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Supporting Information for

Application of the Lithiation-Borylation Reaction to the Rapid and Enantioselective Synthesis of the Bisabolane Family of Sesquiterpenes

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1. General Information

^{1}H NMR spectra were recorded at indicated field strengths using $CDCl_3$ (7.27 ppm) as the internal standard. ^{1}H NMR coupling constants are reported in Hz and refer to apparent multiplicities and not true coupling constants. Data are reported as follows: chemical shift, multiplicity (s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, quin = quintet, sex = sextet, sp = septet, m = multiplet, dd = doublet of doublet, etc.), integration and assignment. ^{13}C NMR spectra were recorded at indicated field strengths with complete proton decoupling using CDCl3 as an internal standard (77.0 ppm), Carbon nuclei attached to boron are not observed in ^{13}C NMR due to quadrupolar relaxation. ^{11}B NMR spectra were recorded at indicated field strengths with complete proton decoupling and using $BF_3 \cdot Et_2O$ (0.0 ppm) as an external standard. All IR data was obtained on a Perkin-Elmer Spectrum One FT-IR spectrometer. Optical rotations were obtained on a Perkin-Elmer 241MC polarimeter. High resolution mass spectra were recorded using Electronic Ionization (EI), Electron Spray Ionization (ESI) or Chemical Ionization (CI).

Analytical TLC was carried out using aluminium backed plates pre-coated (0.25 mm) with Merck Silica Gel 60 F_{254}. Compounds were visualized by exposure to UV-light or by dipping the plates in PMA or $KMnO_4$ followed by heating. Flash chromatography was carried out using Merck Silica Gel 60, 230-400 mesh. Chiral HPLC was performed on Agilent 1100 equipped with HP Chemstation software using Daicel Chiralpak IA, IB or IC columns (4.6 × 250 mm × 5 μm) fitted with guards (4 × 10 mm), and monitored by DAD (Diode Array Detector).

All air- and water-sensitive reactions were carried out in oven-dried glassware under an Ar atmosphere using standard Schlenk manifold technique. Anhydrous solvents were purified by means of a Grubbs-type solvent system and stored over 4 Å molecular sieves under Ar.[1] TMEDA was distilled over CaH_2 and stored under Ar.

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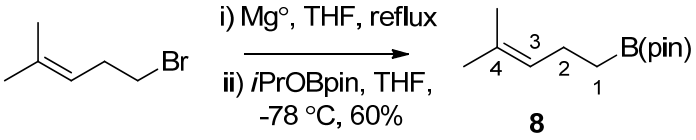
2. Abbreviations

Et_2O	diethyl ether
THF	tetrahydrofuran
EtOAc	ethyl acetate
TMEDA	tetramethylethylenediamine
MeOH	methanol
NMR	nuclear magnetic resonance
PE	petroleum ether
s-BuLi	sec-butyl lithium
tBu	tert-butyl
d.r./dr	diastereomeric ratio
e.r./er	enantiomeric ratio
DCM	dichloromethane
IPA	isopropanol
TBAF	tetra-*n*-butyl ammonium fluoride
CbCl	*N,N'*-diisopropylcarbamoyl chloride
BHT	butylated hydroxy toluene (2,6-di-*tert*-butyl-4-methylphenol)
PhMe	Toluene
AcCl	Acetyl chloride
DMF	dimethylformamide
CAN	Ceric ammonium nitrate

3. Experimental details

4,4,5,5-tetramethyl-2-(4-methylpent-3-enyl)-1,3,2-dioxaborolane 8



8

To a suspension of magnesium filings (0.88 mg, 37 mmol) in THF (10 mL) activated with dibromoethane, was added 5-bromo-2-methyl-2-pentene (2.0 g, 12 mmol) dropwise. After the initial exotherm had subsided the solution was refluxed for 4 h. The reaction mixture was added dropwise to a solution of *i*PrOBpin (3.1 mL, 15 mmol) in THF (10 mL) at −78 °C and stirred for 20 min. The reaction was allowed to warm to rt at which point the grey precipitate formed was observed to dissolve. The reaction mixture was cooled to 0 °C and $NH_4Cl_{(aq)}$ (20 mL) was added before warming to rt. The layers were separated and the aqueous layer extracted with Et_2O (3 × 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (3% EtOAc/PE, SiO_2) gave **8** (1.6 g, 60%) as an oil.

***R*f** (10% EtOAc/PE) 0.75;

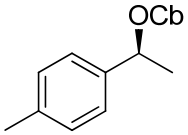
^{1}H NMR (400 MHz; $CDCl_3$) δ 5.12 (tsept, J = 7.2, 1.5 Hz, 1H, 3-H), 2.09 (apparent q, J = 7.7 Hz, 2H, 2-H_2), 1.67 (d, J = 1.5 Hz, 3H, CH_3), 1.61 (apparent s, 3H, CH_3), 1.24 (s, 12H, 2 × $OC(CH_3)_2$), 0.82 (t, J = 7.7 Hz, 2H, 1-H_2);

^{13}C NMR (100 MHz, $CDCl_3$) δ 130.5 (C-4), 126.9 (C-3), 83.0 (2 ×$OC(CH_3)_2$), 25.81 (CH_3), 24.9 (2 ×$OC(CH_3)_2$), 22.6 (CH_3), 17.8 (C-2);

^{11}B NMR (96 MHz, Et_2O) δ 33;

IR($CDCl_3$) ν_{max}/cm^{-1}2981 (C-H), 1380 (B-O), 1144 (B-C);

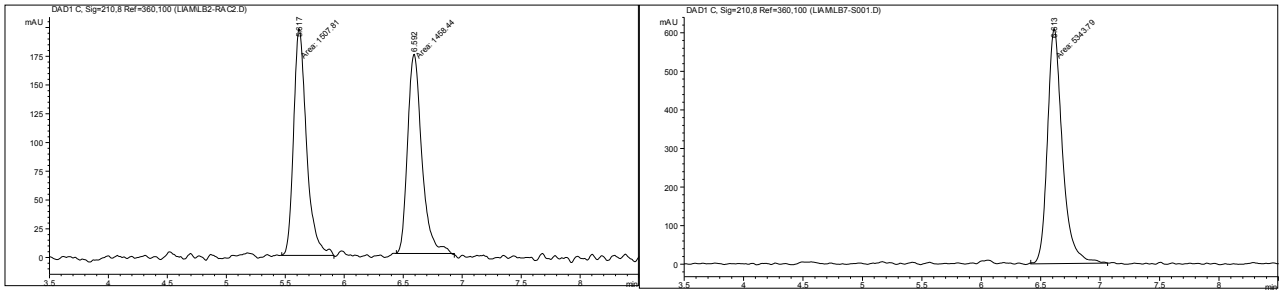
(*S*)-1-tolylethyl diisopropylcarbamate 7a



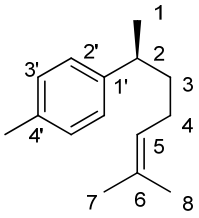
7a

Prepared according to the procedure of T.G. Elford *et* al.[2] (93%, 99:1 e.r.)

HPLC (Chiralpak® IA, 210 nm, 10% isopropanol/*n*-hexane, 0.7 mL min^{-1}), t_r**:** minor (*R*) 5.6 min, major (*S*) 11.8 min.



(*S*)-(+)-α-Curcumene 1



1

s-BuLi (1.3 M in cyclohexane/hexane (92:8); 0.38 mL, 0.49 mmol) was added dropwise to a solution of **7a** (0.10 g, 0.38 mmol, e.r. >99:1) in Et_2O (1.5 mL) at –78 °C, such that the temperature of the reaction did not rise above –70 °C. After stirring for 15 minutes, **8** (1.0 M in Et_2O; 0.57 mL, 0.57 mmol) was added dropwise, such that the temperature of the reaction did not rise above –70 °C. The solution was allowed to stir at –78 °C for a further 1 hour, before $MgBr_2 \cdot OEt_2$ (1.0 M in MeOH; 0.57 mL, 0.57 mmol) was added dropwise. The reaction was allowed to stir at room temperature for 2 h before NaH_2PO_4 (1.0 M aq.; 5.0 mL, 5.0 mmol) was added to the reaction mixture. The layers were separated and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting oil was dissolved in pentane (2 mL), TBAF·$3H_2O$ (0.17 g, 0.57 mmol) was added, and the mixture heated at 50 °C (sealed tube) for 12 h. After cooling to room temperature, the reaction mixture was filtered through silica and concentrated *in vacuo*. Purification by flash column chromatography (0→2% Et_2O/PE; SiO_2) gave (*S*)-(+)-α-curcumene **1** (0.065 g, 85%, e.r. 98:2) as a colourless oil. Characterization data were consistent with literature[3]

R_f (100% PE) 0.7;

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.15-7.10 (m, 4H, ArH), 5.13 (tsept., J = 7.1, 1.4 Hz, 1H, 5-H), 2.69 (apparent sext, J = 7.1 Hz, 1H, 2-H), 2.35 (s, 3H, $ArCH_3$), 1.97-1.86 (m, 2H, 4-H_2),

1.71 (br. s, 3H, 7-H_3), 1.68-1.56 (m, 2H, 3-H_2), 1.56 (br. s, 3H, 8-H_3), 1.25 (d, J = 7.1 Hz, 3H, 1-H_3);

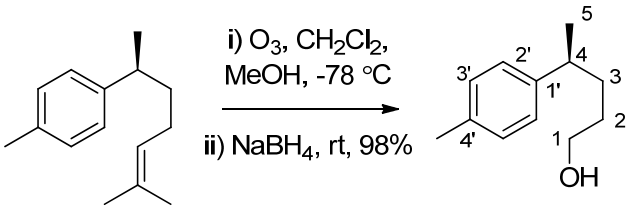
^{13}C NMR (100 MHz, $CDCl_3$)**:** δ 144.6 (C-1'), 135.1 (C-4'), 131.4 (C-6), 128.9 (2 × C-3'), 126.9 (2 × C-2'), 124.6 (C-5), 39.0 (C-2), 38.5 (C-3), 26.2 (C-7), 25.7 (C-4), 22.5 (C-1), 21.0 ($ArCH_3$), 17.7 (C-8);

IR(neat)ν_{max}/cm^{-1}**:** 2920 (C-H), 1514, 1452 (CH_3), 1375 (CH_3), 1020, 814 (Ar C-H).

$[\alpha]_D^{23}$ +34.2 (*c.* 0.76, $CHCl_3$) (Lit.:[S8] $[\alpha]_D^{25}$ +42.7 (*c.* 1.0, $CHCl_3$)).

e.r. inferred from that of **S1** (*vide infra*).

(*S*)-(+)-4-*p*-Tolylpentan-1-ol S1



1 **S1**

A stream of O_3/O_2 was passed through a solution of (*S*)-(+)-α-curcumene **1** (36 mg, 0.18 mmol) in CH_2Cl_2/MeOH (1:1 v/v; 8.5 mL) at –78 °C until a blue tinge persisted (*ca* 15 min). A stream of N_2 was then passed through the solution until loss of colouration (*ca* 15 min). $NaBH_4$ (48 mg, 1.3 mmol) was added, and the solution allowed to warm to room temperature. After stirring at room temperature for 2 h the solvent was removed *in vacuo*, and the residue dissolved in Et_2O (10 mL) and H_2O (10 mL) was added. The layers were separated and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic phases were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give alcohol **(*S*)-S1** (0.030 g, 98%, e.r. 98:2) as a colourless oil. Characterization data were consistent with literature.[3]

***R*$_f$:** (30% EtOAc/PE). 0.21;

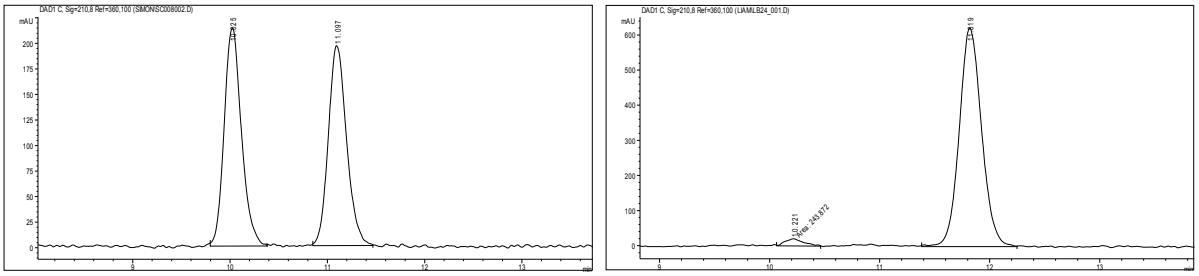
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13-7.08 (m, 4H, ArH), 3.60 (t, J = 6.5 Hz, 2H, 1-H_2), 2.68 (apparent sext, J = 7.0 Hz, 1H, 4-H), 2.33 (s, 3H, $ArCH_3$), 1.67-1.61 (m, 2H, 2-H_2), 1.57-1.40 (m, 2H, 3-H_2), 1.26 (d, J = 7.0 Hz, 3H, 7-H_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ 144.3 (C-1'), 135.4 (C-4'), 129.0 (2 × C-Ar), 126.8 (2 × C-Ar), 63.1 (C-1), 39.3 (C-4), 34.4 (C-2), 31.0 (C-3), 22.5 (C-5), 21.0 ($ArCH_3$).

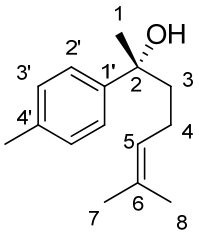
IR(neat)ν_{max}/cm^{-1}**:** 3327 (br., O-H), 2924 (C-H), 1514, 1455 (CH_3), 1375 (CH_3), 1057 (C-O), 815 (Ar C-H).

$[\alpha]_D^{22.5}$ +6.6 (*c.* 0.60, $CHCl_3$) (Lit.:[S8] $[\alpha]_D^{25}$ +30.1 (*c.* 1.0, $CHCl_3$)).

HPLC (Chiralpak® IB, 210 nm, 5% isopropanol/*n*-hexane, 0.7 mL min^{-1}), t_r**:** minor (*R*) 10.2 min, major (*S*) 11.8 min.



(*R*)-(+)-Gossonorol 2



2

s-BuLi (1.3 M in cyclohexane/hexane (92:8); 0.76 mL, 0.98 mmol) was added to a solution of carbamate **7a** (0.20 g, 0.76 mmol) in Et_2O (3 mL) at –78 °C, such that the temperature of the reaction did not rise above –70 °C. After stirring for 15 minutes, pinacol boronic ester **8** (1.0 M in Et_2O; 1.14 mL, 1.14 mmol) was added slowly, such that the temperature of the reaction did not rise above –70 °C. The solution was allowed to stir at –78 °C for a further 1 h, before $MgBr_2 \cdot OEt_2$ (1.0 M in MeOH; 1.14 mL, 1.14 mmol) was added dropwise. The reaction was warmed to rt and stirred for 2 h before THF containing BHT (~6 mg in 5 mL) was added to the reaction mixture. The reaction was cooled to 0 °C and a solution of $NaOH_{(aq)}$ (2.0 M, 2.4 mL, 4.8 mmol) and $H_2O_{2(aq)}$ (30% w/v, 0.92 mL, 9.0 mmol) was added. The resulting biphasic mixture was warmed to rt and stirred for 12 h. The reaction was diluted with H_2O (10 mL), the layers separated and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic phases washed with brine (15 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (10%

EtOAc/PE, SiO_2) gave (*R*)-(+)-gossonorol **2** (0.141 g, 85%, e.r. 98:2) as a colourless oil. Characterization data were consistent with literature.[4]

***R*$_f$:** 0.28 (10% EtOAc/PE).

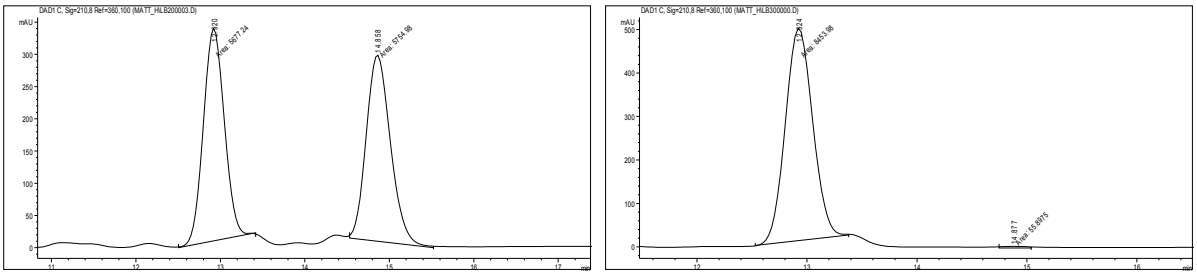
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (d, *J* = 7.8 Hz, 2H, 2 × 2'-H), 7.17 (d, *J* = 7.8 Hz, 2H, 2 × 3'-H), 5.12 (tsept., *J* = 7.0, 1.3 Hz, 1H, 5-H), 2.36 (s, 3H, Ar-CH_3), 2.02-1.81 (m, 5H, 3-H_2, 4-H_2 and OH), 1.67 (br. s, 3H, 7-H_3), 1.55 (s, 3H, 1-H_3), 1.52 (br. s, 3H, 8-H_3);

^{13}C NMR (100 MHz, $CDCl_3$) δ 144.9 (C-1'), 135.9 (C-4'), 132.1 (C-6), 128.8 (2 × C-Ar), 124.7 (2 × C-Ar), 124.2 (C-5), 74.8 (C-2), 43.7 (C-3), 30.5 (C-1), 25.7 (C-7), 22.9 (C-4), 20.9 (ArCH_3), 17.6 (C-8).

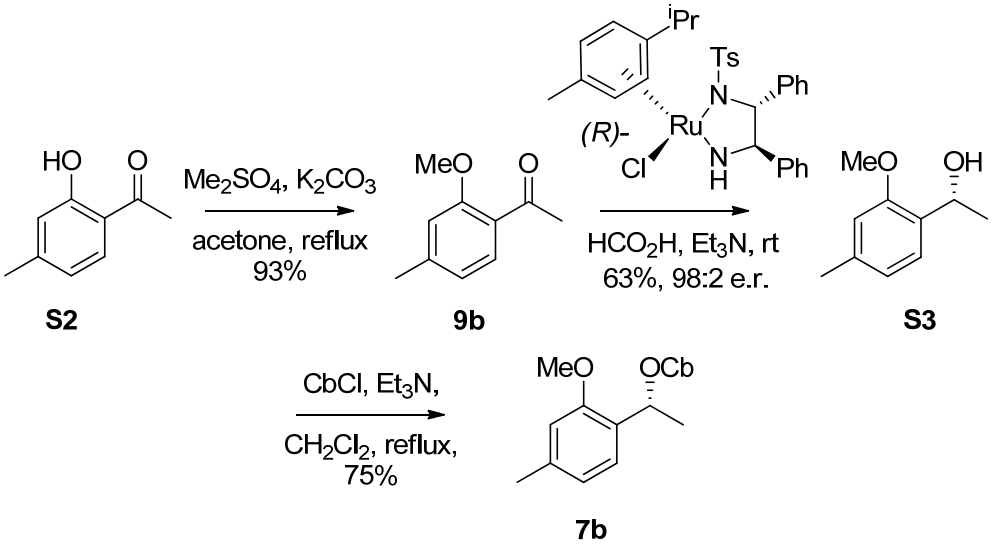
IR(neat)ν_{max}/cm^{-1}**:** 3430 (br., O-H), 2968 (C-H), 2922 (C-H), 1513 (CH_3), 1374 (CH_3), 1019 (C-O), 817 (Ar C-H).

$[\alpha]_D^{23.2}$ +6.0 (*c.* 1.0, $CHCl_3$).

HPLC (Chiralpak® IA, 210 nm, 3% isopropanol/*n*-hexane, 0.7 mL min^{-1})**, *t*$_r$:** major (*R*) 12.9 min, minor (*S*) 14.7 min.



Synthesis of (*R*)-(-)-Curcuphenol **3**



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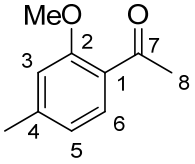
2-Methoxy-4-methylacetophenone S2



9b

K_2CO_3 (9.4 g, 68 mmol) and dimethyl sulfate (2.7 mL, 29 mmol) were added to a solution of 2′-hydroxy-4′-methylacetophenone **S2** (3.8 mL, 27 mmol) in anhydrous acetone (50 mL), and the mixture was heated at reflux for 36 h. After cooling to room temperature the suspension was filtered through Celite. The reaction was diluted with H_2O (100 mL) and the aqueous phase extracted with EtOAc (3 × 75 mL). The combined organic phases were washed sequentially with H_2O (100 mL) and brine (75 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (15% EtOAc/PE, SiO_2) gave methyl ether **9b** (4.14 g, 93%) as white needles, mp 36-38 °C (Lit.[55] 35-37 °C). All analytic data corresponded to that reported in the literature.[5]

***R*$_f$** (25% EtOAc/PE) 0.5;

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, *J* = 7.9 Hz, 1H, 6-ArH), 6.82 (d, *J* = 7.9 Hz, 1H, 5-ArH), 6.77 (s, 1H, 3-ArH), 3.90 (s, 3H, OMe), 2.59 (s, 3H, 8-H_3), 2.38 (s, 3H, $ArCH_3$).

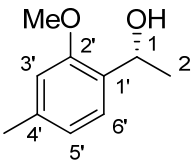
^{13}C NMR (100 MHz, $CDCl_3$): δ 199.1 (C=O), 159.1 (C-6), 144.8 (C-4), 130.5 (C-6), 125.4 (C-1), 121.3 (C-5), 112.2 (C-3), 55.3 (OMe), 31.8 (C-8), 21.8 ($ArCH_3$).

IR ($CHCl_3$) ν_{max}/cm^{-1} 1668 (C=O), 1607 (Ar-H), 1359 (OMe);

m/z (%) (EI) 164 (25, M^+), 149 (100), 91 (30);

Anal Calc'd for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37; Found: C, 73.39; H, 7.43.

