Direct α-halogenation of carboxylic acids with *N*-bromosuccinimide (NBS) or trichloroisocyanuric acid (TCCA) in the presence of catalytic amounts of 4-trifluoromethylbenzoic anhydride and H_2SO_4

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Supplementary Information

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1. General information

Melting points were determined on a Yamato melting point apparatus MP-21 and are uncorrected. IR spectra were recorded using a JEOL FT/IR-4600ST spectrophotometer. NMR spectra were measured on a Varian NMR system 700 spectrometer (700 MHz) using tetramethylsilane as an internal standard. Unless otherwise stated, anhydrous sodium sulfate was employed as the drying agent. Column chromatography was performed on Kanto chemical Silica gel 60 (spherical, 63-210 μm). Anhydride **8** was purchased from TCI. DCE-d_4, CD_3OD and D_2O was purchased from Merck. Detection of Cl_2 was carried out by the ION SELECTIVE PACK TEST kit, WAK-CIO/DP (Kyoritsu Chemical-Check Lab. Corp.), which DPD (diethyl-*p*-phenylenediamine) was employed as a detection agent, or the test paper, Nissan Aqua Check LC, which syringaldazine (3,5-dimethoxy-4-hydroxybenzaldazine) was applied (purchased from AS ONE Co.). IR and ^{1}H-NMR spectra of compounds **2**, **9-11**, **15**, **16** and **27** were completely in accordance with those of the commercially available samples purchased from TCI. IR and ^{1}H-NMR spectra of compounds **12** and **14** were completely in accordance with those of the commercially available samples purchased from Fujifilm-Wako. IR and ^{1}H-NMR spectra of compounds **13**, **17** and **23** were completely in accordance with those of the commercially available samples purchased from Nakalai Tesque. Compounds **19**,[1] **20**,[2] **21**,[3] **22**,[4] **24**,[5] **25**,[6] and **26**[1] were completely identified by the comparison of spectroscopic behaviours with those of the authentic samples reported in the literature.

2. Experimental procedures

General procedure for the synthesis of α-brominated carboxylic acids

NBS (249 mg, 1.4 mmol, 1.4 equiv.) was added to the mixture of sulfuric acid (9.8 mg, 0.1 mmol), hexanoic acid **1** (116 mg, 1.0 mmol) and anhydride **8** (36 mg, 0.1 mmol) in DCE (0.5 mL). After stirring the mixture at 80 °C for 3 h, the mixture was filtered and the filtrate was evaporated under reduced pressure. In order to remove most of 4-trifluoromethylbenzoic acid (**B**) which was difficult to separate from **2**, DCE (25 μL) was added and the mixture was filtered. After the evaporation of the filtrate under reduced pressure, the residue was purified by column chromatography on silica gel using heptane-EtOAc (8:2) to give **2** (170 mg, 87%).

General procedure for the synthesis of α-chlorinated carboxylic acids

TCCA (186 mg, 0.8 mmol, 2.4 equiv.) was added to the mixture of sulfuric acid (9.8 mg, 0.1 mmol), isovaleric acid (102 mg, 1.0 mmol) and anhydride **8** (36 mg, 0.1 mmol) in DCE (0.1 mL). After stirring the mixture at 80 °C for 12 h, the mixture was filtered and the filtrate was evaporated under reduced pressure. In order to remove most of 4-trifluoromethylbenzoic acid (**B**), the mixture was filtered and the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using heptane-EtOAc (8:2) to give **24** (127 mg, 93%).

General procedure for the synthesis of α-iodinated carboxylic acids using I_2

I_2 (356 mg, 1.4 mmol, 1.4 equiv.) was added to the mixture of sulfuric acid (9.8 mg, 0.1 mmol), 3-phenylpropanoic acid (**18**) (150 mg, 1.0 mmol) and anhydride **8** (36 mg, 0.1 mmol) in DCE (0.5

mL). The mixture was stirred at 80 °C for 4 h and then filtered. After the evaporation of the filtrate under reduced pressure, 2-iodo-3-phenylpropanoic acid (**28**) was not detected by the ^{1}H-NMR spectroscopy.

General procedure for the synthesis of α-iodinated carboxylic acids using NIS

NIS (315 mg, 1.4 mmol, 1.4 equiv.) was added to the mixture of sulfuric acid (9.8 mg, 0.1 mmol), 3-phenylpropanoic acid (**18**) (150 mg, 1.0 mmol) and anhydride **8** (36 mg, 0.1 mmol) in DCE (0.5 mL). The mixture was stirred at 80 °C for 4 h and then filtered. After the evaporation of the filtrate under reduced pressure, 2-iodo-3-phenylpropanoic acid (**28**) was not detected by the ^{1}H-NMR spectroscopy.

Preparative-scale procedure for the synthesis of α-brominated carboxylic acids

NBS (4.98 g, 28 mmol, 1.4 equiv.) was added to the mixture of sulfuric acid (196 mg, 2 mmol), hexanoic acid **1** (2.32 g, 20 mmol) and anhydride **8** (724 mg, 2 mmol) in DCE (10 mL). After stirring the mixture at 80 °C for 4.5 h, the mixture was filtered and the filtrate was evaporated under reduced pressure. In order to remove most of 4-trifluoromethylbenzoic acid (**B**), DCE (0.5 mL) was added and the mixture was filtered. After the evaporation of the filtrate under reduced pressure, the residue was purified by column chromatography on silica gel using heptane-EtOAc (8:2) to give **2** (3.52 g, 90%).

Preparative-scale procedure for the synthesis of α-chlorinated carboxylic acids

TCCA (3.72 g, 16 mmol, 2.4 equiv.) was added to the mixture of sulfuric acid (196 mg, 2 mmol), isovaleric acid (2.04 g, 20 mmol) and anhydride **8** (724 mg, 2 mmol) in DCE (2 mL). After stirring the mixture at 80 °C for 18 h, the mixture was filtered and the filtrate was evaporated under reduced pressure. In order to remove most of 4-trifluoromethylbenzoic acid (**B**), the mixture was filtered and the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using heptane-EtOAc (8:2) to give **24** (2.56 g, 94%).

Comparative bromination of hexanoic acid (1) by NBS vs. molecular bromine[1]

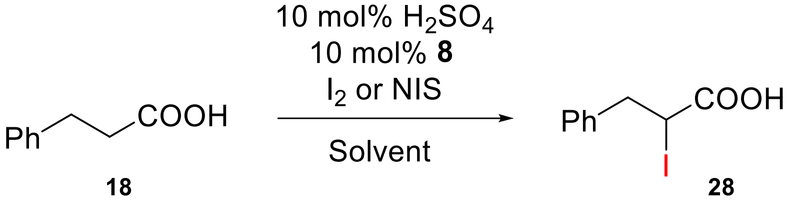
Hexanoic acid **1** (3.25 g, 28 mmol) and sulfuric acid (274 mg, 2.8 mmol) was dissolved in DCE-d_4 (4 mL). The mixture was divided into two equal fractions which were placed in two separate flasks. The latter was cooled in an ice bath. Anhydride **8** (507 mg, 1.4 mmol) and the solution of bromine (3.14 g, 19.6 mmol) in DCE-d_4 (5 mL) were added to one of them. To the other flask, **8** (507 mg, 1.4 mmol), DCE-d_4 (5 mL) and NBS (3.49 g, 19.6 mmol) were added. Both flasks were equipped with condensers fitted with drying tubes and heated simultaneously in the same oil bath at 80 °C. At known intervals of time, aliquots of the reaction mixture were removed from the flasks, which were immediately cooled in an ice bath to quench the reactions. After the filtration, the solution was transferred to NMR tubes. NMR spectra were then measured, and the integration of the triplet of the bromide **2** at δ 4.25 was compared to that of the triplet of **1** at δ 2.35. The resulting ratio increased over time and eventually plateaued, showing completion of the reactions. The results are summarized in Table S2.

Deuteration of carboxylic acid 1 in the presence of CD_3OD

Anhydride **8** (217 mg, 0.6 mmol) was added to the mixture of sulfuric acid (59 mg, 0.6 mmol), CD_3OD (1.0 mL, 24.8 mmol), DCE (3.0 mL) and hexanoic acid **1** (696 mg, 6.0 mmol). After stirring the mixture at 80 °C for 6 h, the solution was extracted with ether (70 mL). The extracts were washed with water (20 mL×3), dried and evaporated. In order to remove most of 4-trifluoromethylbenzoic acid (**B**), DCE (0.15 mL) was added and the mixture was filtered. After the evaporation of the filtrate, the residue was purified by column chromatography on silica gel using heptane-EtOAc (20:1) to give CD_3 ester of **1**. Two independent runs afforded 710 mg (89%) and 742 mg (93%), respectively. Deuterium incorporation at the α-position was determined by integration of the ^1H NMR spectra and was 12% in both runs.

3. Tables

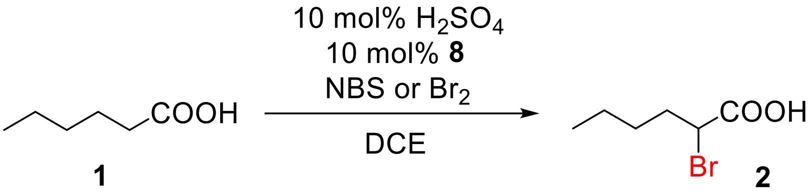
Table S1 α-Iodination of carboxylic acid **18**[a]



Entry	Reagent	Solvent	Temp (°C)	Yield (%)
1	I_2	DCE (0.5 mL)	80	0
2[b]	I_2	–	80	0
3	I_2	DCE (0.1 mL)	80	0
4	I_2	PhCl (0.5 mL)	130	0
5	I_2	PhCl (0.1 mL)	130	0
6	NIS	DCE (0.5 mL)	80	0
7	NIS	–	80	0
8	NIS	DCE (0.1 mL)	80	0
9	NIS	PhCl (0.5 mL)	130	0
10[b]	NIS	–	130	0
11	NIS	PhCl (0.1 mL)	130	0

[a] Conditions: carboxylic acid **18** (1.0 mmol), H_2SO_4 (10 mol%), anhydride **8** (10 mol%), I_2 or NIS (1.4 mmol), solvent, 4 h. [b] A large amount of I_2 sublimed.

Table S2 Comparative bromination of **1** using NBS and Br_2.[a]

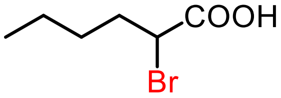


	Conv. (%)[b]	
Time (h)	NBS	Br_2
0	0	0
0.25	35	2
0.5	51	5
0.75	63	6
1.0	75	11
1.5	90	14
2.0	95	20
2.5	100	24
3.0	100	29

[a] Conditions: carboxylic acid **1** (14 mmol), H_2SO_4 (10 mol%), anhydride **8** (10 mol%), NBS or Br_2 (19.6 mmol), DCE (7 mL), 80 °C. [b] Determined by ^{1}H-NMR spectroscopy.

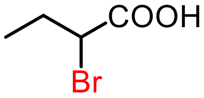
4. Analytical data of compounds 2, 9-11, 15-17 and 21-26

2-Bromohexanoic acid (**2**) (commercially available)



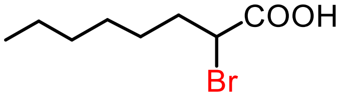
Colourless oil; IR (Neat) 3106, 2959, 2932, 2872, 2667, 1716, 1460, 1424, 1382, 1286, 1245, 1174, 1111, 1065, 929, 733 and 661 cm^{-1}; ^{1}H-NMR (CDCl$_3$) δ = 0.95 (3H, t, *J* = 7.3 Hz), 1.38-1.53 (4H, m), 2.02-2.16 (2H, m) and 4.27 (1H, t, *J* = 7.1 Hz); ^{13}C-NMR (CDCl$_3$) δ = 13.8, 22.0, 29.3, 34.4, 45.3 and 175.1.

2-Bromobutyric acid (**9**) (commercially available)



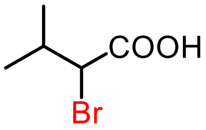
Colourless oil; IR (Neat) 3586, 3438, 3106, 2976, 2940, 2880, 2686, 2596, 1717, 1459, 1421, 1279, 1224, 1172, 1079, 927, 888, 813, 788 and 657 cm^{-1}; ^{1}H-NMR (CDCl$_3$) δ = 1.09 (3H, t, *J* = 7.4 Hz), 2.03-2.19 (2H, m) and 4.22 (1H, dd, *J* = 7.6 and 6.7 Hz); ^{13}C-NMR (CDCl$_3$) δ = 11.8, 28.1. 47.0 and 175.5.

2-Bromooctanoic acid (**10**) (commercially available)



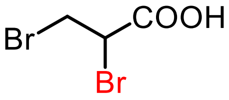
Colourless oil; IR (Neat) 3414, 3102, 2959, 2928, 2858, 2671, 2596, 1717, 1458, 1422, 1379, 1282, 1240, 1186, 1116, 925, 725 and 678 cm^{-1}; ^{1}H-NMR (CDCl$_3$) δ = 0.91 (3H, t, *J* = 7.1 Hz), 1.30-1.55 (8H, m), 1.99-2.16 (2H, m) and 4.27 (1H, dd, *J* = 7.7 and 7.0 Hz); ^{13}C-NMR (CDCl$_3$) δ = 14.0, 22.5, 27.1, 28.5, 31.5, 34.7, 45.3 and 175.3.

2-Bromo-3-methylbutanoic acid (**11**) (commercially available)



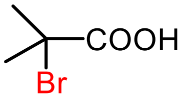
Colourless oil; IR (Neat) 3087, 2979, 2940, 2876, 2686, 2556, 1717, 1469, 1427, 1389, 1369, 1350, 1293, 1226, 1179, 1117, 930, 853, 778, 688, 638 and 489 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ = 1.08 (3H, d, *J* = 6.7 Hz), 1.12 (3H, d, *J* = 6.7 Hz), 2.23-2.28 (1H, m) and 4.09 (1H, d, *J* = 7.6 Hz); ^{13}C-NMR ($CDCl_3$) δ = 19.7, 20.1, 32.1, 54.0 and 174.6.

2,3-Dibromopropanoic acid (**15**) (commercially available)



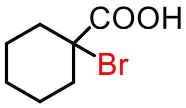
Colourless powder; mp 61-64 °C (EtOAc-heptane); IR (KBr) 3414, 3110, 3045, 2955, 2908, 2755, 2660, 2580, 2496, 1715, 1432, 1336, 1255, 1217, 1154, 951, 909, 828, 790, 661, 633, 553 and 511 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ = 3.72 (1H, dd, *J* = 10.1 and 4.3 Hz), 3.94 (1H, dd, *J* = 11.3 and 10.2 Hz) and 4.51 (1H, dd, *J* = 11.3 and 4.3 Hz); ^{13}C-NMR ($CDCl_3$) δ = 29.1, 40.3 and 172.2.

