Electronic Supplementary Material (ESI) for ChemComm.


# Supporting Information

# Formation of quaternary carbons through Cobalt-catalyzed C($sp^3$)-C($sp^3$) Negishi cross-coupling.

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# Contents

# General Information

GC measurements were performed using a 6890 Series Gas Chromatograph (Agilent Technologies) system comprising a 7683 Series injector and auto sampler, J&W HP-5MS column (20 m x 0.18 mm, 0.18 µm) from Agilent Technologies coupled to a 5973N MSD Mass Selective Detector (single quadrupole, Agilent Technologies). The MS detector was configured with an electronic impact ionization source/chemical ionization source (EI/CI). EI low-resolution mass spectra were acquired by scanning from 50 to 550 at a rate of 14.29 scan/s. The source temperature was maintained at 230°C. Helium was used as the nebulizer gas. Data acquisition was performed with Chemstation-Open Action software. Thin layer chromatography (TLC) was carried out on silica gel 60 F254 plates (Merck) using reagent grade solvents. Unless otherwise specified, reagents were obtained from commercial sources and used without further purification. Flow reactions were carried out on an E-series Vapourtec equipment. $^{1}$H NMR spectra were recorded on Bruker DPX-400 or Bruker AV-500 spectrometers with standard pulse sequences, operating at 400 MHz and 500 MHz respectively. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (TMS), which was used as an internal standard. All microfluidic fittings were purchased from IDEX Health and Science. The syringes were connected to the capillary using ¼-28 flat-bottom flangeless fittings. The peristaltic pumps of the Vapourtec system were used to feed liquid reagents through a high purity perfluoroalkoxyalkane (PFA) capillary tubing (ID = 0.8 mm) to a Tefzel® tee mixer (ID = 500 µm). The UV-visible measurement was performed using an UV/Vis spectrometer (Avantes, AvaSpec 2048).

# Synthesis of starting materials

## General procedure (1) for the preparation of bromo derivatives

Most of the halogenated starting materials were commercially available. If not, the following procedure was followed.

A round-bottom flask was filled with the corresponding carboxylic acid (1.2 eq.), benzyl alcohol (1 eq.) and DMAP (0.1 eq.). Then, DCM was added and the flask was introduced in an ice-water bath for 15 minutes. Afterwards, DCC (1 eq.) dissolved in DCM was added dropwise and the reaction was stirred overnight. The mixture was diluted with brine and DCM and the organic phase was separated. The water phase was extracted with DCM (x3). The organic phases were combined and dried over $Na_2SO4$, filtered and the solvent was evaporated in vacuo. Purification by flash column chromatography using the indicated mixtures generated the corresponding ester derivative.

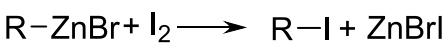
## General procedure (2) for the preparation of organozinc derivatives **2** in flow

*Activation of the Zn column:*

A solution 1.0 M trimethylchlorosilane (TMSCl) and 0.24 M 1-bromo-2-chloroethane was prepared under nitrogen ($N_2$) atmosphere in a dried flask by dissolving 1.25 mL of TMSCl and 0.2 mL of 1-bromo-2-chloroethane in 10 mL of dried tetrahydrofuran (THF). 5 mL of this solution were passed through the 10 mm internal diameter Omni-fit column containing Zn (12 g) using the Vapourtec E-series system at 40°C and 1 mL/min flow rate.

Then, a solution of the corresponding bromo derivative (3 mmol) 0.5 M in THF or DMF was passed through the column containing activated Zn using the Vapourtec E-series system at 40°C and flow rate of 0.5 mL/min. The outcoming solution of the organozinc compound was collected in a closed flask under nitrogen ($N_2$) atmosphere.

*Titration:*



**Scheme S1**. Titration reaction.

Titration with $I_2$ was used to determine approximatively the concentration of the organozinc solution obtained. A known quantity (25mg-30mg approx.) of $I_2$ was weighted and dissolved in 0.5 mL of dry THF in a closed vial under $N_2$ atmosphere. The solution of the organozinc compound was added dropwise until the $I_2$ solution became transparent. The volume of organozinc used to titrate the $I_2$ was used to calculate the molarity (Equation S1).

$$[RZnBr](M) = \frac{W\ iodine\ (mg)}{MW\ iodine\left(\frac{mg}{mmol}\right) * V\ RZnBr\ (ml)}$$

**Equation S1**. Calculation of the molarity of the organozinc compound (W ≡ weight; MW ≡ molecular weight; V ≡ volume).

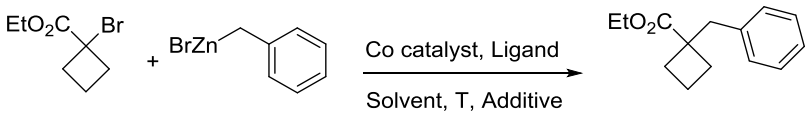
# General procedure (3) for the Cobalt Negishi cross-coupling reaction

A solution of $CoBr_2$ (0.1 eq., 0.1 mmol) and dppe (0.2 eq., 0.2 mmol) was stirred in a mixture of DMF (2 mL) and THF (2 mL) during 15 minutes at rt. Then, the corresponding halo derivative (1 eq., 1 mmol) and the solution of R-ZnBr (2 eq., 2 mmol) were added. The reaction was heated at 40 °C and stirred for 1 hour. The mixture was diluted with EtOAc (10 mL) and a mixture of $NH_4Cl/NH_3$ was added. The layers were separated, and the aqueous layer was extracted with ethyl acetate (2 x 15 mL). The combined organic extracts were washed with brine, dried over $Na_2SO_4$ and concentrated in vacuo. The crude was purified by flash column chromatography using the indicated solvent mixtures giving rise to the corresponding coupling product.

# Screening of the reaction conditions

To a solution of the Cobalt catalyst (0.1 eq., 0.025 mmol), the Ligand (0.2 eq., 0.05 mmol) and the Additive (0.1 eq., 0.025 mmol) stirred in the Solvent (1 mL) was added **1** (1 eq., 0.25 mmol) and **2** (2 eq, 0.5 mmol). The mixture was stirred for 2 hours and the ratio between **3** and **1** was determined by GC-MS.

**Table S1**. Ligand screening for the Co-Negishi cross-coupling reaction.




**1** **2** (2 equiv) **3**

| Entry | Co catalyst (10 mol%) | Ligand (20 mol%) | Solvent | T ($^{O}$C) | Additive (10 mol%) | Ratio 3:1 |
|---|---|---|---|---|---|---|
| 1 | $CoBr_2$ | dppf | DMF | rt | Zn metal | 25:75 |
| 2 | $CoBr_2$ | dppf | DMF | rt | Mg metal | 45:55 |
| 3 | $CoBr_2$ | dppf | DMF | 40 | Mg metal | 48:52 |
| 4 | $CoBr_2$ | dppf | THF | 40 | Mg metal | 6:94 |
| 5 | $CoBr_2$ | dppf | Toluene/THF | 40 | Mg metal | 16:84 |
| 6 | $CoBr_2$ | dppf | DMF/THF | 40 | Mg metal | 65:35 |
| 7 | $CoBr_2$ | $PPh_3$ | DMF/THF | 40 | Mg metal | 24:76 |
| 8 | $CoBr_2$ | $P(4\text{-}OMePh)_3$ | DMF/THF | 40 | Mg metal | 6:94 |
| 9 | $CoBr_2$ | $PMe_3$ | DMF/THF | 40 | Mg metal | 7:93 |
| 10 | $CoBr_2$ | $PCy_3$ | DMF/THF | 40 | Mg metal | 23:77 |
| 11 | $CoBr_2$ | Johnphos | DMF/THF | 40 | Mg metal | 5:95 |
| 12[1] | $CoBr_2$ | dppf | DMF/THF | 40 | - | 97:3 (45%) |
| 13 | $CoBr_2$ | - | DMF/THF | 40 | - | 6:94 |
| 14 | - | - | DMF/THF | 40 | - | 0:100 |
| 15[2] | $CoBr_2$ | dppe | DMF/THF | 40 | - | 94:6 |
| **16[1]** | **$CoBr_2$** | **dppe** | **DMF/THF** | **40** | **-** | **100:0 (55%)** |
| 17 | $CoBr_2$ | dppb | DMF/THF | 40 | - | 41:59 |
| 18[1] | $CoBr_2$ | dppp | DMF/THF | 40 | - | 100:0 (49%) |
| 19 | $CoBr_2$ | dppbz | DMF/THF | 40 | - | 27:73 |
| 20 | $CoBr_2$ | Xantphos | DMF/THF | 40 | - | 40:60 |
| 21[1] | $CoBr_2$ | Josiphos | DMF/THF | 40 | - | 100:0 (38%) |
| 22 | $CoBr_2$ | Symphos | DMF/THF | 40 | - | 50:50 |
| 23 | $CoBr_2$ | rac-Binap | DMF/THF | 40 | - | 6:94 |
| 24 | $CoBr_2$ | $(Et)_2P\text{-}Et\text{-}P(Et)_2$ | DMF/THF | 40 | - | 1:99 |
| 25 | $CoBr_2$ | $(Cy)_2P\text{-}Et\text{-}P(Cy)_2$ | DMF/THF | 40 | - | 76:24 |
| 26 | $Co(dppe)Cl_2$ | - | DMF/THF | 40 | - | 58:42 |
| 27 | $Co(dppe)I_2$ | - | DMF/THF | 40 | - | 98:2 |
| 28 | $Co(dppf)Cl_2$ | - | DMF/THF | 40 | - | 61:39 |

[1] Values in brackets are referred to isolated yields.[2] Reaction carried out with 5 mol% of $CoBr_2$ and 10 mol% of dppe.

A selection of representative bidentate ligands, which shown better results in the screening, is depicted in Table S2 with the corresponding bite angle.[1] From these values, a bite angle between 85 and 93$^{o}$ as well as a diaryl alkyl substitution pattern in the phosphorus provided better results in terms of conversion.

[1] van Leeuwen, P. W. N. M.; Kamer, P. C. J.; Reek, J. N. H.; Dierkers, P. *Chem. Rev.* **2000**, *100*, 2741.

**Table S2**. Bite angle of some phosphane ligands *vs* ratio **3**:**1**.

| Entry | Ligand | Ratio 3:1 | Bite angle |
|---|---|---|---|
| 1 | dppe | 100:0 | 85 |
| 2 | dppp | 100:0 | 91 |
| 3 | dppb | 41:59 | 98 |
| 4 | Josiphos | 100:0 | 93 |
| 5 | dppf | 97:3 | 96 |
| 6 | Xantphos | 40:60 | 111 |
| 7 | Binap | 6:94 | 92 |
| 8 | dppbz | 27:73 | 83 |

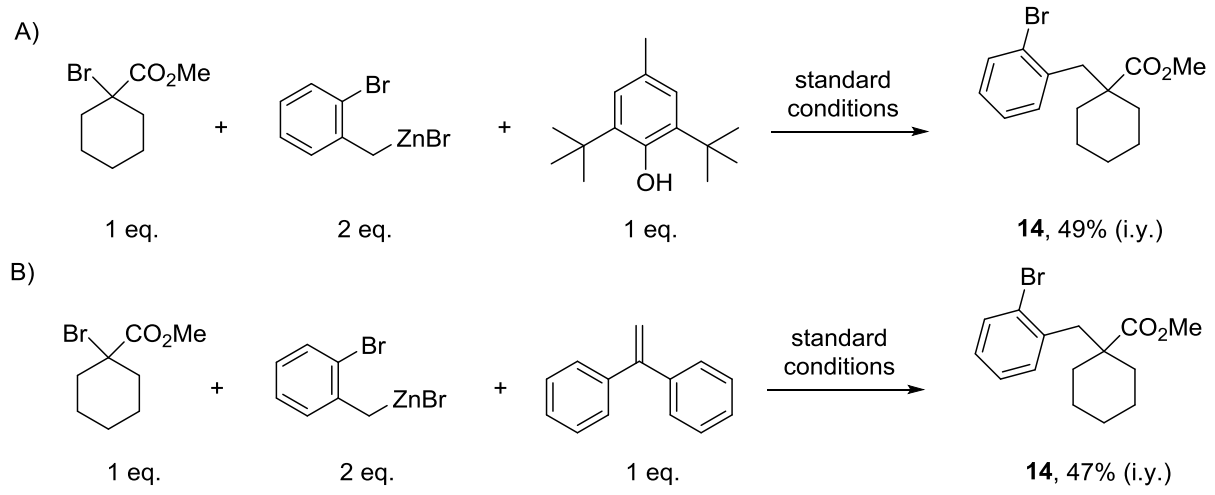
# General procedure (4) for the Buchwald cyclization reaction

A round-bottom flask was filled with the corresponding halogen (1 eq.), amine (1.2 eq.), BRETTPHOS PD G3 (0.01 eq.), X-Phos (0.01 eq.) and $NaO^tBu$ (1.2 eq.). Then, the flask was sealed and degassed with $N_2$. Then, 1,4-dioxane was added and the mixture was heated at 100 degrees until the starting material is consumed. The reaction mixture was cooled down to room temperature, diluted with ethyl acetate, washed with water and concentrated in vacuo. The crude was purified by flash chromatography using the indicated solvent mixtures.

# Mechanistic studies

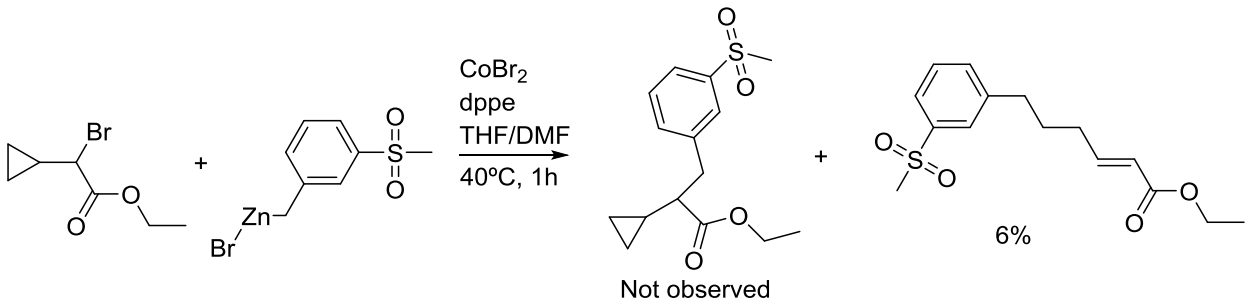
## Radical trap experiments

Methyl 1-bromocyclohexane-1-carboxylate was selected to test the presence of radicals in the reaction media. Considering our previous experience in the reactivity of organozinc derivatives with radical trap reagents, we chose diphenylethylene and dibutylhydroxytoluene (BHT) as trapping reagents. None of them showed reactivity and the conversion of starting material in product **14** remained 100%. These results suggest the absence of radicals in the reaction, although their presence cannot be ruled out.



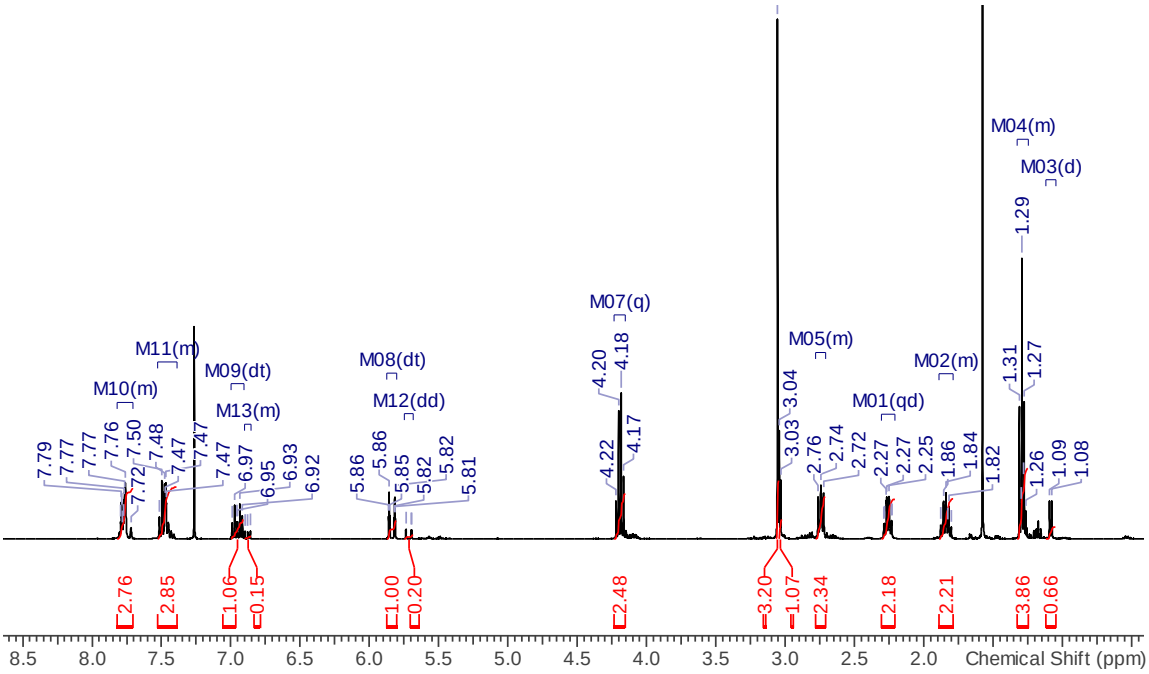

**Scheme S2**. Radical trap experiments.

## Radical clock experiment




**Scheme S3**. Radical clock experiment.

$^{1}$H-NMR isolated radical clock product:




## NMR study

NMR spectra were recorded in a Bruker Avance 500 working at 470.592 MHz for $^{19}$F-NMR and 202.457 MHz for $^{31}$P-NMR in a mixture THF-$H_8$ : DMF-$H_7$ 1 : 1. In consequence spectra were recorded without lock with 16 transients and temperature controlled at 298 K unless otherwise stated. Kinetic experiments were performed with the zincate as the internal reference. Spectra were processed and analysed with MestreNova 10.0.1.[2]

[2] MestreNova version 10.0.1. Mestrelab Research, S.L. www.mestrelab.com.

1,2-bis(2-trifluoromethyl)phenylethane (-60.16) and 2-trifluoromethyltoluene (-62.17) were previously identified.[3]

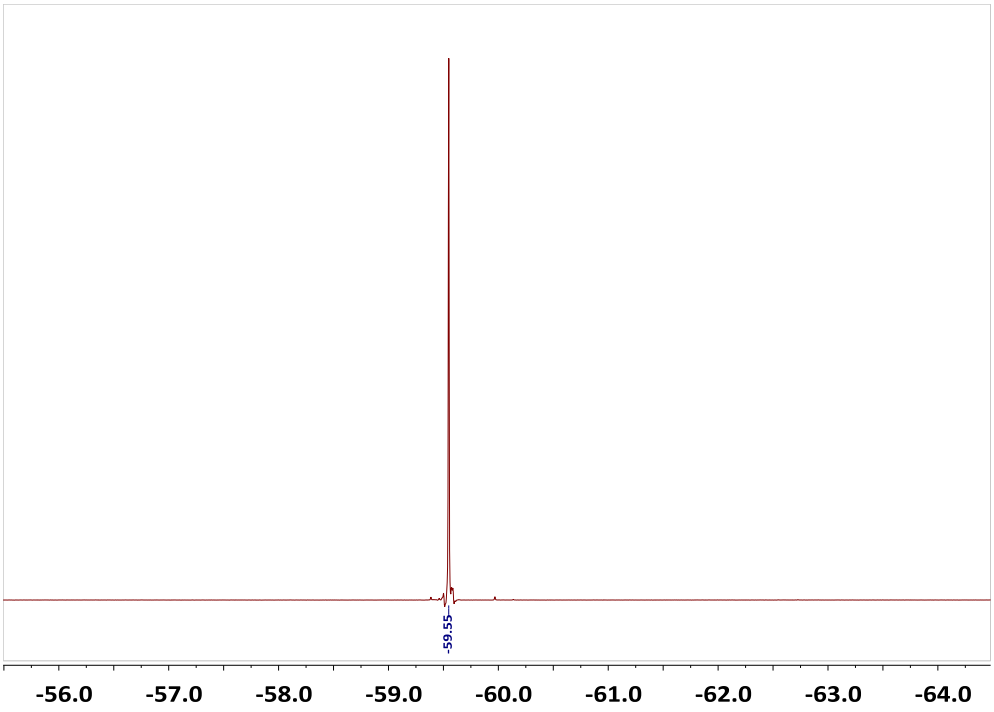



**Figure S1.** $^{19}$F-NMR spectrum of 2-trifluoromethylbenzylbromide (-59.55), solvent THF-$d_8$.

[3] Abdiaj, I.; Fontana, A.; Gómez-Almagro, M. V.; de la Hoz, A.; Alcázar J. *Angew. Chem. Int. Ed.*, **2018**, *57*, 8473-8477

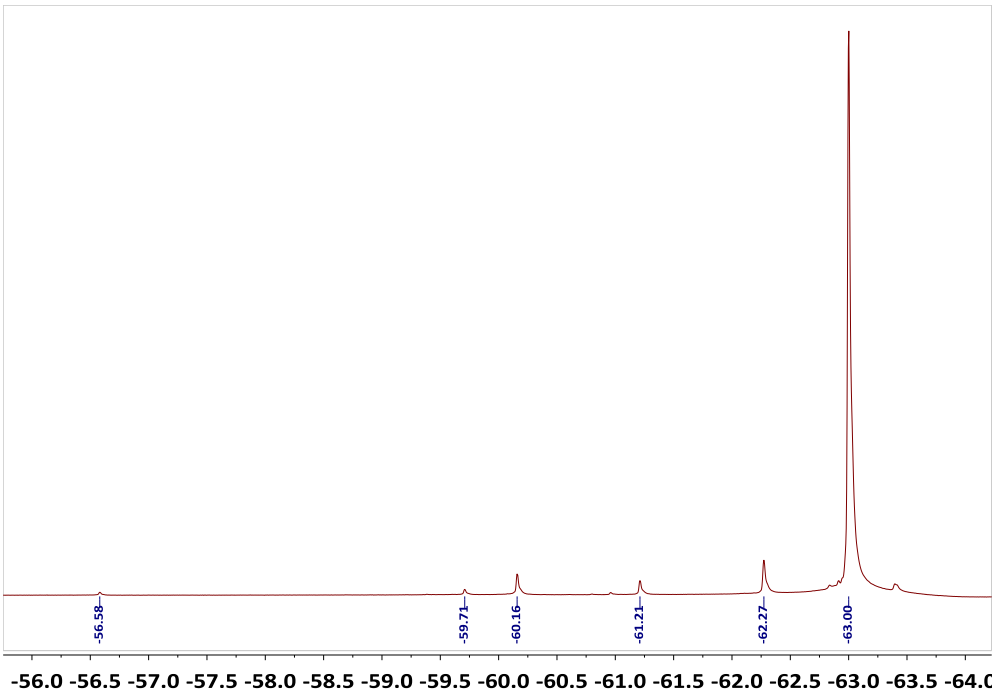



**Figure S2.** $^{19}$F-NMR spectrum of a freshly prepared sample of 2-trifluoromethylbenzylzincbromide **39** (-63.00), solvent THF-$d_8$. Impurities, 2-trifluoromethylbenzaldehyde, -56.58; 1,2-bis(2-trifluoromethyl)phenylethane **40**, -60.16; 2-trifluoromethyltoluene, -62.17; unknown compounds, -59.71 and -61.21.

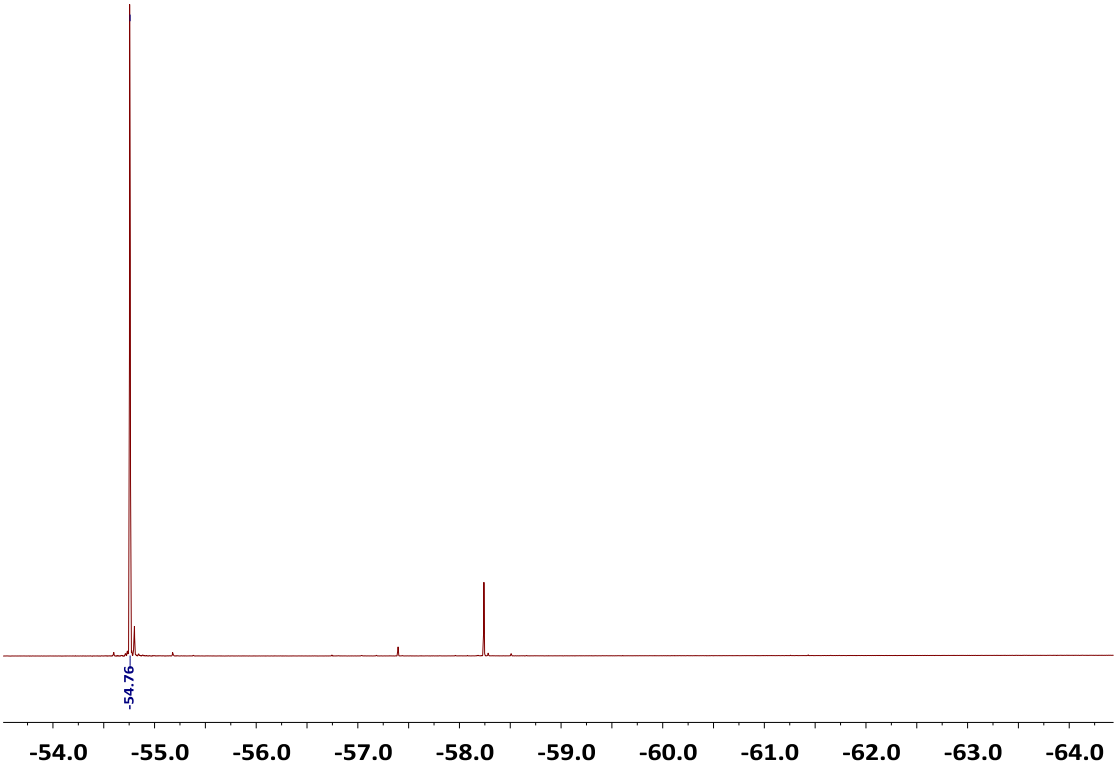



**Figure S3.** $^{19}$F-NMR spectrum of 2-trifluoromethylbenzaldehyde (-54.76), solvent THF-$d_8$.

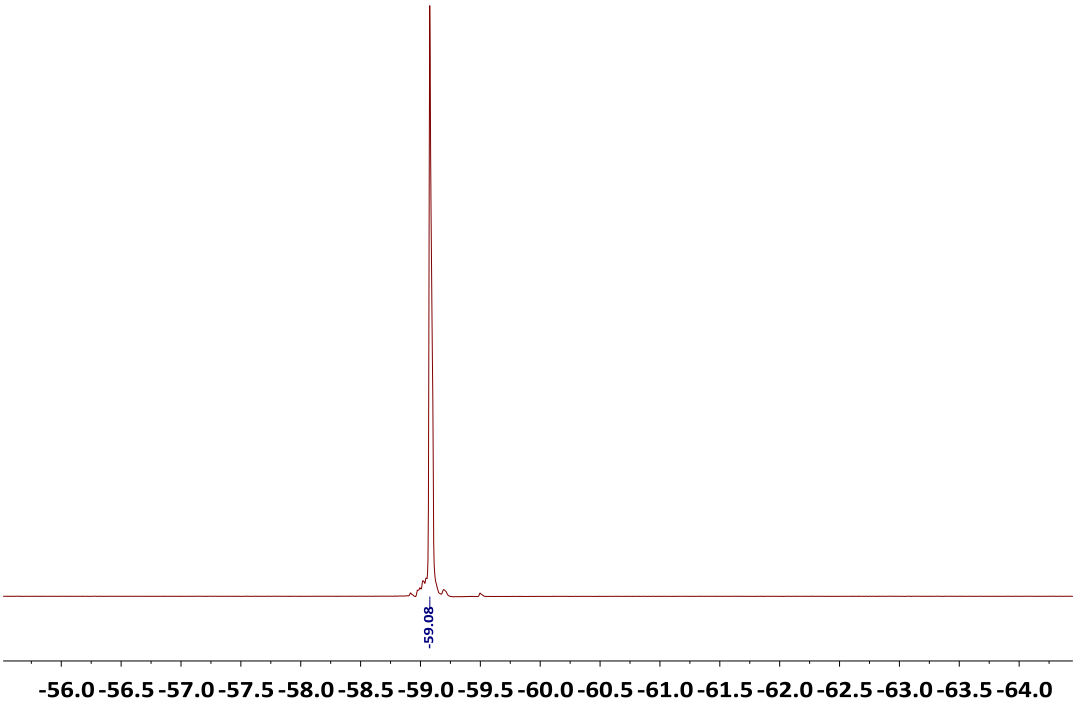



**Figure S4.** $^{19}$F-NMR spectrum of 2-trifluoromethylbenzoic acid (-59.08), solvent THF-$H_8$ : DMF-$H_7$ 1 : 1.

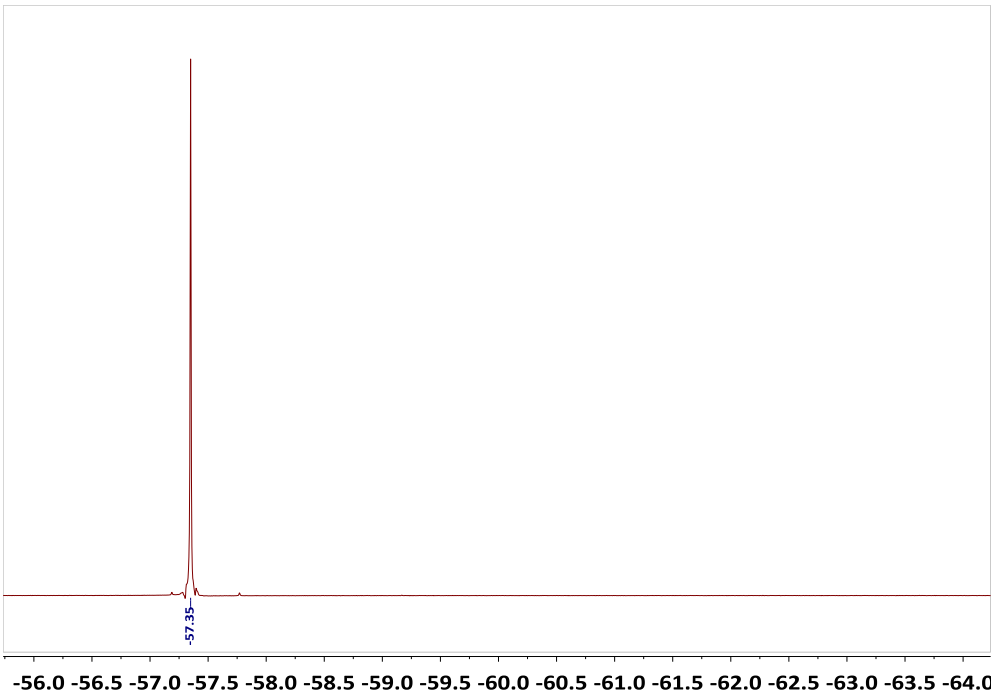



**Figure S5.** $^{19}$F-NMR spectrum of methyl 1-(2-(trifluoromethyl)benzyl)cyclohexane-1-carboxylate (-57.35), solvent THF-$d_8$.

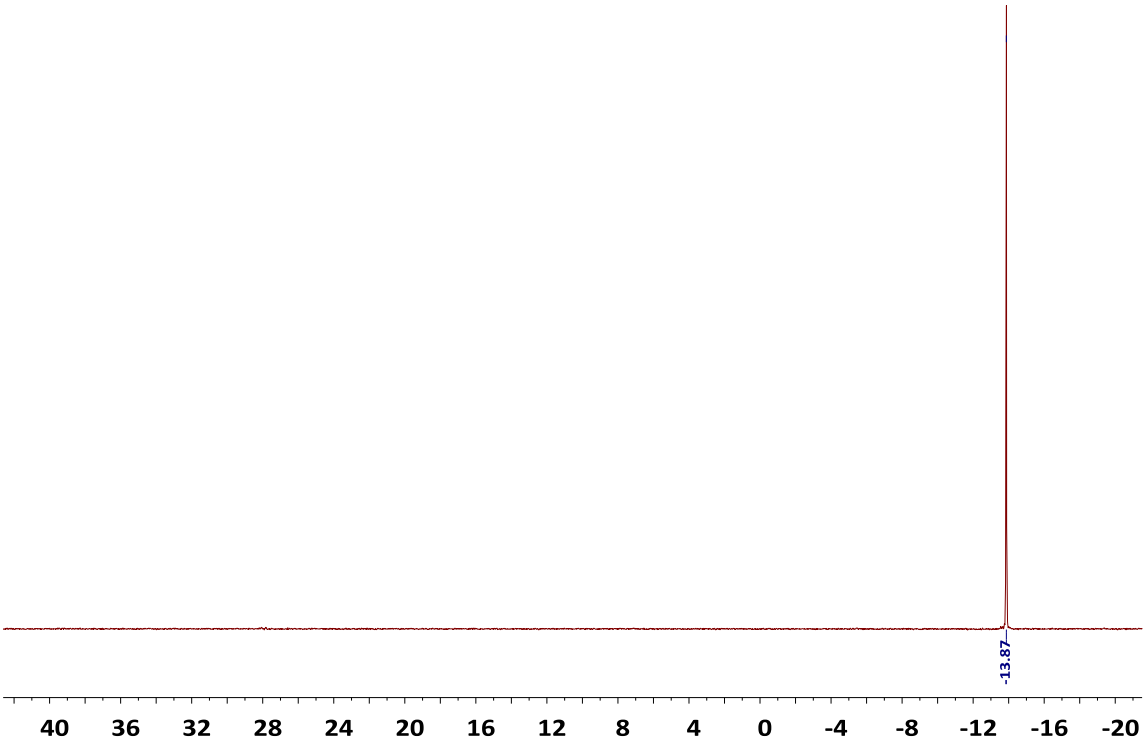


**Figure S6**. $^{31}$P-NMR spectrum of 1,2-Bis(diphenylphosphino)ethane (dppe) (-13.87), solvent THF-$H_8$ : DMF-$H_7$ 1 : 1, temperature 298 K.

**a)** **b)**

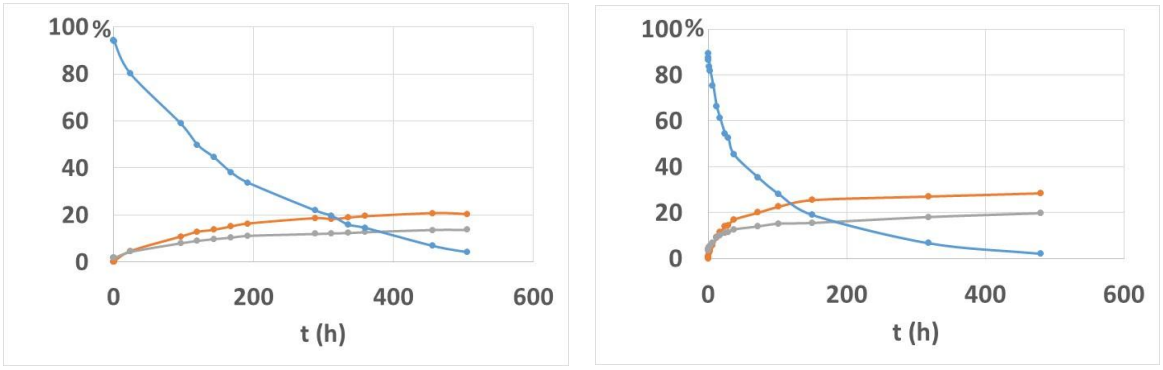



**Figure S7.** Kinetic experiment by $^{19}$F-NMR: dppe 1 eq. of **38** + 2 eq. **39**, solvent THF-H8 : DMF-H7 1 : 1, temperature 298 K. a) 5% $CoBr_2$. b) 20% $CoBr_2$. **39** (**—**), **16** (**—**), **40** (**—**).

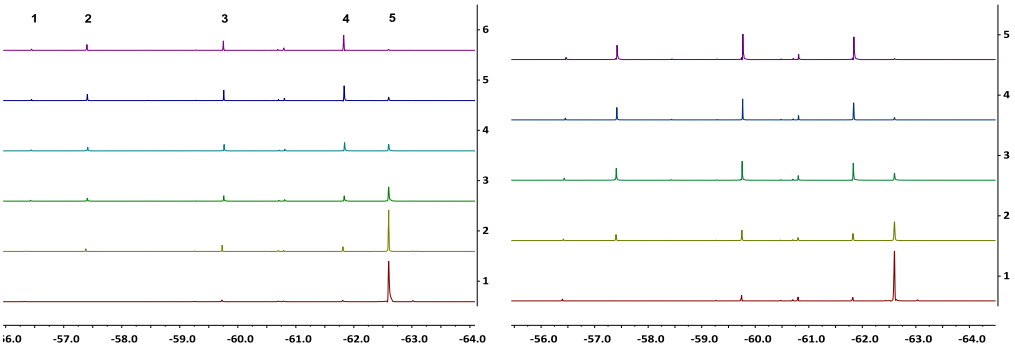



**Figure S8.** Kinetic experiment by $^{19}$F-NMR. dppe + 1 eq. **38** + 2 eq. **39**, solvent THF-$H_8$ : DMF-$H_7$ 1 : 1, temperature 298 K. a) + 5% $CoBr_2$ Spectrum 1) t =0. 2) 24 h, 3) 96 h, 4) 192 h, 5) 360 h, 6) 504 h. b) + 20% $CoBr_2$ Spectrum 1) t =0. 2) 24 h, 3) 168 h, 4) 360 h, 5) 528 h. **1**: 2-trifluoromethylbenzaldehyde. **2**: methyl 1-(2-(trifluoromethyl)benzyl)cyclohexane-1-carboxylate. **3**: 1,2-bis(2-trifluoromethyl)phenylethane **40**. **4**: 2-trifluoromethyltoluene. **5**: 2-trifluoromethylbenzylzinc bromide **39**.

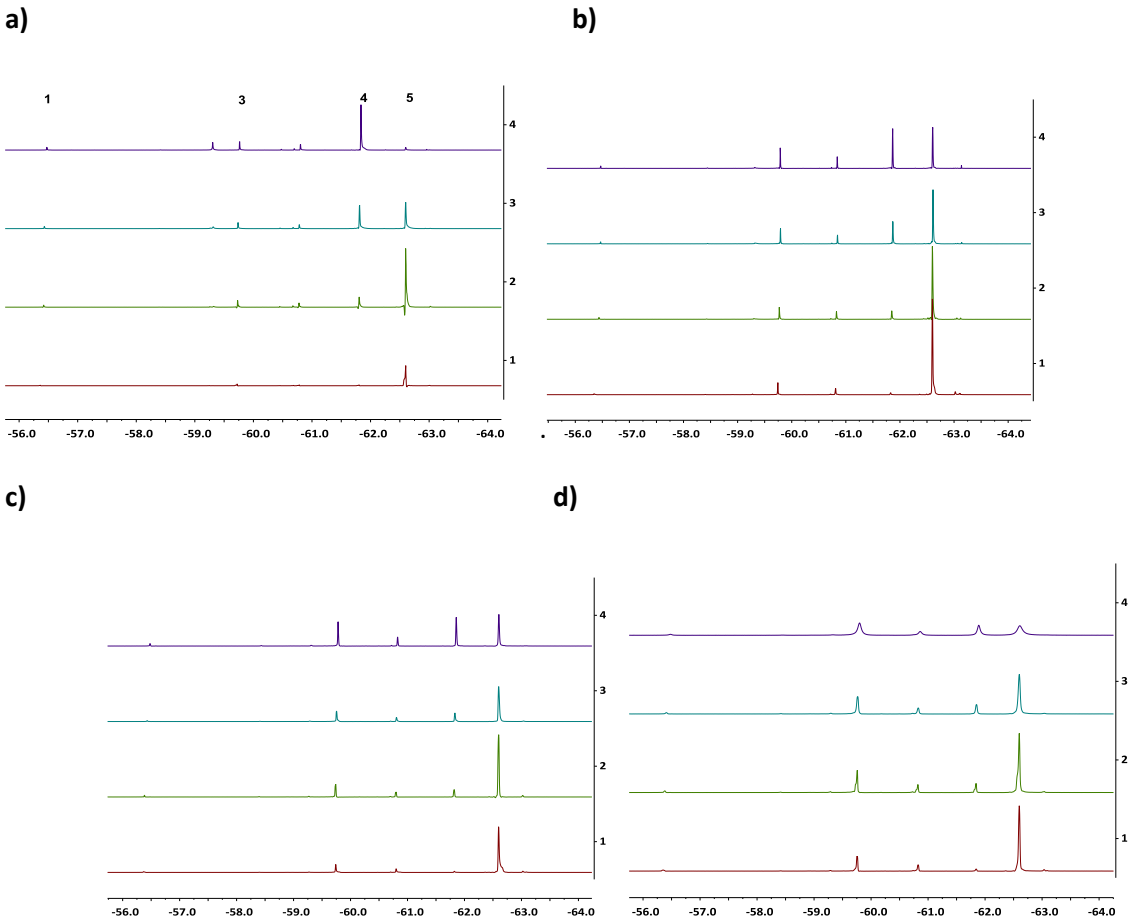



**Figure S9.** $^{19}$F-NMR spectrum dppe + 2 eq. **39** + a) 0% $CoBr_2$, 1) t=0. 2) after 3 days. 3) after 7 days. 4) after 20 days, b) 5% $CoBr_2$ , c) 20% $CoBr_2$, d) 50% $CoBr_2$ b), c), d) 1) t =0. 2) after 3 days. 3) after 5 days. 4) after 12 days. Solvent THF-$H_8$ : DMF-$H_7$ 1 : 1, temperature 298 K. , solvent THF-$H_8$ : DMF-$H_7$ 1 : 1, temperature 298 K. **1**: 2-trifluoromethylbenzaldehyde. **3**: 1,2-bis(2-trifluoromethyl)phenylethane **40**. **4**: 2-trifluoromethyltoluene. **5**: 2-trifluoromethylbenzylzinc bromide **39**.

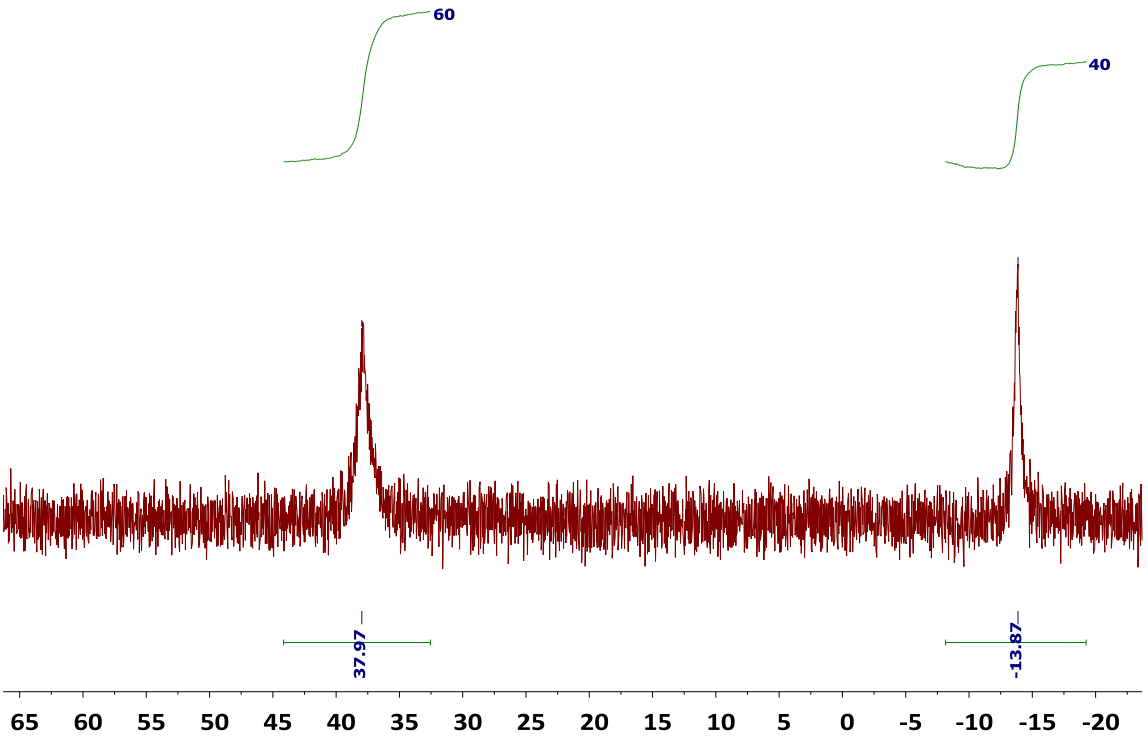



**Figure S10.** $^{31}$P-NMR spectrum of dppe + 2 eq. **39** in the presence of 20% $CoBr_2$, solvent THF-$H_8$ : DMF-$H_7$ 1 : 1, temperature 298 K.

