Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Enantioselective Synthesis of (*R*)-2-Cubylglycine Including Unprecedented Rhodium Mediated C-H Insertion of Cubane

Sevan D. Houston,[a] Benjamin A. Chalmers,[a] G. Paul Savage,[b] and Craig M. Williams[*,a]

[a]School of Chemistry and Molecular Biosciences, University of Queensland (UQ), Brisbane, 4072, Queensland, Australia (AU).

[b]CSIRO Manufacturing, Ian Wark Laboratory, Melbourne, 3168, Victoria, AU.

[*]Correspondence to: c.williams3@uq.edu.au.

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Abbreviations

°C	degrees Celsius	EtOAc	ethyl acetate
Δ	heat/reflux	EtOH	ethanol
δ	chemical shift	eq	equivalents
hυ	photoirradiation	g	gram
^{1}H	proton isotope	H_2	molecular hydrogen
^{13}C	carbon isotope	H_2SO_4	sulphuric acid
2,2-DMB	2,2-Dimethylbutane	HCl	hydrochloric acid
Boc	*t*-butyl carbonate	h	hour(s)
ca	circa (approximately)	HRMS	high resolution mass spectrometry
calcd	calculated	Hz	Hertz
$CDCl_3$	deuterated chloroform	*in situ*	on site (in the reaction vessel)
CH_2N_2	diazomethane	*in vacuo*	in a vacuum
$CHCl_3$	chloroform	*J*	coupling constant
D_2O	deuterium oxide	L	litre
dec	decomposed	M	molar
DCM	dichloromethane	MeOH	methanol
DMAP	*N*,*N*-dimethyl-4-aminopyridine	mg	milligrams
DMF	*N*,*N*-dimethylformamide	MHz	mega-Hertz
DMSO	dimethylsulfoxide	min	minute(s)
DMSO-d_6	deuterated dimethyl sulfoxide	mL	millilitre(s)
ESI	electrospray ionisation	mmol	millimole(s)
Et_2O	diethyl ether	mol	moles
et al	et alii / et aliae (and others)	m.p	melting point

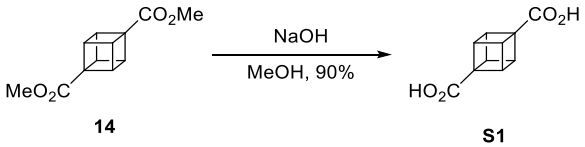
m/z	mass to charge ratio	*t*	tertiary
NaOH	sodium hydroxide	TEA	triethylamine
NMO	*N*-methylmorpholine-*N*-oxide	THF	tetrahydrofuran
NMR	nuclear magnetic resonance	TLC	thin layer chromatography
PMA	phosphomolybdic acid	TMSCN	trimethylsilyl cyanide
ppm	parts per million	TPAP	tetrapropylammonium perruthenate
RBF	round bottom flask	v/v	volume per volume
R_f	retention factor	w/w	weight per weight
RT	retention time	µL	microlitre
rt	room temperature	UV	ultraviolet

General Remarks

NMR spectra were recorded under standard conditions (unless stated otherwise) using Bruker AV 500, 400 and 300 MHz or Bruker AS 500 MHz spectrometers and were referenced with residual monoprotic solvent peaks (e.g. $CDCl_3$, C_6D_6 etc.).[1] Samples run in D_2O were referenced using a dioxane standard (^1H = δ 3.75 ppm, ^{13}C = 67.2 δ ppm). Coupling constants (*J*) are quoted to the nearest 0.1 Hz. The following abbreviations are used to report multiplicities: s = singlet, d = doublet, t = triplet, m = multiplet, quin = quintet, sext = sextet, sep = septet, br. = broad. High resolution ESI mass spectra were recorded using a Bruker MicroTOF-Q (quadrupole-Time of Flight) with a Bruker ESI source. Melting points were determined using a Digimelt MPA 160 melting point apparatus and are reported uncorrected. Flash column chromatography was run using Merck silica gel 60 (230–400 mesh). Fractions were initially visualised using UV irradiation and subsequently by heating TLC plates exposed to either ceric ammonium molybdate (Goofy's stain), 10% ethanolic phosphomolybdic acid (PMA) or 10 % aqueous potassium permanganate. TLC was performed with Merck precoated silica gel plates (silica gel 60 F_{254}) 0.2 mm). Argon was dried by passing through a drying tube containing 4Å molecular sieves and Drierite™. Glassware was oven dried (160 °C) before use with anhydrous solvents and reagents. THF and diethyl ether were freshly distilled to dryness over elemental sodium/benzophenone under an argon atmosphere. DCM was freshly distilled to dryness over calcium hydride under an argon atmosphere. 2,2-DMB was distilled to dryness over calcium hydride under an argon atmosphere. Unless stated otherwise commercially available chemicals were used without further purification. 2-Mercaptopyridine *N*-oxide sodium was concentrated to dryness then washed with ethyl acetate. TMSCN was initially used without further purification, then when required distilled to dryness following known procedures.[2] Diazomethane was freshly prepared from Diazald® with a diazomethane distillation kit. Preparative Chiral HPLC was performed at the Analytical and Preparative Enantioselective Chromatography facility at the School of Chemistry and Molecular Biosciences, University of Queensland.

Experimental Procedures

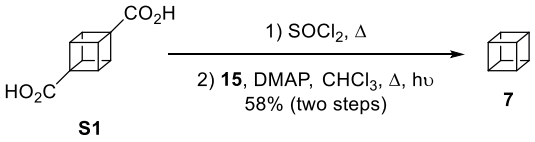
1,4-Cubanedicarboxylic acid (**S1**)



14 **S1**

The entirety of this sequence should be performed behind a blast shield. A PTFE coated spatula should be used. Following the procedure of Priefer *et al*:[3] dimethyl 1,4-cubanedicarboxylate[4] (**14**) (2.013 g, 9.14 mmol) was suspended in methanol (50 mL). Sodium hydroxide (999 mg, 24.98 mmol) was dissolved in methanol (50 mL) and added over 5 min. The mixture was left to stir for 16 h then the methanol was removed *in vauo*. The resulting white solid was dissolved in water (50 mL), washed with DCM (3 x 50 mL) then acidified to pH 1 with 10 M HCl. The resulting white precipitate (1.580 g, 90%) was collected by filtration. ^{1}H-NMR (300 MHz, MeOD): δ (ppm) 4.19 (s, 6H).

Cubane (**7**)

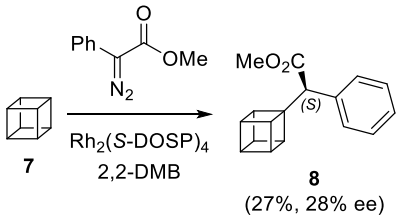


S1 **7**

Until workup the entirety of this sequence should be performed behind a blast shield. A PTFE coated spatula should be used. 1,4-Cubanedicarboxylic acid (**S1**) (1.000 g, 5.20 mmol) was dissolved in thionyl chloride (5 mL) and heated to reflux for 3 h under a nitrogen atmosphere. The thionyl chloride was removed *in vacuo* and the residual material was exposed to high vacuum for 1 h. Separately, freshly ground 2-mercaptopyridine *N*-oxide sodium salt (**15**) (3.100 g, 20.80 mmol) and DMAP (64 mg, 0.52 mmol) were suspended in anhydrous chloroform (60 mL) and heated to reflux whilst under irradiation from a 500-W tungsten lamp under an argon atmosphere. [Note: Chloroform (1000 mL) was washed with water (3 x 1000 mL) and dried over molecular sieves prior to use in order to remove the ethanol stabiliser.] The newly formed acid chloride was suspended in anhydrous chloroform (60 mL) and added over 1 h to the refluxing mixture under an argon atmosphere. After reflux (2 h) the chloroform was removed by distillation at atmospheric pressure. The

residual material was suspended in petroleum ether 30-40 ℃ (50 mL), washed with 1M HCl (50 mL) and water (2 x 50 mL) then dried over sodium sulphate. Concentration by distillation at atmospheric pressure and purification by column chromatography (petroleum ether 30-40 ℃) gave the title compound (316 mg, 58%) as a white solid. At high concentrations cubane was visible on TLC using PMA stain. Alternatively, the fast running fractions were pooled without visualisation. Data are consistent with those reported previously.[5] ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 4.03 (s, 8H).

Methyl (*S*)-2-(Cuban-1-yl)-2-phenylacetate (**8**)



Adapted from the procedure of Davies *et al*:[6] methyl phenyldiazoacetate[6] (28 mg, 0.16 mmol) was suspended in 2,2-DMB (1.5 mL) and degassed with argon for 10 min. Separately, cubane (**7**) (50 mg, 0.48 mmol) and Rh_2(*S*-DOSP)$_4$ (3 mg, 0.0016 mmol) were suspended in 2,2-DMB (1.5 mL) and degassed with argon for 10 min. The methyl phenyldiazoacetate solution was added over 1.5 h under an argon atmosphere then left to stir for a further 20 min. Removal of solvent under a stream of nitrogen then purification by column chromatography (5% ethyl acetate/petroleum ether v/v) gave the title compound (10 mg, 27%) as a clear oil. ^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) 7.34–7.31 (m, 2H), 7.29–7.26 (m, 1H), 7.25–7.23 (m, 2H), 4.00–3.96 (m, 1H), 3.93–3.91 (m, 3H), 3.87–3.84 (m, 4H), 3.69 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) 172.7, 136.2, 128.6, 128.3, 127.2, 58.7, 53.9, 51.9, 48.4, 48.4, 44.3; HRMS-ESI calcd for $C_{17}H_{16}O_2Na^+$ ([M+Na]$^+$): 275.1043; found: 275.1048.

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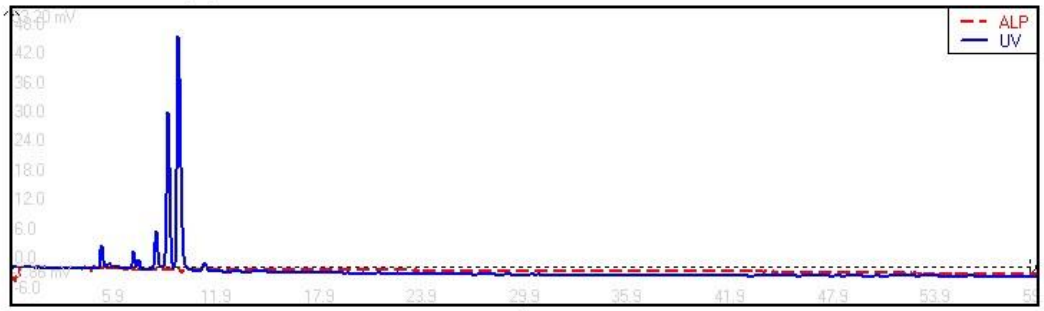

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Selector 2 :2
Inj Vol µL :20
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Equilibrate
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Eq.2 :13.28 min, 0.5 ml/min
Run Time :40.00 min
Meth. Vol mL :30
Repeat :1
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Vial # :1
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Eluent and Gradient

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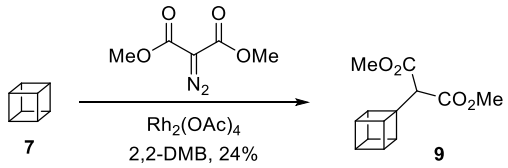
4.00	95.0	5.0
34.00	60.0	40.0
36.00	60.0	40.0
38.00	95.0	5.0
40.00	95.0	5.0

P E A K L I S T R E P O R T

No	*Name*	*Type*	*Start (min)*	*End (min)*	*RT (min)*	*Height (mV)*	*Area (mVs)*	*% Area (%)*
1	PP	(+)	8.87	9.51	9.18	32.150	394.967	35.56
2	PP	(+)	9.54	10.40	9.77	48.485	715.588	64.44

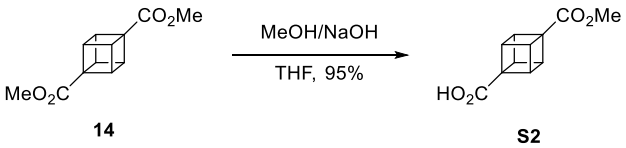
Total Peak Area :1110.554 mVs

Dimethyl 2-(cuban-1-yl)malonate (**9**)



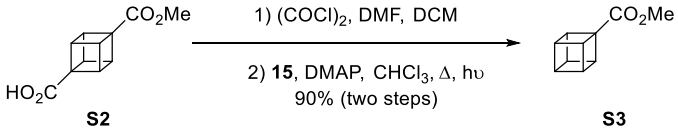
Adapted from the procedure of Davies *et al*:[6] dimethyl 2-diazophenylacetate[7] (25 mg, 0.16 mmol) was suspended in 2,2-DMB (1 mL) and degassed with argon for 10 min. Separately, cubane (**7**) (50 mg, 0.48 mmol) and $Rh_2(OAc)_4$ (4 mg, 0.008 mmol) were suspended in 2,2-DMB (2 mL) and degassed with argon for 10 min. The dimethyl 2-diazophenylacetate solution was added over 3 h under an argon atmosphere then left to stir for a further 2 h. Removal of solvent under a stream of nitrogen then purification by column chromatography (20% ethyl acetate/petroleum ether v/v) gave the title compound (9 mg, 24%) as a clear oil. ^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) 4.03–3.99 (m, 1H), 3.96–3.92 (m, 6H), 3.74 (s, 6H), 3.70 (s, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) 168.3, 55.3, 54.5, 52.4, 48.8, 48.3, 44.7; HRMS-ESI calcd for $C_{13}H_{14}O_4Na^+$ ([M+Na]$^+$): 257.0784; found: 257.0777.

4-(Methoxycarbonyl)cubane-1-carboxylic acid (**S2**)



Following the procedure of Eaton *et al*:[8] dimethyl cubane-1,4-dicarboxylate (**14**) (6.079 g, 27.60 mmol) was suspended in THF (250 mL). A solution of sodium hydroxide (1.220 g, 30.50 mmol) in methanol (14 mL) was added dropwise and the solution was left to stir for 16 h. The THF was removed *in vacuo* and the residual solid was suspended in water (200 mL), and washed with DCM (3 x 100 mL). The aqueous phase was acidified to pH 2 with hydrochloric acid (10 M) and washed again with DCM (3 x 100 mL). The combined organic phases were dried over magnesium sulfate and concentrated to give the title compound (5.385 g, 95%) as a white solid. ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 4.28 (s, 6H), 3.73 (s, 3H).

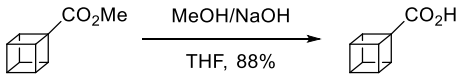
Methyl cubane-1-carboxylate (**S3**)



S2 **S3**

Following the procedure of Ko *et al*:[9] to a solution of 4-methoxycarbonylcubane-1-carboxylic acid (**S2**) (9.654 g, 46.82 mmol) in anhydrous DCM (500 mL) was added oxalyl chloride (4.81 mL, 56.08 mmol) and anhydrous DMF (0.3 mL) under an argon atmosphere. After 1 h, the mixture was concentrated *in vacuo* and further dried under high vacuum (1 h). Separately, freshly ground 2-mercaptopyridine *N*-oxide sodium salt (**15**) (10.639 g, 71.33 mmol) and DMAP (59 mg, 0.48 mmol) were suspended in anhydrous chloroform (500 mL) and heated to reflux whilst under irradiation from a 500-W tungsten lamp under an argon atmosphere. [Note: Chloroform (1000 mL) was washed with water (3 x 1000 mL) and dried over molecular sieves prior to use in order to remove the ethanol stabiliser.] The newly formed acid chloride was suspended in anhydrous chloroform (500 mL) and added slowly over 1 h to the refluxing mixture under an argon atmosphere. After reflux (4 h) the suspension was washed with water (3 x 500 mL), dried over magnesium sulfate and concentrated *in vacuo* to give a brown oil. Purification by column chromatography (10% ethyl acetate/petroleum ether v/v) gave the title compound (6.820 g, 90%) as a white sweet smelling solid. ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 4.26–4.24 (m, 3H), 4.04–3.99 (m, 4H), 3.70 (s, 3H).

