Supporting Information

Process Optimization of Aldol Type Reaction by Process Understanding Using *In situ* IR.

Shionogi & Co., Ltd.

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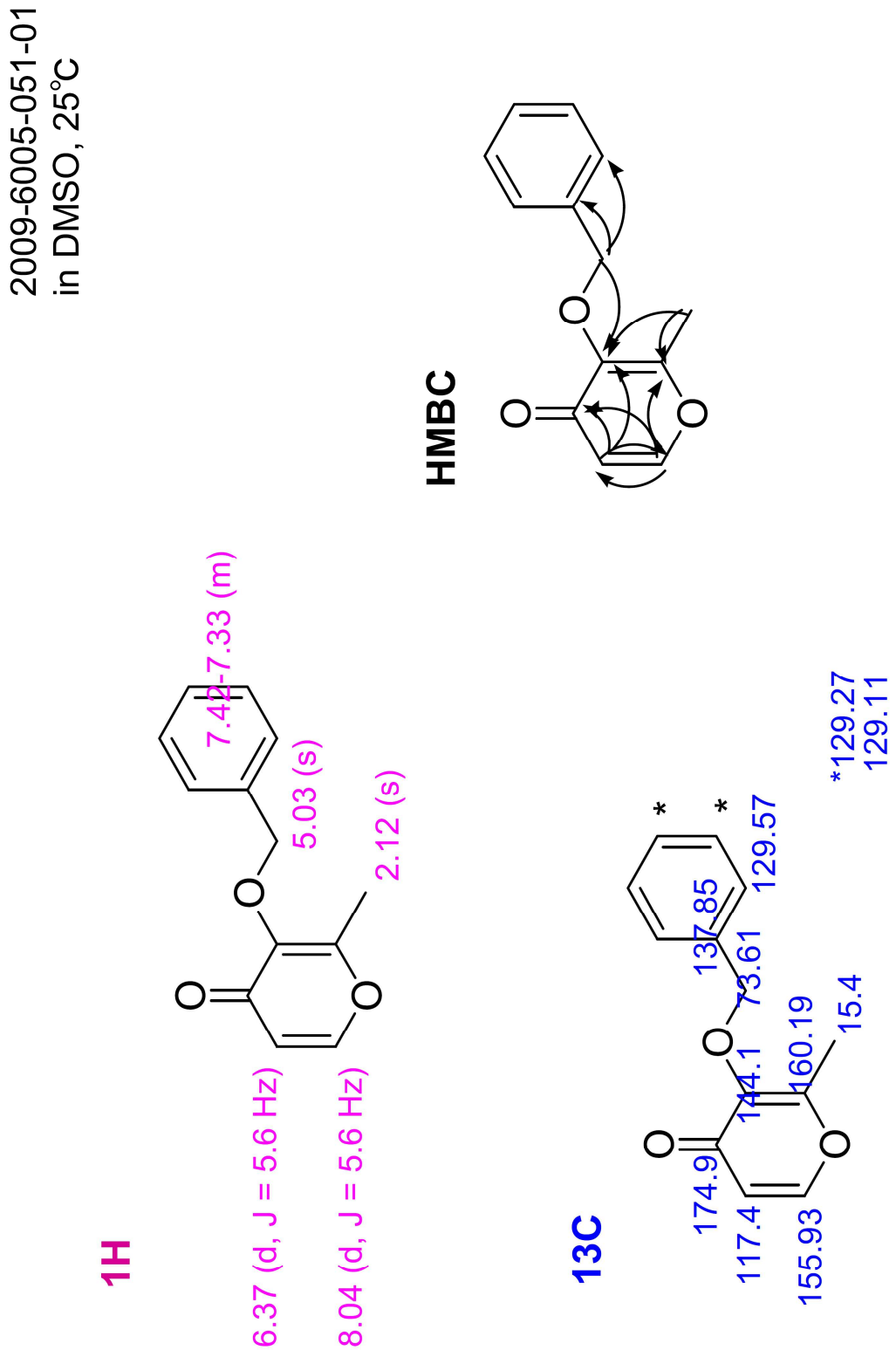
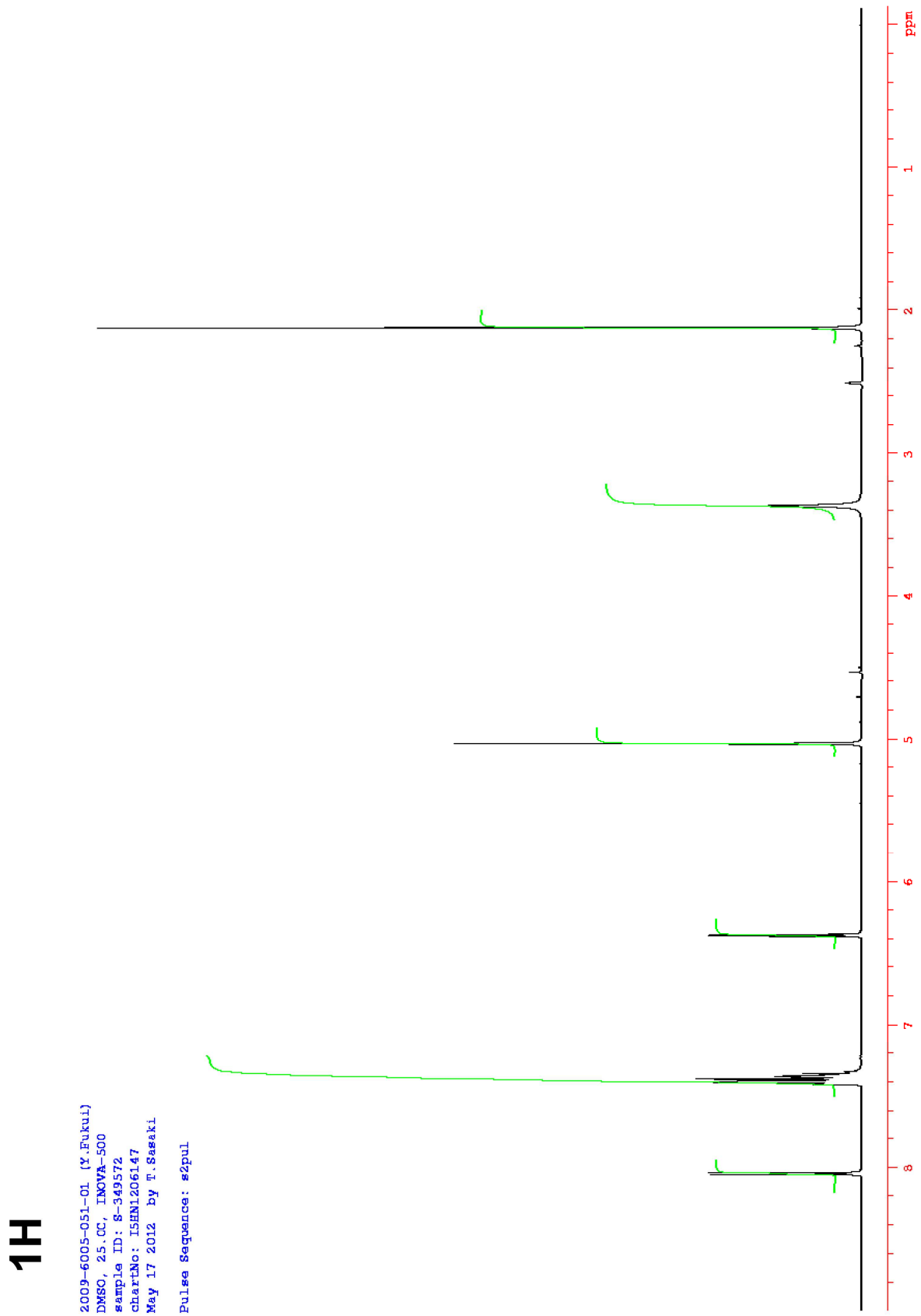
NMR chart of benzyl maltol (**2**). (500 MHz, DMSO-d_6).

