Supporting Information

Synthesis of Noradamantane Derivatives by Ring-Contraction of the Adamantane Framework

Benjamin Zonker,[a] Jonathan Becker[b] and Radim Hrdina*[c]

1. General information

NMR spectra were recorded on 200, 400 or 600 MHz machine at RT (25 °C) unless otherwise stated. ^{1}H-NMR chemical shifts are given in ppm relative to Me_4Si with the solvent resonance used as the internal standard ($CDCl_3$ δ = 7.26 ppm). ^{13}C-NMR (60, 101 or 150 MHz) chemical shifts are given in ppm relative to Me_4Si with the solvent resonance used as the internal standard ($CDCl_3$ = 77.16 ppm). IR spectra were recorded using an ATR sampler and are reported in wave numbers (cm^{-1}). Melting points (m.p.) were measured in open capillary tubes and are uncorrected. All reactions involving air sensitive compounds were carried out under dry and inert atmosphere (N_2 or argon) by means of an inert gas/vacuum double manifold line and standard Schlenk techniques. Flash column chromatography was performed with silicagel 60 as stationary phase. High resolution mass spectra were recorded with Brucker Micro TOF LC.

2. Experimental procedures

2.1 Preparation of starting materials

2.1.1 General procedure A: Carbamate Synthesis

Under inert atmosphere, corresponding alcohol (1 eq., 5 mmol) is dissolved in CH_2Cl_2 (25 mL), cooled to 0 °C and treated with trichloroacetylisocyanate (1.3 eq., 6 mmol). The reaction mixture is stirred at room temperature for 3 hours and concentrated *in vacuo*. The residue is dissolved in MeOH (10 mL), treated with a saturated potassium carbonate solution (*aq.*, 15 mL) and stirred at 50°C overnight. The MeOH is removed *in vacuo* and the precipitate is filtered and washed with water. If the compound is not solid after MeOH evaporation, the aqueous phase is extracted with EtOAc (3x), washed with brine, dried over Na_2SO_4 (anhydrous), filtered and the solvent is evaporated *in vacuo*. The crude product is purified by flash column chromatography (mobile phase: hexanes/EtOAc).

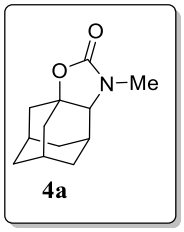
2.1.2 General procedure B: Nitrene Insertion

Under inert atmosphere, the corresponding carbamate (1.0 eq., 2 mmol), iodobenzene I,I-diacetate (1.3 eq., 2.6 mmol), $Rh_2(OAc)_4$ (5-10 mol%, 0.01 mol), and MgO (2.5 eq., 5.0 mmol) are suspended in dry 1,2-dichloroethane (12 mL) and the reaction mixture is heated to 70 °C overnight. After the reaction mixture is cooled down to room temperature, it is filtered through a pad of silica gel and washed with a hexane/EtOAc 1:1 mixture to separate the product from the dirhodium catalyst and salts. The solvents are evaporated *in vacuo*, and the crude product is purified by flash column chromatography on silica gel (mobile phase: hexanes/EtOAc).

2.1.3 General procedure C: *N*-Methylation of Cyclic Carbamates

Under inert atmosphere, the corresponding oxazolidinone (1.0 eq., 2 mmol) is dissolved in dry THF (4 mL) and cooled to -20°C. Methyl lithium (1.05 eq., 2.1 mmol) is added dropwise. After stirring for 30 min, methyl iodide (2eq., 4 mmol) is added and the mixture is heated to reflux overnight. The solvents are evaporated *in vacuo*, and the crude product is purified by flash column chromatography on silica gel (mobile phase: hexanes/EtOAc).

2.1.4 Compound 4a



4a

Compound **4a** was synthesized from adamantane annulated 1,3-oxazolidinone[1] according to *general procedure C* to give the desired product as a white solid in a yield of 76% (7.40 g, 40 mmol).

R_f (silica gel; EtOAc:*n*-hexane 2:3): 0.3.

m.p. (cryst. from $CDCl_3$): 71.1-72.6 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 1.61-1.84 (m, 7H), 1.94-2.09 (m, 4H), 2.27 (m, 2H), 2.78 (s, 3H), 3.28 (m, 1H).

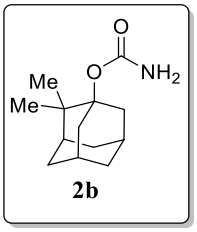
^{13}C NMR (101 MHz, $CDCl_3$): δ/ppm = 29.3 (CH_3), 29.3 (CH), 29.5 (CH_2), 30.3 (CH), 31.3 (CH), 36.2 (CH_2), 36.3 (CH_2), 37.9 (CH_2), 40.0 (CH_2), 68.3 (CH), 77.9 (C), 160.7 (C).

IR (neat): $\tilde{\nu}$ /cm^{-1} = 2916, 2861, 1746, 1472, 1450, 1421, 1405, 1358, 1331, 1307, 1292, 1272, 1183, 1155, 1138, 1100, 1075, 1045, 1024, 990, 962, 901, 856, 828, 817, 774, 672, 648, 546, 515, 441.

HRMS: m/z = 208.1330 ($[M+H]^+$; calculated for $C_{12}H_{18}NO_2^+$ m/z =208.1332).

[1]R. Hrdina, M. Larrosa, C. Logemann, *J. Org. Chem.*, 2017, **82**, 4891-4899.

2.1.5 Compound 2b



2b

Compound **2b** was synthesized from 2,2-dimethyl adamantan-1-ol[2] following *general procedure A* to give a white solid in a yield of 75% (1.02 g, 5 mmol).

R_f (silica gel; EtOAc:*n*-hexane 2:3): 0.4.

m.p. (cryst. from $CDCl_3$): 106.4-107.8 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 1.08 (s, 6H), 1.42-1.46 (m, 2H), 1.56-1.59 (m, 3H), 2.02-2.06 (m, 2H), 2.11-2.15 (m, 4H), 2.60-2.65 (m, 2H), 4.37 (bs, 2H).

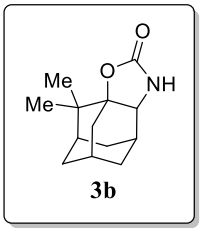
^{13}C NMR (101 MHz, $CDCl_3$): δ/ppm = 23.4 ($2CH_3$), 31.4(2CH), 32.6 ($2CH_2$), 35.8 ($2CH_2$), 37.9 (CH_2), 40.6 (C), 41.8 (CH), 83.9 (C).

IR (neat): $\tilde{\nu}$ /cm^{-1} = 3492, 3307, 3242, 2980, 2909, 2886, 1702, 1596, 1466, 1360, 1345, 1281, 1142, 1113, 1051, 950, 926, 898, 842, 817, 780, 757, 696, 652, 594.

HRMS: m/z = 246.1464 ($[M+Na]^+$; calculated for $C_{13}H_{21}NO_2Na^+$ m/z = 246.1464).

[2]E. Torres, R. Fernandez, S. Miquet, M. Font-Bardia, E. Vanderlinden, L. Naesens and S. Vazquez, *ACS Med. Chem. Lett.*, 2012, **3**, 1065–1069.

2.1.6 Compound 3b



3b

Compound **3b** was synthesized from compound **2b** following *general procedure B* to give the desired product as a clear oil in a yield of 77% (374 mg, 1.7 mmol,) as a single diastereomer.

R_f (silica gel; EtOAc:*n*-hexane 1:4): 0.1.

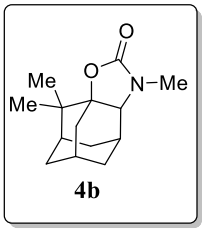
^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 1.15 (s, 3H), 1.18 (s, 3H), 1.44-1.56 (m, 2H), 1.60-1.65 (m, 2H), 1.83 (m, 1H), 1.95-2.05 (m, 4H), 2.13 (m, 1H), 2.26 (m, 1H), 4.10 (m, 1H), 5.67 (s, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ/ppm = 22.7 (CH_3), 22.8 (CH_3), 29.4 (CH), 30.7 (CH_2), 31.9 (CH), 32.1 (CH_2), 32.1 (CH_2), 33.1 (CH_2), 41.3 (C), 58.7 (CH).

IR (neat): $\tilde{\nu}$ /cm^{-1} = 3288, 2920, 1738, 1634, 1462, 1401, 1321, 1285, 1247, 1196, 1143, 1098, 1082, 1047, 992, 951, 924, 898, 851, 785, 772, 727, 645, 622, 553, 522.

HRMS: m/z = 244.1304 ([M+Na]$^+$; calculated for $C_{13}H_{19}NO_2Na^+$ m/z = 244.1308).

2.1.7 Compound 4b



4b

Compound **4b** was synthesized from compound **3b** according to *general procedure C* to give the desired product as a white solid in a yield of 94% (210 mg, 0.9 mmol).

R_f (silica gel; EtOAc:*n*-hexane 2:3): 0.3.

m.p. (cryst. from $CDCl_3$): 76.6-77.4 °C.

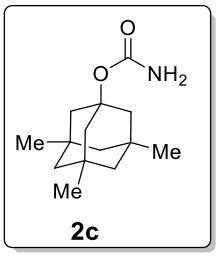
^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 1.14 (s, 3H), 1.20 (s, 3H), 1.47-1.60 (m, 2H), 1.66-1.71 (m, 3H), 1.87 (m, 1H), 1.99-2.08 (m, 3H), 2.15 (m, 1H), 2.25 (m, 1H), 2.79 (s, 3H), 3.71 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ/ppm = 22.6 (CH_3), 22.9 (CH_3), 29.5 (CH), 29.5 (CH), 31.1 (CH), 31.1 (CH_2), 32.2 (CH_2), 32.9 (CH_2), 33.1 (CH_2), 39.6 (C), 41.6 (CH_3), 63.1 (CH), 82.2 (C), 160.6 (C).

IR (neat): $\tilde{\nu}$ /cm^{-1} = 2989, 2921, 2880, 2862, 1748, 1479, 1453, 1423, 1396, 1362, 1346, 1324, 1303, 1268, 1246, 1199, 1162, 1148, 1129, 1101, 1089, 1070, 1045, 1030, 1013, 987, 948, 929, 849, 798, 763, 675, 649, 608, 524.

HRMS: m/z = 236.1642 ($[M+H]^+$; calculated for $C_{14}H_{22}NO_2^+$ m/z = 236.1645).

2.1.8 Compound 2c



2c

Compound **2c** was synthesized from 3,5,7-trimethyl adamantan-1-ol[4] according to *general procedure A* to give the desired product as a white solid in a yield of 90% (1.10 g, 4.6 mmol).

R_f (silica gel; EtOAc:*n*-hexane 2:3): 0.3.

m.p. (cryst. from $CDCl_3$): 126.3-128.0 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 0.88 (s, 9H), 1.01-1.04 (m, 3H), 1.13-1.16 (m, 3H), 1.69 (m, 6H), 4.38 (bs, 2H).

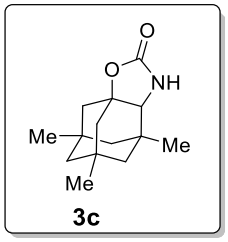
^{13}C NMR (101 MHz, $CDCl_3$): δ/ppm = 29.6 ($3CH_3$), 34.1 (3C), 46.7 ($3CH_2$), 49.9 ($3CH_2$), 81.6 (C), 155.9 (C).

IR (neat): $\tilde{\nu}$ /cm^{-1} = 3281, 2945, 2920, 2897, 2862, 2837, 1715, 1605, 1526, 1454, 1373, 1353, 1334, 1254, 1225, 1205, 1049, 1031, 1001, 922, 845, 781, 745, 667, 643, 551, 486.

HRMS: m/z = 260.1616 ([M+Na]$^+$; calculated for $C_{14}H_{23}NO_2Na^+$ m/z =260.1621).

[4]Y. N. Klimochkin,., A. V. Yudashkin, E. O. Zhilkina, E. A. Ivleva, I. K. Moiseev, and Y. F. Oshis, *Russ. J. Org. Chem.*, 2017, **53**, 971-76.

2.1.9 Compound 3c



3c

Compound **3c** was synthesized from compound **2c** following *general procedure B* to give the desired product as a white solid in a yield of 95% (707 mg, 3.0 mmol).

R_f (silica gel; EtOAc:*n*-hexane 1:4): 0.1.

m.p. (cryst. from $CDCl_3$): 210.5-211.8 °C.

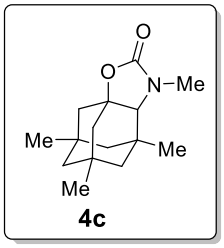
^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 0.91-0.92 (m, 6H), 0.95 (s, 3H), 1.01 (m, 1H), 1.09-1.21 (m, 3H), 1.26 (m, 1H), 1.38-1.48 (m, 2H), 1.69-1.78 (m, 3H), 3.20 (s, 1H), 5.01 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ/ppm = 25.7 (CH_3), 29.0 (CH_3), 29.3 (CH_3), 33.1 (C), 34.9 (C), 35.7 (C), 42.7 (CH_2), 42.8 (CH_2), 45.4 (CH_2), 50.2 (CH_2), 50.8 (CH_2), 67.9 (CH), 82.7 (C), 161.1 (C).

IR (neat): $\tilde{\nu}$ /cm^{-1} = 3251, 2951, 2900, 2867, 2840, 1742, 1455, 1404, 1377, 1356, 1331, 1314, 1296, 1281, 1255, 1223, 1200, 1183, 1135, 1081, 1019, 993, 985, 957, 942, 923, 854, 839, 802, 775, 706, 683, 595, 562, 539, 527, 498, 482, 471, 446.

HRMS: m/z = 258.1466 ([M+Na]$^+$; calculated for $C_{14}H_{21}NO_2Na^+$ m/z = 258.1465).

2.1.10 Compound 4c



4c

Compound **4c** was synthesized from compound **3c** according to *general procedure C* to give the desired product as a white solid in a yield of 96% (213 mg, 0.9 mmol).

R_f (silica gel; EtOAc:*n*-hexane 2:3): 0.4.

m.p. (cryst. from $CDCl_3$): 110.2-111.0 °C.

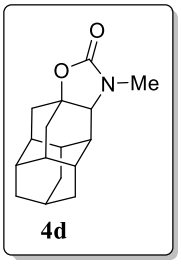
^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 0.90 (s, 3H), 0.94 (s, 3H), 1.05-1.21 (m, 7H), 1.30-1.43 (m, 3H), 1.61-1.72 (m, 3H), 2.89 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$): δ/ppm = 26.5 (CH_3), 29.0 (CH_3), 29.3 (CH_3), 32.6 (CH), 32.9 (C), 35.1 (C), 36.1 (C), 43.6 (CH_2), 43.6 (CH_2), 45.1 (CH_2), 50.0 (CH_2), 52.2 (CH_2), 72.1 (CH_3), 79.5 (C), 161.2 (C).

IR (neat): $\tilde{\nu}$ /cm^{-1} = 2950, 2897, 2865, 2837, 1741, 1453, 1411, 1375, 1343, 1308, 1261, 1209, 1188, 1139, 1120, 1093, 1080, 1031, 1012, 995, 982, 940, 919, 902, 851, 803, 773, 704, 671, 598, 561, 431, 497, 482, 444.

HRMS: m/z = 250.1805 ($[M+H]^+$; calculated for $C_{15}H_{24}NO_2^+$ m/z = 250.1802).

2.1.11 Compound 4d



4d

Compound **4d** was synthesized from diamantane annulated 1,3-oxazolidinone[5] according to *general procedure C* to give the desired product as a white solid in a yield of 95% (250 mg, 1 mmol).

R_f (silica gel; EtOAc:*n*-hexane 1:4): 0.1.

m.p. (cryst. from $CDCl_3$): 166.6-167.5 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 1.73-1.83 (m, 9H), 1.86-1.97 (m, 4H), 2.01-2.06 (m, 2H), 2.13 (m, 2H), 2.79 (s, 3H), 3.22 (m, 1H).

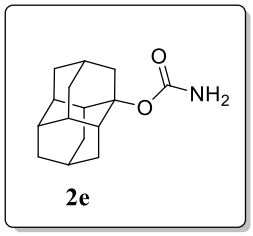
^{13}C NMR (101 MHz, $CDCl_3$): δ/ppm = 25.9 (CH_3), 29.4 (CH), 31.0 (CH), 36.0 (CH_2), 36.7 (CH), 36.8 (CH_2), 37.1 (CH), 37.3 (CH_2), 38.1 (CH_2), 38.3 (CH), 39.1 (CH), 40.0 (CH_2), 40.5 (CH), 69.2 (CH), 77.5 (C), 160.9 (C).

IR (neat): $\tilde{\nu}$ /cm^{-1} = 2879, 1738, 1462, 1427, 1375, 1352, 1334, 1303, 1269, 1258, 1244, 1190, 1127, 1069, 1050, 1039, 1006, 947, 908, 846, 797, 775, 763, 722, 689, 659, 620, 559, 540, 469.

HRMS: m/z = 260.1643 ($[M+H]^+$; calculated for $C_{16}H_{22}NO_2^+$ m/z =260.1645).

[5]B. Zonker, E. Duman, H. Hausmann, J. Becker, R. Hrdina., *Org Biomol. Chem.*, 2020, **18**, 4941-4945.

2.1.12 Compound 2e



2e

Compound **2e** was synthesized from diamantan-1-ol[6] according to *general procedure A* to give the desired product as a white solid in a yield of 87% (680 mg, 2.8 mmol).

R_f (silica gel; EtOAc:*n*-hexane 2:3): 0.2.

m.p. (cryst. from EtOAc): 162.6.-163.9 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 1.43-1.48 (m, 2H), 1.56-1.60 (m, 2H), 1.66-1.76 (m, 6H), 1.97-1.98 (m, 2H), 2.03-2.09 (m, 3H), 2.15-2.16 (m, 2H), 2.30 (m, 2H), 4.47 (bs, 2H).

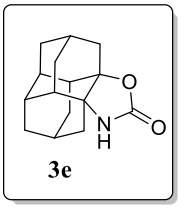
^{13}C NMR (101 MHz, $CDCl_3$): δ/ppm = 25.1 (CH), 30.3 (CH), 32.8 ($2CH_2$), 36.8 (CH), 37.3 ($2CH_2$), 38.1 (CH_2), 40.3 (2CH), 40.4 (2CH), 40.9 (CH_2), 83.0 (C), 156.0 (C).

IR (neat): $\tilde{\nu}$ /cm^{-1} = 3426, 3219, 2901, 2872, 2850, 1716, 1688, 1667, 1606, 1460, 1440, 1372, 1341, 1321, 1297, 1137, 1079, 1041, 1023, 991, 981, 953, 905, 847, 814, 782, 6763, 722, 606, 566, 481, 435.

HRMS: m/z =270.1465 ($[M+Na]^+$; calculated for $C_{15}H_{21}NO_2Na^+$ m/z =270.1465).

[6]Andrey A. Fokin , B. A. Tkachenko, P. A. Gunchenko, D. V. Gusev, P. R. Schreiner , *Chem. Eur. J.*, 2005, **11**, 7091-7101.

2.1.13 Compound 3e



3e

Compound **3e** was synthesized from compound **2e** according to *general procedure B* to give the desired product as a white solid in a yield of 83% (510 mg, 2.1 mmol) as a single regiomer.

R_f (silica gel; EtOAc:*n*-hexane 2:3): 0.2.

m.p. (cryst. from $CDCl_3$): >250 °C

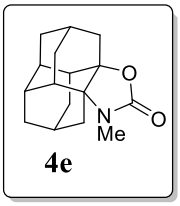
^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 1.47-1.69 (m, 8H), 1.89-2.11 (m, 8H), 2.23-2.28 (m, 2H), 5.17 (bs 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ/ppm = 27.8 (CH), 29.0 (CH), 31.3 (CH_2), 31.5 (CH_2), 36.8 (CH_2), 37.0 (CH_2), 39.4 (CH_2), 39.7 (CH), 39.7 (CH), 40.1 (CH), 41.3 (CH), 42.3 (CH_2), 60.4 (CH), 83.4 (C), 161.5 (C).

IR (neat): $\tilde{\nu}$ /cm^{-1} = 3227, 2918, 2855, 1740, 1634, 1460, 1439, 1337, 1273, 1218, 1188, 1118, 1108, 1063, 1052, 1008, 948, 932, 920, 892, 853, 827, 807, 777, 700, 684, 663, 624, 546, 516, 485, 465.

HRMS: m/z = 246.1491 ($[M+H]^+$; calculated for $C_{15}H_{20}NO_2^+$ m/z =246.1489).

2.1.14 Compound 4e



4e

Compound **4e** was synthesized from compound **3e** according to *general procedure C* to give the desired product as a white solid in a yield of 93% (165 mg, 1.4 mmol).

R_f (silica gel; EtOAc:*n*-hexane 2:3): 0.3.

m.p. (cryst. from $CDCl_3$): 114.2-115.0 °C.

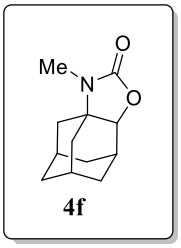
^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 1.52-1.77 (m, 9H), 1.85 (m, 1H), 1.93 (m, 1H), 2.01-2.10 (m, 5H), 2.15 (m, 1H), 2.25 (m, 1H), 2.69 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ/ppm = 25.6 (CH_3), 27.3 (CH), 28.9 (CH), 31.6 (CH_2), 31.7 (CH_2), 36.9 (CH_2), 37.0 (CH_2), 37.5 (CH_2), 38.9 (CH), 39.6 (CH_2), 39.6 2(CH), 41.5 (CH), 62.3 (C), 81.3 (C), 160.1 (C).

IR (neat): $\tilde{\nu}$ /cm^{-1} = 2914, 2851, 1733, 1460, 1483, 1424, 1380, 1346, 1323, 1294, 1283, 1252, 1223, 1123, 1074, 1063, 1034, 1020, 1003, 944, 919, 813, 772, 685, 667, 646, 634, 520, 485, 470.

HRMS: m/z = 260.1642 ($[M+H]^+$; calculated for $C_{16}H_{22}NO_2^+$ m/z =260.1645).

2.1.15 Compound 4f



4f

Compound **4f** was synthesized from corresponding oxazolidinone[7] according to *general procedure C* to give the desired product as a white solid in a yield of 34%[8] (177 mg, 0.9 mmol).

R_f (silica gel; EtOAc:*n*-hexane 2:3): 0.3.

m.p. (cryst. from $CDCl_3$): 105.4-106.7 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 1.56-1.78 (m, 6H), 1.82-1.94 (m, 4H), 2.07 (m, 1H), 2.18 (m, 1H), 2.42 (m, 1H), 2.69 (s, 3H), 3.98.

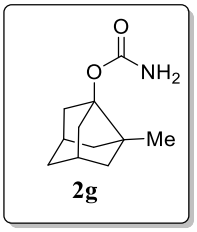
^{13}C NMR (101 MHz, $CDCl_3$): δ/ppm = 26.1 (CH_3), 27.7 (CH), 29.6 (CH), 30.0 (CH_2), 30.2 (CH), 35.1(CH_2), 36.1(CH_2), 36.6(CH_2), 38.4(CH_2), 58.8 (C), 83.8(CH), 160.0 (C).

IR (neat): $\tilde{\nu}$ /cm^{-1} = 2922, 2903, 2857, 1740, 1456, 1423, 1383, 1362, 1334, 1319, 1301, 1267, 1246, 1122, 1081, 1067, 1050, 1017, 997, 965, 928, 856, 811, 772, 756, 690, 673, 617, 548, 511, 465, 441.

HRMS: m/z = 208.1333 ([M+H]$^+$; calculated for $C_{12}H_{18}NO_2^+$ m/z =208.1332).

[7]R, Hrdina, M. Larrosa, C. Logemann, *J. O. Chem*., 2017, **82**, 4891-4899.
[8]starting material recovered.

2.1.16 Compound 2g



2g

Compound **2g** was synthesized from 7-methyl-noradamantan-3-ol[9] according to *general procedure A* to give the desired product as a white solid in a yield of 84% (530 mg, 2.7 mmol).

R_f (silica gel; EtOAc:*n*-hexane 2:3): 0.4.

m.p. (cryst. from $CDCl_3$): 109.0-110.9 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 1.05 (s, 3H), 1.48-1.68 (m, 6H), 1.92-1.96 (m, 2H), 2.23-2.26 (m, 2H), 2.39-2.43 (m, 2H), 4.50 (bs, 2H).

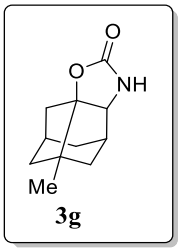
^{13}C NMR (101 MHz, $CDCl_3$): δ/ppm = 22.0 (CH_3), 33.6 (CH_2), 35.9 (CH), 46.1 (C), 48.6 ($2CH_2$), 50.3($2CH_2$), 89.6 (C), 156.5 (C).

IR (neat): $\tilde{\nu}$ /cm^{-1} = 3482, 3322, 3254, 3182, 2934, 2865, 1694, 1594, 1459, 1366, 1324, 1305, 1262, 1221, 1170, 1121, 1045, 963, 934, 901, 866, 783, 705, 638, 607, 495.

HRMS: m/z = 218.1150 ([M+Na]$^+$; calculated for $C_{13}H_{19}NO_2Na^+$ m/z = 218.1151).

[9]M. Takefumi, O. Muraoka, S. Atarashi, and T. Horita, *Chem. Pharm. Bull.*, 1979, **27**, 222-29.

2.1.17 Compound 3g



3g

Compound **3g** was synthesized from compound **2g** according to *general procedure B* to give the desired product as an off-white solid in a yield of 81% (200 mg, 1.0 mmol) as a single diastereomer.

R_f (silica gel; EtOAc:*n*-hexane 2:3): 0.2.

m.p. (cryst. from $CDCl_3$): 107.5-109.2 °C.

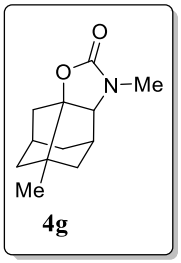
^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 1.05 (s, 3H), 1.51-1.76 (m, 5H), 1.98 (m, 1H), 2.11-2.18 (m, 2H), 2.30-2.40 (m, 5H), 3.79 (m, 1H), 5.31 (bs, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): 21.6 (CH_3), 33.1 (CH_2), 35.1 (CH), 39.5 (CH), 43.9 (CH_2), 45.3 (C), 45.5 (CH_2), 49.9 (CH_2), 71.3 (CH), 92.4 (C), 160.5 (C).

IR (neat): $\tilde{\nu}$ /cm^{-1} = 3280, 2948, 2928, 2864, 1761, 1731, 1479, 1455, 1374, 1324, 1305, 1269, 1257, 1218, 1192, 1169, 1149, 1124, 1112, 1089, 1074, 1018, 970, 954, 931, 916, 790, 768, 757, 689, 659, 627, 590, 534, 511, 494, 444.

HRMS: m/z = 216.0997 ([M+Na]$^+$; calculated for $C_{11}H_{15}NO_2Na^+$ m/z = 216.0995).

2.1.18 Compound 4g



4g

Compound **4g** was synthesized from compound **3g** according to *general procedure C* to give the desired product as a white solid in a yield of 96% (155 mg, 0.8 mmol).

R_f (silica gel; EtOAc:*n*-hexane 3:7): 0.2.

m.p. (cryst. from $CDCl_3$): 74.8-75.6 °C.

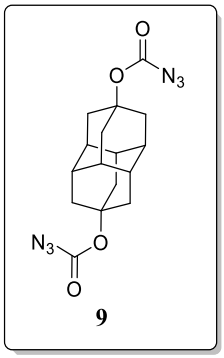
^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 1.02 (s, 3H), 1.51-1.67 (m, 4H), 1.74-1.84 (m, 2H), 1.91-1.94 (m, 1H), 2.14-2.18 (m, 1H), 2.32 (m, 1H), 2.41 (m, 1H), 2.72 (s, 3H), 3.48 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ/ppm = 21.6 (CH_3), 28.5 (CH_3), 32.9 (CH_2), 35.2 (CH), 37.8 (CH), 43.6 (CH_2), 45.2 (C), 45.3 (CH_2), 49.8 (CH_2), 75.6 (CH), 89.3 (C), 159.5 (C).

IR (neat): $\tilde{\nu}$ /cm^{-1} = 2947, 2919, 2862, 1742, 1475, 1459, 1426, 1391, 1331, 1285, 1260, 1228, 1207, 1166, 1112, 1077, 1038, 1016, 995, 956, 910, 848, 785, 766, 756, 699, 663, 640, 598, 533, 511, 484, 442.

HRMS: m/z = 208.1333 ($[M+H]^+$; calculated for $C_{12}H_{18}NO_2^+$ m/z = 208.1332).

2.1.19 Compound 9



9

At -20 °C, 4,9-diamantanediol (1 eq., 220 mg, 1 mmol)[10] and sodium azide (4 eq., 260 mg, 4 mmol) in pyridine (10 mL) were treated with triphosgene (1 eq., 297 mg, 1 mmol) in 2 ml methylene chloride. The reaction mixture was allowed to warm to room temperature and subsequently heated to 50 °C for 6 hours. The reaction was quenched with water and extracted with EtOAc (2x). The combined organic phases were dried over Na_2SO_4 (anhydrous), filtered and the solvents were evaporated *in vacuo*. The crude product was washed with hexane to remove non-polar impurities and used without further purification.

Yield: 89% (320 mg, 0.89 mmol).

^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 1.74 (s, 6H), 1.99 (s, 6H), 2.15 (s, 6H).

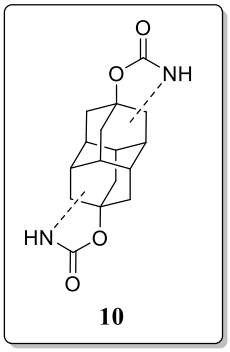
^{13}C NMR (101 MHz, $CDCl_3$): δ/ppm = 38.6 (6CH), 40.0 (6CH_2), 82.8 (C), 155.5 (C).

IR (neat): $\tilde{\nu}$ /cm^{-1} = 3572, 3306, 2895, 2172, 2131, 1716, 1616, 1585, 1525, 1443, 1349, 1291, 1259, 1217, 1195, 1135, 1106, 1073, 1049, 1001, 977, 951, 926, 823, 779, 753, 718, 665, 651, 487, 437.

HRMS: m/z = 381.1280 ([M+Na]$^+$; calculated for $C_{16}H_{18}N_6O_4Na^+$ m/z = 381.1282).

[10]M. A. Gunawan, O. Moncea, D. Poinsot, M. Keskes, B. Domenichini, O. Heintz, R. Chassagnon, F. Herbst, R. M. Carlson, J. E. Dahl, *Adv. Funct. Mater.*, 2018, **28**, 1705786. |

2.1.20 Compound 10



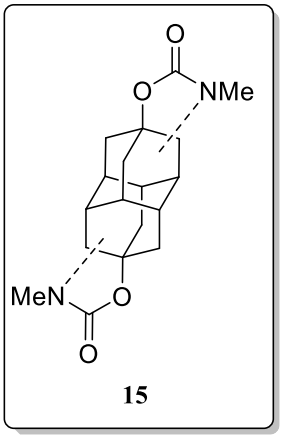
10

Compound **9** (100 mg, 0.28 mmol) was dissolved in 1,2-dichloroethane (10 mL) and heated to 130 °C for 24 hours. The solvent was evaporated *in vacuo* and the crude mixture of six isomers was used in the next step without further purification.

^{1}H NMR (400 MHz, CD_3OD): δ/ppm = 1.80-2.42 (m, 14H), 3.70 (m, 2H), 4.67 (m, 2H).

