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# Supplementary Information

## A Convenient Synthesis of Anthranilic Acids by Pd-Catalyzed Direct Intermolecular *ortho*-C-H Amidation of Benzoic Acids

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## 1. General Information

**General**. All the amidation reactions were performed in a 10 mL Schlenk tube under an atmosphere of nitrogen. Thin layer chromatography was performed on silica gel plates. Flash column chromatography was performed on 230-400 mesh silica gel (NA Chemical). GC-MS analyses were performed on a 6890N-GC (Agilent Technology) with 5973Network-MS (Agilent Technology). $^{1}$H, $^{13}$C, DEPT 135$^{o}$ NMR analyses were performed on a Bruker (400 MHz) spectrometer. Chemical shifts (δ) were given in ppm, and the signals were referenced with the solvent residual peak(s). NMR yields and conversions were determined with dibromomethane (0.1 mmol) as the internal standard, with reference to a singlet signal (2H) at $\delta_H$ 4.9 ppm (in $CDCl_3$) $\delta_H$ 5.3 ppm (in $d_6$-acetone). IR spectra were obtained by a Nicolet-380 FT-IR spectrometer. Melting points were recorded on a BÜCHIB- 545 instrument and were uncorrected. High resolution mass spectra were obtained using a VG MICROMASS Fison VG platform and with an electrospray ionization mode.

**Materials.** Palladium(II) acetate, benzoic acid, 3,4-dimethylbenzoic acid, 3-methoxybenzoic acid, 3-chlorobenzoic acid, 3-bromobenzoic acid, 3-trifluoromethylbenzoic acid, 2-benzylbenzoic acid, 2,4-dimethylbenzoic acid, 2-methyl-4-fluorobenzoic acid, 2-methoxy-4-methylbenzoic acid, 1,4-benzodioxane-6-carboxylic acid, 2-napthoic acid, 1-napthoic acid, sodium hydroxide, lithium hydroxide monohydrate, potassium hydroxide, tetrabutylammonium hydroxide, hydroxylamine hydrochloride, ethyl chloroformate , triethylamine, *p*-nitrobenzenesulfonyl chloride, *p*-toluenesulfonyl chloride, 2-mesitylenesulfonyl chloride, pentafluorobenzoyl chloride, pivaloyl chloride, potassium acetate, potassium pivalate, potassium hydrogenphosphate dibasic, potassium carbonate, potassium hydrogencarbonate and all the solvents (except 1,4-dioxane) were obtained commercially, and used as received without purification. All the lithium benzoates were synthesized from commercially available benzoic acids (except **1f**) by reacting with lithium hydroxide in methanol. Ethyl *N*-carboxylate carbamates,[1] ethyl *N*-sulfonyloxycarbamates,[1] 2,6-$d_2$-benzoic acid[2] and 3-phenylbenzoic acid[3] (**1f**) were prepared according to the literature procedures. 1,4-Dioxane was sodium-dried and distilled before use.

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## 2. Experimental Procedures

### 2.1 General Procedures for Preparation of Lithium Benzoates

Lithium benzoates (3 mmol) were prepared by treating benzoic acids with $LiOH \cdot H_2O$ (0.9 equiv) in MeOH (10 mL) at room temperature for 24 h. After removal of the solvent by rotary evaporation, the residue was rinsed with acetone (3 × 5 mL). The crude products were dried under vaccum for 24 h and were used directly without further purification.

### 2.2 General Procedure for the Pd-Catalyzed C-H Amidation of Lithium Benzoates

A mixture of lithium benzoate (0.2 mmol), $Pd(OAc)_2$ (10 mol%) and KOAc (1 equiv) was dissolved in 1,4-dioxane (0.5 mL) in a 10 mL Schlenk tube, and ethyl *N*-mesitylsulfonyloxycarbamate (1.5 equiv) dissolved in dioxane (1 mL) was added dropwise by a syringe pump at the rate of 0.3 equiv / h. The reaction was stirred at 90 $^oC$ for 6 h under a $N_2$ atmosphere. After cooling to room temperature, the reaction mixture was diluted with EtOAc (ca. 4 mL), and the mixture was acidified with 2 M HCl (2 mL) solution. The aqueous layer was extracted with EtOAc (5 mL × 3). The combined organic extracts were dried over anhydrous $Na_2SO_4$ and then filtered through a short plug of Celite, and the filtrate was evaporated to dryness by rotary evaporation. The residue was redissolved with dichloromethane (DCM). A minimum amount of MeOH may be added (when the reaction crude was sparingly-soluble in DCM). The dissolved mixture was then purified by flash column chromatography on silica gel by gradient elution with 10-50% EtOAc in hexanes (5% increment of EtOAc).

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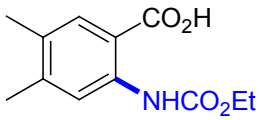
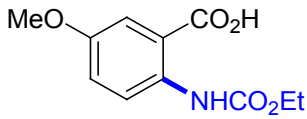
## 3. Physical Characterization Data



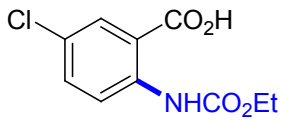
**3a**

**3a** was isolated as a brown solid (30.0 mg, 63% yield). mp = 140-142 °C; $^{1}$H NMR ($CDCl_3$, 400 MHz): $\delta_H$ 10.1 (s, 1H), 8.26 (s, 1H), 7.84 (s, 1H), 4.23 (q, $J$ = 7.2 Hz, 2H), 2.32 (s, 3H), 2.23 (s, 3H), 1.34 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta_C$ 172.6 (C), 153.7 (C), 145.8 (C), 140.4 (C), 132.3 (CH), 130.2 (C), 119.9 (CH), 111.1 (C), 61.2 ($CH_2$), 20.6 ($CH_3$), 18.9 ($CH_3$), 14.5 ($CH_3$); IR (KBr, cm$^{-1}$): 3324, 2980, 1735, 1670, 1584, 1521, 1263, 1226, 1093, 1034; HRMS *m/z* (ESI): calculated for $C_{12}H_{15}NO_4Na^+$: 260.0899, found: 260.0907.



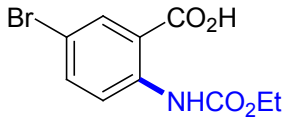
**3b**

**3b** was isolated as a pale yellow solid (33.5 mg, 70% yield). mp = 146-148 °C; $^{1}$H NMR ($d_6$-acetone, 400 MHz): $\delta_H$ 10.4 (s, 1H), 8.36 (d, $J$ = 9.2 Hz, 1H), 7.57 (d, $J$ = 3.2 Hz, 1H), 7.20 (dd, $J$ = 9.2 Hz, 2.8 Hz, 1H), 4.16 (q, $J$ = 7.2 Hz, 2H), 3.81 (s, 3H), 1.26 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR ($d_6$-acetone, 100 MHz): $\delta_C$ 170.1 (C), 154.9 (C), 154.2 (C), 136.8 (C), 121.9 (CH), 120.8 (CH), 116.4 (C), 115.9 (CH), 61.5 ($CH_2$), 56.0 ($CH_3$), 14.9 ($CH_3$); IR (KBr, cm$^{-1}$): 3348, 1738, 1536, 1280, 1250, 1210, 1091, 1063, 1042; HRMS *m/z* (ESI): calculated for $C_{11}H_{13}NO_5Na^+$: 262.0685, found: 262.0685.



**3c**

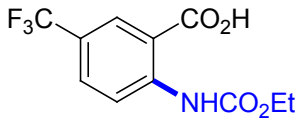
**3c** was isolated as a pale yellow solid (30.6 mg, 63% yield). mp = 146-148 °C; $^{1}$H NMR ($d_6$-DMSO, 400 MHz): $\delta_H$ 12.9 (s, 1H), 8.19 (d, $J$ = 8.8 Hz, 1H), 7.97 (d, $J$ = 2.8 Hz, 1H), 7.38 dd, $J$ = 8.8 Hz, 2.8 Hz, 1H), 4.10 (q, $J$ = 7.2 Hz, 2H), 1.22 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR ($d_6$-DMSO, 100 MHz): $\delta_C$ 169.5 (C), 153.6 (C), 140.1 (C), 131.2 (CH), 131.0 (CH), 124.91 (C), 124.8 (C), 119.2 (CH), 60.7 ($CH_2$), 15.0 ($CH_3$); IR (KBr, cm$^{-1}$): 3217, 3201, 1706, 1664, 1428, 1282, 1224; HRMS *m/z* (ESI): calculated for $C_{10}H_{10}NO_4ClNa^+$: 265.0118, found: 265.0119.



**3d**

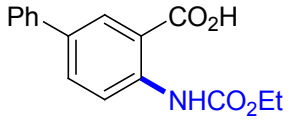
**3d** was isolated as a pale yellow solid (34.3 mg, 60% yield). mp = 146-148 °C; $^{1}$H NMR ($CDCl_3$, 400 MHz): $\delta_H$ 10.2 (s, 1H), 8.42 (d, $J$ = 9.2 Hz, 1H), 8.22 (d, $J$ = 2 Hz, 1H), 7.67 (dd, $J$ = 9.2 Hz, 2 Hz, 1H), 4.25 (q, $J$ = 7.2 Hz, 2H), 1.34 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta_C$ 171.3 (C), 154.4 (C), 142.6 (C), 139.3 (CH), 135.1 (CH), 121.7 (CH), 115.7 (C), 114.8 (C), 62.6 ($CH_2$), 15.4 ($CH_3$); IR (KBr,

$cm^{-1}$): 3233, 1742, 1686, 1606, 1532, 1508, 1246, 1198, 1154, 1037; HRMS *m/z* (ESI): calculated for $C_{10}H_{10}NO_4BrNa^+$: 309.9691, found: 309.9687.



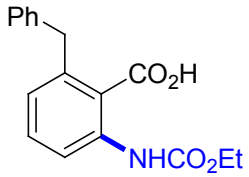

**3e**

**3e** was isolated as a pale yellow solid (30.5 mg, 55% yield). mp = 187-188 °C; $^1$H NMR ($d_6$-acetone, 400 MHz): $\delta_H$ 10.9 (s, 1H), 8.64 (d, $J$ = 8.8 Hz, 1H), 8.33 (s, 1H), 7.90 (d, $J$ = 7.6 Hz, 1H), 4.23 (q, $J$ = 7.2 Hz, 2H), 1.29 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR ($d_6$-acetone, 100 MHz): $\delta_C$ 169.7 (C), 154.0 (C), 146.3 (C), 131.6 (CH), 129.4 (CH), 129.1, 126.4, 123.8, 121.1 (q, $J_{CF}$ = 269 Hz, $CF_3$), 124.0, 123.6, 123.3, 121.1 (q, $J_{CF}$ = 33 Hz, C), 119.6 (CH), 116.2 (C), 62.2 ($CH_2$), 14.7 ($CH_3$); IR (KBr, $cm^{-1}$): 3332, 1732, 1689, 1592, 1542, 1409, 1249, 1121, 1087; HRMS *m/z* (ESI): calculated for $C_{11}H_{10}NO_4F_3Na^+$: 322.0279, found: 322.265.



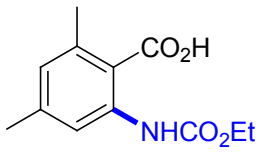

**3f**

**3f** was isolated as a pale yellow solid (26.8 mg, 47% yield). mp = 187-188 °C; $^1$H NMR ($d_4$-methanol, 400 MHz): $\delta_H$ 8.43 (d, $J$ = 8.8, 1H), 8.29 (s, 1H), 7.79 (d, $J$ = 8.8, 1H), 7.59 (d, $J$ = 7.2 Hz, 2H), 7.43 (t, $J$ = 7.6 Hz, 2H), 7.32 (t, $J$ = 7.2 Hz, 1H), 4.22 (q, $J$ = 7.2 Hz, 2H), 1.32 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR ($d_4$-methanol, 100 MHz): $\delta_C$ 153.7 (C), 140.7 (C), 139.5 (C), 134.3 (C), 132.4 (C), 132.0 (CH), 129.2 (CH), 128.5 (CH), 126.9 (CH), 126.5 (C), 126.1 (CH), 118.6 (CH), 60.8 ($CH_2$), 13.3 ($CH_3$); IR (KBr, $cm^{-1}$): 3339, 3028, 2485, 1742, 1670, 1247; HRMS *m/z* (ESI): calculated for $C_{16}H_{15}NNaO_4^+$: 308.0899, found: 308.0890.




**3g**

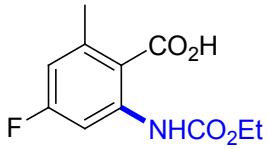
**3g** was isolated as a pale yellow solid (42.5 mg, 71% yield). mp = 117-118°C; $^1$H NMR ($CDCl_3$, 400 MHz): $\delta_H$ 8.78 (s, 1H), 8.06 (d, $J$ = 6.8 Hz, 1H), 7.39 (t, $J$ = 8.0 Hz, 1H), 7.26-7.10 (m, 5H), 6.92 (d, $J$ = 7.6 Hz, 1H), 4.26-4.20 (m, 4H), 1.30 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta_C$ 154.0 (C), 142.1 (C), 140.4 (C), 139.2 (C), 138.7 (C), 132.2 (CH), 128.9 (CH), 128.3 (CH), 126.2 (CH), 126.1 (CH), 119.2 (CH), 61.5 ($CH_2$), 40.5 ($CH_2$), 14.4 ($CH_3$); IR (KBr, $cm^{-1}$): 3360, 3027, 1739, 1653, 1528, 1266, 1216, 1089; HRMS *m/z* (ESI): calculated for $C_{17}H_{17}NO_4Na^+$: 322.1055, found: 322.1059.




**3h**

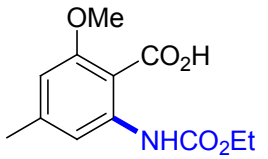
**3h** was isolated as a yellow solid (34.6 mg, 73% yield). mp = 145-146 °C; $^1$H NMR ($d_4$-methanol, 400 MHz): $\delta_H$ 7.69 (s, 1H), 6.80 (s, 1H), 4.17 (q, $J$ = 7.2 Hz, 2H), 2.44 (s, 3H), 2.30 (s, 3H), 1.29 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR ($d_4$-methanol, 100 MHz): $\delta_C$

171.4 (C), 155.3 (C), 142.6 (C), 139.8 (C), 139.4 (C), 127.6 (CH), 119.6 (CH), 61.8 ($CH_2$), 22.1 ($CH_3$), 21.1 ($CH_3$), 14.4 ($CH_3$); IR (KBr, $cm^{-1}$): 3217, 2372, 1706, 1664, 1428, 1224; HRMS *m/z* (ESI): calculated for $C_{12}H_{15}NO_4Na^+$: 260.0899, found: 260.0898.



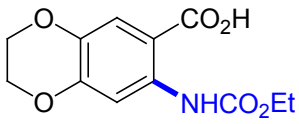
**3i**

**3i** was isolated as a brown solid (22.2 mg, 46% yield). mp = 133-134 °C; $^1$H NMR ($CDCl_3$, 400 MHz): $\delta_H$ 9.71 (s, 1H), 8.03 (dd, *J* = 11.2 Hz, 2 Hz, 1H), 6.66 (dd, *J* = 8.8 Hz, 2 Hz, 1H), 4.24 (q, *J* = 7.2 Hz, 2H), 1.33 (t, *J* = 7.2 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta_C$ 172.4 (C), 166.2, 163.7 (d, *J* = 250 Hz, CF), 153.4 (C), 144.5, 144.4 (d, *J* = 11 Hz, C), 143.5, 143.4 (d, *J* = 13 Hz, C), 113.1, 112.9 (d, *J* = 22 Hz, CH), 104.9, 104.7 (d, *J* = 28 Hz, CH), 61.5 ($CH_2$), 23.8 ($CH_3$), 14.4 ($CH_3$); IR (KBr, $cm^{-1}$): 3256, 1725, 1606, 1523, 1446, 1245, 1197; HRMS *m/z* (ESI): calculated for $C_{11}H_{12}NO_4FNa^+$: 264.0648, found: 264.0659.



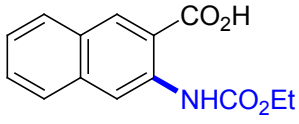
**3j**

**3j** was isolated as a yellow solid (25.3 mg, 50% yield). mp = 102-103 °C; $^1$H NMR ($d_4$-methanol, 400 MHz): $\delta_H$ 7.64 (s, 1H), 6.64 (s, 1H), 4.17 (q, *J* = 7.2 Hz, 2H), 3.90 (s, 3H), 2.34 (s, 3H), 1.29 (t, *J* = 7.2 Hz, 3H); $^{13}$C NMR ($d_4$-methanol, 100 MHz): $\delta_C$ 169.9 (C), 159.9 (C), 154.9 (C), 145.6 (C), 141.5 (C), 114.0 (CH), 107.7 (CH), 106.6 (C), 61.9 ($CH_2$), 56.6 ($CH_3$), 21.9 ($CH_3$), 14.4 ($CH_3$); IR (KBr, $cm^{-1}$): 3199, 2990, 1735, 1707, 1583, 1442, 1366, 1254, 1223, 1049; HRMS *m/z* (ESI): calculated for $C_{12}H_{15}NO_5Na^+$: 276.0848, found: 276.0843.



**3k**

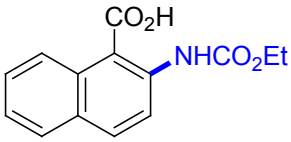
**3k** was isolated as a white solid (21.4 mg, 40% yield). mp = 210-211 °C; $^1$H NMR ($d_4$-methanol, 400 MHz): $\delta_H$ 7.83 (s, 1H), 7.50 (s, 1H), 4.31-4.29 (m, 2H), 4.23-4.21 (m, 2H), 4.18 (q, *J* = 7.2 Hz, 2H), 1.29 (t, *J* = 7.2 Hz, 3H); $^{13}$C NMR ($d_6$-DMSO, 100 MHz): $\delta_C$ 170.5 (C), 154.2 (C), 149.7 (C), 139.1 (C), 137.4 (C), 120.4 (CH), 109.8 (C), 107.9 (CH), 66.3 ($CH_2$), 65.2 ($CH_2$), 62.1 ($CH_2$), 15.8 ($CH_3$); IR (KBr, $cm^{-1}$): 1736, 1646, 1565, 1308, 1266, 1064; HRMS *m/z* (ESI): calculated for $C_{12}H_{13}NO_6Na^+$: 290.0641, found: 296.0650.



**3l**

**3l** was isolated as a yellow solid (28.5 mg, 55% yield). mp = 197-198 °C; $^1$H NMR ($d_6$-acetone, 400 MHz): $\delta_H$ 10.7 (bs, 1H), 8.82 (s, 1H), 8.76 (s, 1H), 7.98 (d, *J* = 8.0 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 1H), 7.61 (t, *J* = 8.0 Hz, 1H), 7.45 (t, *J* = 8.0 Hz, 1H), 4.23 (q, *J* = 7.2, 2H), 1.31 (t, *J* = 7.2 Hz, 3H); $^{13}$C NMR ($d_6$-acetone, 100

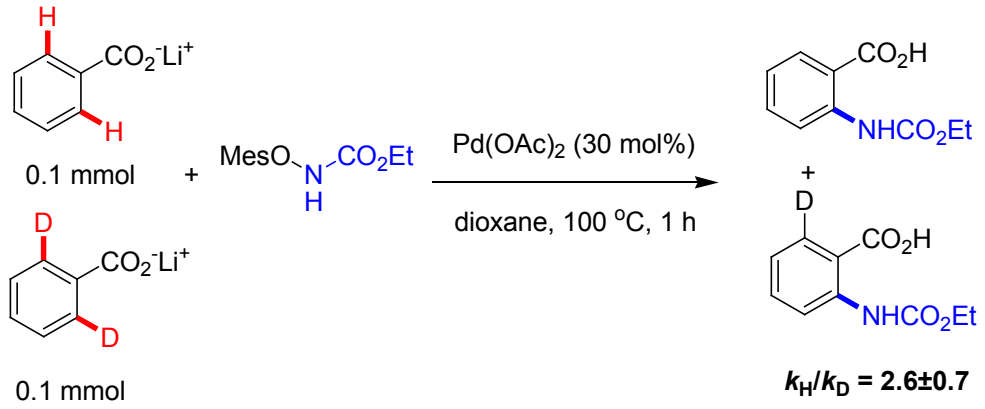
MHz): $\delta_C$ 169.4 (C), 153.2 (C), 137.1 (C), 136.5 (C), 133.6 (CH), 129.2 (CH), 129.0 (CH), 128.0 (C), 127.0 (CH), 125.0 (CH), 115.6 (C), 114.6 (CH), 60.6 ($CH_2$), 13.9 ($CH_3$); IR (KBr, $cm^{-1}$): 3330, 2987, 1723, 1678, 1541, 1284, 1247, 1220, 1041; HRMS *m/z* (ESI): calculated for $C_{14}H_{13}NO_4Na^+$: 282.0742, found: 282.0748.




**3m**

**3m** was isolated as a brown solid (10.9 mg, 21% yield). mp = 140-142 °C; $^1$H NMR ($CDCl_3$, 400 MHz): $\delta_H$ 9.58 (s, 1H), 8.55 (d, *J* = 8.4 Hz, 1H), 8.46 (d, *J* = 9.2 Hz, 1H), 7.98 (d, *J* = 9.2 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.56 (t, *J* = 8.0 Hz, 1H), 7.44 (t, *J* = 7.6 Hz, 1H), 4.27 (q, *J* = 7.2 Hz, 2H), 1.35 (t, *J* = 7.2 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta_C$ 172.9 (C), 153.8 (C), 140.0 (C), 134.3 (CH), 131.4 (C), 129.9 (C), 128.4 (CH), 128.0 (CH), 125.7 (CH), 124.9 (CH), 119.3 (CH), 61.6 ($CH_2$), 14.4 ($CH_3$); IR (KBr, $cm^{-1}$): 1729, 1654, 1577, 1508, 1251, 1214, 1085, 825; HRMS *m/z* (ESI): calculated for $C_{14}H_{13}NO_4Na^+$: 282.0742, found: 282.0747.

## 4. Kinetic Isotope Effect (KIE) Study




To a 8 mL-vial, $Pd(OAc)_2$ (30 mol%) , benzoic acid (**A**) (0.1 mmol) and 2,6-$d_2$-benzoic acid (***d*$_2$-A**) (0.1 mmol) were added, and the vial was sealed with a Teflon® liner cap, the vial was evacuated and back filled with $N_2$ for three times. Freshly distilled dioxane (1 mL) was added to the reaction vial. The reaction mixture was stirred at 100 $^oC$ for 0.5 h, and ethyl *N*-mesitylsulfonyloxycarbamate (30 mol% in 0.5 mL dioxane) was added. The reaction was stirred at 100 $^oC$ for another 0.5 h. After cooling to room temperature, the recaction mixture was diluted with EtOAc (5 mL) and treated with 2 M HCl (2 mL). The organic layer was collected, and the aqueous layer was further extracted with EtOAc (5 mL × 3). The combined organic fractions were dried with $MgSO_4$. Solvent was removed with rotary evaporation. The residue was redissolved in a minimum amount of DCM and then filtered through a plug of silica gel using a 20% EtOAc in hexanes mixture as eluent. The filtrate was then evaporated to dryness for NMR analysis. The conversions of benzoic acids were determined by $^1H$ NMR using dibromomethane as the internal standard.

