Electronic Supplementary Material (ESI) for ChemComm.

Supporting Information

A Tandem Annulation with [1,3]-Hydride Transfer as the Key Step Leading to Isochromans

Contents

General experimental procedures.

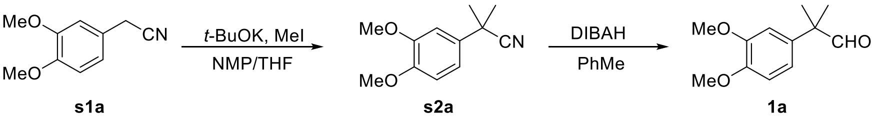
All reactions that required anhydrous or airless conditions were carried by standard procedures under nitrogen atmosphere. Commercially available reagents from Tansoole and Adamas-beta were used as received. The solvents were dried by distillation over the appropriate drying reagents.

^{1}H NMR spectra were recorded on commercial instruments (400 MHz). Chemical shifts were reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$, δ = 7.26). Spectra were reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz), integration and, assignment. ^{13}C NMR spectra were collected on commercial instruments (101 MHz) with complete proton decoupling. Chemical shifts are reported in ppm from the tetramethylsilane with the solvent resonance as internal standard ($CDCl_3$, δ = 77.0). Mass spectra were recorded on ThermoQuest Finnigan LCQDECA system equipped with an ESI source. Enantiomeric excesses (*ee*) were determined by HPLC analysis using the corresponding commercial chiral column as stated in the experimental procedures at 30 ℃ with UV detector at 220 nm.

Procedure and spectral data

1. Preparation of starting materials.

General synthetic route to 2-aryl-2,2-dialkylacetaldehydes. 2-aryl-2,2-dialkylacetaldehydes **1a-f** was synthesized according to the reported procedure.[1] Preparation of **1a** is shown as a representative example.

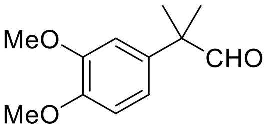


Synthesis of 2-(3,4-dimethoxyphenyl)-2-methylpropanenitrile (**s2a**):

A solution of *t*-BuOK (22.4 g, 200 mmol, 4.0 equiv) in 1-methyl-2-pyrrolidone/THF (1:1, 70 mL) was cooled to 0 ℃, and a solution of 2-(3,4-dimethoxyphenyl)acetonitrile (**s1a**) (8.9 g, 50 mmol) and methyl iodide (12.5 mL, 200 mmol, 4.0 equiv) in THF (10 mL) was added maintaining the reaction temperature below 10 ℃. After 1 h reaction mixture was warmed to room temperature and stirred for 2 h. The mixture was diluted with HCl (3N, 70 mL) and extracted with ethyl acetate (2×100 mL), and the organic layer was separated , washed with saturated sodium bicarbonate (1×100 mL) and brine (1×100 mL) , dried over anhydrous sodium sulfate and evaporated under reduced pressure to afford oil. This material was used to next reaction without further purification.

Synthesis of 2-(3,4-dimethoxyphenyl)-2-methylpropanal (**1a**):

To a solution of 2-(3,4-dimethoxyphenyl)-2-methylpropanenitrile (**s2a**) (9.7 g, 47.3 mmol) in toluene (100 ml) was drop wise DIBAH (61.5 mL, 61.5mmol ,1.3 equiv) (1M solution in toluene) at -50 ℃. Reaction mixture was stirred at -50 ℃ for 2 h, followed by addition of aqueous HCl (6N, 80 mL). After stirring at room temperature for 30 min, the mixture was extracted with ethyl acetate (2×100 mL), and the organic layers were combined, washed with saturated sodium bicarbonate (1×100 mL), brine (1×100 mL), dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was purified by flash chromatography over silica gel with 5% EtOAc/ petroleum ether as eluent to furnish **1a** (8.5 g, 87% yield) as a pale yellow oil.

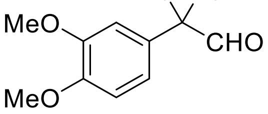


2-(3,4-dimethoxyphenyl)-2-methylpropanal (**1a**).[2]

^{1}H NMR (400 MHz, CDCl$_3$) δ 9.44 (s, 1H), 6.89-6.82 (m, *J* = 8.4, 5.2 Hz, 2H), 6.74 (d, *J* = 2.1 Hz, 1H), 3.88 (s, 6H), 1.45 (s, 6H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 201.94, 148.99, 148.13, 133.29, 118.83, 111.13, 109.93, 55.78, 55.75, 49.88 (s), 22.32 (s).

HRMS (ESI) m/z calcd for $C_{14}H_{20}NaO_3$ (M + Na)$^+$: 231.0992; found: 231.0994.



2-(3,4-dimethoxyphenyl)-2-ethylbutanal (**1b**)

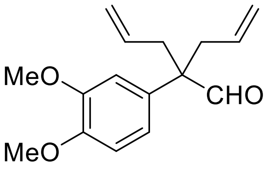
Pale yellow oil.

Yield: 83% （from **s1a** and ethyl bromide）.

^{1}H NMR (400 MHz, CDCl$_3$) δ 9.42 (s, 1H), 6.88 (d, *J* = 8.4 Hz, 1H), 6.79 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.69 (d, *J* = 2.1 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 2.01-1.90 (m, 4H), 0.77 (t, *J* = 7.5 Hz, 6H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 202.97, 149.00, 148.06, 131.12, 120.04, 111.03, 110.78, 57.58, 55.84, 55.76, 23.64, 8.01.

HRMS (ESI) m/z calcd for $C_{14}H_{20}NaO_3$ (M + Na)$^+$: 259.1305; found: 259.1294.



2-allyl-2-(3,4-dimethoxyphenyl)pent-4-enal (**1c**).

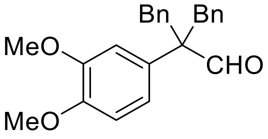
Pale yellow oil.

Yield: 87% （from **s1a** and allyl bromide）

^{1}H NMR (400 MHz, CDCl$_3$) δ 9.48 (s, 1H), 6.88 (d, *J* = 8.4 Hz, 1H), 6.79 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.68 (d, *J* = 2.2 Hz, 1H), 5.61-5.51(m, 2H), 5.12-5.07 (m, 4H), 3.89 (s, 4H), 3.87 (s, 3H), 2.70 (s, 2H), 2.68 (s, 2H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 201.57, 149.11, 148.33, 132.69, 130.02, 119.90, 118.85, 111.12, 110.64, 56.29, 55.89, 55.80, 36.50.

HRMS (ESI) m/z calcd for $C_{16}H_{20}NaO_3$ (M + Na)$^+$: 283.1305; found: 283.1316.



2-benzyl-2-(3,4-dimethoxyphenyl)-3-phenylpropanal (**1d**).

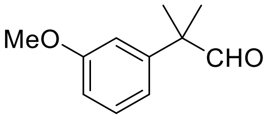
Pale yellow oil.

Yield: 56% （from **s1a** and benzyl bromide）.

^{1}H NMR (400 MHz, CDCl$_3$) δ 9.73 (s, 1H), 7.20 – 7.15 (m, 6H), 6.90-6.88 (m, 4H), 6.86 (d, *J* = 8.4 Hz, 1H), 6.75 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.47 (d, *J* = 2.1 Hz, 1H), 3.89 (s, 3H), 3.70 (s, 3H), 3.24 (dd, *J* = 14.2 Hz, 4H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 202.36, 148.86, 148.39, 136.58, 130.54, 130.29, 128.04, 126.55, 120.47, 111.84, 111.04, 59.17, 55.87, 39.83.

HRMS (ESI) m/z calcd for $C_{24}H_{24}NaO_3$ (M + Na)$^+$: 383.1618; found: 383.1623.



2-(3-methoxyphenyl)-2-methylpropanal (**1e**).[3]

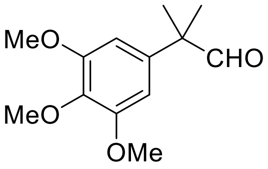
Pale yellow oil.

Yield: 92% （from 2-(3-methoxyphenyl)acetonitrile **s1b** and methyl iodide）

^{1}H NMR (400 MHz, CDCl$_3$) δ 9.48 (s, 1H), 7.31-7.27 (m, 1H), 6.87-6.81 (m, 3H), 3.80 (s, 3H), 1.44 (s, 6H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 201.91, 159.86, 142.75, 129.73, 118.95, 112.98, 111.95, 55.11, 50.36, 22.32.

HRMS (ESI) m/z calcd for $C_{11}H_{14}NaO_2$ (M + Na)$^+$: 201.0886; found: 201.0886.



2-methyl-2-(3,4,5-trimethoxyphenyl)propanal (**1f**).[4]

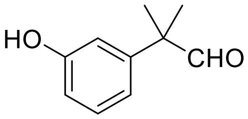
Pale yellow oil.

Yield: 82% （from 2-(3,4,5-trimethoxyphenyl)acetonitrile **s1c** and methyl iodide）

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.46 (s, 1H), 6.46 (s, 2H), 3.87 (s, 6H), 3.84 (s, 3H), 1.46 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 201.66, 153.31, 137.15, 136.59, 103.90, 60.71, 56.09, 50.42, 22.36.

HRMS (ESI) m/z calcd for $C_{13}H_{18}NaO_4$ (M + Na)$^+$: 261.1097; found: 261.1091.



Synthesis of **2-(3-hydroxyphenyl)-2-methylpropanal** (**1g**)

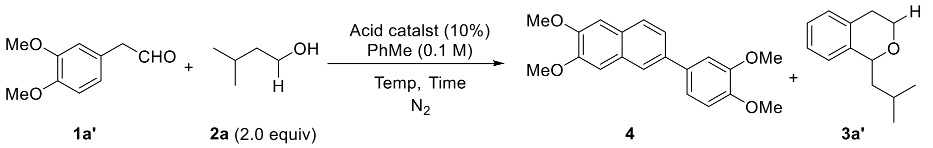
To a solution of 2-(3-methoxyphenyl)-2-methylpropanal（**1e**）(534 mg, 3.0 mmol) in 5 mL of *N*-methylpyrrolidinone was added thiophenol (0.31 mL, 3 mmol) and anhydrous K_2CO_3 (41 mg, 0.3 mmol). The mixture was stirred at 210 ℃ for 8 h. After cooling, the mixture was partitioned between diethyl ether (10 mL) and 5% aqueous NaOH (5 mL). The aqueous layer was acidified with dilute HCl (1N, 5 mL) and extracted with EtOAc (2×10 mL). The combined organic extracts were dried over anhydrous sodium sulfate and evaporated under reduced pressure. Chromatography of the residue using 10% EtOAc/ petroleum ether as eluent gave the title compound as a pale yellow oil (369 mg, 75% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.47 (s, 1H), 7.27-7.23 (m, 1H), 6.84 (dd, *J* = 7.8, 0.7 Hz, 1H), 6.80 – 6.73 (m, 2H), 5.60 (s, 1H), 1.44 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 202.71, 156.08, 142.84, 130.06, 118.92, 114.31, 113.87, 50.39, 22.31.

HRMS (ESI) m/z $C_{10}H_{13}O_2$ (M + H)$^+$: 165.0916; found: 165.0910.

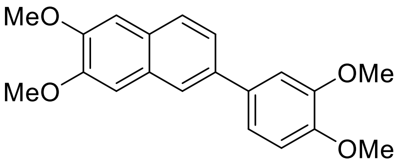
2. Screening reaction conditions for [1,3]-hydride of oxacarbenium ion generated by 2-(3,4-dimethoxyphenyl)acetaldehyde 1a' and 3-methyl-1-butanol 2a.



Entry	Catalyst	Temp [℃]	Time [h]	Yield [%][a]		Recovery of 1a'[%][a]
				4	3a'	
1	TfOH	RT	2	83	0	0
2	AcOH	110	12	0	0	92
3	PhCOOH	110	12	0	0	90
4	$BF_3.Et_2O$	RT	12	23	0	<5
5	TMSOTf	RT	4	68	0	0
6	$In(OTf)_3$	70	2	47	0	32
7	$Sc(OTf)_3$	70	2	59	0	18
8	$InCl_3$	70	2	35	0	32
9	$AlCl_3$	70	2	11	0	62
10[b]	TfOH	RT	2	87	-	0

[a] As determined by NMR. [b] **2a** was not used.

General procedur: 11 reaction tubes were each charged with **1a’** (0.2 mmol) and **2a** (0.4 mmol) and toluene (2 mL), followed by addition of Lewis or Brønsted acid catalyst (10 mol%) at room temperature. The reaction mixture were heated to the given temperature and stirred under nitrogen atmosphere. After 2 h to 12 h, the crude products were analyzed by NMR.



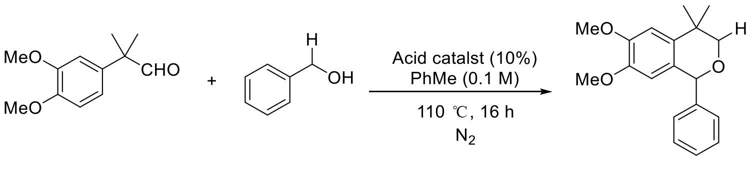
6-(3,4-dimethoxyphenyl)-2,3-dimethoxynaphthalene (**4**)[5]: A 10 mL reaction tube was charged with 1a’ (0.2 mmol) and **2a** (0.4 mmol) and toluene (2 mL), followed by addition of TfOH (10 mol%) at room temperature. The reaction mixture was stirred at room temperature under nitrogen atmosphere. After 2 h, the reaction was stopped by adding saturated aqueous $NaHCO_3$ (2 mL). The crude products were extracted with EtOAc (3×5 mL) and the combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by flash chromatography over silica gel with 30% EtOAc/ petroleum ether as eluent to give title compound as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.74 (d, *J* = 8.4 Hz, 1H), 7.57 (d, *J* = 8.4 Hz, 1H), 7.26 (s, 1H), 7.23 (d, *J* = 5.1 Hz, 1H), 7.18 (s, 1H), 7.14 (s, 1H), 6.98 (d, *J* = 8.2 Hz, 1H), 4.02 (s, 6H), 3.99 (s, 3H), 3.94 (s, 3H).

^{13}C NMR (101 MHz,) δ 149.81, 149.43, 149.18, 148.47, 136.83, 134.41, 129.44, 128.12, 126.75, 123.80, 123.72, 119.45, 111.53, 110.54, 106.44, 106.09, 55.99, 55.96, 55.86.

HRMS (ESI) m/z calcd for $C_{20}H_{20}NaO_4$ $(M + Na)^+$: 347.1259; found: 347.1249.

3. Screening reaction conditions for [1,3]-hydride of oxacarbenium ion generated 1a and benzyl alcohol 2’



1a **2'** (5.0 equiv) **3j**

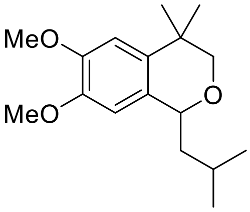
Entry	Catalyst	Yield [%][a]
1	TfOH	0
2	$BF_3.Et_2O$	5
3	$Sc(OTf)_3$	0
4	$In(OTf)_3$	0
5	$Al(OTf)_3$	0
6	$Bi(OTf)_3$	0
7	$Ga(OTf)_3$	0
8	$Y(OTf)_3$	0
9	$ScCl_3.6H_2O$	0
10[b]	$BF_3.Et_2O$	25 [c]

[a] As determined by NMR. [b] 200 mmol% of $BF_3.Et_2O$ was used. [c] Isolated yield.

4. Synthesis of isochroman derivatives.

General procedure A: To a solution of 2-aryl-2,2-dialkylacetaldehyde **1** (0.2 mmol) and alcohol **2** (1.0 mmol) in toluene (2 mL) was $Sc(OTf)_3$ (10 mol%) at room temperature, then the reaction mixture was stirred for 16 h at 110 ℃ under nitrogen atmosphere. After completion of the reaction, the reaction was stopped by adding saturated aqueous $NaHCO_3$ (2 mL). The crude products were extracted with EtOAc (3×5 mL) and the combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by flash chromatography over silica gel or preparative TLC with 5% EtOAc/ petroleum ether as eluent to give isochroman derivatives.

General procedure B: A 10 mL reaction tube was charged with 2-aryl-2,2-dialkylacetaldehyde 1 (0.2 mmol), alcohol 2 (0.25 mL) and $Sc(OTf)_3$ (10 mol%) at room temperature, then the reaction mixture was stirred for 16 h at 110 ℃ under nitrogen atmosphere. After completion of the reaction, the reaction was stopped by adding saturated aqueous $NaHCO_3$ (5 mL). The crude products were extracted with EtOAc (3×5 mL) and the combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by flash chromatography over silica gel or preparative TLC with 5% EtOAc/ petroleum ether as eluent to give isochroman derivatives.

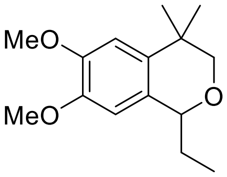


1-ethyl-6,7-dimethoxy-4,4-dimethylisochromane (**3a**): Followed general procedure A, compound **3a** was obtained as a colorless oil in 78% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78 (s, 1H), 6.48 (s, 1H), 4.74 (dd, *J* = 10.3, 2.7 Hz, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 3.67 (d, *J* = 11.1 Hz, 1H), 3.46 (d, *J* = 11.2 Hz, 1H), 2.02-1.77 (m, 1H), 1.84-1.78 (m, 1H), 1.56-1.49 (m, 1H), 1.29 (s, 3H), 1.22 (s, 3H), 1.04 (d, *J* = 6.5 Hz, 1H), 0.97 (d, *J* = 6.7 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.58, 147.00, 135.37, 129.81, 108.30, 107.44, 74.41, 73.84, 55.89, 55.88, 45.20, 33.33, 28.11, 26.54, 24.41, 24.01, 21.52.

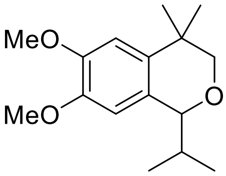
HRMS (ESI) m/z calcd for $C_{17}H_{27}O_3$ $(M + H)^+$: 279.1955; found: 279.1966.



1-ethyl-6,7-dimethoxy-4,4-dimethylisochromane (**3b**): Followed general procedure A, compound **3b** was obtained as a colorless oil in 56% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.79 (s, 1H), 6.51 (s, 1H), 4.68 (dd, *J* = 7.5, 3.2 Hz, 1H), 3.88 (s, 3H), 3.84 (s, 3H), 3.67 (d, *J* = 11.1 Hz, 1H), 3.49 (d, *J* = 11.1 Hz, 1H), 2.01-1.91 (m, 1H), 1.90-1.79 (m, 1H), 1.30 (s, 3H), 1.20 (s, 3H), 0.99 (t, *J* = 7.3 Hz, 1H).

HRMS (ESI) m/z calcd for $C_{15}H_{22}NaO_3$ $(M + Na)^+$: 273.1461; found: 273.1454.

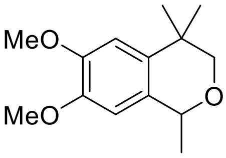


1-isopropyl-6,7-dimethoxy-4,4-dimethylisochromane (**3c**): Followed general procedure A, compound **3c** was obtained as a colorless oil in 76% yield.

^{1}H NMR (400 MHz, CDCl$_3$) δ 6.78 (s, 1H), 6.55 (s, 1H), 4.60 (d, *J* = 2.4 Hz, 1H), 3.88 (s, 3H), 3.84 (s, 3H), 3.66 (d, *J* = 11.0 Hz, 1H), 3.47 (d, *J* = 11.0 Hz, 1H), 2.29-2.22 (m, 1H), 1.31 (s, 3H), 1.19 (d, *J* = 6.9 Hz, 3H), 1.17 (s, 3H), 0.74 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 147.45, 147.11, 136.42, 128.68, 108.15, 106.97, 80.90, 75.52, 55.87, 55.83, 33.40, 32.83, 29.34, 25.06, 19.85, 15.17.

HRMS (ESI) m/z calcd for $C_{16}H_{24}NaO_3$ (M + Na)$^+$: 287.1623; found: 287.1615.

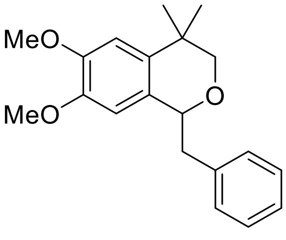


6,7-dimethoxy-1,4,4-trimethylisochromane (**3d**): Followed general procedure B, compound **3d** was obtained as a colorless oil in 57% yield.

^{1}H NMR (400 MHz, CDCl$_3$) δ 6.79 (s, 1H), 6.51 (s, 1H), 4.82 (q, *J* = 6.4 Hz, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 3.68 (d, *J* = 11.1 Hz, 1H), 3.52 (d, *J* = 11.1 Hz, 1H), 1.53 (d, *J* = 6.5 Hz, 3H), 1.32 (s, 3H), 1.20 (s, 3H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 147.72, 147.14, 135.18, 130.30, 108.31, 107.41, 75.10, 72.88, 55.93, 55.87, 33.48, 29.07, 25.63, 22.14.

HRMS (ESI) m/z calcd for $C_{14}H_{20}NaO_3$ (M + Na)$^+$: 259.1305; found: 259.1299.

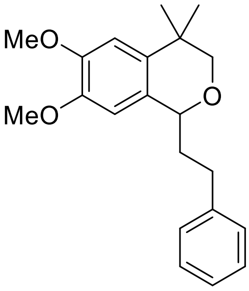


1-benzyl-6,7-dimethoxy-4,4-dimethylisochromane (**3e**): Followed general procedure A, compound **3e** was obtained as a colorless oil in 32% yield.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.32-7.27 (m, 1H), 7.24-7.19 (m, 1H), 6.78 (s, 1H), 6.47 (s, 1H), 5.00 (t, *J* = 6.3 Hz, 1H), 3.88 (s, 3H), 3.77 (s, 3H), 3.69 (d, *J* = 11.1 Hz, 1H), 3.47 (d, *J* = 11.1 Hz, 1H), 3.14 (d, *J* = 6.3 Hz, 1H), 1.22 (s, 3H), 1.19 (s, 3H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 147.74, 146.83, 138.65, 135.73, 129.56, 128.36, 128.17, 126.20, 108.16, 107.79, 76.90, 73.75, 55.85, 55.75, 42.54, 33.33, 27.76, 26.40.

HRMS (ESI) m/z calcd for $C_{20}H_{24}NaO_3$ (M + Na)$^+$: 335.1618; found: 335.1622.

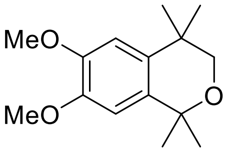


6,7-dimethoxy-4,4-dimethyl-1-phenethylisochromane (**3f**): Followed general procedure A, compound **3f** was obtained as a colorless oil in 57% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.16 (m, 1H), 6.80 (s, 1H), 6.49 (s, 1H), 4.75 (dd, *J* = 7.9, 3.3 Hz, 1H), 3.88 (s, 3H), 3.82 (s, 3H), 3.72 (d, *J* = 11.1 Hz, 1H), 3.52 (d, *J* = 11.1 Hz, 1H), 2.84-2.73 (m, 1H), 2.24 – 2.07 (m, 1H), 1.34 (s, 3H), 1.22 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.71, 147.15, 142.45, 135.75, 128.69, 128.46, 128.32, 125.70, 108.32, 107.20, 75.74, 74.57, 55.91, 55.89, 37.66, 33.43, 31.29, 28.70, 25.96.

HRMS (ESI) m/z calcd for $C_{21}H_{26}NaO_3$ $(M + Na)^+$: 349.1774; found: 349.1774.

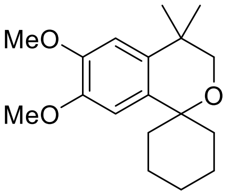


6,7-dimethoxy-1,1,4,4-tetramethylisochromane (**3g**): Followed general procedure B, compound **3g** was obtained as a colorless oil in 31% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.76 (s, 1H), 6.52 (s, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.58 (s, 2H), 1.52 (s, 6H), 1.26 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.52, 147.07, 134.69, 133.73, 108.27, 107.90, 74.93, 70.99, 55.96, 55.88, 33.56, 29.78, 27.00.

HRMS (ESI) m/z calcd for $C_{15}H_{23}O_3$ $(M + H)^+$: 251.1642; found: 251.1626.

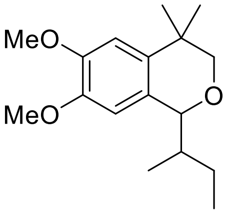


6',7'-dimethoxy-4',4'-dimethylspiro[cyclohexane-1,1'-isochromane] (**3h**): Followed general procedure A, compound **3h** was obtained as a colorless oil in 75% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.76 (s, 1H), 6.55 (s, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.53 (s, 2H), 1.96 (d, *J* = 13.6 Hz, 2H), 1.80-1.69 (m, 3H), 1.65-1.56 (m, 5H), 1.25 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.37, 146.88, 135.27, 134.30, 108.34, 107.90, 75.37, 70.09, 55.93, 55.82, 36.97, 33.44, 27.16, 25.52, 21.75.

HRMS (ESI) m/z calcd for $C_{18}H_{27}O_3$ $(M + H)^+$: 291.1955; found: 291.1953.

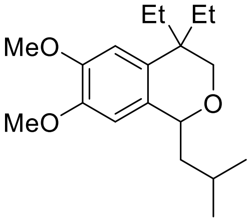


1-(*sec*-butyl)-6,7-dimethoxy-4,4-dimethylisochromane (**3i**): Followed general procedure A with racemic 2-methyl-1-butanol , compound **3i** was obtained as a colorless oil in 47% yield, as a 2:1 mixture of diastereomers.

^{1}H NMR (400 MHz, CDCl$_3$) δ major product: 6.78 (s, 1H), 6.53 (s, 1H), 4.70 (d, *J* = 2.2 Hz, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 3.64 (d, *J* = 10.8 Hz, 1H), 3.46 (d, *J* = 10.8 Hz, 1 H), 1.98-1.87 (m, 1H), 1.69-1.63 (m, 1H), 1.58-1.47 (m, 1H), 1.32 (s, 3H), 1.16 (s, 3H), 1.03 (t, *J* = 7.4 Hz, 3H), 0.71 (d, *J* = 6.8 Hz, 3H); minor product: 6.78 (s, 1H), 6.54 (s, 1H), 4.63 (d, *J* = 2.3 Hz, 1H), 3.88 (s, 3H), 3.83 (s, 3H), 3.65 (d, *J* = 10.8 Hz, 1H), 3.45 (d, *J* = 10.8 Hz, 1 H), 1.98-1.87 (m, 1H), 1.69-1.63 (m, 1H), 1.58-1.47 (m, 1H), 1.31 (s, 3H),1.17 (d, *J* = 5.4 Hz, 3H), 1.16 (s, 3H),0.81 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (101 MHz, CDCl$_3$) δ major product: 147.46, 147.19, 136.58, 128.79, 108.22, 106.88, 79.31, 75.74, 55.97, 55.88, 39.91, 33.45, 29.50, 26.84, 25.01, 13.01, 12.49; minor product: 147.51, 147.10, 136.53, 128.68, 108.22, 106.97, 81.66, 75.71, 55.95, 55.88, 40.01, 33.48, 29.30, 25.14, 22.52, 16.5, 12.72.

HRMS (ESI) m/z calcd for $C_{17}H_{27}O_3$ (M + H)$^+$: 279.1955; found: 279.1959.

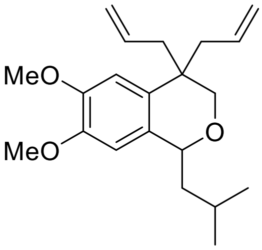


4,4-diethyl-1-isobutyl-6,7-dimethoxyisochromane (**3k**): Followed general procedure A, compound **3k** was obtained as a colorless oil in 72% yield.

^{1}H NMR (400 MHz, CDCl$_3$) δ 6.68 (s, 1H), 6.49 (s, 1H), 4.68 (dd, *J* = 10.4, 2.7 Hz, 1H), 3.86 (s, 6H), 3.79 (d, *J* = 11.4 Hz, 1H), 3.57 (d, *J* = 11.5 Hz, 1H), 2.01-1.95 (m, 1H), 1.77-1.58 (m, 6H), 1.55-1.47 (m, 1H), 1.03 (d, *J* = 6.6 Hz, 3H), 0.97 (d, *J* = 6.7 Hz, 3H), 0.82 (t, *J* = 7.5 Hz, 3H), 0.75 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 147.21, 146.76, 132.13, 131.65, 109.38, 107.38, 74.01, 68.77, 55.94, 55.75, 45.14, 39.06, 31.65, 30.52, 24.41, 24.00, 21.52, 8.89, 8.66.

HRMS (ESI) m/z calcd for $C_{19}H_{30}NaO_3$ (M + Na)$^+$: 329.2087; found: 329.2090.



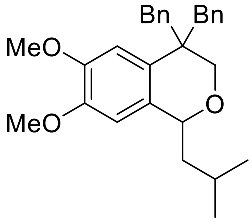
4,4-diallyl-1-isobutyl-6,7-dimethoxyisochromane (**3l**): Followed general procedure A, compound **3l**

was obtained as a pale yellow oil in 51% yield.

^{1}H NMR (400 MHz, CDCl$_3$) δ 6.72 (s, 1H), 6.48 (s, 1H), 5.74-5.59 (m, 2H), 5.07-4.99 (m, 4H), 4.70 (dd, *J* = 10.3, 2.8 Hz, 1H), 3.86 (s, 6H), 3.77 (d, *J* = 11.5 Hz, 1H), 3.56 (d, *J* = 11.5 Hz, 1H), 2.51-2.29 (m, 2H), 2.35 (ddd, *J* = 28.0, 14.1, 7.7 Hz, 2H), 1.98-1.74(m, 1H), 1.78 (ddd, *J* = 14.2, 10.4, 3.8 Hz, 1H), 1.49 (ddd, *J* = 14.1, 9.9, 2.9 Hz, 1H), 1.03 (d, *J* = 6.5 Hz, 3H), 0.96 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 147.11, 147.05, 134.68, 134.50, 131.44, 131.27, 117.76, 117.70, 109.66, 107.46, 74.15, 68.91, 55.96, 55.77, 45.20, 43.00, 41.97, 38.98, 24.39, 24.00, 21.57.

HRMS (ESI) m/z calcd for $C_{21}H_{30}NaO_3$ (M + Na)$^+$: 353.2087; found: 353.2094.

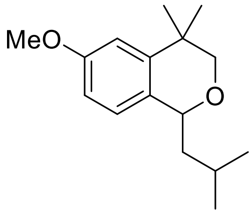


4,4-dibenzyl-1-isobutyl-6,7-dimethoxyisochromane (**3m**): Followed general procedure A, compound **3m** was obtained as a colorless oil in 33% yield.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.22-7.14 (m, 6H), 7.00 (dd, *J* = 7.3, 2.0 Hz, 2H), 6.95 (dd, *J* = 6.5, 2.9 Hz, 2H), 6.44 (s, 1H), 6.42 (s, 1H), 4.59 (dd, *J* = 10.1, 3.0 Hz, 1H), 3.86 (s, 3 H), 3.73 (d, *J* = 11.5 Hz, 1H), 3.65 (s, 3 H), 3.50 (d, *J* = 11.5 Hz, 1H), 3.19-3.12 (m, 1H), 3.00 (d, *J* = 13.5 Hz, 1H), 2.91 (d, *J* = 13.9 Hz, 1H), 1.95-1.85 (m, 1H), 1.51 (ddd, *J* = 14.1, 10.2, 3.9 Hz, 1H), 1.43-1.37 (m, 1H), 0.98 (t, *J* = 6.8 Hz, 3H), 0.89 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 147.03, 146.22, 138.11, 137.77, 131.64, 130.96, 130.64, 127.83, 127.70, 126.11, 126.08, 110.76, 107.31, 74.39, 69.23, 55.71, 55.65, 45.32, 45.25, 43.27, 41.33, 24.27, 24.00, 21.54.

HRMS (ESI) m/z calcd for $C_{29}H_{34}NaO_3$ (M + Na)$^+$: 453.2401; found: 453.2407.

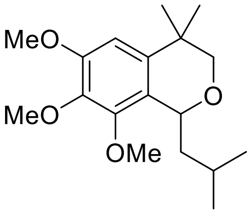


1-isobutyl-6-methoxy-4,4-dimethylisochromane (**3n**): Followed general procedure A, compound **3n** was obtained as a colorless oil in 82% yield.

^{1}H NMR (400 MHz, CDCl$_3$) δ 6.95 (d, *J* = 8.5 Hz, 1H), 6.84 (d, *J* = 2.6 Hz, 1H), 6.71 (dd, *J* = 8.5, 2.7 Hz, 1H), 4.75 (dd, *J* = 10.2, 2.6 Hz, 1H), 3.80 (s, 3H), 3.67 (d, *J* = 11.2 Hz, 1H), 3.47 (d, *J* = 11.2 Hz, 1H), 2.03-1.93 (m, 1H), 1.79 (ddd, *J* = 14.1, 10.3, 3.8 Hz, 1H), 1.55 (ddd, *J* = 14.1, 10.0, 2.8 Hz, 1H), 1.30 (s, 3H), 1.22 (s, 3H), 1.02 (d, *J* = 6.5 Hz, 3H), 0.95 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 157.98, 144.71, 130.00, 125.59, 111.20, 110.87, 74.54, 73.83, 55.17, 45.39, 33.95, 28.30, 26.37, 24.43, 24.02, 21.56.

