	2-deoxy-2-azido-D-mannose (**33**)	**97.1**	**98.9**
Dx37	2-deoxy-2-*N*-trifluoroacetyl-D-glucosamine (**37**)	**98.7**	**109.1**
Dx41	4-deoxy-4-azido-L-ribose (**40**)	**98.5**	**101.9**

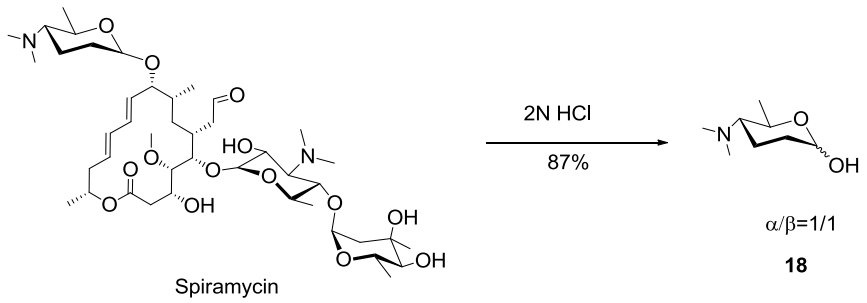
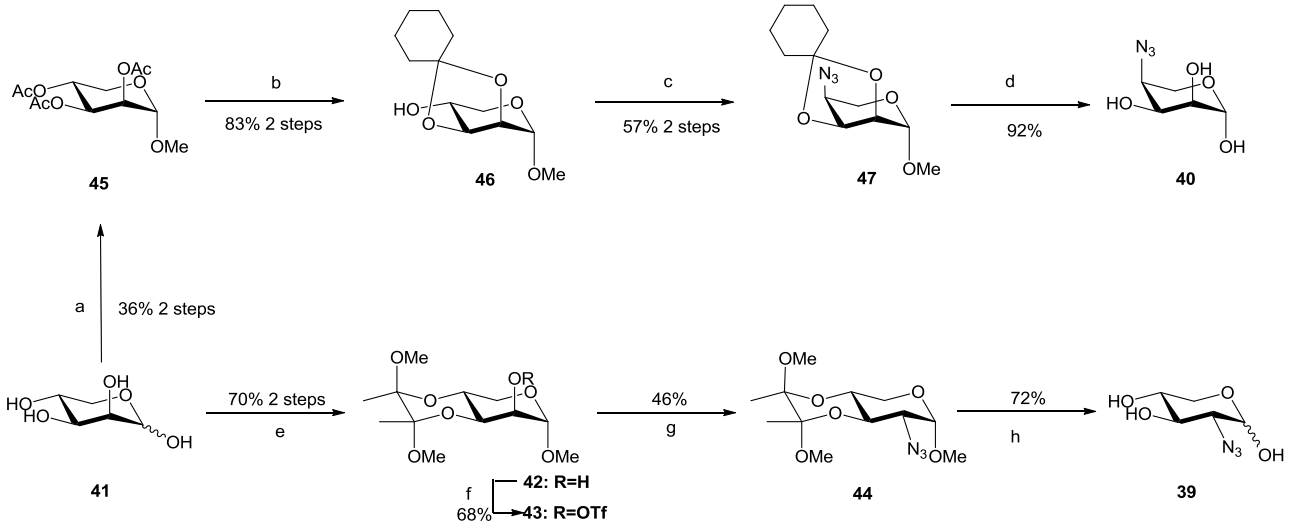


Figure S2. Synthesis of forosamine **18.**



(a) (1) MeOH, HCl, 48h, (2) Ac_2O, DMAP, Et_3N, CH_2Cl_2; (b) (1) NaOMe, MeOH/CH_2Cl_2, (2) Cyclohexanone dimethyl ketal, TsOH, CH_3CN; (c) (1) Tf_2O, Pyridine, CH_2Cl_2, (2) NaN_3, DMF; (d) 1 N HCl, 90°C, 3 h; (e) (1) MeOH, AcCl, 1 h, reflux, (2) Butanedione, $HC(OMe)_3$, CSA, MeOH, Reflux, 3 h; (f) (1) Tf_2O, Pyridine,CH_2Cl_2, (2) NaN_3, DMF (g) NaN_3, DMF, 80°C; (h) 2 N HCl, 90°C, 6h

Figure S3. Synthesis of 2-azido-D-xylose **39** and 4-azido-L-ribose **40**

Supplementary Methods

Forosamine (18).[1] Spiramycin (400 mg, 0.46 mmol) was refluxed for 16 h in 10 mL of 2 N HCl. The mixture was cooled to rt and filtered. The filtrate was neutralized to pH 7 by saturated NaOH solution and lyophilized. The residue was then extracted with 10 mL EtOH and the EtOH layer was concentrated under reduced pressure. The residue was purified by normal phase column chromatography using 10% MeOH/CH_2Cl_2 (with 0.5% Et_3N) to give forosamine (64 mg, 0.40 mmol, 87 %) as a white powder. ^{1}H NMR (500 MHz, CD_3OD) δ 5.22 (dd, *J* = 2.5, 2.0 Hz, 1 H, 1-Hα), 4.72 (dd, *J* = 9.0, 2.0 Hz, 1 H, 1-Hβ), 4.24 (dq, *J* = 9.5, 6.5 Hz, 1 H, 5-Hα), 3.79 (dq, *J* = 9.5, 6.5 Hz,1 H, 5-Hβ), 2.71 (s, 6 H, N(CH_3)α), 2.62 (s, 6 H, N(CH_3)β), 1.42–2.38 (m, 5 H + 5 H, 2-H, 3-H, 4-H), 1.32 (d, *J* = 6.5 Hz, 3 H, 6-Hβ), 1.25 (d, *J* = 6.5 Hz, 3 H, 6-Hα); ^{13}C NMR (100 MHz, CD_3OD) δ 95.6, 90.2, 74.2, 66.3, 65.6, 64.3, 39.6, 39.5, 32.0 (2C), 30.0 (2C), 19.1 (2C), 18.1, 15.2; HRESIMS *m/z* 160.1336 $[M + H]^+$ (Calcd for $C_8H_{17}NO$ 160.1332).

2-deoxy-2-azido-D-xylospyranoside (39). α/β=2/3 The solution of **44** (0.12 g, 0.40 mmol) in 1 mL 2 N HCl was heated under 90 ^oC for 6 h. After cool down of the solution, it was added with charcoal and $NaHCO_3$ (0.168 g, 2 mmol) and kept stirring until the evolution of gas stopped and tested neutral by PH paper. The solvent was removed and lyophilized to dry. The dried residue was loaded to a short column packed with layers of celite and silica gel and it was washed with 200 mL EtOAc, EtOAc/MeOH = 90/10, and CH_2Cl_2/MeOH = 80/20 solutions, respectively. After the 200 mL CH_2Cl_2/MeOH = 80/20 effluent was collected and removed solvent, the product (0.05 g, 0.29 mmol) was obtained with a yield of 72%. Colorless oil: ^{1}H NMR (CD_3OD, 400 MHz) δ 5.12 (d, *J* = 3.5 Hz, αH1, 1H), 4.42 (d, *J* = 8.0 Hz, βH1, 1 H), 3.9 (m,2 H), 3.8 (m, 2 H), 3.7 (m, 2 H), 3.6 (m, 2 H), 3.5 (m, 4 H), 3.2 (m, 2 H), 3.1 (m, 2 H); ^{13}C NMR (CD_3OD, 100 MHz) δ 96.8, 92.3, 75.3, 71.5, 70.8, 70.0, 68.2, 65.9, 64.1, 61.3; HRESI m/z 198.04854 $[M + Na]^+$ (Calcd for $C_5H_9N_3NaO_4$ 198.0485).

4-deoxy-4-azido-α-L-ribopyranoside (40). The solution of **47** (0.20 g, 0.74 mmol) in 2 mL 1 N HCl was heated under 90 ^oC for 3 hours. After cool down of the solution, it was added with charcoal and $NaHCO_3$ (0.168 g, 2 mmol) and kept stirring until the evolution of gas stopped and tested neutral by PH paper. The solvent was removed and lyophilized to dry and formed a white powder. The white powder was loaded on a short column packed with layers of celite and silica gel and washed with 200 mL EtOAc, EtOAc/MeOH = 90/10, and CH_2Cl_2/MeOH = 80/20 solutions, respectively. After the CH_2Cl_2/MeOH = 80/20 effluents was collected and removed solvent, the product (0.12 g, 0.69 mmol) was obtained with a yield of 92%. Colorless oil: ^{1}H NMR (CD_3OD, 500 MHz) δ 4.29 (d, *J* = 3.2 Hz, 1 H), 4.05 - 4.11 (m, 1 H), 3.99 - 4.04 (m, 1 H), 3.64 (dd, *J* = 13.2, 3.9 Hz, 1 H), 3.35 - 3.41 (m, 1 H), 3.14 (dd, *J* = 13.1, 2.3 Hz, 1 H); ^{13}C NMR (CD_3OD, 125 MHz) δ 71.3, 70.3, 67.4, 67.3, 44.9; HRESI m/z 198.04834 $[M + Na]^+$ (Calcd for $C_5H_9N_3NaO_4$ 198.0485).

1-methyl-3,4-*O*-(1,2-dimethoxy-1,2-dimethyl-1,2-ethanediyl)-α-D-lyxopyranoside (42). To a suspension of D-lyxose **41** (2 g, 13.3 mmol) in 60 mL MeOH, 1 mL acetyl chloride (15.5 mmol) was added dropwise and the resulting solution was reflux for 1 h. The reaction was cooled down to room temperature and was quenched by adding $NaHCO_3$ until the evolution of gas stopped. After filtration through celite and removal of the solvent, the residue was dissolved into 50 mL MeOH and to this was added anhydrous trimethyl orthoformate (10 mL, 91 mmol) and butanedione (4 mL, 46 mmol). To this was added camphorsulfonic acid (1.08 g, 4.6 mmol) with stirring and the solution was reflux for 3 h until the reaction was complete based upon TLC. The reaction was quenched by adding Et_3N (0.65 mL, 4.6 mmol). After the removal of the solvent *in vacuo*, the residue was diluted with EtOAc, washed with

[1]Procedure modified from that of Kuehne and Benson (Kuehne, M. E.; Benson, B. W. *J. Am. Chem. Soc*. **1965**, *87*, 4660). The spectral data for isolated forosamine was identical to that previously reported for synthetic standard (Tietze, L. F.; Böhnke, N.; Dietz, S. *Org. Lett.* **2009**, *11*, 2948).

$NaHCO_3$(sat), water and brine, dried over Na_2SO_4, and the solvent removed. The crude residue was purified by normal phase silica gel column (Gradient: Hexane/EtOAc = 90/10 to Hexane/EtOAc = 10/90). The product (2.58 g, 9.3 mmol) was obtained with a yield of 70% after two steps. White crystal: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.69 (d, *J* = 1.2 Hz, 1 H), 4.1 - 4.2 (m, 1 H), 3.9 (m, 1 H), 3.6 (m, 2 H), 3.3 (m, 1 H), 3.37 (s, 3 H), 3.27 (s, 3 H), 3.26 (s, 3 H), 2.68 (s, 1 H), 1.33 (s, 3 H), 1.28 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 101.3, 100.7, 99.9, 69.8, 68.8, 63.0, 60.6, 55.1, 48.2, 48.1, 17.95, 17.93; HRESI m/z 301.12519 $[M + Na]^+$ (Calcd for $C_{12}H_{22}NaO_7$ 301.1258).

1-methyl-2-triflyl-3,4-*O*-(1,2-dimethoxy-1,2-dimethyl-1,2-ethanediyl)-α-D-lyxopyranoside (43). To a solution of **42** (2.0 g, 7.2 mmol) and pyridine (0.92 mL, 11.5 mmol) in anhydrous CH_2Cl_2 (100 mL) cooled to 0 ^{o}C was added Tf_2O (1.81 mL, 10.8 mmol) in dropwise fashion. The reaction was stirred at 0 ^{o}C for 30 min until reaction was complete based upon TLC. The reaction was diluted with CH_2Cl_2 and washed with water, $NaHCO_3$(sat), and brine and organics dried over Na_2SO_4 and concentrated to 10 mL. The concentrated CH_2Cl_2 solution was added to a stirring 200 mL solution of NaN_3 (1.40 g, 21.6 mmol) in DMF and the reaction was stirred at room temperature for 24 h. The reaction was filtered through celite and washed with EtOAc (50 mL, x3). After the removal of the solvent, the residue was purified by normal phase silica gel column (Gradient: Hexane/EtOAc = 100/0 to Hexane/EtOAc = 50/50). The product **43** (2.0 g, 4.9 mmol) was obtained with a yield of 68%. White oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.8 (m, 1 H), 4.81 (d, *J* = 1.5 Hz, 1 H), 4.1 (m, 2 H), 3.6 - 3.7 (m, 2 H), 3.40 (s, 3 H), 3.26 (s, 3 H), 3.25 (s, 3 H), 1.28 (s, 3 H), 1.27 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 120.0 (q, 1 C), 100.9, 100.1, 99.1, 83.0, 65.8, 62.7, 60.7, 55.5, 48.4, 48.2, 17.8, 17.5; HRESI m/z 433.07457 $[M + Na]^+$ (Calcd for $C_{13}H_{21}F_3O_9SNa$ 433.0751).