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**Table S1.** Experimental Data of the KIE Study

| runs | % conv. of **A**[a] | $\mathbf{R}_{unused}$[a] = integral ratio of $\boldsymbol{d_2}$-**A** / **A** unused | amount of **A** unused[b] (mol) | amount of $\boldsymbol{d_2}$-**A** unused[c] (mol) | ratio of **A** / $\boldsymbol{d_2}$-**A** consumed[d] (mol ratio) | $k_H/k_D$ |
|---|---|---|---|---|---|---|
| 1st run | 48 | 1.60/1.00 | 0.0515 | 0.0816 | 0.0490/0.0184 | 2.66 |
| 2nd run | 46 | 1.60/1.00 | 0.0540 | 0.8640 | 0.0460/0.0136 | 3.38 |
| 3rd run | 51 | 1.46/1.00 | 0.0490 | 0.0715 | 0.0510/0.0285 | 1.79 |
| | | | | | average | 2.6±0.7 |

[a]determined by $^1$H NMR using dibromomethane as internal standard.

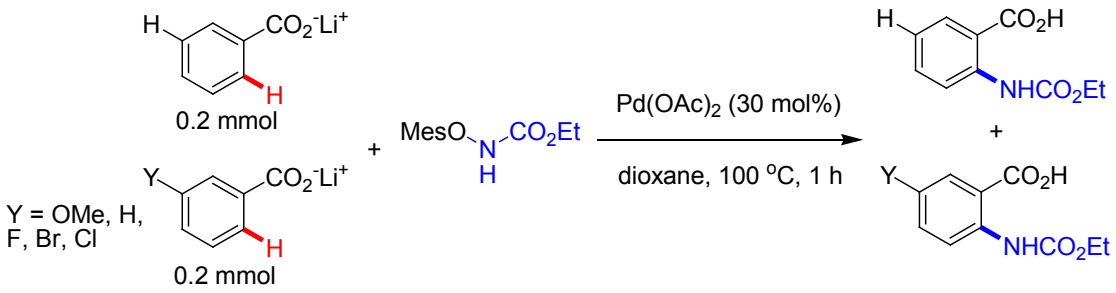
[b]amount of **A** unused $= 0.1 \times (1 - \%\ \text{conv. of}\ \mathbf{A})$

[c]amount of $\boldsymbol{d_2}$**A** unused $= \mathbf{R}_{unused} \times 0.1 \times (1 - \%\ \text{conv. of}\ \mathbf{A})$

[d]amount of $\boldsymbol{d_2}$**A** comsumed $= 0.1 -$ amount of $\boldsymbol{d_2}$**A** unused

[e]amount of **A** consumed $= 0.1 -$ amount of **A** unused

## 5. Hammett Correlation Studies




To a 8 mL-vial, $Pd(OAc)_2$ (30 mol%) , benzoic acid (**A**) (0.2 mmol) and 3-Y-benzoic acid (0.2 mmol) (**YA)** were added and the vial was sealed with a Teflon® liner cap, the vial was evacuated and back filled with $N_2$ for three times. Freshly distilled dioxane (1 mL) was added to the reaction vial. The reaction mixture was stirred at 100 $^{o}$C for 0.5 h and ethyl *N*-mesitylsulfonyloxycarbamate (30 mol% in 0.5 mL dioxane) was added. The reaction was stirred at 100 $^{o}$C for another 0.5 h. After cooling to room temperature, the reaction mixture was diluted with EtOAc (5 mL) and treated with 2 M HCl (2 mL). The organic layer was collected, and the aqueous layer was further extracted by EtOAc (5 mL × 3). The combined organic fractions were dried with $MgSO_4$. Solvent was removed with rotary evaporation. The residue was redissolved in a minimum amount of DCM and then filtered through a plug of silica gel using a 20% EtOAc in hexanes mixture as eluent. The filtrate was then evaporated to dryness for NMR analysis. The conversions of benzoic acids were determined by $^{1}$H NMR using dibromomethane as the internal standard. Each experiment was duplicated and the average values were listed below:

**Table S2.** Data for the Hammett Correlation Study

| Y | % conv. of **A**[a] | $\mathbf{R}_{unused}$[a] = integral ratios of **YA** / **A** unused | amount of **A** unused[b] (mol) | amount of **YA** unused[c] (mol) | ratio of **YA** / **A** consume[d,e] (mol/mol) | $k_Y/k_H$ | log ($k_Y/k_H$) | $\sigma^+$ |
|---|---|---|---|---|---|---|---|---|
| OMe | 7.4 | 0.65/1.00 | 0.185 | 0.116 | 0.084/0.015 | 5.60 | 0.75 | -0.78 |
| F | 7.8 | 0.78/1.00 | 0.185 | 0.144 | 0.056/0.015 | 1.63 | 0.21 | -0.07 |
| H | / | 1.00/1.00 | / | / | 1.000/1.000 | 1.00 | 0.00 | 0.00 |
| Cl | 23 | 1.13/1.00 | 0.154 | 0.173 | 0.027/0.046 | 0.58 | -0.24 | 0.11 |
| Br | 13 | 1.05/1.00 | 0.174 | 0.182 | 0.018/0.026 | 0.67 | -0.17 | 0.15 |

[a]determined by $^1$H NMR using dibromomethane as internal standard.

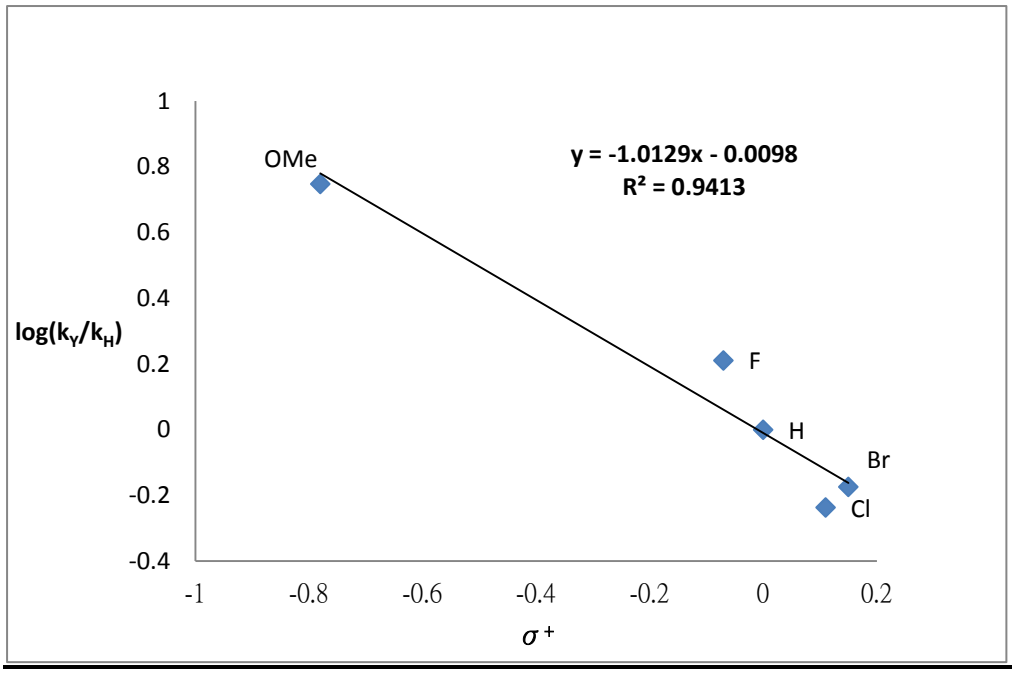
[b]amount of **A** unused $= 0.2 \times (1 - \%$ conv. of **A**$)$

[c]amount of **YA** unused $= \mathbf{R}_{unused} \times 0.2 \times (1 - \%$ conv. of **A**$)$

[d]amount of **YA** comsumed $= 0.2 -$ amount of **YA** unused

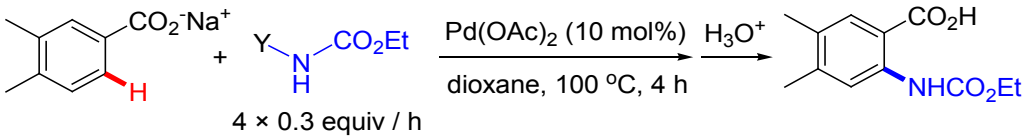
[e]amount of **A** consumed $= 0.2 -$ amount of **A** unused

**Figure 1.** Result of the Hammett Correlation Studies



## 6. Reaction Optimizations

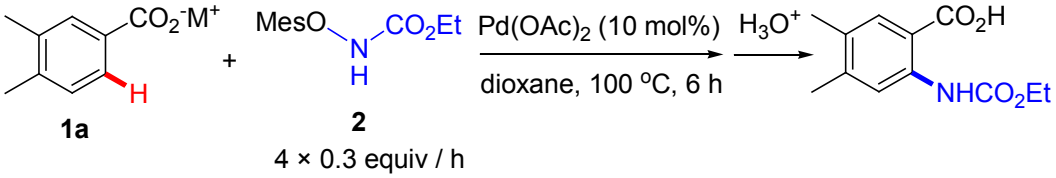
**Table S3.** Effect of *N*-leaving Groups




| entry | Y | conversion (%) | yield (%) |
|---|---|---|---|
| 1 | NsO | 50 | 5 |
| 2 | TsO | n.d. | 27 |
| 3 | MesO (**2**) | 67 | 30 |
| 4 | PFB | 64 | 25 |
| 5 | PivO | 76 | 32 |

[a] Reaction conditions: Sodium 3,4-dimethylbenzoate (0.2 mmol), carbamates (4 × 0.3 equiv / h), $Pd(OAc)_2$ (10 mol%), dioxane (2 mL). NsO = *p*-nitrobenzenesulfonate; TsO = *p*-toluenesulfonate; MesO = *p*-mesitylenesulfonate; PFB = pentafluorobenzoate; PivO = 2,2-dimethylpropionate; n.d. = not determined. Conversions and yields were determined by $^1$H NMR with dibromomethane as internal standard.

**Table S4.** Effect of Counter-ions [a]



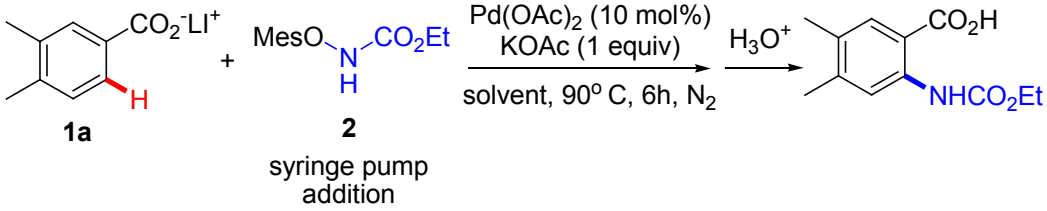

**1a** **2**

4 × 0.3 equiv / h

| entry | $M^+$ | conversion (%) | yield (%) |
|---|---|---|---|
| 1 | H | 0 | 0 |
| 2 | Li | 70 | 40 |
| 3 | Na | 66 | 30 |
| 4 | K | 56 | 16 |
| 5 | $(n\text{-Bu})_4N$ | n.d. | 14 |

[a] Reaction conditions: **1a** (0.2 mmol), **2** ( 4 × 0.3 equiv / h), $Pd(OAc)_2$ (10 mol%), solvent (2 mL). n.d. = not determined. Conversions and yields were determined by $^1$H NMR with dibromomethane as internal standard.

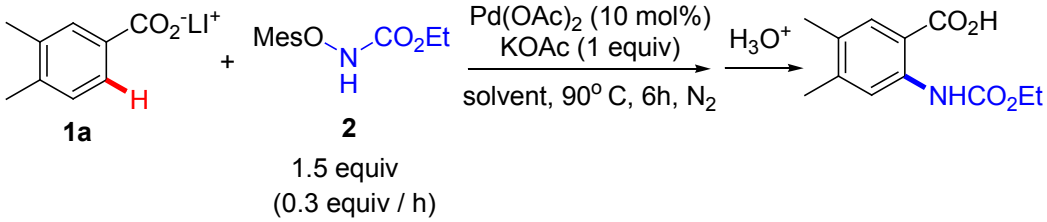
**Table S5.** Effect of Reagent Quantities and Addition Rates[a]




| entry | **2** (equiv) | reaction time (h) | addition rate (equiv / h) | conversion (%) | yield (%) |
|---|---|---|---|---|---|
| 1 | 1.2 | 6 | 0.3 | 95 | 45 |
| 2 | 1.5 | 6 | 0.3 | 95 | 47 |
| 3 | 2 | 6 | 0.3 | 95 | 41 |
| 4 | 1.5 | 4 | 0.6 | 91 | 45 |
| 5 | 1.5 | 2 | 1.2 | 87 | 40 |
| 6 (under $N_2$) | 1.5 | 6 | 0.3 | 83 | 65 |

[a] Reaction conditions: **1a** (0.2 mmol), **2** (syringe pump addition), $Pd(OAc)_2$ (10 mol%), KOAc (1 equiv), dioxane (1.5 mL). Conversions and yields were determined by $^1H$ NMR with dibromomethane as internal standard.

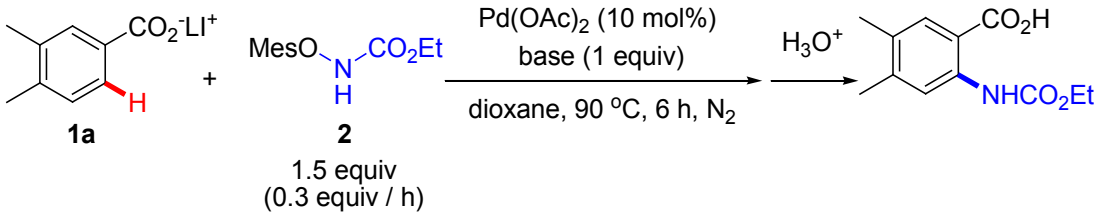
**Table S6.** Effect of Solvents[a]




| entry | solvent | conversion (%) | yield (%) |
|---|---|---|---|
| 1 | DMF | 50 | 20 |
| 2 | DMSO | 80 | 5 |
| 3 | DMA | 21 | 13 |
| 4 | Diglyme | 67 | 45 |
| 5[b] | *t*-BuOH | 90 | 57 |
| 6[c] | DCE | 87 | 45 |
| 7 | dioxane | 83 | 65(63)[d] |

[a] Reaction conditions: **1a** (0.2 mmol), **2** (1.5 equiv, 0.3 equiv / h, syringe pump addition), $Pd(OAc)_2$ (10 mol%), KOAc (1 equiv), solvent (1.5 mL) under $N_2$. Conversions and yields were determined by $^1H$ NMR with dibromomethane as internal standard.[b] 20% dioxane was added. [c] 10% dioxane was added to dissolve the reagent. [d] isolated yield in parentheses.

**Table S7 .** Effect of Bases[a]




| entry | base (equiv) | conversion (%) | yield (%) |
|---|---|---|---|
| 1 | KOAc | 83 | 65(63)[b] |
| 2 | KOPiv | 67 | 41 |
| 3 | $K_2HPO_4$ | 80 | 54 |
| 4 | $KHCO_3$ | 80 | 59 |
| 5 | $K_2CO_3$ (0.5) | 71 | 60 |
| 6 | $K_2CO_3$ (0.75) | 80 | 56 |
| 7 | $K_2CO_3$ | 76 | 48 |

[a] Reaction conditions: **1a** (0.2 mmol), **2** (1.5 equiv, 0.3 equiv / h, syringe pump addition), $Pd(OAc)_2$ (10 mol%), base (0.5 – 1 equiv), dioxane (1.5 mL) under $N_2$. Conversions and yields were determined by $^1H$ NMR with dibromomethane as internal standard. [b] isolated yield in parentheses.

## 7. References

1. K.-H. Ng, A. S. C. Chan, and W.-Y. Yu, *J. Am. Chem. Soc*., 2010, **132**, 12864.
2. D. R. Boyd, N. D. Sharma, J. S. Harrison, J. F. Malone, W. C. McRoberts, J. T. G. Hamilton, and D. B. Harper, *Org. Biomol. Chem*., 2008, **6**, 1251.
3. A. Herschhorn, L. Lerman, M. Weitman, I. O. Gleenberg, A. Nudelman, and A. Hizi, *J. Med. Chem*., 2007, **50**, 2370.

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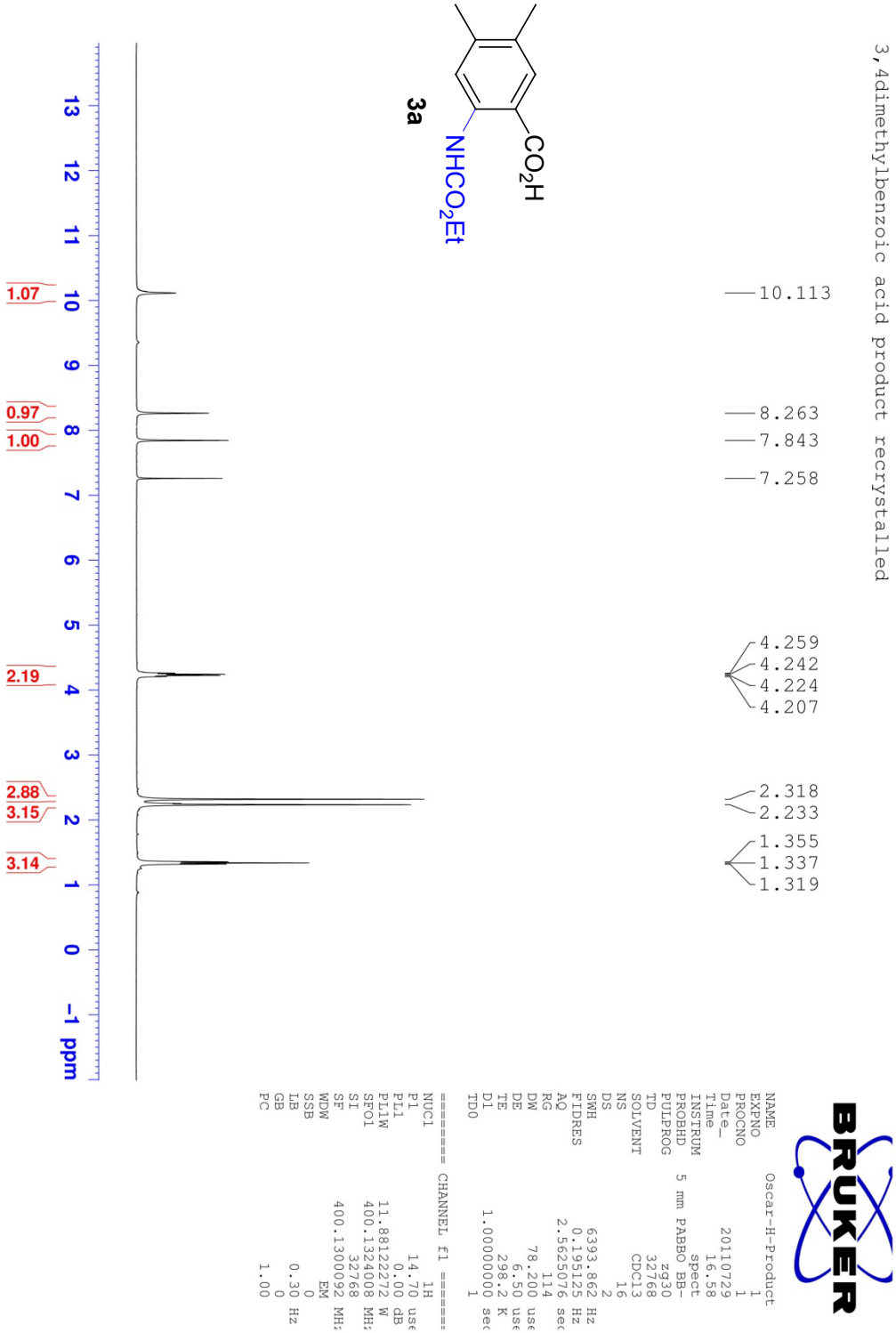
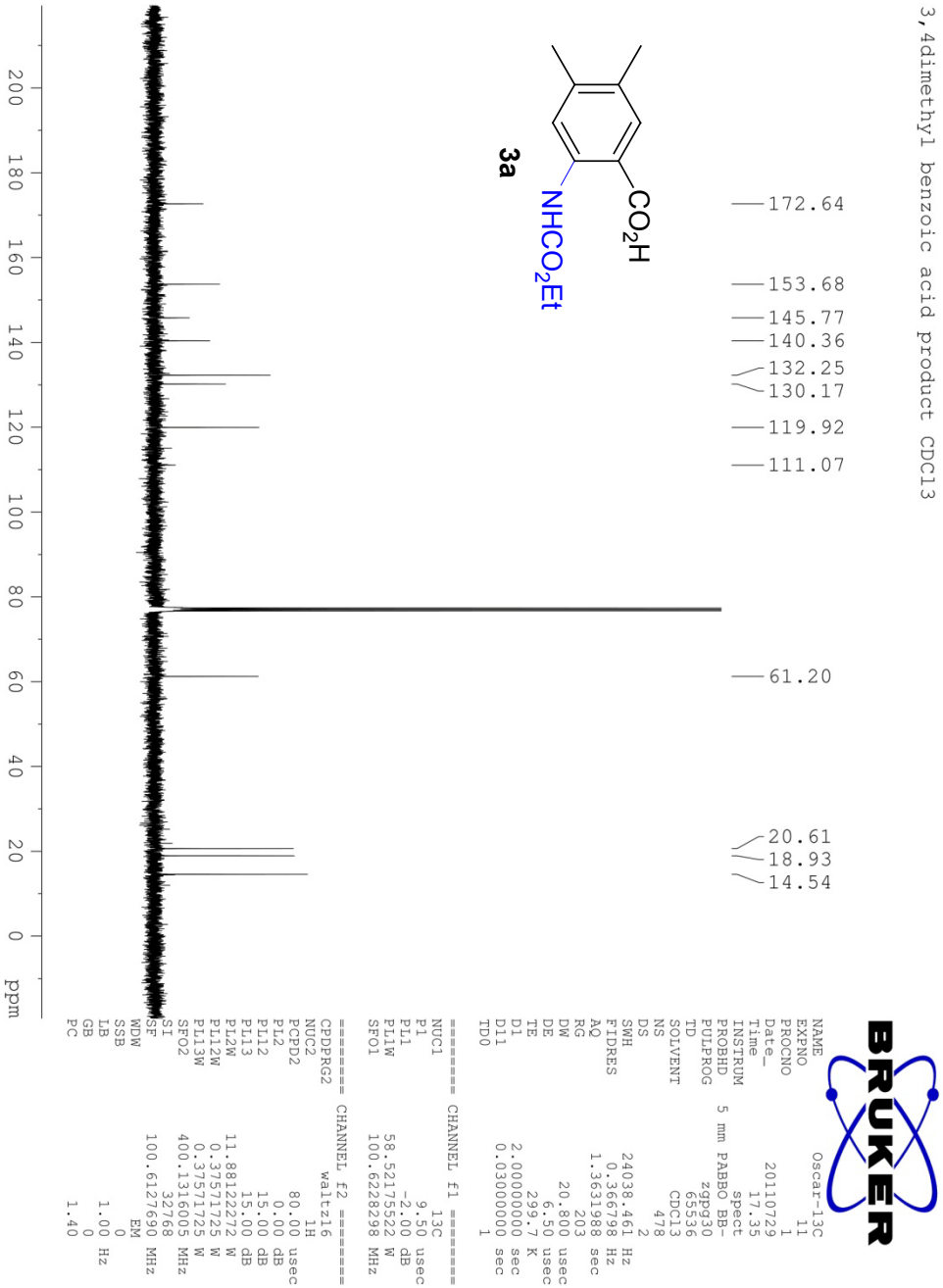
## 8. $^{1}$H NMR and $^{13}$C NMR Spectra

