

Electronic Supplementary Information

Asymmetric Synthesis of a Tricyclic Benzofuran motif: A Privileged Core Structure in Biologically Active Molecules

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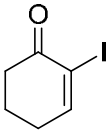
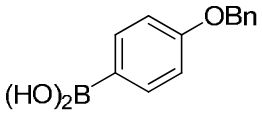
General

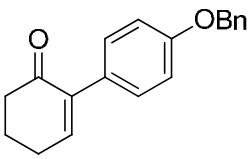
Chemicals and solvents were purchased from Sigma-Aldrich. Reactions involving oxygen and/or moisture sensitive reagents were carried out under an atmosphere of nitrogen using anhydrous Toluene. Toluene was distilled from benzophenone/sodium and used freshly distilled. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a JEOL JNM-EX 400-spectrometer at 400 and 100 MHz, respectively or ^{13}C NMR spectra on a 500 Varian Unity Inova-spectrometer at 126 MHz. Chemical shifts are reported in ppm with the solvent residual peak as internal standard ($CHCl_3$ δ 7.26, CDCl3 δ 77.0). The reactions were monitored by thin-layer chromatography (TLC), on silica plated aluminum sheets (Silica gel 60 F254, E. Merck) detecting spots by UV (254 and 365 nm). Flash chromatography was performed on Merck Silica gel 60 (0.040-0.063 mm). Optical rotation was measured on a Perkin Elmer polarimeter 341 LC. Gas chromatography/mass spectrometry analyses were performed on a Varian Saturn 2000 GCMS with a Supelco SLB-5ms fused silica capillary column using helium as carrier gas. Injector temperature 300°C, temperature program: 70 to 330 °C (12 °C/min) with 4 minutes hold time. The MS detector consisted of an ion trap with 70eV ionization. The HRMS-analyses were conducted by SP Sveriges Tekniska Forskningsinstitut Kemi och Materialteknik- Organisk analytisk kemi. Chiral HPLC chromatography analyses were performed on a Varian 9012Q/9050 UV-VIS detector using HPLC-grade solvents; n-hexane and isopropanol.



8: To a stirred solution of cyclohex-2-enone (3 g, 31.2 mmol) in 1:1 THF-H_2O (100 mL) was added K_2CO_3 (5.18 g, 37.5 mmol), I_2 (1.18 g, 46.8 mmol) and DMAP (669 mg, 6.24 mmol) successively. The reaction was stirred for 16 h and then diluted with EtOAc (100 mL) and washed with sat. $Na_2S_2O_3$ (20 mL) and 0.1 M HCl (20 mL), dried over $MgSO_4$, concentrated *in vacuo* and purified by flash chromatography (pentane:EtOAc, 5:1). α-iodoenone **8** isolated as colorless wet crystals in 82% yield.[1] ^{1}H NMR (400 Hz; $CDCl_3$) δ 7.76 (t, *J* = 4.4 Hz, 1H), 2.65 (d, *J* = 6.8 Hz, 2H), 2.43 (dd, *J* = 10.5, 6.0 Hz, 2H), 2.08 (dt, *J* = 12.6, 6.1 Hz, 2H); ^{13}C NMR (101 MHz; $CDCl_3$) δ 192.15, 159.43, 103.80, 37.19, 29.87, 22.78; *m/z* (EI) 222 (M+, 100%), 194 (50), 166 (14).

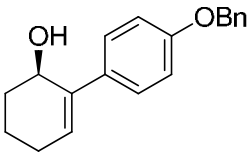


(4-(benzyloxy)phenyl)boronic acid. 4-Benzyloxyphenylbromide (14.0 g, 53.2 mmol) was dissolved in distilled THF (100 mL) in a septa equipped round-bottom flask. The solution was purged with N_2 and cooled to -75 °C in a CO_2/acetone bath. N-Butyllithium (2.5 M in hexanes, 27 mL) was added slowly while maintaining the temperature below -65 °C. The mixture was stirred for 1 h below -65 °C and then triisopropyl borate (39 mL, 170 mmol) was added while maintaining the temperature at -65 °C. The resulting clear solution was warmed to room temperature and stirred for 16 h. Conc. HCl was added until a pH of 6-7 was reached. The reaction mixture was poured into diethyl ether (200 mL) and the organic layer was washed three times with water, dried over anhydrous $MgSO_4$ and filtered. The solvent was removed and the product was recrystallized from EtOAc/hexanes (1:10). Yield: 82%. ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.17 (d, *J* = 8.4 Hz, 2H), 7.47 (d, *J* = 7.6 Hz, 2H), 7.41 (t, *J* = 7.4 Hz, 2H), 7.35 (dd, *J* = 8.4, 5.8 Hz, 1H), 7.09 (d, *J* = 8.4 Hz, 2H), 5.16 (s, 2H); ^{13}C NMR (101 MHz; $CDCl_3$) δ 162.38, 137.51, 136.67, 128.63, 128.07, 127.53, 114.36, 99.77, 69.82.

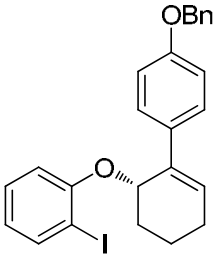


9: To a Mw-vial containing, iodoenone **8**, (167 mg, 0.75 mmol) , Na_2CO_3 (159 mg, 1.5 mmol), Ar-$B(OH)_2$ (342 mg, 1.5 mmol), and Pd/C (40 mg, 5 mol%) was added DME (1.5

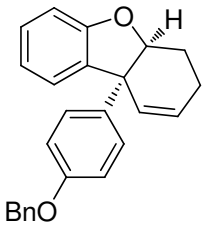
mL) and H_2O (1.5 mL). The mixture was degassed by alternating vacuum and N_2 three times, pre stirred for 5 min and then subjected to microwave irradiation (80 °C) for 15 min. Without removing the Mw-cap the reaction mixture was extracted with diethylether (5 x 3ml), the combined organic phase was dried (Na_2SO_4), evaporated and purified by flash chromatography (pentane:EtOAc, 5:1). The title compound **9** was obtained in 168mg, 80% yield as an of white solid.[2] ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.46 – 7.35 (m, *J* = 7.6, 6.6 Hz, 4H), 7.35 – 7.30 (m, 1H), 7.25 (d, *J* = 8.7 Hz, 2H), 6.99 (t, *J* = 4.3 Hz, 1H), 6.95 (d, *J* = 8.8 Hz, 2H), 5.07 (s, 2H), 2.58 (t, *J* = 6.9 Hz, 2H), 2.52 (dd, *J* = 10.4, 6.0 Hz, 2H), 2.10 (p, *J* = 6.1 Hz, 2H); ^{13}C NMR (101 MHz; $CDCl_3$) δ 198.24, 158.36, 146.96, 139.74, 137.02, 129.76, 129.25, 128.56, 127.92, 127.43, 114.39, 69.98, 39.11, 26.60, 22.96; *m/z* (EI) 278 (M+, 48%), 187 (9), 91 (100).



10: A prestirred (10 min, rt) solution of (*S*)-(−)-2-Methyl-CBS-oxazaborolidine (60mg, 0.22 mmol) and borane dimethyl sulfide complex (BMS) (0.377 mL, 0.75 mmol, 2M solution in toluene) in toluene (3 mL) was placed in an ice bath. The cold reaction mixture was then added a solution of **9** (200 mg, 0.72 mmol) in toluene (3 mL) via a syringe pump over 2h. The reaction was continued at 0 °C for an additional 2h before it was quenched with 2 ml of 1M HCl and diluted with 75 mL diethylether, extracted, washed with water (5mL), brine (5mL) and dried over $MgSO_4$. The crude product was purified by silica gel chromatography (pentane:EtOAc, 10:1) to give the allylic alcohol **10** (168 mg, 83% yield and 98% ee) as an of white solid ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.49 – 7.37 (m, 6H), 7.36 – 7.29 (m, 1H), 6.97 (d, *J* = 8.6 Hz, 2H), 6.14 – 6.07 (m, 1H), 5.08 (s, 2H), 4.68 (t, *J* = 3.5 Hz, 1H), 2.35 – 2.09 (m, 2H), 2.03 – 1.93 (m, 1H), 1.91 – 1.57 (m, 4H); ^{13}C NMR (101 MHz; $CDCl_3$) δ 158.00, 138.31, 136.97, 132.87, 128.54, 127.91, 127.43, 127.18, 127.03, 114.82, 69.96, 65.42, 31.51, 25.97, 17.26; *m/z* (EI) 281 (M+1, 24%), 171 (11), 128 (7), 91 (100); $[\alpha]_D^{20}$=+66.1 (c 1, $CHCl_3$); HPLC: Diacel Chiralpak AD column (n-hexane: 2-Propanol = 95:5, flow rate 1 mL/min, λ = 254 nm). Retention time (min): 27.9 (minor) and 31.3 (major). The racemic standard was prepared by reducing **9** under Luche conditions.[3]

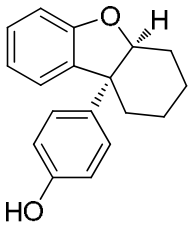


12: To a stirred solution of **10** (85mg, 0.30 mmol), 2-iodophenol (133mg, 0.61 mmol), and PPh_3 (159 mg, 0.61 mmol) in toluene (15ml) was added DIAD (122 mg, 0.61 mmol) at 0°C. The solution was allowed to reach room temperature and stirred over night and then diluted with 15 mL toluene and quenched with 4ml 1 M NaOH. The organic layer was separated and washed with water (5 ml), brine (5ml) and dried over $MgSO_4$ and concentrated. The crude product was purified by flash chromatograph (pentane:EtOAc, 20:1) to render the product in 88mg, 60% yield. ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.77 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.45 – 7.22 (m, 8H), 6.92 (d, *J* = 8.6 Hz, 1H), 6.89 (d, *J* = 8.8 Hz, 2H), 6.69 (td, *J* = 7.4, 1.1 Hz, 1H), 6.28 (dd, *J* = 5.0, 2.8 Hz, 1H), 5.17 (t, *J* = 3.0 Hz, 1H), 5.04 (s, 2H), 2.45 – 2.37 (m, 1H), 2.26 – 2.13 (m, 2H), 2.07 – 1.95 (m, 1H), 1.75 – 1.63 (m, 2H); ^{13}C NMR (126 MHz; $CDCl_3$) δ 157.82, 156.63, 139.70, 137.04, 135.07, 134.05, 129.81, 129.23, 128.50, 127.84, 127.40, 127.04, 122.41, 114.60, 113.55, 88.40, 73.24, 69.92, 27.42, 25.89, 17.10; $[\alpha]_D^{20}$=-26.9 (c 1, $CHCl_3$); HPLC: Diacel Chiralpak AD column (n-hexane: 2-Propanol = 95:5, flow rate 1 mL/min, λ = 254 nm). Retention time (min): 6.6 (minor) and 7.3 (major).



