BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Supporting Information

for

Sustainable tandem acylation/Diels–Alder reaction toward versatile tricyclic epoxyisoindole-7-carboxylic acids in renewable green solvents

Ayhan Yıldırım

Beilstein J. Org. Chem. **2024,** *20,* 1308–1319. doi:10.3762/bjoc.20.114

Tables S1 and S2, Cartesian coordinates of the optimized structures and copies of NMR spectra

Table of contents

Table S1: Composition and physical parameters of the used vegetable oils, oleic acid and wax ester.

Parameters (%)	SSO	OO
Saturated fatty acids	14	16
Monounsaturated fatty acids	29	65
Polyunsaturated fatty acids	57	10
Carbohydrate	0	0
Protein	0	0
Salt	0	0
OA		
Technical grade: 90% Vapour pressure 1 mmHg (176 °C) Refractive index, n20/D: 1.459 Boiling point: 194-195 °C/1.2 mmHg Melting point: 13-14 °C Density: 0.887 g/mL at 25 °C		
LM		
Name: Lauryl myristate Analytical grade Melting point: 38–39 °C Synthesized according to ref. [1]		

Table S2: Literature methods given in literature for the cyclization of *N*-benzyl-1-(furan-2-yl)methanamine **1a** with maleic anhydride to afford **2a**.

Entry	Solvent	Temperature (°C)	Time	Product isolation	Yield (%)	Ref.
1	benzene	–	–	recrystallization (AcOH)	99.5	[2]
2	benzene	rt	48-72 h	filtration and washing with benzene	90	[3]
3	benzene	rt	10 h	recrystallization (hexane-EtOAc)	95	[4]
4	toluene	MW, 60	10 min	filtration and washing with ether	76	[5]
5	benzene	rt	24 h	filtration and washing with benzene-ether	90	[6]
6	toluene	rx	5 h	filtration and washing with ether	86	[7]
7	THF or toluene	rx-rt	24 h	filtration and washing with ether	-	[8]
8	diethyl ether	rt	24 h	filtration and washing with ether	-	[9]
9	toluene	rt	16 h	recrystallization (acetone)	55	[10]
10	chloroform	rt	48 h	filtration and	75	[11]

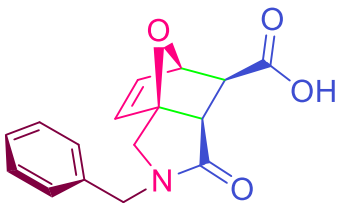
				washing with MeOH or acetone		
11	chloroform	rt-rx	7 h	filtration and washing with acetone	80	[12]
12	SSO	50	30 min	filtration and washing with hexane-ether	96	this work
13	OO	50	30 min	filtration and washing with hexane-ether	96	this work
14	OA	50	30 min	filtration and washing with hexane-ether	99	this work
15	LM	50	30 min	filtration and washing with hexane-ether	99	this work

References for Tables S1 and S2

1. Yıldırım, A.; Mudaber, S.; Öztürk, S. *Eur. J. Lipid Sci. Technol.* 2019, *121,* 1800303. doi: 10.1002/ejlt.201800303
2. Takano S.; Oshima Y.; Ito F.; Ogasawara K. *Yakugaku Zasshi* 1980, *100,* 1194–1202. doi: 10.1248/yakushi1947.100.12_1194
3. Varlamov, A. V.; Boltukhina, E. V.; Zubkov, F. I.; Sidorenko, N. V.; Chernyshev, A. I.; Grudinin, D. G. *Chem. Heterocycl. Compd.* **2004**, *40,* 22–28. doi: 10.1023/B:COHC.0000023763.75894.63
4. Sarang, P. S.; Yadava, A. A.; Patila, P. S.; Krishna, U. M.; Trivedi, G. K.; Salunkhe, M. M. *Synthesis* **2007**, 7, 1091–1095. doi: 10.1055/s-2007-965950
5. Gordon, C. P.; Byrne, N.; McCluskey, A. *Green Chem.* **2010**, *12,* 1000–1006. doi: 10.1039/B924835H
6. Zubkov, F. I.; Airiyan, I. K.; Ershova, J. D.; Galeev, T. R.; Zaytsev, V. P.; Nikitina, E. V.; Varlamov, A. V. *RSC Adv.* **2012,** *2,* 4103–4109. doi: 10.1039/C2RA20295F
7. De Cesco, S.; Deslandes, S.; Therrien, E.; Levan, D.; Cueto, M.; Schmidt, R.; Cantin, L. D.; Mittermaier, A.; Jeanneret, L. J.; Moitessier, N. *J. Med. Chem.* **2012**, *55,* 6306–6315. doi: 10.1021/jm3002839
8. Papeo, G.; Posteri, H.; Borghi, D.; Busel, A. A.; Caprera, F.; Casale, E.; Ciomei, M.; Cirla, A.; Corti, E.; D'Anello, M.; Fasolini, M.; Forte, B.; Galvani, A.; Isacchi, A.; Khvat, A.; Krasavin, M. Y.; Lupi, R.; Orsini, P.; Perego, R.; Pesenti, E.; Pezzetta, D.; Rainoldi, S.; Sirtori, F. R.; Scolaro, .; Sola, F.; Zuccotto, F.; Felder, E. R.; Donati, D.; Montagnoli, A. *J. Med. Chem.* **2015**, *58,* 6875–6898. doi: 10.1021/acs.jmedchem.5b00680

9. Hizartzidis, L.; Gilbert, J.; Gordon, C. P.; Sakoff, J. A.; McCluskey, A. *ChemMedChem* **2019**, *14,* 1152–1161. doi: 10.1002/cmdc.201900180
10. Blanpain, A.; Clark, J. H.; Farmer, T. J.; Guo, Y.; Ingram, I. D. V.; Kendrick, J. E.; Lawrenson, S. B.; North, M.; Rodgers, G.; Whitwood, A. C. *ChemSusChem* **2019,** *12,* 2393–2401. doi: 10.1002/cssc.201900748
11. Naguib, M.; Rashed, A.; Keddie, D. J. *J. Mater. Sci.* **2021**, *56,* 8900–8909. doi: 10.1007/s10853-021-05853-x
12. Naguib, M.; Yassin, M. A. *ACS Appl. Polym. Mater.* **2022**, *4,* 2181–2188. doi: 10.1021/acsapm.2c00158

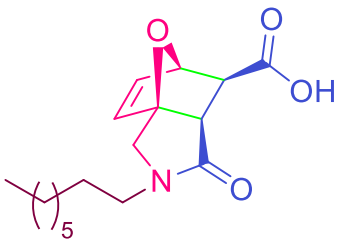
2-Benzyl-1-oxo-1,2,3,6,7,7a-hexahydro-3a,6-epoxyisoindole-7-carboxylic acid ***(2a)***



Beige crystalline solid, mp 171–172 °C (EtOAc/MeOH), (The analytical data of compound **2a** agree with the literature [6], lit. 170.3–171.8 °C); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33 (*t*, *J* = 7.6 Hz, 2H, Ar), 7.28 (*d*, *J* = 7.4 Hz, 1H, Ar), 7.24 (*t*, *J* = 7.4 Hz, 2H, Ar), 6.42-6.39 (*m*, 2H, H_f, H_g), 5.25 (*d*, *J* = 1.6 Hz, 1H, H_c), 4.63 (*d*, *J* = 15.1 Hz, 1H, H_h), 4.42 (*d*, *J* = 15.1 Hz, 1H, H_i), 3.83 (*d*, *J* = 12 Hz, 1H, H_d), 3.65 (*d*, *J* = 12 Hz, 1H, H_e), 2.96 (*d*, *J* = 9.1 Hz, 1H, H_a), 2.84 (*d*, *J* = 9.1 Hz, 1H, H_b); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.10, 172.51, 137.22, 135.20, 134.83, 128.92, 127.98, 127.87, 88.79, 82.36, 50.72, 48.53, 47.03, 45.86; Anal calc for $C_{16}H_{15}NO_4$ (285.30): C 67.36, H 5.30, N 4.91. Found: C 67.30, H 5.26, N 4.86.

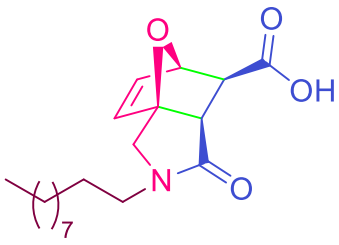
[6] Zubkov, F. I.; Airiyan, I. K.; Ershova, J. D.; Galeev, T. R.; Zaytsev, V. P.; Nikitina, E. V.; Varlamov, A. V. *RSC Adv.* **2012,** *2,* 4103–4109. doi: 10.1039/C2RA20295F

2-Octyl-1-oxo-1,2,3,6,7,7a-hexahydro-3a,6-epoxyisoindole-7-carboxylic acid ***(2b)***



Beige crystalline solid, mp 119–120 °C (EtOAc/MeOH); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.47 (*s*, 2H, H_f, H_g), 5.28 (*s*, 1H, H_c), 3.98 (*d*, *J* = 11.9 Hz, 1H, H_d), 3.73 (*d*, *J* = 11.9 Hz, 1H, H_e), 3.44-3.40 (*m*, 1H, H_h), 3.24-3.19 (*m*, 1H, H_i), 2.89 (*d*, *J* = 9.1 Hz, 1H, H_a), 2.82 (*d*, *J* = 9.1 Hz, 1H, H_b), 1.52 (*quin*, *J* = 7.6 Hz, 2H, -$NCH_2C\underline{H}_2CH_2$-), 1.27-1.23 (*m*, 10H, $5CH_2$), 0.85 (*t*, *J* = 7.2 Hz, 3H, -CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.88, 172.52, 137.30, 134.77, 88.94, 82.49, 50.51, 49.00, 46.05, 43.25, 31.73, 29.14, 29.10, 27.02, 26.62, 22.58, 14.04; Anal calc for $C_{17}H_{25}NO_4$ (307.39): C 66.43, H 8.20, N 4.56. Found: C 66.38, H 8.28, N 4.47.

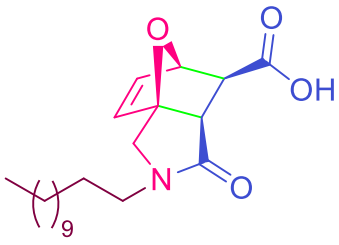
2-Decyl-1-oxo-1,2,3,6,7,7a-hexahydro-3a,6-epoxyisoindole-7-carboxylic acid ***(2c)***



Beige crystalline solid, mp 103–104 °C (EtOAc/MeOH); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.47 (*s*, 2H, H_f, H_g), 5.29 (*s*, 1H, H_c), 3.98 (*d*, *J* = 11.9 Hz, 1H, H_d), 3.73 (*d*, *J* = 11.9 Hz, 1H, H_e), 3.44-3.40 (*m*, 1H, H_h), 3.24-3.19 (*m*, 1H, H_i), 2.89 (*d*, *J* = 9.1 Hz, 1H, H_a), 2.83 (*d*, *J* = 9.1 Hz, 1H, H_b), 1.52 (*quin*, *J* = 7.2 Hz, 2H, -$NCH_2C\underline{H}_2CH_2$-), 1.27-1.23 (*m*, 14H, $7CH_2$), 0.86 (*t*, *J* = 7.4 Hz, 3H, -CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.89,

172.52, 137.30, 134.77, 88.94, 82.49, 50.51, 49.00, 46.05, 43.25, 31.84, 29.49, 29.45, 29.25, 29.19, 27.03, 26.63, 22.63, 14.07; Anal calc for $C_{19}H_{29}NO_4$ (335.44): C 68.03, H 8.71, N 4.18. Found: C 68.08, H 8.64, N 4.23.

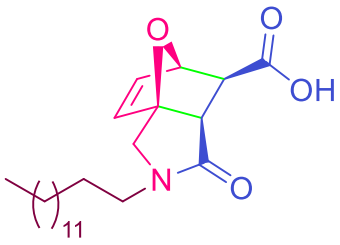
2-Dodecyl-1-oxo-1,2,3,6,7,7a-hexahydro-3a,6-epoxyisoindole-7-carboxylic acid ***(2d)***



Beige crystalline solid, mp 103.5–104 °C (EtOAc/MeOH); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.46 (*s*, 2H, H_f, H_g), 5.27 (*s*, 1H, H_c), 3.98 (*d*, *J* = 11.9 Hz, 1H, H_d), 3.74 (*d*, *J* = 11.9 Hz, 1H, H_e), 3.46-3.39 (*m*, 1H, H_h), 3.23-3.17 (*m*, 1H, H_i), 2.89 (*d*, *J* = 9.1 Hz, 1H, H_a), 2.83 (*d*, *J* = 9.1 Hz, 1H, H_b), 1.52 (*quin*, *J* = 7.2 Hz, 2H, -$NCH_2C\underline{H}_2CH_2$-), 1.28-1.22 (*m*, 18H, $9CH_2$), 0.85 (*t*, *J* = 7.4 Hz, 3H, -CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.12, 172.47, 137.25, 134.81, 88.90, 82.41, 50.64, 48.99, 45.91, 43.26, 31.87, 29.60, 29.59, 29.55, 29.45, 29.30, 29.21, 27.04, 26.65, 22.64, 14.07; Anal calc for $C_{21}H_{33}NO_4$ (363.50): C 69.39, H 9.15, N 3.85. Found: C 69.45, H 9.09, N 3.91.

2-Tetradecyl-1-oxo-1,2,3,6,7,7a-hexahydro-3a,6-epoxyisoindole-7-carboxylic acid

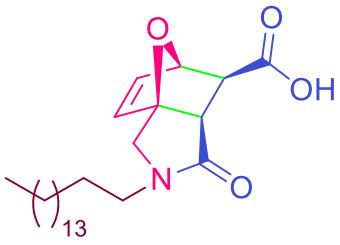
(2e)



Beige crystalline solid, mp 112–113 °C (EtOAc/MeOH); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.47 (*s*, 2H, H_f, H_g), 5.31 (*s*, 1H, H_c), 3.98 (*d*, *J* = 11.9 Hz, 1H, H_d), 3.74 (*d*, *J* = 11.9 Hz, 1H, H_e), 3.45-3.40 (*m*, 1H, H_h), 3.25-3.20 (*m*, 1H, H_i), 2.89 (*d*, *J* = 9.1 Hz, 1H, H_a), 2.84 (*d*, *J* = 9.1 Hz, 1H, H_b), 1.53 (*quin*, *J* = 7.2 Hz, 2H, -$NCH_2C\underline{H}_2CH_2$-), 1.27-1.23 (*m*, 22H, $11CH_2$), 0.86 (*t*, *J* = 7.2 Hz, 3H, -CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.73, 172.57, 137.37, 134.70, 88.99, 82.57, 50.39, 49.02, 46.21, 43.27, 31.89, 29.66, 29.64, 29.61, 29.56, 29.46, 29.32, 29.20, 27.03, 26.64, 22.65, 14.08; Anal calc for $C_{23}H_{37}NO_4$ (391.55): C 70.55, H 9.53, N 3.58. Found: C 70.50, H 9.48, N 3.66.

2-Hexadecyl-1-oxo-1,2,3,6,7,7a-hexahydro-3a,6-epoxyisoindole-7-carboxylic acid

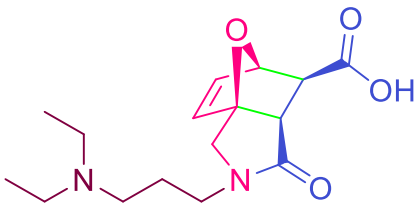
(2f)



Beige crystalline solid, mp 114–115 °C (EtOAc/MeOH); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.47 (*s*, 2H, H_f, H_g), 5.31 (*s*, 1H, H_c), 3.98 (*d*, *J* = 11.9 Hz, 1H, H_d), 3.74 (*d*, *J* = 11.9 Hz, 1H, H_e), 3.45-3.40 (*m*, 1H, H_h), 3.25-3.20 (*m*, 1H, H_i), 2.89 (*d*, *J* = 9.1 Hz, 1H, H_a),

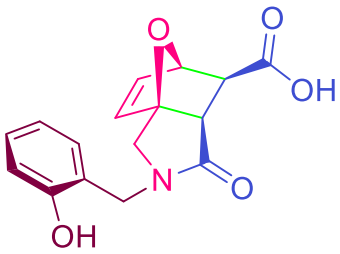
2.84 (*d*, *J* = 9.1 Hz, 1H, H_b), 1.53 (*quin*, *J* = 7.2 Hz, 2H, -$NCH_2C\underline{H}_2CH_2$-), 1.27-1.23 (*m*, 26H, $13CH_2$), 0.86 (*t*, *J* = 7.2 Hz, 3H, -CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.68, 172.58, 137.39, 134.67, 89.00, 82.60, 50.35, 49.02, 46.26, 43.28, 31.89, 29.66, 29.63, 29.61, 29.56, 29.46, 29.33, 29.20, 27.03, 26.64, 22.65, 14.08; Anal calc for $C_{25}H_{41}NO_4$ (419.61): C 71.56, H 9.85, N 3.34. Found: C 71.50, H 9.80, N 3.29.

2-(3-(Diethylamino)propyl)-1-oxo-1,2,3,6,7,7a-hexahydro-3a,6-epoxyisoindole-7-carboxylic acid ***(2g)***



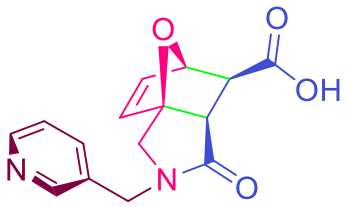
Orange oily liquid; ^{1}H NMR (600 MHz, DMSO-d_6) δ 6.53 (*d*, *J* = 5.9 Hz, 1H, H_f), 6.39 (*d*, *J* = 5.9 Hz, 1H, H_g), 4.91 (*s*, 1H, H_c), 3.96 (*d*, *J* = 11.6 Hz, 1H, H_d), 3.54 (*d*, *J* = 11.6 Hz, 1H, H_e), 3.22-3.19 (*m*, 1H, H_h), 3.16-3.12 (*m*, 1H, H_i), 2.67 (*d*, *J* = 9.2 Hz, 1H, H_a), 2.46 (*q*, 4H, *J* = 13.2 Hz,-$NCH_2CH_2CH_2N(C\underline{H}_2CH_3)_2$), 2.40 (*d*, *J* = 9.2 Hz, 1H, H_b), 1.59 (*t*, *J* = 7.4 Hz, 2H, -$NCH_2CH_2C\underline{H}_2N(CH_2CH_3)_2$), 1.02 (*quin*, 2H, *J* = 7.2 Hz, -$NCH_2C\underline{H}_2CH_2N(CH_2CH_3)_2$), 0.95 (*t*, *J* = 7.3 Hz, 6H, -$NCH_2CH_2CH_2N(CH_2C\underline{H}_3)_2$); ^{13}C NMR (150 MHz, DMSO-d_6) δ 172.68, 172.58, 137.39, 134.67, 89.00, 82.60, 56.47, 50.62, 49.58, 48.14, 46.42, 45.29, 24.06, 18.96, 11.20; Anal calc for $C_{16}H_{24}N_2O_4$ (308.38): C 62.32, H 7.84, N 9.08. Found: C 62.28, H 7.90, N 9.13.