2-Bromo-2-methylpropanoic acid (**16**) (commercially available)



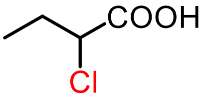
Colourless oil; IR (Neat) 3074, 3011, 2983, 2904, 2825, 2667, 2565, 2473, 1712, 1466, 1449, 1436, 1413, 1375, 1298, 1182, 1111, 1011, 937, 813, 634, 550 and 472 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ = 1.98 (6H, s); ^{13}C-NMR ($CDCl_3$) δ = 30.5, 54.9 and 177.3.

1-Bromocyclohexane-1-carboxylic acid (**17**) (commercially available)



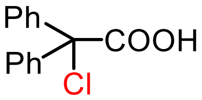
Colourless powder; mp 62-63 °C (EtOAc-heptane); IR (KBr) 3316, 3074, 2952, 2866, 2659, 2540 1698, 1435, 1411, 1347, 1292, 1266, 1244, 1207, 1142, 1117, 1071, 1059, 937, 907, 874, 800, 741, 689, 529, 510 and 474 cm^{-1}; ^{1}H-NMR (CDCl$_3$) δ = 1.45-1.61 (4H, m), 1.76-1.81 (2H, m), and 2.20 (4H, t, J = 6.4 Hz); ^{13}C-NMR (CDCl$_3$) δ = 23.7, 24.7, 37.6, 62.3, and 176.4.

2-Chlorobutanoic acid (**21**)[3]



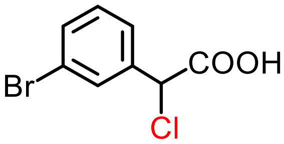
Colourless oil; IR (Neat) 3437, 3117, 2979, 2940, 2884, 2686, 2596, 1729, 1460, 1437, 1420, 1384, 1288, 1204, 1108, 1084, 1035, 930, 881, 827, 795 and 688 cm^{-1}; ^{1}H-NMR (CDCl$_3$) δ = 1.10 (3H, t, J = 7.4 Hz), 1.99-2.15 (2H, m) and 4.31 (1H, dd, J = 7.7 and 5.7 Hz); ^{13}C-NMR (CDCl$_3$) δ = 10.4, 28.3, 58.5 and 175.2.

2-Chloro-2,2-diphenylacetic acid (**22**)[4]



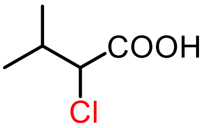
Colourless powder; mp 144-146 °C (toluene-heptane); IR (KBr) 3399, 3066, 3031, 2912, 2631, 2478, 1718, 1496, 1448, 1342, 1248, 1200, 1176, 1091, 1054, 1033, 1006, 982, 925, 773, 762, 741, 720, 699, 662, 627, 593 and 526 cm^{-1}; ^{1}H-NMR (CDCl$_3$) δ = 7.35-7.39 (6H, m) and 7.49 (4H, dd, J = 8.0 and 2.0 Hz); ^{13}C-NMR (CDCl$_3$) δ = 81.2, 127.4, 128.3, 128.4, 141.2 and 177.7.

2-(3-Bromophenyl)-2-chloroacetic acid (**23**) (commercially available)



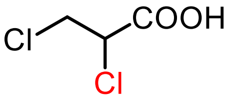
Colourless powder; mp 54-57 °C (toluene-heptane); IR (KBr) 3114, 3057, 2960, 2912, 2676, 2588, 1751, 1726, 1574, 1475, 1432, 1405, 1312, 1303, 1272, 1230, 1201, 1181, 1075, 998, 943, 895, 881, 811, 779, 741, 690, 677, 637, 560, 445 and 429 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ = 5.34 (1H, s), 7.29 (1H, dd, *J* = 7.8 and 7.8 Hz), 7.46 (1H, d, *J* = 7.8 Hz), 7.54 (1H, dt, *J* = 7.8 and 1.7 Hz) and 7.69 (1H, t, *J* = 1.7 Hz); ^{13}C-NMR ($CDCl_3$) δ = 57.9, 122.8, 126.6, 130.4, 131.1, 132.7, 137.2 and 172.1.

2-Chloro-3-methylbutanoic acid (**24**)[5]



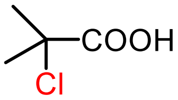
Colourless oil; IR (Neat) 3367, 2972, 2703, 2588, 2500, 1731, 1461, 1424, 1390, 1371, 1336, 1301, 1220, 1119, 1083, 975, 914, 844, 795, 712, 620, 523 and 456 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ = 1.10 (6H, dd, *J* = 10.9 and 6.8 Hz), 2.36-2.41 (1H, m) and 4.22 (1H, d, *J* = 6.0 Hz); ^{13}C-NMR ($CDCl_3$) δ = 17.8, 19.6, 32.5, 64.0 and 175.2.

2,3-Dichloropropanoic acid (**25**)[6]



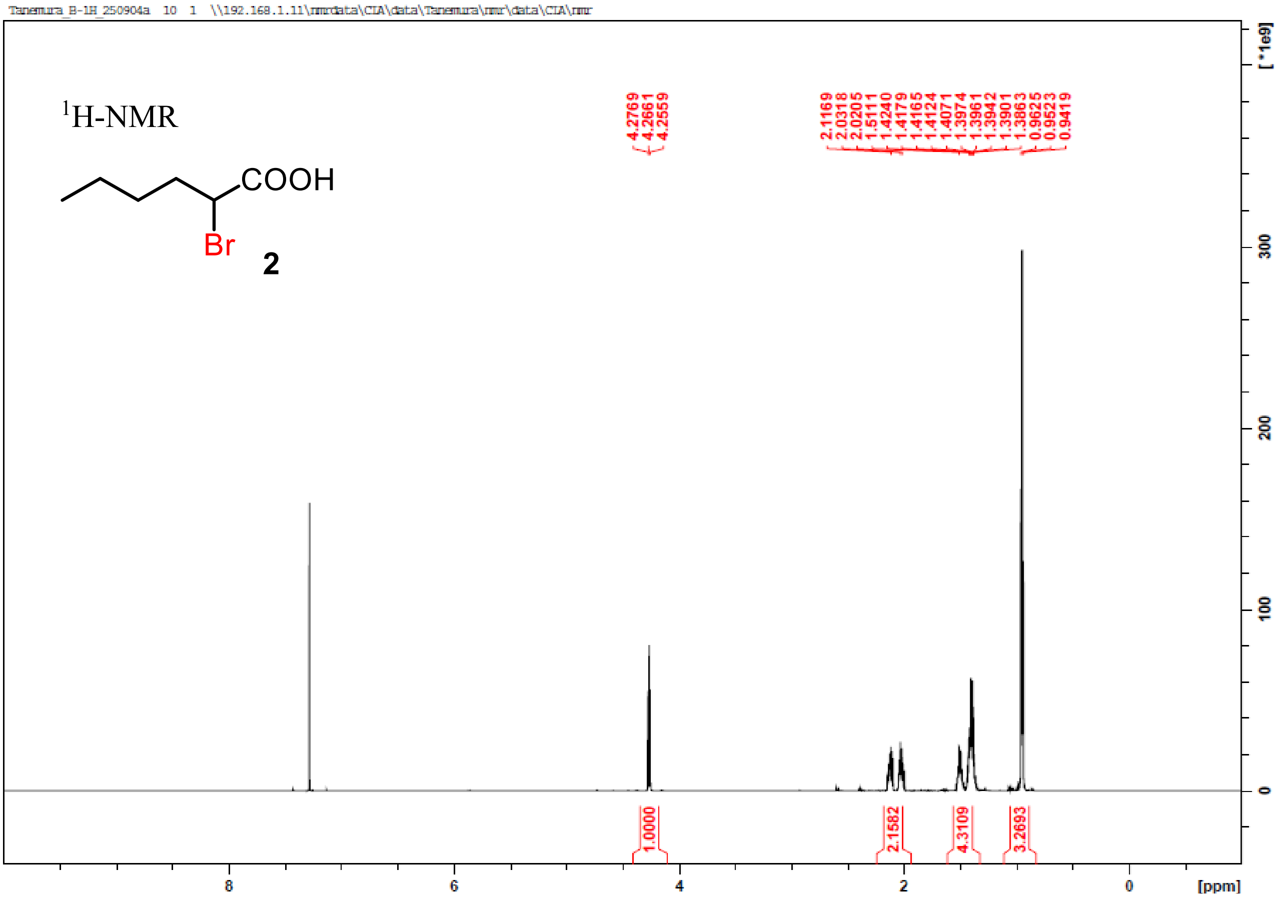
Colourless powder; mp 51-52 °C (EtOAc-heptane); IR (KBr) 3363, 3031, 2943, 2707, 2607, 1731, 1433, 1404, 1302, 1275, 1232, 1205, 1024, 978, 905, 857, 824, 714, 679, 610, 465 and 447 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ = 3.85 (1H, dd, *J* = 11.3 and 5.1 Hz), 3.97 (1H, dd, *J* = 11.3 and 8.4 Hz), 4.50 (1H, dd, *J* = 8.3 and 5.2 Hz) and 7.66 (1H, br s); ^{13}C-NMR ($CDCl_3$) δ = 43.6, 54.9 and 172.1.

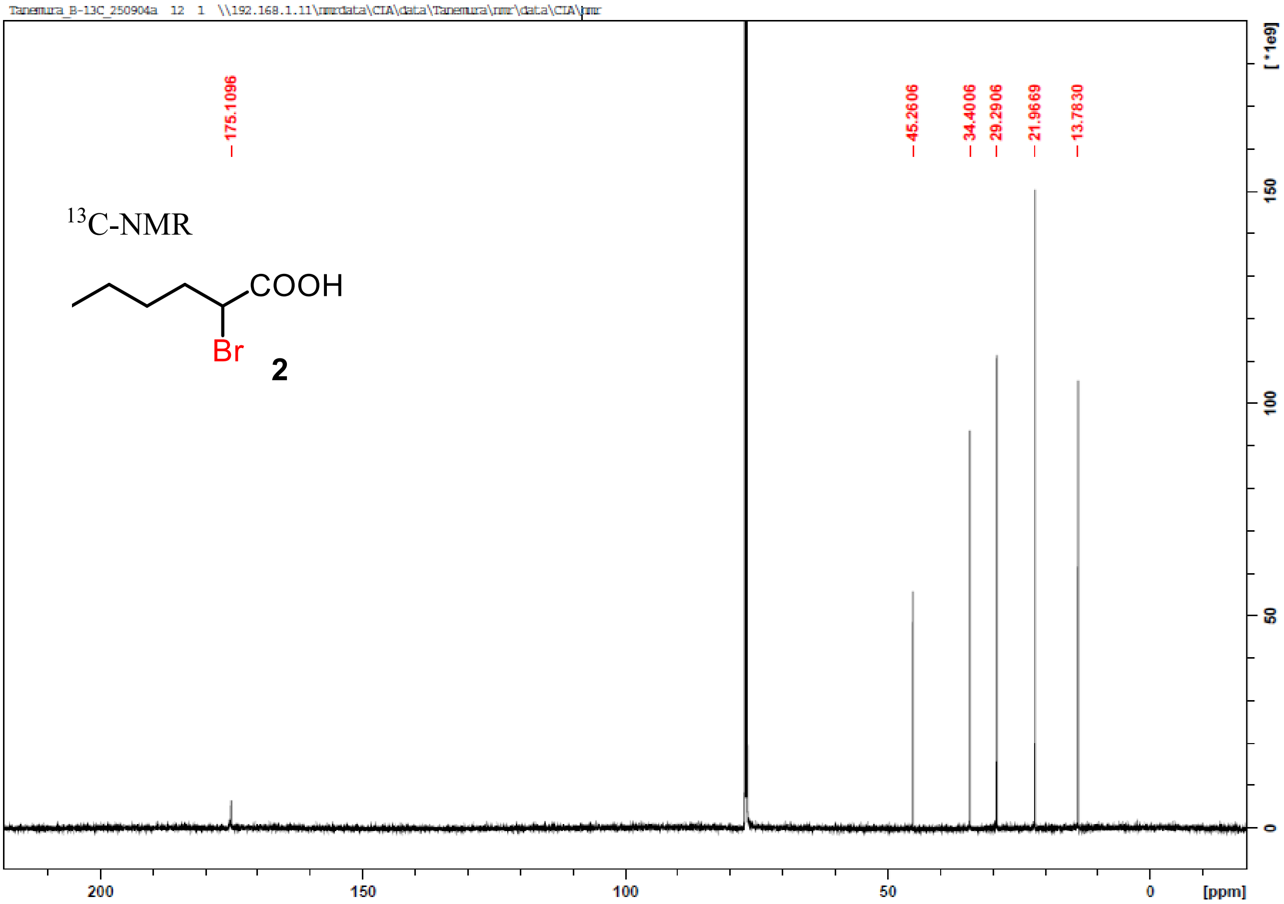
2-Chloro-2-methylpropanoic acid (**26**)[1]

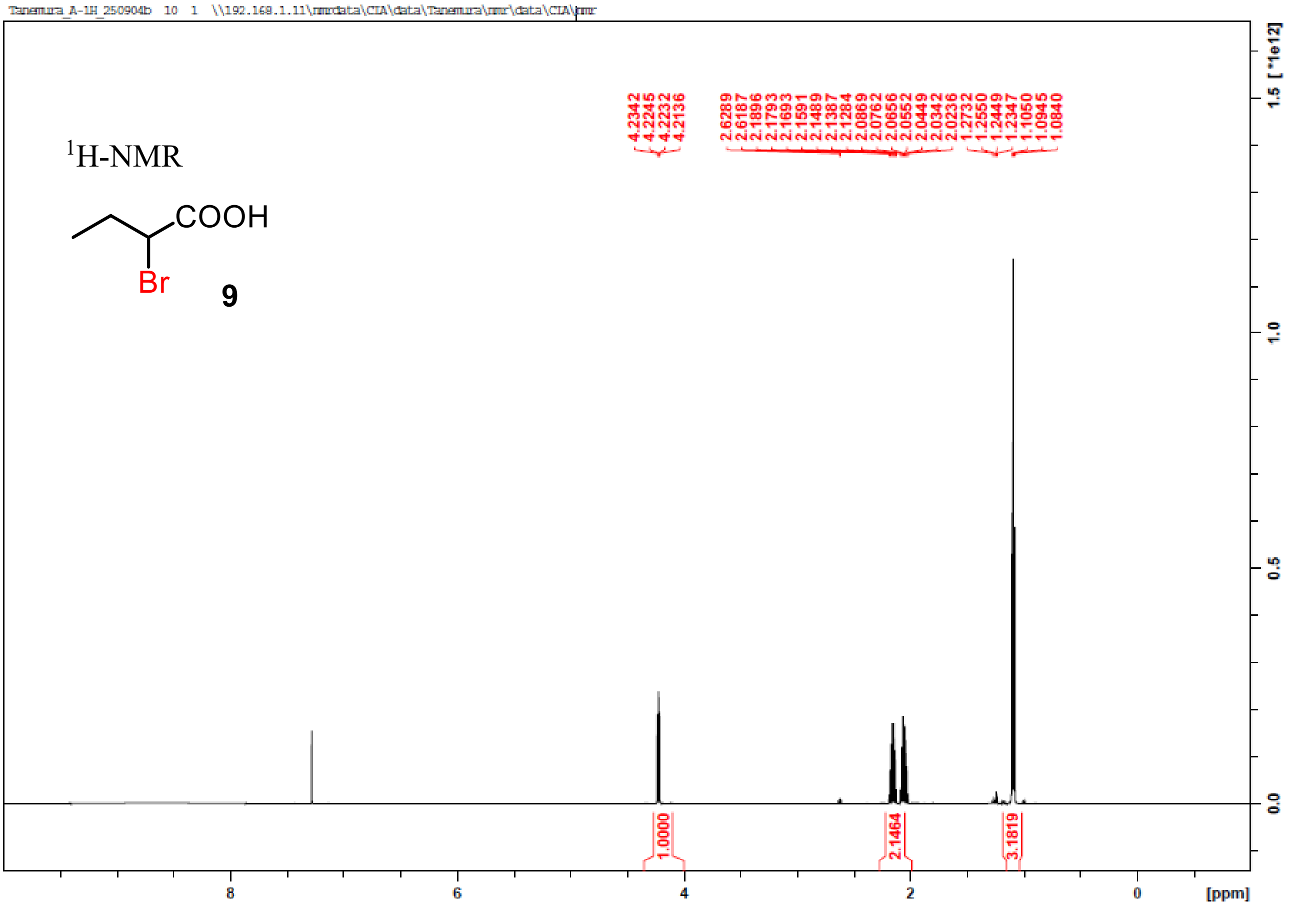


Colourless oil; IR (Neat) 3442, 3098, 2988, 2940, 2667, 2560, 1719, 1465, 1414, 1371, 1288, 1182, 1122, 931, 815, 661 and 544 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ = 1.82 (6H, s); ^{13}C-NMR ($CDCl_3$) δ = 29.6, 64.2 and 177.0.