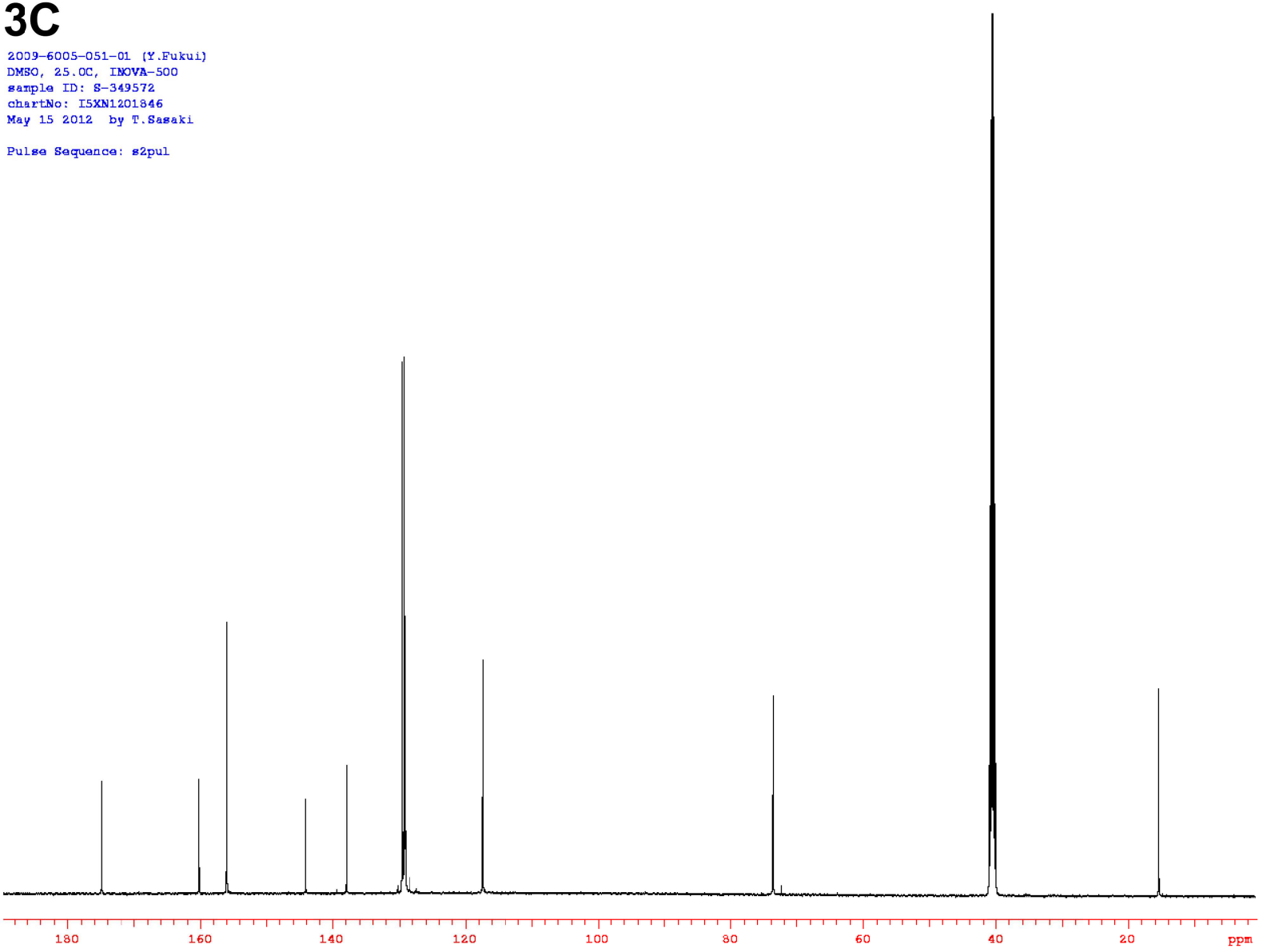



1H
2009-6005-051-01 (Y.Fukui)
DMSO, 25.CC, INOVA-500
sample ID: S-349572
chartNo: ISHN1206147
May 17 2012 by T.Sasaki
Pulse Sequence: s2pul
ppm
1
2
3
4
5
6
7
8

13C

2009-6005-051-01 (Y.Fukui)
DMSO, 25.0C, INOVA-500
sample ID: S-349572
chartNo: I5XN1201846
May 15 2012 by T.Sasaki

Pulse Sequence: s2pul

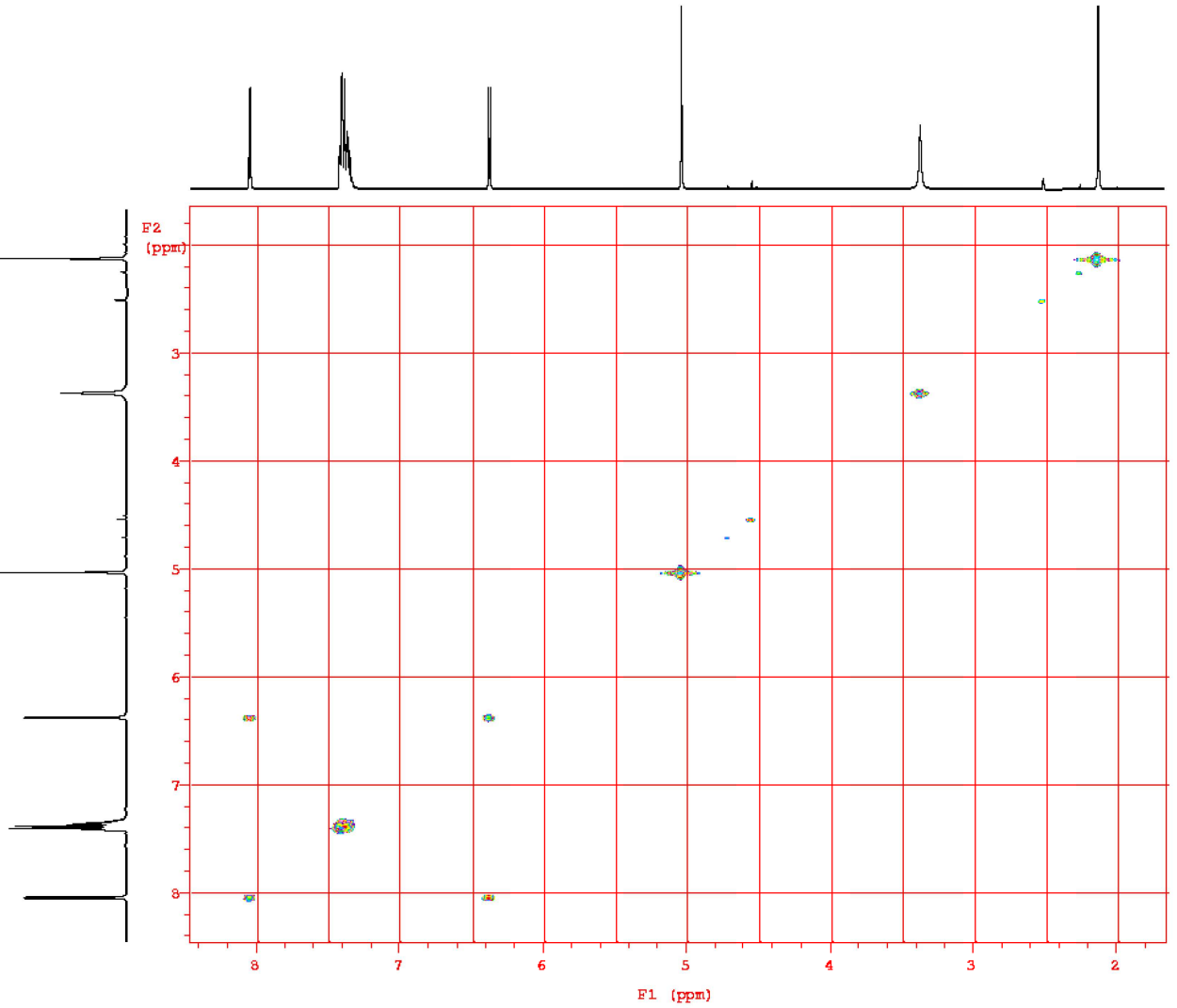


COSY

2009-6005-051-01 (Y.Fukui)
DMSO, 25.0C, INOVA-500
sample ID: S-349572
chartNo: I5HS1202148
May 15 2012 by T.Sasaki