HRMS (ESI) m/z calcd for $C_{16}H_{25}O_2$ (M + H)$^+$: 249.1855; found: 249.1831

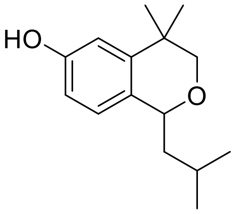


1-isobutyl-6,7,8-trimethoxy-4,4-dimethylisochromane (**3o**): Followed general procedure A, compound **3o** was obtained as a pale yellow oil in 73% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.59 (s, 1H), 4.89 (dd, *J* = 10.5, 2.0 Hz, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 3.84 (s, 3H), 3.69 (d, *J* = 11.4 Hz, 1H), 3.38 (d, *J* = 11.4 Hz, 1H), 1.99-1.89 (m, 1H), 1.81 (ddd, *J* = 14.2, 10.6, 3.6 Hz, 1H), 1.56-1.49 (m, 1H), 1.25 (s, 3H), 1.23 (s, 3H), 1.05 (d, *J* = 6.5 Hz, 3H), 0.96 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 152.06, 149.06, 139.80, 138.53, 123.88, 104.02, 70.91, 70.32, 60.61, 60.29, 55.93, 42.39, 33.35, 29.31, 25.63, 24.87, 23.88, 21.17.

HRMS (ESI) m/z calcd for $C_{18}H_{28}NaO_4$ (M + Na)$^+$: 331.1880; found: 331.1874.

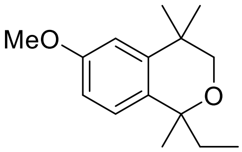


1-isobutyl-4,4-dimethylisochroman-6-ol (**3p**): Followed general procedure A, compound **3p** was obtained as a pale yellow oil in 28% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 (d, *J* = 8.4 Hz, 1H), 6.78 (d, *J* = 2.6 Hz, 1H), 6.63 (dd, *J* = 8.4, 2.6 Hz, 1H), 5.16 (s, 1H), 4.76 (dd, *J* = 10.2, 2.6 Hz, 1H), 3.67 (d, *J* = 11.2 Hz, 1H), 3.47 (d, *J* = 11.2 Hz, 1H), 2.02-1.93 (m, 1H), 1.79 (ddd, *J* = 14.1, 10.3, 3.8 Hz, 1H), 1.53 (ddd, *J* = 14.2, 10.0, 2.8 Hz, 1H), 1.27 (d, *J* = 4.8 Hz, 3H), 1.20 (s, 3H), 1.01 (d, *J* = 6.5 Hz, 3H), 0.95 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 154.03, 144.91, 129.85, 125.84, 113.07, 111.94, 74.62, 73.64, 45.34, 33.85, 28.16, 26.45, 24.43, 24.00, 21.56.

HRMS (ESI) m/z calcd for $C_{15}H_{23}O_2$ (M + H)$^+$: 235.1698; found: 235.1687.



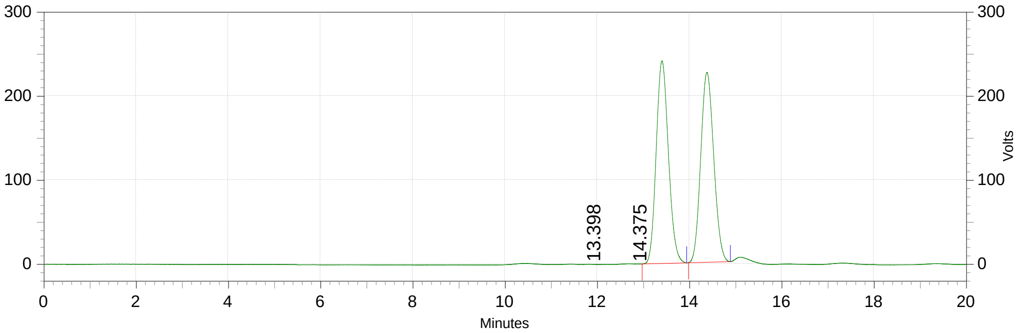
1-ethyl-6-methoxy-1,4,4-trimethylisochromane （**3q**）: (*S*)-2-butanol was used and followed general procedure A, compound **3q** was obtained as a colorless oil in 56% yield and 0% *ee*. The *ee* was determined by chiral stationary phase HPLC analysis [Daicel Chiralcel OJ-H, isopropanol/hexane = 2/98, 0.3 mL/min, λ= 220 nm, t_R = 11.46min, t_R = 13.24 min].

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (d, *J* = 8.6 Hz, 1H), 6.83 (d, *J* = 2.5 Hz, 1H), 6.72 (dd, *J* = 8.6, 2.5 Hz, 1H), 3.80 (s, 2H), 3.63 (d, *J* = 11.4 Hz, 1H), 3.51 (d, *J* = 11.4 Hz, 1H), 1.97 - 1.88 (m, 1H), 1.82 – 1.69 (m, 1H), 1.45 (s, 3H), 1.28 (s, 3H), 1.23 (s, 3H), 0.81 (t, *J* = 7.3 Hz, 3H).

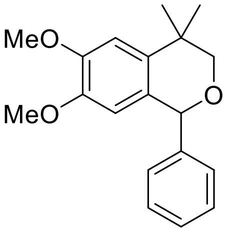
^{13}C NMR (101 MHz, $CDCl_3$) δ 157.73 (s), 144.62 (s), 133.09 (s), 126.22 (s), 111.44 (s), 110.50 (s), 77.18 (s), 70.51 (s), 55.14 (s), 35.01 (s), 34.03 (s), 27.95 (s), 27.28 (s), 26.42 (s), 8.26 (s).

HRMS (ESI) m/z calcd for $C_{15}H_{23}O$ $(M + H)^+$: 235.1698, found: 235.1689.

HPLC



RT (min)	Area	Area (%)	Height	Height (%)
13.398	4446004	50.140	240869	51.608
14.375	4421207	49.860	225863	48.392



6,7-dimethoxy-4,4-dimethyl-1-phenylisochromane (**3j**): To a solution of 2-(3,4-dimethoxyphenyl)-2-methylpropanal **1a** (0.2 mmol) and benzyl alcohol (1.0 mmol) in toluene (2 mL) was $BF_3.Et_2O$ (200 mol%) at room temperature, then the reaction mixture was stirred for 16 h at 110 ℃ under nitrogen atmosphere. After completion of the reaction, the reaction was stopped by adding saturated aqueous $NaHCO_3$ (2 mL). The crude products were extracted with EtOAc (3×5 mL) and the combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by preparative TLC with 10% EtOAc/ petroleum ether as eluent to give the title compound 3j as a colorless oil in 25% yield.

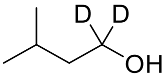
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.01 (m, 5H), 6.84 (s, 1H), 6.17 (s, 1H), 5.69 (s, 1H), 3.90 (s, 3H), 3.72 (d, J = 11.2 Hz, 1H), 3.62 (s, 3H), 3.61 (d, J = 11.2 Hz, 1H), 1.41 (s, 3H), 1.28 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 148.07, 146.93, 142.16, 135.82, 128.89, 128.38, 128.10, 127.82, 109.32, 108.02, 80.23, 75.01, 55.89, 55.75, 33.36, 29.02, 26.16.

HRMS (ESI) m/z calcd for $C_{19}H_{22}NaO_3$ $(M + Na)^+$: 321.1461; found: 321.1466.

5. D-labeling experiments

The starting material ethanol-d6 **[D$_6$]-2d** was commercially available synthesized and 3-methyl-1-butanol-1,1-d2 **[D$_2$]-2a** according to the reported procedure.[6]



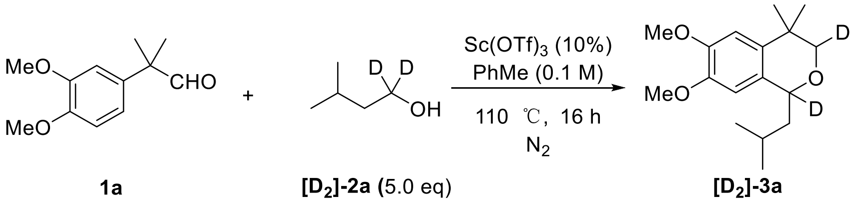
3-methyl-1-butanol-1,1-d2 (**[D$_2$]-2a**)

Colorless oil

Yield: 97%

^{1}H NMR (400 MHz, CDCl$_3$) δ 1.77-1.69 (m, 1H), 1.46 (d, *J* = 7.0 Hz, 2H), 0.92 (d, *J* = 6.6 Hz, 6H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 41.55, 29.70, 24.66, 22.61.

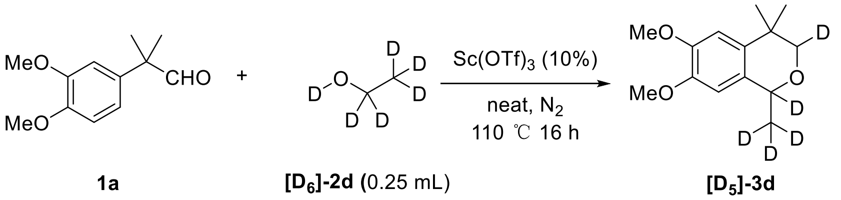


To a solution of **1a** (0.2 mmol) and **[D$_2$]-2a** (1.0 mmol) in toluene (2 mL) was Sc(OTf)$_3$ (10 mol%) at room temperature, then the reaction mixture was stirred for 16 h at 110 ℃ under nitrogen atmosphere. After completion of the reaction, the reaction was stopped by adding saturated aqueous NaHCO$_3$ (2 mL). The crude products were extracted with EtOAc (3×5 mL) and the combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by flash chromatography over silica gel with 5% EtOAc/ petroleum ether as eluent to give the title compound **[D$_2$]-3a** as a colorless oil in 68% yield.

^{1}H NMR (400 MHz, CDCl$_3$) δ 6.79 (s, 1H), 6.48 (s, 1H), 3.88 (s, 1H), 3.85 (s, 1H), 3.65 (s, 0.5H), 3.44 (s, 0.5H), 2.051.95 (m, 1H), 1.83-1.79 (m, 1H), 1.51 (ddd, *J* = 14.2, 10.0, 2.1 Hz, 1H), 1.29 (s, 3H), 1.22 (s, 3H), 1.04 (d, *J* = 6.5 Hz, 3H), 0.97 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 147.59, 146.99, 135.39, 129.75, 108.30, 108.30, 107.46, 107.46, 33.24, 28.03, 27.97, 26.66, 26.60, 24.42, 24.02, 21.53.

HRMS (ESI) m/z calcd for $C_{17}H_{25}D_2O_3$ (M + H)$^+$: 281.2080; found: 281.2083.



A 10 mL reaction tube was charged with **1a** (0.2 mmol), **[D$_6$]-2d** (0.25 mL) and Sc(OTf)$_3$ (10 mol%) at room temperature, then the reaction mixture was stirred for 16 h at 110 ℃ under nitrogen atmosphere. After completion of the reaction, the reaction was stopped by adding saturated aqueous NaHCO$_3$ (5 mL). The crude products were extracted with EtOAc (3×5 mL) and the combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by flash chromatography over silica gel with 5% EtOAc/ petroleum ether as eluent to give the title compound **[D$_5$]-3d** as a colorless oil in 45% yield.

^{1}H NMR (400 MHz, CDCl$_3$) δ 6.79 (s, 1H), 6.51 (s, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 3.66 (s, 0.5H), 3.50 (s, 0.5H), 1.32 (s, 3H), 1.20 (s, 3H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 147.74, 147.15, 135.23, 130.24, 108.34, 107.42, 55.96, 55.89, 33.41, 29.04, 25.69.

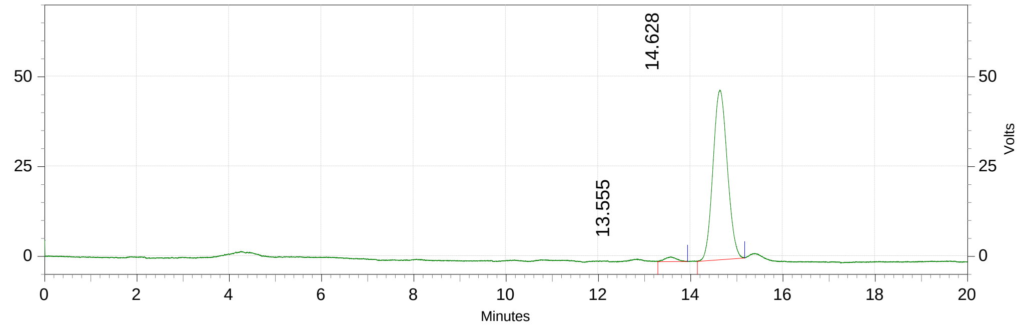
HRMS (ESI) m/z calcd for $C_{14}H_{16}D_5O_3$ (M + H)$^+$: 242.1799; found: 242.1799.

6. Racemization of 3q .

Racemic **3q** was separated by chiral stationary phase HPLC to give analyzable amount of enantiomeric **3q** with 96% *ee*. Then, the enantiomeric **3q** was respectively subjected to the following reactions: (1) **3q** with 88% *ee* was observed in the presence of Sc(OTf)$_3$ with n-hexane as solvent at 50 ℃ for one hour. (2) **3q** with 50% *ee* was observed in the presence of Sc(OTf)$_3$ with n-hexane as solvent at

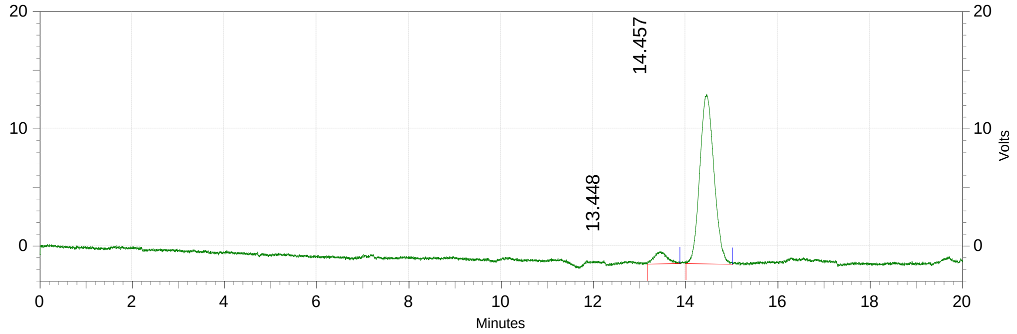
110 ℃ for one hour.

(a) enantiomeric **3q**



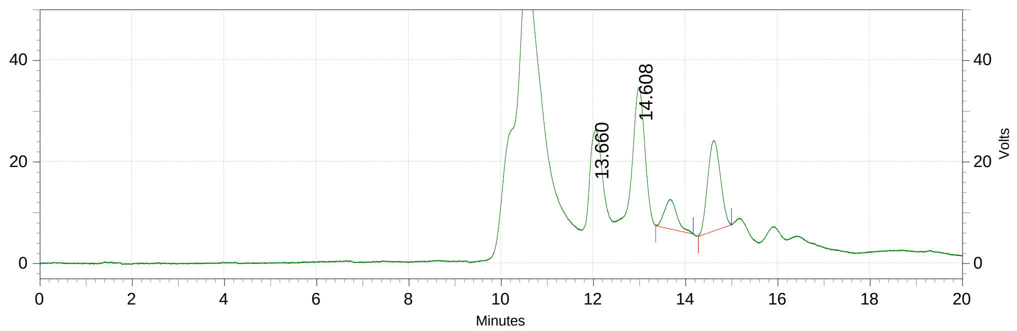
RT (min)	Area	Area (%)	Height	Height (%)
13.555	23291	2.234	1317	2.713
14.628	1019215	97.766	47223	97.287

(b) **3q** obtained at 50 ℃



RT (min)	Area	Area (%)	Height	Height (%)
13.448	20506	6.207	1062	6.831
14.457	309856	93.793	14484	93.169

(c) **3q** obtained at 110 ℃



RT (min)	Area	Area (%)	Height	Height (%)
13.660	110974	24.396	5856	24.750
14.608	343916	75.604	17805	75.250

References

1 M. Yamashita, Y. Ono, H. Tawada, *Tetrahedron* **2004**; 60: 2843-2849.

2 S. Agarwal, A. Patil, U. Aware, P. Deshmukh, B. Darji, S. Sasane, K. V. V. M. Sairam, P. Priyadarsiny, P. Giri, H. Patel, S. Giri, M. Jain, R. C. Desai, *Acs. Med. Chem. Lett.* **2016**; 7: 51-55.

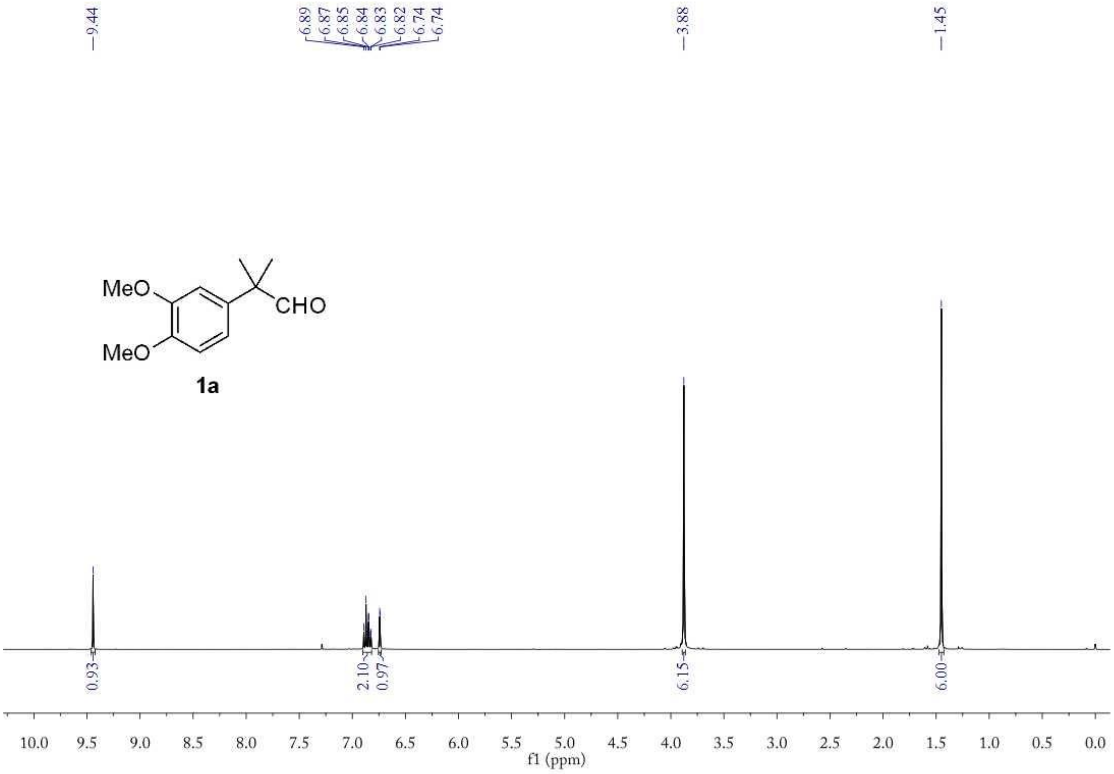
3 H. Kuntzel, H. Wolf, Schaffne.K, *Helv. Chim. Acta.* **1971**; 54: 868-&.

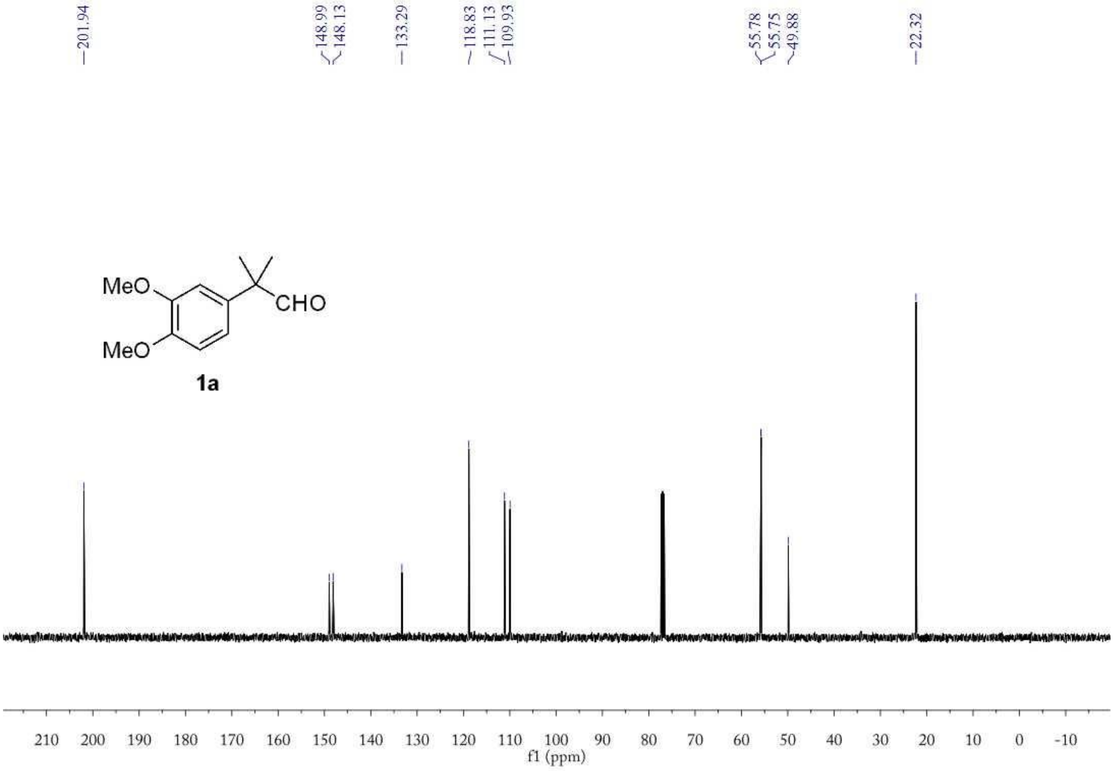
4 M. K. J. ter Wiel, S. Odermatt, P. Schanen, P. Seiler, F. Diederich, *Eur. J. Org. Chem.* **2007**: 3449-3462.

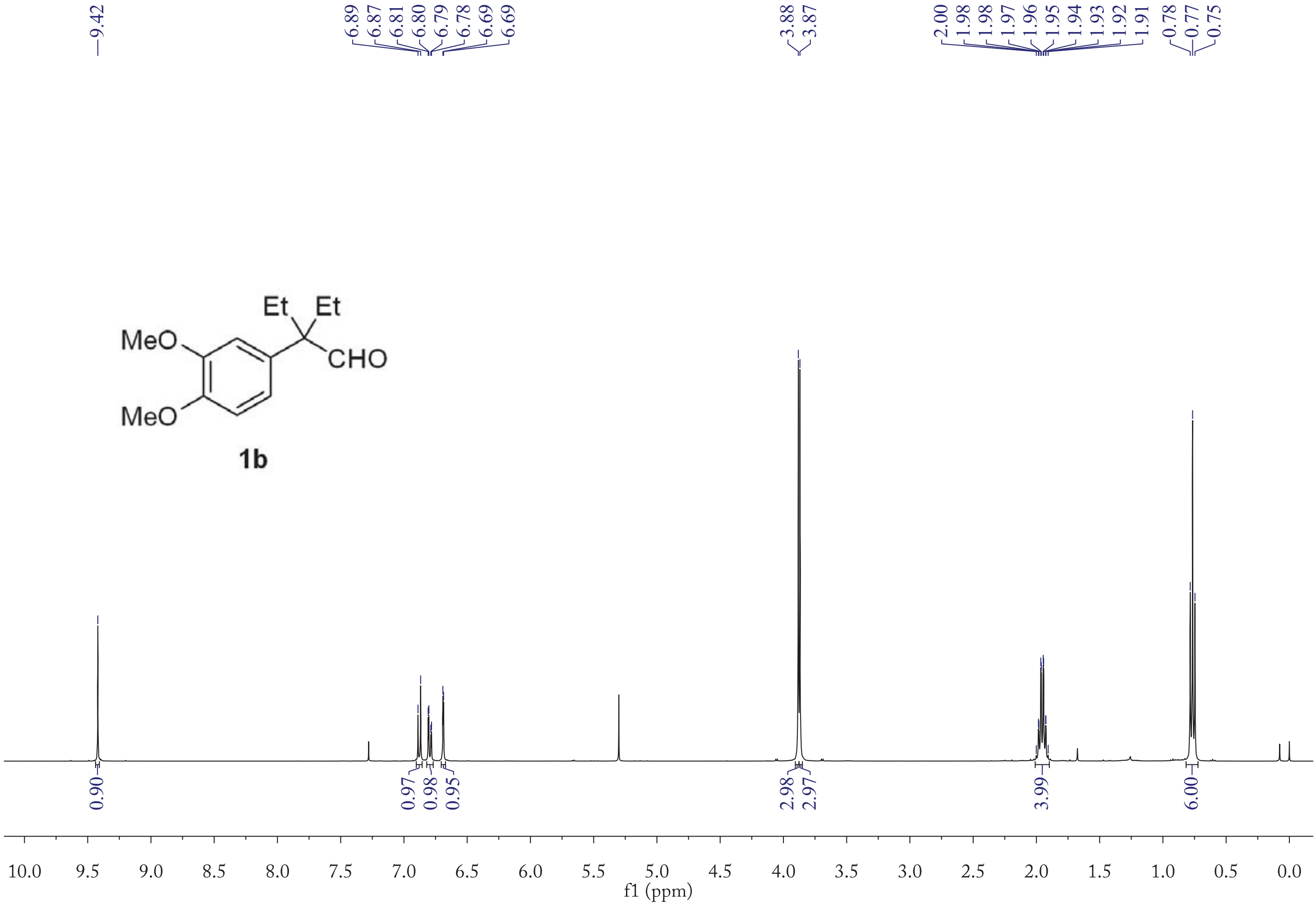
5 C. Maurin, F. Bailly, P. Cotelle, *Tetrahedron* **2005**; 61: 7054-7058.

6 A. V. Kel'in, A. W. Sromek, V. Gevorgyan, *J. Am. Chem. Soc.* **2001**; 123: 2074-2075.

Copies of f 1H and 13C NMR spectra



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6.79
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6.69
3.88
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1.98
1.98
1.97
1.96
1.95
1.94
1.93
1.92
1.91
0.78
0.77
0.75
Et
Et
MeO
CHO
MeO
1b
0.90
0.97
0.98
0.95
2.98
2.97
3.99
6.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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3.5
3.0
2.5
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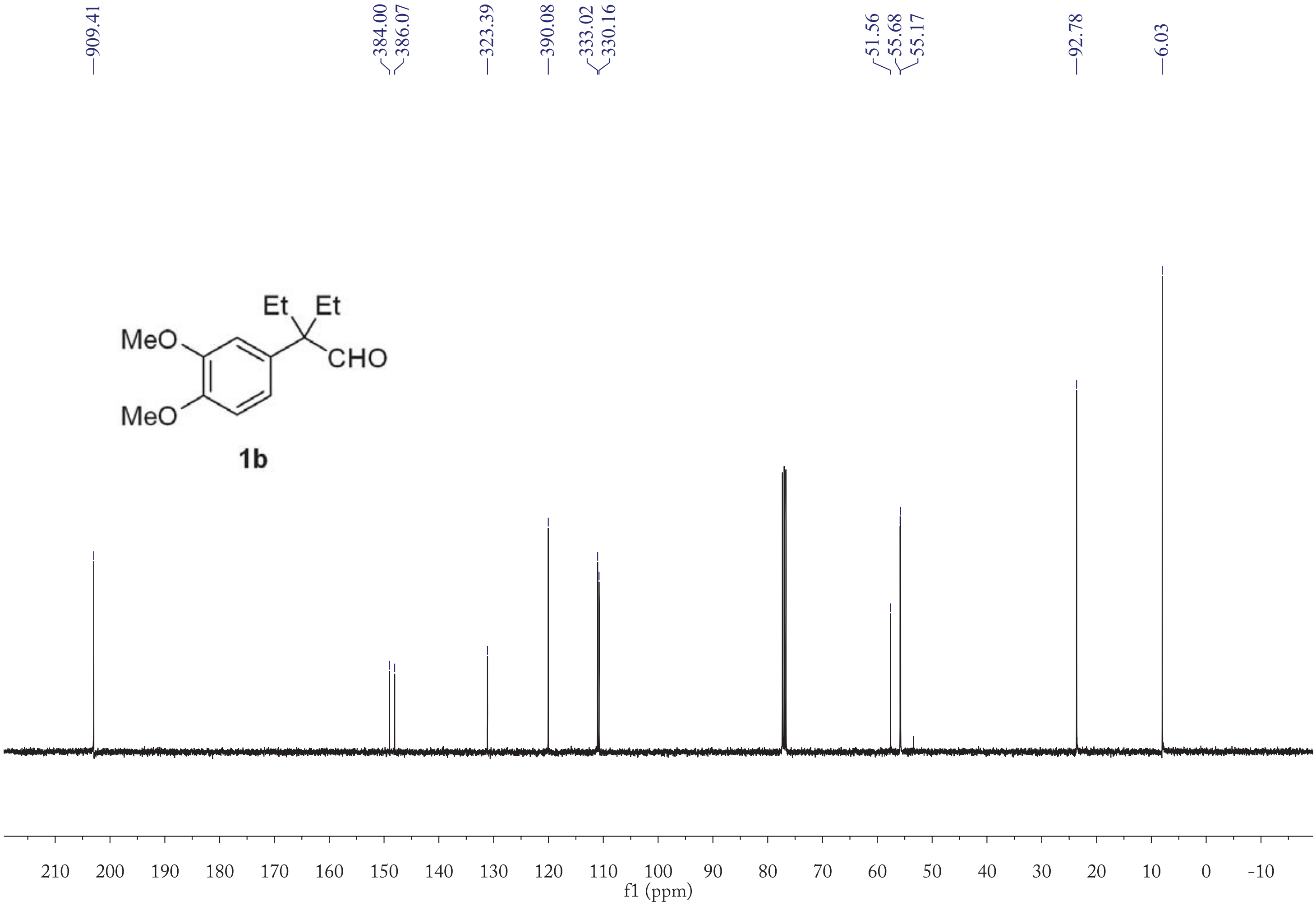
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390.08
333.02
330.16
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55.17
92.78
6.03
Et
Et
MeO
CHO
MeO
1b
210
200
190
180
170
160
150
140
130
120
110
100
90
80
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50
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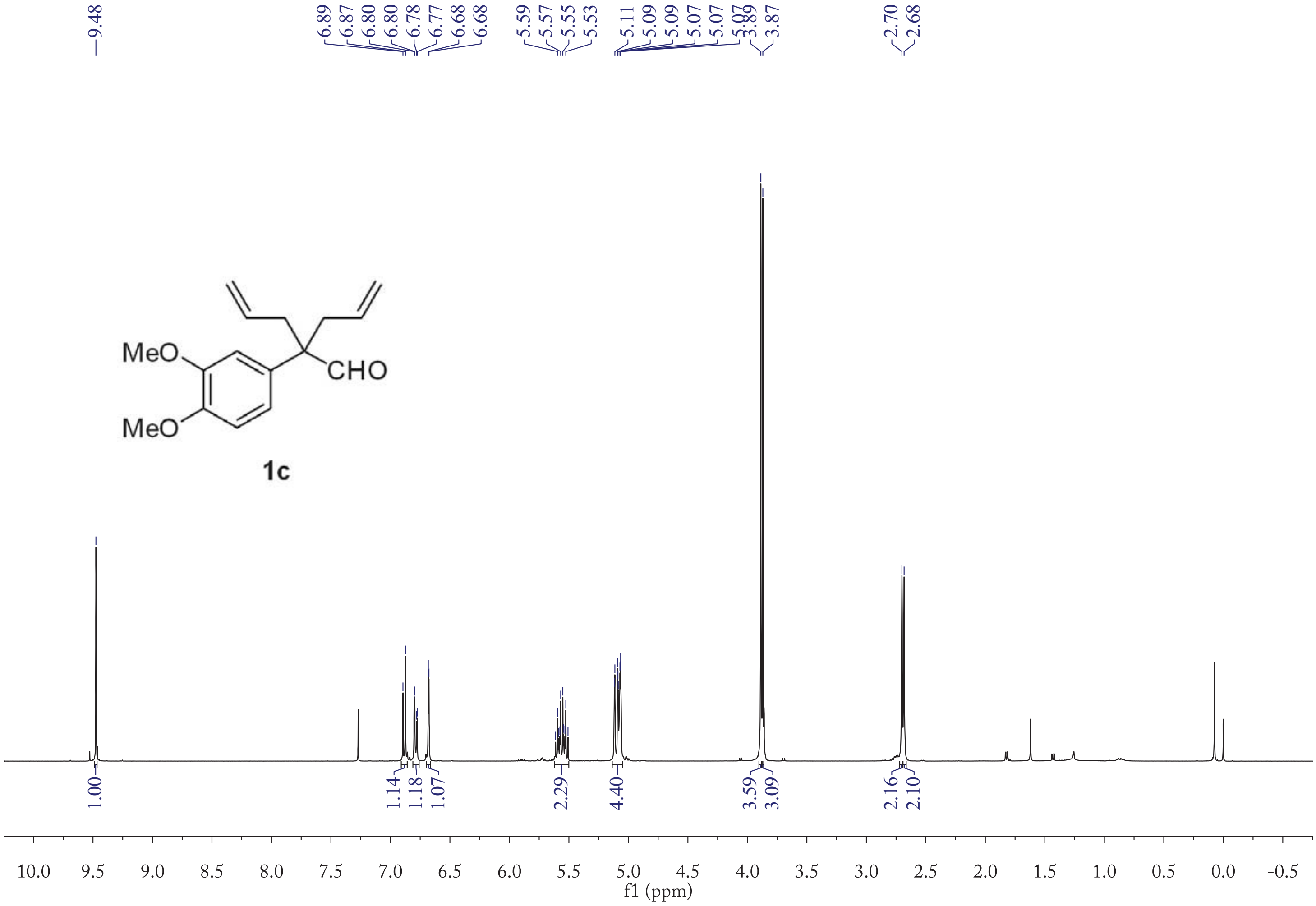
f1 (ppm)



