Supporting Information

Use of an iridium-catalyzed redox-neutral alcohol-amine coupling on kilogram scale for the synthesis of a GlyT1 inhibitor.

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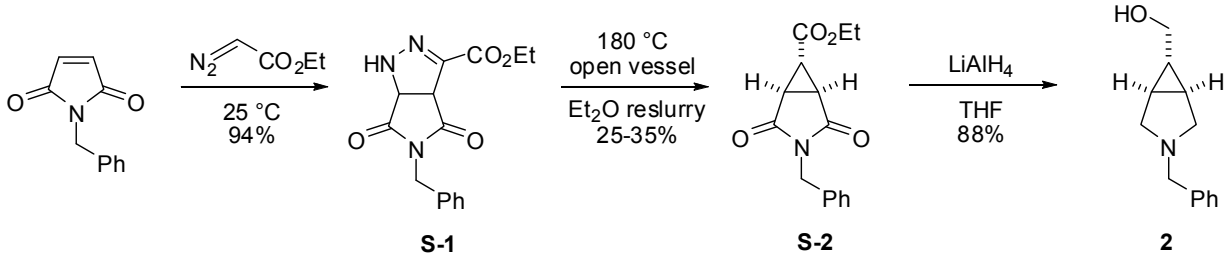
Contents

Synthesis of azabicyclo[3.1.0]hexane-6-methanol (2) – Initial and Improved Route

This compound was first prepared by Brighty and Castaldi[1] as part of the trovafloxacin discovery program, and its synthesis is shown in Scheme SI-1. Cycloaddition of ethyl diazoacetate with *N*-benzylmaleimide in ether to provide crystalline **S-1**, which is isolated by filtration. Thermolysis of **S-1** results in nitrogen extrusion and ring contraction to form the *exo* isomer **S-2** which is isolated after the reaction mixture is reslurried in diethyl ether. Exhaustive reduction of all three carbonyls with $LiAlH_4$ in THF provides **2** as a low melting, reluctant solid after a non-aqueous workup and solvent removal. This chemistry was sourced to an external toller to provide sufficient **2** to prepare the first clinical batch of **1**. However, the brevity of this route is outweighed by modest yields and overall scalability issues for the last two steps.

Scheme SI-1 – First-Generation Synthesis of azabicyclo[3.1.0]hexane 2

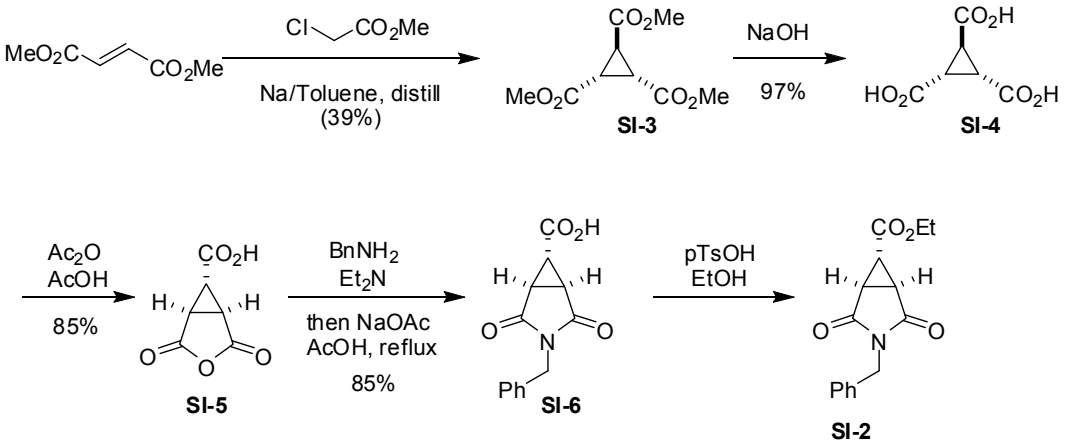


S-1 **S-2** **2**

Since compound **2** was clearly identified as an intermediate in the synthesis of trovafloxacin, several alternative syntheses of **2**, **S-2** and close-in derivatives were developed and published in the patent literature during the years 1997-1999. Not surprisingly, these applications were all abandoned when the use of trovafloxacin as first-line antibiotic was curtailed. Urata, et. al. at Chisso Corporation (US5623078, 1997; JP9012546, 1997) described a five-step process to **S-2** as shown in Scheme SI-2. This chemistry uses inexpensive and readily available starting materials, requires no chromatography, and generates the desired compound in high yield and purity without the use of hazardous reagents or conditions.

[1] Brighty and Castaldi, *Synlett* **1996**, 1097; http://dx.doi.org/10.1055/s-1996-5684

Scheme SI-2 –Chisso Route to SI-2



A series of improvements were made to the procedure prior to sending it out to an external vendor for scaleup, and additional process optimizations were realized by the vendor. These are summarized in a per-step list below.

1. The original process for step 1 was replaced with improved conditions based directly on work by de Meijere and co-workers (*Synthesis*, **2003**, 956; http://dx/doi.org/10.1055/s-2003-38687).

2. The hydrolysis step was modified by employing toluene as a co-solvent for azeotropic drying of the acid/NaCl solution; the resulting solids are isolated by filtration before the product is extracted into acetone. The triacid **SI-4** is obtained as a while solid on evaporation of the acetone.

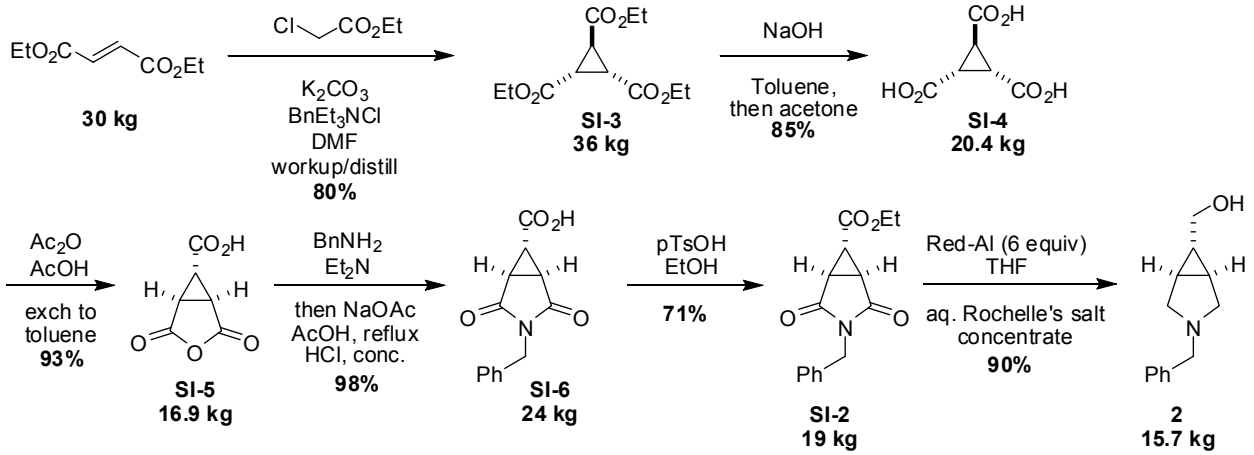
3. The procedure was improved by exchanging the solvent for toluene prior to crystallization, as the product is extremely soluble in acetic acid.