exp13 gCOSY

SAMPLE		FLAGS	
date	May 15 2012	hs	nn
solvent	DMSO	sspul	n
sample	2009-6005-0-51-01	hsglvl	2500
ACQUISITION		SPECIAL	
sw	3400.2	temp	25.0
at	0.151	gain	34
np	1024	spin	not used
fb	not used	F2 PROCESSING	
ss	16	sb	0.075
d1	1.000	sbs	not used
nt	2	fn	2048
2D ACQUISITION		F1 PROCESSING	
sw1	3400.2	sb1	0.038
ni	256	sbs1	not used
TRANSMITTER		fn1	2048
tn	H1	DISPLAY	
sfrq	499.744	sp	826.6
tof	11.6	wp	3396.9
tpwr	49	sp1	828.2
pw	9.800	wp1	3396.9
GRADIENTS		rfl	-823.3
gzlvl1	2500	rfp	0
gt1	0.001000	rfl1	-824.9
gstab	0.000500	rfp1	0
DECOUPLER		PLOT	
dn	H1	wc	160.0
dm	nnn	sc	0
		wc2	120.0
		sc2	0
		vs	65
		th	5
		ai	av

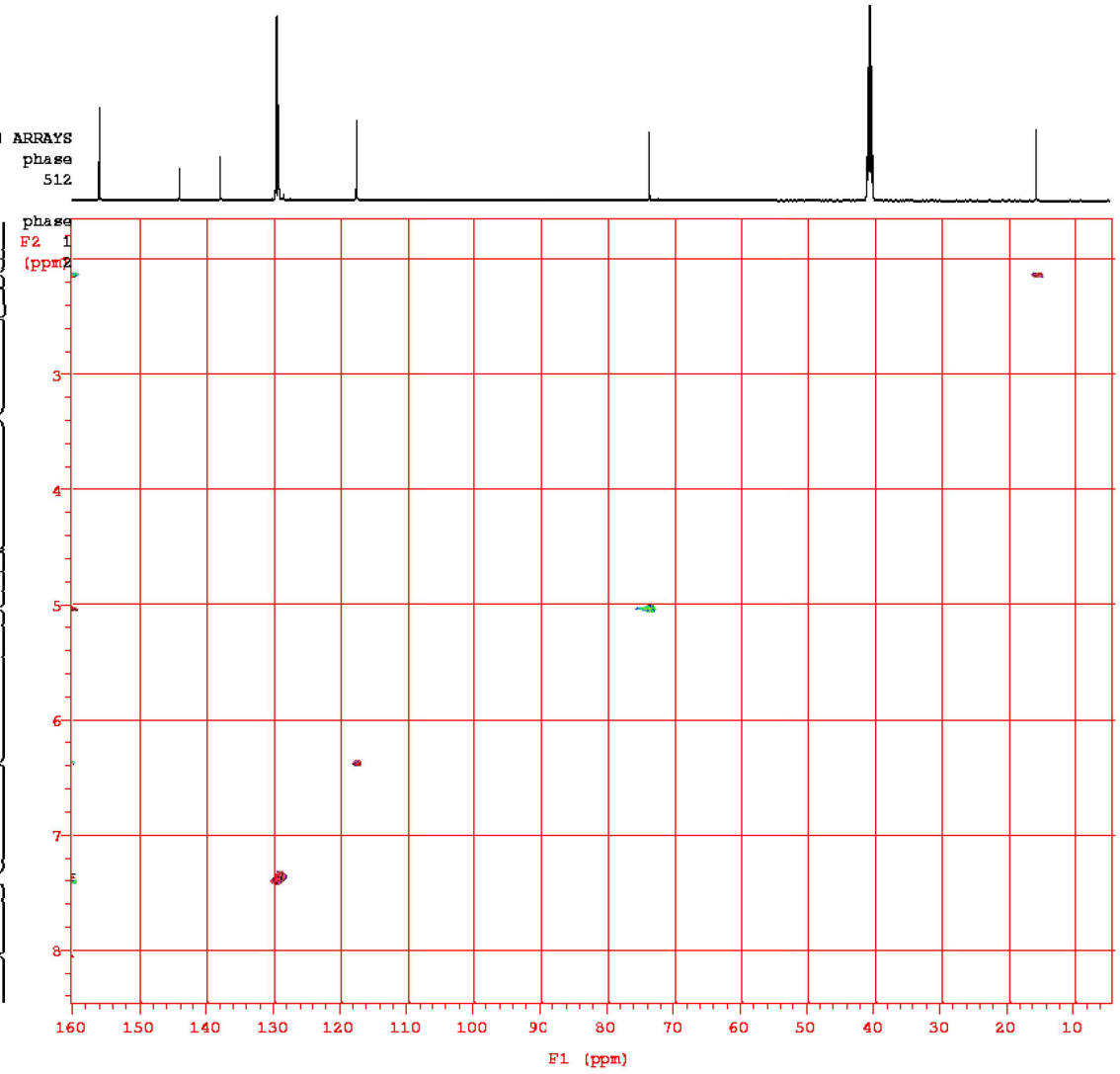


HSQC

2009-6005-051-01 (Y.Fukui)
DMSO, 25.0C, INOVA-500
sample ID: S-349572
chartNo: I5XS1203532
May 15 2012 by T.Sasaki

exp14 gHSQC

SAMPLE		FLAGS		ACQUISITION ARRAYS	
date	May 15 2012	hs	n	array	phase
solvent	DMSO	sspul	y	arraydim	512
sample	2009-6005-0~	PFGflg	y		
	51-01	hsglvl	2500	i	phase
ACQUISITION		SPECIAL		1	F2
sw	3400.2	temp	25.0	2	(ppm)
at	0.151	gain	34		
np	1024	spin	not used		
fb	not used	GRADIENTS			
ss	32	gzlvl1	2500		
d1	1.000	gt1	0.002000		
nt	4	gzlvl3	1250		
2D ACQUISITION		gt3	0.001000		
sw1	21361.8	gstab	0.000500		
ni	256	F2 PROCESSING			
phase	arrayed	gf	0.070		
TRANSMITTER		gfs	not used		
tn	H1	fn	1024		
sfrq	499.744	F1 PROCESSING			
tof	11.6	gf1	0.006		
tpwr	49	gfs1	not used		
pw	9.800	fn1	2048		
DECOUPLER		DISPLAY			
dn	C13	sp	829.9		
dof	-2514.7	wp	3393.6		
dm	nny	sp1	537.6		
dmm	ccg	wp1	19567.8		
dmf	14815	rfl	-823.3		
dpwr	42	rfp	0		
pwxlvl	60	rfl1	1256.4		
pwx	12.500	rfp1	0		
HSQC		PLOT			
j1xh	140.0	wc	160.0		
nullflg	y	sc	0		
mult	2	wc2	120.0		
		sc2	0		
		vs	668		
		th	5		
		ai	ph		