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6.87
6.80
6.80
6.78
6.77
6.68
6.68
5.59
5.57
5.55
5.53
5.11
5.09
5.09
5.07
5.07
5.07
3.89
3.87
2.70
2.68
MeO
MeO
CHO
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1.14
1.18
1.07
2.29
4.40
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3.09
2.16
2.10
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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3.0
2.5
2.0
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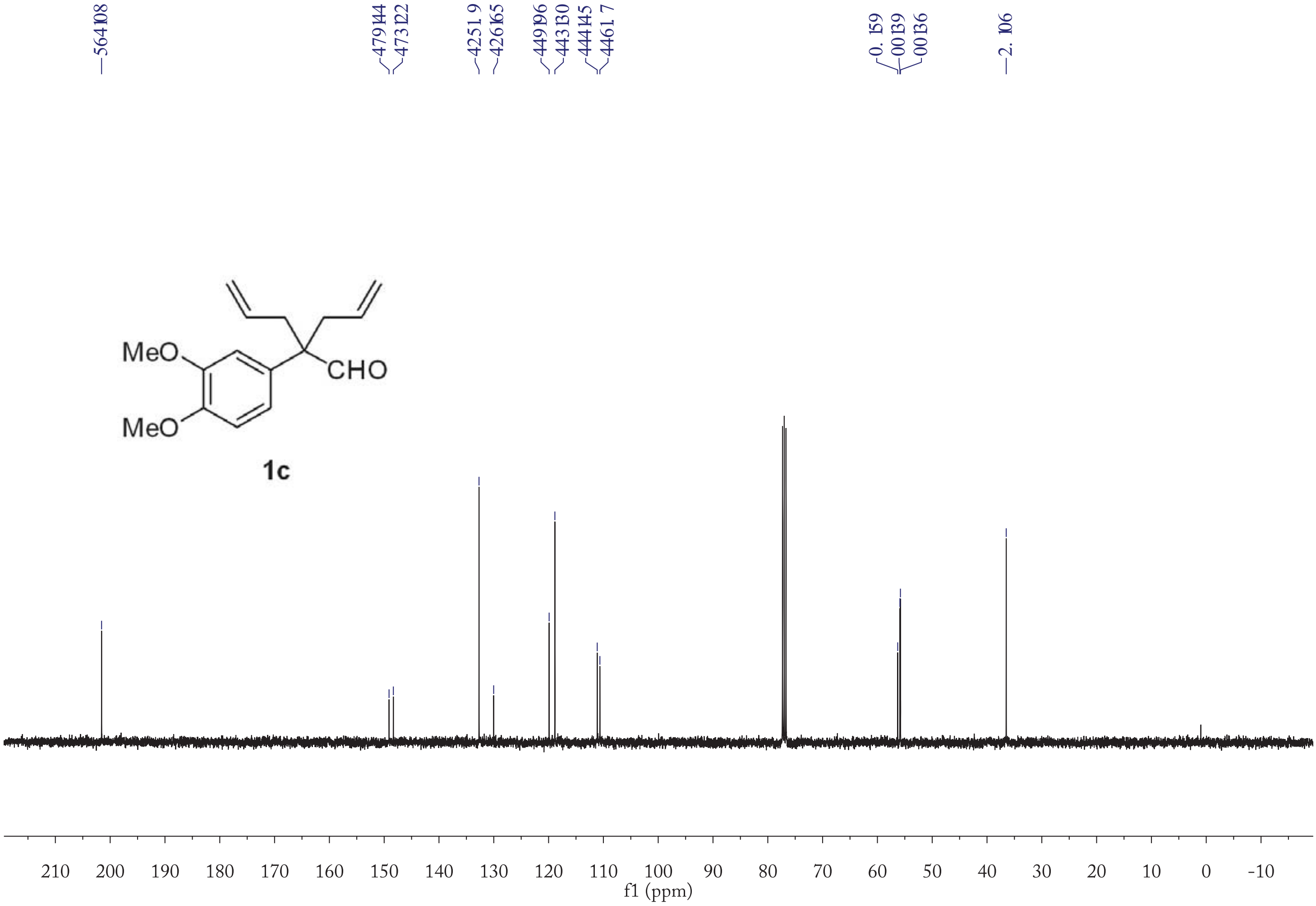
f1 (ppm)