4. The procedure was conducted as described. Product yield was maximized by removing as much acetic acid as possible prior to acidification. The product crystallized after acidification and was isolated.

We also replaced the final $LiAlH_4$ reduction of **SI-2** with a Red-Al reduction in toluene. This generated material of similar quality and was much easier to execute on scale.

This chemistry was executed on large scale at an external vendor to supply **2** (Scheme SI-3). Procedures from this scaleup effort are included below.

Scheme SI-3. Scaled Route to 2.



(*trans*)-Triethyl cyclopropane-1,2,3-tricarboxylate (SI-3).[2] In a 500 L reactor, DMF (5 volumes, 150 L), K_2CO_3 (350 mesh, 52.9 kg, 2.2 equiv) and benzyltriethylammonium chloride (396 g, 0.01 equiv) were charged and the mixture was heated to 40 °C. A solution of ethyl chloroacetate (28.8 kg, 235 mol, 1.35 equiv) and diethylfumarate (30 kg, 174 mol, 1 equiv) in DMF (1 volume, 30 L) was added maintaining the reaction temperature at 40 °C. After the addition, the reaction mixture was stirred at 40 °C for 15 h. The reaction was quenched with water and the reaction mixture was extracted with TBME three times. The combined organic layers were dried, filtered through silica gel, and concentrated under reduced pressure to give the crude product as oil. The crude product was distilled at 118-120 °C/0.9-1mmHg. 36kg product (139.4 mol, 80% yield) was obtained. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.15 (m, 6H), 2.75 (dd, *J* = 5.7, 5.6 Hz, 1H), 2.51 (d, *J* = 5.7 Hz, 2H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.24 (t, *J* = 7.1 Hz, 6H).

(*trans*)-Cyclopropane-1,2,3-tricarboxylic acid (SI-4). In a 300 L glass-lined reactor, 10N NaOH (442 mol, 44.2 L, 3.3 equiv) and EtOH (17.3L, 0.5 vol) were charged and the mixture was heated to 50 °C. Triester **SI-3** (34.6 kg, 134 mol, 1 equiv) was added dropwise keeping the reaction temperature below reflux. After the addition, the reaction mixture was refluxed for 2h. The reaction mixture was concentrated to remove EtOH. Cooling to rt, conc. HCl (44.6 L, 536 mol, 4 equiv) was added to adjust the pH of the reaction mixture to pH =1. The reaction mixture was concentrated to remove water. Toluene was added and continued to concentrate until all water was azeotroped off. The crude product was isolated by filtration and was reslurried in acetone (800 L, 6 volumes) by refluxing for 2h. The solids (NaCl) were removed by filtration and the filtrate was concentrated to give the product. A total of 20.4 kg (117 mol, 85% yield) of **SI-4** was isolated as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.8 (br s, 3 H), 2.35 (m, 3H). ^{13}C NMR (100 MHz, DMSO) δ 171.3, 168.9 (2C), 28.3 (2C), 25.4.

(1*R*,5*S*,6*s*)-2,4-dioxo-3-oxabicyclo[3.1.0]hexane-6-carboxylic acid (SI-5): In a 300 L reactor, triacid **SI-4** (20.4 kg, 117 mol, 1 equiv), acetic acid (44.9 L, 2.2 volumes), and acetic anhydride (11.9 kg, 1.32 equiv) were mixed. The mixture was refluxed for 2 hours during which time the starting material dissolved. After the reaction, the acetic acid was removed under reduced

[2] Kozhushkov, Leonov, De Meijere. *Synthesis* **2003**, *6*, 956-958.

pressure. Toluene (20 L, 1 volume) was added and distillation was continued to remove acetic acid. Toluene (40 L, 2 volumes) was added and the slurry cooled to 0–5 °C and stirred for 0.5h. The solid was filtered, washed with toluene (20 L, 1 volue) and dried. Anhydride **SI-5** (16.9 kg, 108 mol, 93% yield) was isolated as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.4 (br s, 1H), 3.24 (d, J = 3.2 Hz, 2H), 3.07 (d, J = 3.2 Hz, 1H).

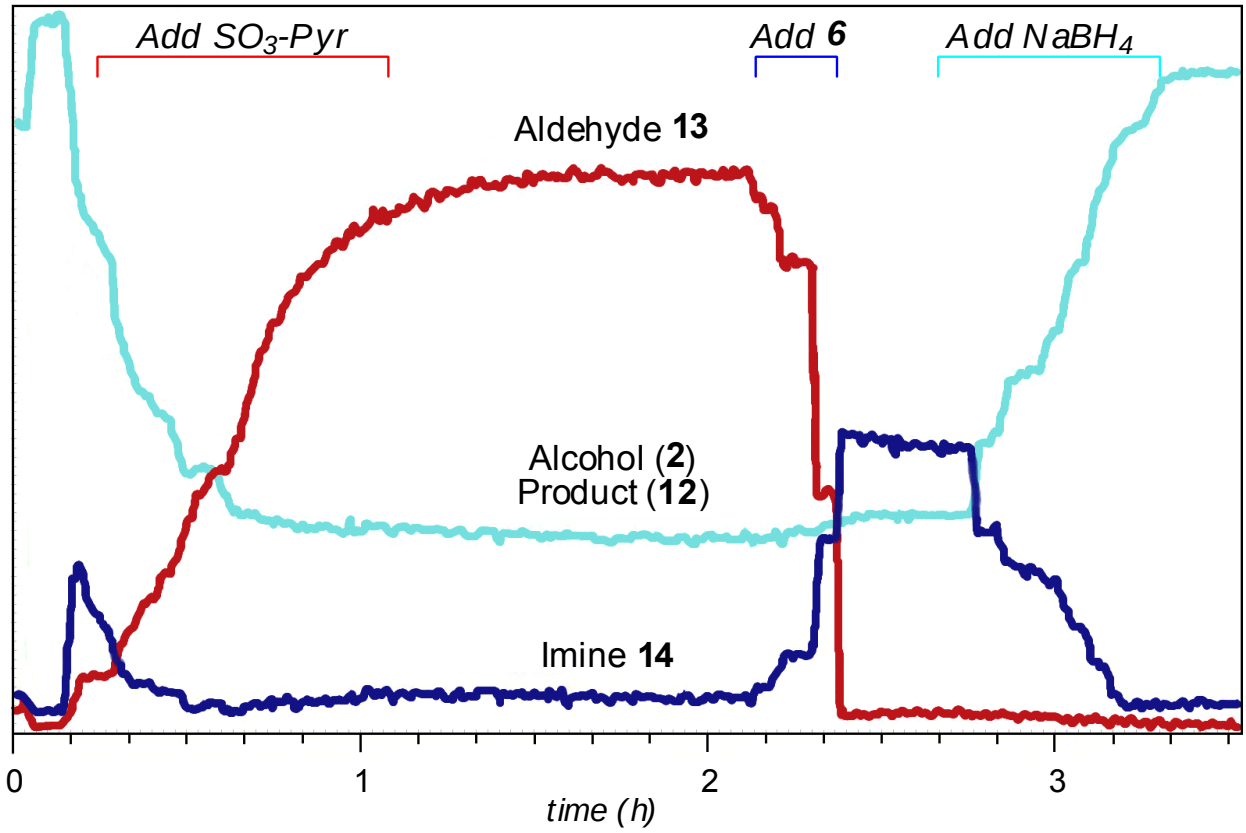
(1*R*,5*S*,6*r*)-3-benzyl-2,4-dioxo-3-azabicyclo[3.1.0]hexane-6-carboxylic acid (SI-6). Anyhdride **SI-5** (15.4 kg, 100 mol, 1equiv), acetone (83.7 L, 5.35 volumes) and triethylamine (10.1 kg, 1.0 equiv) were charged to a 300 L reactor. Benzylamine (1.2 equiv, 12.9 kg) was added and the reaction mixture was stirred at rt for 3h. The reaction mixture was concentrated to remove acetone. Sodium acetate (4.9 kg, 0.6 equiv) and acetic anhydride (49.0 kg, 4.8 equiv) were added and the mixture was heated to reflux for 1h. The reaction was concentrated and quenched with water. The reaction mixture was adjusted with conc HCl to pH =2 to crystallize the product. The resulting solids were filtered and dried to provide 24 kg (97.9 mol, 98% yield) of crude product. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.17 (br. s., 1 H) 7.07-7.42 (m, 5 H) 4.35 (s, 2 H) 2.93 (d, J=2.88 Hz, 2 H) 2.61 (t, J=2.88 Hz, 1 H).