5. ^{1}H- and ^{13}C-NMR spectra of 2, 9-11, 15-17 and 21-26







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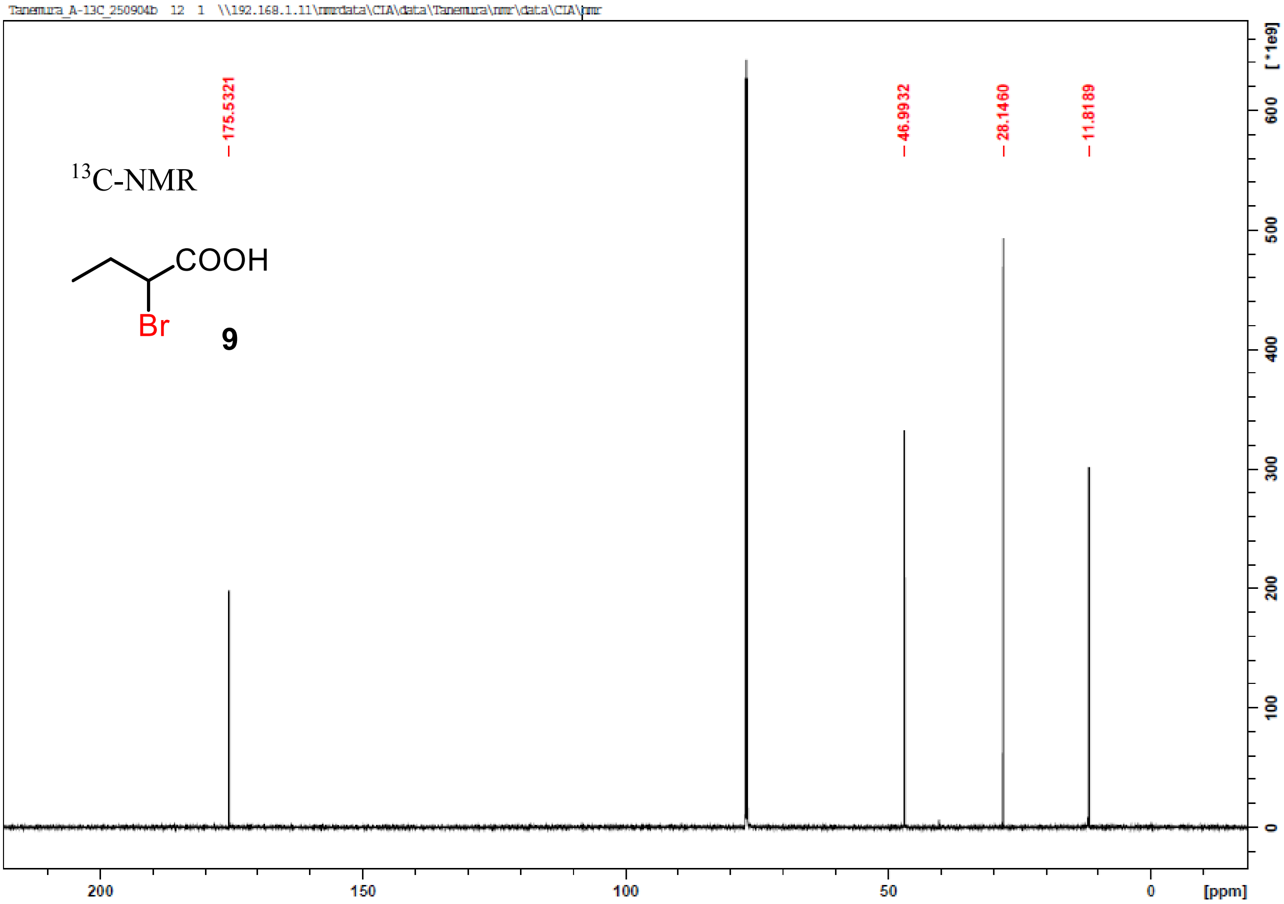