HRMS: m/z = 325.1160 ($[M+Na]^+$; calculated for $C_{16}H_{18}N_2O_4Na^+$ m/z = 325.1159).

2.1.21 Compound 15



15

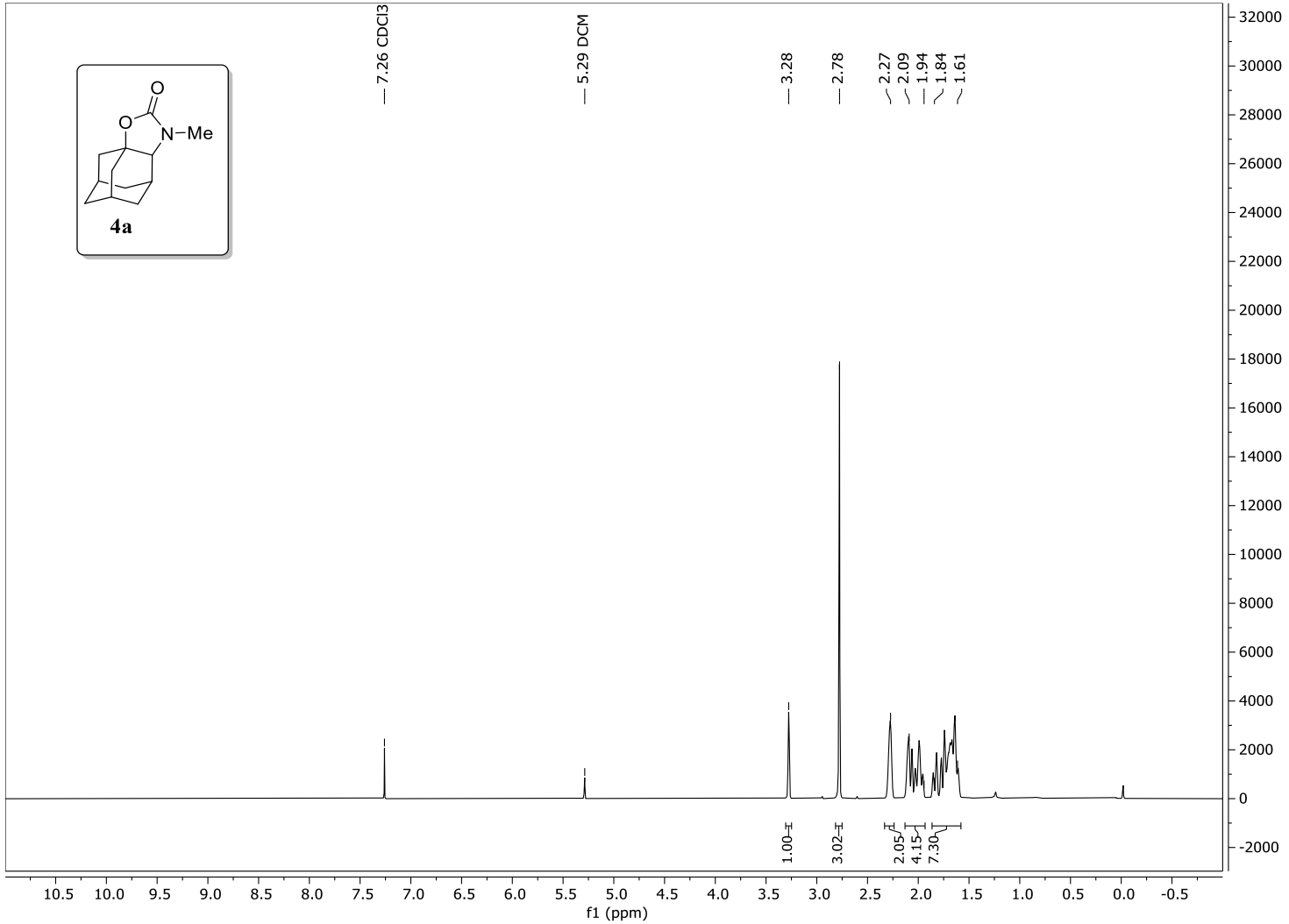
Compound **15** was synthesized from compound 10 according to *general procedure C*. The crude mixture was purified by flash column chromatography on silica gel (mobile phase: EtOAc) to isolate the product as a mixture of six isomers.

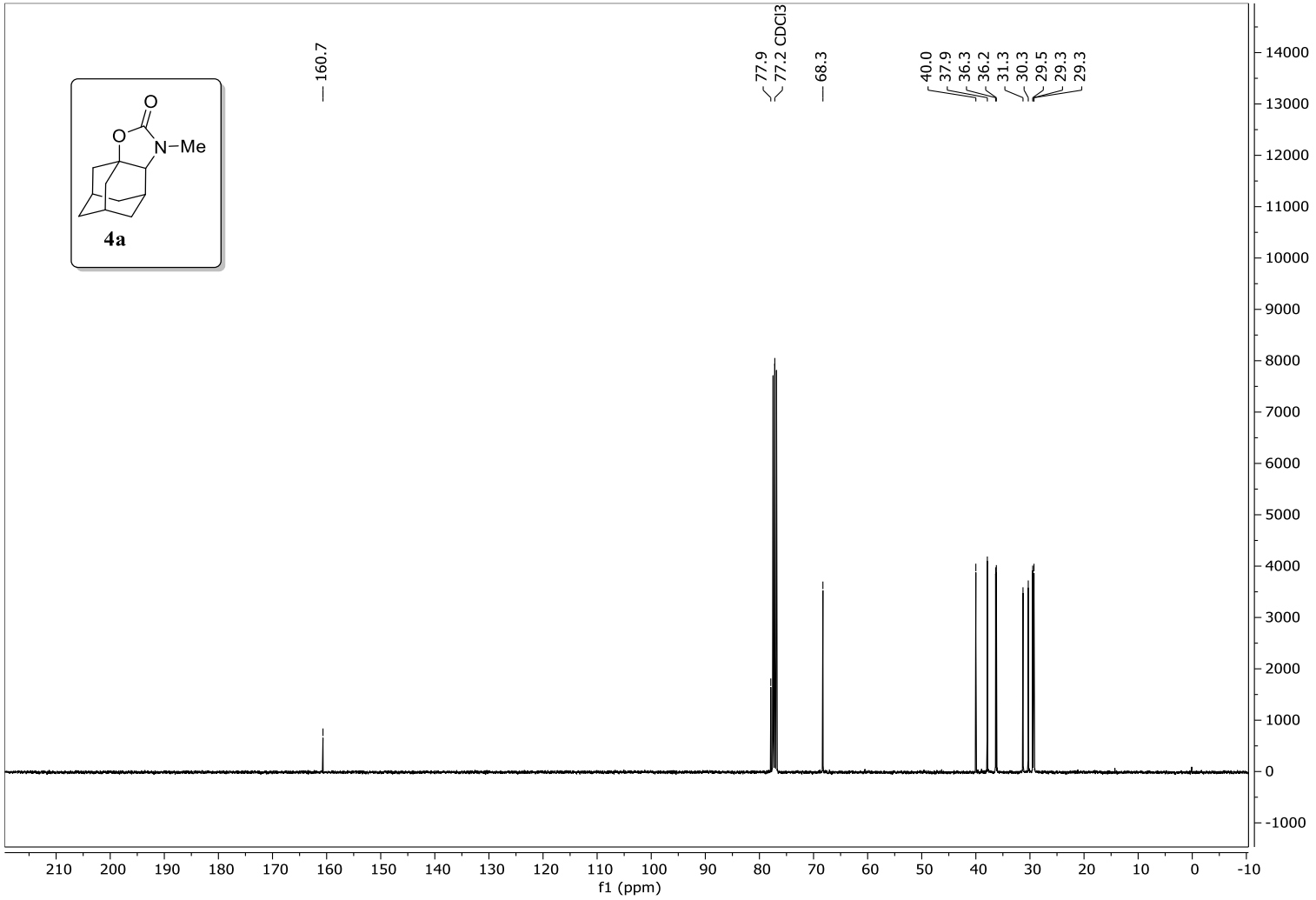
^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 1.75-2.26 (m, 16H), 2.78-2.81 (m, 6H), 3.30-3.36 (m, 2H).

HRMS: m/z = 353.1473 ($[M+Na]^+$; calculated for $C_{18}H_{22}N_2O_4Na^+$ m/z = 353.1472).

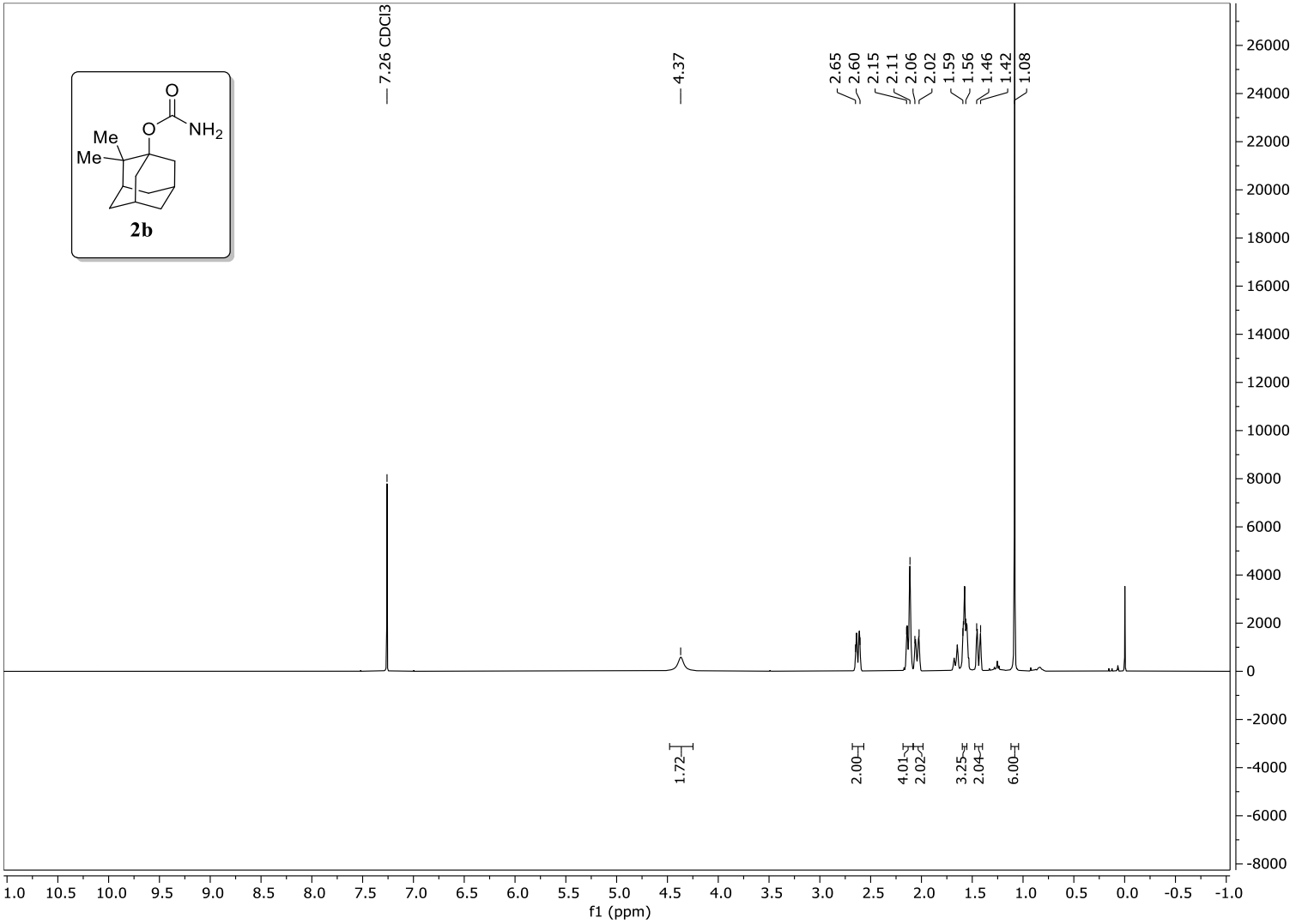
2.2 NMR spectra of starting materials

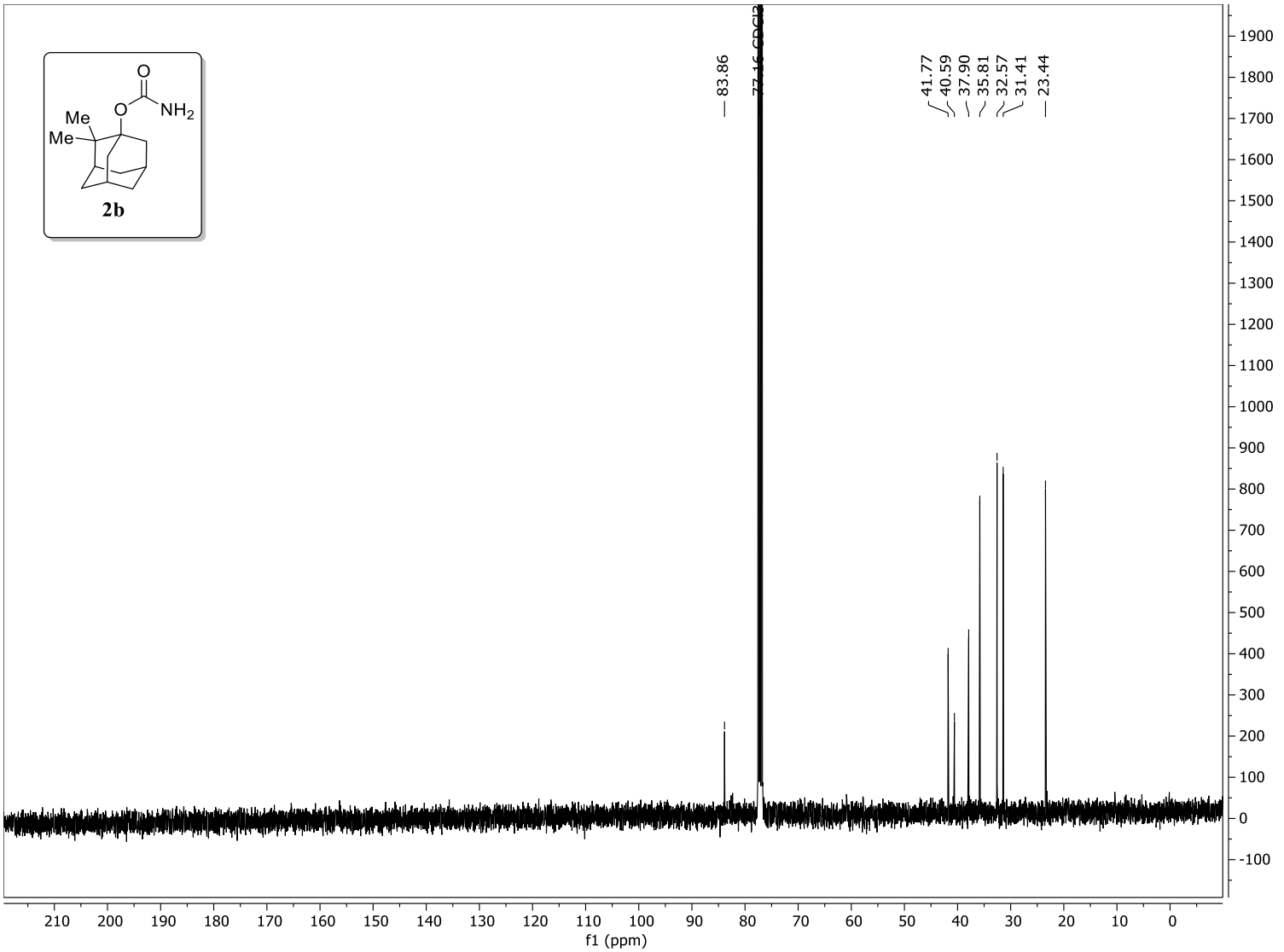
2.2.1 Compound 4a



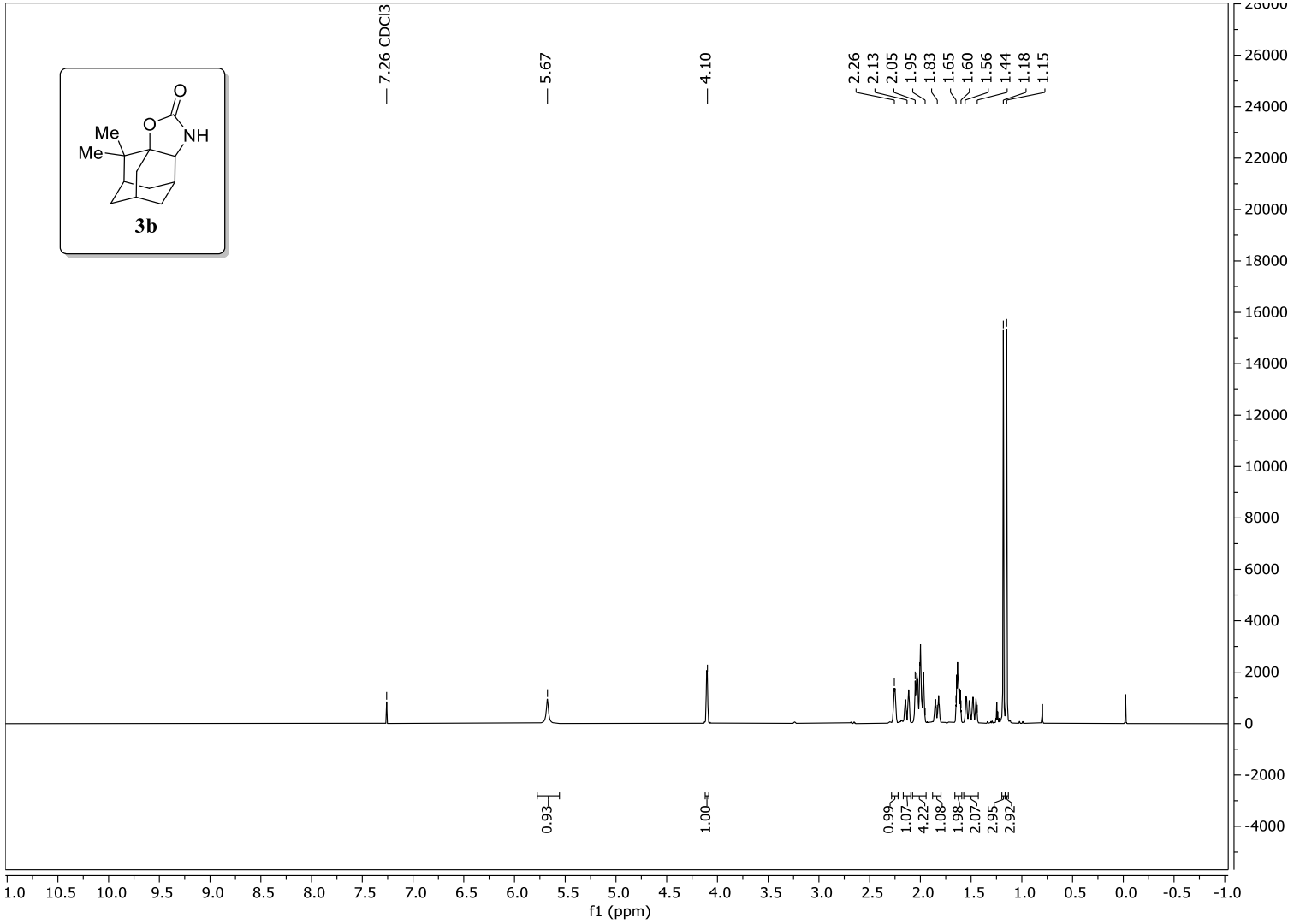

160.7
77.9
77.2 CDCl3
68.3
40.0
37.9
36.3
36.2
31.3
30.3
29.5
29.3
29.3
O
O
N–Me
4a
f1 (ppm)

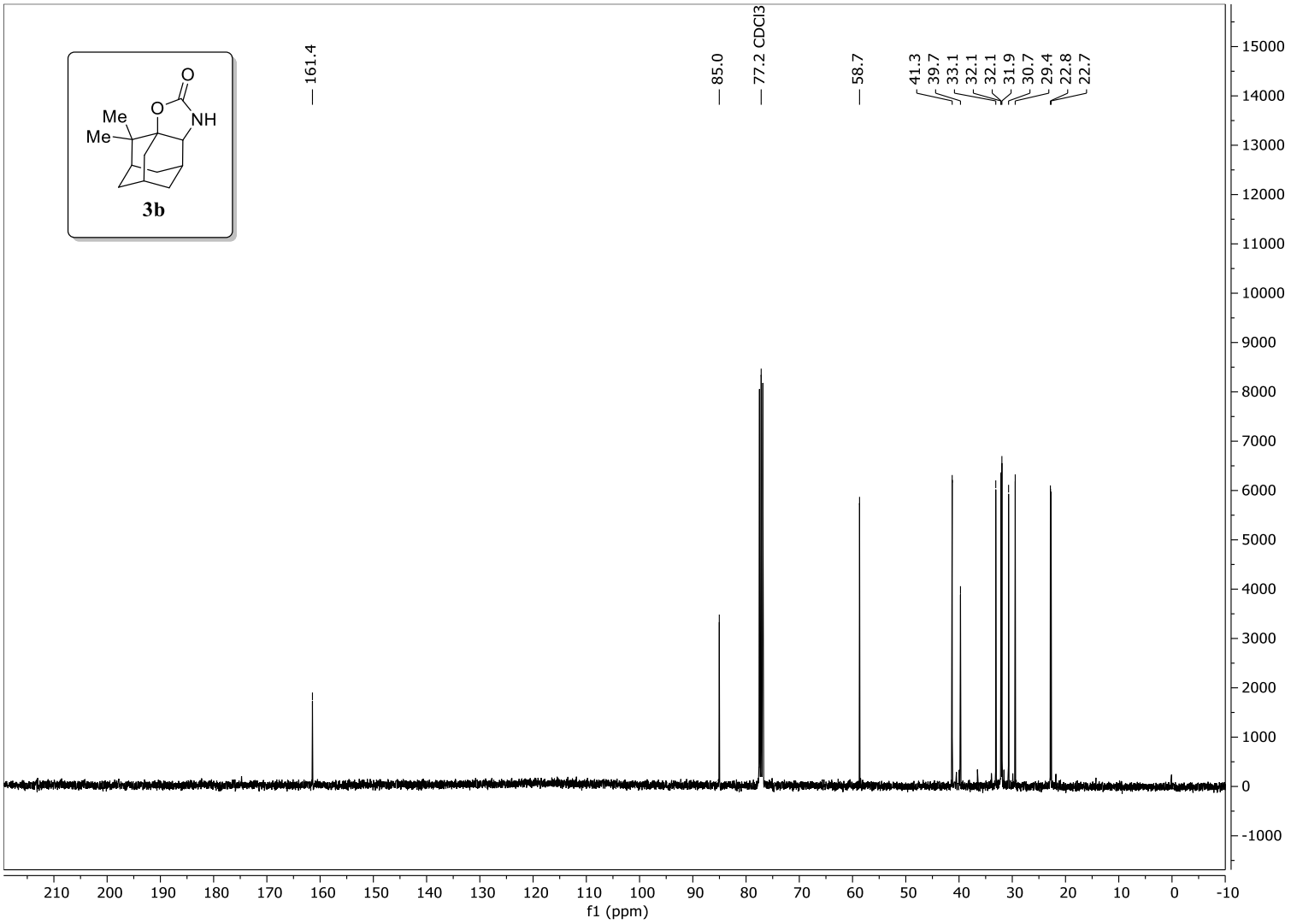
2.2.2 Compound 2b



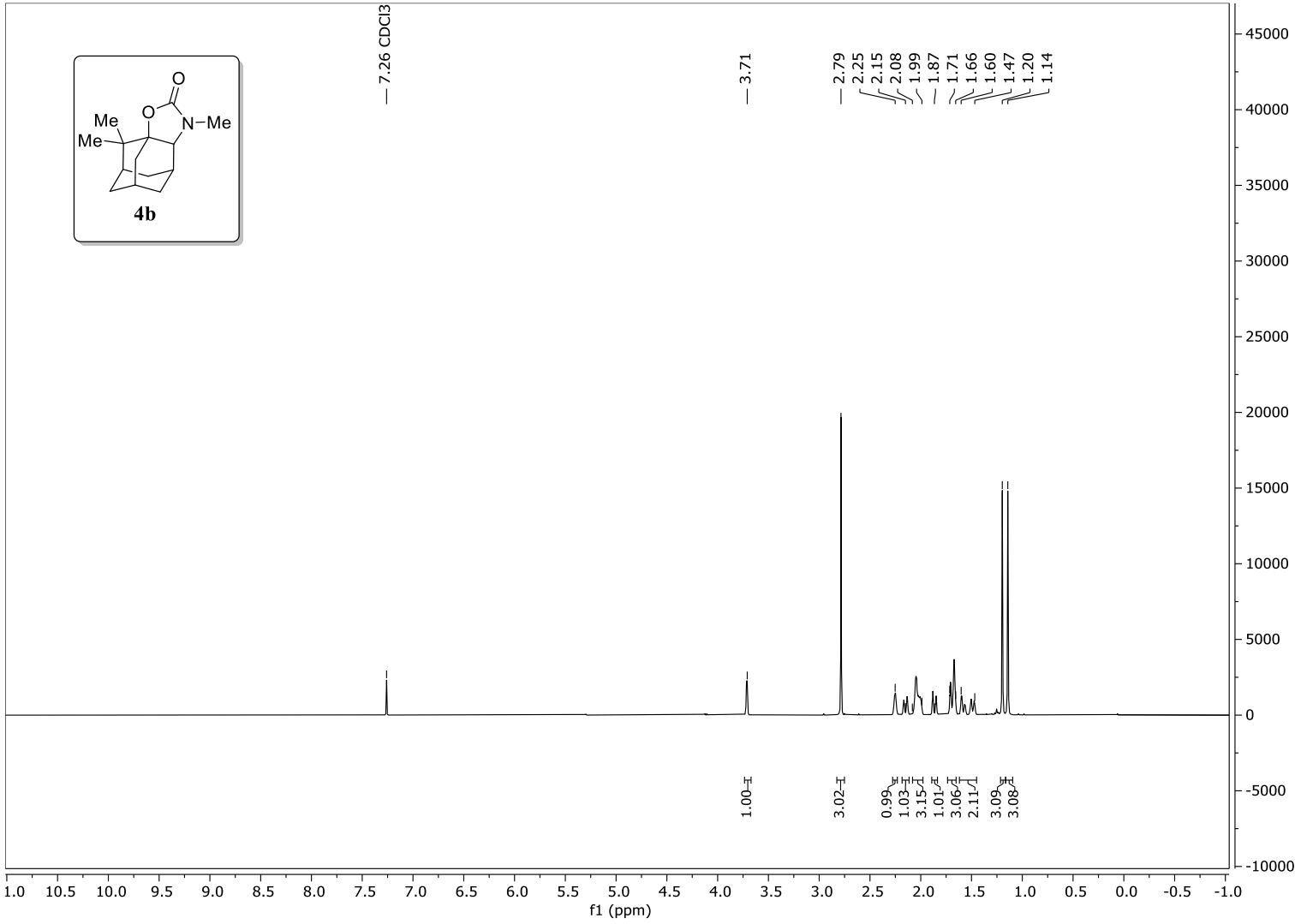

O
O
NH2
Me
Me
2b
83.86
77.16 CDCl3
41.77
40.59
37.90
35.81
32.57
31.41
23.44
f1 (ppm)

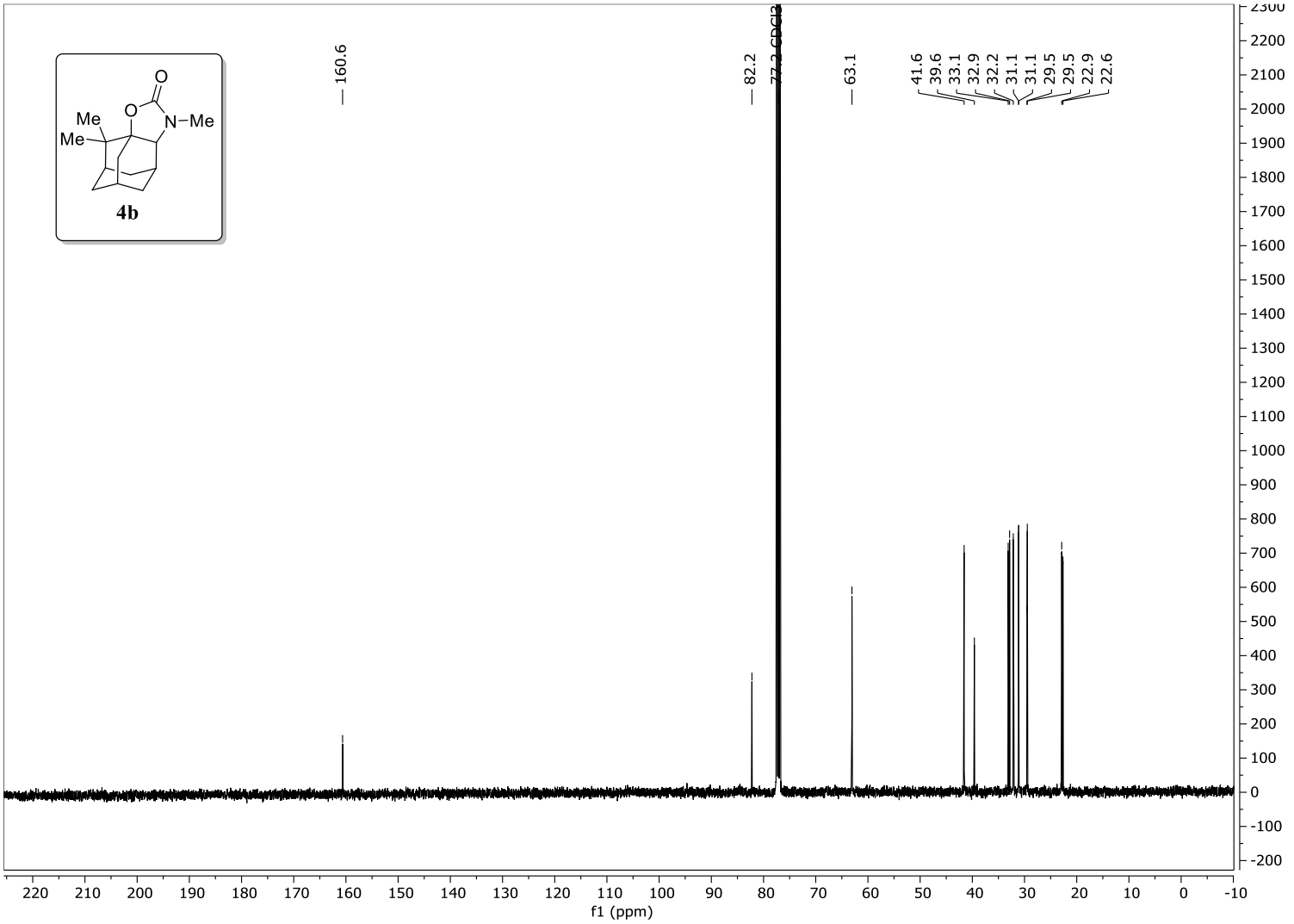
2.2.3 Compound 3b



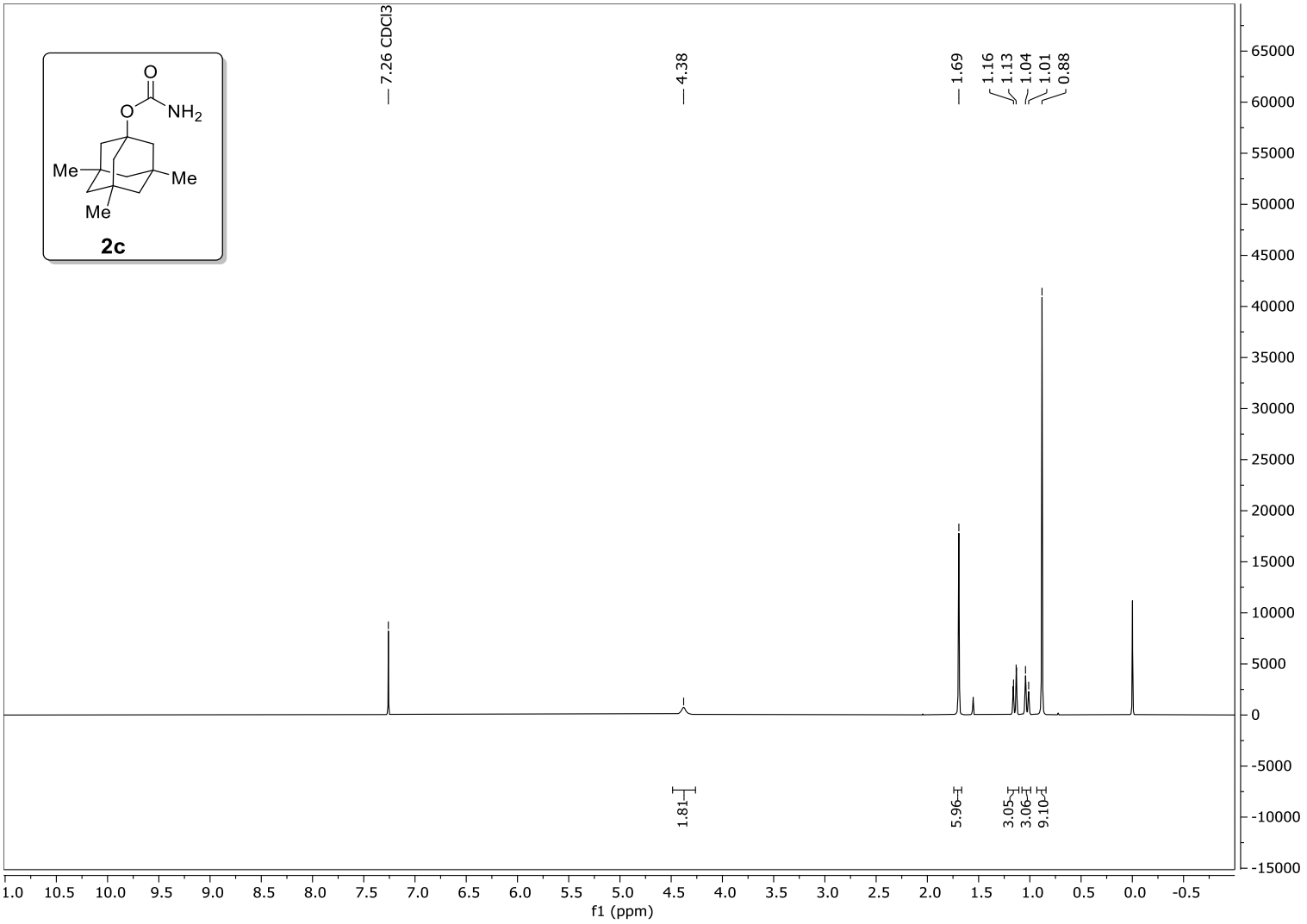

O
O
NH
Me
Me
3b
161.4
85.0
77.2 CDCl3
58.7
41.3
39.7
33.1
32.1
32.1
31.9
30.7
29.4
22.8
22.7
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