(*R*)-(+)-1-(2′-Methoxy-4′-methylphenyl)ethanol S3



S3

HCO_2H (0.6 mL, 15 mmol) was added slowly to triethylamine (0.9 mL, 6 mmol) at 0 °C. The mixture was allowed to warm to room temperature before addition of **9b** (0.46 g, 2.81 mmol) and (*R*)-RuCl[(1*R*,2*R*)-*p*-TsNCH(C_6H_5)CH(C_6H_5)NH_2](η^6-*p*-cymene) (19 mg, 0.03 mmol).

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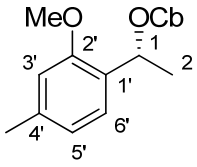
After stirring for 96 h, H_2O (15 mL) was added, and the aqueous phase was extracted with EtOAc (3 × 15 mL). The combined organic phases were washed sequentially with saturated aqueous $NaHCO_3$ solution (20 mL) and brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a black oil. Purification by flash column chromatography (25% EtOAc/PE, SiO_2) gave *alcohol* **S3** (296 mg, 63%, e.r. 98:2 inferred from **7b,** *vide infra*) as a colourless oil; unreacted ketone **S1** (0.074 g, 16%) was recovered as colourless needles.

***R*$_f$:** (25% EtOAc/PE) 0.33;
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22 (d, *J* = 7.7 Hz, 1H, 6'-Ar), 6.79 (d, *J* = 7.7 Hz, 1H, 5'-ArH), 6.72 (s, 1H, 3'-ArH), 5.07 (app. quin., *J* = 6.6 Hz, 1H, 1-H), 3.86 (s, 3H, OMe), 2.64 (br. d, *J* = 5.4 Hz, 1H, O*H*), 2.36 (s, 3H, Ar-CH_3), 1.51 (d, *J* = 6.6 Hz, 3H, 2-H_3);
^{13}C NMR (100 MHz, $CDCl_3$): δ 156.5 (C-2'), 138.3 (C-4'), 130.4 (C-6'), 125.9 (C-1'), 121.2 (C-5'), 111.4 (C-3'), 66.4 (C-2), 55.2 (OMe), 22.8 (C-1), 21.5 ($ArCH_3$).
IR(neat) ν_{max}/cm^{-1}**:** 3374 (O-H), 2969 (C-H), 1613 (Ar-H);
m/z (%) (EI) 166 (20, M^+), 151 (80), 133 (80), 121 (40), 105 (100), 91 (25), 77 (35);
Anal Calc'd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49; Found: C, 71.48; H, 8.42;
$[\alpha]^{4.2}$**:** +21.4 (*c.* 0.98, $CHCl_3$);

(*R*)-1-(2'-Methoxy-4'-methylphenyl)ethyl diisopropylcarbamate 7b



7b

Et_3N (0.29 mL, 2.1 mmol) was added dropwise to a solution of **S3** (0.28 g, 1.7 mmol) and CbCl (0.33 g, 2.0 mmol) in CH_2Cl_2 (8 mL) at rt, the reaction mixture was then heated to reflux and stirred for 96 h. The reaction was cooled to rt and quenched by addition of H_2O (10 mL), the layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo,* purification by flash column chromatography (10% EtOAc/PE, SiO_2) gave *carbamate* **7b** (0.37 g, 75%, e.r. 98:2) as a colourless oil.

***R*$_f$:** (10% EtOAc/PE). 0.31;

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24 (d, *J* = 7.6 Hz, 1H, 6'-ArH), 6.77 (d, *J* = 7.6 Hz, 1H, 5'-ArH), 6.69 (s, 1H, 3'-ArH), 6.15 (q, *J* = 6.4 Hz, 1H, 1-H), 4.09-3.78 (br. m, 2H, 2 × NC*H*$(CH_3)_2$), 3.82 (s, 3H, OMe), 2.34 (s, 3H, Ar-CH_3), 1.49 (d, *J* = 6.4 Hz, 3H, 2-H_3), 1.30- 1.20 (br. m, 12H, 2 × NCH(C*H*$_3)_2$);

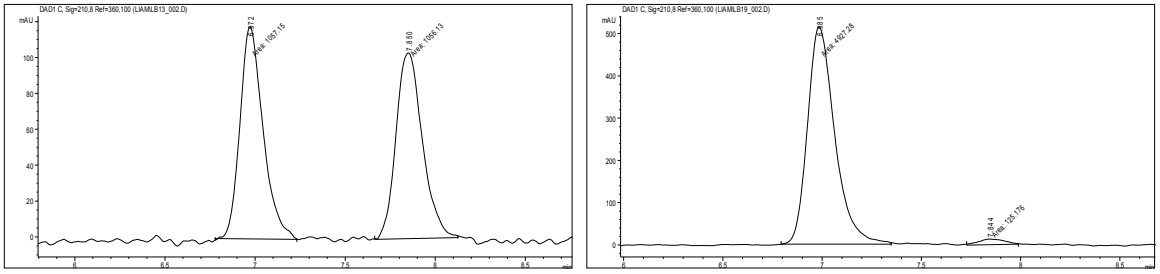
^{13}C NMR (100 MHz, $CDCl_3$): δ 155.8 (2'-C), 155.1 (C=O), 138.1 (4'-C), 128.7 (6'-C), 125.9 (1'-C), 121.0 (5'-C), 111.4 (3'-C), 67.8 (1-C), 55.3 (OMe), 45.7 (br., 2 × N*C*H$(CH_3)_2$), 21.9 (2-C), 21.5 (ArCH_3), 21.1 (br., 2 × NCH(*C*H$_3)_2$);

IR(neat) ν_{max}/cm^{-1}**:** 2969 (C-H), 2923 (C-H), 1685 (C=O);

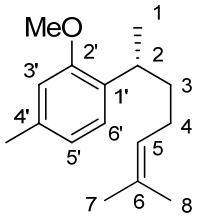
HRMS(ESI) Calc'd for $C_{17}H_{28}NO_3$ 294.2064 ($[M+H]^+$); Found 294.2063

$[\alpha]^{D}_{22.8}$**:** −12.2 (*c.* 0.98, $CHCl_3$).

HPLC (Chiralpak® IA, 210 nm, 3% isopropanol/*n*-hexane, 0.7 mL min−1)**, *t*r:** major (*R*) 7.0 min, minor (*S*) 7.8 min.



(*R*)-(−)-Curcuphenol methyl ether <u>10b</u>



10b

s-BuLi (1.3 M in cyclohexane/hexane (92:8); 0.11 mL, 0.14 mmol) was added to a solution of **7b** (32 mg, 0.11 mmol) and TMEDA (26 µL, 0.17 mmol) in Et_2O (1.0 mL) at –78 °C, such that the temperature of the reaction did not rise above –70 °C. After stirring for 1 h, **8** (1.0 M in Et_2O; 0.17 mL, 0.17 mmol) was added slowly, such that the temperature of the reaction did not rise above −70 °C. The solution was allowed to stir at −78 °C for a further 1 h, before $MgBr_2$ OEt_2 (1.0 M in MeOH; 0.18 mL, 0.18 mmol) was added dropwise. The cooling bath was removed, and the reaction allowed to stir at room temperature for 4 h before addition of NaH_2PO_4 (1.0 M aq.; 1.5 mL). The layers were separated, the aqueous phase extracted with

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Et_2O (3 × 10 mL), and the combined organic phases dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting oil was dissolved in PhMe (1.0 mL), TBAF·$3H_2O$ (52 mg, 0.17 mmol) was added, and the mixture heated at 50 °C for 12 h. After cooling to room temperature, filtration through SiO_2 and concentration *in vacuo*, purification by flash column chromatography (5% EtOAc/PE, SiO_2) gave (*R*)-(−)-curcuphenol methyl ether **10b** (17 mg, 58%) as a colourless oil. Characterisation data were consistent with those reported in the literature.[3]

***R*$_f$:** (5% EtOAc/PE) 0.47;

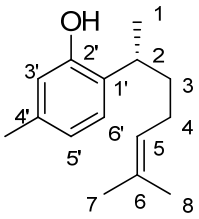
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (d, *J* = 7.7 Hz, 1H, 6'-ArH), 6.76 (d, *J* = 7.7 Hz, 1H, 5'-ArH), 6.69 (s, 1H, 3'-ArH), 5.13 (tsept., *J* = 7.1, 1.4Hz, 1H, 5-H), 3.82 (s, 3H, OMe), 3.15 (apparent sext, *J* = 7.1 Hz, 1H, 2-H), 2.35 (s, 3H, $ArCH_3$), 2.03-1.85 (m, 2H, 4-H_2), 1.71-1.62 (m, 1H, 3-H*H*), 1.69 (br. s, 3H, 7-H_3), 1.58-1.49 (m, 1H, 3-*H*H) 1.56 (br. s, 3H, 8-H_3), 1.19 (d, *J* = 7.1 Hz, 3H, 1-H_3);

^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9 (C-2'), 136.2 (C-4')', 132.8 (C-1'), 131.1 (C-6), 126.5 (C-6'), 124.9 (C-5), 121.1 (C-5'), 111.5 (C-3'), 55.3 (OMe), 37.2 (C-3), 31.4 (C-2), 26.3 (C-4), 25.7 (C-7), 21.4 ($ArCH_3$), 21.1 (C-1), 17.6 (C-8).

IR(neat)ν_{max}/cm^{-1}**:** 2917 (C-H), 1612 (Ar-H), 1506,1452 (CH_3), 1258 (C-O-C (Ar C-H).

$[\alpha]_D^{23.1}$ −3.9 (*c*. 0.26, $CHCl_3$) (Lit.:[S8] $[\alpha]_D^{25}$ −5.8 (*c*. 1.0, $CHCl_3$)).

(*R*)-(-)-Curcuphenol 3



3

A solution of EtSH (28 µL, 0.38 mmol) in DMF (1 mL) was added dropwise to NaH (60% dispersion in mineral oil, 15 mg, 0.38mmol), previously washed with anhydrous hexane (3 × 1mL), in DMF (1 mL) at rt. A solution of **10b** (18 mg, 0.08 mmol) in DMF (0.5mL) was added and the reaction was heated to 120 °C and stirred for 24 h. The reaction was cooled to rt and 1M $HCl_{(aq)}$ (0.5 mL) and H_2O (2 mL) were added to the reaction mixture. The aqueous phase was extracted with Et_2O (3 × 5 mL) and the combined organic phases were washed

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with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (5% Et_2O/PE, SiO_2) gave (*R*)-(-)-curcuphenol **3** (14 mg, 81%, e.r. 96:4) as a colourless oil. Characterisation data were consistent with those reported in the literature.[3]

***R*f:** (5% EtOAc/PE) 0.18;

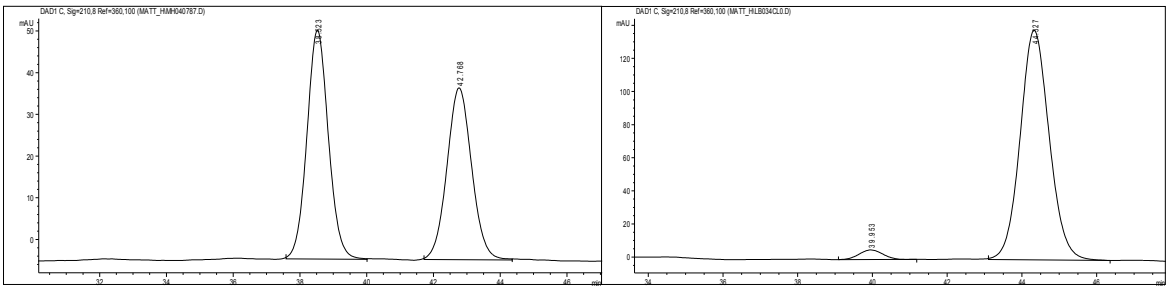
^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.05 (d, *J* = 7.8 Hz, 1H, 6'-ArH), 6.73 (d, *J* = 7.8 Hz, 1H, 5'-ArH), 6.60 (s, 1H, 3'-ArH), 5.14 (tsept, *J* = 7.0, 1.4 Hz, 1H, 5-H), 4.63 (s, 1H, OH), 2.97 (apparent sext, *J* = 7.0 Hz, 1H, 2-H), 2.28 (s, 3H, $ArCH_3$), 2.03-1.92 (m, 2H, 4-H_2), 1.72-1.56 (m, 2H, 3-H_2), 1.70 (br. s, 3H, 7-H_3), 1.55 (br. s, 3H, 8-CH_3), 1.24 (d, *J* = 7.0 Hz, 3H, 1-H_3);

^{13}C NMR (126 MHz, $CDCl_3$): δ = 152.8 (C-2'), 136.5 (C-4'), 132.0 (C-1'), 129.9 (C-6), 126.8 (C-6'), 124.6 (C-5), 121.7 (C-5'), 116.2 (C-3'), 37.3 (C-3), 31.4 (C-2), 26.1 (C-4), 25.7 (C-7), 21.1 ($ArCH_3$), 20.9 (C-1), 17.7 (C-8).

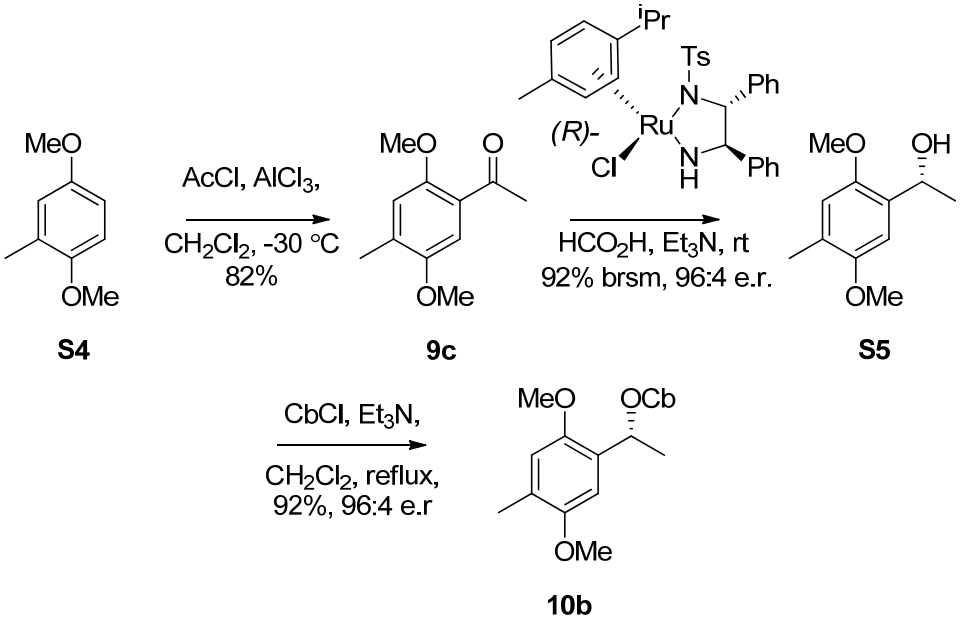
IR(neat)ν_{max}/cm^{-1}: 3340 (br., OH), 2925 (C-H), 1507,1446 (CH_3), 1120 (C-OH), 806 (Ar C-H);

$[\alpha]_D^{21.3}$: −18.4 (*c.* 0.40, $CHCl_3$) (Lit.: [S10] $[\alpha]_D^{25}$: −20.9 (*c.* 1.0, $CHCl_3$))

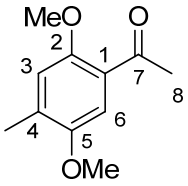
HPLC (Chiralpak® IA, 210 nm, 1% isopropanol/*n*-hexane, 0.7 mL min−1), ***t*r:** minor (*S*) 39.9 min, major (*R*) 44.8 min.



Synthesis of (*R*)-(-)-curcuquinone **5** and (*R*)-(-)-curcuhydroquinone **4**



1-(2,5-Dimethoxy-4-methylphenyl)acetophenone 9c



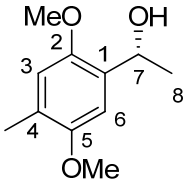
9c

1,4-dimethoxy-2-methylbenzene **S4** (2.0 mL, 17.4 mmol) was added to a solution of AcCl (3.1 mL, 43.5 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was cooled to -30 °C and $AlCl_3$ (2.78 g, 20.9 mmol) was added in portions to the reacting mixture at -30 °C. The reaction mixture was stirred for 2 h at -30 °C, before pouring onto H_2O and ice (200 mL). The slurry was diluted with CH_2Cl_2 (100 mL), the layers separated and the aqueous layer extracted with CH_2Cl_2 (3 × 100 mL). The combined organic phases were washed with H_2O (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (10% EtOAc/PE, SiO_2) gave ketone **9c** (2.76 g, 82%) as colourless needles (mp 74-76 °C (CH_3Cl), (lit.: [S8] 76 °C (hexane));. Characterisation data were consistent with those reported in the literature.[5]

R_f = 0.40 (10% EtOAc/PE);

^{1}H NMR (400 MHz, $CDCl_3$) 7.29 (s, 1H, 3-ArH), 6.79 (s, 1H, 6-ArH), 3.88 (s, 3H, OMe), 3.82 (s, 3H, OMe), 2.62 (s, 3H, 8-H_3), 2.26 (s, 3H, $ArCH_3$);
^{13}C NMR (101MHz, $CDCl_3$) 198.7 (C=O), 153.6 (C-5), 151.6 (C-2), 133.7 (C-1), 125.3 (C-4), 114.8 (C-3), 110.9 (C-6), 56.0 (OMe), 55.8 (OMe), 32.0 (C-8), 16.7 ($ArCH_3$);
IR(neat)ν_{max}/cm^{-1}**:** 1661 (C=O) , 1610 (ArH), 1398 (CH_3), 1214 (C-O-C), 1042 (C-O-C), 886, 802 (Ar C-H);
***m/z* (EI)** 195(M^+ + 1,6%), 194 (M^+, 51), 179 (M^+ -H_2O 100), 164 (M –CH_3 –H_2O, 9),

(+)-(*R*)-1-(2,5-Dimethoxy-4-methylphenyl)ethanol S5



S5

HCO_2H (6 mL, 140 mmol) was added slowly to Et_3N (9 mL, 60 mmol) at 0 °C. The mixture was stirred for 10 minutes at 0 °C and was allowed to warm to room temperature. Acetophenone **9c** (5.00 g, 25 mmol) and RuCl[(1R, 2R)-p-TsNCH(C_6H_5)CH(C_6H_5)NH_2](η^6-p-cymene) (163 mg, 0.25 mmol, 0.01 eq) were added and the reaction was stirred at rt for 10 days. H_2O (100 mL) was added and the reaction was extracted with Et_2O (3 × 100 mL). The combined organic phases were washed sequentially with saturated $NaHCO_{3(aq)}$ (100 mL) and brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (10→15% EtOAc/PE, SiO_2) gave *alcohol* **S5** (2.63 g, 52%, 92% bsrm, e.r. 96:4 inferred from **7c**) as colourless needles (mp= 46-48 °C (PE));

***R*$_f$** (15% EtOAc:PE) 0.25;
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.87 (s, 1H, 6-ArH), 6.71 (s, 1H, 3-ArH), 5.08 (q, *J* = 6.7 Hz, 1H, 7-H), 3.82 (s, 3H, OMe), 3.81 (s, 3H, OMe), 2.68 (br. s., 1H, OH), 2.23 (s, 3H, $ArCH_3$), 1.50 (d, *J* = 6.7 Hz, 3H, 8-H_3);
^{13}C NMR (101 MHz, $CDCl_3$) δ 151.7 (C-5), 150.0 (C-2), 131.4 (C-1), 125.9 (C-4), 113.8 (C-3), 108.8 (C-6), 66.5 (C-7), 56.0 (OMe), 55.9 (OMe), 23.2 (C-8), 16.2 ($ArCH_3$).

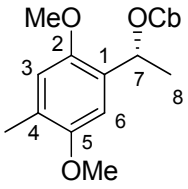
IR(neat)ν_{max}/cm^{-1}**:** 3489 (br. O-H), 2932 (C-H), 1453 (CH_3), 1202 (C-O-C), 1080, 1040 (C-O-C), 824 (Ar C-H).

***m/z* (EI)** 207.1 (11), 197.1 (M+2%, 16), 196.1 (M, 30), 179.1 (M –OH, 100), 178.1 (M – H_2O, 34), 164.1 (M – 2 × CH_3 –H_2O, 8).

HRMS (CI): calculated for $C_{11}H_{17}O_3$: 197.1178 found 197.1171.

$[\alpha]_D^{20.1}$**:** +6.81 (*c.* 0.29, $CHCl_3$)

(*R*)-1-(2,5-Dimethoxy-4-methylphenyl)ethyl diisopropylcarbamate 7c



7c

Alcohol **S5** (100 mg, 0.51 mmol) was added to a solution of NaH (60% dispersion in mineral oil, 31 mg, 0.76 mmol), previously washed with hexane (3 × 0.5 mL), in THF (3 mL) at rt and the reaction was stirred for 1 h. CbCl (102 mg, 0.62 mmol) was added and the reaction was then stirred at reflux for 16 h. The reaction was cooled to rt and H_2O (5 mL) was added dropwise. The layers were separated and the aqueous phase was extracted with Et_2O (3 × 10 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (10% EtOAc/PE, SiO_2) gave *carbamate* **7c** (157 mg, 92%, e.r. 96:4) as colourless needles (mp 77-79 °C (PE)) after crystallisation.

^{1}H NMR (400MHz, $CDCl_3$) δ 6.87 (s, 1H, 6-ArH), 6.69 (s, 1H, 3-ArH), 6.14 (q, *J* = 6.5 Hz, 1H, 7-H), 4.28-3.68 (br. m., 2H, 2 × NC*H*$(CH_3)_2$), 3.80 (s, 3H, OMe), 3.78 (s, 3H, OMe), 2.21 (s, 3H, $ArCH_3$), 1.50 (d, *J* = 6.5 Hz, 3H, 8-H_3), 1.27 (br. m., 12H, 2 × NCH(C$H_3)_2$).

