Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

Supporting Information

Radical Addition of Ketones and Cyanide to Olefins via Acid Catalyzed Formation of Intermediate Alkenyl Peroxides

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General Methods

Unless otherwise indicated, all reagents and solvents were purchased from commercial distributors and used as received. Ethanesulfonyl cyanide ($EtSO_2CN$) and Methanesulfonyl cyanide ($MeSO_2CN$) were synthesized according to reported literature procedures with a few modifications using 8.0 equivalent of trifluoroacetic acid anhydride instead of described 10 equivalents.[1]

Solvents (hexanes, ethyl acetate) used for column chromatography were of technical grade and used directly.

TLC was used to check the reactions for full conversion and was performed on Macherey-Nagel Polygram Sil G/UV254 thin layer plates. TLC spots were visualized by UV-light irradiation and staining with a basic $KMnO_4$ solution or an acidic Ceric ammonium molybdate solution and heating.

Routine GC-MS analyses were performed with an Agilent Technologies 7890A GC System equipped with a MN Optima® 5 Accent capillary column (0.32 mm × 30 m × 0.25 μm) and coupled with an Agilent Technologies 5975C VL MSD mass detector.

Flash column chromatography was carried out using Merck Silica Gel 60 (40-63 μm). Yields refer to pure isolated compounds.

^1H and ^{13}C NMR spectra were measured with Bruker AV 500 spectrometers (500 MHz and 125 MHz, respectively). ^{19}F NMR spectra were recorded on Bruker AV 500 spectrometers (470 MHz) and referenced relative to $CFCl_3$. All chemical shifts are given in ppm downfield relative to TMS and were referenced to the solvent residual peaks.[2] ^1H NMR chemical shifts are designated using the following abbreviations as well as their combinations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad signal. For ^{13}C NMR data the following abbreviations are used: p = primary (CH_3), s = secondary (CH_2), t = tertiary (CH), q = quaternary (C).

High resolution mass spectra were recorded with a Bruker APEX III FTICR-MS or a Finnigan SSQ 7000 quadrupole MS or a Finnigan MAT 95 double focusing sector field MS instrument.

High performance liquid chromatography (HPLC) was performed on a Shimadzu LC-20A HPLC-System.

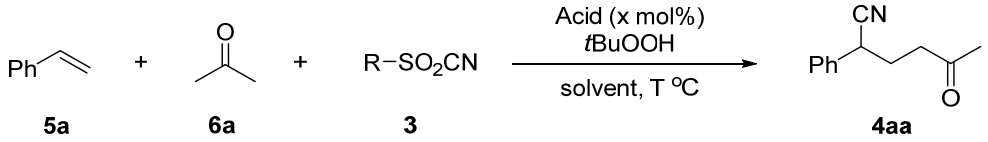
Abbreviations: MsOH: methanesulfonic acid; *p*TSA: paratoluene sulfonic acid; Me: methyl; Et: ethyl; *p*-Tol: *para*-tolyl; *t*Bu: *tert*-butyl; Ph: phenyl; EtOAc: ethyl acetate; *i*PrOAc: isopropyl acetate; DCM: dichloromethane; DCE: 1,2-dichloroethane.

Warning: working with peroxides

Although we never experienced any problem in working with or handling the compounds described in this work, precautions should be taken when working with peroxides. In particular, it should be avoided as much as possible to expose neat peroxides to heat or to mix them with metals or metal salts. Performing such reactions behind a blast shield is recommended.

Variation of Reaction Conditions

Table S1. Effects of Reagents on the Reaction Outcome [a]

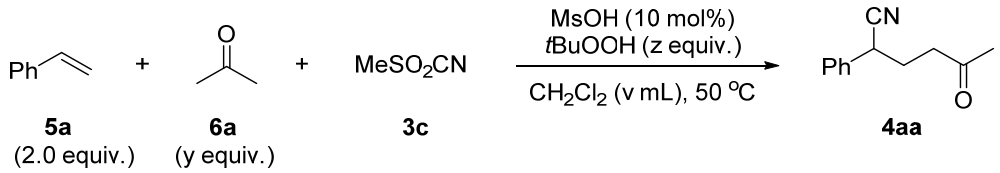


5a **6a** **3** **4aa**

Entry	R	Cat. (x)	T (°C)	Solvent	Yield (%) [b]
1	*p*-Tol	MsOH (10)	50	EtOAc	60
2	*p*-Tol	MsOH (10)	50	*i*PrOAc	57
3	*p*-Tol	MsOH (10)	50	$CHCl_3$	48
4	*p*-Tol	MsOH (10)	50	DCE	61
5	*p*-Tol	MsOH (10)	50	CH_2Cl_2	61
6	*p*-Tol	*p*TSA·H_2O (10)	50	CH_2Cl_2	55
7	*p*-Tol	MsOH (5)	50	CH_2Cl_2	57
8	*p*-Tol	MsOH (20)	50	CH_2Cl_2	51
9	*p*-Tol	MsOH (10)	40	CH_2Cl_2	44
10	*p*-Tol	MsOH (10)	60	CH_2Cl_2	51
11	Et	MsOH (10)	50	CH_2Cl_2	64
12	**Me**	**MsOH (10)**	**50**	**CH_2Cl_2**	**67**
13	Me	MsOH (10)	50	EtOAc	62

[a] All reactions performed on a 0.25 mmol scale: styrene **5a** (0.5 mmol, 2.0 equiv.), acetone **6a** (1.25 mmol, 5.0 equiv.), sulfonyl cyanide **3** (0.25 mmol, 1.0 equiv.), *t*BuOOH (5.5 M solution in decane, 1.0 mmol, 4.0 equiv.) and acid (x mol%) in solvent (0.2 mL), at noted temperature for 20 h. [b] NMR yields using an internal standard.

Table S2. Optimization on the Amount of Reagents [a]



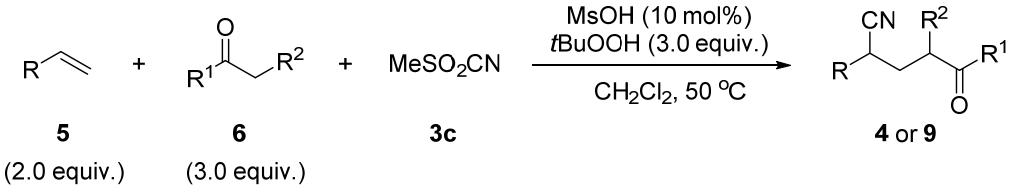
5a (2.0 equiv.) **6a** (y equiv.) **3c** **4aa**

Entry	time (h)	v (mL)	y	z	Yield (%) [b]
1	20	0.2	5	4	67
2	20	0.3	5	4	69
3	20	0.4	5	4	67
4	20	0.3	4	4	70
5 [c]	20	0.3	4	4	57
6	20	0.3	4	3	67
7	20	0.3	3	3	70
8	20	0.3	2	2	44
9	20	0.2	3	3	62
10	20	0.4	3	3	69
11 [d]	20	0.4	3	3	70
12 [d]	20	0.6	3	3	69
13 [d]	7	0.4	3	3	60
14 [d]	12	0.4	3	3	67
15 [d,e]	20	0.8	3	3	68 (62)
16 [e]	20	0.6	3	3	57
17 [e]	20	0.8	3	3	63
18 [e]	**20**	**1.0**	**3**	**3**	**69 (63)**

[a] All reactions performed on a 0.25 mmol scale:: styrene **5a** (0.5 mmol, 2.0 equiv.), acetone **6a** (0.25*y mmol, y equiv.), Methanesulfonyl cyanide **3c** (0.25 mmol, 1.0 equiv.), *t*BuOOH (5.5 M solution in decane, 0.25*z mmol, z equiv.) and MsOH (10 mol%) in CH_2Cl_2 (v mL), at 50 °C for corresponding time. [b] NMR yields using an internal standard, isolated yield in parentheses. [c] 1.5 equivalent of styrene. [d] *t*BuOOH (7.5 M in DCM). [e] 0.5 mmol scale reaction.

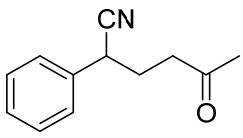
Synthesis of Products

General procedure: Radical Addition of Ketones and Cyanide



In an oven-dried 10 mL of seal tube charged with a magnetic stirring bar, methanesulfonyl cyanide **3c** (0.5 mmol, 1.0 equiv.), olefin **5** (1.0 mmol, 2.0 equiv.), ketone **6** (1.5 mmol, 3.0 equiv. or 0.75 mmol, 1.5 equiv.) and *t*BuOOH (5.5M solution in decane, 1.5 mmol, 3.0 equiv.) were dissolved in dry CH_2Cl_2 (1.0 mL). methanesulfonic acid (0.05 mmol, 10 mol%) was then added under a stream of argon and after sealing the tube, the reaction mixture was allowed to react overnight at 50°C (generally about 20 h). The reaction mixture was then diluted with EtOAc and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel using mixtures of hexanes and ethyl acetate to afford the desired γ-cyanoketones **4** and **9**, respectively, sometimes together with the sulfonyl peroxides **7**.

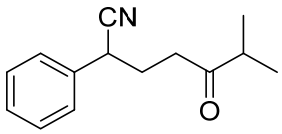
5-Oxo-2-phenylhexanenitrile (4aa)



Synthesized according to the general procedure and a 4/1 mixture of hexane and ethyl acetate for chromatography to afford a mixture of **4aa** and **7ac** (similar R_f value), then the mixture was dissolved in MeCN (1.0 mL), DBU (10 μL) was added as catalyst and the reaction mixture allowed to react overnight at 50 °C to transform **7ac** to 2-(methylsulfonyl)-1-phenylethan-1-one. Solvent was evaporated and the residue directly purified by column chromatography (hexane/ethyl acetate = 4/1) to isolate **4aa** as a pale yellow oil (59.1 mg, 63% yield).

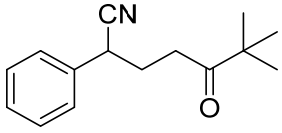
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.28 (m, 2H), 7.28 – 7.22 (m, 3H), 3.88 (dd, *J* = 8.8, 6.2 Hz, 1H), 2.61 (dt, *J* = 18.4, 7.4 Hz, 1H), 2.51 (ddd, *J* = 18.4, 7.4, 5.9 Hz, 1H), 2.16 – 1.99 (m, 2H), 2.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.7, 135.3, 129.2, 128.3, 127.2, 120.4, 39.9, 36.2, 30.1, 29.5; HRMS (EI) calcd for $C_{12}H_{13}NO$ $[M]^+$: 187.099164, Found: 187.099490; HRMS (ESI) calcd for $C_{12}H_{13}NONa$ $[M+Na]^+$: 201.088933, Found: 210.088910.

6-Methyl-5-oxo-2-phenylheptanenitrile (4ab)



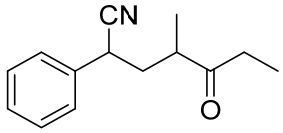
Synthesized according to the general procedure and a 15/1 mixture of hexane and ethyl acetate for chromatography, isolated **4ab** as colorless oil (68.6 mg, 64% yield).
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.23 (m, 5H), 3.88 (dd, *J* = 9.0, 6.1 Hz, 1H), 2.65 (dt, *J* = 18.3, 7.3 Hz, 1H), 2.57 – 2.48 (m, 2H), 2.18 – 2.08 (m, 1H), 2.08 – 1.99 (m, 1H), 1.04 (d, *J* = 7.0 Hz, 3H), 1.02 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.0, 135.4, 129.2, 128.2, 127.2, 120.5, 41.0, 36.7, 36.2, 29.6, 18.3, 18.2; HRMS (ESI) calcd for $C_{14}H_{17}NONa$ $[M+Na]^+$: 238.120233, Found: 238.120280.

6,6-Dimethyl-5-oxo-2-phenylheptanenitrile (4ac)



Synthesized according to the general procedure and a 10/1 mixture of hexane and ethyl acetate for chromatography, isolated **4ac** as colorless oil (69.0 mg, 60% yield).
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.21 (m, 5H), 3.87 (dd, *J* = 9.3, 6.0 Hz, 1H), 2.71 (dt, *J* = 18.3, 7.3 Hz, 1H), 2.55 (dt, *J* = 18.3, 6.3 Hz, 1H), 2.17 – 2.07 (m, 1H), 2.07 – 1.96 (m, 1H), 1.07 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.5, 135.5, 129.1, 128.2, 127.2, 120.5, 44.2, 36.2, 33.2, 29.9, 26.4; HRMS (ESI) calcd for $C_{15}H_{19}NONa$ $[M+Na]^+$: 252.135882, Found: 252.135800.

4-Methyl-5-oxo-2-phenylheptanenitrile (4ad)

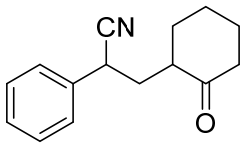


Synthesized according to the general procedure and a 7/1 mixture of hexane and ethyl acetate for chromatography, isolated **4ad** as colorless viscous oil (40.2 mg, 37% yield) in a 1.0:1 dr as determined by crude NMR analysis.

For diastereoisomer 1: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.21 (m, 5H), 3.74 (dd, *J* = 11.0, 5.4 Hz, 1H), 2.95 – 2.80 (m, 1H), 2.57 (dq, *J* = 17.8, 7.3 Hz, 1H), 2.40 (dq, *J* = 17.8, 7.3 Hz, 1H), 2.22 (ddd, *J* = 13.7, 10.3, 5.4 Hz, 1H), 1.70 (ddd, *J* = 13.7, 11.0, 3.8 Hz, 1H), 1.11 (d, *J* = 7.2 Hz, 3H), 1.03 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.7, 135.9, 129.1, 128.1, 127.1, 120.6, 43.8, 38.8, 35.6, 34.9, 18.0, 7.8; HRMS (ESI) $C_{14}H_{17}NONa$ $[M+Na]^+$: calcd for 238.120233, Found: 238.120330.

For diastereoisomer 2: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.28 (m, 2H), 7.28 – 7.23 (m, 1H), 7.23 – 7.19 (m, 2H), 3.77 (dd, *J* = 8.7, 7.3 Hz, 1H), 2.61 – 2.52 (m, 1H), 2.45 (dq, *J* = 17.9, 7.3 Hz, 1H), 2.34 – 2.21 (m, 2H), 1.76 (dt, *J* = 14.1, 7.1 Hz, 1H), 1.10 (d, *J* = 7.1 Hz, 3H), 0.95 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.1, 135.3, 129.2, 128.3, 127.4, 120.5, 43.1, 37.9, 35.0, 34.4, 16.8, 7.7; HRMS (ESI) calcd for $C_{14}H_{17}NONa$ $[M+Na]^+$: 238.120233, Found: 238.120300.

3-(2-Oxocyclohexyl)-2-phenylpropanenitrile (4ae)



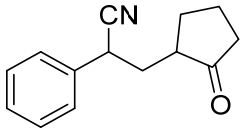
Synthesized according to the general procedure and a 10/1 mixture of hexane and ethyl acetate for chromatography, isolated **4ae** as colorless viscous oil (64.0 mg (40.3 mg + 23.7 mg), 56% yield) in a 2.0:1 dr as determined by crude NMR analysis.

For major diastereoisomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.20 (m, 5H), 4.09 (dd, *J* = 11.4, 4.9 Hz, 1H), 2.70 – 2.57 (m, 1H), 2.41 – 2.29 (m, 2H), 2.18 (ddd, *J* = 13.8, 10.1, 4.9 Hz, 1H), 2.11 – 2.00 (m, 2H), 1.87 – 1.78 (m, 1H), 1.69 (ddt, *J* = 13.5, 12.5,

3.5 Hz, 1H), 1.63 – 1.51 (m, 2H), 1.33 (ddd, *J* = 13.0, 12.5, 3.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.3, 136.3, 129.1, 128.0, 127.1, 121.0, 48.4, 42.4, 37.2, 35.8, 35.2, 28.2, 25.3; HRMS (ESI) calcd for $C_{15}H_{17}NONa$ $[M+Na]^+$: 250.120233, Found: 250.120140.

For minor diastereoisomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.19 (m, 5H), 3.92 (t, *J* = 8.1 Hz, 1H), 2.42 (ddd, *J* = 14.1, 8.1, 7.0 Hz, 1H), 2.37 – 2.31 (m, 1H), 2.28 – 2.14 (m, 2H), 2.10 – 1.98 (m, 2H), 1.85 – 1.76 (m, 1H), 1.64 (ddd, *J* = 14.2, 8.0, 6.4 Hz, 1H), 1.61 – 1.50 (m, 2H), 1.35 (ddd, *J* = 13.0, 12.6, 3.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.7, 135.5, 129.2, 128.2, 127.4, 120.9, 47.3, 42.2, 35.6, 34.4, 34.0, 27.8, 25.1; HRMS (ESI) calcd for $C_{15}H_{17}NONa$ $[M+Na]^+$: 250.120233, Found: 250.120010.

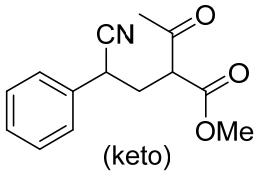
3-(2-Oxocyclopentyl)-2-phenylpropanenitrile (4af)



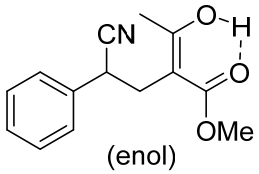
Synthesized according to the general procedure and a 6/1 mixture of hexane and ethyl acetate for chromatography, isolated **4af** as colorless viscous oil (53.5 mg, 50% yield) in a 1.0:1 dr as determined by crude NMR analysis.

^{1}H NMR (500 MHz, $CDCl_3$, 2 diastereoisomers) δ 7.36 – 7.22 (m, 5H), 4.16 (dd, *J* = 9.6, 6.2 Hz, 1H, diastereoisomer 1), 4.01 (dd, *J* = 8.4, 7.1 Hz, 1H, diastereoisomer 2), 2.36 (ddd, *J* = 14.1, 8.5, 5.7 Hz, 1H, diastereoisomer 1), 2.32 – 2.15 (m, 3H, 2H + diastereoisomer 2), 2.15 – 2.01 (m, 2H), 2.01 – 1.91 (m, 1H), 1.84 (ddd, *J* = 13.7, 9.5, 6.3 Hz, 1H, diastereoisomer 1), 1.79 – 1.66 (m, 2H, 1H + diastereoisomer 2), 1.53– 1.41 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (219.7, 219.4), (135.7, 135.2), 129.2, (128.3, 128.3), (127.5, 127.3), (120.9, 120.5), (46.6, 46.1), 37.8, (36.5, 35.9), (35.7, 35.0), (30.1, 29.8), 20.6; HRMS (ESI) calcd for $C_{14}H_{15}NONa$ $[M+Na]^+$: 236.104583, Found: 236.104490.

Methyl 2-acetyl-4-cyano-4-phenylbutanoate (4ag)



(keto)

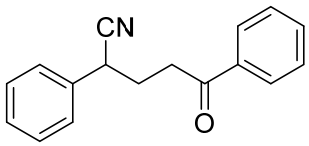


(enol)

Synthesized according to the general procedure and a 6/1 mixture of hexane and ethyl acetate for chromatography, isolated **4ag** as colorless viscous oil (45.1 mg, 37% yield) in a 1.0:1 dr as determined by crude NMR analysis. On the NMR timescale, **4ag** was observed as a mixture of the two components of a keto-enol equilibrium in a 83:17 ratio in $CDCl_3$.

^{1}H NMR (500 MHz, $CDCl_3$, keto: 2 diastereoisomers) δ 7.50 – 7.21 (m, 5H), 3.90 – 3.78 (m, 1H), 3.72 (s, 3H, diastereoisomer 1), 3.67 (s, 3H, diastereoisomer 2), 3.65 – 3.59 (m, 1H), 2.46 – 2.25 (m, 2H), 2.23 (s, 3H, diastereoisomer 1), 2.19 (s, 3H, diastereoisomer 2); ^{1}H NMR (500 MHz, $CDCl_3$, enol) 7.50 – 7.21 (m, 5H), 3.90 – 3.78 (m, 1H), 3.73 (s, 3H), 2.80 (dd, *J* = 14.6, 8.3 Hz, 1H), 2.63 (dd, *J* = 14.6, 7.0 Hz, 1H), 1.78 (s, 3H), 1.27 (d, *J* = 1.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, keto: 2 diastereoisomers) δ (201.2, 201.0), (168.9, 168.7), (134.7, 134.6), (129.33, 129.29), (128.6, 128.5), (127.31, 127.30), (119.92, 119.90), (56.42, 56.40), (52.93, 52.90), (35.12, 35.07), (33.56, 33.44), (29.8, 29.5); ^{13}C NMR (125 MHz, $CDCl_3$, enol) δ 175.9, 172.7, 135.4, 129.1, 128.2, 127.4, 120.7, 95.8, 51.9, 37.7, 33.6, 18.9; HRMS (ESI) calcd for $C_{14}H_{15}NO_3Na$ $[M+Na]^+$: 268.094413, Found: 268.094370.

5-Oxo-2,5-diphenylpentanenitrile (4ah)

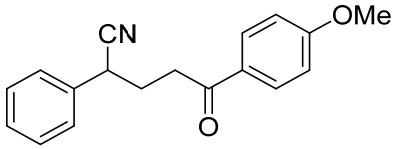


Synthesized according to the general procedure and a 8/1 mixture of hexane and ethyl acetate for chromatography, isolated **4ah** as colorless viscous oil (73.5 mg, 59% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 – 7.81 (m, 2H), 7.52 – 7.46 (m, 1H), 7.42 – 7.35

(m, 2H), 7.34 – 7.21 (m, 5H), 3.98 (dd, *J* = 8.9, 6.1 Hz, 1H), 3.15 (dt, *J* = 18.0, 7.3 Hz, 1H), 3.04 (ddd, *J* = 18.0, 7.3, 5.9 Hz, 1H), 2.36 – 2.27 (m, 1H), 2.27 – 2.18 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.2, 136.5, 135.4, 133.5, 129.2, 128.7, 128.3, 128.0, 127.3, 120.6, 36.4, 35.1, 30.0; HRMS (ESI) calcd for $C_{17}H_{15}NONa$ $[M+Na]^+$: 272.104583, Found: 272.104380.

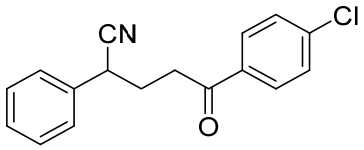
5-(4-Methoxyphenyl)-5-oxo-2-phenylpentanenitrile (4ai)



Synthesized according to the general procedure and a 7/1 mixture of hexane and ethyl acetate for chromatography, isolated **4ai** as pale yellow viscous oil (100.7 mg, 72% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.9 Hz, 2H), 7.35 – 7.23 (m, 5H), 6.86 (d, *J* = 8.9 Hz, 2H), 3.98 (dd, *J* = 9.0, 6.1 Hz, 1H), 3.79 (s, 3H), 3.11 (dt, *J* = 17.7, 7.3 Hz, 1H), 2.99 (ddd, *J* = 17.7, 7.2, 5.9 Hz, 1H), 2.29 (dt, *J* = 13.4, 6.8 Hz, 1H), 2.26 – 2.16 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.7, 163.8, 135.5, 130.3, 129.6, 129.2, 128.2, 127.3, 120.7, 113.9, 55.5, 36.5, 34.7, 30.2; HRMS (ESI) calcd for $C_{18}H_{17}NO_2Na$ $[M+Na]^+$: 302.115148, Found: 302.114830.

5-(4-Chlorophenyl)-5-oxo-2-phenylpentanenitrile (4aj)

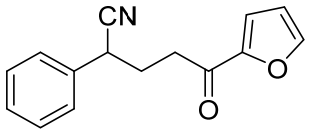


Synthesized according to the general procedure and a 10/1 mixture of hexane and ethyl acetate for chromatography, isolated **4aj** as colorless viscous oil (76.0 mg, 54% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.6 Hz, 2H), 7.36 (d, *J* = 8.6 Hz, 2H), 7.34 – 7.24 (m, 5H), 3.98 (dd, *J* = 8.9, 6.1 Hz, 1H), 3.12 (dt, *J* = 18.0, 7.3 Hz, 1H), 3.01 (ddd, *J*

= 18.1, 7.3, 5.9 Hz, 1H), 2.30 (dt, *J* = 13.5, 6.9 Hz, 1H), 2.27 – 2.18 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.0, 140.0, 135.2, 134.7, 129.4, 129.2, 129.1, 128.3, 127.3, 120.5, 36.4, 35.1, 29.9; HRMS (ESI) calcd for $C_{17}H_{14}NOClNa$ $[M+Na]^+$: 306.065611, Found: 306.065510.

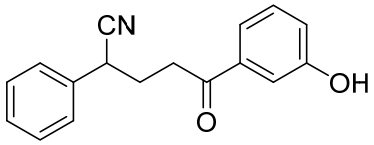
5-(Furan-2-yl)-5-oxo-2-phenylpentanenitrile (4ak)



Synthesized according to the general procedure and a 6/1 mixture of hexane and ethyl acetate for chromatography, isolated **4ak** as colorless viscous oil (43.2 mg, 36% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (dd, *J* = 1.6, 0.7 Hz, 1H), 7.35 – 7.24 (m, 5H), 7.13 (dd, *J* = 3.6, 0.6 Hz, 1H), 6.47 (dd, *J* = 3.6, 1.7 Hz, 1H), 3.95 (dd, *J* = 8.9, 6.2 Hz, 1H), 3.03 (dt, *J* = 17.6, 7.5 Hz, 1H), 2.91 (ddd, *J* = 17.6, 7.5, 5.9 Hz, 1H), 2.33 – 2.17 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.3, 152.3, 146.6, 135.2, 129.2, 128.3, 127.3, 120.4, 117.4, 112.4, 36.4, 34.9, 29.7; HRMS (ESI) calcd for $C_{15}H_{13}NO_2Na$ $[M+Na]^+$: 262.08348, Found: 262.083900.

5-(3-Hydroxyphenyl)-5-oxo-2-phenylpentanenitrile (4al)

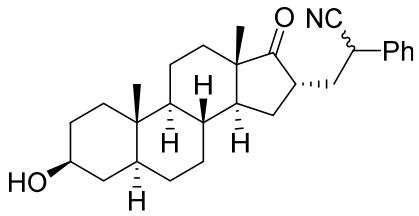


Synthesized according to the general procedure and a 4/1 mixture of hexane and ethyl acetate for chromatography, isolated **4al** as light yellow viscous oil (67.6 mg, 51% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.37 (m, 2H), 7.34 – 7.21 (m, 6H), 7.03 – 6.99 (ddd, *J* = 8.0, 2.5, 0.5 Hz 1H), 6.36 (s, 1H), 3.97 (dd, *J* = 8.8, 6.1 Hz, 1H), 3.12 (dt, *J* = 18.0, 7.3 Hz, 1H), 3.02 (ddd, *J* = 18.0, 7.5, 5.9 Hz, 1H), 2.34 – 2.17 (m, 2H); ^{13}C NMR

(125 MHz, $CDCl_3$) δ 198.8, 156.4, 137.7, 135.1, 130.1, 129.3, 128.4, 127.3, 121.0, 120.6, 120.5, 114.5, 36.4, 35.3, 30.0; HRMS (ESI) calcd for $C_{17}H_{15}NO_2Na$ $[M+Na]^+$: 288.099498, Found: 288.099560.

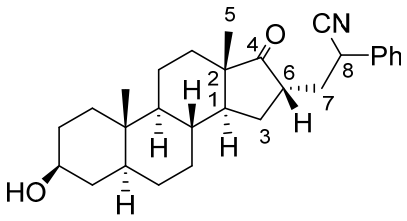
3-((3*S*,5*S*,8*R*,9*S*,10*S*,13*S*,14*S*,16*S*)-3-Hydroxy-10,13-dimethyl-17-oxohexadecahydro-1*H*-cyclopenta[*a*]phenanthren-16-yl)-2-phenylpropanenitrile (4am)



Synthesized according to the general procedure using 1.5 equivalent of Epiandrosterone as ketone and a 2/1 mixture of hexane and ethyl acetate for chromatography affording a mixture containing some impurities, using preparative HPLC isolated **4am** as white solid (23 mg, 11% yield) in a 1.2:1 dr as determined by crude NMR analysis.

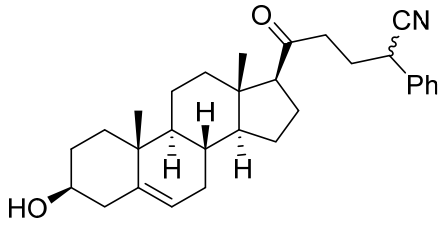
^{1}H NMR (500 MHz, $CDCl_3$, 2 diastereoisomers) δ 7.34 – 7.22 (m, 5H), 4.17 (dd, *J* = 9.5, 6.5 Hz, 1H, minor), 4.02 (dd, *J* = 8.6, 7.1 Hz, 1H, major), 3.59 – 3.46 (m, 1H), 2.59 – 2.42 (m, 1H), 2.31 (ddd, *J* = 14.4, 8.7, 6.0 Hz, 1H, major), 2.07 (dt, *J* = 14.2, 7.2 Hz, 1H, minor), 1.88 – 1.46 (m, 11H), 1.36 – 1.13 (m, 7H), 1.10 – 1.00 (m, 1H), 0.96 – 0.81 (m, 2H), 0.84 (s, 3H, minor), 0.83 (s, 3H, major), 0.76 (s, 3H), 0.65 – 0.55 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, 2 diastereoisomers) δ 220.97 (C, minor), 220.53 (C, major), 135.62 (Ar q, minor), 135.27 (Ar q, major), 129.19 (2 Ar CH, minor), 129.17 (2 Ar CH, major), 128.28 (Ar CH, major), 128.24 (Ar CH, minor), 127.57 (2 Ar CH, major), 127.36 (2 Ar CH, minor), 120.91 (CN, minor), 120.58 (CN, major), 71.10 (CH, major + minor), 54.45 (CH, major), 54.43 (CH, minor), 49.26 (CH, major), 49.19 (CH, minor), 48.79 (C, minor), 48.65 (C, major), 44.81 (CH, major + minor), 41.76 (CH, minor), 41.45 (CH, major), 38.28 (CH_2, minor) 38.02 (CH_2, major + minor), 37.31 (CH_2, major), 36.91 (CH_2, major + minor), 36.26 (CH, minor), 35.64 (C, major + minor), 35.46 (CH, major), 34.95 (CH, minor), 34.93 (CH, major), 31.68 (CH_2, major + minor), 31.40 (CH_2,

major + minor), 30.76 (CH_2, major), 30.74 (CH_2, minor), 28.58 (CH_2, minor), 28.29 (CH_2, major + minor), 27.92 (CH_2, major), 20.34 (CH_2, major + minor), 14.405 (CH_3, major), 14.395 (CH_3, minor), 12.30 (CH_3, major + minor); HRMS (ESI) calcd for $C_{28}H_{37}NO_2Na$ $[M+Na]^+$: 442.271648, Found: 442.271540.



Configuration at carbon no. 6: A NOESY experiment of the diastereoisomeric mixture showed for both molecules a cross signal of the proton bond to carbon no. 6 with the protons bond to carbon no. 5. This shows in each case a spatial orientation of the named protons to the same face of the molecule and a (*S*)-configuration for the isolated diastereoisomers at carbon no. 6. Since all other stereogenic centers are dictated by the starting material, the two diastereoisomeres differ in the configuration at carbon no. 8.

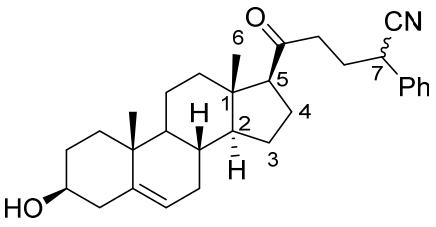
5-((3*S*,8*S*,9*S*,10*R*,13*S*,14*S*,17*S*)-3-Hydroxy-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl)-5-oxo-2-phenylpentanenitrile (4an)



Synthesized according to the general procedure using 1.5 equivalent of Pregnenolone as ketone and a 4/1 mixture of hexane and ethyl acetate for chromatography, isolated **4an** as white solid (95.6 mg, 43% yield) in a 1.1:1 dr as determined by crude NMR analysis.

^{1}H NMR (500 MHz, $CDCl_3$, 2 diastereoisomers) δ 7.28 (m, 5H), 5.34 – 5.20 (m, 1H), 3.91 (ddd, J = 14.1, 9.3, 5.9 Hz, 1H), 3.45 (ddd, *J* = 11.3, 6.7, 4.8 Hz, 1H), 2.66 – 2.51 (m, 1H), 2.50 – 2.39 (m, 2H), 2.26 – 1.89 (m, 7H), 1.83 – 1.74 (m, 3H), 1.66 – 1.28 (m,

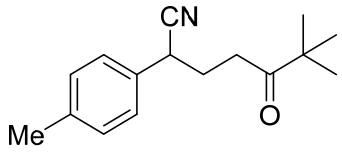
10H), 1.21 – 0.97 (m, 4H), 0.95 – 0.87 (m, 4H, CH_3 + 1H) 0.56 (s, 3H, diastereoisomer 1), 0.52 (s, 3H, diastereoisomer 2); ^{13}C NMR (125 MHz, $CDCl_3$, 2 diastereoisomers) δ 209.76 (C, minor), 209.73 (C, major), 140.83 (CH=*C*, minor), 140.77(CH=*C*, major), 135.49 (Ar q, minor), 135.42 (Ar q, major), 129.14 (Ar CH) 128.21 (Ar CH, major), 128.18 (Ar CH, minor), 127.26 (Ar CH, major), 127.21 (Ar CH, minor), 121.32 (*C*H=C, major), 121.29 (*C*H=C, minor), 120.56 (CN, minor), 120.55 (CN, major), 71.68 (CH, minor), 71.66 (CH, major), 63.14 (CH, major), 62.95 (CH, minor), 56.98 (CH, minor), 56.90 (CH, major), 49.96 (CH, minor), 49.93 (CH, major), 44.39 (CH, minor), 44.31 (CH, major), 42.23 (CH_2), 40.75 (CH_2, minor), 40.66 (CH_2, major), 38.86 (CH_2, minor), 38.78 (CH_2, major), 37.25 (CH_2), 36.53 (C, major), 36.51 (C, minor), 36.32 (CH, major), 36.29 (CH, minor), 31.87 (CH, minor), 31.86 (CH, major), 31.77 (CH_2, minor), 31.75 (CH_2, major), 31.62 (CH_2, minor), 31.59 (CH_2, major), 29.80 (CH_2, minor), 29.72 (CH_2, major), 24.52 (CH, minor), 24.50 (CH, major), 23.01 (CH, minor), 22.99 (CH, major), 21.12 (CH, minor), 21.05 (CH, major), 19.39 (CH_3), 13.47(CH_3, minor), 13.39 (CH_3, major); HRMS (ESI) calcd for $C_{30}H_{39}NO_2Na$ $[M+Na]^+$: 468.287298, Found: 468.287200.



Configuration at carbon no.5: In a NOESY experiment for the minor diastereoisomere a cross signal was found for the proton bond to carbon no. 2 (1.12-1.17 ppm) with the proton bond to carbon no. 5 (2.46-2.51 ppm). This proves that the mentioned protons are on the same face of the cyclopentane ring (configuration at carbon no. 2, given by starting material). In the major diastereomer, this cross signal was not unambigously detectable due to overlapping with other peaks. However, the chemical shifts of carbon no. 5 in both diastereomers are not differing very much (63.14 ppm vs. 62.95 ppm). This suggests the same configuration for both diastereoisomers at carbon no. 5 and leads to the conclusion that **no** epimerization at this α-position of the carbonyl group occured during formation and isolation of the compounds. The two diastereomers thus differ in the configuration

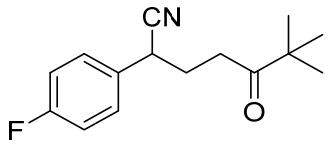
at carbon no. 7, which could not be determined for either diastereoisomers by NMR means.

6,6-Dimethyl-5-oxo-2-(*p*-tolyl)heptanenitrile (4bc)



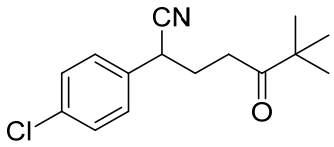
Synthesized according to the general procedure and a 15/1 mixture of hexane and ethyl acetate for chromatography, isolated **4bc** as colorless oil (77.7 mg, 64% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (d, *J* = 8.1 Hz, 2H), 7.11 (d, *J* = 8.0 Hz, 2H), 3.82 (dd, *J* = 9.2, 6.1 Hz, 1H), 2.70 (dt, *J* = 18.3, 7.3 Hz, 1H), 2.54 (ddd, *J* = 18.3, 6.8, 6.0 Hz, 1H), 2.27 (s, 3H), 2.13 – 2.05 (m, 1H), 2.04 – 1.96 (m, 1H), 1.07 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.5, 138.0, 132.5, 129.8, 127.1, 120.7, 44.2, 35.8, 33.2, 29.9, 26.4, 21.1; HRMS (ESI) calcd for $C_{16}H_{21}NONa$ $[M+Na]^+$: 266.151533, Found: 266.151430.

2-(4-Fluorophenyl)-6,6-dimethyl-5-oxoheptanenitrile (4cc)



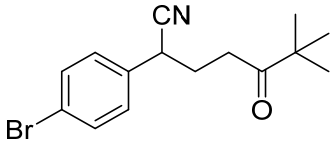
Synthesized according to the general procedure and a 15/1 mixture of hexane and ethyl acetate for chromatography, isolated **4cc** as colorless oil (67.9 mg, 55% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.21 (m, 2H), 7.04 – 6.97 (m, 2H), 3.87 (dd, *J* = 9.5, 5.9 Hz, 1H), 2.72 (ddd, *J* = 18.3, 7.7, 6.8 Hz, 1H), 2.56 (dt, *J* = 18.3, 6.2 Hz, 1H), 2.14 – 2.05 (m, 1H), 2.04 – 1.94 (m, 1H), 1.08 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.4, 162.4 (d, *J* = 247.5 Hz), 131.4 (d, *J* = 3.3 Hz), 128.9 (d, *J* = 8.3 Hz), 120.4, 116.1 (d, *J* = 21.8 Hz), 44.2, 35.5, 33.1, 30.0, 26.4; ^{19}F NMR (470 MHz, $CDCl_3$) δ -113.6; HRMS (ESI) calcd for $C_{15}H_{18}FNONa$ $[M+Na]^+$: 270.126461, Found: 270.126270.

2-(4-Chlorophenyl)-6,6-dimethyl-5-oxoheptanenitrile (4dc)



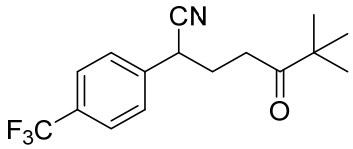
Synthesized according to the general procedure and a 15/1 mixture of hexane and ethyl acetate for chromatography, isolated **4dc** as colorless oil (72.1 mg, 55% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.5 Hz, 2H), 7.22 (d, *J* = 8.5 Hz, 2H), 2.73 (ddd, *J* = 18.4, 7.8, 6.7 Hz, 1H), 2.55 (dt, *J* = 18.4, 6.1 Hz, 1H), 2.15 – 2.04 (m, 1H), 2.03 – 1.94 (m, 1H), 1.08 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.4, 134.2, 134.1, 129.3, 128.6, 120.1, 44.2, 35.7, 33.1, 29.9, 26.4; HRMS (ESI) calcd for $C_{15}H_{18}ClNONa$ $[M+Na]^+$: 286.096911, Found: 286.096800.

2-(4-Bromophenyl)-6,6-dimethyl-5-oxoheptanenitrile (4ec)



Synthesized according to the general procedure and a 15/1 mixture of hexane and ethyl acetate for chromatography, isolated **4ec** as colorless oil (81.3 mg, 53% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.4 Hz, 2H), 7.16 (d, *J* = 8.4 Hz, 2H), 3.85 (dd, *J* = 9.5, 5.8 Hz, 1H), 2.73 (ddd, *J* = 18.4, 7.8, 6.7 Hz, 1H), 2.55 (dt, *J* = 18.4, 6.1 Hz, 1H), 2.15 – 2.04 (m, 1H), 2.02 – 1.93 (m, 1H), 1.08 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.4, 134.6, 132.3, 128.9, 122.3, 120.0, 44.2, 35.7, 33.1, 29.9, 26.4; HRMS (ESI) calcd for $C_{15}H_{18}BrNONa$ $[M+Na]^+$: 330.046408, Found: 330.046270.

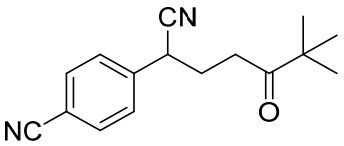
6,6-Dimethyl-5-oxo-2-(4-(trifluoromethyl)phenyl)heptanenitrile (4fc)



Synthesized according to the general procedure and a 15/1 mixture of hexane and ethyl acetate for chromatography, isolated **4fc** as white solid (51.8 mg, 35% yield).

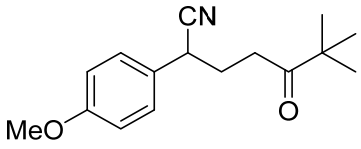
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.1 Hz, 2H), 7.43 (d, *J* = 8.1 Hz, 2H), 3.97 (dd, *J* = 9.8, 5.6 Hz, 1H), 2.77 (ddd, *J* = 18.4, 8.1, 6.4 Hz, 1H), 2.59 (dt, *J* = 18.4, 6.0 Hz, 1H), 2.19 – 2.09 (m, 1H), 2.05 – 1.94 (m, 1H), 1.09 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.4, 139.6, 130.6 (q, *J* = 32.8 Hz), 127.7, 126.2 (q, *J* = 3.7 Hz), 123.8 (q, *J* = 272.2 Hz), 119.7, 44.2, 36.1, 33.1, 29.9, 26.4; ^{19}F NMR (470 MHz, $CDCl_3$) δ -62.7; HRMS (ESI) calcd for $C_{16}H_{18}F_3NONa$ $[M+Na]^+$: 320.123268, Found: 320.123080.

4-(1-Cyano-5,5-dimethyl-4-oxohexyl)benzonitrile (4gc)



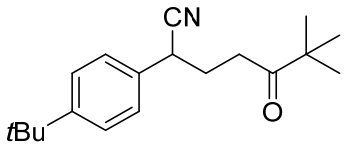
Synthesized according to the general procedure and a 5/1 mixture of hexane and ethyl acetate for chromatography, isolated **4gc** as colorless oil (25.3 mg, 20% yield).
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.3 Hz, 2H), 7.44 (d, *J* = 8.2 Hz, 2H), 3.98 (dd, *J* = 10.0, 5.5 Hz, 1H), 2.79 (ddd, *J* = 18.5, 8.4, 6.1 Hz, 1H), 2.60 (dt, *J* = 18.5, 5.8 Hz, 1H), 2.18 – 2.09 (m, 1H), 2.04 – 1.94 (m, 1H), 1.10 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.3, 140.8, 133.0, 128.1, 119.3, 118.1, 112.5, 44.2, 36.3, 33.1, 29.9, 26.4; HRMS (ESI) calcd for $C_{16}H_{18}N_2ONa$ $[M+Na]^+$: 277.131131, Found: 277.131140.

2-(4-Methoxyphenyl)-6,6-dimethyl-5-oxoheptanenitrile (4hc)



Synthesized according to the general procedure and a 15/1 mixture of hexane and ethyl acetate for chromatography, isolated **4hc** as yellow oil (31.2 mg, 24% yield).
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 (d, *J* = 8.7 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 3.81 (dd, *J* = 9.1, 6.2 Hz, 1H), 3.74 (s, 3H), 2.69 (dt, *J* = 18.3, 7.3 Hz, 1H), 2.58 – 2.49 (m, 1H), 2.13 – 2.04 (m, 1H), 2.04 – 1.95 (m, 1H), 1.07 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.5, 159.4, 128.4, 127.4, 120.8, 114.5, 55.3, 44.2, 35.4, 33.2, 30.0, 26.4; HRMS (ESI) calcd for $C_{16}H_{21}NO_2Na$ $[M+Na]^+$: 282.146448, Found: 282.146440.

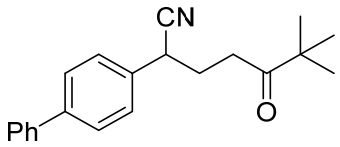
2-(4-(*tert*-Butyl)phenyl)-6,6-dimethyl-5-oxoheptanenitrile (4ic)



Synthesized according to the general procedure and a 15/1 mixture of hexane and ethyl acetate for chromatography, isolated **4ic** as colorless viscous oil (83.8 mg, 59% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.4 Hz, 2H), 7.19 (d, *J* = 8.2 Hz, 2H), 3.83 (dd, *J* = 9.4, 6.0 Hz, 1H), 2.71 (dt, *J* = 18.3, 7.3 Hz, 1H), 2.57 (ddd, *J* = 18.3, 6.8, 5.9 Hz, 1H), 2.15 – 2.06 (m, 1H), 2.05 – 1.96 (m, 1H), 1.24 (s, 9H), 1.07 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.5, 151.2, 132.4, 126.9, 126.0, 120.7, 44.2, 35.8, 34.6, 33.3, 31.3, 29.9, 26.4; HRMS (ESI) calcd for $C_{19}H_{27}NONa$ $[M+Na]^+$: 308.198483, Found: 308.198240.

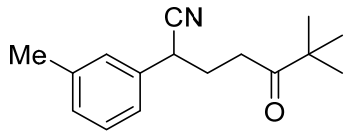
2-(4-Biphenyl)-6,6-dimethyl-5-oxoheptanenitrile (4jc)



Synthesized according to the general procedure and a 15/1 mixture of hexane and ethyl acetate for chromatography, isolated **4jc** as white solid (76.8 mg, 50% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 – 7.47 (m, 4H), 7.38 – 7.32 (m, 4H), 7.30 – 7.25 (m, 1H), 3.91 (dd, *J* = 9.3, 6.0 Hz, 1H), 2.74 (dt, *J* = 18.3, 7.3 Hz, 1H), 2.58 (dt, *J* = 18.3, 6.3 Hz, 1H), 2.19 – 2.10 (m, 1H), 2.09 – 2.00 (m, 1H), 1.08 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.5, 141.2, 140.2, 134.5, 128.9, 127.8, 127.7, 127.6, 127.1, 120.5, 44.2, 35.9, 33.2, 29.9, 26.5; HRMS (ESI) calcd for $C_{21}H_{23}NONa$ $[M+Na]^+$: 328.167183, Found: 328.167030.

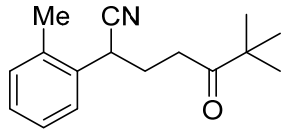
6,6-Dimethyl-5-oxo-2-(*m*-tolyl)heptanenitrile (4kc)



Synthesized according to the general procedure and a 15/1 mixture of hexane and ethyl acetate for chromatography, isolated **4kc** as colorless viscous oil (76.4 mg, 63% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 – 7.16 (m, 1H), 7.10 – 7.02 (m, 3H), 3.82 (dd, *J* = 9.3, 6.1 Hz, 1H), 2.71 (dt, *J* = 18.3, 7.3 Hz, 1H), 2.55 (dt, *J* = 18.3, 6.3 Hz, 1H), 2.28 (s, 3H), 2.09 (dt, *J* = 13.8, 6.9 Hz, 1H), 2.05 – 1.96 (m, 1H), 1.07 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.5, 139.0, 135.4, 129.0, 128.9, 127.9, 124.3, 120.7, 44.2, 36.1, 33.2, 30.0, 26.4, 21.4; HRMS (ESI) calcd for $C_{16}H_{21}NONa$ $[M+Na]^+$: 266.151533, Found: 266.151330.

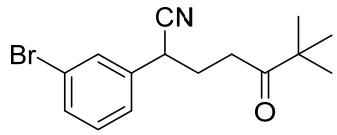
6,6-Dimethyl-5-oxo-2-(*o*-tolyl)heptanenitrile (4lc)



Synthesized according to the general procedure and a 15/1 mixture of hexane and ethyl acetate for chromatography, isolated **4lc** as colorless viscous oil (72.9 mg, 60% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.32 (m, 1H), 7.19 – 7.09 (m, 3H), 4.04 (dd, *J* = 10.3, 5.4 Hz, 1H), 2.81 (ddd, *J* = 18.4, 8.6, 6.2 Hz, 1H), 2.62 (dt, *J* = 18.4, 5.8 Hz, 1H), 2.33 (s, 3H), 2.13 – 2.04 (m, 1H), 1.94 – 1.84 (m, 1H), 1.09 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13C NMR (126 MHz, CDCl3) δ 214.7, 135.3, 134.0, 131.1, 128.2, 127.3, 126.8, 120.8, 44.2, 33.4, 33.2, 28.6, 26.5, 19.1; HRMS (ESI) calcd for $C_{16}H_{21}NONa$ $[M+Na]^+$: 266.151533, Found: 266.151520.

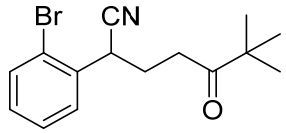
2-(3-Bromophenyl)-6,6-dimethyl-5-oxoheptanenitrile (4mc)



Synthesized according to the general procedure and a 15/1 mixture of hexane and ethyl acetate for chromatography, isolated **4mc** as colorless oil (78.5 mg, 51% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (t, *J* = 1.7 Hz, 1H), 7.40 (dt, *J* = 7.6, 1.5 Hz, 1H), 7.24 – 7.21 (m, 1H), 7.21 – 7.17 (m, 1H), 3.86 (dd, *J* = 9.6, 5.9 Hz, 1H), 2.74 (ddd, *J* = 18.4, 7.9, 6.5 Hz, 1H), 2.57 (dt, *J* = 18.4, 6.1 Hz, 1H), 2.15 – 2.06 (m, 1H), 2.03 – 1.95 (m, 1H), 1.09 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.4, 137.7, 131.4, 130.7, 130.4, 125.9, 123.1, 119.9, 44.2, 35.8, 33.1, 29.9, 26.4; HRMS (ESI) calcd for $C_{15}H_{18}BrNONa$ $[M+Na]^+$: 330.046408, Found: 330.046420.

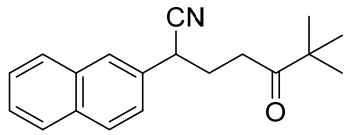
2-(2-Bromophenyl)-6,6-dimethyl-5-oxoheptanenitrile (4nc)



Synthesized according to the general procedure and a 15/1 mixture of hexane and ethyl acetate for chromatography, isolated **4nc** as colorless viscous oil (36.9 mg, 24% yield).

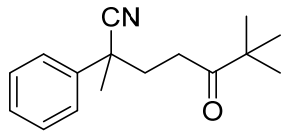
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.48 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.31 (td, *J* = 7.6, 1.1 Hz, 1H), 7.14 (td, *J* = 7.8, 1.6 Hz, 1H), 4.33 (dd, *J* = 9.6, 5.7 Hz, 1H), 2.77 – 2.61 (m, 2H), 2.21 – 2.10 (m, 1H), 2.02 – 1.94 (m, 1H), 1.09 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.0, 135.1, 133.5, 129.9, 128.9, 128.3, 123.1, 120.0, 44.2, 36.3, 33.5, 28.5, 26.5; HRMS (ESI) calcd for $C_{15}H_{18}BrNONa$ $[M+Na]^+$: 330.046408, Found: 330.046350.

6,6-Dimethyl-2-(naphthalen-2-yl)-5-oxoheptanenitrile (4oc)



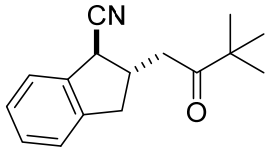
Synthesized according to the general procedure and a 15/1 mixture of hexane and ethyl acetate for chromatography, isolated **4oc** as colorless oil (79.7 mg, 57% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 – 7.69 (m, 4H), 7.46 – 7.39 (m, 2H), 7.35 (dd, *J* = 8.5, 1.8 Hz, 1H), 4.03 (dd, *J* = 9.3, 6.0 Hz, 1H), 2.75 (dt, *J* = 18.3, 7.5 Hz, 1H), 2.56 (dt, *J* = 18.3, 6.1 Hz, 1H), 2.26 – 2.15 (m, 1H), 2.14 – 2.04 (m, 1H), 1.06 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.5, 133.3, 132.9, 132.8, 129.2, 127.9, 127.7, 126.8, 126.5, 126.3, 124.7, 120.6, 44.2, 36.4, 33.2, 29.9, 26.5; HRMS (ESI) calcd for $C_{19}H_{21}NONa$ $[M+Na]^+$: 302.151532, Found: 302.151460.

2,6,6-Trimethyl-5-oxo-2-phenylheptanenitrile (4pc)



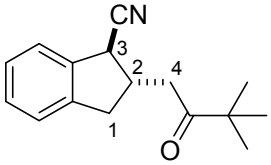
Synthesized according to the general procedure and a 18/1 mixture of hexane and ethyl acetate for chromatography, isolated **4pc** as colorless oil (21.2 mg, 17% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.35 (m, 2H), 7.36 – 7.29 (m, 3H), 7.28 – 7.22 (m, 1H), 2.63 (ddd, *J* = 17.4, 10.4, 5.6 Hz, 1H), 2.26 (ddd, *J* = 17.4, 10.7, 4.8 Hz, 1H), 2.21 – 2.09 (m, 2H), 1.66 (s, 3H), 1.00 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.2, 139.4, 129.1, 128.0, 125.4, 123.0, 44.2, 42.1, 35.7, 32.7, 28.4, 26.3; HRMS (ESI) calcd for $C_{16}H_{21}NONa$ $[M+Na]^+$: 266.151533, Found: 266.151500.

***trans*-2-(3,3-Dimethyl-2-oxobutyl)-2,3-dihydro-1*H*-indene-1-carbonitrile (4qc)**



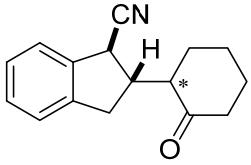
Synthesized according to the general procedure and a 15/1 mixture of hexane and ethyl acetate for chromatography, isolated **4qc** as pale yellow oil (56.5 mg, 47% yield) in a > 19:1 dr as determined by crude NMR analysis. Isolated was the pure *trans* diastereoisomer.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.28 (m, 1H), 7.22 – 7.13 (m, 3H), 3.82 (d, *J* = 9.1 Hz, 1H), 3.26 (dd, *J* = 15.8, 7.9 Hz, 1H), 3.13 – 3.03 (m, 1H), 2.89 (dd, *J* = 17.6, 4.8 Hz, 1H), 2.73 (dd, *J* = 17.6, 8.7 Hz, 1H), 2.48 (dd, *J* = 15.8, 8.8 Hz, 1H), 1.10 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.7, 142.0, 136.8, 128.7, 127.3, 125.0, 124.2, 120.4, 44.3, 41.8, 40.2, 39.9, 37.7, 26.3; HRMS (ESI) calcd for $C_{16}H_{19}NONa$ $[M+Na]^+$: 264.135882, Found: 264.135810.



Relative configuration: In a NOESY NMR experiment, the hydrogen atom at carbon no. 3 shows a cross signal to a single hydrogen atom only, bound to carbon no. 1. The other hydrogen atom at carbon no. 1 shows a much more intense cross signal with the hydrogen at carbon no. 2. This finding suggests a *trans* orientation of the hydrogen atoms at carbons no. 2 and no. 3, the isolated diastereomer is thus *trans*-oriented with regard to the cyano and ketone residues.

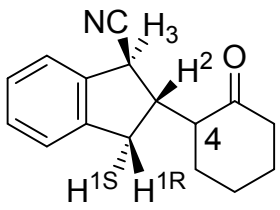
2-(2-Oxocyclohexyl)-2,3-dihydro-1*H*-indene-1-carbonitrile (4qe)



Synthesized according to the general procedure and a 6/1 mixture of hexane and ethyl acetate for chromatography, isolated **4qe** as yellow viscous oil (58.8 mg, 49%

yield) in a 1.6:1 dr as determined by crude NMR analysis.

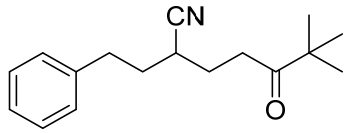
^{1}H NMR (500 MHz, $CDCl_3$, two diastereoisomers) δ 7.35 – 7.29 (m, 1H), 7.22 – 7.16 (m, 2H), 7.16 – 7.10 (m, 1H), 4.06 (d, *J* = 9.8 Hz, 1H, major), 4.02 (d, *J* = 9.1 Hz, 1H, minor), 3.23 (dd, *J* = 15.8, 8.3 Hz, 1H, major), 3.11 (dd, *J* = 15.3, 8.4 Hz, 1H, minor), 3.07 – 2.99 (m, 1H, minor), 2.90 – 2.80 (m, 1H, major), 2.77 – 2.56 (m, 2H), 2.46 – 2.25 (m, 2H), 2.25 – 2.18 (m, 1H, major), 2.11 – 1.97 (m, 1H + minor diastereoisomer), 1.96 – 1.84 (m, 1H), 1.73 – 1.58 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, two diastereoisomers) δ 211.34 (C, major), 211.33 (C, minor), 142.16 (Ar q, major), 141.84 (Ar q, minor), 137.10 (Ar q, minor), 136.95 (Ar q, major), 128.54 (Ar CH, minor), 128.52 (Ar CH, major), 127.27 (Ar CH, minor), 127.21 (Ar CH, major), 124.88 (Ar CH, minor), 124.84 (Ar CH, major), 124.23 (Ar CH, minor), 124.03 (Ar CH, major), 121.34 (CN, major), 121.16 (CN, minor), 53.74 (CH, major), 52.24 (CH, minor), 46.41 (CH, major), 45.40 (CH, minor), 42.61 (CH_2, major), 42.36 (CH_2, minor), 38.28 (CH, major), 37.66 (CH, minor), 36.29 (CH_2, major), 34.68 (CH_2, minor), 33.20 (CH_2, major), 30.96 (CH_2, minor), 27.97 (CH_2, major), 27.68 (CH_2, minor), 25.12 (CH_2, major), 24.81 (CH_2, minor); HRMS (ESI) calcd for $C_{16}H_{17}NONa$ $[M+Na]^+$: 262.120233, Found: 262.120100.



<u>Relative configuration of the isolated diastereoisomers:</u> Two diastereoisomers were observed in the isolated product mixture. A NOESY experiment of the mixture showed that for each diastereoisomer there are strong cross signals between the hydrogen atoms H^2 and H^{1R}. In contrast, both diastereomers only show a weak and no cross signal, respectively, between hydrogen atoms H^2 and H^{1S}. Similarly, for both diastereoisomers the hydrogen atom H^3 shows a weak cross signal to H^{1S} and no cross signal to H^{1R}. This suggests for both diastereoisomers a *trans* orientation for H^2 and H^{1S} and a *cis* orientation for H^2 and H^{1R}. Furthermore the hydrogen atom H^3 appears as *trans* to H^{1R} and as *cis* to H^{1S}, again for both diastereoisomers. In conclusion, hydrogen atoms H^2 and H^3 as well as the cyano and ketone residues are *trans* for both

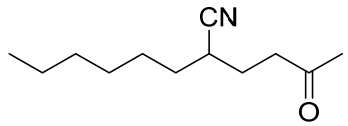
diastereoisomers. The two diastereoisomers therefore differ in their configuration at carbon no. 4. This is supported by the significant differences of the coupling constants of H^4 for both diastereoisomers.

6,6-Dimethyl-5-oxo-2-phenethylheptanenitrile (9ac)



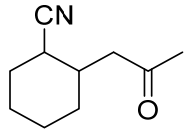
Synthesized according to the general procedure and a 15/1 mixture of hexane and ethyl acetate for chromatography, isolated **9ac** as pale yellow oil (37.2 mg, 29% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 – 7.19 (m, 2H), 7.18 – 7.07 (m, 3H), 2.82 (ddd, *J* = 14.3, 9.4, 5.4 Hz, 1H), 2.71 – 2.59 (m, 3H), 2.51 (tt, *J* = 10.1, 5.1 Hz, 1H), 1.96 – 1.76 (m, 3H), 1.75 – 1.66 (m, 1H), 1.08 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.4, 140.1, 128.7, 128.4, 126.4, 121.6, 44.2, 34.3, 33.7, 33.3, 30.5, 26.42, 26.37; HRMS (ESI) calcd for $C_{17}H_{23}NONa$ $[M+Na]^+$: 280.167183, Found: 280.167130.

2-(3-Oxobutyl)octanenitrile (9ba)



Synthesized according to the general procedure and a 8/1 mixture of hexane and ethyl acetate for chromatography, isolated **9ba** as colorless oil (50.2 mg, 51% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.68 – 2.50 (m, 3H), 2.11 (s, 3H), 1.91 – 1.80 (m, 1H), 1.72 – 1.61 (m, 1H), 1.58 – 1.20 (m, 10H), 0.82 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.9, 121.8, 40.5, 32.4, 31.5, 30.9, 30.1, 28.7, 27.1, 25.9, 22.5, 14.0; HRMS (ESI) calcd for $C_{12}H_{21}NONa$ $[M+Na]^+$: 218.151533, Found: 218.151660.

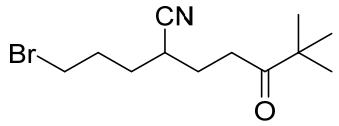
2-(2-Oxopropyl)cyclohexane-1-carbonitrile (9ca)



Synthesized according to the general procedure and a 8/1 mixture of hexane and ethyl acetate for chromatography, isolated **9ca** as colorless oil (17.1 mg, 21% yield) in a 3.0:1 dr as determined by crude NMR analysis.

^{1}H NMR (500 MHz, $CDCl_3$, major diastereoisomer) δ 2.74 (dd, *J* = 17.2, 3.3 Hz, 1H), 2.35 (dd, *J* = 17.2, 9.1 Hz, 1H), 2.25 (td, *J* = 11.5, 3.6 Hz, 1H), 2.10 (s, 3H), 2.08 – 1.96 (m, 2H), 1.85 – 1.78 (m, 1H), 1.75 – 1.68 (m, 1H), 1.67 – 1.60 (m, 1H), 1.59 – 1.49 (m, 1H), 1.31 – 1.21 (m, 1H), 1.21 – 1.10 (m, 1H), 0.96 – 0.85 (m, 1H); ^{1}H NMR (500 MHz, $CDCl_3$, minor diastereoisomer) δ 3.00 – 2.95 (m, 1H), 2.55 (dd, *J* = 18.3, 8.0 Hz, 1H), 2.43 (dd, *J* = 18.3, 5.6 Hz, 1H), 2.10 (s, 3H), 2.07 – 2.00 (m, 1H), 1.95 – 1.89 (m, 1H), 1.74 – 1.67 (m, 1H), 1.64 – 1.58 (m, 1H), 1.56 – 1.46 (m, 2H), 1.31 – 1.20 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, major diastereoisomer) δ 206.5, 121.7, 48.0, 35.9, 33.8, 31.1, 30.6, 29.9, 24.80, 24.77; HRMS (ESI) calcd for $C_{10}H_{15}NONa$ $[M+Na]^+$: 188.104583, Found: 188.104640.

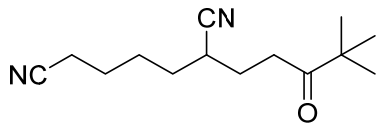
2-(3-Bromopropyl)-6,6-dimethyl-5-oxoheptanenitrile (9dc)



Synthesized according to the general procedure and a 7/1 mixture of hexane and ethyl acetate for chromatography, isolated **9dc** as colorless oil (31.4 mg, 23% yield).

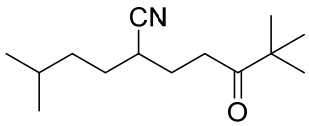
^{1}H NMR (500 MHz, $CDCl_3$) δ 3.38 (t, *J* = 6.5 Hz, 2H), 2.73 – 2.63 (m, 2H), 2.63 – 2.56 (m, 1H), 2.09 – 1.99 (m, 1H), 1.98 – 1.83 (m, 2H), 1.78 – 1.66 (m, 3H), 1.10 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.5, 121.4, 44.2, 33.5, 32.4, 31.0, 30.2, 29.9, 26.4, 26.3; HRMS (ESI) calcd for $C_{12}H_{20}BrNONa$ $[M+Na]^+$: 296.062058, Found: 296.062070.

2-(4,4-Dimethyl-3-oxopentyl)heptanedinitrile (9ec)



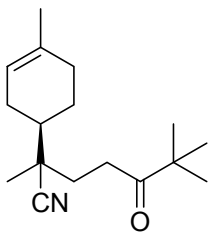
Synthesized according to the general procedure and a 4/1 to 2/1 mixture of hexane and ethyl acetate for chromatography, isolated **9ec** as colorless oil (63.8 mg, 58% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.74 – 2.61 (m, 2H), 2.61 – 2.52 (m, 1H), 2.32 (*t*, J = 6.9 Hz, 2H), 1.93 – 1.82 (m, 1H), 1.70 – 1.52 (m, 7H), 1.10 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.5, 121.4, 119.2, 44.2, 33.5, 31.8, 30.7, 26.4, 26.31, 26.29, 24.9, 17.0; HRMS (ESI) calcd for $C_{14}H_{22}N_2ONa$ $[M+Na]^+$: 257.162431, Found: 257.162500.

2-Isopentyl-6,6-dimethyl-5-oxoheptanenitrile (9fc)



Synthesized according to the general procedure and a 9/1 mixture of hexane and ethyl acetate for chromatography, isolated **9fc** as colorless oil (20.0 mg, 18% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.72 – 2.59 (m, 2H), 2.55 – 2.45 (m, 1H), 1.91 – 1.81 (m, 1H), 1.70 – 1.63 (m, 1H), 1.57 – 1.46 (m, 3H), 1.39 – 1.31 (m, 1H), 1.29 – 1.22 (m, 1H), 1.09 (s, 9H), 0.84 (d, *J* = 2.4 Hz, 3H), 0.83 (d, *J* = 2.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.6, 122.0, 44.2, 36.1, 33.7, 31.2, 30.4, 27.7, 26.41, 26.39, 22.5, 22.3; HRMS (ESI) calcd for $C_{14}H_{25}NONa$ $[M+Na]^+$: 246.182833, Found: 246.182540.

2,6,6-Trimethyl-2-((*R*)-4-methylcyclohex-3-en-1-yl)-5-oxoheptanenitrile (9gc)

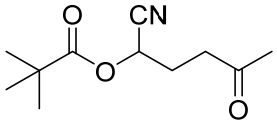


Synthesized according to the general procedure and a X/1 mixture of hexane and ethyl acetate for chromatography, isolated **9gc** as colourless, viscous oil that solidifies

upon freezing (1:1 dr from ^{1}H NMR, 29.0 mg, 22% yield).

^{1}H NMR (300 MHz, $CDCl_3$, two diastereoisomers) δ 5.50 – 5.09 (m, 1H), 2.72 – 2.50 (m, 2H), 2.17 – 1.77 (m, 6H), 1.73 – 1.52 (m, 1H), 1.59 (br, 3H), 1.45 – 1.27 (m, 1H), 1.21 (s, 3H of diastereoisomer 1), 1.19 (s, 3H of diastereoisomer 2), 1.10 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, two diastereoisomers) δ 214.59 (C, two diastereoisomers), (134.40, 134.12) (*C*=CH), (123.89, 123.73) (CN), (119.73, 119.46) (*C*H=C), 44.48 (C, two diastereoisomers), (41.12, 40.79) (C), (40.00, 39.90) (CH), (32.32, 32.29) (CH_2), (31.02, 30.78) (CH_2), (30.74, 30.50) (CH_2), (27.46 , 26.26 (CH_2), 26.60 (CH_3, two diastereoisomers), (25.16, 24.14) (CH_2), (23.31, 23.29) (CH_3), (21.12, 20.47) (CH_3); HRMS (ESI) calcd for $C_{17}H_{27}NONa$ $[M+Na]^+$: 284.198483, Found: 284.198700.

1-Cyano-4-oxopentyl pivalate (9ha)



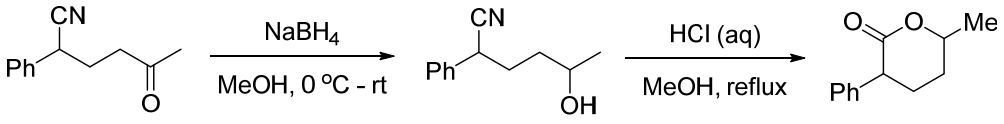
Synthesized according to the general procedure and a 6/1 mixture of hexane and ethyl acetate for chromatography, isolated **9ha** as colorless oil (20.5 mg, 19% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.31 (t, *J* = 6.6 Hz, 1H), 2.60 (t, *J* = 6.9 Hz, 2H), 2.14 (m, CH_3 + 2H), 1.17 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.6, 176.5, 116.6, 60.2, 38.8, 37.9, 30.0, 26.9, 26.2; HRMS (ESI) calcd for $C_{11}H_{17}NO_3Na$ $[M+Na]^+$: 234.110062, Found: 234.109990.

Synthetic Transformations of Selected Products

6-Methyl-3-phenyltetrahydro-2*H*-pyran-2-one (10)

The following rocedure for the cyclization reaction to transform γ–cyanoketone **4aa** into a lactone was performed in analogy to a reported method.[3]



5-oxo-2-phenylhexanenitrile (**4aa**, 37.8 mg, 0.2 mmol) was dissolved in 2 mL of methanol and cooled to 0 °C and then solid $NaBH_4$ (15.1 mg, 0.4 mmol, 2.0 equiv.) was added in one portion. After 1 h, the methanol was evaporated, the residue was dissolved in EtOAc, and the organic phase was then washed with saturated, aqueous NH_4Cl. The organic phase was dried over anhydrous $MgSO_4$, the solvent was removed under reduced pressure. The resulting oil is pure enough which could be used directly according to crude ^{1}H NMR (ca. 1.0:1 dr).

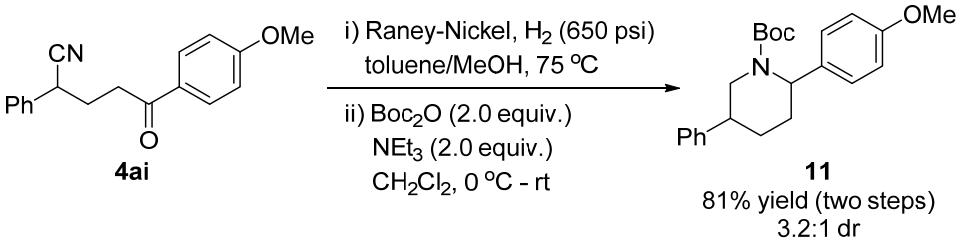
The corresponding alcohol was dissolved in a 1:1 solution of MeOH (5 mL) and hydrochloric acid (37%, 5 mL) (0.02 M). The solution was then warmed to 66 °C and stirred overnight under reflux. The reaction was quenched with water and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and then concentrated under reduced pressure. The dr value was determined by ^{1}H NMR of the crude reaction mixture. Then the residue was purified by silica gel column chromatography (hexane/EtOAc = 4/1) to afford the desired lactone **10** as light yellow solid (1.0:1 dr, 25.8 mg, 68% yield, two steps).

^{1}H NMR (500 MHz, $CDCl_3$, two diastereoisomers) δ 7.32 – 7.23 (m, 2H), 7.23 – 7.18 (m, 1H), 7.18 – 7.11 (m, 2H), 4.61 – 4.47 (m, 1H), 3.72 (dd, *J* = 9.0, 8.0 Hz, 1H, diastereoisomer 1), 3.59 (dd, *J* = 11.2, 6.6 Hz, 1H, diastereoisomer 2), 2.25 – 2.12 (m, 1H), 2.06 – 1.86 (m, 2H), 1.74 – 1.60 (m, 1H), 1.36 (t, *J* = 6.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, two diastereoisomers) δ (173.30, 172.10), (139.50, 138.68), (128.79,

128.64), (128.38, 128.12), (127.29, 127.24), (78.16, 75.57), (47.95, 45.30), (30.62, 29.07), (28.05, 26.73), (22.16, 21.41); HRMS (ESI) calcd for $C_{12}H_{14}O_2Na$ $[M+Na]^+$: 213.088599, Found: 213.088650.

tert-Butyl 2-(4-methoxyphenyl)-5-phenylpiperidine-1-carboxylate (10)

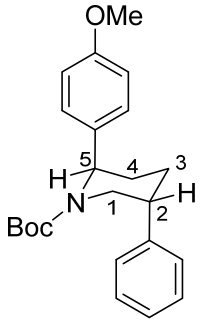
The following procedure for the reductive cyclization to a piperidine was performed in analogy to a reported method.[4]



Raney nickel (8.2 mg, 2800 mesh) was added to a solution of 5-(4-methoxyphenyl)-5-oxo-2-phenylpentanenitrile (**4ai**, 42 mg, 0.15 mmol) in 4:1 toluene/methanol (2.0 mL). The mixture was subjected to 650 PSI hydrogen pressure in a stainless steel autoclave, heated to 75°C, and stirred for 15 hours. The mixture was cooled to room temperature, vented, and filtered through Celite, eluting with EtOAc. The solution was concentrated, yielding unprotected piperidine as a colorless oil, which was dissolved in CH_2Cl_2 (2.0 mL). DMAP (ca. 5 mol%) was added, then NEt_3 (42 μL, 0.30 mmol, 2.0 equiv.) and Boc_2O (69 μL, 0.30 mmol, 2.0 equiv.) were added dropwise at 0 °C. The mixture was continued to be stirred at room temperature for 4 hours. The reaction mixture was quenched by water, then extracted with CH_2Cl_2 (3 x 10 mL), the combined organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated in *vacuo*. The dr value was determined by ^{1}H NMR of the crude reaction mixture. Then the residue was purified by silica gel column chromatography (hexane/EtOAc = 15/1) to afford the desired piperidine **11** as colorless viscous oil (3.2:1 dr, 44.5 mg, 81% yield, two steps).

^{1}H NMR (500 MHz, $CDCl_3$, two diastereoisomers) δ 7.28 (d, *J* = 7.4 Hz, 2H, major), 7.24 (t, *J* = 7.7 Hz, 2H, major), 7.19 – 7.16 (m, 2H, minor), 7.16 – 7.12 (m, 1H), 7.09 (d, *J* = 8.6 Hz, 2H), 7.04 (d, *J* = 7.2 Hz, 2H, minor), 6.86 – 6.78 (m, 2H), 5.61 – 5.26 (br,

1H, minor), 5.17 (t, J = 4.3 Hz, 1H, major), 4.31 – 4.22 (m, 1H, major), 4.21 – 3.90 (br, 1H, minor), 3.75 (s, 3H, minor), 3.74 (s, 3H, major), 3.31 (dd, J = 14.0, 4.8 Hz, 1H, major), 2.94 – 2.84 (m, 1H, major), 2.77 – 2.60 (br, 2H, minor), 2.41 – 2.33 (m, 1H, minor), 2.02 – 1.83 (m, 3H major + 1H minor), 1.81 – 1.70 (m, 1H), 1.69 – 1.57 (m, 1H, minor), 1.42 (s, 9H, minor), 1.34 (s, 9H, major); ^{13}C NMR (125 MHz, $CDCl_3$, two diastereoisomers) δ 158.20, 155.69 (major), 155.50 (minor), 144.13, 133.23, 128.40 (minor), 128.28 (major), 127.68 (minor), 127.54 (major), 127.21 (major), 127.05 (minor), 126.54 (minor), 126.01 (major), 114.04 (minor), 113.91 (major), 79.79 (minor), 79.75 (major), 55.28 (major), 55.27 (minor), 53.53, 43.37, 38.11, 28.51 (minor), 28.39 (major), 26.05, 25.05; HRMS (ESI) calcd for $C_{23}H_{29}NO_3Na$ $[M+Na]^+$: 390.203963, Found: 390.204100.

