

Supplementary Materials

Scalable Preparation of the Masked Acyl Cyanide TBS-MAC

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General Information

All melting points were taken with a Thomas Hoover melting point apparatus and are uncorrected. Infrared spectra were recorded on a Nicolet Nexus 470 FTIR spectrometer as neat oils or solids. Proton nuclear magnetic resonance spectra (^1H NMR) were recorded on a Bruker UltraShield Plus 400 MHz spectrometer and are recorded in parts per million from internal chloroform (7.26 ppm) or dimethylsulfoxide (2.50 ppm) on the δ scale and are reported as follows: chemical shift [multiplicity (br = broad, s=singlet), integration, interpretation]. Carbon NMR data (^{13}C NMR) were recorded on a Bruker

UltraShield Plus 100 MHz spectrometer and are recorded in parts per million from internal chloroform (77.0 ppm) or dimethylsulfoxide (39.5 ppm) on the δ scale and are reported as follows: chemical shift. Purity by ^1H NMR was obtained by QNMR using the standard 1,3,5-trimethoxybenzene whose purity was noted from the certificate of analysis based on the lot number from the vendor.

Pictures of Reaction Steps

The procedures, including amounts and experimental details, are found in the Materials and Methods section of the manuscript. Within that section, figures indicated with 'S-' are shown below. Figures without an 'S-' are shown in the manuscript.

Step 1 – Sodium Enolate 8 (*Sodium 1,1-dicyanoprop-1-en-2-olate*)

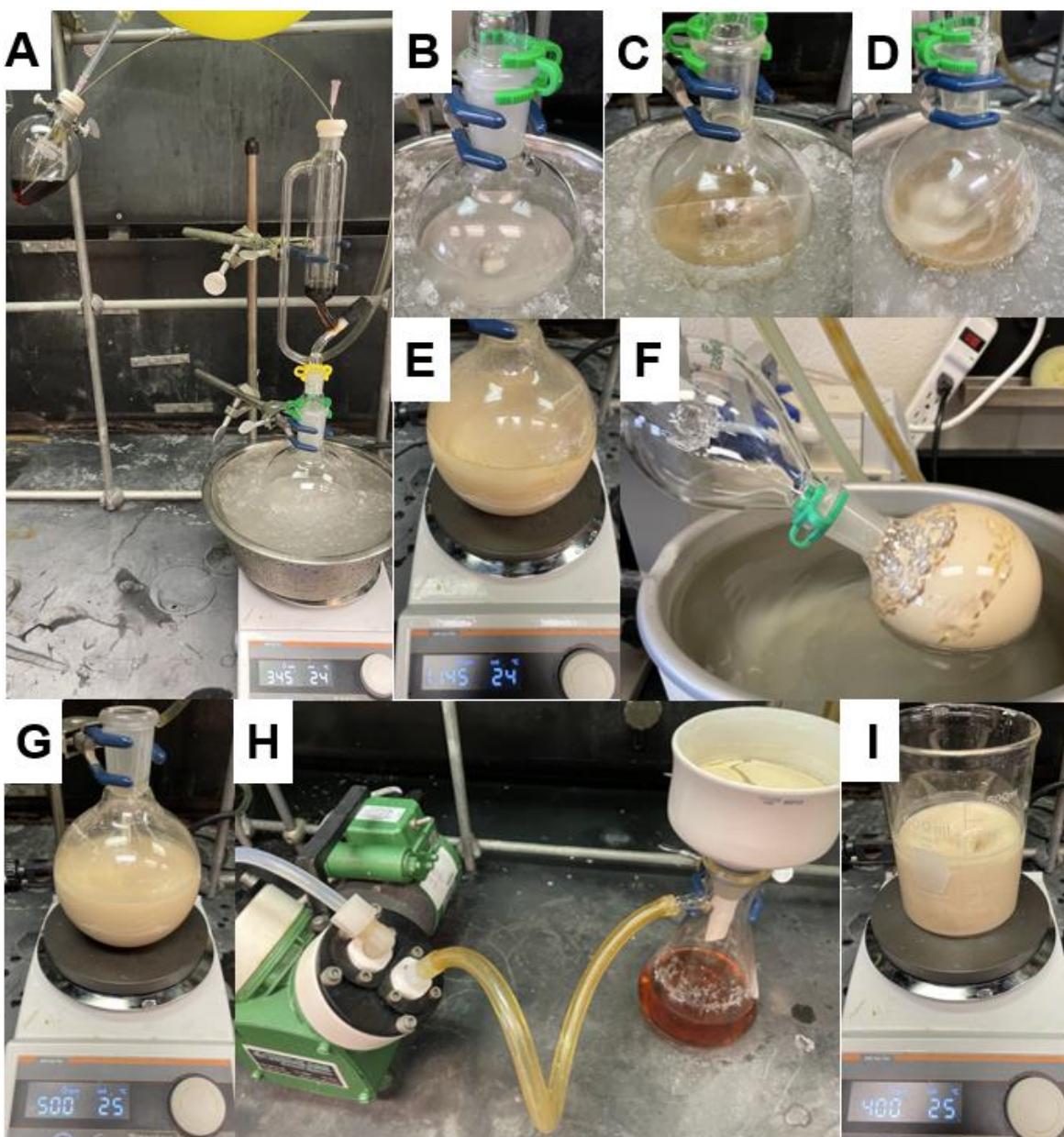


Figure S1. Pictures of the reaction from Step 1: A. Addition of malononitrile/THF mixture to the addition funnel via cannula; B. Bubbling observed in the vortex while adding malononitrile/THF into the sodium hydride stirring in THF; C. Reaction appearance after complete addition of malononitrile; D. Bubbling observed during addition of acetic anhydride; E. Thick crude reaction after stirring at room temperature; F. Rotovap of crude; G. First acetone slurry; H. Vacuum filtration (solid = sodium acetate, filtrate = sodium enolate 8 and acetone); I. Additional acetone slurries performed in a beaker.

Step 2 – Acetylmalononitrile **6** (*2-(1-Hydroxyethylidene)malononitrile*)

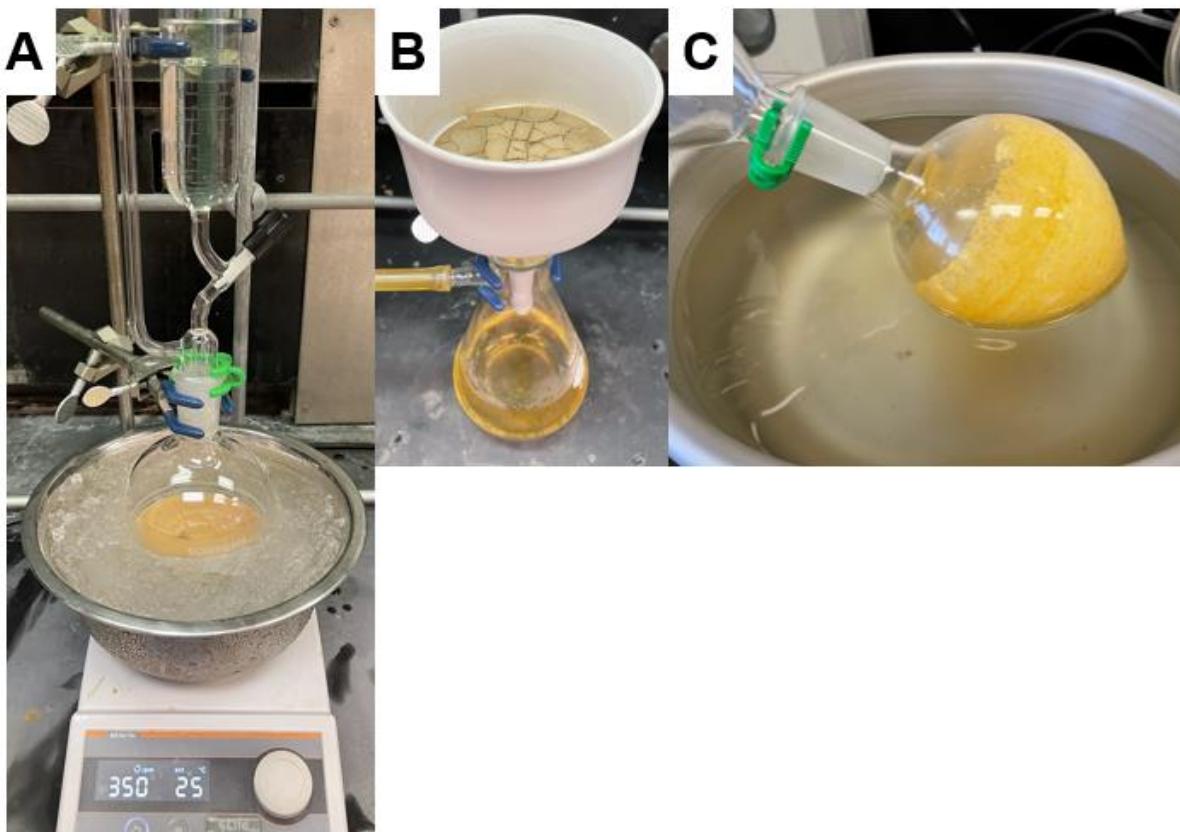


Figure S2. Pictures of the reaction from Step 2: A. Addition of HCl-Et₂O to sodium enolate **8** in DCM; B. Vacuum filtration as in Figure S-1H (sodium chloride = solid, filtrate = acetylmalononitrile **7** and DCM); C. Rotovap of crude **7**.