Cubane-1-carboxylic acid (**S4**)

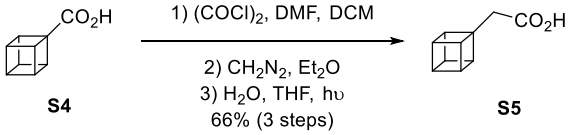


S3 **S4**

Methyl cubane-1-carboxylate (**S3**) (6.600 g, 40.69 mmol) was suspended in THF (200 mL). A solution of sodium hydroxide (2.004 g, 50.10 mmol) in methanol (12 mL) was added dropwise and the solution was left to stir for 16 h. The THF was removed *in vacuo* and the residual solid was suspended in water (200 mL) and washed with DCM (3 x 100 mL). The aqueous phase was acidified to pH 2 with hydrochloric acid (10 M) and washed again with DCM (3 x 100 mL). The combined organic phases were dried over magnesium sulfate and concentrated to give the title

compound (5.324 g, 88%) as a yellow solid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 4.33–4.29 (m, 3H), 4.07–4.00 (m, 4H).

2-Cubylacetic acid (**S5**)

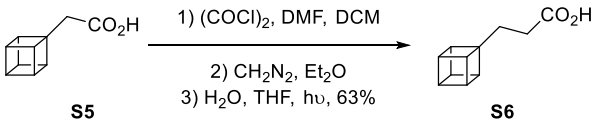


S4 **S5**

Following the procedure of Eaton *et al*:[10] cubanecarboxylic acid (**S4**) (838 mg, 5.65 mmol) was dissolved in anhydrous DCM (30 mL) under an argon atmosphere. Oxalyl chloride (0.58 mL, 6.76 mmol) and anhydrous DMF (3 drops) were added and the solution was left to stir for 40 min. The DCM was removed in vacuo and the residual brown oil was exposed to high vacuum for 1 h. *The remainder of this sequence should be performed behind a blast shield.* The resulting acid chloride was suspended in anhydrous diethyl ether (25 mL). Ethereal diazomethane (*ca* 55 mL) was added and the reaction monitored by TLC (30% ethyl acetate/petroleum ether v/v) until complete consumption of the acid chloride (R_f = 0.10), and formation of the diazide (R_f = 0.40), had been observed. Excess diazomethane was blown off with argon and the remaining diethyl ether was removed under reduced pressure. The resulting yellow solid was, *without mechanical agitation*, taken up in a degassed THF (40 mL) and water (15 mL) solution. The resulting solution was added to a Pyrex cold finger and then irradiated with a 400-W medium pressure Hanovia mercury arc lamp filtered through quartz for 4.5 h. [Note: The Pyrex cold finger had a diameter of 3.0 cm. The light source was housed in the centre of a quartz water jacket which had a diameter of 5.0 cm. The distance between the outer walls of the Pyrex cold finger and the quartz water jacket was 2.0 cm. The Pyrex cold finger and quartz water jacket were cooled with circulating water chilled to ca 5 °C. Magnetic stirring was not required as the solution was homogenised by the resulting convection current.] The THF was removed *in vacuo* and the remaining water was washed with ethyl acetate (3 x 30 mL). The combined organic extracts were dried over magnesium sulfate, concentrated and purified by column chromatography (20% ethyl acetate/petroleum ether) to give the title compound (602 mg, 66%) as a yellow rancid-smelling solid. m.p. 134.4–135.8 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 4.06–4.03 (m, 1H), 3.95–3.91 (m, 3H), 3.90–3.86 (m, 3H), 2.69 (s, 2H) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$): δ

(ppm) 176.4, 54.1, 49.0, 48.3, 44.3, 38.0 ppm; HRMS-ESI calcd for $C_{10}H_9O_2$ ([M-H]$^-$): 161.0608, found 161.0608.

3-Cubylpropanoic acid (**S6**)

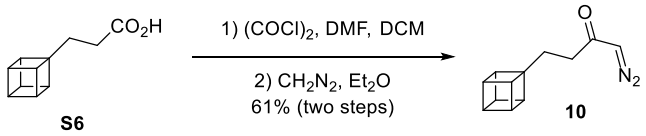


S5 **S6**

2-Cubylacetic acid (**S5**) (500 mg, 3.08 mmol) was dissolved in anhydrous DCM (25 mL) under an argon atmosphere. Oxalyl chloride (0.32 mL, 3.70 mmol) and anhydrous DMF (2 drops) were added and the solution was left to stir for 1 h. The DCM was removed in vacuo and the residual brown oil was exposed to high vacuum for 1 h. *The remainder of this sequence should be performed behind a blast shield.* The resulting acid chloride was suspended in anhydrous diethyl ether (15 mL). Ethereal diazomethane (*ca* 40 mL) was added and the reaction monitored by TLC (30% ethyl acetate/petroleum ether v/v) until complete consumption of the acid chloride (R_f = 0.15), and formation of the diazide (R_f = 0.50), had been observed. Excess diazomethane was blown off with argon and the remaining diethyl was removed under reduced pressure. The resulting yellow solid was, without mechanical agitation, taken up in a degassed THF (40 mL) and water (15 mL) solution. The resulting solution was added to a Pyrex cold finger and then irradiated with a 400-W medium pressure Hanovia mercury arc lamp filtered through quartz for 5 h. [Note: The Pyrex cold finger had a diameter of 3.0 cm. The light source was housed in the centre of a quartz water jacket which had a diameter of 5.0 cm. The distance between the outer walls of the Pyrex cold finger and the quartz water jacket was 2.0 cm. The Pyrex cold finger and quartz water jacket were cooled with circulating water chilled to ca 5 °C. Magnetic stirring was not required as the solution was homogenised by the resulting convection current.] The THF was removed *in vacuo* and the remaining water was washed with ethyl acetate (3 x 20 mL). The combined organic extracts were dried over magnesium sulfate, concentrated and purified by column chromatography (20% ethyl acetate/petroleum ether v/v) to give the title compound (343 mg, 1.95 mmol, 63%) as a yellow solid. m.p. 74.9–75.7 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 4.06–4.01 (m, 1H), 3.89–3.85 (m, 3H), 3.77–3.74 (m, 3H), 2.33 (t, *J* = 7.6 Hz, 2H), 1.94 (t, *J* = 7.9 Hz, 2H); ^{13}C-NMR (100 MHz,

$CDCl_3$): δ (ppm) 178.0, 58.3, 48.7, 48.2, 44.2, 29.1, 28.3; HRMS-ESI calcd for $C_{11}H_{11}O_2$ ($[M-H]^-$): 175.0765, found 175.0764.

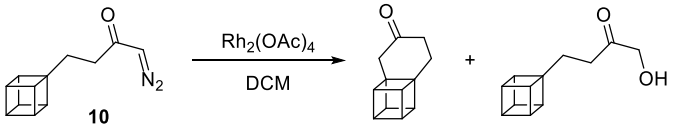
4-(Cuban-1-yl)-1-diazobutan-2-one (**10**)



S6 **10**

3-Cubylpropanoic acid (**S6**) (72 mg, 0.41 mmol) was dissolved in anhydrous DCM (7 mL) under an argon atmosphere. Oxalyl chloride (0.05 mL, 0.061 mmol) and anhydrous DMF (1 drop) were added and the solution was left to stir for 1 h. The DCM was removed *in vacuo* and the residual brown oil was exposed to high vacuum for 1 h. *The remainder of this sequence should be performed behind a blast shield.* The resulting acid chloride was suspended in anhydrous diethyl ether (5 mL). Ethereal diazomethane (ca 4 mL) was added and the reaction monitored by TLC (20% ethyl acetate/petroleum ether v/v) until complete consumption of the acid chloride (R_f = 0.10), and formation of the diazide (R_f = 0.40), had been observed. Excess diazomethane and residual diethyl ether were blown off with argon and the residue purified by column chromatography (20% ethyl acetate/petroleum ether v/v) to give the target material (50 mg, 61%) as an off–white solid. m.p. 65.1–67.1 °C; ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm) 5.26 (br s, 1H), 4.05–4.01 (m, 1H), 3.87–3.84 (m, 3H), 3.74–3.72 (m, 3H), 2.28 (br s, 2H), 1.90 (t, *J* = 8.1 Hz, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) 195.5, 58.5, 54.3, 48.7, 48.3, 44.2, 36.0, 28.8; HRMS-ESI calcd for $C_{12}H_{12}N_2ONa$ ($[M+Na]^+$): 223.0842, found 223.0849.

Fused cubane **11** and α-hydroxy cubane **12**



10 **11** (9%) **12** (24%)

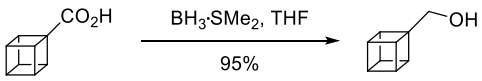
4-(Cuban-1-yl)-1-diazobut-2-one (**10**) (13 mg, 0.065 mmol) was suspended in anhydrous DCM (2 mL) and degassed with argon for 15 min then added over 2 h to a solution of $Rh_2(OAc)_4$ (2 mg, 0.004 mmol) in anhydrous DCM (1 mL) that had been degassed with argon for 15 min. After 20 min the DCM was blown off with nitrogen

and the residue purified by column chromatography (2% ethyl acetate/petroleum ether v/v) to give **11** (1 mg, 8%) as a clear oil and **12** (3 mg, 24%) as a white solid.

11: ^{1}H-NMR (700 MHz, C_6D_6) δ (ppm) 3.77–3.74 (m, 1H), 3.73–3.70 (m, 1H), 3.54–3.52 (m, 2H), 3.42–3.40 (m, 2H), 2.34 (s, 2H), 2.02 (t, *J* = 6.7 Hz, 2H), 1.55 (t, *J* = 6.7 Hz, 2H); ^{13}C-NMR (175 MHz, C_6D_6): δ (ppm) 208.1, 51.9, 51.1, 48.5, 47.7, 46.0, 45.4, 42.5, 36.4, 25.2; HRMS-ESI calcd for $C_{12}H_{12}ONa$ ($[M+Na]^+$): 195.0780, found 195.0789.

12: m.p. 64.9–66.3 °C; ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm) 4.27 (d, *J* = 4.7 Hz, 2H), 4.06–4.01 (m, 1H), 3.88–3.84 (m, 3H), 3.73–3.70 (m, 3H), 3.10 (t, *J* = 4.8 Hz, 1H), 2.38 (t, *J* = 7.9 Hz, 2H), 1.93 (t, *J* = 7.9 Hz, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) 210.3, 68.2, 58.2, 48.7, 48.1, 44.1, 33.3, 27.5; HRMS-ESI calcd for $C_{12}H_{14}O_2Na$ ($[M+Na]^+$): 213.0886, found 213.0889.

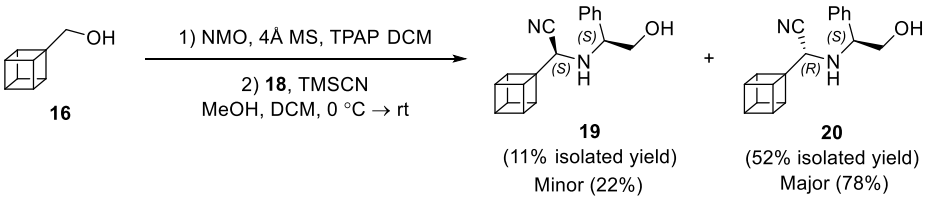
Cubylmethanol (**16**)



S4 **16**

Following the procedure of Priefer *et al*:[11] to a solution of cubane-1-carboxylic acid (**S4**) (100 mg, 0.67 mmol) in anhydrous THF (10 mL) was slowly added borane dimethylsulfide complex (5 M in diethyl ether, 0.40 mL, 2.02 mmol) under an argon atmosphere. The solution was left to stir for 1 h then water (5 mL) was cautiously added. The THF was removed *in vacuo* and the residue was washed with DCM (3 x 10 mL). The combined organic phases were dried over magnesium sulfate, concentrated and purified by column chromatography (50% ethyl acetate/petroleum ether v/v) to give the title compound (85 mg, 95%) as a white solid. ^{1}H-NMR (300 MHz, $CDCl_3$): *δ* (ppm) 4.08–4.01 (m, 1H), 3.96–3.88 (m, 6H), 3.76 (d, *J* = 5.5 Hz, 1H).

Strecker adducts **19** and **20**

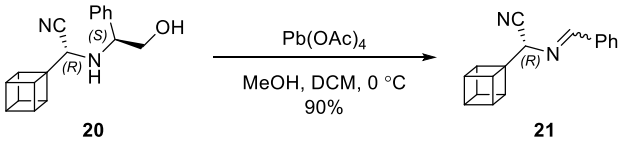


Adapted from the procedure of Chakraborty *et al*:[12] to a solution of cubylmethanol (**16**) (865 mg, 6.45 mmol), NMO (832 mg, 7.10 mmol) and 4Å molecular sieves (0.20 g) in anhydrous DCM (20 mL) was added TPAP (113 mg, 0.32 mmol) under an argon atmosphere. The solution was stirred until TLC showed oxidation was complete then filtered through Celite^{TM} and eluted with additional DCM (20 mL). To the resulting solution of cubane carboxaldehyde (**17**) was added anhydrous methanol (40 mL) and (*R*)-2-phenylglycinol (1.06 g, 7.72 mmol). The mixture was cooled to 0 ℃ then TMSCN (0.97 mL, 7.72 mmol) was added. The solution was left to warm to rt for 2 h then concentrated *in vacuo* and purified by column chromatography (30% ethyl acetate/petroleum ether v/v) to give the title compounds **19** (189 mg, 11%) and **20** (929 mg, 52%) as white foams and mixed fractions (144 mg, 8%). HRMS-ESI calcd for $C_{18}H_{18}N_2ONa$ ($[M+Na]^+$): 301.1311, found 301.1317.

19: ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 7.34 (m, 5H), 4.11 (m, 1H), 3.94 (m, 7H), 3.78 (m, 1H), 3.65 (m, 1H), 3.49 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 139.6, 128.8, 128.2, 127.4, 118.1, 66.2, 62.9, 57.3, 51.1, 48.6, 47.0, 44.3.

20: ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 7.32 (m, 5H), 4.09 (m, 1H), 3.98 (m, 7H), 3.79 (m, 1H), 3.58 (m, 1H), 3.48 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 138.2, 128.9, 128.3, 127.7, 117.9, 67.3, 63.0, 56.8, 50.2, 48.6, 46.9, 44.4.

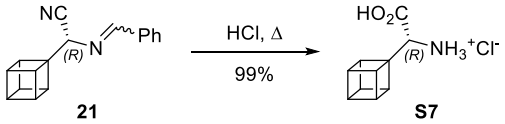
Schiff base **21**



Adapted from the procedure of Rebenstorf and Leonard:[13] to a solution of lead tetraacetate (126 mg, 0.29 mmol) in anhydrous methanol/DCM (5:5 mL v/v) at 0 ℃ under an argon atmosphere was added a solution of **20** (54 mg, 0.19 mmol) in anhydrous methanol/DCM (5:5 mLv/v). After 5 min saturated sodium bicarbonate (10

mL) was added and a precipitate immediately formed. The mixture was extracted with DCM (3 x 10 mL) and the combined organic phases were dried over magnesium sulfate then concentrated *in vacuo* to give the title compound (43 mg, 90%) as a pale-yellow liquid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 8.48 (d, *J* = 1.6 Hz, 1H), 7.78 (m, 2H), 7.44 (m, 3H), 4.85 (d, *J* = 1.6 Hz, 1H), 4.04 (m, 4H), 3.94 (m, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 163.2, 135.1, 131.6, 129.7, 129.0, 115.9, 60.6, 57.6, 48.8, 47.0, 44.4; HRMS-ESI calcd for $C_{17}H_{14}N_2Na$ ($[M+Na]^+$): 269.1049, found 269.1055.

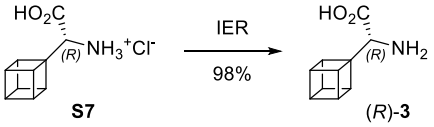
(*R*)-2-Cubylglycine hydrochloride (**S7**)



21 **S7**

To a recently formed sample of Schiff base **21** (43 mg, 0.18 mmol) was added concentrated hydrochloric acid (4 mL) and the solution was stirred at 60 ºC for 2 h. The solvent was removed *in vacuo* (aspirator) and the residue was washed with acetone and diethyl ether to give the title compound (37 mg, 99%) as an off-white solid. m.p. > 250 ℃; ^{1}H-NMR (500 MHz, D_2O) δ (ppm) 4.20 (s, 1H), 4.08–4.01 (m, 4H), 3.97–3.94 (m, 3H); ^{13}C-NMR (125 MHz, D_2O): δ (ppm) 171.5, 55.5, 55.3, 48.8, 47.6, 44.5; HRMS-ESI calcd for $C_{10}H_{12}NO_2$ ($[M+H^+]$): 178.0863, found 178.0857.