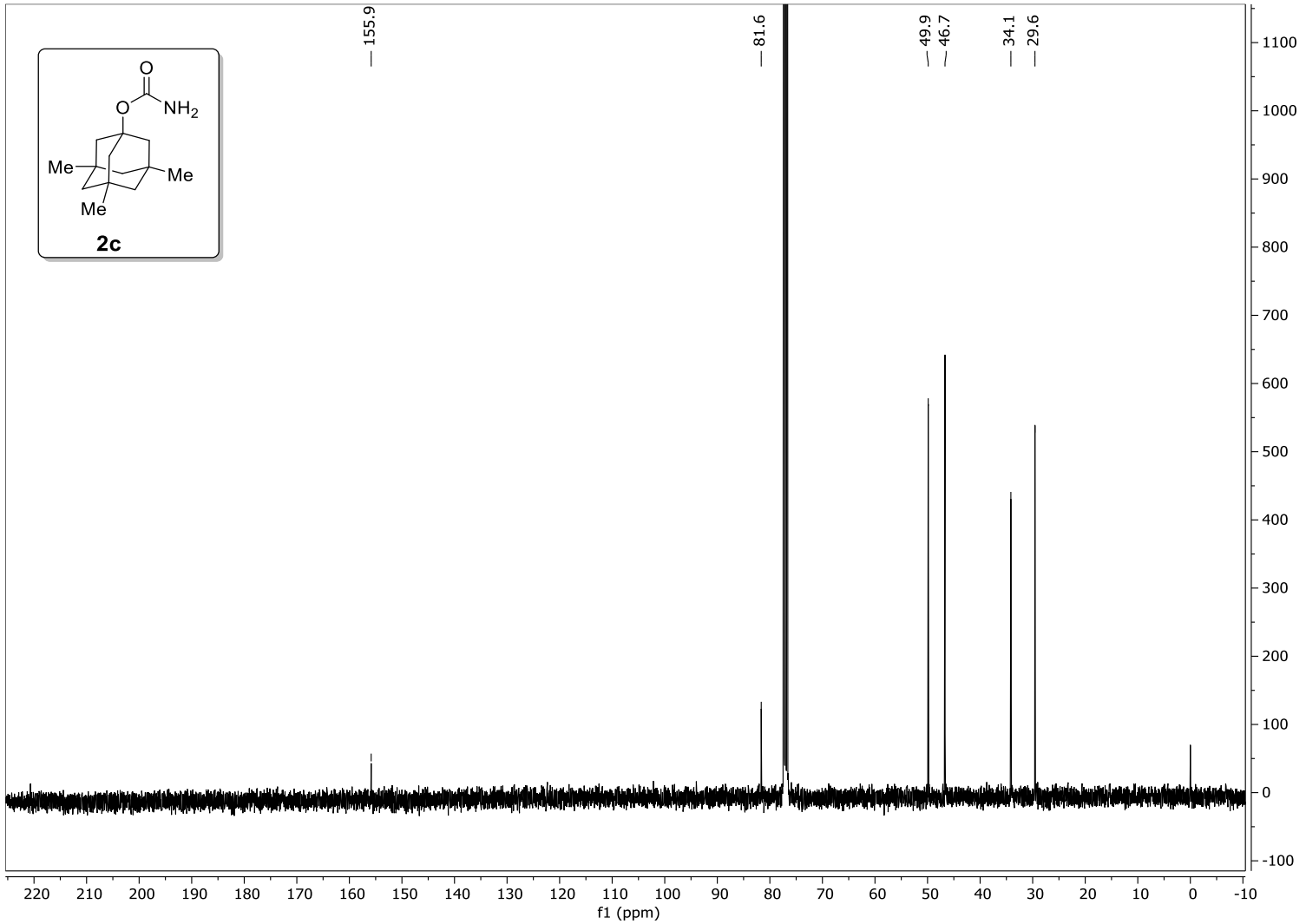
2.2.4 Compound 4b



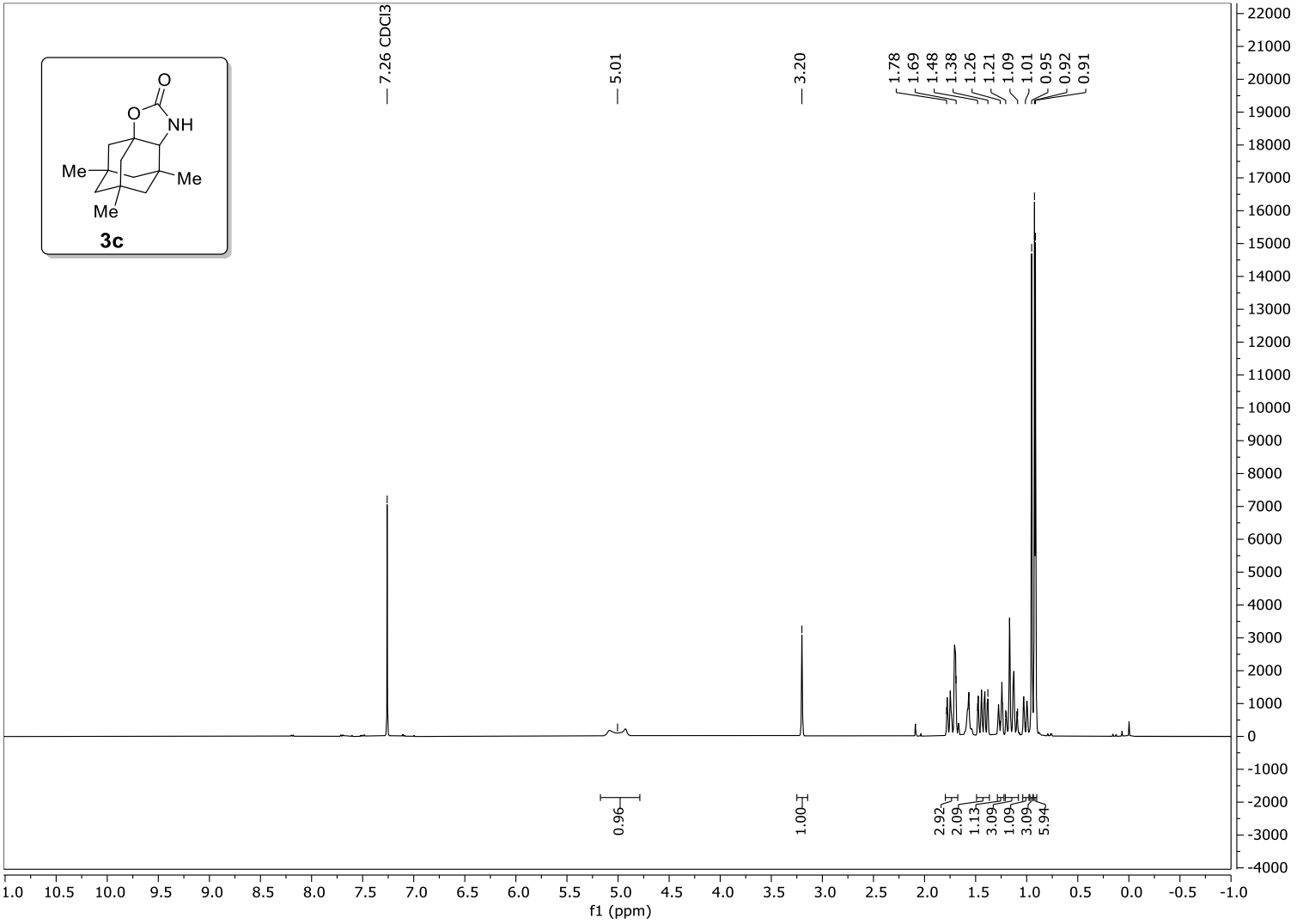

4b
160.6
82.2
77.3 CDCl3
63.1
41.6
39.6
33.1
32.9
32.2
31.1
31.1
29.5
29.5
22.9
22.6
f1 (ppm)

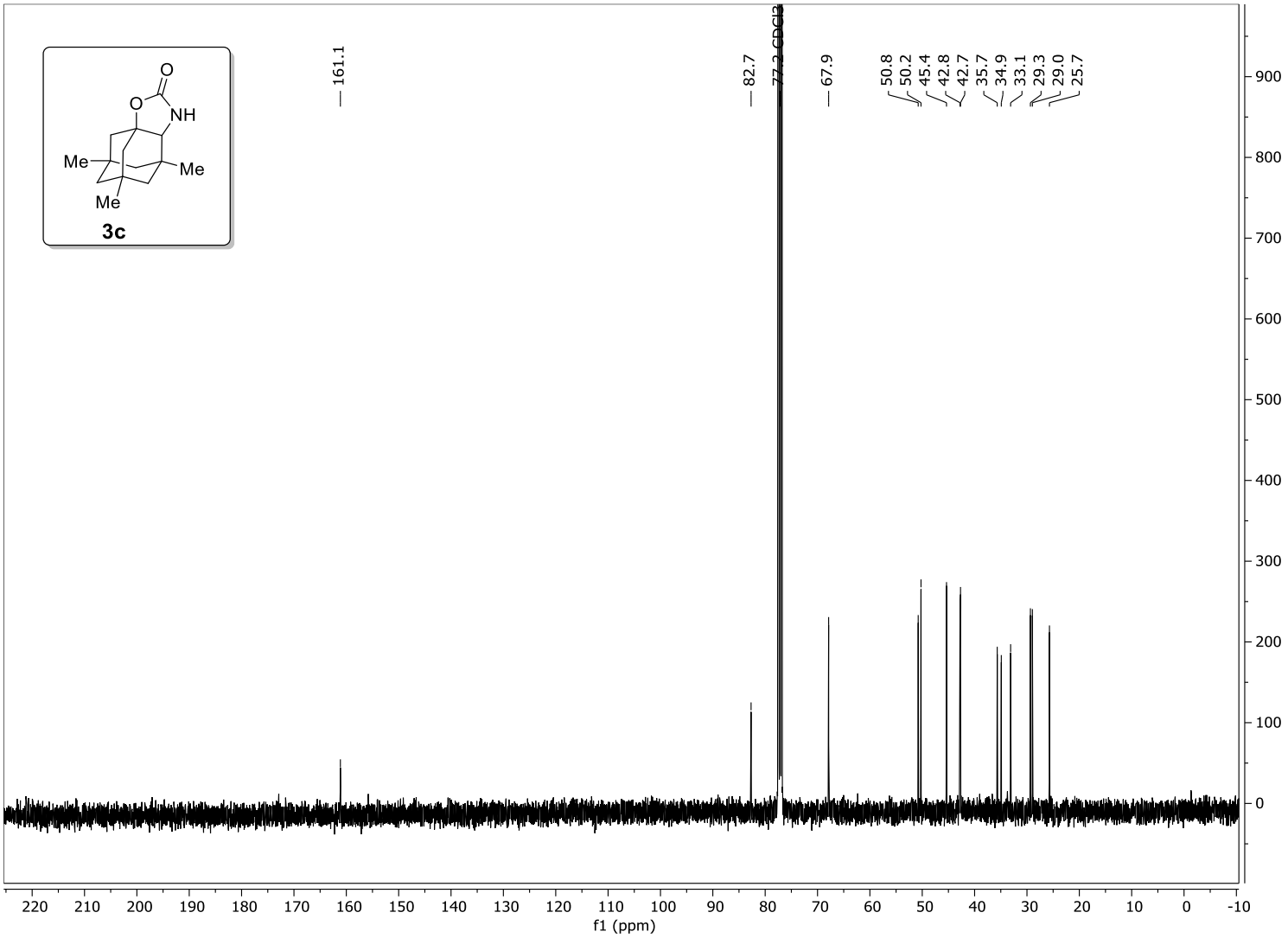
2.2.5 Compound 2c



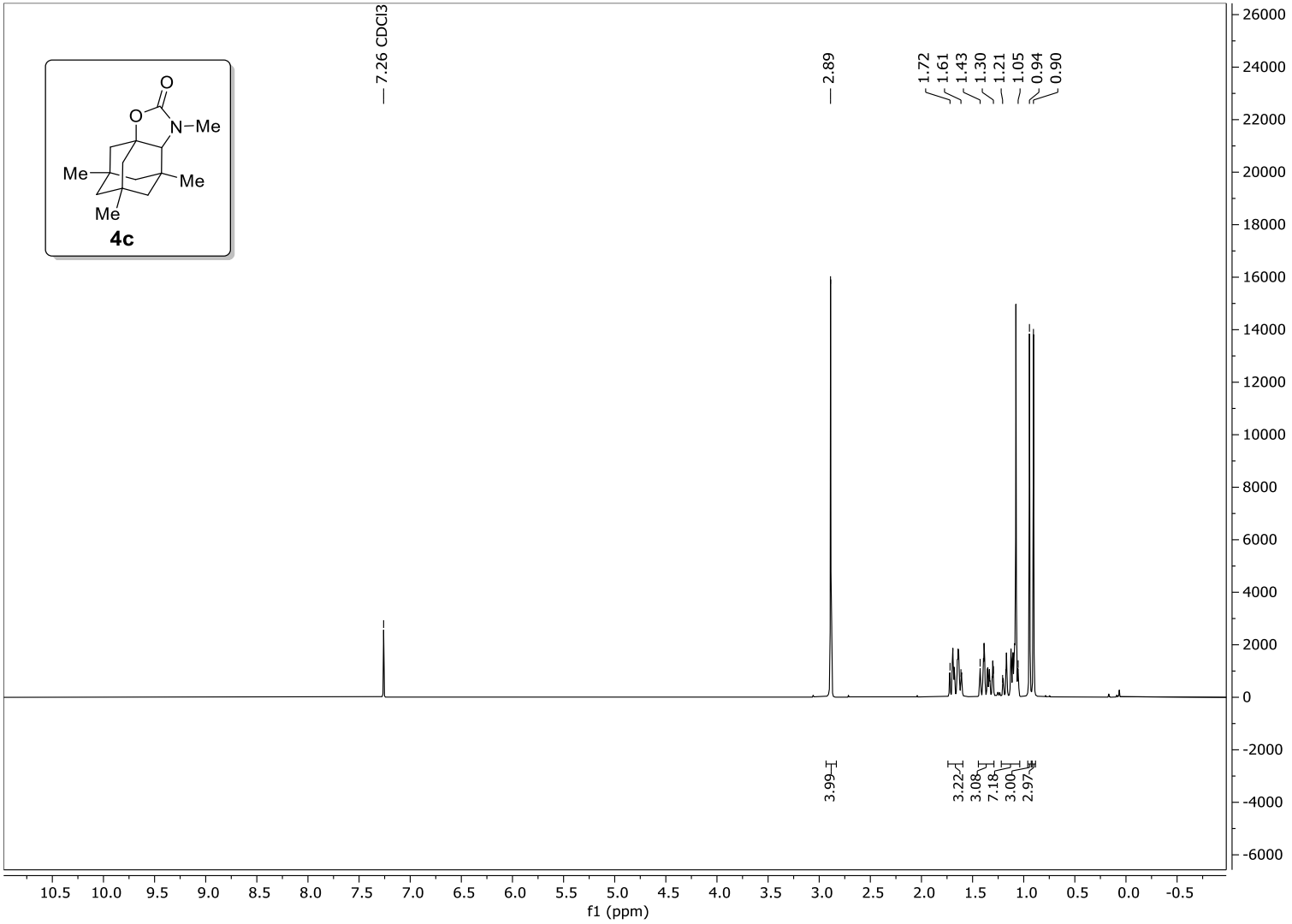

155.9
81.6
49.9
46.7
34.1
29.6
O
O
NH2
Me
Me
Me
2c
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

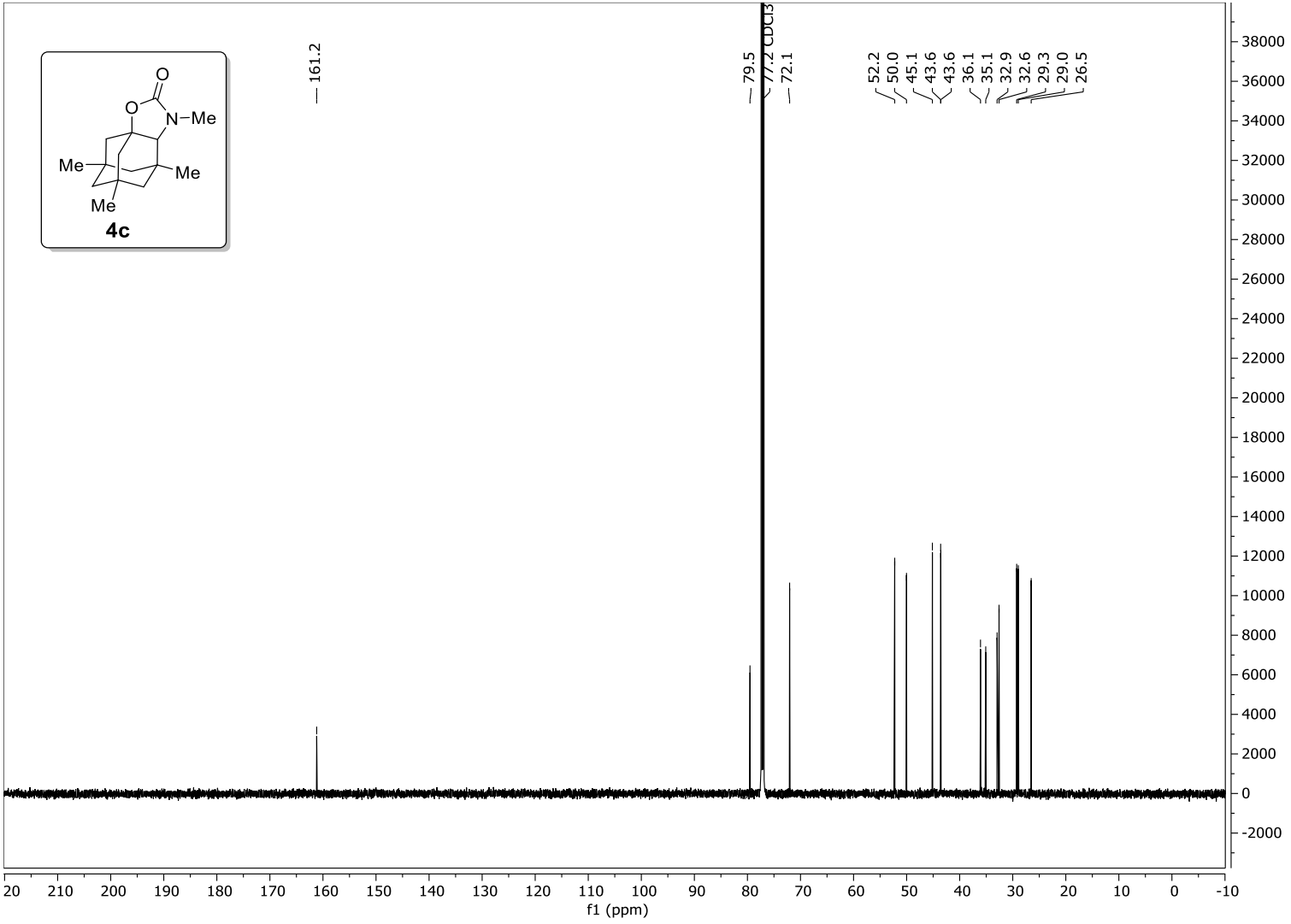
2.2.6 Compound 3c



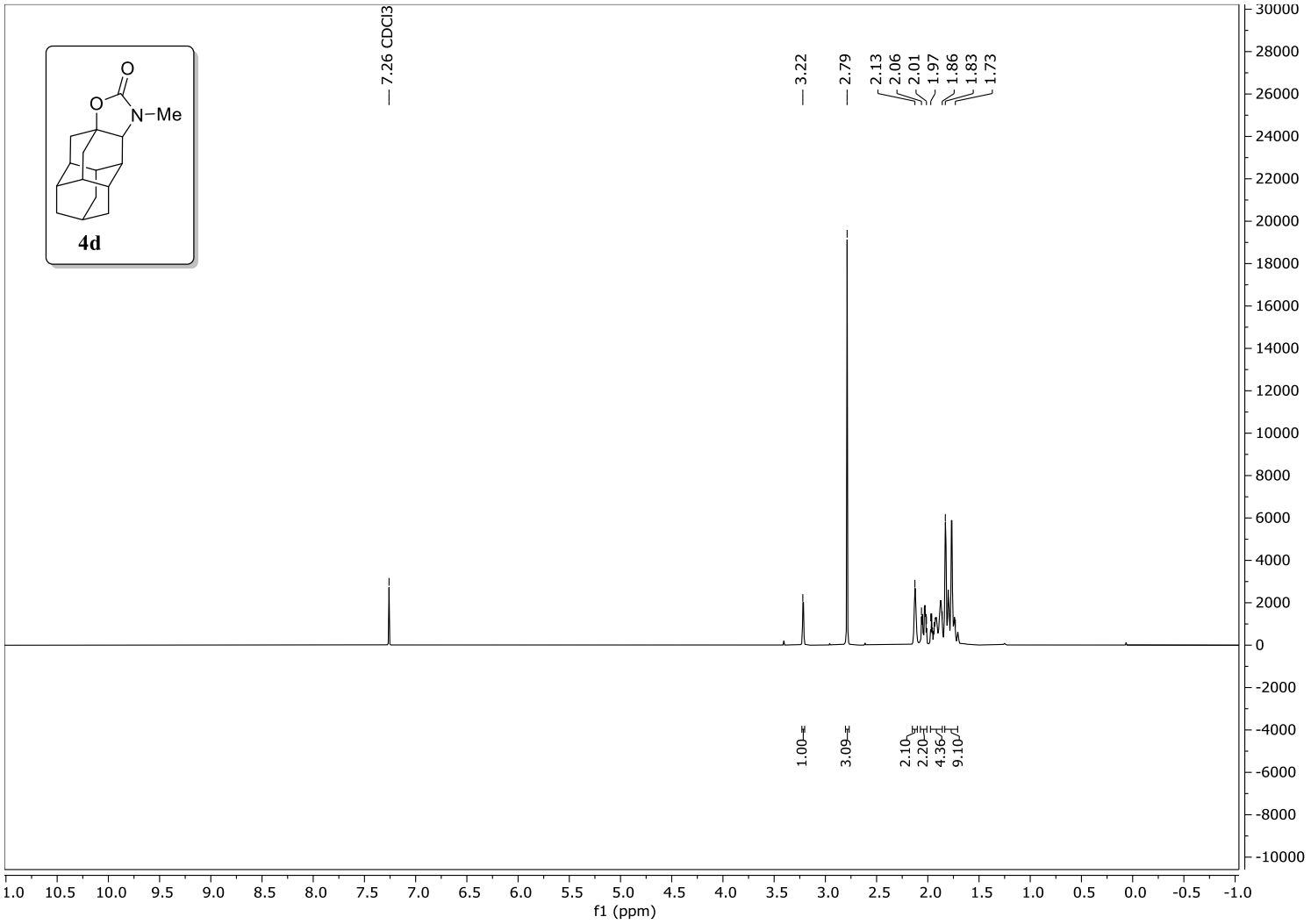

O
O
NH
Me
Me
Me
3c
161.1
82.7
77.2 CDCl3
67.9
50.8
50.2
45.4
42.8
42.7
35.7
34.9
33.1
29.3
29.0
25.7
f1 (ppm)

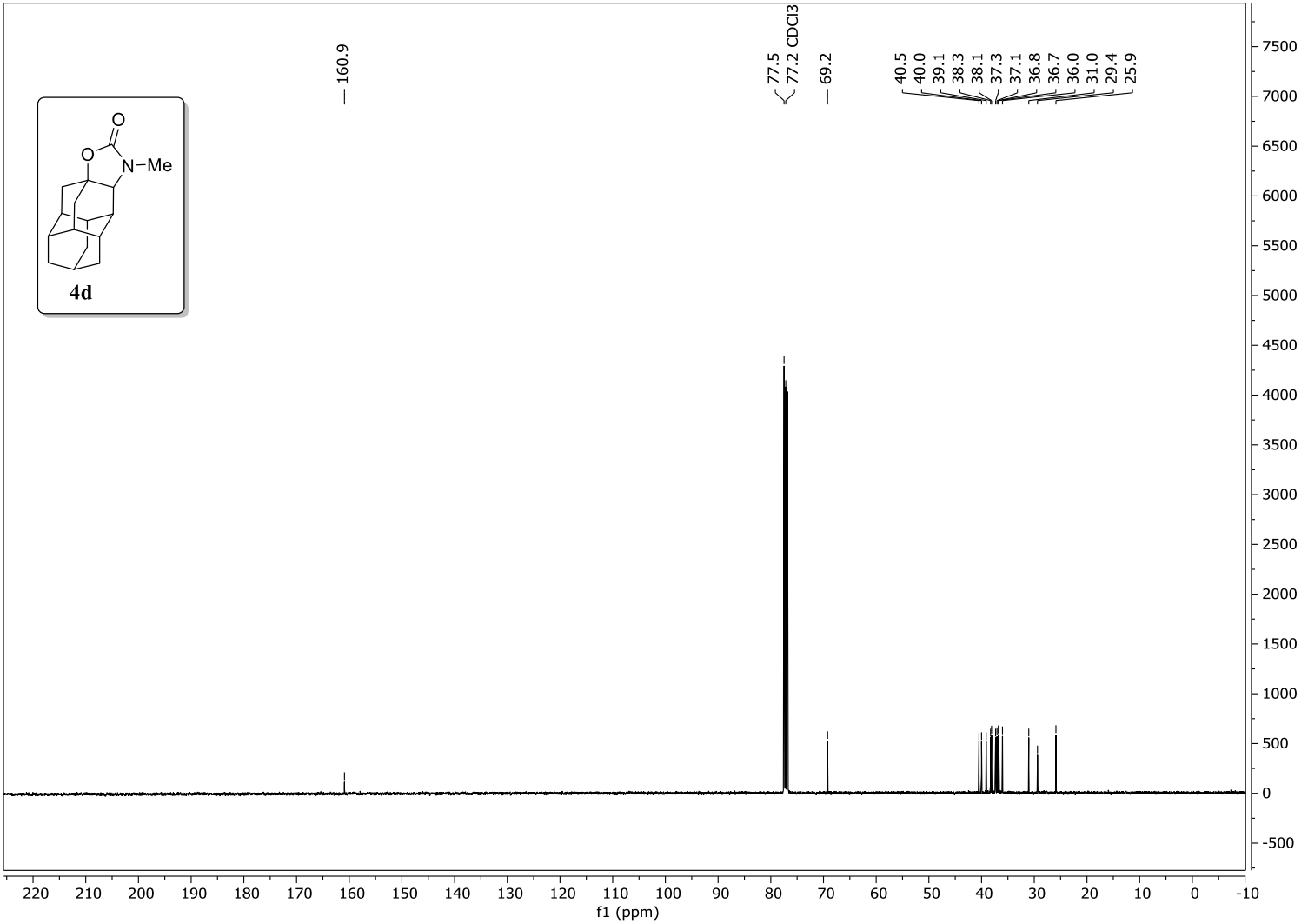
2.2.7 Compound 4c



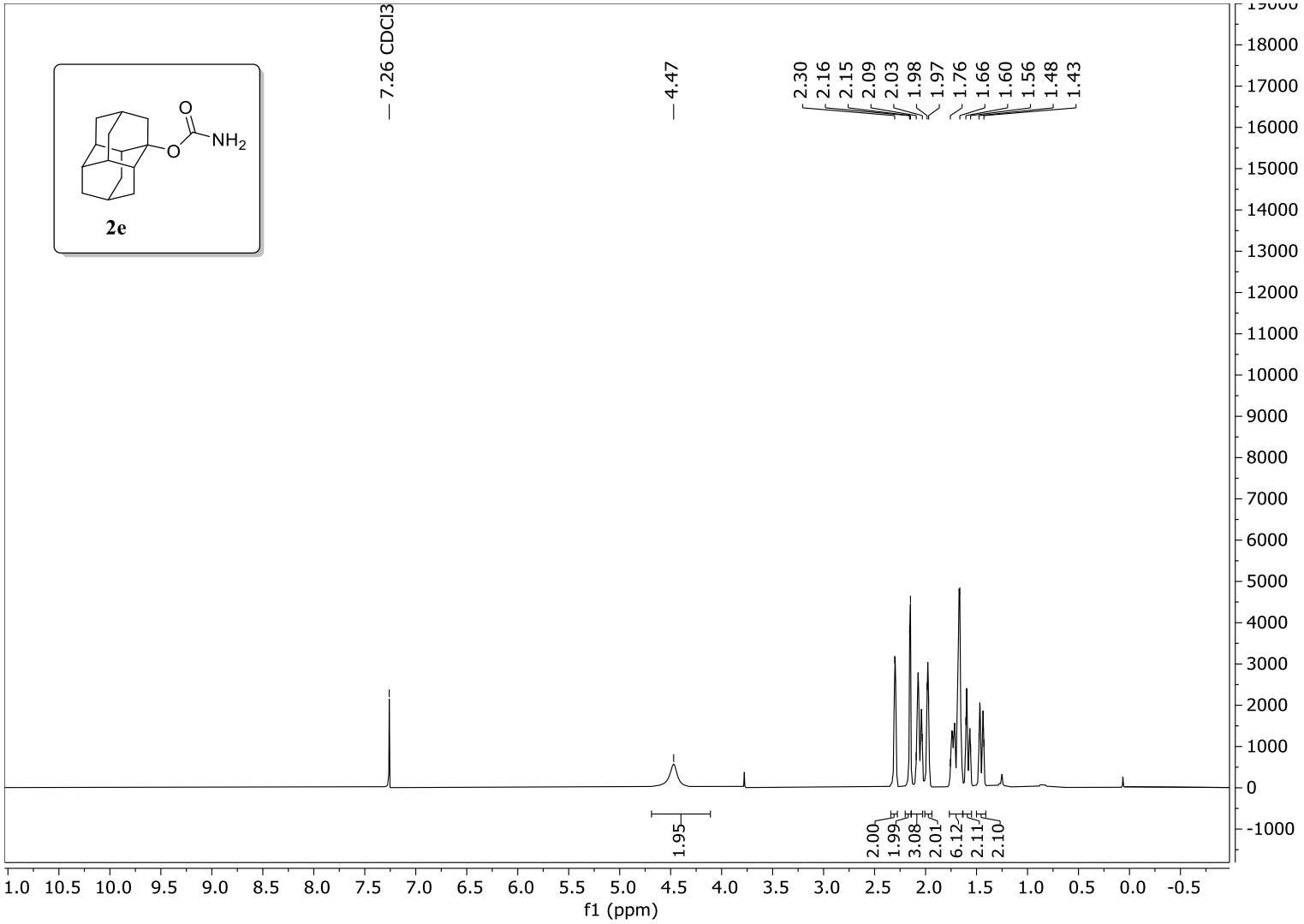

O
O
N–Me
Me
Me
Me
4c
161.2
79.5
77.2 CDCl3
72.1
52.2
50.0
45.1
43.6
43.6
36.1
35.1
32.9
32.6
29.3
29.0
26.5
38000
36000
34000
32000
30000
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
20 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