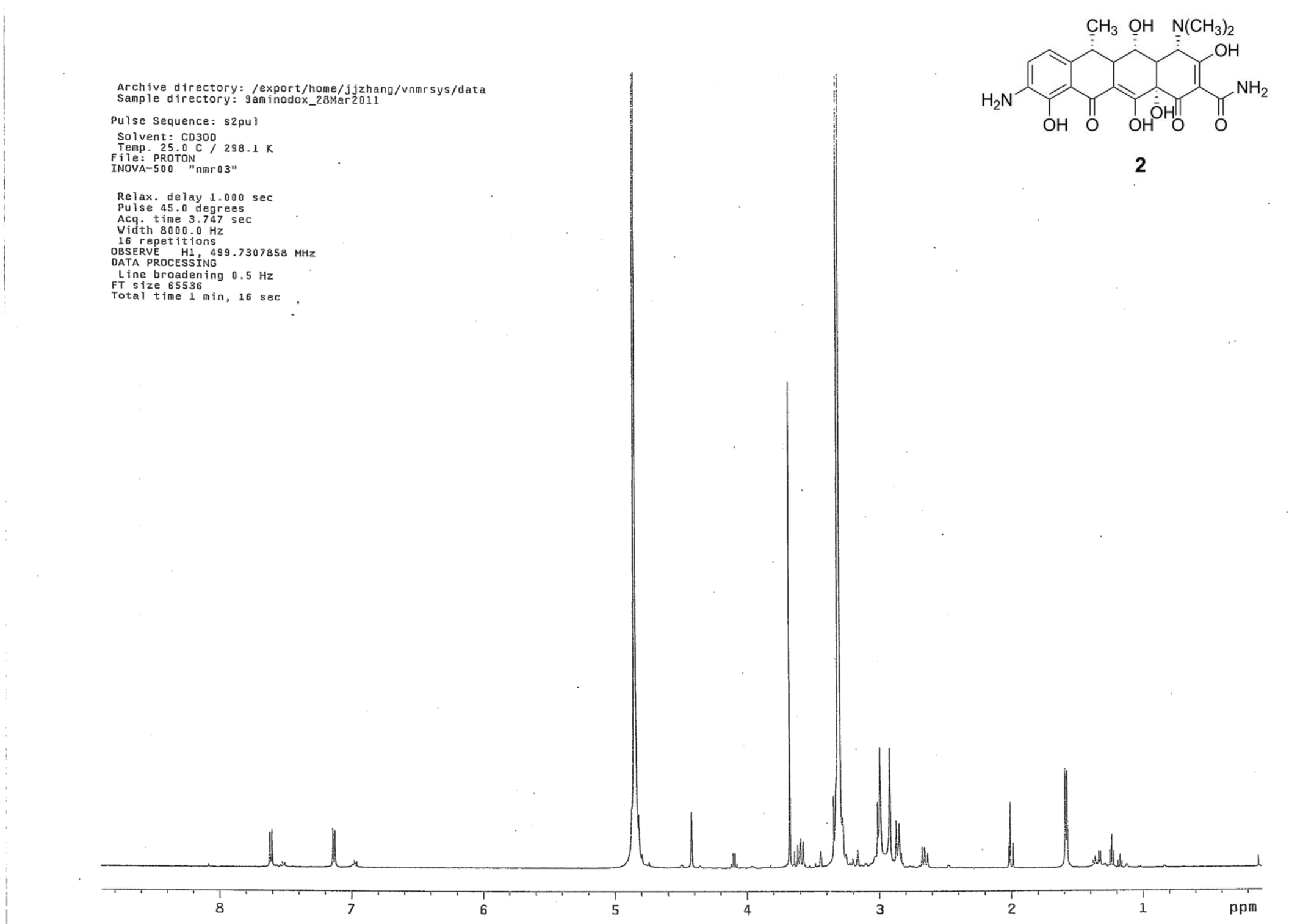
1-methyl-2-deoxy-2-azido-3,4-*O*-(1,2-dimethoxy-1,2-dimethyl-1,2-ethanediyl)-α-D-xylopyranoside (44). A solution of **43** (2.0 g, 4.9 mmol) and NaN_3 (1.40 g, 21.6 mmol) in 100 mL DMF was heated to 80 ^{o}C for 12 h. The reaction was cooled down to room temperature and was filtered and washed with 200 mL of EtOAc. After the removal of solvent under reduced pressure, the residue was purified by normal phase silica gel column (Gradient: Hexane/EtOAc = 100/0 to Hexane/EtOAc = 50/50). The product (0.68 g, 2.24 mmol) was obtained with a yield of 46%. White solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.73 (d, *J* = 3.4 Hz, 1 H), 4.18 (dd, *J* = 10.6, 9.6 Hz, 1 H), 3.80 (ddd, *J* = 10.9, 9.6, 5.4 Hz, 1 H), 3.66 (t, *J* = 10.6 Hz, 1 H), 3.6 (m, 1 H), 3.34 (dd, *J* = 3.3, 1.6 Hz, 1 H), 3.41 (s, 3 H), 3.36 (s, 3 H), 3.28 (s, 3 H), 1.35 (s, 3 H), 1.30 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 100.4, 100.0, 99.5, 68.2, 66.9, 60.4, 59.8, 55.4, 48.5, 48.2, 17.9, 17.7; HRESI m/z 326.13206 $[M + Na]^+$ (Calcd for $C_{12}H_{21}N_3NaO_6$ 326.1323).

1-methyl-2,3,4-acetyl-α-D-lyxopyranoside (45). To a suspension of D-lyxose **41** (1.0 g, 6.7 mmol) in 100 mL MeOH at 0 ^{o}C, HCl (0.4 mL) was added in dropwise fashion and the reaction was stirred at room temperature until the reaction was completed based upon TLC (2 days). The reaction was quenched by adding $NaHCO_3$ (1.0 g, 9.4 mmol) and stirred until the evolution of gas stopped. The mixture was filtered through celite and the solvent of the filtrate was removed *in vacuo* to give a sticky oil. To this oil was added 200 mL CH_2Cl_2, Et_3N (4.5 mL, 32 mmol) and DMAP (0.1 g, 0.8 mmol), and Ac_2O (1.9 mL, 20 mmol) was subsequently added in dropwise fashion and the reaction stirred at room temperature for 2 h. The reaction was quenched by diluting with EtOAc and adding $NaHCO_3$ (sat) solution follwed by stirring for 1 h. The organic layer was washed with 1 N HCl, $NaHCO_3$, H_2O and brine, the organics were dried over Na_2SO_4, and upon removal of solvent the crude product was purified by normal phase silica gel column (Gradient: Hexane/EtOAc = 100:0 to Hexane/EtOAc = 40/60). The α anomer **45** (0.69 g, 2.38 mmol, 36%) and β anomer (0.64 g, 3.1 mmol, 33%) where chromatographically resolved under these conditions. The α anomer was a white powder: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.28 (dd, *J* = 9.7, 3.5 Hz, 1 H), 5.12 (m, 2 H), 4.59 (d, *J* = 2.5 Hz, 1 H), 3.83 (dd, *J* = 11.0, 5.4 Hz, 1 H), 3.56 (dd, *J* = 10.7, 9.9 Hz, 1 H), 3.36 (s, 3 H), 2.09 (s, 3 H), 2.00 (s, 3 H), 1.98 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.2, 170.1, 169.9, 98.8, 69.6, 68.6, 67.0, 59.8, 55.5, 21.01, 20.98, 20.93; HRESI m/z 313.08842 $[M + Na]^+$ (Calcd for $C_{12}H_{18}NaO_8$ 313.0894).

1-methyl-2,3-*O*-cyclohexylidene-α-D-lyxopyranoside (46). To the solution of **45** (0.69 g, 2.38 mmol) in 50 mL MeOH was added 0.2 M NaOMe solution and the reaction was stirred for 1 h. The reaction was quenched by adding Amberlite acidic resin and stirred for 15 min. Filtration and removal of the solvent gave the crude product which was dissolved in 50 mL CH_3CN and to which was added TsOH (0.23 g, 1.21 mmol) and cyclohexanol dimethyl ketal (1.48 mL, 9.76 mmol). The reaction was stirred under room temperature for 4 h. The reaction was quenched by adding Et_3N (0.34 mL, 2.44 mmol) and solvent removed under vacuum. The residue was diluted with EtOAc and washed with water and brine. The organics were dried over Na_2SO_4 and solvent removed. Crude product was purified via normal phase silica gel column (Gradient: Hexane/EtOAc = 100/0 to Hexane/EtOAc = 50/50), to give 0.48 g of desired product (1.97 mmol 83% after 2 steps). White oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.66 (d, *J* = 2.7 Hz, 1 H), 4.21 (dd, *J* = 5.7, 4.8 Hz, 1 H), 4.11 (dd, *J* = 6.1, 2.7 Hz, 1 H), 3.8 (m, 2 H), 3.7 (m, 1 H), 3.46 (s, 3 H), 3.15 (d, *J* = 7.3 Hz, 1 H), 1.6 - 1.7 (m, 4 H), 1.5 - 1.6 (m, 4 H), 1.4 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 110.3, 100.3, 76.3, 74.3, 67.7, 63.0, 56.0, 37.6, 35.1, 25.2, 24.2, 23.8; HRESI m/z 267.11964 $[M + Na]^+$ (Calcd for $C_{12}H_{20}NaO_5$ 267.1203).

1-methyl-2,3-*O*-cyclohexylidene-4-deoxy-4-azido-α-L-ribopyranoside (47). To the solution of **46** (0.48 g, 1.97 mmol) and pyridine (0.25 mL, 3.2 mmol) in anhydrous CH_2Cl_2 (100 mL) at 0 ^{o}C was added Tf_2O (0.50 mL, 3.0 mmol) in dropwise fashion. The reaction was stirred at 0 ^{o}C until the reaction was complete based upon TLC (30 min). The reaction was diluted with CH_2Cl_2 (100 mL) and the organics were washed with water, $NaHCO_3$ (sat), and brine, dried over Na_2SO_4 and concentrated to 10 mL. The concentrated CH_2Cl_2 solution was added to a stirring solution of NaN_3 (0.38 g, 5.9 mmol) in DMF (150 mL) and the reaction was stirred at room temperature for 24 h. The reaction was filtered through celite and washed with EtOAc (50 mL, x3). After the removal of the solvent, the crude residue was purified by silica gel column (Gradient: Hexane/EtOAc = 100/0 to Hexane/EtOAc = 60/40) to give 0.30 g of the desired product (1.12 mmol, 57% after 2 steps). White oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.5 (m, 1 H), 4.51 (d, *J* = 3.9 Hz, 1 H), 4.04 (dd, *J* = 6.2, 3.9 Hz, 1 H), 3.8 (m, 1 H), 3.7 - 3.8 (m, 2 H), 3.45 (s, 3 H), 1.7 - 1.8 (m, 2 H), 1.5 - 1.7 (m, 6 H), 1.4 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 111.5, 101.3, 75.1, 72.8, 60.3, 56.5, 54.8, 36.8, 34.9, 25.2, 24.2, 23.8; HRESI m/z 292.12601 $[M + Na]^+$ (Calcd for $C_{12}H_{19}N_3NaO_4$ 292.1268).

