Stereoselective Synthesis of the Diazonamide A Macrocyclic Core

Ilga Mutule,[†] Beomjun Joo,[‡] Zane Medne,[†] Toms Kalnins[†], Edwin Vedejs[‡] and Edgars Suna*[†]

[†]*Latvian Institute of Organic Synthesis, Aizkraukles 21, LV-1006, Riga, Latvia*

[‡]*Department of Chemistry, University of Michigan, Ann Arbor, Michigan 48109*

edgars@osi.lv

CONTENTS

Dynamic Light Scattering (DLS) and Transmission Electron Microscopy (TEM) studies

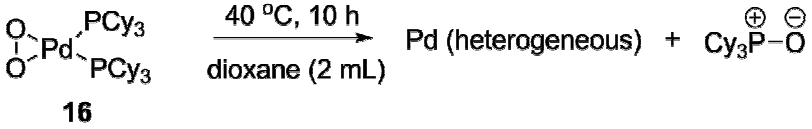
General Information

$(PCy_3)_2Pd(\eta^2\text{-}O_2)$ (**16**) complex was freshly prepared from $(PCy_3)_2Pd$ and stored at –20 °C. Dioxane was distilled from Na/benzophenone and degassed using freeze-pump-thaw technique. Thermal decomposition of the Pd-dioxygen complex **16** and Suzuki cross-coupling reaction between the hemiaminal bromide (*R,R*)–**5** and indolyl boronate **4** were carried out under argon atmosphere in an oven–dried glassware.

The size distribution and the mean sizes of nanoparticles were determined by *Malvern* Zetasizer Nano ZSP system. Data were analyzed by Malvern Zetasize software 7.10. Following specifications were used for dioxane solutions: viscosity η=1.194 mPa/s, refractive index n=1.422, temperature T=25°C; dielectric constant ε=2.25.

Transmission electron micrographs (TEM) were recorded on *Tecnai GF20* transmission electron microscope. Samples for TEM were prepared by drop-casting ~3 μL of the analyte on a holey carbon-coated 400-mesh copper TEM grid (S147-4 Agar scientific) The excess of the solution was carefully removed by filter paper and the grid was dried under air at ambient conditions.

Thermal decomposition of the $(PCy_3)_2Pd(\eta^2\text{-}O_2)$ (16) complex.



16

The Pd-dioxygen complex **16** (5 mg) was dissolved in dioxane (2 mL) under an argon atmosphere. The solution was transferred to cuvette (12 mm square glass cell with stopper) and placed into preheated (40° C) Zetasizer Nano system. After heating at 40° C for 10 hours three measurements were carried out (Table S1 and Figure S1).

Table S1. Mean count, $D_{Z\text{-}aver}$, PDI and maximum peaks of DLS measurements for the reaction mixture of thermal decomposition of the $(PCy_3)_2Pd(\eta^2\text{-}O_2)$ (**16**).

Entry	Mean count rate,[a] kcps	$D_{Z\text{-}aver}$,[b] nm	PDI[c]	Maximum peaks[d]			
				Peak 1 mean int. d, nm	Peak 1 area, %	Peak 2 mean int. d, nm	Peak 2 area, %
1	189	363	0.533	3	71	150	22
2	192	251	0.382	3	71	220	29
3	195	368	0.540	3	77	144	23

[a] Mean count rate is number of photons detected during the measurement. [b] Z-avarage diameter ($D_{Z\text{-}aver}$) is harmonic intensity averaged particle diameter, measured as a diameter of dynamic solvated particles. [c] Polydispersity index (PDI) describes particle size distribution; [d] Intensity of maximum peaks shows the most abundant particle size.

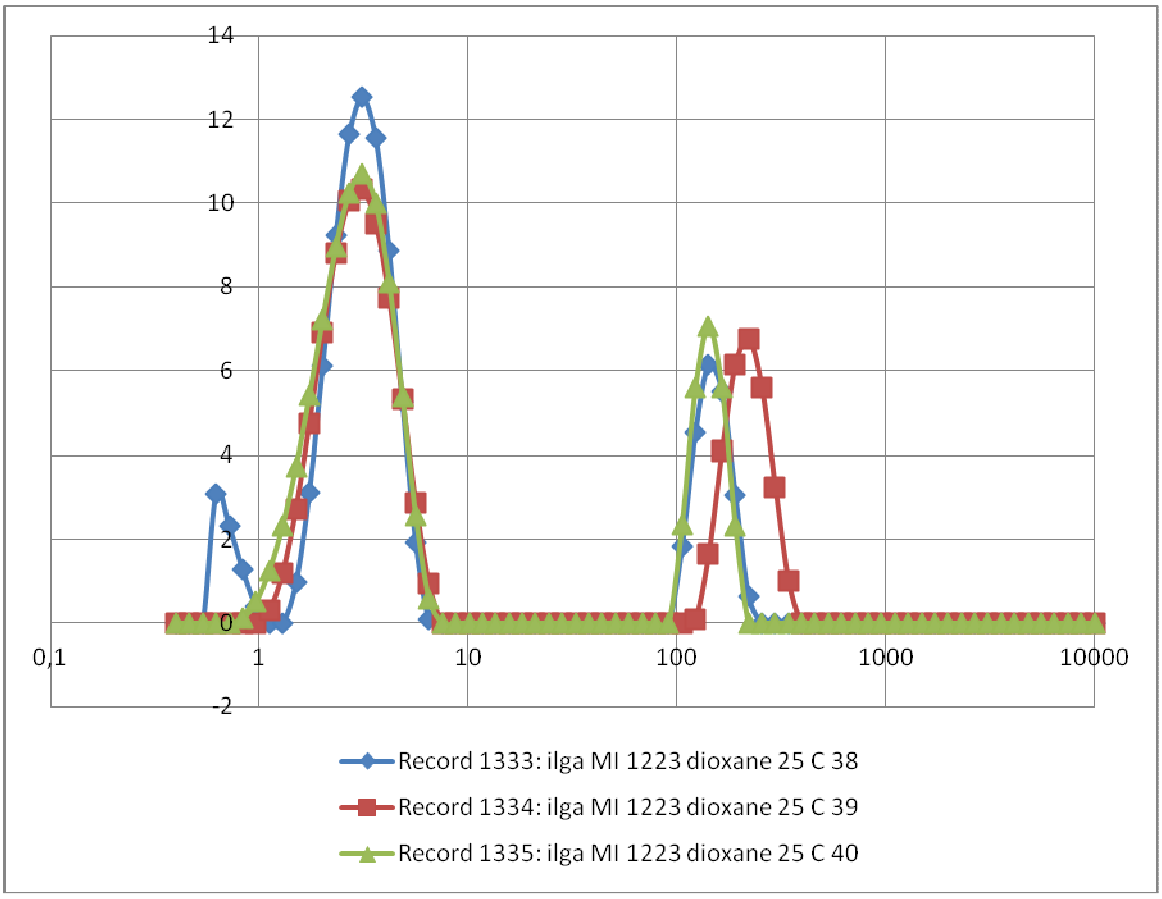


Figure S1. DLS analysis of particle size distribution in the thermal decomposition of Pd-dioxygen complex **16**.

DLS measurements suggest that the thermal decomposition of $(PCy_3)_2Pd(\eta^2\text{-}O_2)$ (**16**) results in the formation of particles of different sizes (avarage size ~250-400 nm, polydispersity index ~0.3-0.6). A considerable amount of the detected particles

fall into category of small particle group (< 10nm). The mean count of measurements is low (180-190 kcps) indicating the low concentration of the particles.

Subsequently, the solution of Pd–dioxygen complex **16** from above (the thermal decomposition reaction mixture) was diluted with chloroform (10 times) and submitted to TEM analysis (Figures S2 and S3).

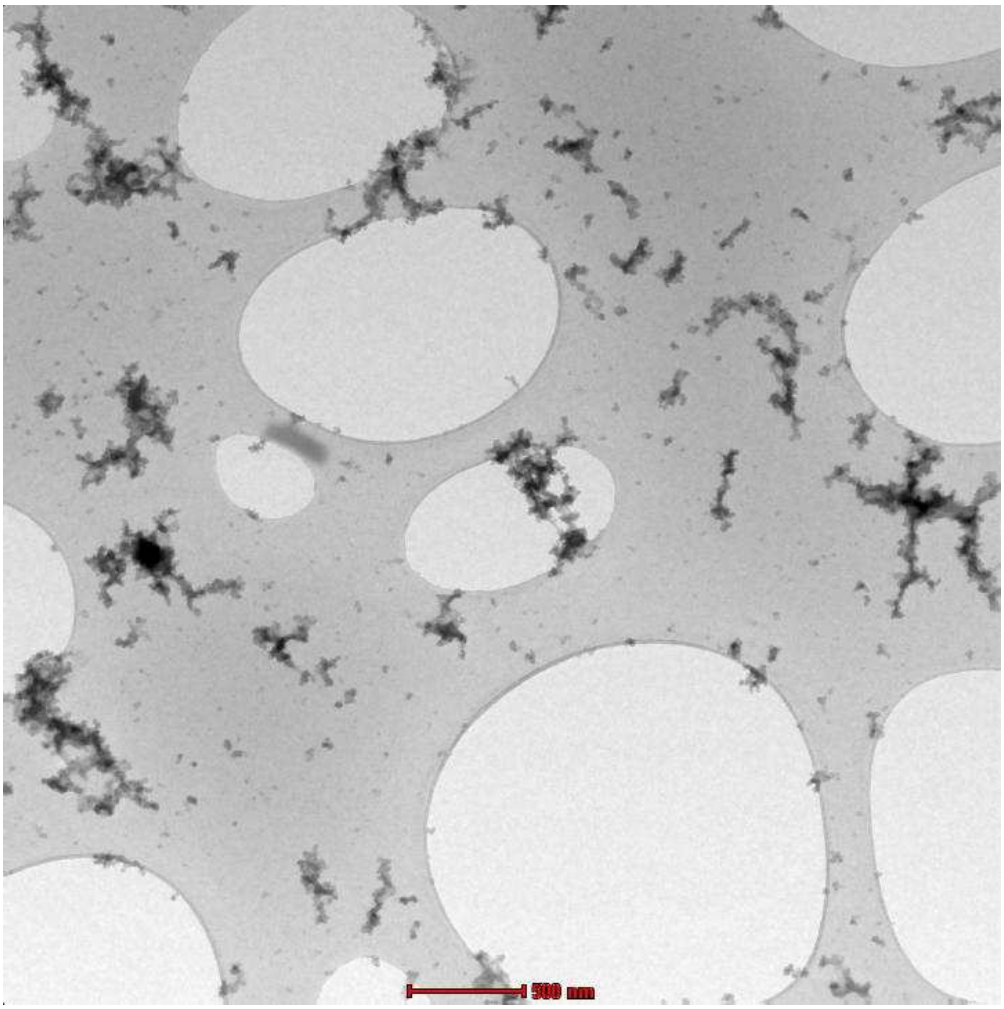


Figure S2. TEM image of the Pd–dioxygen complex **16** thermal decomposition reaction mixture (500 nm scale bar is shown at the bottom of the picture).

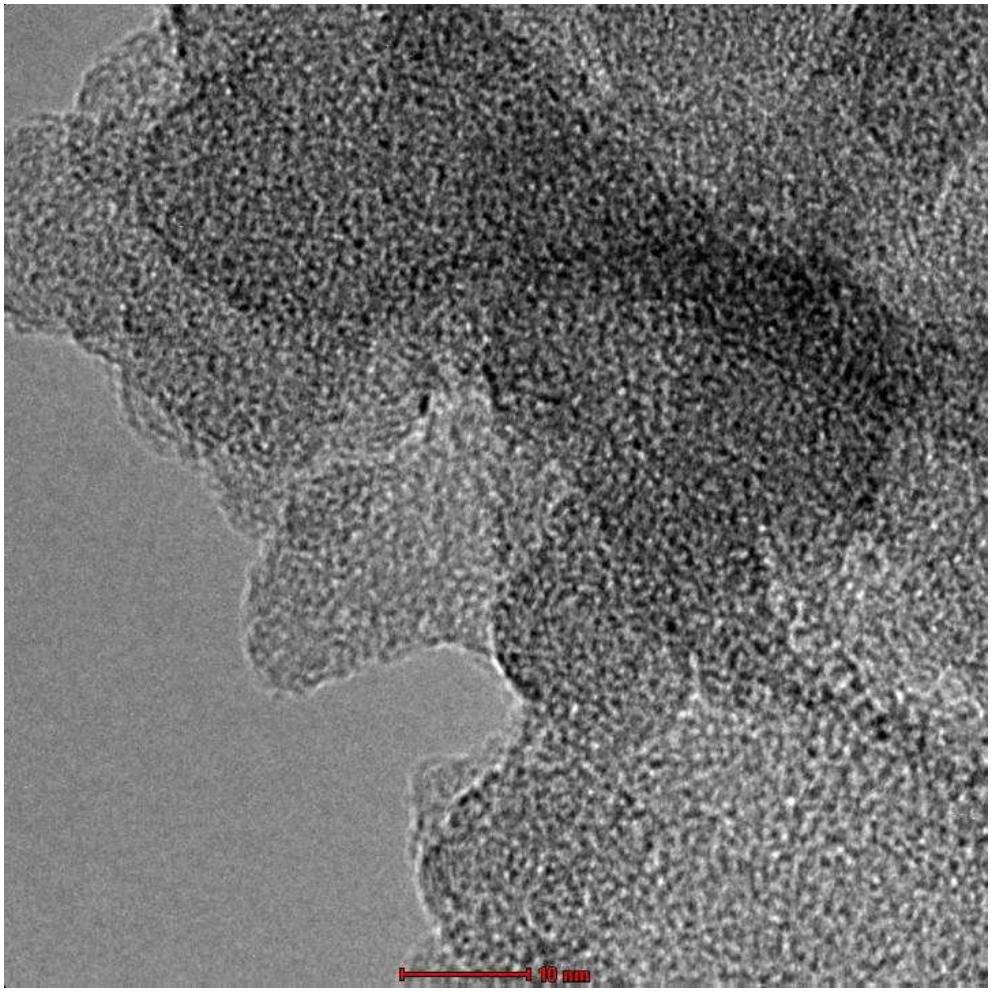
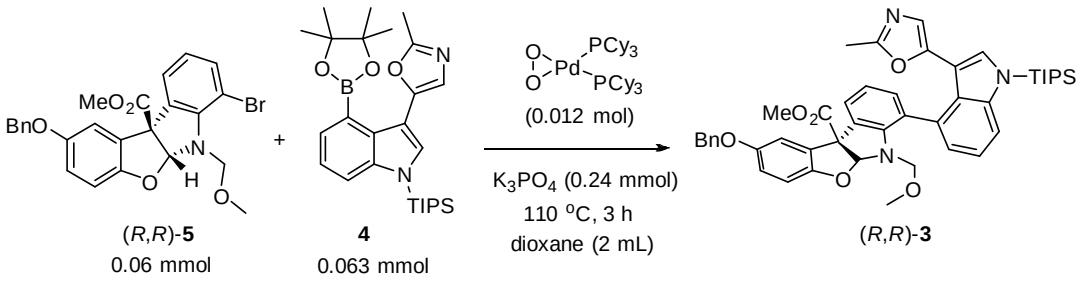


Figure S3. TEM image of the Pd–dioxygen complex **16** thermal decomposition reaction mixture (10 nm scale bar is shown at the bottom of the picture).

TEM images show the formation of amorphous products after the thermal decomposition of Pd–dioxygen complex **16.** However, there are no structures that could be attributed to nanoparticle-sized Pd species.

Analysis of the Suzuki cross-coupling reaction mixture.



The Suzuki cross-coupling reaction mixture was prepared as described in the Experimental. After heating at 110 °C for 3 h under atmosphere of argon the green–colored reaction mixture was filtered through a plug of Celite and subsequently through a microfilter (400 nm). The filtrate was transferred to cuvette (12 mm square glass cell with stopper) and analyzed by Zetasizer Nano system.

Table S2. DLS measurements of the Suzuki cross-coupling reaction mixture.

Entry	Mean count rate,[a] kcps	$D_{Z\text{-}aver}$,[b] nm	PDI[c]	Maximum peaks[d]			
				Peak 1 mean int. d, nm	Peak 1 area, %	Peak 2 mean int. d, nm	Peak 2 area, %
1	210	340	0.751	2	73	255	53
2	205	772	0.821	1	47	276	53
3	181	1570	1.0	2	51	185	49

[a] Mean count rate is number of photons detected during the measurement. [b] Z-avarage diameter ($D_{Z\text{-}aver}$) is harmonic intensity averaged particle diameter, measured as a diameter of dynamic solvated particles. [c] Polydispersity index (PDI) describes particle size distribution; [d] Intensity of maximum peaks shows the most abundant particle size.

The polydispersity of the Suzuki cross-coupling reaction mixture is high (the polydispersity index is ~0.7-1.0). An average size of the deteceted particles varies in a wide range from ~300 to 1500 nm. Two main groups of particles with size below 10 nm and with size of 200–300 nm have been identified (see Figure S4). Palladium species from both of these groups could in principle serve as active catalysts in the Suzuki cross-coupling. However, the low mean count of measurements (180-210 kcps) indicates low concentration of theses particles.

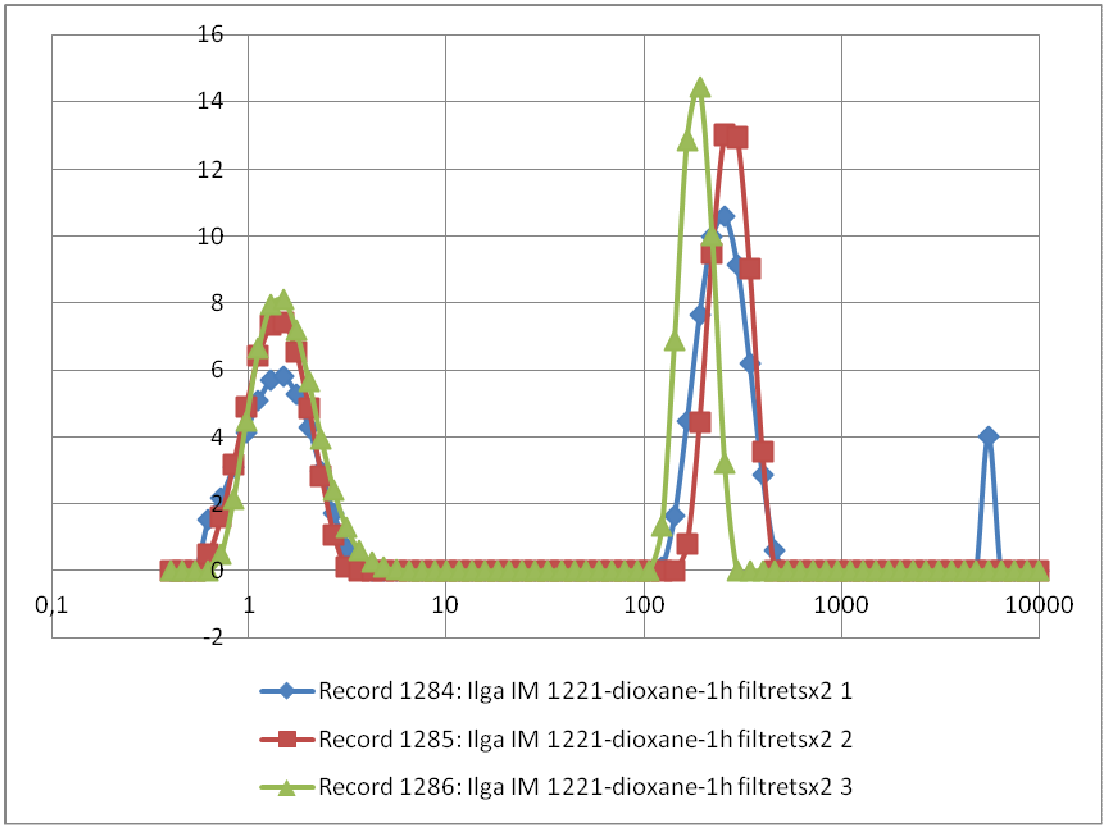


Figure S4. DLS analysis of particle size distribution in the Suzuki cross-coupling reaction.

For TEM analysis, the Suzuki cross-coupling reaction mixture was filtered through a plug of Celite and the filtrate was diluted with chloroform (10 times). Acquired TEM images revealed agglomerates of different size, ranging from 1 to 200 nm (Figure S5). Particles of 1–2 nm in size can be observed as individual species as well as a part of larger agglomerates. A crystalline structure of the representative individual particle could be also observed (Figure S6).

