

Supplementary Information

Synthesis, evaluation and application of novel bifunctional *N,N*-di-isopropylbenzylamineboronic acid catalysts for direct amide formation between carboxylic acids and amines

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General experimental

All ^1H and ^{13}C NMR were recorded with either a Varian Mercury-400, Bruker Avance-400 or Varian Inova-500 spectrometer. ^{11}B NMR were recorded with the Bruker Avance-400 at a frequency of 128 MHz. Chemical shifts are expressed as parts per million (ppm) downfield from the internal standard TMS. Mass spectra were performed with a Micromass Autospec. IR spectra were recorded with a Perkin-Elmer 1615 FTIR spectrometer. Elemental analysis was performed using an Exeter Analytical E-440 Elemental Analyser. Melting points were determined using an electrothermal melting point apparatus. All reagents were obtained from Aldrich or Acros and were used as received. All HPLC injections employed a Phenomenex Gemini C18 5 μm , 150 mm x 4.60 mm column. Catalyst screening was performed on a Gilson 215 Synthesis Workstation equipped with ReactArray racks and RS1000 heating block, carried out using ReactArrray Control Software (version 3,0,0,3048) and HPLC data analysed using ReactArray DataManager (version 1,1,33,0). HPLC conditions were under Gilson Unipoint (version 5.11) control and injections carried out in conjunction with ReactArray DataManager. The HPLC system consisted of Gilson 322 Pump, Gilson 402 Syringe Pump and Agilent 1100 Series UV Diode Array Detector. Design of Experiments was carried out on a Gilson SK233 with Reactivate heating block, using ReactArray software (version 2.00). The HPLC system consisted of Agilent 1100 series comprising G1322A degasser, G1312A binary pump, G1316A column compartment and variable wavelength detector (254 nm) with HPLC injections controlled by Waters Empower (Build 1154). Design of Experiments setup and analysis was carried out using Design-Expert (Version 7.0.0), Stat-Ease Inc.

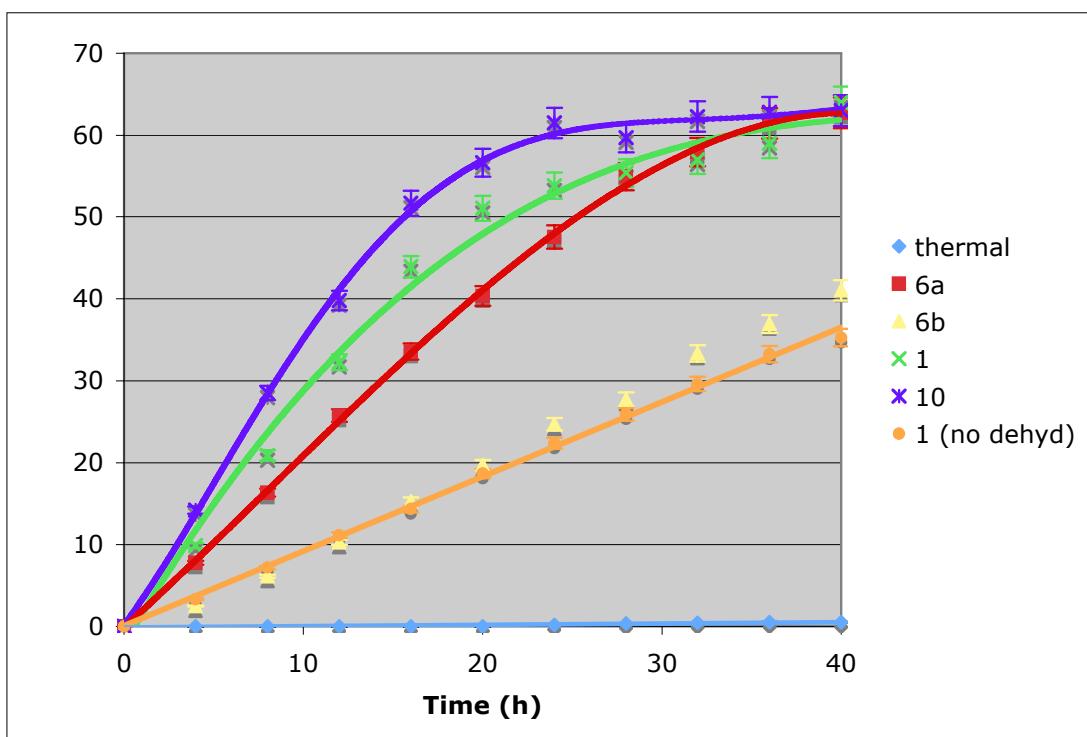


Figure 6. Yield *versus* time data including error bars for catalysed and thermal direct amide condensation between benzoic acid and benzylamine in refluxing fluorobenzene.

X-ray crystallography

Diffraction experiments (see Table 4) were carried out on a SMART 3-circle diffractometer with a 1K CCD area detector, using graphite-monochromated Mo- K_{α} radiation ($\bar{\lambda}=0.71073$ Å) and a Cryostream (Oxford Cryosystems) open-flow N₂ cryostat. The structure was solved by direct methods and refined by full-matrix least squares against F^2 of all reflections, using SHELXTL software (version 6.14, Bruker AXS, Madison WI, USA, 2003). All non-hydrogen atoms were refined in anisotropic and all H atoms (located in difference Fourier maps) in isotropic approximation.

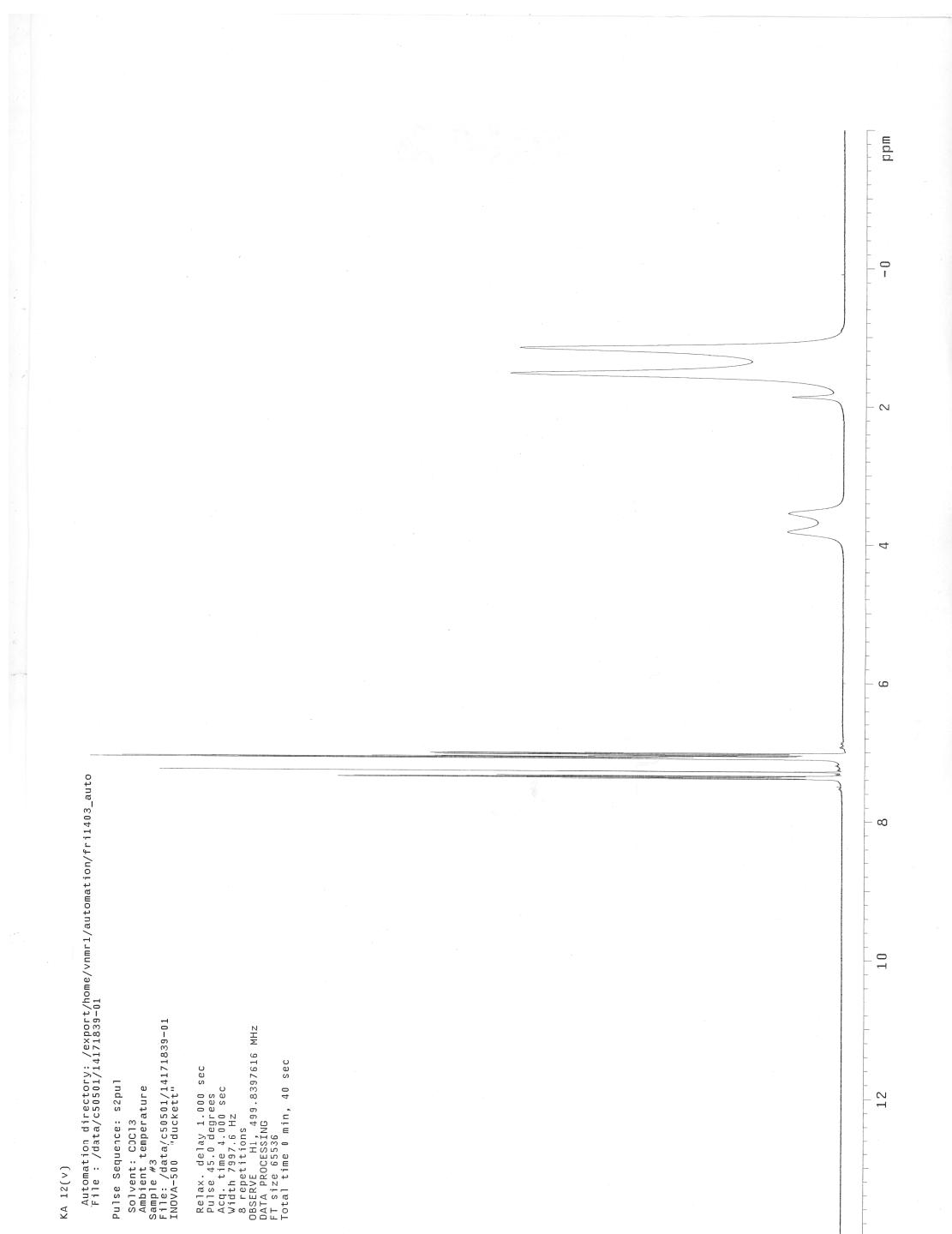
Table 1. Crystal data

Compound	6a	10
CCDC dep. no.	632237	632238
Formula	C ₁₃ H ₂₁ BFNO ₂	C ₁₄ H ₂₁ BF ₃ NO ₂
Formula weight	253.12	303.13
T, K	120	120
Symmetry	monoclinic	monoclinic
Space group	P2 ₁ /c (# 14)	P2 ₁ /c (# 14)
<i>a</i> , Å	13.748(2)	15.4653(18)
<i>b</i> , Å	7.701(1)	7.7851(9)
<i>c</i> , Å	13.781(2)	13.2548(15)
β, °	110.97(1)	105.71(1)
<i>V</i> , Å ³	1362.4(3)	1536.2(3)
<i>Z</i>	4	4
ƒ, mm ⁻¹	0.09	0.11
Refls collected	15676	12199
Unique refls	3616, 3192 ^a	4059, 3248 ^a
<i>R</i> _{int} , %	4.2	4.0
<i>R</i> (<i>F</i>) ^a , w <i>R</i> (<i>F</i> ²), %	3.7, 10.7	4.2, 11.2