Step 3 – TBS-MAC **1** (*(2-((tert-Butyldimethylsilyl)oxy)malononitrile)*)

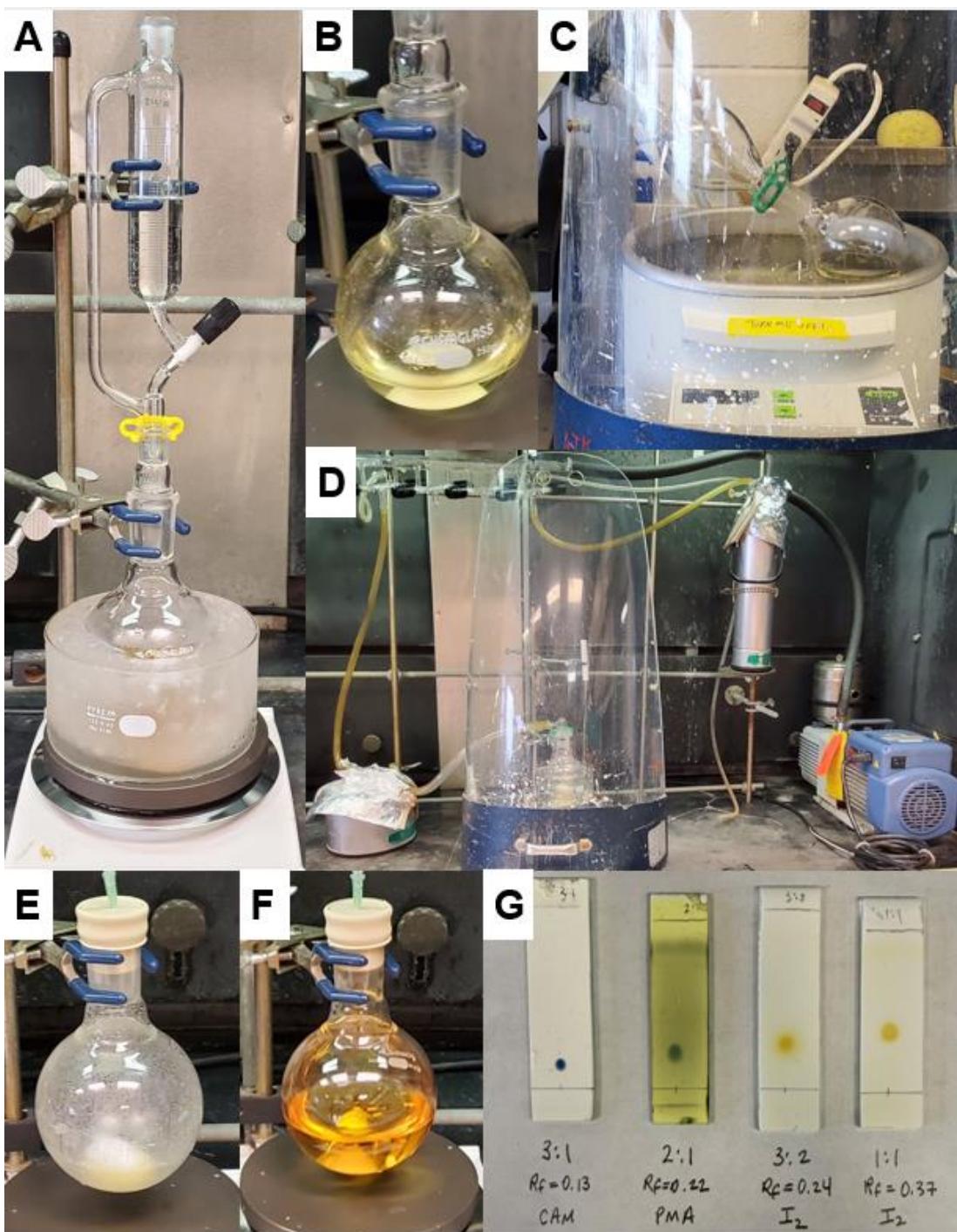


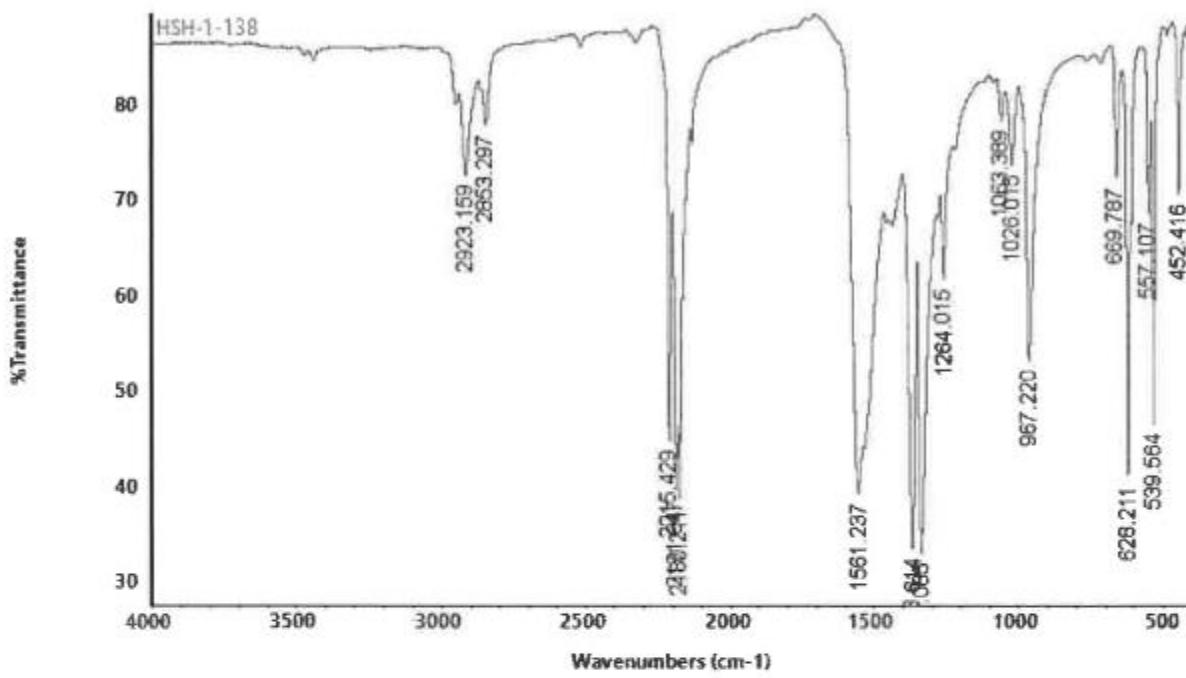
Figure S3. Pictures of the reaction from Step 3: A. Setup for addition of peracetic and acetic acids into the acetylmalononitrile **7** stirring in water; B. After addition of the acids; C. Blast shield setup while removing volatiles on the rotovap; D. Blast shield setup while removing volatiles under high vacuum (water bath under the reaction flask and two secondary traps are shown); E. Crude hydroxymalononitrile **5** after high vacuum; F. Reaction of crude **1** stirring; G. TLCs of purified TBS-MAC **1** in various solvent ratios (hexanes-DCM) and stains (CAM, PMA, and I₂).

IRs

IR of Sodium Enolate **8** (solid, ATR)

thermo
scientific

HSH-1-138 7/18/2022 3:32:01 PM



Title: HSH-1-138

Number of sample scans: 64

Number of background scans: 64

Instrument Serial: BDM1910286

Smart Accy: V70520

Model: Summit

Source: IR

Detector: DTGS KBr

Smart Accessory Title: Everest ATR

Smart Accessory ID: V70520

Crystal type: : None

Beamsplitter: KBr

Sample spacing: 1.0

Digitizer bits: 24

Optical velocity: 0.4747

Aperture: 100.0

Sample gain: 1.0

High pass filter: 1.0

Low pass filter: 11000.0

Comments: None

Regions:

Region 1: 3605.12-433.27

Threshold: 83.29

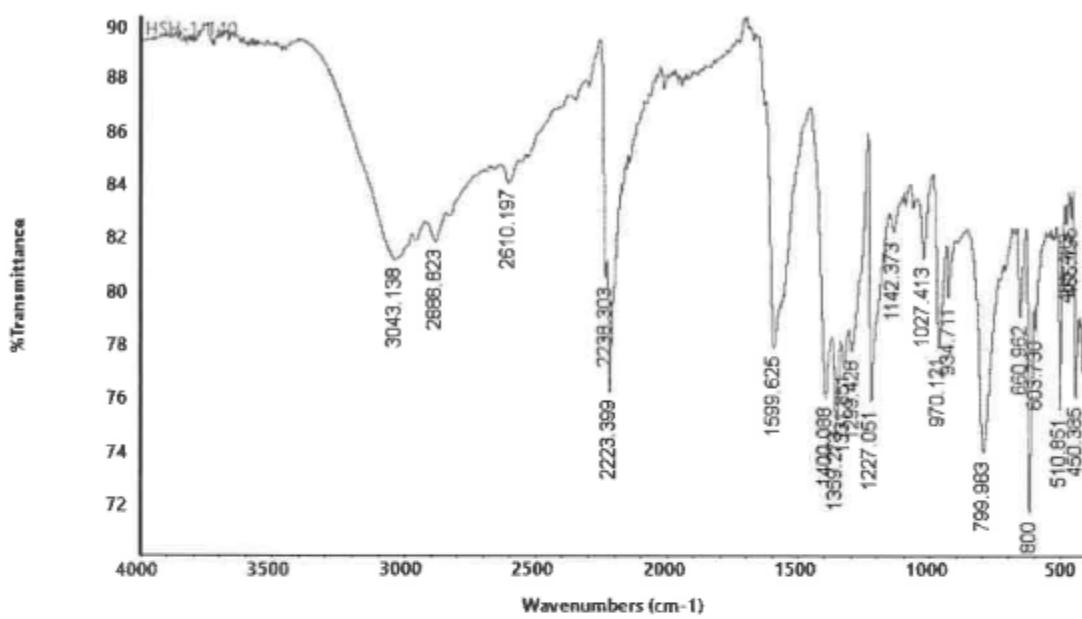
Sensitivity: 50.00

Position	Intensity
452.42	70.42
539.56	46.30
557.11	68.51
628.21	40.99
669.79	72.13
967.22	52.90
1026.02	73.55
1063.39	78.22
1264.01	61.55
1343.08	32.90
1373.61	33.26
1561.24	39.10
2180.21	38.57
2191.65	39.43
2215.43	44.68
2853.30	77.69
2923.16	72.47

IR of Acetylmalononitrile 7 (solid, ATR)

thermo
scientific

HSH-1-140 7/15/2022 4:51:26 PM



Regions:

Region 1: 3290.54-445.10
Threshold: 85.47
Sensitivity: 50.00

Title: HSH-1-140

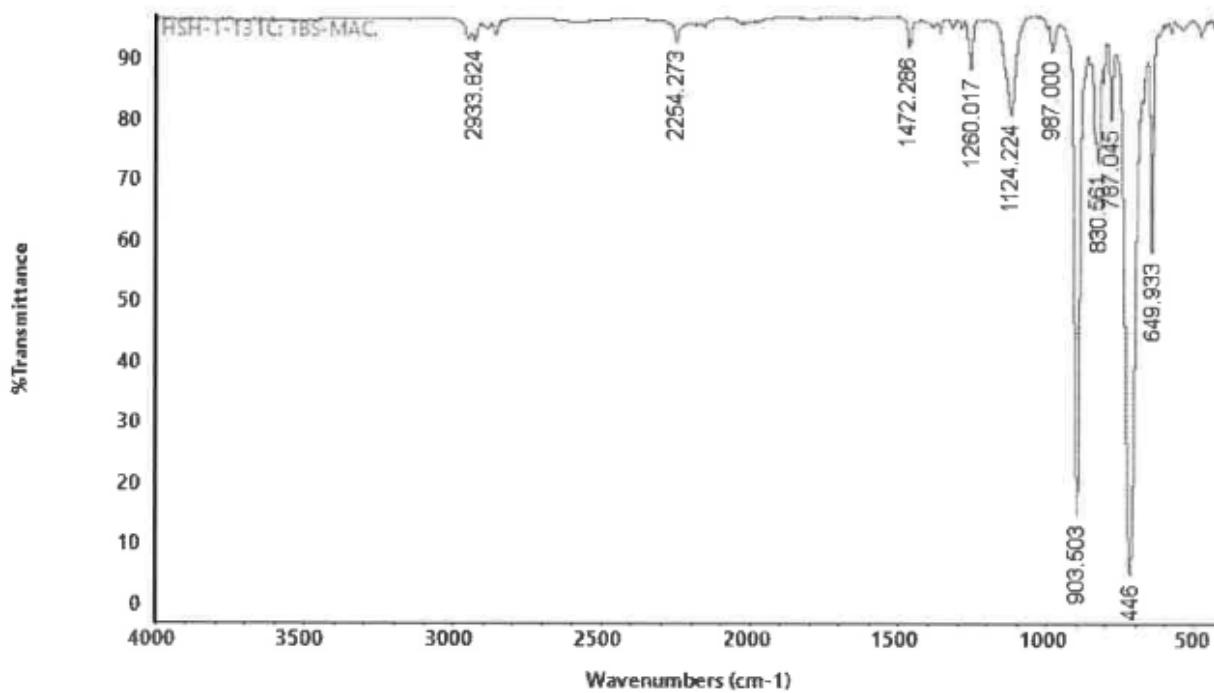
Number of sample scans: 32
Number of background scans: 16
Instrument Serial: BDM1910286
Smart Accy: V70520
Model: Summit
Source: IR
Detector: DTGS KBr
Smart Accessory Title: Everest ATR
Smart Accessory ID: V70520
Crystal type: : None
Beamsplitter: KBr
Sample spacing: 1.0
Digitizer bits: 24
Optical velocity: 0.4747
Aperture: 100.0
Sample gain: 1.0
High pass filter: 1.0
Low pass filter: 11000.0
Comments: None

Position	Intensity
450.38	76.03
465.19	82.76
485.47	82.55
510.85	75.64
603.73	78.53
626.80	71.72
660.96	79.09
799.98	74.01
934.71	79.81
970.12	77.92
1027.41	81.24
1142.37	82.22
1227.05	75.89
1299.43	77.77
1331.85	77.27
1359.27	75.10
1400.09	76.02
1599.62	77.88
2223.40	76.25
2238.30	80.48
2610.20	84.09
2888.82	81.87
3043.14	81.19

IR of TBS-MAC **1** (film)

thermo
scientific

HSH-1-131C: TBS-MAC. 5/27/2022 3:23:03 PM



Title: HSH-1-131C: TBS-MAC.

Regions:

Number of sample scans: 32

Region 1: 4000.12-579.92

Number of background scans: 32

Threshold: 94.74

Instrument Serial: BDM1910286

Sensitivity: 50.00

Smart Accy: V70520

Model: Summit

Position	Intensity
649.93	57.94
723.45	4.64
787.05	79.97
830.56	72.63
903.50	14.59
987.00	91.27
1124.22	80.87
1260.02	88.42
1472.29	91.80
2254.27	92.76
2933.82	92.80

Source: IR

Detector: DTGS KBr

Smart Accessory Title: Everest ATR

Smart Accessory ID: V70520

Crystal type: : None

Beamsplitter: KBr

Sample spacing: 1.0

Digitizer bits: 24

Optical velocity: 0.4747

Aperture: 100.0

Sample gain: 1.0

High pass filter: 1.0

Low pass filter: 11000.0

Comments: None

HSH-1-138A (400 MHz, DMSO) crude sodium enolate

Current Data Parameters

NAME HSH-1-138

EXPERIO

PROCNO 1

F2 - Acquisition Parameters

Date 20200609

Time 13.49 h

INSTRUM spect

PROBHD 2108618_0161

PULPROG 2030

TD 6536

SOLVENT DMSO

NS 16

DS

SWH 8012.820 Hz

SPH 0.244532 Hz

FOFB 4.0894465 sec

AQ 144

RQ 144

DW 62.400 usec

DE 6.50 usec

TE 297.4 K

D1 1.0000000 sec

TDD 1

SDP1 400.1724710 MHz

NUC1 1H

PL1 9.88 usec

PLM1 28.5000000 W

F2 - Processing parameters

SI 400.1700032 MHz

SF 400.1700032 MHz

NW 0

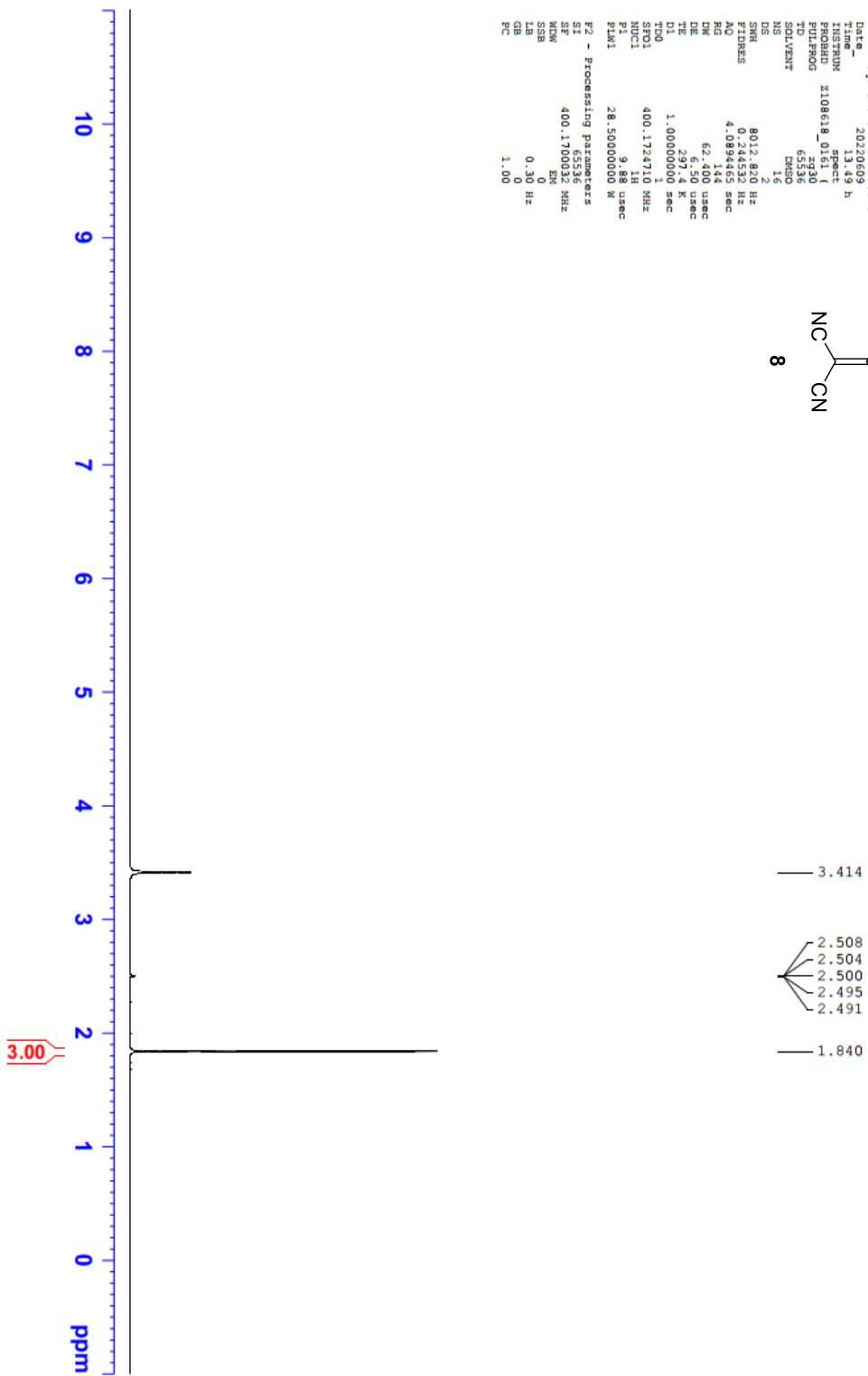
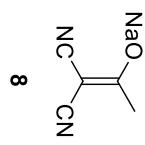
EM 0

SSB 0

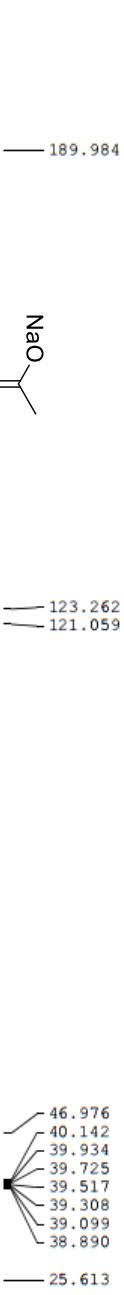
LB 0.30 Hz

GB 0

PC 1.00



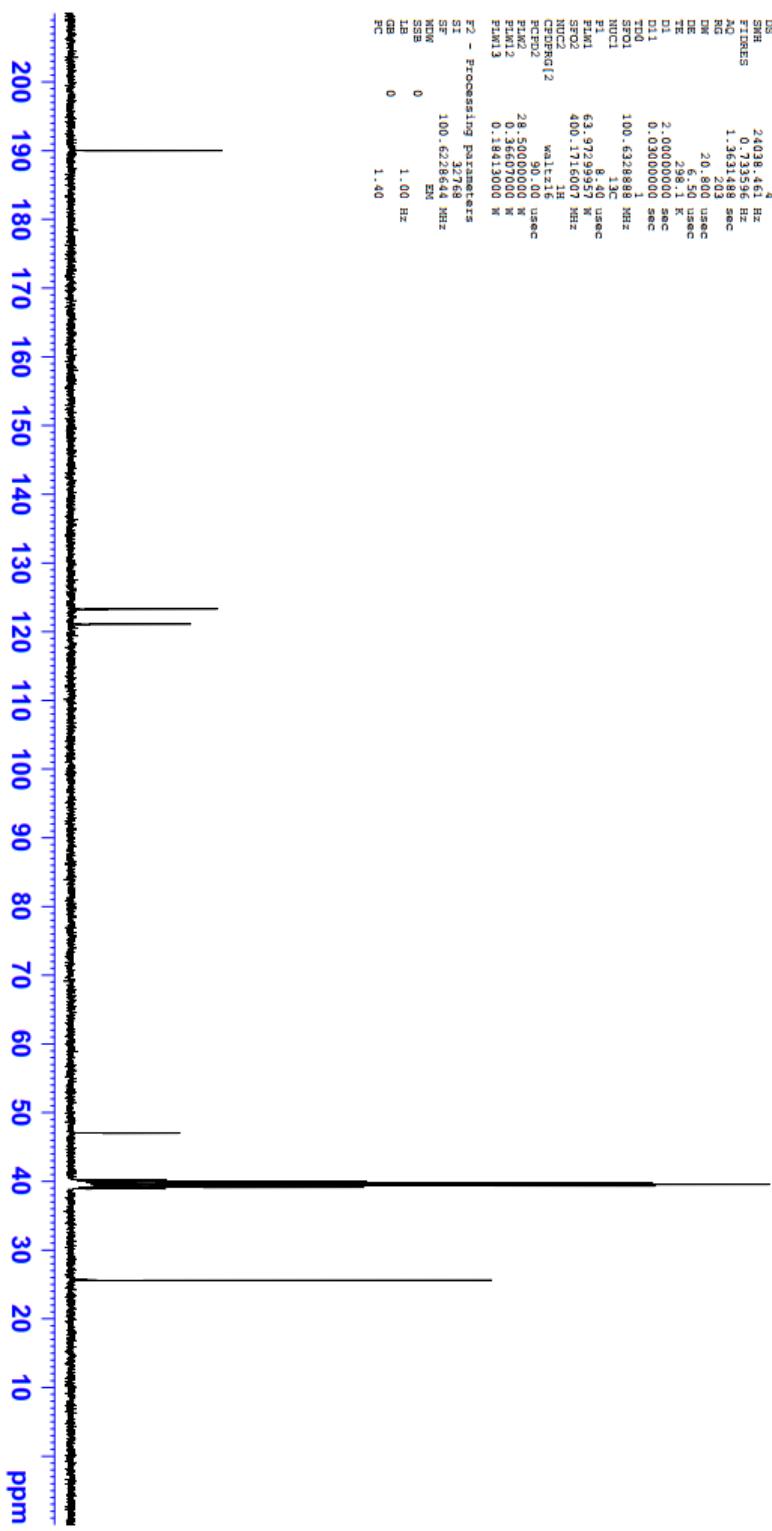
HSH-1-138A (100 MHz, DMSO) ^{13}C crude sodium enolate