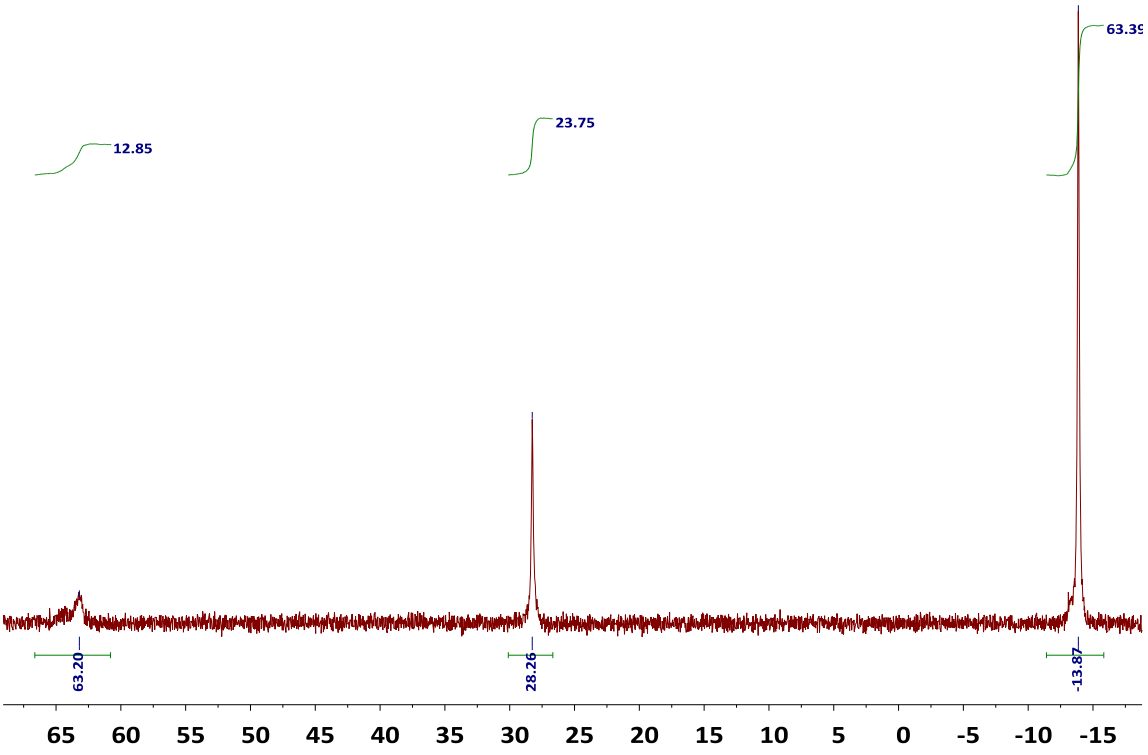
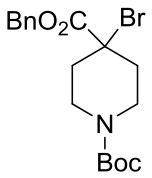



**Figure S11.** $^{31}$P-NMR spectrum of dppe after addition of 1 eq. of $Co(CO)_2Cp$, solvent THF-$H_8$ : DMF-$H_7$ 1 : 1, temperature 298 K.

# Characterization of the starting materials

## Characterization of bromo derivatives

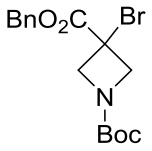
*4-benzyl 1-(tert-butyl) 4-bromopiperidine-1,4-dicarboxylate*:




Prepared following the General procedure 1: 4-bromo-1-[(*tert*-butoxy)carbonyl]piperidine-4-carboxylic acid (375 mg, 1.2 mmol); benzyl alcohol (0.1 mL, 1 mmol); DMAP (12.2 mg, 0.1 mmol); DCC (206 mg, 1 mmol). Purification by flash chromatography (silica; EtOAc in heptane 0/100 to 25/75) afforded the product as a transparent liquid; isolated yield: 98%.

**$^{1}$H NMR** ($CDCl_3$, 400 MHz): δ = 7.36 (m, 5H), 5.24 (s, 2H), 3.71 (br d, *J* = 12.2 Hz, 2H), 2.24-2.20 (m, 2H), 2.13-2.06 (m, 2H), 1.45 (s, 9H) ppm.
**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 170.0, 154.5, 135.2 128.7, 128.5, 128.1, 80.0, 67.8, 60.5, 36.4, 28.4 ppm.
**HRMS** (ESI-TOF): mass calcd. for $C_{18}H_{24}BrNO_4$, 397.0889; m/z found, 397.9944 $[M+H]^+$.

3-*benzyl 1-(tert-butyl) 3-bromopiperidine-1,3-dicarboxylate*:



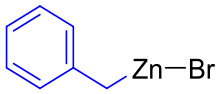

Prepared following the General procedure 1: 3-bromo-1-(*tert*-butoxycarbonyl)azetidine-3-carboxylic acid (336 mg, 1.2 mmol), previously synthesized following the procedure described by Vitnik V.D. *et al.*,[4] benzyl alcohol (0.1 mL, 1 mmol), DMAP (12.2 mg, 0.1 mmol) and DCC (206 mg, 1 mmol). Purification by flash chromatography (silica; EtOAc in heptane 0/100 to 15/85) afforded the product as a transparent liquid; isolated yield: 78%.

**$^{1}$H NMR** ($CDCl_3$, 400 MHz): δ = 7.38 (m, 5H), 5.25 (s, 2H), 4.66-4.63 (m, 2H), 4.31-4.28 (m, 2H), 1.43 (s, 9H) ppm.
**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 168.8, 155.7, 134.7 128.7, 128.3, 80.7, 68.4, 62.5, 44.5, 28.3 ppm.
**GC-MS** (EI): mass calcd. for $C_{16}H_{20}BrNO_4$, 369.1; m/z found, 369.0.

[4] Vitnik, V. D.; Ivanovic, M. D.; Vitnik, Z. J.; Dordevic, J. B.; Zizak, Z. S.; Juranic, Z. D.; Juranic, I. O. *Synth. Commun.* **2009**, *39*, 1457.

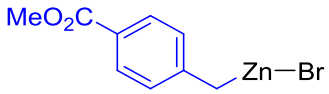
## Characterization of organozinc derivatives

*Benzyl zinc(II) bromide*



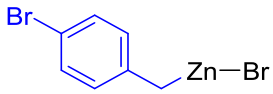

Prepared following General procedure 2; **Titration**: 0.40M.

*(4-(ethoxycarbonyl)-benzyl) zinc(II) bromide*



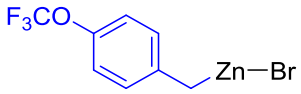

Prepared following General procedure 2; **Titration**: 0.29M.

*4-bromobenzyl zinc(II) bromide*



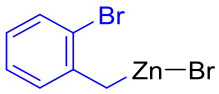

Prepared following General procedure 2; **Titration**: 0.34M.

*(4-(trifluoromethoxy)benzyl) zinc(II) bromide*



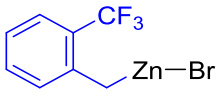

Prepared following General procedure 2; **Titration**: 0.33M.

*2-bromobenzyl zinc(II) bromide*



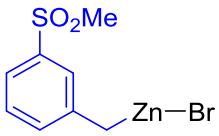

Prepared following General procedure 2; **Titration**: 0.32M.

*2-trifluromethylbenzyl zinc(II) bromide*



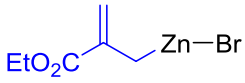

Prepared following General procedure 2; **Titration**: 0.37M.

*(3-(methylsulfonyl)benzyl) zinc(II) bromide*




Prepared following General procedure 2; **Titration**: 0.30M.

*(2-(ethoxycarbonyl)allyl) zinc(II) bromide*

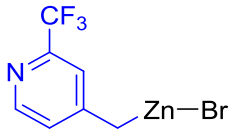



Prepared following General procedure 2; **Titration**: 0.40M.

*((3,5-dimethylisoxazol-4-yl)methyl )zinc(II) bromide*


Prepared following General procedure 2; **Titration**: 0.40M.

*((2-(trifluoromethyl)pyridin-4-yl)methyl) zinc(II) bromide*



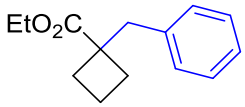

Prepared following General procedure 2; **Titration**: not suitable

*((2-chloropyridin-3-yl)methyl) zinc(II) bromide*


Prepared following General procedure 2; **Titration**: not suitable

# Characterization of products

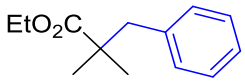
*Ethyl 1-benzylcyclobutane-1-carboxylate* (**3**):



Prepared following the General procedure 3 on 1 mmol scale with ethyl 1-bromocyclobutane-1-carboxylate (1 eq., 1 mmol); benzyl zinc(II) bromide (2 eq., 2 mmol); $CoBr_2$ (0.1 eq., 0.1 mmol); dppe (0.2 eq., 0.20 mmol). Purification by flash chromatography (silica; heptane in DCM 100/0 to 50/50) afforded the product as a transparent liquid; isolated yield: 55%.

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 7.26-7.16 (m, 3H), 7.13-7.10 (m, 2H), 4.10 (q, *J* = 7.2 Hz, 2H), 3.10 (s, 3H), 2.46-2.38 (m, 2H), 2.10-2.00 (m, 2H), 1.90-1.83 (m, 2H), 1.19 ppm (t, *J* = 7.05 Hz, 3H).
**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 176.7, 138.2, 129.3, 128.2, 126.4, 60.4, 48.7, 43.4, 30.0, 29.7, 15.6, 14.2 ppm.
**GC-MS** (EI): mass calcd. for $C_{13}H_{16}O_2$, 218.1; m/z found, 218.1.

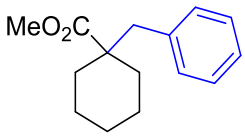
*Ethyl 2,2-dimethyl-3-phenylpropanoate* (**4**):



Prepared following the General procedure 3 on 1 mmol scale with ethyl 2-bromo-2-methylpropanoate (1 eq., 1 mmol); benzyl zinc(II) bromide (2 eq., 2 mmol); $CoBr_2$ (0.1 eq., 0.1 mmol); dppe (0.2 eq., 0.20 mmol). Purification by flash chromatography (silica; pentane in DCM 100/0 to 80/20) afforded the product as a transparent liquid; isolated yield: 40%.

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 7.42-7.35 (m, 3H), 7.28-7.26 (m, 2H), 4.26 (q, *J* = 7.2 Hz, 2H), 2.07 (s, 2H), 1.38 (t, *J* = 7.1 Hz, 3H), 1.33 (s, 6H).
**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 177.5, 138.1, 130.2, 128.0, 126.4, 60.4, 46.3, 43.5, 25.0, 14.2 ppm.
**HRMS** (ESI-TOF): mass calcd. for $C_{13}H_{18}O_2$, 206.1307; m/z found, 207.1349 $[M+H]^+$.

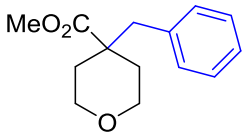
*Methyl 1-benzylcyclohexane-1-carboxylate* (**5**):



Prepared following the General procedure 3 on 1 mmol scale with methyl 1-bromocyclohexane-1-carboxylate (1 eq., 1 mmol); benzyl zinc(II) bromide (2 eq., 2 mmol); $CoBr_2$ (0.1 eq., 0.1 mmol); dppe (0.2 eq., 0.20 mmol). Purification by flash chromatography (silica; pentane in DCM 100/0 to 80/20) afforded the product as a transparent liquid; isolated yield: 46%.

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 7.26-7.19 (m, 3H), 7.05-7.02 (m, 3H), 3.61 (s, 3 H), 2.79 (s, 2H), 2.08-2.05 (m, 2H), 1.64-1.59 (m, 3H), 1.33-1.18 (m, 5H).
**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 176.5, 137.3, 129.2, 127.9, 126.5, 51.3, 47.0, 34.1, 25.8, 23.4 ppm.
**GC-MS** (EI): mass calcd. for $C_{15}H_{20}O_2$, 232.1; m/z found, 232.1.

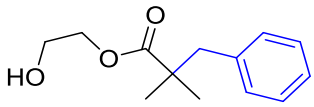
*Methyl 4-benzyltetrahydro-2H-pyran-4-carboxylate* (**6**):




Prepared following the General procedure 3 on 1 mmol scale with methyl 4-bromotetrahydro-*2H*-pyran-4-carboxylate (1 eq., 1 mmol); benzyl zinc(II) bromide (2 eq., 2 mmol); $CoBr_2$ (0.1 eq., 0.1 mmol); dppe (0.2 eq., 0.20 mmol). Purification by flash chromatography (silica; pentane in DCM 100/0 to 50/50) afforded the product as a transparent liquid; isolated yield: 51%.

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 7.28-7.19 (m, 3H), 7.04-7.02 (m, 2H), 3.87-3.82 (m, 2H), 3.64 (s, 3H), 3.43-3.36 (m, 2H), 2.84 (s, 2H), 2.07-2.03 (m, 2H), 1.65-1.58 (m, 2H) ppm.
**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 175.5, 136.2, 129.8, 128.1, 126.8, 65.5, 51.6, 47.0, 46.8, 34.1 ppm.
**GC-MS** (EI): mass calcd. for $C_{14}H_{18}O_3$, 234.1; m/z found, 234.1.

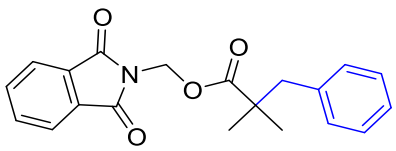
*2-hydroxyethyl 2,2-dimethyl-3-phenylpropanoate* (**7**):




Prepared following the General procedure 3 on 1 mmol scale with 2-hydroxyethyl-2-bromo-2-methylpropanoate (1 eq., 1 mmol); benzyl zinc(II) bromide (2 eq., 2 mmol); $CoBr_2$ (0.1 eq., 0.1 mmol); dppe (0.2 eq., 0.20 mmol). Purification by flash chromatography (silica; pentane in DCM 100/0 to 50/50) afforded the product as a transparent liquid; isolated yield: 44%.

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 7.29-7.20 (m, 3H), 7.14-7.11 (m, 2H), 4.18-4.16 (m, 2H), 3.77-3.74 (m, 2H), 2.87 (s, 2H), 1.22 ppm (s, 6H).
**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 177.8, 137.8, 130.1, 128.1, 126.6, 66.3, 61.3, 46.6, 43.8, 25.1 ppm.
**GC-MS** (EI): mass calcd. for $C_{13}H_{18}O_3$, 222.1; m/z found, 222.1.

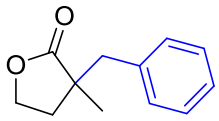
*(1,3-dioxoisoindolin-2-yl)methyl 2,2-dimethyl-3-phenylpropanoate* (**8**):



Prepared following the General procedure 3 on 1 mmol scale with (1,3-dioxoisoindolin-2-yl)methyl 2-bromo-2-methylpropanoate (1 eq., 1 mmol); benzyl zinc(II) bromide (2 eq., 2 mmol); $CoBr_2$ (0.1 eq., 0.1 mmol); dppe (0.2 eq., 0.20 mmol). Purification by flash chromatography (silica; pentane in DCM 100/0 to 50/50) afforded the product as a transparent liquid; isolated yield: 59%.

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 7.96-7.91 (m, 2H), 7.81-7.77 (m, 2H), 7.21-7.10 (m, 5H), 5.71 (s, 2H), 2.83 (s, 2H), 1.18 ppm (s, 6H).
**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 176.3, 166.7, 137.4, 134.6, 131.8, 130.1, 128.0, 126.5, 124.0, 61.2, 46.1, 43.7, 24.8 ppm.
**HRMS** (ESI-TOF): mass calcd. for $C_{20}H_{19}NO_4$, 337.1314; m/z found, 360.1215 $[M+Na]^+$.

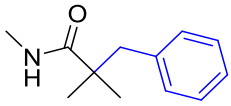
*3-benzyl-3-methyldihydrofuran-2(3H)-one* (**9**):



Prepared following the General procedure 3 on 1 mmol scale with 3-bromo-3-methyldihydrofuran-2(3H)-one; benzyl zinc(II) bromide (2 eq., 2 mmol); $CoBr_2$ (0.1 eq., 0.1 mmol); dppe (0.2 eq., 0.20 mmol). Purification by flash chromatography (silica; heptane in ethyl acetate 100/0 to 75/25) afforded the product as a transparent liquid; isolated yield: 56%.

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 7.32-7.24 (m, 3H), 7.20-7.18 (m, 2H). 4.11 (ddd, *J* = 9.1, 8.0 and 6.5 Hz, 1H), 3.75 (ddd, *J* = 9.0, 8.1 and 6.0 Hz, 1H), 3.04 (d, *J* = 13.4 Hz, 1H), 2.74 (d, *J* = 13.4 Hz, 1H), 2.29 (m, 1H), 1.93 (ddd, *J* = 12.8, 8.0 and 6.0 Hz, 1H), 1.30 (s, 3H) ppm.
**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 181.8, 136.7, 130.0, 128.5, 127.0, 65.0, 43.9, 43.5, 33.5, 23.7 ppm.
**GC-MS** (EI): mass calcd. for $C_{12}H_{14}O_2$, 190.1; m/z found, 190.1.

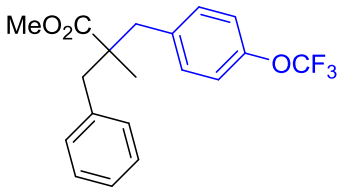
*N,2,2-trimethyl-3-phenylpropanamide* (**10**):



Prepared following the General procedure 3 on 1 mmol scale with 2-bromo-N,2-dimethylpropanamide (1 eq., 1 mmol); benzyl zinc(II) bromide (2 eq., 2 mmol); $CoBr_2$ (0.1 eq., 0.1 mmol); dppe (0.2 eq., 0.20 mmol). Purification by flash chromatography (silica; pentane in DCM 100/0 to 50/50) afforded the product as a transparent liquid; isolated yield: 45%.

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 7.27-7.17 (m, 3H), 7.12-7.09 (m, 2H), 5.47 (br s, 1H), 2.83 (s, 2H), 2.71 (d, *J* = 4.6 Hz, 3H), 1.17 (s, 6H) ppm.
**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 177.6, 138.2, 130.1, 127.9, 126.3, 47.0, 43.5, 26.4, 25.1 ppm.
**GC-MS** (EI): mass calcd. for $C_{12}H_{17}NO$, 191.1; m/z found, 191.2.

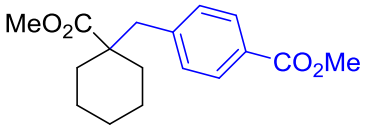
*Methyl 2-benzyl-2-methyl-3-(4-(trifluoromethoxy)phenyl)propanoate* (**11**):




Prepared following the General procedure 3 on 1 mmol scale with methyl 2-chloro-2-methyl-3-phenylpropanoate (1 eq., 1 mmol); (4-(trifluoromethoxy)benzyl) zinc(II) bromide (2 eq., 2 mmol); $CoBr_2$ (0.1 eq., 0.1 mmol); dppe (0.2 eq., 0.20 mmol). Purification by flash chromatography (silica; pentane in DCM 100/0 to 50/50) afforded the product as a transparent liquid; isolated yield: 64%.

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 7.28-7.19 (m, 3H), 7.14-7.08 (m, 6H), 3.59 (s, 3H), 3.21 (m, 2H), 2.68 (dd, *J* = 16.2 and 13.2 Hz, 2H), 1.03 (s, 3H) ppm.
**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 176.1, 148.1, 137.2, 136.3, 131.4, 130.2, 128.2, 126.7, 120.5, 51.5, 40.1, 46.4, 45.3, 19.9 ppm.
**GC-MS** (EI): mass calcd. for $C_{19}H_{19}F_3O_3$, 352.1; m/z found, 352.2.

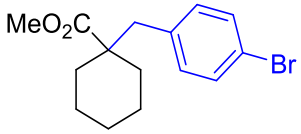
*Ethyl 4-((1-(methoxycarbonyl)cyclohexyl)methyl)benzoate* (**12**):




Prepared following the General procedure 3 on 1 mmol scale with methyl 1-bromocyclohexane-1-carboxylate (1 eq., 1 mmol); (4-(ethoxycarbonyl)-benzyl) zinc(II) bromide (2 eq., 2 mmol); $CoBr_2$ (0.1 eq., 0.1 mmol); dppe (0.2 eq., 0.20 mmol). Purification by flash chromatography (silica; pentane in DCM 100/0 to 50/50) afforded the product as a transparent liquid; isolated yield: 53%.

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 7.94-7.91 (m, 2H), 7.12-7.10 (m, 2H), 3.89 (s, 3H), 3.60 (s, 3H), 2.83 (s, 2H), 2.08-2.05 (m, 2H), 1.63-1.57 (m, 3H), 1.33-1.21 (m, 5H) ppm.
**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 176.1, 167.0, 142.8, 129.9, 129.2, 128.4, 52.0, 51.3, 48.8, 46.9, 34.1, 25.7, 23.3 ppm.
**GC-MS** (EI): mass calcd. for $C_{18}H_{24}O_4$, 290.2; m/z found, 290.2.

*Methyl 1-(4-bromobenzyl)cyclohexane-1-carboxylate* (**13**):

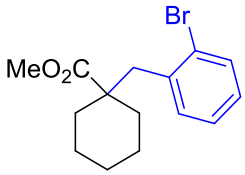



Prepared following the General procedure 3 on 1 mmol scale with methyl 1-bromocyclohexane-1-carboxylate (1 eq., 1 mmol); 4-bromobenzyl zinc(II) bromide (2 eq., 2 mmol); $CoBr_2$ (0.1 eq., 0.1 mmol);

dppe (0.2 eq., 0.20 mmol). Purification by flash chromatography (silica; pentane in DCM 100/0 to 50/50) afforded the product as a transparent liquid; isolated yield: 60%.

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 7.37-7.34 (m, 2H), 6.92-6.88 (m, 2H), 3.60 (s, 3H), 2.73 (s, 2H), 2.06-2.02 (m, 2H), 1.63-1.55 (m, 3H), 1.35-1.17 (m, 5H) ppm.
**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 176.3, 136.3, 131.6, 131.0, 120.5, 51.4, 48.7, 46.3, 34.0, 25.7, 23.3 ppm.
**GC-MS** (EI): mass calcd. for $C_{15}H_{19}BrO_2$, 310.1; m/z found, 310.1.

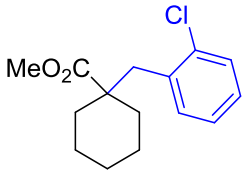
*Methyl 1-(2-bromobenzyl)cyclohexane-1-carboxylate* (**14**):




Prepared following the General procedure 3 on 1 mmol scale with methyl 1-bromocyclohexane-1-carboxylate (1 eq., 1 mmol); 2-bromobenzyl zinc(II) bromide (2 eq., 2 mmol); $CoBr_2$ (0.1 eq., 0.1 mmol); dppe (0.2 eq., 0.20 mmol). Purification by flash chromatography (silica; pentane in DCM 100/0 to 50/50) afforded the product as a transparent liquid; isolated yield: 59%.

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 7.54-7.51 (m, 1H), 7.21-7.17 (m, 1H), 7.07-7.03 (m, 2H), 3.66 (s, 3H), 3.02 (s, 2H), 2.17-2.14 (m, 2H), 1.65-1.61 (m, 2H), 1.38-1.17 (m, 6H) ppm.
**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 176.2, 137.1, 132.9, 131.7, 128.1, 126.8, 125.8, 51.5, 49.3, 45.8, 34.3, 25.7, 23.5 ppm.
**HRMS** (ESI-TOF): mass calcd. for $C_{15}H_{19}BrO_2$, 310.0568; m/z found, 311.0649 $[M+H]^+$.

*Methyl 1-(2-chlorobenzyl)cyclohexane-1-carboxylate* (**15**):

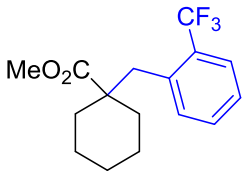



Prepared following the General procedure 3 on 1 mmol scale with methyl 1-bromocyclohexane-1-carboxylate (1 eq., 1 mmol); 2-chlorobenzyl zinc(II) bromide (2 eq., 2 mmol); $CoBr_2$ (0.1 eq., 0.1 mmol); dppe (0.2 eq., 0.20 mmol). Purification by flash chromatography (silica; pentane in DCM 100/0 to 50/50) afforded the product as a transparent liquid; isolated yield: 47%.

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 7.34-7.31 (m, 1H), 7.15-7.12 (m, 2H), 7.07-7.05 (m, 1H), 3.65 (s, 3H), 2.98 (s, 2H), 2.16-2.13 (m, 2H), 1.64-1.58 (m, 3H), 1.35-1.21 (m, 5H) ppm.
**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 176.2, 135.3, 135.0, 131.9, 129.5, 127.9, 126.2, 51.5, 49.2, 43.5, 34.3, 25.7, 23.5 ppm.

**GC-MS** (EI): mass calcd. for $C_{15}H_{19}ClO_2$, 266.1; m/z found, 266.1.

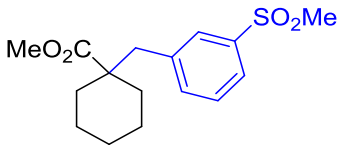
*Methyl 1-(2-(trifluoromethyl)benzyl)cyclohexane-1-carboxylate* (**16**):




Prepared following the General procedure 3 on 1 mmol scale with methyl 1-bromocyclohexane-1-carboxylate (1 eq., 1 mmol); 2-trifluoromethylbenzyl zinc(II) bromide (2 eq., 2 mmol); $CoBr_2$ (0.1 eq., 0.1 mmol); dppe (0.2 eq., 0.20 mmol). Purification by flash chromatography (silica; heptane in ethyl acetate 100/0 to 10/90) afforded the product as a transparent liquid; isolated yield: 27%.

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 7.63 (d, *J* = 7.9 Hz, 1H), 7.43 (m, 1H), 7.31 (m, 1H), 7.17 (d, *J* = 7.9 Hz, 1H), 3.66 (s, 3H), 3.05 (s, 2H), 2.10 (m, 2H), 1.61 (m, 2H), 1.33-1.14 (m, 6H) ppm.
**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 176.5, 136.3, 131.6, 131.0, 129.4, 126.4, 126.2, 51.5, 46.5, 42.2, 36.7, 25.6, 23.3 ppm.
**HRMS** (ESI-TOF): mass calcd. for $C_{16}H_{19}F_3O_2$, 300.1337; m/z found, 301.1423 $[M+H]^+$.

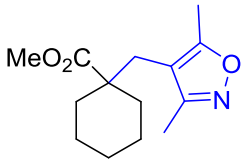
*Methyl 1-(3-(methylsulfonyl)benzyl)cyclohexane-1-carboxylate* (**17**):




Prepared following the General procedure 3 on 1 mmol scale with methyl 1-bromocyclohexane-1-carboxylate (1 eq., 1 mmol); (3-(methylsulfonyl)benzyl) zinc(II) bromide (2 eq., 2 mmol); $CoBr_2$ (0.1 eq., 0.1 mmol); dppe (0.2 eq., 0.20 mmol). Purification by flash chromatography (silica; heptane in ethyl acetate 100/0 to 75/25) afforded the product as a transparent liquid; isolated yield: 46%.

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 8.00-7.78 (m, 1H), 7.61 (m, 1H), 7.48-7.44 (m, 1H), 7.34-7.31 (m, 1H), 3.65 (s, 3H), 3.03 (s, 3H), 2.88 (s, 2H), 2.07-2.04 (m, 2H), 1.61-1.59 (m, 3H), 1.33-1.27 (m, 5H) ppm.
**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 175.9, 140.3, 139.1, 135.1, 129.0, 128.4, 125.5, 51.5, 48.8, 46.6, 44.6, 34.1, 25.7, 23.2 ppm.
**GC-MS** (EI): mass calcd. for $C_{16}H_{22}O_4S$, 310.1; m/z found, 310.2.

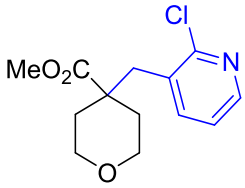
*Methyl 1-((3,5-dimethylisoxazol-4-yl)methyl)cyclohexane-1-carboxylate* (**18**):




Prepared following the General procedure 3 on 1 mmol scale with methyl 1-bromocyclohexane-1-carboxylate (1 eq., 1 mmol); ((3,5-dimethylisoxazol-4-yl)methyl) zinc(II) bromide (2 eq., 2 mmol); $CoBr_2$ (0.1 eq., 0.1 mmol); dppe (0.2 eq., 0.20 mmol). Purification by flash chromatography (silica; pentane in DCM 100/0 to 50/50) afforded the product as a transparent liquid; isolated yield: 41%.

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 3.67 (s, 3H), 2.47 (s, 2H), 2.27 (s, 3H), 2.16 (s, 3H), 2.14-2.11 (m, 2H), 1.66-1.61 (m, 3H), 1.27-1.10 (m, 5H) ppm.
**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 176.3, 166.5, 160.1, 109.7, 51.7, 49.2, 34.2, 34.0, 25.5, 23.5, 11.7, 10.6 ppm.
**GC-MS** (EI): mass calcd. for $C_{14}H_{21}NO_3$, 251.2; m/z found, 251.2.

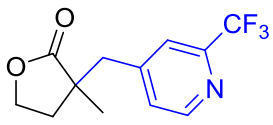
*Methyl 4-((2-chloropyridin-3-yl)methyl)tetrahydro-2H-pyran-4-carboxylate* (**19**):




Prepared following the General procedure 3 on 1 mmol scale with methyl 4-bromotetrahydro-2H-pyran-4-carboxylate (1 eq., 1 mmol); ((2-chloropyridin-3-yl)methyl) zinc(II) bromide (2 eq., 2 mmol); $CoBr_2$ (0.1 eq., 0.1 mmol); dppe (0.2 eq., 0.20 mmol). Purification by flash chromatography (silica; heptane in ethyl acetate 100/0 to 75/25) afforded the product as a transparent liquid; isolated yield: 35%.

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 8.29 (dd, *J* = 4.7 and 2.0 Hz, 1H), 7.42 (dd, *J* = 7.5 and 2.0 Hz, 1H), 7.17 (dd, *J* = 7.6 and 4.6 Hz, 1H), 3.90-3.80 (m, 2H), 3.70 (s, 3H), 3.37 (td, *J* = 12.0 and 2.0 Hz, 2H), 3.02 (s, 2H), 2.12-2.08 (m, 2H), 1.70 (ddd, *J* = 13.5, 12.0 and 4.6 Hz, 2H) ppm.
**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 174.8, 148.2, 140.3, 131.1, 122.1, 65.4, 52.1, 46.8, 42.8, 34.2 ppm.
**GC-MS** (EI): mass calcd. for $C_{13}H_{16}ClNO_3$, 269.1; m/z found, 269.1.

*3-Methyl-3-((2-(trifluoromethyl)pyridin-4-yl)methyl)dihydrofuran-2(3H)-one* (**20**):

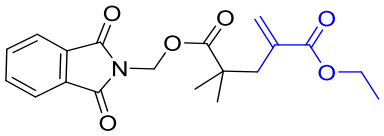



Prepared following the General procedure 3 on 1 mmol scale with 3-bromo-3-methyldihydrofuran-2(3H)-one; ((2-(trifluoromethyl)pyridin-4-yl)methyl) zinc(II) bromide (2 eq., 2 mmol); $CoBr_2$ (0.1 eq., 0.1

mmol); dppe (0.2 eq., 0.20 mmol). Purification by flash chromatography (silica; heptane in ethyl acetate 100/0 to 70/30) afforded the product as a transparent liquid; isolated yield: 64%.

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 8.66 (d, *J* = 4.8 Hz, 1H), 7.53 (br s, 1H), 7.37 (dd, *J* = 5.0 and 1.0 Hz, 1H), 4.24 (ddd, *J* = 9.4, 8.3 and 7.3 Hz, 1H), 4.09 (m, 1H), 3.12 (d, *J* = 13.4 Hz, 1H), 2.90 (d, *J* = 13.4 Hz, 1H), 2.23 (m, 1H), 2.01 (ddd, *J* = 12.9, 7.2 and 4.2 Hz, 1H), 1.33 (s, 3H) ppm.
**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 180.3, 150.1, 147.8, 128.0, 122.0, 64.9, 43.5, 42.3, 33.3, 23.1 ppm.
**GC-MS** (ES): mass calcd. for $C_{12}H_{12}F_3NO_2$, 259.1; m/z found, 259.1.

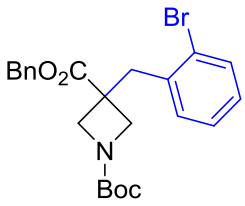
*1-((1,3-dioxoisoindolin-2-yl)methyl) 5-ethyl 2,2-dimethyl-4-methylenepentanedioate* (**21**):



Prepared following the General procedure 3 on 1 mmol scale with (1,3-dioxoisoindolin-2-yl)methyl 2-bromo-2-methylpropanoate (1 eq., 1 mmol); (2-(ethoxycarbonyl)allyl) zinc(II) bromide (2 eq., 2 mmol); $CoBr_2$ (0.1 eq., 0.1 mmol); dppe (0.2 eq., 0.20 mmol). Purification by flash chromatography (silica; heptane in ethyl acetate 100/0 to 70/30) afforded the product as a transparent liquid; isolated yield: 56%.

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 7.94 (m, 2H), 7.81 (m, 2H), 6.20 (d, *J* = 1.4 Hz, 1H), 5.70 (s, 2H), 5.57 (d, *J* = 1.4 Hz, 1H), 4.14 (q, *J* = 7.2 Hz, 2H), 2.62 (d, *J* = 0.9 Hz, 2H), 1.26 (t, *J* = 7.2 Hz, 3H), 1.16 (s, 6H) ppm.
**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 176.0, 167.4, 166.7, 137.3, 134.6, 131.8, 128.0, 123.9, 61.2, 60.8, 43.2, 40.7, 38.6, 33.1, 29.7, 24.7, 14.1 ppm.
**HRMS** (ESI-TOF): mass calcd. for $C_{19}H_{21}NO_6$, 359.1369; m/z found, 360.1448 $[M+H]^+$.

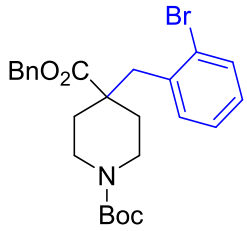
*3-Benzyl-1-(tert-butyl)-3-(2-bromobenzyl)azetidine-1,3-dicarboxylate* (**22**):



Prepared following the General procedure 3 on 1 mmol scale with 3-benzyl-1-(tert-butyl)-3-bromopiperidine-1,3-dicarboxylate (1 eq., 1 mmol); 2-bromobenzyl zinc(II) bromide (2 eq., 2 mmol); $CoBr_2$ (0.1 eq., 0.1 mmol); dppe (0.2 eq., 0.20 mmol). Purification by flash chromatography (silica; heptane in ethyl acetate 100/0 to 70/30) afforded the product as a transparent liquid; isolated yield: 43%.

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 7.54 (dd, *J* = 7.9 and 1.4 Hz, 1H), 7.37-7.32 (m, 3H), 7.27-7.24 (m, 2H), 7.14 (m, 1H), 7.06 (m, 1H), 6.92 (dd, *J* = 7.5 and 1.7 Hz, 1H), 5.15 (s, 2H), 4.26 (d, *J* = 9.0 Hz, 2H), 3.94 (d, *J* = 9.0 Hz, 2H), 3.42 (s, 2H), 1.41 (s, 9H) ppm.
**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 173.4, 156.1, 136.1, 135.3, 133.2, 129.5, 128.6, 128.5, 127.6, 125.4, 79.9, 67.3, 56.5, 43.1, 40.8, 28.4 ppm.
**HRMS** (ESI-TOF): mass calcd. for $C_{23}H_{26}BrNO_4$, 459.1045; m/z found, 460.1119 $[M+H]^+$.

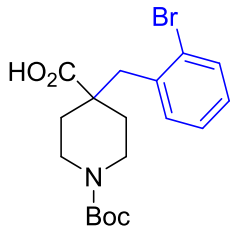
*4-Benzyl-1-(tert-butyl)-4-(2-bromobenzyl)piperidine-1,4-dicarboxylate* (**23**):




Prepared following the General procedure 3 on 1 mmol scale with 4-benzyl-1-(*tert*-butyl)-4-bromopiperidine-1,4-dicarboxylate (1 eq., 1 mmol); 2-bromobenzyl zinc(II) bromide (2 eq., 2 mmol); $CoBr_2$ (0.1 eq., 0.1 mmol); dppe (0.2 eq., 0.20 mmol). Purification by flash chromatography (silica; heptane in ethyl acetate 100/0 to 75/25) afforded the product as a transparent liquid; isolated yield: 40%.

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 7.52 (dd, *J* = 8.0 and 1.2 Hz, 1H), 7.35-7.30 (m, 3H), 7.26-7.23 (m, 2H), 7.15 (m, 1H), 7.05 (m, 1H), 6.98 (dd, *J* = 7.4 and 1.8 Hz, 1H), 5.13 (s, 2H), 3.96 (m, 2H), 3.10 (s, 2H), 2.72 (m, 2H), 2.16 (m, 2H), 1.55 (m, 2H), 1.43 (s, 9H) ppm.
**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 174.4, 154.8, 136.1, 135.6, 133.1, 131.8, 128.6, 128.4, 128.3, 128.3, 127.0, 125.8, 79.5, 66.8, 47.9, 45.0, 33.3, 28.5 ppm.
**HRMS** (ESI-TOF): mass calcd. for $C_{25}H_{30}BrNO_4$, 487.1358; m/z found, 488.1438 $[M+H]^+$.

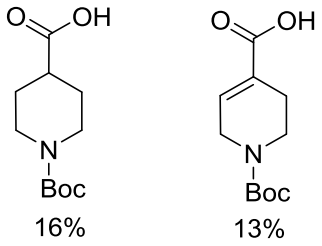
*4-(2-bromobenzyl)-1-(tert-butoxycarbonyl)piperidine-4-carboxylic acid* (**24**):



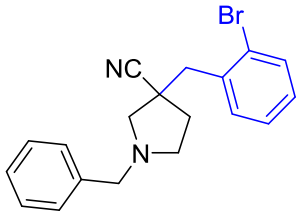

Prepared following the General procedure 3 on 1 mmol scale with 4-bromo-1-(*tert*-butoxycarbonyl)piperidine-4-carboxylic acid (1 eq., 1 mmol); 2-bromobenzyl zinc(II) bromide (3 eq., 3 mmol); $CoBr_2$ (0.1 eq., 0.1 mmol); dppe (0.2 eq., 0.20 mmol). Purification by flash chromatography (silica; heptane in ethyl acetate 100/0 to 50/50) afforded the product as an off-white solid; isolated yield: 36%.

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 7.56 (dd, *J* = 7.98, 1.04 Hz, 1H), 7.22-7.16 (m, 2H), 7.10-7.06 (m, 1H), 4 (br s, 2H), 3.12 (s, 2H), 2.82 (m, 2H), 2.14-2.10 (m, 2H), 1.60-1.52 (m, 2H), 1.44 (s, 9H) ppm.
**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 180.3, 154.9, 135.9, 133.2, 131.9, 128.5, 127.1, 125.9, 79.7, 47.7, 44.8, 32.9, 28.5 ppm.
**GC-MS** (EI): mass calcd. for $C_{18}H_{24}BrNO_4$, 397.1; m/z found, 397.1.

This reaction was scaled up: 4-bromo-1-(*tert*-butoxycarbonyl)piperidine-4-carboxylic acid (1 eq., 3 mmol); 2-bromobenzyl zinc(II) bromide (3 eq., 6 mmol); $CoBr_2$ (0.1 eq., 0.3 mmol); dppe (0.2 eq., 0.60 mmol). Purification by flash chromatography (silica; heptane in ethyl acetate 100/0 to 50/50) afforded the product as an off-white solid; isolated yield: 37%. Additionally, the following two by products were isolated from this experiment:



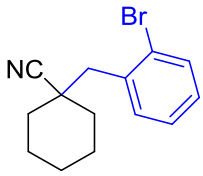

*1-Benzyl-3-(2-bromobenzyl)pyrrolidine-3-carbonitrile* (**25**):




Prepared following the General procedure 3 on 1 mmol scale with 1-benzyl-3-chloropyrrolidine-3-carbonitrile (1 eq., 1 mmol); 2-bromobenzyl zinc(II) bromide (2 eq., 2 mmol); $CoBr_2$ (0.1 eq., 0.1 mmol); dppe (0.2 eq., 0.20 mmol). Purification by flash chromatography (silica; heptane in ethyl acetate 100/0 to 70/30) afforded the product as a transparent liquid; isolated yield: 34%.

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 7.57 (dd, *J* = 8.0 and 1.3 Hz, 1H), 7.51 (dd, *J* = 7.6 and 1.6 Hz, 1H), 7.34-7.25 (m, 6H), 7.13 (td, *J* = 7.7 and 1.7 Hz, 1H), 3.71-3.63 (m, 2H), 3.26-3.18 (m, 2H), 2.90 (m, 1H), 2.82 (m, 1H), 2.75 (m, 2H), 2.35-2.28 (m, 1H), 2.15-2.10 (m, 1H) ppm.
**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 138.4, 135.8, 133.2, 131.6, 129.0, 128.6, 128.4, 127.7, 127.2, 125.6, 124.4, 62.9, 59.1, 52.3, 42.1, 41.7, 36.3 ppm.
**GC-MS** (EI): mass calcd. for $C_{19}H_{19}BrN_2$, 354.1; m/z found, 353.1.

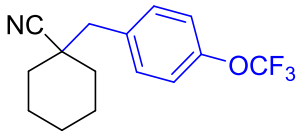
*1-(2-bromobenzyl)cyclohexane-1-carbonitrile* (**26**):




Prepared following the General procedure 3 on 1 mmol scale with 1-bromocyclohexane-1-carbonitrile (1 eq., 1 mmol); 2-bromobenzyl zinc(II) bromide (2 eq., 2 mmol); $CoBr_2$ (0.1 eq., 0.1 mmol); dppe (0.2 eq., 0.20 mmol). Purification by flash chromatography (silica; heptane in ethyl acetate 100/0 to 75/25) afforded the product as a transparent liquid; isolated yield: 52%.

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 7.57 (dd, *J* = 7.98 and 1.27 Hz, 1H), 7.52 (dd, *C*, 1H), 7.30 (td, *J* = 7.3 and 1.2 Hz, 1H), 7.13 (td, *J* = 7.7 and 1.6 Hz, 1H), 3.10 (s, 2H), 1.95-1.92 (m, 2H), 1.76-1.75 (m, 3H), 1.64-1.56 (m, 2H), 1.51-1.45 (m, 2H), 1.23-1.12 (m, 1H) ppm.
**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 135.3, 133.1, 132.2, 128.8, 127.5, 126.0, 123.1, 44.5, 41.0, 35.5, 25.2, 23.1 ppm.
**GC-MS** (EI): mass calcd. for $C_{14}H_{16}BrN$, 277.0; m/z found, 277.1.

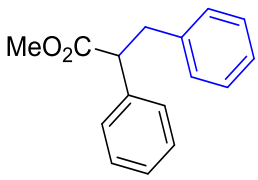
*1-(4-(trifluoromethoxy)benzyl)cyclohexane-1-carbonitrile* (**27**):




Prepared following the General procedure 3 on 1 mmol scale with 1-chlorocyclohexane-1-carbonitrile (1 eq., 1 mmol); (4-(trifluoromethoxy)benzyl) zinc(II) bromide (2 eq., 2 mmol); $CoBr_2$ (0.1 eq., 0.1 mmol); dppe (0.2 eq., 0.20 mmol). Purification by flash chromatography (silica; pentane in DCM 100/0 to 50/50) afforded the product as a transparent liquid; isolated yield: 68%.

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 7.31 (m, 2H), 7.17 (m, 2H), 2.81 (s, 2H), 1.92-1.88 (m, 2H), 1.77-1.71 (m, 3H), 1.64-1.57 (m, 2H), 1.33-1.14 (m, 3H) ppm.
**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 148.5, 134.0, 131.7, 122.9, 120.7, 45.6, 40.2, 35.6, 30.9, 25.2, 23.0 ppm.
**GC-MS** (EI): mass calcd. for $C_{15}H_{16}F_3NO$, 283.1; m/z found, 283.1.

*Methyl 2,3-diphenylpropanoate* (**28**):

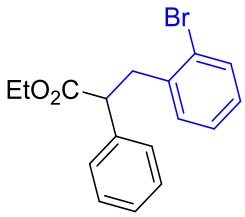



Prepared following the General procedure 3 on 1 mmol scale with methyl 2-bromo-2-phenylacetate (1 eq., 1 mmol); benzyl zinc(II) bromide (2 eq., 2 mmol); $CoBr_2$ (0.1 eq., 0.1 mmol); dppe (0.2 eq., 0.20

mmol). Purification by flash chromatography (silica, pentane in DCM 100:0 to 70:30) afforded the product as a transparent liquid; isolated yield: 48%.

**$^{1}$H NMR** ($CDCl_3$, 400 MHz): δ = 7.31-7.10 (m, 10H), 3.85 (dd, *J* = 8.8 and 6.7 Hz, 1H), 3.60 (s, 3H), 3.42 (dd, *J* = 13.6 and 8.8 Hz, 1H), 3.02 (dd, *J* = 13.6 and 6.7 Hz, 1H) ppm.
**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 173.8, 139.1, 138.6, 128.9, 128.7, 128.3, 128.0, 127.4, 126.4, 53.7, 52.0, 39.9 ppm.
**GC-MS** (EI): mass calcd. for $C_{16}H_{16}O_2$, 240.1; m/z found, 240.1.