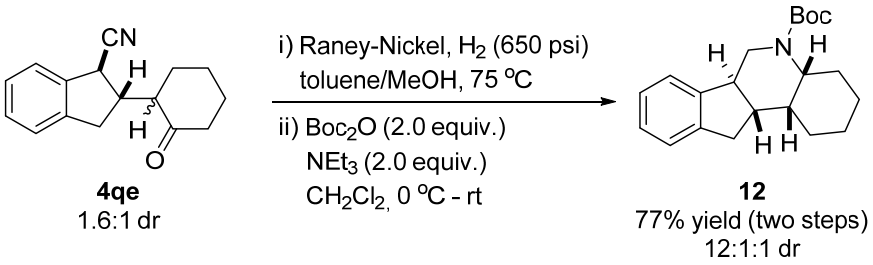


Major diastereoisomer: The proton attached to carbon no. 5 (^{1}H NMR: 5.25 ppm) shows two $^3J^{H–H}$ couplings of 4.6 Hz, indicating a gauche relation to both protons connected to carbon no. 4 (^{1}H NMR: 2.08-1.95 ppm (m)).

Thus first mentioned proton has an equatorial positioning in the piperidine ring, resulting in an axial oriented *p*-methoxyphenyl group at carbon no. 5. From ^{1}H NMR signal of the proton connected to carbon no. 2 (^{1}H NMR: 3.00-2.95 ppm (m)) no distinct $^3J^{H–H}$ couplings can be assured. The rather narrow multiplett suggests small coupling constants to all vicinal protons, corresponding to an equatorial positioning of the proton at carbon no. 2. This was further enlightened by a NOESY experiment, showing cross signals of the proton attached to carbon no. 2 with both protons bond to carbon no. 1 (^{1}H NMR: 4.38-4.30 ppm (m) and 3.39 ppm (dd)), as well as to the protons bond to carbon no. 3 (^{1}H NMR: 2.08-1.95 ppm (m), 1.87-1.79 ppm (m)). In conclusion this implies a gauche positioning of the proton at carbon no. 2 in respect to all vicinal protons, giving evidence for the shown axial phenyl group at carbon no. 2 and an overall *trans* relation between the two axial oriented aryl substituents on the piperidine ring.

***tert*-Butyl-1,2,3,4,4a,6,6a,11,11a,11b-decahydro-5*H*-indeno[1,2-*c*]quinoline-5-carbo xylate (12)**

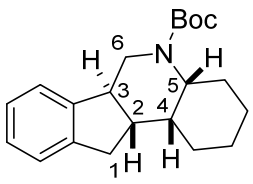
The following procedure for the reductive cyclization to a piperidine was performed in analogy to a reported method.[4]



Raney nickel (8.0 mg, 2800 mesh) was added to a solution of 2-(2-oxocyclohexyl)-2,3-dihydro-1*H*-indene-1-carbonitrile (**4qe**, 34 mg, 0.14 mmol) in 4:1 toluene/methanol (2.0 mL). The mixture was subjected to 650 PSI hydrogen pressure in a stainless steel autoclave, heated to 75°C, and stirred for 15 hours. The mixture was cooled to room temperature, vented, and filtered through Celite, eluting with EtOAc. The solution was concentrated, yielding unprotected decahydro-5*H*-indeno[1,2-*c*]quinoline as a green oil, which was dissolved in CH_2Cl_2 (2.0 mL). DMAP (ca. 5 mol%) was added, then NEt_3 (39 μL, 0.28 mmol, 2.0 equiv.) and Boc_2O (64 μL, 0.28 mmol, 2.0 equiv.) were added dropwise at 0 °C. The mixture was continued to be stirred at room temperature for 4 hours. The reaction mixture was quenched by water, extracted with CH_2Cl_2 (3 x 10 mL), the combined organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated in *vacuo*. The dr value was determined by ^{1}H NMR of the crude reaction mixture. Then the residue was purified by silica gel column chromatography (hexane/EtOAc = 20/1) to afford the desired product **12** as colorless viscous oil (12:1:1 dr, 35.7 mg, 77% yield, two steps).

^{1}H NMR (500 MHz, $CDCl_3$, major diastereoisomer) δ 7.18 – 7.14 (m, 1H), 7.10 – 7.03 (m, 3H), 4.27 – 4.16 (m, 1H), 3.97 – 3.86 (m, 1H), 3.21 – 3.10 (m, 2H), 2.71 – 2.59 (m, 2H), 2.24 – 2.12 (m, 2H), 2.12 – 2.02 (m, 1H), 1.68 – 1.58 (m, 1H), 1.56 – 1.42 (m, 5H), 1.41 (s, 9H), 1.36 – 1.29 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, major diastereoisomer) δ 156.2, 144.7, 144.1, 126.5, 126.2, 124.7, 122.3, 79.4, 54.0, 49.1, 48.1, 41.2, 36.3, 32.9,

29.3, 28.5, 23.6, 22.8, 22.4; HRMS (ESI) calcd for $C_{21}H_{29}NO_2Na$ $[M+Na]^+$: 350.209047, Found: 350.209150.



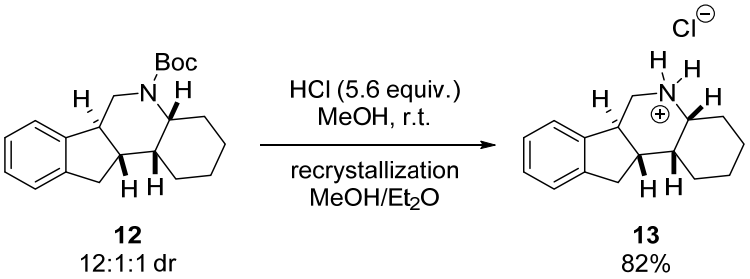
Major diastereoisomer: In a NOESY experiment the proton at carbon no. 4 (^{1}H NMR: 2.28 ppm (dq)) shows cross signals to the protons bond to carbon no. 5 (^{1}H NMR: 3.99 ppm (ddd)) and to carbon no. 2 (^{1}H NMR: 2.14 ppm (tt)). There is also a cross signal between the protons of carbons no. 2 and no. 5. This is a proof for relative *cis* orientation of these three protons.

The coupling pattern of the proton connected to carbon no. 2 is tt with $^3J^{H-H}$ coupling constants 12.3 Hz, 11.3 Hz, 7.5 Hz and 6.9 Hz. This can be caused by two *trans* and two *cis* directed vicinal protons. Since one proton bond to carbon no. 1 should be in *trans* and the other one in *cis* relation to the refered proton and the NOESY experiment showed a *cis* relation to proton at carbon no. 4, another *trans* orientated proton has to be present at the vicinal carbon no. 3. This relative configuration of carbons no. 2 and no. 3 is also in line with the relative configuration of the starting materials major diastereoisomer. It results in the depicted relative configurations. Furthermore the crystal structure of the follow up reaction product **13** (racemic compound crystal) is in line with the relative configuration in the stated structure.

The relative configuration of the minor diastereoisomers could not be determined due to their low amount.

2,3,4,4a,5,6,6a,11,11a,11b-Decahydro-1*H*-indeno[1,2-*c*]quinolin-5-ium chloride (13)

The following procedure for deprotection and isolation as a hydrochloride salt was performed in analogy to a reported method.[5]



12
12:1:1 dr

13
82%

A stock solution of hydrogen chloride in methanol (1.52 M, 0.50 mL) was prepared by dropwise addition of acetyl chloride (54 µL) to stirred methanol (0.50 mL).

The stock solution of hydrogen chloride (0.10 mL, 5.6 equiv.) was added to *tert*-butyl-1,2,3,4,4a,6,6a,11,11a,11b-decahydro-5*H*-indeno[1,2-*c*]quinoline-5-carboxyla -te (**12**) (8.8 mg, 0.027 mmol, 1.0 equiv.). The resulting solution was stirred for 5 h at room temperature. The yielded white precipitate (7.1 mg, 0.027 mmol, 97%) was separated by filtration, dried *in vacuo* and recrystalized from methanol/diethyl ether by gas phase diffusion. The single crystals of **13** (6.2 mg, 0.024 mmol, 82%) were suitable for X-ray diffractometry (see "X-ray Crystallography" below).

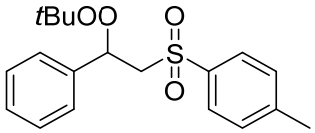
After drying the compound over night in high vacuum ^{1}H NMR spectrum shows still a signal of water (s, 4.87 ppm) due to the high hygroscopicity of the hydrochloride. Furthermore one proton signal of the ammonium group is believed to be overlayed by this high integral signal.

^{1}H NMR (501 MHz, CD_3OD) δ 7.33 – 7.23 (m, 1H), 7.22 – 7.10 (m, 3H), 4.59 (s, 1H), 4.02 (dd, *J* = 11.3, 3.5 Hz, 1H), 3.57 – 3.43 (m, 1H), 3.21 (td, *J* = 12.0, 3.6 Hz, 1H), 3.16 – 3.06 (m, 1H), 2.77 (d, *J* = 9.2 Hz, 2H), 2.34 – 2.16 (m, 2H), 2.07 – 1.96 (m, 1H), 1.95 – 1.78 (m, 3H), 1.63 – 1.48 (m, 2H), 1.50 – 1.37 (m, 1H); ^{13}C NMR (126 MHz, , CD_3OD) δ 144.46, 142.44, 128.37, 127.51, 126.00, 123.02, 58.30, 52.47, 49.45, 40.74, 37.88, 33.60, 29.86, 25.79, 22.29, 20.80; HRMS (ESI) calcd for $C_{16}H_{22}N^{+}$ $[M\text{-}Cl]^{+}$: 228.174674, Found: 228.174490.

Characterization of Side Products

The sulfonyl peroxides described below could be isolated from the reactions forming γ-cyanoketones, as described. Not in all cases could the sulfonyl peroxides be isolated, for example, in reactions employing alkyl olefins they were usually not formed or in traces only.

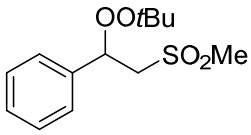
1-((2-(*tert*-Butylperoxy)-2-phenylethyl)sulfonyl)-4-methylbenzene (7aa)



Synthesized according to the general procedure using 1.0 equivlent of *p*-Toluenesulfonyl cyanide, 2.0 equiv. of styrene and 3.0 equivalent of 3,3-dimethyl-2-butanone, formed as a byproduct to **4ac**. Isolated using a 7/1 to 5/1 mixture of hexane and ethyl acetate for chromatography, isolated as colourless oil (112.4 mg, 65% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 – 7.56 (m, 2H), 7.24 – 7.09 (m, 7H), 5.27 (t, *J* = 6.2 Hz, 1H), 3.85 (dd, *J* = 14.7, 6.2 Hz, 1H), 3.40 (dd, *J* = 14.7, 6.2 Hz, 1H), 2.31 (s, 3H), 1.01 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.36, 136.47, 135.95, 128.59, 127.63, 127.42, 126.95, 126.46, 79.86, 79.15, 58.77, 25.24, 20.53; HRMS (ESI) calcd for $C_{19}H_{24}O_4SNa$ $[M+Na]^+$: 371.1288, Found: 371.1288.

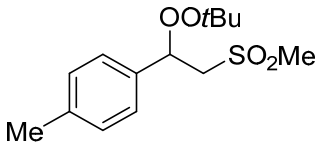
(1-(*tert*-Butylperoxy)-2-(methylsulfonyl)ethyl)benzene (7ac)



Synthesized according to the general procedure as a byproduct to **4ac**, using 3.0 equivalent of 3,3-dimethyl-2-butanone. Isolated using a 4/1 mixture of hexane and ethyl acetate for chromatography, isolated **7ac** as white solid (68.1 mg, 50% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.25 (m, 5H), 5.35 (dd, *J* = 8.3, 4.6 Hz, 1H), 3.75 (dd, *J* = 15.1, 8.3 Hz, 1H), 3.18 (ddd, *J* = 15.1, 4.6, 1.0 Hz, 1H), 2.81 (s, 3H), 1.09 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.6, 129.0, 128.7, 127.5, 81.0, 80.4, 58.7, 42.6, 26.4; HRMS (ESI) calcd for $C_{13}H_{20}O_4SNa$ $[M+Na]^+$: 295.097452, Found: 295.097260.

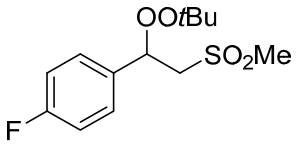
1-(1-(*tert*-Butylperoxy)-2-(methylsulfonyl)ethyl)-4-methylbenzene (7bc)



Synthesized according to the general procedure as a byproduct to **4bc**. Isolated using a 4/1 mixture of hexane and ethyl acetate for chromatography, isolated **7bc** as white solid (68.2 mg, 48% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 (d, *J* = 8.1 Hz, 2H), 7.12 (d, *J* = 7.9 Hz, 2H), 5.31 (dd, *J* = 7.9, 5.0 Hz, 1H), 3.76 (dd, *J* = 15.1, 8.0 Hz, 1H), 3.22 – 3.14 (m, 1H), 2.77 (s, 3H), 2.29 (s, 3H), 1.09 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.0, 134.5, 129.4, 127.5, 81.0, 80.3, 58.7, 42.5, 26.4, 21.3; HRMS (ESI) calcd for $C_{14}H_{22}O_4SNa$ $[M+Na]^+$: 309.113102, Found: 309.112950.

1-(1-(*tert*-Butylperoxy)-2-(methylsulfonyl)ethyl)-4-fluorobenzene (7cc)

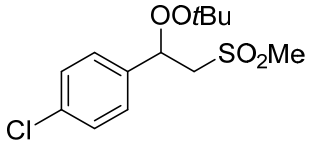


Synthesized according to the general procedure as a byproduct to **4cc**. Isolated using a 3/1 mixture of hexane and ethyl acetate for chromatography, isolated **7cc** as white solid (65.7 mg, 45% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.25 (m, 2H), 7.04 – 6.97 (m, 2H), 5.34 (dd, *J* = 8.5, 4.4 Hz, 1H), 3.73 (dd, *J* = 15.1, 8.5 Hz, 1H), 3.18 – 3.10 (m, 1H), 2.86 (s, 3H), 1.08 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.9 (d, *J* = 248.0 Hz), 133.6 (d, *J* = 3.2 Hz), 129.3 (d, *J* = 8.3 Hz), 115.7 (d, *J* = 21.6 Hz), 81.1, 79.6, 58.6, 42.6, 26.4; ^{19}F NMR (470

MHz, $CDCl_3$) δ -112.3; HRMS (ESI) calcd for $C_{13}H_{19}FO_4SNa$ $[M+Na]^+$: 313.088030, Found: 313.087920.

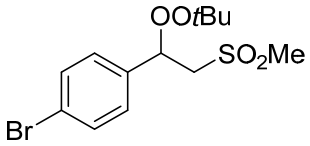
1-(1-(*tert*-Butylperoxy)-2-(methylsulfonyl)ethyl)-4-chlorobenzene (7dc)



Synthesized according to the general procedure as a byproduct to **4dc**. Isolated using a 4/1 mixture of hexane and ethyl acetate for chromatography, isolated **7dc** as white solid (67.6 mg, 44% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.5 Hz, 2H), 7.24 (d, *J* = 8.4 Hz, 2H), 5.34 (dd, *J* = 8.7, 4.2 Hz, 1H), 3.69 (dd, *J* = 15.1, 8.7 Hz, 1H), 3.12 (dd, *J* = 15.2, 3.4 Hz, 1H), 2.89 (s, 3H), 1.09 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.3, 134.8, 128.9, 128.7, 81.2, 79.6, 58.5, 42.7, 26.4; HRMS (ESI) calcd for $C_{13}H_{19}ClO_4SNa$ $[M+Na]^+$: 329.058480, Found: 329.058440.

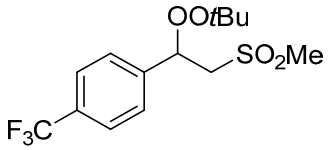
1-Bromo-4-(1-(*tert*-butylperoxy)-2-(methylsulfonyl)ethyl)benzene (7ec)



Synthesized according to the general procedure as a byproduct to **4ec**. Isolated using a 4/1 mixture of hexane and ethyl acetate for chromatography, isolated **7ec** as white solid (74.1 mg, 42% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.4 Hz, 2H), 7.18 (d, *J* = 8.4 Hz, 2H), 5.33 (dd, *J* = 8.7, 4.1 Hz, 1H), 3.68 (dd, *J* = 15.2, 8.7 Hz, 1H), 3.16 – 3.07 (m, 1H), 2.89 (s, 3H), 1.09 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.8, 131.9, 129.0, 123.0, 81.2, 79.7, 58.5, 42.7, 26.4; HRMS (ESI) calcd for $C_{13}H_{19}BrO_4SNa$ $[M+Na]^+$: 373.007977, Found: 373.007910.

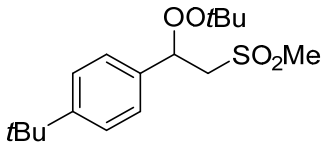
1-(1-(*tert*-Butylperoxy)-2-(methylsulfonyl)ethyl)-4-(trifluoromethyl)benzene (7fc)



Synthesized according to the general procedure as a byproduct to **4fc**. Isolated using a 4/1 mixture of hexane and ethyl acetate for chromatography, isolated **7fc** as white solid (53.7 mg, 32% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.1 Hz, 2H), 7.44 (d, *J* = 8.1 Hz, 2H), 5.45 (dd, *J* = 9.0, 3.7 Hz, 1H), 3.66 (dd, *J* = 15.2, 9.1 Hz, 1H), 3.13 (dd, *J* = 15.2, 2.9 Hz, 1H), 2.94 (s, 3H), 1.10 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.9, 131.0 (q, *J* = 32.5 Hz), 127.5, 125.7 (q, *J* = 3.7 Hz), 123.9 (q, *J* = 272.2 Hz), 81.4, 79.6, 58.6, 42.8, 26.4; ^{19}F NMR (470 MHz, $CDCl_3$) δ -62.7; HRMS (ESI) calcd for $C_{14}H_{19}F_3O_4SNa$ $[M+Na]^+$: 363.084837, Found: 363.084680.

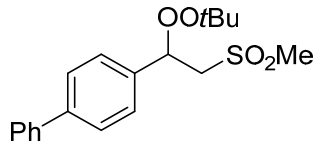
1-(*tert*-Butyl)-4-(1-(*tert*-butylperoxy)-2-(methylsulfonyl)ethyl)benzene (7ic)



Synthesized according to the general procedure as a byproduct to **4ic**. Isolated using a 9/1 mixture of hexane and ethyl acetate for chromatography, isolated **7ic** as colorless viscous oil (82.3 mg, 50% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 8.3 Hz, 2H), 5.33 (dd, *J* = 8.0, 4.9 Hz, 1H), 3.77 (dd, *J* = 15.1, 8.0 Hz, 1H), 3.24 – 3.14 (m, 1H), 2.77 (s, 3H), 1.25 (s, 9H), 1.10 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.2, 134.4, 127.2, 125.6, 81.0, 80.3, 58.7, 42.5, 34.7, 31.3, 26.4; HRMS (ESI) calcd for $C_{17}H_{28}O_4SNa$ $[M+Na]^+$: 351.160052, Found: 351.159830.

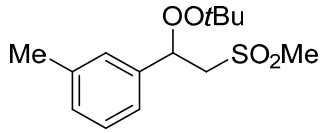
4-(1-(*tert*-Butylperoxy)-2-(methylsulfonyl)ethyl)-1,1'-biphenyl (7jc)



Synthesized according to the general procedure as a byproduct to **4jc**. Isolated using a a 4/1 mixture of hexane and ethyl acetate for chromatography, isolated **7jc** as pale yellow solid (69.4 mg, 40% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 – 7.49 (m, 4H), 7.40 – 7.33 (m, 4H), 7.28 (t, *J* = 7.4 Hz, 1H), 5.40 (dd, *J* = 8.3, 4.6 Hz, 1H), 3.77 (dd, *J* = 15.1, 8.3 Hz, 1H), 3.22 (dd, *J* = 15.1, 3.9 Hz, 1H), 2.85 (s, 3H), 1.11 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.9, 140.3, 136.5, 128.9, 127.9, 127.6, 127.4, 127.1, 81.1, 80.2, 58.7, 42.7, 26.5; HRMS (ESI) calcd for $C_{19}H_{24}O_4SNa$ $[M+Na]^+$: 371.128752, Found: 371.128620.

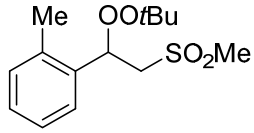
1-(1-(*tert*-Butylperoxy)-2-(methylsulfonyl)ethyl)-3-methylbenzene (7kc)



Synthesized according to the general procedure as a byproduct to **4kc**. Isolated using a 4/1 mixture of hexane and ethyl acetate for chromatography, isolated **7kc** as colorless viscous oil (72.8 mg, 51% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 – 7.18 (m, 1H), 7.12 – 7.06 (m, 3H), 5.31 (dd, *J* = 8.1, 4.8 Hz, 1H), 3.73 (dd, *J* = 15.1, 8.1 Hz, 1H), 3.18 (dd, *J* = 15.1, 4.2 Hz, 1H), 2.79 (s, 3H), 2.29 (s, 3H), 1.10 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.5, 137.5, 129.8, 128.6, 128.1, 124.5, 81.0, 80.5, 58.8, 42.5, 26.4, 21.4; HRMS (ESI) calcd for $C_{14}H_{22}O_4SNa$ $[M+Na]^+$: 309.113102, Found: 309.112830.

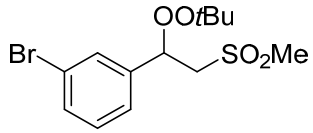
1-(1-(*tert*-Butylperoxy)-2-(methylsulfonyl)ethyl)-2-methylbenzene (7lc)



Synthesized according to the general procedure as a byproduct to **4lc**. Isolated using a 4/1 mixture of hexane and ethyl acetate for chromatography, isolated **7lc** as colorless viscous oil (60.6 mg, 42% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 – 7.23 (m, 1H), 7.18 – 7.08 (m, 3H), 5.64 (dd, *J* = 8.3, 4.4 Hz, 1H), 3.75 (dd, *J* = 15.2, 8.3 Hz, 1H), 3.20 – 3.10 (m, 1H), 2.82 (s, 3H), 2.36 (s, 3H), 1.08 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.1, 135.7, 130.9, 128.7, 126.9, 126.2, 80.9, 76.8, 58.3, 42.5, 26.4, 19.2; HRMS (ESI) calcd for $C_{14}H_{22}O_4SNa$ $[M+Na]^+$: 309.113101, Found: 309.113080.

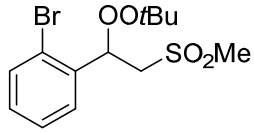
1-Bromo-3-(1-(*tert*-butylperoxy)-2-(methylsulfonyl)ethyl)benzene (7mc)



Synthesized according to the general procedure as a byproduct to **4mc**. Isolated using a 4/1 mixture of hexane and ethyl acetate for chromatography, isolated **7mc** as colorless viscous oil (64.8 mg, 37% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (s, 1H), 7.42 (d, *J* = 7.8 Hz, 1H), 7.23 (d, *J* = 7.7 Hz, 1H), 7.21 – 7.17 (m, 1H), 5.33 (dd, *J* = 8.9, 3.8 Hz, 1H), 3.65 (dd, *J* = 15.2, 9.0 Hz, 1H), 3.12 (dd, *J* = 15.2, 3.1 Hz, 1H), 2.91 (s, 3H), 1.10 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.2, 132.0, 130.29, 130.28, 125.9, 122.7, 81.3, 79.6, 58.6, 42.7, 26.4; HRMS (ESI) calcd for $C_{13}H_{19}BrO_4SNa$ $[M+Na]^+$: 373.007977, Found: 373.008020.

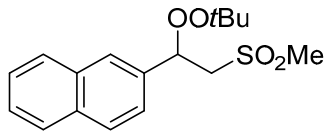
1-Bromo-2-(1-(*tert*-butylperoxy)-2-(methylsulfonyl)ethyl)benzene (7nc)



Synthesized according to the general procedure as a byproduct to **4nc**. Isolated using a 4/1 mixture of hexane and ethyl acetate for chromatography, isolated **7nc** as colorless viscous oil (49.5 mg, 28% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.41 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.29 (td, *J* = 7.8, 1.0 Hz, 1H), 7.14 (td, *J* = 7.8, 1.6 Hz, 1H), 5.83 (dd, *J* = 9.8, 2.9 Hz, 1H), 3.48 (dd, *J* = 15.3, 9.9 Hz, 1H), 3.23 (dd, *J* = 15.3, 1.7 Hz, 1H), 3.00 (s, 3H), 1.14 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.1, 133.2, 130.0, 128.5, 127.6, 122.6, 81.4, 79.3, 57.8, 42.9, 26.5; HRMS (ESI) calcd for $C_{13}H_{19}BrO_4SNa$ $[M+Na]^+$: 373.007977, Found: 373.008140.

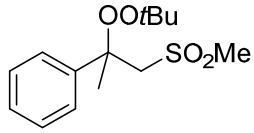
2-(1-(*tert*-Butylperoxy)-2-(methylsulfonyl)ethyl)naphthalene (7oc)



Synthesized according to the general procedure as a byproduct to **4oc**. Isolated using a 4/1 mixture of hexane and ethyl acetate for chromatography, isolated **7oc** as pale yellow solid (66.3 mg, 41% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 – 7.74 (m, 4H), 7.47 – 7.42 (m, 2H), 7.40 (dd, *J* = 8.5, 1.6 Hz, 1H), 5.52 (dd, *J* = 8.4, 4.5 Hz, 1H), 3.81 (dd, *J* = 15.1, 8.4 Hz, 1H), 3.32 – 3.20 (m, 1H), 2.83 (s, 3H), 1.10 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.0, 133.5, 133.1, 128.7, 128.2, 127.8, 127.0, 126.7, 126.6, 124.5, 81.1, 80.6, 58.8, 42.7, 26.5; HRMS (ESI) calcd for $C_{17}H_{22}O_4SNa$ $[M+Na]^+$: 345.113101, Found: 345.113060.

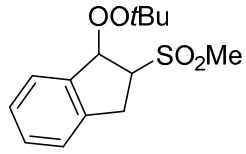
(2-(*tert*-Butylperoxy)-1-(methylsulfonyl)propan-2-yl)benzene (7pc)



Synthesized according to the general procedure as a byproduct to **4oc**. Isolated using a 6/1 mixture of hexane and ethyl acetate for chromatography, isolated **7pc** as white solid (29.7 mg, 21% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 – 7.37 (m, 2H), 7.36 – 7.28 (m, 2H), 7.28 – 7.23 (m, 1H), 3.66 (d, *J* = 15.1 Hz, 1H), 3.53 (d, *J* = 15.1 Hz, 1H), 2.57 (s, 3H), 1.84 (s, 3H), 1.19 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.2, 128.4, 128.2, 125.9, 81.3, 80.3, 63.1, 42.8, 26.7, 23.7; HRMS (ESI) calcd for $C_{14}H_{22}O_4SNa$ $[M+Na]^+$: 309.113101, Found: 309.113080.

1-(*tert*-Butylperoxy)-2-(methylsulfonyl)-2,3-dihydro-1*H*-indene (7qc)

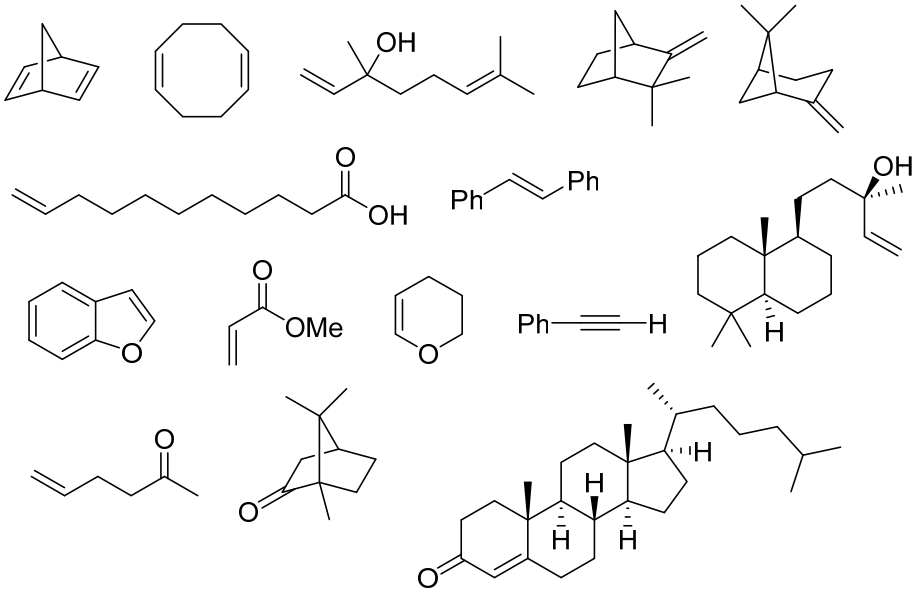


Synthesized according to the general procedure as a byproduct to **4qc**. Isolated using a 6/1 mixture of hexane and ethyl acetate for chromatography, isolated **7qc** as colorless viscous oil (70.2 mg, 49% yield) in a 5.6:1 dr as determined by crude NMR analysis.

^{1}H NMR (500 MHz, $CDCl_3$, major diastereoisomer) δ 7.40 – 7.36 (m, 1H), 7.31 – 7.24 (m, 1H), 7.24 – 7.19 (m, 2H), 5.81 (d, *J* = 3.4 Hz, 1H), 4.05 (ddd, *J* = 9.3, 5.7, 3.5 Hz, 1H), 3.48 (dd, *J* = 17.4, 5.7 Hz, 1H), 3.41 (dd, *J* = 17.4, 9.3 Hz, 1H), 2.98 (s, 3H), 1.23 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.9, 137.2, 130.1, 127.5, 126.1, 124.9, 87.9, 81.2, 66.1, 40.1, 30.1, 26.5; HRMS (ESI) calcd for $C_{14}H_{20}O_4SNa$ $[M+Na]^+$: 307.097451, Found: 307.097430.

Substrates not giving the desired products

The following olefins and ketones were employed in the general procedure but did not give the desired γ-cyanoketones and product mixtures from which clean products could not be isolated, respectively.



X-ray Crystallography

X-Ray Structure of **13**. Recrystalized from methanol/diethyl ether.

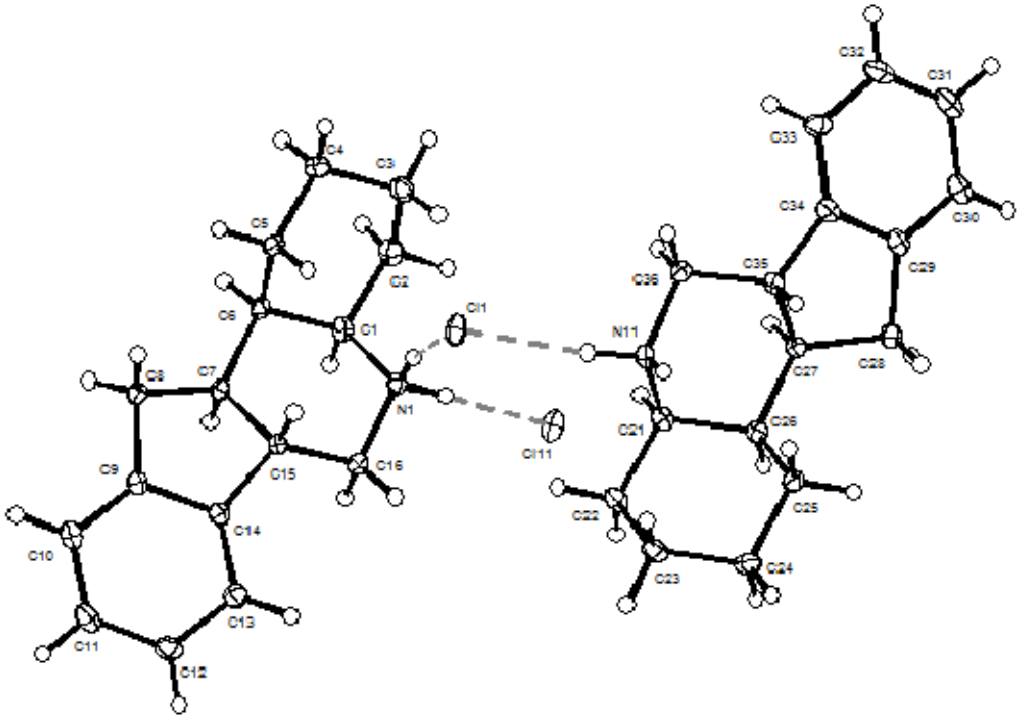


Table S3. Crystal data and structure refinement.

Identification code	CCDC-1878410	
Empirical formula	$C_{16}H_{22}ClN$	
Color	colourless	
Formula weight	263.79 g · mol^{-1}	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	MONOCLINIC	
Space group	**$P2_1/n$, (no. 14)**	
Unit cell dimensions	a = 11.4837(13) Å	α= 90°.
	b = 7.6493(9) Å	β= 90.774(2)°.
	c = 31.513(4) Å	γ = 90°.
Volume	2768.0(5) Å^3	
Z	8	
Density (calculated)	1.266 Mg · m^{-3}	

Absorption coefficient	0.259 mm^{-1}	
F(000)	1136 e	
Crystal size	0.051 x 0.042 x 0.023 mm^3	
θ range for data collection	1.292 to 31.250°.	
Index ranges	$-16 \leq h \leq 16$, $-11 \leq k \leq 11$, $-46 \leq l \leq 45$	
Reflections collected	73006	
Independent reflections	8928 [$R_{int} = 0.0750$]	
Reflections with I>2σ(I)	6540	
Completeness to θ = 25.242°	100.0 %	
Absorption correction	Gaussian	
Max. and min. transmission	1.00 and 0.99	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	8928 / 0 / 373	
Goodness-of-fit on F^2	1.026	
Final R indices [I>2 σ (I)]	$R_1 = 0.0444$	$wR^2 = 0.0994$
R indices (all data)	$R_1 = 0.0717$	$wR^2 = 0.1108$
Largest diff. peak and hole	0.4 and -0.3 e · $Å^{-3}$	

Table S4. Bond lengths [Å] and angles [°].

N(1)-C(1)	1.5127(19)	N(1)-C(16)	1.4982(18)
C(1)-C(2)	1.525(2)	C(1)-C(6)	1.5417(19)
C(2)-C(3)	1.525(2)	C(3)-C(4)	1.527(2)
C(4)-C(5)	1.528(2)	C(5)-C(6)	1.531(2)
C(6)-C(7)	1.5260(19)	C(7)-C(8)	1.5419(18)
C(7)-C(15)	1.5381(19)	C(8)-C(9)	1.515(2)
C(9)-C(10)	1.3912(19)	C(9)-C(14)	1.4048(19)
C(10)-C(11)	1.392(2)	C(11)-C(12)	1.389(2)
C(12)-C(13)	1.398(2)	C(13)-C(14)	1.383(2)
C(14)-C(15)	1.5124(19)	C(15)-C(16)	1.5111(19)
N(11)-C(21)	1.5121(19)	N(11)-C(36)	1.4961(18)
C(21)-C(22)	1.5255(19)	C(21)-C(26)	1.5369(19)
C(22)-C(23)	1.530(2)	C(23)-C(24)	1.527(2)

C(24)-C(25)	1.529(2)	C(25)-C(26)	1.532(2)
C(26)-C(27)	1.5203(19)	C(27)-C(28)	1.5407(18)
C(27)-C(35)	1.5393(19)	C(28)-C(29)	1.515(2)
C(29)-C(30)	1.3885(19)	C(29)-C(34)	1.403(2)
C(30)-C(31)	1.394(2)	C(31)-C(32)	1.387(2)
C(32)-C(33)	1.402(2)	C(33)-C(34)	1.387(2)
C(34)-C(35)	1.5119(19)	C(35)-C(36)	1.5112(18)

C(16)-N(1)-C(1)	114.05(11)	N(1)-C(1)-C(2)	109.46(11)
N(1)-C(1)-C(6)	111.08(11)	C(2)-C(1)-C(6)	112.63(12)
C(1)-C(2)-C(3)	112.90(12)	C(2)-C(3)-C(4)	110.49(12)
C(3)-C(4)-C(5)	110.40(12)	C(4)-C(5)-C(6)	111.02(12)
C(5)-C(6)-C(1)	111.73(11)	C(7)-C(6)-C(1)	107.23(11)
C(7)-C(6)-C(5)	115.75(11)	C(6)-C(7)-C(8)	121.97(12)
C(6)-C(7)-C(15)	112.81(11)	C(15)-C(7)-C(8)	102.41(11)
C(9)-C(8)-C(7)	100.45(11)	C(10)-C(9)-C(8)	129.92(13)
C(10)-C(9)-C(14)	119.97(14)	C(14)-C(9)-C(8)	110.08(12)
C(9)-C(10)-C(11)	118.91(13)	C(12)-C(11)-C(10)	120.74(13)
C(11)-C(12)-C(13)	120.71(15)	C(14)-C(13)-C(12)	118.42(14)
C(9)-C(14)-C(15)	108.30(12)	C(13)-C(14)-C(9)	121.15(13)
C(13)-C(14)-C(15)	130.55(13)	C(14)-C(15)-C(7)	101.04(11)
C(16)-C(15)-C(7)	110.98(11)	C(16)-C(15)-C(14)	119.29(12)
N(1)-C(16)-C(15)	107.56(11)	C(36)-N(11)-C(21)	113.38(11)
N(11)-C(21)-C(22)	110.27(11)	N(11)-C(21)-C(26)	110.74(11)
C(22)-C(21)-C(26)	112.34(12)	C(21)-C(22)-C(23)	113.27(12)
C(24)-C(23)-C(22)	110.85(12)	C(23)-C(24)-C(25)	111.17(12)
C(24)-C(25)-C(26)	110.85(12)	C(25)-C(26)-C(21)	111.61(11)
C(27)-C(26)-C(21)	107.50(11)	C(27)-C(26)-C(25)	115.42(11)
C(26)-C(27)-C(28)	121.80(12)	C(26)-C(27)-C(35)	113.39(11)
C(35)-C(27)-C(28)	102.03(11)	C(29)-C(28)-C(27)	100.52(11)
C(30)-C(29)-C(28)	129.76(14)	C(30)-C(29)-C(34)	120.26(14)
C(34)-C(29)-C(28)	109.95(12)	C(29)-C(30)-C(31)	118.77(14)
C(32)-C(31)-C(30)	121.02(14)	C(31)-C(32)-C(33)	120.47(15)
C(34)-C(33)-C(32)	118.49(14)	C(29)-C(34)-C(35)	108.19(13)
C(33)-C(34)-C(29)	120.96(13)	C(33)-C(34)-C(35)	130.84(13)
C(34)-C(35)-C(27)	100.70(10)	C(36)-C(35)-C(27)	111.60(11)
C(36)-C(35)-C(34)	120.37(12)	N(11)-C(36)-C(35)	107.38(11)

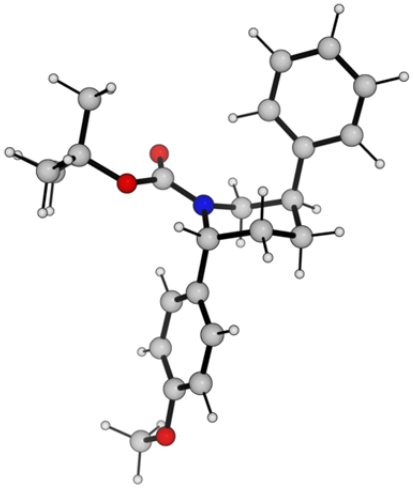
Table S5. Selected torsion angles [°].

H(1)-C(1)-N(1)-C(16)	-57.5(11)
H(1)-C(1)-C(2)-C(3)	172.2(12)
H(1)-C(1)-C(6)-C(5)	-173.3(12)
H(1)-C(1)-C(6)-H(6)	-56.3(15)
H(6)-C(6)-C(1)-N(1)	-169.6(10)
H(6)-C(6)-C(1)-H(1)	-56.3(15)
H(6)-C(6)-C(1)-C(2)	67.2(10)
H(6)-C(6)-C(5)-C(4)	-60.2(9)
H(7)-C(7)-C(6)-C(5)	174.4(9)
H(7)-C(7)-C(6)-H(6)	52.1(13)
H(7)-C(7)-C(15)-H(15)	175.6(13)
H(7)-C(7)-C(15)-C(16)	57.2(8)
H(15)-C(15)-C(7)-C(6)	59.2(10)
H(15)-C(15)-C(7)-H(7)	175.6(13)
H(15)-C(15)-C(14)-C(13)	-91.9(10)
H(15)-C(15)-C(16)-N(1)	-63.1(10)

Computational Details

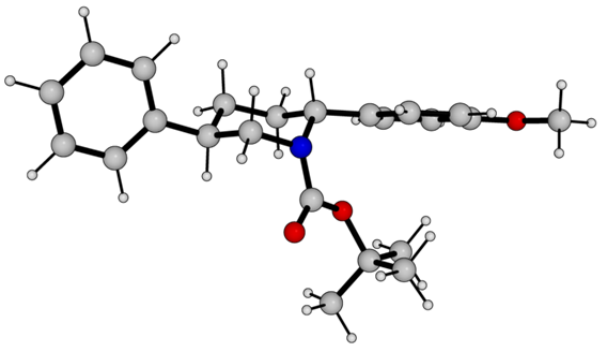
The conformational space for each intermediate was explored using the OPLS-2005 force field[6] and a modified Monte Carlo search routine implemented in MacroModel.[7] An energy cut-off of 84 kJ mol^{-1} was used for the conformational analysis, and structures with heavy-atom RMSDs less than 0.5 Å after the initial force field optimization were considered to be the same conformer. The remaining structures where subsequently optimized with the TPSS functional,[8] Grimme's D3 dispersion correction with Becke-Johnson damping,[9] the triple-ζ basis set 6-311+G(d,p) and the IEFPCM continuum model for chloroform.[10] Vibrational analysis verified that each structure was a minimum. Thermal corrections were calculated from unscaled harmonic vibrational frequencies at the same level of theory for a standard state of 1 mol L^{-1} and 298.15 K. Entropic contributions to free energies were obtained from partition functions evaluated with Grimme's quasi-harmonic approximation.[11] This method employs the free-rotor approximation for all frequencies below 100 cm^{-1}, the rigid-rotor-harmonic-oscillator (RRHO) approximation for all frequencies above 100 cm^{-1}, and a damping function to interpolate between the two expressions. Electronic energies were subsequently from single point calculations of the TPSS-D3BJ geometries employing Neese's domain-based local pair-natural orbital (DLPNO) approach to the CCSD(T) method [DLPNO-CCSD(T)] with the default normalPNO settings, the triple-ζ def2-TZVPP,[12] together with the appropriate auxiliary basis,[13] and the CPCM solvation model for chloroform.[14] All density functional theory calculations were performed with Gaussian 16,[15] natural, while the DLPNO-CCSD(T) calculations were performed with ORCA 4.[16]

Summary of Conformers



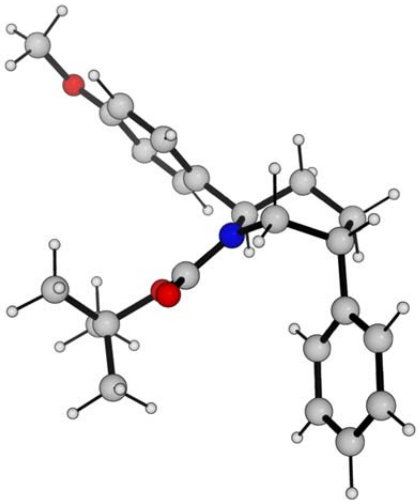
axial-axial chair

$\Delta\Delta G$ = 0.0 kJ mol^{-1}



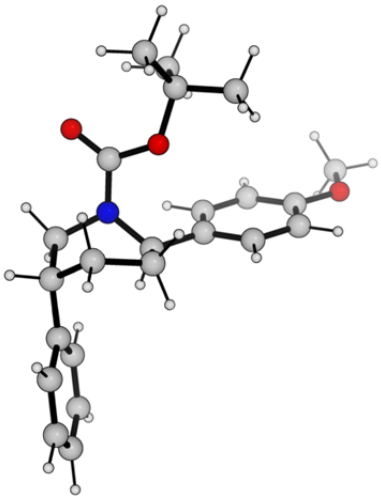
equatorial-equatorial chair

$\Delta\Delta G$ = +3.3 kJ mol^{-1}



axial-equatorial boat

$\Delta\Delta G$ = +7.1 kJ mol^{-1}



half-boat

$\Delta\Delta G$ = +35 kJ mol^{-1}

Structures and Energies for Different Conformers of 11

Axial-Axial Orientation

SCF energy:	–1172.355782
Zero-point correction:	+0.471330
Enthalpy correction:	+0.498578
Free energy correction:	+0.413050
Grimme's Delta G correction:	+0.419057

Cartesian Coordinates

C	-0.29116	-0.37045	0.88681
N	0.40168	0.11571	-0.32465
C	0.69051	-0.87631	-1.37471
C	0.50922	-1.56435	1.44805
C	0.71911	-2.65136	0.38853
H	-0.00013	-1.97251	2.32703
H	1.48264	-1.18586	1.78522
C	1.48562	-2.07336	-0.82771
H	-0.25434	-3.02922	0.04628
H	1.26553	-3.49816	0.81795
H	1.21992	-0.35693	-2.17469
H	-0.26155	-1.25028	-1.77805
C	0.61431	1.44291	-0.58911
O	0.17004	2.22313	0.43343
O	1.15324	1.86370	-1.61663
C	0.35432	3.70093	0.39151
C	-0.25832	4.13335	1.72657
H	-1.31165	3.83722	1.77819
H	-0.19404	5.22276	1.82418
H	0.28015	3.67362	2.56250
C	1.84765	4.04066	0.33982
H	2.37614	3.54154	1.16020
H	1.97128	5.12378	0.45867
H	2.28749	3.73435	-0.61156
C	-0.43112	4.28912	-0.78532
H	-1.47860	3.97015	-0.73525
H	-0.00243	3.97394	-1.73894
H	-0.40073	5.38358	-0.72373
C	-1.76483	-0.68026	0.59900

H	-0.24845	0.44553	1.61137
C	-2.52702	-1.47777	1.47287
C	-2.41831	-0.12627	-0.50738
C	-3.77681	-0.35842	-0.75877
C	-4.51369	-1.16180	0.12156
C	-3.87975	-1.71825	1.24417
H	-4.23943	0.08827	-1.63284
H	-1.86442	0.50311	-1.19918
H	-2.06696	-1.91865	2.35347
O	-5.84675	-1.45928	-0.02695
C	-6.51972	-0.89913	-1.16815
H	-7.54927	-1.25235	-1.09862
H	-6.06507	-1.25376	-2.10175
H	-6.49773	0.19743	-1.13477
C	2.94106	-1.76575	-0.48350
H	1.48603	-2.83468	-1.62101
C	3.50602	-0.48734	-0.61464
C	4.84822	-0.25832	-0.28410
C	5.65289	-1.30298	0.17923
C	5.10562	-2.58631	0.30133
C	3.76586	-2.81025	-0.02620
H	2.90932	0.34161	-0.98432
H	5.26163	0.74212	-0.39250
H	6.69421	-1.12360	0.43607
H	5.72232	-3.41256	0.64813
H	3.35636	-3.81463	0.06824
H	-4.46020	-2.33587	1.92435

Axial-Equatorial Orientation

SCF energy: –1172.353410

Zero-point correction: +0.470673

Enthalpy correction: +0.498168

Free energy correction: +0.411520

Grimme's Delta G correction: +0.417992

Cartesian Coordinates

C	-0.17268	-1.16505	0.58988
N	0.55548	-0.57880	-0.56058
C	1.41223	-1.45267	-1.36268

C	0.23039	-2.64877	0.71107
C	1.75825	-2.80373	0.76718
H	-0.19231	-3.21309	-0.13013
H	-0.22925	-3.04854	1.62163
C	2.46756	-2.14678	-0.46094
H	2.02132	-3.86582	0.82086
H	2.12458	-2.34224	1.69236
H	1.88911	-0.83052	-2.12124
H	0.80013	-2.20913	-1.87036
C	0.56985	0.77354	-0.78884
O	-0.07990	1.41180	0.22171
O	1.09490	1.31684	-1.76115
C	-0.43367	2.85100	0.10812
C	-1.23747	3.08251	1.39083
H	-2.11514	2.42793	1.41299
H	-1.56967	4.12581	1.43449
H	-0.61954	2.87457	2.27149
C	0.84052	3.70197	0.09363
H	1.45866	3.46835	0.96820
H	0.56504	4.76274	0.13849
H	1.42127	3.51943	-0.81293
C	-1.31005	3.06781	-1.13006
H	-2.16991	2.38867	-1.10347
H	-0.74189	2.89598	-2.04726
H	-1.68137	4.09950	-1.13073
C	-1.67680	-0.98924	0.45872
H	0.15224	-0.64888	1.50406
C	-2.46379	-0.77921	1.60163
C	-2.31395	-1.05013	-0.78351
C	-3.70214	-0.90271	-0.89990
C	-4.47238	-0.69310	0.25332
C	-3.84593	-0.63325	1.50917
H	-4.16307	-0.94527	-1.88140
H	-1.72129	-1.18969	-1.68497
H	-1.98499	-0.71085	2.57716
O	-5.83762	-0.52712	0.25512
C	-6.50490	-0.56694	-1.01798
H	-6.36335	-1.54092	-1.50331
H	-6.14120	0.23364	-1.67459
H	-7.56161	-0.41336	-0.79544
C	3.55045	-1.15225	-0.08095
H	2.93196	-2.92986	-1.07268
C	4.78674	-1.17124	-0.74640
C	5.77333	-0.22028	-0.46459

C	5.53415	0.77709	0.48723
C	4.30688	0.80707	1.15908
C	3.32791	-0.15194	0.88137
H	4.97533	-1.93996	-1.49436
H	6.72568	-0.25748	-0.98871
H	6.29674	1.52082	0.70555
H	4.10954	1.57844	1.90017
H	2.38282	-0.11388	1.41774
H	-4.45410	-0.45927	2.39288

Equatorial-Equatorial Orientation

SCF energy:	–1172.352260
Zero-point correction:	+0.470572
Enthalpy correction:	+0.498057
Free energy correction:	+0.412429
Grimme's Delta G correction:	+0.418262

Cartesian Coordinates

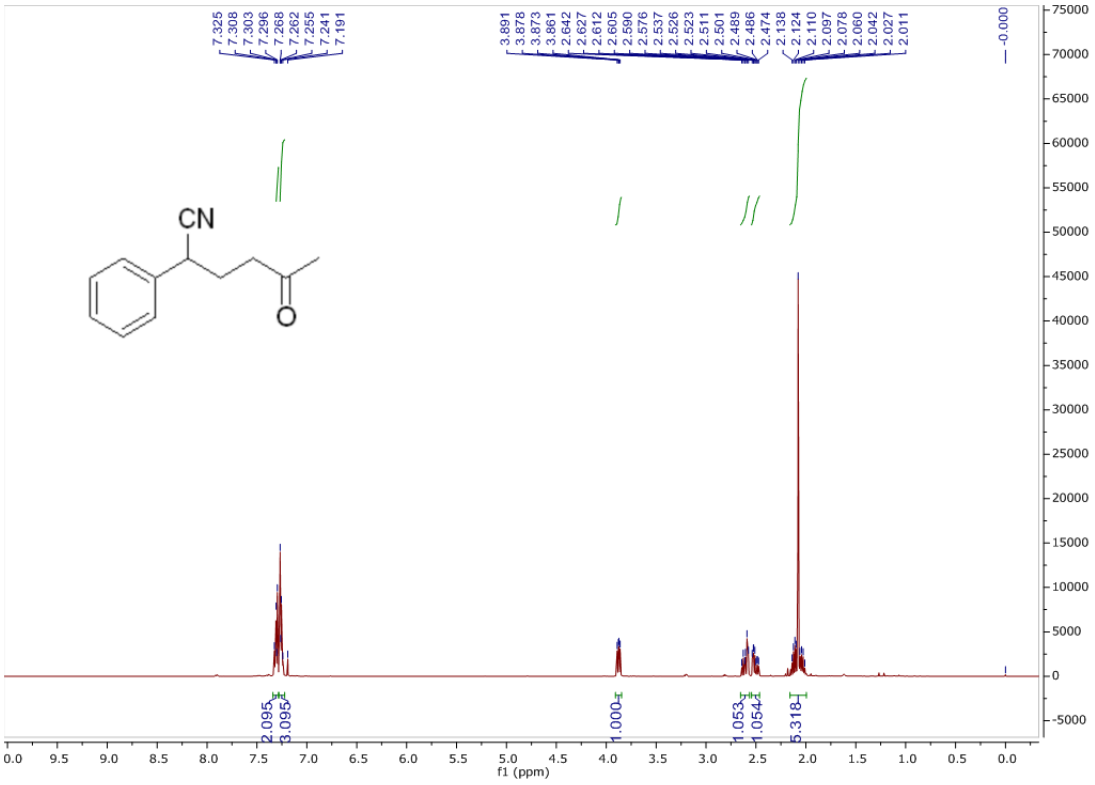
C	0.01569	-1.14521	0.18389
N	-0.50683	-0.02496	-0.65068
C	-1.93748	-0.19526	-0.95381
C	-0.67925	-1.10711	1.55418
C	-2.20512	-1.20939	1.35947
H	-0.40954	-0.17635	2.07014
H	-0.34093	-1.94597	2.17456
C	-2.75417	-0.16036	0.36343
H	-2.71935	-1.09854	2.32179
H	-2.44279	-2.21571	0.98513
H	-2.06385	-1.15870	-1.46256
H	-2.24828	0.60529	-1.62607
C	-0.06745	1.28277	-0.55155
O	1.01685	1.38101	0.25232
O	-0.60319	2.22266	-1.14110
C	1.86917	2.60407	0.23381
C	3.02929	2.19919	1.14620
H	2.66209	1.96276	2.15078
H	3.74361	3.02720	1.21898
H	3.54040	1.31829	0.74577
C	2.36494	2.86284	-1.19240

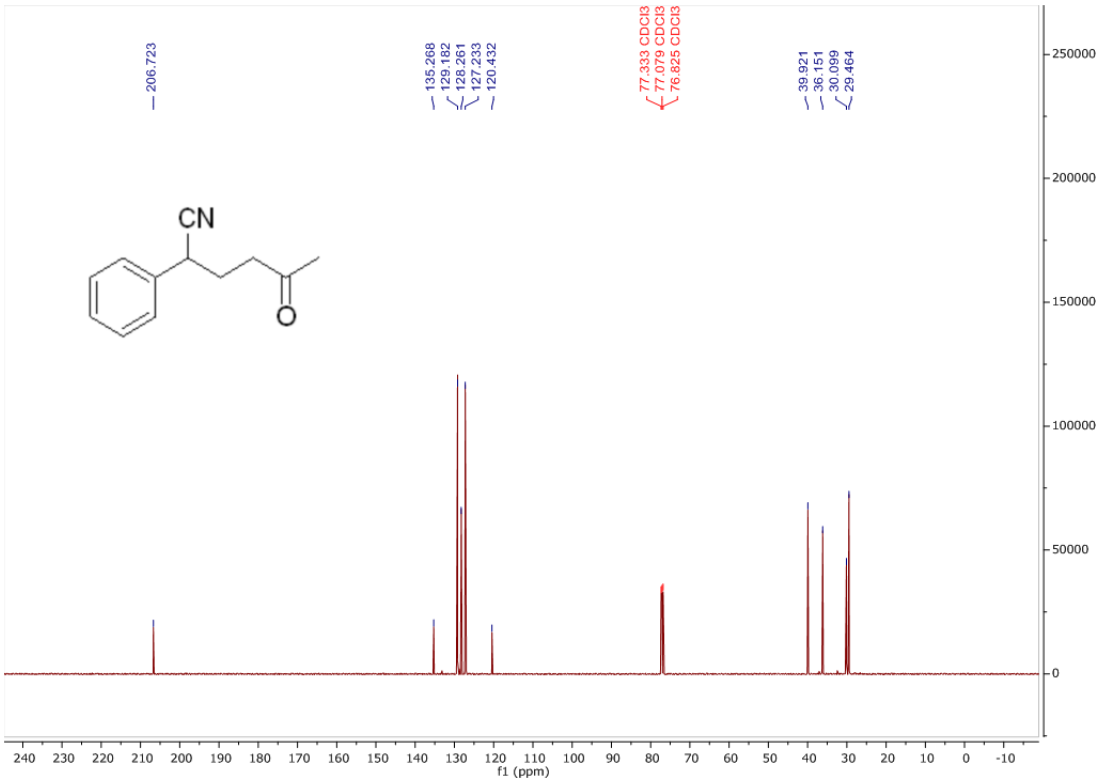
H	3.09075	3.68450	-1.17453
H	2.86340	1.96833	-1.58273
H	1.53937	3.13616	-1.85379
C	1.09283	3.78784	0.81899
H	1.77089	4.64350	0.92519
H	0.70624	3.53023	1.81188
H	0.26032	4.06850	0.17046
C	1.53144	-1.25432	0.17154
H	-0.36309	-2.03806	-0.33878
C	2.21151	-1.23052	-1.05220
C	2.28419	-1.42699	1.34141
C	3.67183	-1.55863	1.29392
C	4.34028	-1.51101	0.06200
C	3.60317	-1.34769	-1.12150
H	4.25299	-1.68304	2.20375
H	1.79311	-1.44159	2.31036
H	1.64693	-1.09197	-1.97198
O	5.70971	-1.63064	0.11251
C	6.41966	-1.56269	-1.13599
H	7.47383	-1.66540	-0.87536
H	6.24928	-0.59752	-1.62989
H	6.11867	-2.38096	-1.80238
C	-4.23507	-0.33216	0.09082
H	-2.60304	0.83843	0.79680
C	-4.74674	-1.53483	-0.42819
C	-6.11205	-1.67716	-0.69463
C	-6.99263	-0.61752	-0.44539
C	-6.49577	0.58497	0.06894
C	-5.12824	0.72388	0.33120
H	-4.07614	-2.36923	-0.62511
H	-6.48878	-2.61521	-1.09607
H	-8.05458	-0.72866	-0.65070
H	-7.17090	1.41479	0.26524
H	-4.74490	1.66270	0.72738
H	4.09494	-1.31157	-2.08826

Copies of NMR Spectra

Cyanoketones

NMR Spectra of **4aa**




206.723
135.268
129.182
128.261
127.233
120.432
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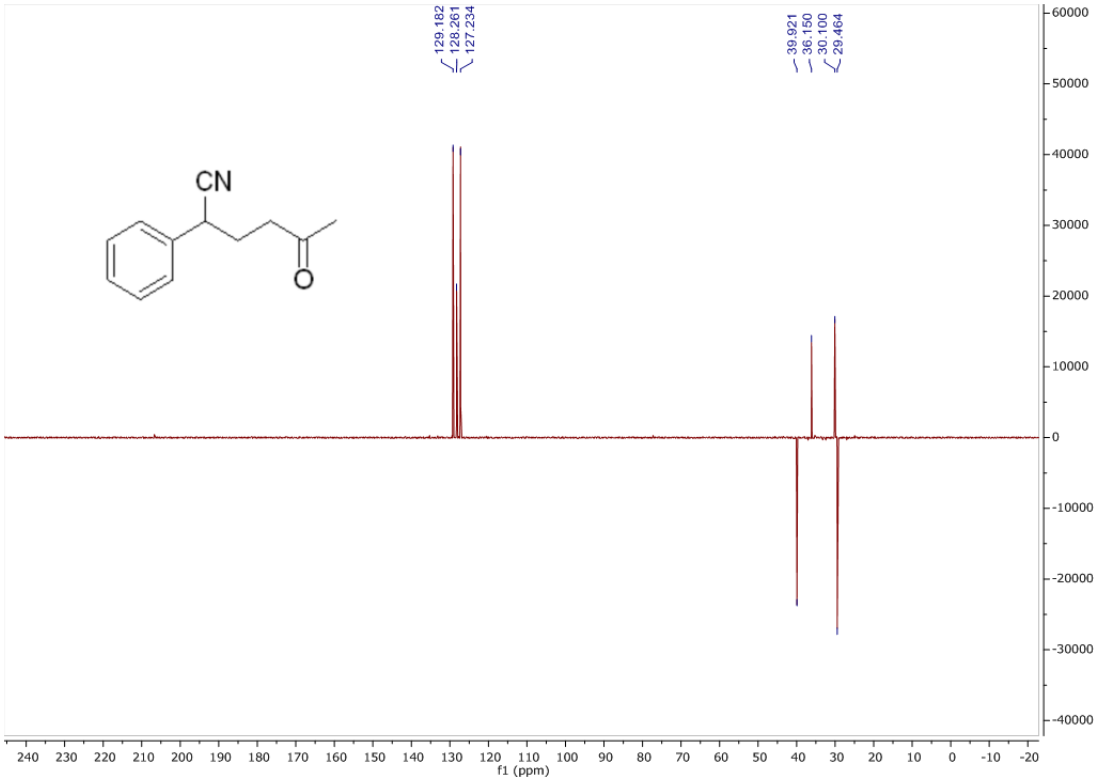
77.079 CDCl3
76.825 CDCl3
39.921
36.151
30.099
29.464
CN
O
f1 (ppm)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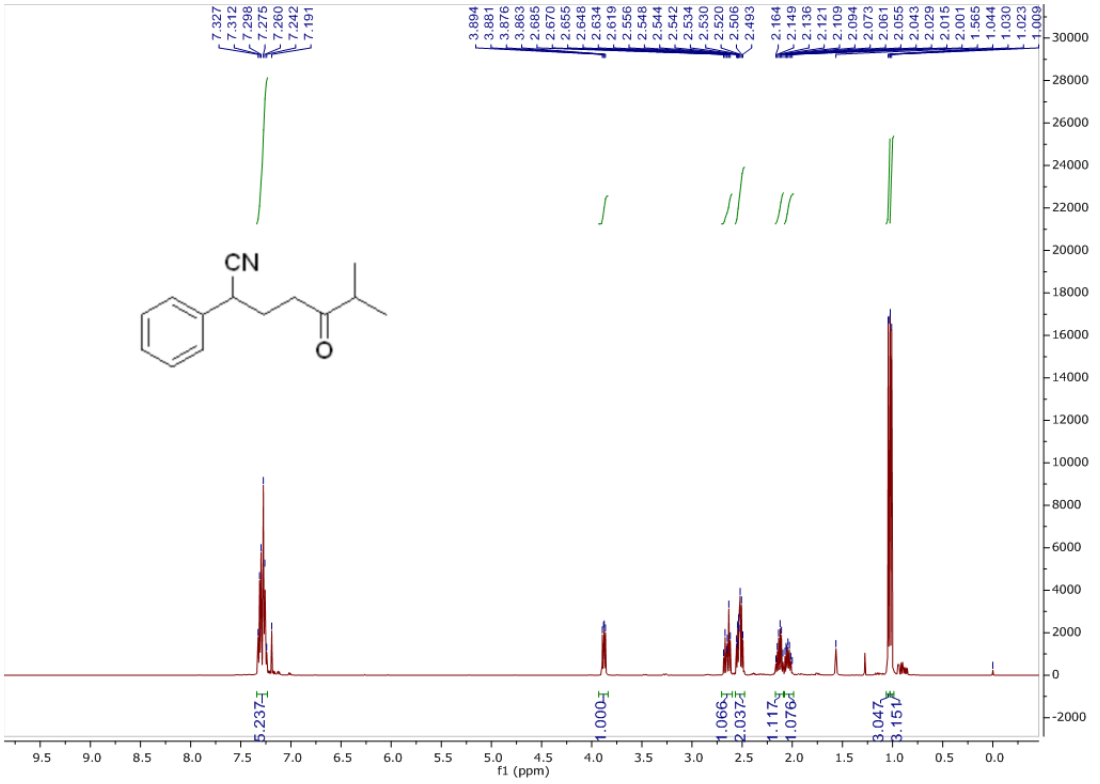
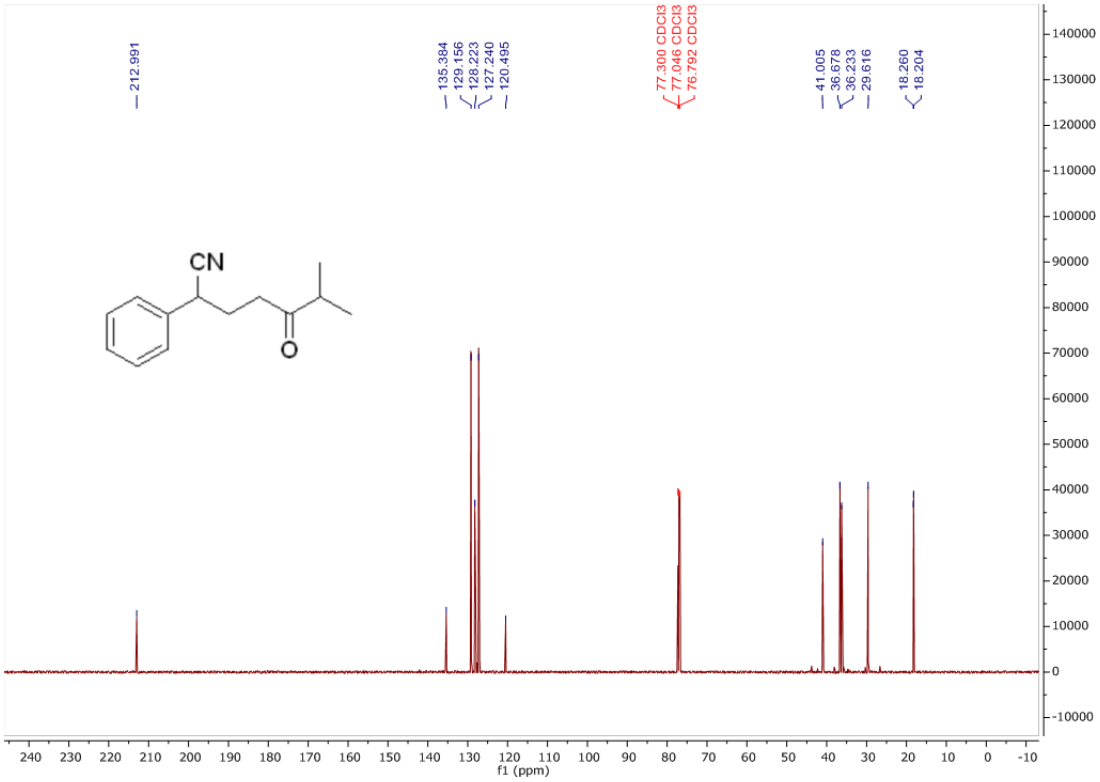
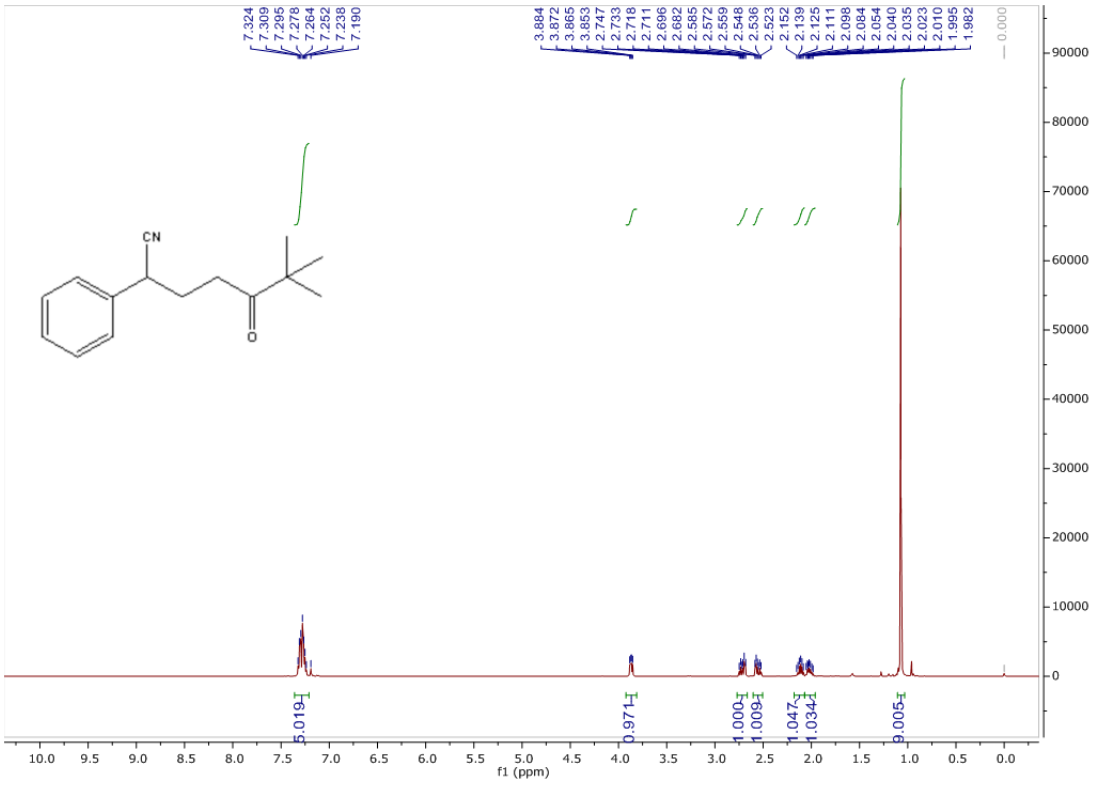
128.261
127.234
39.921
36.150
30.100
29.464
CN
O
f1 (ppm)

NMR Spectra of **4ab**





NMR Spectra of **4ac**

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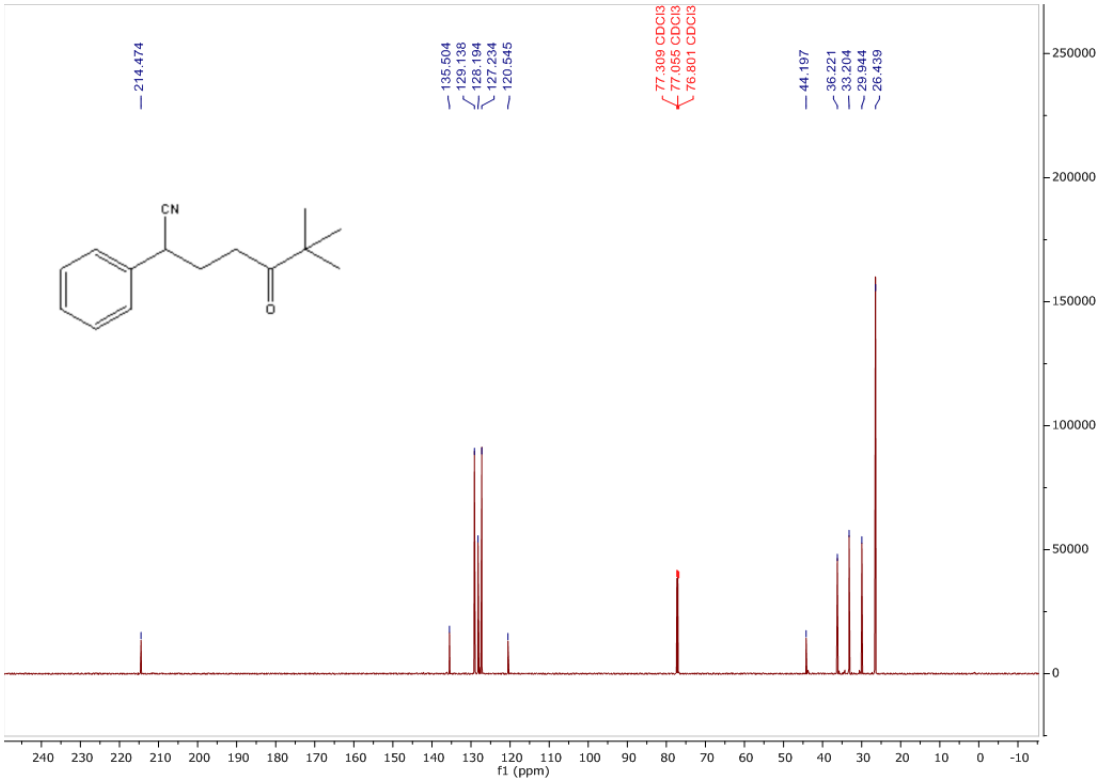
29.943
26.437
CN
O
f1 (ppm)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120.545
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77.055 CDCl3
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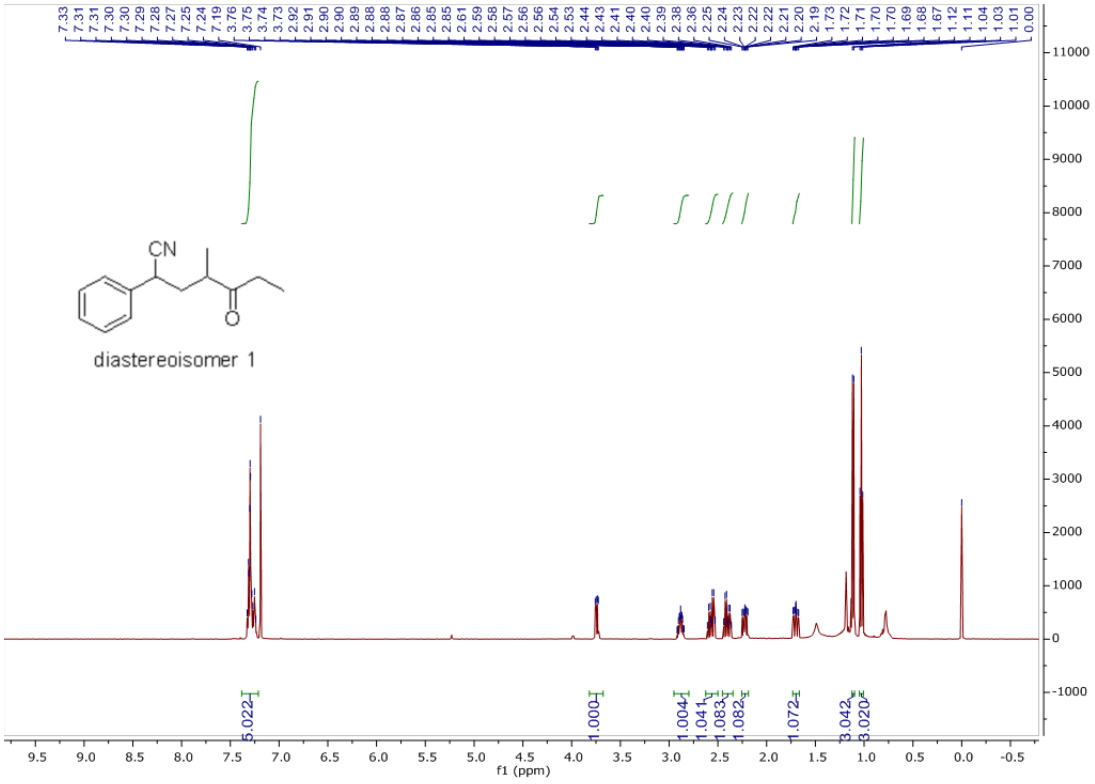
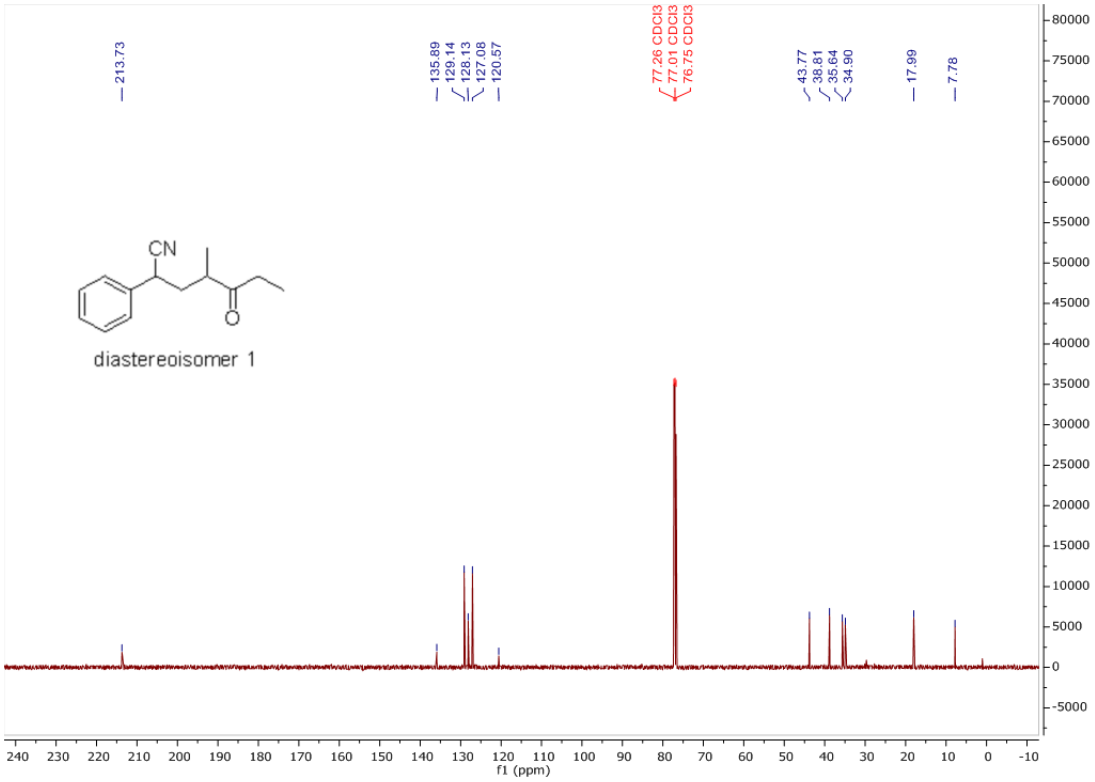
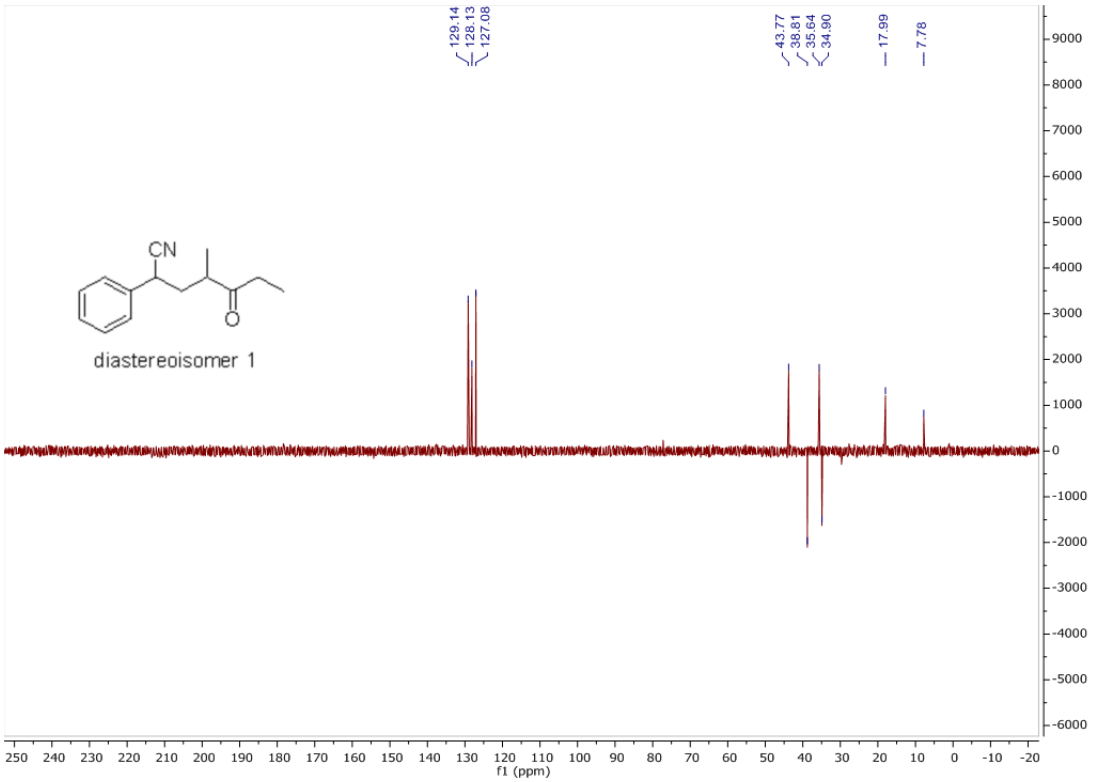
36.221
33.204
29.944
26.439
CN
O
f1 (ppm)