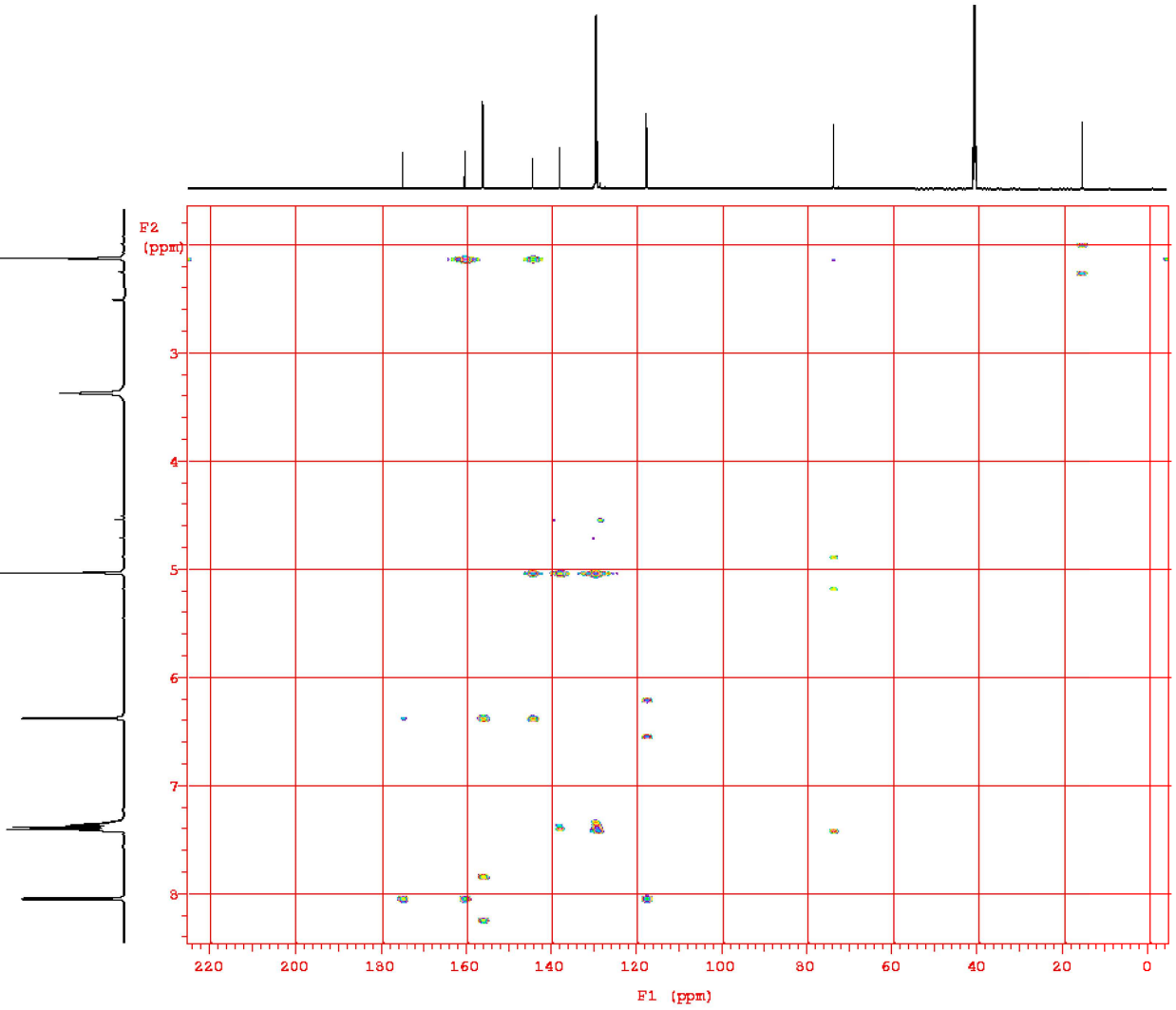


HMBC

2009-6005-051-01 (Y.Fukui)
DMSO, 25.0C, INOVA-500
sample ID: S-349572
chartNo: I5XS1203533
May 15 2012 by T.Sasaki

exp15 gHMBC

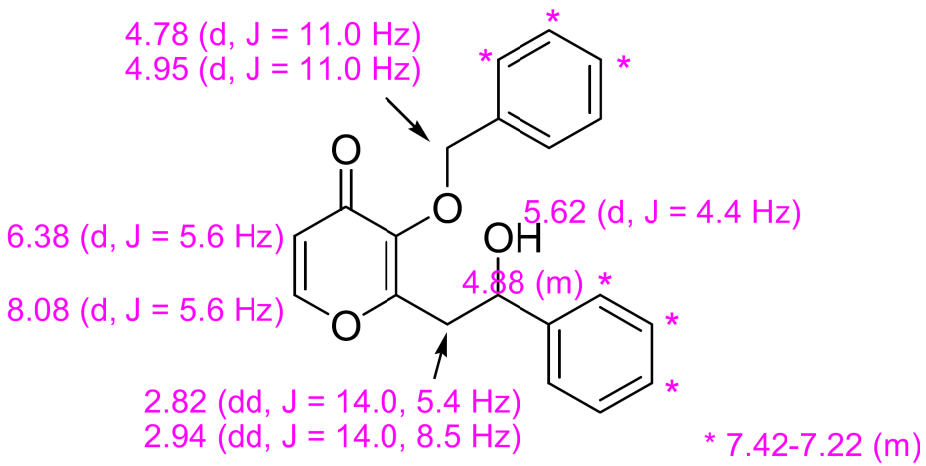
SAMPLE		FLAGS	
date	May 15 2012	hs	nn
solvent	DMSO	sspul	n
sample	2009-6005-0~	PFGflg	y
	51-01	hsglvl	2500
ACQUISITION		SPECIAL	
sw	3400.2	temp	25.0
at	0.151	gain	54
np	1024	spin	not used
fb	not used	GRADIENTS	
ss	32	gzlvl1	2500
d1	1.500	gt1	0.001000
nt	8	gzlvl3	1250
2D ACQUISITION		gt3	0.001000
sw1	28901.7	gstab	0.000500
ni	256	F2 PROCESSING	
phase	0	sb	0.075
TRANSMITTER		sbs	not used
tn	H1	fn	2048
sfrq	499.744	F1 PROCESSING	
tof	11.6	sb1	0.004
tpwr	49	sbs1	not used
pw	9.800	fn1	2048
DECOUPLER		DISPLAY	
dn	C13	sp	826.6
dof	1883.4	wp	3396.9
dm	nnn	sp1	-600.0
dmm	ccp	wp1	28873.5
dmf	14815	rfl	-823.3
dpwr	42	rfp	0
pwxlvl	57	rfl1	628.3
pwx	18.500	rfp1	0
HMBC		PLOT	
j1xh	140.0	wc	160.0
jnxh	8.0	sc	0
		wc2	120.0
		sc2	0
		vs	63
		th	10
		ai	av



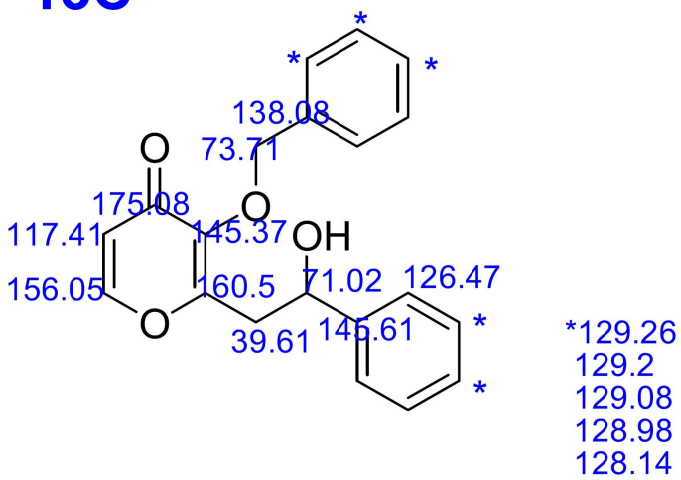
NMR chart of 3-(benzyloxy)-2-(2-hydroxy-2-phenylethyl)-4H-pyran-4-one (**4**)