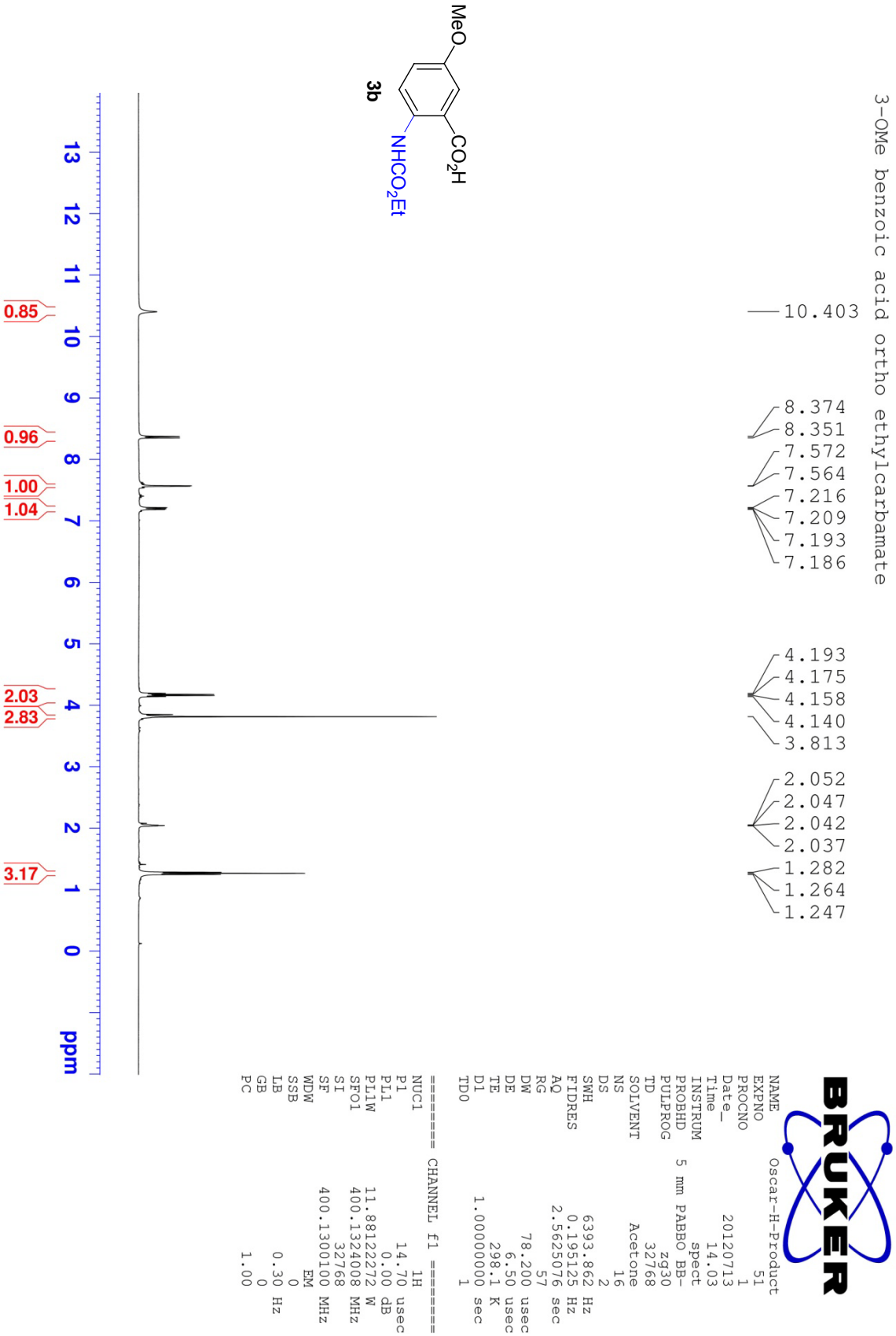
$^{1}$H NMR spectrum of **3a**



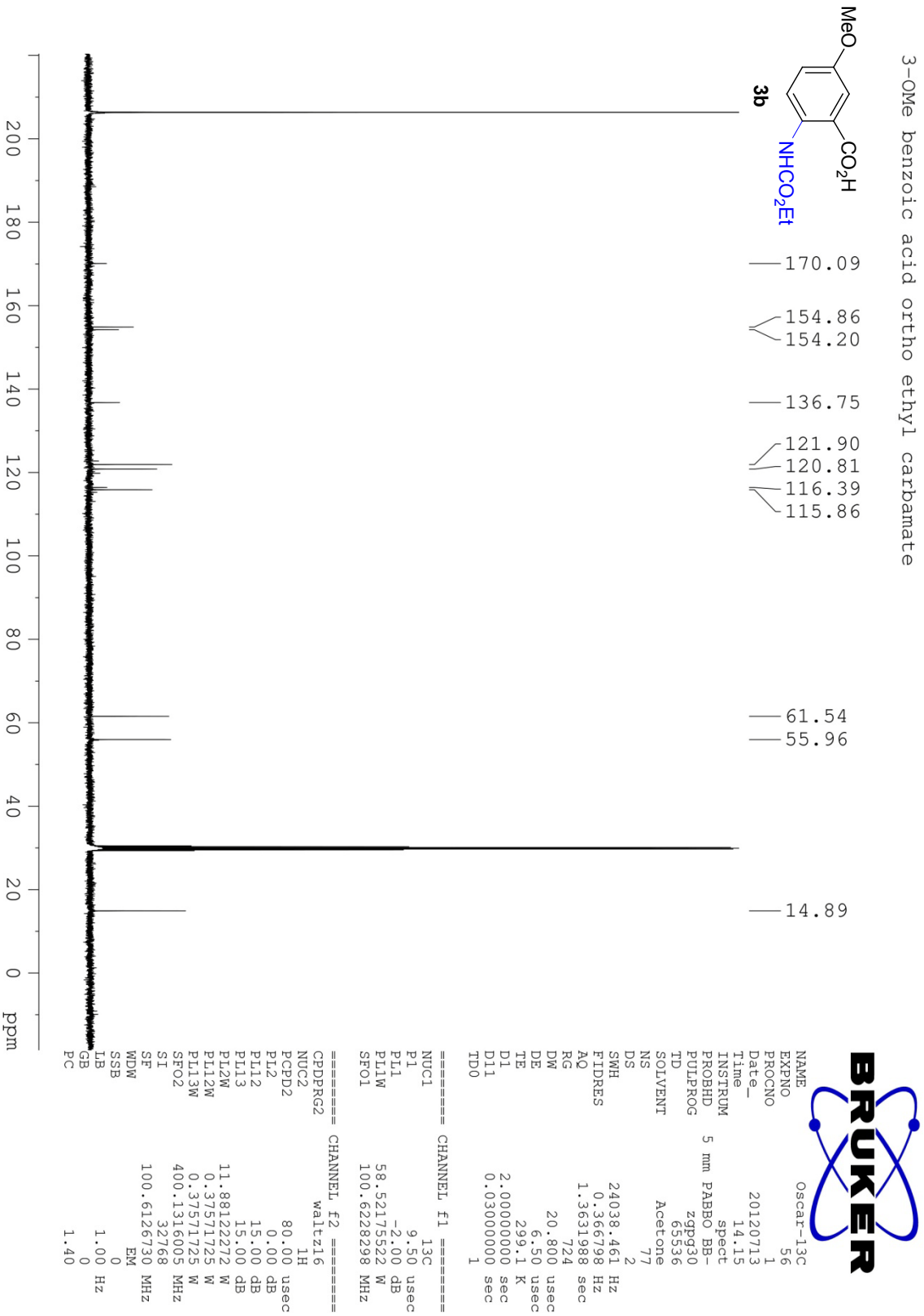
$^{13}$C NMR spectrum of **3a**



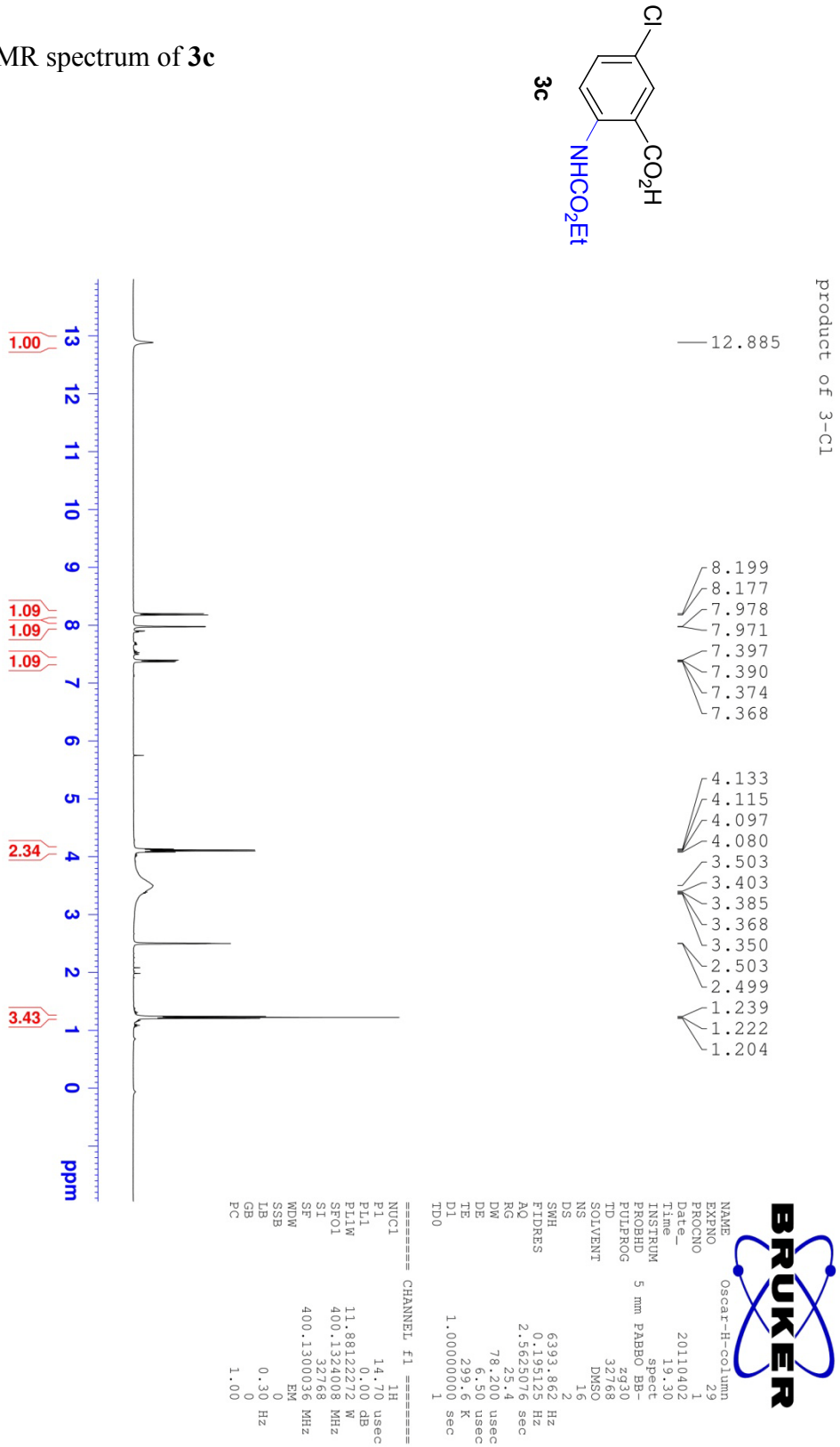
[1]H NMR spectrum of **3b**



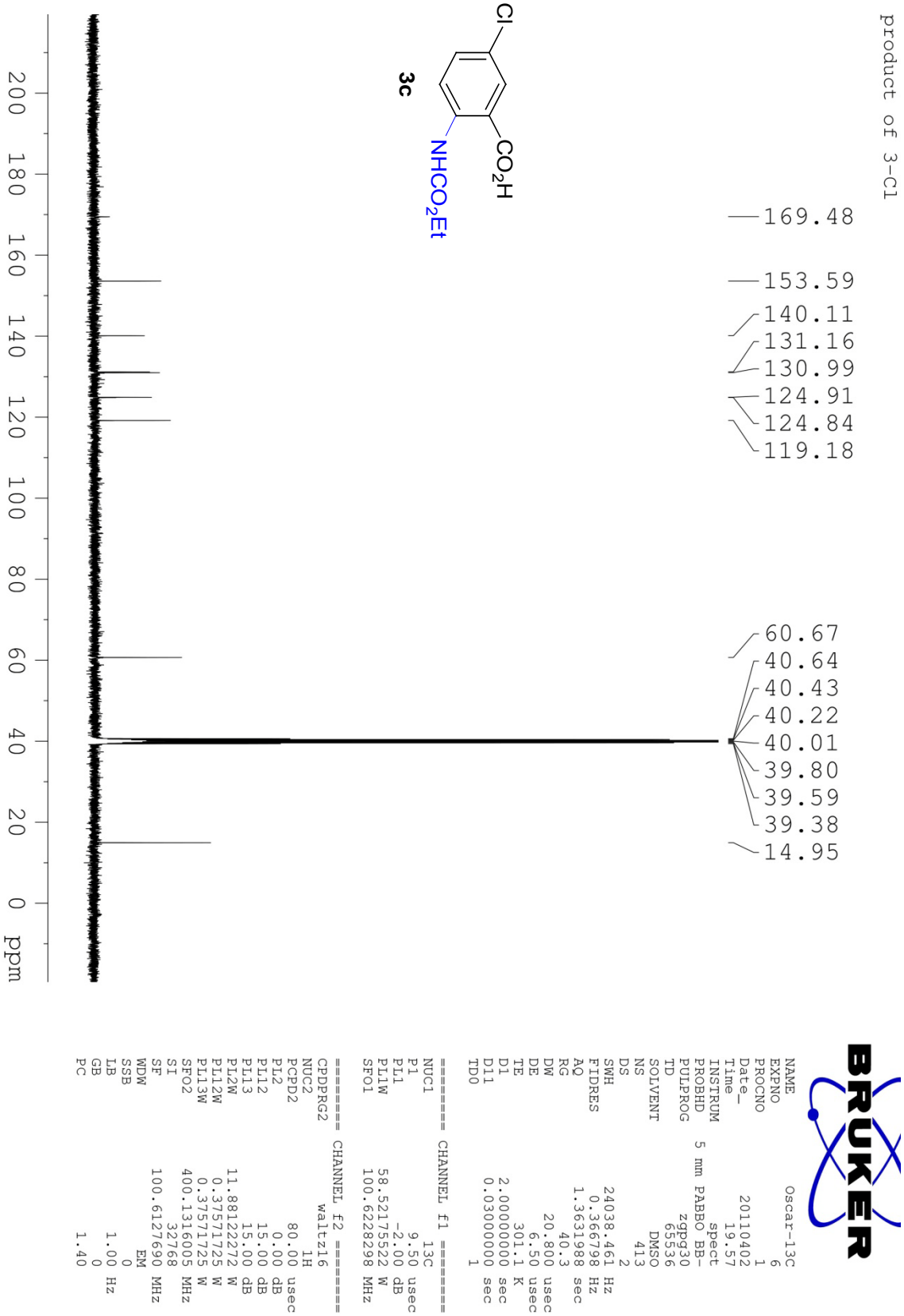
$^{13}$C NMR spectrum of **3b**



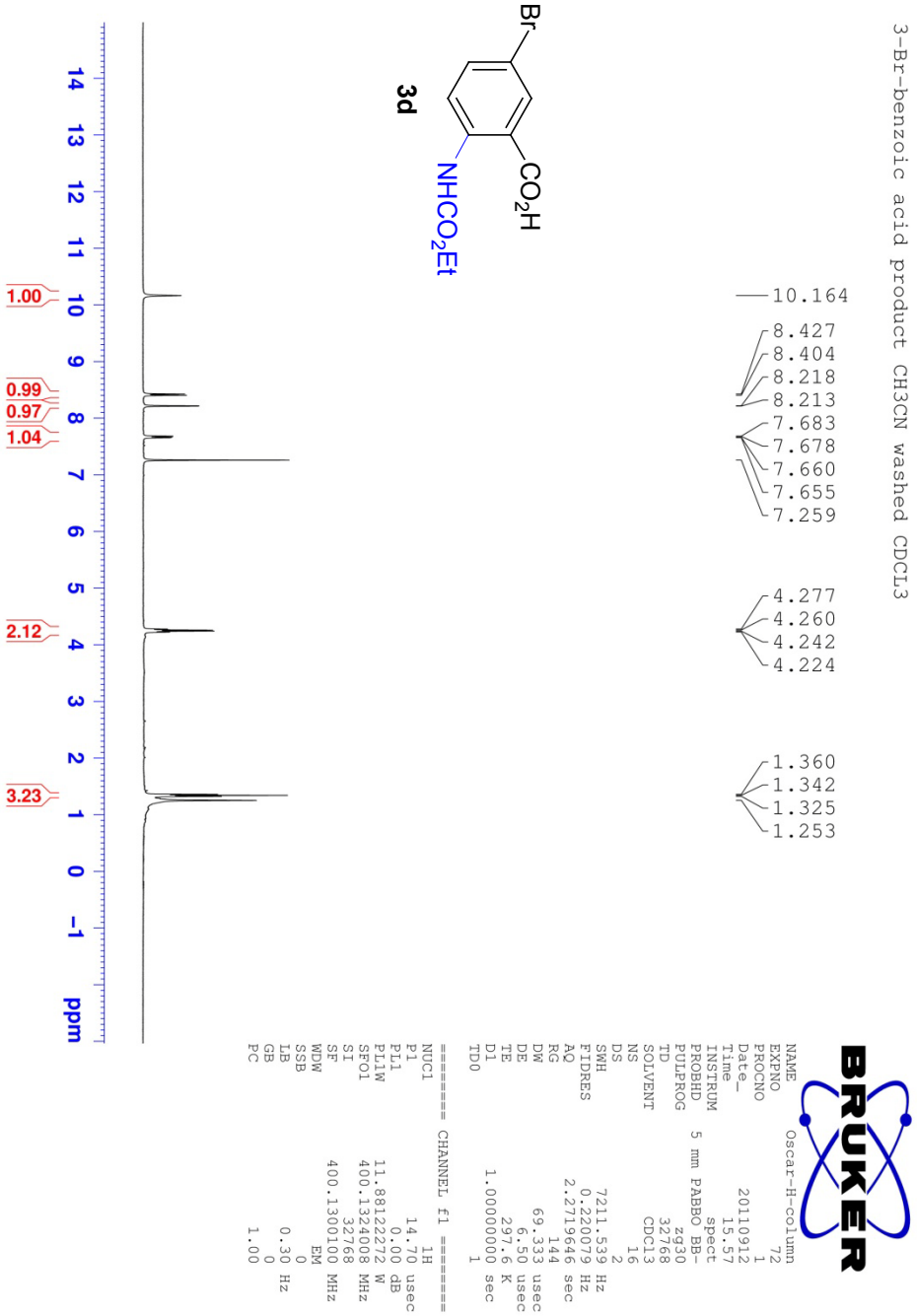
$^1$H NMR spectrum of **3c**



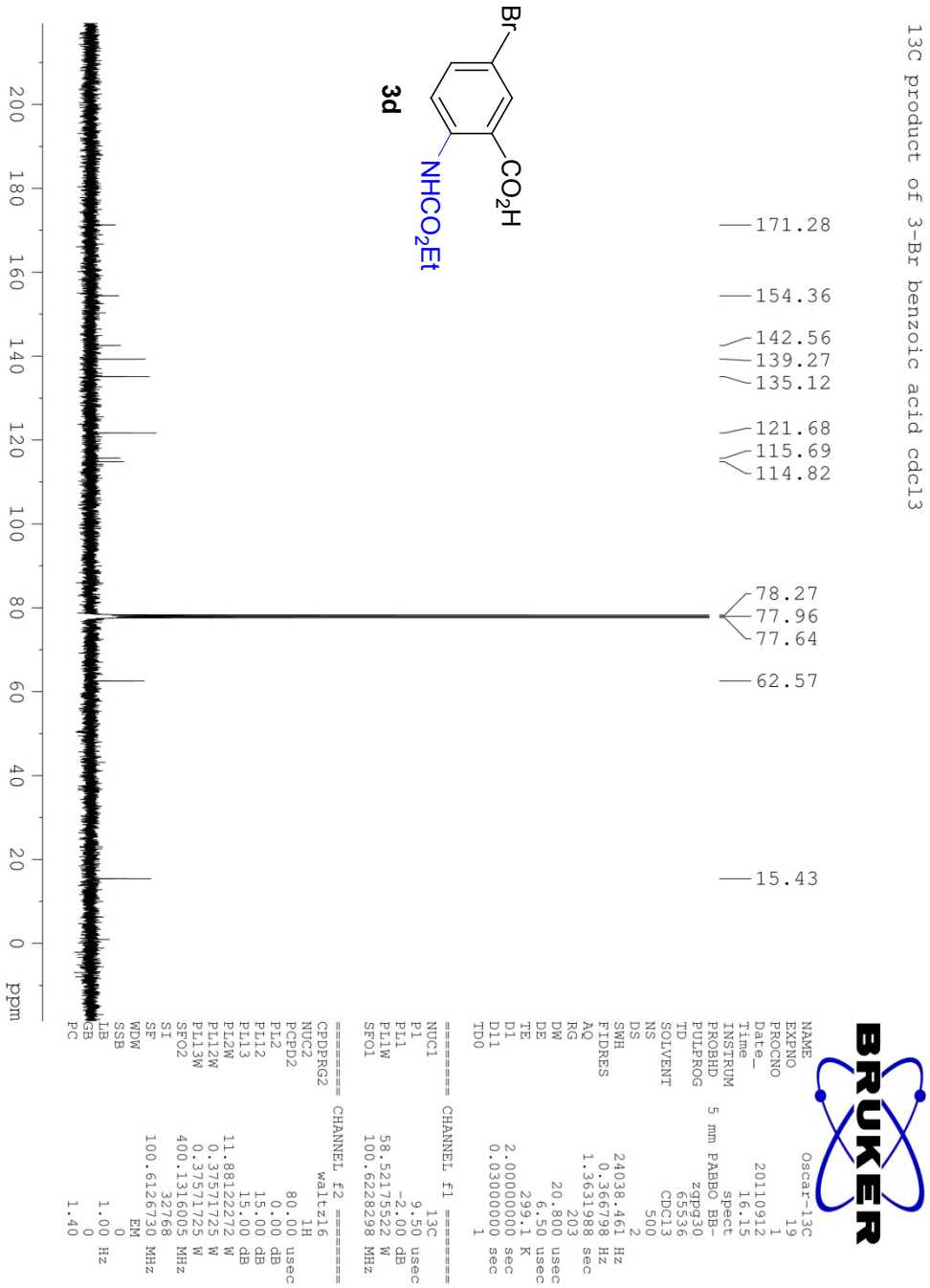