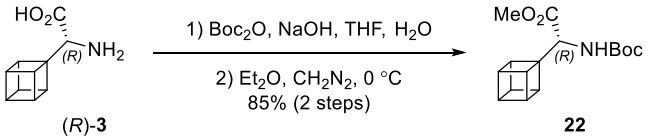
(*R*)-2-Cubylglycine [(*R*)-**3**]



S7 (*R*)-**3**

A column packed with ion exchange resin (Amberlite IR-120H, hydrogen form cation exchange resin) was flushed with 1M HCl then water. **S7** (37 mg, 0.17 mmol) was dissolved in H_2O (5 mL) then loaded onto the column. Elution with 5% aqueous ammonia solution gave the title compound as an off-white solid (30 mg, 98%). (*R*)-**3** was freshly prepared as needed and used for subsequent reactions immediately after drying. HRMS-ESI calcd for $C_{10}H_{12}NO_2$ ($[M+H]^+$): 178.0863, found 178.0868.

Boc-protected amino acid ester **22**



(*R*)-**3** **22**
(>99.5% ee)

To a stirred solution of (*R*)-**3** (50 mg, 0.28 mmol) in THF: water (1:1, 6 mL) was added di-*tert*-butyl dicarbonate (66 mg, 0.30 mmol) and NaOH (24 mg, 0.60 mmol). After stirring (16 h) the THF was removed *in vacuo* and the aqueous phase was washed with diethyl ether (2 x 5 mL) then acidified with 1N HCl to pH 3 and extracted with DCM (3 x 5 mL). The organic phases were combined, dried over magnesium sulfate then concentrated *in vacuo*. The resulting solid was then dissolved in diethyl ether and cooled to 0 ºC. Ethereal diazomethane was added until the yellow colouration remained. After stirring (5 min) excess diazomethane and residual diethyl ether were blown off with argon and the residue passed through a silica plug then concentrated *in vacuo* to give the title compound (70 mg, 89%) as a white solid. m.p. 87–89 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) 4.96 (s, 1H); 4.48 (m, 1H), 3.88–3.97 (m, 7H), 3.71 (s, 3H), 1.42 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) 171.2, 155.7, 79.9, 57.5, 55.0, 52.0, 48.5, 47.1, 28.3; HRMS-ESI calcd for $C_{16}H_{21}NO_4Na$ ($[M+Na]^+$): 314.1363, found 314.1368; $[\alpha]^{25}_D$ -79.7 (*c* 0.24, $CHCl_3$).

Chiral HPLC was performed with seven different columns and in each case only one peak was observed.

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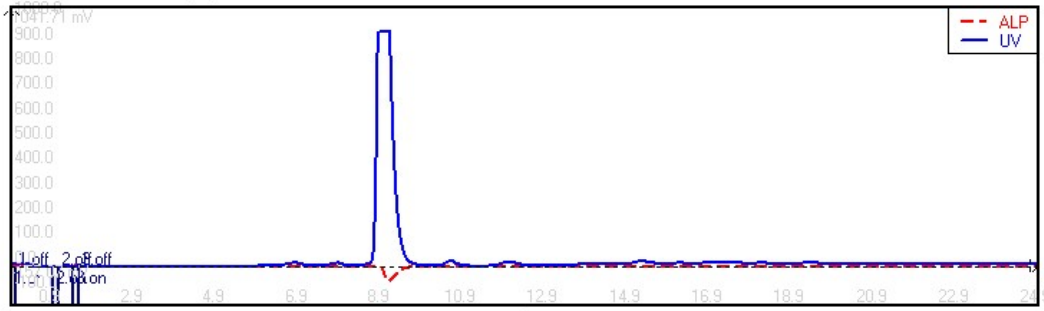

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Selector 2 :1
Inj Vol µL :10
UV Wavelengths (nm) :215,-,-,-,-
Flow mL/min :0.50

Press bar :150
Equilibrate
Eq.1 :11.1 min, 0.3 ml/min
Eq.2 :13.28 min, 0.5 ml/min
Run Time :25.00 min
Meth. Vol mL :22.47
Repeat :1
Comments :2 mg in 30%IPA/Hex_ gradient
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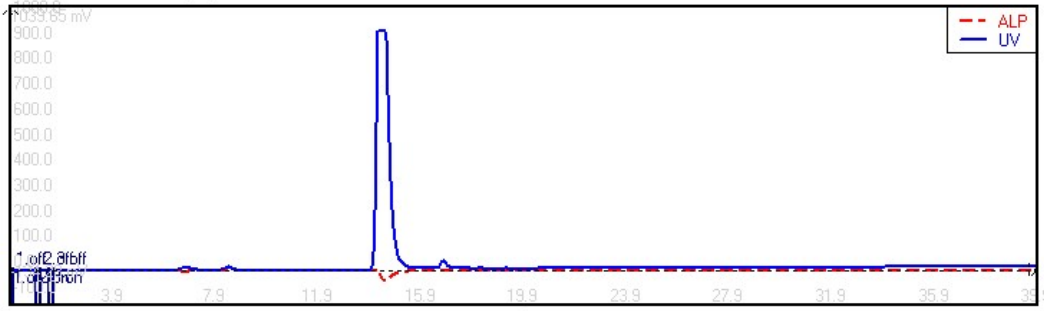

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Inj Vol µL :10
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Press bar :150
Equilibrate
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Eq.2 :13.28 min, 0.5 ml/min
Run Time :40.00 min
Meth. Vol mL :29.97
Repeat :1
Comments :2 mg in 30%IPA/Hex_ gradient
Vial # :2
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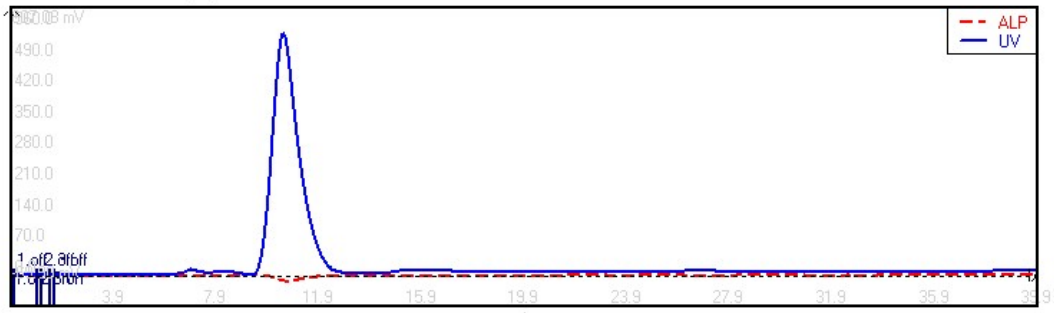

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Column Size
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Inner Diameter :0.4600
Selector 1 :4
Selector 2 :1
Inj Vol µL :10
UV Wavelengths (nm) :215,-,-,-,-
Flow mL/min :0.50

Press bar :150
Equilibrate
Eq.1 :11.1 min, 0.3 ml/min
Eq.2 :13.28 min, 0.5 ml/min
Run Time :40.00 min
Meth. Vol mL :29.97
Repeat :1
Comments :2 mg in 30%IPA/Hex_ gradient
Vial # :2
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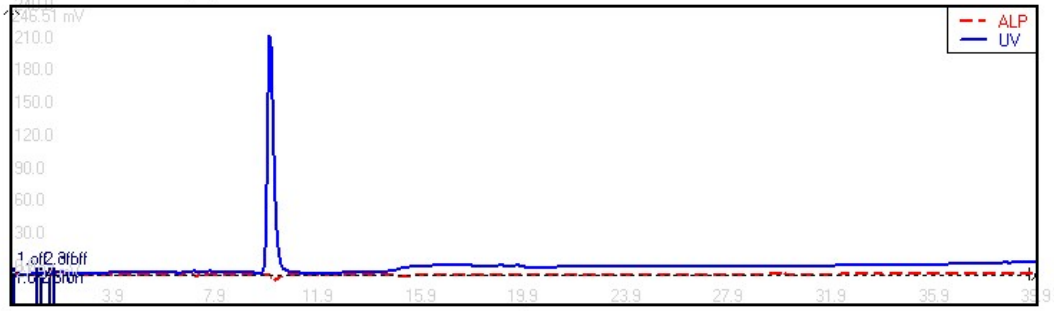

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Inner Diameter :0.4600
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Selector 2 :1
Inj Vol µL :1
UV Wavelengths (nm) :215,-,-,-,-
Flow mL/min :0.50

Press bar :150
Equilibrate
Eq.1 :11.1 min, 0.3 ml/min
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Run Time :40.00 min
Meth. Vol mL :29.97
Repeat :1
Comments :2 mg in 30%IPA/Hex_ gradient
Vial # :2
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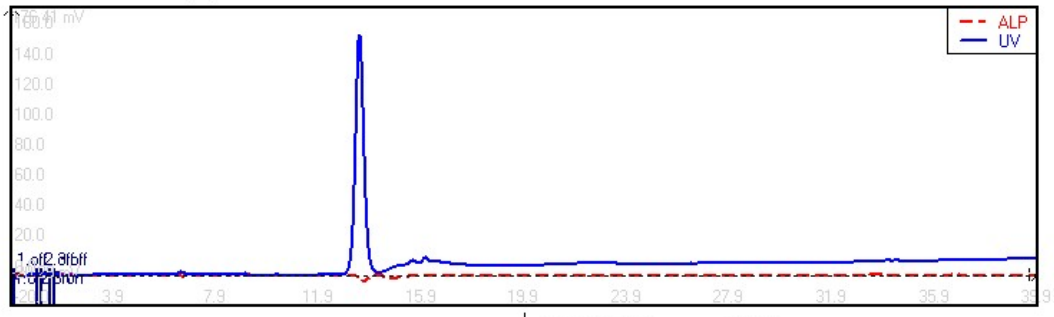

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Selector 2 :1
Inj Vol µL :1
UV Wavelengths (nm) :215,-,-,-,-
Flow mL/min :0.50

Press bar :150
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Run Time :40.00 min
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Repeat :1
Comments :2 mg in 30%IPA/Hex_ gradient
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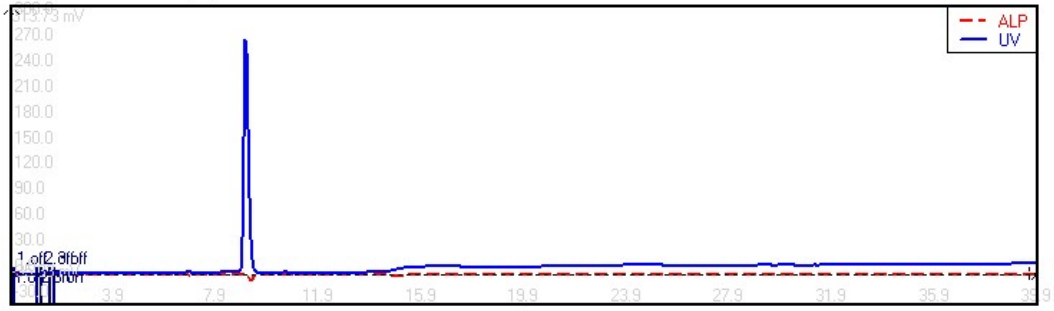

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Selector 2 :1
Inj Vol µL :1
UV Wavelengths (nm) :215,-,-,-,-
Flow mL/min :0.50

Press bar :150
Equilibrate
Eq.1 :11.1 min, 0.3 ml/min
Eq.2 :13.28 min, 0.5 ml/min
Run Time :40.00 min
Meth. Vol mL :29.97
Repeat :1
Comments :2 mg in 30%IPA/Hex_ gradient
Vial # :2
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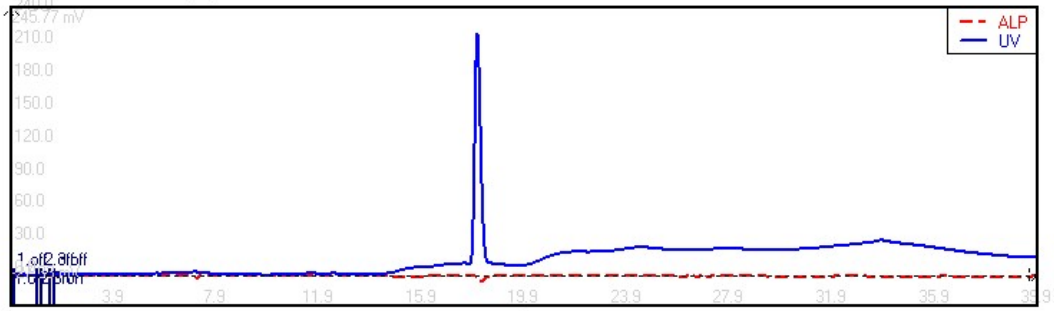

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Press bar :150
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Run Time :40.00 min
Meth. Vol mL :29.97
Repeat :1
Comments :2 mg in 30%IPA/Hex_ gradient
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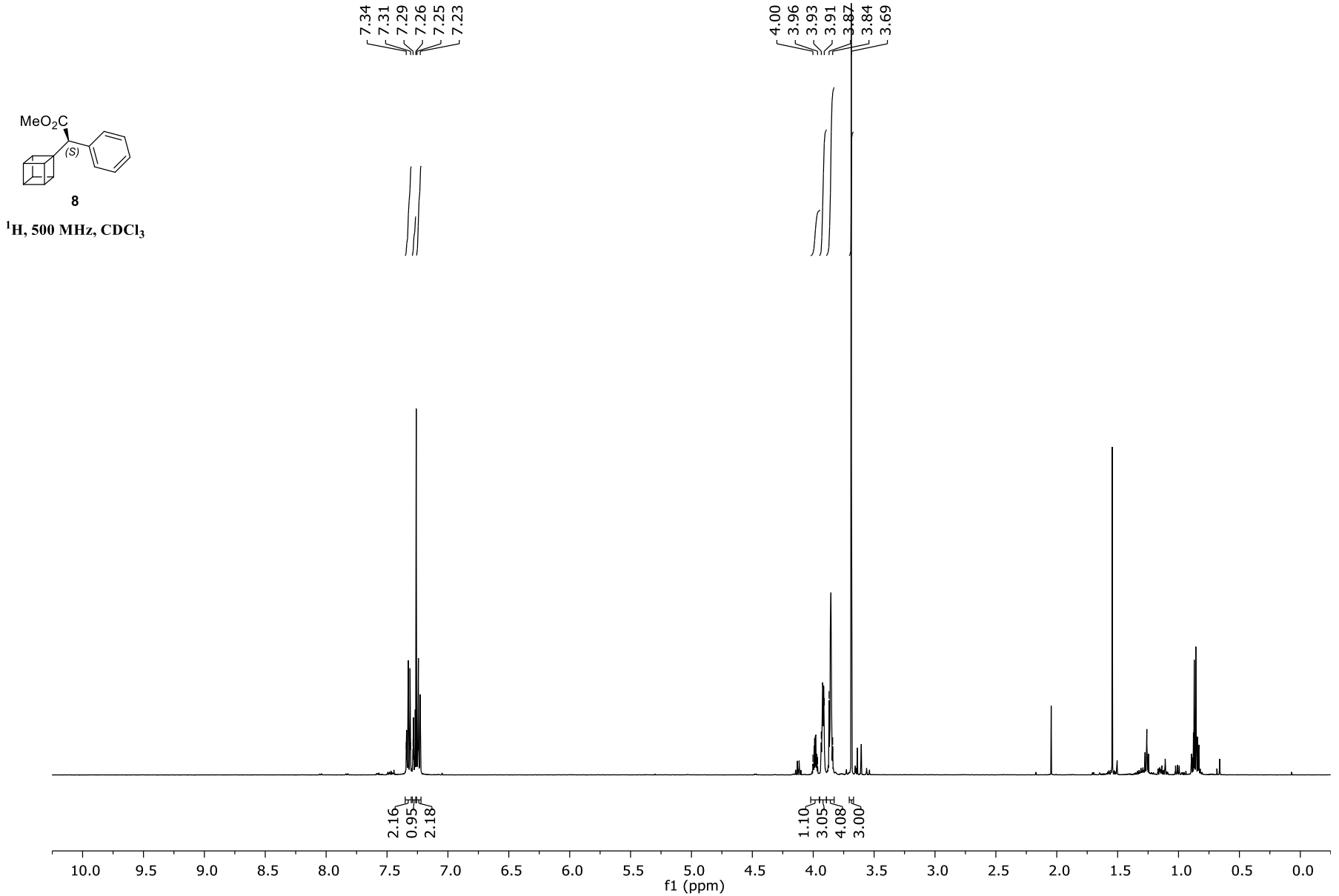
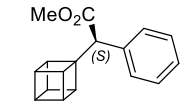
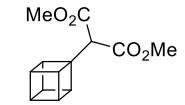
^{1}H and ^{13}C Spectra