2006-6080-094-01
In DMSO, 25℃

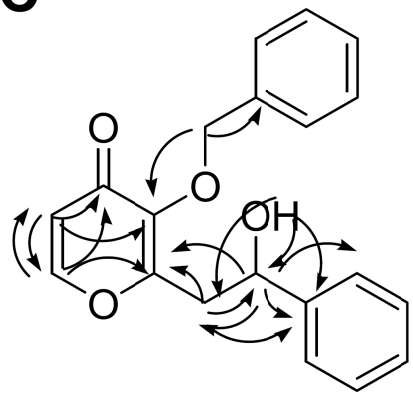
1H



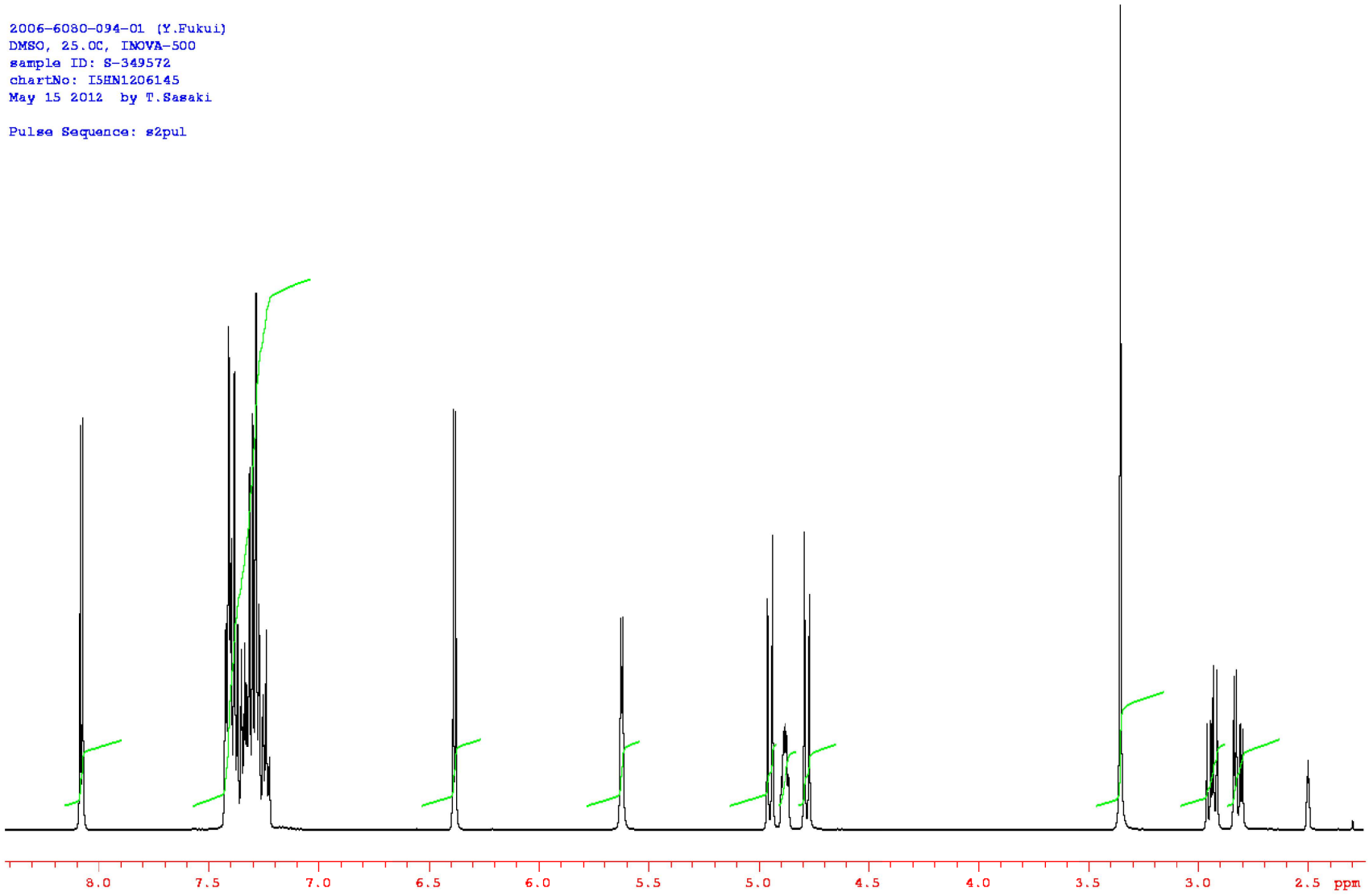
13C



HMBC



1H

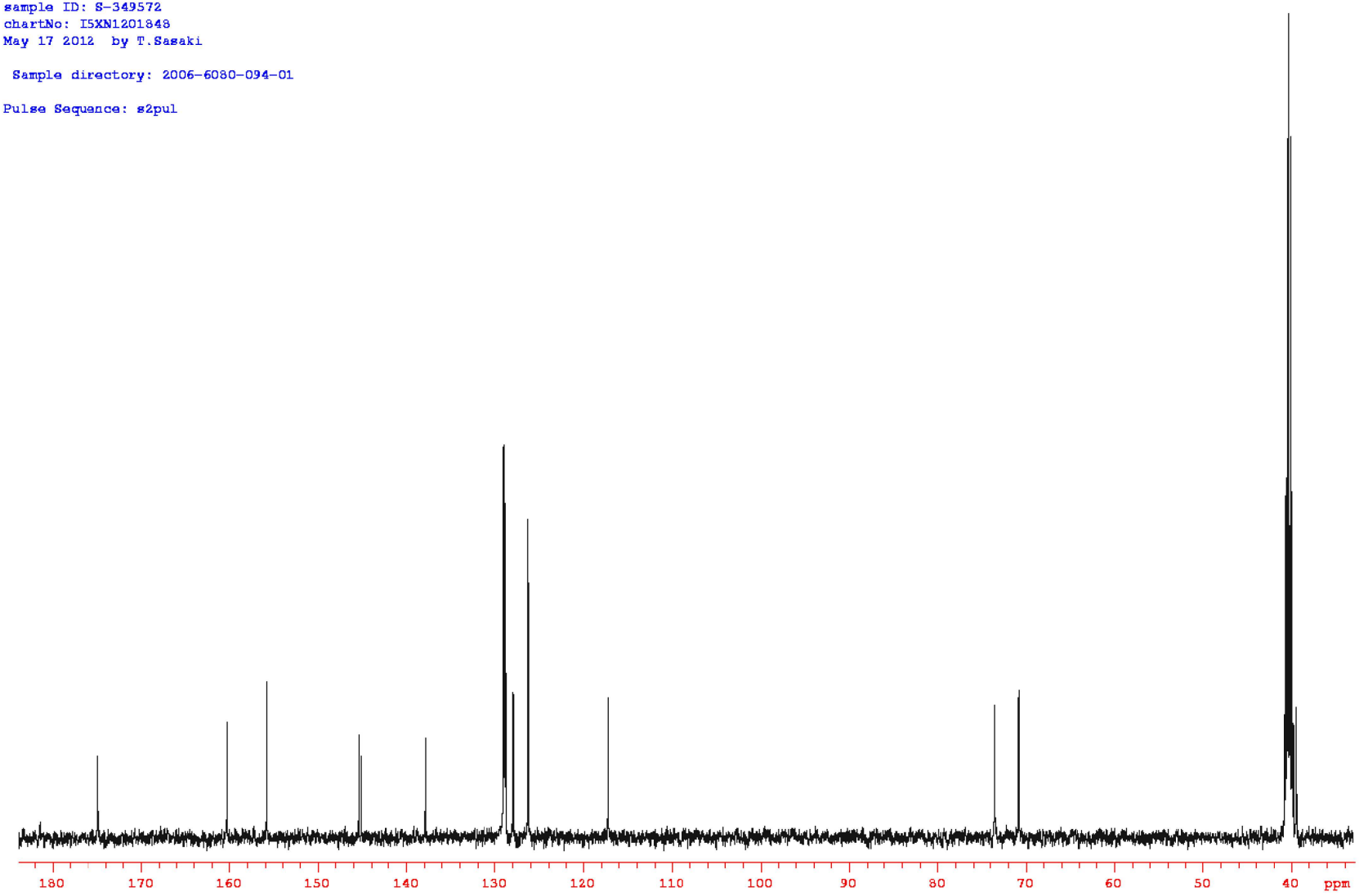

2006-6080-094-01 (Y.Fukui)
DMSO, 25.0C, INOVA-500
sample ID: S-349572
chartNo: I5HN1206145
May 15 2012 by T.Sasaki
Pulse Sequence: s2pul
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5 ppm

13C

2006-6080-094-01 (Y.Fukui)
DMSO, 25.0C, INOVA-500
sample ID: S-349572
chartNo: I5XN1201848