2-(2-Hydroxybenzyl)-1-oxo-1,2,3,6,7,7a-hexahydro-3a,6-epoxyisoindole-7-carboxylic acid ***(2h)***



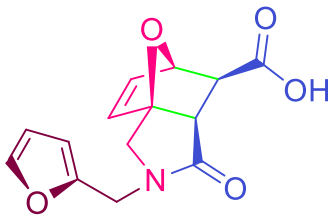
White crystalline solid, mp 103–104 °C (EtOAc/MeOH); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.19 (*t*, *J* = 9.7 Hz, 1H, Ar), 7.11 (*d*, *J* = 9.7 Hz, 1H, Ar), 6.92 (*d*, *J* = 7.5 Hz, 1H, Ar), 6.82 (*t*, *J* = 7.5 Hz, 1H, Ar), 6.44 (*d*, *J* = 5.9 Hz, 1H, H_g), 6.41 (*dd*, J_1 = 5.9 Hz, J_2 = 1.7 Hz, 1H, H_f), 5.20 (*d*, *J* = 1.7 Hz, 1H, H_c), 4.75 (*d*, *J* = 14.9 Hz, 1H, H_h), 4.12 (*d*, *J* = 14.9 Hz, 1H, H_i), 3.97 (*d*, *J* = 12 Hz, 1H, H_d), 3.79 (*d*, *J* = 12 Hz, 1H, H_e), 2.86 (*d*, *J* = 9.1 Hz, 1H, H_a), 2.78 (*d*, *J* = 9.1 Hz, 1H, H_b); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.36, 173.41, 155.53, 136.89, 135.17, 130.81, 130.21, 121.30, 119.95, 117.49, 88.82, 82.13, 51.32, 49.32, 45.07, 44.07; Anal calc for $C_{16}H_{15}NO_5$ (301.30): C 63.78, H 5.02, N 4.65. Found: C 63.84, H 5.07, N 4.59.

1-Oxo-2-(pyridin-3-ylmethyl)-1,2,3,6,7,7a-hexahydro-3a,6-epoxyisoindole-7-carboxylic acid ***(2i)***



Yellowish solid, mp 183–184 °C (dec.) (EtOAc/MeOH); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.58-8.56 (*m*, 2H, Py), 7.64 (*d*, *J* = 5.7 Hz, 1H, Py), 7.32-7.30 (*m*, 1H, Py), 6.47 (*d*, *J* = 2.6 Hz, 2H, H_f, H_g), 5.29 (*d*, *J* = 1.4 Hz, 1H, H_c), 4.67 (*d*, *J* = 15.4 Hz, 1H, H_h), 4.44 (*d*, *J* = 15.4 Hz, 1H, H_i), 3.91 (*d*, *J* = 11.8 Hz, 1H, H_d), 3.66 (*d*, *J* = 11.8 Hz, 1H, H_e), 2.87 (*d*, *J* = 9.1 Hz, 1H, H_a), 2.83 (*d*, *J* = 9.1 Hz, 1H, H_b); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.93, 172.22, 148.58, 137.28, 136.28, 134.74, 131.62, 128.31, 124.06, 88.77, 82.32, 50.48, 48.52, 46.02, 44.31; Anal calc for $C_{15}H_{14}N_2O_4$ (286.29): C 62.93, H 4.93, N 9.79. Found: C 62.88, H 4.98, N 9.85.

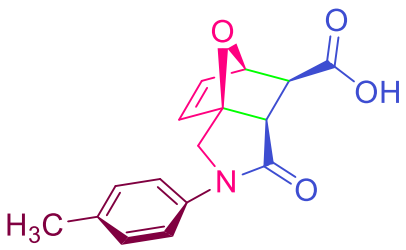
2-(Furan-2-ylmethyl)-1-oxo-1,2,3,6,7,7a-hexahydro-3a,6-epoxyisoindole-7-carboxylic acid ***(2j)***



Beige crystalline solid, mp 148–150 °C (EtOAc/MeOH), (The analytical data of compound **2j** agree with the literature [13], lit. 150–151 °C); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35 (*dd*, J_1 = 1.9 Hz, J_2 = 0.9 Hz, 1H, Furyl), 6.44 (*m*, 2H, H_f, H_g), 6.31 (*dd*, J_1 = 3.2 Hz, J_2 = 1.8 Hz, 1H, Furyl), 6.28 (*dd*, J_1 = 3.2 Hz, J_2 = 0.9 Hz, 1H, Furyl), 5.24 (*d*, *J* = 1.6 Hz, 1H, H_c), 4.75 (*d*, *J* = 15.5 Hz, 1H, H_h), 4.26 (*d*, *J* = 15.5 Hz, 1H, H_i), 3.92 (*d*, *J* = 12 Hz, 1H, H_d), 3.76 (*d*, *J* = 12 Hz, 1H, H_e), 2.90 (*d*, *J* = 9.1 Hz, 1H, H_a), 2.81 (*d*, *J* = 9.1 Hz, 1H, H_b); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.47, 172.04, 149.06, 142.67, 137.15, 134.95, 110.58, 108.84, 88.72, 82.23, 50.72, 48.92, 45.60, 39.86; Anal calc for $C_{14}H_{13}NO_5$ (275.26): C 61.09, H 4.76, N 5.09. Found: C 61.03, H 4.81, N 5.16.

[13] Zaytsev, V. P.; Mikhailova, N. M.; Airiyan, I. K.; Galkina, E. V.; Golubev, V. D.; Nikitina, E. V.; Zubkov, F. I; Varlamov, A. V. *Chem. Heterocycl. Compd.* **2012**, *48*, 505–513. doi: 10.1007/s10593-012-1023-1

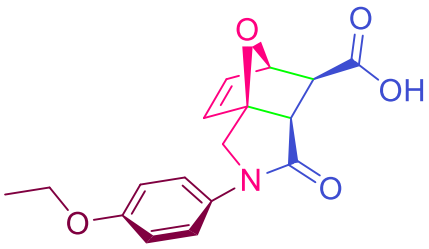
1-Oxo-2-(p-tolyl)-1,2,3,6,7,7a-hexahydro-3a,6-epoxyisoindole-7-carboxylic acid ***(2k)***



White crystalline solid, mp 188–190 °C (EtOAc/MeOH), (The analytical data of compound **2k** agree with the literature [14], lit. 183–184 °C); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43 (*d*, *J* = 8.5 Hz, 2H, Ar), 7.18 (*d*, *J* = 8.5 Hz, 2H, Ar), 6.56 (*d*, *J* = 1 Hz, 2H, H_f, H_g), 5.41 (*s*, 1H, H_c), 4.47 (*d*, *J* = 11.8 Hz, 1H, H_d), 4.21 (*d*, *J* = 11.8 Hz, 1H, H_e), 3.05 (*d*, *J* = 9.1 Hz, 1H, H_a), 2.95 (*d*, *J* = 9.1 Hz, 1H, H_b), 2.33 (*s*, 3H, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.97, 171.42, 144.52, 137.49, 135.70, 134.63, 129.58, 121.01, 88.30, 82.74, 51.14, 50.76, 46.88, 20.09; Anal calc for $C_{16}H_{15}NO_4$ (285.10): C 67.36, H 5.30, N 4.91. Found: C 67.41, H 5.25, N 4.85.

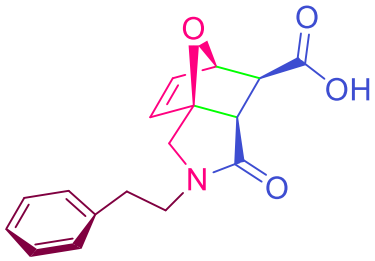
[14] Bilović, D. C*roat. Chem. Acta* **1966**, *38,* 293–298. doi: https://hrcak.srce.hr/208149

2-(4-Ethoxyphenyl)-1-oxo-1,2,3,6,7,7a-hexahydro-3a,6-epoxyisoindole-7-carboxylic acid ***(2l)***



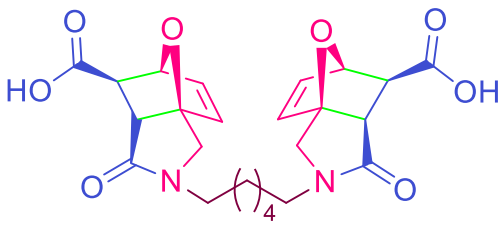
White crystalline solid, mp 171–172 °C (EtOAc/MeOH); ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.51 (*d*, *J* = 9.1 Hz, 2H, Ar), 6.90 (*d*, *J* = 9.1 Hz, 2H, Ar), 6.61 (*d*, *J* = 5.6 Hz, 1H, H_g), 6.45 (*dd*, J_1 = 5.6 Hz, J_2 = 1.7 Hz, 1H, H_f), 5.01 (*d*, J_1 = 1.7 Hz, 1H, H_c), 4.48 (*d*, *J* = 12 Hz, 1H, H_d), 3.99 (*d*, *J* = 12 Hz, 1H, H_e), 4.00-3.96 (*m*, 2H, -OC$\underline{H}_2$CH$_3$), 3.00 (*d*, *J* = 9.1 Hz, 1H, H_a), 2.54 (*d*, *J* = 9.1 Hz, 1H, H_b), 1.28 (*t*, *J* = 7.1 Hz, 3H, -OCH$_2$C$\underline{H}_3$); ^{13}C NMR (150 MHz, DMSO-d_6) δ 173.39, 170.30, 155.45, 137.36, 135.87, 133.05, 121.54, 114.77, 87.85, 81.75, 63.58, 51.78, 49.88, 45.60, 15.08; Anal calc for $C_{17}H_{17}NO_5$ (315.33): C 64.75, H 5.43, N 4.44. Found: C 64.70, H 5.38, N 4.50.

1-Oxo-2-phenethyl-1,2,3,6,7,7a-hexahydro-3a,6-epoxyisoindole-7-carboxylic acid ***(2m)***



Beige crystalline solid, mp 116–117 °C (EtOAc/MeOH), (lit. 89–90 °C, ref.[4]; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.28 (*t*, *J* = 7.6 Hz, 2H, Ar), 7.22-7.19 (*d*, *J* = 7.4 Hz, 3H, Ar), 6.42-6.39 (*m*, 2H, H_f, H_g), 5.24 (*d*, *J* = 1.7 Hz, 1H, H_c), 3.77 (*d*, *J* = 13.9 Hz, 1H, H_h), 3.62 (*d*, *J* = 13.9 Hz, 1H, H_i), 3.74-3.69 (*m*, 1H, H_d), 3.45-3.40 (*m*, 1H, H_e), 2.91-2.81 (*m*, 2H, -$CH_2C\underline{H}_2$Ph), 2.96 (*d*, *J* = 9.1 Hz, 1H, H_a), 2.84 (*d*, *J* = 9.1 Hz, 1H, H_b); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.19, 172.47, 138.30, 137.11, 134.91, 128.71, 128.66, 126.63, 88.87, 82.29, 50.68, 49.74, 45.71, 44.86, 33.54; Anal calc for $C_{17}H_{17}NO_4$ (299.33): C 68.22, H 5.72, N 4.68. Found: C 68.17, H 5.76, N 4.74.

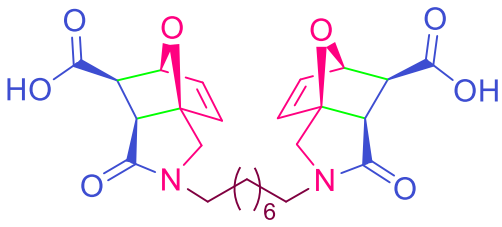
7-Carboxy-1-oxo-1,6,7,7a-tetrahydro-3a,6-epoxyisoindol-2(3H)-yl)hexyl)-1-oxo-1,2,3,6,7,7a-hexahydro-3a,6-epoxyisoindole-7-carboxylic acid ***(2n)***



Orange solid, mp 68–69 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 6.55-6.53 (*m*, 2H, H_g), 6.40-6.38 (*m*, 2H, H_f), 4.93 (*s*, 2H, H_c), 3.95 (*d*, *J* = 11.7 Hz, 2H, H_d), 3.83 (*d*, *J* = 11.9 Hz, 2H, H_e), 3.53-3.50 (*m*, 2H, H_h), 3.26-3.16 (*m*, 2H, H_i), 3.12-3.03 (*m*, 2H, H_a), 2.75-

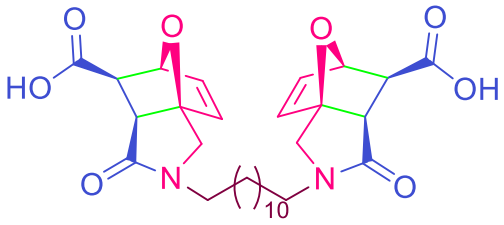
2.70 (*m*, 2H, H_b), 1.45-1.38 (*m*, 4H, $2CH_2$), 1.27-1.19 (*m*, 4H, $2CH_2$); ^{13}C NMR (150 MHz, DMSO-d_6) δ 173.44, 170.70, 137.09, 136.10, 88.80, 81.52, 50.64, 47.96, 44.98, 26.96, 25.99, 25.84; Anal calc for $C_{24}H_{28}N_2O_8$ (472.49): C 61.01, H 5.97, N 5.93. Found: C 61.08, H 5.90, N 5.86.

7-Carboxy-1-oxo-1,6,7,7a-tetrahydro-3a,6-epoxyisoindol-2(3H)-yl)octyl)-1-oxo-1,2,3,6,7,7a-hexahydro-3a,6-epoxyisoindole-7-carboxylic acid ***(2o)***



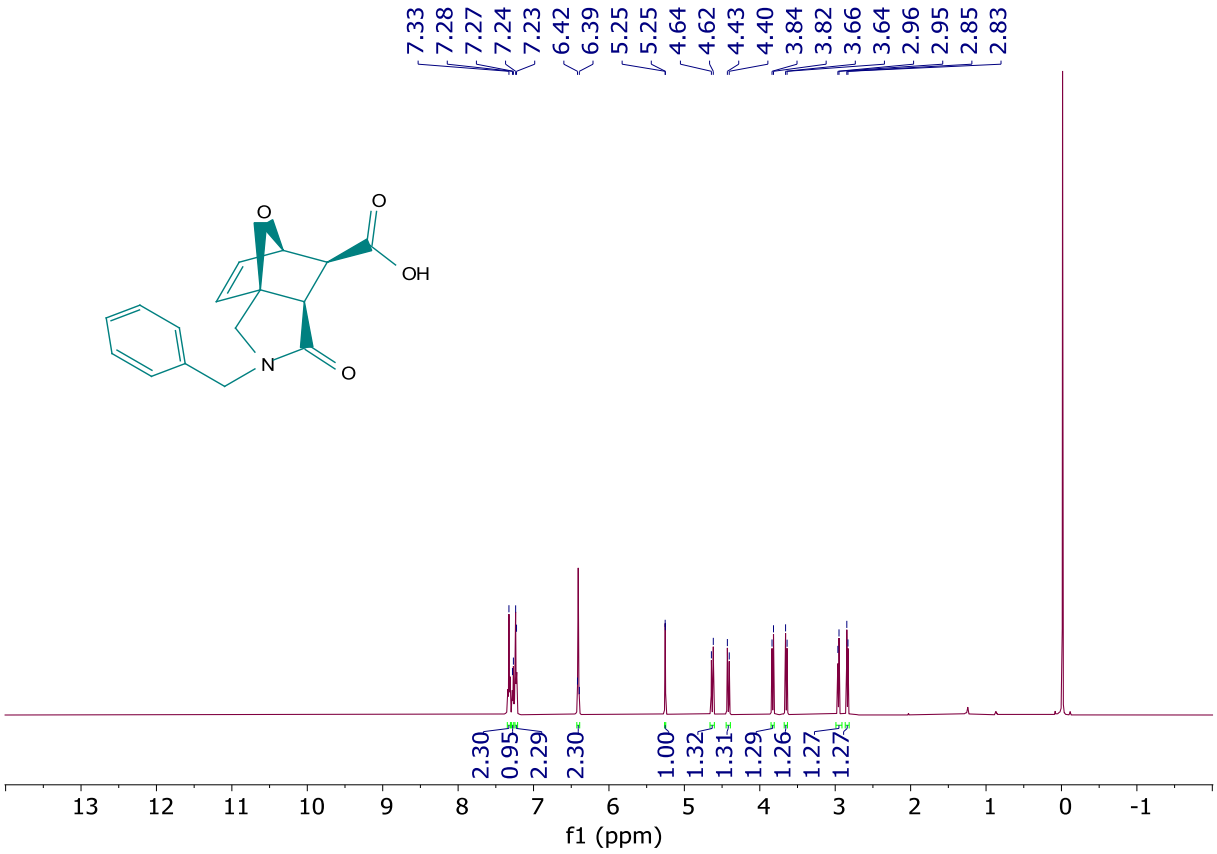
Orange solid, mp 66–67 °C; ^1H NMR (600 MHz, DMSO-d_6) δ 6.54 (*d*, *J* = 5.7 Hz, 2H, H_g), 6.39 (*dd*, J_1 = 5.7 Hz, J_2 = 1.8 Hz, 2H, H_f), 4.93 (*d*, *J* = 1.7 Hz, 2H, H_c), 3.99 (*d*, *J* = 11.7 Hz, 2H, H_d), 3.95 (*d*, *J* = 11.9 Hz, 2H, H_e), 3.51 (*d*, *J* = 11.7 Hz, 2H, H_h), 3.25-3.20 (*m*, 2H, H_i), 3.07-3.02 (*m*, 2H, H_a), 2.72 (*d*, *J* = 9.1 Hz, 2H, H_b), 1.43-1.39 (*m*, 4H, $2CH_2$), 1.27-1.18 (*m*, 8H, $4CH_2$); ^{13}C NMR (150 MHz, DMSO-d_6) δ 173.35, 170.60, 137.10, 136.09, 88.80, 81.52, 50.66, 48.03, 44.93, 42.07, 29.00, 27.07, 26.36; Anal calc for $C_{26}H_{32}N_2O_8$ (500.55): C 62.39, H 6.44, N 5.60. Found: C 62.46, H 6.50, N 5.67.