MeO2C
(S)
8
1H, 500 MHz, CDCl3
7.34
7.31
7.29
7.26
7.25
7.23
4.00
3.96
3.93
3.91
3.87
3.84
3.69
2.16
0.95
2.18
1.10
3.05
4.08
3.00
10.0
9.5
9.0
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)



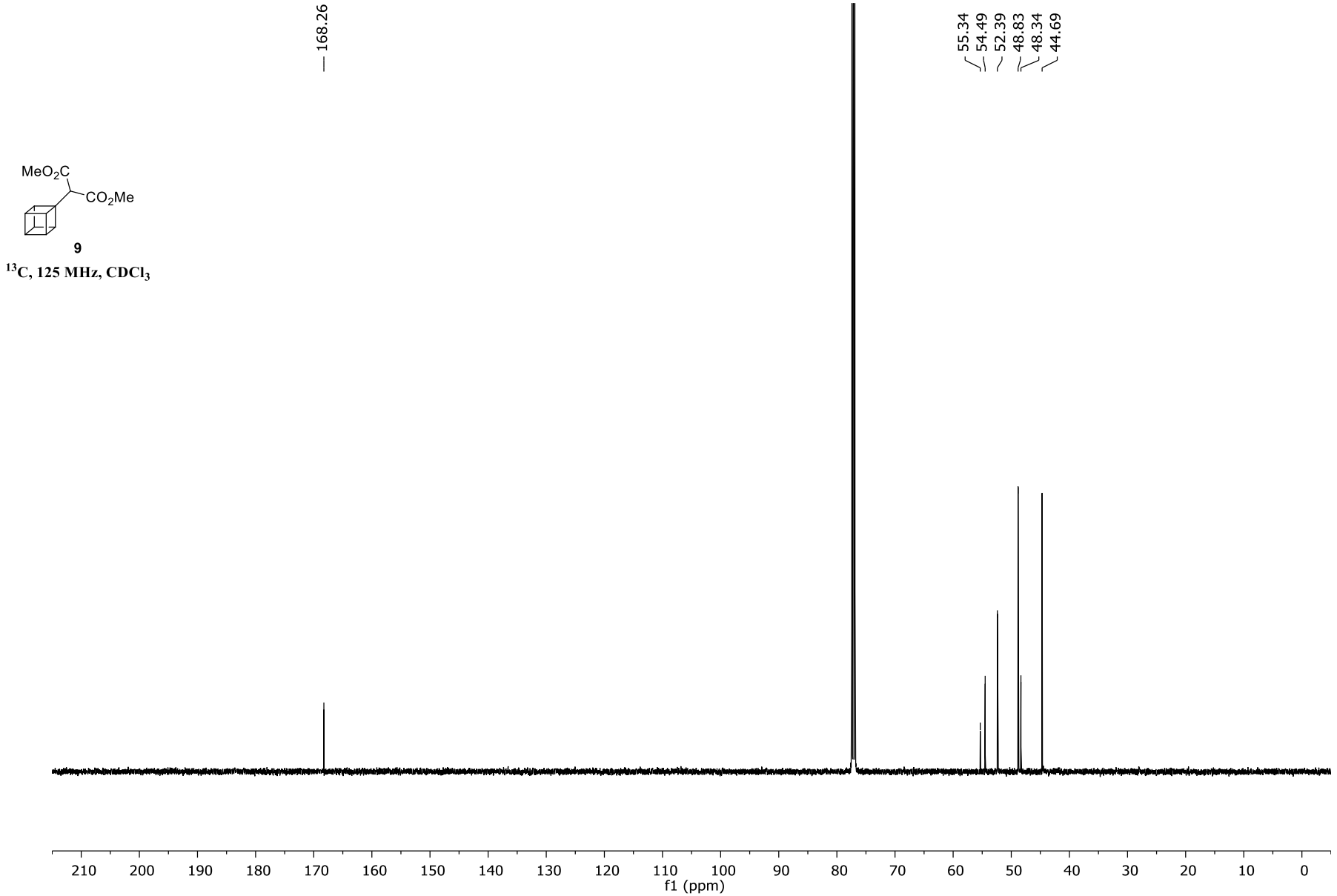
8

^{13}C, 125 MHz, $CDCl_3$



9

^{1}H, 500 MHz, $CDCl_3$


168.26
55.34
54.49
52.39
48.83
48.34
44.69
MeO2C
CO2Me
9
13C, 125 MHz, CDCl3
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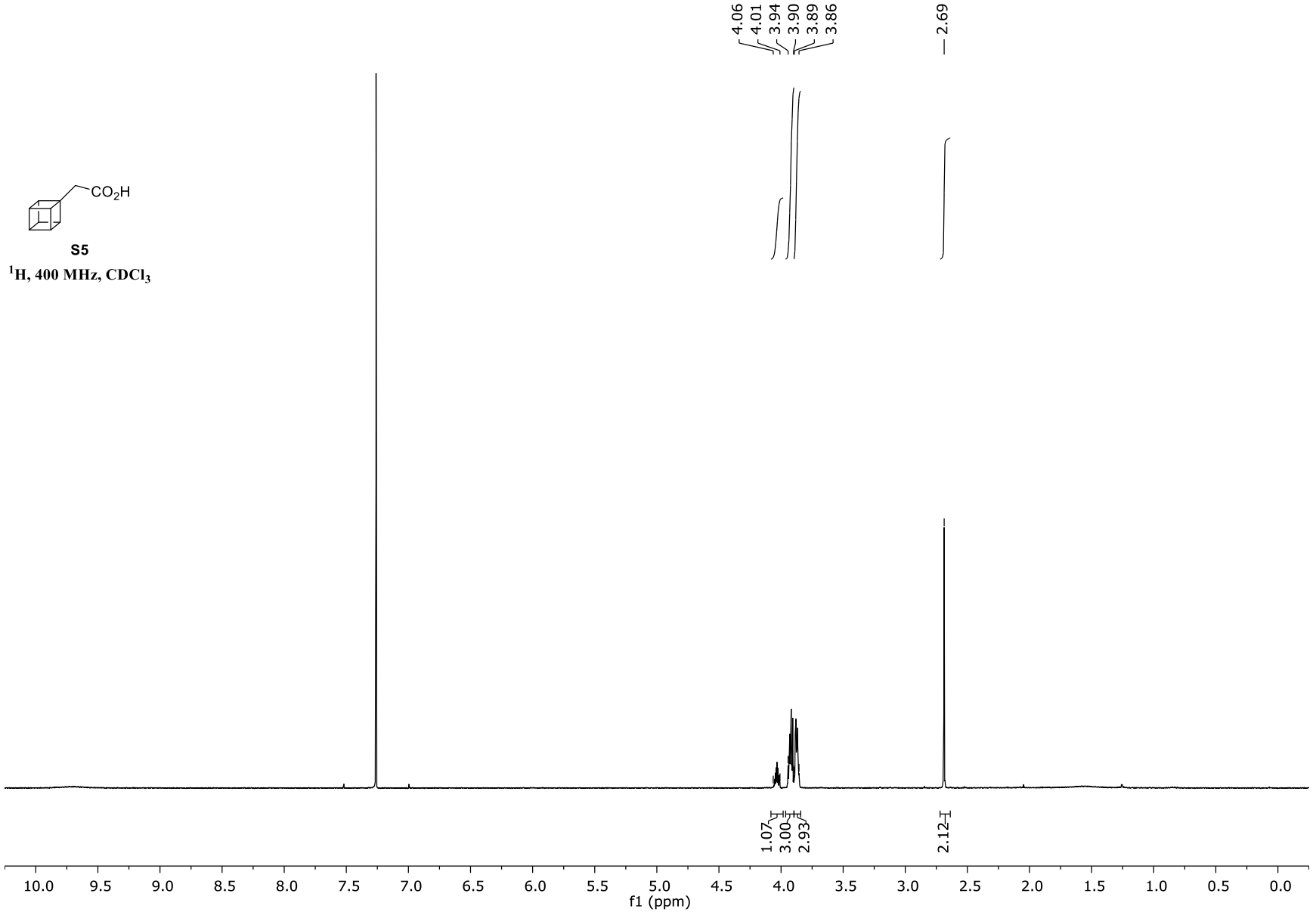
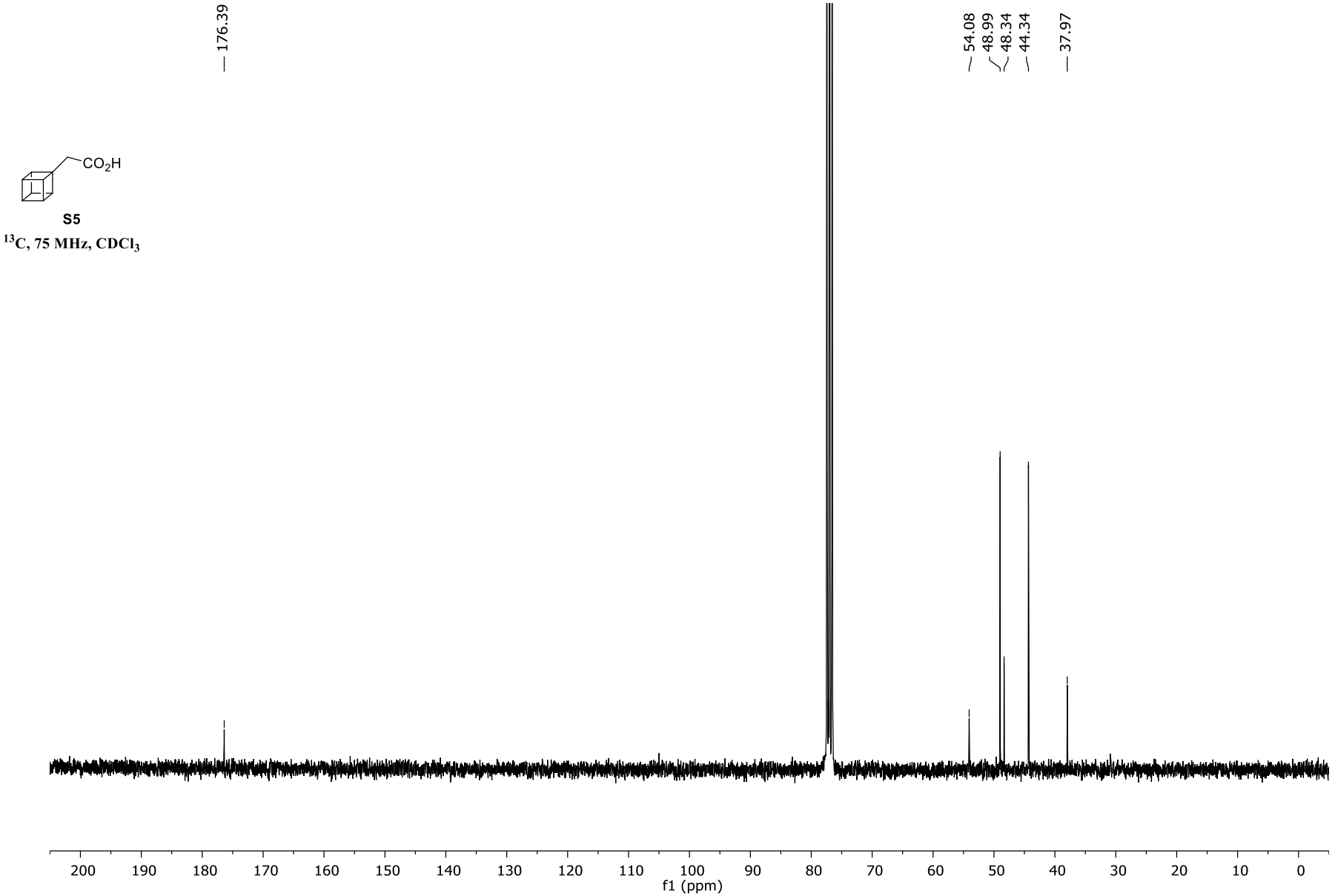
f1 (ppm)