(1*R*,5*S*,6*r*)-Ethyl 3-benzyl-2,4-dioxo-3-azabicyclo[3.1.0]hexane-6-carboxylate (SI-2): Acid **SI-6** (23.9 kg, 97.5 mol, 1 equiv) was dissolved in ethanol (240 L, 10 volumes) at 60 °C. Concentratrated sulfuric acid (3.9 kg, 0.4 equiv) was added and the reaction mixture was stirred at 60 °C for 6 h. The reaction mixture was cooled to 0-5 °C and the resulting solid isolated by filtration and dried. A total of 19kg (69.5 mol, 71% yield) of **SI-2** was obtained as a white solid.

((1*R*,5*S*,6*r*)-3-Benzyl-3-azabicyclo[3.1.0]hexan-6-yl)methanol (2): Red-Al (160 kg, 6 equiv, 65% w/w in toluene) was added to a mixture of **SI-2** (23.4 kg, 85.6 mol, 1 equiv) and THF (140 L) in a 500 mL reactor at 15-30 °C. After the reaction mixture was stirred at 15-30 °C overnight, excess 30% aqueous Rochelle's salt solution was added slowly (gas evolution) and the mixture stirred overnight. A clear two phase solution was observed. The aqueous phase was removed and was extracted three times with toluene. The combined organic phases were concentrated to provide **2** (15.7 kg, 77.2 mol, 90% yield) as a thick oil that solidified upon standing. Spectral data is consistent with literature.[3]

[3] Brighty, K.; Castaldi, M. *Synlett* **1996**, *1996*, 1097-1099.

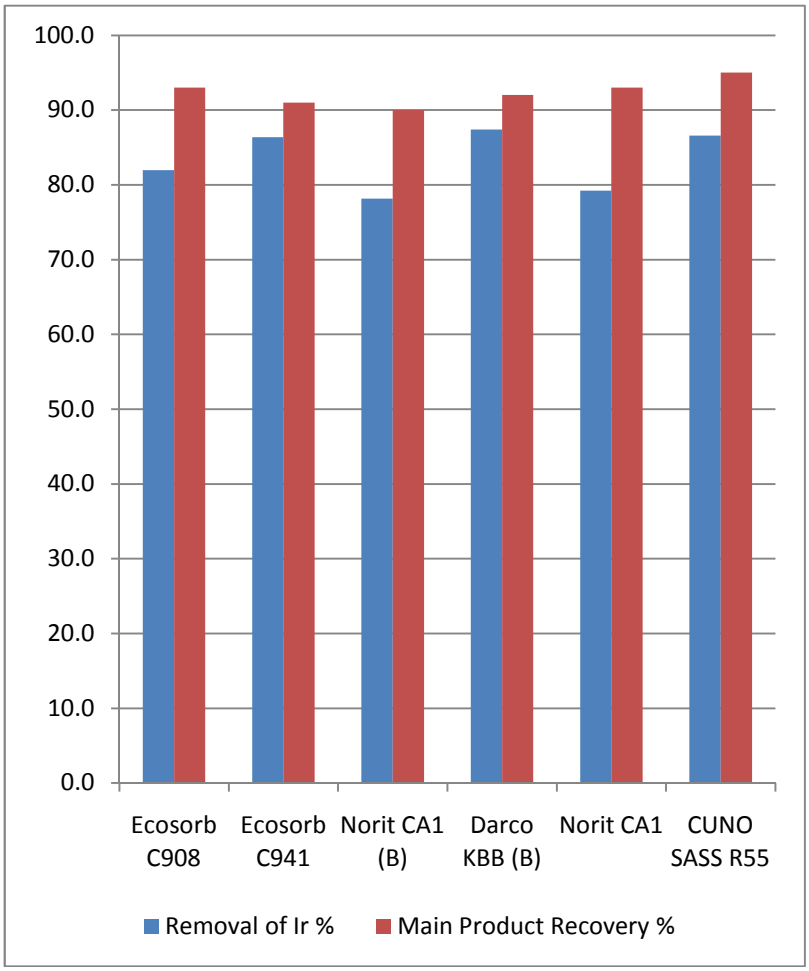
ReactIR Profile, SO_3-Pyridine Oxidation-Reduction Process



Full Resin/Support List, Ir Removal Screening

All screening reactions were conducted on 20 mg scale of **1** in 1 mL of methanol with a 100 % w/w loading of resin. Contact times were 16 hours.