Table S4. NMR spectra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Pulse Sequence: s2pul
Solvent: CD3OD
Temp. 25.0 C / 298.1 K
File: PROTON
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Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 3.747 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7307858 MHz
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 1 min, 16 sec
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H2N
NH2
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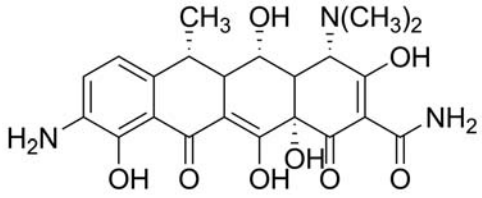
OH
2
8
7
6
5
4
3
2
1
ppm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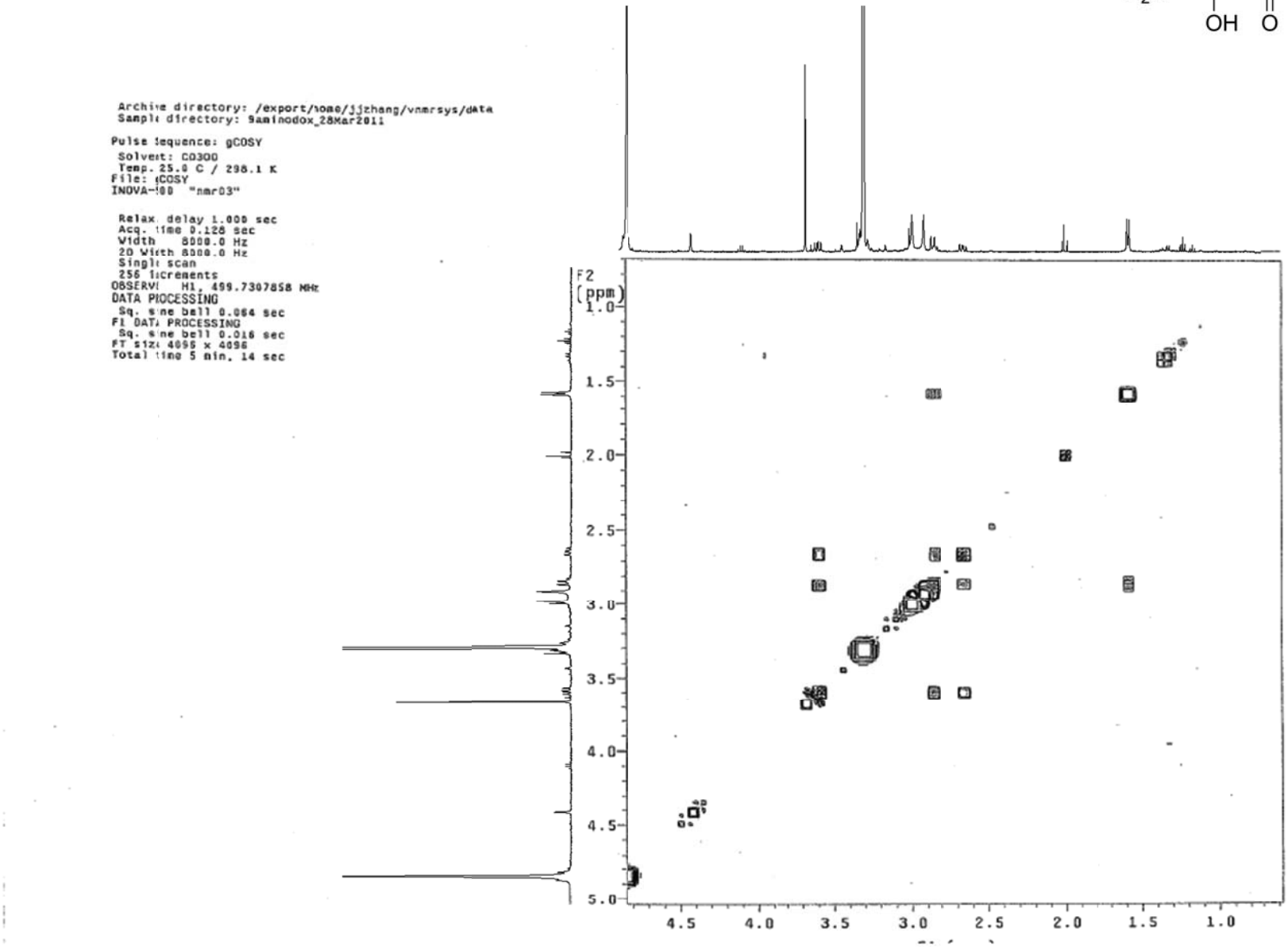
OH
H2N
NH2
OH O OH OH O O

2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Sample directory: 9aminodox_28Mar2011
Pulse sequence: gCOSY
Solvent: CD3OD
Temp. 25.0 C / 298.1 K
File: gCOSY
INOVA-500 "nmr03"
Relax. delay 1.000 sec
Acq. time 0.128 sec
Width 8000.0 Hz
2D Width 8000.0 Hz
Single scan
256 increments
OBSERVE H1, 499.7307858 MHz
DATA PROCESSING
Sq. sine bell 0.064 sec
FI DATA PROCESSING
Sq. sine bell 0.016 sec
FT size 4096 x 4096
Total time 5 min, 14 sec
F2 (ppm)
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
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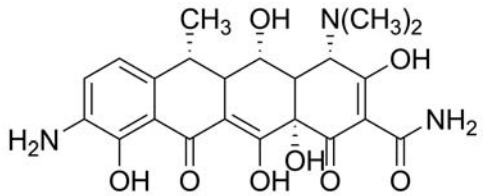

2

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File: CARBON

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 Solvent: DMSO
 Temp. 25.0 C / 298.1 K
INOVA-400  "ui400"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.197 sec
 Width 25157.2 Hz
 512 repetitions
OBSERVE  C13, 100.5268572 MHz
DECOUPLE  H1, 399.7904313 MHz
 Power 41 dB
 continuously on
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 0.8 Hz
FT size 65536
Total time 18 min, 49 sec
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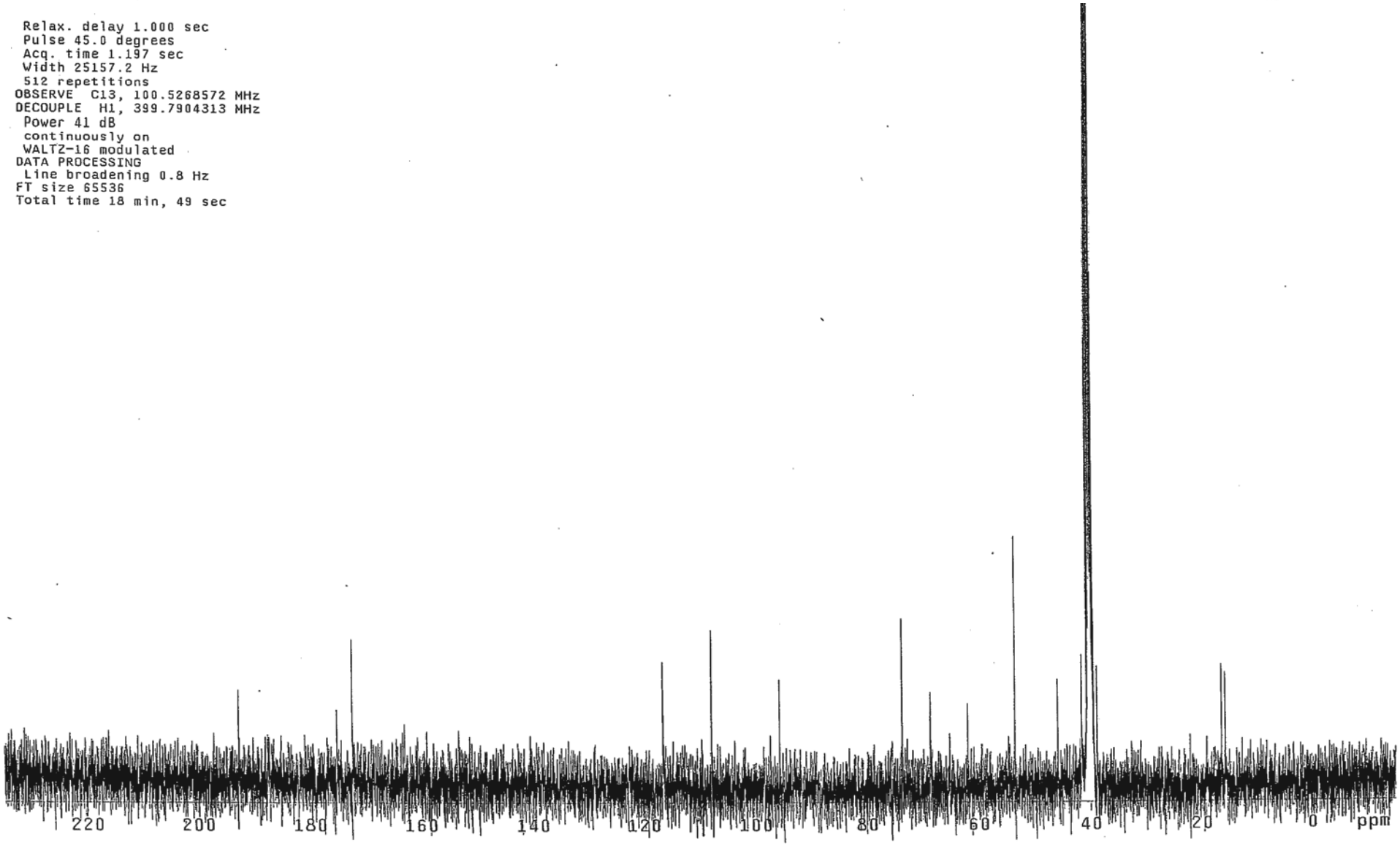

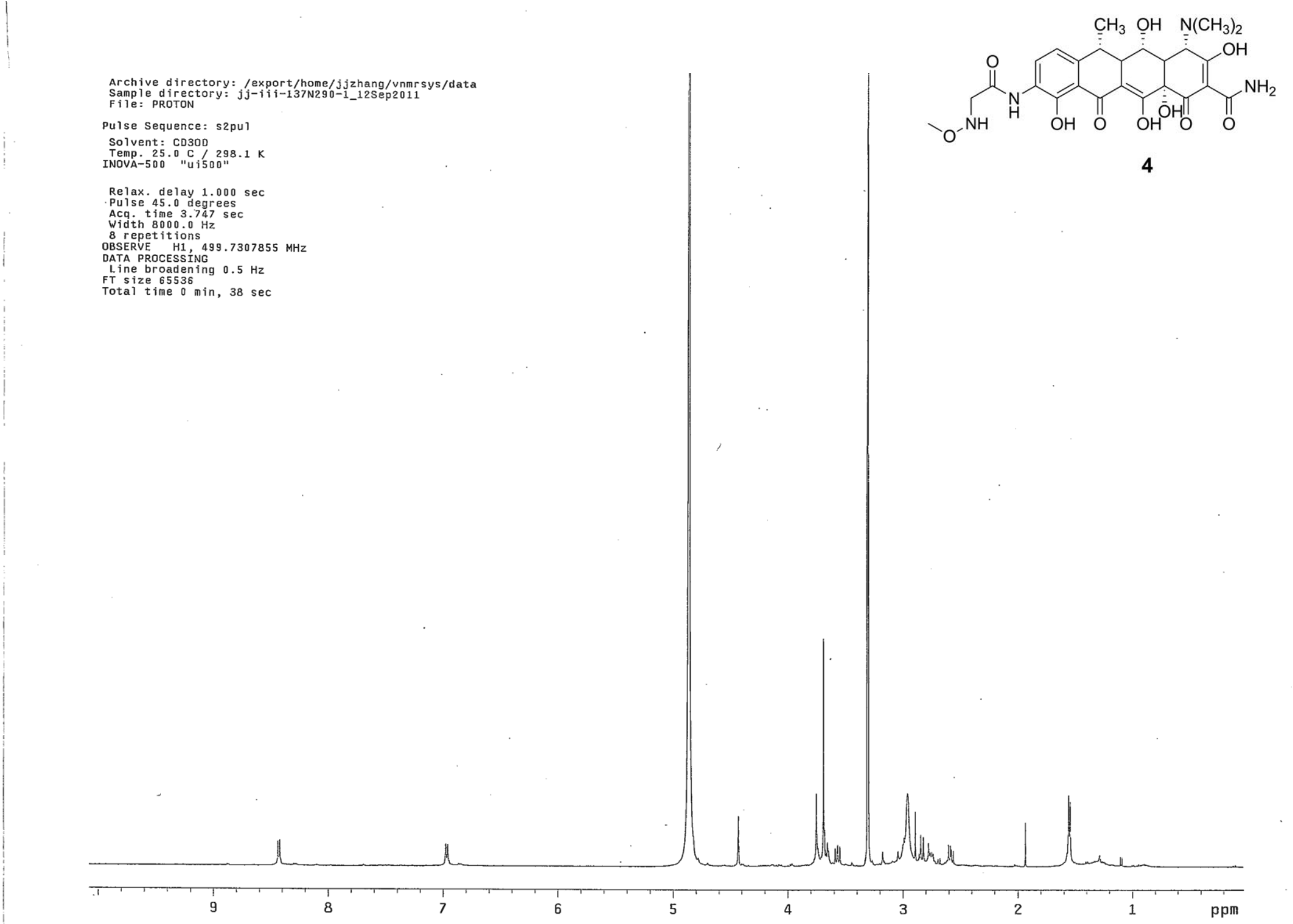
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Sample directory: jj-iii-137N290-1_12Sep2011
File: PROTON
Pulse Sequence: s2pul
Solvent: CD3OD
Temp. 25.0 C / 298.1 K
INOVA-500 "ui500"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 3.747 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7307855 MHz
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 0 min, 38 sec
CH3 OH N(CH3)2
OH
NH2
O
N
H
NH
OH
O
OH
OH
O
O
4
9
8
7
6
5
4
3
2
1
ppm