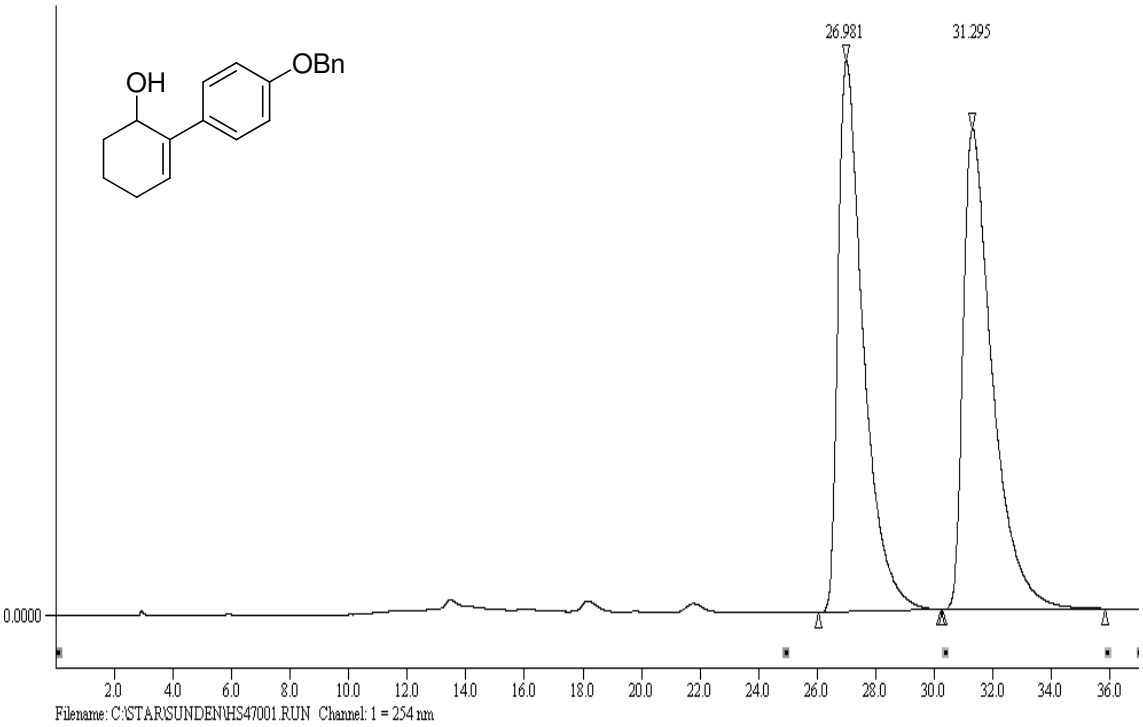
13: To a vial containing Ag_2CO_3 (56 mg, 0,20 mmol), PPh_3 (5.2 mg, 0.020 mmol) and $Pd(OAc)_2$ (2.2 mg, 0.010 mmol) was added a solution of aryl ether **12** (33 mg, 0.068 mmol) in toluene (1.5 mL). The mixture was degassed by alternating vacuum and N_2 three times and heated at 80° C in a sealed vial for 16h at which the completion and selectivity of the reaction was measured by crude-NMR. The reaction was directly purified by silica gel chromatography (pentane:EtOAc, 20:1) to yield the cyclic product as a colorless oil in 95% yield. ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.50 – 7.27 (m, 7H), 7.17 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.00 – 6.93 (m,

3H), 6.91 – 6.82 (m, 2H), 6.02 – 5.93 (m, 1H), 5.72 – 5.64 (m, 1H), 5.06 (s, 2H), 4.73 (t, *J* = 1.7 Hz, 1H), 2.41 – 2.29 (m, 1H), 2.22 – 2.12 (m, 1H), 2.12 – 2.01 (m, 1H), 1.87 – 1.69 (m, 1H); ^{13}C NMR (126 MHz; $CDCl_3$) δ 159.94, 157.75, 136.96, 136.69, 134.42, 129.51, 129.38, 128.58, 128.36, 127.97, 127.48, 126.75, 124.67, 120.92, 114.56, 109.95, 89.59, 70.04, 53.27, 21.56, 18.96; *m/z* (EI) 354 (M+, 100%), 235 (2), 91 (7); $[\alpha]_D^{20}$=+60.2 (c 1, $CHCl_3$).



14: To a stirred solution of **13** (99mg, 0.28 mmol) in ethanol (3mL) was added Pd/C (10mg, 10% wt). The reaction vessel was purged by alternating vacuum and H_2 three times before it was subjected to an atmosphere of H_2. When complete conversion of starting material could be determined (TLC) the reaction was directly purified by silica gel chromatography (pentane:EtOAc, 5:1) to yield the final product as a colorless oil in 49 mg, 67% yield. ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.24 (d, *J* = 8.7 Hz, 2H), 7.19 – 7.11 (m, 1H), 6.90 – 6.83 (m, 3H), 6.78 (d, *J* = 8.7 Hz, 2H), 4.83 (t, *J* = 3.6 Hz, 1H), 4.68 (s, 1H), 2.37 – 2.24 (m, 1H), 2.08 – 1.95 (m, 1H), 1.87 – 1.51 (m, 6H); ^{13}C NMR (101 MHz; $CDCl_3$) δ 158.63, 153.97, 137.98, 136.84, 128.79, 127.95, 123.63, 120.84, 115.05, 110.12, 89.78, 50.95, 33.81, 26.19, 21.44, 19.64; *m/z* (EI) 266 (M+, 100), 223 (84), 195 (17); $[\alpha]_D^{20}$=+2.5 (c 0.4, $CHCl_3$); HRMS (FI-ICR-MS) *m/z* Calcd for: $C_{18}H_{18}O_2$ $[M+H]^+$ 267.1379, (found) 267.1385.

1. C. R. Johnson, J. P. Adams, M. P. Braun, C. B. W. Senanayake, P. M. Wovkulich and M. R. Uskokovi´c, *Tetrahedron Lett.*, 1992, **33**, 917-918.
2. F.-X. Felpin, *J. Org. Chem.*, 2005, **70**, 8575-8578.
3. A. L. Gemal and J. L. Luche, *J. Am. Chem. Soc.*, 1981, **103**, 5454-5459.

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Method File  : c:\star\sunden\untitled.mth
Sample ID    : hs4701_ad_95_c

Injection Date: 17-MAR-10 11:42 AM    Calculation Date: 18-MAR-10 5:40 PM

Operator    : Operator                Detector Type: 9050
Workstation:                          Bus Address  : 3
Instrument :                          Sample Rate  : 10.00 Hz
Channel     : 1 = 254 nm              Run Time     : 44.987 min

*********** Star Chromatography Workstation ******* Version 4.51 **************

Run Mode         : Analysis
Peak Measurement: Peak Area
Calculation Type: Percent
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Peak No.	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	Width 1/2 (sec)	Status Codes
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2		50.0598	31.295	0.000	17659234	BB	60.6	
Totals:		100.0000		0.000	35276256			

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Total Unidentified Counts :   35276256 counts

Detected Peaks: 2            Rejected Peaks: 0      Identified Peaks: 0

Multiplier: 1          Divisor: 1

Baseline Offset: -3 microAU

Noise (used): 40 microAU - monitored before this run

Manual injection

Revision Log:

17-MAR-10 12:27 PM: Calculated results from channel 1 using method:
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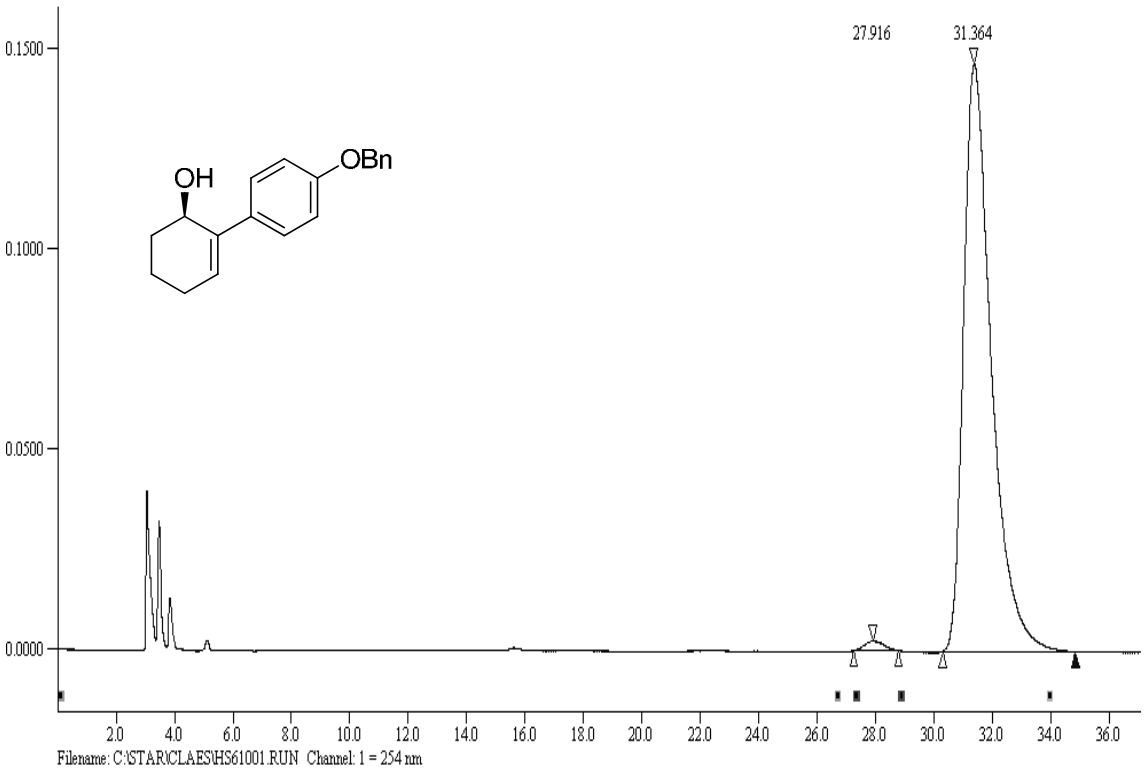