NMR Spectra of **4ad**



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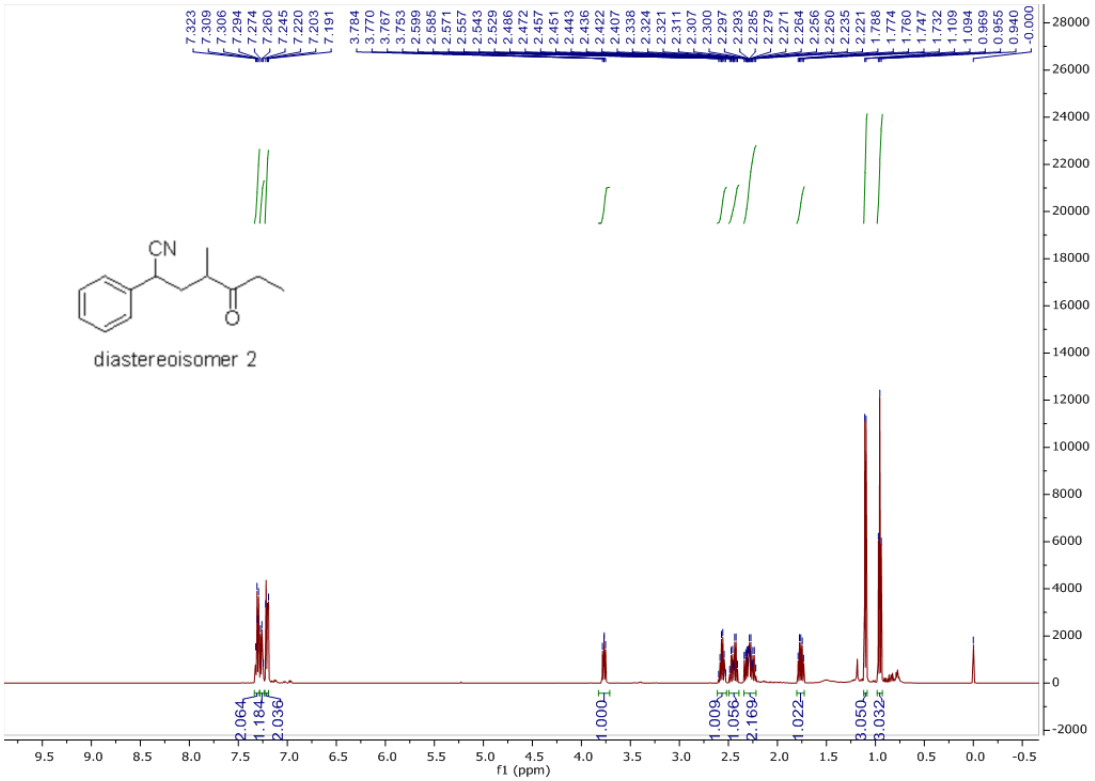
17.99
7.78
CN
O
diastereoisomer 1
f1 (ppm)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2.585
2.571
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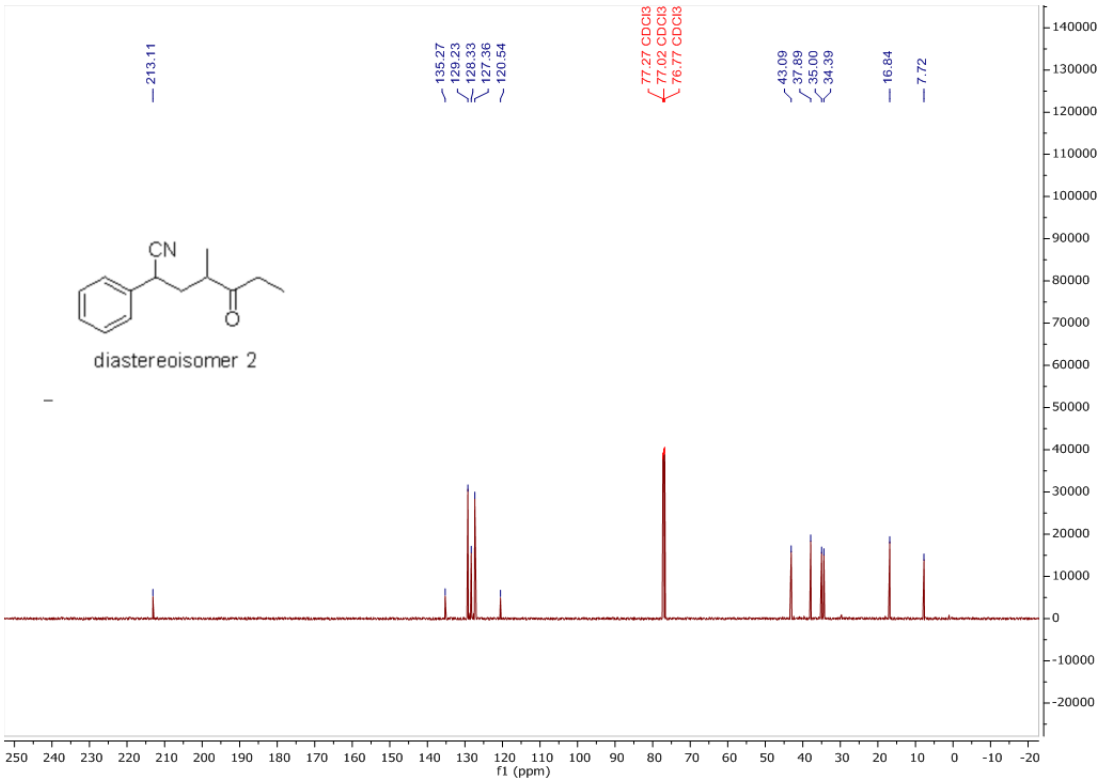
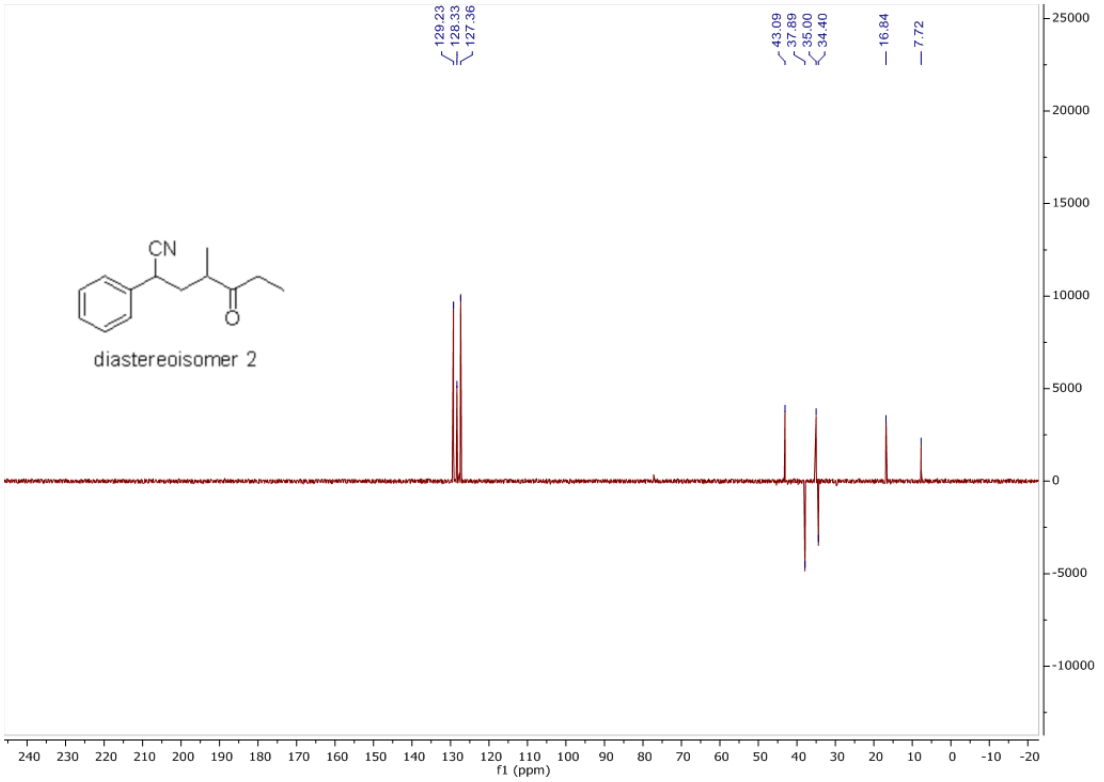
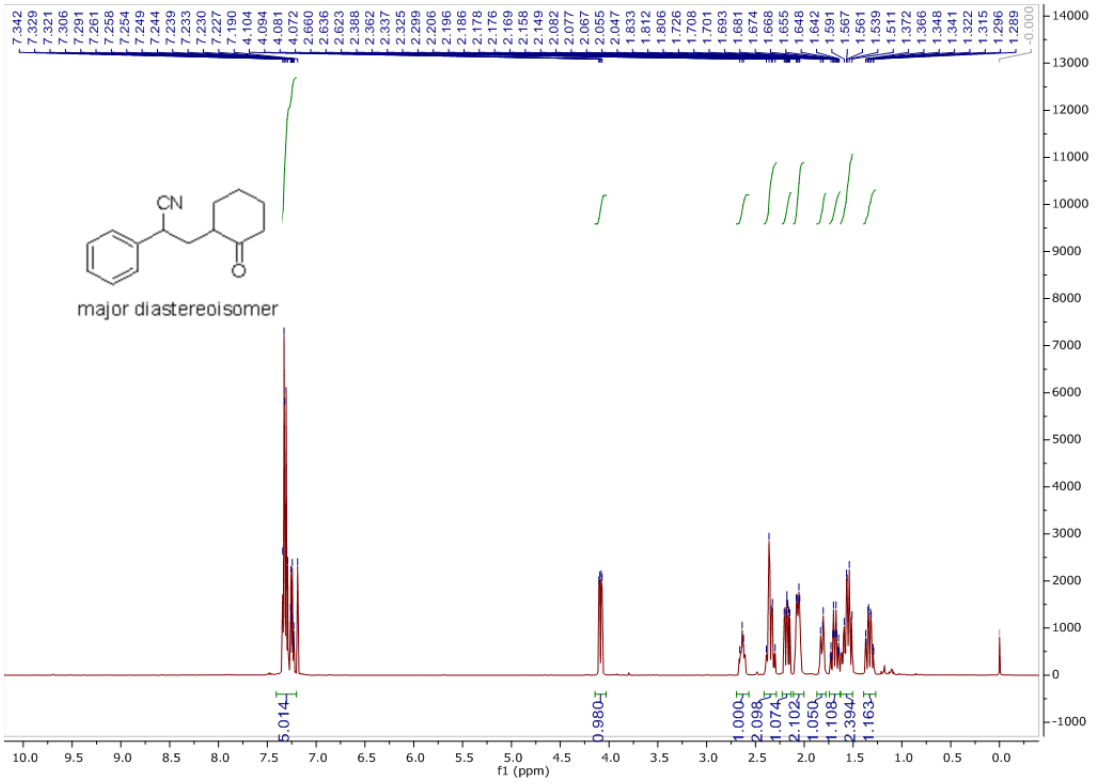
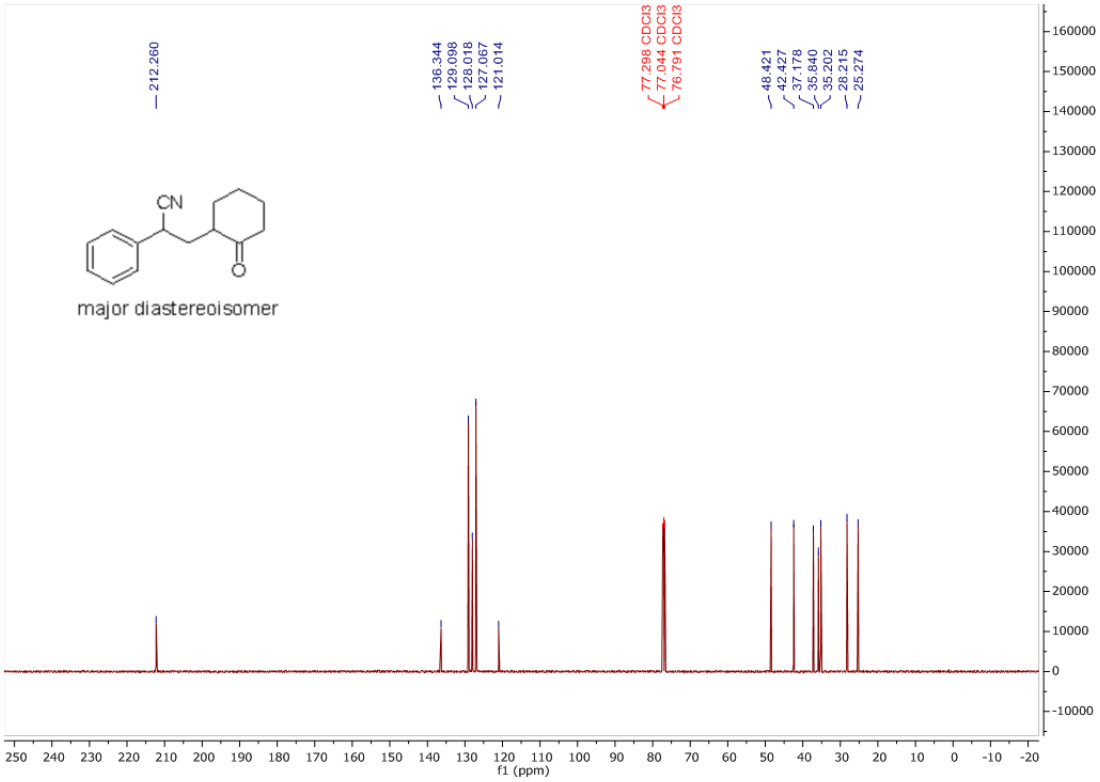
2.543
2.529
2.486
2.472
2.457
2.451
2.443
2.436
2.422
2.407
2.338
2.324
2.321
2.311
2.307
2.300
2.297
2.293
2.285
2.279
2.271
2.264
2.256
2.250
2.235
2.221
1.788
1.774
1.760
1.747
1.732
1.109
1.094
0.969
0.955
0.940
-0.000
2.064
1.184
2.036
1.000
1.009
1.056
2.169
1.022
3.050
3.032
CN
O
diastereoisomer 2
f1 (ppm)


213.11
135.27
129.23
128.33
127.36
120.54
77.27 CDCl3
77.02 CDCl3
76.77 CDCl3
43.09
37.89
35.00
34.39
16.84
7.72
CN
O
diastereoisomer 2
f1 (ppm)

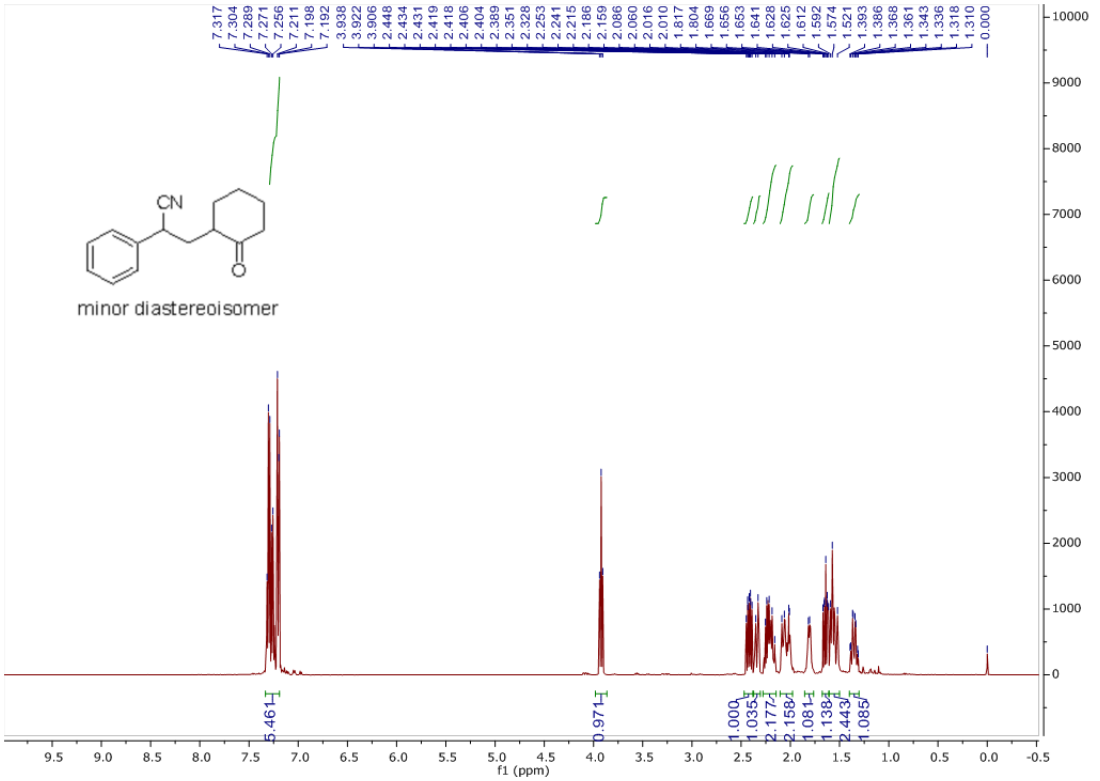

129.23
128.33
127.36
43.09
37.89
35.00
34.40
16.84
7.72
CN
O
diastereoisomer 2
f1 (ppm)

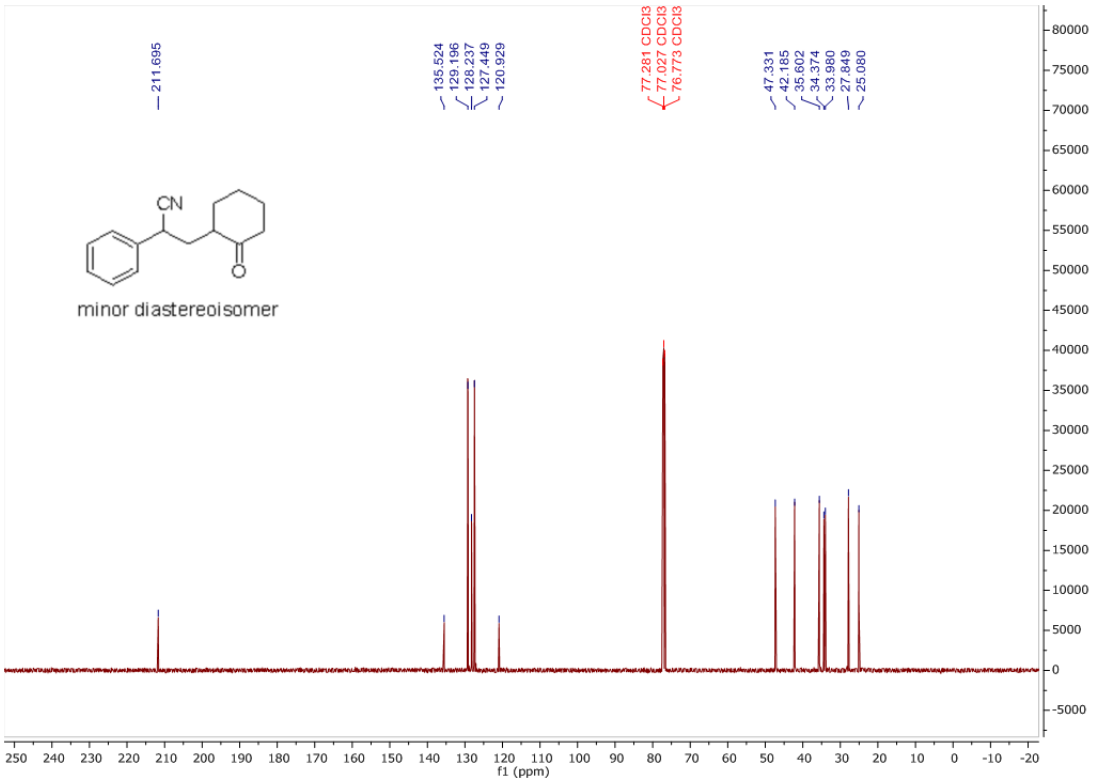
NMR Spectra of **4ae**

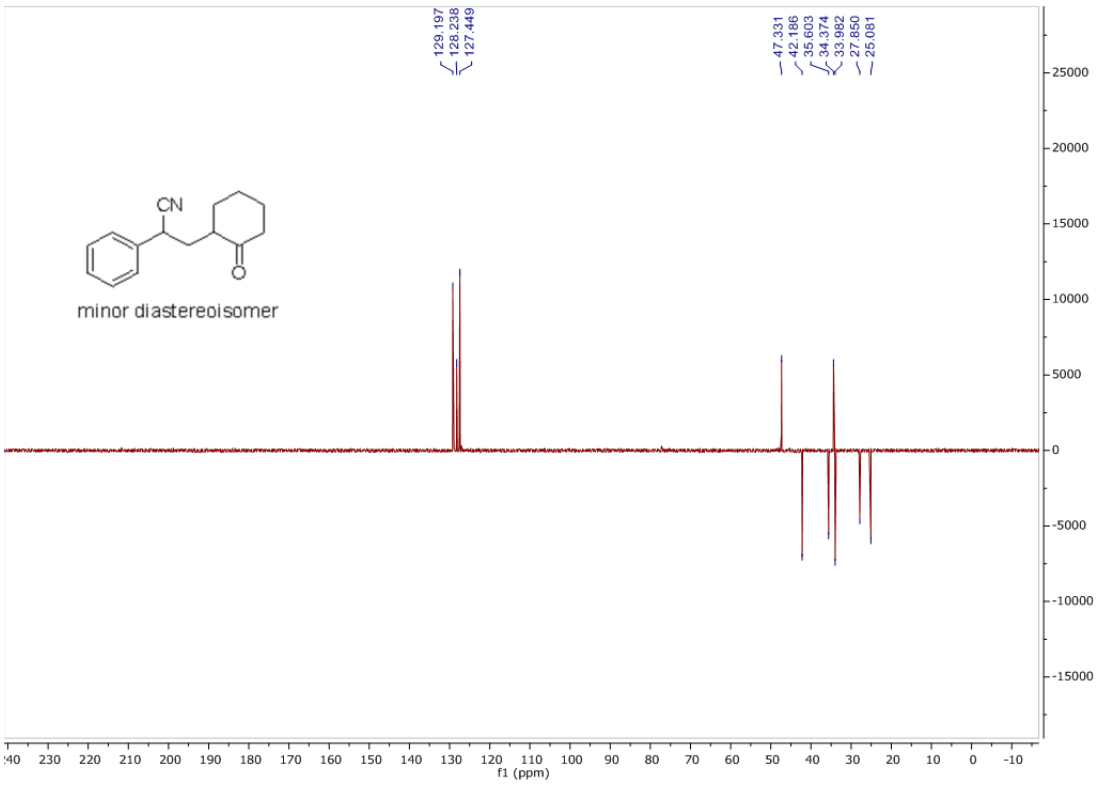




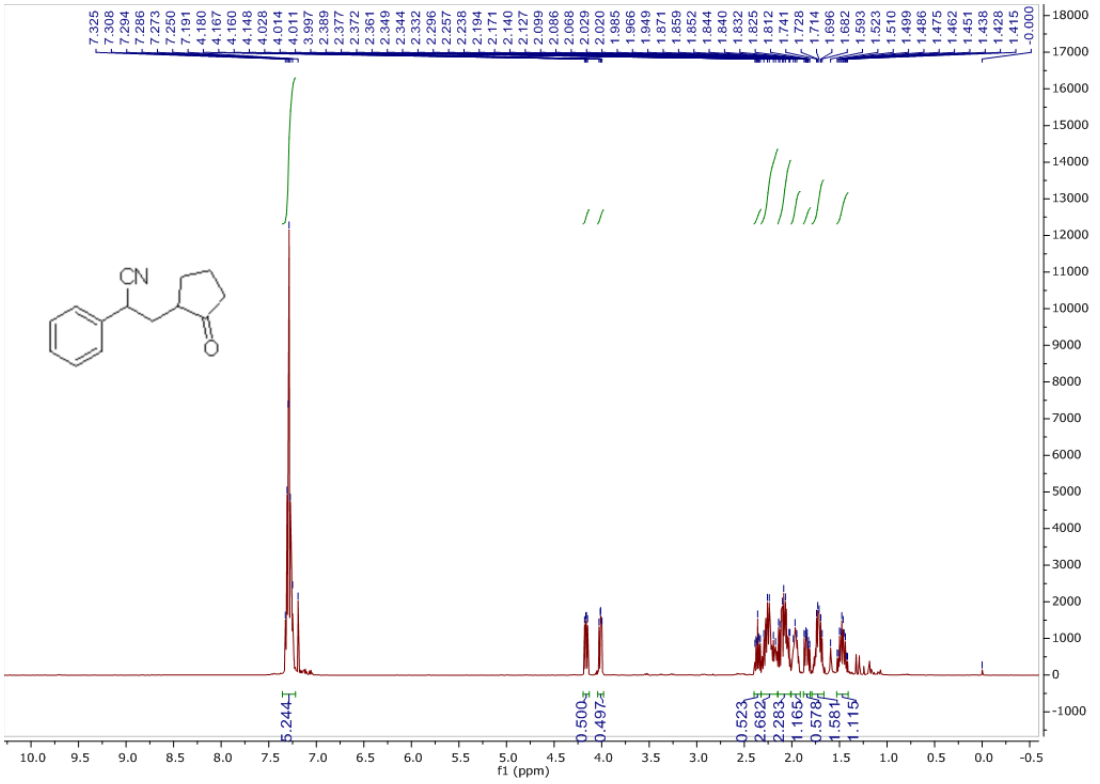

129.099
128.021
127.068
48.420
42.429
37.177
35.839
35.201
28.214
25.273
CN
major diastereoisomer
f1 (ppm)

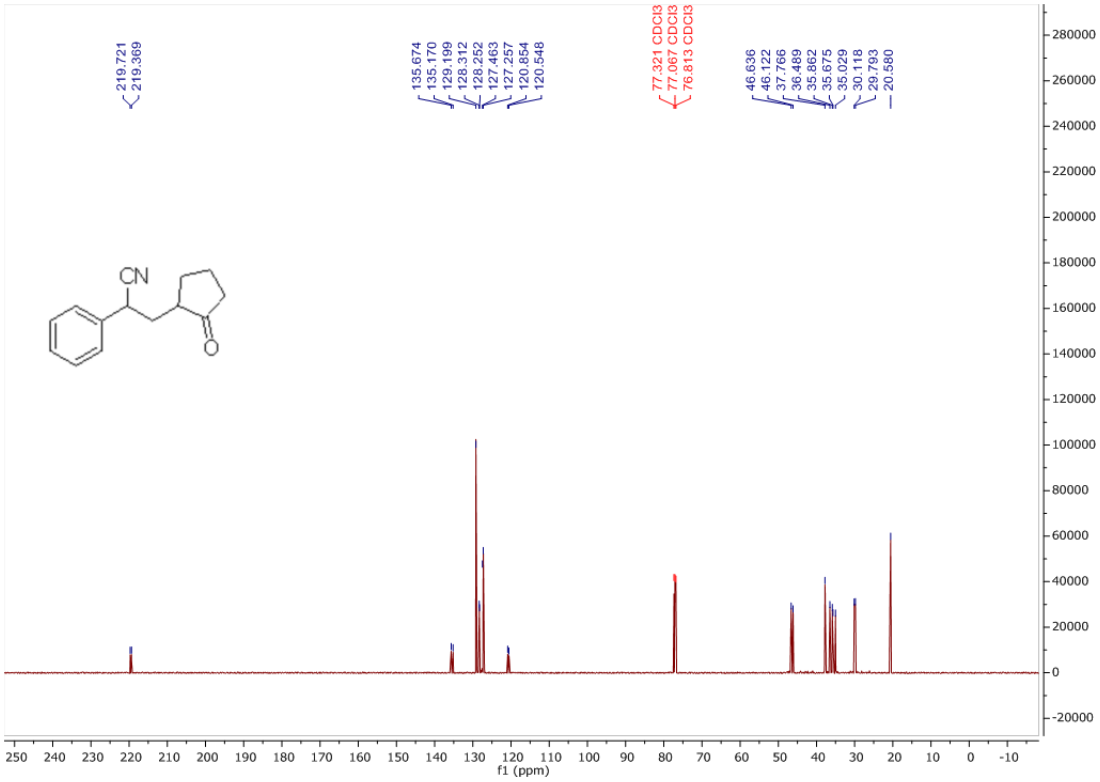

7.317
7.304
7.289
7.271
7.256
7.211
7.198
7.192
3.938
3.922
3.906
2.448
2.434
2.431
2.419
2.418
2.406
2.404
2.389
2.351
2.328
2.253
2.241
2.215
2.186
2.159
2.086
2.060
2.016
2.010
1.817
1.804
1.669
1.656
1.653
1.641
1.628
1.625
1.612
1.592
1.574
1.521
1.393
1.386
1.368
1.361
1.343
1.336
1.318
1.310
0.000
CN
minor diastereoisomer
5.461
0.971
1.000
1.035
2.177
2.158
1.081
1.138
2.443
1.085
f1 (ppm)

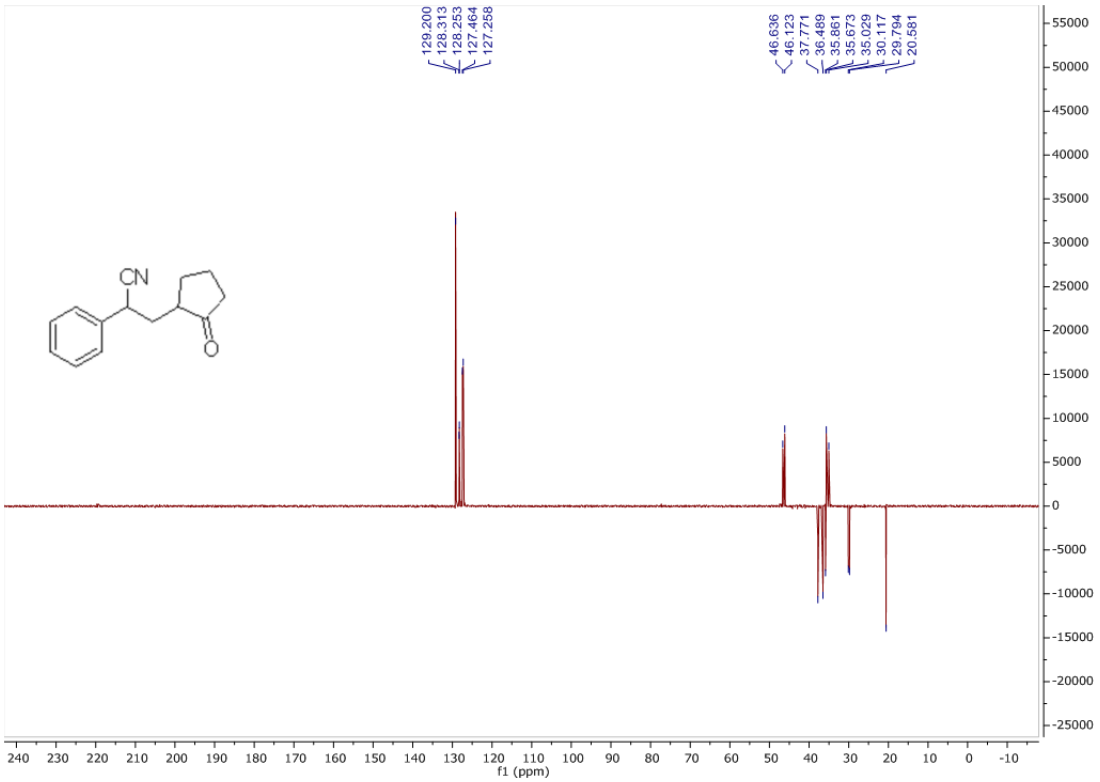

211.695
135.524
129.196
128.237
127.449
120.929
77.281 CDCl3
77.027 CDCl3
76.773 CDCl3
47.331
42.185
35.602
34.374
33.980
27.849
25.080
CN
O
minor diastereoisomer
f1 (ppm)


129.197
128.238
127.449
47.331
42.186
35.603
34.374
33.982
27.850
25.081
CN
O
minor diastereoisomer
f1 (ppm)

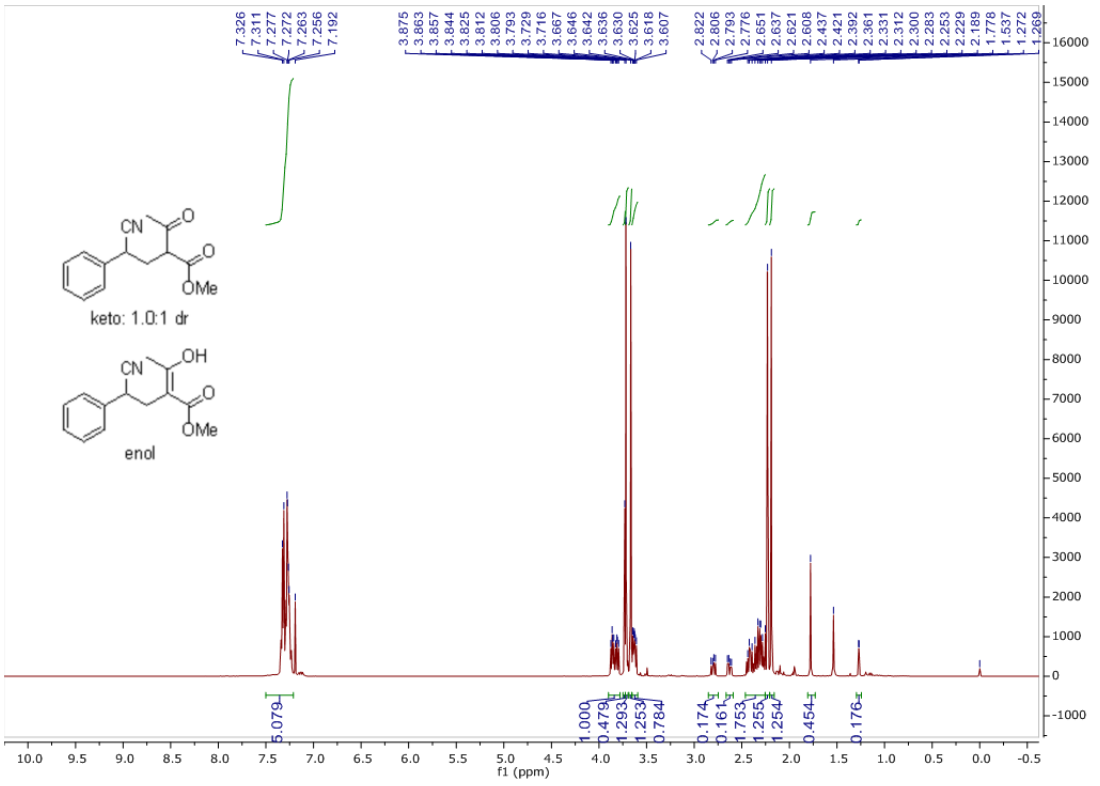
NMR Spectra of **4af**

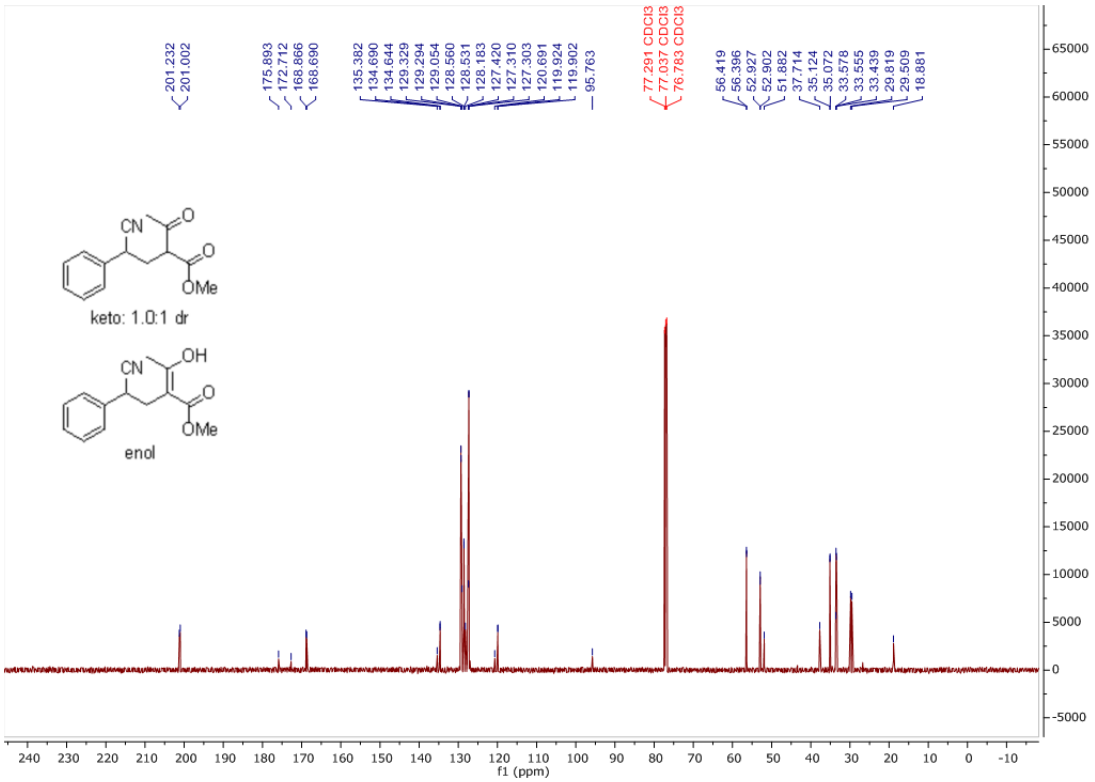


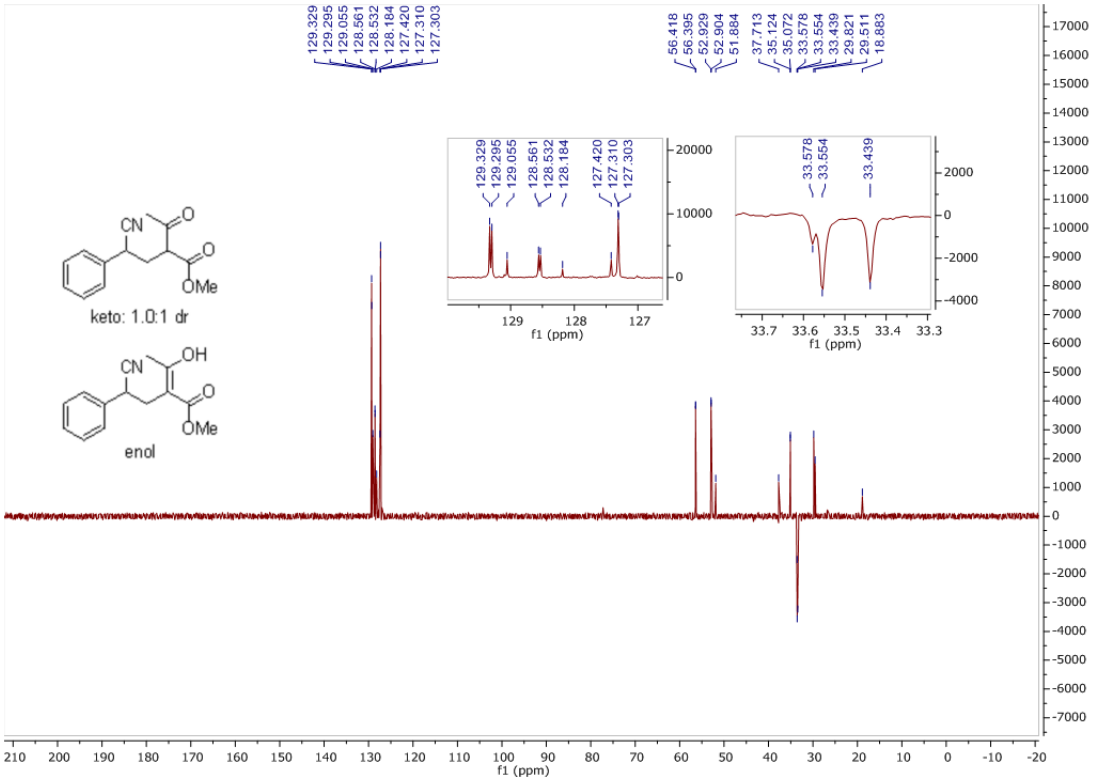




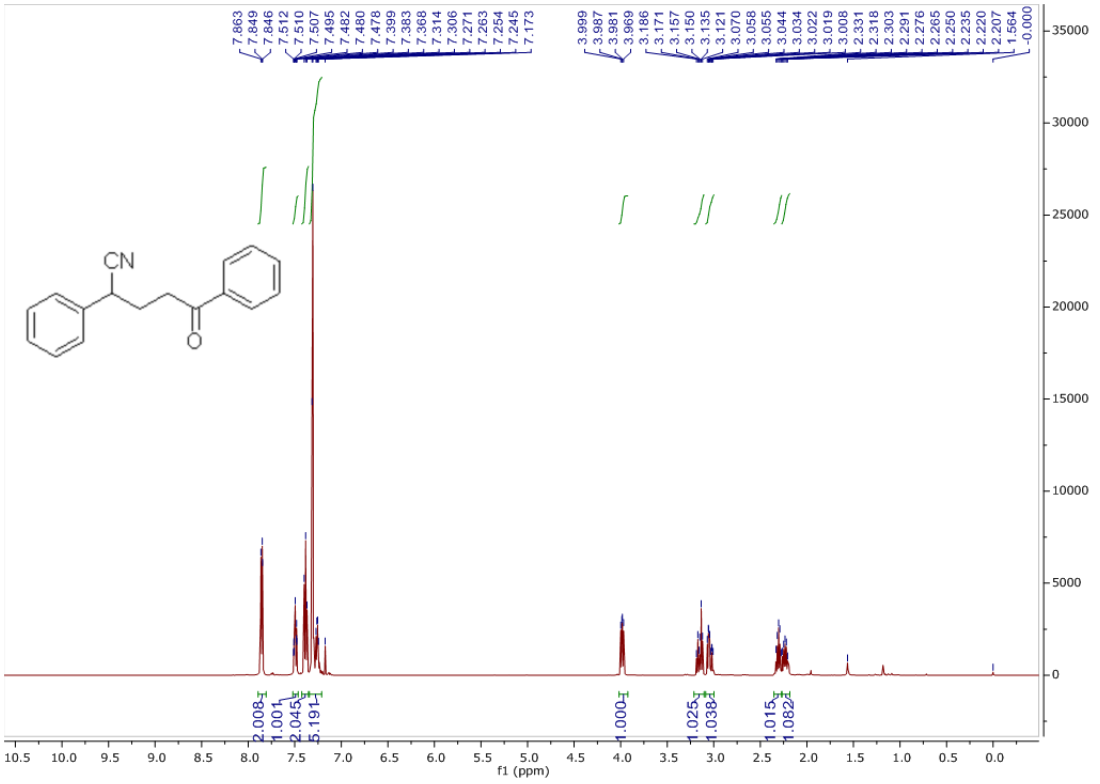
NMR Spectra of **4ag**

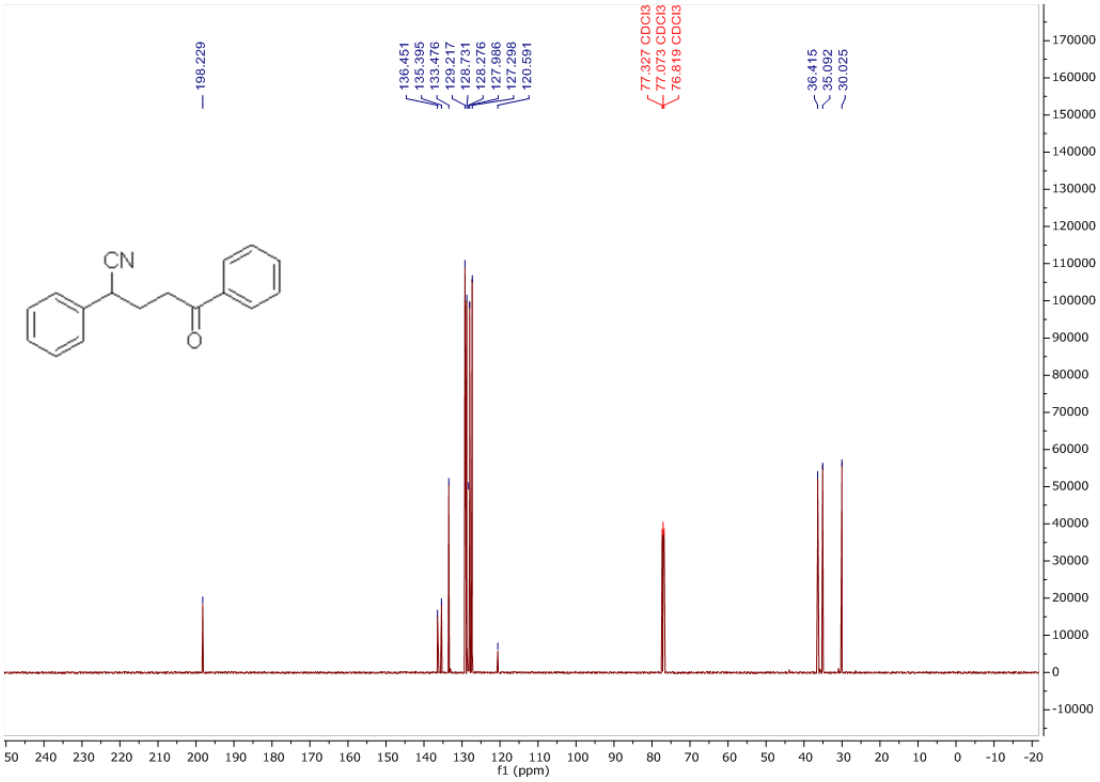


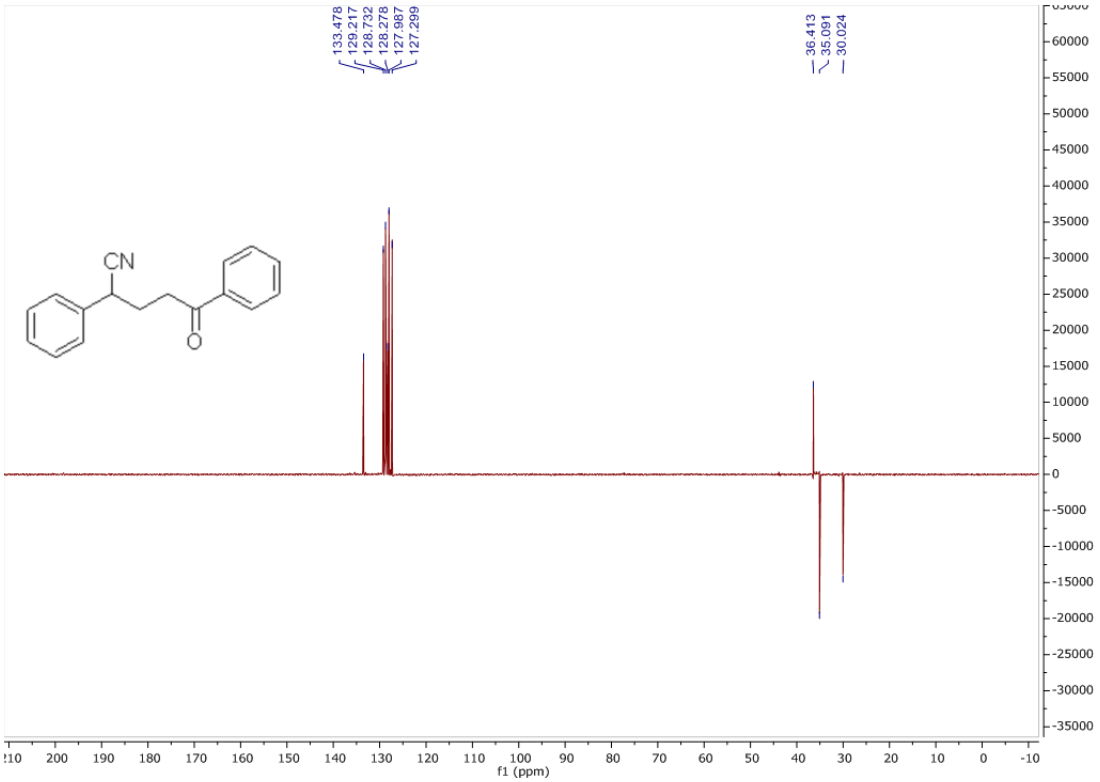

201.232
201.002
175.893
172.712
168.866
168.690
135.382
134.690
134.644
129.329
129.294
129.054
128.560
128.531
128.183
127.420
127.310
127.303
120.691
119.924
119.902
95.763
77.291 CDCl3
77.037 CDCl3
76.783 CDCl3
56.419
56.396
52.927
52.902
51.882
37.714
35.124
35.072
33.578
33.555
33.439
29.819
29.509
18.881
CN
O
O
OMe
keto: 1.0:1 dr
CN
OH
O
OMe
enol
f1 (ppm)


129.329
129.295
129.055
128.561
128.532
128.184
127.420
127.310
127.303
56.418
56.395
52.929
52.904
51.884
37.713
35.124
35.072
33.578
33.554
33.439
29.821
29.511
18.883
CN
O
O
OMe
keto: 1.0:1 dr
CN
OH
O
OMe
enol
f1 (ppm)

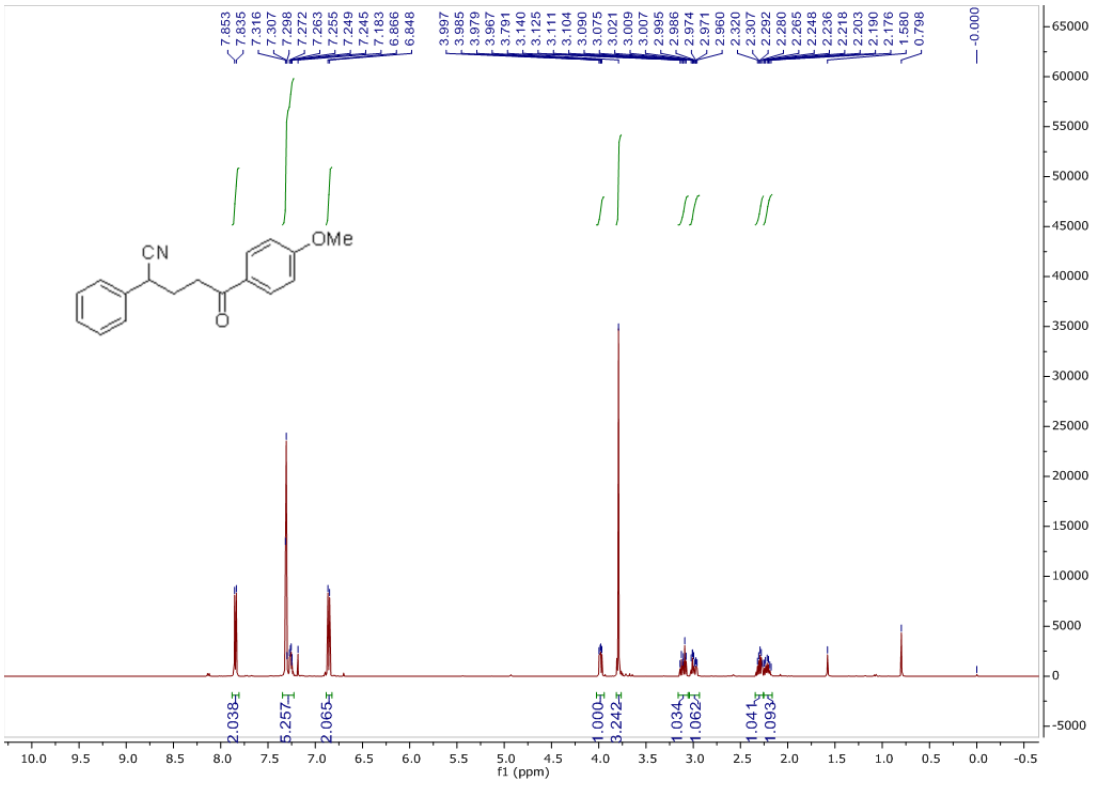
NMR Spectra of **4ah**

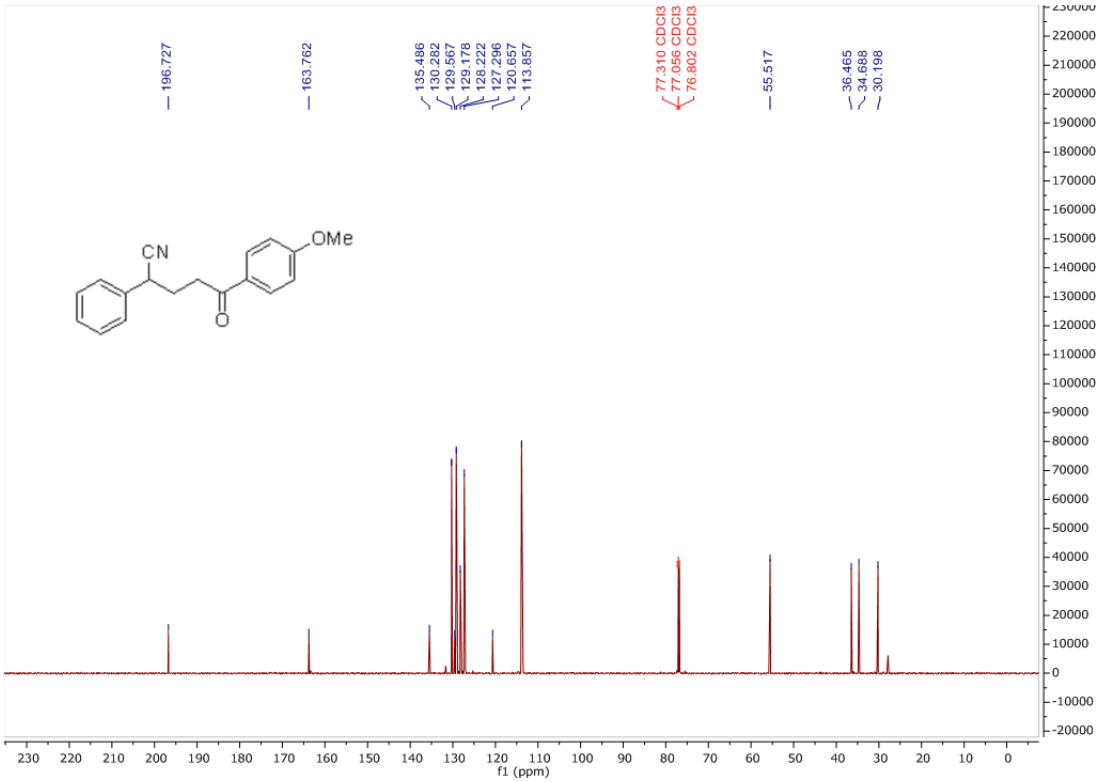


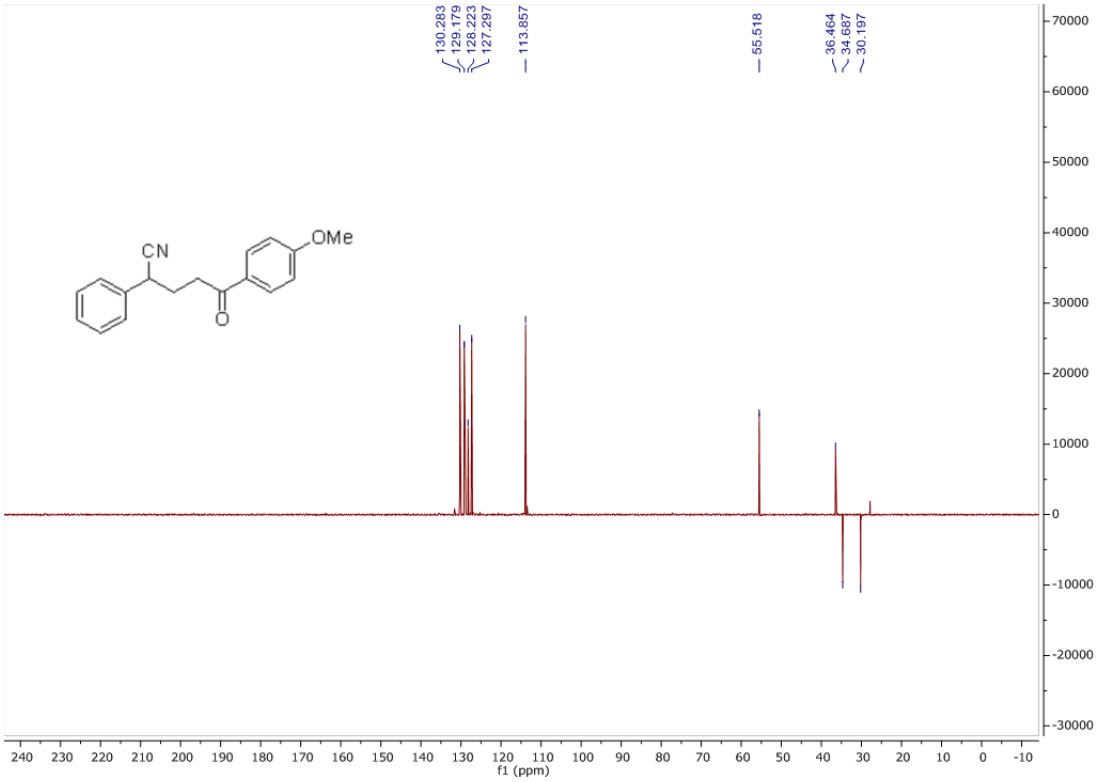




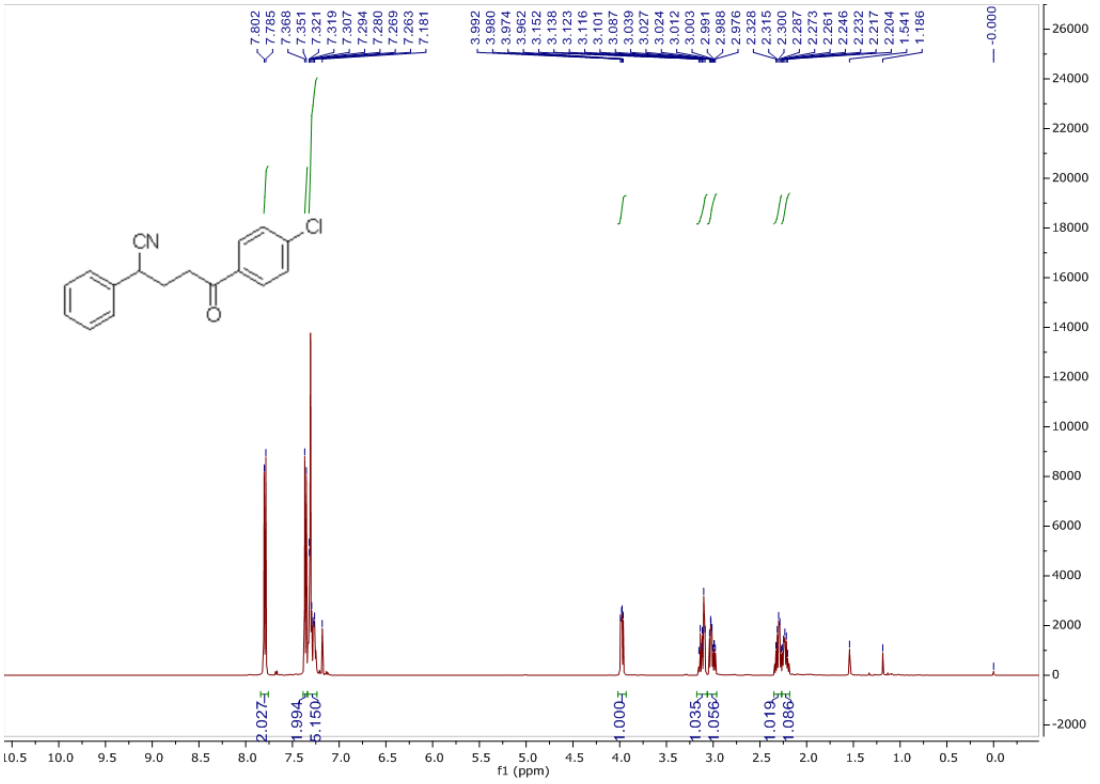
NMR Spectra of **4ai**

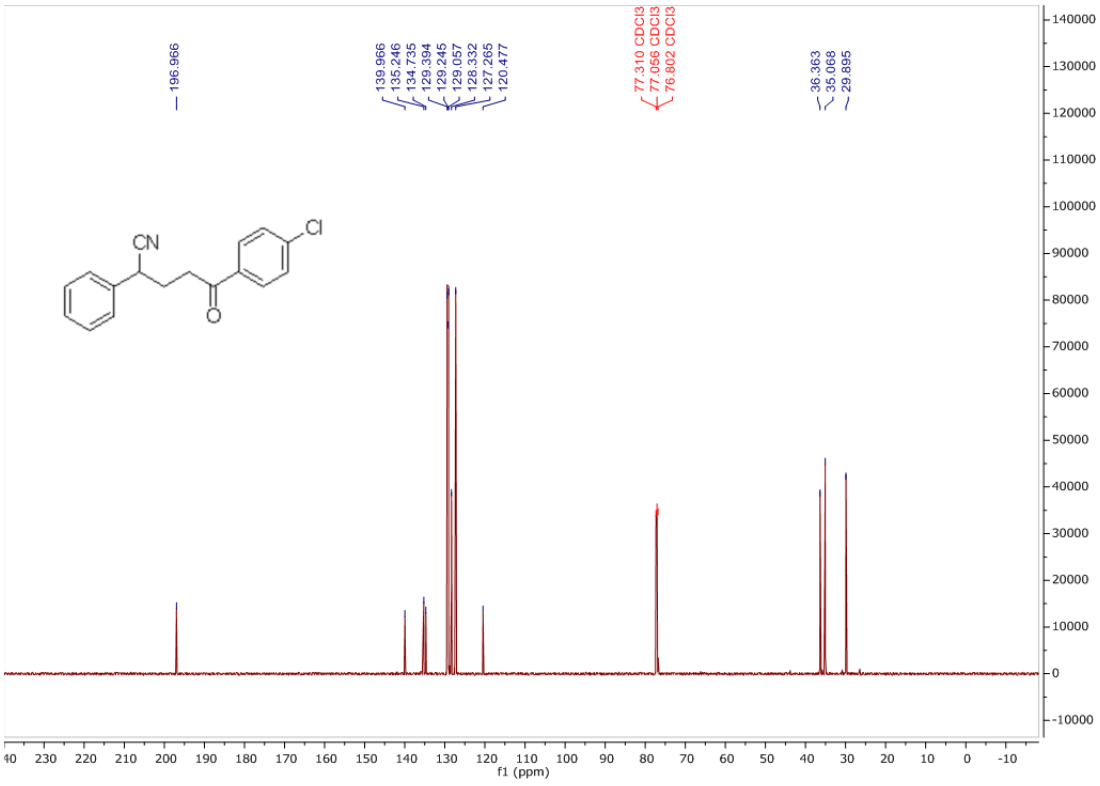


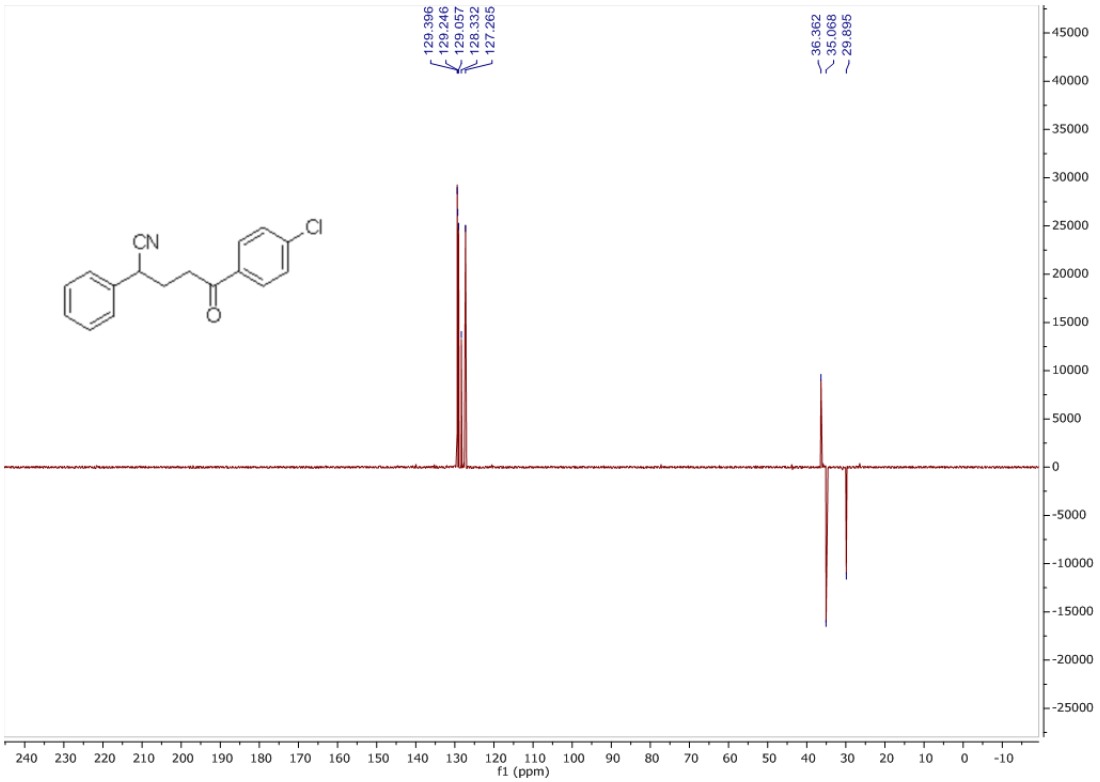

196.727
163.762
135.486
130.282
129.567
129.178
128.222
127.296
120.657
113.857
77.310 CDCl3
77.056 CDCl3
76.802 CDCl3
55.517
36.465
34.688
30.198
CN
OMe
O
f1 (ppm)


130.283
129.179
128.223
127.297
113.857
55.518
36.464
34.687
30.197
CN
OMe
O
f1 (ppm)