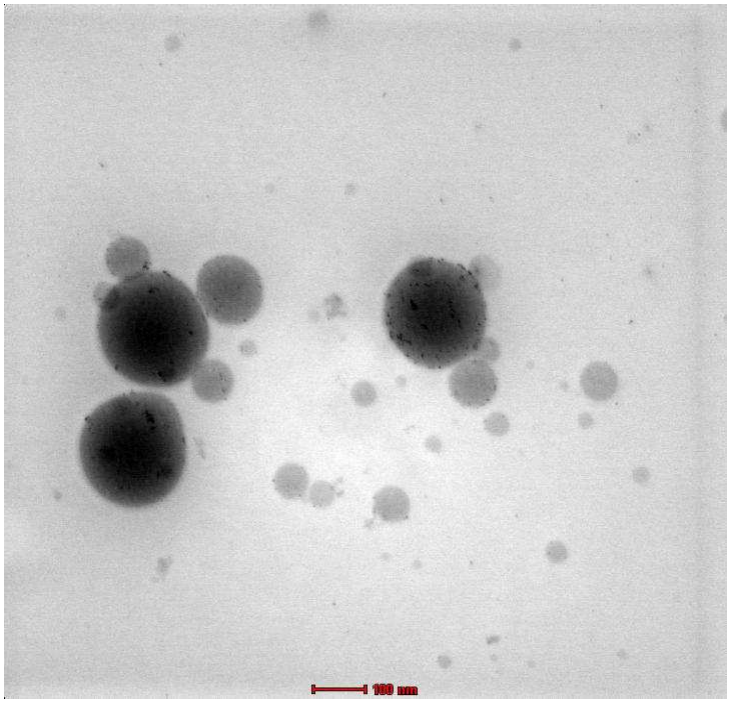


Figure S5. TEM image of the Suzuki reaction mixture (100 nm scale bar is shown at the bottom of the picture)

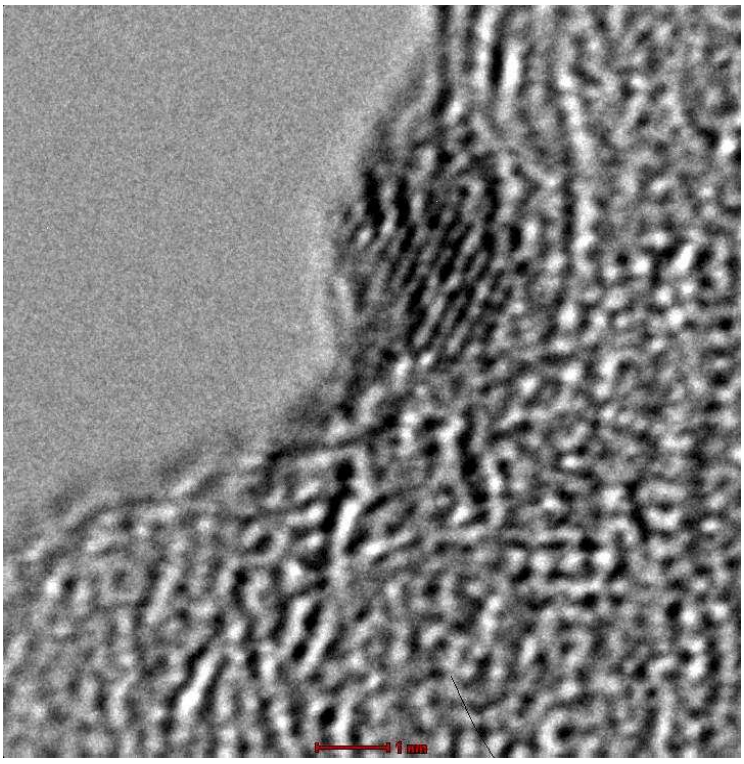


Figure S6. TEM image of a representative individual particle from the Suzuki reaction mixture (1 nm scale bar shown at the bottom of the picture)

Scanning transmission electron microscopy (S/TEM) coupled with EDX (EDAX) detector was used also to determine composition of elements in four

different regions of the heterogeneous Suzuki cross-coupling reaction sample (see Figure S7; regions of interest #1-#4 are marked by circle with diameter ca. 10 nm).

1) region #1 is chosen in the area of large agglomerate containing small (1-2 nm in size) particles;

2) region #2 is positioned in the area of large agglomerates lacking the presence of the small particles;

3) region#3 is in the area of large agglomerates with explicit presence of small particles;

4) region#4 is apart from the area of agglomerates.

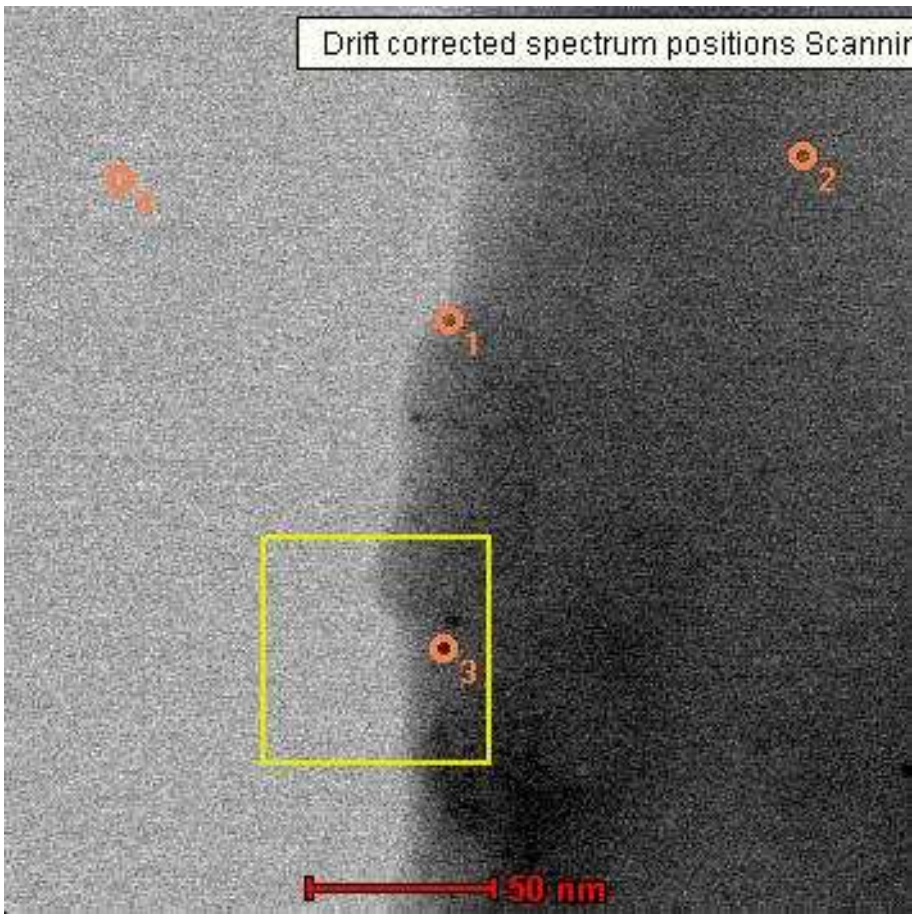


Figure S7. Spectrum positions for elemental analysis of Suzuki reaction mixture sample (50 nm scale bar is shown).

Elemental analysis for the selected regions #1-#4 is depicted in Figures S8-S11.

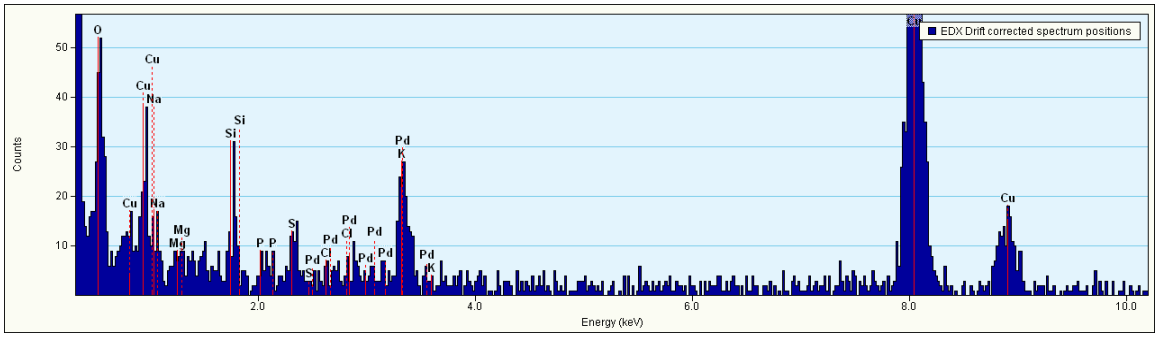


Figure S8. Composition of elements in region #1.

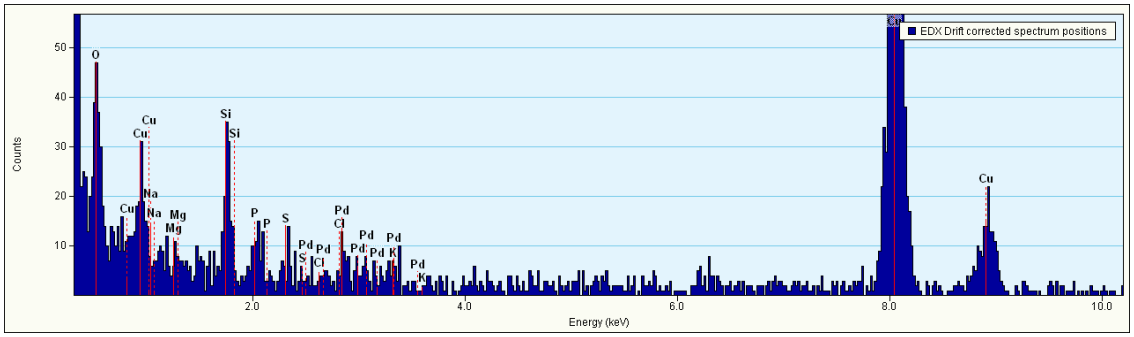


Figure S9. Composition of elements in region #2.

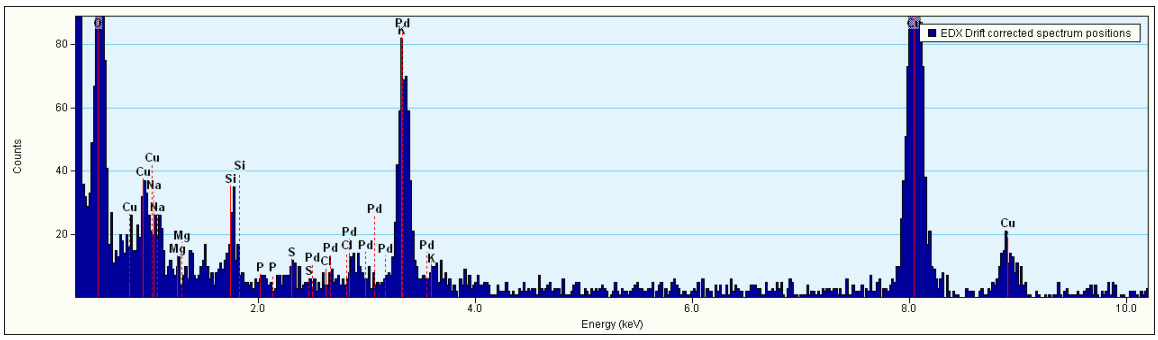


Figure S10. Composition of elements in region #3.

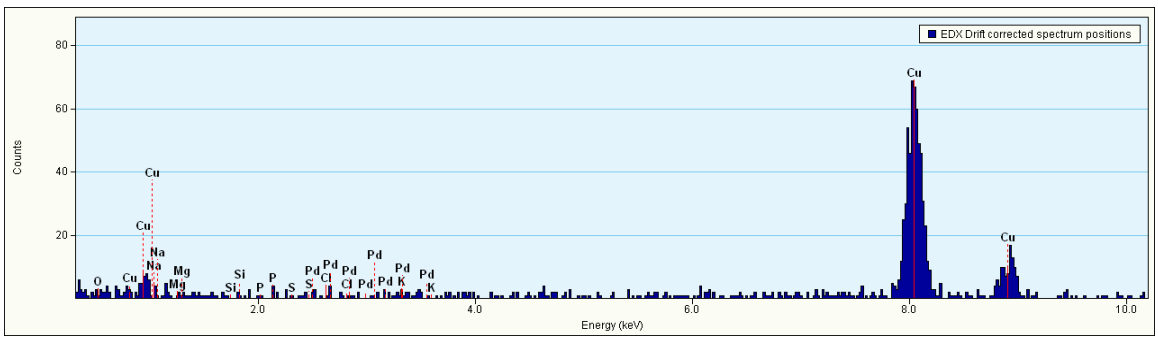


Figure S11. Composition of elements in region #3

Composition of elements in regions #1 and #3 which contained small size particles (1-2 nm) displays intense potassium signals suggesting that the small particles are potassium phosphate crystals. The potassium $K\alpha_1 K\alpha_2$ located at 3,31keV

in images overlaps with palladium Lγ band, however the palladium Lα and Lβ lines are not present at expected intensities. Large agglomerates consist mainly of organic elements incorporated into reactants. Traces of palladium can be found in every position of spectra. Consequently, the presence of palladium nanoparticles in the Suzuki cross-coupling reaction was not observed by STEM/EDX studies.

Atropisomerization of biaryl (*R*,*R*)-3 in C_6D_6

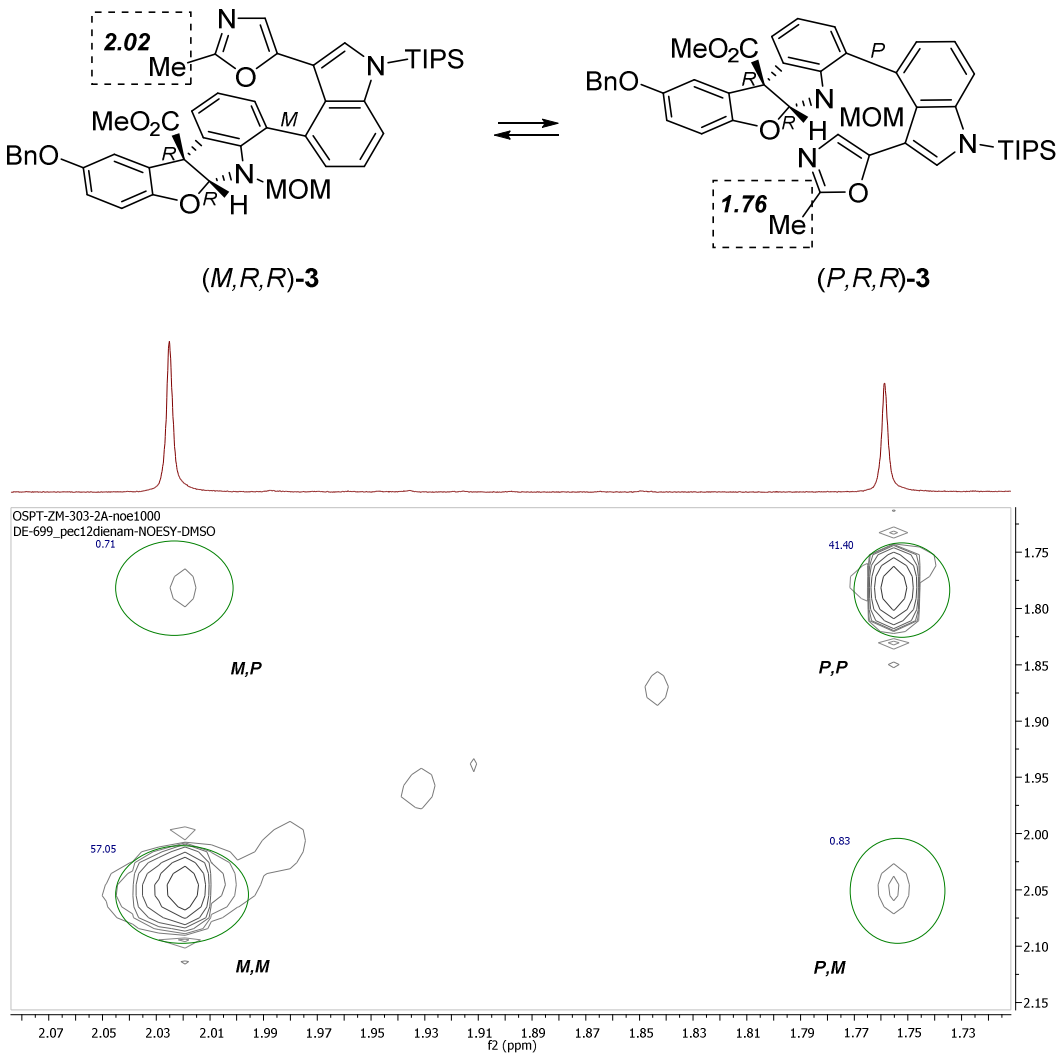


Figure S12. 2D-EXSY data in C_6D_6 for (*R*,*R*)-**3** at T=313 K and mixing time t_m=1 s.

The rate constant for chemical exchange k was calculated based on equations (1-2)[1] for uncoupled pair of spins (*M*,*R*,*R*)-**3** (designated as *M*) and (*P*,*R*,*R*)-**3** (designated as *P*), present in mole fractions X_M and X_P, with diagonal intensities I_{MM} and I_{PP} and cross-peak intensities I_{MP} and I_{PM}, respectively.

$$k = \frac{1}{t_m} \cdot \ln \frac{r+1}{r-1} \qquad (1)$$

(1) (a) Perrin, C. L.; Dwyer, T. G. *Chem. Rev.* **1990**, *90*, 935. (b) Gibson, K. R.; Hitzel, L.; Mortishire-Smith, R. J.; Gerhard, U.; Jelley, R. A.; Reeve, A. J.; Rowley, M.; Nadin, A.; Owens, A. P. *J. Org. Chem.* **2002**, *67*, 9354.

$$r = \frac{4X_M X_P (I_{MM} + I_{PP})}{(I_{MP} + I_{PM})} - (X_M - X_P)^2 \qquad (2)$$

The rate constant represents a sum of forward and reverse rate constants, which are proportional to the mole fractions X_P and X_M under equilibrium conditions (equation 3).

$$k = k_{M\to P} + k_{P\to M} = k \cdot X_P + k \cdot X_M \qquad (3)$$

Based on the determined rate constants, free energy of activation $\Delta G^{\neq}$ for atropisomerization of biaryl (*R*,*R*)-**3** was calculated at T = 289 K and T = 313 (equation 4).

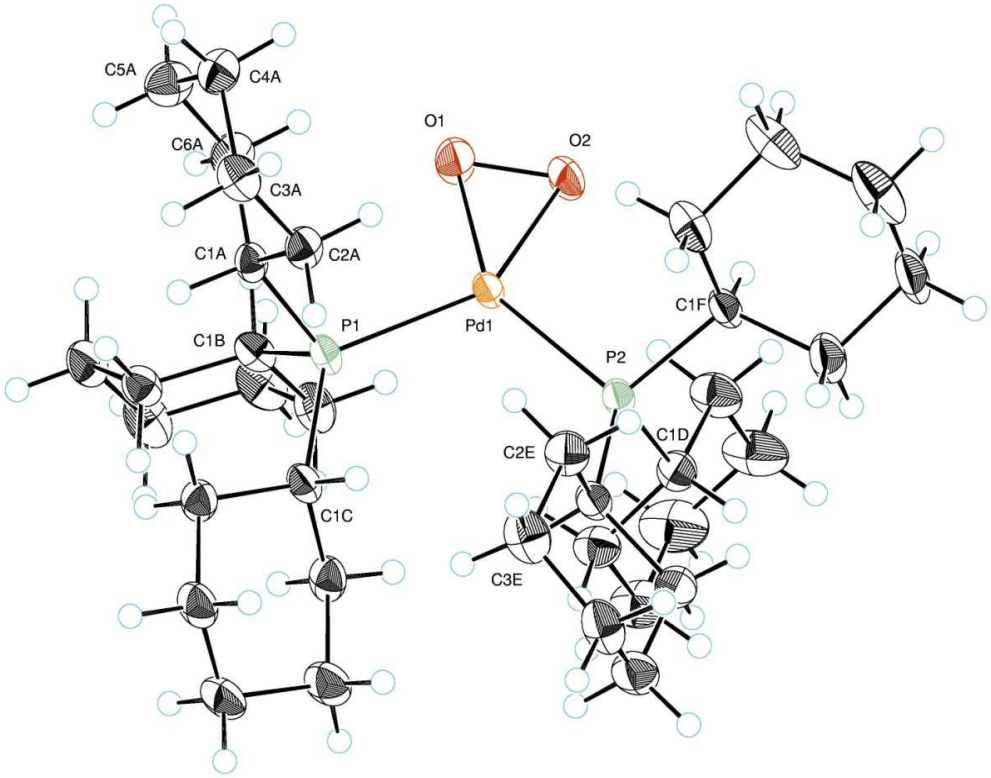
$$k = \frac{k_B \cdot T}{h} \cdot e^{\frac{-\Delta G^{\neq}}{RT}} \qquad (4)$$

Table S3. Calculated constants and the energy of activation for atropisomerization of biaryl (*R*,*R*)-**3** in C_6D_6.