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Title        :
Run File     : C:\STAR\CLAES\HS61001.RUN
Method File  : c:\star\claes\untitled.mth
Sample ID    : hs6110

Injection Date: 1-JUN-10 3:52 PM     Calculation Date: 1-JUN-10 4:34 PM

Operator    : Operator               Detector Type: 9050
Workstation:                         Bus Address  : 3
Instrument  : 1                      Sample Rate  : 10.00 Hz
Channel     : 1 = 254 nm             Run Time     : 37.102 min

*********** Star Chromatography Workstation ******* Version 4.51 **************

Run Mode         : Analysis
Peak Measurement: Peak Area
Calculation Type: Percent
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Peak No.	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	Width 1/2 (sec)	Status Codes
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2		98.8798	31.364	0.000	5094479	BB	62.3	U
Totals:		100.0000		0.000	5152196			

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Status Codes:
U - User-defined peak endpoint(s)

Total Unidentified Counts :    5152196 counts

Detected Peaks: 2           Rejected Peaks: 0      Identified Peaks: 0

Multiplier: 1          Divisor: 1

Baseline Offset: -21 microAU

Noise (used): 116 microAU - monitored before this run

Manual injection
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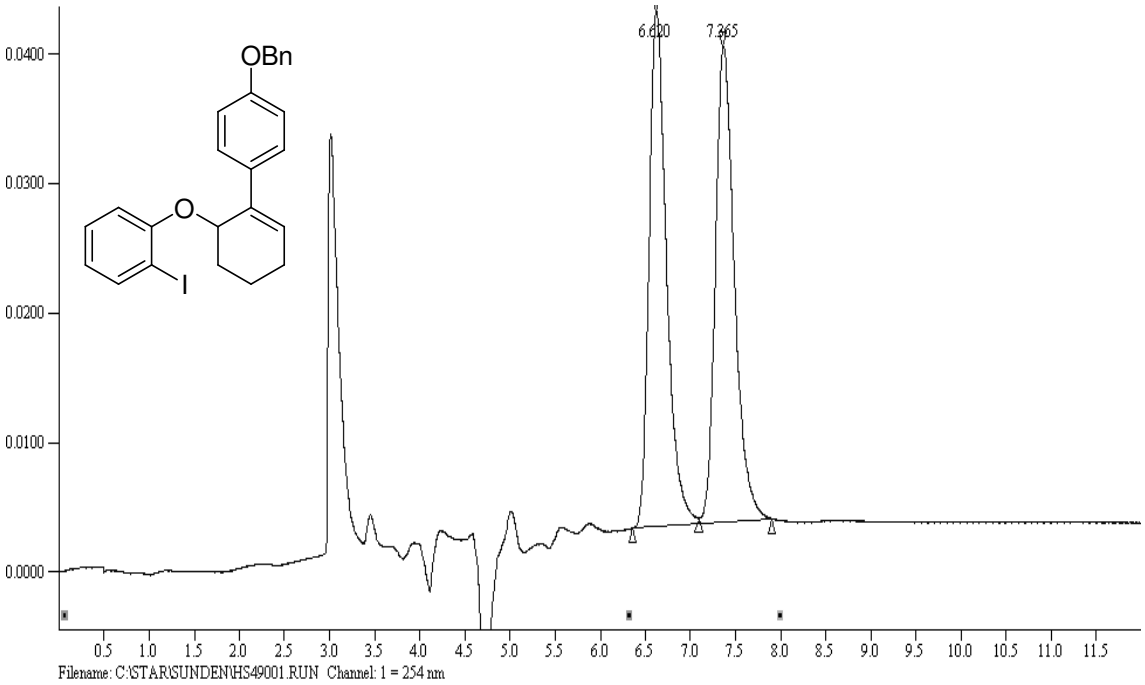

Title :
Run File : C:\STAR\SUNDEN\HS49001.RUN
Method File : c:\star\sunden\hs49001.mth
Sample ID : hs4902

Injection Date: 20-MAY-10 4:19 PM Calculation Date: 10-JUN-10 11:23 AM

Operator : Operator Detector Type: 9050
Workstation: Bus Address : 3
Instrument : Sample Rate : 10.00 Hz
Channel : 1 = 254 nm Run Time : 17.102 min

********** Star Chromatography Workstation ******* Version 4.51 **********

Run Mode : Analysis - Subtract Blank Baseline
Peak Measurement: Peak Area
Calculation Type: Percent

Peak No.	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	Width 1/2 (sec)	Status Codes
1		49.8528	6.620	0.000	281672	BV	12.1	
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Totals:		100.0000		0.000	565008			

Total Unidentified Counts : 565009 counts

Detected Peaks: 2 Rejected Peaks: 0 Identified Peaks: 0

Multiplier: 1 Divisor: 1

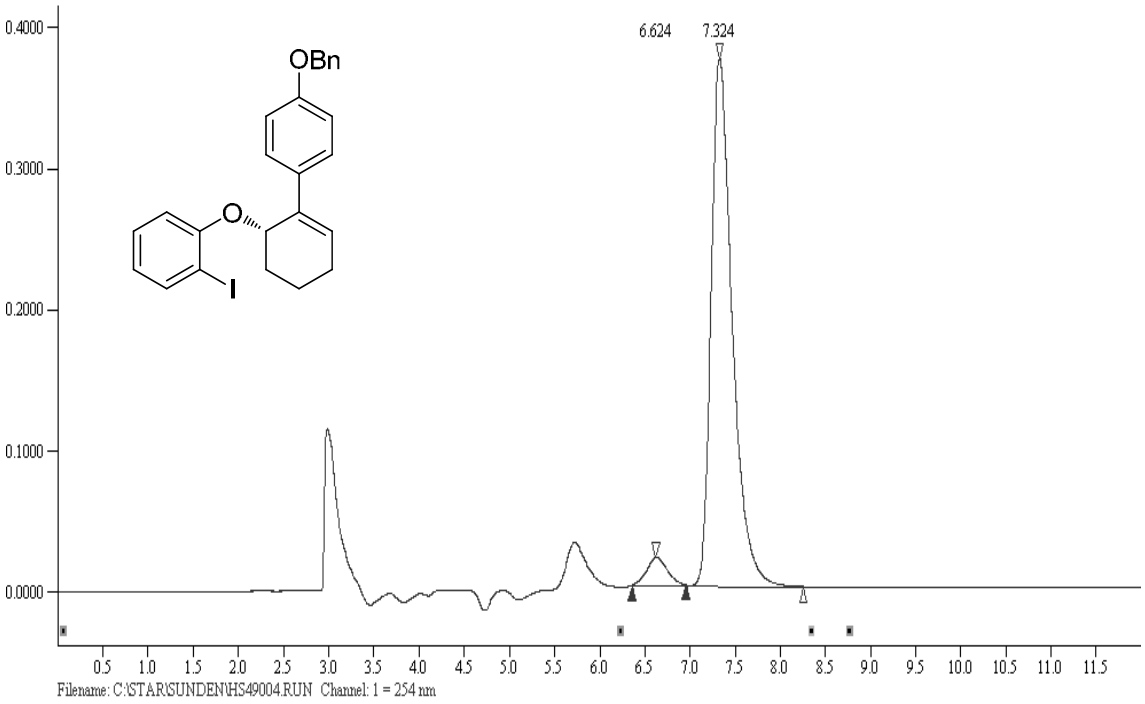
Baseline Offset: -6 microAU

Noise (used): 102 microAU - monitored before this run

Manual injection

Revision Log:

20-MAY-10 4:37 PM: Calculated results from channel 1 using method:



Title :
Run File : C:\STAR\SUNDEN\HS49004.RUN
Method File : c:\star\sunden\hs49001.mth
Sample ID : hs4906

Injection Date: 2-JUN-10 3:20 PM Calculation Date: 10-JUN-10 2:15 PM

Operator : Operator Detector Type: 9050
Workstation: Bus Address : 3
Instrument : 1 Sample Rate : 10.00 Hz
Channel : 1 = 254 nm Run Time : 27.860 min

********** Star Chromatography Workstation ******* Version 4.51 **********

Run Mode : Analysis - Subtract Blank Baseline
Peak Measurement: Peak Area
Calculation Type: Percent

Peak No.	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	Width 1/2 (sec)	Status Codes
1		4.9799	6.624	0.000	167211	BV	15.0	U
2		95.0201	7.324	0.000	3190484	VB	14.6	U
Totals:		100.0000		0.000	3357695			

Status Codes:
U - User-defined peak endpoint(s)