^{13}C NMR (101MHz, $CDCl_3$) δ 155.0 (C=O), 151.7 (C-5), 149.5 (C-2), 129.6 (C-1), 125.9 (C-4), 114.2 (C-3), 108.6 (C-6) , 68.1 (C-7), 56.2 (OMe), 55.9 (OMe), 46.0 (br. 2 × N*C*H$(CH_3)_2$), 22.1 (C-8), 21.0 (br. 2 × NCH(CH$_3)_2$), 16.2 ($ArCH_3$).

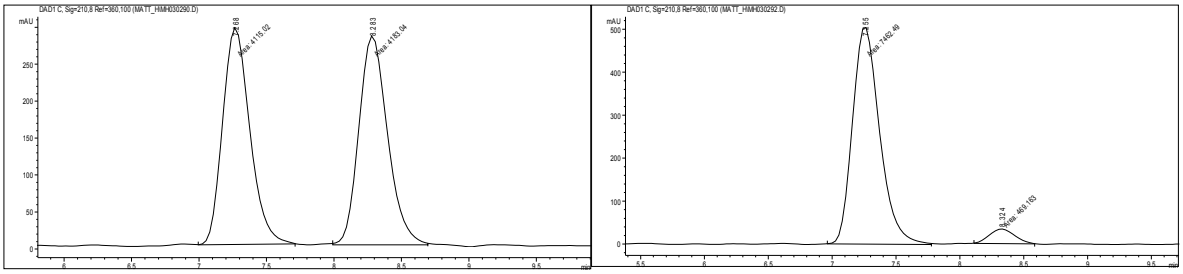
IR(neat)ν_{max}/cm^{-1}: 2968 (C-H), 1683 (C=O), 1428 (CH_3), 1287 (C-O-C), 1044 (C-O-C), 794 (Ar C-H);

m/z (CI) 385.2 (3), 324.2 (M + 1%, 2), 323.2 (M, 16), 180.1 (13), 179.1 (M -HOCb, 100), 178.1 (M – Cb –H_2O, 35);

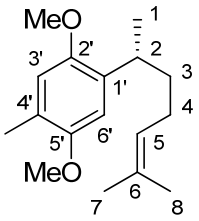
HRMS (CI): calculated for $C_{18}H_{29}NO_4$: 323.2097 found 323.2091.

$[\alpha]_D^{21.4}$**:** +7.14 (*c.* 1.4, $CHCl_3$).

HPLC (Chiralpak® IB, 210 nm, 2% isopropanol/hexane, 0.8 ml/min),t_r= 9.3 min major (*R*), 11.4 min minor (S).



(*R*)-(-)-Curcuhydroquinone dimethyl ether **10c**



10c

s-BuLi (1.37 M in cyclohexane/hexane (92:8), 0.43 mL, 0.59 mmol) was added dropwise to a solution of carbamate **7c** (146 mg, 0.45 mmol) and TMEDA (0.09 mL, 0.59 mmol) in Et_2O (1.5 mL) at -78 °C such that the temperature of the reaction did not rise above –70 °C. After stirring for 15 minutes, a solution of pinacol boronic ester **8** (142 mg, 0.68 mmol) in Et_2O (0.4 mL) was then added dropwise over 10 min. The reaction was stirred at -78 °C for 2 h and a solution of $MgBr_2$ (1M in MeOH, 0.68 mL, 0.68 mmol) was then added and the reaction was warmed to rt and stirred overnight. The reaction was quenched with an aqueous solution of NaH_2PO_4 (1M, 8 mL), the layers were separated and the aqueous layer extracted into Et_2O (3 × 10 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. TBAF·$3H_2O$ (213 mg, 0.68 mmol) was added to a solution of the crude material in PhMe (3 mL) and the reaction heated to 50 °C and stirred for 20 h. The reaction was cooled to room temperature and filtered through SiO_2, eluting with pentane, the crude material was concentrated *in vacuo* and purified by flash column chromatography (5% EtOAc:PE, SiO_2) to give the Curcuhydroquinone dimethyl

ether **10c** as a clear, colourless oil (79 mg, 67%, 94:6 e.r.).All characterisation data matched that reported in the literature. [6]

R_f (5% EtOAc:PE) = 0.60

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.69 (s, 1H, 6'-ArH), 6.68 (s, 1H, 3'-ArH), 5.13 (br. t, *J* = 7.2 Hz, 1H, 5-H), 3.80 (s, 3H, OMe), 3.78 (s, 3H, OMe), 3.15 (apparent sext, *J* = 7.0 Hz, 1H, 2-H), 2.22 (s, 3H, $ArCH_3$), 2.01-1.85 (m, 2H, 4-H_2), 1.68 (s, 3H, 7-H_3), 1.67-1.56 (m, 2H, 3-H_2), 1.55 (s, 3 H, 8-H_3), 1.20 (d, *J* = 7.0 Hz, 3H, 1-H_3);

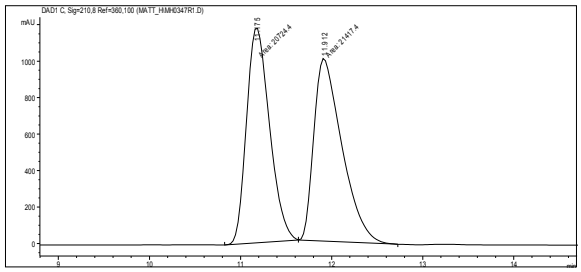
^{13}C NMR (101 MHz, $CDCl_3$) δ 151.8 (C-5'), 150.8 (C-2'), 134.0 (C-1'), 131.1 (C-6) , 124.8 (C-5), 124.2 (C-4'), 114.3 (C-3'), 109.8 (C-6'), 56.4 (OMe), 56.1 (OMe), 37.3 (C-3), 31.8 (C-2), 26.3 (C-4), 25.7 (C-7) , 21.3 (C-1), 17.6 (C-8), 16.1 ($ArCH_3$).

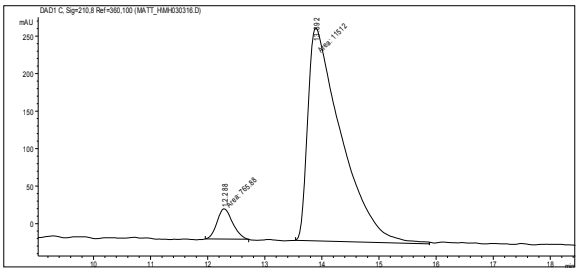
IR(neat)ν_{max}/cm^{-1}: 2961 (C-H), 1464 (CH_3), 1398, 1206 (C-O-C), 1048 (C-O-C), 825, 798 (Ar C-H).

***m/z* (EI)** 262 (M^+, 56), 179 (M –methylpentene, 100), 165 (M –methylpentene -CH_3, 20), 152 (M –methylpentene -2 × CH_3, 27), 91 (tropylium,15).

$[\alpha]_D^{21}$ -32.0 (*c* 1.0, CH_3Cl) Lit. (*S*)-enantiomer $[\alpha]_D^{20}$ + 40.9, (*c* 2.0, CH_3Cl)

HPLC (Chiralpak® IA, 210 nm, 2% isopropyl alcohol/hexane, 0.5 mL/min, rt) t_r = 12.3 min minor (S), 13.8 min major(R) 94:6





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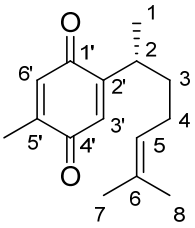
(*R*)-(-)-curcuquinone **5**



5

A solution of CAN (227 mg, 0.41 mmol) in H_2O (1 mL) was added dropwise to a solution of Curcuhydroquinone dimethyl ether **10c** (35 mg, 0.13 mmol) in MeCN (2 mL) and one drop of PE at rt. The reaction was stirred for 30 min before being extracted into CH_3Cl (2 × 10 mL), concentrated in vacuo and purified by flash column chromatography (5% EtOAc:PE, SiO_2) to yield the product (*R*)-(-)-curcuquinone **5** as a bright yellow oil (12 mg, 41%). All characterisation data matched that reported in the literature.[7]

R_f (5% EtOAc:PE) = 0.37

^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.59 (q, *J* = 1.6 Hz, 1H, 6'-H), 6.51 (d, *J* = 1.0 Hz, 1H, 3'-H), 5.06 (apparent tsept, *J* = 7.1, 1.4 Hz, 1H, 5-H), 2.92 (1H, apparent sextd, *J* = 6.9, 1.0 Hz, 2-H), 2.04 (d, *J* = 1.6 Hz, 3H, $ArCH_3$), 2.01-1.91 (m, 2H, 4-H_2), 1.67 (apparent q, 3H, *J* = 1.4 Hz, 7-H_3), 1.61-1.53 (m, 1H, 3-*H*H), 1.56 (br. s, 3H, 8-H_3,), 1.48-1.41 (m, 1H, 3-H*H*), 1.12 (d, *J* = 6.9, 3H, 1-H_3);

^{13}C NMR ($CDCl_3$, 126 MHz) δ 188.5 (C=O), 187.4 (C=O), 154.2 (C-2'), 145.1 (C-5'), 133.8 (C-6'), 132.1 (C-6), 131.1 (C-3'), 123.8 (C-5), 35.8 (C-2), 31.3 (C-3), 25.8 (C-7), 25.7 (C-4), 19.5 (CH_3), 17.7(CH_3), 15.4(C-8)

$[\alpha]_D^{21}$ 0.0 (*c* 0.4, CH_3Cl) Lit. (*S*)-enantiomer $[\alpha]_D^{20}$ + 0.9 (*c* 1.0, CH_3Cl)

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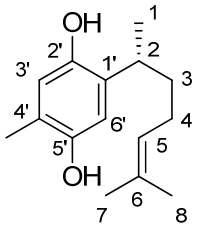
(*R*)-(-)-curcuhydroquinone 4



4

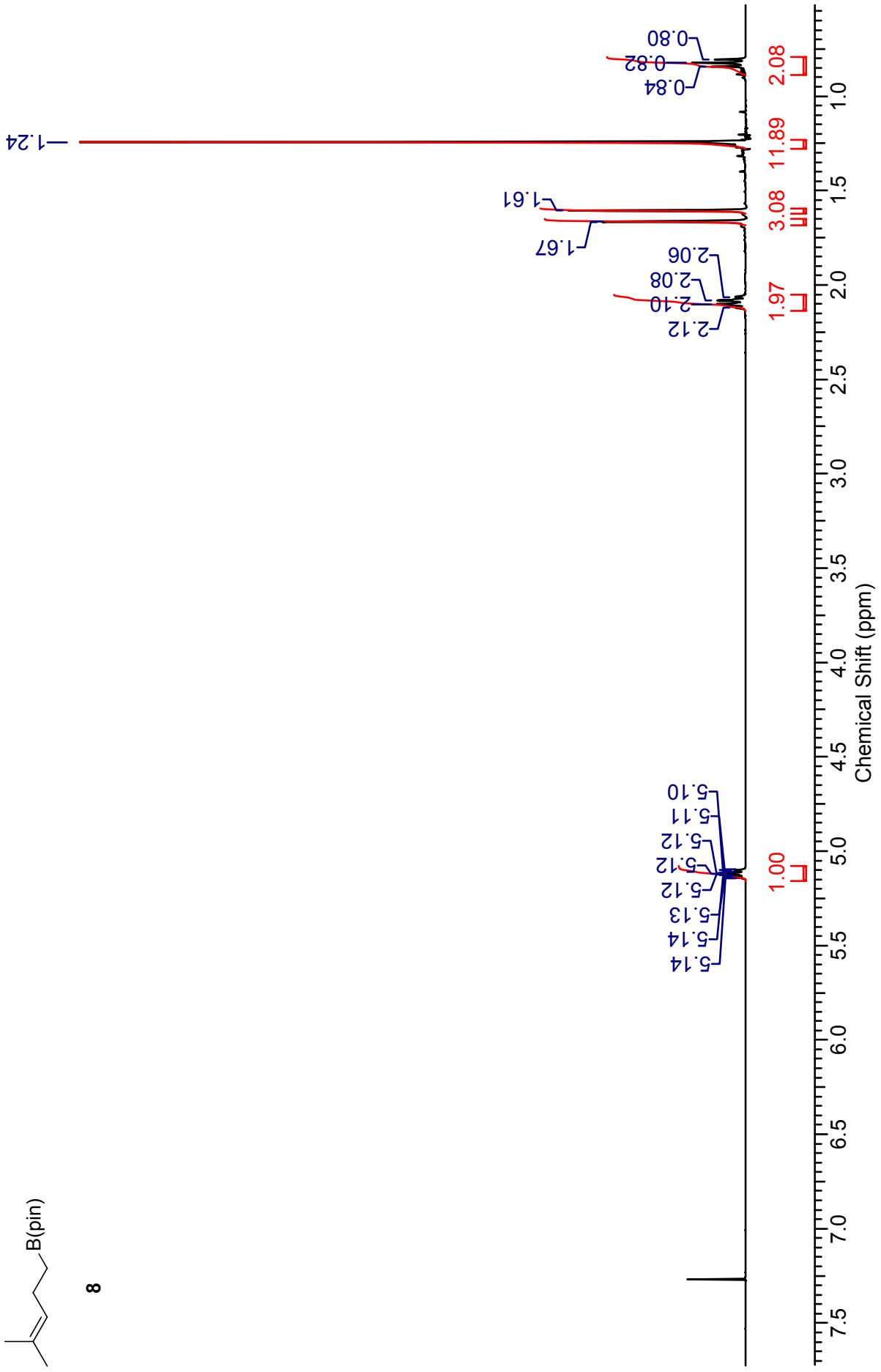
$NaBH_4$ (5.7 mg, 0.15 mmol) was slowly added to a solution of curcuquinone **5** (12 mg, 0.05 mmol) in MeOH (0.5 mL) at 0 °C. The reaction was warmed to rt and stirred for 15 min. $NH_4Cl_{(aq)}$ (1 mL) and H_2O (1 mL) were added and the reaction was extracted with EtOAc (3 × 4mL). The combined organic phases were washed with brine (2 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give (*R*)-(-)-curcuhydroquinone **4** as a clear, colourless oil (11 mg, 92%). All characterisation data matched that reported in the literature.[7]

^{1}H NMR($CDCl_3$, 500 MHz) 6.59 (s, 1H, 6'-H), 6.57 (q, J = 0.6 Hz, 1H, 3'-H), 5.13 (tsept, J = 7.0, 1.4 Hz, 1H, 5-H), 4.32 (br. s, 1H, OH), 4.28 (br. s, 1H, OH), 2.94 (apparent sext., J = 7.0 Hz, 1H, 2-H), 2.18 (s, 3H, $ArCH_3$), 2.00-1.89 (m, 2H, 4-H_2), 1.69 (apparent q, J = 1.4 Hz, 3H, 7-H_3), 1.67-1.54 (m, 2H, 3-H_2), 1.55 (d, J = 1.2 Hz, 3H, 8-H_3), 1.21 (d, J = 7.0 Hz, 3H, 1-H_3)

^{13}C NMR ($CDCl_3$, 126 MHz) 147.8 (C-5'), 146.6 (C-2'), 132.2 (C-1'), 131.7 (C-6), 124.5 (C-4'), 121.7 (C-6'), 117.9 (C-5), 113.4 (C-3'), 37.4 (C-3), 31.4 (C-2), 26.0 (C-4), 25.7 (C-7), 21.1 (C-1), 15.4 (C-8) 12.7 ($ArCH_3$)

$[\alpha]_D^{21}$ -40.0 (*c* 0.2, CH_3Cl) Lit. (*S*)-enantiomer $[\alpha]_D^{20}$ + 47.1 (*c* 1.0, CH_3Cl)

4. Copies of ^{1}H NMR and ^{13}C NMR spectra



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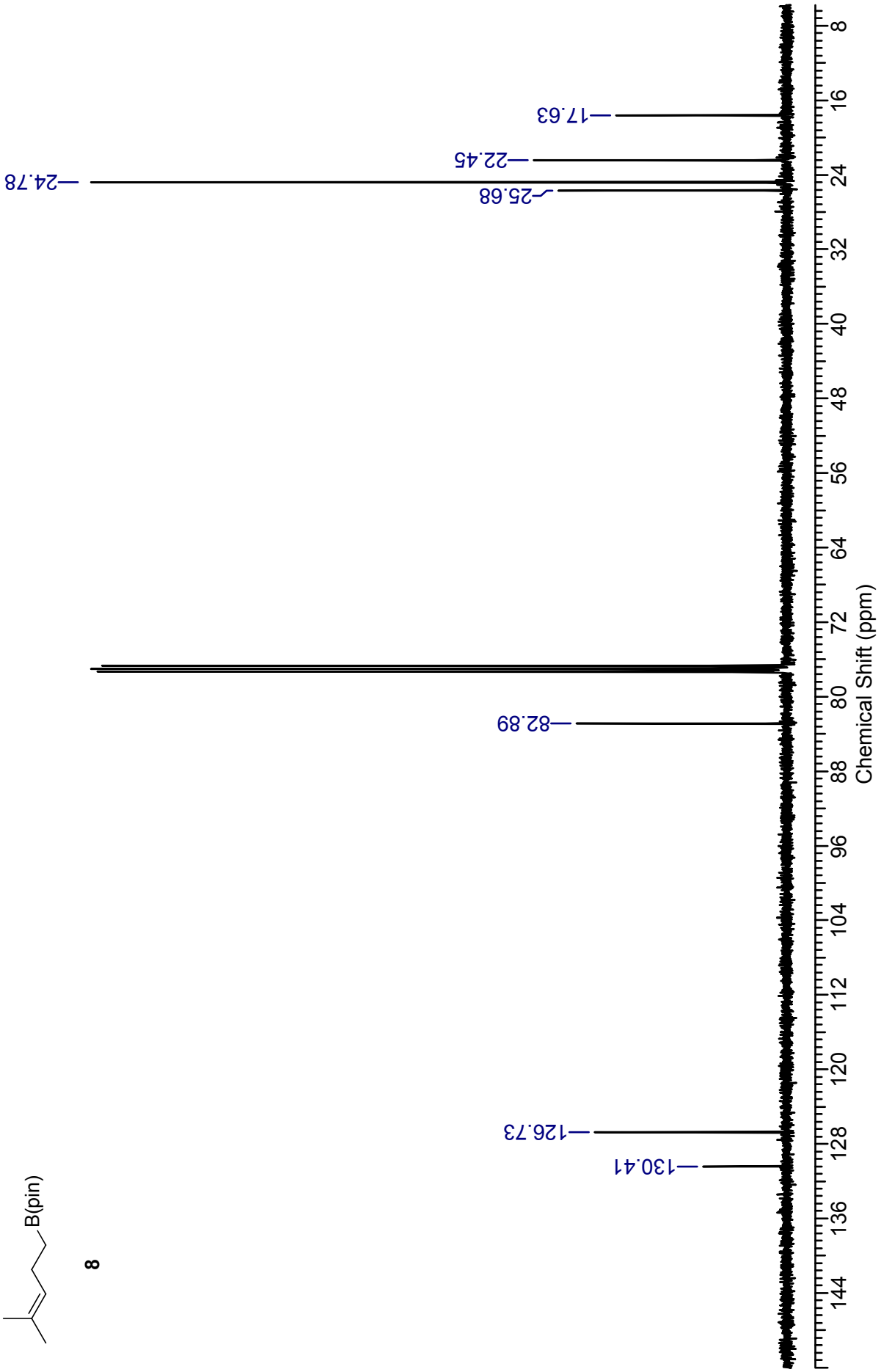

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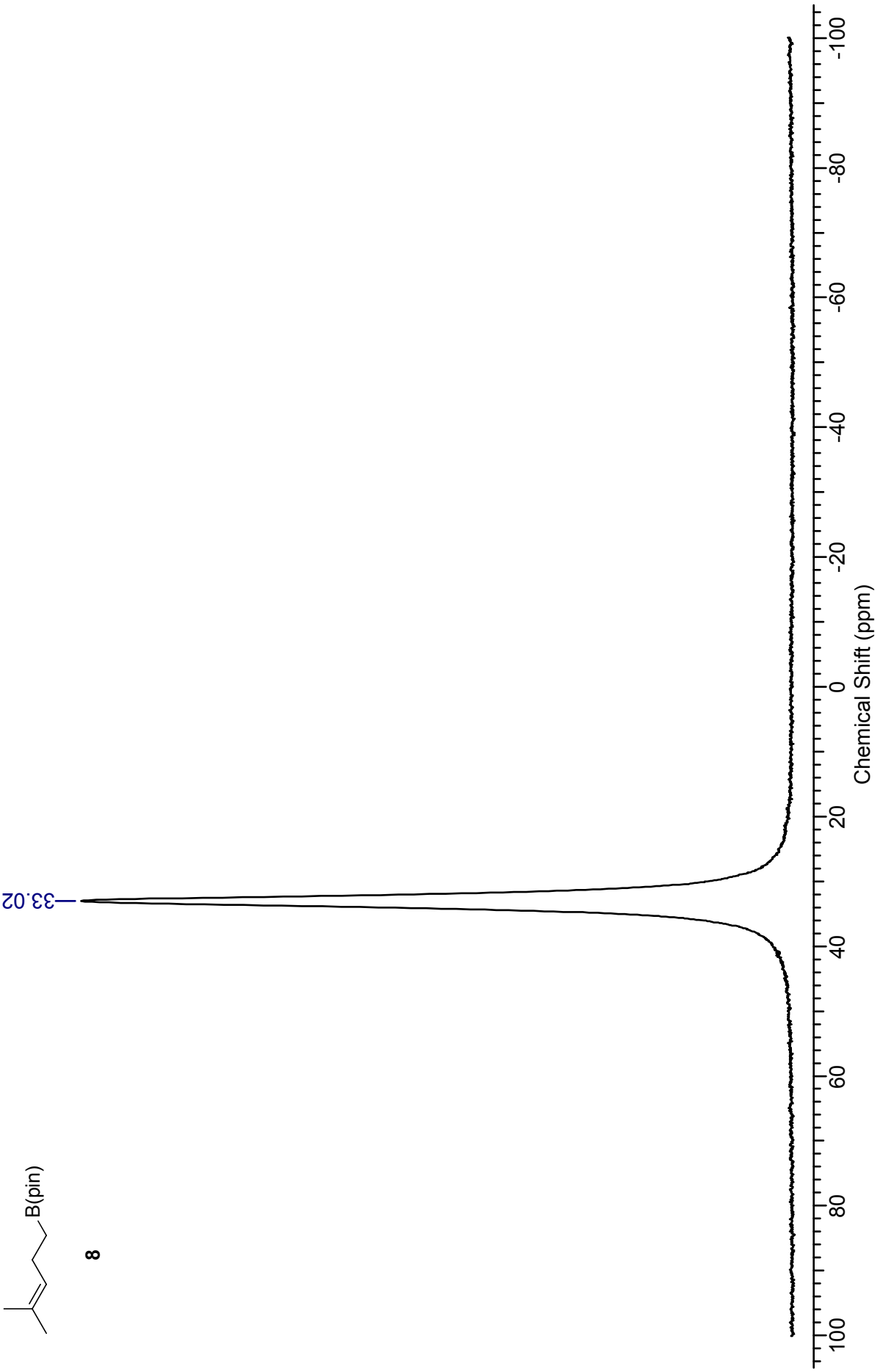