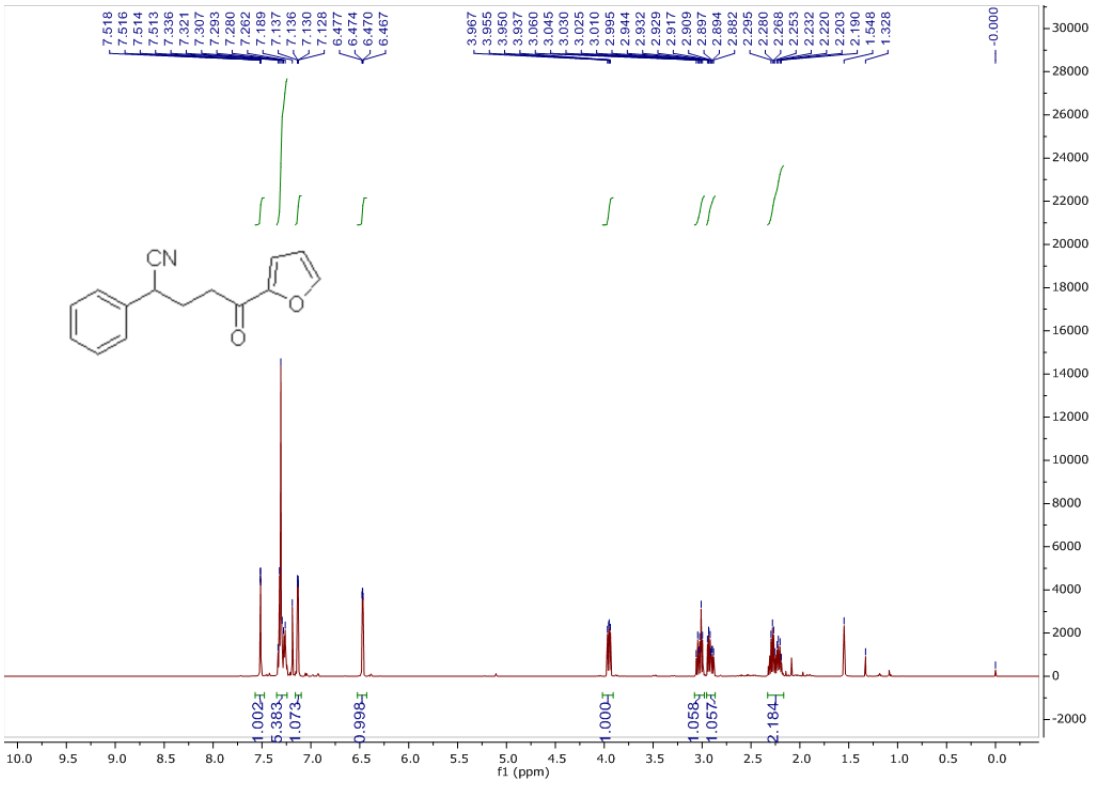
NMR Spectra of **4aj**

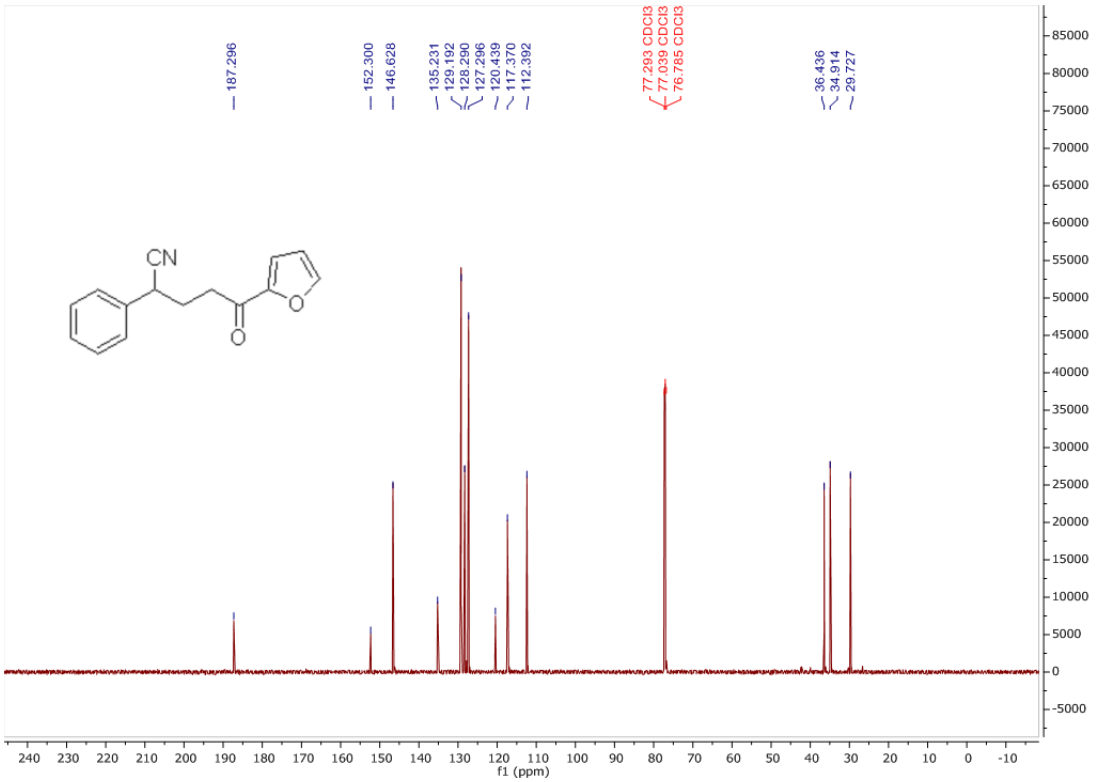






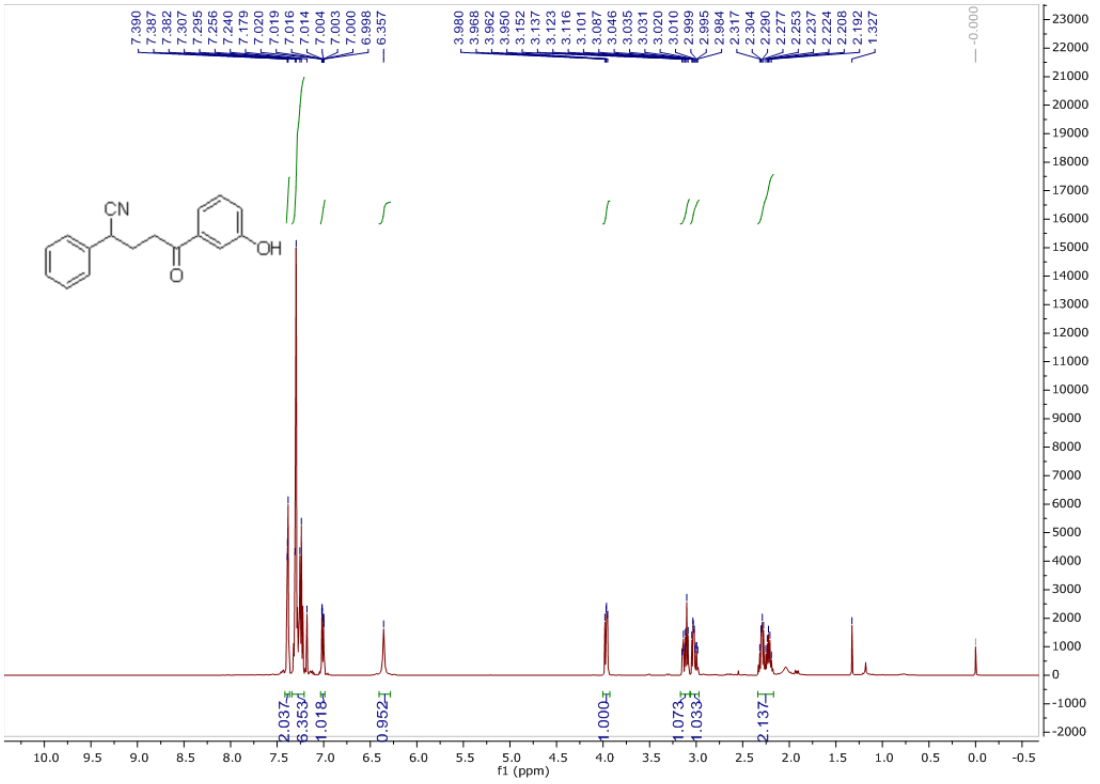
NMR Spectra of **4ak**

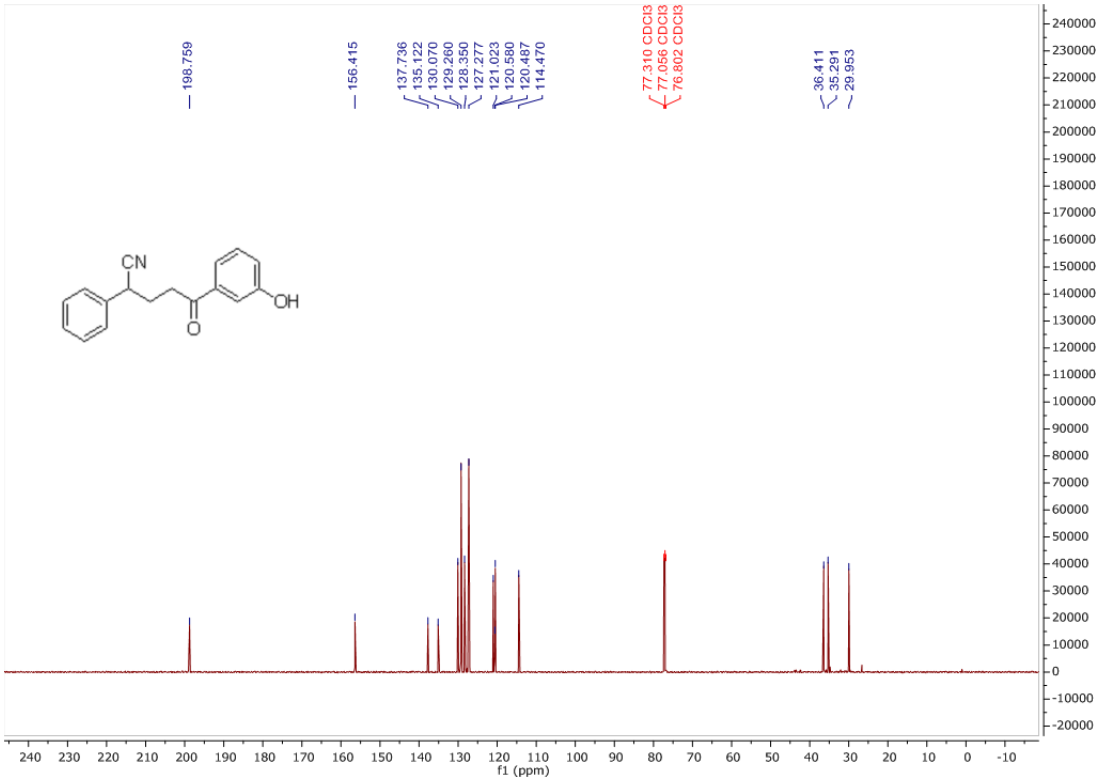


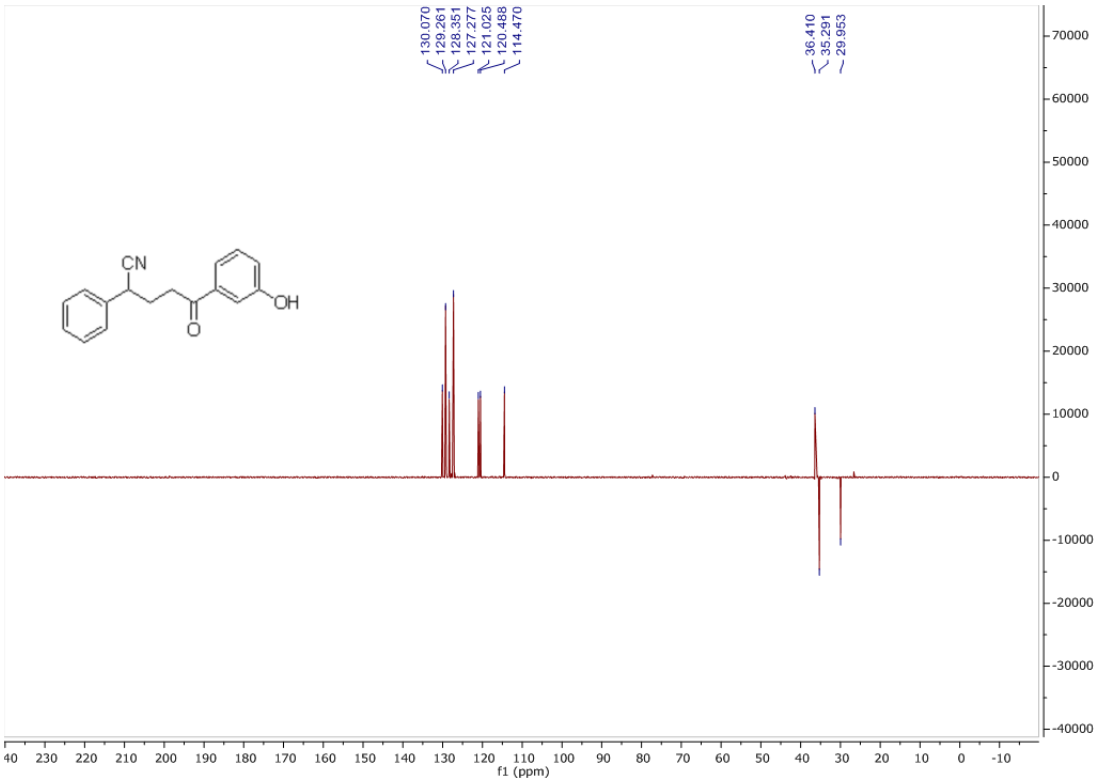

187.296
152.300
146.628
135.231
129.192
128.290
127.296
120.439
117.370
112.392
77.293 CDCl3
77.039 CDCl3
76.785 CDCl3
36.436
34.914
29.727
CN
O
O
f1 (ppm)


146.630
129.193
128.290
127.297
117.373
112.393
36.435
34.912
29.728
CN
O
O
f1 (ppm)

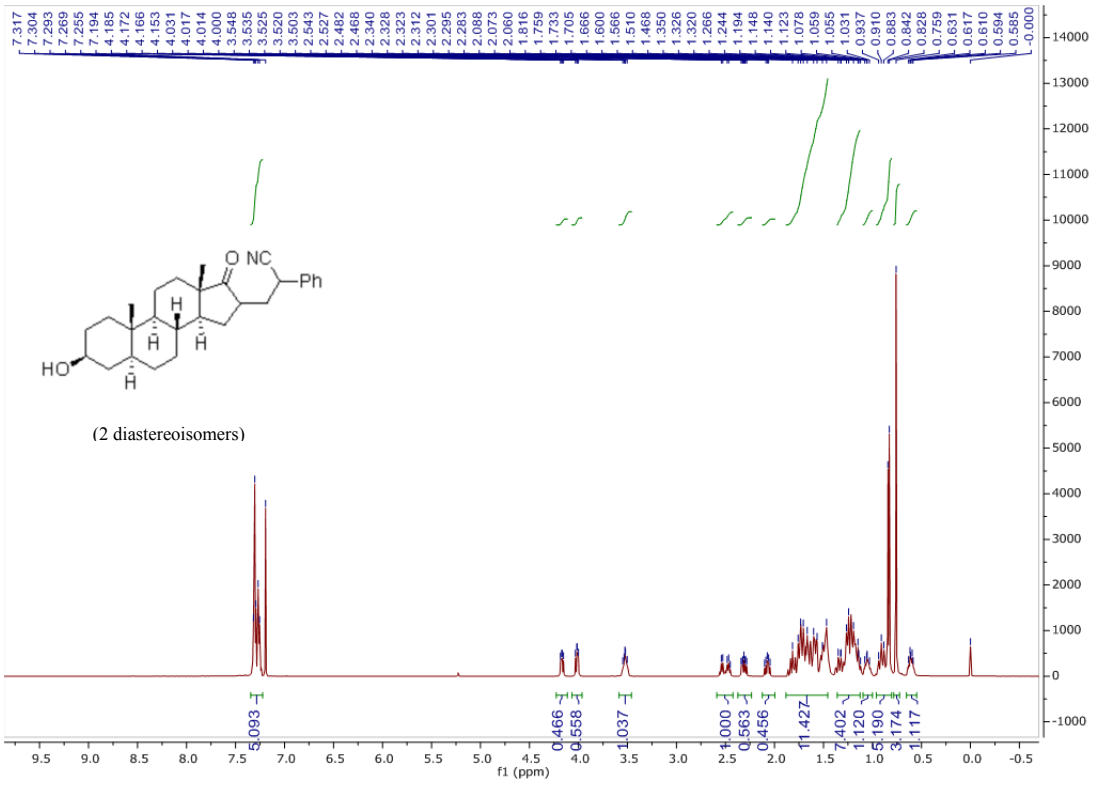
NMR Spectra of **4al**

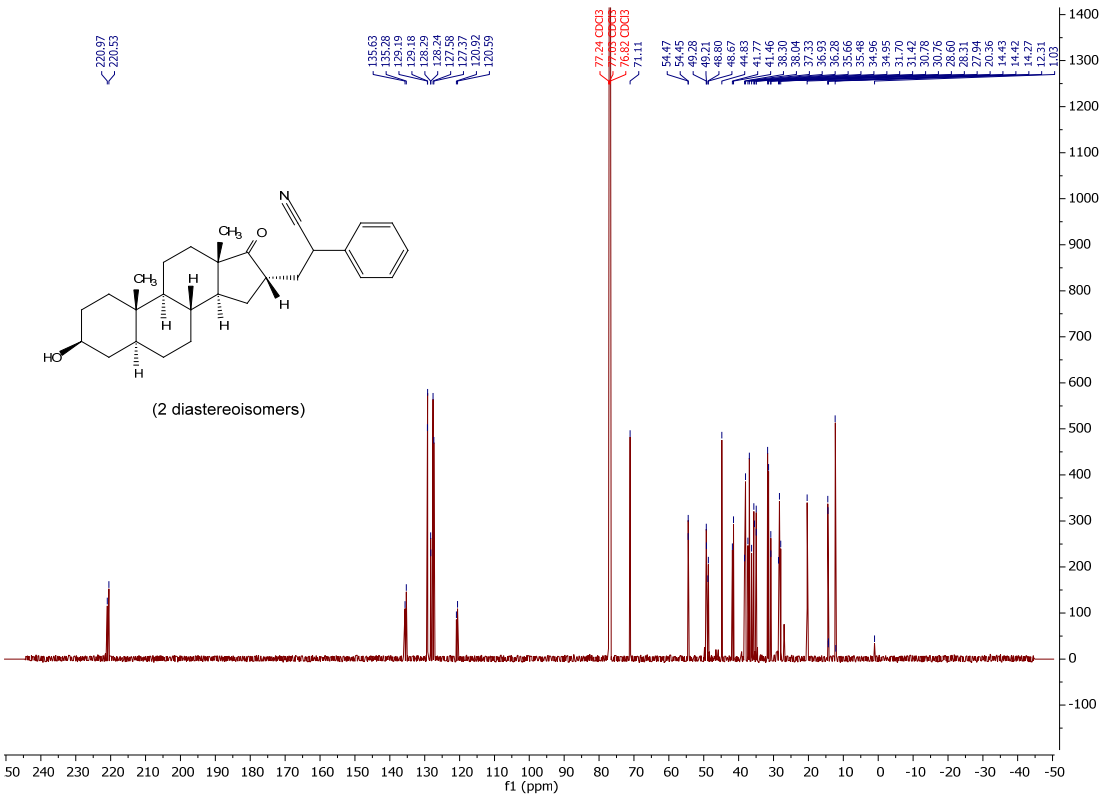


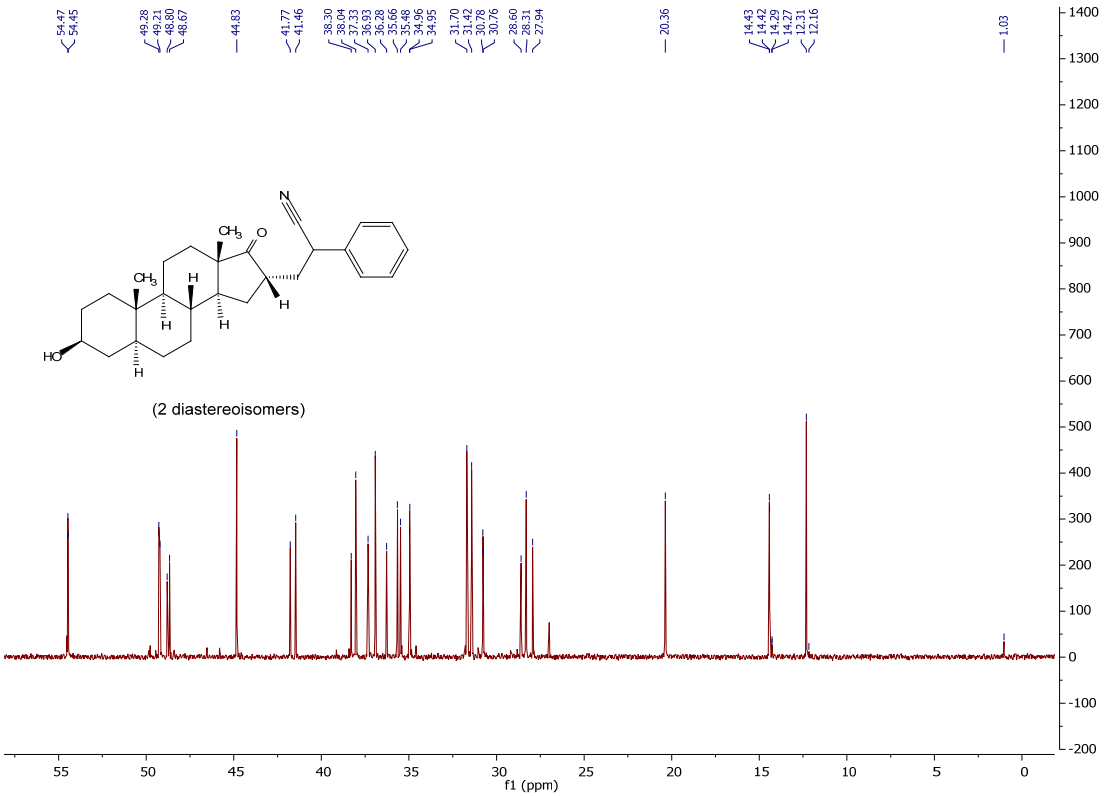


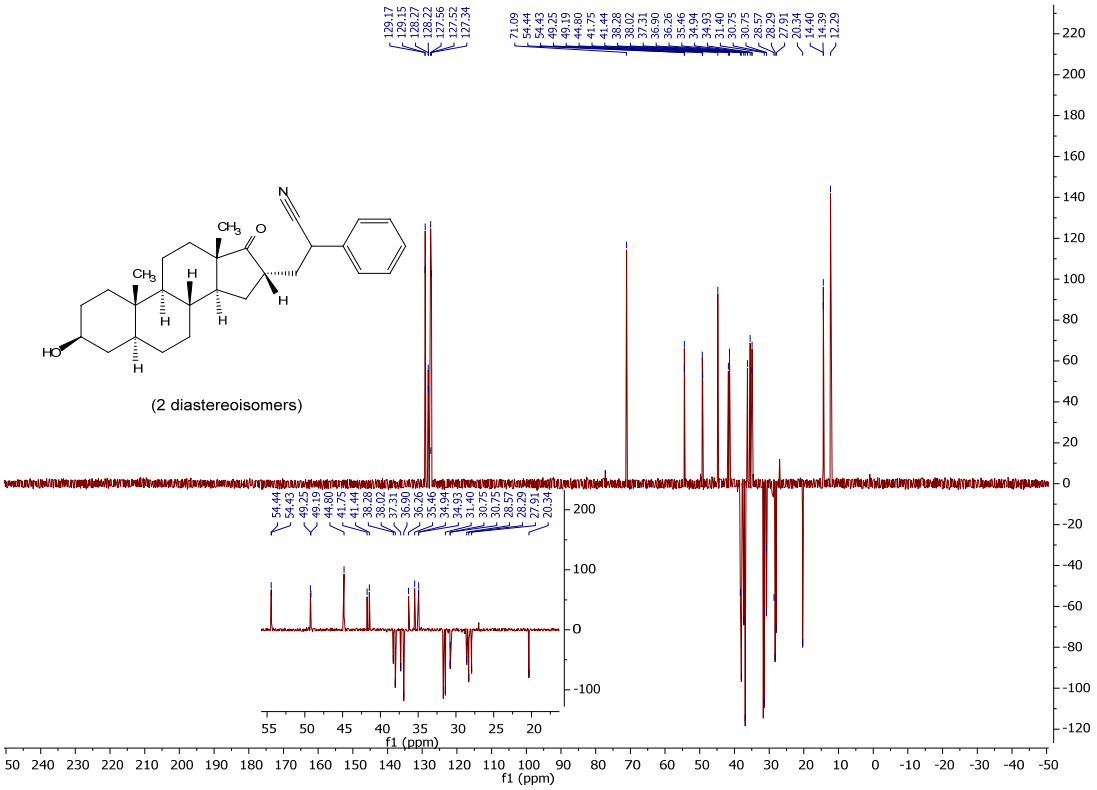


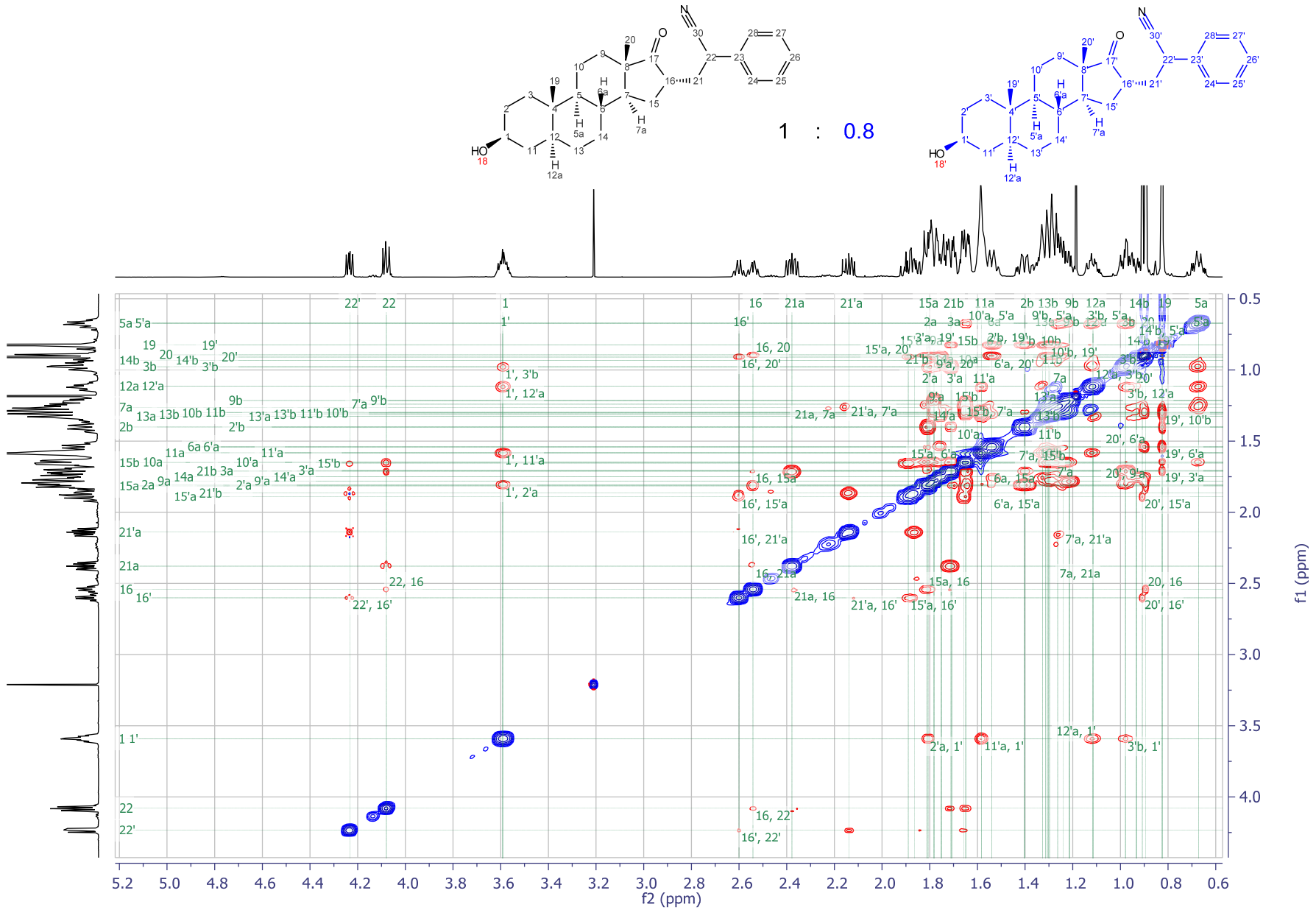
NMR Spectra of **4am**



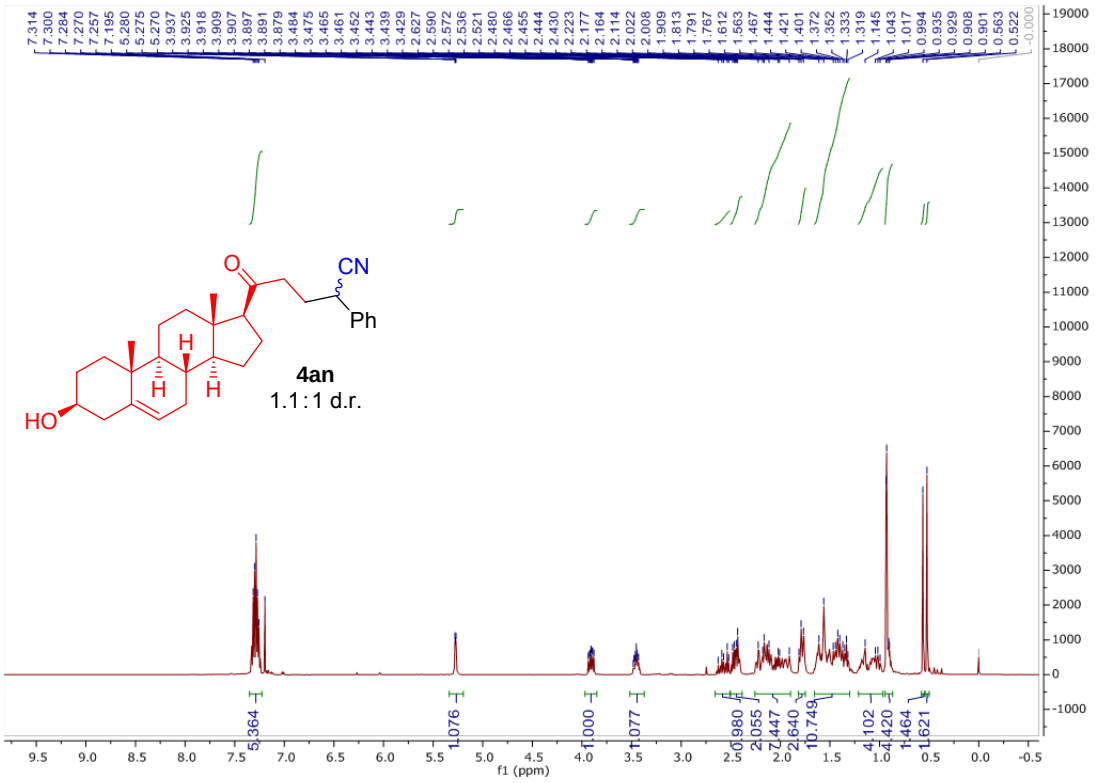

(2 diastereoisomers)
f1 (ppm)

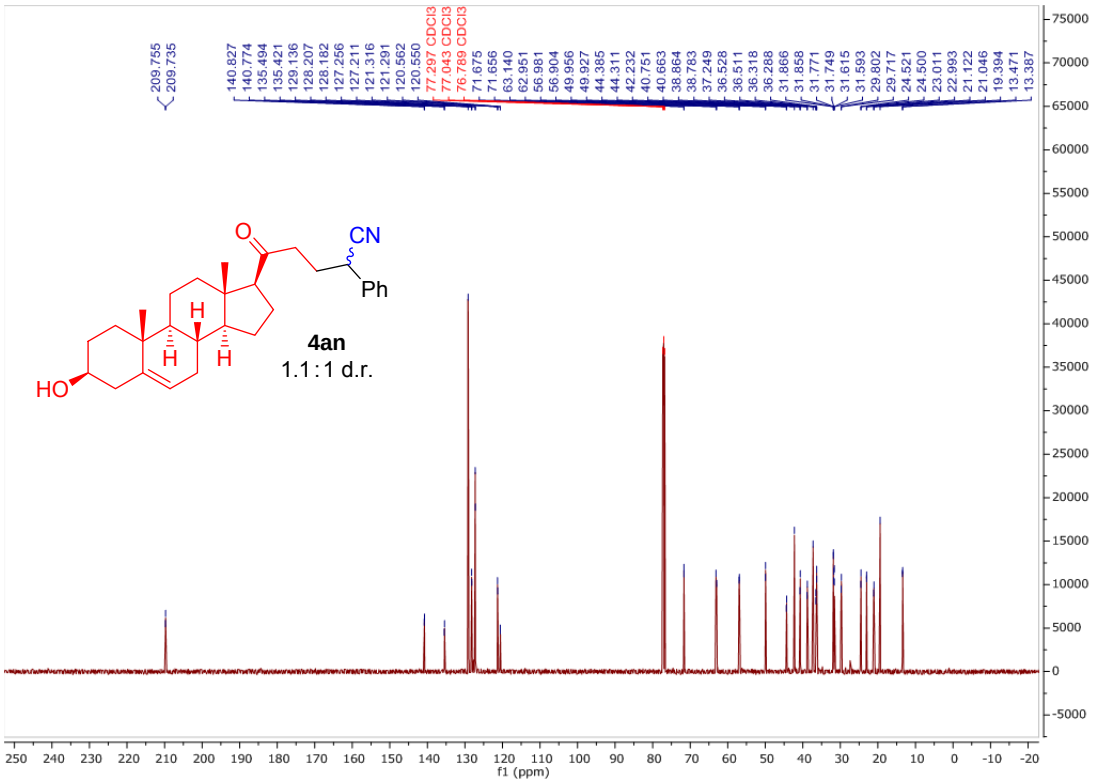

(2 diastereoisomers)
f1 (ppm)

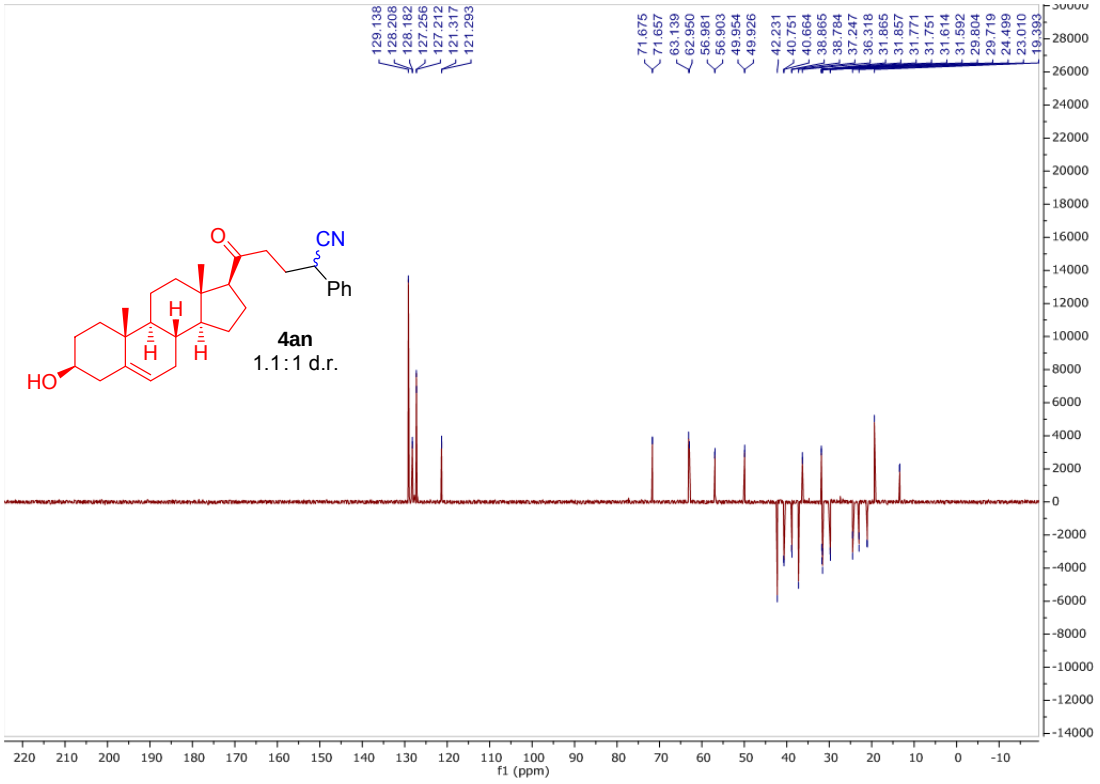

(2 diastereoisomers)
f1 (ppm)

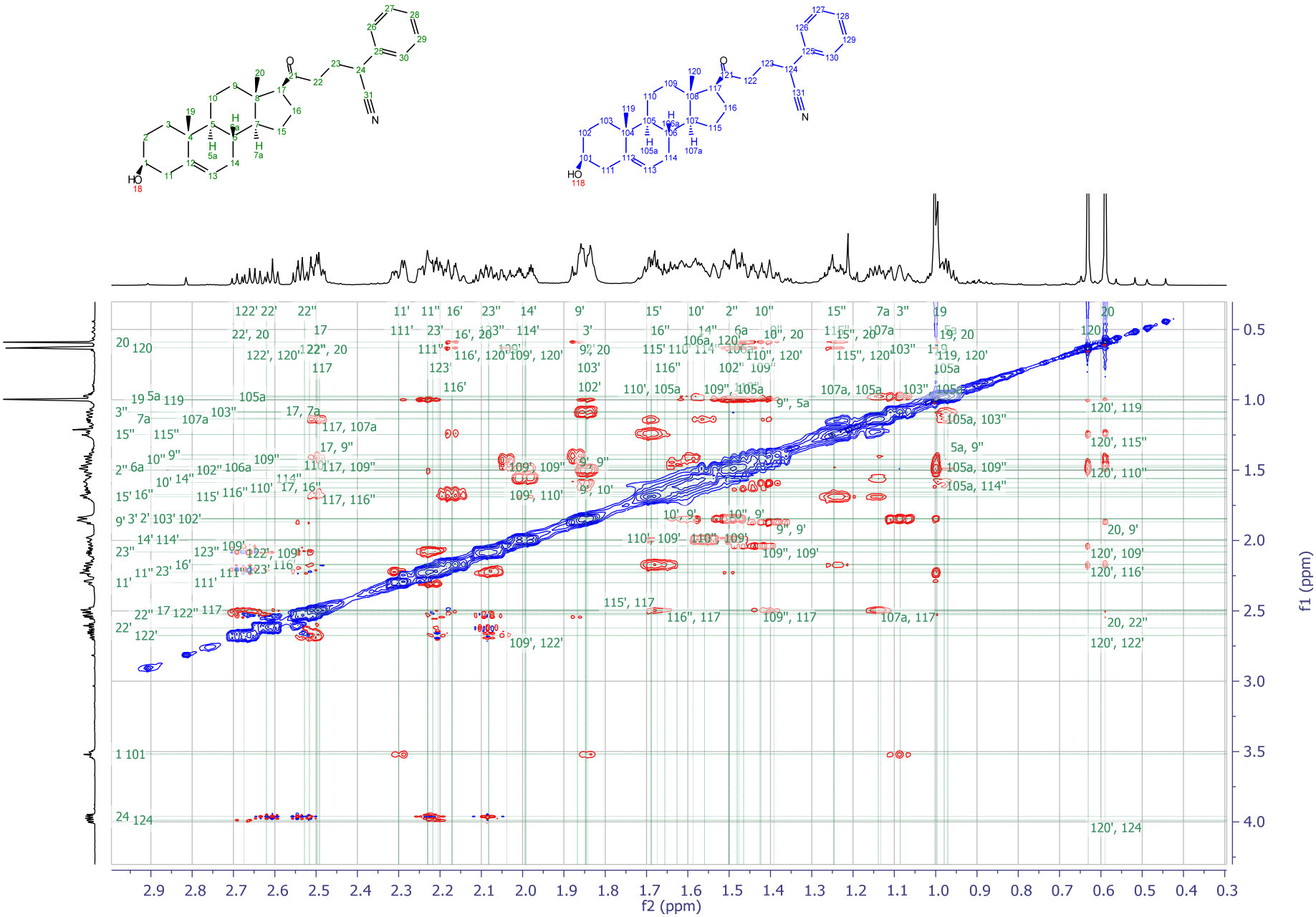

1 : 0.8
f2 (ppm)
f1 (ppm)

NMR Spectra of **4an**

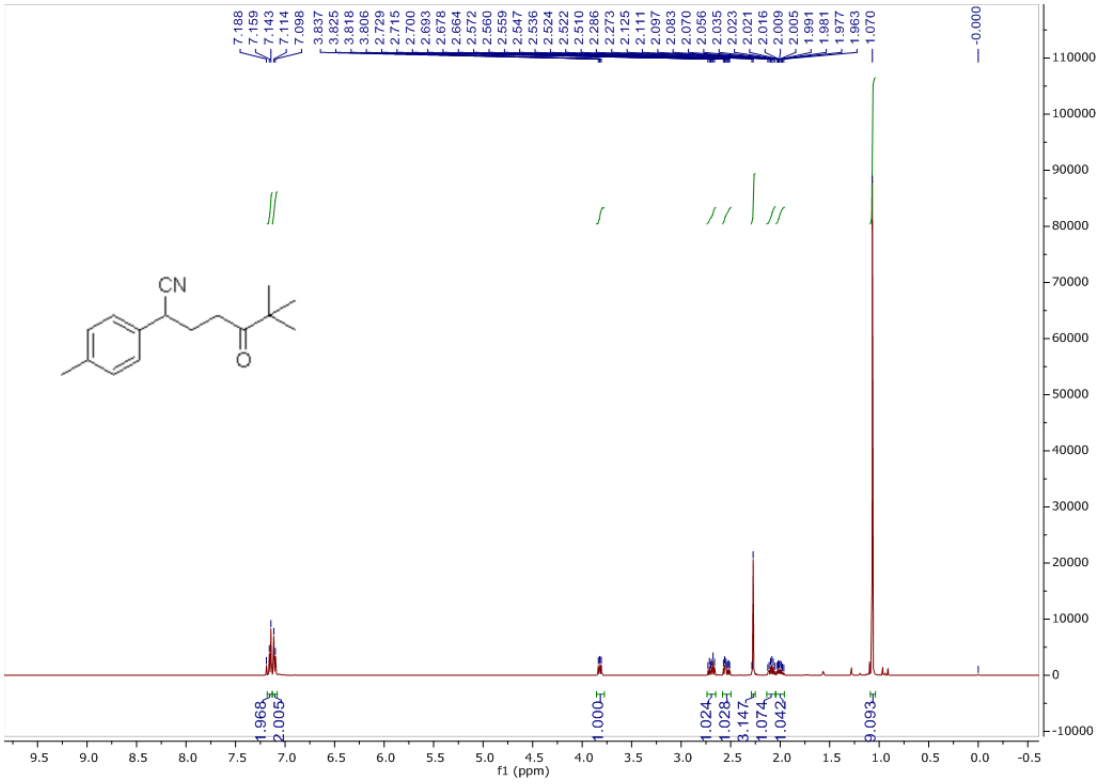


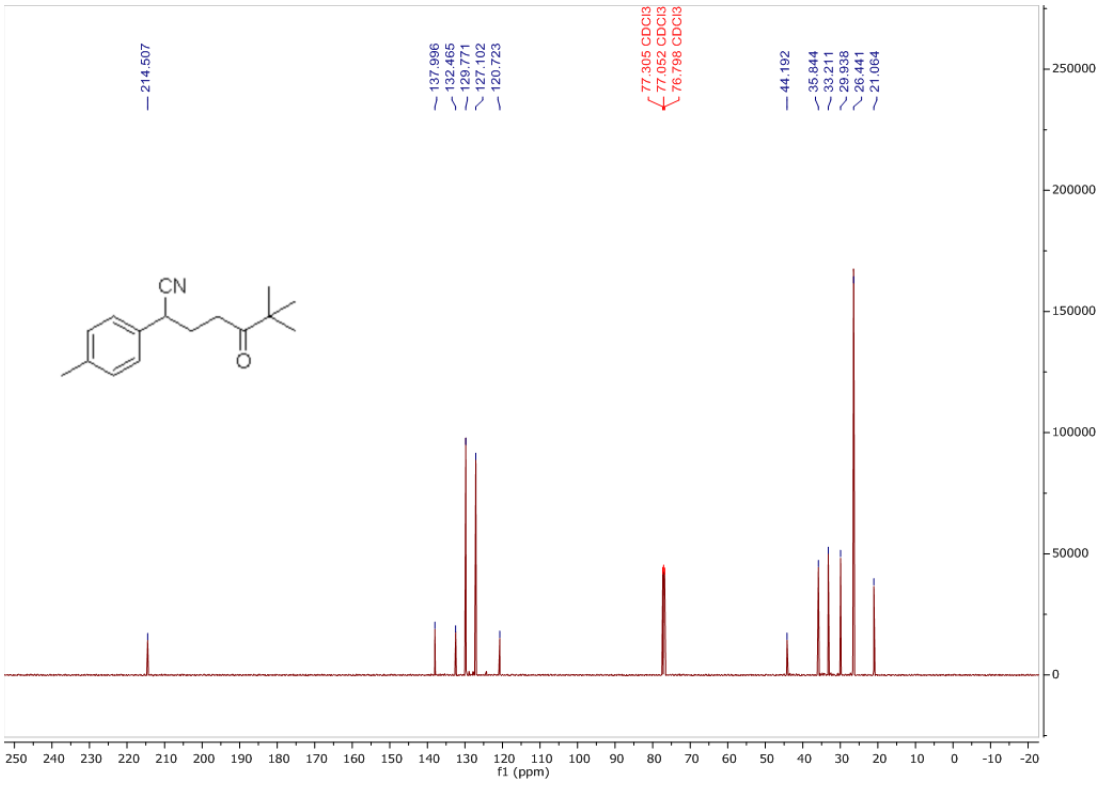


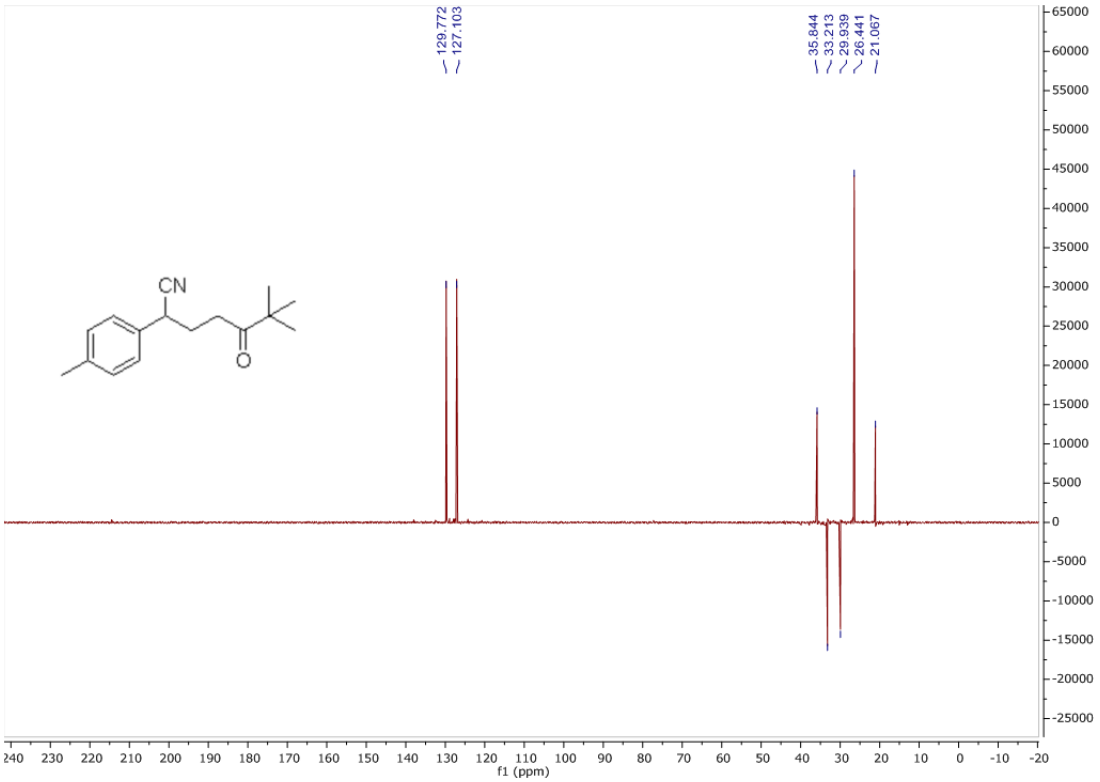

129.138
128.208
128.182
127.256
127.212
121.317
121.293
71.675
71.657
63.139
62.950
56.981
56.903
49.954
49.926
42.231
40.751
40.664
38.865
38.784
37.247
36.318
31.885
31.857
31.771
31.751
31.614
31.592
29.804
29.719
24.499
23.010
19.393
O
CN
Ph
H
H
H
HO
4an
1.1:1 d.r.
f1 (ppm)


f2 (ppm)
f1 (ppm)

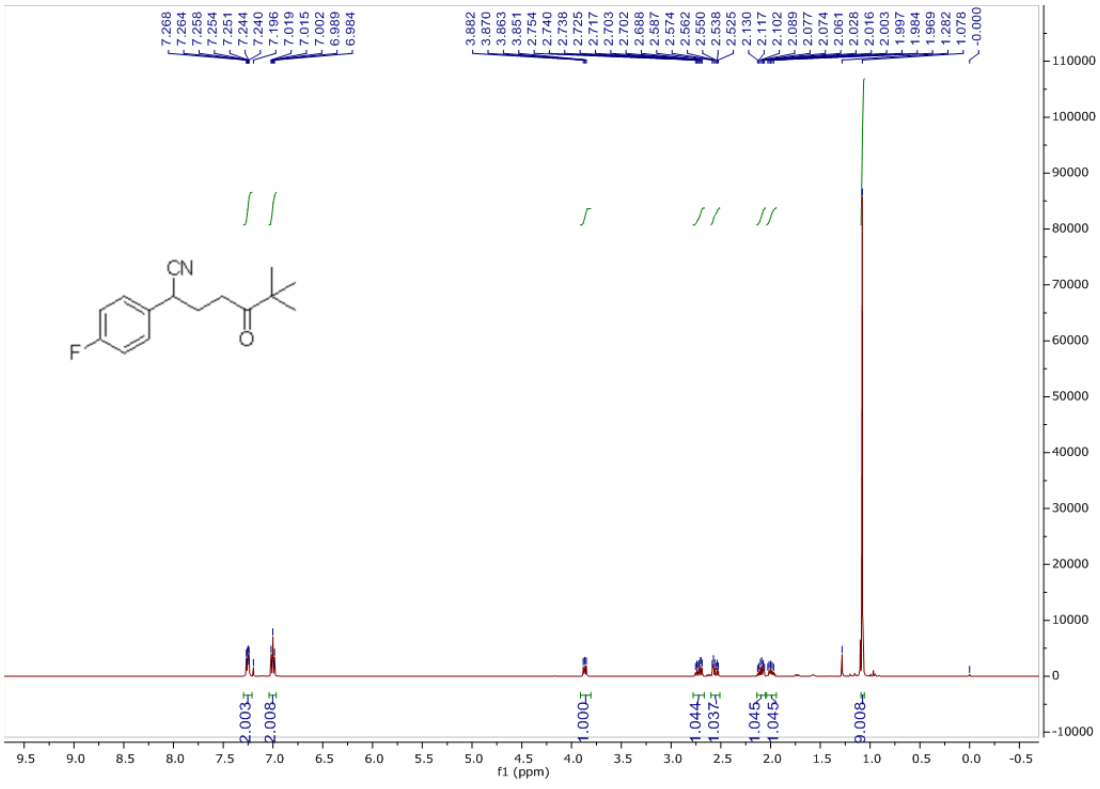
NMR Spectra of **4bc**

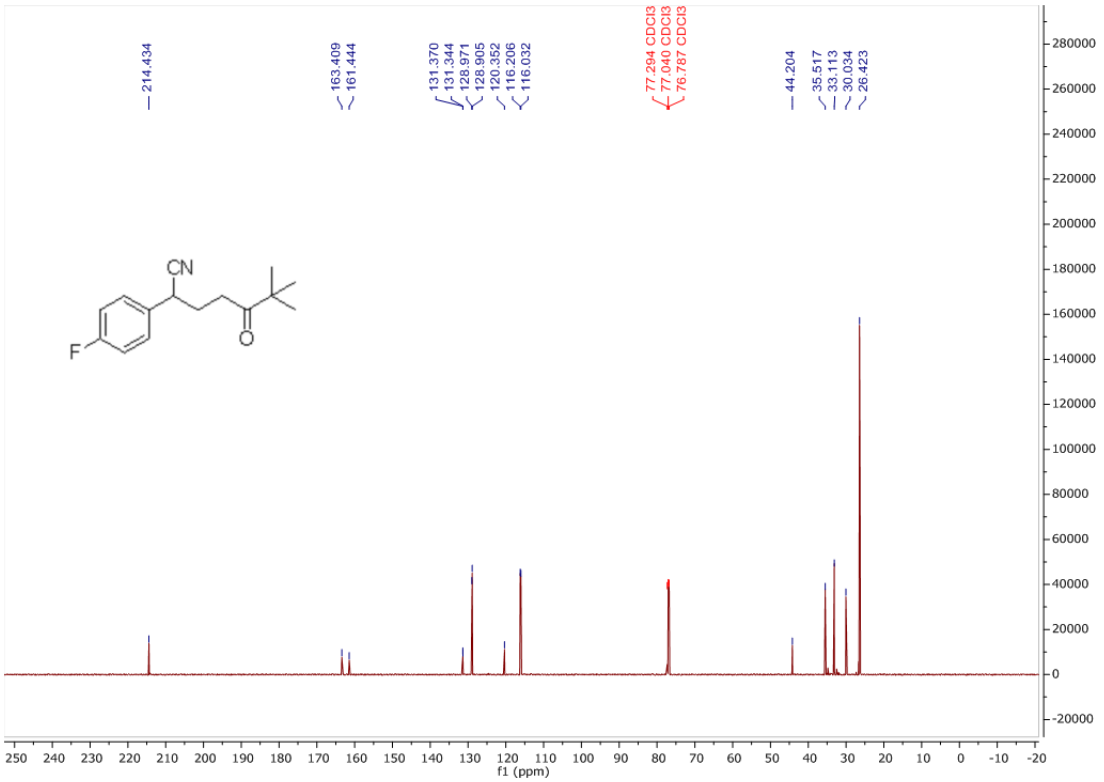




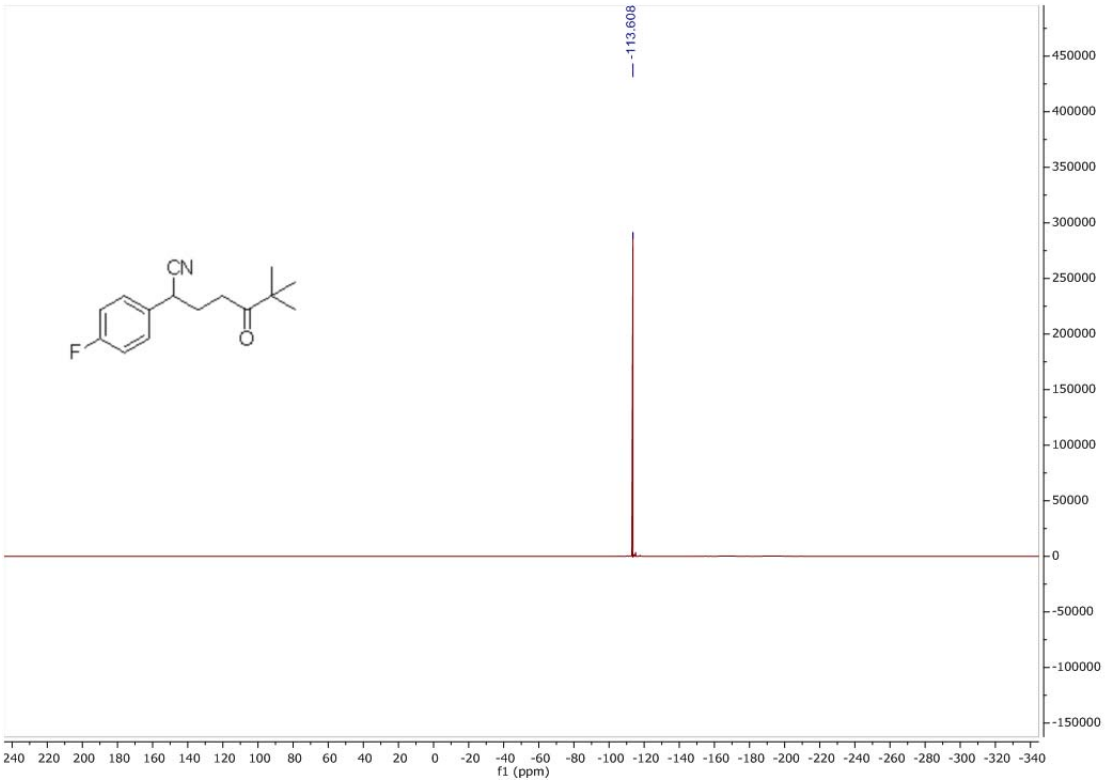


NMR Spectra of **4cc**

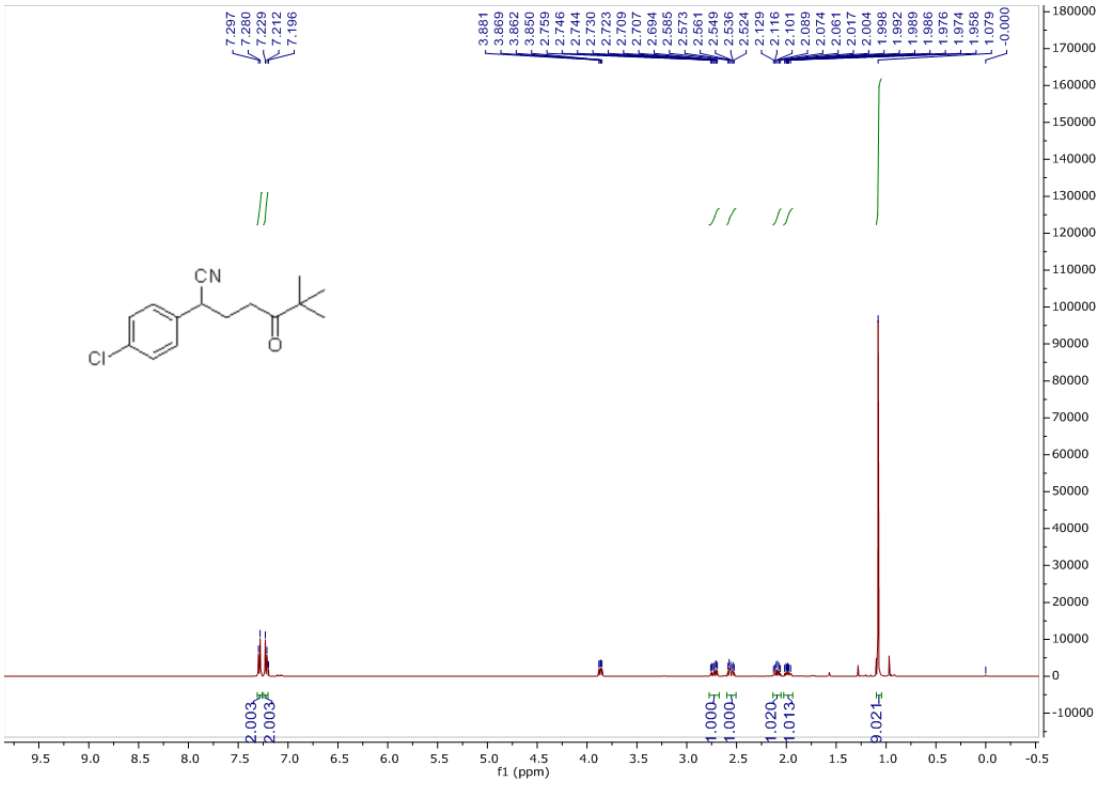


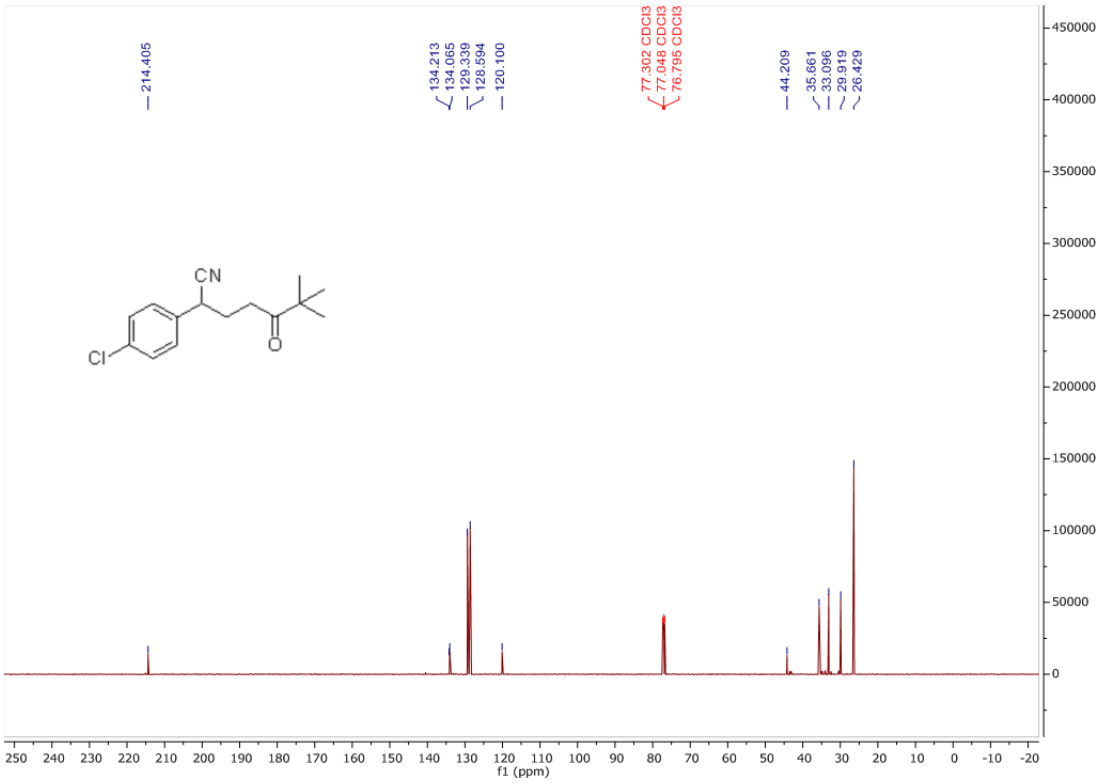

214.434
163.409
161.444
131.370
131.344
128.971
128.905
120.352
116.206
116.032
77.294 CDCl3
77.040 CDCl3
76.787 CDCl3
44.204
35.517
33.113
30.034
26.423
CN
F
O
f1 (ppm)

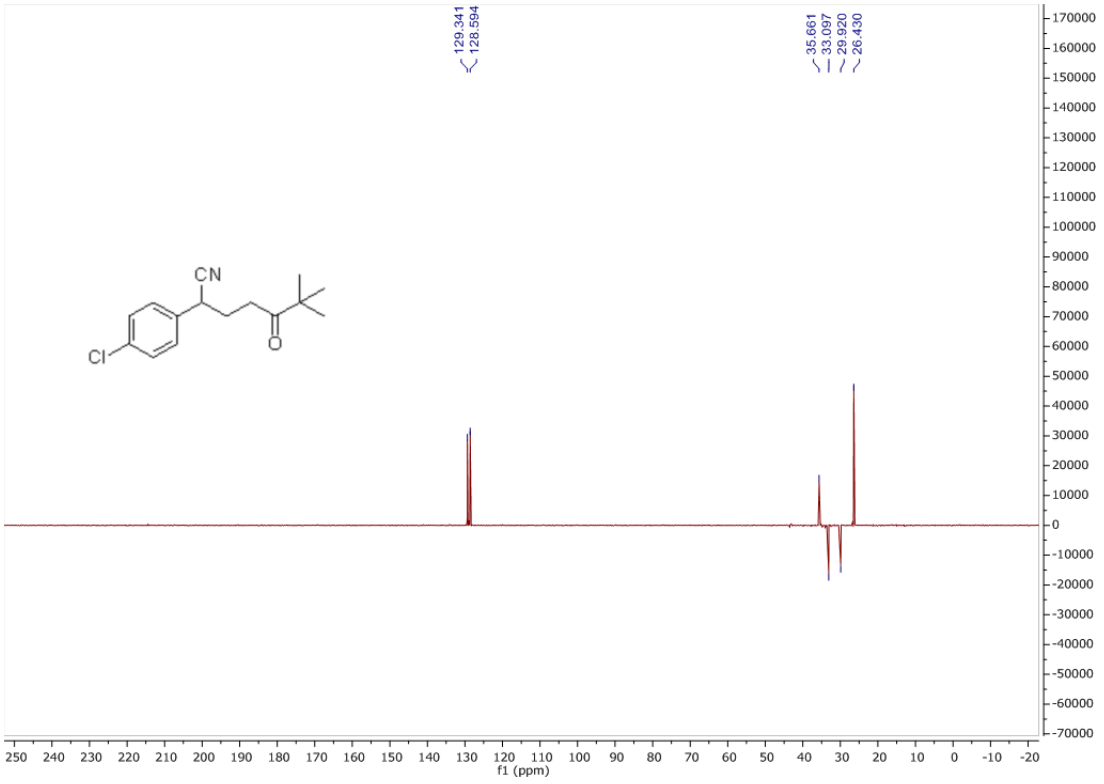

128.972
128.905
116.207
116.033
35.517
33.115
30.035
26.423
CN
F
O
f1 (ppm)



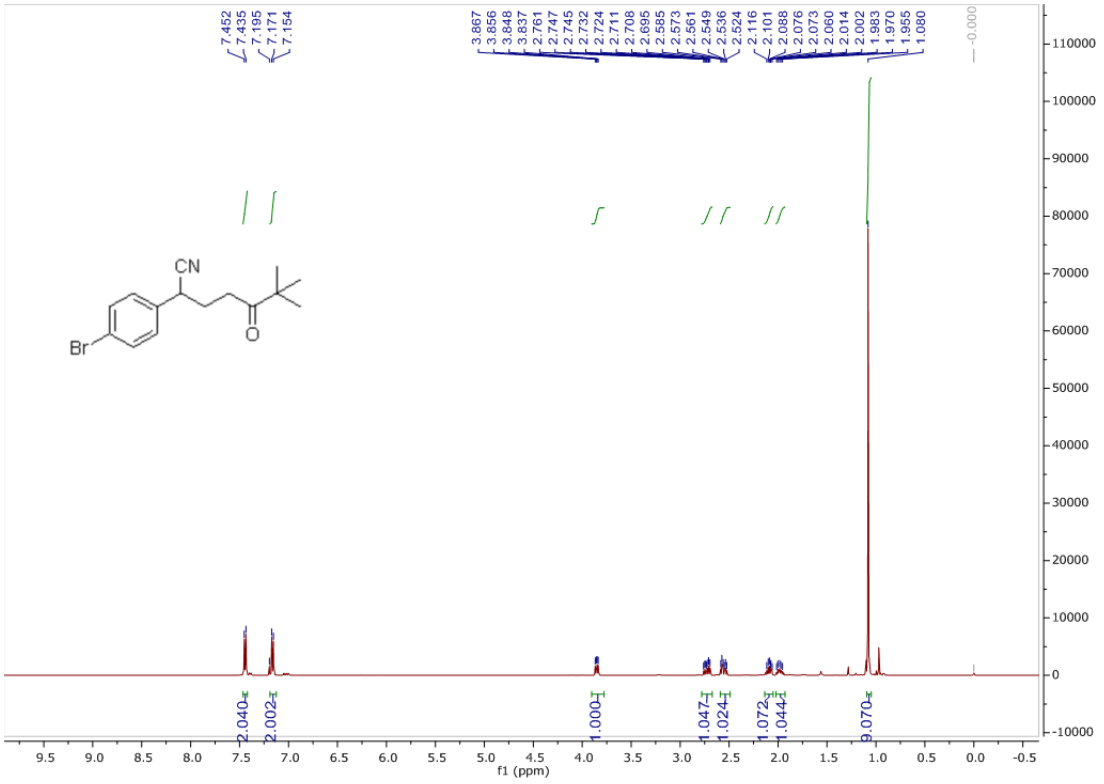
NMR Spectra of **4dc**

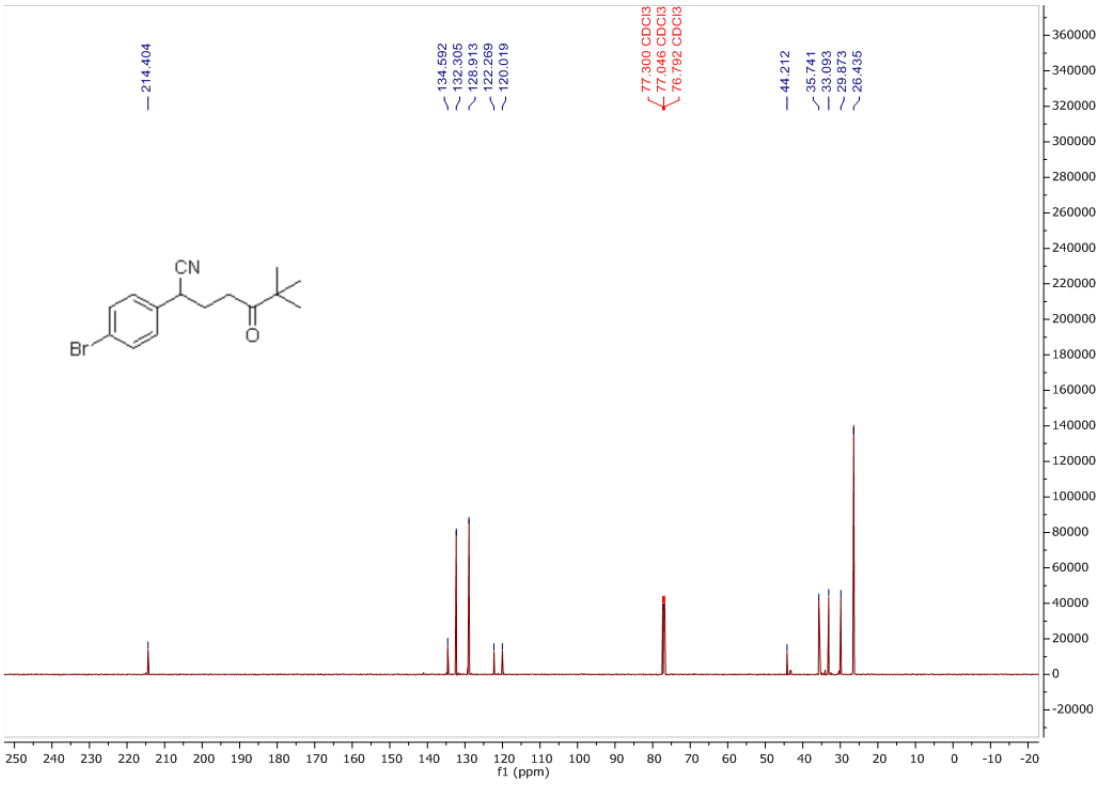



214.405
134.213
134.065
129.339
128.594
120.100
77.302 CDCl3
77.048 CDCl3
76.795 CDCl3
44.209
35.661
33.096
29.919
26.429
CN
Cl
O
f1 (ppm)

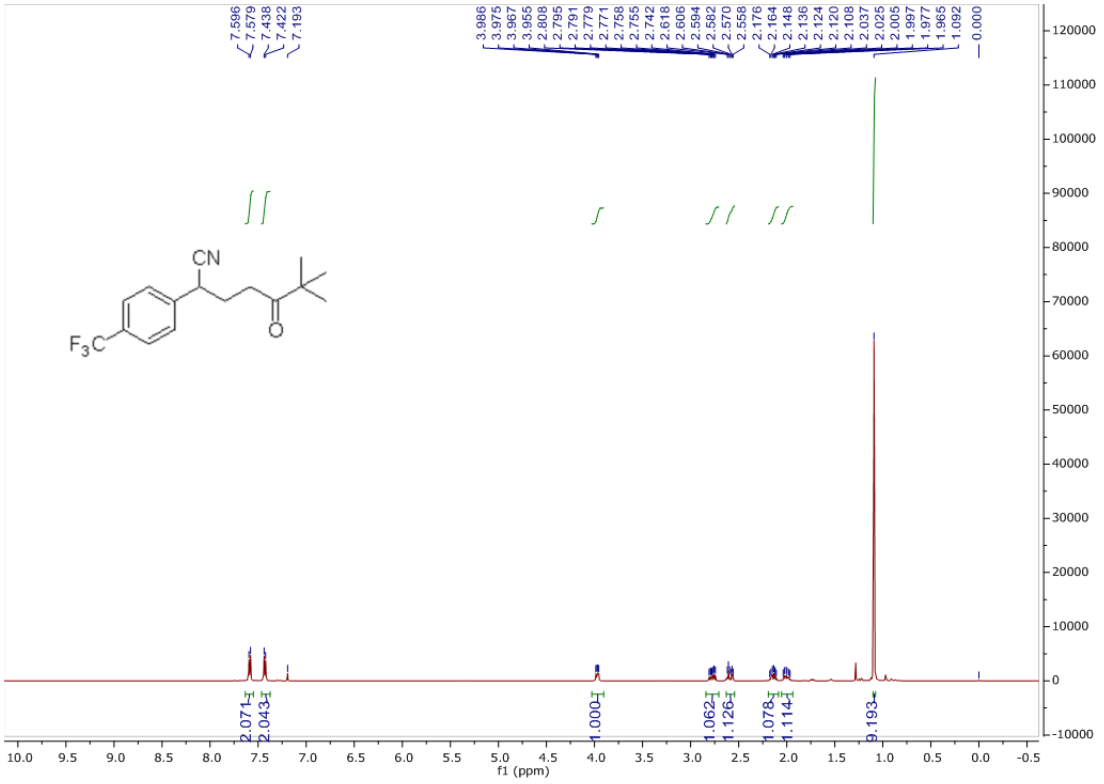

129.341
128.594
35.661
33.097
29.920
26.430
CN
Cl
O
f1 (ppm)