7-Carboxy-1-oxo-1,6,7,7a-tetrahydro-3a,6-epoxyisoindol-2(3H)-yl)dodecyl)-1-oxo-1,2,3,6,7,7a-hexahydro-3a,6-epoxyisoindole-7-carboxylic acid ***(2p)***

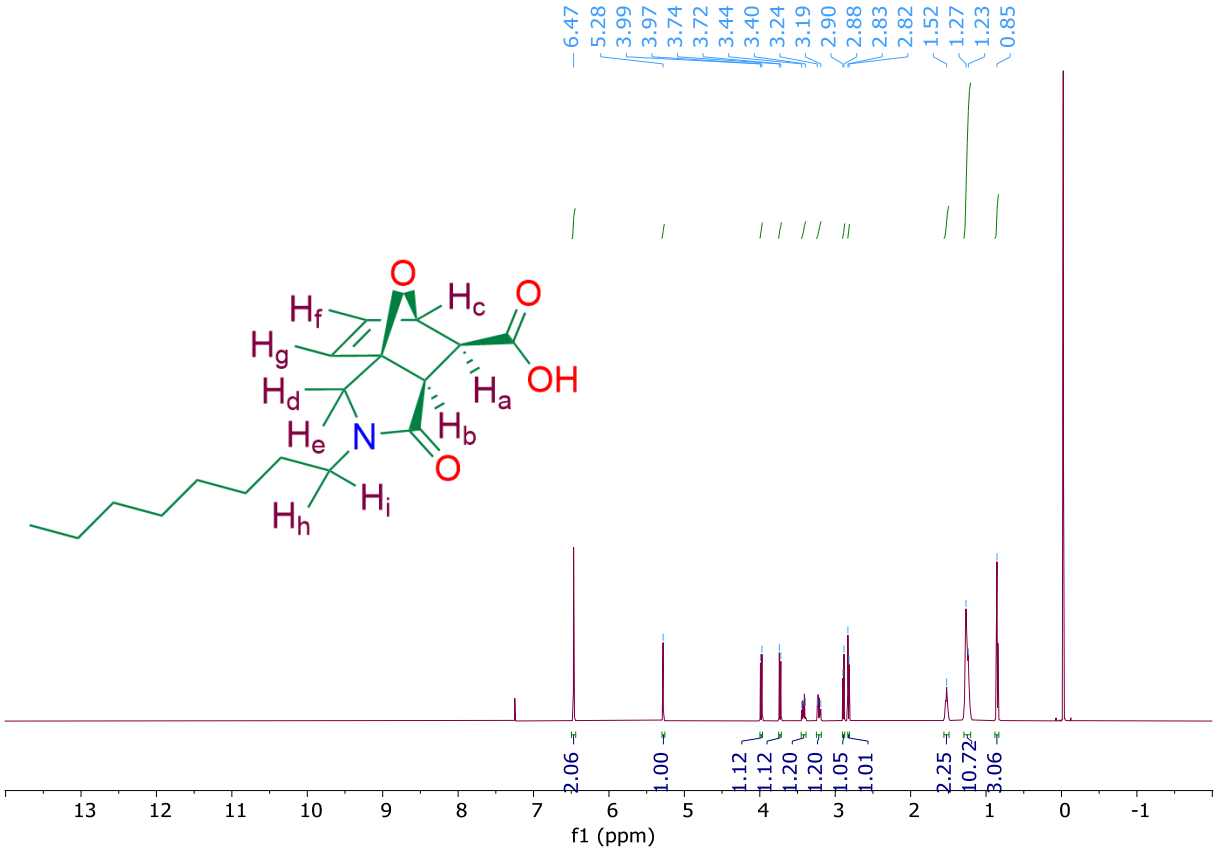


Beige solid, mp 94–95 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.49 (*d*, *J* = 5.7 Hz, 2H, H_g), 6.45 (*d*, *J* = 5.7 Hz, 2H, H_f), 5.24 (*d*, *J* = 2 Hz, 2H, H_c), 3.98 (*m*, 2H, H_d), 3.72 (*d*, *J* = 11.9 Hz, 2H, H_e), 3.41-3.32 (*m*, 2H, H_h), 3.28-3.19 (*m*, 2H, H_i), 2.89 (*d*, *J* = 9.1 Hz, 2H, H_a), 2.80-2.78 (*m*, 2H, H_b), 1.51 (*quin*, *J* = 7.02 Hz, 4H, $2CH_2$), 1.26-1.22 (*m*, 16H, $8CH_2$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.46, 172.37, 137.17, 134.95, 88.91, 82.35, 50.76, 48.95, 45.85, 43.16, 29.31, 29.26, 29.05, 26.94, 26.48; Anal calc for $C_{30}H_{40}N_2O_8$ (556.66): C 64.73, H 7.24, N 5.03. Found: C 64.68, H 7.18, N 5.10.