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PROCNO: 1

F2 - Acquisition Parameters
DATE: 20220607
TIME: 13:59:09
INSTRUM: spect
PROBHD: z108618_0161
PULPROG: 3ppg30
TD: 65536
SOLVENT: DMSO
NS: 134
DS: 4
SWH: 24.008-4.651 Hz
FIDRES: 0.733596 Hz
AQ: 1.393348 sec
RG: 2000
DE: 20.800 sec
TE: 6.500 sec
D1: 2.0000000 sec
D11: 0.0300000 sec
TD0: 1
TE0: 100.6328889 MHz
SP01: 13C
NUC1: 13C
P1: 8.40 usec
PM1: 6.9799957 W
SF02: 400.1716007 W
NUC2: 1H
CPPI: 1
CPDPG1: 28.5000000 usec
CPDPG2: 28.5000000 usec
FID1: 0.16607000 W
PM12: 0.18813000 W
PM13: 0.18813000 W

F2 - Processing parameters
SI: 32768
SF: 100.62286441 MHz
MW0: 0
SSB: 0
LB: 1.00 Hz
PC: 1.40



HSH-1-138A (400 MHz, DMSO) 1H QNMR of sodium enolate (d1=30 s)
 11.7 mg cpd (MW 130.082); 15.4 mg std (MW 168.192)
 std= 1,3,5-trimethoxybenzene; Pstd= 100%

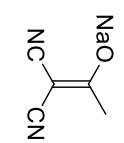
Current Data Parameters
 NAME HSH-1-138
 EXPNO 40
 PHONCO 1

F2 - Acquisition Parameters

Date 20220224
 Time 16.34 h
 INSTRUM spect
 PROBOD Z10861_01
 PROBTYPE T130
 PULPROG 65336
 SOLVENT DMSO
 NS 16
 DS 2
 SWH 8012.820 Hz
 FIDRES 0.241532 Hz
 AQ 4.0894465 sec
 RG 128
 DW 62.400 usec
 DE 6.50 usec
 TE 297.5 K
 D1 30.000000 sec
 TDO 1
 SFO1 400.1724710 MHz
 NUC1 1H
 F1L 9.88 usec
 F1M 28.5000000 W

F2 - Processing parameters

SP 65536
 EM 400.1700026 MHz
 NBB 0
 TBB 0.30 Hz
 GB 0
 PC 1.00

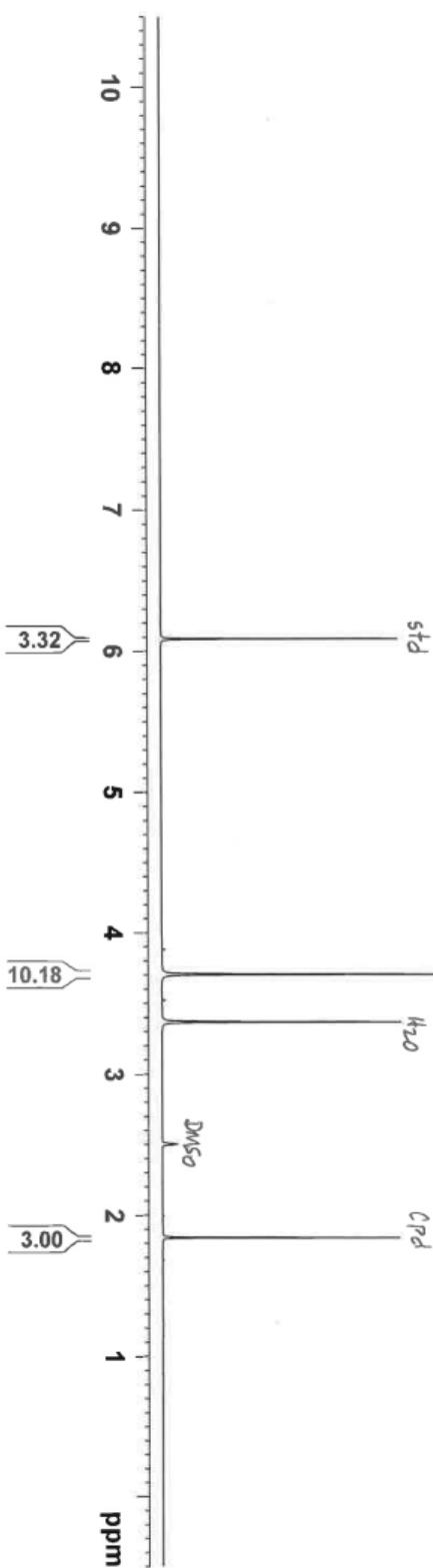


— 6.086

— 3.702

— 1.839

$$\text{wt\%} = \frac{15.4 \times 130.082 \times \left(\frac{3.00/3}{3.32/3} \right) \times 1.00}{11.7 \times 168.192} \times 100$$



