

# Total Synthesis and Structure Revision of Diplobifuranylone B

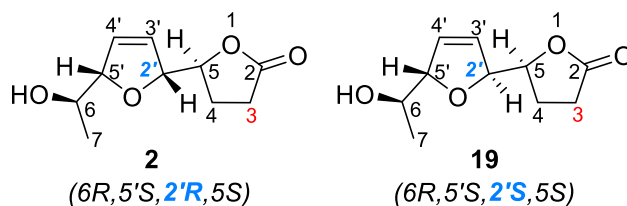
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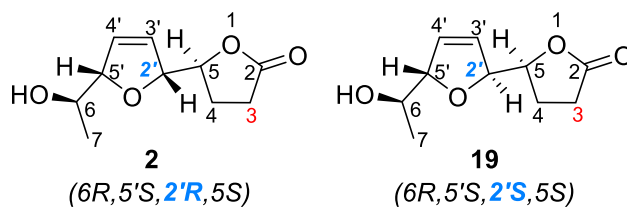
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## <sup>1</sup>H NMR Comparison



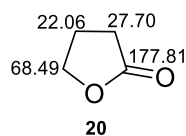
| Position | <b>2</b>                         | <b>19</b>                                    | Literature <sup>1</sup>                |
|----------|----------------------------------|--|--|
| 5        | 4.53 (dt, $J = 7.3, 5.8$ Hz, 1H) | 4.54 (ddd, $J = 8.0, 5.3, 2.8$ Hz, 1H)       | 4.55 (ddd, $J = 8.0, 5.3, 2.8, 1$ H)   |
| 4        | 2.39 – 2.31 (m, 1H)              | 2.34 – 2.27 (m, 1H)                          | 2.29 (m, 1H)                           |
|          | 2.19 – 2.11 (m, 1H)              | 2.26 – 2.18 (m, 1H)                          | 2.22 (m, 1H)                           |
| 3        | 2.61 – 2.49 (m, 2H)              | 2.66 (ddd, $J = 17.7, 10.1, 7.0, 1$ H)       | 2.66 (ddd, $J = 16.7, 10.1, 7.0, 1$ H) |
|          |                                  | 2.47 (ddd, $J = 17.7, 10.3, 6.4, 1$ H)       | 2.45 (ddd, $J = 16.7, 10.3, 6.4, 1$ H) |
| 2'       | 4.85 – 4.81 (m, 1H)              | 4.97 (dtd, $J = 6.1, 2.5, 1.7$ Hz)           | 4.97 (m, 1H)                           |
| 3'       | 5.96 (dt, $J = 6.3, 1.8$ Hz, 1H) | 5.90 (dt, $J = 6.3, 2.0$ Hz, 1H)             | 5.92 (br,d, $J = 9.3$ Hz, 1H)          |
| 4'       | 6.07 (dt, $J = 6.6, 1.7$ Hz, 1H) | 6.01 (dt, $J = 6.3, 2.0$ Hz, 1H)             | 6.01(br,d, $J = 9.3$ Hz, 1H)           |
| 5'       | 4.74 – 4.71 (m, 1H)              | 4.79 (dddd, $J = 5.9, 3.7, 2.3, 1.5$ Hz, 1H) | 4.79 (m, 1H)                           |
| 6        | 3.89 (dq, $J = 6.5, 3.8$ Hz)     | 3.90 (dq, $J = 6.5, 3.4$ Hz)                 | 3.90 (dq, $J = 6.6, 3.4$ Hz, 1H)       |
| 7        | 1.22 (d, $J = 6.5$ Hz)           | 1.17 (d, $J = 6.5$ Hz)                       | 1.18 (d, $J = 6.6$ Hz, 1H)             |
| OH       | -                                | 1.64, br, s                                  | 1.85, br,s                             |

## <sup>13</sup>C NMR Comparison



| Position | <b>2</b> | <b>19</b> | Literature <sup>1</sup> | $\Delta$ ( <b>2</b> -Lit.) | $\Delta$ ( <b>19</b> -Lit.) |
|----------|----------|-----------|-------------------------|----------------------------|-----------------------------|
| 5        | 81.04    | 80.12     | 80.1                    | +0.94                      | +0.02                       |
| 4        | 23.54    | 23.75     | 23.7                    | -0.16                      | +0.05                       |
| 3        | 27.74    | 27.97     | 22.9                    | +4.84                      | +5.07                       |
|          | 176.39   | 177.24    | 177.2                   | -0.85                      | +0.04                       |
| 2'       | 87.11    | 87.97     | 87.9                    | -0.79                      | +0.07                       |
| 3'       | 129.50   | 128.79    | 128.7                   | +0.80                      | +0.09                       |
| 4'       | 127.20   | 127.33    | 127.3                   | -0.10                      | +0.03                       |
| 5'       | 91.00    | 91.01     | 90.9                    | +0.10                      | +0.11                       |
| 6        | 69.08    | 69.09     | 69.1                    | -0.02                      | -0.01                       |
| 7        | 18.92    | 17.94     | 17.9                    | +1.02                      | +0.04                       |