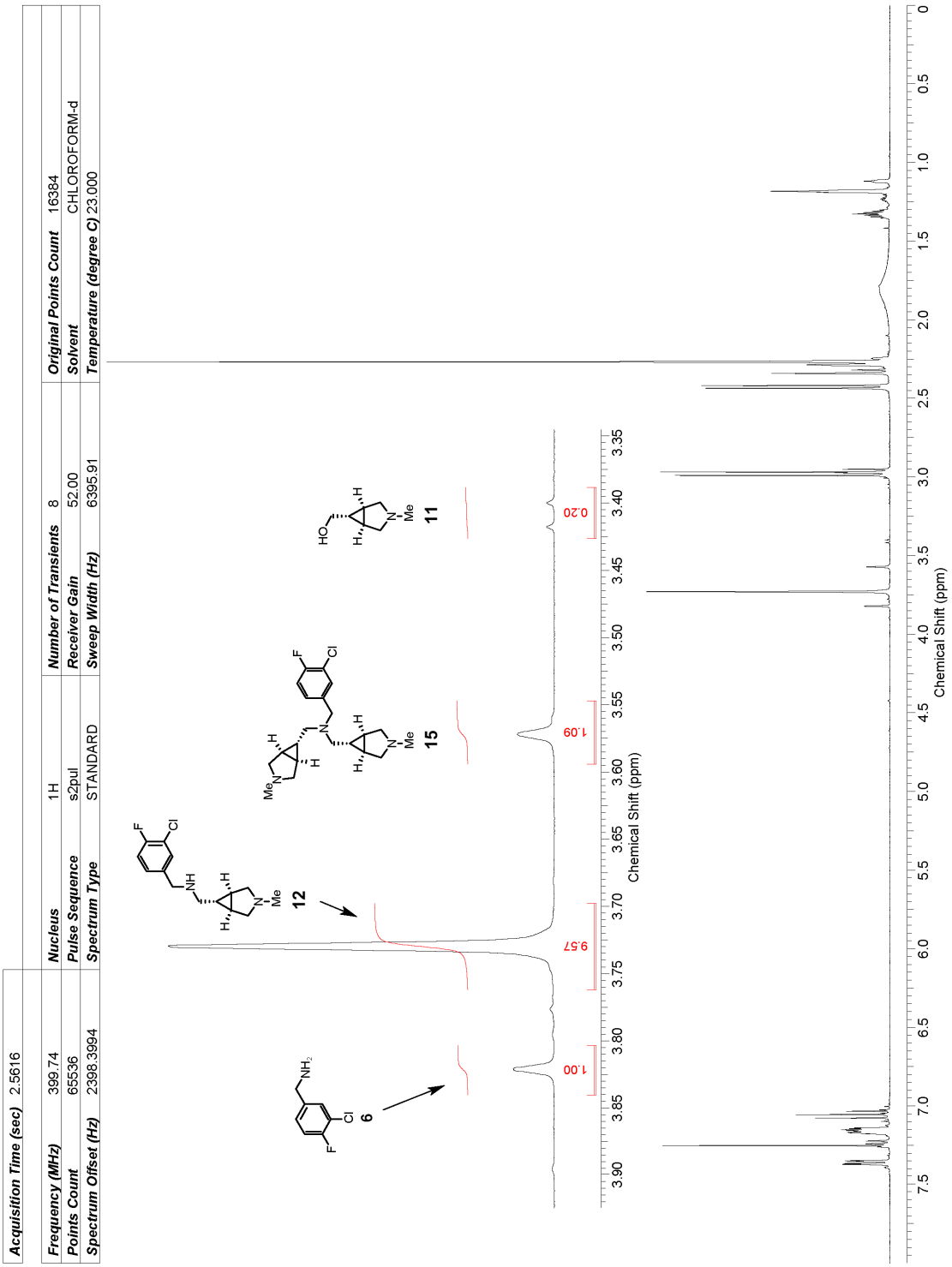
While most resins demonstrated high API recovery, many did not result in desirable (>80%) amounts of Ir reduction. The best are shown in the graph below (>90% recovery; red bar) and ~80% or more Ir removal. Of these, Darco KB-B demonstrated the optimim combination of Ir scavenging capability, cost, and API recovery.



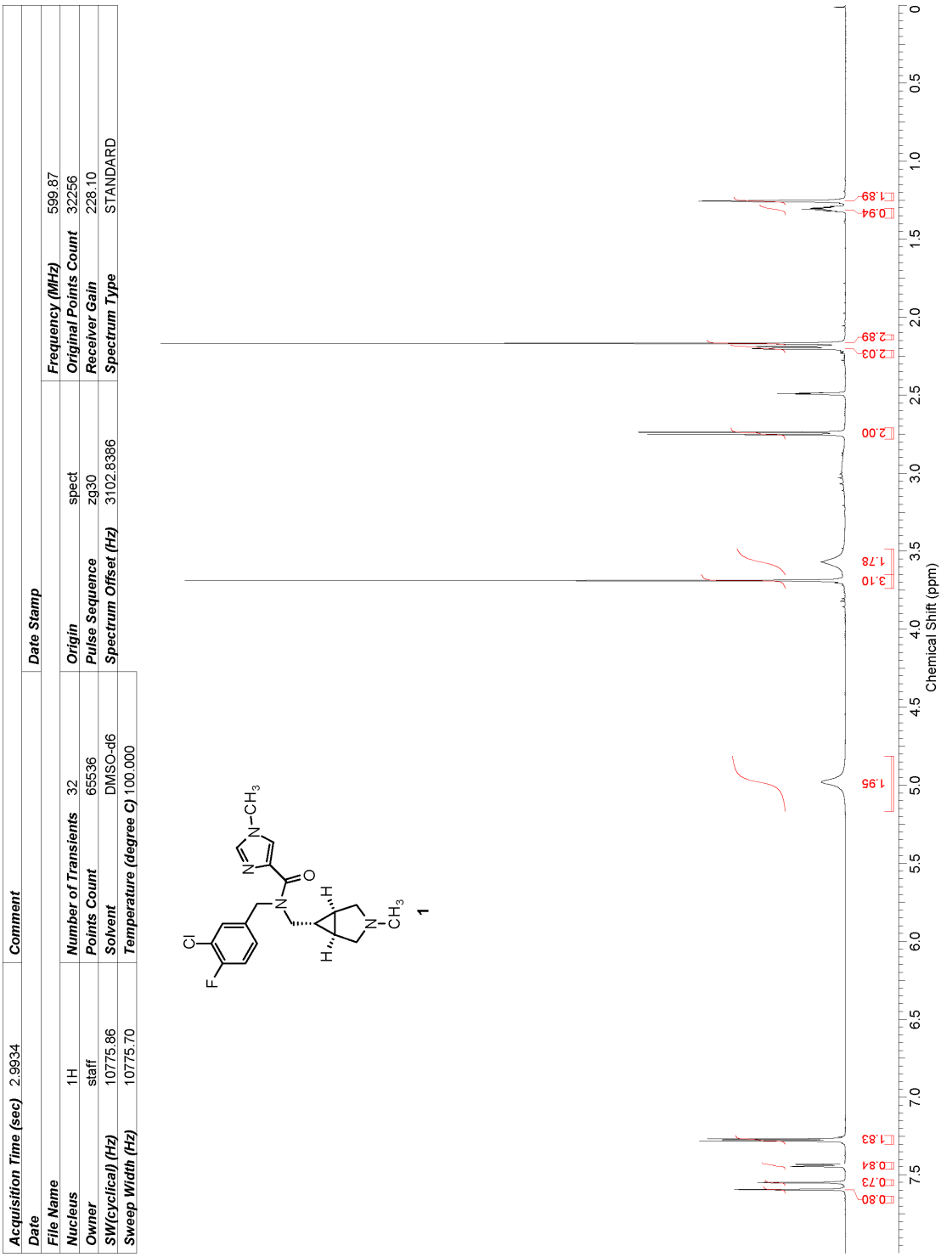
The full list of resins and scavenging results are shown in the table on the following page. Green highlights cells of resins that hit our criteria for scavenging efficiency.