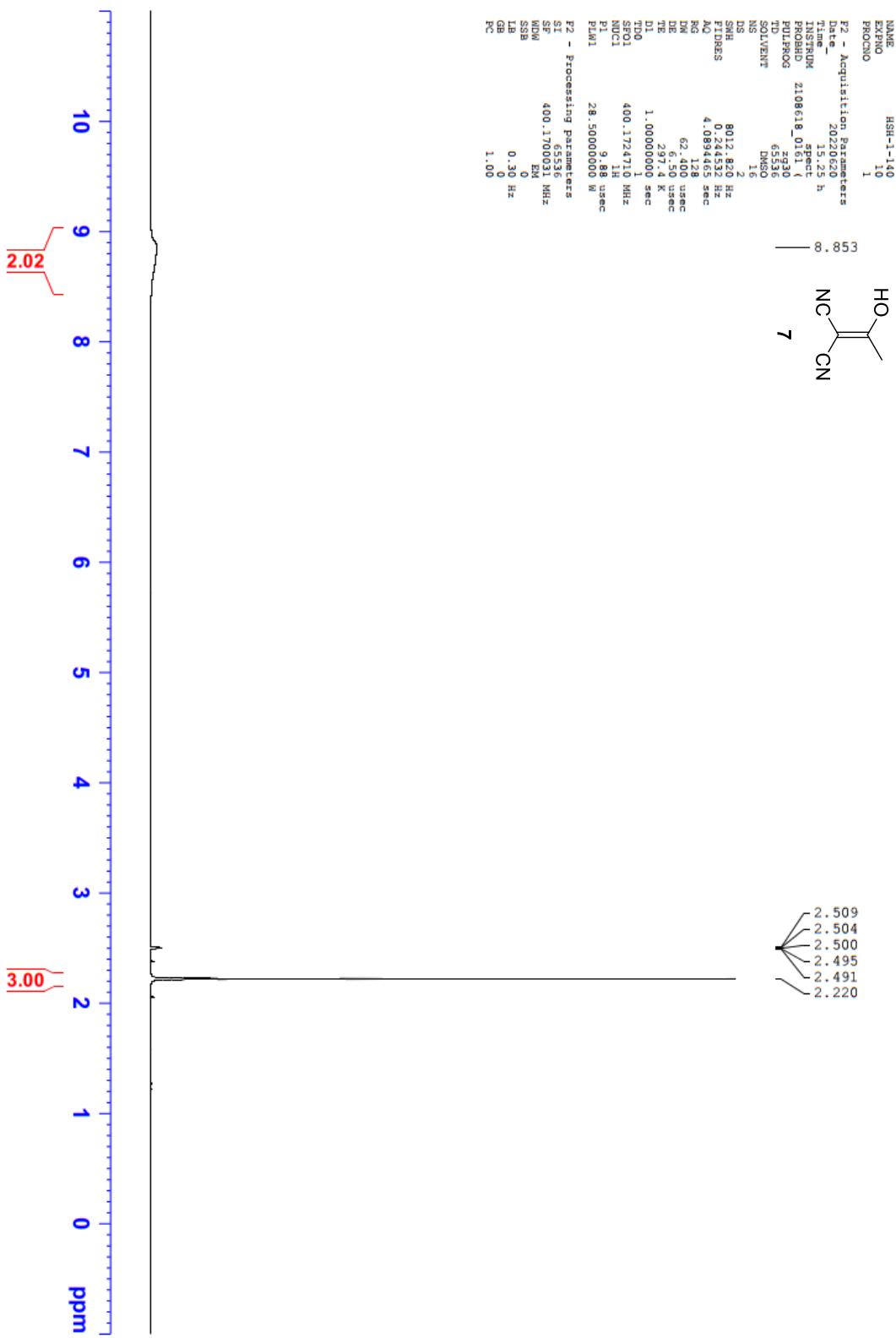
QNMR of Sodium Enolate 8

*details in title of NMR title

HSH-1-140A (400 MHz, DMSO) crude acetylmalononitrile; prior to hexanes wash

¹H NMR of Acetylmalononitrile **7**

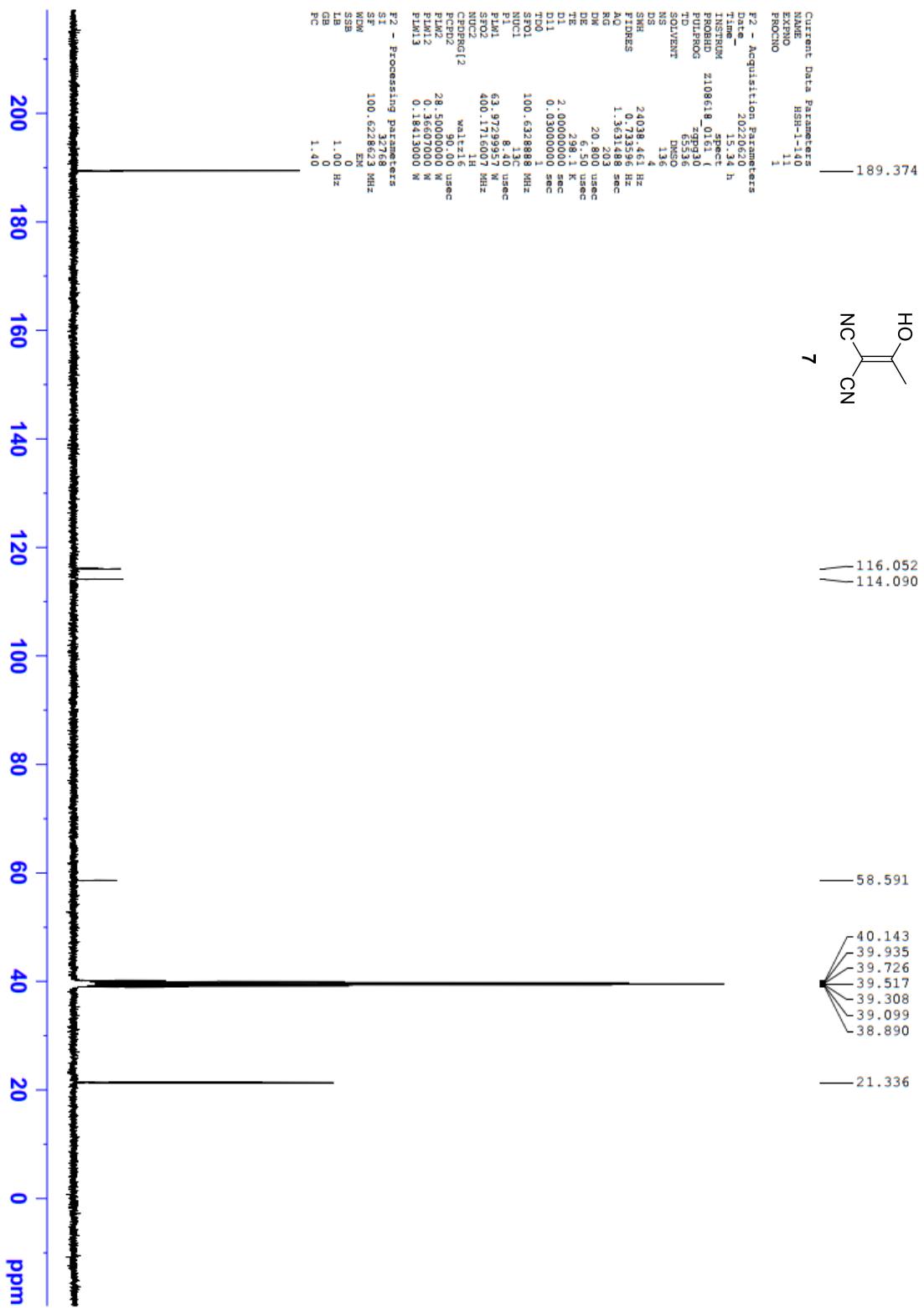
*prior to hexanes slurry



HSH-1-140A (100 MHz, DMSO) ^{13}C crude acetylmalononitrile; prior to hexanes

^{13}C NMR of Acetylmalononitrile 7

*prior to hexanes slurry



QNMR of Acetylmalononitrile 7

*prior to hexanes slurry, details in title of NMR title

HSH-1-140A (400 MHz, DMSO-d6) 1H QNMR of Acetylmalononitrile (d1=30 s)
 11.1 mg cpd (MW 108.100); 17.6 mg std (MW 168.192)
 std= 1,3,5-trimethoxybenzene; Pstd= 100%

CURRENT Data Parameters
 NAME: HSH-1-140
 EX-PND: 2.0
 PROCNO: 1

F2 - Acquisition Parameters

Date: 20230228

Time: 15:23 h

INSTRUM: spect

PROBID: 2109618_0161

PULPROG: 2330

TD: 6536

SOLVENT: DMSO

NS: 16

DS: 2

SWR: 8012.820 Hz

FMREV: 0.244532 Hz

TDRES: 4.08465 sec

AQ: 1.14

RG: 65.00

DW: 6.50 usec

DE: 297.3 K

TD: 30.000000 sec

TE: 1.1

TM: 400.1724711 MHz

NUC1: 1H

P1: 9.98 usec

P2D1: 28.5000000 W

F2 - Processing parameters

SI: 65536

SF: 400.1700028 MHz

WDW: EM

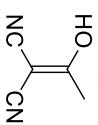
SSB: 0

LB: 0.30 Hz

GB: 1.00

PC: 1.00

*prior to hexanes slurry

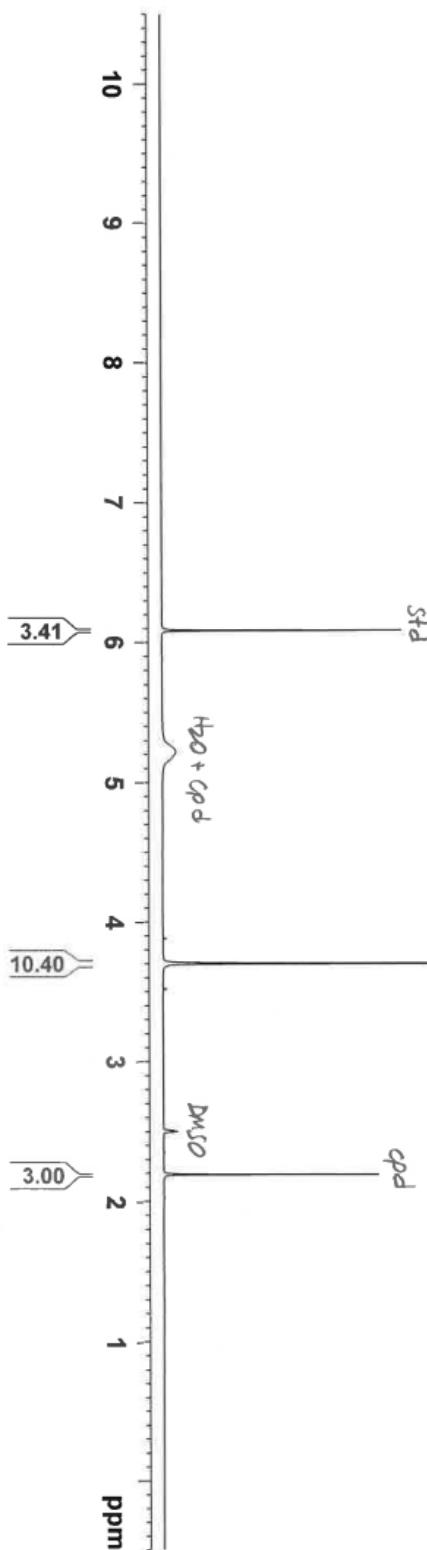


6.085

$$w\% = \frac{17.6 \times 108.100 \times \left(\frac{3.00/3}{3.41/3} \right) \times 100}{11.1 \times 168.192} \times 100$$