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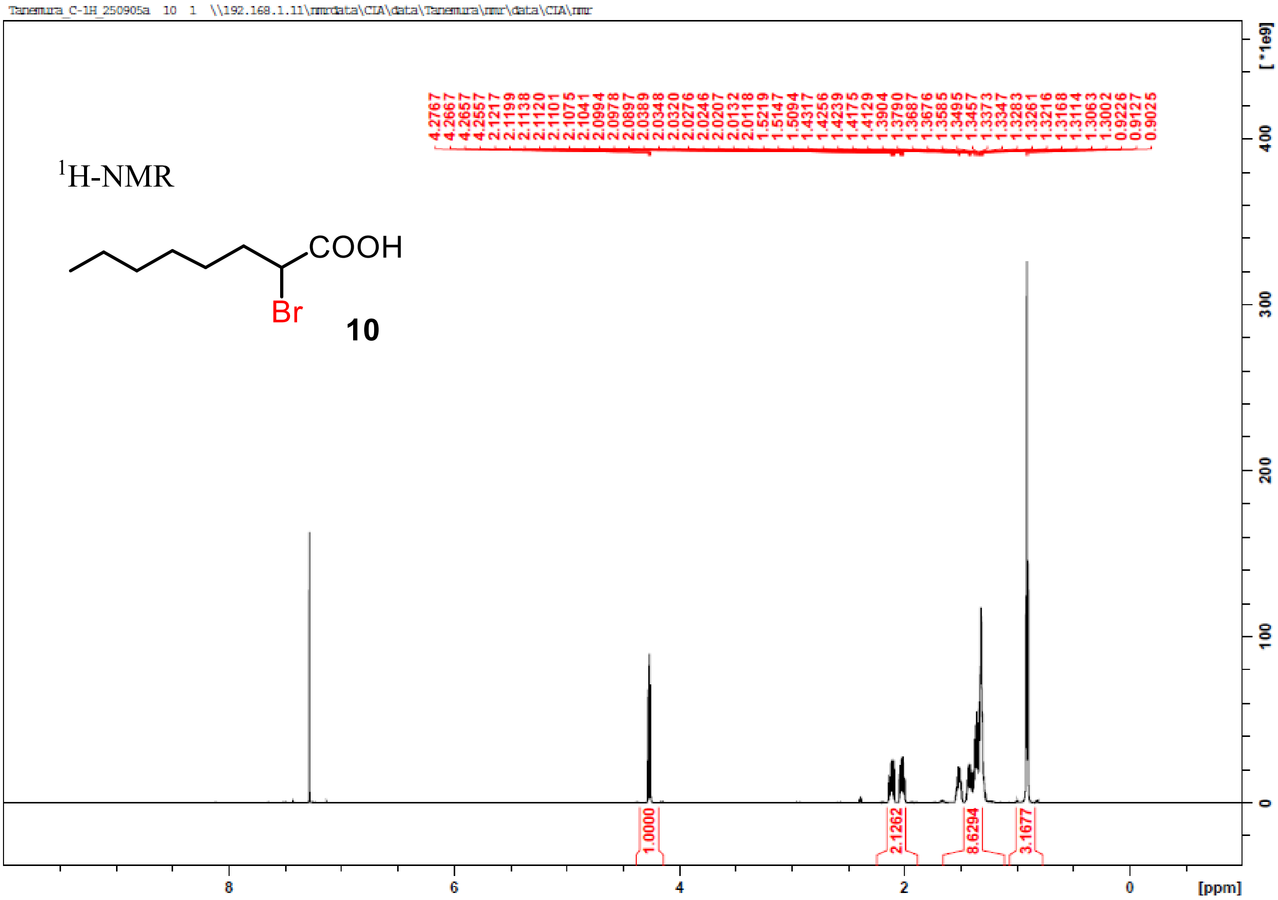
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2.0897
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2.0207
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2.0118
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1.5094
1.4317
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1.4239
1.4175
1.4129
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1.3790
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1.3676
1.3585
1.3495
1.3457
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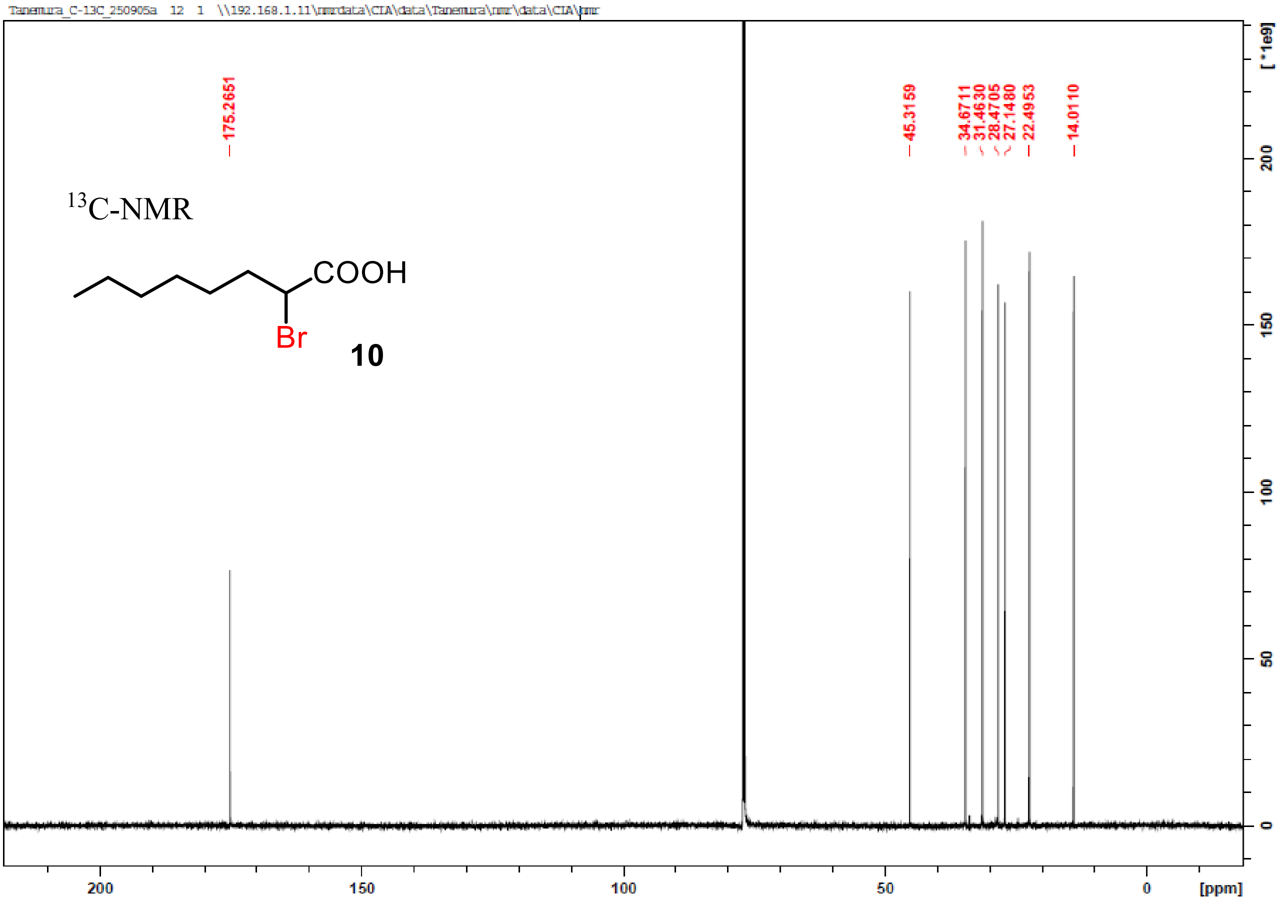
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COOH
Br
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31.4630
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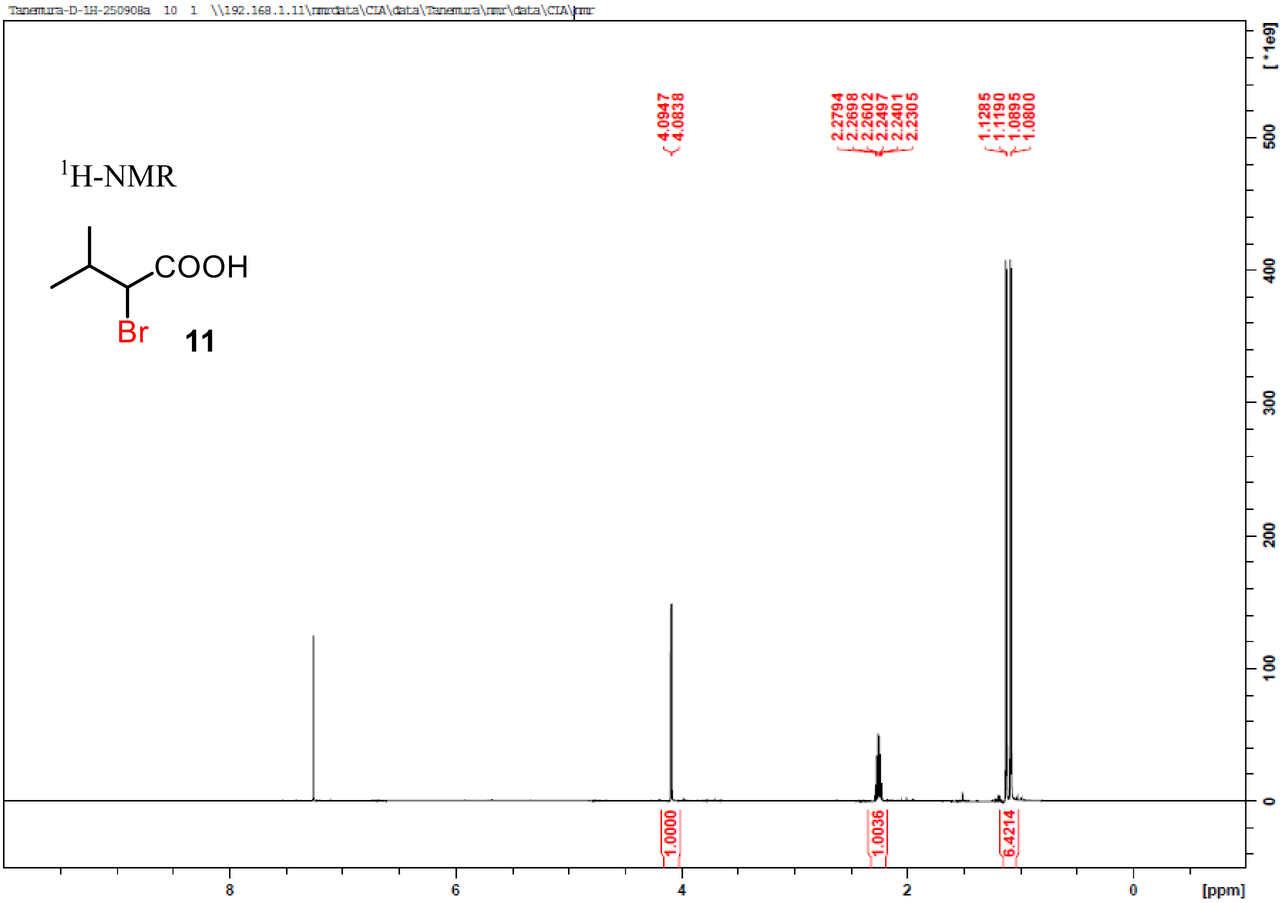
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COOH
Br
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4.0838
2.2794
2.2698
2.2602
2.2497
2.2401
2.2305
1.1285
1.1190
1.0895
1.0800
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200
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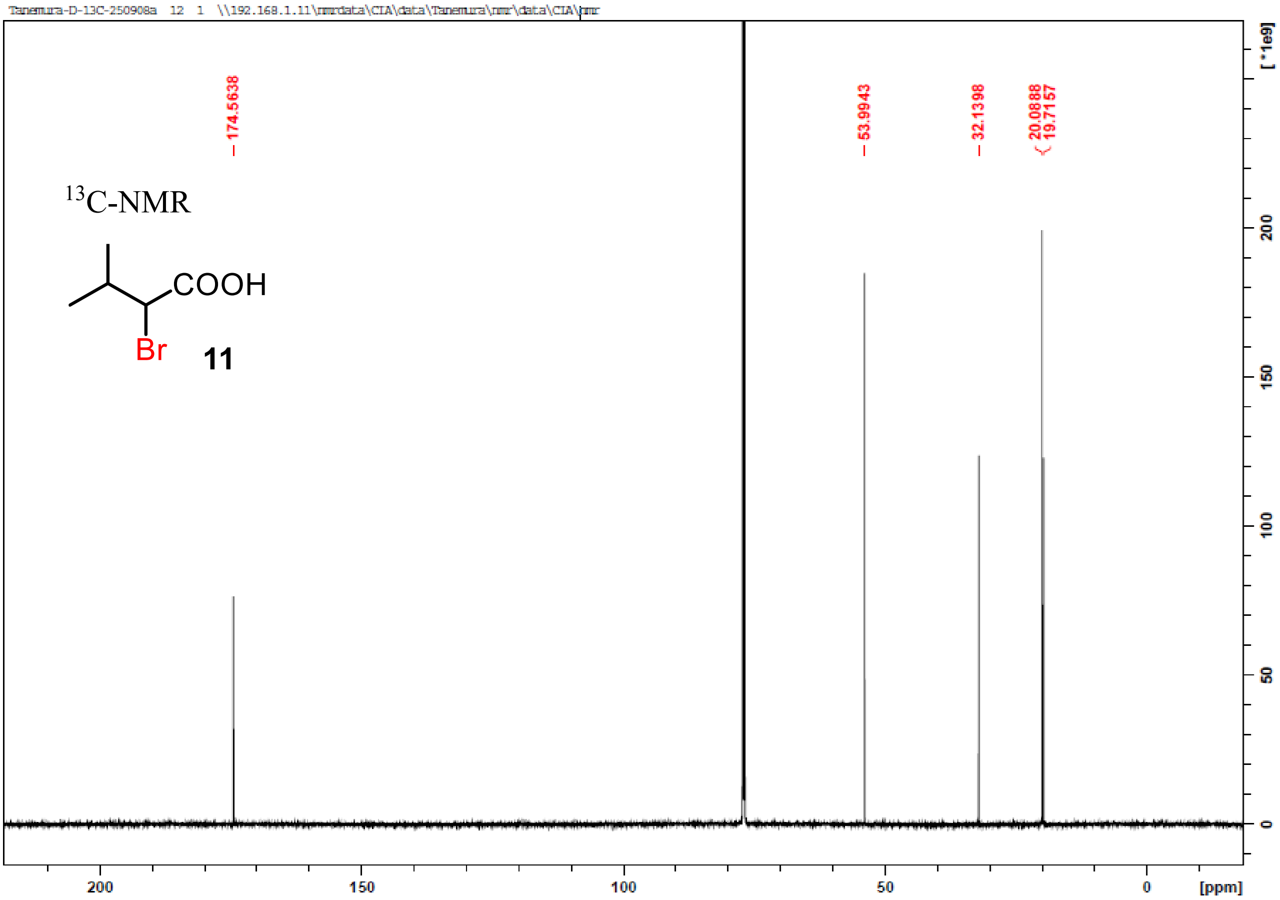
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COOH
Br
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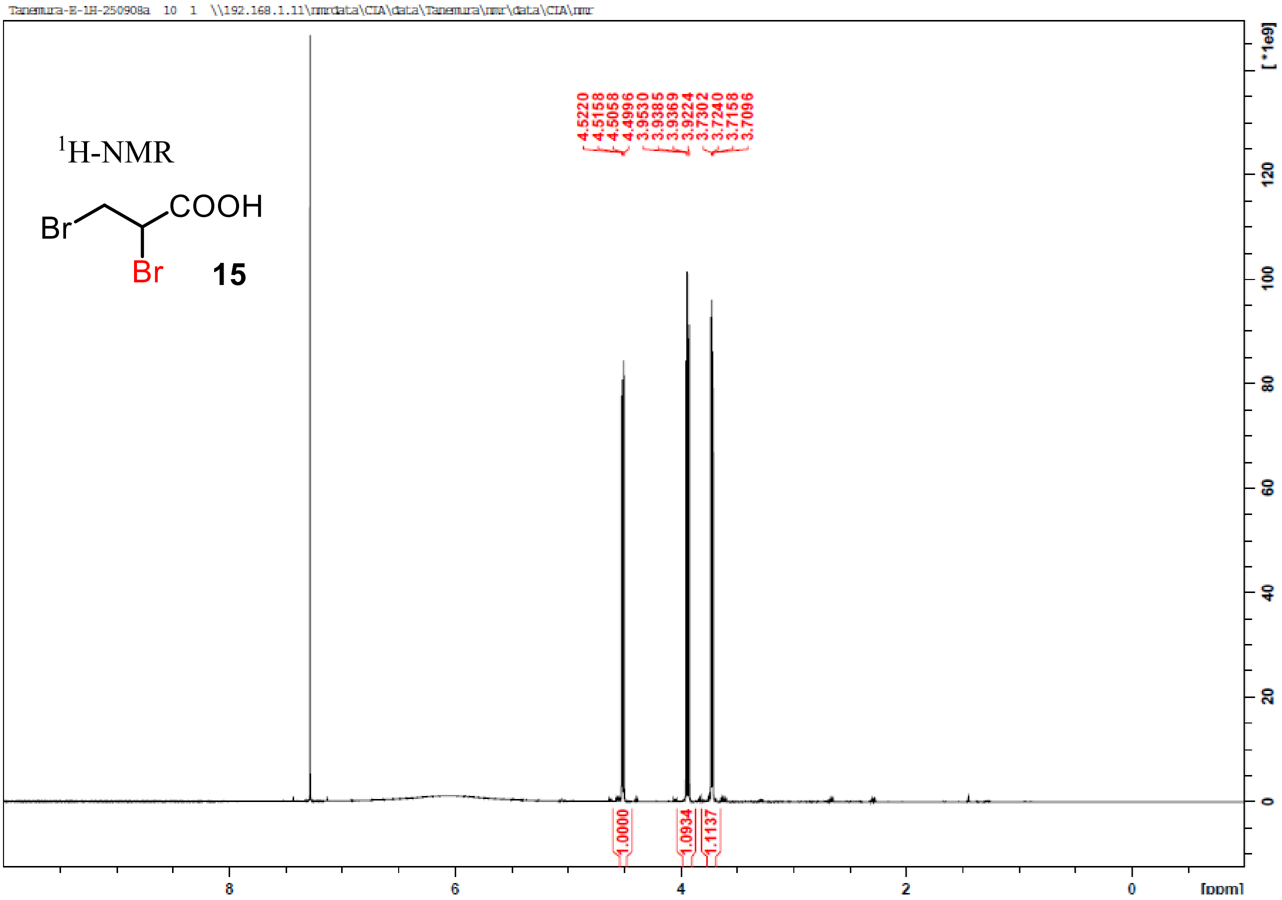
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Br
COOH
Br
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3.9385
3.9369