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4251 9
426165
449196
443130
444145
4461 7
0. 159
00139
00136
2. 106
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MeO
CHO
1c
210
200
190
180
170
160
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120
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100
90
80
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60
50
40
30
20
10
0
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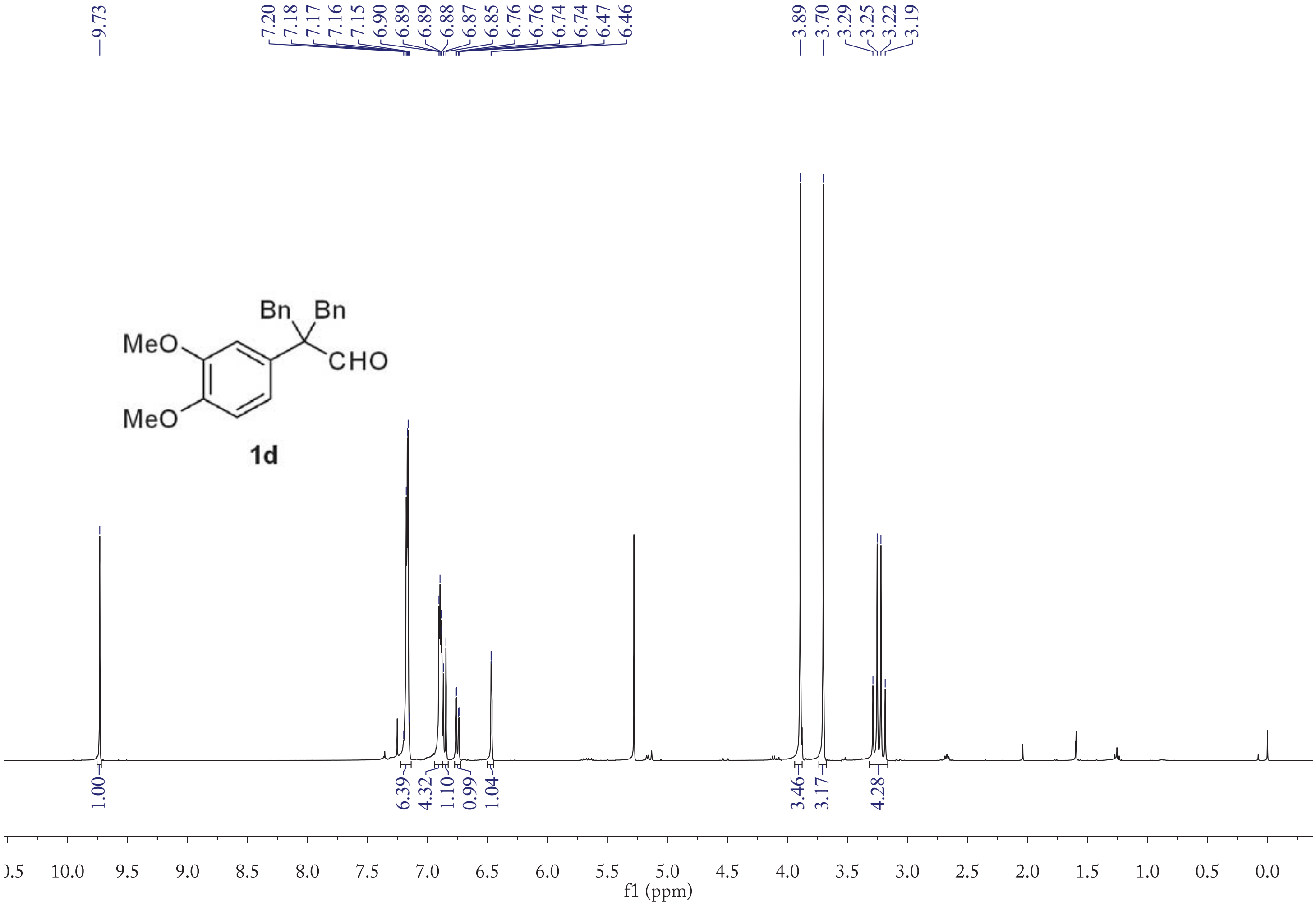
f1 (ppm)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6.76
6.74
6.74
6.47
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3.25
3.22
3.19
Bn
Bn
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CHO
MeO
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6.39
4.32
1.10
0.99
1.04
3.46
3.17
4.28
0.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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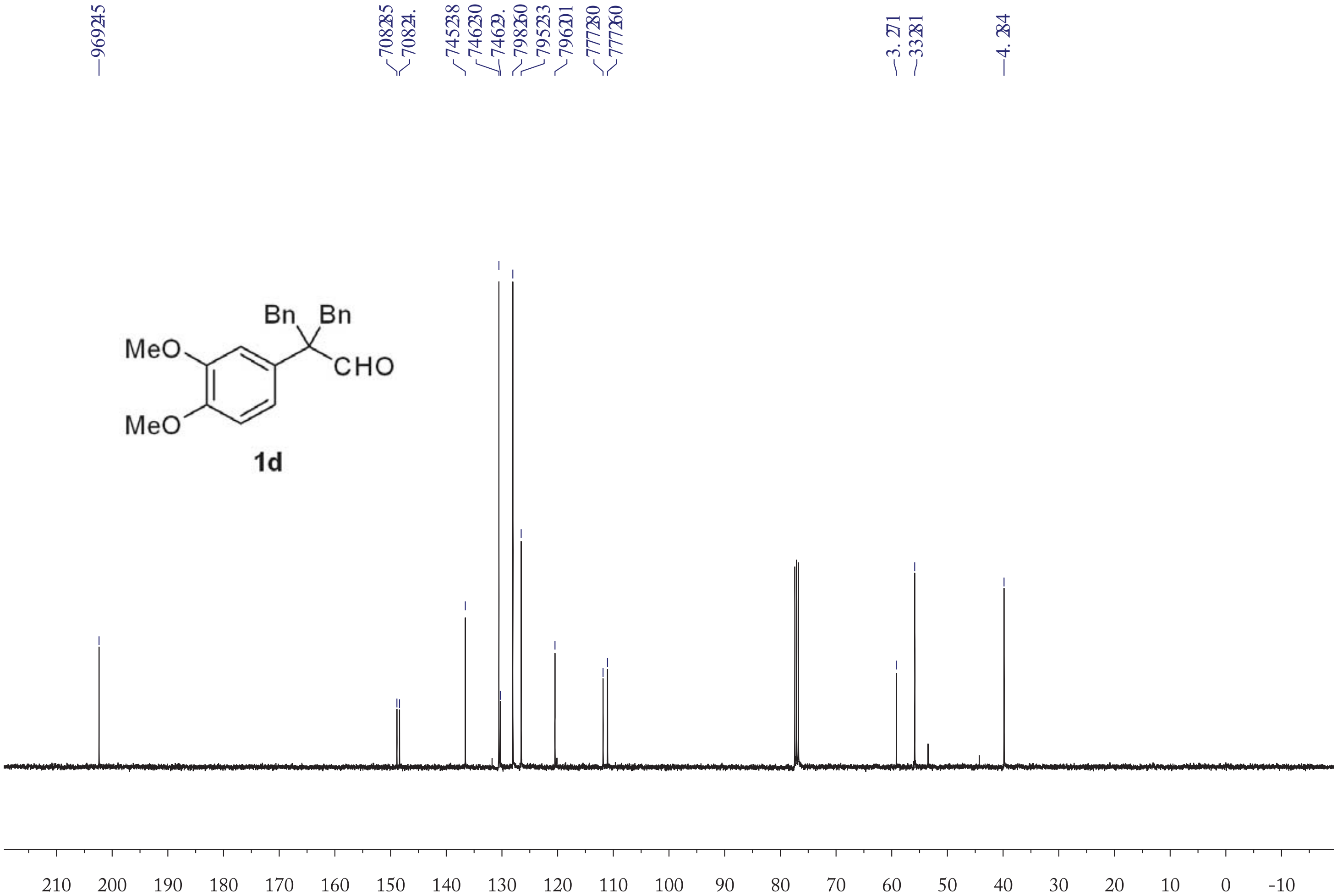
f1 (ppm)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7462 9.
7982 60
7952 33
7962 01
7772 80
7772 60
3. 271
332 81
4. 284
Bn
Bn
MeO
CHO
MeO
1d
210
200
190
180
170
160
150
140
130
120
110
100
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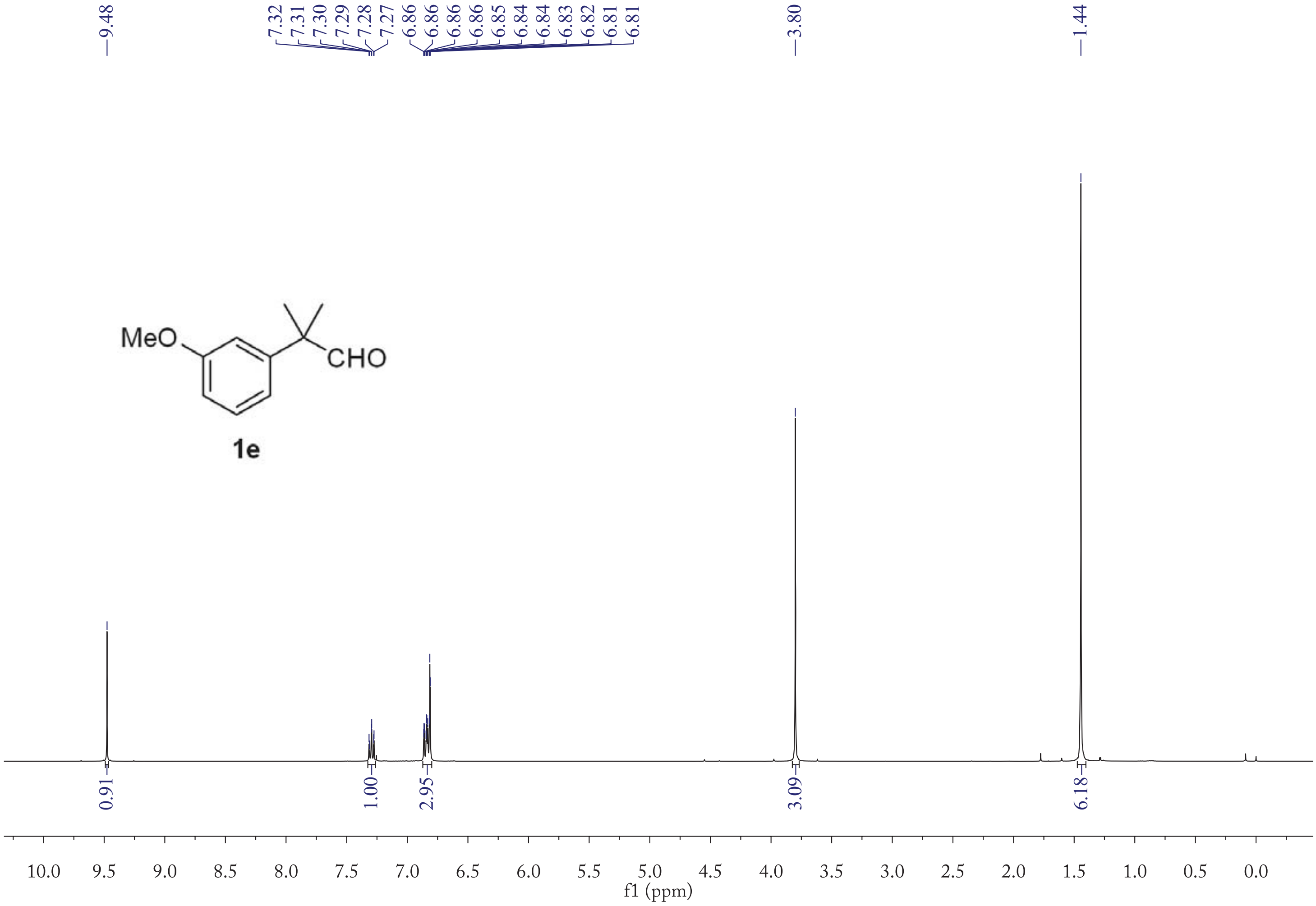
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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7.29
7.28
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6.86
6.86
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6.84
6.84
6.83
6.82
6.81
6.81
3.80
1.44
MeO
CHO
1e
0.91
1.00
2.95
3.09
6.18
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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4.5
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3.5
3.0
2.5
2.0
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1.0
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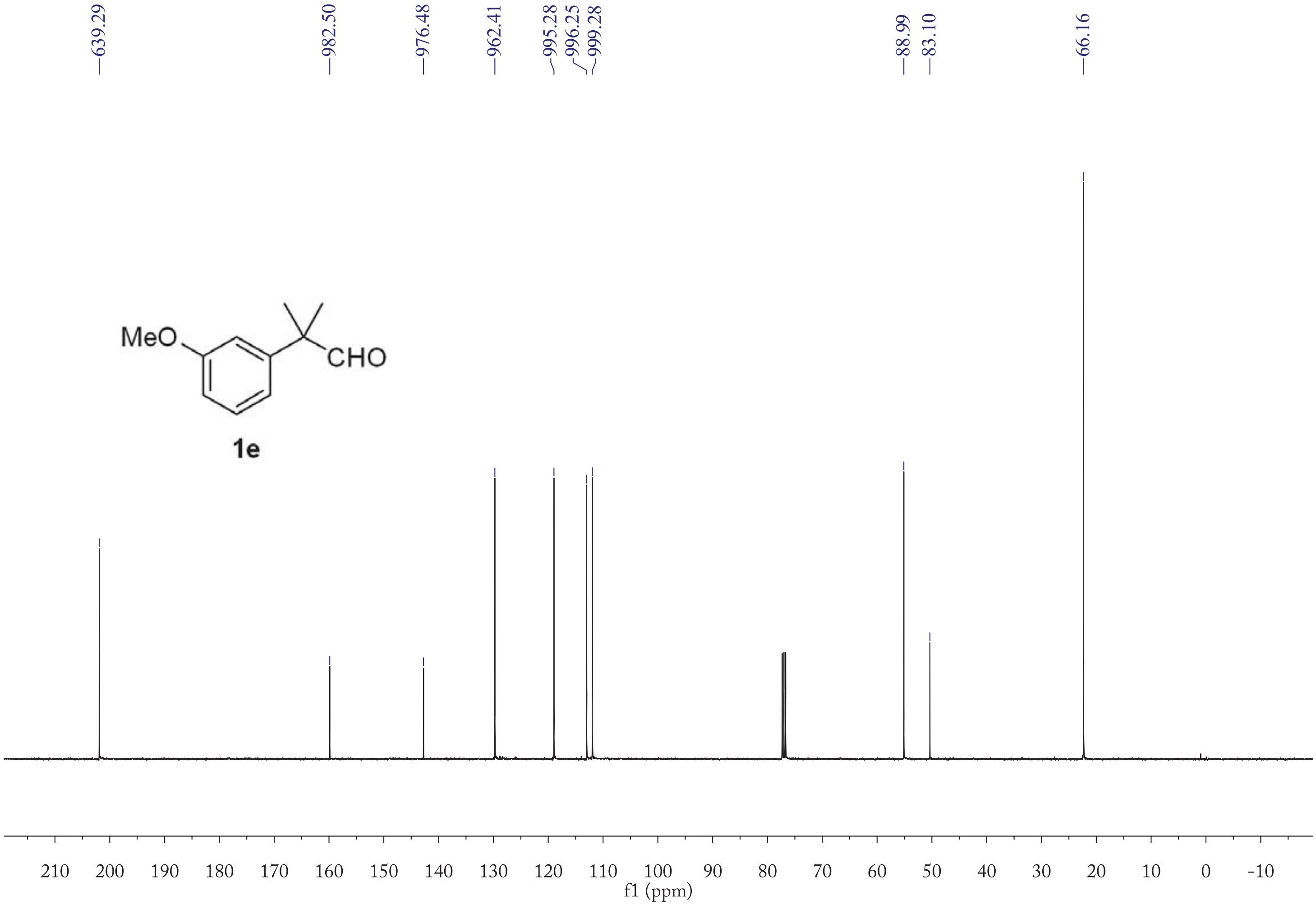
0.0
f1 (ppm)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66.16
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210
200
190
180
170
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120
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80
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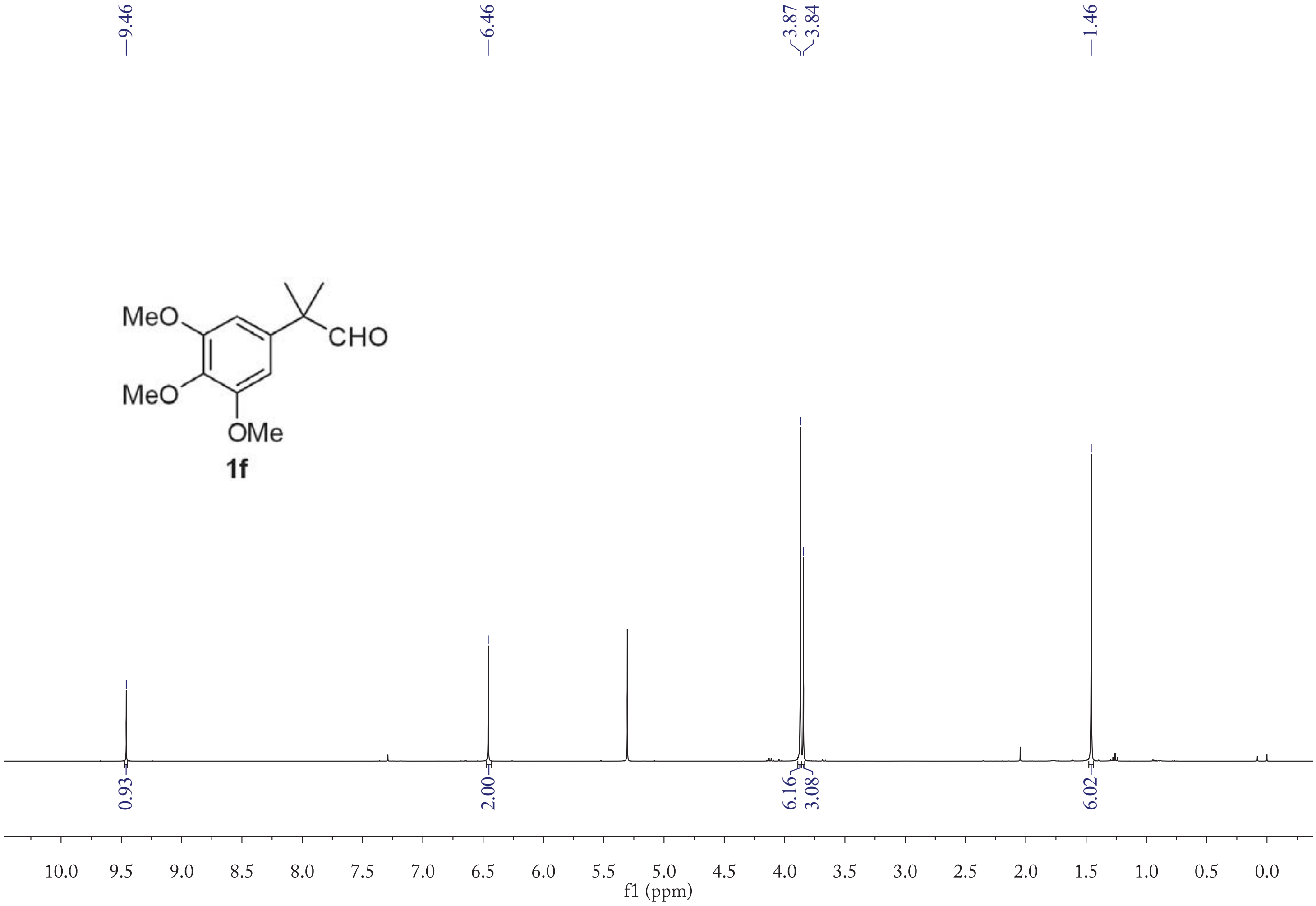
40
30
20
10
0
-10
f1 (ppm)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6.02
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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3.5
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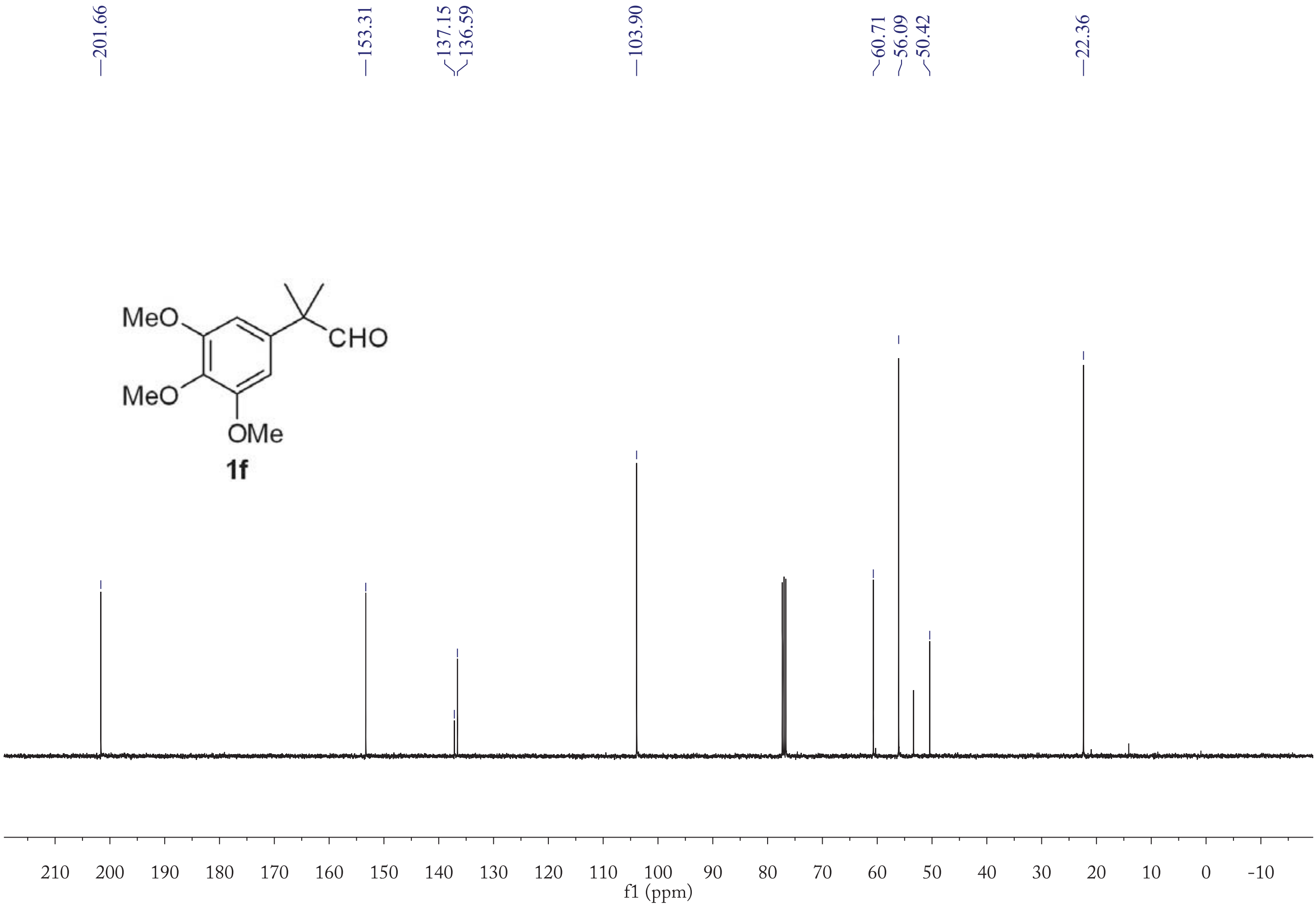
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1f
210
200
190
180
170
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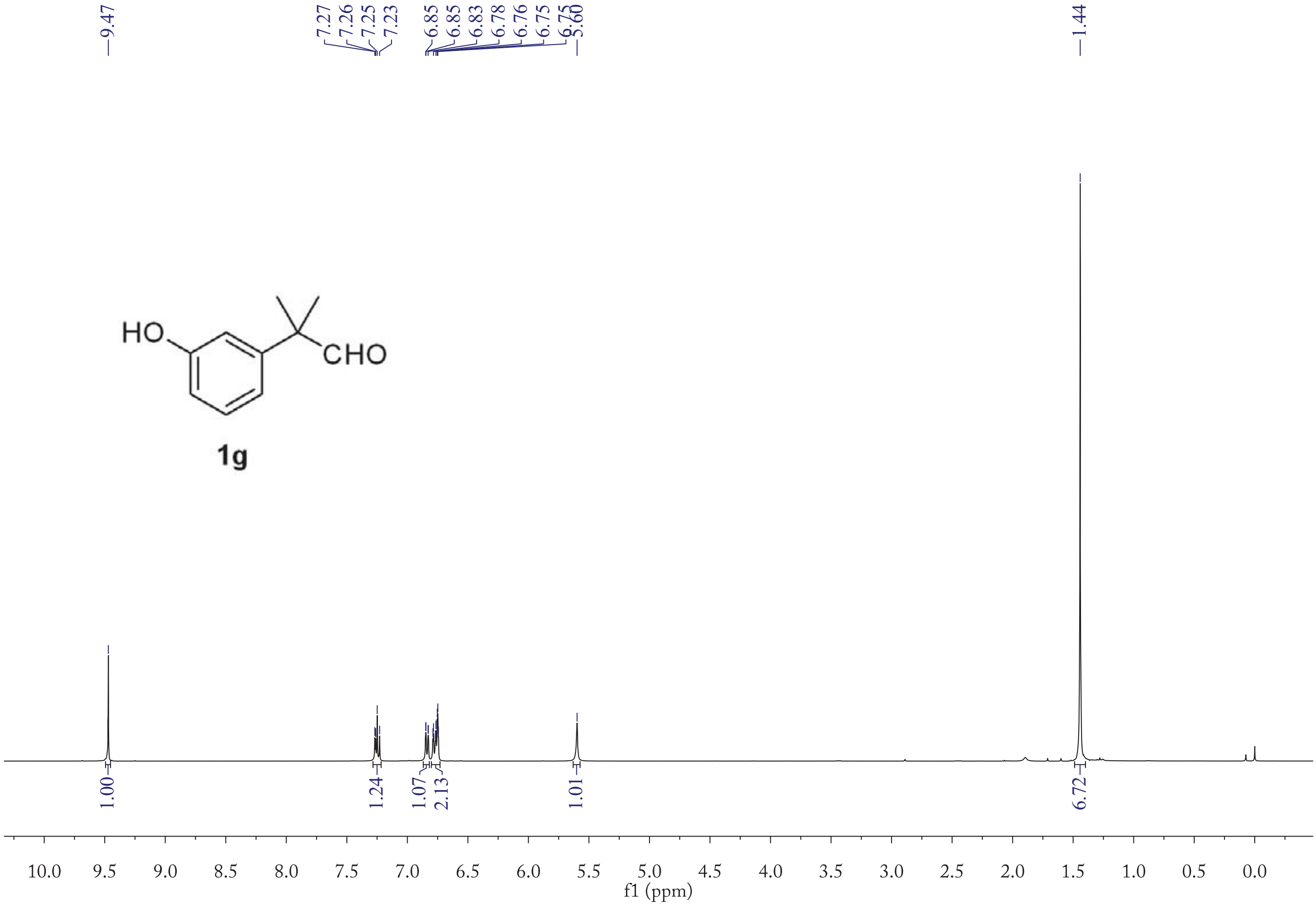
f1 (ppm)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5.60
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CHO
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1.24
1.07
2.13
1.01
6.72
10.0
9.5
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8.5
8.0
7.5
7.0
6.5
6.0
5.5
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4.5
4.0
3.5
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2.5
2.0
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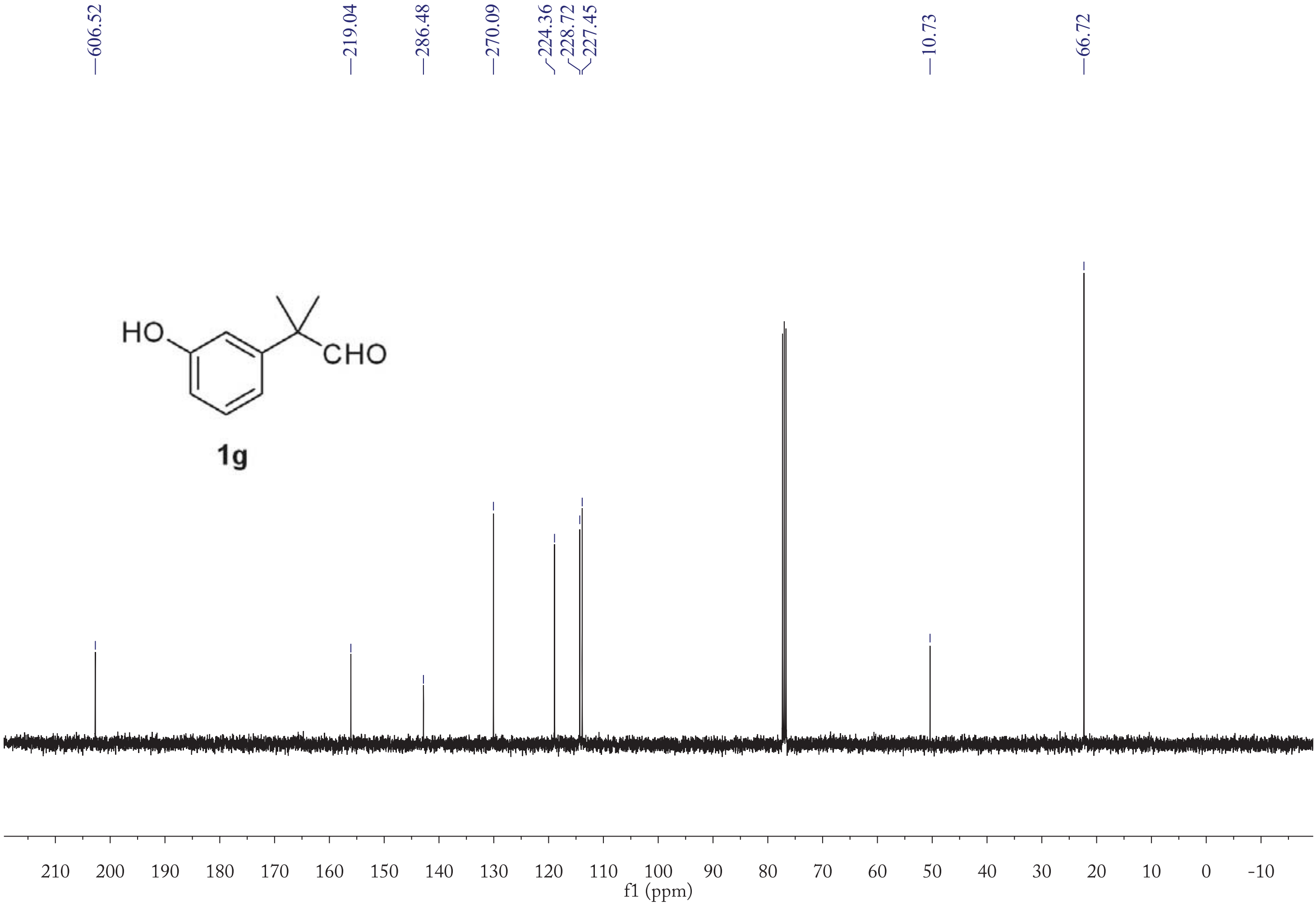
f1 (ppm)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HO
CHO
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200
190
180
170
160
150
140
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120
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100
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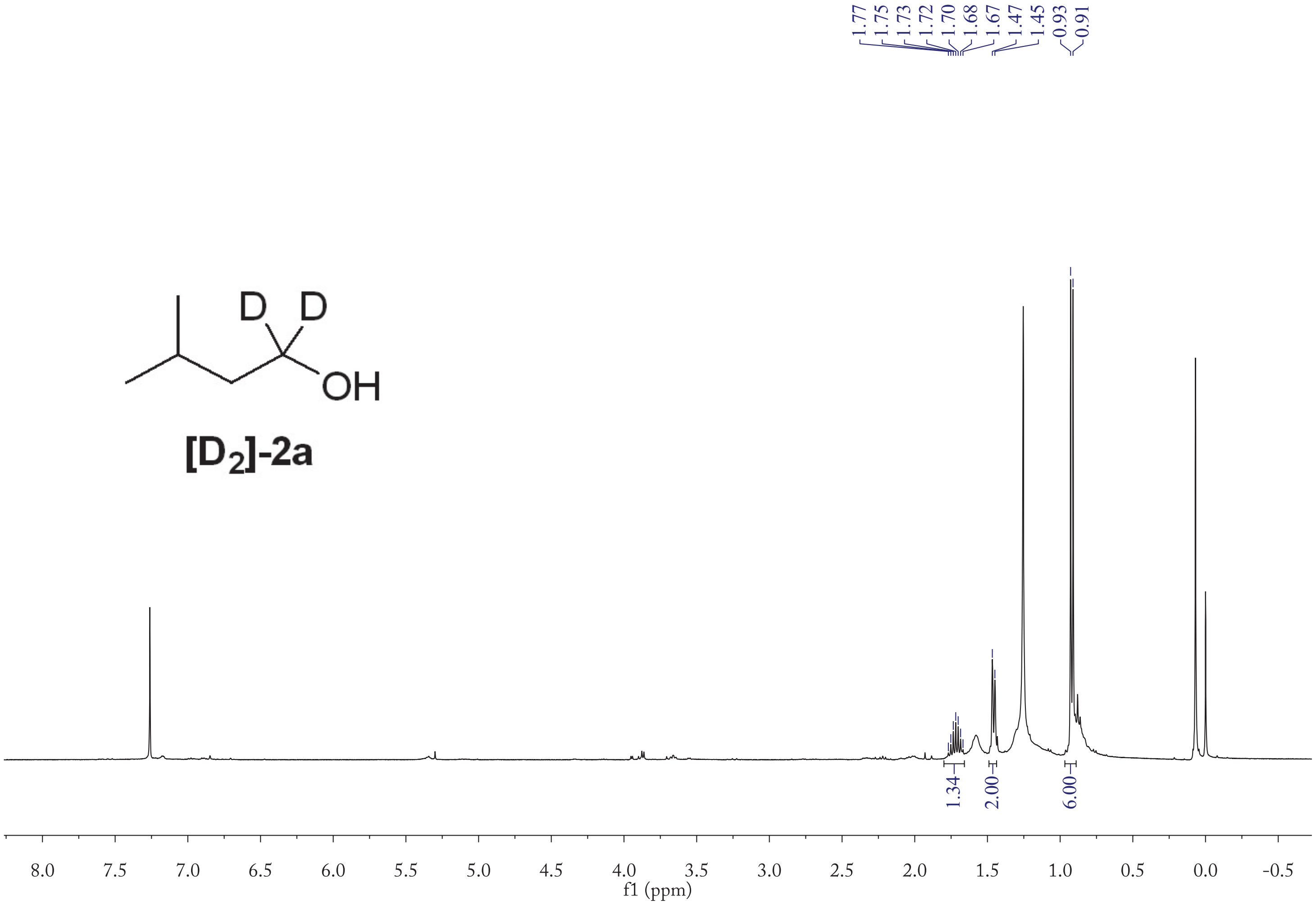
40
30
20
10
0
-10
f1 (ppm)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OH
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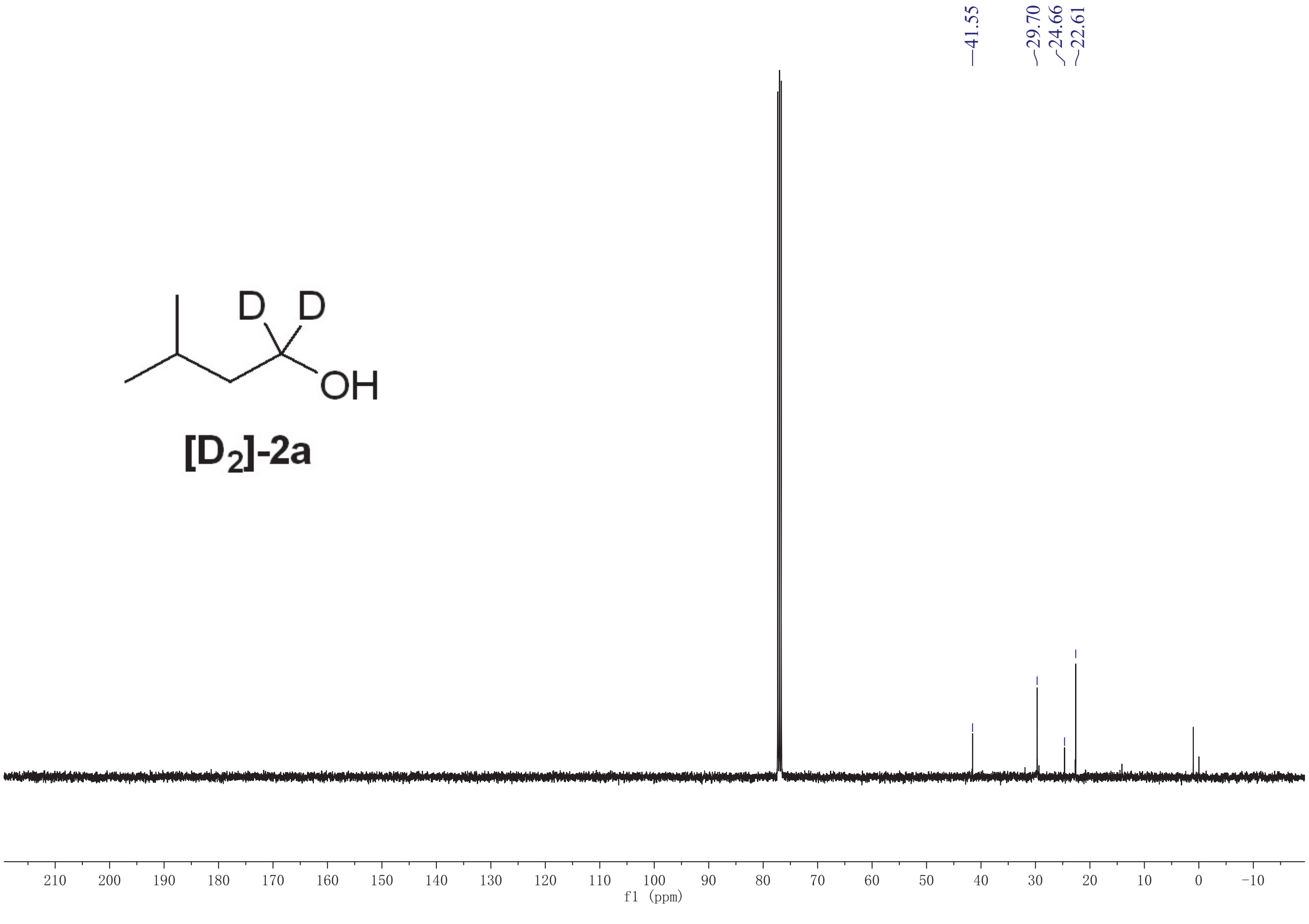
f1 (ppm)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D
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200
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120
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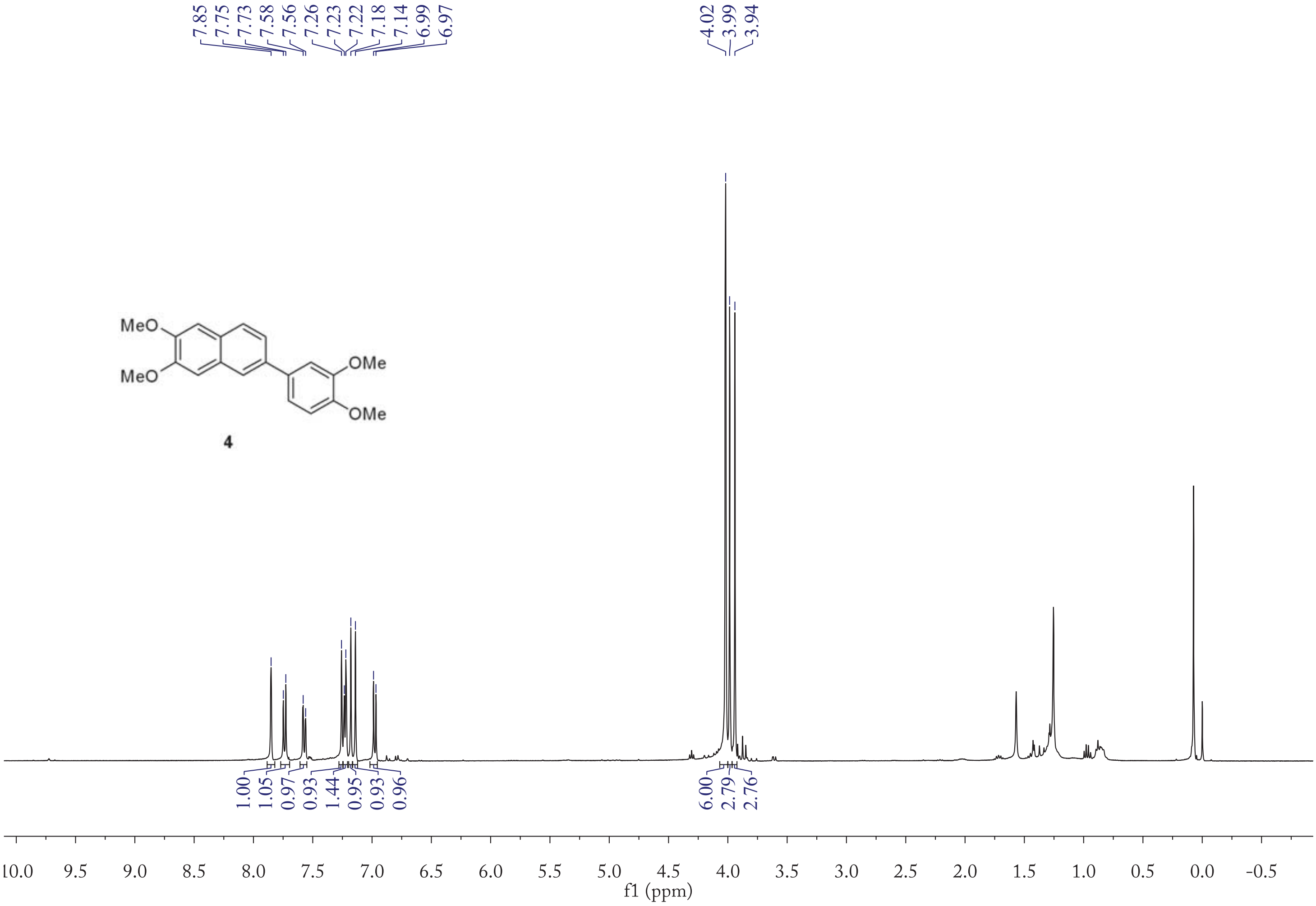
f1 (ppm)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4.02
3.99
3.94
MeO
MeO
OMe
OMe
4
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1.05
0.97
0.93
1.44
0.95
0.93
0.96
6.00
2.79
2.76
10.0
9.5
9.0
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7.0
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5.5
5.0
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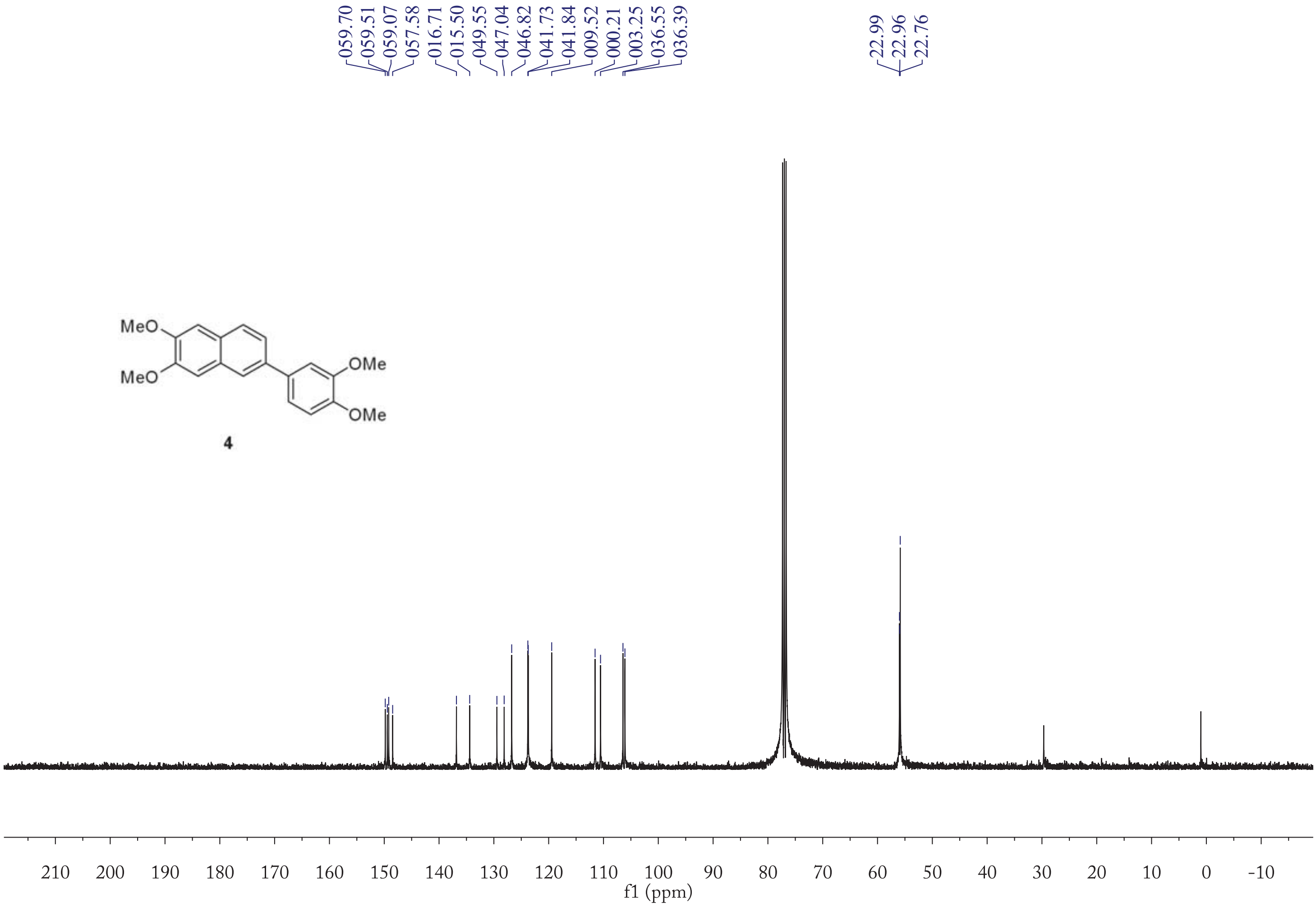
f1 (ppm)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047.04
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041.73
041.84
009.52
000.21
003.25
036.55
036.39
22.99
22.96
22.76
MeO
MeO
OMe
OMe
4
210
200
190
180
170
160
150
140
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100
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80
70
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40
30
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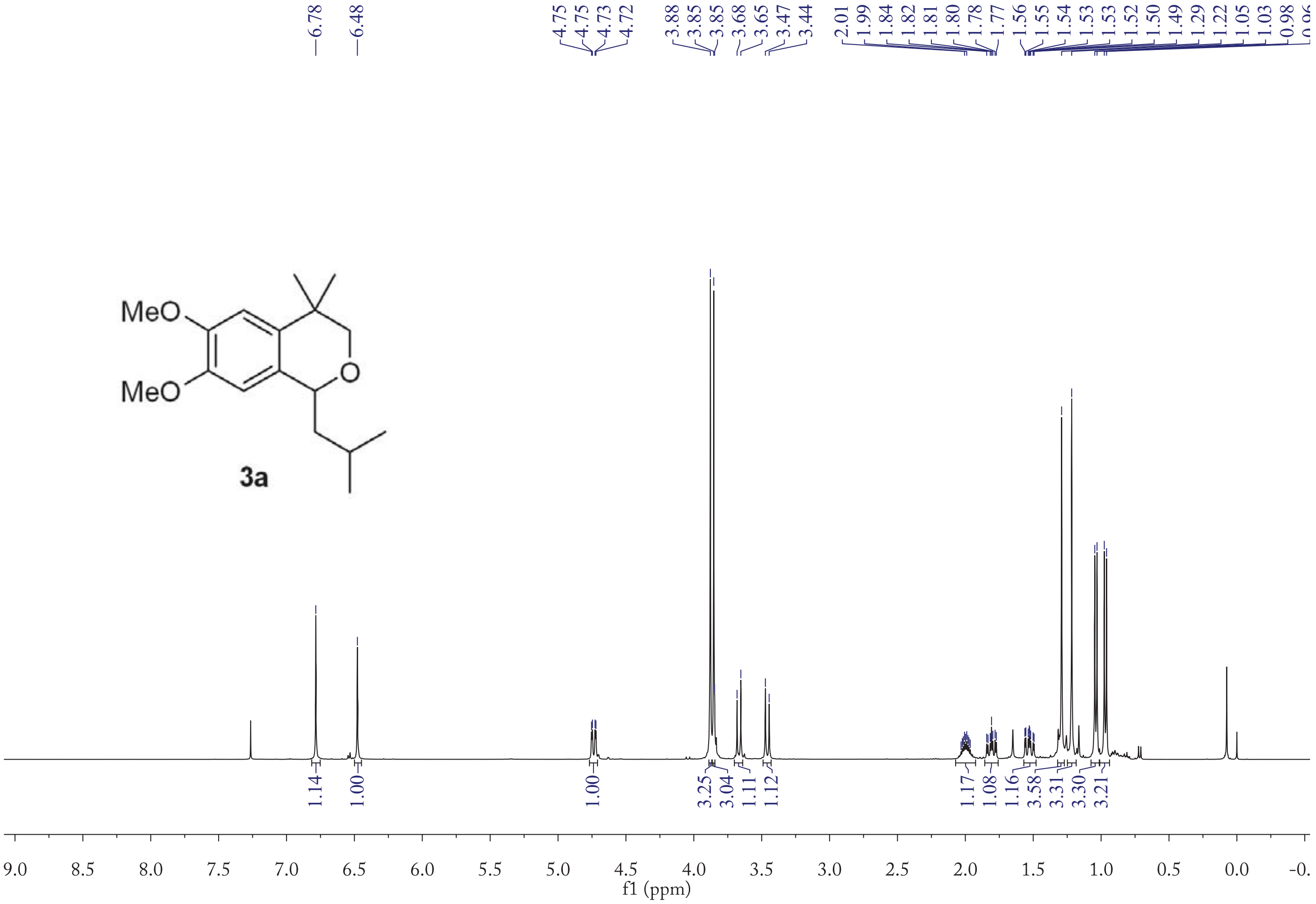
f1 (ppm)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3.47
3.44
2.01
1.99
1.84
1.82
1.81
1.80
1.78
1.77
1.56
1.55
1.54
1.53
1.53
1.52
1.50
1.49
1.29
1.22
1.05
1.03
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MeO
O
3a
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1.00
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3.04
1.11
1.12
1.17
1.08
1.16
3.58
3.31
3.30
3.21
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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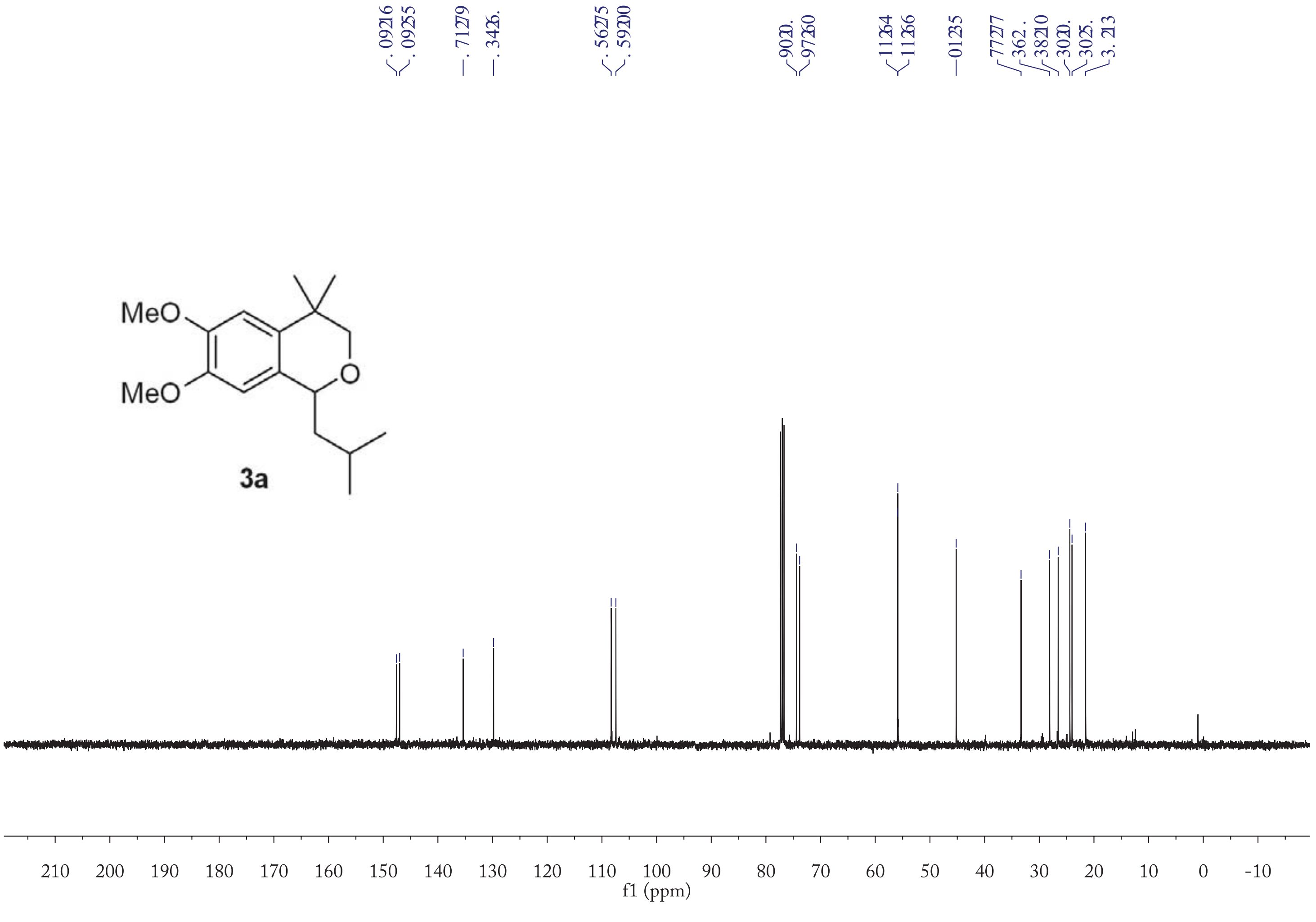
f1 (ppm)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362 .
38210
3020.
3025.
3. 213
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MeO
O
3a
210
200
190
180
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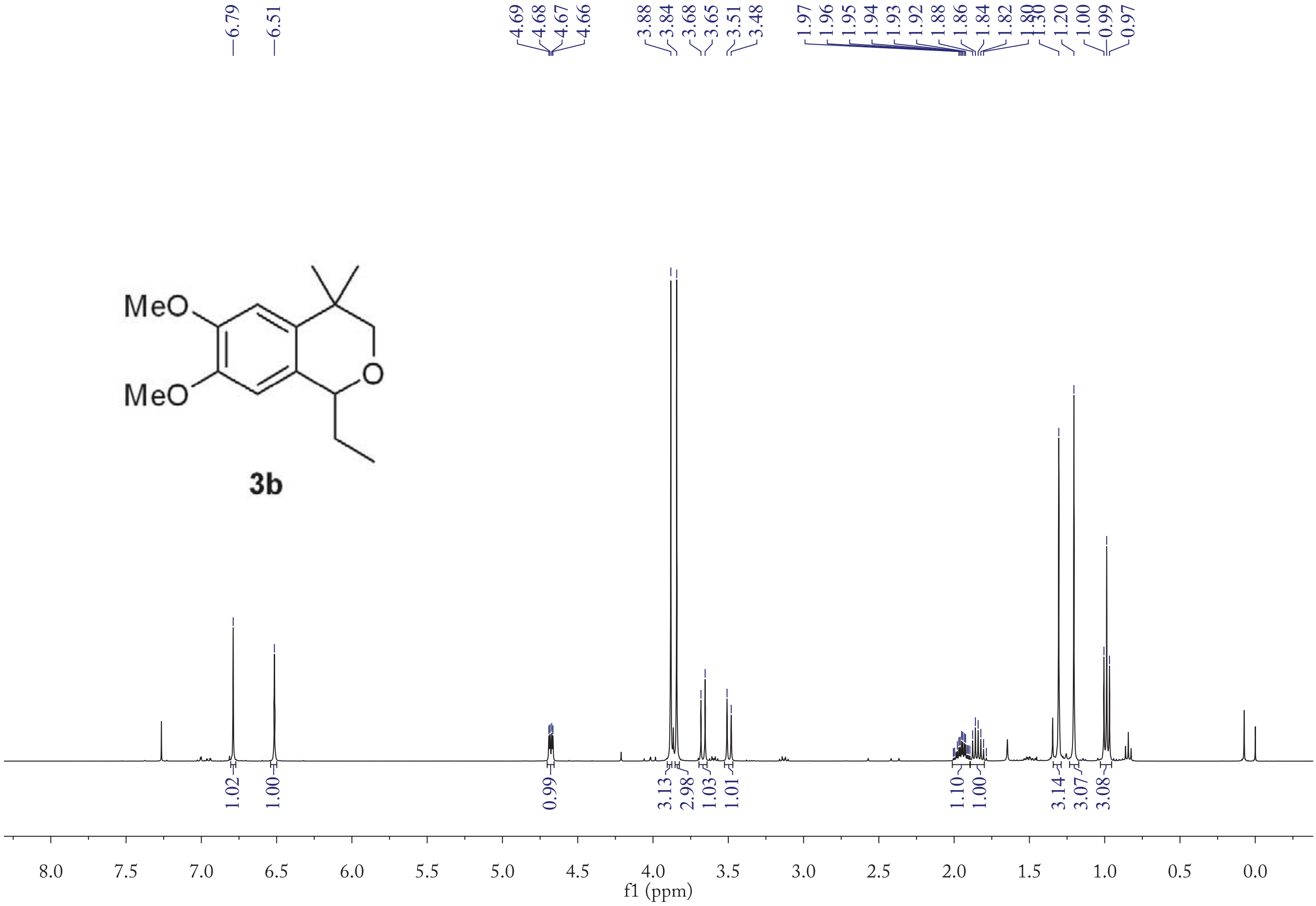
f1 (ppm)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3.65
3.51
3.48
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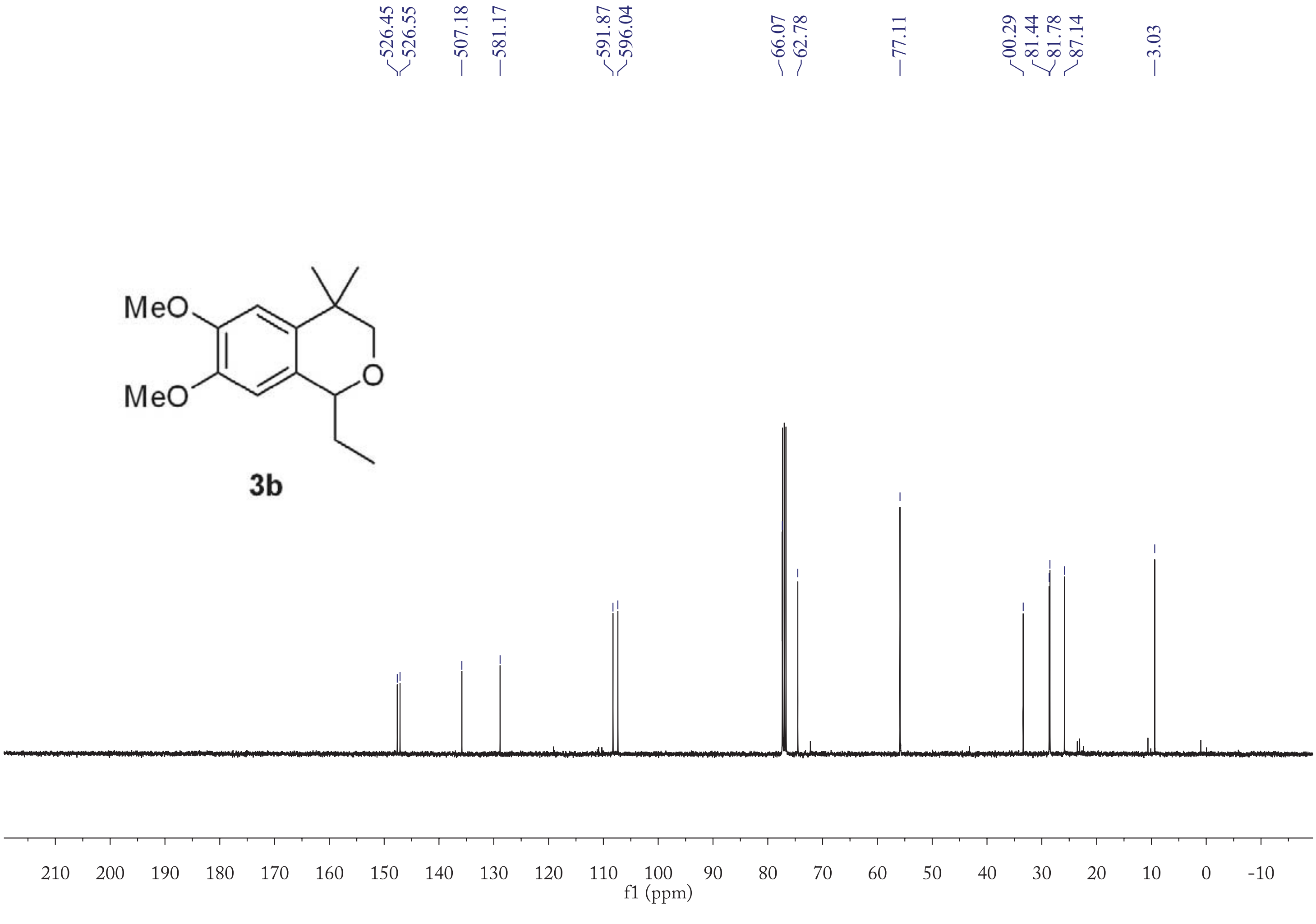
1.95
1.94
1.93
1.92
1.88
1.86
1.84
1.82
1.80
1.30
1.20
1.00
0.99
0.97
MeO
MeO
O
1.02
1.00
0.99
3.13
2.98
1.03
1.01
1.10
1.00
3.14
3.07
3.08
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

