

## 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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### Experimental section

#### Typical procedure for the preparation of $\alpha,\beta$ -unsaturated aldehyde

#### (Table 1 1 entries 1-14)

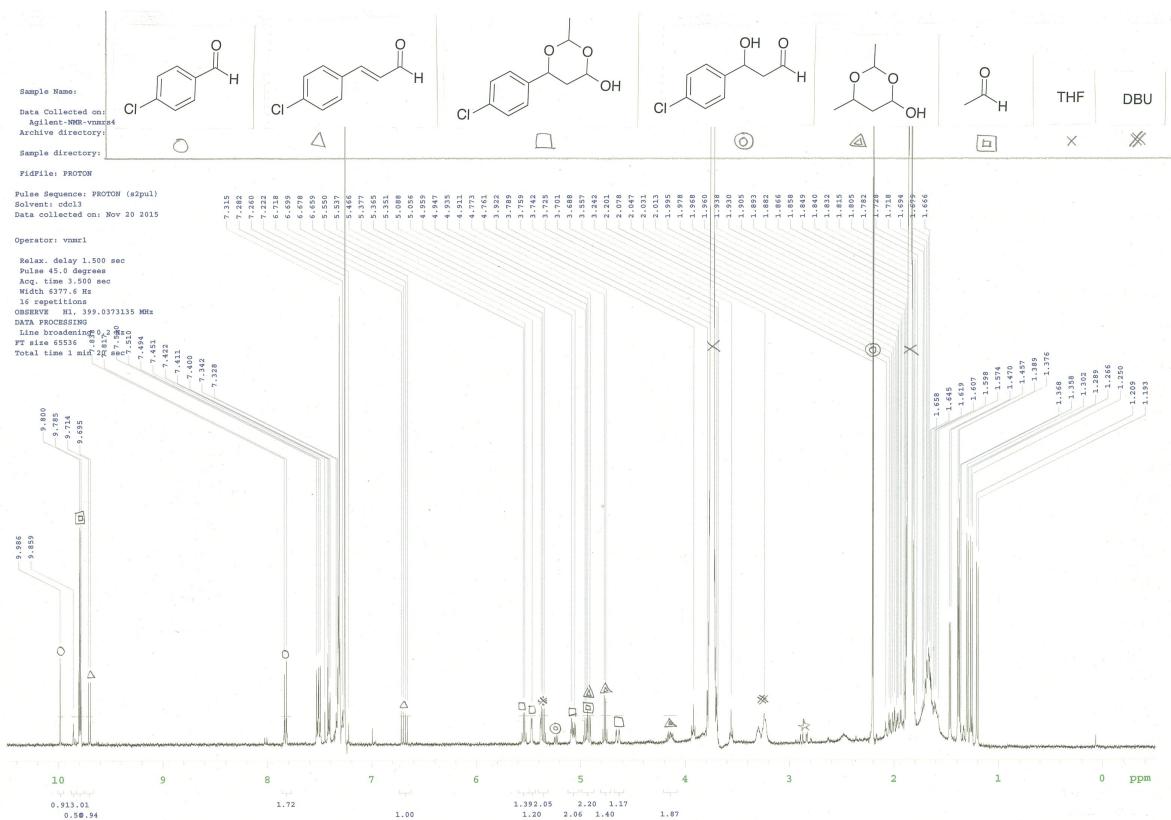
A THF solution (0.5 mL) of aromatic aldehyde (0.5 mmol) and DBU (0.1 mmol) in a one-neck flask (10 mL) was added freshly distilled acetaldehyde (2.5 mmol) and a stirring bar under an argon atmosphere. The reaction flask was closed with a greased glass cap to prevent the leak of the volatile acetaldehyde. 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-chlorobenzaldehyd). 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 ( $^1\text{H-NMR}$  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  $\text{CHCl}_3$  3 times and combined organic phase was dried over  $\text{MgSO}_4$ . After filtration of inorganic materials and removal of volatile organic compounds under reduced pressure ( $^1\text{H-NMR}$  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

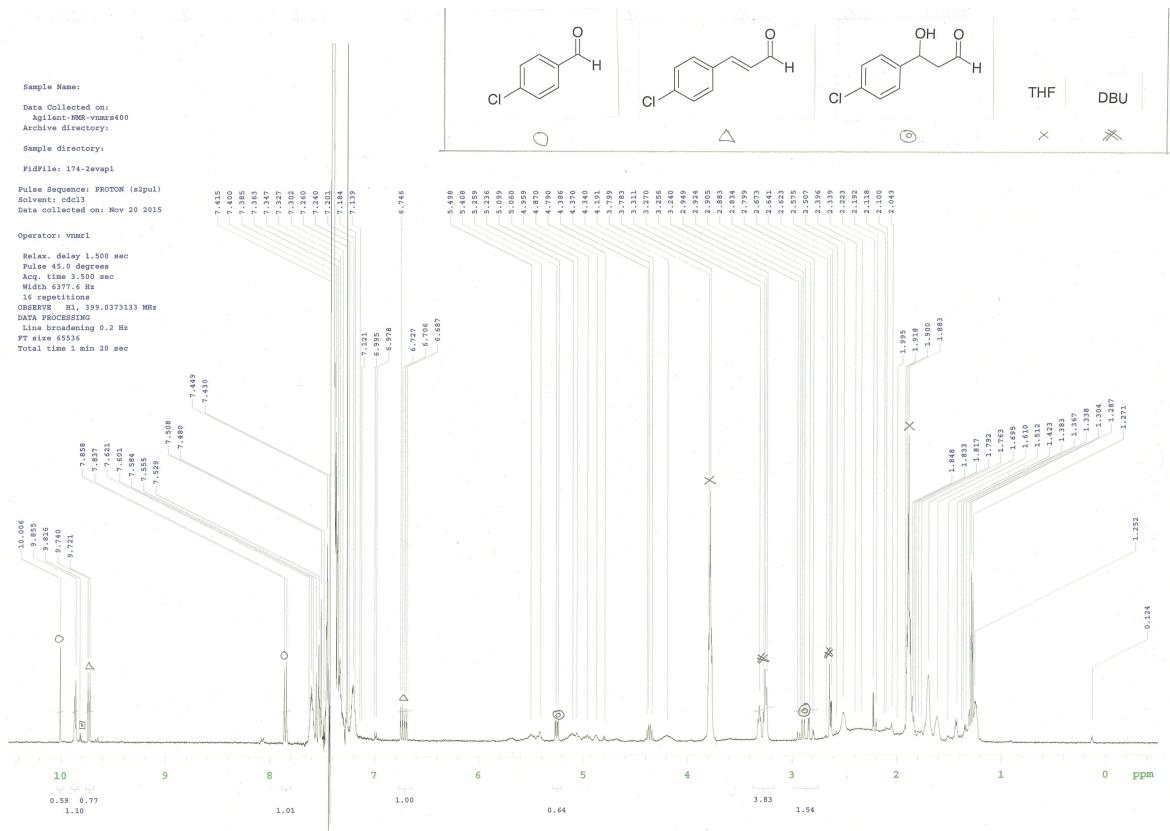


Figure 3

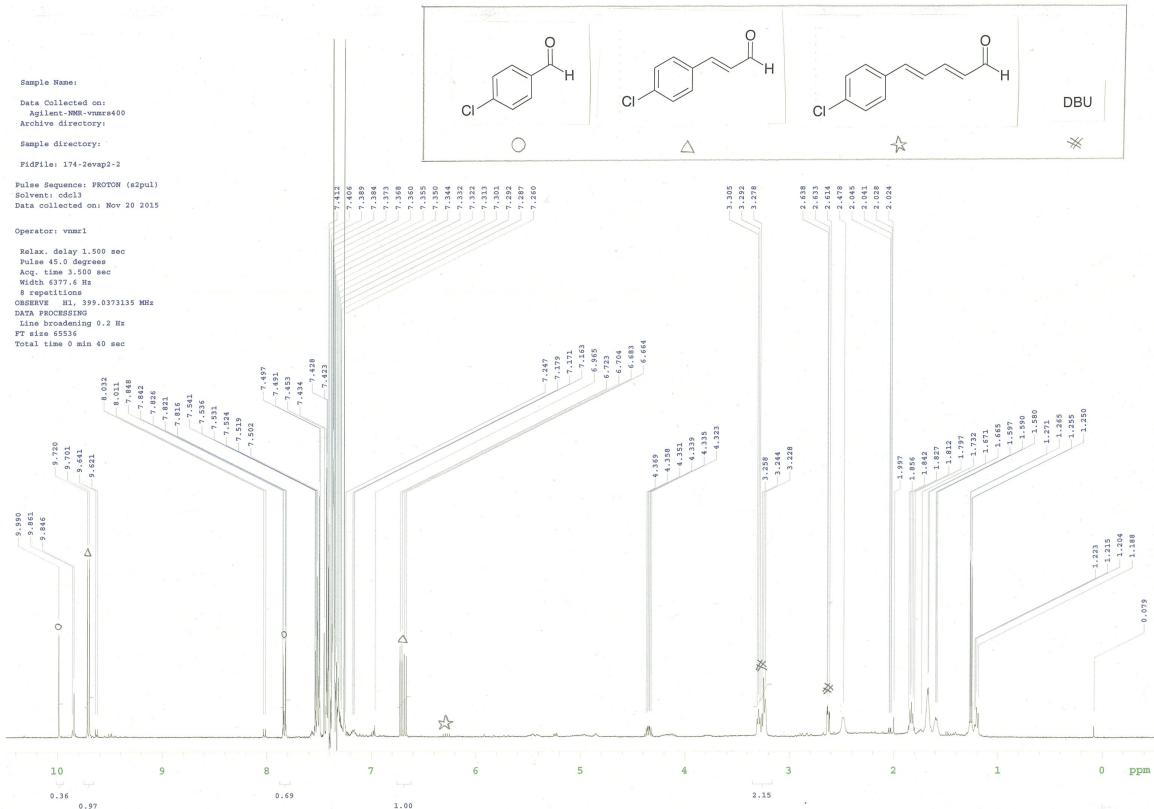
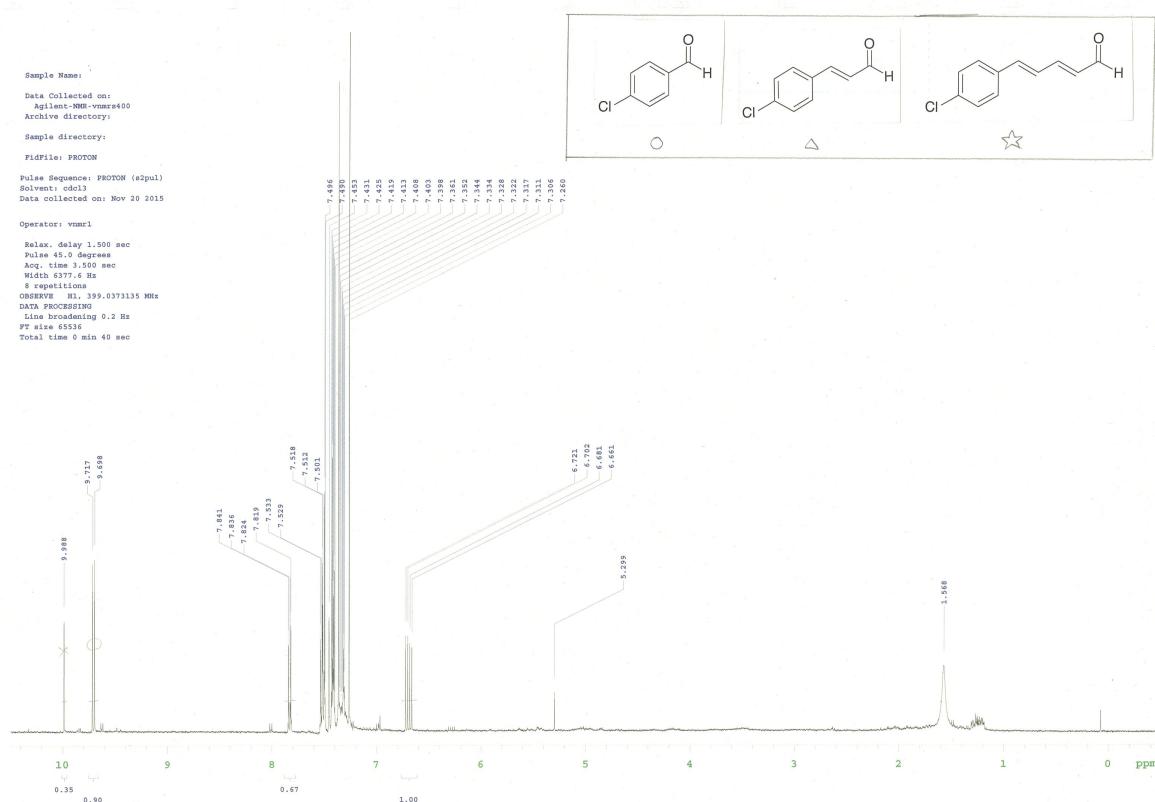