$^{13}$C NMR spectrum of **3c**



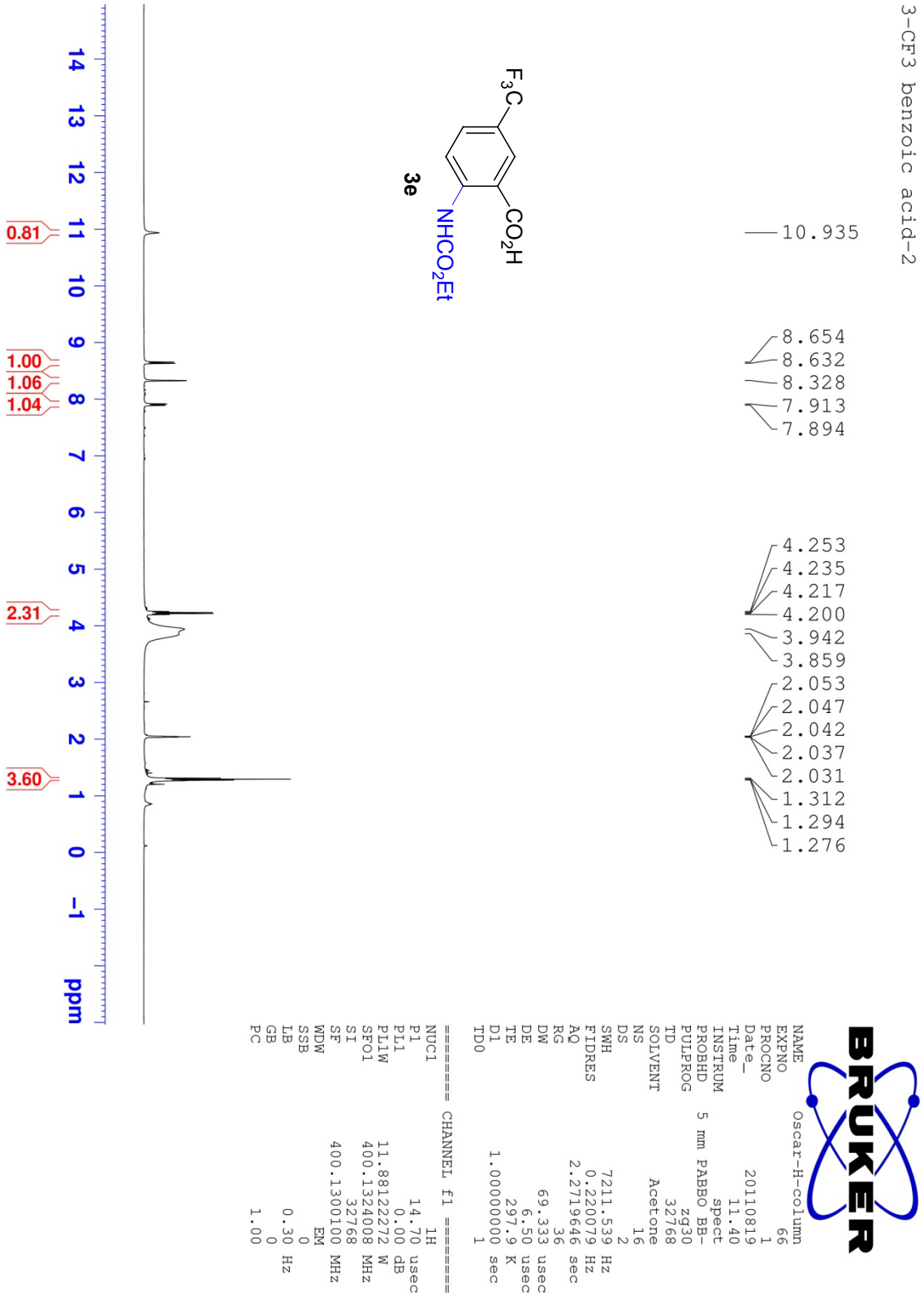
$^{1}$H NMR spectrum of **3d**



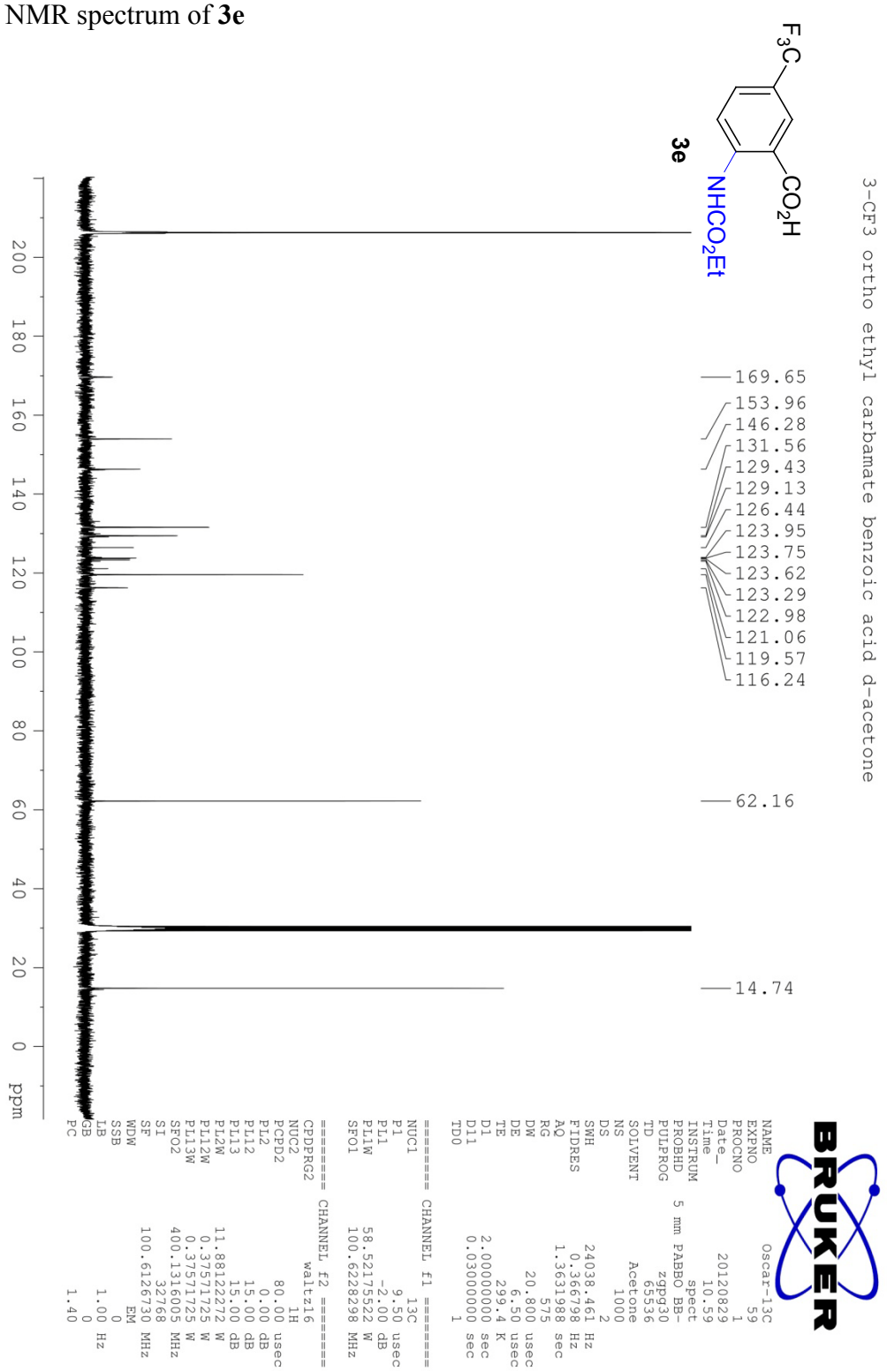
$^{13}$C NMR spectrum of **3d**



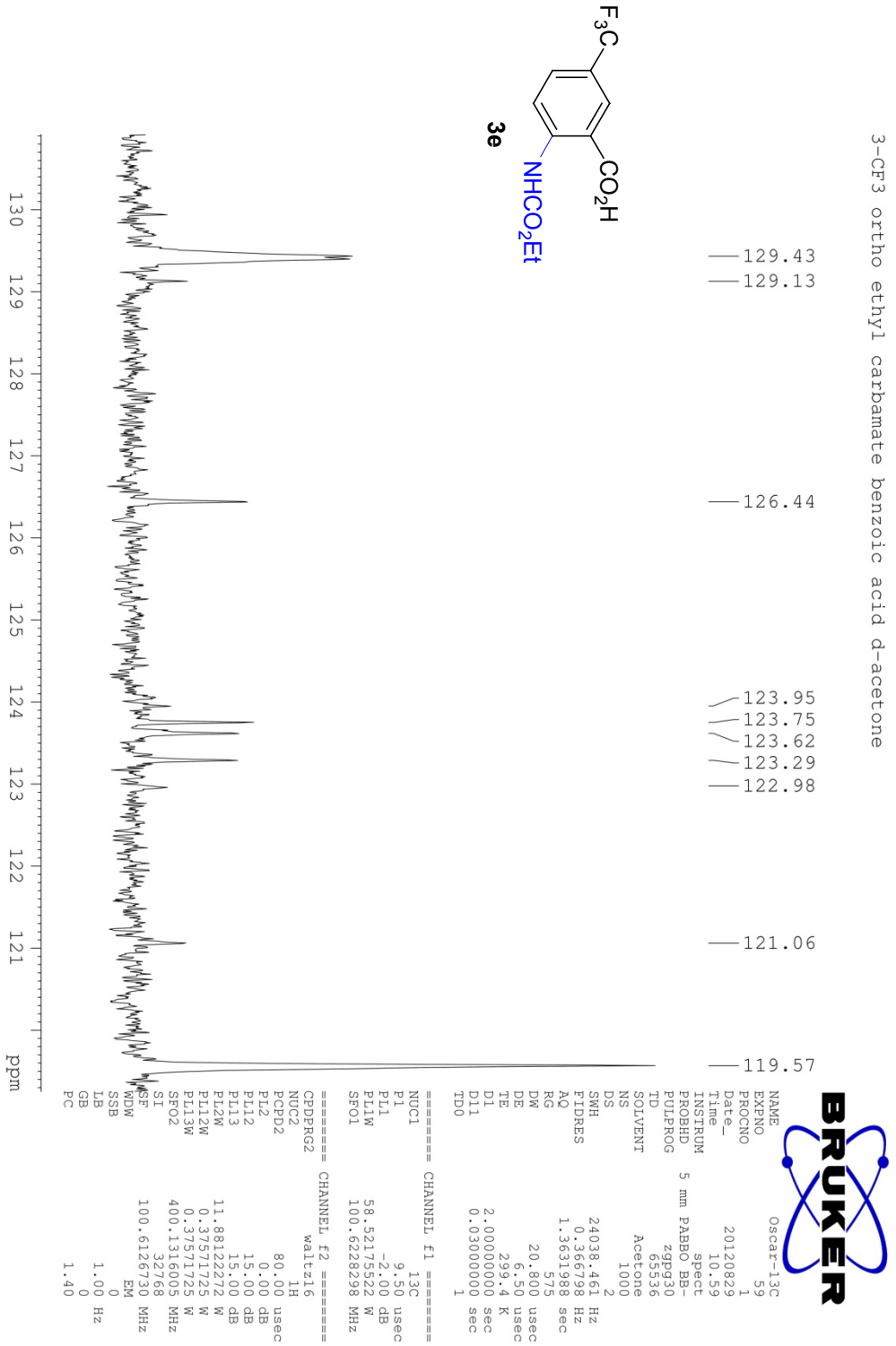
[1]H NMR spectrum of **3e**



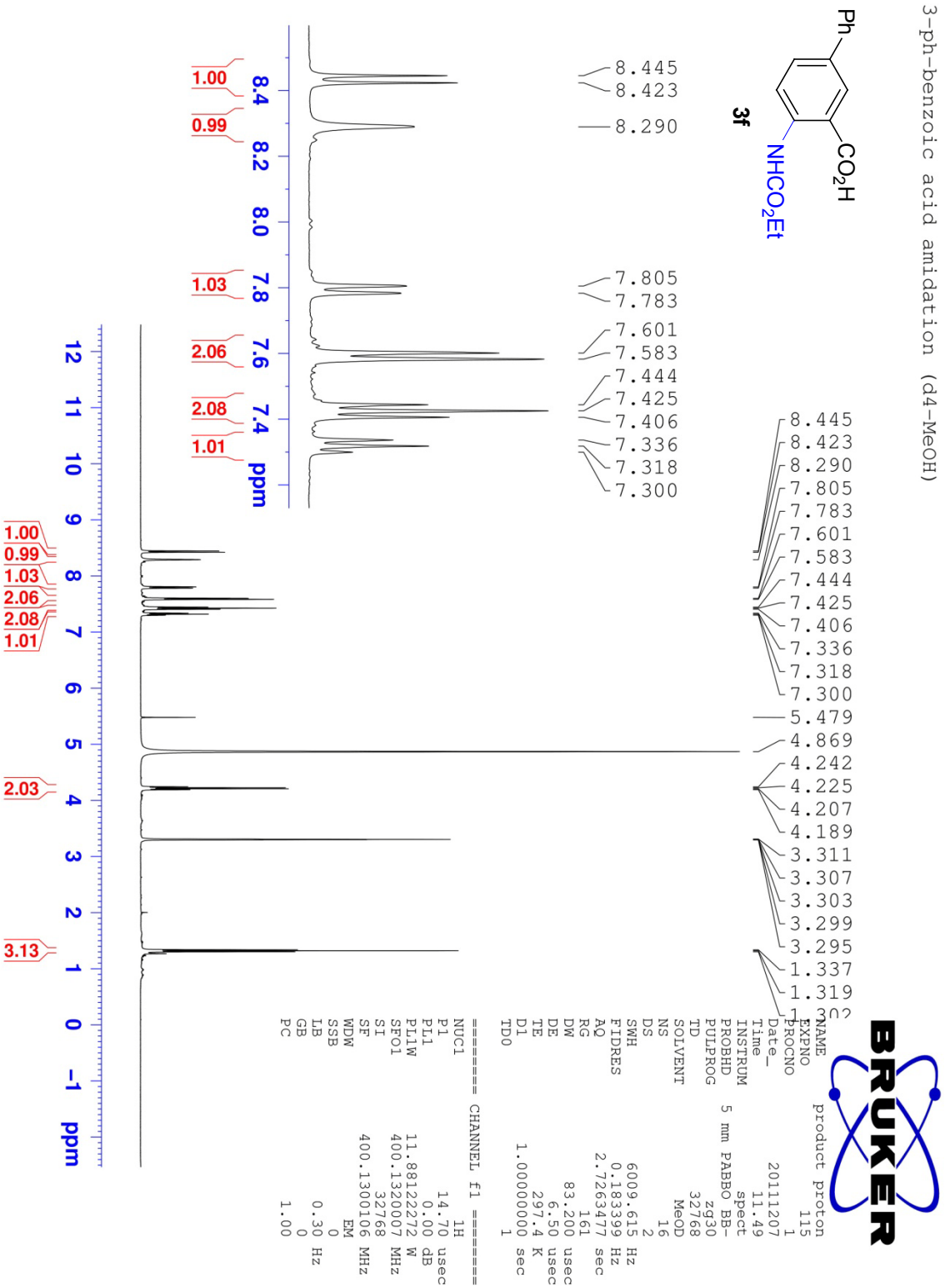
$^{13}$C NMR spectrum of **3e**



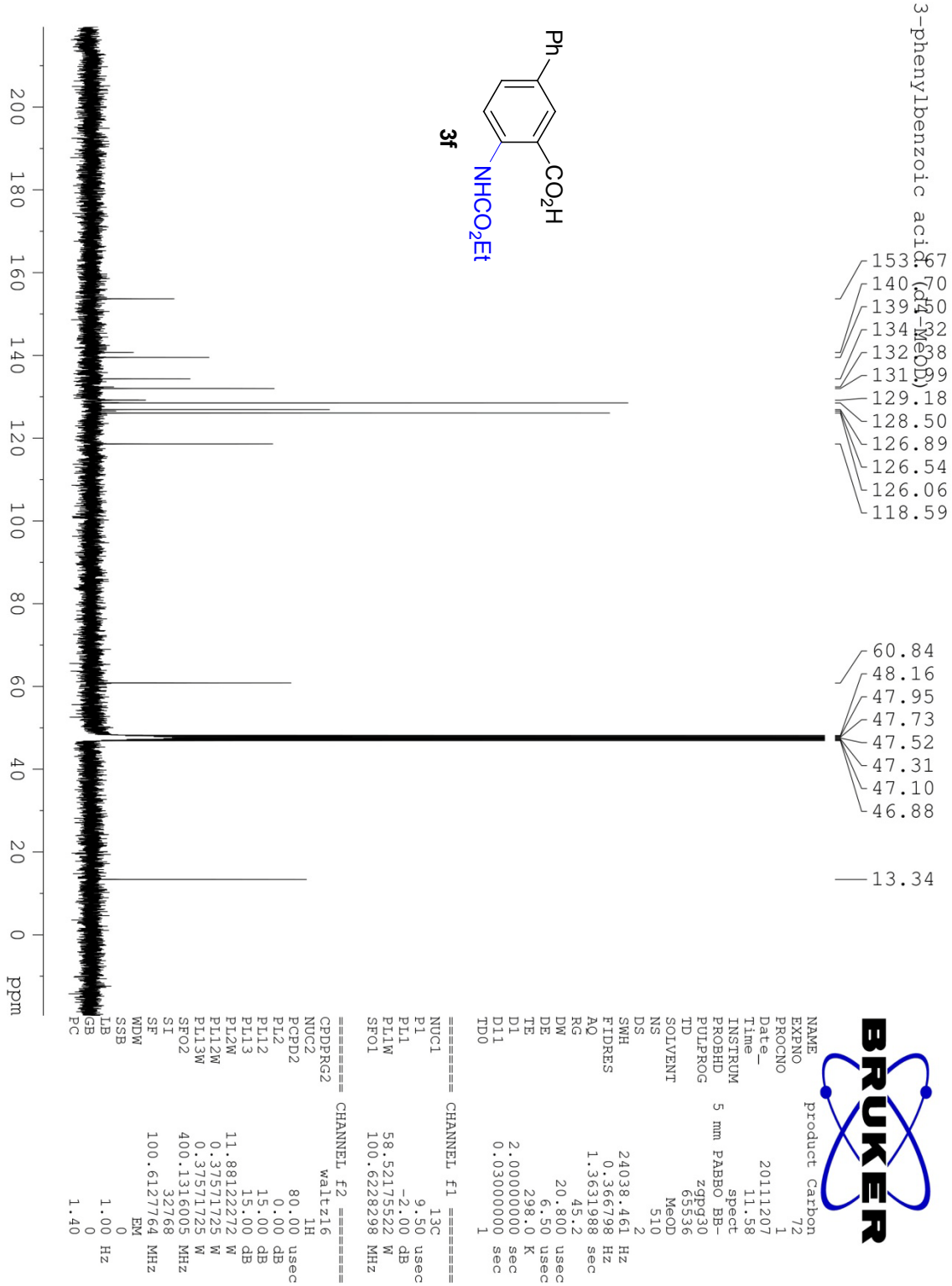
$^{13}$C NMR spectrum of **3e** (magnified)



