

Supporting information

One-pot synthesis of (*S*)-baclofen via aldol condensation of acetaldehyde with diphenylprolinol silyl ether-mediated asymmetric Michael reaction as a key step

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Home page: <http://www.ykbsc-chem.com/>

Table of contents

• Experimental section.....	S-1
Typical procedure for the preparation of α,β -unsaturated aldehyde.....	S-1
One-pot synthesis of (<i>S</i>)-baclofen.....	S-20
• Reference.....	S-22

Experimental section

Typical procedure for the preparation of α,β -unsaturated aldehyde (Table 1 entries 1-14)

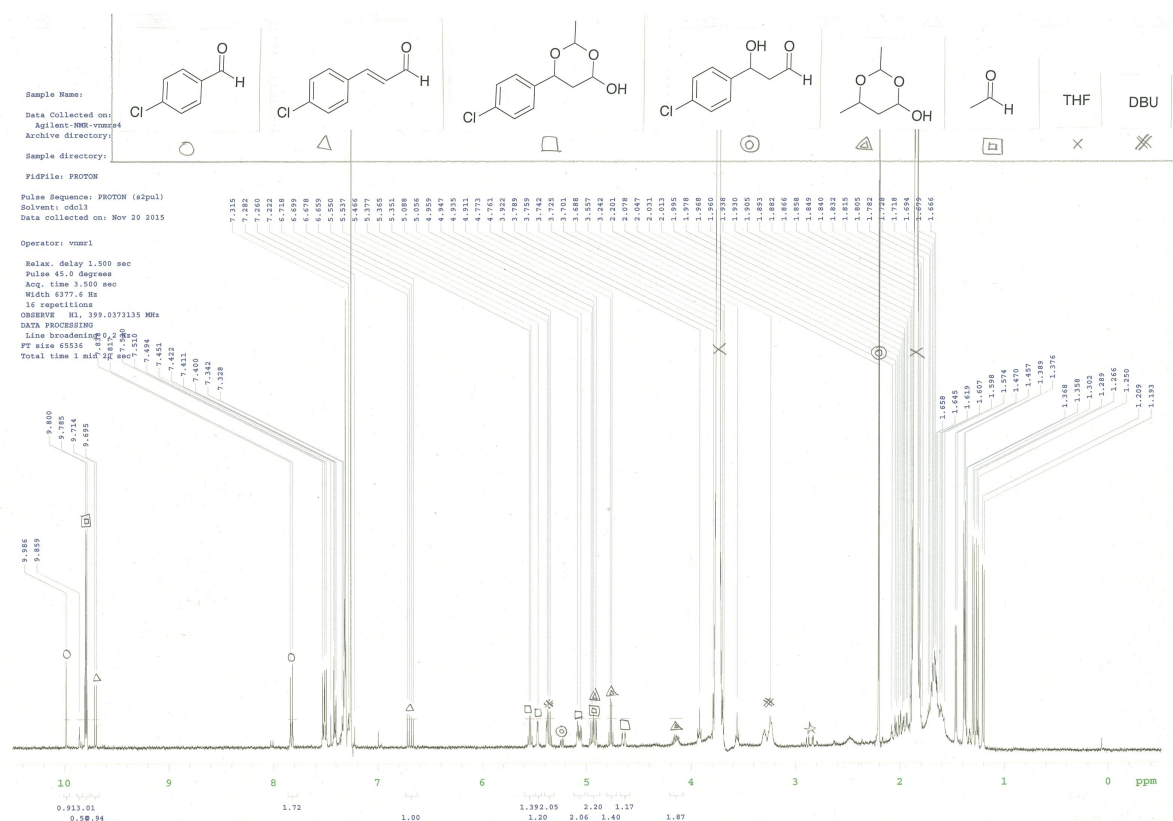
A THF solution (0.5 mL) of aromatic aldehyde (0.5 mmol) and DBU (0.1 mmol) in a one-neck flask (10 mL) was added freshly distilled acetaldehyde (2.5 mmol) and a stirring bar under an argon atmosphere. The reaction flask was closed with a greased glass cap to prevent the leak of the volatile acetaldehyde. The progress of the reaction can be monitored by $^1\text{H-NMR}$ by taking a small portion of a reaction mixture. After stirring the reaction mixture for 2 days at room temperature ($^1\text{H-NMR}$ spectra is shown in Figure 1 in the case of 4-chlorobenzaldehyde), benzene (10-15 mL) was added to a reaction mixture.* Excess acetaldehyde was removed and retro-acetalization proceeded under reduced pressure (100 mmHg) at 25 °C for 40 minutes ($^1\text{H-NMR}$ spectra is shown in Figure 2 in the case of 4-chlorobenzaldehyde). If the amount of solvent is reduced less than 3 mL, benzene (3 ~ 4 mL) is added to keep the volume of solvent constant. To promote the dehydration, the reaction mixture was heated at

50 °C under reduced pressure (200 mmHg) for 30 minutes (^1H -NMR spectra is shown in Figure 3 in the case of 4-chlorobenzaldehyde). After cooling the reaction mixture at 0 °C, the reaction was quenched by the addition of HCl solution (1N, about 3 mL), and the organic materials were extracted with CHCl_3 3 times and combined organic phase was dried over MgSO_4 . After filtration of inorganic materials and removal of volatile organic compounds under reduced pressure (^1H -NMR spectra of crude is shown in Figure 4 in the case of 4-chlorobenzaldehyde), the purification was performed using column chromatography to provide the pure compound.

* We added benzene to keep the reaction mixture not completely dry under reduced pressure.

In using 4-chlorobenzaldehyde case, column chromatography was performed AcOEt/Hexane = 1/9. Desired compound was obtained as white solid (76% yield, 63.3 mg).

Figure 1



※ This peak isn't from 4-chlorobenzaldehyde.

