

# Chemoselective Conversion of $\alpha$ -Unbranched Aldehyde to Amide, Ester, and Carboxylic Acid by NHC-Catalysis

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## Experimental Section

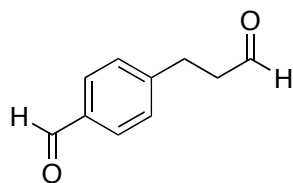
### General Methods

Reactions were performed using dried glassware in dry solvent under argon atmosphere, unless otherwise mentioned. Column chromatography was performed using silica gel. All melting points are uncorrected.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded in  $\text{CDCl}_3$  at 500 and 125 MHz, respectively, unless otherwise mentioned. Chemical shifts and coupling constants are presented in ppm  $\delta$  relative to tetramethylsilane and Hz, respectively. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, and m = multiplet), coupling constants, integration, and assignment.  $^{13}\text{C}$  peak multiplicity assignments were made on the basis of DEPT data. IR spectroscopy of oil and solid samples were measured as neat liquid films and KBr pellets, respectively. The wave numbers of maximum absorption peaks of IR spectroscopy are presented in  $\text{cm}^{-1}$ .

### Materials

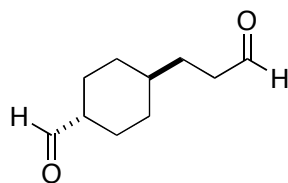
DMSO,  $(\text{COCl})_2$ , benzaldehyde, hydrocinnamaldehyde (**1a**), heptanal (**1b**), and benzyl alcohol were distilled prior to used.  $\text{Et}_2\text{NH}$  and  $\text{Et}_3\text{N}$  were dried over  $\text{CaH}_2$  and distilled. Aldehyde **1c**,<sup>1</sup> triazolium tetrafluoroborate **2a**,<sup>2</sup> and benzotriazolyl ester **11**<sup>3</sup> were prepared according to the reported procedures. Other known reagents and solvents were purchased and used as received.

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1. Kim, T.-S.; Kim, D.-R.; Ahn, H.-C.; Shin, D.; Ahn, D.-R. *ChemBioChem* **2009**, *11*, 75–78.
  2. Kerr, M. S.; Read de Alaniz, J.; Rovis, T. *J. Org. Chem.* **2005**, *70*, 5725–5728.
  3. Sheikh, Md. C.; Takagi, S.; Yoshimura, T.; Morita, H. *Tetrahedron* **2010**, *66*, 7272–7278.



**4-Formylbenzenepropanal (1d):** A solution of methyl 4-(methoxycarbonyl)benzenepropanoate (5.00 g, 22.5 mmol) in THF (30 mL) was added dropwise to a slurry of  $\text{LiAlH}_4$  (2.14 g, 56.3 mmol) in THF (50 mL) at 0 °C. When the addition was complete, the cooling bath was removed, and the mixture was stirred at rt. After 15 min, the mixture was cooled to 0 °C, and the reaction was carefully quenched with  $\text{H}_2\text{O}$  (2.1 mL), 15% NaOH (2.1 mL), and  $\text{H}_2\text{O}$  (6.4 mL). After 40 min, the mixture was filtered through Celite (EtOAc wash), dried over  $\text{Na}_2\text{SO}_4$ , and concentrated *in vacuo* to give 4-(hydroxymethyl)benzenepropanol (**S1**) (3.48 g, 93%) as colorless oil:  $^1\text{H}$  NMR: 1.68 (br s, 2H), 1.85–1.91 (m, 2H), 2.70 (t,  $J = 7.8$ , 2H), 3.66 (t,  $J = 6.3$ , 2H), 4.65 (s, 2H), 7.19 (d,  $J = 8.0$ , 2H), 7.28 (d,  $J = 8.0$ , 2H).  $^{13}\text{C}$  NMR: 31.7 ( $\text{CH}_2$ ), 34.2 ( $\text{CH}_2$ ), 62.2 ( $\text{CH}_2$ ), 65.2 ( $\text{CH}_2$ ), 127.2 (CH), 128.6 (CH), 138.4 (C), 141.3 (C). IR: 3341, 2932, 2870, 1420, 1042. MS  $m/z$ : 166 ( $\text{M}^+$ ). HRMS–EI ( $m/z$ ): ( $\text{M}^+$ ) calcd for  $\text{C}_{10}\text{H}_{14}\text{O}_2$ , 166.0994; found, 166.0993.

The diol **S1** was converted into the titled compound according to the reported procedure.<sup>4</sup>



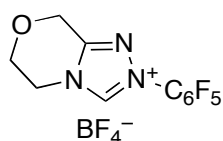
**trans-4-Formylcyclohexanepropanal (1e):** A mixture of 4-carboxybenzenepropanoic acid (2.50 g, 12.8 mmol) and 5% Rh/C (500 mg) in EtOH (100 mL) was stirred under  $\text{H}_2$  (5 atm) in a sealed tube at 70 °C for 16 h. After cooled, the mixture was filtered through Celite, and the residue was washed with hot EtOH. Concentration of the combined filtrate and washings *in vacuo* gave a 1:2 *trans,cis*-mixture of 4-carboxycyclohexanepropanoic acid (**S2**) (2.57 g, 99%). The mixture was dissolved in 6 N NaOH (24 mL), stirred in a sealed tube at 200 °C for 41 h, and acidified (pH 1) by 10% HCl. The resulting precipitates were collected by filtration, washed with cold EtOH, and dried at 60 °C at 8 mmHg to give *trans*-**S2** (2.05 g, 80% yield, a single diastereomer) as white solids of mp 117–120 °C:  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ ): 0.94–1.02 (m, 2H), 1.24–1.28 (m, 1H), 1.35–1.43 (m, 2H), 1.52 (q,  $J = 7.5$ , 2H), 1.82–1.85 (m, 2H), 1.96–1.99 (m, 2H), 2.17–2.24 (m, 1H), 2.31 (t,  $J = 7.5$ , 2H), 4.93 (br s, 2H).  $^{13}\text{C}$  NMR ( $\text{CD}_3\text{OD}$ ): 30.2 ( $\text{CH}_2$ ), 32.5 ( $\text{CH}_2$ ), 33.1 ( $\text{CH}_2$ ), 33.3 ( $\text{CH}_2$ ), 37.9 (CH), 44.5 (CH), 177.8 (C), 180.0 (C). IR: 2940, 1705. FABMS  $m/z$ : 199 ( $\text{M} - \text{H}$ ). HRMS–FAB ( $m/z$ ): [ $\text{M} - \text{H}$ ] $^-$  calcd for  $\text{C}_{10}\text{H}_{15}\text{O}_4$ , 199.0970; found, 199.0970.

The dicarboxylic acid **S2** (2.50 g, 12.5 mmol) in THF (20 mL) was added dropwise to a slurry of  $\text{LiAlH}_4$  (1.19 g, 31.3 mmol) in THF (80 mL) at 0 °C, and the cooling bath was removed. After 3 h, satd potassium sodium tartrate (200 mL) was added at 0 °C. The mixture was stirred for 12 h at rt

4. Tanaka, K.; Shibata, Y.; Suda, T.; Hagiwara, Y.; Hirano, M. *Org. Lett.* **2007**, *9*, 1215–1218.

and extracted with  $\text{CHCl}_3$ . The organic layer was washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , and concentrated *in vacuo*. The resulting residue was purified by column chromatography (hexane/EtOAc 1:3) to give *trans*-4-(hydroxymethyl)cyclohexanepropanol (**S3**) (1.84 g, 85% yield) as colorless oil:  $^1\text{H}$  NMR: 0.91–0.96 (m, 4H), 1.18–1.45 (m, 6H), 1.55–1.61 (m, 2H), 1.78–1.80 (m, 4H), 3.45 (d,  $J = 6.6$ , 2H), 3.63 (t,  $J = 6.9$ , 2H).  $^{13}\text{C}$  NMR: 29.4 ( $\text{CH}_2$ ), 30.1 ( $\text{CH}_2$ ), 32.6 ( $\text{CH}_2$ ), 33.2 ( $\text{CH}_2$ ), 37.6 (CH), 40.6 (CH), 63.3 ( $\text{CH}_2$ ), 68.6 ( $\text{CH}_2$ ). IR: 3333, 2855, 1450, 1057. MS  $m/z$ : 172 ( $\text{M}^+$ ). Anal. Calcd for  $\text{C}_{10}\text{H}_{20}\text{O}_2$ : C, 69.72; H, 11.70. Found: C, 69.44; H, 11.92.

The diol **S3** (1.72 g, 10.0 mmol), TEMPO (94 mg, 0.6 mmol), and KBr (2.6 g, 22 mmol) were added to a two-phase mixture of  $\text{CH}_2\text{Cl}_2$  (100 mL) and  $\text{H}_2\text{O}$  (40 mL) at 0 °C. A 12% NaOCl solution (12.4 mL) was added dropwise over 30 min under vigorous stirring. After 15 min, MeOH (8 mL) was added, and the whole was stirred at rt for 20 min and extracted with  $\text{CH}_2\text{Cl}_2$ . The organic layer was washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , and concentrated *in vacuo*. The resulting residue was purified by column chromatography (hexane/EtOAc 10:1) to give the titled compound (1.17 g, 70% yield) as colorless oil:  $^1\text{H}$  NMR: 0.91–1.00 (m, 2H), 1.17–1.27 (m, 3H), 1.54 (q,  $J = 7.8$ , 2H), 1.83–1.86 (m, 2H), 1.96–1.99 (m, 2H), 2.12–2.19 (m, 1H), 2.44 (dt,  $J = 7.8, 1.7$ , 2H), 9.59 (d,  $J = 1.4$ , 1H), 9.75 (t,  $J = 1.7$ , 1H).  $^{13}\text{C}$  NMR: 25.6 ( $\text{CH}_2$ ), 28.8 ( $\text{CH}_2$ ), 31.5 ( $\text{CH}_2$ ), 36.5 (CH), 41.3 ( $\text{CH}_2$ ), 50.1 (CH), 202.5 (CH), 204.4 (CH). IR: 2855, 1720, 1450. MS  $m/z$ : 168 ( $\text{M}^+$ ). Anal. Calcd for  $\text{C}_{10}\text{H}_{16}\text{O}_2$ : C, 71.39; H, 9.59. Found: C, 71.28; H, 9.49.



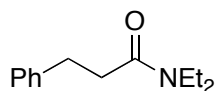
**Triazolium tetrafluoroborate 2b:** 3-Morpholinone was prepared according to the procedure reported in patent:<sup>5</sup> To a solution of ethanol amine (6.0 ml, 0.10 mol) in *i*-PrOH (100 mL), was portionwise added small pieces of sodium (2.3 g, 0.10 mol). The mixture was heated at 50 °C for 5 h, and the resulting yellow solution was cooled in an ice-water bath. Ethyl chloroacetate (9.6 mL, 0.090 mol) was dropwise added at 0–6 °C, and the resulting yellow suspension was heated at 80 °C for 2 h. Insoluble materials were removed by paper filtration and washed with *i*-PrOH. The combined filtrate and washings were concentrated *in vacuo*, and the resulting brown solids were recrystallized from *i*-PrOH/EtOAc to afford 3-morpholinone (3.5 g, 34%) as colorless needles of mp 106–107 °C.

To a solution of the above morpholinone (1.0 g, 10 mmol) in  $\text{CH}_2\text{Cl}_2$  (200 mL), was added trimethyloxonium tetrafluoroborate (1.5 g, 10 mmol), and the mixture was stirred for 9 h at rt. Then, pentafluorophenylhydrazine (2.0 g, 10 mmol) was added, and the mixture was stirred for another 9 h. The mixture was concentrated *in vacuo*, and the residue was dissolved in chlorobenzene (100 mL) followed by addition of triethyl orthoformate (13.3 mL, 40 mmol). The mixture was heated at 130 °C for 12 h. Then, additional triethyl orthoformate (13.3 mL, 40 mmol) was added and stirring

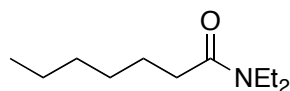
5. Chu, H.; Liu, S.; Luo, Y.; Ren, H.; Tang, M. Preparation Method of 3-Morpholone. CN 101735165 (A), June 16, 2010.

at 130 °C was continued. After 12 h, toluene (100 mL) was added at rt, and the resulting brown solids were collected by filtration. Recrystallization from EtOH gave the titled compound (686 mg, 18%) as pale brown solids of mp 179–181 °C: <sup>1</sup>H NMR (acetone-d<sub>6</sub>): 4.38 (t, *J* = 5.2, 2H), 4.77 (t, *J* = 5.2, 2H), 5.28 (s, 2H), 10.4 (s, 2H). <sup>13</sup>C NMR (acetone-d<sub>6</sub>): 46.8 (CH<sub>2</sub>), 62.3 (CH<sub>2</sub>), 63.4 (CH<sub>2</sub>), 112.1 (m, C), 139.1 (m, C), 144.0 (m, C), 144.6 (m, C), 147.1 (CH), 152.5 (C). IR: 3140, 2955, 1597, 1528, 1450, 1072. FABMS *m/z*: 292 (M – BF<sub>4</sub>). HRMS–FAB (*m/z*): [M – BF<sub>4</sub>]<sup>+</sup> calcd for C<sub>11</sub>H<sub>7</sub>F<sub>5</sub>N<sub>3</sub>O, 292.0504; found, 292.0510.

