The development of acyclic chiral hydrazides for asymmetric iminium ion organocatalysis

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SUPPLEMENTARY INFORMATION

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General experimental details

All reactions involving moisture sensitive reagents were performed under an atmosphere of argon or nitrogen using standard vacuum line techniques and with freshly distilled solvents. Glassware was flame dried and allowed to cool under vacuum.

All dried and purified solvents were obtained from a solvent purification system (MBraun, SPS-800) except for dry *N*,*N*′-dimethylformamide (DMF) which was purchased directly from Aldrich. Petrol refers to the fraction of petroleum ether boiling between 40 °C and 60 °C and brine refers to a saturated aqueous solution of sodium chloride. Cyclopentadiene was obtained by cracking of the dimer at 170 °C, after drying over $MgSO_4$, and stored in the freezer. Aldehydes for catalytic runs were purified according to the guidelines of Perrin and Chai.[1] All other reagents were used directly as supplied without further purification.

Flash column chromatography was carried out according to the method of Still[2] with silica gel 60 (0.043-0.060 mm) (Merck) in the solvent system stated. Analytical thin layer chromatography was performed on commercially available pre-coated aluminium-backed plates (Merck silica Kieselgel 60 F_{254}). TLCs were visualised either by UV fluorescence (254 nm), or by staining with basic $KMnO_4$ solution.

Melting points were recorded on an Electrothermal apparatus and are uncorrected. Microanalyses were carried out on a Carlo Erba CHNS analyser. Infrared spectra were recorded on a Perkin-Elmer Spectrum GX FT-IR Spectrometer and analysed either as thin films between NaCl plates (film) or KBr discs (KBr disc) as stated or a Shimadzu IRAffinity-1 fourier transform IR spectrophotometer using using Pike MIRacle ATR accessory (ATR). Analysis was carried out using Shimadzu IRsolution v1.50, Absorption maxima (ν_{max}) are quoted in wavenumbers (cm^{-1}) and only structurally significant peaks are quoted.

^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were acquired on either a Bruker Avance 300 (300 MHz ^{1}H, 75 MHz ^{13}C), a Bruker Avance 400 (400 MHz ^{1}H, 100 MHz ^{13}C) or a Bruker Avance 500 (500 MHz ^{1}H, 125 MHz ^{13}C) spectrometer in the deuterated solvent stated. ^{13}C NMR spectra were recorded with proton decoupling. ^{15}N NMR spectra were acquired indirectly by ^{1}H, ^{15}N-HMBC experiments on a Bruker Avance 500 equipped by a 5 mm inverse tuneable double resonance probe. Chemical shifts (δ) are quoted in parts per million (ppm) and referenced to residual solvent peaks. Coupling constants, *J*, are quoted in Hz. The abbreviations s, d, dd, dt, td, q, quin and m denote singlet, doublet, doublet of doublets, doublet of triplets, triplet of doublets, quartet, quintet and multiplet respectively. The abbreviation Ar is used to denote aromatic. For compounds displaying

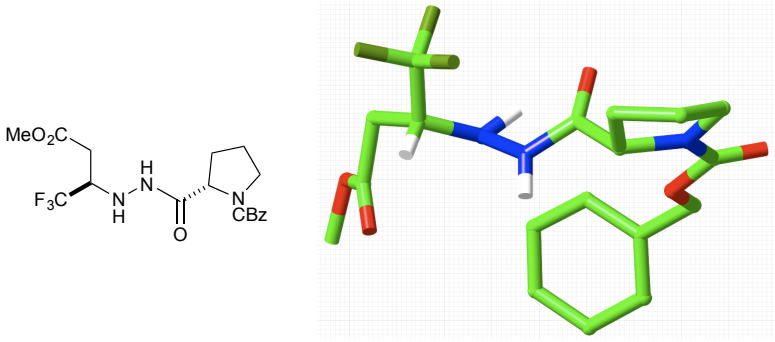
rotamers in ^{1}H NMR spectroscopy, the integral ratio of the two species is given with the more abundant designated A and the less abundant designated B.

Mass spectrometric (*m*/*z*) data was acquired by electrospray ionisation (ESI) or chemical ionisation (CI), either at the University of St Andrews Mass Spectrometry facility or at the EPSRC National Mass Spectrometry Service Centre, Swansea. At the University of St Andrews, low and high resolution ESI MS was carried out on a Micromass LCT spectrometer. At the EPSRC National Mass Spectrometry Service Centre, CI MS was carried out on a Micromass Quattro II spectrometer. High resolution ESI was carried out on a Finnigan MAT 900 XLT; a Thermofisher LTQ Orbitrap XL spectrometer was used to obtain high resolution ESI MS for accurate mass determination but also provided fragmentation data for the characterisation of samples. Values are quoted as a ratio of mass to charge in Daltons.

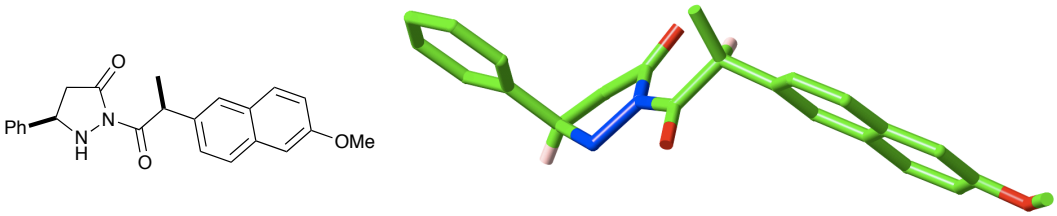
Temperatures of 5 °C were obtained using an immersion cooler (HAAKE EK 90) while temperatures of −78 °C were obtained using a dry ice/acetone bath.

Crystal structure information for compounds **6**, **11**, **17**, **18**, **19**, **20**, **21** and **29**

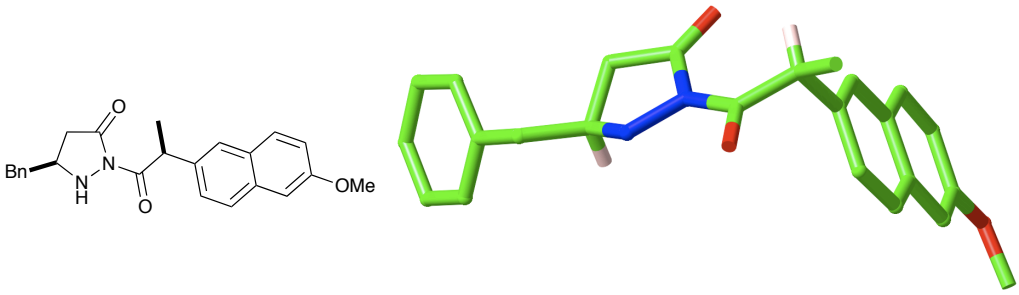
Crystallographic data (excluding structure factors) for compounds **6**, **11**, **17**, **18**, **19**, **20**, **21** and **29** have been deposited with the Cambridge Crystallographic Data Centre and allocated the deposition numbers CCDC 915107, CCDC 956166, CCDC 956167, CCDC 956168, CCDC 956169, CCDC 956170, CCDC 956171 and CCDC 925705, respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).



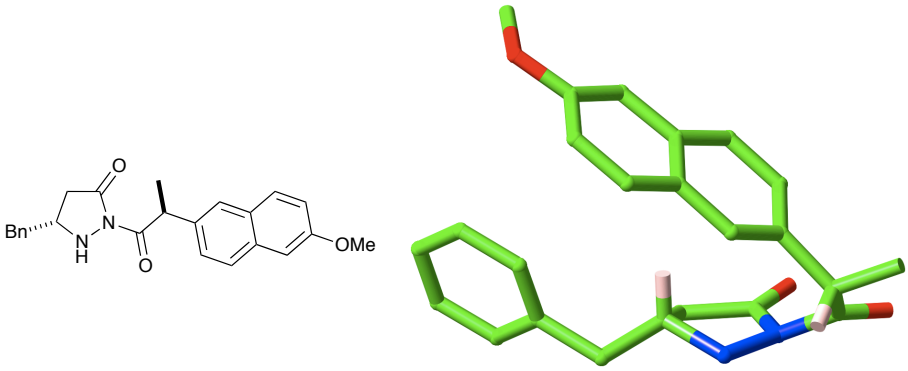
Crystal structure of compound **6**



Crystal structure of compound **11**



Crystal structure of compound **17**



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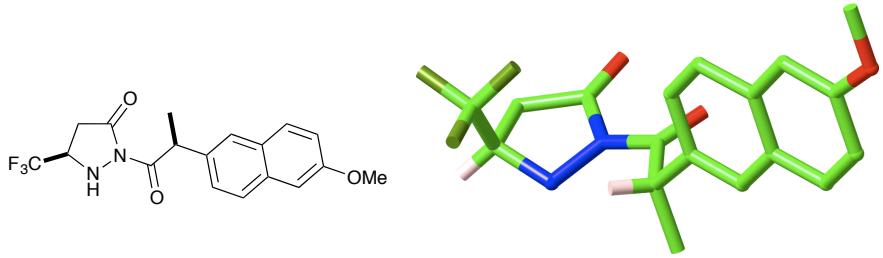
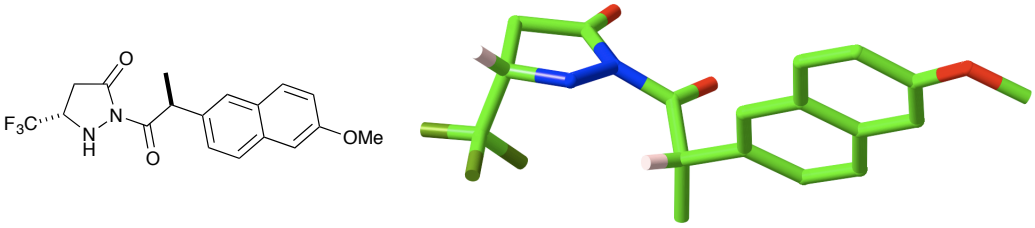
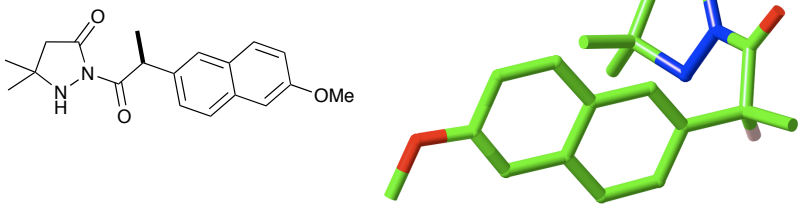


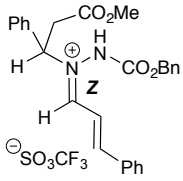
Crystal structure of compound **19**

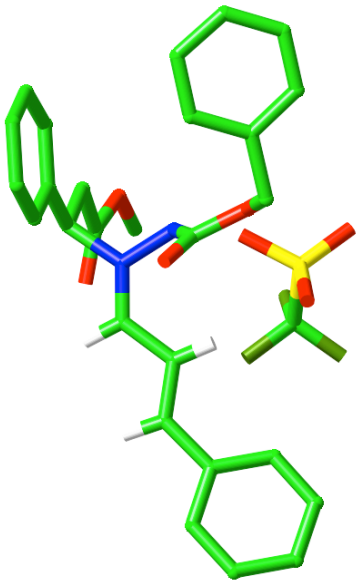


Crystal structure of compound **20**



Crystal structure of compound **21**

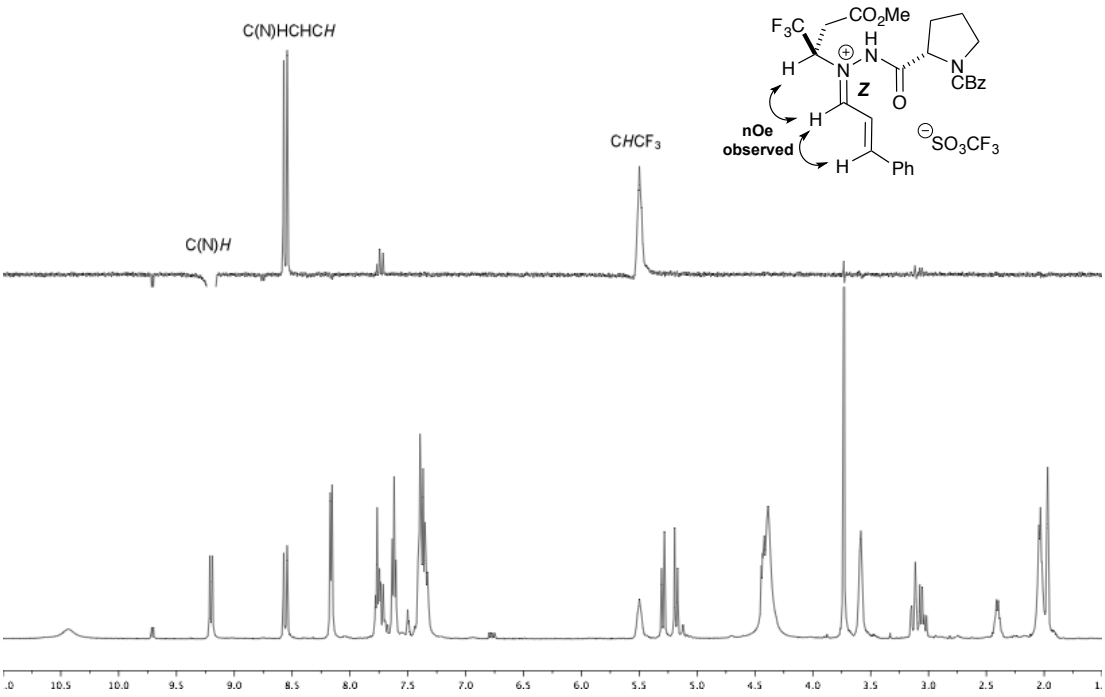




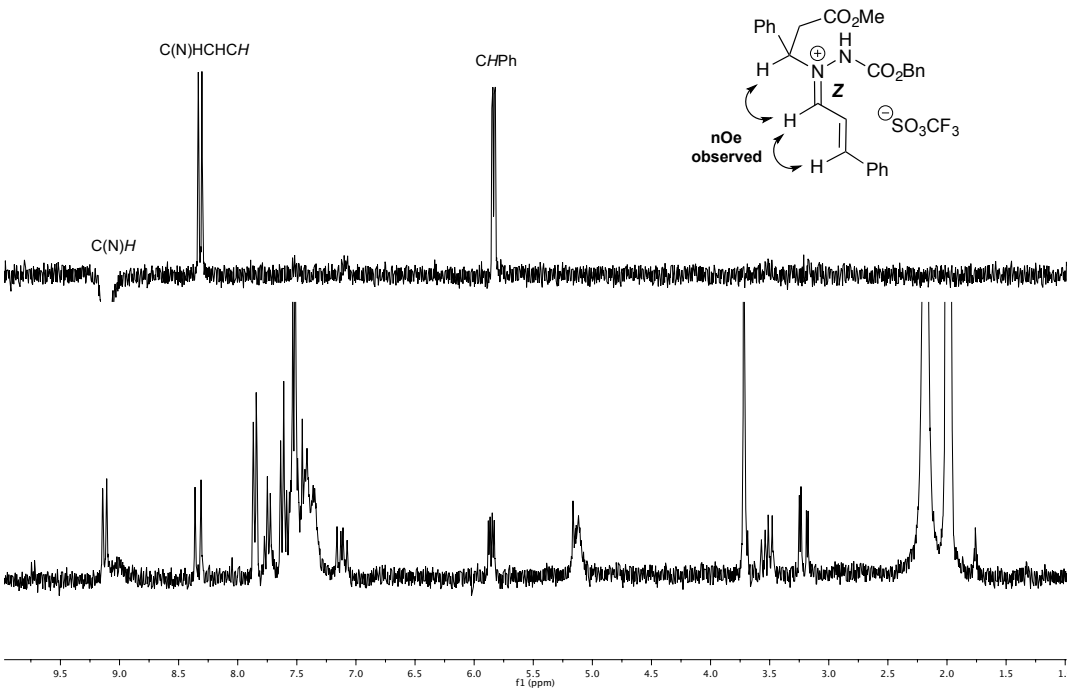
Crystal structure of compound **29**

NOESY analysis for iminium ions 28 and 29

28: Spectra were acquired out on a Bruker Avance 500 (500 MHz ^{1}H) spectrometer in CD_3CN. 1D gradient NOESY shows reciprocal NOE between C*H*CF3 and C(N)*H*.



29: Spectra were acquired out on a Bruker Avance 500 (500 MHz ^{1}H) spectrometer in CD_3CN. 1D gradient NOESY shows reciprocal NOE between C*H*Ph and C(N)*H*.



Determination of catalyst absolute configuration

Compounds **5**, **9** and **10** have been reported previously.[3]

Compound **6**: The relative configuration of **6** was assigned by X-ray crystallographic analysis (see S2). Absolute configuration could then be inferred from the known (*S*)-configuration of L-proline.

Compounds **7** and **8**: The absolute *C*(5)-configuration within **7** was confirmed by hydrolysis of the (*R*)-mandelic acid unit using 6 M hydrochloric acid followed by *N*-alkylation to generate the known *N*(1)-benzyl analogue.[3] Absolute C(5)-(*S*)-configuration could then be determined by comparison of the optical rotation ($[\alpha]_D^{20}$ –125 (*c* 0.9, dichloromethane)) to the literature value ($[\alpha]_D^{20}$ –163 (*c* 0.9, dichloromethane)).[4] This then allowed a *C*(5)-(*R*)-configuration to be assigned to compound **8**.

Compounds **11** and **12**: The relative configuration of **11** was assigned by X-ray crystallographic analysis (see S2). Absolute configuration could then be inferred from the known (*S*)-configuration of Naproxen. This then allowed a *C*(5)-(*R*)-configuration to be assigned to compound **12**.

Compounds **13** and **14**: As with compound **7**, the absolute *C*(5)-(*S*)-configuration within **13** was confirmed by acid hydrolysis/*N*-alkylation to generate the known *N*(1)-benzyl analogue ($[\alpha]^{20}_D$ –145 (*c* 0.15, dichloromethane). This then allowed a *C*(5)-(*R*)-configuration to be assigned to compound **14**.

Compounds **15** and **16**: The absolute configuration of **15** and **16** were initially assigned by their respective R_f values (in comparison to other compounds in the series) and later by comparison of results in catalysis.

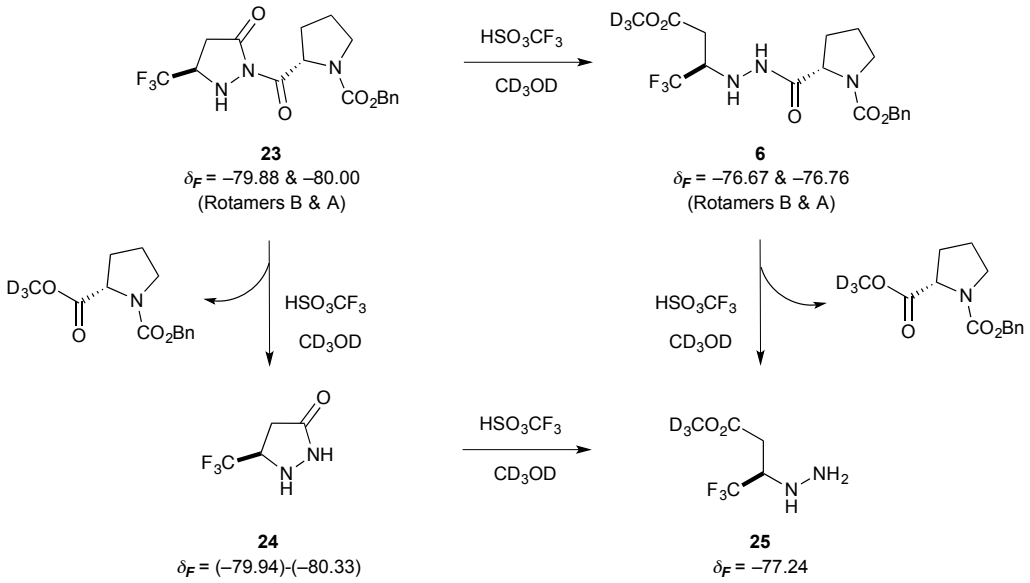
Compounds **17** and **18**: The relative configuration of both **17** and **18** was assigned by X-ray crystallographic analysis (see S2). Absolute configuration could then be inferred from the known (*S*)-configuration of Naproxen.

Compounds **19** and **20**: The relative configuration of both **19** and **20** was assigned by X-ray crystallographic analysis (see S2). Absolute configuration could then be inferred from the known (*S*)-configuration of Naproxen.

Compounds **22** and **23**: As compound **6** arises from methanolysis of **23**, the absolute configuration of **23** (and by extension **22**) could be inferred from that of **6**.

Data for ^{19}F NMR spectroscopic monitoring of ring-opening of catalyst 23

Reactions were carried out on a Bruker Avance 300 (282 MHz ^{19}F) or Bruker Avance 500 (500 MHz ^{1}H) spectrometer in CD_3OD. All chemical shift values are quoted in parts per million (ppm).



Catalyst **23** (37.0 mg, 95.0 μmol) and triflic acid (0.190 M solution in CD_3OD, 0.5 mL, 95.0 μmol) were combined in an NMR tube at t = 0 and the NMR spectrometer was locked and shimmed to this solution. Reaction was monitored by ^{1}H decoupled ^{19}F NMR spectroscopy with a delay between spectrum acquisition of 30 min for the first 4.82 h and 60 min thereafter, up to 16.42 h. Integrals were determined manually and scaled to the triflate anion peak (δ_F –80.57, integral= 1).

The chemical shift corresponding to **24** drifted slightly over the course of the reaction from δ_F = -79.94 to –80.33. At timepoint t = 1.28 h, this led to complete overlap of the **24** peak with the A rotamer of **23** (δ_F = –80.00). Hence, a single integral is given for these two compounds at this timepoint.

^{19}F NMR spectroscopy integral values

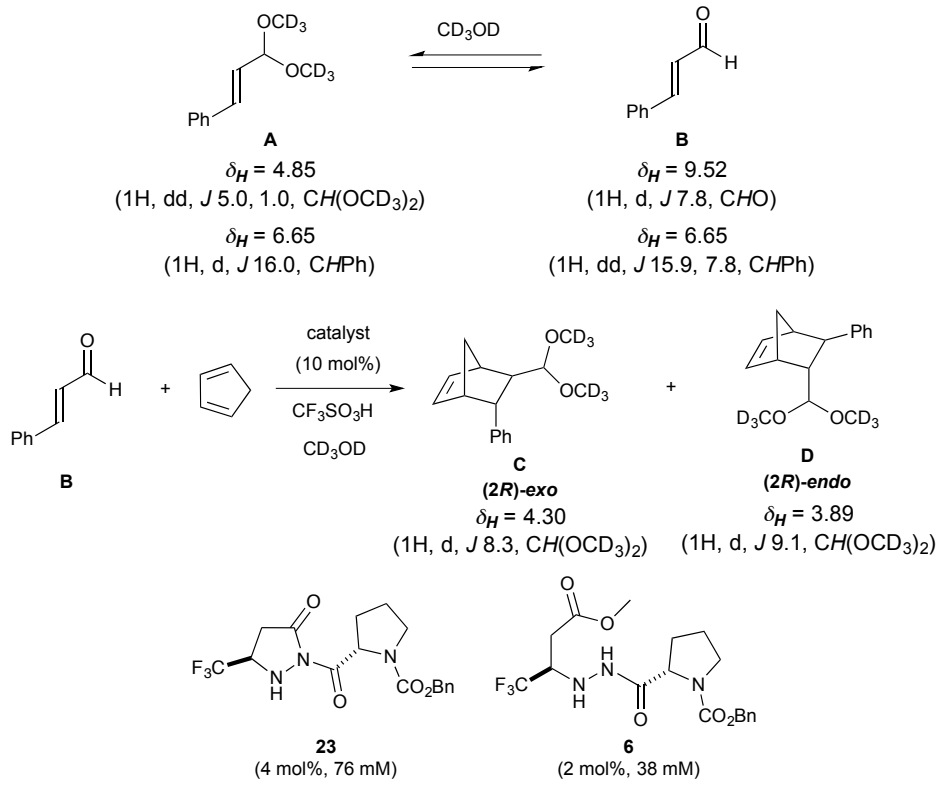
Time (h)	**6** B (-76.67)	**6** A (-76.76)	**25** (-77.24)	**23** B (-79.88)	**23** A (-80.00)	**24** ((-79.94)-(–80.33))	**23** Total (A+B)	**6** Total (A+B)	Integral Sum
0.22	0.031	0.039	0.003	0.437	0.505	0.119	0.942	0.07	1.134
0.27	0.040	0.050	0.005	0.423	0.470	0.118	0.893	0.09	1.106
0.78	0.095	0.113	0.026	0.327	0.324	0.231	0.651	0.208	1.116
1.28	0.133	0.156	0.055	0.249	-	0.517[a]	-	0.289	1.11
1.78	0.162	0.193	0.092	0.186	0.198	0.260	0.384	0.355	1.091
2.30	0.185	0.216	0.129	0.141	0.170	0.263	0.311	0.401	1.104
2.80	0.195	0.237	0.161	0.107	0.118	0.253	0.225	0.432	1.071
3.30	0.213	0.257	0.198	0.086	0.096	0.252	0.182	0.47	1.102
3.82	0.223	0.266	0.229	0.070	0.080	0.239	0.15	0.489	1.107
4.32	0.228	0.273	0.258	0.052	0.063	0.219	0.115	0.501	1.093
4.82	0.240	0.277	0.285	0.043	0.052	0.210	0.095	0.517	1.107
5.83	0.253	0.295	0.337	0.031	0.036	0.184	0.067	0.548	1.136
6.83	0.258	0.304	0.375	0.020	0.023	0.156	0.043	0.562	1.136
7.85	0.253	0.305	0.409	0.015	0.016	0.134	0.031	0.558	1.132
8.85	0.264	0.310	0.438	0.010	0.011	0.111	0.021	0.574	1.144
9.87	0.266	0.320	0.467	0.008	0.009	0.098	0.017	0.586	1.168
10.88	0.269	0.320	0.488	0.005	0.006	0.082	0.011	0.589	1.17
11.88	0.268	0.320	0.505	0.004	0.004	0.067	0.008	0.588	1.168
12.90	0.273	0.321	0.521	0.003	0.003	0.059	0.006	0.594	1.180
13.90	0.269	0.326	0.534	0.002	0.003	0.050	0.005	0.595	1.184
14.92	0.275	0.330	0.546	0.002	0.002	0.045	0.004	0.605	1.200
15.92	0.274	0.328	0.553	0.001	0.001	0.035	0.002	0.602	1.192
16.42	0.273	0.330	0.560	0.001	0.001	0.032	0.002	0.603	1.197

a) Combined integral of **23** A and **24**

Integral values as percentage composition

Time (h)	**6** Total (A+B)	**23** Total (A+B)	**25**	**24**
0.22	6	83	0	10
0.27	8	81	0	11
0.78	19	58	2	21
1.28	26	-	5	-
1.78	33	35	8	24
2.30	36	28	12	24
2.80	40	21	15	24
3.30	43	17	18	23
3.82	44	14	21	22
4.32	46	11	24	20
4.82	47	9	26	19
5.83	48	6	30	16
6.83	49	4	33	14
7.85	49	3	36	12
8.85	50	2	38	10
9.87	50	1	40	8
10.88	50	1	42	7
11.88	50	1	43	6
12.90	50	1	44	5
13.90	50	0	45	4
14.92	50	0	46	4
15.92	51	0	46	3
16.42	50	0	47	3

^{1}H NMR spectroscopic monitoring of Diels-Alder reaction of (*E*)-cinnamaldehyde and cyclopentadiene catalysed by 23 or 6



*Reaction with **23***

(*E*)-Cinnamaldehyde **A** (0.120 mL, 0.950 mmol), triflic acid (76.0 mM solution in CD_3OD, 0.5 mL, 38.0 μmol), cyclopentadiene (94.0 mg, 1.43 mmol) and 1-methylnaphthalene (26.0 μL, 0.190 mmol) were combined in an NMR tube and the NMR spectrometer was locked and shimmed to this solution. Catalyst **23** (4 mol%, 14.6 mg, 38.0 μmol) was added at t = 0 and reaction monitored by ^{1}H NMR spectroscopy with a delay between spectrum acquisition of 5 min for the first 17 min and 10 min thereafter, up to 256 min. Integrals were determined manually and scaled to 1-methylnaphthalene (δ_H 7.78, integral=1).

*Reaction with **6***

(*E*)-Cinnamaldehyde **A** (0.120 mL, 0.950 mmol), triflic acid (38.0 mM solution in CD_3OD, 0.5 mL, 19.0 μmol), cyclopentadiene (94.0 mg, 1.43 mmol) and 1-methylnaphthalene (26.0 μL, 0.190 mmol) were combined in an NMR tube and the NMR spectrometer was locked and shimmed to this solution. Catalyst **6** (2 mol%, 7.90 mg, 19.0 μmol) was added at t = 0 and reaction monitored by ^{1}H NMR spectroscopy with a delay between spectrum acquisition of 5 min for the first 17 min and 10 min thereafter, up to 256 min. Integrals were determined manually and scaled to 1-methylnaphthalene (δ_H 7.78, integral= 1).

From the timepoint t = 87 min onwards, the acetal peak at δ_H = 4.85 was obscured by a peak due to residual water. Hence, integral values are given only up to this timepoint.