May 17 2012 by T.Sasaki

Sample directory: 2006-6080-094-01

Pulse Sequence: s2pul

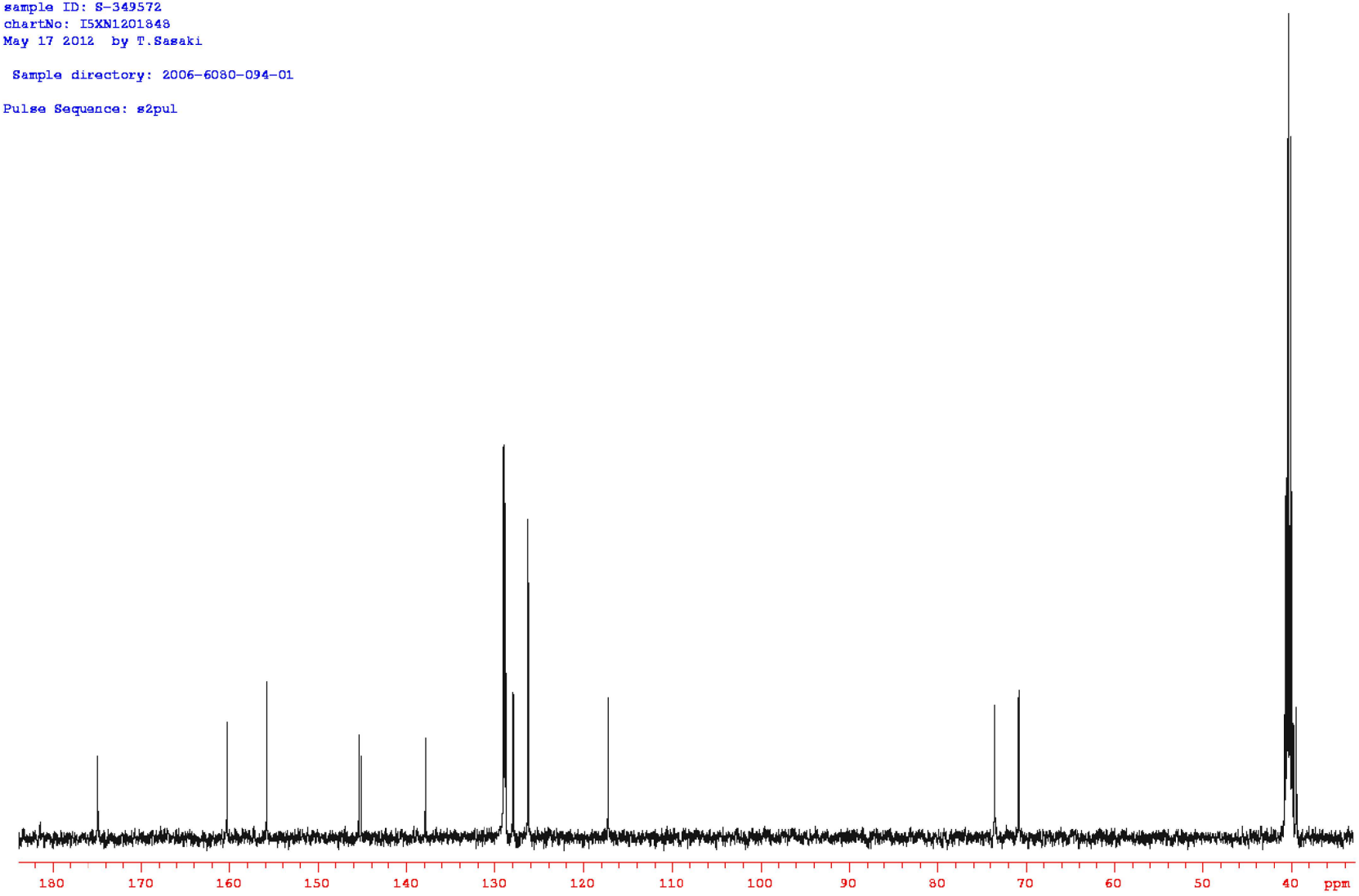


13C

2006-6080-094-01 (Y.Fukui)
DMSO, 25.0C, INOVA-500
sample ID: S-349572
chartNo: I5XN1201848
May 17 2012 by T.Sasaki

Sample directory: 2006-6080-094-01

Pulse Sequence: s2pul



HSQC

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2006-6080-094-01 (Y.Fukui)
DMSO, 25.0C, INOVA-500
sample ID: S-349572
chartNo: I5XS1203530
May 15 2012  by T.Sasaki