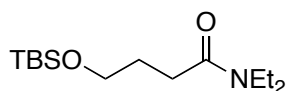
### Conversion of Aldehyde to Amide, Carboxylic Acid, and Ester The Typical Procedure without L-Proline.



***N,N*-Diethyl-3-phenylpropanamide (3a):** To a stirred ice-cooled solution of hydrocinnamaldehyde (**1a**) (134 mg, 1.0 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL), were added Et<sub>2</sub>NH (0.21 mL, 2.0 mmol) and NCS (134 mg, 1.0 mmol), and the cooling bath was removed. After 0.5 h, the aldehyde was no longer detected by TLC monitoring. To the mixture, were added HOBt (27 mg, 0.20 mmol) and a premixed solution of triazolium salt **2a** (24 mg, 0.050 mmol) and Et<sub>3</sub>N (0.17 mL, 1.2 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (8 mL). After 12 h, the mixture was concentrated *in vacuo*, and the resulting residue was purified by column chromatography (hexane/EtOAc 2:1) to give the titled compound (180 mg, 88% yield) as colorless oil: <sup>1</sup>H and <sup>13</sup>C NMR, IR, and MS were identical to those reported.<sup>6</sup>



***N,N*-Diethylheptanamide (3b):** Following the procedure without L-proline, the titled compound was obtained in 91% yield (168 mg) as colorless oil: MS *m/z*: 185 (M<sup>+</sup>), 156, 142, 128, 100. <sup>1</sup>H and <sup>13</sup>C NMR, and IR were identical to those reported.<sup>7</sup>

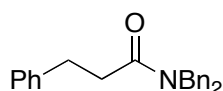


**4-(*tert*-Butyldimethylsiloxy)-*N,N*-diethylheptanamide (3c):** Following the procedure without L-proline, using 0.10 mmol **2a**, the titled compound was obtained in 87% yield (240 mg) as colorless oil: <sup>1</sup>H NMR: 0.05 (s, 6H), 0.89 (s, 9H), 1.11 (t, *J* = 7.2, 3H), 1.17 (t, *J* = 7.2, 3H), 1.84–1.88 (m, 2H), 2.39 (t, *J* = 7.5, 2H), 3.32 (q, *J* = 7.2, 2H), 3.37 (q, *J* = 7.2, 2H), 3.66 (t, *J* = 6.0, 2H). <sup>13</sup>C NMR: –5.4 (CH<sub>3</sub>), 13.1 (CH<sub>3</sub>), 14.3 (CH<sub>3</sub>), 18.2 (C), 25.9 (CH<sub>3</sub>), 28.5 (CH<sub>2</sub>), 29.2 (CH<sub>2</sub>), 40.0 (CH<sub>2</sub>), 41.9 (CH<sub>2</sub>), 62.2 (CH<sub>2</sub>), 172.0 (C). IR: 2932, 2862, 1643, 1103. MS *m/z*: 273 (M<sup>+</sup>), 217 (M<sup>+</sup> – C<sub>4</sub>H<sub>8</sub>). HRMS–FAB (*m/z*): [M + H]<sup>+</sup> calcd for C<sub>14</sub>H<sub>32</sub>NO<sub>2</sub>Si, 274.2202; found, 274.2199.

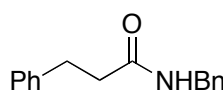
6. Concellon, J, M.; Rodríguez-Solla, H. *Chem. Eur. J.* **2001**, *7*, 4266–4271.

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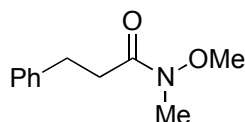
### The Typical Procedure with L-Proline.



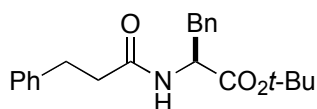
***N,N*-Dibenzyl-3-phenylpropanamide (3d)**: To a stirred ice-cooled solution of hydrocinnamaldehyde (**1a**) (134 mg, 1.0 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL), were added L-proline (5 mg, 0.05 mmol) and NCS (134 mg, 1.0 mmol), and the cooling bath was removed. After 9 h, the aldehyde was no longer detected by TLC monitoring. To the mixture, were added HOBT (27 mg, 0.2 mmol), a premixed solution of triazolium salt **2a** (24 mg, 0.050 mmol) and Et<sub>3</sub>N (0.17 mL, 1.2 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (8 mL), and Bn<sub>2</sub>NH (0.29 mL, 1.5 mmol). After 11 h, the mixture was concentrated *in vacuo*, and the resulting residue was purified by column chromatography (hexane/EtOAc 5:1) to give the titled compound (234 mg, 71% yield) as white solids of mp 103–105 °C (lit.<sup>8</sup> 104–105 °C): <sup>1</sup>H and <sup>13</sup>C NMR, IR, and MS were identical to those reported.<sup>9</sup>



***N*-Benzyl-3-phenylpropanamide (3e)**: Following the procedure with L-proline, except that BnNH<sub>2</sub> in place of Bn<sub>2</sub>NH was added over 3 h, purification by column chromatography (hexane/EtOAc 4:3) gave the titled compound (172 mg, 72% yield) as light yellow solids of mp 79–81 °C (lit.<sup>10</sup> 80–82 °C): IR: 3287, 1636, 1543. MS *m/z*: 239 (M<sup>+</sup>), 148, 105, 91. <sup>1</sup>H and <sup>13</sup>C NMR were identical to those reported.<sup>11</sup>



***N*-Methoxy-*N*-methyl-3-phenylpropanamide (3f)**: Following the procedure with L-proline, except that *N,O*-dimethylhydroxylamine hydrochloride (147 mg, 1.5 mmol) was used in place of Bn<sub>2</sub>NH, purification by column chromatography (hexane/EtOAc 4:1) gave the titled compound (157 mg, 81% yield) as colorless oil: IR: 2939, 1666, 1450, 733. MS *m/z*: 193 (M<sup>+</sup>), 133, 105. <sup>1</sup>H and <sup>13</sup>C NMR were identical to those reported.<sup>12</sup>



***tert*-Butyl (*S*)-3-phenyl-2-(3-phenylpropanamido)propanoate (3g)**: Following the procedure with L-proline, except that L-phenylalanine *tert*-butyl ester hydrochloride (387 mg, 1.5 mmol) was added in place of Bn<sub>2</sub>NH, purification by column chromatography (hexane/EtOAc 5:1) gave the titled

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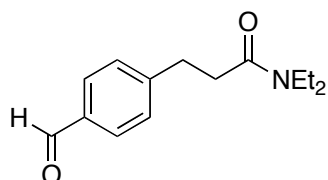
9. Zhou, S.; Junge, K.; Addis, D.; Das, S.; Beller, M. *Angew. Chem. Int. Ed.* **2009**, *48*, 9507–9510.

10. Saito, Y.; Ouchi, H.; Takahata, H. *Tetrahedron* **2008**, *64*, 11129–11135.

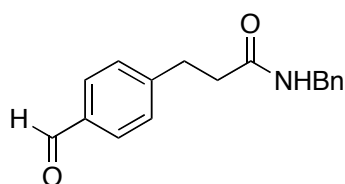
11. Watson, A, J, A.; Maxwell, A, C.; Williams, M, J. *Org. Lett.* **2009**, *11*, 2667–2670.

12. Chiang, P.-C.; Kim, Y.; Bode, J. W. *Chem. Commun.* **2009**, 4566–4568.

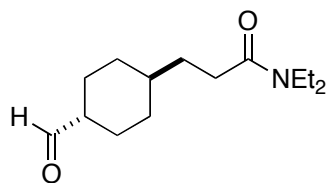
compound (270 mg, 76% yield) with >99% ee as colorless oil:  $[\alpha]_D^{25} +70.9$  ( $c$  1.02,  $\text{CHCl}_3$ ).  $^1\text{H}$  NMR: 1.39 (s, 9H), 2.45 (ddd,  $J = 7.1, 7.5, 16.1$ , 1H), 2.53 (ddd,  $J = 6.3, 7.1, 16.1$ , 1H), 2.90–3.00 (m, 2H), 3.01 (dd,  $J = 6.5, 13.7$ , 1H), 3.06 (dd,  $J = 5.2, 13.7$ , 1H), 4.76 (ddd,  $J = 5.2, 6.5, 7.5$ , 1H), 5.85 (d,  $J = 7.5$ , 1H), 7.00–7.02 (m, 2H), 7.19–7.32 (m, 8H).  $^{13}\text{C}$  NMR: 27.9 ( $\text{CH}_3$ ), 31.4 ( $\text{CH}_2$ ), 38.0 ( $\text{CH}_2$ ), 38.2 ( $\text{CH}_2$ ), 53.3 (CH), 82.3 (C), 126.2 (CH), 126.8 (CH), 128.2 (CH), 128.3 (CH), 128.5 (CH), 129.5 (CH), 136.0 (C), 140.7 (C), 170.6 (C), 171.3 (C). IR: 3302, 1736, 1651, 1535. MS  $m/z$ : 353 ( $\text{M}^+$ ), 280. HRMS–FAB ( $m/z$ ):  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{22}\text{H}_{28}\text{NO}_3$ , 354.2069; found, 354.2068. Enantiopurity was confirmed by HPLC (*vide infra*).



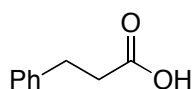
***N,N*-Diethyl-3-(4-formylphenyl)propanamide (3h)**: Following the procedure without L-proline in 0.50 mmol scale using 10 mol % **2a**, purification by column chromatography by column chromatography (hexane/EtOAc 2:1) to give the titled compound (96 mg, 82% yield) as pale yellow oil:  $^1\text{H}$  NMR: 1.10 (t,  $J = 7.2$ , 3H), 1.11 (t,  $J = 7.2$ , 3H), 2.63 (t,  $J = 8.0$ , 2H), 3.08 (t,  $J = 7.8$ , 2H), 3.24 (q,  $J = 7.2$ , 2H), 3.38 (q,  $J = 7.2$ , 2H), 7.40 (d,  $J = 8.0$ , 2H), 7.81 (d,  $J = 8.0$ , 2H), 9.98 (s, 1H).  $^{13}\text{C}$  NMR: 13.1 ( $\text{CH}_3$ ), 14.3 ( $\text{CH}_3$ ), 31.6 ( $\text{CH}_2$ ), 34.3 ( $\text{CH}_2$ ), 40.3 ( $\text{CH}_2$ ), 41.9 ( $\text{CH}_2$ ), 129.2 (CH), 130.0 (CH), 134.7 (C), 149.1 (C), 170.5 (C), 191.9 (CH). IR: 2978, 2932, 1697, 1636, 1435. MS  $m/z$ : 233 ( $\text{M}^+$ ), 204, 133. HRMS–FAB ( $m/z$ ):  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{14}\text{H}_{20}\text{NO}_2$ , 234.1494; found, 234.1494.



***N*-Benzyl-3-(4-formylphenyl)propanamide (3i)**: Following the procedure with L-proline in 0.70 mmol scale using 10 mol % **2a**, except that 2 equiv  $\text{BnNH}_2$  in place of  $\text{Bn}_2\text{NH}$  was added over 3 h, purification by column chromatography (hexane/EtOAc 1:1) gave the titled compound (121 mg, 65% yield) as light yellow oil:  $^1\text{H}$  NMR: 2.54 (t,  $J = 7.7$ , 2H), 3.08 (t,  $J = 7.7$ , 2H), 4.40 (d,  $J = 5.8$ , 2H), 5.70 (s, 1H), 7.15 (d,  $J = 7.5$ , 2H), 7.26–7.30 (m, 3H), 7.36 (d,  $J = 8.0$ , 2H), 7.78 (d,  $J = 8.0$ , 2H), 9.96 (s, 1H).  $^{13}\text{C}$  NMR: 31.7 ( $\text{CH}_2$ ), 37.7 ( $\text{CH}_2$ ), 43.6 ( $\text{CH}_2$ ), 127.6 (CH), 127.7 (CH), 128.7 (CH), 129.1 (CH), 130.1 (CH), 134.8 (C), 138.0 (C), 148.2 (C), 171.1 (C), 191.9 (CH). IR: 2924, 1697, 1651, 1072. MS  $m/z$ : 267 ( $\text{M}^+$ ), 148, 106, 91. HRMS–FAB ( $m/z$ ):  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{17}\text{H}_{18}\text{NO}_2$ , 268.1338; found, 268.1331.