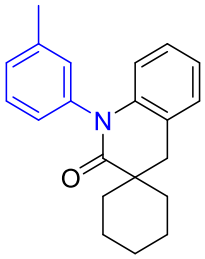
*Ethyl 3-(2-bromophenyl)-2-phenylpropanoate* (**29**):




Prepared following the General procedure 3 on 1 mmol scale with ethyl 2-chloro-2-phenylacetate (1 eq., 1 mmol); 2-bromobenzyl zinc(II) bromide (2 eq., 2 mmol); $CoBr_2$ (0.1 eq., 0.1 mmol); dppe (0.2 eq., 0.20 mmol). Purification by flash chromatography (silica; heptane in ethyl acetate 100/0 to 85/15) afforded the product as a transparent liquid; isolated yield: 65%.

**$^{1}$H NMR** ($CDCl_3$, 400 MHz): δ = 7.52 (d, *J* = 8.1 Hz, 1H), 7.34-7.22 (m, 5H), 7.14-7.01 (m, 3H), 4.12-4.00 (m, 3H), 3.49 (dd, *J* = 13.6 and 9.0 Hz, 1H), 3.13 (dd, *J* = 13.6 and 6.2 Hz, 1H), 1.11 (t, *J* = 7.2 Hz, 3H), ppm.
**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 173.1, 138.7, 138.3, 132.8, 131.6, 128.7, 128.2, 127.9, 127.4, 127.4, 124.8, 60.8, 51.3, 40.3, 14.1 ppm.
**GC-MS** (EI): mass calcd. for $C_{17}H_{17}BrO_2$, 333.2; m/z found, 333.3.

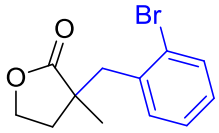
*1'-(m-tolyl)-1',4'-dihydro-2'H-spiro[cyclohexane-1,3'-quinolin]-2'-one* (**33**):




Prepared following the General procedure 4; methyl 1-(2-bromobenzyl)cyclohexane-1-carboxylate (1 eq., 0.29 mmol); *m*-toluidine (1.2 eq., 0.35 mmol); BRETTPHOS PD G3 (0.01 eq., 0.003 mmol); X-phos (0.01 eq., 0.003 mmol); $NaO^tBu$ (1.2 eq., 0.35 mmol) and 1,4-dioxane (0.3 mL). Purification by flash chromatography (silica; heptane in ethyl acetate 100/0 to 15/85) afforded the product as a white solid; isolated yield: 65%.

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 7.40-7.35 (m, 1H), 7.22-7.17 (m, 2H), 7.05-6.94 (m, 4H), 6.30 (dd, *J* = 8.0 and 1.0 Hz, 1H), 2.99 (s, 2H), 2.38 (s, 3H), 1.94-1.87 (m, 2H), 1.71-1.66 (m, 2H), 1.54-1.39 (m, 6H) ppm.
**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 175.5, 141.1, 139.8, 139.0, 129.6, 129.6, 128.8, 128.4, 126.9, 126.0, 124.0, 122.7, 116.2, 40.4, 35.5, 31.7, 25.9, 21.6, 21.4 ppm.
**GC-MS** (EI): mass calcd. for $C_{21}H_{23}NO$, 305.2; m/z found, 305.2.

*3-(2-bromobenzyl)-3-methyldihydrofuran-2(3H)-one* (**34**):

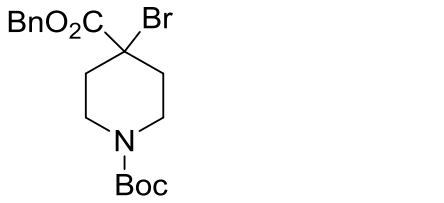


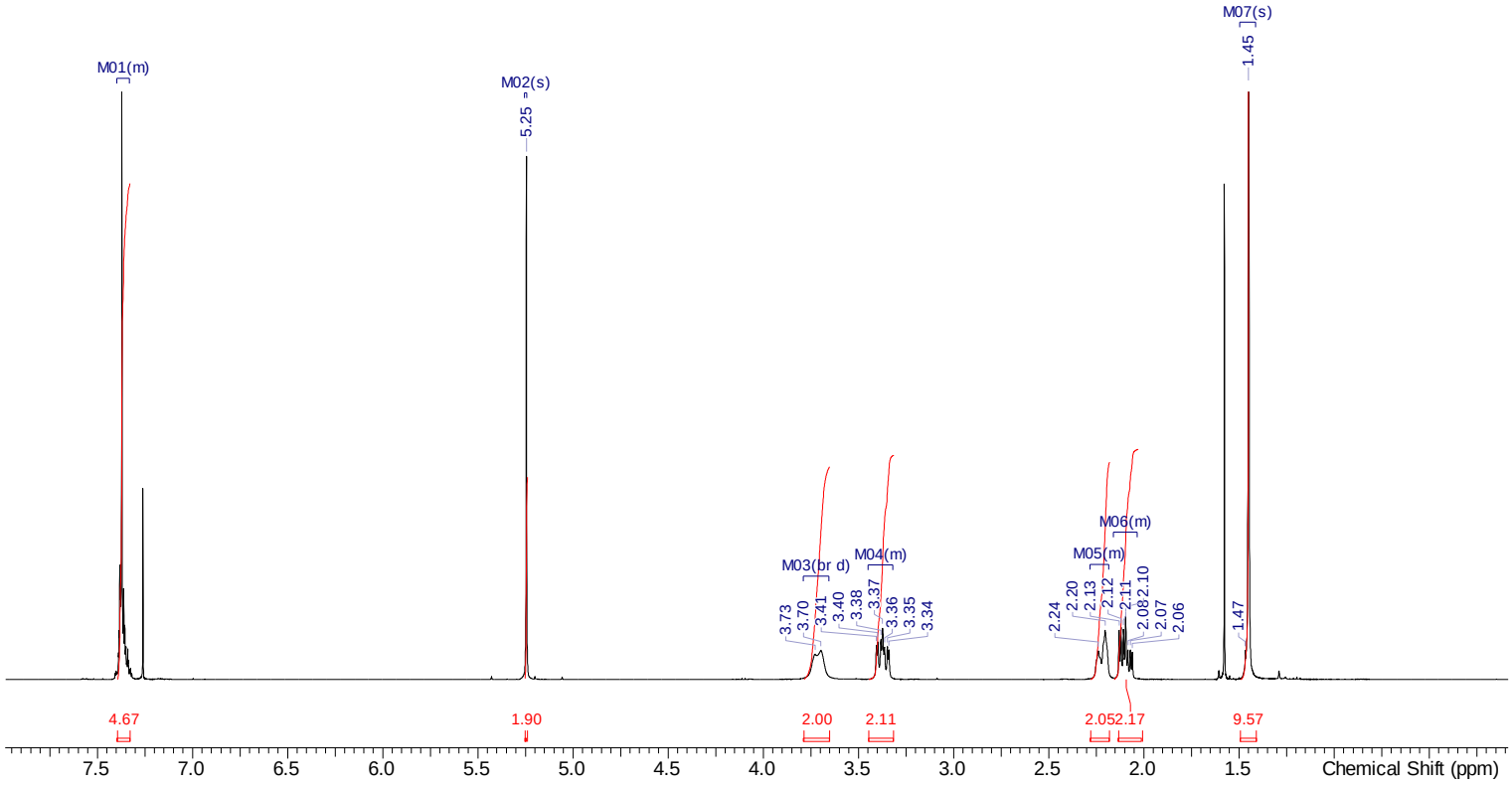

Prepared following the General procedure 3 on 1 mmol scale with 3-bromo-3-methyldihydrofuran-2(3H)-one; methyl 2-bromobenzoate (1 eq., 1 mmol); 2-bromobenzyl zinc(II) bromide (2 eq., 2 mmol); $CoBr_2$ (0.1 eq., 0.1 mmol); dppe (0.2 eq., 0.20 mmol). Purification by flash chromatography (silica; heptane in ethyl acetate 100/0 to 75/25) afforded the product as a transparent liquid; isolated yield: 37%. Selectivity according to the crude of the reaction ($sp^3$-$sp^3$ *vs* $sp^3$-$sp^2$ coupling) 19:1.

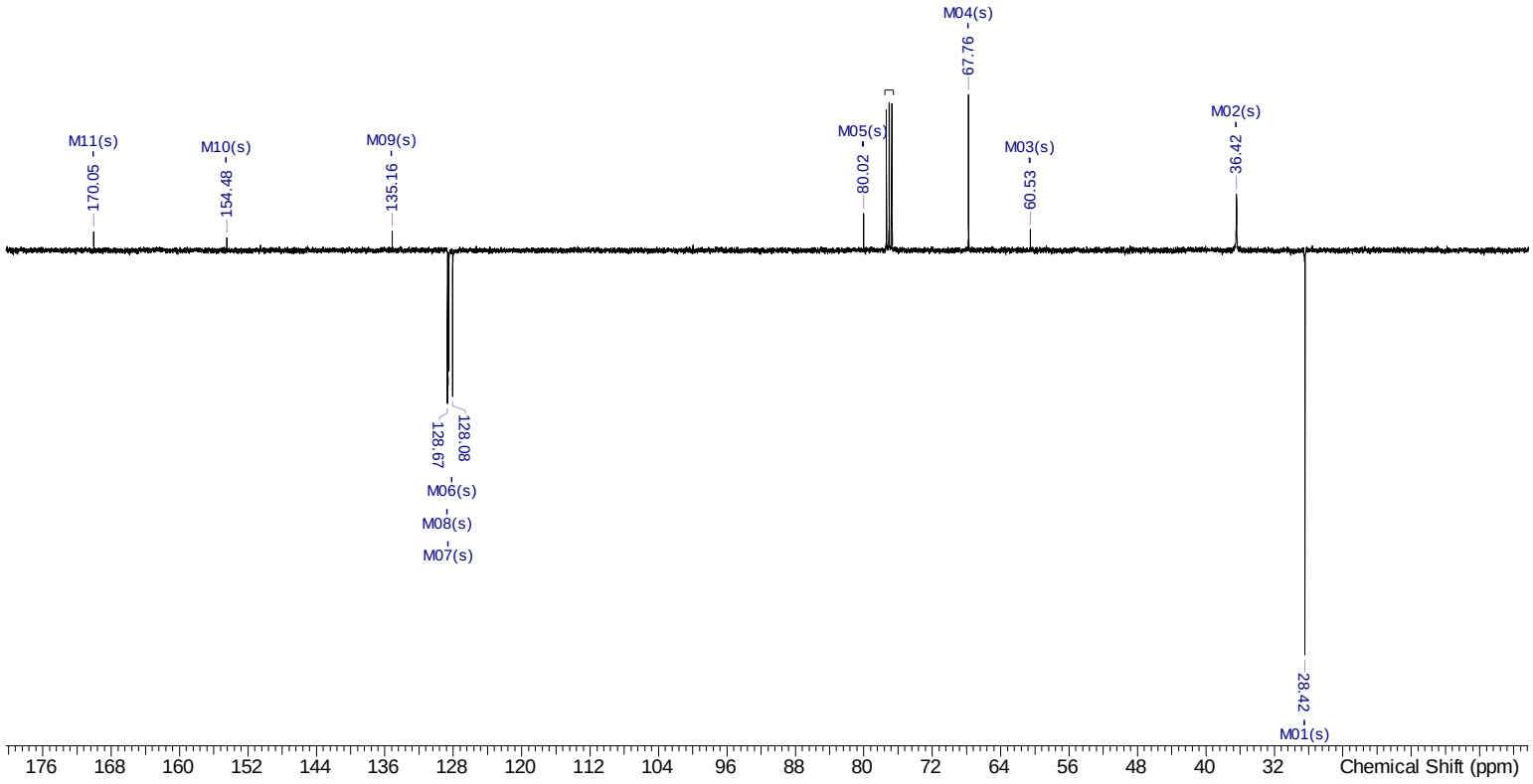
**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 7.56 (dd, *J* = 8.0 and 1.3 Hz, 1H), 7.32 (m, 1H), 7.23 (m, 1H), 7.11 (td, *J* = 7.6 and 1.8 Hz, 1H), 4.15 (dt, *J* = 9.1 and 7.5 Hz, 1H), 3.91 (ddd, *J* = 9.1, 8.1 and 5.2 Hz, 1H), 3.17 (s, 2H), 2.31 (ddd, *J* = 12.9, 9.1 and 7.4 Hz, 1H), 1.99 (ddd, *J* = 12.9, 7.6 and 5.1 Hz, 1H), 1.37 (s, 3H) ppm.
**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 181.5, 136.7, 133.0, 131.9, 128.7, 127.8, 125.9, 65.3, 44.6, 41.5, 33.0, 24.0 ppm.
**HRMS** (ESI-TOF): mass calcd. for $C_{12}H_{13}BrO_2$, 268.0099; m/z found, 268.9989 $[M+H]^+$.

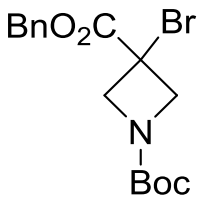
# NMR Spectra

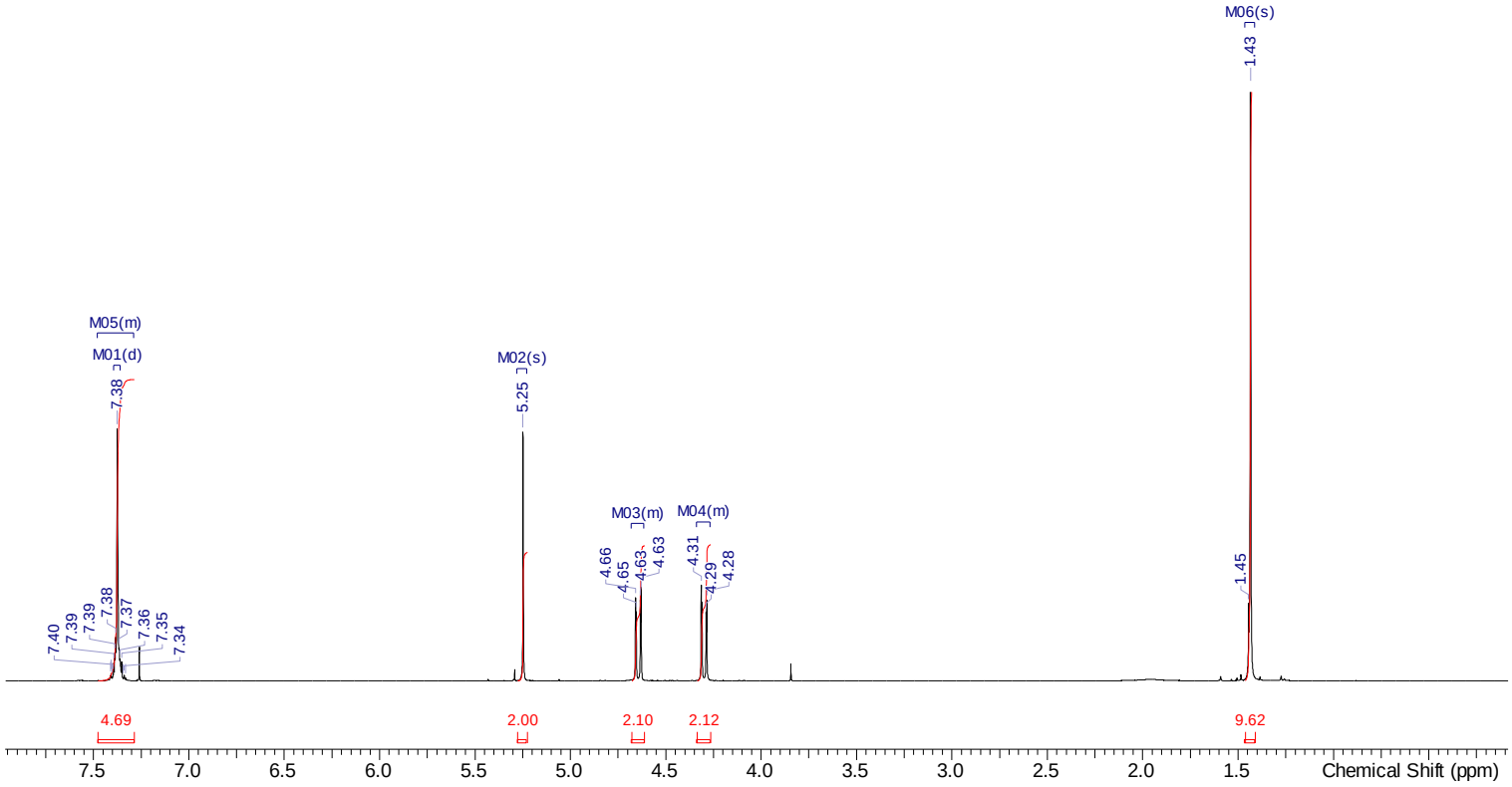
## NMR spectra of bromo derivatives

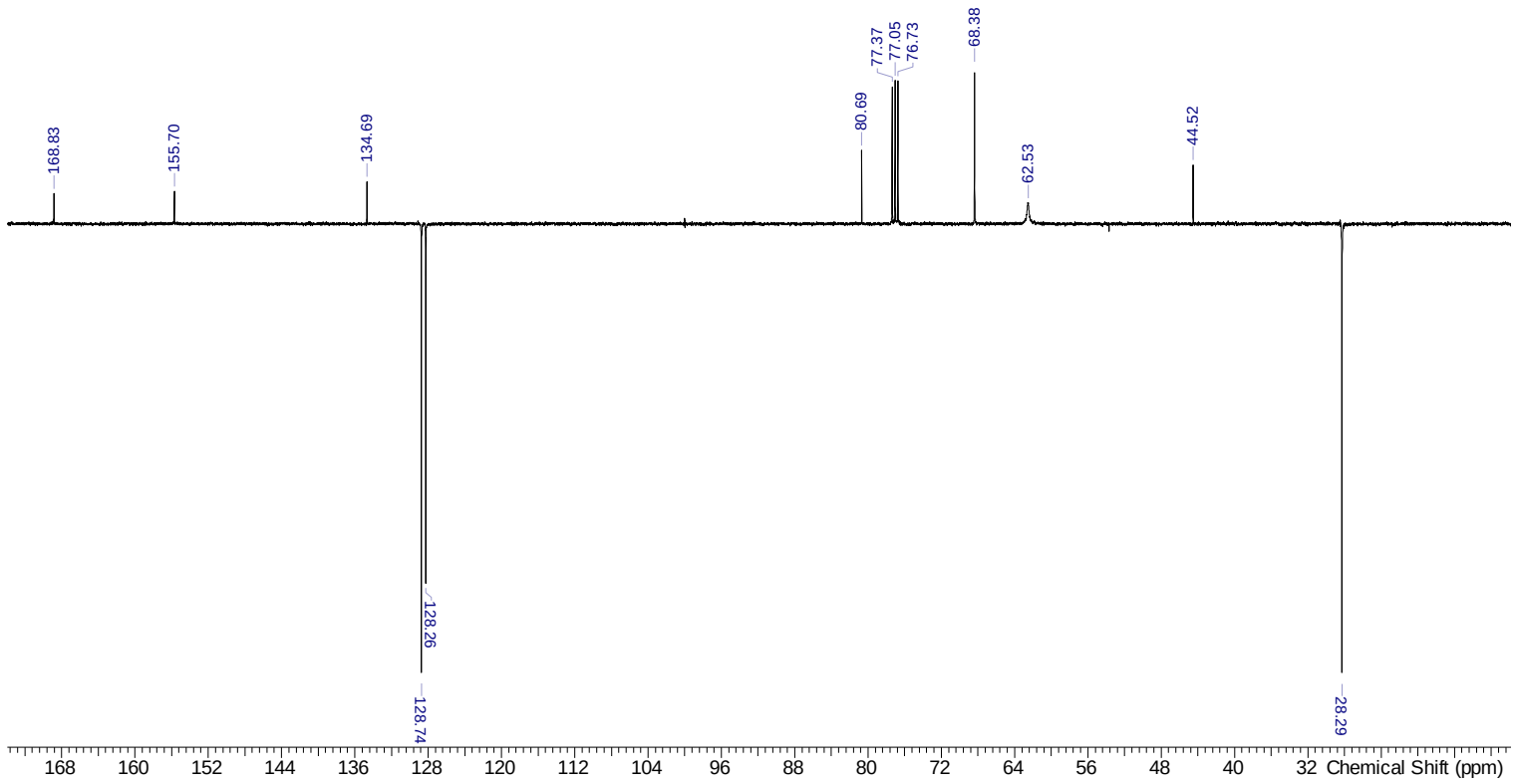


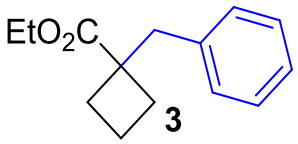

M04(s)
67.76
M11(s)
170.05
M10(s)
154.48
M09(s)
135.16
M05(s)
80.02
M03(s)
60.53
M02(s)
36.42
128.67
128.08
M06(s)
M08(s)
M07(s)
28.42
M01(s)
176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32
Chemical Shift (ppm)

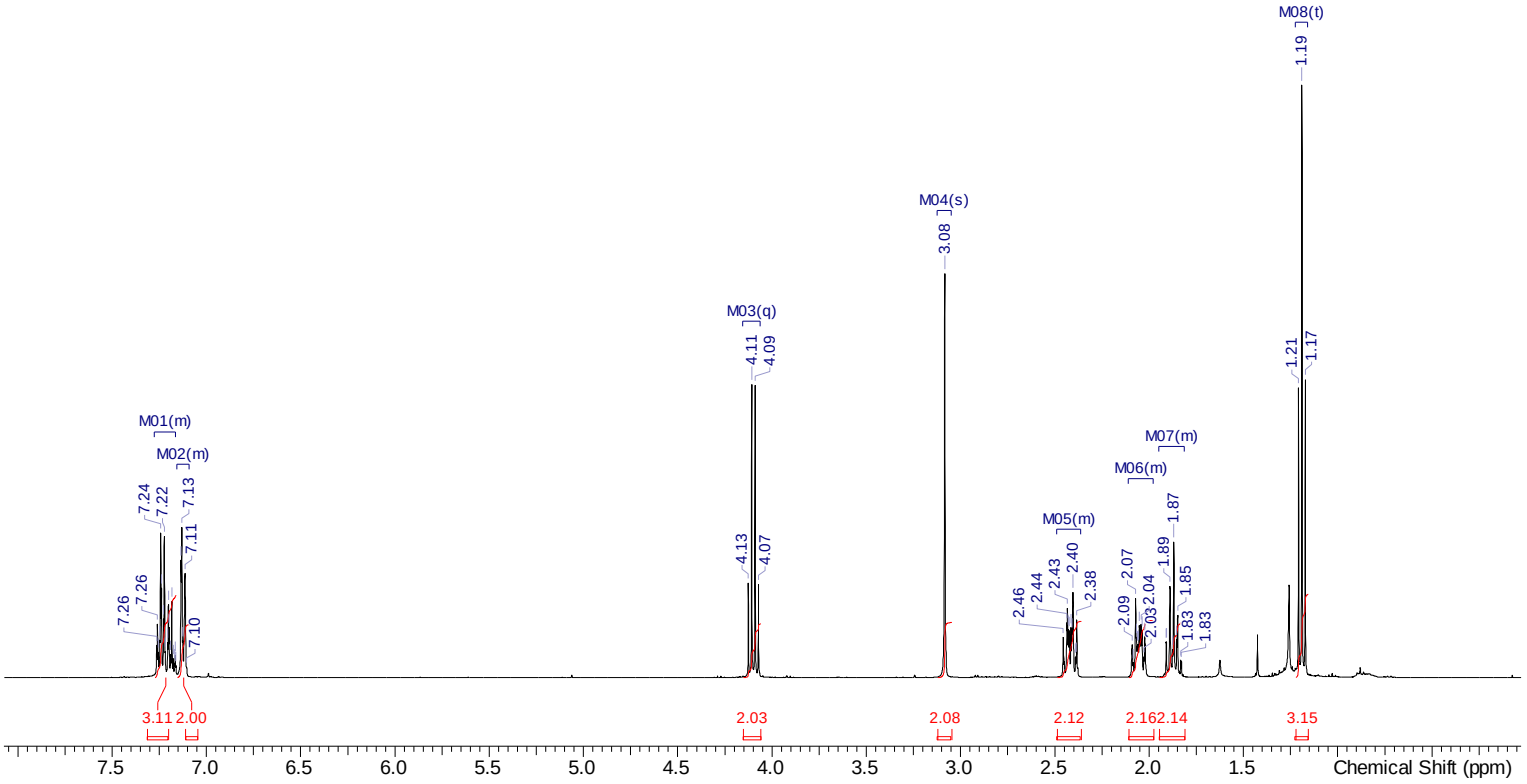

BnO2C
Br
N
Boc

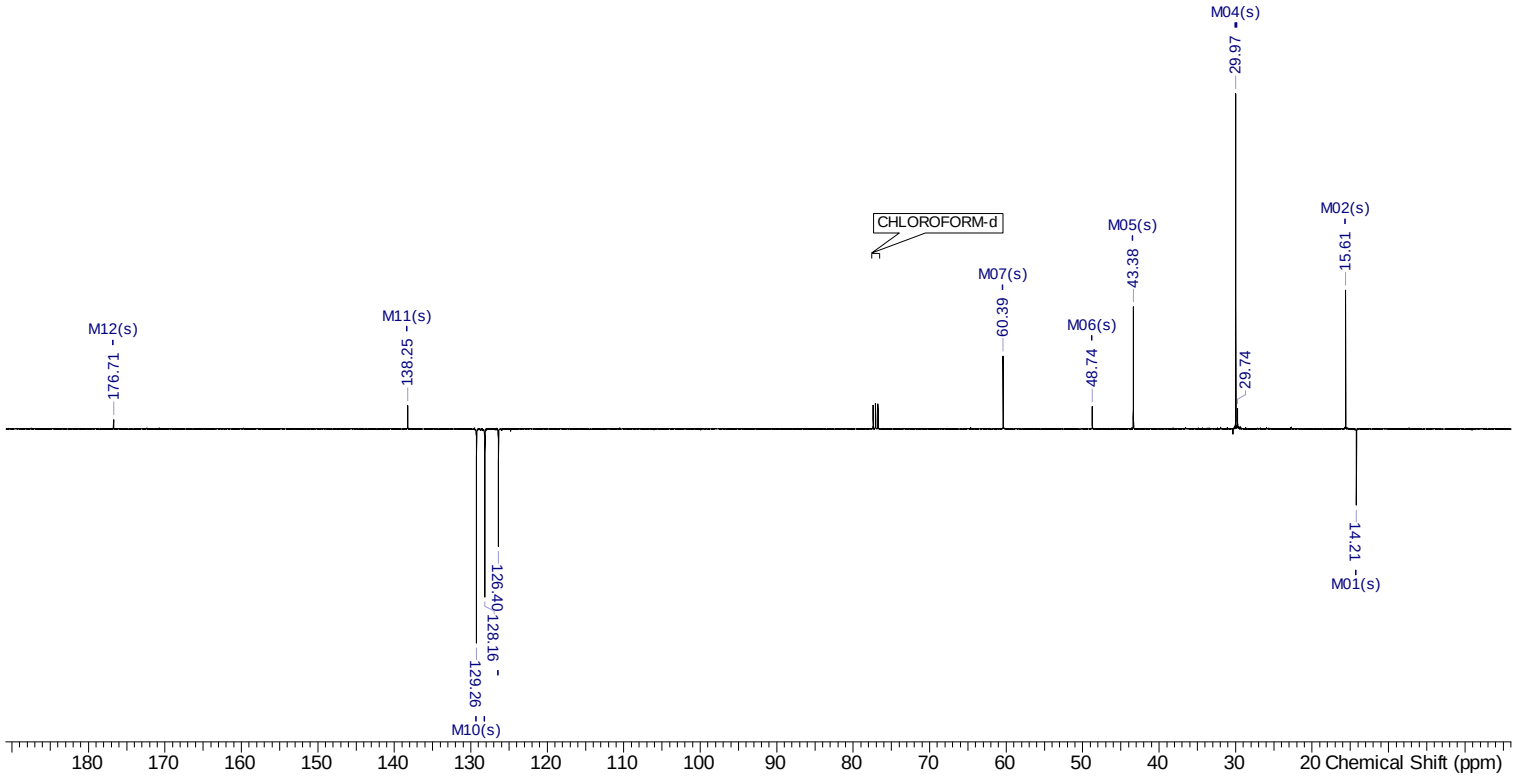

M06(s)
1.43
M05(m)
M01(d)
7.38
M02(s)
5.25
M03(m)
M04(m)
4.66
4.65
4.63
4.63
4.31
4.29
4.28
1.45
7.40
7.39
7.39
7.38
7.37
7.36
7.35
7.34
4.69
2.00
2.10
2.12
9.62
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
Chemical Shift (ppm)

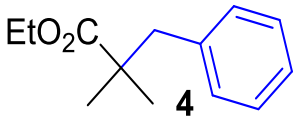

168.83
155.70
134.69
80.69
77.37
77.05
76.73
68.38
62.53
44.52
128.26
128.74
28.29
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
Chemical Shift (ppm)

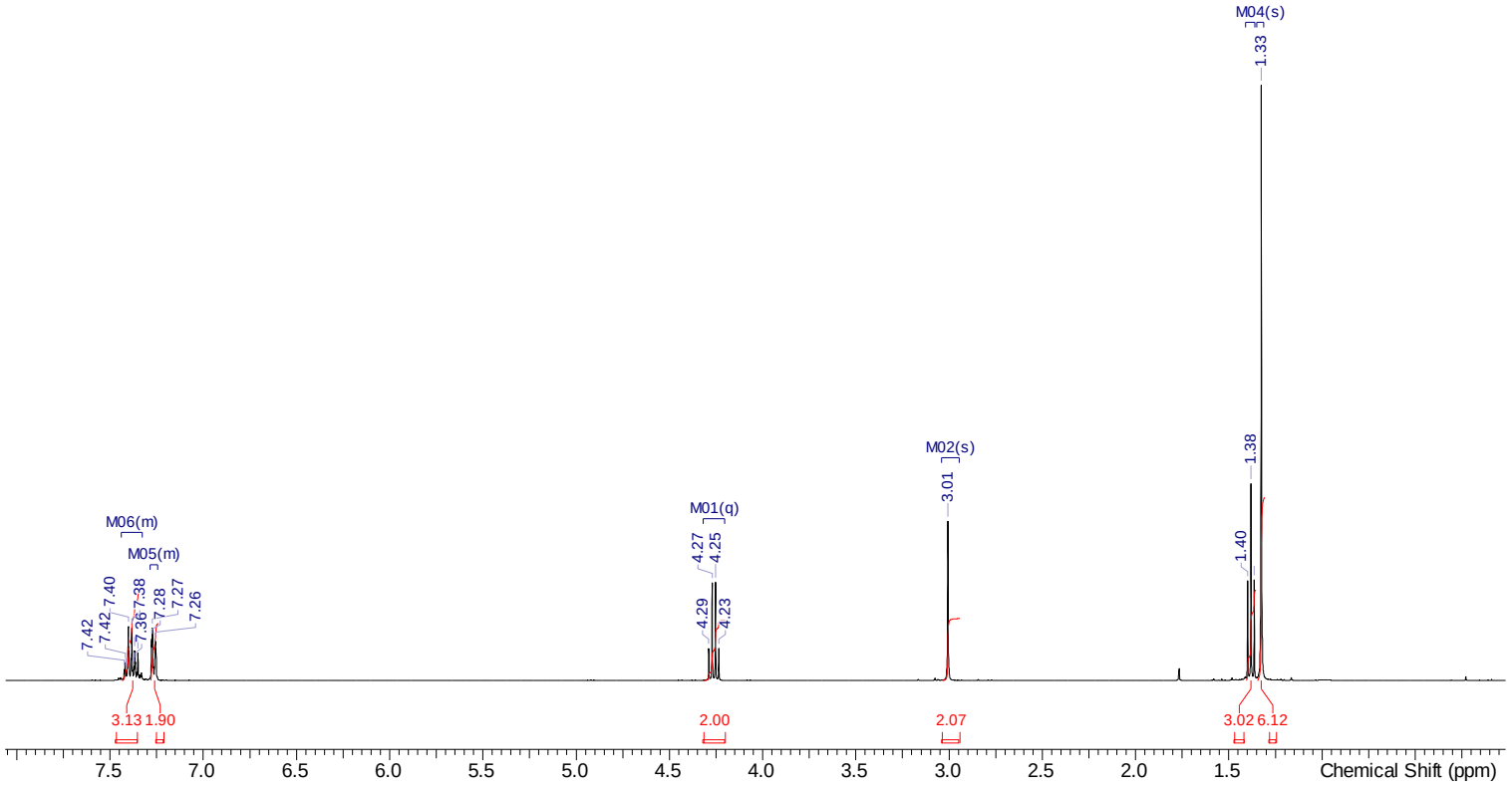
NMR spectra of products

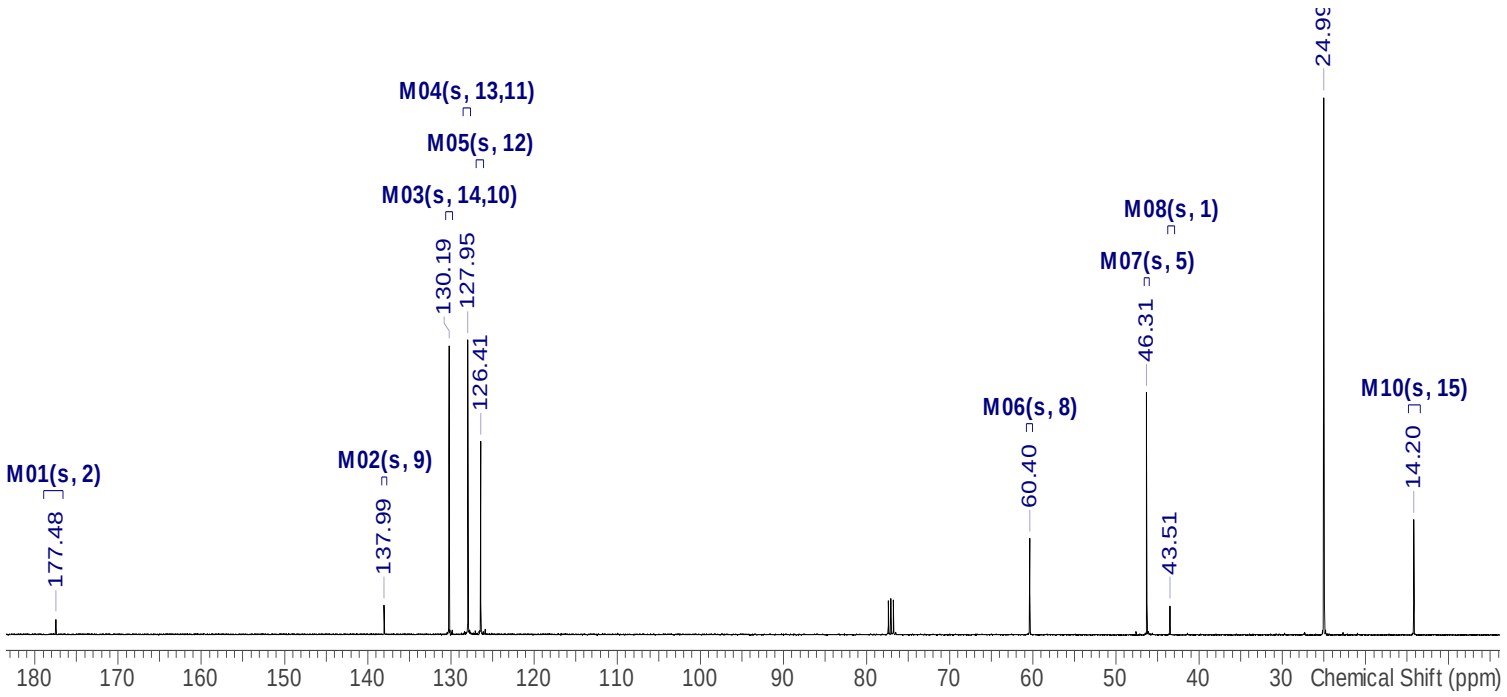


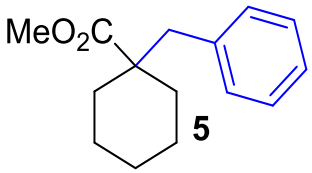



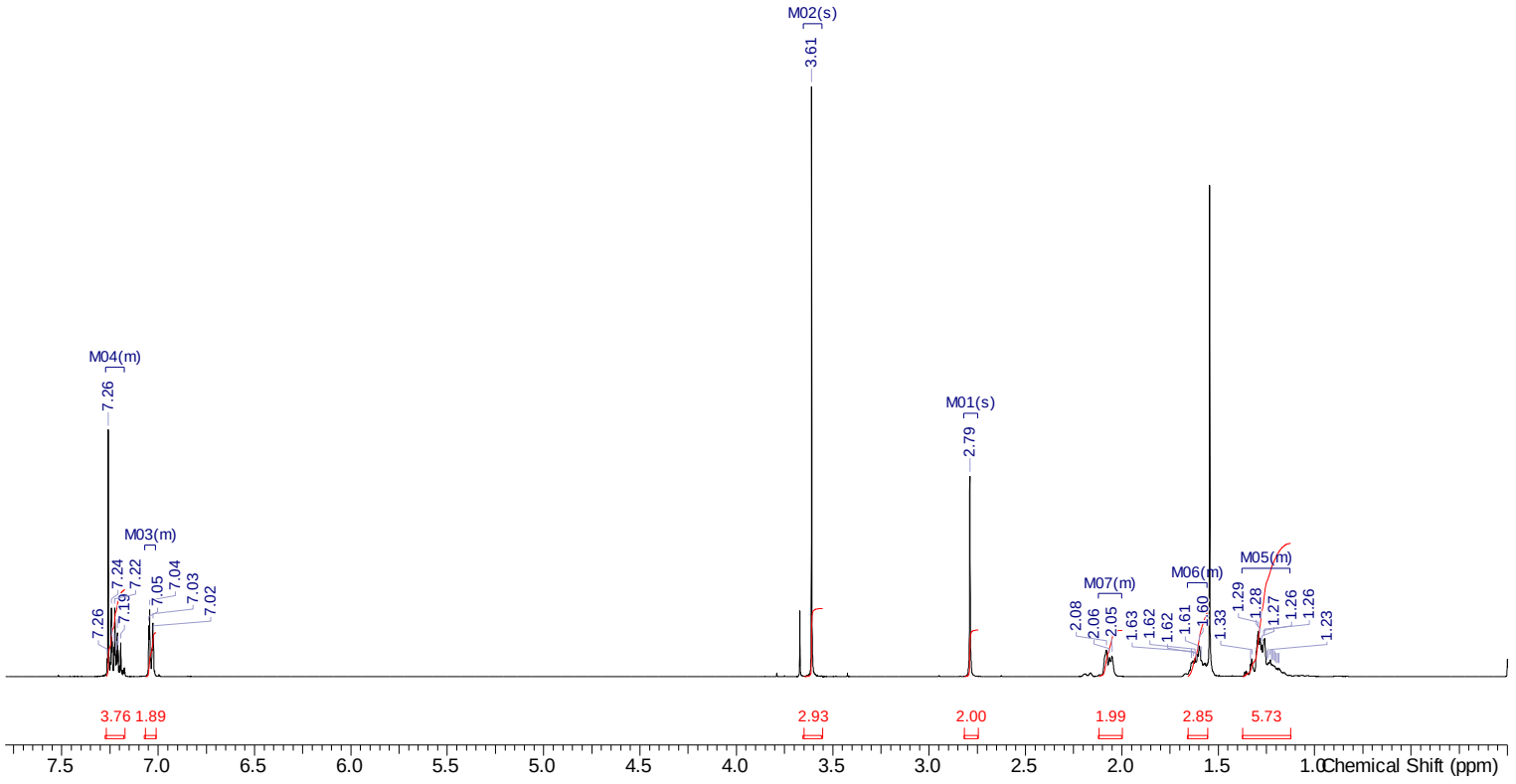

M04(s)
29.97
CHLOROFORM-d
M05(s)
43.38
M02(s)
15.61
M07(s)
60.39
M06(s)
48.74
29.74
M12(s)
176.71
M11(s)
138.25
126.40
128.16
129.26
M10(s)
14.21
M01(s)
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 Chemical Shift (ppm)

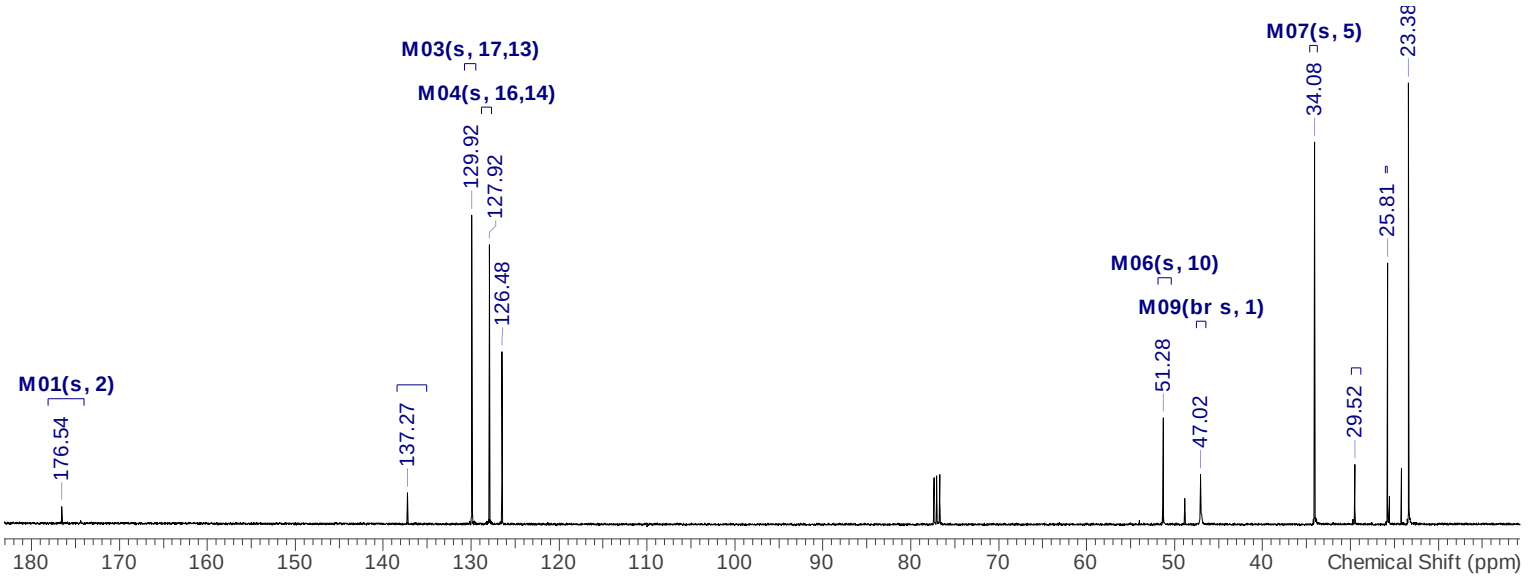

EtO2C
4

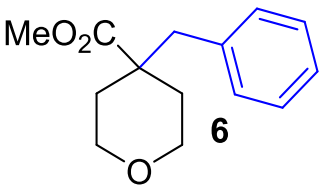

M04(s)
1.33
M02(s)
3.01
1.38
M01(q)
4.27
4.25
4.29
4.23
1.40
M06(m)
M05(m)
7.42
7.40
7.42
7.38
7.36
7.28
7.27
7.26
3.13
1.90
2.00
2.07
3.02
6.12
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
Chemical Shift (ppm)


M01(s, 2)
M02(s, 9)
M03(s, 14,10)
M04(s, 13,11)
M05(s, 12)
M06(s, 8)
M07(s, 5)
M08(s, 1)
M10(s, 15)
177.48
137.99
130.19
127.95
126.41
60.40
46.31
43.51
24.9
14.20
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 Chemical Shift (ppm)