Temperature	$k_{M\to P}$ (s^{-1})	$k_{P\to M}$ (s^{-1})	$\Delta G^{\neq}_{M\to P}$ (kJ/mol)	$\Delta G^{\neq}_{P\to M}$ (kJ/mol)
289 K	0.018	0.012	83.0	83.9
313 K	0.075	0.055	83.5	84.4

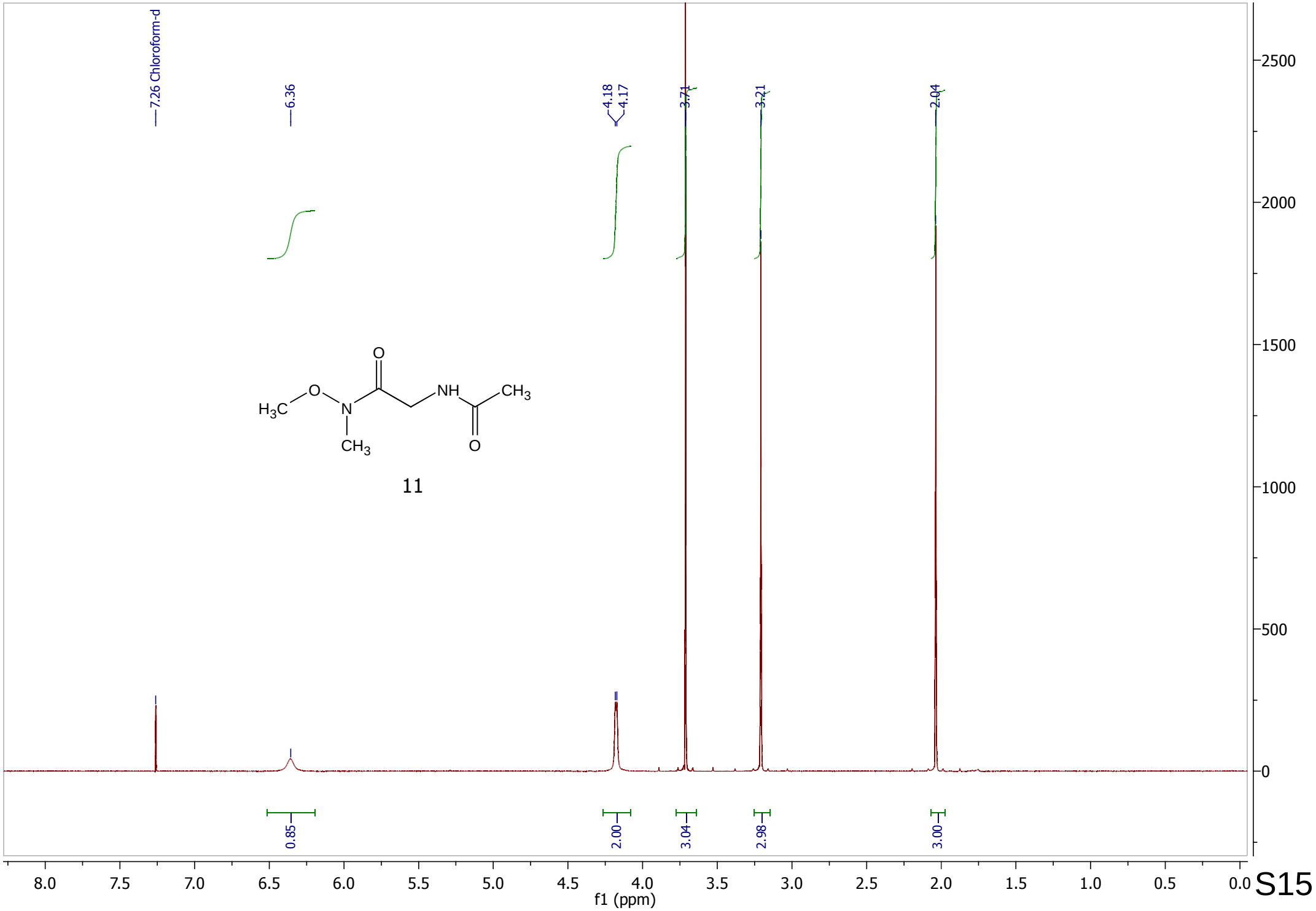
Calculated half-life at 289 K ($t_{1/2} = \frac{\ln 2}{k}$) for *M*→*P* atropisomerization is 39 s and for *P*→*M* atropisomerization is 53 s. At 313 K the half-life is 9.2 s for *M*→*P* and 12.6 s for *P*→*M* interconversion.

The X-ray structure of $(PCy_3)_2Pd(\eta^2\text{-}O_2)$ (**16**)



Crystal data and structure refinement for $(PCy_3)_2Pd(\eta^2\text{-}O_2)$ (**16**).

Identification code	ZM-698
Empirical formula	C40 H76 O3 P2 Pd
Formula weight	773.35
Temperature	173(2) K
Wavelength	0.71073 A
Crystal system	monoclinic
Space group	P 21/n
Unit cell dimensions	a = 10.6143(1) A alpha = 90 deg. b = 29.5816(4) A beta = 98.3194(7) deg. c = 13.6374(2) A gamma = 90 deg.
Volume	4236.92(9) A^3
Z	4
Density (calculated)	1.212 Mg/m^3
Absorption coefficient	0.546 mm^-1
F(000)	1664
Crystal size	0.16 x 0.17 x 0.21 mm
Two-theta max. for data	57.0 deg.
Index ranges	-14<=h<=14, -39<=k<=36, -18<=l<=18
Reflections collected	18649
Independent reflections	10845 [R(int) = 0.029]
Max. and min. transmission	0.916 and 0.895
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	8267 / 0 / 370
Goodness-of-fit	1.528
Final R indices [I>3sigma(I)]	R1 = 0.064, wR2 = 0.194
R indices (all data)	R1 = 0.097, wR2 = 0.281
Largest diff. peak and hole	1.49 and -1.23 e.A^-3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4.17
3.71
3.21
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O
NH
CH3
H3C
N
CH3
O
11
0.85
2.00
3.04
2.98
3.00
2500
2000
1500
1000
500
0
8.0
7.5
7.0
6.5
6.0
5.5
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4.5
4.0
3.5
3.0
2.5
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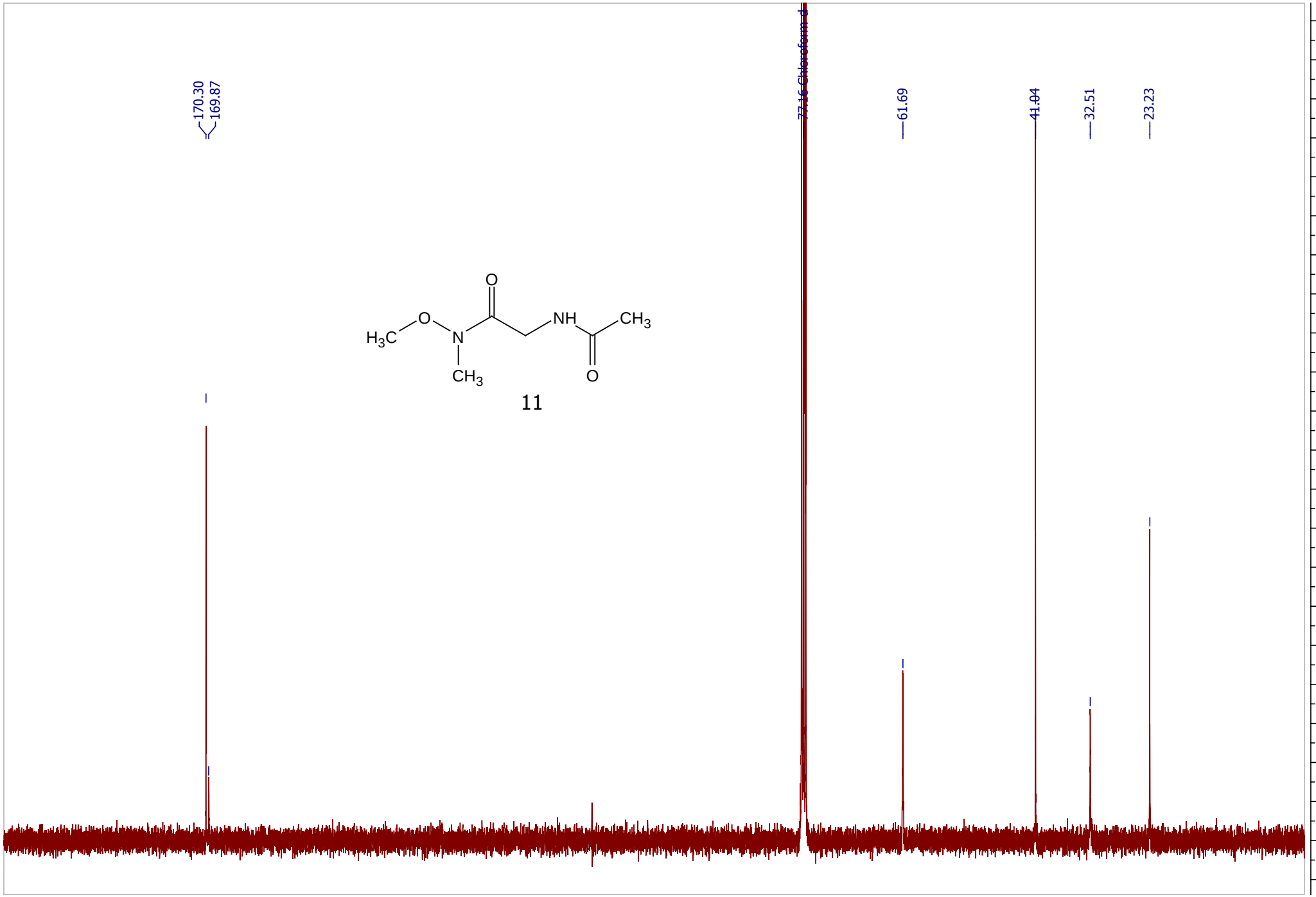
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CH3
O
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2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
200
190
180
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10
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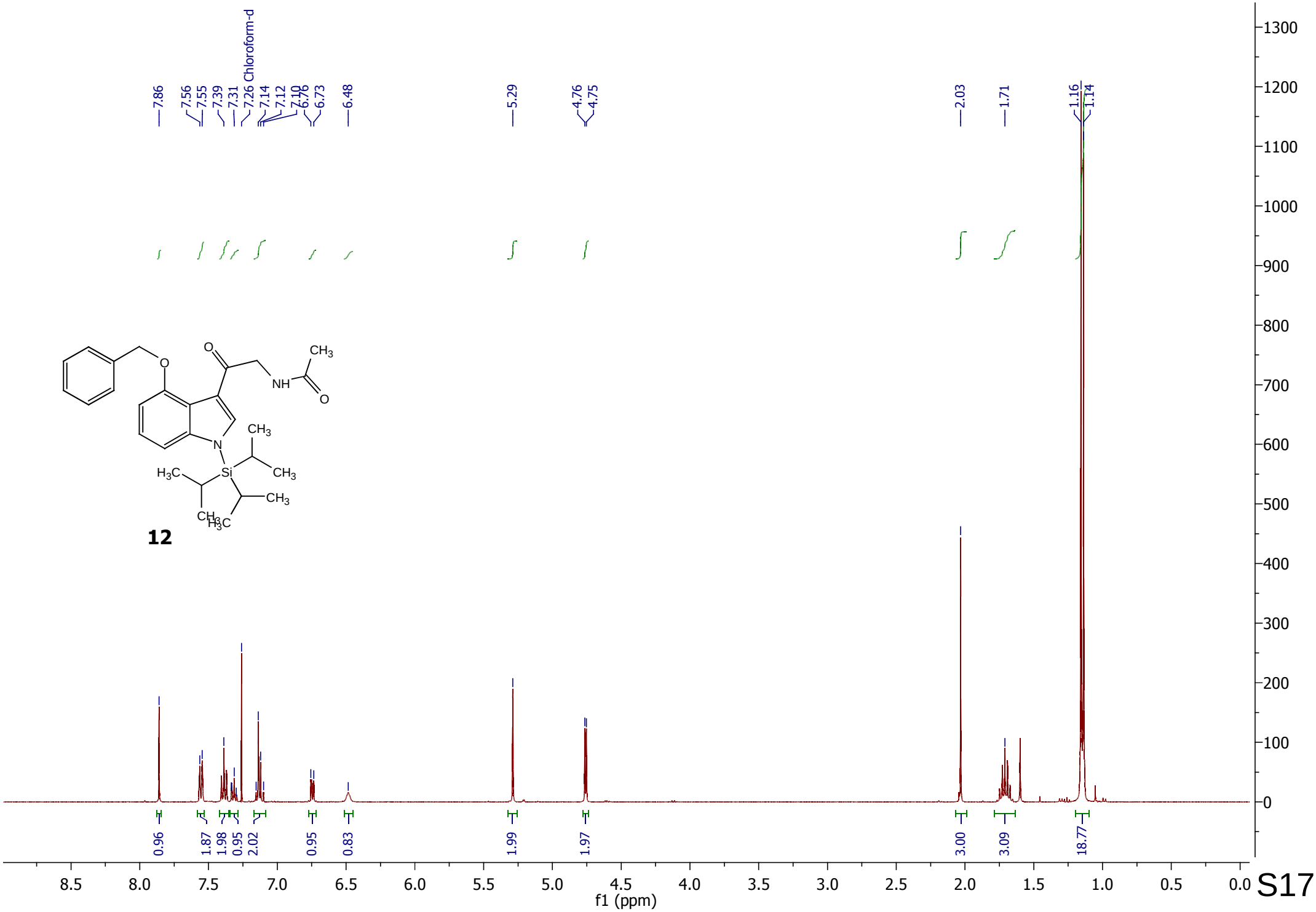
f1 (ppm)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4.76
4.75
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1.14
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1.87
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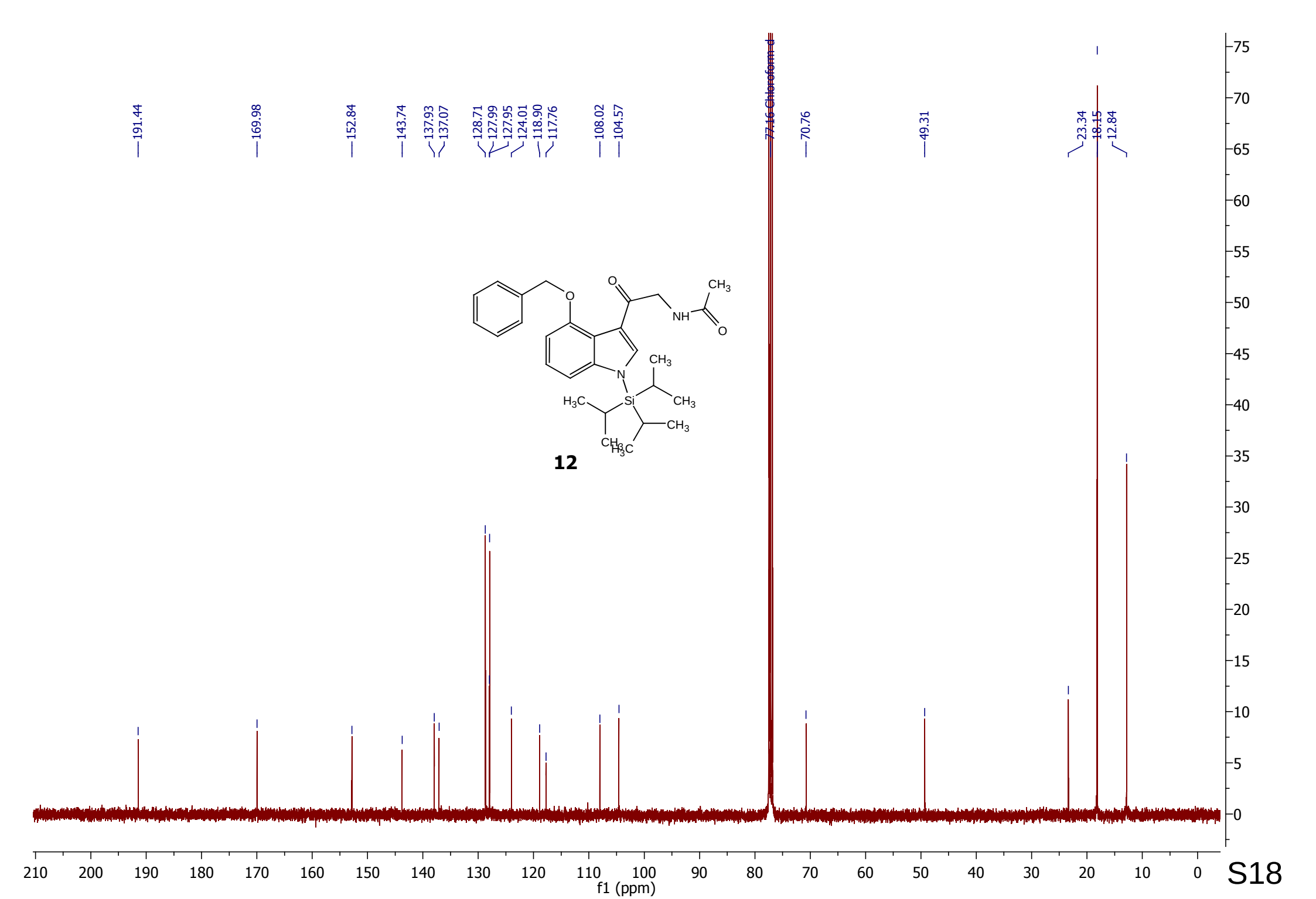
12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127.99
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124.01
118.90
117.76
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104.57
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70.76
49.31
23.34
18.15
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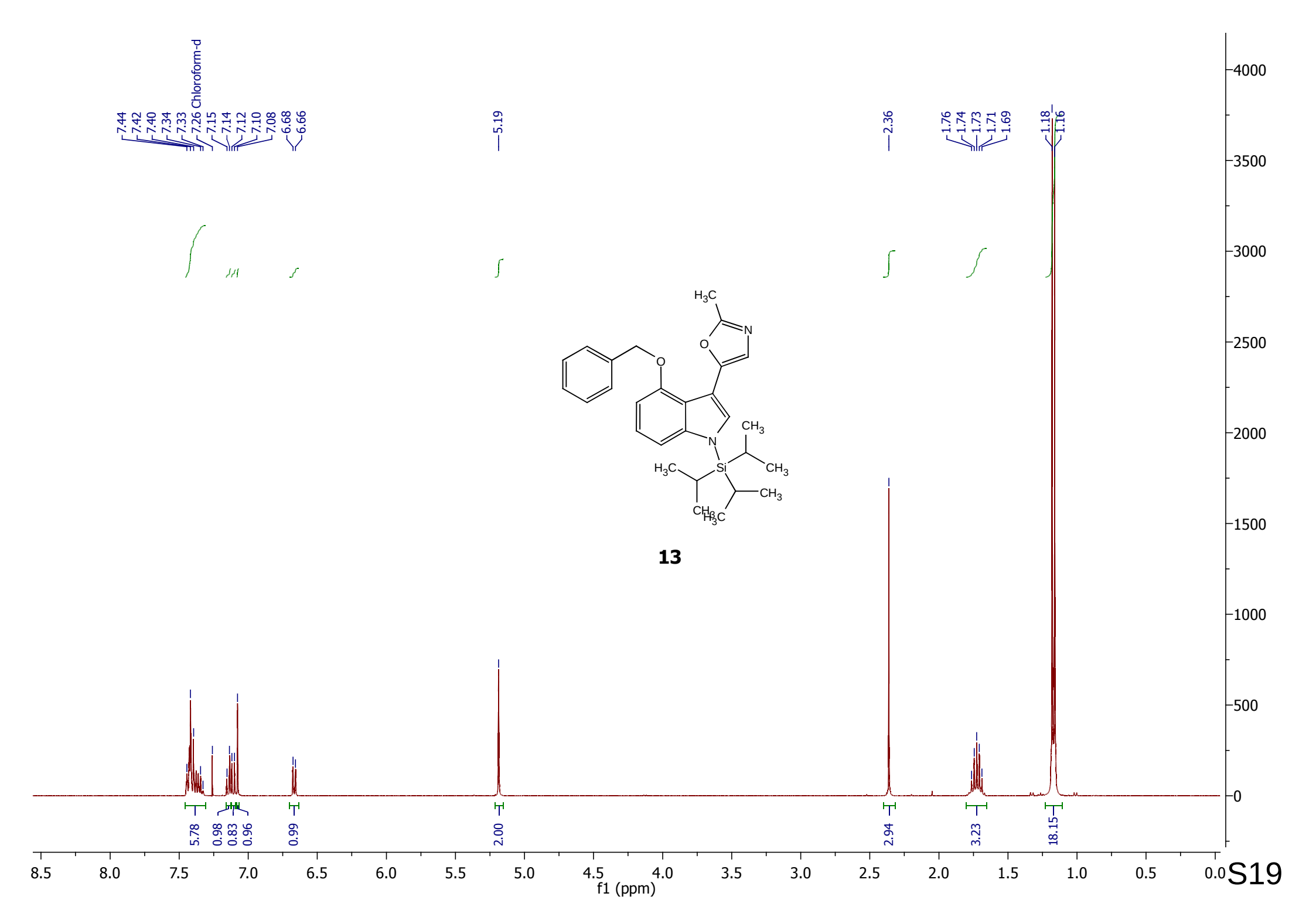
f1 (ppm)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5.19
2.36
1.76
1.74
1.73
1.71
1.69
1.18
1.16
H3C
N
O
O
N
Si
CH3
CH3
CH3
CH3
H3C
5.78
0.98
0.83
0.96
0.99
2.00
2.94
3.23
18.15
4000
3500
3000
2500
2000
1500
1000
500
0
8.5
8.0
7.5
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6.5
6.0
5.5
5.0
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3.0
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1.0
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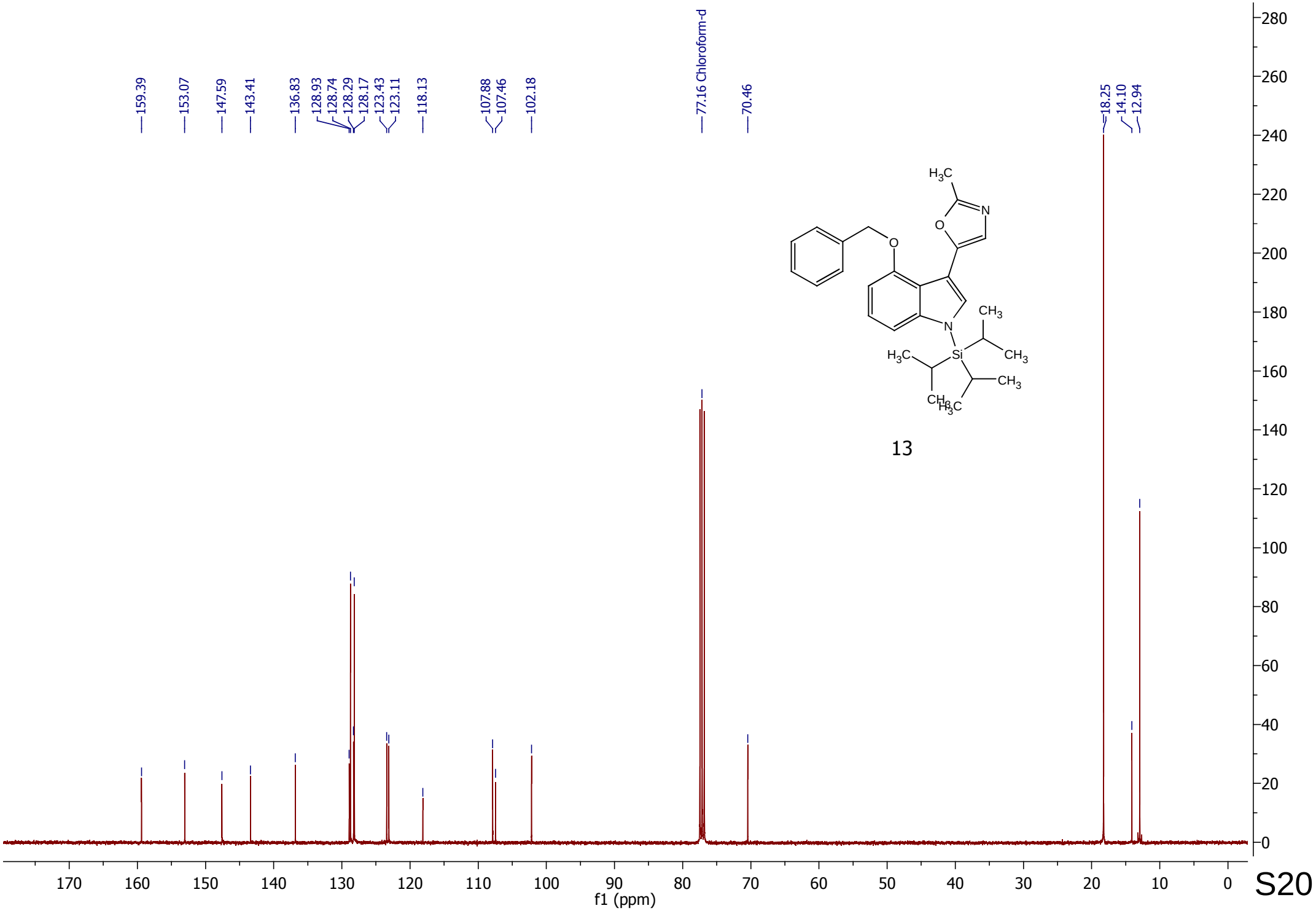
0.0
f1 (ppm)