Figure 4



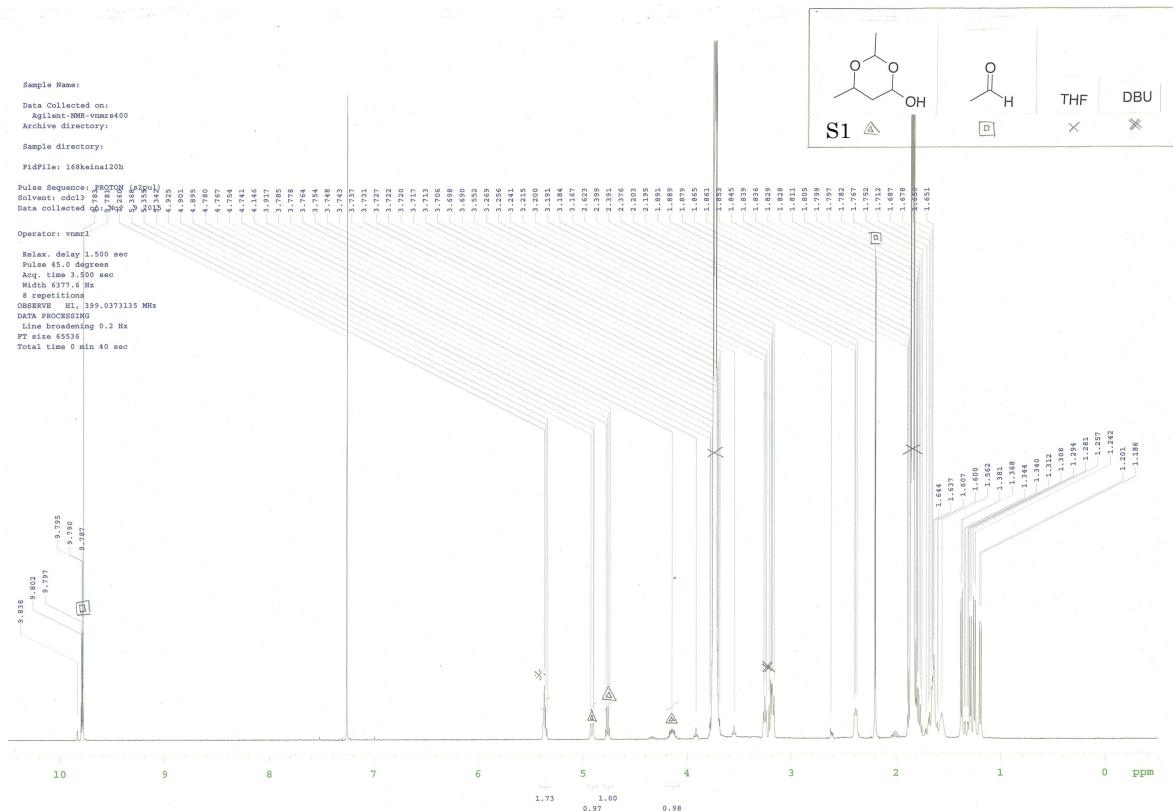
As a side product in the aldol reaction, self aldol product of acetaldehyde would be generated.[SR1]



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

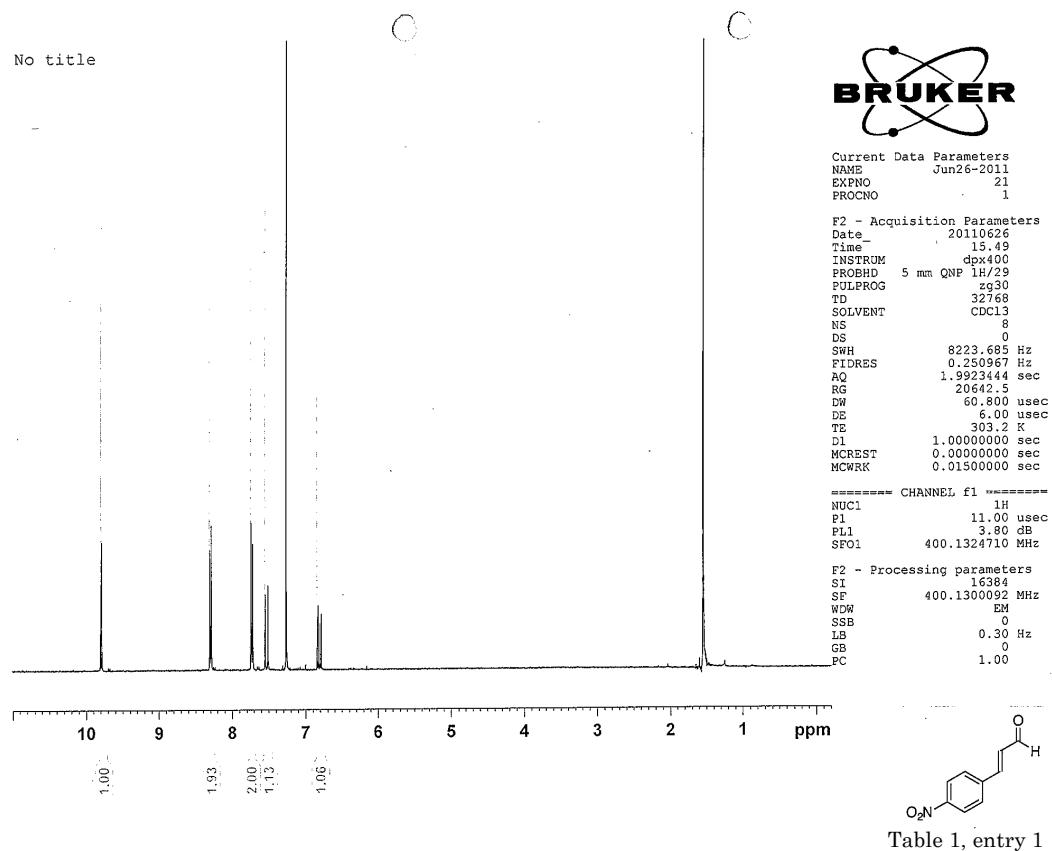
Figure 5

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  $^1\text{H-NMR}$  by taking a small portion of a reaction mixture.