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3.7240
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8
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4
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60
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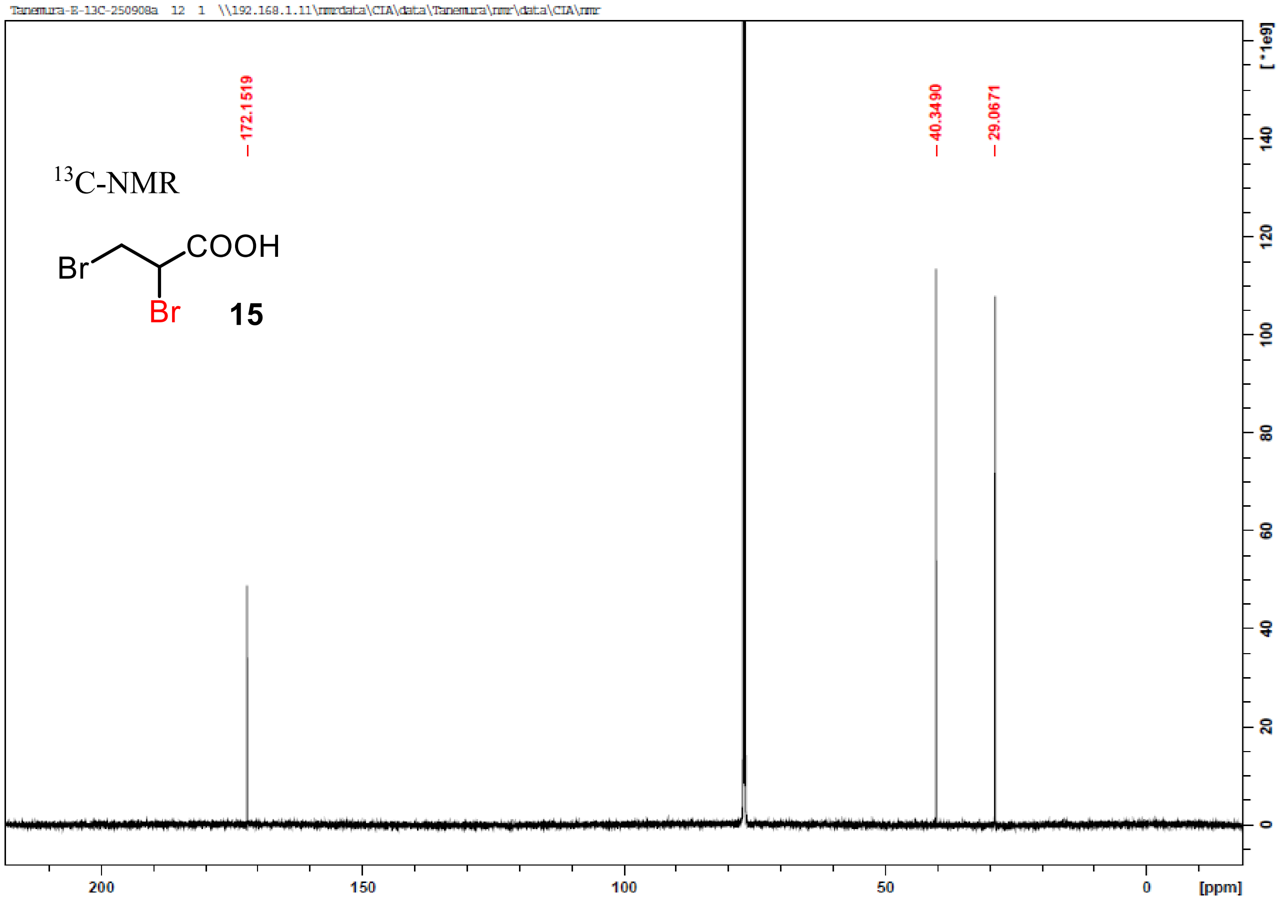
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Br
COOH
Br
15
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29.0671
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150
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50
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80
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40
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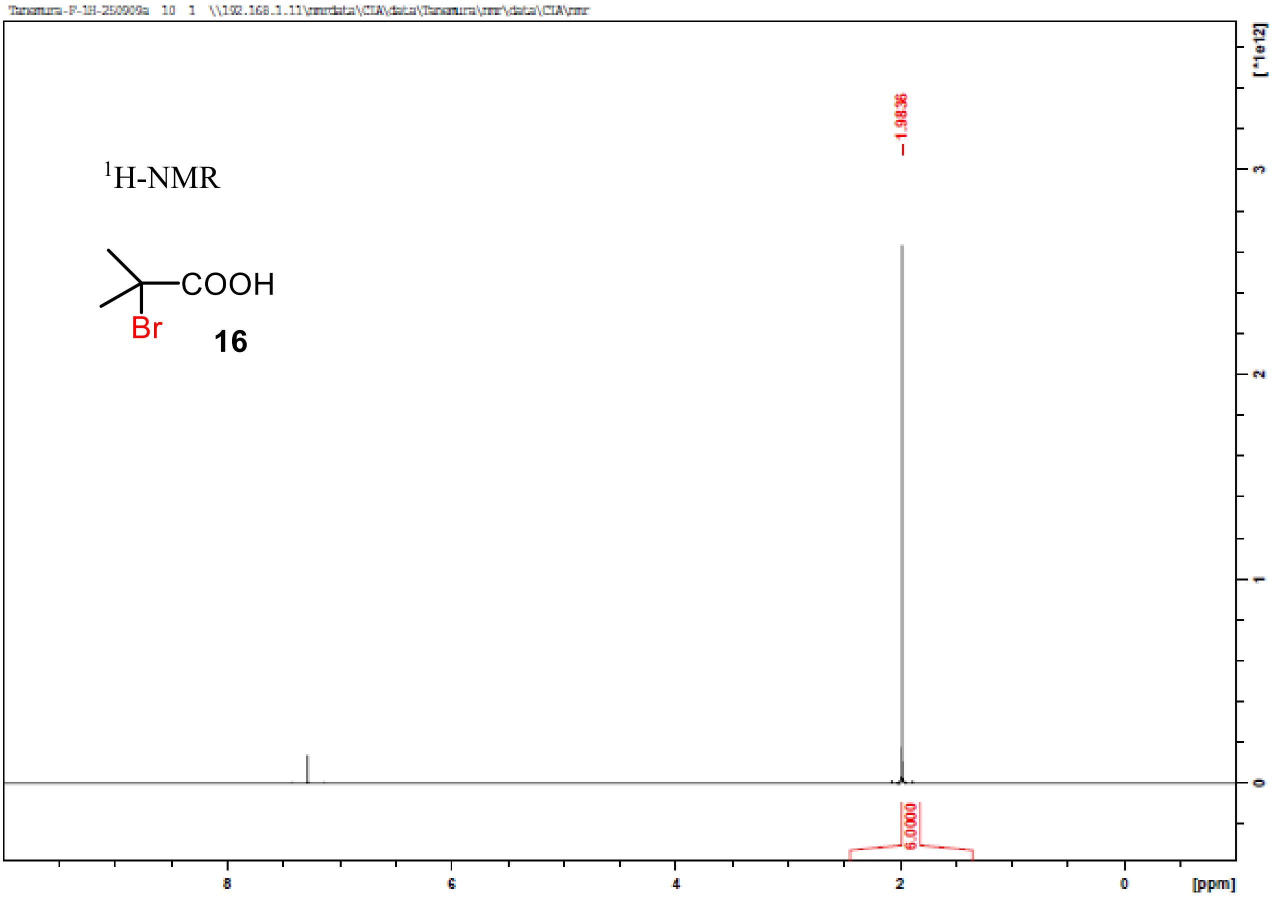
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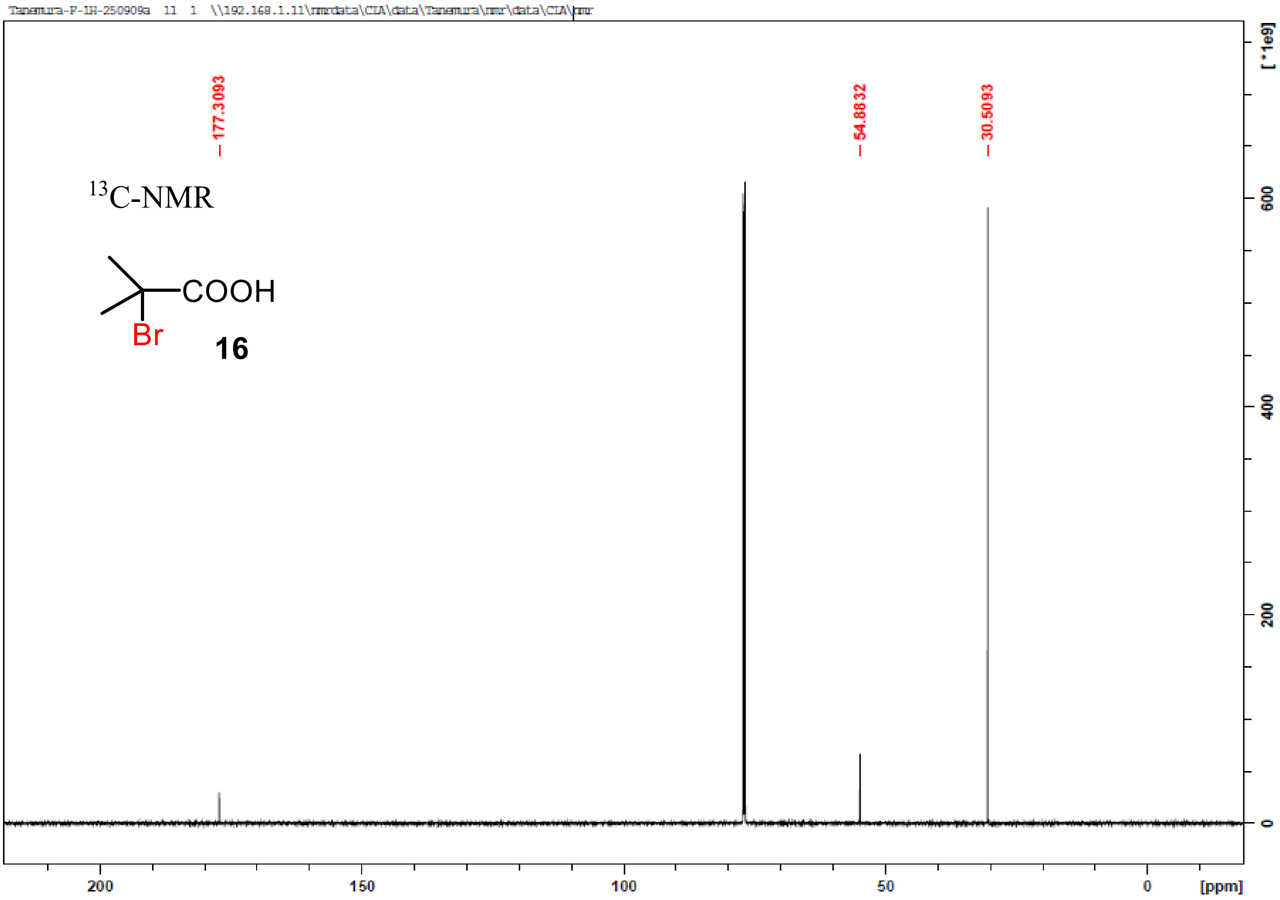
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13C-NMR
COOH
Br
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400
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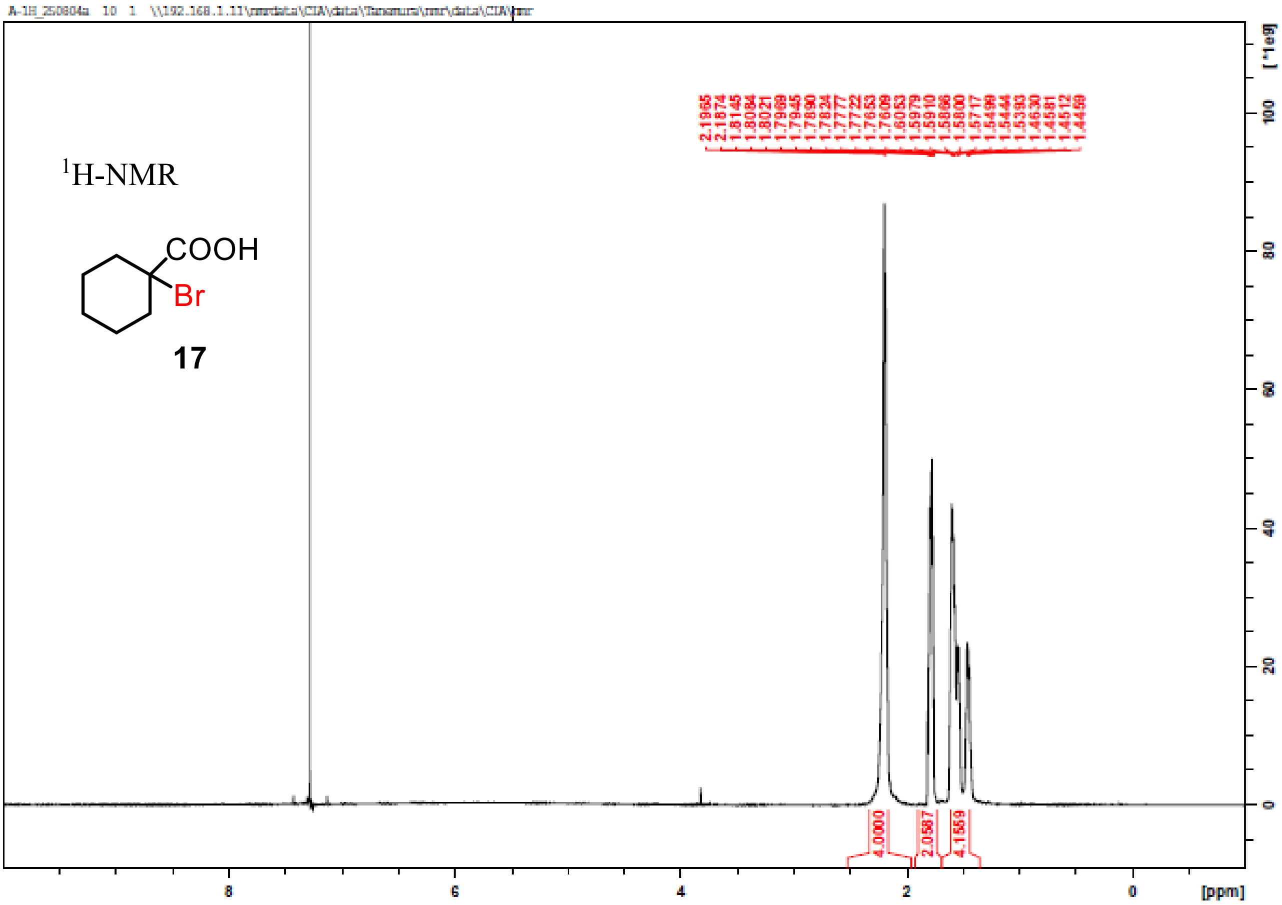
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COOH
Br
17
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2.0587
4.1559
8
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60
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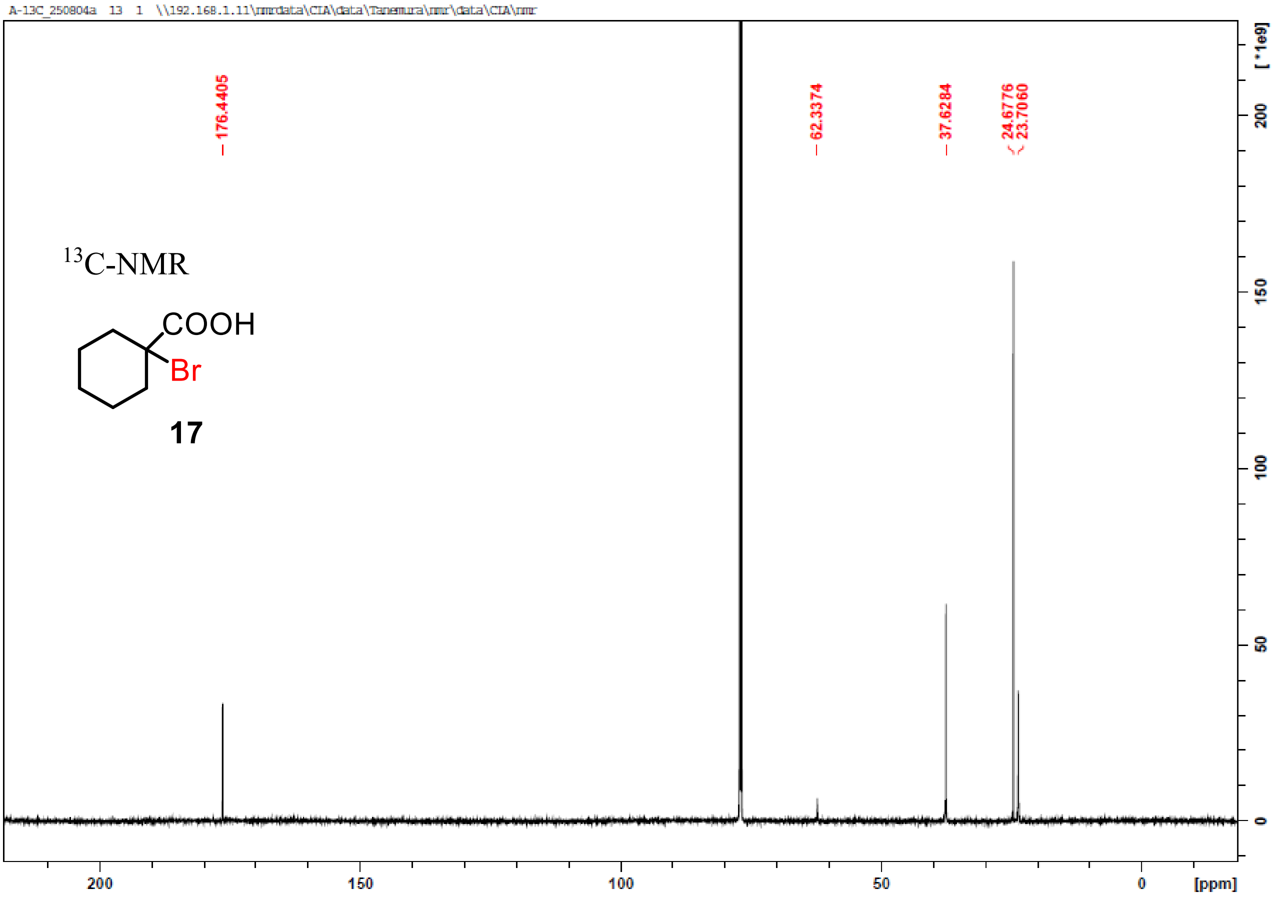
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COOH
Br
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62.3374
37.6284