Reaction with ***23*** **- ^{1}H NMR spectroscopy integral values**

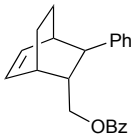
Time (min)	**B** (9.52)	**A+B** (6.65)	**A** (4.85)	**C (*exo*)** (4.30)	**D (*endo*)** (3.89)	**C and D Combined** (4.30+3.89)	% conversion
5	2.58	5.89	2.84	0.15	0.21	0.36	5.9
7	2.60	5.76	2.80	0.19	0.26	0.45	7.4
12	2.50	5.43	2.66	0.25	0.37	0.62	10.2
17	2.42	5.12	2.44	0.30	0.47	0.77	12.6
28	2.34	4.91	2.39	0.45	0.72	1.17	19.2
38	2.13	4.40	2.04	0.52	0.87	1.39	22.8
48	2.06	4.24	1.97	0.66	1.09	1.75	28.7
59	1.90	3.80	1.70	0.70	1.19	1.89	31.0
69	1.83	3.77	1.70	0.85	1.45	2.30	37.7
79	1.74	3.50	1.59	0.91	1.59	2.50	41.0
89	1.63	3.20	1.42	0.97	1.68	2.65	43.4
100	1.53	3.02	1.33	1.03	1.82	2.85	46.7
110	1.44	2.82	1.24	1.09	1.92	3.01	49.3
121	1.36	2.72	1.18	1.17	2.08	3.25	53.3
131	1.27	2.56	1.10	1.23	2.18	3.41	55.9
142	1.22	2.35	1.02	1.25	2.21	3.46	56.7
152	1.15	2.32	1.00	1.37	2.41	3.78	62.0
163	1.09	2.11	0.91	1.35	2.41	3.76	61.6
173	1.00	2.00	0.86	1.4	2.49	3.89	63.8
184	0.98	1.88	0.8	1.42	2.53	3.95	64.8
194	0.92	1.79	0.77	1.48	2.64	4.12	67.5
204	0.82	1.66	0.69	1.46	2.62	4.08	66.9
214	0.82	1.57	0.67	1.51	2.69	4.20	68.9
225	0.72	1.52	0.64	1.56	2.8	4.36	71.5
235	0.71	1.42	0.6	1.56	2.82	4.38	71.8
246	0.69	1.35	0.58	1.6	2.87	4.47	73.3
256	0.66	1.31	0.53	1.65	2.97	4.62	75.7

Reaction with ***6*** *-* ^{1}**H NMR spectroscopy integral values**

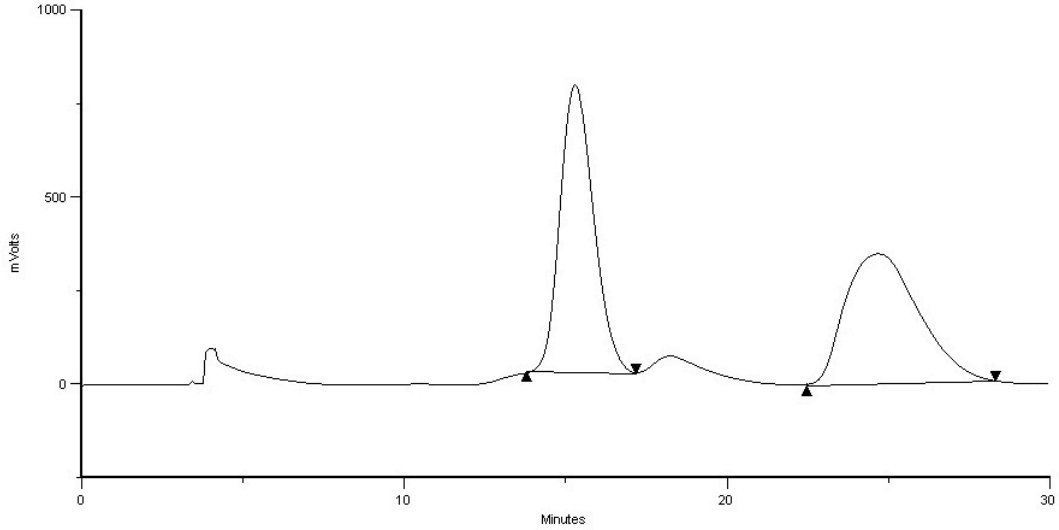
Time (min)	**B** (9.52)	**A+B** (6.65)	**A** (4.85)	**C (*exo*)** (4.30)	**D (*endo*)** (3.89)	**C and D Combined** (4.30+3.89)	% conversion
8	2.21	4.6	2.21	0.17	0.21	0.38	7.8
10	2.13	4.42	2.08	0.2	0.26	0.46	9.4
15	1.93	3.84	1.86	0.33	0.46	0.79	16.1
25	1.70	3.37	1.56	0.57	0.91	1.48	30.2
35	1.41	2.65	1.17	0.71	1.18	1.89	38.6
46	1.22	2.22	0.96	0.85	1.45	2.30	46.9
56	1.08	2.01	0.86	1.04	1.80	2.84	58.0
67	0.94	1.69	0.69	1.11	1.95	3.06	62.4
78	0.83	1.47	0.65	1.20	2.12	3.32	67.8
87	0.73	1.30	-	1.28	2.27	3.55	72.4
98	0.66	1.13	-	1.31	2.37	3.68	75.1
108	0.56	1.02	-	1.39	2.50	3.89	79.4
113	0.53	0.95	-	1.39	2.51	3.90	79.6
119	0.50	0.89	-	1.39	2.52	3.91	79.8
124	0.48	0.86	-	1.44	2.62	4.06	82.9
129	0.45	0.83	-	1.49	2.71	4.20	85.7
139	0.40	0.75	-	1.52	2.77	4.29	87.6
160	0.33	0.59	-	1.52	2.80	4.32	88.2
181	0.28	0.49	-	1.57	2.89	4.46	91.0
202	0.23	0.41	-	1.59	2.92	4.51	92.0
223	0.18	0.35	-	1.65	3.04	4.69	95.7
243	0.14	0.3	-	1.67	3.09	4.76	97.1
259	0.12	0.26	-	1.67	3.09	4.76	97.1

HPLC data of benzoyl ester derived from *endo*-(1*S*,2*R*,3*R*,4*R*)-phenylbicyclo[2.2.2]oct-5-ene-2-carbaldehyde

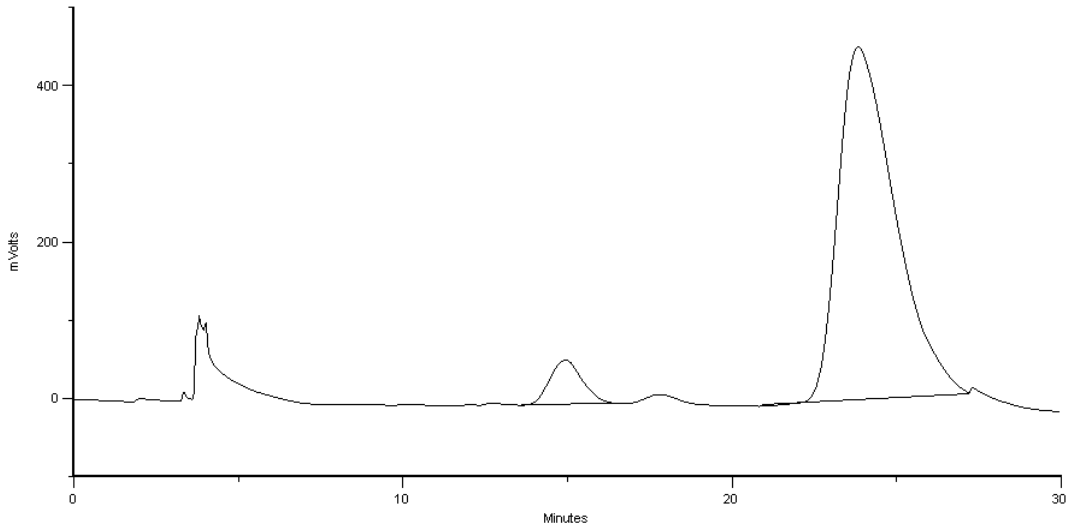
Chiral HPLC was performed on Gilson apparatus, using a ChiralPak OJ-H silica column, 0.46 cm ϕ x 25 cm, 0.5% isopropanol:hexane as eluents, flow rate = 1.0 mL min^{-1}, 211 nm, 85% ee.



	Inj. Number	Peak Name	R. Time	Area	Area %
1	1.00	*1	15.29	3960912.00	49.95
	1.00	*2	24.68	4132192.00	50.05

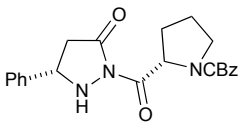


	Inj. Number	Peak Name	R. Time	Area	Area %
1	1.00	*1	14.93	6887895.00	7.05
2	1.00	*2	23.83	90860744.00	92.95



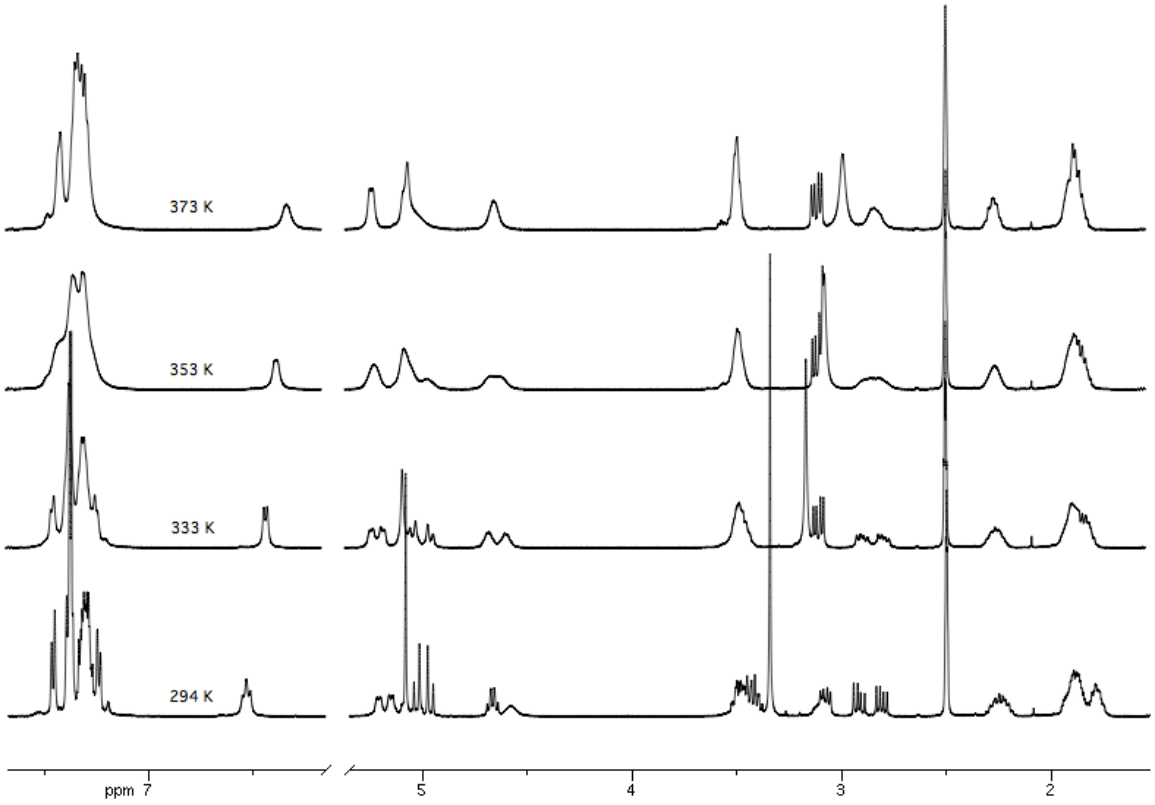
Variable temperature ^{1}H NMR spectra of rotameric compounds 13 and 23

(*S*)-2-((*S*)-1'-((benzyloxy)carbonyl)pyrrolidine-2'-carbonyl)-5-phenylpyrazolidin-3-one 13

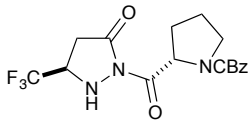


13 $(CD_3)_2S(O)$)

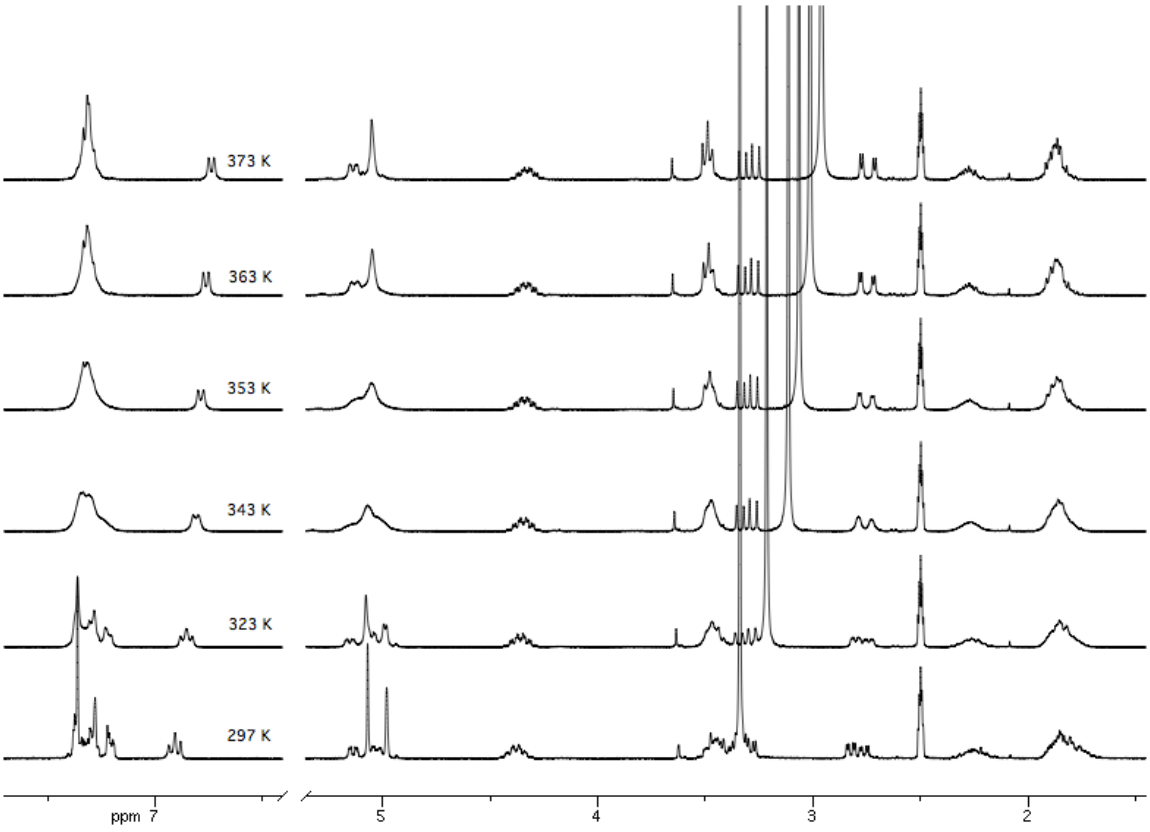
Consistent with, but not conclusive for, rotamers



(*R*)-2-((*S*)-1'-((benzyloxy)carbonyl)pyrrolidine-2'-carbonyl)-5-(trifluoromethyl)-pyrazolidin-3-one 23



23 $(CD_3)_2S(O)$)

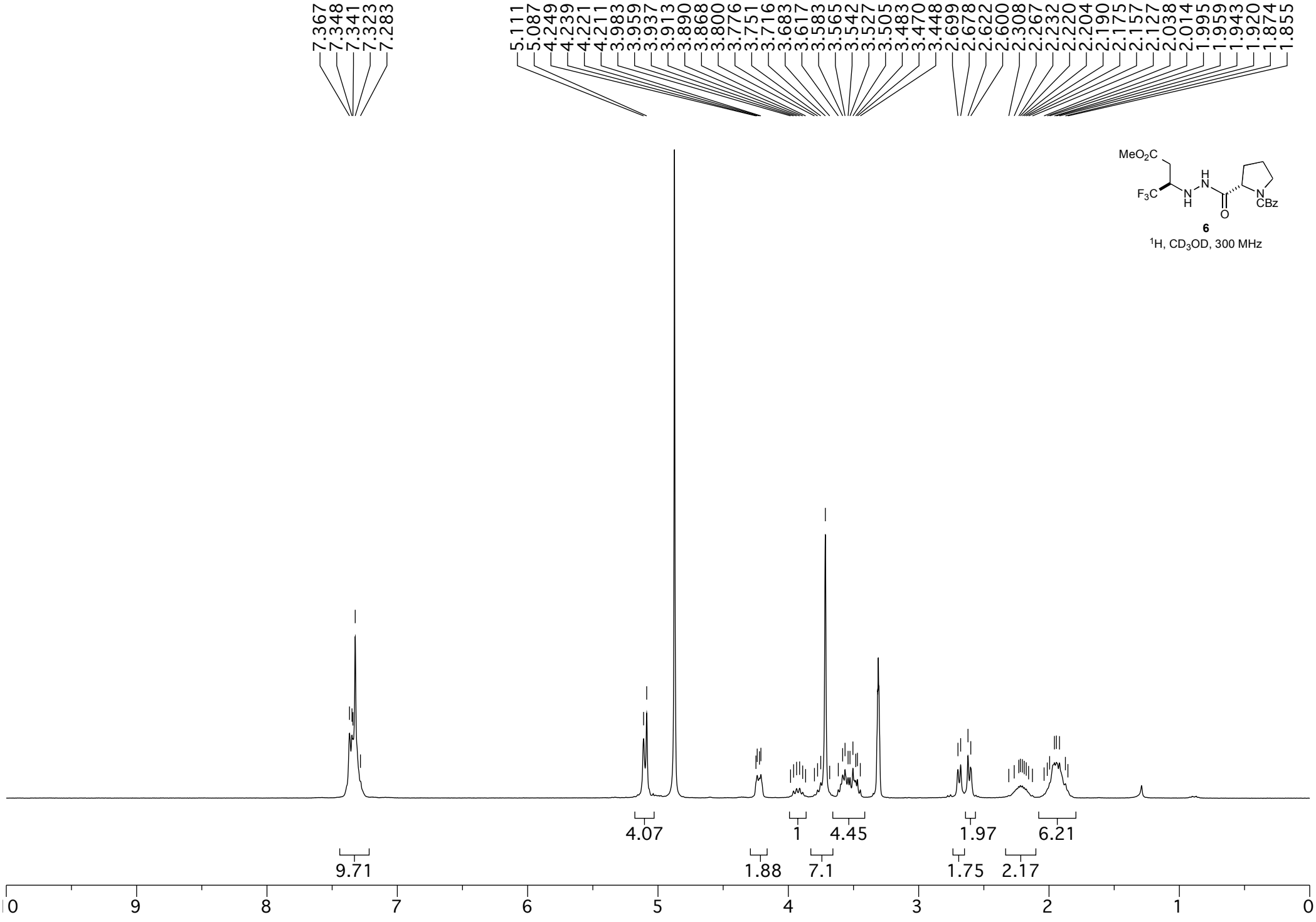


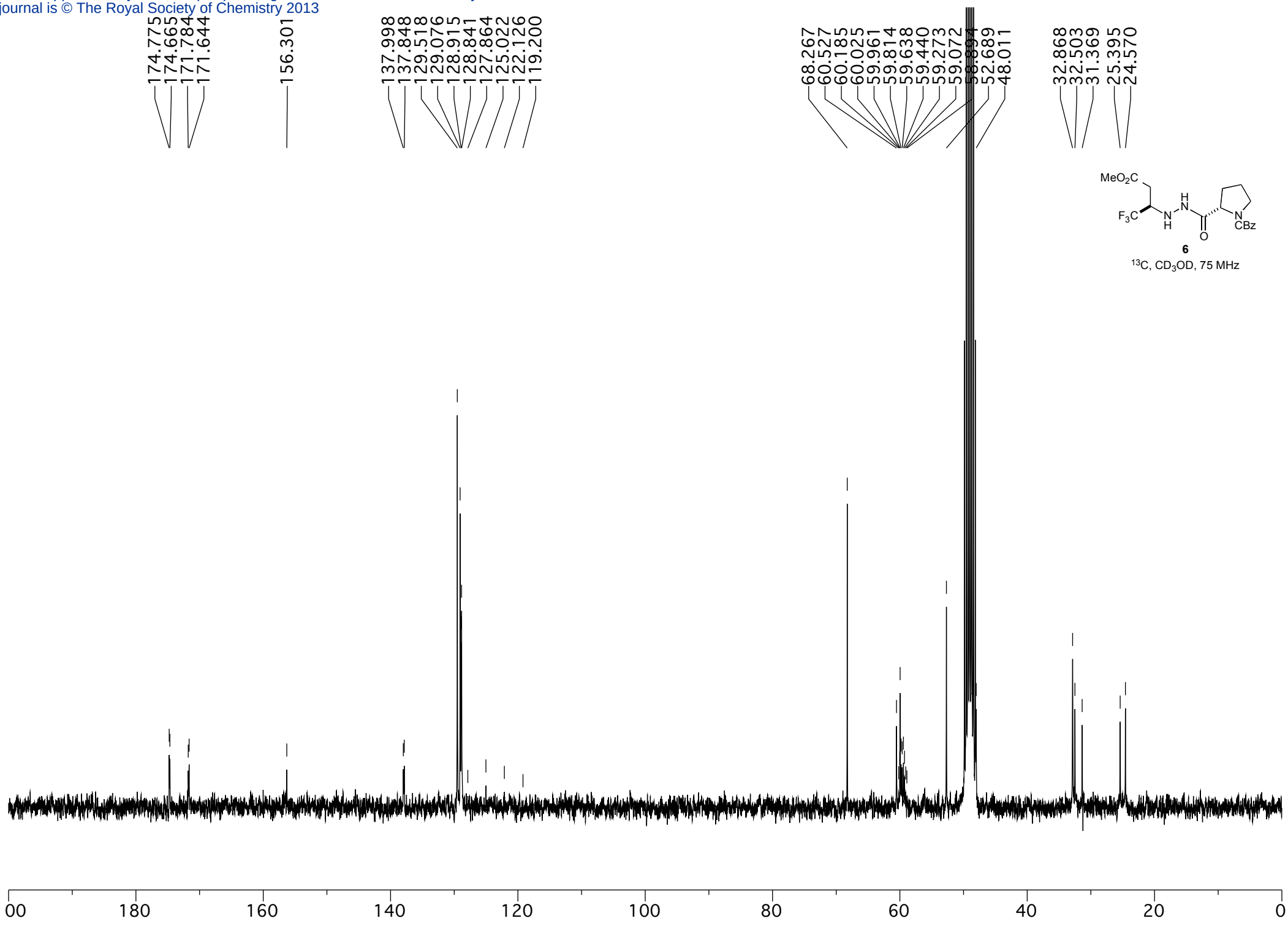
References and notes

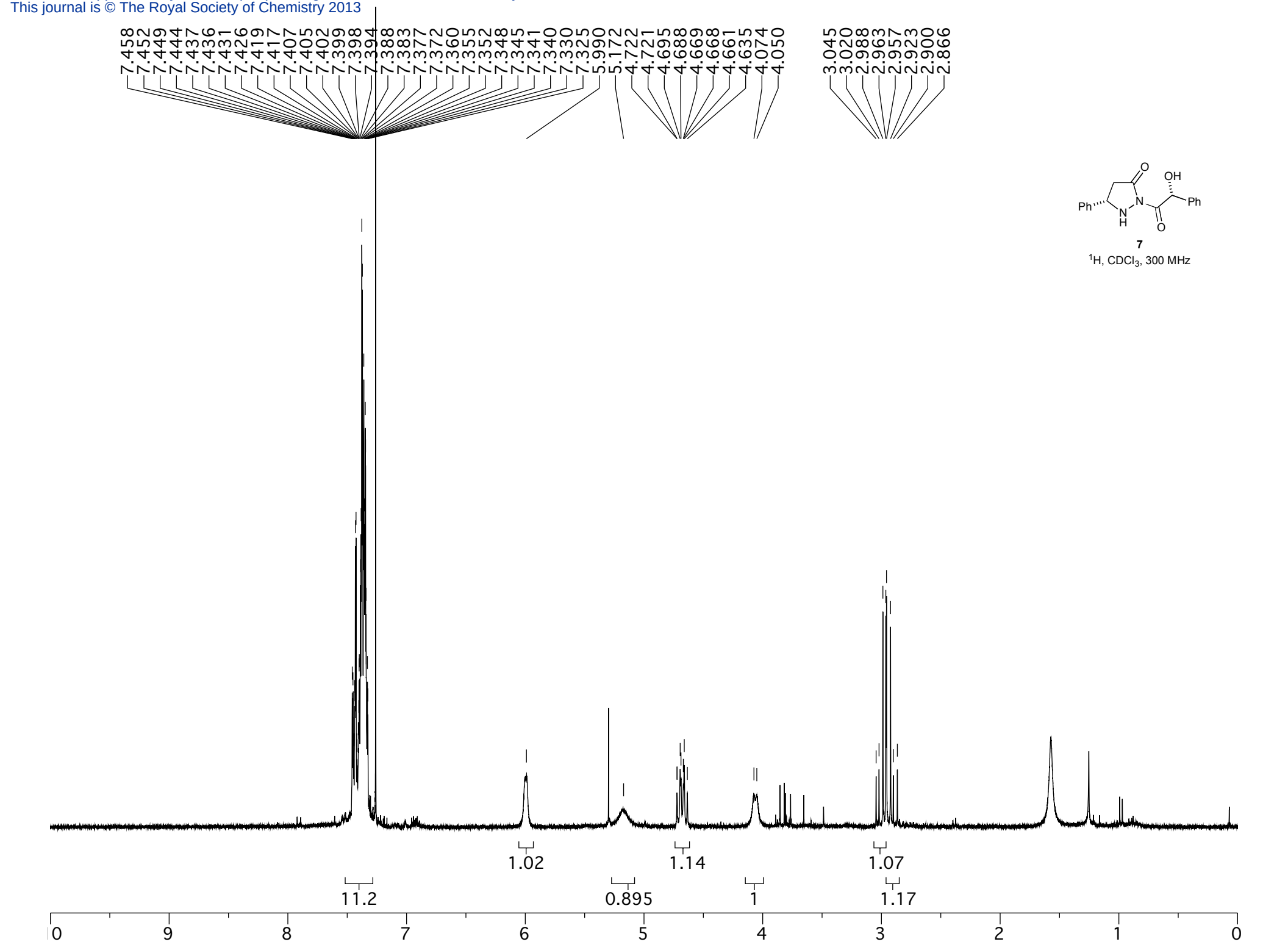
[1] W. L. F. Armarego, C. L. L. Chai, *Purification of Laboratory Chemicals*, Butterworth-Heinemann, Oxford, 5th edn., **2003**.
[2] W. C. Still, M. Kahn, A. Mitra, *J. Org. Chem.* **1978**, *43*, 2923–2925.
[3] E. Gould, T. Lebl, A. M. Z. Slawin, M. Reid, A. D. Smith, *Tetrahedron* **2010**, *66*, 8992–9008.
[4] A. Suarez, C. W. Downey, G. C. Fu, *J. Am. Chem. Soc.* **2005**, *127*, 11244–11245.