3b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87.14
3.03
MeO
MeO
O
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
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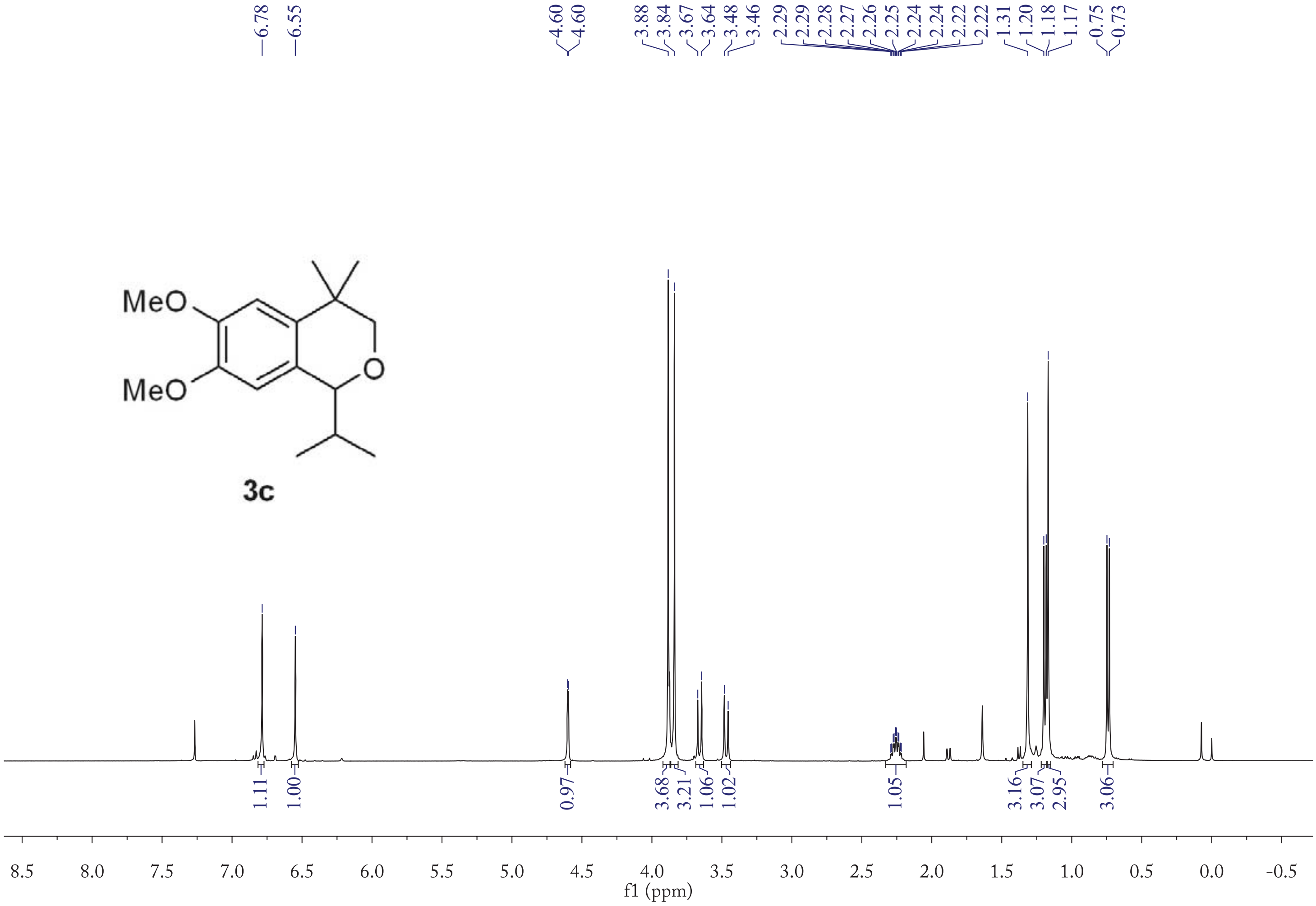
-10
f1 (ppm)

3b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3.84
3.67
3.64
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3.46
2.29
2.29
2.28
2.27
2.26
2.25
2.24
2.24
2.22
2.22
1.31
1.20
1.18
1.17
0.75
0.73
MeO
MeO
O
3c
1.11
1.00
0.97
3.68
3.21
1.06
1.02
1.05
3.16
3.07
2.95
3.06
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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3.0
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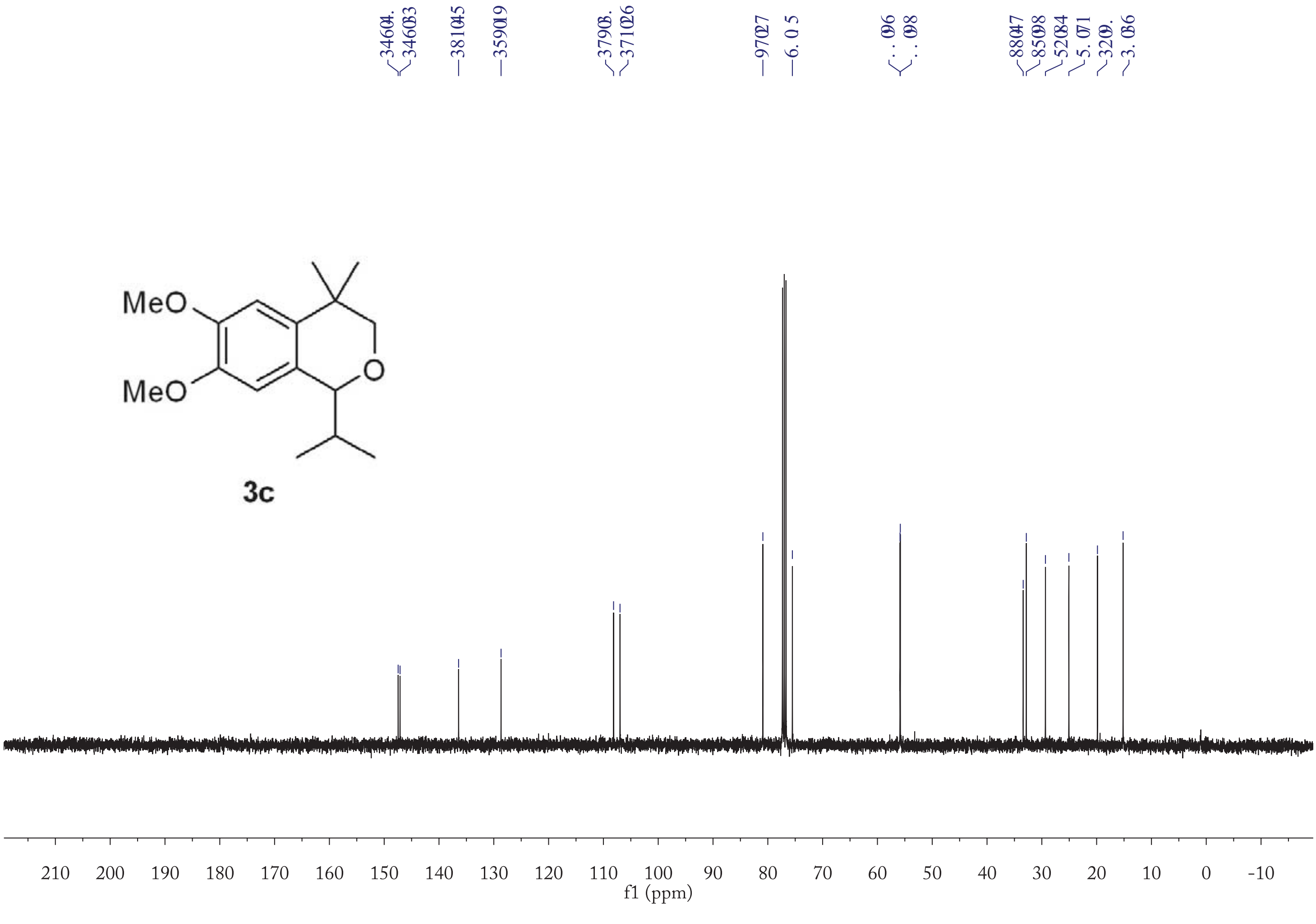
f1 (ppm)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37102
9702
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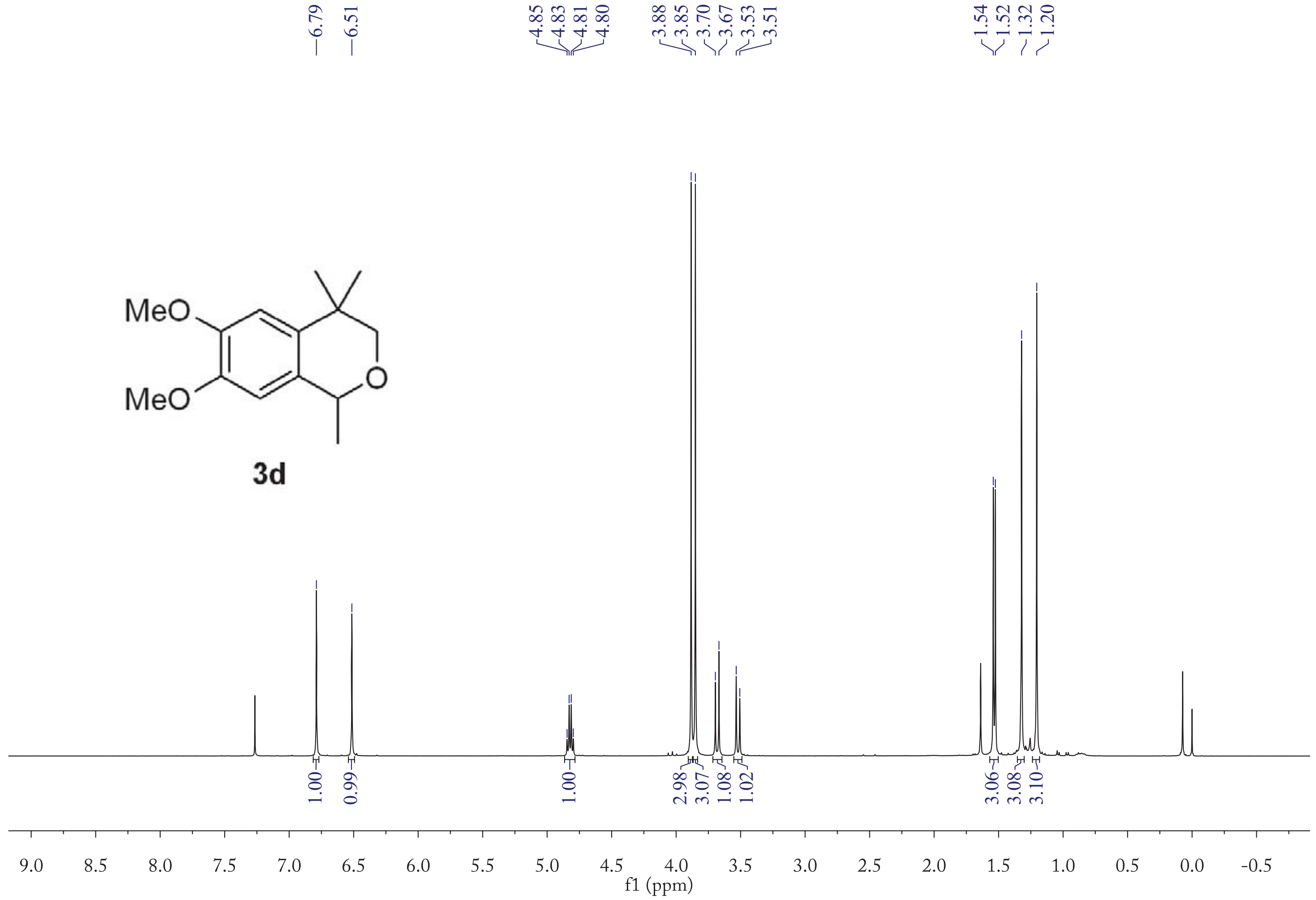
: 06
: 08
8804
8509
5208
5. 07
320.
3. 06
MeO
MeO
O
3c
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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1.52
1.32
1.20
MeO
MeO
O
3d
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0.99
1.00
2.98
3.07
1.08
1.02
3.06
3.08
3.10
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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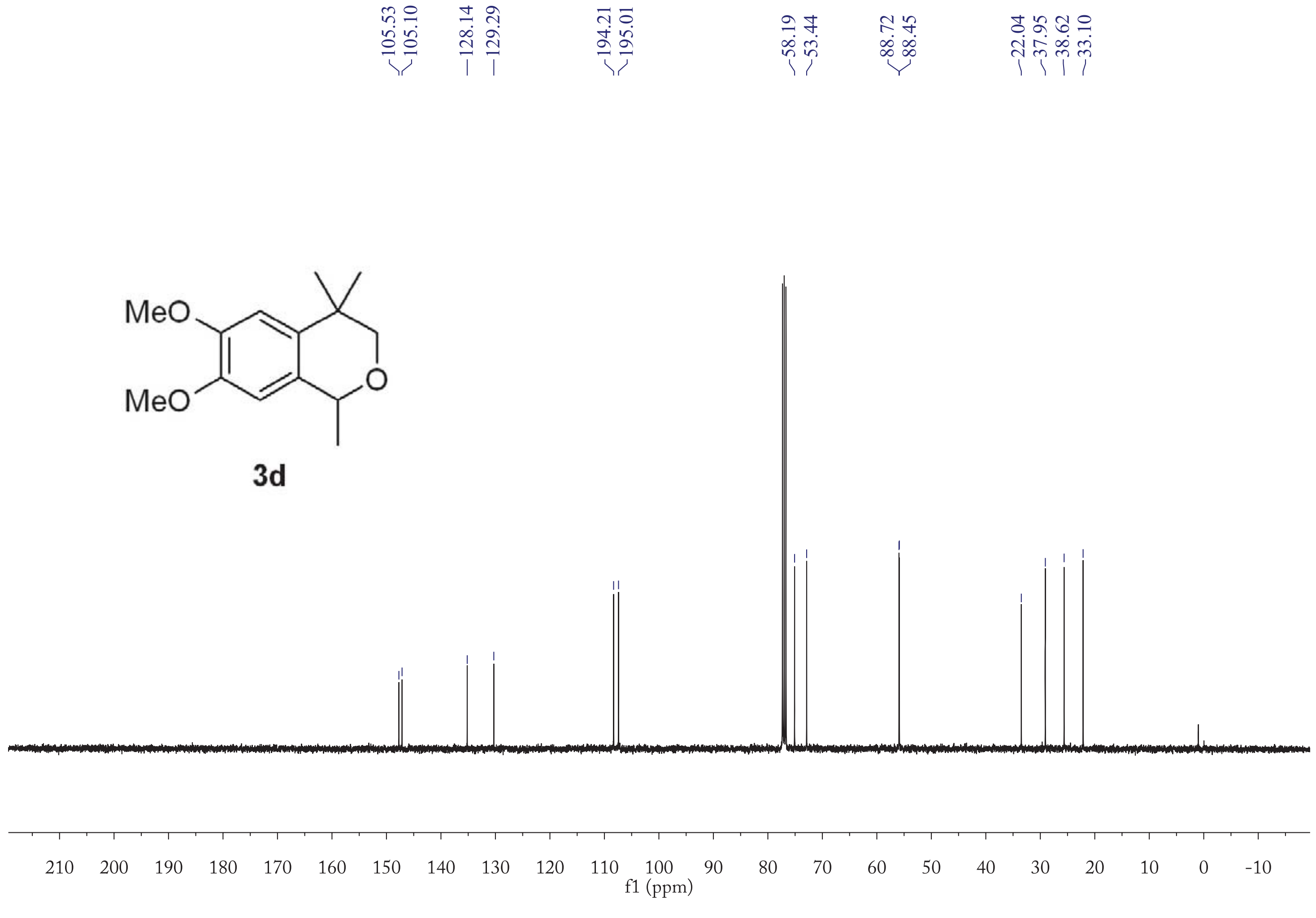
f1 (ppm)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88.45
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37.95
38.62
33.10
MeO
MeO
O
3d
210
200
190
180
170
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100
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80
70
60
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40
30
20
10
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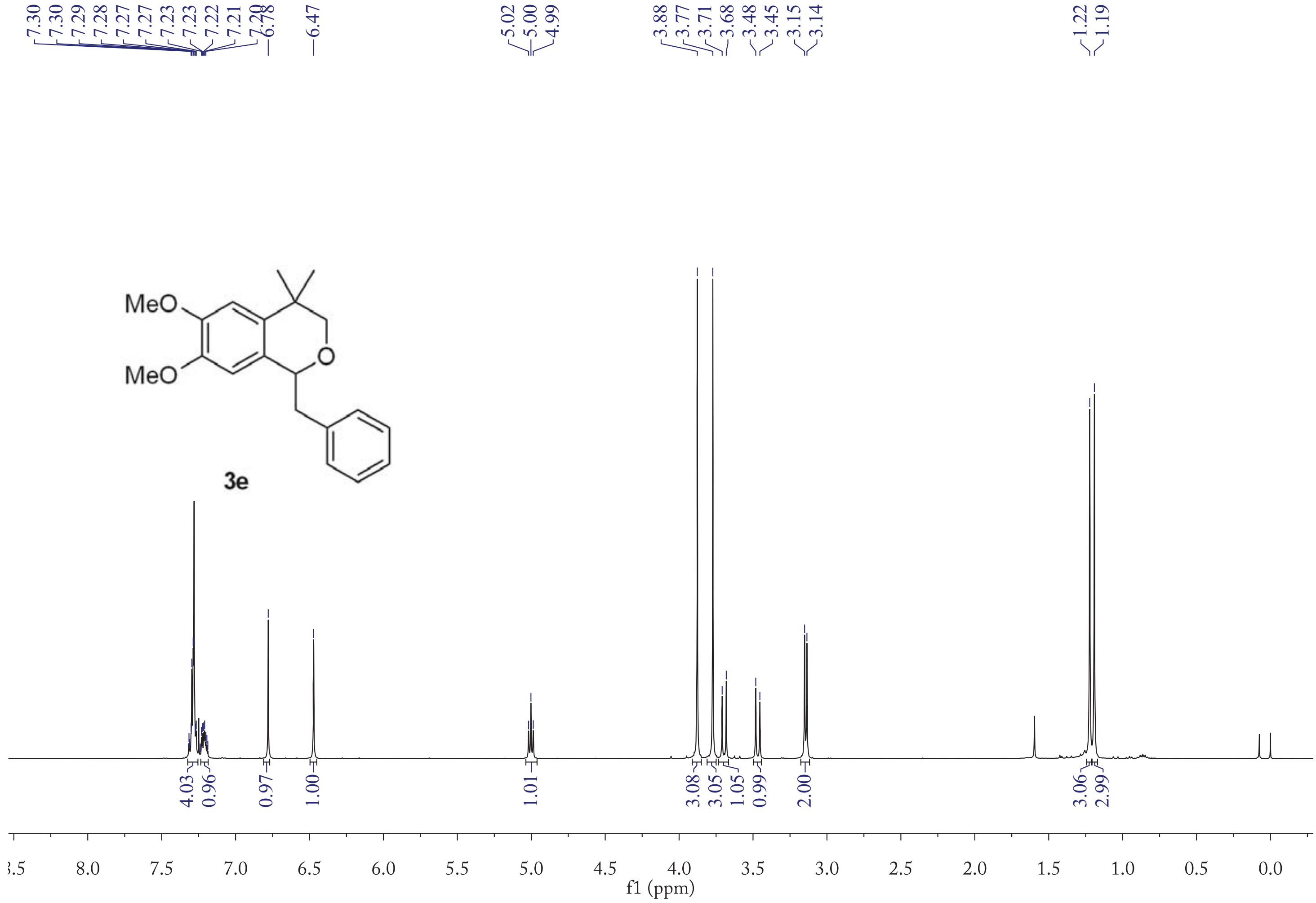
-10
f1 (ppm)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5.00
4.99
3.88
3.77
3.71
3.68
3.48
3.45
3.15
3.14
1.22
1.19
MeO
MeO
O
3e
4.03
0.96
0.97
1.00
1.01
3.08
3.05
1.05
0.99
2.00
3.06
2.99
.5
8.0
7.5
7.0
6.5
6.0
5.5
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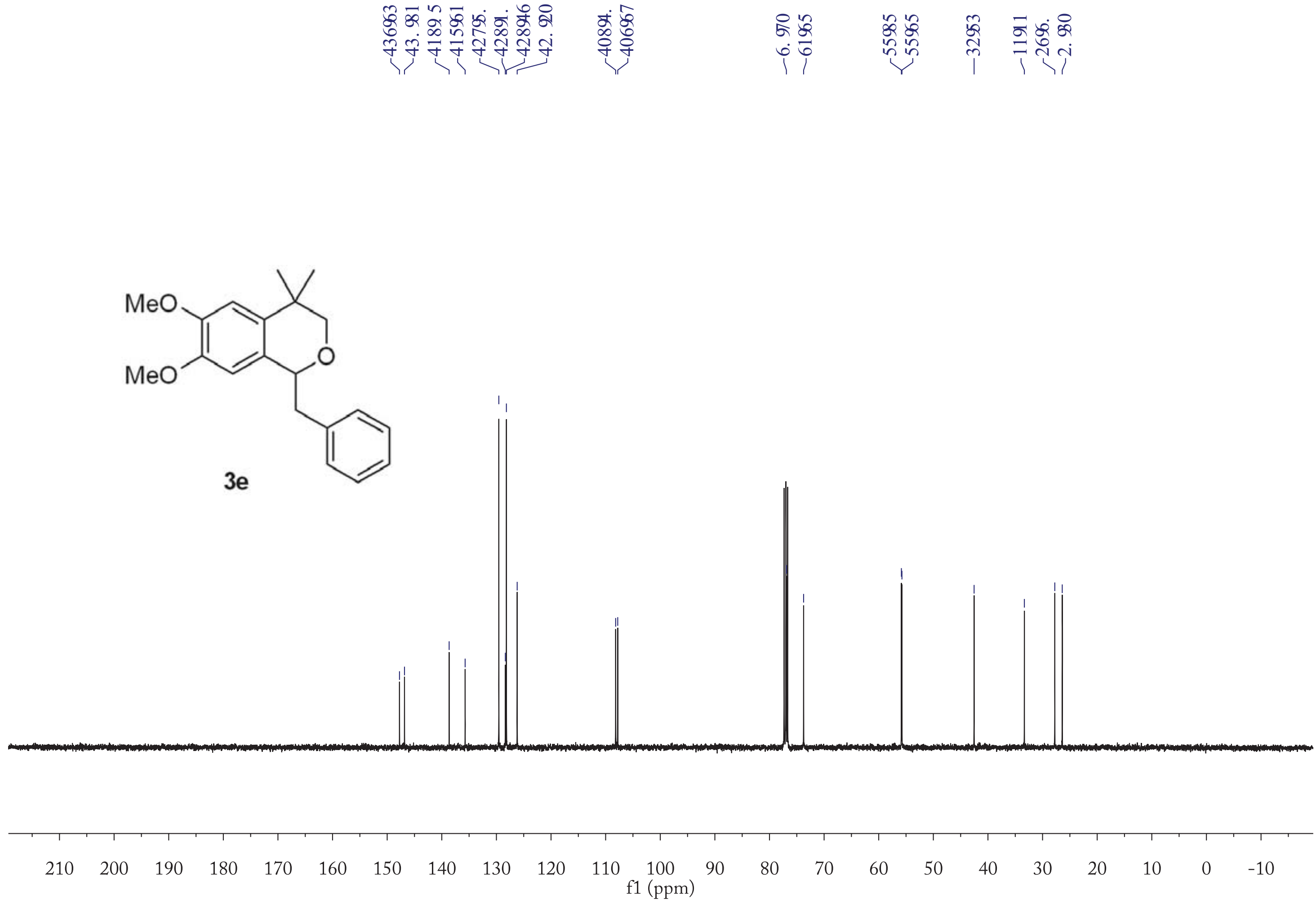
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6. 970
61965
55985
55965
32953
119.11
2696.
2. 930
MeO
MeO
O
3e
210
200
190
180
170
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100
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80
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40
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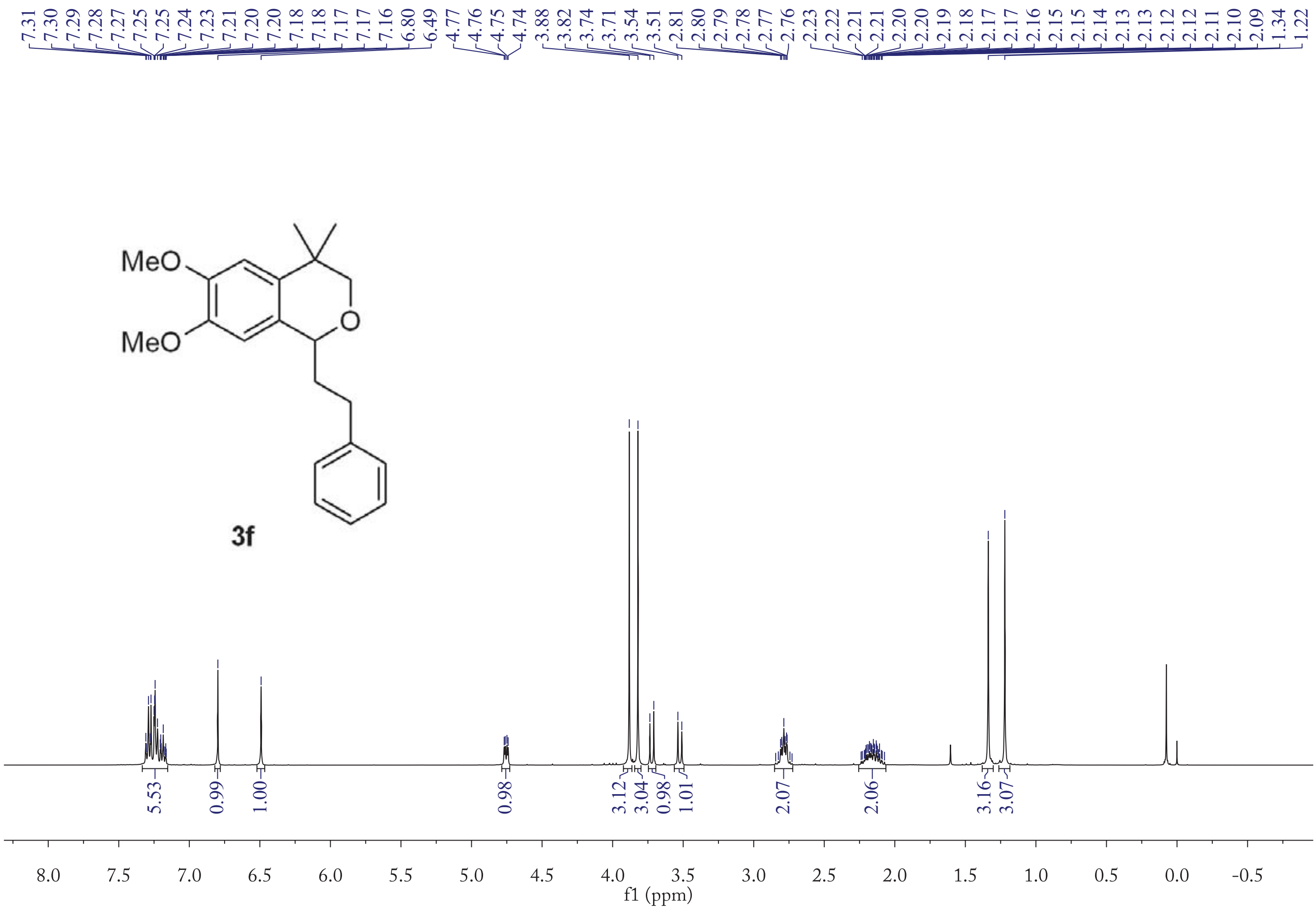
-10
f1 (ppm)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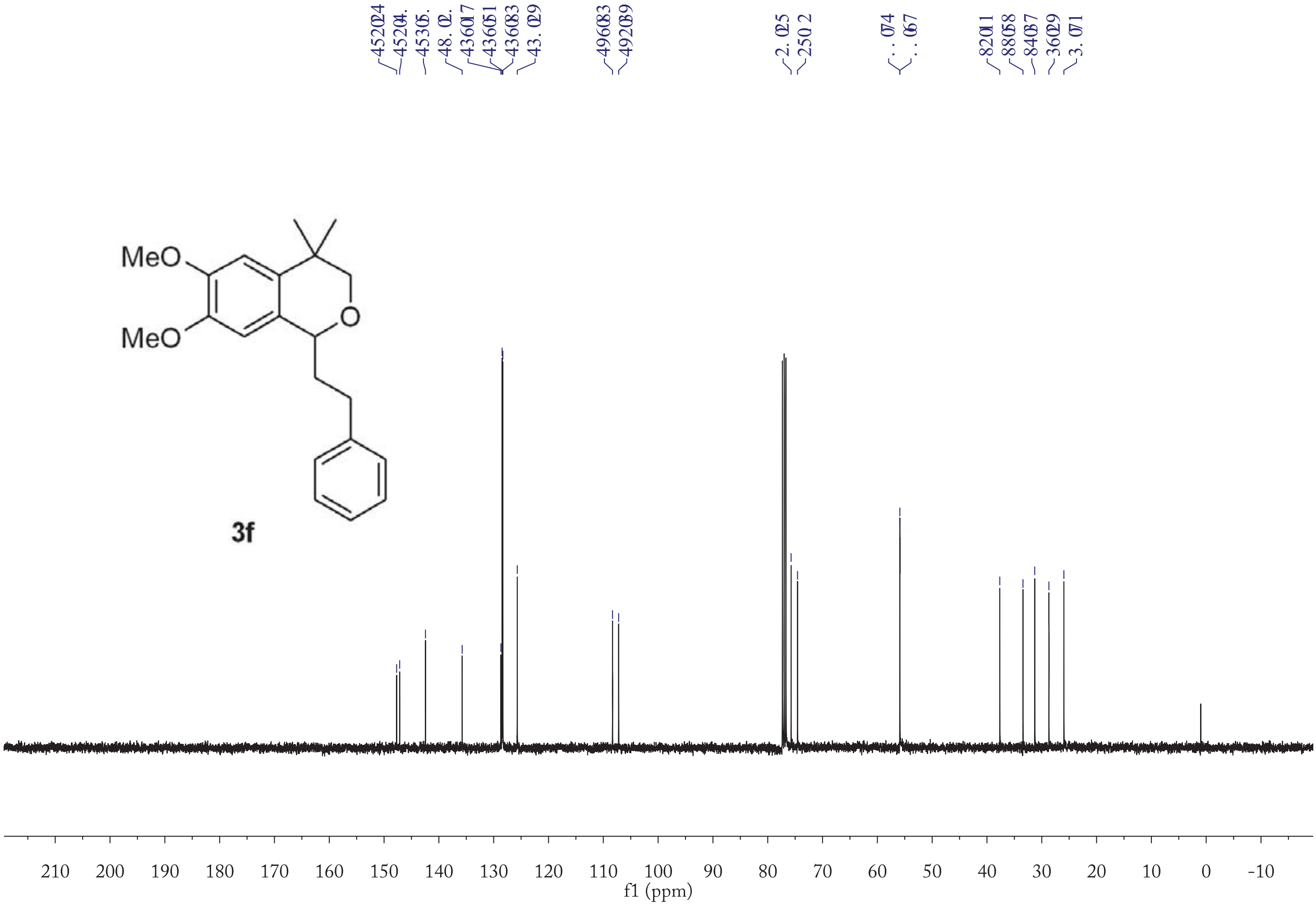
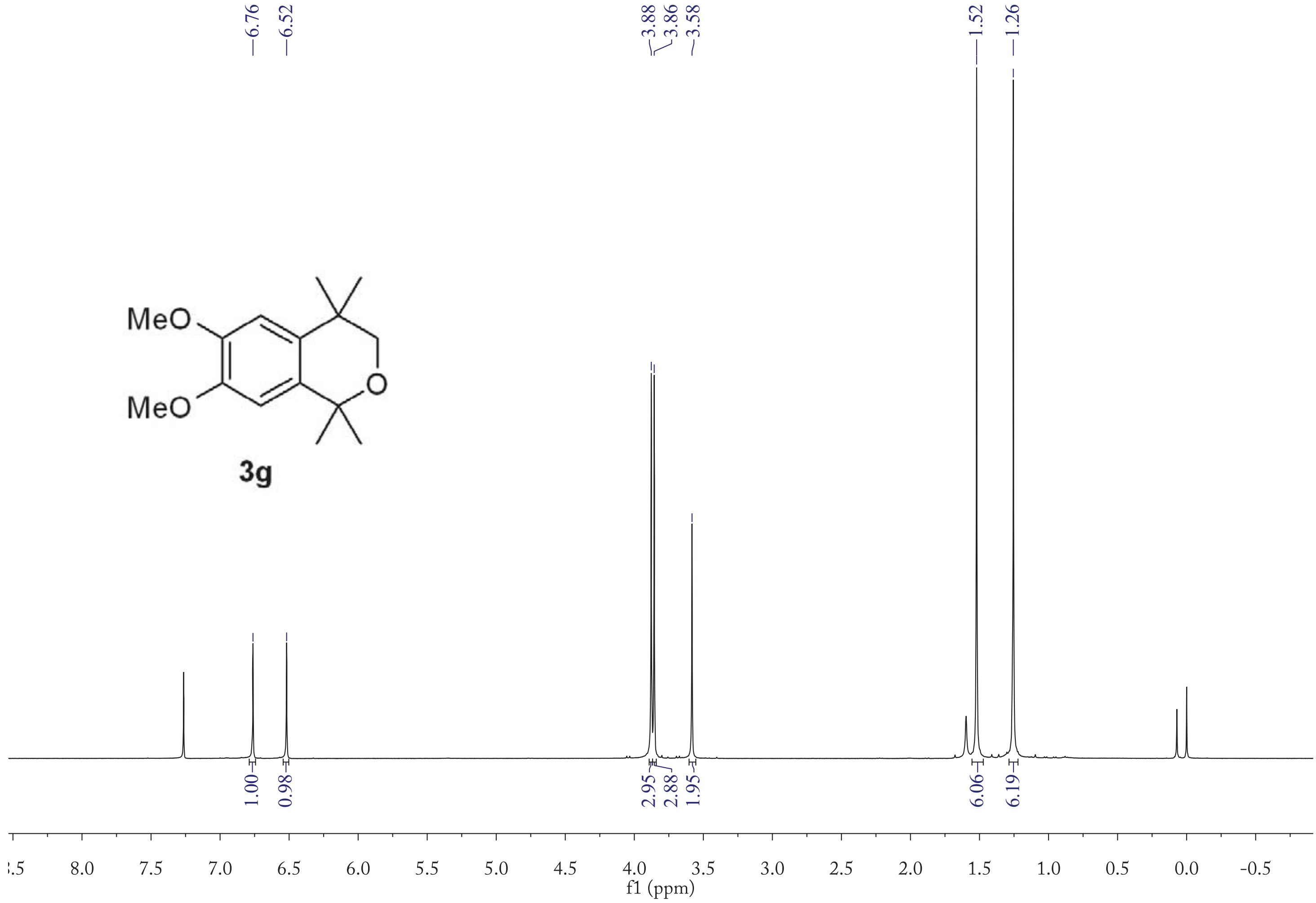
MeO
MeO
O
5.53
0.99
1.00
0.98
3.12
3.04
0.98
1.01
2.07
2.06
3.16
3.07
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