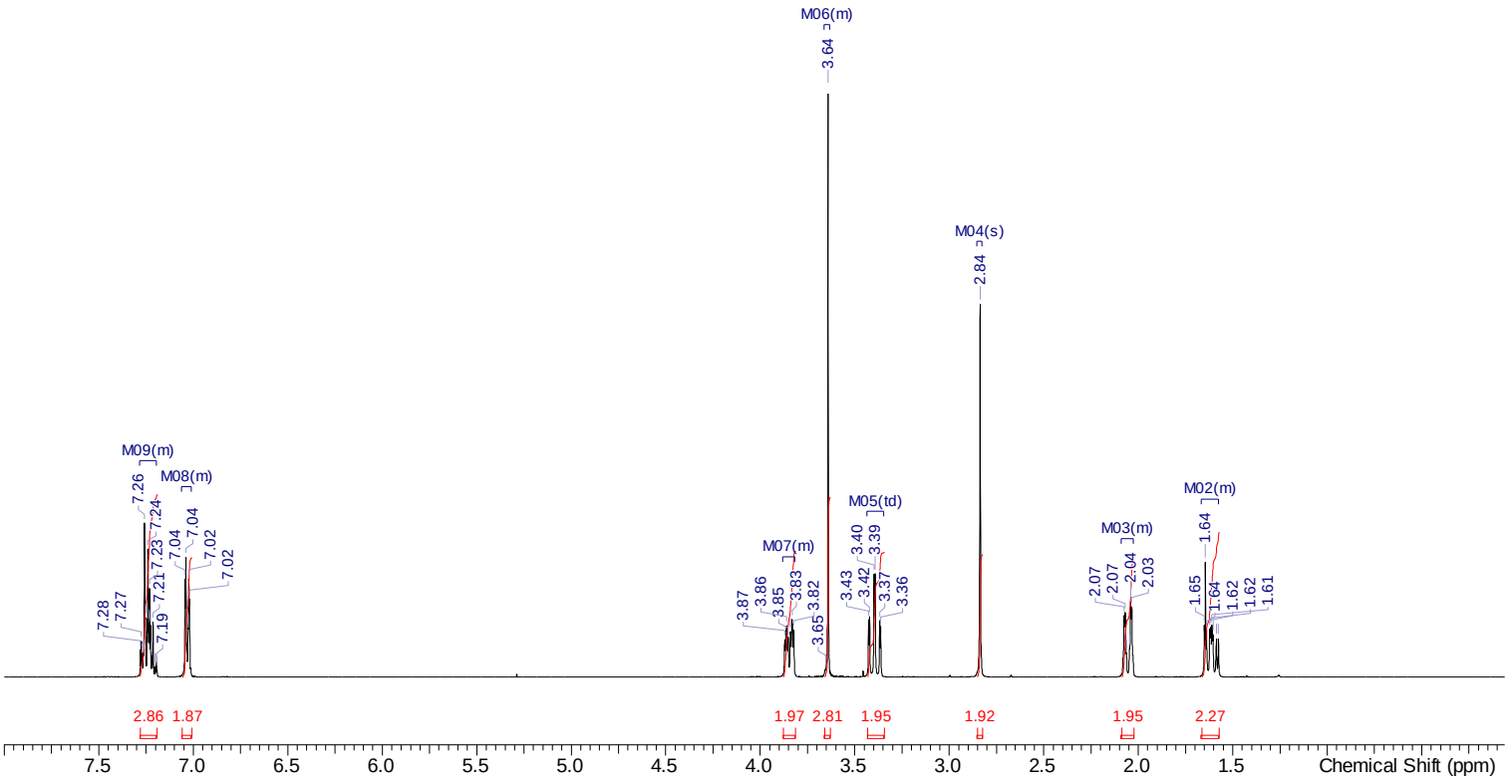

MeO2C
5

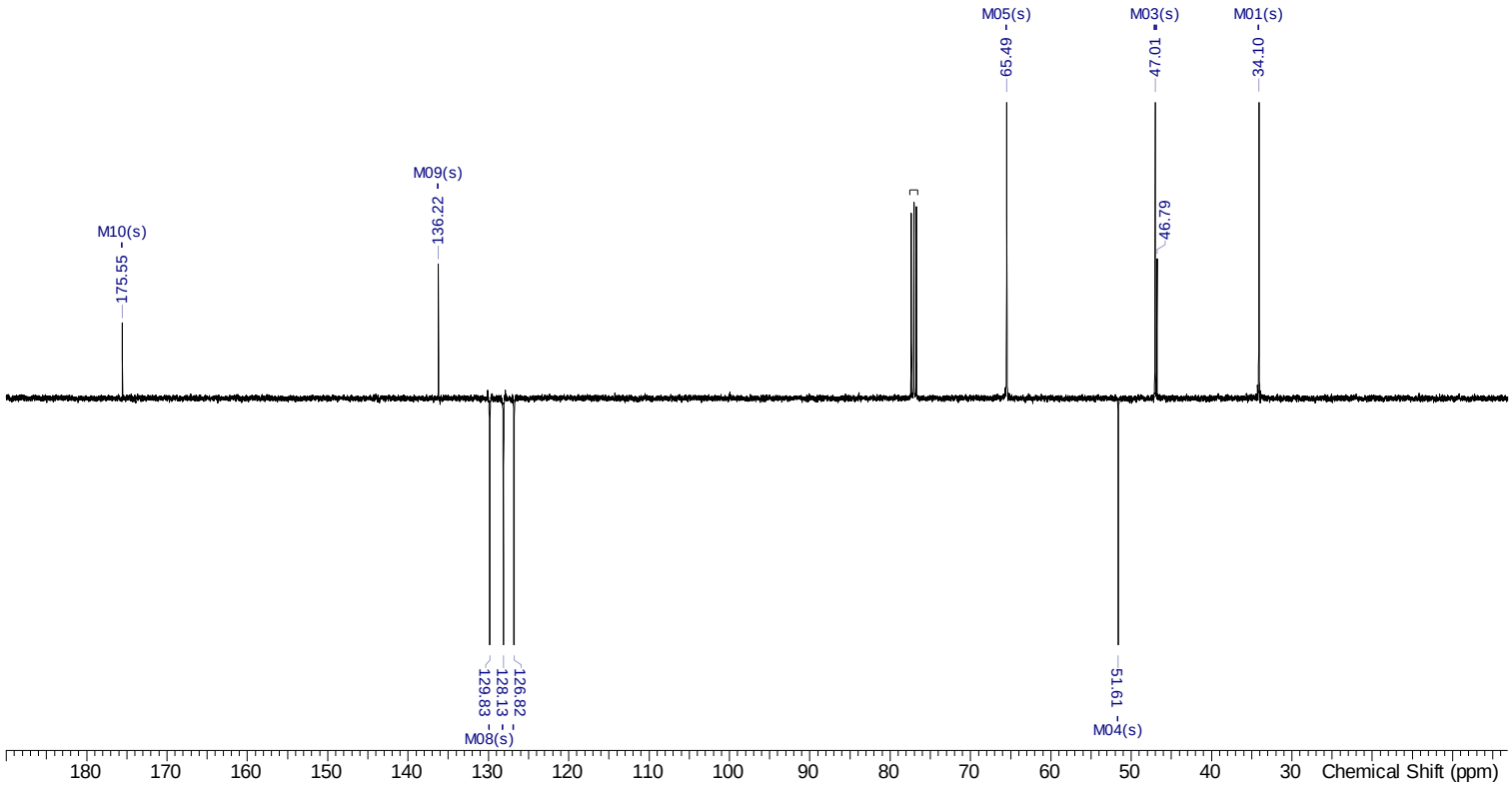

M02(s)
3.61
M04(m)
7.26
M01(s)
2.79
M03(m)
M07(m)
M06(m)
M05(m)
7.26
7.24
7.22
7.19
7.05
7.04
7.03
7.02
2.08
2.06
2.05
1.63
1.62
1.62
1.61
1.60
1.33
1.29
1.28
1.27
1.26
1.26
1.23
3.76
1.89
2.93
2.00
1.99
2.85
5.73
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
Chemical Shift (ppm)

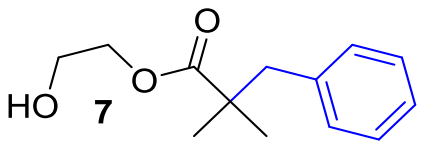

M01(s, 2)
176.54
137.27
M03(s, 17,13)
M04(s, 16,14)
129.92
127.92
126.48
M06(s, 10)
M09(br s, 1)
51.28
47.02
M07(s, 5)
34.08
29.52
25.81
23.38
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
Chemical Shift (ppm)


MeO2C
O

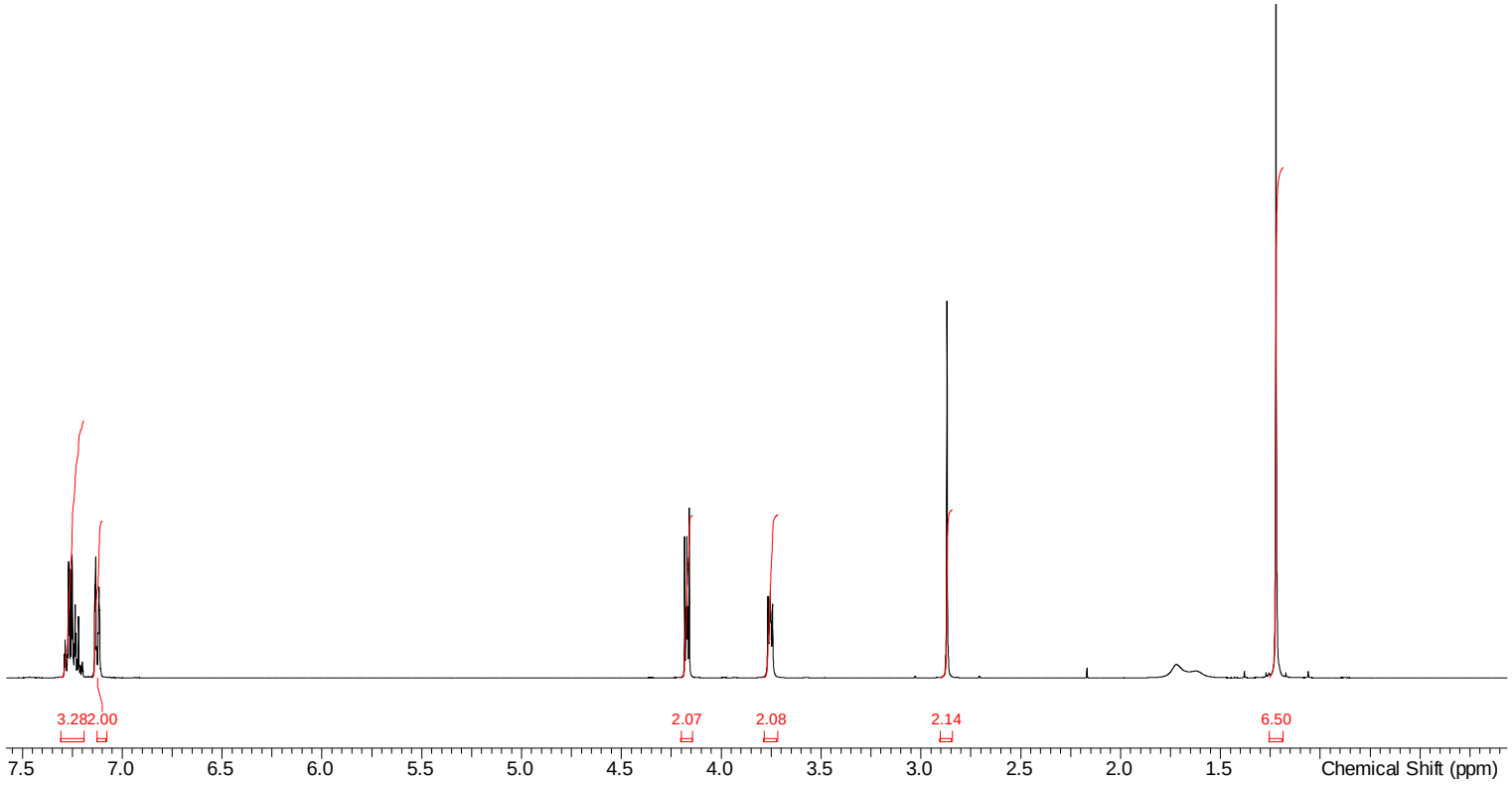
**6**

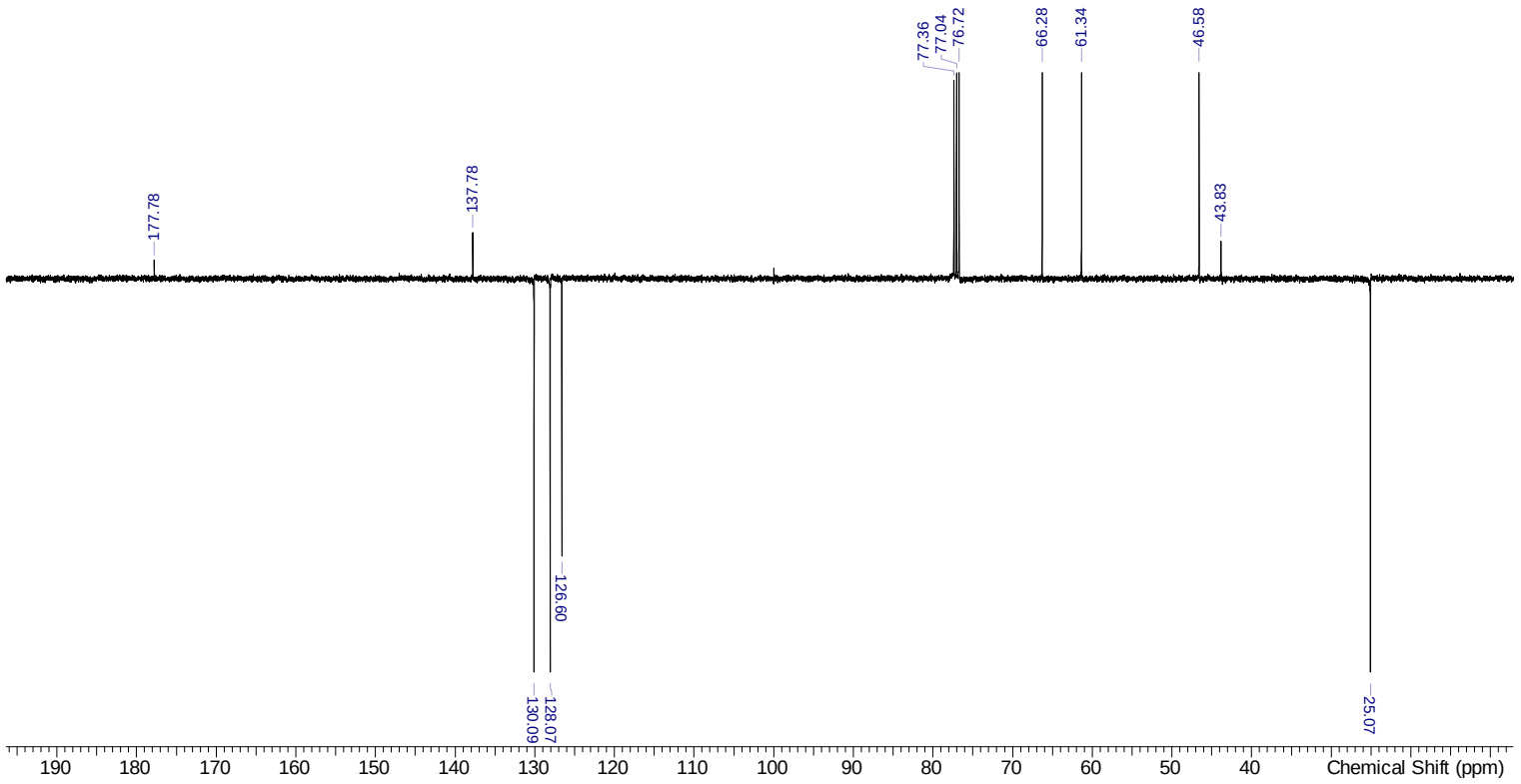

M06(m)
3.64
M04(s)
2.84
M09(m)
M08(m)
M05(td)
M07(m)
M03(m)
M02(m)
7.28
7.27
7.26
7.24
7.23
7.21
7.19
7.04
7.04
7.02
7.02
3.87
3.86
3.85
3.83
3.82
3.65
3.43
3.42
3.40
3.39
3.37
3.36
2.07
2.07
2.04
2.03
1.65
1.64
1.64
1.62
1.62
1.61
2.86
1.87
1.97
2.81
1.95
1.92
1.95
2.27
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
Chemical Shift (ppm)

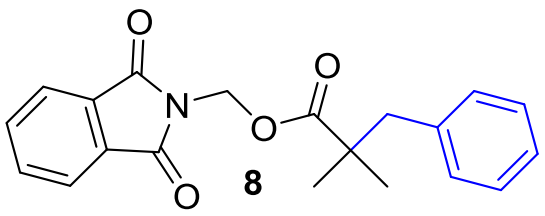

M10(s)
175.55
M09(s)
136.22
M05(s)
65.49
M03(s)
47.01
46.79
M01(s)
34.10
129.83
128.13
126.82
M08(s)
51.91
M04(s)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
Chemical Shift (ppm)

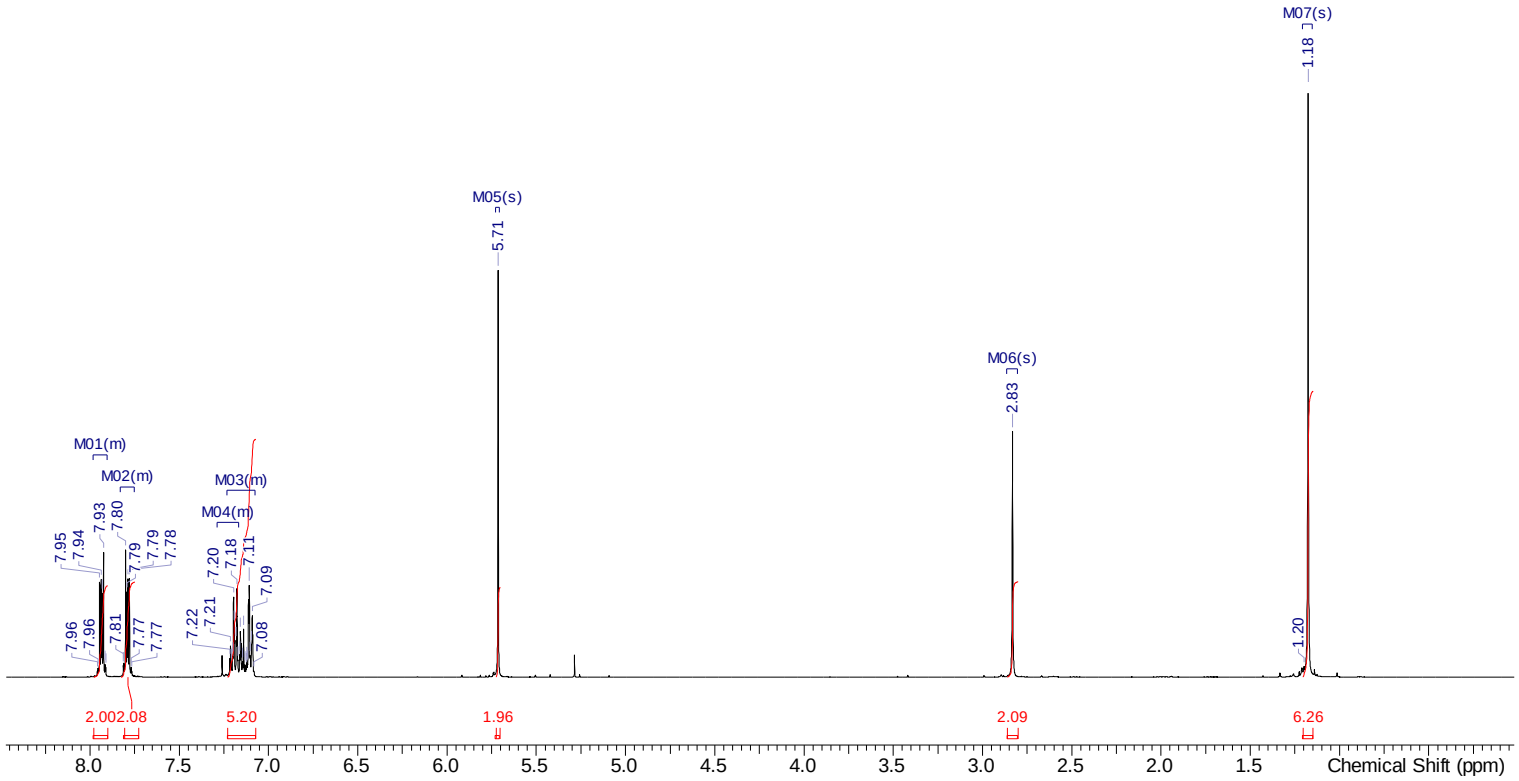

HO
O
O

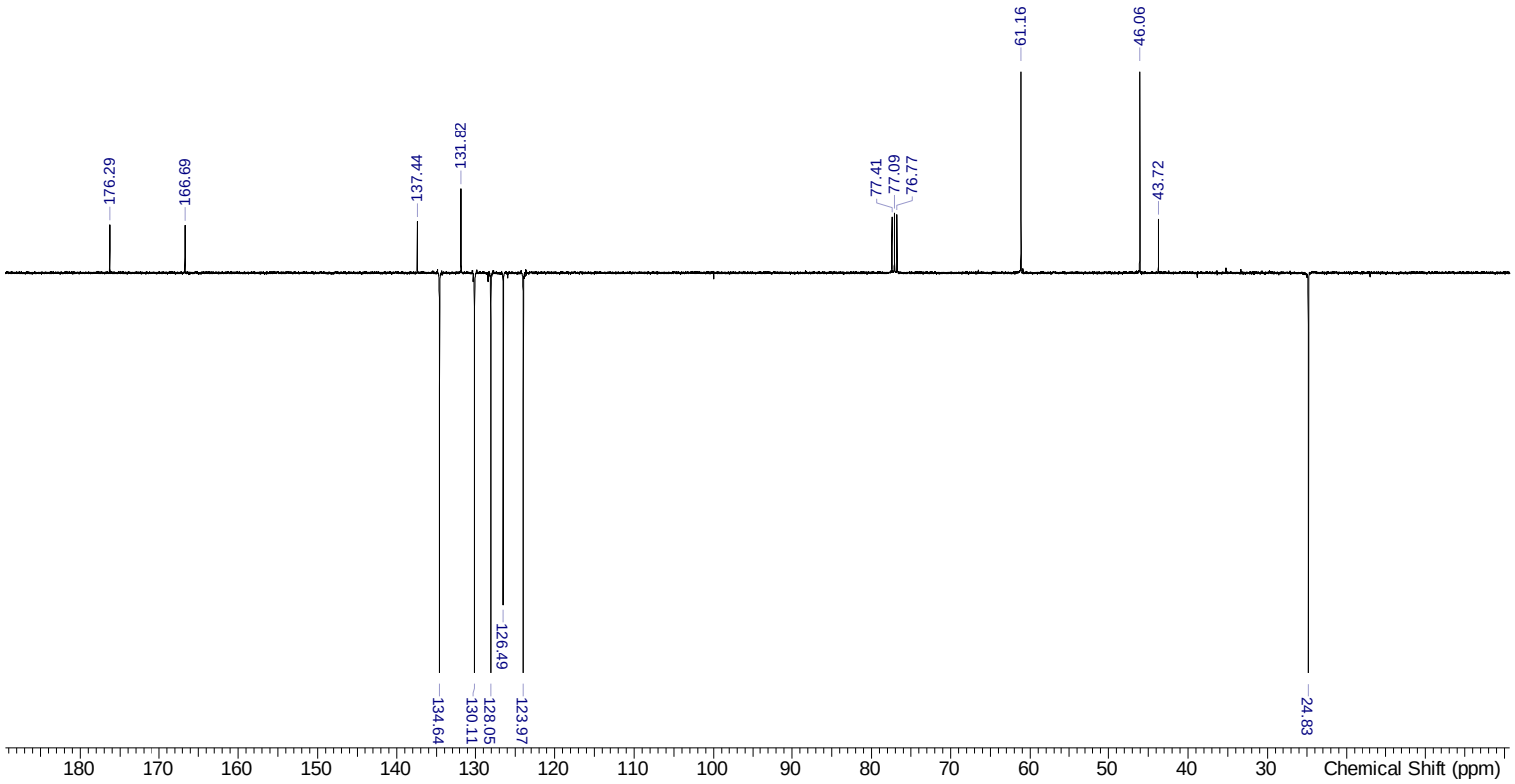
**7**

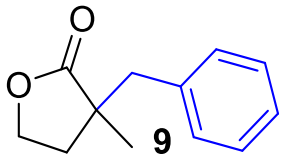

3.28
2.00
2.07
2.08
2.14
6.50
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
Chemical Shift (ppm)

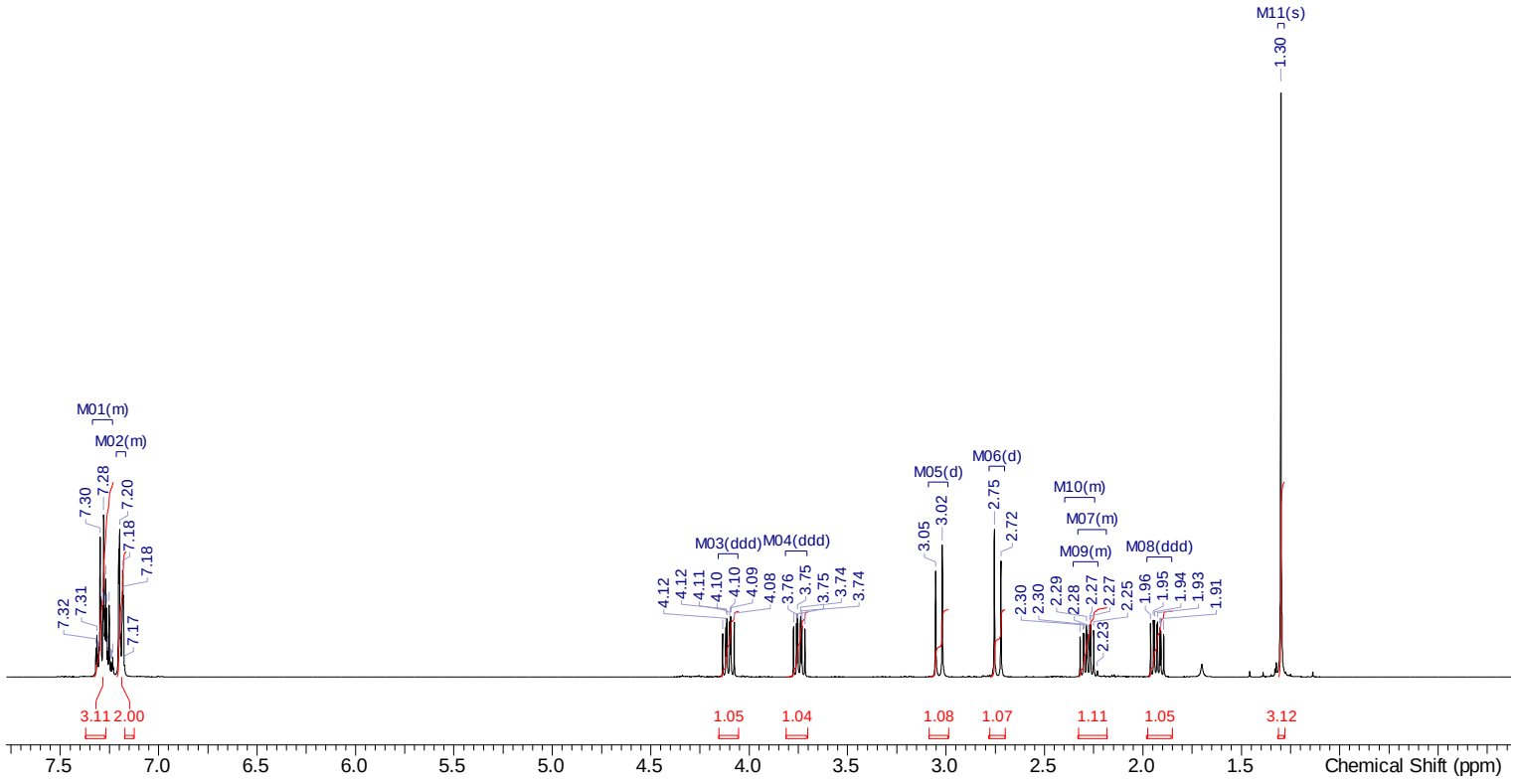

177.78
137.78
77.36
77.04
76.72
66.28
61.34
46.58
43.83
130.09
128.07
126.60
25.07
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
Chemical Shift (ppm)

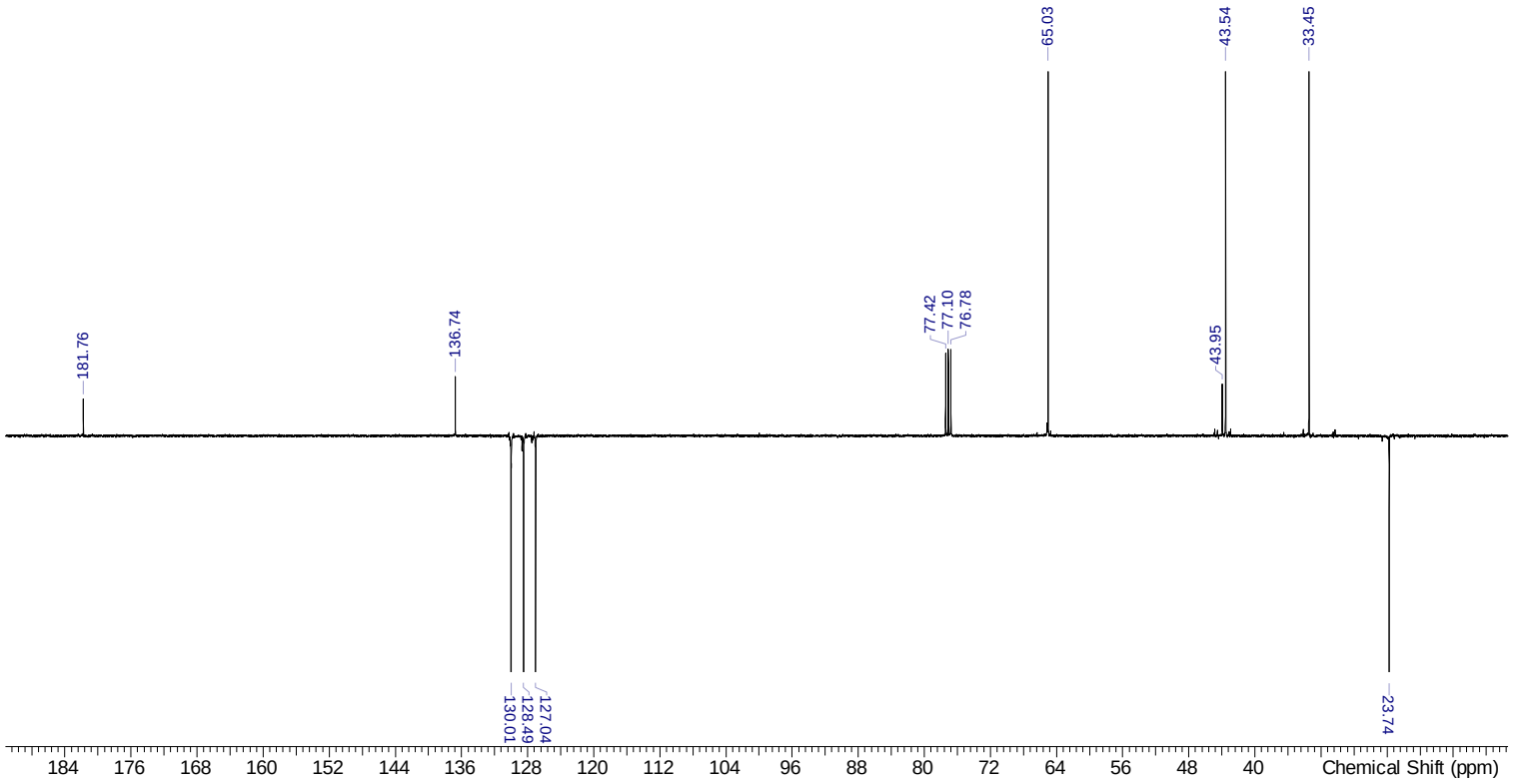

O
N
O
O
O
8

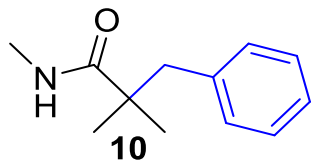

M07(s)
1.18
M05(s)
5.71
M06(s)
2.83
M01(m)
M02(m)
M03(m)
M04(m)
7.95
7.94
7.93
7.80
7.79
7.79
7.78
7.96
7.96
7.81
7.77
7.77
7.22
7.21
7.20
7.18
7.11
7.09
7.08
1.20
2.00
2.08
5.20
1.96
2.09
6.26
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
Chemical Shift (ppm)


176.29
166.69
137.44
131.82
77.41
77.09
76.77
61.16
46.06
43.72
134.64
130.11
128.05
126.49
123.97
24.83
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
Chemical Shift (ppm)

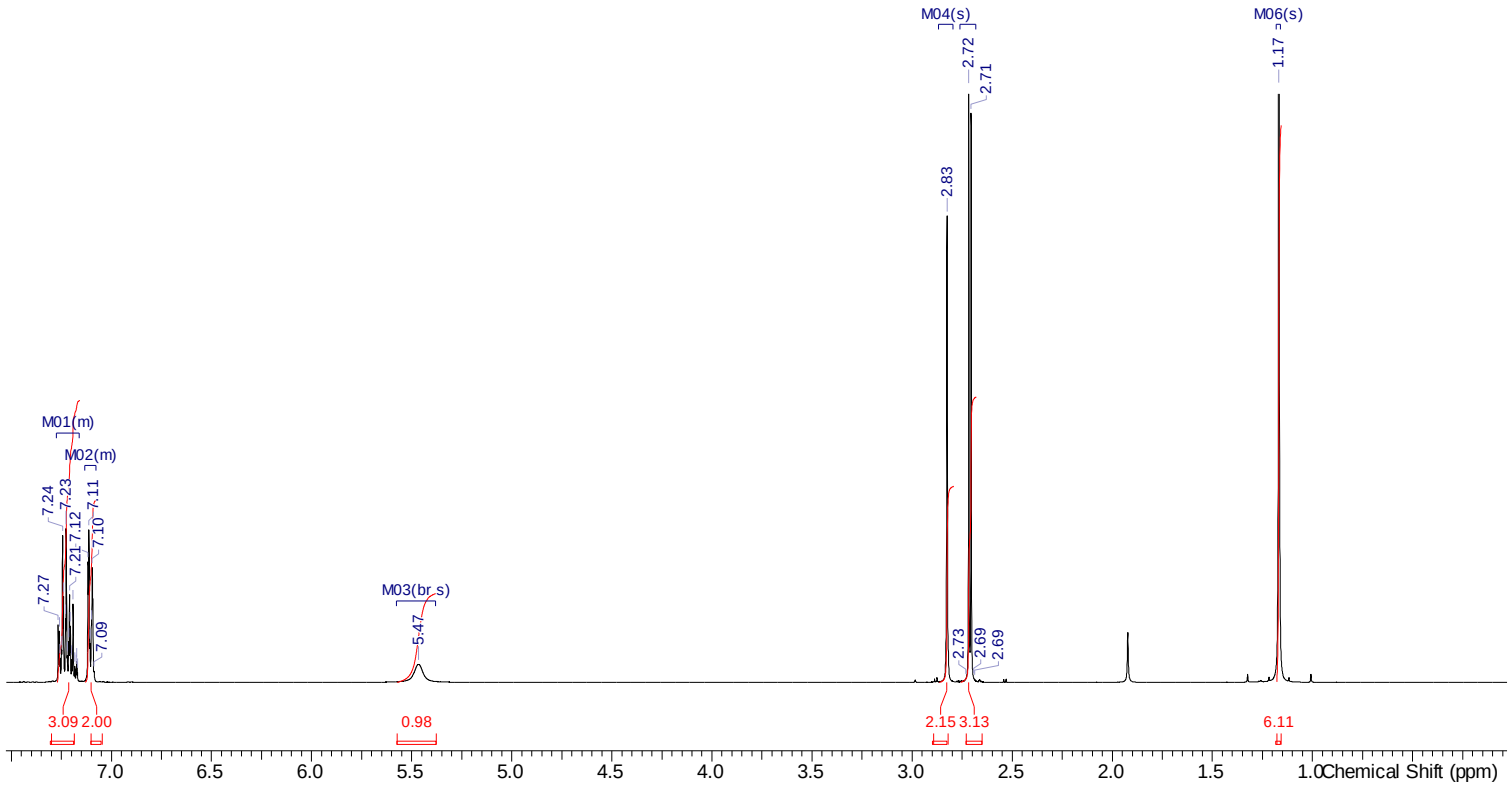

O
O
9

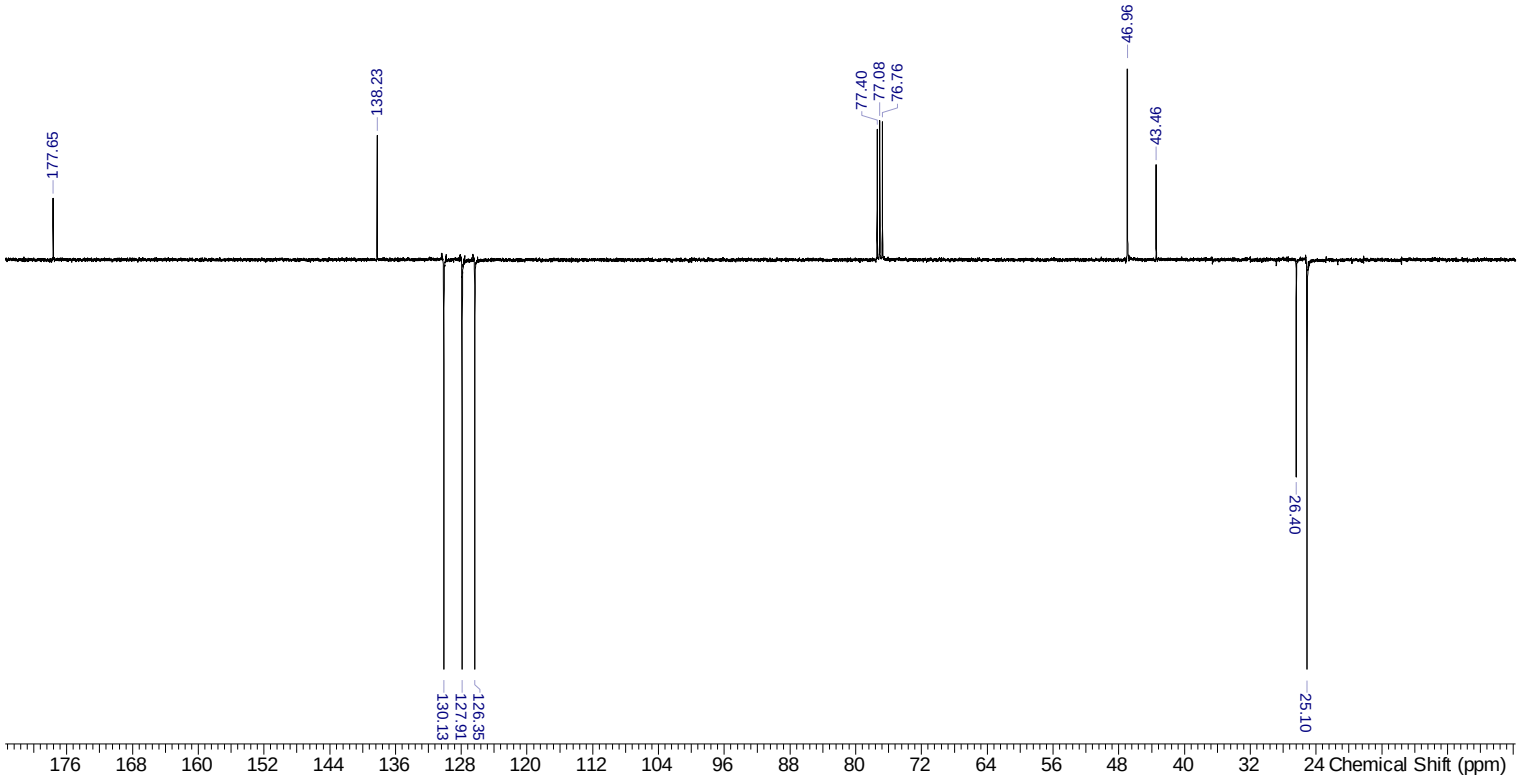

M11(s)
1.30
M01(m)
M02(m)
M03(ddd)
M04(ddd)
M05(d)
M06(d)
M10(m)
M07(m)
M09(m)
M08(ddd)
7.32
7.31
7.30
7.28
7.20
7.18
7.18
7.17
4.12
4.12
4.11
4.10
4.10
4.09
4.08
3.76
3.75
3.75
3.74
3.74
3.05
3.02
2.75
2.72
2.30
2.30
2.29
2.28
2.27
2.27
2.25
2.23
1.96
1.95
1.94
1.93
1.91
3.11
2.00
1.05
1.04
1.08
1.07
1.11
1.05
3.12
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
Chemical Shift (ppm)

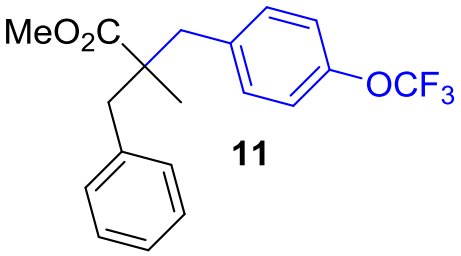

181.76
136.74
77.42
77.10
76.78
65.03
43.95
43.54
33.45
130.01
128.49
127.04
23.74
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
Chemical Shift (ppm)


O
N
H

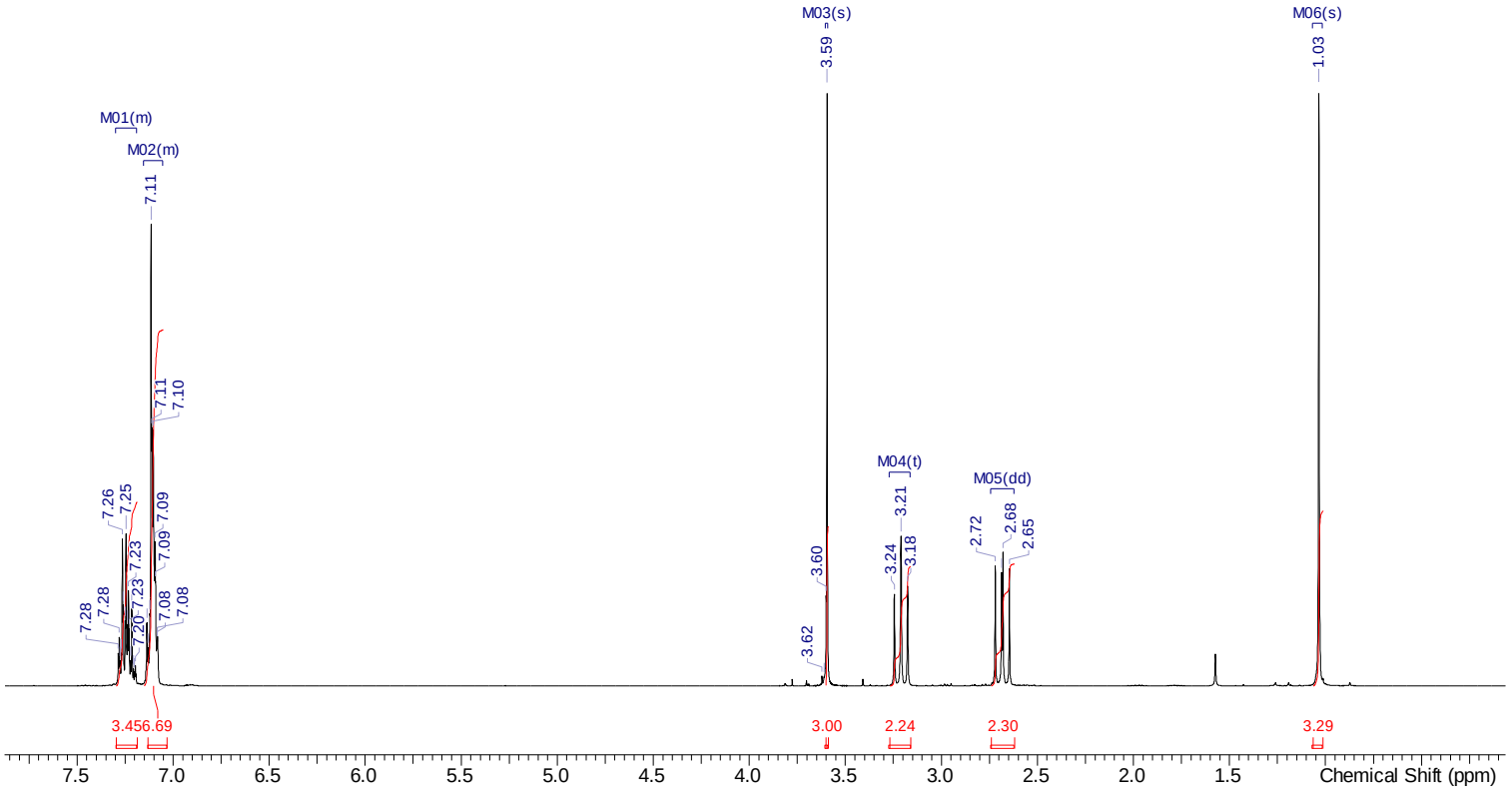
**10**

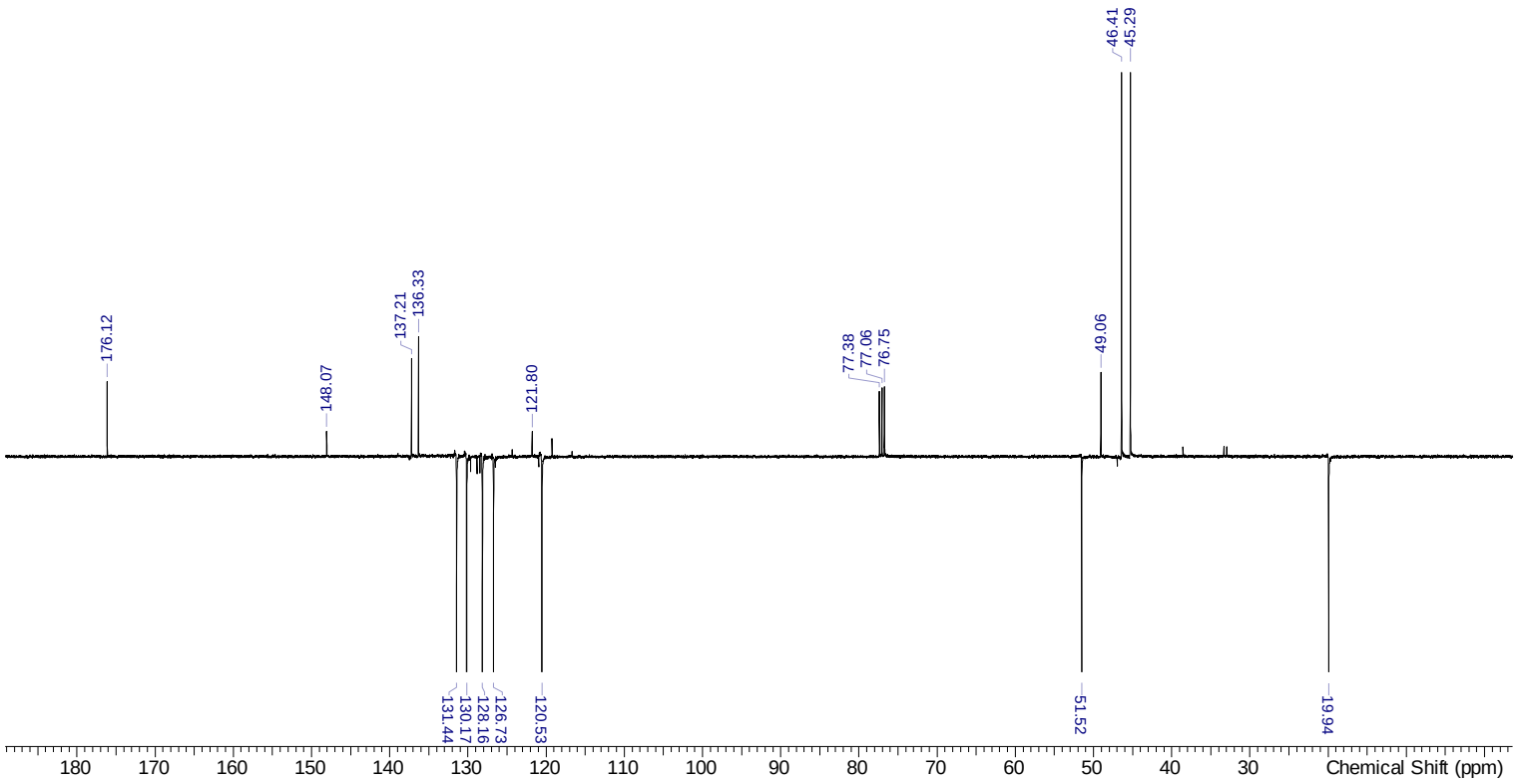

M04(s)
M06(s)
2.72
2.71
1.17
2.83
M01(m)
M02(m)
7.24
7.23
7.12
7.11
7.10
7.27
7.21
M03(br s)
5.47
7.09
2.73
2.69
2.69
3.09
2.00
0.98
2.15
3.13
6.11
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
Chemical Shift (ppm)