Figure 2

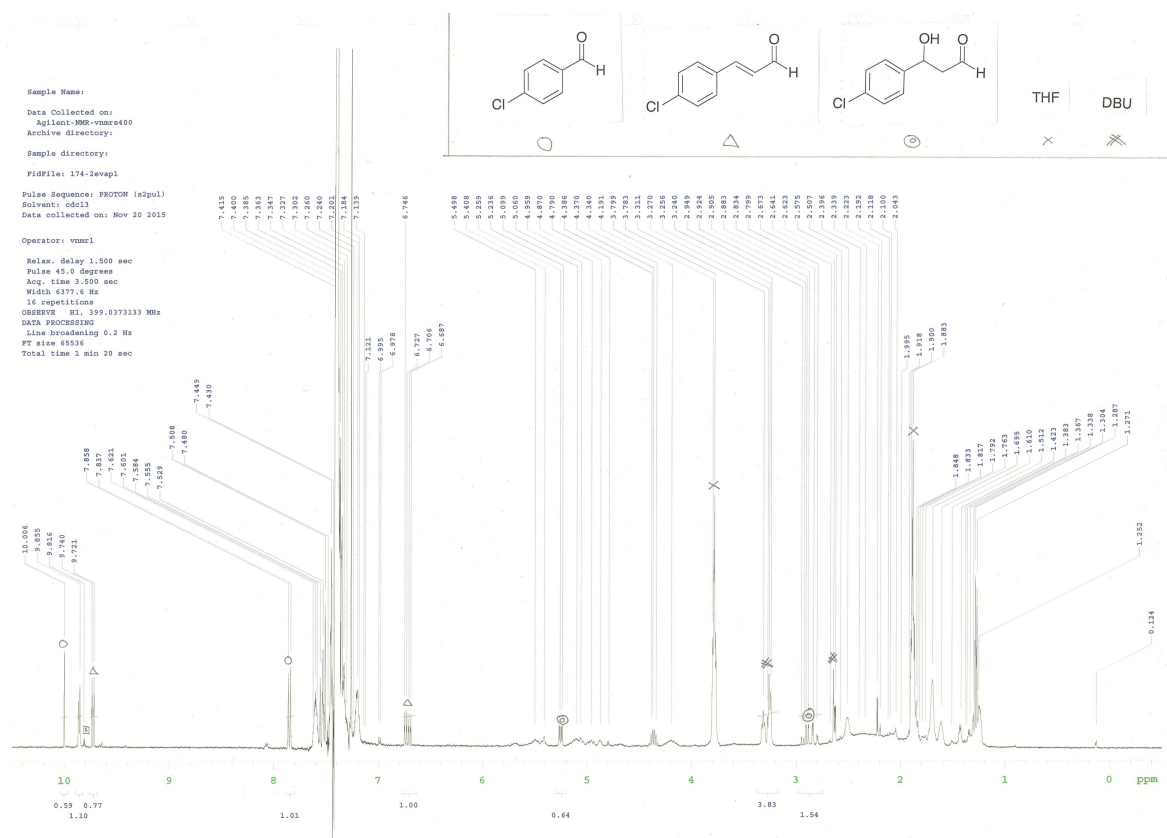


Figure 3

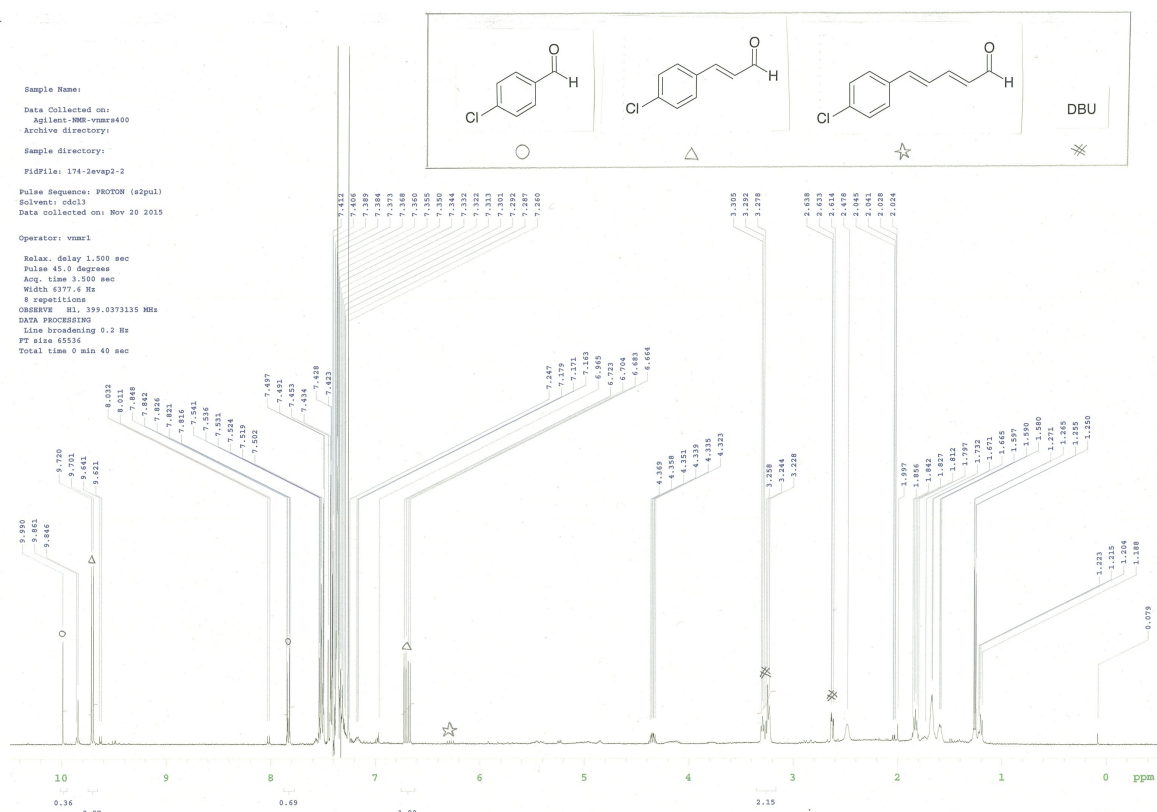
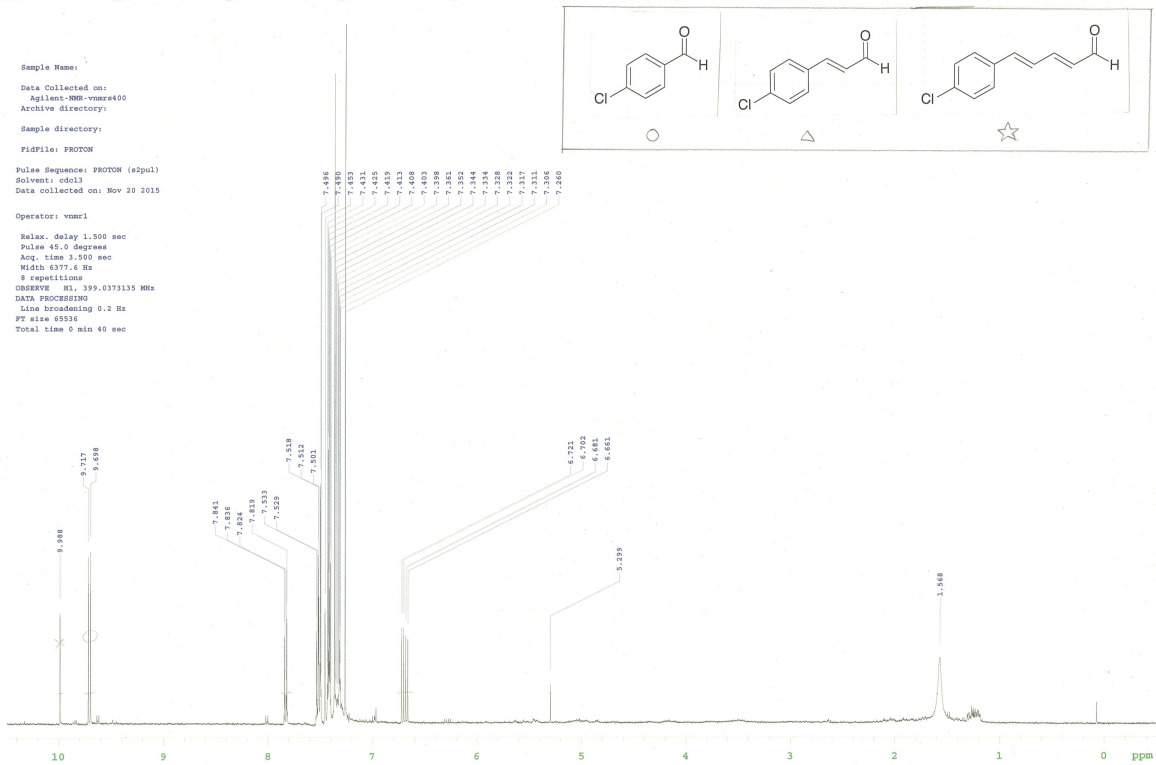
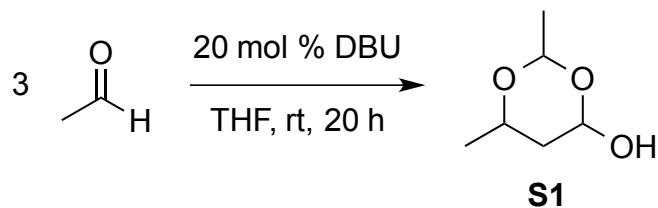


Figure 4



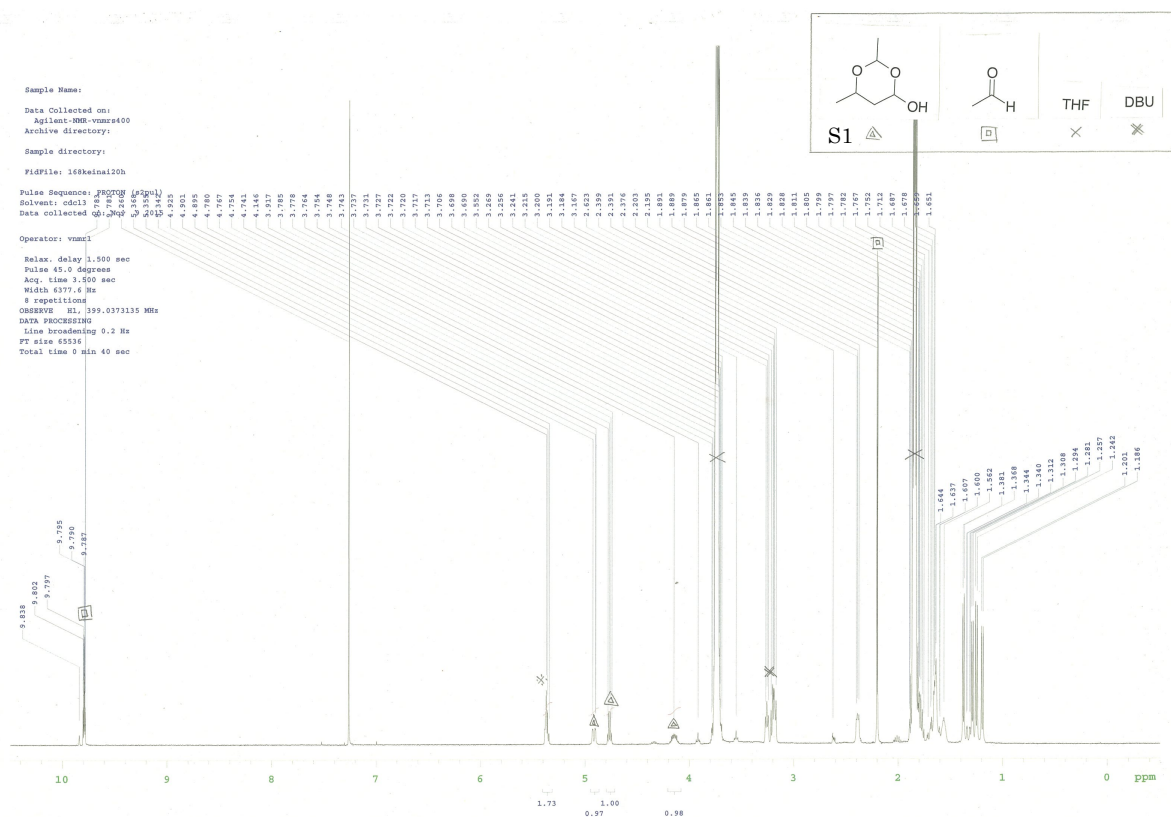
As a side product in the aldol reaction, self aldol product of acetaldehyde would be generated.[SR1]



In order to assign the ^1H -NMR of the acetal **S1**, we carried out the following experiment and obtained the ^1H -NMR of the mixture (Figure 5).

Figure 5

A THF solution (0.5 mL) of DBU (0.1 mmol) in a one-neck flask (10 mL) was added freshly distilled acetaldehyde (2.5 mmol) and a stirring bar under an argon atmosphere. After stirring the reaction mixture for 20 h at room temperature, the reaction was monitored by ^1H -NMR by taking a small portion of a reaction mixture.



All α,β -unsaturated aldehydes in Table 1 are known compounds and physical data are in good agreement of that in the literatures.

- Table 1, entry 1 : 3-(4-nitrophenyl)-2-Propenal (0.5 mmol scale, 82% yield, 72.6 mg)
CAS Registry Number 1734-79-8

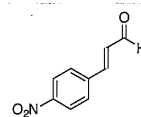
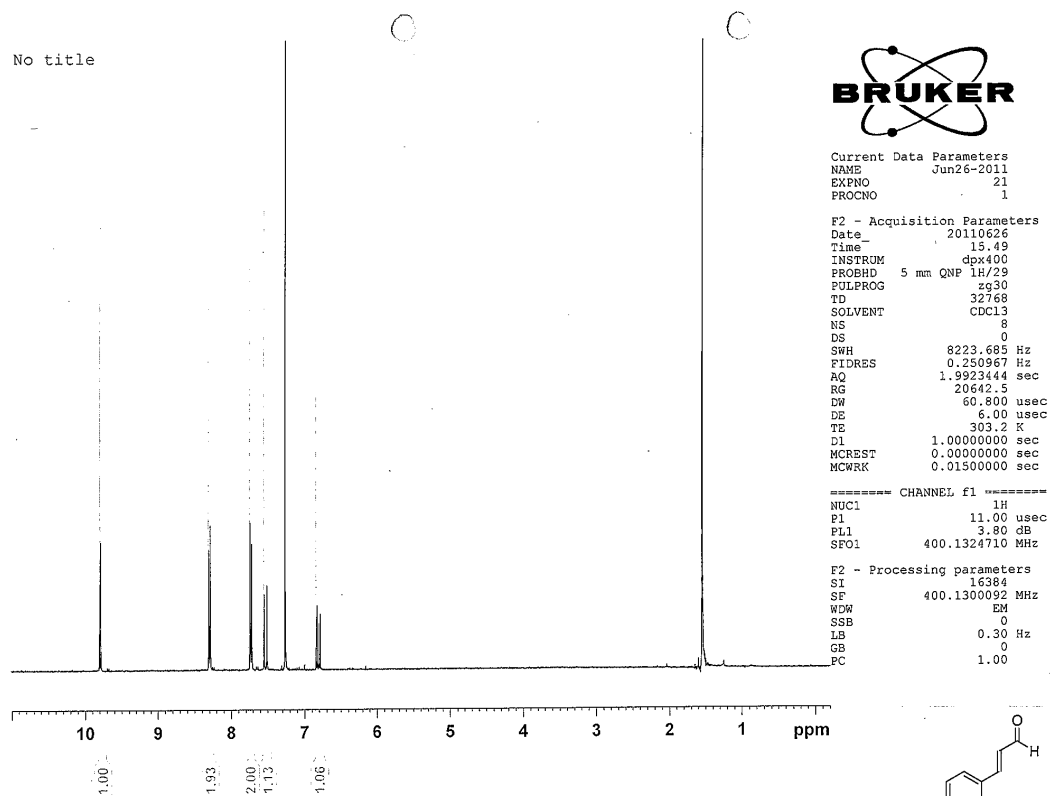
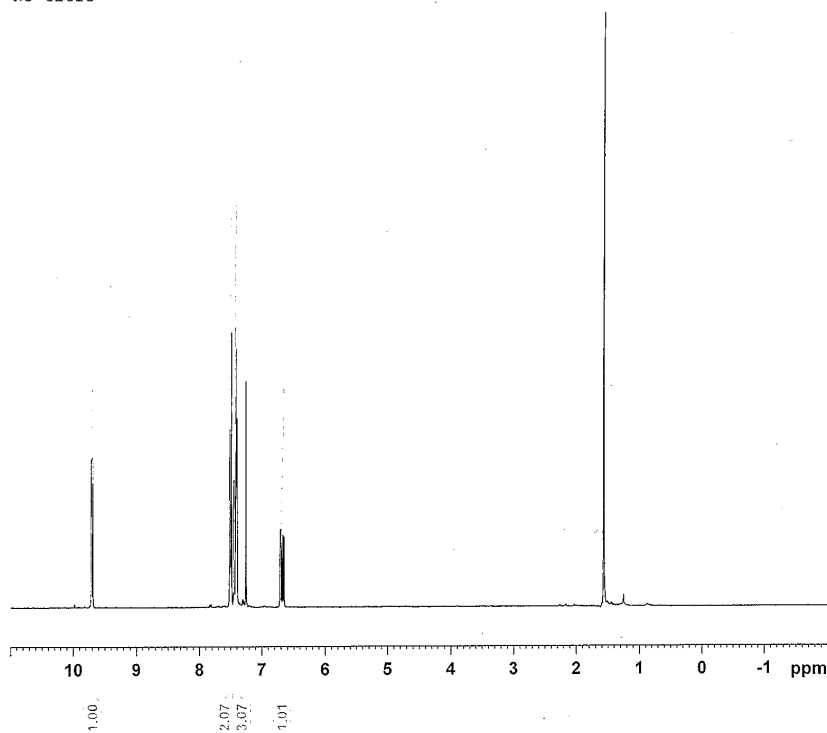