Total Unidentified Counts : 3357694 counts

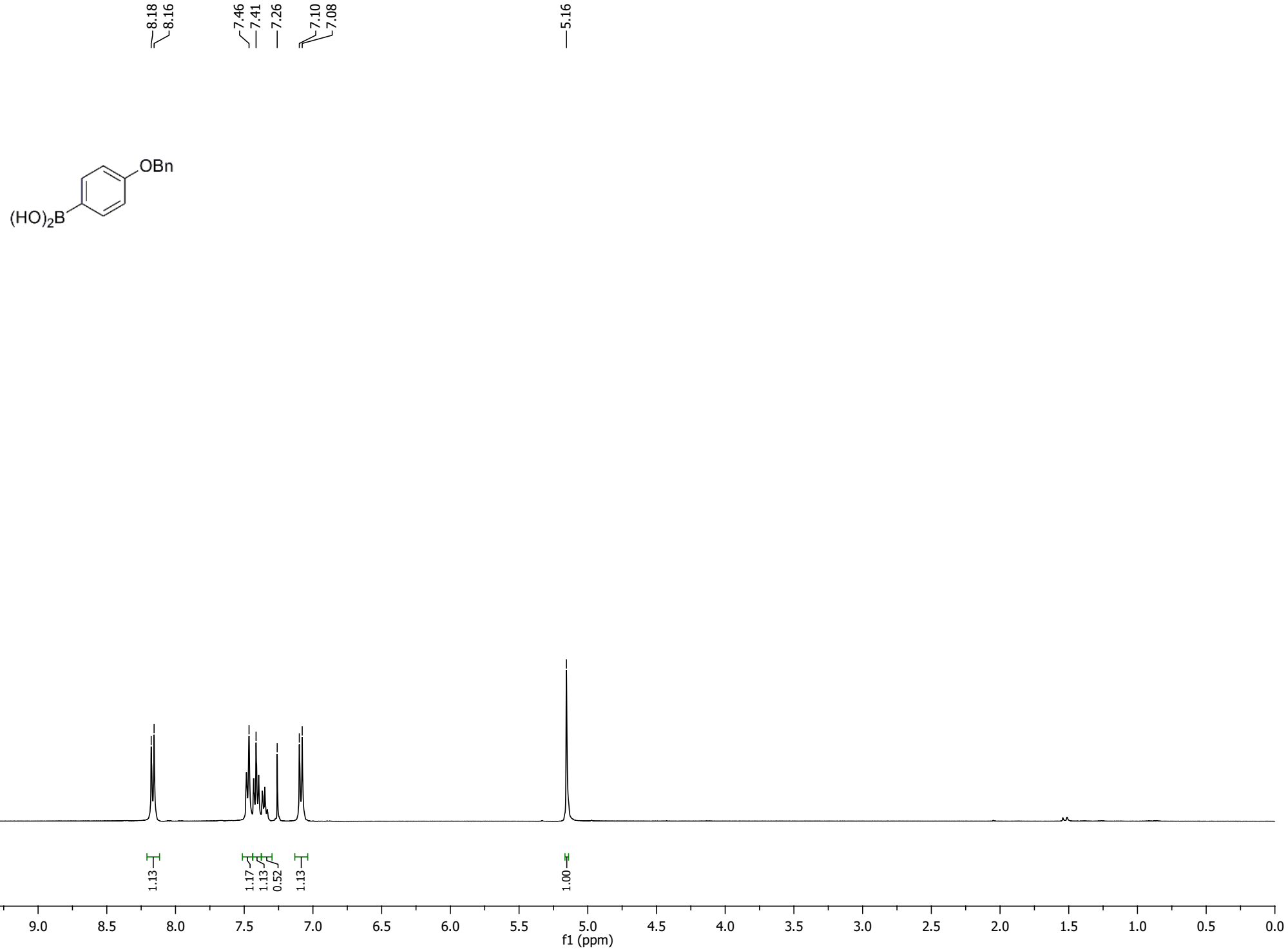
Detected Peaks: 2 Rejected Peaks: 0 Identified Peaks: 0