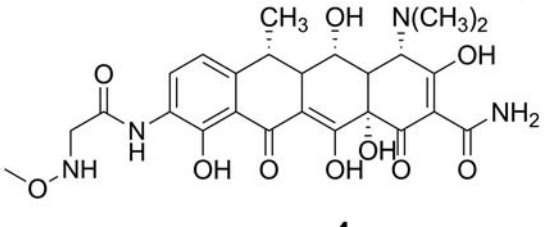
jj-iii-40No202_10Jun2011

Archive directory: /export/home/jjzhang/vnmrsys/data
Sample directory: jj-iii-40No202_10Jun2011

Pulse Sequence: gCOSY

Solvent: CD3OD
Temp. 25.0 C / 298.1 K
File: gCOSY
INOVA-500 "nmr03"

Relax. delay 1.000 sec
Acq. time 0.128 sec
Width 8000.0 Hz
2D Width 8000.0 Hz
Single scan
128 increments
OBSERVE H1, 499.7307855 MHz
DATA PROCESSING
Sq. sine bell 0.064 sec
F1 DATA PROCESSING
Sq. sine bell 0.016 sec
FT size 4096 x 4096
Total time 2 min, 45 sec



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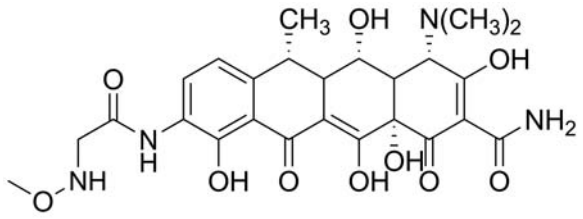

4

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jj-iii-40No202_10Jun2011

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Pulse Sequence: s2pul

 Solvent: CD3OD
 Temp. 25.0 C / 298.1 K
User:  1-14-87
INOVA-500  "ui500"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.299 sec
 Width 31446.5 Hz
 2000 repetitions
OBSERVE  C13, 125.6573720 MHz
DECOUPLE  H1, 499.7332686 MHz
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 continuously on
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 0.5 Hz
FT size 131072
Total time 1 hr, 17 min, 0 sec
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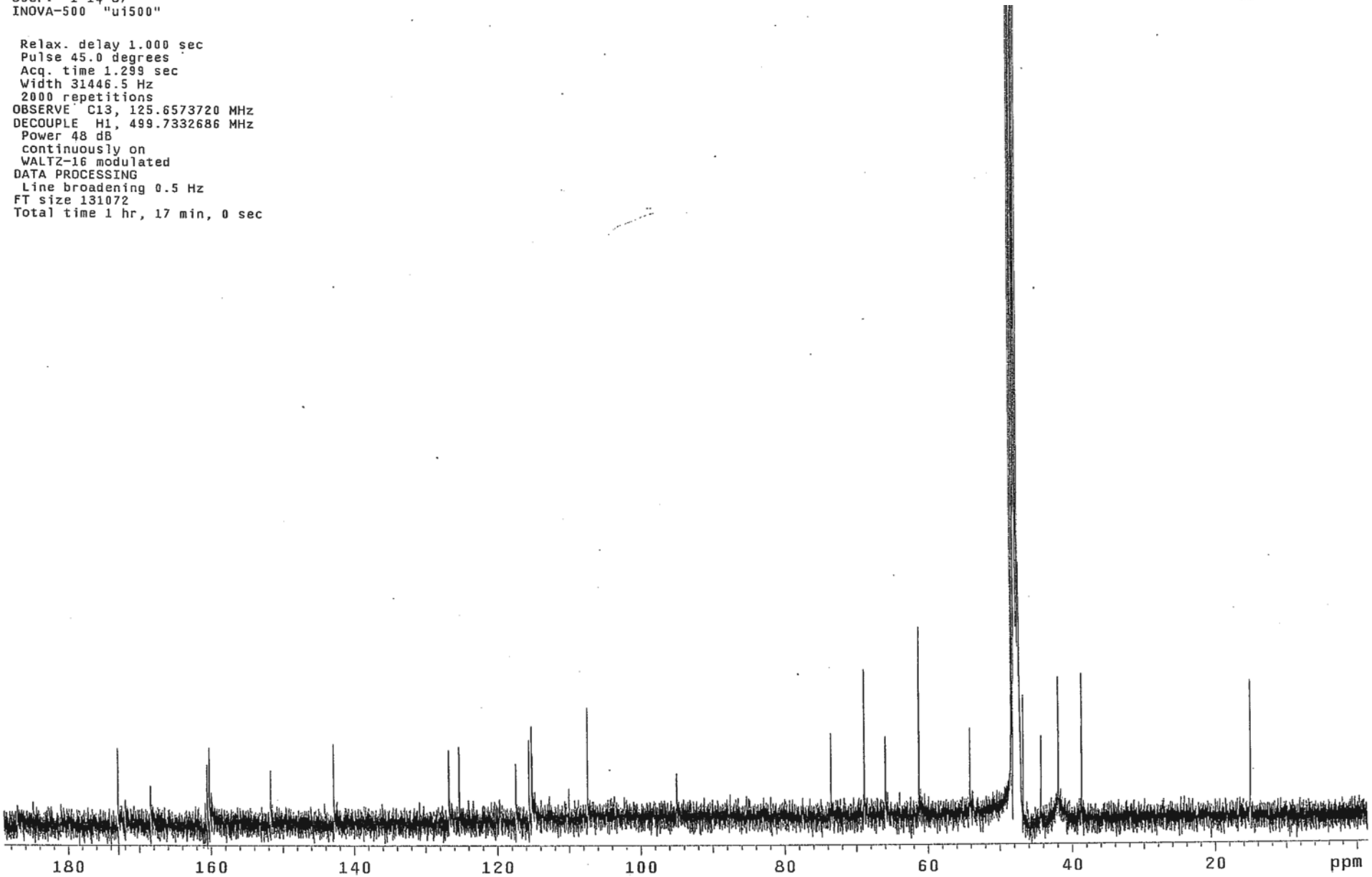

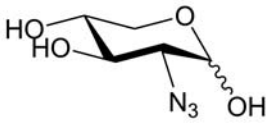

39

Archive directory: /export/home/jjzhang/vnmrsys/data
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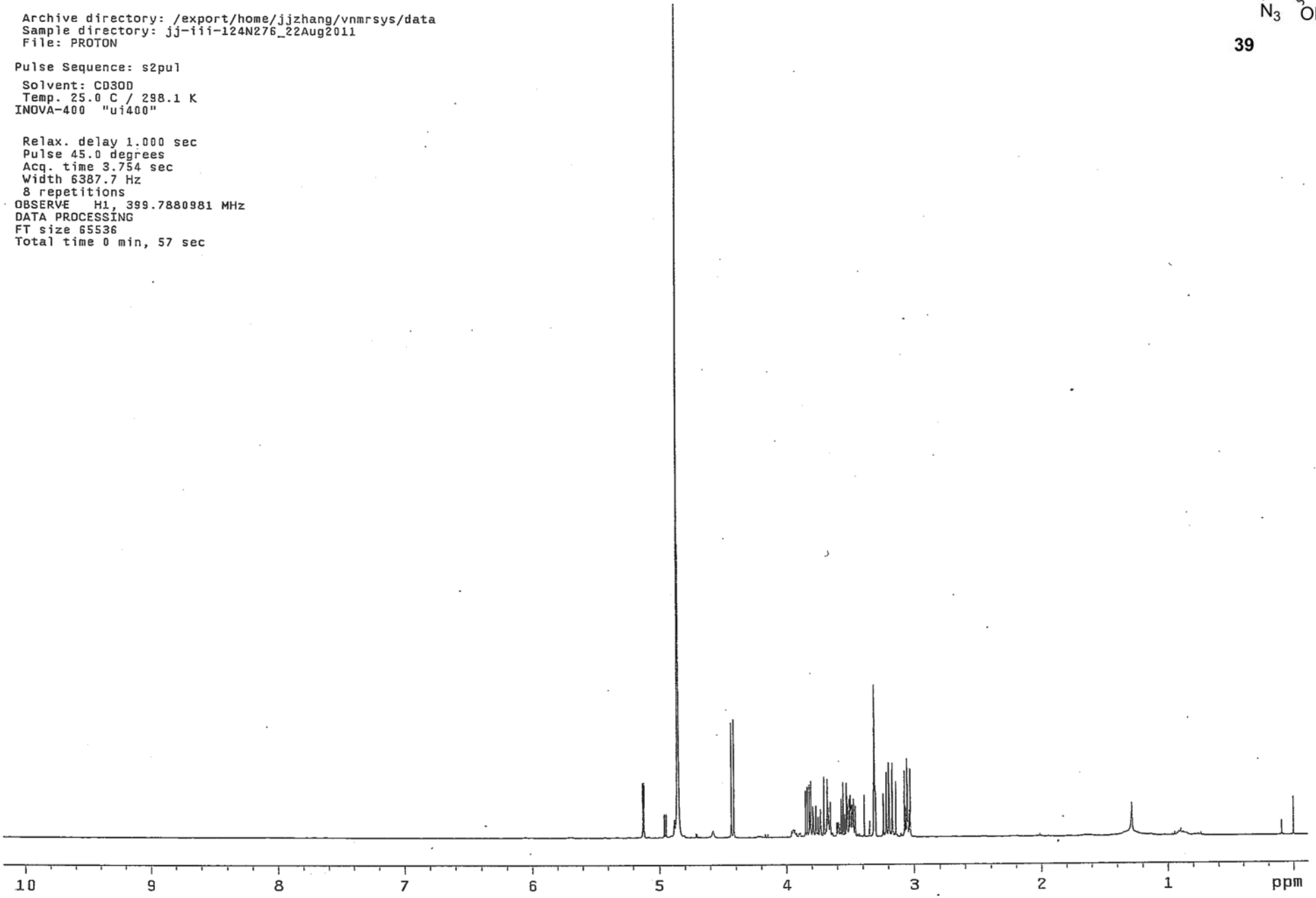
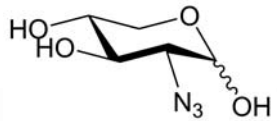
File: PROTON

Pulse Sequence: s2pul
Solvent: CD3OD
Temp. 25.0 C / 298.1 K
INOVA-400 "ui400"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 3.754 sec
Width 6387.7 Hz
8 repetitions
OBSERVE H1, 399.7880981 MHz
DATA PROCESSING
FT size 65536
Total time 0 min, 57 sec





39

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Sample directory: jj-iii-124N276_22Aug2011-14:24:54
File: CARBON

Pulse Sequence: s2pul
Solvent: CD3OD
Temp. 25.0 C / 298.1 K
INOVA-400 "ui400"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.197 sec
Width 25157.2 Hz
112 repetitions
OBSERVE C13, 100.5267758 MHz
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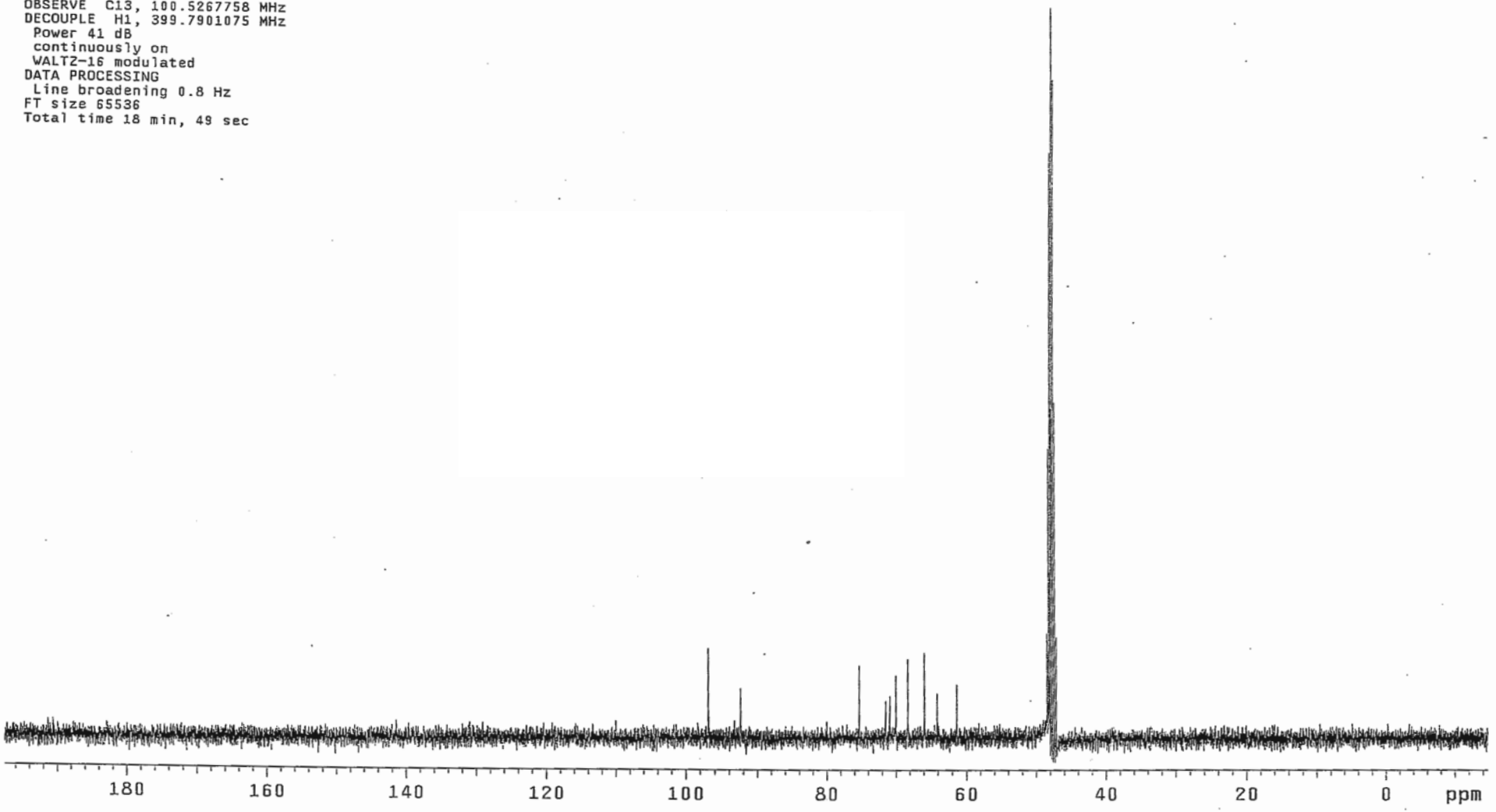
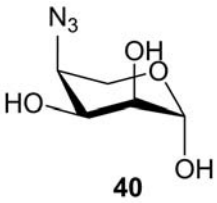
Power 41 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.8 Hz
FT size 65536
Total time 18 min, 49 sec