Table 1, entry 1

• Table 1, entry 2 : 3-(4-chlorophenyl)-2-Propenal (0.5 mmol scale, 76% yield, 63.3 mg)
CAS Registry Number 1075-77-0

No title



Current Data Parameters
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EXPNO 51
PROCNO 1

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Time 14.02
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PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 8
DS 2
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 16384
DW 60.400 usec
DE 6.00 usec
TE 303.2 K
D1 1.0000000 sec
MCREST 0.0000000 sec
MCWRK 0.01500000 sec

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PL1 3.80 dB
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F2 - Processing parameters
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GB 0
PC 1.00

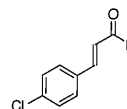


Table 1, entry 2

• Table 1, entry 3 : 3-(4-bromophenyl)-2-Propenal (0.5 mmol scale, 70% yield, 73.9 mg)
CAS Registry Number 3893-18-3

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Archive directory:
Sample directory:
FIDFile: PROTON
Pulse Sequence: PROTON (zgpg3)
Solvent: cdcl3
Data collected on: Nov 13 2015
Operator: vnmr1
Relax. delay 1.500 sec
Pulse 45.0 degrees
Acq. time 3.500 sec
Width 6377.6 Hz
8 repetitions
OBSERVE H1, 399.0373135 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min 40 sec

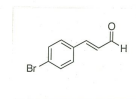
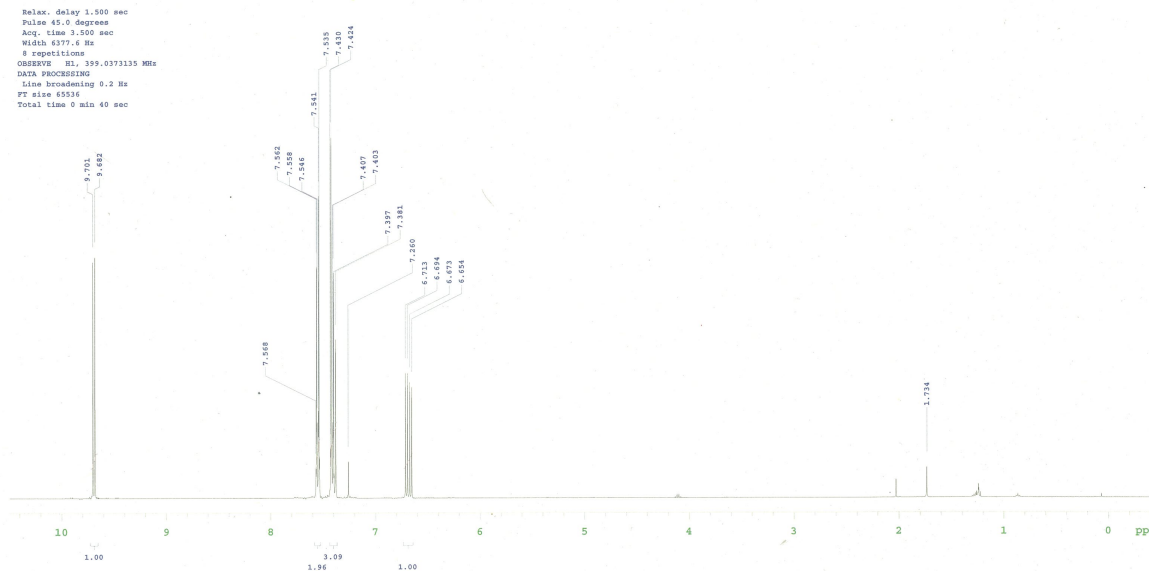


Table 1, entry 3



Sample Name:
Data Collected on:
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Archive directory:
Sample directory:
FIDFile: p-bromocinnamaldehyde-carbon
Pulse Sequence: CARBON (zgpg3)
Solvent: cdcl3
Data collected on: Nov 13 2015
Operator: vnmr1
Relax. delay 1.689 sec
Pulse 45.0 degrees
Acq. time 1.111 sec
Width 25500.0 Hz
64 repetitions
OBSERVE C13, 100.3380187 MHz
DECOUPLE H1, 399.0393159 MHz
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DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 3 min 12 sec

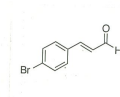
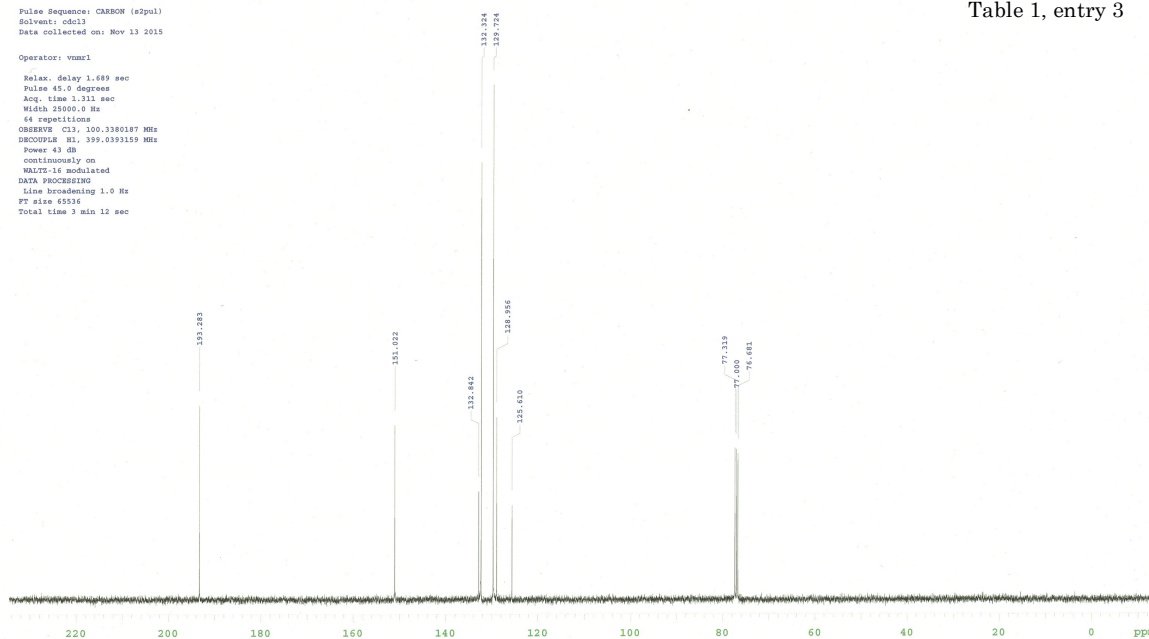
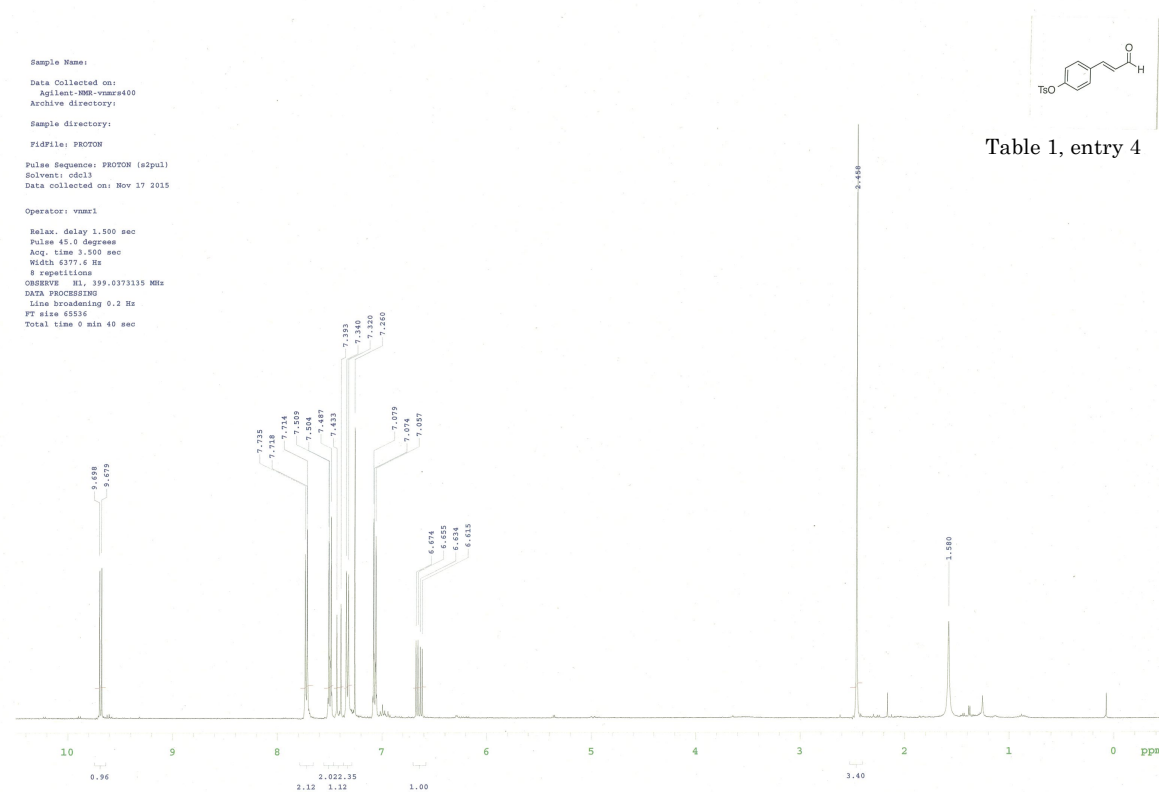
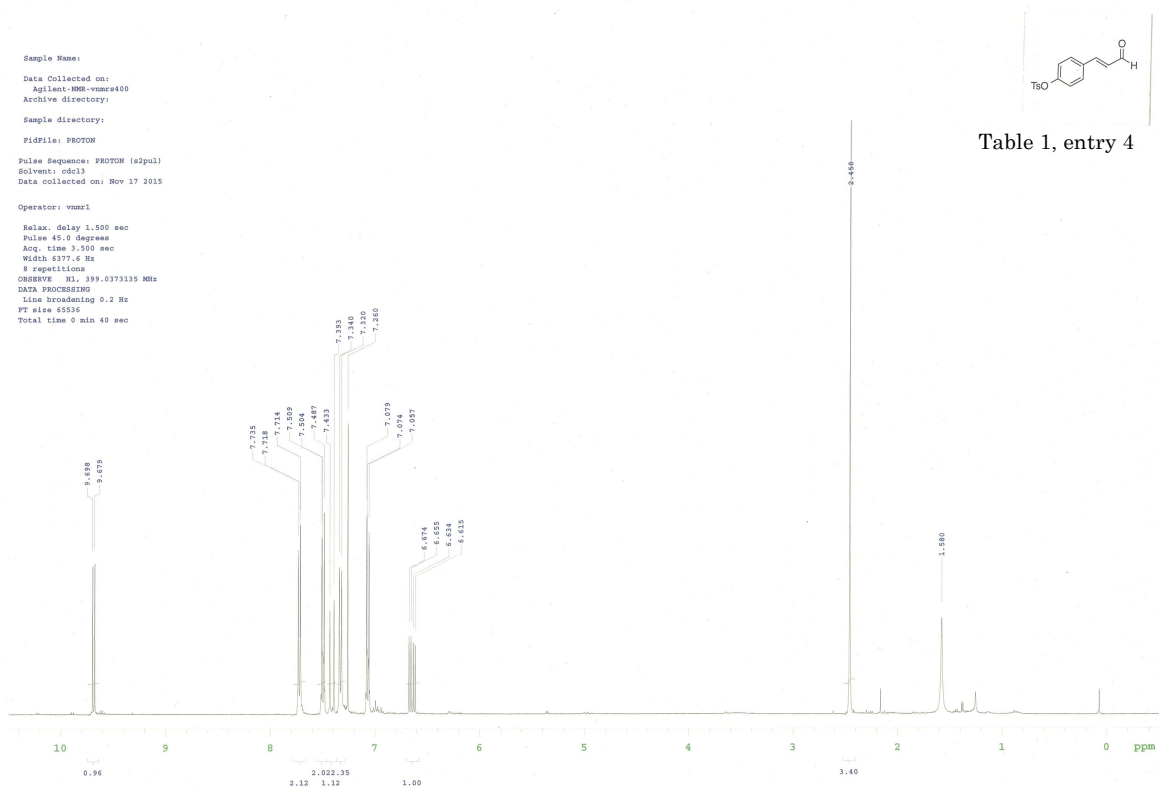