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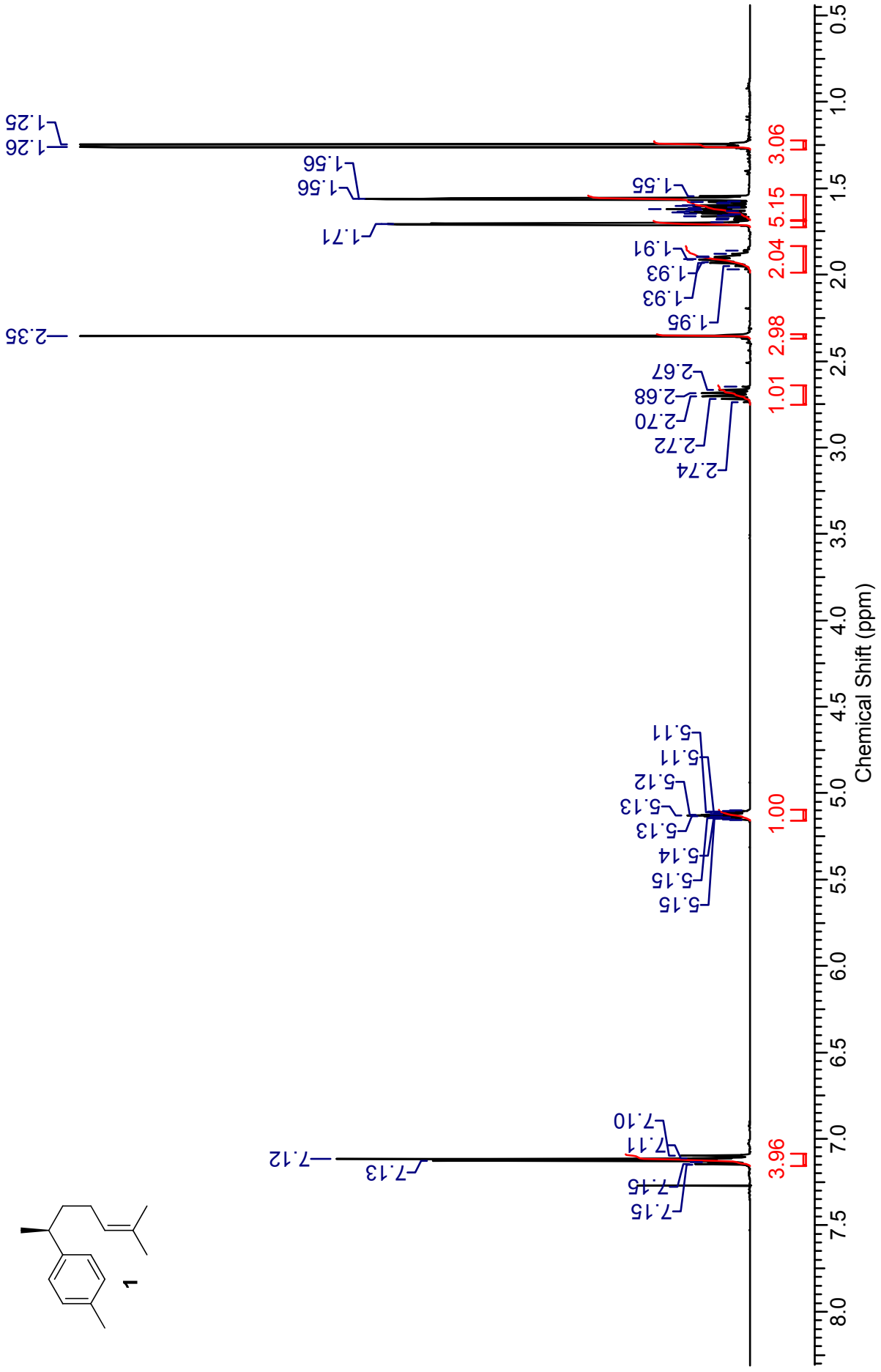

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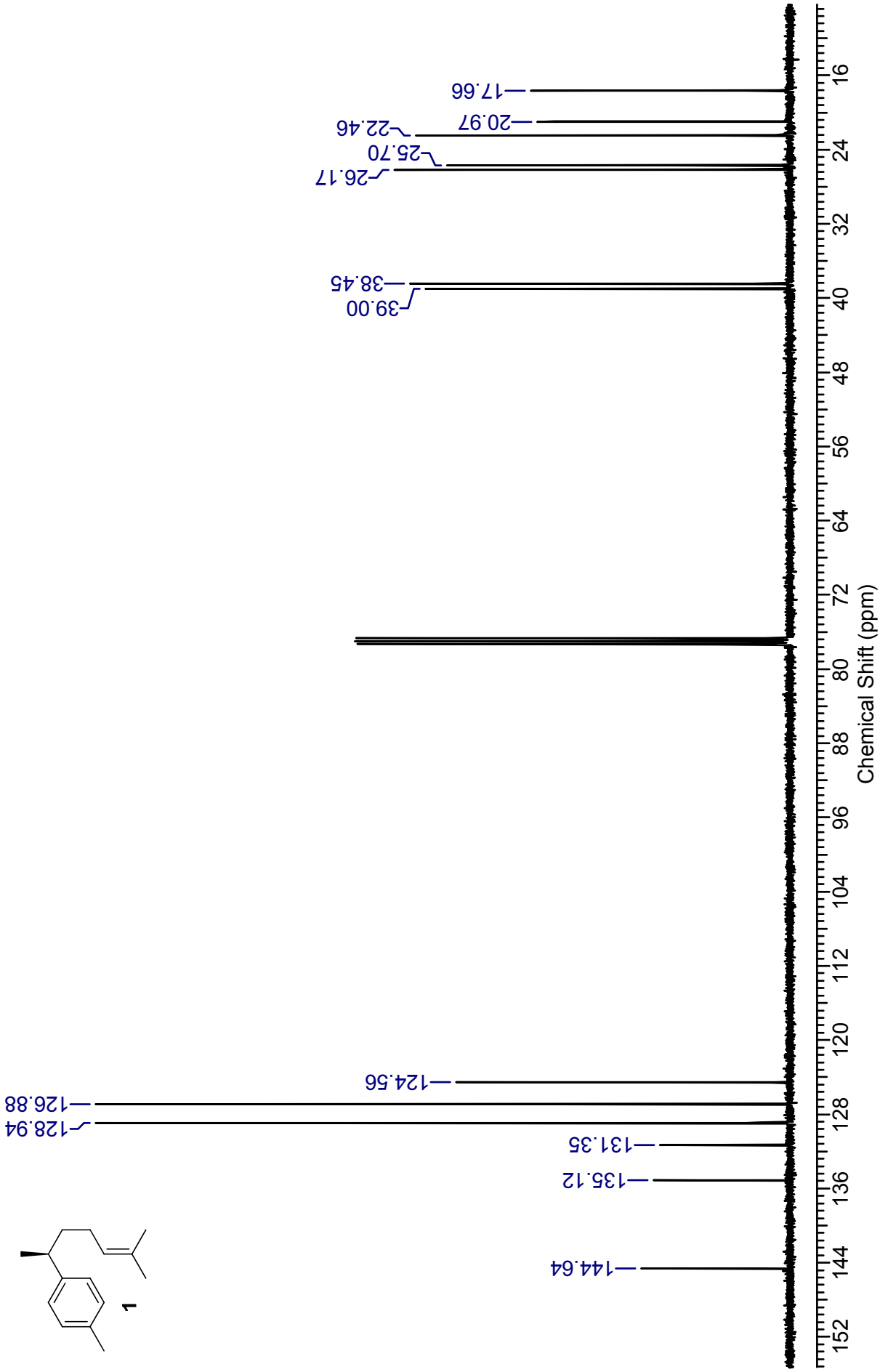

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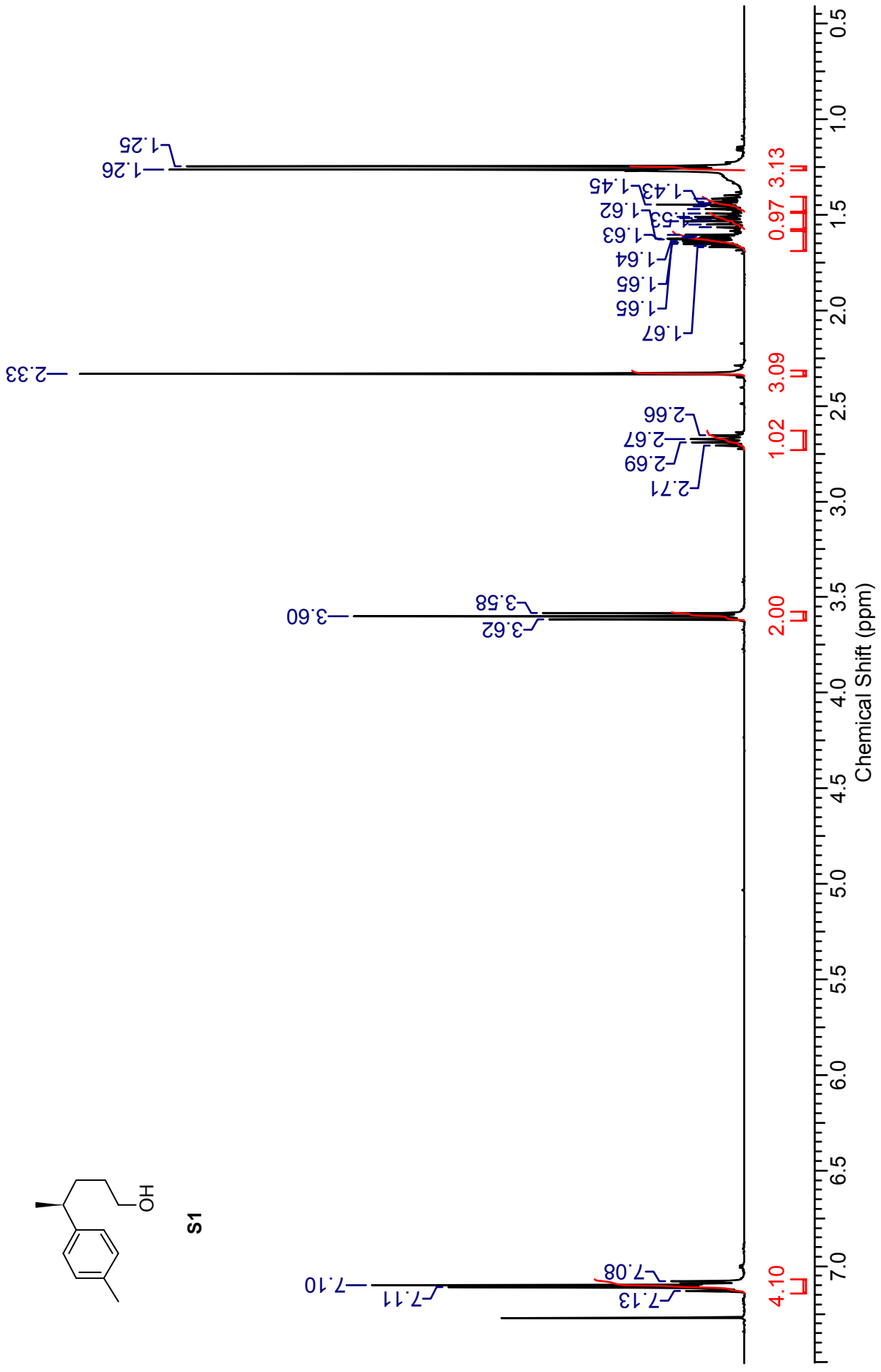

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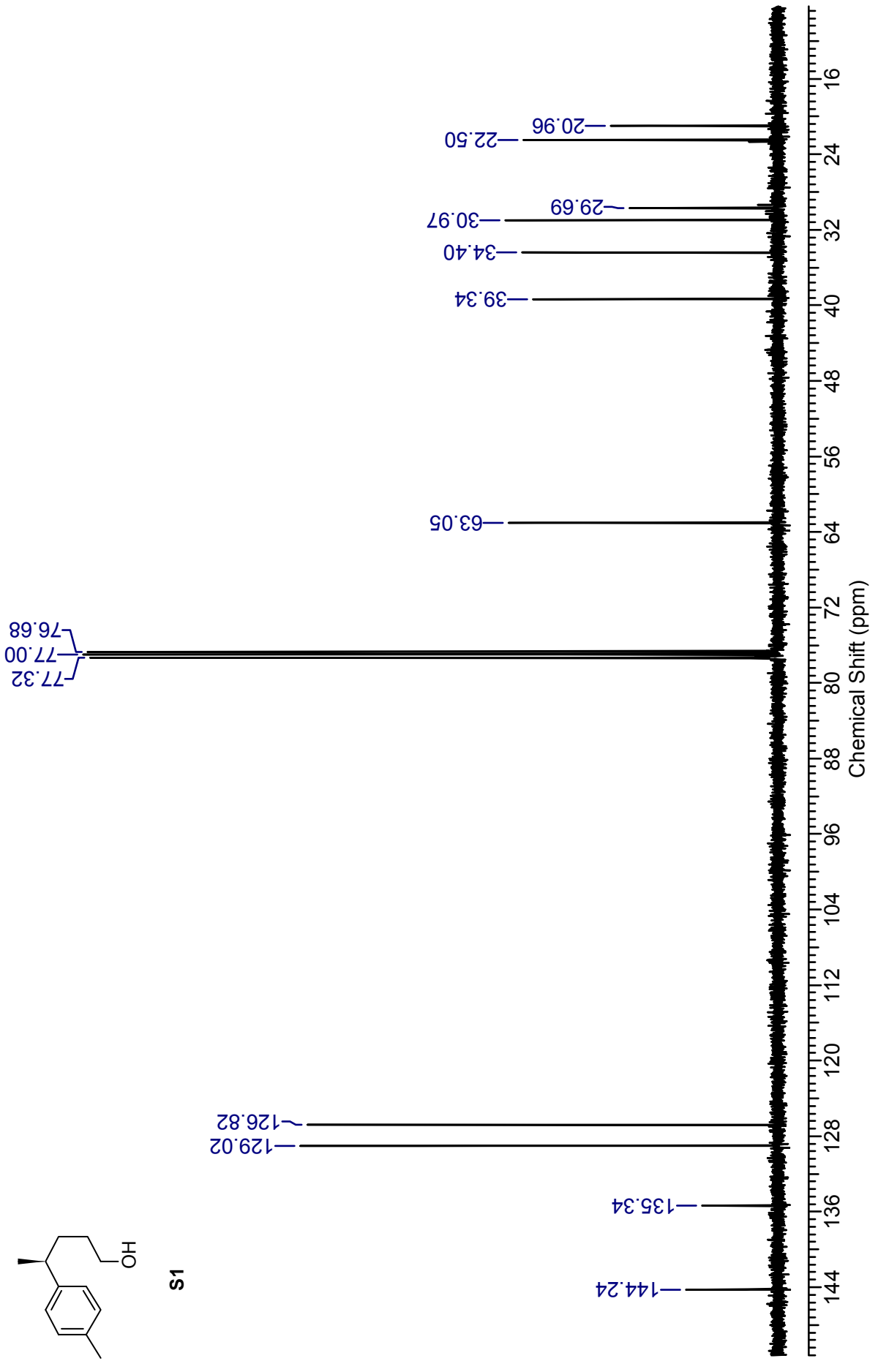

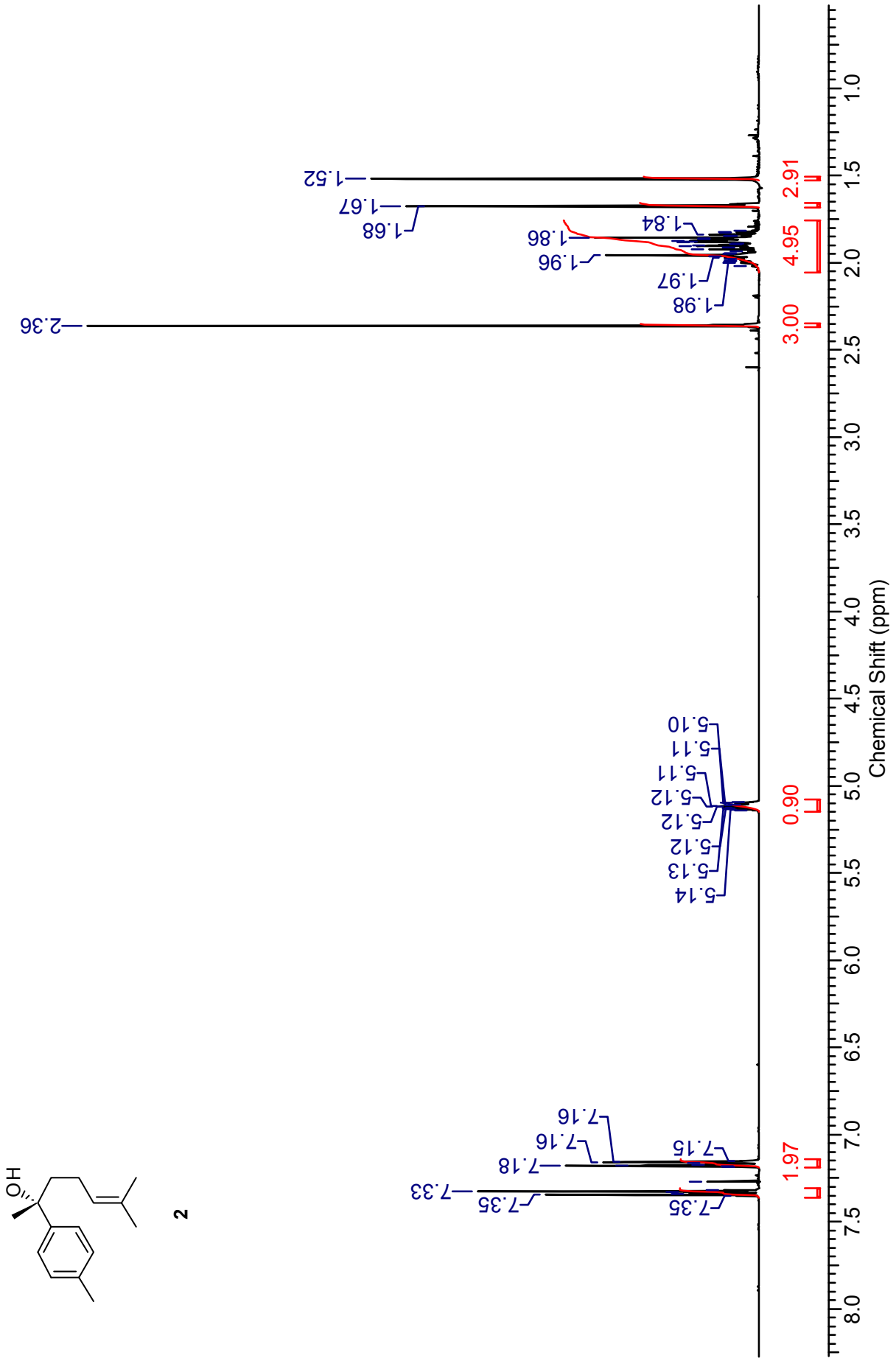
OH
2
7.35
7.33
7.18
7.16
7.16
7.15
5.14
5.13
5.12
5.12
5.12
5.11
5.11
5.10
2.36
1.98
1.97
1.96
1.86
1.84
1.68
1.67
1.52
1.97
0.90
3.00
4.95
2.91
Chemical Shift (ppm)