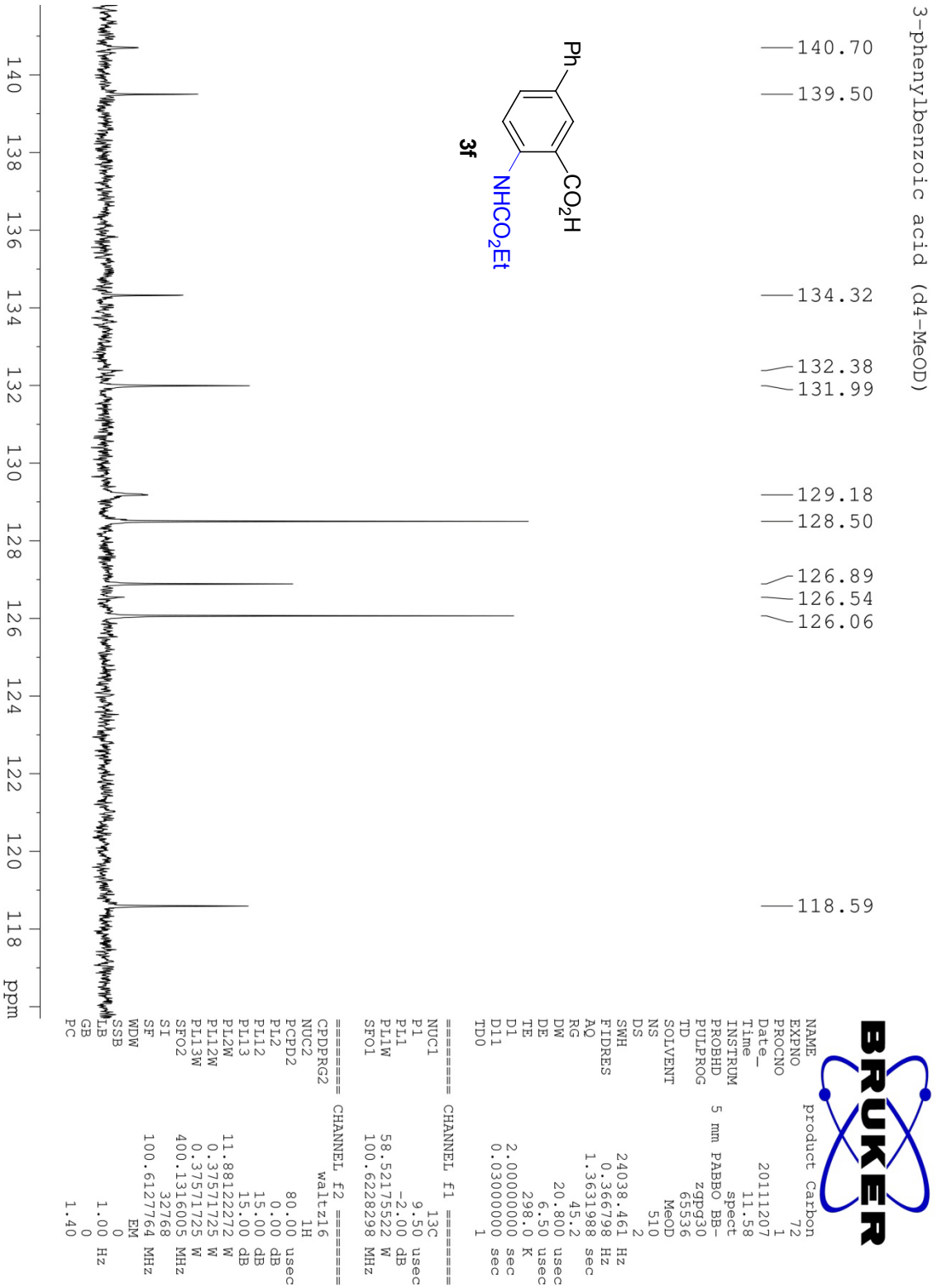
$^{1}$H NMR spectrum of **3f**



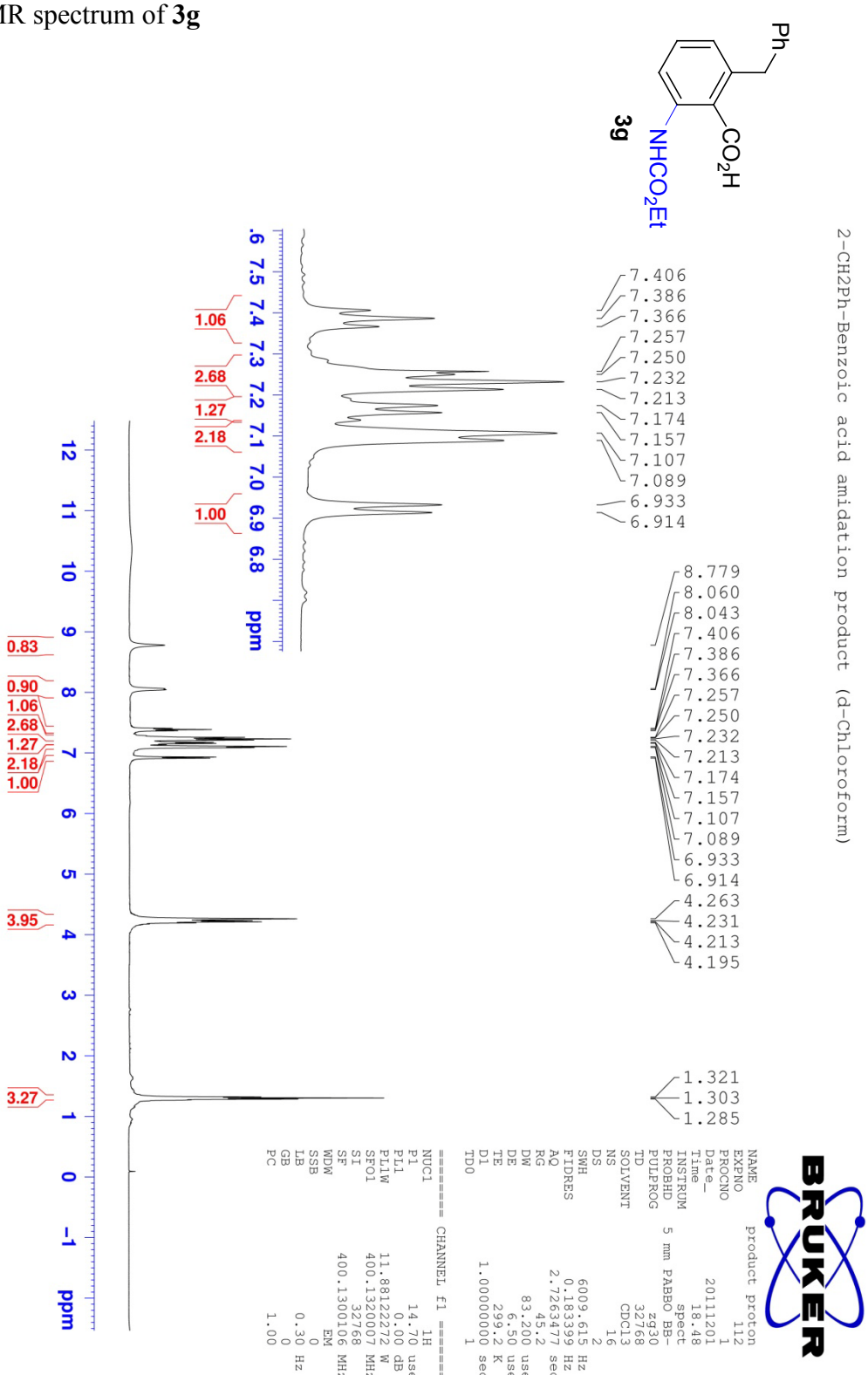
$^{13}$C NMR spectrum of **3f**



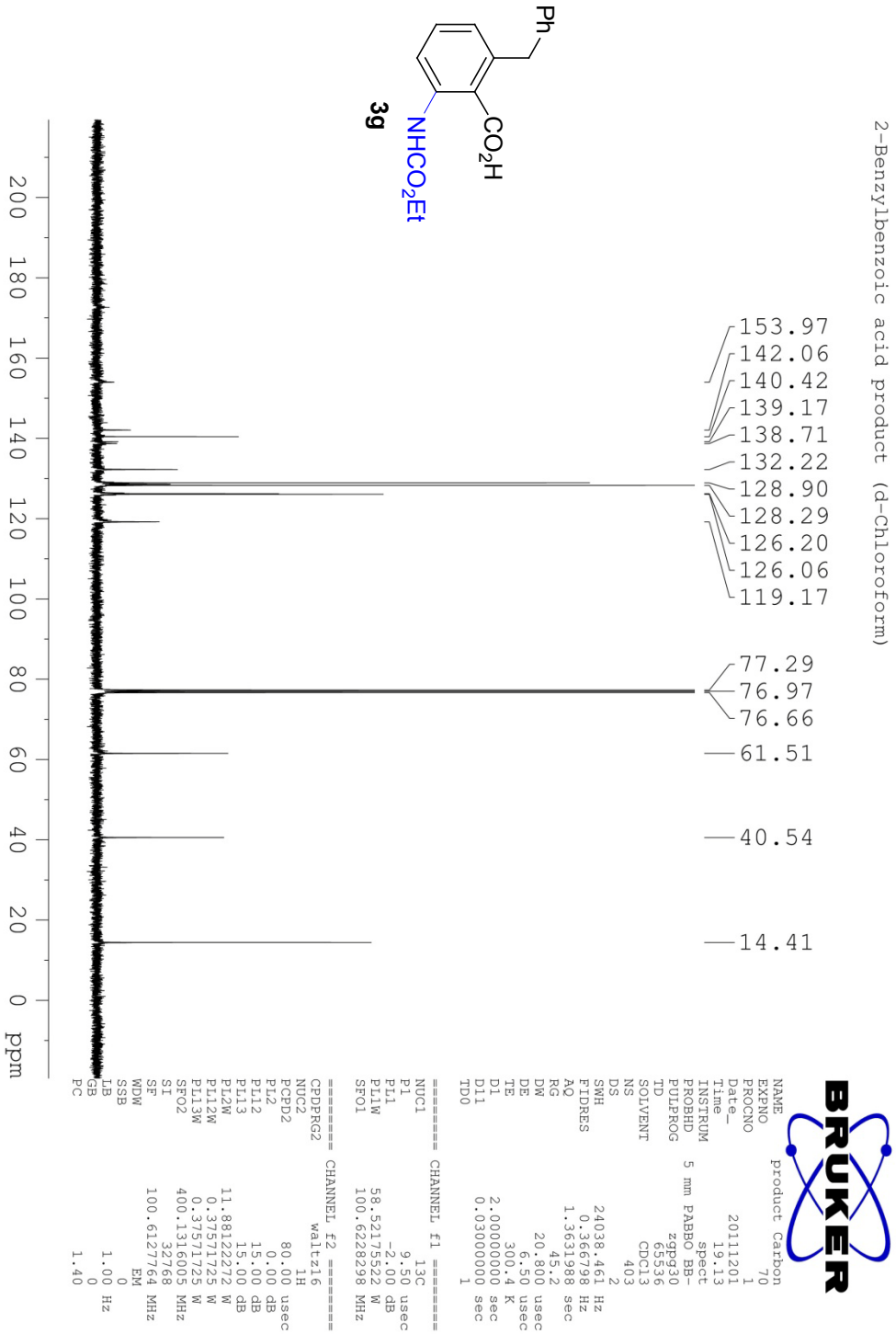
$^{13}$C NMR spectrum of **3f** (magnified)