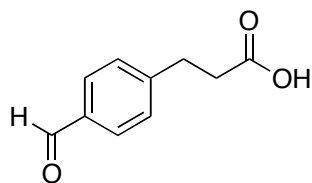
**trans- and cis-N,N-Diethyl-3-(4-formylcyclohexyl)propanamide (3j):** Following the procedure without L-proline using 20 mol % **2a**, purification by column chromatography ( $\text{CHCl}_3$ ) gave an 83:17 diastereomer mixture of the titled compound (213 mg, 89% yield) as pale yellow oil:  $^1\text{H}$  NMR (*trans*): 0.95–1.04 (m, 2H), 1.10 (t,  $J = 7.2$ , 3H), 1.21–1.29 (m, 3H), 1.51–1.65 (m, 2H), 1.86–1.89 (m, 2H), 1.96–1.99 (m, 2H), 2.17 (tt,  $J = 12.2, 3.4$ , 1H), 2.30 (t,  $J = 7.9$ , 2H), 3.29 (t,  $J = 7.2$ , 2H), 3.36 (t,  $J = 7.2$ , 2H), 9.60 (s, 1H). (*cis*): 0.95–1.04 (m, 2H), 1.09 (t,  $J = 7.2$ , 3H), 1.15 (t,  $J = 7.2$ , 3H), 1.37 (m, 1H), 1.51–1.65 (m, 6H), 2.07–2.11 (m, 2H), 2.26 (t,  $J = 7.9$ , 2H), 2.38 (m, 1H), 3.27 (t,  $J = 7.2$ , 2H), 3.35 (t,  $J = 7.2$ , 2H), 9.68 (s, 1H).  $^{13}\text{C}$  NMR (*trans*): 13.1 ( $\text{CH}_3$ ), 14.4 ( $\text{CH}_3$ ), 25.8 ( $\text{CH}_2$ ), 30.5 ( $\text{CH}_2$ ), 31.7 ( $\text{CH}_2$ ), 32.4 ( $\text{CH}_2$ ), 36.9 (CH), 40.06 ( $\text{CH}_2$ ), 41.9 ( $\text{CH}_2$ ), 50.4 (CH), 172.1 (CH), 204.7 (CH). (*cis*): 13.1 ( $\text{CH}_3$ ), 14.4 ( $\text{CH}_3$ ), 23.9 ( $\text{CH}_2$ ), 29.3 ( $\text{CH}_2$ ), 31.4 ( $\text{CH}_2$ ), 32.1 ( $\text{CH}_2$ ), 36.0 (CH), 40.02 ( $\text{CH}_2$ ), 41.9 ( $\text{CH}_2$ ), 47.3 ( $\text{CH}_2$ ), 172.2 (C), 205.6 (CH). IR: 2924, 2855, 1720, 1636, 1450. MS  $m/z$ : 239 ( $\text{M}^+$ ), 210, 115. HRMS–FAB ( $m/z$ ):  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{14}\text{H}_{26}\text{NO}_2$ , 240.1964; found, 240.1966.



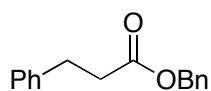
**Hydrocinnamic acid (8a):** To a stirred ice-cooled solution of hydrocinnamaldehyde (**1a**) (134 mg, 1.0 mmol) in  $\text{CH}_2\text{Cl}_2$  (42 mL), were added  $\text{Et}_2\text{NH}$  (0.11 mL, 1.1 mmol) and NCS (134 mg, 1.0 mmol), and the cooling bath was removed. After 0.5 h, the aldehyde was no longer detected by TLC monitoring. To the mixture, were added  $\text{H}_2\text{O}$  (0.04 mL, 2 mmol) and a premixed solution of triazolium salt **2c** (19 mg, 0.050 mmol) and  $\text{Et}_3\text{N}$  (0.17 mL, 1.2 mmol) in  $\text{CH}_2\text{Cl}_2$  (8 mL). After 7 h, the mixture was concentrated *in vacuo*, and the resulting residue, whose  $^1\text{H}$  NMR showed no trace of **3a**, was dissolved in EtOAc (10 mL) and extracted with 10%  $\text{Na}_2\text{CO}_3$  (10 mL). The aqueous layer was acidified to pH 1 by 10% HCl and extracted with  $\text{CHCl}_3$ . The organic layer was washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , and concentrated *in vacuo* to give the titled compound (127 mg, 85% yield) as white solids of mp 45–47 °C (lit.<sup>13</sup> 47.6–47.7 °C):  $^1\text{H}$  and  $^{13}\text{C}$  NMR, IR, and MS were identical to those reported.<sup>13,14</sup>

13. Nambu, H.; Hata, K.; Matsugi, M.; Kita, Y. *Chem. Eur. J.* **2005**, *11*, 719–727.

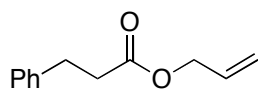
14. Concellón, J. M.; Rodríguez-Solla, H. *Chem. Eur. J.* **2002**, *11*, 4493–4497.



**4-Formylbenzenepropanoic acid (8d):** The above procedure was followed using 10 mol % **2c** to give the titled compound (130 mg, 73% yield) as white solids of mp 134–136 °C:  $^{13}\text{C}$  NMR: 30.8 ( $\text{CH}_2$ ), 35.0 ( $\text{CH}_2$ ), 129.0 (CH), 130.1 (CH), 134.8 (C), 147.7 (C), 177.2 (C), 192.0 (CH). IR: 3433, 2932, 1697, 1605, 1057. MS  $m/z$ : 178 ( $\text{M}^+$ ).  $^1\text{H}$  NMR was identical to those reported.<sup>13</sup>



**Benzyl hydrocinnamate (9):** To a stirred ice-cooled solution of hydrocinnamaldehyde (**1a**) (134 mg, 1.0 mmol) in  $\text{CH}_2\text{Cl}_2$  (2 mL), were added  $\text{Et}_2\text{NH}$  (0.11 mL, 1.1 mmol) and NCS (134 mg, 1.0 mmol), and the cooling bath was removed. After 0.5 h, the aldehyde was no longer detected by TLC monitoring. To the mixture, were added BnOH (0.21 mL, 2.0 mmol) and a premixed solution of triazolium salt **2c** (19 mg, 0.050 mmol) and  $\text{Et}_3\text{N}$  (0.17 mL, 1.2 mmol) in  $\text{CH}_2\text{Cl}_2$  (8 mL). After 5 h, the mixture was concentrated *in vacuo*, and the resulting residue was purified by column chromatography (hexane/EtOAc 20:1) to give the titled compound (210 mg, 87% yield) as colorless oil:  $^1\text{H}$  and  $^{13}\text{C}$  NMR, IR, and MS were identical to those reported.<sup>15</sup>

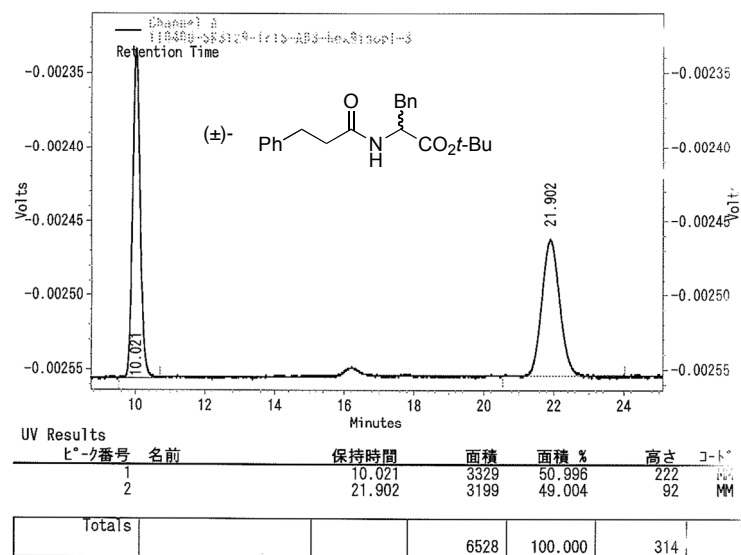
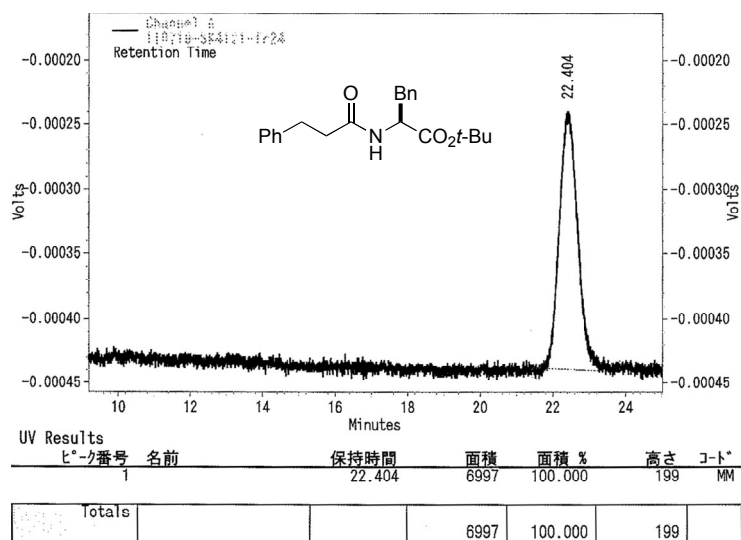


**Allyl hydrocinnamate (10):** The above procedure was followed to give the titled compound (157 mg, 83% yield) as colorless oil:  $^1\text{H}$  and  $^{13}\text{C}$  NMR, IR, and MS were identical to those reported.<sup>15</sup>

15. Iwasaki, T.; Maegawa, Y.; Hayashi, Y.; Ohshima, T.; Mashima, K. *J. Org. Chem.* **2008**, *73*, 5147–5150.



HPLC traces of **3g** (Daicel Chiralcel AD-3; hexane/*i*-PrOH = 9:1; 1 mL/min; 254 nm).



**DFT calculations of NHC complexes:** All the calculations were performed using Gaussian 03W program<sup>16</sup> at B3LYP/6-311+G(d,p) level of theory with tight SCF convergence and ultrafine integration grids. Basis set superposition error (BSSE) was corrected using counterpoise corrections. Difference of the stability between complexes ( $\Delta\Delta G$ ) was calculated by the following equation:

$$\begin{aligned}\Delta\Delta G &= \Delta G_{\text{NHC-HOt}} - \Delta G_{\text{NHC-H}_2\text{O}} \\ &= (G_{\text{NHC-HOt}} + E_{\text{BSSE (NHC-HOt)}} - G_{\text{NHC}} - G_{\text{HOt}}) - (G_{\text{NHC-H}_2\text{O}} + E_{\text{BSSE (NHC-H}_2\text{O)}} - G_{\text{NHC}} - G_{\text{H}_2\text{O}}) \\ &= G_{\text{NHC-HOt}} + E_{\text{BSSE (NHC-HOt)}} - G_{\text{HOt}} - G_{\text{NHC-H}_2\text{O}} - E_{\text{BSSE (NHC-H}_2\text{O)}} + G_{\text{H}_2\text{O}} \\ &= -677.601914 + 0.001261613 + 317.444376 + 436.599820 - 0.000816811 - 76.455479 \text{ au} \\ &= -0.012752 \text{ au} \\ &= -8.00199 \text{ kcal/mol}\end{aligned}$$

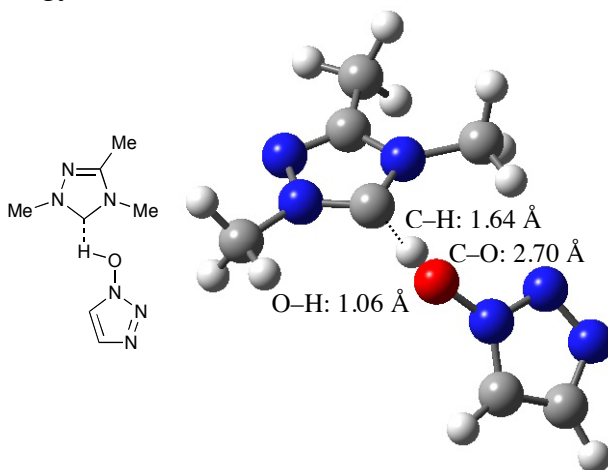
where  $\Delta G$ ,  $G$ , and  $E_{\text{BSSE}}$  stand for stability in free energy, free energy, and BSSE energy, respectively, and subscripts NHC-HOt, NHC-H<sub>2</sub>O, NHC, HOt, and H<sub>2</sub>O stand for a complex of 1,3,4-trimethyl-4,5-dihydro-1*H*-1,2,4-triazol-5-ylidene with 1-hydroxy-1*H*-1,2,3-triazole, a complex of 1,3,4-trimethyl-4,5-dihydro-1*H*-1,2,4-triazol-5-ylidene with water, 1,3,4-trimethyl-4,5-dihydro-1*H*-1,2,4-triazol-5-ylidene, 1-hydroxy-1*H*-1,2,3-triazole, and water, respectively.

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16. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, Jr., J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; and Pople, J. A.; Gaussian, Inc., Wallingford CT, 2004.