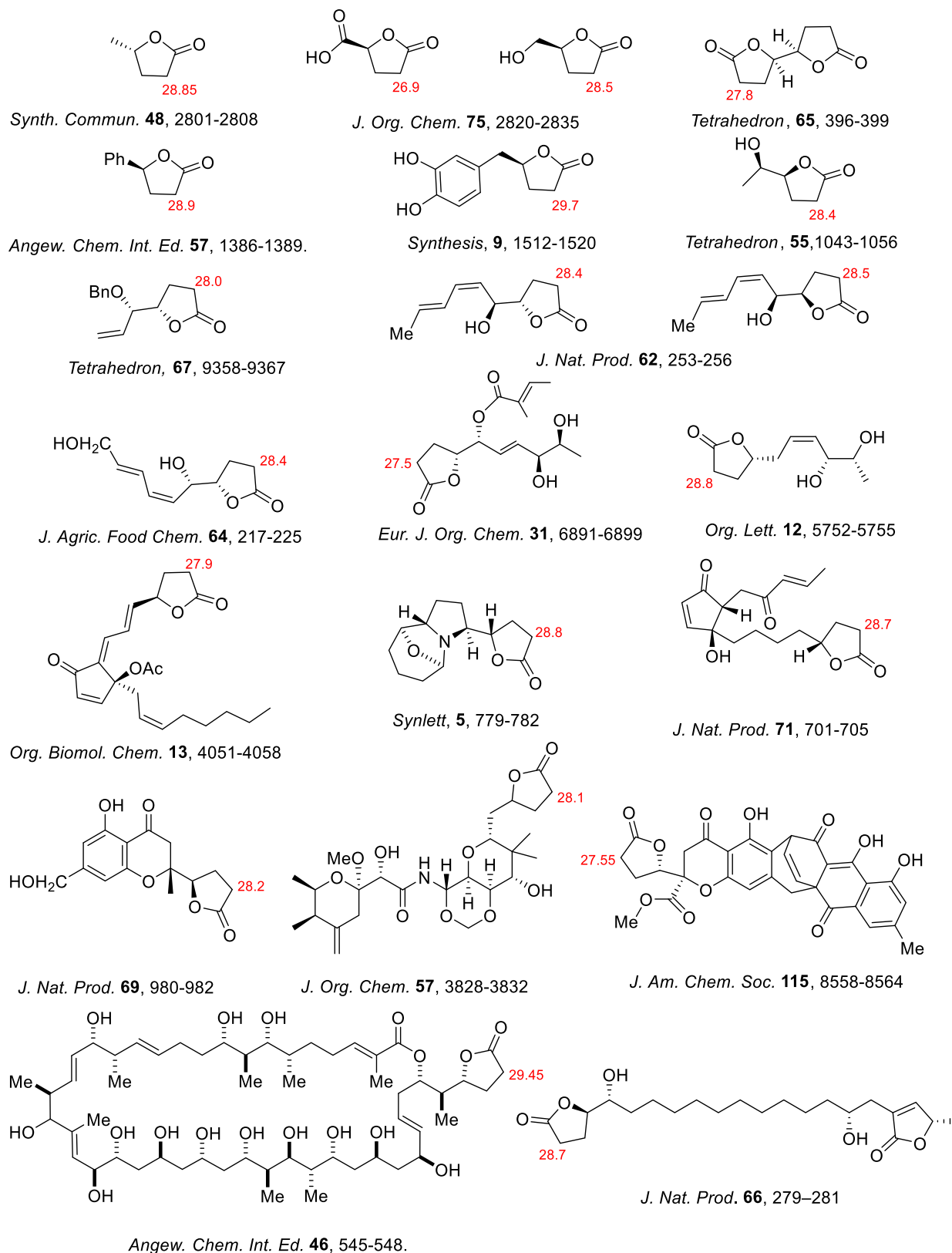
## Dihydrofuran-2(3H)-one



Literature<sup>2</sup>: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  4.30 (t, J = 7.1 Hz, 2 H), 2.45 (t, J = 7.9 Hz, 2 H), 2.26 - 2.18 (m, 2 H).

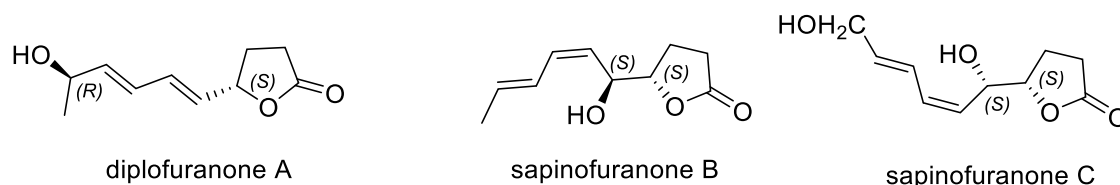
<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  177.81, 68.49, 27.70, 22.06;