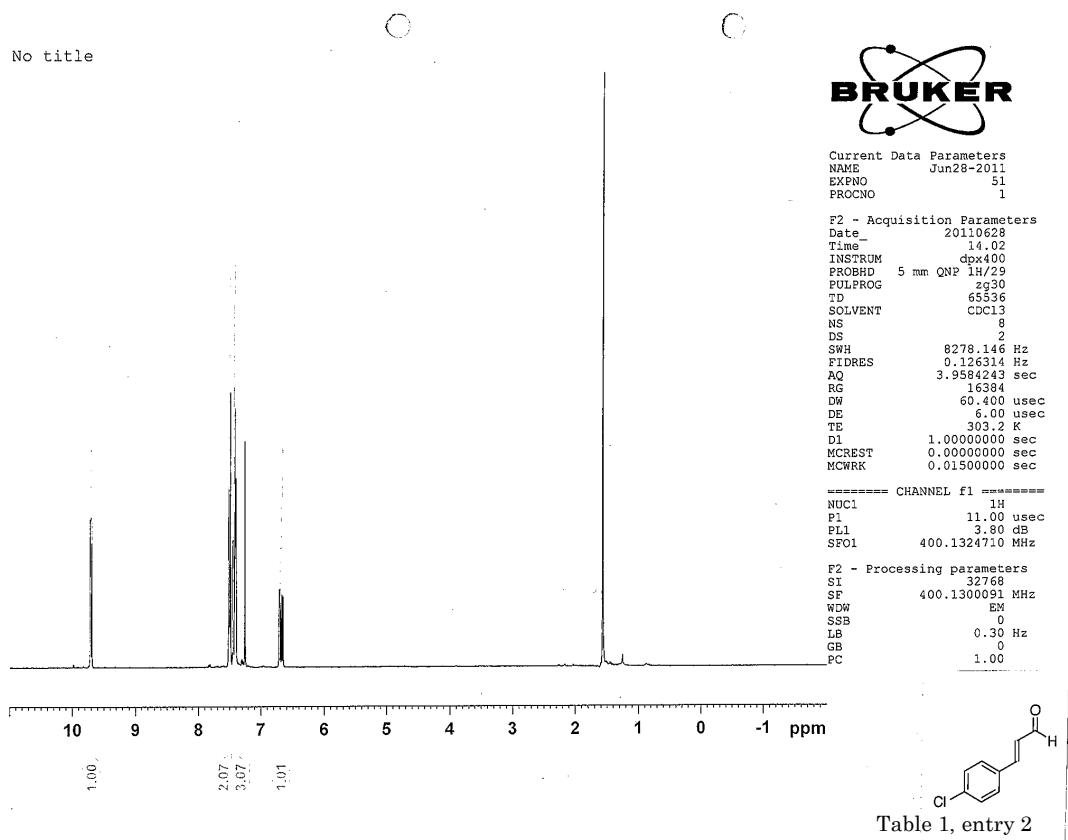


All  $\alpha,\beta$ -unsaturated aldehydes in Table 1 are known compounds and physical data are in good agreement of that in the literatures.

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



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

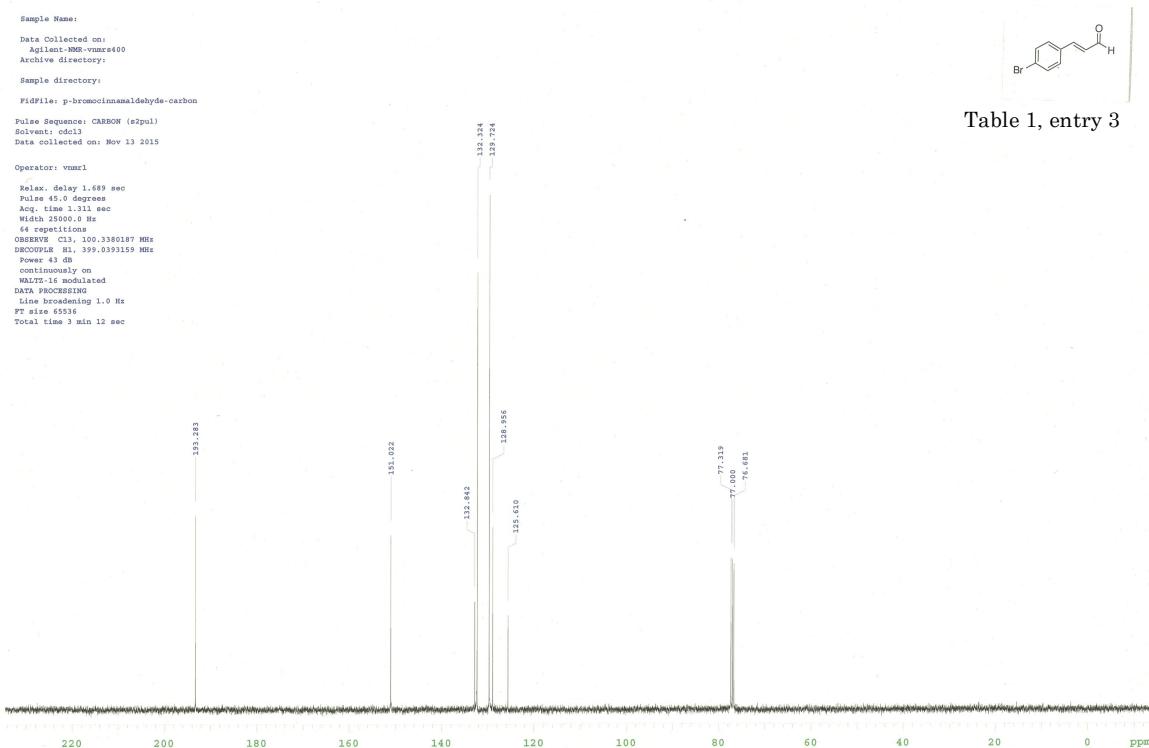
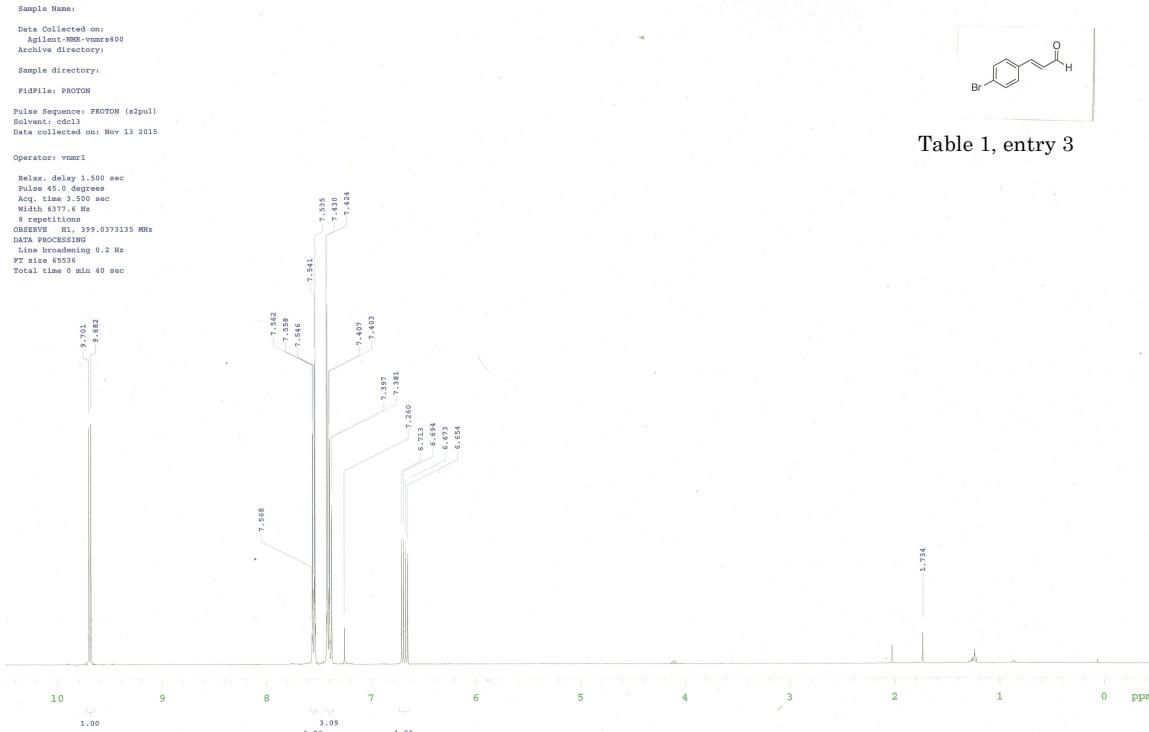
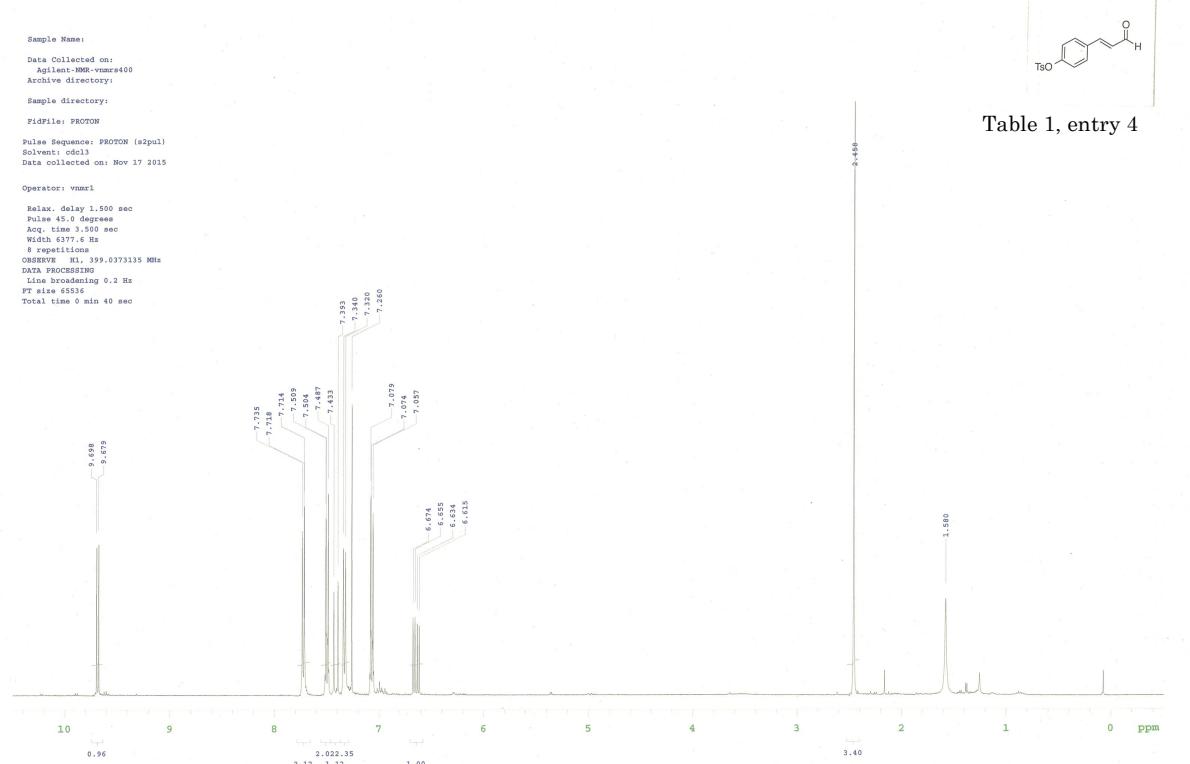
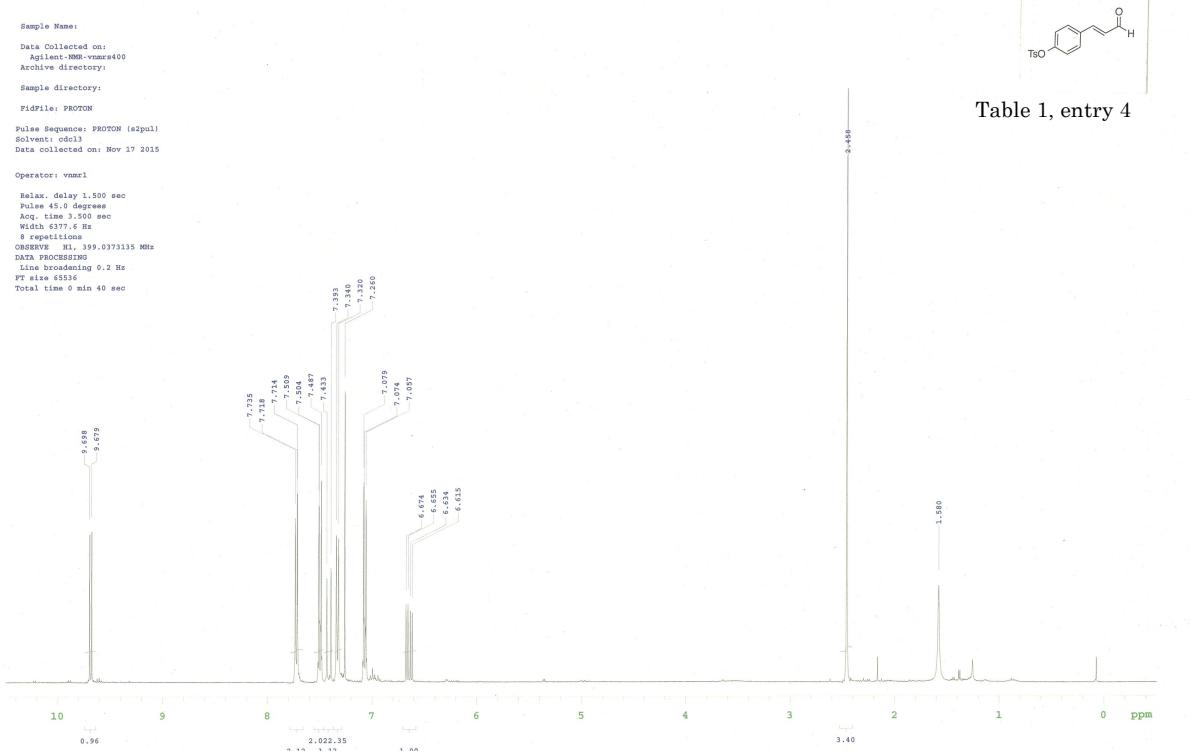