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Sample directory: jj-iii-123N275_19Aug2011
File: PROTON

Pulse Sequence: s2pul
 Solvent: CD3OD
 Temp. 25.0 C / 298.1 K
INOVA-500  "ui500"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 3.747 sec
 Width 8000.0 Hz
 8 repetitions
OBSERVE   H1, 499.7307855 MHz
DATA PROCESSING
 Line broadening 0.5 Hz
FT size 65536
Total time 0 min, 38 sec
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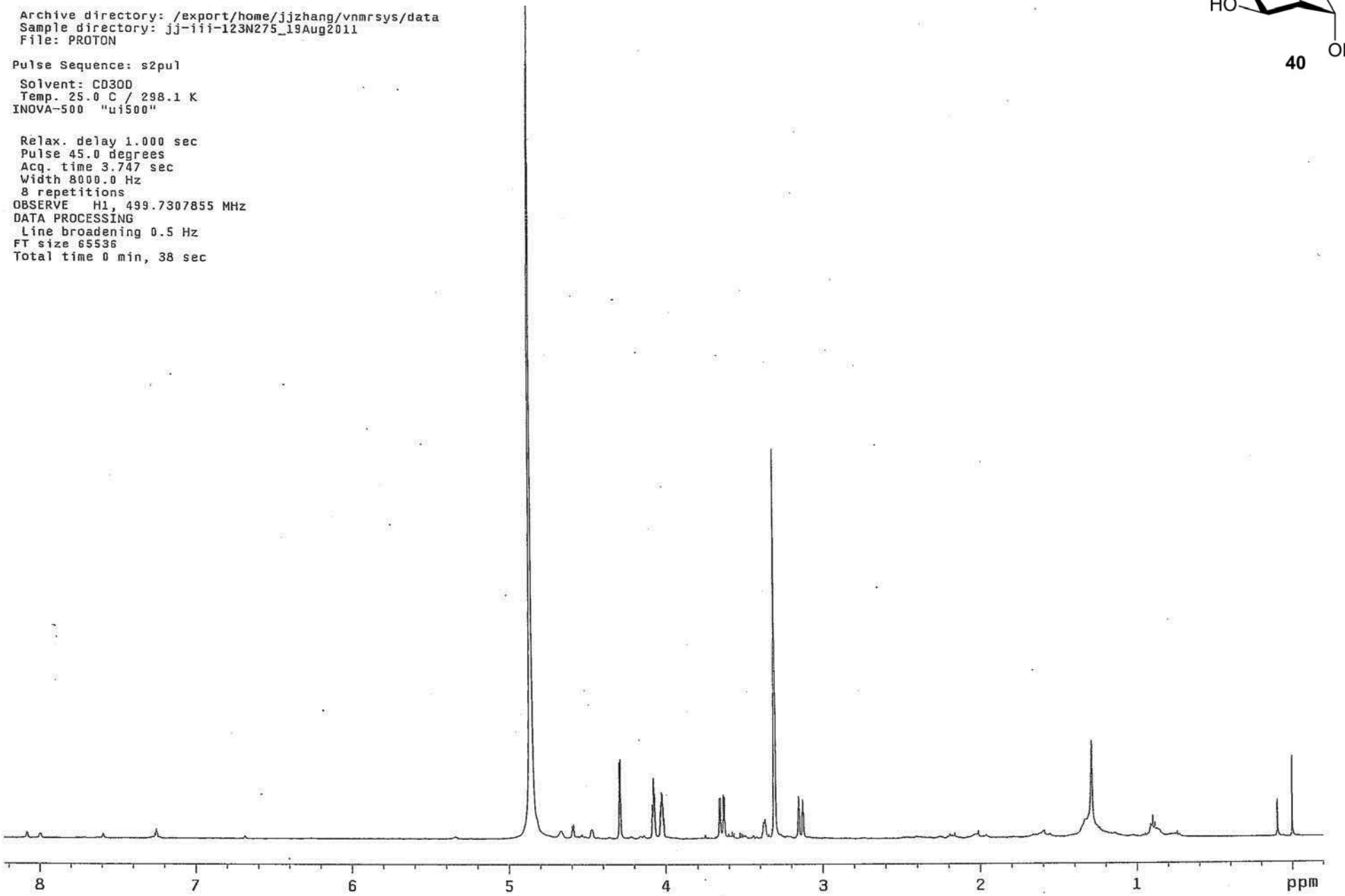

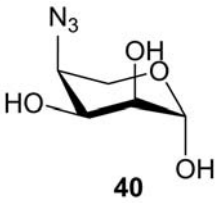

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 Sample directory: jj-iii-123N275C13_19Aug2011

Pulse Sequence: s2pul

 Solvent: CD3OD
 Temp. 25.0 C / 298.1 K
User:  1-14-87
File: CARBON
INOVA-500  "nmr03"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.299 sec
 Width 31446.5 Hz
 2000 repetitions
OBSERVE  C13, 125.6573720 MHz
DECOUPLE  H1, 499.7332686 MHz
 Power 48 dB
 continuously on
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 0.5 Hz
FT size 131072
Total time 1 hr, 17 min, 0 sec
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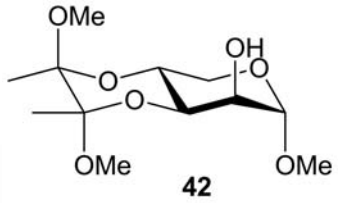

42

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Sample directory: jj-iii-86N241_26Jul2011

Pulse Sequence: s2pul
 Solvent: CDCl3
 Temp. 25.0 C / 298.1 K
File: PROTON
INOVA-400  "ui400"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 3.754 sec
 Width 6387.7 Hz
 8 repetitions
OBSERVE   H1, 399.7865157 MHz
DATA PROCESSING
FT size 65536
Total time 0 min, 57 sec
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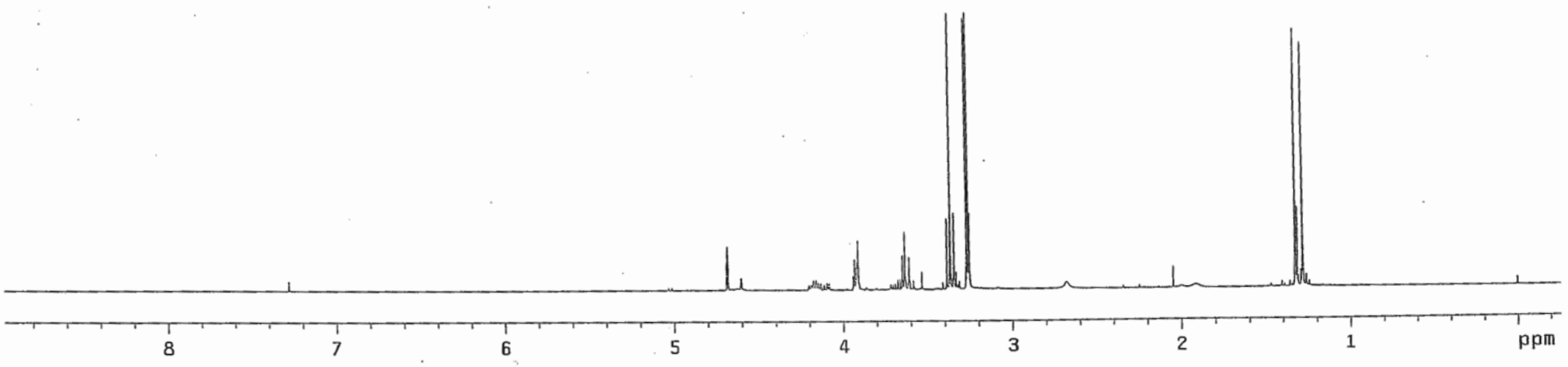

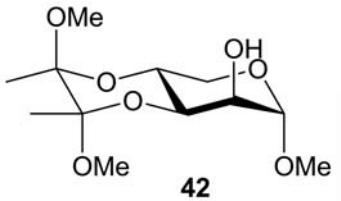

42

```
jj-iii-86N241C13_26Jul2011

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 Sample directory: jj-iii-86N241C13_26Jul2011
 File: CARBON

Pulse Sequence: s2pul
 Solvent: CDCl3
 Temp. 25.0 C / 298.1 K
INOVA-400  "ui400"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.197 sec
 Width 25157.2 Hz
 512 repetitions
OBSERVE  C13, 100.5263777 MHz
DECOUPLE  H1, 399.7885243 MHz
 Power 41 dB
 continuously on
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 0.8 Hz
FT size 65536
Total time 18 min, 49 sec
```
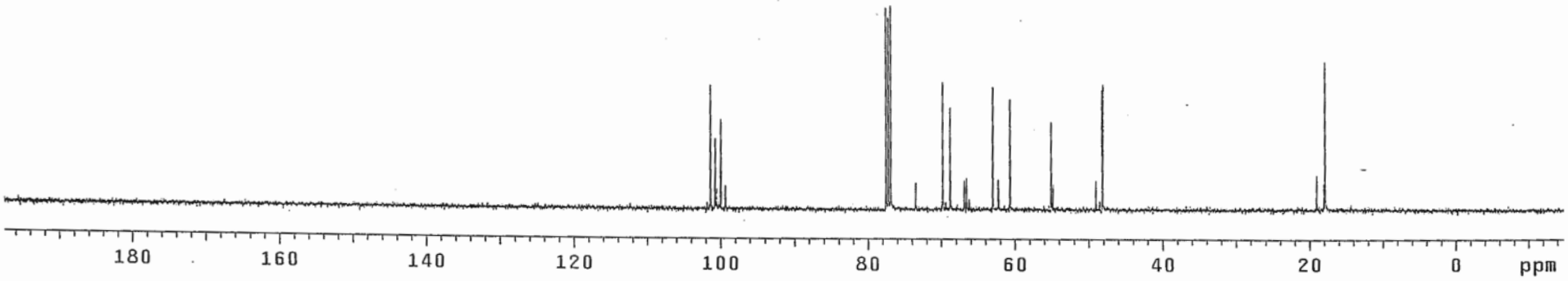
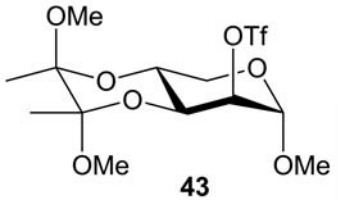
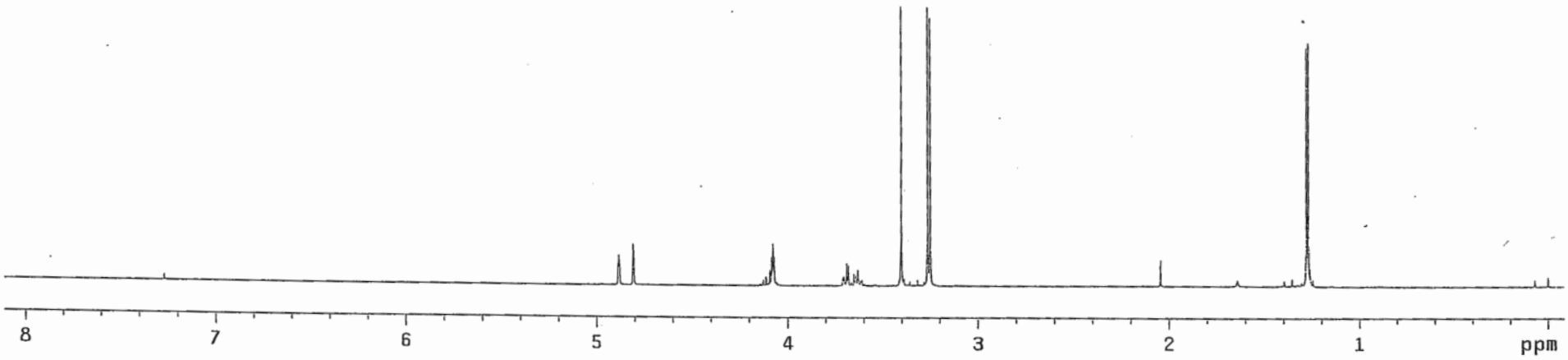
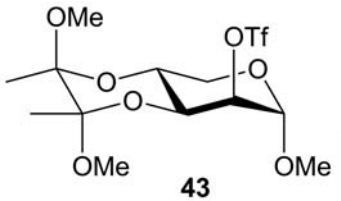