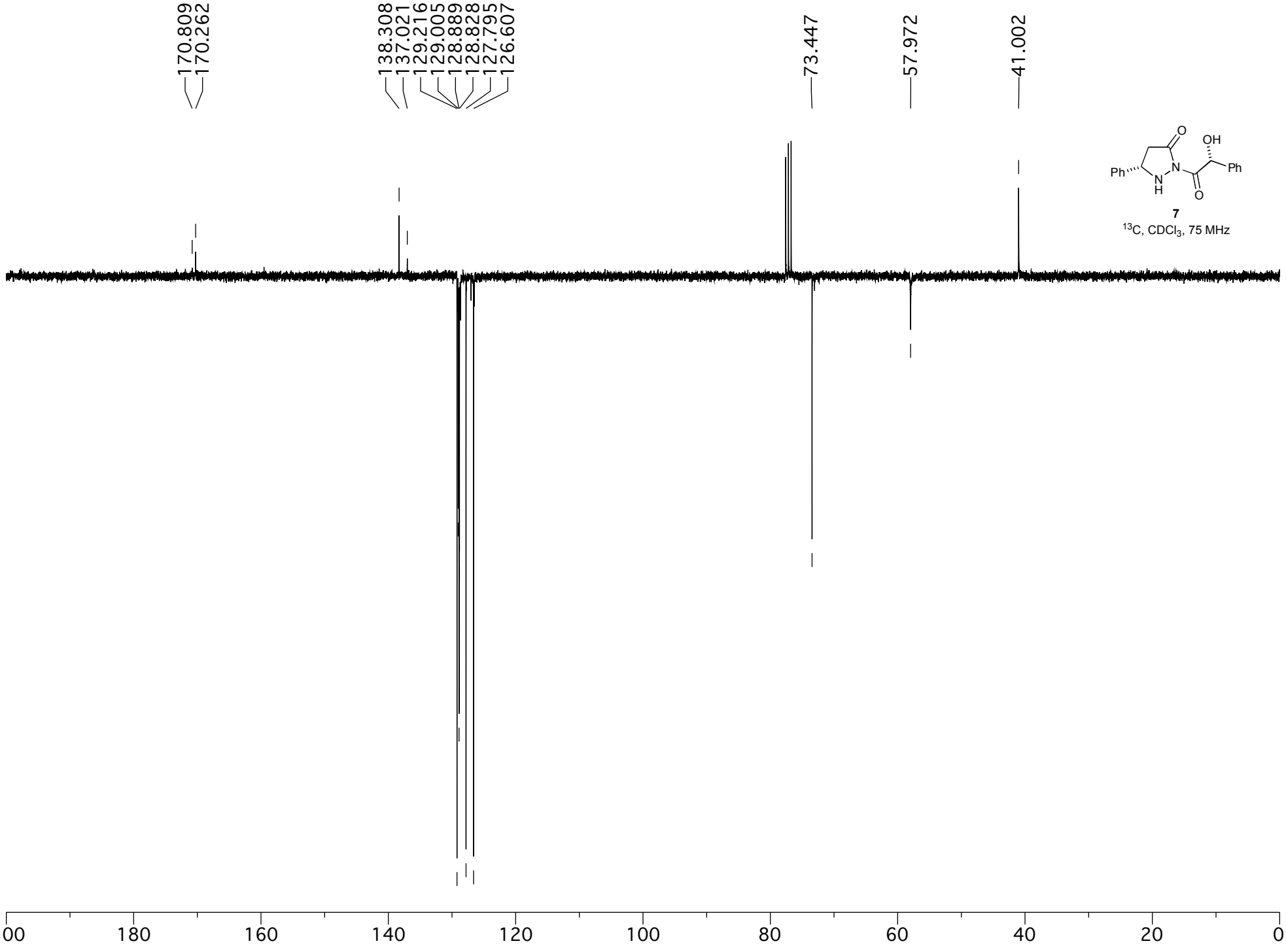
Appendix

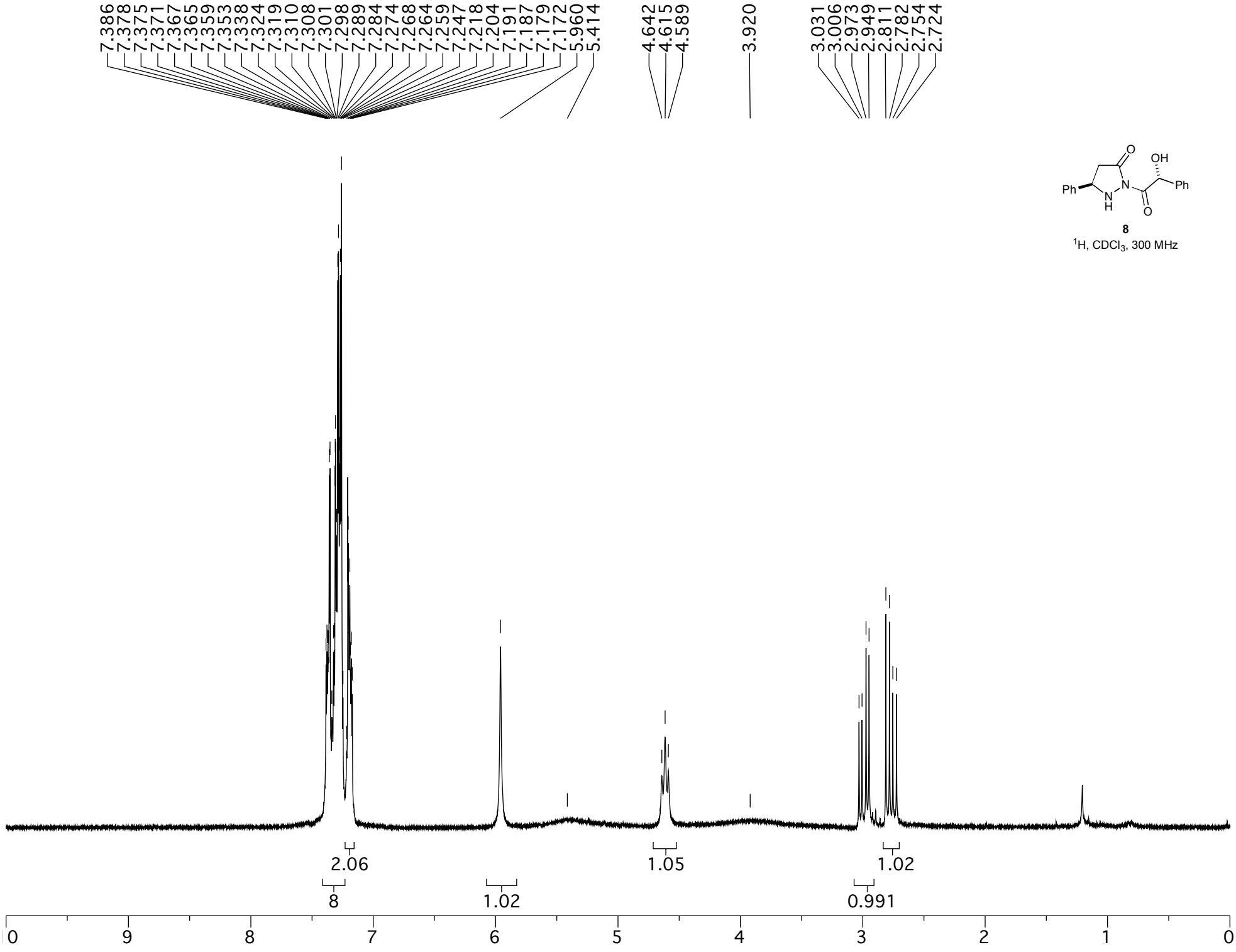
^{1}H and ^{13}C NMR spectra for novel compounds