3f


452024 45204. 45305. 48. 02. 436017 436051 436083 43. 029
496083 492039
2. 025 250 2
: 074 : 067
82011 88058 84037 36029 3. 071
MeO
MeO
O
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

3f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6.52
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3.58
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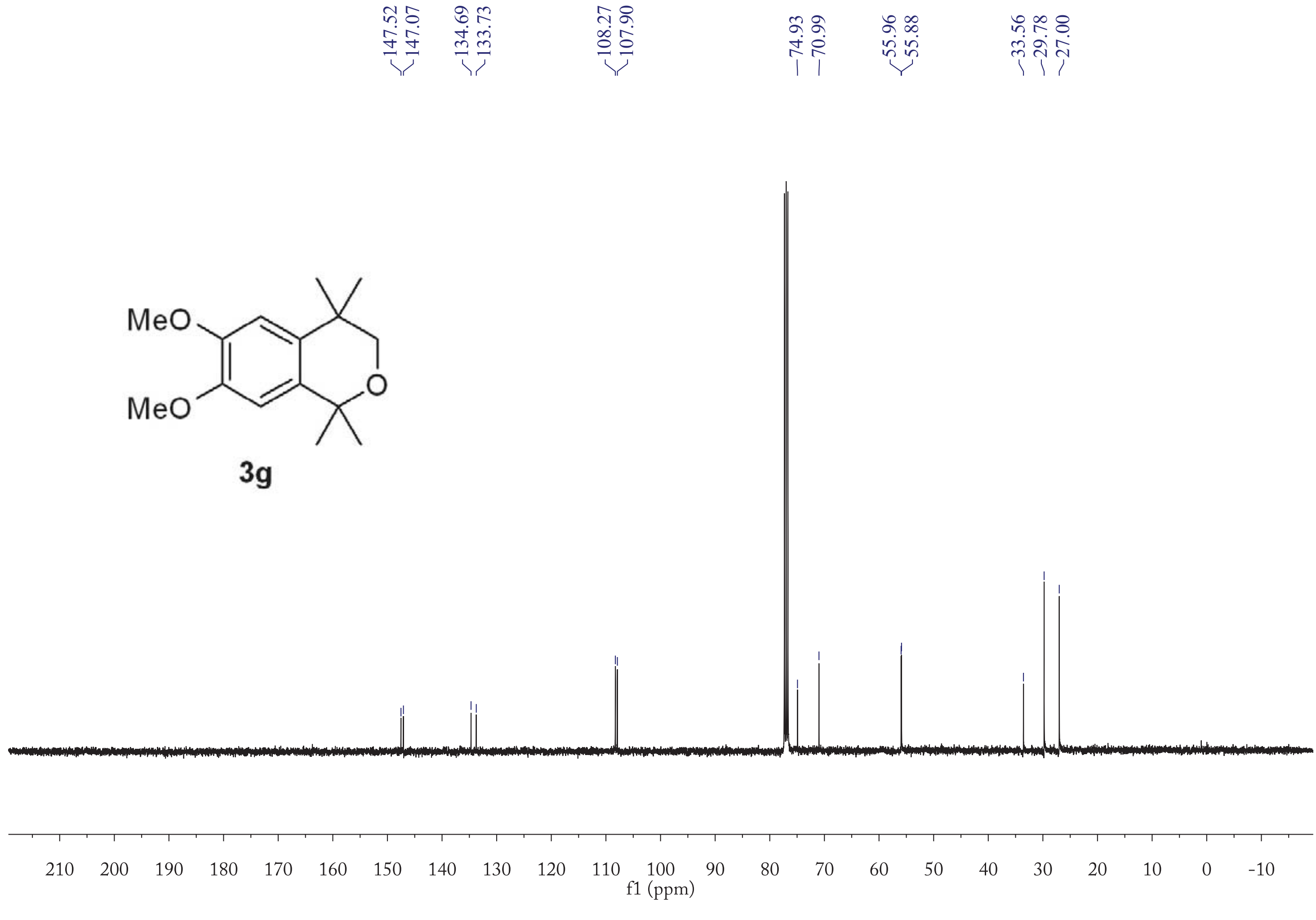
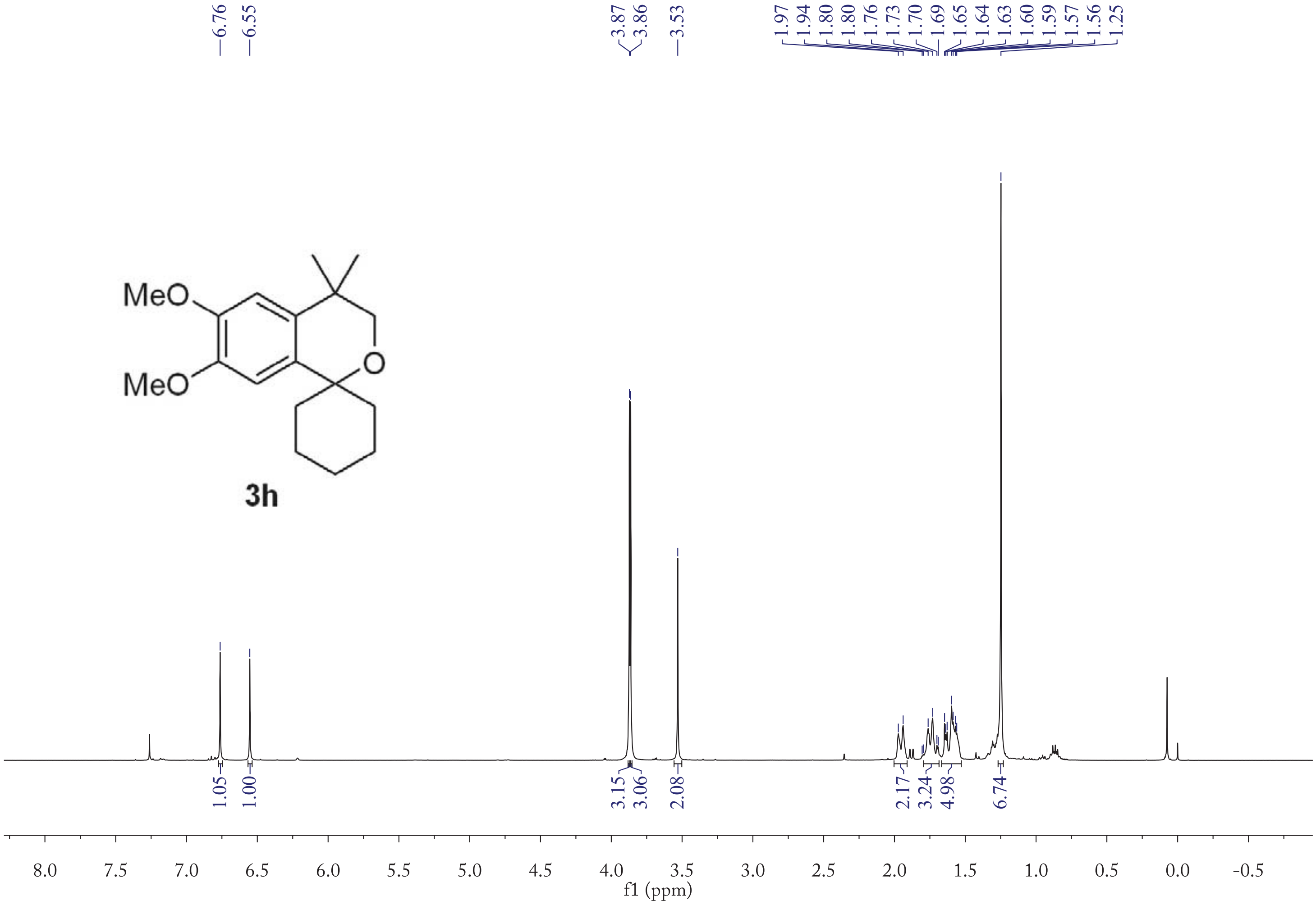
1.26
MeO
MeO
O
3g
1.00
0.98
2.95
2.88
1.95
6.06
6.19
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


147.52
147.07
134.69
133.73
108.27
107.90
74.93
70.99
55.96
55.88
33.56
29.78
27.00
MeO
MeO
O
3g
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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1.80
1.80
1.76
1.73
1.70
1.69
1.65
1.64
1.63
1.60
1.59
1.57
1.56
1.25
MeO
MeO
O
3h
1.05
1.00
3.15
3.06
2.08
2.17
3.24
4.98
6.74
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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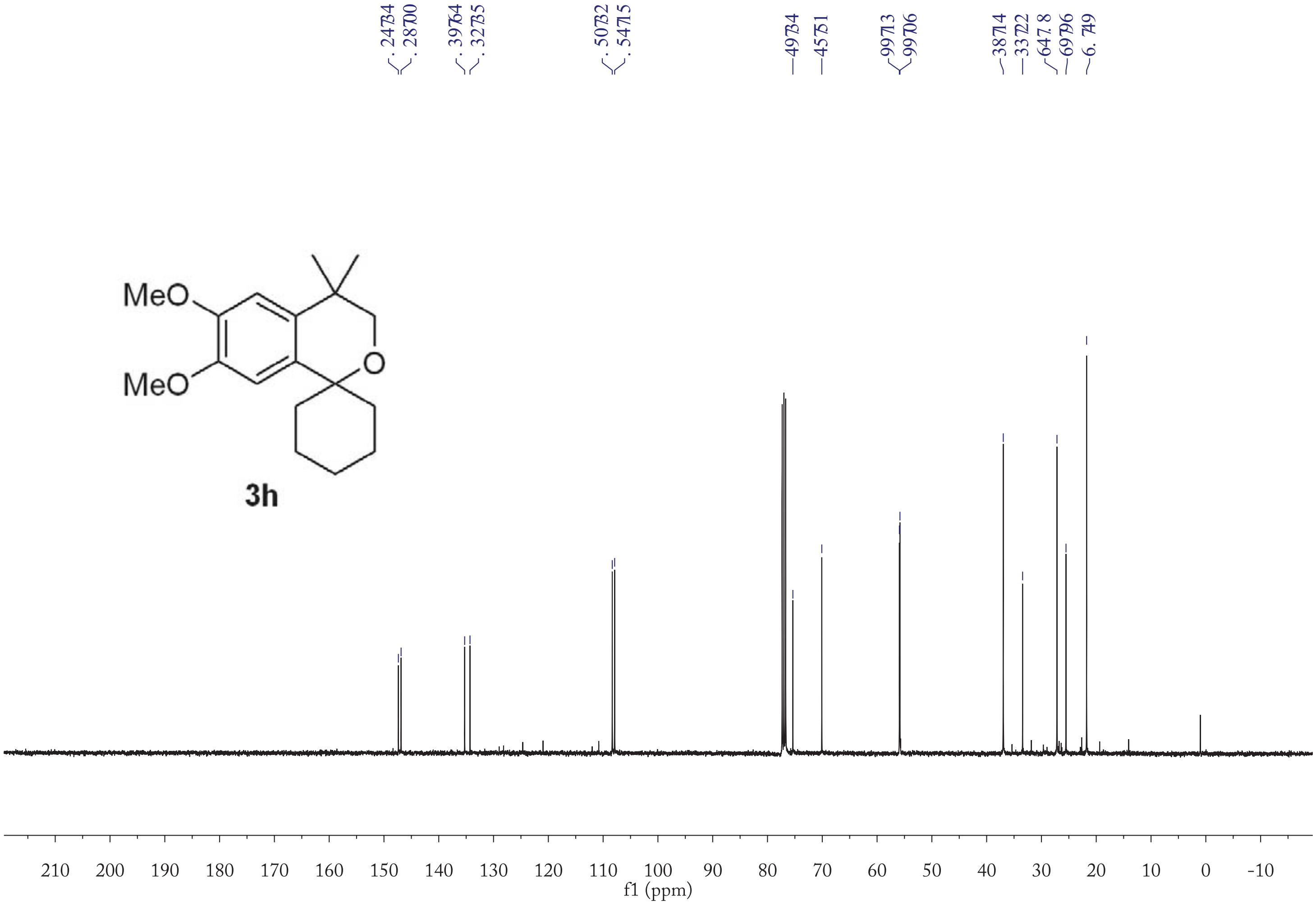
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)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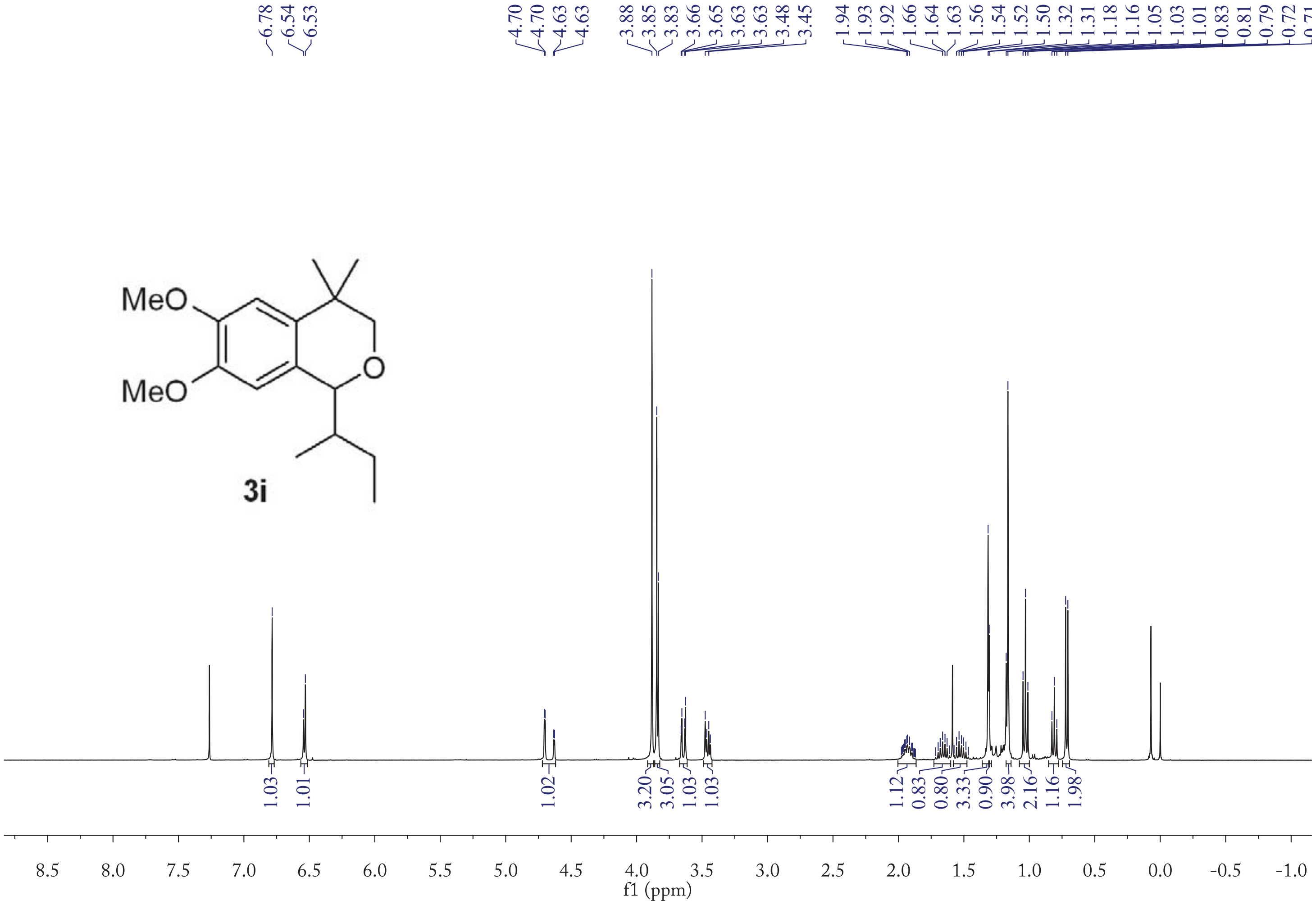
. 39764
. 32735
. 50732
. 54715
49734
45751
99713
99706
38714
33722
647.8
69796
6. 749
MeO
MeO
O
3h
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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4.63
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3.88
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3.83
3.66
3.65
3.63
3.63
3.48
3.45
1.94
1.93
1.92
1.66
1.64
1.63
1.56
1.54
1.52
1.50
1.32
1.31
1.18
1.16
1.05
1.03
1.01
0.83
0.81
0.79
0.72
MeO
MeO
O
3i
1.03
1.01
1.02
3.20
3.05
1.03
1.03
1.12
0.83
0.80
3.33
0.90
3.98
2.16
1.16
1.98
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
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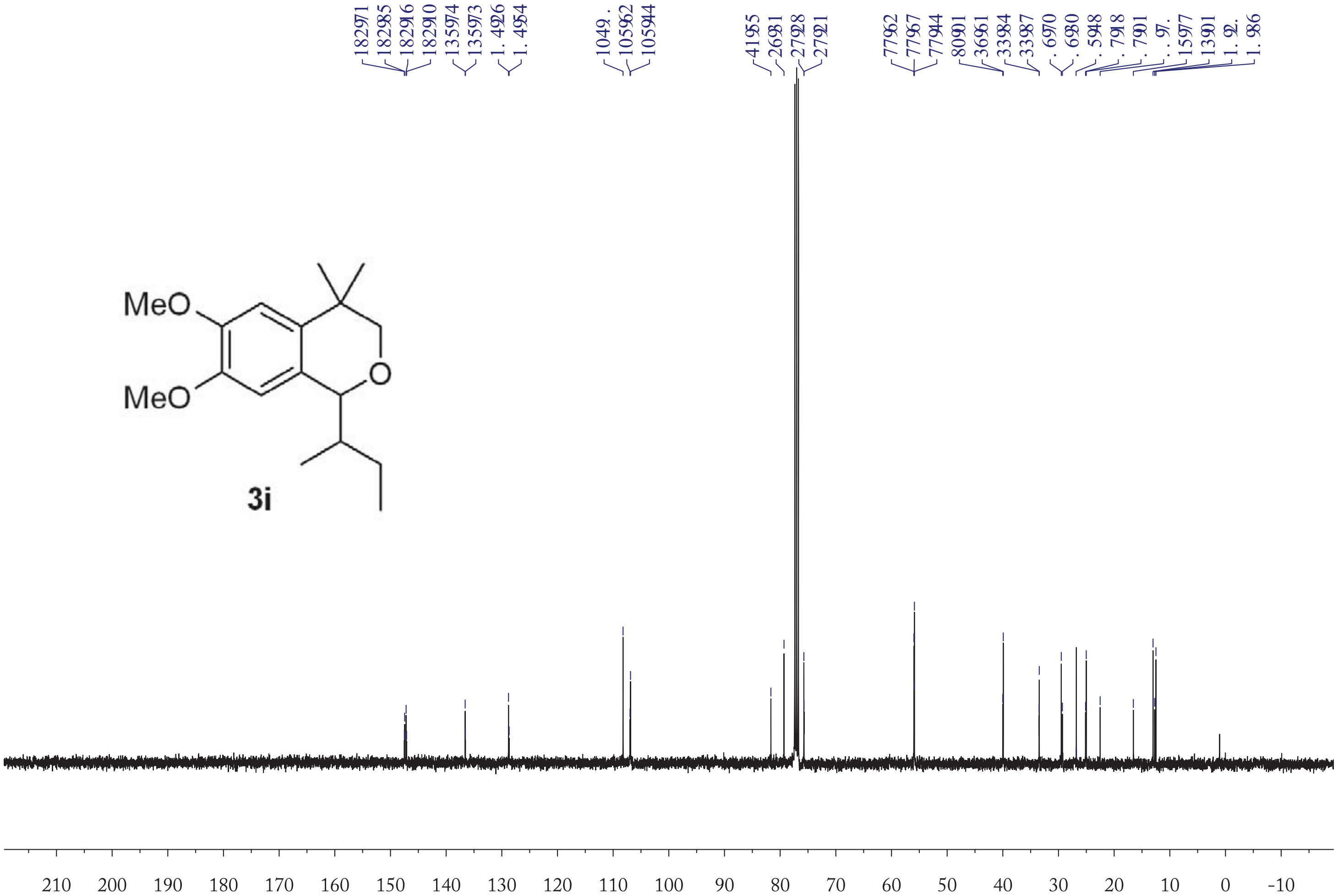
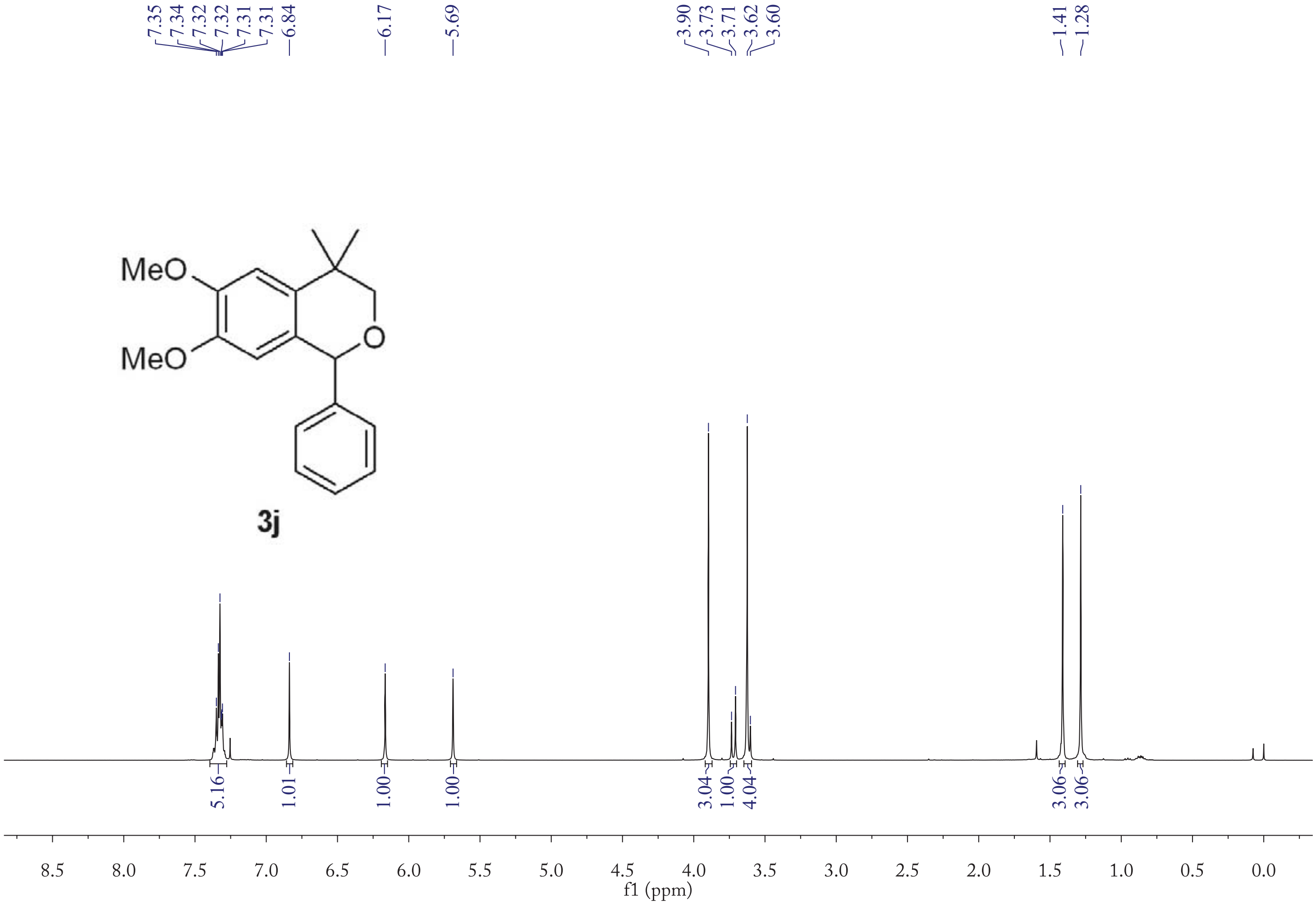
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)


MeO
MeO
O
3i
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)



3j

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7.32
7.32
7.31
7.31
6.84
6.17
5.69
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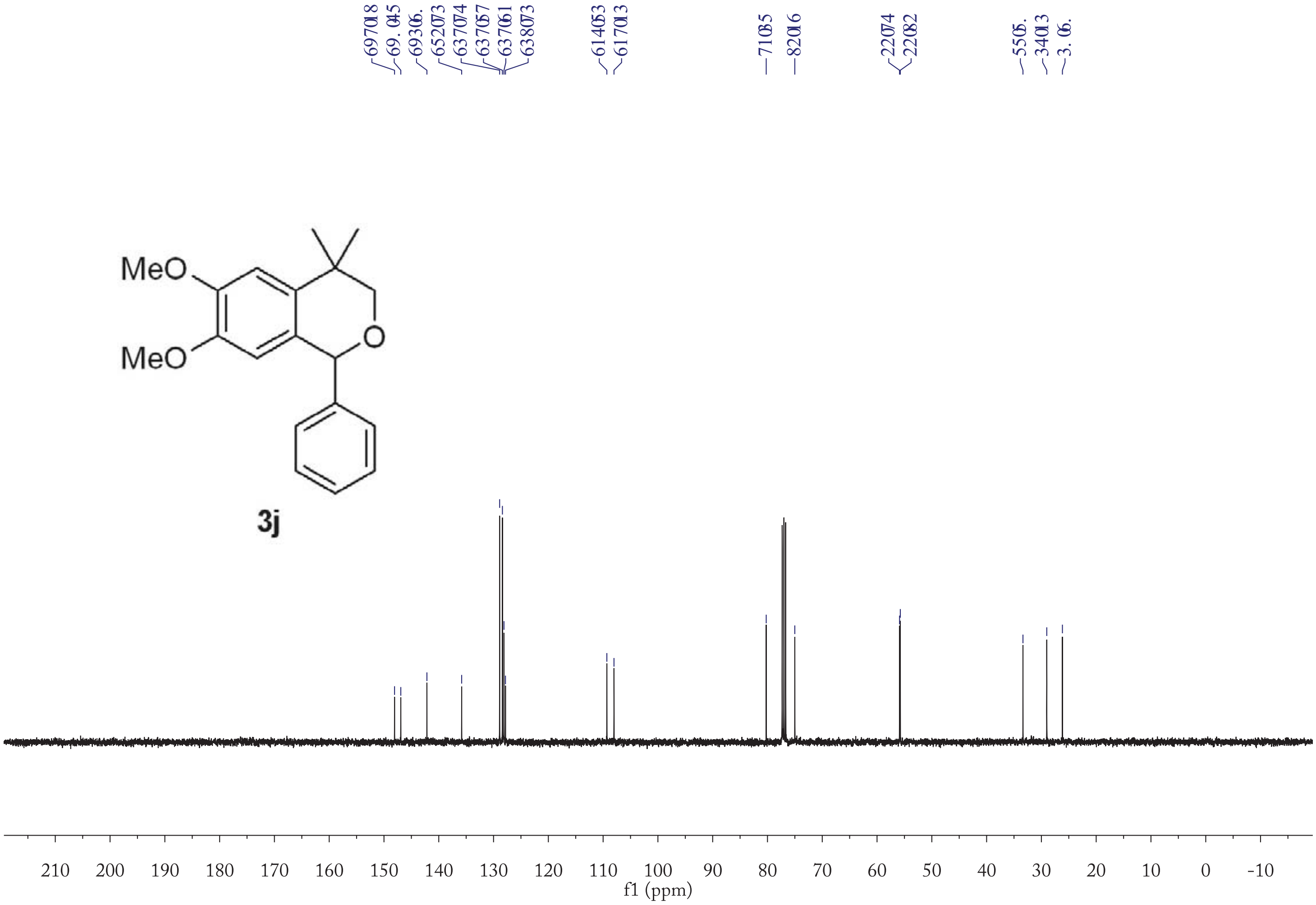
3.73
3.71
3.62
3.60
1.41
1.28
MeO
MeO
O
5.16
1.01
1.00
1.00
3.04
1.00
4.04
3.06
3.06
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)