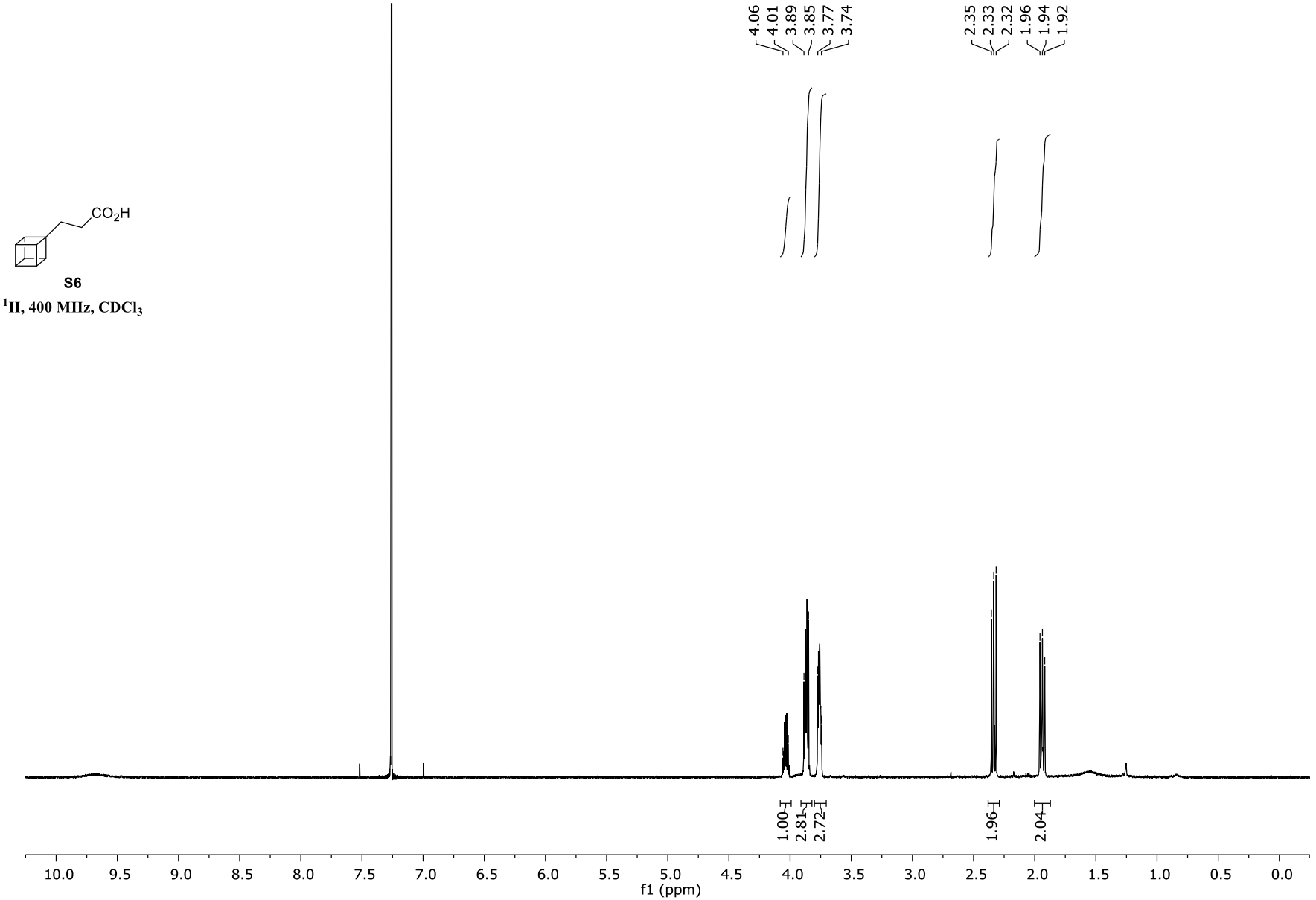
S5

^{1}H, 400 MHz, $CDCl_3$



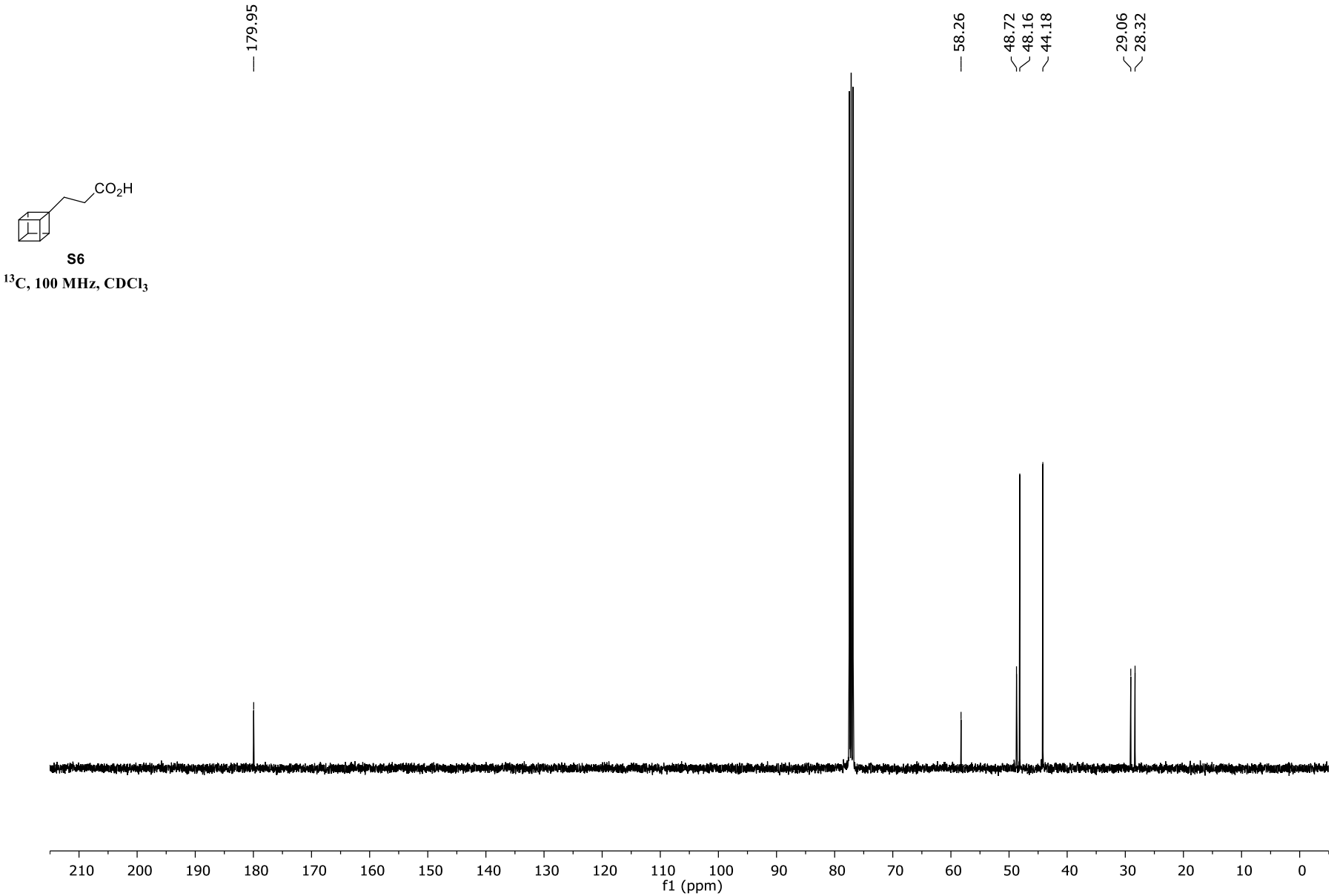
S5

^{13}C, 75 MHz, $CDCl_3$



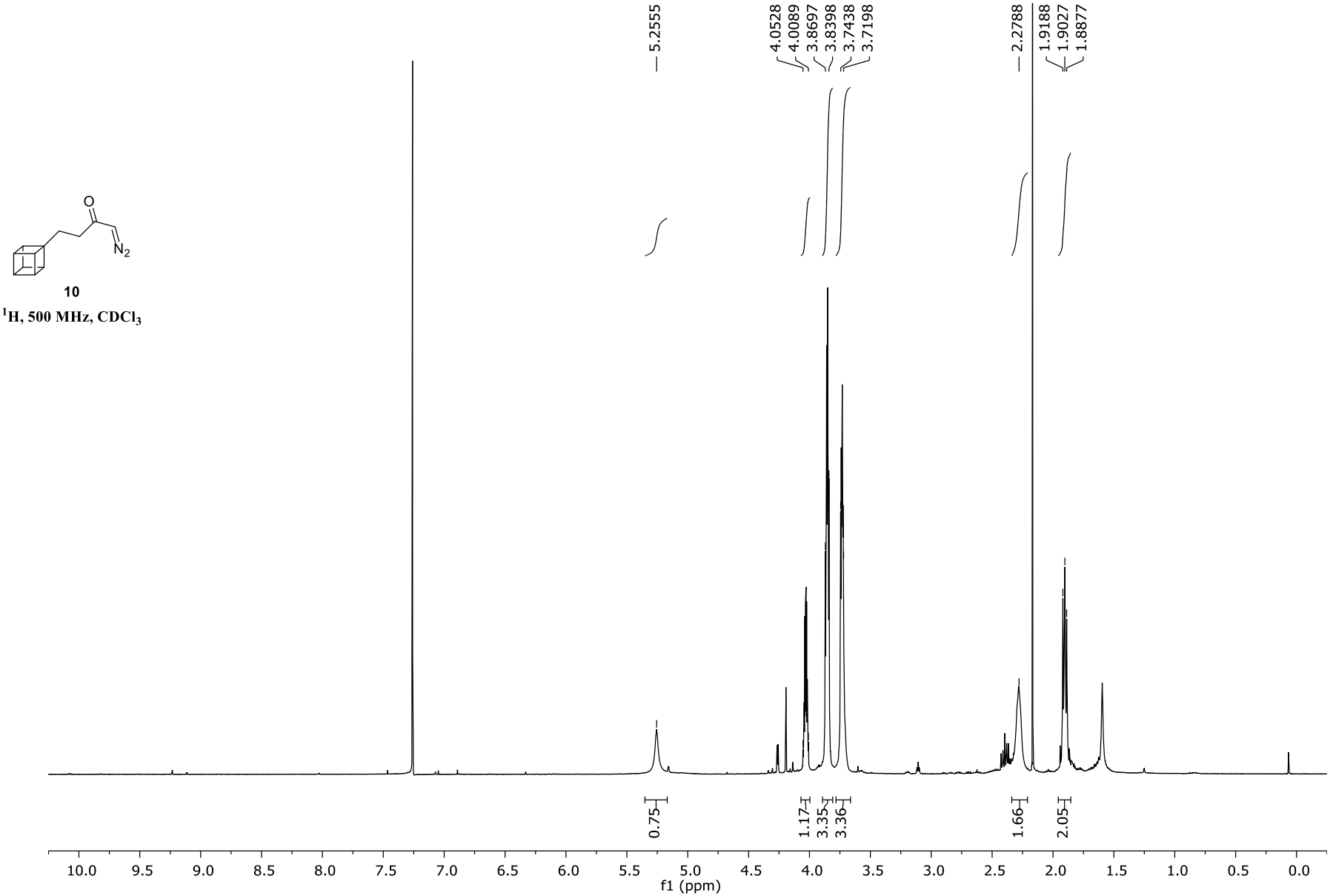
S6

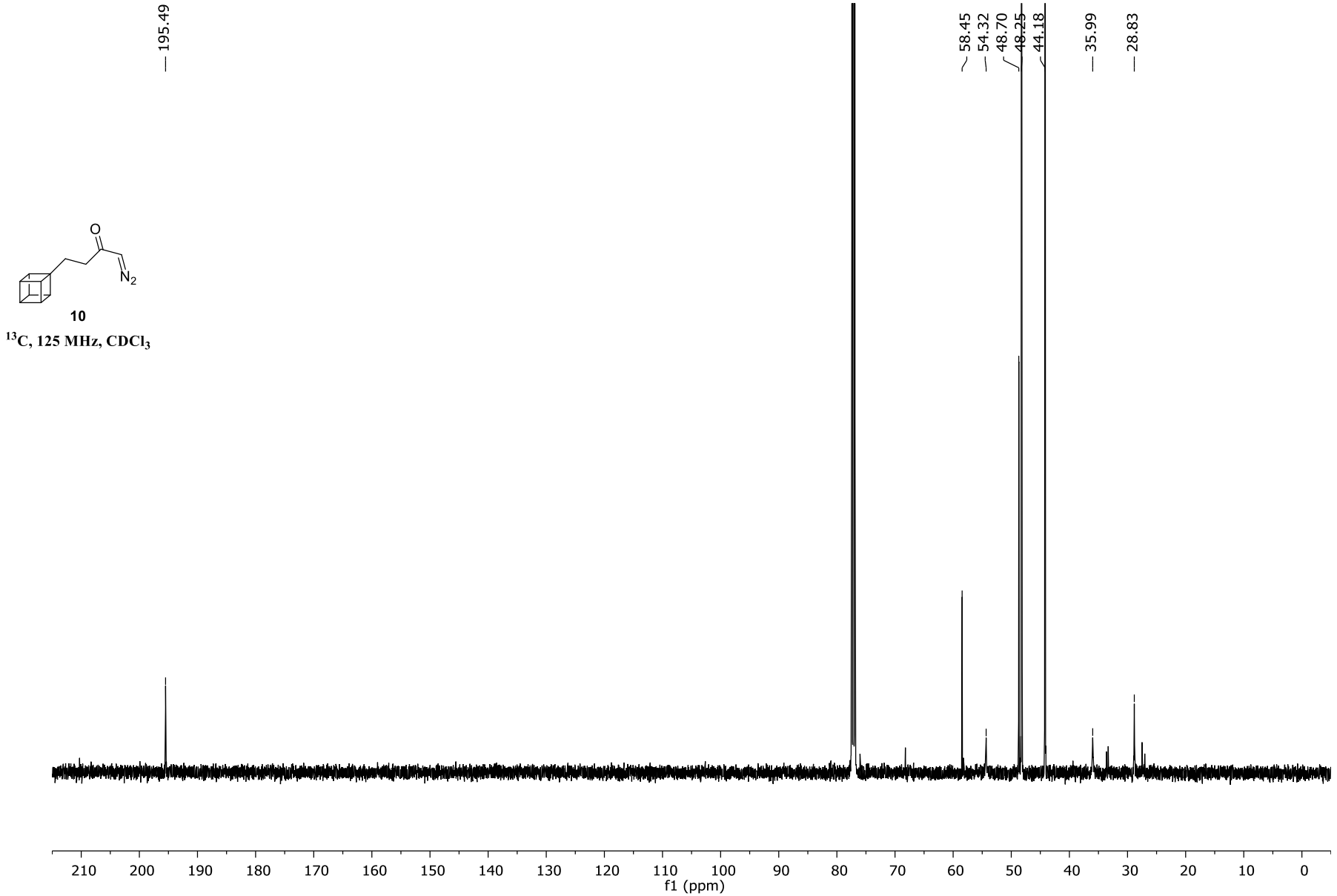
^{1}H, 400 MHz, $CDCl_3$

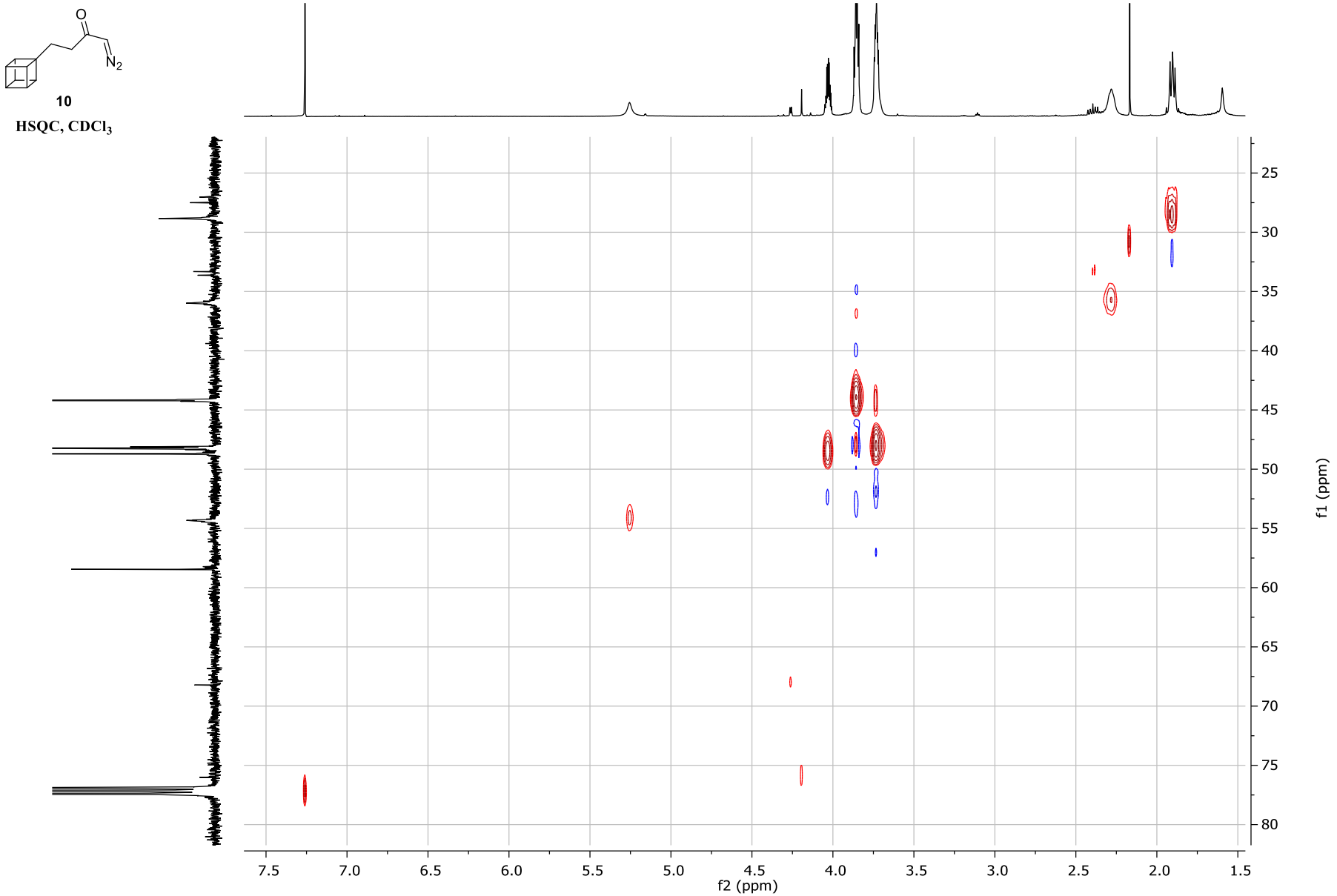


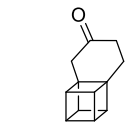
S6

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


O
N2
10
1H, 500 MHz, CDCl3
5.2555
4.0528
4.0089
3.8697
3.8398
3.7438
3.7198
2.2788
1.9188
1.9027
1.8877
0.75
1.17
3.35
3.36
1.66
2.05
10.0 9.5 9.0 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)