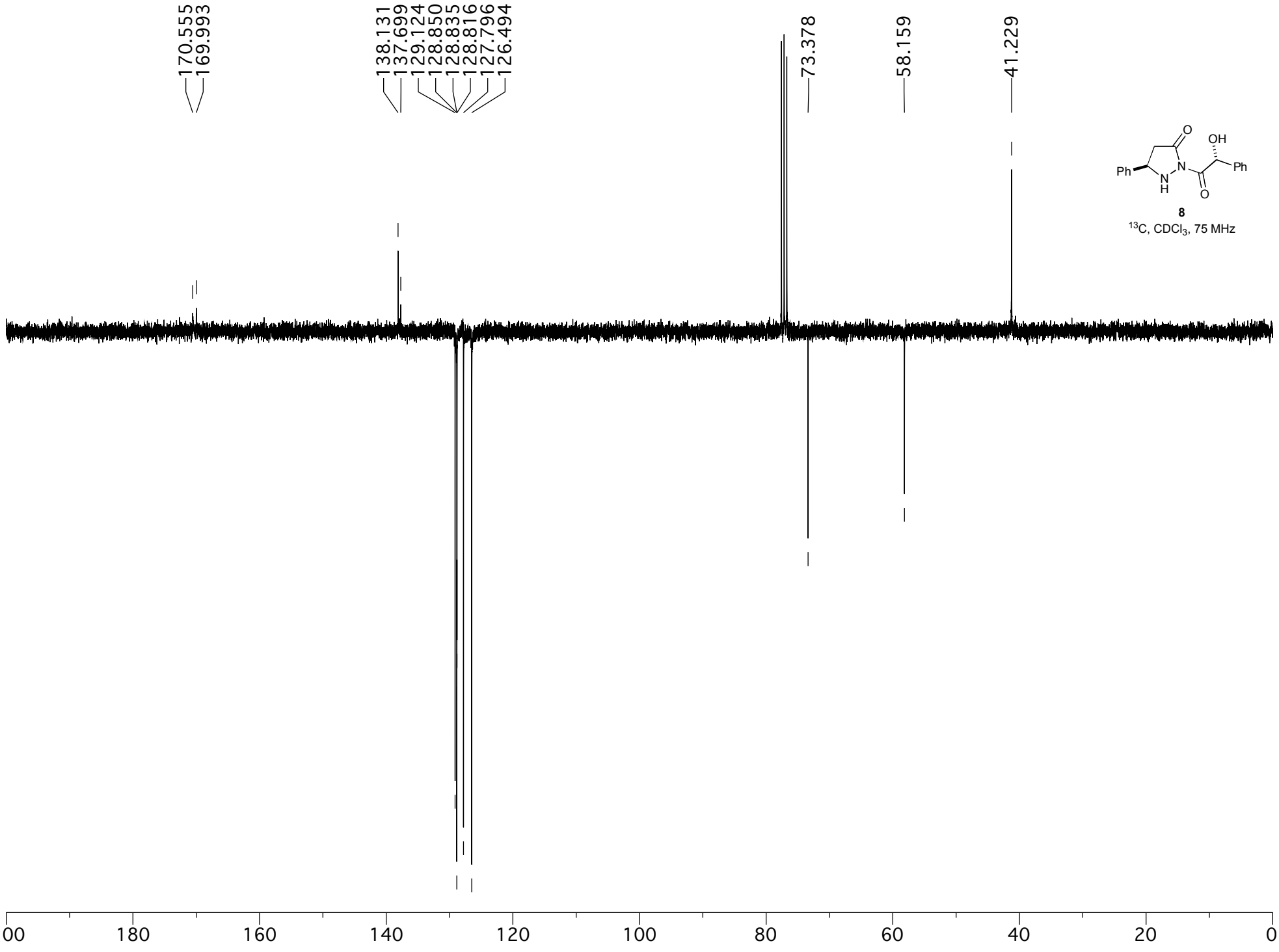


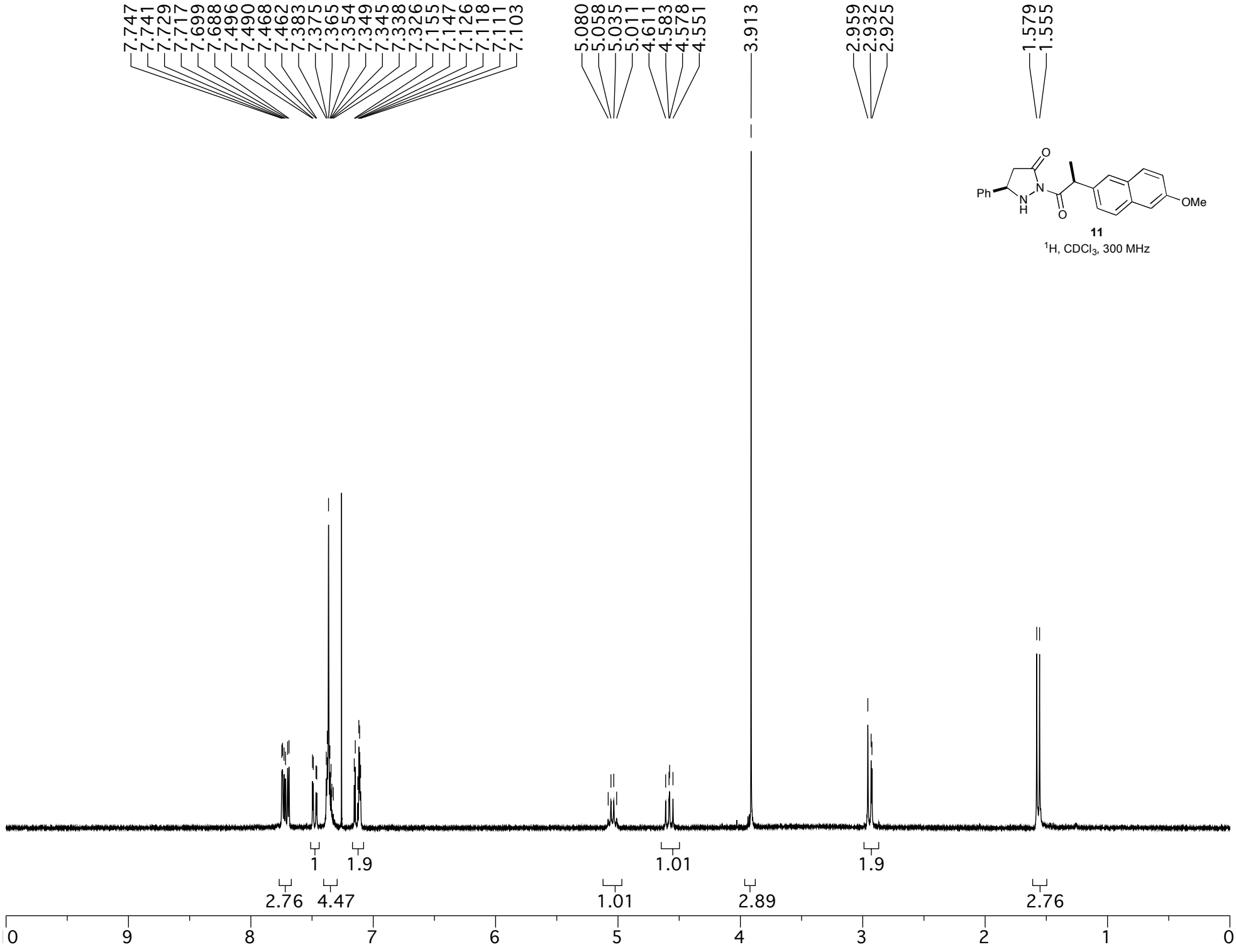


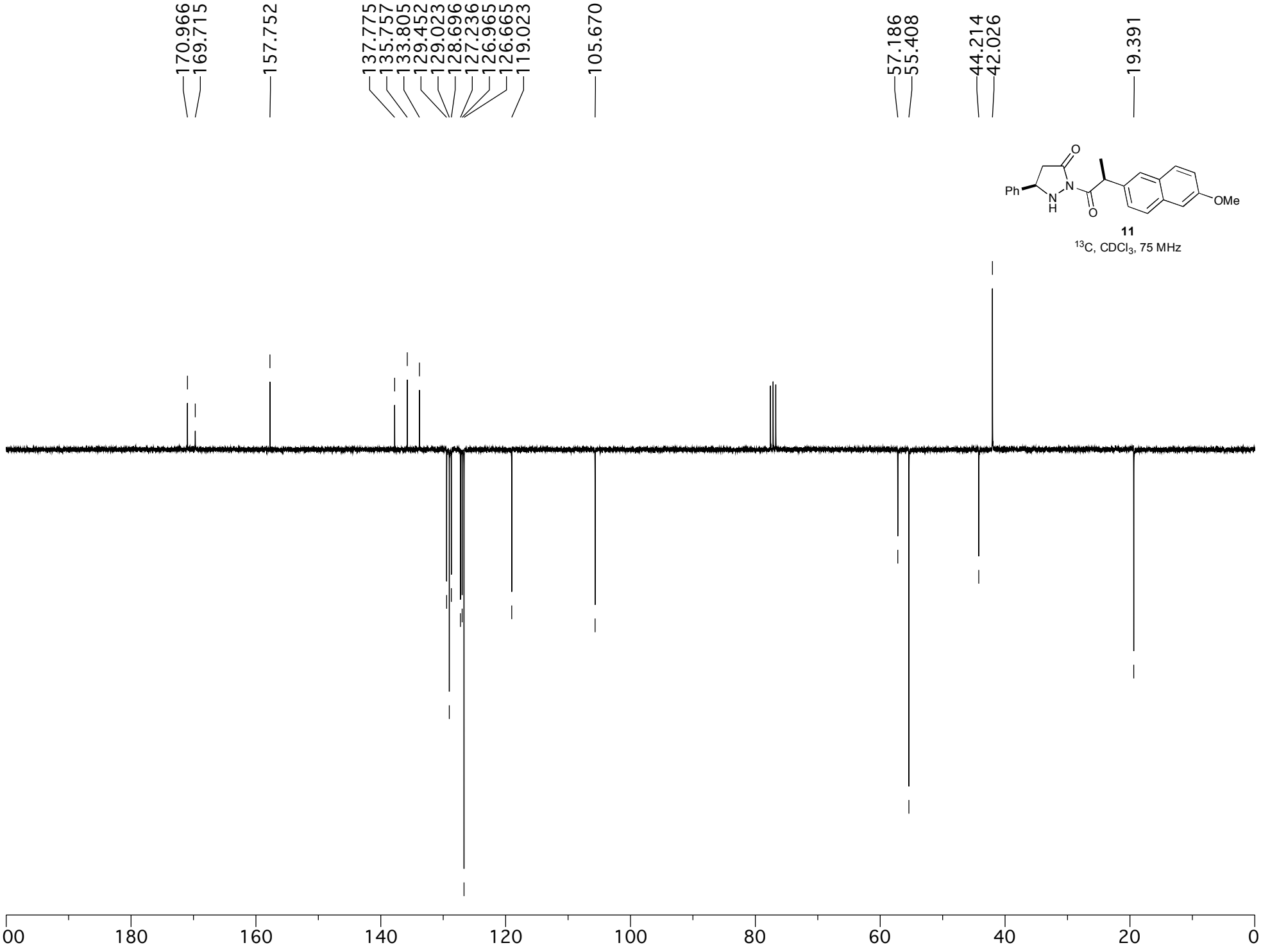


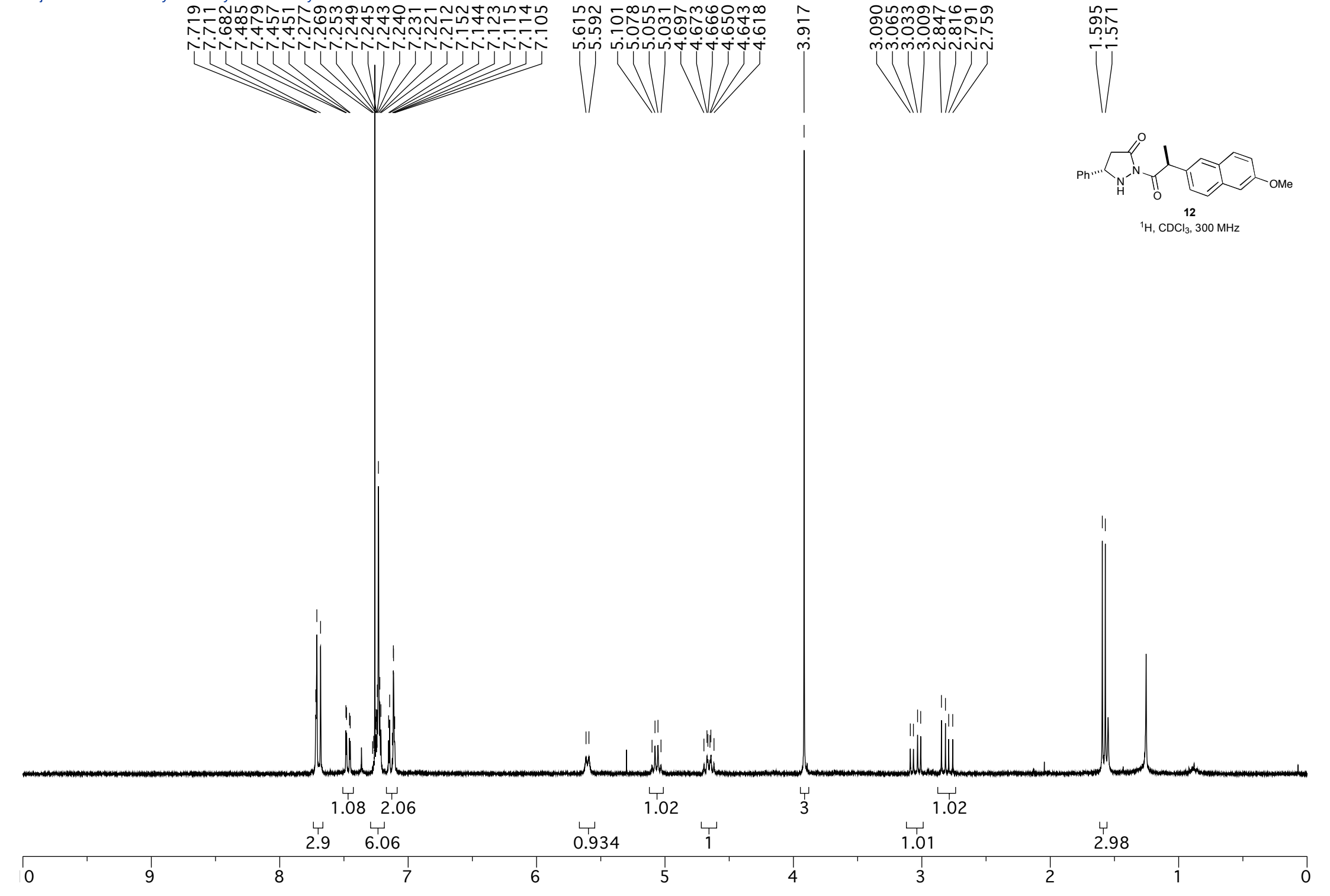


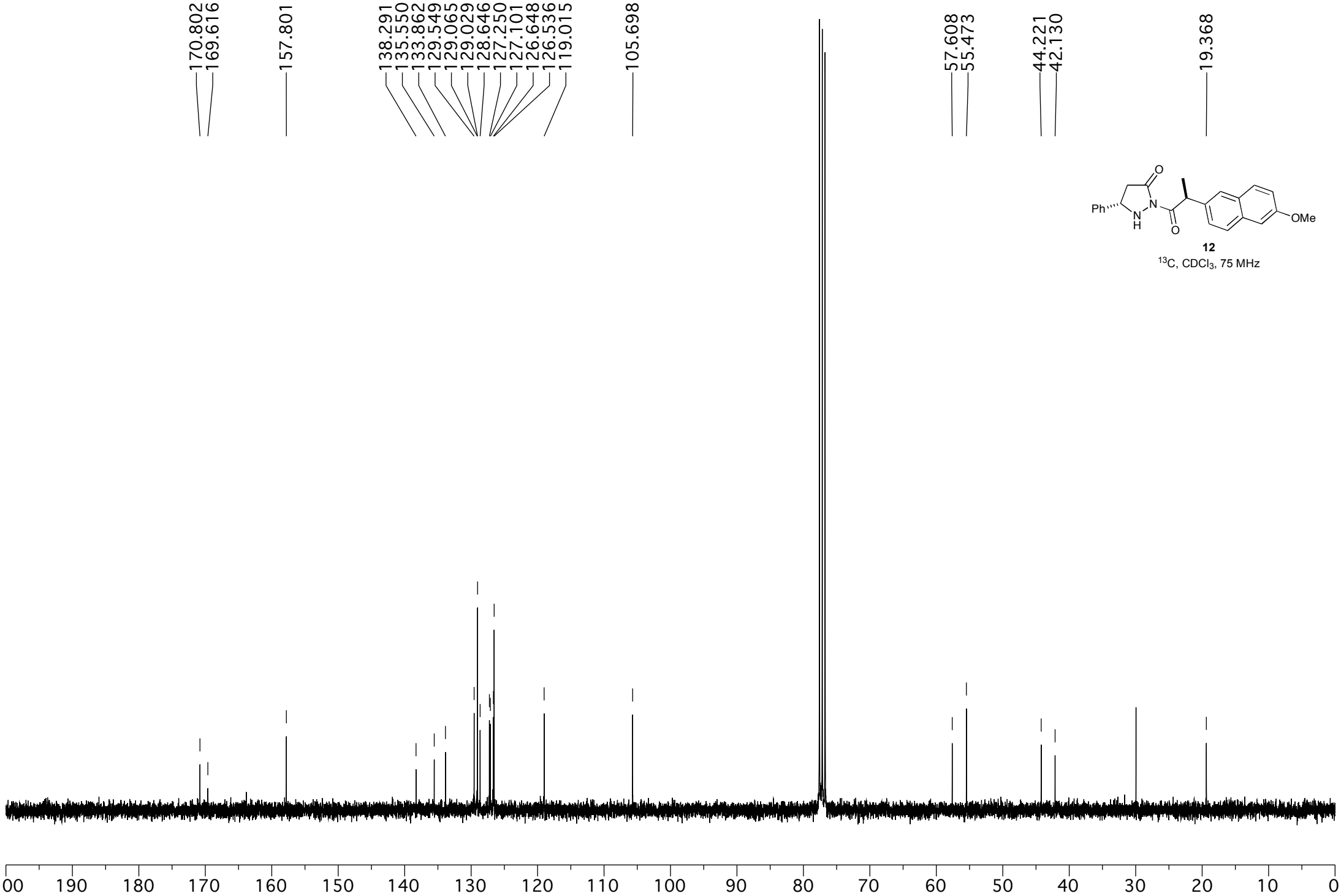


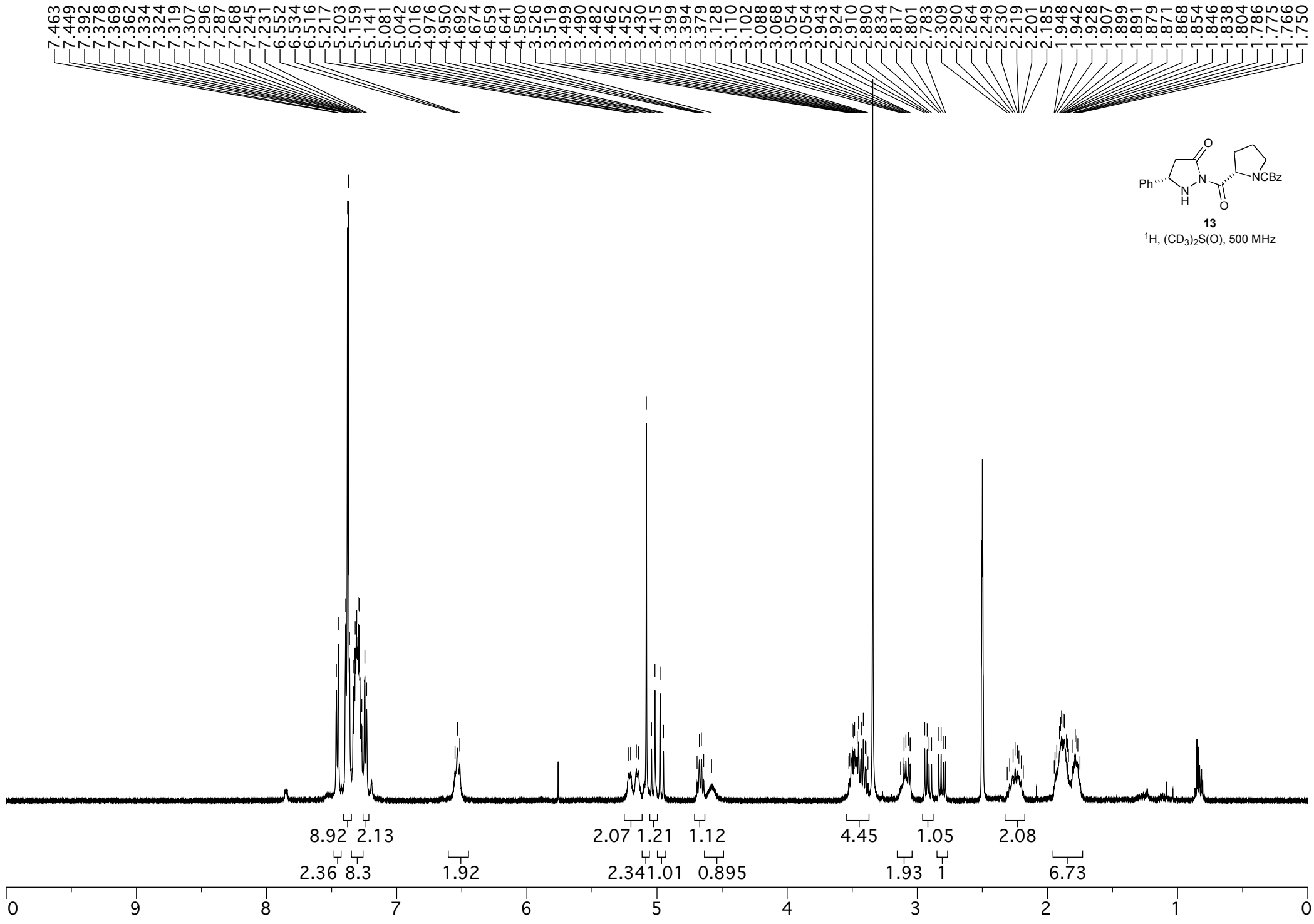


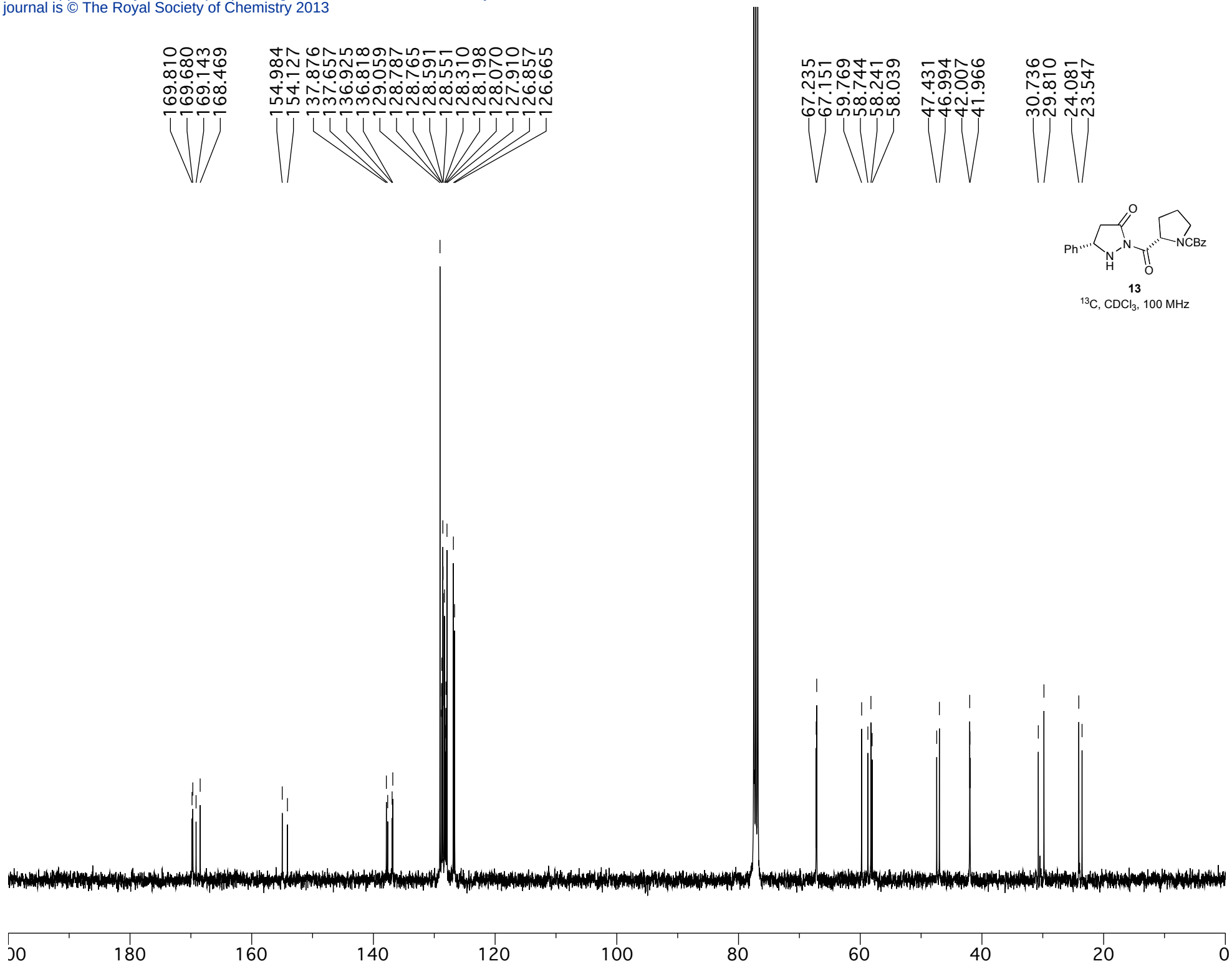


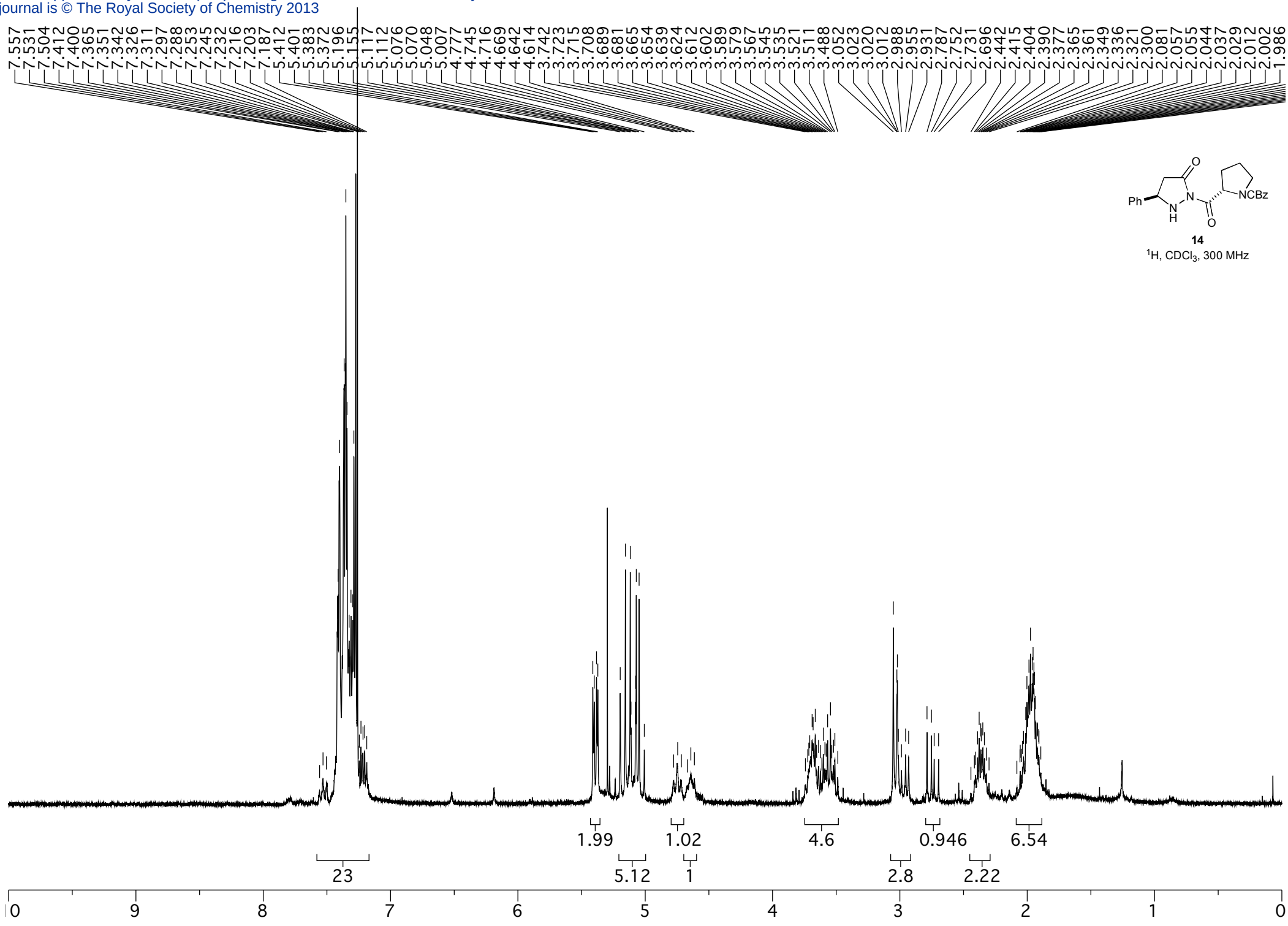


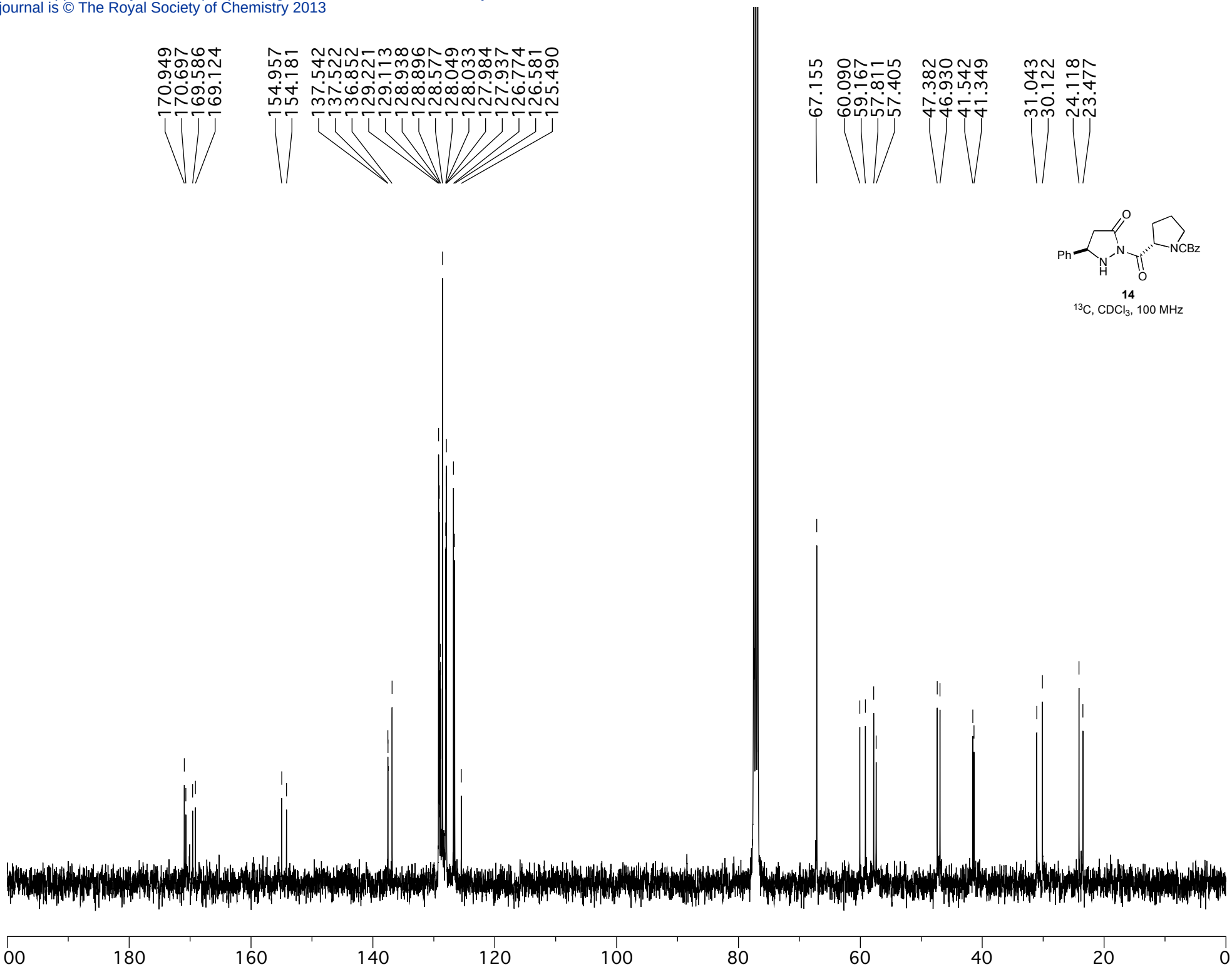


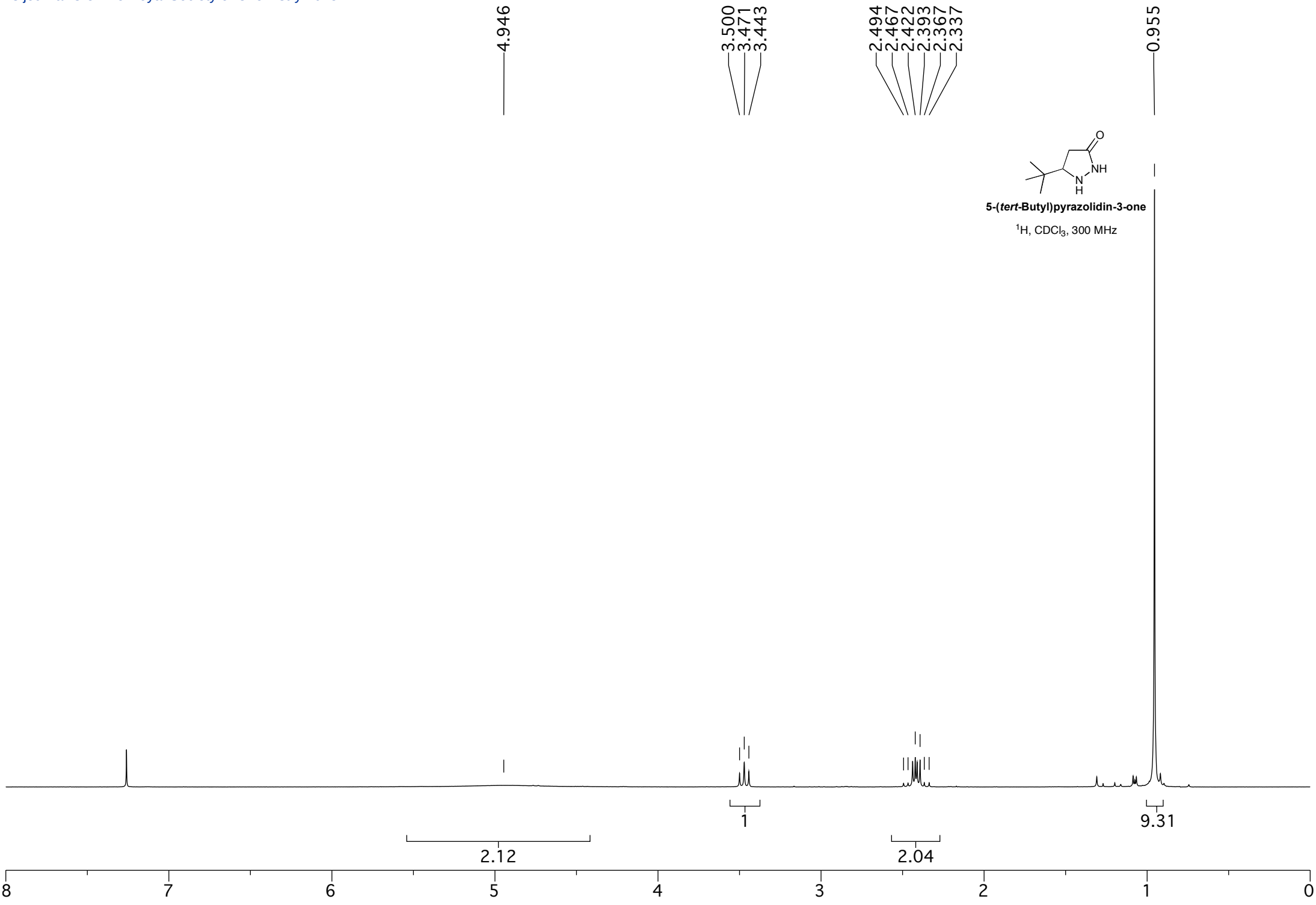