Table 1, entry 3

• 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

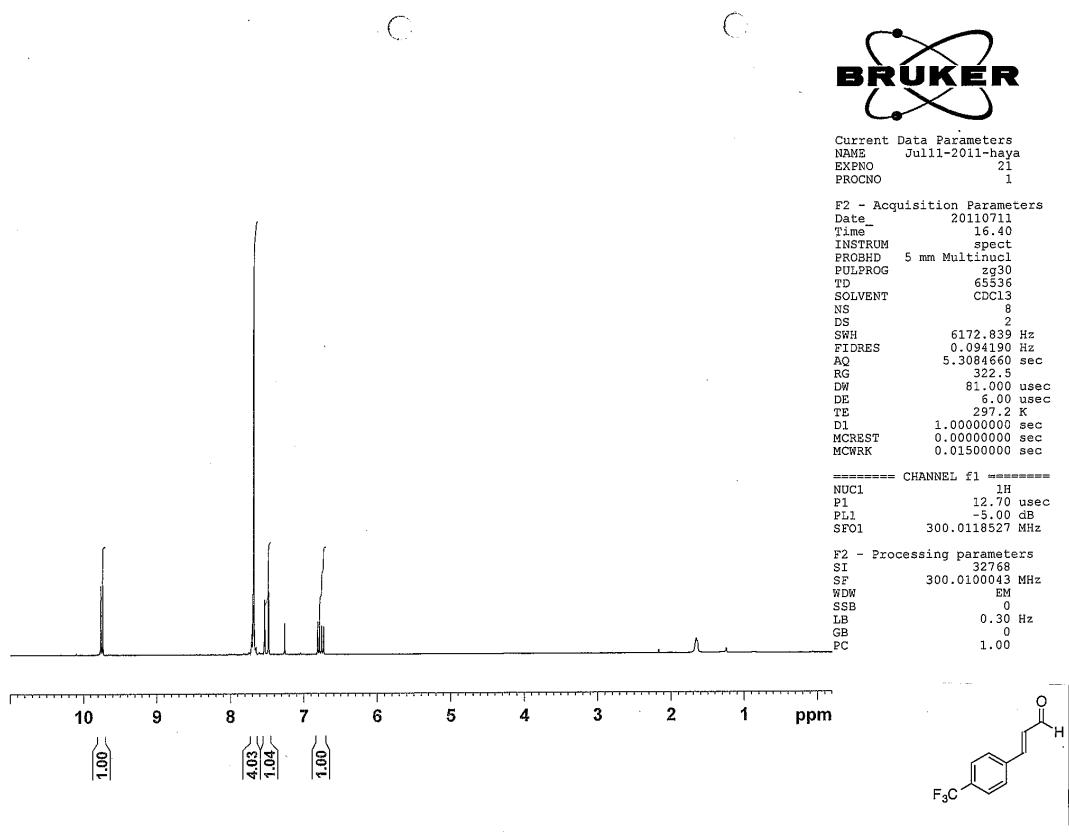


Table 1, entry 5

• 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

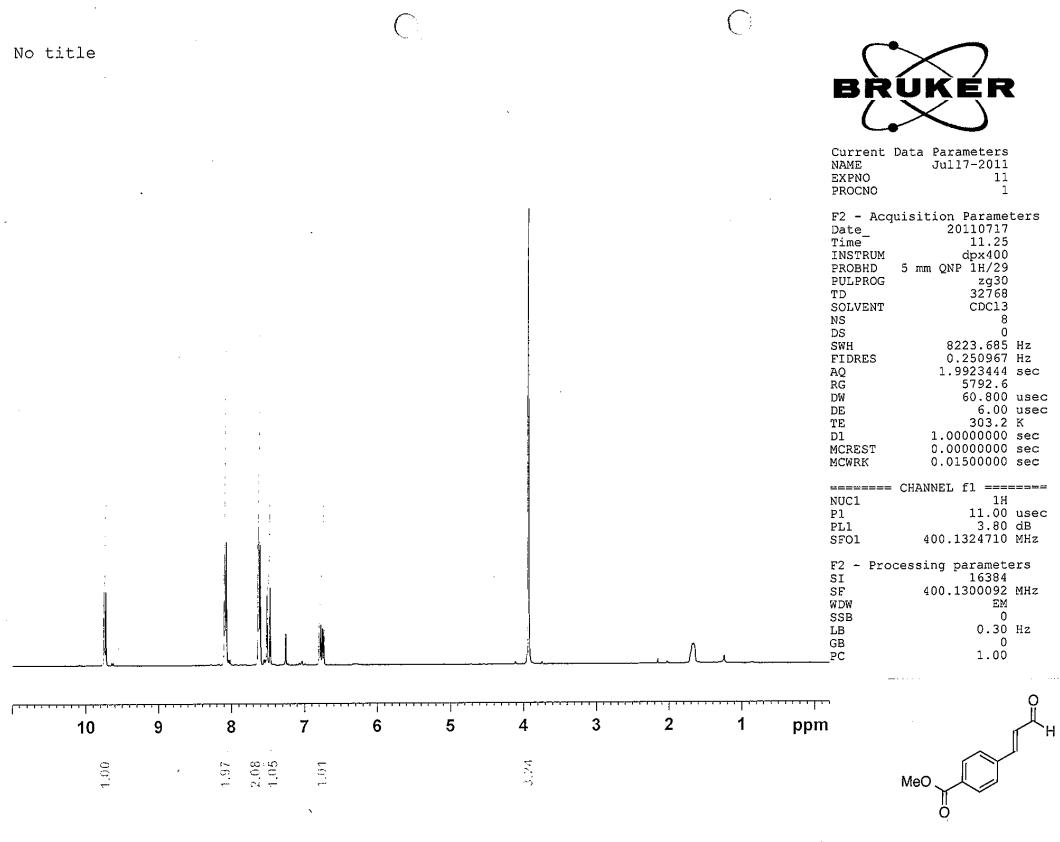
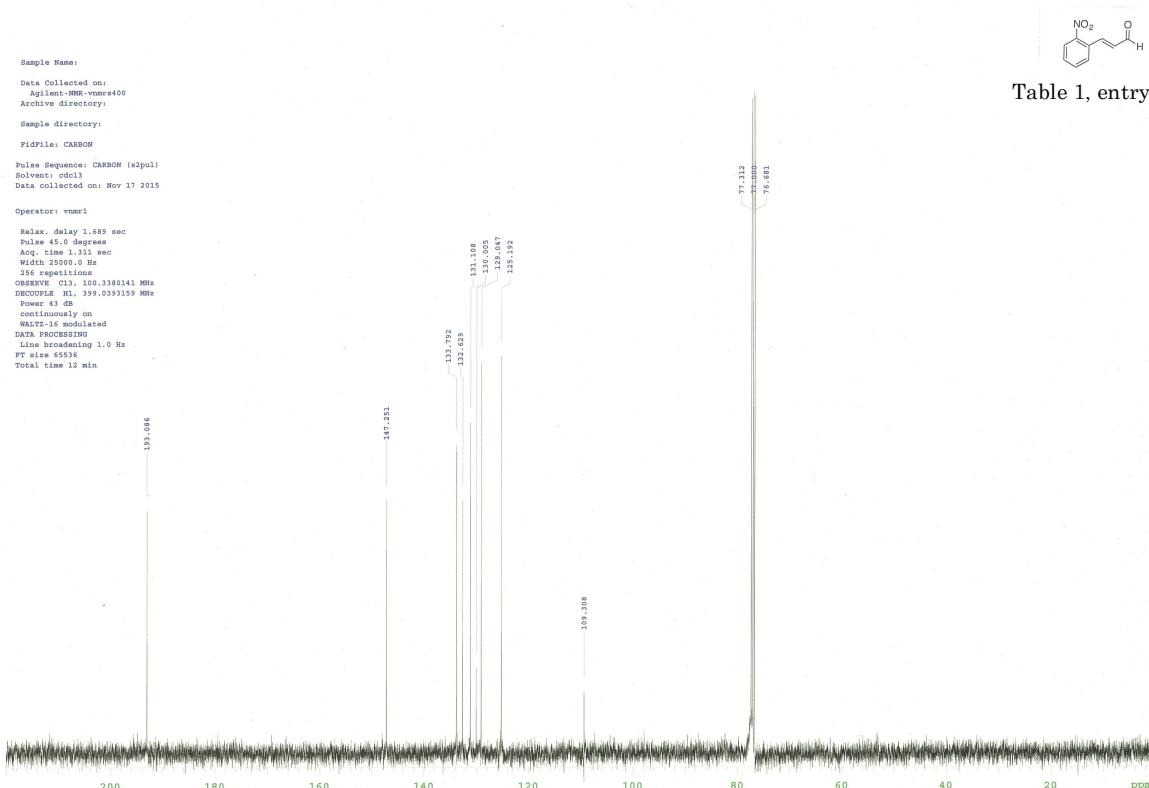
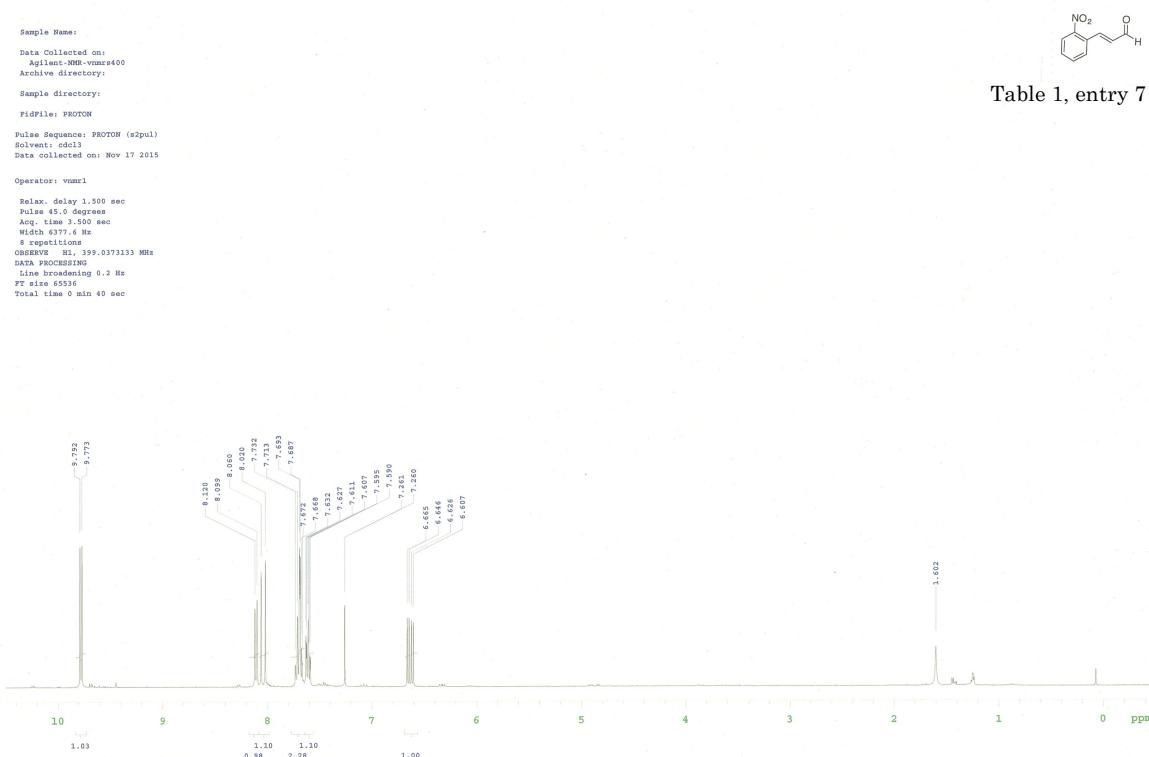
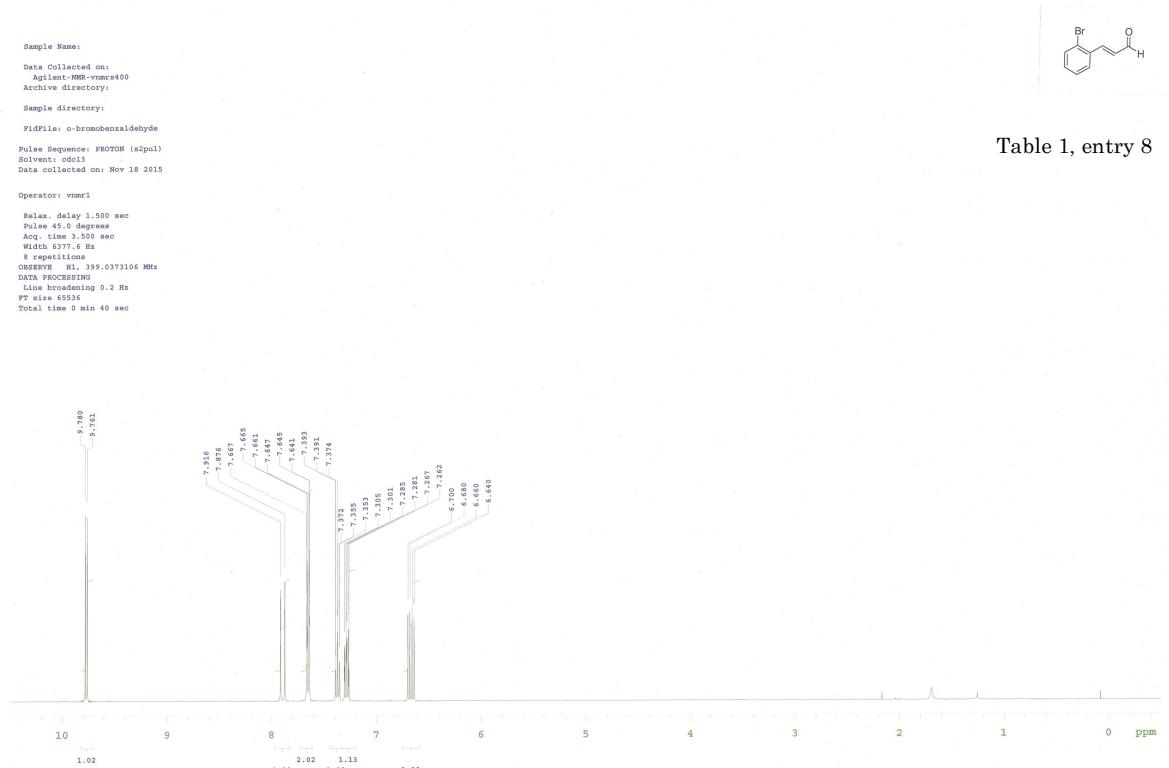