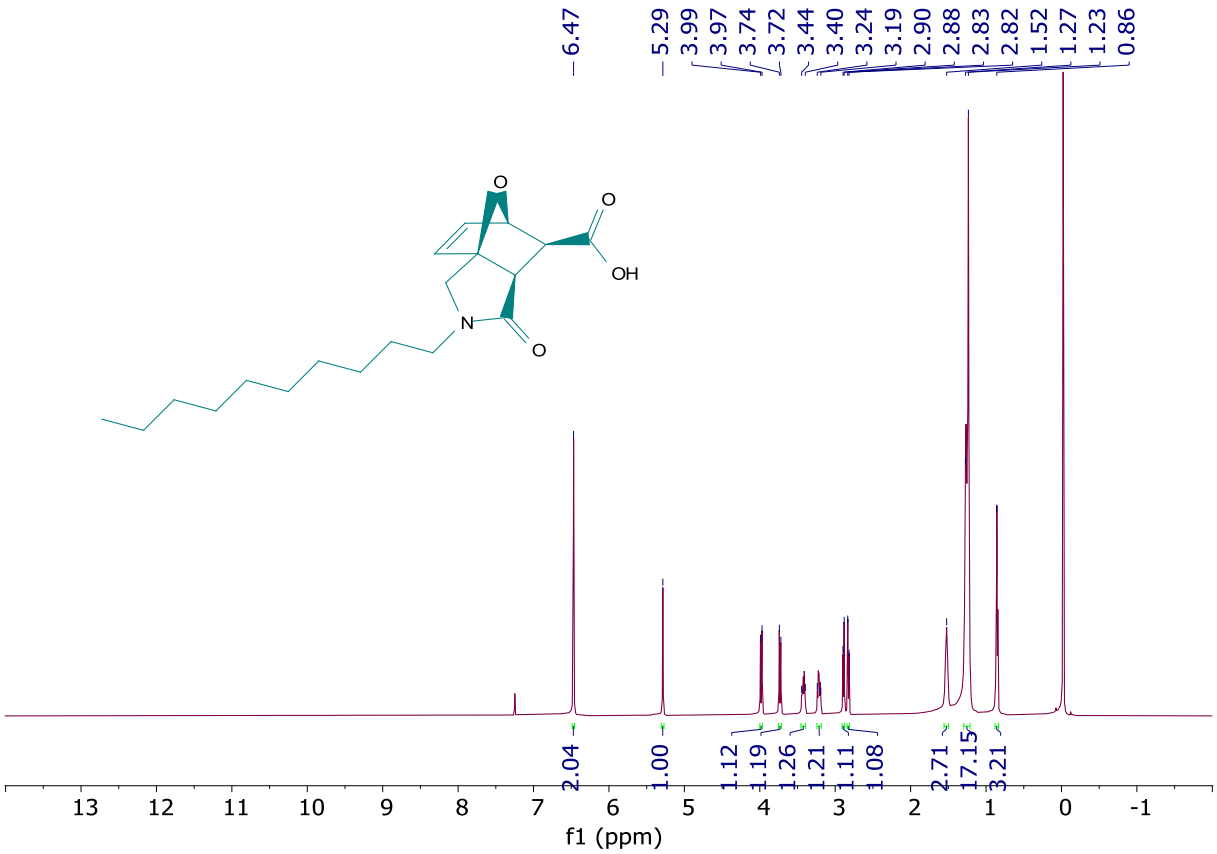
^{1}H NMR spectrum of compound **2a**



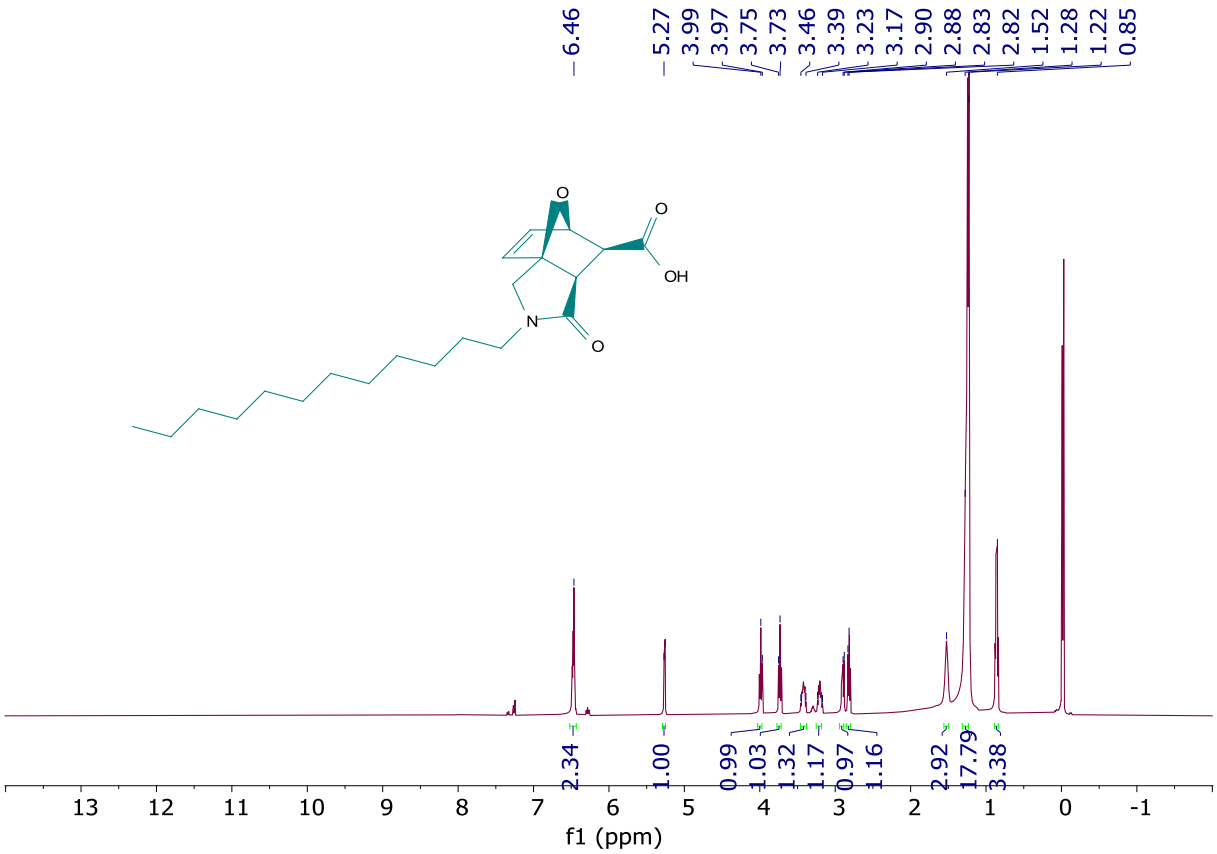
^{1}H NMR spectrum of compound **2b**



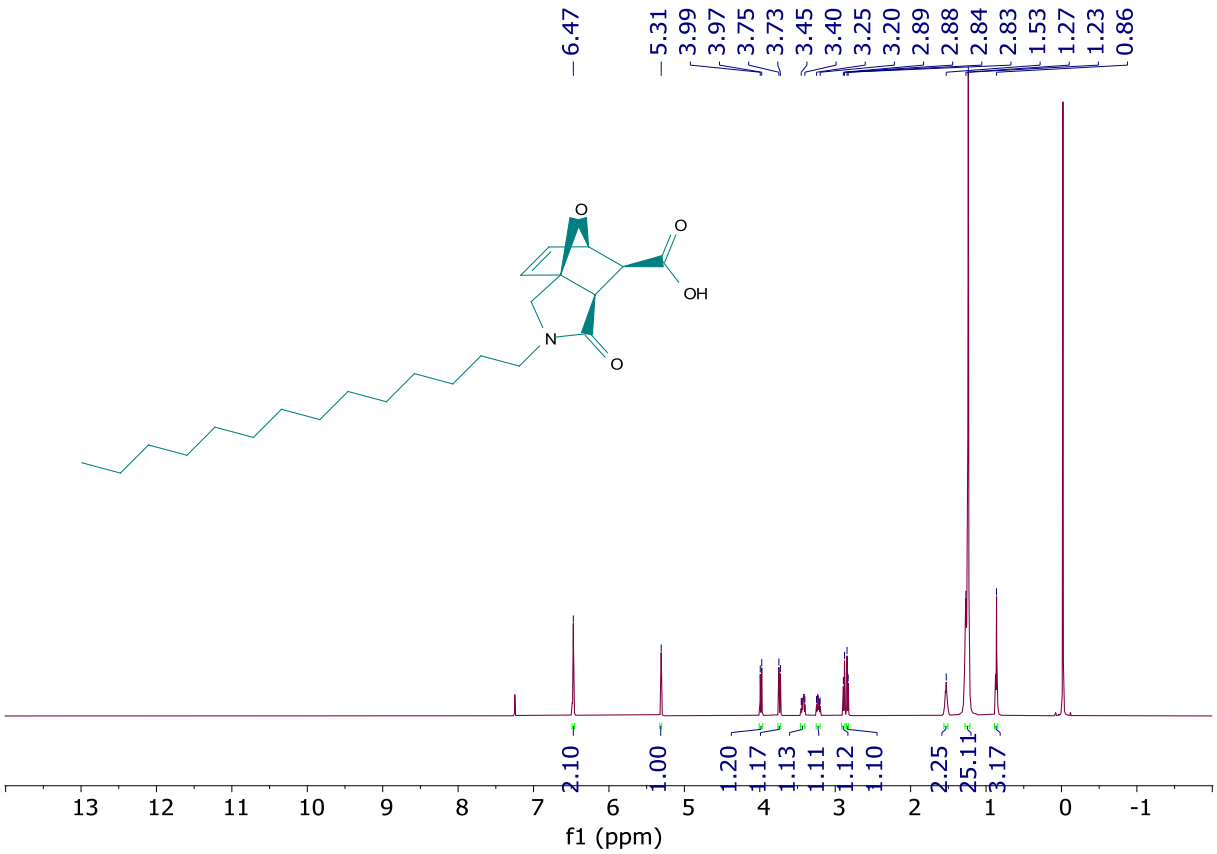
^{1}H NMR spectrum of compound **2c**



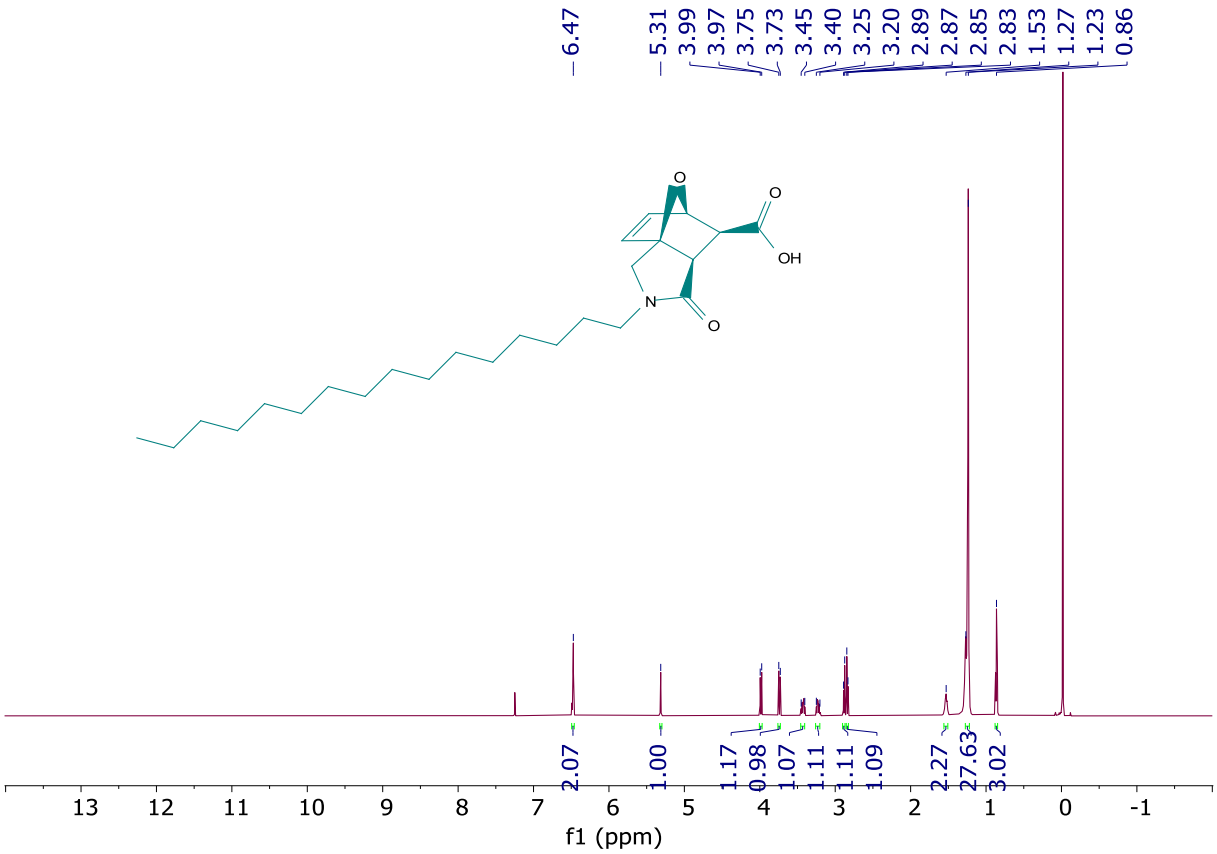
^{1}H NMR spectrum of compound **2d**



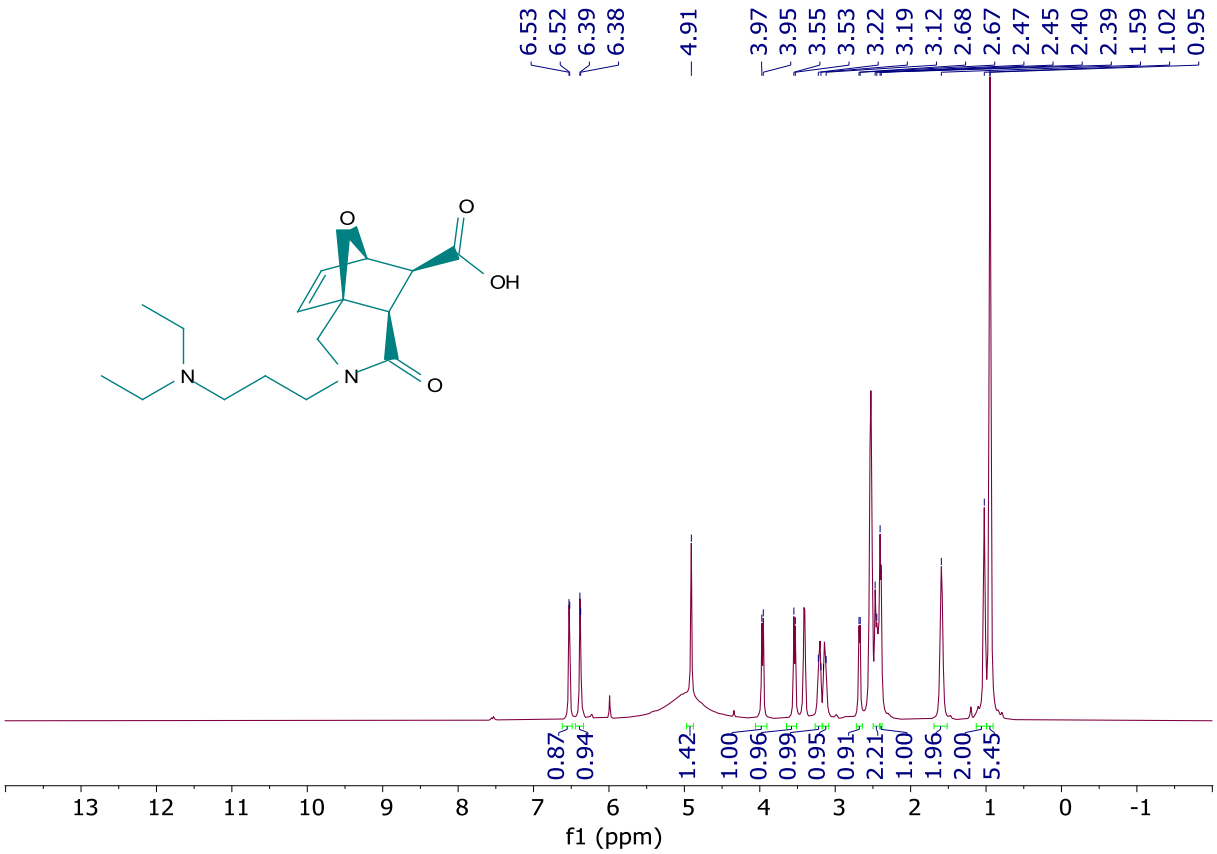
^{1}H NMR spectrum of compound **2e**



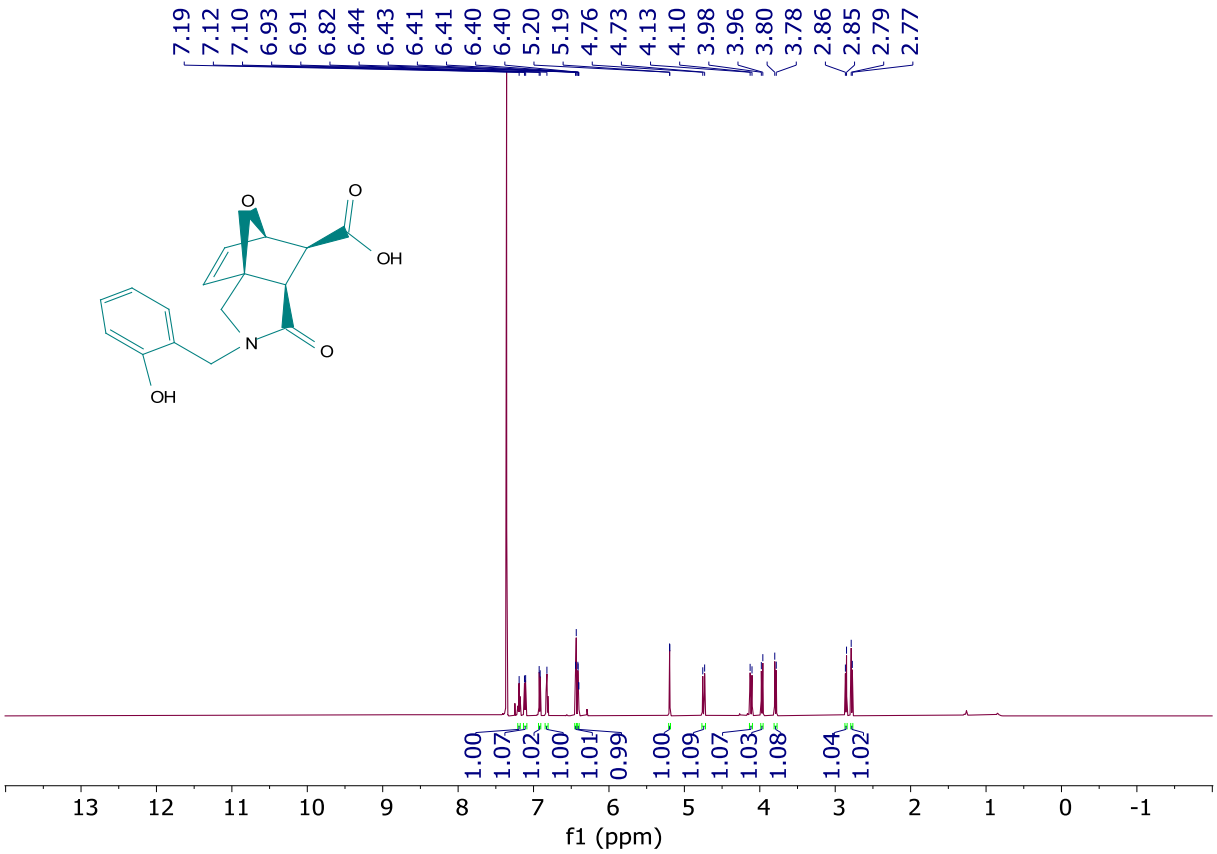
^{1}H NMR spectrum of compound **2f**



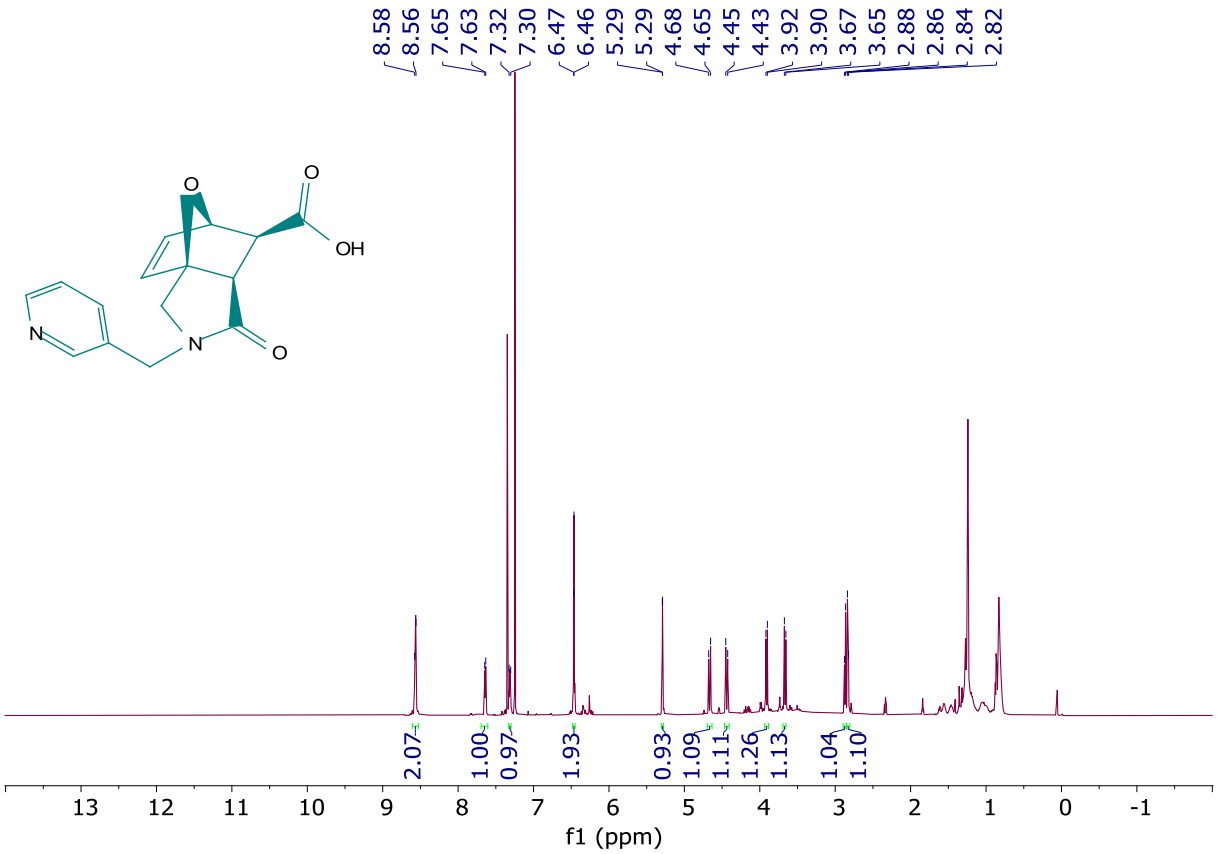
^{1}H NMR spectrum of compound **2g**



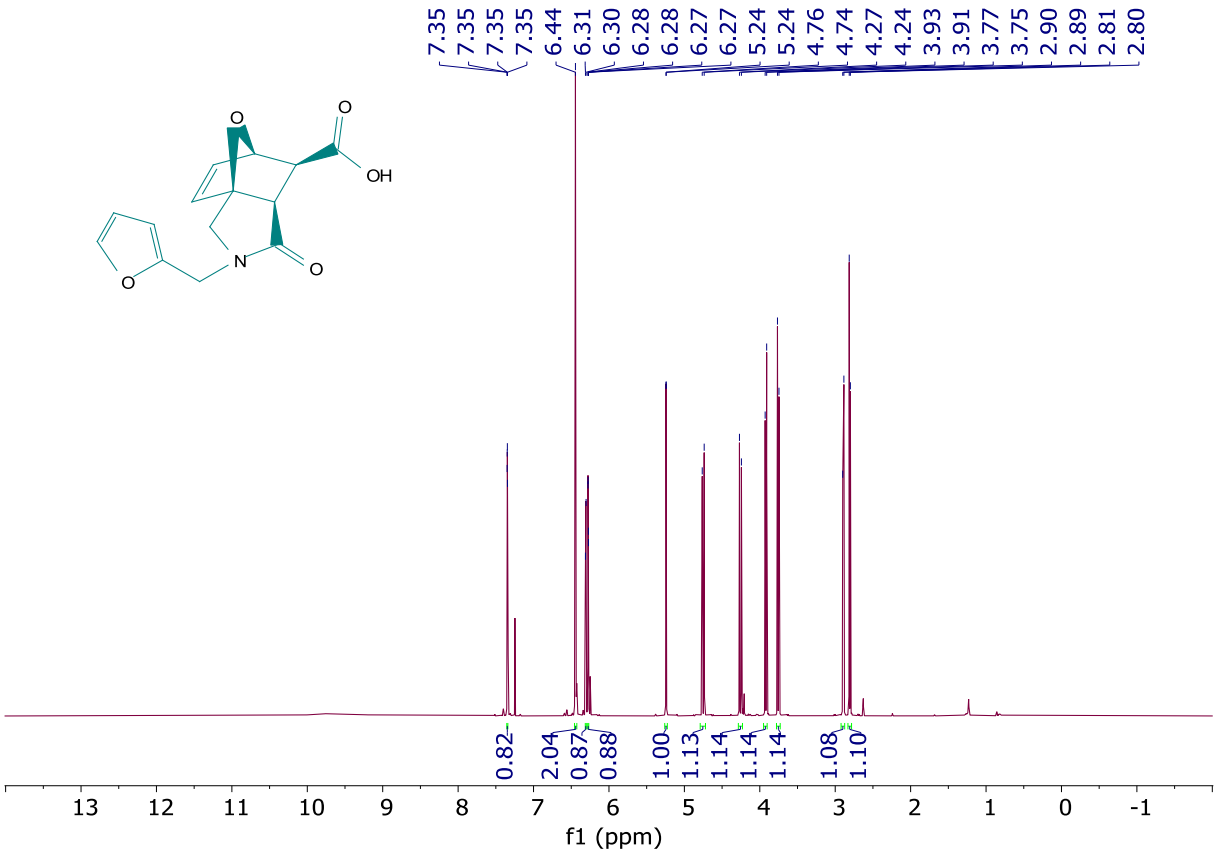
^{1}H NMR spectrum of compound **2h**



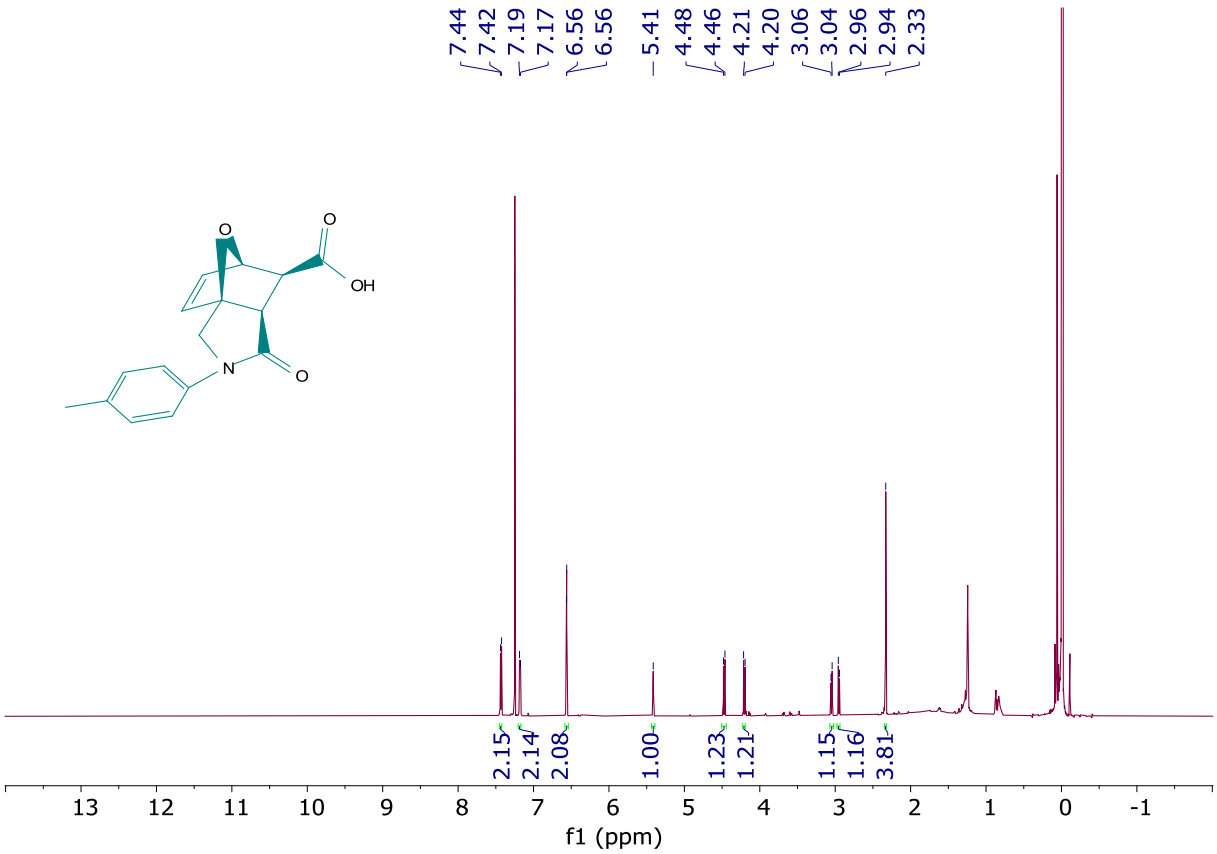
^{1}H NMR spectrum of compound **2i**



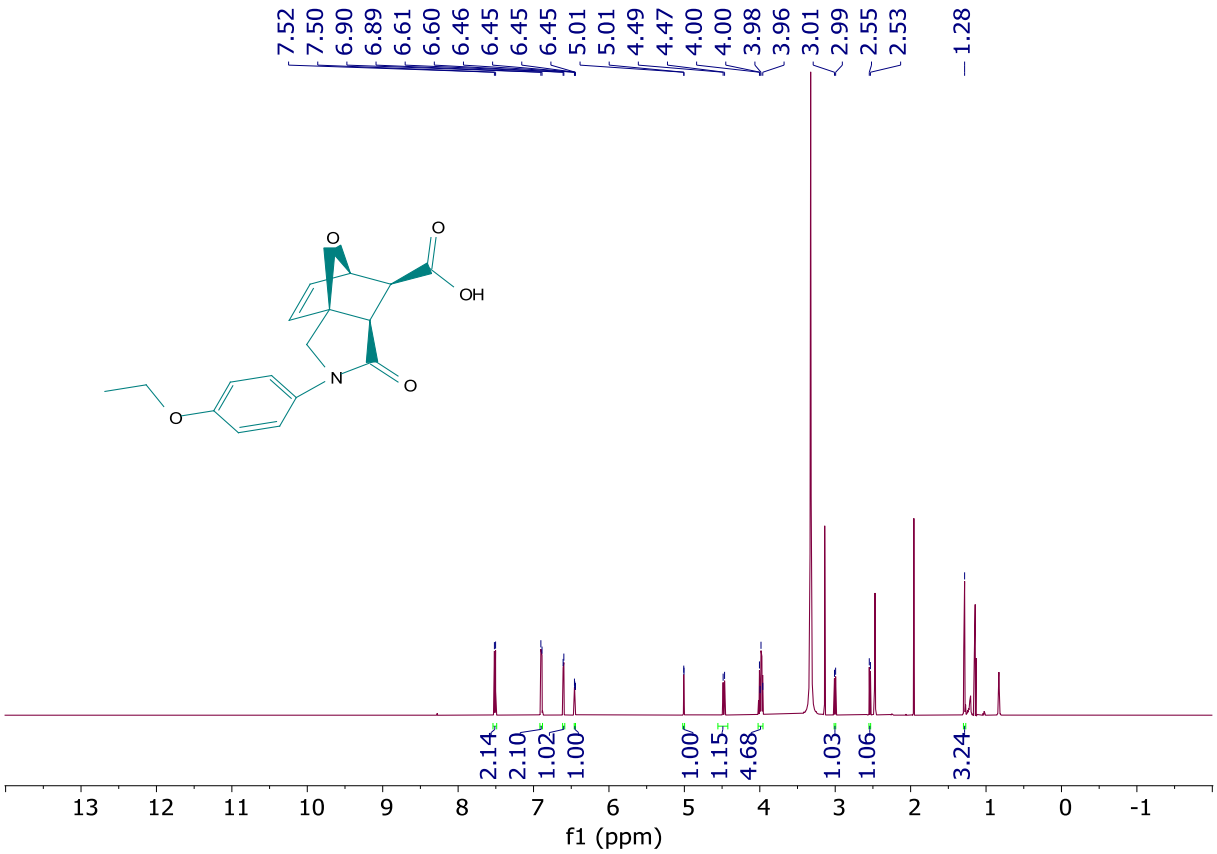
^{1}H NMR spectrum of compound **2j**



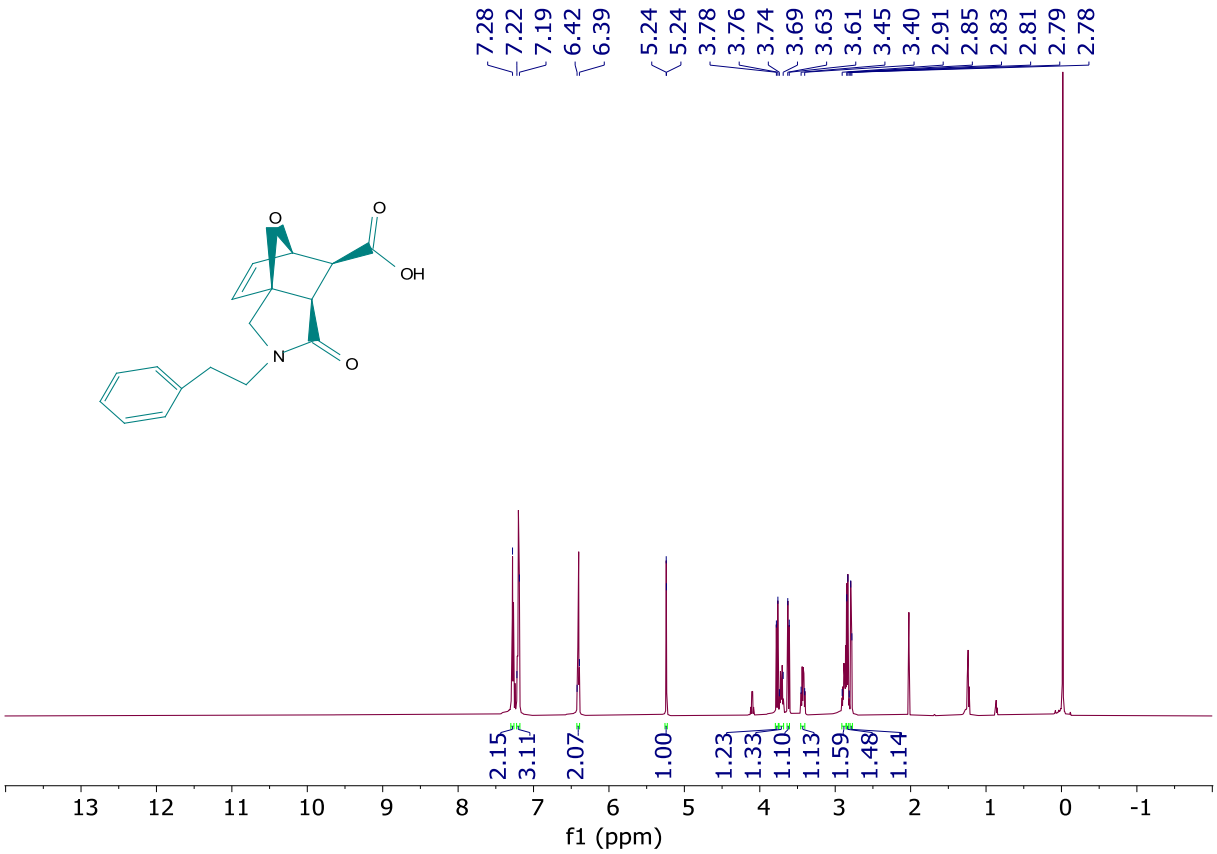
^{1}H NMR spectrum of compound **2k**



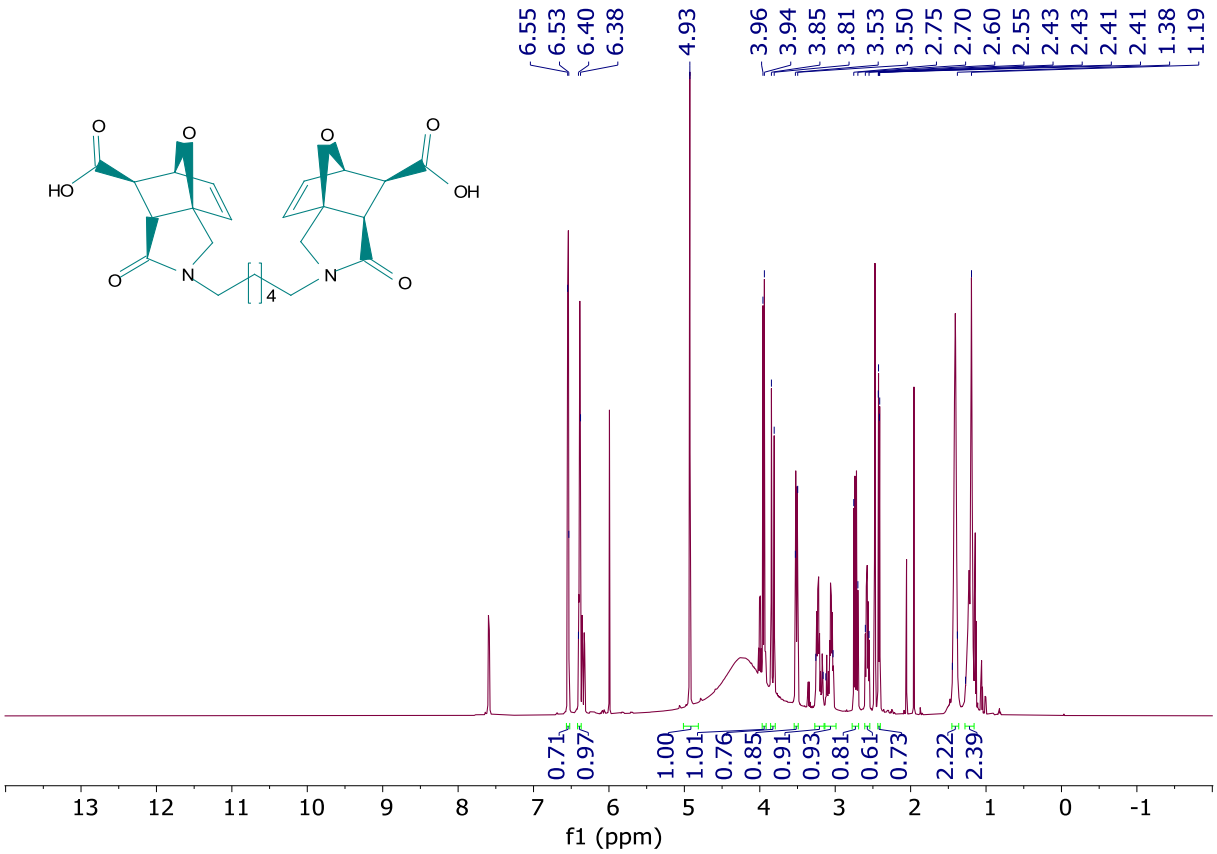
^{1}H NMR spectrum of compound **2l**



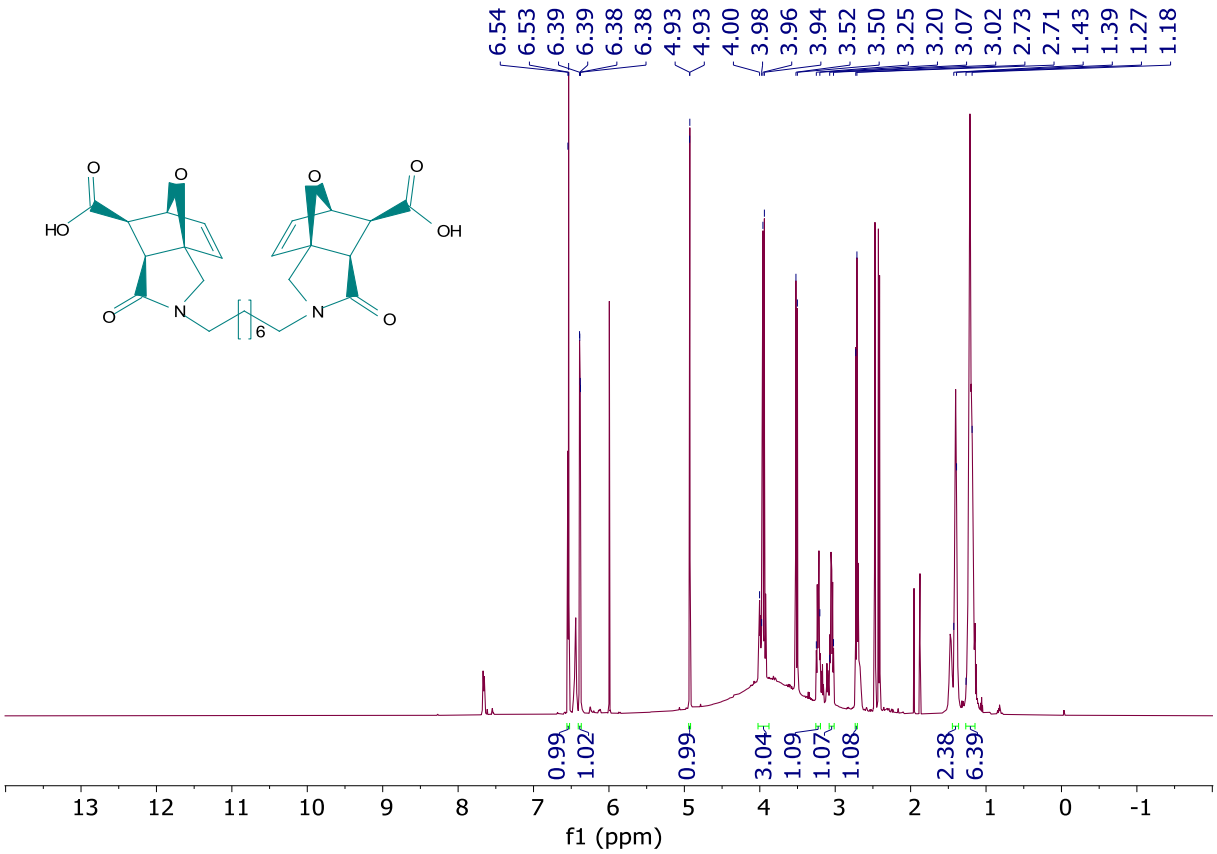
^{1}H NMR spectrum of compound **2m**



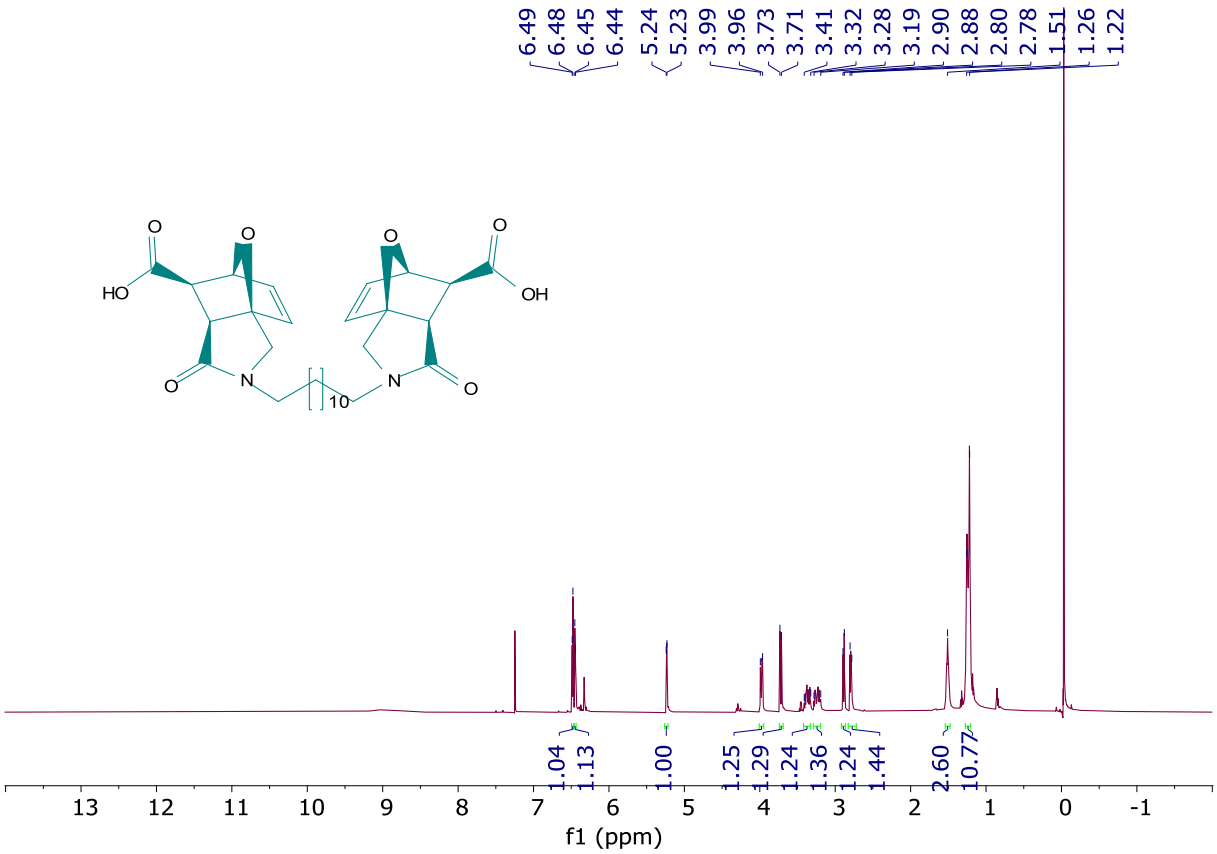
^{1}H NMR spectrum of compound **2n**



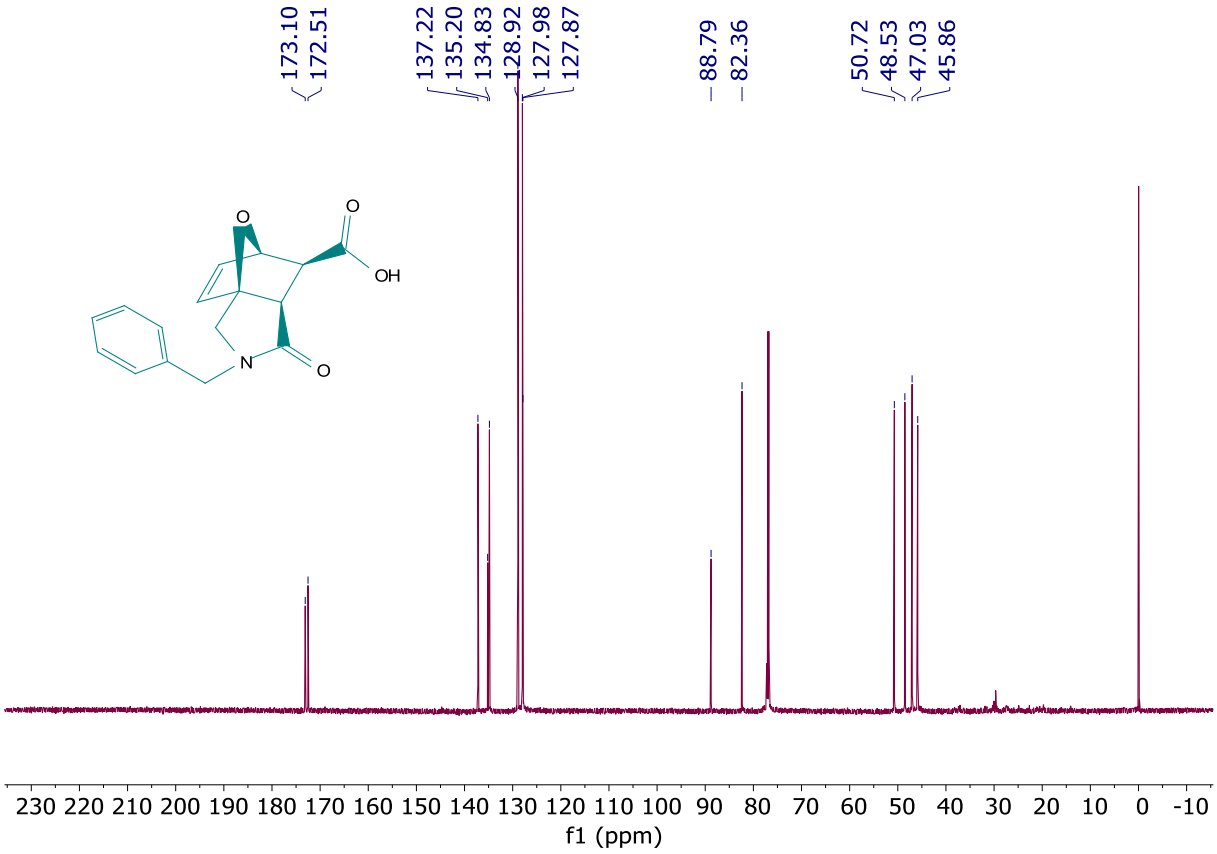
^{1}H NMR spectrum of compound **2o**



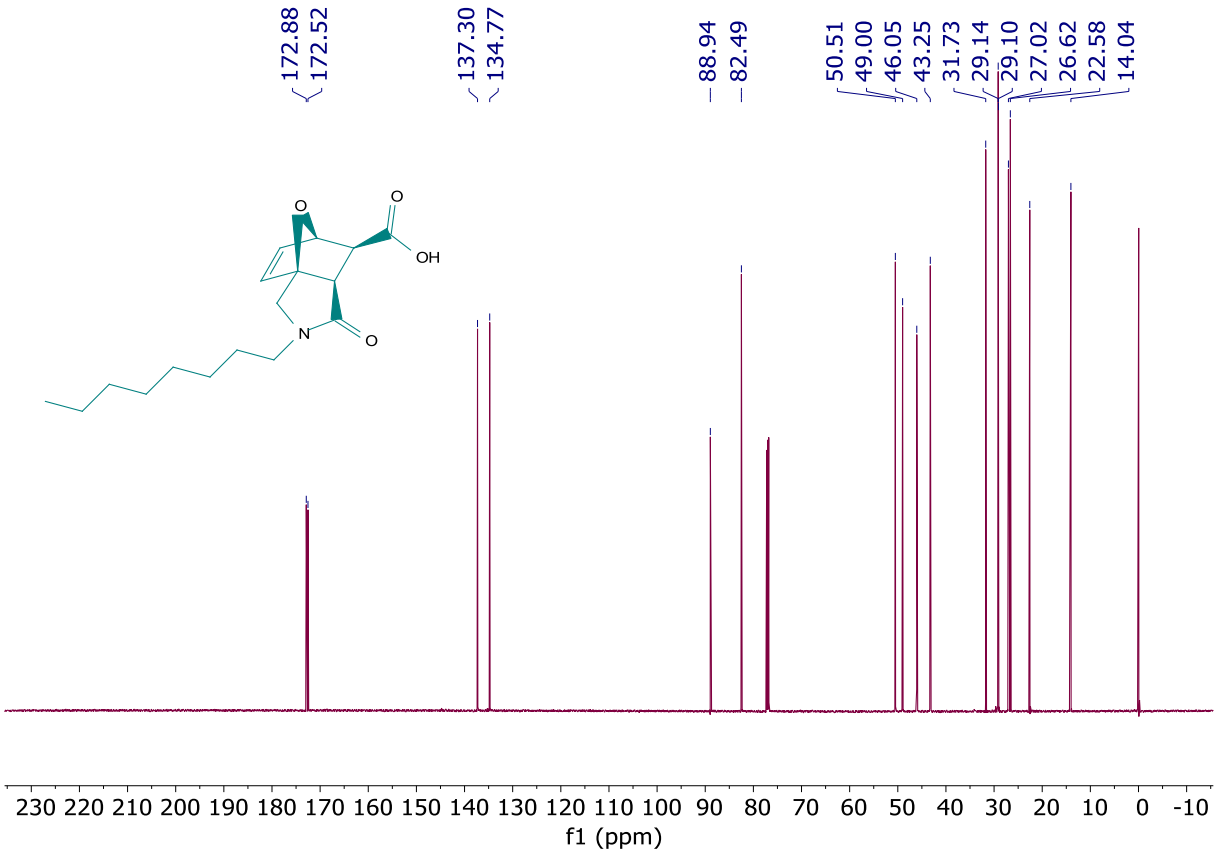
^{1}H NMR spectrum of compound **2p**



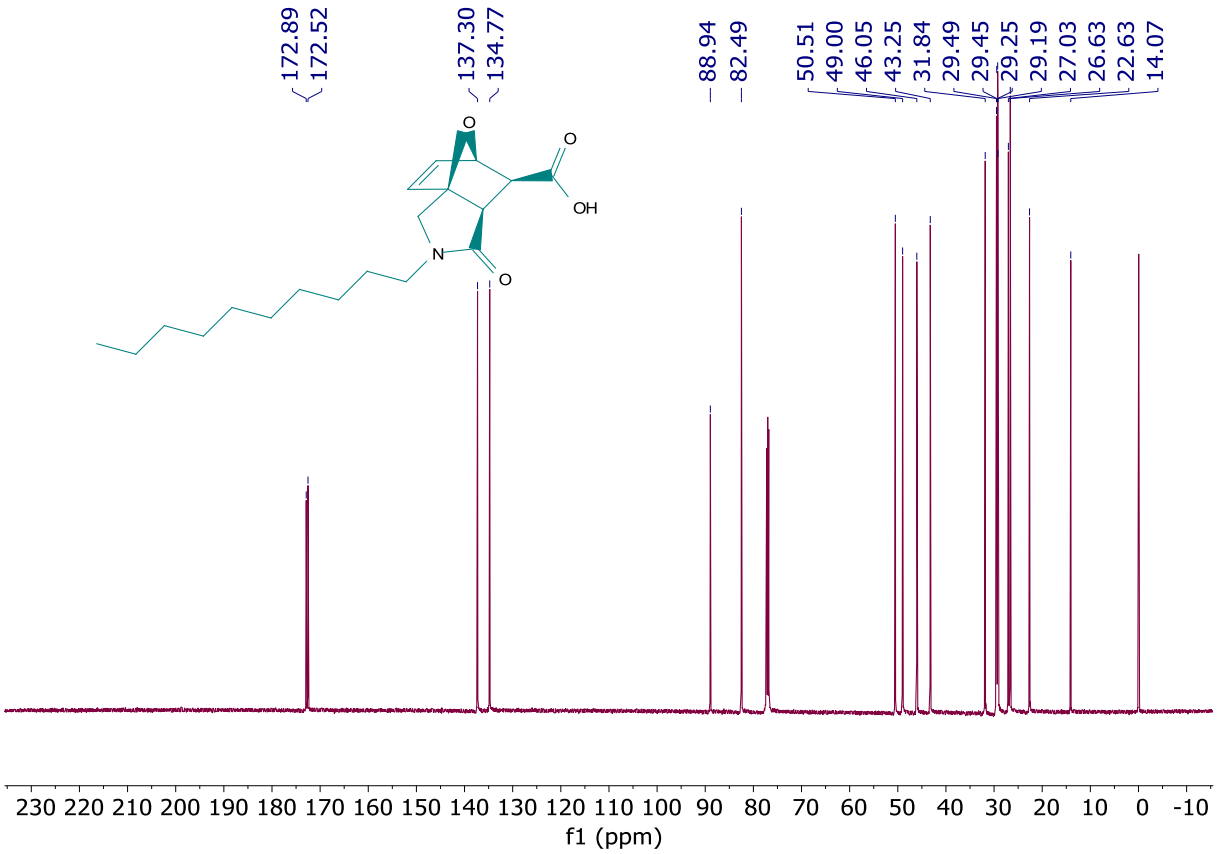
^{13}C NMR spectrum of compound **2a**



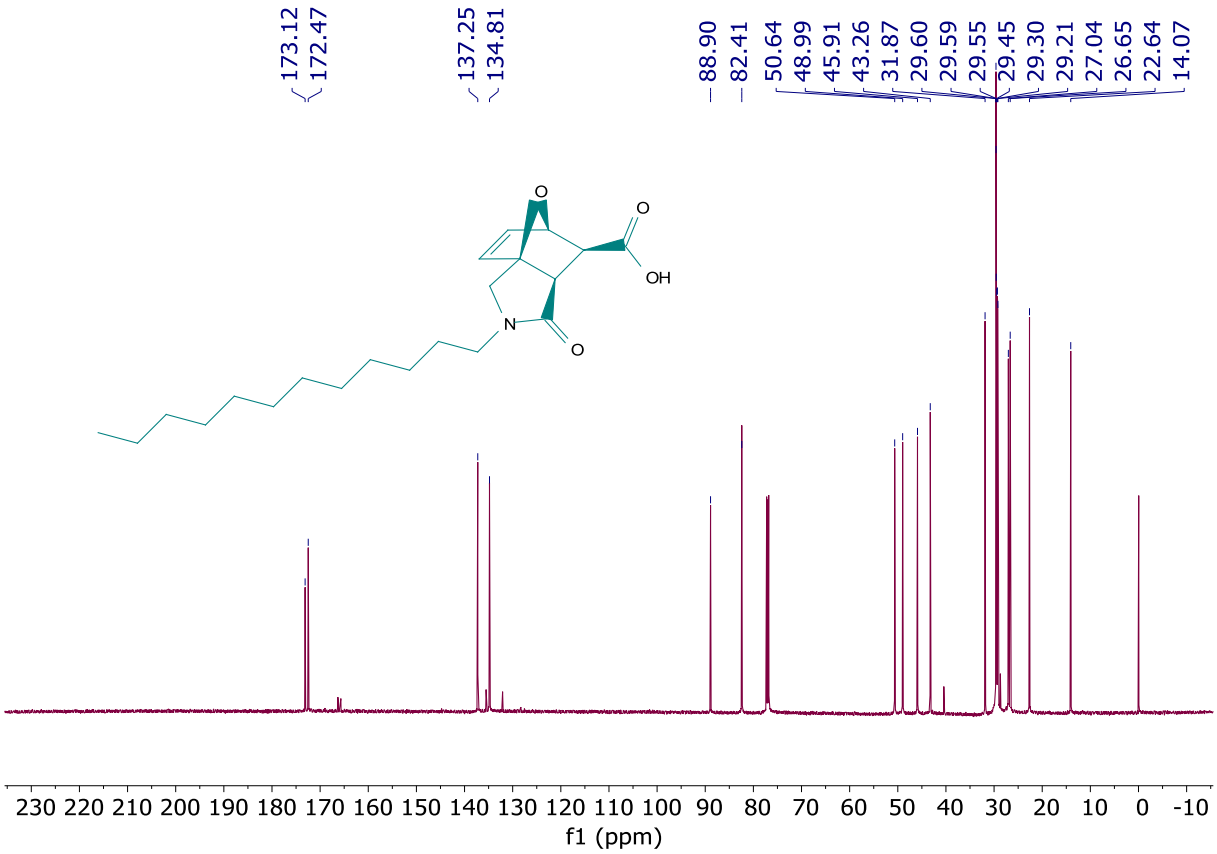
^{13}C NMR spectrum of compound **2b**



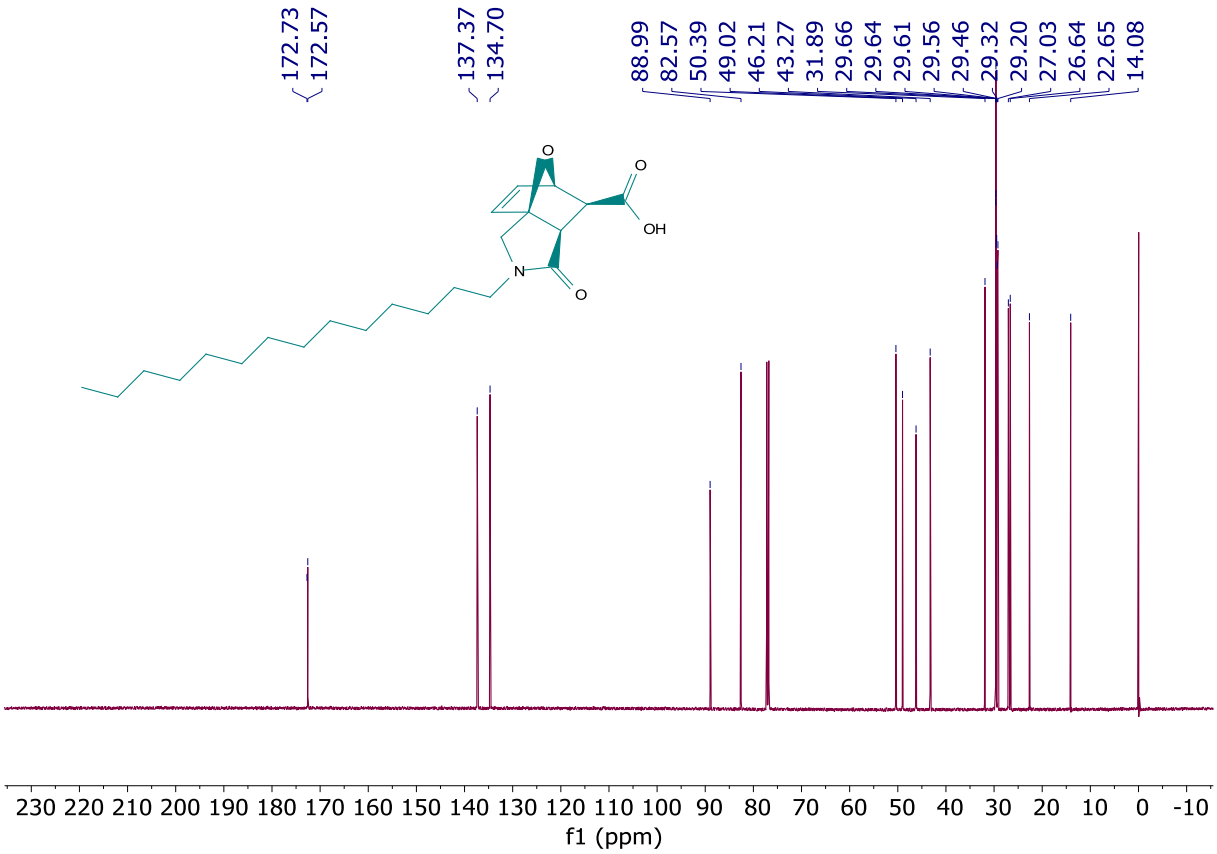
^{13}C NMR spectrum of compound **2c**



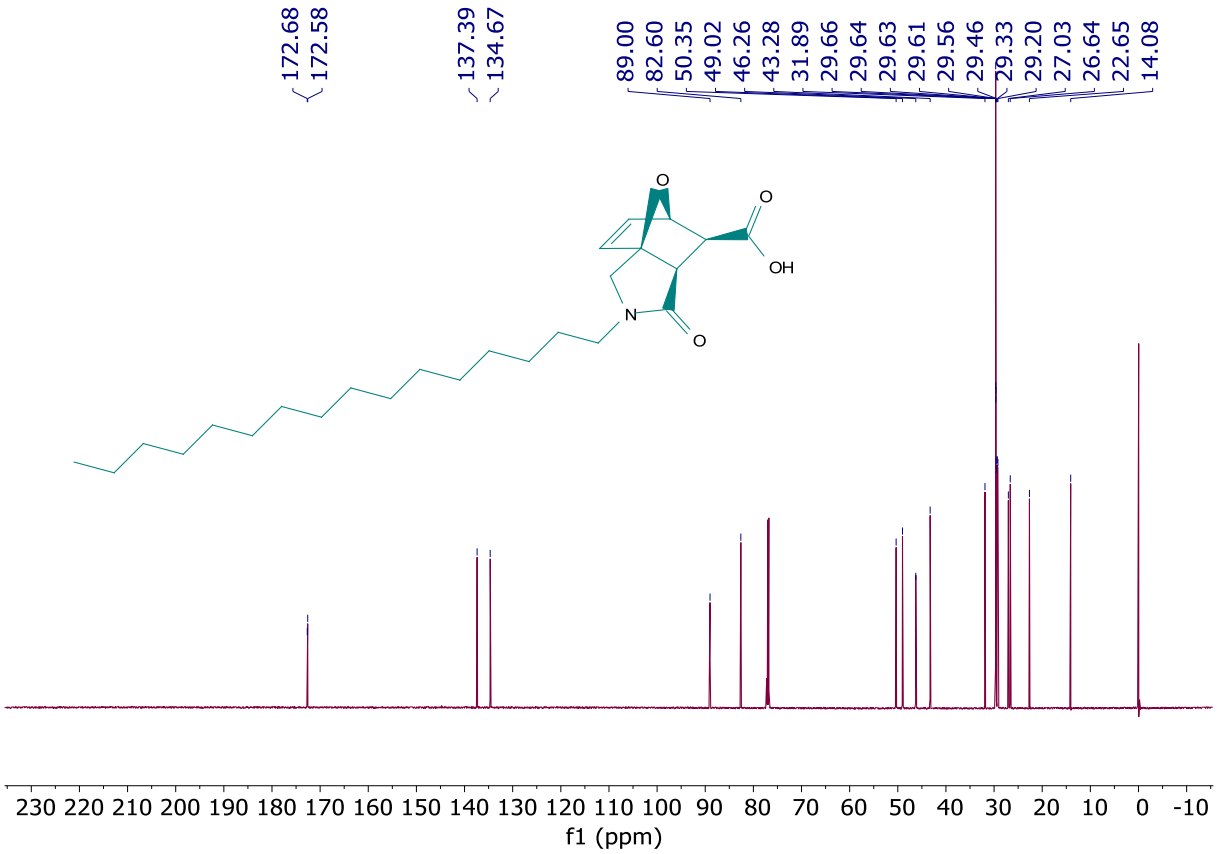
^{13}C NMR spectrum of compound **2d**



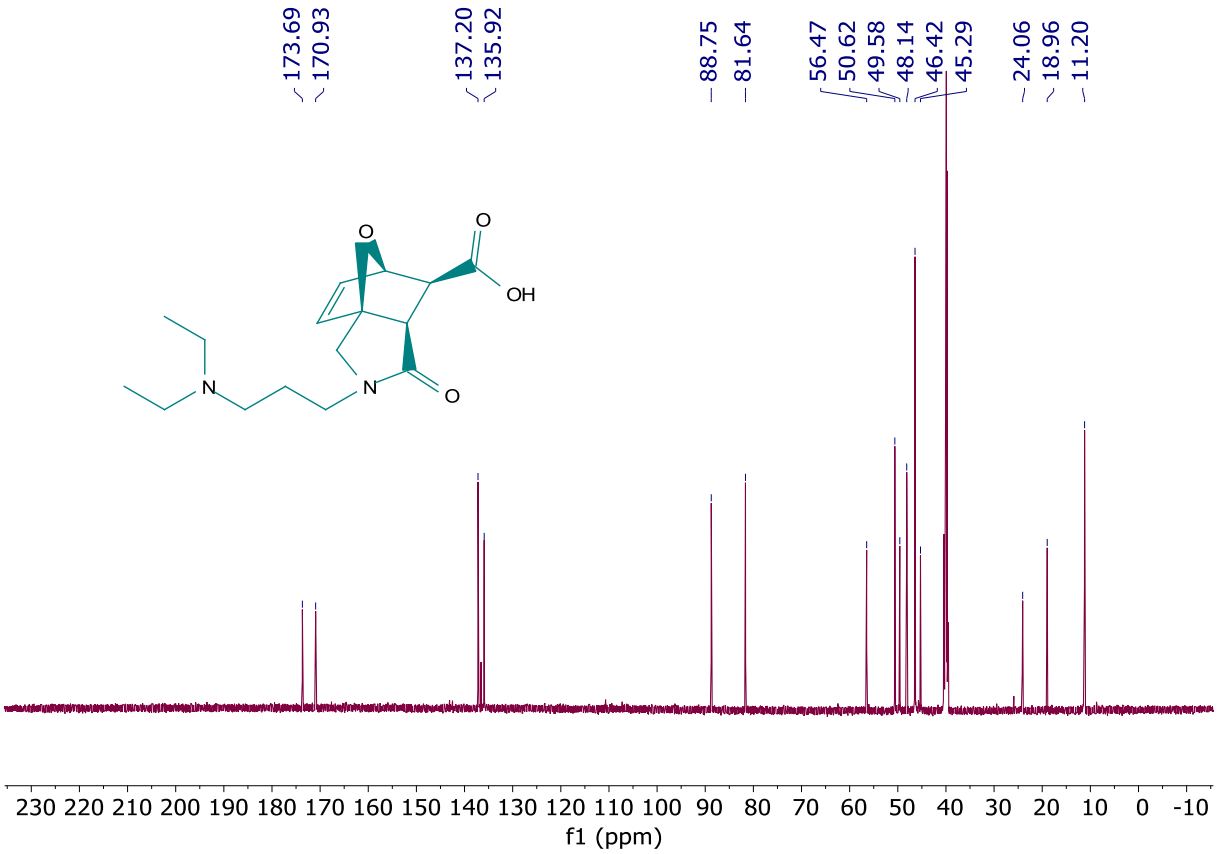
^{13}C NMR spectrum of compound **2e**



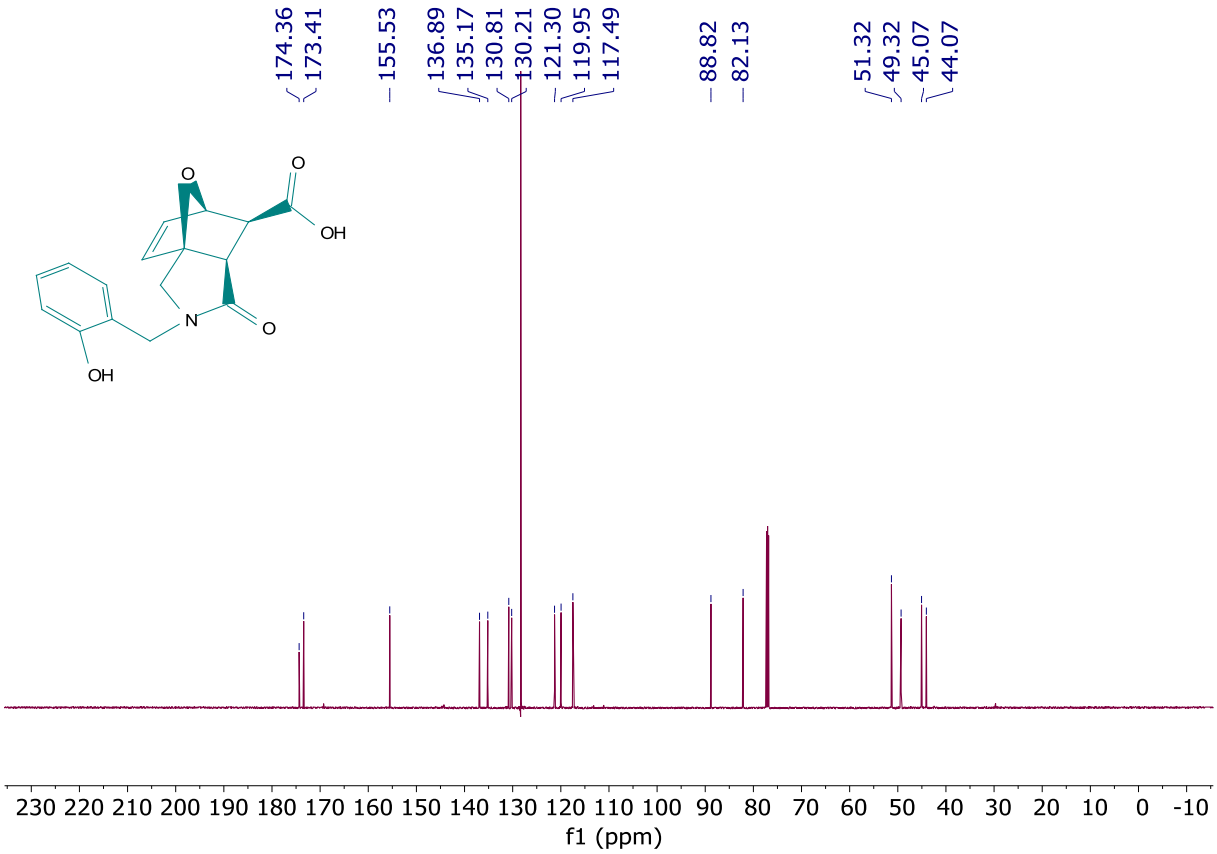
^{13}C NMR spectrum of compound **2f**



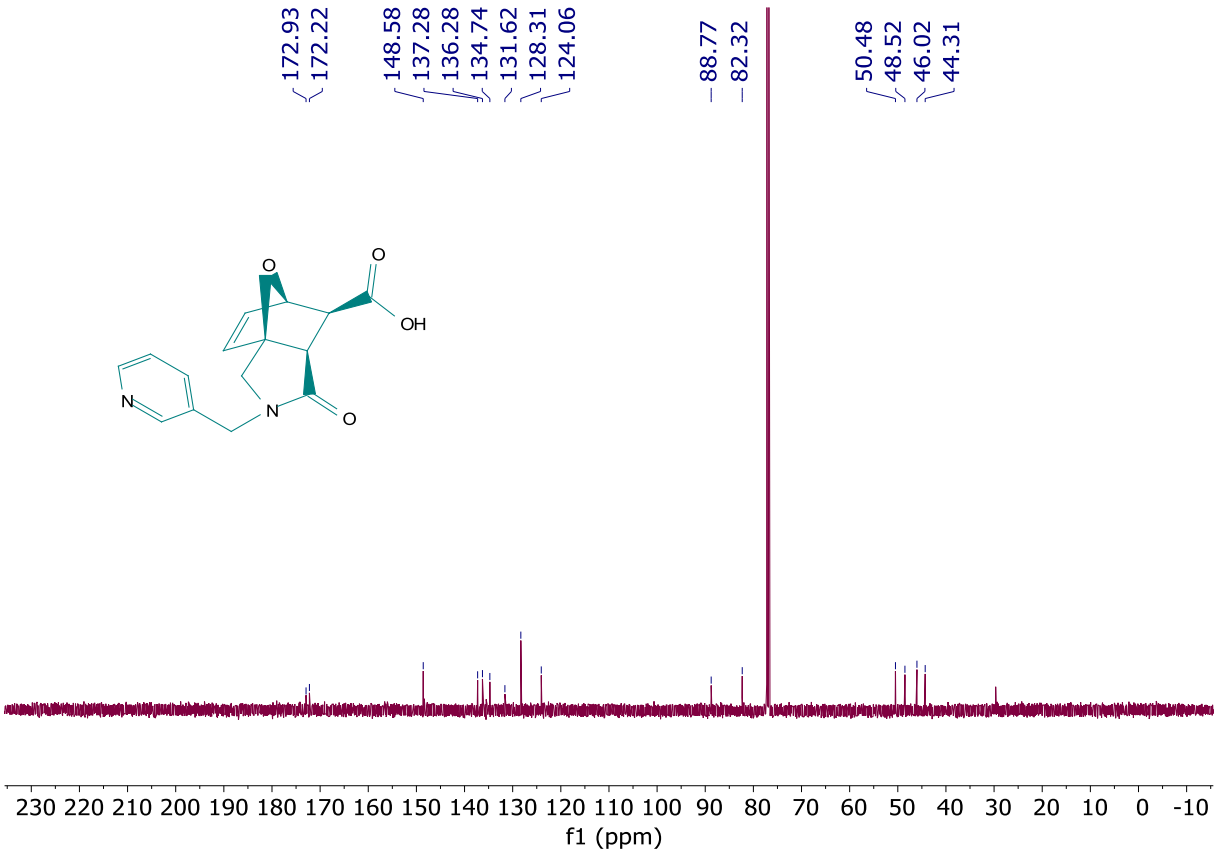
^{13}C NMR spectrum of compound **2g**



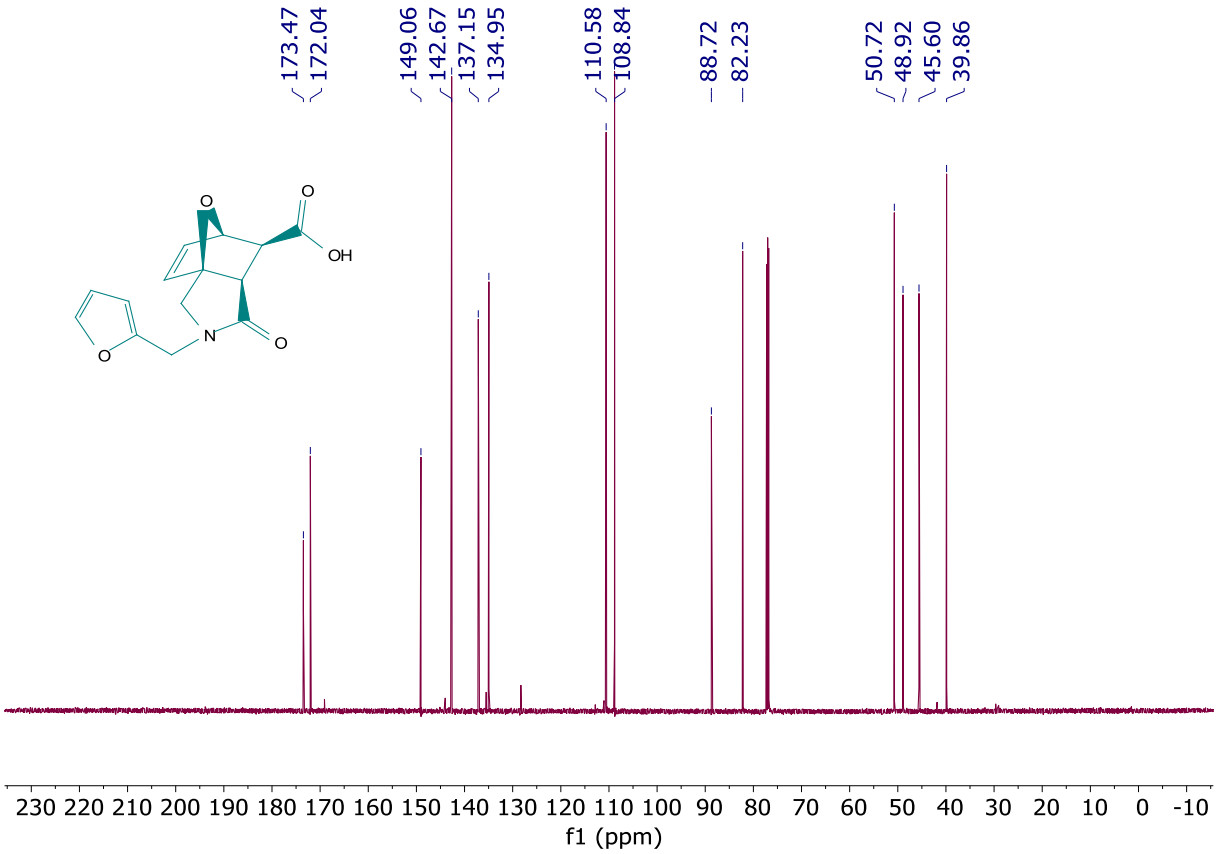
^{13}C NMR spectrum of compound **2h**



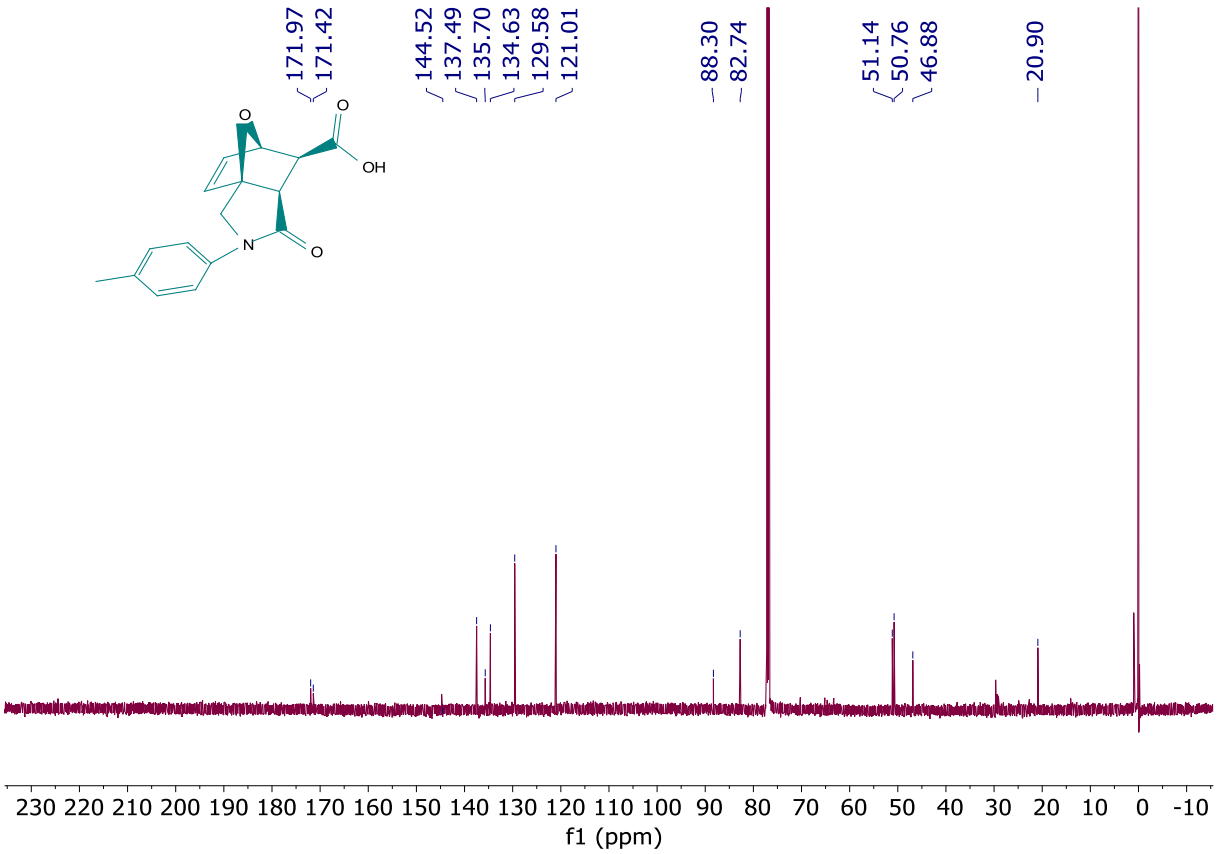
^{13}C NMR spectrum of compound **2i**



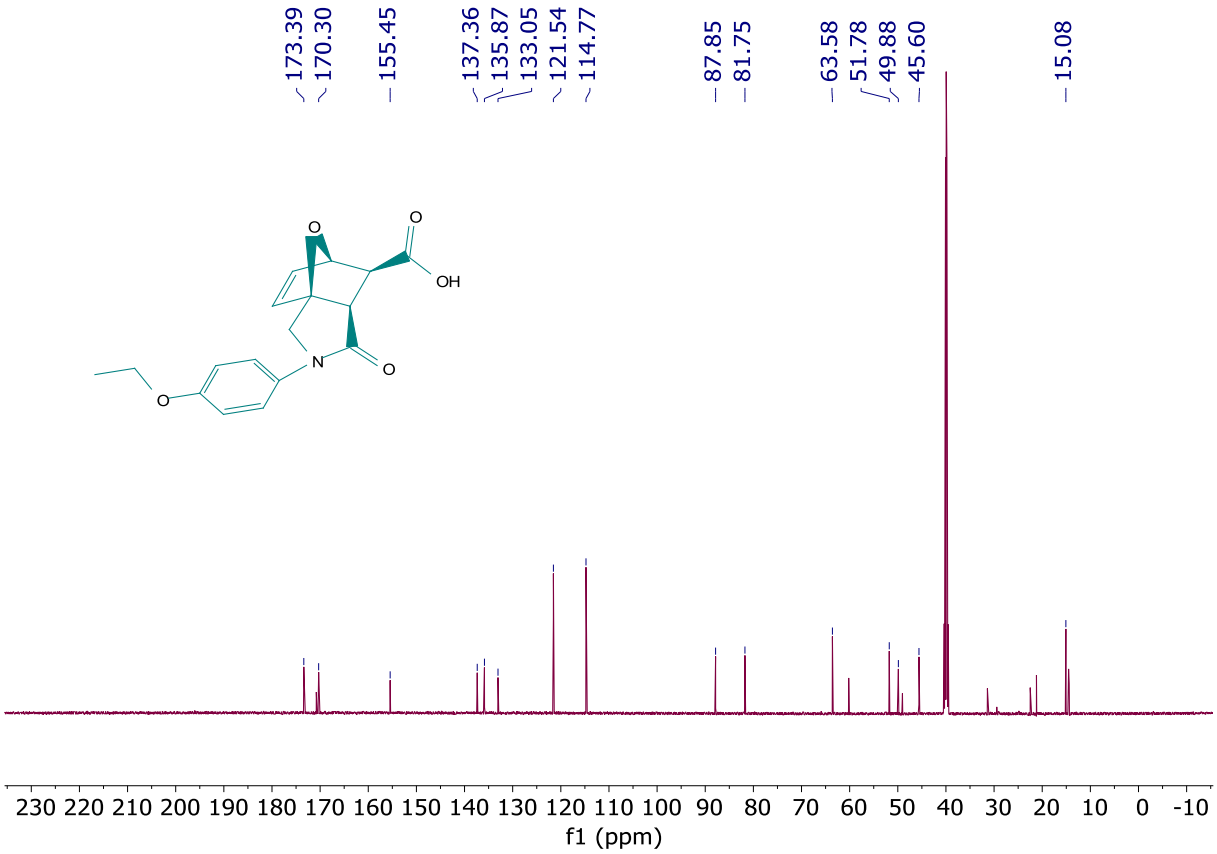