Table 1, entry 3



• Table 1, entry 4 : (2E)-3-[4-[[[(4-methylphenyl)sulfonyl]oxy]phenyl]-2-Propenal
(0.5 mmol scale, 62% yield, 93.7 mg)
CAS Registry Number 1171118-72-1



• Table 1, entry 5 : 3-[4-(trifluoromethyl)phenyl]-2-Propenal
 (0.5 mmol scale, 65% yield, 65.1 mg)
 CAS Registry Number 41917-83-3

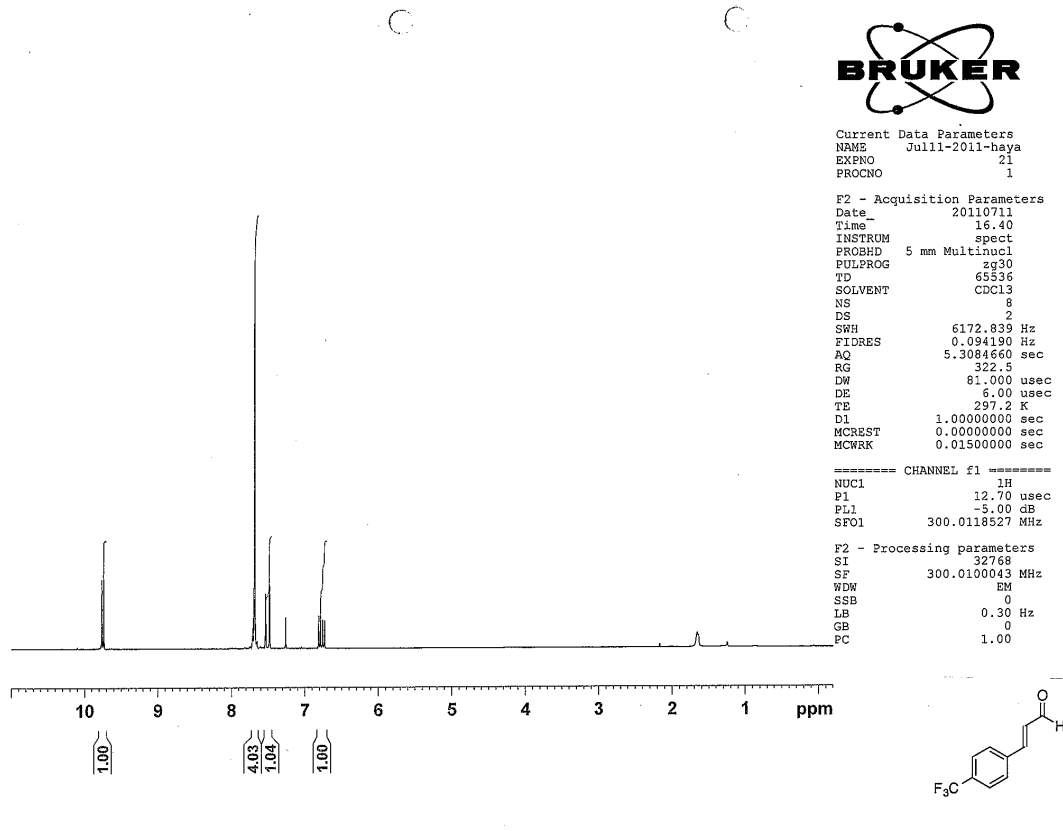


Table 1, entry 5

• Table 1, entry 6 : 4-(3-oxo-1-propen-1-yl)-Benzoic acid methyl ester
 (0.5 mmol scale, 74% yield, 70.4 mg)
 CAS Registry Number 73166-52-6