Table 1, entry 6

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



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

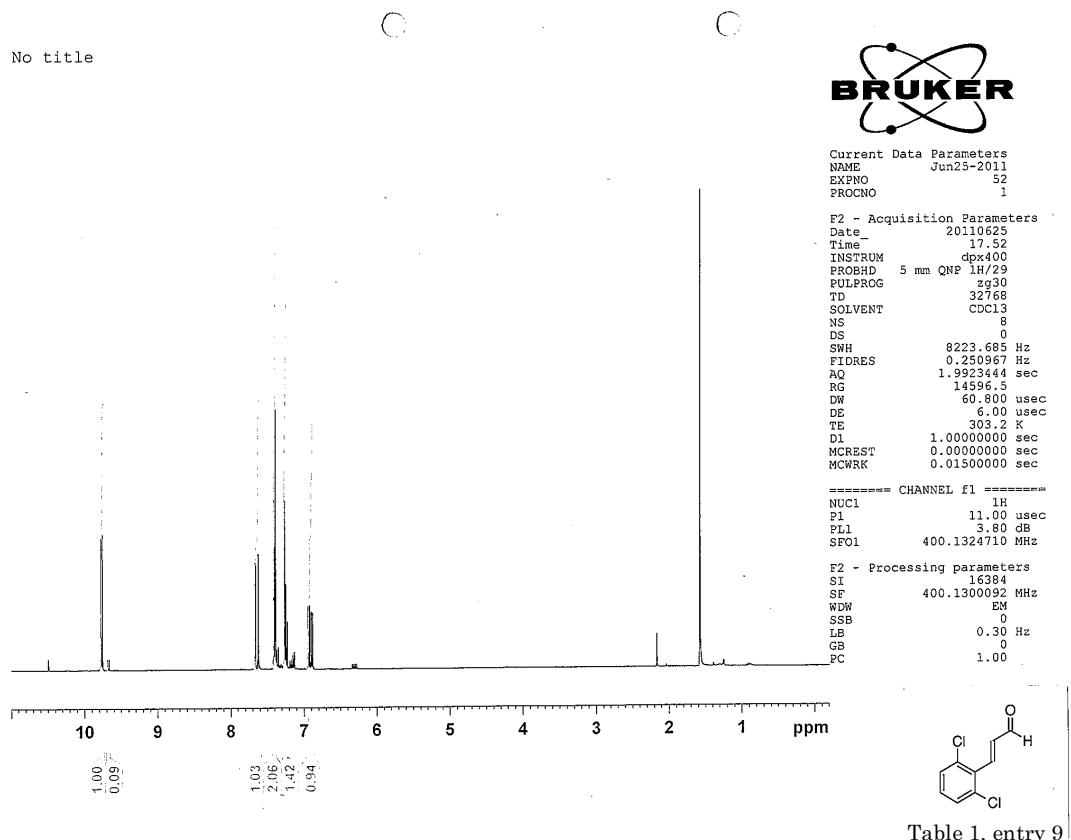


Table 1, entry 9

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

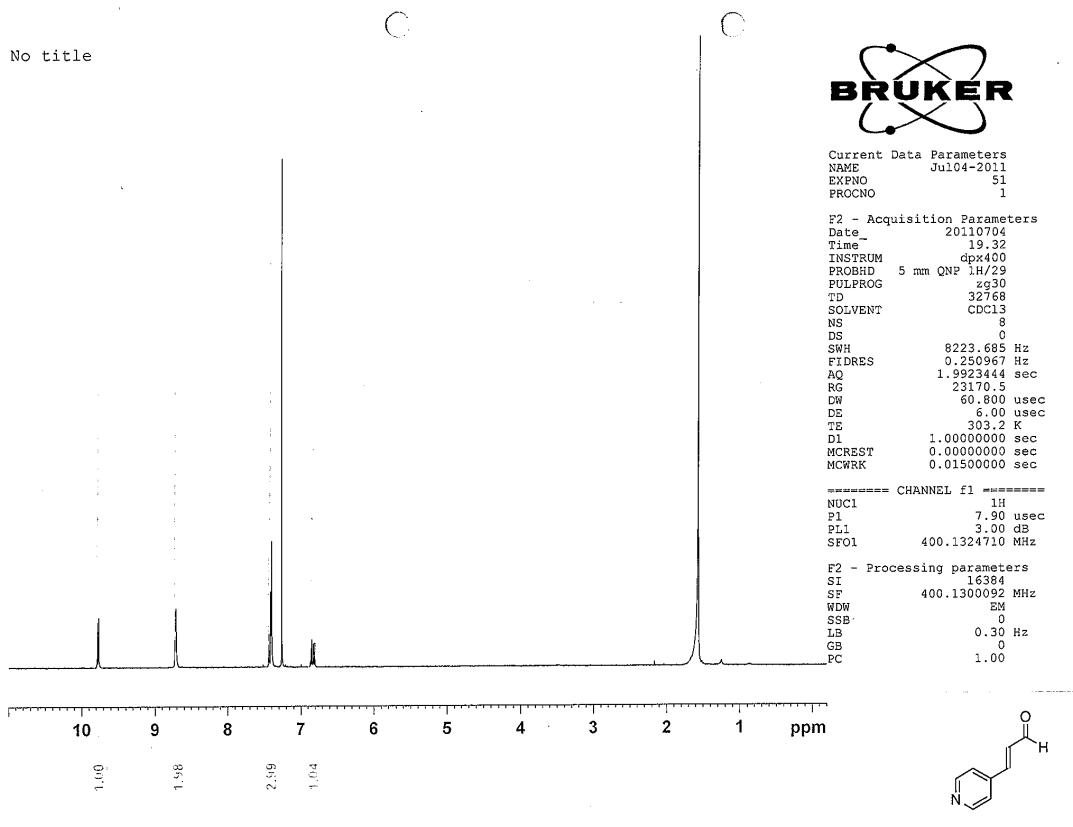


Table 1, entry 10

• 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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  Archive directory:
PidFile: PROTON

Pulse Sequence: PROTON (m2pul)
Solvent: eddm3
Data collected on: Mon 16 2015

Operator: vnmr1

Relax: delay 1.500 sec
Pulse 4.0 degrees
Kaig: 1.000000 sec
AcqTime: 6377.6 Hz
N: 8 repetitions
OBSEVRE NL 399.073137 MHz
DATA PROCESSING:
  Line broadening 0.2 Hz
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Total: 1 min 40. sec

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Table 1, entry 11

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Solvent: cdcl3
Data collected on: Nov 16 2015

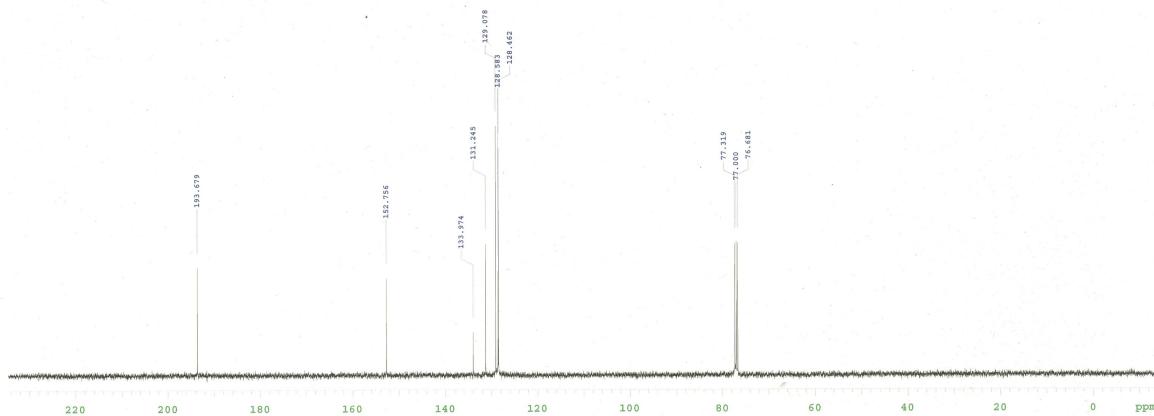
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Aqc. ref. 1.0 sec
128 repetitions
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DEC1FOOT H1, 399.0393159 MHz
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continuously on
WALT16 modulated
DATA PROCESSING
Integration time 1.0 sec
F1 size 65536