Entry	Resin Manufacturer	Resin Name	Ir amount (ppm)	Removal of Ir (%)	Main Product Recovery %
1	Smopex (JM)	101	362	24.0	92
2	Smopex (JM)	102	151	68.3	91
3	Smopex (JM)	105pp	297	37.7	67
4	Scavnet (Engelhard)	C-1	159	66.6	87
5	Scavnet (Engelhard)	Si-1	497	-4.3	92
6	Scavnet (Engelhard)	Si-2	506	-6.2	78
7	Scavnet (Engelhard)	AI-1	316	33.7	82
8	Quadrapure (Reaxa)	TU	343	28.0	87
9	Quadrapure (Reaxa)	AMPA	199	58.2	68
10	Quadrapure (Reaxa)	MPA	567	-19.0	67
11	Quadrapure (Reaxa)	AEA	588	-23.4	95
12	Quadrapure (Reaxa)	IMADZ	343	28.0	84
13	Quadrapure (Reaxa)	BDZ	237	50.3	58
14	Quadrapure (Reaxa)	EDA	423	11.2	87
15	Quadrapure (Reaxa)	BzA	314	34.1	86
16	Quadrapure (Reaxa)	DET	237	50.3	92
17	Ecosorb	C905	135	71.7	88
18	Ecosorb	C908	86	82.0	93
19	Ecosorb	C941	65	86.4	91
20	Degussa	Deloxan THP	387	18.8	84
21	Phosphonics	Si-STA3 SP-12-1041b	410	14.0	72
22	Phosphonics	Si-SEM26 SP-12-023b	269	43.5	84
23	Phosphonics	SI-SPM3 SP-12-031b	319	33.1	73
24	Phosphonics	Si-SPM36 SP-12-033b	366	23.2	93
25	Phosphonics	Si-SCR SP-12-012b	223	53.2	86
26	Phosphonics	Si-SDOL SP-12-014b	454	4.7	87
27	Silicycle	Si-Pyridine	594	-24.7	98
28	Sigma-Aldrich	Norit CA1 (B) (12)	104	78.2	90
29	Sigma-Aldrich	Darco KBB (B) (14)	60	87.4	92
30	Sigma-Aldrich	Norit CA1 (16)	99	79.2	93
31	CUNO	CUNO SASS R54 (18)	111	76.7	85
32	CUNO	CUNO SASS R53 (19)	153	67.9	78
33	CUNO	CUNO SASS R55 (20)	64	86.6	95
34	CUNO	CUNO SASS R52 (30)	154	67.7	84
35	Sigma-Aldrich	Darco 242233 (22)	172	63.9	92
36	Sigma-Aldrich	Darco 242441 (24)	161	66.2	97
37	Sigma-Aldrich	Darco 242268 (25)	244	48.8	98
38	Sigma-Aldrich	Darco G-60 242276 (26)	157	67.1	79
39	Sigma-Aldrich	Darco KB 278092 (27)	76	84.1	87
40	Sigma-Aldrich	Darco KB-B 278106 (28)	83	82.6	91
41	Biotage	Biotage AC 2604-1 (29)	81	83.0	90
42	Silicycle	Si-thiourea	358	24.9	75

In-Process Control NMR Spectra for 6 + 11 → 12 (Table 6, entry 1)



NMR Spectra of 1, 11, 12, 22 and 24



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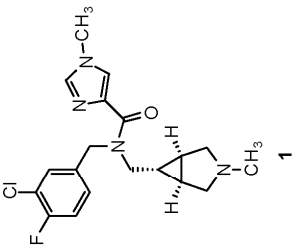
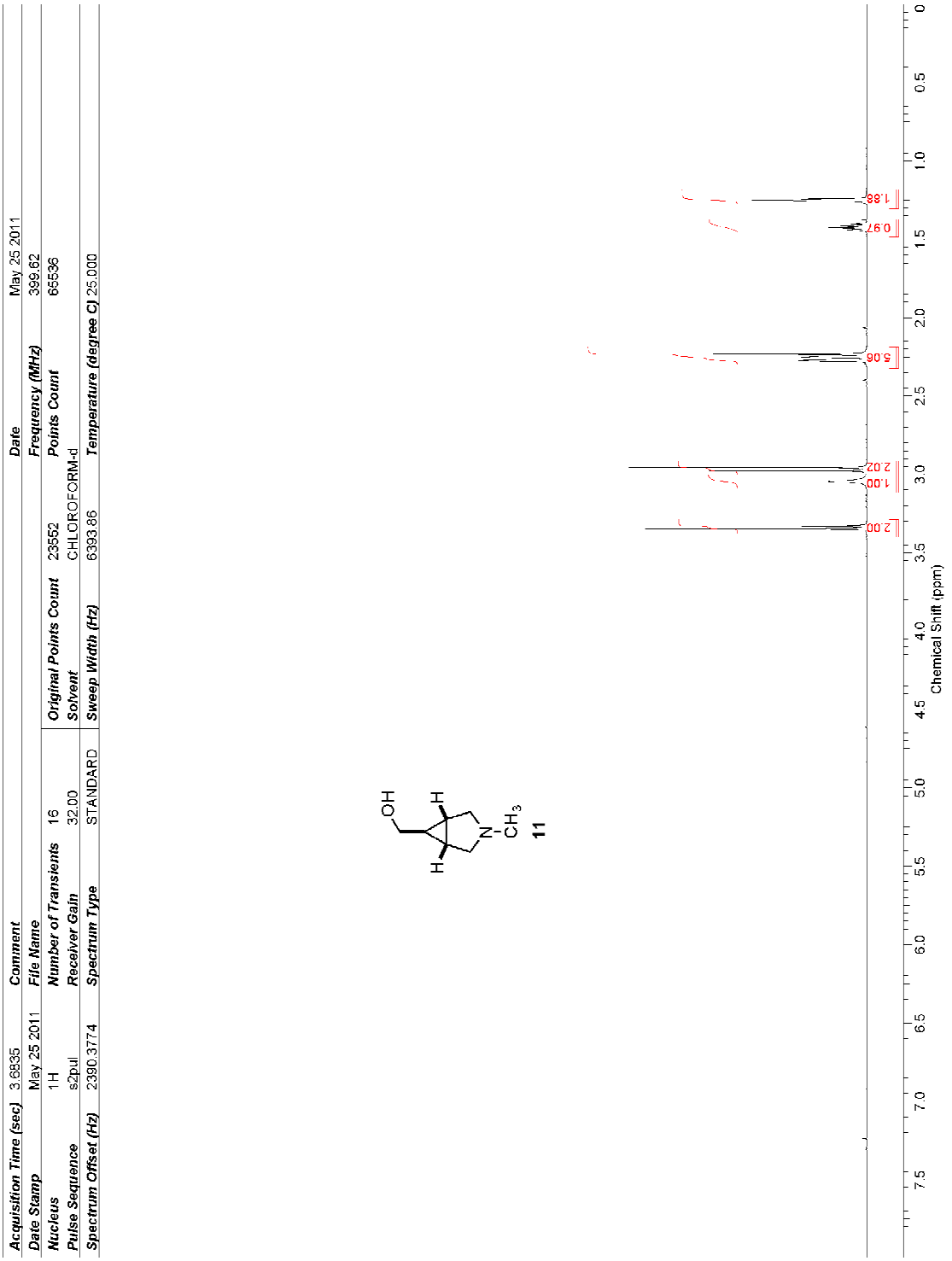