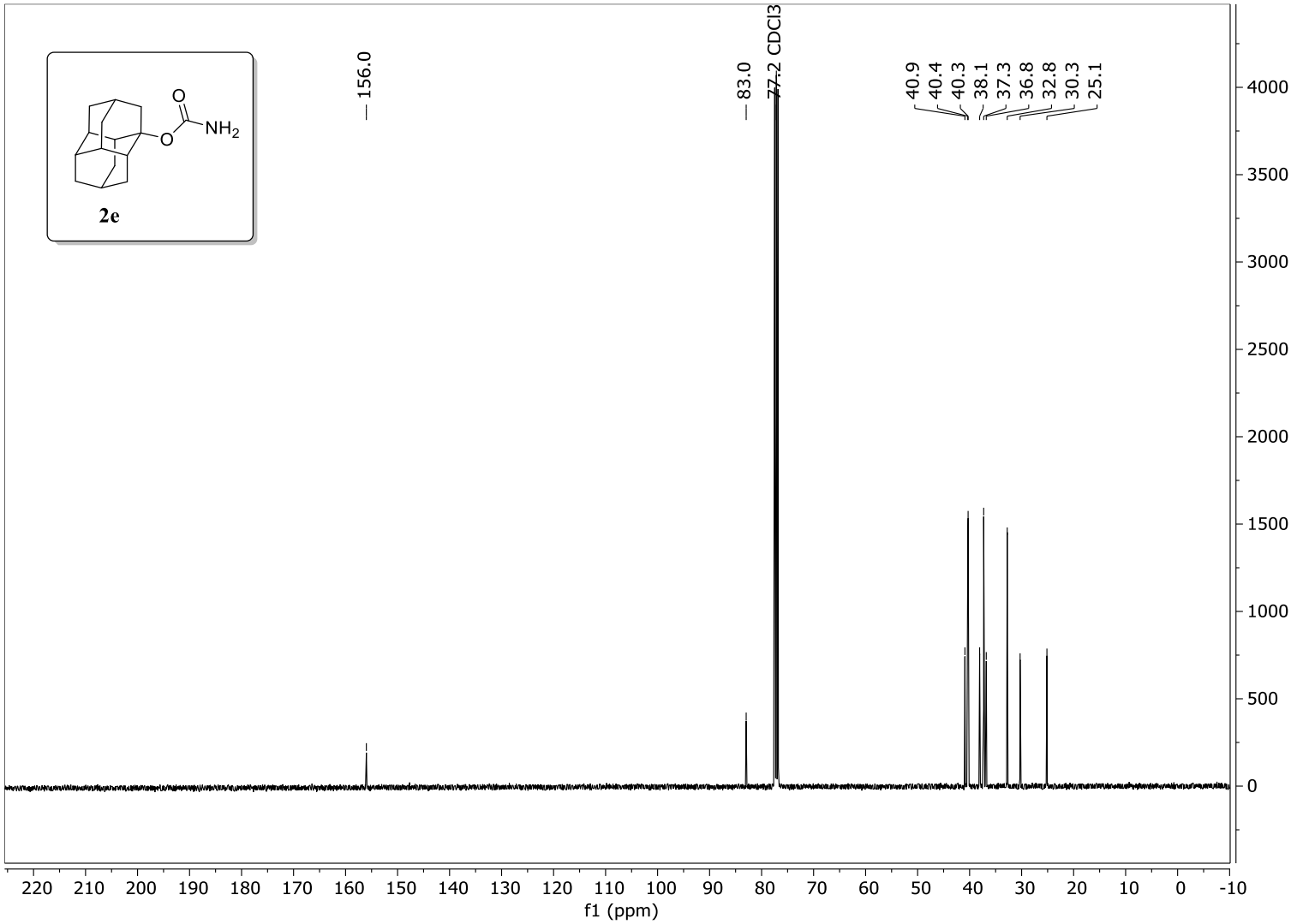
2.2.8 Compound 4d



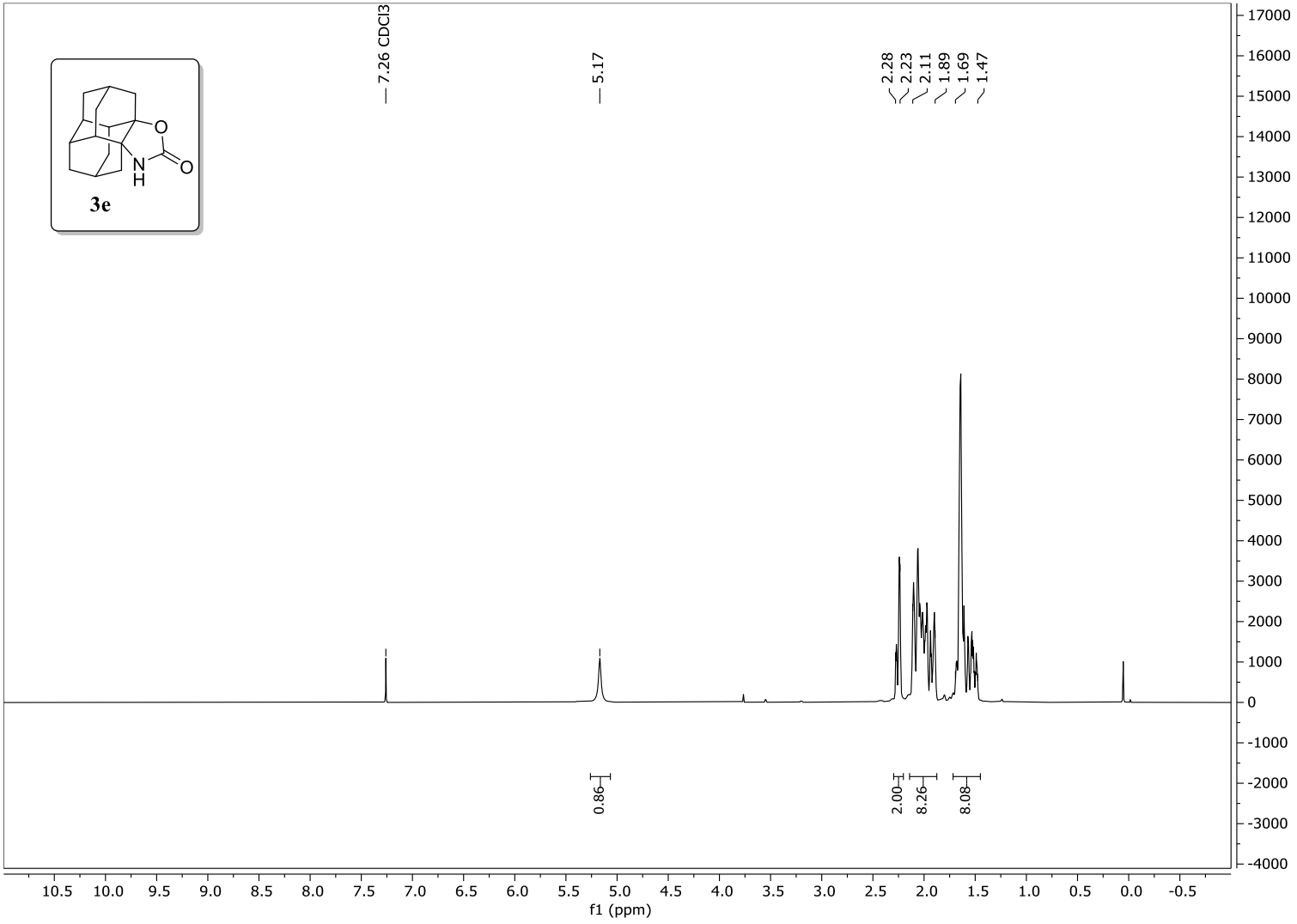

160.9
77.5
77.2 CDCl3
69.2
40.5
40.0
39.1
38.3
38.1
37.3
37.1
36.8
36.7
36.0
31.0
29.4
25.9
O
O
N–Me
4d
f1 (ppm)

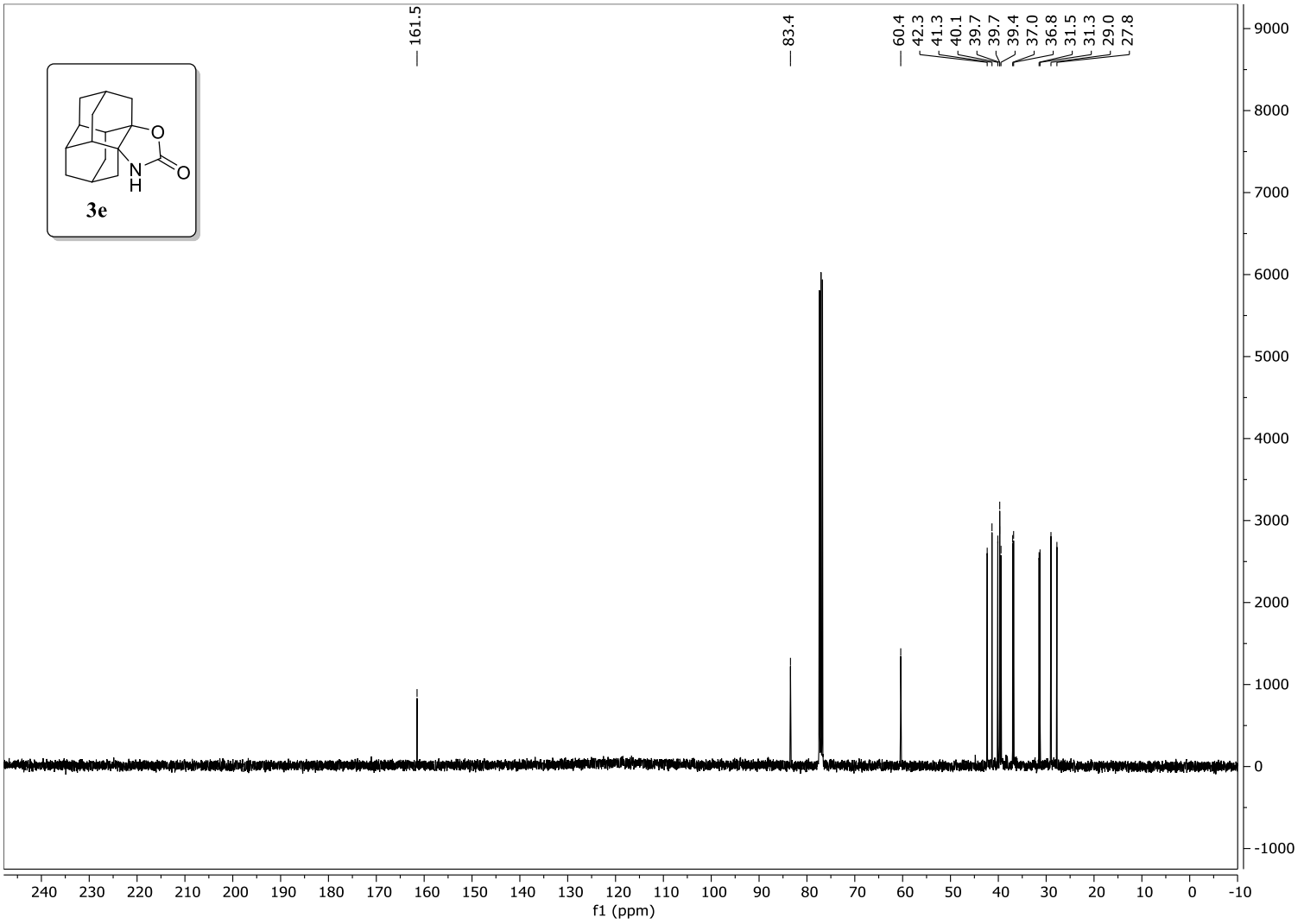
2.2.9 Compound 2e



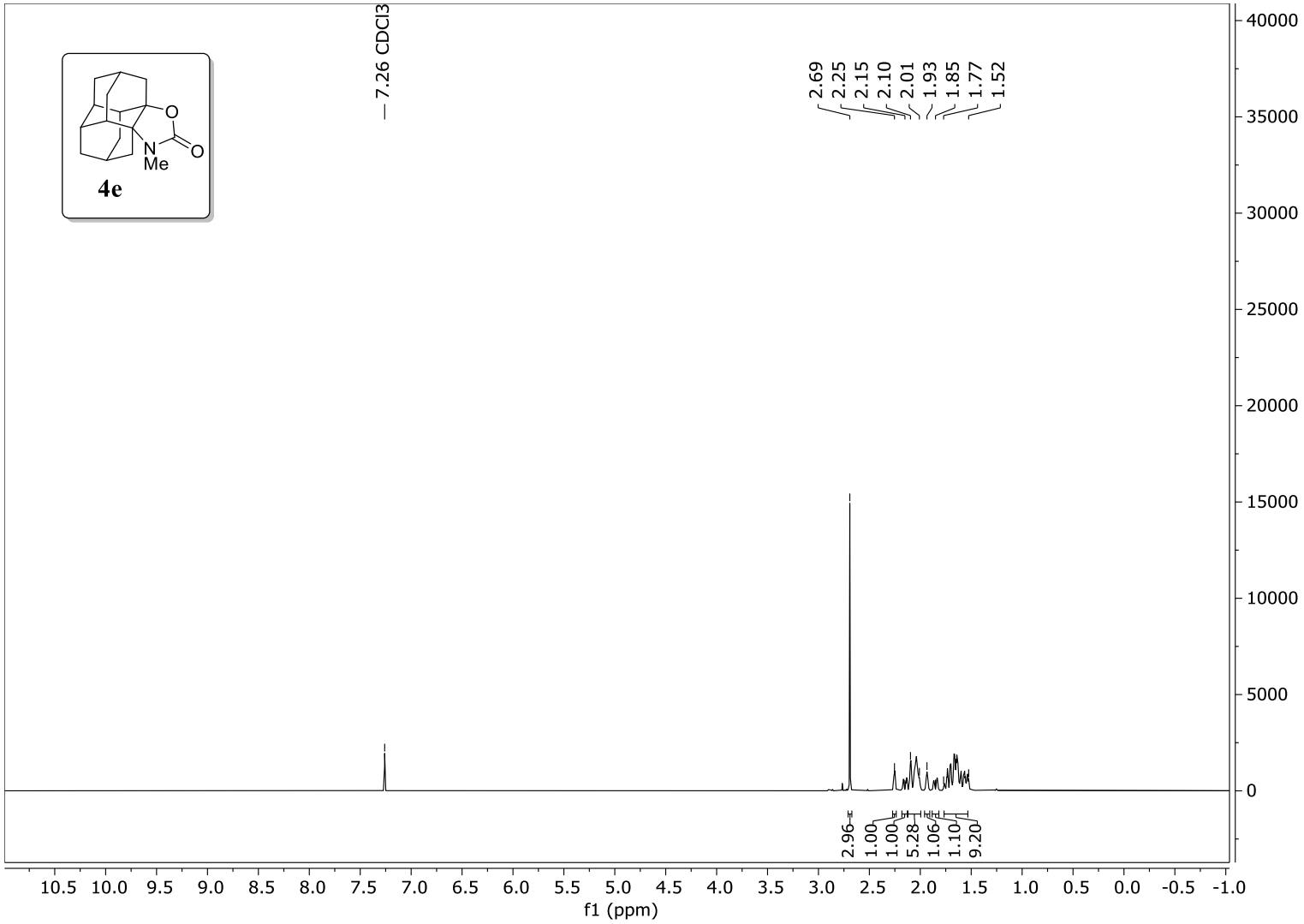

2e
156.0
83.0
77.2 CDCl3
40.9
40.4
40.3
38.1
37.3
36.8
32.8
30.3
25.1
f1 (ppm)

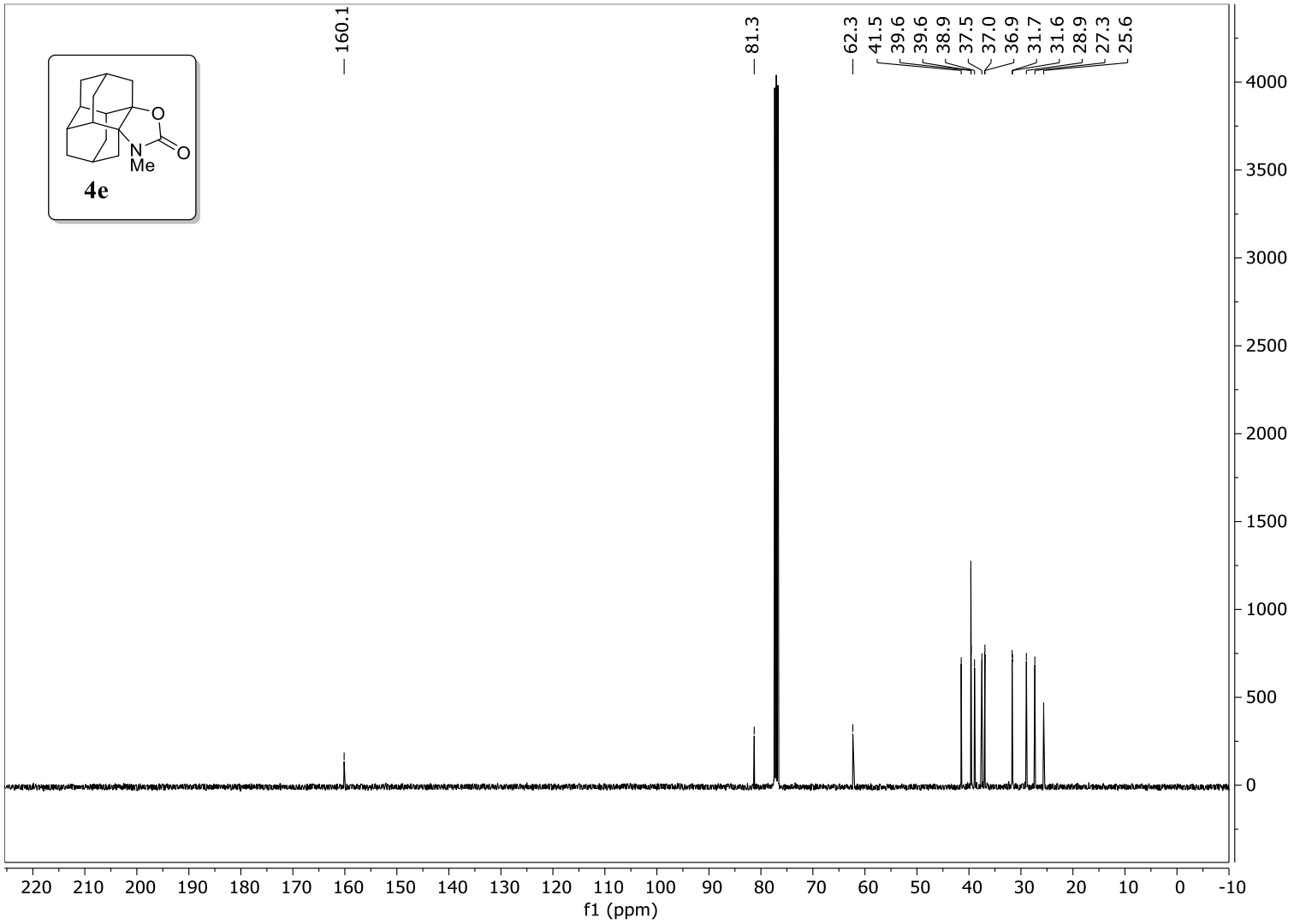
2.2.10 Compound 3e



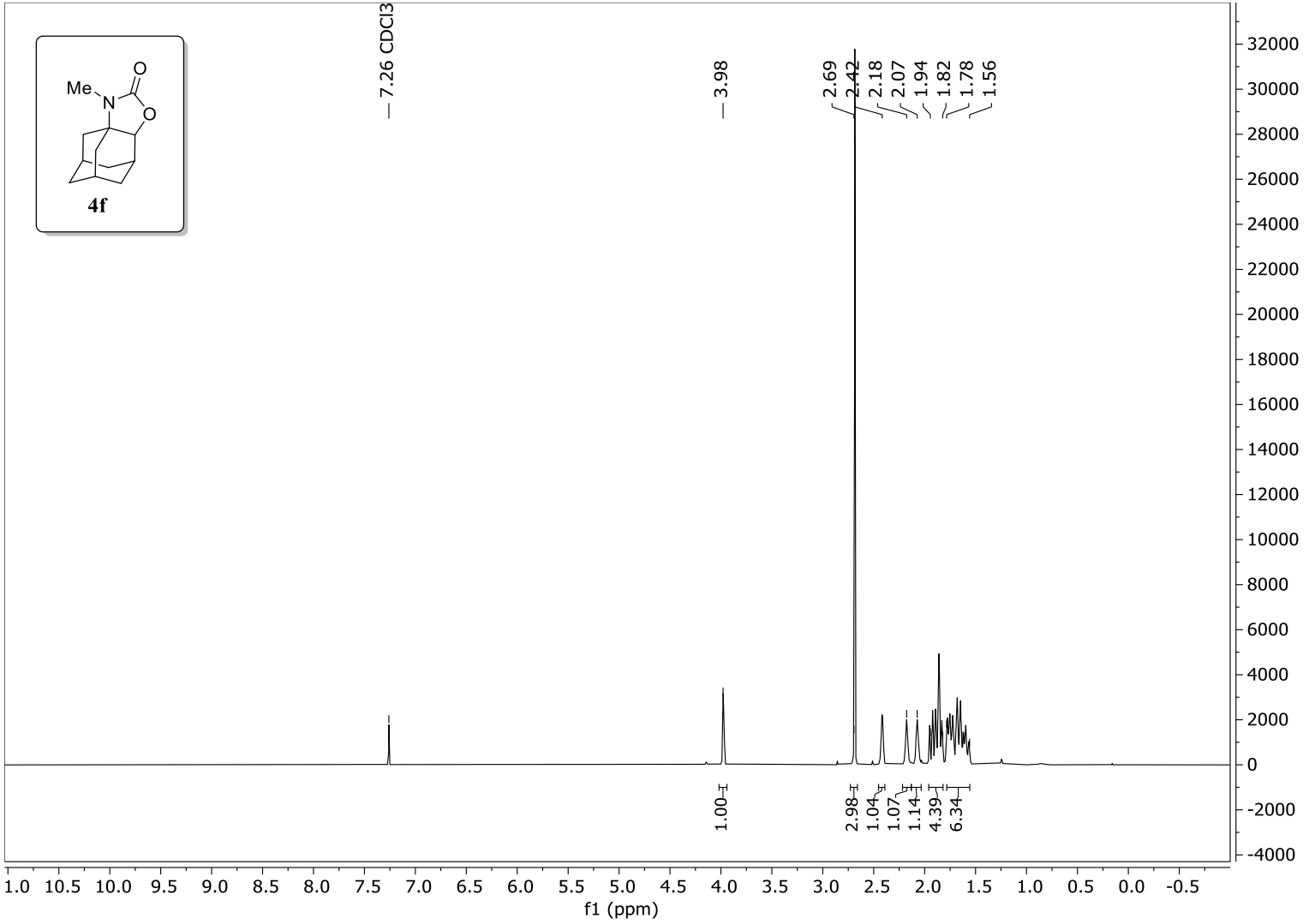

161.5
83.4
60.4
42.3
41.3
40.1
39.7
39.7
39.4
37.0
36.8
31.5
31.3
29.0
27.8
3e
f1 (ppm)

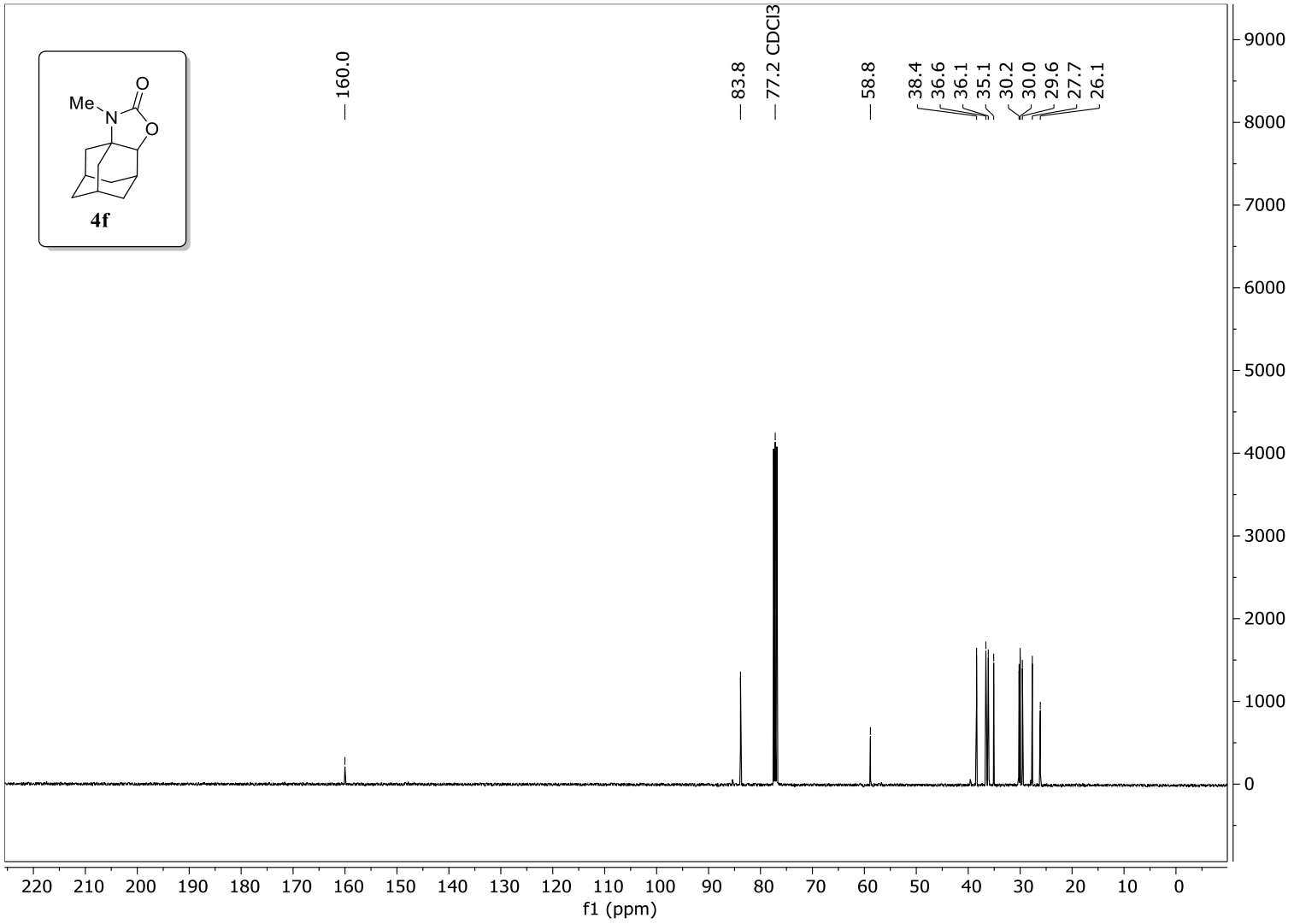
2.2.11 Compound 4e



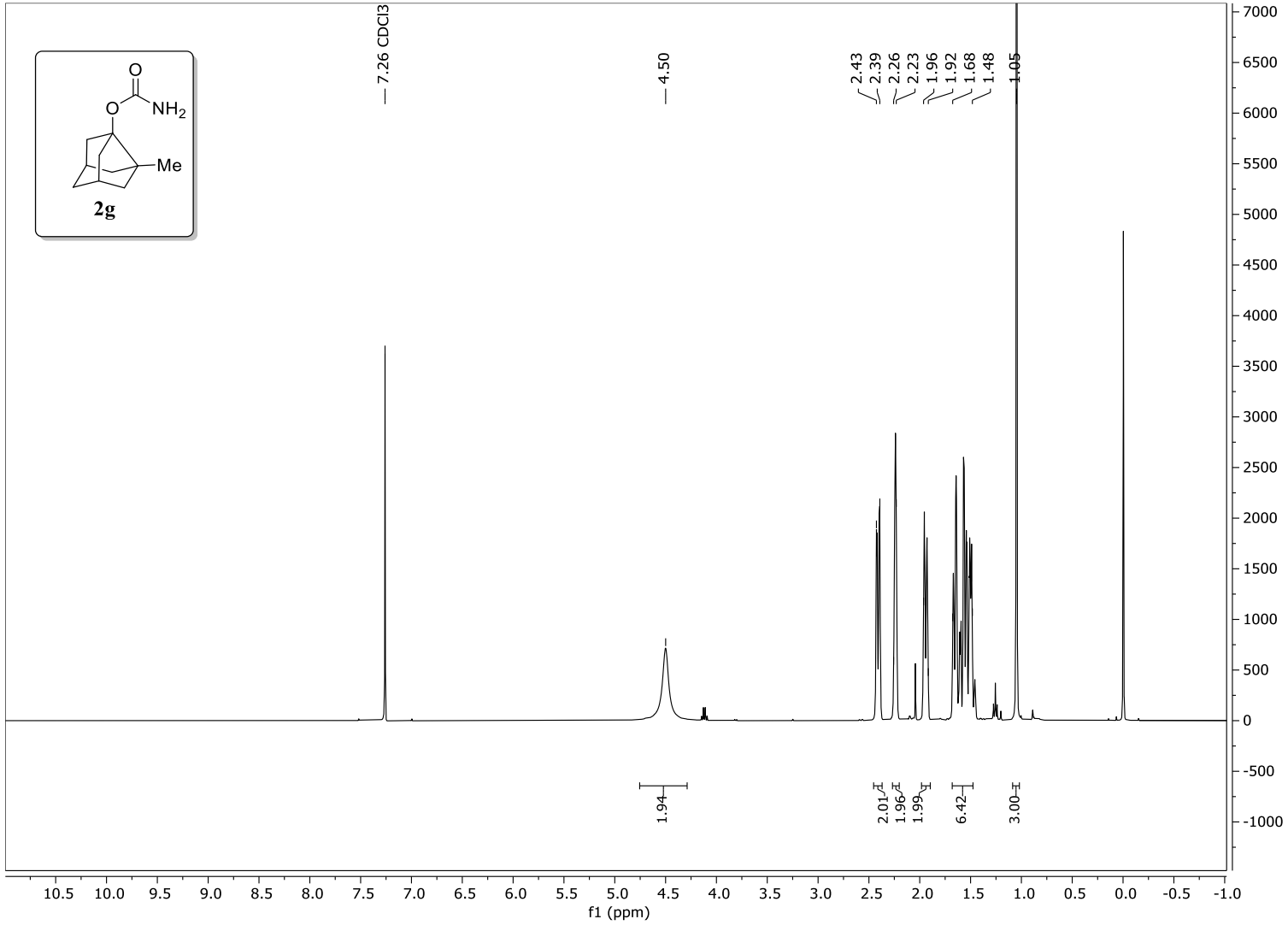

160.1
81.3
62.3
41.5
39.6
39.6
38.9
37.5
37.0
36.9
31.7
31.6
28.9
27.3
25.6
O
N
Me
O
4e
4000
3500
3000
2500
2000
1500
1000
500
0
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