13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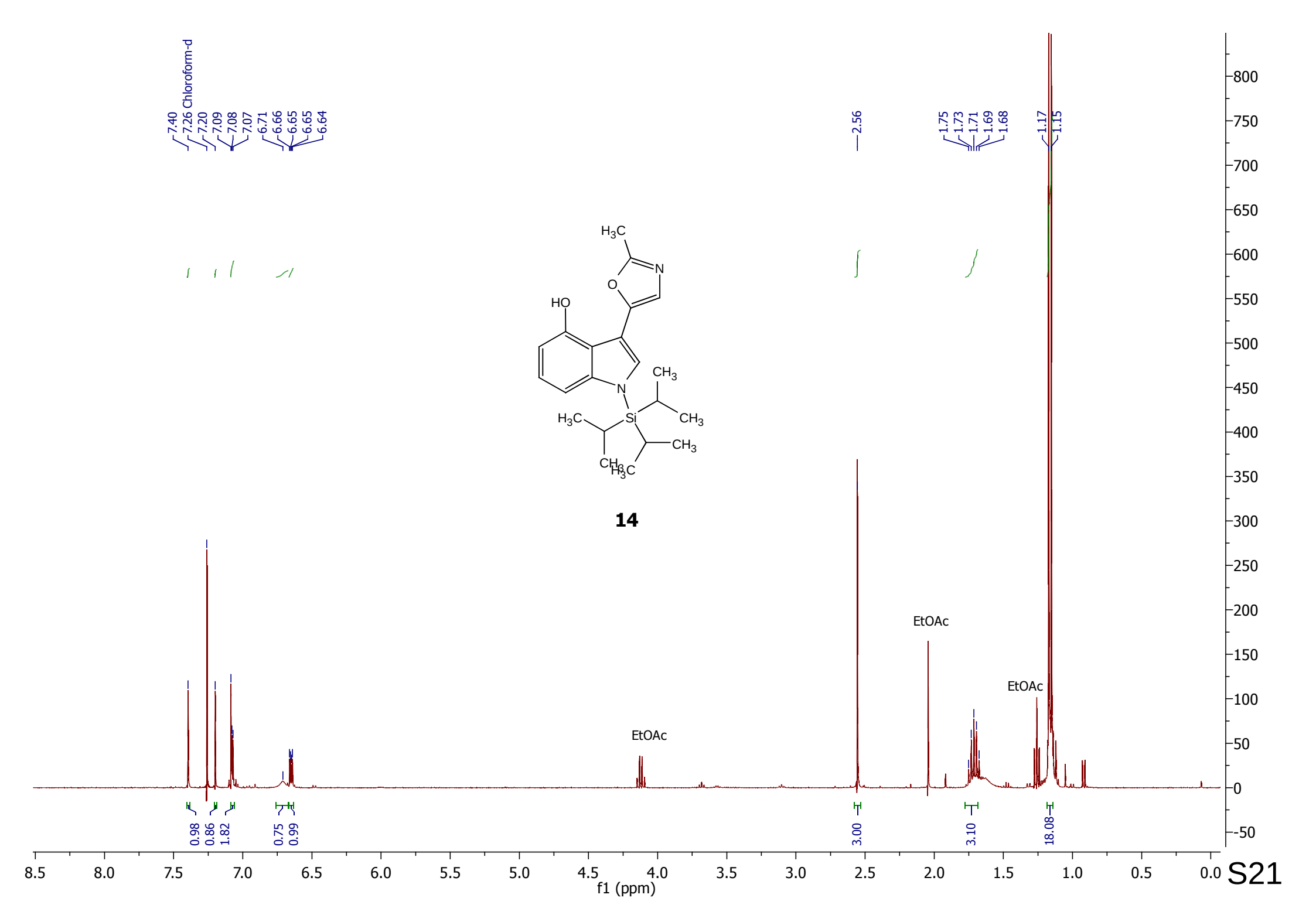
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1.71
1.69
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1.15
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N
O
HO
CH3
N
H3C
Si
CH3
CH3
CH3
H3C
14
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EtOAc
EtOAc
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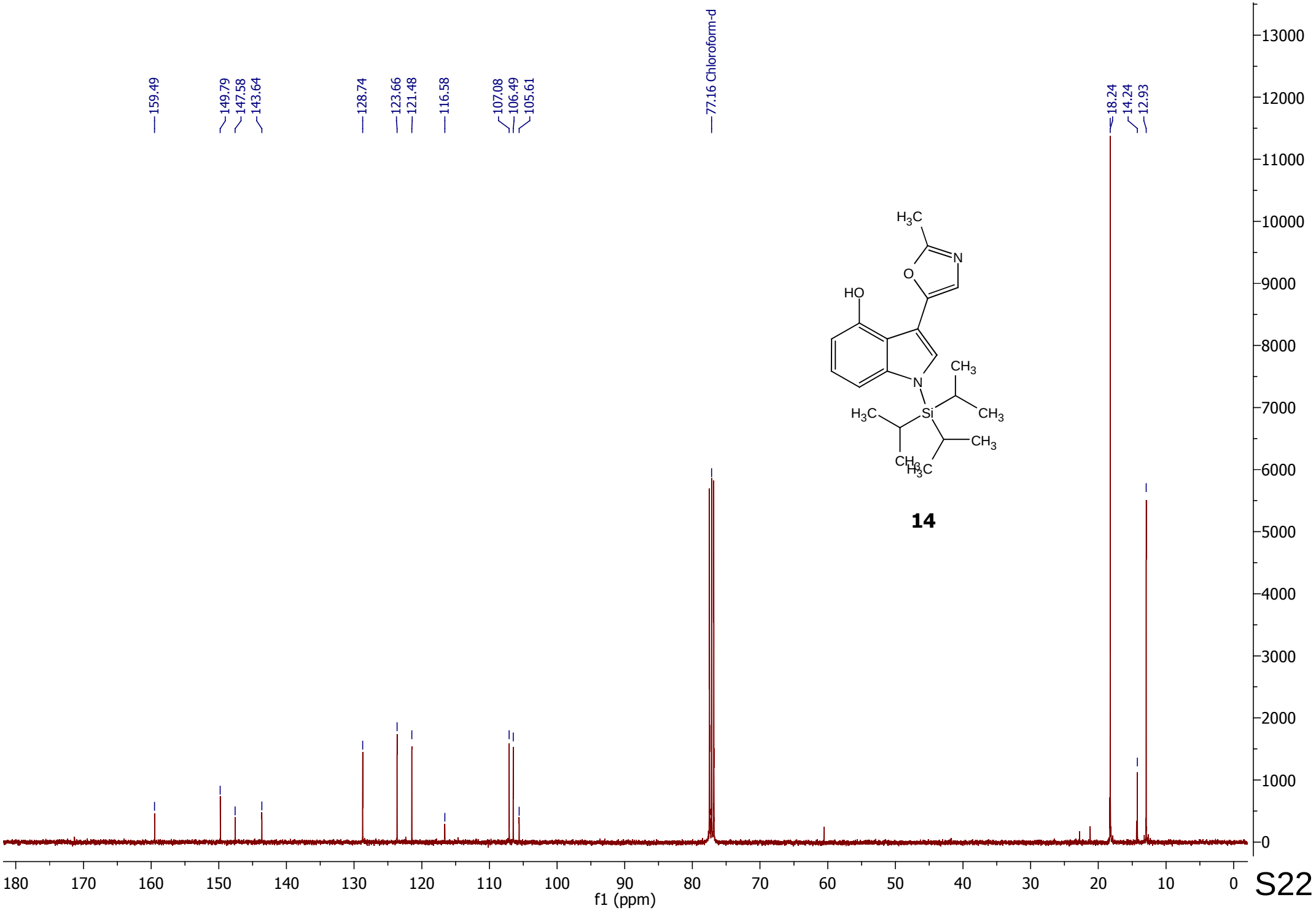
0.75
0.99
3.00
3.10
18.08
f1 (ppm)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123.66
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106.49
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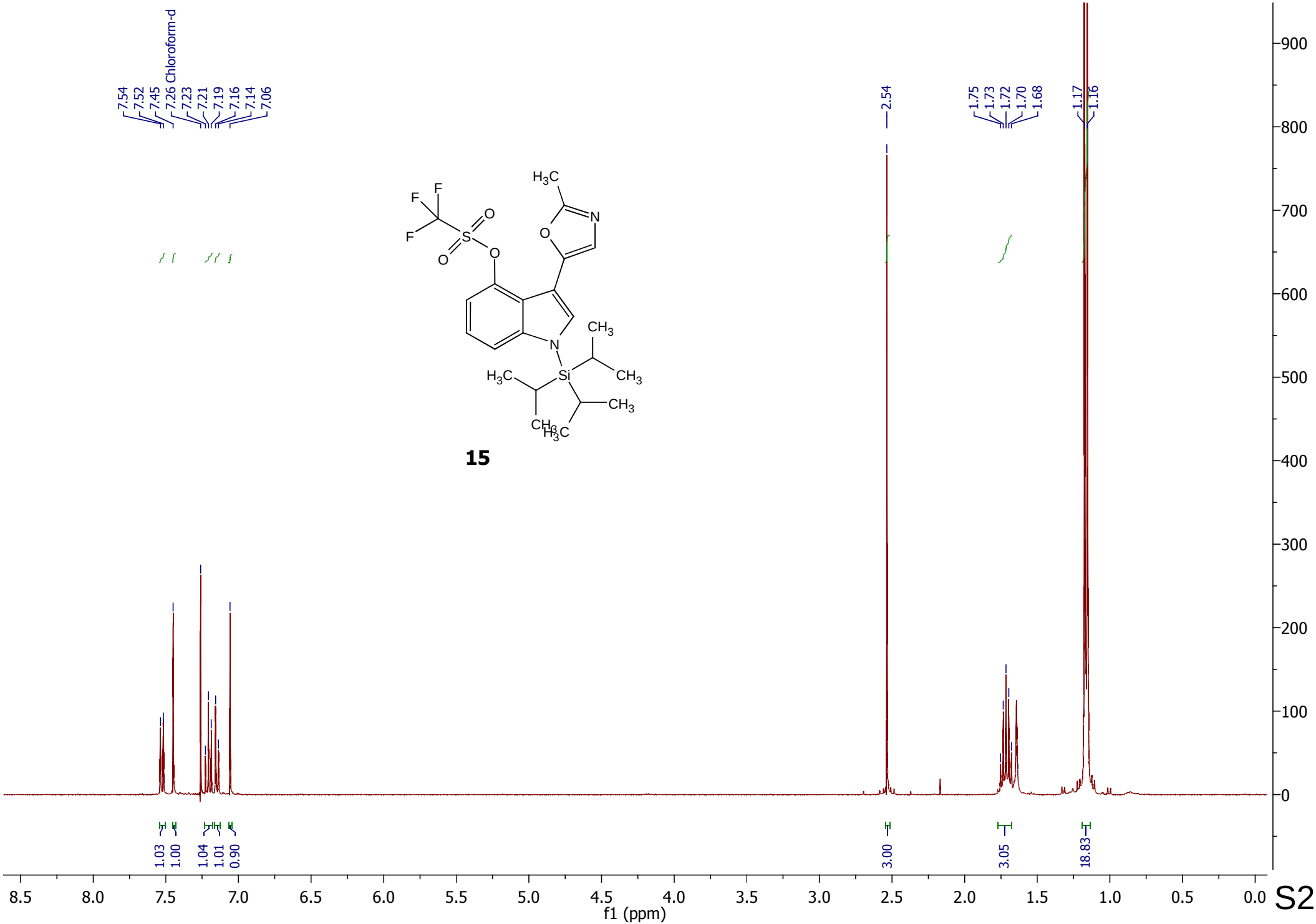
14.24
12.93
HO
O
N
Si
CH3
f1 (ppm)