^a reflections with $F^2 > 2\sigma(F^2)$

N,N-Diisopropyl-3-fluorobenzamide 4a

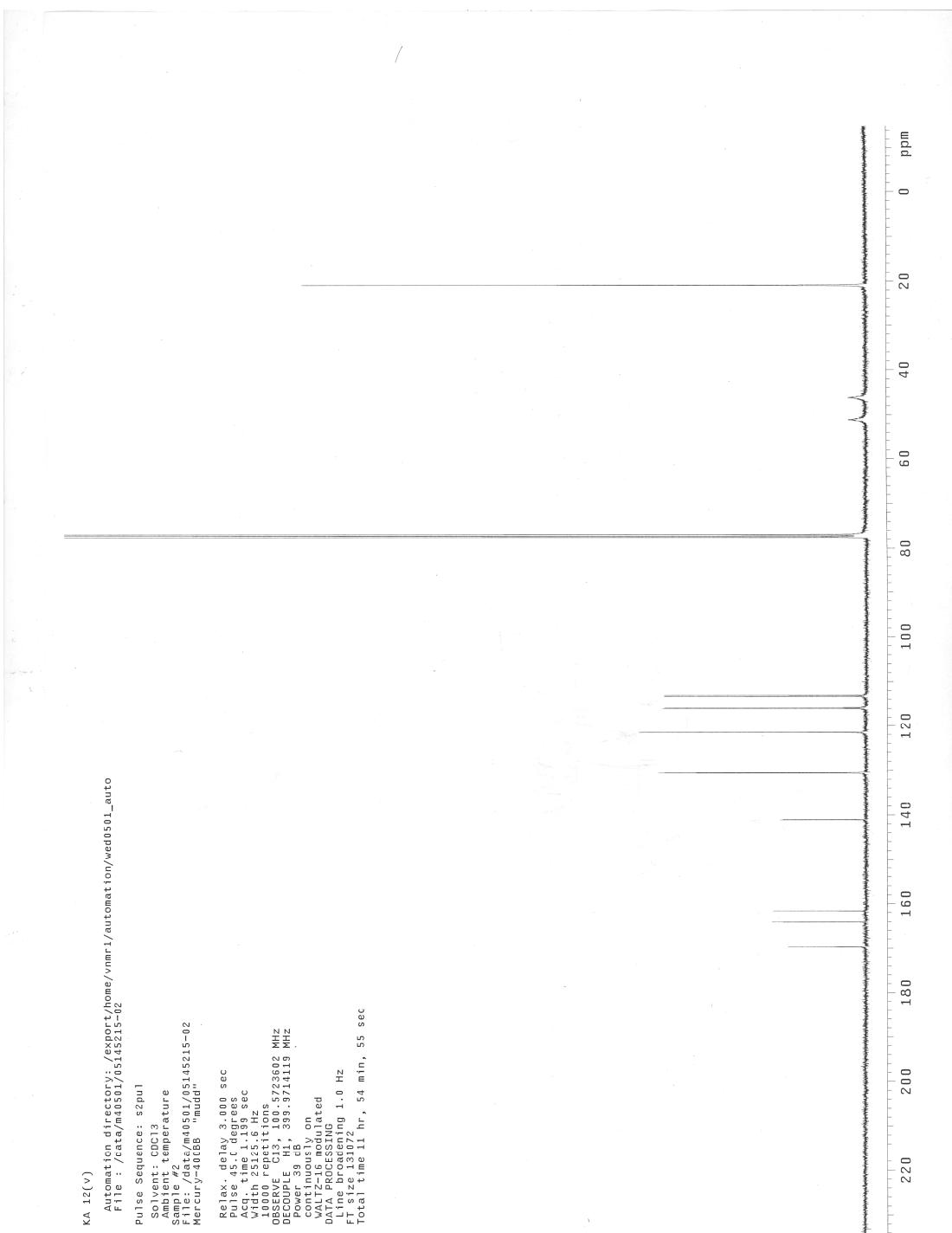
^1H NMR (500 MHz, CDCl_3)



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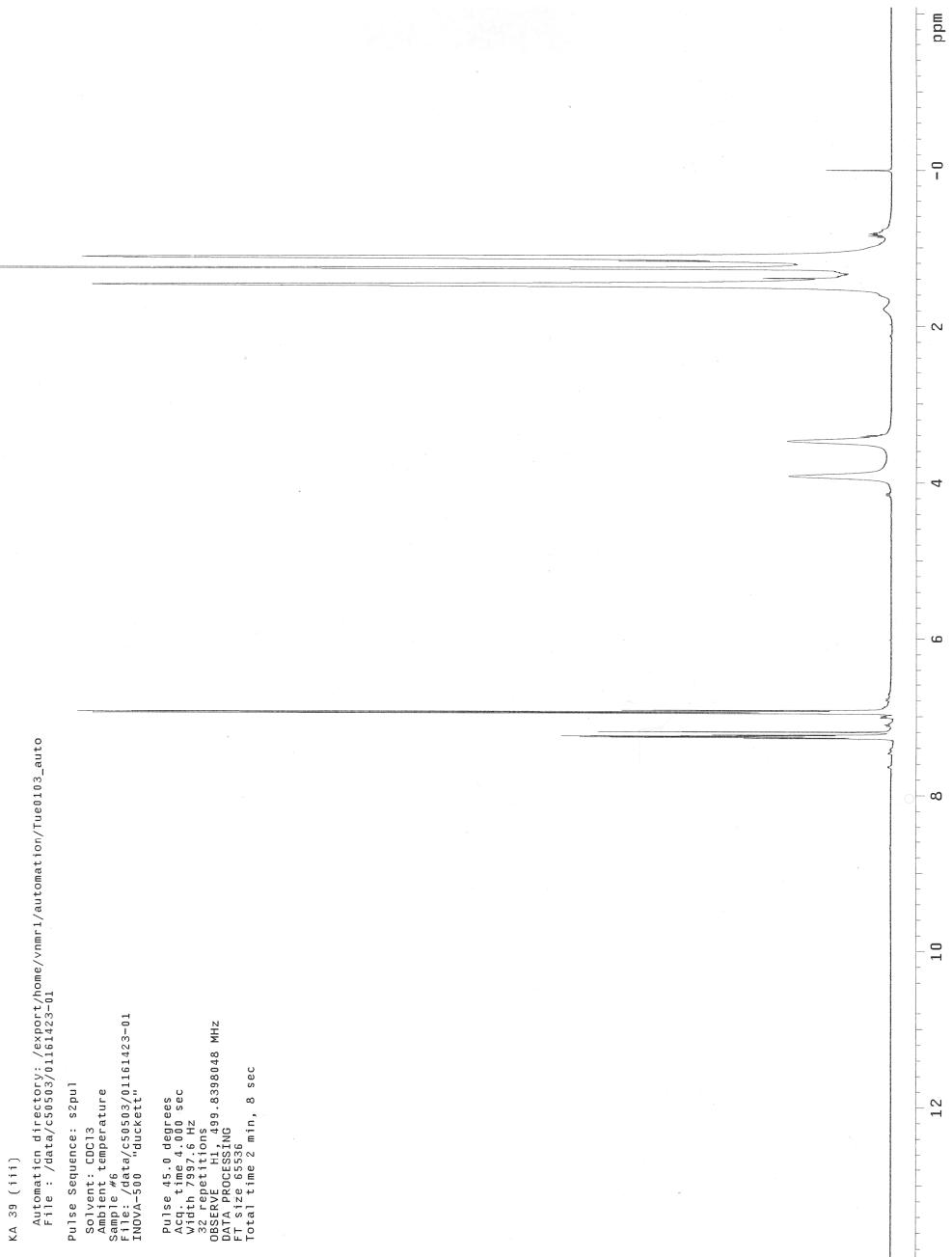
N,N-Diisopropyl-3-fluorobenzamide 4a

¹³C NMR (100.6 MHz, CDCl₃)



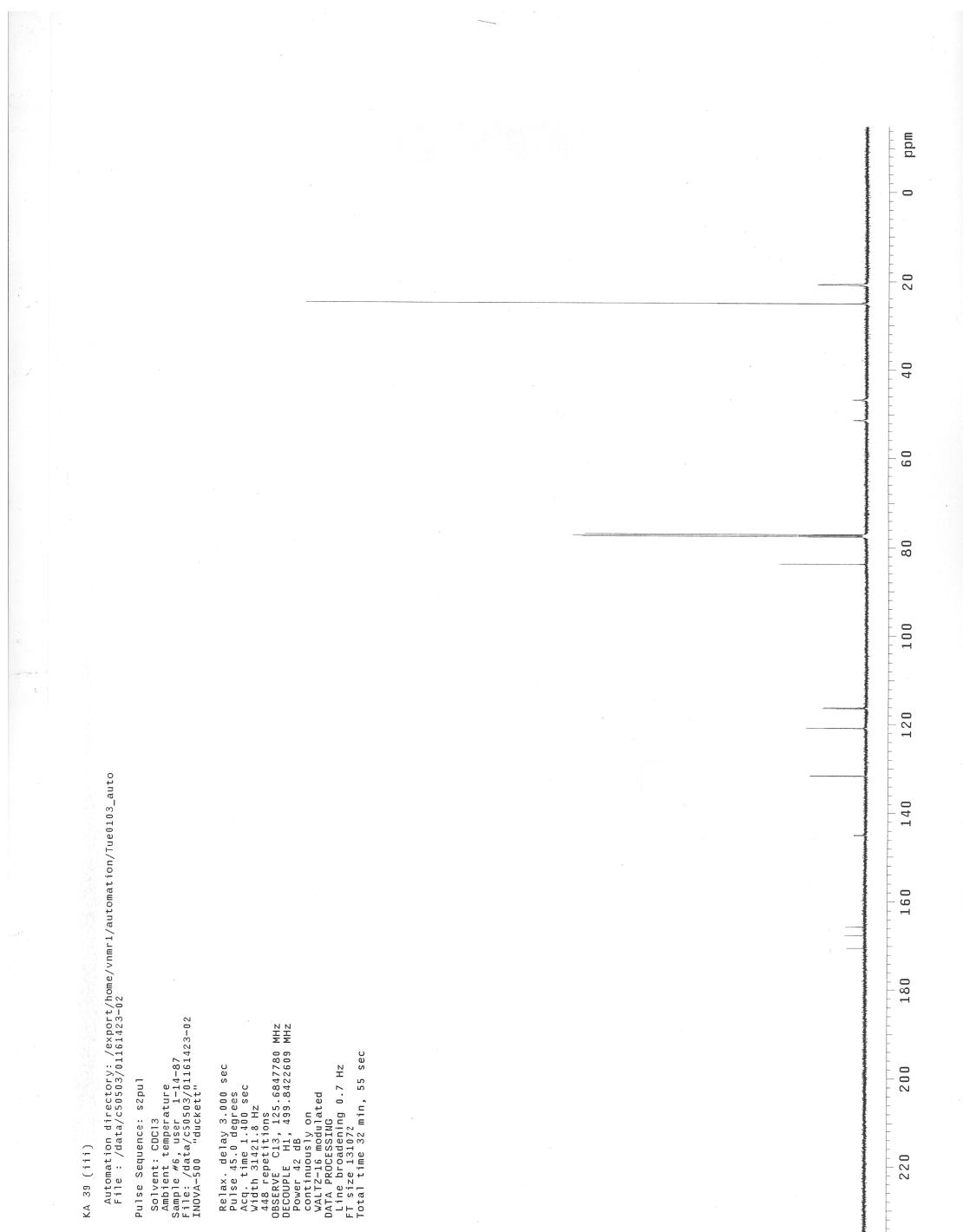
N,N-Diisopropyl-3-fluoro-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzamide 5a

^1H NMR (500 MHz, CDCl_3)