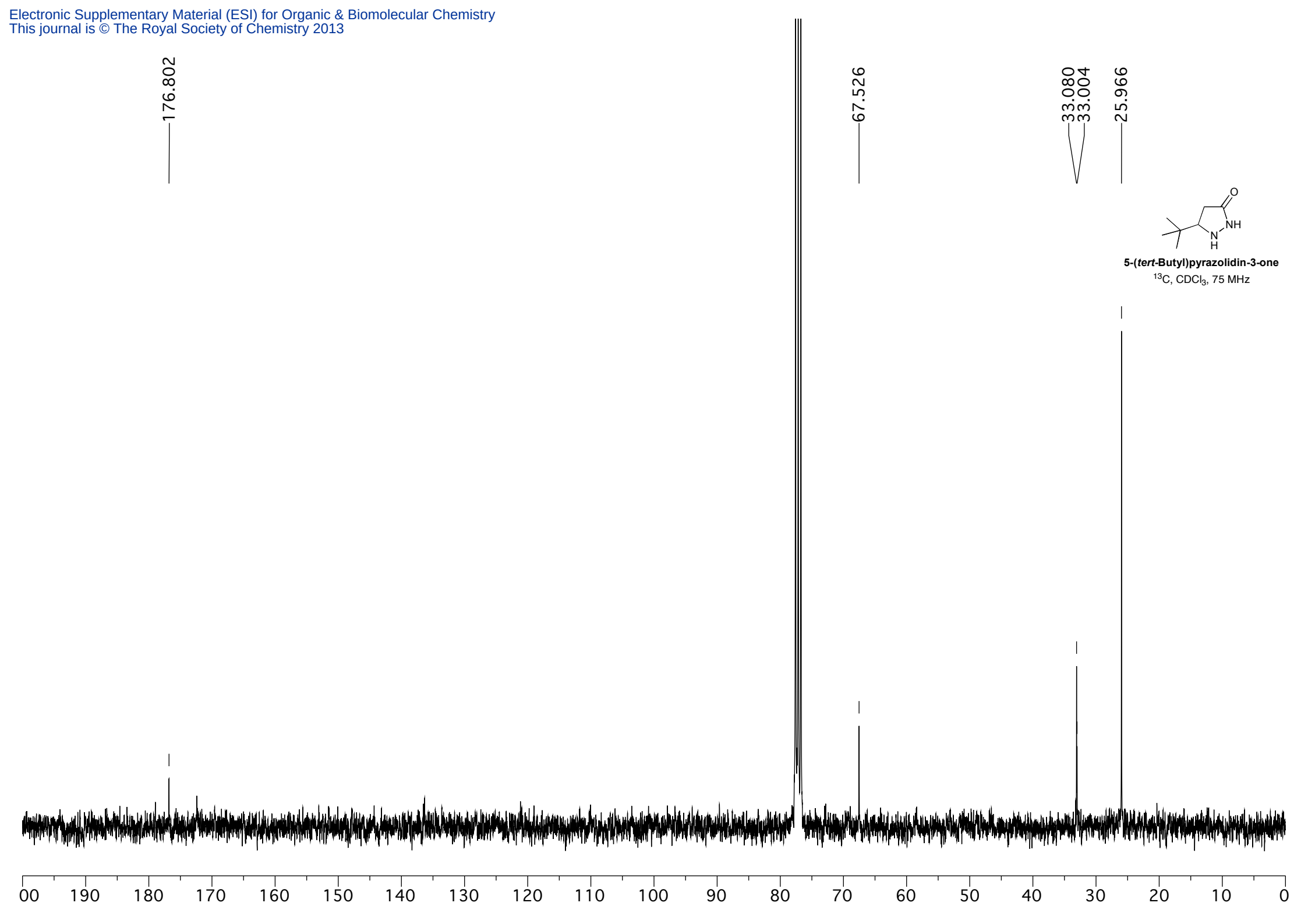


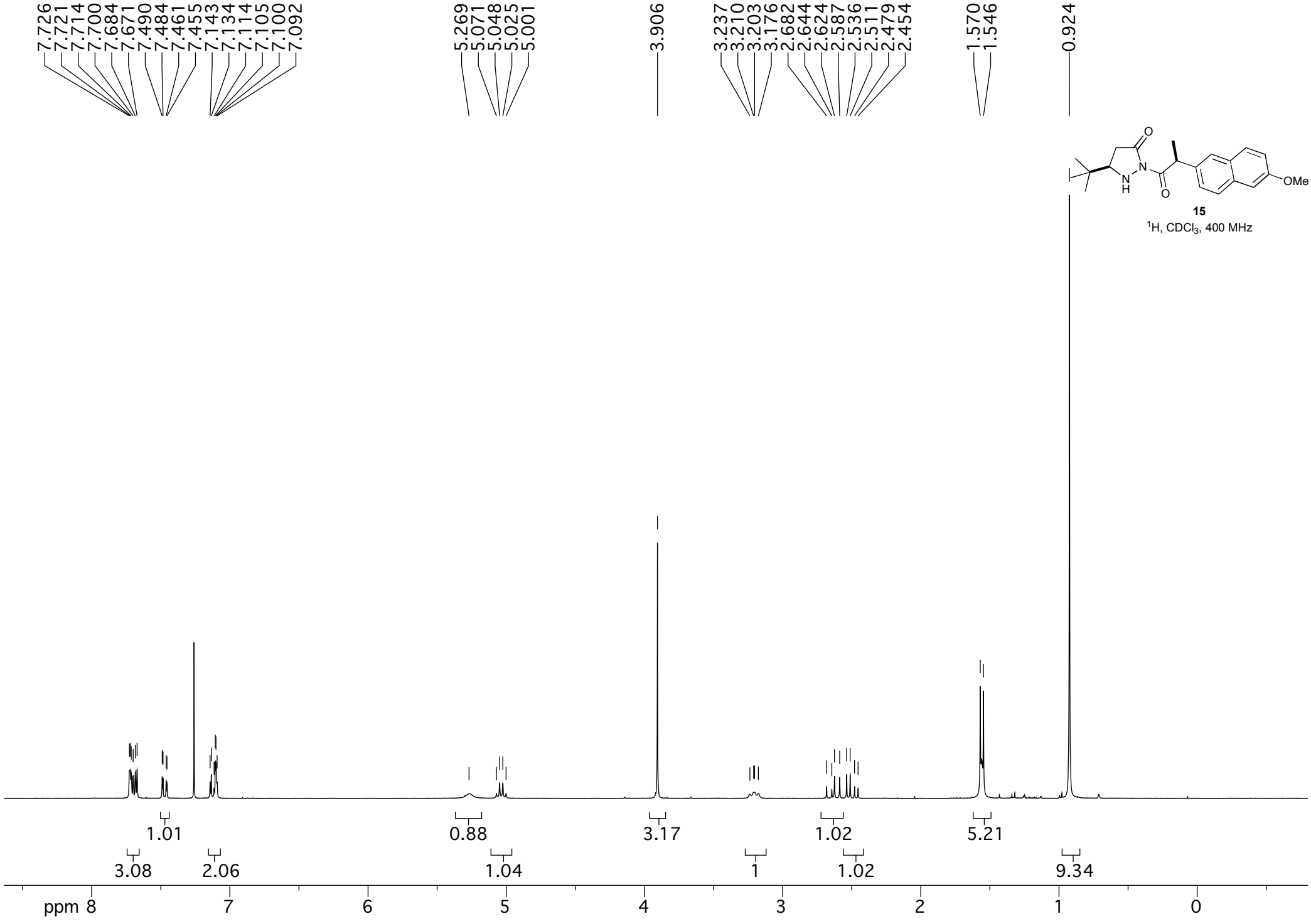


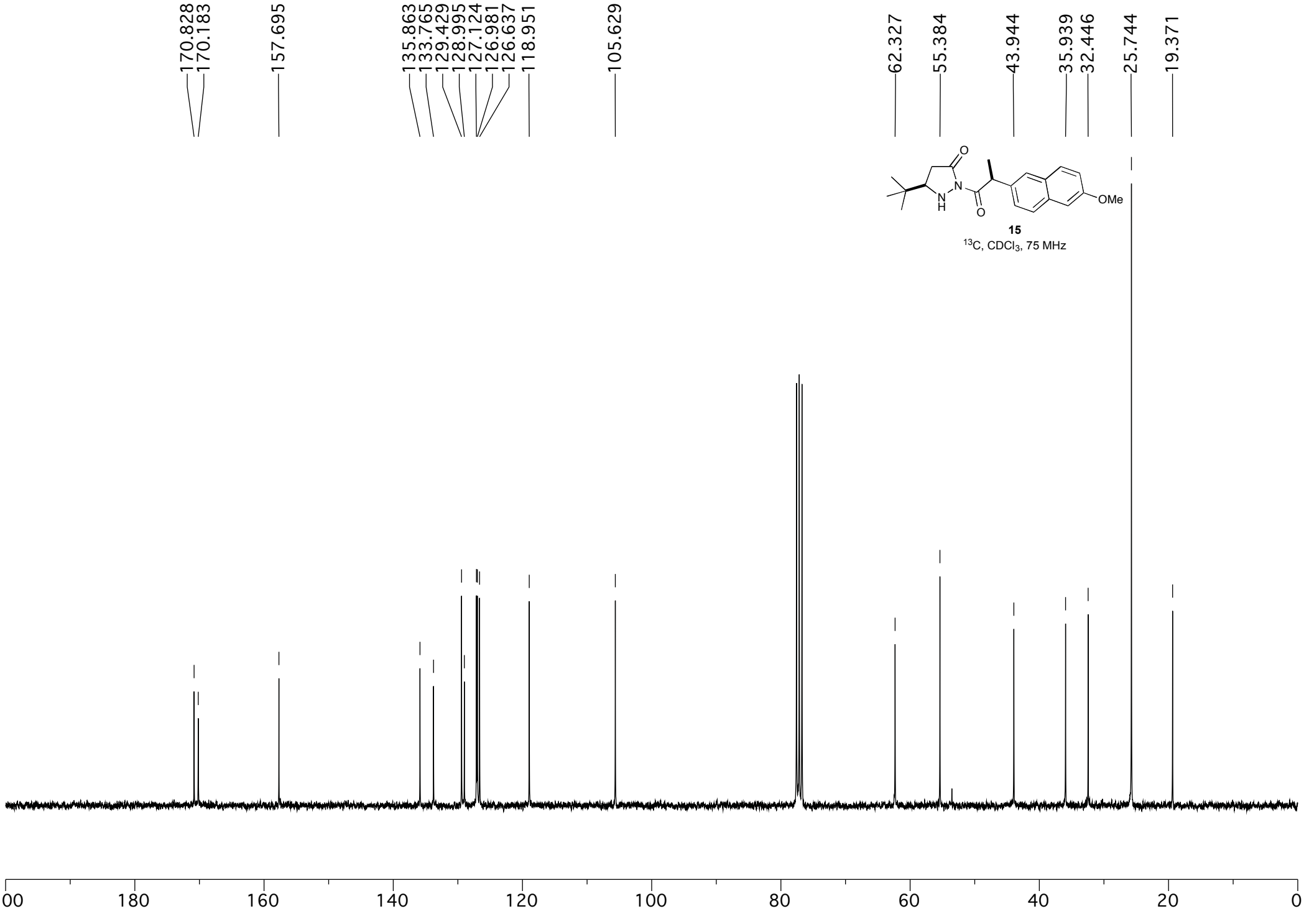


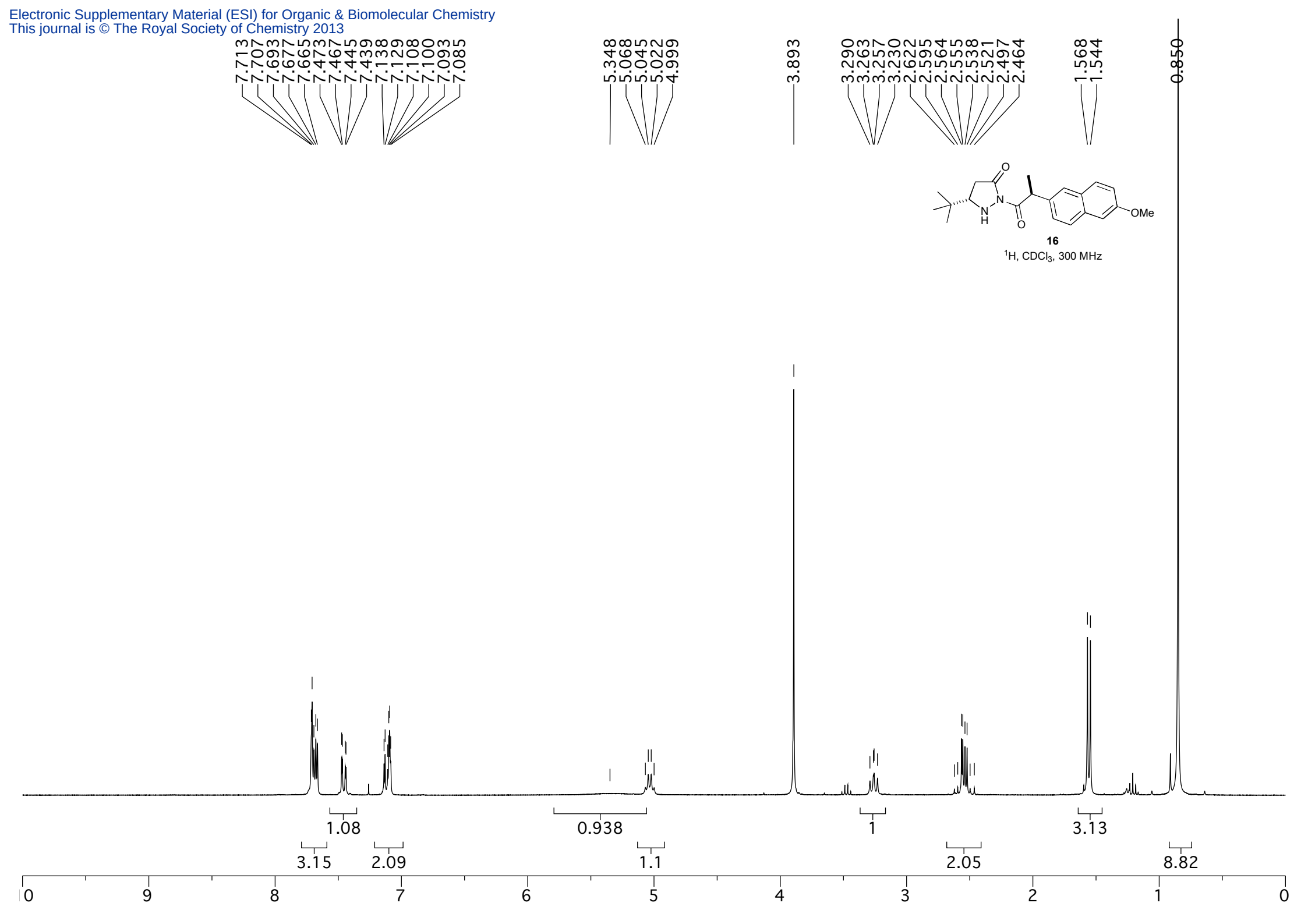


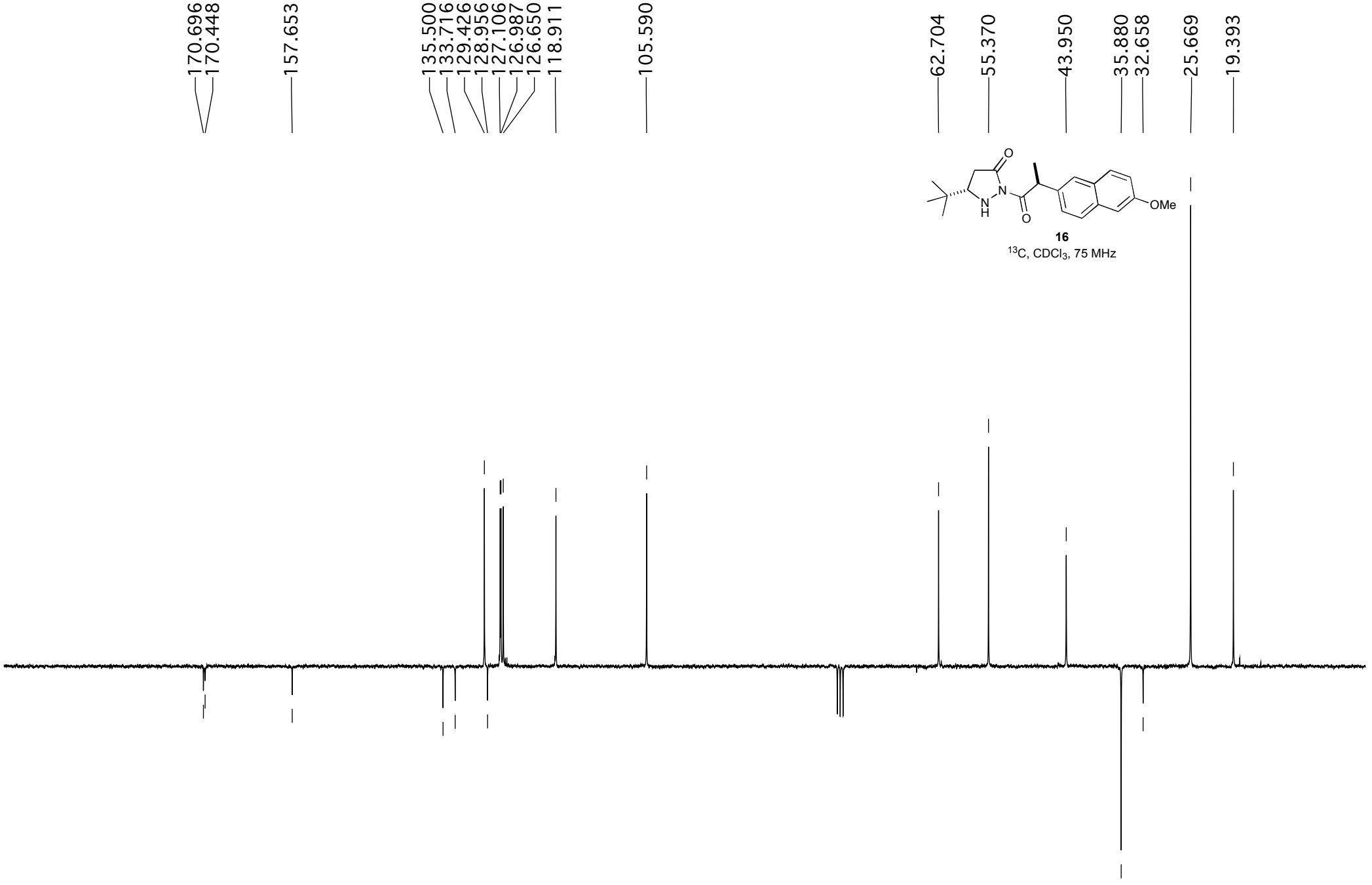


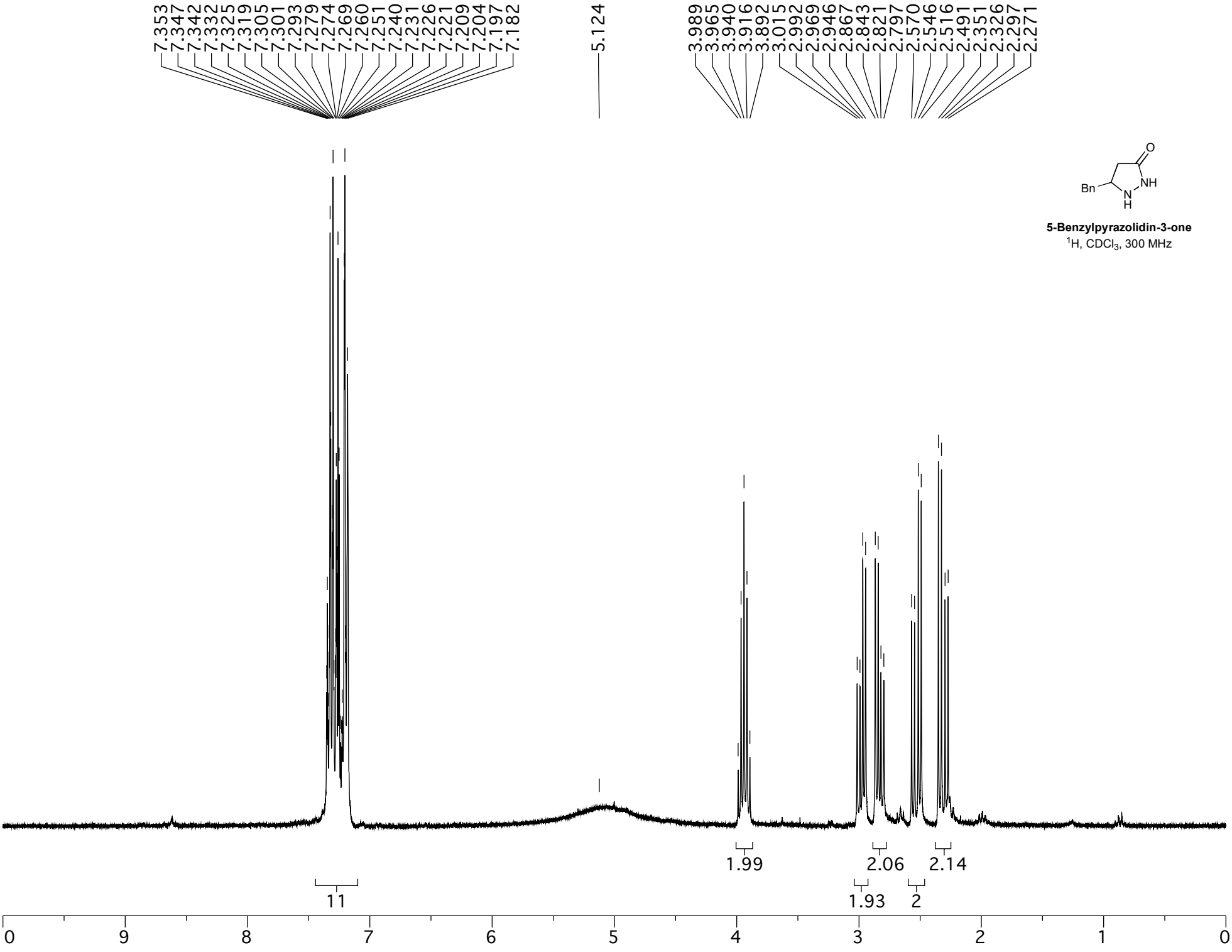


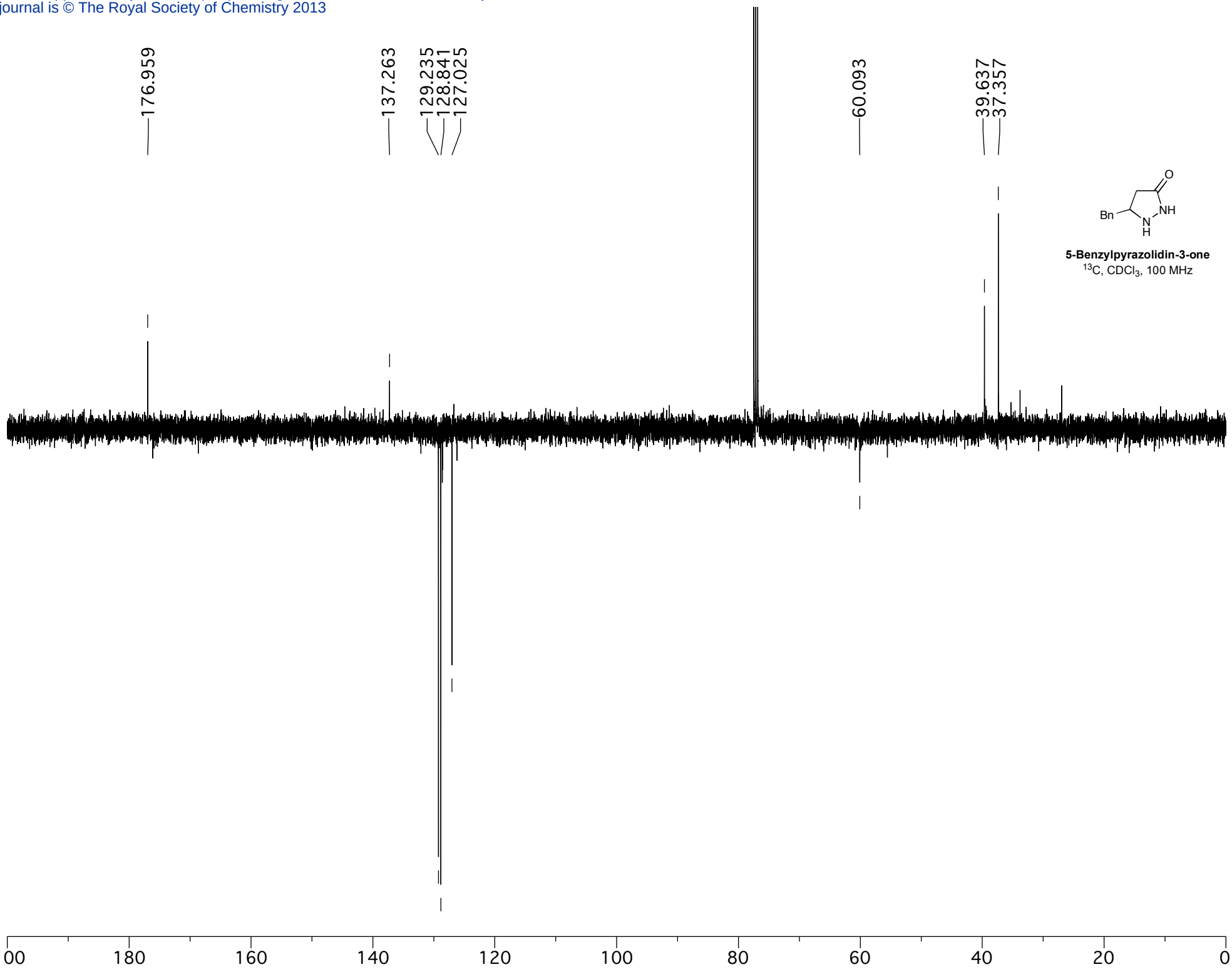


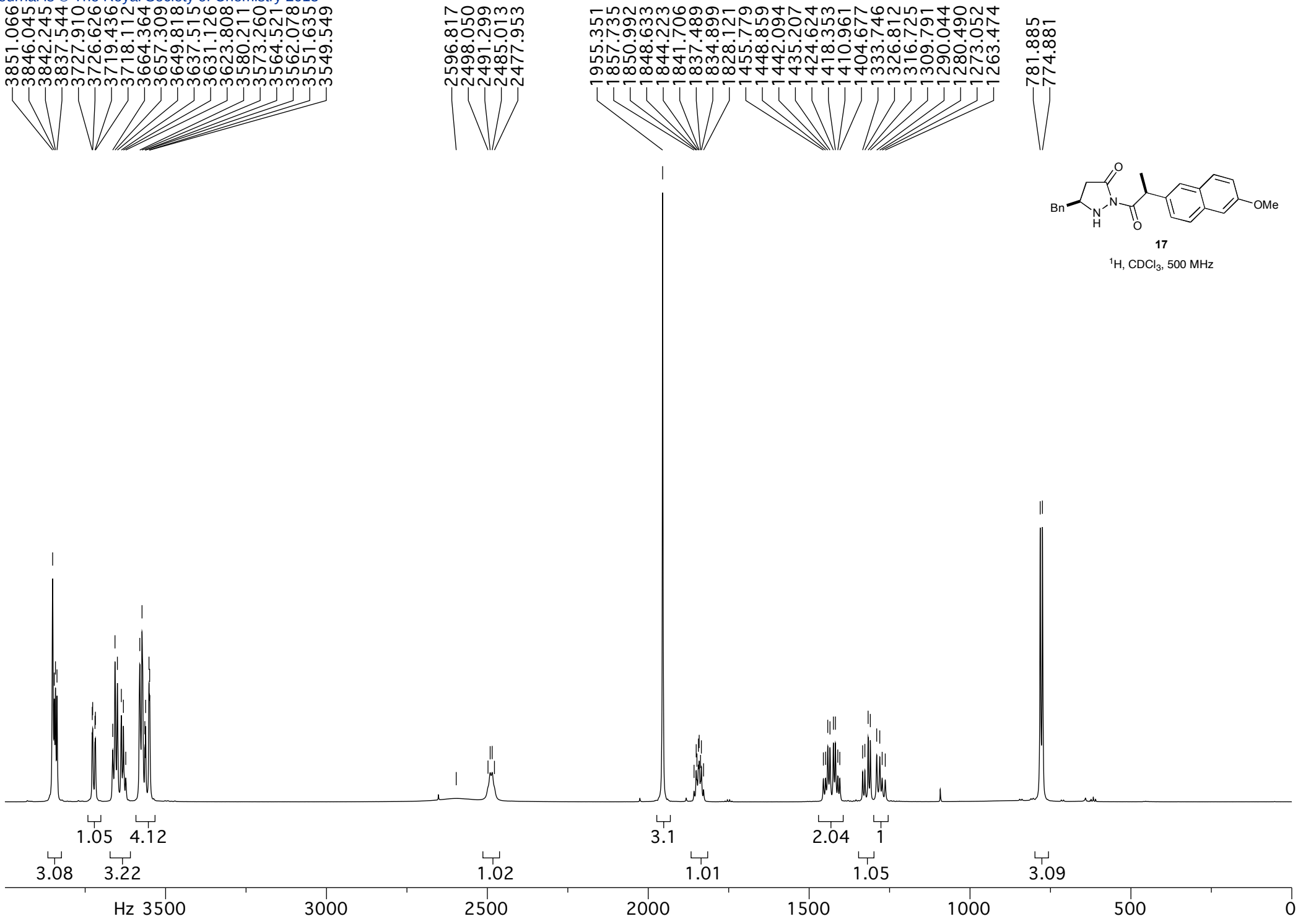


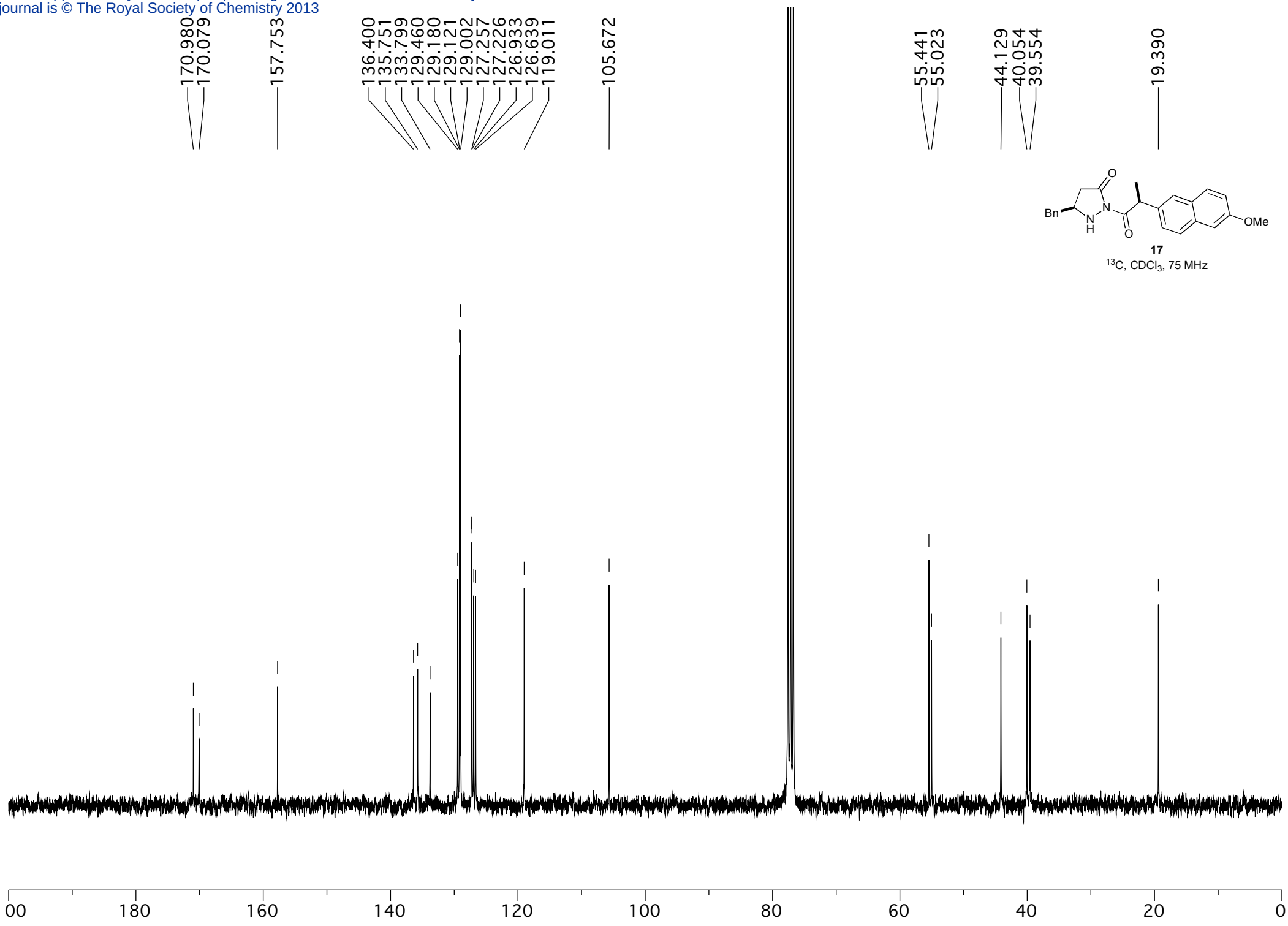


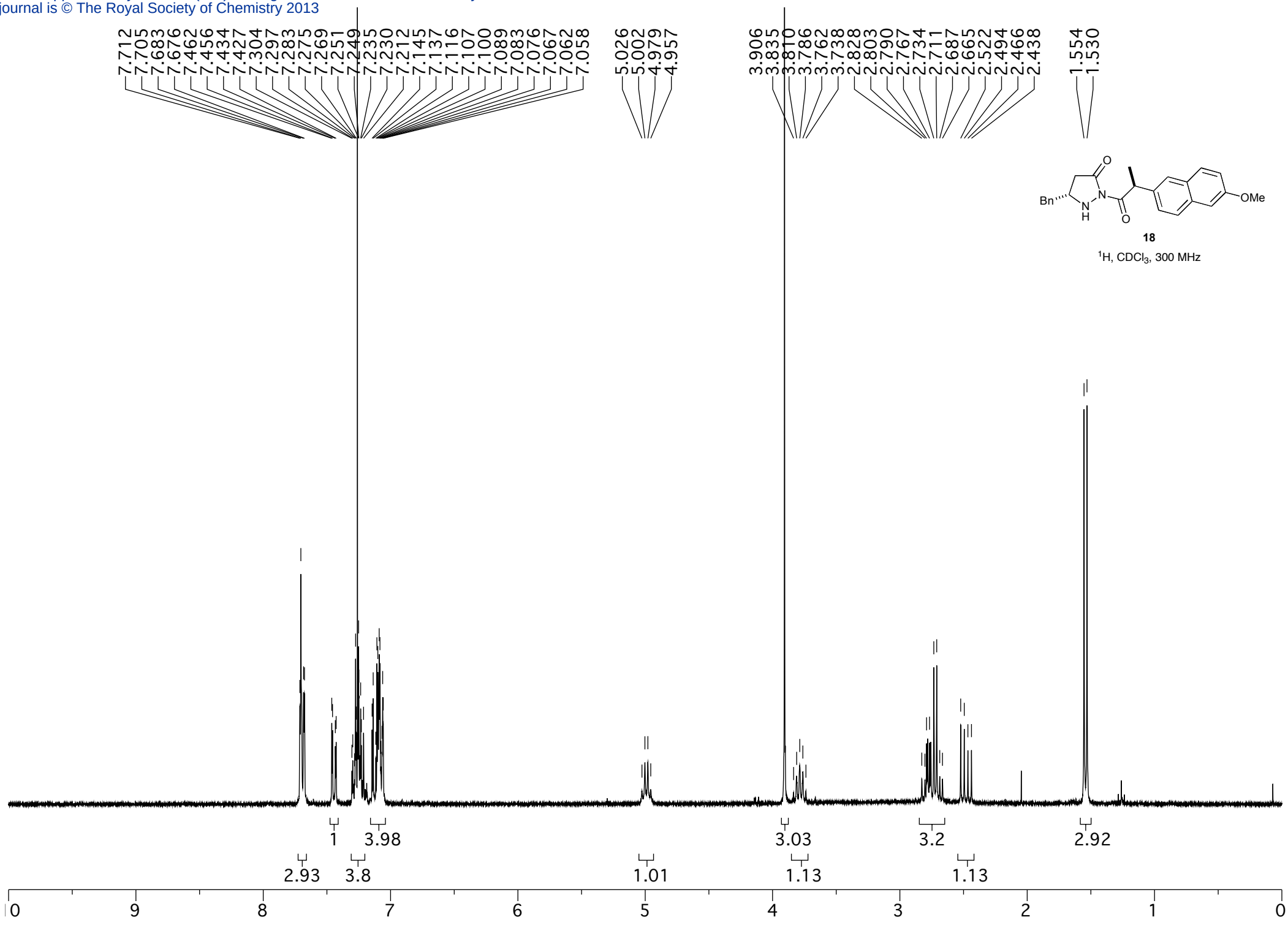