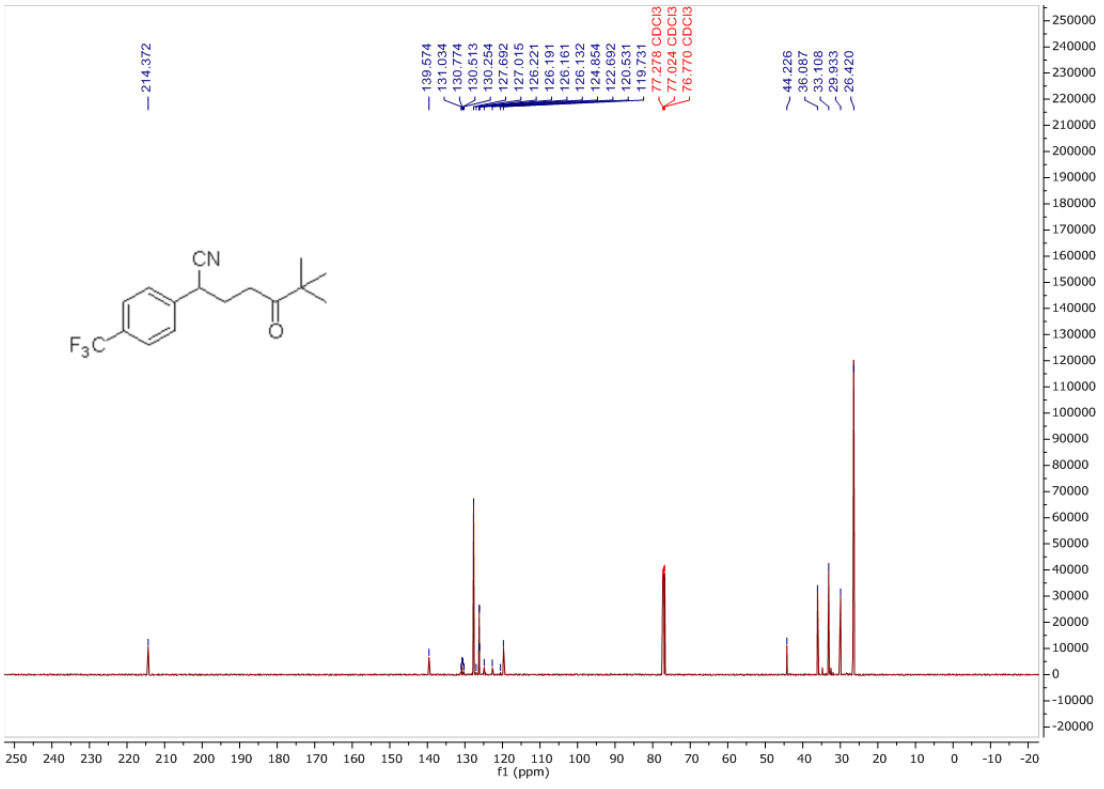
NMR Spectra of **4ec**

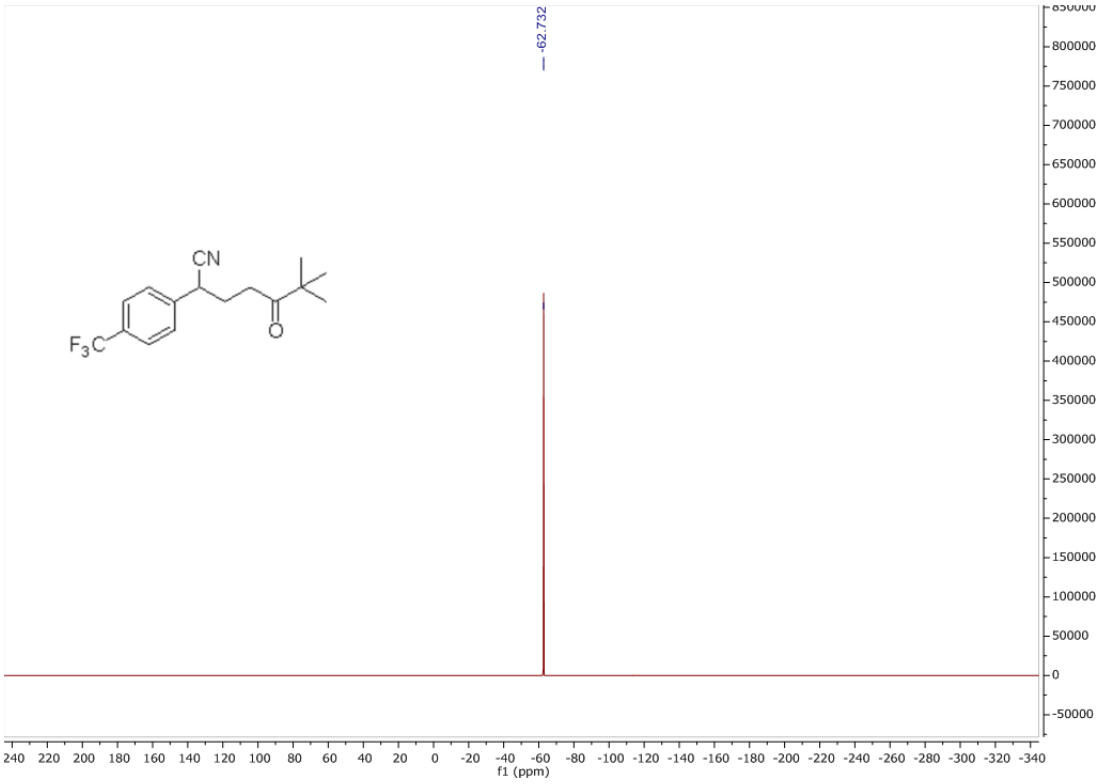




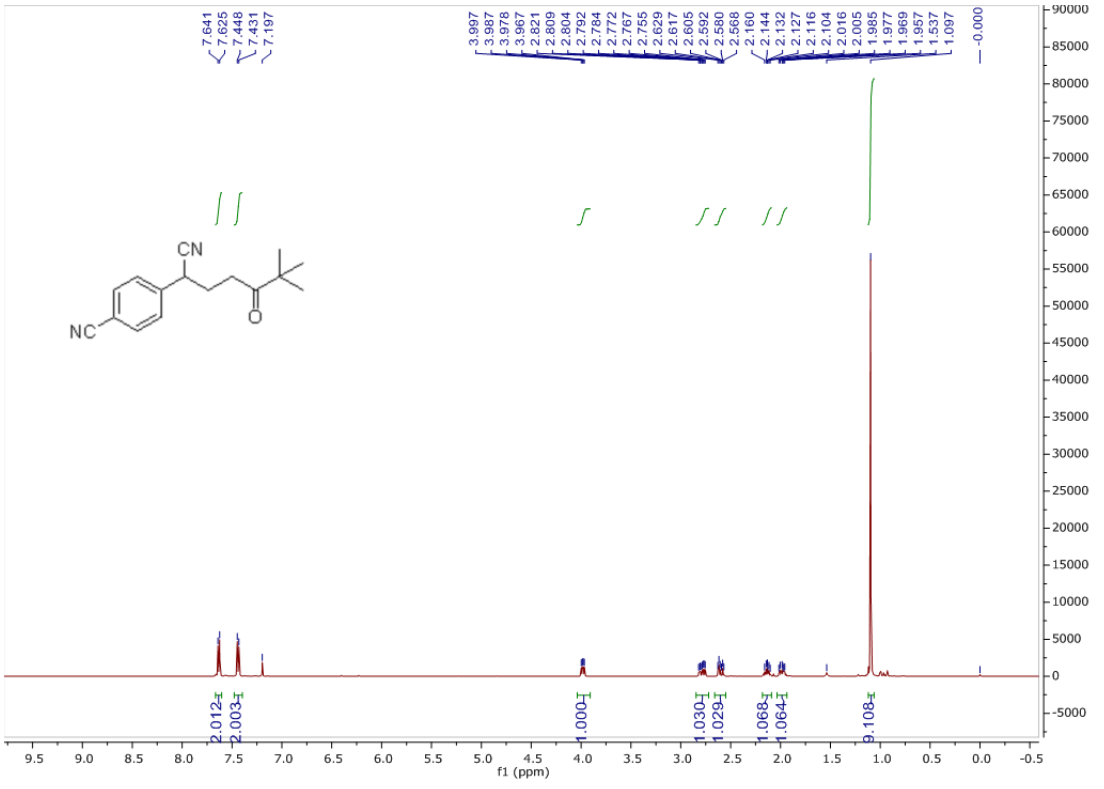
NMR Spectra of **4fc**

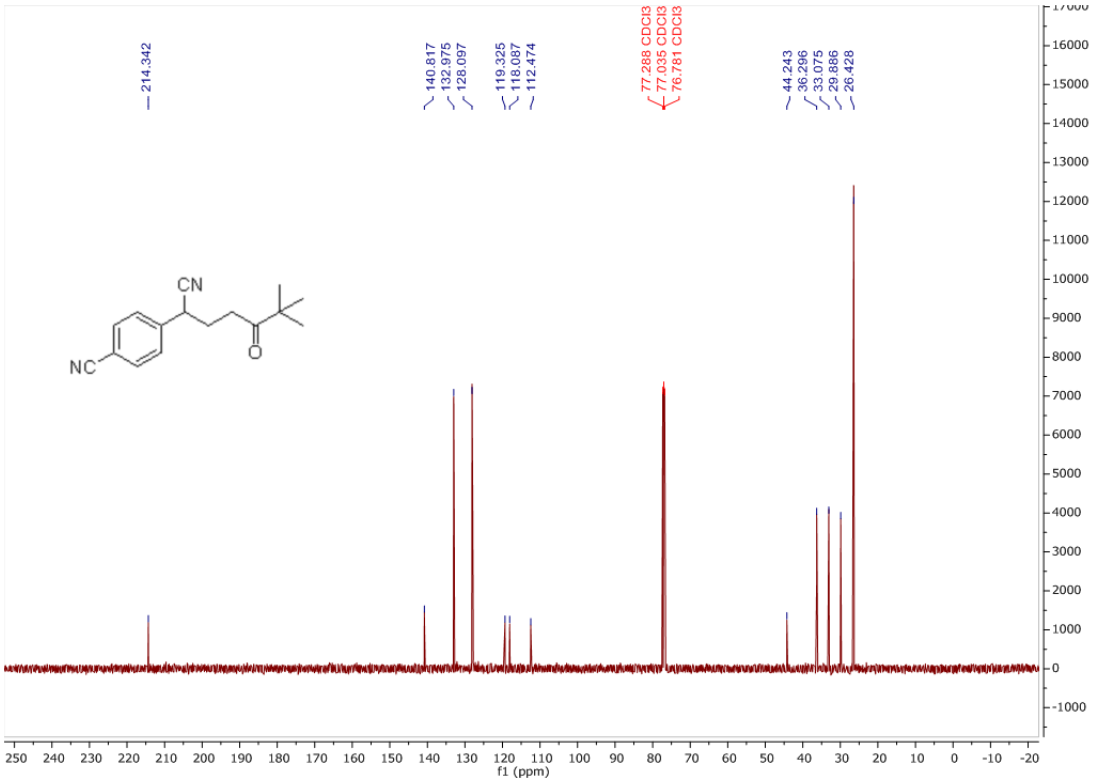


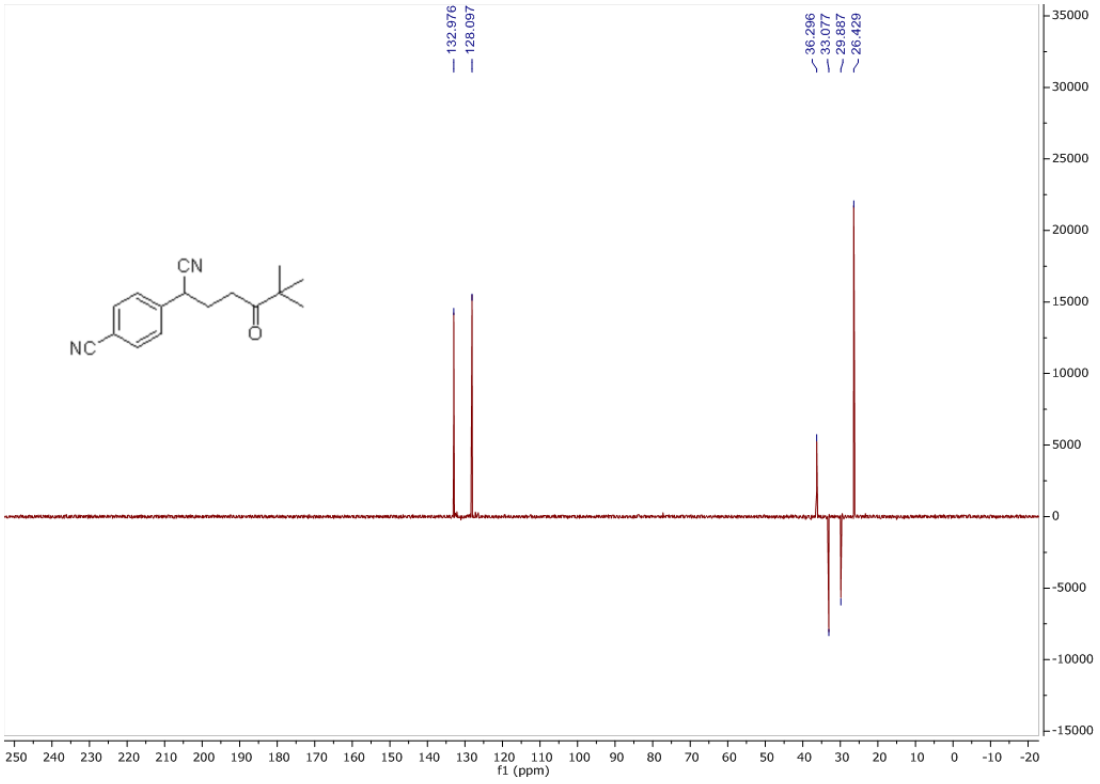




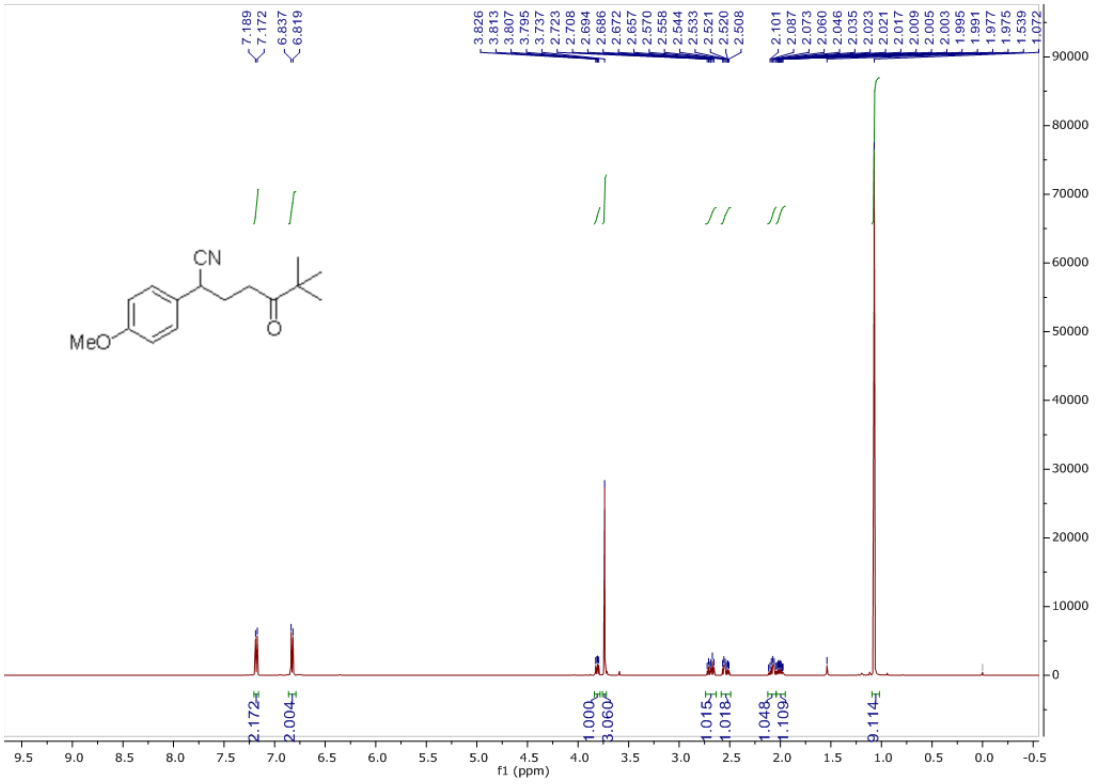
NMR Spectra of **4gc**

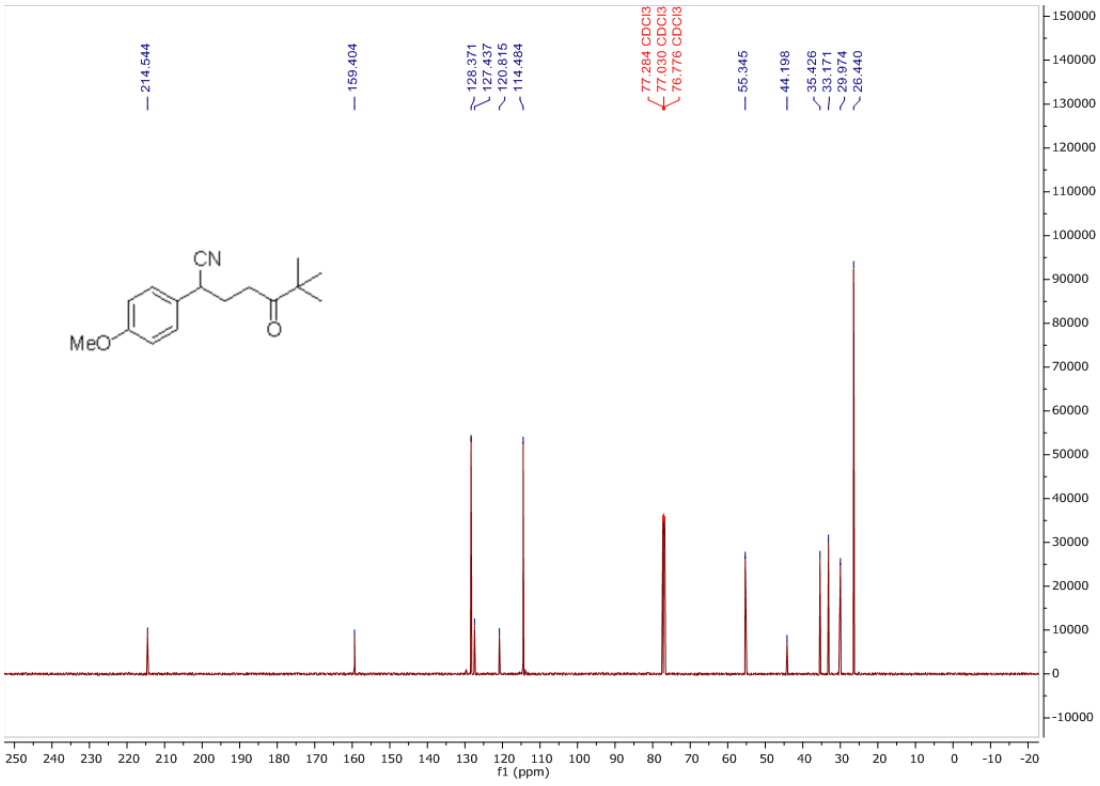



214.342
140.817
132.975
128.097
119.325
118.087
112.474
77.288 CDCl3
77.035 CDCl3
76.781 CDCl3
44.243
36.296
33.075
29.886
26.428
CN
NC
O
f1 (ppm)

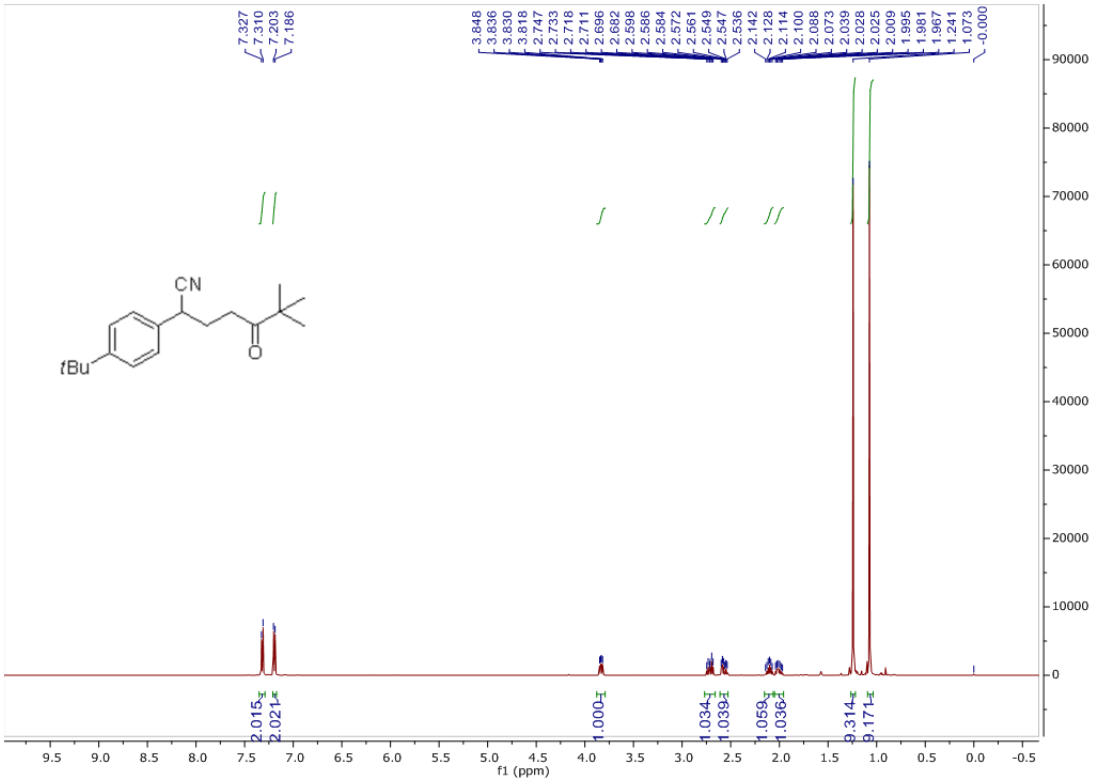

132.976
128.097
36.296
33.077
29.887
26.429
CN
NC
O
f1 (ppm)

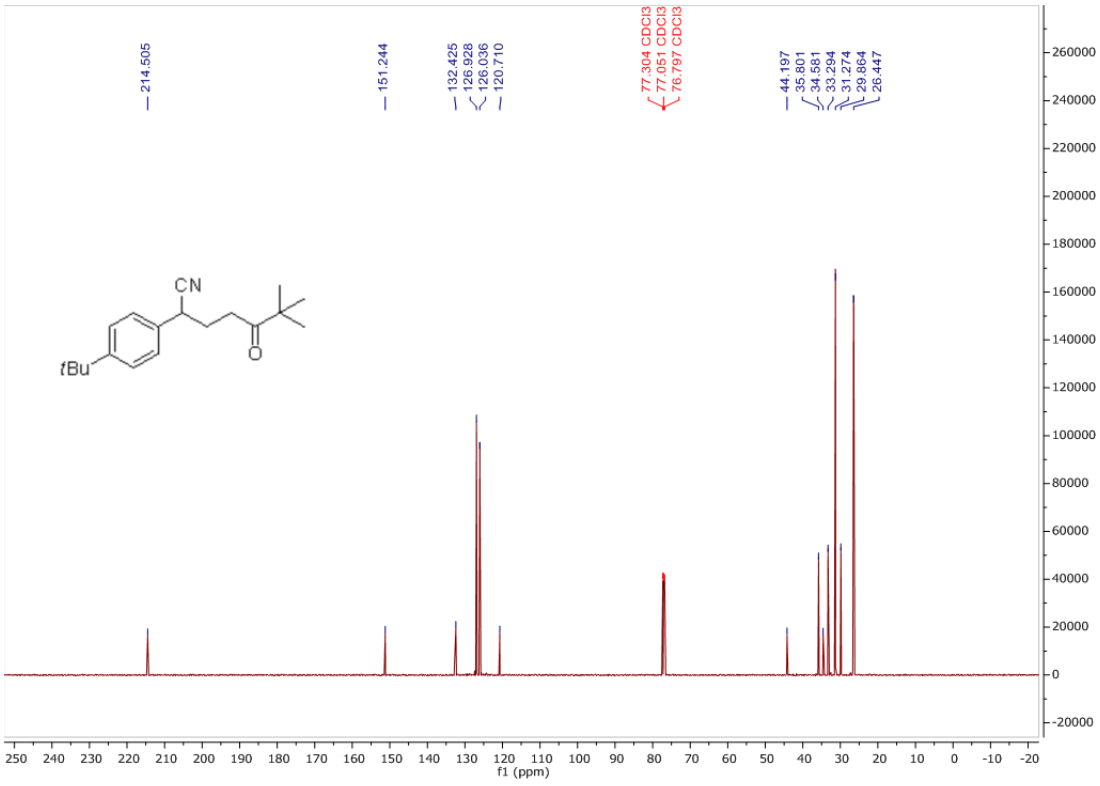
NMR Spectra of **4hc**



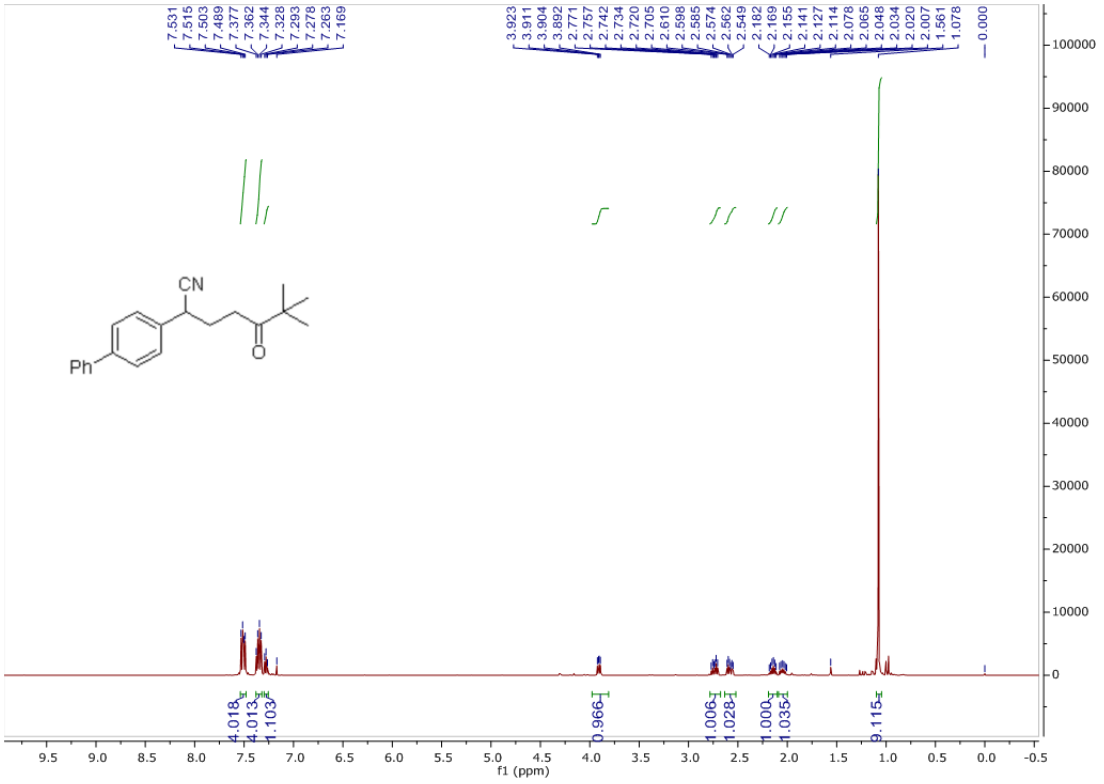


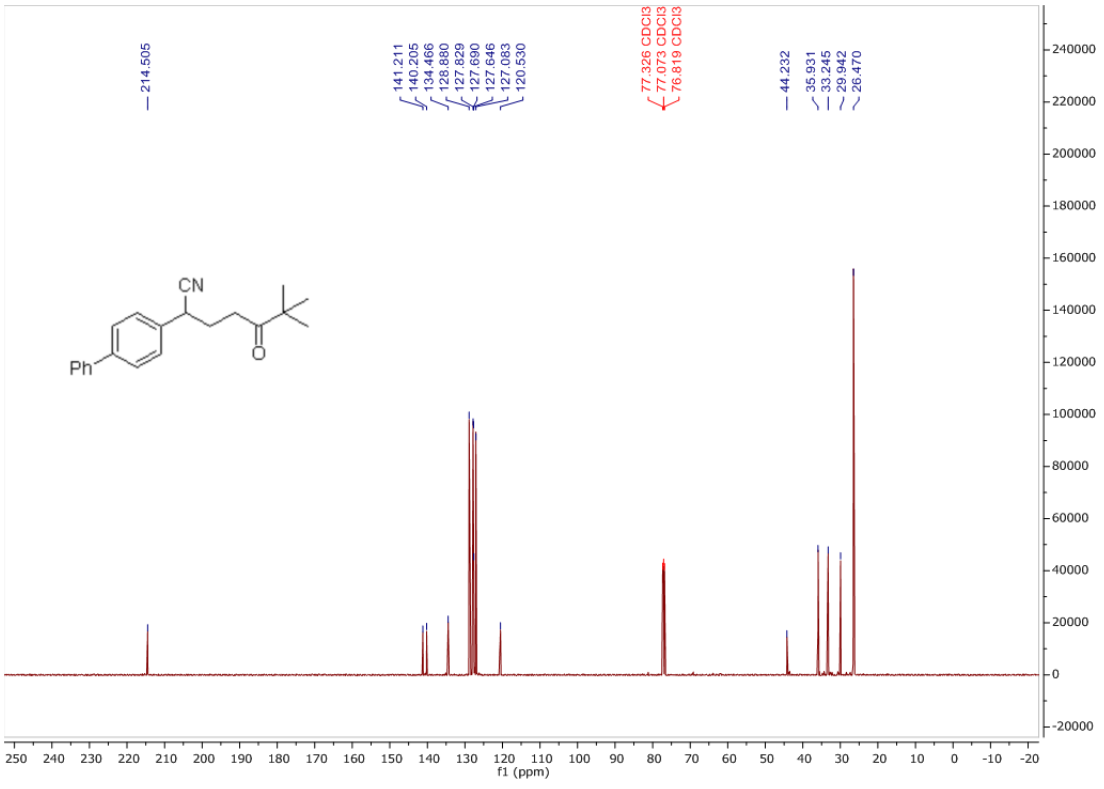
NMR Spectra of **4ic**



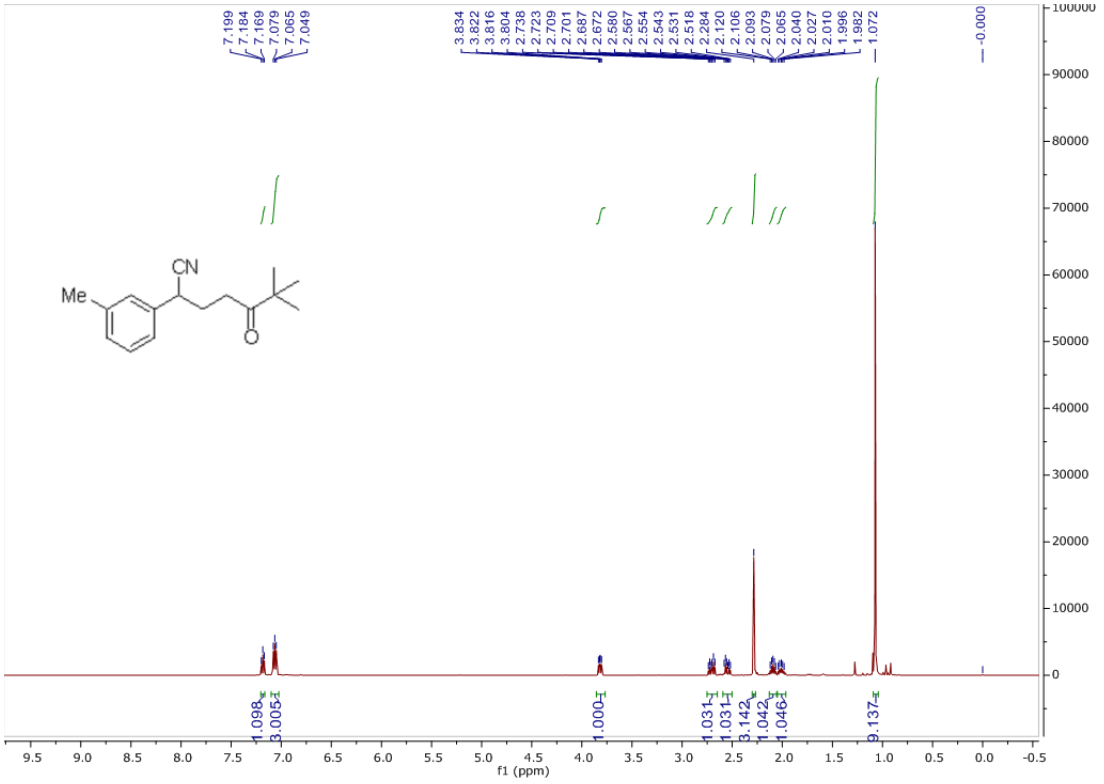


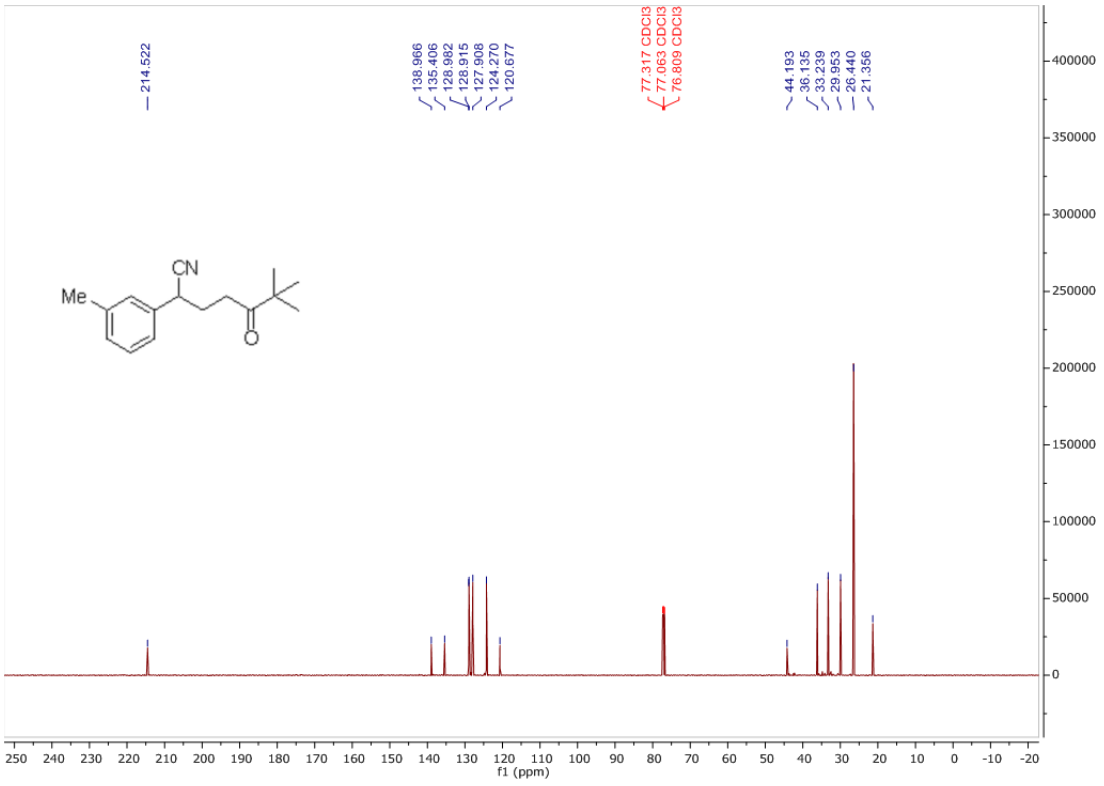
NMR Spectra of **4jc**



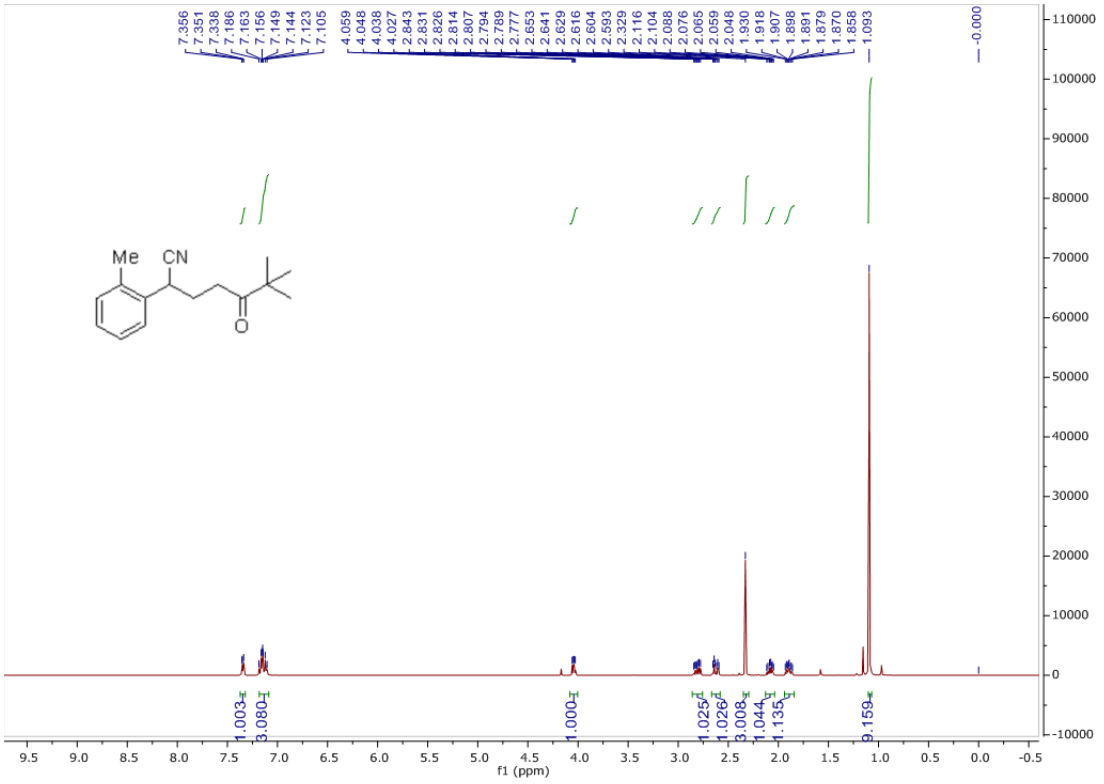


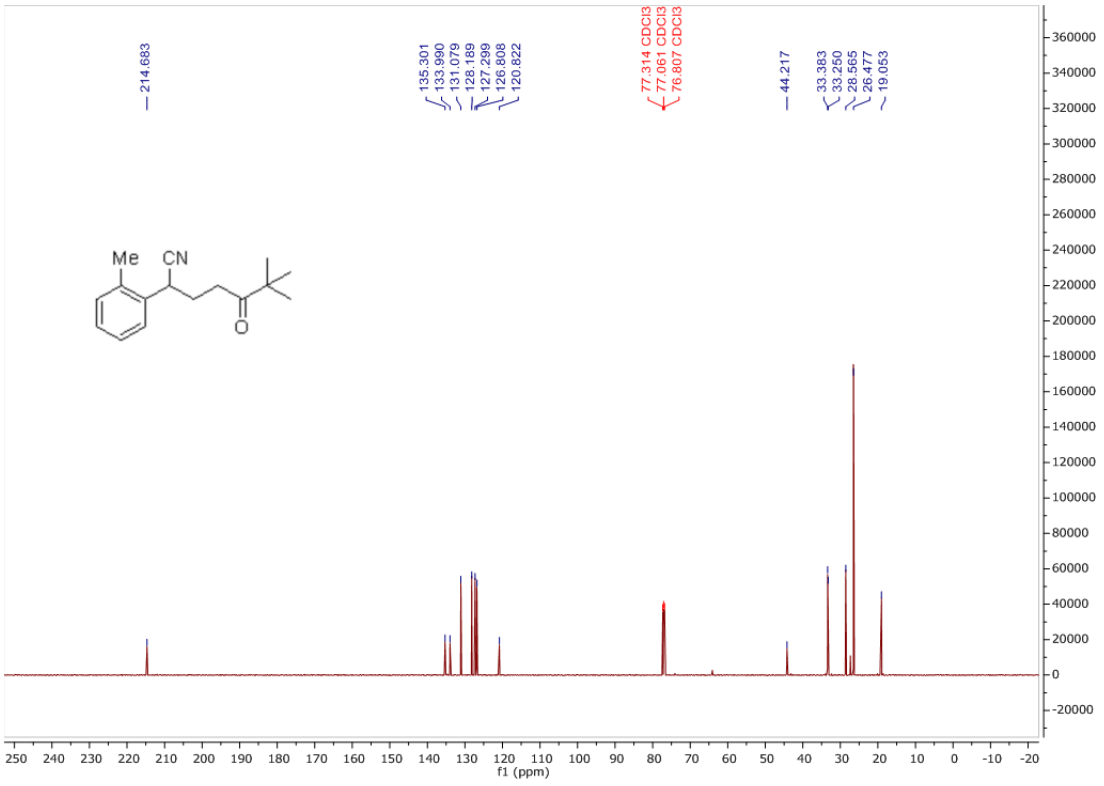
NMR Spectra of **4kc**



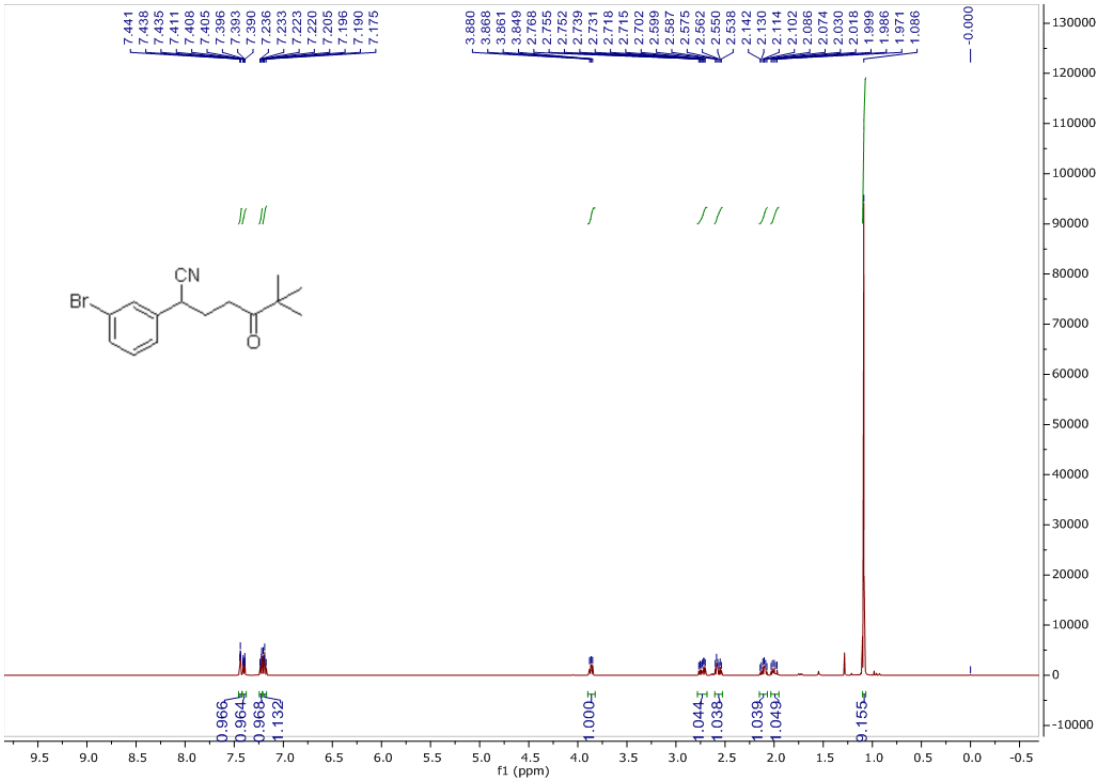


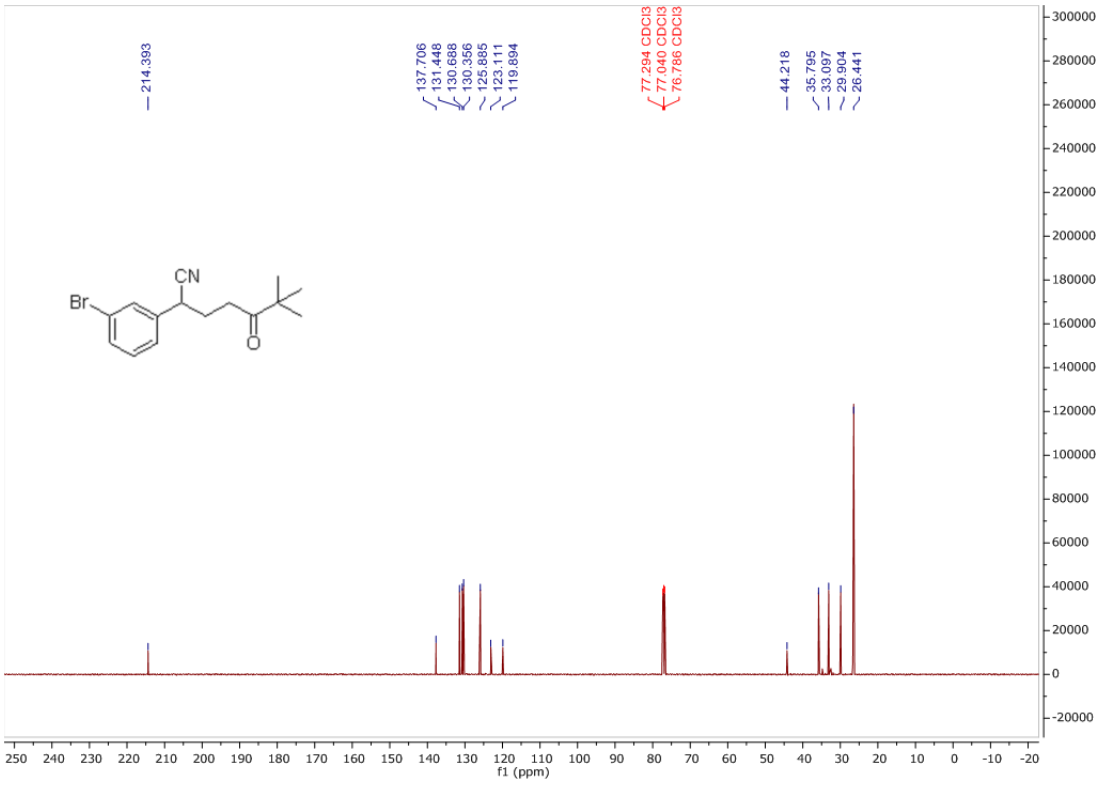
NMR Spectra of **4lc**



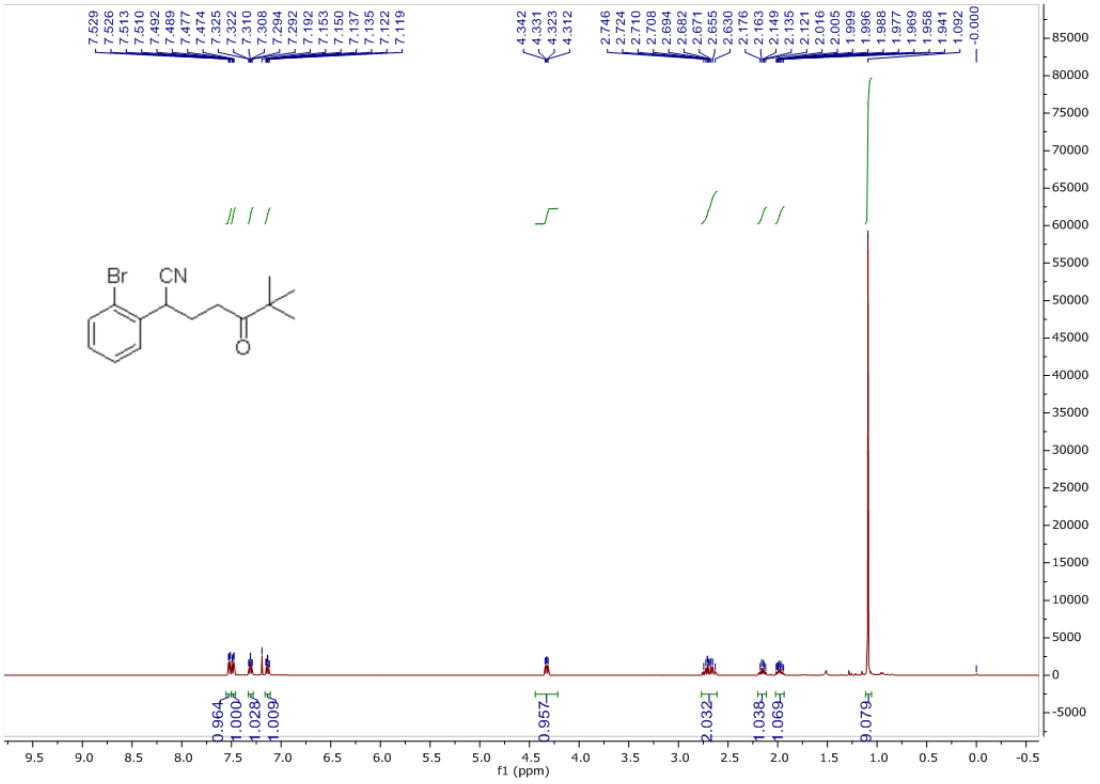


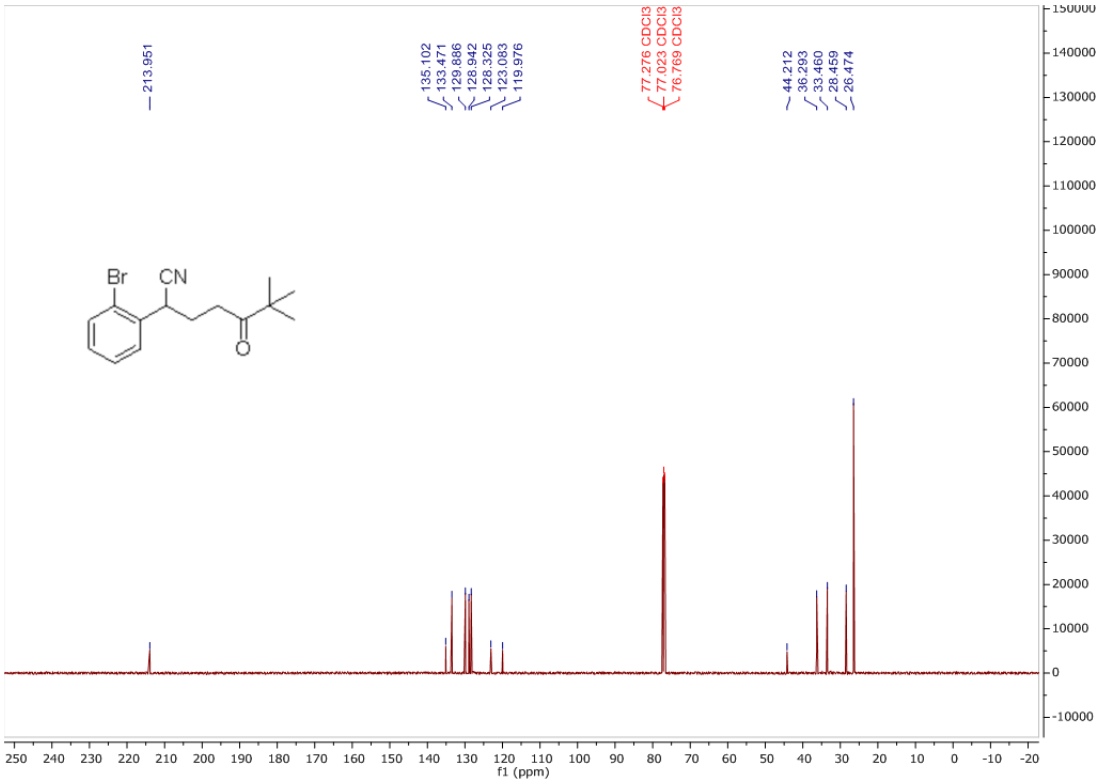
NMR Spectra of **4mc**



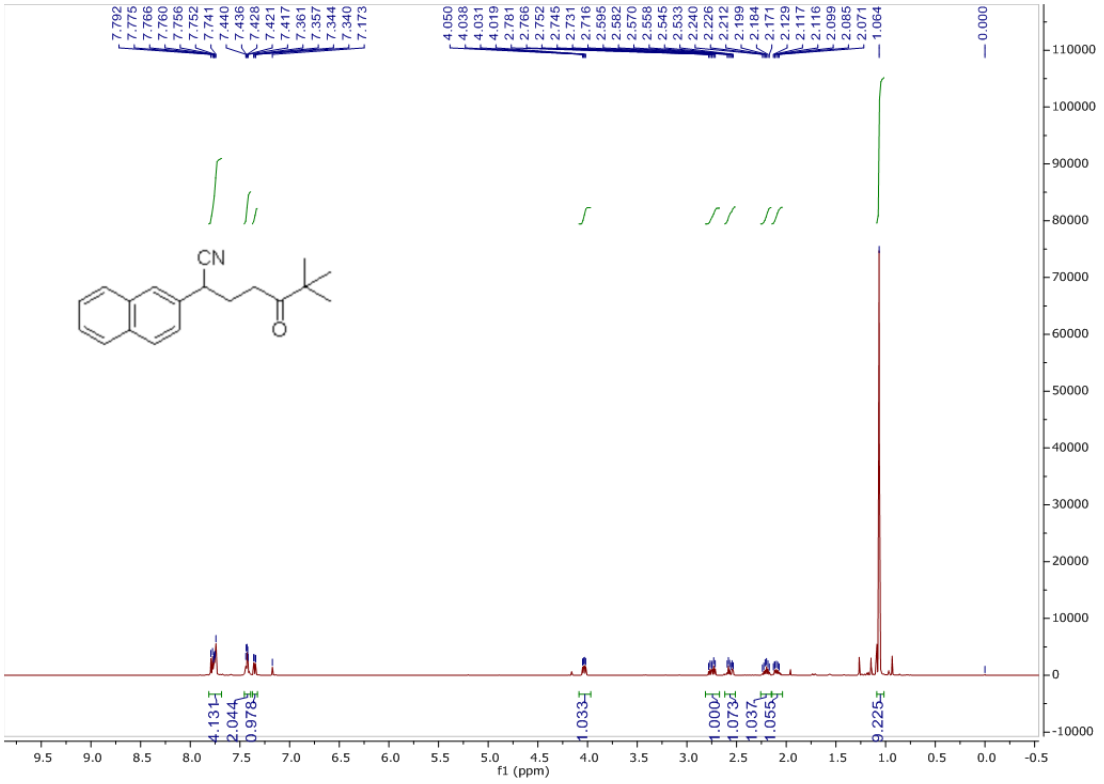


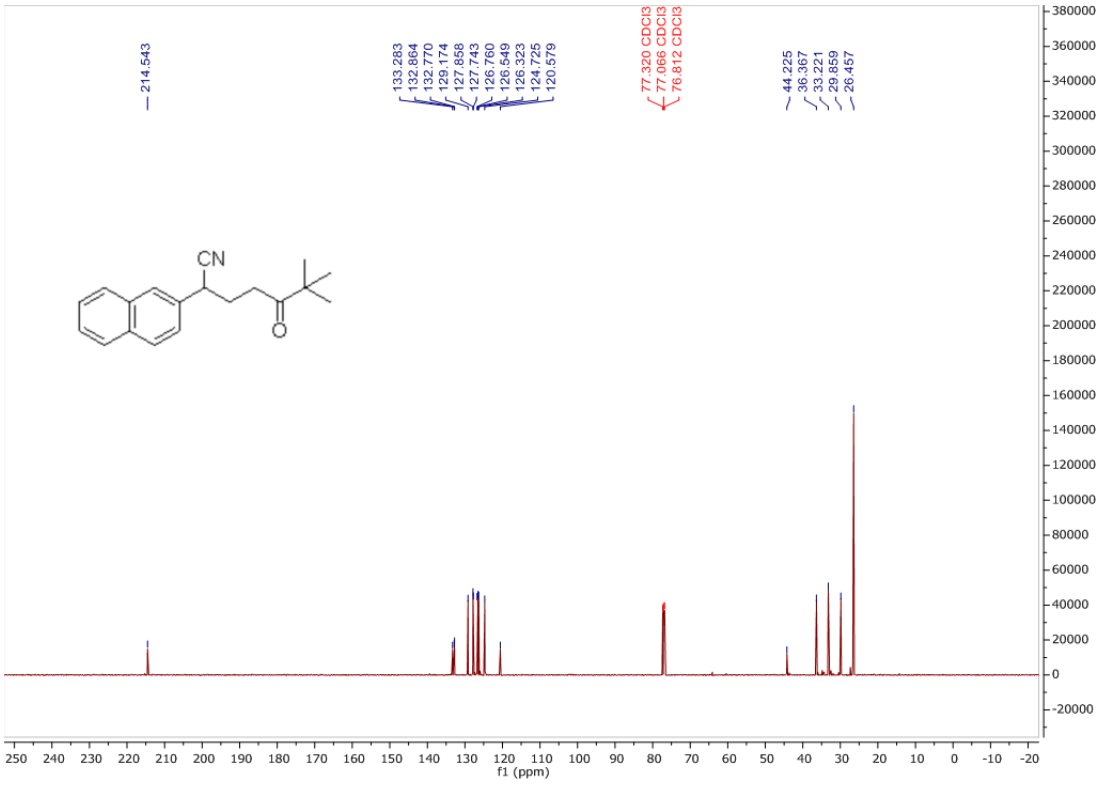
NMR Spectra of **4nc**



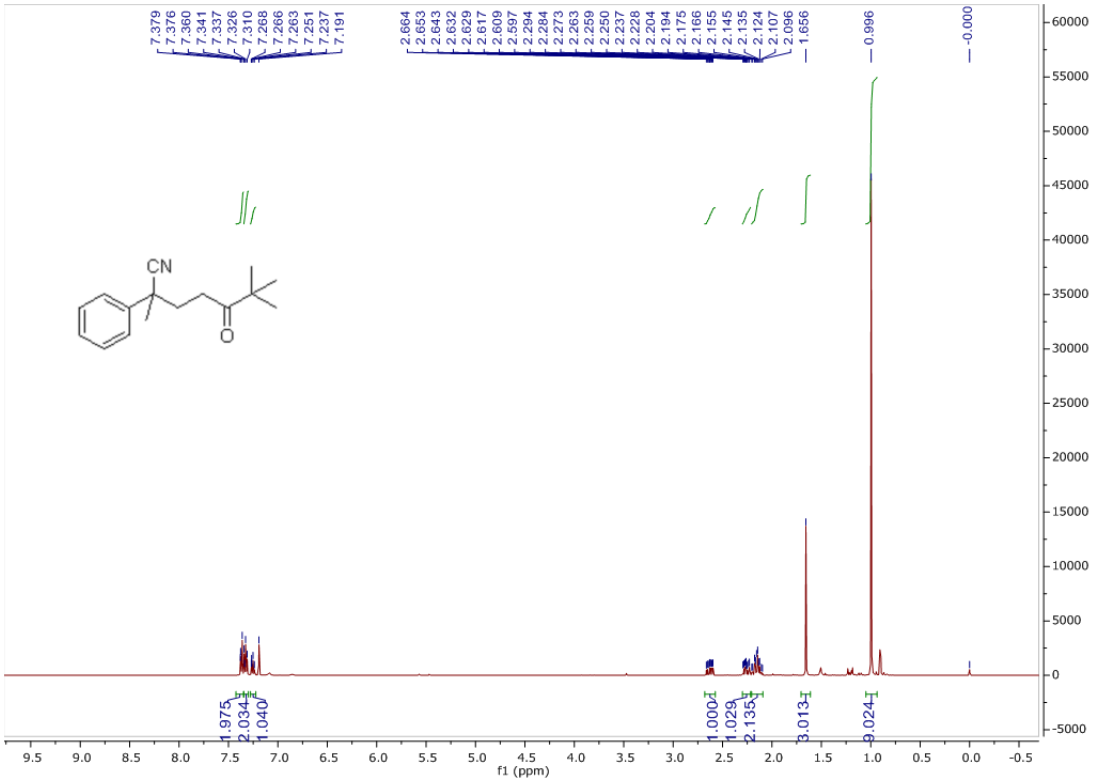


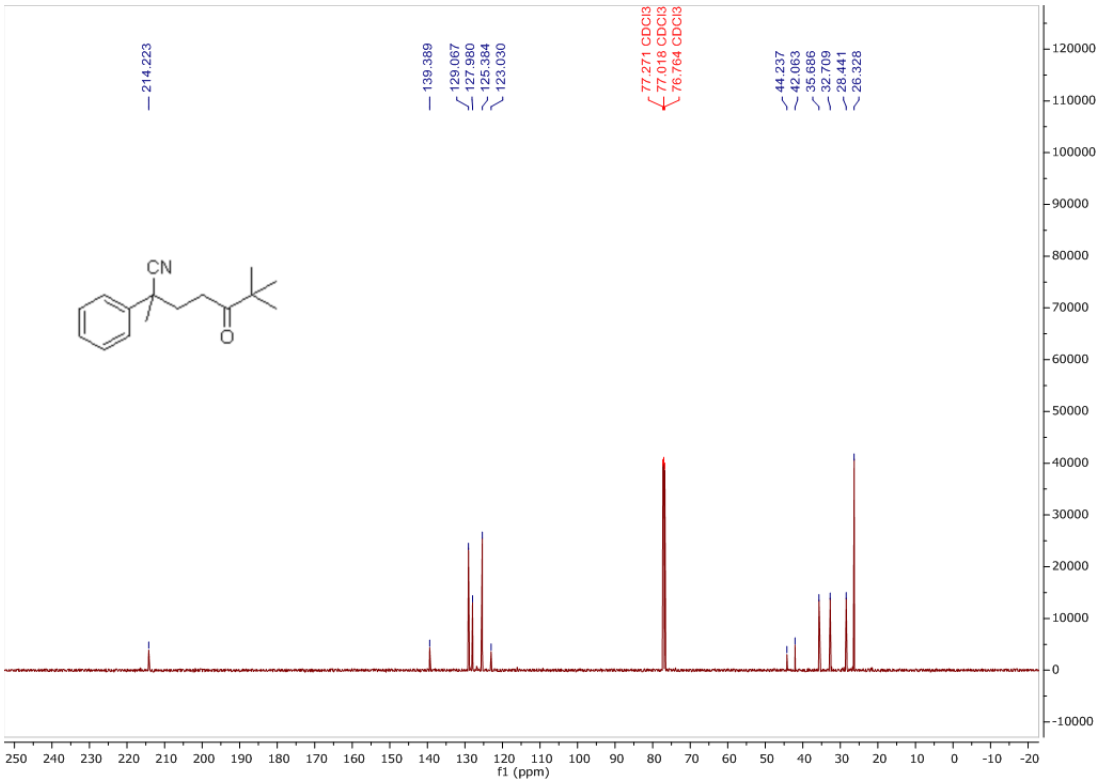
NMR Spectra of **4oc**



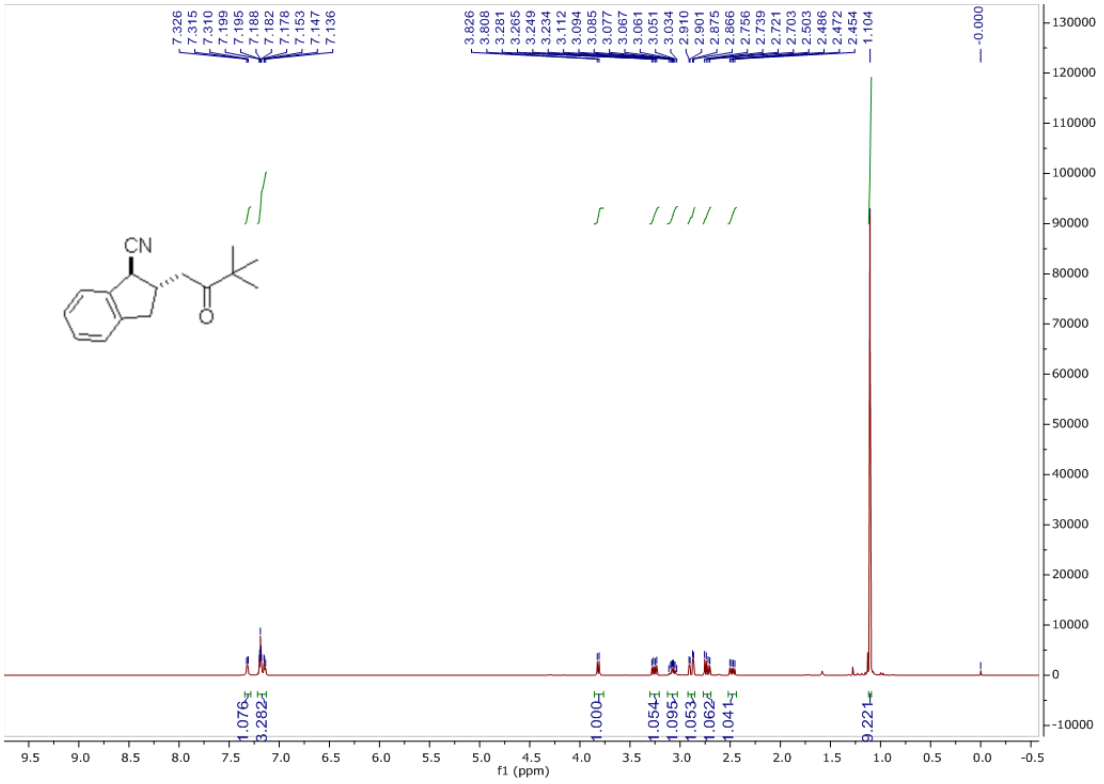


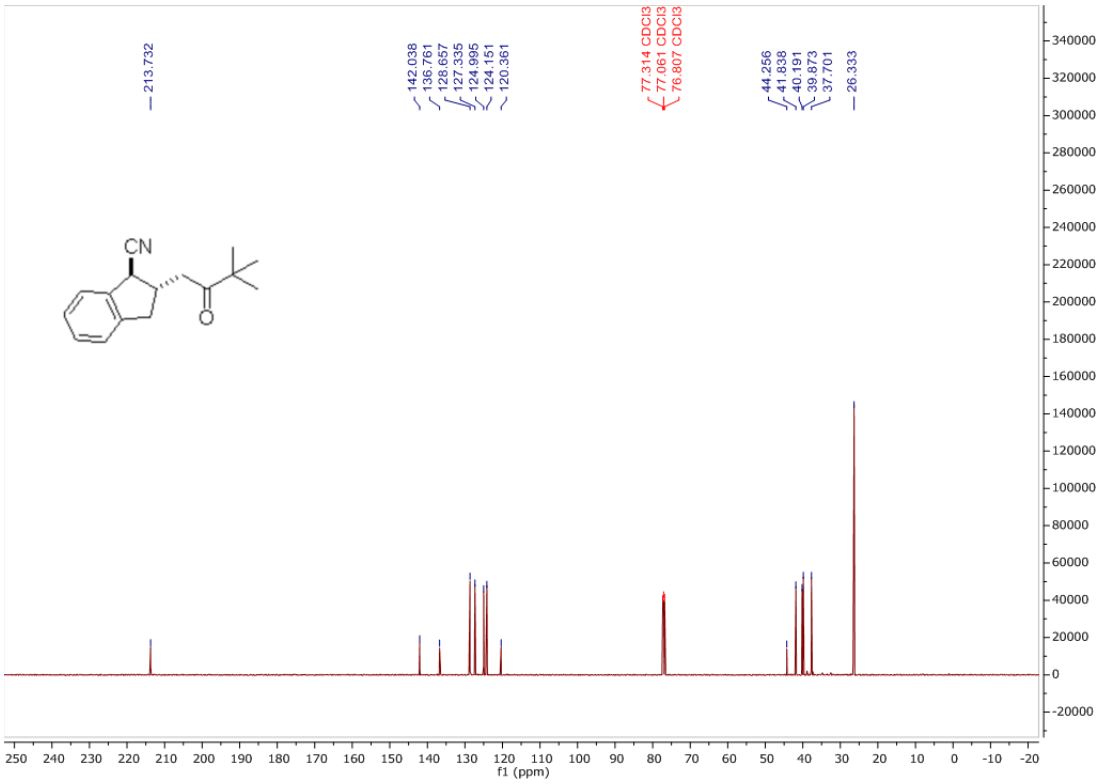
NMR Spectra of **4pc**

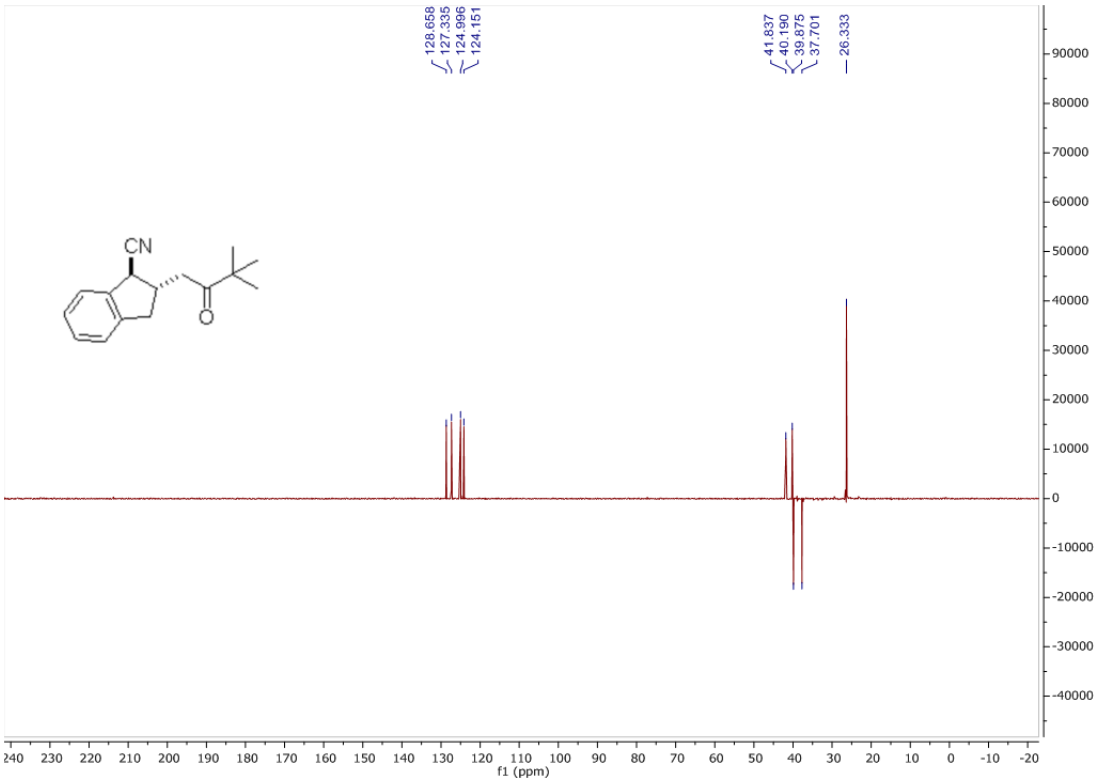


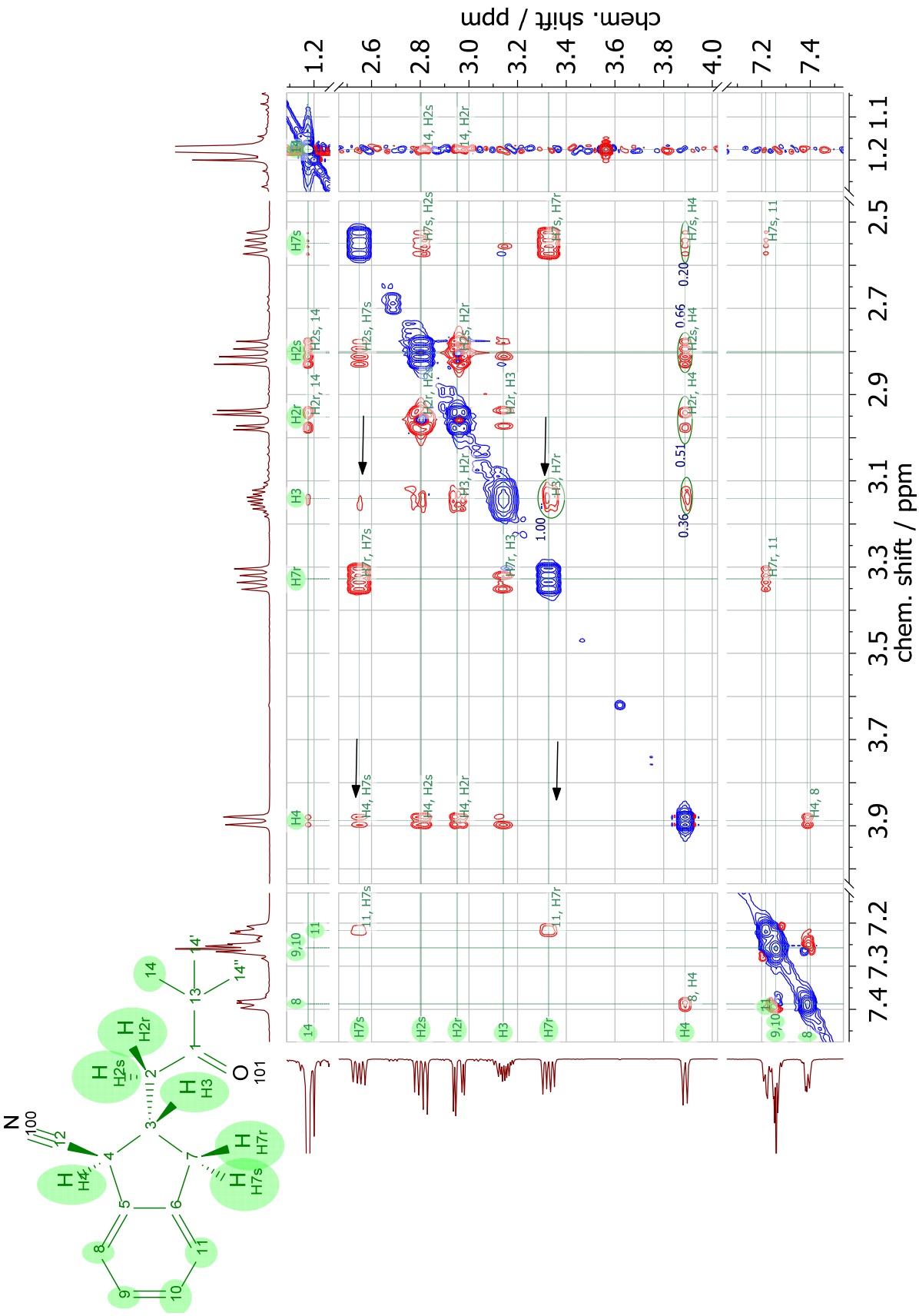


NMR Spectra of **4qc**



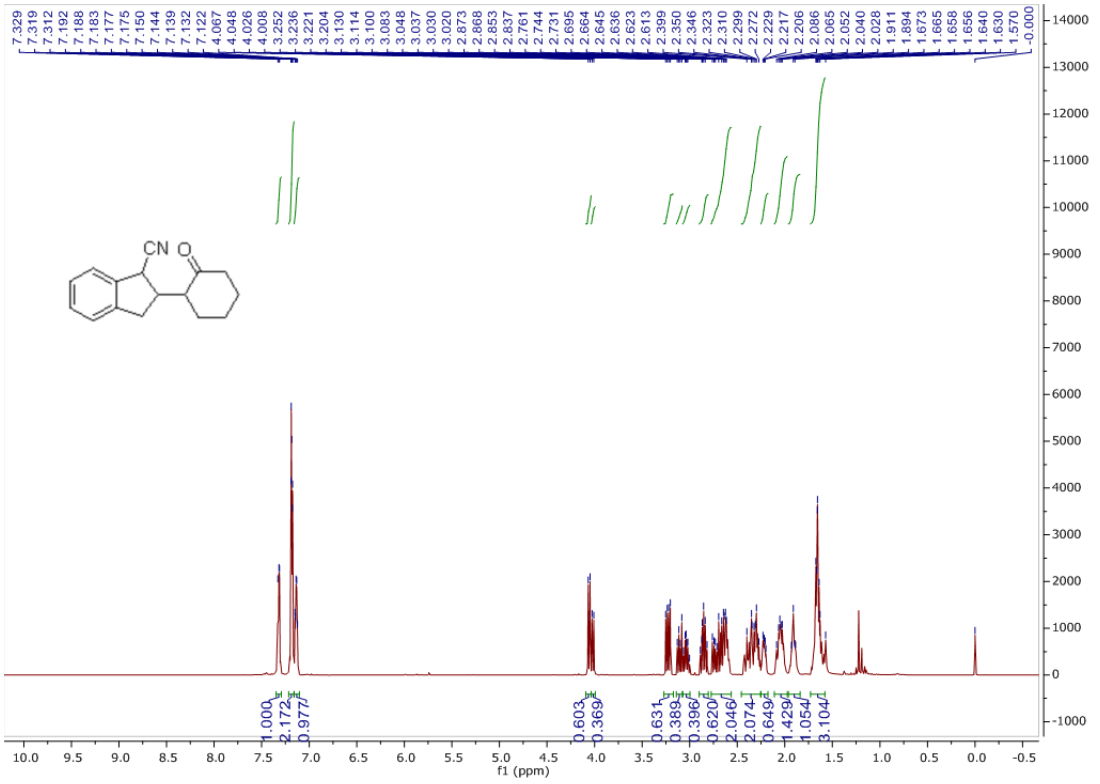


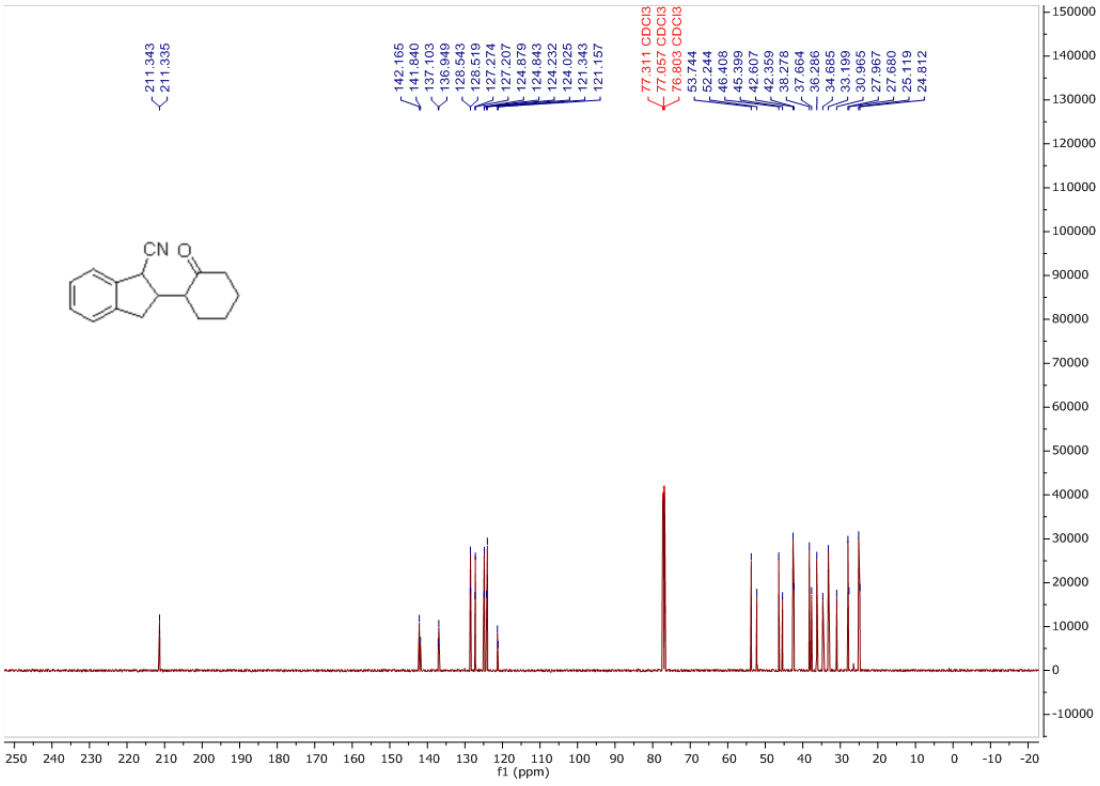

128.658
127.335
124.996
124.151
41.837
40.190
39.875
37.701
26.333
CN
O
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
-10000
-20000
-30000
-40000
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