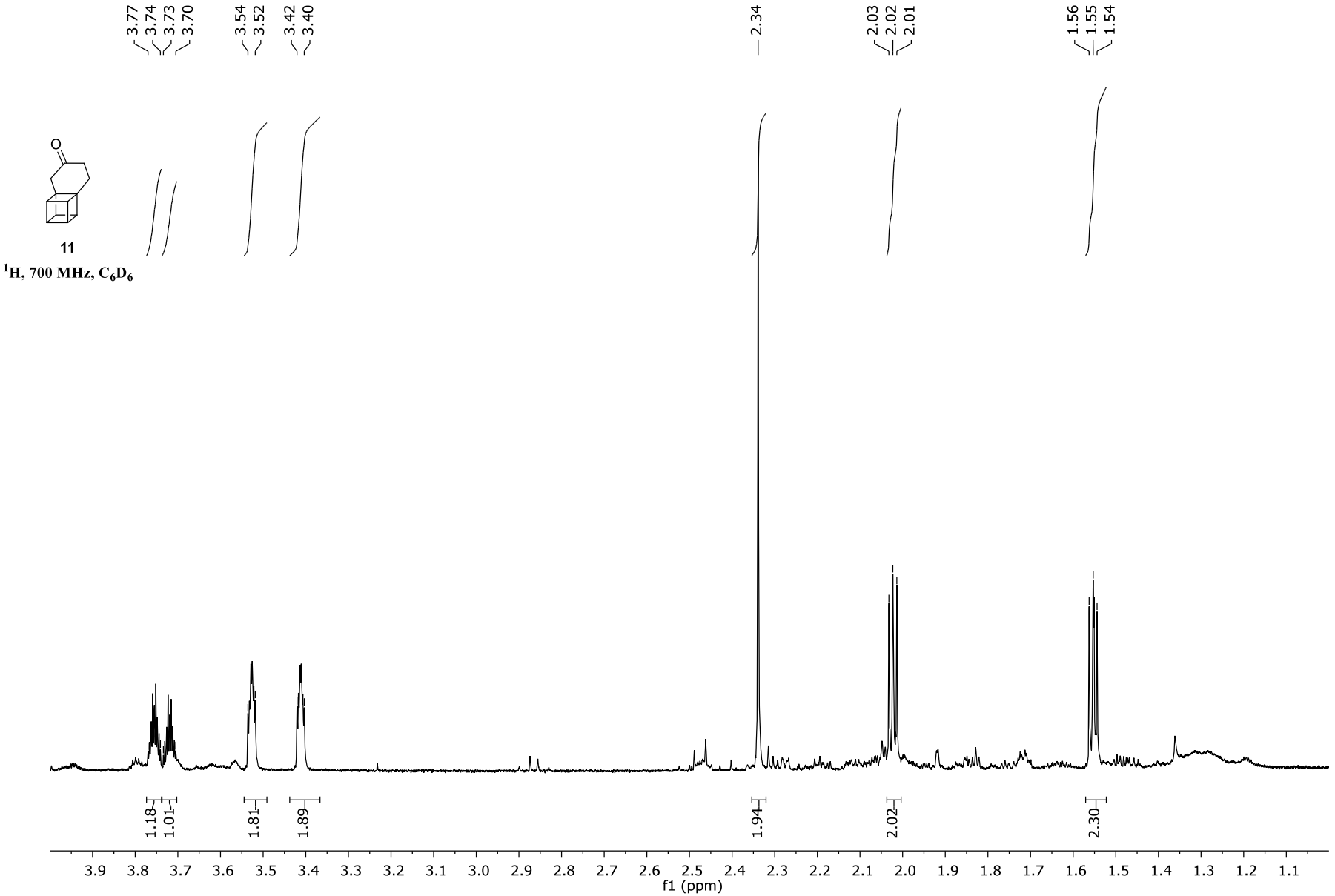

195.49
58.45
54.32
48.70
48.25
44.18
35.99
28.83
O
N2
10
13C, 125 MHz, CDCl3
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

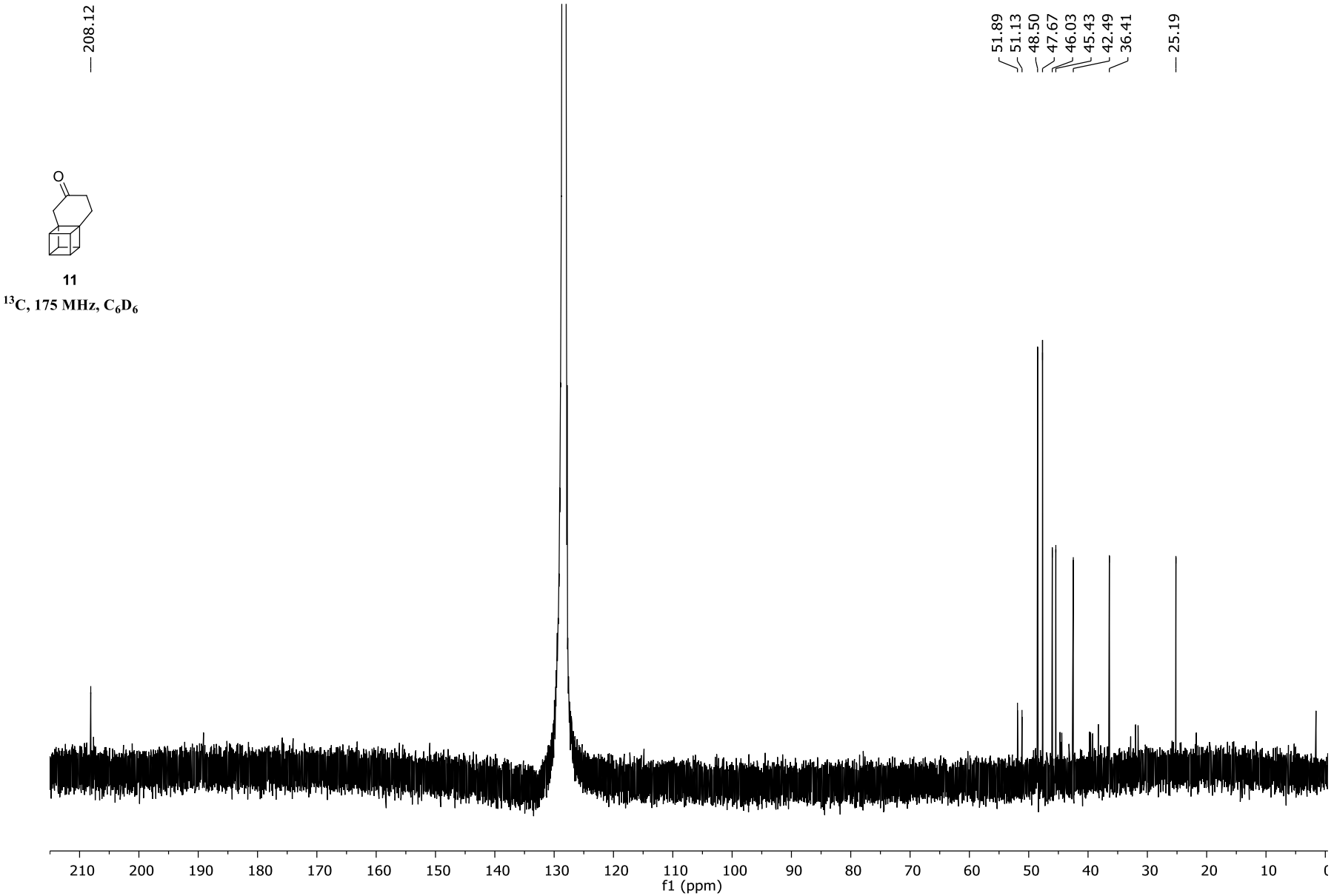

O
N2
10
HSQC, CDCl3
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
f2 (ppm)
25
30
35
40
45
50
55
60
65
70
75
80
f1 (ppm)

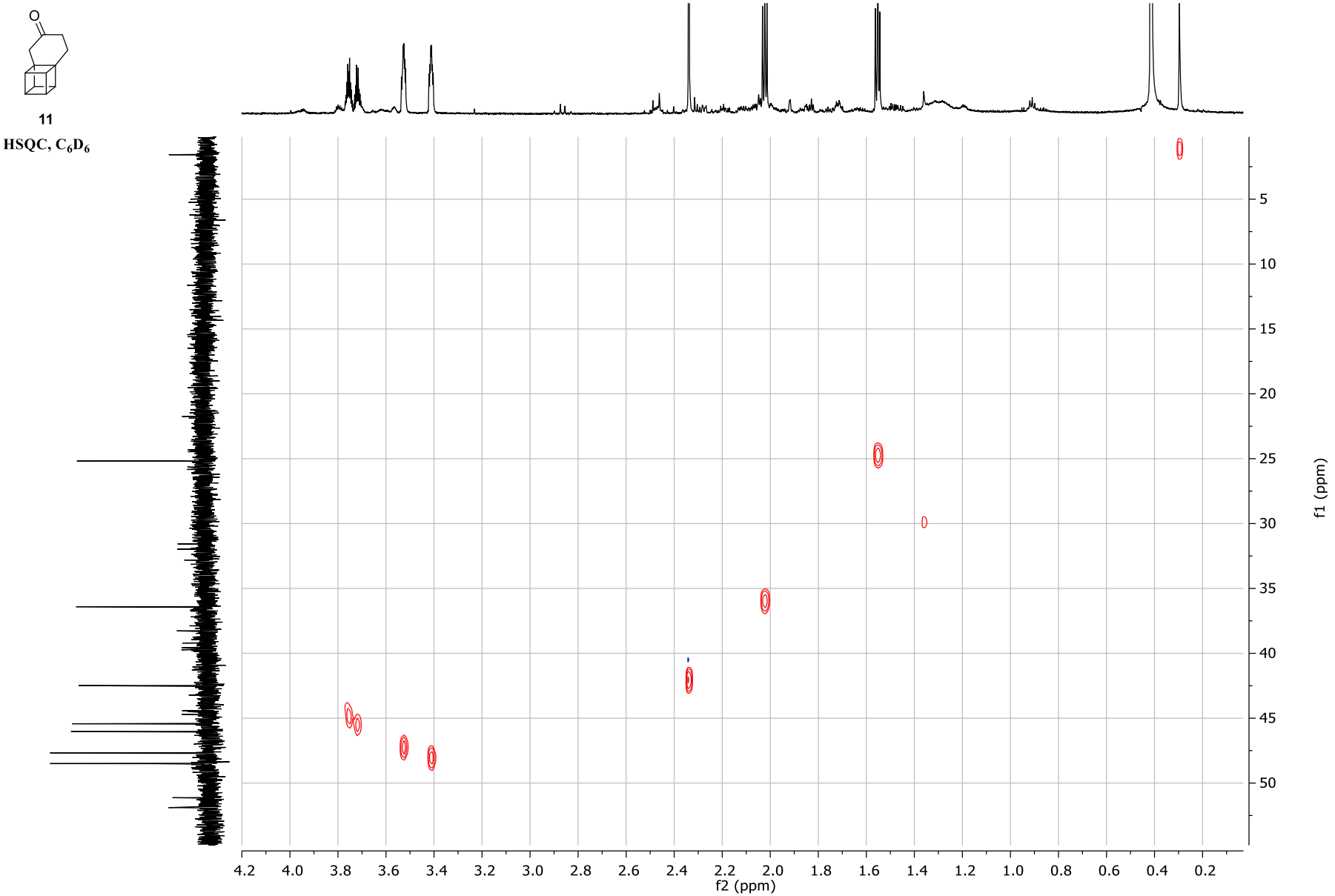


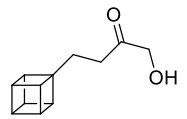
11

^{1}H, 700 MHz, C_6D_6


3.77
3.74
3.73
3.70
3.54
3.52
3.42
3.40
2.34
2.03
2.02
2.01
1.56
1.55
1.54
O
11
1H, 700 MHz, C6D6
1.18
1.01
1.81
1.89
1.94
2.02
2.30
3.9 3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1 3.0 2.9 2.8 2.7 2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8 1.7 1.6 1.5 1.4 1.3 1.2 1.1
f1 (ppm)

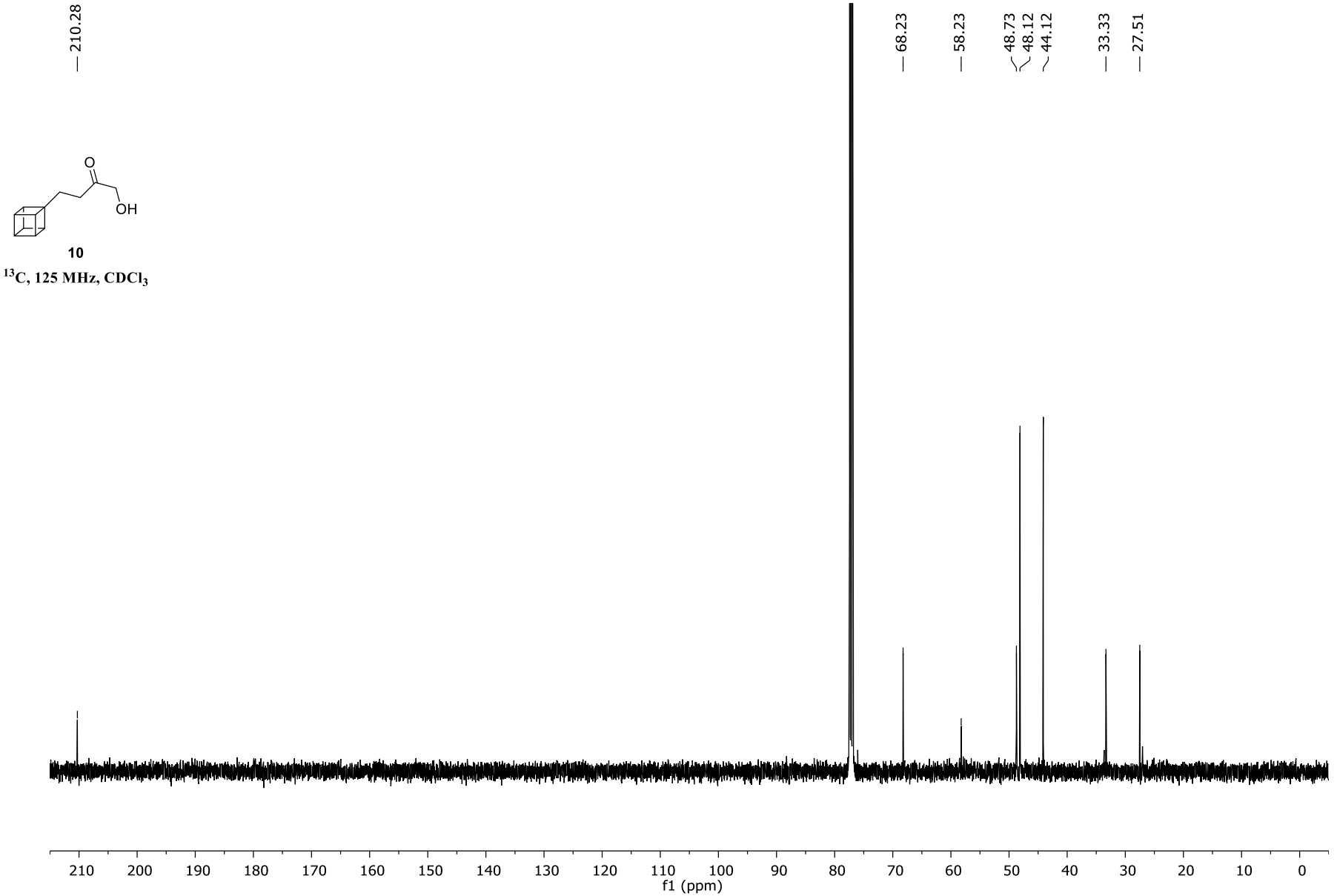

208.12
51.89
51.13
48.50
47.67
46.03
45.43
42.49
36.41
25.19
O
11
^{13}C, 175 MHz, C_6D_6
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)