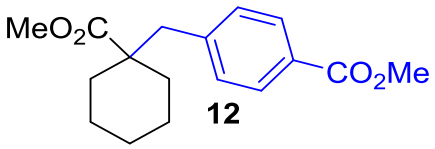

177.65
138.23
77.40
77.08
76.76
46.96
43.46
26.40
130.13
127.91
126.35
25.10
176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 Chemical Shift (ppm)


MeO2C
OCF3

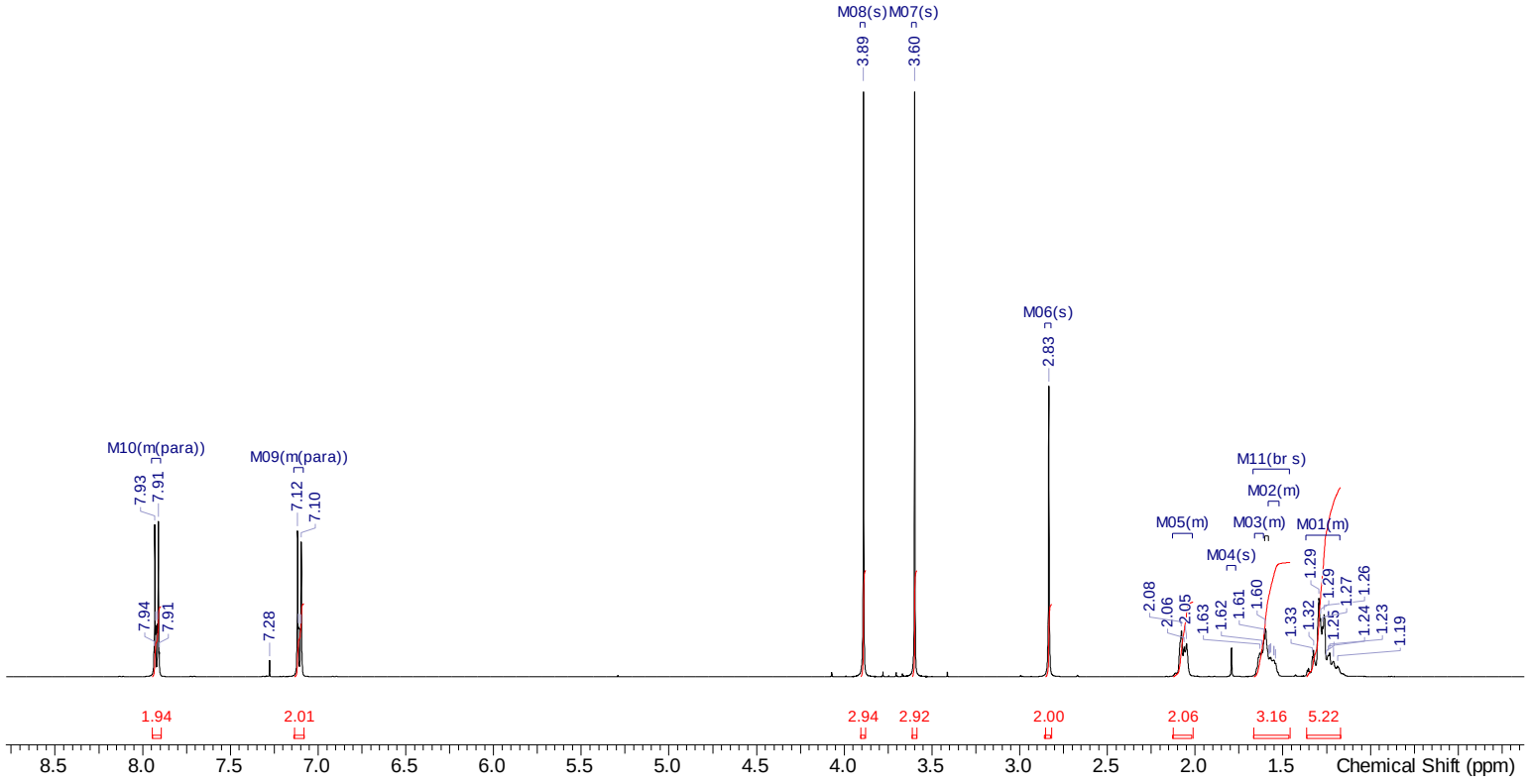
**11**

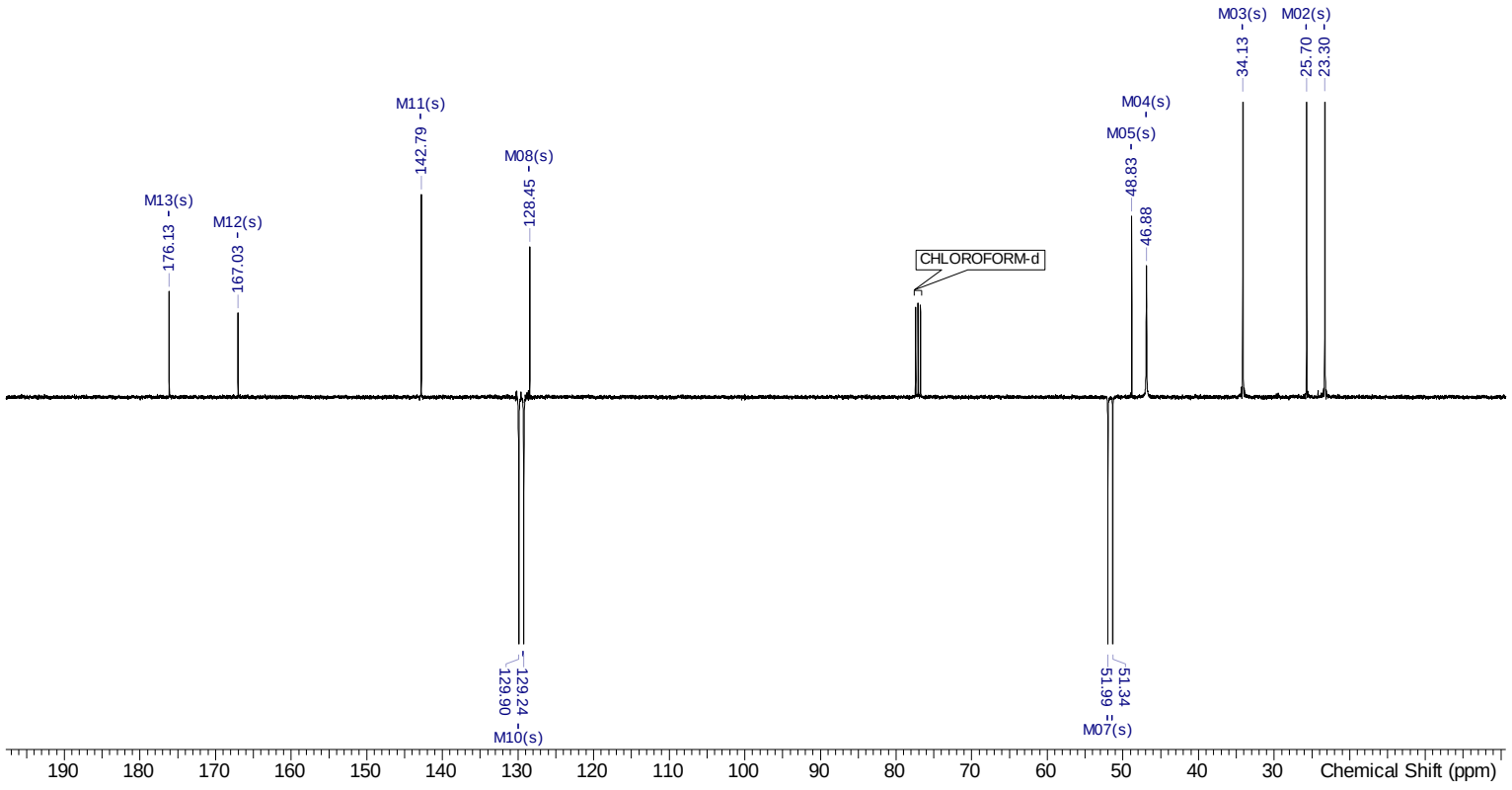

M03(s)
3.59
M06(s)
1.03
M01(m)
M02(m)
7.11
M04(t)
M05(dd)
7.11
7.10
7.26
7.25
7.09
7.09
7.23
7.23
7.28
7.28
7.20
7.08
7.08
3.60
3.62
3.24
3.18
3.21
2.72
2.68
2.65
3.45
6.69
3.00
2.24
2.30
3.29
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
Chemical Shift (ppm)

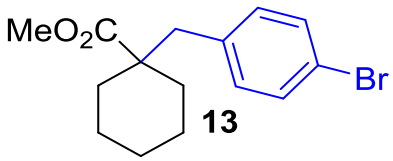

176.12
148.07
137.21
136.33
121.80
77.38
77.06
76.75
49.06
46.41
45.29
131.44
130.17
128.16
126.73
120.53
51.52
19.94
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
Chemical Shift (ppm)

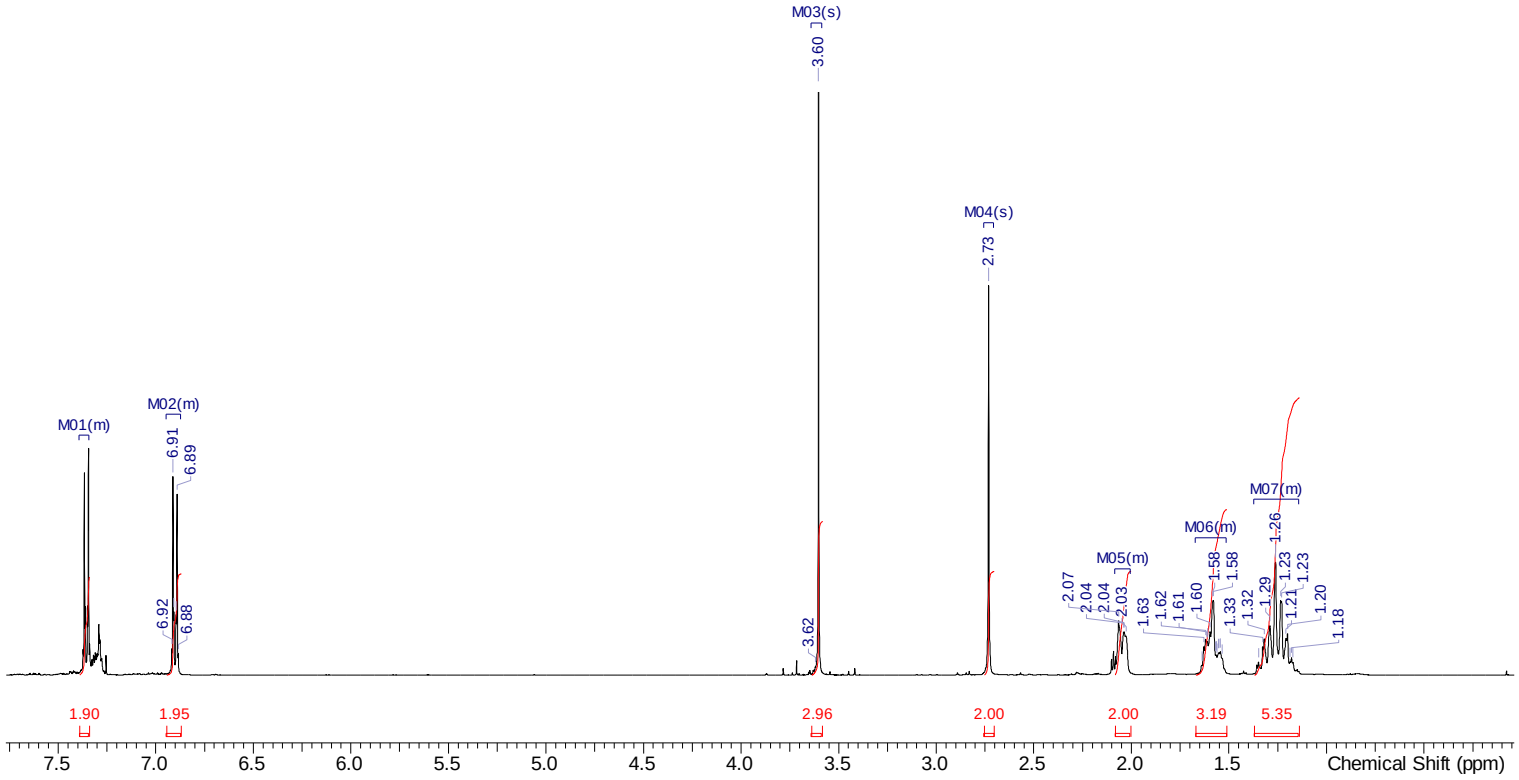

MeO2C
CO2Me

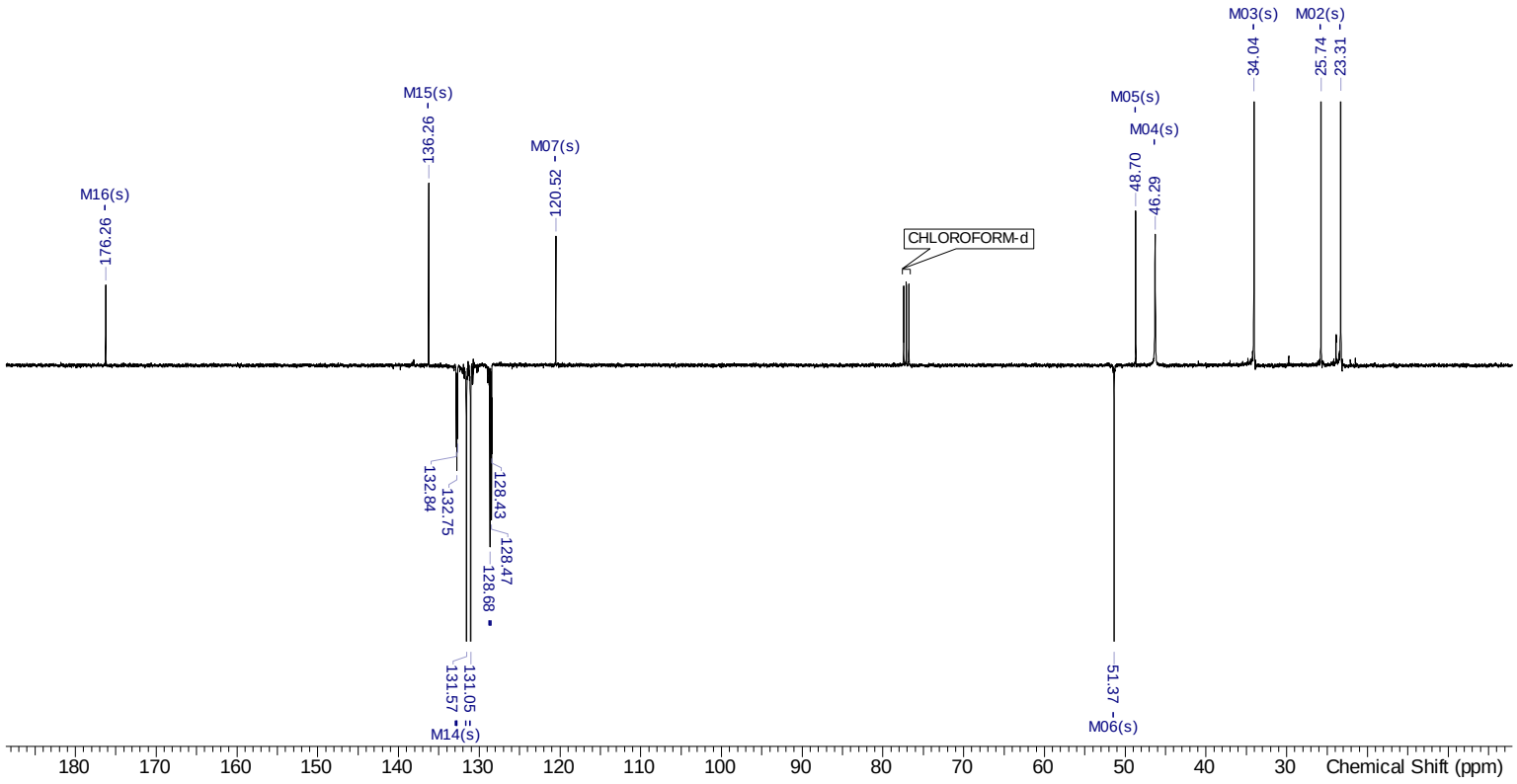
**12**

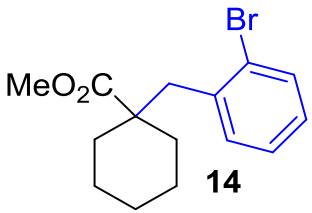

M08(s)
M07(s)
3.89
3.60
M06(s)
2.83
M10(m(para))
7.93
7.91
7.94
7.91
M09(m(para))
7.12
7.10
7.28
M11(br s)
M02(m)
M05(m)
M03(m)
M01(m)
M04(s)
2.08
2.06
2.05
1.63
1.62
1.61
1.60
1.33
1.32
1.29
1.29
1.27
1.26
1.25
1.24
1.23
1.19
1.94
2.01
2.94
2.92
2.00
2.06
3.16
5.22
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
Chemical Shift (ppm)


M03(s)
M02(s)
34.13
25.70
23.30
M11(s)
142.79
M04(s)
M05(s)
48.83
46.88
M08(s)
128.45
M13(s)
176.13
M12(s)
167.03
CHLOROFORM-d
129.24
129.90
M10(s)
51.34
51.99
M07(s)
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 Chemical Shift (ppm)

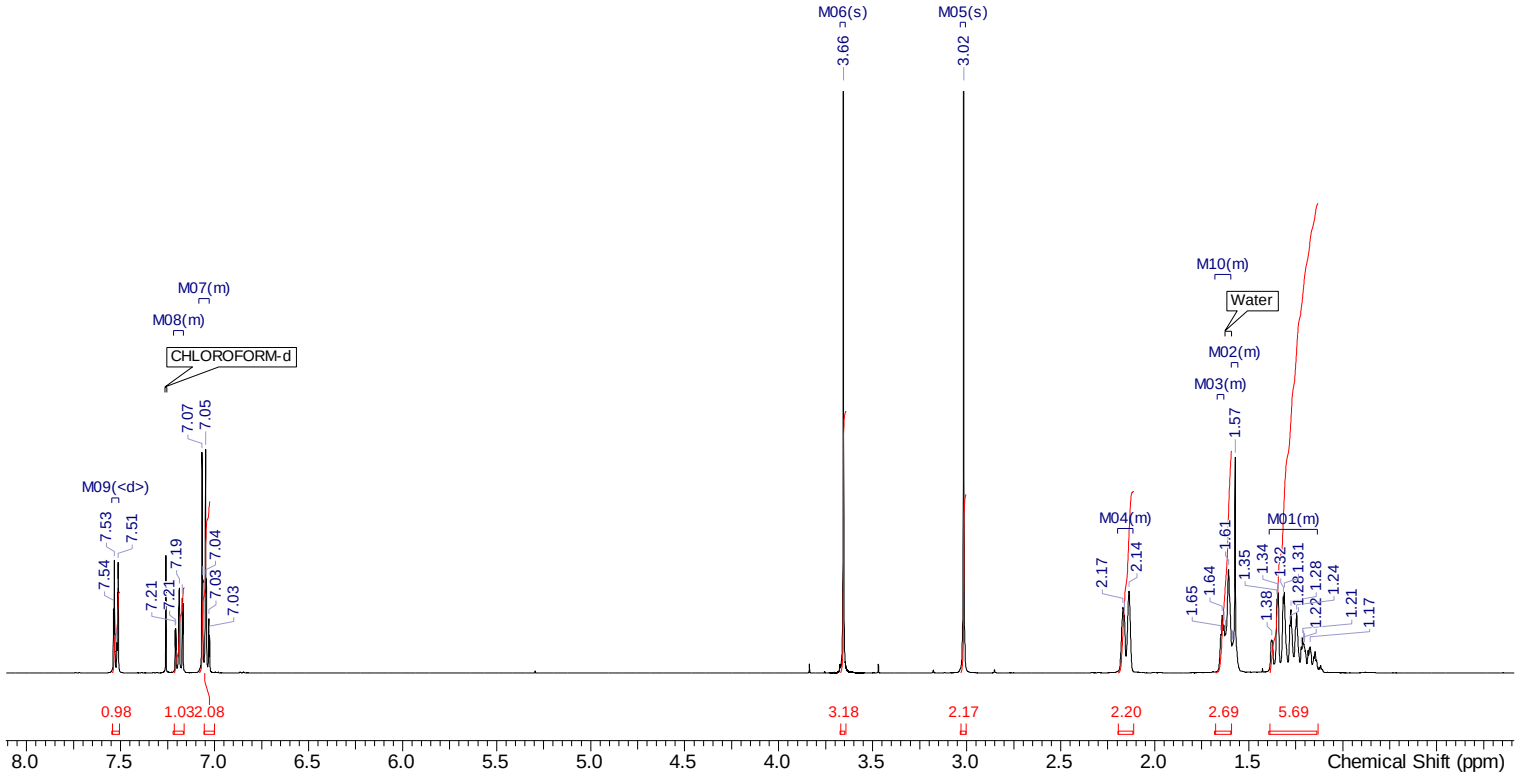

MeO2C
Br
13

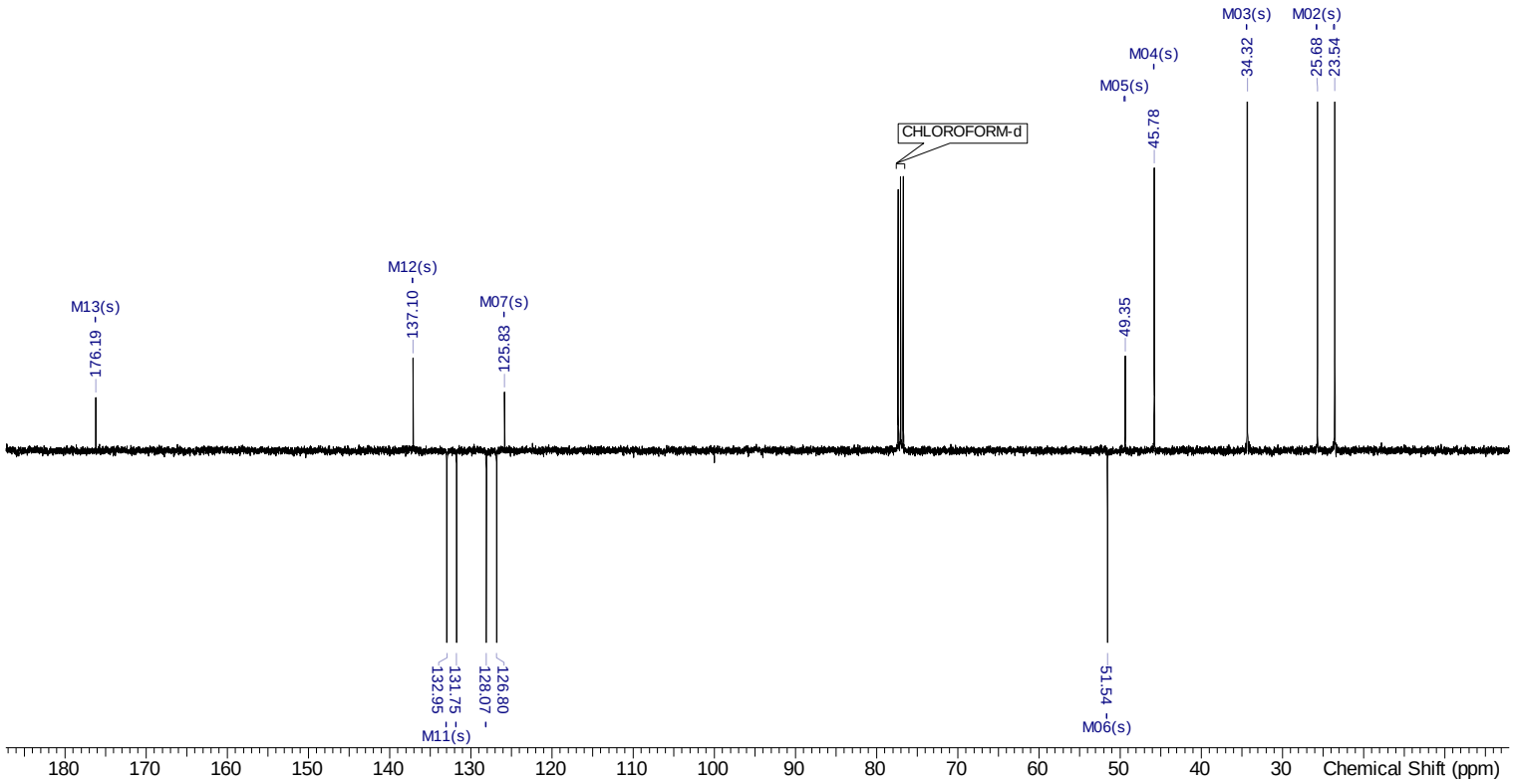

M03(s)
3.60
M04(s)
2.73
M01(m)
M02(m)
6.91
6.89
6.92
6.88
3.62
M05(m)
M06(m)
M07(m)
2.07
2.04
2.04
2.03
1.63
1.62
1.61
1.60
1.58
1.58
1.33
1.32
1.29
1.26
1.23
1.23
1.21
1.20
1.18
1.90
1.95
2.96
2.00
2.00
3.19
5.35
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
Chemical Shift (ppm)

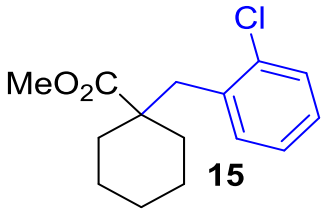

M03(s)
M02(s)
34.04
25.74
23.31
M15(s)
136.26
M05(s)
M04(s)
M07(s)
120.52
48.70
46.29
M16(s)
176.26
CHLOROFORM-d
132.84
132.75
128.43
128.47
128.68
131.57
131.05
M14(s)
51.37
M06(s)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
Chemical Shift (ppm)


Br
MeO2C

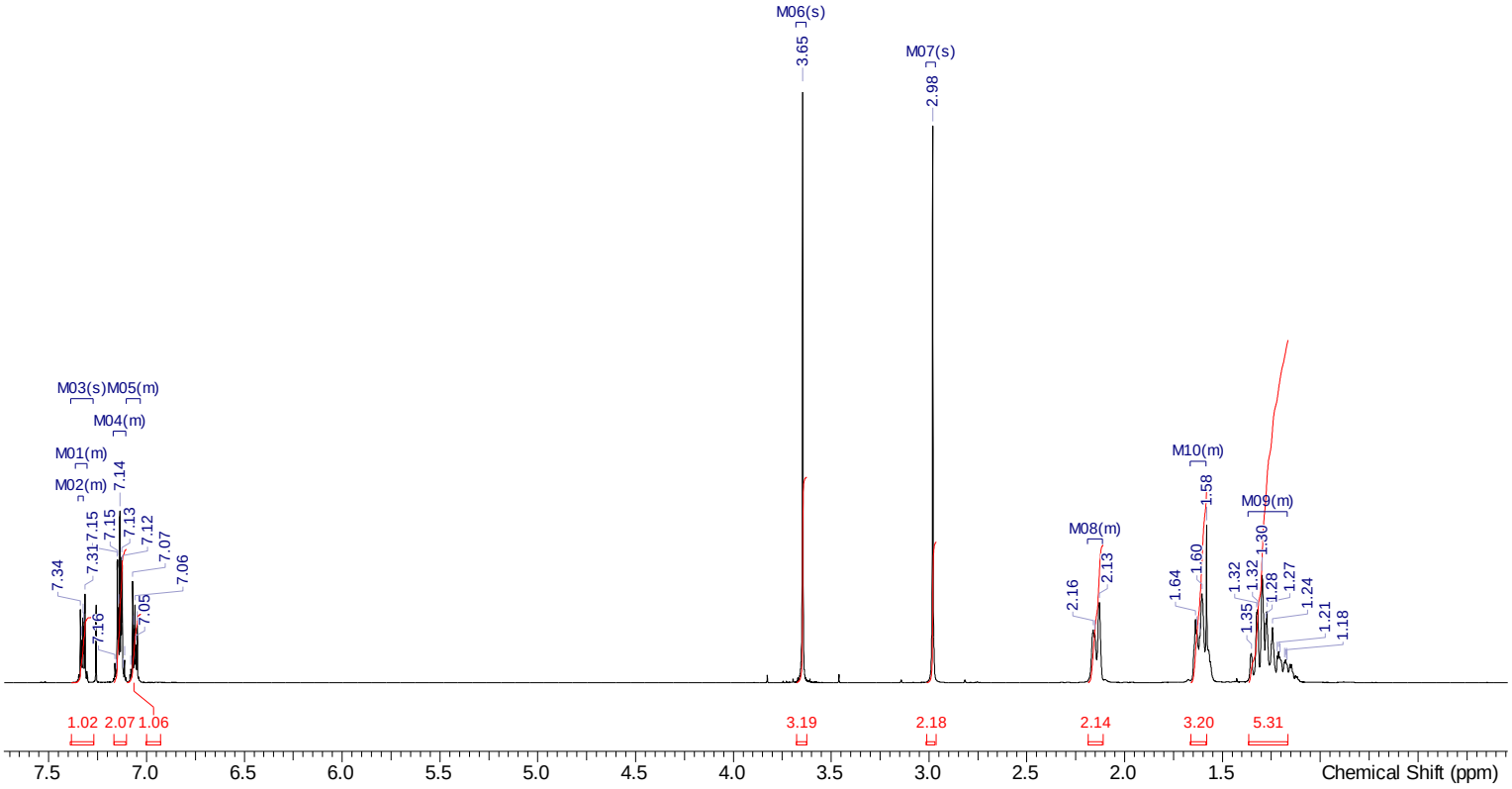
**14**

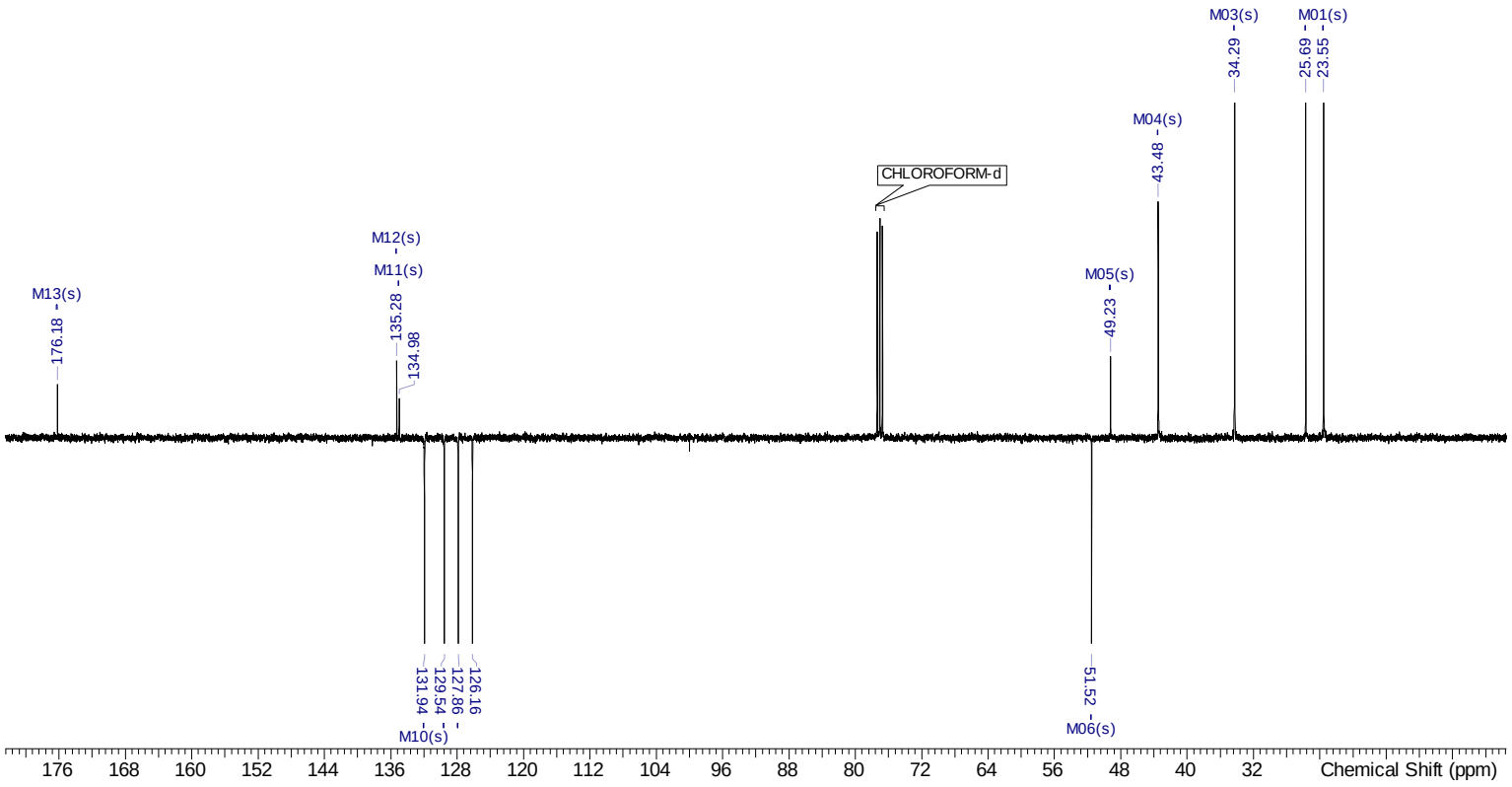

M06(s)
3.66
M05(s)
3.02
M10(m)
Water
M02(m)
M03(m)
M07(m)
M08(m)
CHLOROFORM-d
M09(<d>)
M04(m)
M01(m)
7.54
7.53
7.51
7.21
7.21
7.19
7.07
7.05
7.04
7.03
7.03
2.17
2.14
1.65
1.64
1.61
1.57
1.38
1.35
1.34
1.32
1.31
1.28
1.24
1.22
1.21
1.17
0.98
1.03
2.08
3.18
2.17
2.20
2.69
5.69
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
Chemical Shift (ppm)

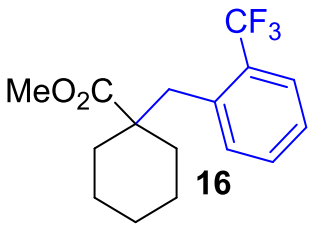

M03(s)
M02(s)
M04(s)
34.32
25.68
23.54
M05(s)
45.78
CHLOROFORM-d
M12(s)
M13(s)
137.10
M07(s)
176.19
125.83
49.35
132.95
131.75
128.07
126.80
51.54
M11(s)
M06(s)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
Chemical Shift (ppm)

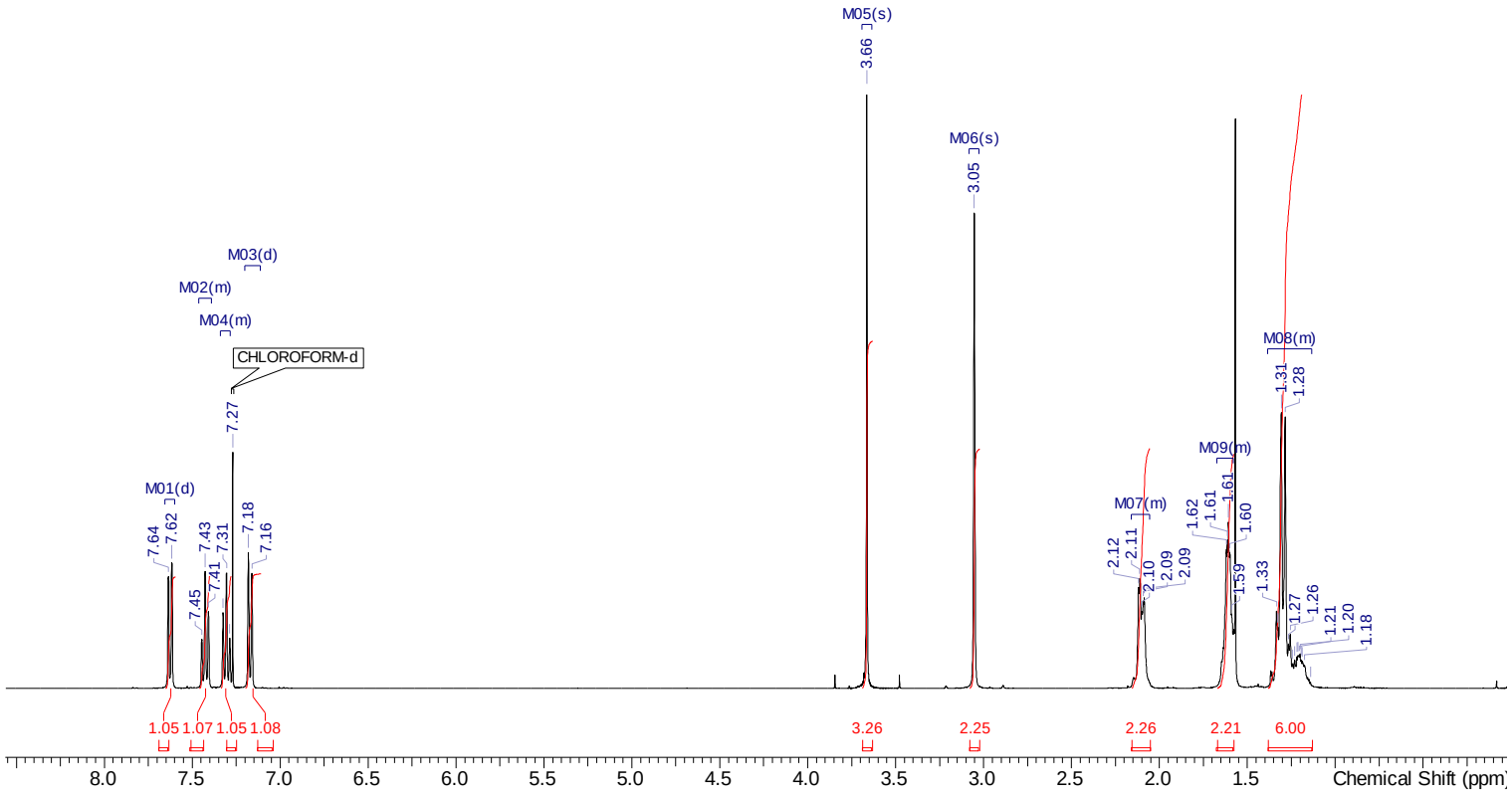

Cl
MeO2C

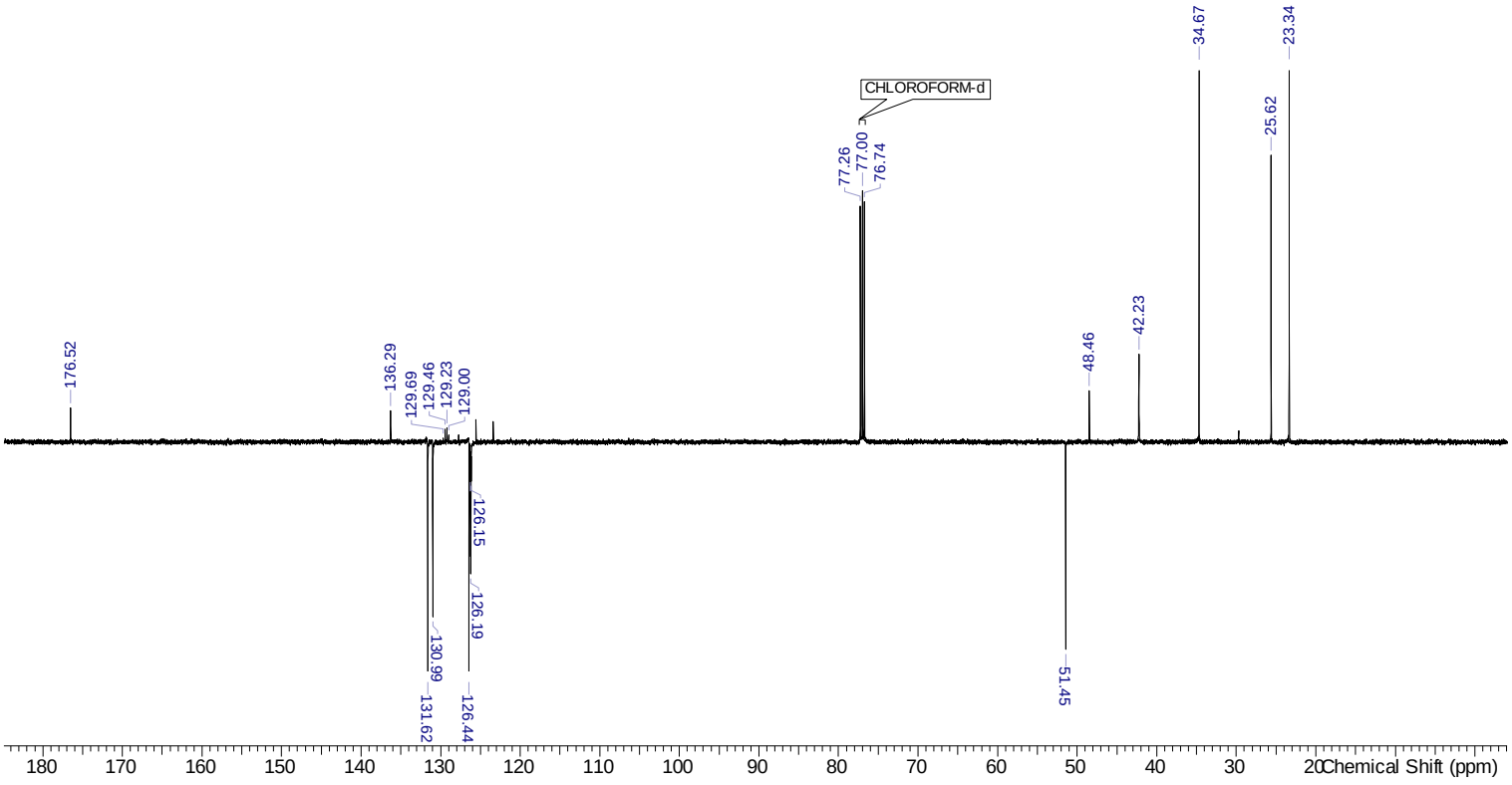
**15**

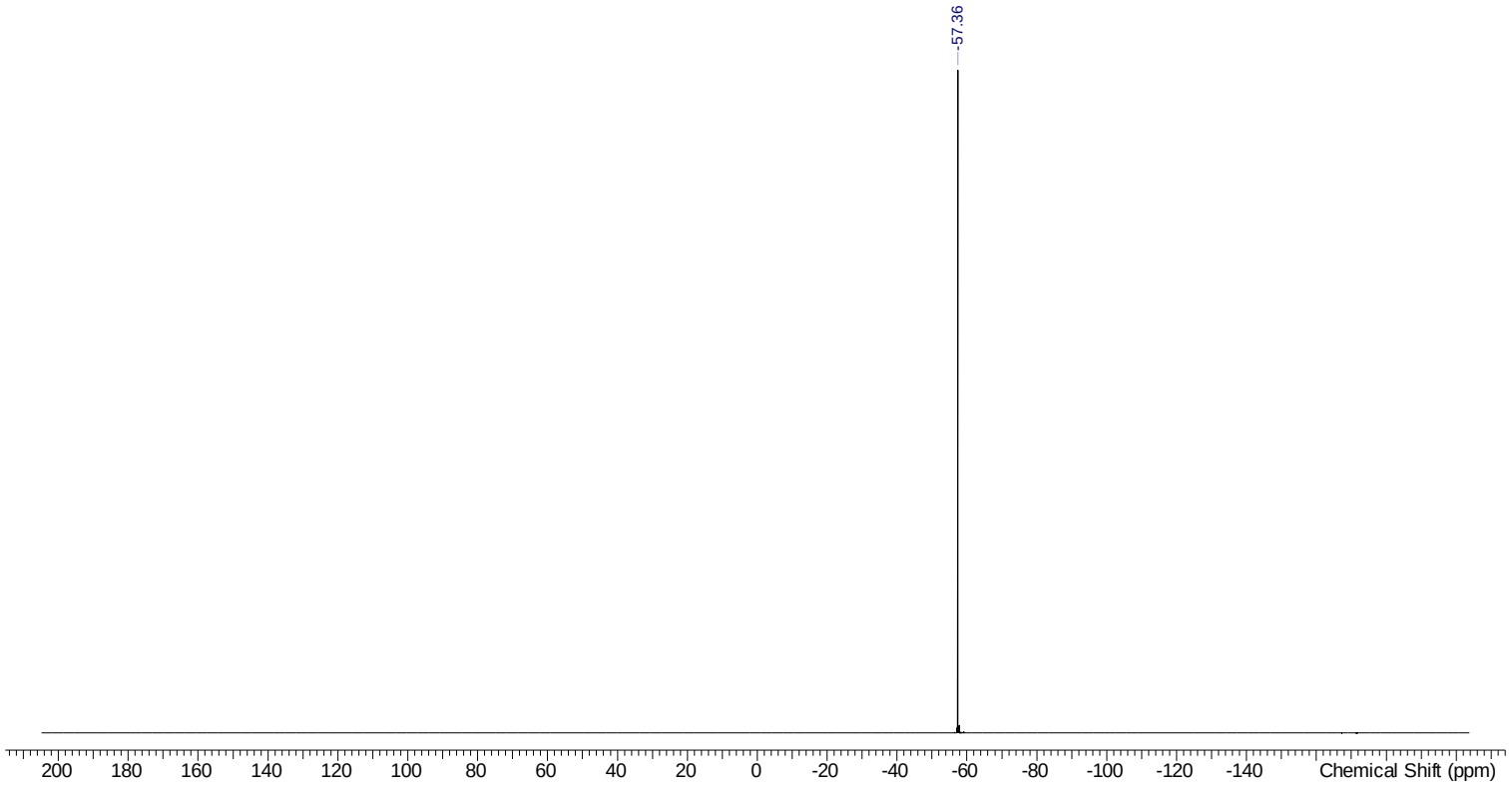

M06(s)
3.65
M07(s)
2.98
M03(s)M05(m)
M04(m)
M01(m)
M02(m)
7.34
7.31
7.16
7.15
7.15
7.14
7.13
7.12
7.07
7.06
7.05
M08(m)
2.16
2.13
M10(m)
1.64
1.60
1.58
M09(m)
1.35
1.32
1.32
1.30
1.28
1.27
1.24
1.21
1.18
1.02
2.07
1.06
3.19
2.18
2.14
3.20
5.31
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
Chemical Shift (ppm)