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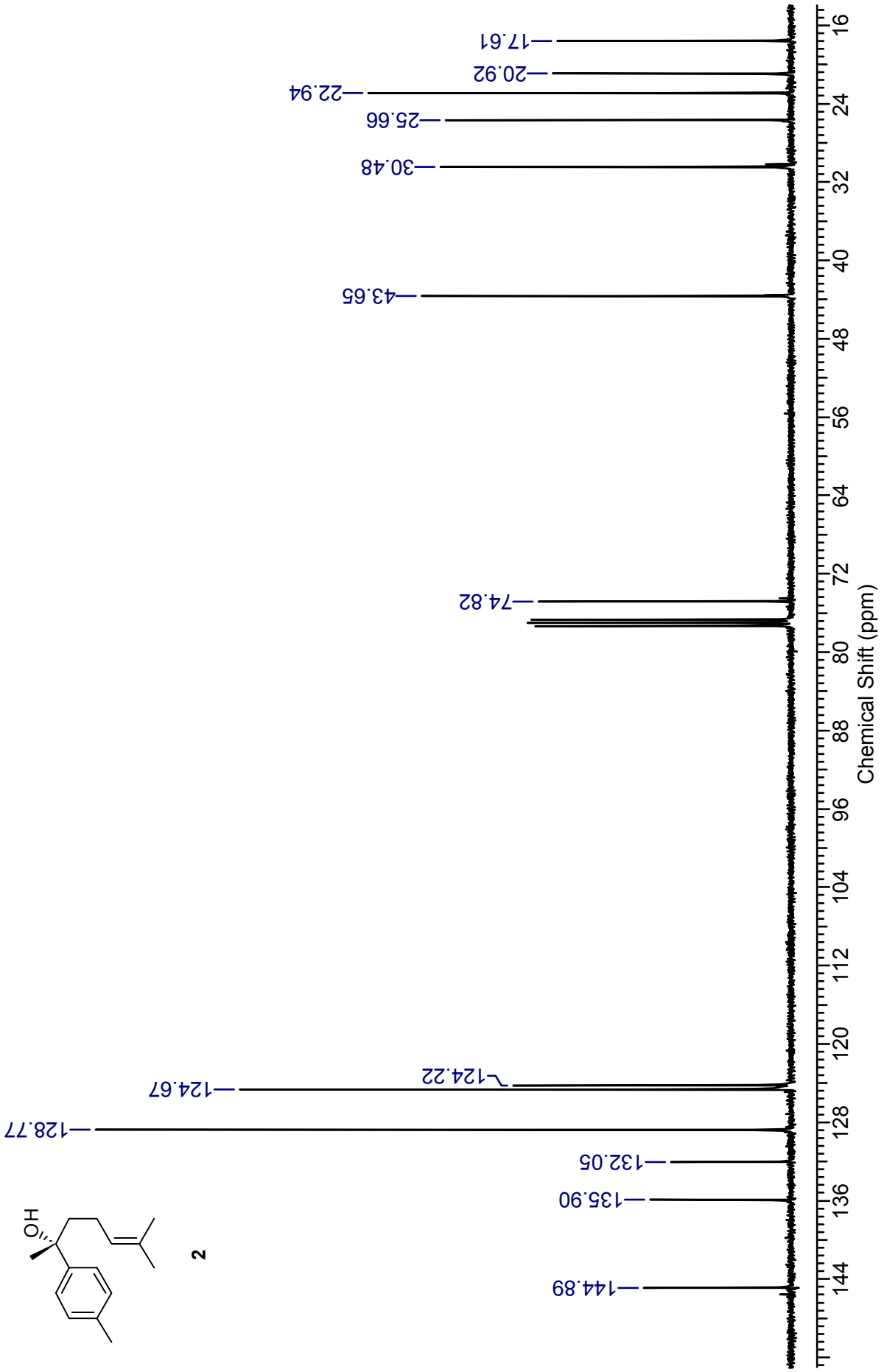

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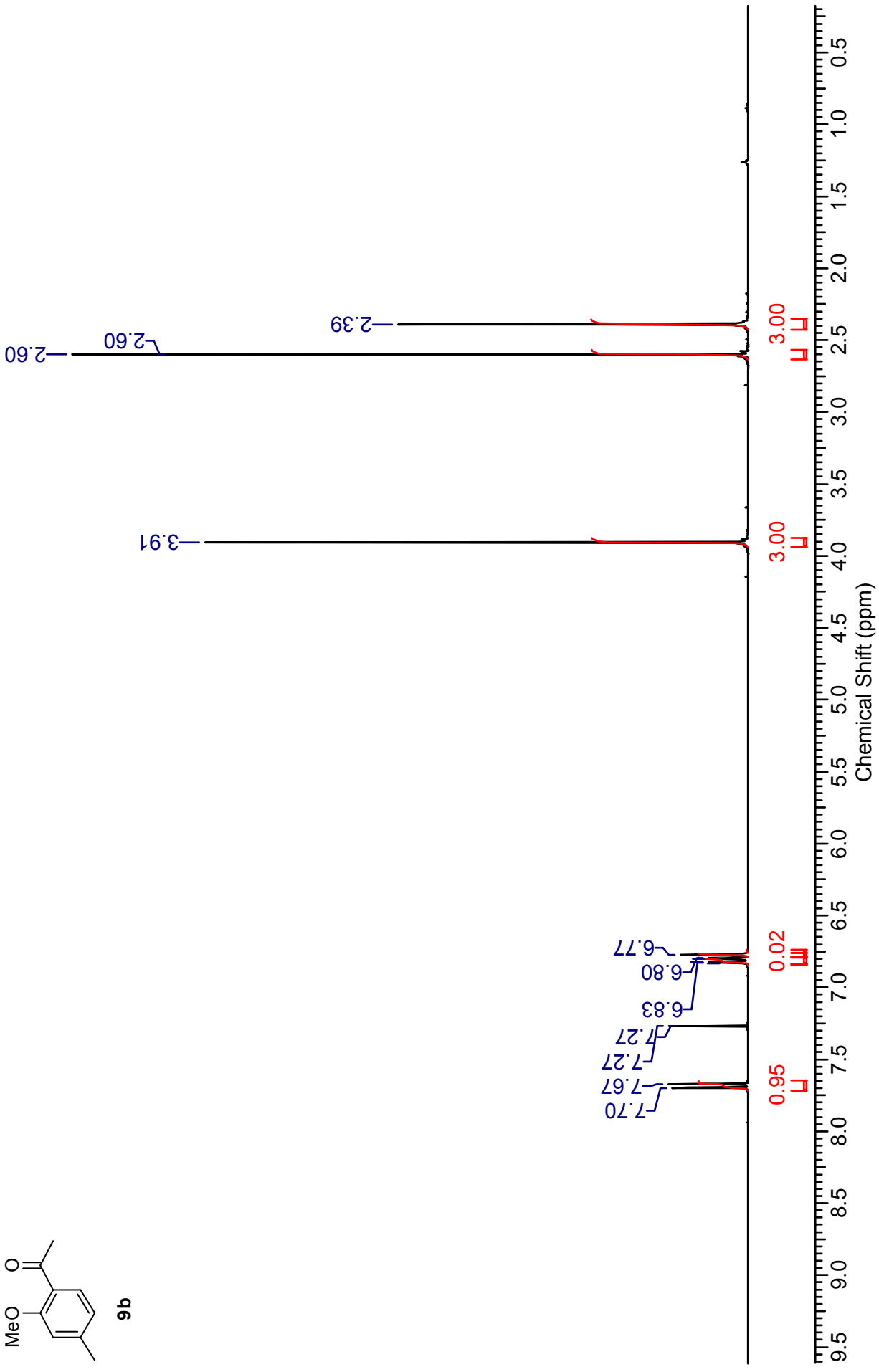

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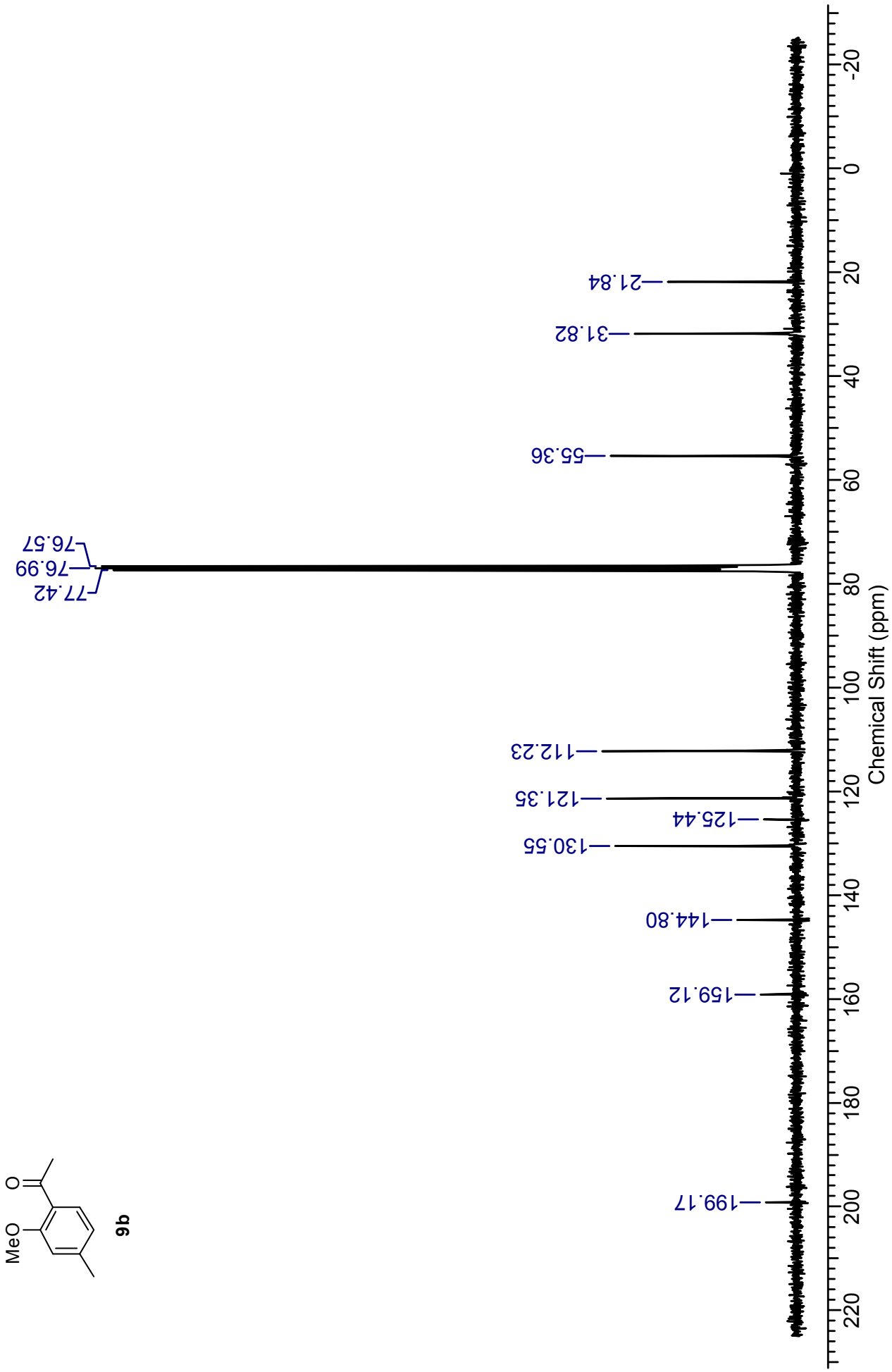

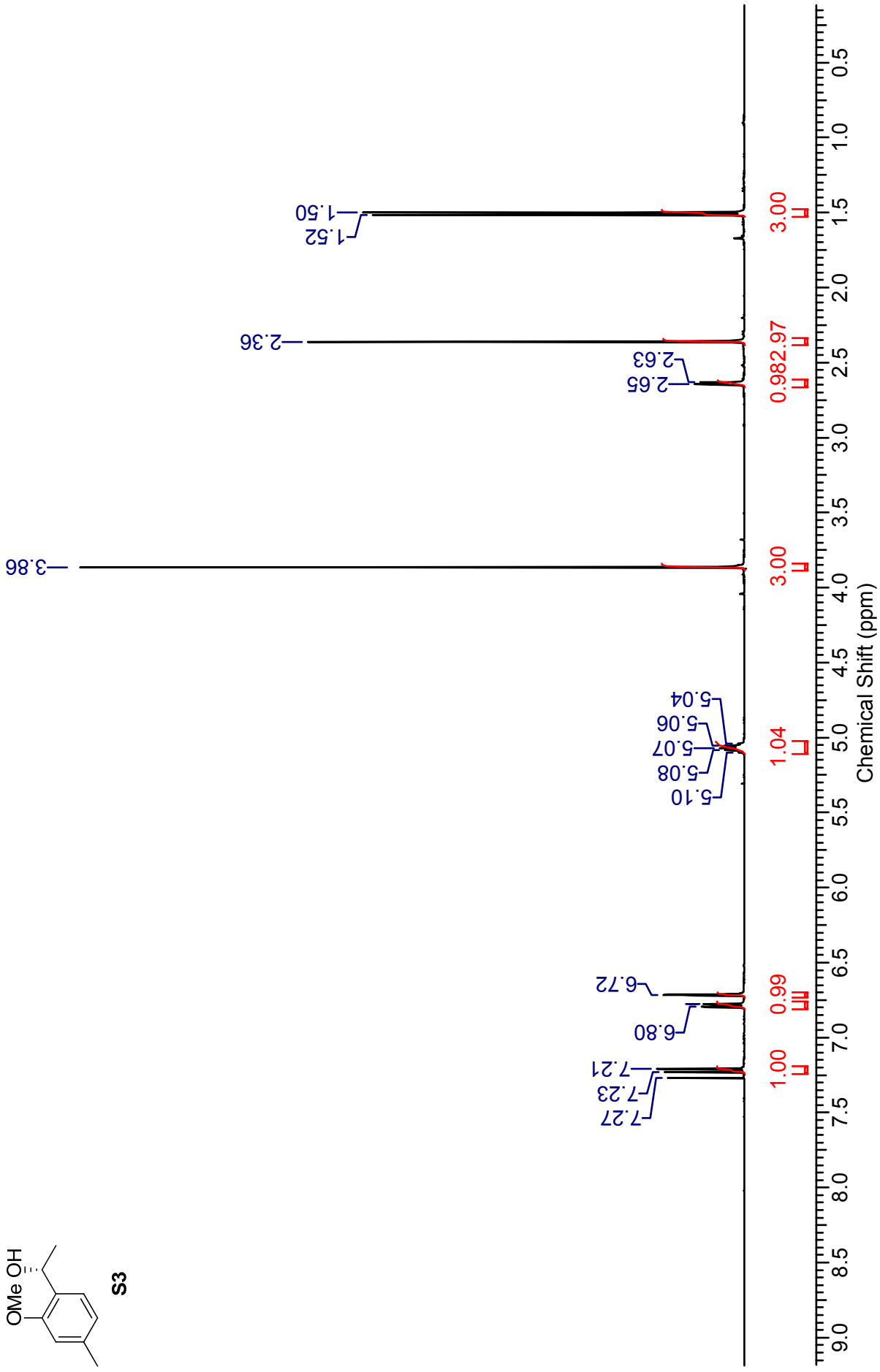
OMe OH
S3
1.50
1.52
2.36
2.63
2.65
3.86
5.04
5.06
5.07
5.08
5.10
6.72
6.80
7.21
7.23
7.27
3.00
0.98
2.97
3.00
1.04
0.99
1.00
Chemical Shift (ppm)

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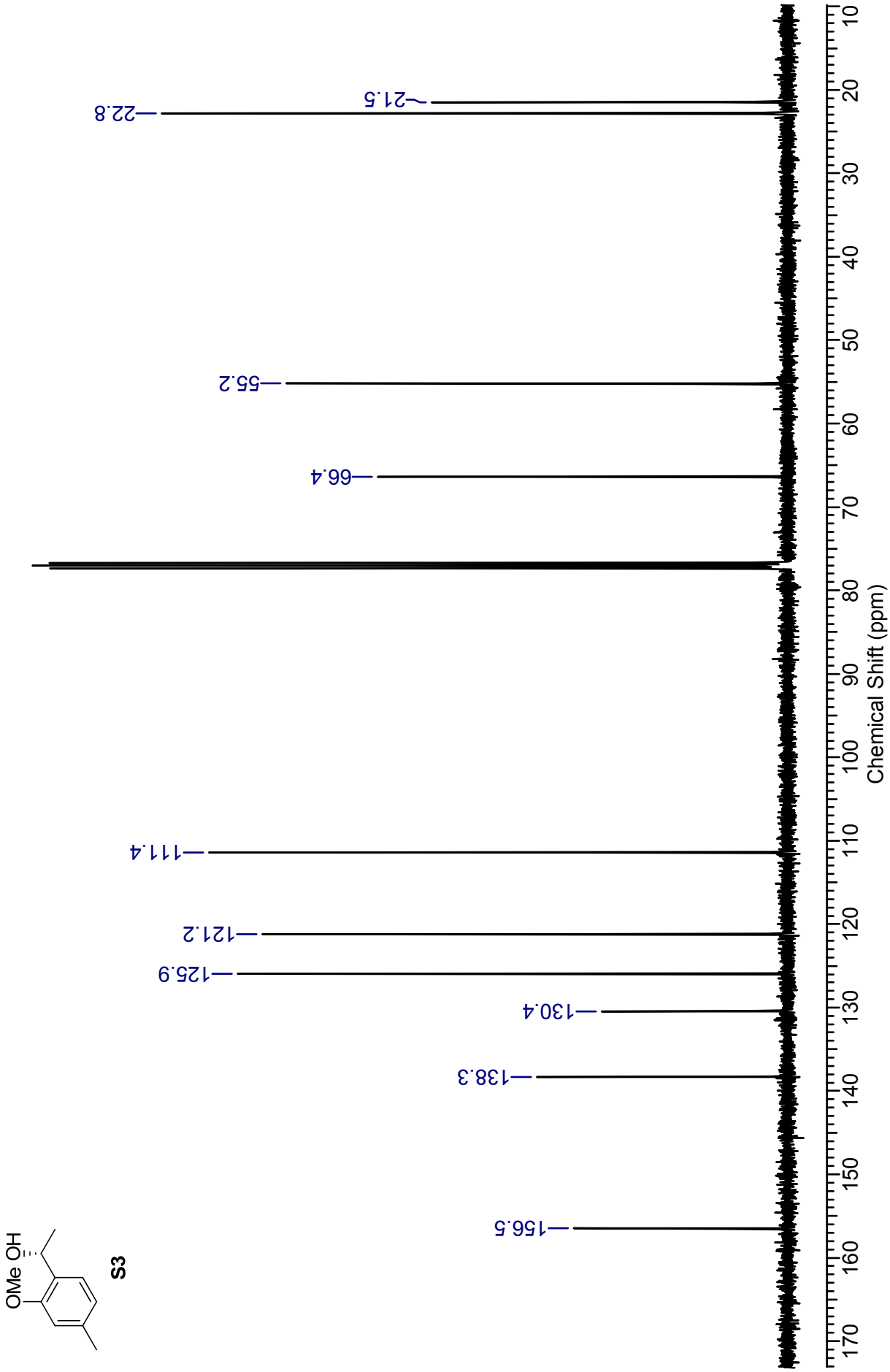

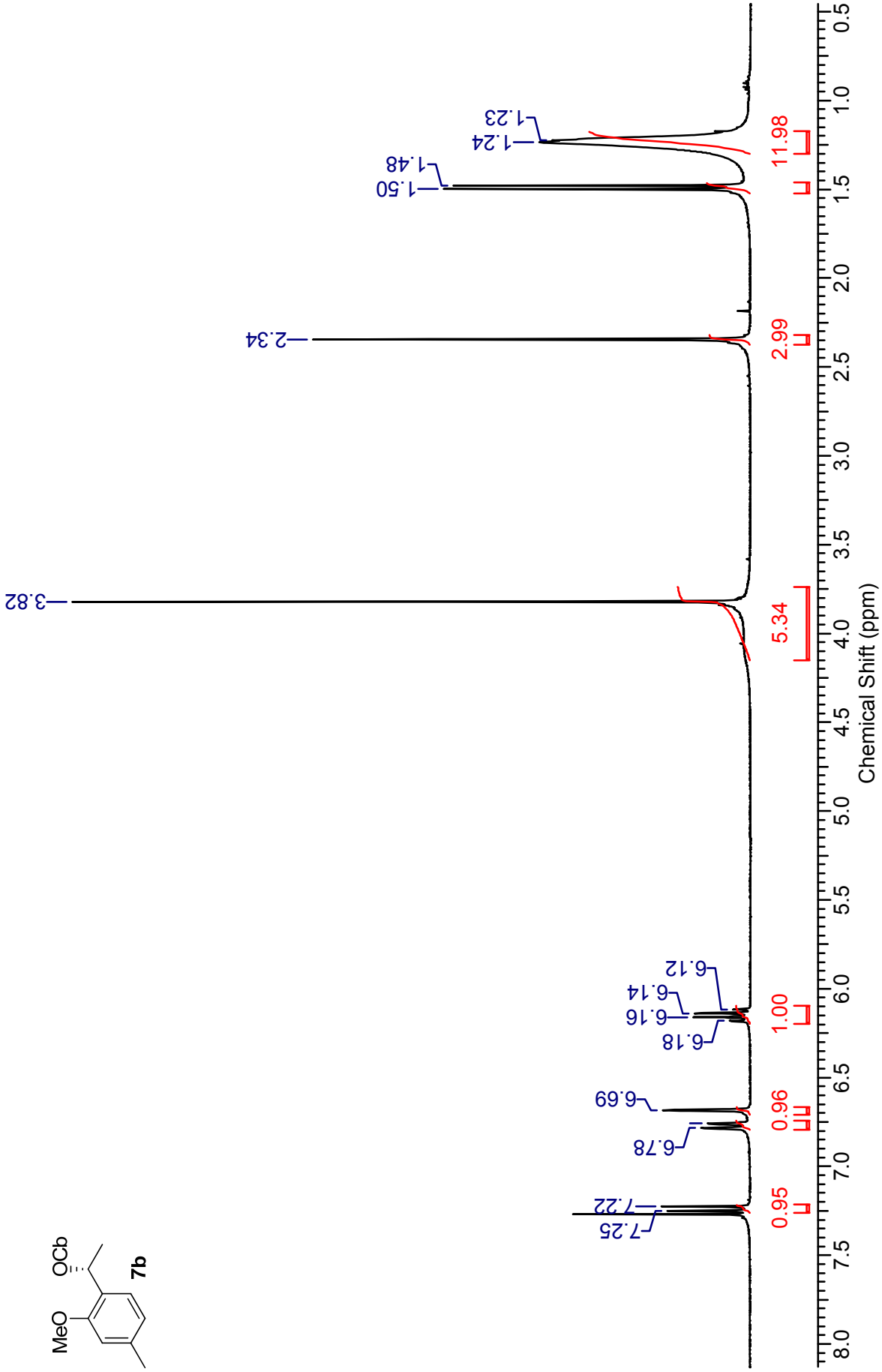
7b
OCb
MeO
7.25
7.22
6.78
6.69
6.18
6.16
6.14
6.12
3.82
2.34
1.50
1.48
1.24
1.23
0.95
0.96
1.00
5.34
2.99
11.98
Chemical Shift (ppm)