14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1.73
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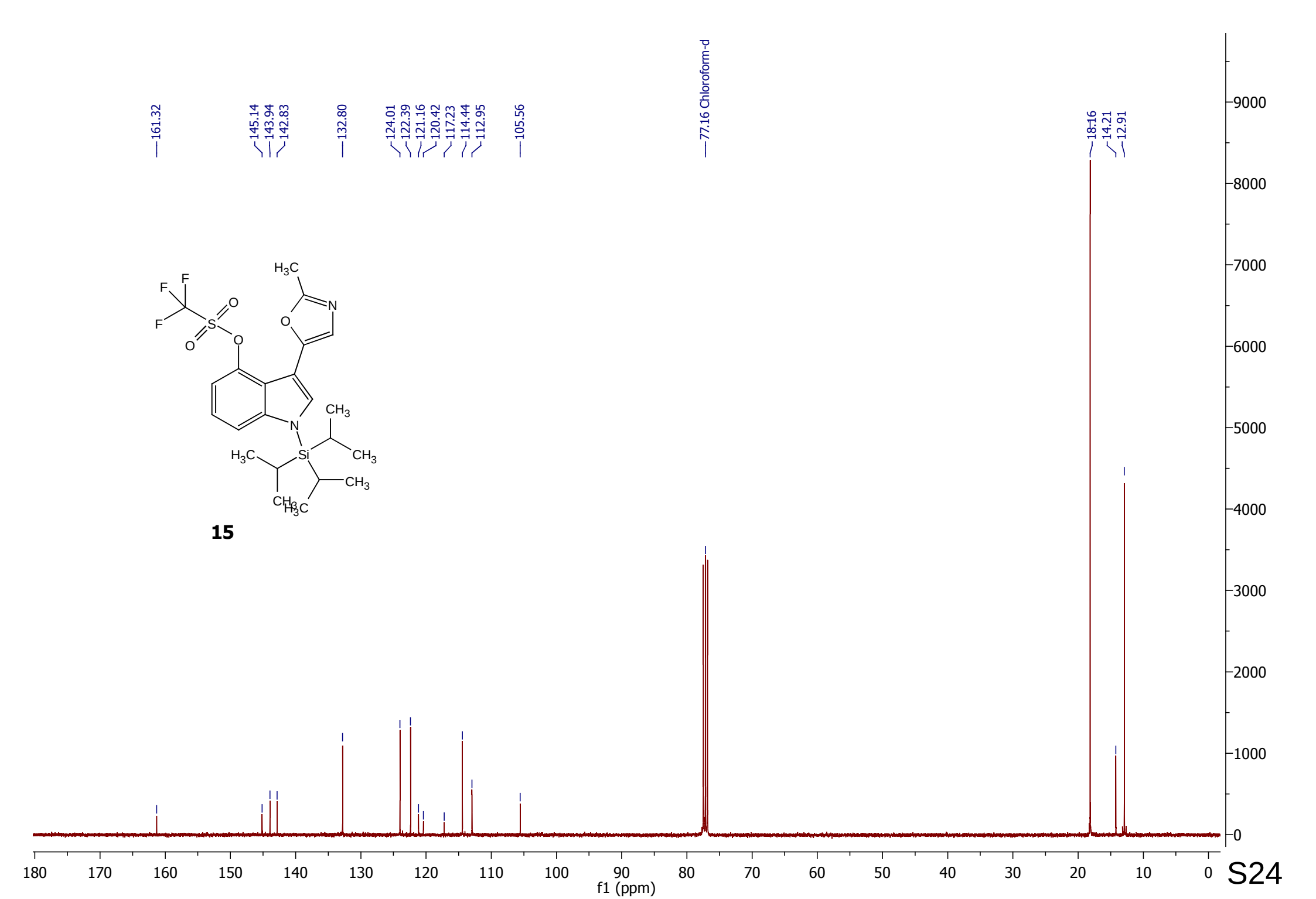
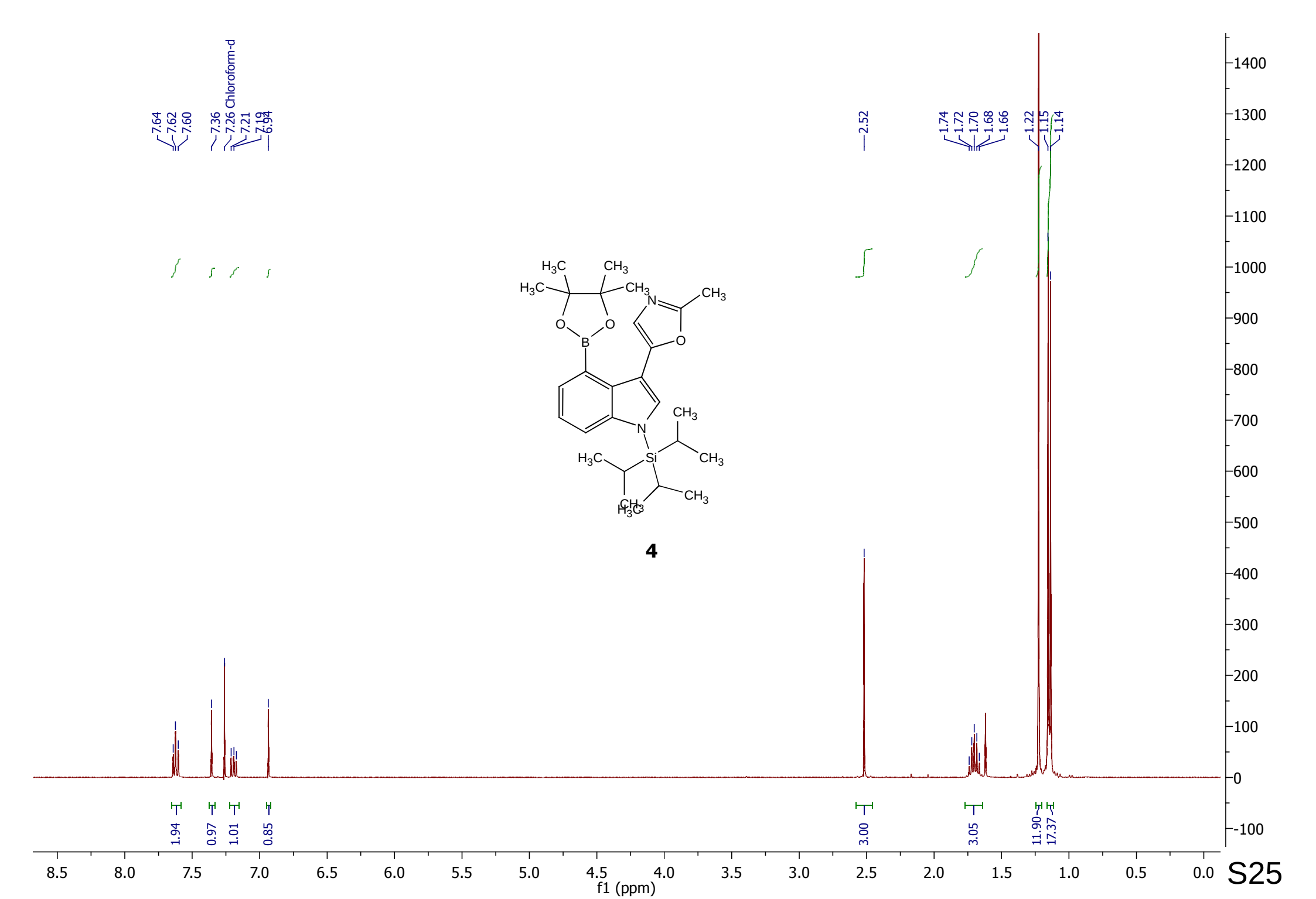
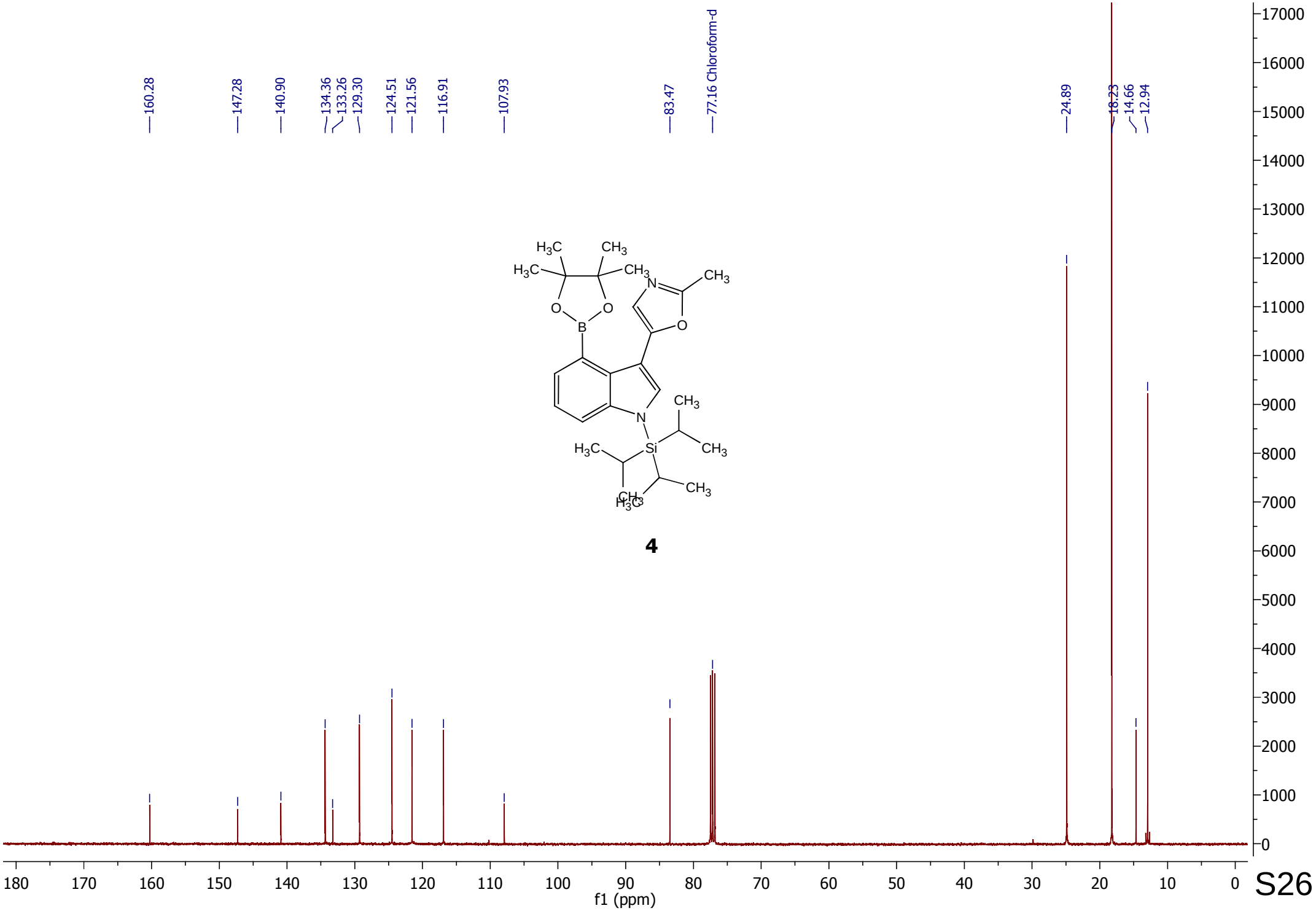
1.70
1.68
1.17
1.16
1.03
1.00
1.04
1.01
0.90
3.00
3.05
18.83
f1 (ppm)

15

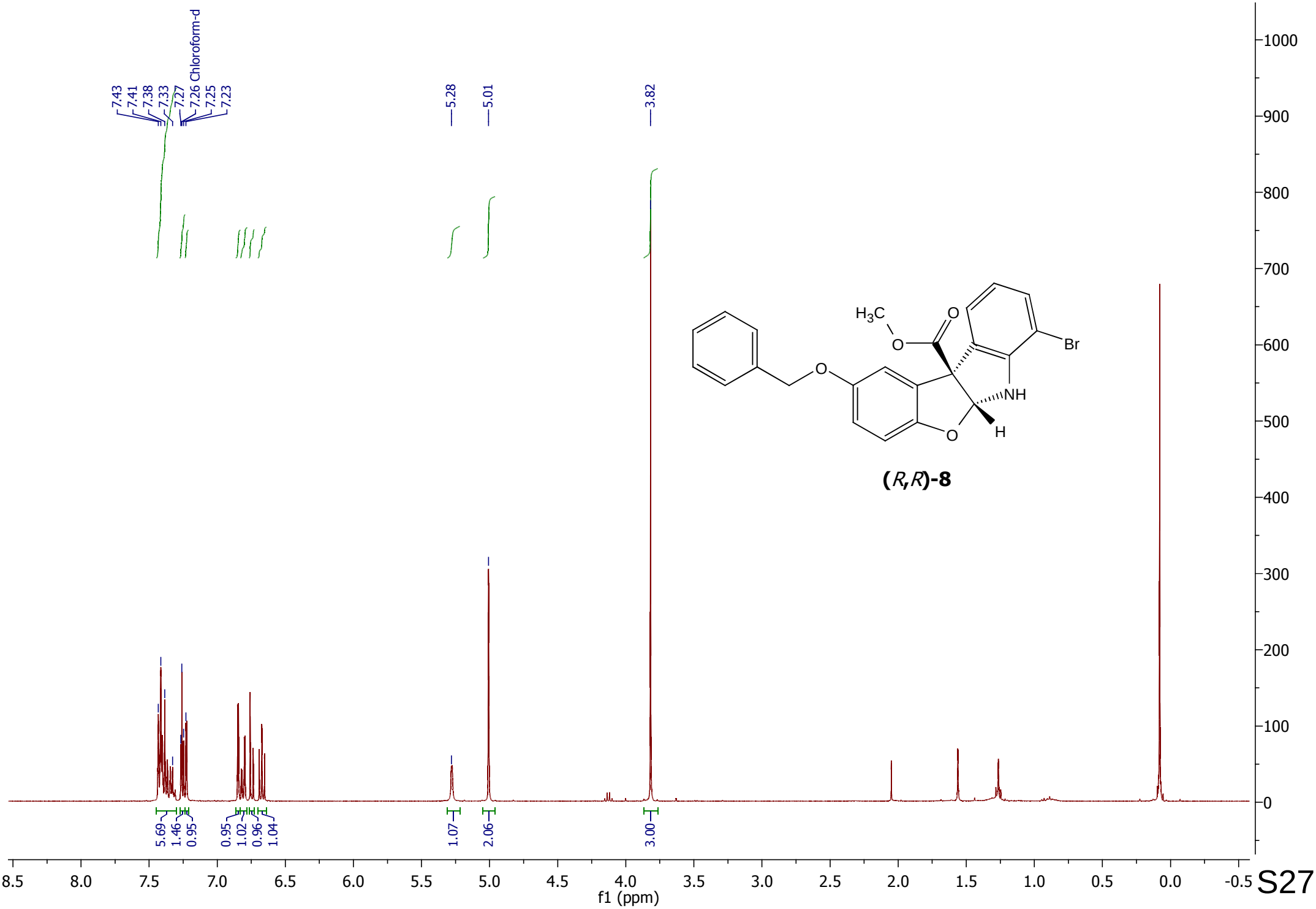

161.32
145.14
143.94
142.83
132.80
124.01
122.39
121.16
120.42
117.23
114.44
112.95
105.56
77.16 Chloroform-d
18.16
14.21
12.91
15
f1 (ppm)

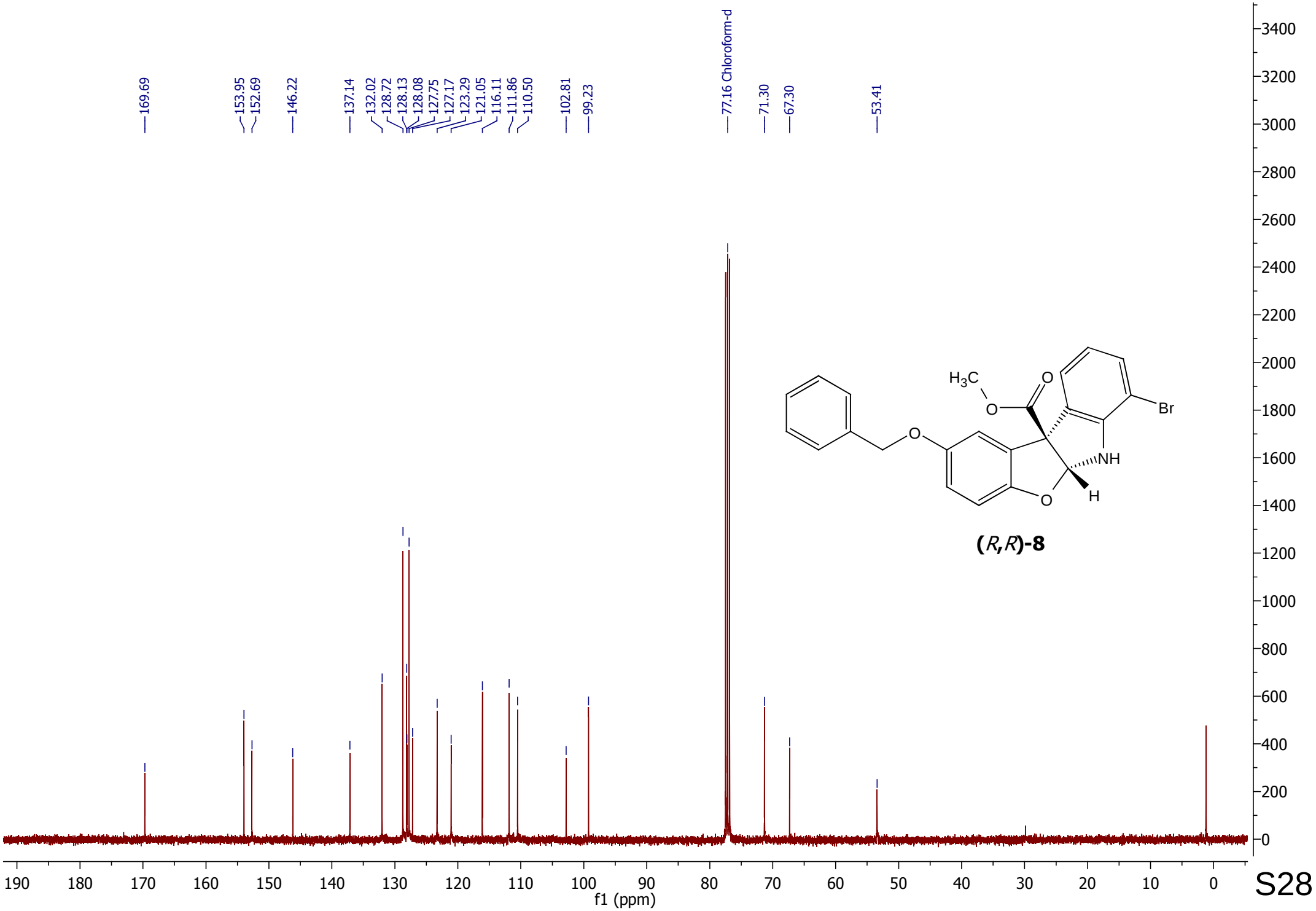

7.64
7.62
7.60
7.36
7.26 Chloroform-d
7.21
7.19
6.94
2.52
1.74
1.72
1.70
1.68
1.66
1.22
1.15
1.14
1.94
0.97
1.01
0.85
3.00
3.05
11.90
17.37
f1 (ppm)

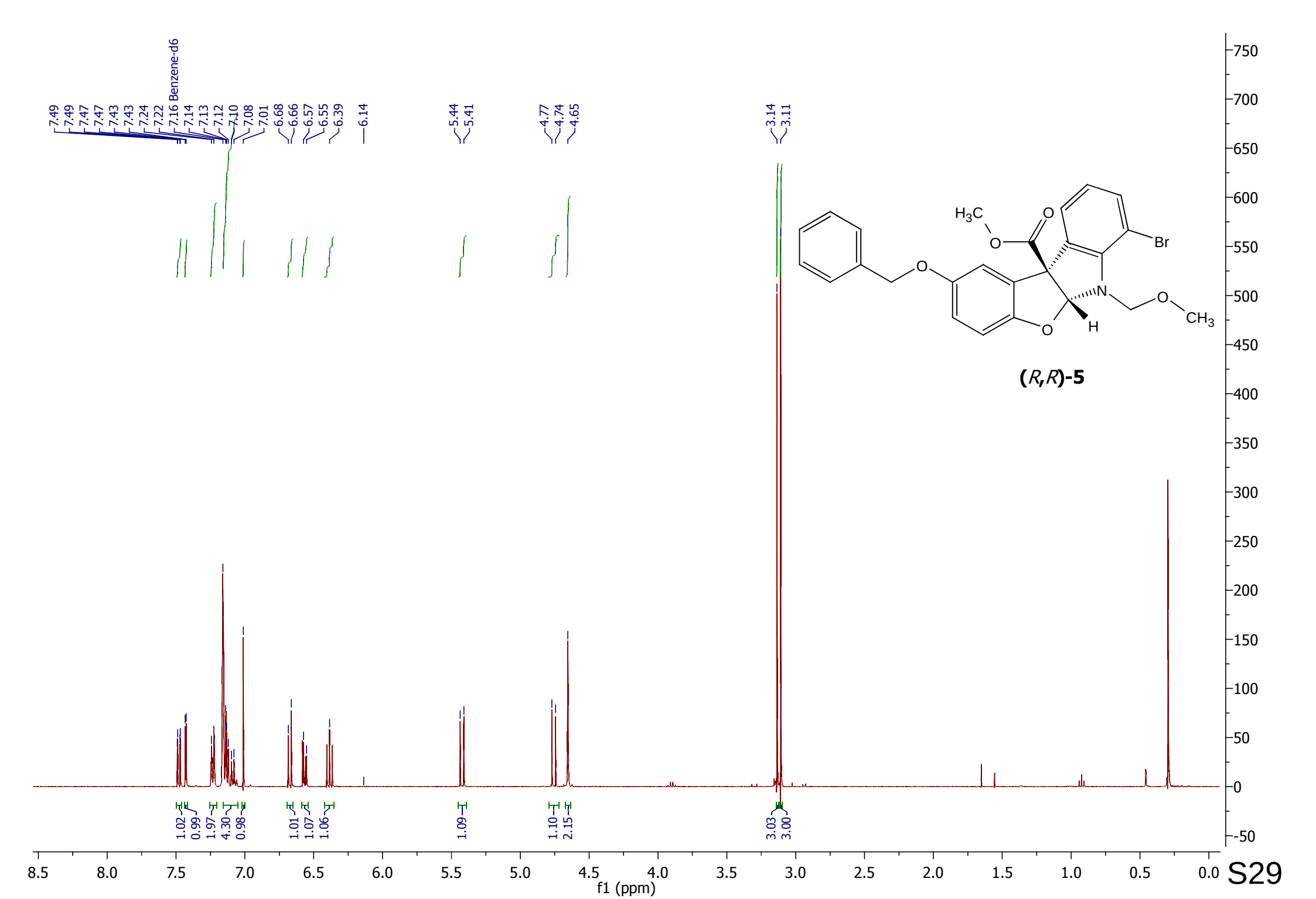
4


160.28
147.28
140.90
134.36
133.26
129.30
124.51
121.56
116.91
107.93
83.47
77.16 Chloroform-d
24.89
18.23
14.66
12.94
f1 (ppm)