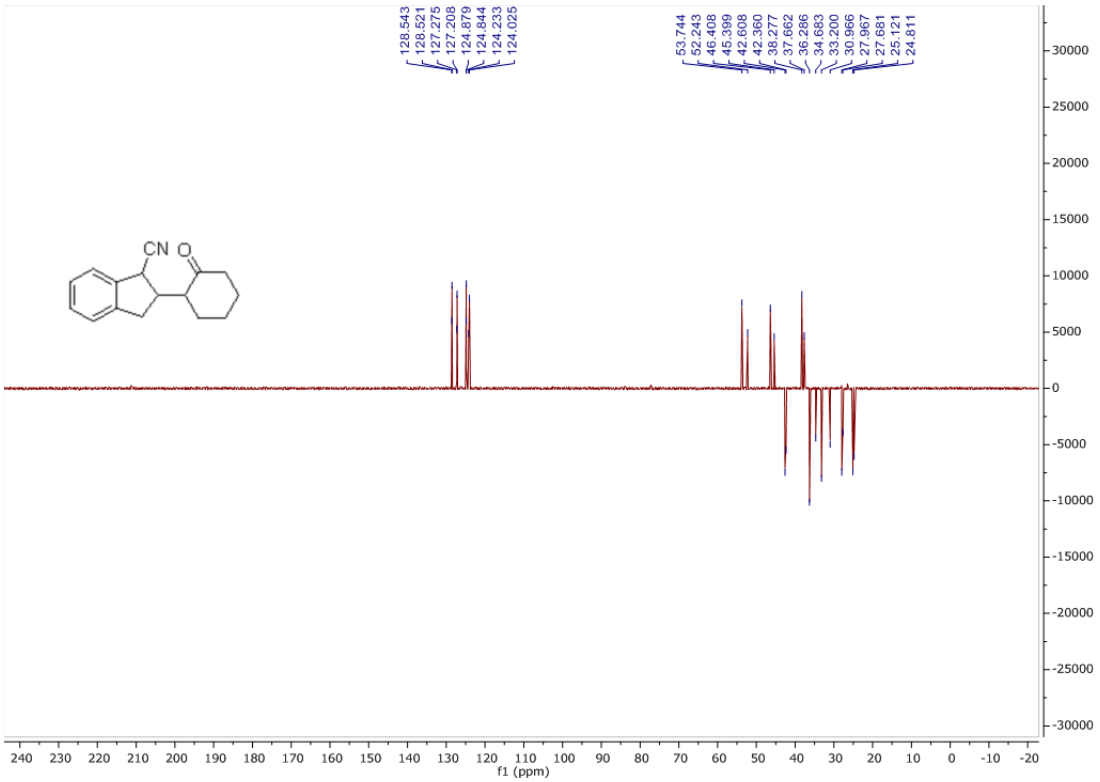


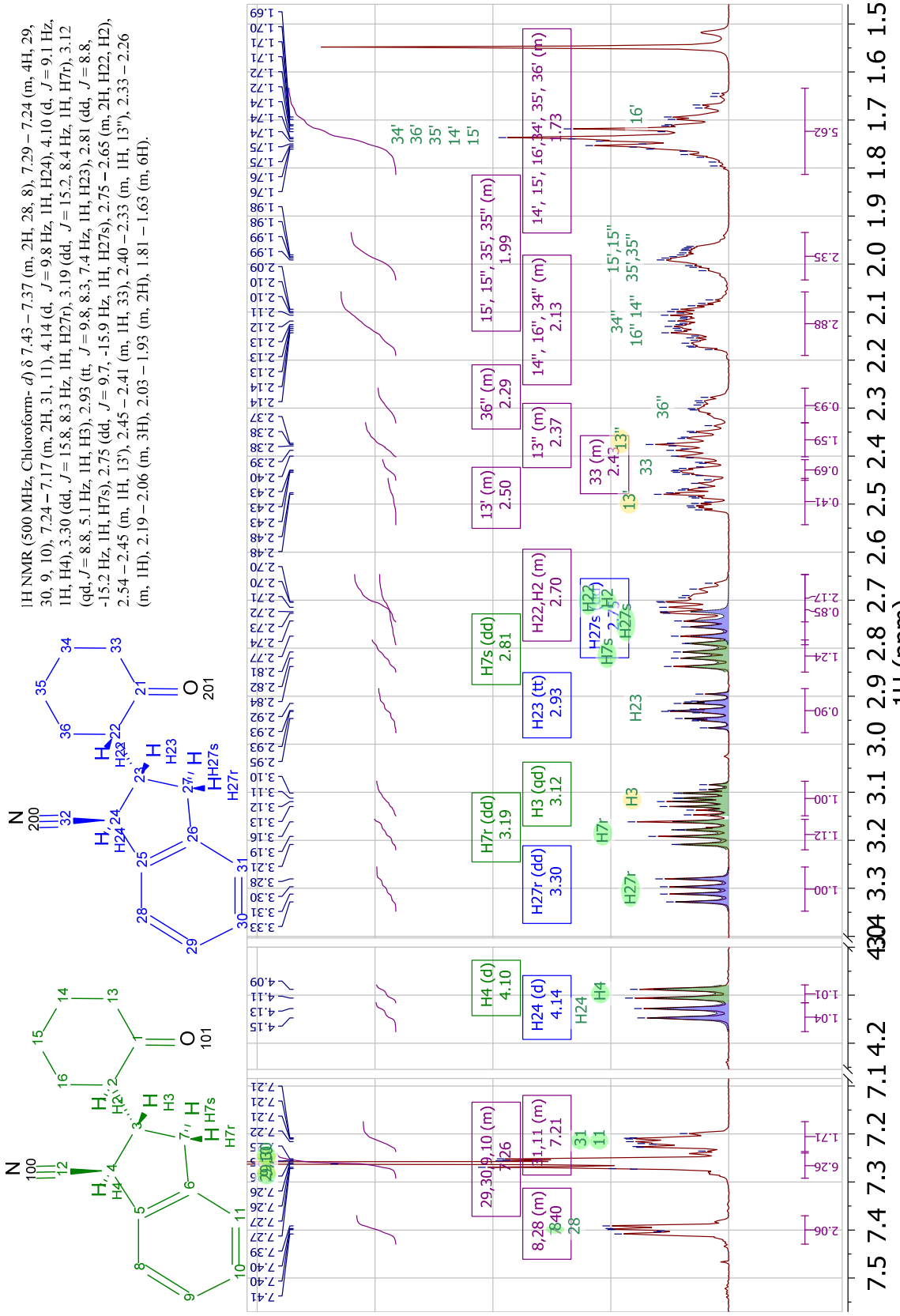
NOESY of **4qc**

NMR Spectra of **4qe**

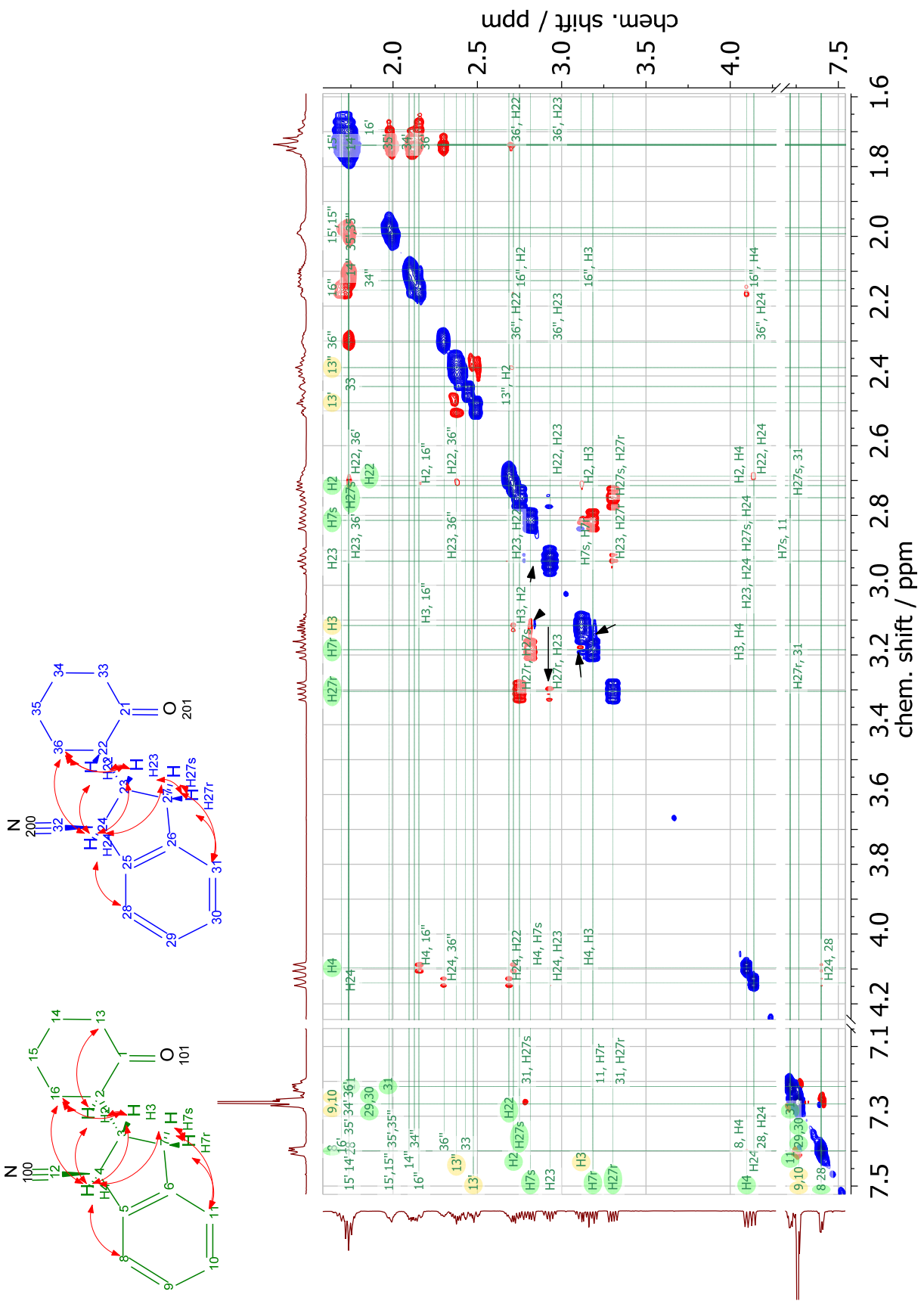





128.543
128.521
127.275
127.208
124.879
124.844
124.233
124.025
53.744
52.243
46.408
45.399
42.608
42.360
38.277
37.662
36.286
34.683
33.200
30.966
27.967
27.681
25.121
24.811
CN
O
30000
25000
20000
15000
10000
5000
0
-5000
-10000
-15000
-20000
-25000
-30000
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

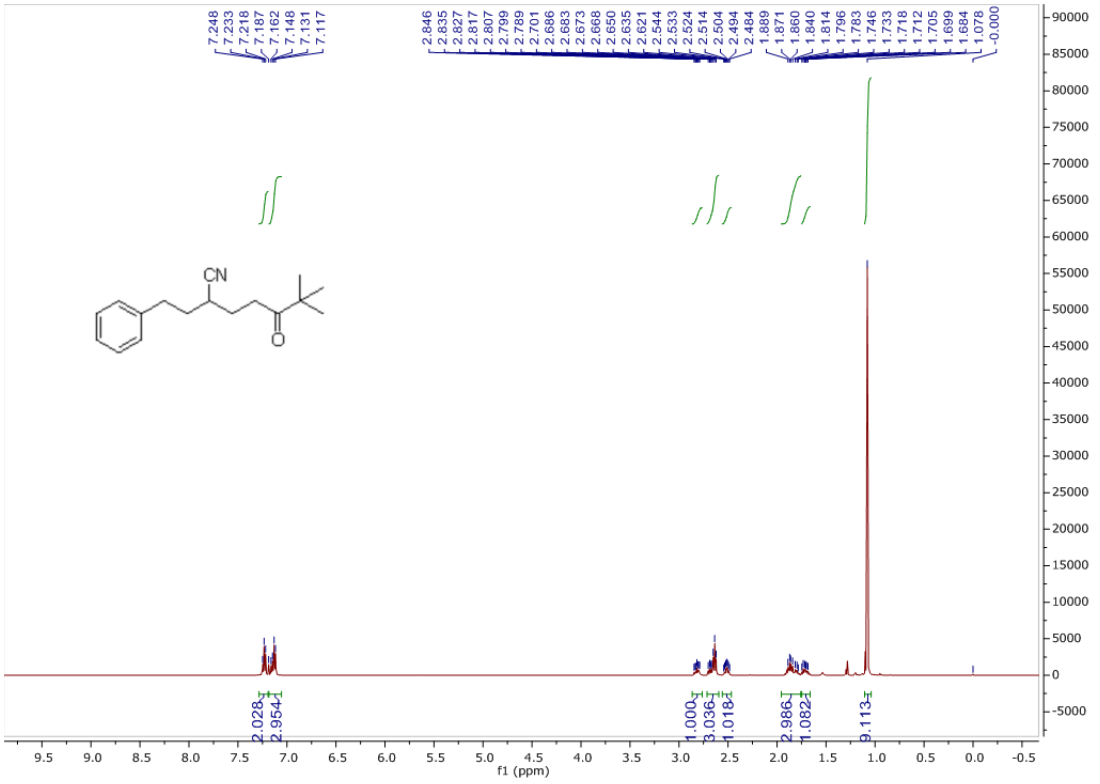

1H NMR (500 MHz, Chloroform- d) δ 7.43 – 7.37 (m, 2H, 28, 8), 7.29 – 7.24 (m, 4H, 29, 30, 9, 10), 7.24 – 7.17 (m, 2H, 31, 11), 4.14 (d, J = 9.8 Hz, 1H, H24), 4.10 (d, J = 9.1 Hz, 1H, H4), 3.30 (dd, J = 15.8, 8.3 Hz, 1H, H27r), 3.19 (dd, J = 15.2, 8.4 Hz, 1H, H7r), 3.12 (qd, J = 8.8, 5.1 Hz, 1H, H3), 2.93 (tt, J = 9.8, 8.3, 7.4 Hz, 1H, H23), 2.81 (dd, J = 8.8, -15.2 Hz, 1H, H7s), 2.75 (dd, J = 9.7, -15.9 Hz, 1H, H27s), 2.75 – 2.65 (m, 2H, H22, H2), 2.54 – 2.45 (m, 1H, 13'), 2.45 – 2.41 (m, 1H, 33), 2.40 – 2.33 (m, 1H, 13''), 2.33 – 2.26 (m, 1H), 2.19 – 2.06 (m, 3H), 2.03 – 1.93 (m, 2H), 1.81 – 1.63 (m, 6H).
1H (ppm)

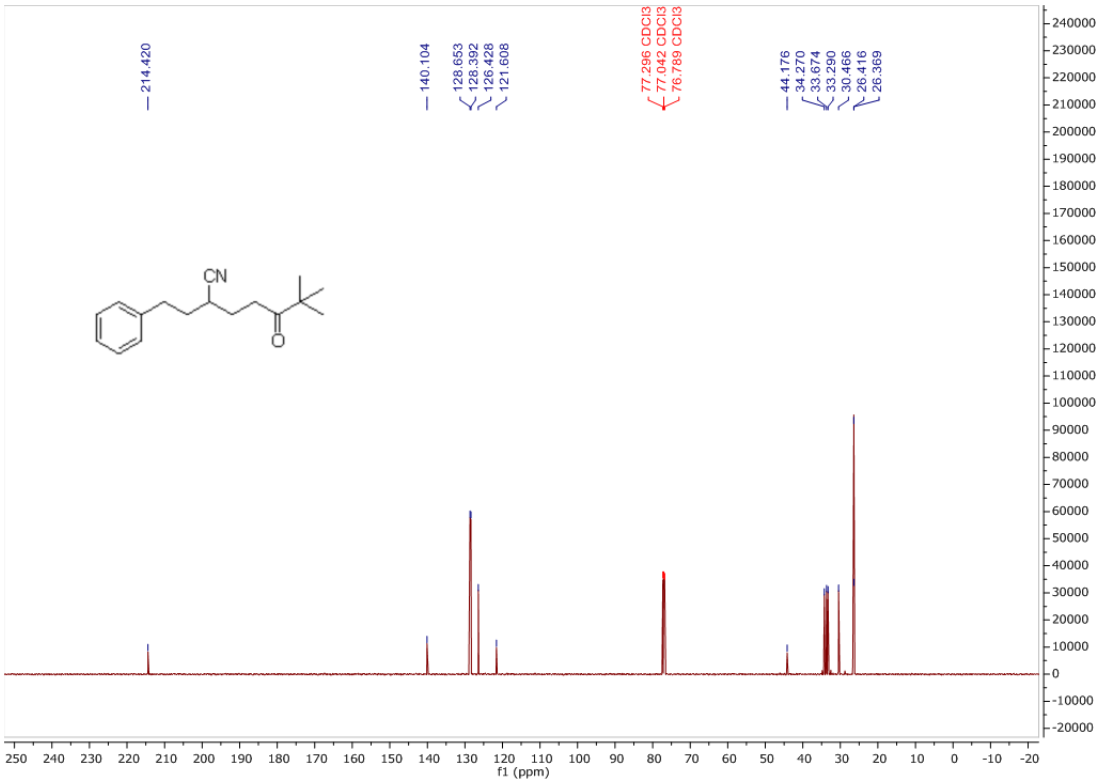
1H of **4qe**

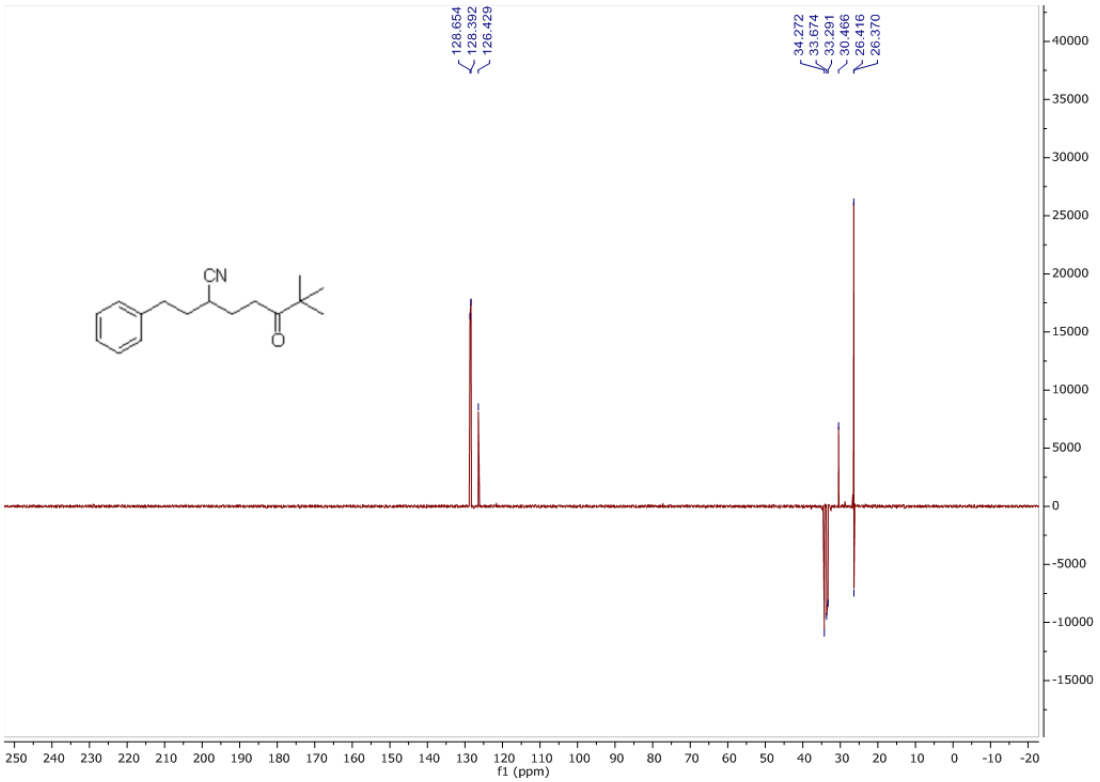


NOESY of **4qe**

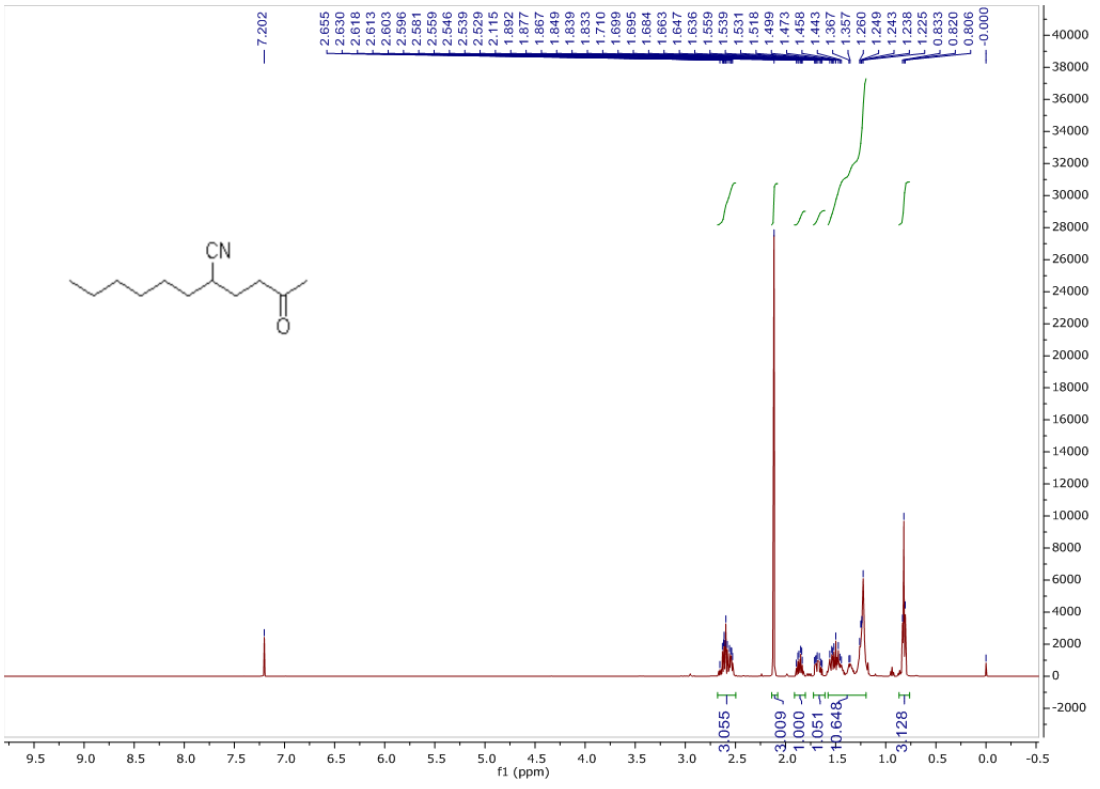
NMR Spectra of **9ac**

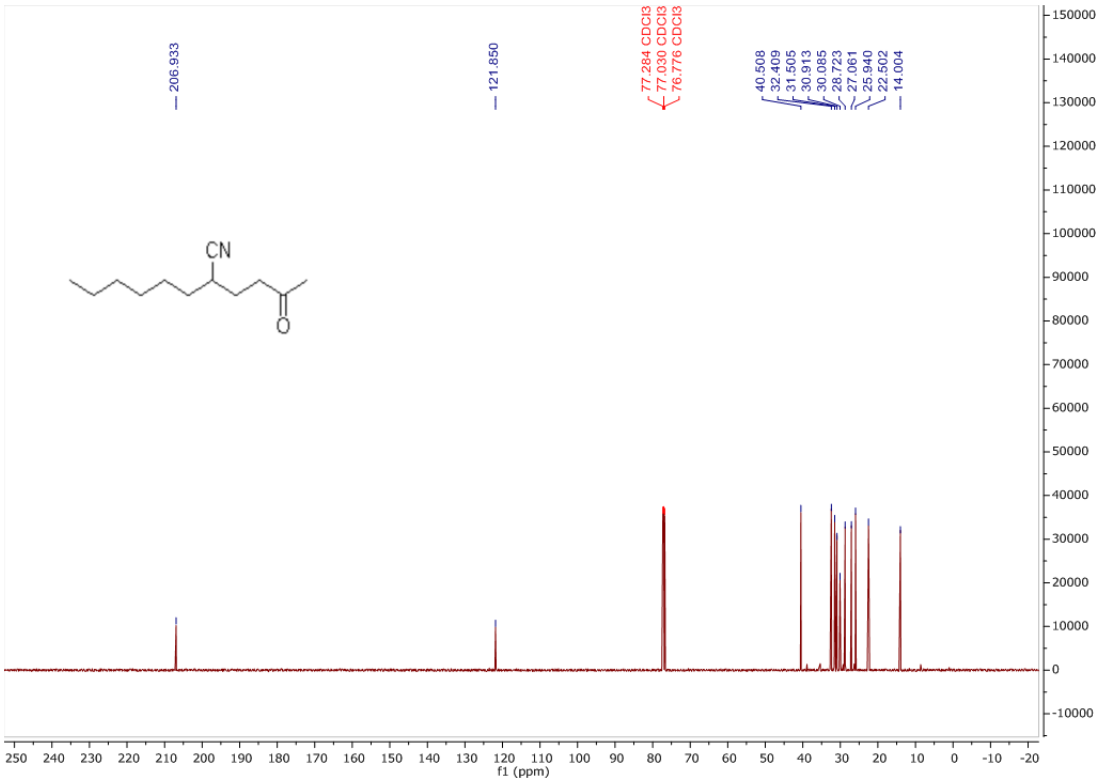


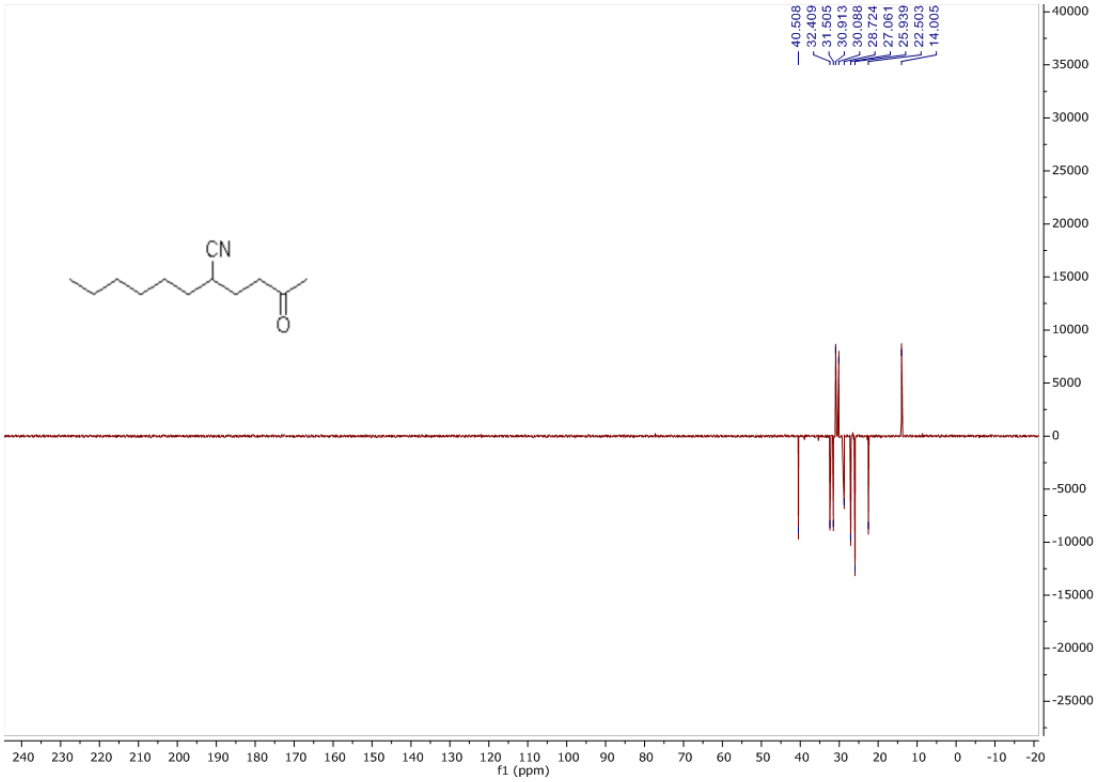




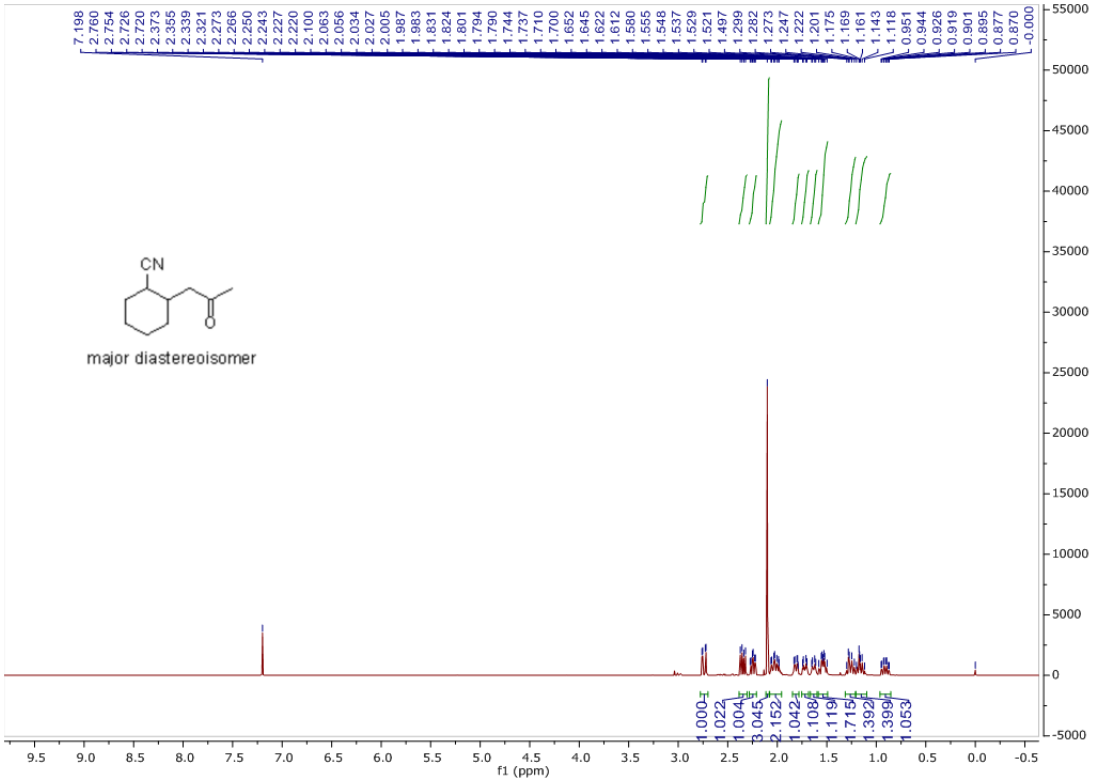
NMR Spectra of **9ba**

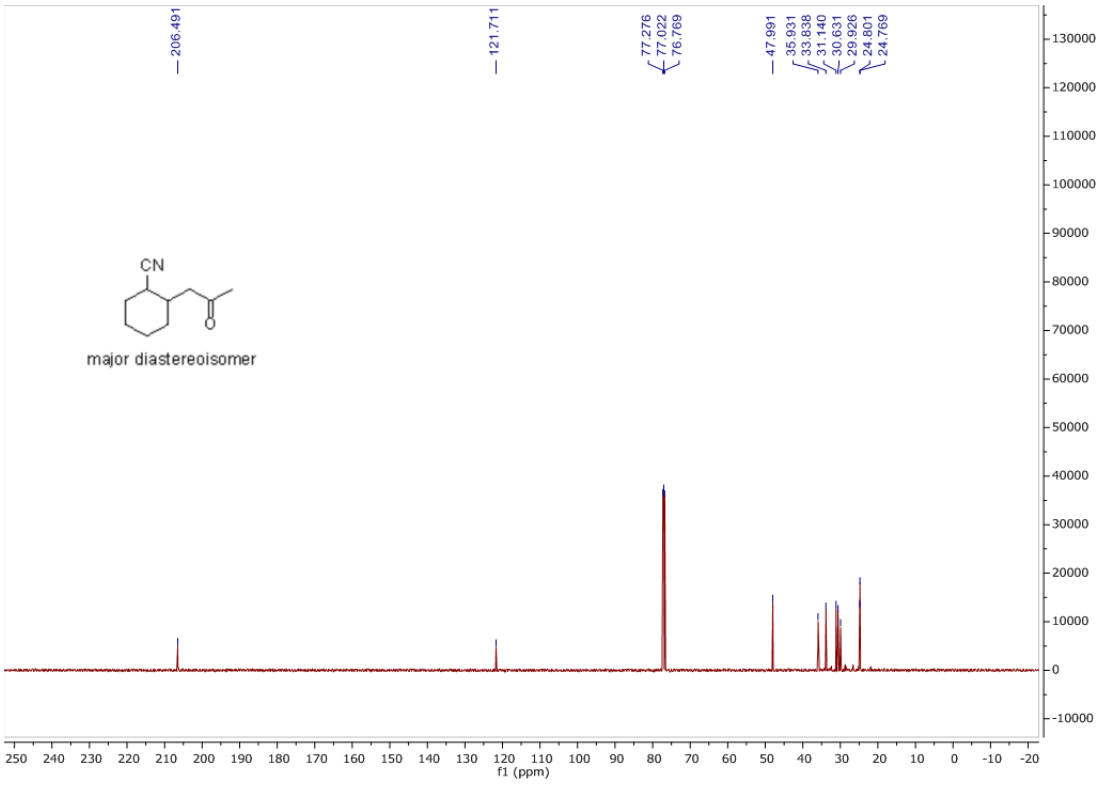


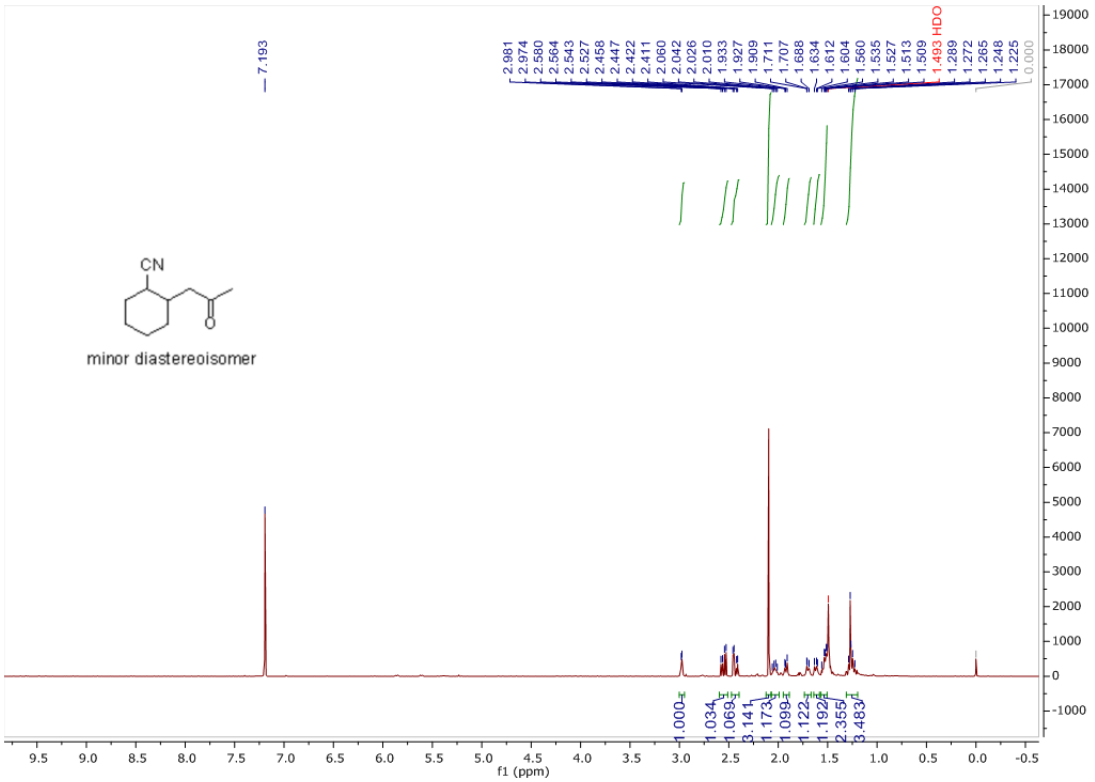

206.933
121.850
77.284 CDCl3
77.030 CDCl3
76.776 CDCl3
40.508
32.409
31.505
30.913
30.085
28.723
27.061
25.940
22.502
14.004
CN
O
f1 (ppm)


40.508
32.409
31.505
30.913
30.088
28.724
27.061
25.939
22.503
14.005
CN
O
f1 (ppm)

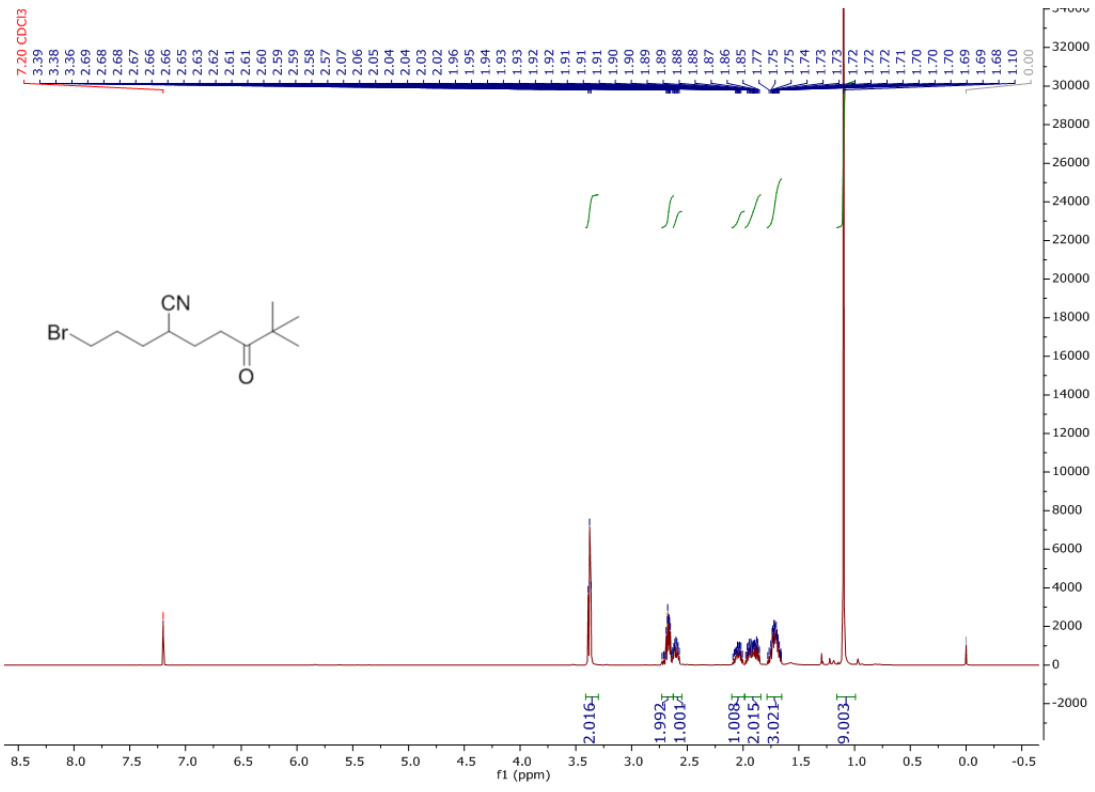
NMR Spectra of **9ca**

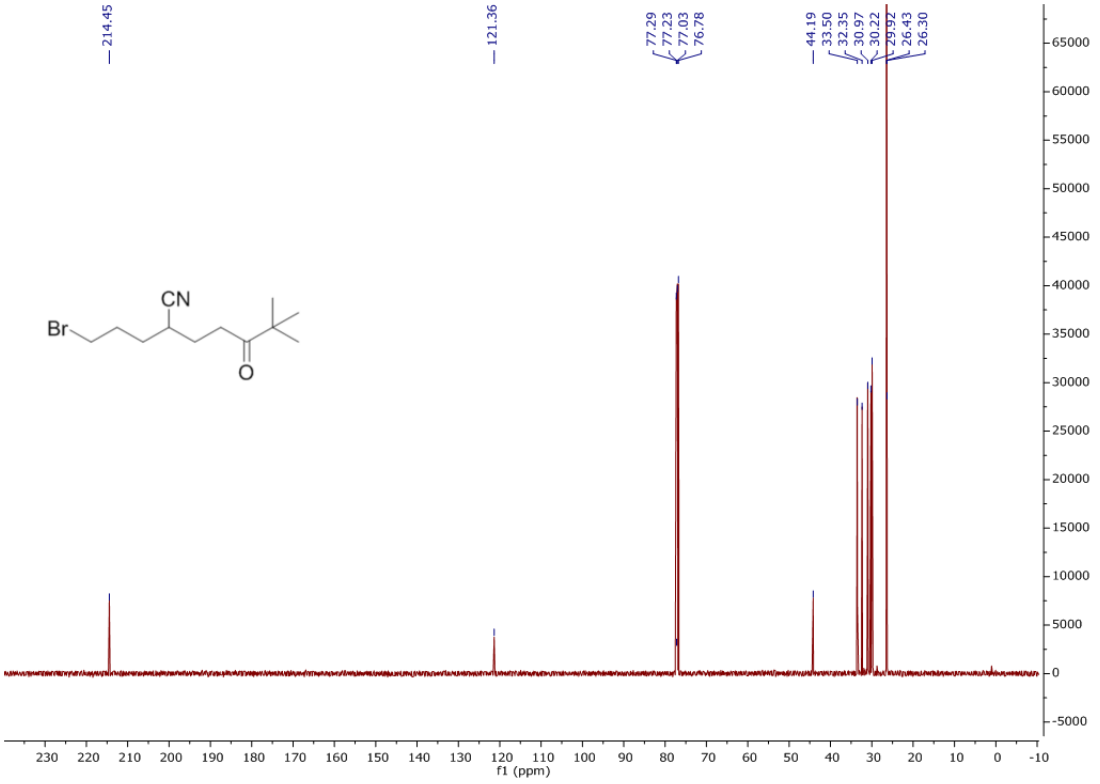


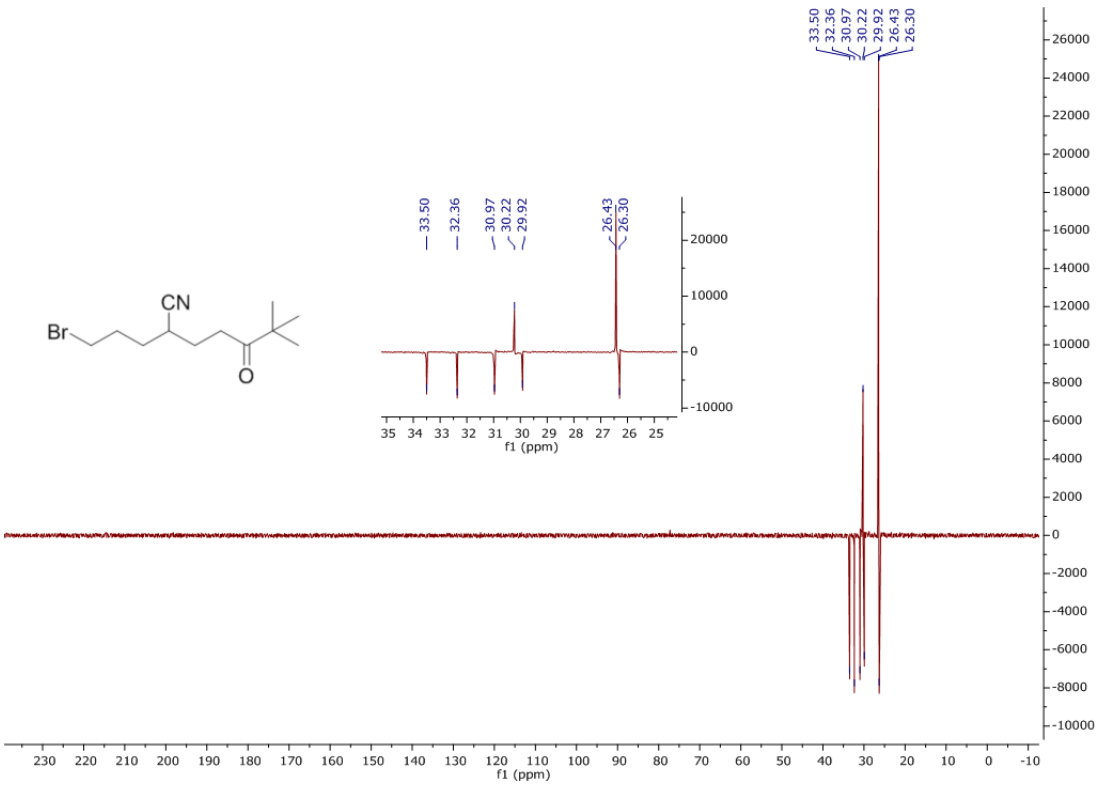




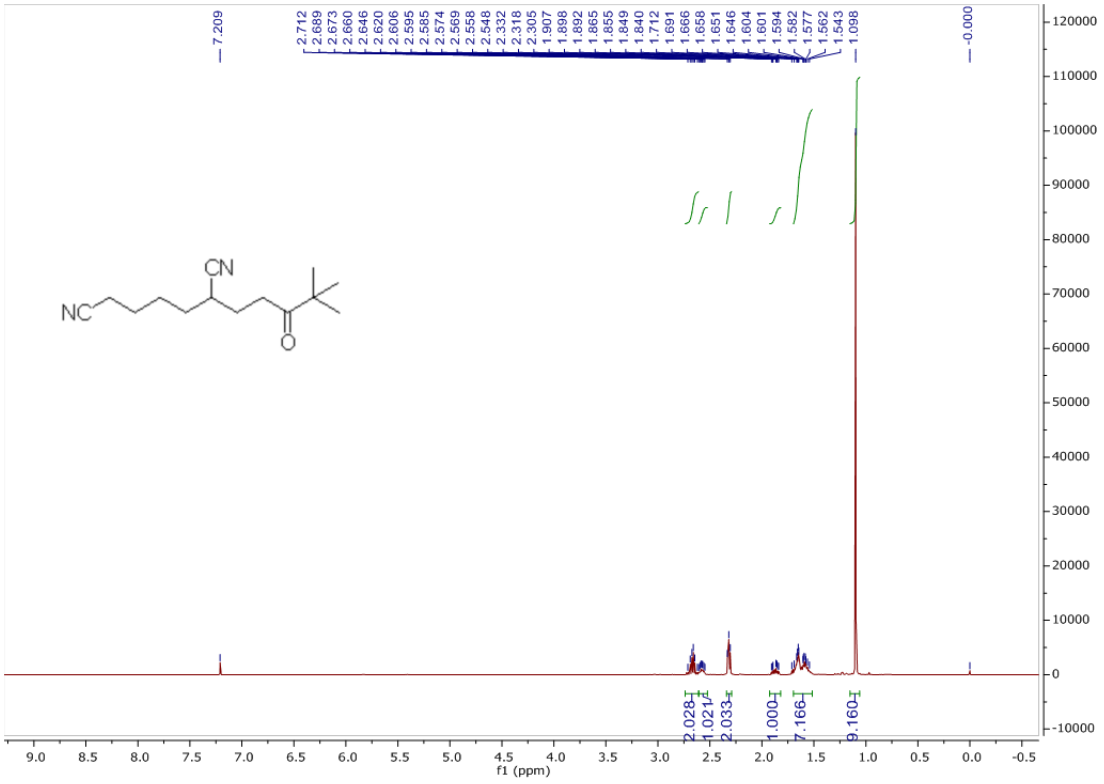
NMR Spectra of **9dc**

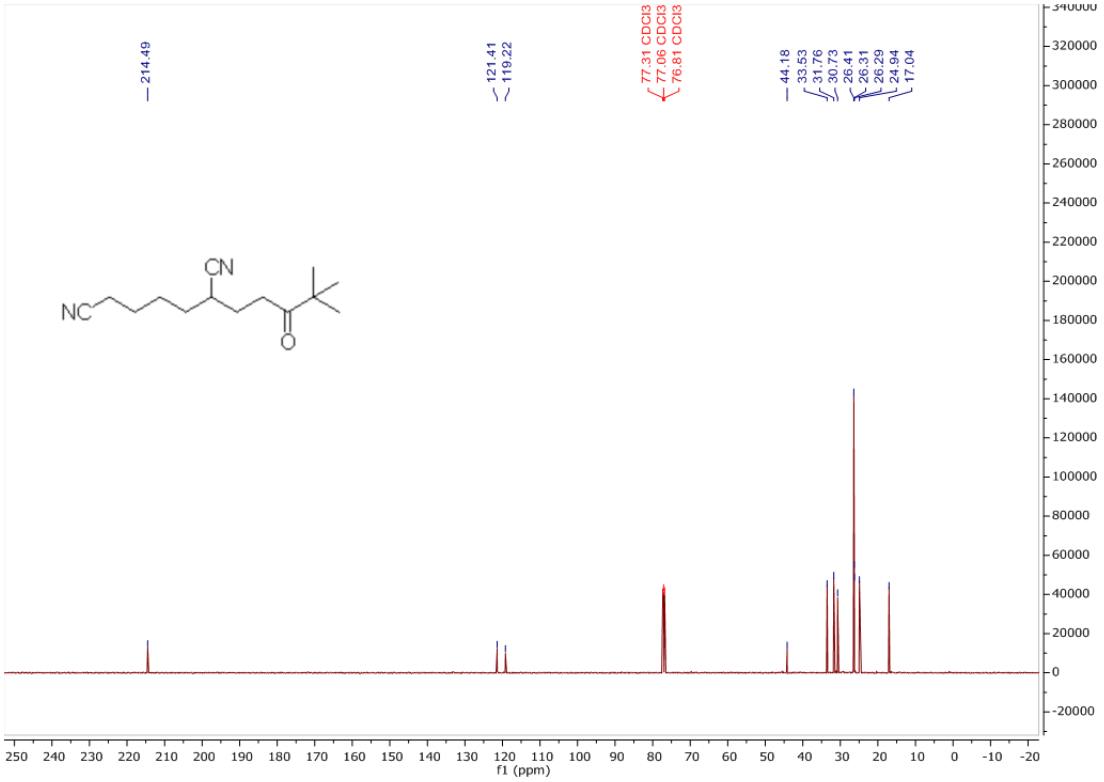


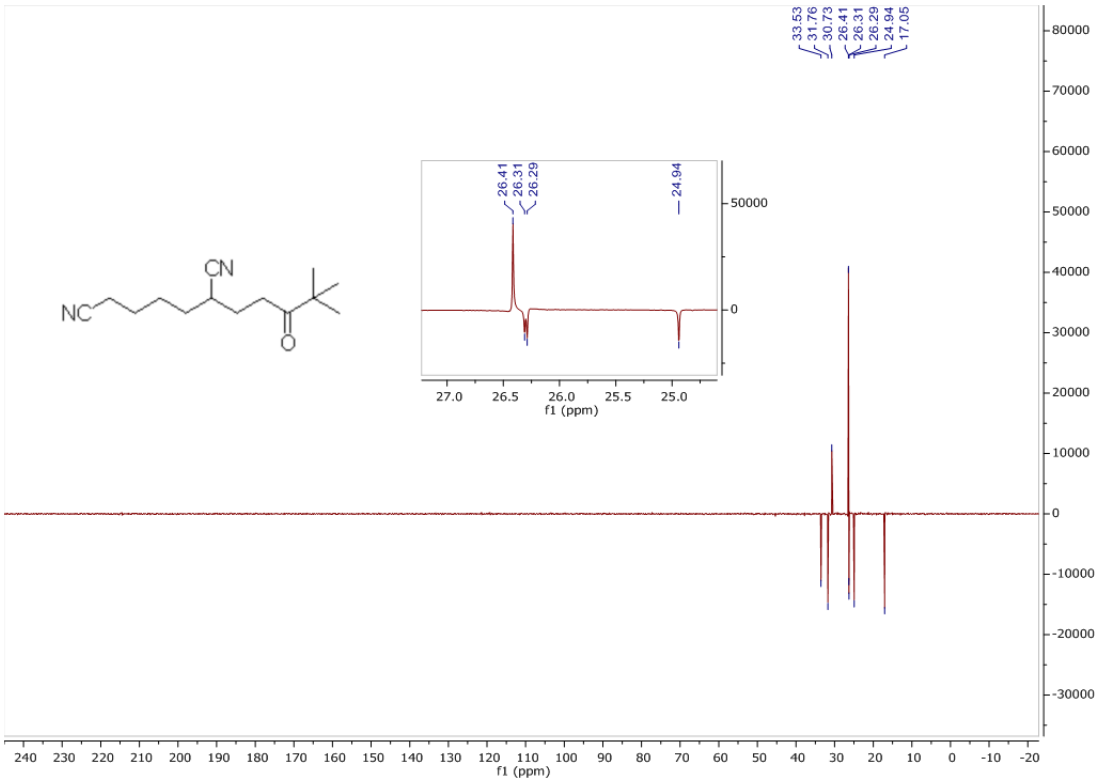

214.45
121.36
77.29
77.23
77.03
76.78
44.19
33.50
32.35
30.97
30.22
29.92
26.43
26.30
CN
Br
O
f1 (ppm)


33.50
32.36
30.97
30.22
29.92
26.43
26.30
CN
Br
O
f1 (ppm)

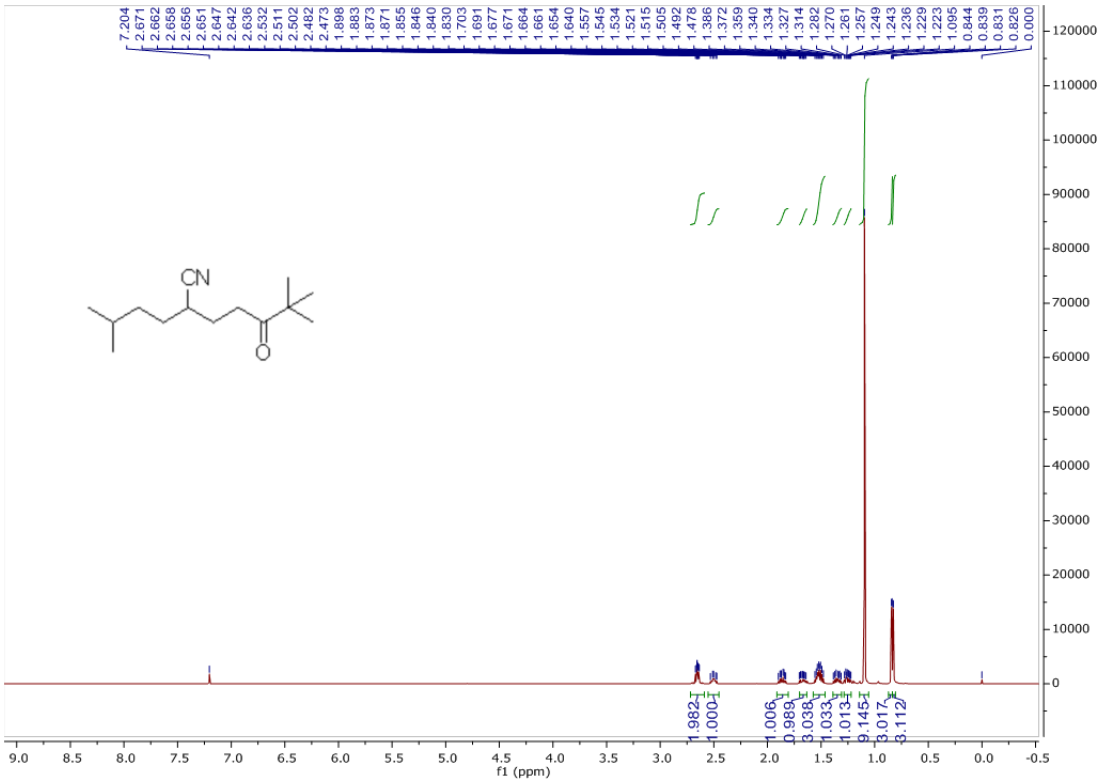
NMR Spectra of **9ec**

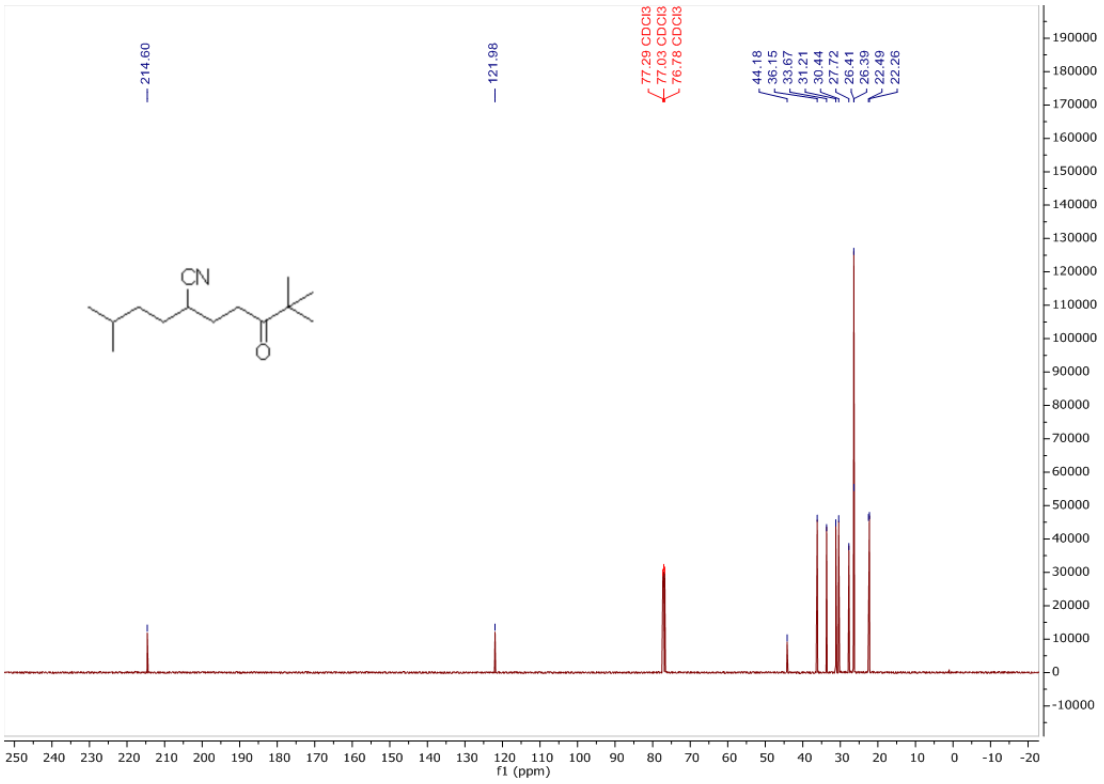


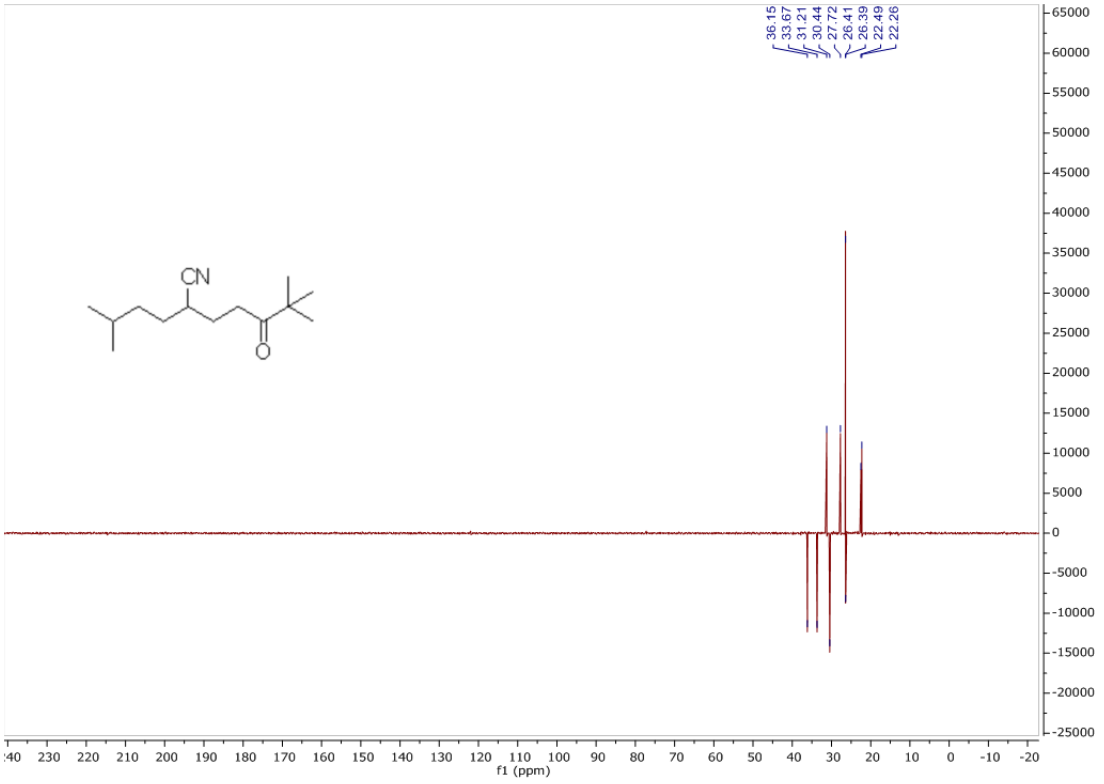




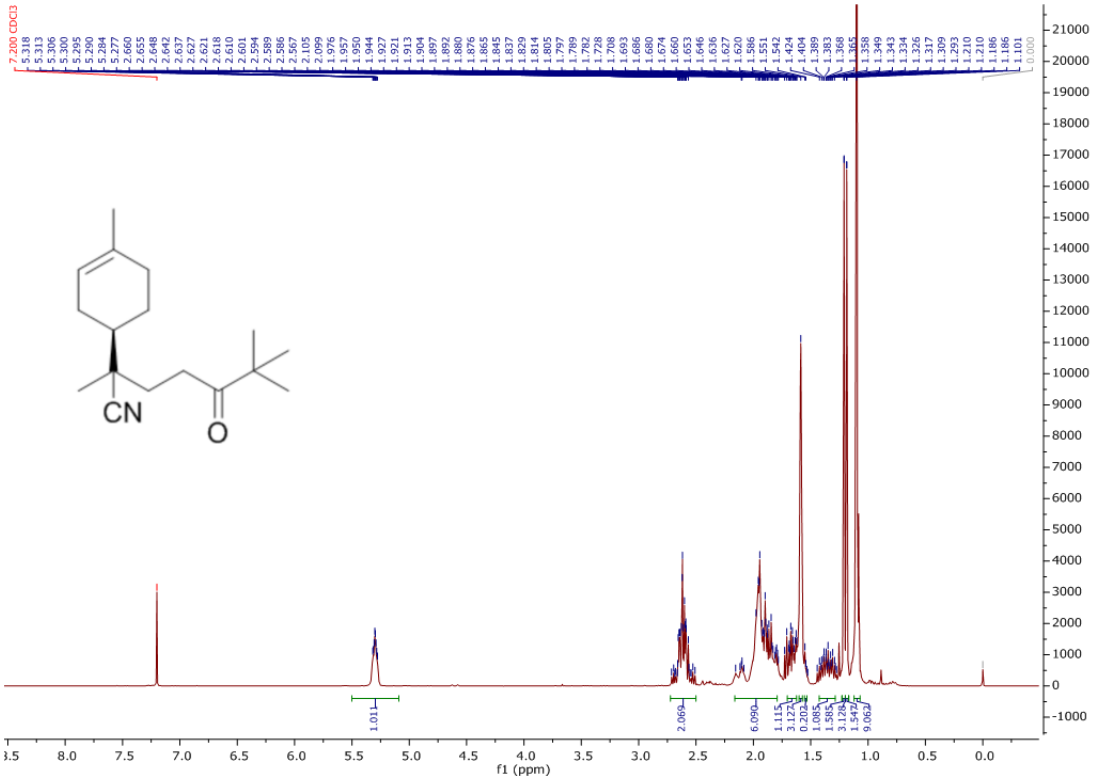
NMR Spectra of **9fc**

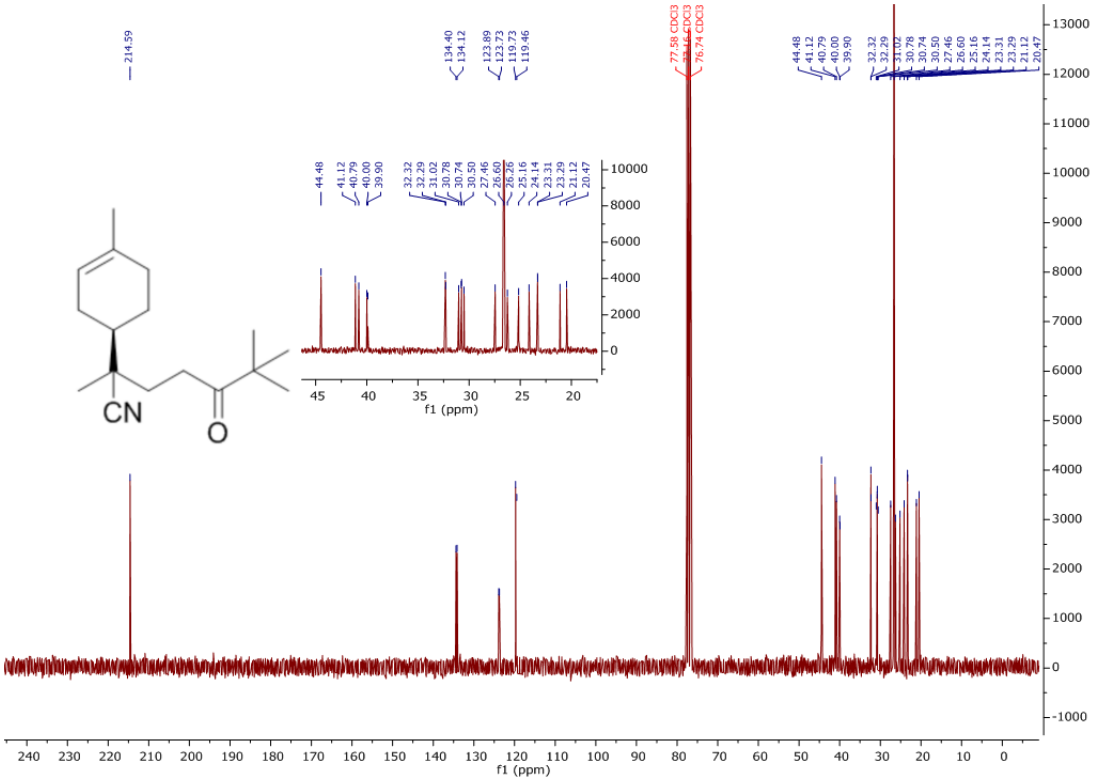


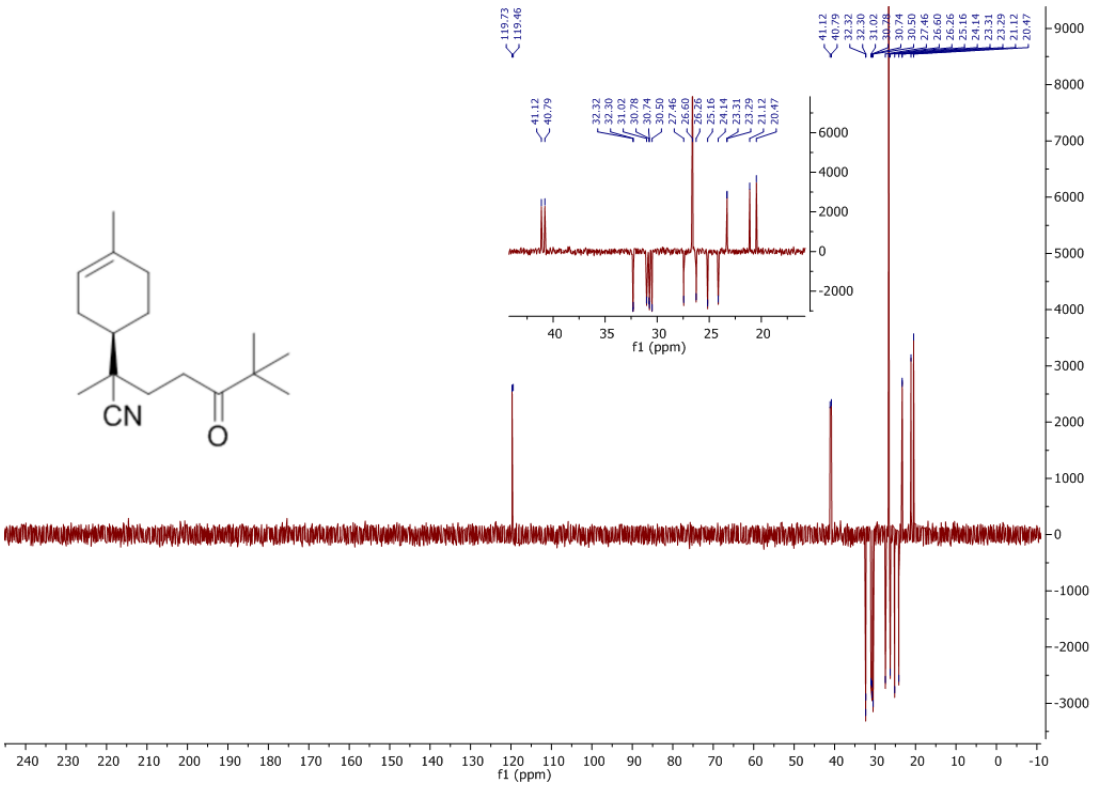

214.60
121.98
77.29 CDCl3
77.03 CDCl3
76.78 CDCl3
44.18
36.15
33.67
31.21
30.44
27.72
26.41
26.39
22.49
22.26
CN
O
f1 (ppm)


36.15
33.67
31.21
30.44
27.72
26.41
26.39
22.49
22.26
CN
O
f1 (ppm)