**Complex of 1,3,4-trimethyl-4,5-dihydro-1*H*-1,2,4-triazol-5-ylidene with 1-hydroxy-1*H*-1,2,3-triazole (NHC–HOT).**

Zero-point vibrational energy	538774.3 (Joules/Mol)
	128.77014 (Kcal/Mol)
Zero-point correction =	0.205208 (Hartree/Particle)
Thermal correction to Energy =	0.219661
Thermal correction to Enthalpy =	0.220606
Thermal correction to Gibbs Free Energy =	0.161216
Sum of electronic and zero-point Energies =	-677.557922
Sum of electronic and thermal Energies =	-677.543468
Sum of electronic and thermal Enthalpies =	-677.542524
Sum of electronic and thermal Free Energies =	-677.601914
Energies (RB + HF – LYP) =	-677.763129820
Counterpoise: BSSE energy =	0.001261612823
Counterpoise: corrected energy =	-677.761868206540



Atomic Type	Coordinates (Angstroms)		
	X	Y	Z
N	3.05966600	0.68830400	-0.39794700
N	1.87297800	1.31624800	-0.09655600
C	0.88904300	0.49151600	0.28513800
N	1.49239200	-0.73186800	0.21843600
C	2.80109800	-0.57450700	-0.19520800
C	1.79636100	2.76356600	-0.21519000
H	0.79187100	3.07227500	0.06640500
H	2.00283800	3.06203500	-1.24397500
H	2.52725100	3.22816700	0.44808300
C	0.84655700	-2.00128800	0.55616500
H	1.26065400	-2.40152600	1.48429800
H	1.00102900	-2.72201900	-0.24836600
H	-0.22134000	-1.82319800	0.67310800
C	3.77314100	-1.68530000	-0.38594600
H	4.73199500	-1.27076000	-0.69351600
H	3.43071100	-2.38353100	-1.15502100
H	3.91481800	-2.25156700	0.53875900
H	-0.63008600	0.86578700	0.76293600
O	-1.60785300	1.12878200	1.08396700
N	-2.46400100	0.37734700	0.35556000
N	-2.39334200	-0.95736600	0.34977000
C	-3.49156400	0.83384200	-0.39160100
H	-3.70289000	1.88326200	-0.49244600
N	-3.36906600	-1.38962600	-0.41889000
C	-4.06653300	-0.32259800	-0.88021800
H	-4.92304600	-0.44183400	-1.52345600

**Complex of 1,3,4-trimethyl-4,5-dihydro-1*H*-1,2,4-triazol-5-ylidene and water (NHC–H<sub>2</sub>O).**

Zero-point vibrational energy 437403.2 (Joules/Mol)

104.54188 (Kcal/Mol)

Zero-point correction = 0.166598 (Hartree/Particle)

Thermal correction to Energy = 0.178354

Thermal correction to Enthalpy = 0.179299

Thermal correction to Gibbs Free Energy = 0.128461

Sum of electronic and zero-point Energies = -436.561682

Sum of electronic and thermal Energies = -436.549926

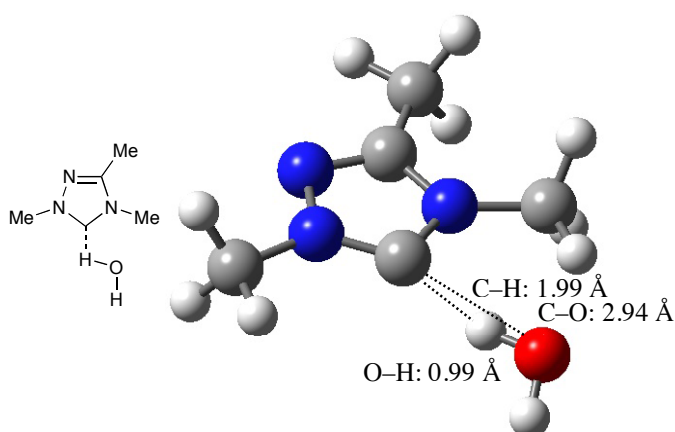
Sum of electronic and thermal Enthalpies = -436.548982

Sum of electronic and thermal Free Energies = -436.599820

Energies (RB + HF – LYP) = -436.728280424

Counterpoise: BSSE energy = 0.000816811349

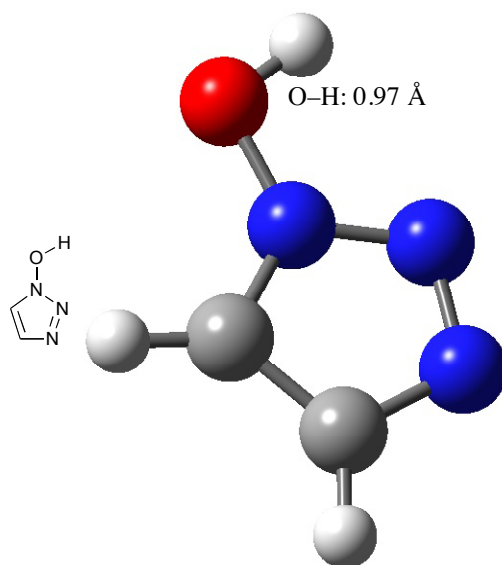
Counterpoise: corrected energy = -436.727463612794



Atomic Type	Coordinates (Angstroms)		
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C	0.74360800	0.36223800	0.02188500
N	-0.08883600	-0.72890400	0.01725900
C	-1.40779400	-0.31657400	-0.00206900
C	0.16545700	2.78933500	-0.00149400
H	1.24805700	2.89425900	-0.00092800
H	-0.25561500	3.26895100	0.88396300
H	-0.25190500	3.25728600	-0.89472300
C	0.37379200	-2.11429800	0.02221400
H	0.03750200	-2.63292700	-0.87842600
H	-0.00542400	-2.64056800	0.90118600
H	1.46173900	-2.10594000	0.04743700
C	-2.58653300	-1.22630100	-0.01363900
H	-3.49798200	-0.63040800	-0.02973500
H	-2.60293400	-1.86712000	0.87280300
H	-2.57782600	-1.87652900	-0.89327800
H	2.66469100	-0.14654600	-0.03402800
O	3.47767400	-0.70147400	-0.08764300
H	4.13137000	-0.26313500	0.46392100
N	-1.46879800	0.98553200	-0.00868500
N	-0.14297400	1.37023900	0.00593600
C	0.74360800	0.36223800	0.02188500
N	-0.08883600	-0.72890400	0.01725900
C	-1.40779400	-0.31657400	-0.00206900
C	0.16545700	2.78933500	-0.00149400

### 1-Hydroxy-1*H*-1,2,3-triazole (HOt).

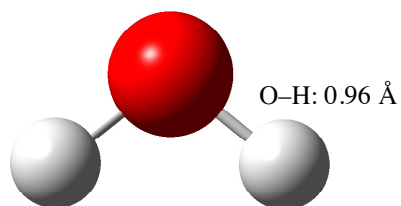
Zero-point vibrational energy	162864.7 (Joules/Mol)
	38.92560 (Kcal/Mol)
Zero-point correction =	0.062032 (Hartree/Particle)
Thermal correction to Energy =	0.066948
Thermal correction to Enthalpy =	0.067892
Thermal correction to Gibbs Free Energy =	0.033874
Sum of electronic and zero-point Energies =	-317.405819
Sum of electronic and thermal Energies =	-317.400904
Sum of electronic and thermal Enthalpies =	-317.399960
Sum of electronic and thermal Free Energies =	-317.433977
Energies (RB + HF – LYP) =	-317.467851392



Atomic Type	Coordinates (Angstroms)		
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N	-0.59650600	0.06531500	0.00001200
N	0.03377200	-1.10333200	-0.00002200
C	0.23682600	1.12316400	-0.00007000
H	-0.11034300	2.14069900	0.00002100
N	1.24805700	2.89425900	-0.00092800
C	1.31920600	-0.83120200	-0.00007700
H	1.47870100	0.51425300	0.00011100
C	2.45568200	0.96841600	0.00017000

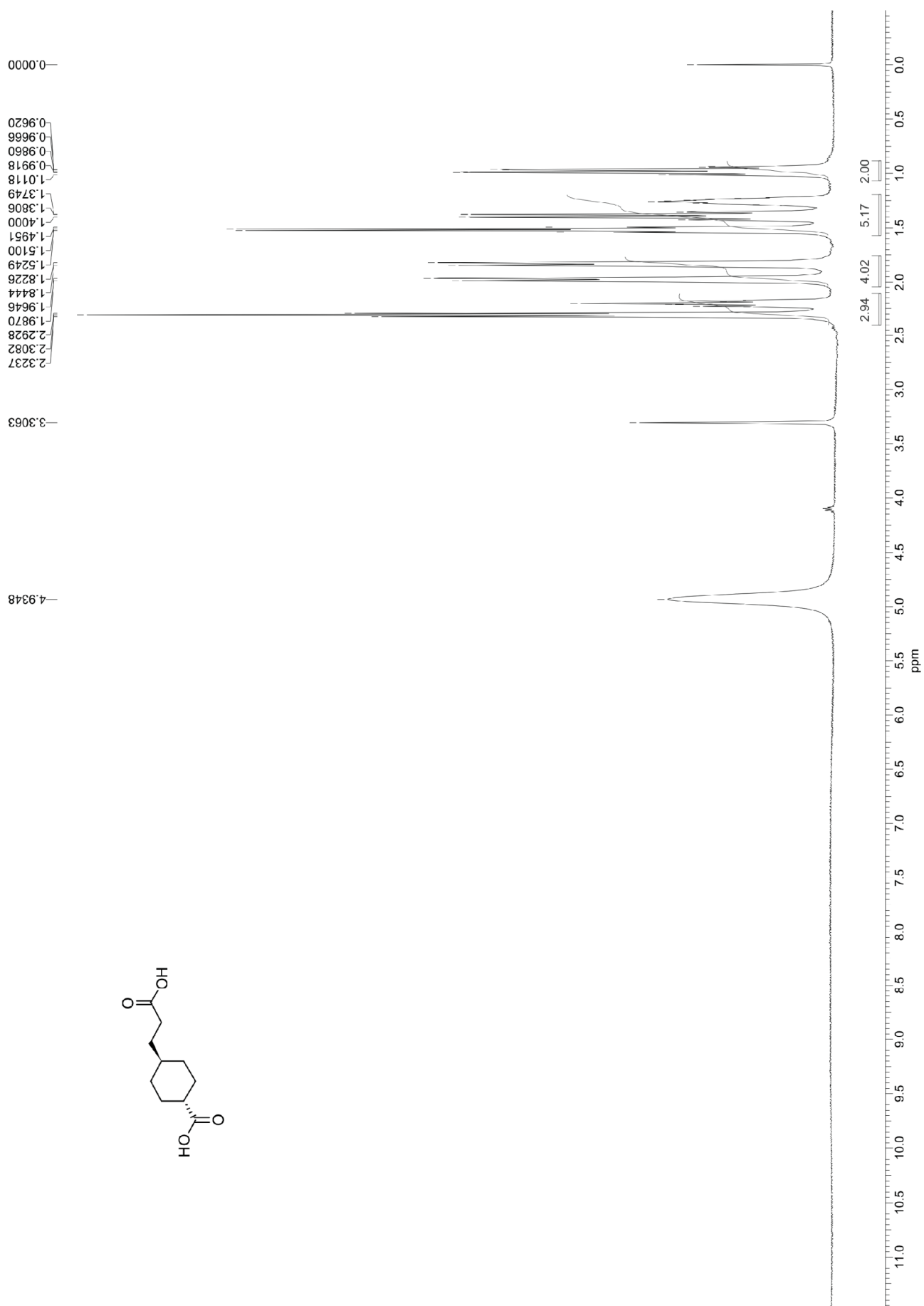
### Water (H<sub>2</sub>O).

Zero-point vibrational energy	55966.2 (Joules/Mol)
	13.37625 (Kcal/Mol)
Zero-point correction =	0.021316 (Hartree/Particle)
Thermal correction to Energy =	0.024152
Thermal correction to Enthalpy =	0.025096
Thermal correction to Gibbs Free Energy =	0.003015
Sum of electronic and zero-point Energies =	-76.426132
Sum of electronic and thermal Energies =	-76.423297
Sum of electronic and thermal Enthalpies =	-76.422353
Sum of electronic and thermal Free Energies =	-76.444433
Energies (RB + HF - LYP) =	-76.4474485616