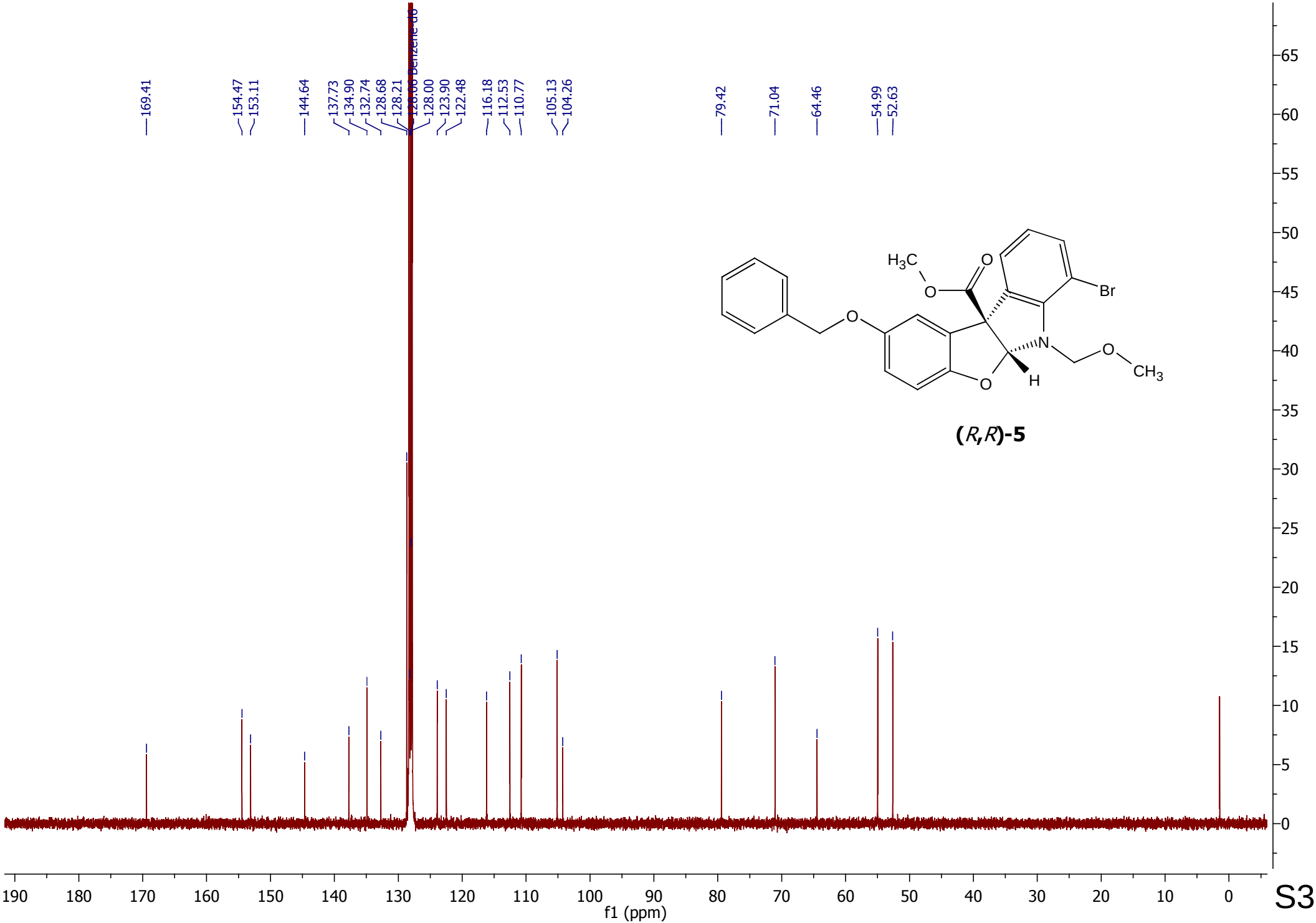
4

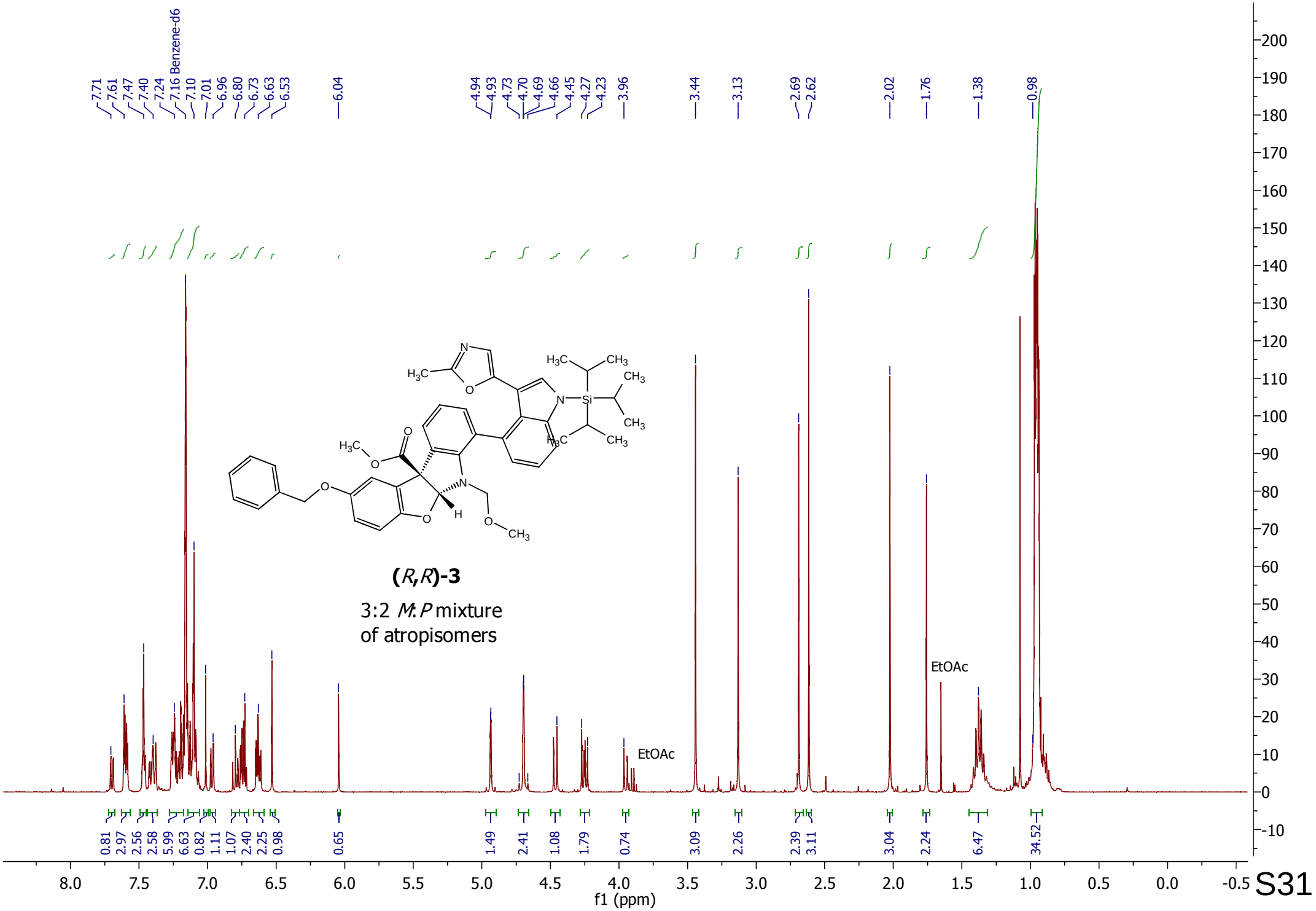

7.43
7.41
7.38
7.33
7.27
7.26 Chloroform-d
7.25
7.23
5.28
5.01
3.82
H3C
O
O
O
Br
NH
H
O
(R,R)-8
5.69
1.46
0.95
0.95
1.02
0.96
1.04
1.07
2.06
3.00
f1 (ppm)


169.69
153.95
152.69
146.22
137.14
132.02
128.72
128.13
128.08
127.75
127.17
123.29
121.05
116.11
111.86
110.50
102.81
99.23
77.16 Chloroform-d
71.30
67.30
53.41
H3C
O
O
O
Br
NH
H
O
(R,R)-8
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


Benzene-d6
7.49
7.49
7.47
7.47
7.43
7.43
7.24
7.22
7.16
7.14
7.13
7.12
7.10
7.08
7.01
6.68
6.66
6.57
6.55
6.39
6.14
5.44
5.41
4.77
4.74
4.65
3.14
3.11
1.02
0.99
1.97
4.30
0.98
1.01
1.07
1.06
1.09
1.10
2.15
3.03
3.00
f1 (ppm)

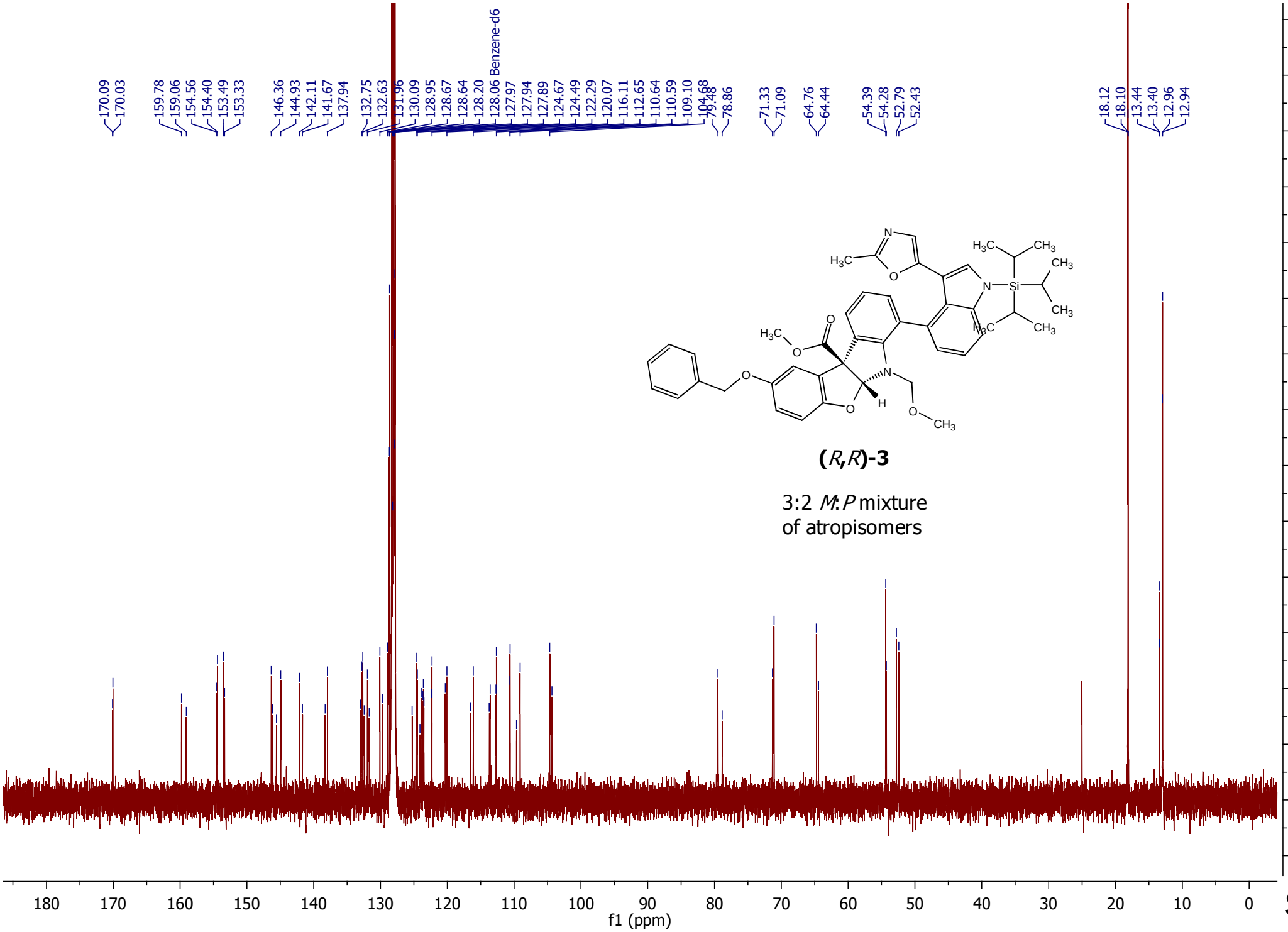
(*R*,*R*)-5


169.41
154.47
153.11
144.64
137.73
134.90
132.74
128.68
128.21
128.00
123.90
122.48
116.18
112.53
110.77
105.13
104.26
79.42
71.04
64.46
54.99
52.63
H3C
O
O
Br
O
N
O
CH3
O
H
(R,R)-5
f1 (ppm)