11
HSQC, C6D6
4.2
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
f2 (ppm)
5
10
15
20
25
30
35
40
45
50
f1 (ppm)



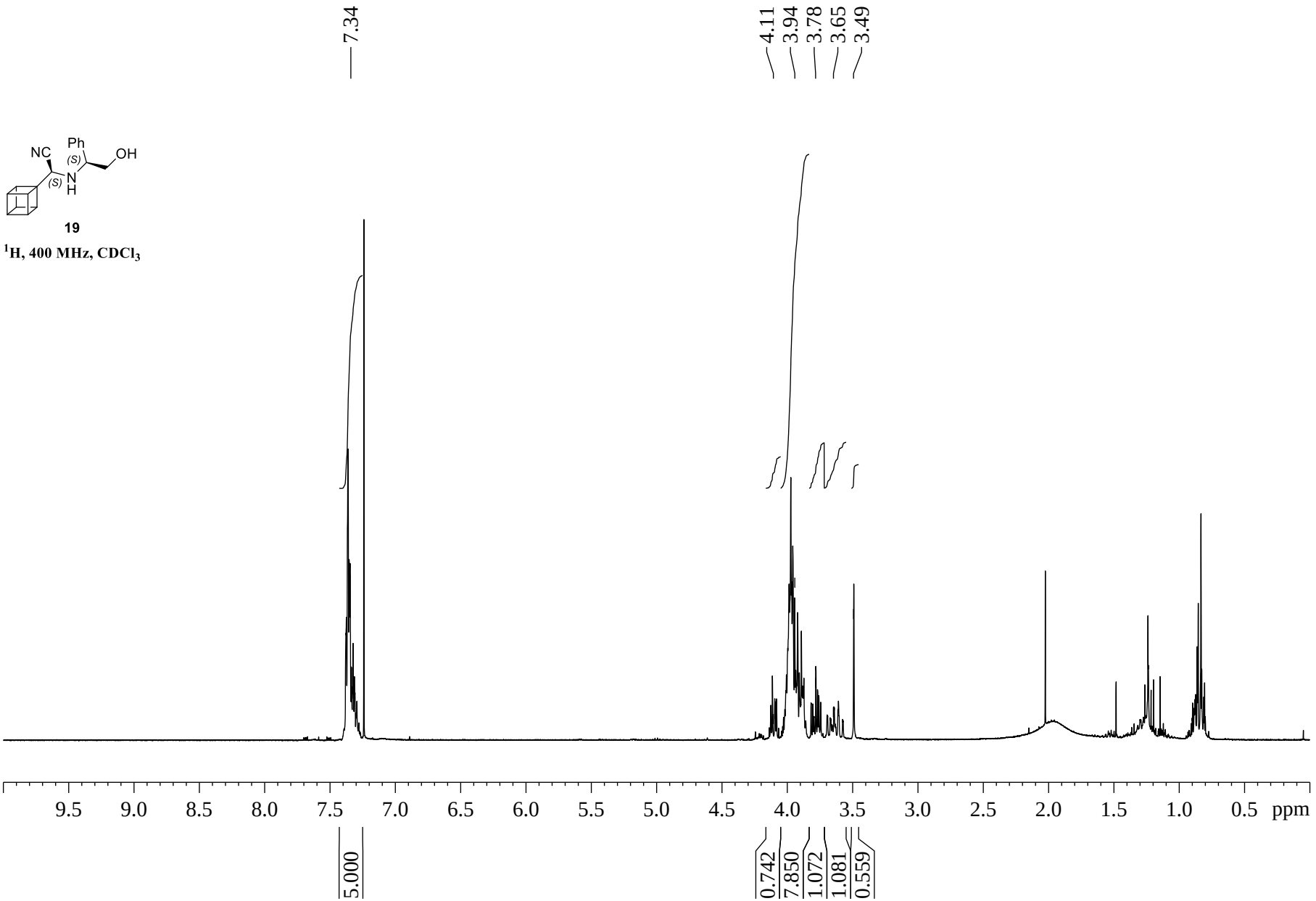
10

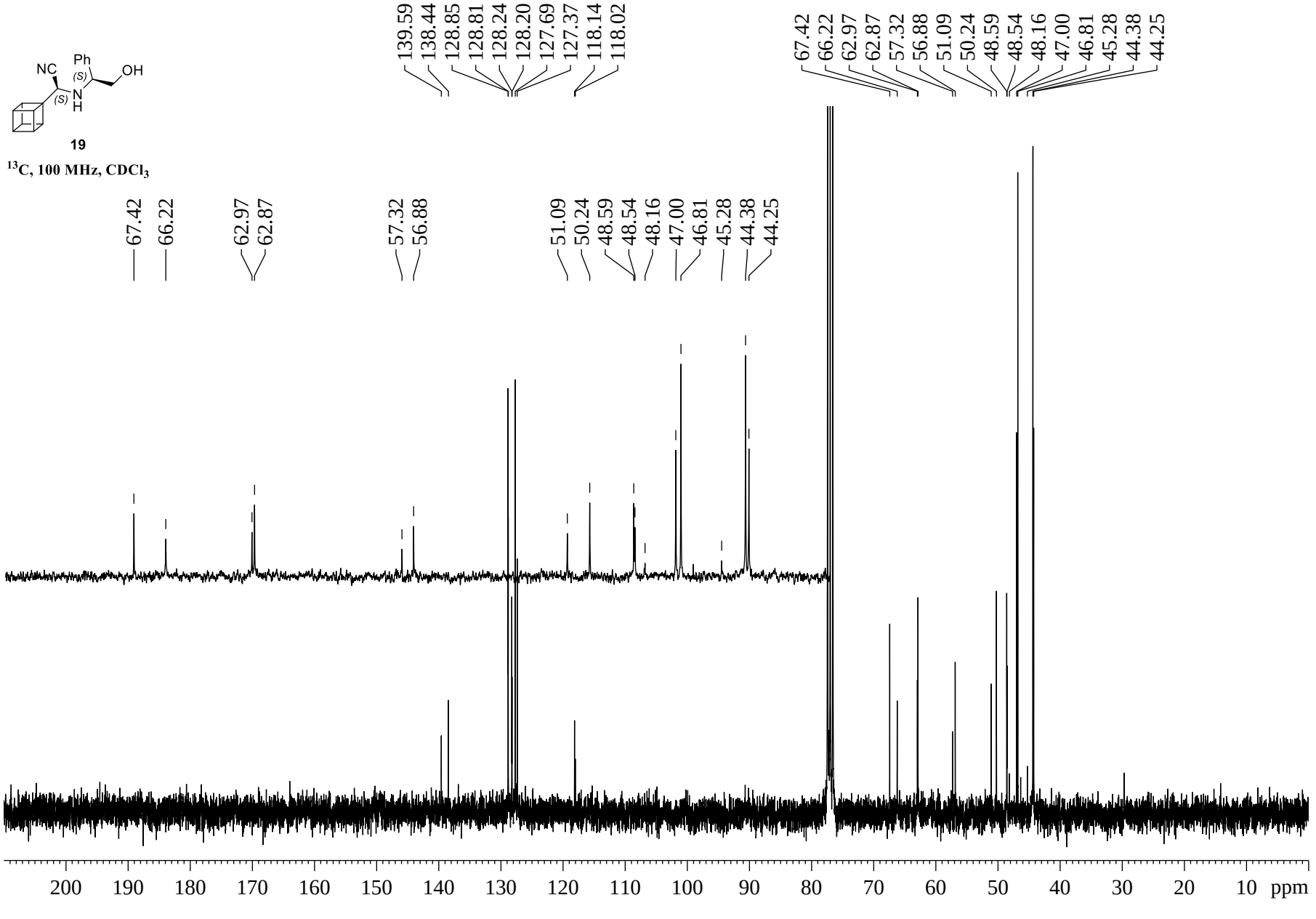
^{1}H, 500 MHz, $CDCl_3$

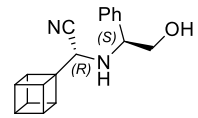


10

^{13}C, 125 MHz, $CDCl_3$

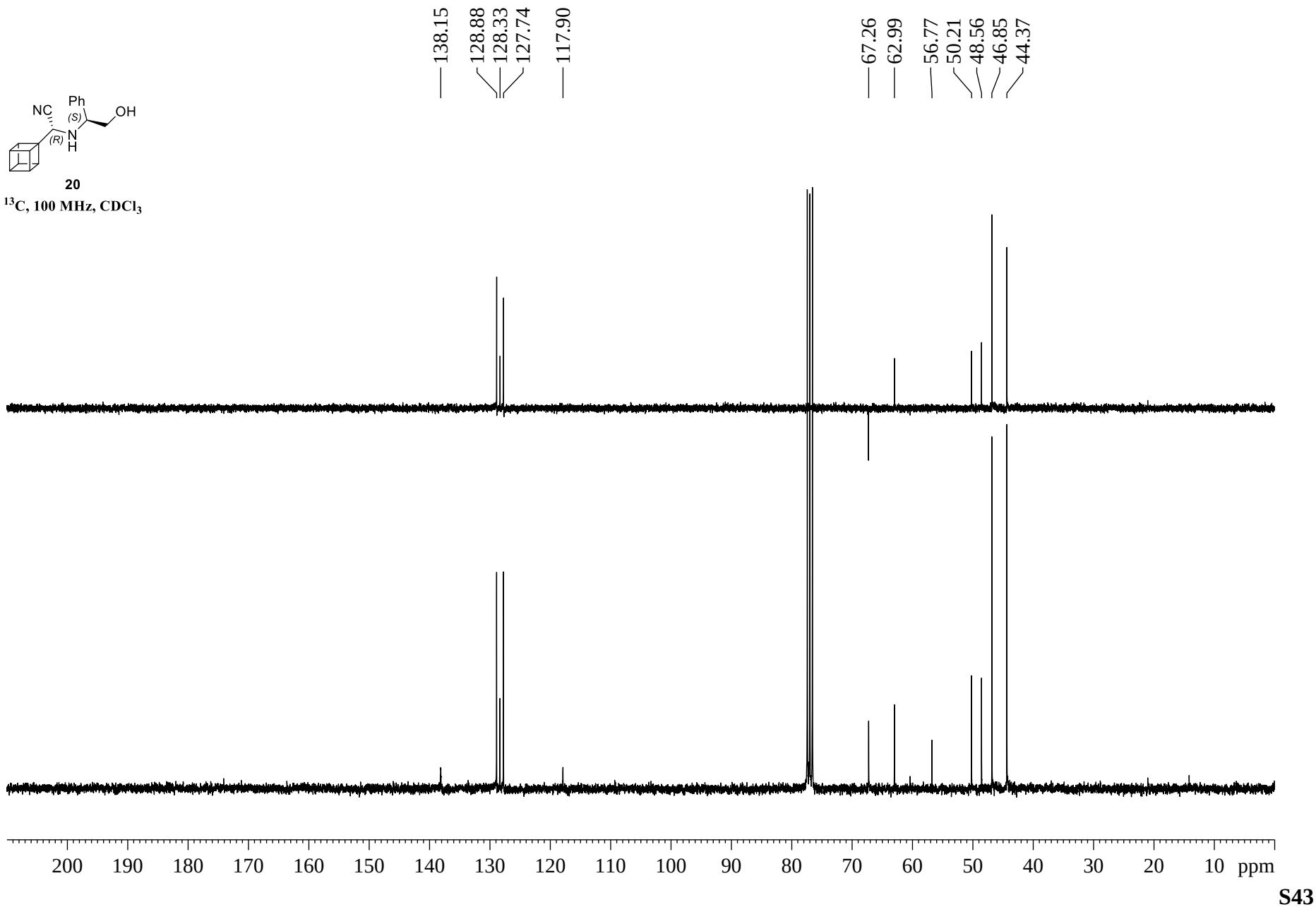

7.34
4.11
3.94
3.78
3.65
3.49
NC
Ph
(S)
OH
(S)
N
H
19
^{1}H, 400 MHz, CDCl$_3$
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
5.000
0.742
7.850
1.072
1.081
0.559

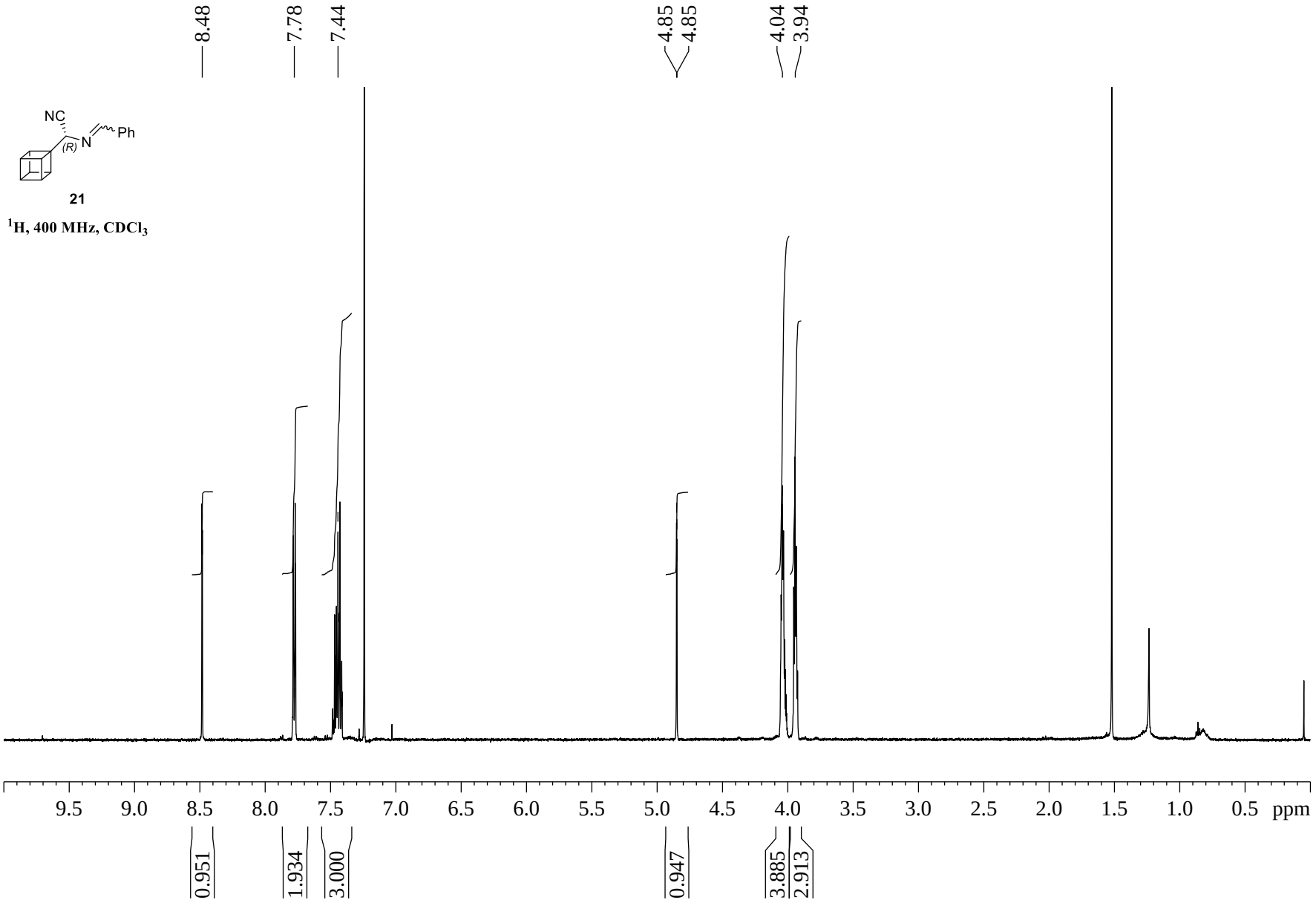

NC
Ph
(S)
OH
(S)
N
H
19
13C, 100 MHz, CDCl3
139.59
138.44
128.85
128.81
128.24
128.20
127.69
127.37
118.14
118.02
67.42
66.22
62.97
62.87
57.32
56.88
51.09
50.24
48.59
48.54
48.16
47.00
46.81
45.28
44.38
44.25
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