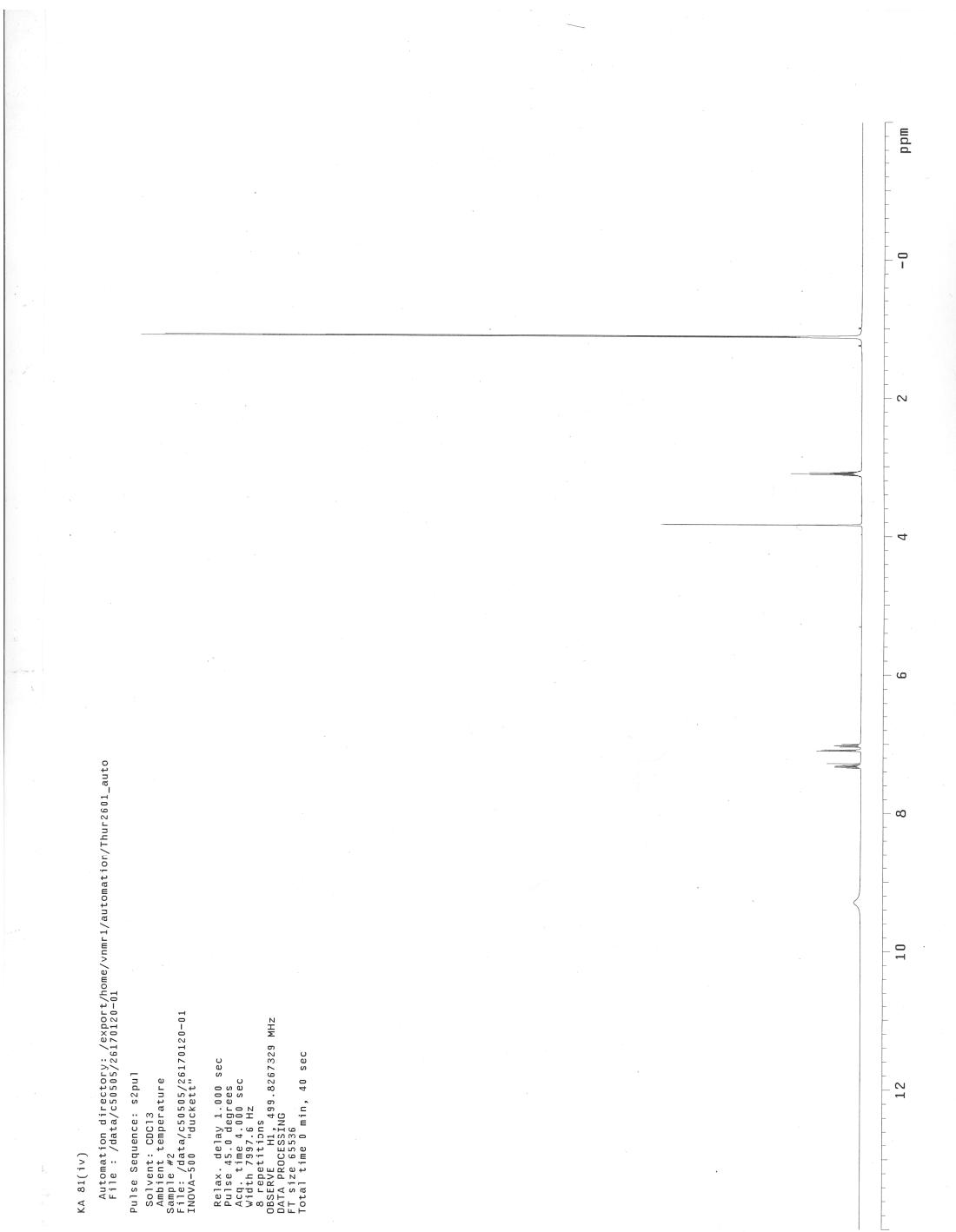
N,N-Diisopropyl-3-fluoro-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-
benzamide **5a**

¹³C NMR (125.7 MHz, CDCl₃)



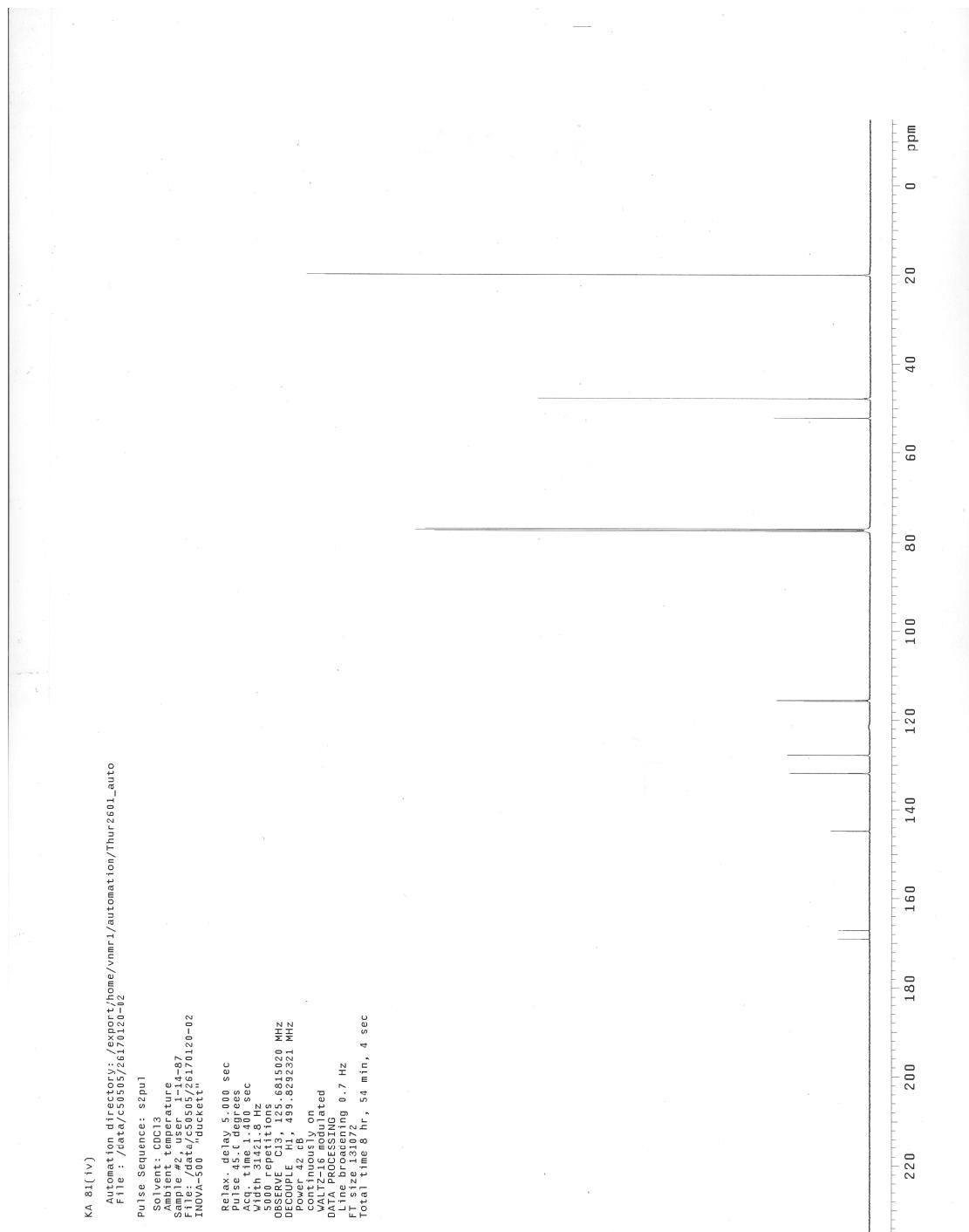
N,N-Diisopropyl-3-fluorobenzylamine-2-boronic acid 6a

^1H NMR (500 MHz, CDCl_3)



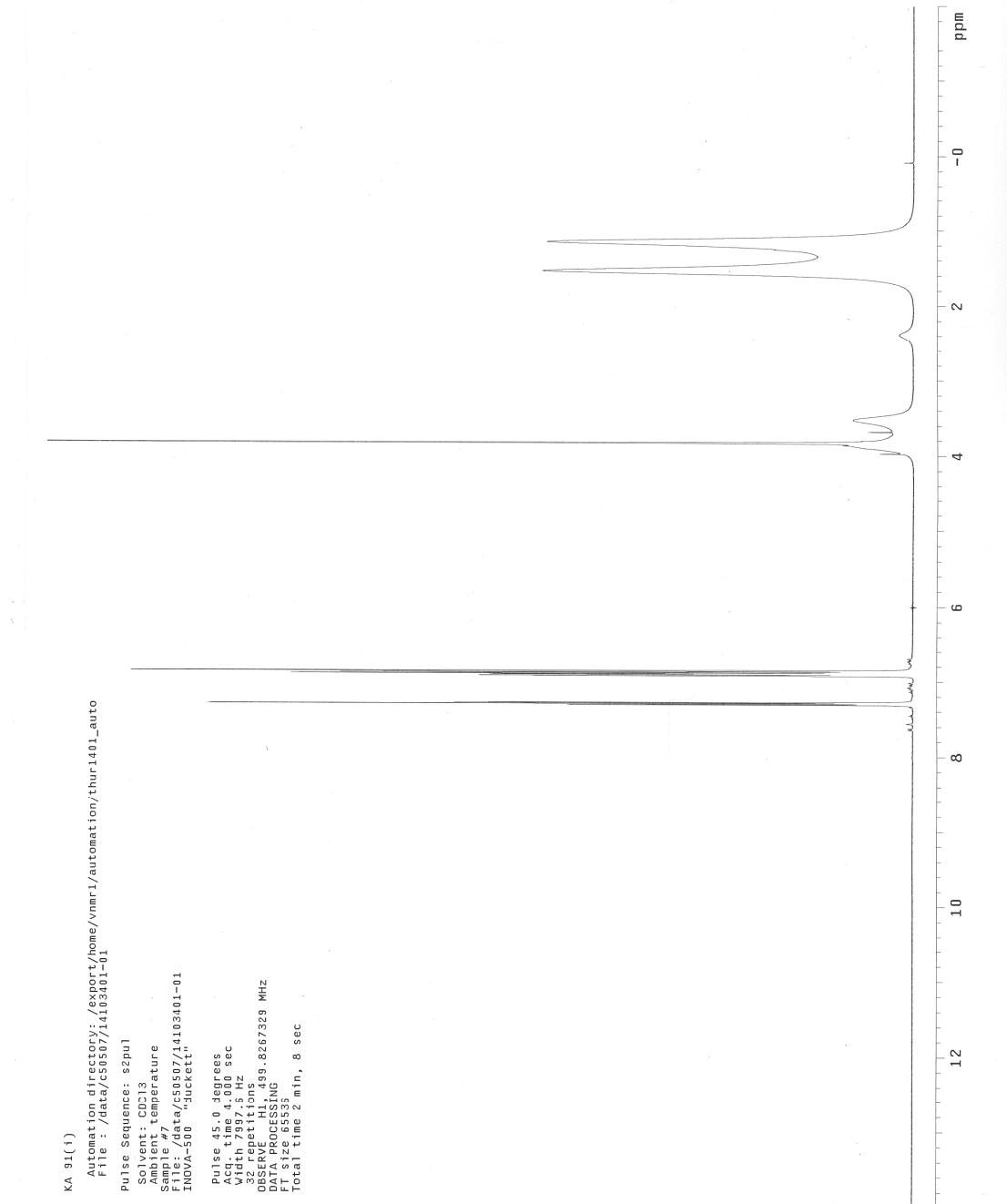
N,N-Diisopropyl-3-fluorobenzylamine-2-boronic acid 6a

^{13}C NMR (125.7 MHz, CDCl_3)