43

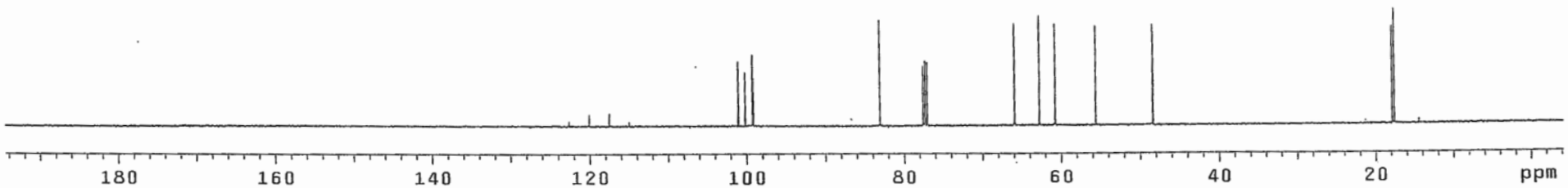
```
Archive directory: /export/home/jjzhang/vnmrsys/data
Sample directory: jj-iii-93N243-A_29Jul2011
File: PROTON

Pulse Sequence: s2pul
 Solvent: CDCl3
 Temp. 25.0 C / 298.1 K
INOVA-500  "ui500"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 3.747 sec
 Width 8000.0 Hz
 8 repetitions
OBSERVE    H1, 499.7288114 MHz
DATA PROCESSING
 Line broadening 0.5 Hz
FT size 65536
Total time 0 min, 38 sec
```

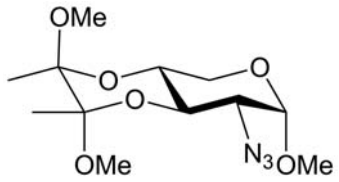




43

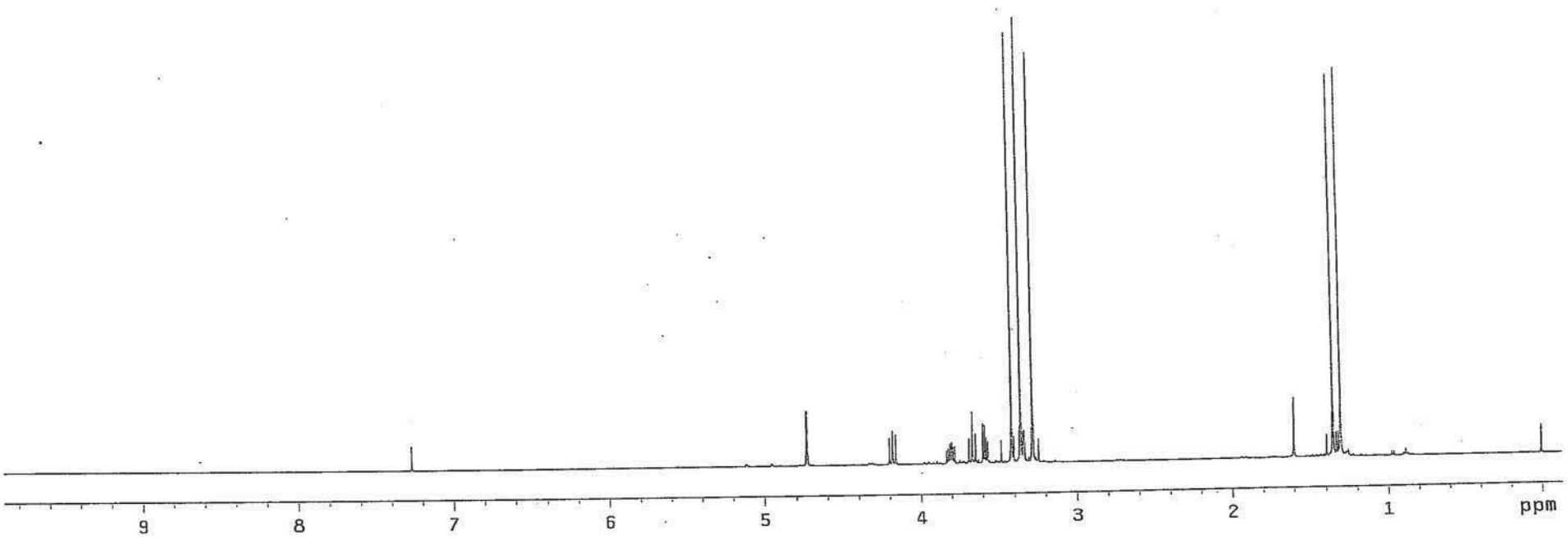
```
Archive directory: /export/home/jjzhang/vnmrsys/data
Sample directory: jj-iii-93N243_29Jul2011
File: CARBON

Pulse Sequence: s2pul
 Solvent: CDCl3
 Temp. 25.0 C / 298.1 K
User:  1-14-87
INOVA-500  "ui500"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.299 sec
 Width 31446.5 Hz
 128 repetitions
OBSERVE  C13, 125.6568744 MHz
DECOUPLE  H1, 499.7312897 MHz
 Power 48 dB
 continuously on
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 0.5 Hz
FT size 131072
Total time 19 min, 46 sec
```

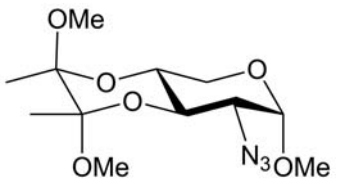




44

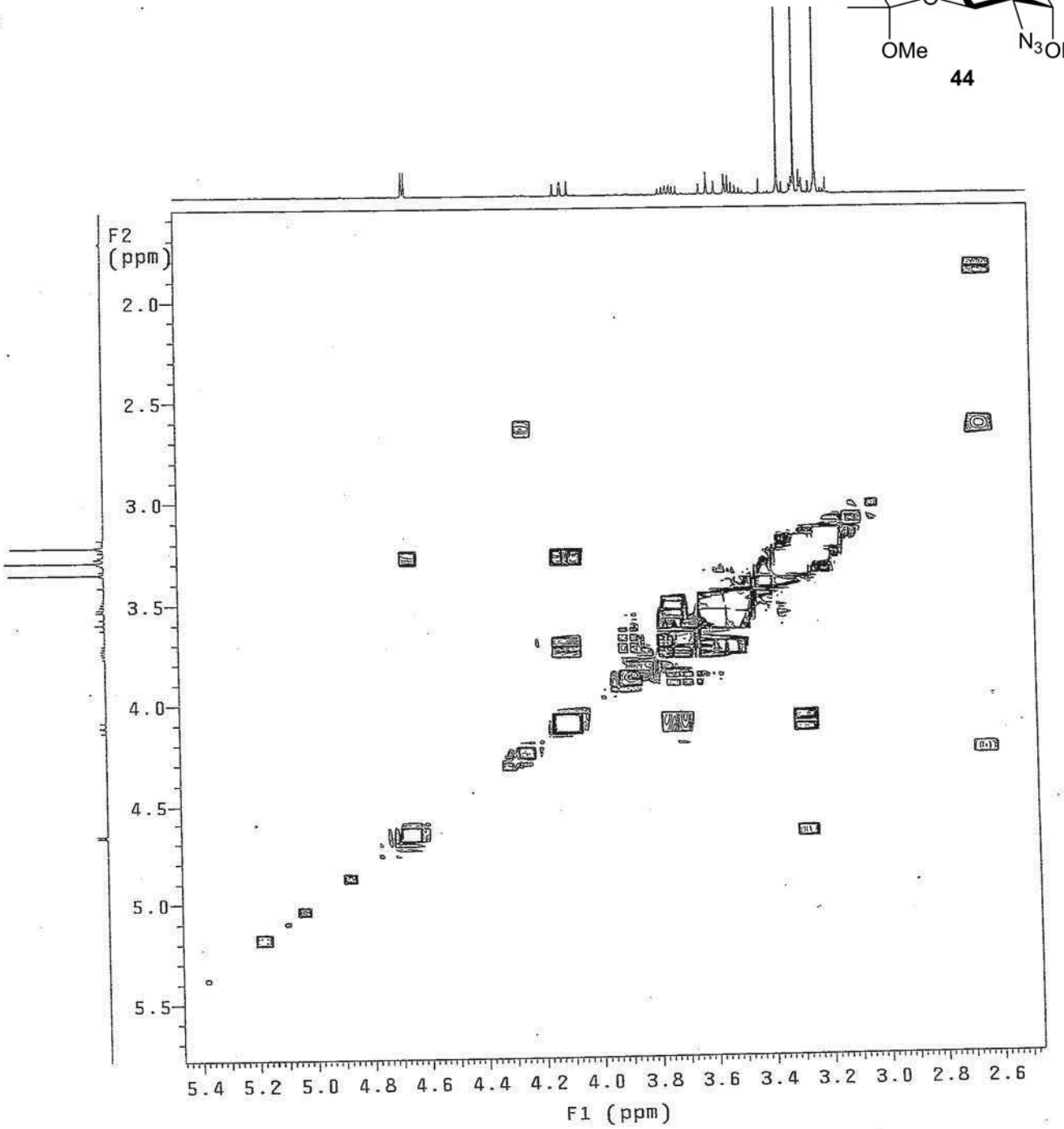
```
Archive directory: /export/home/jjzhang/vnmrsys/data
Sample directory: jj-iii-112N259-A_11Aug2011
File: PROTON

Pulse Sequence: s2pul
 Solvent: CDCl3
 Temp. 25.0 C / 298.1 K
INOVA-500  "ui500"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 3.747 sec
 Width 8000.0 Hz
 16 repetitions
OBSERVE   H1, 499.7288143 MHz
DATA PROCESSING
 Line broadening 0.5 Hz
FT size 65536
Total time 1 min, 16 sec
```