^{13}C NMR spectrum of compound **2j**



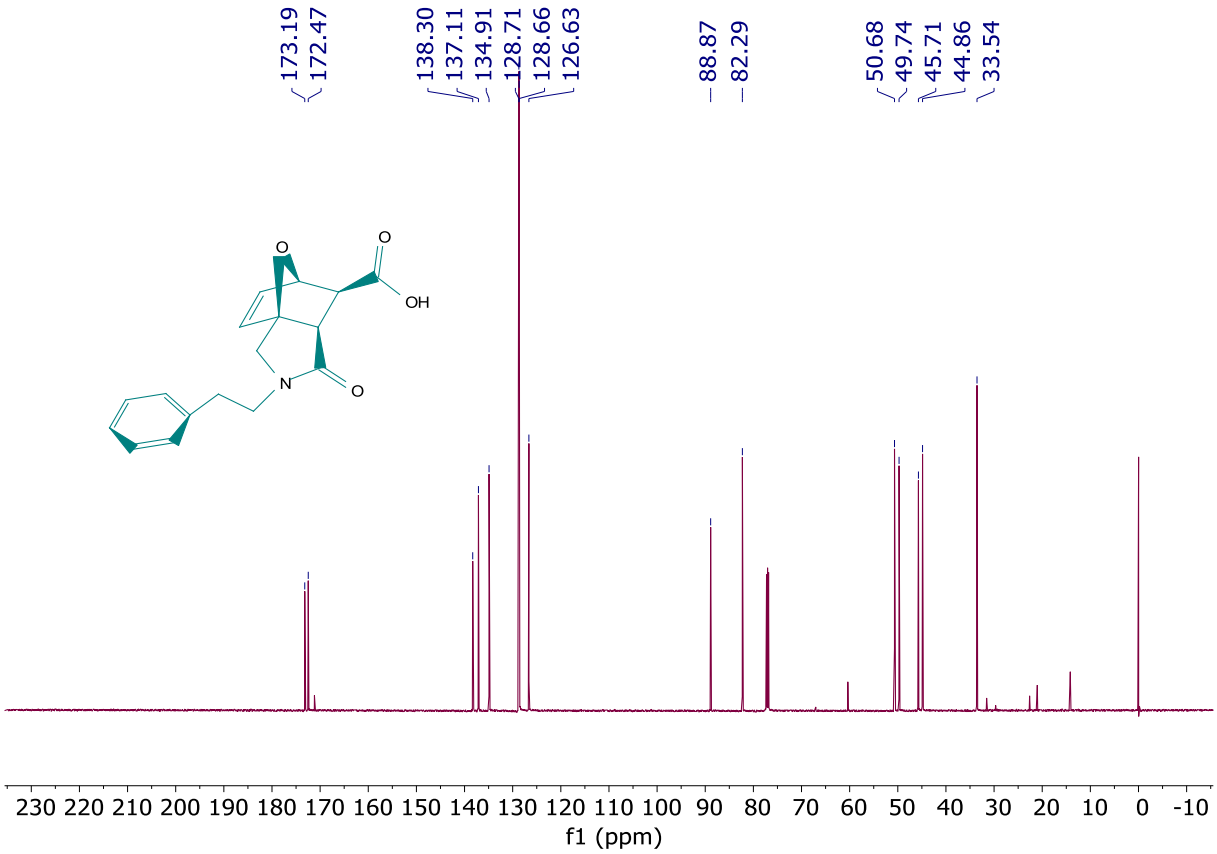
^{13}C NMR spectrum of compound **2k**



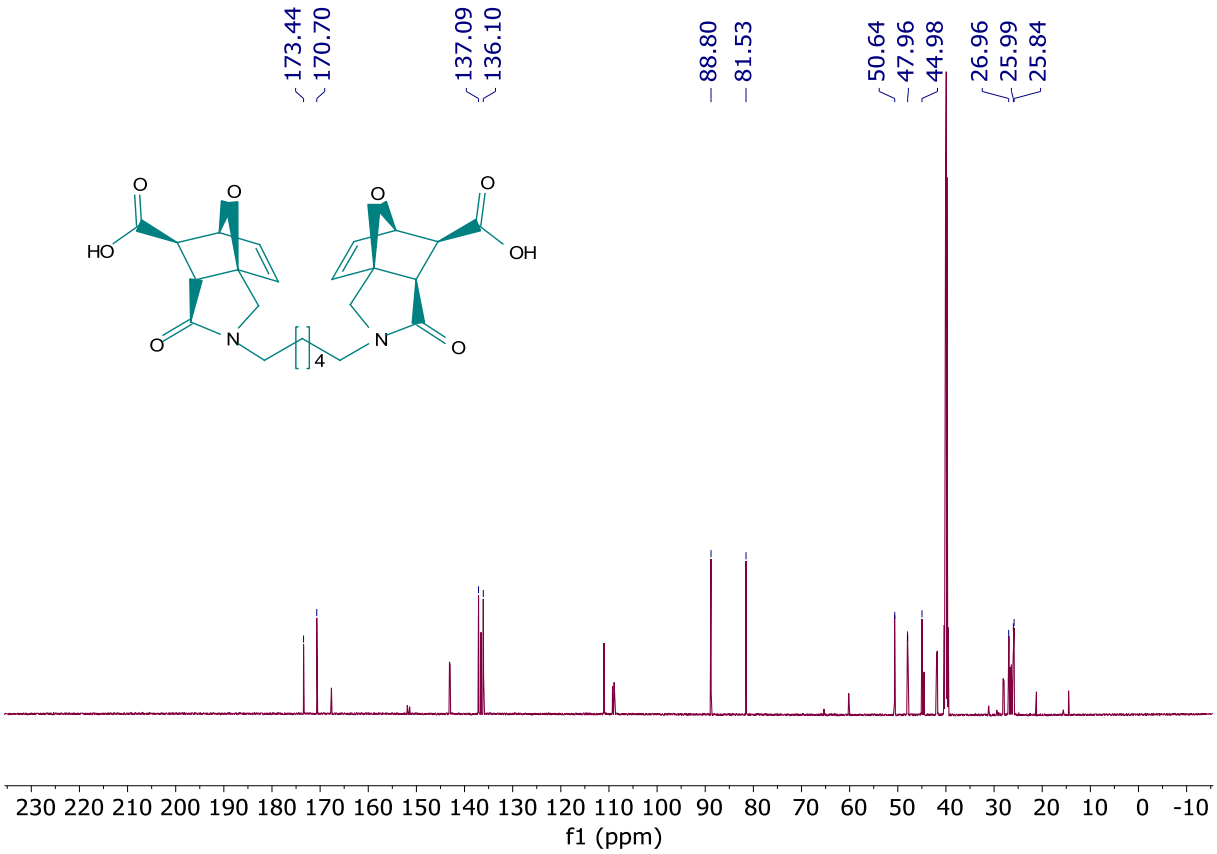
^{13}C NMR spectrum of compound **2l**



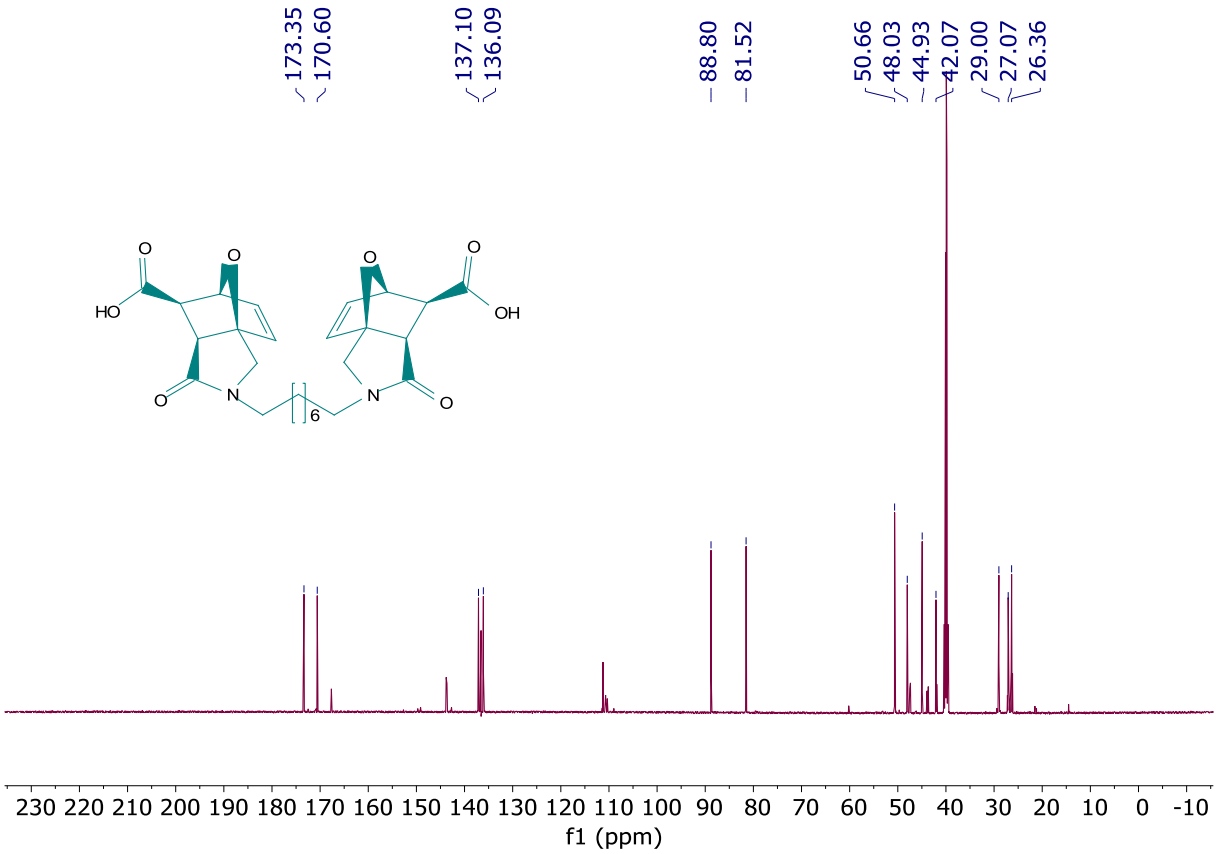
^{13}C NMR spectrum of compound **2m**



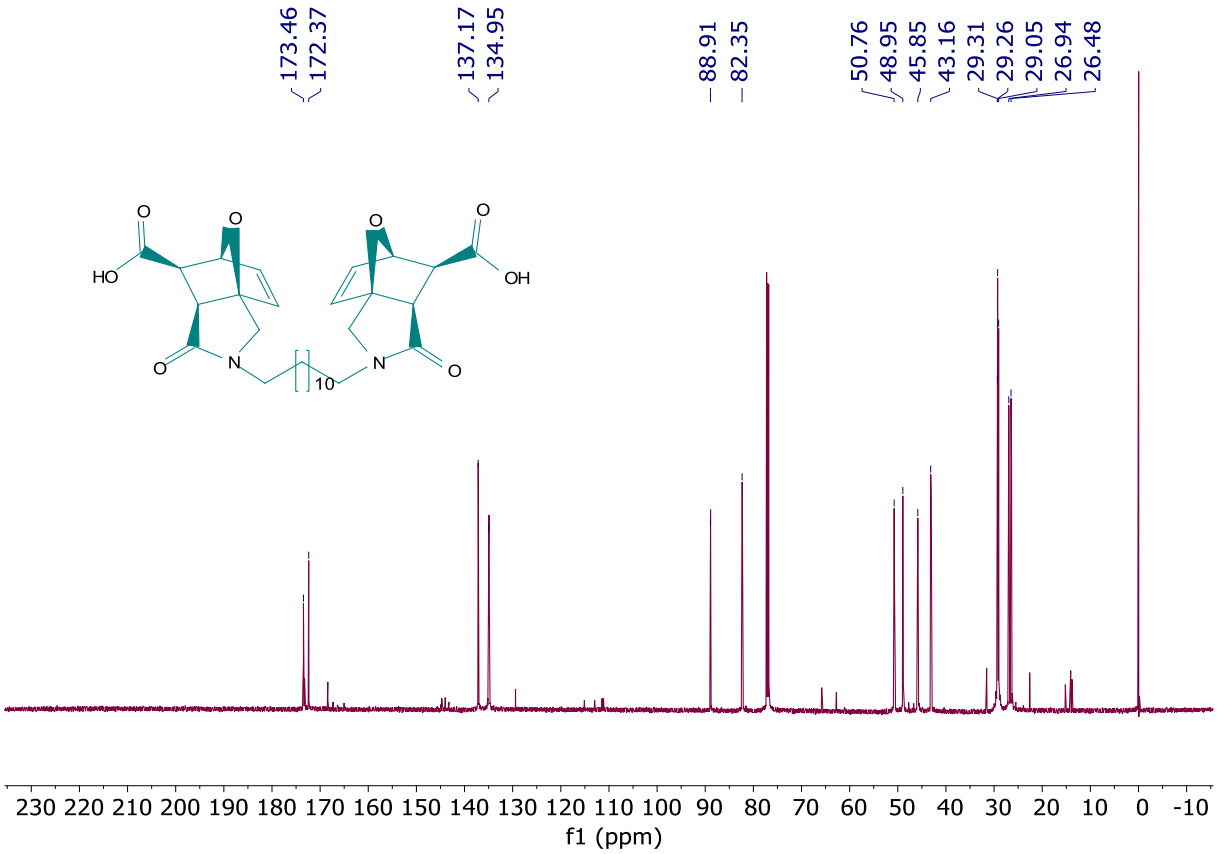
^{13}C NMR spectrum of compound **2n**



^{13}C NMR spectrum of compound **2o**



^{13}C NMR spectrum of compound **2p**



Endo reactant

0 1

C	-0.68105319	-0.42057247	-4.11655978
C	0.67717376	-0.61758367	-3.41798477
C	2.20217097	-0.68078790	-0.38879074
C	1.03385670	1.28062232	-0.51828232
C	1.15126655	0.25597251	0.26261424
C	2.00261092	0.95440145	-1.61502520
C	0.72519654	-1.78751769	-2.40935384
O	3.15491965	0.23470299	-0.94739991
O	-1.05028924	0.73221371	-4.46057830
O	-1.52266159	-1.54759791	-4.37436038
C	2.23788731	-1.94945660	0.28603198
C	-0.14091623	-2.09482392	-1.11056701
N	0.80701641	-2.90980363	0.11435415
O	-1.39120403	-2.01085108	-1.22567187
C	-0.18900290	-2.77756389	1.70676446
C	-0.16008257	-3.91513651	2.74441710
C	-0.10595988	-6.05373890	4.69522228
C	0.94594425	-3.95267374	3.81538034
C	-1.10798220	-4.88319819	2.71510692
C	-1.07921688	-6.02073575	3.75275397
C	0.97125142	-4.95369454	4.72854950
H	1.41933988	-0.77081073	-4.17337926
H	0.39064704	2.12997472	-0.41948176
H	0.60640214	0.07592032	1.16572718
H	2.27442299	1.83710026	-2.15529099
H	1.10095772	-2.61627141	-2.97226298
H	-2.44177875	-1.27081862	-4.35853577

H	2.31968236	-1.42768837	1.21660884
H	3.10313300	-2.56825575	0.17057691
H	-1.20041544	-2.58799675	1.41350027
H	0.22965087	-1.89173360	2.13685694
H	-0.08600498	-6.84414607	5.41621417
H	1.69443971	-3.18836860	3.83851036
H	-1.87639970	-4.85716564	1.97096744
H	-1.82768047	-6.78506326	3.72961340
H	1.73966316	-4.97970448	5.47270480

Endo TS

0 1

C	2.56949297	-0.03606042	0.89292158
C	1.35625953	0.09799597	1.66514517
C	1.95536874	0.94378641	4.01274227
C	3.10498688	-0.97728403	3.55171276
C	3.28364420	0.37019541	3.79190636
C	1.71067887	-1.23145297	3.69421548
C	1.11973698	1.22946305	2.48168094
O	1.09494876	-0.19205110	4.34592178