24.6776
23.7060
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100
50
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[*1e9]
200
150
100
50
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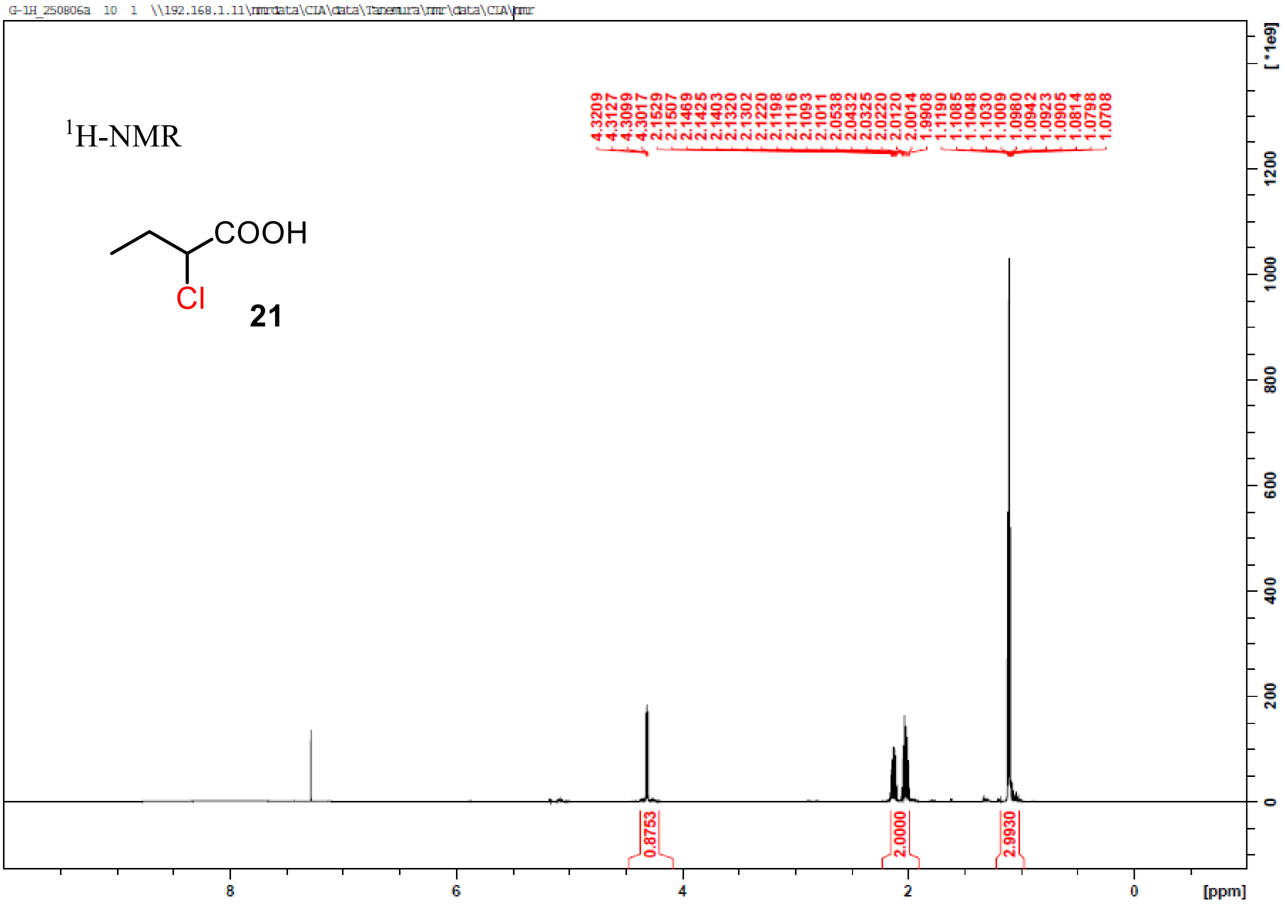
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¹H-NMR
COOH
Cl
21
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4.3127
4.3099
4.3017
2.1529
2.1507
2.1469
2.1425
2.1403
2.1320
2.1302
2.1220
2.1198
2.1116
2.1093
2.1011
2.0538
2.0432
2.0325
2.0220
2.0120
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1.1048
1.1030
1.1009
1.0980
1.0942
1.0923
1.0905
1.0814
1.0798
1.0708
0.8753
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8
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4
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800
600
400
200
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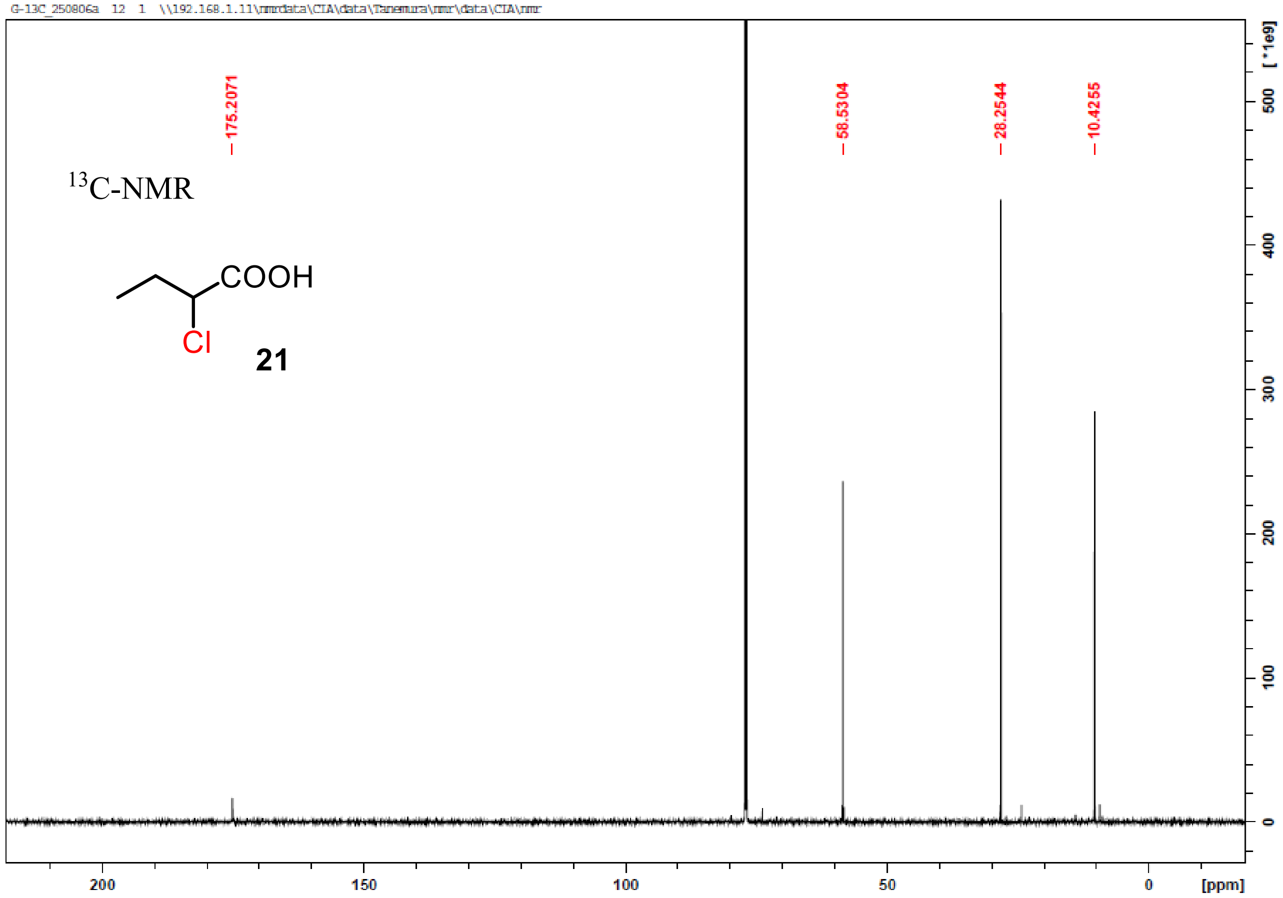
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¹³C-NMR
COOH
Cl
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100
50
0
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300
200
100
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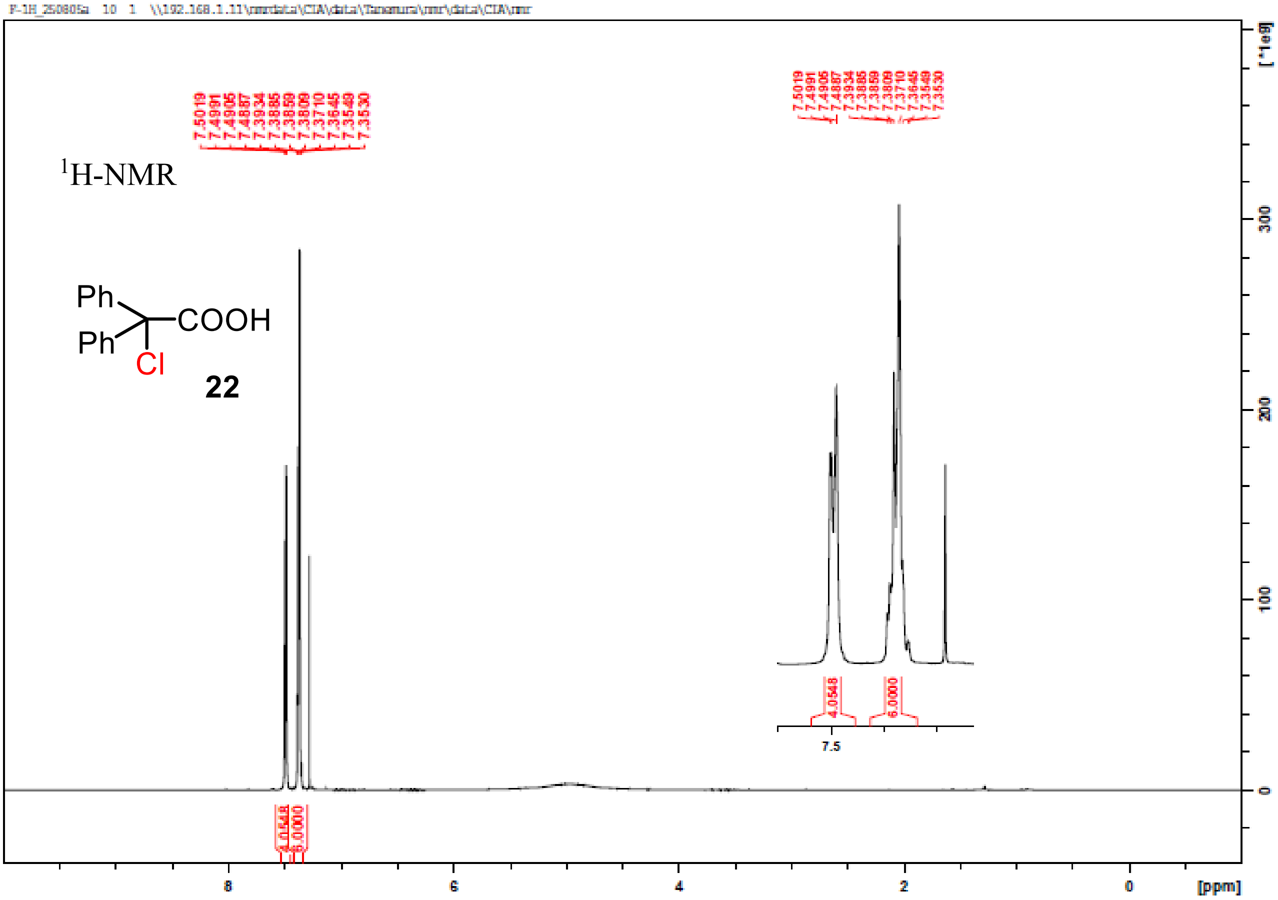
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1H-NMR
Ph
Ph
COOH
Cl
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7.3934
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7.3809
7.3710
7.3645
7.3549
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6
4
2