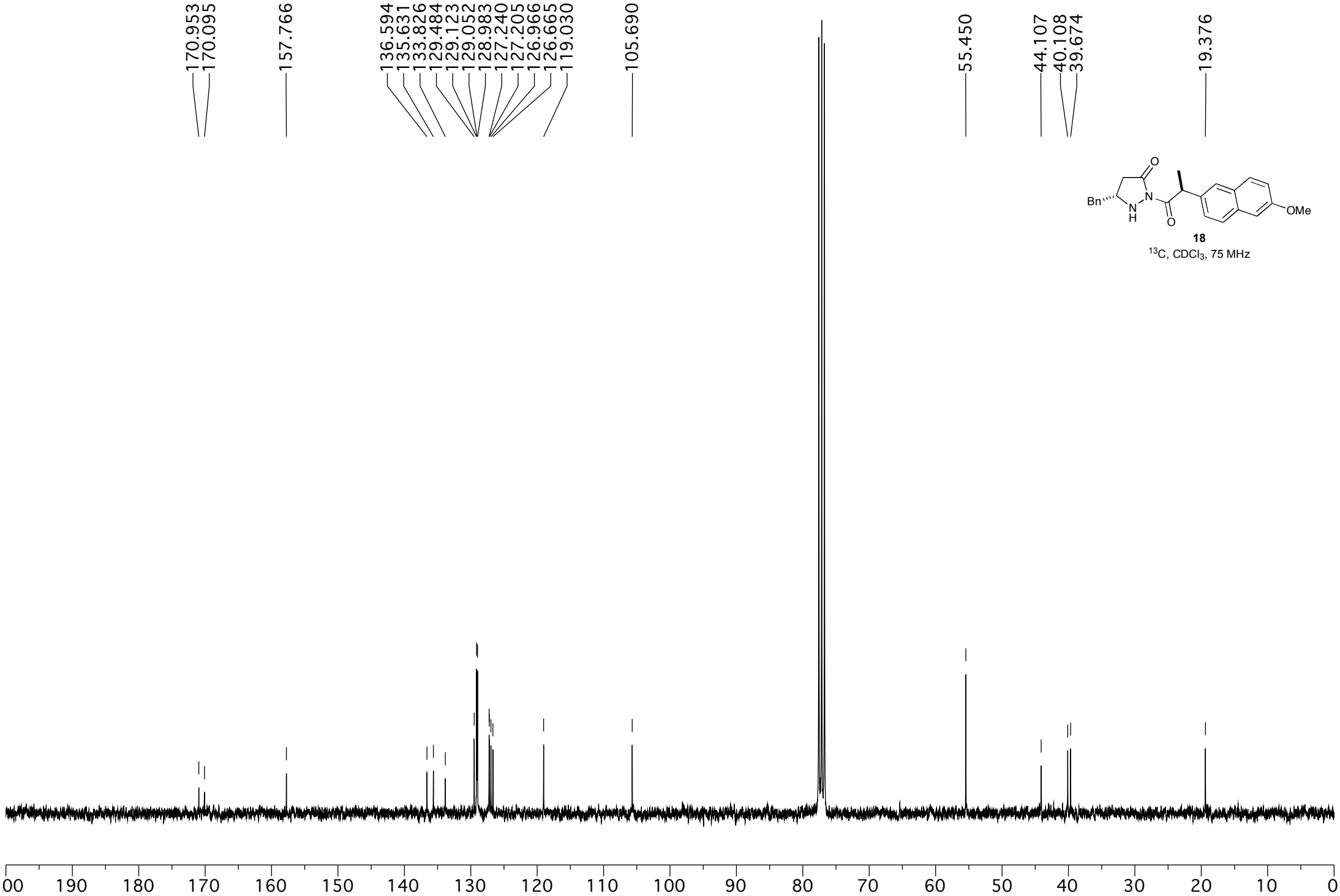


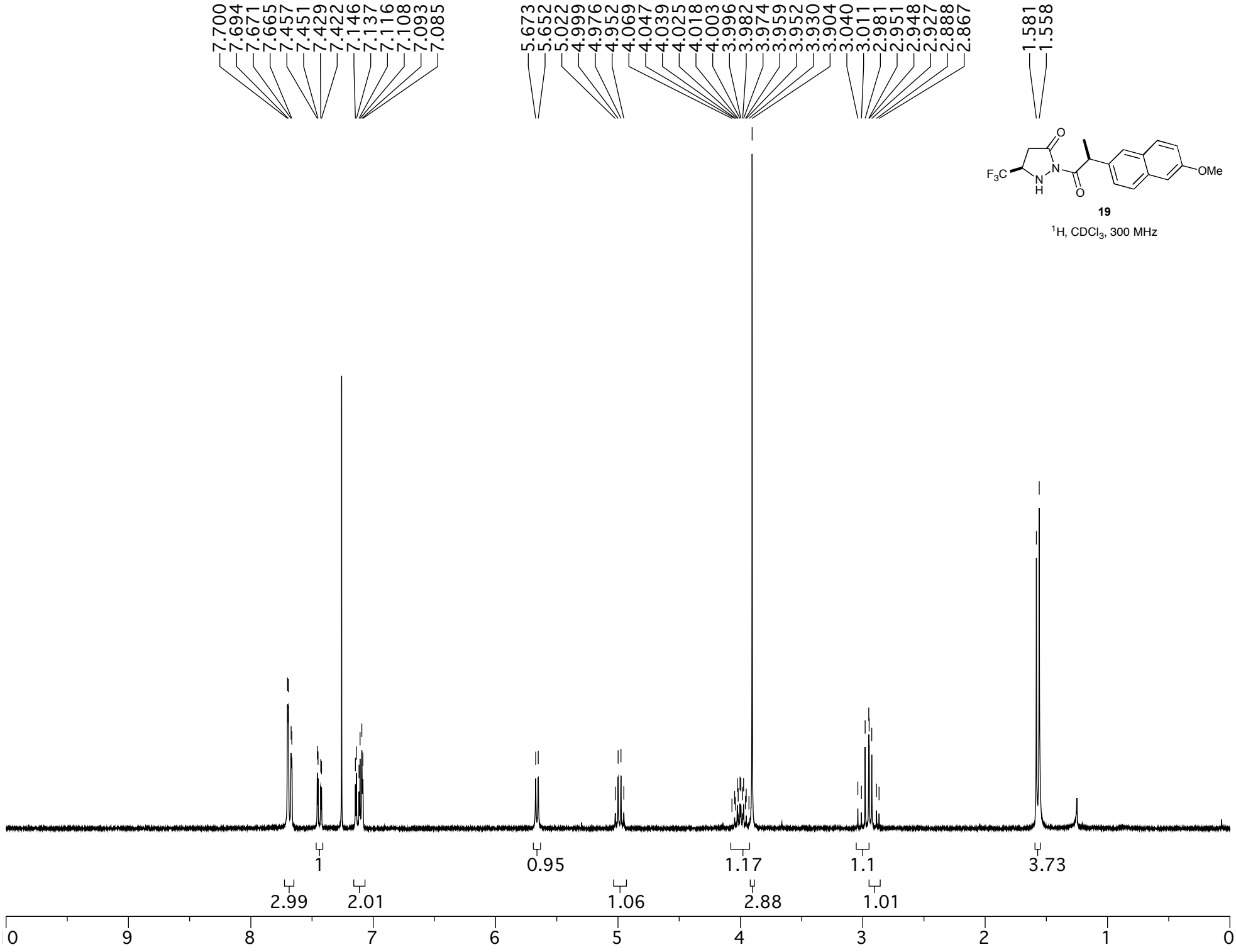


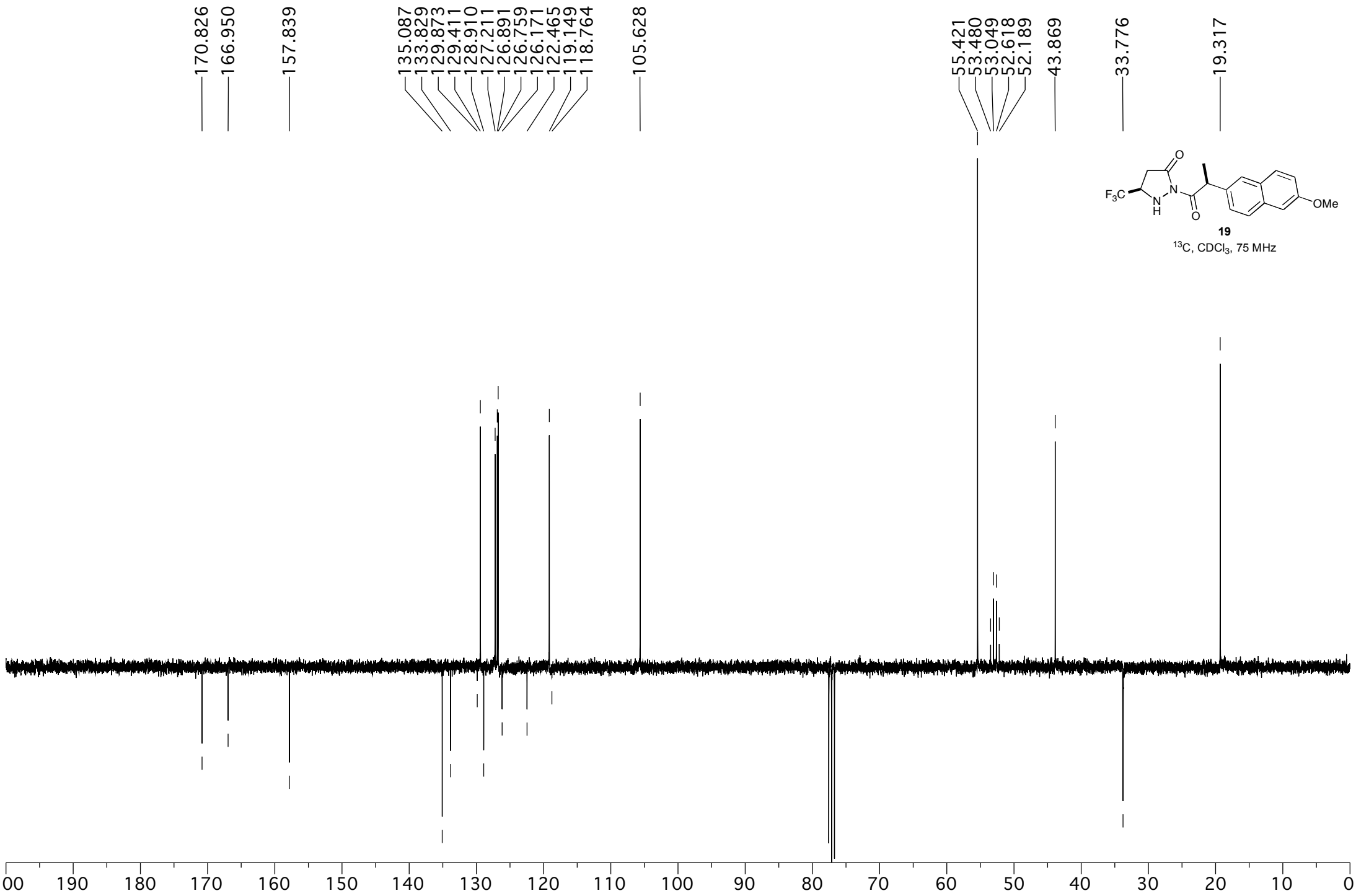


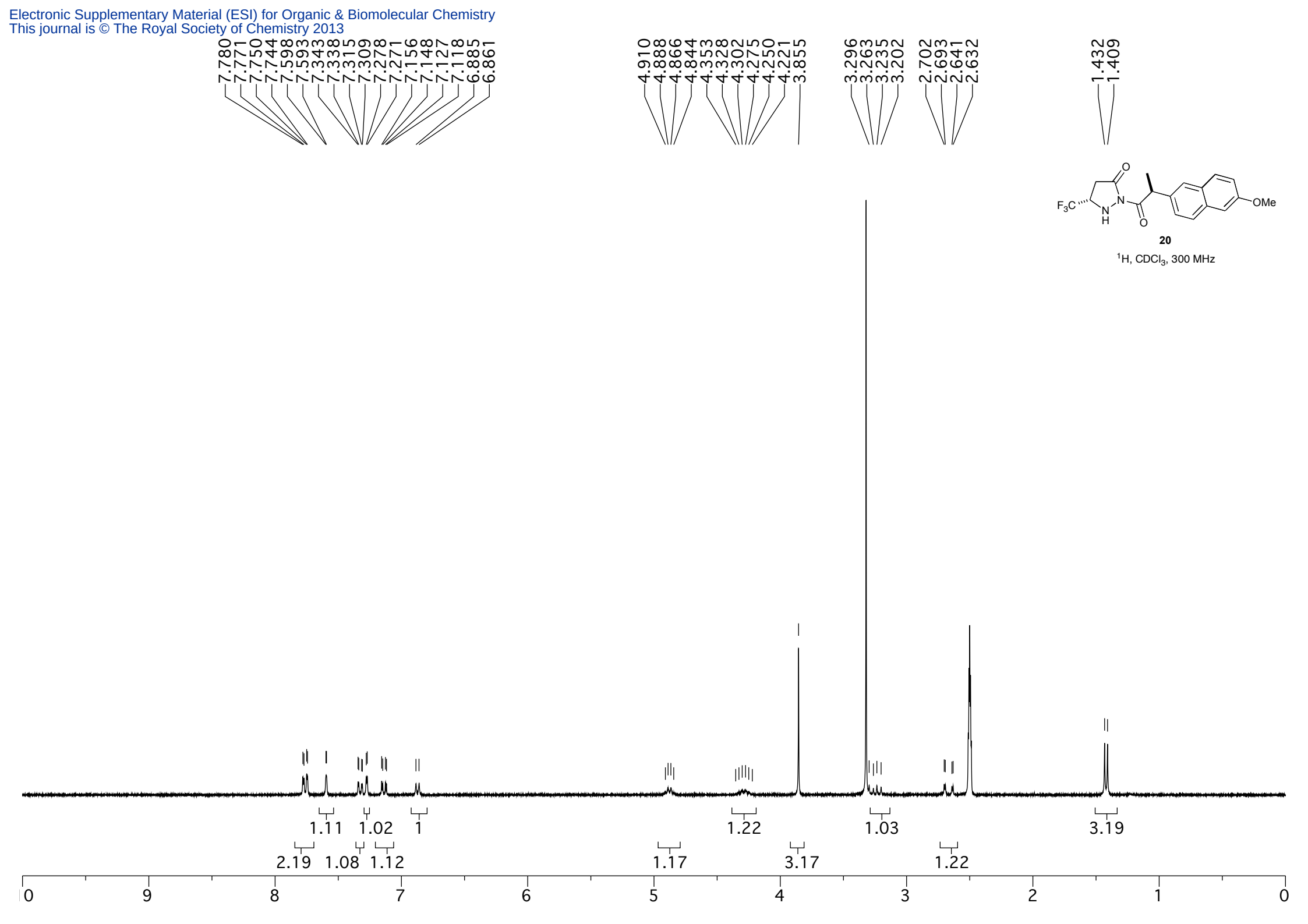


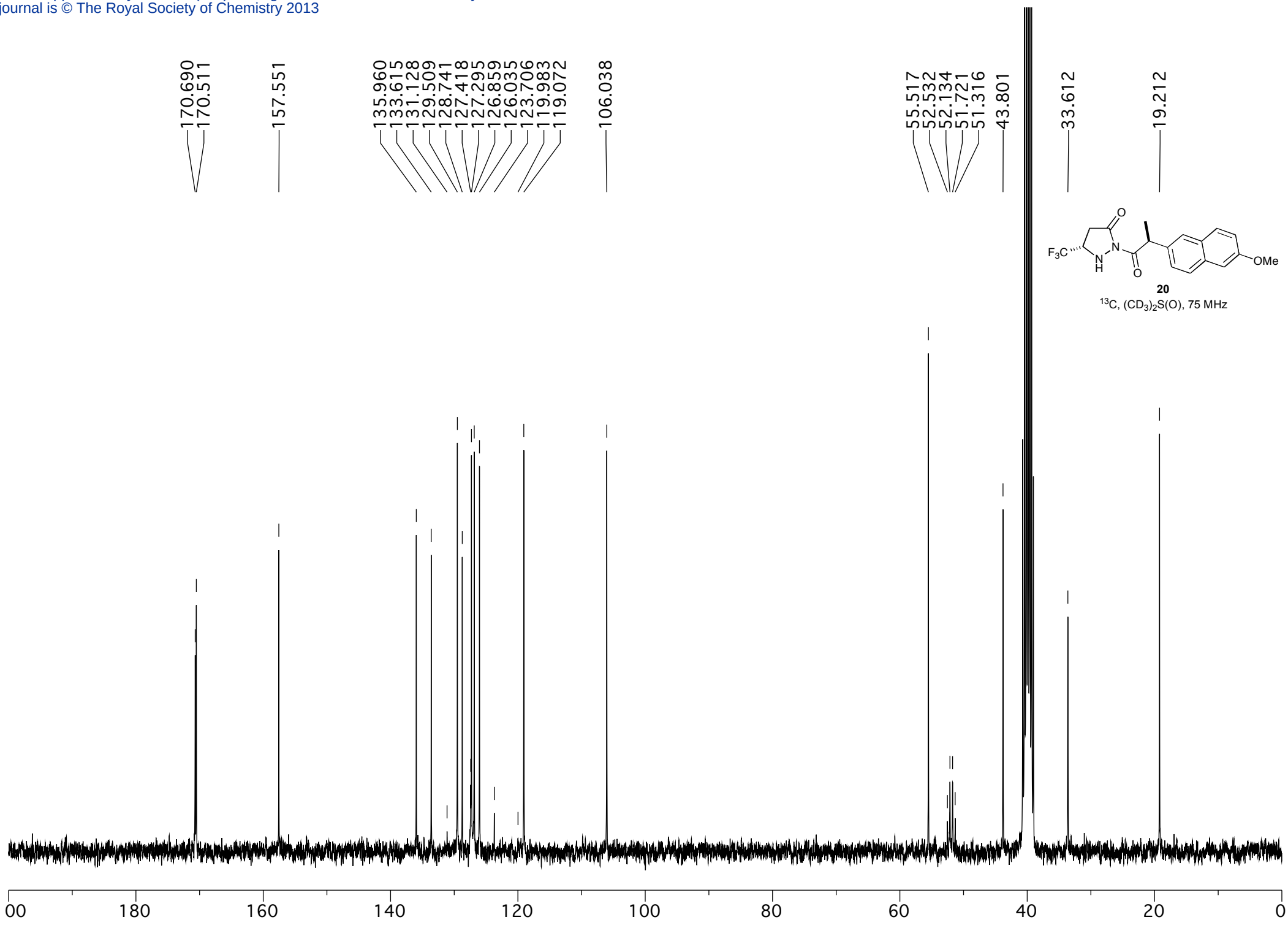


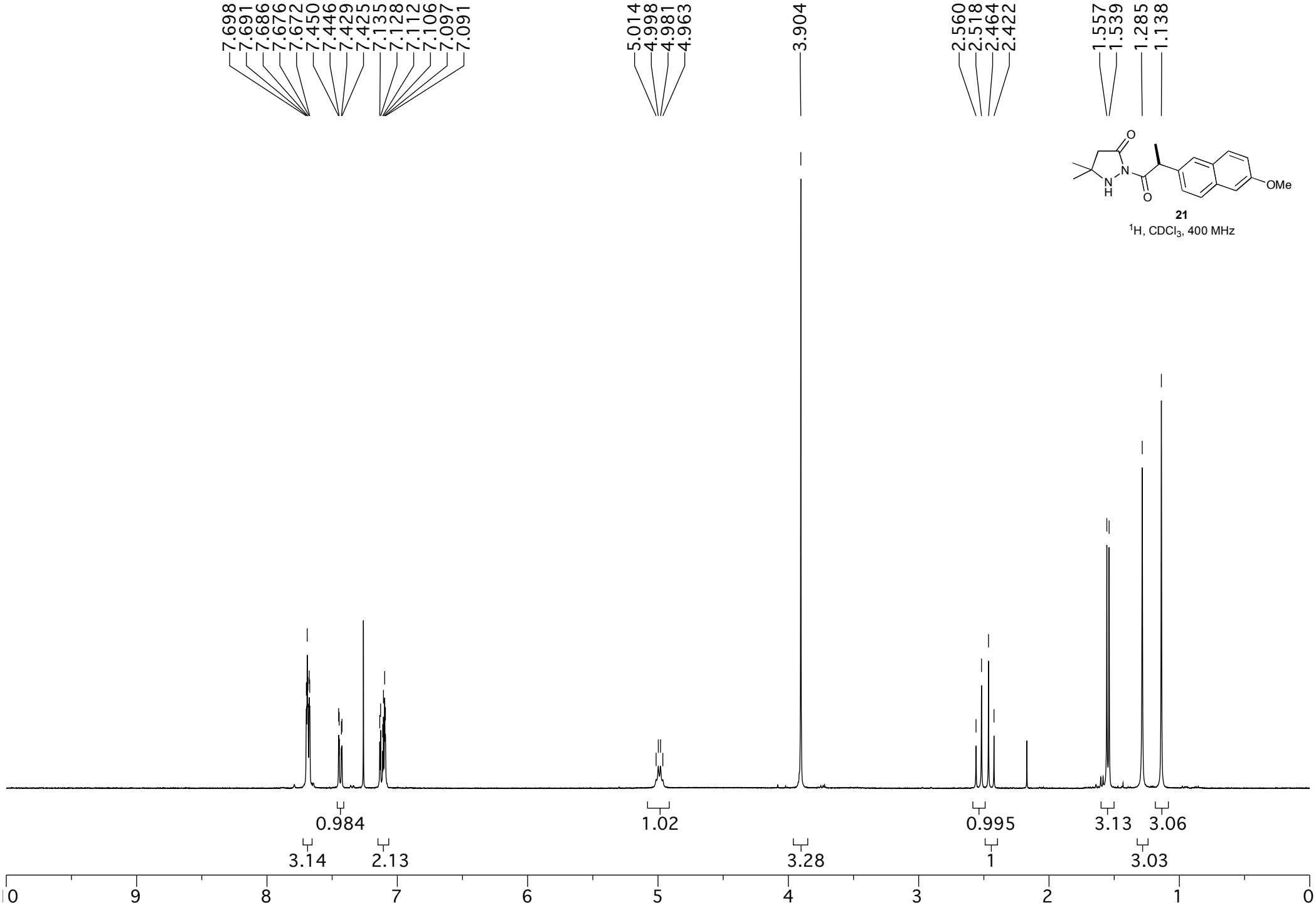


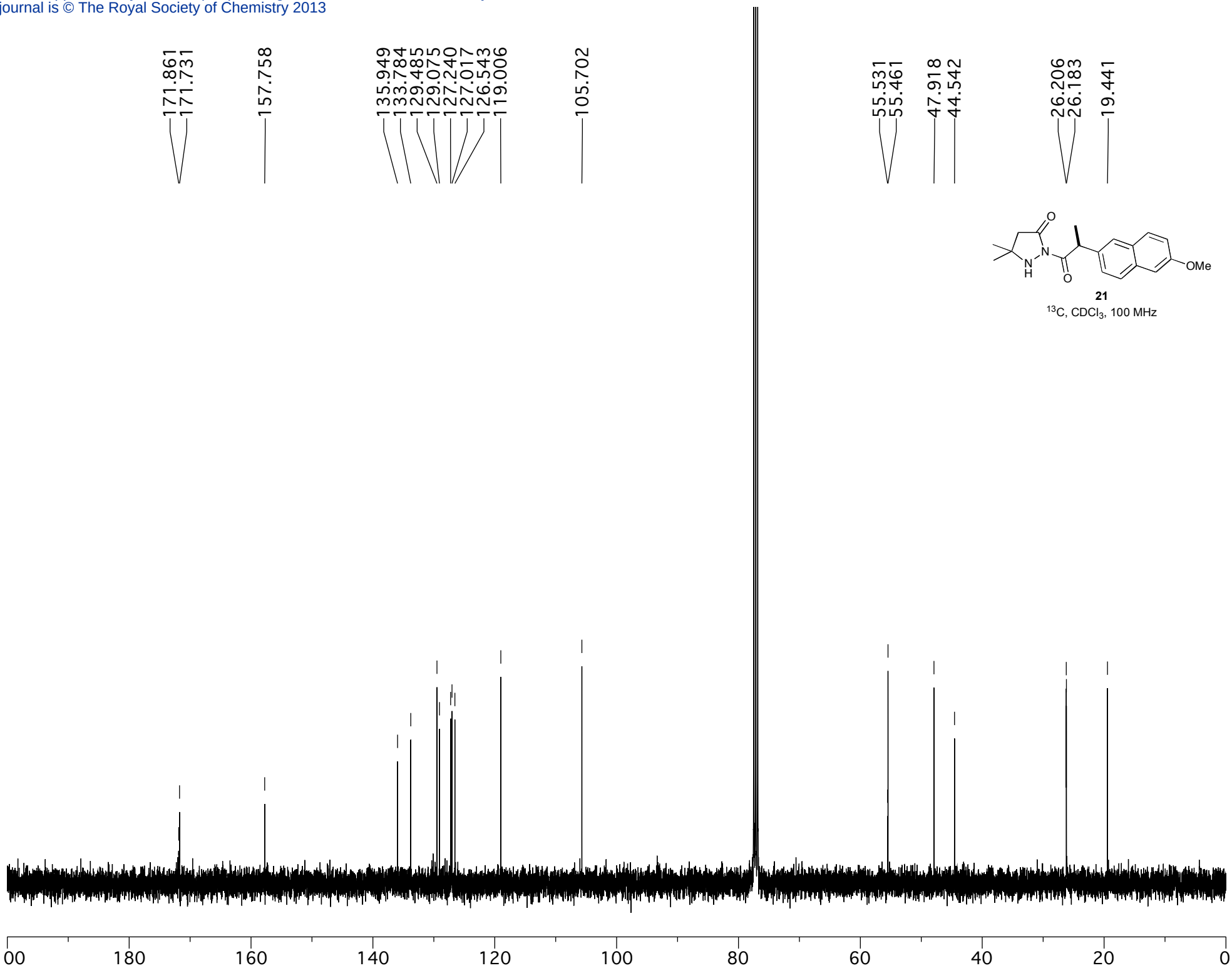






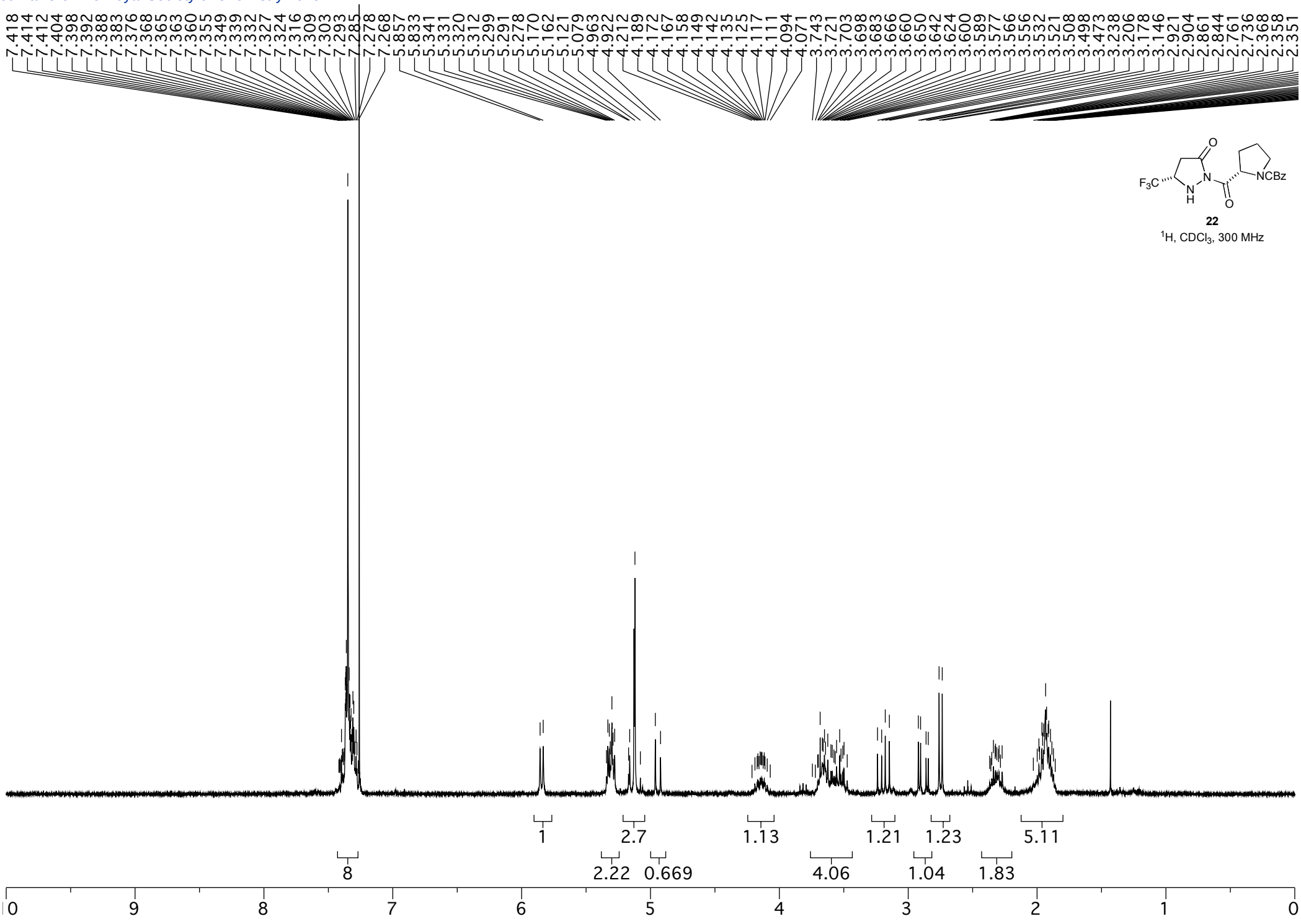


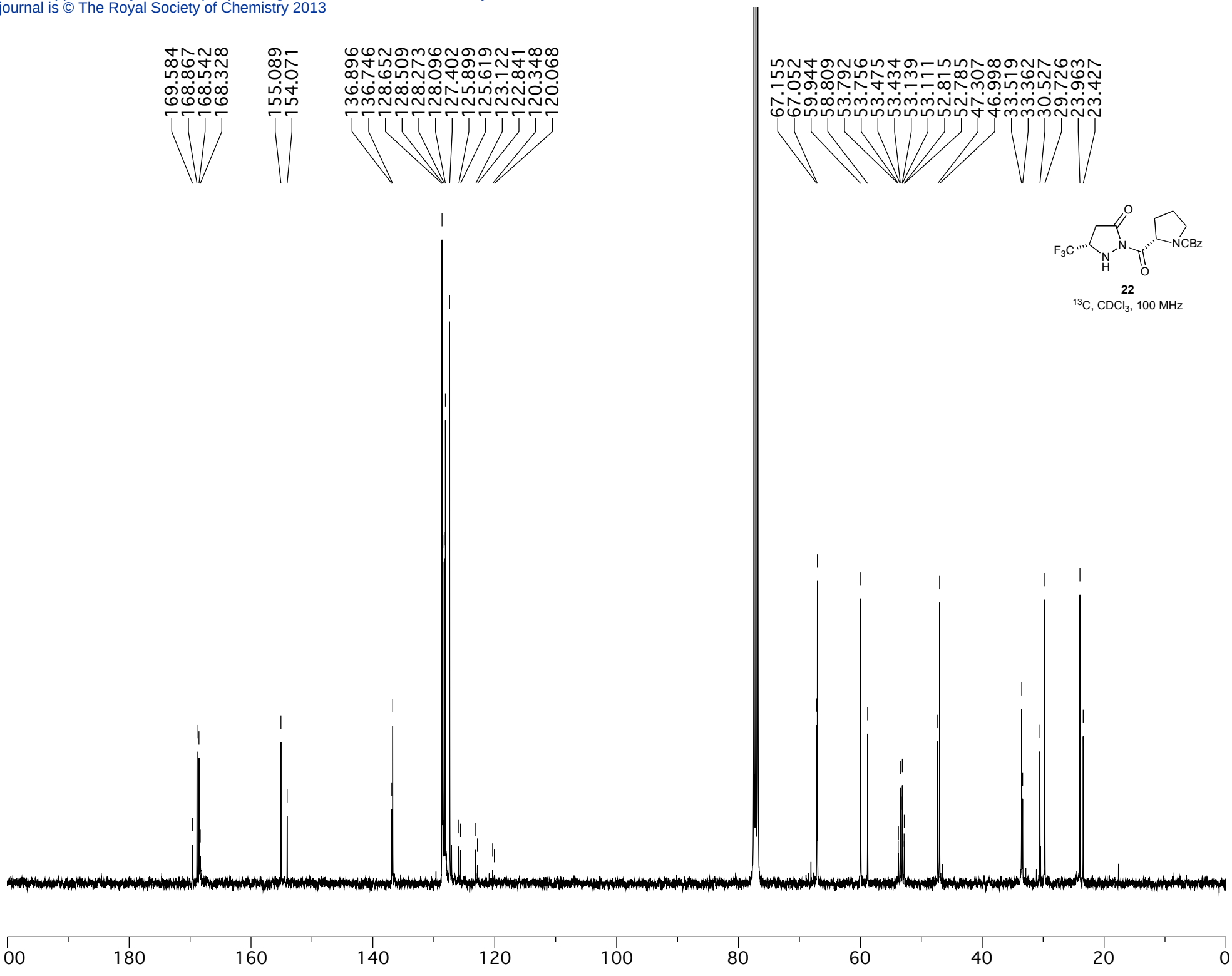