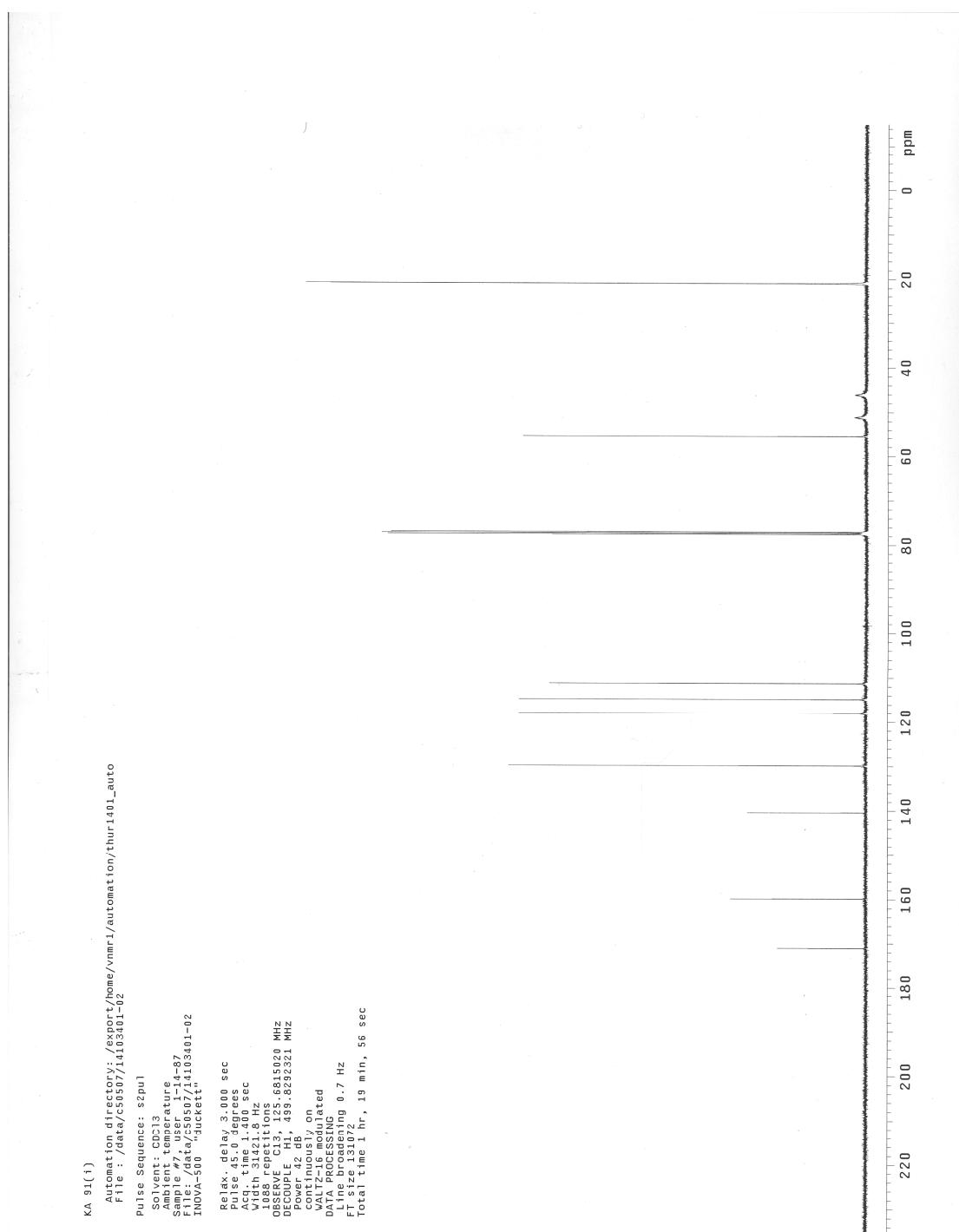
N,N-Diisopropyl-3-methoxybenzamide 4b

¹H NMR (500 MHz, CDCl₃)



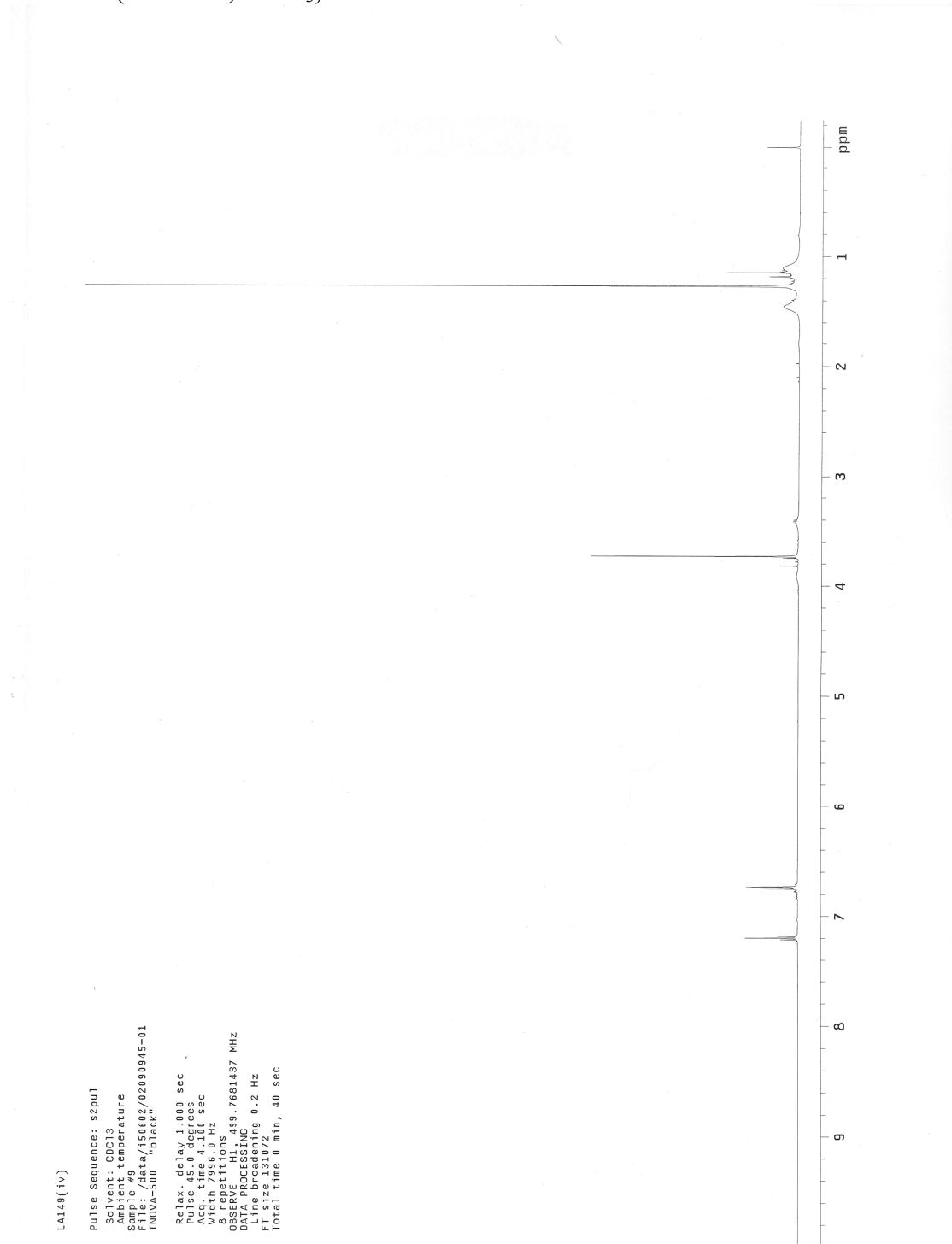
N,N-Diisopropyl-3-methoxybenzamide **4b**

¹³C NMR (125.7 MHz, CDCl₃)



N,N-Diisopropyl-3-methoxy-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzamide **5b**

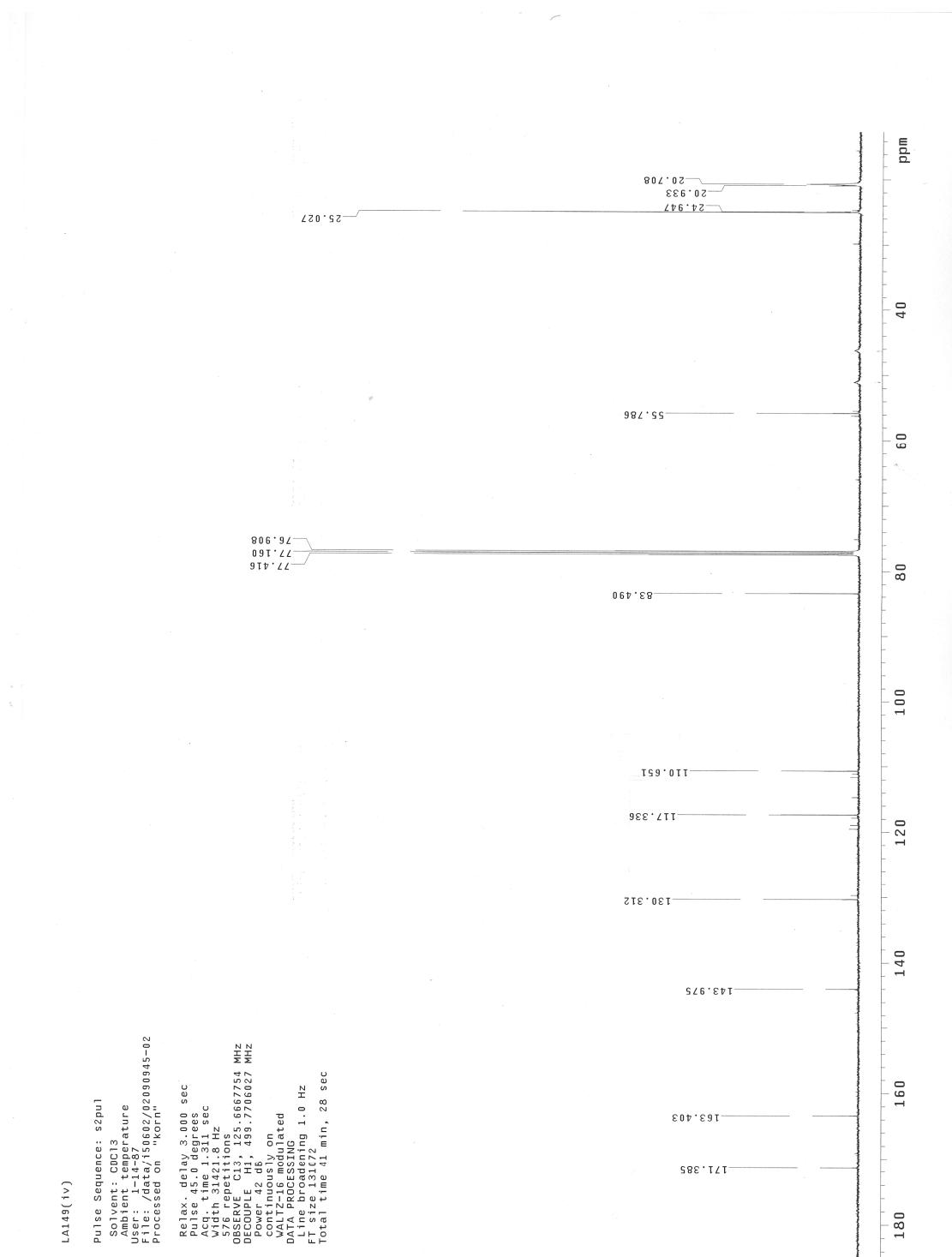
¹H NMR (500 MHz, CDCl₃)