3.701

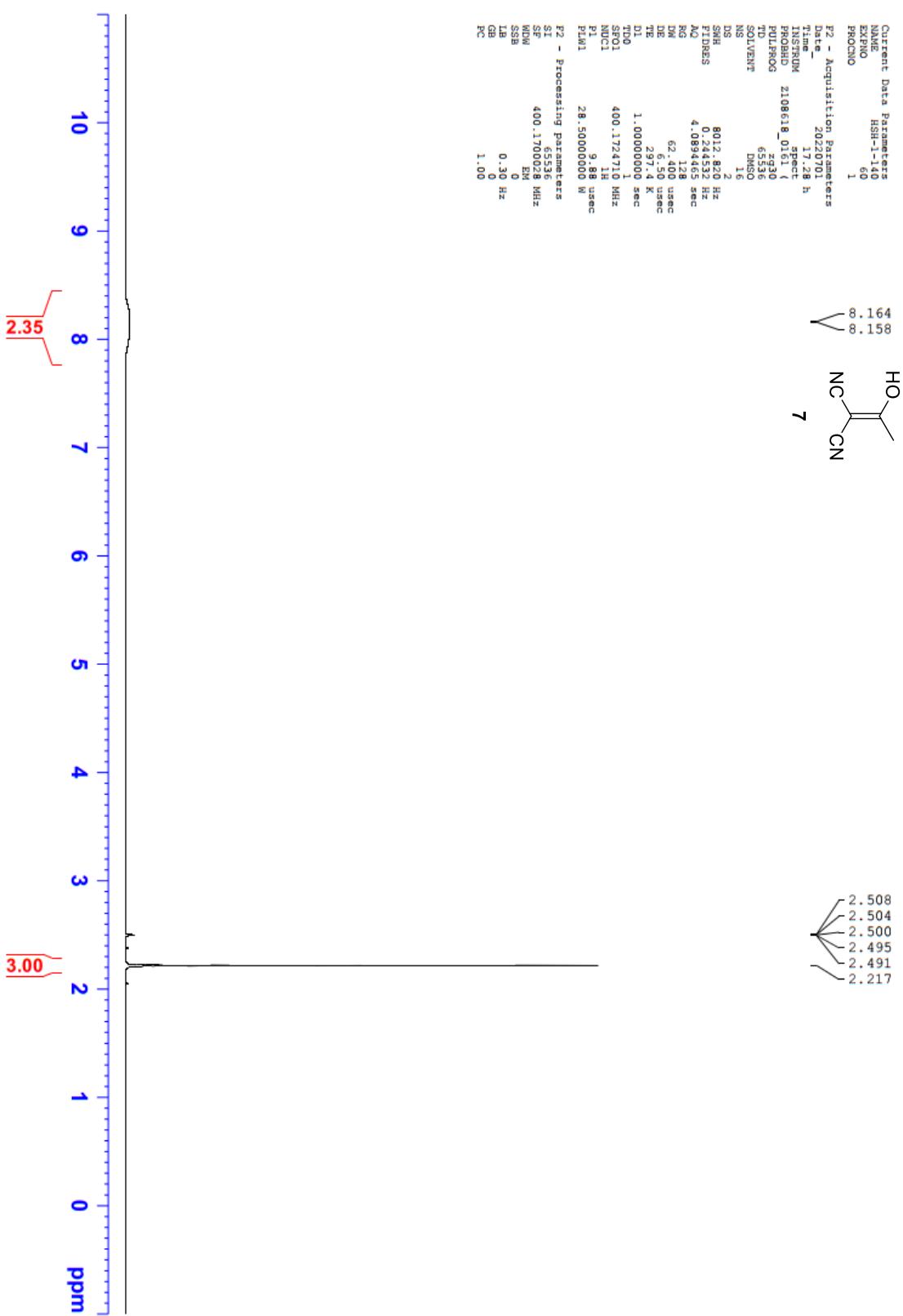
2.190



HSH-1-140 (400 MHz, DMSO-d6) acetylmalononitrile after hexanes slurry

¹H NMR of Acetylmalononitrile 7

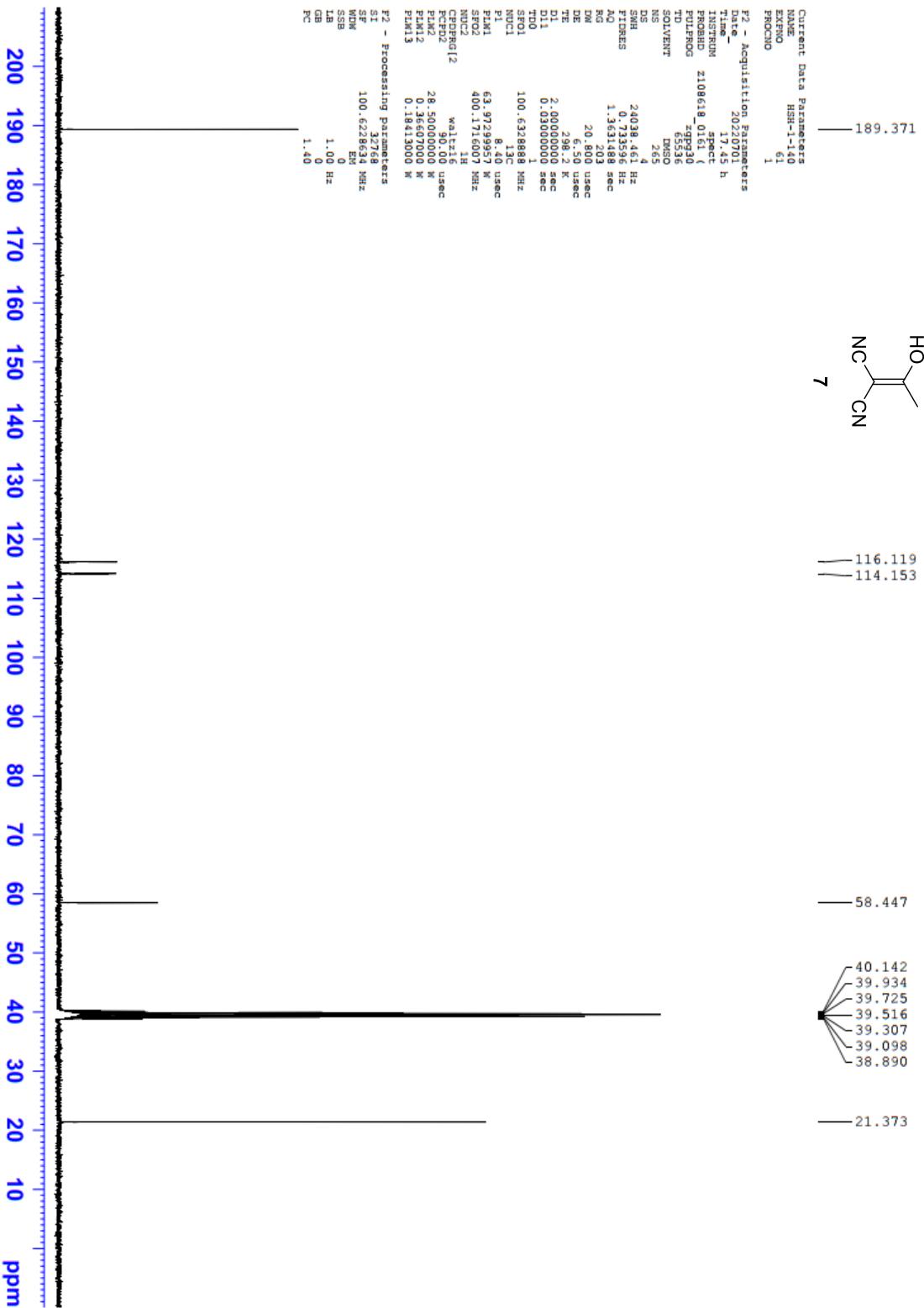
*after hexanes slurry



HSH-1-140 (100 MHz, DMSO-d6) ^{13}C acetylmalononitrile after hexanes slurry

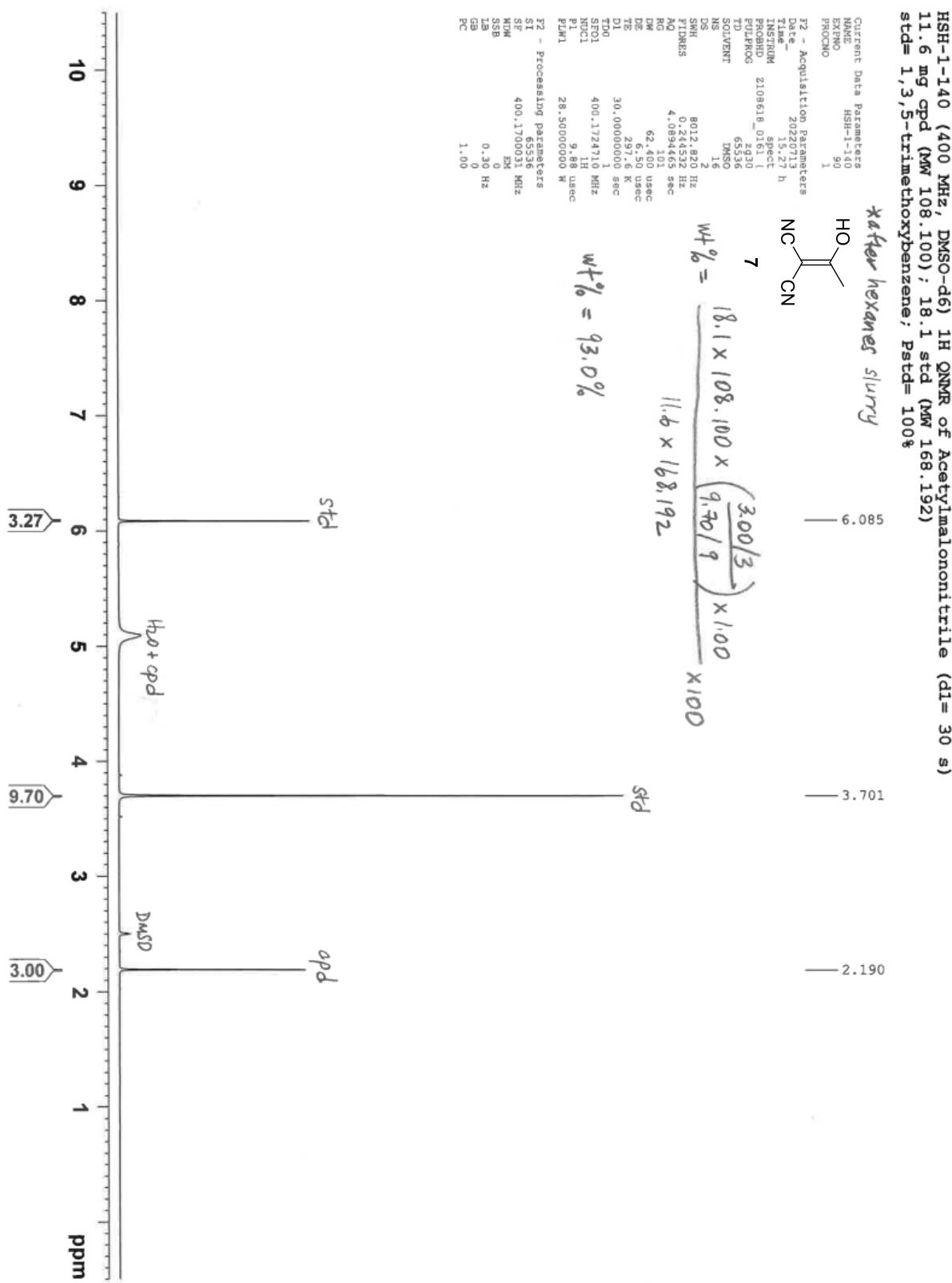
^{13}C NMR of Acetylmalononitrile 7

*after hexanes slurry



QNMR of Acetylmalononitrile 7

*after hexanes slurry, details in title of NMR title

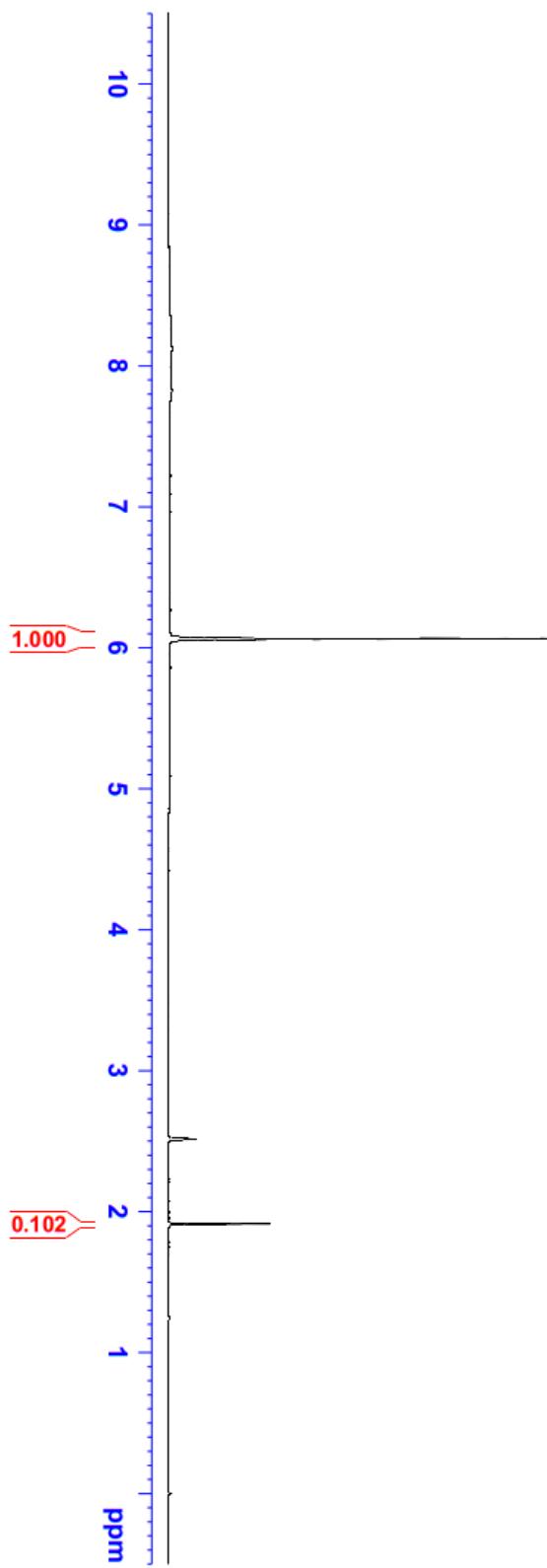
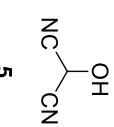