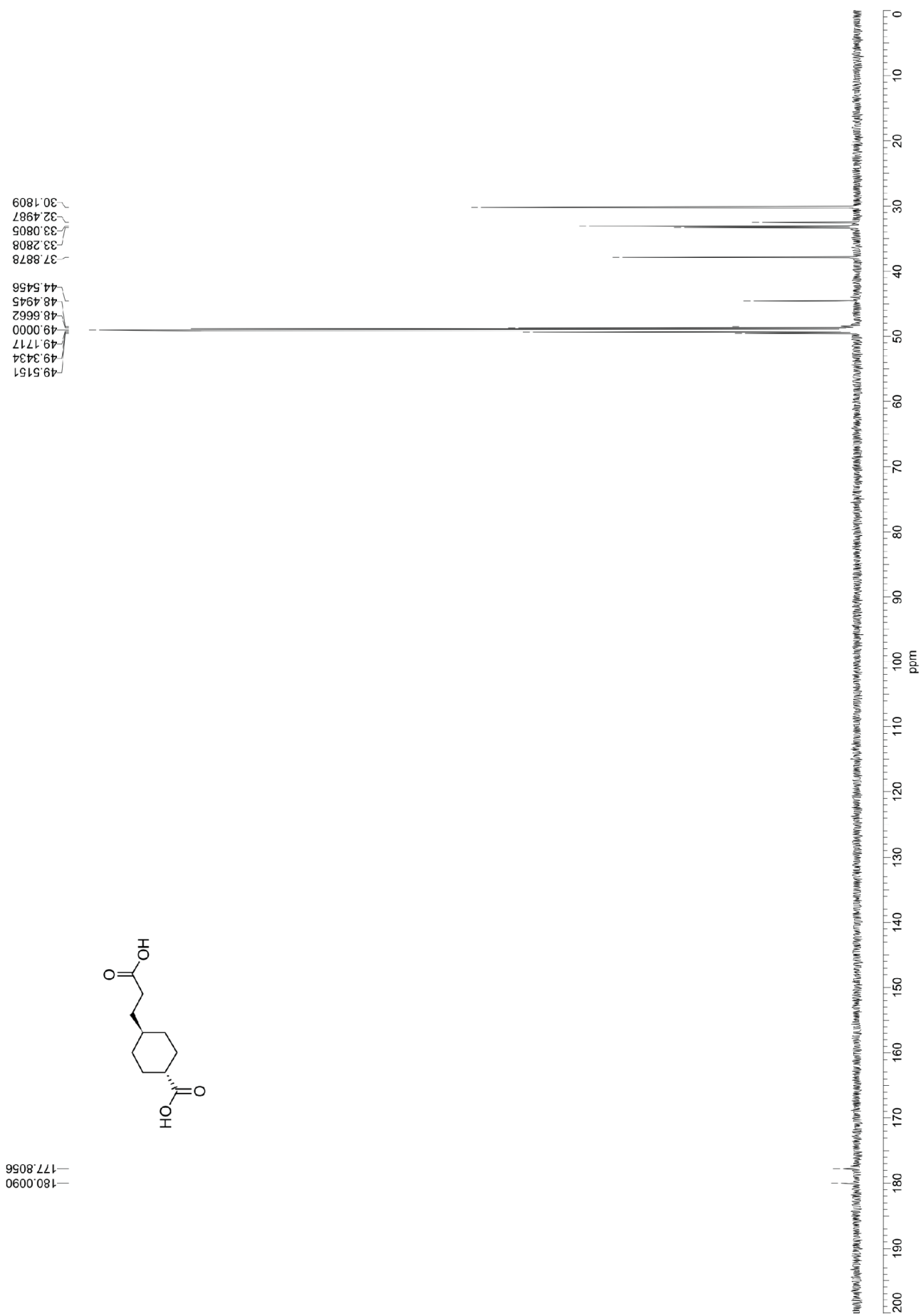


Atomic Type	Coordinates (Angstroms)		
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H	-0.75705200	-0.47473300	0.00000000

*trans*-S2 (<sup>1</sup>H NMR)

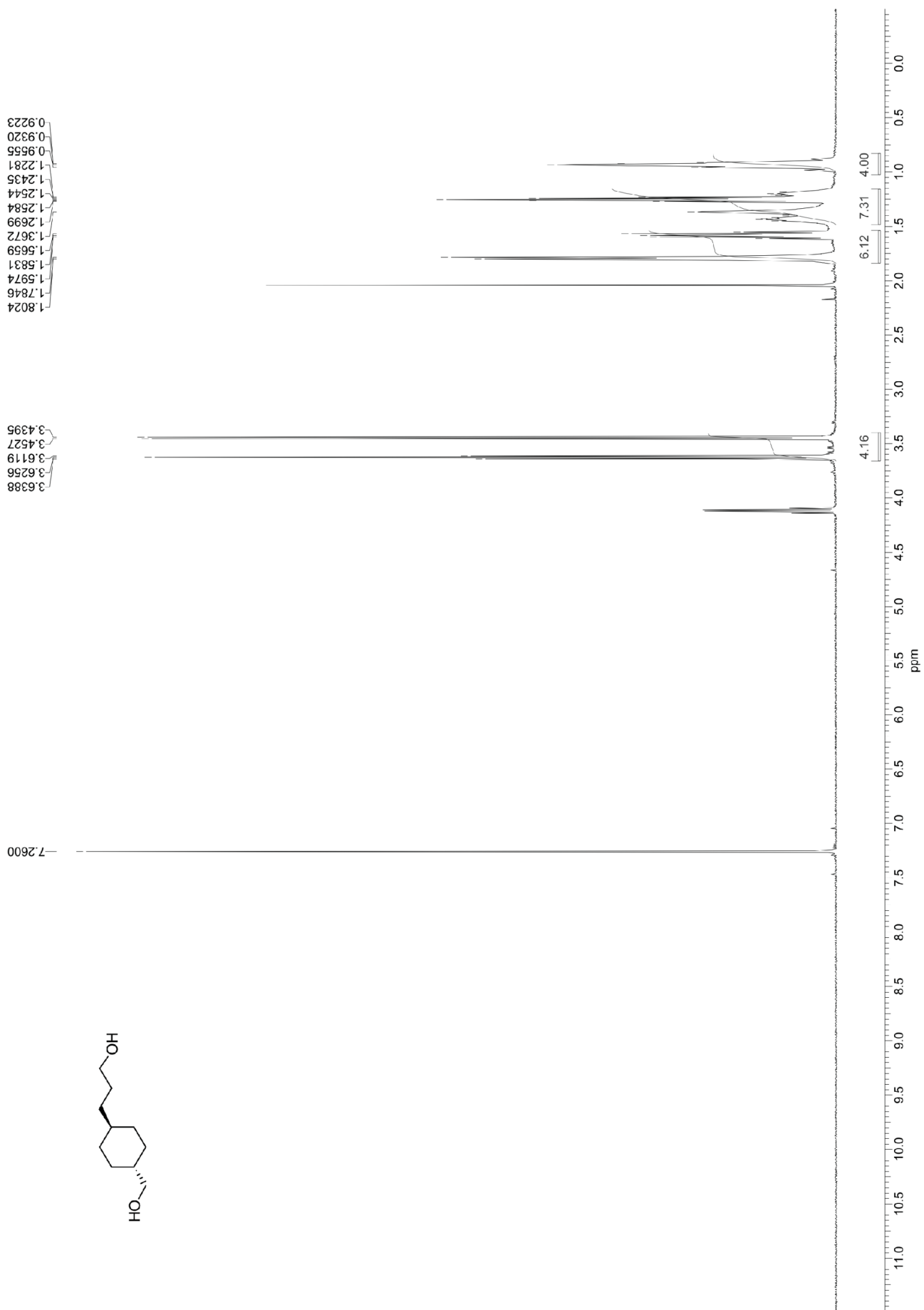


*trans*-S2 (<sup>13</sup>C NMR)

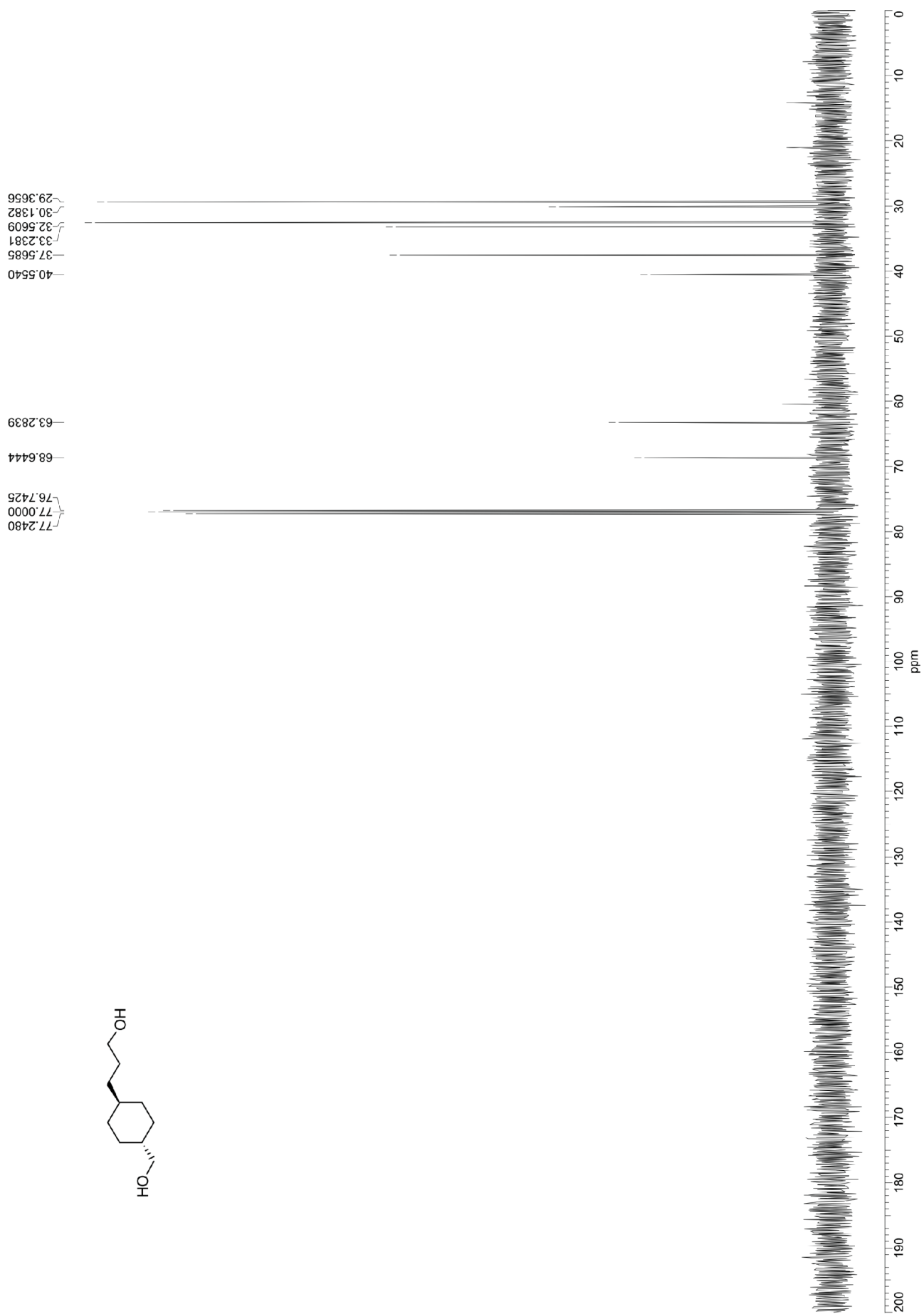




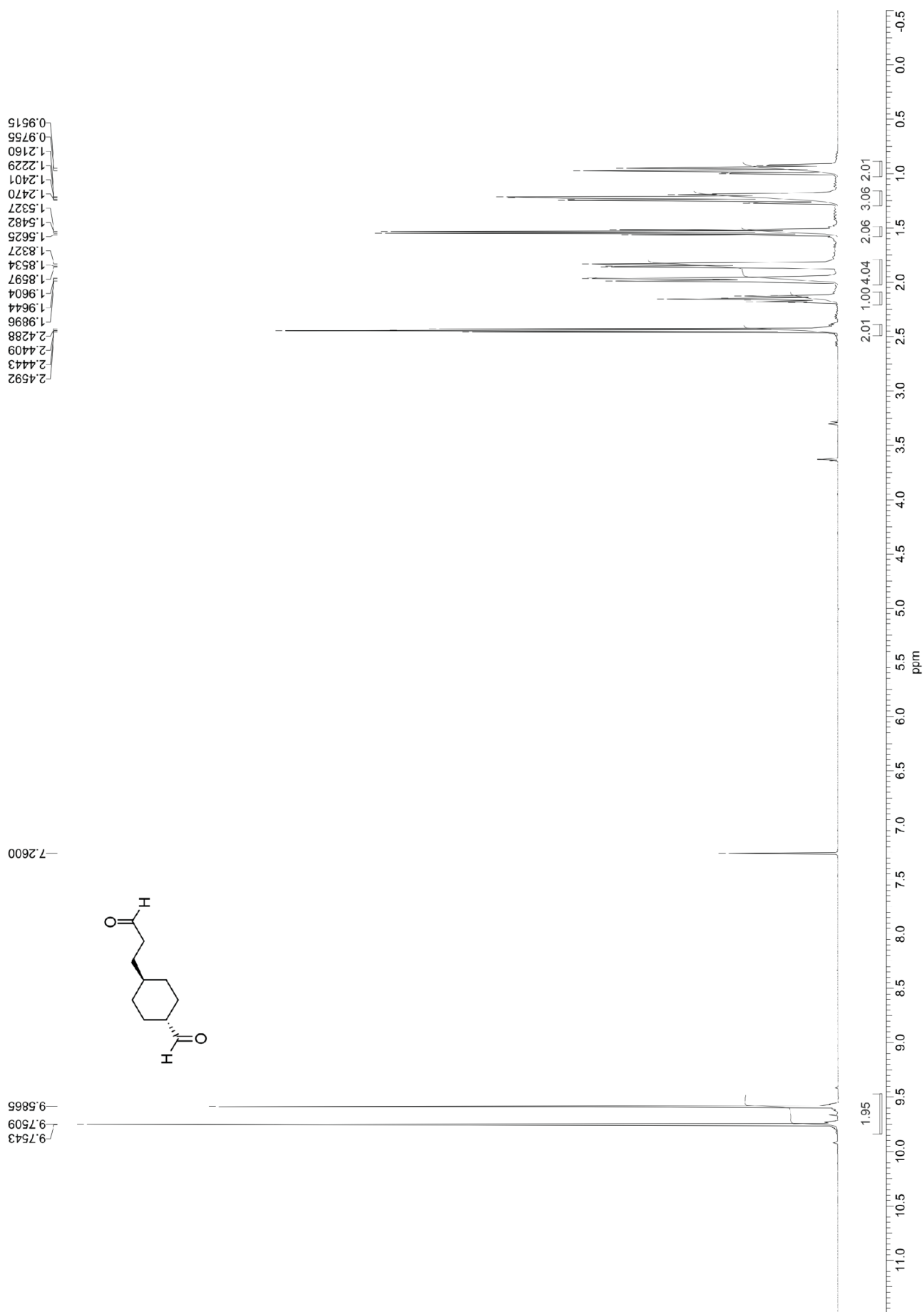
S3 (<sup>1</sup>H NMR)