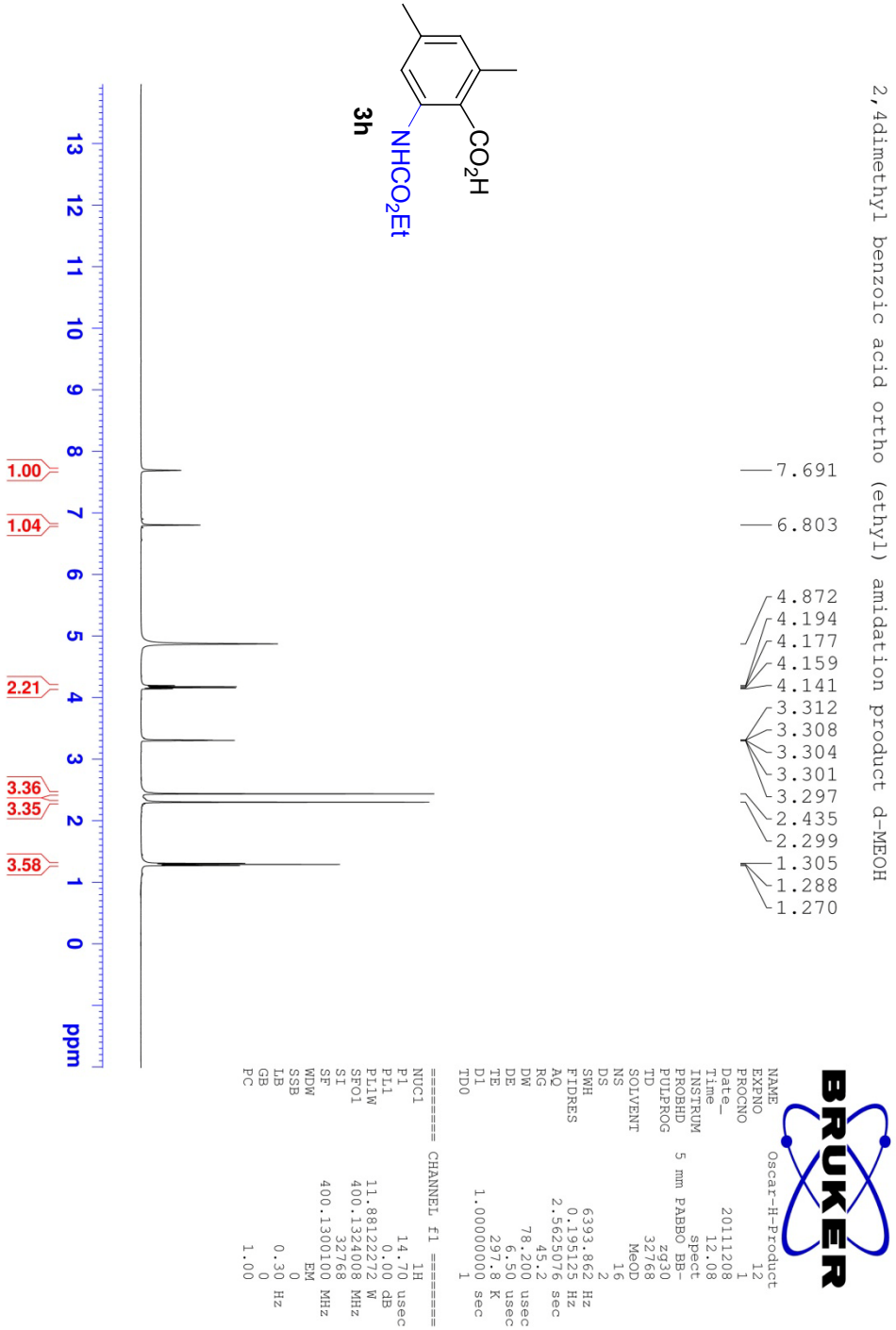
$^{1}$H NMR spectrum of **3g**



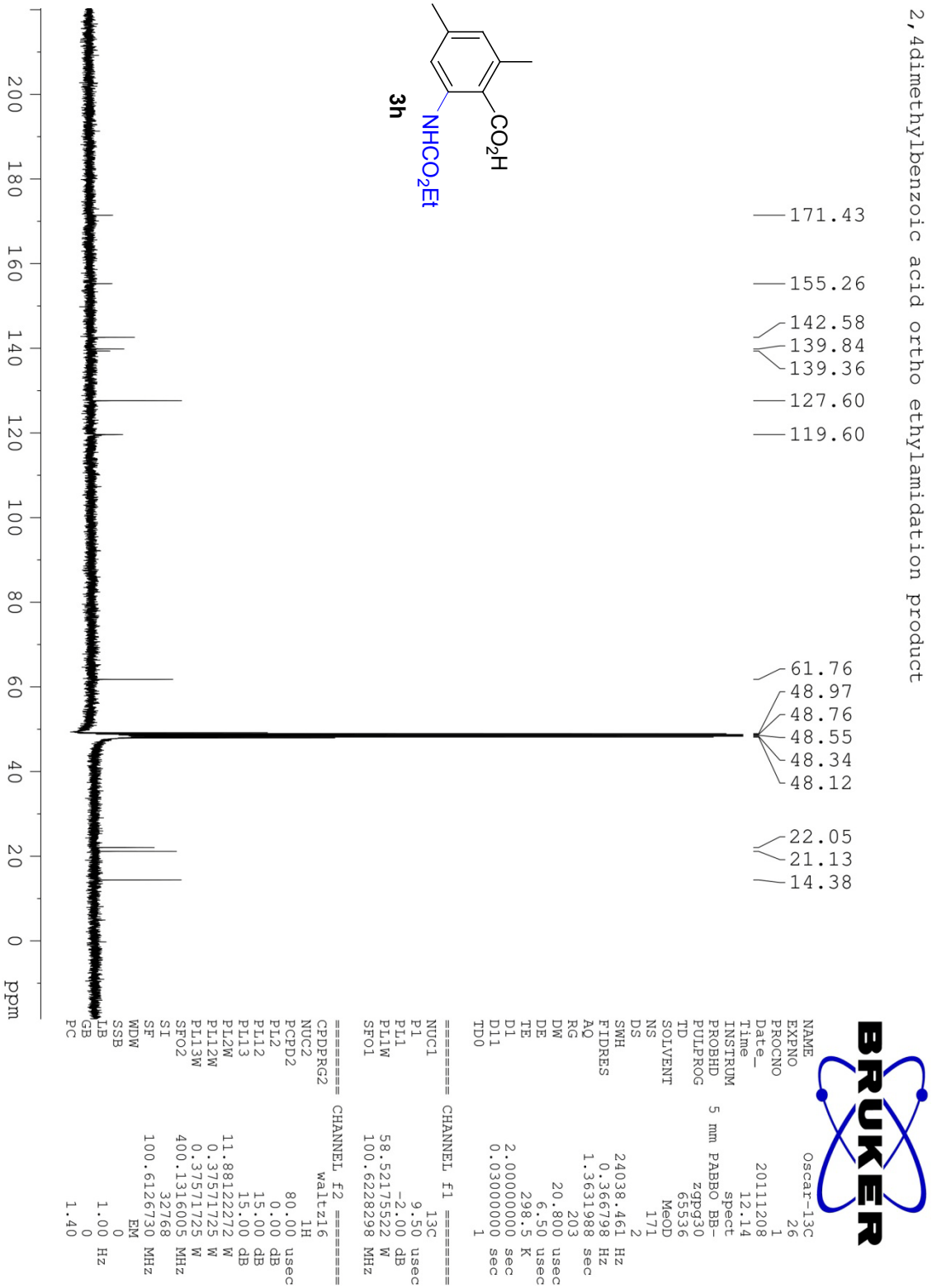
$^{13}$C NMR spectrum of **3g**



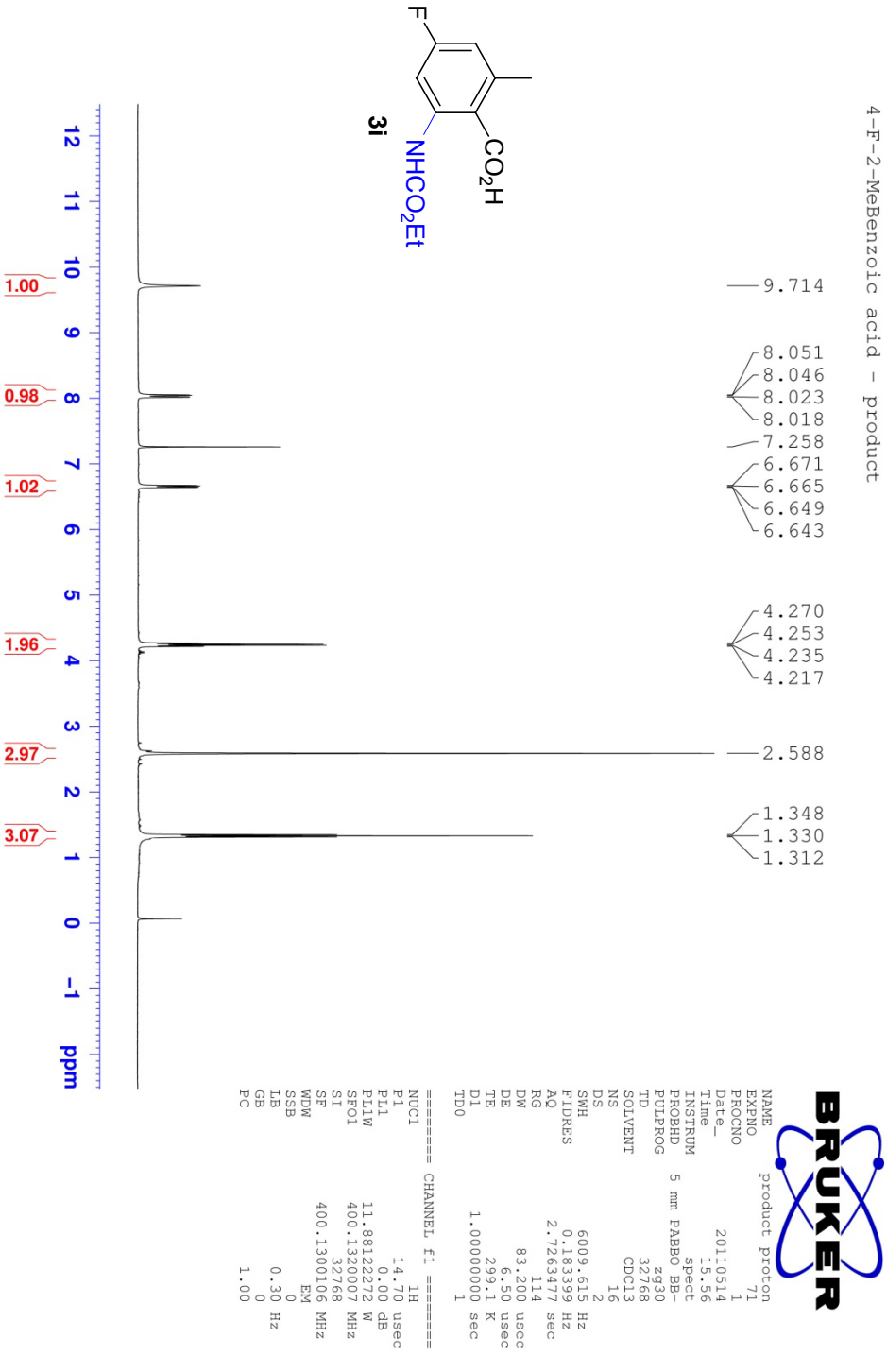
$^{1}$H NMR spectrum of **3h**



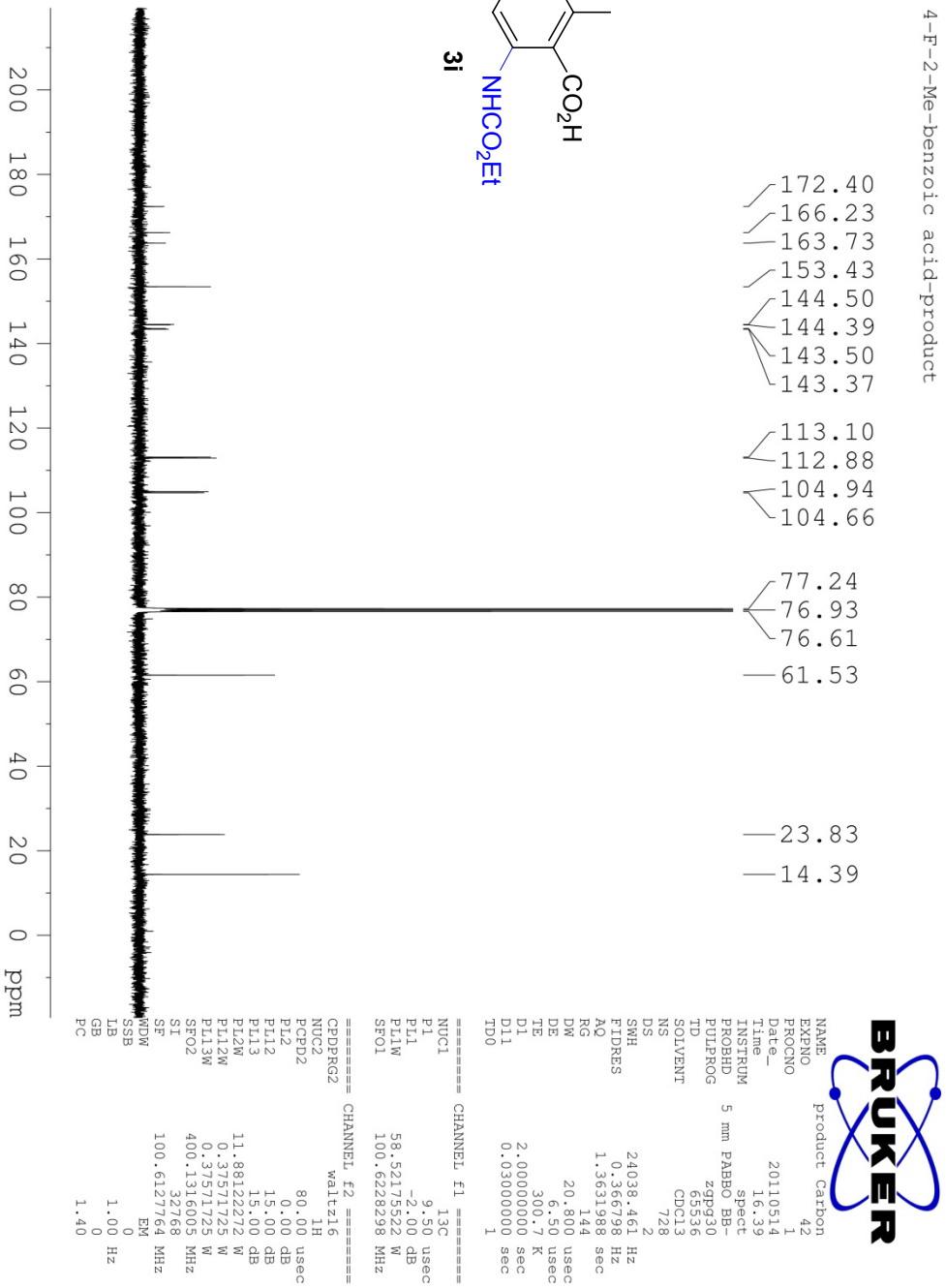
$^{13}$C NMR spectrum of **3h**



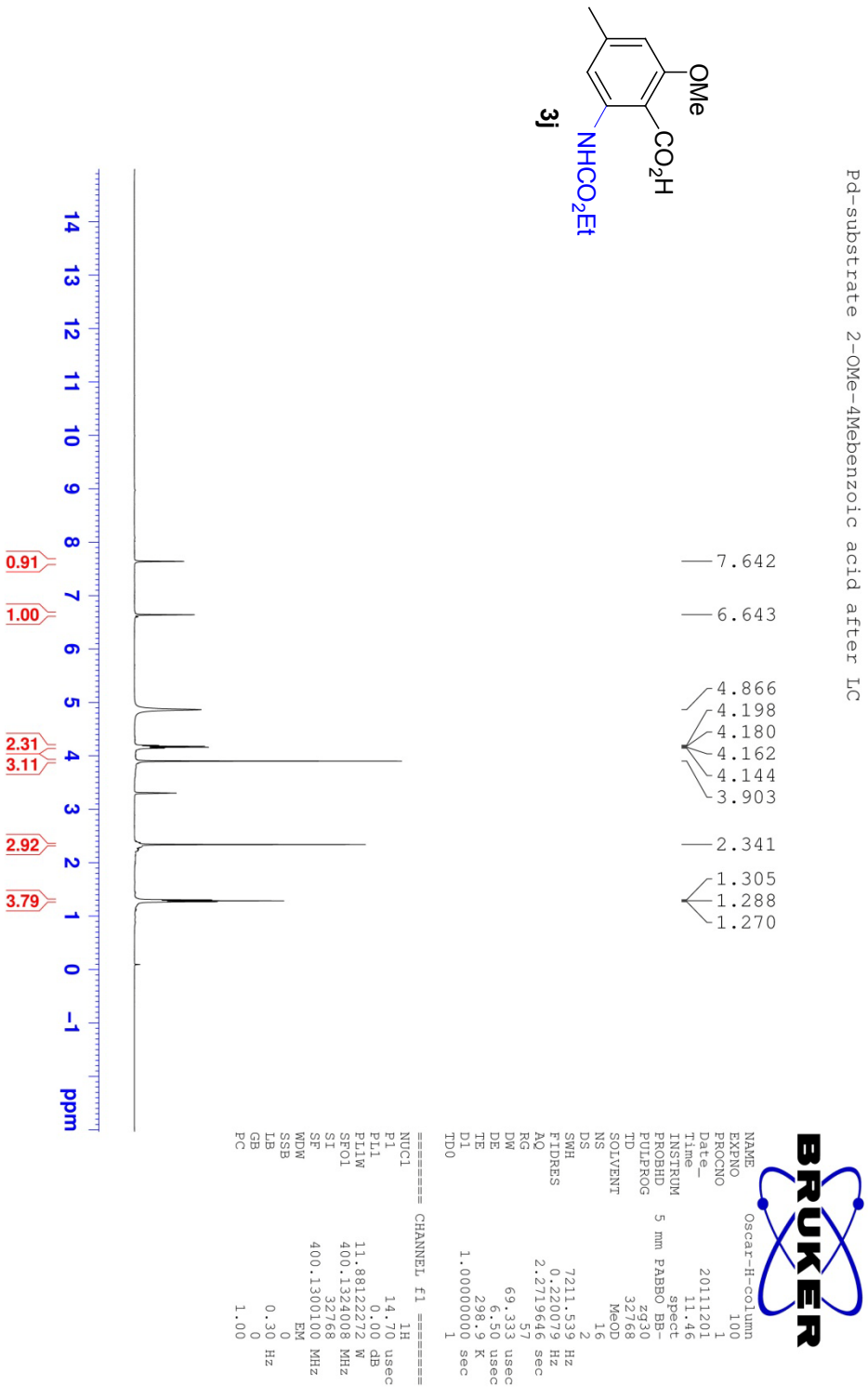
$^{1}$H NMR spectrum of **3i**



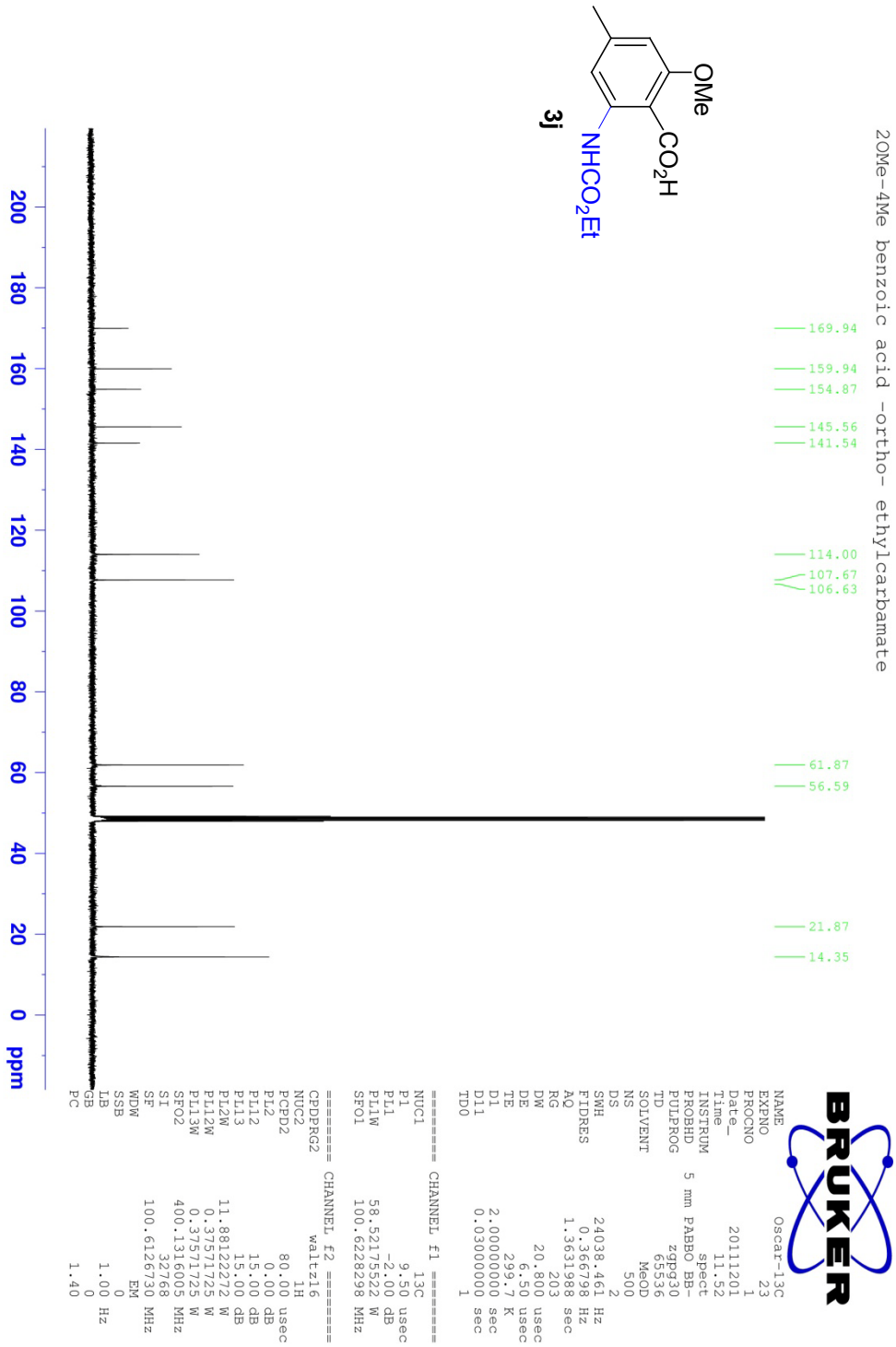
$^{13}$C NMR spectrum of **3i**



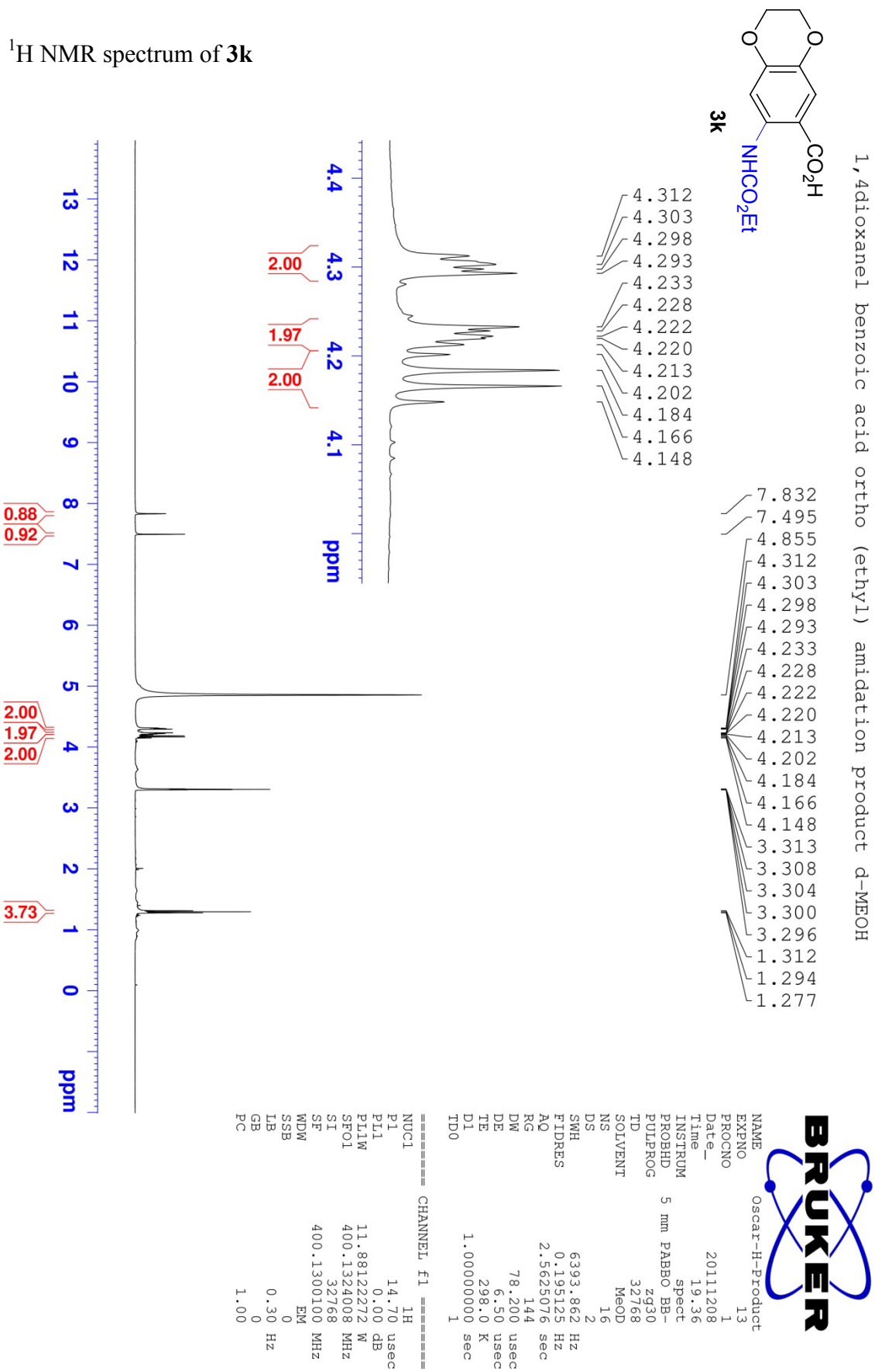
$^{1}$H NMR spectrum of **3j**



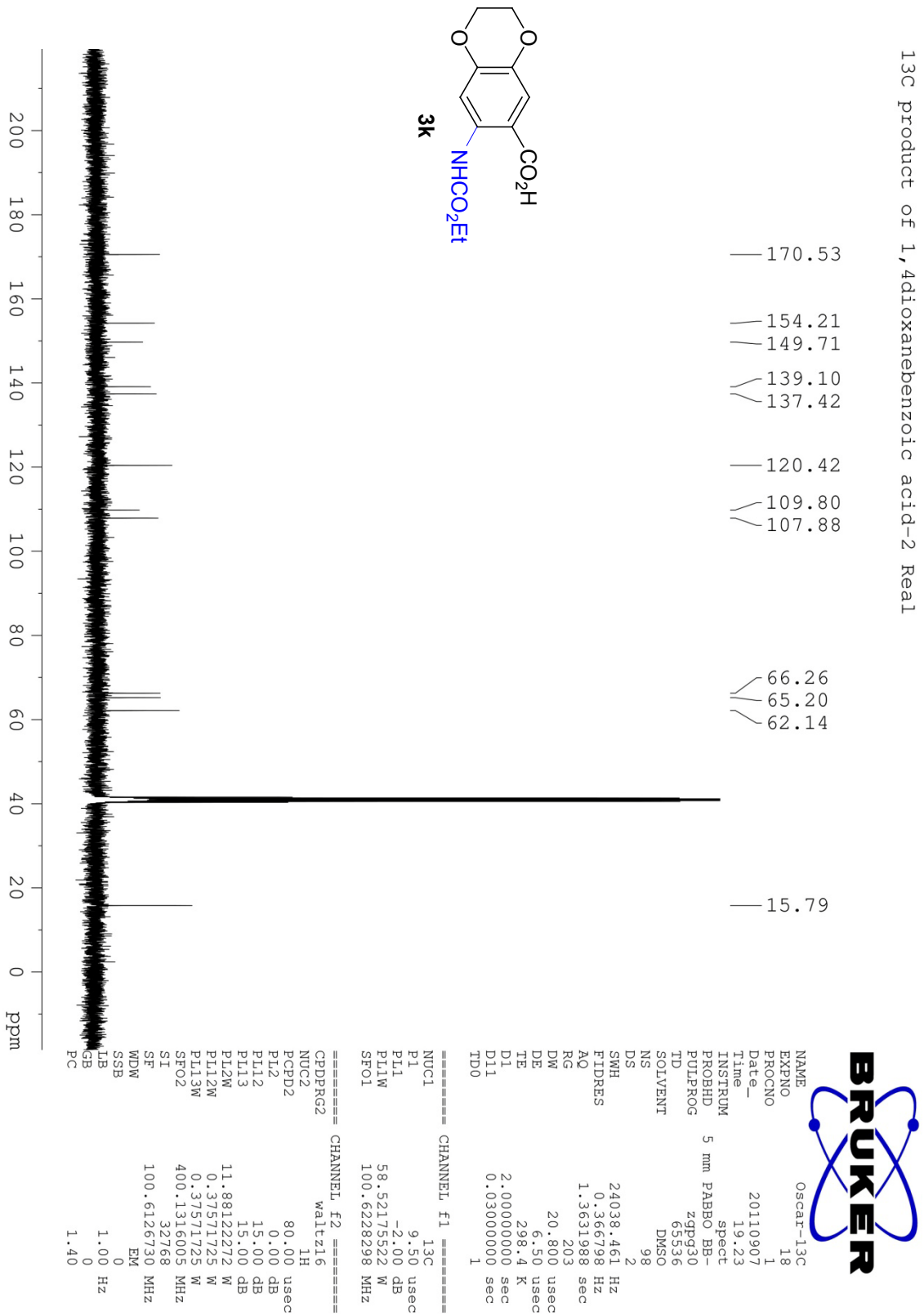
$^{13}$C NMR spectrum of **3j**



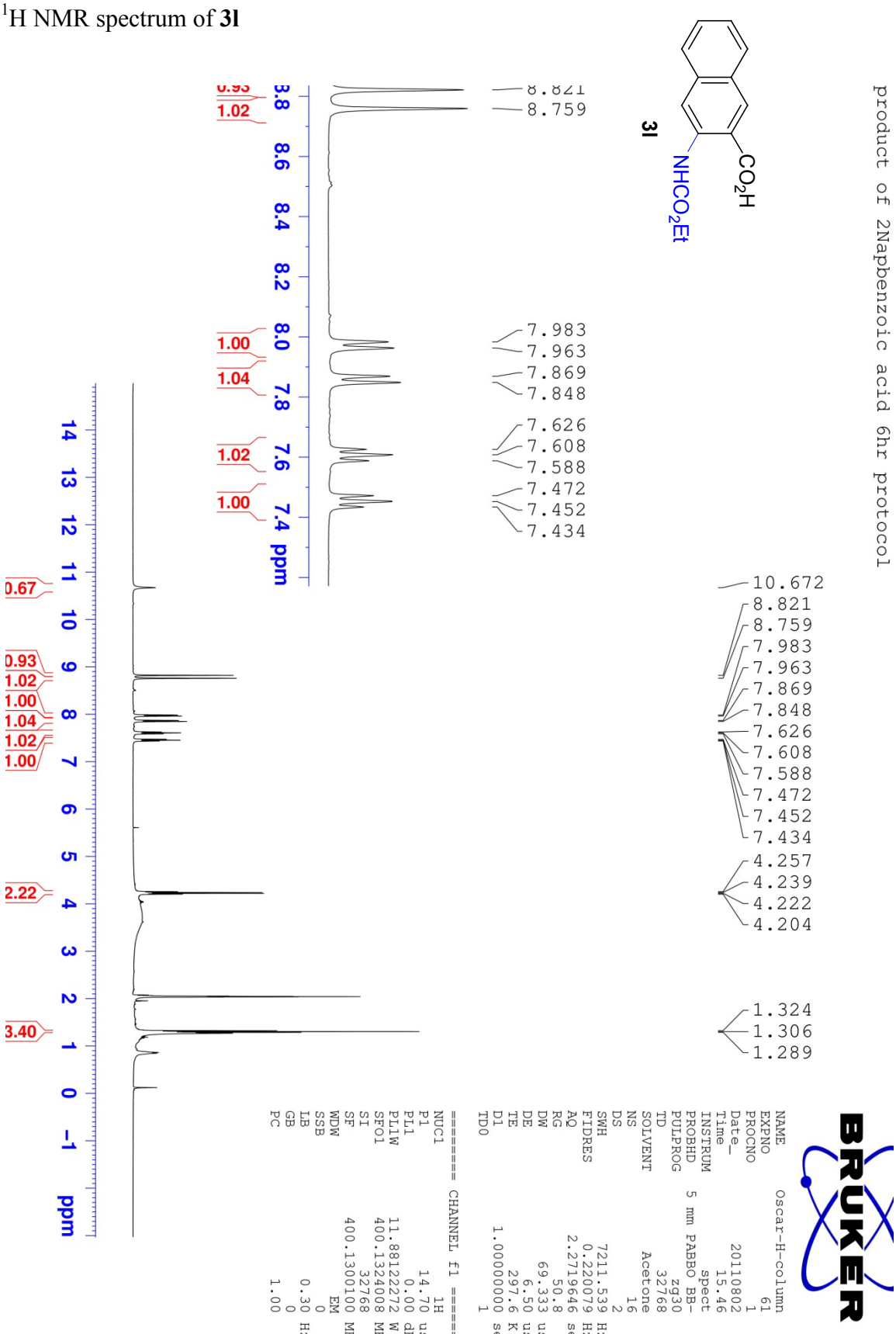
$^{1}$H NMR spectrum of **3k**



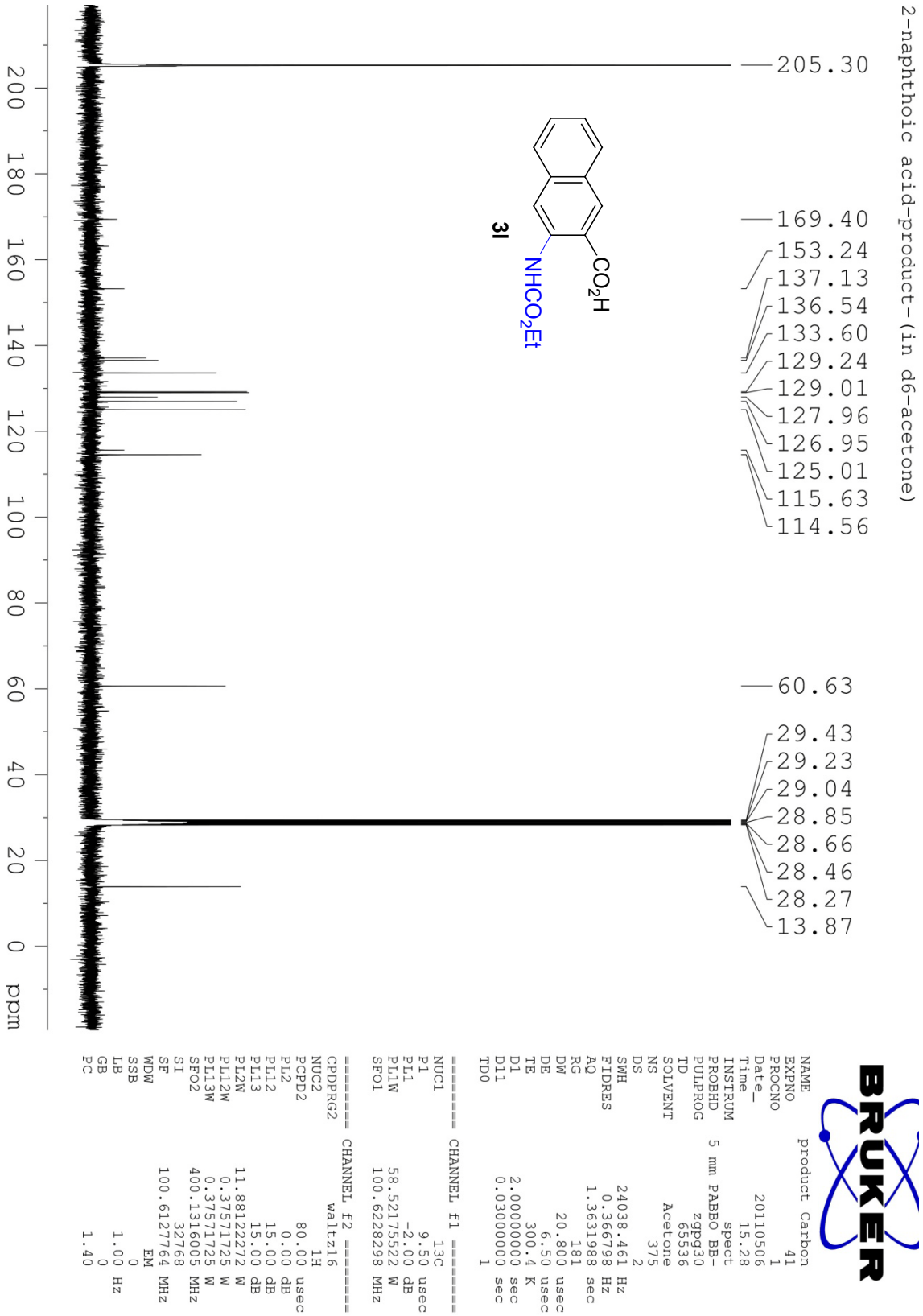
$^{13}$C NMR spectrum of **3k**



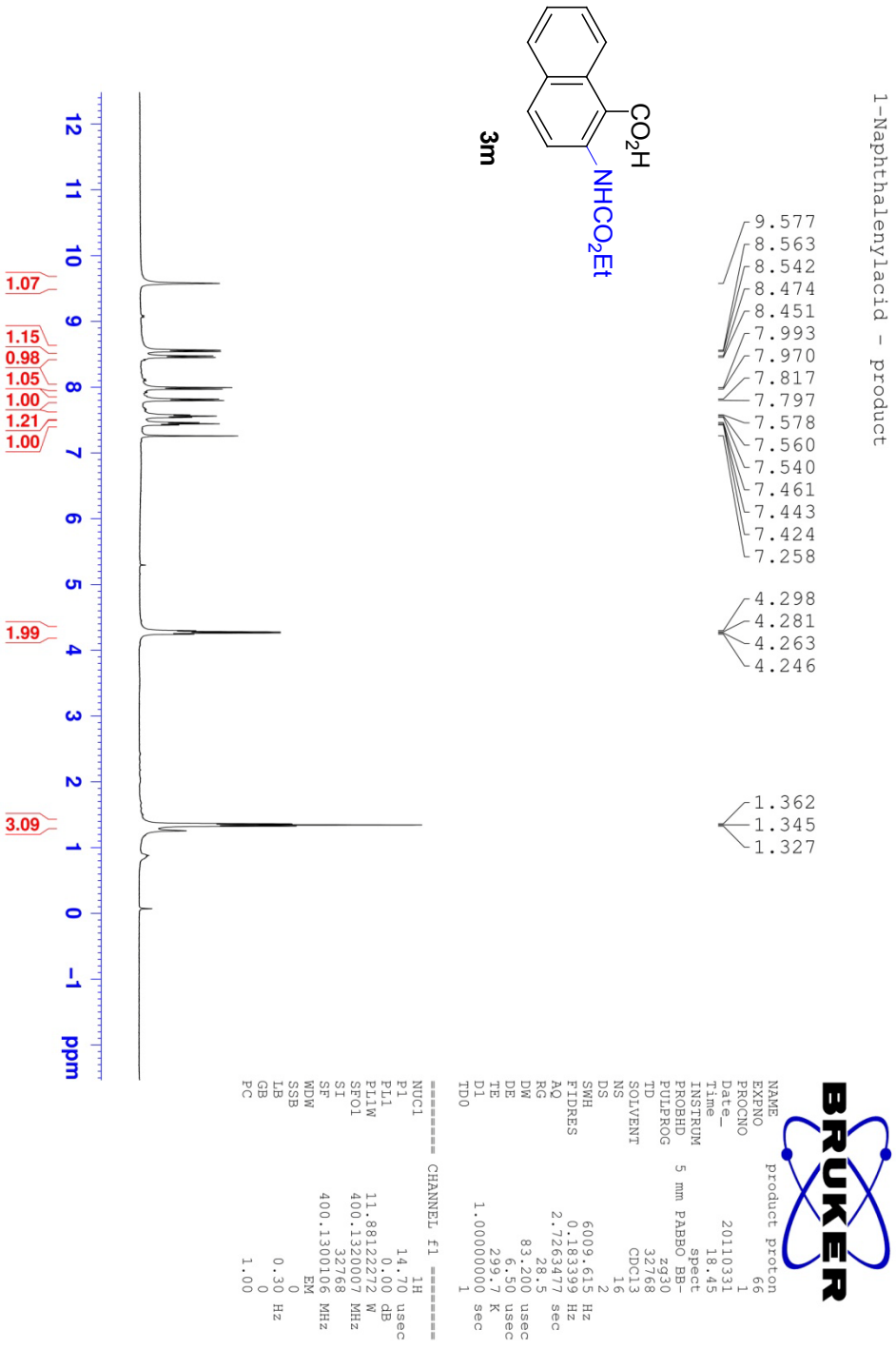
$^1$H NMR spectrum of **3l**



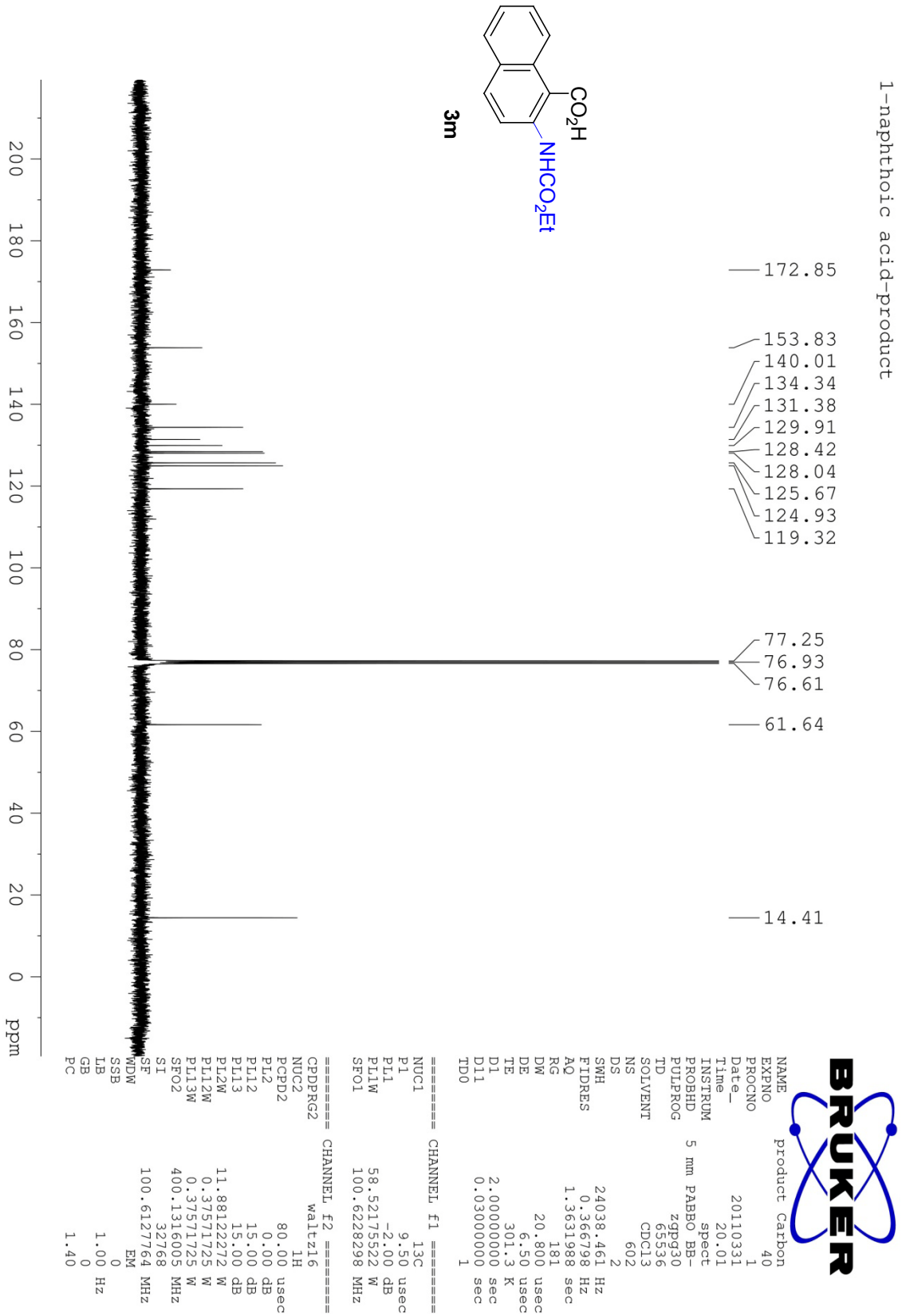
$^{13}$C NMR spectrum of **3l**