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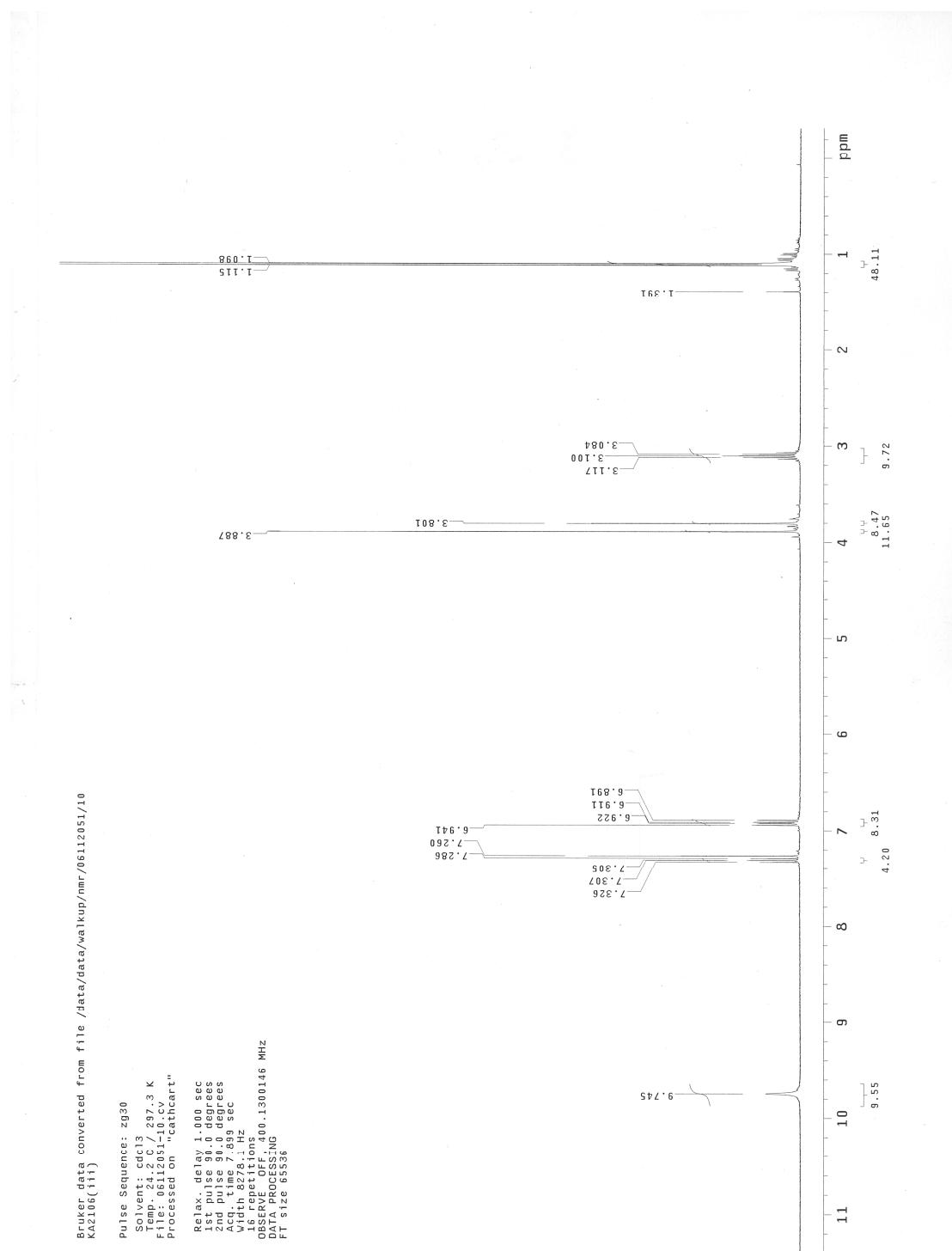
N,N-Diisopropyl-3-methoxy-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzamide 5b

^{13}C NMR (125.7 MHz, CDCl_3)



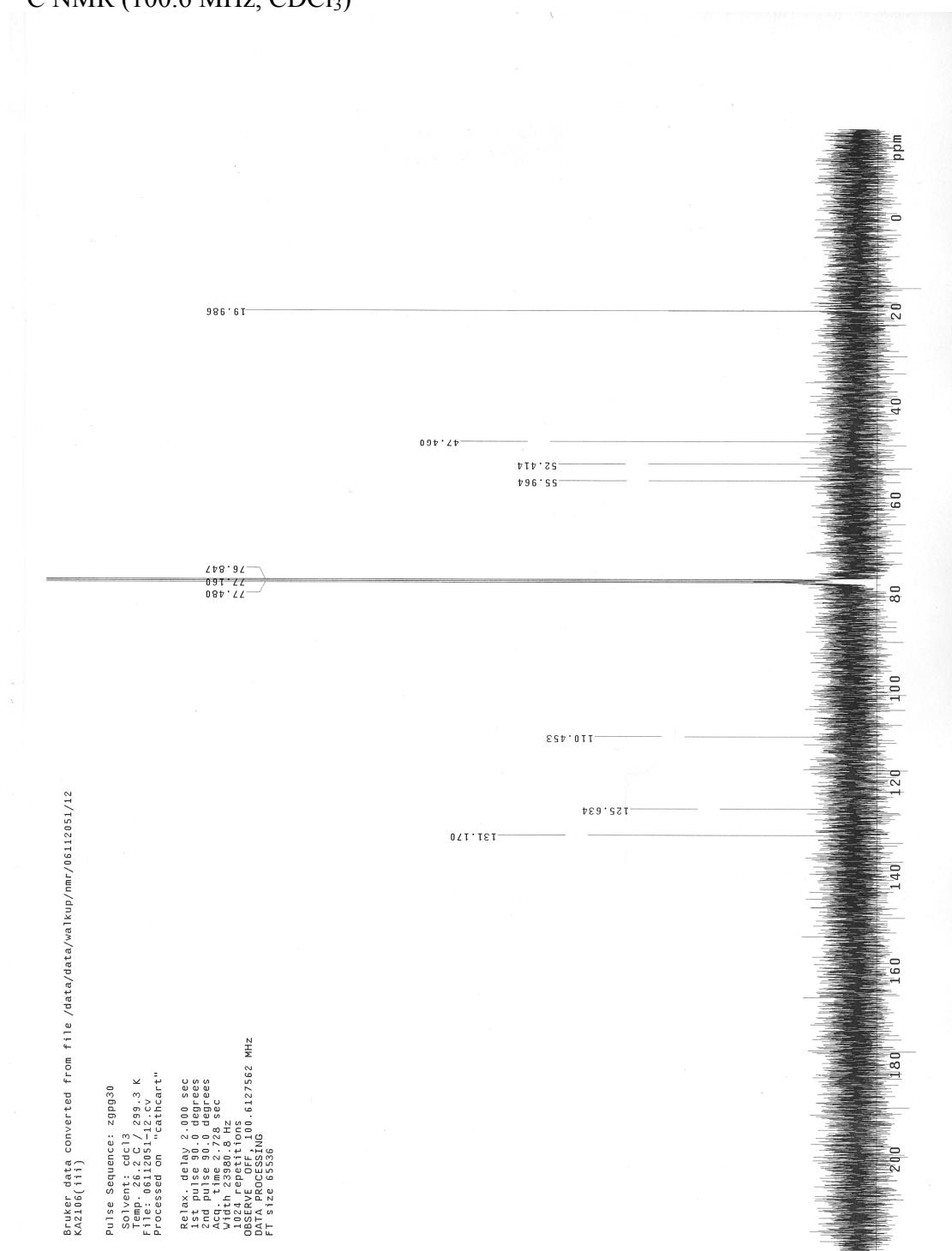
N,N-Diisopropyl-3-methoxybenzylamine-2-boronic acid **6b**

¹H NMR (400 MHz, CDCl₃)



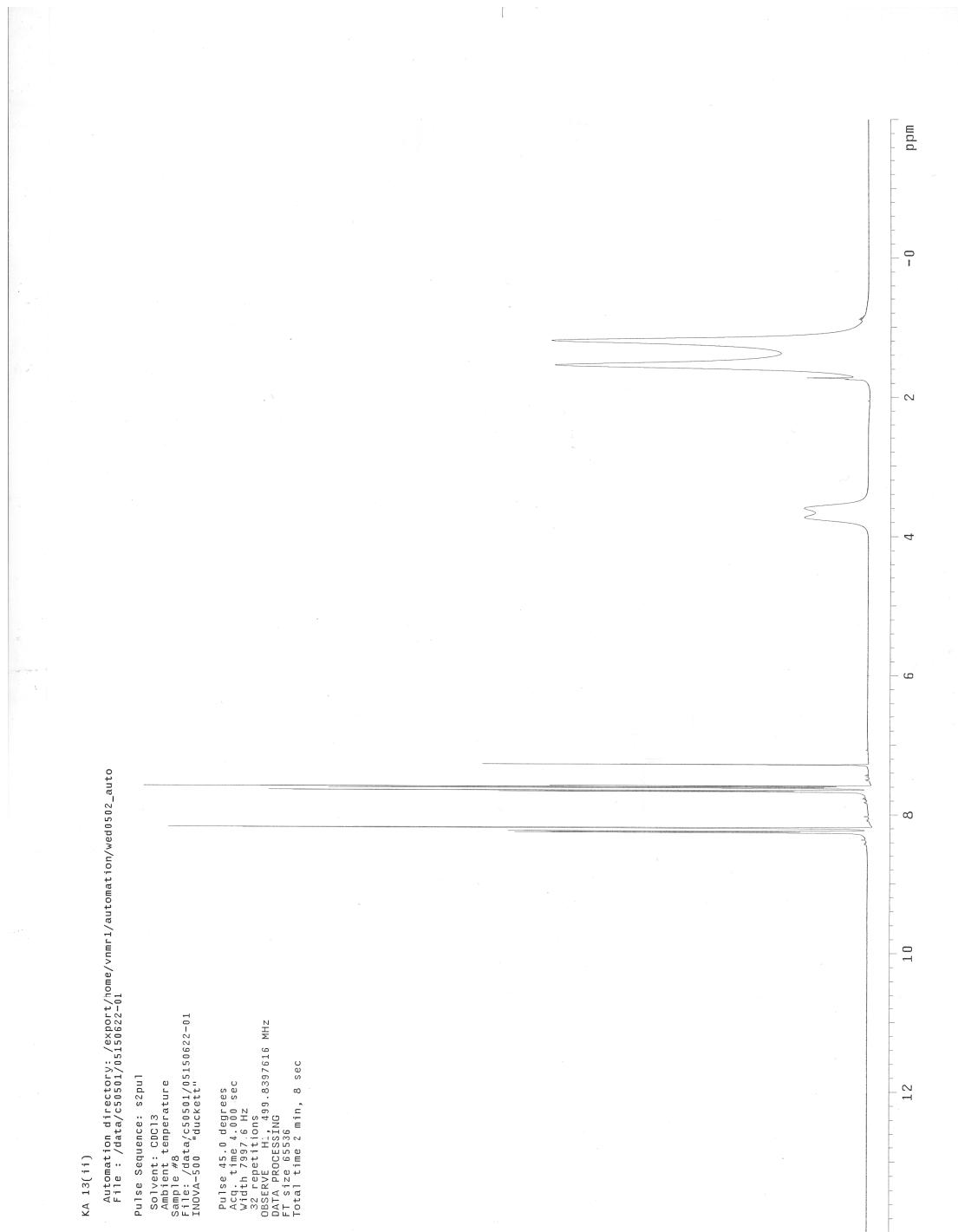
N,N-Diisopropyl-3-methoxybenzylamine-2-boronic acid **6b**