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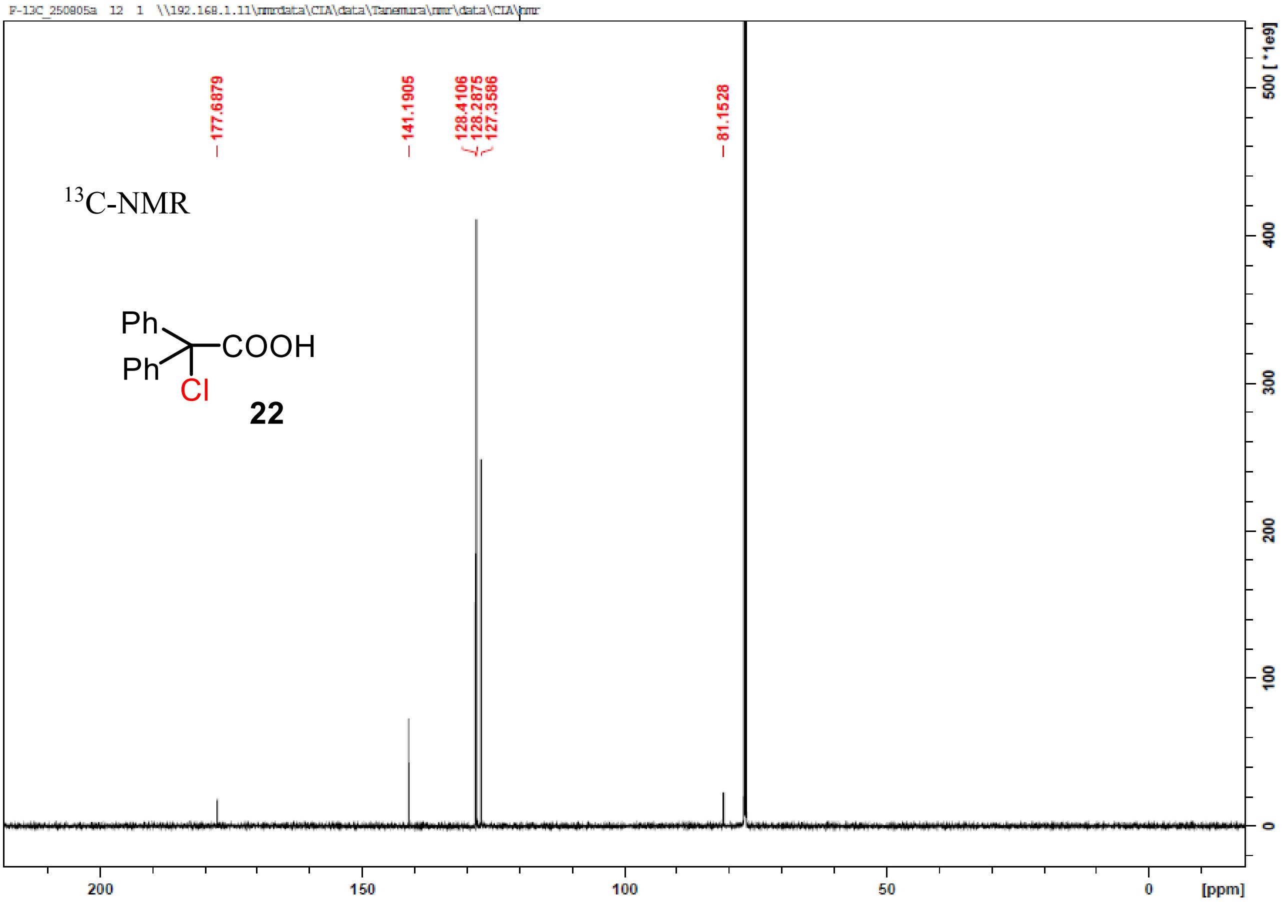
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13C-NMR
Ph
Ph
COOH
Cl
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141.1905
128.4106
128.2875
127.3586
81.1528
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0
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50
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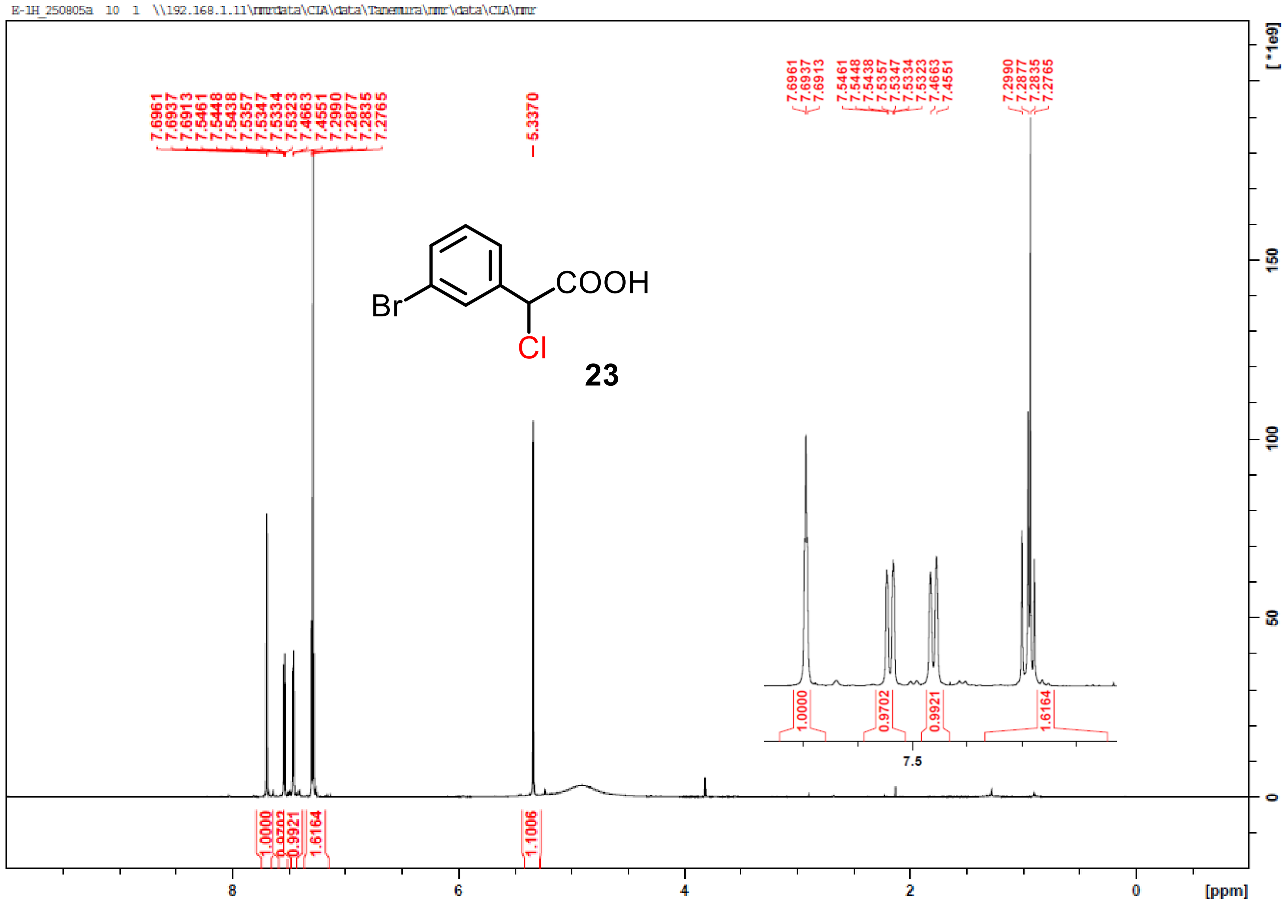
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7.4551
7.2990
7.2877
7.2835
7.2765
5.3370
Br
COOH
Cl
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7.5
8
6
4
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0
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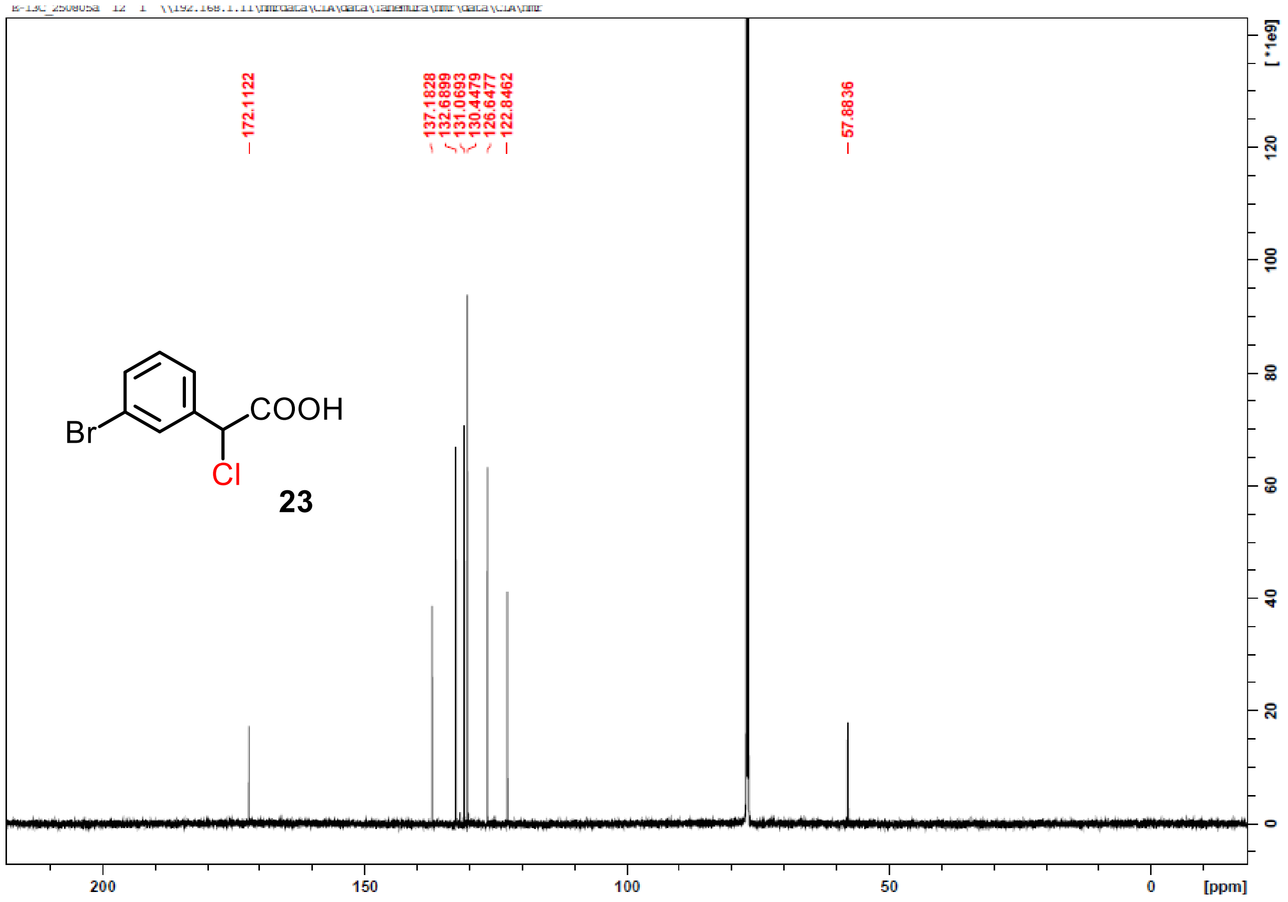
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131.0693
130.4479
126.6477
122.8462
57.8836
Br
COOH
Cl
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200
150
100
50
0
[ppm]
[*1e9]
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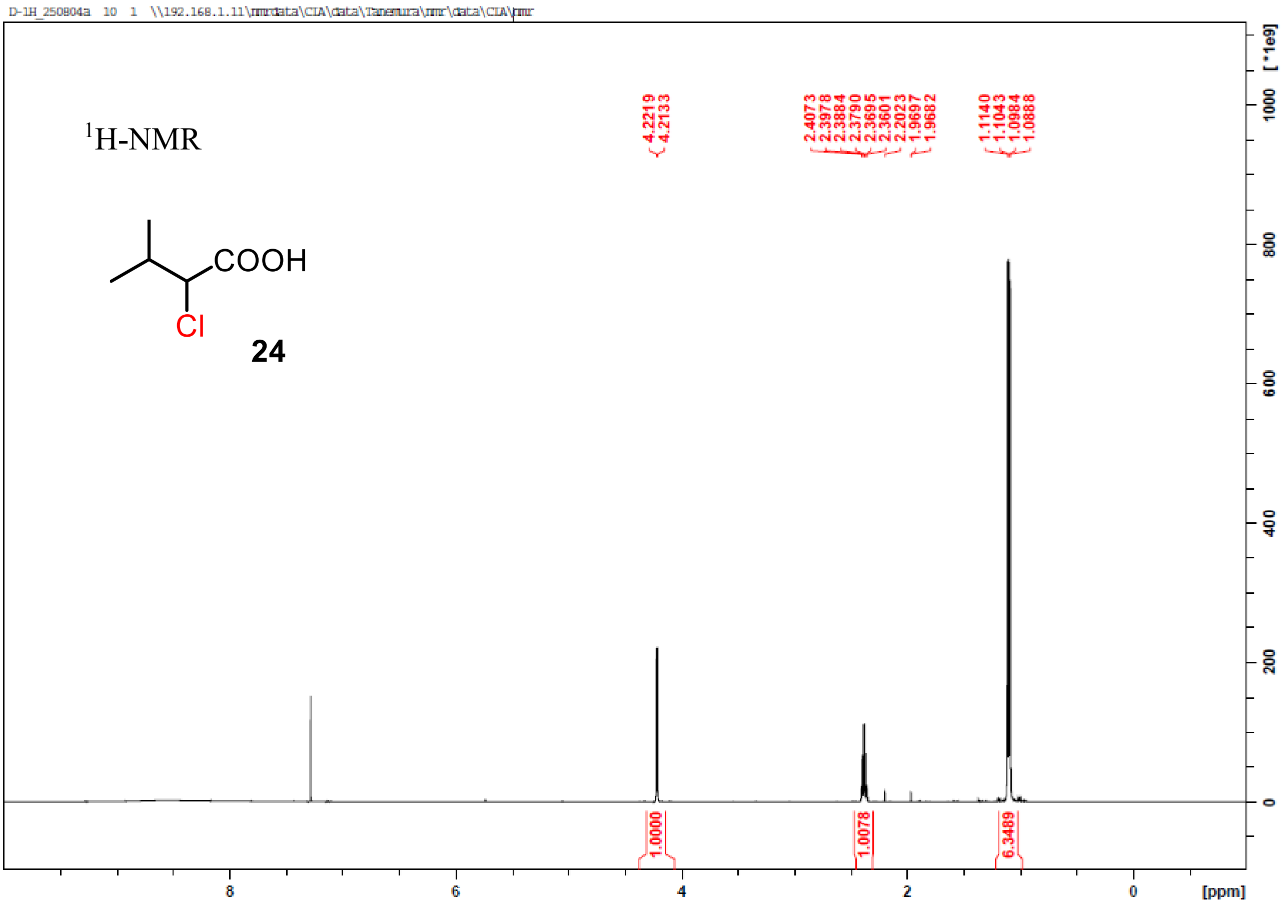
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Cl
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2.3790
2.3695
2.3601
2.2023
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1.9682
1.1140
1.1043
1.0984
1.0888
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8
6
4
2
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[ppm]
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600
800
1000