O	3.63339071	0.55447160	0.96286120
O	2.46222354	-1.07275396	-0.02478465
C	1.76002894	2.27773734	4.69238106
C	1.62892495	2.64682886	2.27555887
N	1.79862964	3.26242858	3.56219574
O	1.74617124	3.26272424	1.24570507
C	2.71984396	4.41766875	3.68779130
C	4.16814728	4.00964918	3.83127399
C	6.85320193	3.25532162	4.09453193
C	4.86938450	4.30687862	5.00761662
C	4.81512036	3.33458672	2.78510728
C	6.15309863	2.95749328	2.92013701
C	6.21048664	3.93145142	5.13569059
H	0.53789030	-0.56938396	1.41223471
H	3.84736140	-1.69915042	3.25260102
H	4.19355453	0.94887153	3.72065187
H	1.11298832	-2.11471683	3.58174209
H	0.04796750	1.29225386	2.80299571
H	3.27919049	-1.16253901	-0.57814799

H	2.54012312	2.48626701	5.45534980
H	0.77056544	2.34957724	5.19848292
H	2.37923655	5.03963539	4.54572322
H	2.59267521	5.05102584	2.77044431
H	7.89713445	2.96457035	4.19487782
H	4.37872286	4.83689506	5.82121173
H	4.27571472	3.09713283	1.86110073
H	6.64941974	2.43187549	2.10395399
H	6.75468215	4.16886387	6.04812797

Endo product

0 1

C	-0.02653584	0.15567848	-3.26308240
C	1.18873004	-0.42703240	-2.51798048
C	1.58884181	-1.59877832	-0.56364500
C	0.72178144	0.47077928	-0.19907896
C	0.62582889	-0.73219852	0.28058230
C	1.75978767	0.30967281	-1.27701791
C	0.96282978	-1.82182629	-1.89921826
O	2.71558141	-0.73057451	-0.74925765
O	-0.21130984	1.40017132	-3.28890296
O	-0.94502655	-0.71742925	-3.92562122
C	1.59102231	-2.96353643	0.00459331
C	-0.31471734	-2.40743388	-1.34966937
N	0.09959290	-3.25401072	-0.14356407
O	-1.48290703	-2.20884179	-1.77330197
C	-0.70627668	-2.81486741	1.00475094
C	-0.27258936	-3.59012705	2.26272066
C	0.54274250	-5.04761496	4.62770395
C	0.84573606	-3.03309792	3.16309102
C	-0.87507089	-4.76254117	2.57740808
C	-0.44138316	-5.53780111	3.83537747
C	1.22737918	-3.71532515	4.27010574
H	2.00859800	-0.47227376	-3.20403422
H	0.18327329	1.35017930	0.08651617
H	-0.01679527	-1.06190410	1.07003048
H	2.19986557	1.25499319	-1.51701960
H	1.34428573	-2.51955020	-2.61516010
H	-1.82011206	-0.32268860	-3.92334695

H	1.94422903	-3.05829932	1.01016032
H	2.18933747	-3.60010546	-0.61322449
H	-1.74076586	-3.00453236	0.80787704