1

No.	(ppm)	(Hz)	Height
1	18.83	2840.9	0.0501
2	21.67	3268.3	0.4924
3	32.48	4898.7	0.1522
4	48.17	7266.0	0.0228
5	48.66	7339.5	0.0287
6	55.93	8436.9	0.5688
7	115.76	17460.6	0.1019
8	115.90	17481.6	0.1023
9	118.66	17899.0	0.0320
10	118.78	17916.7	0.0306
11	125.60	18944.5	0.1079
12	127.30	19202.1	0.1099
13	127.35	19209.3	0.1069
14	128.80	19427.7	0.1920
15	136.50	20588.7	0.0499
16	136.52	20592.5	0.0496
17	136.70	20619.1	0.1425
18	136.79	20633.5	0.0616
19	154.92	23368.4	0.0418
20	156.55	23613.9	0.0461
21	162.91	24573.6	0.0627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H
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1.00
2.02
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6.5
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Chemical Shift (ppm)

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Spectrum Offset (Hz)	10021.5488	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	24118.18

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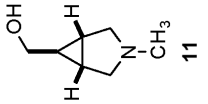
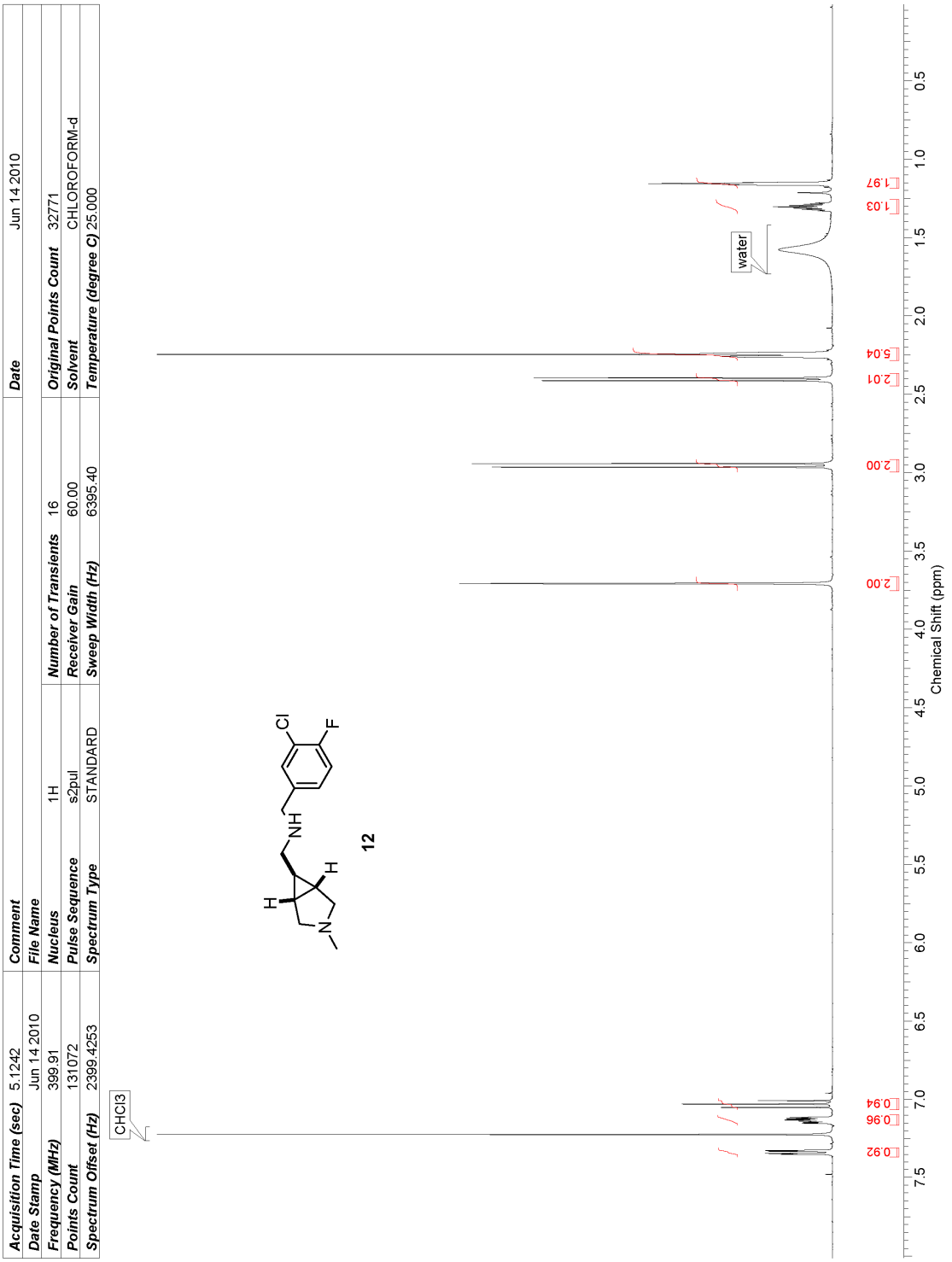
Solvent	CHLOROFORM-d		
Temperature (degree C)	25.000		

No.	(ppm)	(Hz)	Height
1	21.52	2162.8	0.9375
2	22.48	2258.9	0.4235
3	41.47	4167.0	0.4573
4	56.99	5726.9	1.0000
5	64.73	6505.1	0.4669



11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Cl
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H
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2.00
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2.01
1.03
1.97
7.5
7.0
6.5
6.0
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Chemical Shift (ppm)

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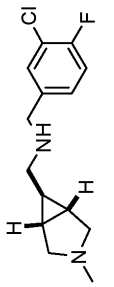
Temperature (degree C)	25.000				