3j

697018
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22082
5505.
34013
3. 06.
MeO
MeO
O
210
200
190
180
170
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100
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80
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40
30
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10
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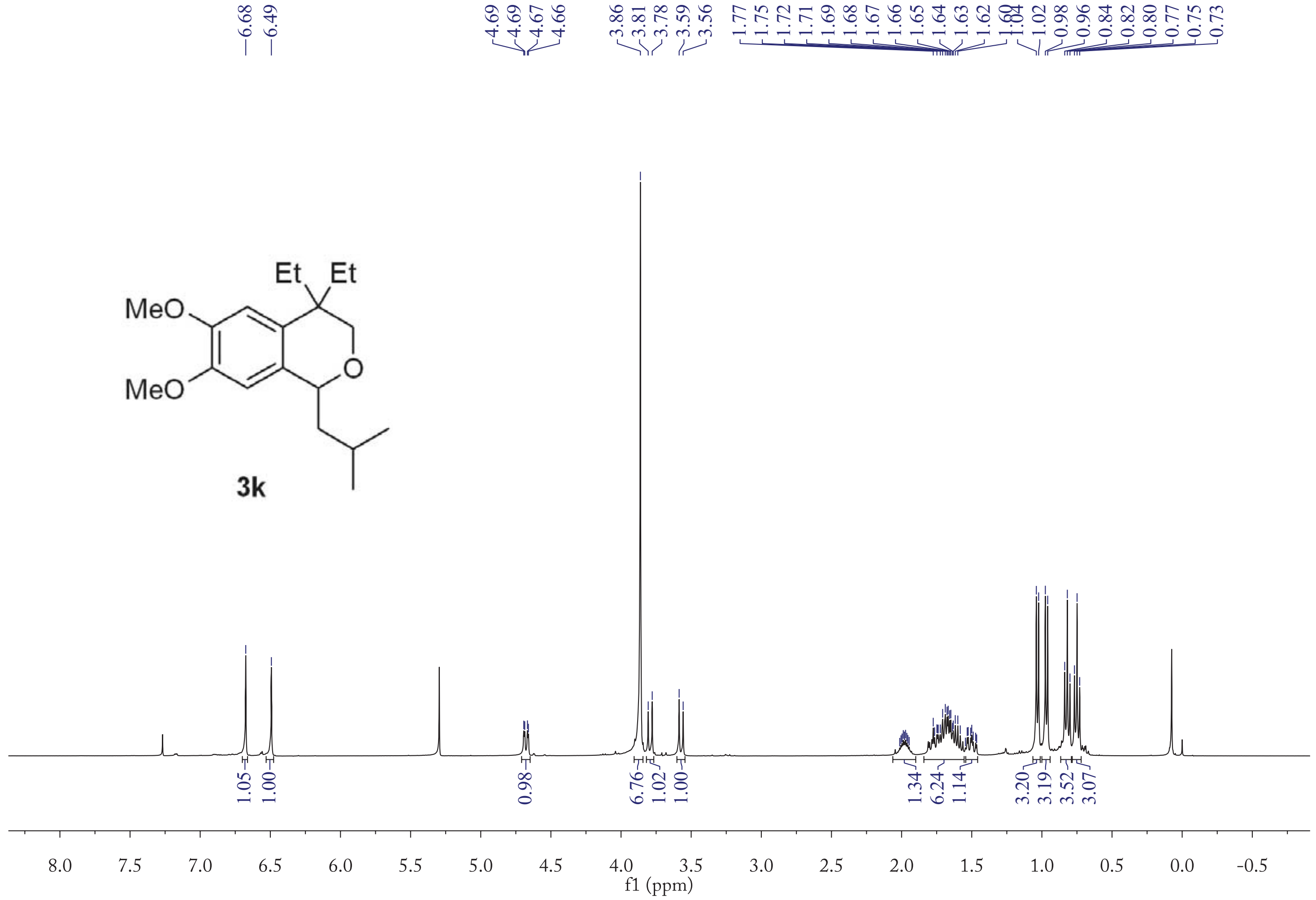
f1 (ppm)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3.59
3.56
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1.75
1.72
1.71
1.69
1.68
1.67
1.66
1.65
1.64
1.63
1.62
1.60
1.04
1.02
0.98
0.96
0.84
0.82
0.80
0.77
0.75
0.73
Et
Et
MeO
MeO
O
3k
1.05
1.00
0.98
6.76
1.02
1.00
1.34
6.24
1.14
3.20
3.19
3.52
3.07
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
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3.0
2.5
2.0
1.5
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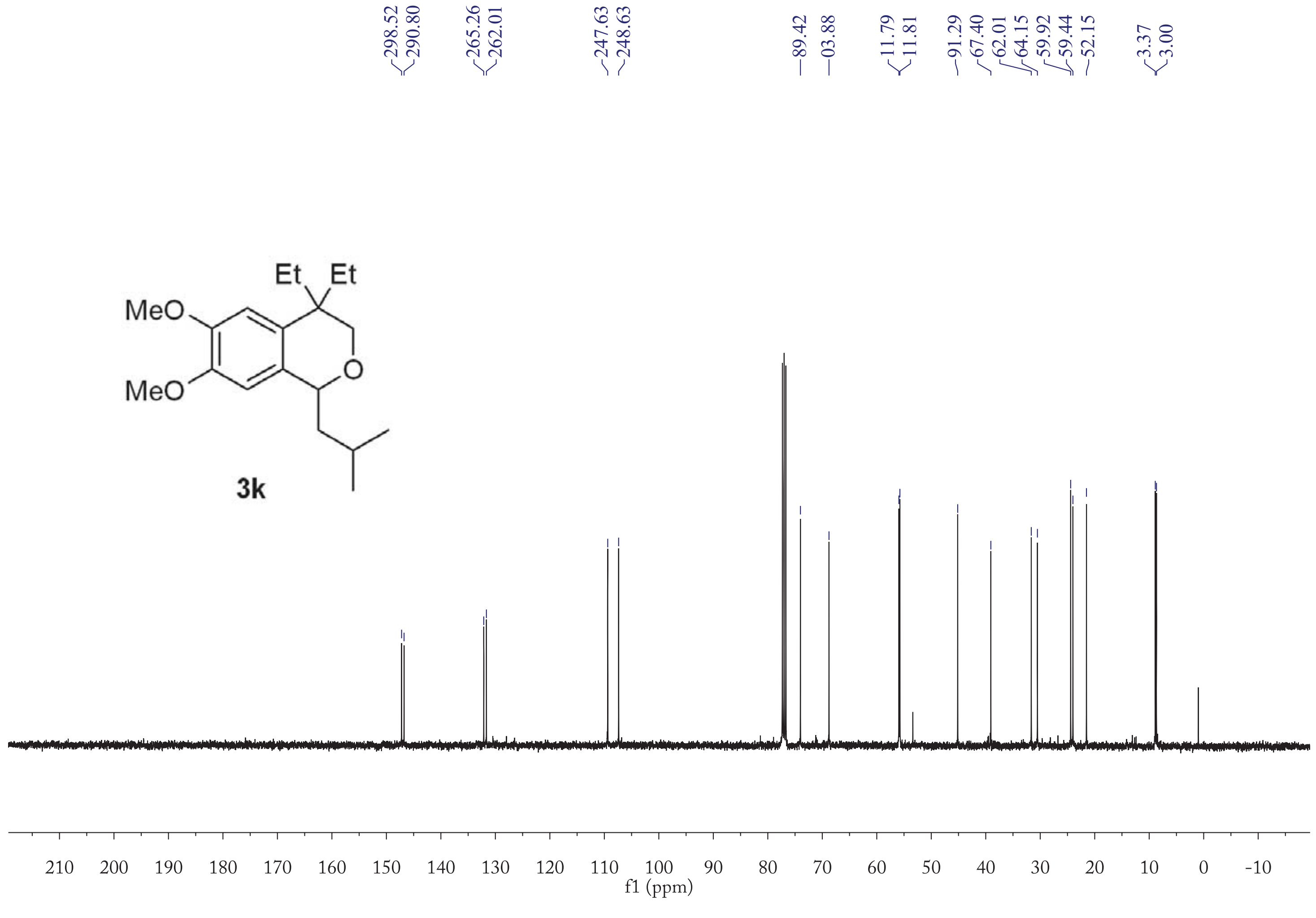
0.5
0.0
-0.5
f1 (ppm)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11.81
91.29
67.40
62.01
64.15
59.92
59.44
52.15
3.37
3.00
Et
Et
MeO
MeO
O
3k
210
200
190
180
170
160
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140
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120
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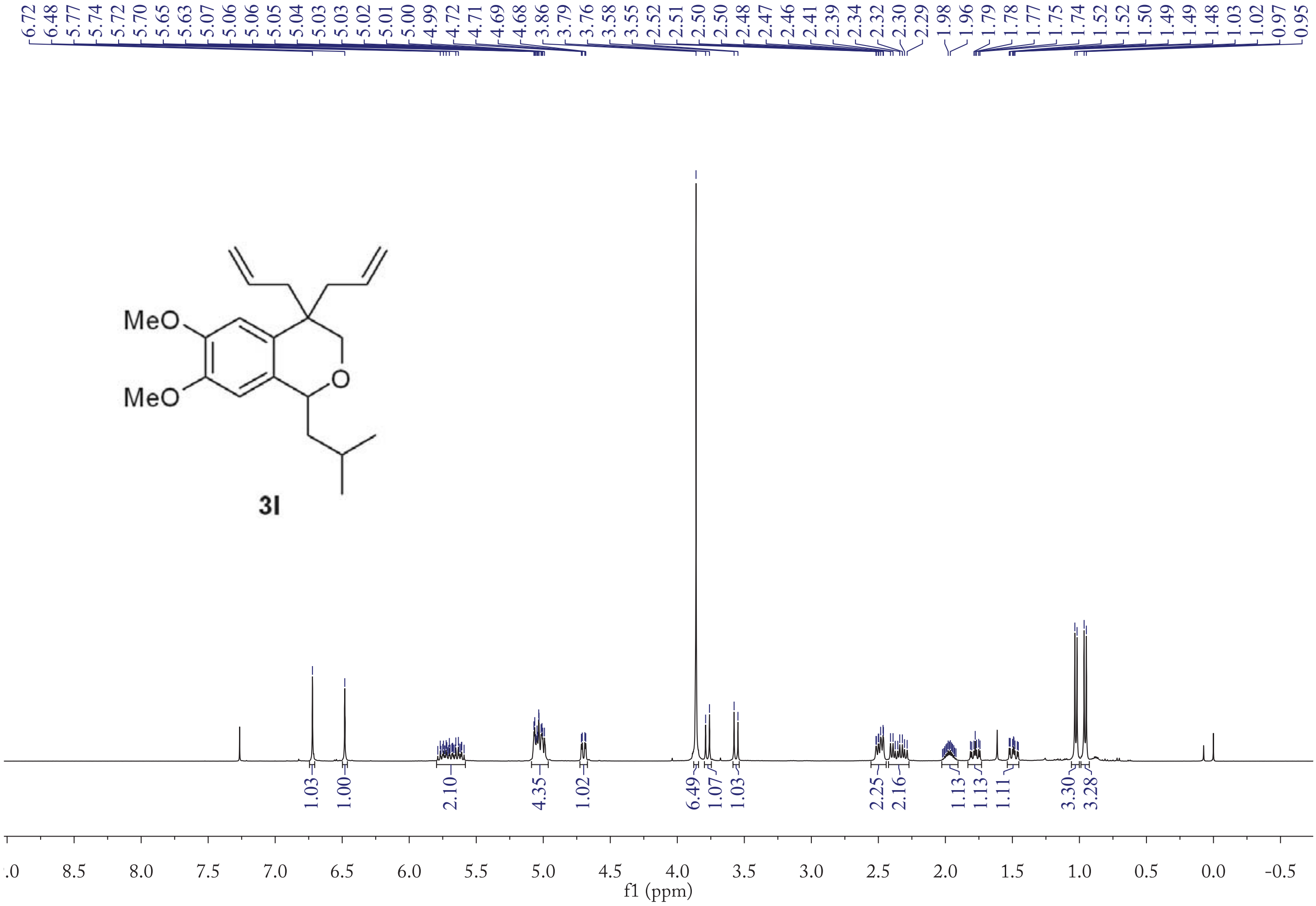
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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5.63
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5.06
5.06
5.05
5.04
5.03
5.03
5.02
5.01
5.00
4.99
4.72
4.71
4.69
4.68
3.86
3.79
3.76
3.58
3.55
2.52
2.51
2.50
2.50
2.48
2.47
2.46
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2.39
2.34
2.32
2.30
2.29
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1.96
1.79
1.78
1.77
1.75
1.74
1.52
1.50
1.49
1.49
1.48
1.03
1.02
0.97
0.95
MeO
MeO
O
3l
1.03
1.00
2.10
4.35
1.02
6.49
1.07
1.03
2.25
2.16
1.13
1.13
1.11
3.30
3.28
.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
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3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
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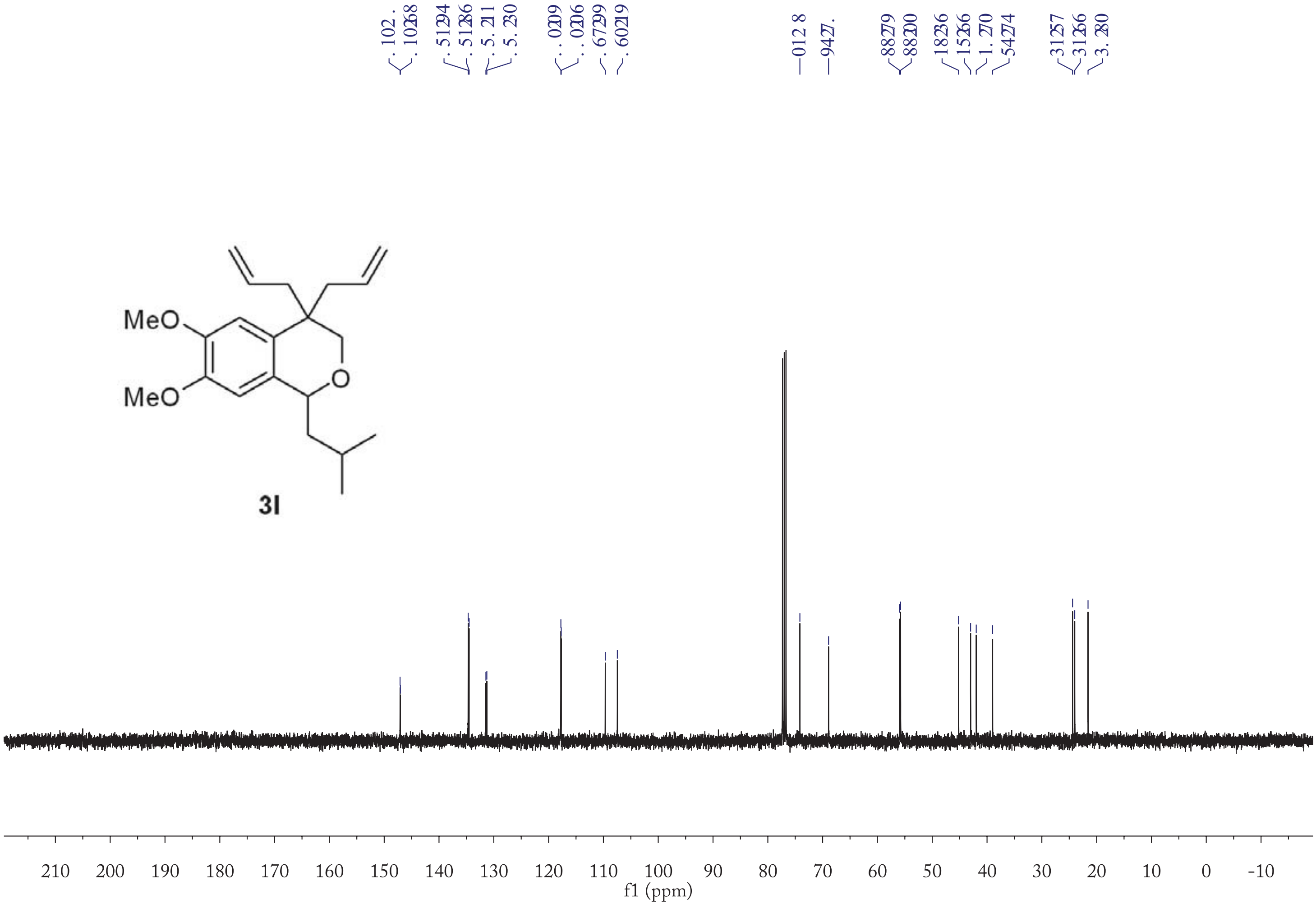
f1 (ppm)


MeO
MeO
O
3l
210
200
190
180
170
160
150
140
130
120
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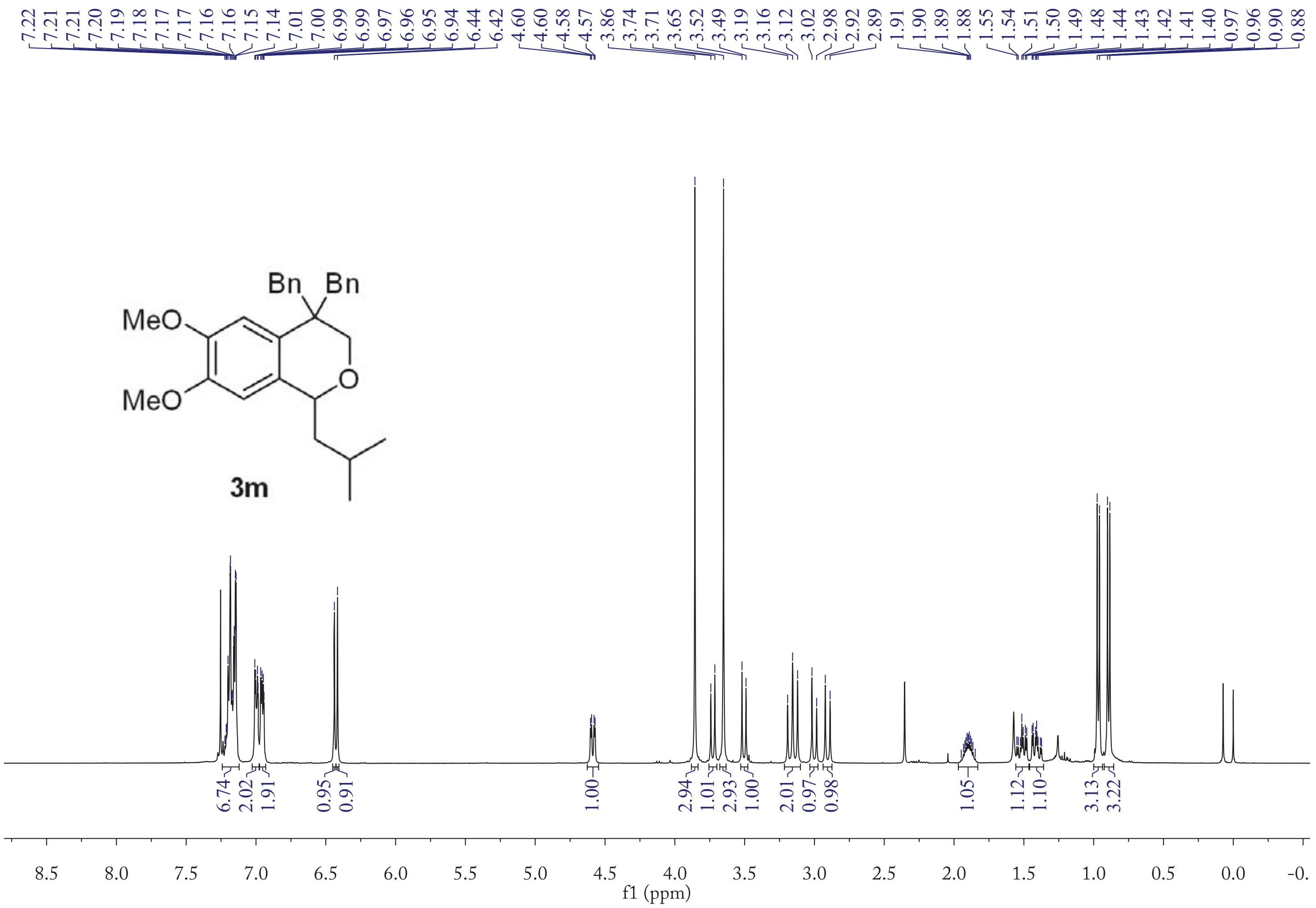
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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7.00
6.99
6.99
6.97
6.96
6.95
6.94
6.44
6.42
4.60
4.60
4.58
4.57
3.86
3.74
3.71
3.65
3.52
3.49
3.19
3.16
3.12
3.02
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2.92
2.89
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1.90
1.89
1.88
1.55
1.54
1.51
1.50
1.49
1.48
1.44
1.43
1.42
1.41
1.40
0.97
0.96
0.90
0.88
Bn
Bn
MeO
MeO
O
3m
6.74
2.02
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0.95
0.91
1.00
2.94
1.01
2.93
1.00
2.01
0.97
0.98
1.05
1.12
1.10
3.13
3.22
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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3.0
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2.0
1.5
1.0
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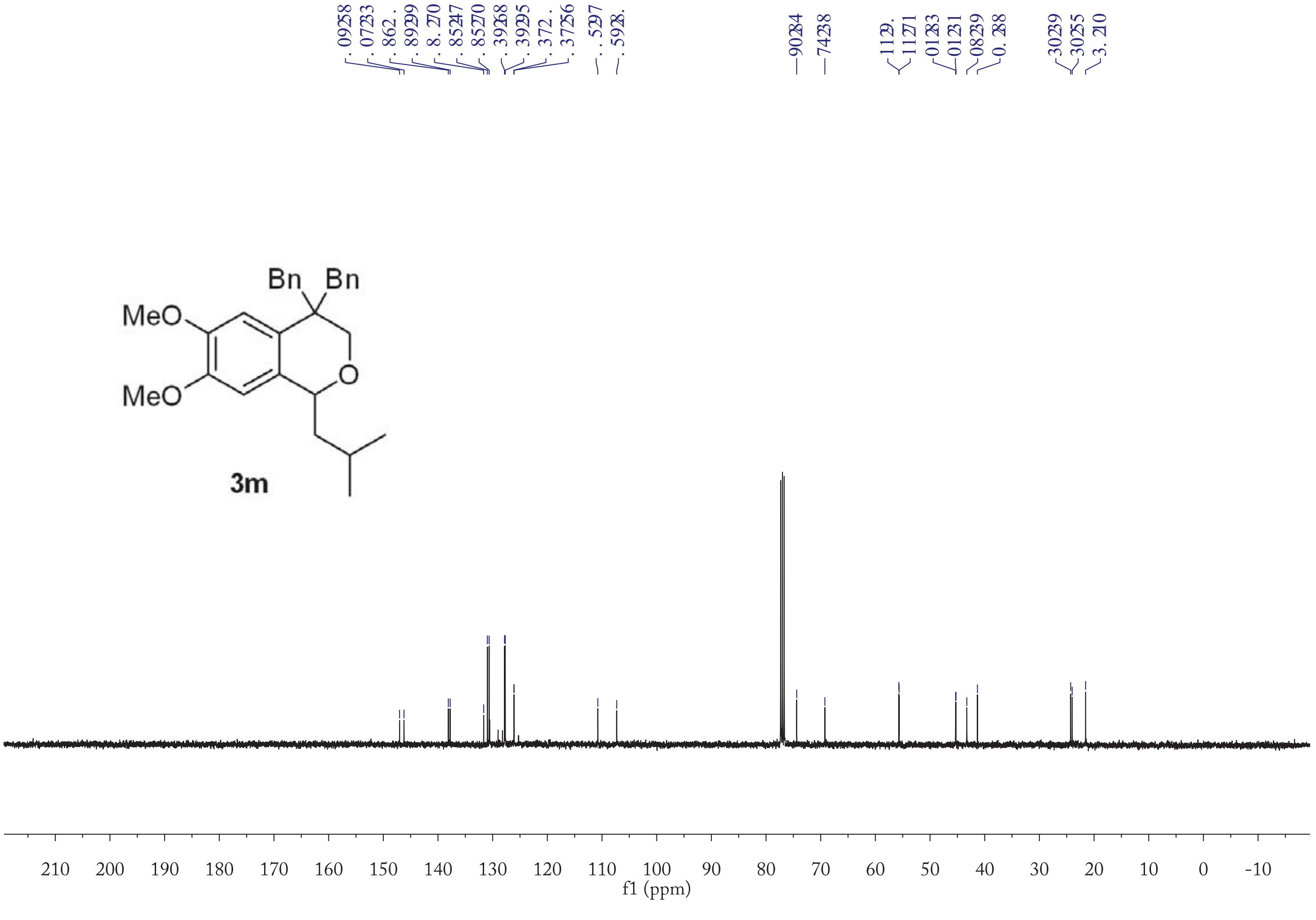
0.0
-0.
f1 (ppm)


Bn
Bn
MeO
MeO
O
3m
210
200
190
180
170
160
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140
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120
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100
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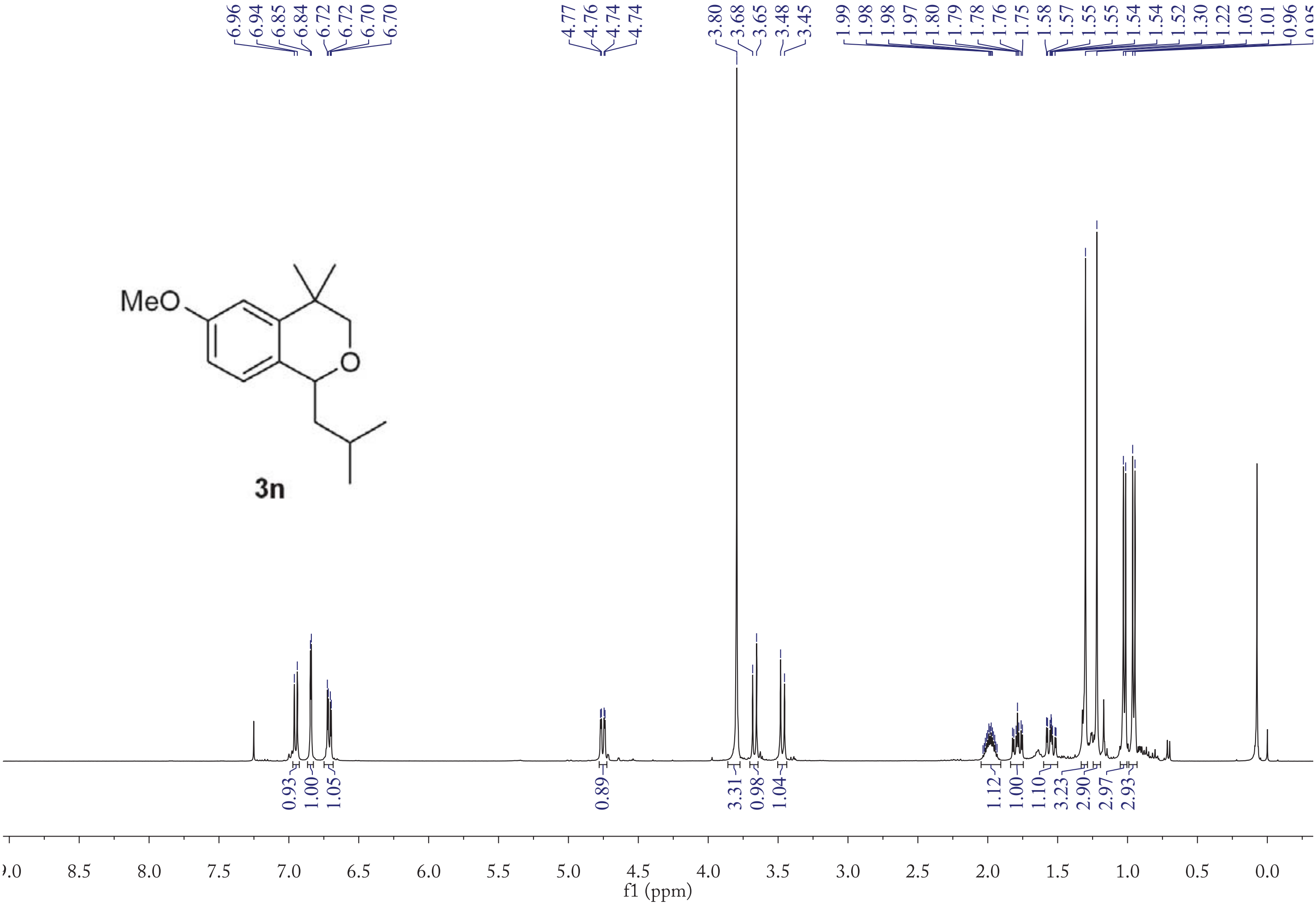
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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6.72
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6.70
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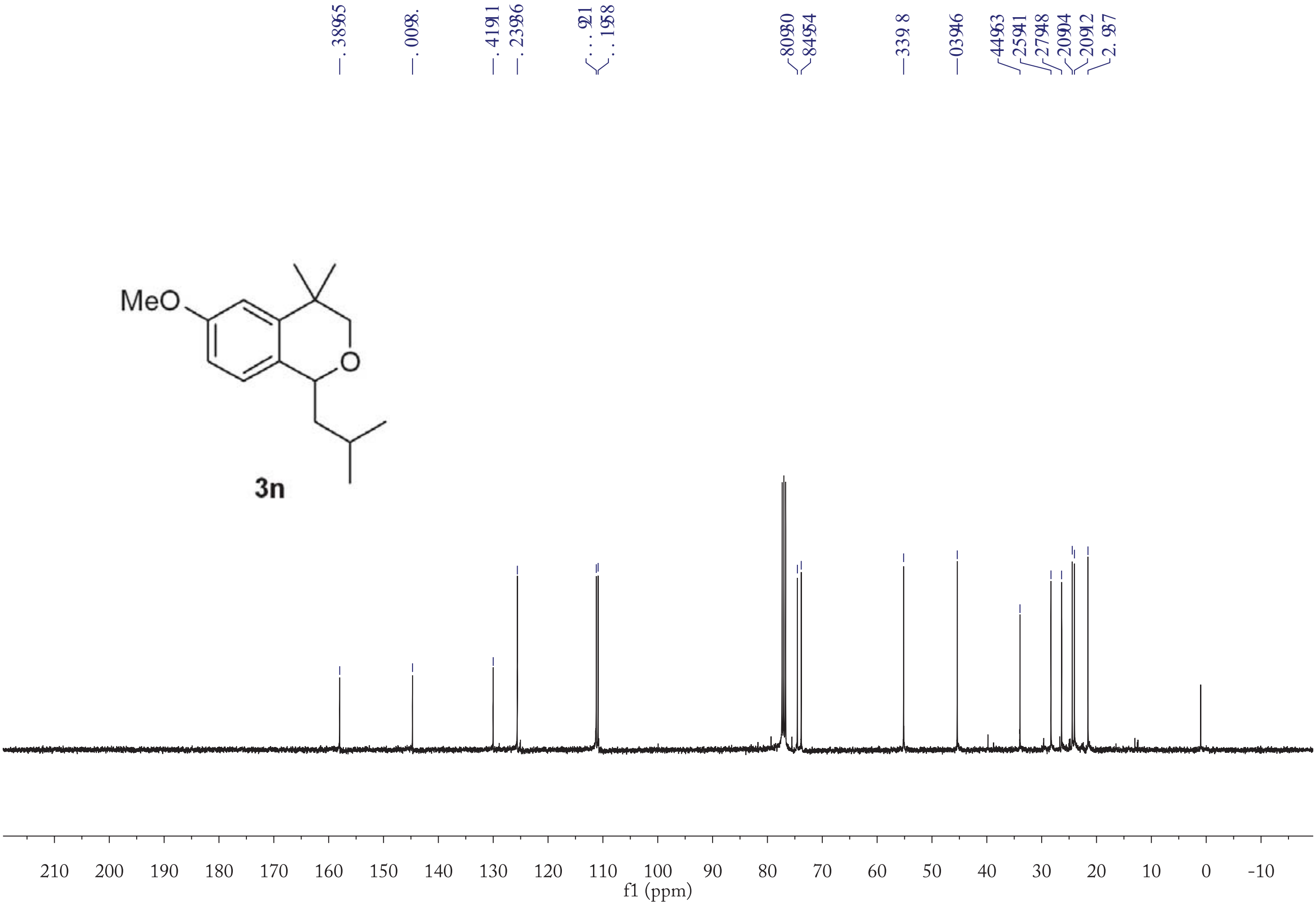
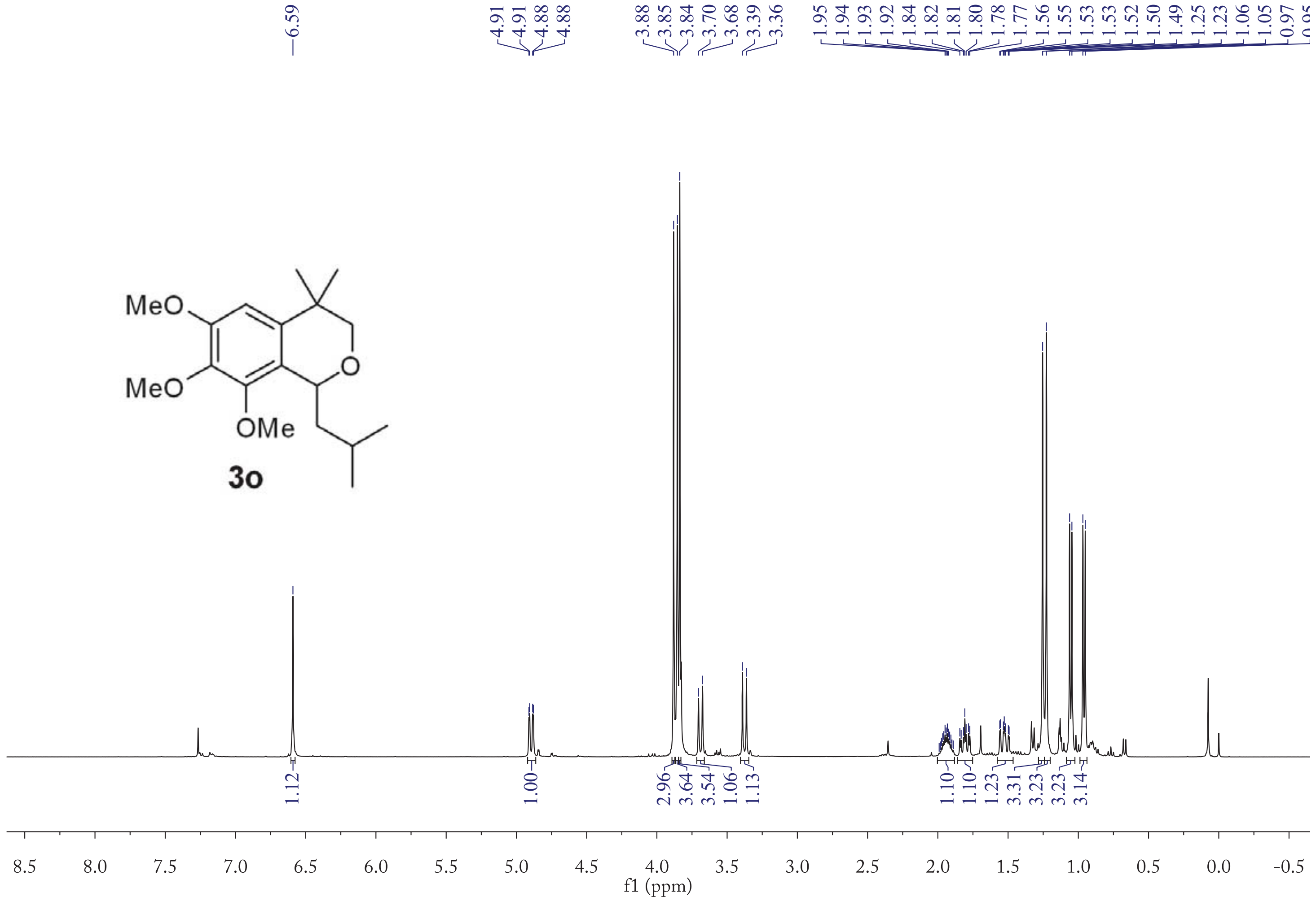
4.74
4.74
3.80
3.68
3.65
3.48
3.45
1.99
1.98
1.98
1.97
1.80
1.79
1.78
1.76
1.75
1.58
1.57
1.55
1.55
1.54
1.54
1.52
1.30
1.22
1.03
1.01
0.96
MeO
O
0.93
1.00
1.05
0.89
3.31
0.98
1.04
1.12
1.00
1.10
3.23
2.90
2.97
2.93
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

3n


MeO
O
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

3n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4.91
4.91
4.88
4.88
3.88
3.85
3.84
3.70
3.68
3.39
3.36
1.95
1.94
1.93
1.92
1.84
1.82
1.81
1.80
1.78
1.77
1.56
1.55
1.53
1.53
1.52
1.50
1.49
1.25
1.23
1.06
1.05
0.97
MeO
MeO
OMe
O
1.12
1.00
2.96
3.64
3.54
1.06
1.13
1.10
1.10
1.23
3.31
3.23
3.23
3.14
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
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2.5
2.0
1.5
1.0
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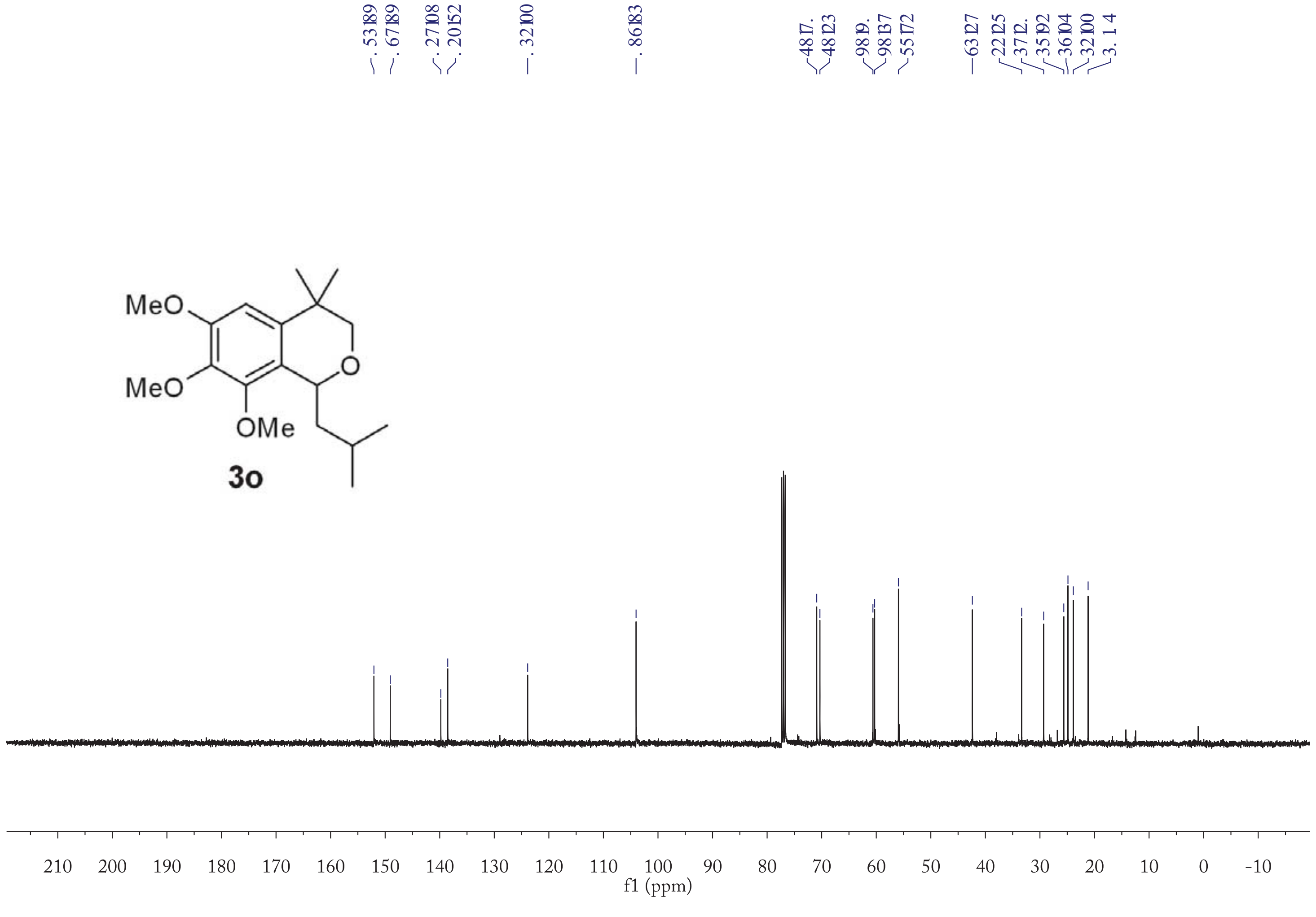
0.0
-0.5
f1 (ppm)