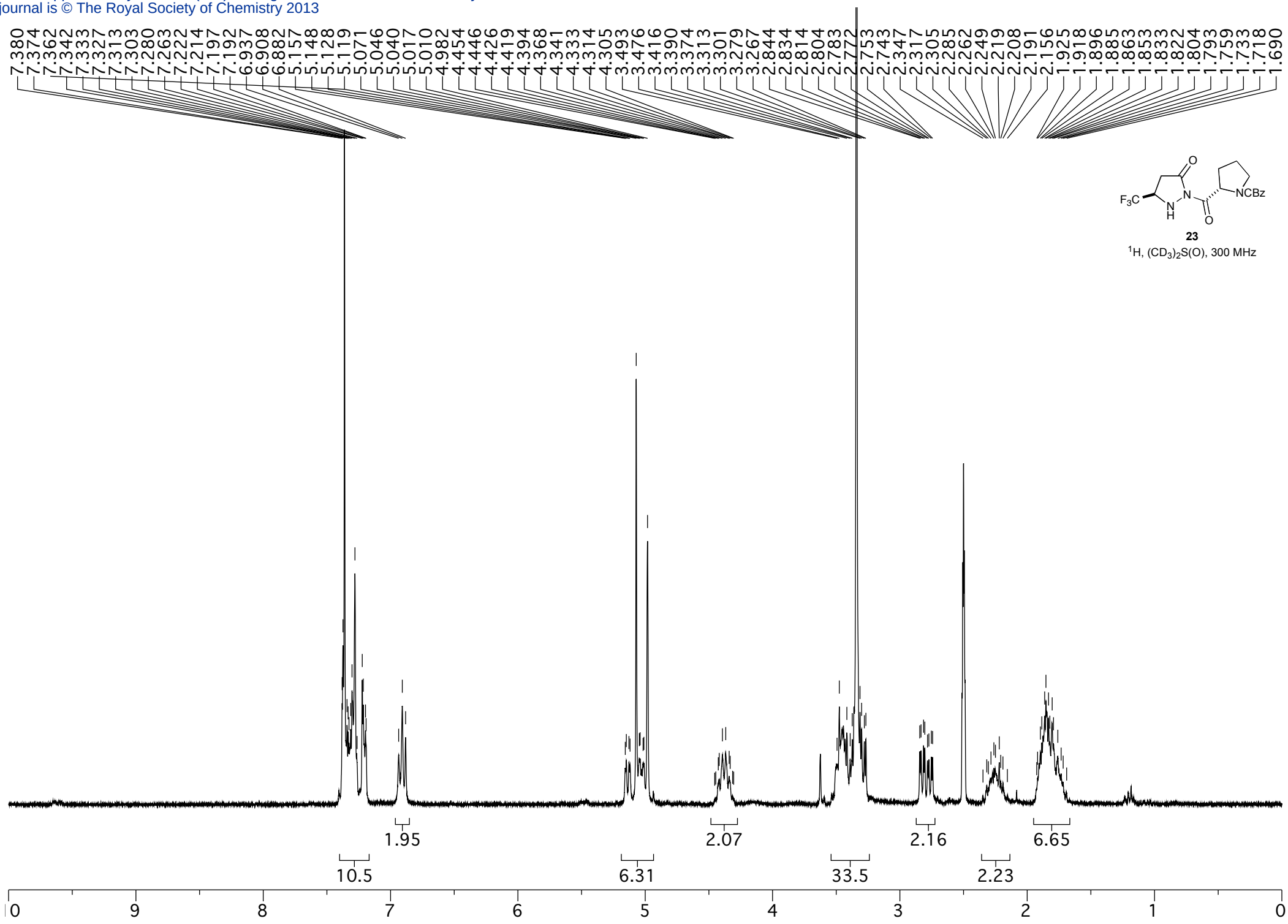


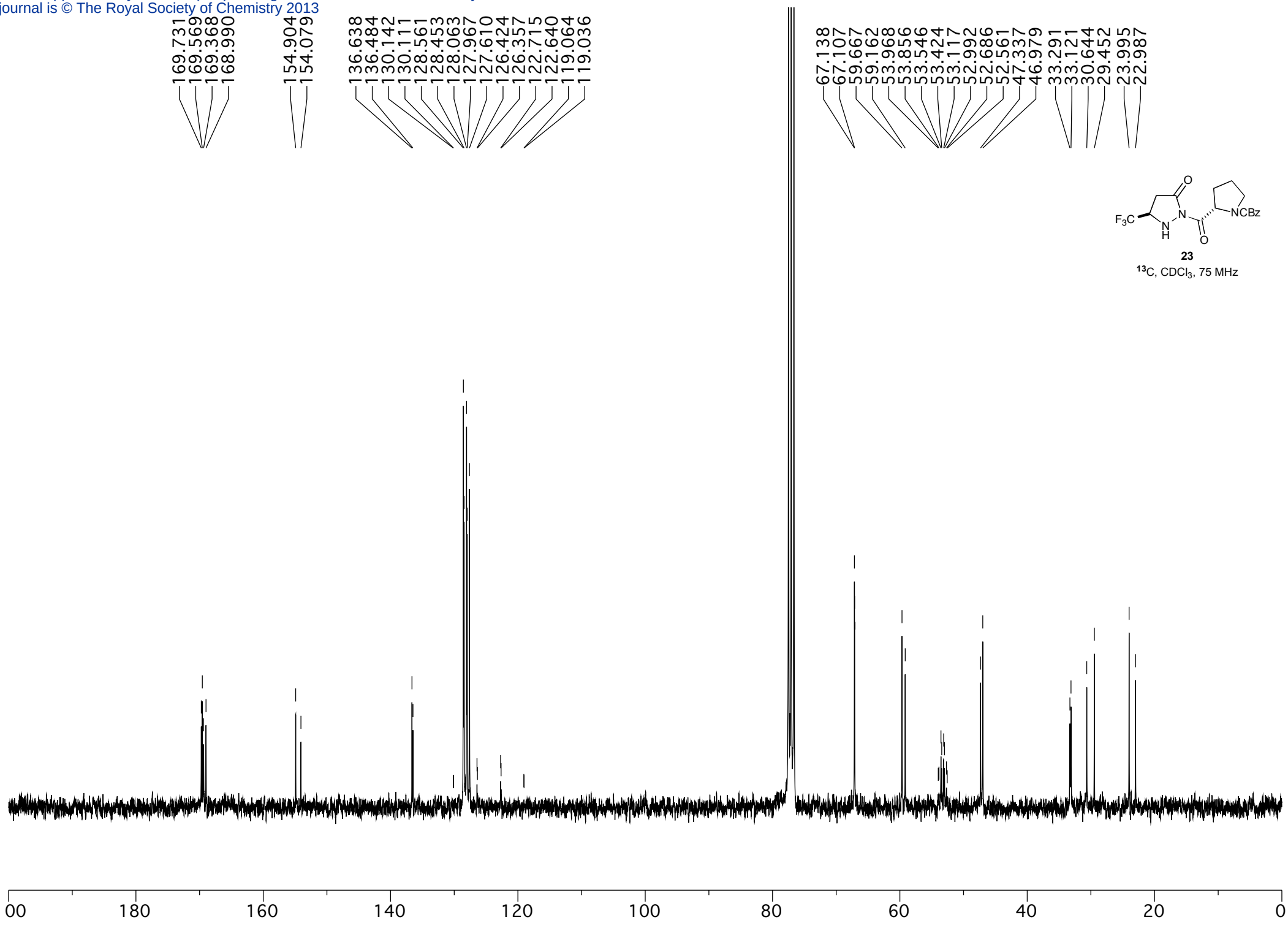
21

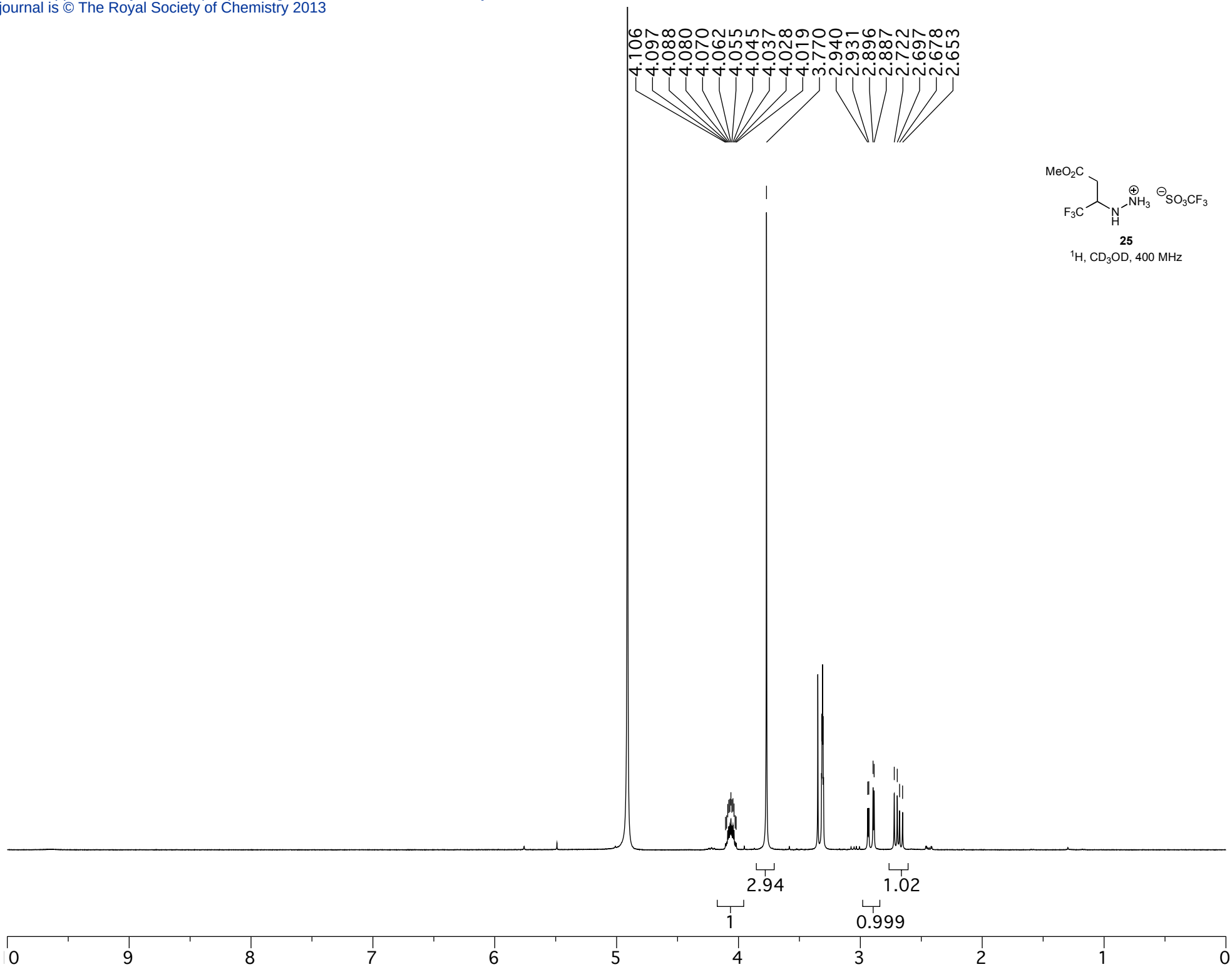
^{13}C, $CDCl_3$, 100 MHz

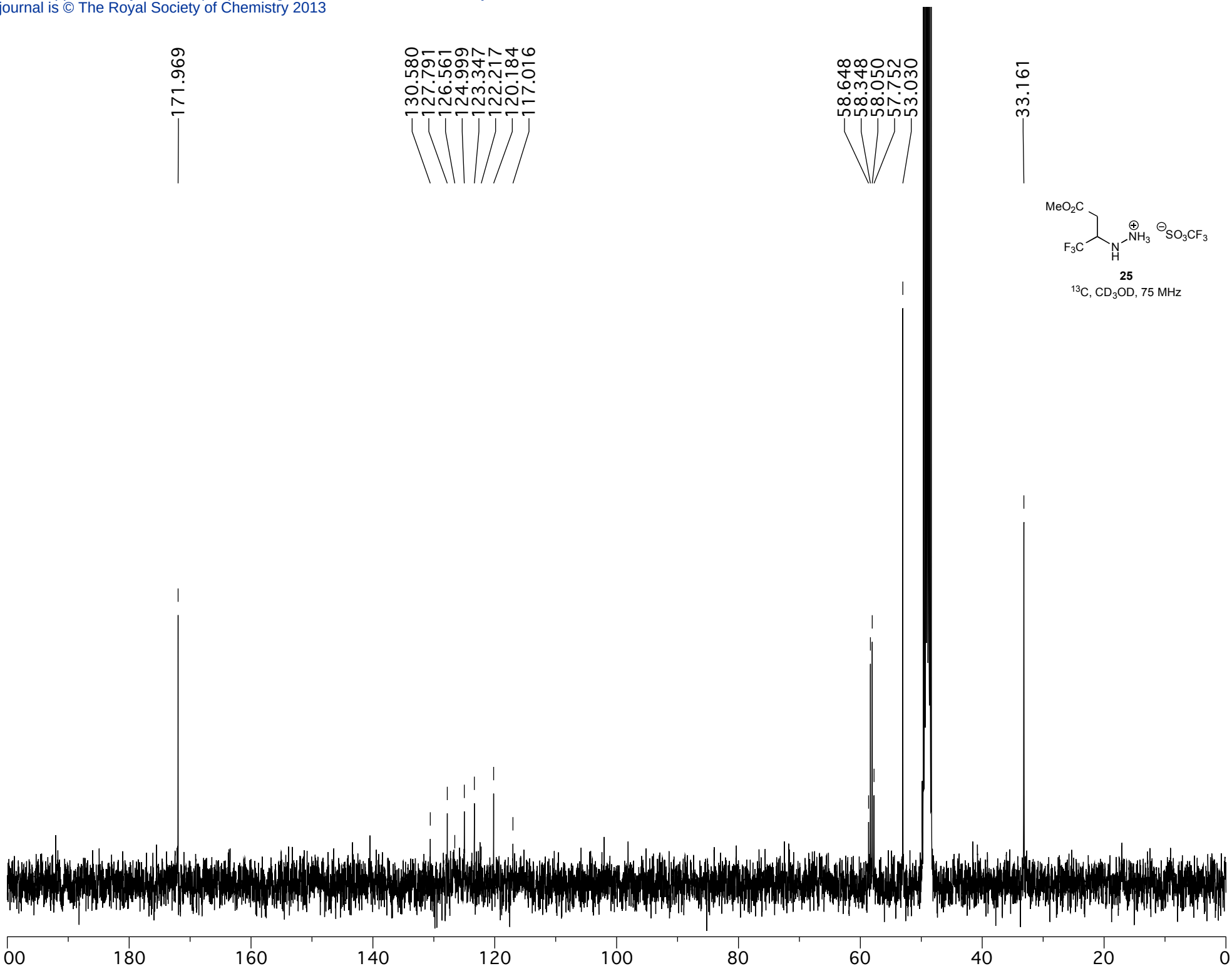


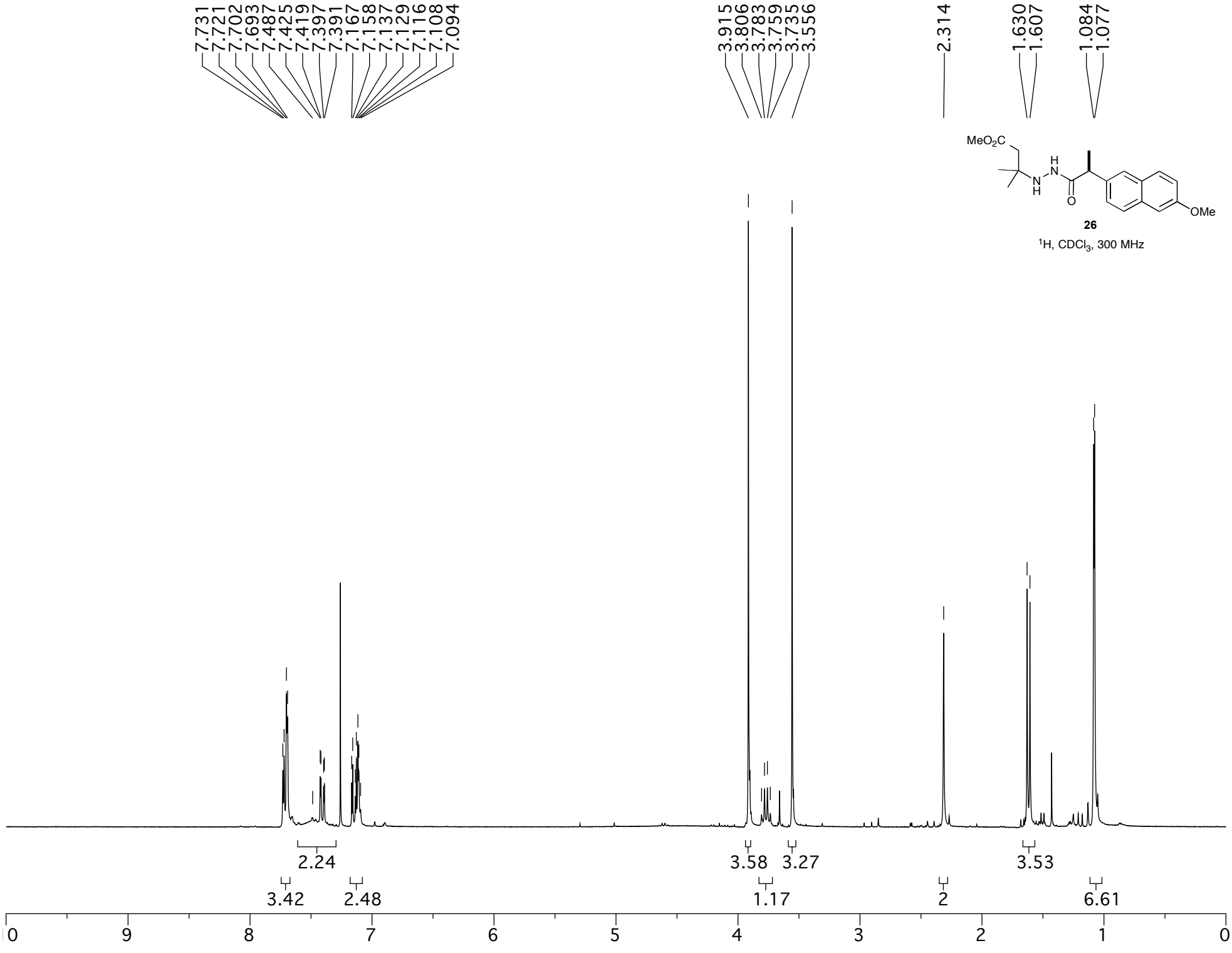


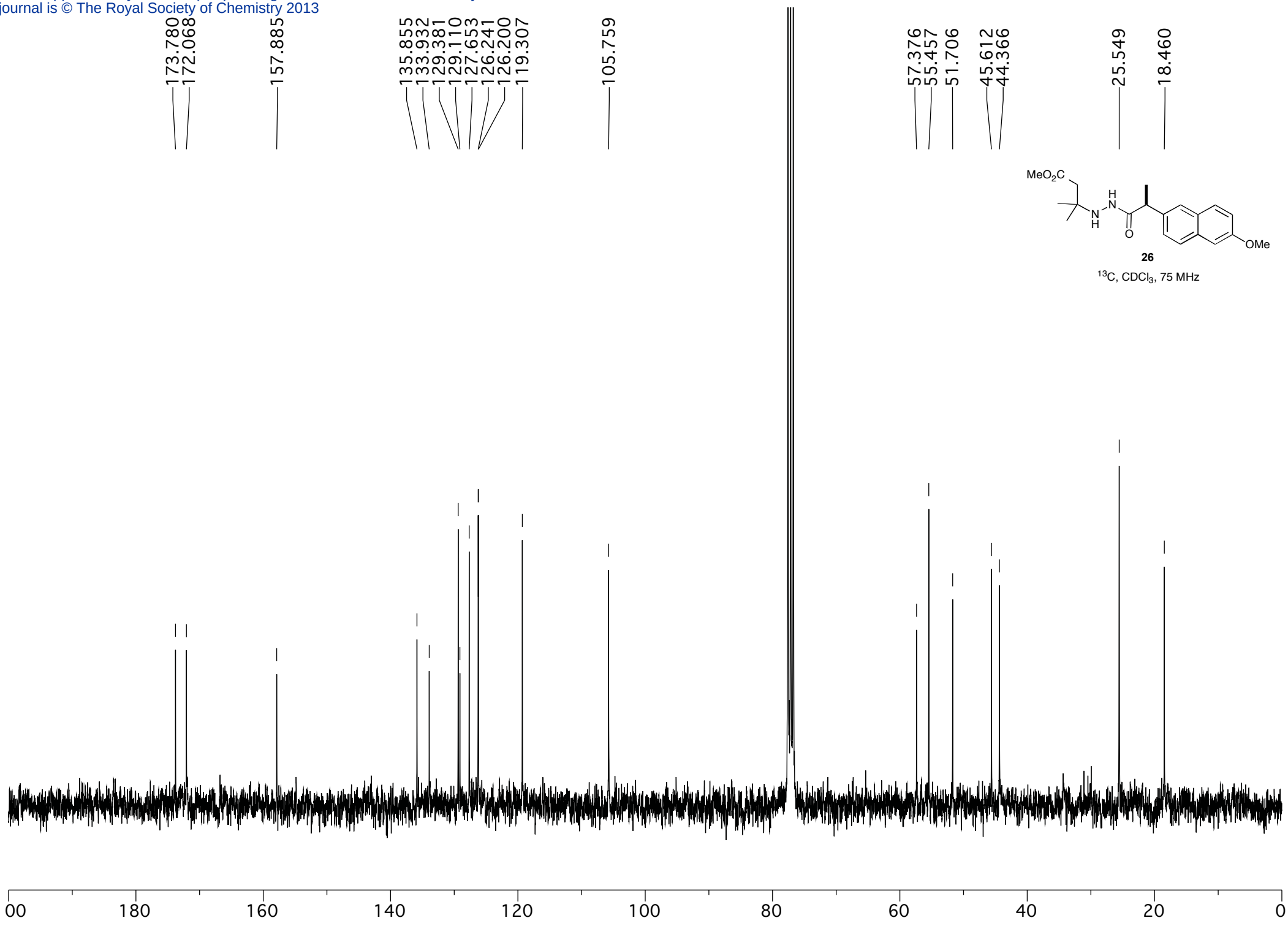


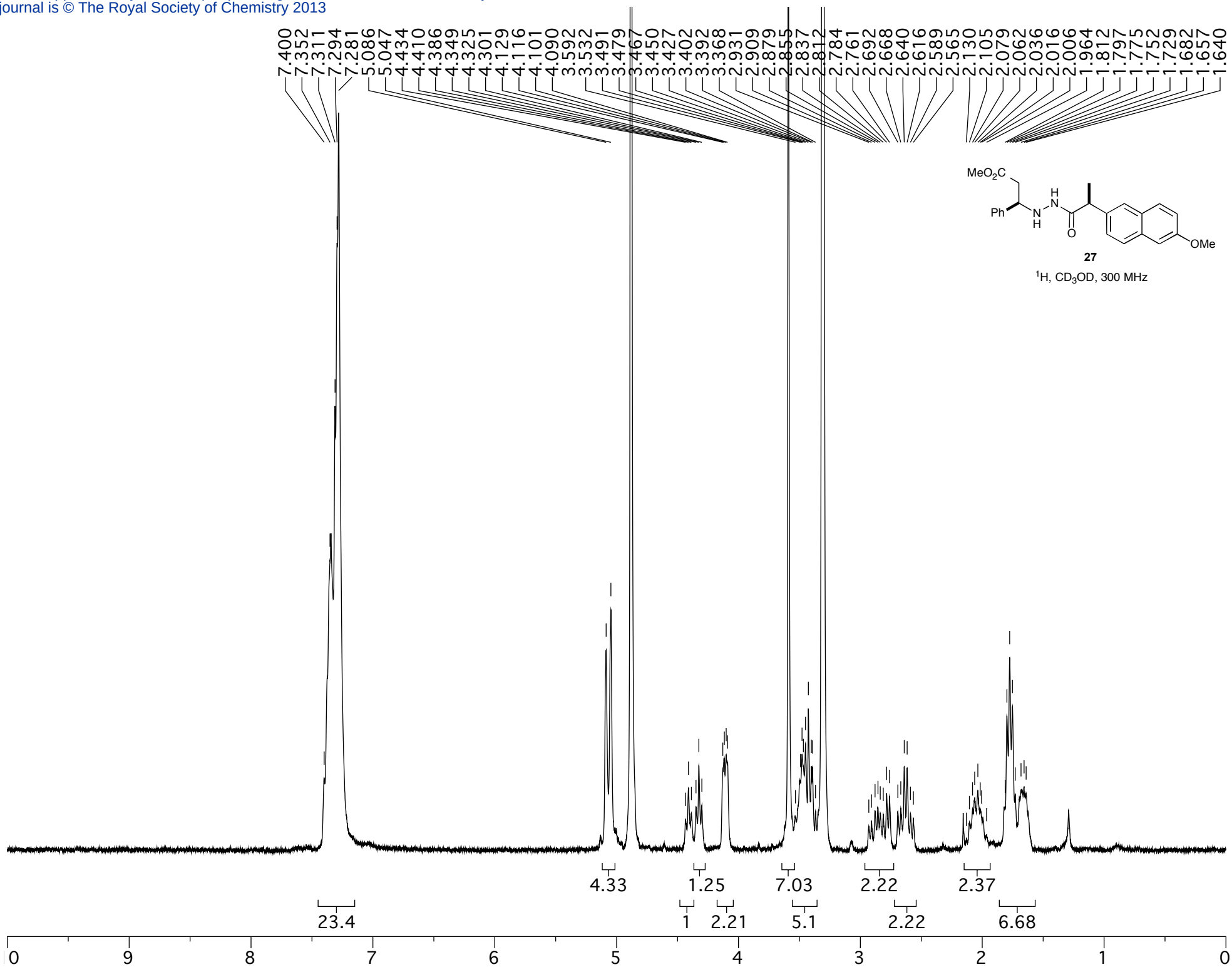


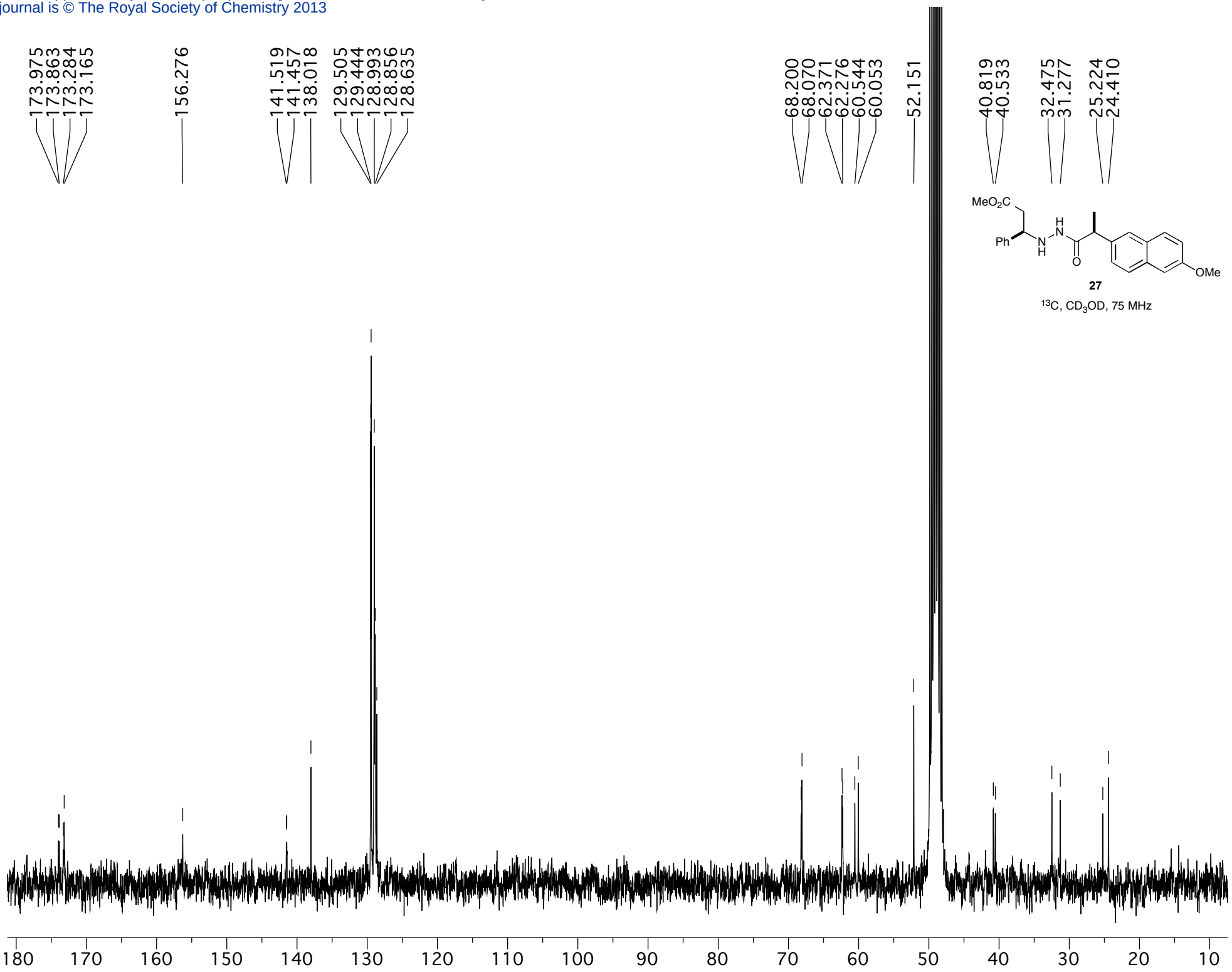


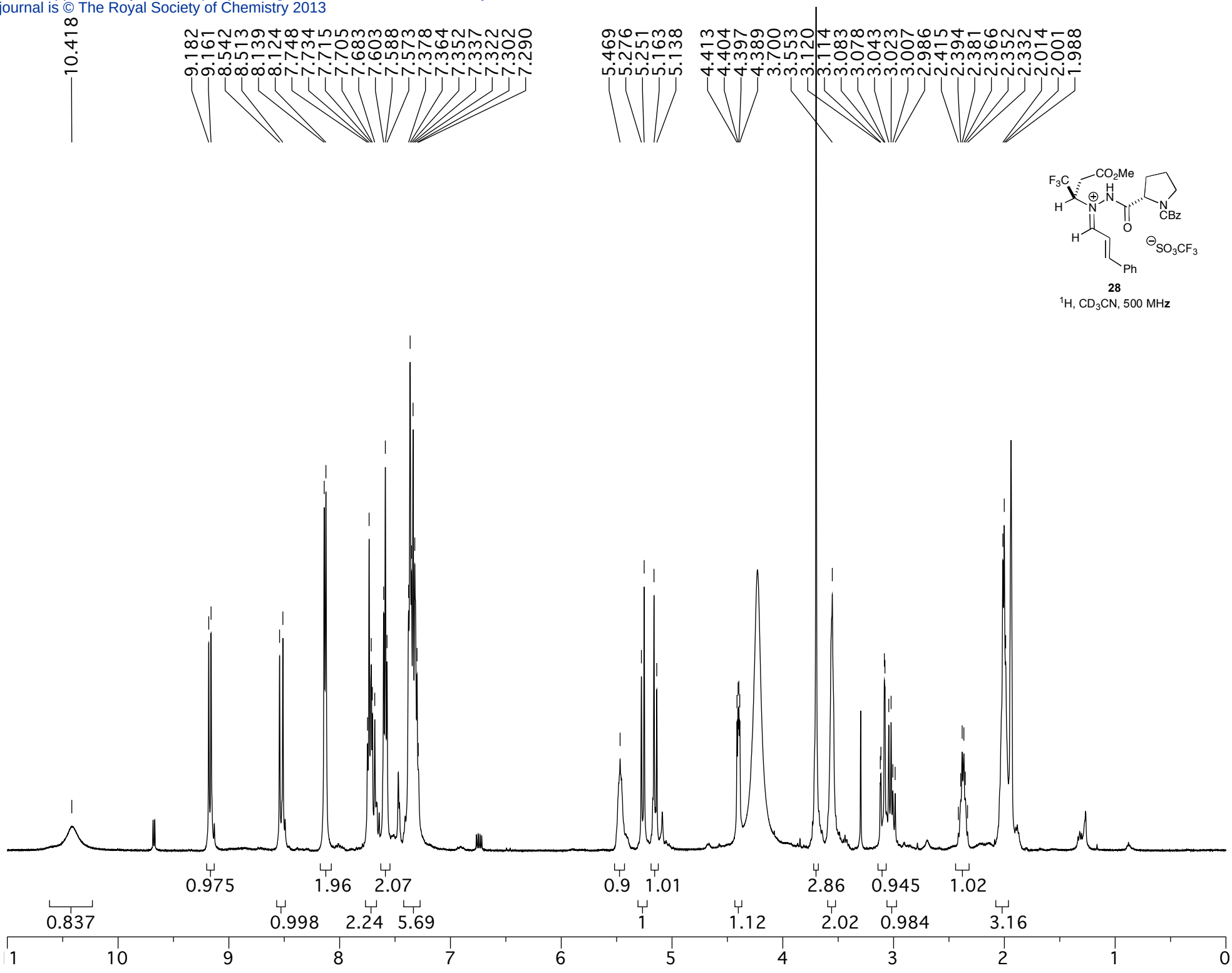