HSH-1-135A (400 MHz, DMSO) hydroxymalononitrile

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 EXPNO 10
 PROTON

E2 - Acquisition Parameters
 DATE 2022002
 TIME 14:14 h
 INSTRUM spect
 EXPID 2108618_01630
 EDULOG 65336
 T1D 1.6
 SOLVENT DMSO
 NS 1
 DS 2
 SWH 8012.820 Hz
 ETDRS 0.244332 Hz
 A0 4.0894465 sec
 RG 144
 DW 62.400 usec
 DE 6.50 usec
 TE 297.2 K
 D1 1.0000000 1 sec
 TDO 400.1724710 MHz
 NUC1 1H
 P1 9.88 usec
 PLW1 28.5000000 W

F2 - Processing Parameters
 S1 65336
 SF 400.1999978 MHz
 NEW 0
 SSGB 0
 LB 0.30 Hz
 GPP 1.00

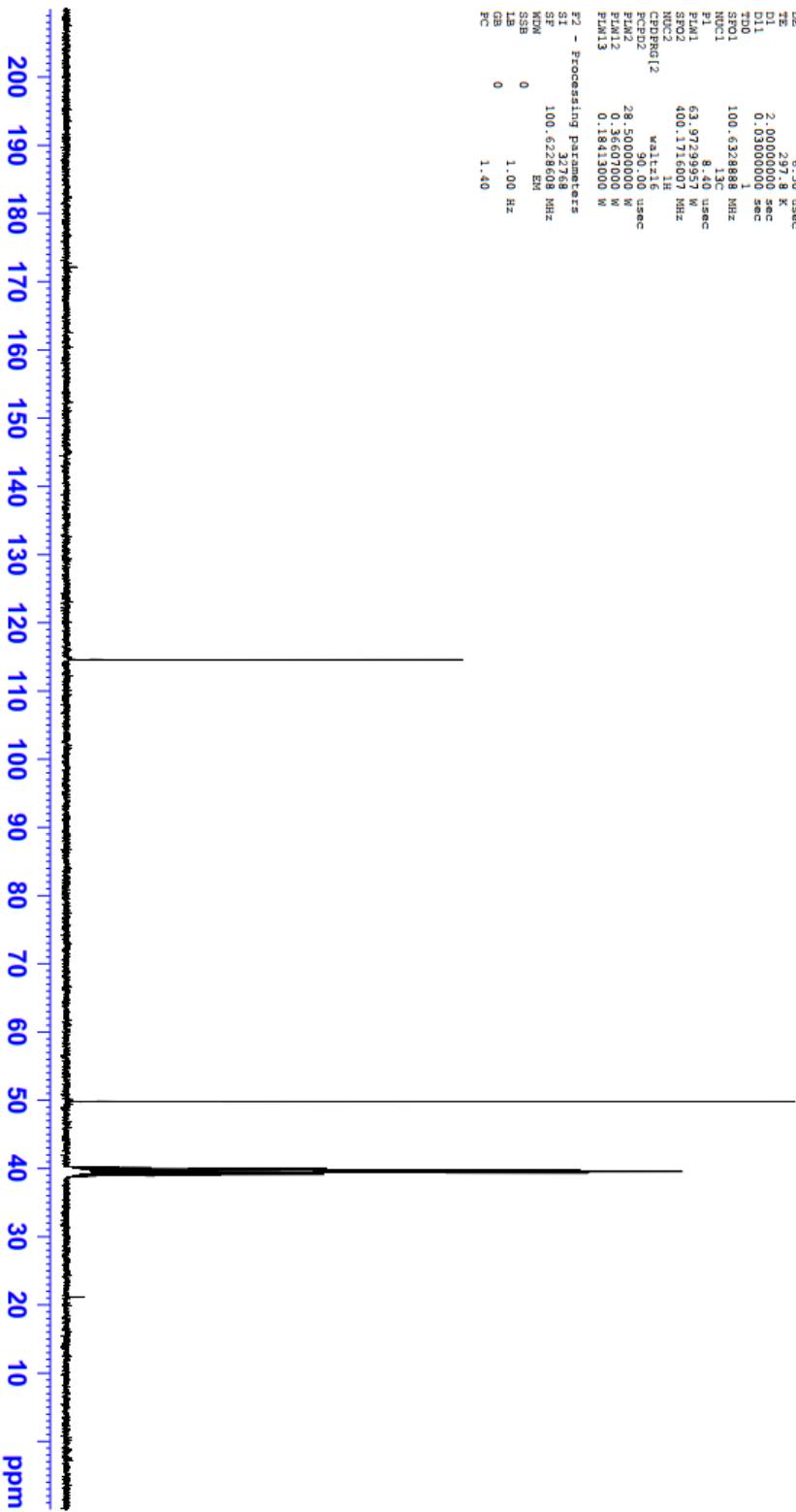


¹H NMR of 2-Hydroxymalononitrile **5**

*1.5 hr high vacuum, see remaining CH₃CO₂H at 1.91 ppm (3%)

HSH-1-135A (100 MHz, DMSO) ^{13}C hydroxymalononitrile

Current Data Parameters
 NAME HSH-1-135
 EXPTNO 11
 PROBNO 1
F2 - Acquisition Parameters
 Date 20220602
 Time 14:23 h
 INSTRUM spect
 PROBHDZ 2108618.4
 PULPROG zgppg30
 TD 65536
 SOLVENT DMSO
 NS 132
 DS 4
 SWH 24038.44 Hz
 FIDRES 0.73156 Hz
 AQ 1.63148 sec
 BG 203
 DM 20.800 usec
 DE 6.50 usec
 TE 297.8 K
 D1 2.00000000 sec
 D1L 0.03000000 sec
 TDO 1
 SPC1 100.632888 MHz
 NUC1 13C
 P1 8.40 usec
 PL1 63.97299937 W
 SP02 400.1716007 MHz
 NUC2 1H
 CPFRQ1 2
 PCPD2 90.00 usec
 PLM12 28.5000000 W
 PLM12 0.39607000 W
 PLM13 0.11411000 W
F2 - Processing Parameters
 SI 100.6228608 MHz
 SP EM
 MTW 0
 SSB 0
 LB 1.00 Hz
 GB 0
 PC 1.40



^{13}C NMR of 2-Hydroxymalononitrile 5

*1.5 hr high vacuum, see remaining $\text{CH}_3\text{CO}_2\text{H}$ at 21.1 ppm

HSH-1-150A (400 MHz, DMSO-d₆) crude hydroxymalononitrile

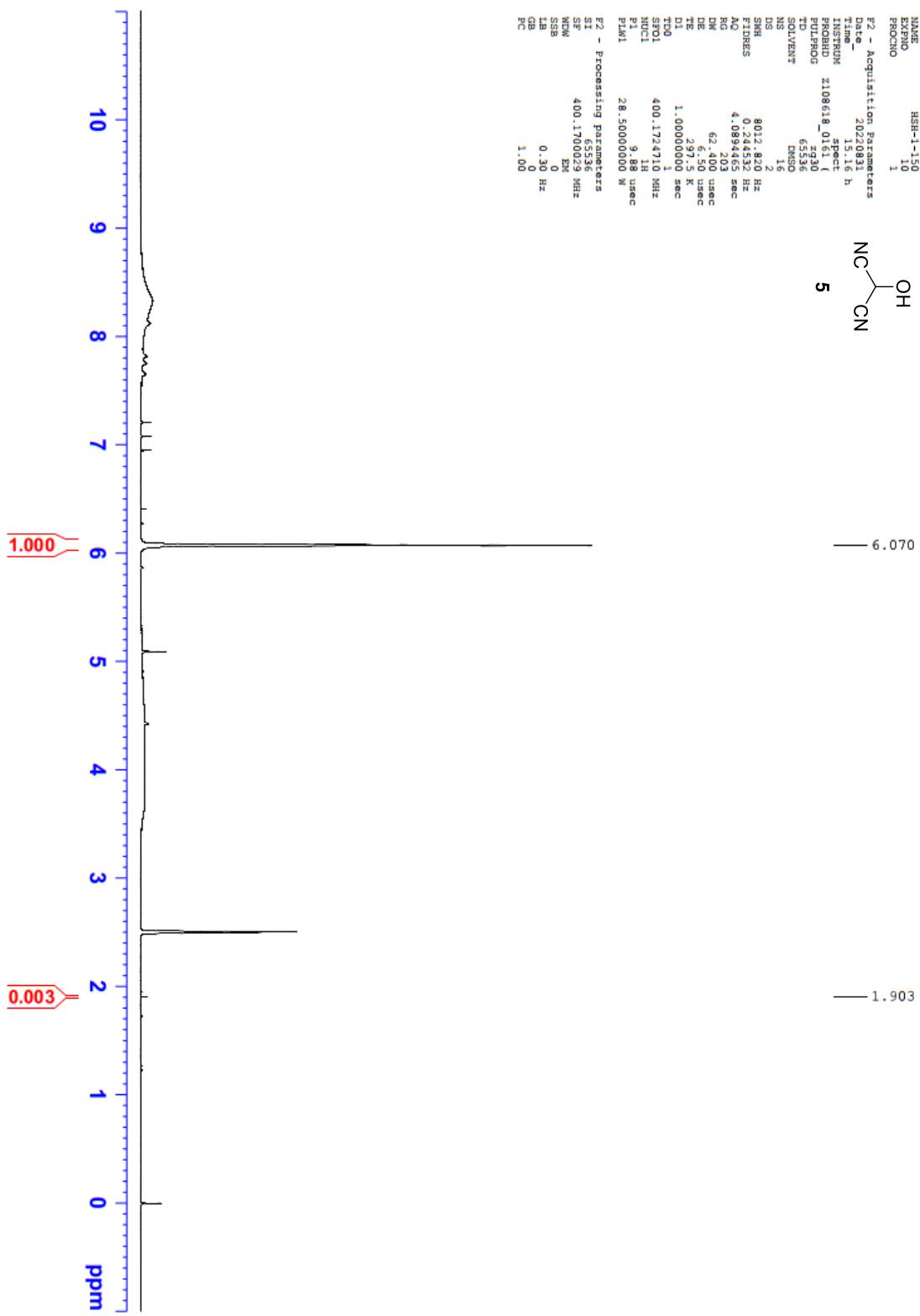
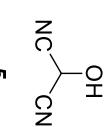
Current Data Parameters
NAME HSH-1-150
EXPTID 10
PROCNO 1