¹³C NMR (100.6 MHz, CDCl₃)



N,N-Diisopropyl-3-nitrobenzamide **4c**

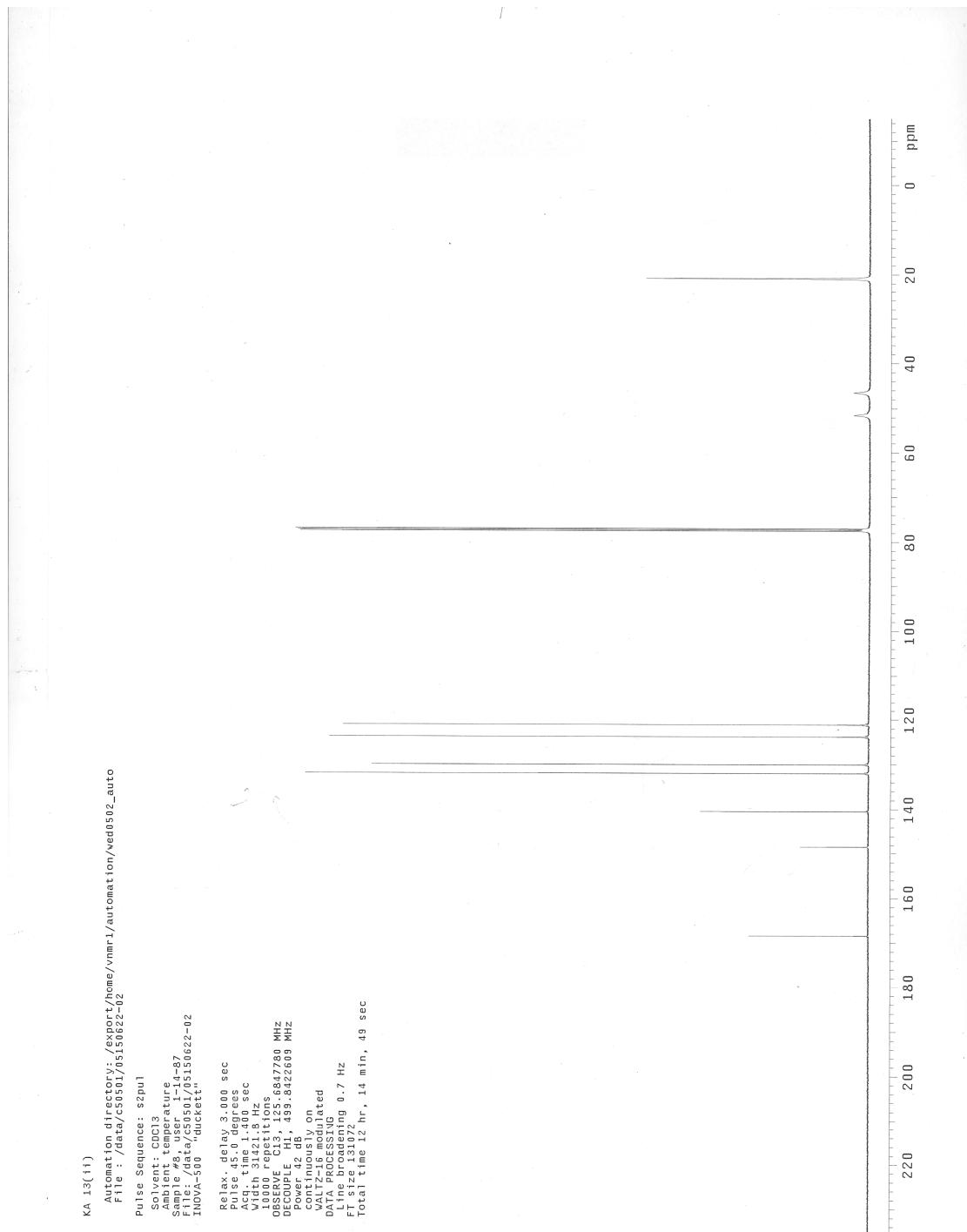
¹H NMR (500 MHz, CDCl₃)



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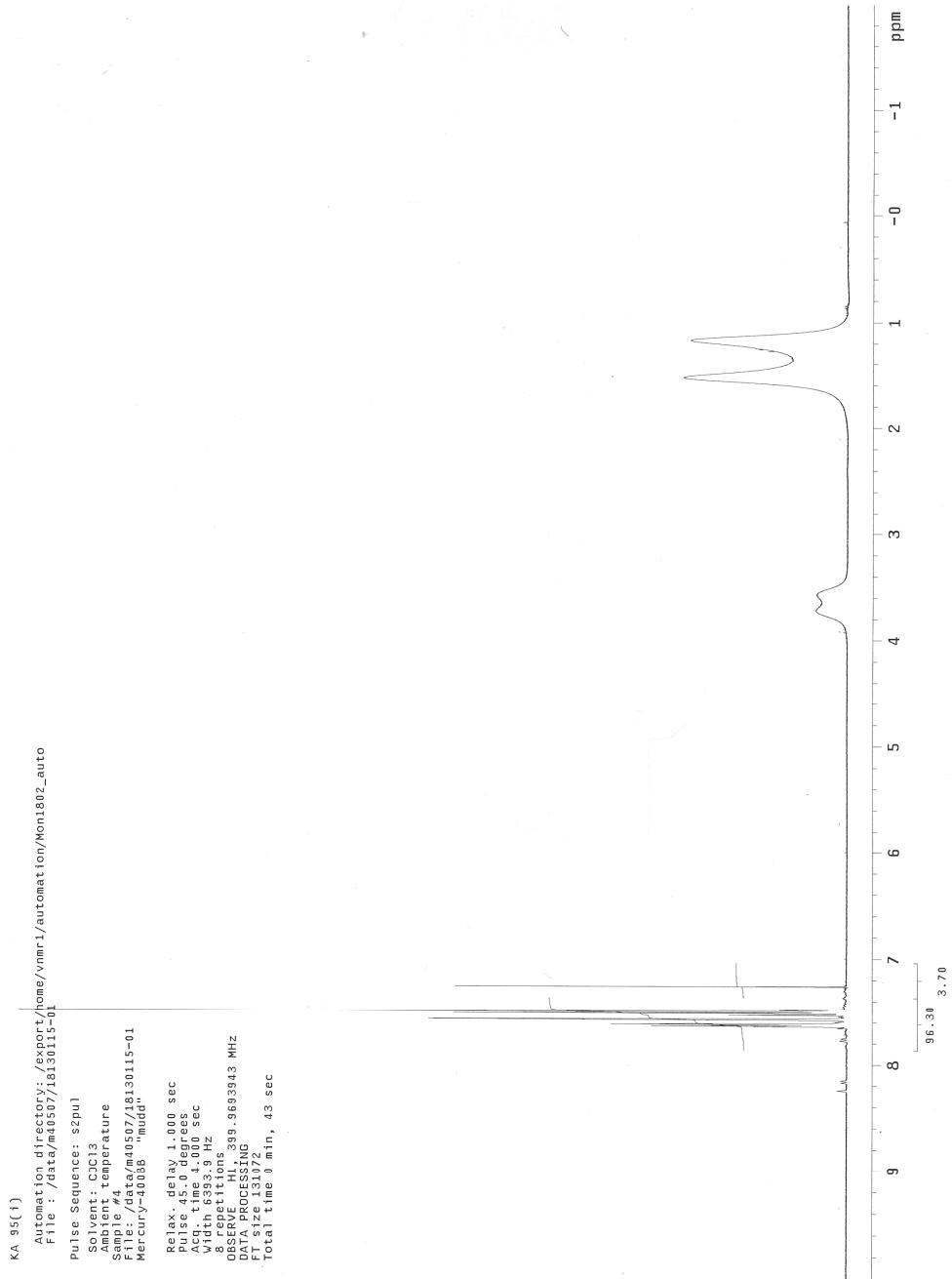
N,N-Diisopropyl-3-nitrobenzamide **4c**

¹³C NMR (125.7 MHz, CDCl₃)



N,N-Diisopropyl-3-trifluoromethylbenzamide **8**

¹H NMR (500 MHz, CDCl₃)



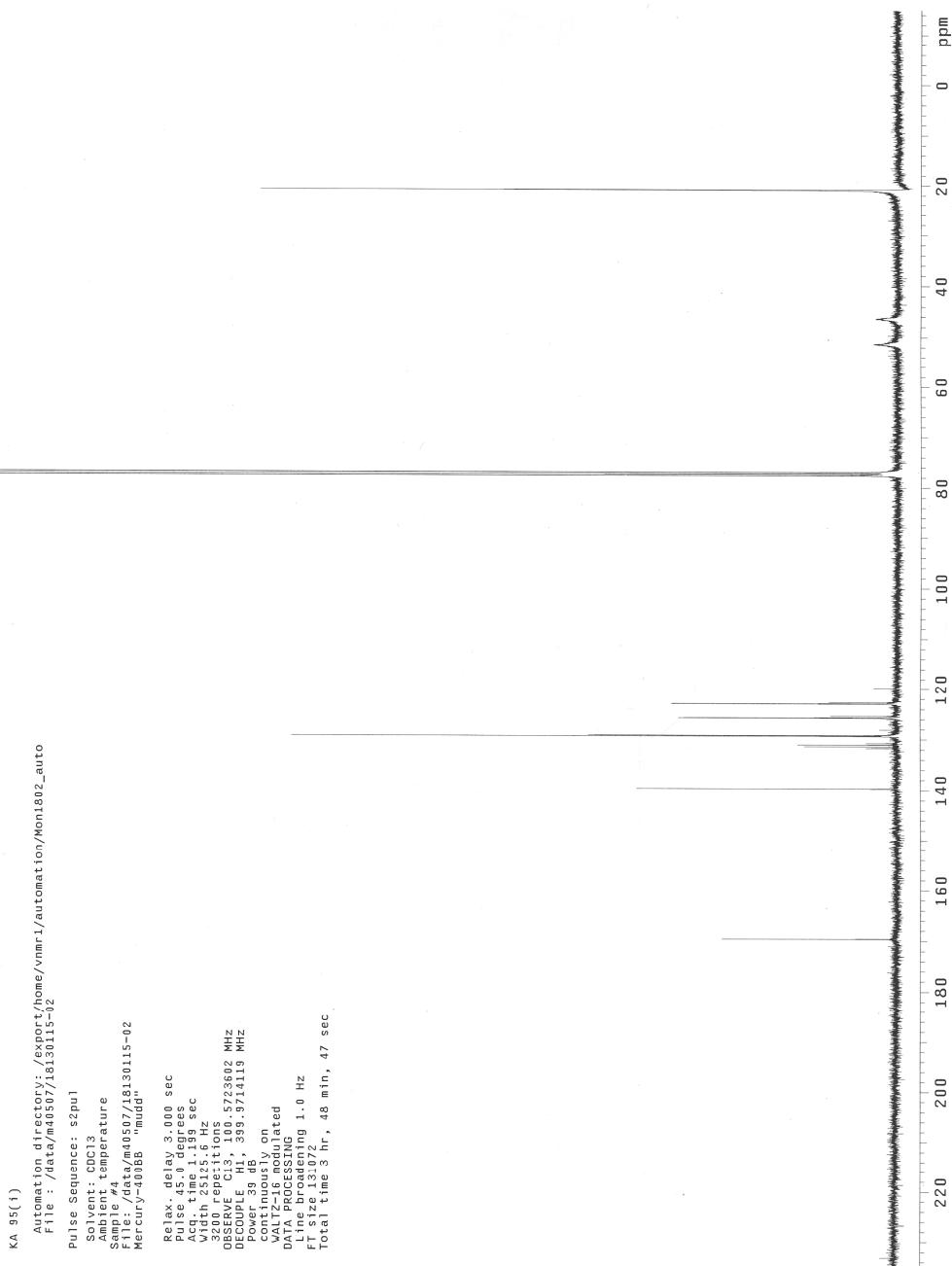
N,N-Diisopropyl-3-trifluoromethylbenzamide **8**