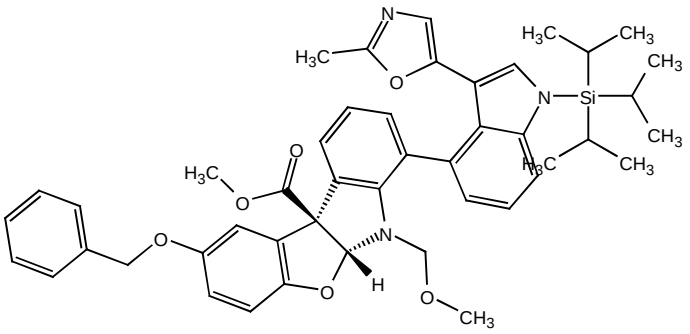
(*R*,*R*)-3

3:2 *M*:*P* mixture
of atropisomers



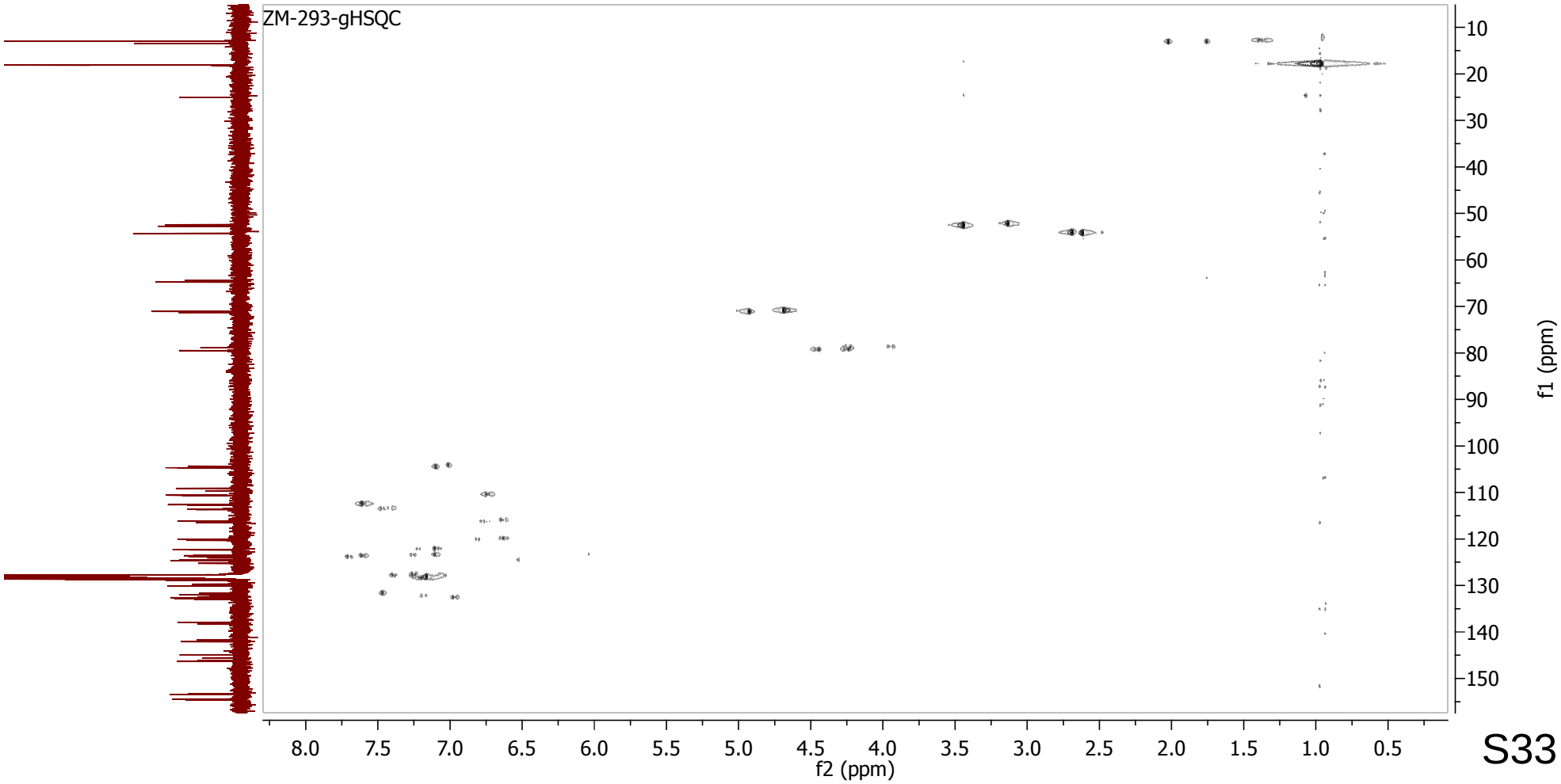
(*R*,*R*)-3

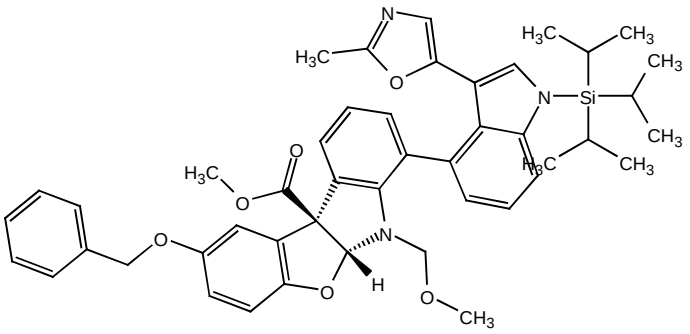
3:2 *M*:*P* mixture
of atropisomers



(*R*,*R*)-3

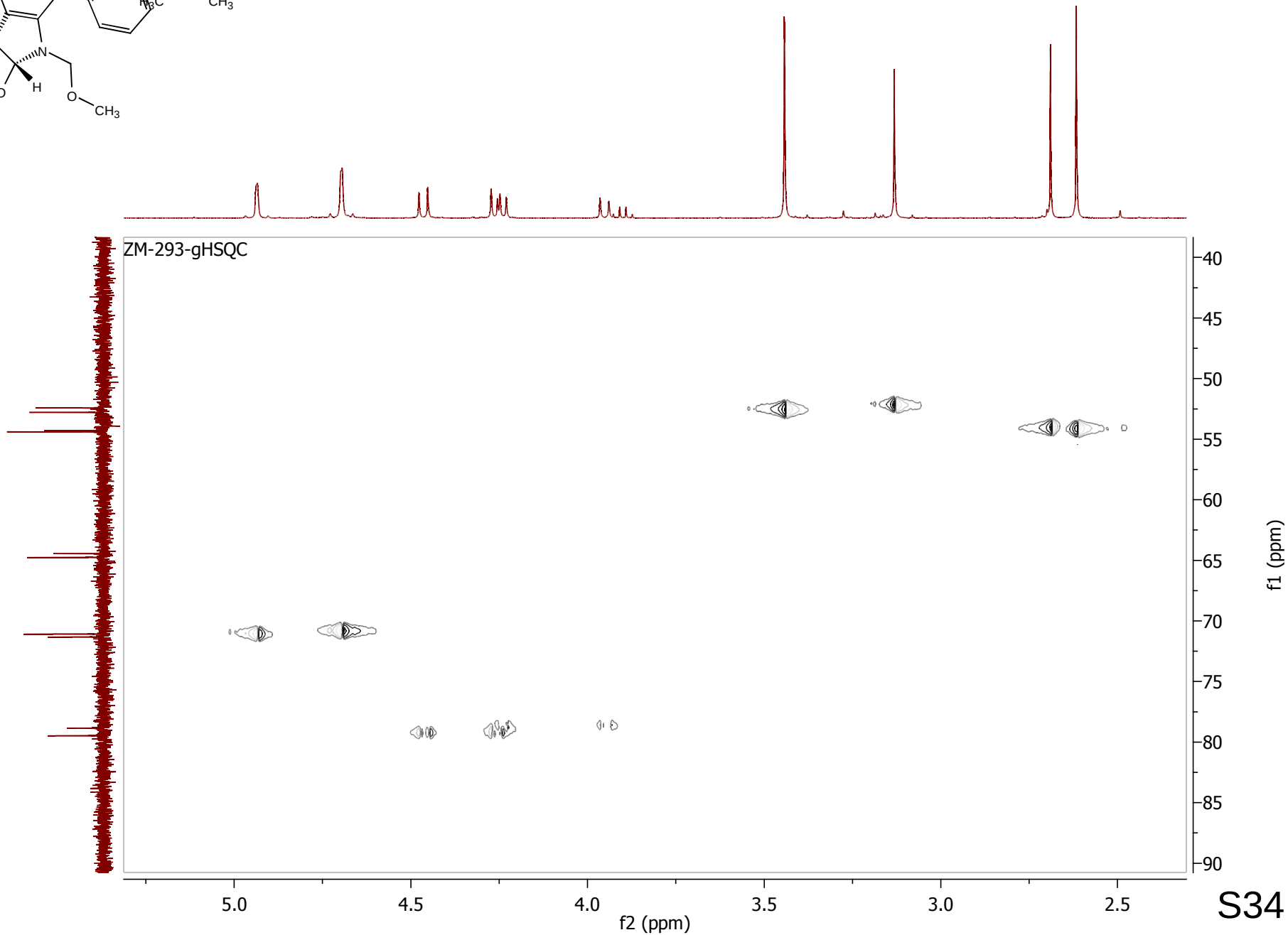
3:2 *M*:*P* mixture
of atropisomers

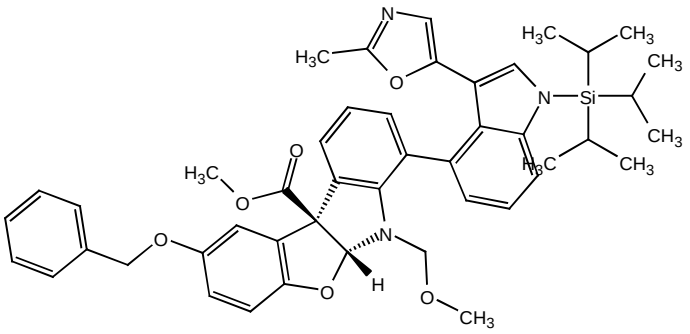




(*R*,*R*)-3

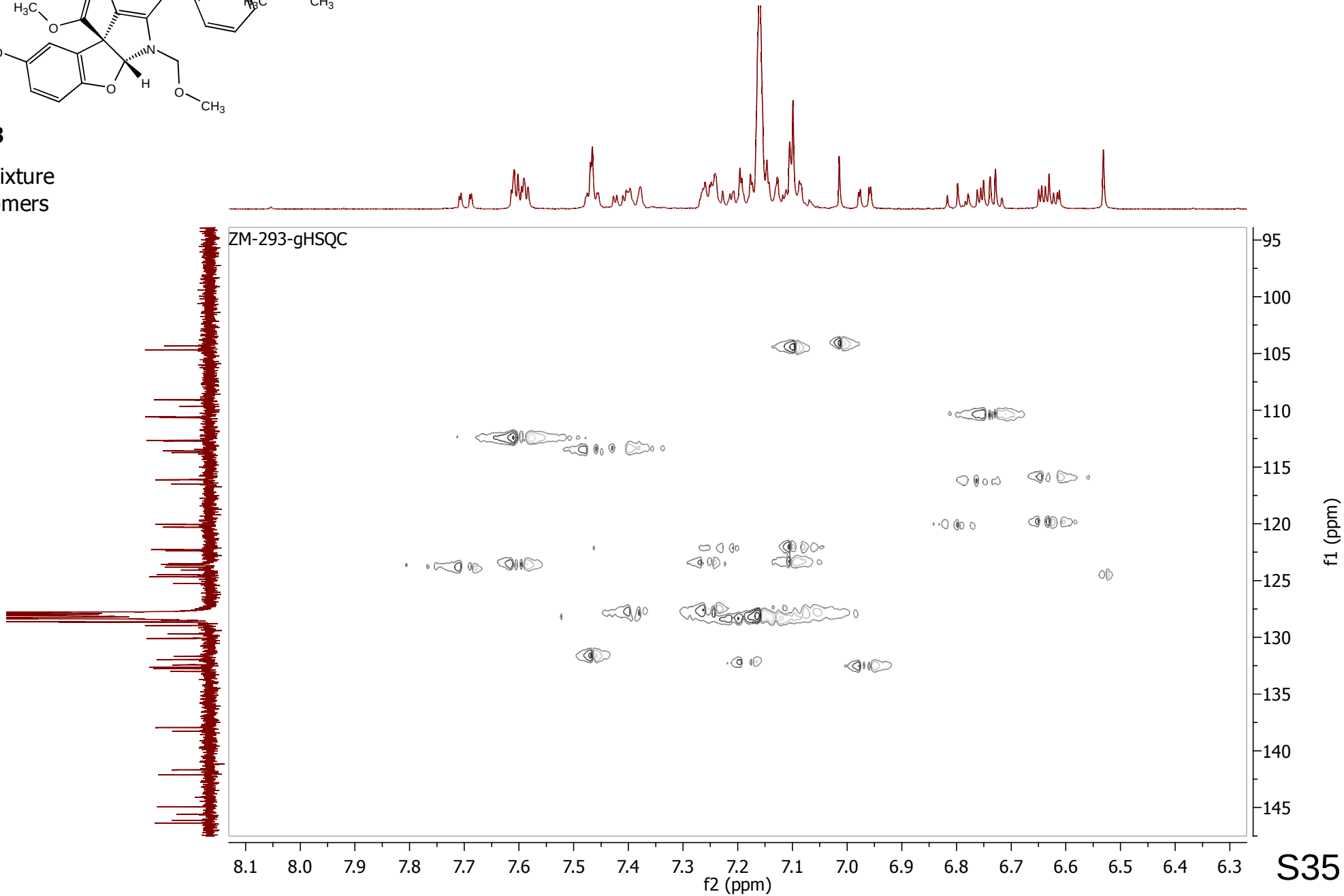
3:2 *M*:*P* mixture
of atropisomers

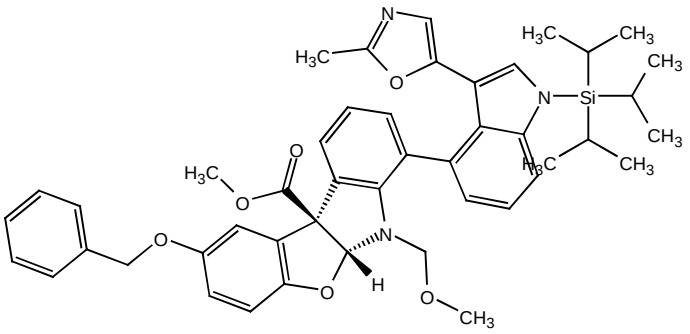




(*R*,*R*)-3

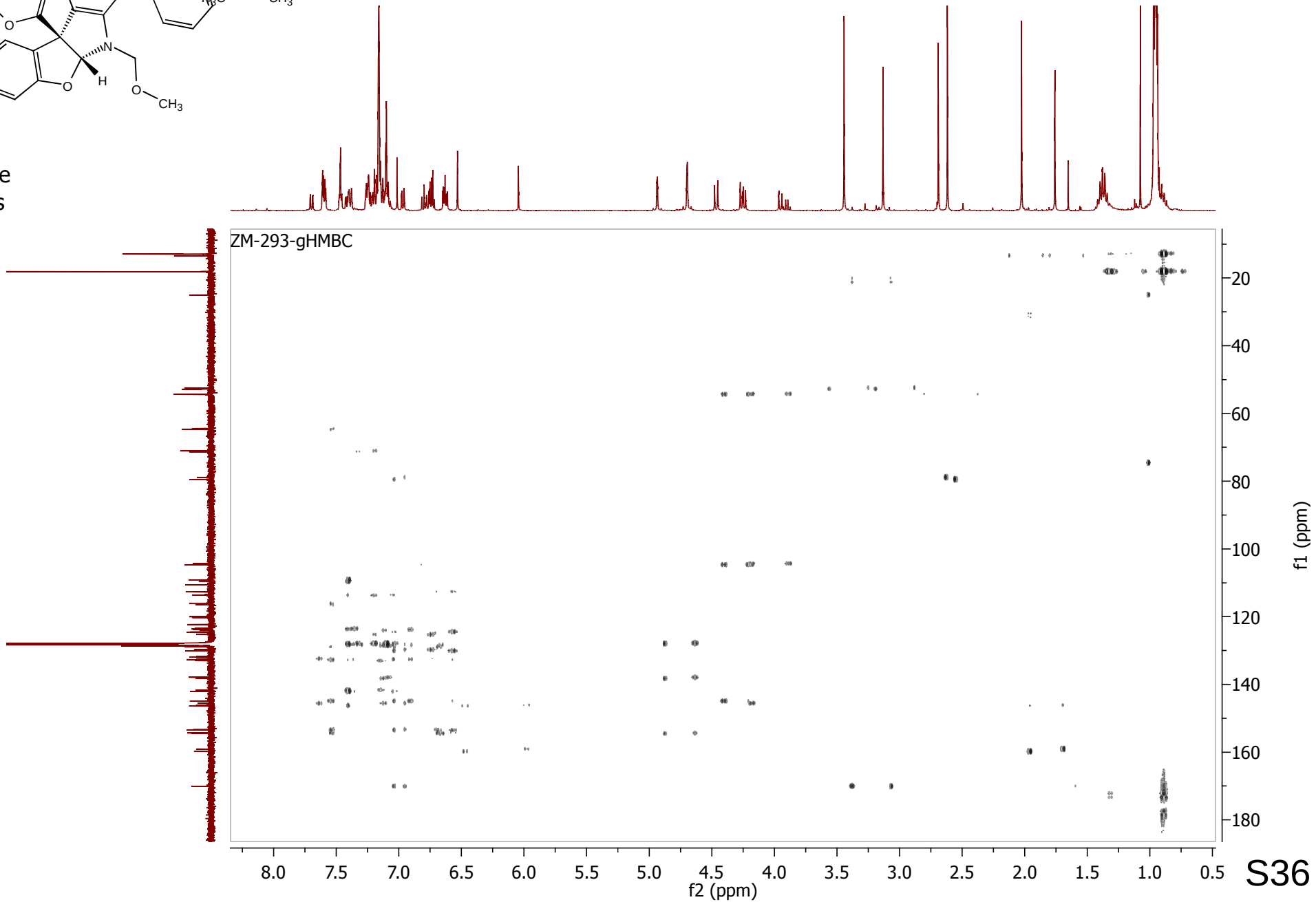
3:2 *M*:*P* mixture
of atropisomers

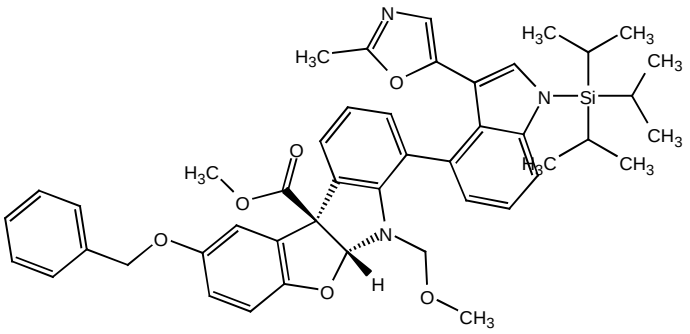




(*R*,*R*)-3

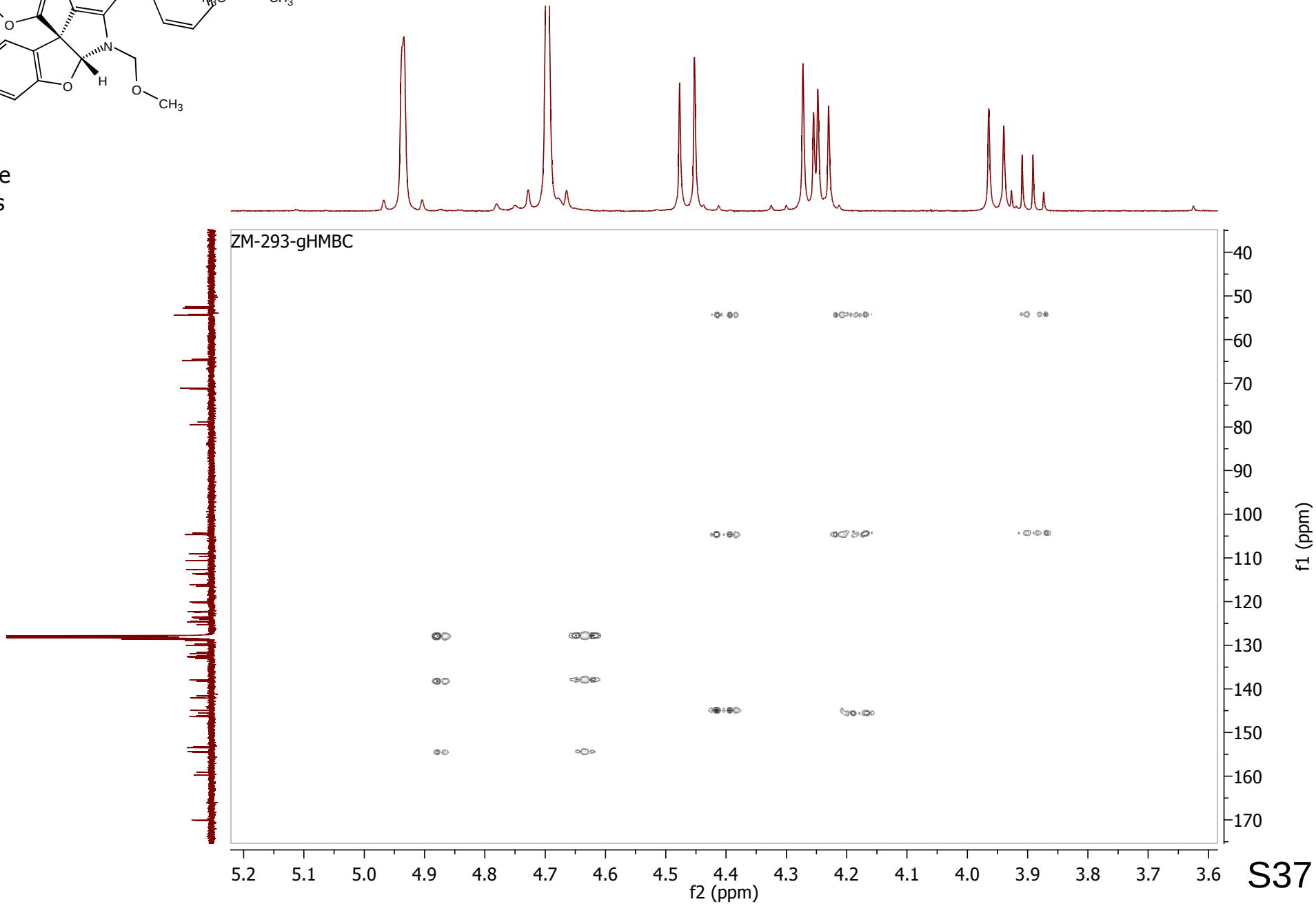
3:2 *M*:*P* mixture
of atropisomers

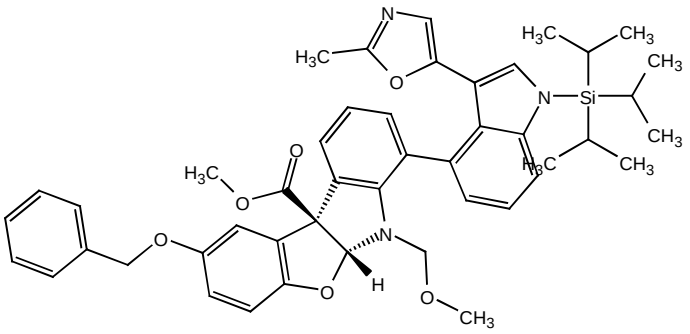




(*R*,*R*)-3

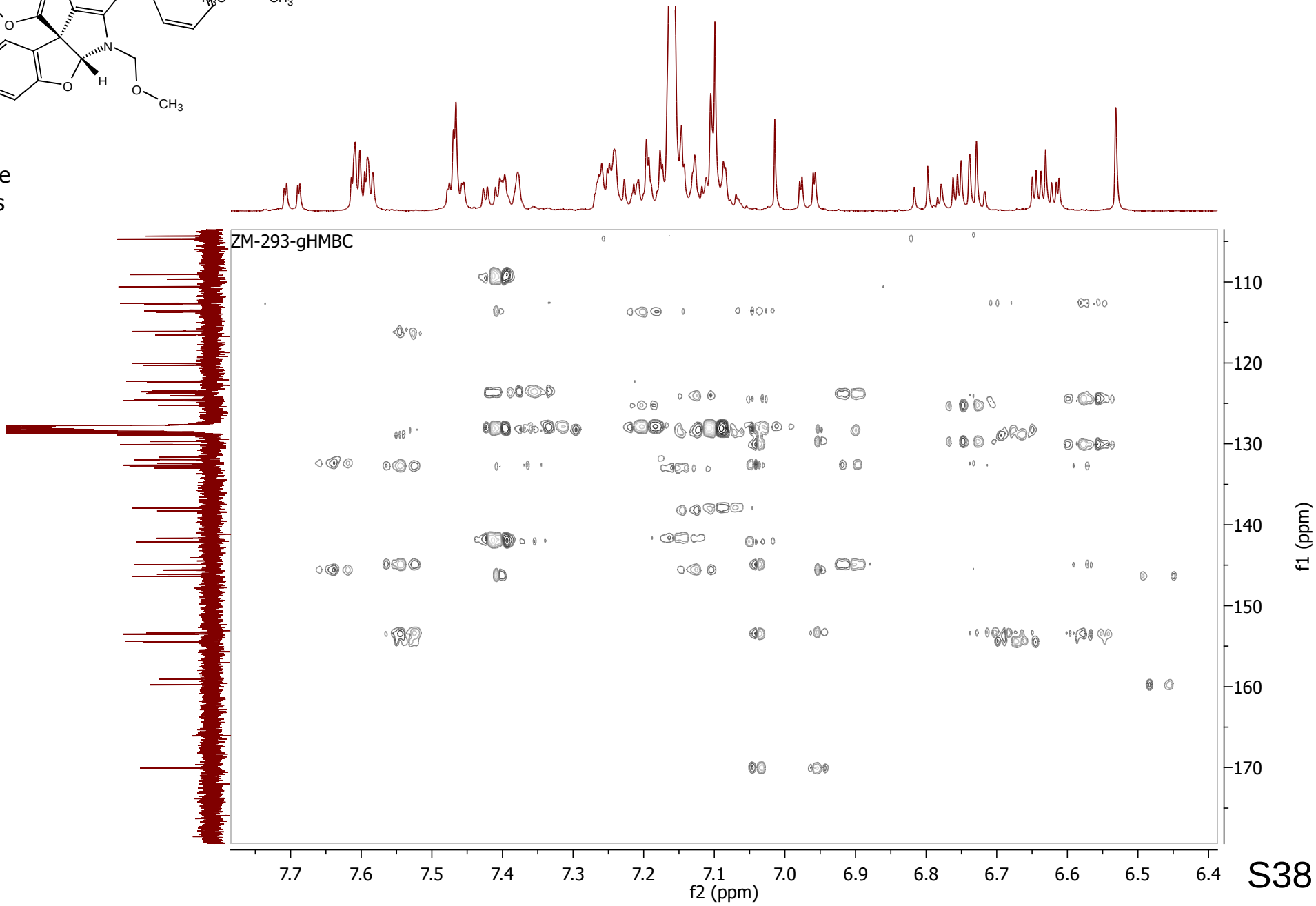
3:2 *M*:*P* mixture
of atropisomers

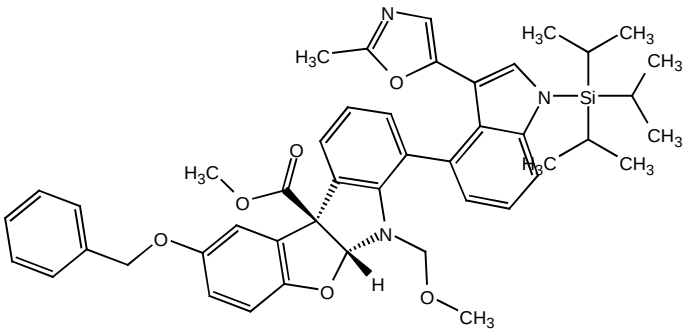




(*R*,*R*)-3

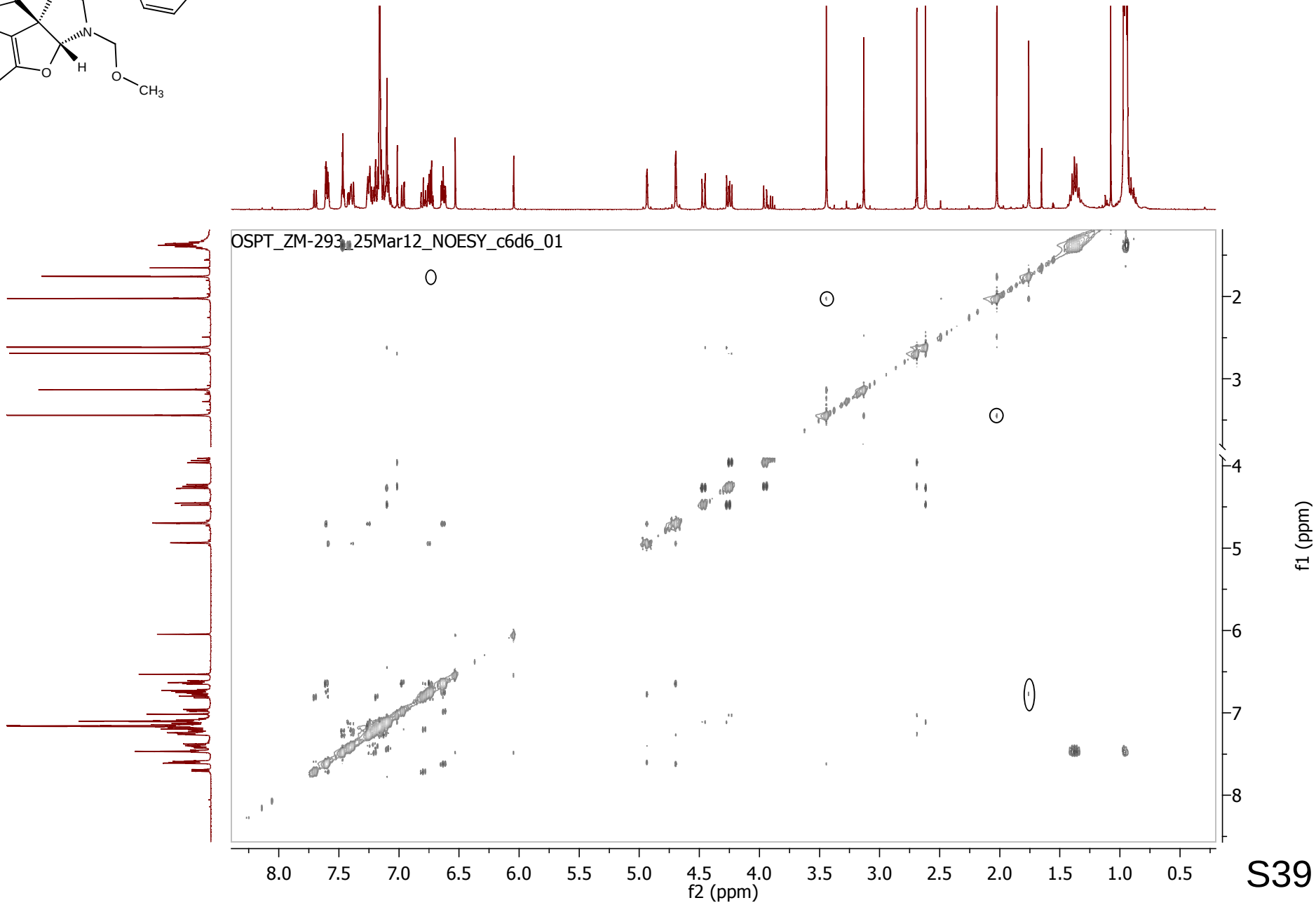