## The Chemical Shifts of the C3 of $\gamma$ -lactones Possessing Only One Substituent at C5

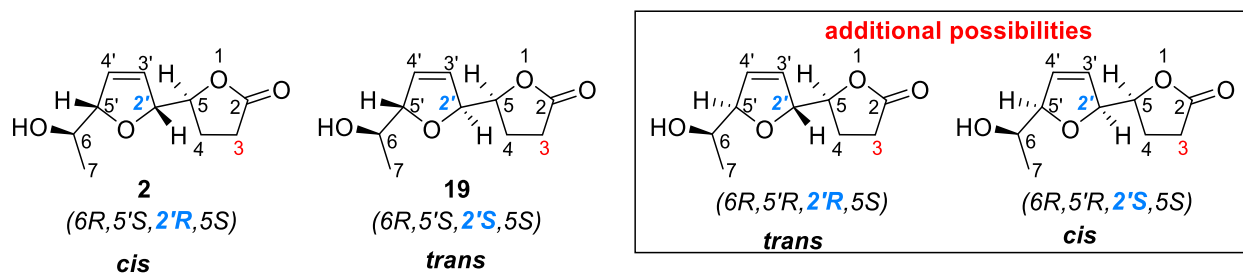


## Comments about Literature Misassignment

The absolute stereochemistry of C6, i.e., (*R*) is determined by the Mosher's method in the initial report.<sup>1</sup> The absolute stereochemistry of the other chiral centers are assigned in 2017 by the chiroptical methods.<sup>3</sup> In addition, *D. corticola* produces several metabolites: furanones such as sapinofuranone B, sapinofuranone C, diplofuranones A, and diplobifuranylonones A–C. All the known structures have lactone rings with *S* configuration at the C5 position. So, the C6 and C5 configurations, being *R* and *S*, respectively, are secure.



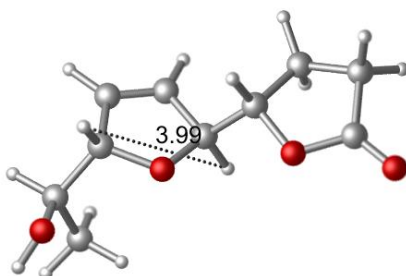
The only other potential stereoisomers are (*6R,5'R,2'R,5S*) and (*6R,5'R,2'S,5S*). Based on the coupling constant between H-2' and H-5' reported in the initial report,<sup>1</sup> the relative stereochemistry of the dihydrofuran moiety should be *trans*. In this way, only two possible stereoisomers are left: (*6R,5'S,2'S,5S*) and (*6R,5'R,2'R,5S*). It is reasonable that <sup>1</sup>H and <sup>13</sup>C NMR spectra should be able to rule them out.



## Computational Details.

Structural optimizations were performed at the B3LYP<sup>4-5</sup> level of theory with cc-pVDZ basis set.

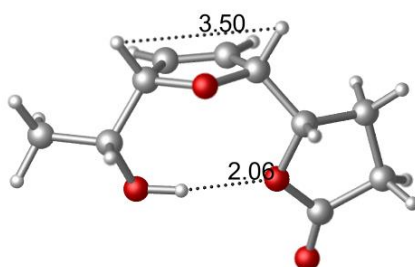
The Cartesian coordinates of **19**, the revised structure of diplobifuranylone B with a *trans*-dihydrofuran ring.



|   |           |           |           |
|---|-----------|-----------|-----------|
| C | 0.616300  | 1.830200  | 0.255100  |
| C | 1.797000  | 1.714200  | -0.354800 |
| C | 2.074300  | 0.271100  | -0.682300 |
| C | -0.023500 | 0.468600  | 0.382100  |
| H | 0.159700  | 2.752400  | 0.616000  |
| H | 2.484600  | 2.527000  | -0.593900 |
| O | 0.929600  | -0.435900 | -0.179400 |
| H | -0.207900 | 0.191000  | 1.440100  |
| H | 2.144800  | 0.108700  | -1.775900 |
| C | 3.384700  | -0.280800 | -0.092300 |
| H | 4.175400  | 0.464200  | -0.331700 |
| C | -1.362500 | 0.355800  | -0.350900 |
| C | -2.438200 | 1.359500  | 0.102500  |
| H | -1.174400 | 0.426700  | -1.436600 |
| C | -3.291500 | -0.878000 | 0.033400  |

|   |           |           |           |
|---|-----------|-----------|-----------|
| C | -3.731400 | 0.575100  | -0.119200 |
| H | -2.383700 | 2.305000  | -0.454500 |
| H | -2.309400 | 1.585900  | 1.174800  |
| H | -4.122200 | 0.701600  | -1.143600 |
| H | -4.547800 | 0.802700  | 0.578600  |
| C | 3.326800  | -0.491100 | 1.417400  |
| H | 4.295000  | -0.865000 | 1.791400  |
| H | 3.108500  | 0.450900  | 1.945900  |
| H | 2.544600  | -1.224800 | 1.660100  |
| O | 3.639000  | -1.497400 | -0.788800 |
| H | 4.386800  | -1.934400 | -0.357100 |
| O | -1.931800 | -0.947000 | -0.087300 |
| O | -3.970100 | -1.849700 | 0.223300  |

The Cartesian coordinates of **2**, the normal structure of diplobifuranylone B with a *cis*-dihydrofuran ring. It has an intramolecular H-bond.



|   |           |           |           |
|---|-----------|-----------|-----------|
| C | -0.323600 | -1.428000 | 1.197200  |
| C | -1.580100 | -0.983500 | 1.230000  |
| C | -2.102400 | -0.778600 | -0.166600 |
| C | 0.125600  | -1.579800 | -0.235300 |
| H | 0.299300  | -1.667300 | 2.059400  |