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¹³C NMR (100.6 MHz, CDCl₃)

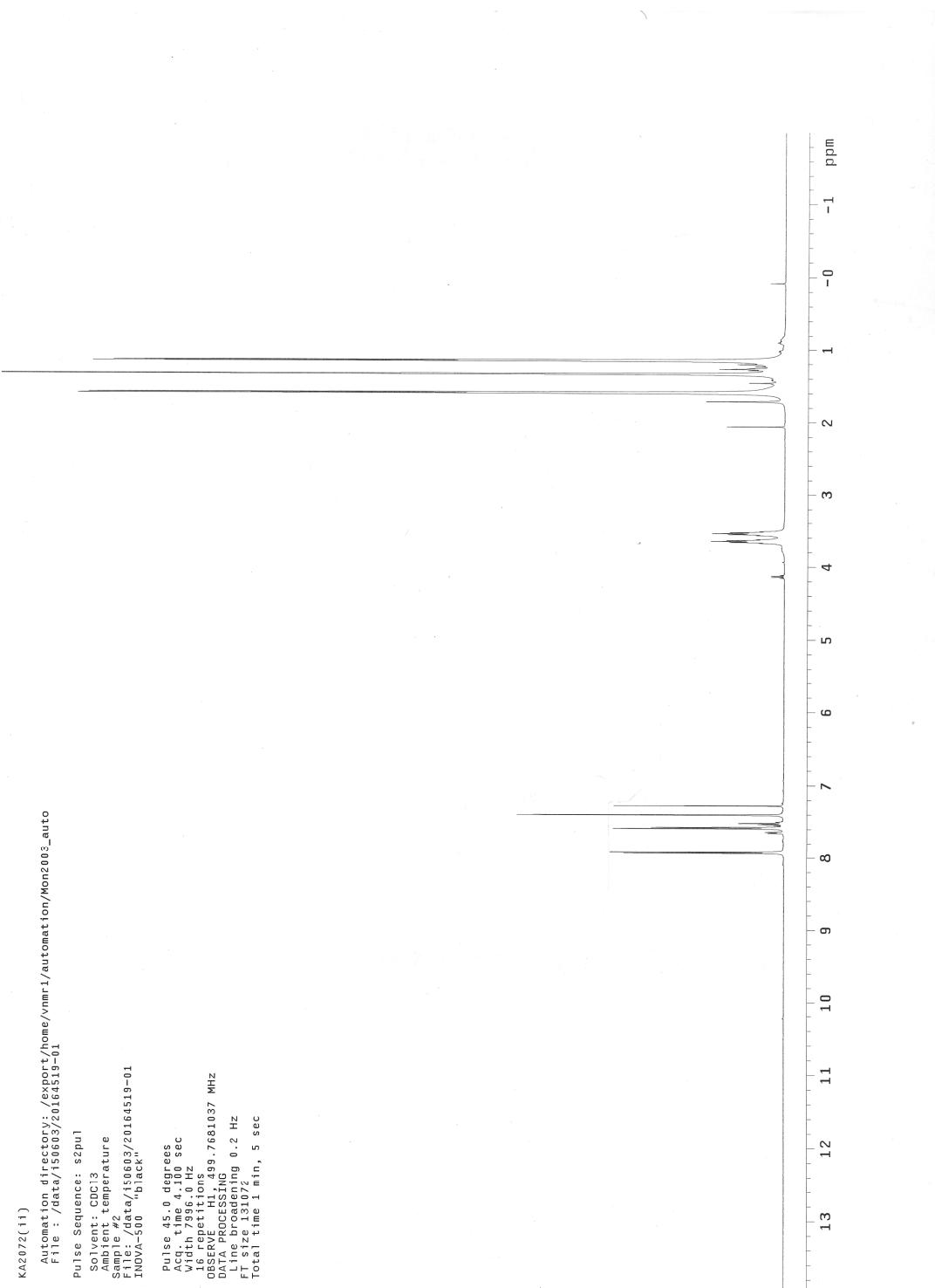
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Solvent: CDCl₃
Ambient temperature
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Mercury-400BB "liquid"

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0.600 sec FID time
0.3 s scan time
DE90°(1.4), FID 5733.602 MHz
DE90°(1.4), H 39.3714119 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 13172
Total time 3 hr , 48 min , 47 sec



N,N-Diisopropyl-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-5-trifluoromethyl-benzamide **9**

¹H NMR (500 MHz, CDCl₃)



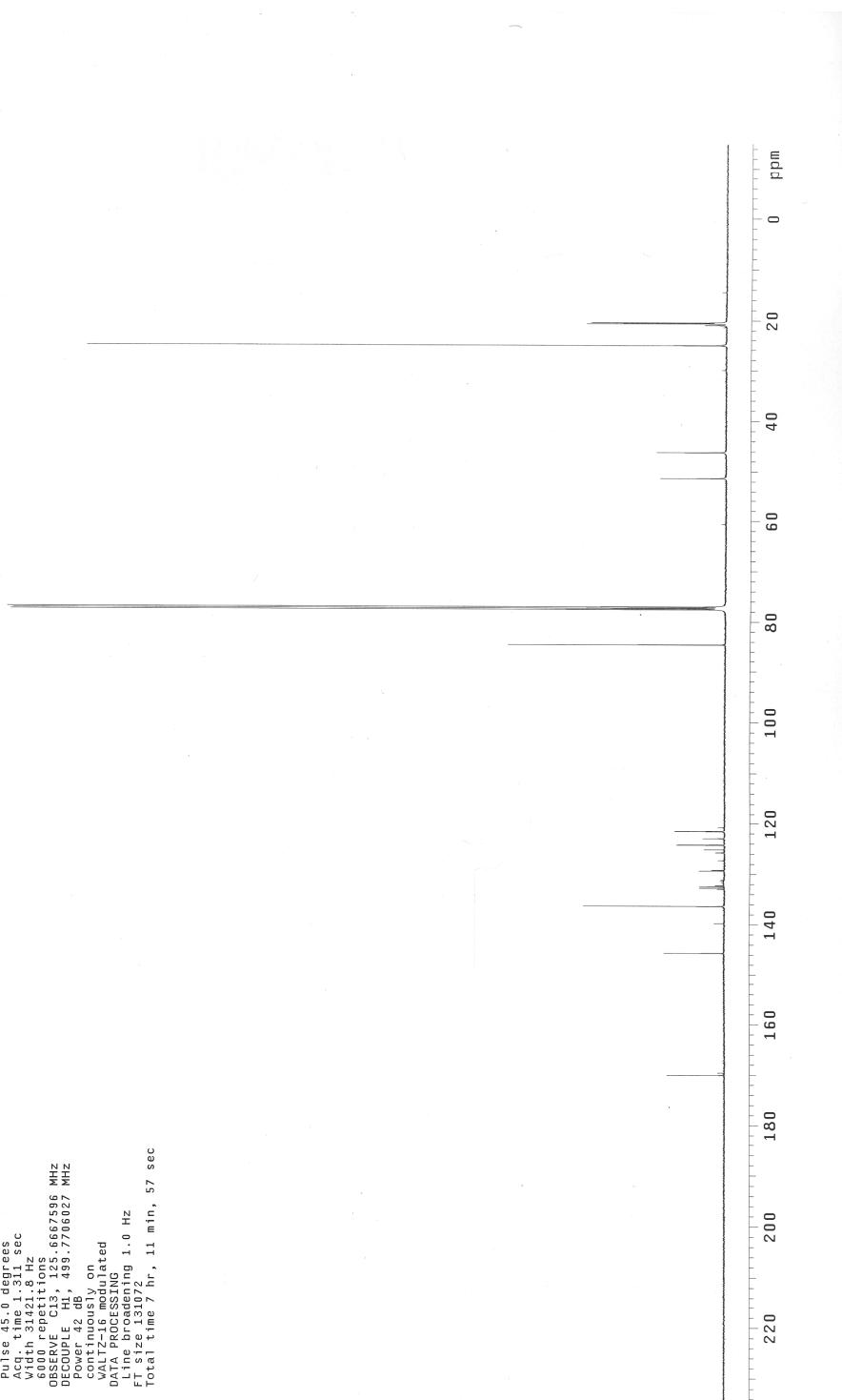
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N,N-Diisopropyl-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-5-trifluoromethyl-benzamide **9**

¹³C NMR (125.7 MHz, CDCl₃)