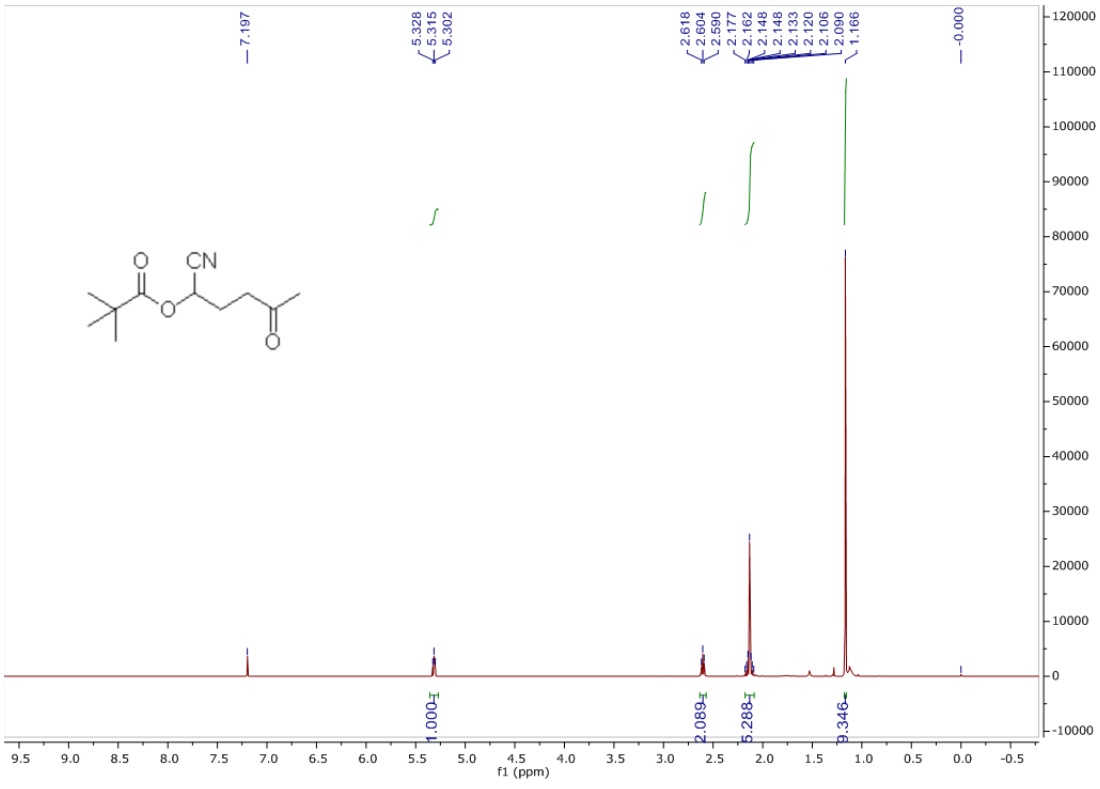
NMR Spectra of **9gc**

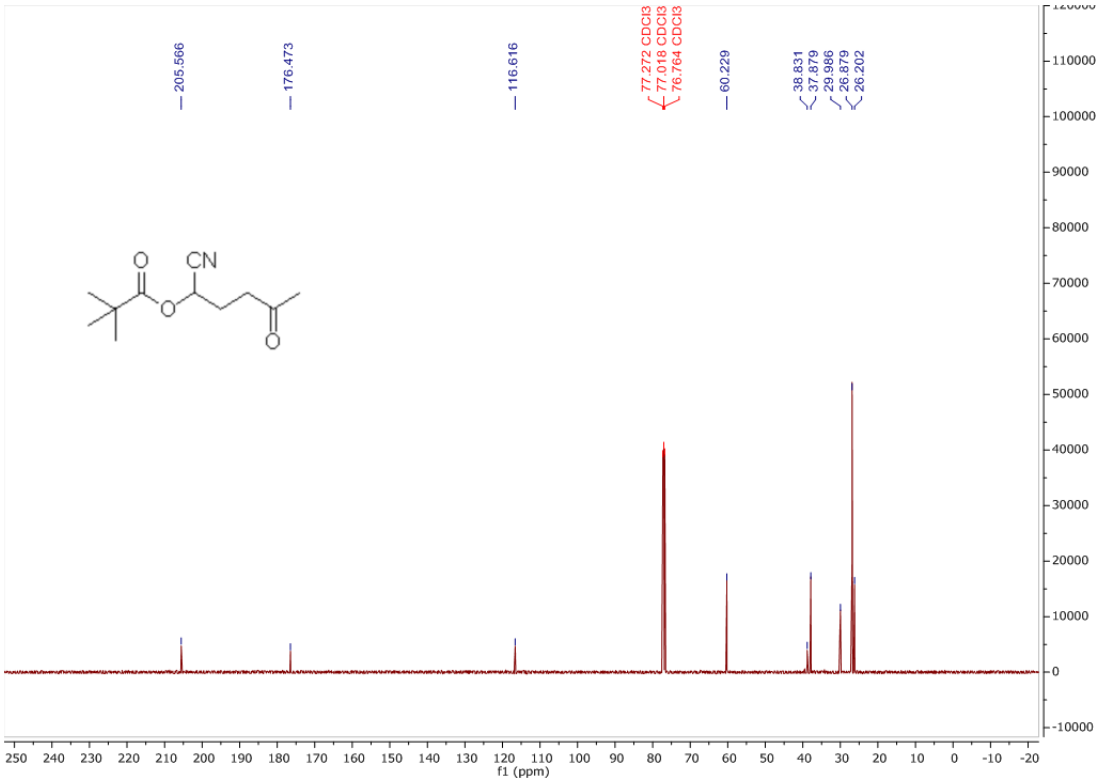


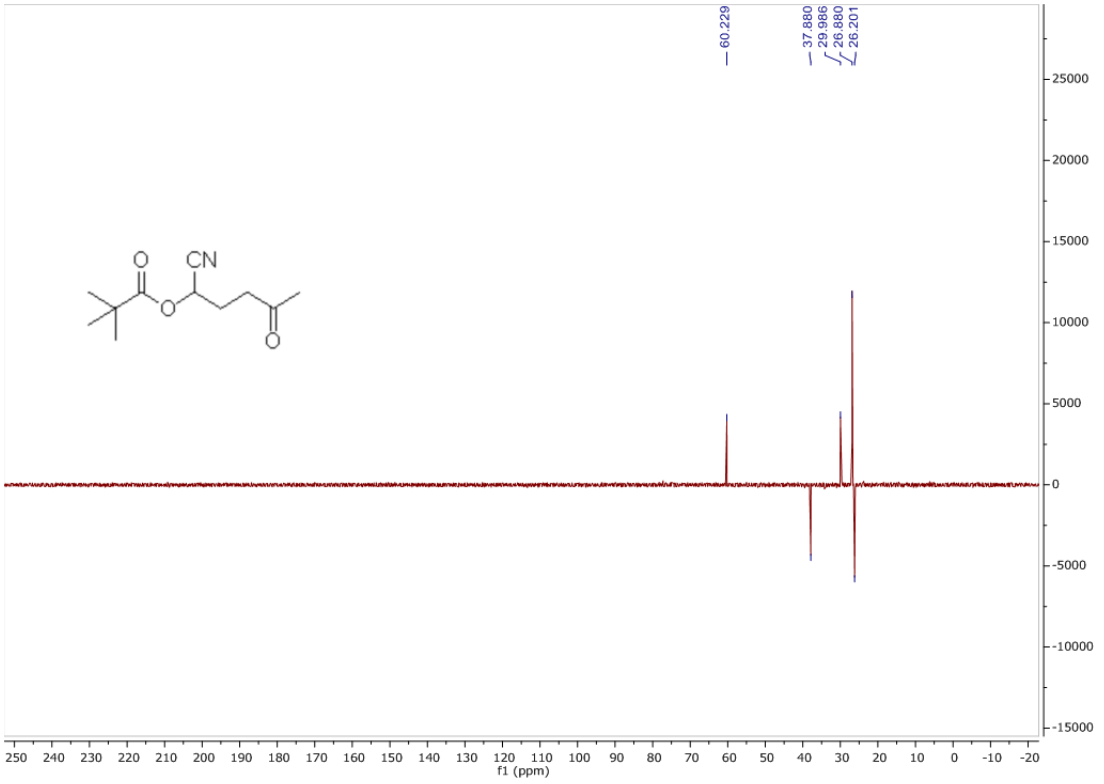




NMR Spectra of **9ha**

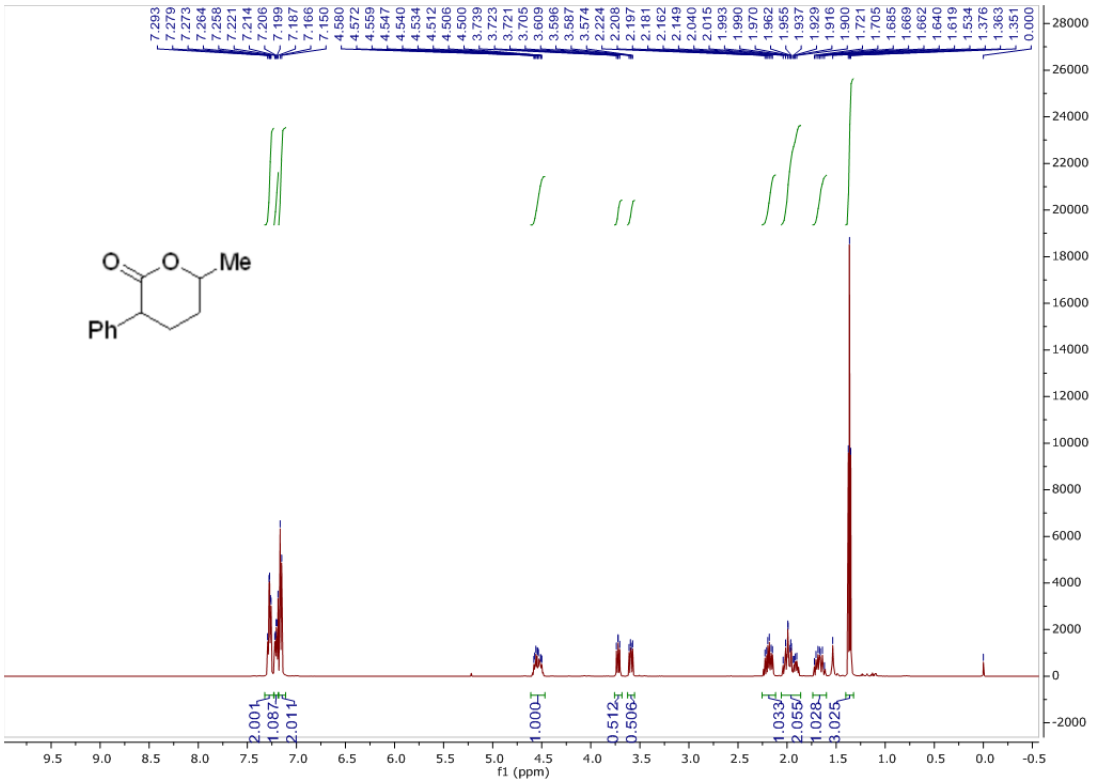


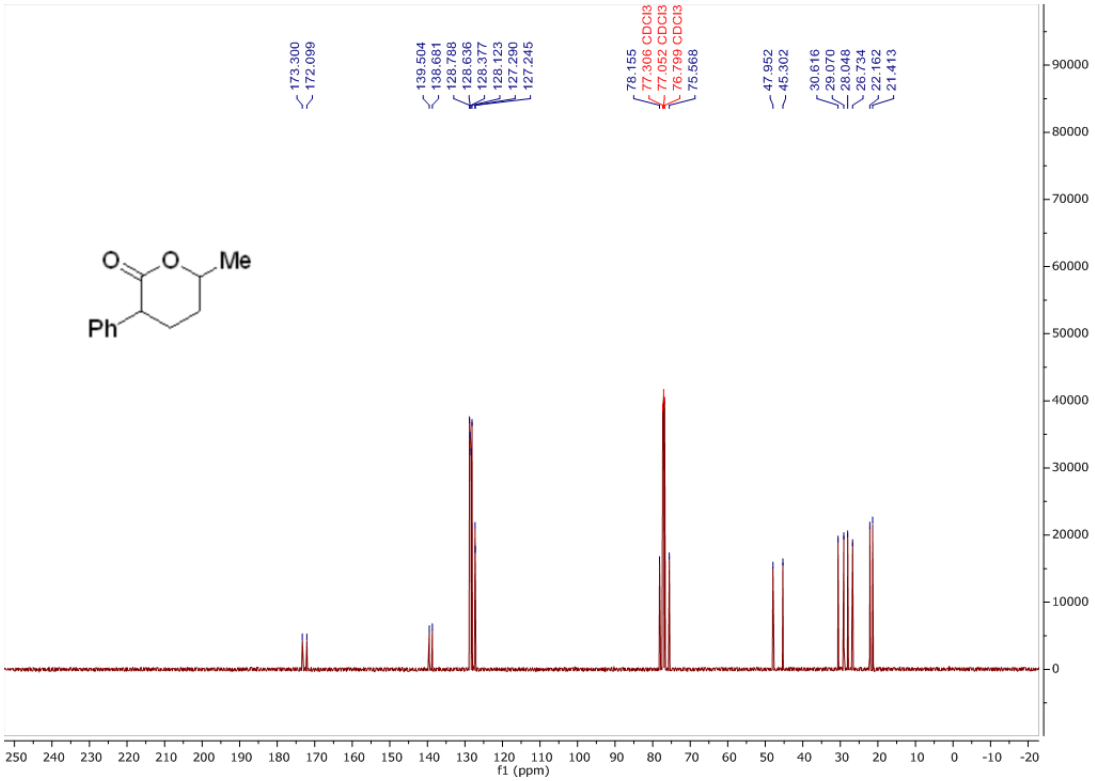

205.566
176.473
116.616
77.272 CDCl3
77.018 CDCl3
76.764 CDCl3
60.229
38.831
37.879
29.986
26.879
26.202
O
CN
O
O
f1 (ppm)

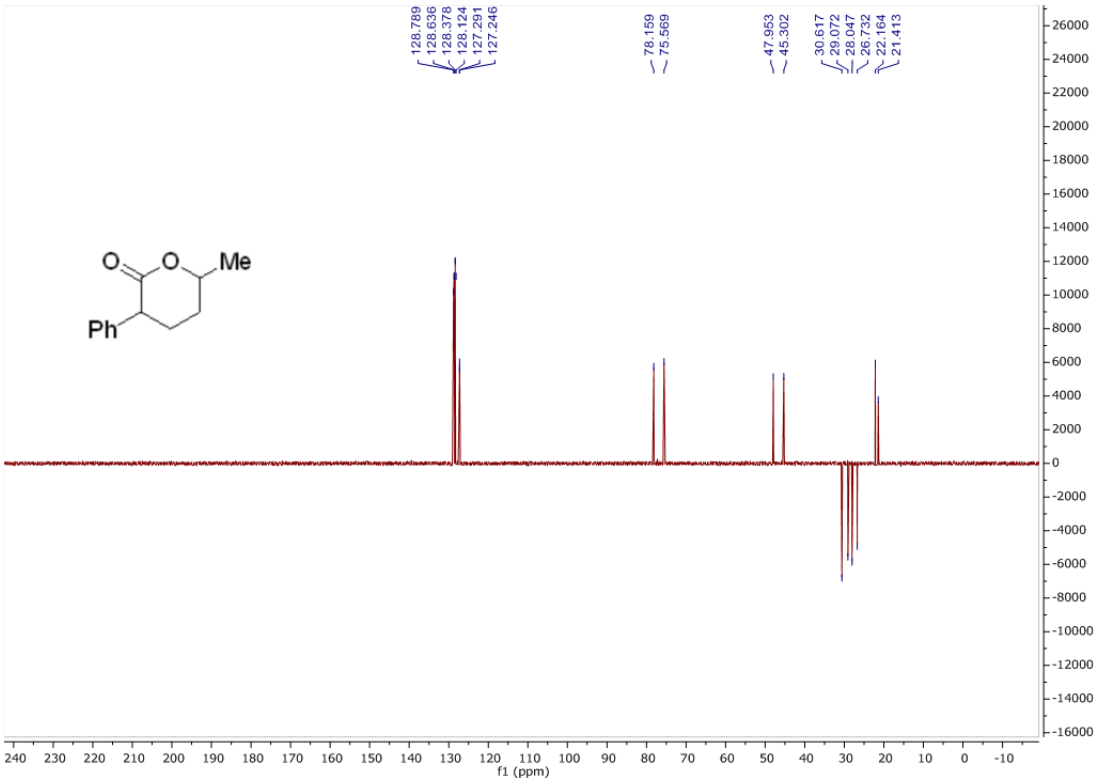

60.229
37.880
29.986
26.880
26.201
O
CN
O
O
f1 (ppm)

Cyclized Products

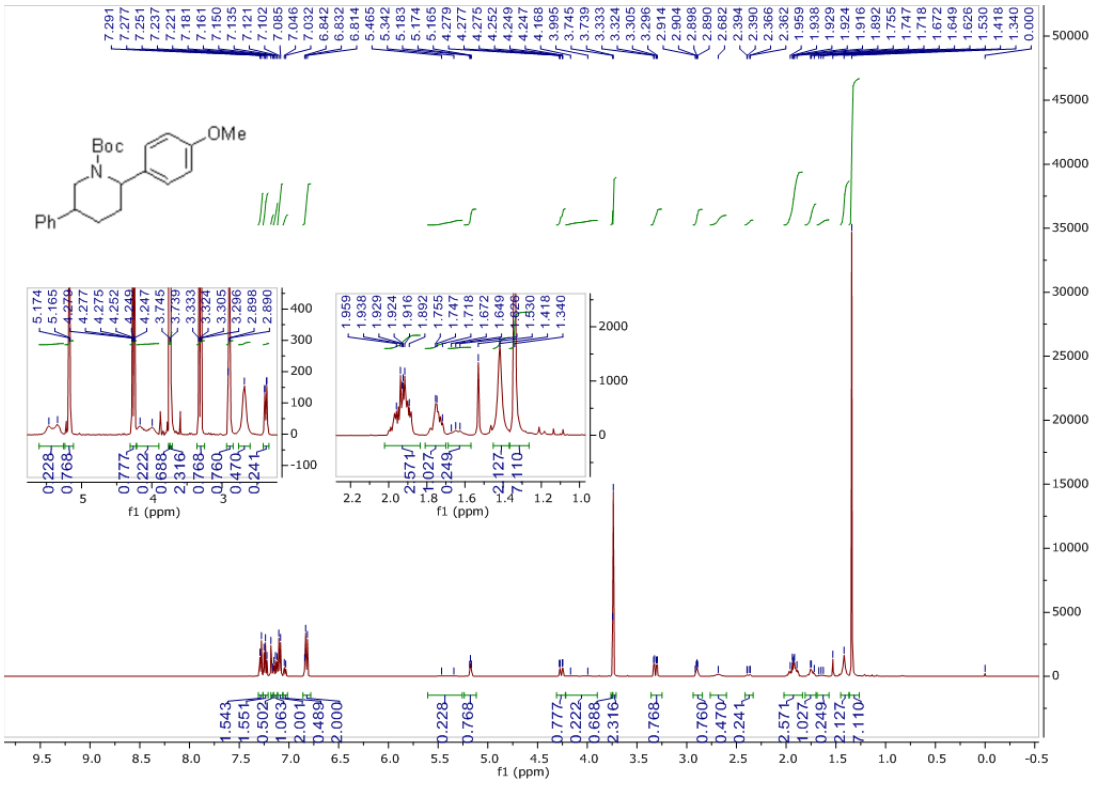
NMR Spectra of **10**

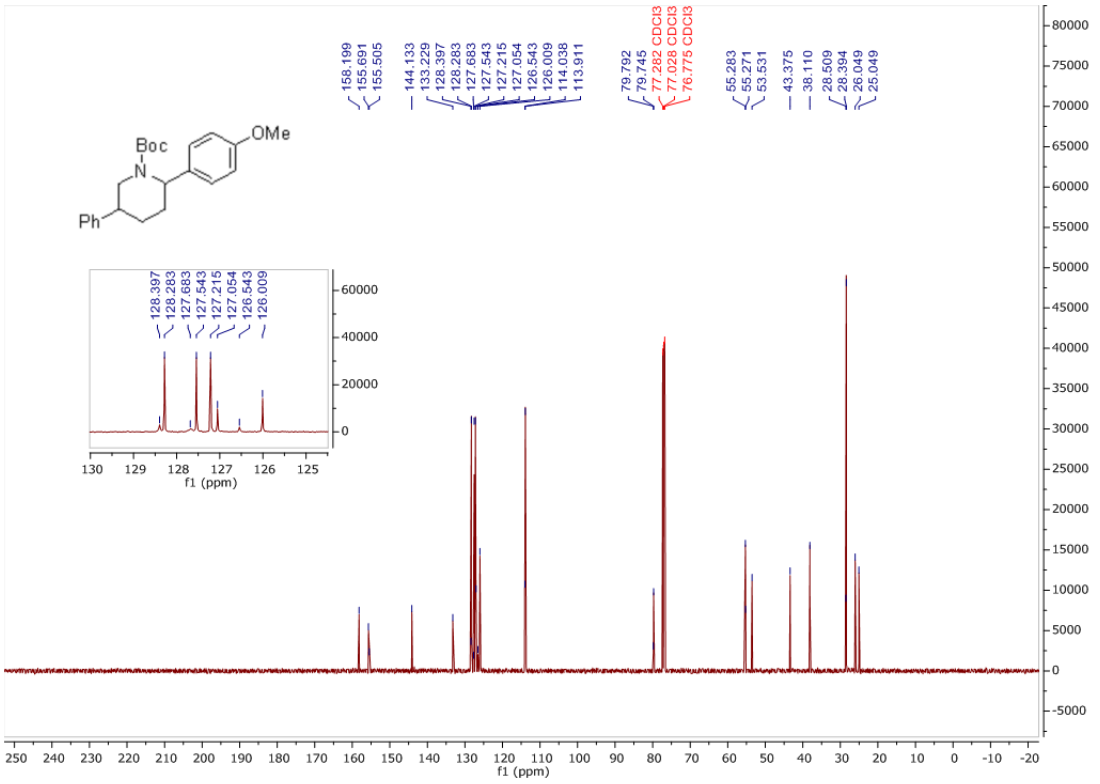


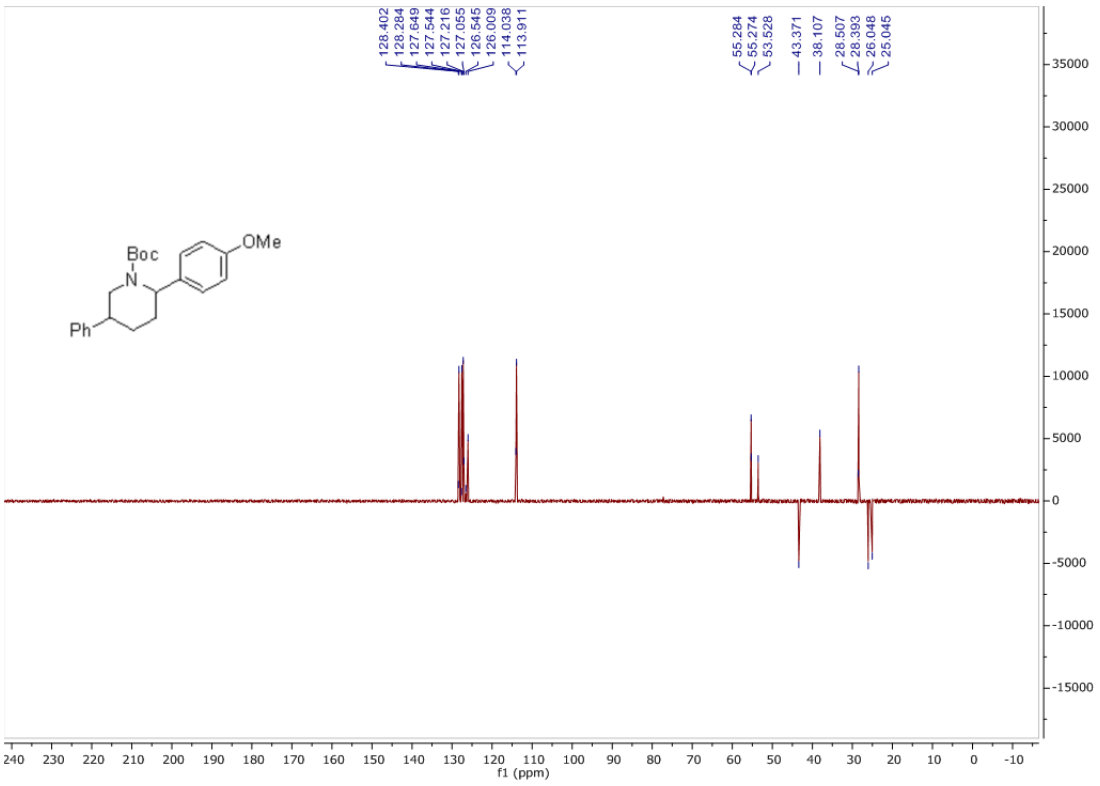


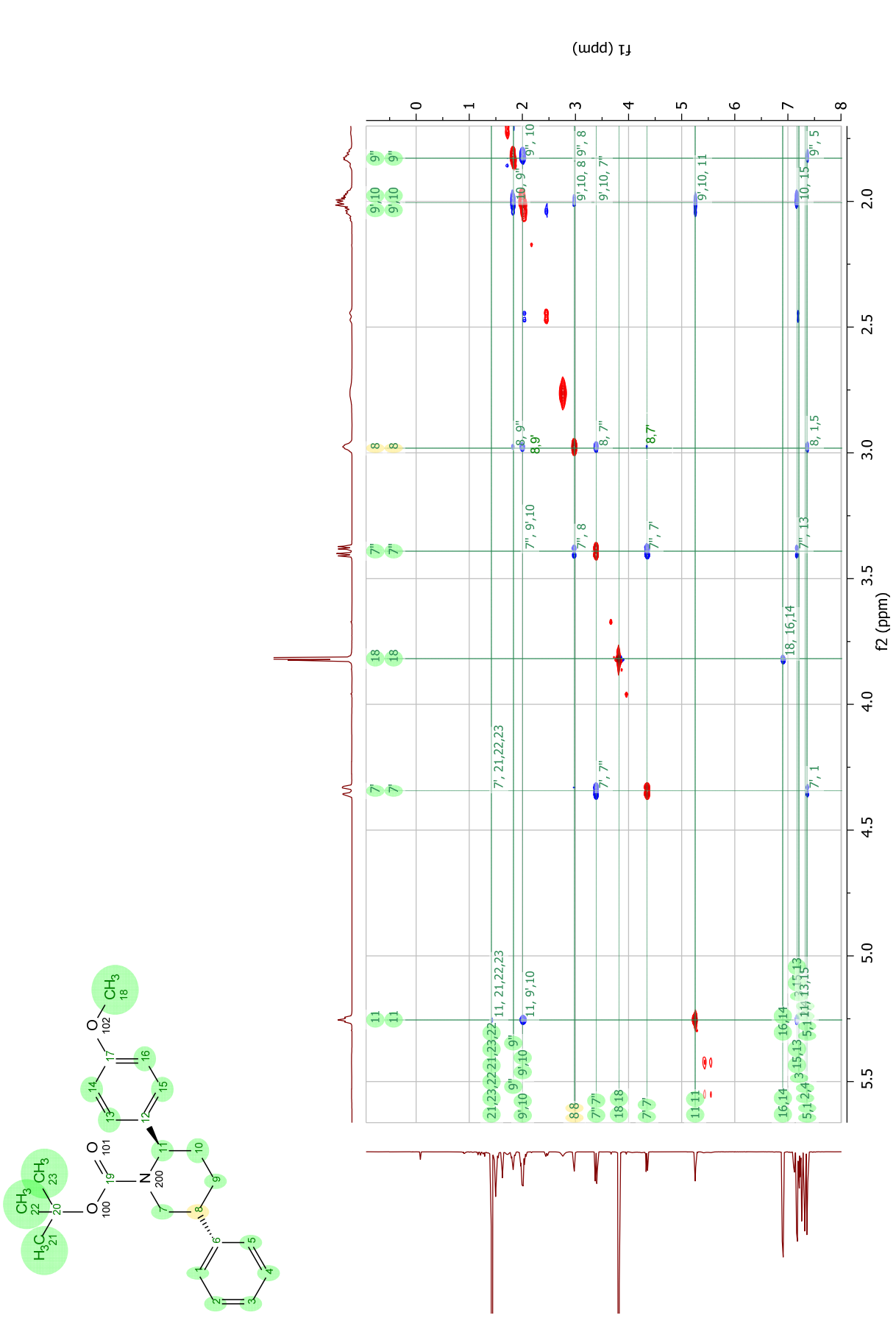


NMR Spectra of **11**



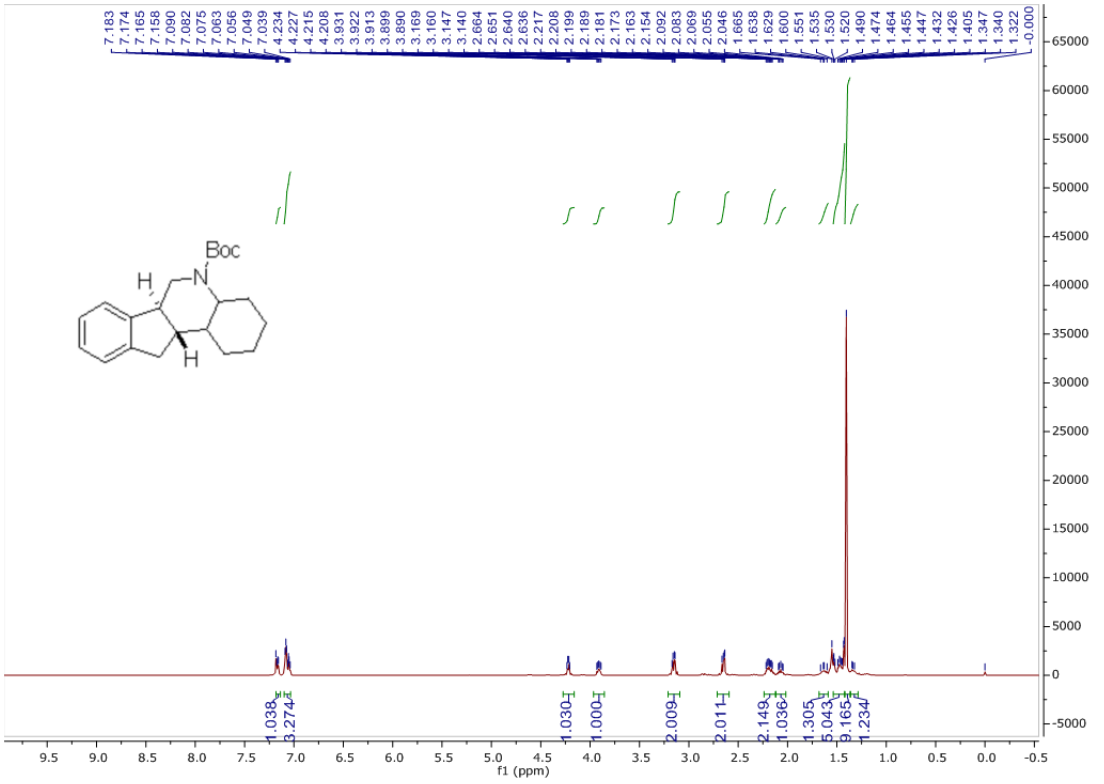

158.199
155.691
155.505
144.133
133.229
128.397
128.283
127.683
127.543
127.215
127.054
126.543
126.009
114.038
113.911
79.792
79.745
77.282 CDCl3
77.028 CDCl3
76.775 CDCl3
55.283
55.271
53.531
43.375
38.110
28.509
28.394
26.049
25.049
Boc
N
OMe
Ph
f1 (ppm)

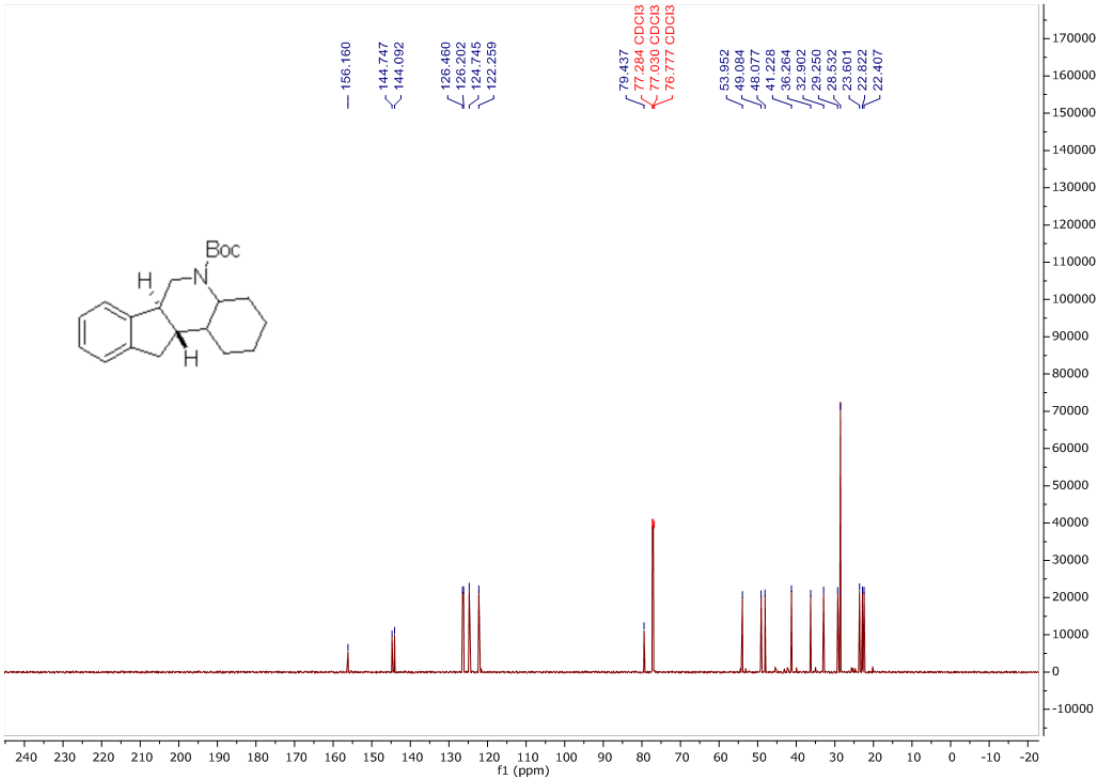

128.402
128.284
127.649
127.544
127.216
127.055
126.545
126.009
114.038
113.911
55.284
55.274
53.528
43.371
38.107
28.507
28.393
26.048
25.045
Boc
N
OMe
Ph
f1 (ppm)

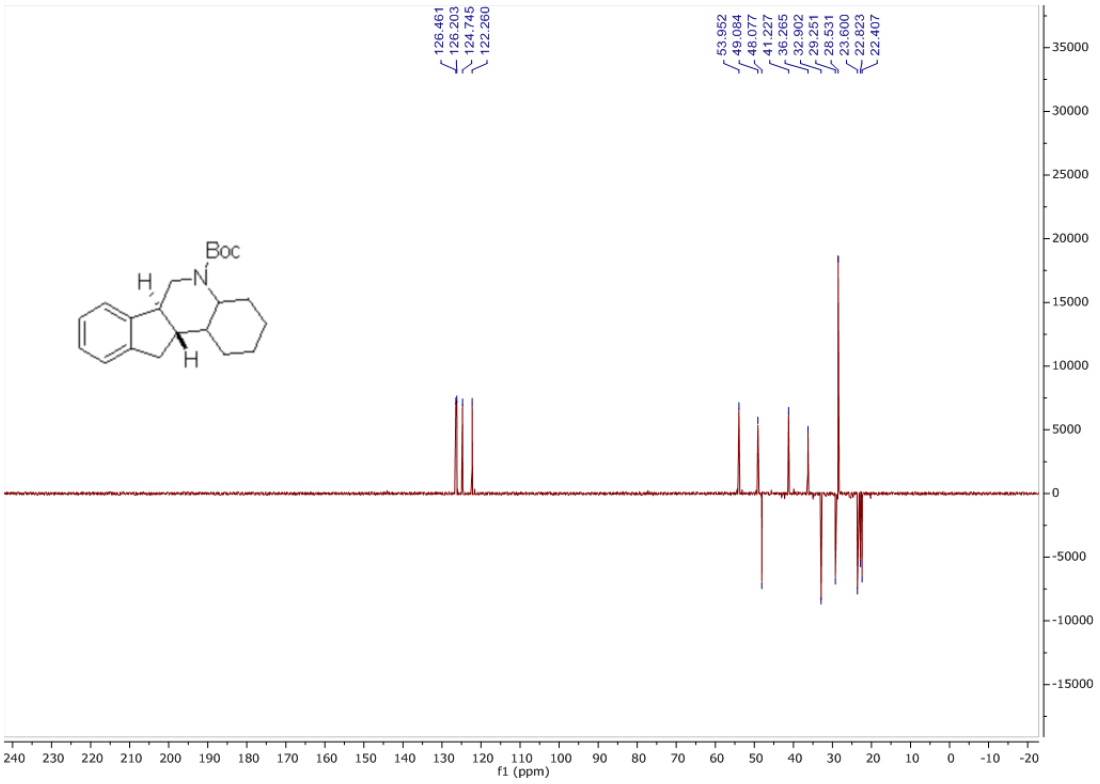


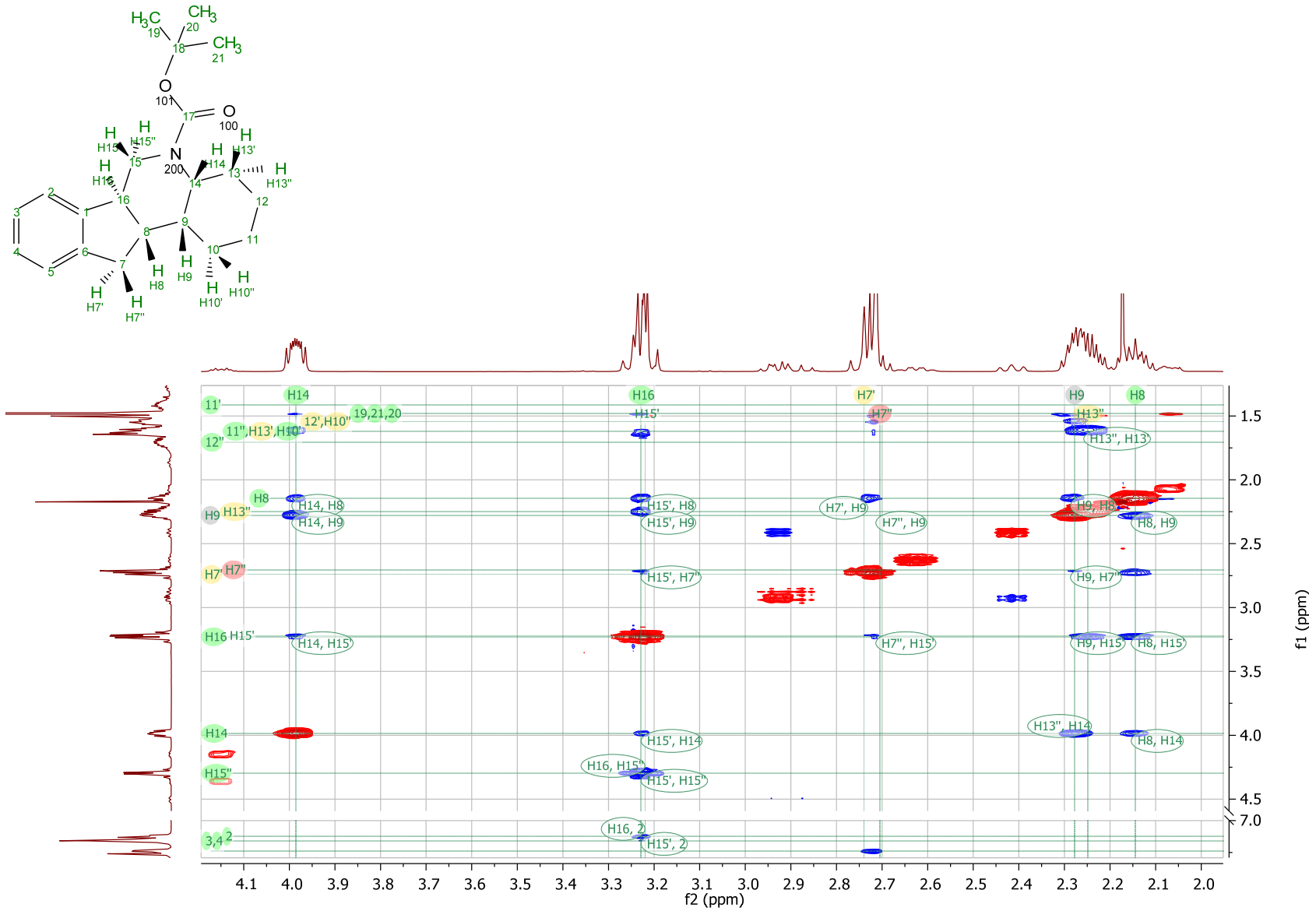
NOESY of **11**.

NMR Spectra of **12**

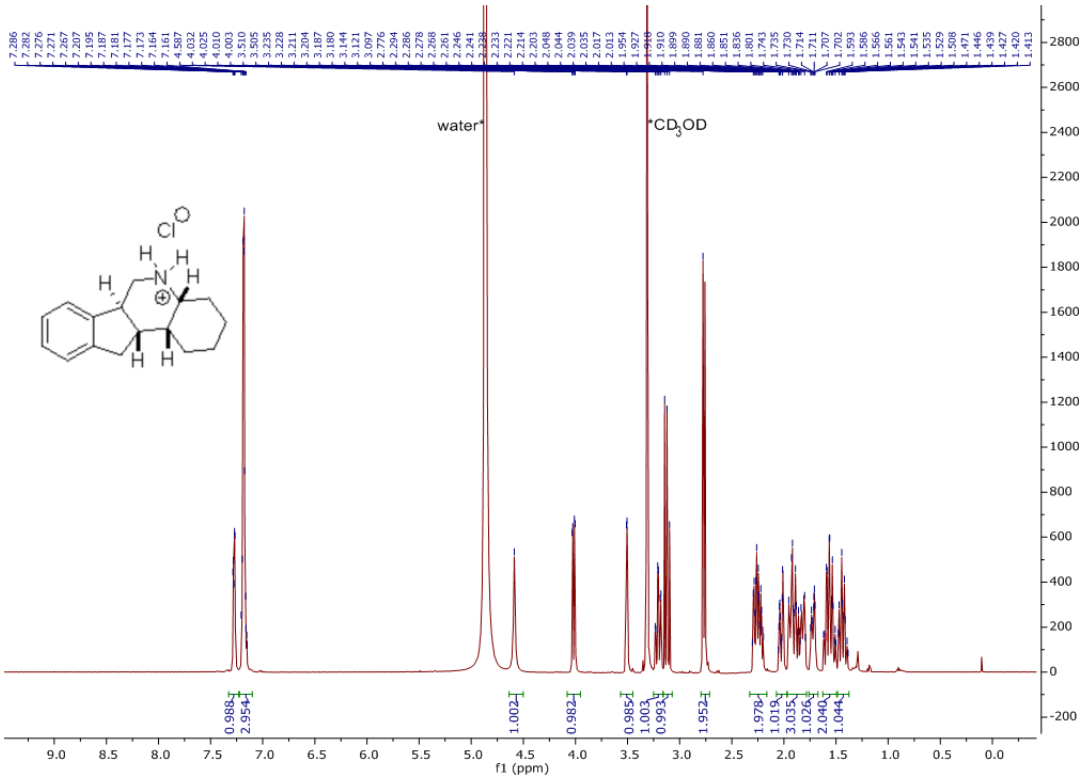


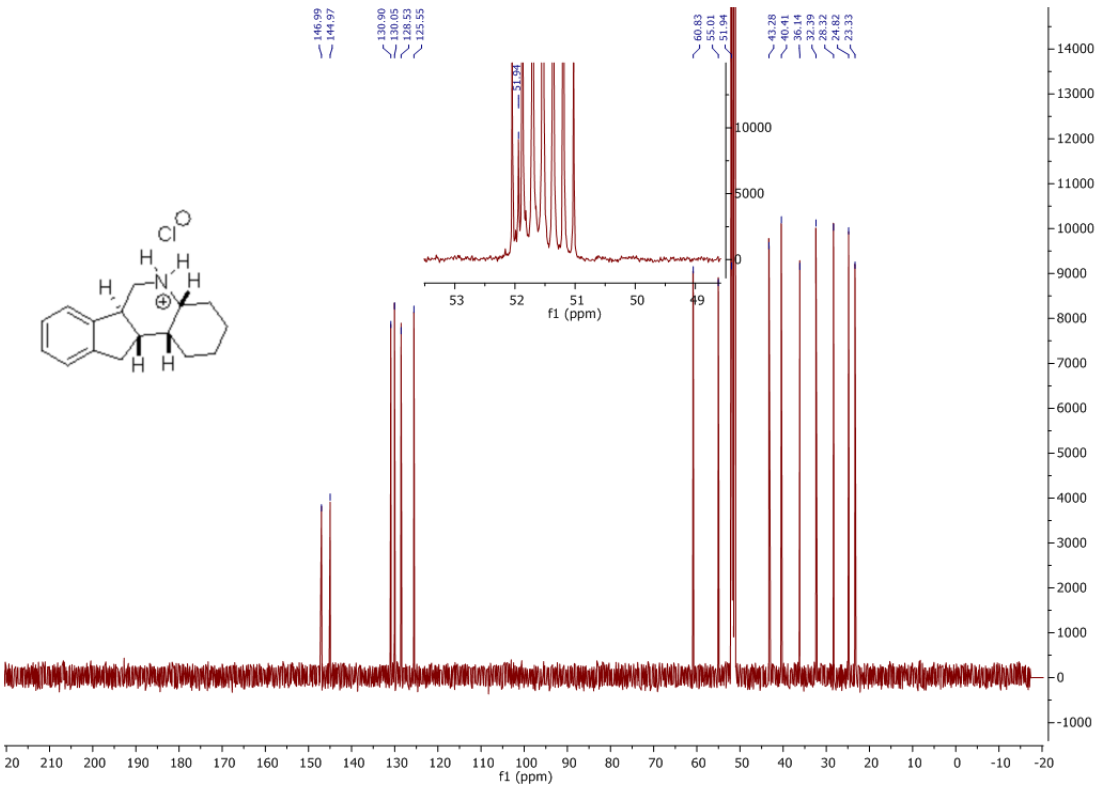


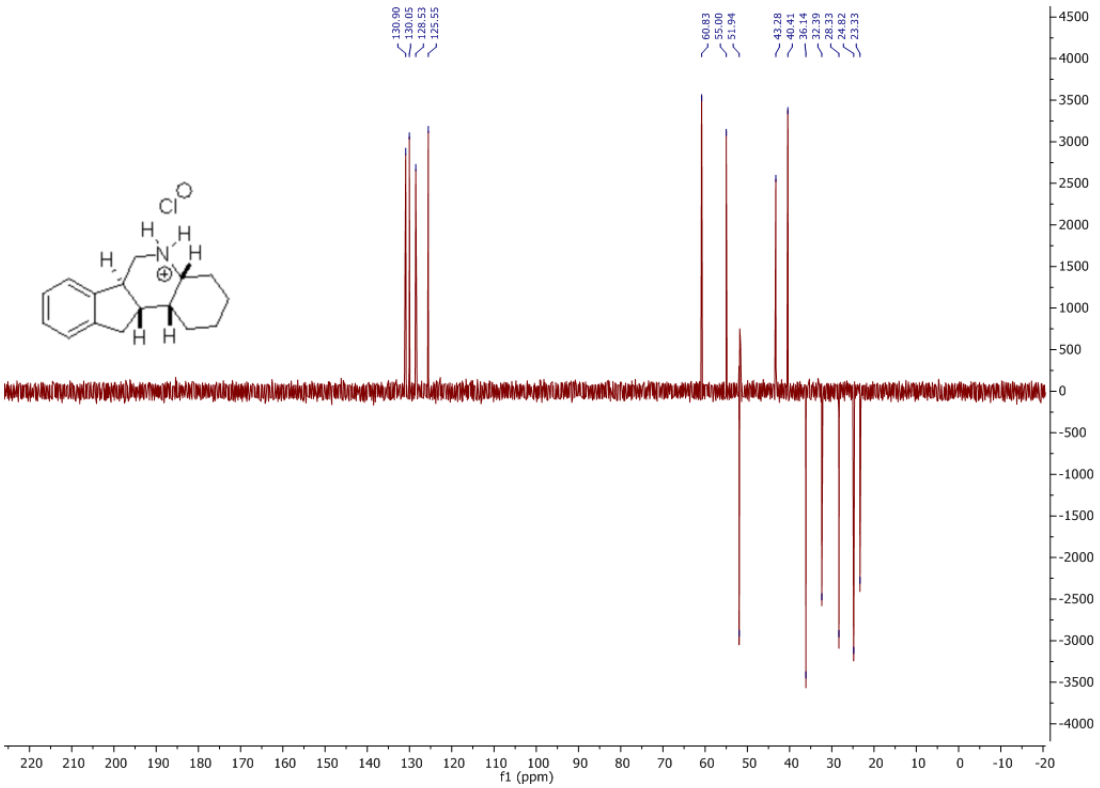

126.461
126.203
124.745
122.260
53.952
49.084
48.077
41.227
36.265
32.902
29.251
28.531
23.600
22.823
22.407
Boc
H
N
H
35000
30000
25000
20000
15000
10000
5000
0
-5000
-10000
-15000
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)


f2 (ppm)
f1 (ppm)
4.1 4.0 3.9 3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1 3.0 2.9 2.8 2.7 2.6 2.5 2.4 2.3 2.2 2.1 2.0
1.5 2.0 2.5 3.0 3.5 4.0 4.5 7.0
H14, H8
H14, H9
H15', H8
H15', H9
H7', H9
H7", H9
H8, H9
H15', H7"
H9, H7"
H14, H15
H7", H15'
H9, H15'
H8, H15'
H13", H14
H8, H14
H15', H14
H16, H15"
H15', H15"
H16, 2
H15', 2

NMR Spectra of **13**

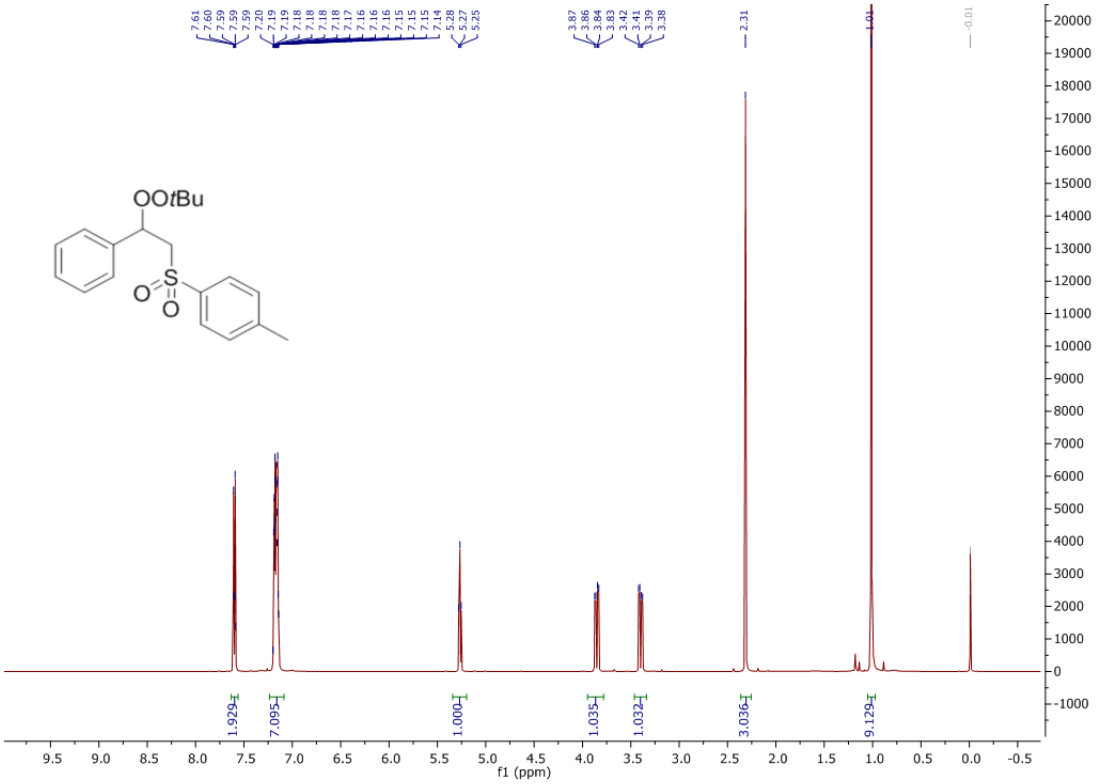


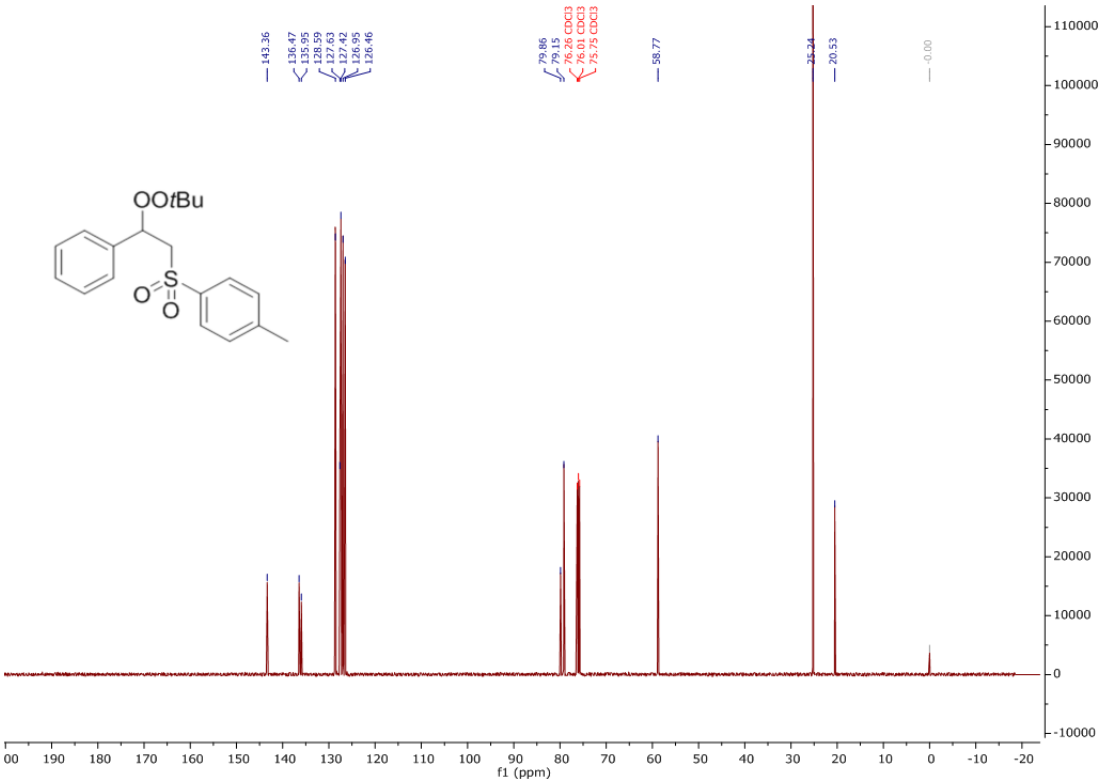


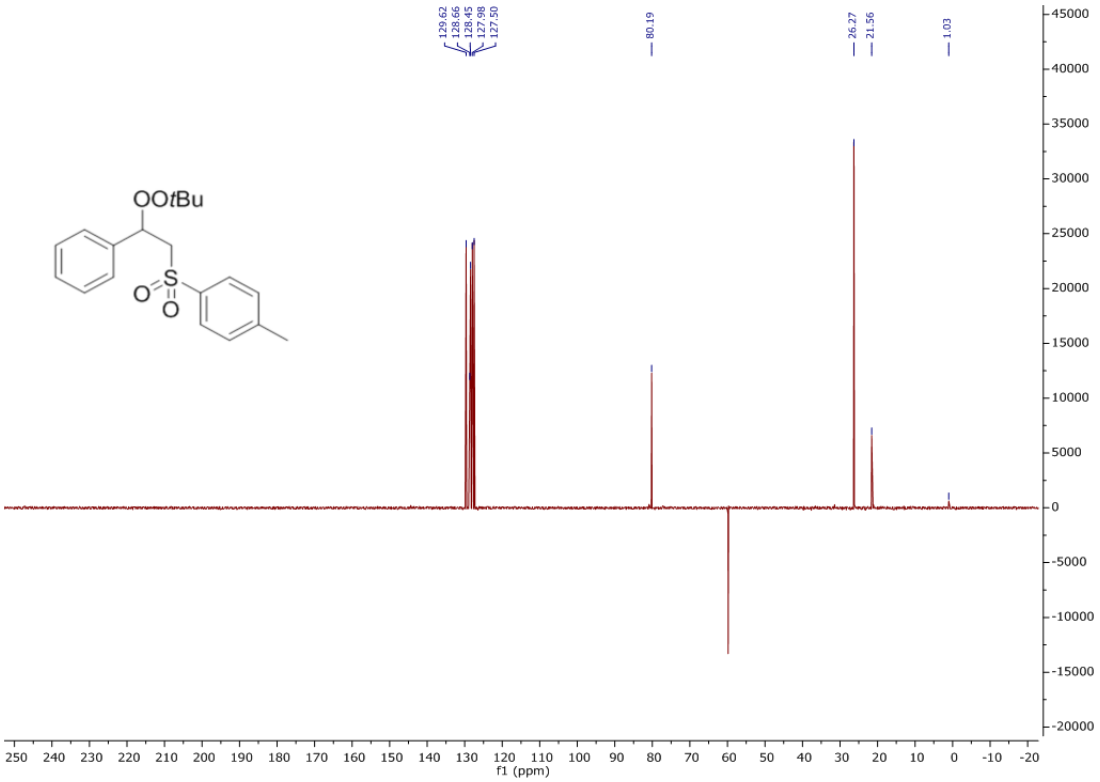

130.90
130.05
128.53
125.55
60.83
55.00
51.94
43.28
40.41
36.14
32.39
28.33
24.82
23.33
Cl
O
H
H
N
H
H
H
H
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
-1000
-1500
-2000
-2500
-3000
-3500
-4000
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

Sulfonylperoxides

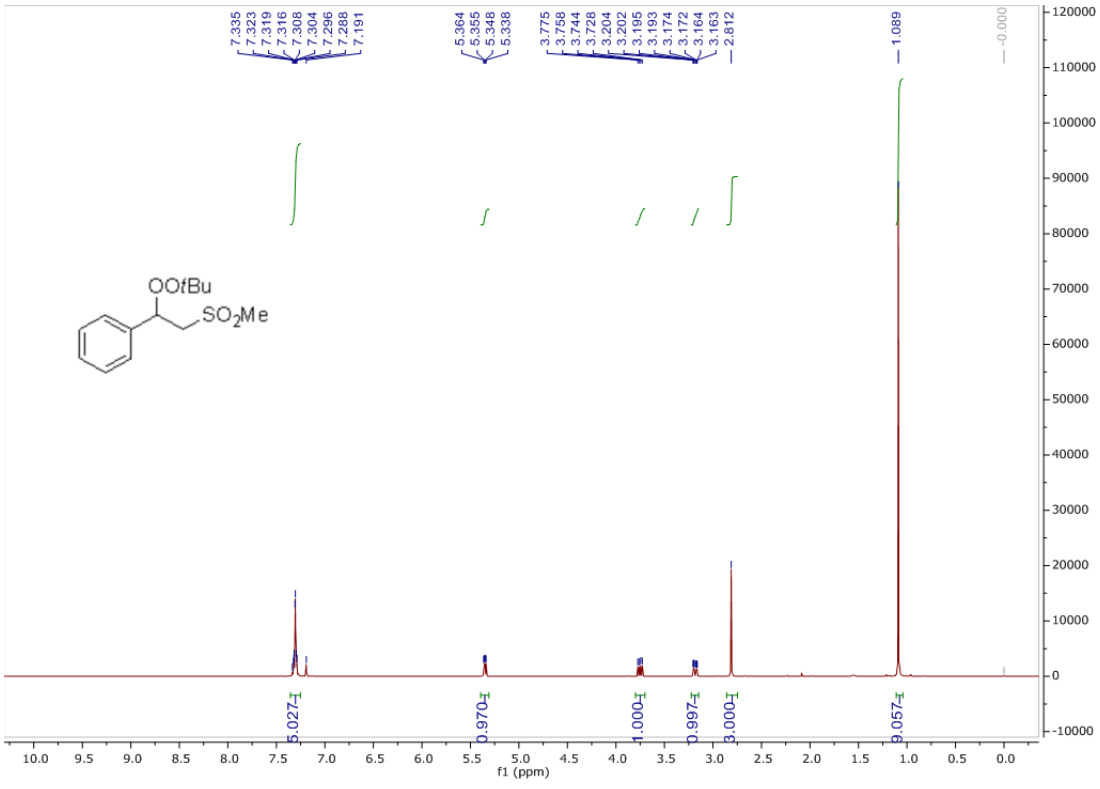
NMR Spectra of **7aa**

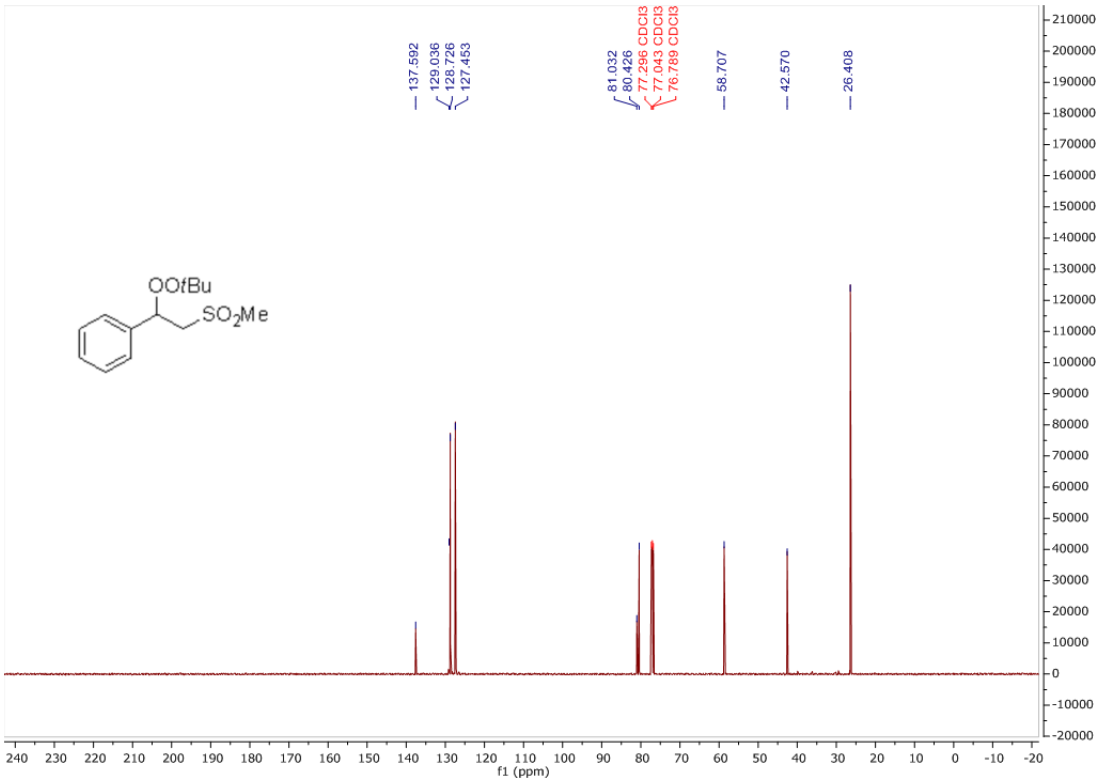


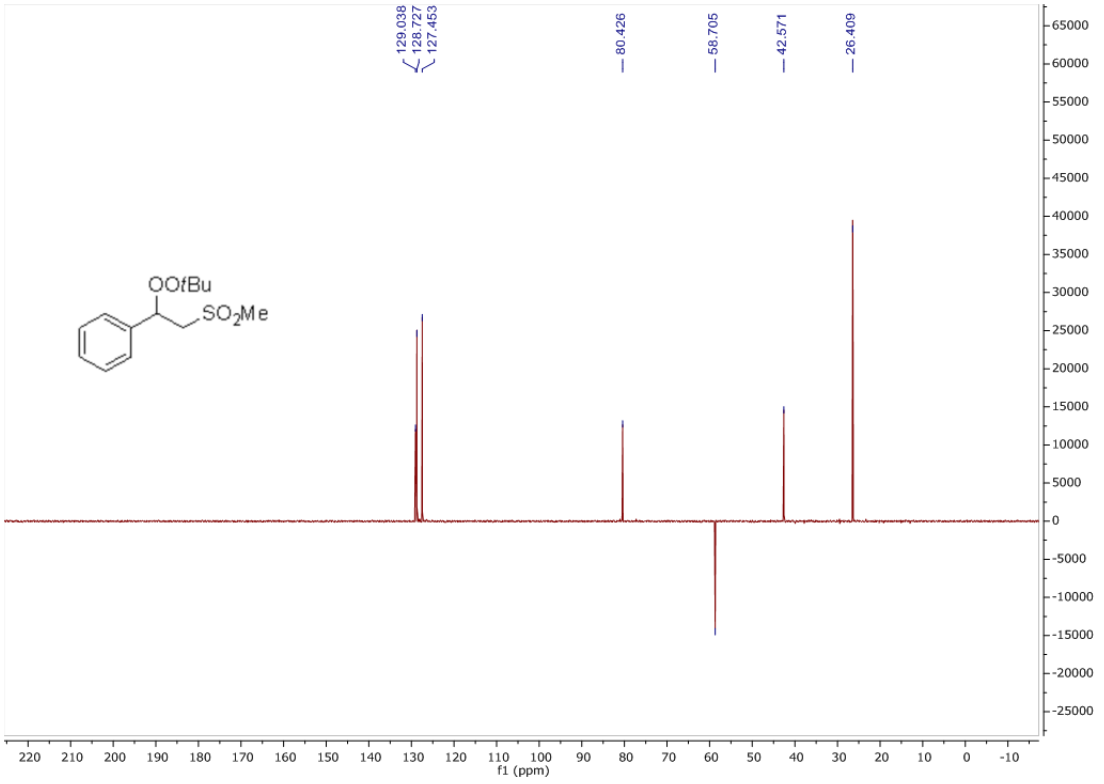




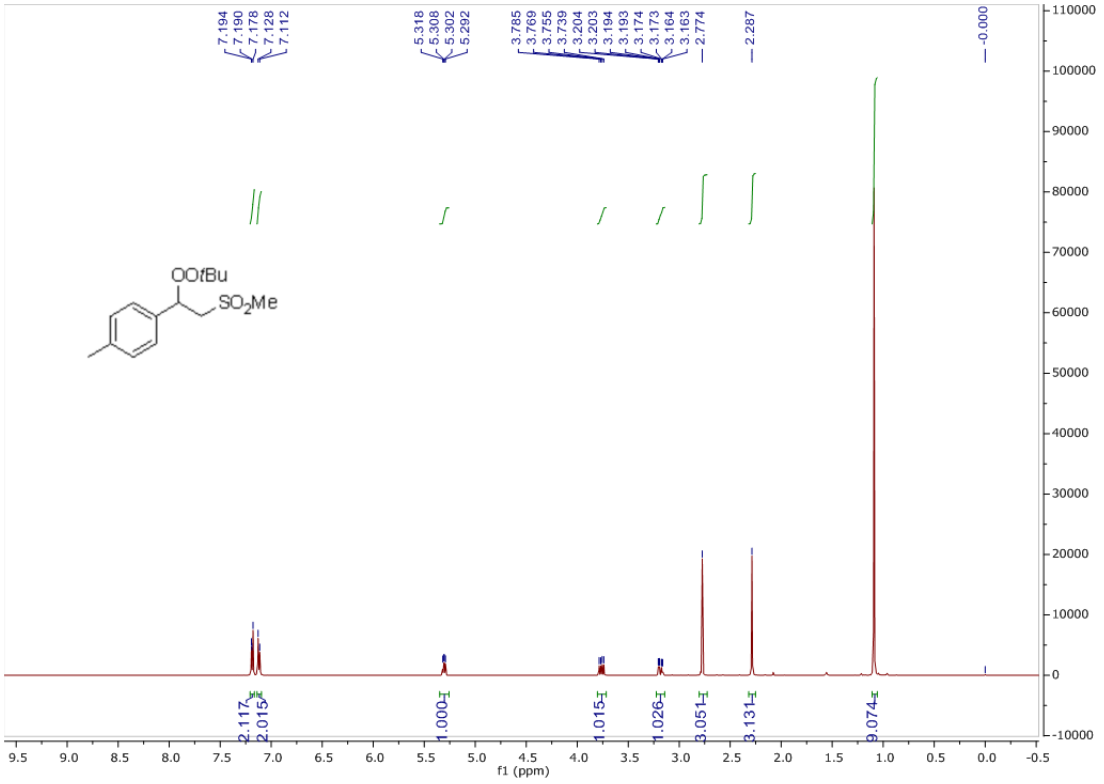
NMR Spectra of **7ac**

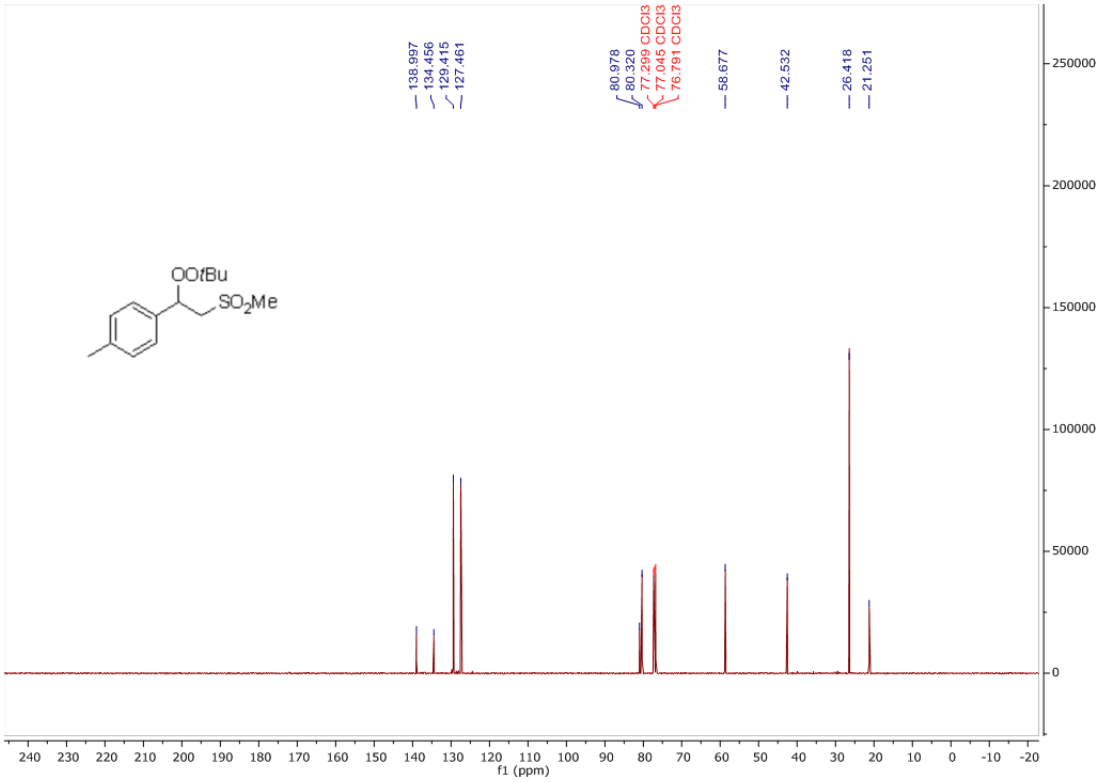


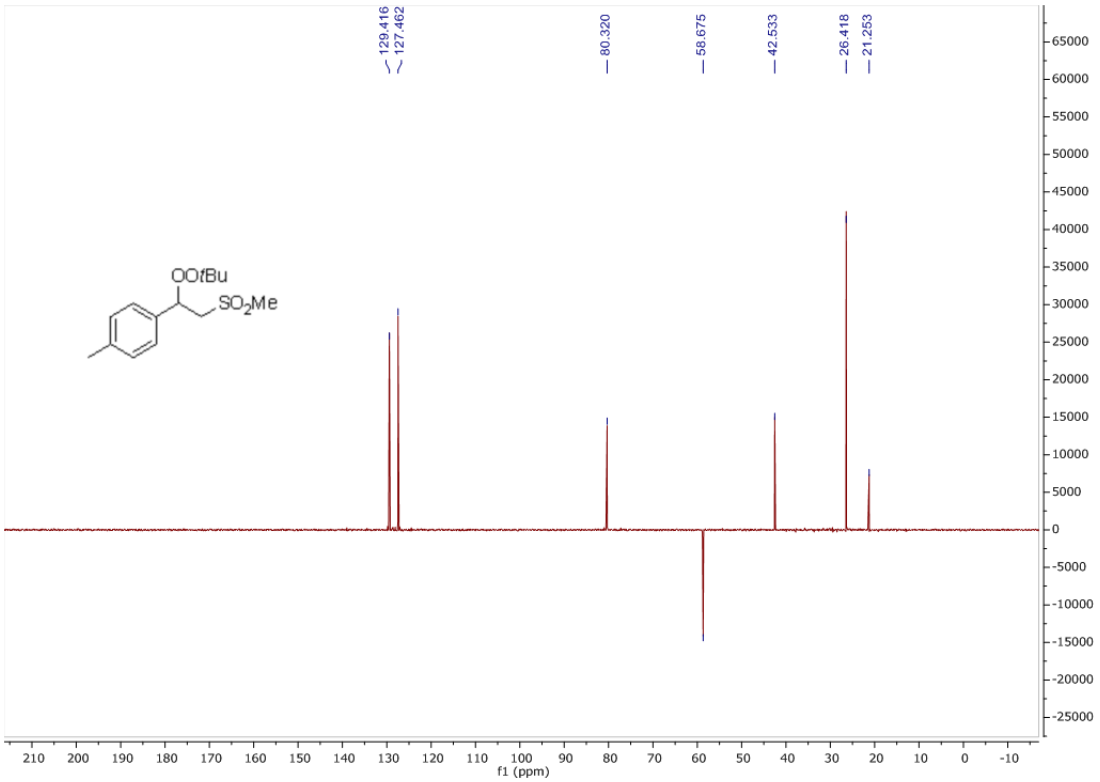

137.592
129.036
128.726
127.453
81.032
80.426
77.296 CDCl3
77.043 CDCl3
76.789 CDCl3
58.707
42.570
26.408
OOtBu
SO2Me
f1 (ppm)


129.038
128.727
127.453
80.426
58.705
42.571
26.409
OOtBu
SO2Me
f1 (ppm)