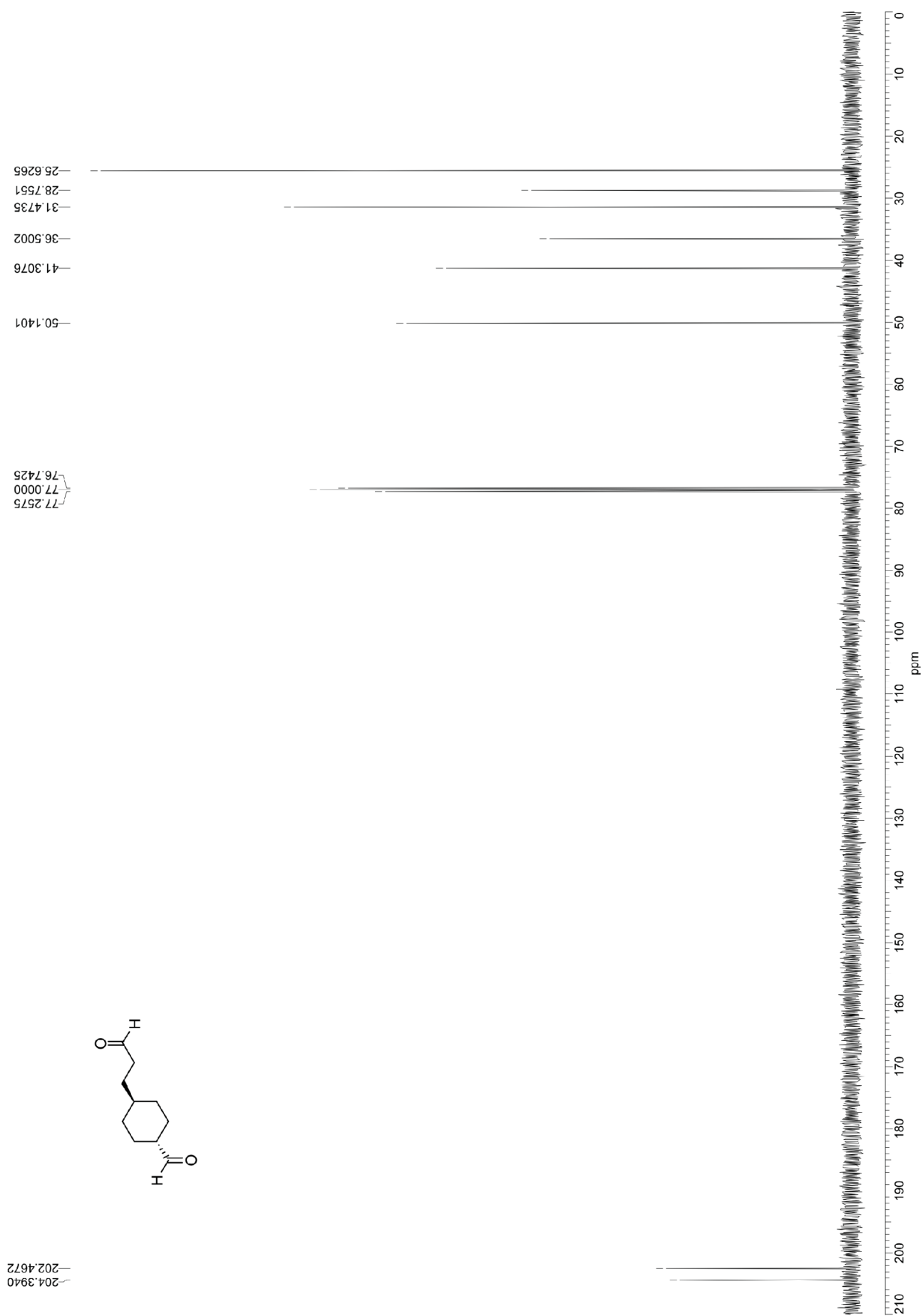
### S3 (<sup>13</sup>C NMR)



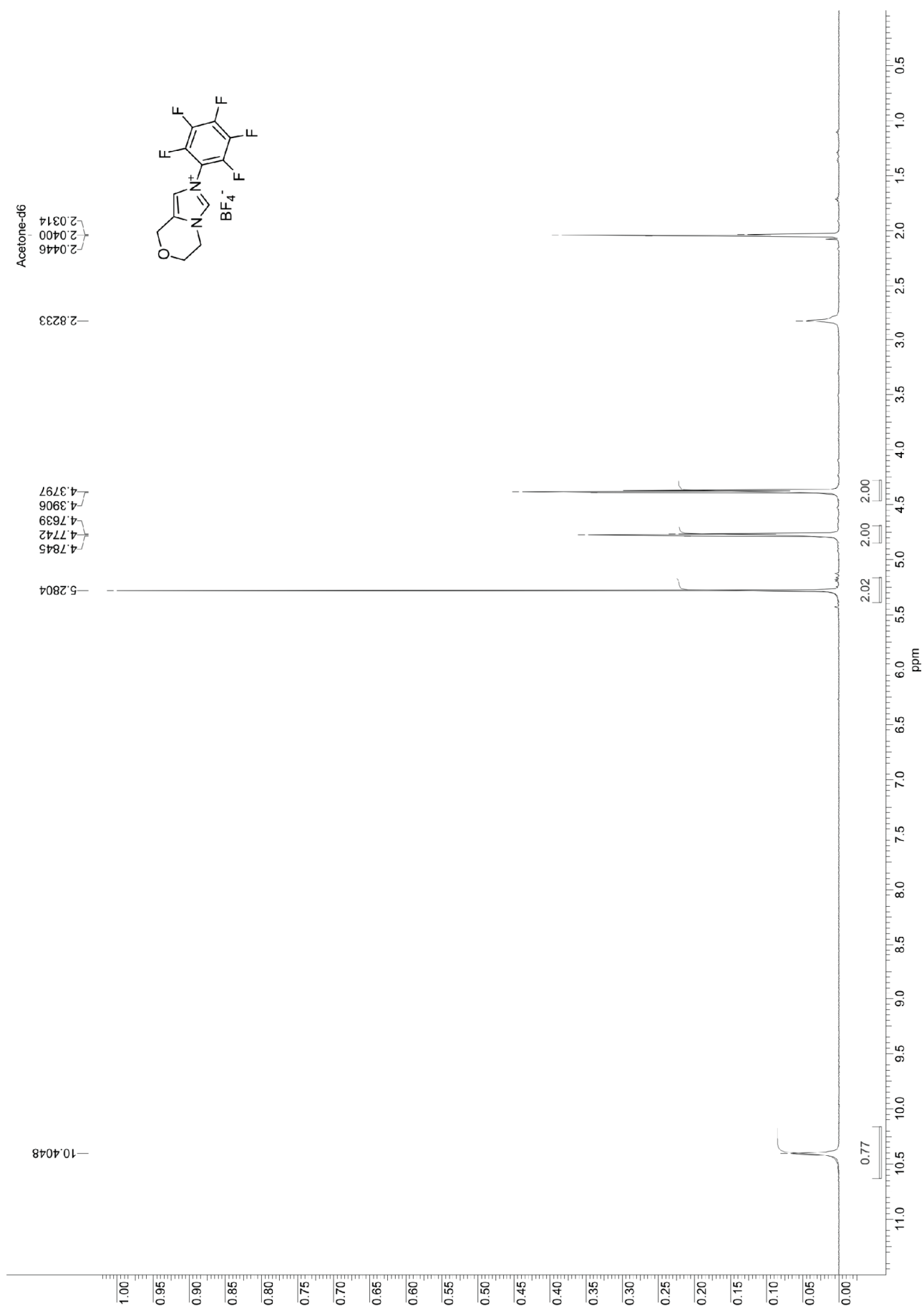
**1e** ( $^1\text{H}$  NMR)



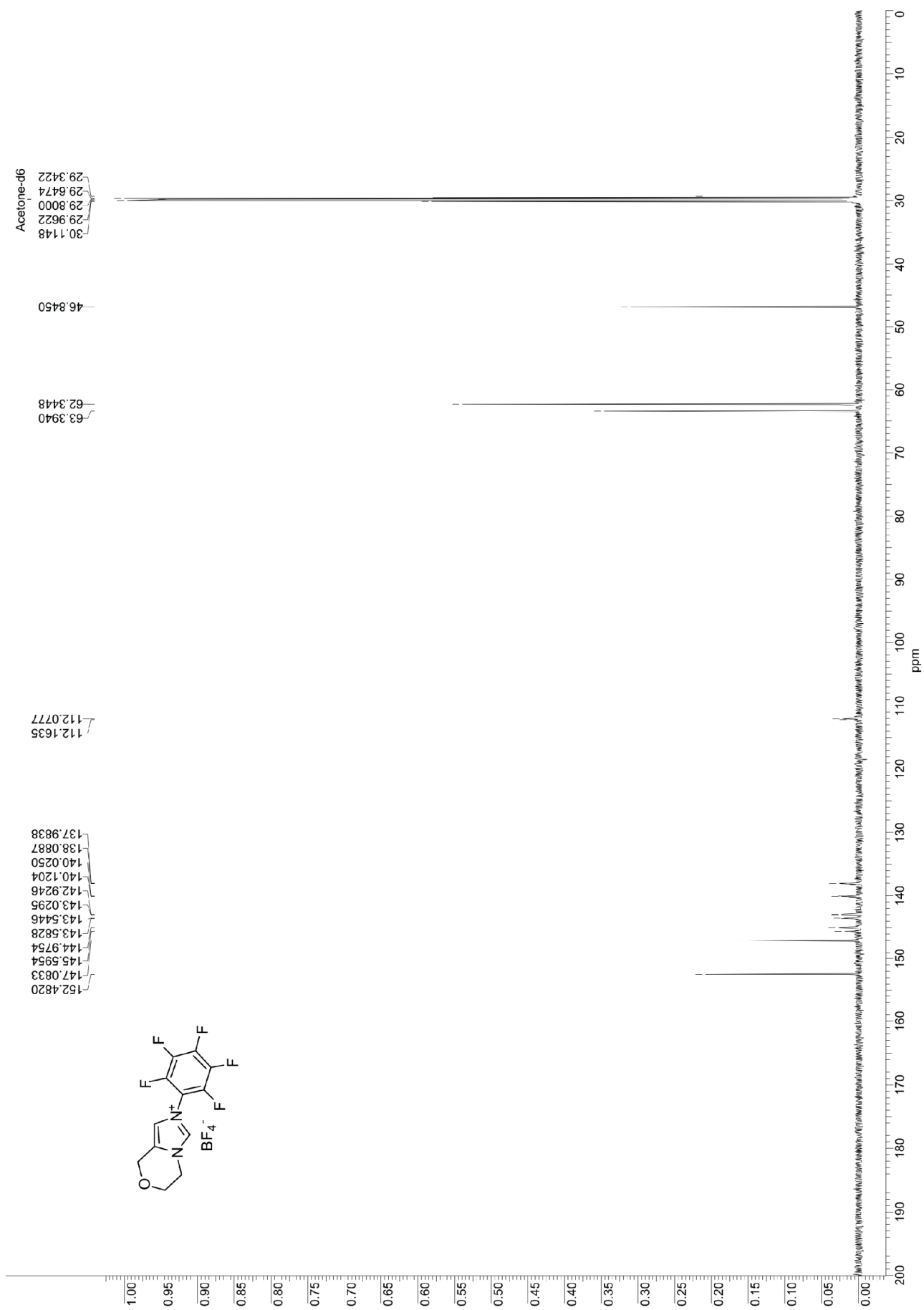
**1e** ( $^{13}\text{C}$  NMR)