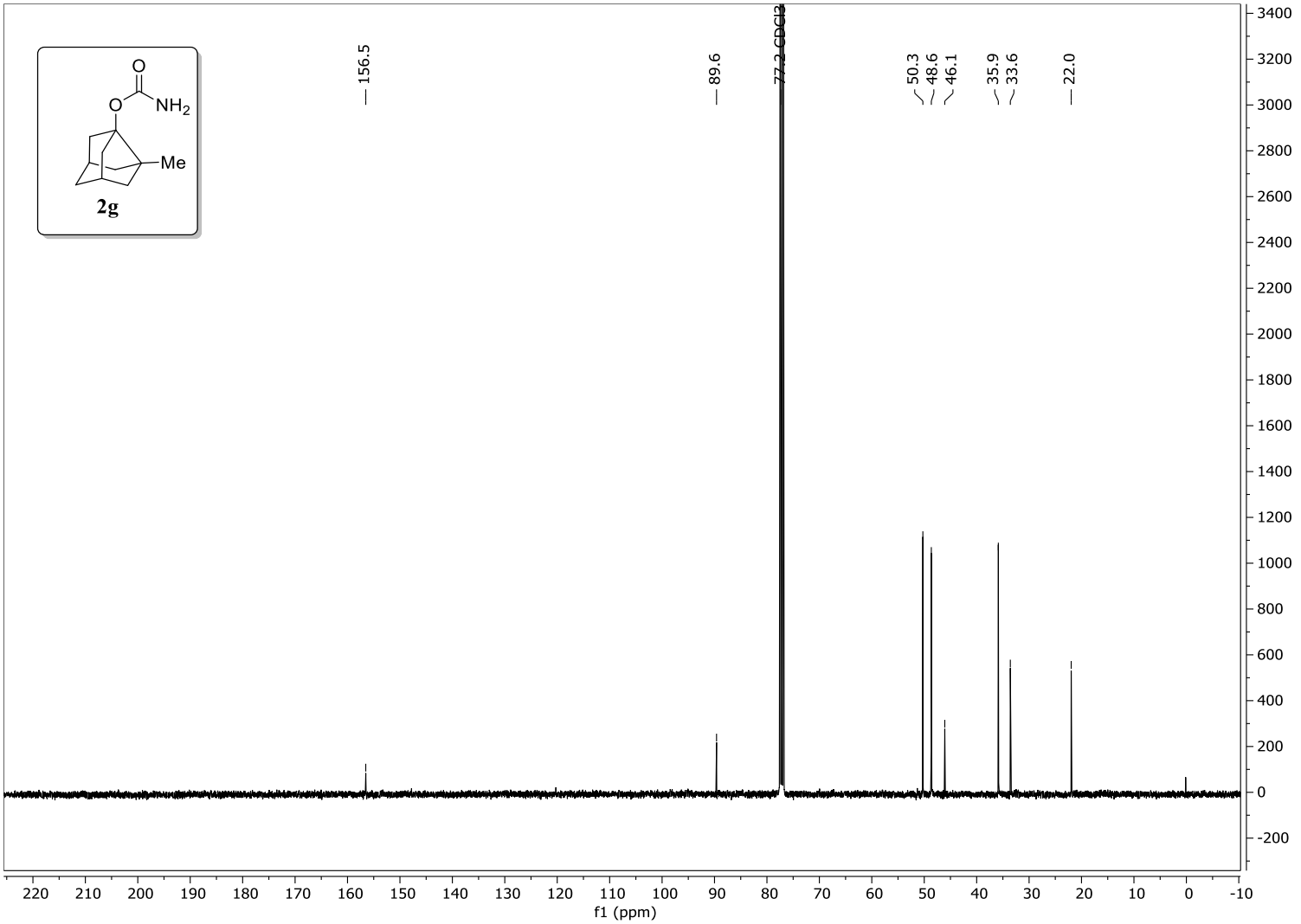
2.2.12 Compound 4f



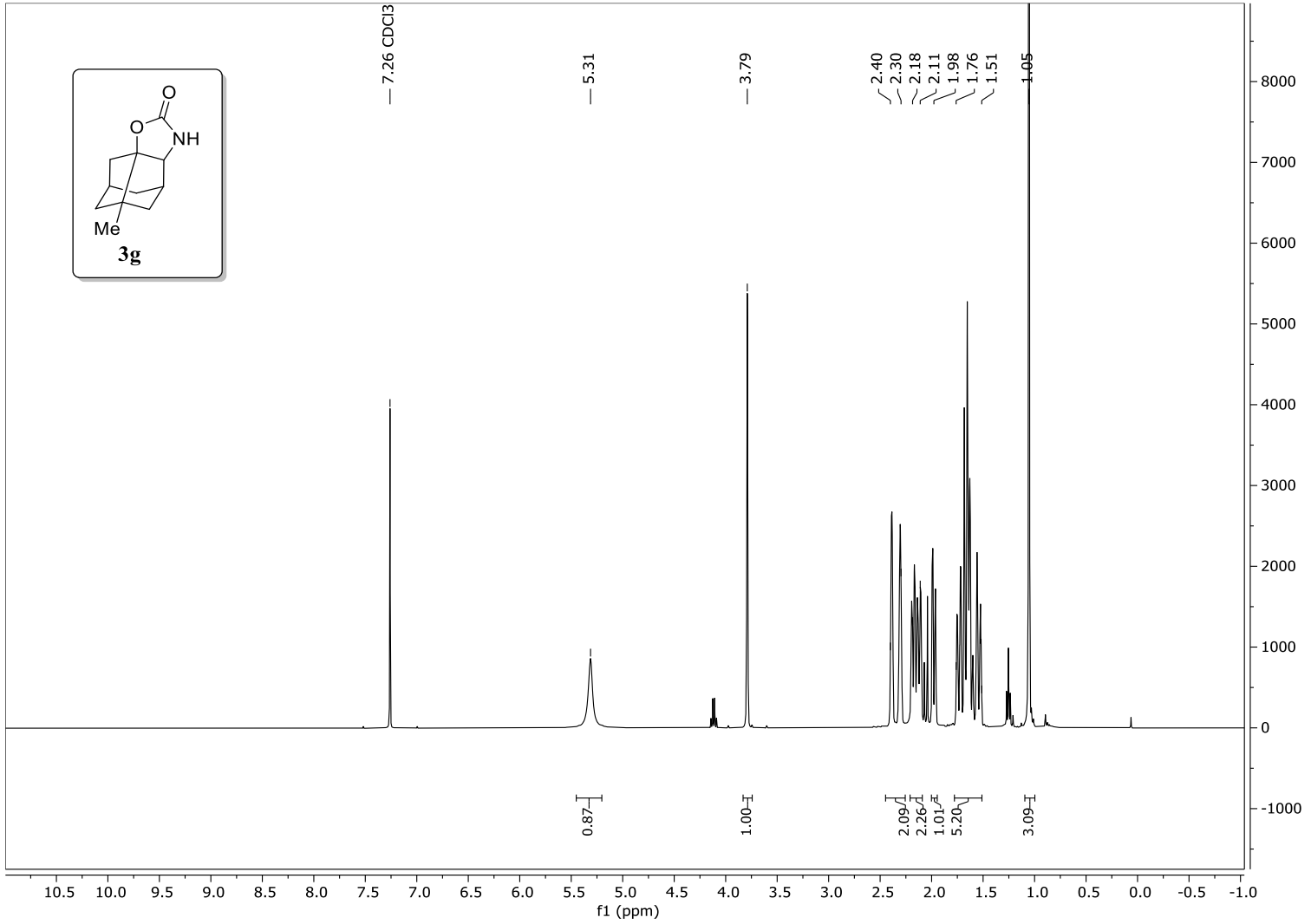

Me
N
O
O
4f
160.0
83.8
77.2 CDCl3
58.8
38.4
36.6
36.1
35.1
30.2
30.0
29.6
27.7
26.1
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

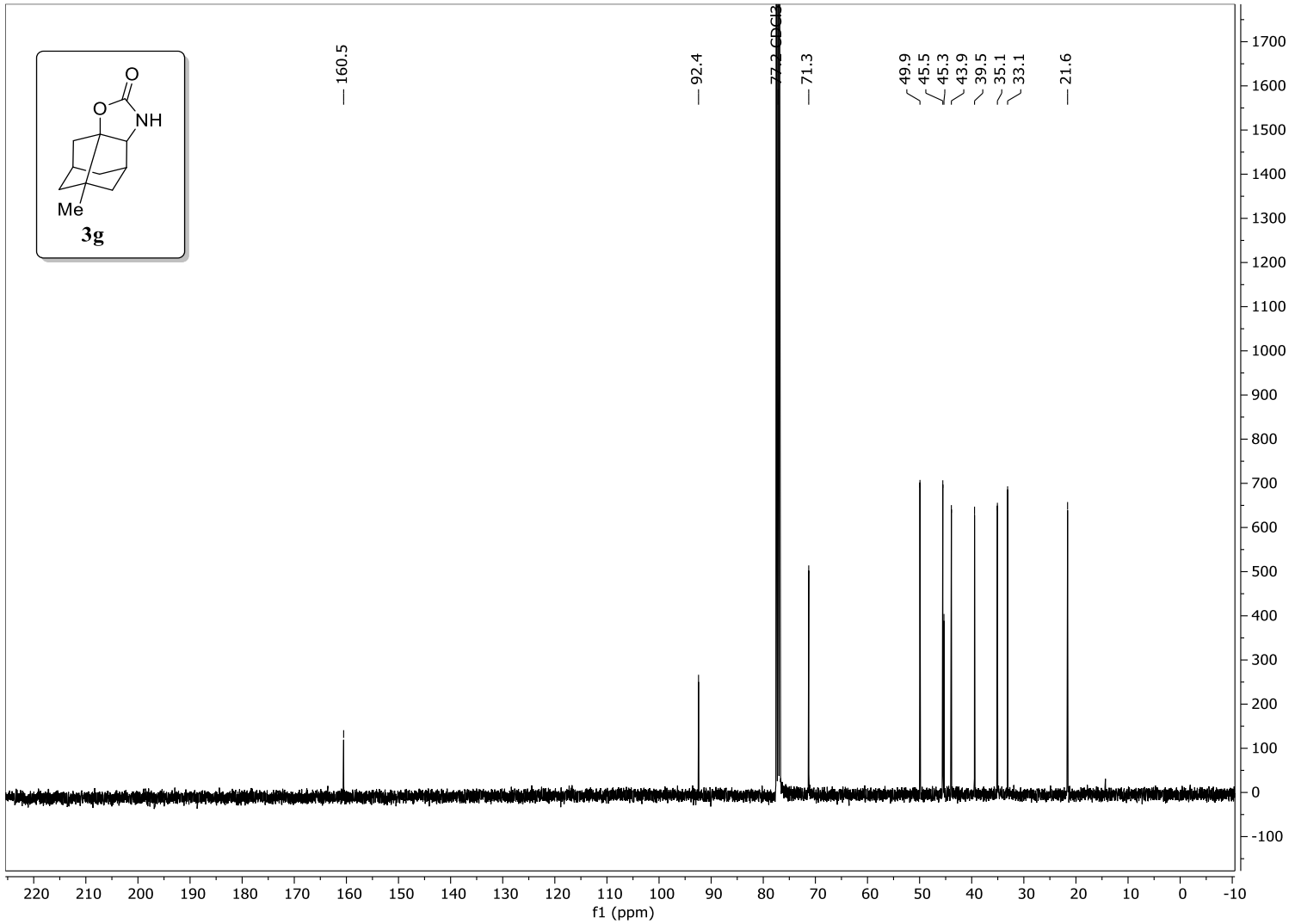
2.2.13 Compound 2g



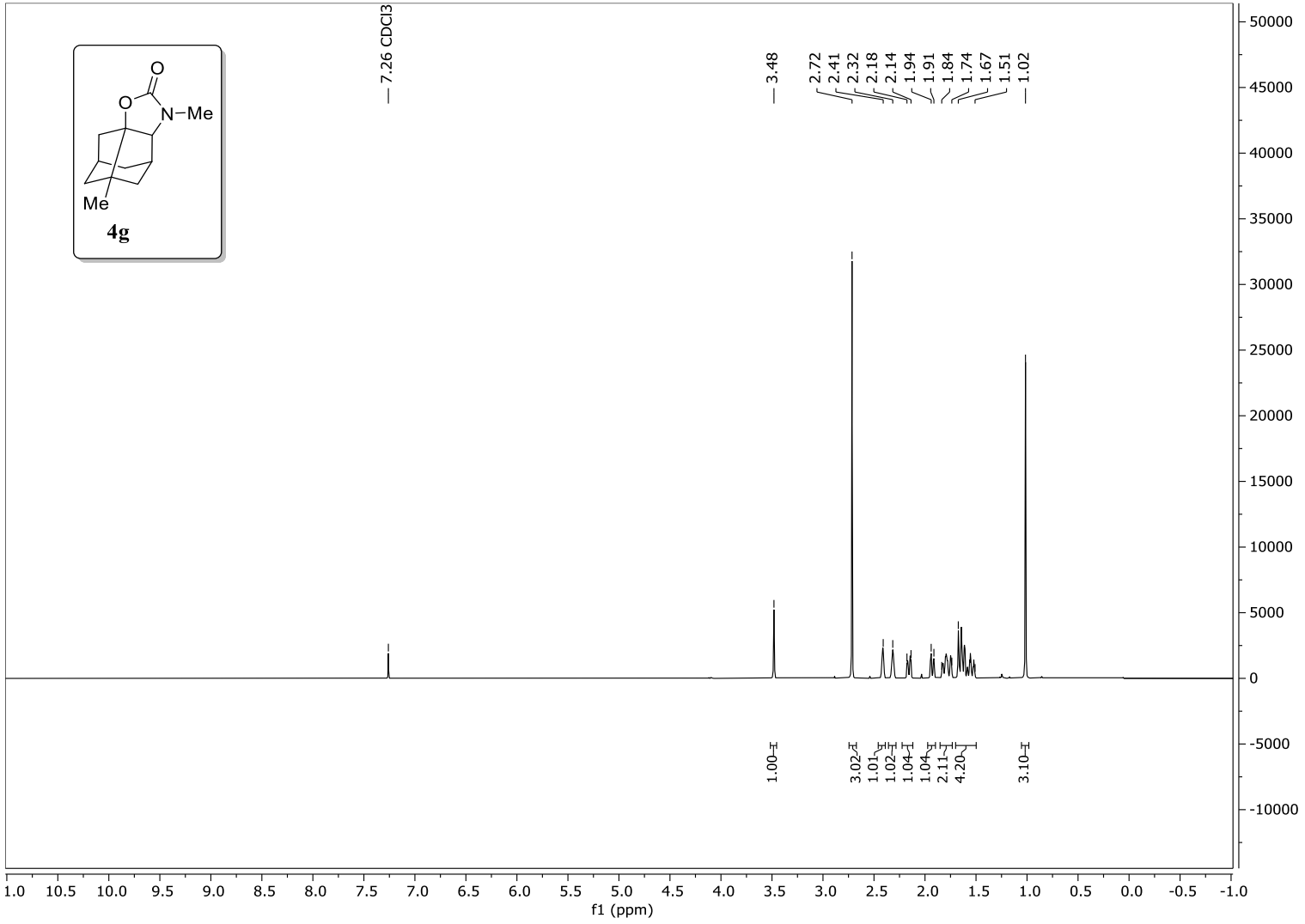

O
O
NH2
Me
2g
156.5
89.6
77.2 CDCl3
50.3
48.6
46.1
35.9
33.6
22.0
f1 (ppm)

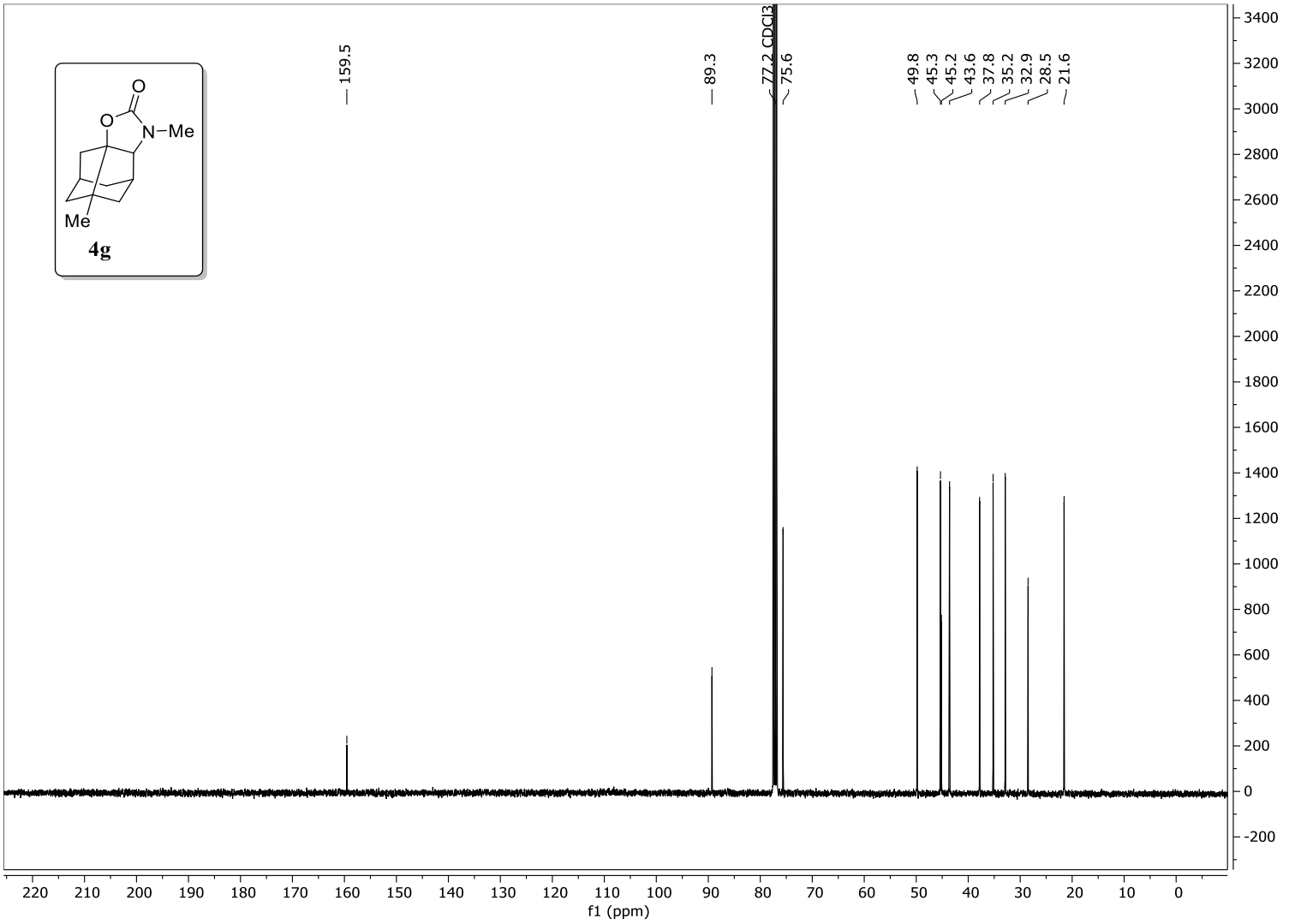
2.2.14 Compound 3g



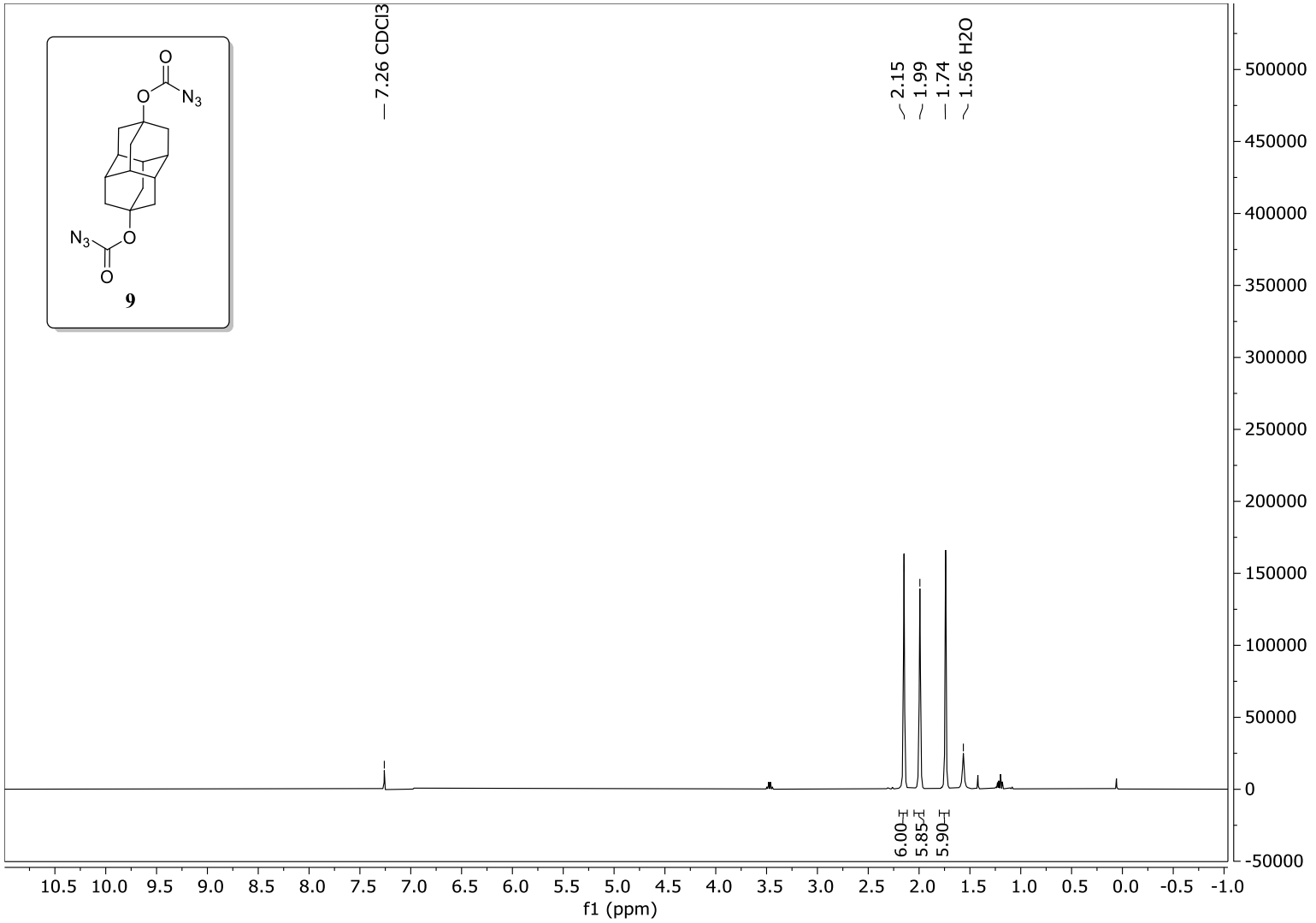

O
O
NH
Me
3g
160.5
92.4
77.3 CDCl3
71.3
49.9
45.5
45.3
43.9
39.5
35.1
33.1
21.6
f1 (ppm)

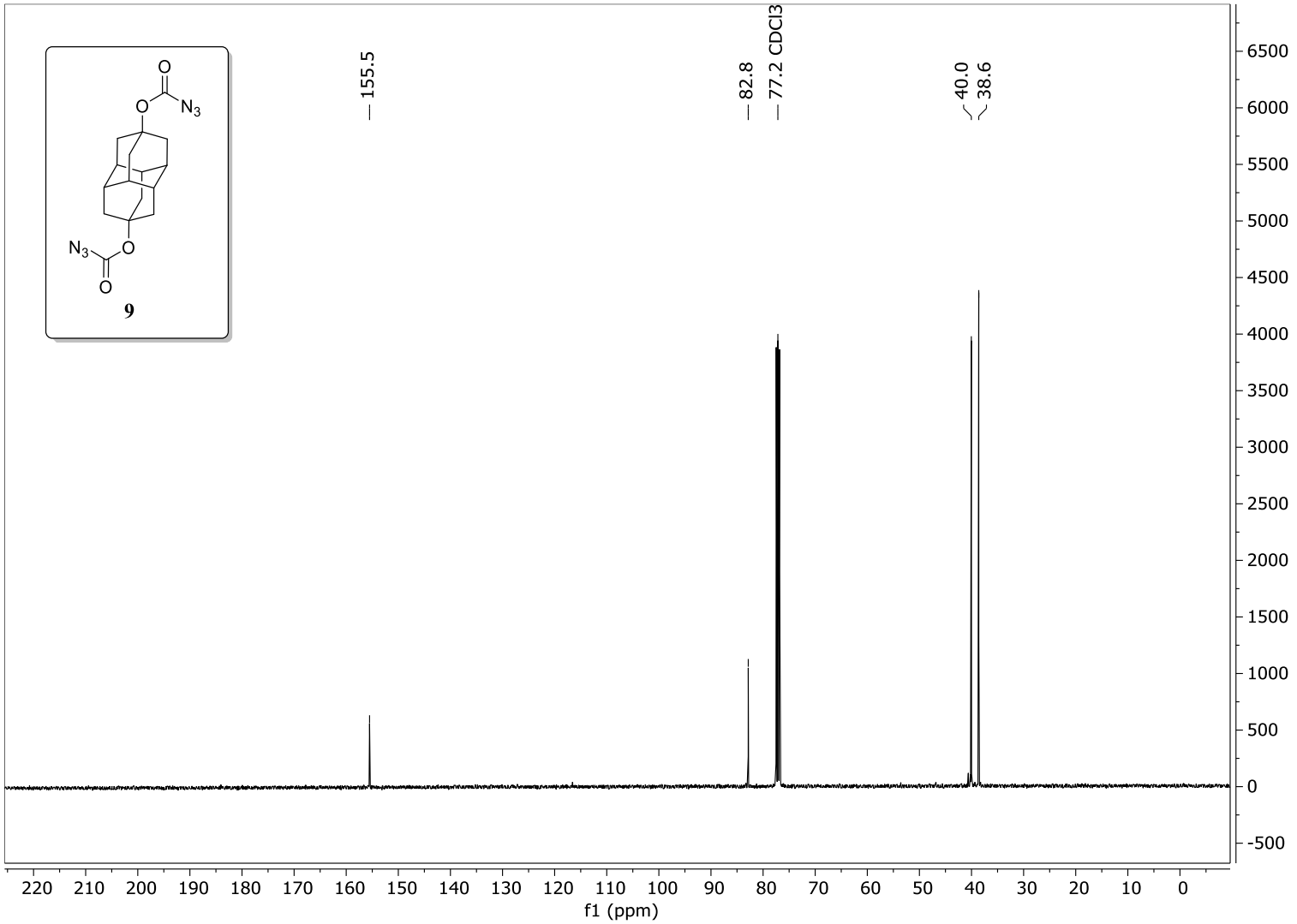
2.2.15 Compound 4g



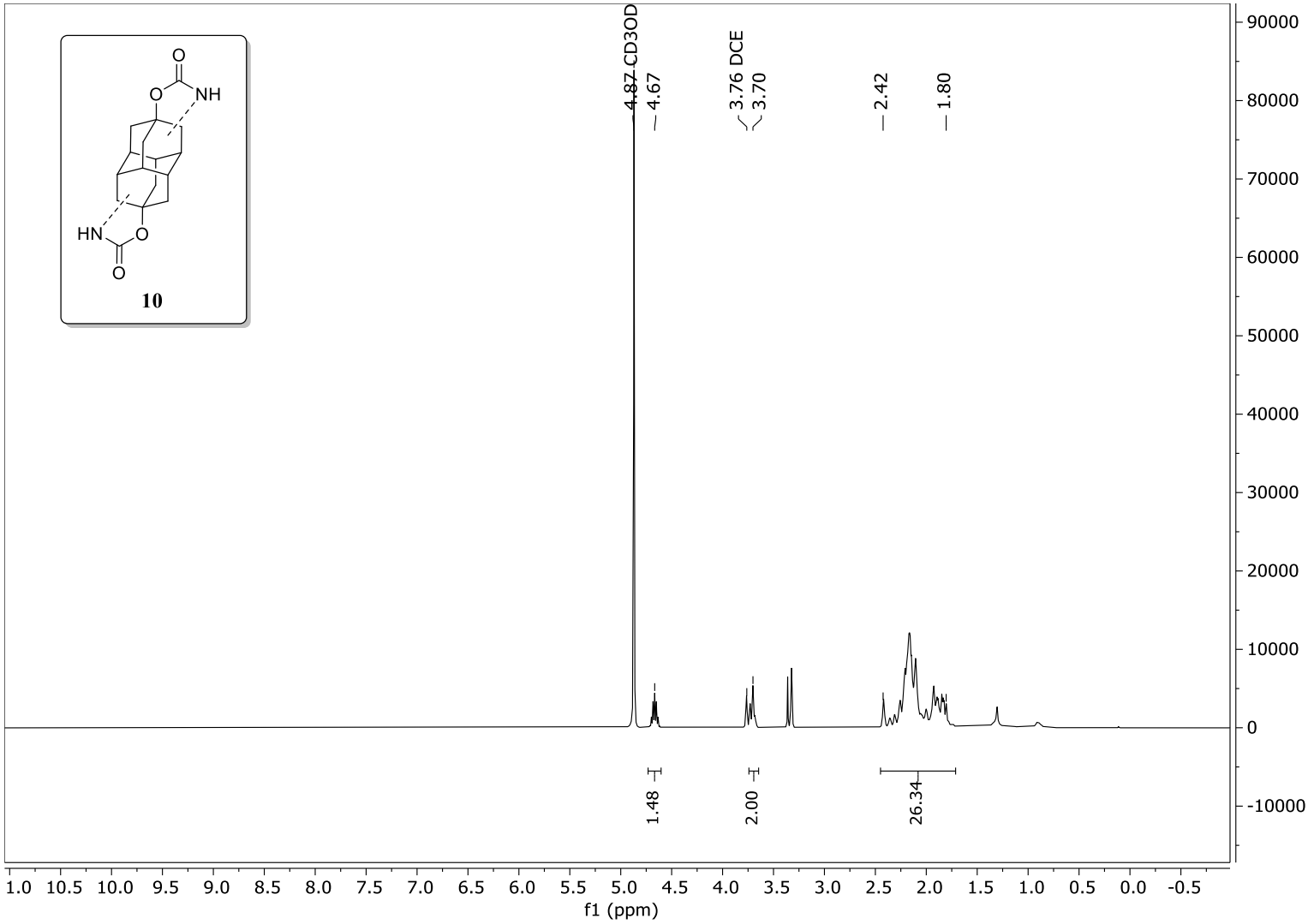

O
O
N–Me
Me
4g
159.5
89.3
77.2 CDCl3
75.6
49.8
45.3
45.2
43.6
37.8
35.2
32.9
28.5
21.6
f1 (ppm)