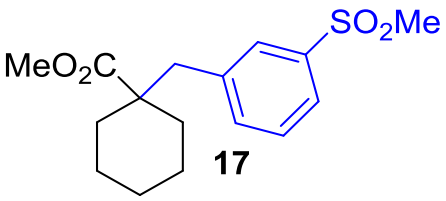

M03(s)
M01(s)
34.29
25.69
23.55
M04(s)
43.48
CHLOROFORM-d
M12(s)
M11(s)
M13(s)
176.18
135.28
134.98
M05(s)
49.23
131.94
129.54
127.86
126.16
M10(s)
51.52
M06(s)
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
Chemical Shift (ppm)


CF3
MeO2C
16

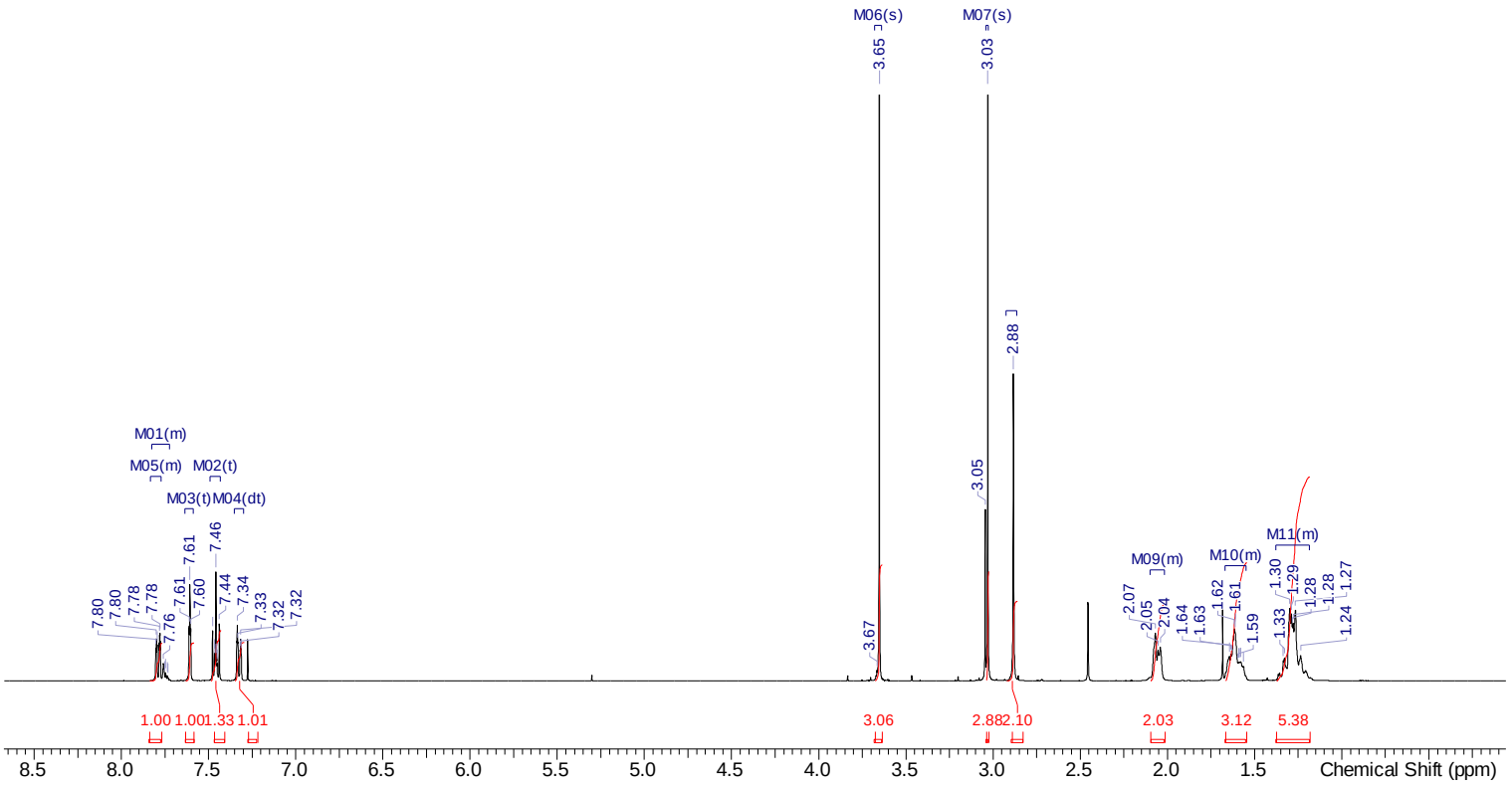

M05(s)
3.66
M06(s)
3.05
M03(d)
M02(m)
M04(m)
CHLOROFORM-d
7.27
M01(d)
7.64
7.62
7.43
7.31
7.18
7.16
7.45
7.41
M07(m)
2.12
2.11
2.10
2.09
2.09
M09(m)
1.62
1.61
1.61
1.60
1.59
M08(m)
1.31
1.28
1.33
1.27
1.26
1.21
1.20
1.18
1.05
1.07
1.05
1.08
3.26
2.25
2.26
2.21
6.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
Chemical Shift (ppm)

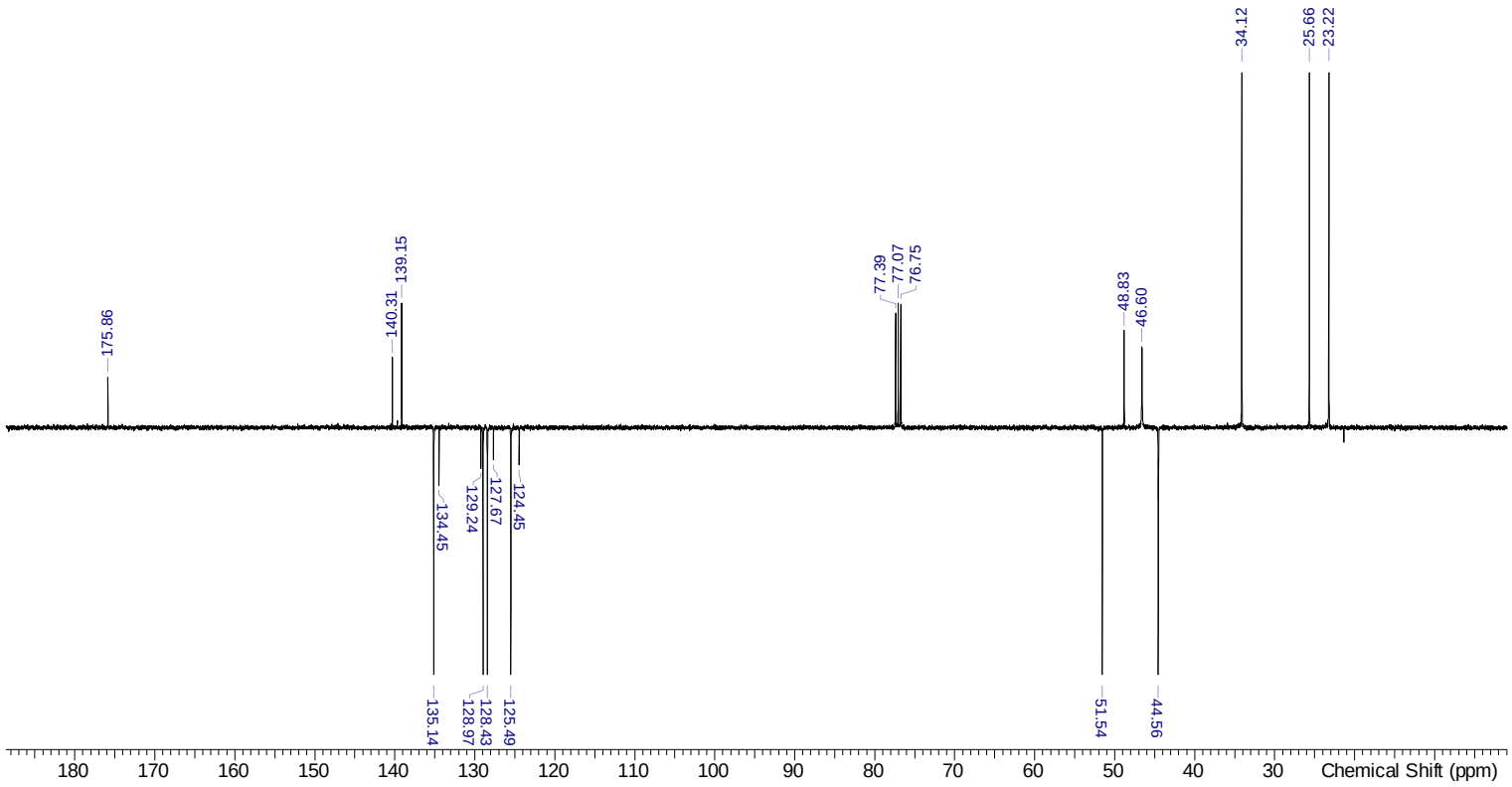

CHLOROFORM-d
176.52
136.29
129.69
129.46
129.23
129.00
126.15
126.19
130.99
131.62
126.44
77.26
77.00
76.74
48.46
51.45
42.23
34.67
25.62
23.34
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
Chemical Shift (ppm)

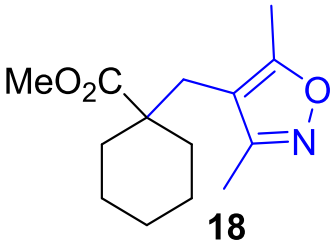

-57.36
200
180
160
140
120
100
80
60
40
20
0
-20
-40
-60
-80
-100
-120
-140
Chemical Shift (ppm)


$SO_2Me$
$MeO_2C$

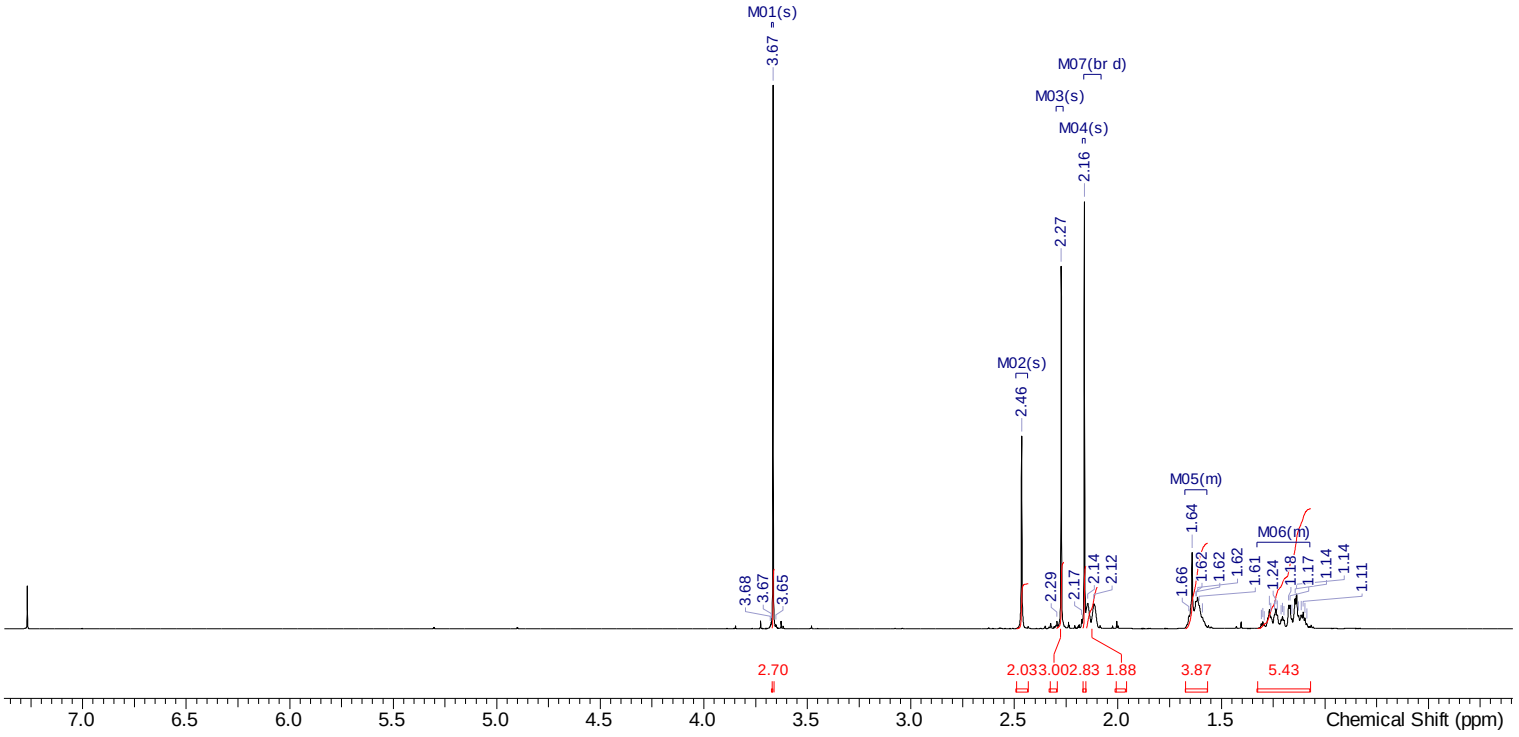
**17**

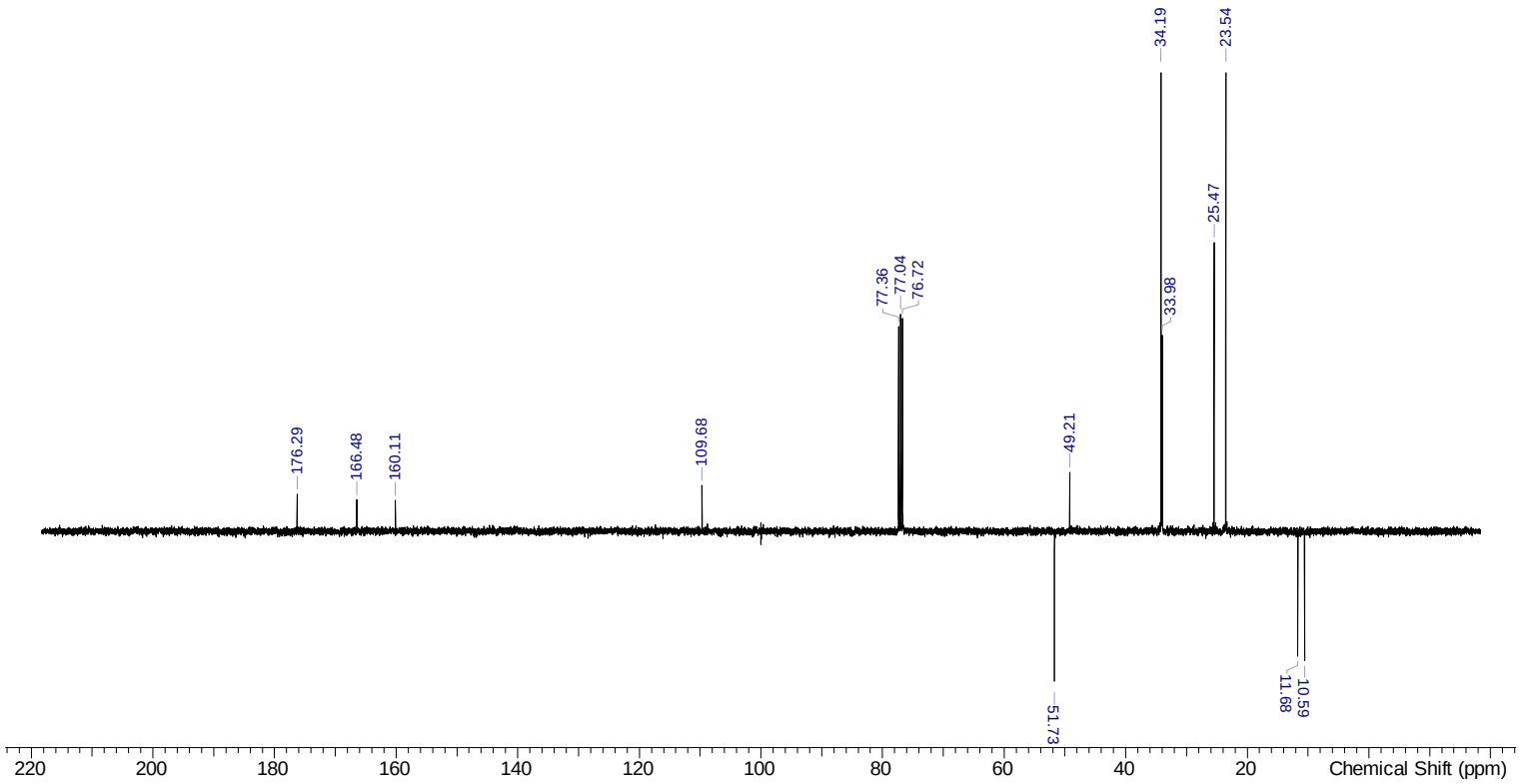

M06(s)
M07(s)
3.65
3.03
2.88
3.05
3.67
M01(m)
M05(m)
M02(t)
M03(t)
M04(dt)
7.80
7.80
7.78
7.78
7.76
7.61
7.61
7.60
7.46
7.44
7.34
7.33
7.32
7.32
M09(m)
M10(m)
M11(m)
2.07
2.05
2.04
1.64
1.63
1.62
1.61
1.59
1.33
1.30
1.29
1.28
1.28
1.27
1.24
1.00
1.00
1.33
1.01
3.06
2.88
2.10
2.03
3.12
5.38
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
Chemical Shift (ppm)

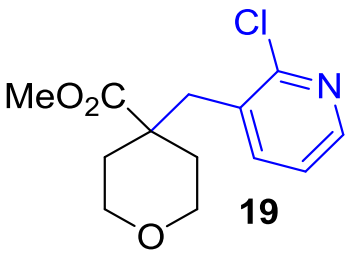

175.86
140.31
139.15
77.39
77.07
76.75
48.83
46.60
34.12
25.66
23.22
134.45
129.24
127.67
124.45
135.14
128.97
128.43
125.49
51.54
44.56
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
Chemical Shift (ppm)


MeO2C
O
N

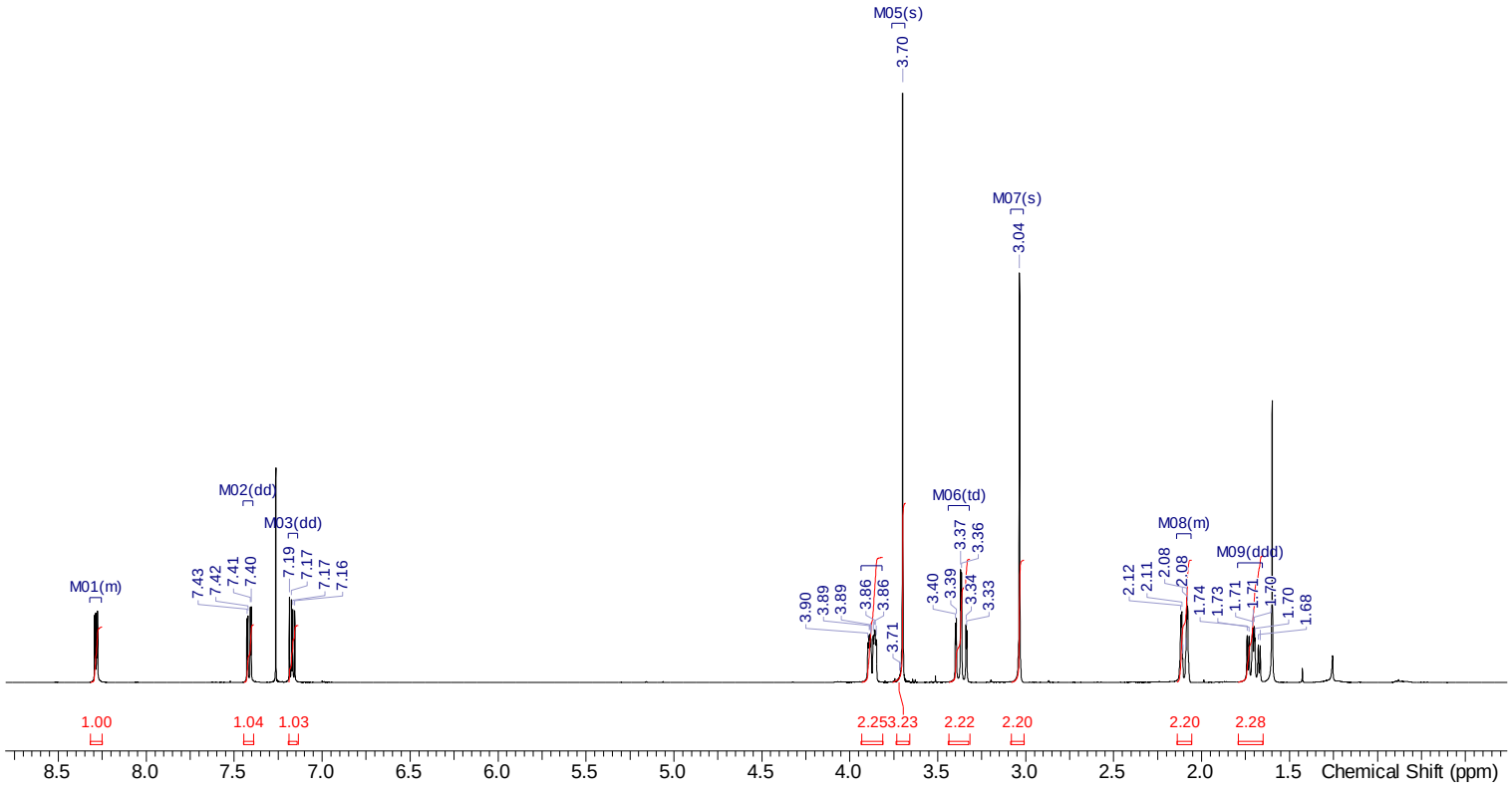
**18**

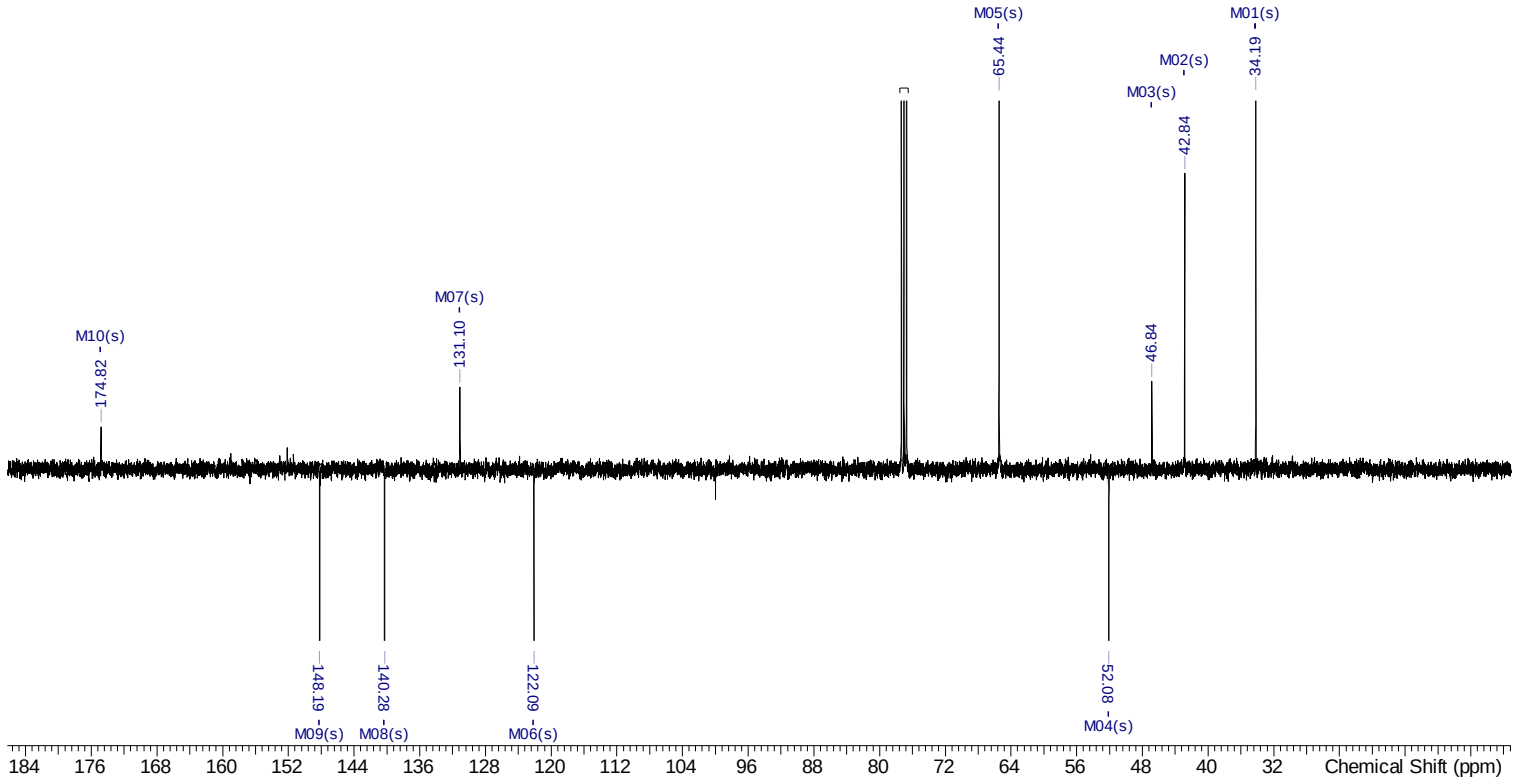

M01(s)
3.67
M07(br d)
M03(s)
M04(s)
2.16
2.27
M02(s)
2.46
M05(m)
1.64
M06(m)
3.68
3.67
3.65
2.29
2.17
2.14
2.12
1.66
1.62
1.62
1.61
1.24
1.18
1.17
1.14
1.14
1.11
2.70
2.03
3.00
2.83
1.88
3.87
5.43
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
Chemical Shift (ppm)

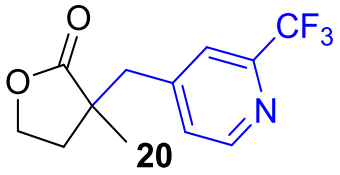

176.29
166.48
160.11
109.68
77.36
77.04
76.72
49.21
34.19
33.98
25.47
23.54
11.68
10.59
51.73
220
200
180
160
140
120
100
80
60
40
20
Chemical Shift (ppm)


Cl
N
MeO2C
O

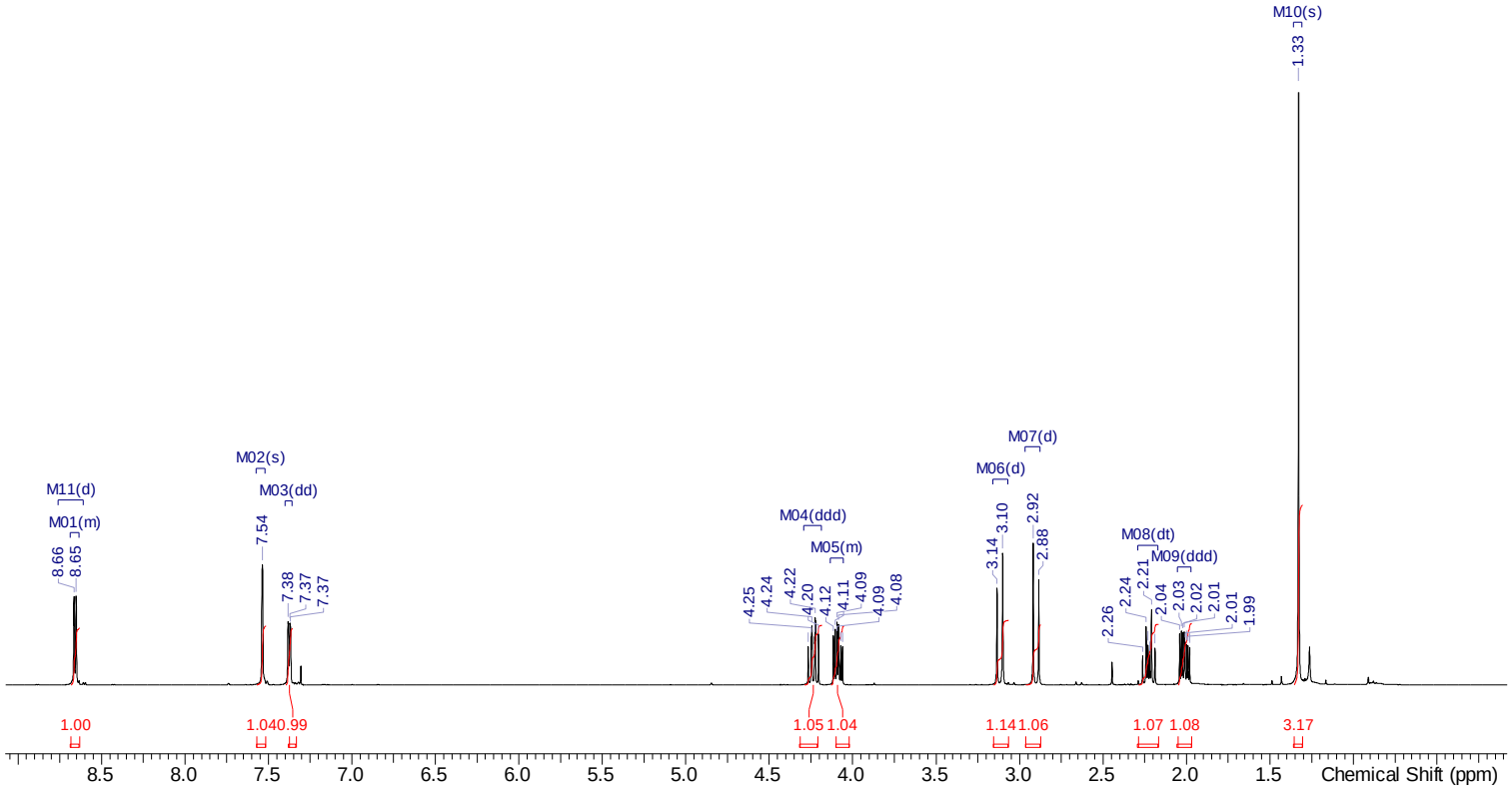
**19**

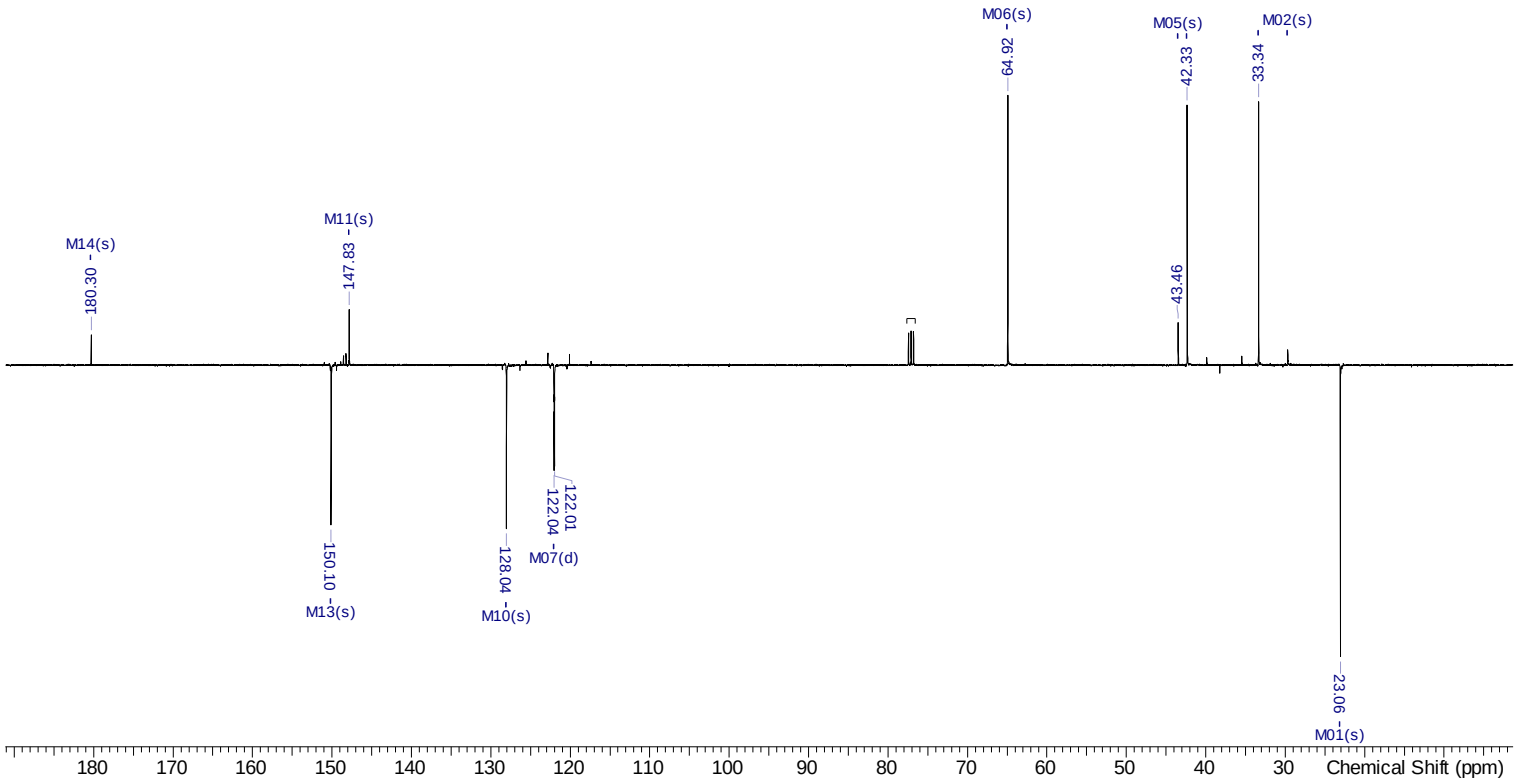

M05(s)
3.70
M07(s)
3.04
M06(td)
M02(dd)
M03(dd)
M08(m)
M09(ddd)
M01(m)
7.43
7.42
7.41
7.40
7.19
7.17
7.17
7.16
3.90
3.89
3.89
3.86
3.86
3.71
3.40
3.39
3.37
3.36
3.34
3.33
2.12
2.11
2.08
2.08
1.74
1.73
1.71
1.71
1.70
1.70
1.68
1.00
1.04
1.03
2.25
3.23
2.22
2.20
2.20
2.28
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
Chemical Shift (ppm)

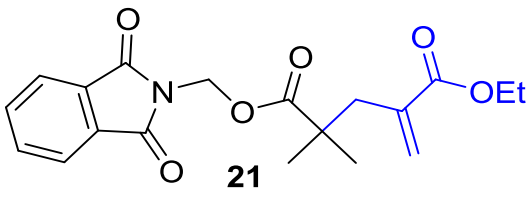

M05(s)
65.44
M01(s)
34.19
M02(s)
M03(s)
42.84
M07(s)
131.10
M10(s)
174.82
46.84
148.19
140.28
122.09
52.08
M09(s)
M08(s)
M06(s)
M04(s)
184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32
Chemical Shift (ppm)


O
O
CF3
N

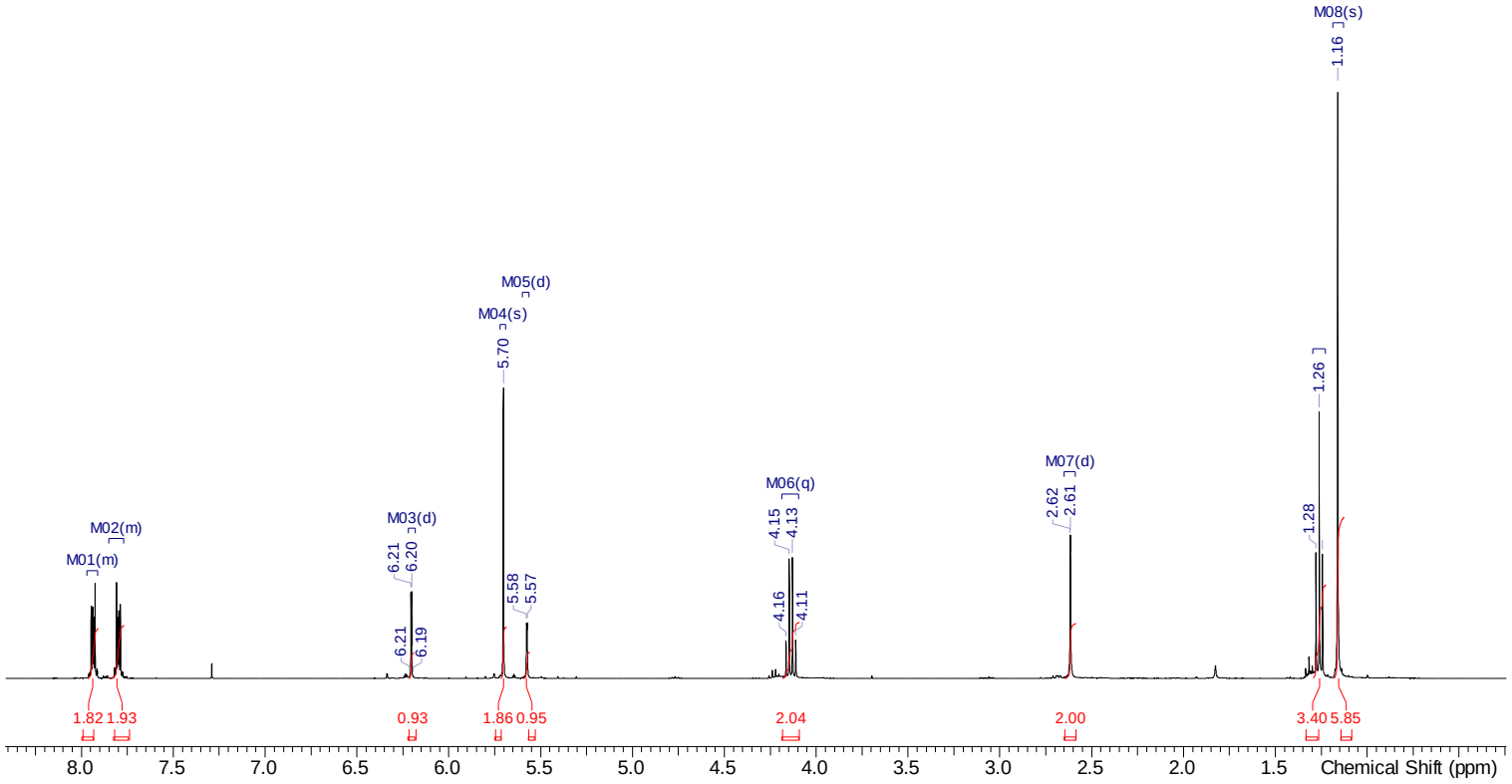
**20**

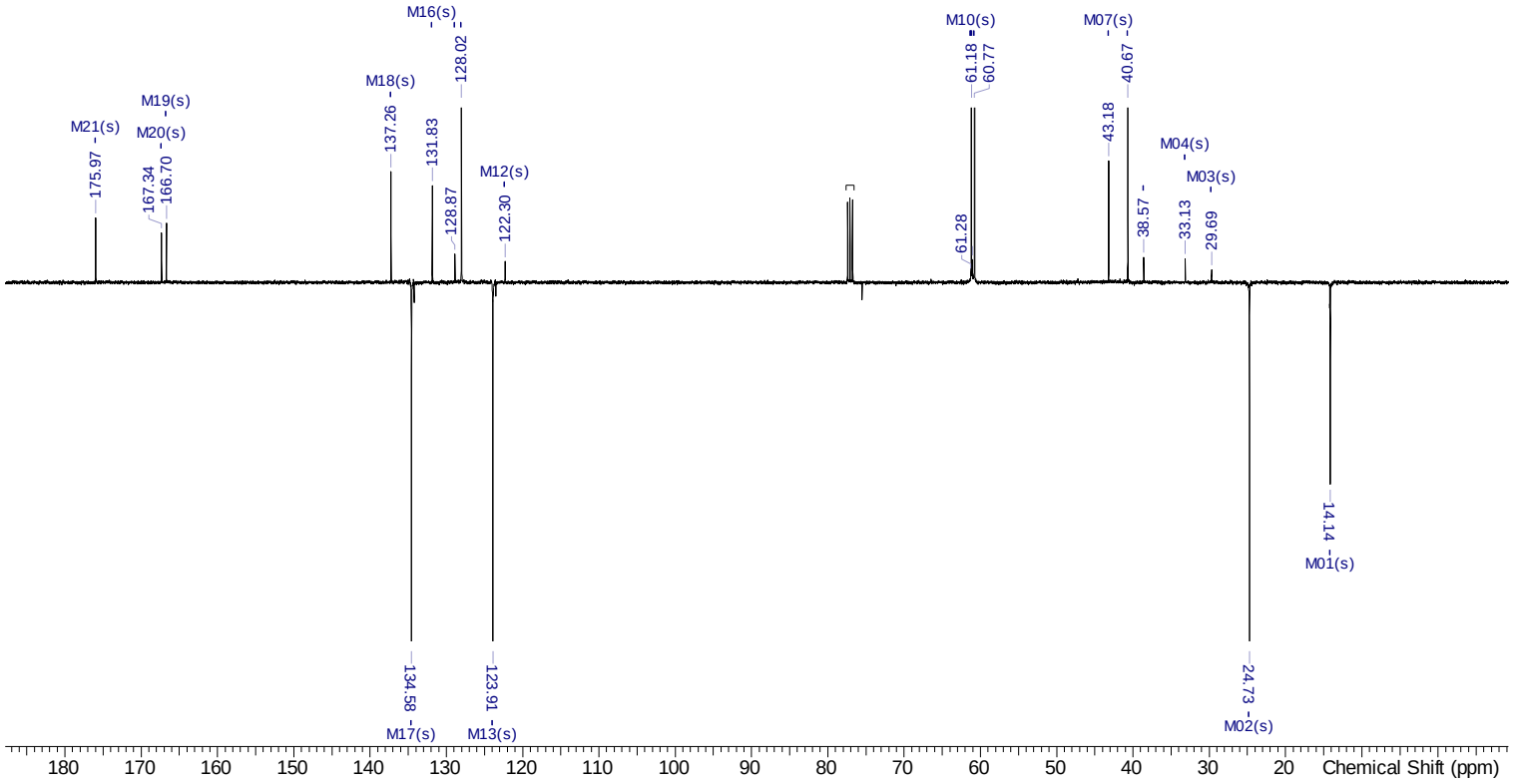

M10(s)
1.33
M07(d)
M06(d)
M02(s)
M03(dd)
M11(d)
M01(m)
M04(ddd)
M05(m)
M08(dt)
M09(ddd)
8.66
8.65
7.54
7.38
7.37
7.37
4.25
4.24
4.22
4.20
4.12
4.11
4.09
4.09
4.08
3.14
3.10
2.92
2.88
2.26
2.24
2.21
2.04
2.03
2.02
2.01
2.01
1.99
1.00
1.04
0.99
1.05
1.04
1.14
1.06
1.07
1.08
3.17
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
Chemical Shift (ppm)