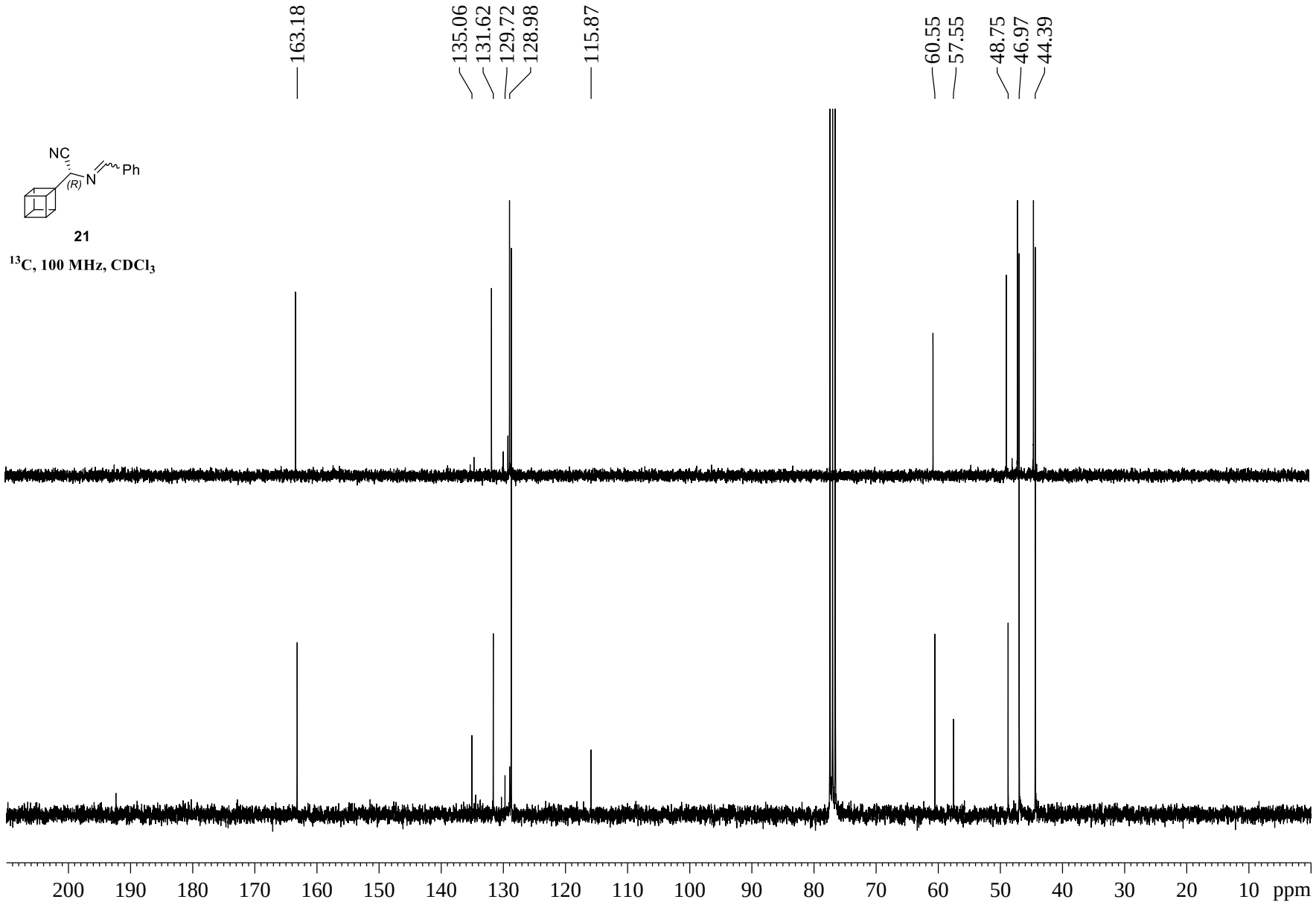


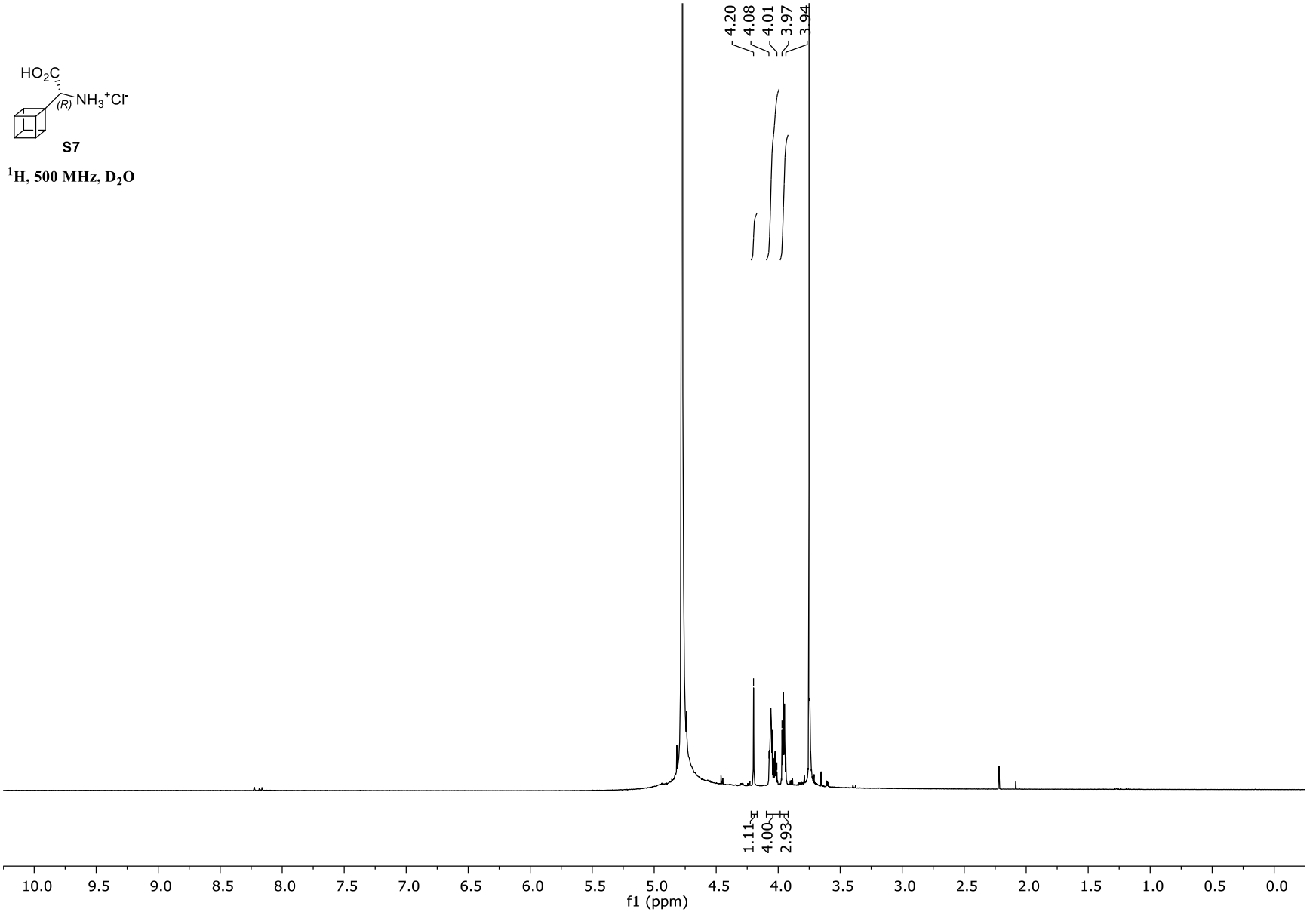
20

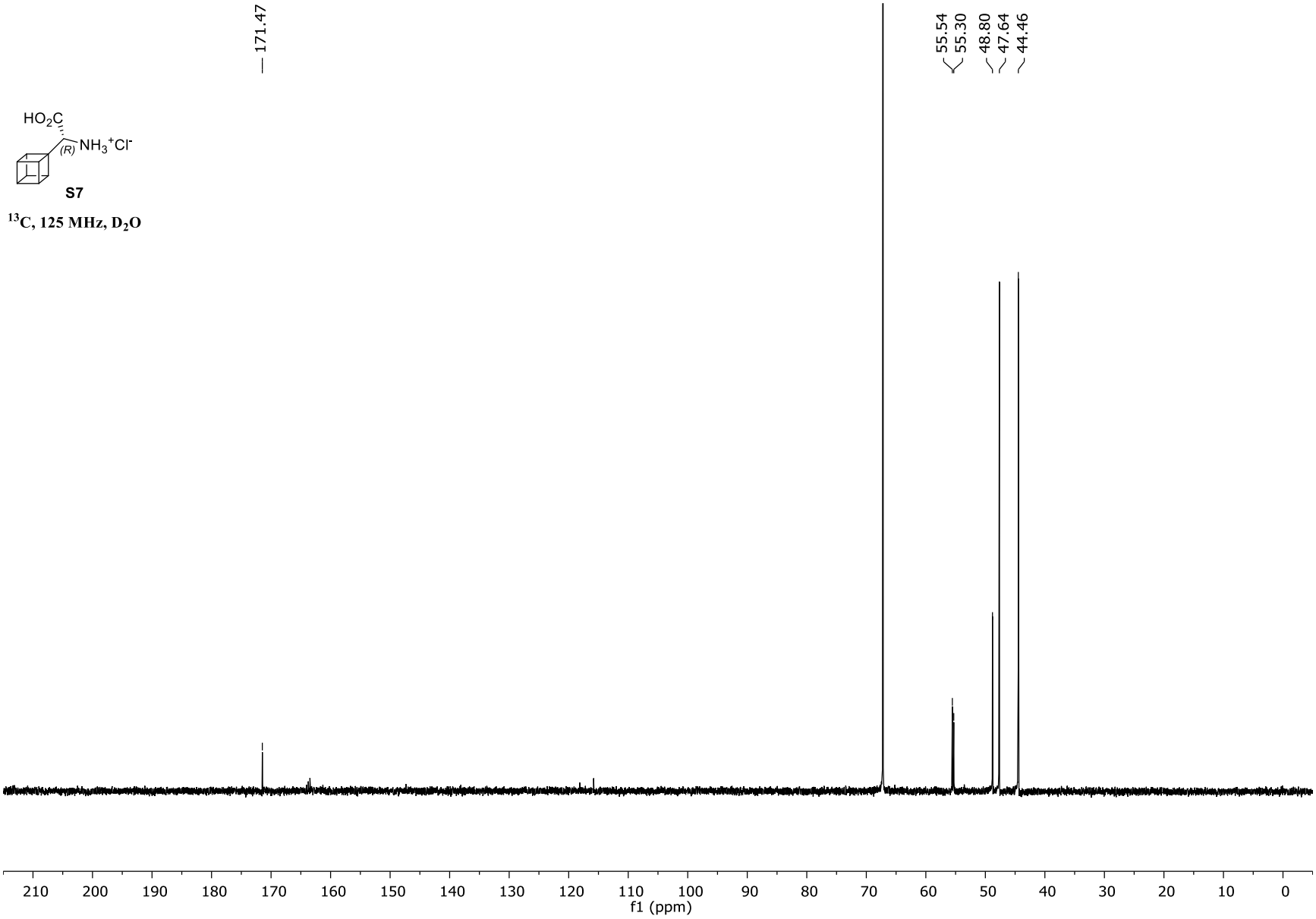
^{1}H, 400 MHz, $CDCl_3$

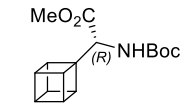

138.15
128.88
128.33
127.74
117.90
67.26
62.99
56.77
50.21
48.56
46.85
44.37
NC
Ph
(S)
OH
(R)
N
H
20
13C, 100 MHz, CDCl3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


8.48
7.78
7.44
4.85
4.85
4.04
3.94
NC
(R)
N
Ph
21
1H, 400 MHz, CDCl3
9.5
9.0
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
ppm
0.951
1.934
3.000
0.947
3.885
2.913


163.18
135.06
131.62
129.72
128.98
115.87
60.55
57.55
48.75
46.97
44.39
NC
(R)
N
Ph
21
^{13}C, 100 MHz, CDCl$_3$
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

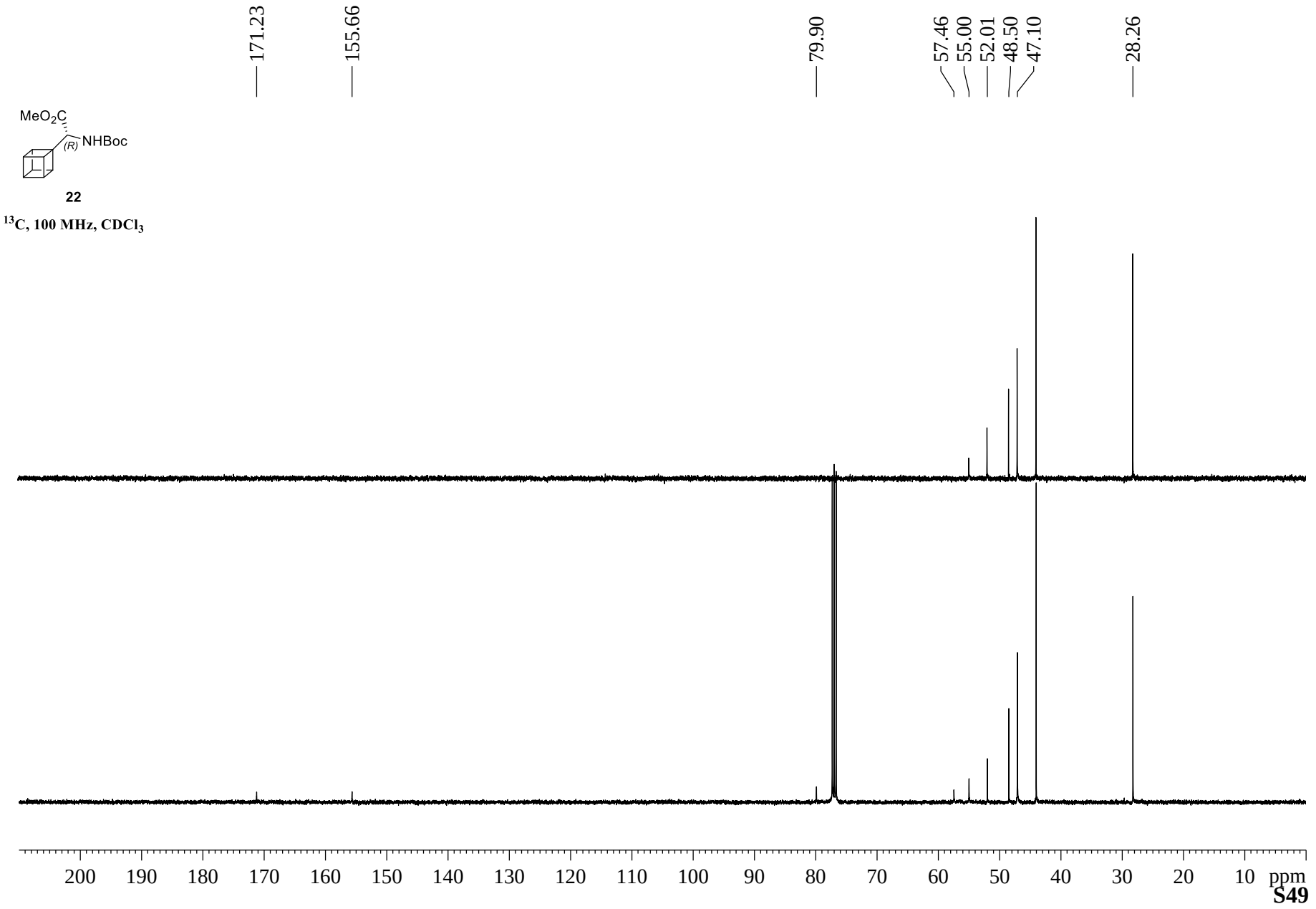

HO2C
(R)
NH3+Cl-
S7
1H, 500 MHz, D2O
4.20
4.08
4.01
3.97
3.94
1.11
4.00
2.93
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


171.47
55.54
55.30
48.80
47.64
44.46
HO2C
(R) NH3+Cl-
S7
13C, 125 MHz, D2O
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



22

^{1}H, 400 MHz, $CDCl_3$


171.23
155.66
79.90
57.46
55.00
52.01
48.50
47.10
28.26
MeO2C
(R) NHBoc
22
13C, 100 MHz, CDCl3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

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