2.2.16 Compound 9

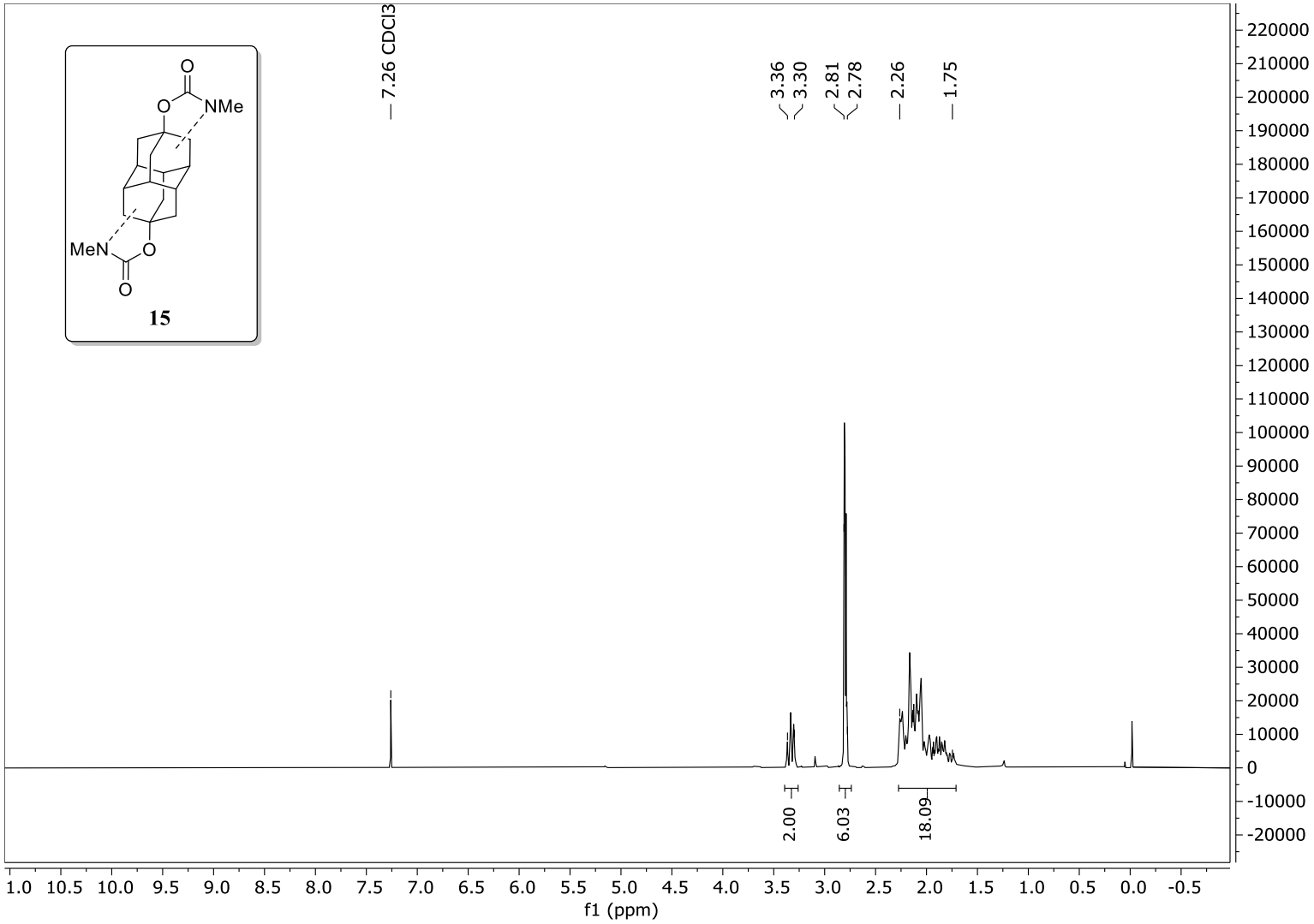


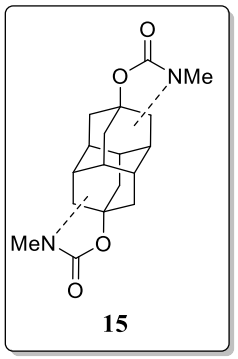

155.5
82.8
77.2 CDCl3
40.0
38.6
9
f1 (ppm)

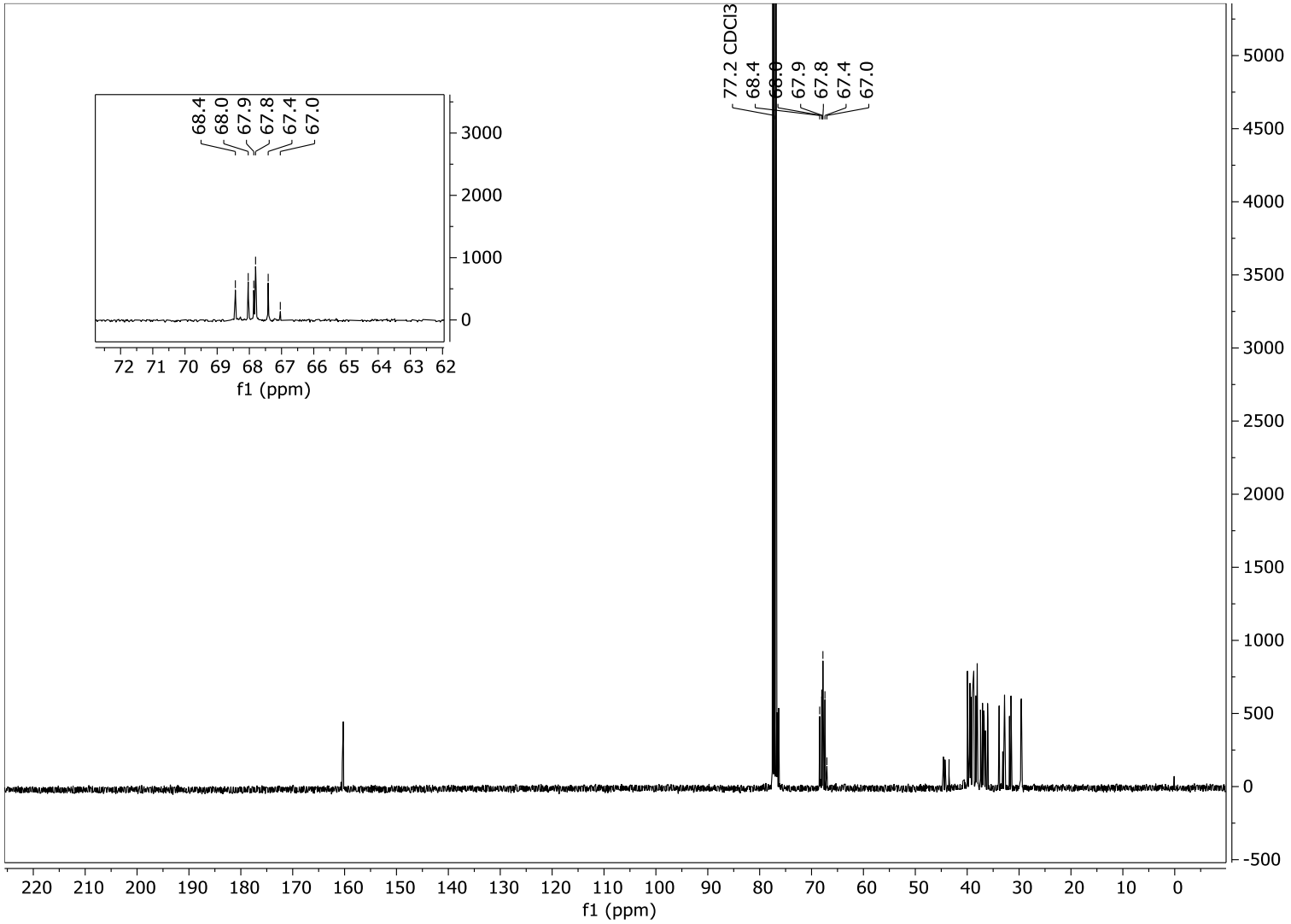
2.2.17 Compound 10



2.2.18 Compound 15




O
O
NMe
MeN
O
O
15


77.2 CDCl3
68.4
68.0
67.9
67.8
67.4
67.0
f1 (ppm)
68.4
68.0
67.9
67.8
67.4
67.0
f1 (ppm)

2.3 Syntheses and description of aldehydes **6a-f** and **11**

2.3.1 Optimization of reaction conditions

Table 1 shows the result of the reaction optimization. Under inert atmosphere, 1.0 equivalent of substrate **3a** or **4a** was dissolved and stated equivalents of corresponding Brønsted acid and or additive were added. The reaction vessel was transferred into a preheated oil bath at the given temperature and stirred for the given time. After cooling down, the reaction mixture was transferred in a round bottom flask with CH_2Cl_2 and evaporated *in vacuo*. The crude residue was analysed *via* ^{1}H NMR analysis.

Table 1. Screening of Brønsted/Lewis acids, additives and reaction conditions

3a: R=H
4a: R=Me

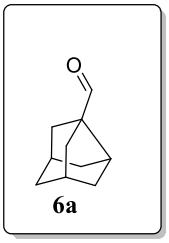
5a

Entry	R	Brønsted acid (equiv.)	Additive (equiv.)	Solvent	Temperature	time	Conversion in %[a]
1	Me	TfOH (2)		CH_2Cl_2	23 °C	17 h	0
2	Me	TfOH (2)		CH_2Cl_2	40 °C	17 h	0
3	Me	TfOH (2)		$C_6H_4Cl_2$	110 °C	17 h	50
4	Me	TfOH (2)		$C_6H_4Cl_2$	140 °C	17 h	91
5	**Me**	**TfOH** (2)		**$C_6H_3Cl_3$**	**140 °C**	**3 h**	**93**
6	Me	TfOH (2)		$C_6H_3Cl_3$	120 °C	3 h	30
7	**Me**	**TfOH** (2)		**$C_6H_3Cl_3$**	**120 °C**	**17 h**	**92**
8	Me	*p*-TsOH (2)		$C_6H_4Cl_2$	140 °C	17 h	0
9	Me	TFA (2)		$C_6H_4Cl_2$	140 °C	17 h	0
10	Me	TfOH (2)		$CH_3CON(CH_3)_2$	140 °C	17 h	0
11	Me	TfOH (1.2)		$C_6H_3Cl_3$	120 °C	17 h	25
12	Me	TfOH (1)	$Al(OTf)_3$ (1)	$C_6H_3Cl_3$	120 °C	17 h	30
13	Me		$Al(OTf)_3$ (2)	$C_6H_3Cl_3$	140 °C	17 h	*n.d.*
14	H	TfOH (2)		$C_6H_3Cl_3$	120 °C	17 h	*n.d.*

2.3.2 General procedure D: Acidic Rearrangement and Hydrolysis

Under inert atmosphere, corresponding *N*-methyl carbamate (1.0 eq.) is dissolved in dry 1,2,4-trichlorobenzene (2.5 mL/ mmol) and treated with triflic acid (2.0 eq.). The reaction mixture is heated to the specified temperature and heated for the given time. After the reaction vessel is cooled to room temperature the solvent is evaporated from CH_2Cl_2, EtOAc and n-hexane *in vacuo* to remove as much of the high-boiling solvent as possible. For hydrolysis, the residue is dissolved in EtOAc (15mL/mmol; degassed), treated with NaOH (2M, *aq*., 15mL/mmol; degassed) and stirred at room temperature overnight in the dark. The two phases are separated, the aqueous phase is extracted with EtOAc, the combined organic phases are washed with water and brine, dried over Na_2SO_4 (anhydrous), filtered and the solvent is evaporated *in vacuo*. If necessary, the crude mixture is purified by silica filtration in 1-5% EtOAc in hexanes.

2.3.3 Compound 6a

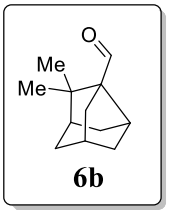


Compound **6a** was synthesized rom compound **4a** according to *general procedure D* (140 °C, 3h) to give the desired product as an off-white solid in a yield of 90% (130 mg, 0.9 mmol).

^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 1.58-1.71 (m, 8H), 1.98-2.04 (m, 2H), 2.33-2.35 (m, 2H), 2.57 (m, 1H), 9.72 (s, 1H).

Spectrum in accordance with literature: B. Zonker, E. Duman, H. Hausmann, J. Becker, R. Hrdina., *Org Biomol. Chem.*, 2020, **18**, 4941-4945.

2.3.4 Compound 6b



Compound **6b** was synthesized from compound **4b** according to *general procedure D* (120 °C, 18h) to give a white solid in a yield of 50% (45 mg, 0.3 mmol).

R_f (silica gel; EtOAc:*n*-hexane 4:96): 0.4.

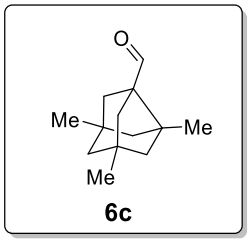
^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 1.04 (s, 3H), 1.19 (s, 3H), 1.41-1.50 (m, 3H), 1.66 (m, 3H), 1.89 (m, 1H), 2.15-2.26 (m, 3H), 2.75 (m, 1H), 9.84 (s, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ/ppm = 22.7 (CH_3), 27.2 (CH_3), 32.1 (CH_2), 36.2 (CH), 37.0 (CH_2), 40.2 (CH_2), 40.2 (CH), 44.4 (CH_2), 47.5 (C), 47.7 (CH), 65.3 (C), 206.1 (CH).

IR (neat): $\tilde{\nu}$ /cm^{-1} = 2920, 2871, 1687, 1551, 1456, 1409, 1385, 1366, 1294, 1255, 1233, 1204, 1179 1140, 1088, 1067, 1042, 943, 846, 815, 744, 569, 514, 454.

HRMS: m/z = 177.1282 ([M-H]$^-$; calculated for $C_{12}H_{17}O^-$ m/z = 177.1285).

2.3.5 Compound 6c



6c

Compound **6c** was synthesized from compound **4c** according to *general procedure D* (120 °C, 20h) to give an off-white solid in a yield of 77% (101 mg, 0.5 mmol).

R_f (silica gel; EtOAc:*n*-hexane 4:96): 0.4.

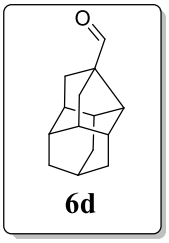
^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 1.02 (s, 6H), 1.08 (s, 3H), 1.19-1.24 (m, 2H), 1.34-1.38 (m, 2H), 1.40 (m, 2H), 1.44-1.47 (m, 2H), 1.96-1.99 (m, 2H), 9.63(s, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ/ppm = 22.8 (CH_3), 24.5 ($2CH_3$), 41.1 (2C), 48.9 (CH_2), 49.5 ($2CH_2$), 52.9 (C), 57.0 ($2CH_2$), 62.2 (C), 206.9 (CH).

IR (neat): $\tilde{\nu}$ /cm^{-1} = 2947, 2924, 2865, 1798, 1714, 1457, 1376, 1329, 1278, 1231, 1206, 1173, 1146, 1067, 1026, 991, 970, 732, 635, 527.

HRMS: m/z = 193.1589 ($[M+H]^+$; calculated for $C13H_{21}O^+$ m/z = 193.1587).

2.3.6 Compound 6d



6d

Compound **6d** was synthesized from compound **4d** according to *general procedure D* (140 °C, 3h) to give a white solid in a yield of 52% (81 mg, 0.4 mmol).

R_f (silica gel; EtOAc:*n*-hexane 1:9): 0.2.

m.p. (cryst. from $CDCl_3$): 165.0-166.0 °C.

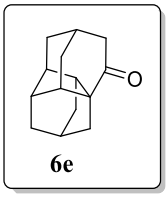
^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 1.57-1.60 (m, 2H), 1.72 (m, 2H), 1.80-1.84 (m, 4H), 1.90-1.93 (m, 4H), 1.98-2.02 (m, 2H), 2.07 (m, 2H), 2.39 (m, 1H), 9.73 (s, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ/ppm = 25.0 (CH), 33.8 ($2CH_2$), 35.1 (CH_2), 36.1 (CH), 42.3 (2CH), 42.8 ($2CH_2$), 45.8 (2CH), 46.0 (CH), 62.6 (C), 205.6 (CH).

IR (neat): $\tilde{\nu}$ /cm^{-1} = 293, 2848, 2690, 1804, 1722, 1686, 1470, 1460, 1441, 1418, 1320, 1287, 1261, 1186, 1171, 1075, 1053, 1029, 996, 950, 933, 844, 820, 804, 752, 737, 634, 565, 533, 490, 448.

HRMS: m/z = 201.1287 ([M-H]$^-$; calculated for $C_{14}H_{17}^-$ m/z = 201.1285).

2.3.7 Compound 6e



Compound **6e** was synthesized from compound **4e** according to *general procedure D* (120 °C, 21h) to give a white solid in a yield of 60% (70 mg, 0.4 mmol).

R_f (silica gel; EtOAc:*n*-hexane 1:9): 0.2.

m.p. (cryst. from Et_2O): 124.8-125.6 °C

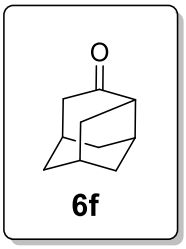
^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 1.44 (m, 1H), 1.51-1.66 (m, 6H), 1.70-1.80 (m, 1H), 2.00 (m, 1H), 2.08-2.10 (m, 2H), 2.20 (m, 1H), 2.26-2.33 (m, 3H), 2.42 (m, 1H), 2.56 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ/ppm = 30.4 (CH), 33.9 (CH_2), 37.0 (CH_2), 37.1 (CH), 37.9 (CH_2), 40.9 ($2CH_2$), 45.9 (CH_2), 47.6 (CH), 50.3 (CH), 53.0 (CH), 53.8 (CH), 62.3 (C), 214.6 (C).

IR (neat): $\tilde{\nu}$ /cm^{-1} = 2904, 2858, 1706, 1438, 1407, 1333, 1310, 1282, 1248, 1226, 1173, 1117, 1056, 1028, 1011, 982, 945, 921, 877, 836, 788, 772, 746, 696, 654, 600, 493, 475, 458.

HRMS: m/z = 225.1253 ([M+Na]$^+$; calculated for $C_{14}H_{18}ONa^+$ m/z = 225.1250).

2.3.8 Compound 6f

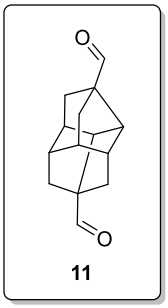


Compound **6f** was synthesized from compound **4f** according to *general procedure D* (120 °C, 19h) to give a white solid in a yield of 70% (71 mg, 0.5 mmol).

^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 1.53 (m, 1H), 1.61-1.81 (m, 5H), 1.91-1.98 (m, 2H), 2.23-2.32 (m, 2H), 2.41 (m, 1H), 2.51-2.63 (m, 2H), 2.73 (m, 1H).

Spectrum in accordance with literature: Z. Majerski, Z.Hamersak, *Org. Synth.* 1979, **59**, 147-153.

2.3.9 Compound 11



Compound **11** was synthesized from compound **15** according to *general procedure D* (4. eq. TfOH, 160 °C, 48h) to give a white solid in a yield of 10% (21 mg, 0.1 mmol) as a racemic isomer. Formation of the second achiral isomer was not detected.

R_f (silica gel; EtOAc:n-hexane 1:1) 0.4.

^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 1.59-1.61 (m, 2H), 1.92-1.95 (m, 2H), 2.07-2.12 (m, 2H), 2.18-2.22 (m, 4H), 2.46-2.48 (m, 2H), 2.75-2.79 (m, 2H), 9.71 (s, 2H).

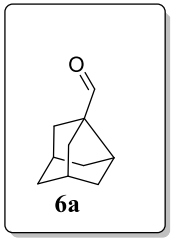
^{13}C NMR (101 MHz, $CDCl_3$): δ/ppm = 40.3 ($2CH_2$), 41.9 ($2CH_2$), 43.0 (2CH), 51.4 (2CH), 55.7 (2CH), 59.4 (C), 203.9 (C).

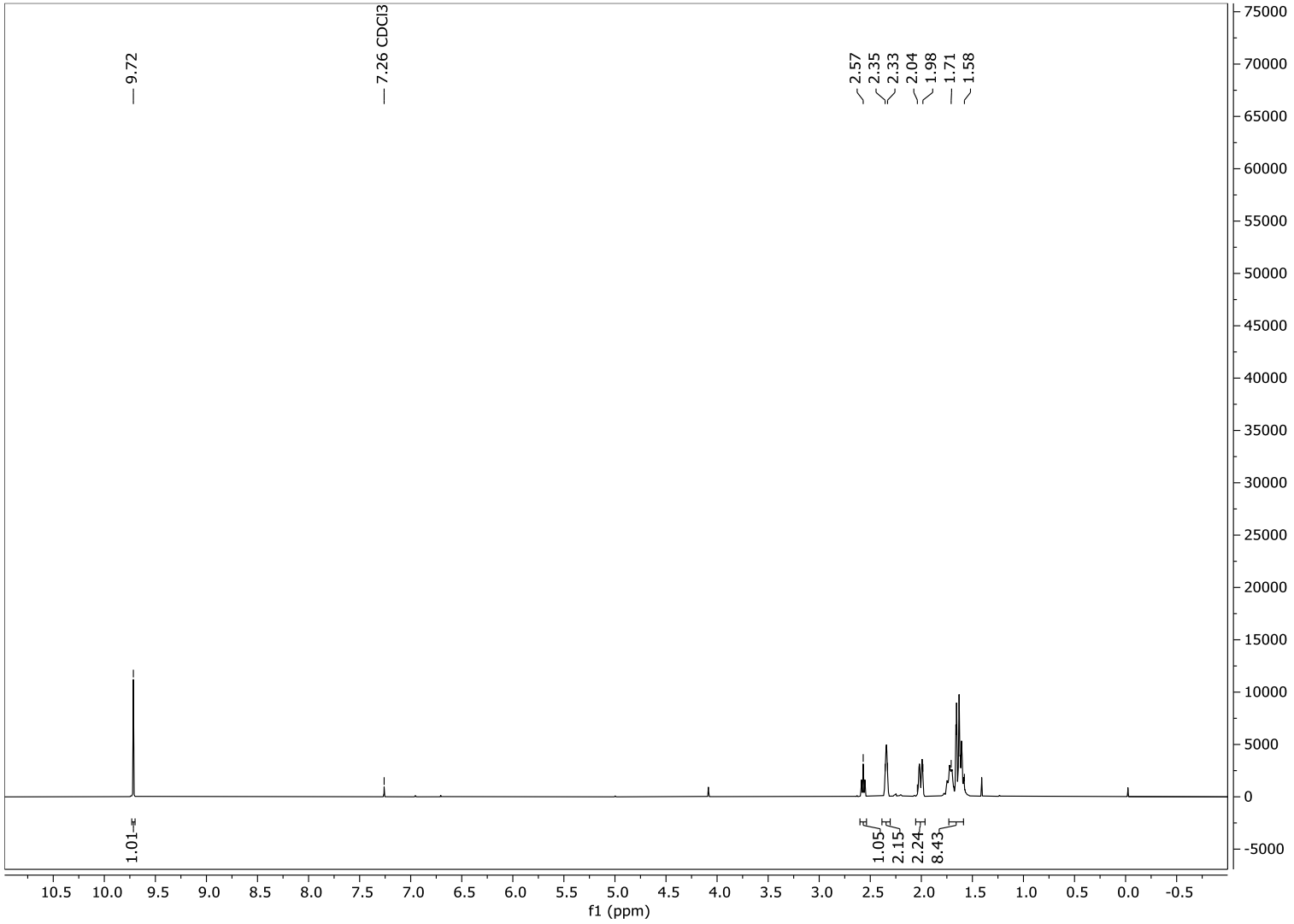
IR (neat): $\tilde{\nu}$ /cm^{-1} = 2922, 2858, 2702, 1712, 1464, 1389, 1325, 1246, 1184, 1074, 811, 723.

HRMS: m/z = 217.1225 ($[M+Na]^+$; calculated for $C_{14}H_{16}O_2Na^+$ m/z = 217.1223).

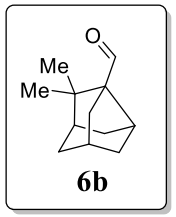
2.4 NMR spectra of aldehydes **6a-f** and **11**