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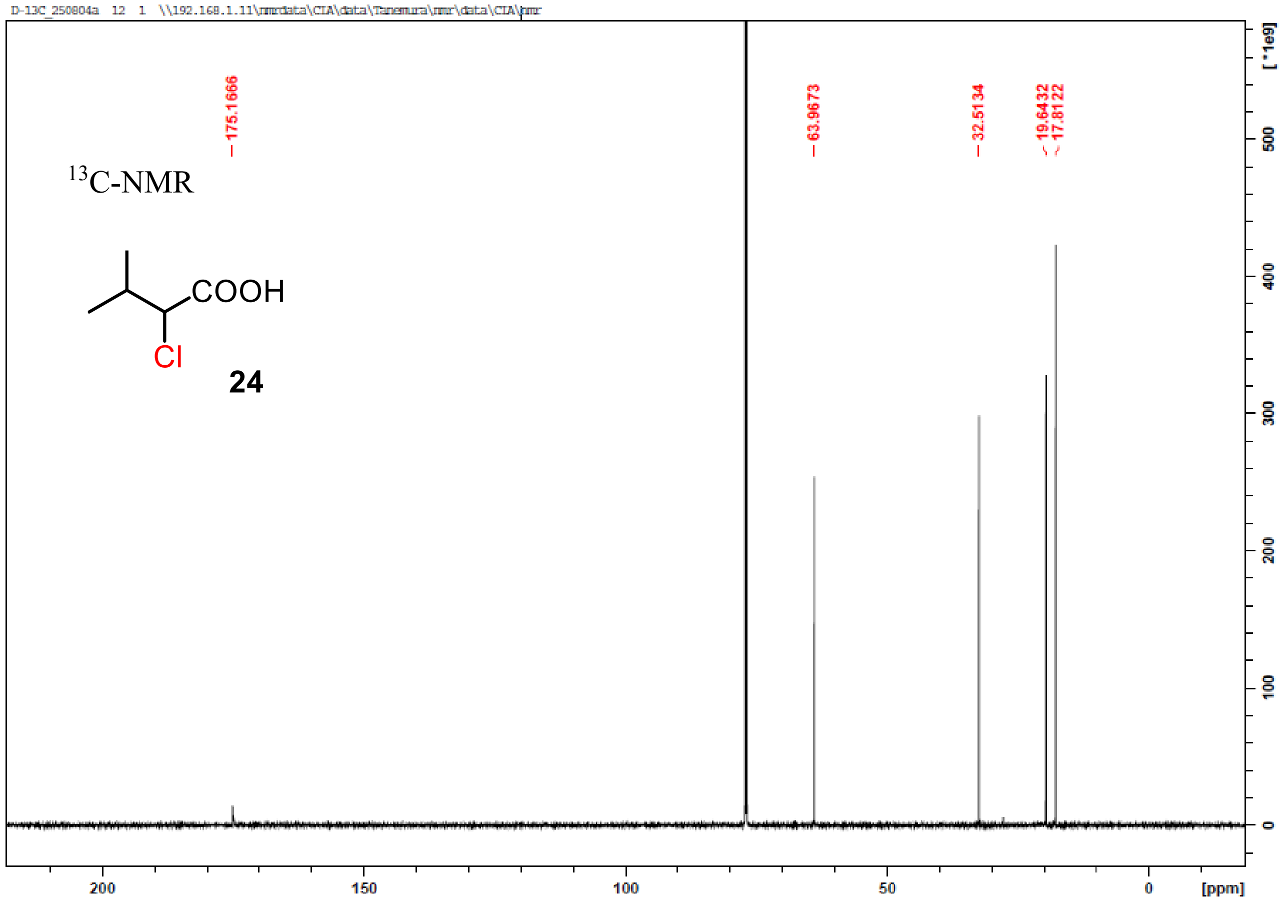
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Cl
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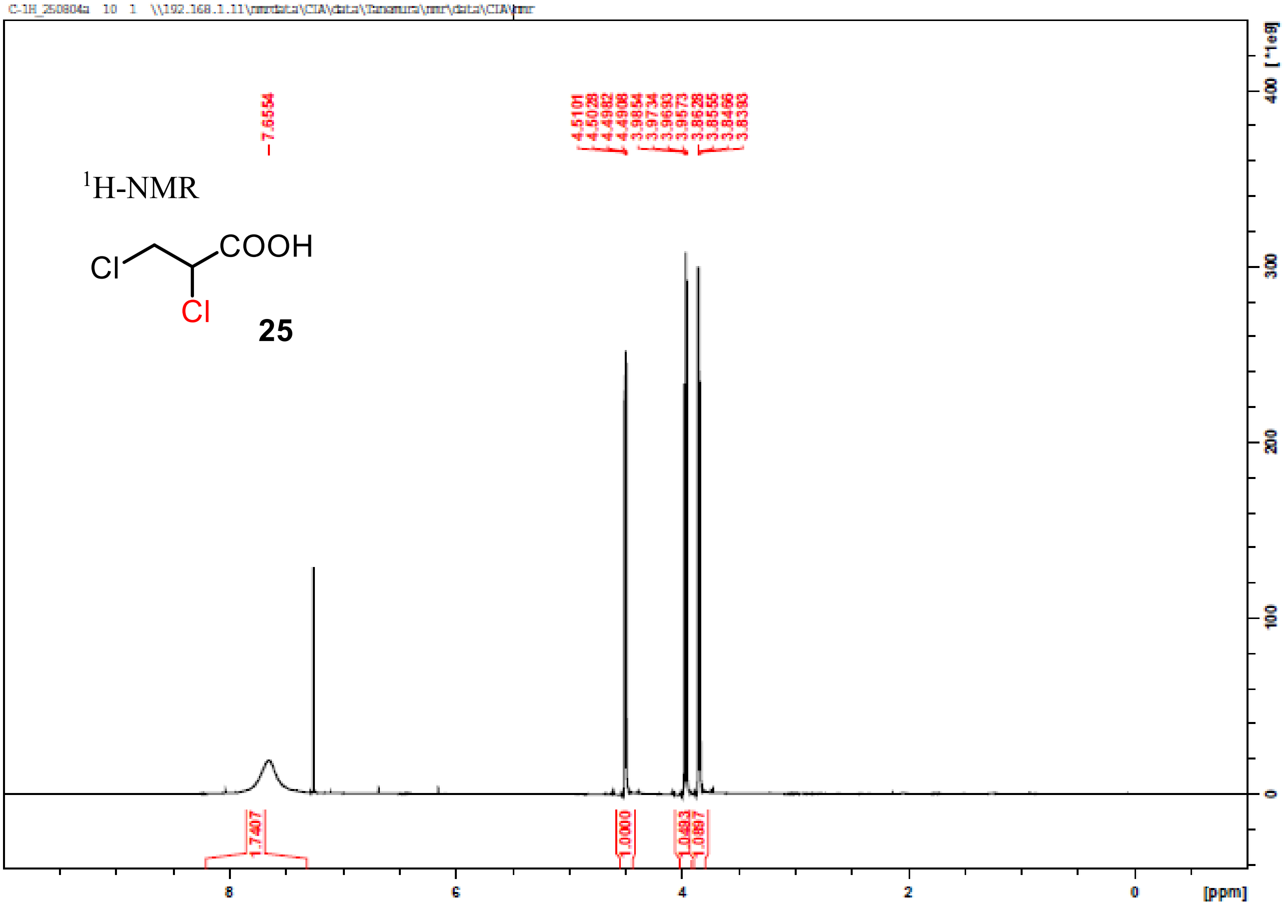
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COOH
Cl
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4.4908
3.9854
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3.9573
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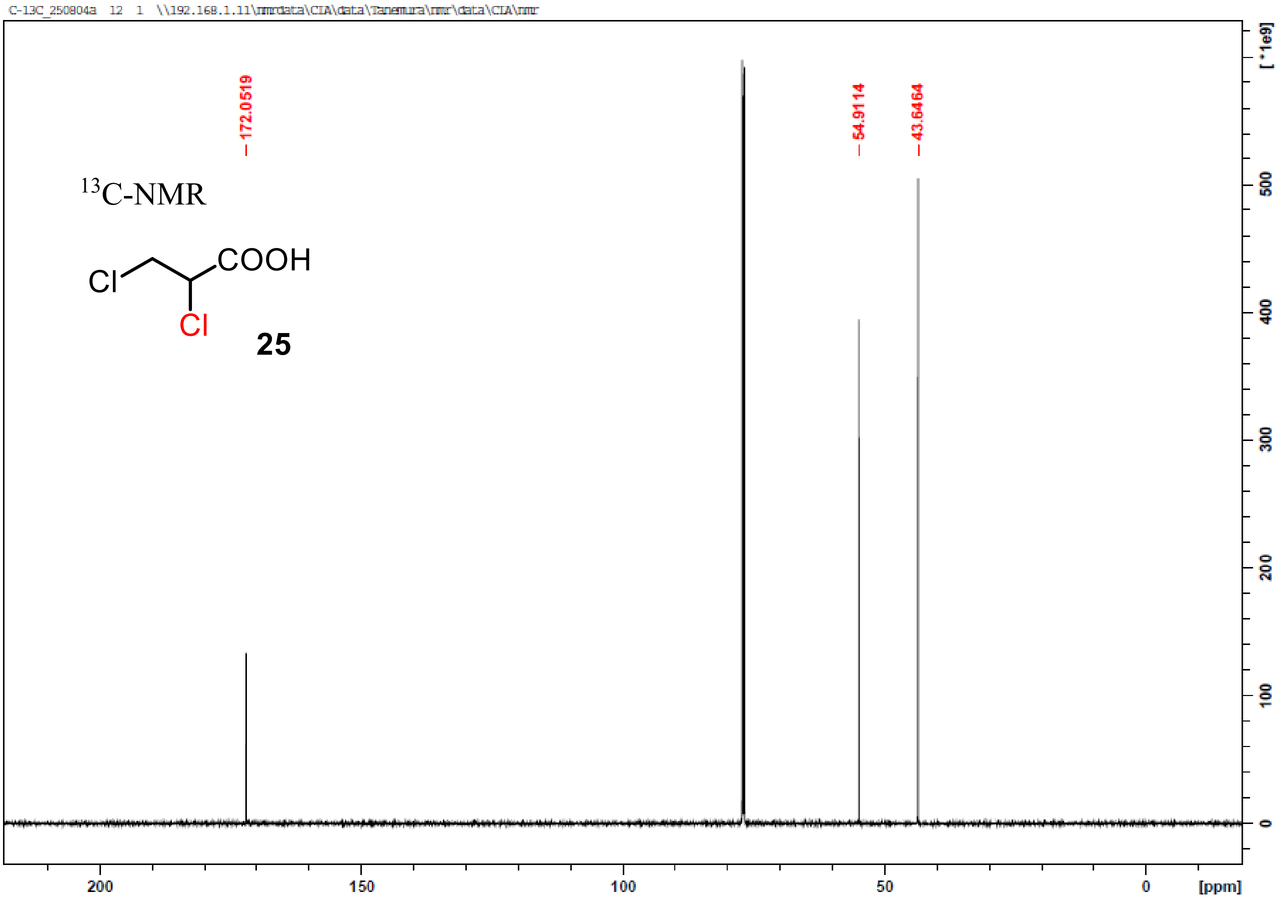
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COOH
Cl
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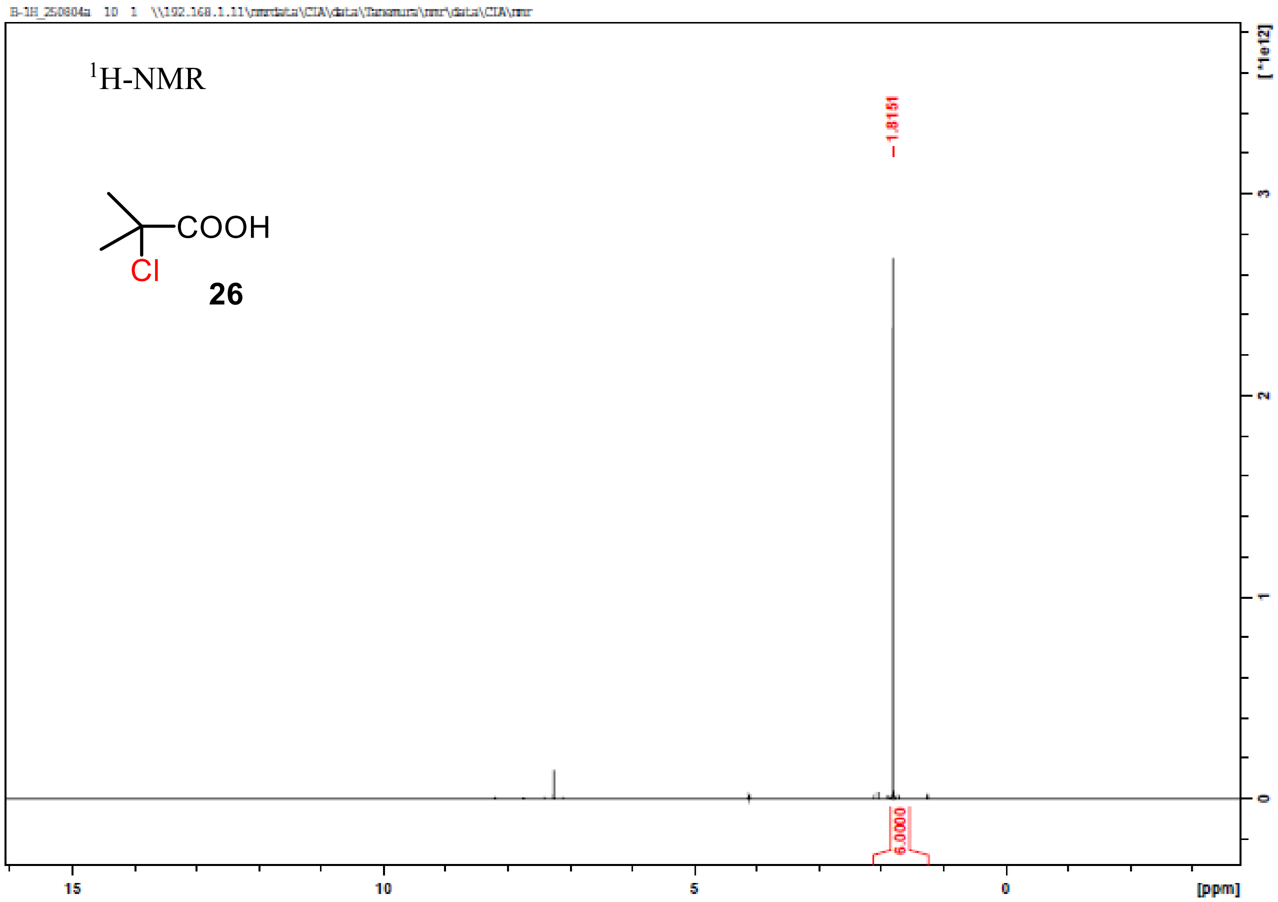
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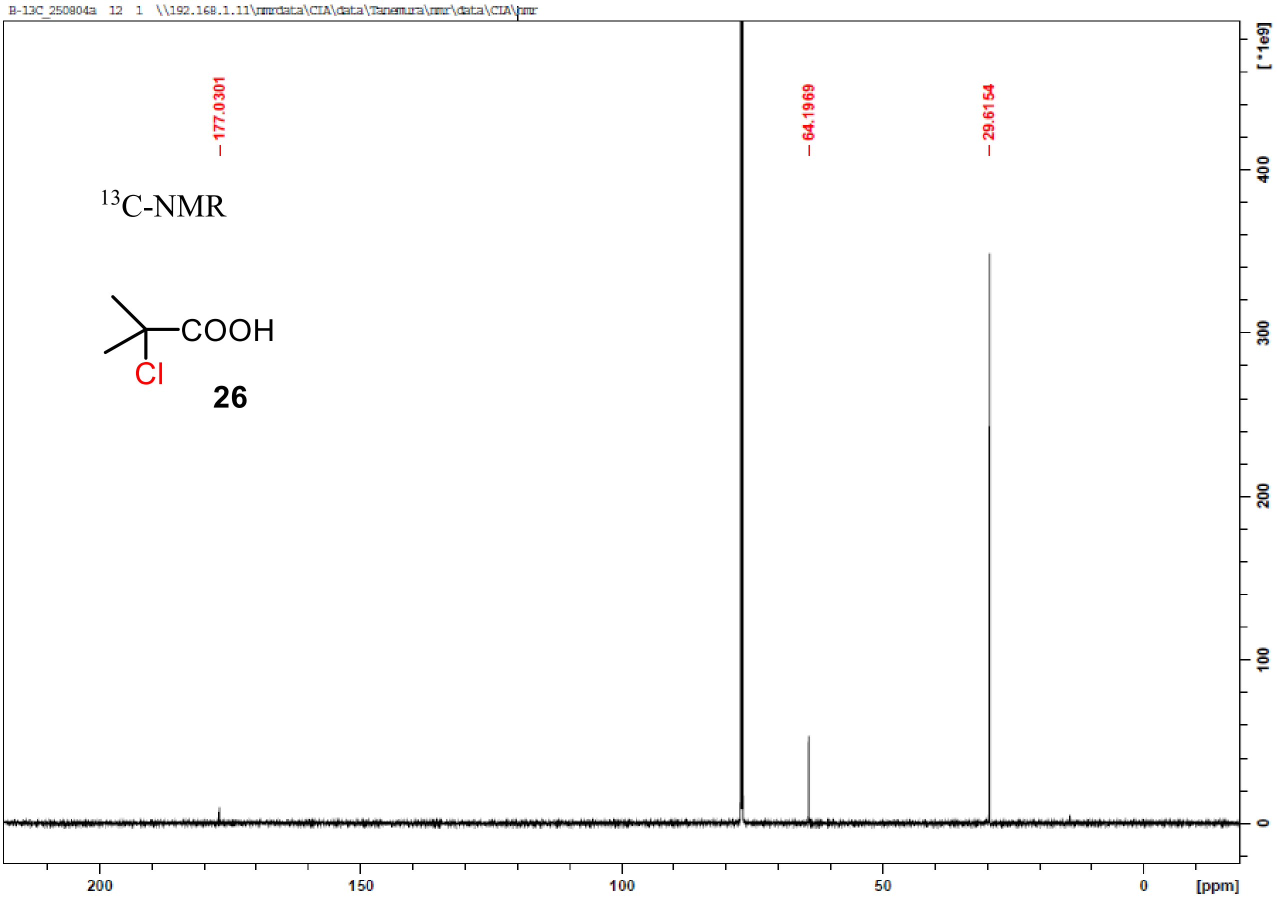
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^{13}C-NMR
COOH
Cl
26
200
150
100
50
0
[ppm]
0
100
200
300
400
[*1e9]

6. References

1 D. N. Harpp, L. Bao, C. J. Black, J. G. Gleason and R. A. Smith, *J. Org. Chem.*, 1975, **40**, 3420.

2 A. McKenzie and F. Barrow, *J. Chem. Soc., Trans.*, 1911, **99**, 1910.

3 R. Jakobsen and J. Katon, *Spectrochim. Acta A Mol. Spectrosc.*, 1973, **29**, 1953.

4 P. Urbani, M. G. Cascio, A. Ramunno, T. Bisogno, C. Saturnino and V. Di Marzo, *Biorg. Med. Chem.*, 2008, **16**, 7510.

5 R. J. Peters, R. J. Biesheuvel, W. de Leer and L. de Galan, *J. Environ. Sci. Health A*, 1992, **27**, 929.

6 P. Maki-Arvela, T. Salmi, E. Paatero and R. Sjoholm, *Ind. Eng. Chem. Res.*, 1995, **34**, 1976.