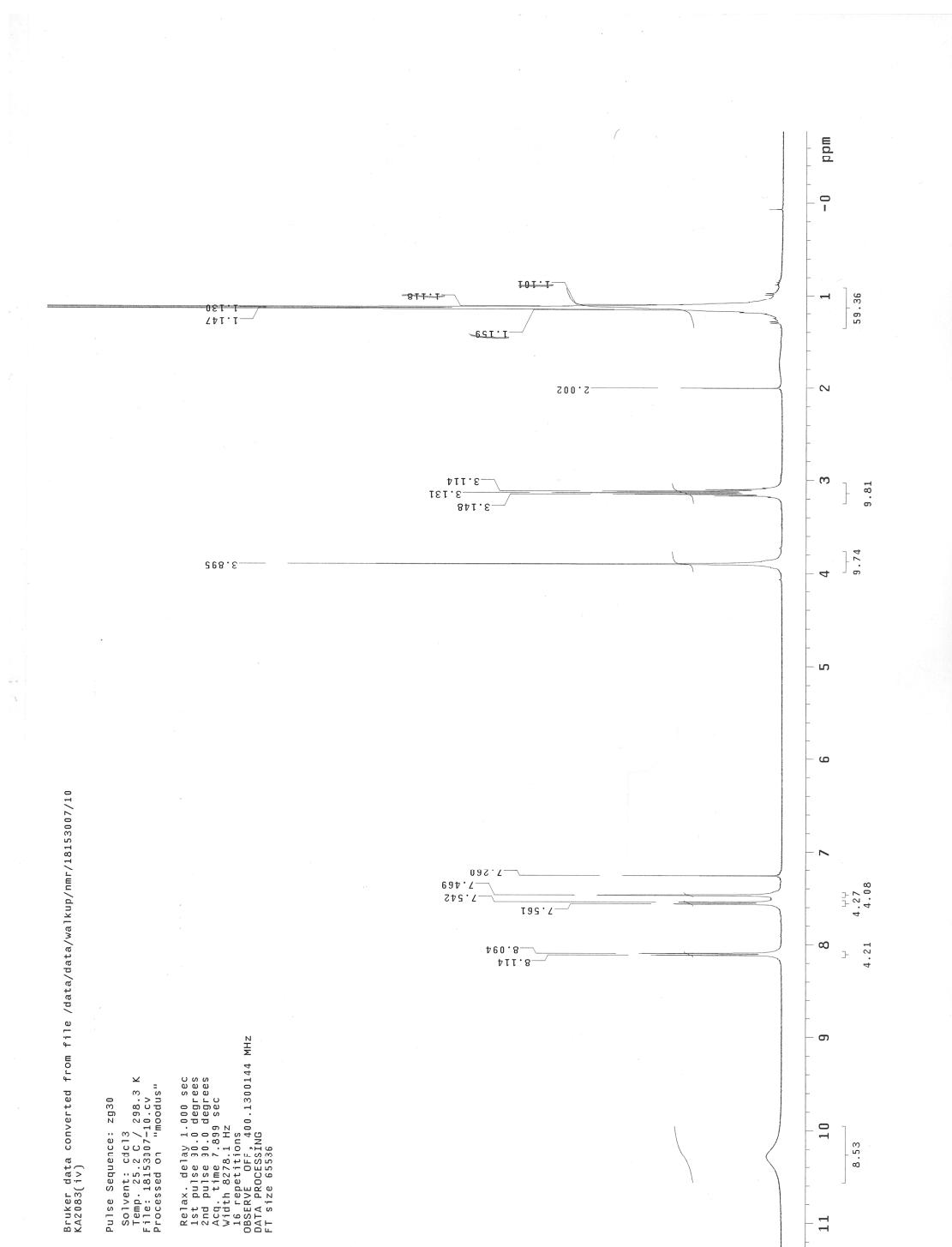
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Pulse Sequence: sspul
Solvent: QDC13
Ambient temperature
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File: /data/15603/20164519-02
INNOVA-500
black

Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 1.311 sec
Width 1.421.8 Hz
W0.0 rep 111.1 Hz
OBSERVE C13, 125.6667596 MHz
DECOUPLE H1, 49.7706027 Hz
Power 42 dB
continuously on
WALTZ-16 modulated
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Line broadening 1.0 Hz
FT size 131072
Total time 7 hr, 11 min, 57 sec



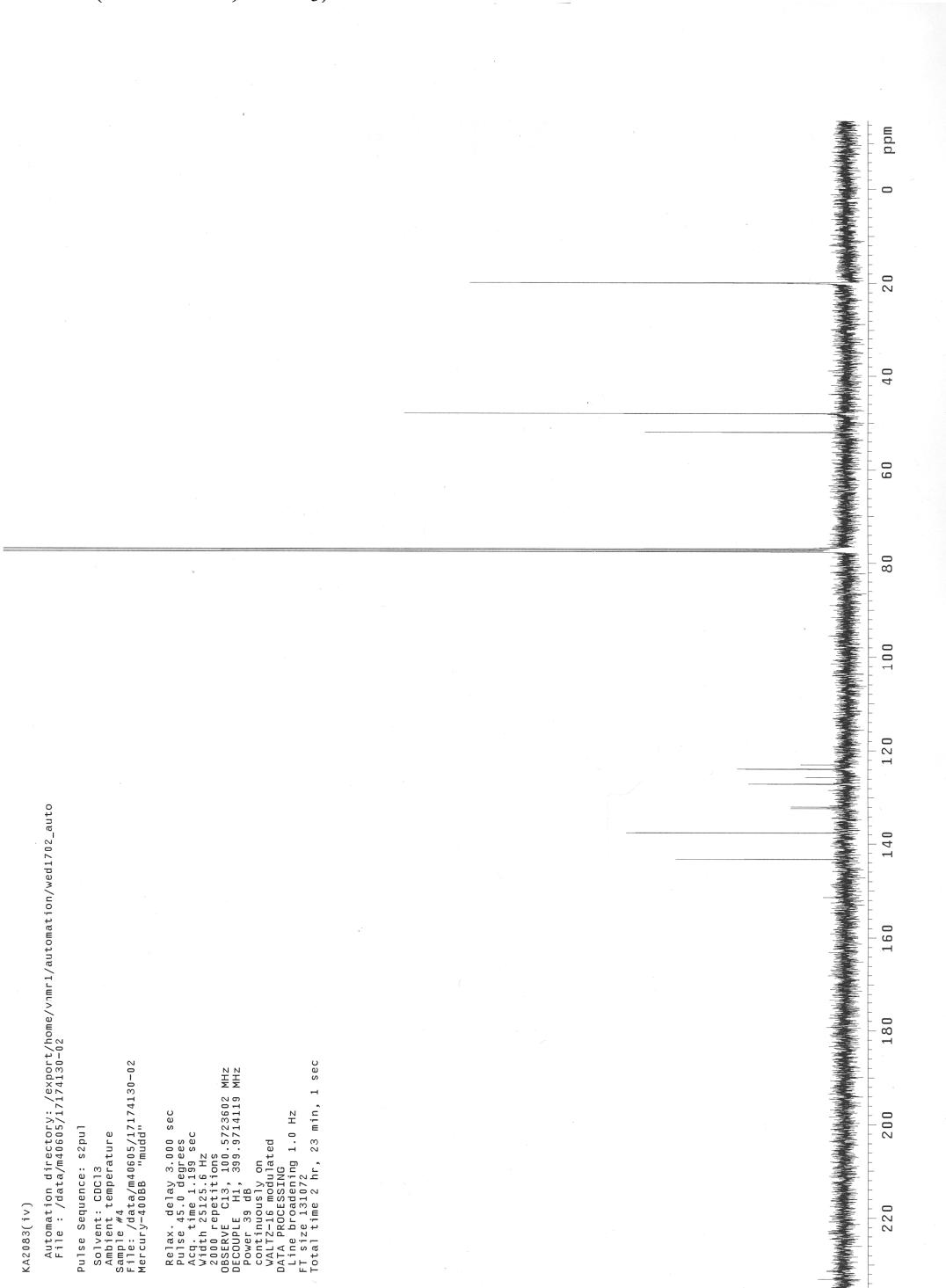
N,N-Diisopropyl-5-trifluoromethylbenzylamine-2-boronic acid 10

^1H NMR (400 MHz, CDCl_3)



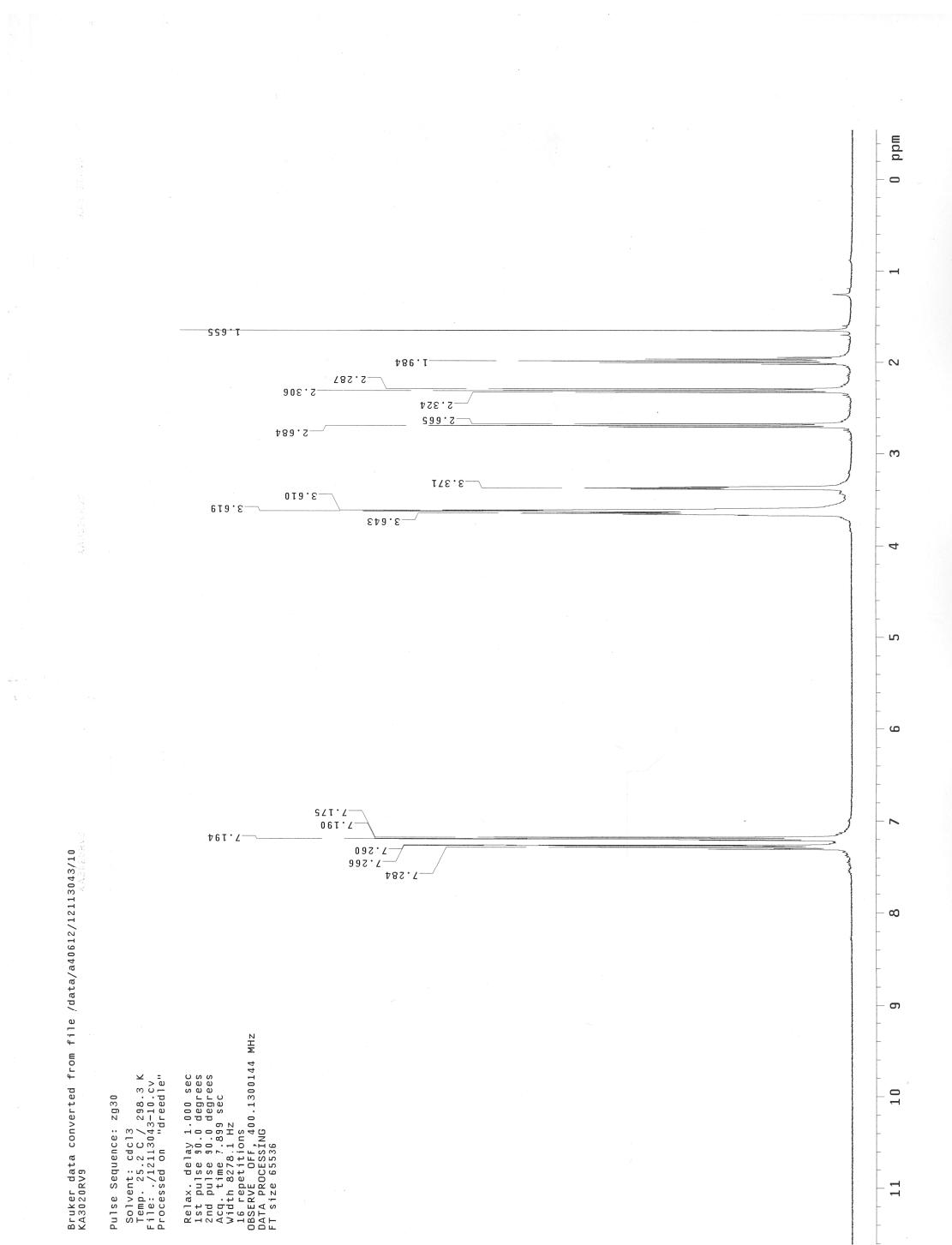
N,N-Diisopropyl-5-trifluoromethylbenzylamine-2-boronic acid 10

^{13}C NMR (100.6 MHz, CDCl_3)



1-Morpholin-4-yl-4-phenylbutan-1-one

¹H NMR (400 MHz, CDCl₃)



1-Morpholin-4-yl-4-phenylbutan-1-one

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¹³C NMR (100.6 MHz, CDCl₃)