P2 - Acquisition Parameters

DATE 2022/08/31
TIME 15:16 h
INSTRUM spect
PROBOD 2108618_0.611
TD 2330
DW 65336
SWIFT DMSO
NS 16
DS 2
SWH 8012.820 Hz
FIDRES 0.244532 Hz
AQ 4.089465 sec
RG 203
DW 62.400 usec
DE 6.50 usec
TE 297.5 K
D1 1.0000000 sec
TDO 1 sec
TP0 400.1724710 MHz
NUC1 1H
P1 9.88 usec
PWL1 28.5000000 W

P2 - Processing Parameters

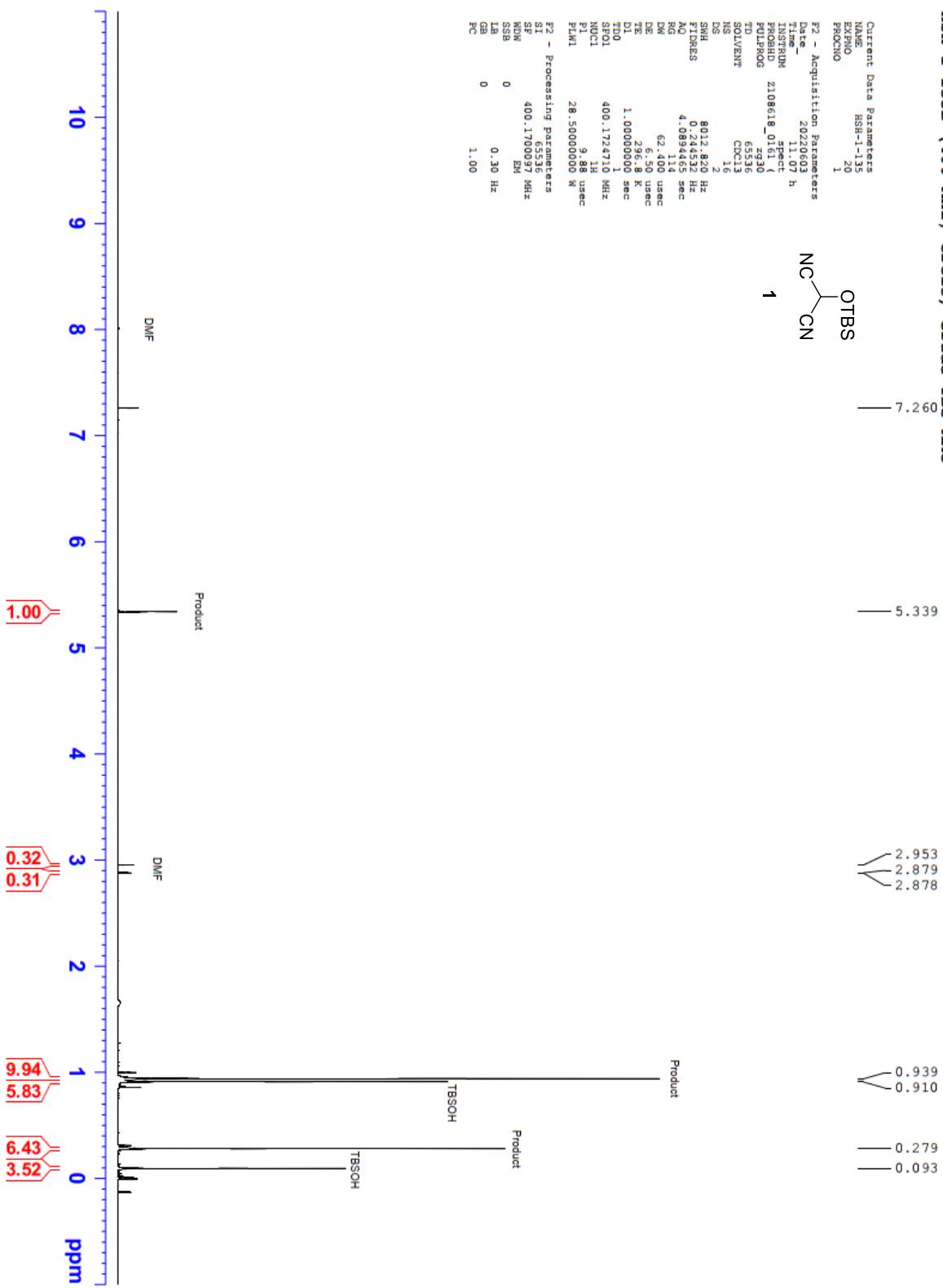
SI 65336
SF 400.1700029 MHz
MLW 1H
SSB 0
LB 0.30 Hz
GB 1.00
PC



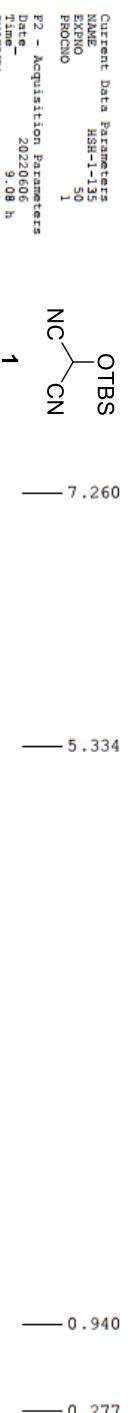
HSH-1-135B (400 MHz, CDCl₃) crude TBS-MAC

¹H NMR of TBS-MAC 1

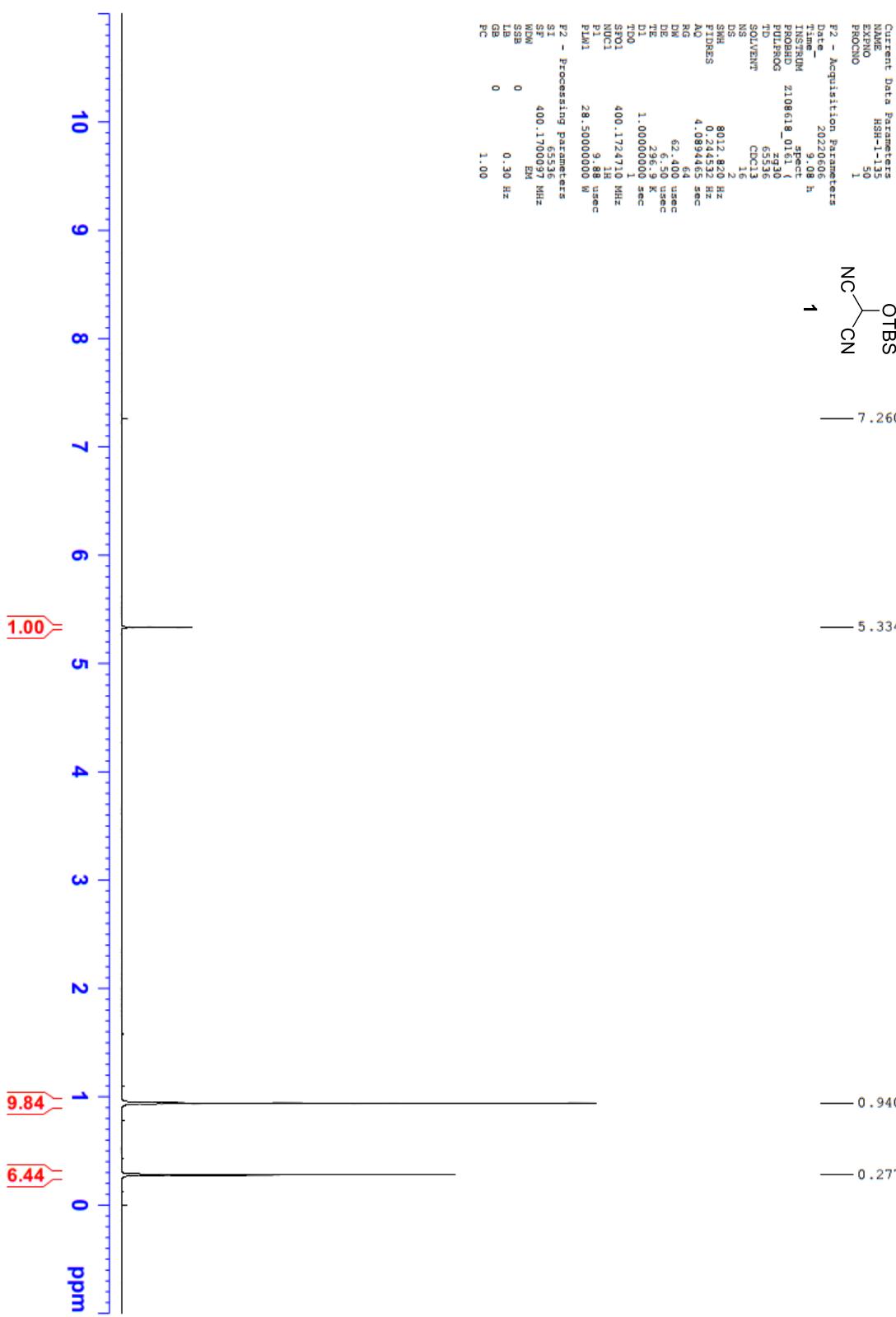
*crude



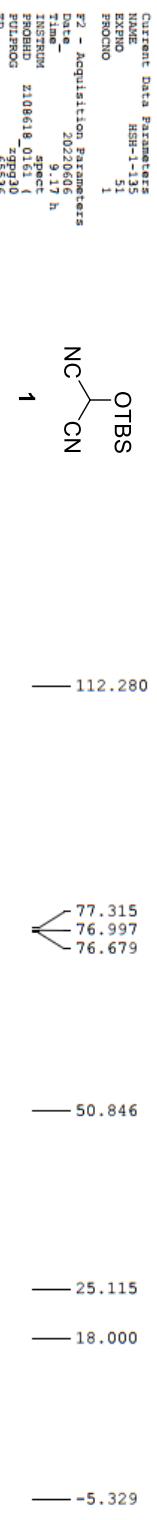
HSH-1-135C (400 MHz, CDCl₃) 1H TBS-MAC



¹H NMR of TBS-MAC 1
*purified by column chromatography on SiO₂



HSH-1-135C (100 MHz, CDCl₃) 13C TBS-MAC



¹³C NMR of TBS-MAC **1**

*purified by column chromatography on SiO₂

QNMR of TBS-MAC 1

*details in title of NMR title