No title



```

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NAME          Jul17-2011
EXPNO         11
PROCNO        1

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Time_         11.25
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TD            32768
SOLVENT       CDCl3
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DS            0
SWH           8223.685 Hz
FIDRES        0.250967 Hz
AQ            1.9923444 sec
RG            5792.6
DW            60.800 usec
DE            6.00 usec
TE            303.2 K
D1            1.00000000 sec
MCREST        0.00000000 sec
MCWRK         0.01500000 sec

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PL1           3.80 dB
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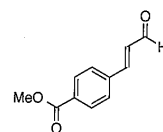
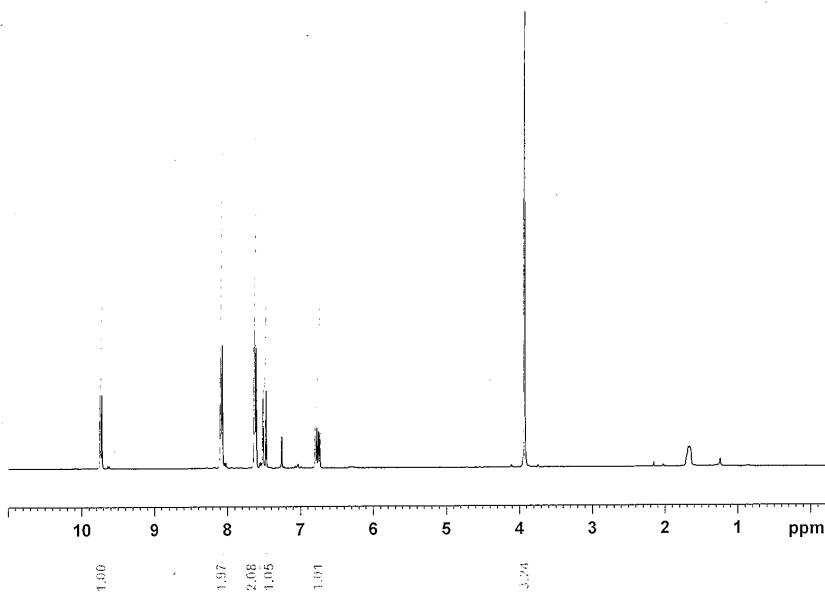


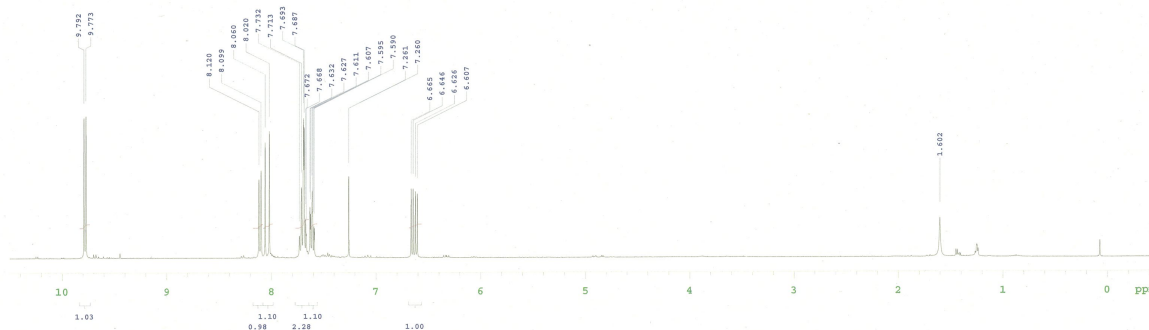
Table 1, entry 6

• Table 1, entry 7 : 3-(2-nitrophenyl)-2-Propenal (0.5 mmol scale, 71% yield, 62.9 mg)
CAS Registry Number 1466-88-2

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Archive directory:
Sample directory:
FidFile: PROTON
Pulse Sequence: PROTON (zgpg3)
Solvent: cdcl3
Data collected on: Nov 17 2015
Operator: vnmr1
Relax. delay 1.500 sec
Pulse 45.0 degrees
Acq. time 3.500 sec
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Line broadening 0.2 Hz
FT size 65536
Total time 0 min 40 sec



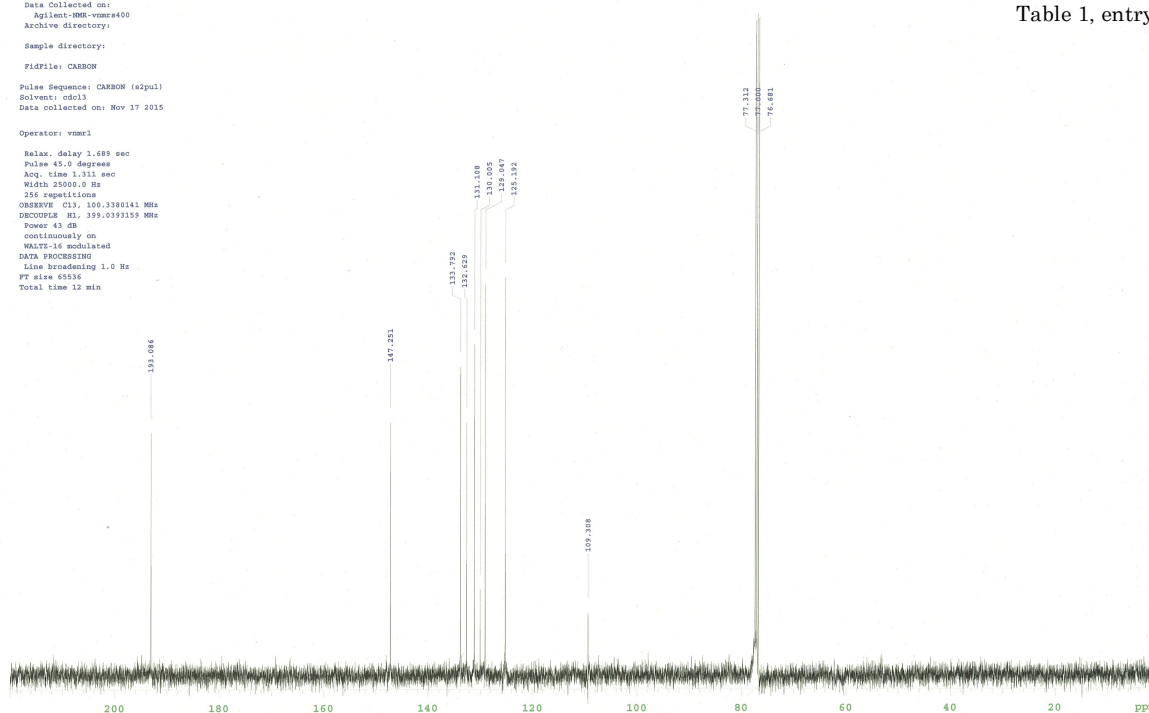
Table 1, entry 7



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Data Collected on:
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Archive directory:
Sample directory:
FidFile: CARBON
Pulse Sequence: CARBON (zgpg3)
Solvent: cdcl3
Data collected on: Nov 17 2015
Operator: vnmr1
Relax. delay 1.689 sec
Pulse 45.0 degrees
Acq. time 1.311 sec
Width 25000.0 Hz
256 repetitions
OBSERVE C13 100.3380141 MHz
DECOUPLE H1 399.9393159 MHz
Power 43 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 12 min



Table 1, entry 7



• Table 1, entry 8 : 3-(2-bromophenyl)-2-Propenal (0.5 mmol scale, 76% yield, 80.2 mg)
CAS Registry Number 66223-53-8

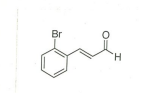


Table 1, entry 8

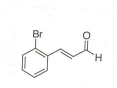
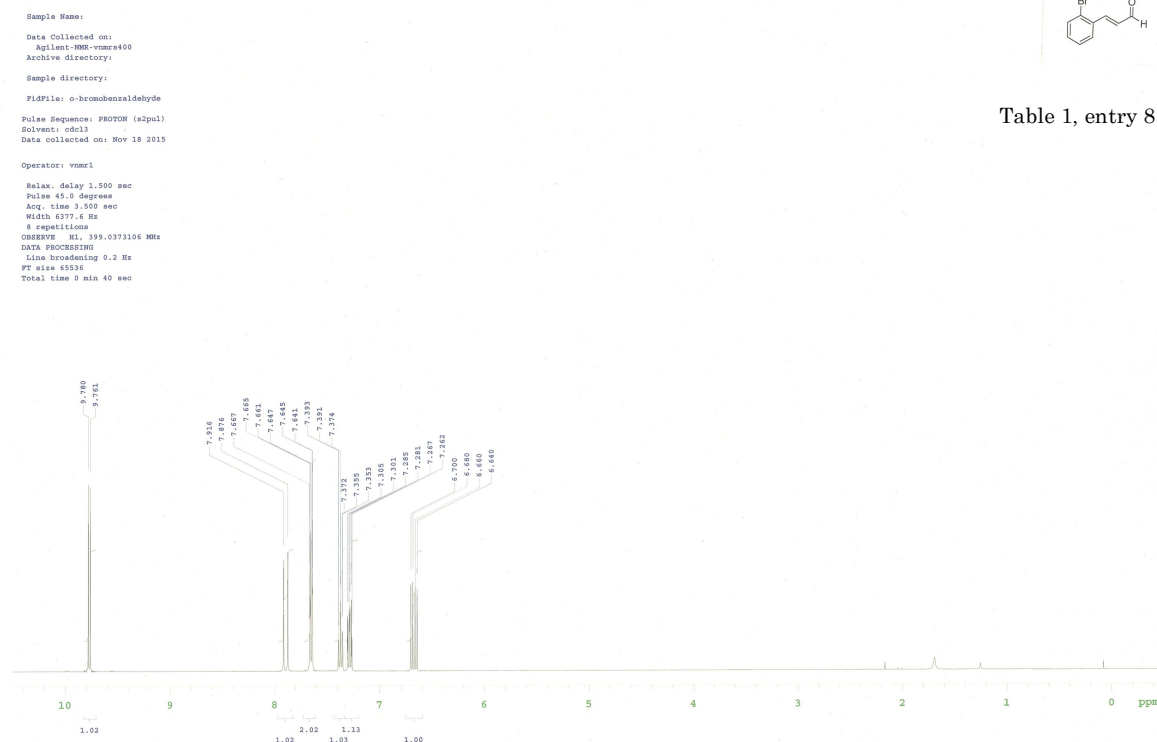
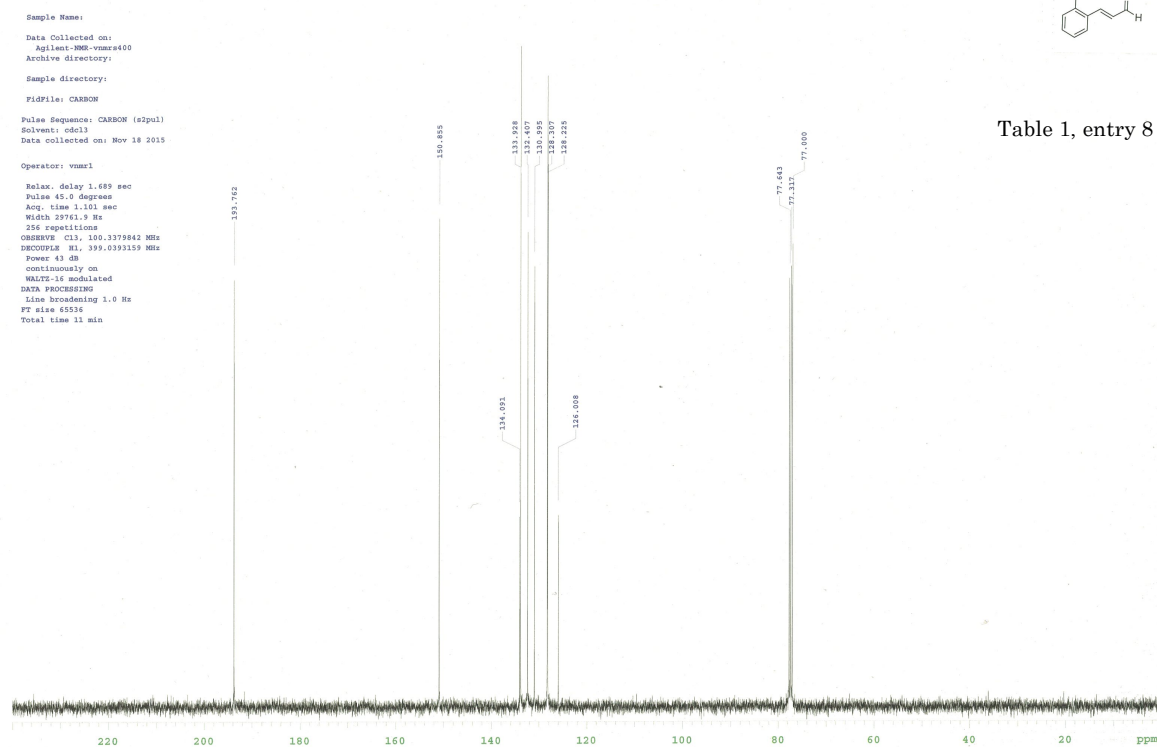


Table 1, entry 8



• Table 1, entry 9 : 3-(2,6-dichlorophenyl)-2-Propenal