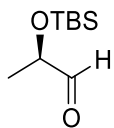
|   |           |           |           |
|---|-----------|-----------|-----------|
| H | -2.167300 | -0.780900 | 2.125400  |
| O | -0.989200 | -1.140800 | -1.013600 |
| H | -2.944900 | -1.463700 | -0.391900 |
| C | -2.545000 | 0.662100  | -0.496100 |
| H | -2.606600 | 0.707400  | -1.604400 |
| C | 1.358700  | -0.775800 | -0.653600 |
| C | 2.692200  | -1.188500 | -0.008300 |
| H | 1.420900  | -0.819000 | -1.754800 |
| C | 2.368600  | 1.190600  | 0.090900  |
| C | 3.463600  | 0.132800  | 0.025400  |
| H | 3.193800  | -1.983800 | -0.576800 |
| H | 2.524300  | -1.558200 | 1.016000  |
| H | 4.033800  | 0.304100  | -0.903900 |
| H | 4.158200  | 0.251600  | 0.867100  |
| C | -3.914700 | 0.990500  | 0.086300  |
| H | -4.185500 | 2.024600  | -0.173400 |
| H | -4.691800 | 0.316200  | -0.307300 |
| H | -3.903200 | 0.916700  | 1.186100  |
| O | -1.638100 | 1.625300  | 0.002000  |
| O | 1.180100  | 0.617000  | -0.293300 |
| O | 2.446500  | 2.345400  | 0.400800  |
| H | 0.351600  | -2.641300 | -0.477800 |
| H | -0.734000 | 1.368200  | -0.250500 |



## Reference

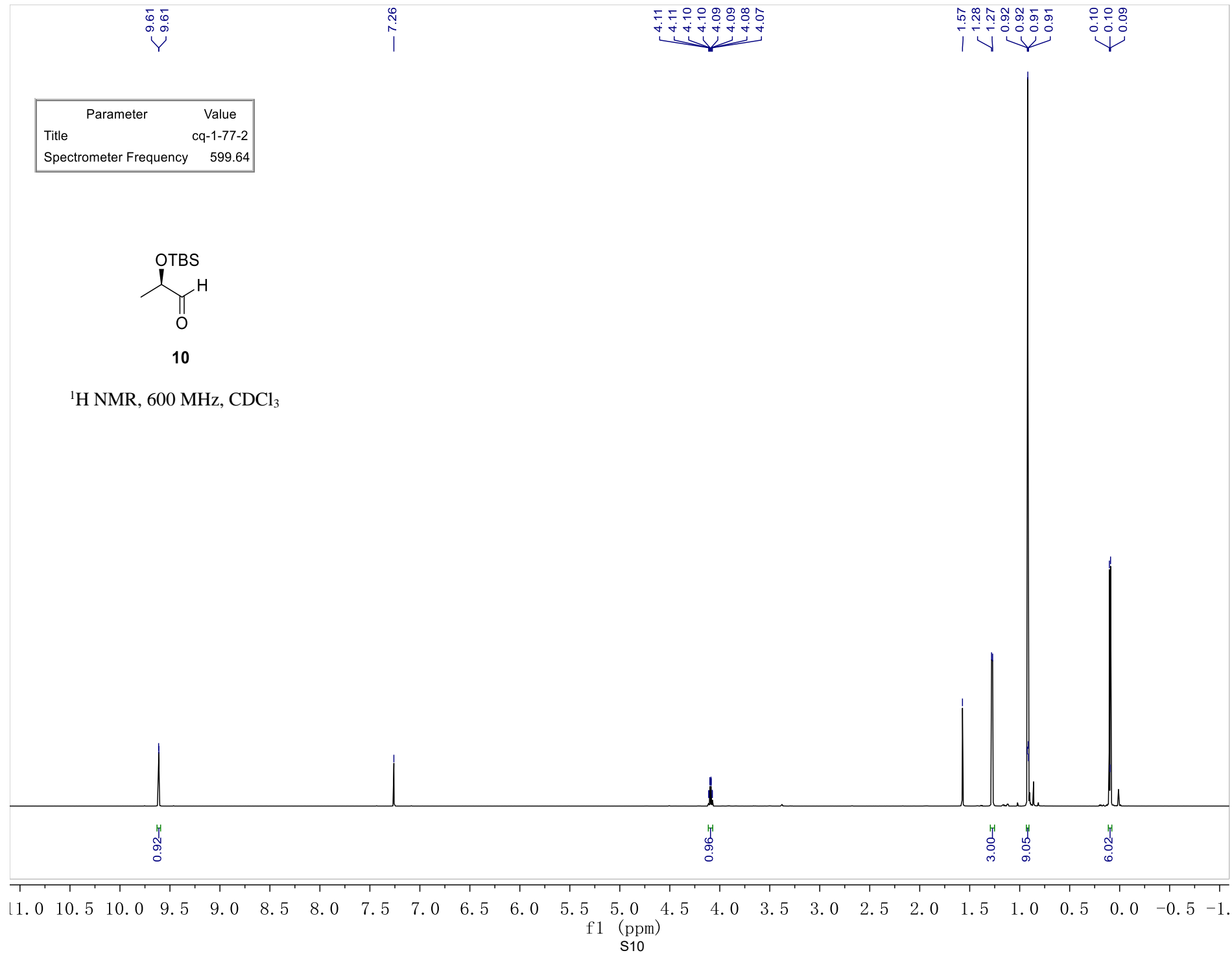
1. Evidente, A.; Andolfi, A.; Fiore, M.; Spanu, E.; Maddau, L.; Franceschini, A.; Marras, F.; Motta, A. Diplobifuranylones A and B, 5'-Monosubstituted Tetrahydro-2H-bifuranyl-5-ones Produced by *Diplodia corticola*, a Fungus Pathogen of Cork Oak. *J. Nat. Prod.* **2006**, 69, 671-674.
2. Das, A.; Chaudhuri, R.; Liu, R.-S. Gold-Catalyzed Oxidative Cleavage of Aryl-Substituted Alkynyl Ethers Using Molecular Oxygen. Simultaneous Degradation of C–H and Single and Triple Carbon–Carbon Bonds Under Ambient Conditions. *Chem. Comm.* **2009**, 4046-4048.
3. Mazzeo, G.; Cimmino, A.; Masi, M.; Longhi, G.; Maddau, L.; Memo, M.; Evidente, A.; Abbate, S. Importance and Difficulties in the Use of Chiroptical Methods to Assign the Absolute Configuration of Natural Products: The Case of Phytotoxic Pyrones and Furanones Produced by *Diplodia Corticola*. *J. Nat. Prod.* **2017**, 80, 2406-2415.
4. Becke, A. D. Density-Functional Thermochemistry. III. The Role of Exact Exchange. *J. Chem. Phys.* **1993**, 98, 5648-5652.
5. Lee, C.; Yang, W.; Parr, R. G. Development of the Colle-Salvetti Correlation-Energy Formula into a Functional of the Electron Density. *Physical Review B.* **1988**, 37, 785-789.