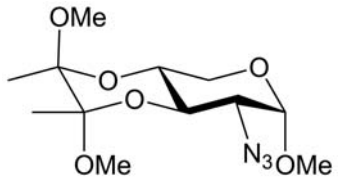




44

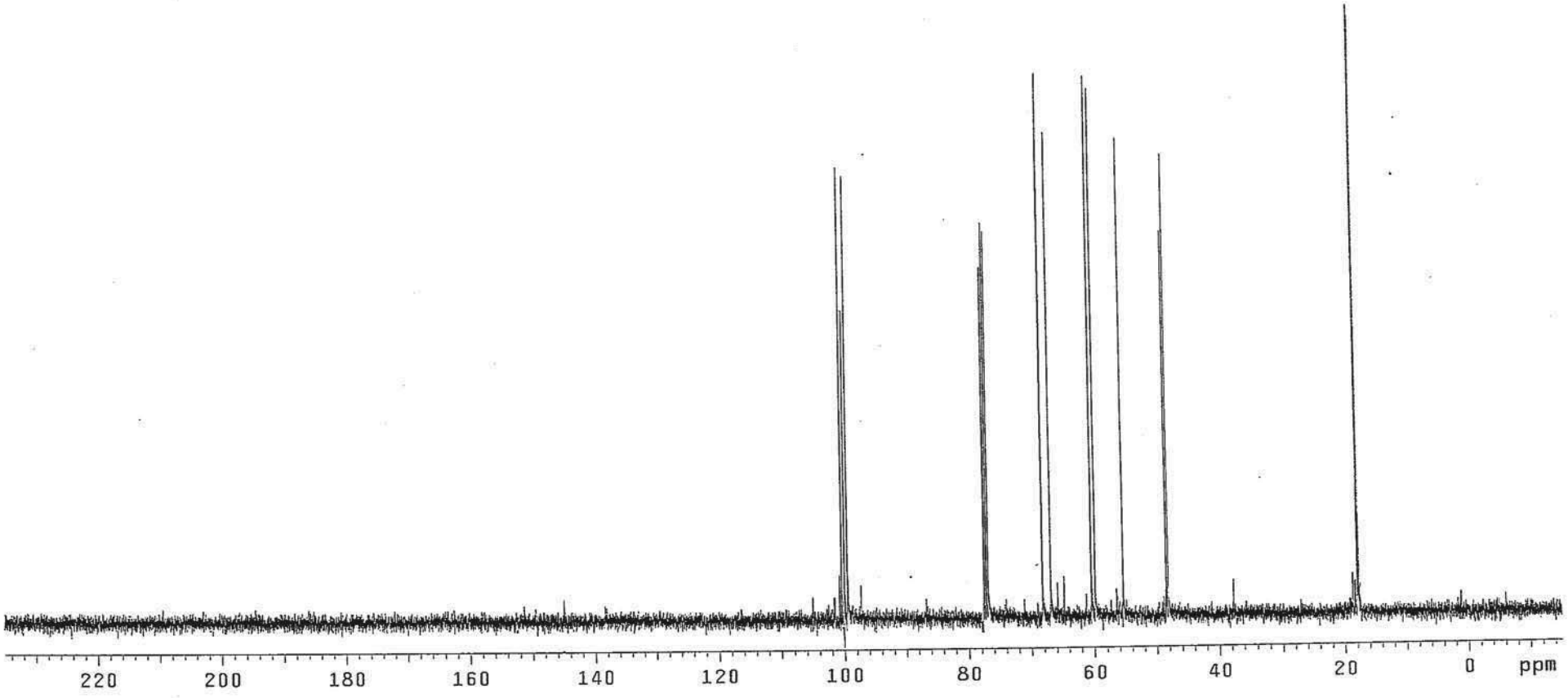
```
Archive directory: /export/home/jjzhang/vnmrsys/data
Sample directory: jj-iii-114N263-12_15Aug2011

Pulse Sequence: gCOSY
 Solvent: CDCl3
 Temp. 25.0 C / 298.1 K
File: gCOSY
INOVA-400  "ui400"

 Relax. delay 1.000 sec
 Acq. time 0.160 sec
 Width    6387.7 Hz
 2D Width 6387.7 Hz
 Single scan
 128 increments
OBSERVE   H1, 399.7865360 MHz
DATA PROCESSING
 Sq. sine bell 0.080 sec
F1 DATA PROCESSING
 Sq. sine bell 0.020 sec
FT size 4096 x 4096
Total time 2 min, 50 sec
```

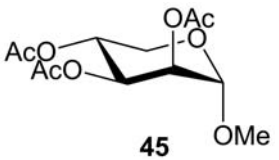




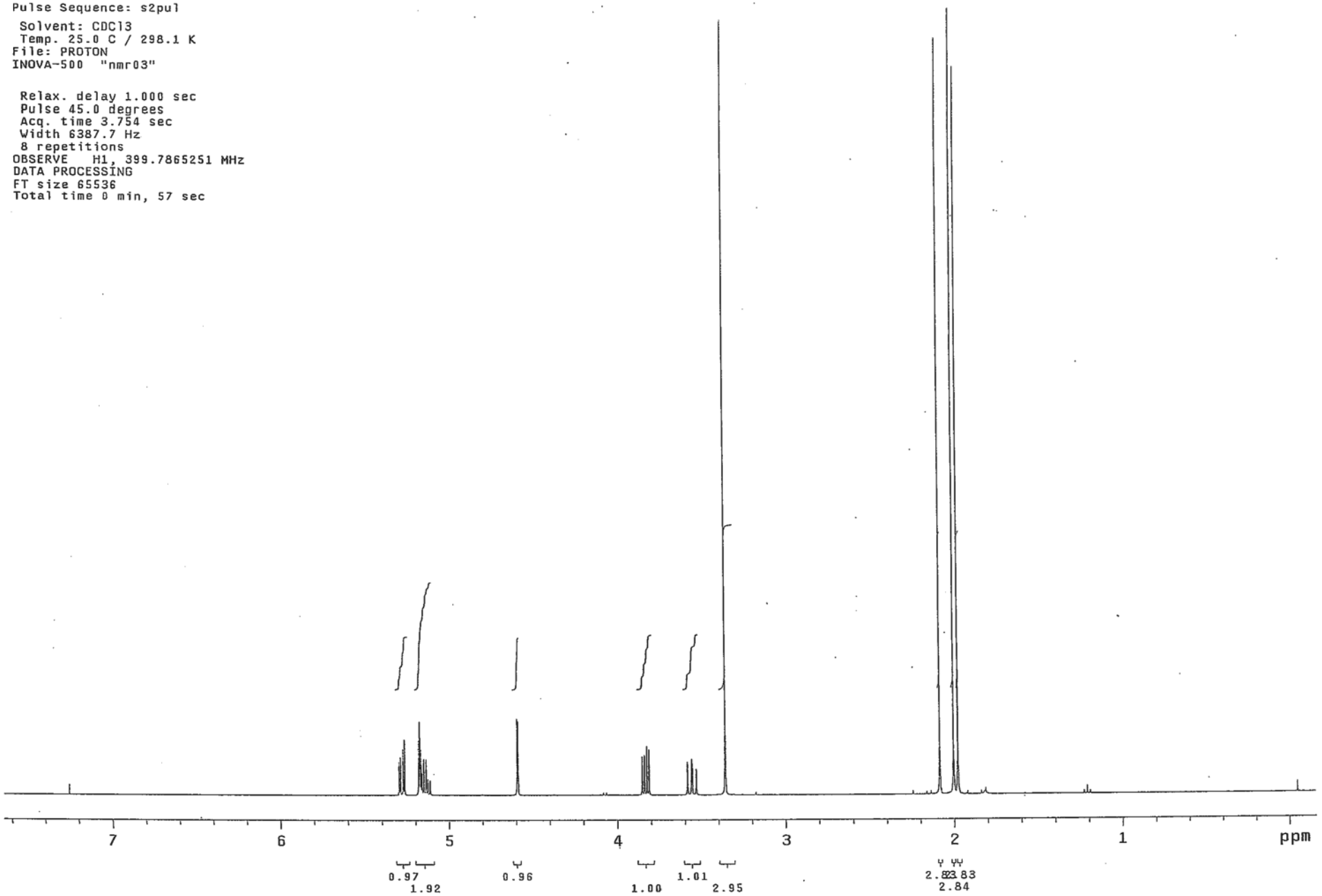
44

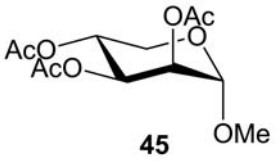
```
Archive directory: /export/home/jjzhang/vnmrsys/data
Sample directory: jj-iii-114N263-12_15Aug2011
File: CARBON

Pulse Sequence: s2pul
 Solvent: CDCl3
 Temp. 25.0 C / 298.1 K
INOVA-400  "ui400"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.197 sec
 Width 25157.2 Hz
 160 repetitions
OBSERVE  C13, 100.5263777 MHz
DECOUPLE  H1, 399.7885243 MHz
 Power 41 dB
 continuously on
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 0.8 Hz
FT size 65536
Total time 18 min, 49 sec
```




OAc
AcO
AcO
O
OMe

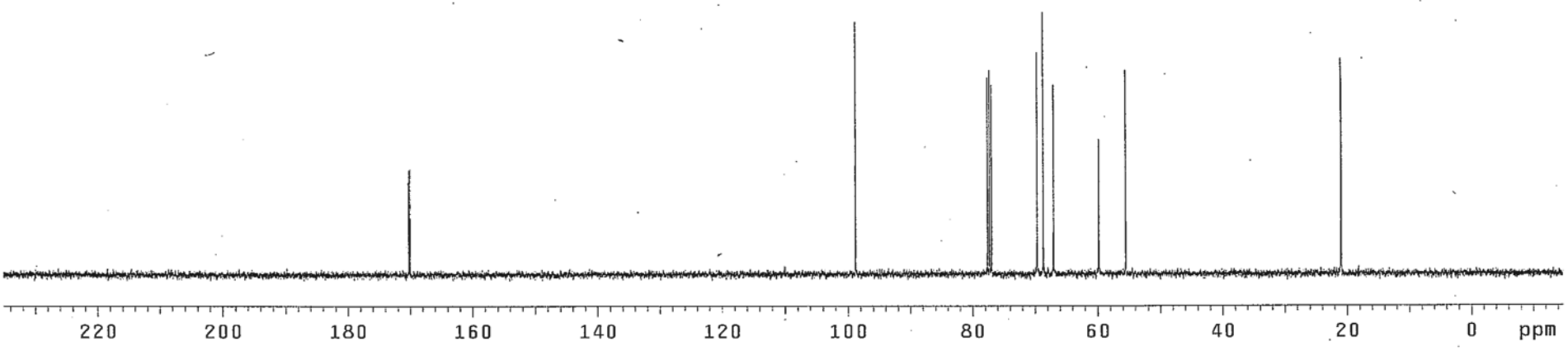
45

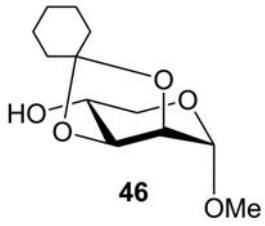

Archive directory: /export/home/jjzhang/vnmrsys/data
Sample directory: jj-iii-55N215-61_28Jun2011
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
File: PROTON
INOVA-500 "nmr03"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 3.754 sec
Width 6387.7 Hz
8 repetitions
OBSERVE H1, 399.7865251 MHz
DATA PROCESSING
FT size 65536
Total time 0 min, 57 sec
7
6
5
4
3
2
1
ppm
0.97
1.92
0.96
1.00
1.01
2.95
2.83
2.84



45

```
Archive directory: /export/home/jjzhang/vnmrsys/data
Sample directory: jj-iii-55N217C13_03Jan2012
File: CARBON

Pulse Sequence: s2pul
 Solvent: CDCl3
 Temp. 25.0 C / 298.1 K
INOVA-400  "ui400"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.197 sec
 Width 25157.2 Hz
 208 repetitions
OBSERVE  C13, 100.5263777 MHz
DECOUPLE  H1, 399.7885243 MHz
 Power 41 dB
 continuously on
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 0.8 Hz
FT size 65536
Total time 18 min, 49 sec
```

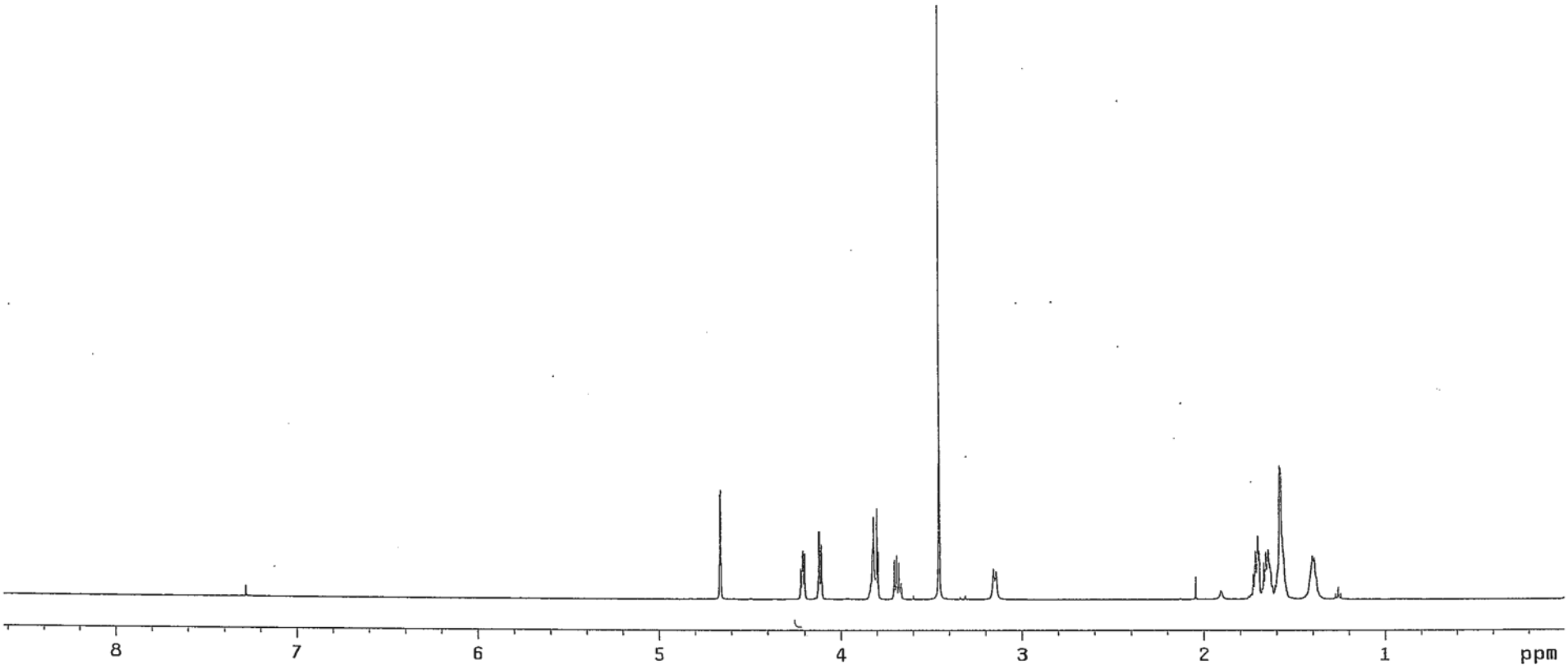


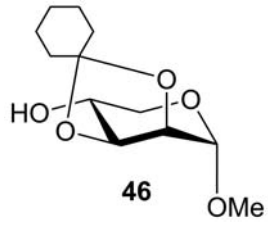


Archive directory: /export/home/jjzhang/vnmrsys/data
Sample directory: jj-iii-82N239_20Jul2011
File: PROTON