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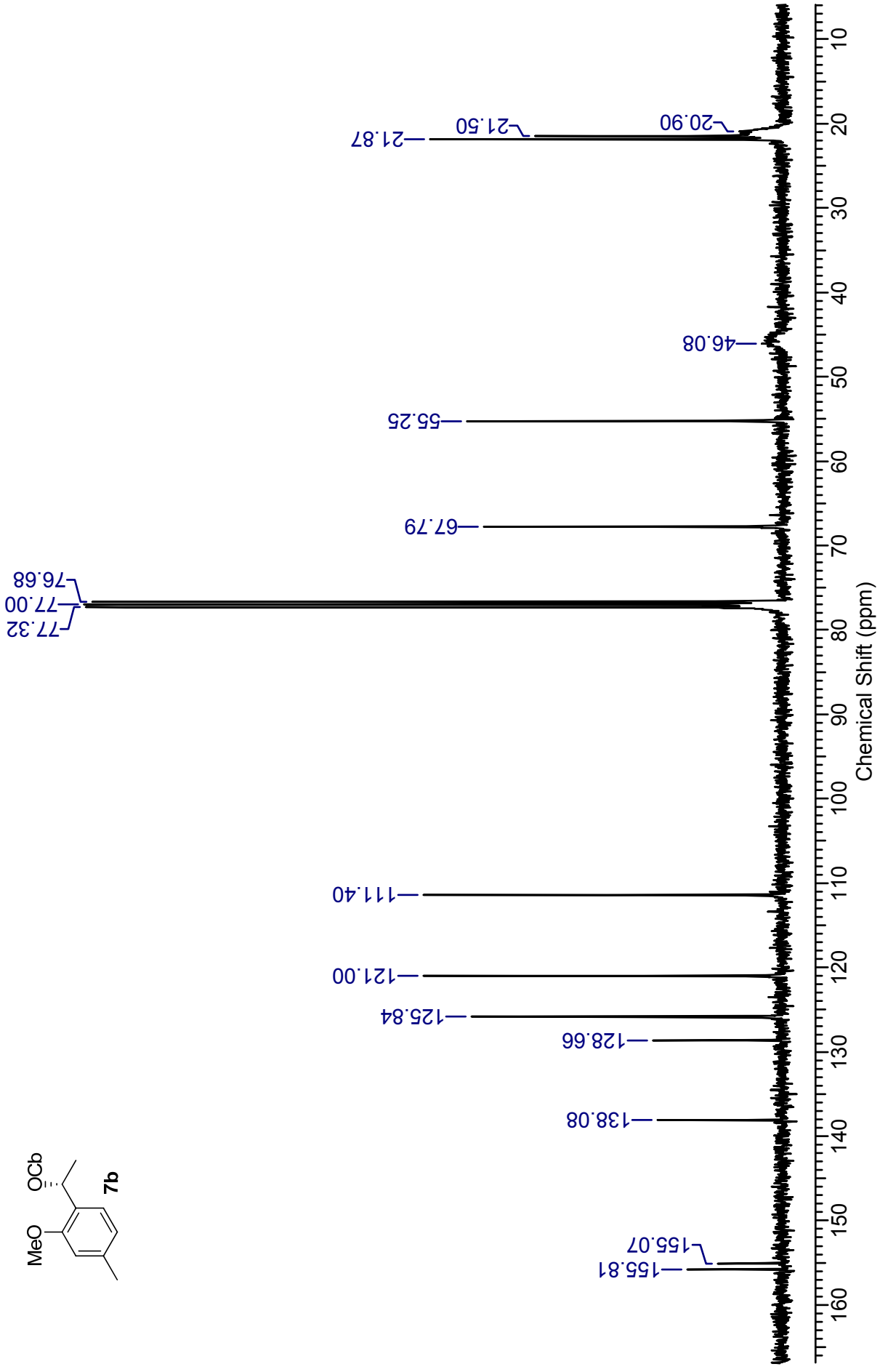

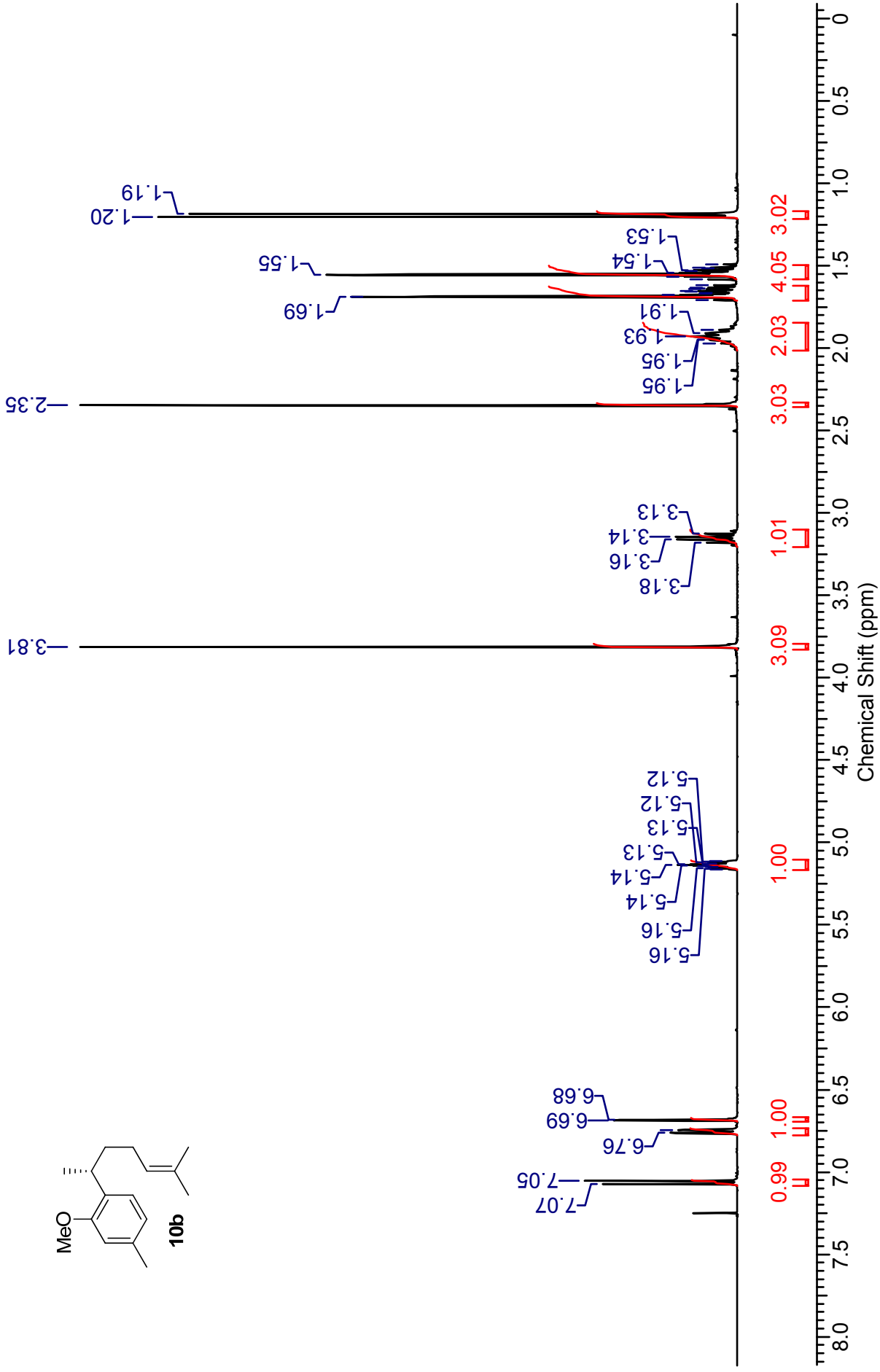
1.19
1.20
1.55
1.69
1.53
1.54
1.91
1.93
1.95
1.95
2.35
3.13
3.14
3.16
3.18
3.81
5.12
5.12
5.13
5.13
5.14
5.14
5.16
5.16
6.68
6.69
6.76
7.05
7.07
3.02
4.05
2.03
3.03
1.01
3.09
1.00
1.00
0.99
Chemical Shift (ppm)
MeO
10b

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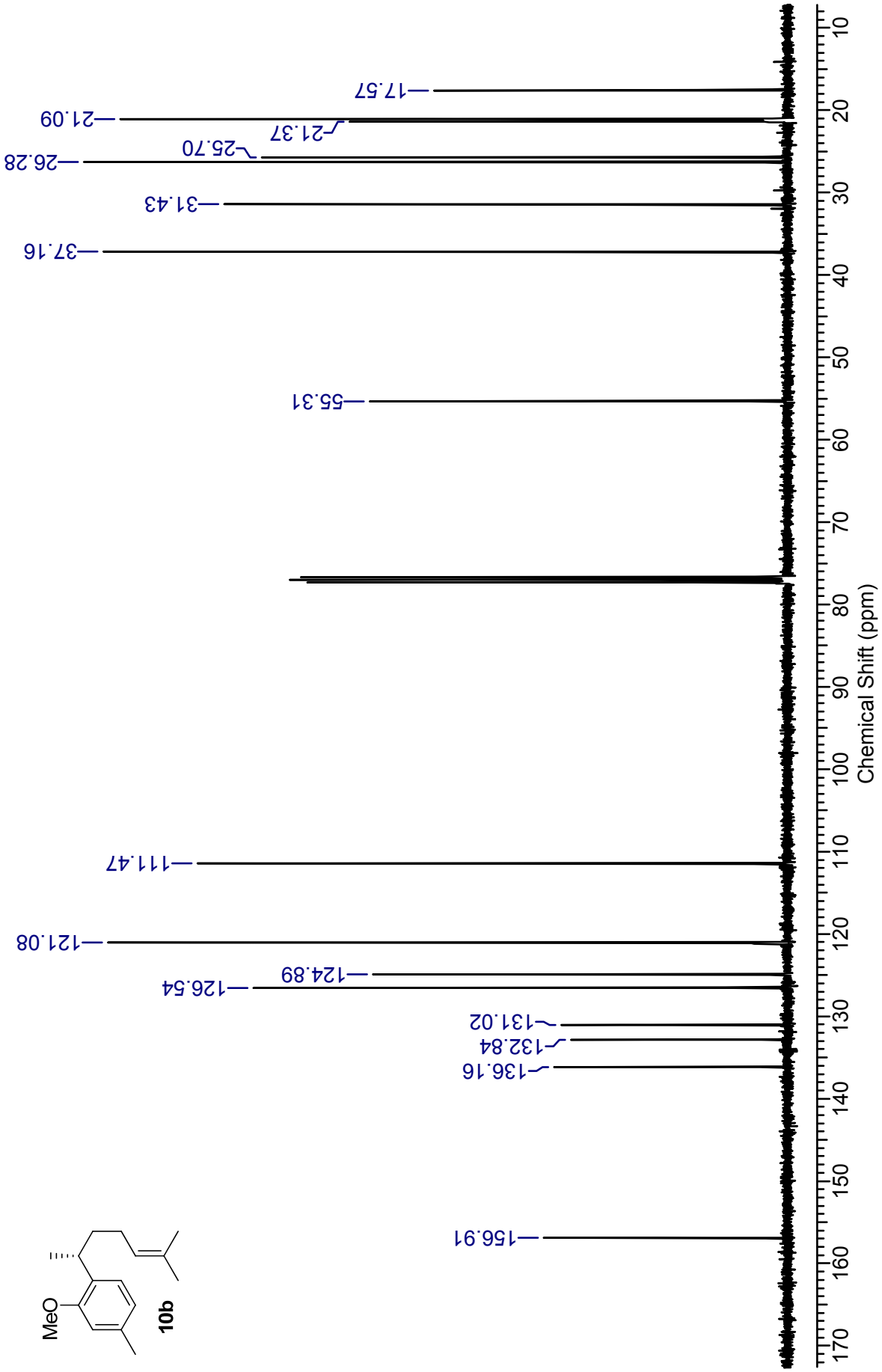

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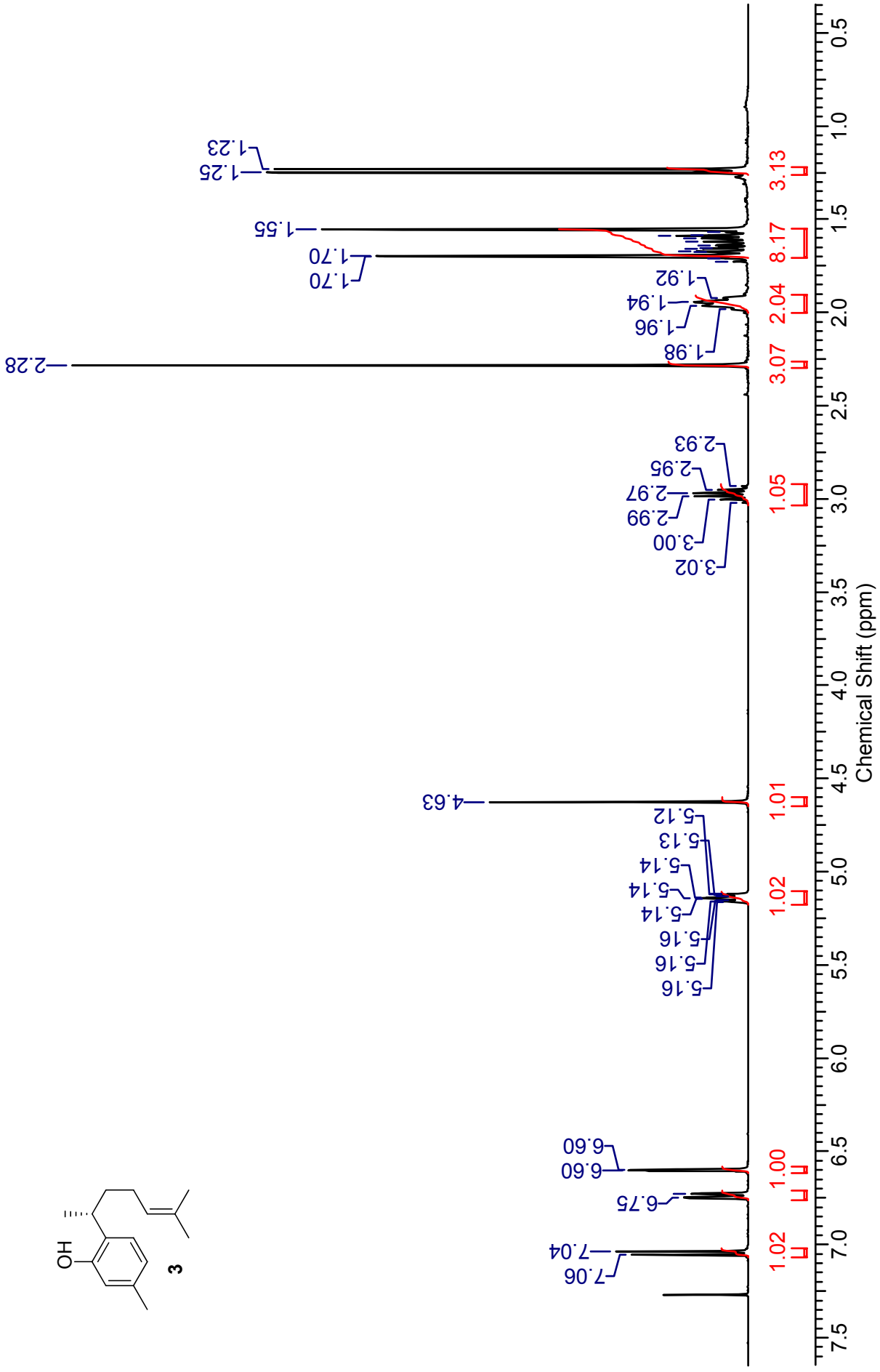

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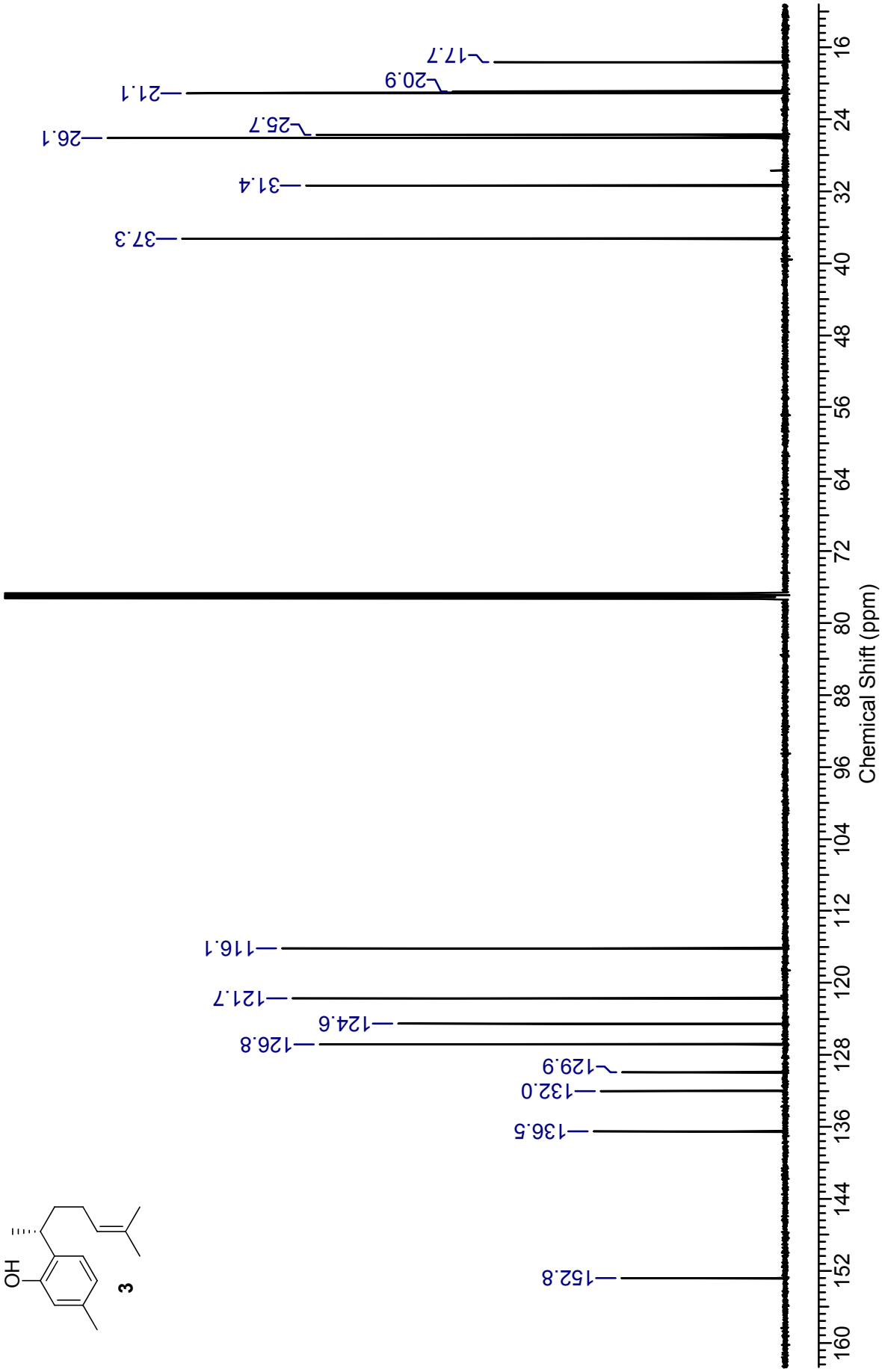

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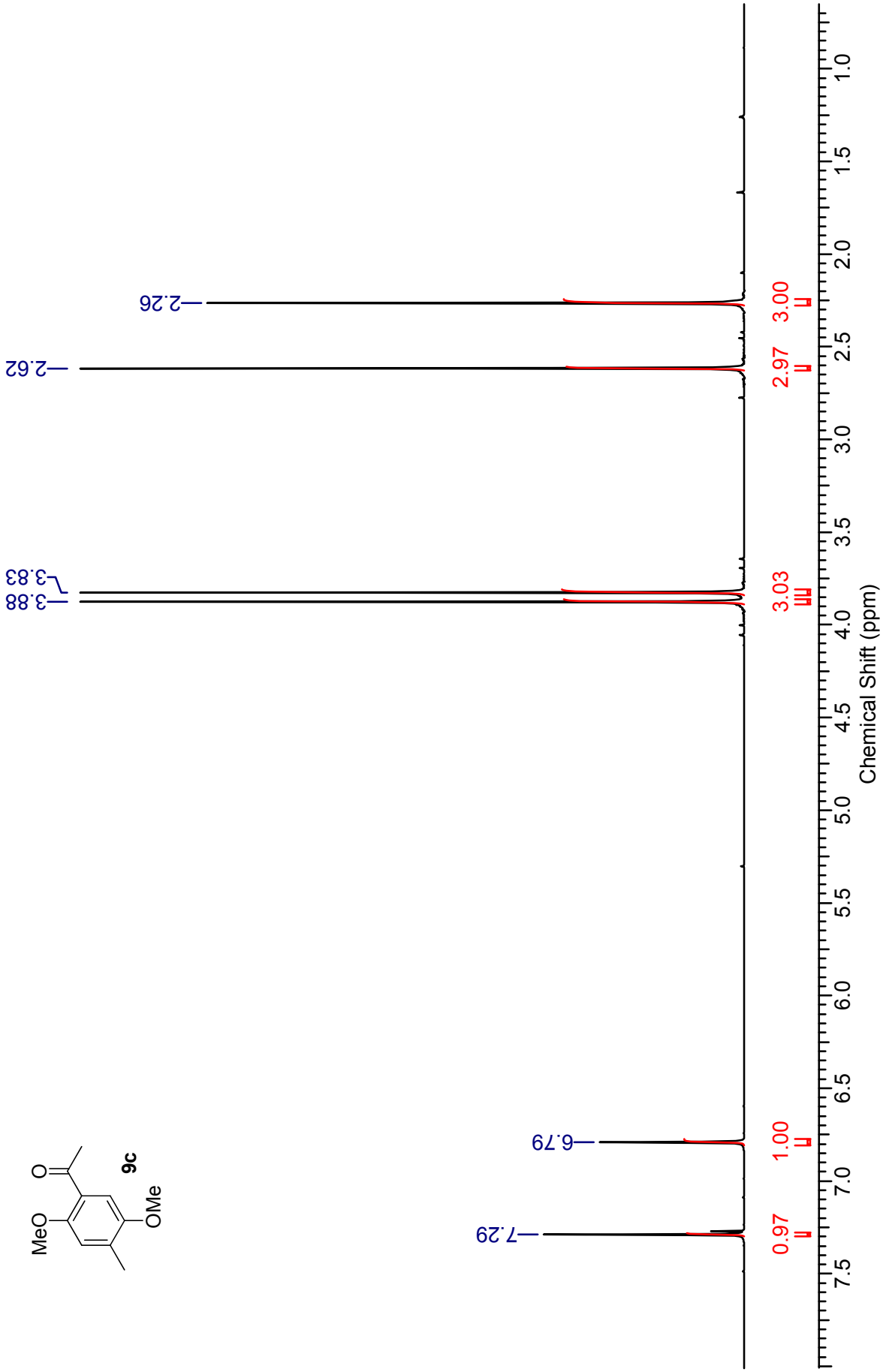