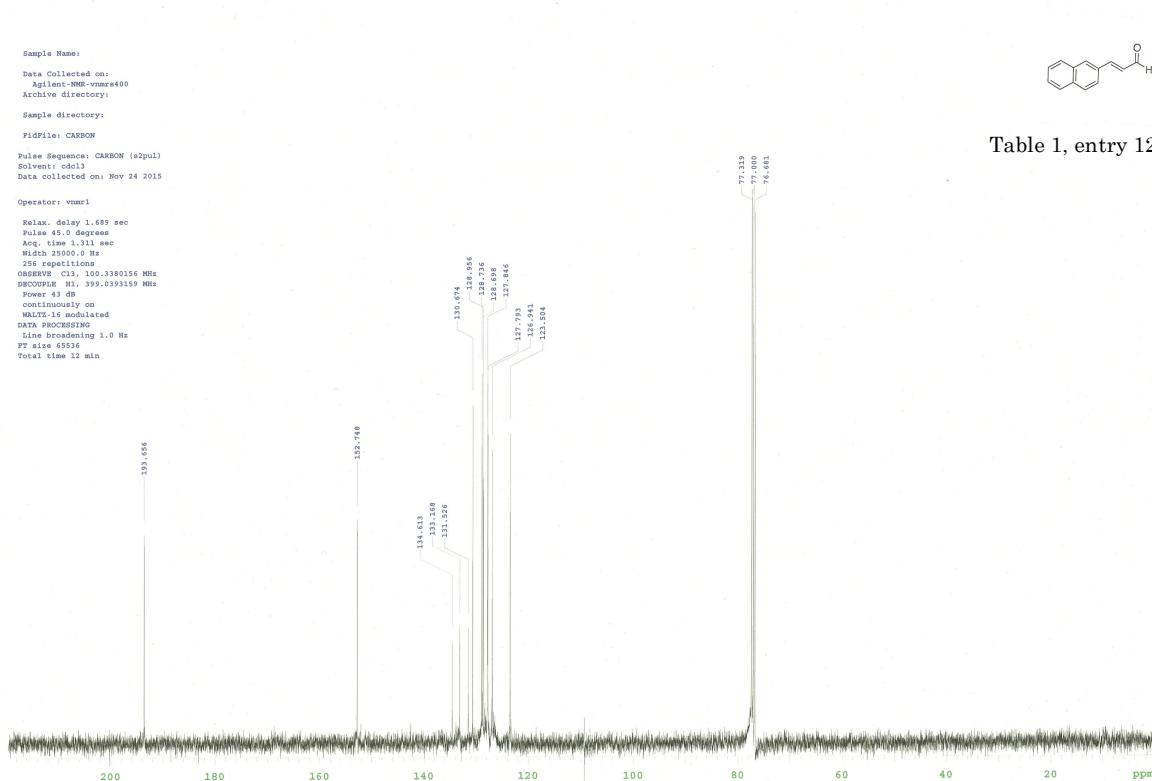
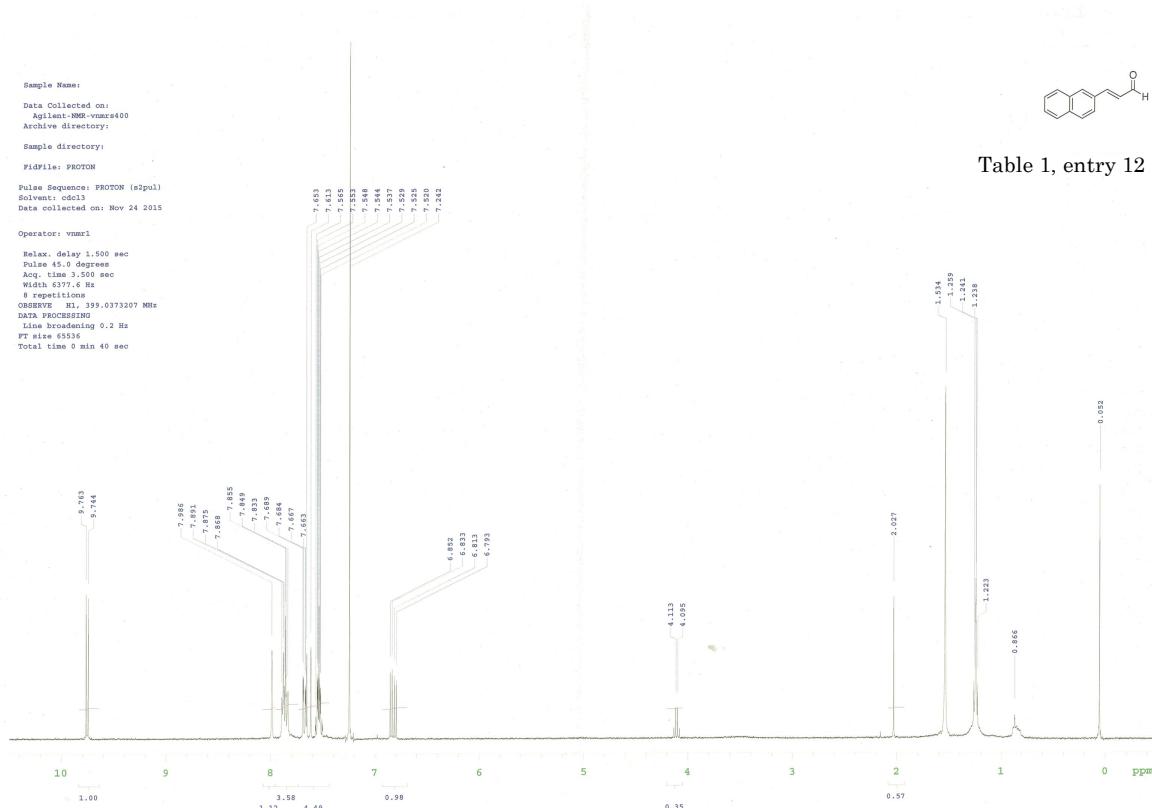
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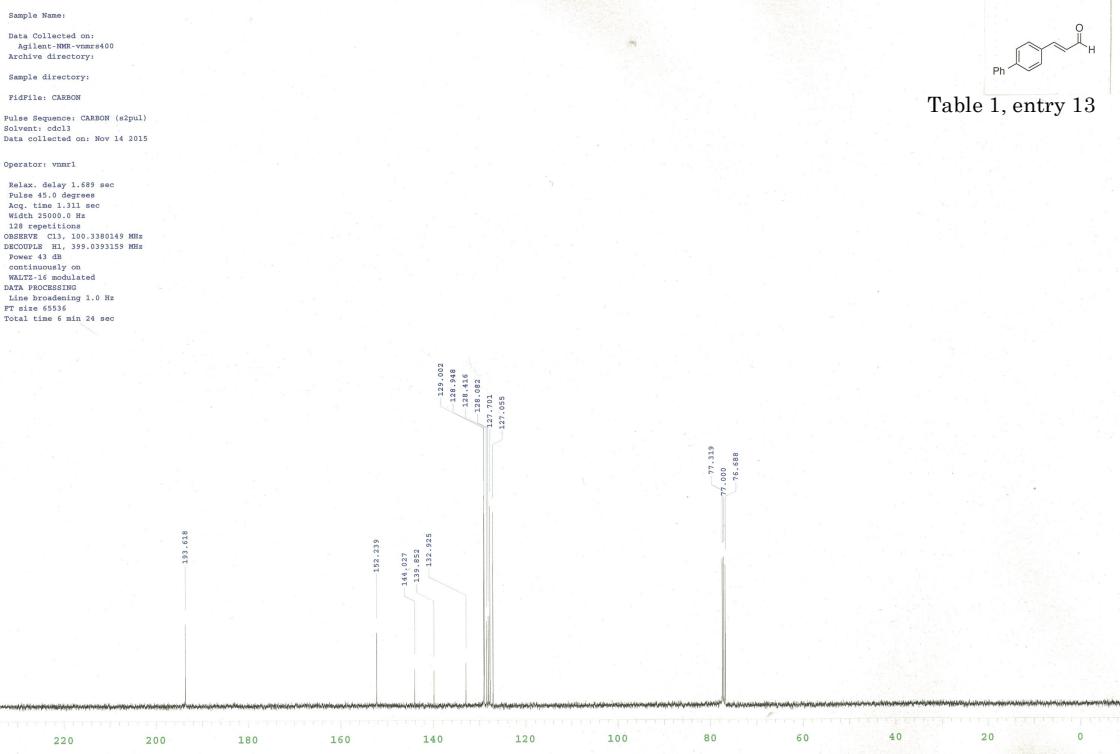
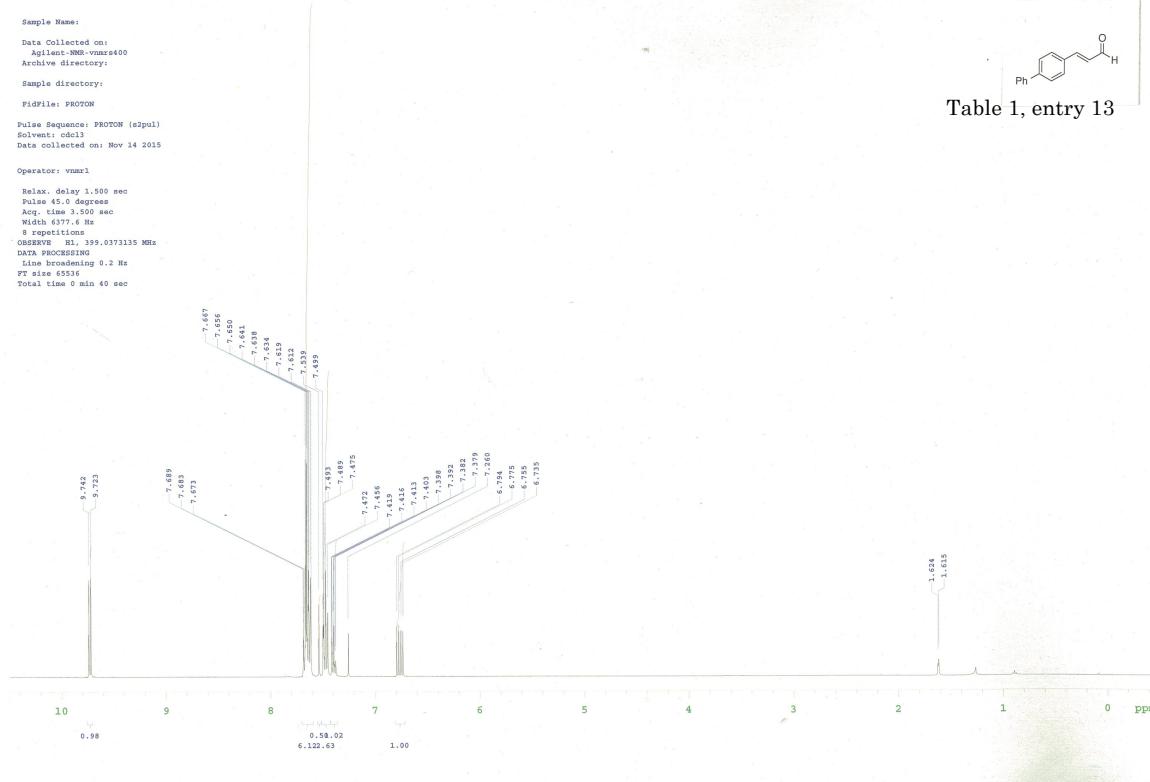