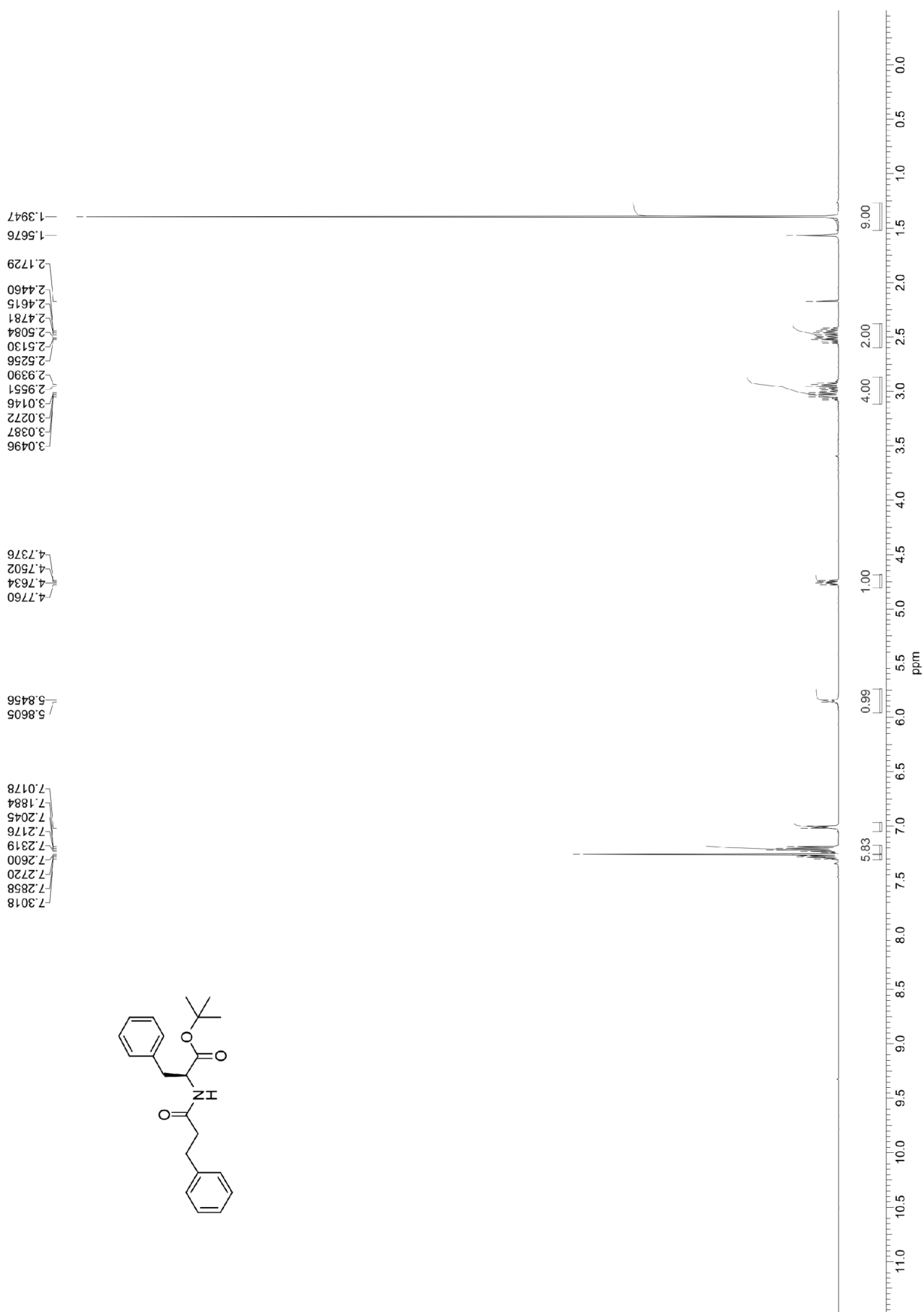
**2b** ( $^1\text{H}$  NMR)



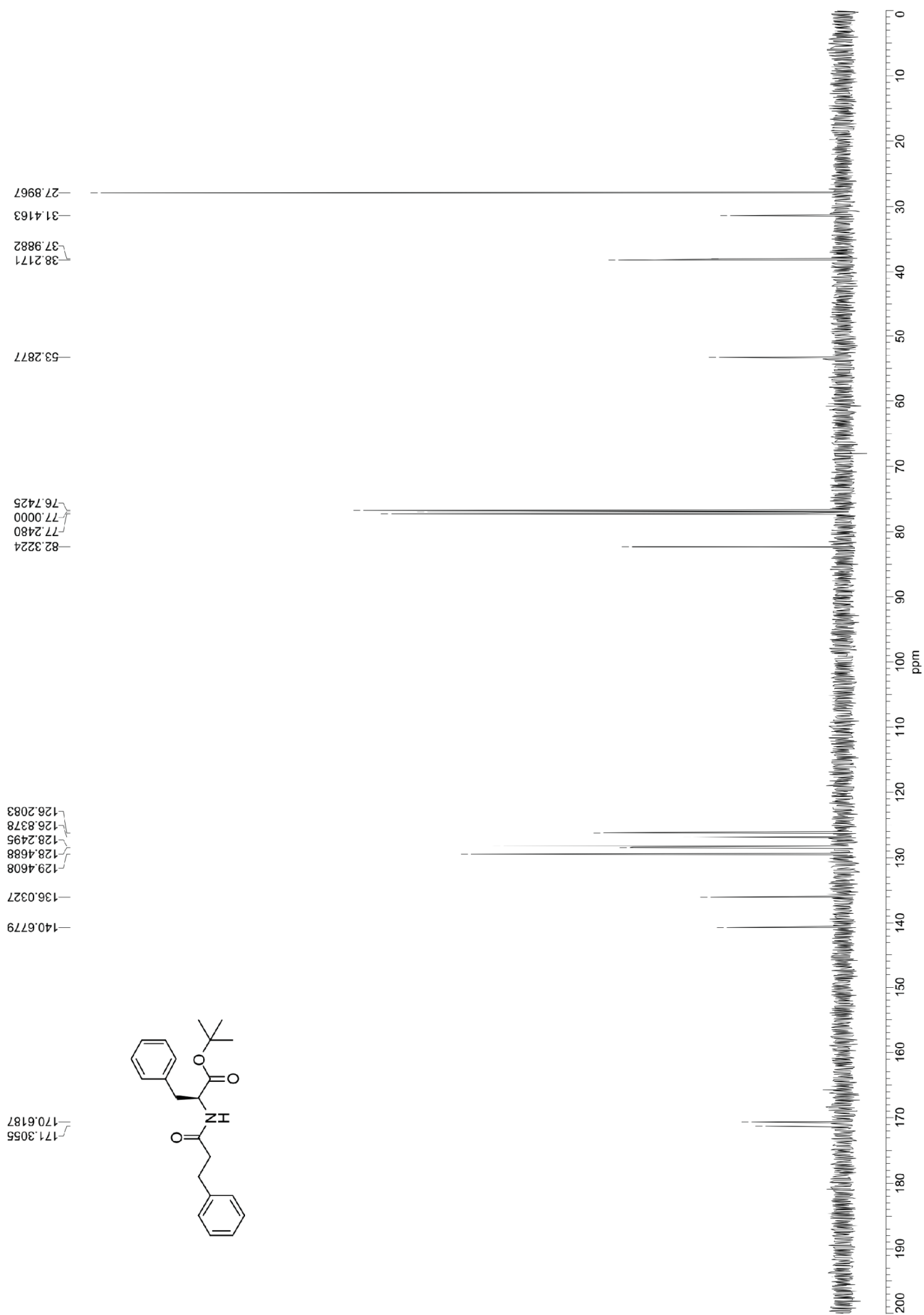
**2b** ( $^{13}\text{C}$  NMR)



3g (<sup>1</sup>H NMR)