2.4.1 Compound 6a

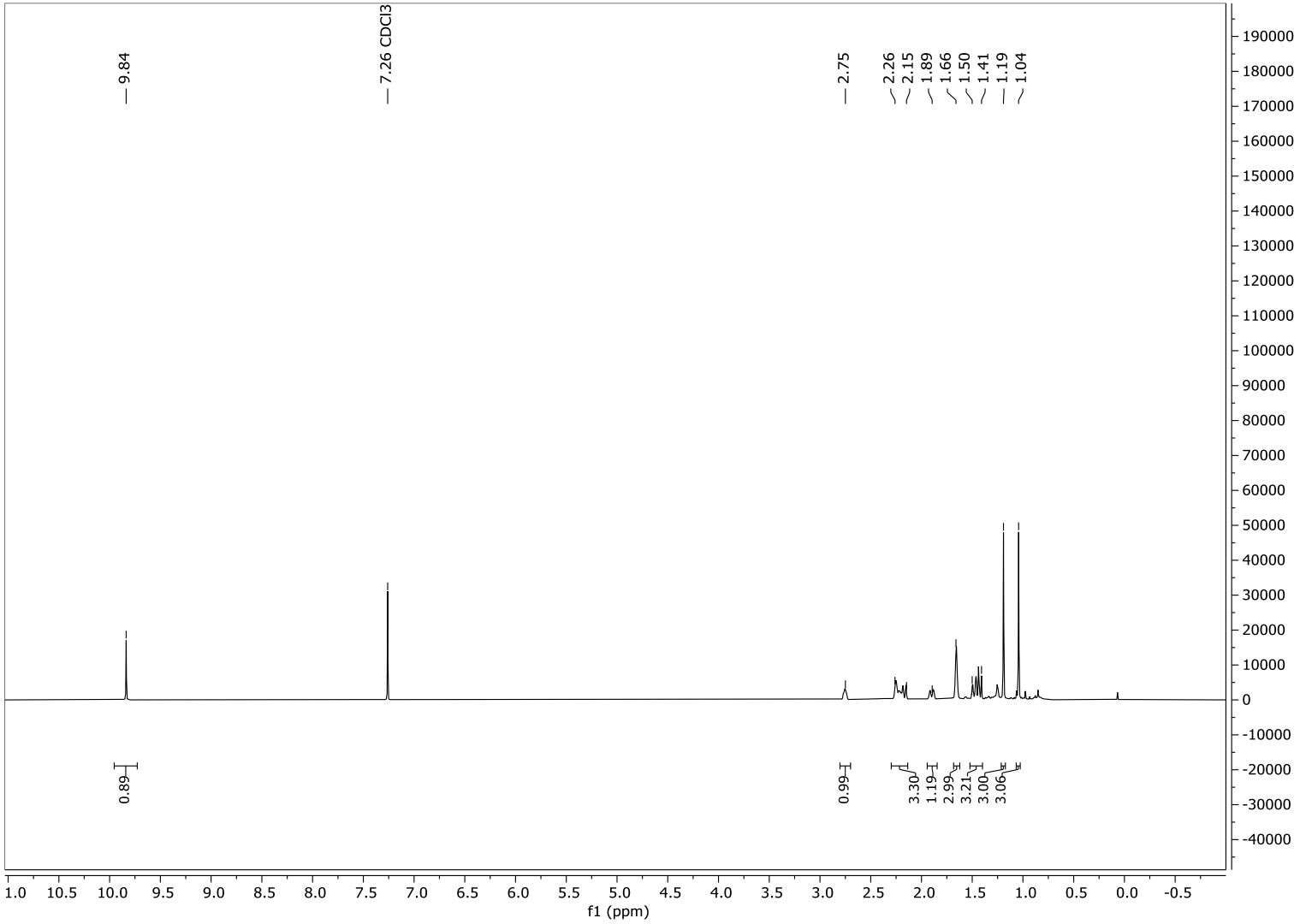


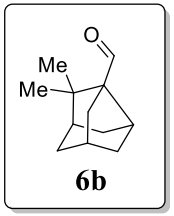


2.4.2 Compound 6b

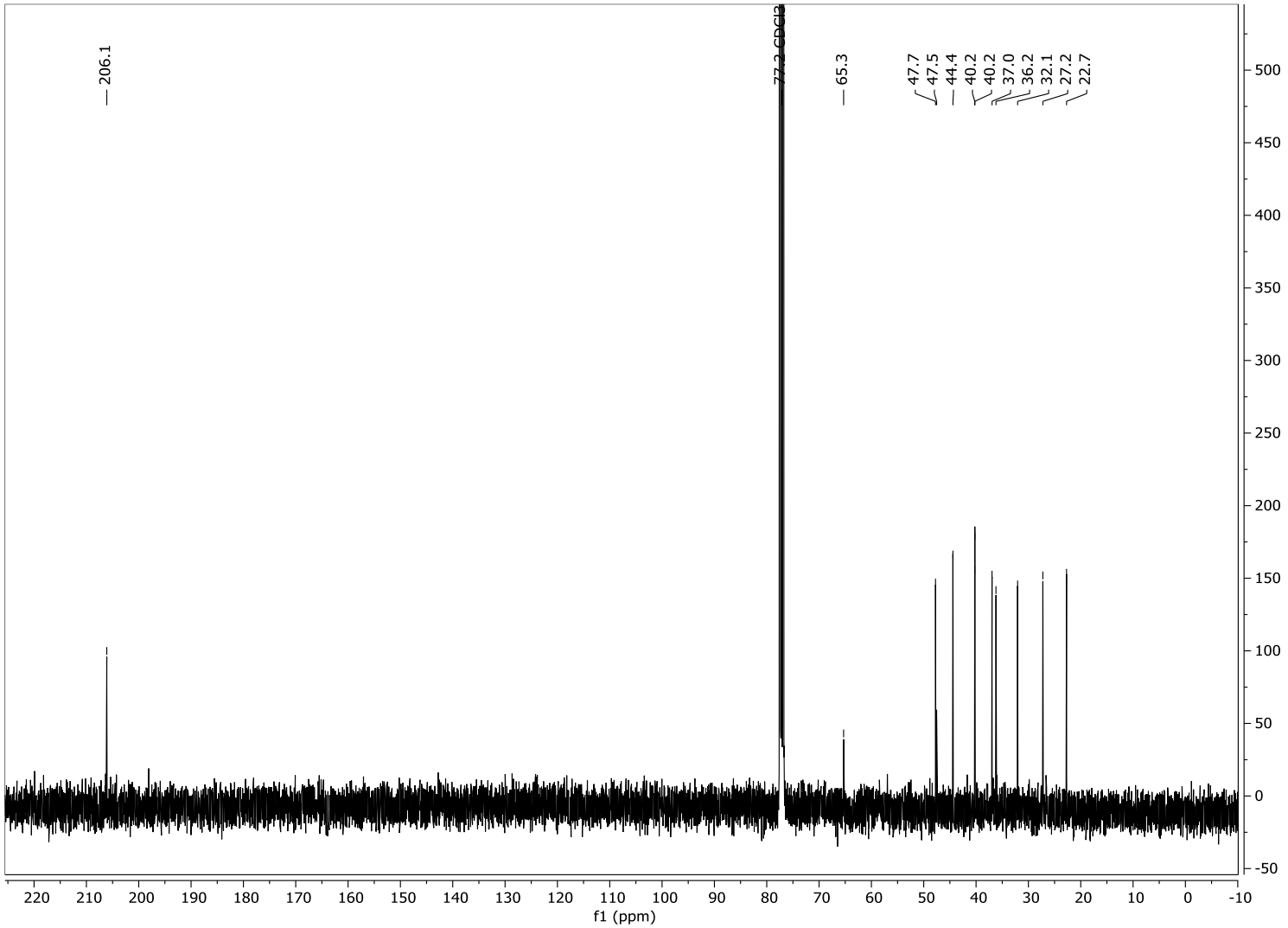


6b

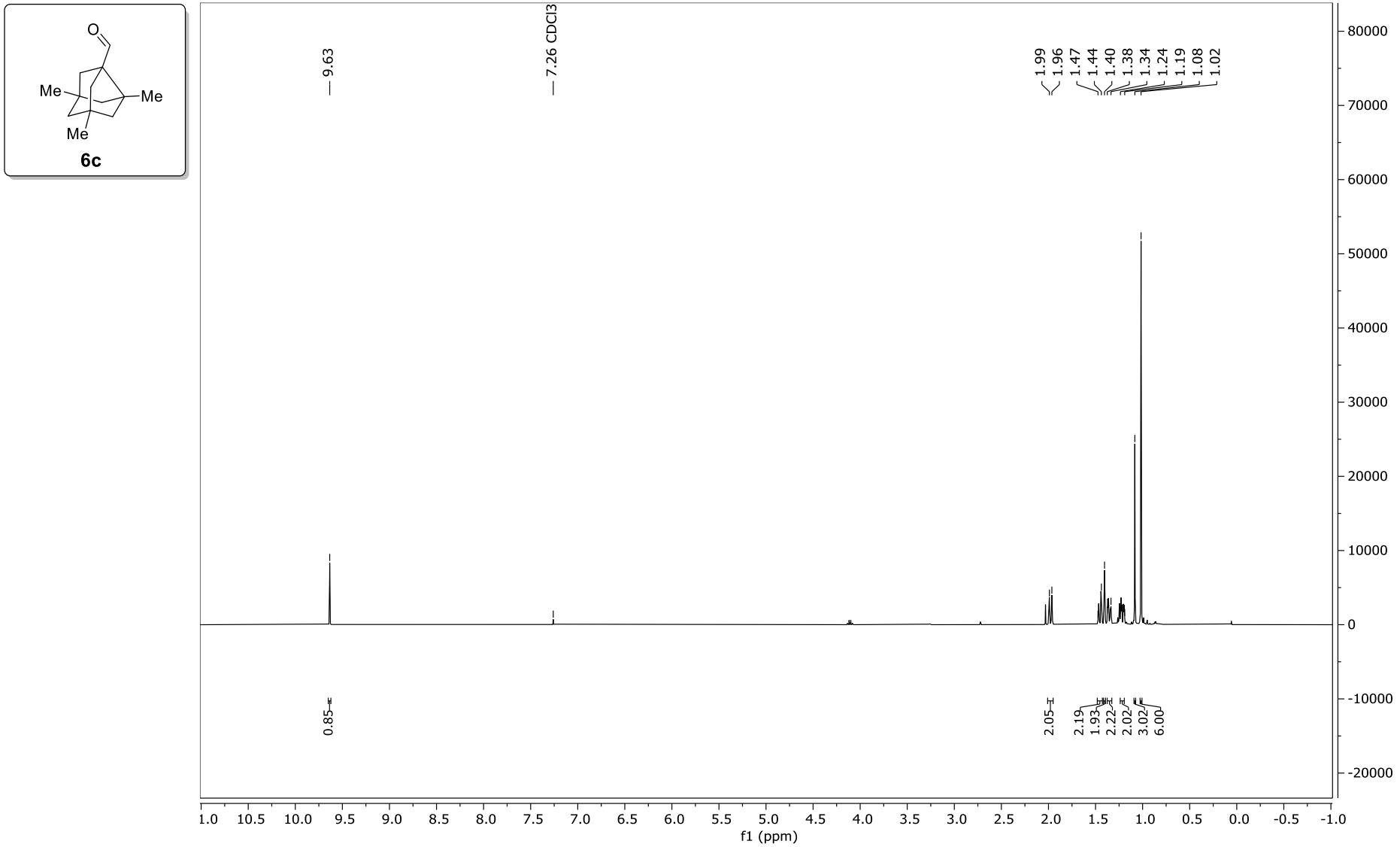


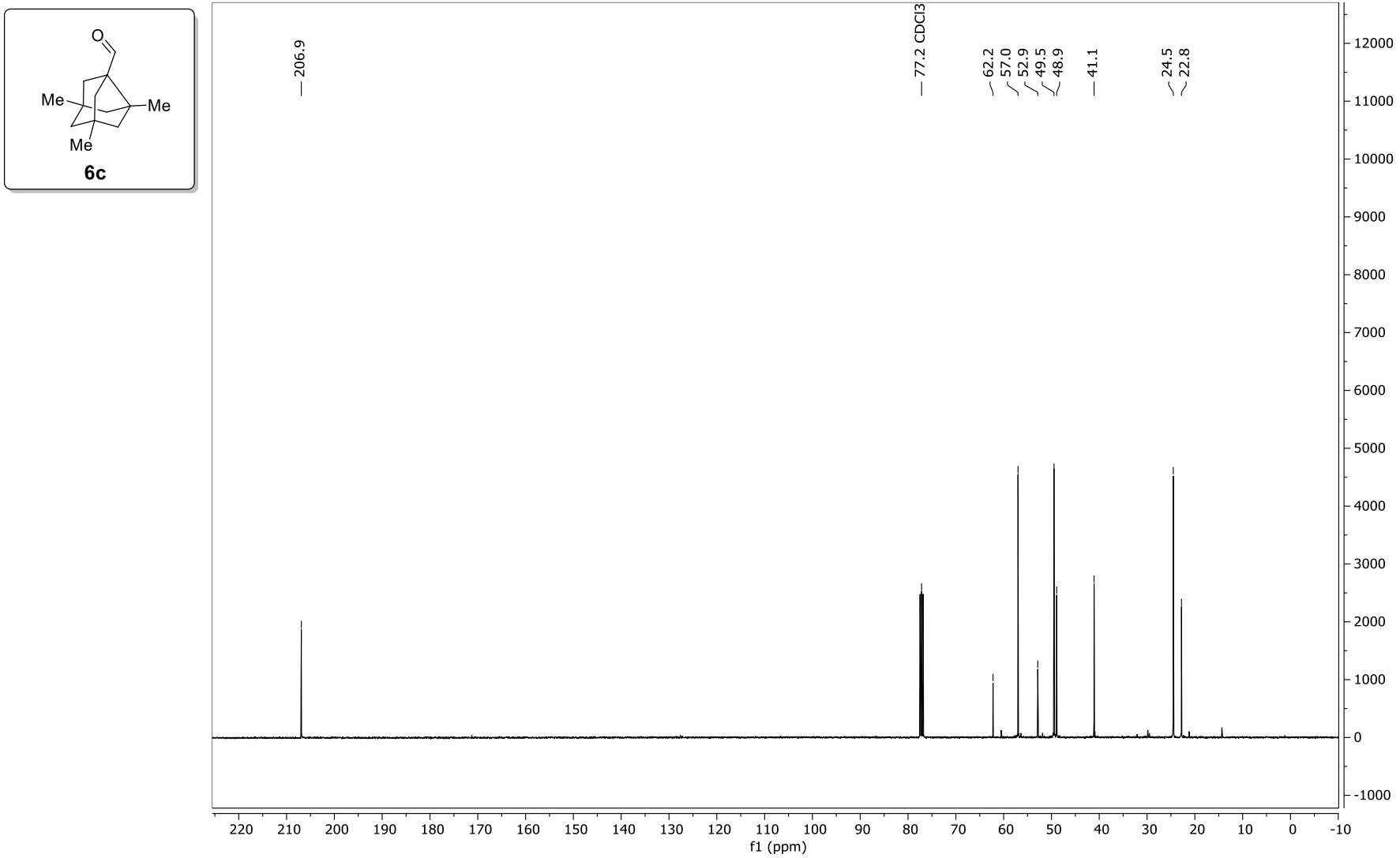

O
Me
Me

6b

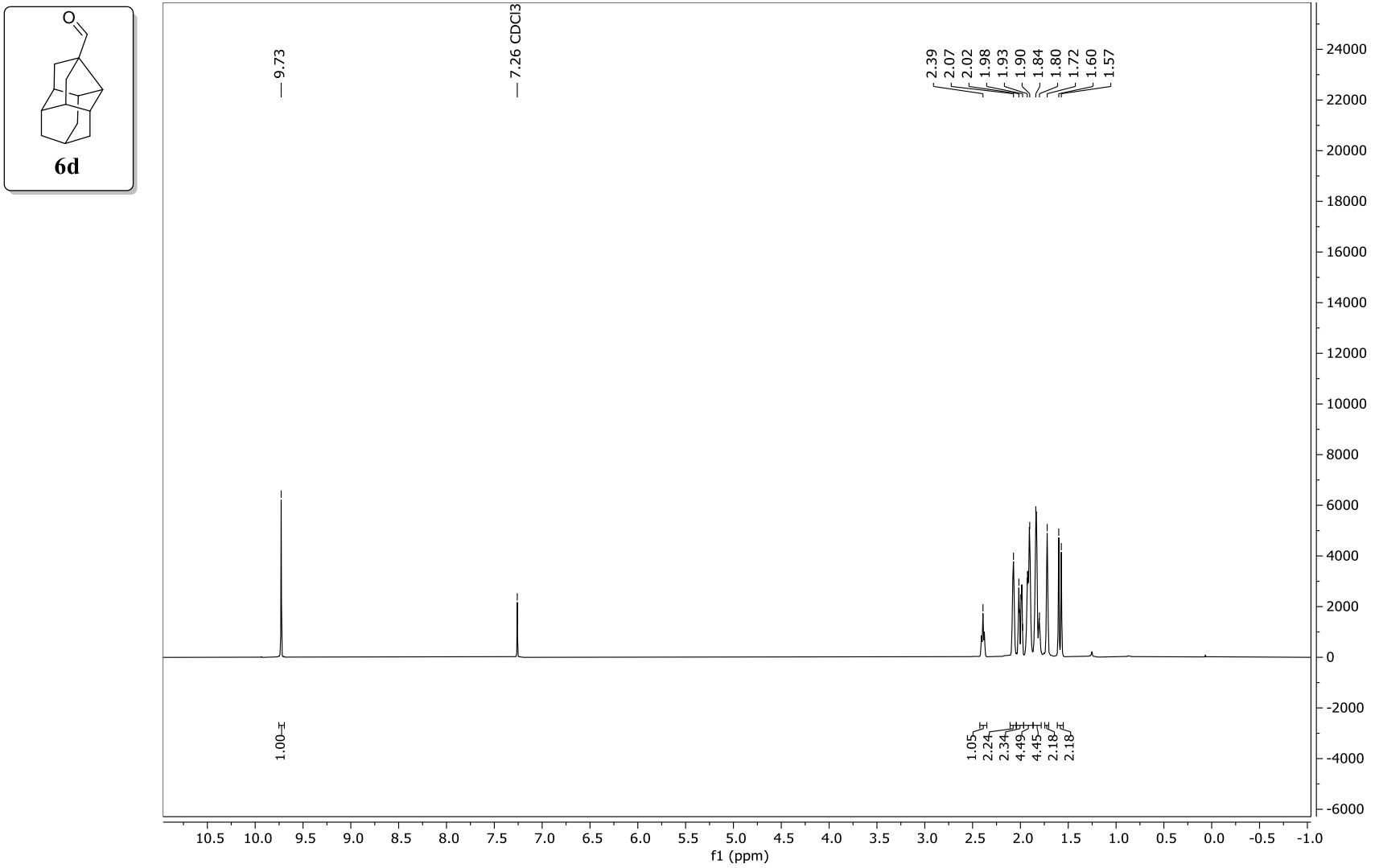

206.1
77.3 CDCl3
65.3
47.7
47.5
44.4
40.2
40.2
37.0
36.2
32.1
27.2
22.7
f1 (ppm)

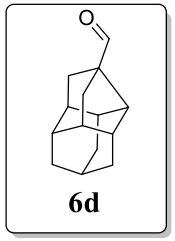
2.4.3 Compound 6c



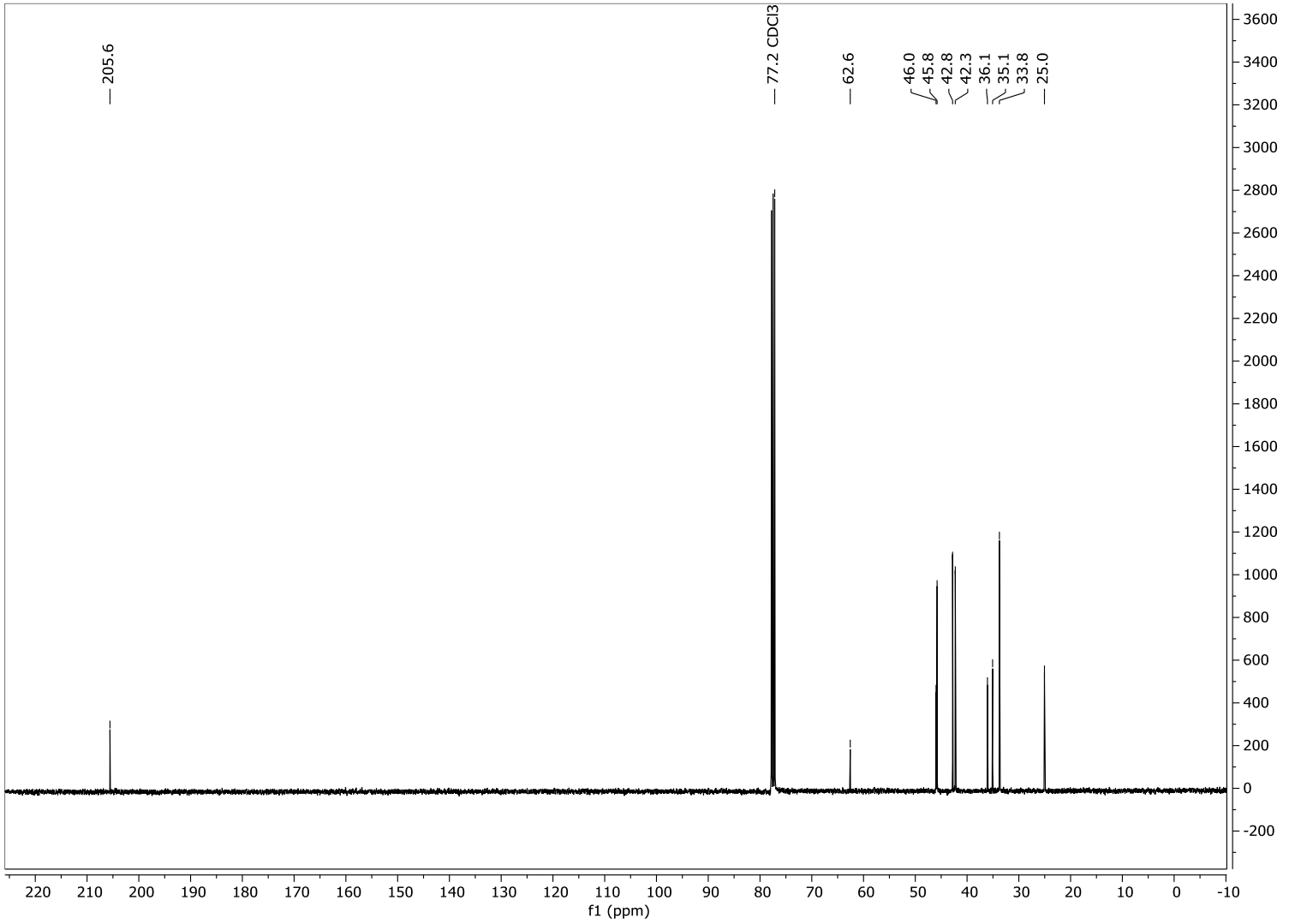

O
Me
Me
Me
6c
206.9
77.2 CDCl3
62.2
57.0
52.9
49.5
48.9
41.1
24.5
22.8
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

2.4.4 Compound 6d

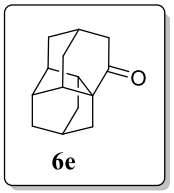


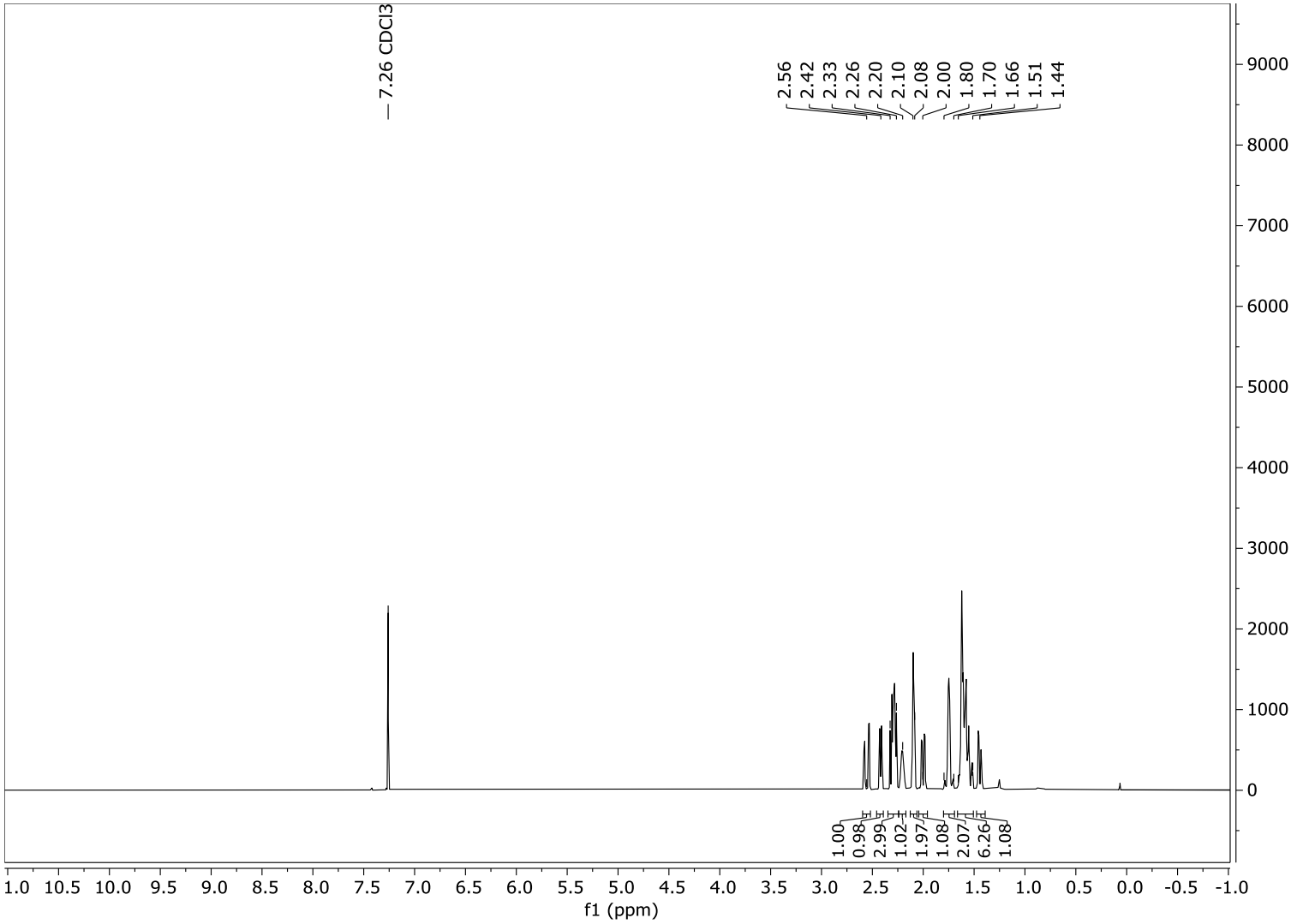


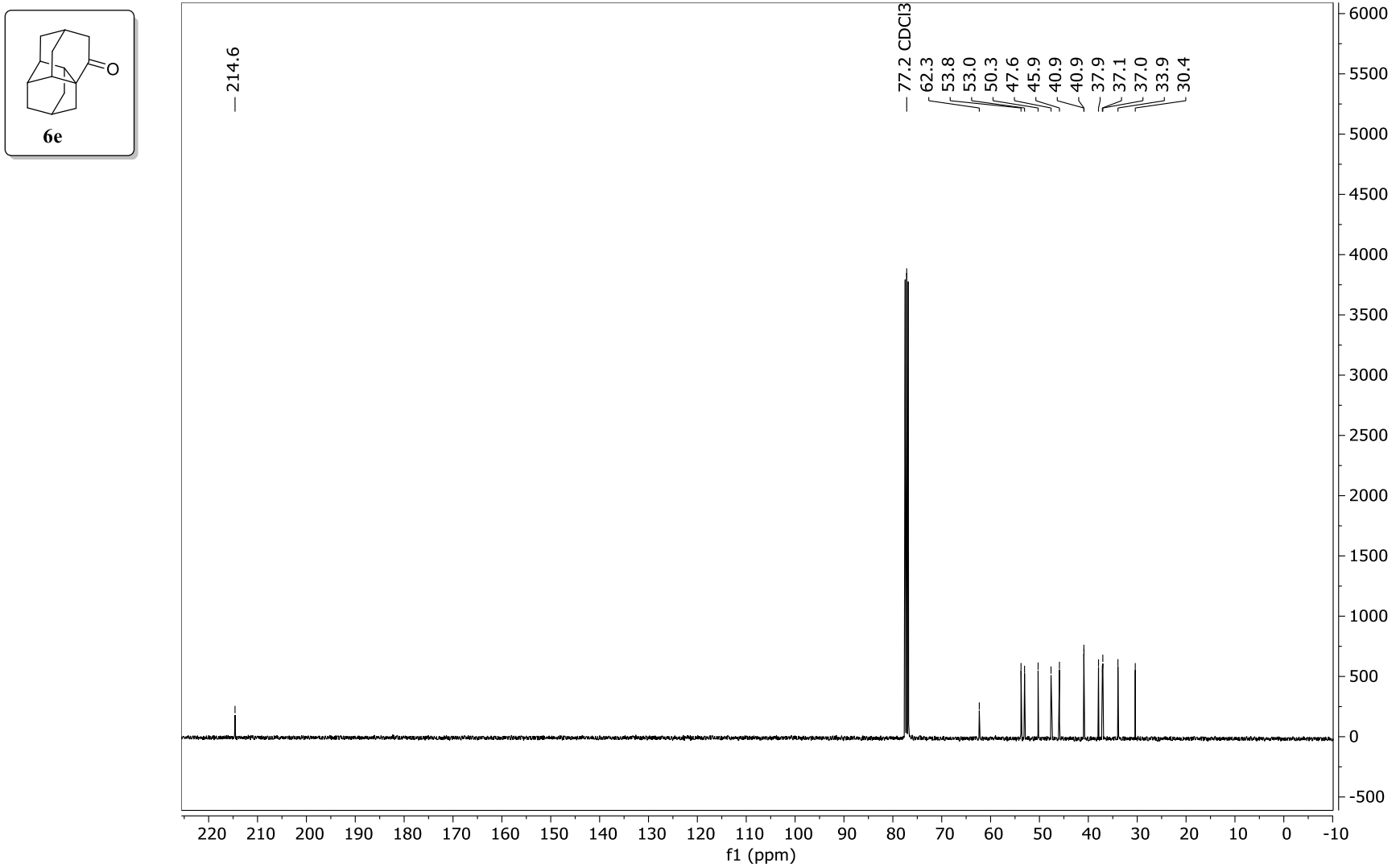
6d



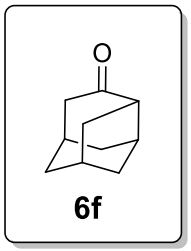
2.4.5 Compound 6e

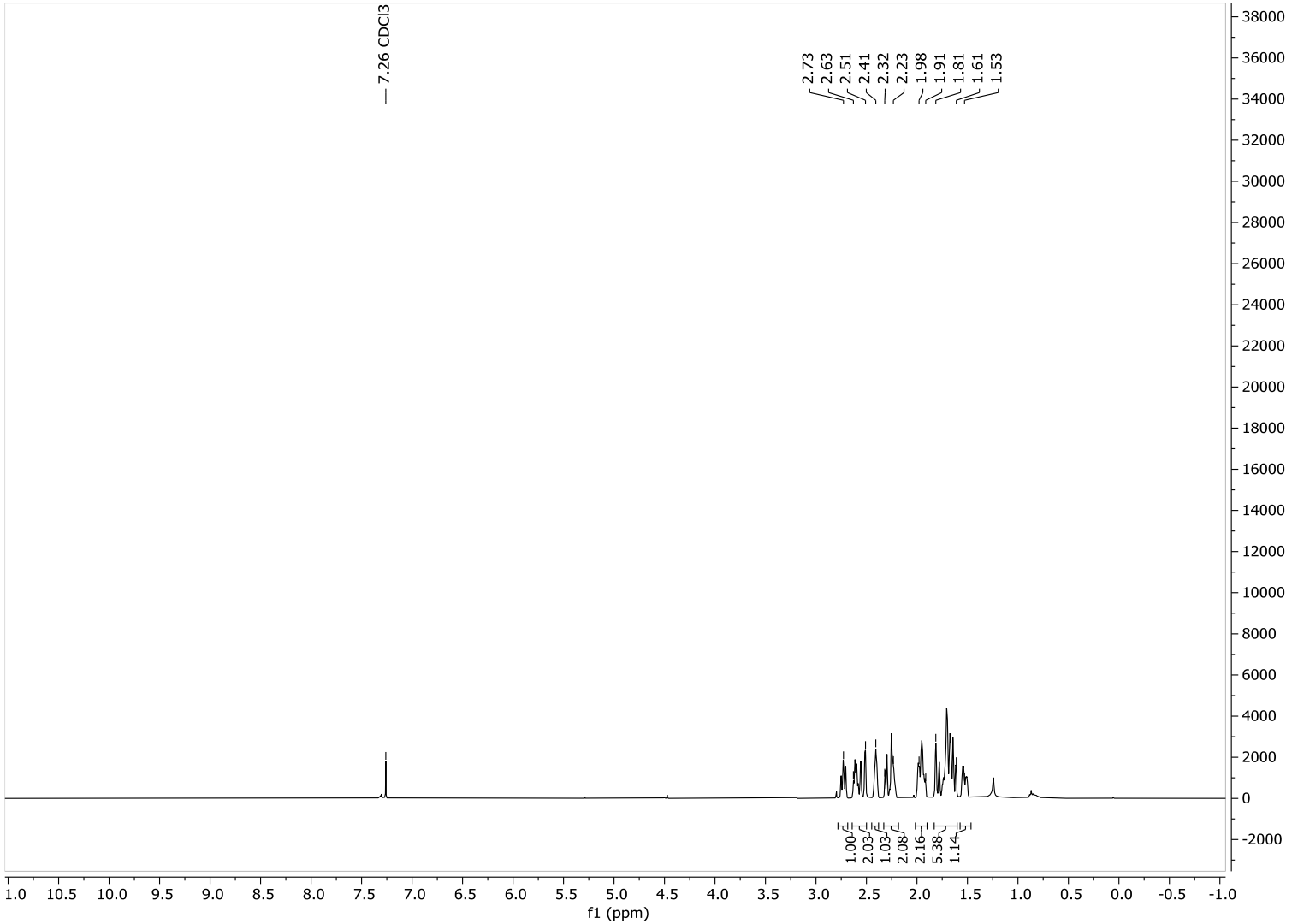




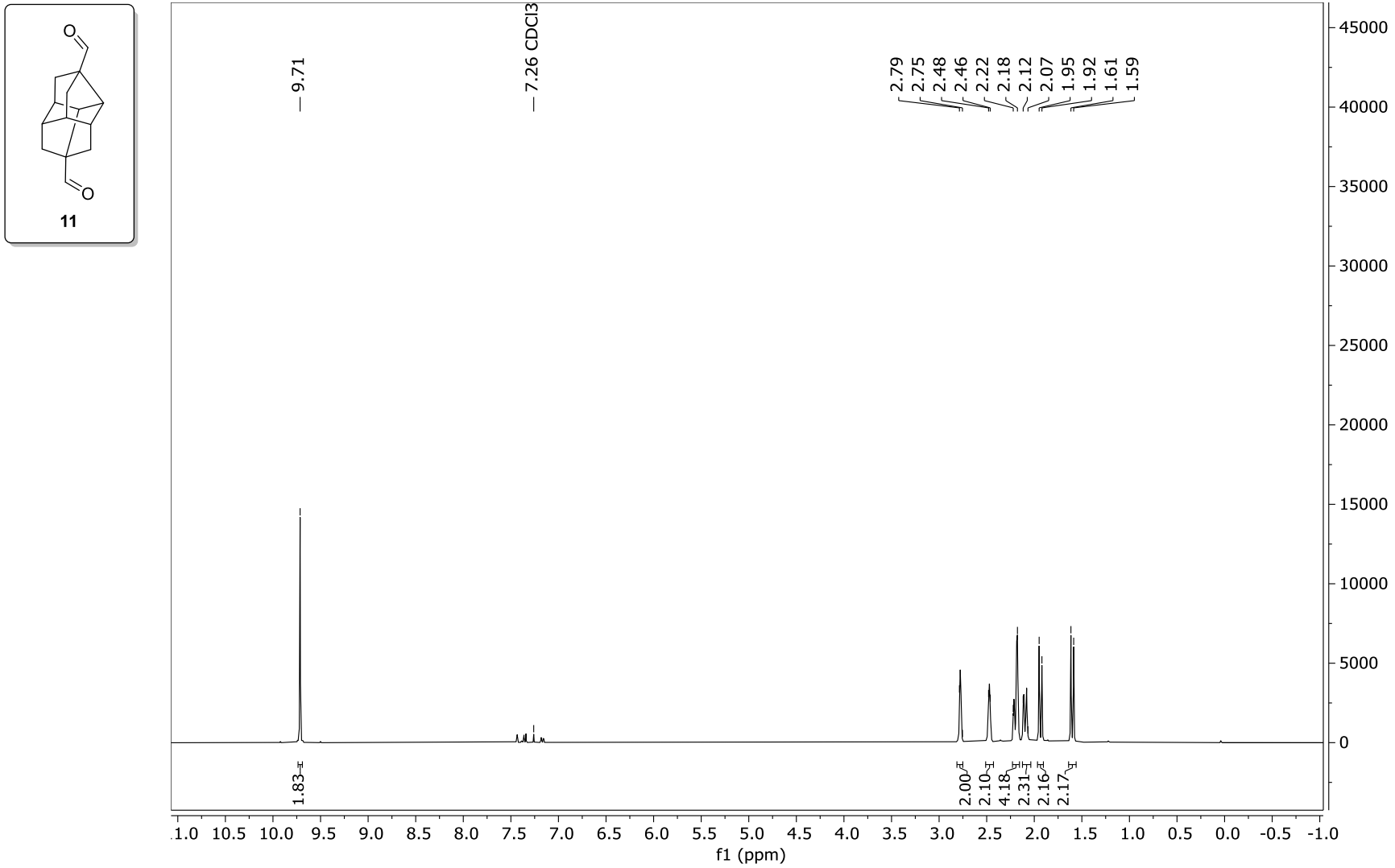

6e
O
214.6
77.2 CDCl3
62.3
53.8
53.0
50.3
47.6
45.9
40.9
40.9
37.9
37.1
37.0
33.9
30.4
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