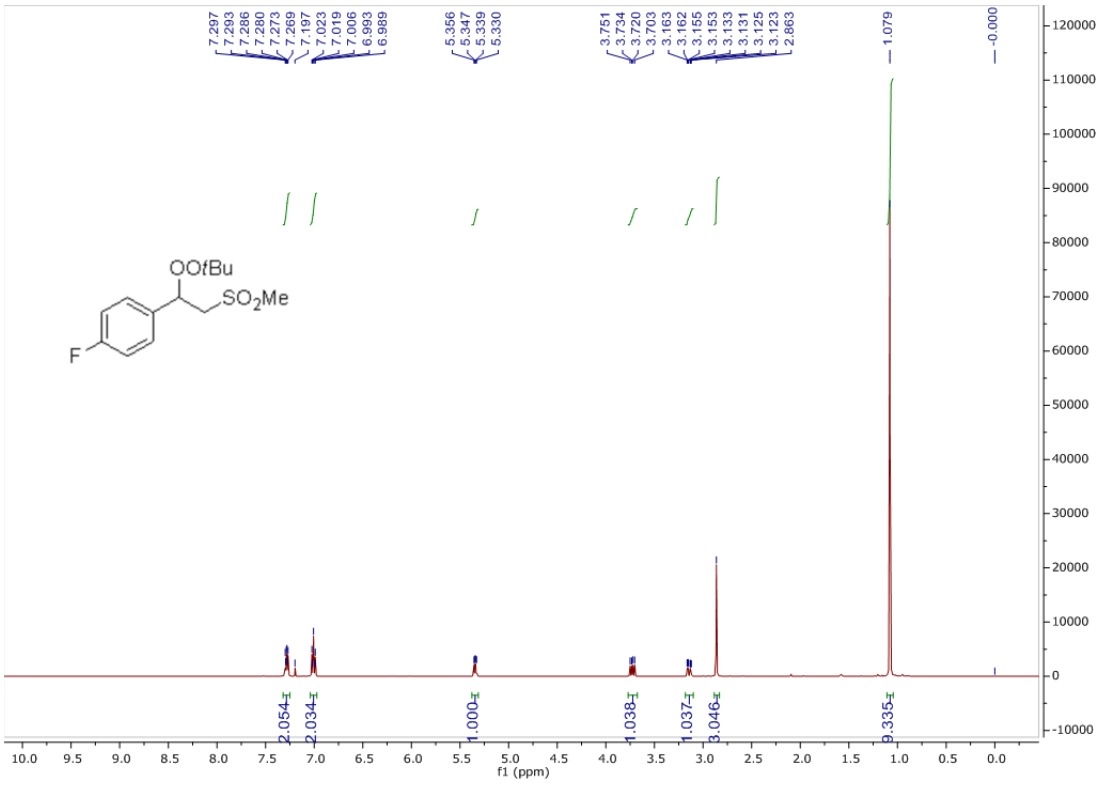
NMR Spectra of **7bc**

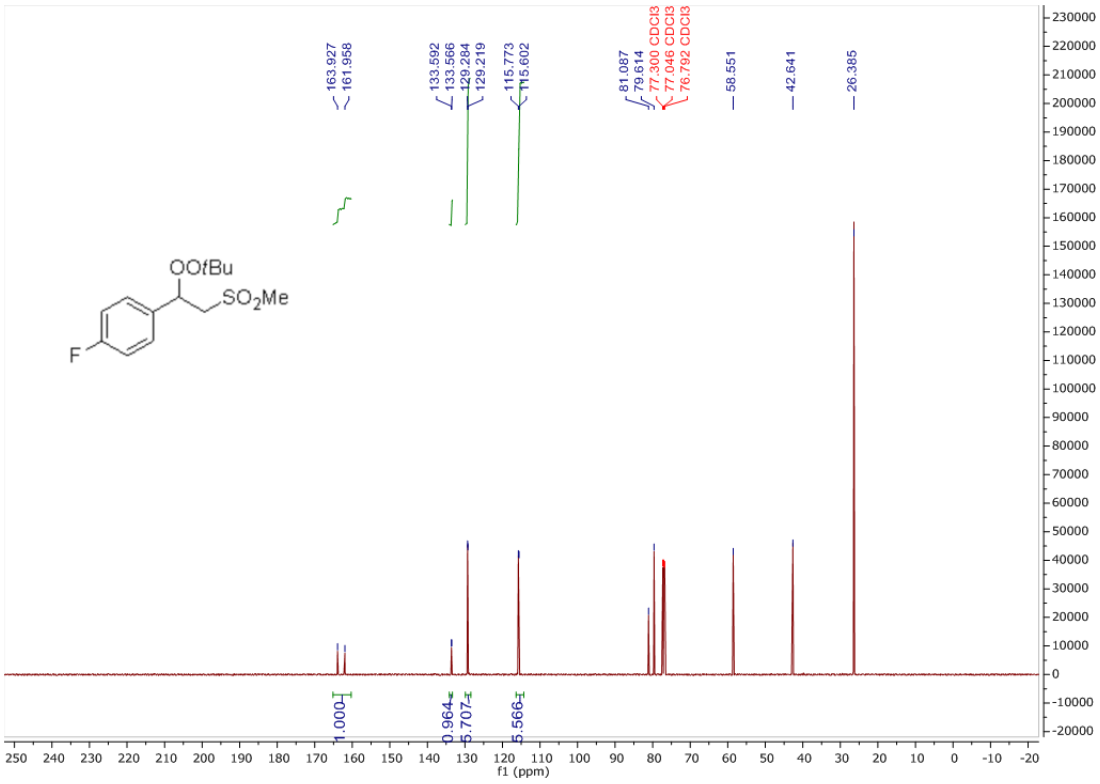


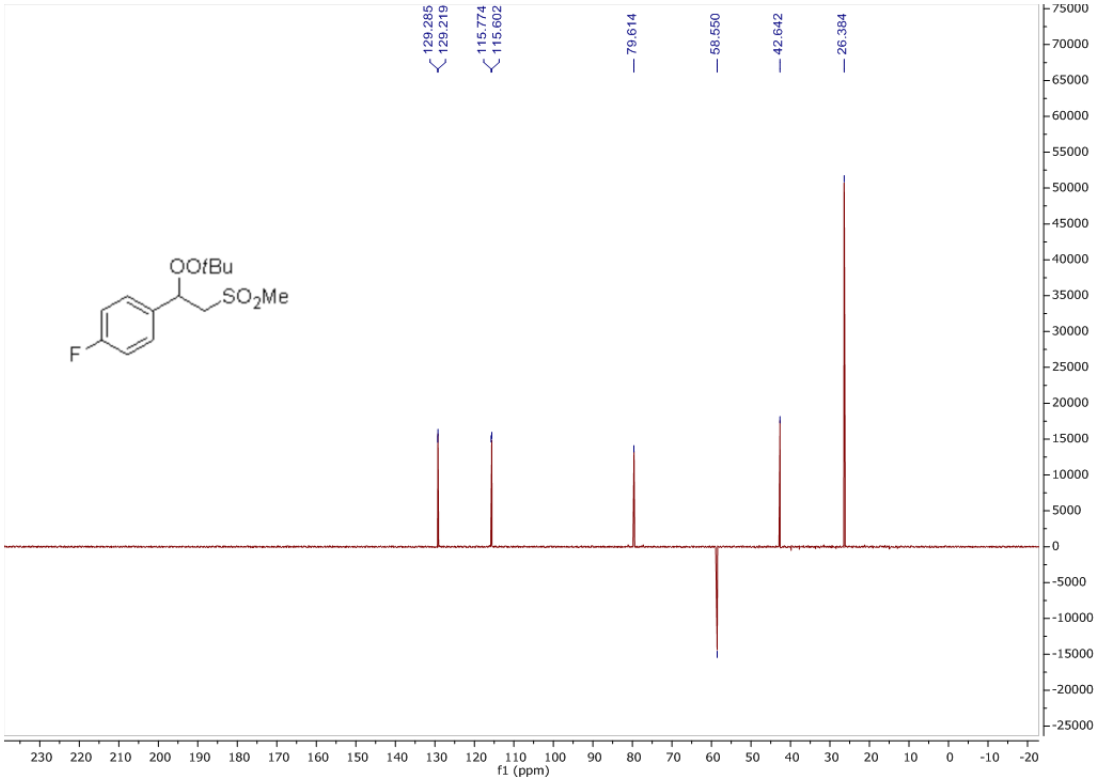


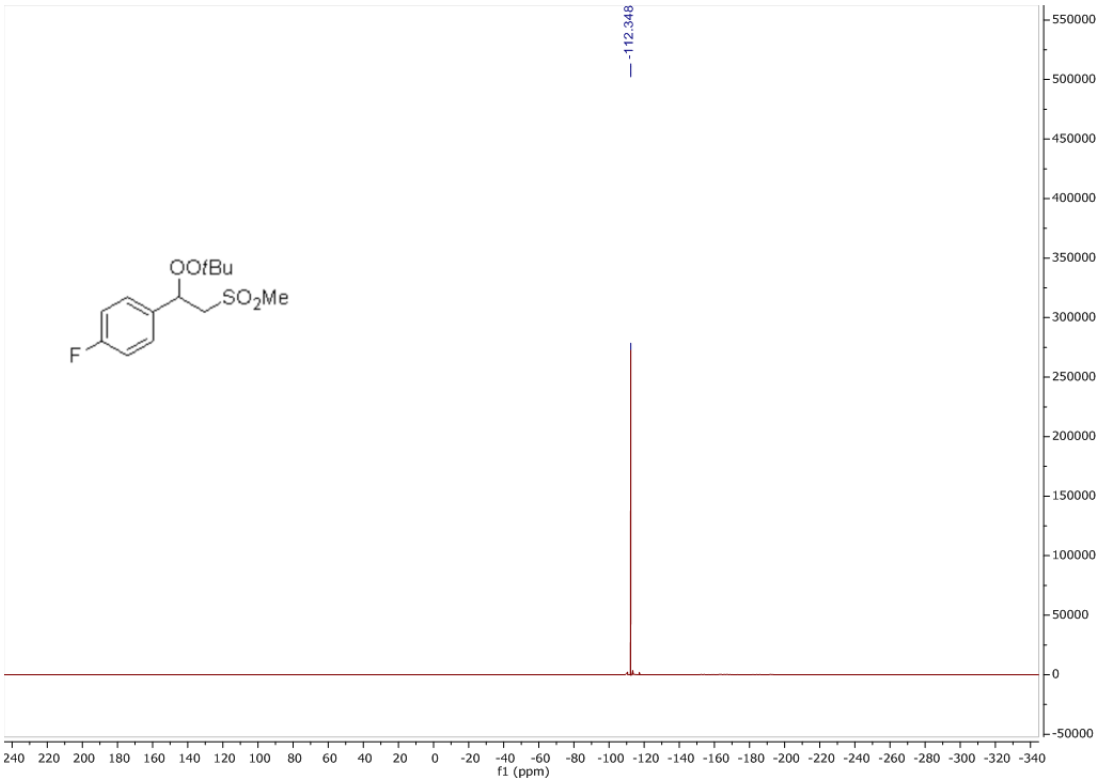


NMR Spectra of **7cc**

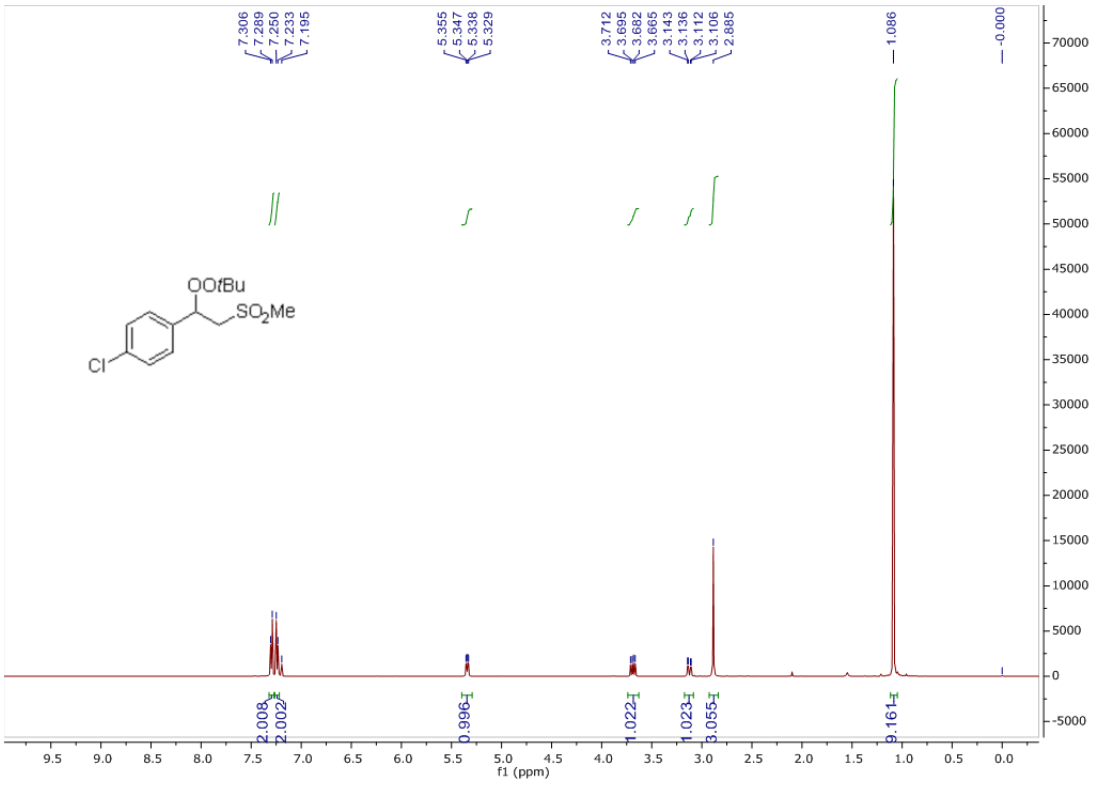


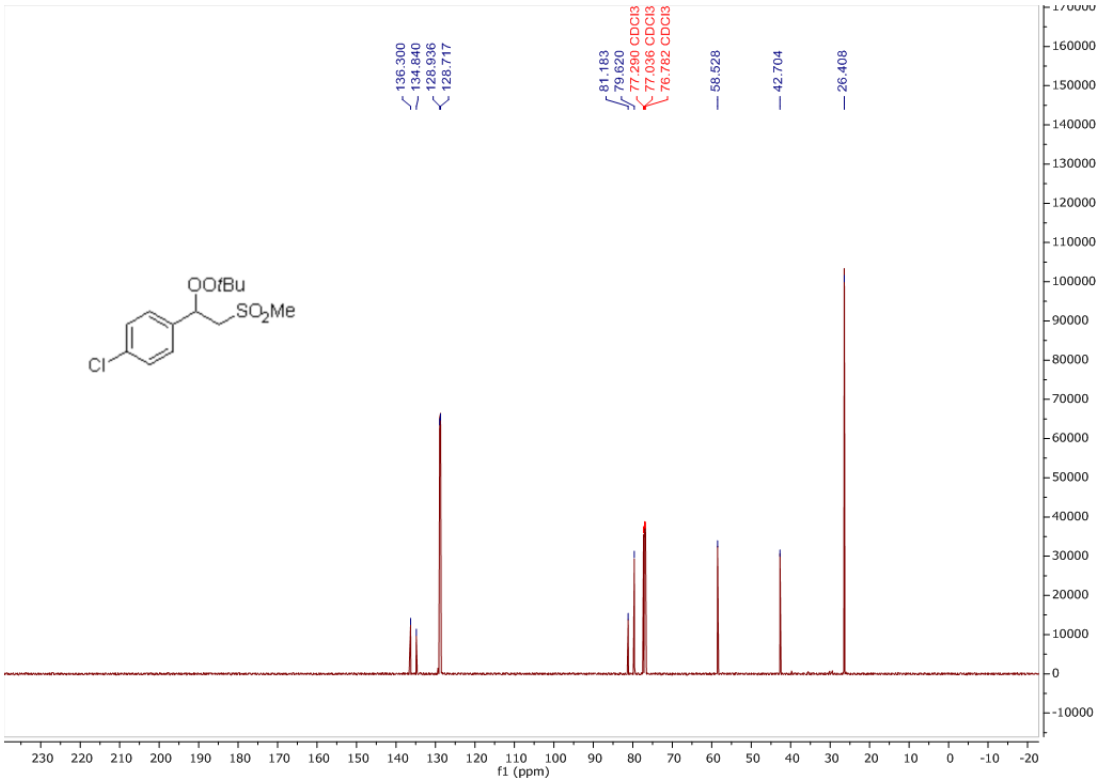

163.927
161.958
133.592
133.566
129.284
129.219
115.773
115.602
81.087
79.614
77.300 CDCl3
77.046 CDCl3
76.792 CDCl3
58.551
42.641
26.385
OOtBu
SO2Me
F
1.000
0.964
5.707
5.566
f1 (ppm)

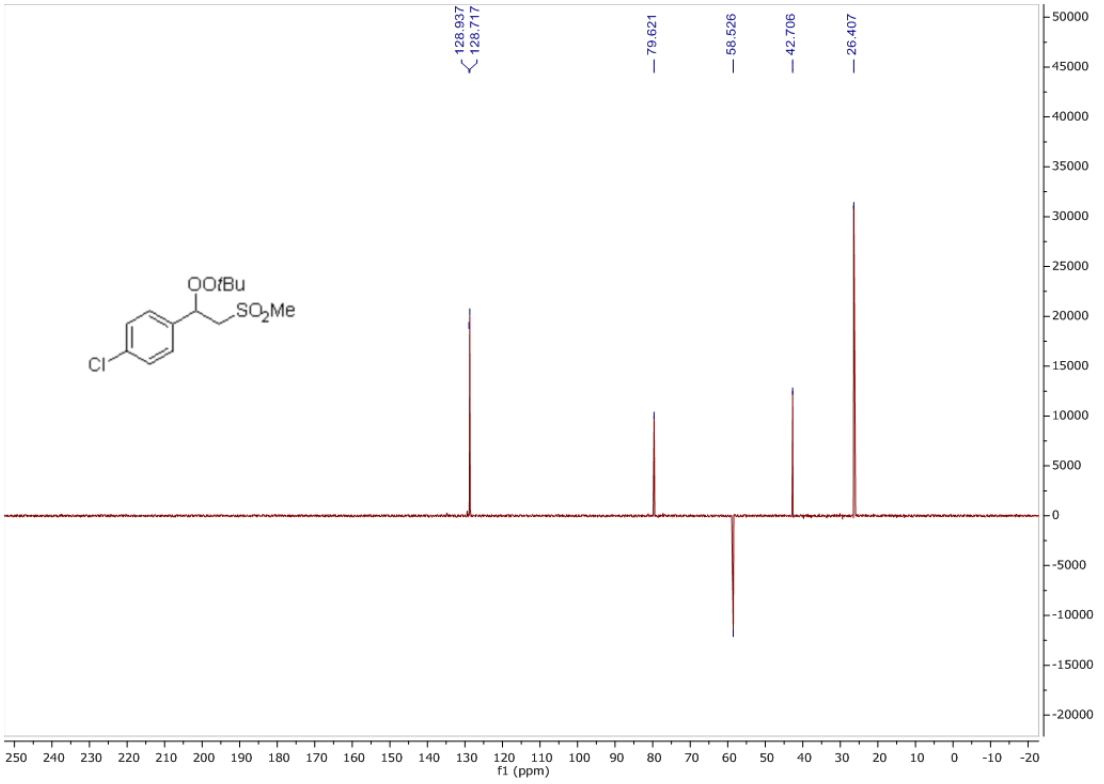

129.285
129.219
115.774
115.602
79.614
58.550
42.642
26.384
OOtBu
SO2Me
F
f1 (ppm)



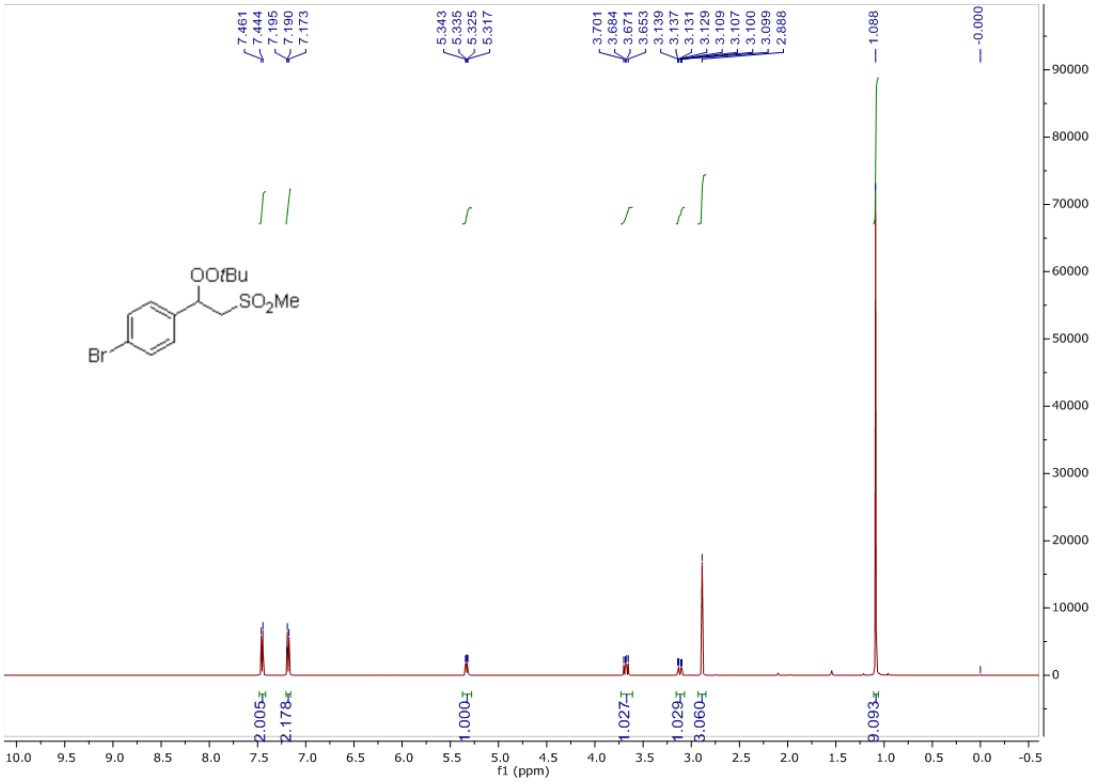
NMR Spectra of **7dc**

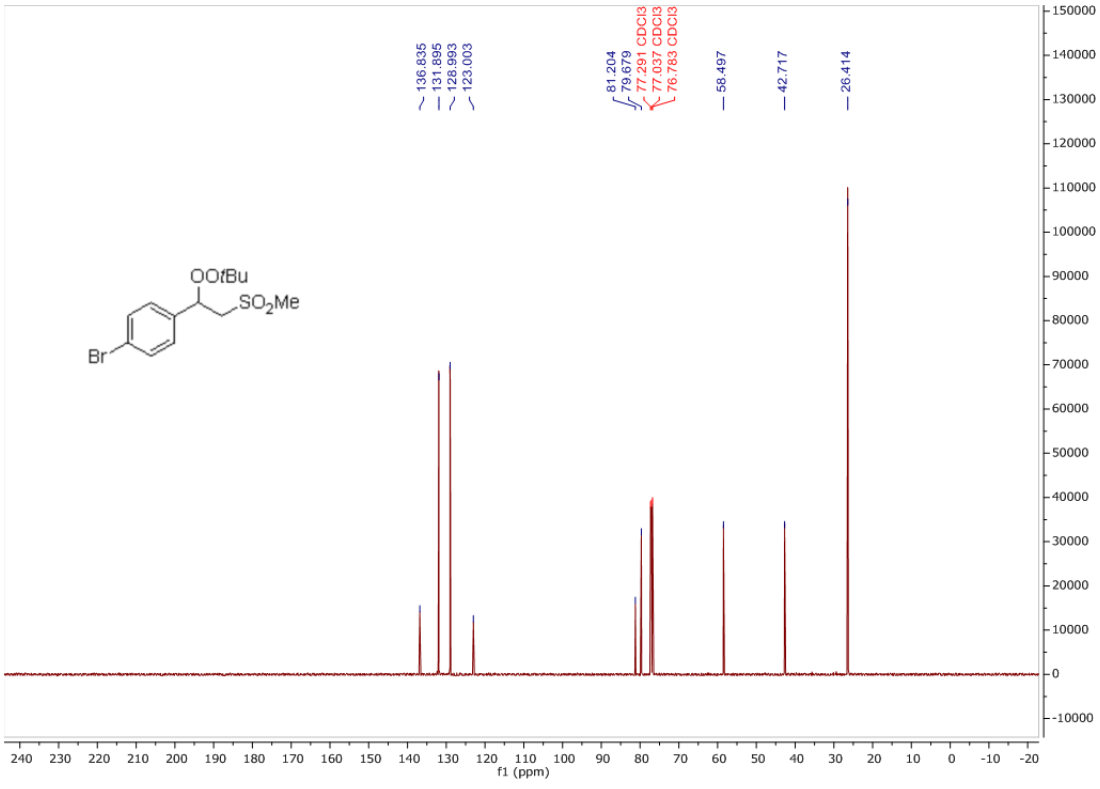



136.300
134.840
128.936
128.717
81.183
79.620
77.290 CDCl3
77.036 CDCl3
76.782 CDCl3
58.528
42.704
26.408
OOtBu
SO2Me
Cl
f1 (ppm)

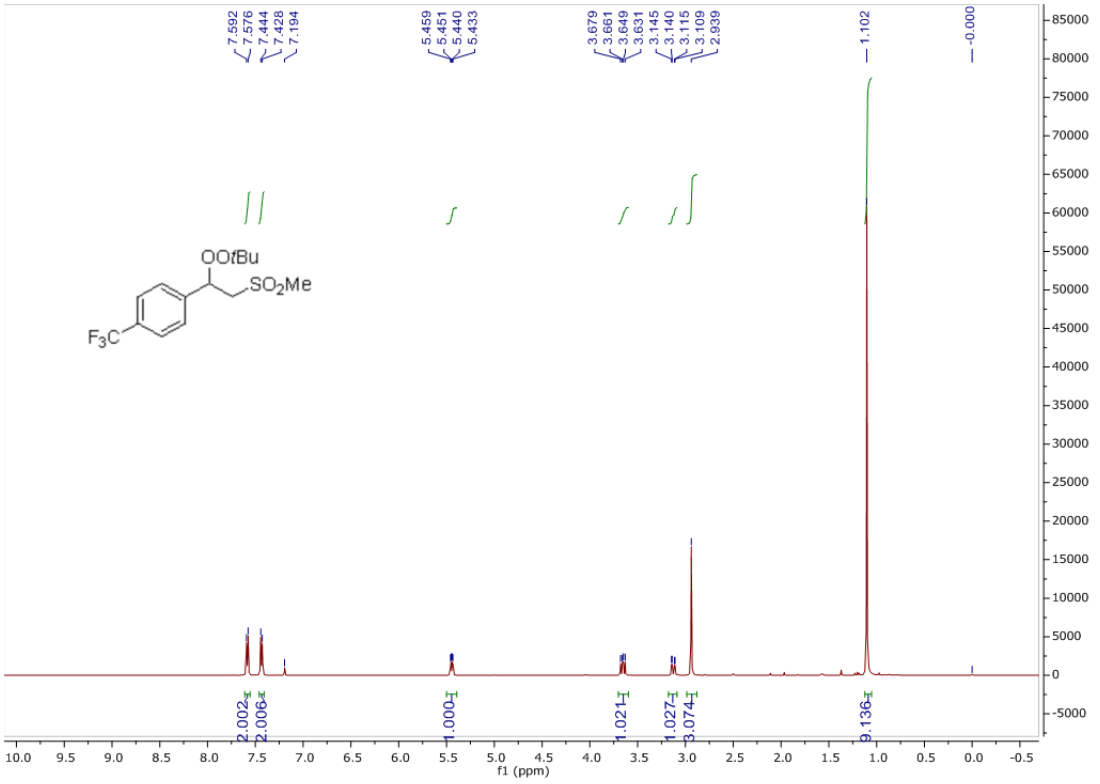

128.937
128.717
79.621
58.526
42.706
26.407
OOtBu
SO2Me
Cl
f1 (ppm)

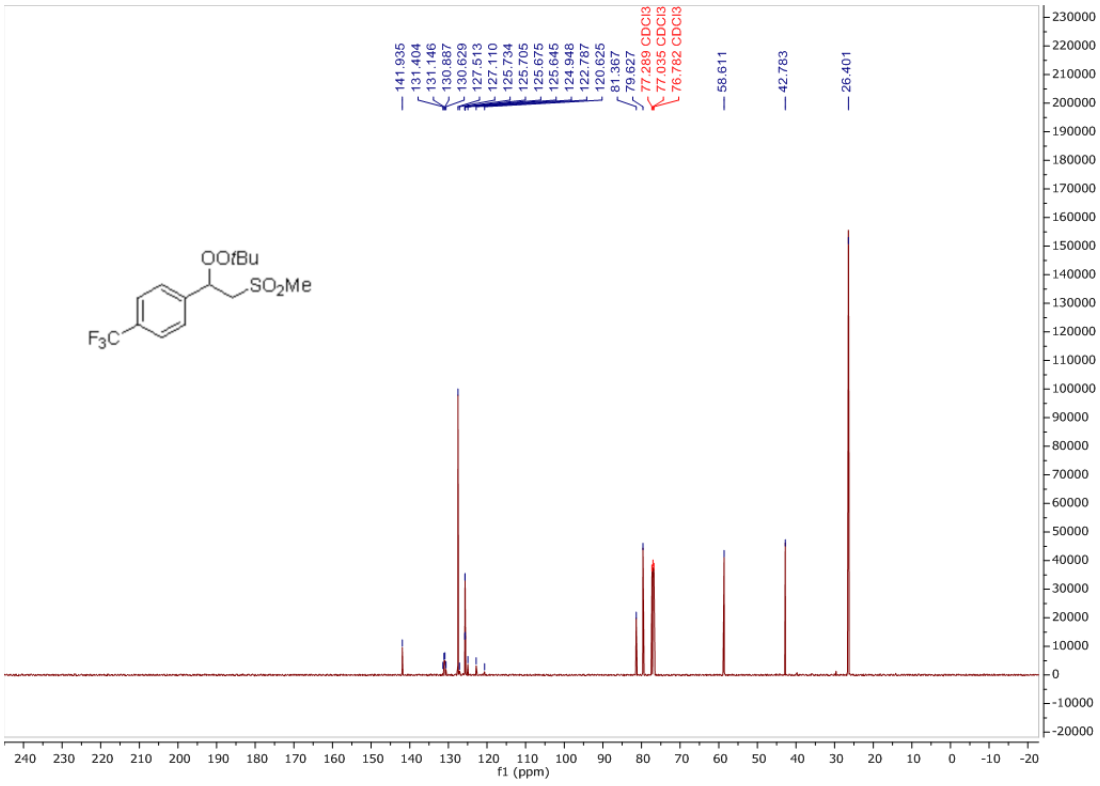
NMR Spectra of **7ec**

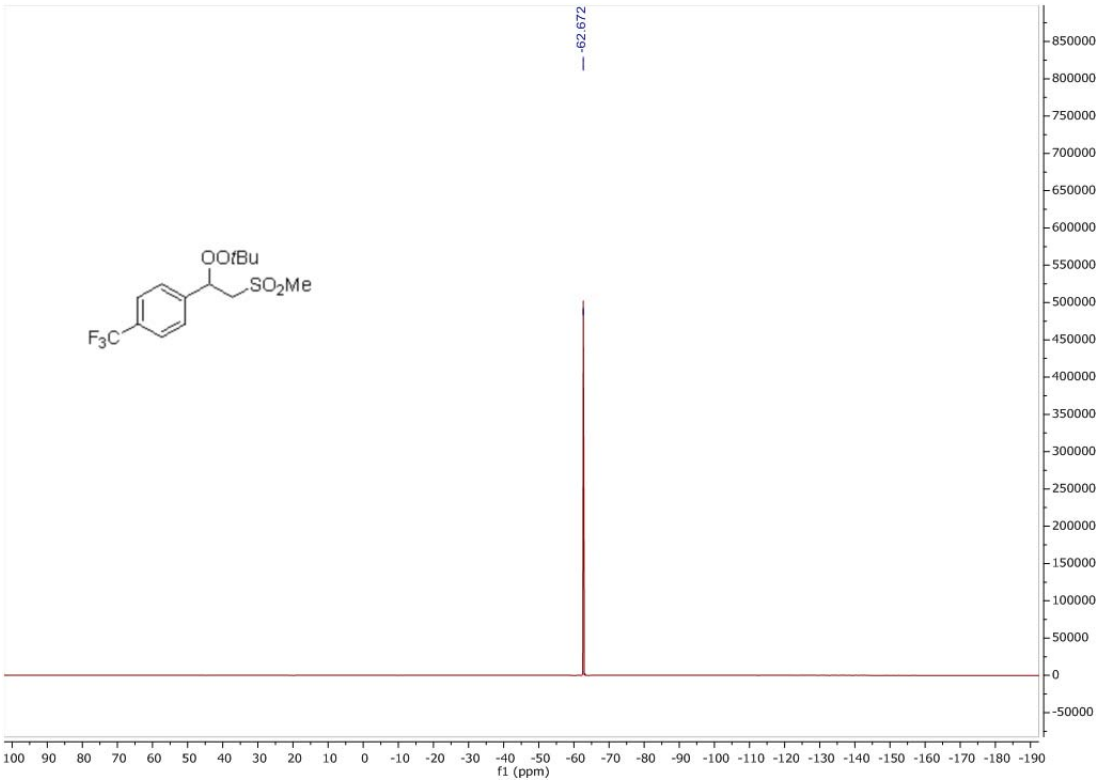




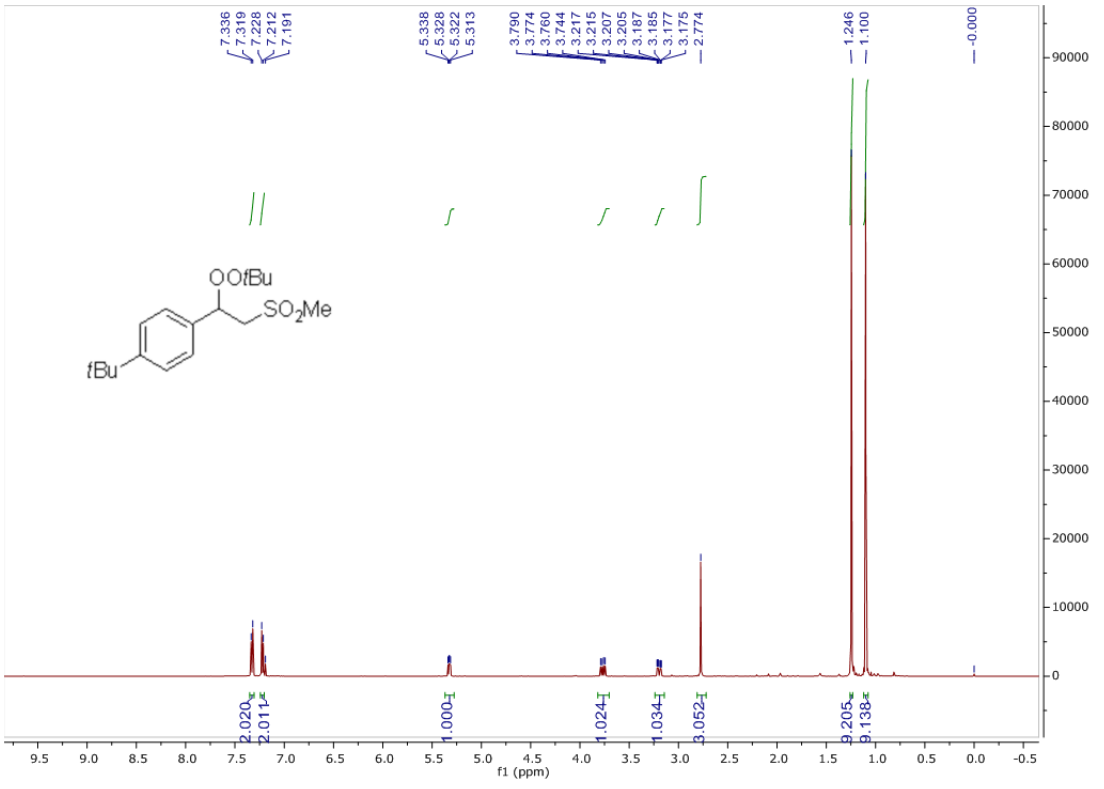
NMR Spectra of **7fc**

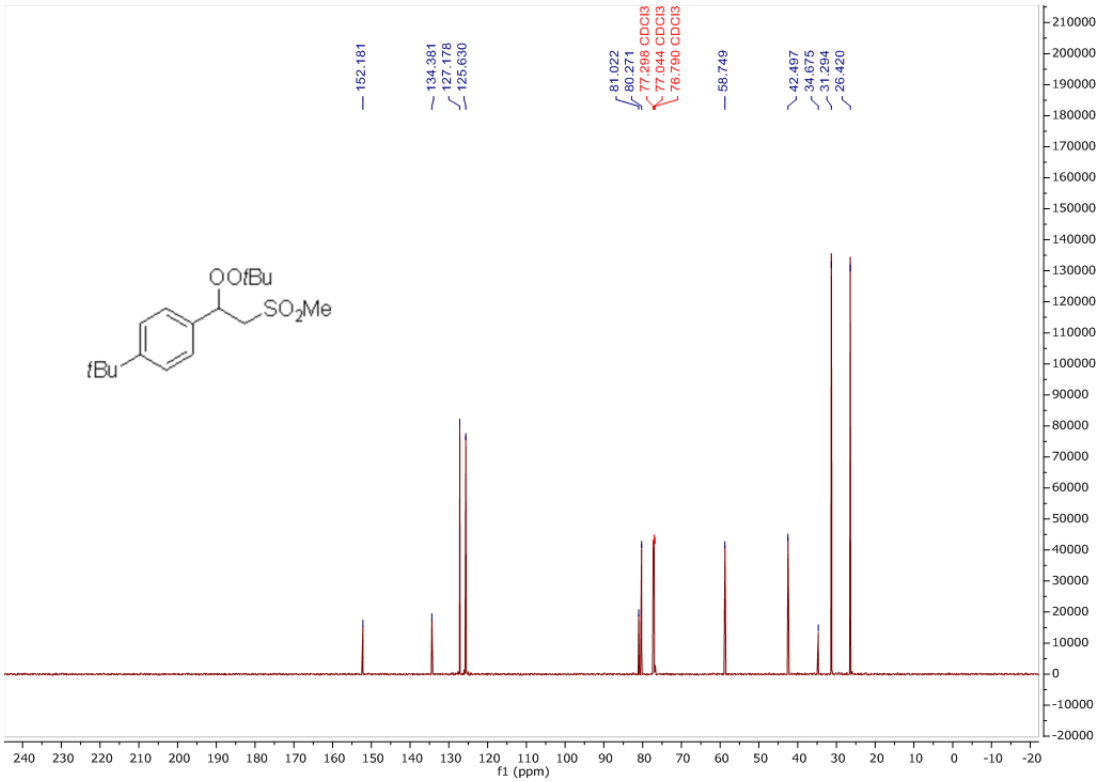






NMR Spectra of **7ic**





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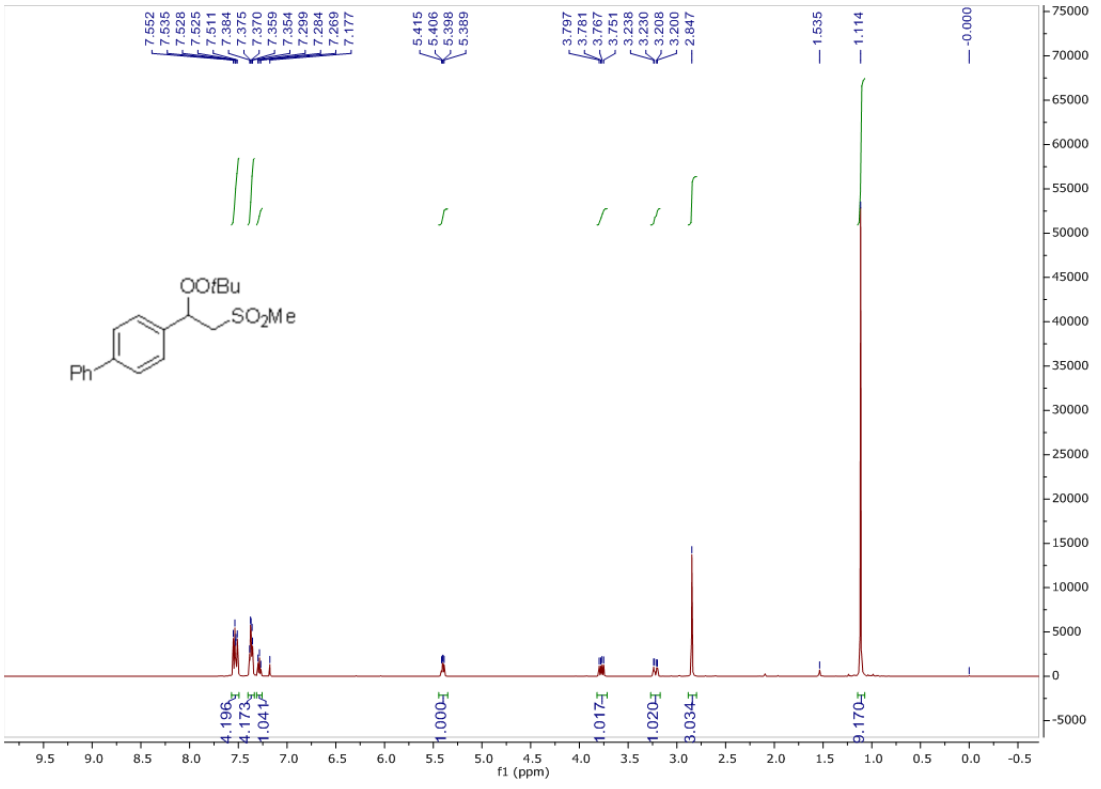

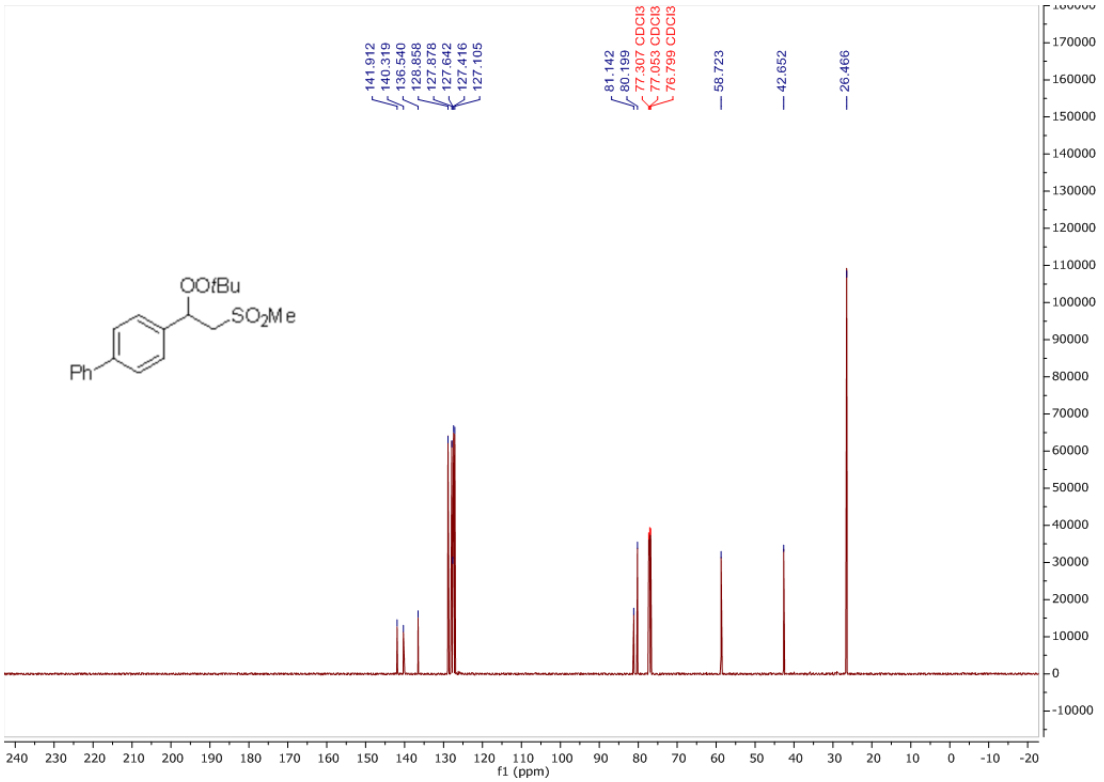

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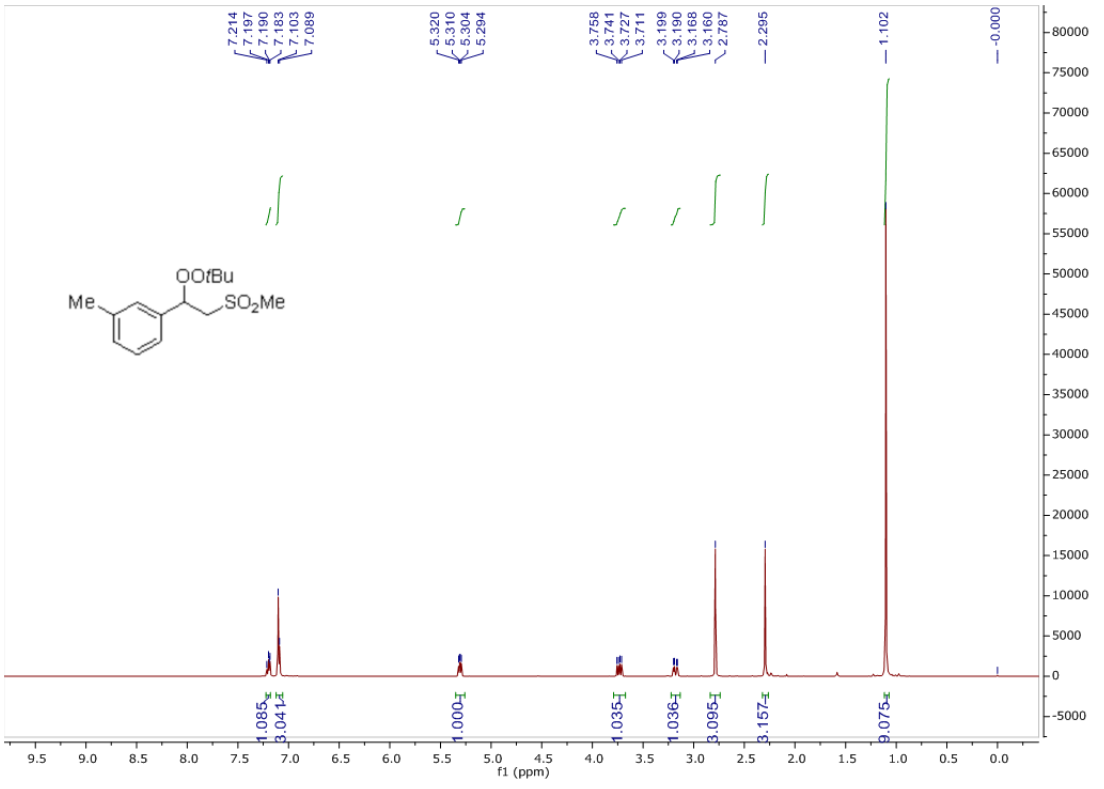

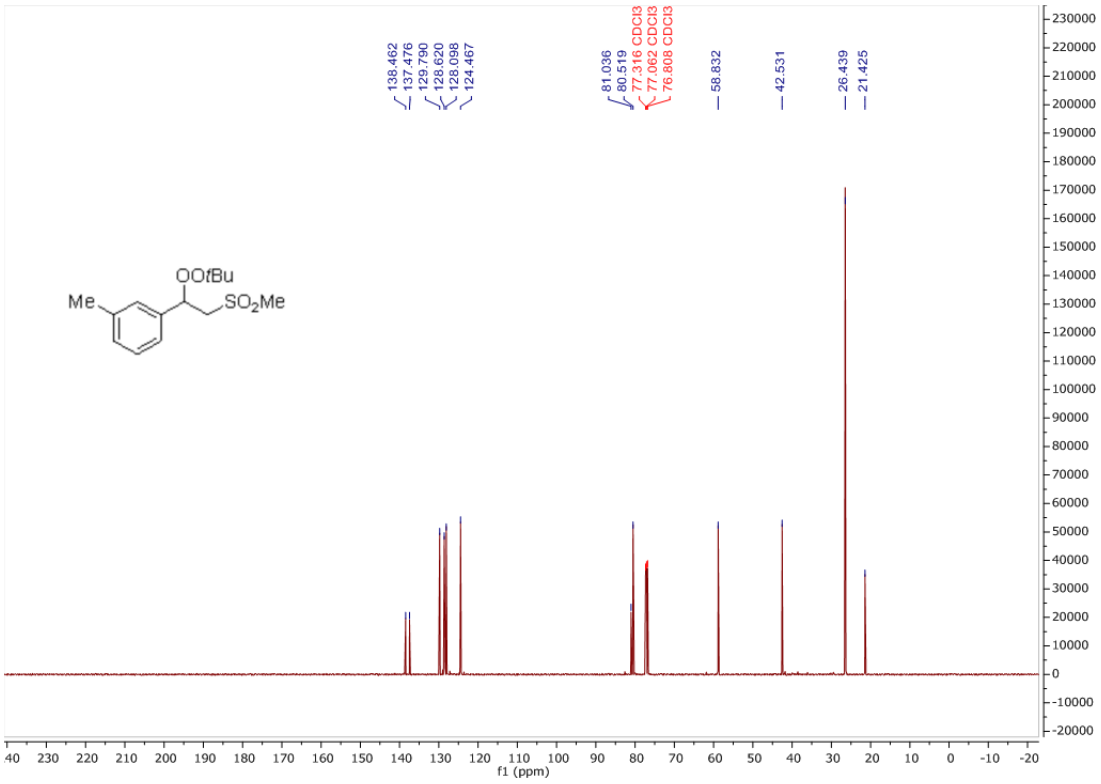

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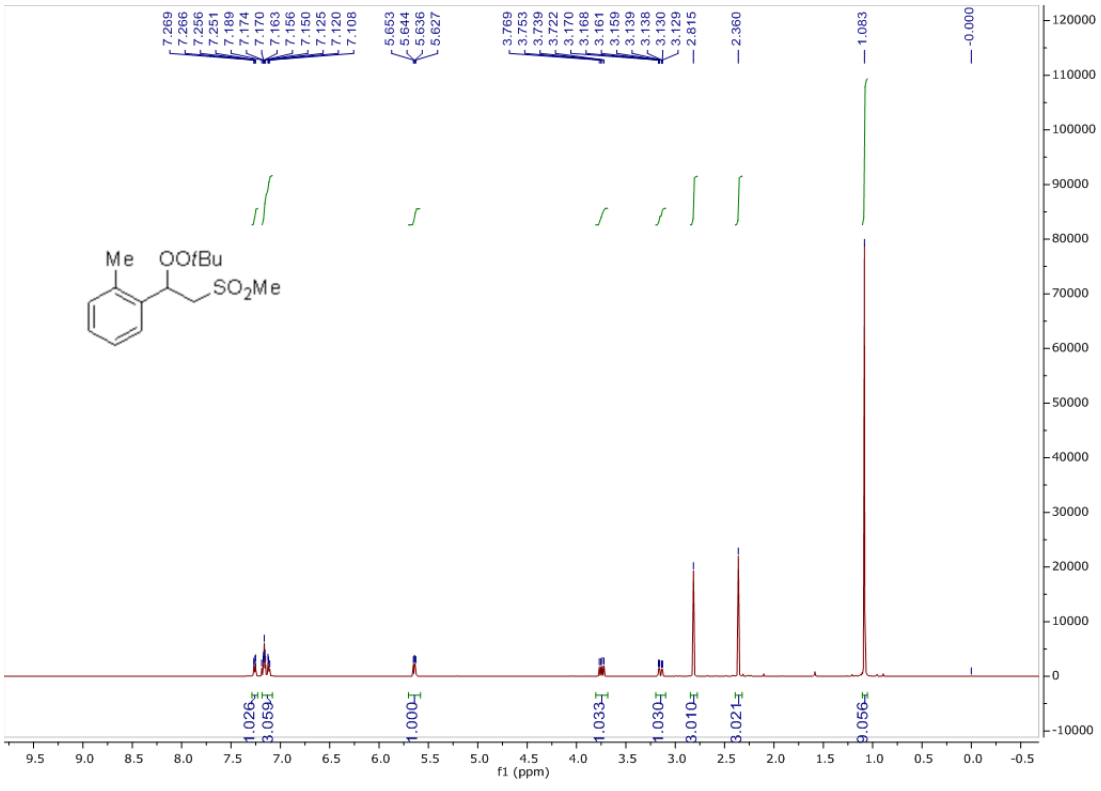

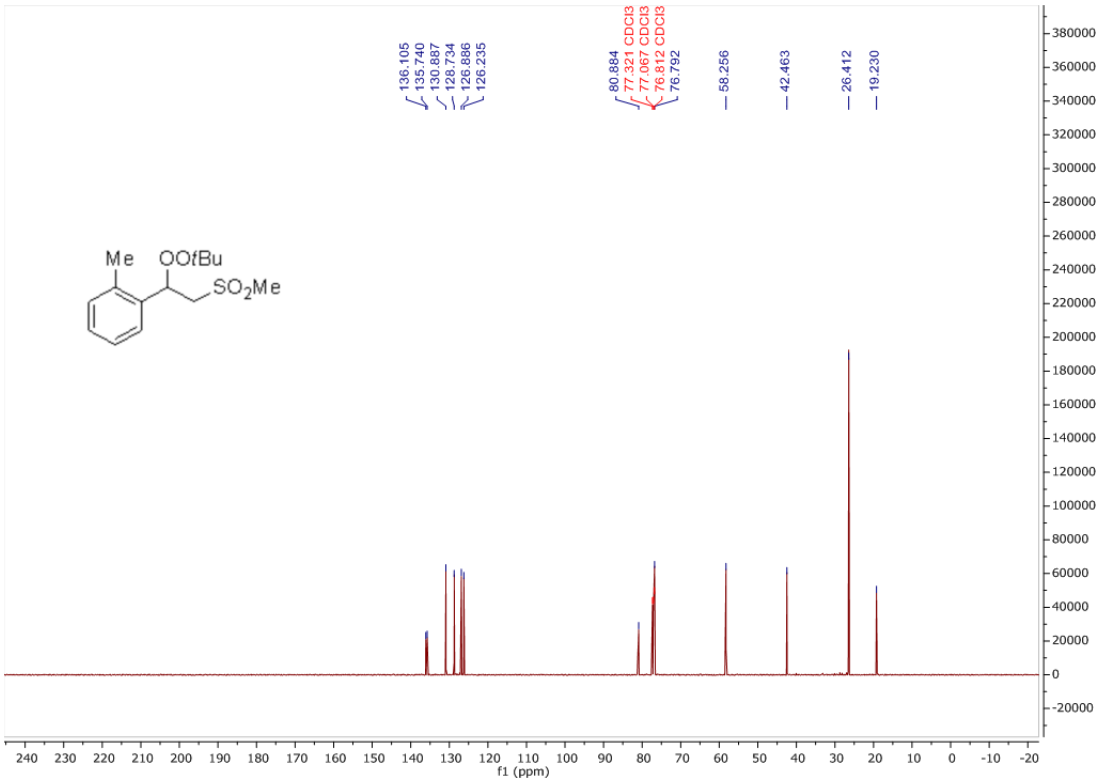

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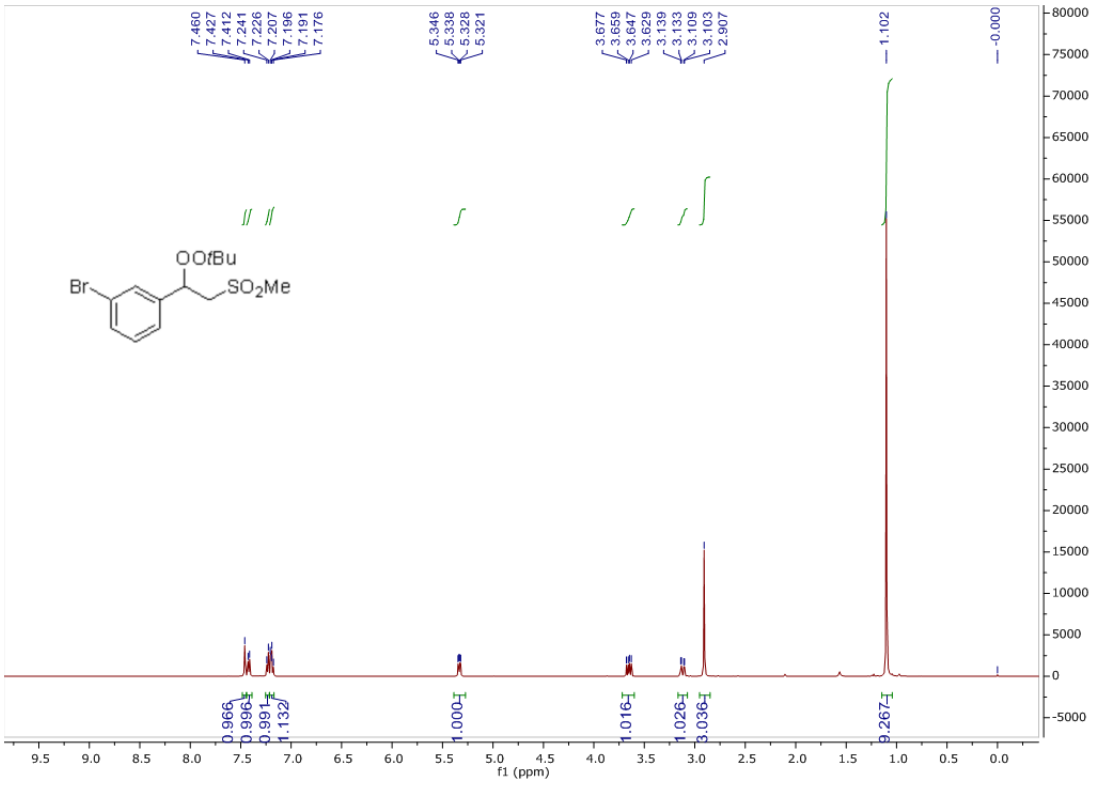

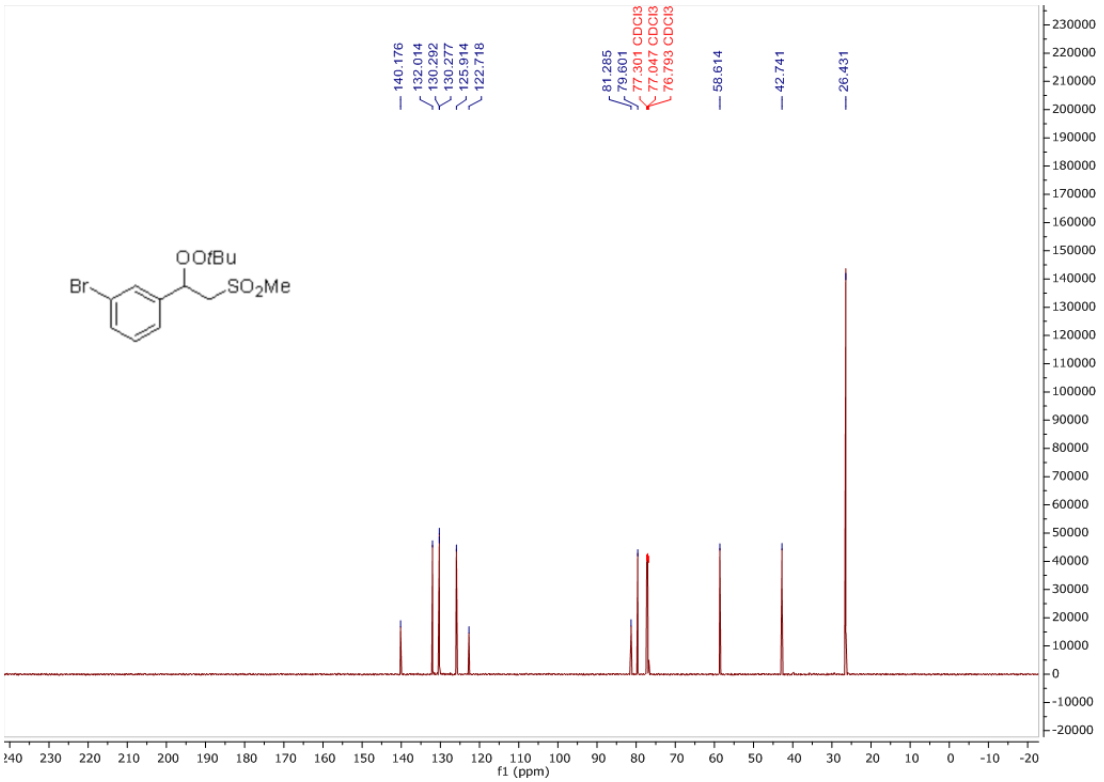

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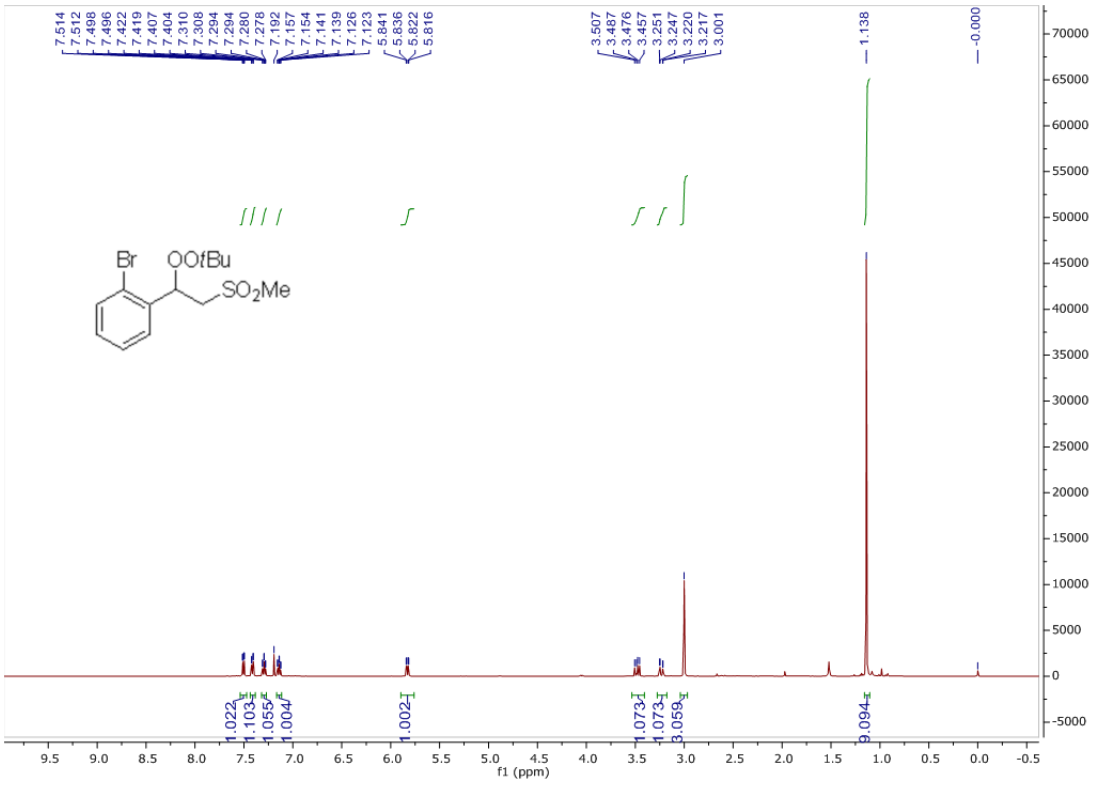

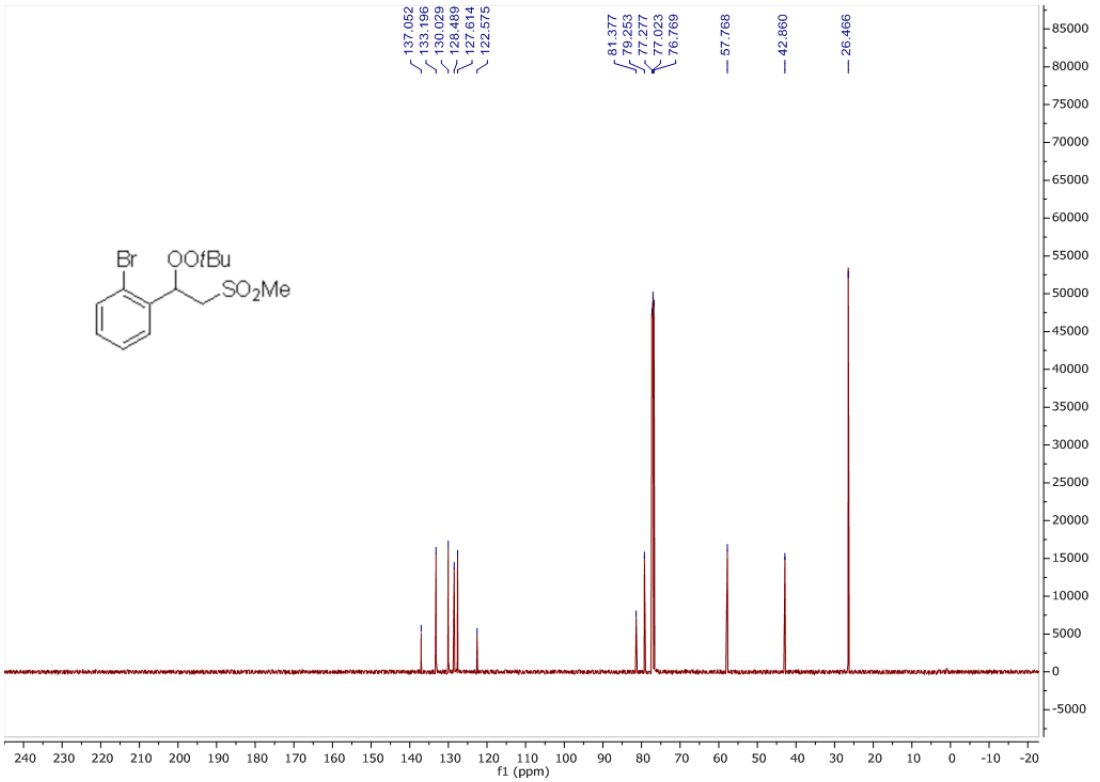

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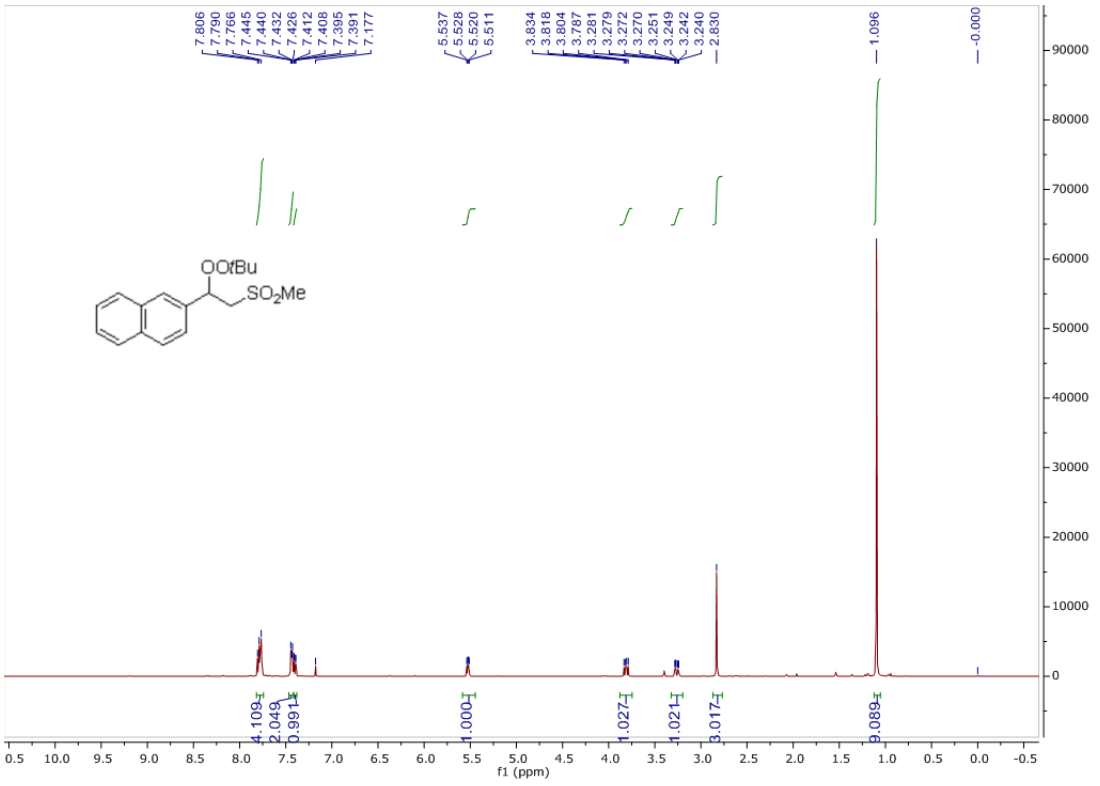

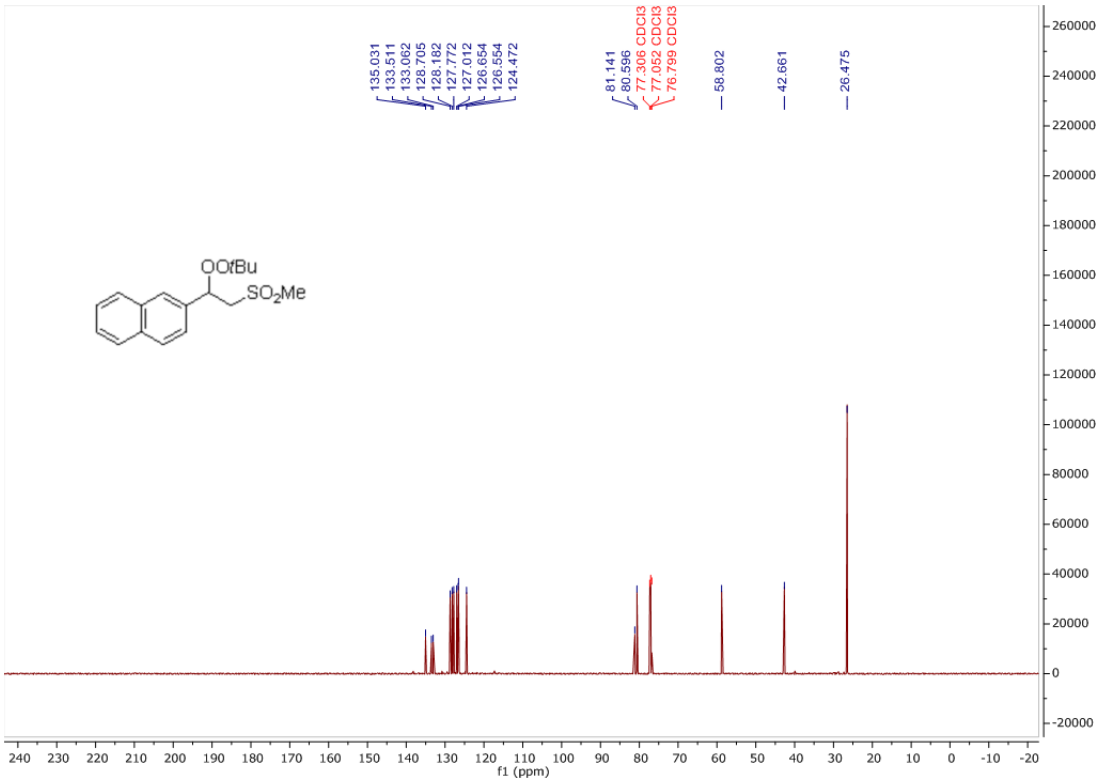

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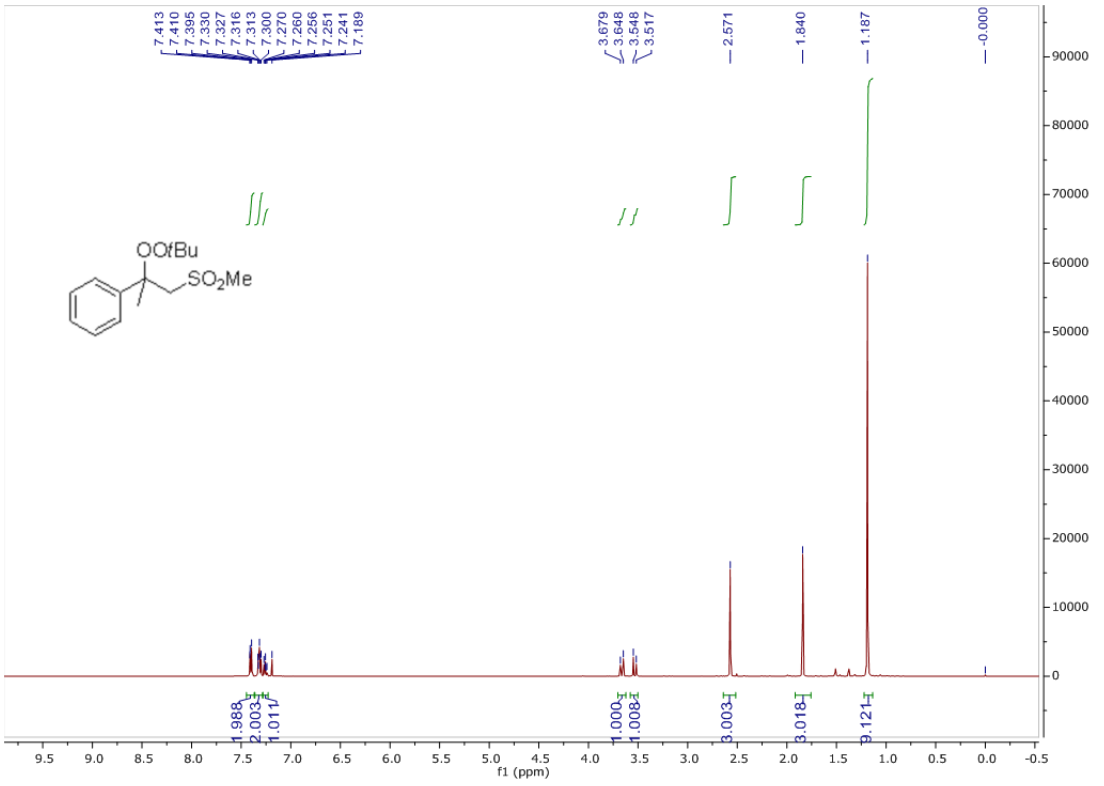
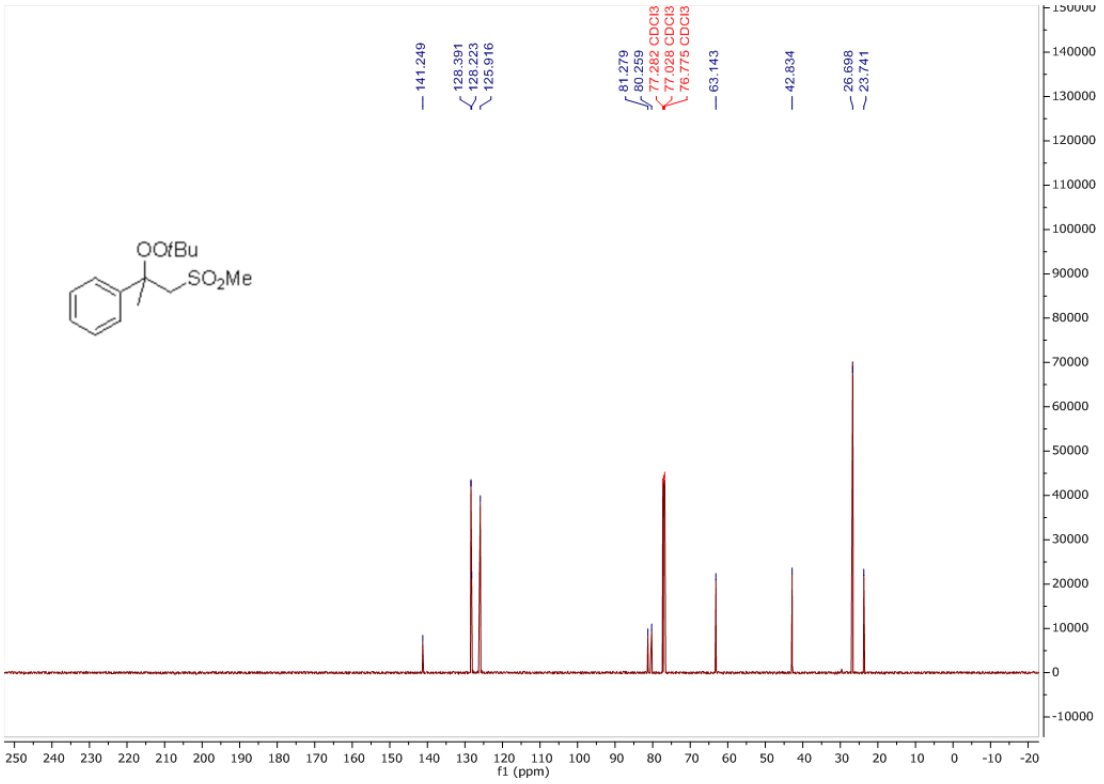
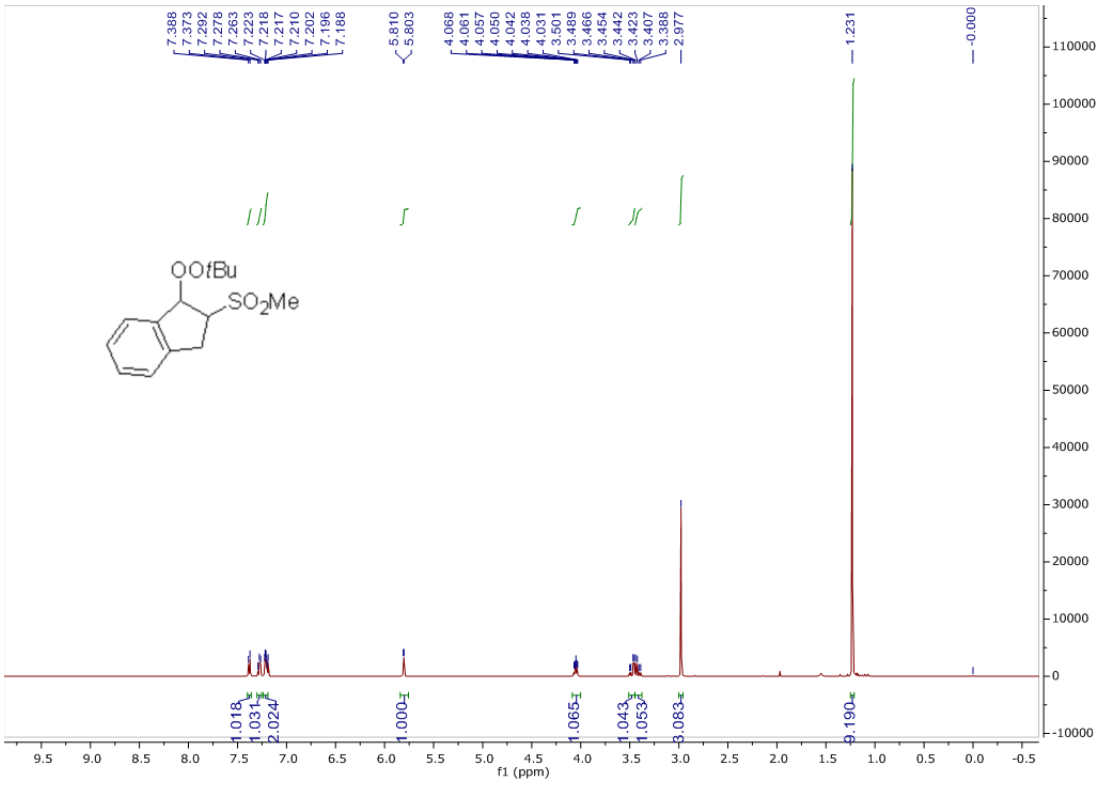
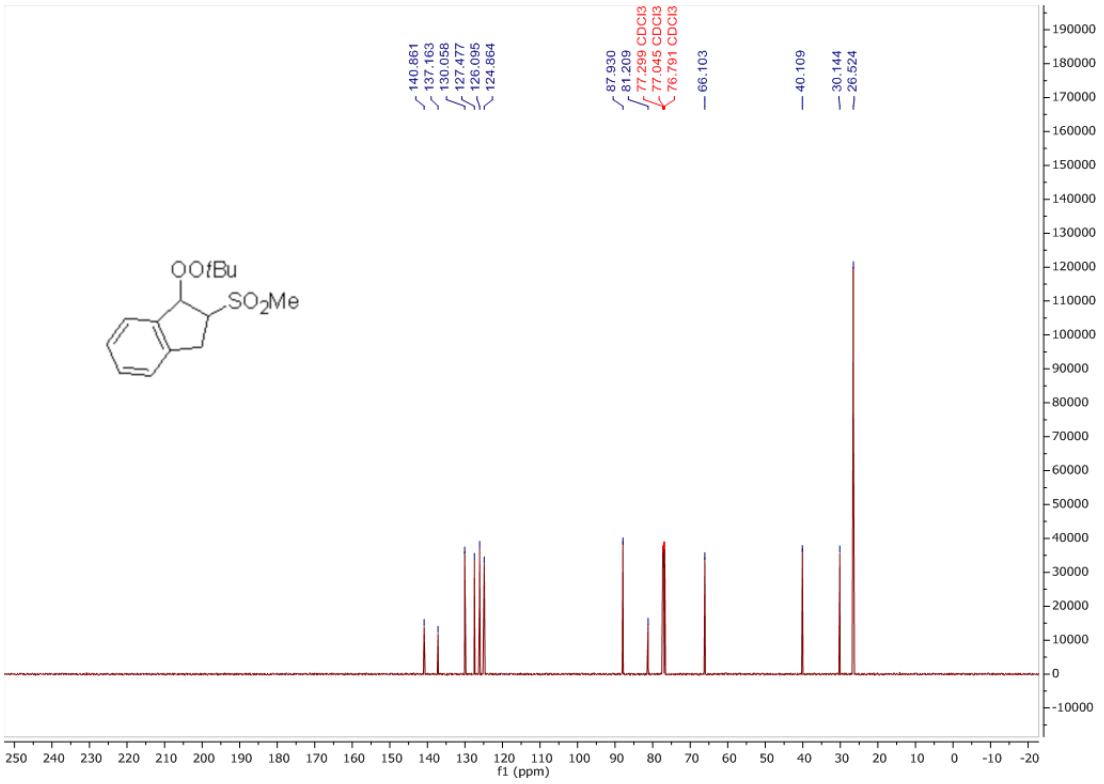




NMR Spectra of **7qc**

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66.103
40.109
30.144
26.524
OOtBu
SO2Me
f1 (ppm)

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