$^{1}$H NMR spectrum of **3m**

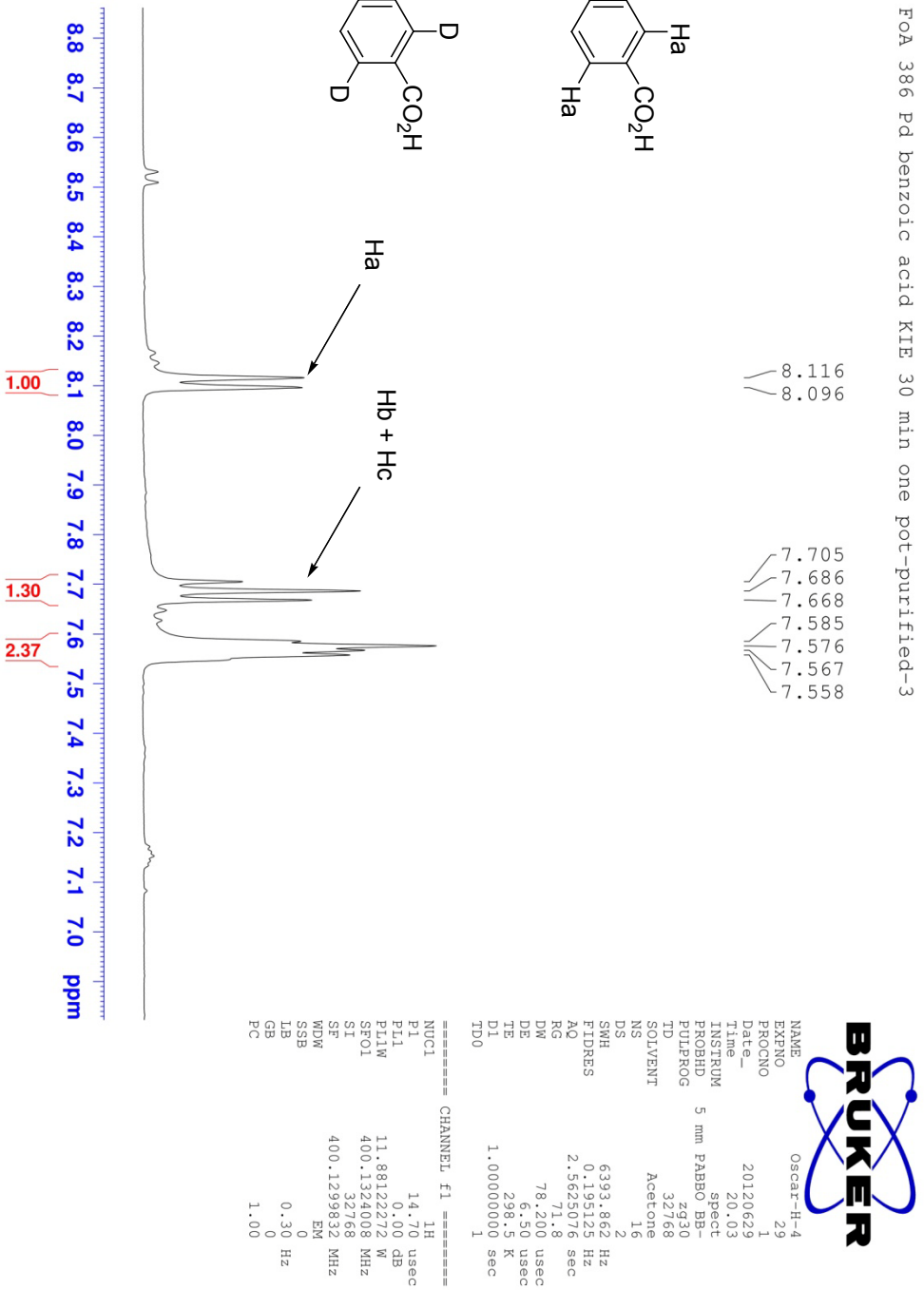


$^{13}$C NMR spectrum of **3m**

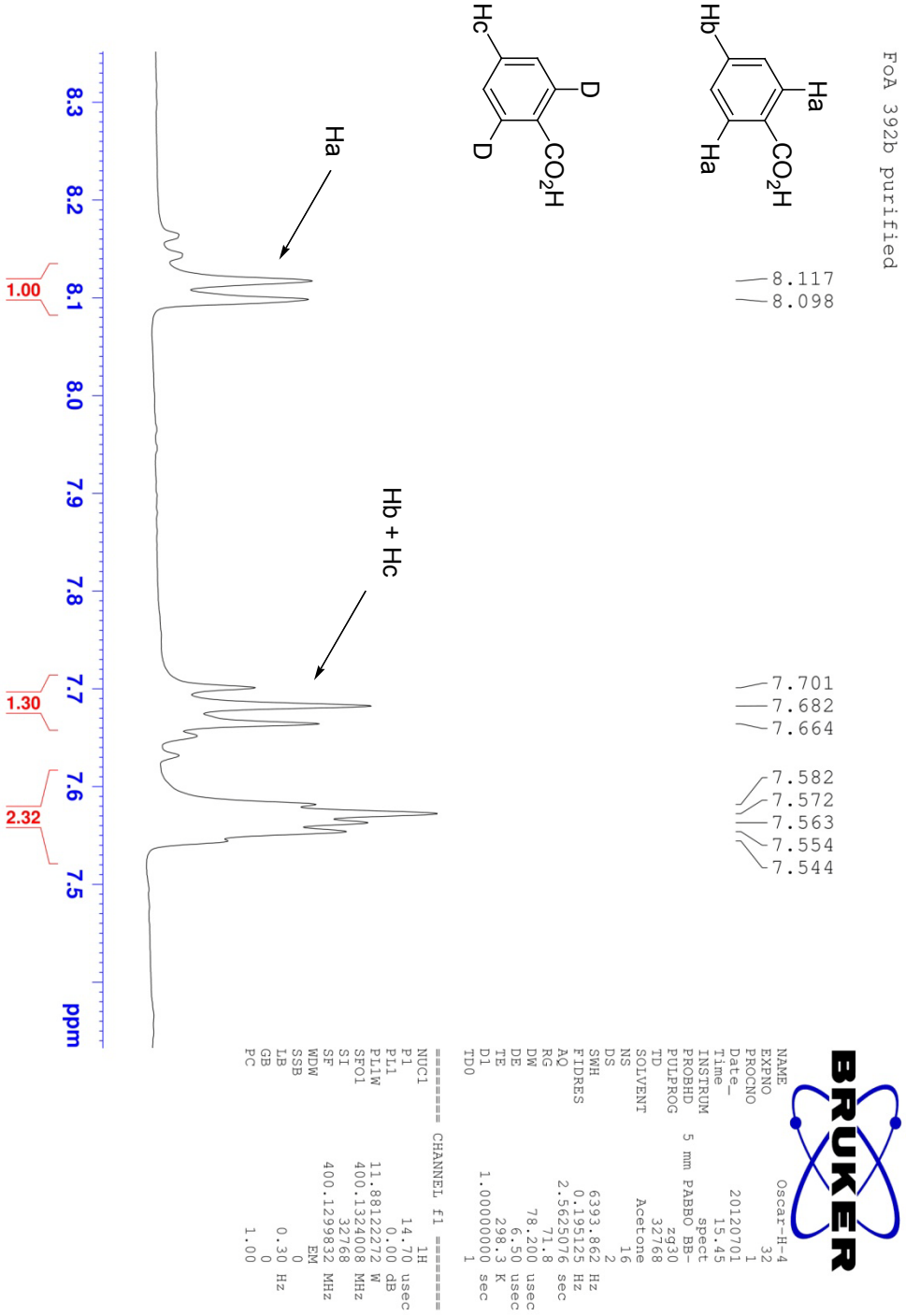


## KIE NMR data

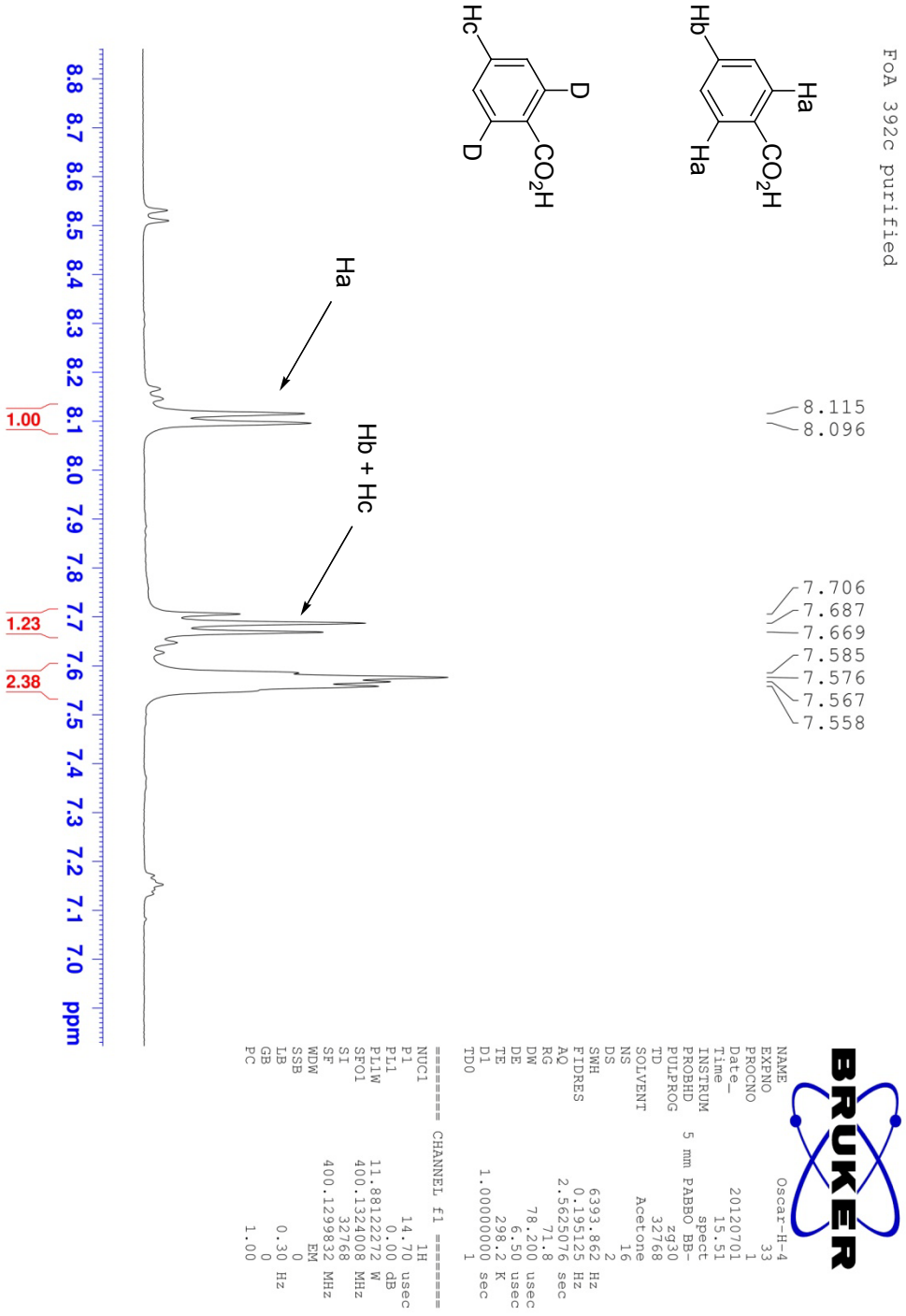
$k_H/k_D$ 1st run



$k_H/k_D$ 2nd run

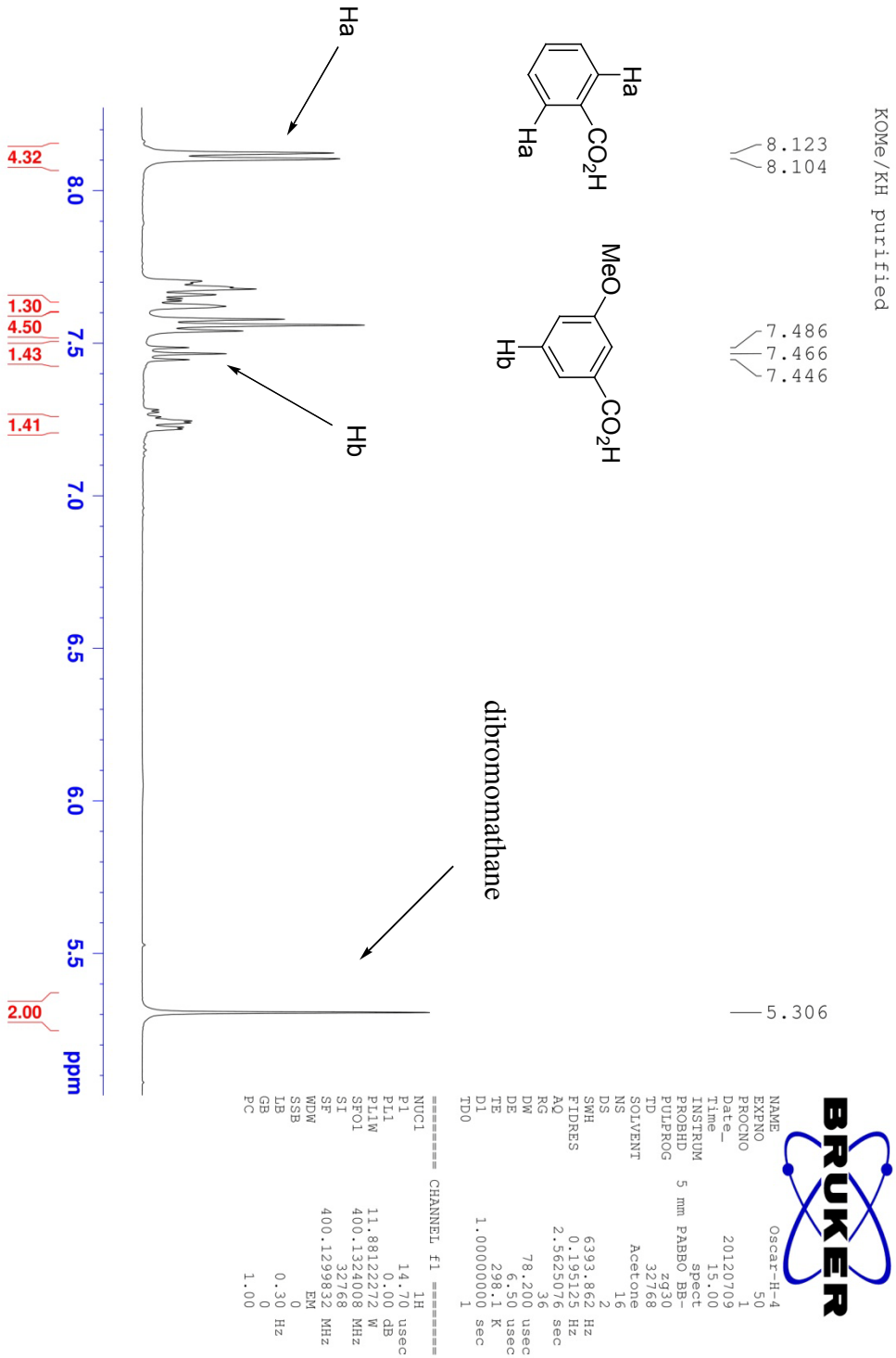

FoA 392b purified
Hb
Ha
Ha
CO2H
8.117
8.098
Hc
D
D
CO2H
7.701
7.682
7.664
7.582
7.572
7.563
7.554
7.544
Ha
Hb + Hc
1.00
1.30
2.32
8.3
8.2
8.1
8.0
7.9
7.8
7.7
7.6
7.5
ppm
BRUKER
NAME Oscar-H-4
EXPNO 32
PROCNO 1
Date_ 20120701
Time_ 15.45
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 32768
SOLVENT Acetone
NS 16
DS 2
SWH 6393.862 Hz
FIDRES 0.195125 Hz
AQ 2.5625076 sec
RG 71.8
DW 78.200 usec
DE 6.50 usec
TE 298.3 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 14.70 usec
PL1 0.00 dB
PLIW 11.88122272 W
SFO1 400.1324008 MHz
SI 32768
SF 400.1299832 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