exp9  gHSQC

      SAMPLE                FLAGS          ACQUISITION ARRAYS
date    May 15 2012  hs                n   array          phase
solvent        DMSO  sspul             y   arraydim         512
sample 2006-6080-0~  PFGflg            y
              94-01  hsglvl         2500    i             phase
   ACQUISITION           SPECIAL           1             F2  1
sw           4278.1  temp           25.0    2             (ppm2
at            0.239  gain             32
np             2048  spin       not used
fb         not used       GRADIENTS
ss               32  gzlvl1         2500
d1            1.000  gt1        0.002000
nt                4  gzlvl3         1250
  2D ACQUISITION     gt3        0.001000
sw1         21361.8  gstab      0.000500
ni              256    F2 PROCESSING
phase      arrayed  gf             0.111
   TRANSMITTER      gfs        not used
tn                H1  fn             2048
sfrq        499.743    F1 PROCESSING
tof          -470.8  gf1            0.006
tpwr             49  gfs1       not used
pw            9.825  fn1            2048
    DECOUPLER           DISPLAY
dn              C13  sp           1056.1
dof         -2514.7  wp           3041.4
dm              nny  sp1          4271.8
dmm             ccg  wp1         12662.7
dmf           14815  rfl            101.2
dpwr             42  rfp                0
pwxlvl           60  rfl1          1256.4
pwx          12.500  rfp1               0
       HSQC                PLOT
j1xh         140.0  wc             160.0
nullflg          y  sc                 0
mult             2  wc2            120.0
                    sc2                0
                    vs               152
                    th                 4
                    ai    ph
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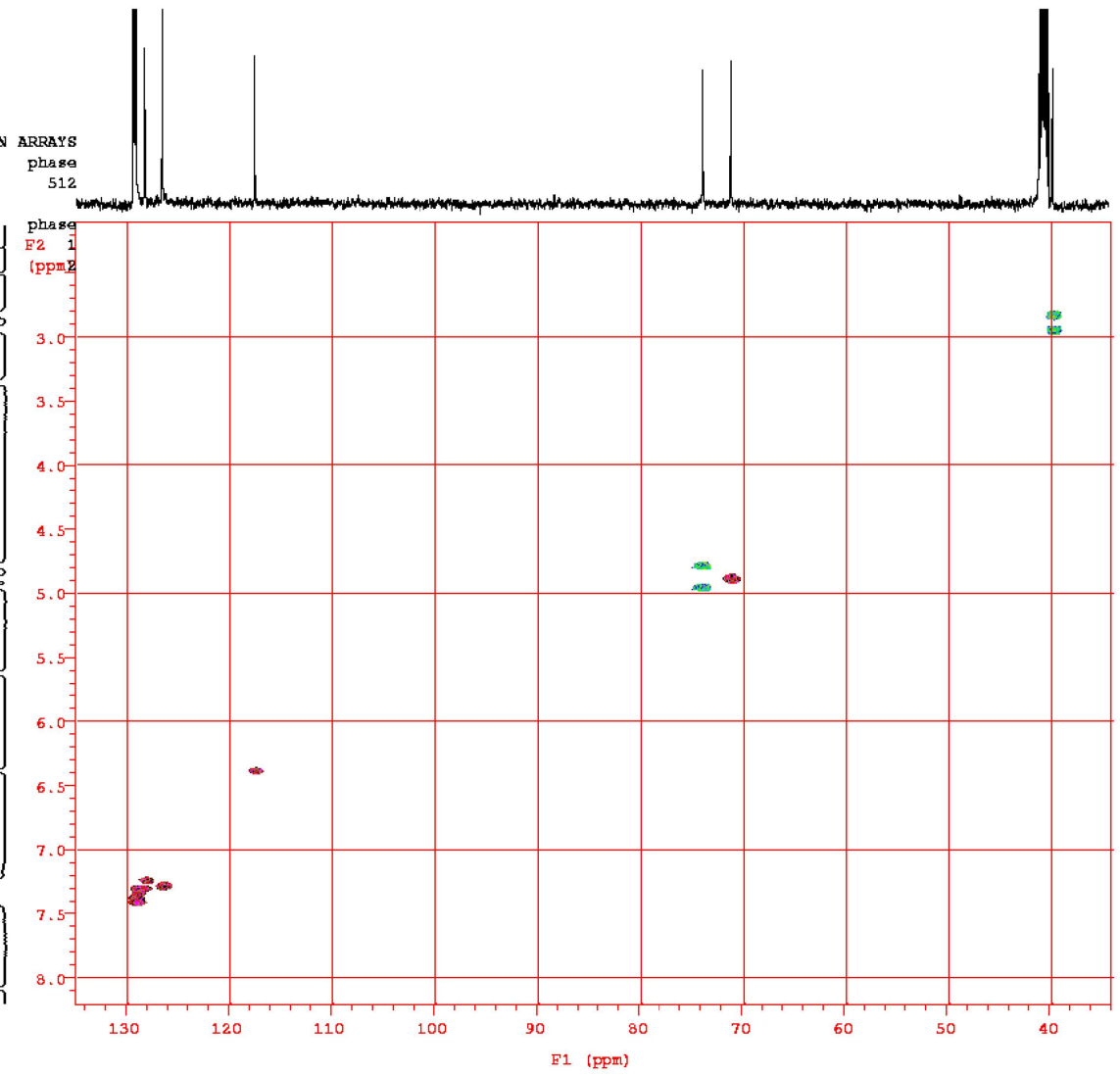

HMBC

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2006-6080-094-01 (Y.Fukui)
DMSO, 25.0C, INOVA-500
sample ID: S-349572
chartNo: I5XS1203531
May 15 2012  by T.Sasaki

exp10  gHMBC

      SAMPLE                FLAGS
date    May 15 2012  hs                nn
solvent        DMSO  sspul             n
sample 2006-6080-0~  PFGflg            y
               94-01  hsglvl         2500
   ACQUISITION            SPECIAL
sw          4278.1  temp           25.0
at           0.239  gain             52
np            2048  spin       not used
fb        not used       GRADIENTS
ss              32  gzlvl1         2500
d1           1.500  gt1       0.001000
nt               8  gzlvl3         1250
  2D ACQUISITION    gt3       0.001000
sw1        28901.7  gstab     0.000500
ni             256    F2 PROCESSING
phase            0  sb            0.120
   TRANSMITTER      sbs        not used
tn              H1  fn             2048
sfrq       499.743    F1 PROCESSING
tof         -470.8  sb1           0.004
tpwr            49  sbs1       not used
pw           9.825  fn1            2048
    DECOUPLER            DISPLAY
dn              C13  sp          1173.0
dof          1883.4  wp          2983.0
dm              nnn  sp1         4367.4
dmm             ccp  wp1        18176.5
dmf           14815  rfl           101.2
dpwr             42  rfp               0
pwxlvl           57  rfl1          628.3
pwx          18.500  rfp1              0
      HMBC                   PLOT
j1xh         140.0  wc            160.0
jnxh           8.0  sc                0
                    wc2           120.0
                    sc2               1
                    vs               85
                    th                9
                    ai     av
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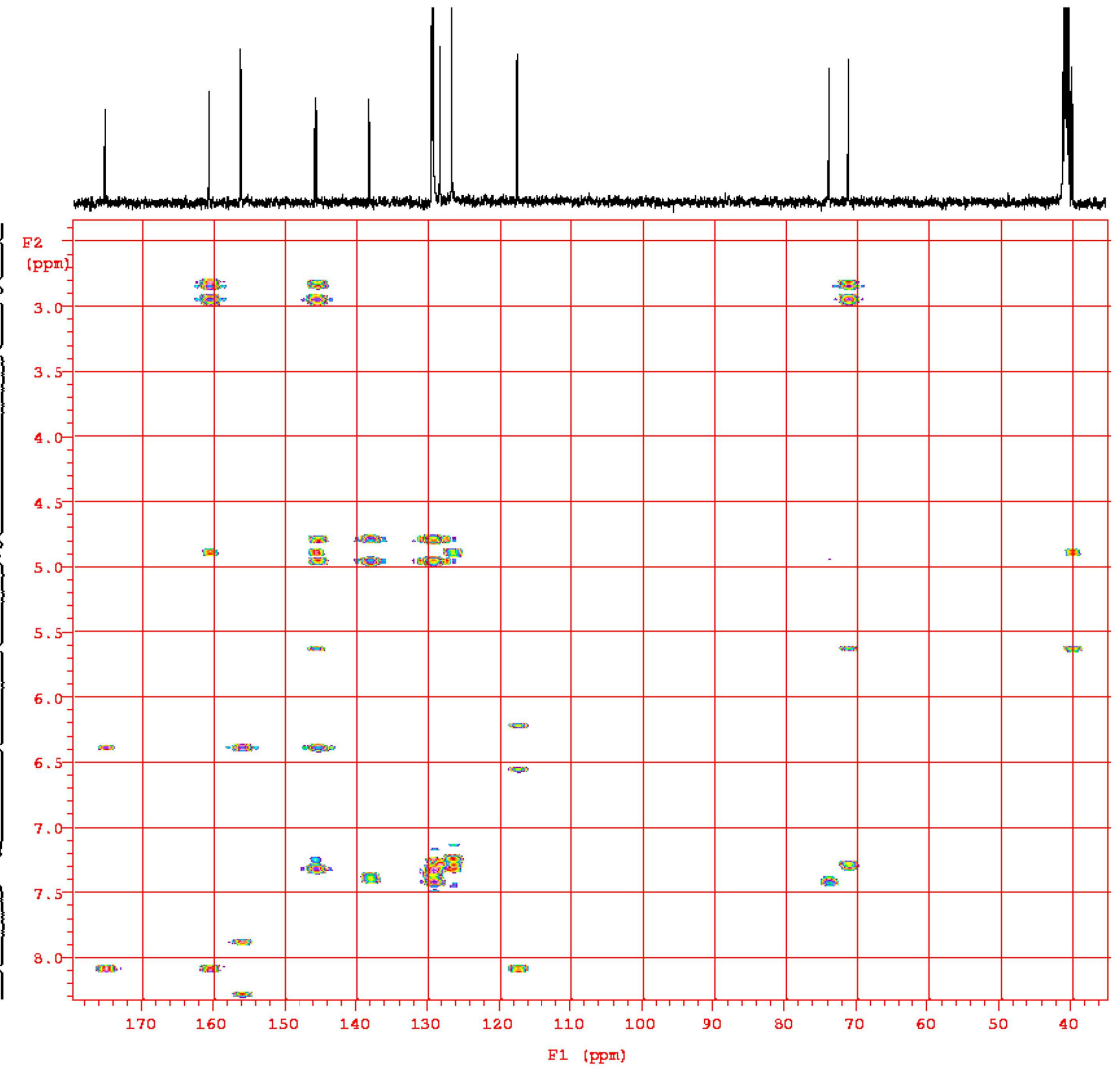
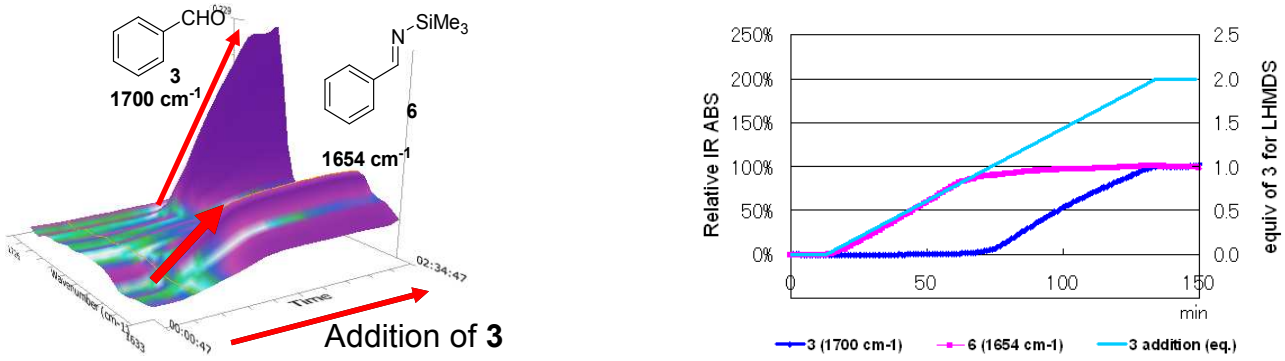