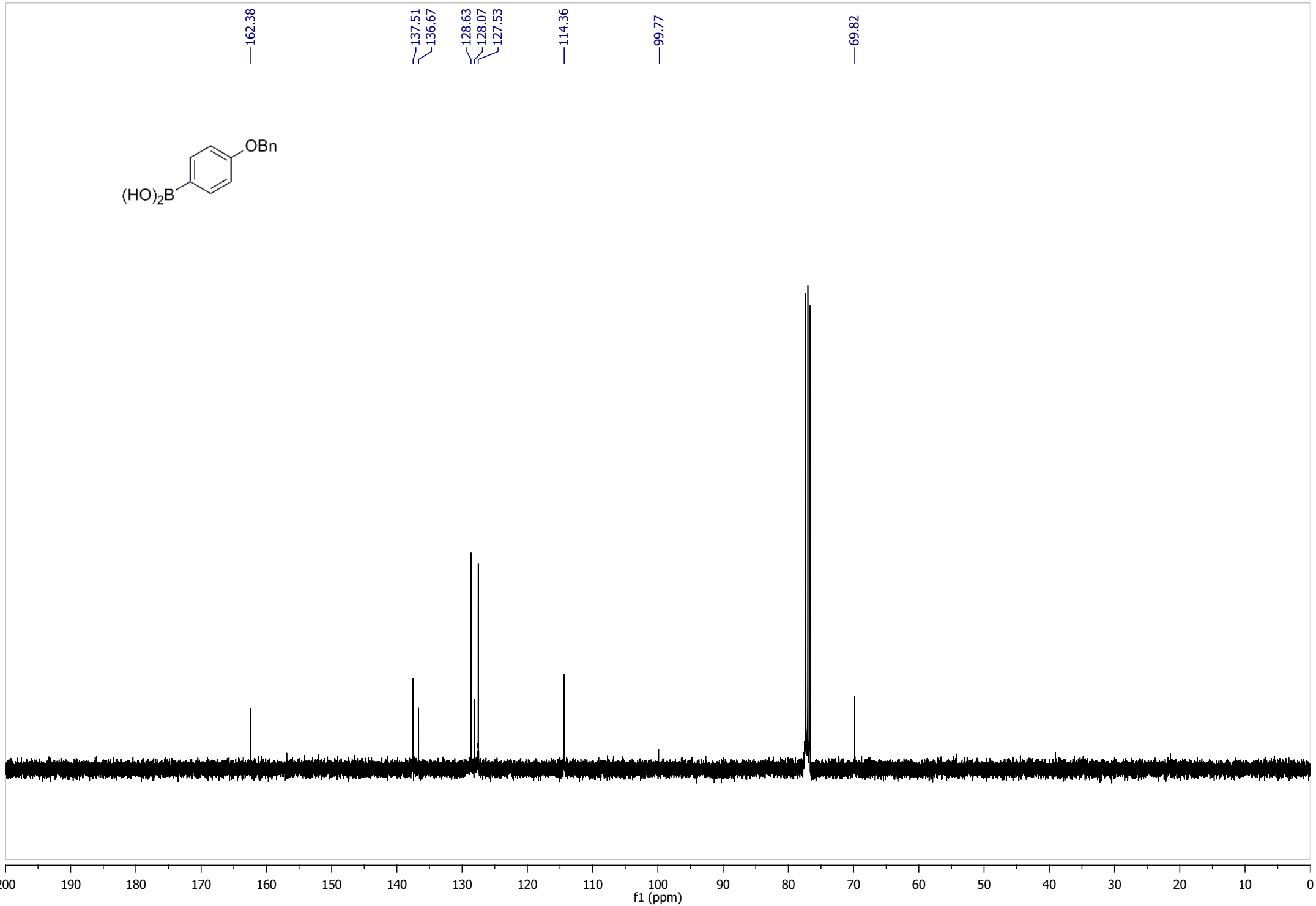
Multiplier: 1 Divisor: 1

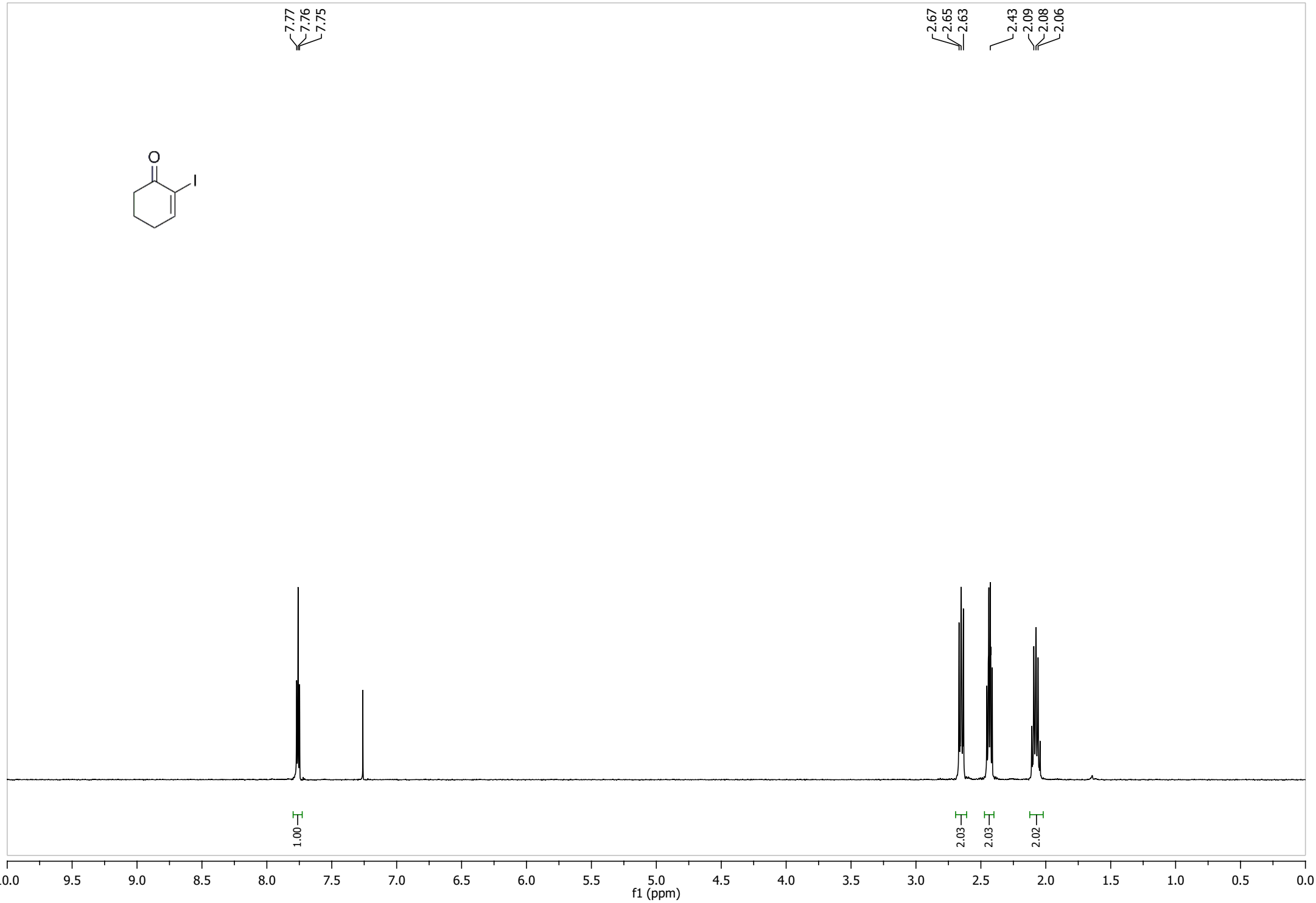
Baseline Offset: -21 microAU

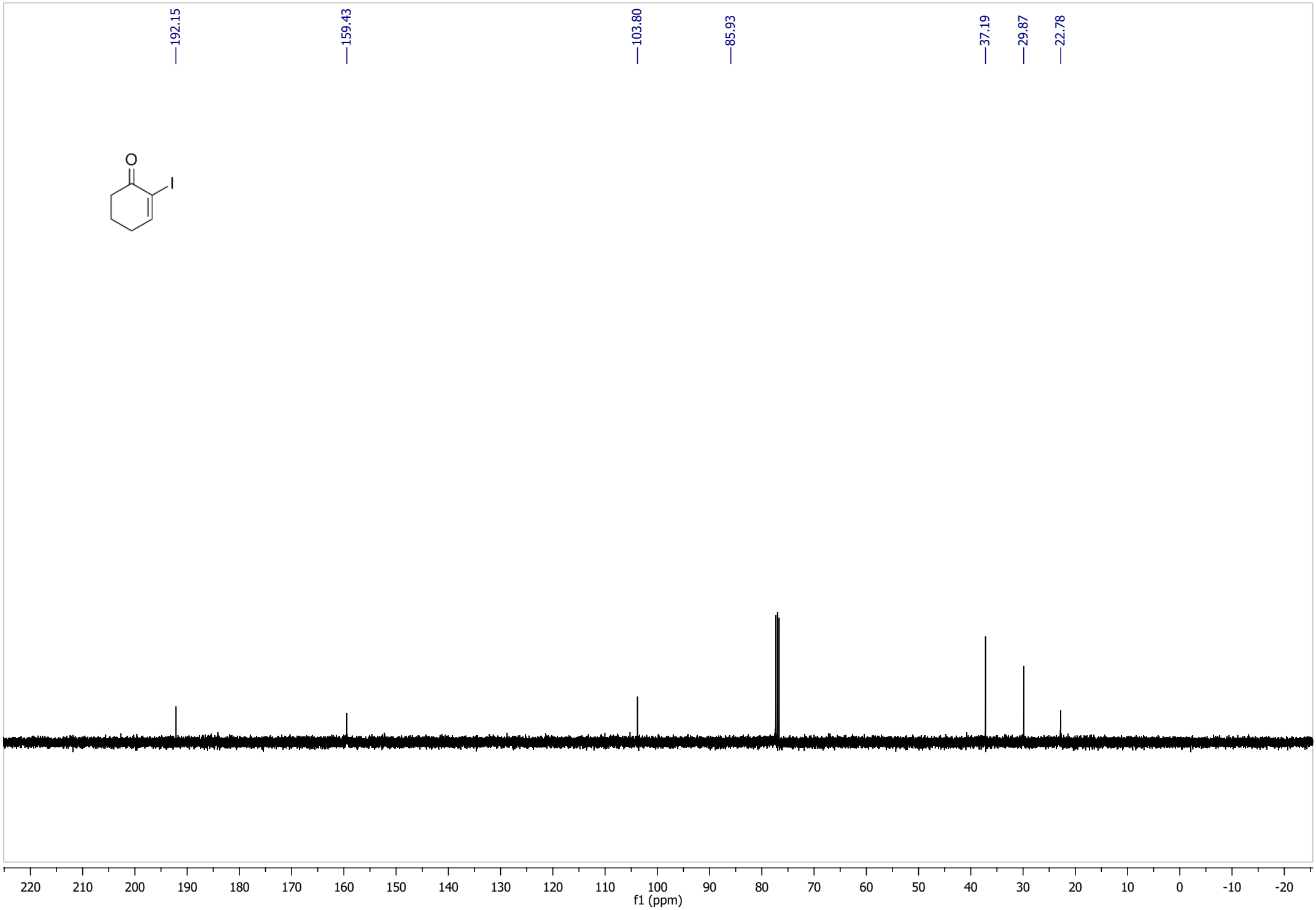
Noise (used): 129 microAU - monitored before this run