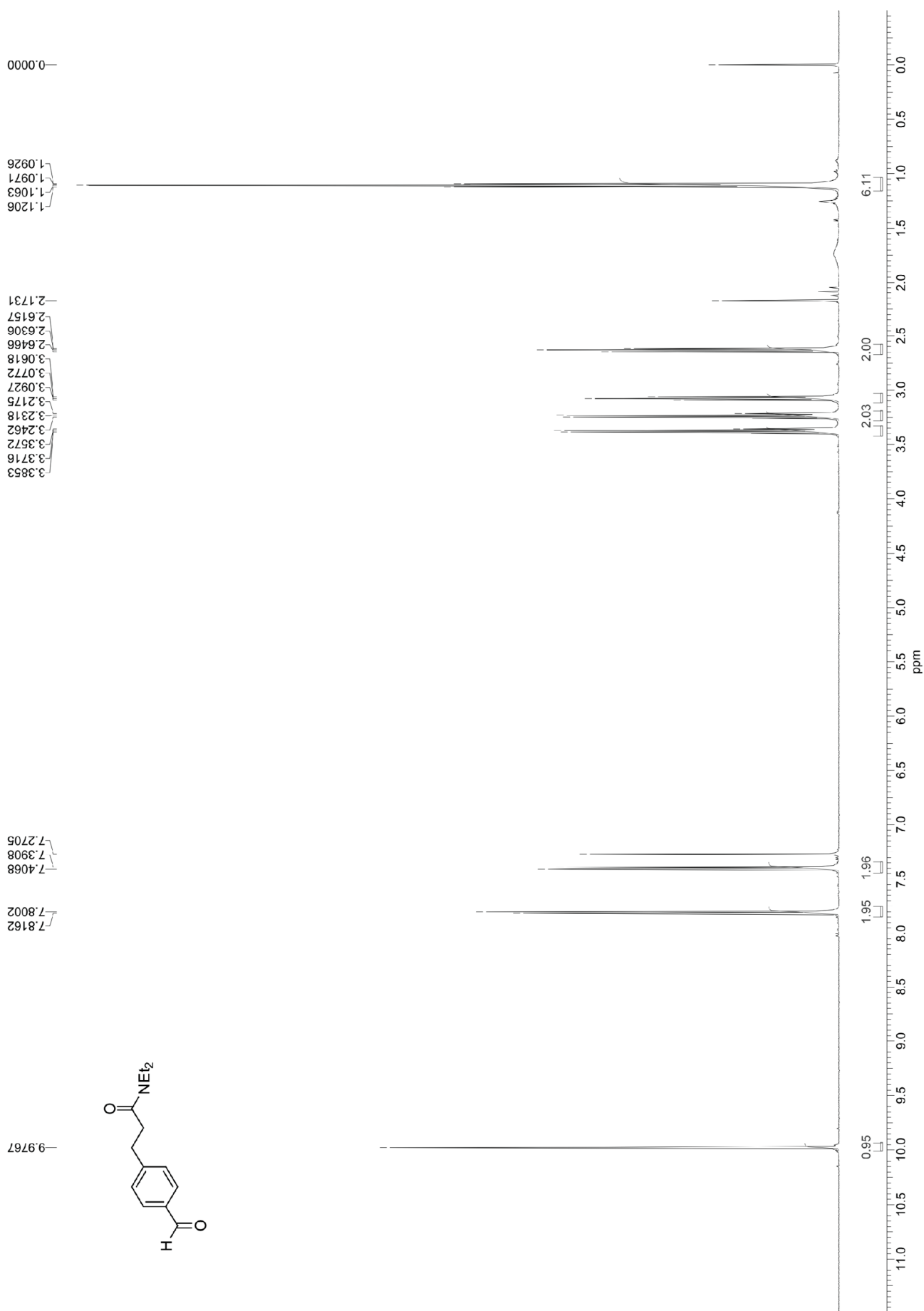


**3g** ( $^{13}\text{C}$  NMR)

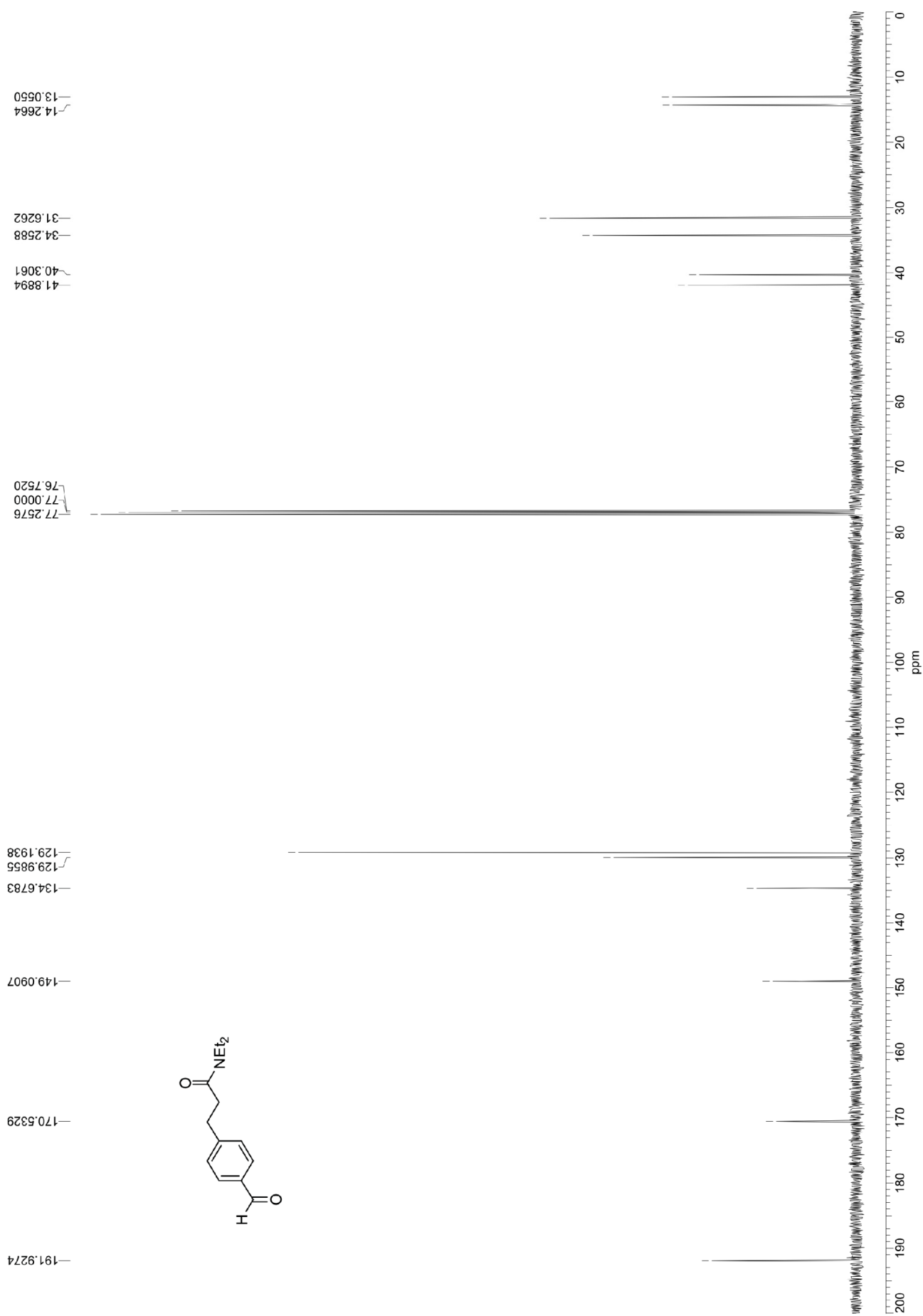




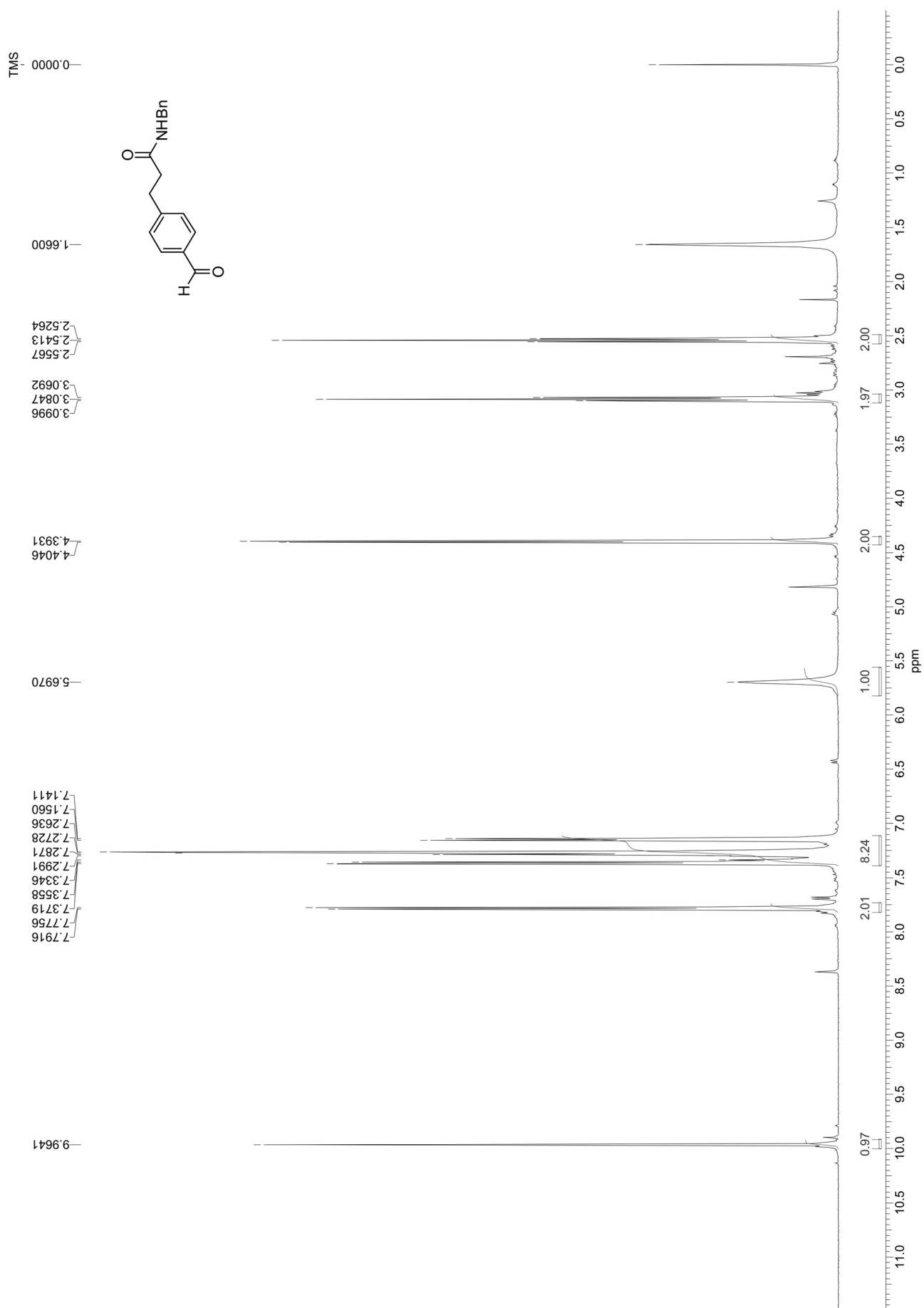
### 3h (<sup>1</sup>H NMR)



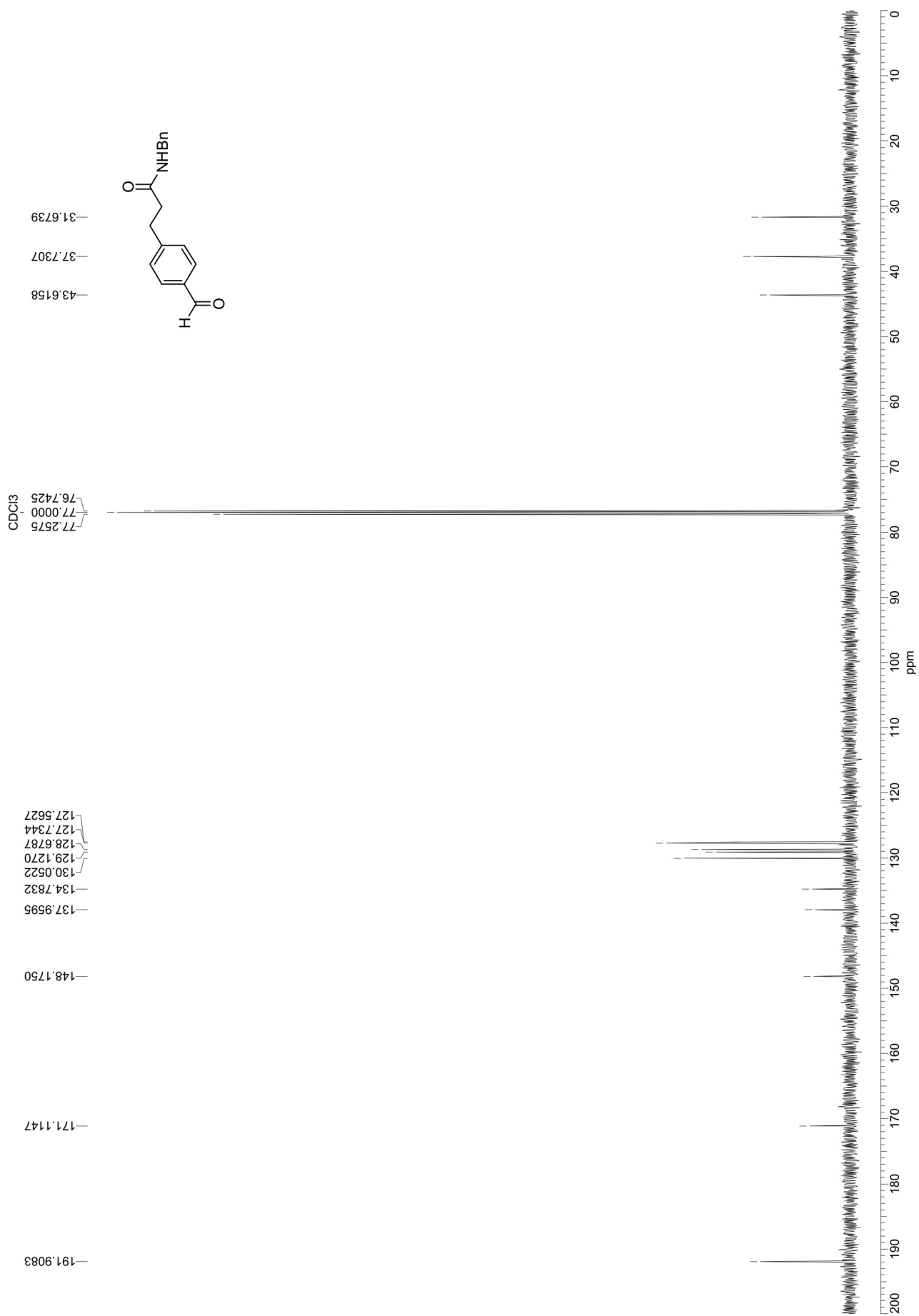
**3h** ( $^{13}\text{C}$  NMR)



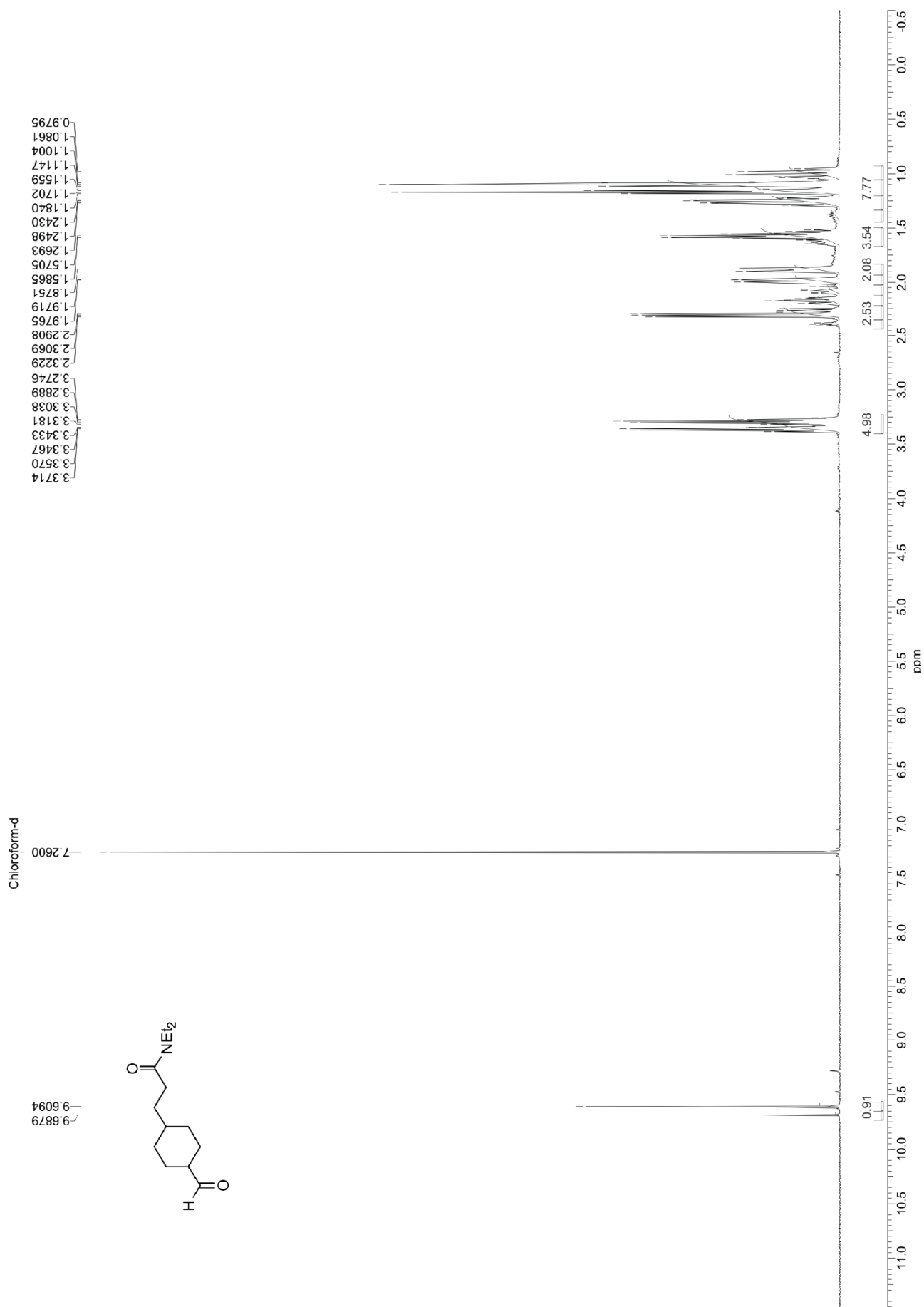
**3i** ( $^1\text{H}$  NMR)



**3i** ( $^{13}\text{C}$  NMR)



3j (<sup>1</sup>H NMR)



3j (<sup>13</sup>C NMR)