(0.5 mmol scale, 80% yield, 80.4 mg)
CAS Registry Number 194026-34-1

No title



Current Data Parameters
NAME Jun25-2011
EXPNO 52
PROCNO 1

F2 - Acquisition Parameters
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Time 17.52
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TD 32768
SOLVENT CDCl3
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DS 0
SWH 8223.685 Hz
FIDRES 0.250967 Hz
AQ 1.9923444 sec
RG 14596.5
DW 60.800 usec
DE 6.00 usec
TE 303.2 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

===== CHANNEL f1 =====
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P1 11.00 usec
PL1 3.80 dB
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F2 - Processing parameters
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PC 1.00

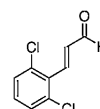
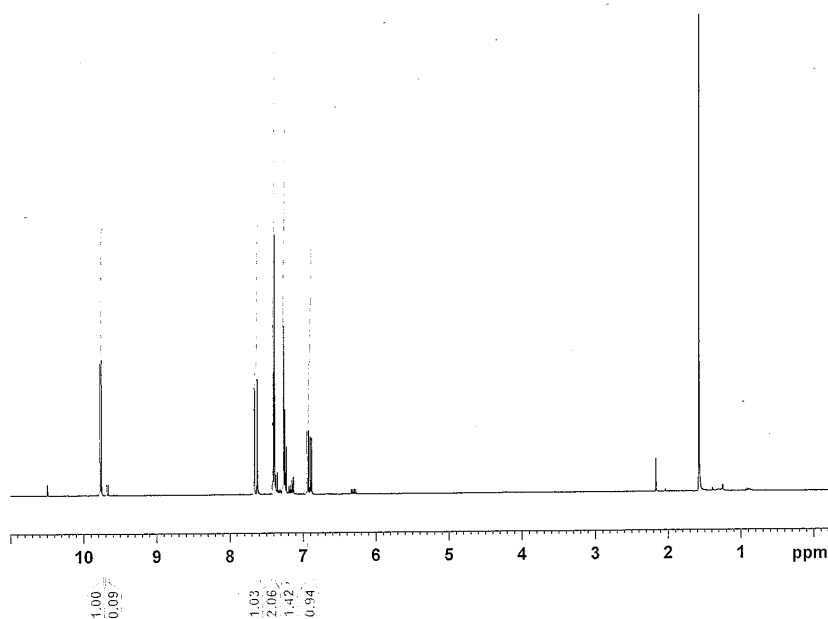


Table 1, entry 9

• Table 1, entry 10 : 3-(4-pyridinyl)-2-Propenal (0.5 mmol scale, 60% yield, 39.9 mg)
CAS Registry Number 26505-36-2

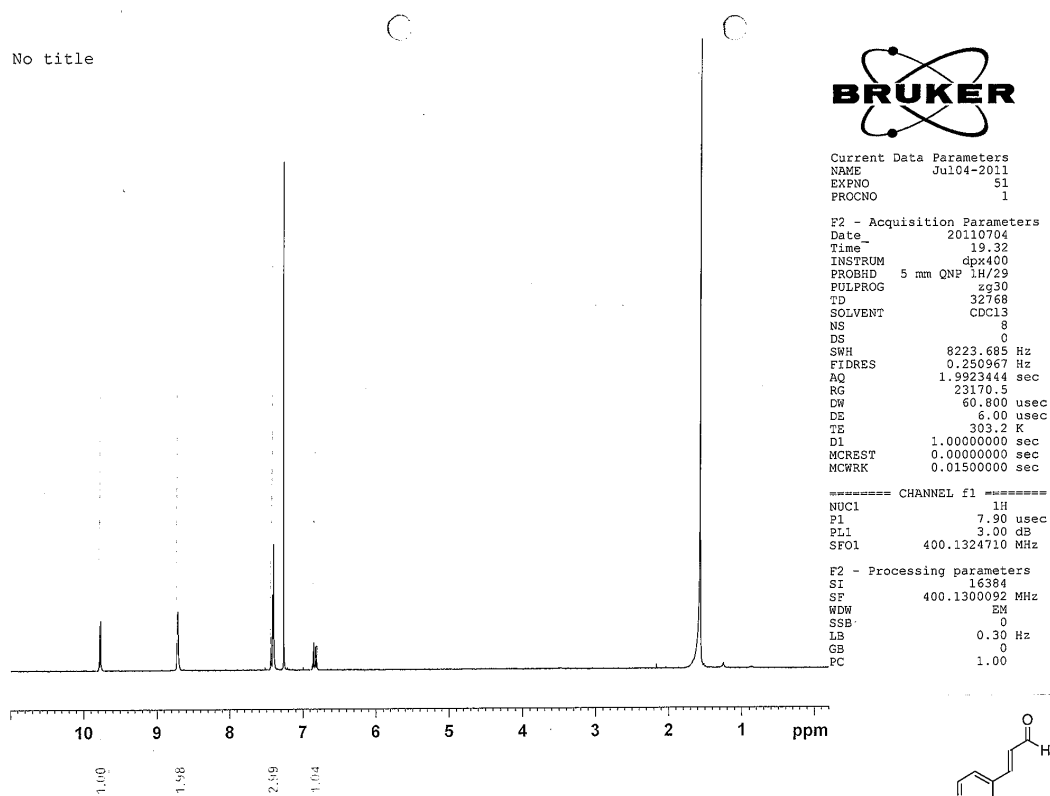


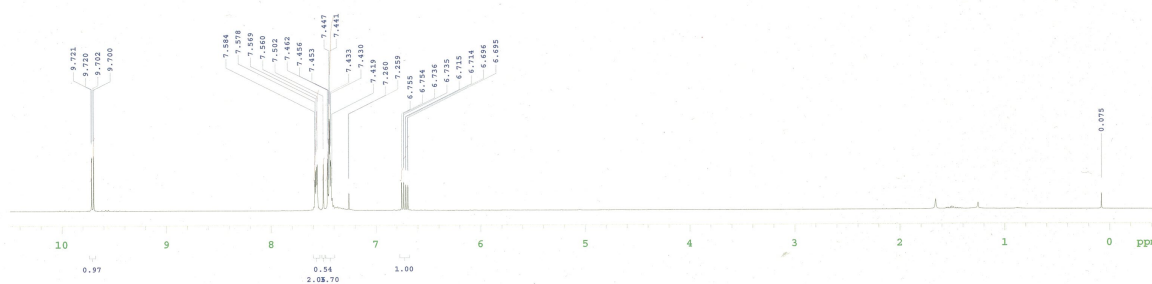
Table 1, entry 10

• Table 1, entry 11 : 3-phenyl-2-Propenal (0.5 mmol scale, 63% yield, 41.6 mg)
CAS Registry Number 104-55-2

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Sample directory:
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Solvent: cdcl3
Data collected on: Nov 16 2015
Operator: vnmr1
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Pulse 45.0 degrees
Acq. time 3.500 sec
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DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 2 min 40 sec



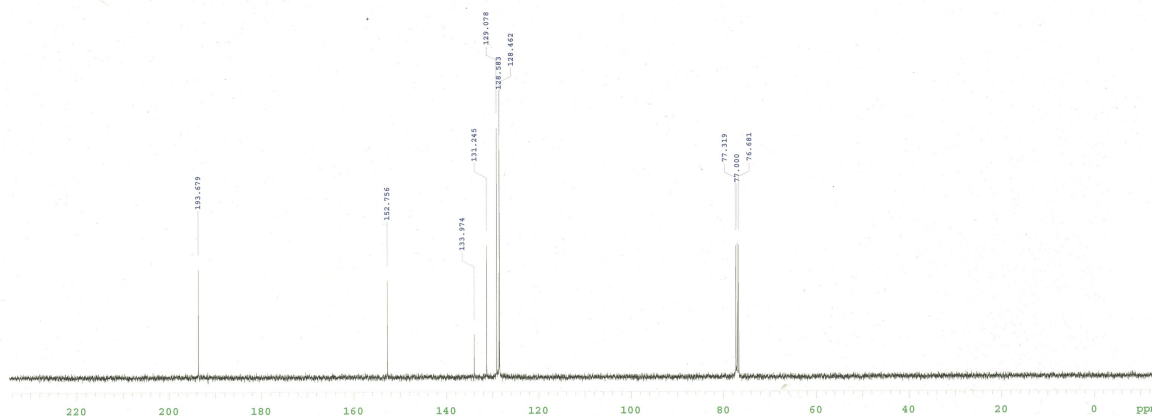
Table 1, entry 11



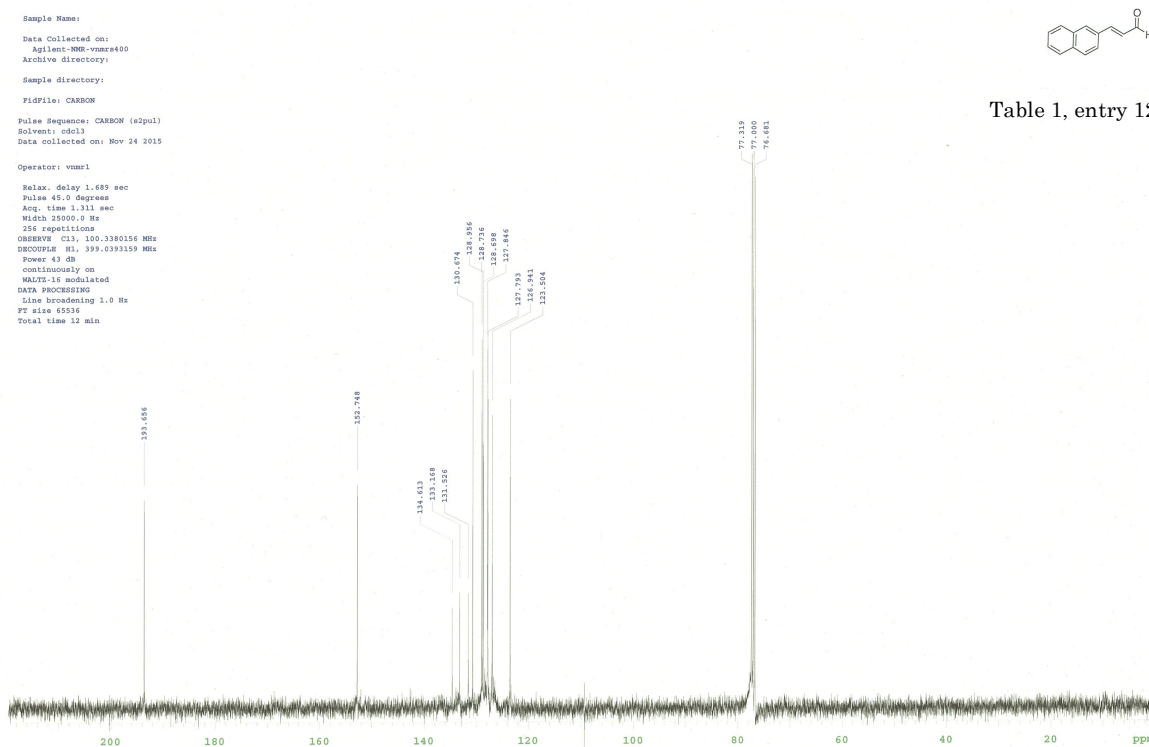
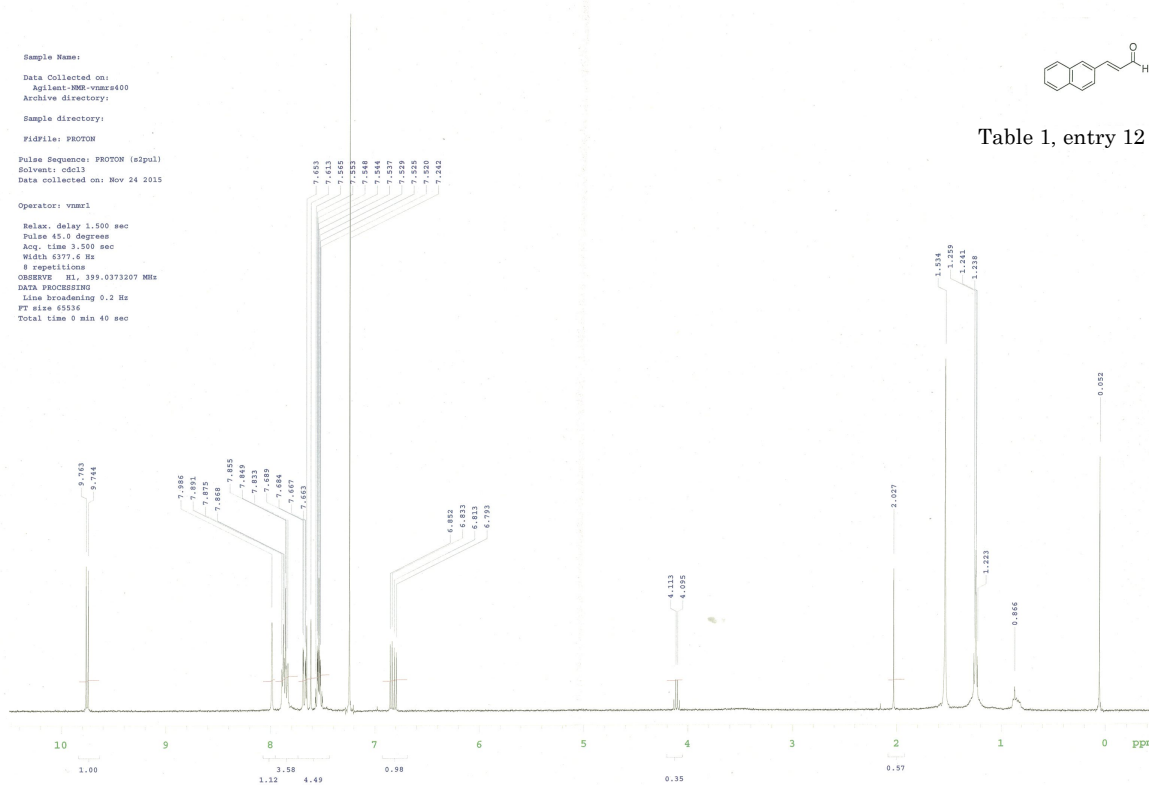
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Archive directory:
Sample directory:
FidFile: CARBON
Pulse Sequence: CARBON (zgpg30)
Solvent: cdcl3
Data collected on: Nov 16 2015
Operator: vnmr1
Relax. delay 1.689 sec
Pulse 45.0 degrees
Acq. time 1.311 sec
Width 25000.0 Hz
128 repetitions
OBSERVE C13, 100.3380156 MHz
DECOUPLE H1, 399.0393159 MHz
Power 43 dB
continuously on
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DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 4 min 34 sec



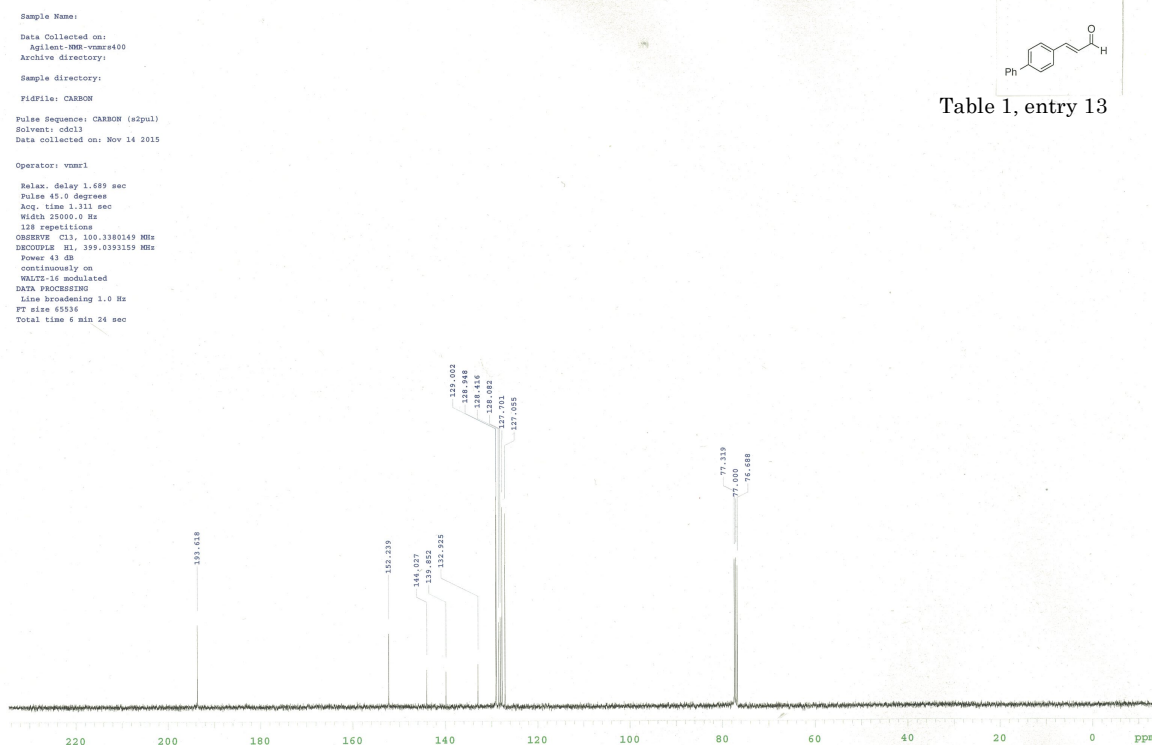