3o


. 53189
. 67189
. 27108
. 20152
. 32100
. 86183
4817.
48123
9819.
98137
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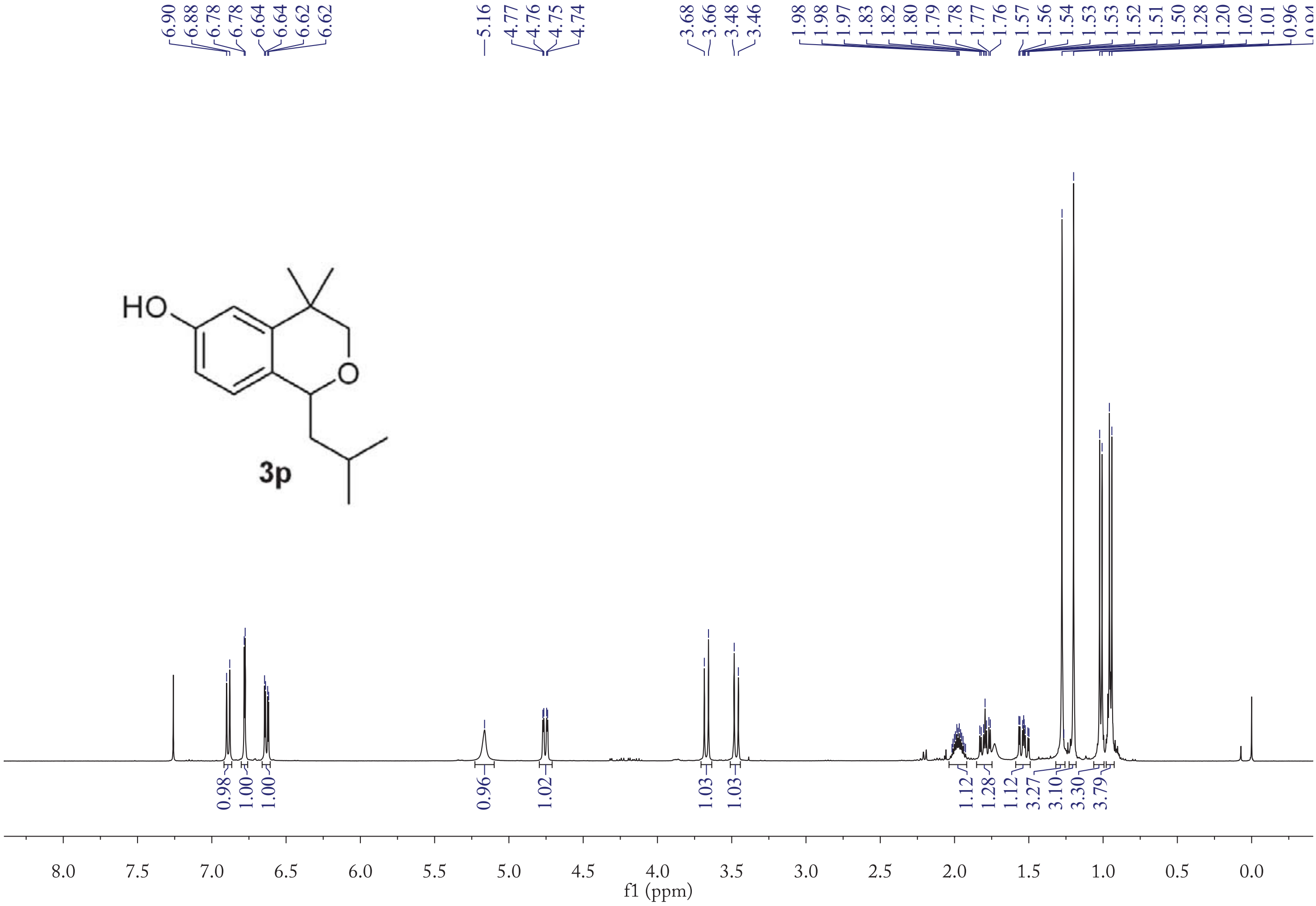
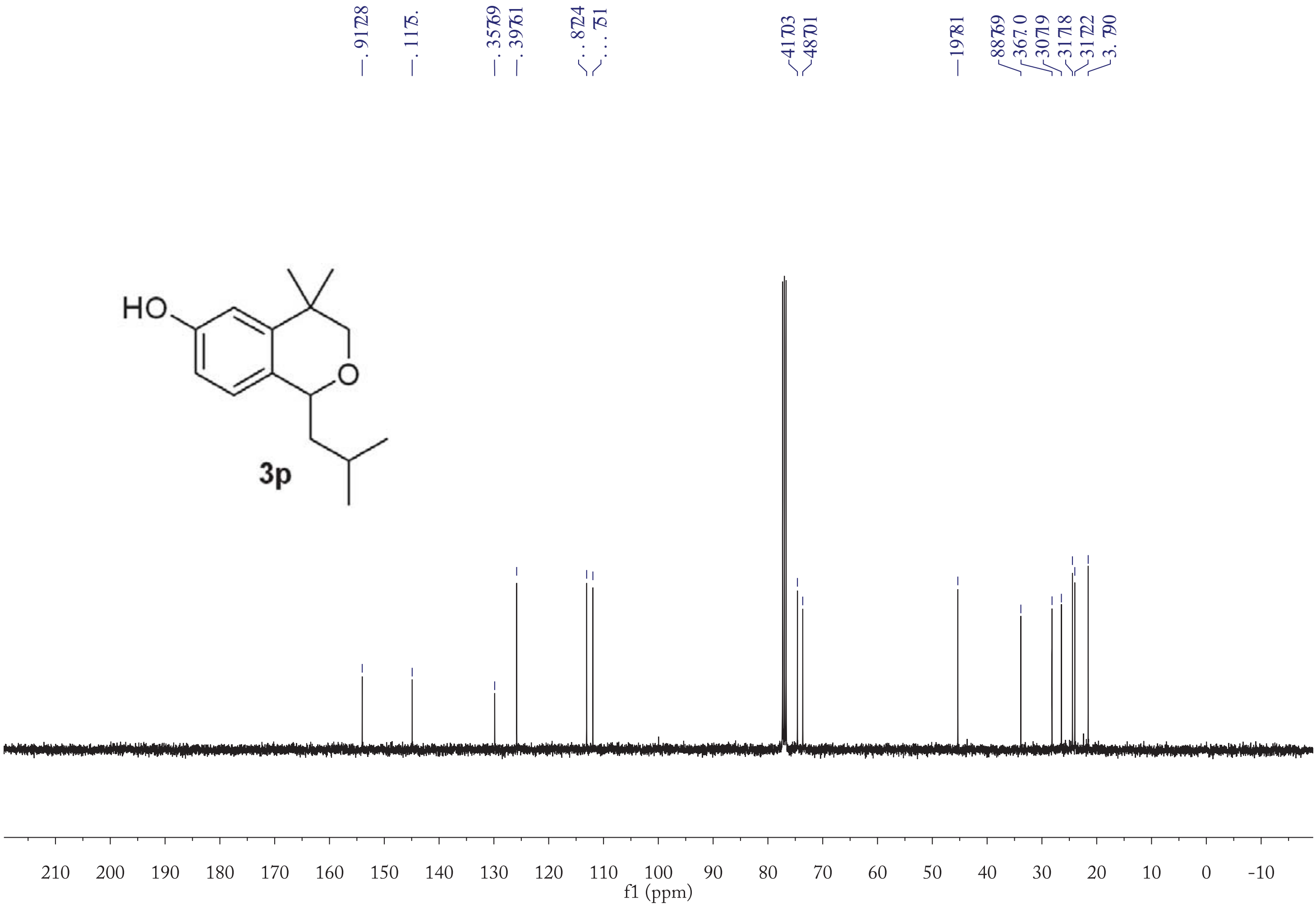
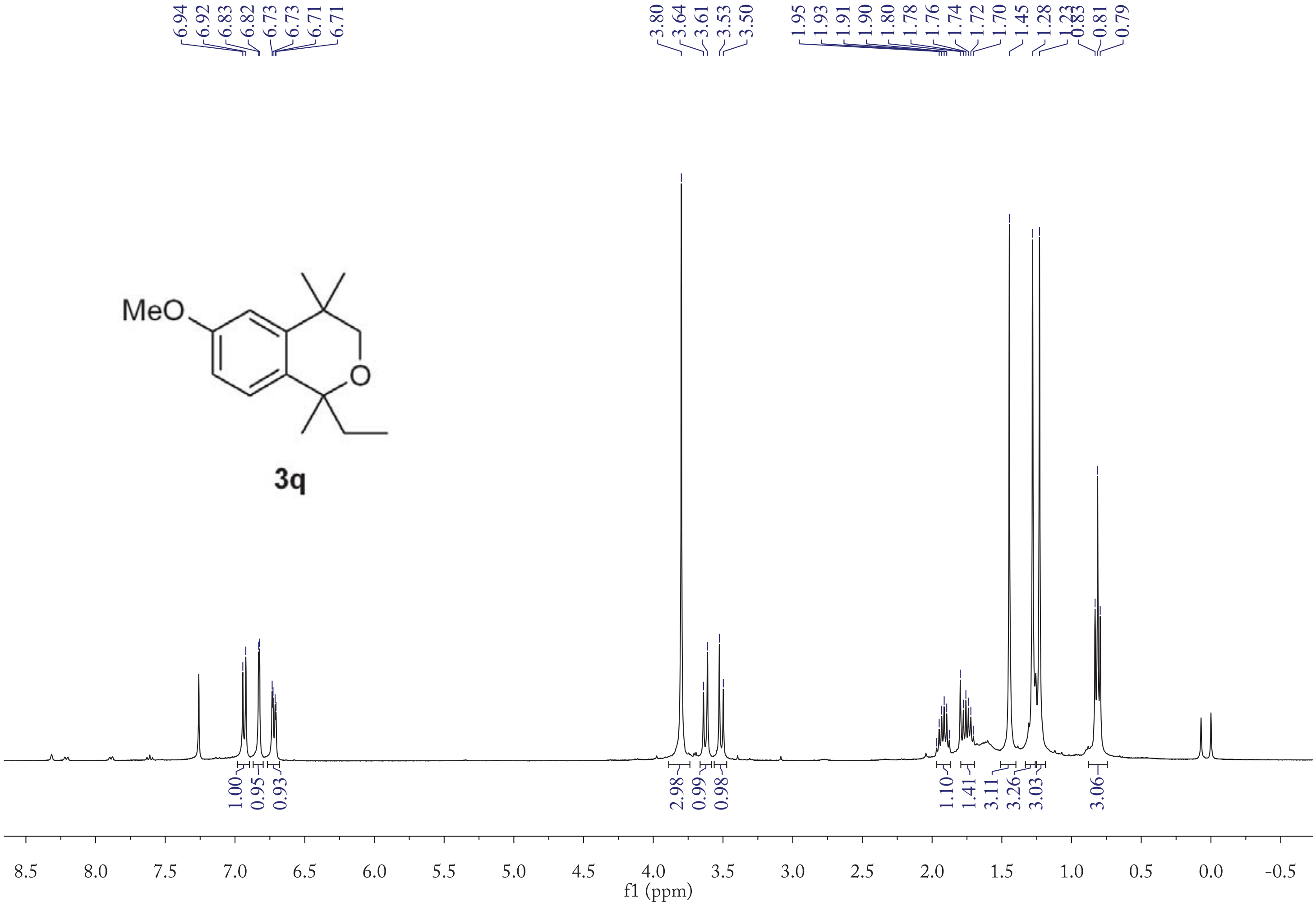
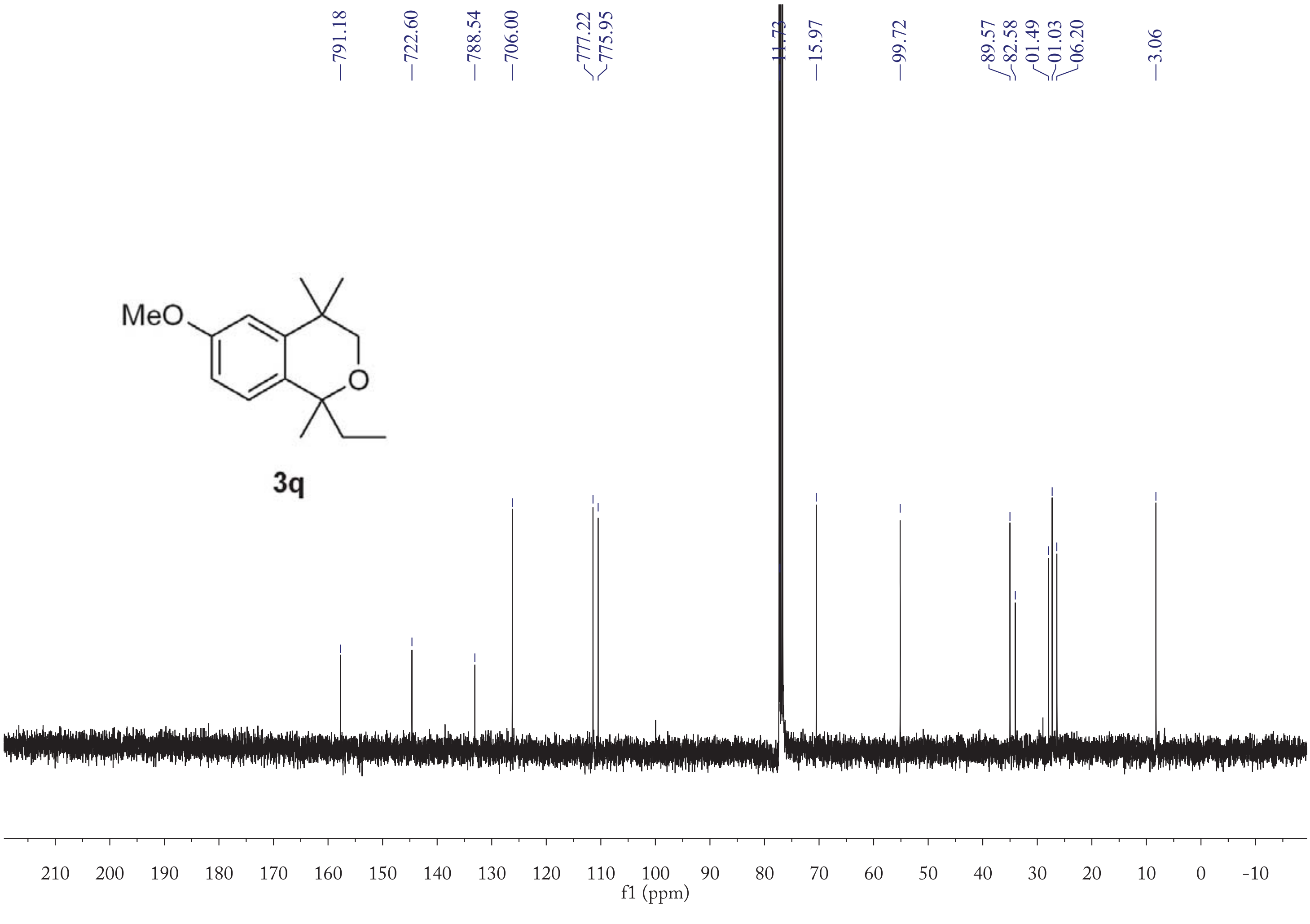
63127
22125
3712.
35192
36104
32100
3. 1 4
MeO
MeO
OMe
O
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

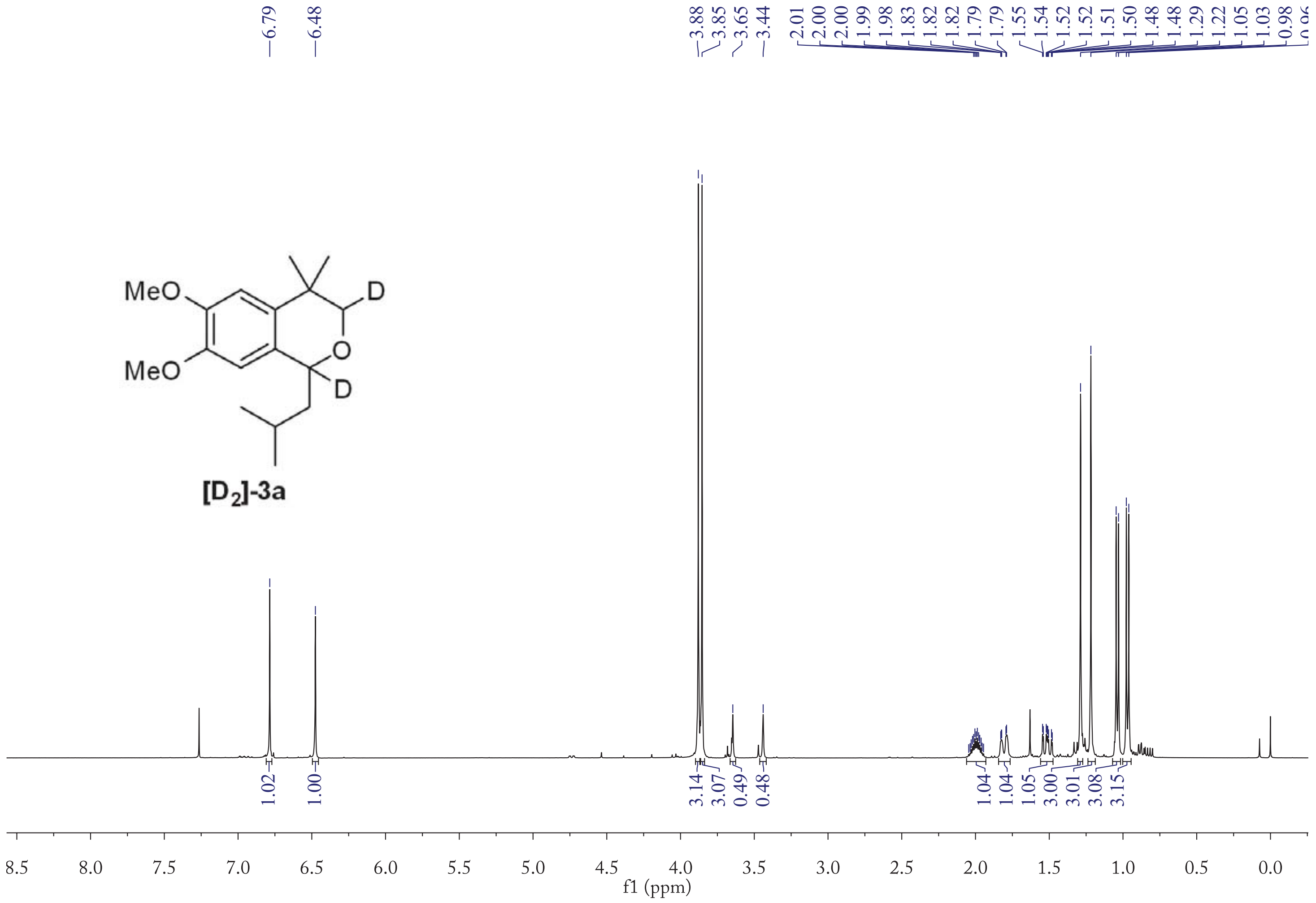
3o

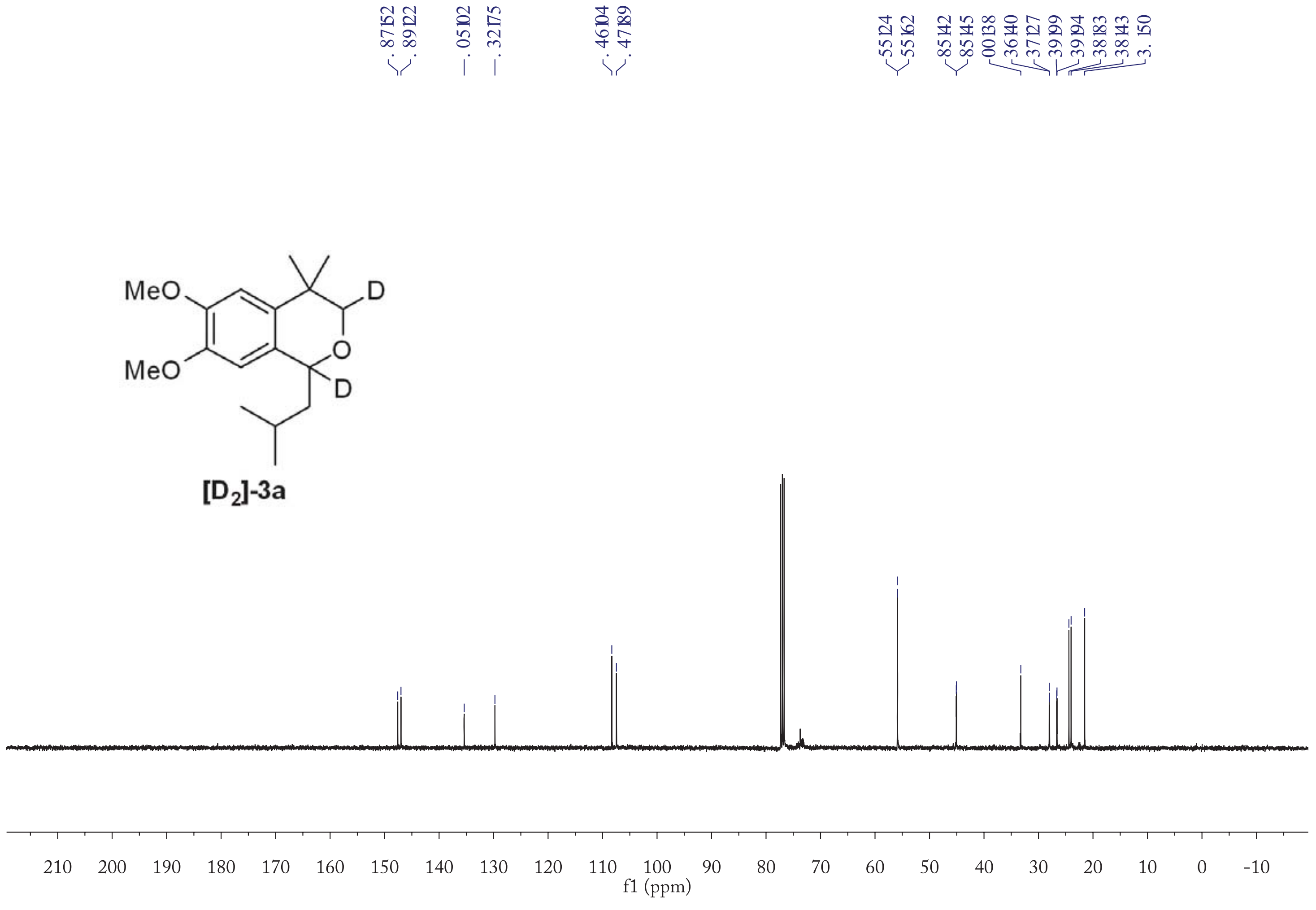

6.90
6.88
6.78
6.78
6.64
6.64
6.62
6.62
5.16
4.77
4.76
4.75
4.74
3.68
3.66
3.48
3.46
1.98
1.98
1.97
1.83
1.82
1.80
1.79
1.78
1.77
1.76
1.57
1.56
1.54
1.53
1.53
1.52
1.51
1.50
1.28
1.20
1.02
1.01
0.96
HO
O
3p
0.98
1.00
1.00
0.96
1.02
1.03
1.03
1.12
1.28
1.12
3.27
3.10
3.30
3.79
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

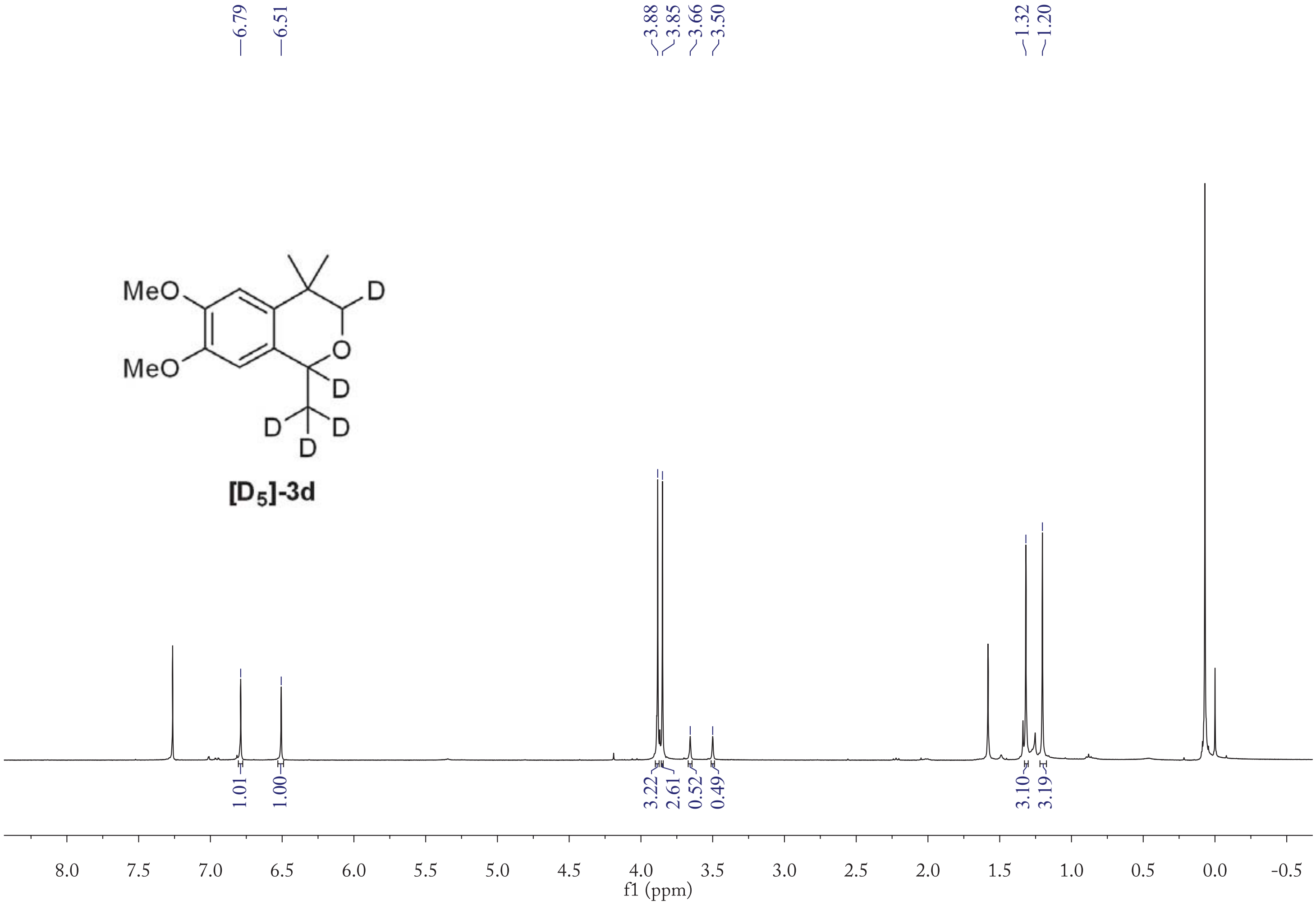

. 91728
. 1175.
. 35769
. 39761
. . 8724
. . . 751
41703
48701
19781
88769
367.0
30719
31718
31722
3. 790
HO
O
3p
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

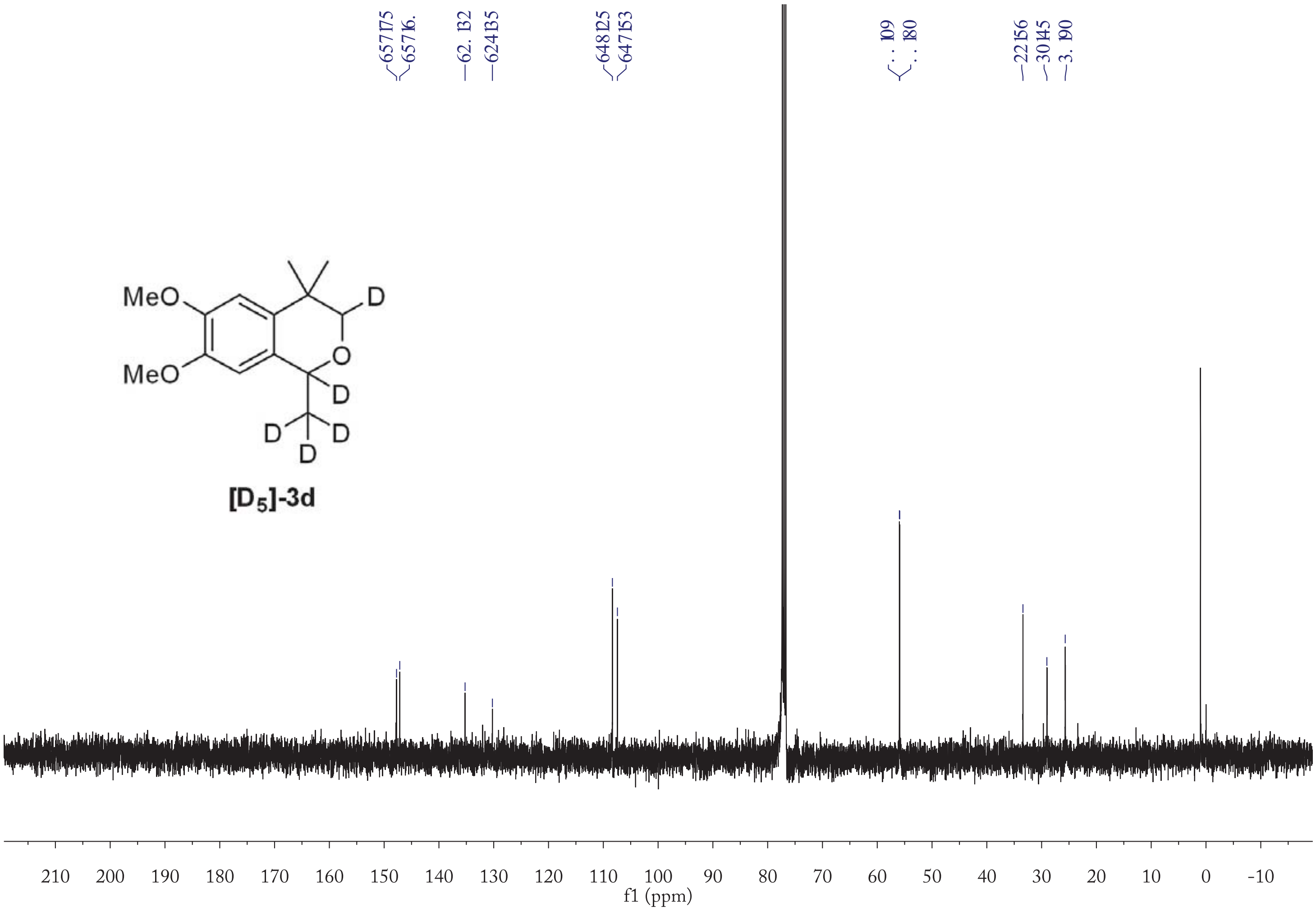

6.94
6.92
6.83
6.82
6.73
6.73
6.71
6.71
3.80
3.64
3.61
3.53
3.50
1.95
1.93
1.91
1.90
1.80
1.78
1.76
1.74
1.72
1.70
1.45
1.28
1.23
0.83
0.81
0.79
MeO
O
3q
1.00
0.95
0.93
2.98
0.99
0.98
1.10
1.41
3.11
3.26
3.03
3.06
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


791.18
722.60
788.54
706.00
777.22
775.95
11.73
15.97
99.72
89.57
82.58
01.49
01.03
06.20
3.06
MeO
O
3q
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


6.79
6.48
3.88
3.85
3.65
3.44
2.01
2.00
2.00
1.99
1.98
1.83
1.82
1.82
1.79
1.79
1.55
1.54
1.52
1.52
1.51
1.50
1.48
1.48
1.29
1.22
1.05
1.03
0.98
MeO
MeO
D
O
D
[D2]-3a
1.02
1.00
3.14
3.07
0.49
0.48
1.04
1.04
1.05
3.00
3.01
3.08
3.15
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


. 87152
. 89122
. 05102
. 32175
. 46104
. 47189
55124
55162
85142
85145
00138
36140
37127
39199
39194
38183
38143
3. 150
MeO
MeO
D
O
D
[D2]-3a
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


6.79
6.51
3.88
3.85
3.66
3.50
1.32
1.20
MeO
MeO
O
D
D
D
D
D
[D$_5$]-3d
1.01
1.00
3.22
2.61
0.52
0.49
3.10
3.19
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


657175
65716.
62. 132
624135
648125
647153
: : 109
. . 180
22156
30145
3. 190
MeO
MeO
O
D
D
D
D
D
[D$_5$]-3d
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)