Table 1, entry 11



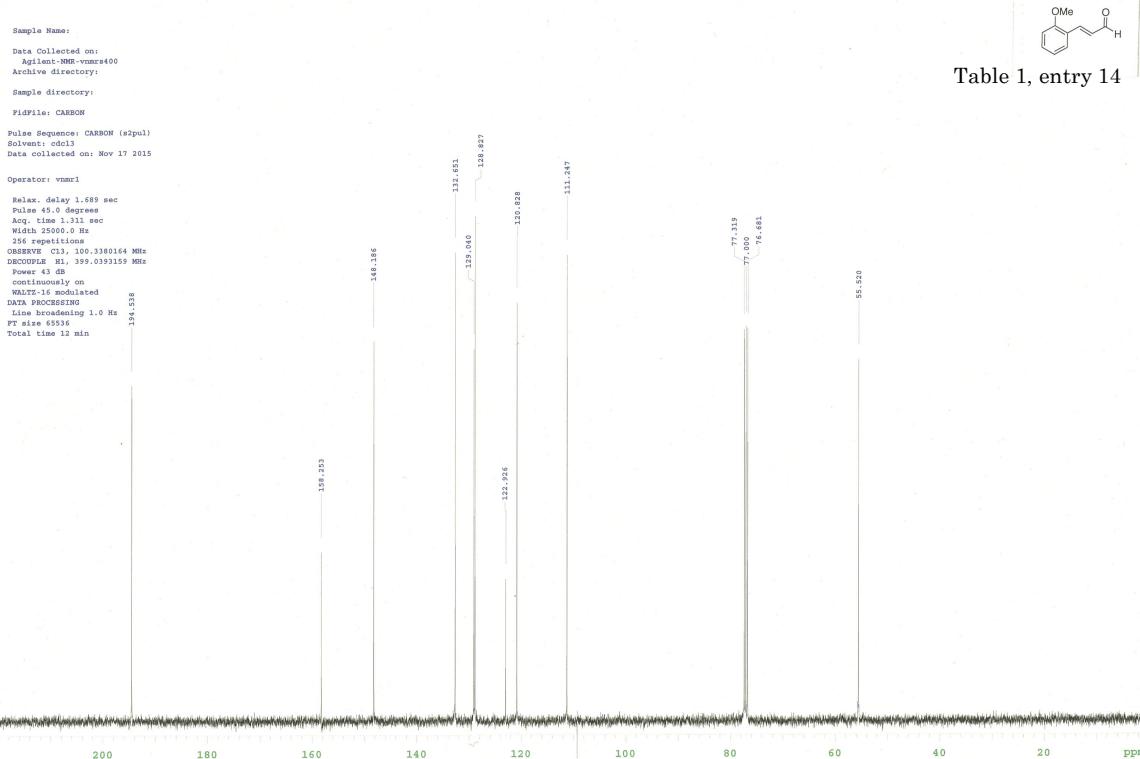
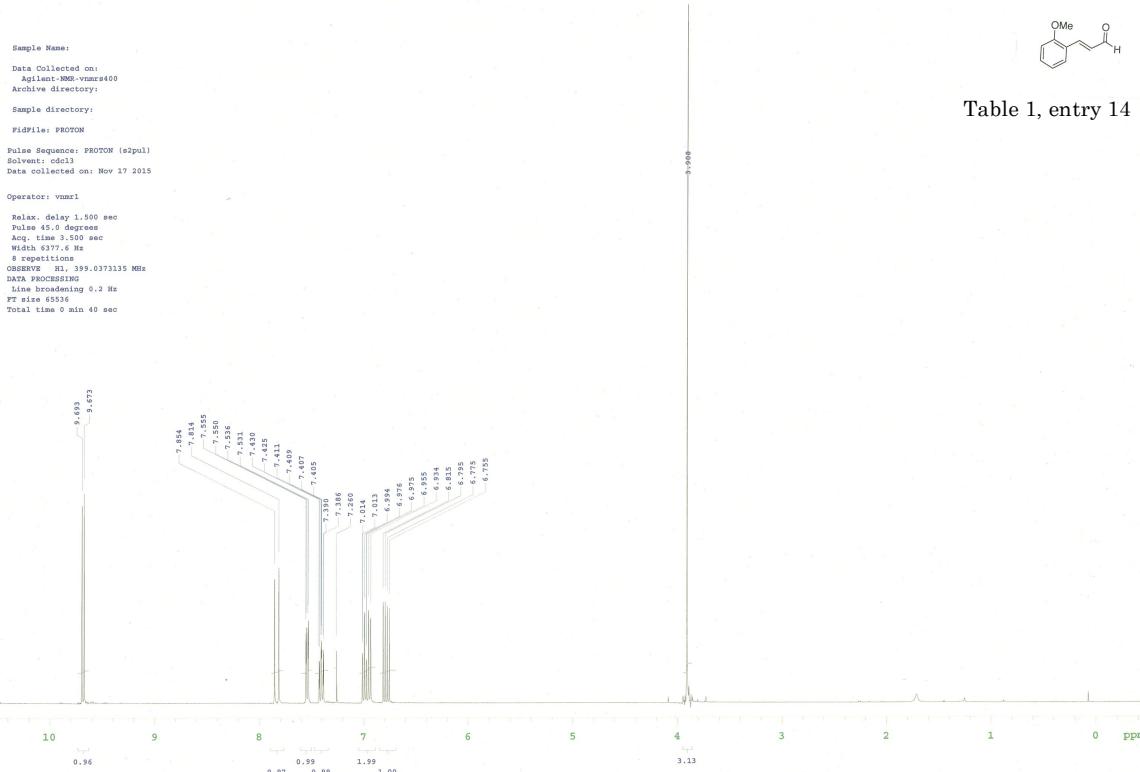
• Table 1, entry 12 : 3-(2-naphthalenyl)-2-Propenal (0.5 mmol scale, 75% yield, 68.3 mg)  
CAS Registry Number 20884-05-3