H	-0.55970104	-1.76689949	1.16342930
H	0.84406981	-5.58626873	5.50174856
H	1.32142691	-2.10741729	2.91462856
H	-1.65208861	-5.14956834	1.95182560
H	-0.91707085	-6.46348403	4.08383743
H	2.00439586	-3.32829723	4.89568904

Exo reactant

0 1

C	-1.17820105	-1.23217408	-4.05694251
C	-0.77913379	0.04024213	-3.28375272
C	1.52558979	1.28522061	-1.01440636
C	1.66418979	2.81962061	-2.65290636
C	1.63778979	2.74372061	-1.31310636
C	1.62133379	1.40915787	-3.17484728
C	-0.87328979	0.09397939	-1.75019364
O	2.34388979	0.75652061	-2.09840636
O	-1.03230463	-2.19415155	-3.32016370
O	-1.56647570	-1.40957828	-5.33206227
C	1.70179355	0.48812966	0.50614496
C	-0.77057348	-1.20326561	-1.01991228
N	0.62865641	-1.21745628	0.42594412
O	-1.56497348	-2.09536561	-1.27051228
C	0.75645641	-2.26515628	1.41834412
C	0.17185641	-1.85305628	2.74644412
C	-0.93054359	-1.05155628	5.19764412
C	-1.21924359	-1.78695628	2.91514412
C	1.00355641	-1.50715628	3.82084412
C	0.45335641	-1.11025628	5.04104412
C	-1.76674359	-1.38935628	4.13534412
H	-1.37897919	0.79844458	-4.19903091
H	1.68678979	3.71102061	-3.26050636
H	1.62358979	3.56042061	-0.60980636
H	2.10703379	1.24225787	-4.13784728
H	-1.68328979	0.71487939	-1.35049364
H	-1.68611518	-2.37828911	-5.42474739

H	1.33919355	1.09142966	1.34384496
H	2.76039355	0.24252966	0.62884496
H	1.81955641	-2.51355628	1.51434412
H	0.24705641	-3.17025628	1.06714412
H	-1.35784359	-0.74415628	6.14844412
H	-1.88114359	-2.04755628	2.09044412
H	2.08525641	-1.54625628	3.71514412
H	1.10445641	-0.84755628	5.87094412
H	-2.84594359	-1.34465628	4.25574412

Exo TS

0 1

C	0.69460351	0.32751386	0.63243955
C	0.19369104	-0.16994905	1.92314545
C	2.00411275	-0.35500348	3.88841768
C	0.35042481	1.11917008	4.33629712
C	0.99998701	0.00468662	4.84987818
C	1.00321884	1.44586990	3.10649324
C	0.76698338	-1.26131406	2.58543085
O	2.22609855	0.77985224	3.06041605
O	1.67834133	0.08632787	-0.02368892
O	-0.19666040	1.28641230	0.15545271
C	3.15945274	-1.29719849	3.90256113
C	1.80561692	-2.18884907	2.01127252
N	3.02418311	-2.16419141	2.70275480
O	1.60959075	-2.96978918	1.09897063
C	4.12668433	-3.09374328	2.37085417