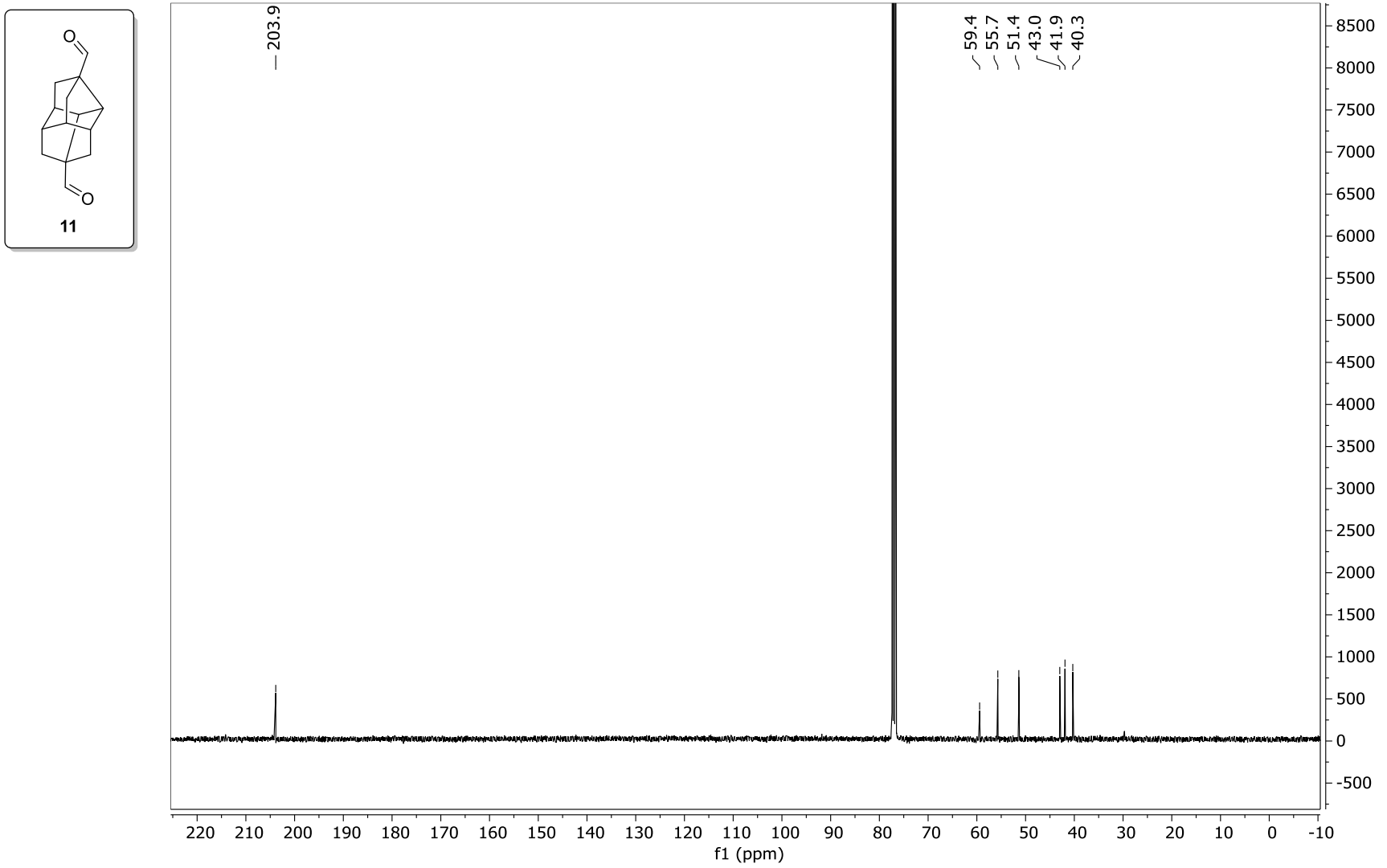
2.4.6 Compound 6f





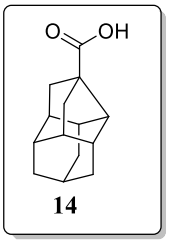
2.4.7 Compound 11




O
O
11
203.9
59.4
55.7
51.4
43.0
41.9
40.3
8500
8000
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

2.5 Postfunctionalization

2.5.1 Compound 14



14

A solution of aldehyde **6d** (40 mg, 0.2 mmol) in DPDME (8 eq.) was heated to 80 °C overnight while connected to an oxygen balloon. The solvent was evaporated to give the clean desired compound as a white solid in a yield of 99% (45 mg, 0.2 mmol).

R_f (silica gel; MeOH:CH_2Cl_2 1:99): 0.2.

m.p. (cryst. from $CDCl_3$): 177.7-178.6 °C.

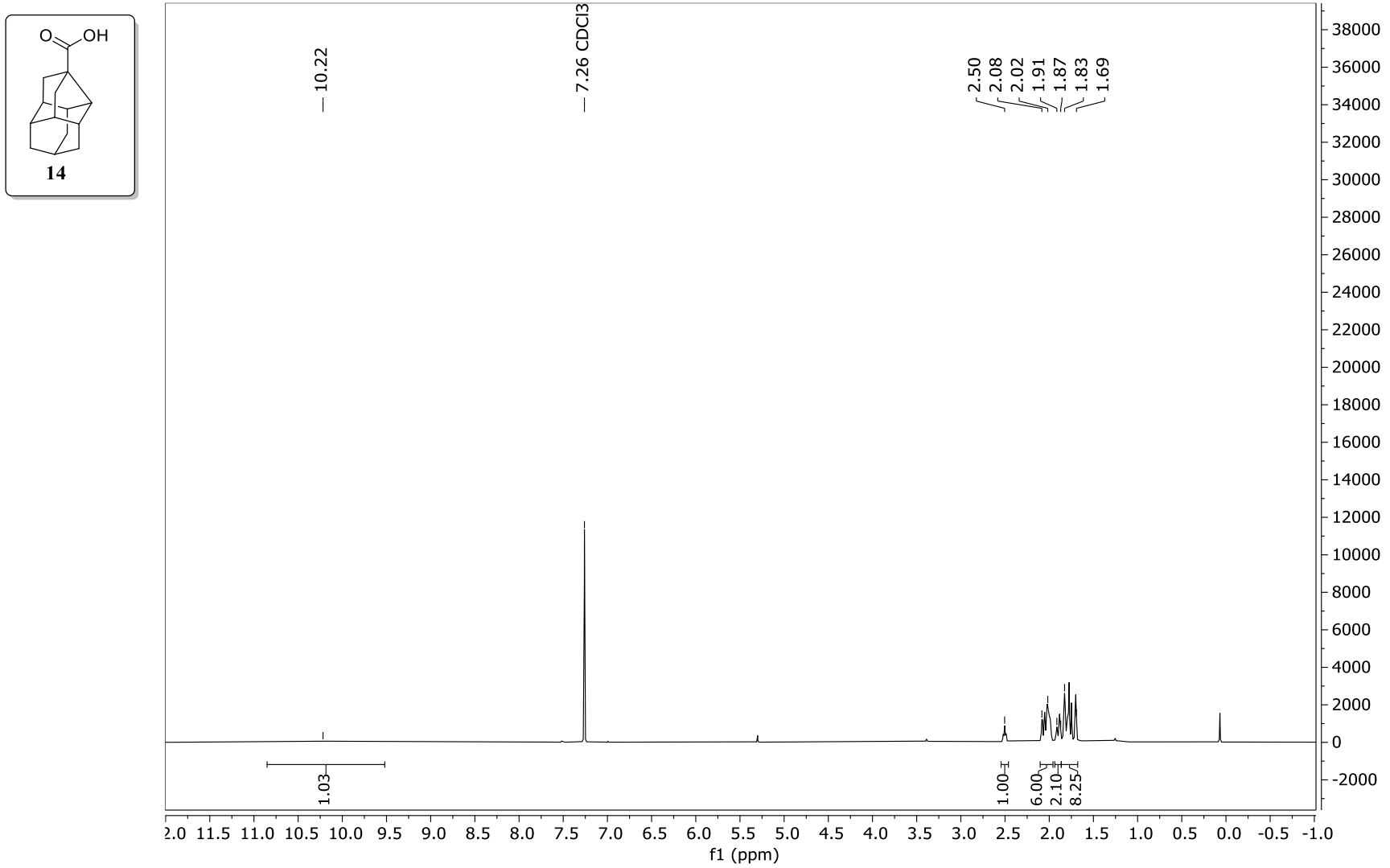
^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 1.69-1.83 (m, 8H), 1.87-1.91 (m, 2H), 2.02-2.08 (m, 6H), 2.50 (m, 1H), 10.22 (bs, 1H).

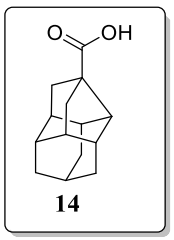
^{13}C NMR (101 MHz, $CDCl_3$): δ/ppm = 24.8 (CH), 33.4 ($2CH_2$), 34.7 (CH_2), 35.0 (CH), 41.8 (2CH), 45.5 (2CH), 45.6 ($2CH_2$), 48.1 (CH), 55.1 (C), 182.5 (C).

IR (neat): $\tilde{\nu}$ /cm^{-1} = 2903, 2880, 2596, 1834, 1682, 1470, 1418, 1320, 1287, 1261, 1215, 1194, 1088, 1056, 997, 986, 953, 935, 857, 845, 821, 753, 738, 634, 567, 534, 490, 448.

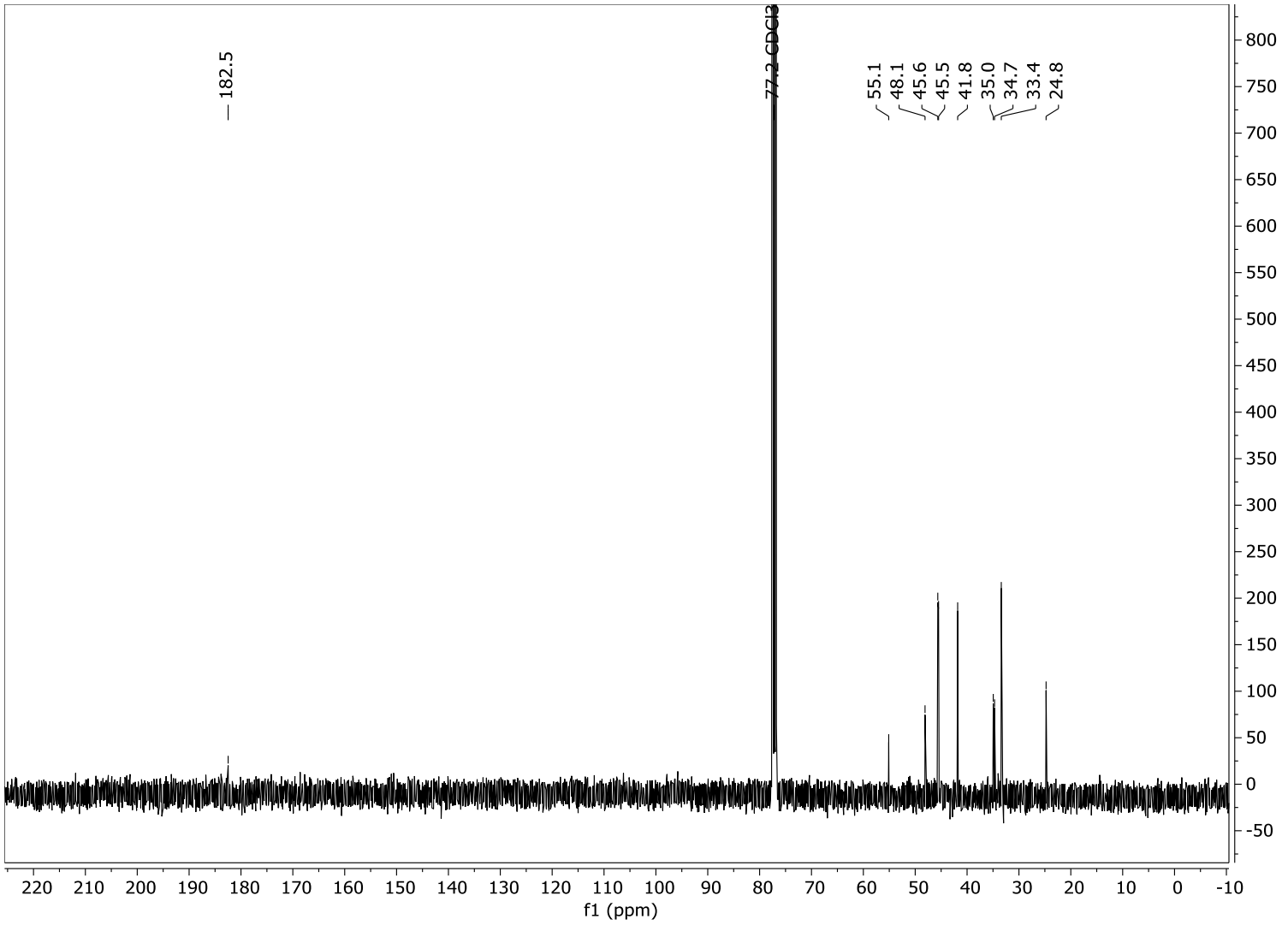
HRMS: m/z = 241.1198 ($[M+Na]^+$; calculated for $C_{14}H_{18}O_2Na^+$ m/z = 241.1199).

2.6 NMR spectra of acid **14**




O
OH

14


182.5
77.2 CDCl3
55.1
48.1
45.6
45.5
41.8
35.0
34.7
33.4
24.8
800
750
700
650
600
550
500
450
400
350
300
250
200
150
100
50
0
-50
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

3. DFT analysis of cations 12^+ and 5^+

3.1 Geometric Structures and Electronic energies (Hartree)

Cation 12^+

1 1

6	1.094749000	0.380585000	0.509932000
1	1.293275000	1.283414000	1.100637000
6	0.283602000	0.695249000	-0.673942000
6	-0.041118000	-0.465942000	1.319907000
1	0.450242000	-0.762402000	2.247284000
6	-1.241562000	0.443930000	1.595294000
1	-0.948081000	1.303536000	2.198609000
1	-1.982851000	-0.104872000	2.178365000
6	-0.732444000	1.728896000	-0.535234000
1	-1.149154000	2.059890000	-1.482348000
1	-0.420565000	2.575774000	0.069583000
6	-1.861340000	0.897858000	0.270045000
1	-2.688701000	1.587869000	0.426499000
6	-2.272198000	-0.296189000	-0.596106000
1	-3.051095000	-0.865953000	-0.085632000
1	-2.703073000	0.040671000	-1.539562000
6	0.071206000	-0.343668000	-1.656156000
1	0.931184000	-0.985840000	-1.811095000
1	-0.369196000	0.002348000	-2.586112000
6	-0.441142000	-1.678220000	0.472760000
1	0.415792000	-2.320172000	0.281633000

1	-1.170367000	-2.275585000	1.023500000
6	-1.062813000	-1.201104000	-0.840447000
1	-1.304152000	-2.032178000	-1.500931000
7	2.256583000	-0.435008000	0.256184000
1	2.514006000	-0.938360000	1.095552000
6	3.410408000	0.327344000	-0.241074000
1	3.193243000	0.716028000	-1.236851000
1	3.685877000	1.169470000	0.403691000
1	4.263441000	-0.341018000	-0.325984000

Temperature 298.150 Kelvin. Pressure 1.00000 Atm.

Zero-point correction= 0.275387 (Hartree/Particle)

Thermal correction to Energy= 0.285384

Thermal correction to Enthalpy= 0.286328

Thermal correction to Gibbs Free Energy= 0.240980

Sum of electronic and zero-point Energies= -484.357053

Sum of electronic and thermal Energies= -484.347056

Sum of electronic and thermal Enthalpies= -484.346112

Sum of electronic and thermal Free Energies= -484.391459

Cation 5^+

1 1

6	-0.398146000	-1.251957000	-1.021040000
1	0.169124000	-2.165383000	-0.837942000
1	-0.506921000	-1.124755000	-2.096375000
6	0.277819000	-0.000001000	-0.350354000
6	-1.721086000	-1.281344000	-0.240066000
1	-2.304602000	-2.173319000	-0.461622000
6	-1.180683000	-1.248454000	1.198507000
1	-0.617956000	-2.157583000	1.415945000
1	-1.953778000	-1.149643000	1.957892000
6	-0.274176000	-0.000002000	1.142861000
1	0.487265000	-0.000005000	1.924574000
6	-1.180679000	1.248452000	1.198511000
1	-1.953774000	1.149641000	1.957896000
1	-0.617950000	2.157578000	1.415951000
6	-0.398144000	1.251959000	-1.021037000
1	-0.506921000	1.124758000	-2.096372000
1	0.169128000	2.165383000	-0.837938000
6	-2.540447000	0.000003000	-0.534402000
1	-2.863830000	0.000005000	-1.576909000
1	-3.445532000	0.000002000	0.074413000
6	-1.721084000	1.281346000	-0.240062000
1	-2.304597000	2.173324000	-0.461614000
6	1.719978000	0.000001000	-0.588255000
1	2.068770000	0.000006000	-1.617915000

7	2.640039000	-0.000006000	0.311217000
6	4.089099000	0.000002000	0.074859000
1	4.279467000	0.000014000	-0.993751000
1	4.524392000	-0.887641000	0.528674000
1	2.338356000	-0.000010000	1.280746000
1	4.524383000	0.887640000	0.528693000

Temperature 298.150 Kelvin. Pressure 1.00000 Atm.

Zero-point correction= 0.276647 (Hartree/Particle)

Thermal correction to Energy= 0.286892

Thermal correction to Enthalpy= 0.287836

Thermal correction to Gibbs Free Energy= 0.240993

Sum of electronic and zero-point Energies= -484.392153

Sum of electronic and thermal Energies= -484.381908

Sum of electronic and thermal Enthalpies= -484.380964

Sum of electronic and thermal Free Energies= -484.427807

4. Crystallographic data collection and refinement details

Diffraction data were collected at low temperatures (100K) using φ- and ω-scans on a BRUKER D8 Venture system equipped with dual IμS microfocus sources, a PHOTON100 detector and an OXFORD CRYOSYSTEMS 700 low temperature system. Mo-K_α radiation with wavelength 0.71073 Å and a collimating Quazar multilayer mirror were used. The data was corrected for absorption using semi-empirical absorption correction from equivalents using SADABS-2016/2[10] and the structure of 14 was solved in the monoclinic space group $P2_1/n$ by the dual space algorithm implemented in SHELXT2014/5.[11] Refinement was performed against F^2 on all data by full-matrix least squares using SHELXL2018/3.[11]All non-hydrogen atoms were refined anisotropically and C-H hydrogen atoms were positioned at geometrically calculated positions and refined using a riding model. The O-H hydrogen atom was located in the difference map and was set to ideal distance. The isotropic displacement parameters of all hydrogen atoms were fixed to 1.2x or 1.5x (OH hydrogen) the U_{eq} value of the atoms they are linked to. The asymmetric unit contains one molecule of **14** which forms a dimer with its symmetry equivalent *via* hydrogen bonding.

The crystallographic data has been deposited with the Cambridge Crystallographic Data Centre as CCDC No. 2063017 and can be obtained free of charge.[12]

[10] L. Krause, R. Herbst-Irmer, G. M. Sheldrick, D. J. Stalke, *Appl. Cryst.,* 2015, **48**, 3–10.
[11] G. M. Sheldrick, *Acta Cryst. A,* 2015, **71**, 3–8.
[12] https://www.ccdc.cam.ac.uk/structures/

Table S1. Crystal data and structure refinement for **14**.

CCDC No	2063017	
Empirical formula	$C_{14}H_{18}O_2$	
Formula weight	218.28	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/n$	
Unit cell dimensions	a = 6.5170(4) Å	α= 90°.
	b = 10.4112(7) Å	β= 97.934(2)°.
	c = 15.8832(10) Å	γ = 90°.
Volume	1067.36(12) $Å^3$	
Z	4	
Density (calculated)	1.358 Mg/m^3	
Absorption coefficient	0.089 mm^{-1}	
F(000)	472	
Crystal size	0.240 x 0.146 x 0.056 mm^3	
Theta range for data collection	2.346 to 30.019°.	
Index ranges	$-9 \le h \le 9$, $-14 \le k \le 14$, $-22 \le l \le 22$	
Reflections collected	77056	
Independent reflections	3129 [R(int) = 0.0505]	
Completeness to theta = 25.242°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3129 / 1 / 148	
Goodness-of-fit on F^2	1.051	
Final R indices [I>2σ(I)]	R1 = 0.0424, wR2 = 0.1069	
R indices (all data)	R1 = 0.0529, wR2 = 0.1145	
Largest diff. peak and hole	0.359 and -0.285 $e.Å^{-3}$	

Table S2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **14**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	4201(1)	5011(1)	5929(1)	17(1)
O(2)	6435(1)	6392(1)	5467(1)	20(1)
C(1)	5356(2)	5948(1)	6048(1)	12(1)
C(2)	5586(2)	6711(1)	6857(1)	12(1)
C(3)	5351(2)	5890(1)	7682(1)	12(1)
C(4)	3474(2)	6502(1)	8029(1)	13(1)
C(5)	3753(2)	7911(1)	7776(1)	14(1)
C(6)	3851(2)	7747(1)	6824(1)	15(1)
C(7)	7645(2)	7444(1)	7076(1)	13(1)
C(8)	7698(2)	7602(1)	8038(1)	12(1)
C(9)	7366(2)	6200(1)	8292(1)	12(1)
C(10)	5834(2)	8397(1)	8267(1)	14(1)
C(11)	5749(2)	8276(1)	9230(1)	16(1)
C(12)	5440(2)	6862(1)	9475(1)	16(1)
C(13)	3426(2)	6336(1)	8982(1)	16(1)
C(14)	7227(2)	6042(1)	9240(1)	15(1)

Table S3. Bond lengths [Å] and angles [°] for **14**.

O(1)-C(1)	1.2309(14)	C(14)-H(14B)	0.9900
O(2)-C(1)	1.3180(13)		
O(2)-H(2)	0.879(14)	C(1)-O(2)-H(2)	108.3(12)
C(1)-C(2)	1.5009(15)	O(1)-C(1)-O(2)	123.01(10)
C(2)-C(7)	1.5421(15)	O(1)-C(1)-C(2)	122.47(10)
C(2)-C(6)	1.5586(15)	O(2)-C(1)-C(2)	114.48(10)
C(2)-C(3)	1.5888(14)	C(1)-C(2)-C(7)	115.82(9)
C(3)-C(4)	1.5472(15)	C(1)-C(2)-C(6)	110.58(9)
C(3)-C(9)	1.5540(15)	C(7)-C(2)-C(6)	105.61(9)
C(3)-H(3)	1.0000	C(1)-C(2)-C(3)	114.39(9)
C(4)-C(13)	1.5280(15)	C(7)-C(2)-C(3)	105.10(8)
C(4)-C(5)	1.5381(16)	C(6)-C(2)-C(3)	104.35(8)
C(4)-H(4)	1.0000	C(4)-C(3)-C(9)	109.53(8)
C(5)-C(6)	1.5316(15)	C(4)-C(3)-C(2)	104.10(8)
C(5)-C(10)	1.5529(16)	C(9)-C(3)-C(2)	103.51(8)
C(5)-H(5)	1.0000	C(4)-C(3)-H(3)	113.0
C(6)-H(6A)	0.9900	C(9)-C(3)-H(3)	113.0
C(6)-H(6AB)	0.9900	C(2)-C(3)-H(3)	113.0
C(7)-C(8)	1.5325(14)	C(13)-C(4)-C(5)	112.70(9)
C(7)-H(7A)	0.9900	C(13)-C(4)-C(3)	115.58(9)
C(7)-H(7AB)	0.9900	C(5)-C(4)-C(3)	99.88(8)
C(8)-C(9)	1.5379(15)	C(13)-C(4)-H(4)	109.4
C(8)-C(10)	1.5546(15)	C(5)-C(4)-H(4)	109.4
C(8)-H(8)	1.0000	C(3)-C(4)-H(4)	109.4
C(9)-C(14)	1.5293(14)	C(6)-C(5)-C(4)	100.04(9)
C(9)-H(9)	1.0000	C(6)-C(5)-C(10)	112.29(9)
C(10)-C(11)	1.5428(15)	C(4)-C(5)-C(10)	107.83(9)
C(10)-H(10)	1.0000	C(6)-C(5)-H(5)	112.0
C(11)-C(12)	1.5434(17)	C(4)-C(5)-H(5)	112.0
C(11)-H(11A)	0.9900	C(10)-C(5)-H(5)	112.0
C(11)-H(11B)	0.9900	C(5)-C(6)-C(2)	99.97(8)
C(12)-C(14)	1.5313(16)	C(5)-C(6)-H(6A)	111.8
C(12)-C(13)	1.5332(16)	C(2)-C(6)-H(6A)	111.8
C(12)-H(12)	1.0000	C(5)-C(6)-H(6AB)	111.8
C(13)-H(13A)	0.9900	C(2)-C(6)-H(6AB)	111.8
C(13)-H(13B)	0.9900	H(6A)-C(6)-H(6AB)	109.5
C(14)-H(14A)	0.9900	C(8)-C(7)-C(2)	100.15(8)

C(8)-C(7)-H(7A)	111.7	C(12)-C(13)-H(13B)	109.8
C(2)-C(7)-H(7A)	111.7	H(13A)-C(13)-H(13B)	108.2
C(8)-C(7)-H(7AB)	111.7	C(9)-C(14)-C(12)	109.33(9)
C(2)-C(7)-H(7AB)	111.7	C(9)-C(14)-H(14A)	109.8
H(7A)-C(7)-H(7AB)	109.5	C(12)-C(14)-H(14A)	109.8
C(7)-C(8)-C(9)	100.12(8)	C(9)-C(14)-H(14B)	109.8
C(7)-C(8)-C(10)	112.35(9)	C(12)-C(14)-H(14B)	109.8
C(9)-C(8)-C(10)	107.52(9)	H(14A)-C(14)-H(14B)	108.3
C(7)-C(8)-H(8)	112.1		
C(9)-C(8)-H(8)	112.1		
C(10)-C(8)-H(8)	112.1		
C(14)-C(9)-C(8)	112.97(9)		
C(14)-C(9)-C(3)	115.55(9)		
C(8)-C(9)-C(3)	99.81(8)		
C(14)-C(9)-H(9)	109.4		
C(8)-C(9)-H(9)	109.4		
C(3)-C(9)-H(9)	109.4		
C(11)-C(10)-C(5)	108.83(9)		
C(11)-C(10)-C(8)	108.97(9)		
C(5)-C(10)-C(8)	111.43(9)		
C(11)-C(10)-H(10)	109.2		
C(5)-C(10)-H(10)	109.2		
C(8)-C(10)-H(10)	109.2		
C(10)-C(11)-C(12)	110.59(9)		
C(10)-C(11)-H(11A)	109.5		
C(12)-C(11)-H(11A)	109.5		
C(10)-C(11)-H(11B)	109.5		
C(12)-C(11)-H(11B)	109.5		
H(11A)-C(11)-H(11B)	108.1		
C(14)-C(12)-C(13)	107.62(9)		
C(14)-C(12)-C(11)	109.88(9)		
C(13)-C(12)-C(11)	110.11(10)		
C(14)-C(12)-H(12)	109.7		
C(13)-C(12)-H(12)	109.7		
C(11)-C(12)-H(12)	109.7		
C(4)-C(13)-C(12)	109.42(9)		
C(4)-C(13)-H(13A)	109.8		
C(12)-C(13)-H(13A)	109.8		
C(4)-C(13)-H(13B)	109.8		

Table S4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **14**. The anisotropic displacement factor exponent takes the form: $-2p^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	21(1)	17(1)	12(1)	-2(1)	3(1)	-5(1)
O(2)	26(1)	22(1)	12(1)	-3(1)	7(1)	-9(1)
C(1)	14(1)	13(1)	10(1)	1(1)	1(1)	1(1)
C(2)	14(1)	11(1)	10(1)	0(1)	2(1)	0(1)
C(3)	14(1)	11(1)	9(1)	0(1)	1(1)	0(1)
C(4)	12(1)	17(1)	11(1)	-1(1)	2(1)	-1(1)
C(5)	14(1)	15(1)	13(1)	-1(1)	2(1)	4(1)
C(6)	16(1)	16(1)	12(1)	1(1)	1(1)	2(1)
C(7)	14(1)	13(1)	12(1)	-1(1)	3(1)	-2(1)
C(8)	13(1)	13(1)	11(1)	-1(1)	1(1)	-2(1)
C(9)	12(1)	13(1)	11(1)	0(1)	1(1)	1(1)
C(10)	18(1)	11(1)	13(1)	-1(1)	3(1)	0(1)
C(11)	19(1)	17(1)	13(1)	-4(1)	3(1)	-1(1)
C(12)	17(1)	19(1)	10(1)	-2(1)	2(1)	-2(1)
C(13)	16(1)	21(1)	12(1)	-1(1)	4(1)	-4(1)
C(14)	17(1)	18(1)	10(1)	1(1)	0(1)	1(1)

Table S5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **14**.

	x	y	z	U(eq)
H(2)	6160(30)	5916(16)	5008(10)	29
H(3)	5167	4952	7562	14
H(4)	2162	6157	7708	16
H(5)	2556	8458	7886	17
H(6A)	4250	8555	6561	18
H(6AB)	2520	7435	6516	18
H(7A)	8838	6936	6936	16
H(7AB)	7612	8285	6782	16
H(8)	9055	7950	8316	15
H(9)	8525	5659	8137	15
H(10)	6030	9320	8123	17
H(11A)	4592	8802	9385	20
H(11B)	7054	8606	9550	20
H(12)	5385	6798	10100	19
H(13A)	3276	5415	9116	20
H(13B)	2226	6804	9152	20
H(14A)	8544	6315	9578	18
H(14B)	6988	5128	9368	18

Table S6. Hydrogen bonds for **14** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(2)-H(2)...O(1)#1	0.879(14)	1.762(14)	2.6394(12)	175.4(17)

Symmetry transformations used to generate equivalent atoms:

#1 -x+1,-y+1,-z+1