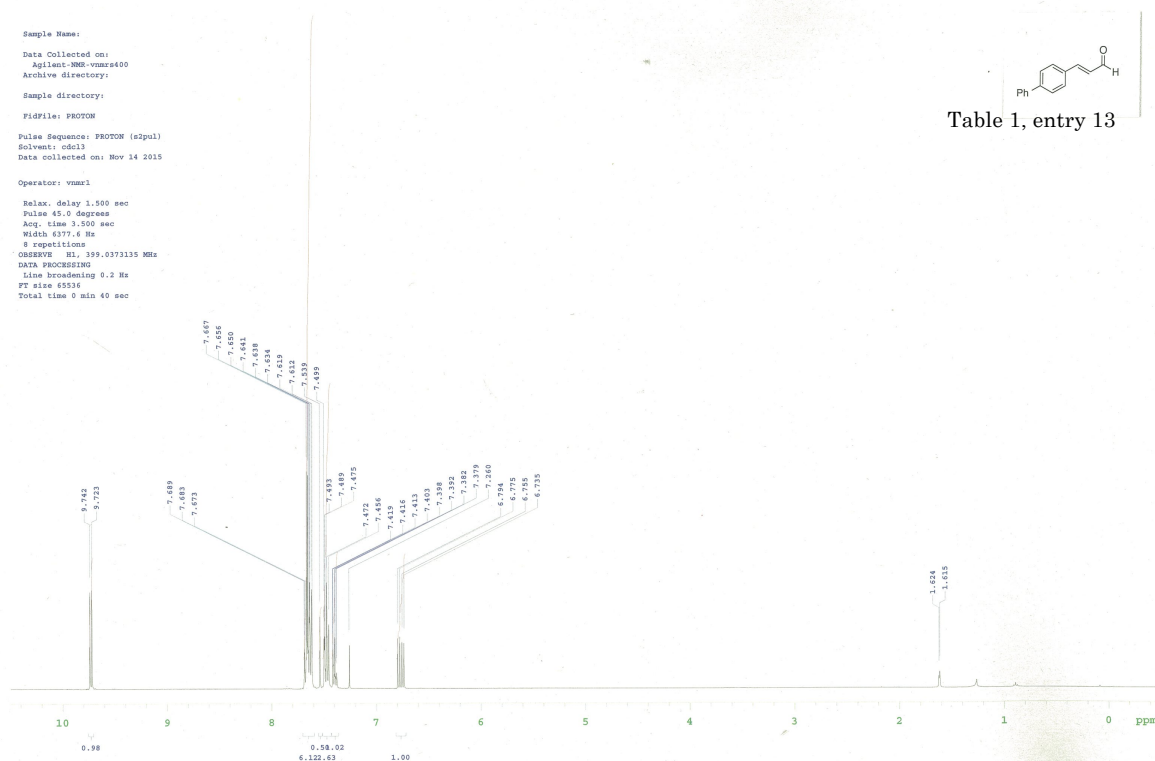
Table 1, entry 11



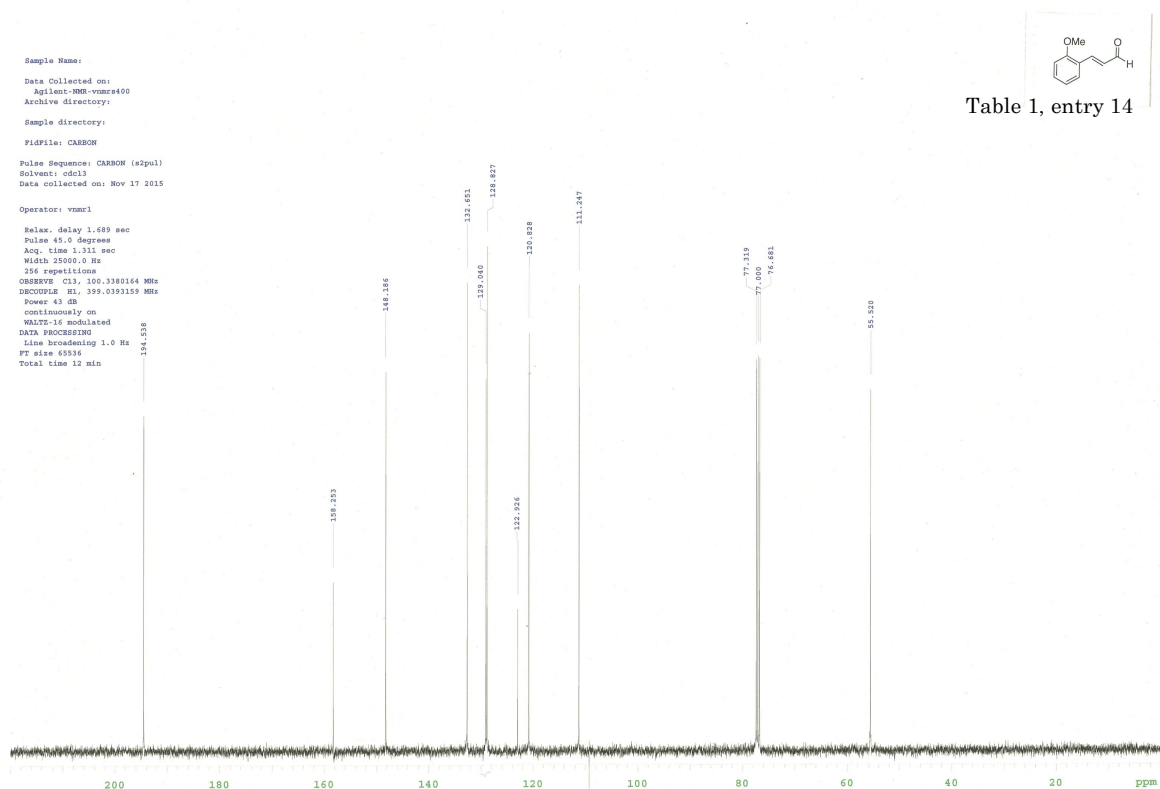
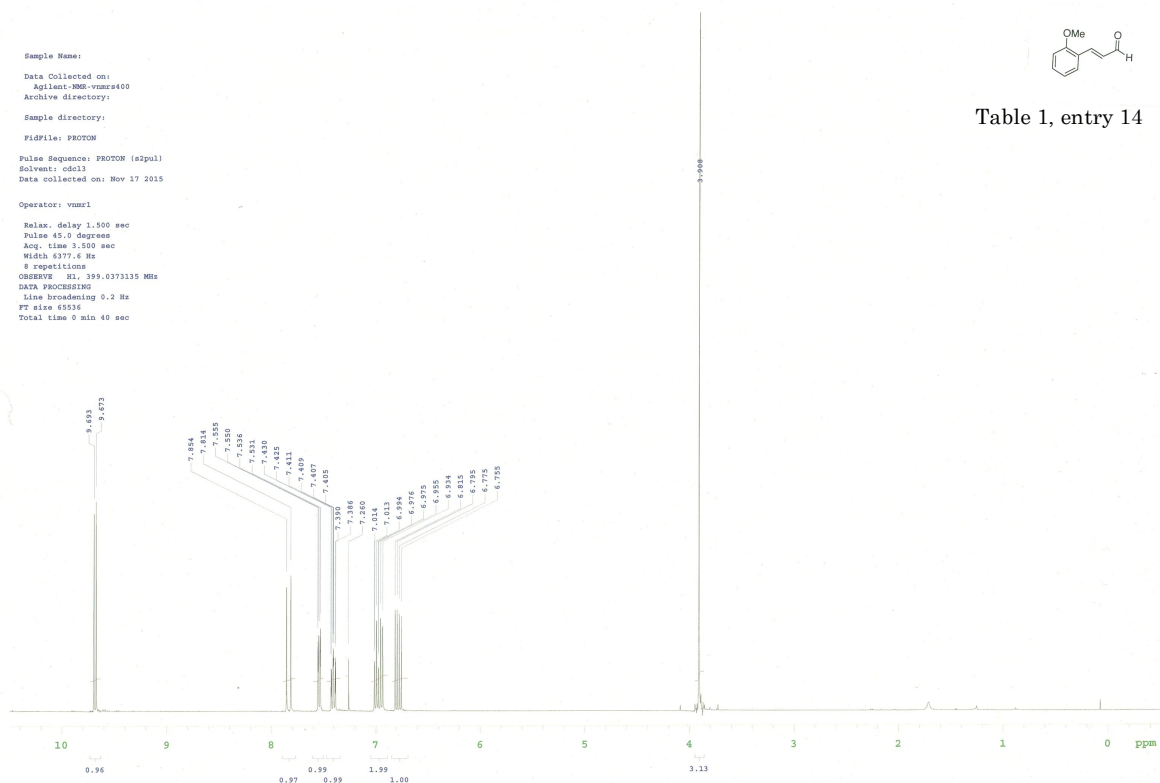
• Table 1, entry 12 : 3-(2-naphthalenyl)-2-Propenal (0.5 mmol scale, 75% yield, 68.3 mg)
CAS Registry Number 20884-05-3



• Table 1, entry 13 : 3-[1,1'-biphenyl]-4-yl-2-Propenal
(0.5 mmol scale, 53% yield, 55.2 mg)
CAS Registry Number 39703-89-4



• Table 1, entry 14 : 3-(2-methoxyphenyl)-2-Propenal
 (0.5 mmol scale, 53% yield, 43.0 mg)
 CAS Registry Number 1504-74-1



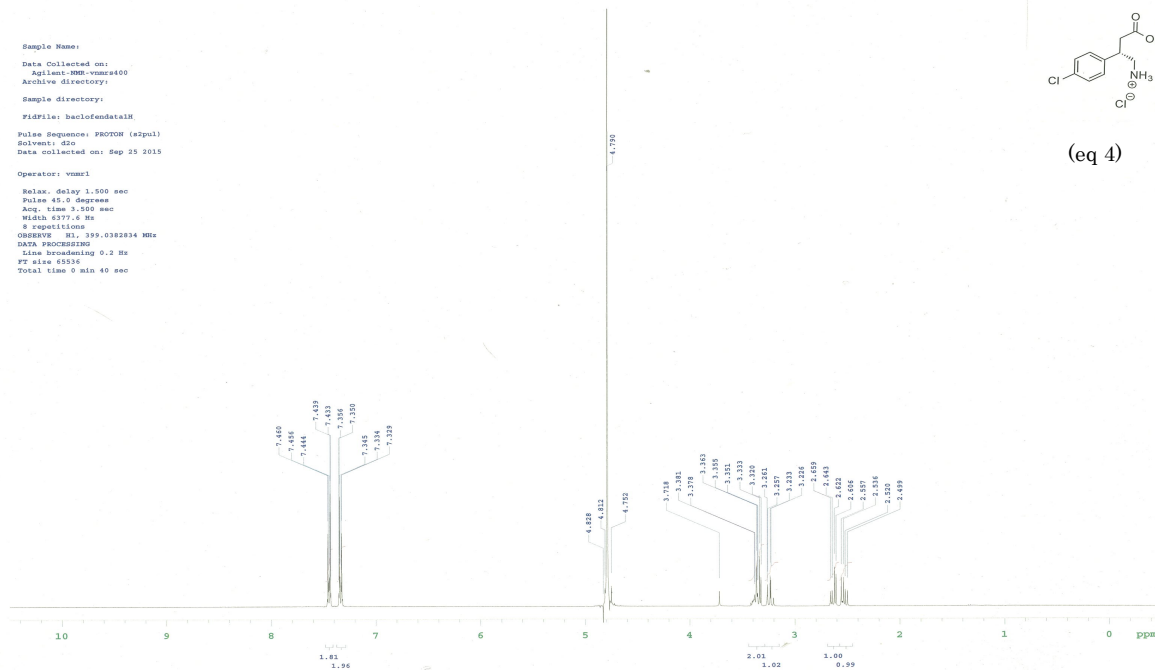
One-pot synthesis of (*S*)-baclofen

A THF solution (21.3 mL) of *p*-chlorobenzaldehyde (21.3 mmol) and DBU (4.3 mmol, 20 mol%) in a one-necked flask (50 mL) was added freshly distilled acetaldehyde (106.7 mmol, 5 equiv.) and a stirring bar under an argon atmosphere. The reaction flask was closed with a greased glass cap to prevent a leak of volatile acetaldehyde. The progress of the reaction can be monitored by ^1H -NMR by taking a small portion of a reaction mixture. After stirring the reaction mixture for 2 days at room temperature, excess acetaldehyde was removed under reduced pressure (350 mmHg) at 25 °C for 1~3 h to check the disappearance of acetaldehyde by ^1H -NMR. To promote the retro-acetalization with removal of the generated acetaldehyde, the reaction mixture was heated at 50 °C under reduced pressure (400 mmHg) for 2~3 h to check ^1H -NMR of the progress of this reaction. Volume of the reaction mixture is about 20 mL. After addition of nitromethane (64.0 mmol), diphenylprolinol trimethyl silyl ether **1** (0.85 mmol, 4 mol%), HCO_2H (8.5 mmol), and H_2O (4.3 mL) to the reaction mixture, which was stirred at room temperature for 2 days. After removal of THF and nitromethane under reduced pressure, addition of a solution (10.7 mL) of NaClO_2 (21.3 mmol), $\text{NaH}_2\text{PO}_4 \cdot 2\text{H}_2\text{O}$ (32.0 mmol), 2-methyl-2-butene (64.9 mmol), and *t*-BuOH (32.0 mL) to a reaction mixture, which was stirred at room temperature for 3 h. After addition of $\text{Na}_2\text{HPO}_3 \cdot 5\text{H}_2\text{O}$ (21.3 mmol) to a reaction mixture to reduce the remaining oxidant, the reaction mixture was stirred at room temperature for 1 h. After addition of MeOH (85.2 mL) and Raney Ni (W-2 form, about 3 g), the reaction was performed under