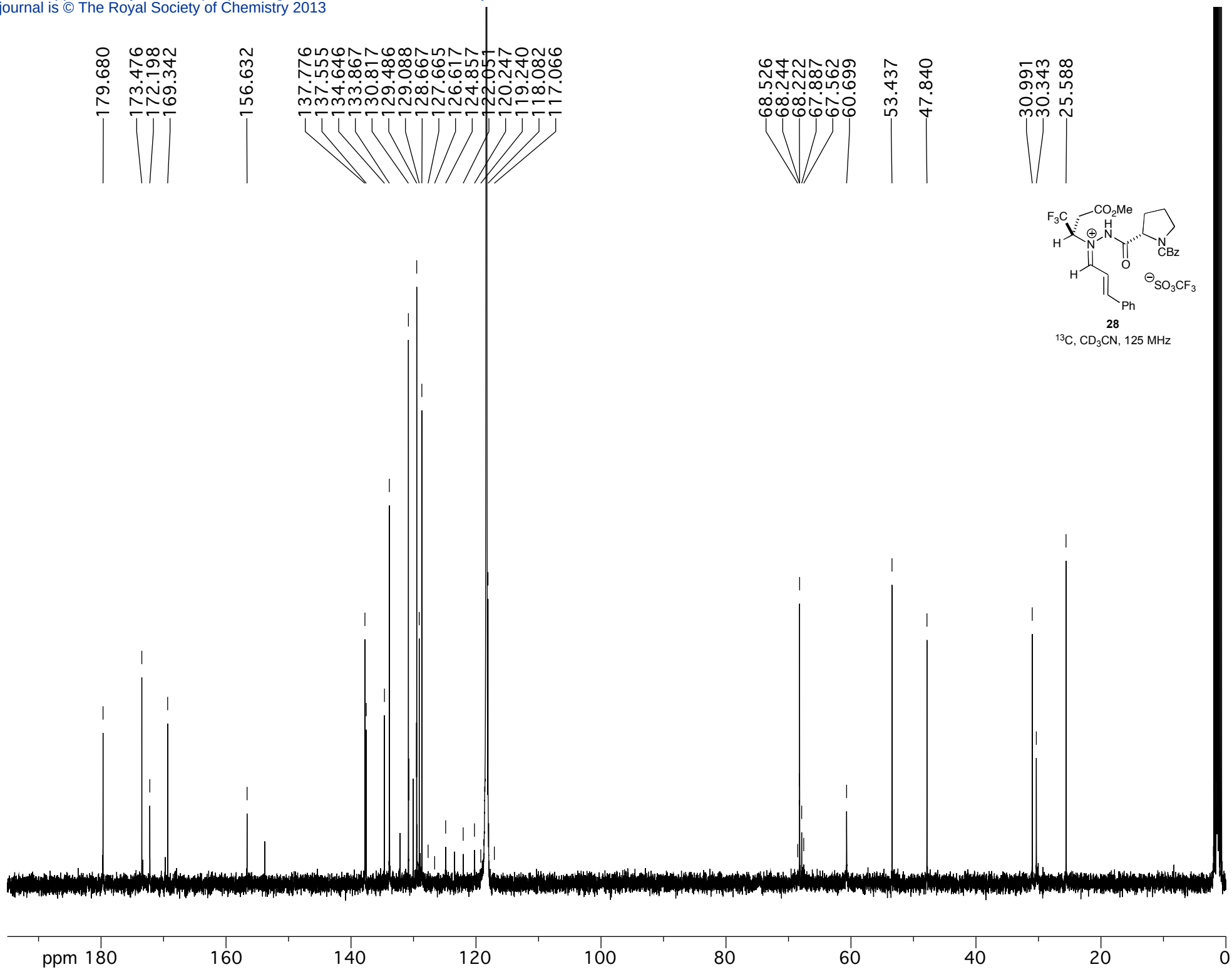






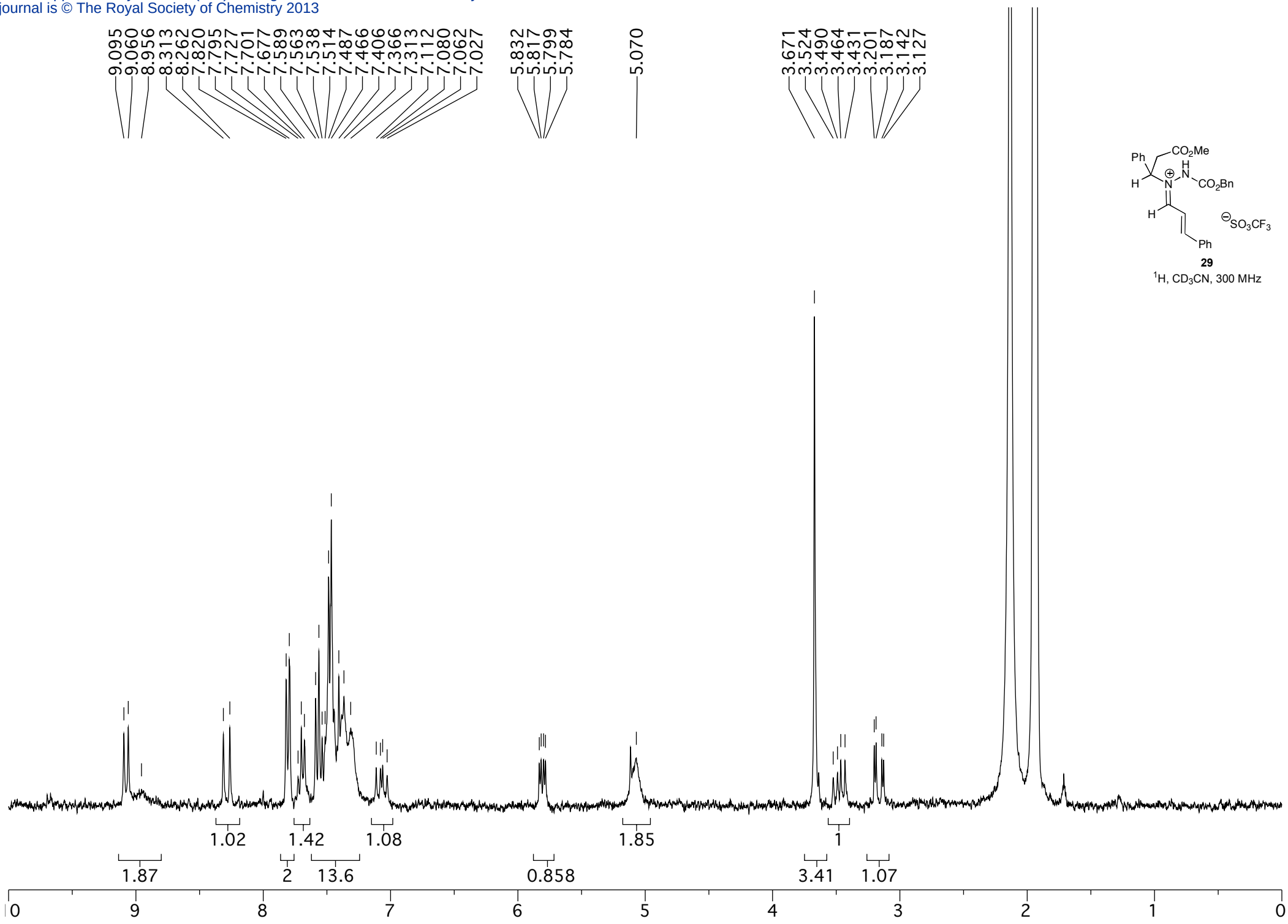


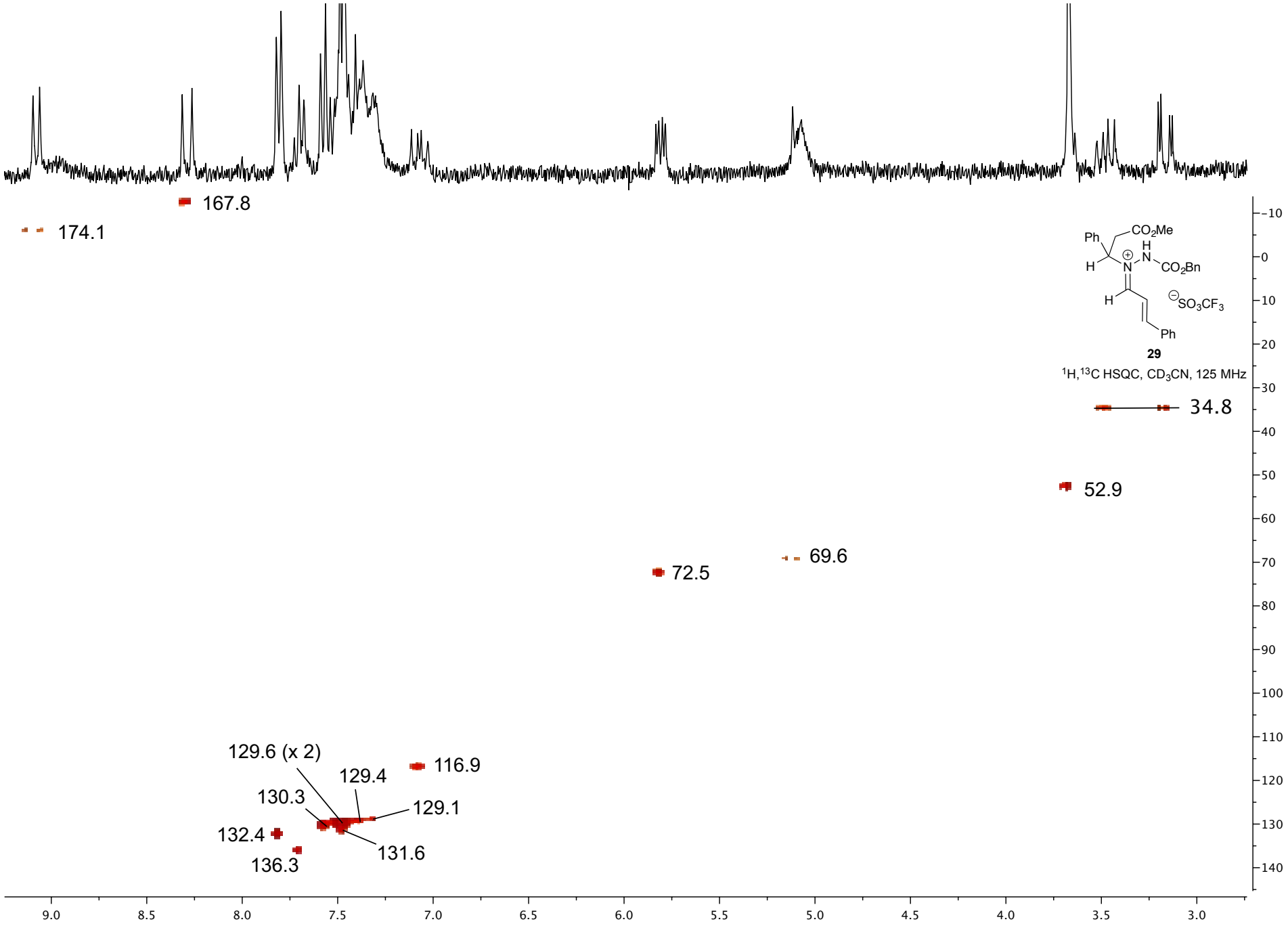


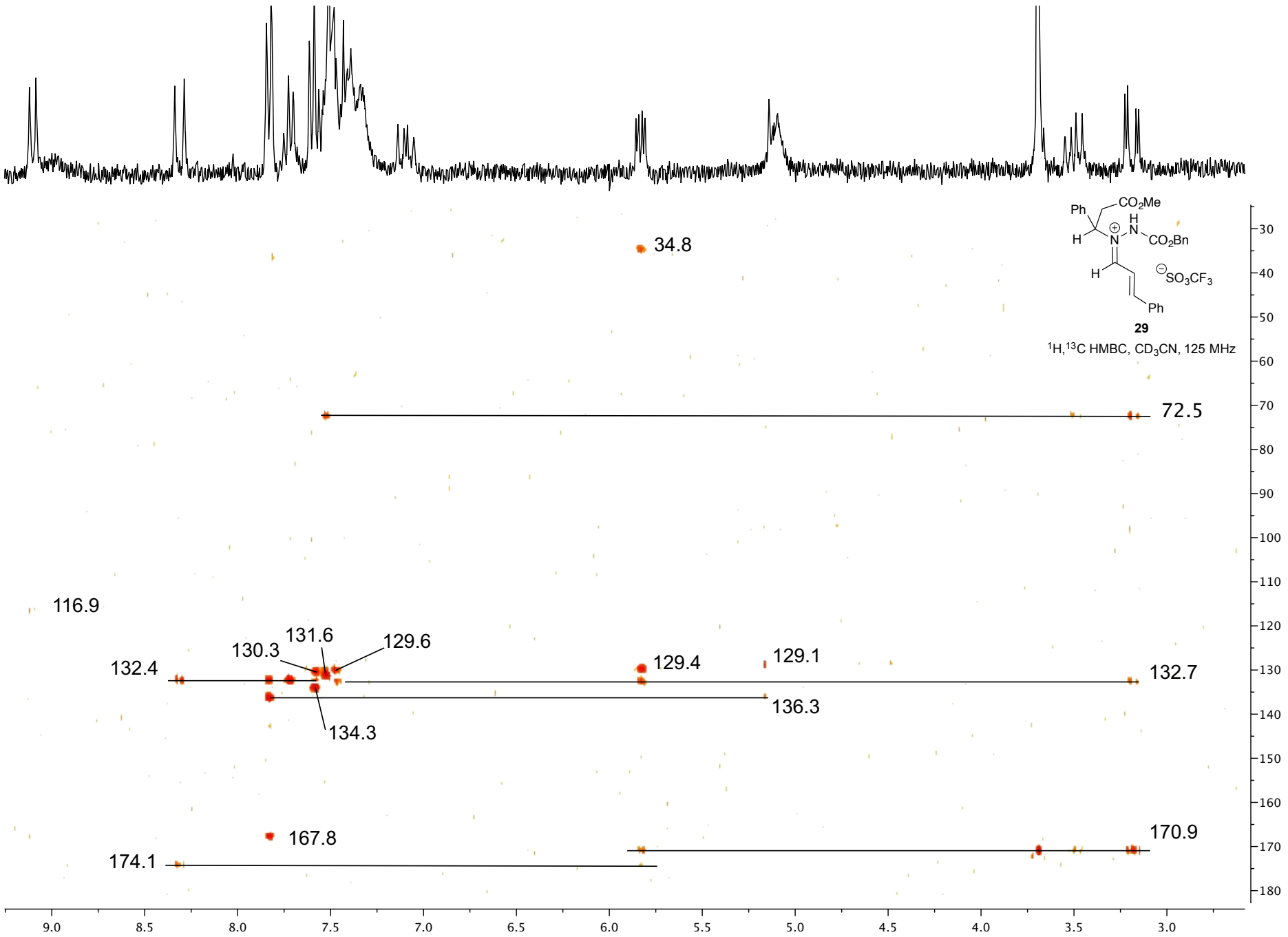


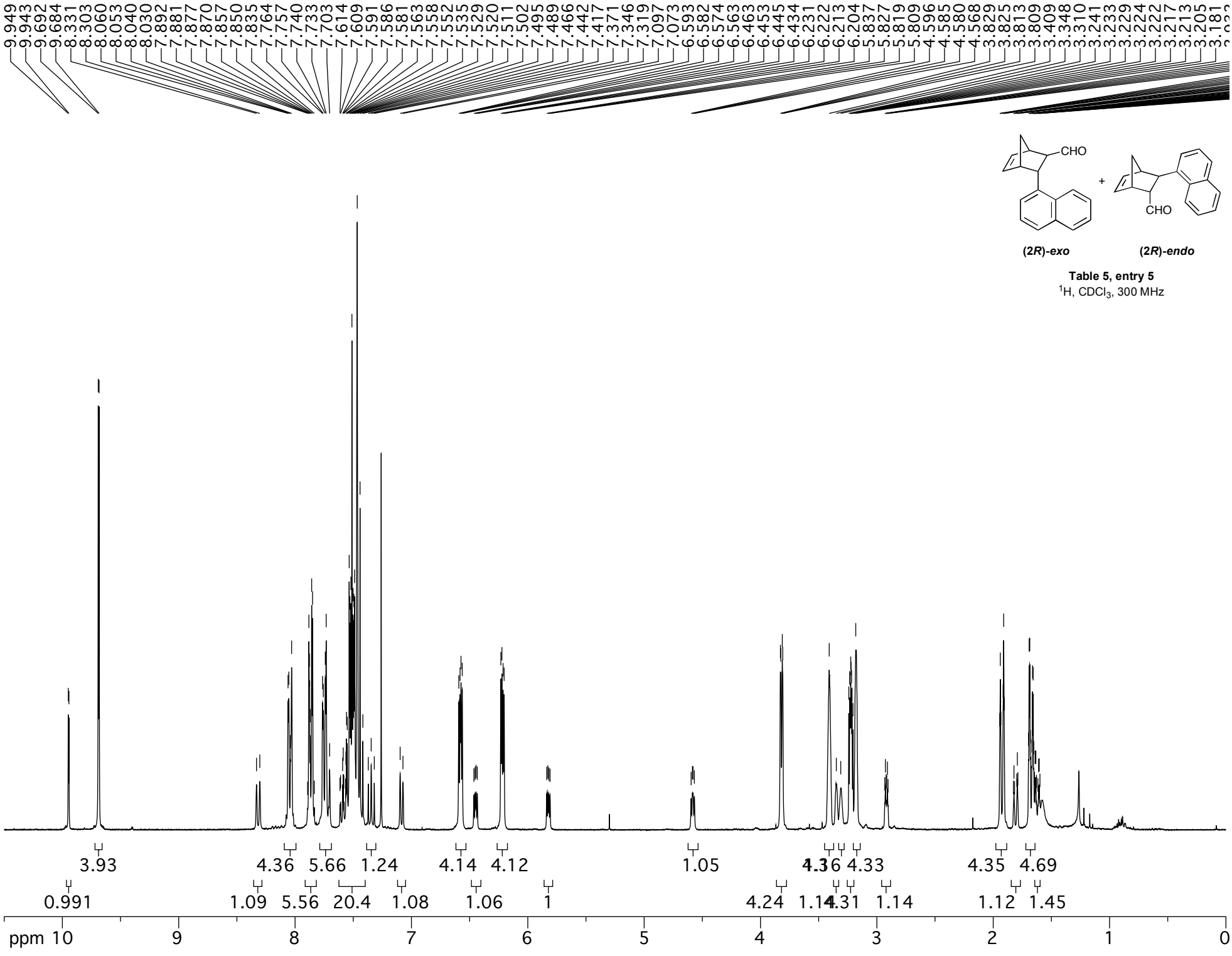
28

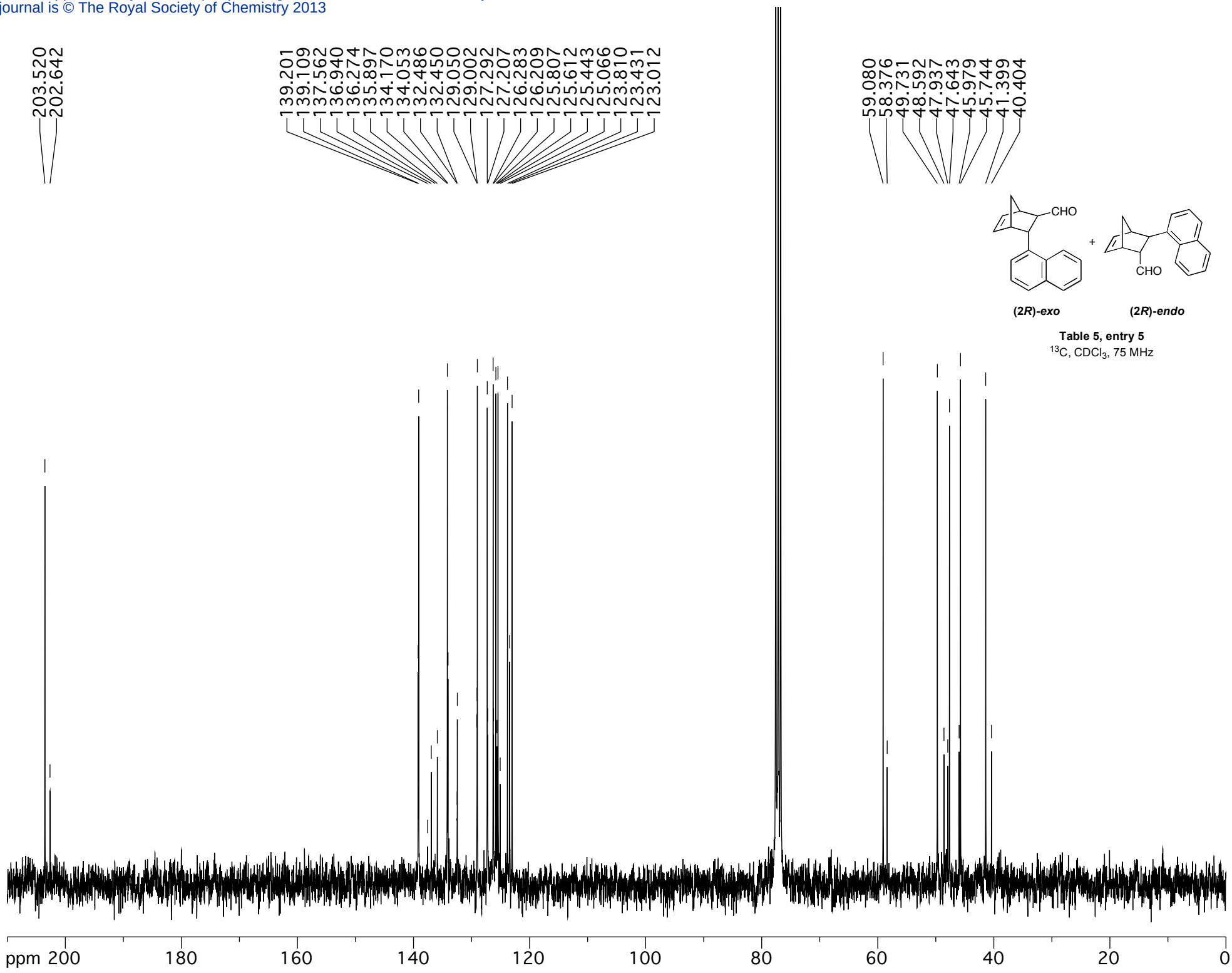
^{13}C, CD_3CN, 125 MHz

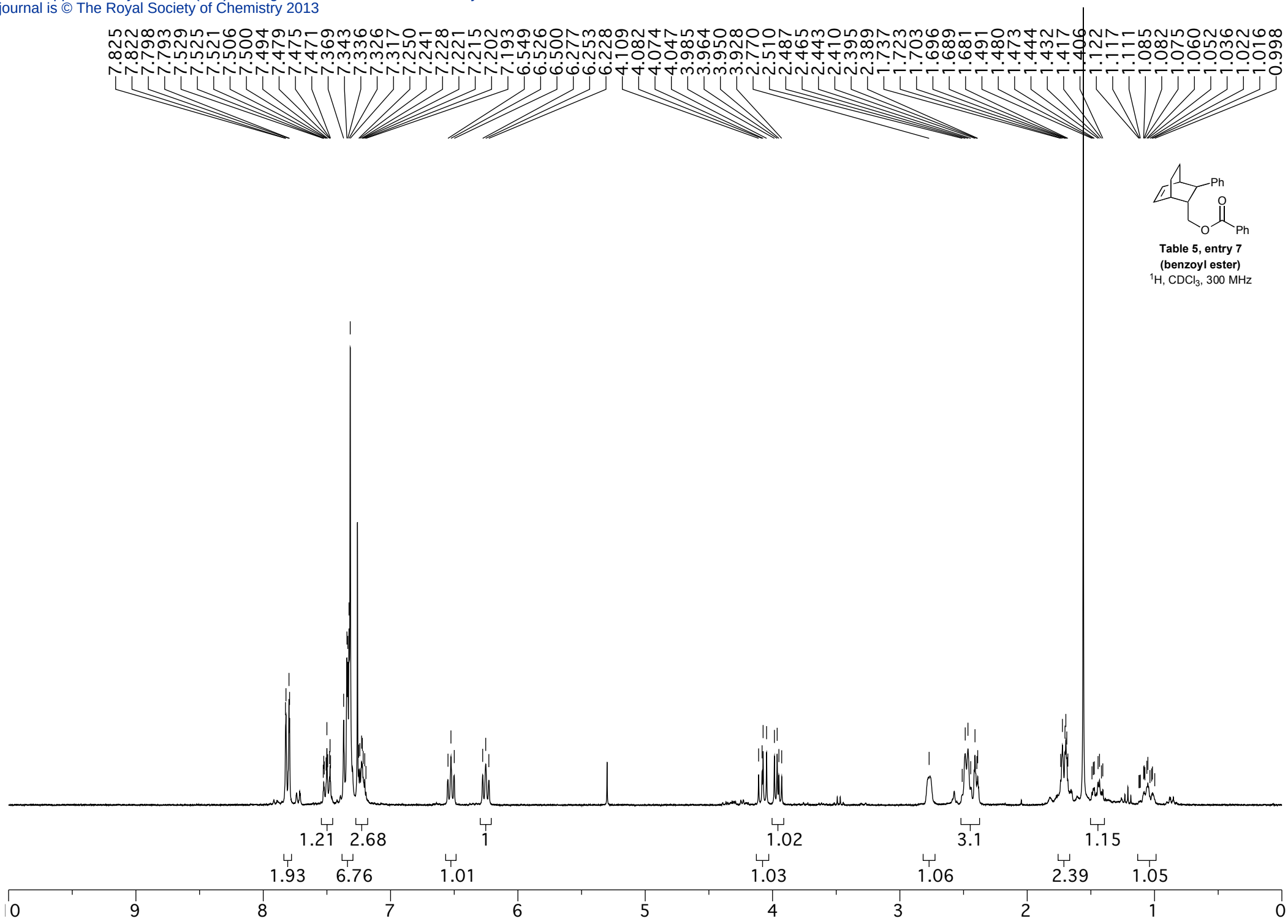












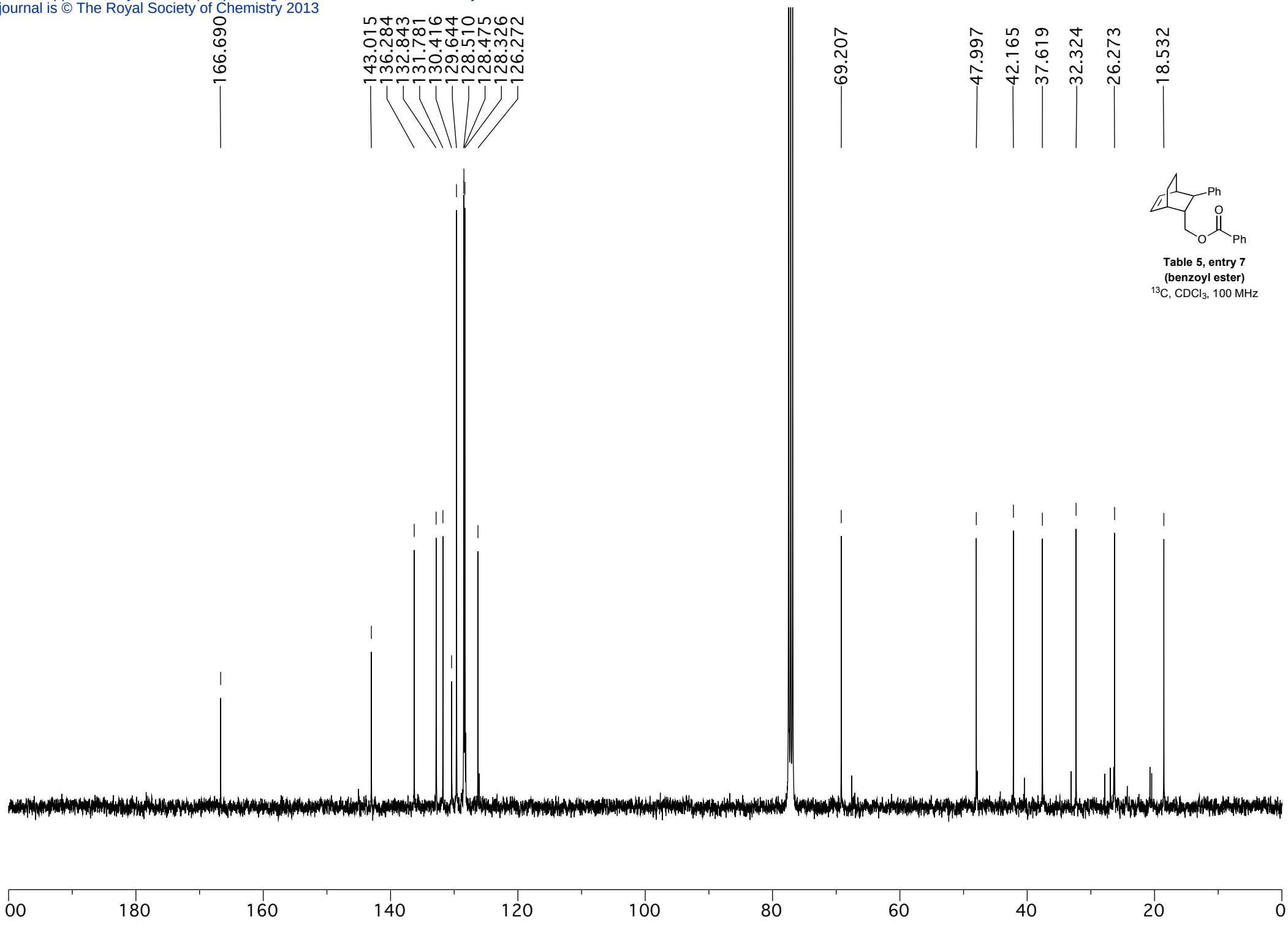


Table 5, entry 7
(benzoyl ester)
^{13}C, $CDCl_3$, 100 MHz