C	4.08568933	-4.32318320	3.24882316
C	3.98792417	-6.61371732	4.85476617
C	3.08465162	-5.28463026	3.04158381
C	5.03519379	-4.50936999	4.26163605
C	4.98502231	-5.65596804	5.06118542
C	3.03787994	-6.42611938	3.84414998
H	-0.84655713	0.09895536	2.13926755
H	-0.51538646	1.61749937	4.73341690
H	0.75669896	-0.55142970	5.73651279
H	0.93519804	2.30373215	2.46534568
H	0.12463611	-1.80077392	3.30096726
H	0.06778335	1.63276953	-0.73512118

H	3.17601134	-1.91670416	4.83059866
H	4.12699786	-0.73900668	3.85320944
H	5.09907992	-2.55980965	2.45007361
H	4.01704473	-3.38875756	1.29286195
H	3.95159120	-7.50581591	5.47684699
H	2.34605596	-5.13194412	2.24921692
H	5.81647094	-3.77079525	4.42574100
H	5.72637804	-5.80276583	5.84459581
H	2.26225513	-7.17289357	3.68050961

Exo product

0 1

C	-1.41447282	-0.57320259	-2.99072490
C	-0.47252564	0.50691805	-2.42709831
C	1.35533894	0.42819564	-0.99087127
C	1.47756984	2.02617597	-2.52624057
C	1.70538188	1.88524403	-1.22076937
C	0.97418548	0.63584588	-3.00098750
C	-0.10135286	0.16025758	-0.97572353
O	1.78278102	-0.25570216	-2.22575231
O	-1.39707297	-1.73615905	-2.51030834
O	-2.30891061	-0.25463031	-4.06002034
C	1.84042425	-0.25398406	0.27562569
C	-0.03660817	-1.33045956	-0.59755066
N	1.28680151	-1.61569116	0.04294328
O	-0.94540323	-2.17637293	-0.80271564
C	1.20734103	-2.43232988	1.26265113
C	0.32212308	-1.71883951	2.30136219
C	-1.34208676	-0.37747714	4.25413858
C	-1.19432562	-1.98519628	2.33357074
C	0.87760615	-0.85657403	3.18708440
C	-0.00761188	-0.14308328	4.22579515
C	-1.97331746	-1.35732455	3.24763630
H	-0.93768854	1.45942077	-2.57291339
H	1.58929662	2.91358394	-3.11354307
H	2.02988756	2.61874709	-0.51255378
H	1.03483534	0.51468220	-4.06237383
H	-0.73524303	0.64995376	-0.26630061
H	-1.87572888	-0.42209728	-4.90020389

H	1.40592422	0.21602683	1.13306343
H	2.90273979	-0.25737893	0.40358727
H	2.18938747	-2.56923580	1.66482219
H	0.78251005	-3.38558488	1.02659278
H	-1.95714084	0.11825993	4.97584021
H	-1.63290750	-2.66600193	1.63424991
H	1.93124287	-0.67150940	3.16470697
H	0.43097017	0.53772147	4.92511673
H	-3.02695344	-1.54239302	3.27001700