H_2 atmosphere at room temperature for 2 days. After addition of NaOH solution (0.1 N, 21.3 mL), insoluble compounds are removed by filtration. Volatile compounds such as MeOH were removed under reduced pressure, and HCl solution (2N) was added to the reaction mixture until the pH of the solution becomes 2. Neutral organic compounds were removed from the aqueous phase via extraction using AcOEt two times, and baclofen hydrochloric salt stays in the aqueous phase. Water was removed from the aqueous phase under reduced pressure, and purification by silica gel chromatography ($\text{MeOH}/\text{CHCl}_3/\text{H}_2\text{O} = 3/7/1$) gave baclofen hydrochloric salt as white solid (31% yield, 1.6 g).

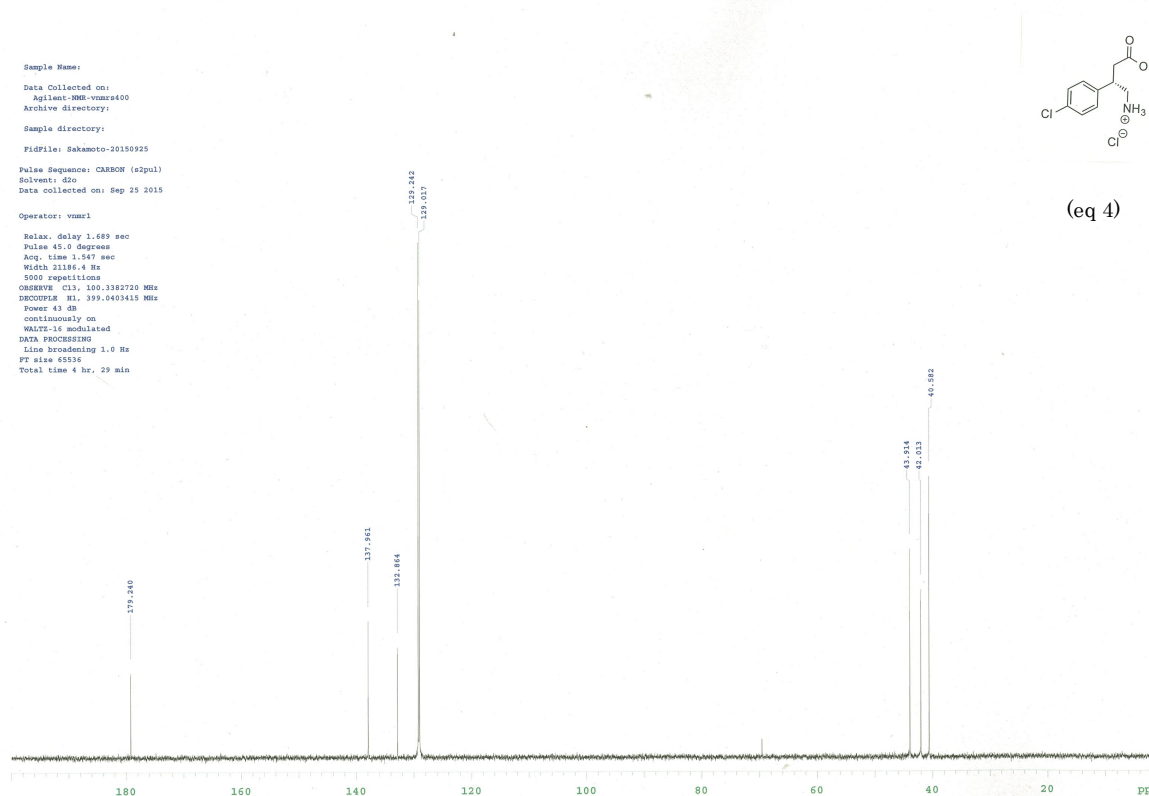
^1H NMR (400 MHz, D_2O) δ 7.47-7.7.42 (m, 2H), 7.36-7.32 (m, 2H), 3.43-3.31 (m, 2H), 3.25 (dd, $J = 13.6, 9.6$ Hz, 1H), 2.63 (dd, $J = 14.8, 6.4$ Hz, 1H), 2.53 (d, $J = 14.8, 8.4$ Hz, 2H); ^{13}C NMR (100 MHz, D_2O) δ 179.2, 138.0, 132.9, 129.2, 129.0, 43.9, 42.0, 40.6; HRMS (ESI): $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{10}\text{H}_{13}\text{O}_2\text{NCl}$: 214.0629, found: 214.0632.

The physical data of (*S*)-baclofen is in good agreement of that in the literature.[SR2]

Sample Name:
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 Sample directory:
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 Solvent: d2o
 Data collected on: Sep 25 2015
 Operator: vnmr1
 Relax. delay 1.500 sec
 Pulse 45.0 degrees
 Acq. time 1.500 sec
 Width 6377.6 Hz
 4 repetitions
 OBSERVE H1, 399.0382834 MHz
 DATA PROCESSING
 Line broadening 0.2 Hz
 FT size 65536
 Total time 0 min 40 sec



Sample Name:
 Data Collected on:
 Agilent-VNM-vnmr400
 Archive directory:
 Sample directory:
 FidFile: Sakamoto-20150925
 Pulse Sequence: CARBON (zgpg3)
 Solvent: d2o
 Data collected on: Sep 25 2015
 Operator: vnmr1
 Relax. delay 1.689 sec
 Pulse 45.0 degrees
 Acq. time 1.547 sec
 Width 21186.4 Hz
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 DECOUPLE H1, 399.0403415 MHz
 Power 43 dB
 continuously on
 WALTZ-16 modulated
 DATA PROCESSING
 Line broadening 1.0 Hz
 FT size 65536
 Total time 4 hr, 29 min



Reference

[SR1] Hayashi, H.; Samanta, S.; Itoh, T.; Ishikawa, H. *Org. Lett.*, **2008**, *10*, 5581.

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