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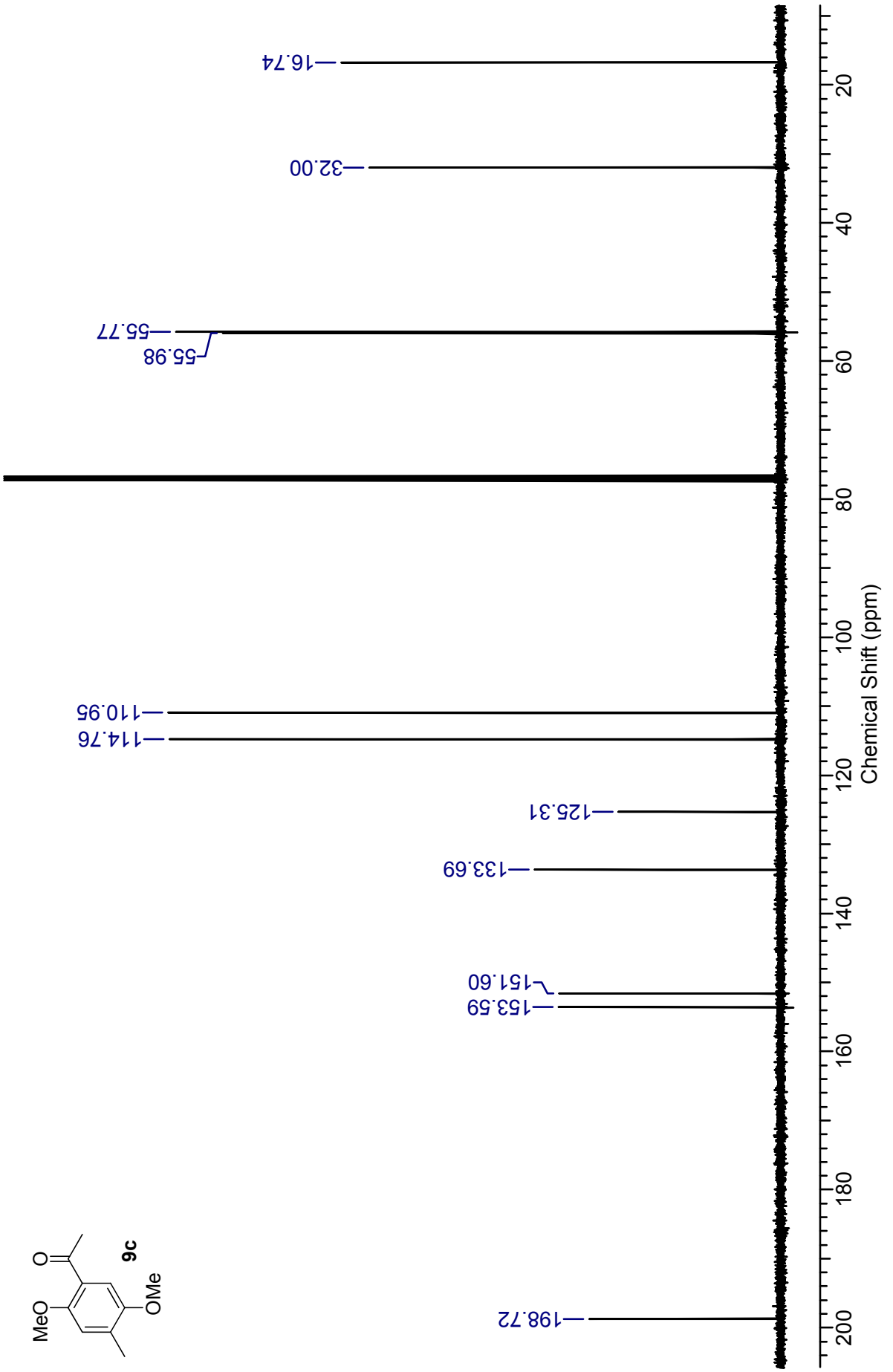

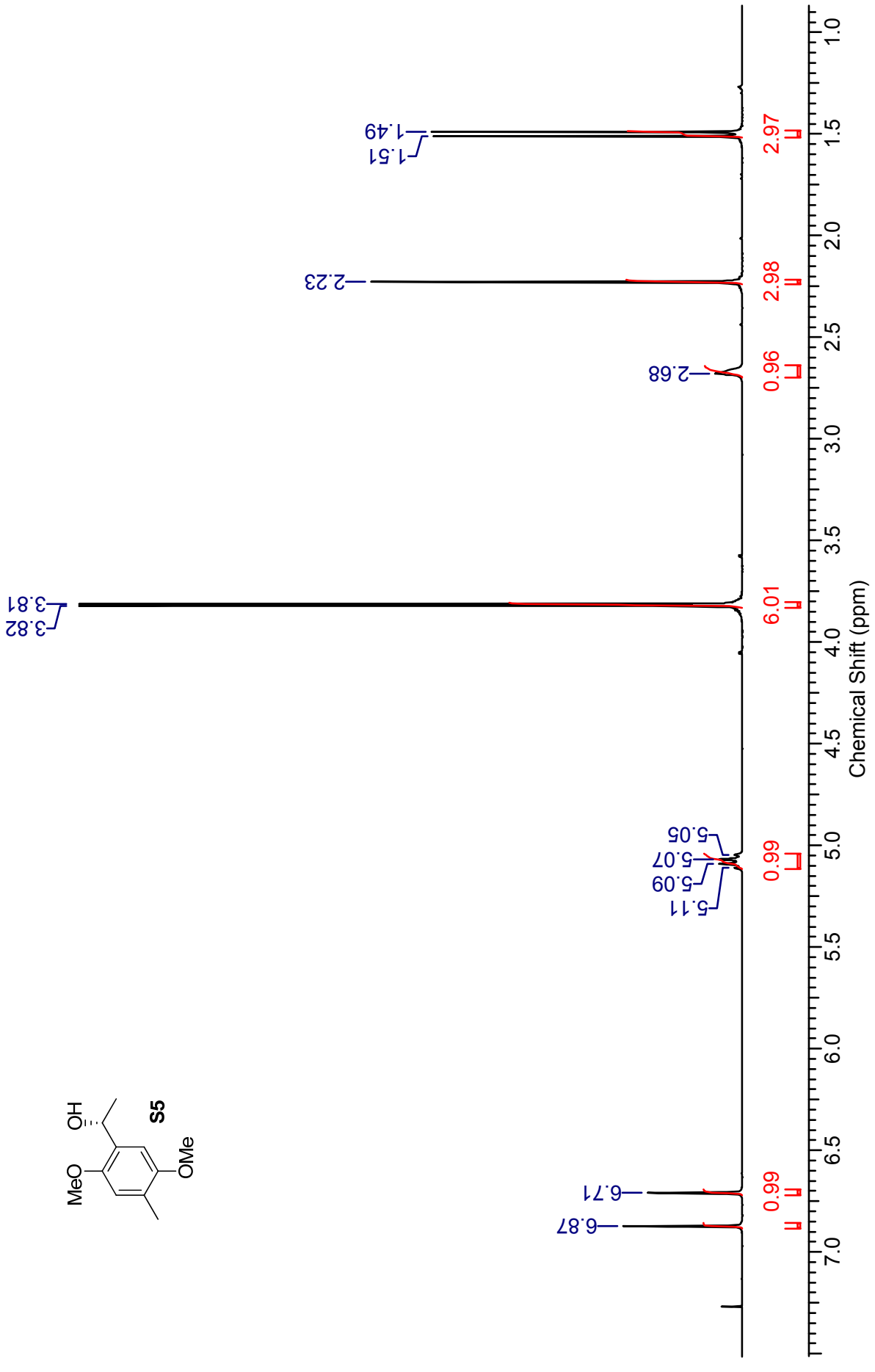
S5
OH
MeO
OMe
6.87
6.71
5.11
5.09
5.07
5.05
3.82
3.81
2.68
2.23
1.51
1.49
0.99
0.99
0.99
6.01
0.96
2.98
2.97
Chemical Shift (ppm)

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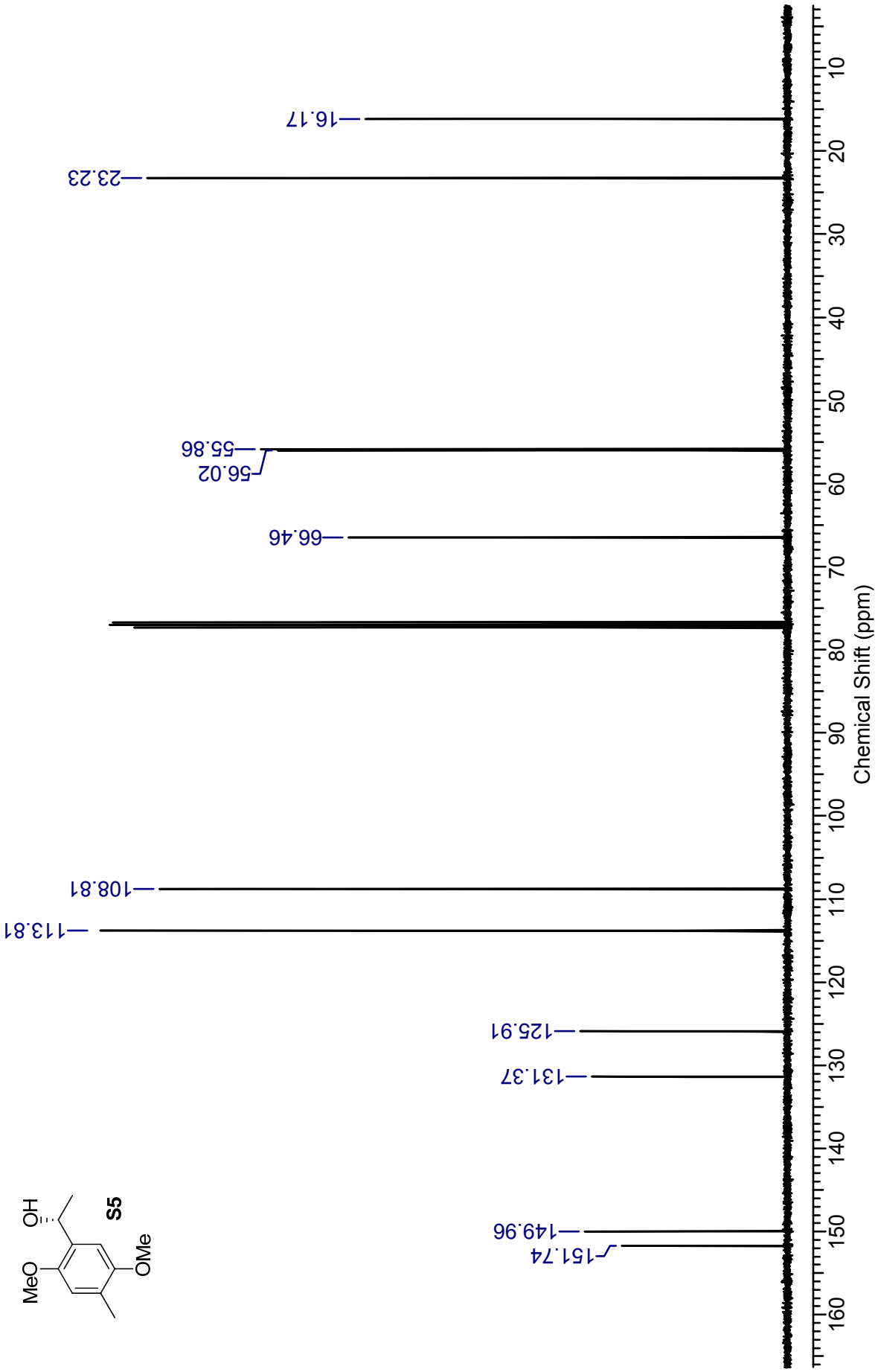

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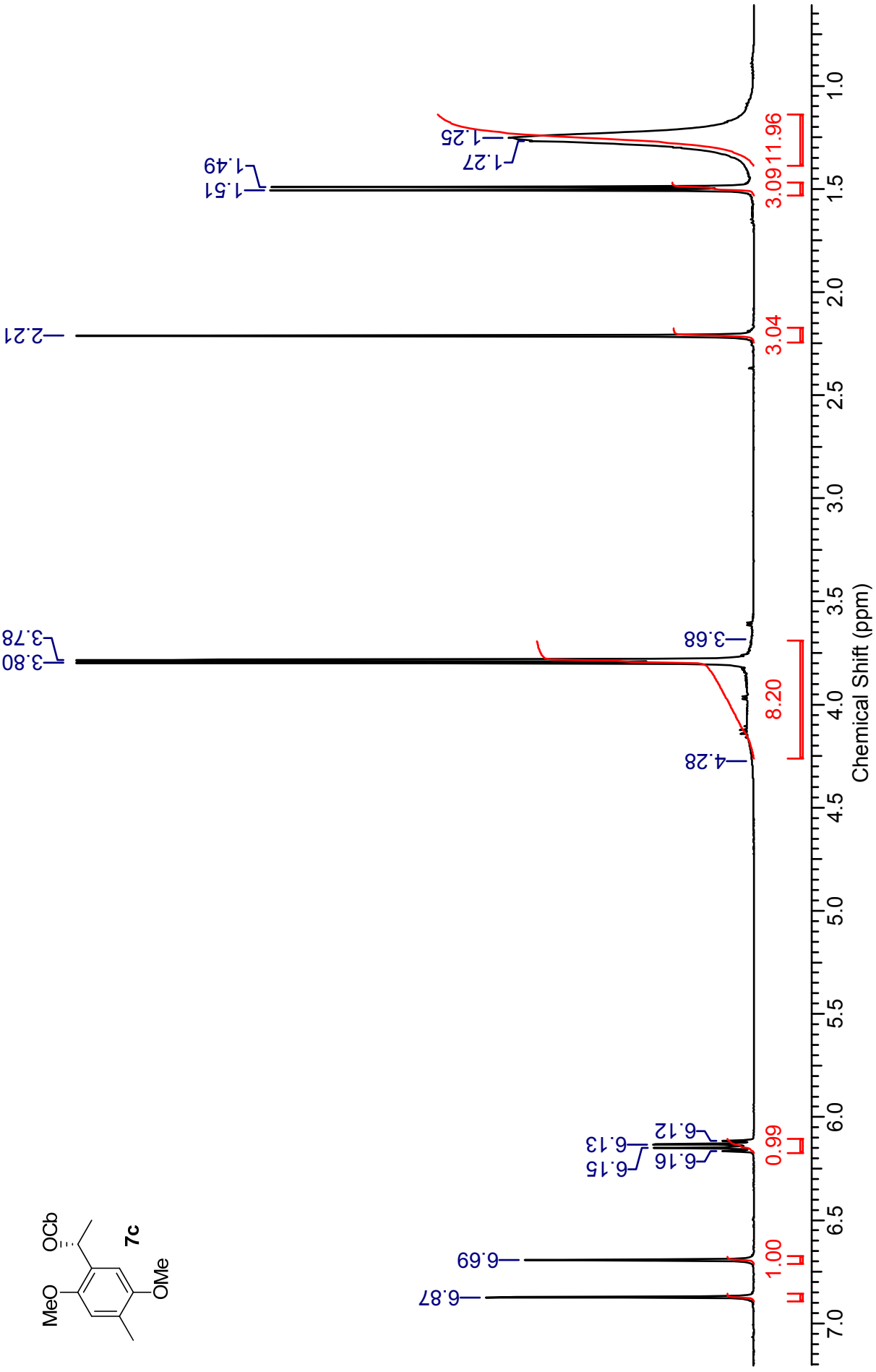

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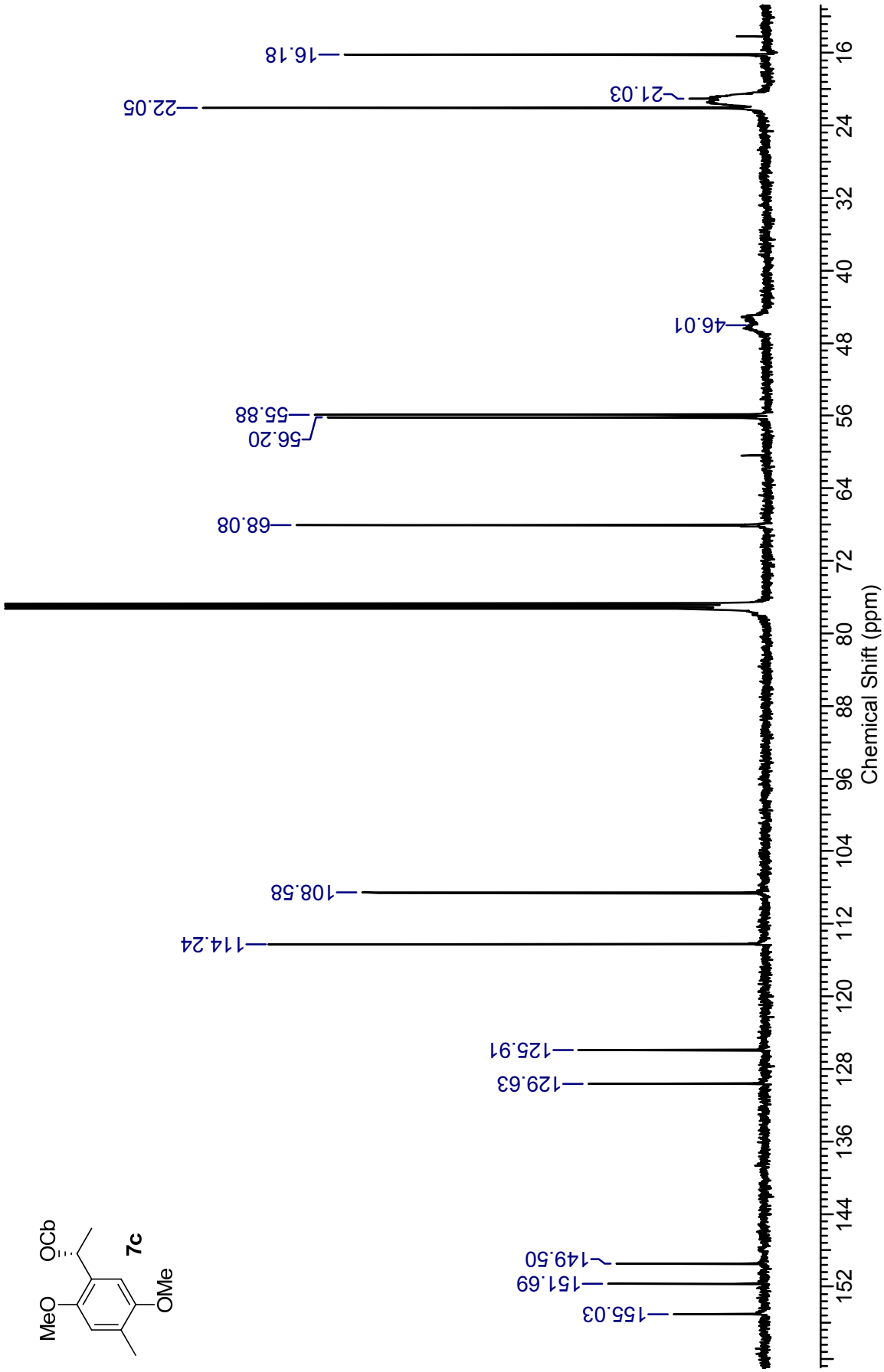