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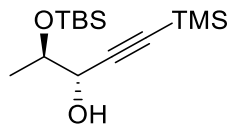


**10**

<sup>1</sup>H NMR, 600 MHz, CDCl<sub>3</sub>



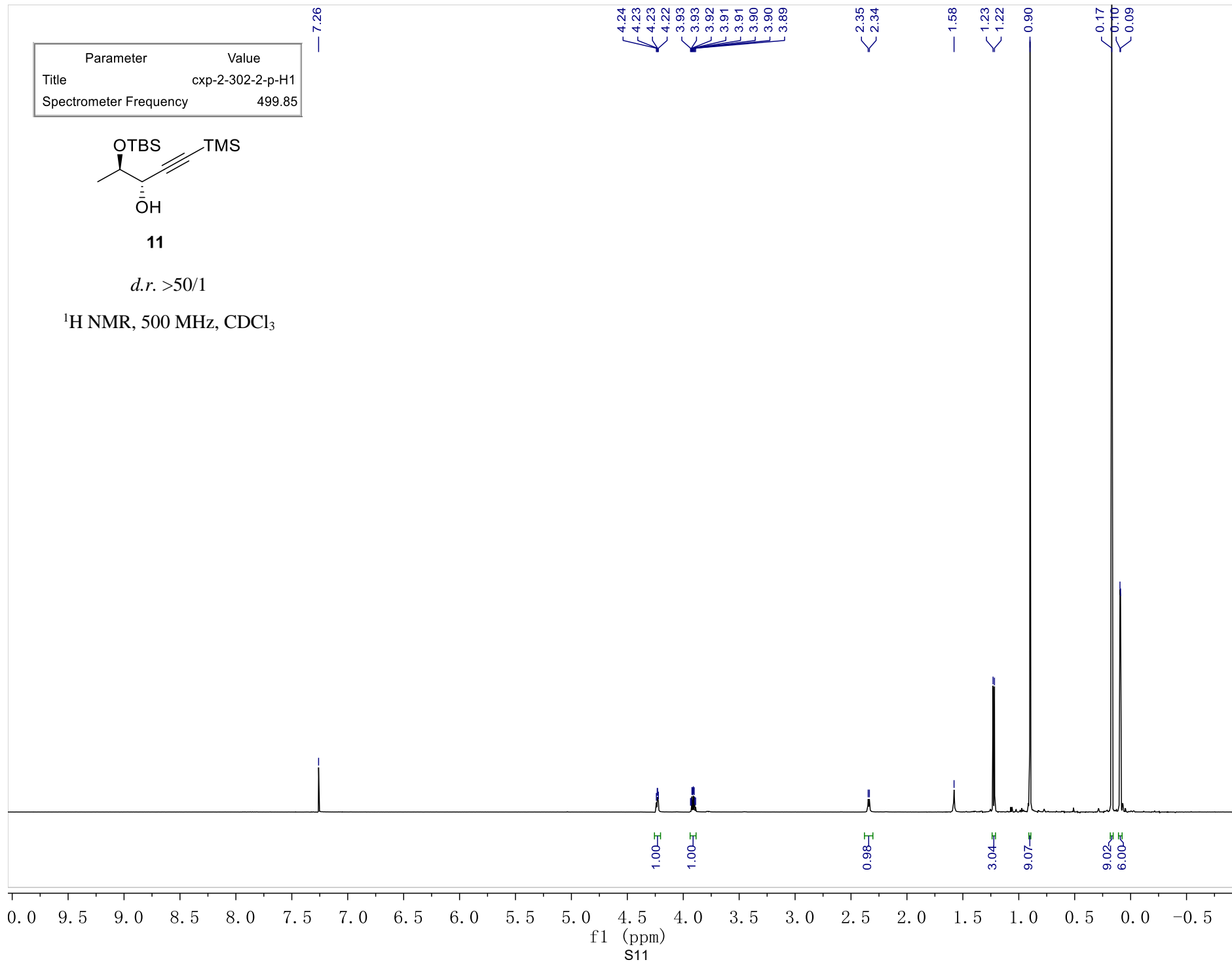
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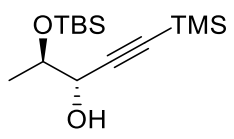
**11**