$k_H/k_D$ 3rd run

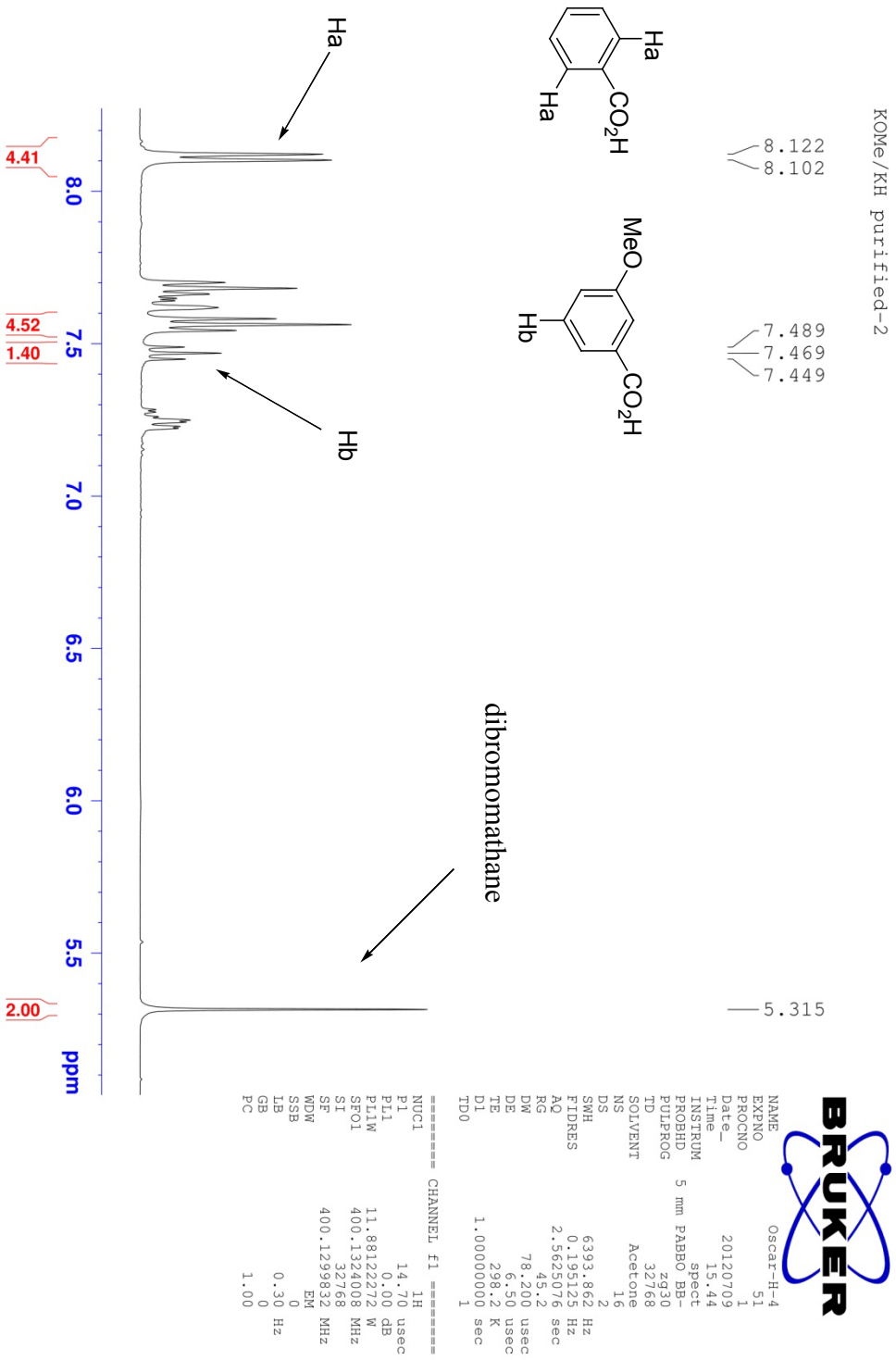

FoA 392c purified
Ha
Hb
Ha
CO2H
D
Hc
D
CO2H
8.115
8.096
7.706
7.687
7.669
7.585
7.576
7.567
7.558
Ha
Hb + Hc
1.00
1.23
2.38
8.8 8.7 8.6 8.5 8.4 8.3 8.2 8.1 8.0 7.9 7.8 7.7 7.6 7.5 7.4 7.3 7.2 7.1 7.0 ppm
BRUKER
NAME Oscar-H-4
EXPNO 33
PROCNO 1
Date_ 20120701
Time_ 15.51
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 32768
SOLVENT Acetone
NS 16
DS 2
SWH 6393.862 Hz
FIDRES 0.195125 Hz
AQ 2.5625076 sec
RG 71.8
DW 78.200 usec
DE 6.50 usec
TE 298.2 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 14.70 usec
PL1 0.00 dB
PL1W 11.88122272 W
SFO1 400.1324008 MHz
SI 32768
SF 400.1299832 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

## Experimental Data of the Hammett Correlation Study

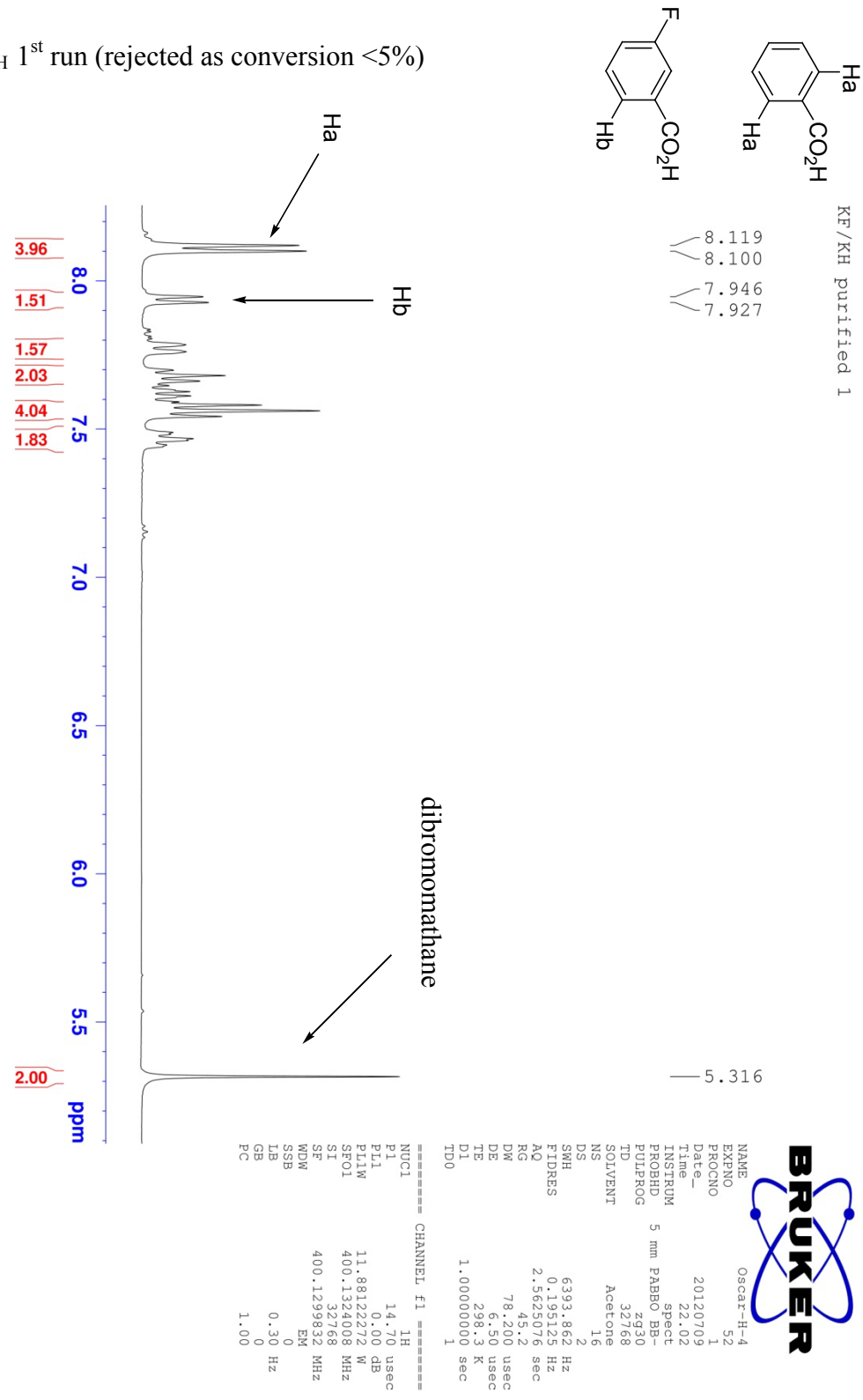
$k_{OMe}/k_H$ 1st run



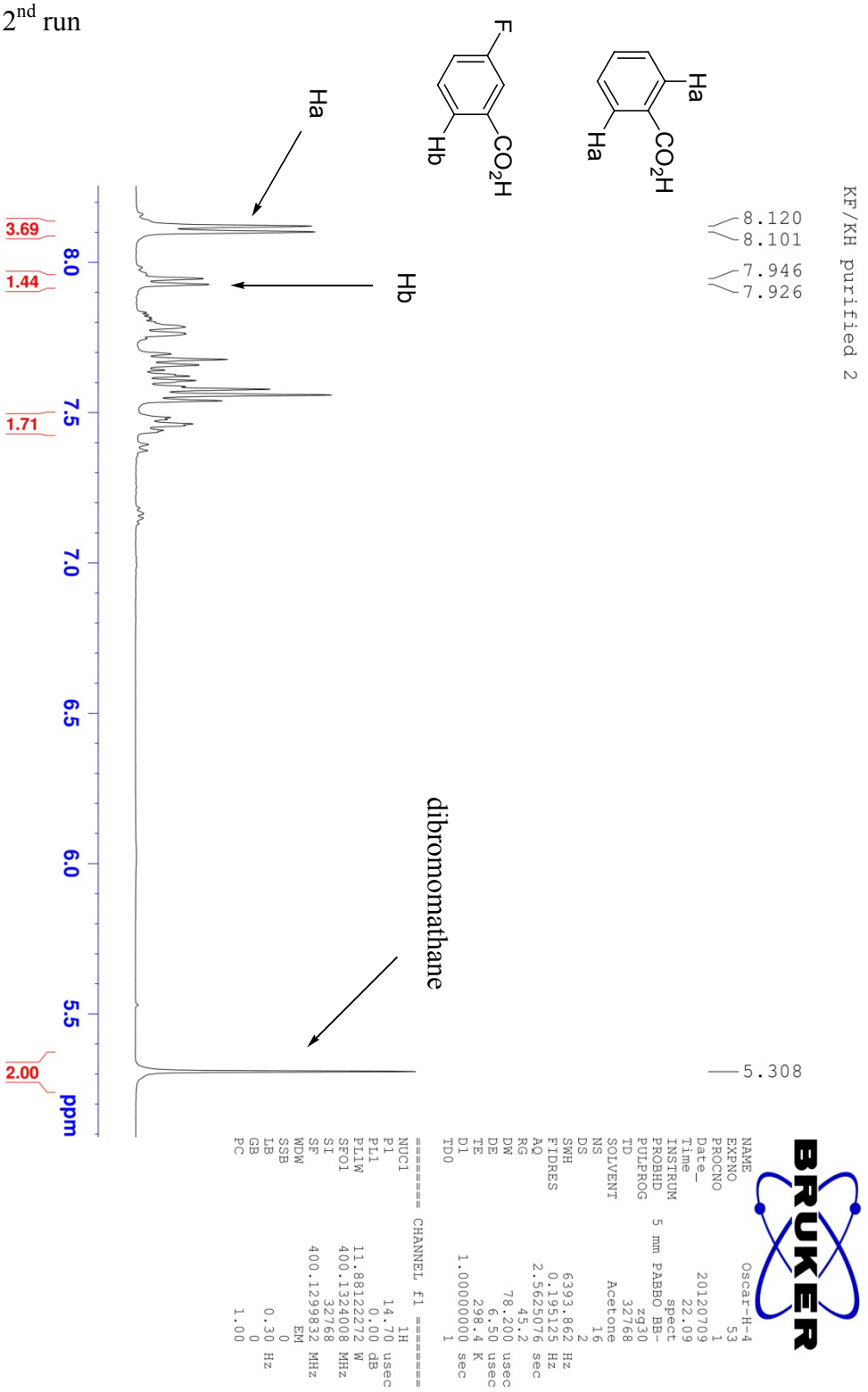
$k_{OM}e/k_H$ 2nd run



$k_F/k_H$ 1st run (rejected as conversion <5%)



$k_F/k_H$ 2nd run


KF/KH purified 2
8.120
8.101
7.946
7.926
5.308
Ha
Hb
F
CO2H
Ha
Ha
CO2H
Ha
Hb
dibromomathane
3.69
1.44
1.71
2.00
8.0
7.5
7.0
6.5
6.0
5.5
ppm
BRUKER
NAME Oscar-H-4
EXPNO 53
PROCNO 1
Date_ 20120709
Time 22.09
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 32768
SOLVENT Acetone
NS 16
DS 2
SWH 6393.862 Hz
FIDRES 0.195125 Hz
AQ 2.5625076 sec
RG 45.2
DW 78.200 usec
DE 6.50 usec
TE 298.4 K
D1 1.00000000 sec
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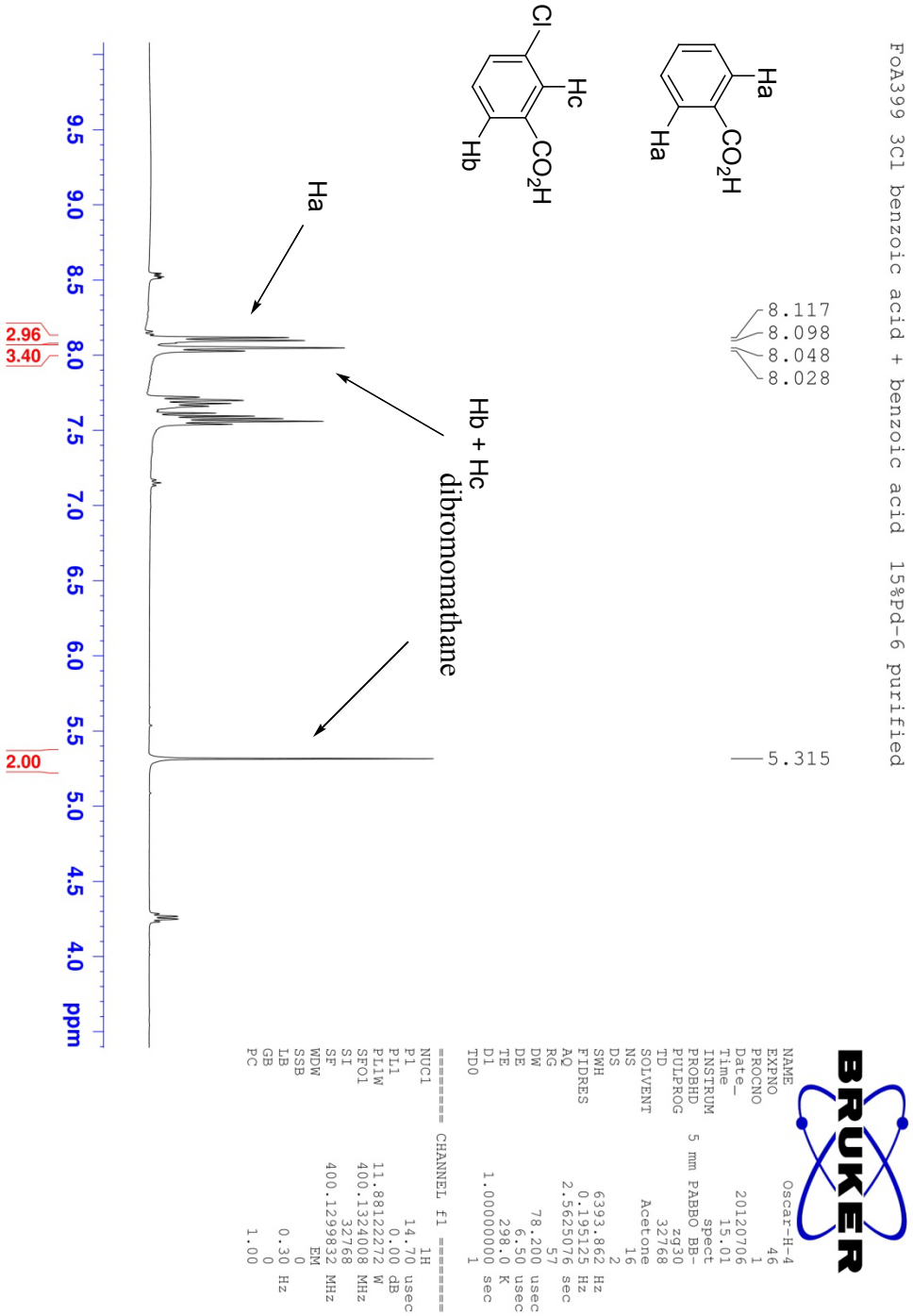
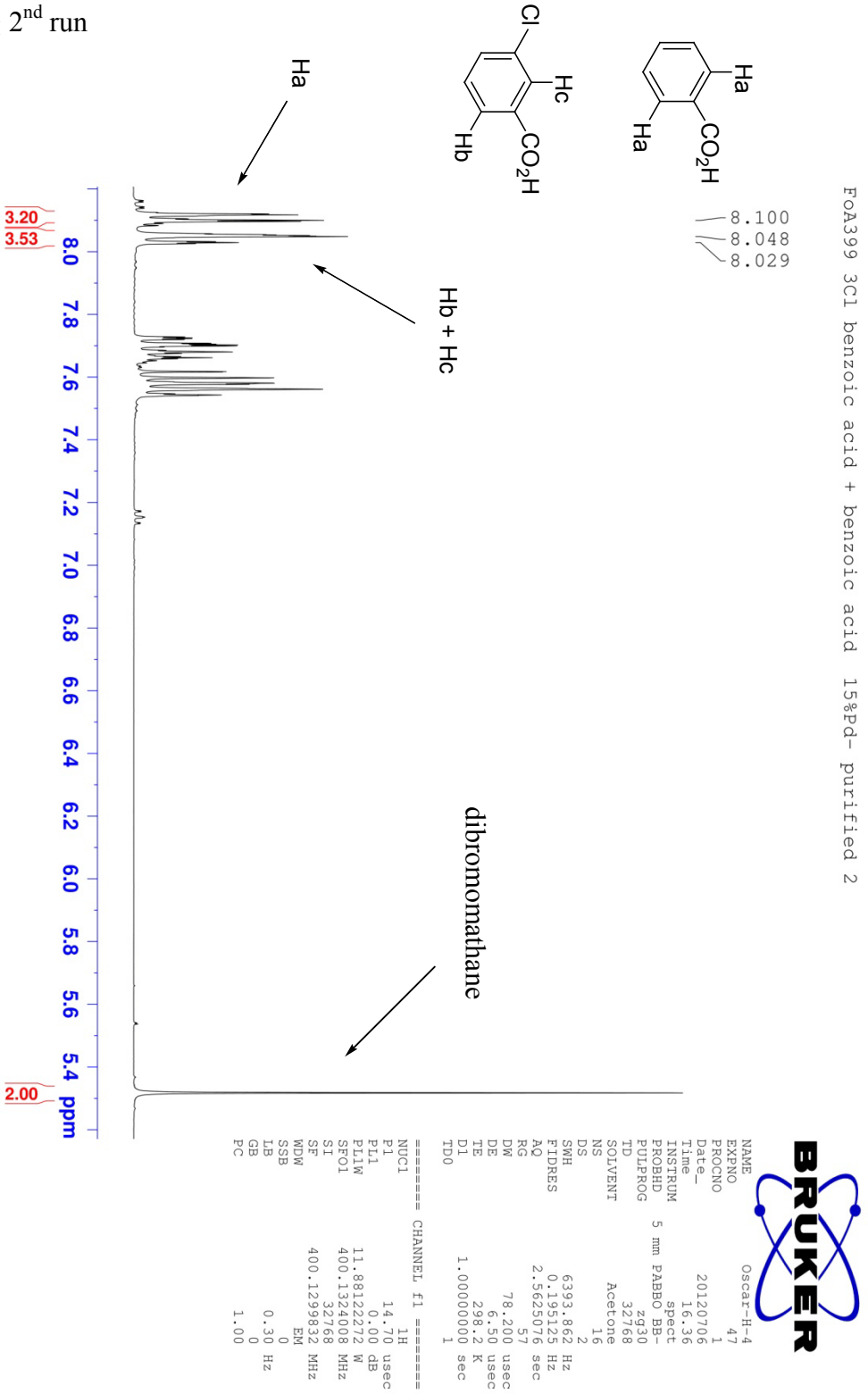
P1 14.70 usec
PL1 0.00 dB
PL1W 11.88122272 W
SFO1 400.1324008 MHz
SI 32768
SF 400.1299832 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

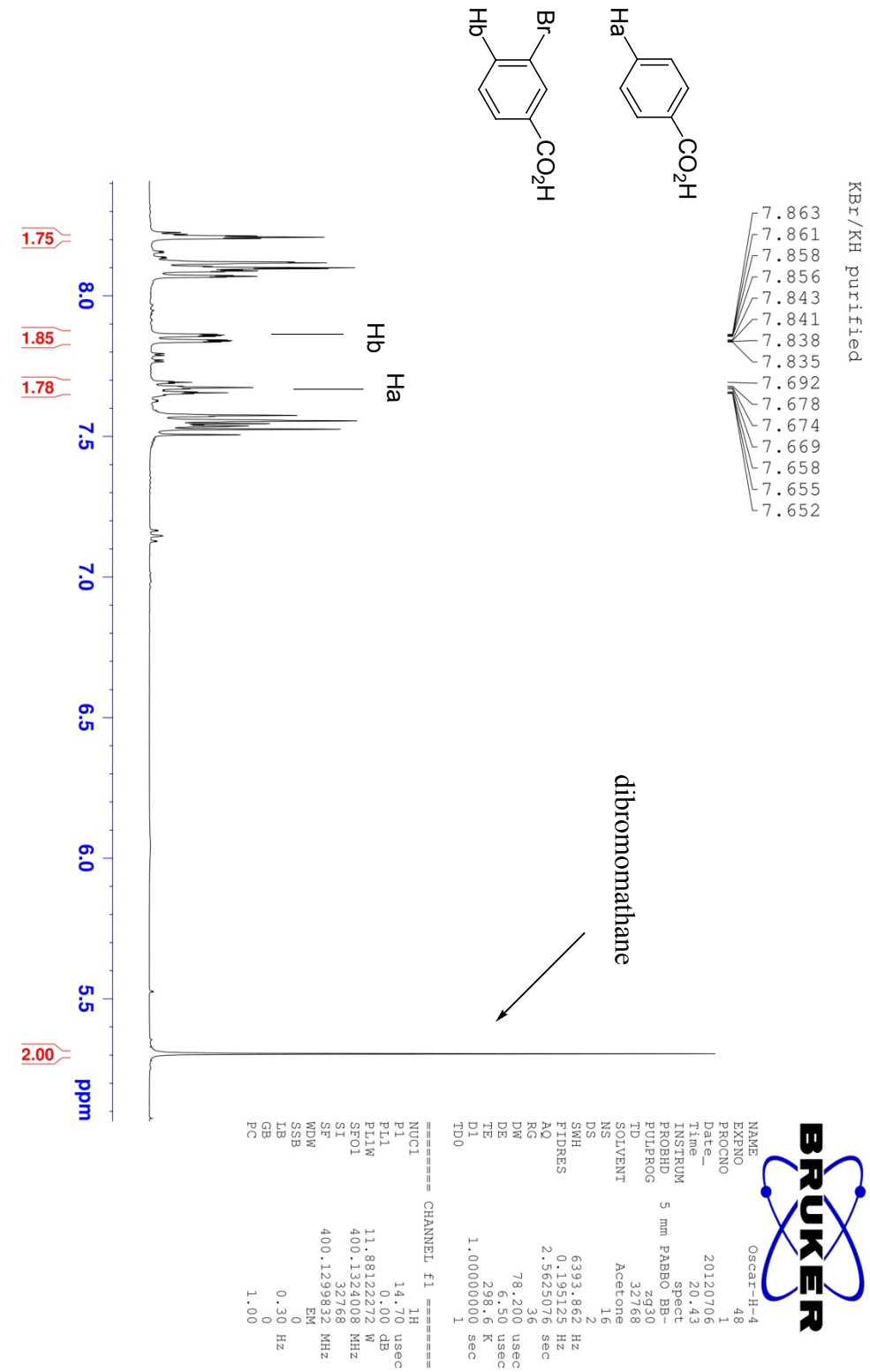
$k_{Cl}/k_H$ 1st run



$k_{Cl}/k_H$ 2nd run



$k_{Br}/k_{H}$ 1st run



$k_{Br}/k_{H}$ 2nd run