3:2 *M*:*P* mixture
of atropisomers

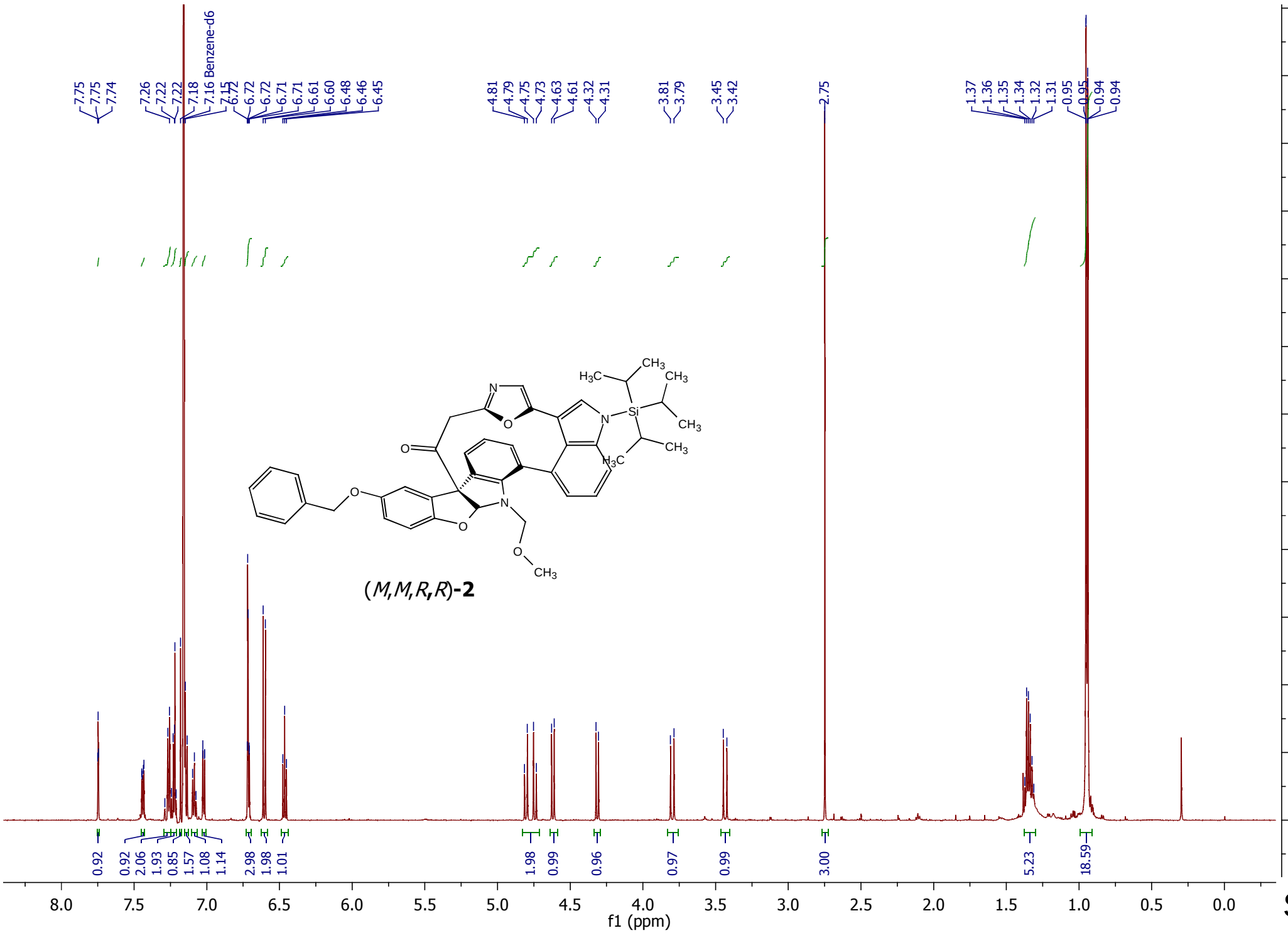




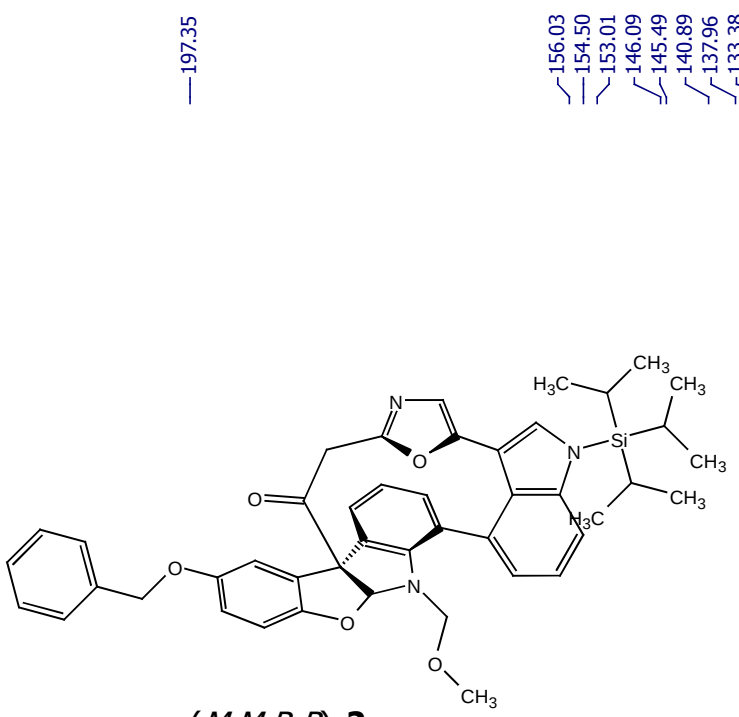
(*R*,*R*)-3

3:2 *M*:*P* mixture of atropisomers

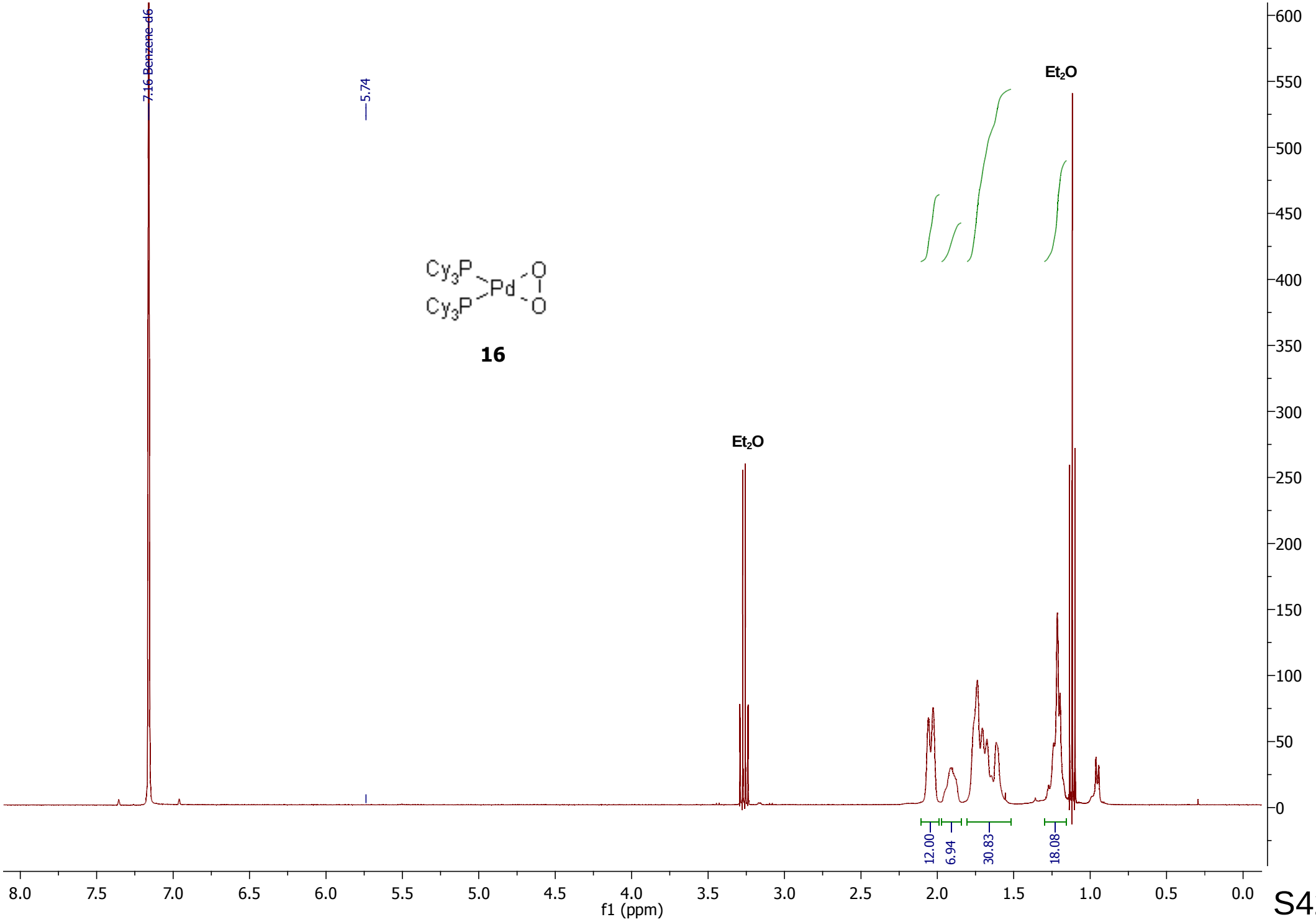


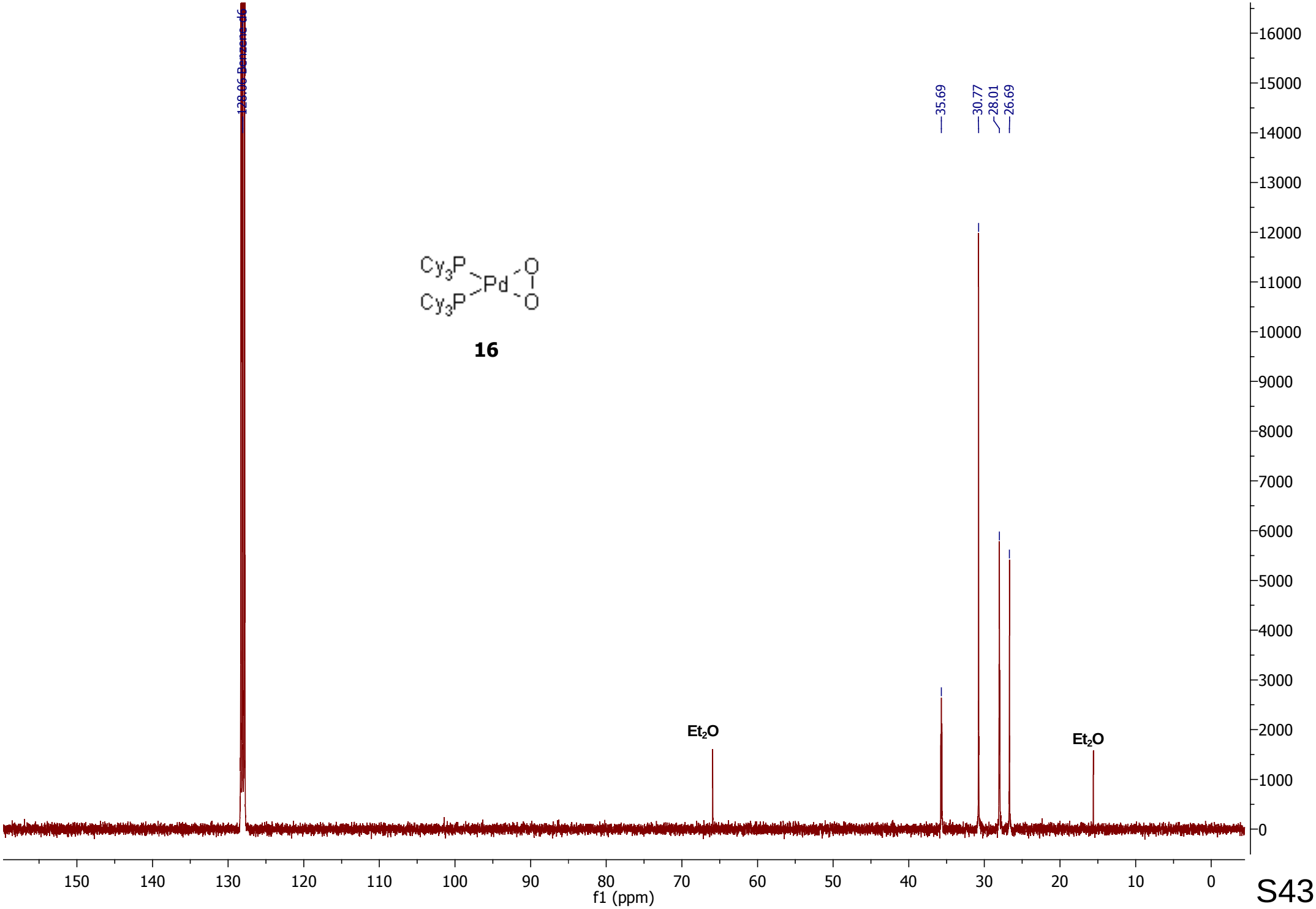

7.75
7.75
7.74
7.26
7.22
7.22
7.18
7.16 Benzene-d6
7.15
6.72
6.72
6.72
6.71
6.71
6.61
6.60
6.48
6.46
6.45
4.81
4.79
4.75
4.73
4.63
4.61
4.32
4.31
3.81
3.79
3.45
3.42
2.75
1.37
1.36
1.35
1.34
1.32
1.31
0.95
0.95
0.94
0.94
0.92
0.92
2.06
1.93
0.85
1.57
1.08
1.14
2.98
1.98
1.01
1.98
0.99
0.96
0.97
0.99
3.00
5.23
18.59
f1 (ppm)

(*M*,*M*,*R*,*R*)-**2**



(*M*,*M*,*R*,*R*)-**2**


7.16 Benzene-d6
5.74
Et2O
Et2O
Cy3P
Pd
O
O
Cy3P
16
12.00
6.94
30.83
18.08
f1 (ppm)



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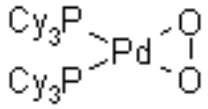
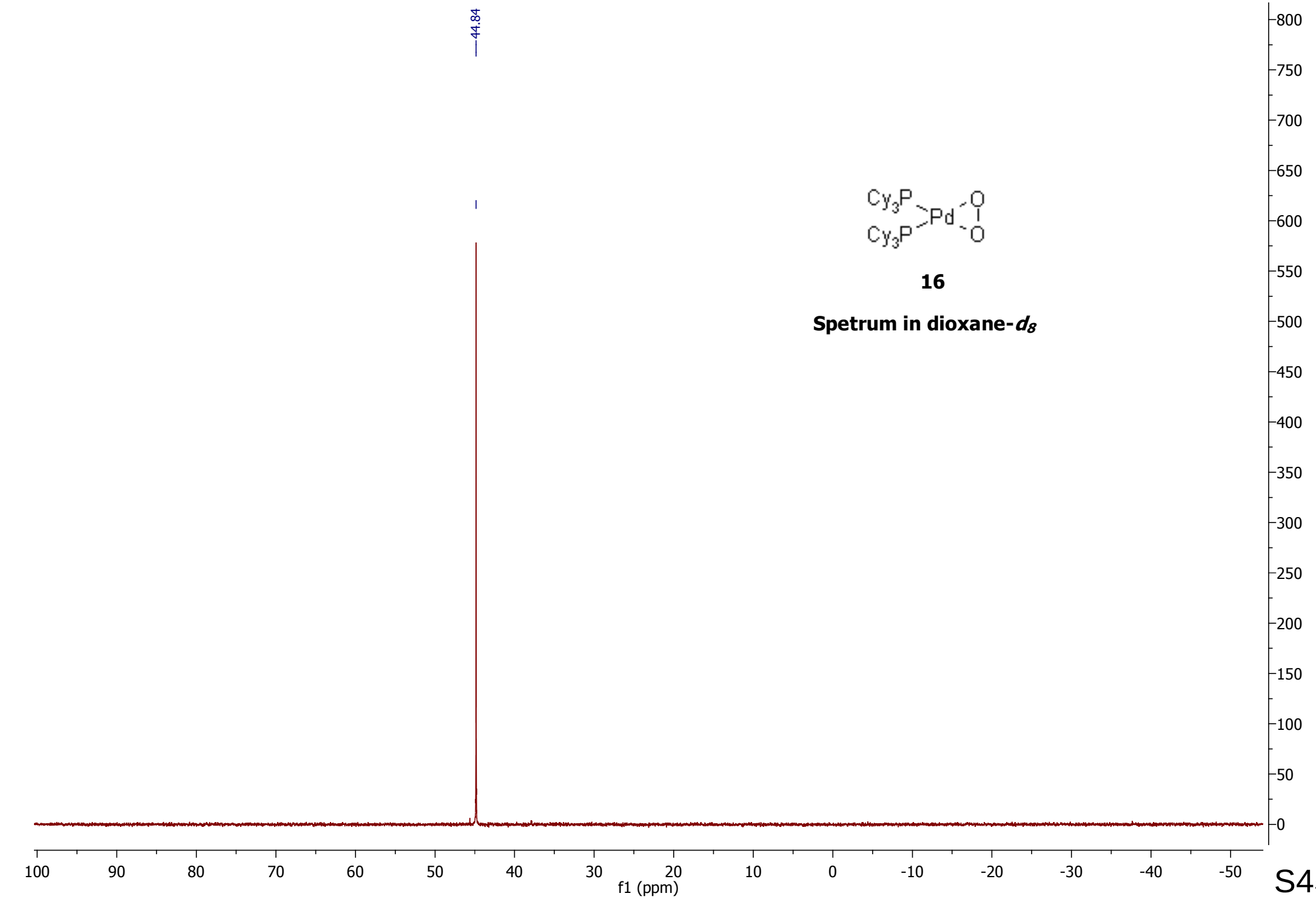
OSPT-ZM-663-A_11Aug2014_PHOSPHORUS_c6d6_01



16

Spetrum in C_6D_6



16

Spetrum in dioxane-*d*$_8$