12

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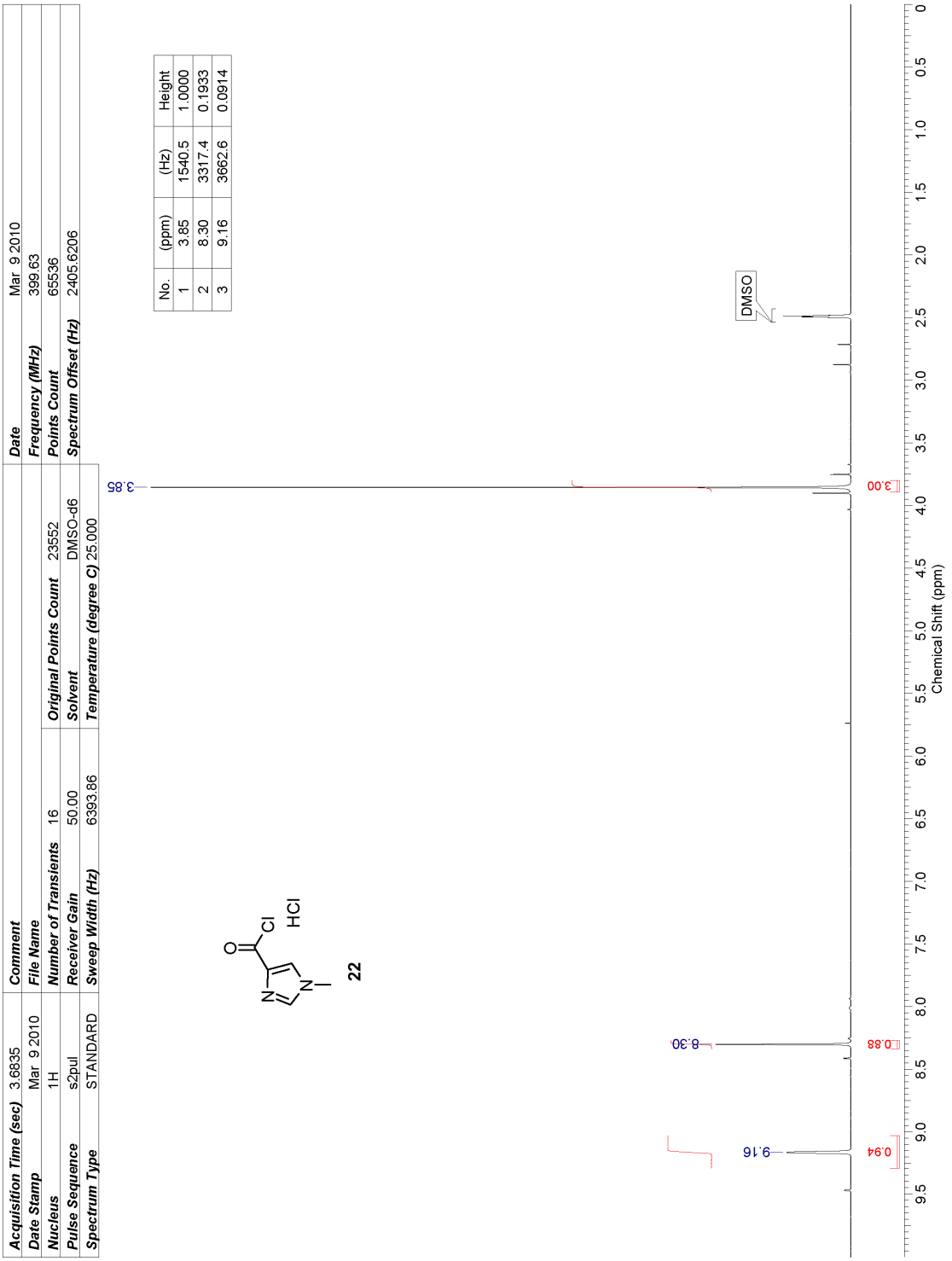
1	20.17	2027.4	0.4413
2	22.31	2241.8	0.8757
3	41.40	4160.2	0.4573
4	51.52	5177.6	0.5013
5	52.27	5252.9	0.4671
6	57.10	5738.5	1.0000
7	76.68	7706.1	0.2400
8	77.00	7738.1	0.2403
9	77.21	7758.7	0.0352
10	77.32	7769.9	0.2305
11	116.15	11672.2	0.2120
12	116.35	11693.0	0.2181
13	120.57	12116.4	0.0279
14	120.74	12133.9	0.0323
15	127.50	12813.2	0.2036
16	127.57	12820.4	0.2103
17	130.01	13065.3	0.4207
18	137.63	13831.4	0.0824
19	137.67	13835.0	0.0823
20	155.77	15653.6	0.0641
21	158.23	15900.9	0.0704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9.16
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HCl
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N
N
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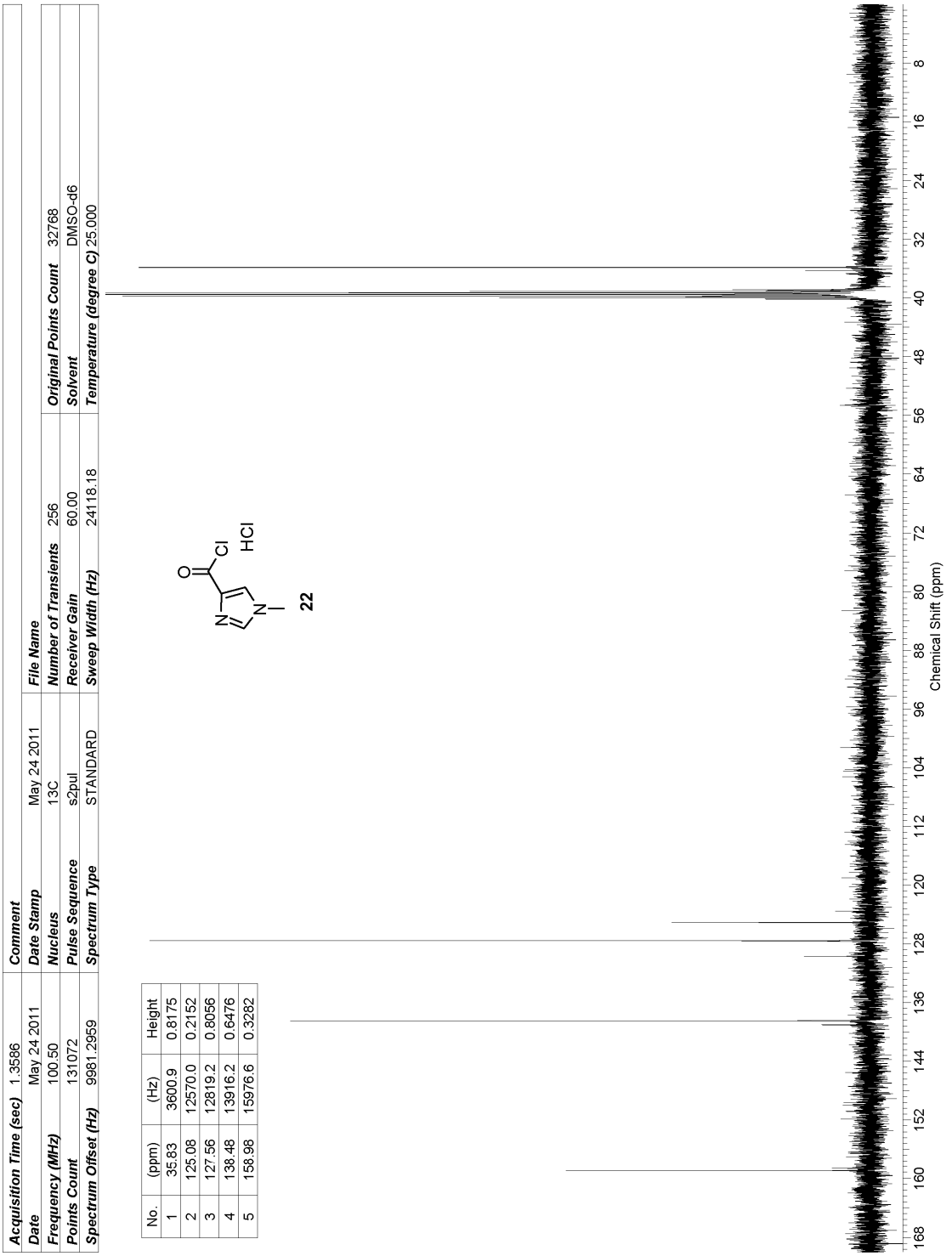
Chemical Shift (ppm)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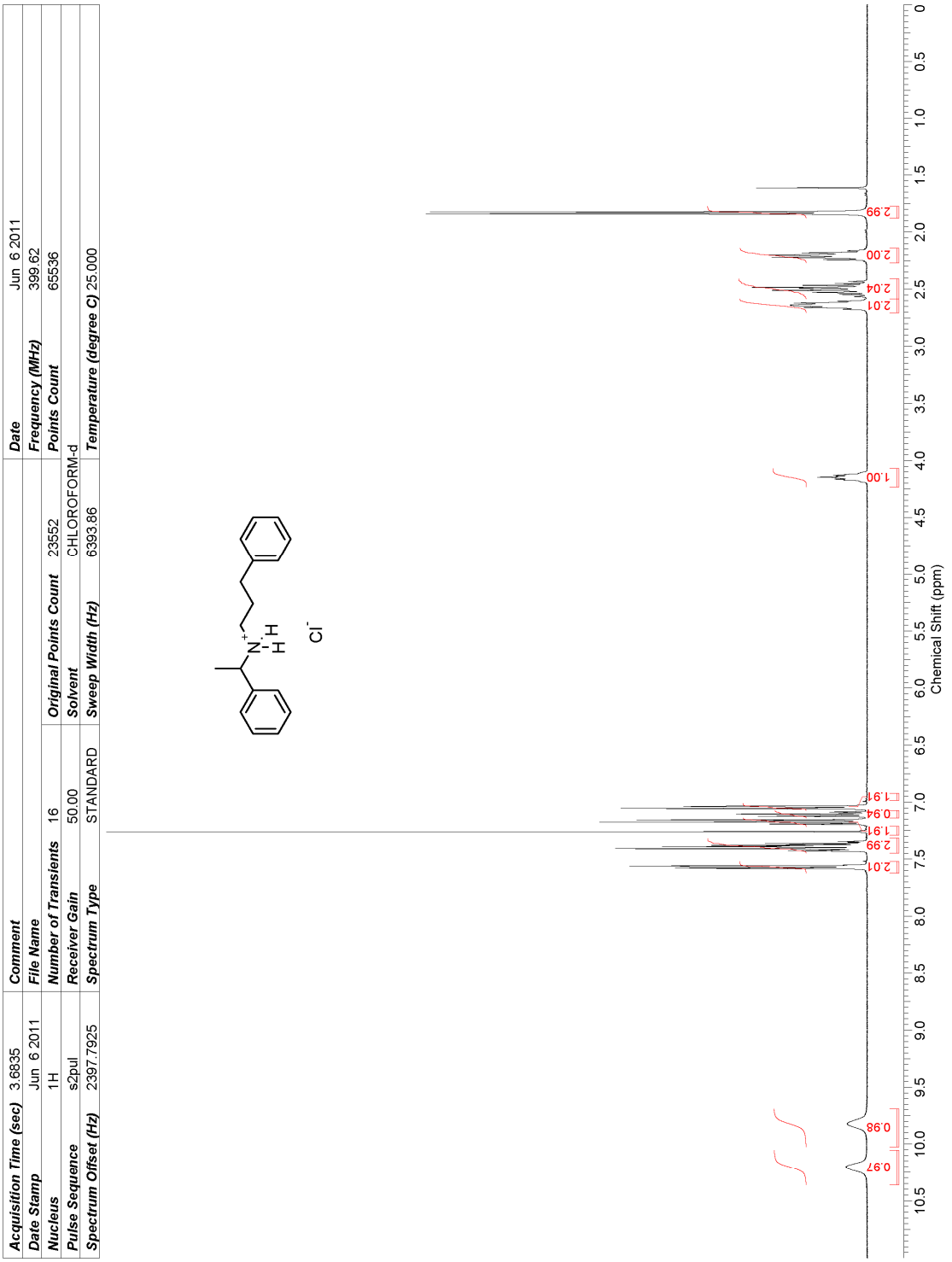
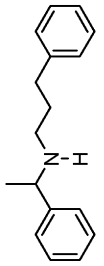
Points Count 131072
Pulse Sequence s2pul
Receiver Gain 60.00
Solvent DMSO-d6
Spectrum Offset (Hz) 9981.2959
Spectrum Type STANDARD
Sweep Width (Hz) 24118.18
Temperature (degree C) 25.000
No. (ppm) (Hz) Height
1 35.83 3600.9 0.8175
2 125.08 12570.0 0.2152
3 127.56 12819.2 0.8056
4 138.48 13916.2 0.6476
5 158.98 15976.6 0.3282
HCl
22
Chemical Shift (ppm)