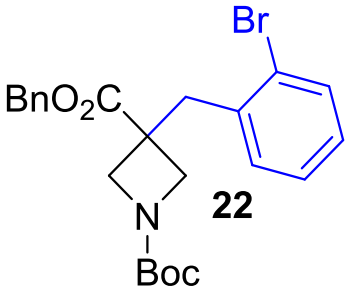

M06(s)
64.92
M05(s)
42.33
M02(s)
33.34
M14(s)
180.30
M11(s)
147.83
43.46
150.10
M13(s)
128.04
M10(s)
122.01
122.04
M07(d)
23.06
M01(s)
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 Chemical Shift (ppm)

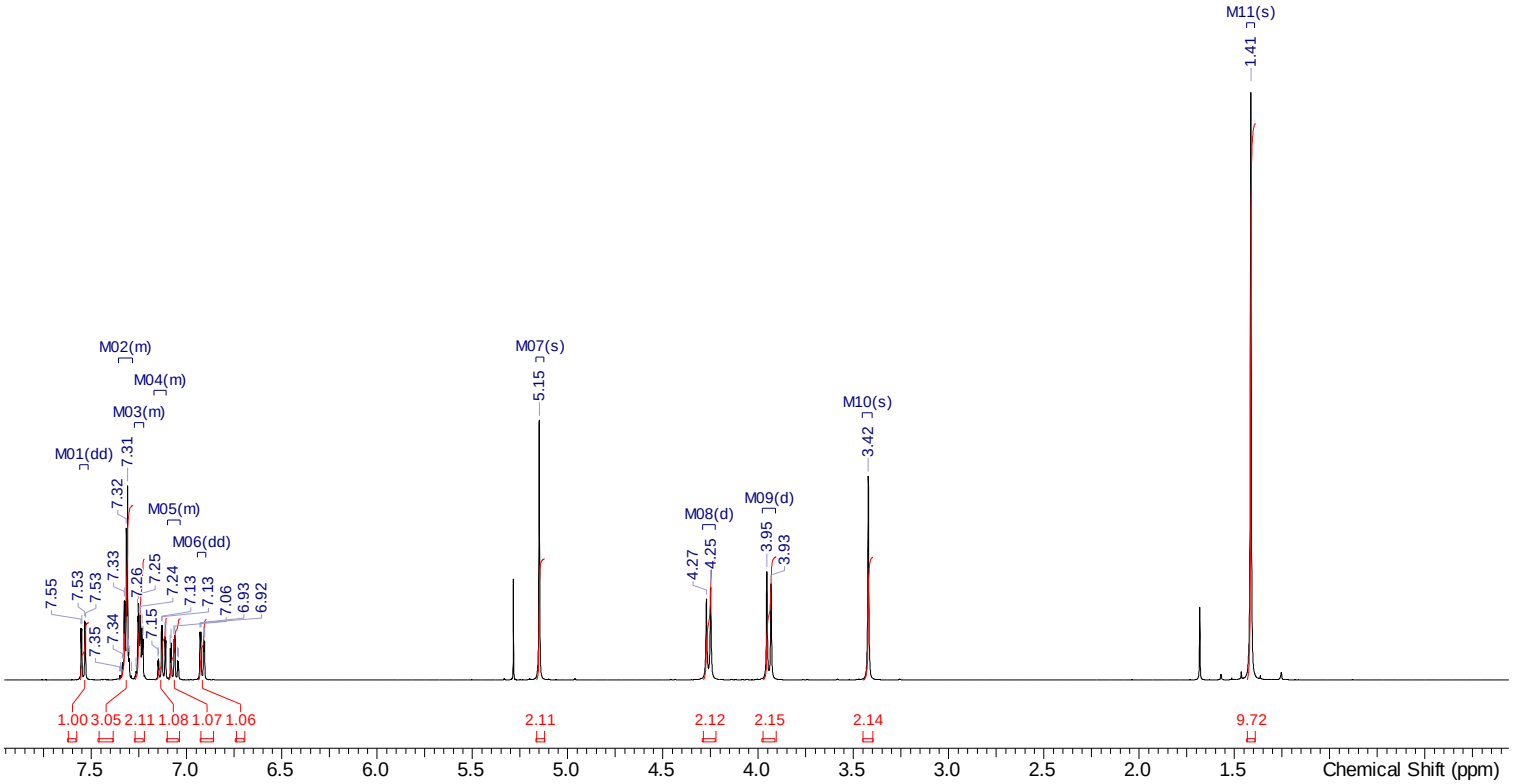

O
N
O
O
O
O
OEt

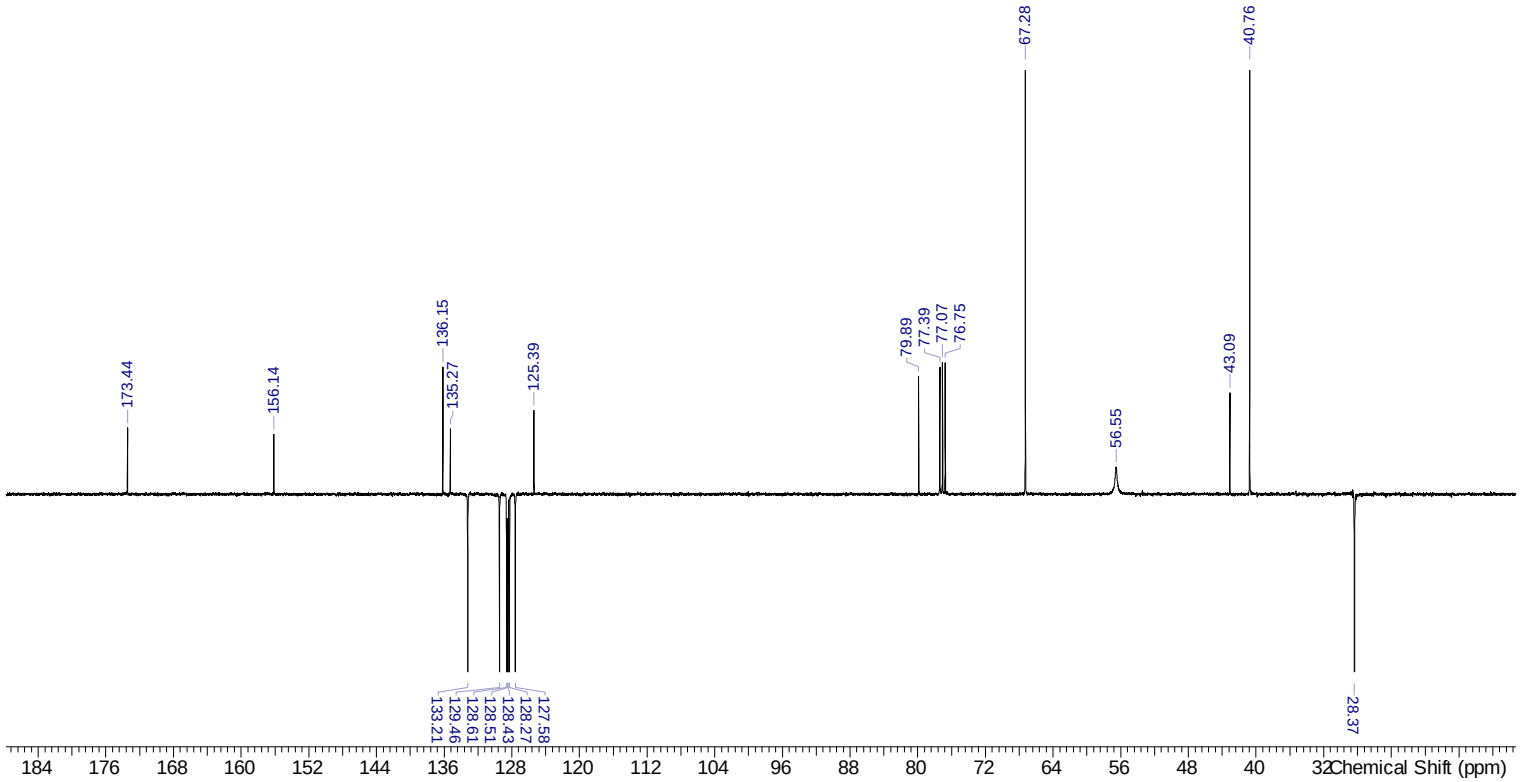
**21**

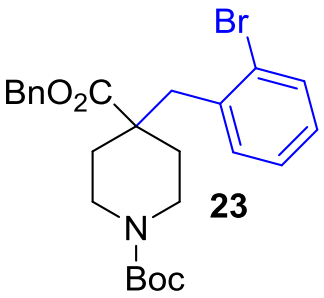

M08(s)
1.16
M05(d)
M04(s)
5.70
1.26
M07(d)
M06(q)
2.62
2.61
4.15
4.13
1.28
M03(d)
M02(m)
M01(m)
6.21
6.20
5.58
5.57
4.16
4.11
6.21
6.19
1.82
1.93
0.93
1.86
0.95
2.04
2.00
3.40
5.85
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
Chemical Shift (ppm)


M16(s)
128.02
M10(s)
61.18
60.77
M07(s)
40.67
M18(s)
137.26
M19(s)
M21(s)
M20(s)
175.97
167.34
166.70
131.83
128.87
M12(s)
122.30
61.28
43.18
M04(s)
M03(s)
38.57
33.13
29.69
14.14
M01(s)
134.58
M17(s)
123.91
M13(s)
24.73
M02(s)
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 Chemical Shift (ppm)

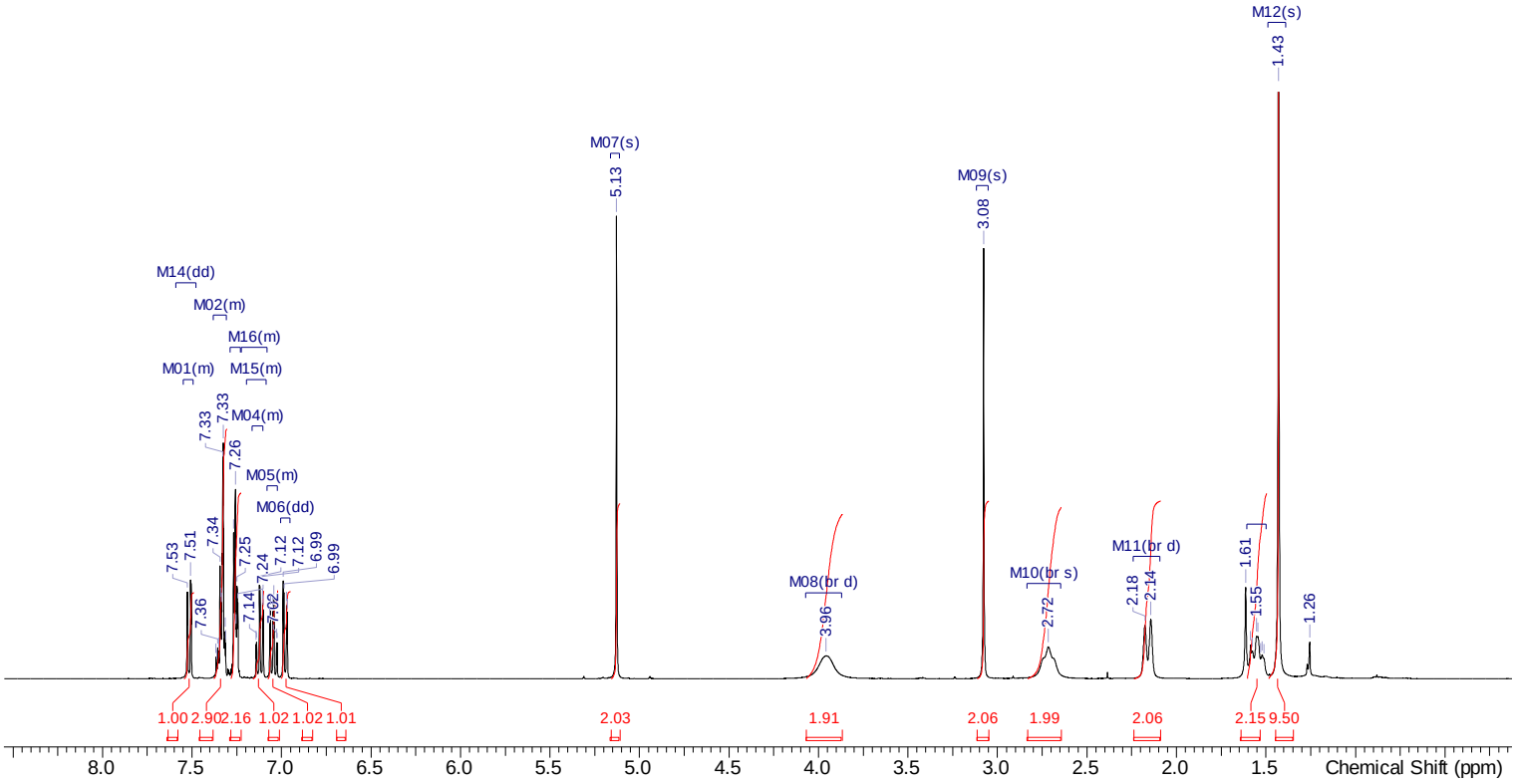

Br
BnO2C
N
Boc
22

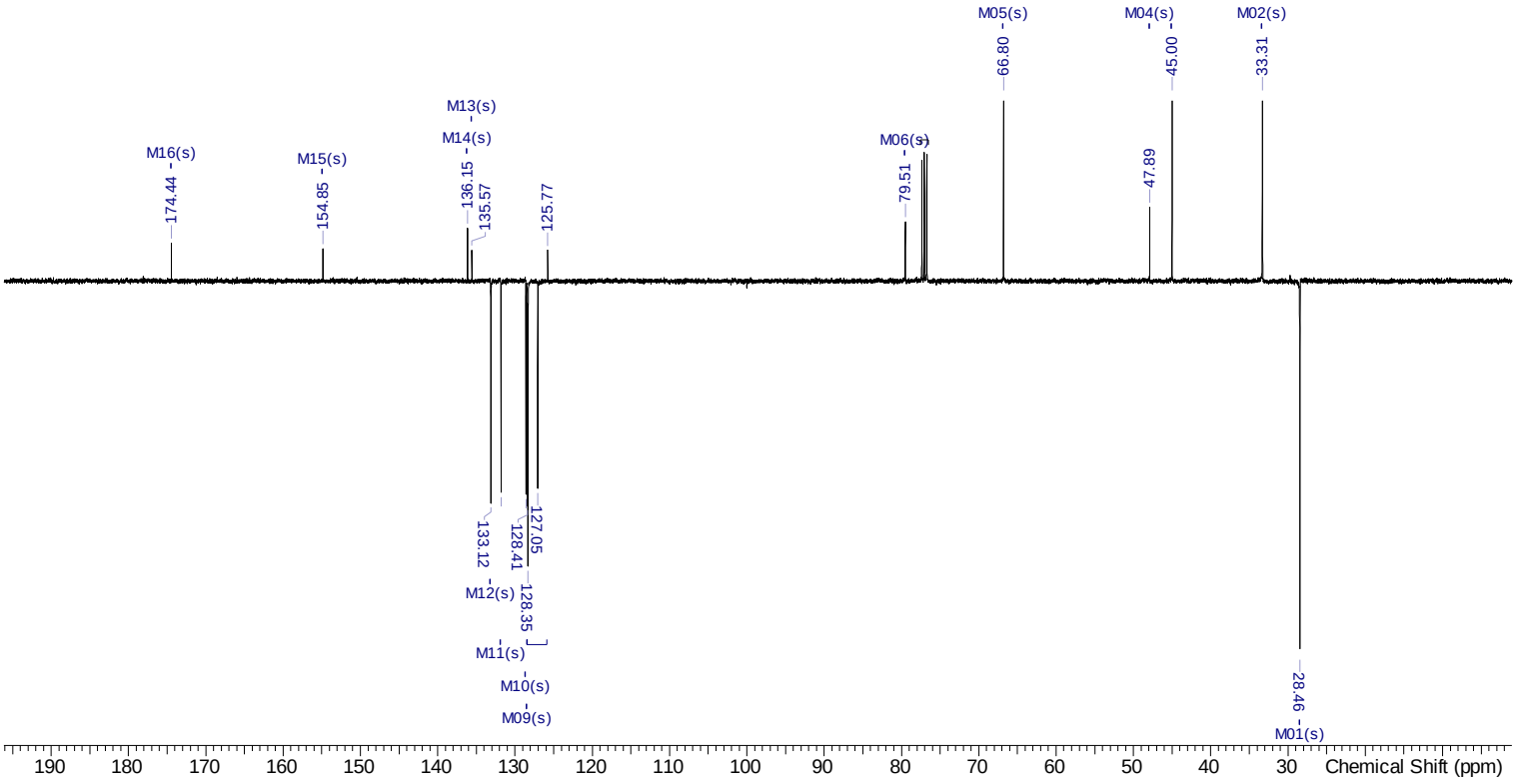

M11(s)
1.41
M02(m)
M04(m)
M03(m)
M01(dd)
7.31
7.32
M05(m)
M06(dd)
7.55
7.53
7.53
7.33
7.35
7.34
7.26
7.25
7.24
7.15
7.13
7.13
7.06
6.93
6.92
M07(s)
5.15
M08(d)
4.27
4.25
M09(d)
3.95
3.93
M10(s)
3.42
1.00 3.05 2.11 1.08 1.07 1.06
2.11
2.12
2.15
2.14
9.72
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5
Chemical Shift (ppm)

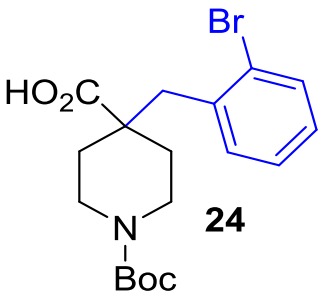

173.44
156.14
136.15
135.27
125.39
79.89
77.39
77.07
76.75
67.28
56.55
43.09
40.76
28.37
133.21
129.46
128.61
128.51
128.43
128.27
127.58
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
Chemical Shift (ppm)


Br
BnO2C
N
Boc

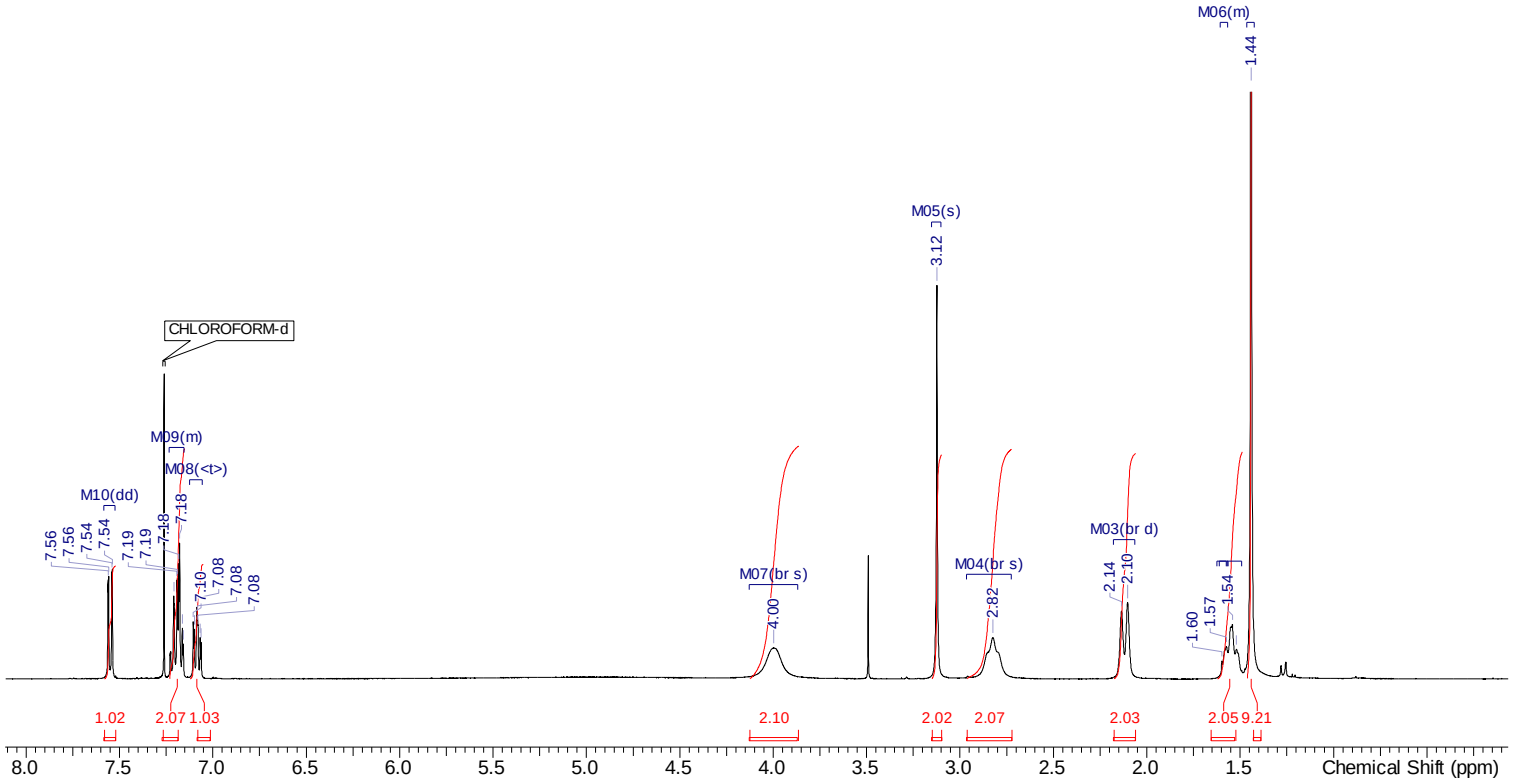
**23**

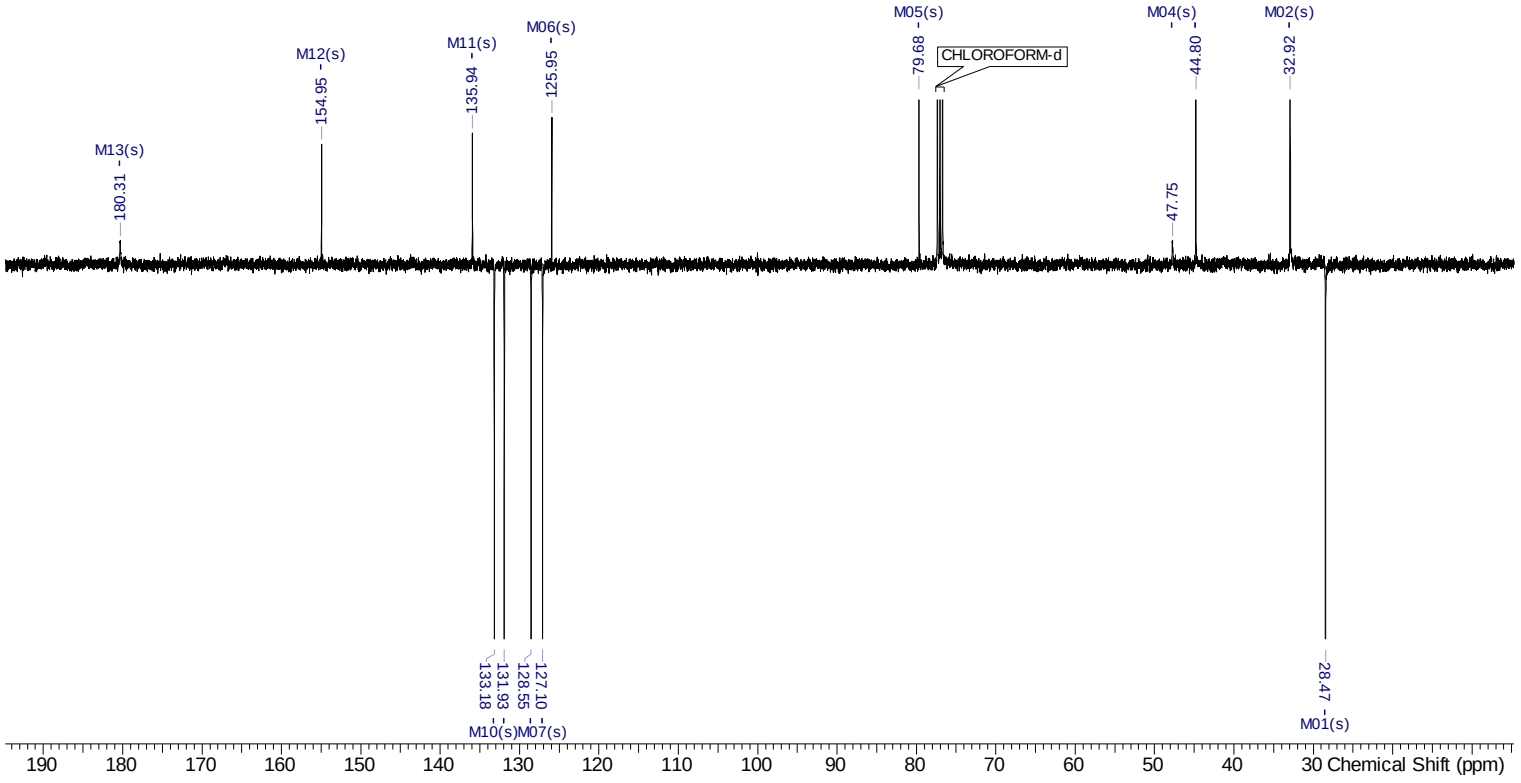

M12(s)
1.43
M07(s)
5.13
M09(s)
3.08
M14(dd)
M02(m)
M16(m)
M01(m)
M15(m)
M04(m)
M05(m)
M06(dd)
M08(br d)
M10(br s)
M11(br d)
7.53
7.51
7.34
7.33
7.33
7.26
7.25
7.24
7.14
7.12
7.12
7.02
6.99
6.99
7.36
3.96
2.72
2.18
2.14
1.61
1.55
1.26
1.00 2.90 2.16 1.02 1.02 1.01
2.03
1.91
2.06
1.99
2.06
2.15 9.50
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5
Chemical Shift (ppm)

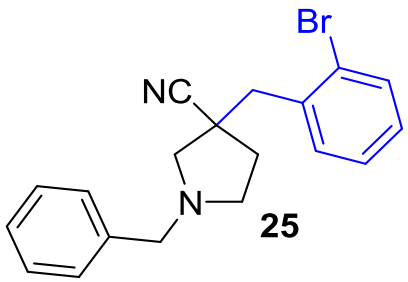

M16(s)
174.44
M15(s)
154.85
M13(s)
M14(s)
136.15
135.57
125.77
M06(s)
79.51
M05(s)
66.80
M04(s)
45.00
47.89
M02(s)
33.31
133.12
M12(s)
128.41
127.05
128.35
M11(s)
M10(s)
M09(s)
28.46
M01(s)
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30
Chemical Shift (ppm)


Br
HO2C
N
Boc

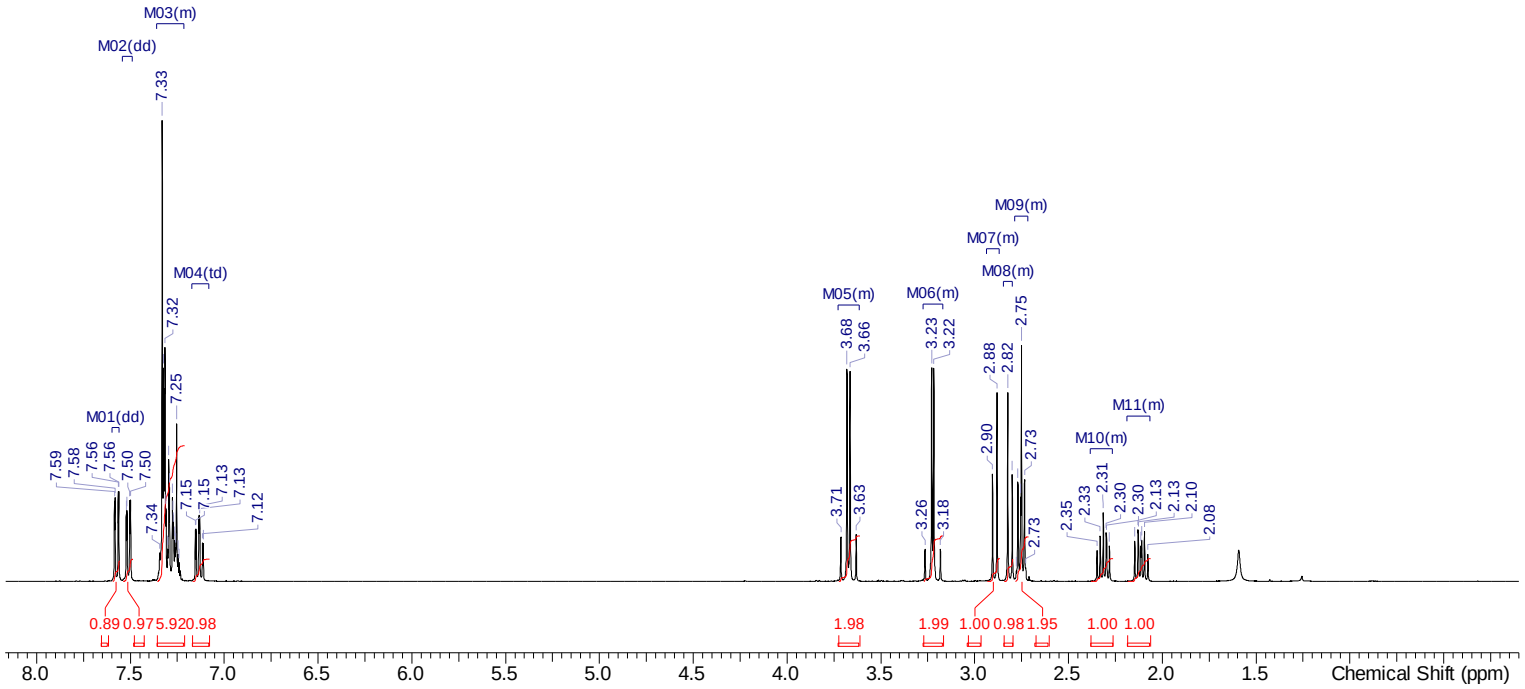
**24**

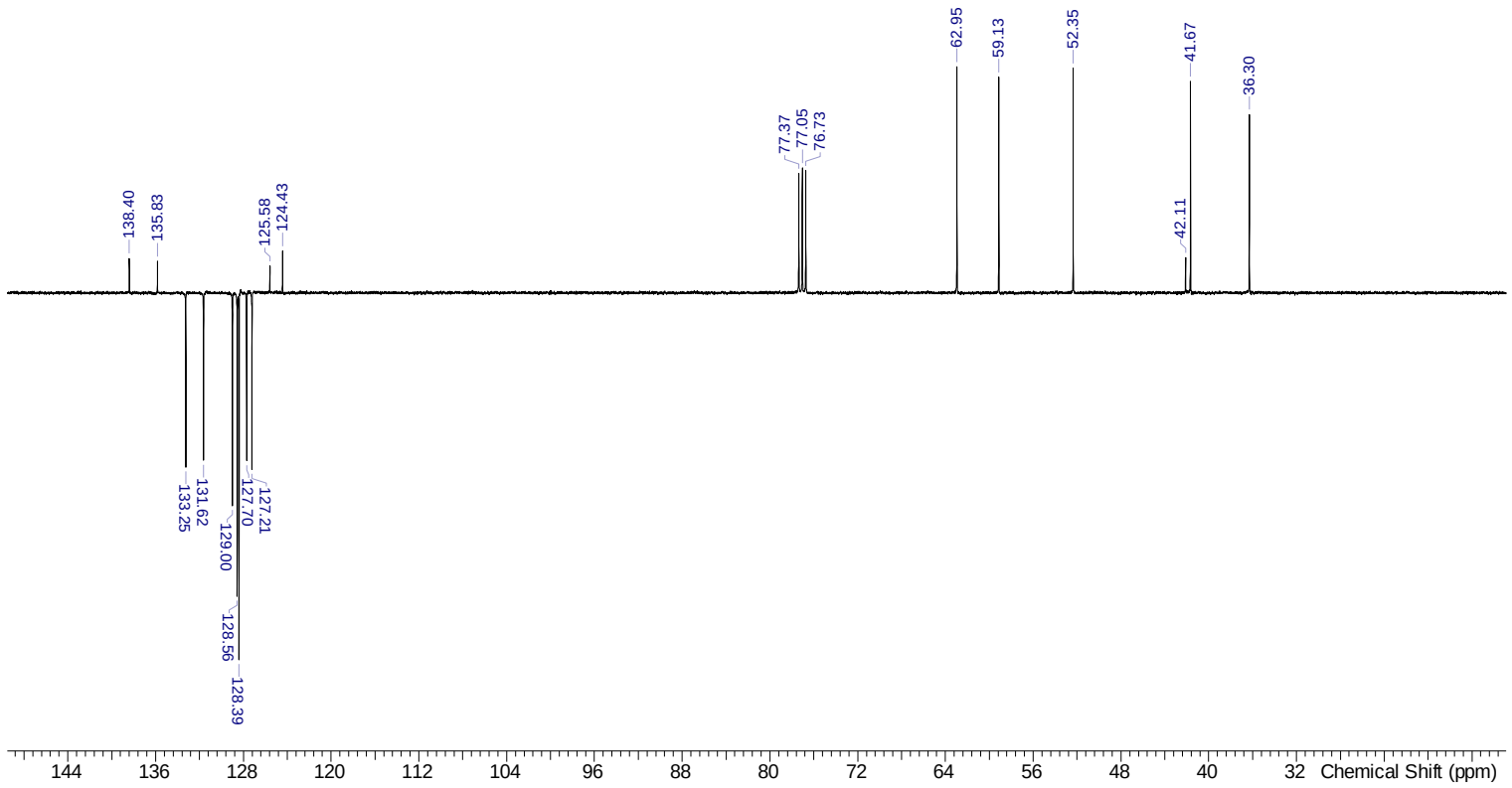

M06(m)
1.44
M05(s)
3.12
CHLOROFORM-d
M09(m)
M08(<t>)
M10(dd)
7.56
7.56
7.54
7.54
7.19
7.19
7.18
7.18
7.10
7.08
7.08
7.08
M07(br s)
4.00
M04(br s)
2.82
M03(br d)
2.14
2.10
1.60
1.57
1.54
1.02
2.07
1.03
2.10
2.02
2.07
2.03
2.05
9.21
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
Chemical Shift (ppm)

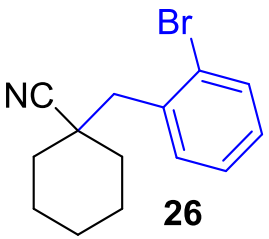

M13(s)
180.31
M12(s)
154.95
M11(s)
135.94
M06(s)
125.95
M05(s)
79.68
CHLOROFORM-d
47.75
M04(s)
44.80
M02(s)
32.92
133.18
131.93
128.55
127.10
M10(s)
M07(s)
28.47
M01(s)
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 Chemical Shift (ppm)


Br
NC
N

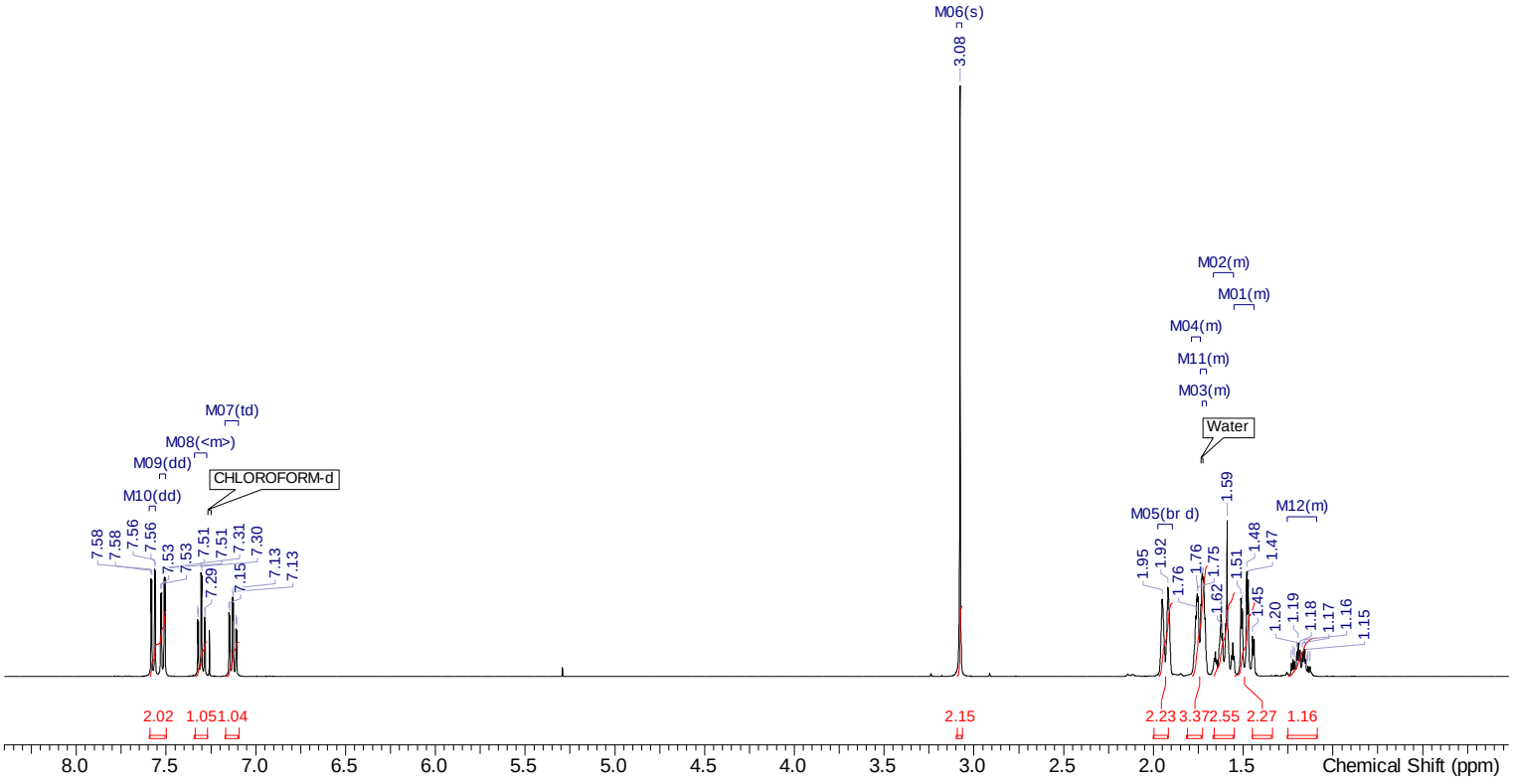
**25**

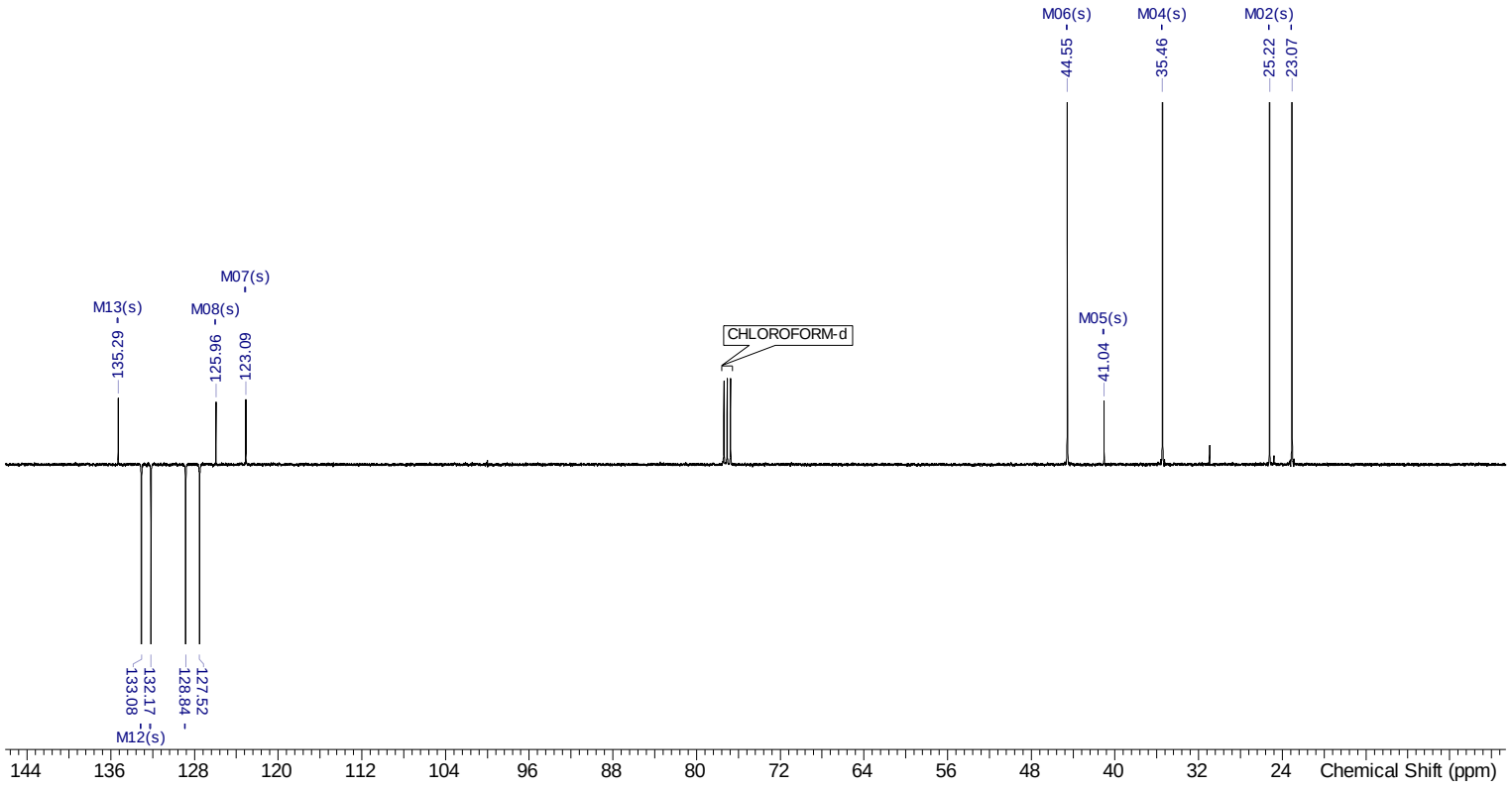

M03(m)
M02(dd)
7.33
M04(td)
7.32
7.25
M01(dd)
7.59
7.58
7.56
7.56
7.50
7.50
7.34
7.15
7.15
7.13
7.13
7.12
M09(m)
M07(m)
M08(m)
M05(m)
M06(m)
3.68
3.66
3.23
3.22
2.88
2.82
2.75
2.90
2.73
3.71
3.63
3.26
3.18
2.73
M11(m)
M10(m)
2.35
2.33
2.31
2.30
2.30
2.13
2.13
2.10
2.08
0.89
0.97
5.92
0.98
1.98
1.99
1.00
0.98
1.95
1.00
1.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
Chemical Shift (ppm)