*d.r.* >50/1

<sup>1</sup>H NMR, 500 MHz, CDCl<sub>3</sub>

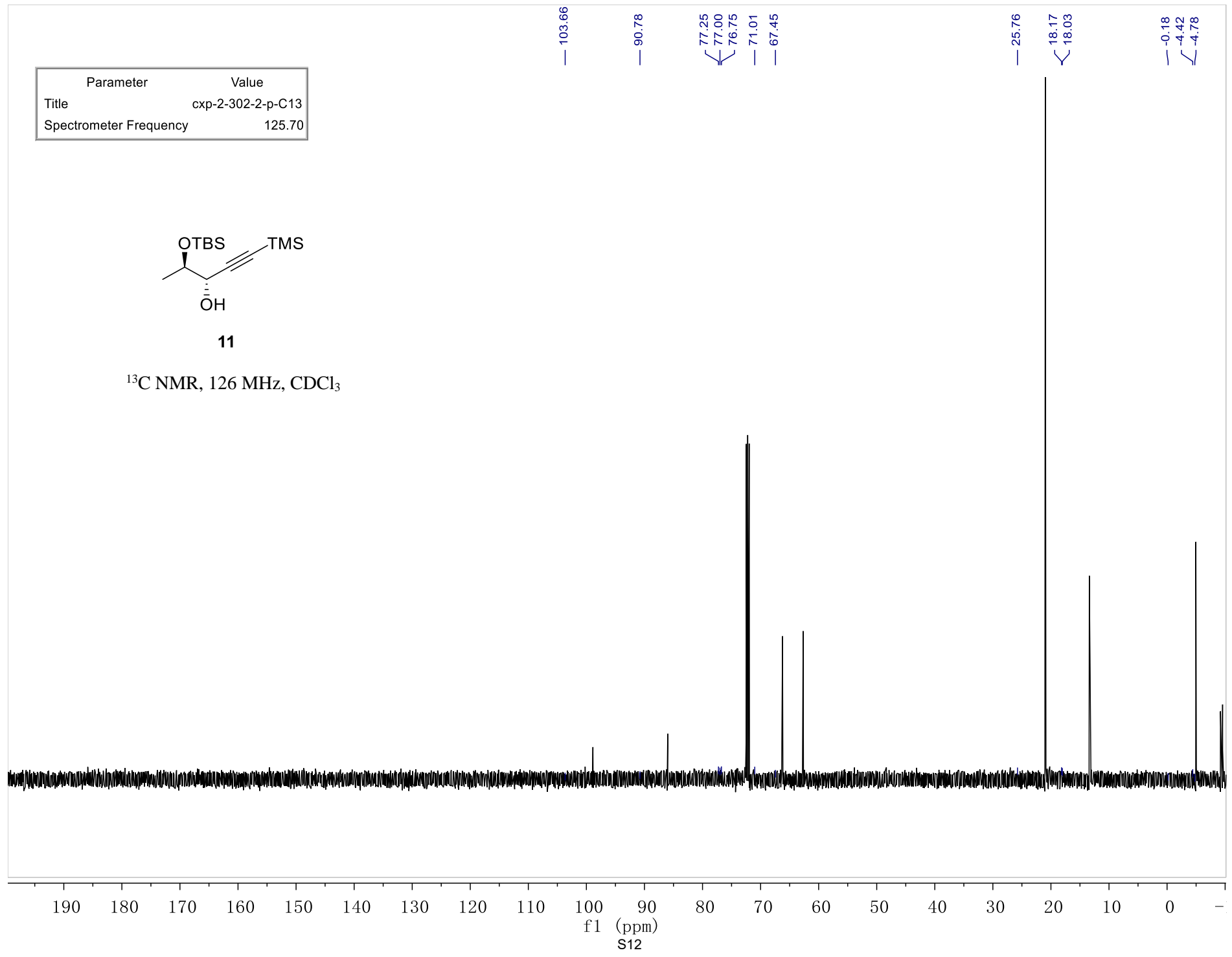


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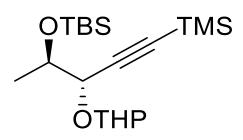