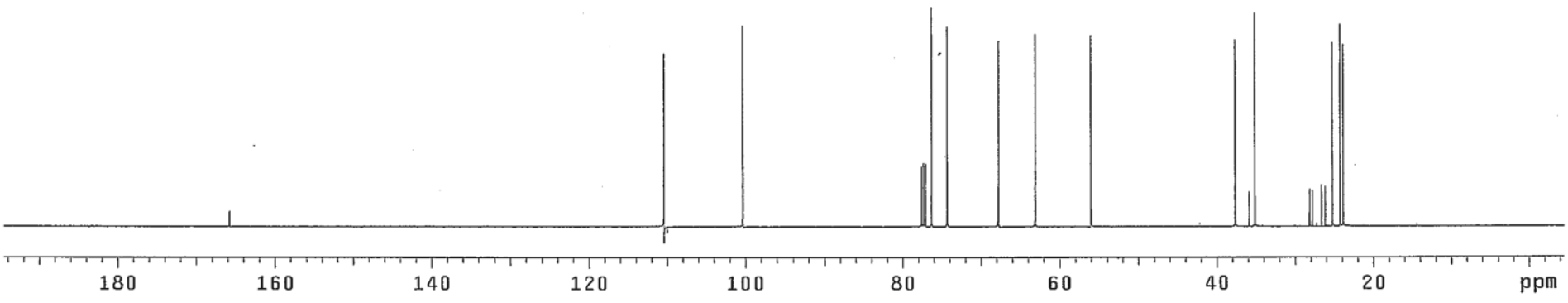
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
INOVA-500 "ui500"

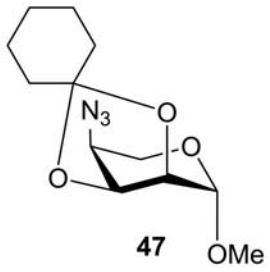
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 3.747 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7288082 MHz
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 0 min, 38 sec






```
 Archive directory: /export/home/jjzhang/vnmrsys/data
 Sample directory: jj-iii-69N228_10Jul2011-20:30:18
 File: CARBON

Pulse Sequence: s2pul
 Solvent: CDCl3
 Temp. 25.0 C / 298.1 K
User:  1-14-87
INOVA-500  "ui500"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.299 sec
 Width 31446.5 Hz
 512 repetitions
OBSERVE  C13, 125.6568744 MHz
DECOUPLE  H1, 499.7312897 MHz
 Power 48 dB
 continuously on
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 0.5 Hz
FT size 131072
Total time 19 min, 46 sec
```



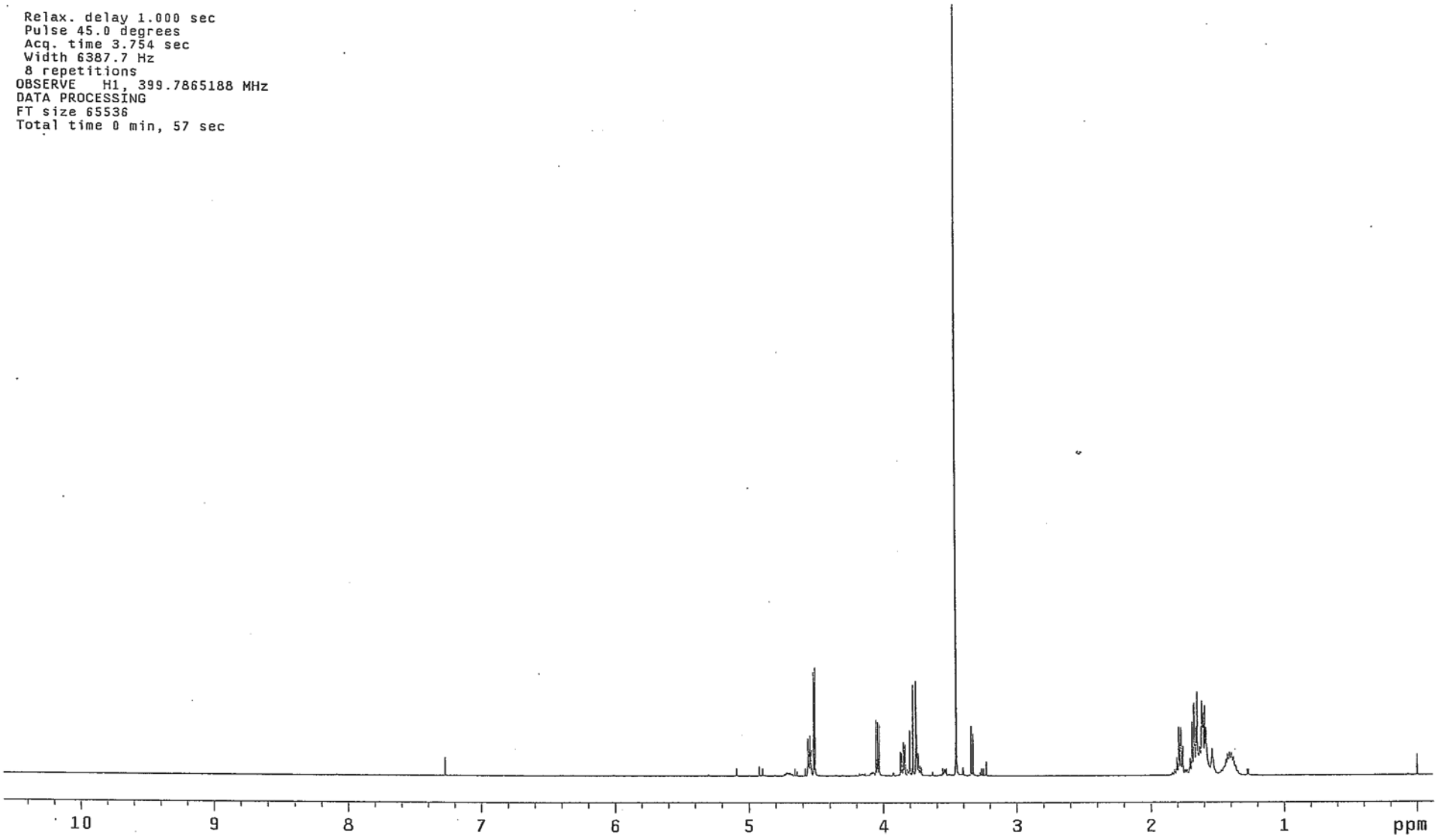


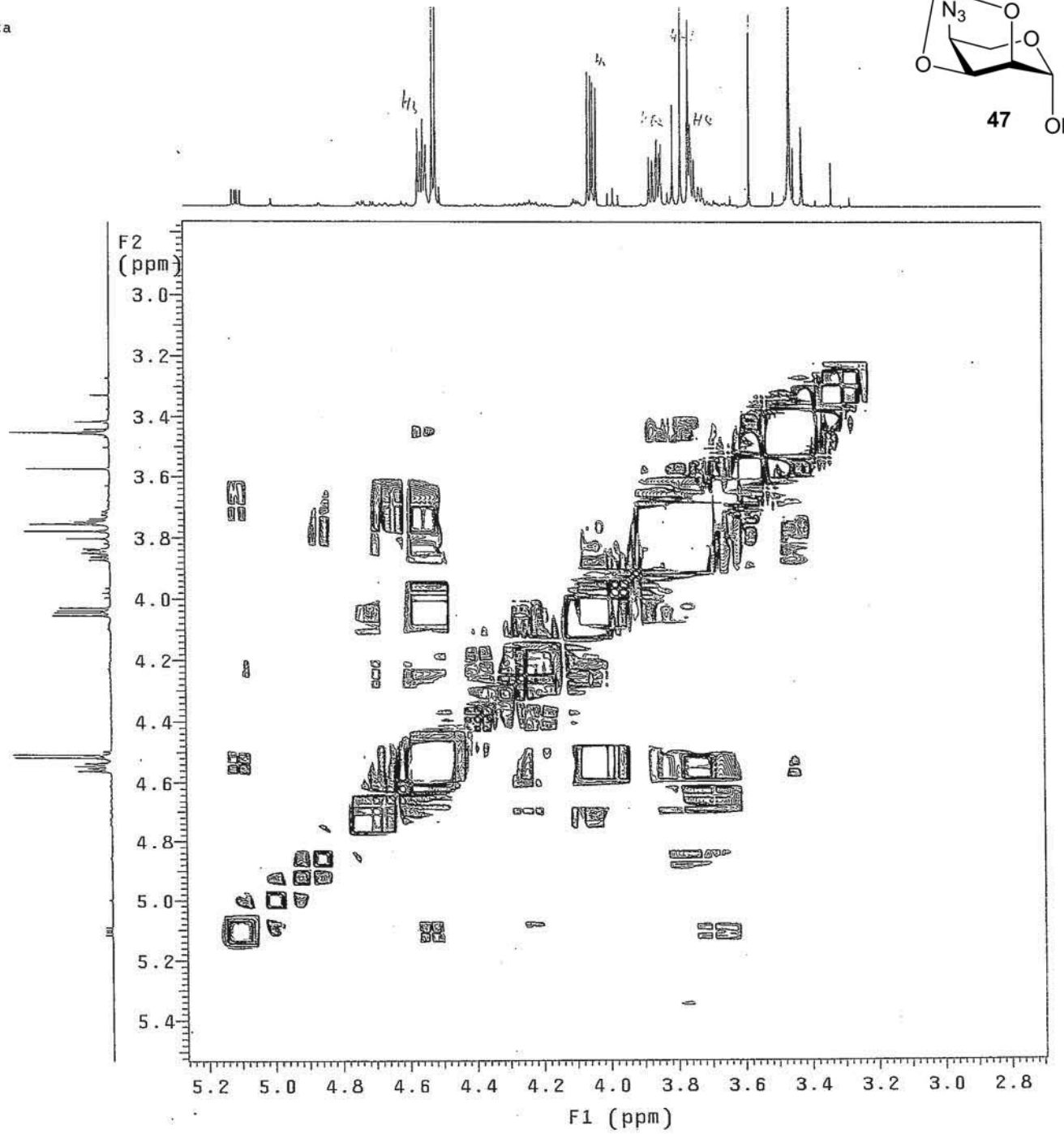
Archive directory: /export/home/jjzhang/vnmrsys/data
Sample directory: jj-iii-106N255-B_10Aug2011
File: PROTON

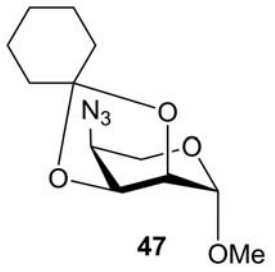
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 25.0 C / 298.1 K
INOVA-400 "ui400"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 3.754 sec
Width 6387.7 Hz
8 repetitions
OBSERVE H1, 399.7865188 MHz
DATA PROCESSING
FT size 65536
Total time 0 min, 57 sec




Archive directory: /export/home/jjzhang/vnmrsys/data
Sample directory: jj-iii-71N236-_14Jul2011
Pulse Sequence: gCOSY
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
File: gCOSY
INOVA-500 "nmr03"
Relax. delay 1.000 sec
Acq. time 0.160 sec
Width 6387.7 Hz
2D Width 6387.7 Hz
Single scan
128 increments
OBSERVE H1, 399.7865175 MHz
DATA PROCESSING
Sq. sine bell 0.080 sec
F1 DATA PROCESSING
Sq. sine bell 0.020 sec
FT size 4096 x 4096
Total time 2 min, 50 sec
F2 (ppm)
3.0
3.2
3.4
3.6
3.8
4.0
4.2
4.4
4.6
4.8
5.0
5.2
5.4
5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8
F1 (ppm)
N3
O
O
O
47
OMe




```
Archive directory: /export/home/jjzhang/vnmrsys/data
Sample directory: jj-iii-71N236_14Jul2011-10:00:31
File: CARBON

Pulse Sequence: s2pul
 Solvent: CDCl3
 Temp. 25.0 C / 298.1 K
INOVA-400  "ui400"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.197 sec
 Width 25157.2 Hz
 512 repetitions
OBSERVE  C13, 100.5263777 MHz
DECOUPLE  H1, 399.7885243 MHz
 Power 41 dB
 continuously on
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 0.8 Hz
FT size 65536
Total time 18 min, 49 sec
```