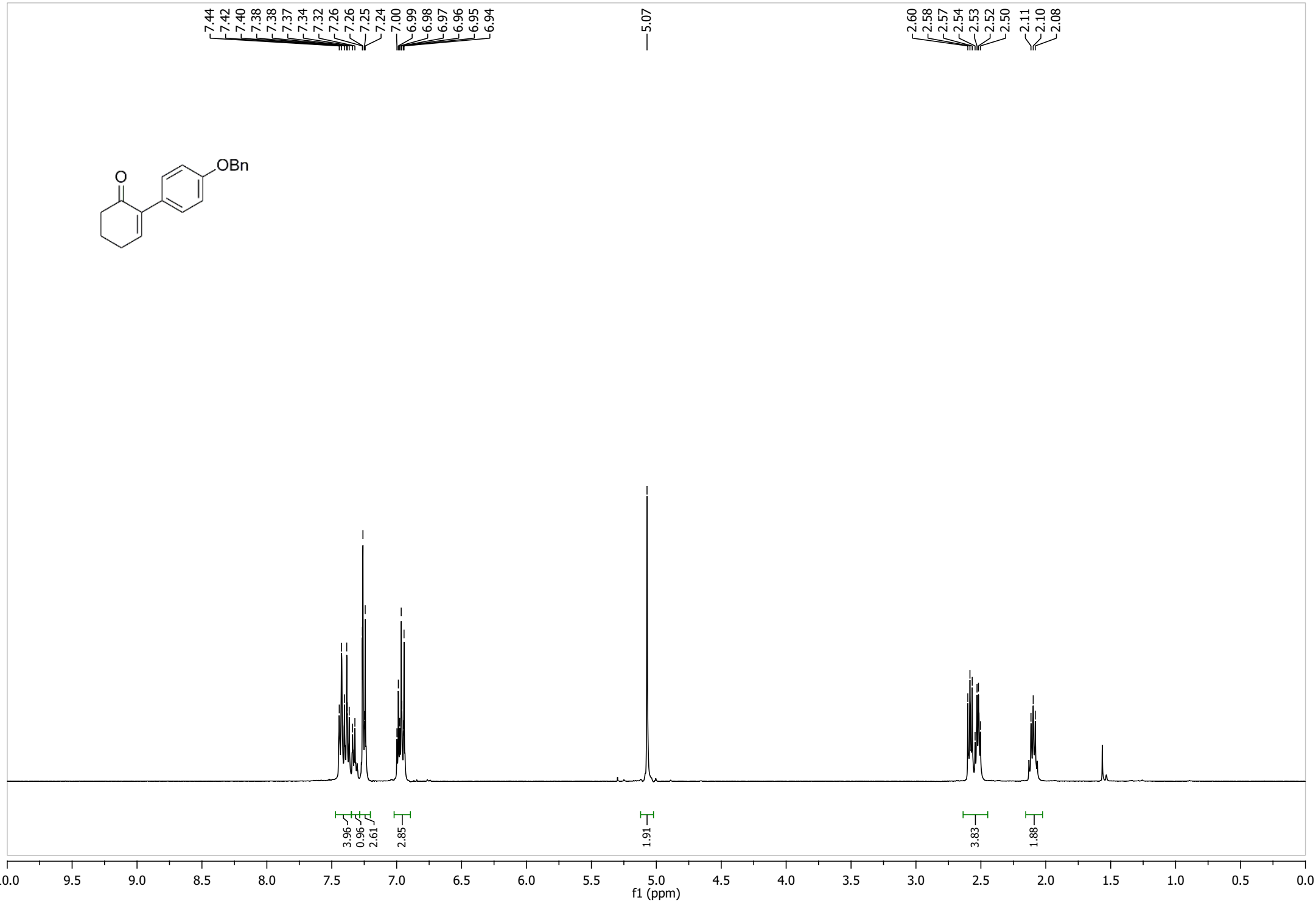
Manual injection

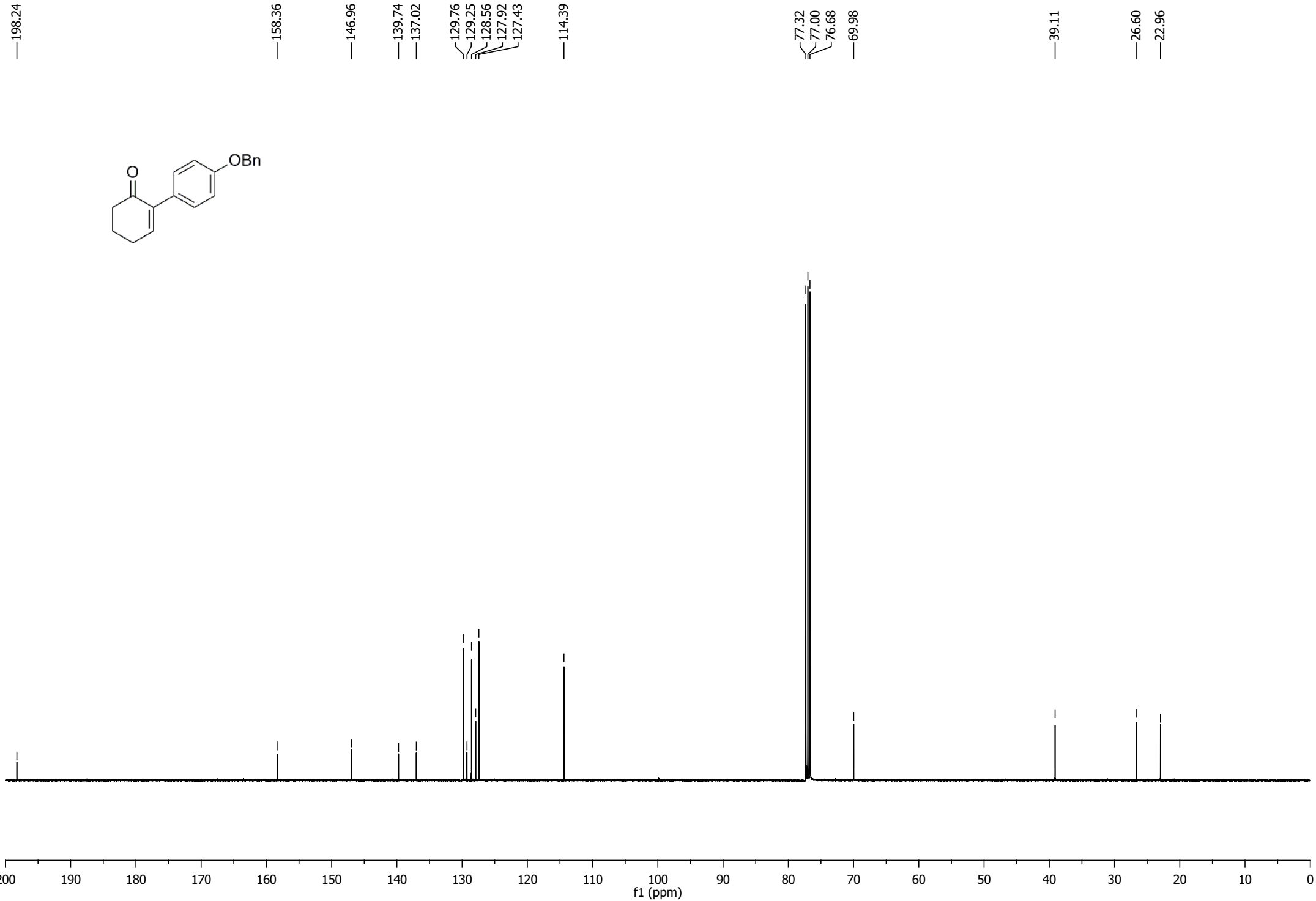


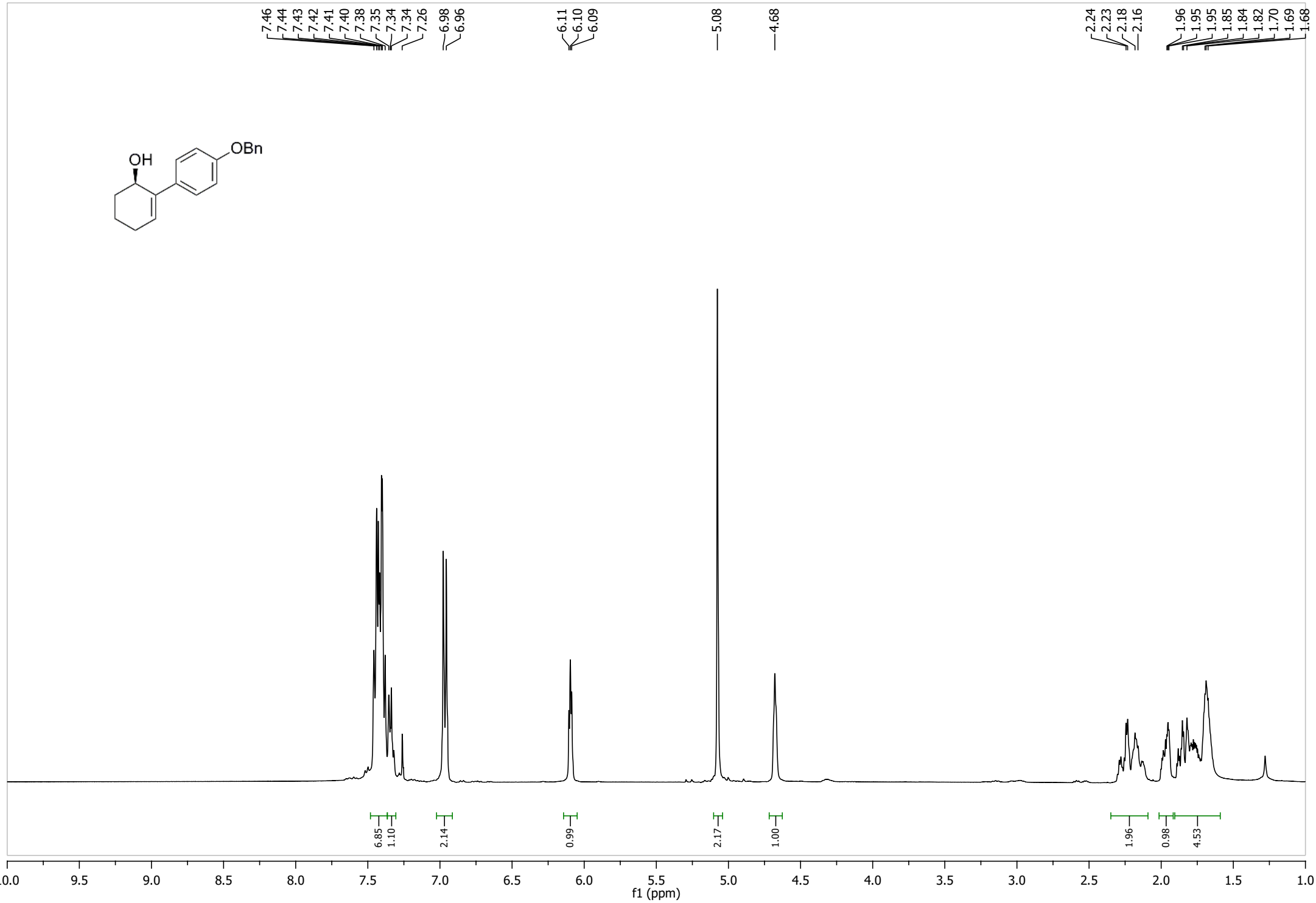


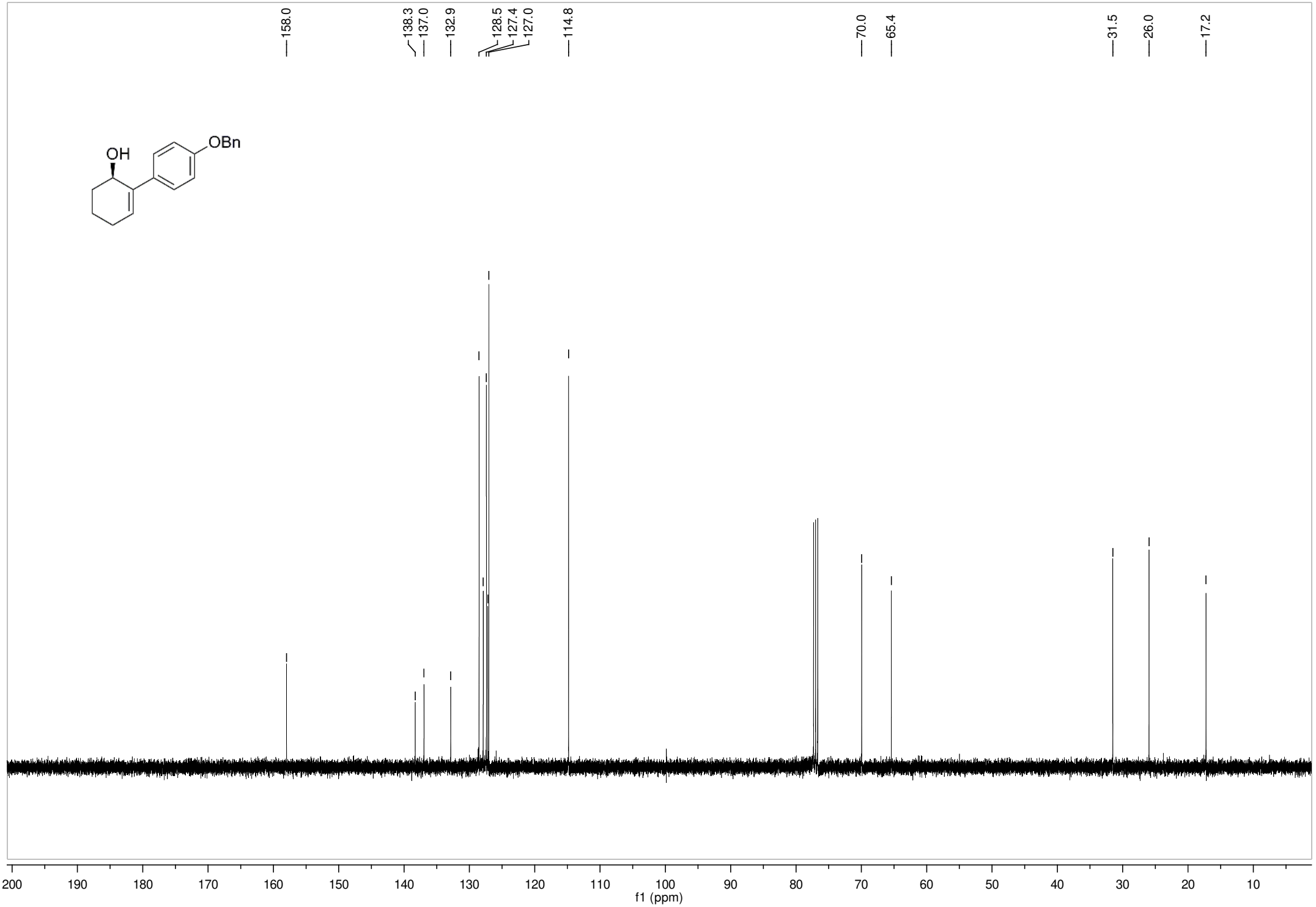


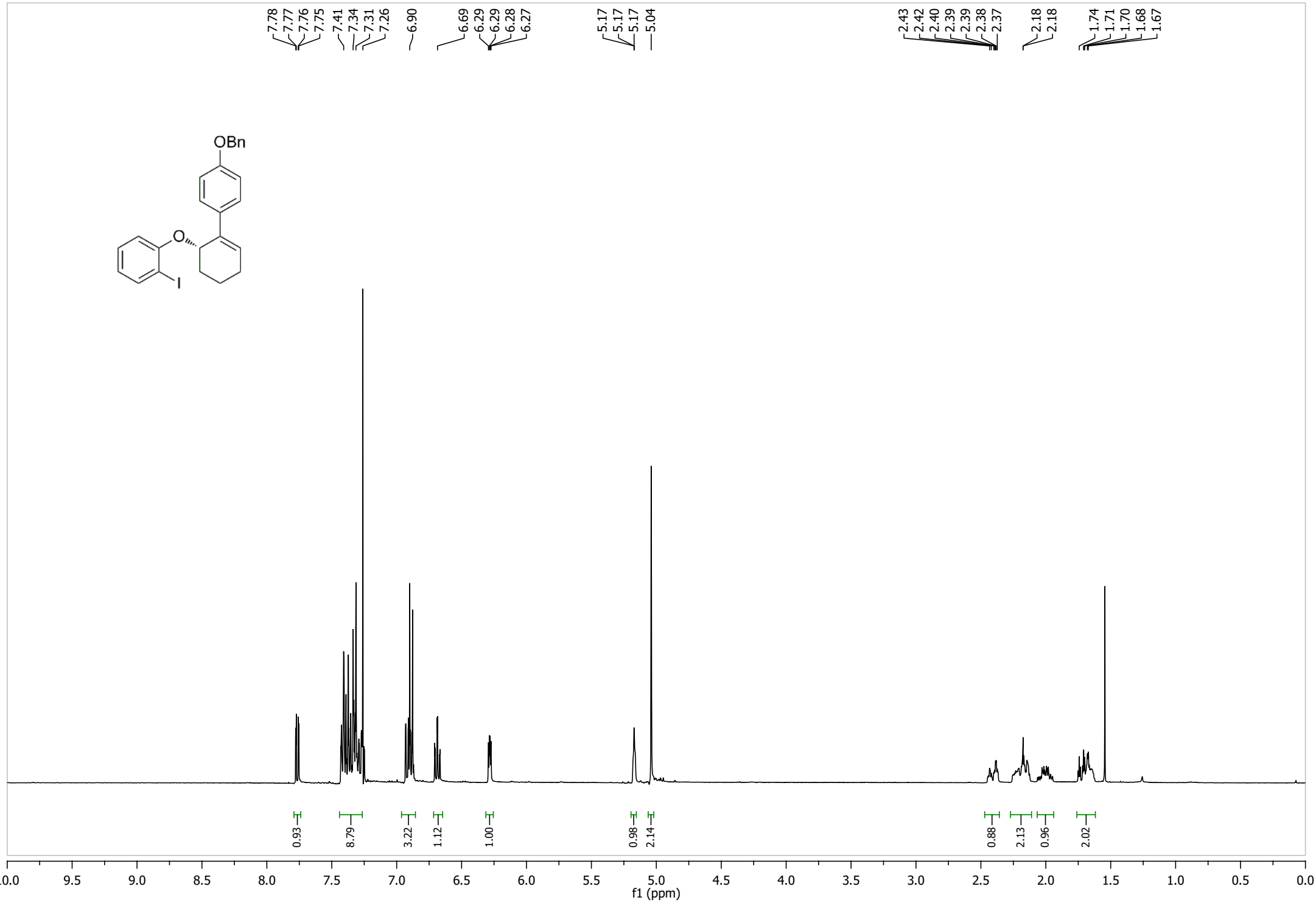


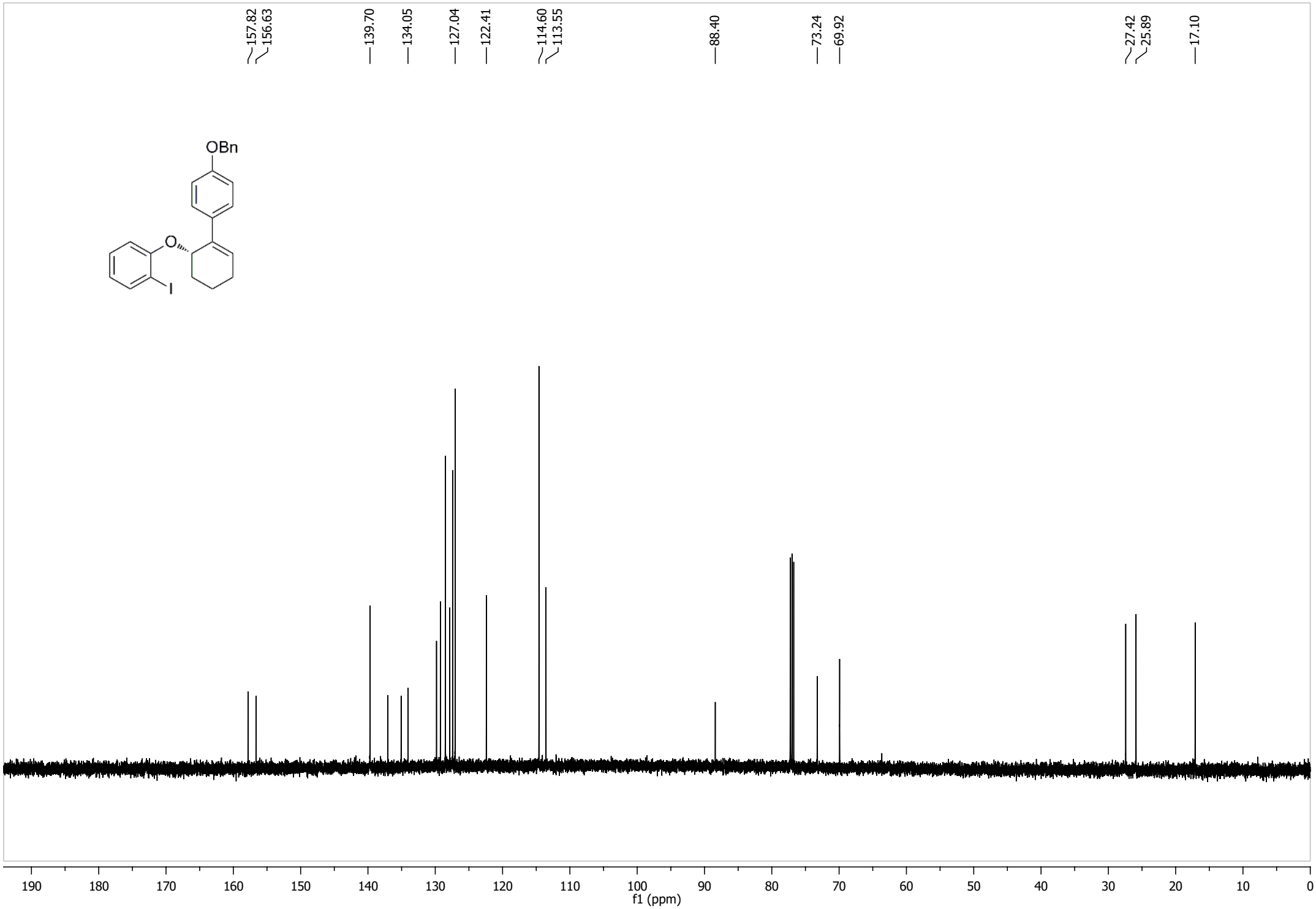