11

<sup>13</sup>C NMR, 126 MHz, CDCl<sub>3</sub>



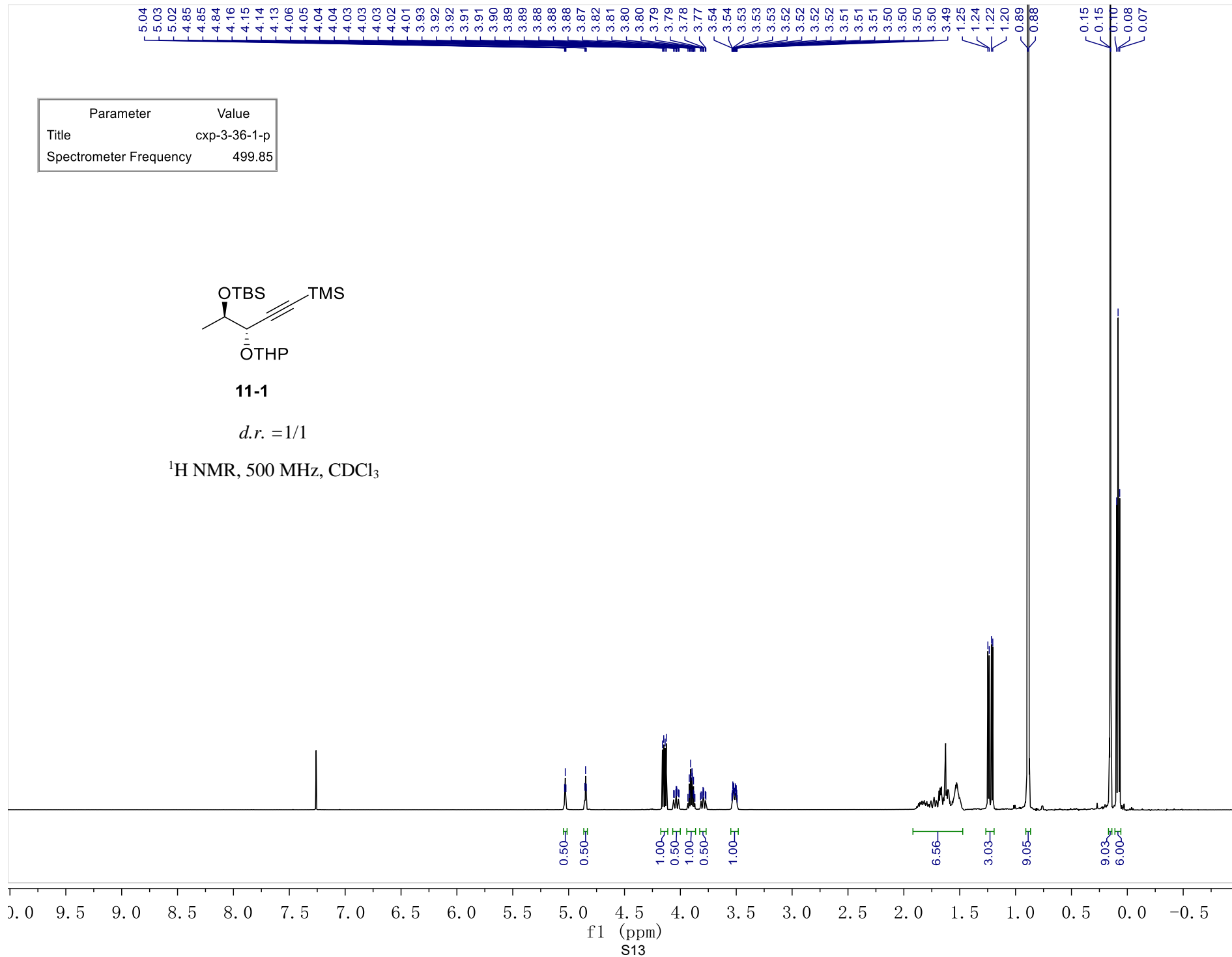
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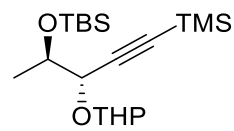
**11-1**