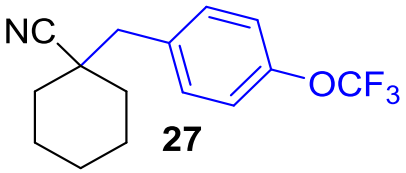

138.40
135.83
125.58
124.43
77.37
77.05
76.73
62.95
59.13
52.35
42.11
41.67
36.30
133.25
131.62
129.00
127.70
127.21
128.56
128.39
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
Chemical Shift (ppm)


Br
NC

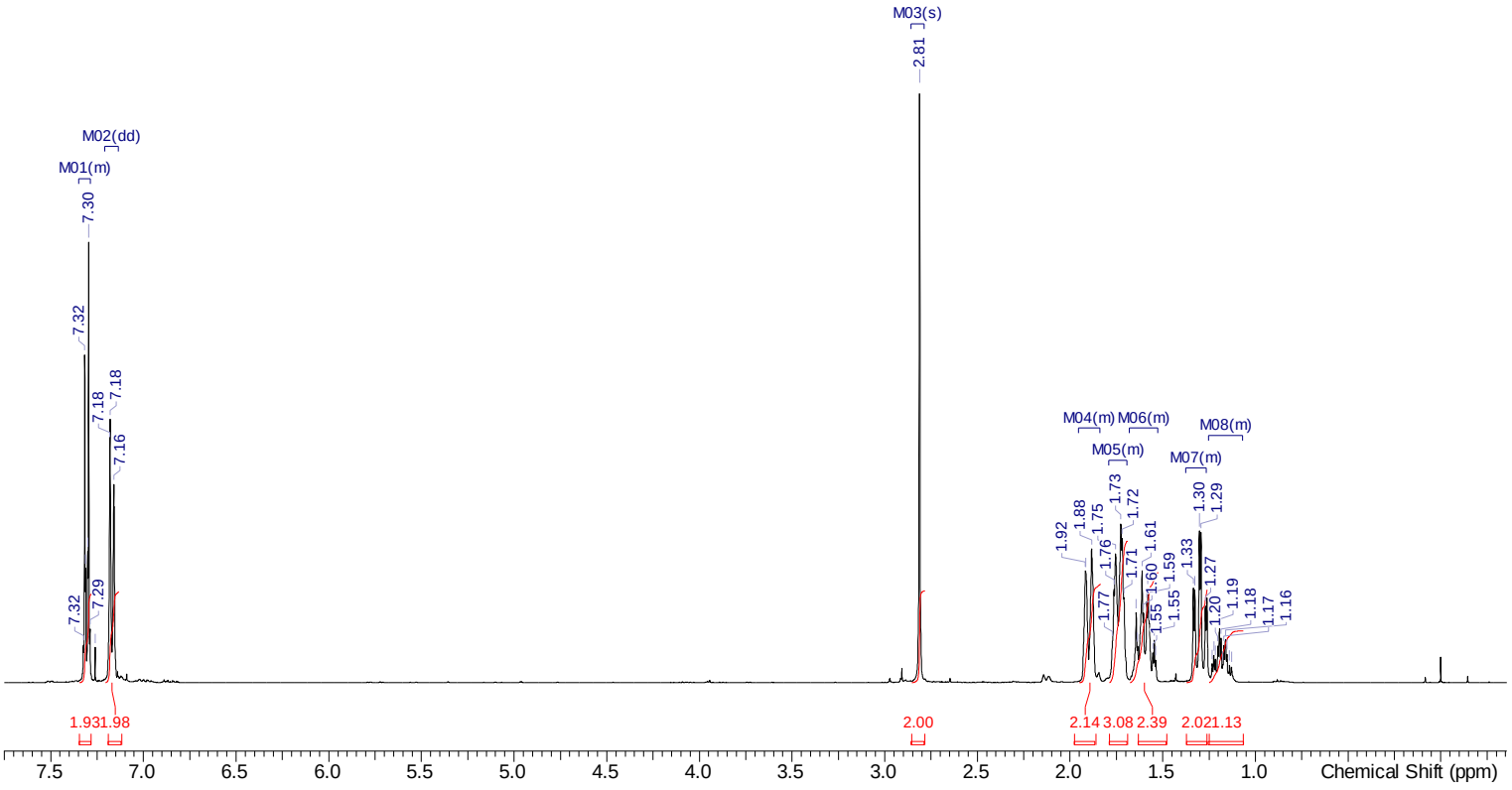
**26**

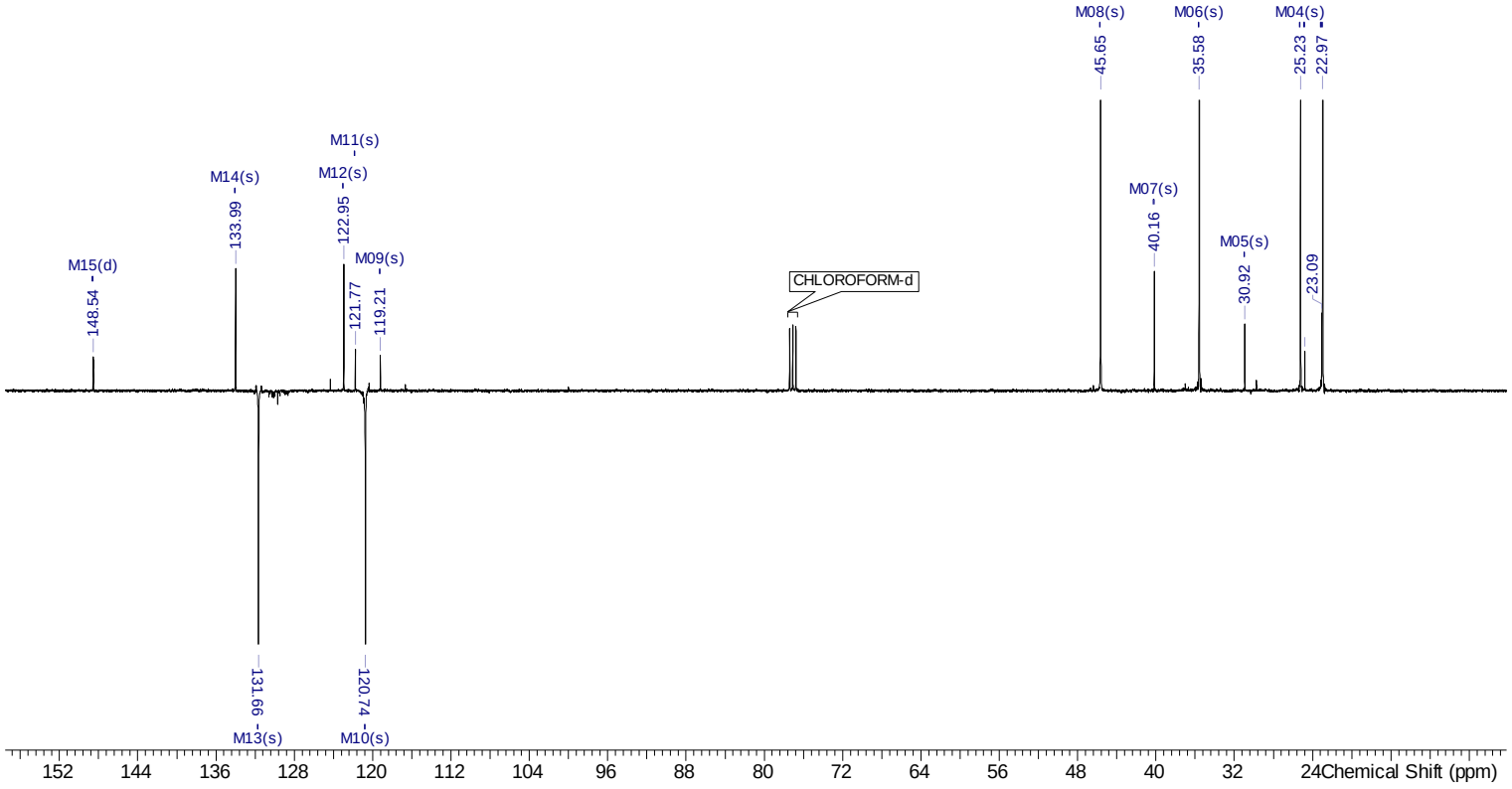

M06(s)
3.08
M02(m)
M01(m)
M04(m)
M11(m)
M03(m)
Water
M07(td)
M08(<m>)
M09(dd)
CHLOROFORM-d
M10(dd)
M05(br d)
M12(m)
7.58
7.58
7.56
7.56
7.53
7.53
7.51
7.51
7.31
7.30
7.29
7.15
7.13
7.13
1.95
1.92
1.76
1.76
1.75
1.62
1.59
1.51
1.48
1.47
1.45
1.20
1.19
1.18
1.17
1.16
1.15
2.02
1.05
1.04
2.15
2.23
3.37
2.55
2.27
1.16
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
Chemical Shift (ppm)

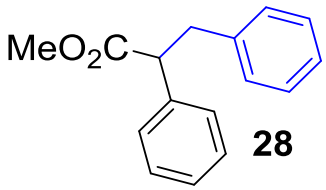

M06(s)
M04(s)
M02(s)
44.55
35.46
25.22
23.07
M07(s)
M13(s)
M08(s)
135.29
125.96
123.09
CHLOROFORM-d
M05(s)
41.04
133.08
132.17
128.84
127.52
M12(s)
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
Chemical Shift (ppm)


NC
OCF3

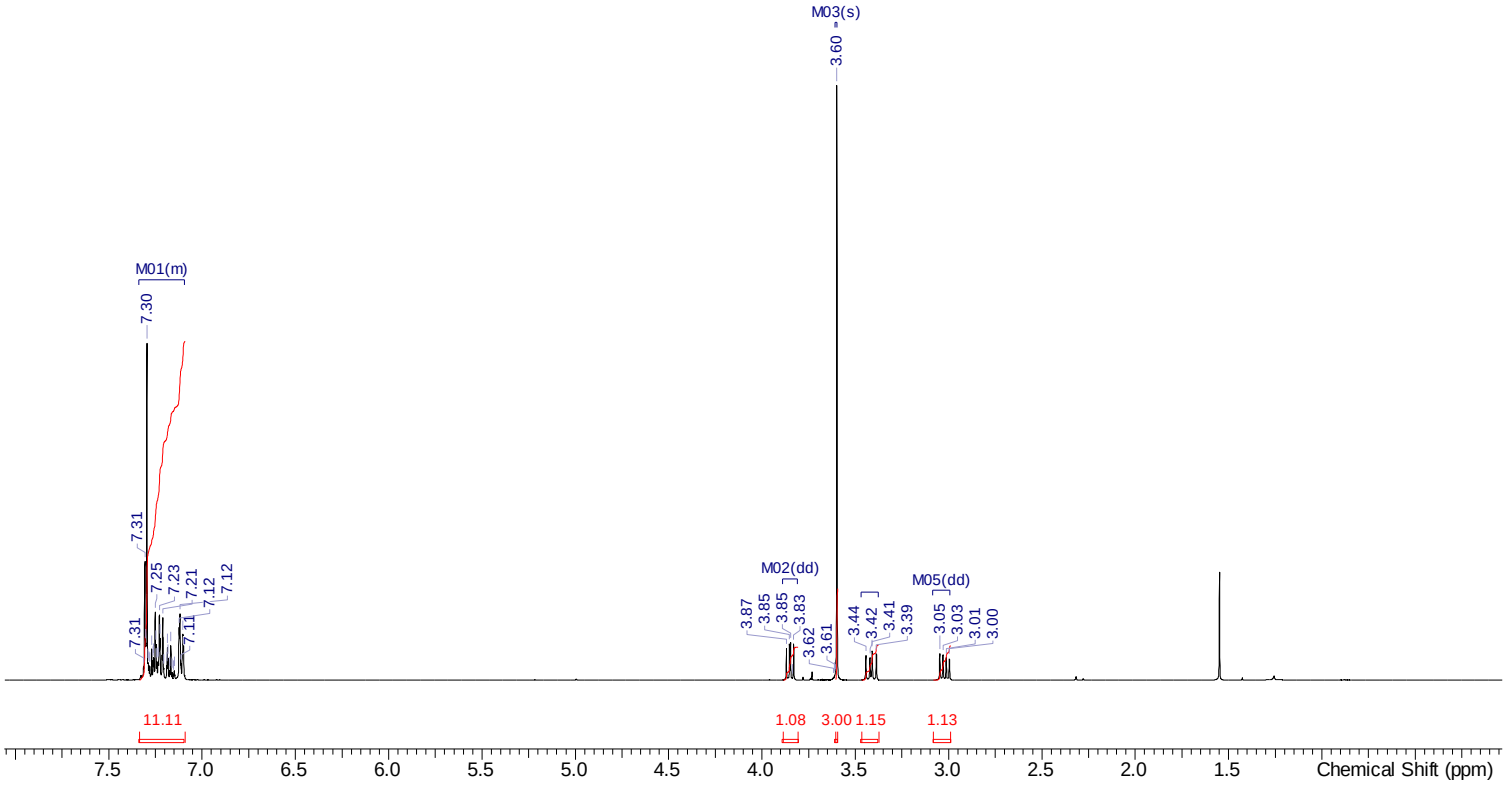
**27**

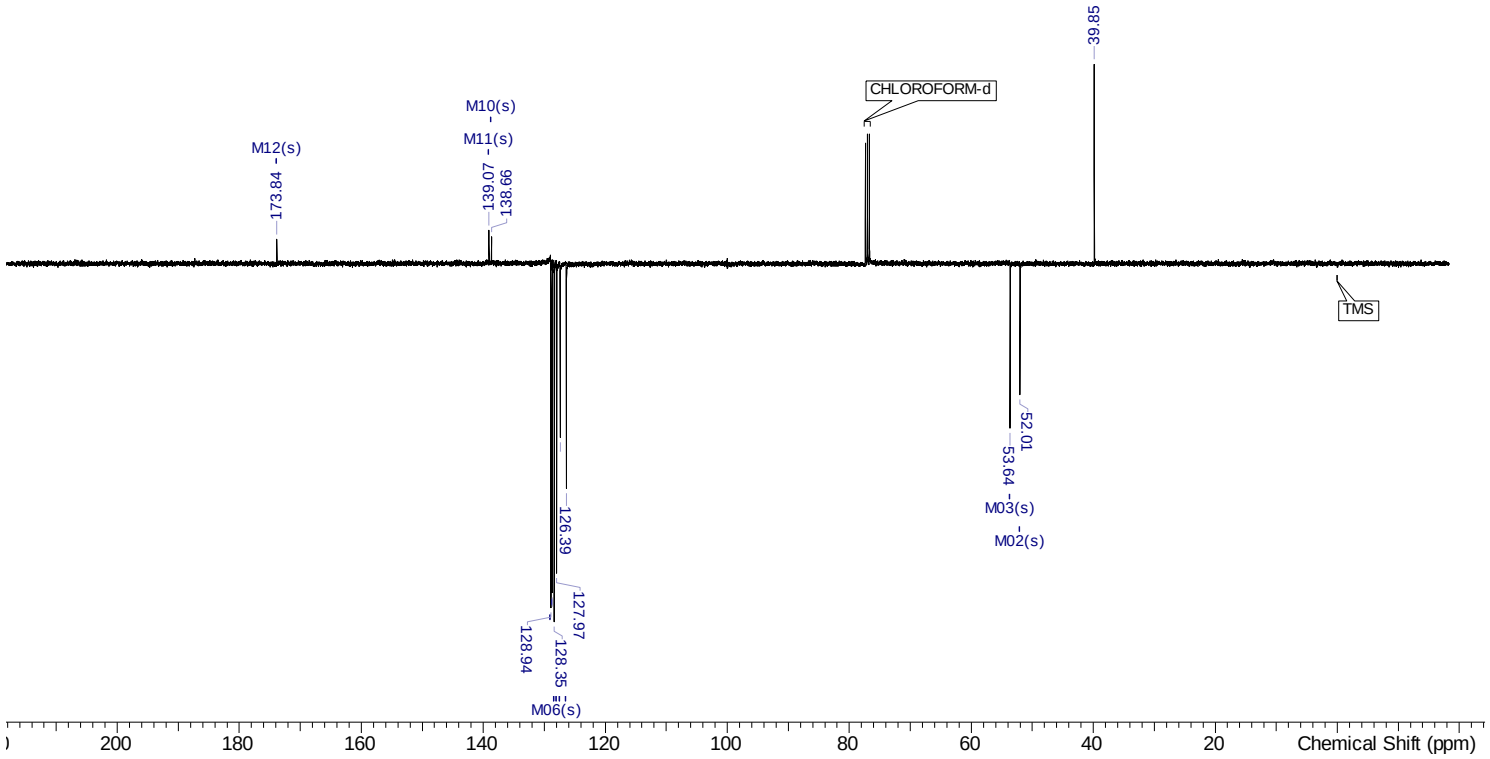

M03(s)
2.81
M02(dd)
M01(m)
7.30
7.32
7.18
7.18
7.16
7.32
7.29
M04(m)
M06(m)
M08(m)
M05(m)
M07(m)
1.92
1.88
1.75
1.73
1.72
1.76
1.71
1.61
1.60
1.59
1.55
1.55
1.33
1.30
1.29
1.27
1.20
1.19
1.18
1.17
1.16
1.93
1.98
2.00
2.14
3.08
2.39
2.02
1.13
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
Chemical Shift (ppm)

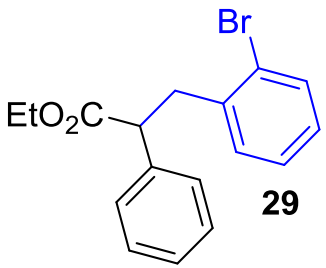

M08(s)
M06(s)
M04(s)
45.65
35.58
25.23
22.97
M11(s)
M12(s)
M14(s)
133.99
122.95
M07(s)
40.16
M05(s)
30.92
M15(d)
148.54
M09(s)
121.77
119.21
CHLOROFORM-d
23.09
131.66
120.74
M13(s)
M10(s)
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
Chemical Shift (ppm)


MeO2C

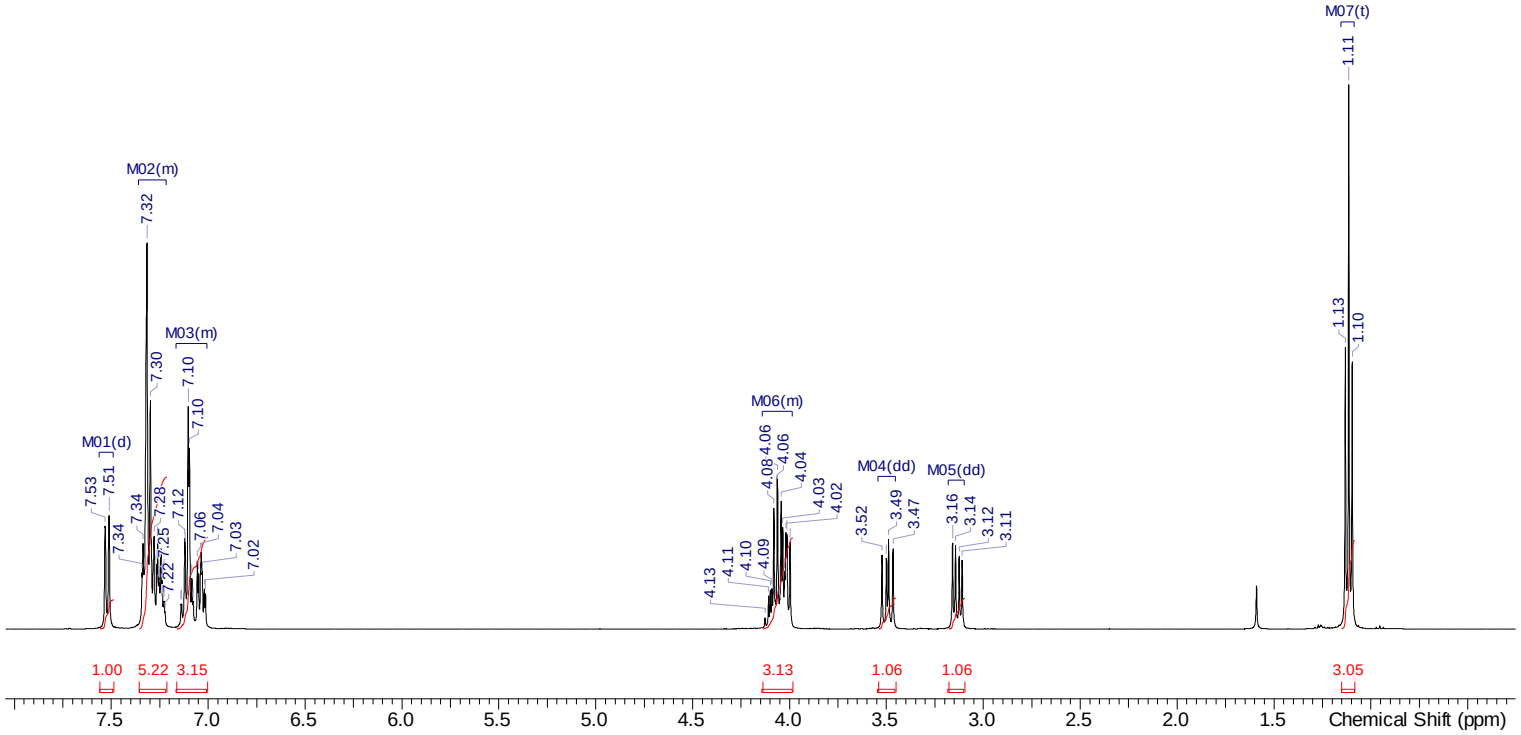
**28**

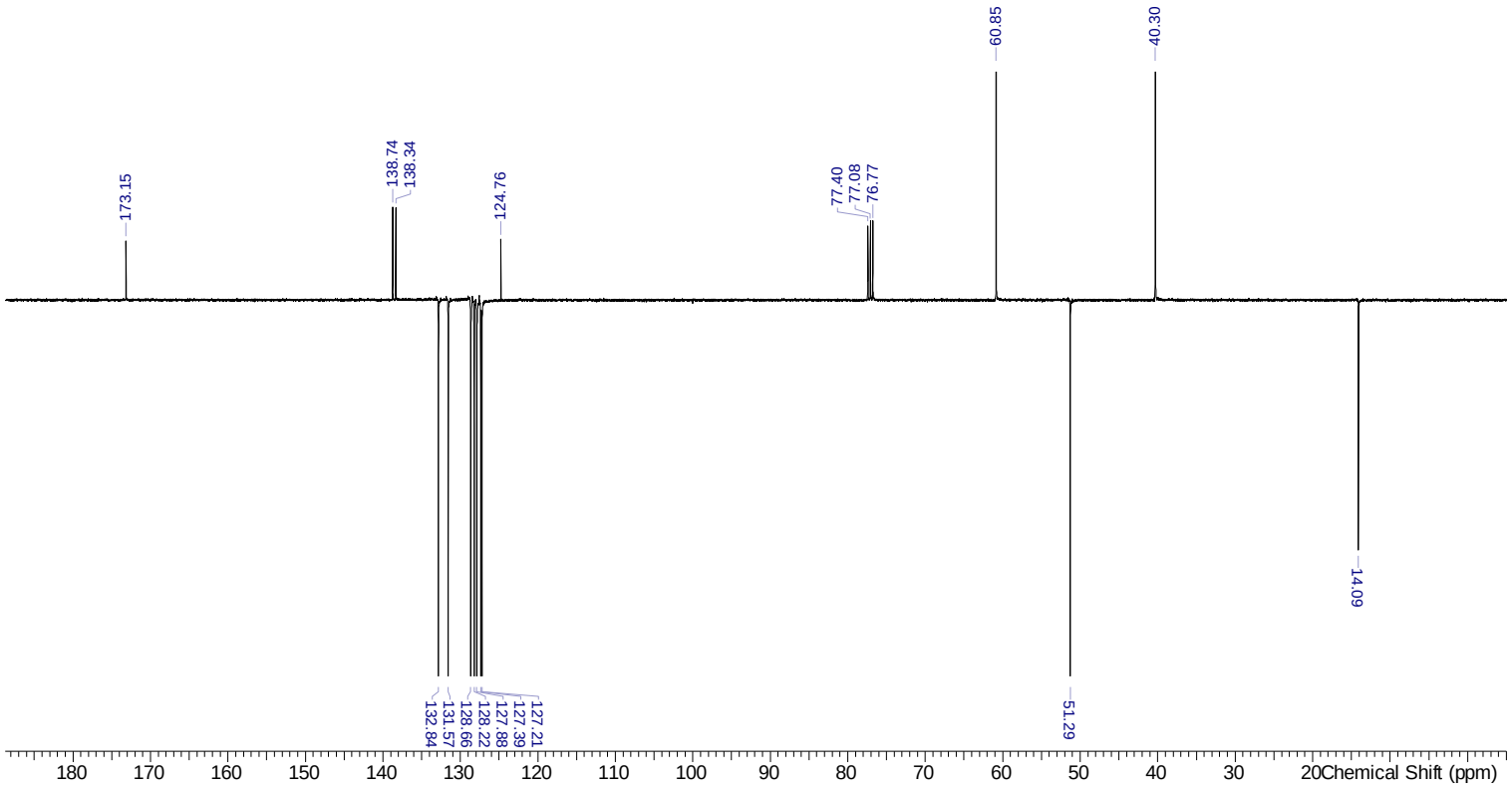

M03(s)
3.60
M01(m)
7.30
7.31
7.25
7.23
7.21
7.12
7.12
7.31
7.11
M02(dd)
3.87
3.85
3.85
3.83
3.62
3.61
3.44
3.42
3.41
3.39
M05(dd)
3.05
3.03
3.01
3.00
11.11
1.08
3.00
1.15
1.13
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
Chemical Shift (ppm)

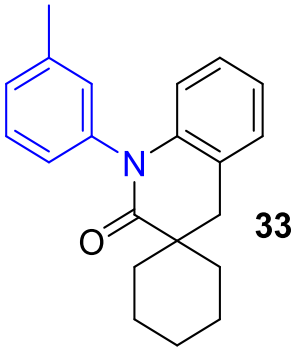

39.55
CHLOROFORM-d
M10(s)
M11(s)
M12(s)
173.84
139.07
138.66
TMS
52.01
53.64
M03(s)
M02(s)
126.39
127.97
128.94
128.35
M06(s)
200
180
160
140
120
100
80
60
40
20
Chemical Shift (ppm)


Br
EtO2C

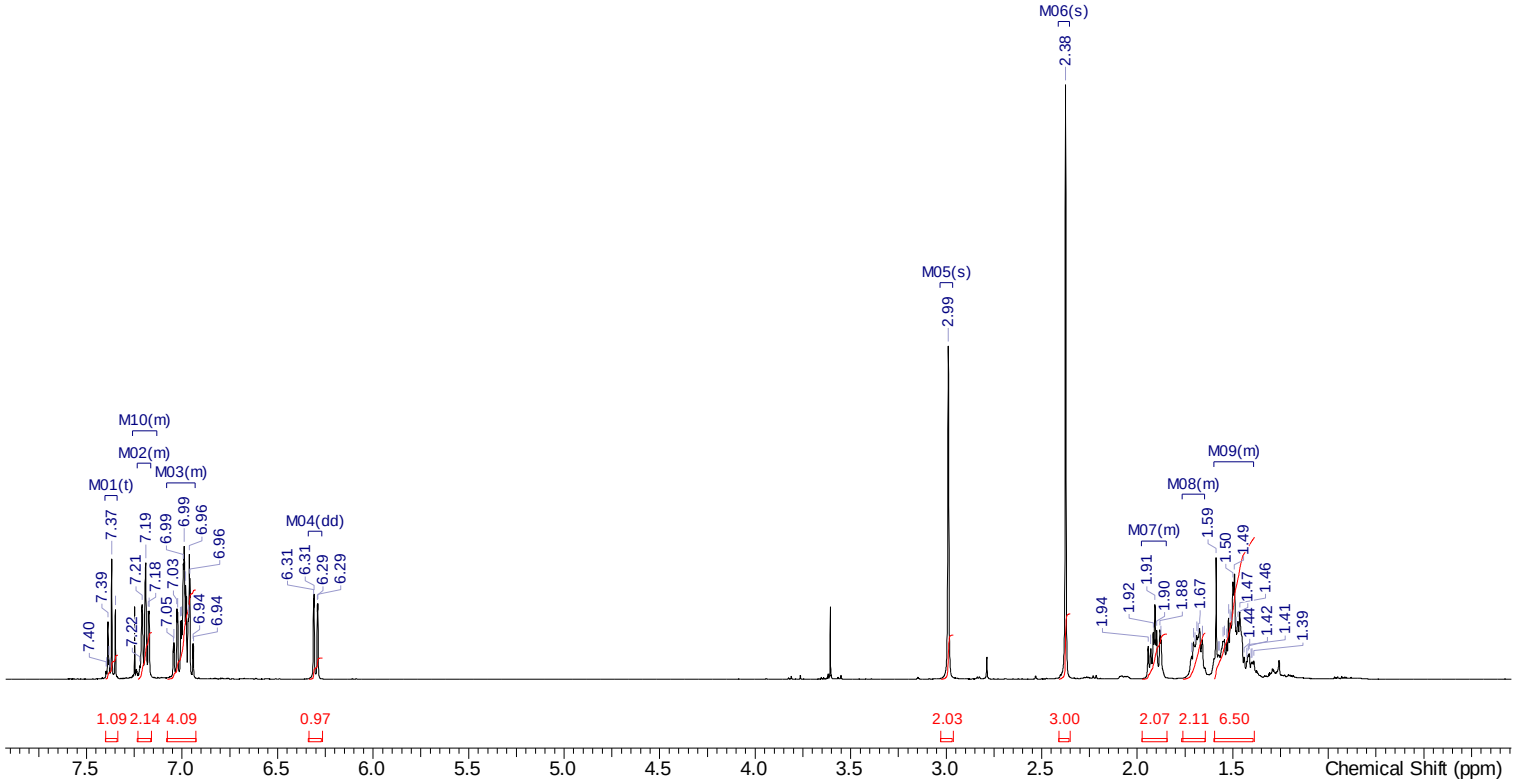
**29**

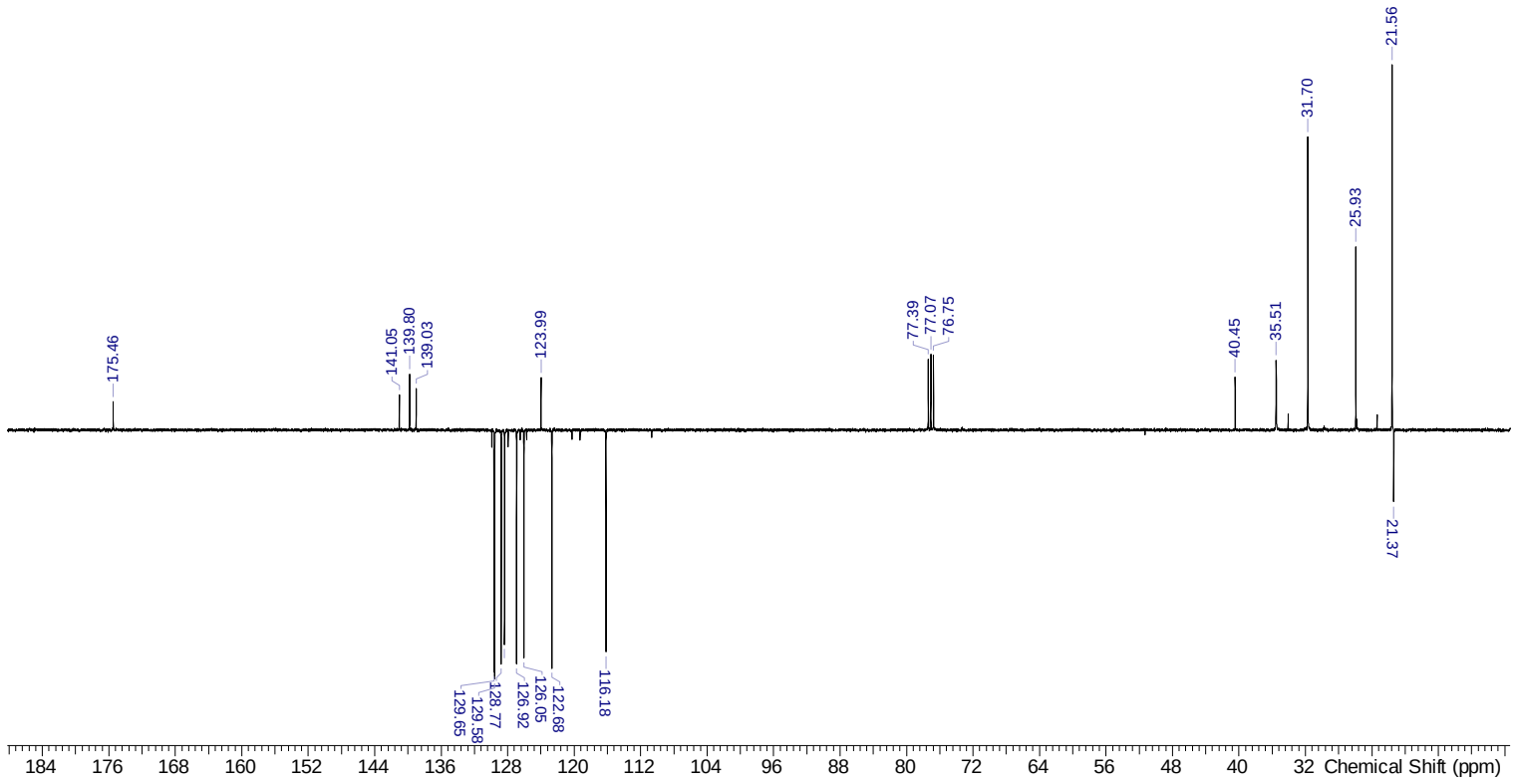

M07(t)
1.11
1.13
1.10
M02(m)
7.32
7.30
M03(m)
7.10
7.10
M01(d)
7.53
7.51
7.34
7.34
7.28
7.25
7.22
7.12
7.06
7.04
7.03
7.02
M06(m)
4.06
4.06
4.08
4.04
4.03
4.02
4.13
4.11
4.10
4.09
M04(dd)
3.52
3.49
3.47
M05(dd)
3.16
3.14
3.12
3.11
1.00
5.22
3.15
3.13
1.06
1.06
3.05
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
Chemical Shift (ppm)

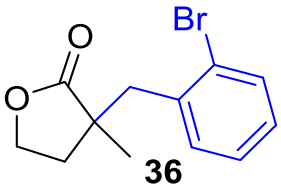

173.15
138.74
138.34
124.76
77.40
77.08
76.77
60.85
40.30
14.09
132.84
131.57
128.66
128.22
127.88
127.39
127.21
51.29
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
Chemical Shift (ppm)


N
O

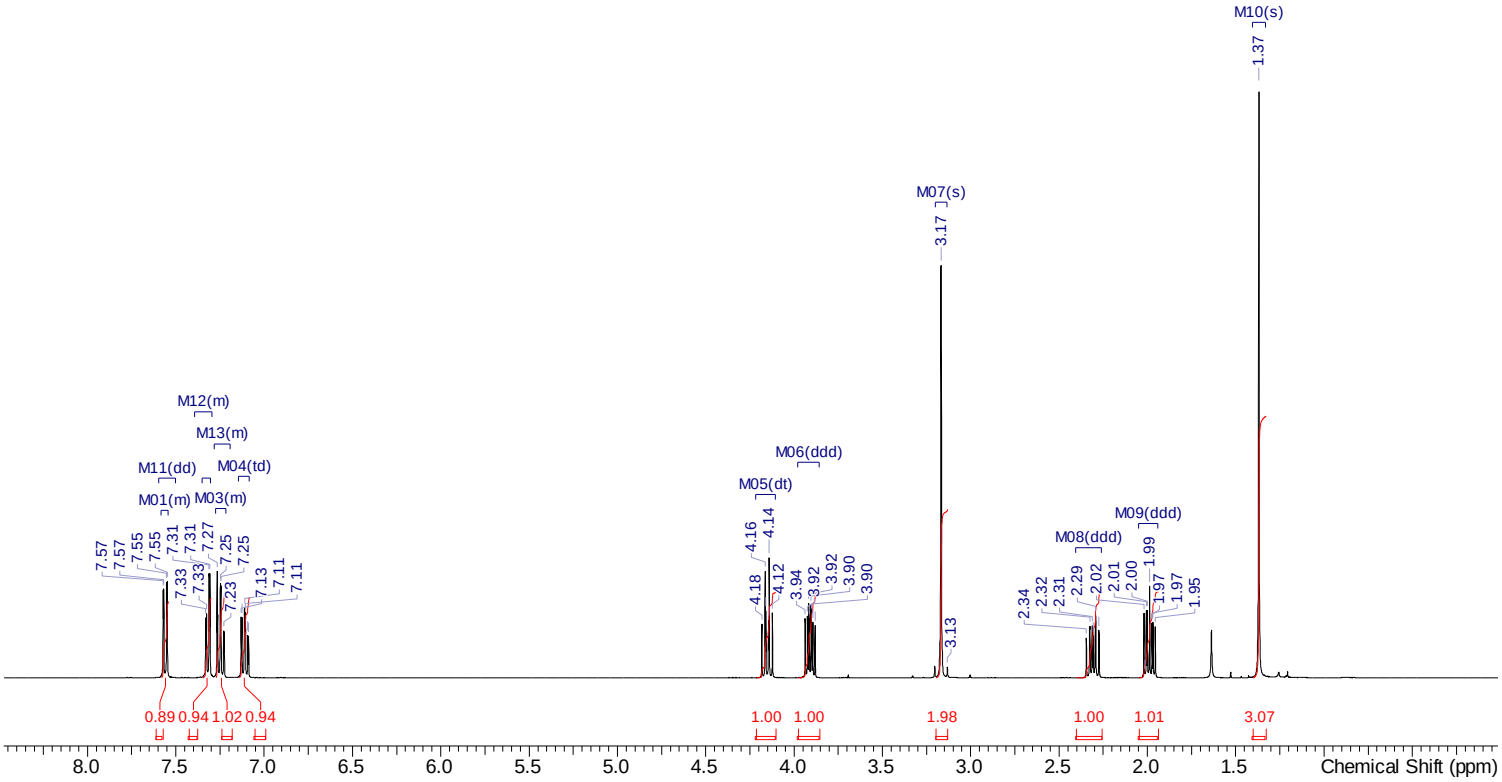
**33**

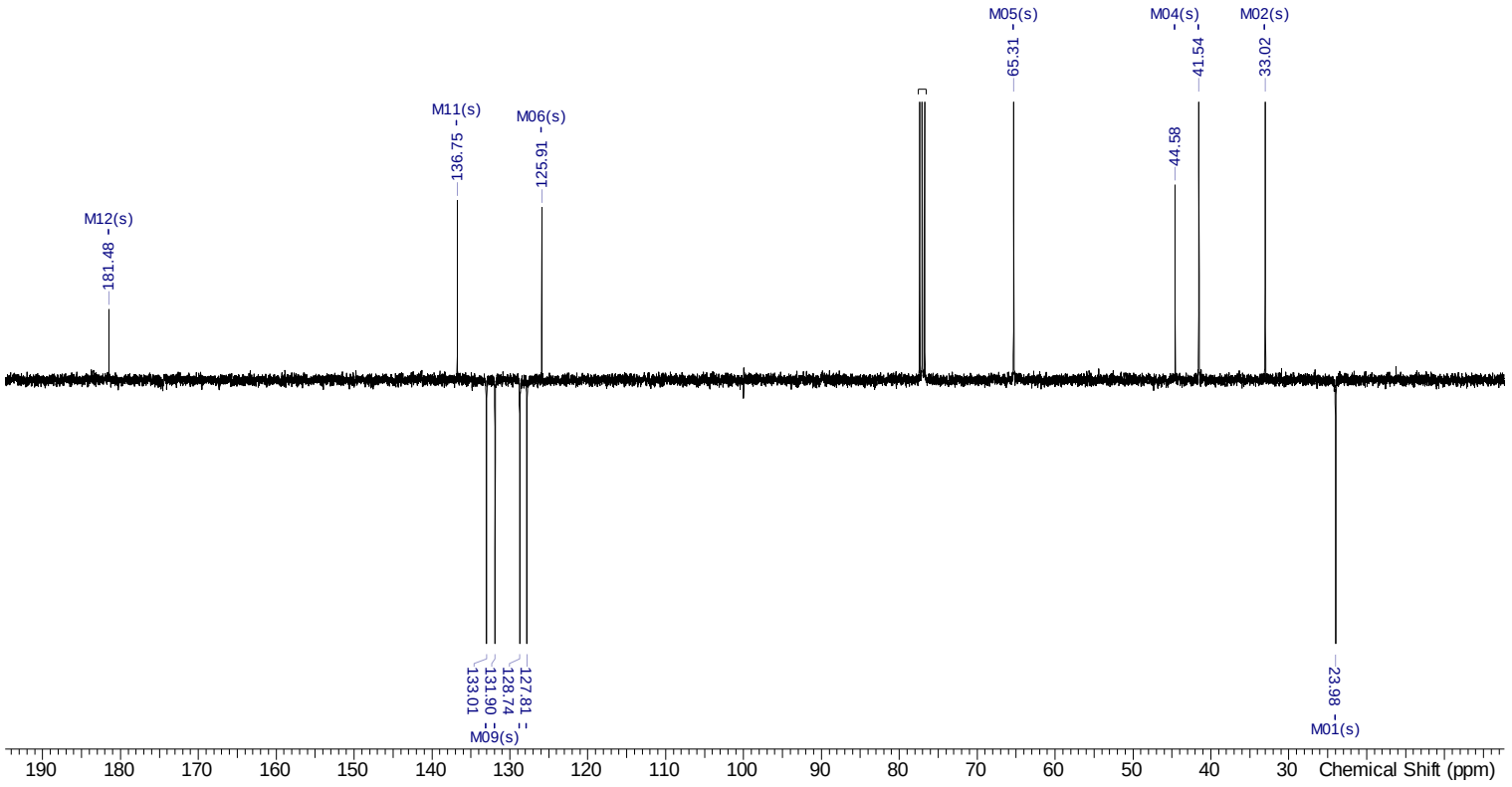

M06(s)
2.38
M05(s)
2.99
M10(m)
M02(m)
M03(m)
M01(t)
M04(dd)
M09(m)
M08(m)
M07(m)
7.40
7.39
7.37
7.22
7.21
7.19
7.18
7.05
7.03
6.99
6.99
6.96
6.96
6.94
6.94
6.31
6.31
6.29
6.29
1.94
1.92
1.91
1.90
1.88
1.67
1.59
1.50
1.49
1.47
1.46
1.44
1.42
1.41
1.39
1.09
2.14
4.09
0.97
2.03
3.00
2.07
2.11
6.50
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
Chemical Shift (ppm)


175.46
141.05
139.80
139.03
123.99
77.39
77.07
76.75
40.45
35.51
31.70
25.93
21.56
21.37
129.65
129.58
128.77
126.92
126.05
122.68
116.18
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
Chemical Shift (ppm)


O
O
Br

**36**


M10(s)
1.37
M07(s)
3.17
M12(m)
M13(m)
M11(dd)
M04(td)
M01(m)
M03(m)
M06(ddd)
M05(dt)
M09(ddd)
M08(ddd)
7.57
7.57
7.55
7.55
7.31
7.31
7.27
7.33
7.33
7.25
7.25
7.23
7.13
7.11
7.11
4.16
4.14
4.18
4.12
3.94
3.92
3.92
3.90
3.90
3.13
2.34
2.32
2.31
2.29
2.02
2.01
2.00
1.99
1.97
1.97
1.95
0.89
0.94
1.02
0.94
1.00
1.00
1.98
1.00
1.01
3.07
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
Chemical Shift (ppm)


M12(s)
181.48
M11(s)
136.75
M06(s)
125.91
M05(s)
65.31
M04(s)
44.58
41.54
M02(s)
33.02
133.01
131.90
128.74
127.81
M09(s)
23.98
M01(s)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
Chemical Shift (ppm)