Acquisition Time (sec) 3.6835
Date Stamp Jun 6 2011
Nucleus 1H
Pulse Sequence s2pul
Spectrum Offset (Hz) 2397.7925
Comment
File Name
Number of Transients 16
Receiver Gain 50.00
Spectrum Type STANDARD
Original Points Count 23552
Solvent CHLOROFORM-d
Sweep Width (Hz) 6393.86
Date Jun 6 2011
Frequency (MHz) 399.62
Points Count 65536
Temperature (degree C) 25.000
Cl⁻
2.99
2.00
2.04
2.01
1.00
1.97
0.94
1.97
2.99
2.01
0.98
0.97
Chemical Shift (ppm)

Acquisition Time (sec)	1.3586	***Comment***			
Date	Jun 6 2011	***Date Stamp***	Jun 6 2011	***File Name***	
Frequency (MHz)	100.49	***Nucleus***	13C	***Number of Transients***	2048
Points Count	131072	***Pulse Sequence***	s2pul	***Receiver Gain***	60.00
Spectrum Offset (Hz)	10020.2607	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	24118.18

Original Points Count	32768	
Solvent	CHLOROFORM-d	
Temperature (degree C)	25.000	



No.	(ppm)	(Hz)	Height
1	20.44	2053.7	0.3032
2	27.15	2728.5	0.3843
3	32.62	3278.1	0.4085
4	45.11	4533.2	0.3291
5	58.98	5927.3	0.3486
6	76.68	7706.1	0.2534
7	77.00	7738.1	0.2591
8	77.32	7769.9	0.2484
9	126.09	12671.4	0.4767
10	127.75	12838.3	0.7378
11	128.20	12883.2	1.0000
12	128.36	12899.3	0.9653
13	129.20	12983.4	0.3622
14	129.33	12996.7	0.7603
15	135.93	13660.0	0.2838
16	139.86	14054.9	0.2434