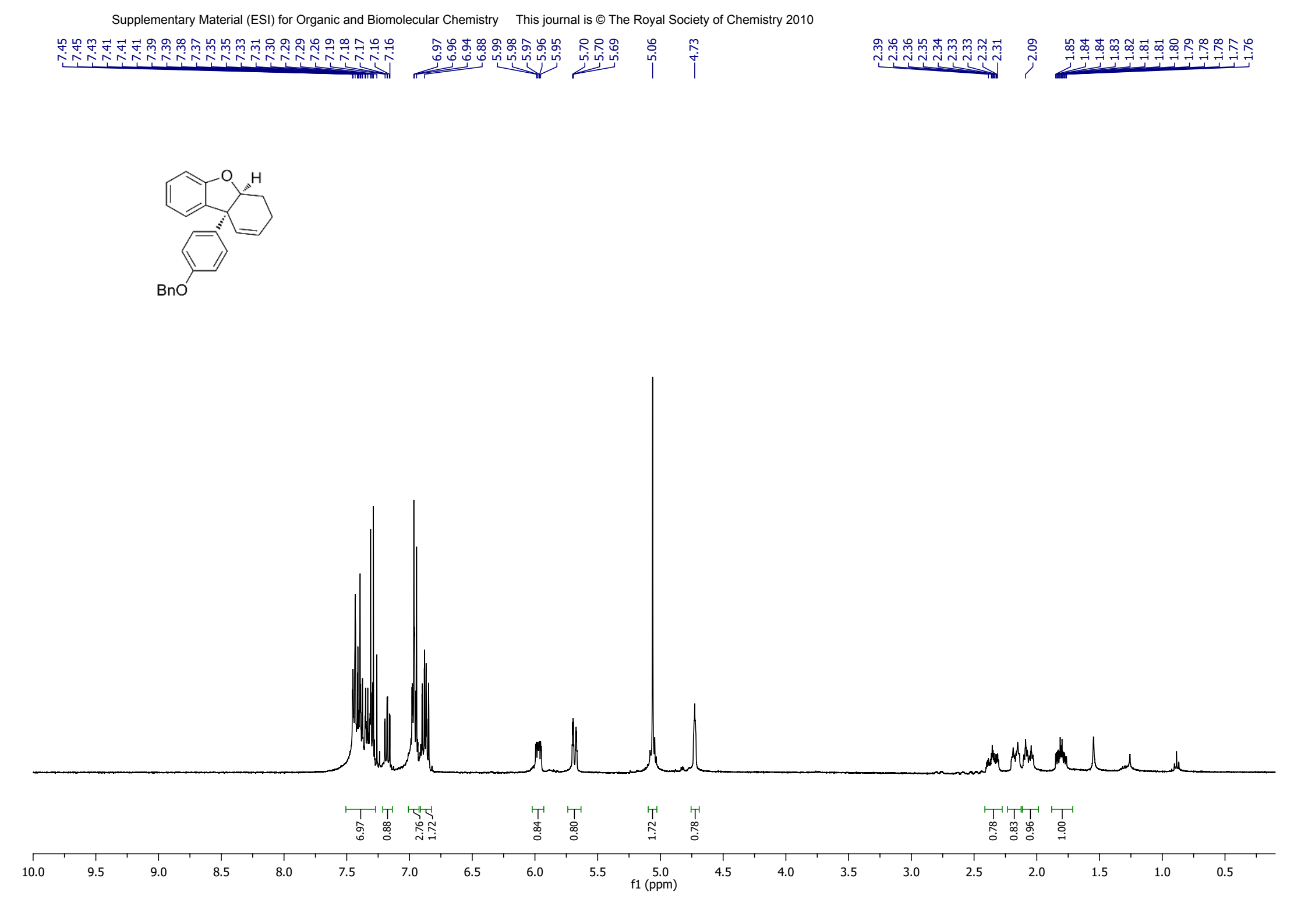


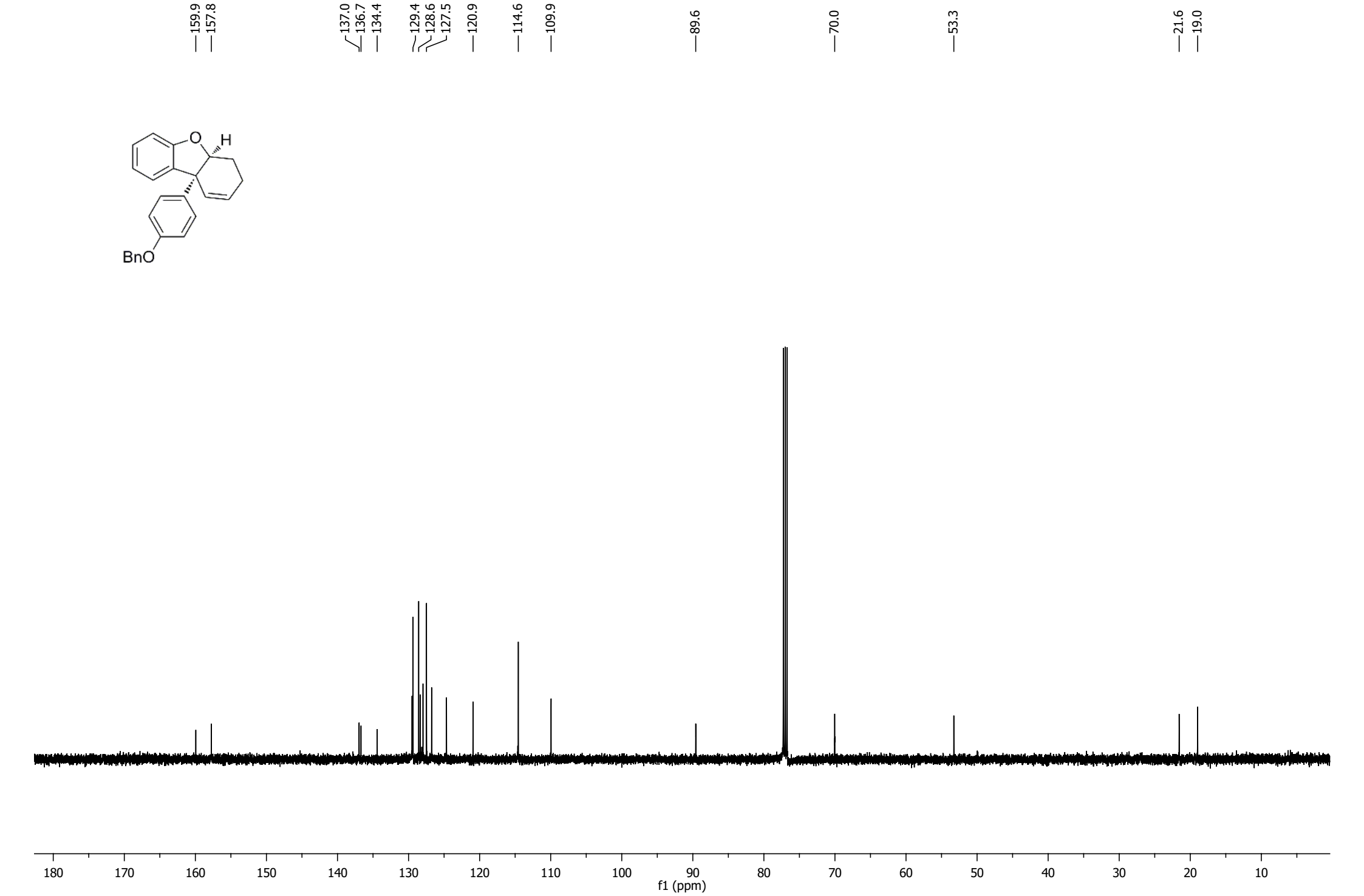


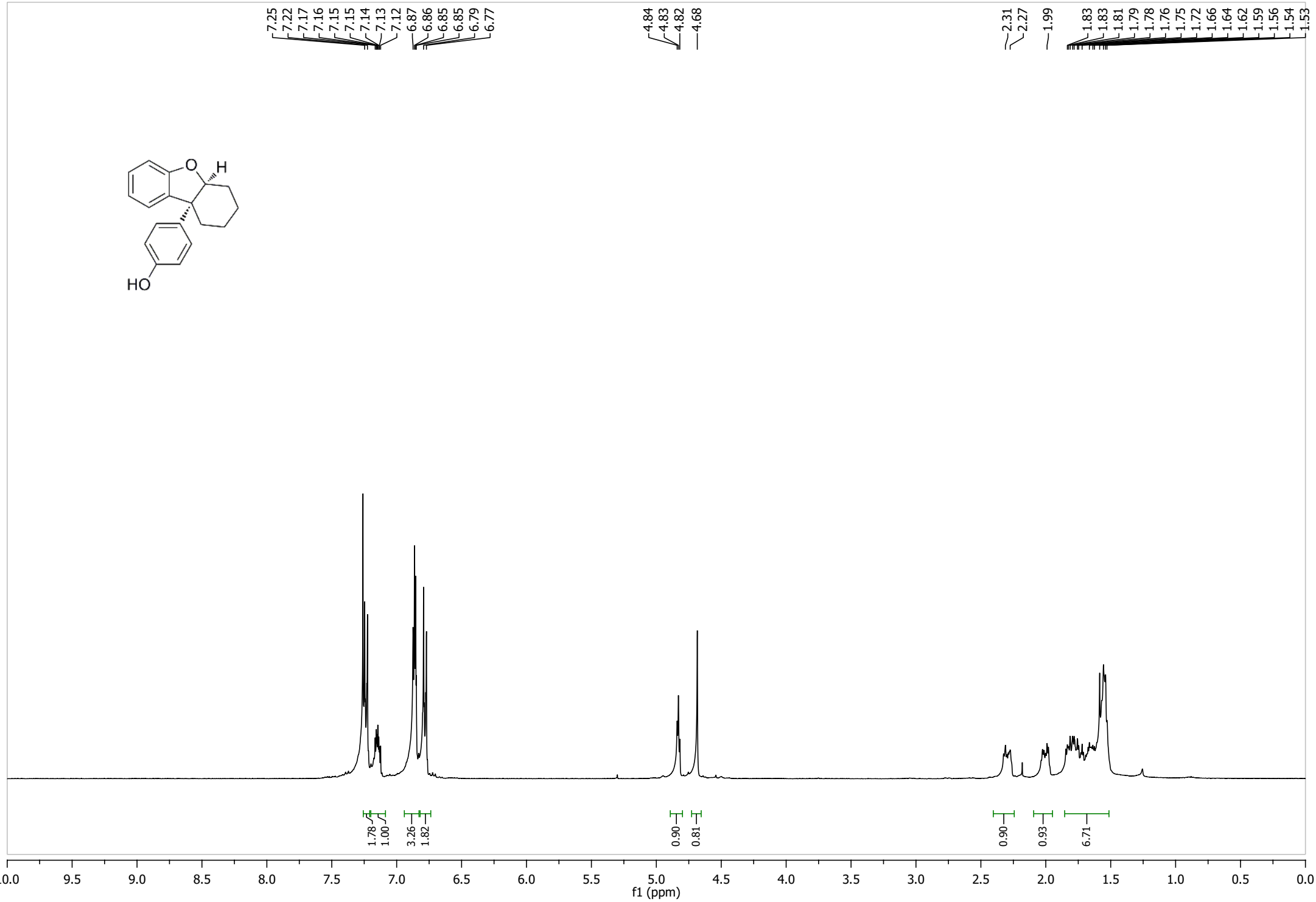


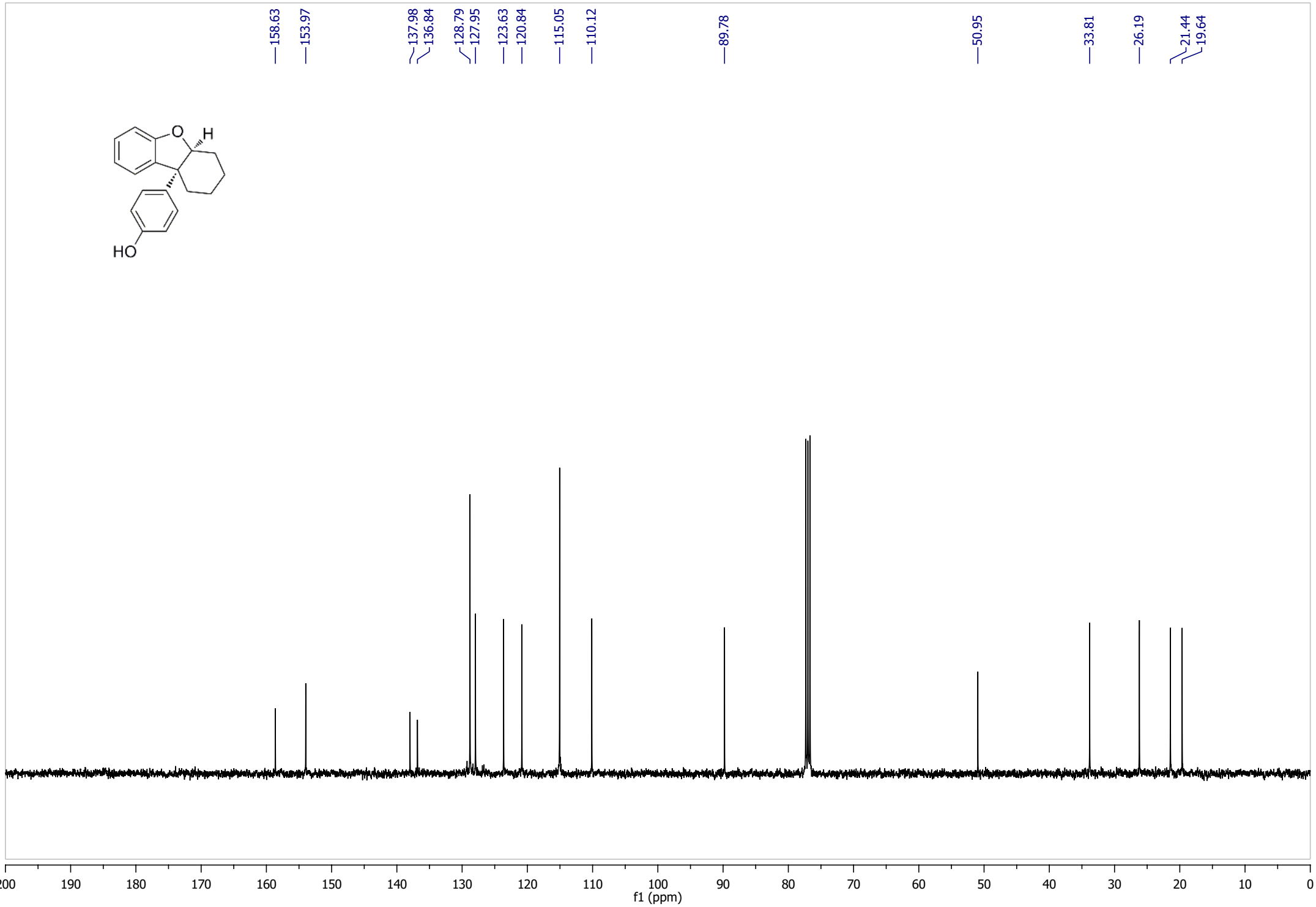












Compound 14 was used in a standard ^{1}H-^{1}H NOESY NMR experiment (400 MHz; CDCl3). A cross peak representing a nuclear overhauser effect (NOE) of the ether proton (H20) and the aromatic protons (H22 and H23) is clearly detectable. This finding is an excellent indication of the cis-fused conformation.