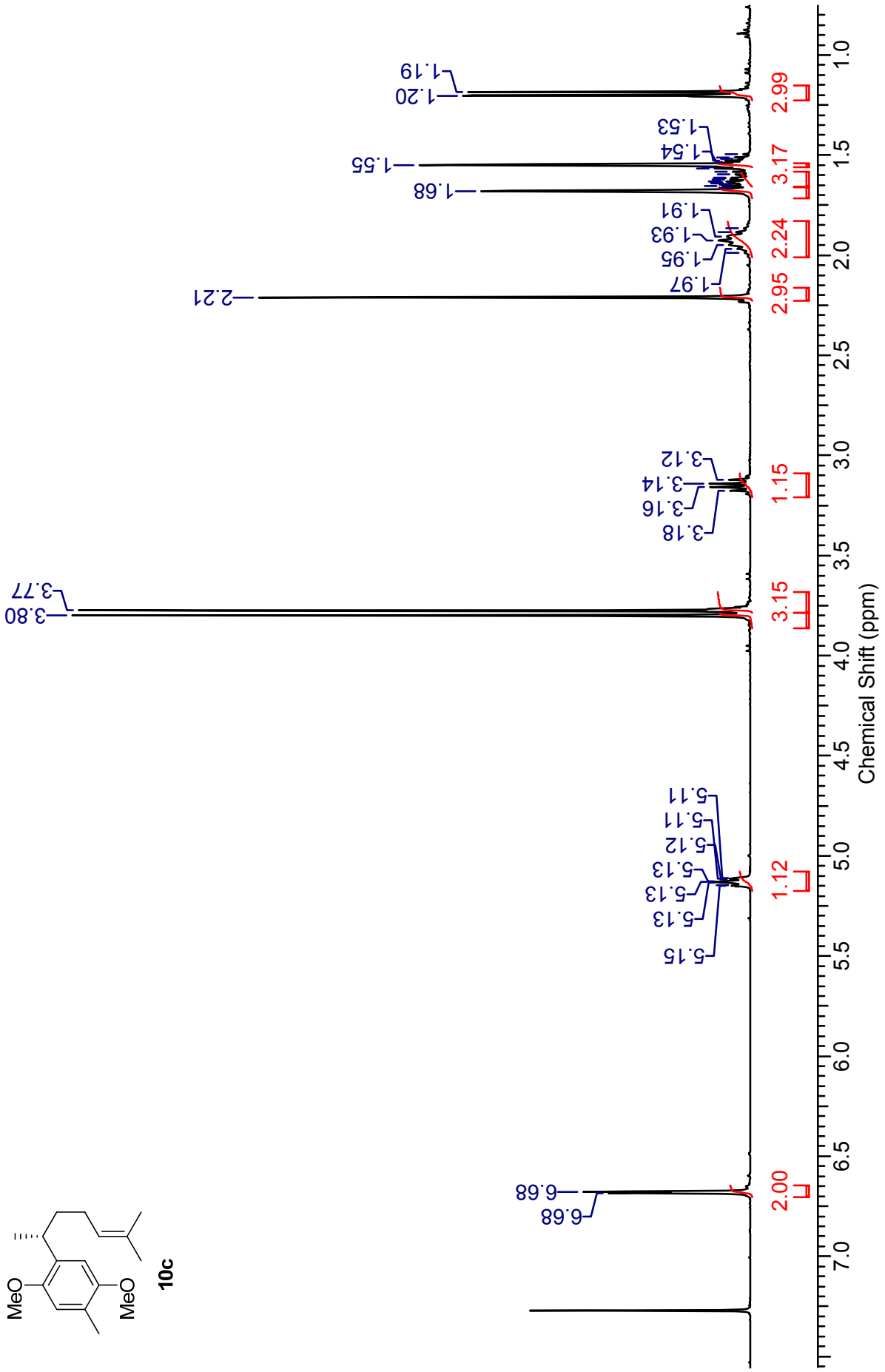
6.68
6.68
5.15
5.13
5.13
5.13
5.12
5.11
5.11
3.80
3.77
3.18
3.16
3.14
3.12
2.21
1.97
1.95
1.93
1.91
1.68
1.55
1.54
1.53
1.20
1.19
2.00
1.12
3.15
1.15
2.95
2.24
3.17
2.99
Chemical Shift (ppm)
MeO
MeO
10c

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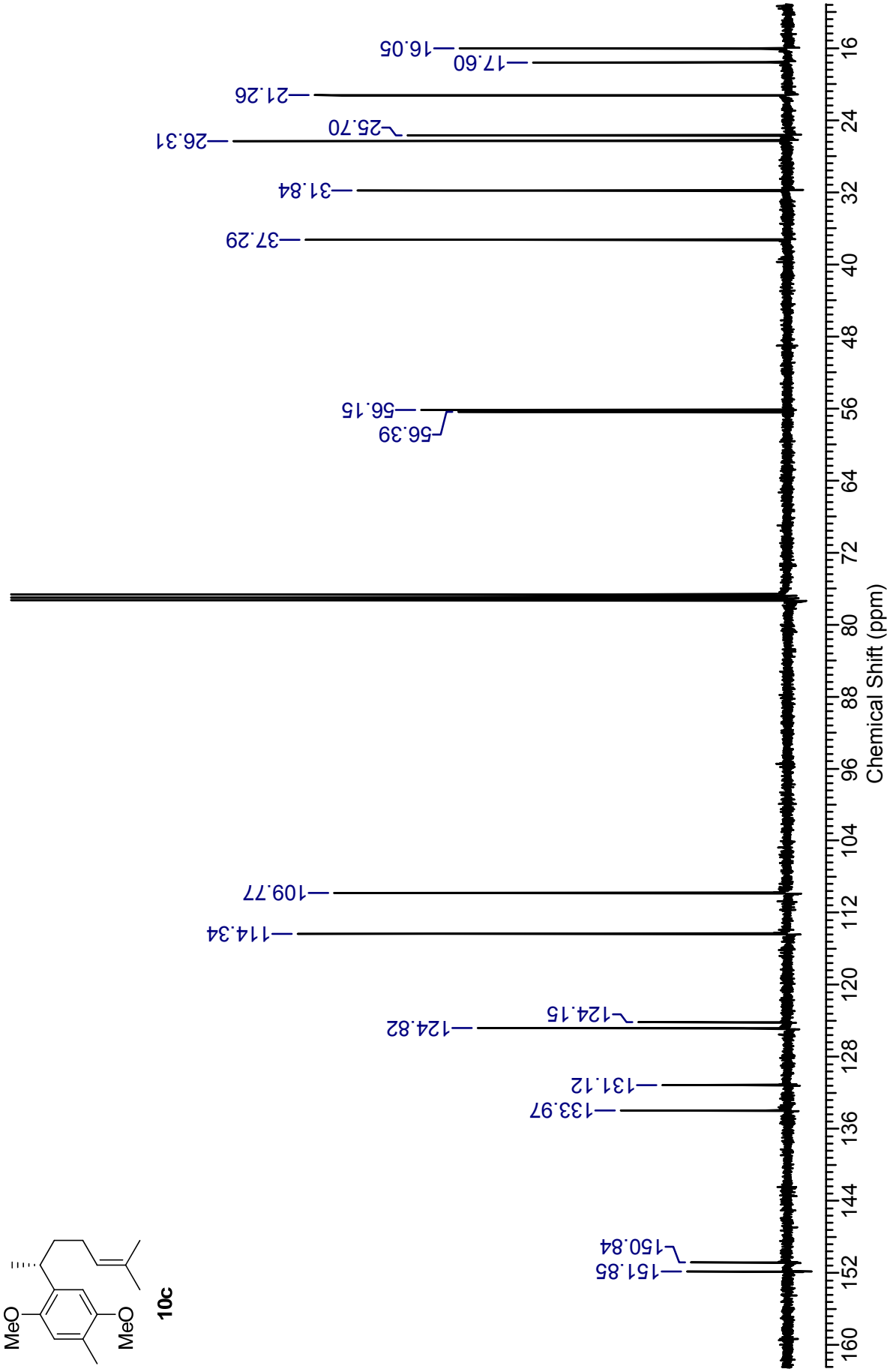

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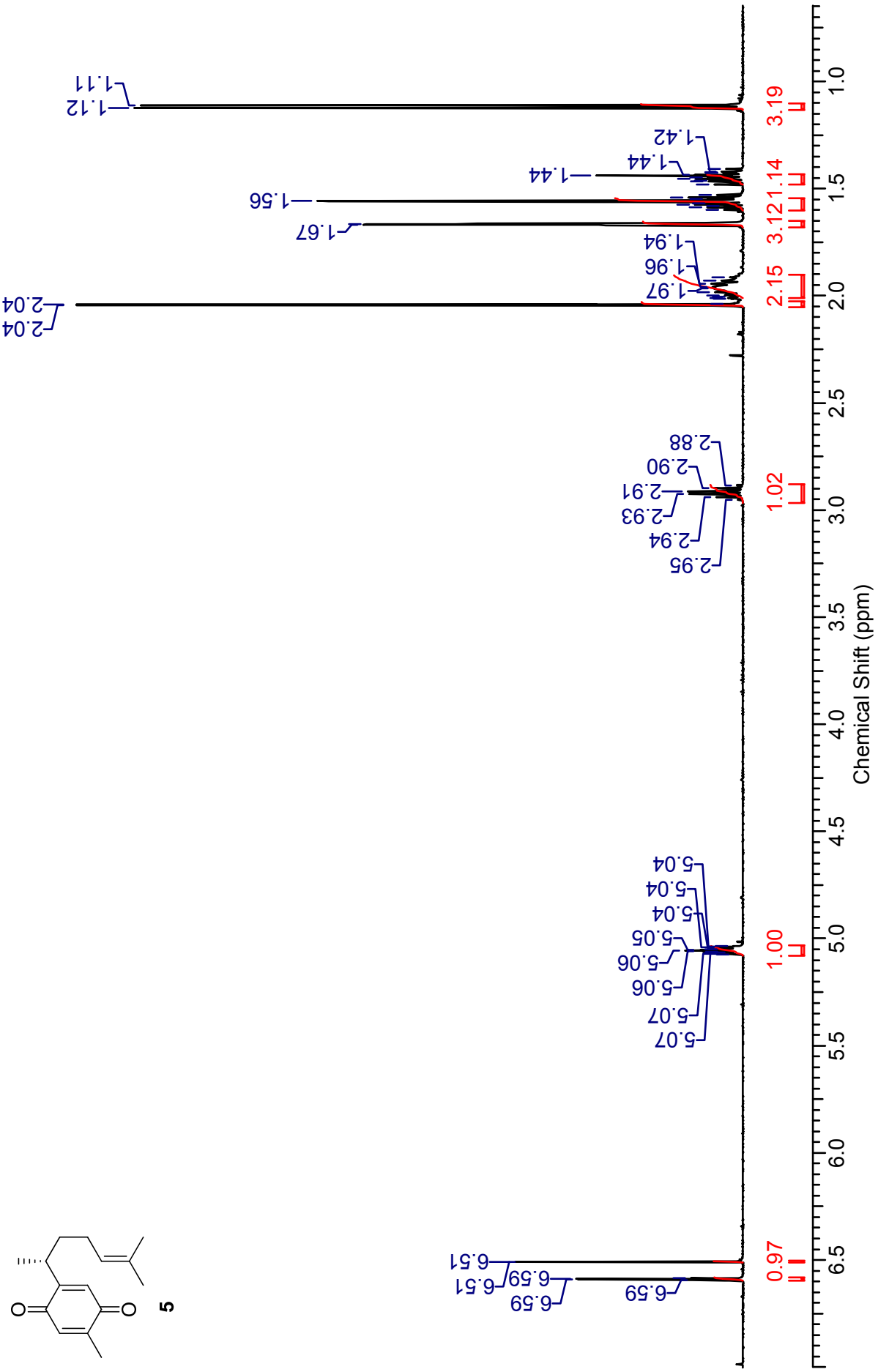

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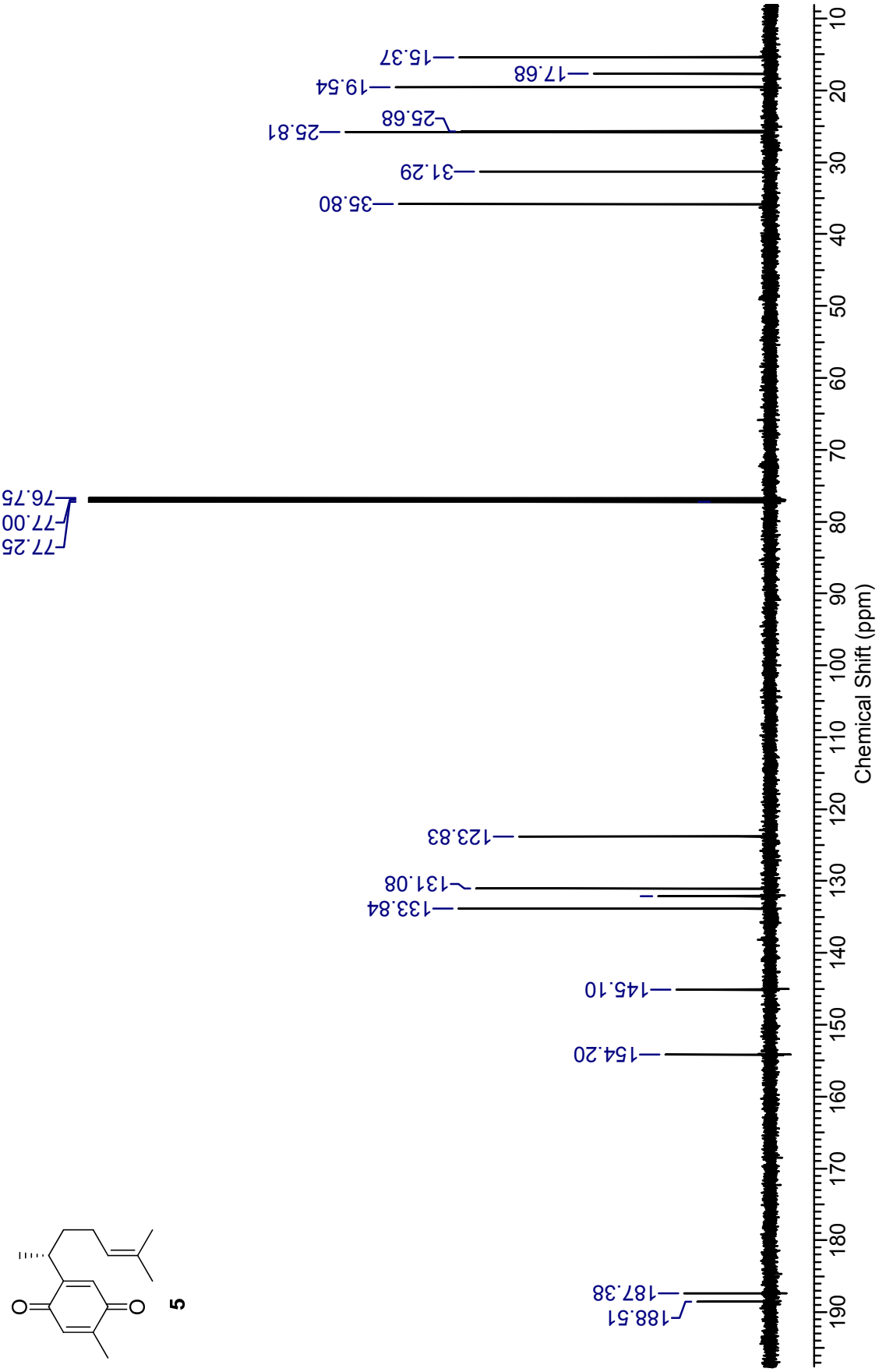

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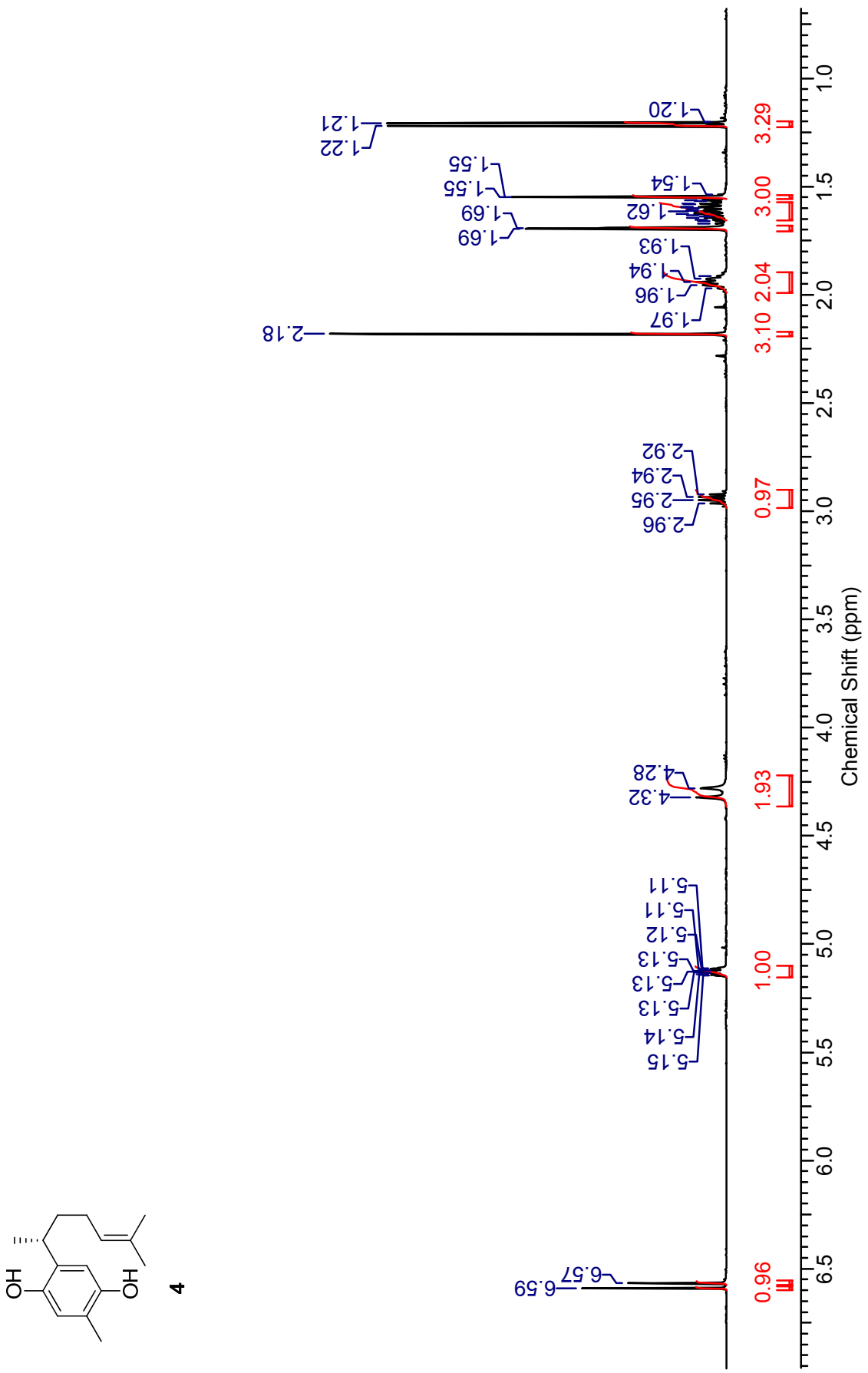

4

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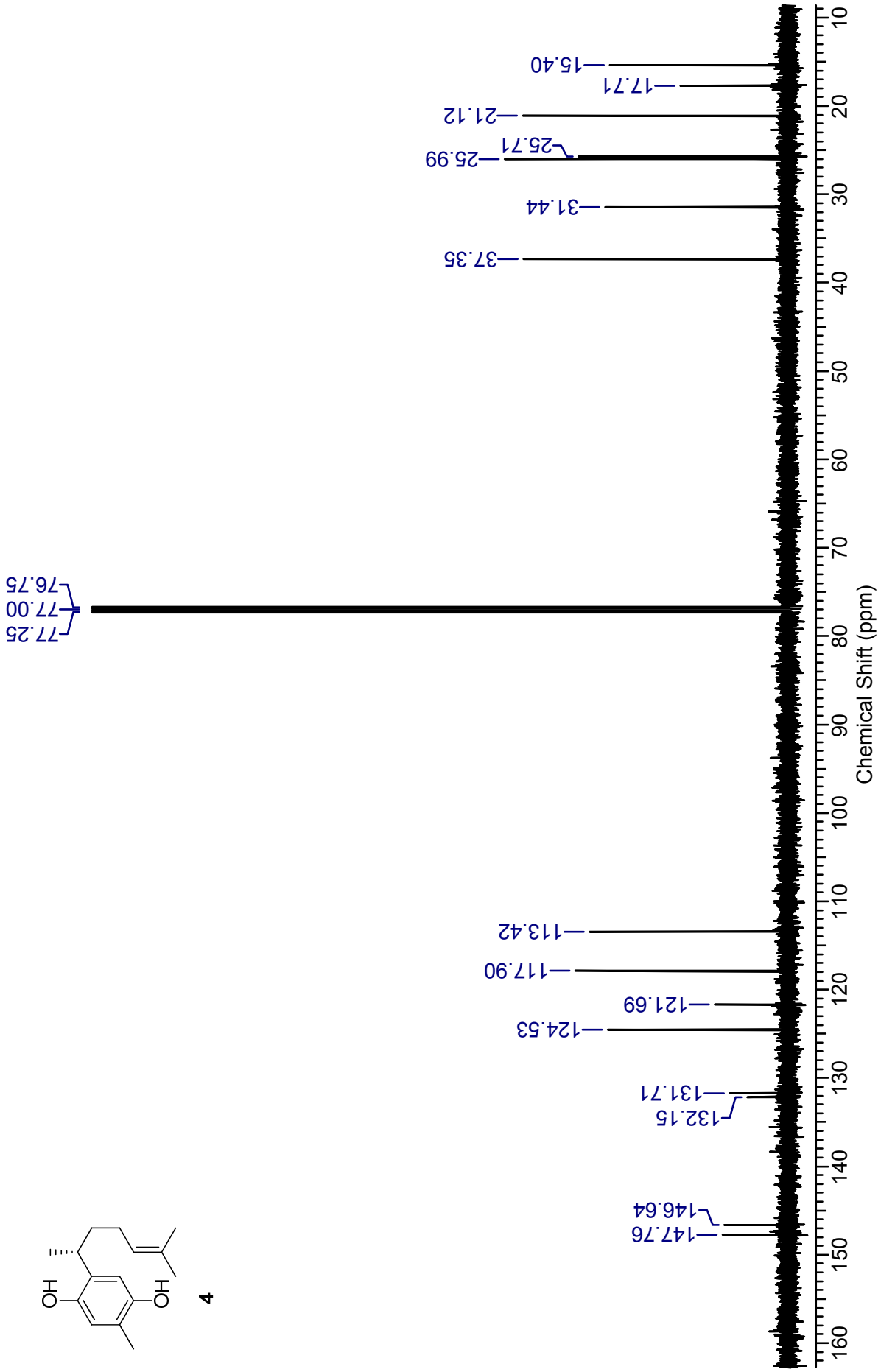

4

5. References

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