Experimental procedure. (Observation of addition of 3 to LHMDS. Figure 3)

In a four-neck flask equipped with in-situ IR censor (Mettler Toledo ReactIR^{TM} iC10.), LHMDS (20% in THF, Ethylbenzene, 39.8 g, 47.6 mmol, 1 equiv.) was mixed with THF (58 mL) under nitrogen atmosphere and the mixture was cooled to -70 degree. Then **3** (10.1 g, 95.2 mmol, 2 equiv.) was added dropwise to the mixture at the same condition.

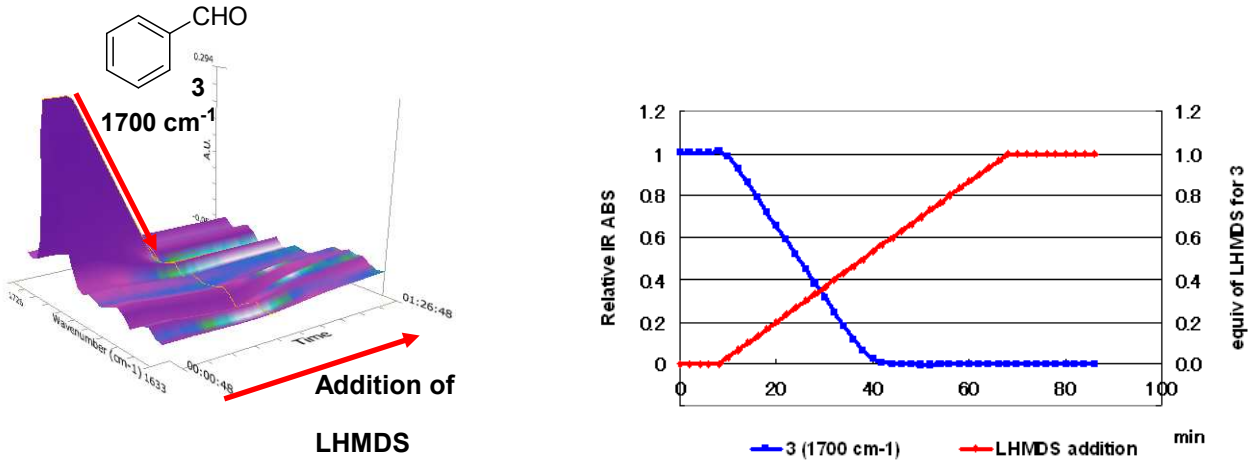
Figure 3. Observation of addition of **3** to LHMDS.



Experimental procedure (Observation of addition of LHMDS to 3. Figure 5.)

In a four-neck flask equipped with in-situ IR censor (Mettler Toledo ReactIR^{TM} iC10.), **3** (5.05 g, 47.6 mmol, 1 equiv.) was mixed with THF (58 mL) under nitrogen atmosphere and the mixture was cooled to -70 degree. Then LHMDS (20% in THF, Ethylbenzene, 39.8 g, 47.6 mmol, 1 equiv.) was added dropwise to the mixture at the same condition.

Figure 5. Observation of addition of LHMDS to **3**.



Information for complex 7.

^{1}H-NMR analysis was carried out in THF-d_6 at -46 degree. NMR spectra were measured on a 400 MHz Agilent 400-MR spectrometer. Complete structure determination of complex **7** was not achieved because the complex easily decomposed into benzaldimine **6**. However some chemical shifts which correspond to acetal and hemi-acetal of the complex were detected (see following experimental procedure.). Therefore there in no solid evidence. However there are many circumstance evidences which prove it.

To be specific,

1, Carbonyl peak of **3** completely disappeared and there in no peak at 1630-1720 cm^{-1} as shown in figure 5 (left). The fact indicates that there is no carbon-hetero atom double bond compounds in the reaction mixture.

2, The complex can reverse to **3** by water addition. The fact indicates that the complex has easily broken bond. Considering the components of the reaction mixture (**3**, LHMDS and THF), the bond should be O-C-O acetal and/or O-C-N hemi-acetal.

3, There is no reaction point except for carbonyl group of **3** and Nitrogen atom of LHMDS.

4, Reaction ratio of **3** and LHMDS is 2:1 as shown in figure 5 (right).

Considering those four conditions, it is speculated that complex **7** was formed. And following NMR data indicates that the complex seems to have some conformations.

Experimental procedure for NMR analysis of complex 7.

3 (202 µL, 1.982 mmol, 1 equiv.) was mixed with THF (3 mL) under nitrogen atmosphere and the mixture was cooled to -70 degree. Then LHMDS (20% in THF, Ethylbenzene, 37 µL, 0.198 mmol, 0.1 equiv.) was added and stirred for 5 minutes. One drop of the mixture was added to THF-d_6 (0.75 mL) in NMR tube at -70 degree under nitrogen atmosphere. Then the diluted sample was quickly set into NMR spectrometer and analysis was carried out at -46 degree.