• 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



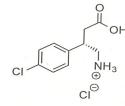
### One-pot synthesis of (*S*)-baclofen

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 <sup>1</sup>H-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 <sup>1</sup>H-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 <sup>1</sup>H-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<sub>2</sub>H (8.5 mmol), and H<sub>2</sub>O (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<sub>2</sub> (21.3 mmol), NaH<sub>2</sub>PO<sub>4</sub>·2H<sub>2</sub>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 Na<sub>2</sub>HPO<sub>3</sub>·5H<sub>2</sub>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<sub>2</sub> 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 (MeOH/CHCl<sub>3</sub>/H<sub>2</sub>O = 3/7/1) gave baclofen hydrochloric salt as white solid (31% yield, 1.6 g).

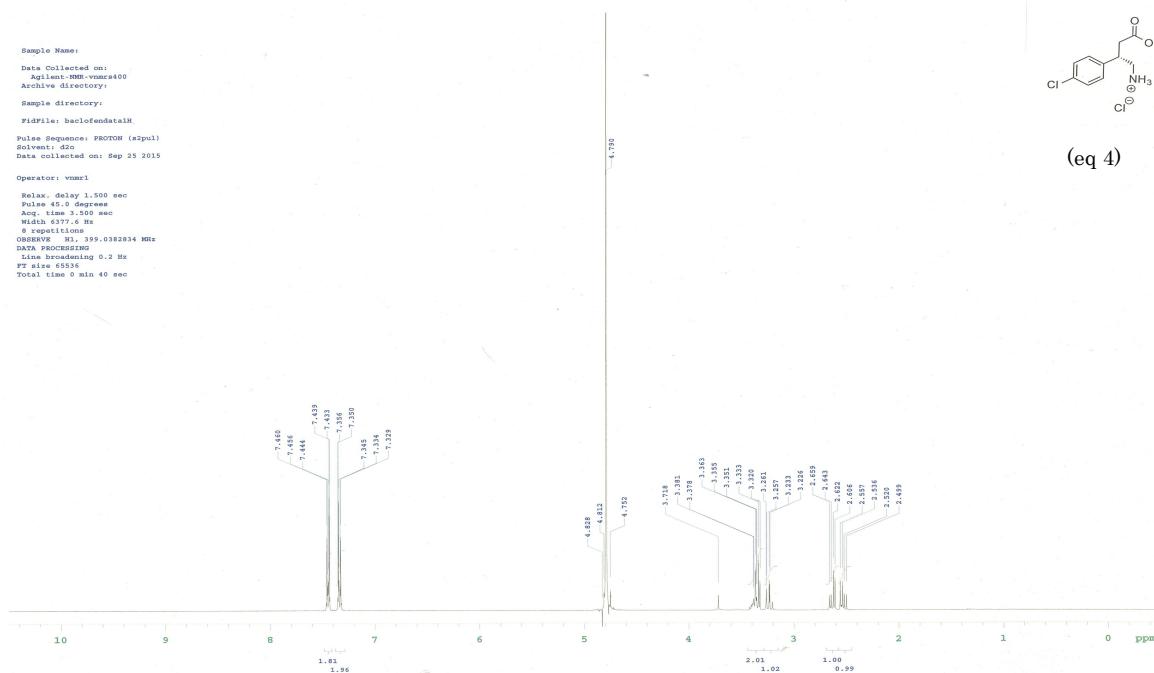
<sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O) δ 7.47-7.42 (m, 2H), 7.36-7.32 (m, 2H), 3.43-3.31 (m, 2H), 3.25 (dd, J = 13.6, 9.6 Hz, 1H), 2.63 (dd, J = 14.8, 6.4 Hz, 1H), 2.53 (d, J = 14.8, 8.4 Hz, 2H); <sup>13</sup>C NMR (100 MHz, D<sub>2</sub>O) δ 179.2, 138.0, 132.9, 129.2, 129.0, 43.9, 42.0, 40.6; HRMS (ESI): [M+H]<sup>+</sup> calculated for C<sub>10</sub>H<sub>13</sub>O<sub>2</sub>NCl: 214.0629, found: 214.0632.

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

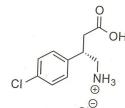
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 Solvent:  
 Data collected on: Sep 25 2015  
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 DEC1 1000 Hz  
 Line broadening 0.2 Hz  
 FT size 65536  
 Total time 0 min 40 sec



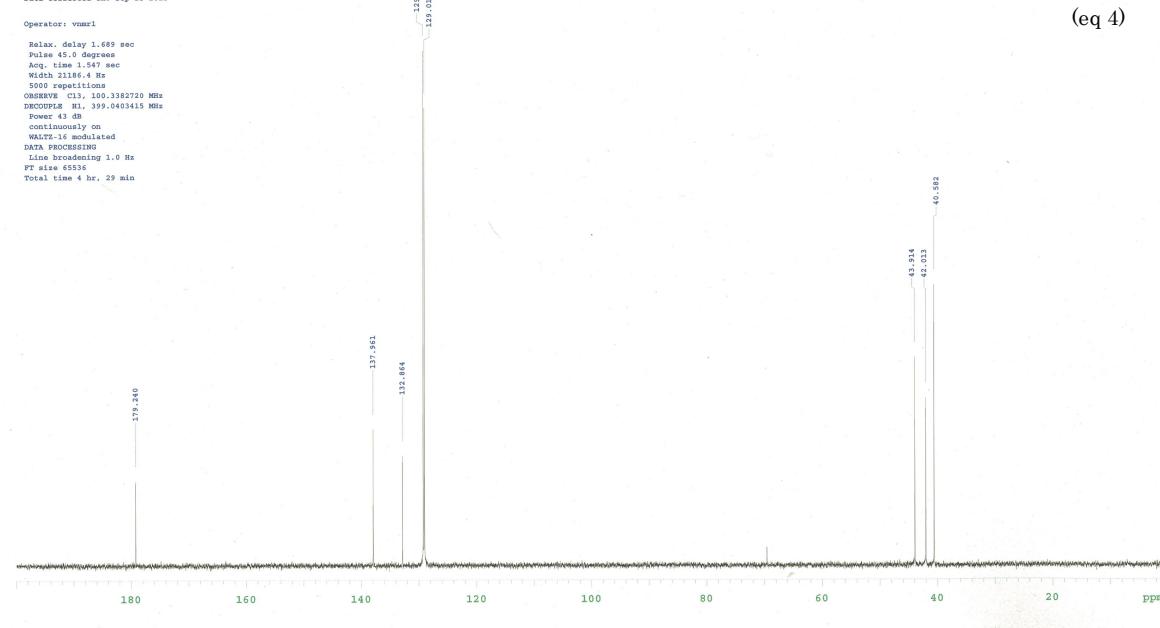
(eq 4)



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 DEC1 1000 Hz  
 continuously on  
 WALTZ-16 modulated  
 DATA PROCESSING  
 Line broadening 1.0 Hz  
 FT size 65536  
 Total time 4 hr, 29 min



(eq 4)



## Reference

- [SR1] Hayashi, H.; Samanta, S.; Itoh, T.; Ishikawa, H. *Org. Lett.*, **2008**, *10*, 5581.
- [SR2] a) Chan, M. Y.; Pai, C. L.; Kung, Y. H. *Tetrahedron lett.* **2006**, *47*, 855. b) Camps, P.; Munoz-Torrero, D.; Sanchez, L. *Tetrahedron: Asymmetry* **2004**, *15*, 2039.