*d.r.* = 1/1

<sup>1</sup>H NMR, 500 MHz, CDCl<sub>3</sub>



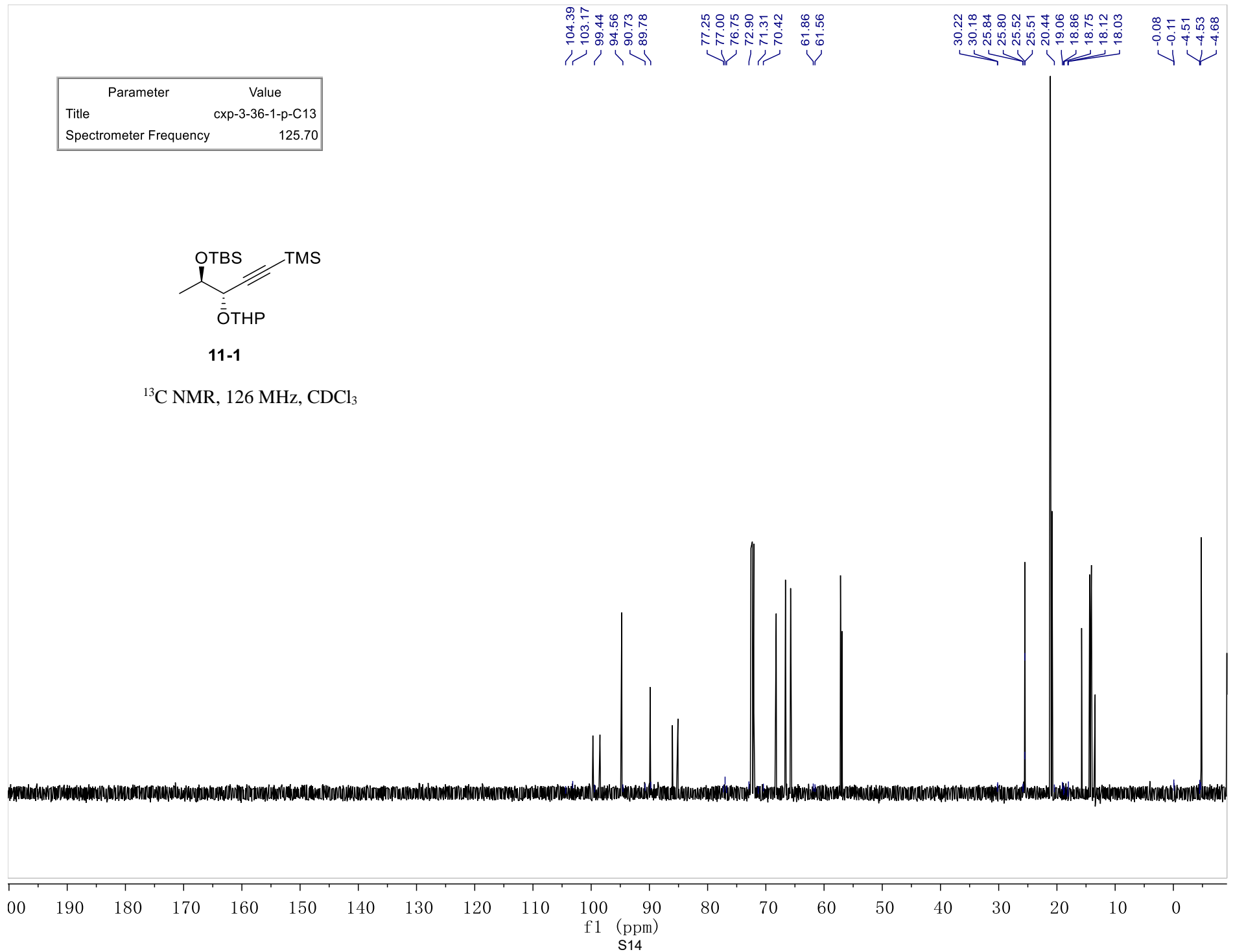
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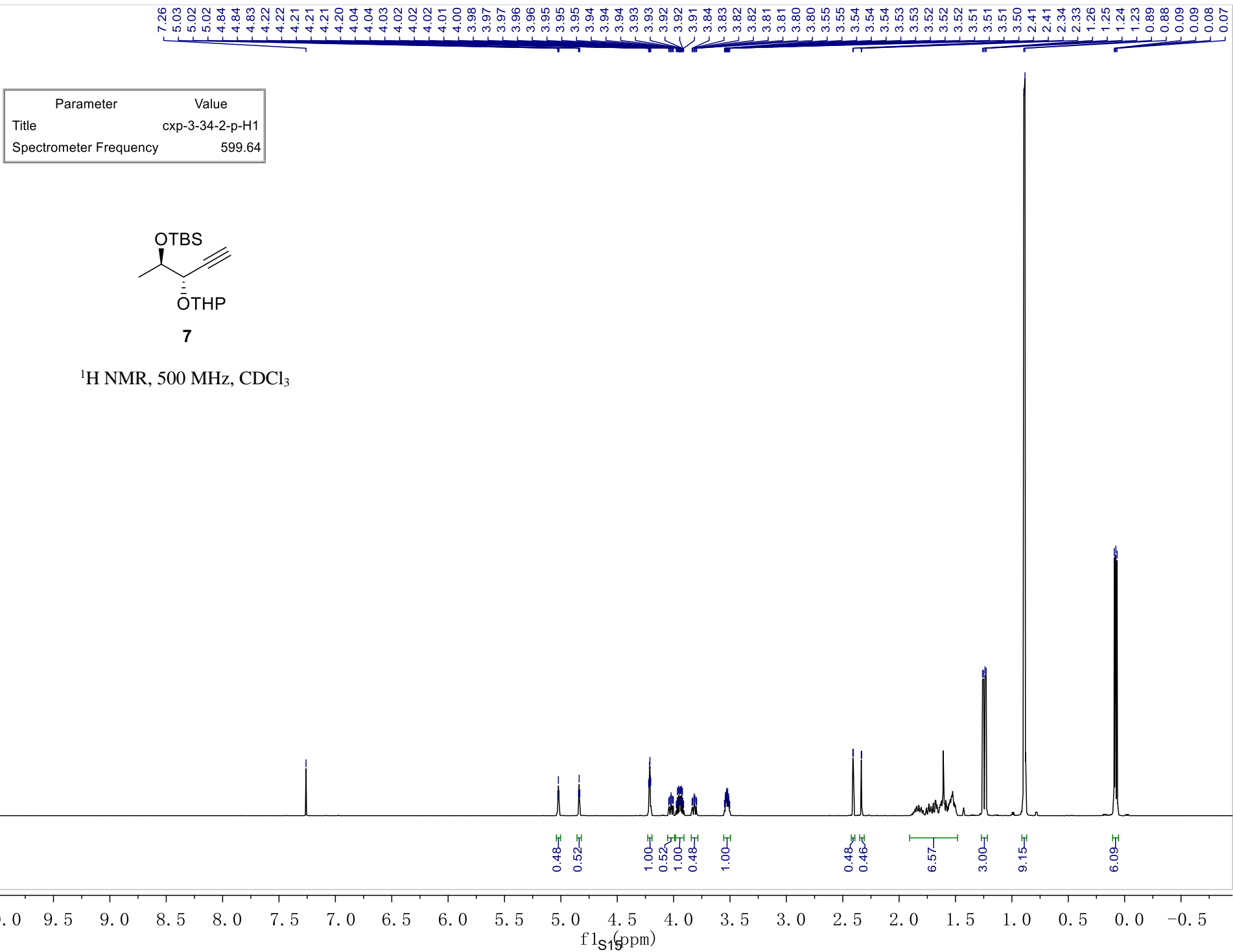
**11-1**

<sup>13</sup>C NMR, 126 MHz, CDCl<sub>3</sub>

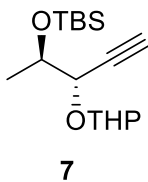
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- 103.17
- 99.44
- 94.56
- 90.73
- 89.78
- 77.25
- 77.00
- 76.75
- 72.90
- 71.31
- 70.42
- 61.86
- 61.56
- 30.22
- 30.18
- 25.84
- 25.80
- 25.52
- 25.51
- 20.44
- 19.06
- 18.86
- 18.75
- 18.12
- 18.03
- 0.08
- 0.11
- 4.51
- 4.53
- 4.68



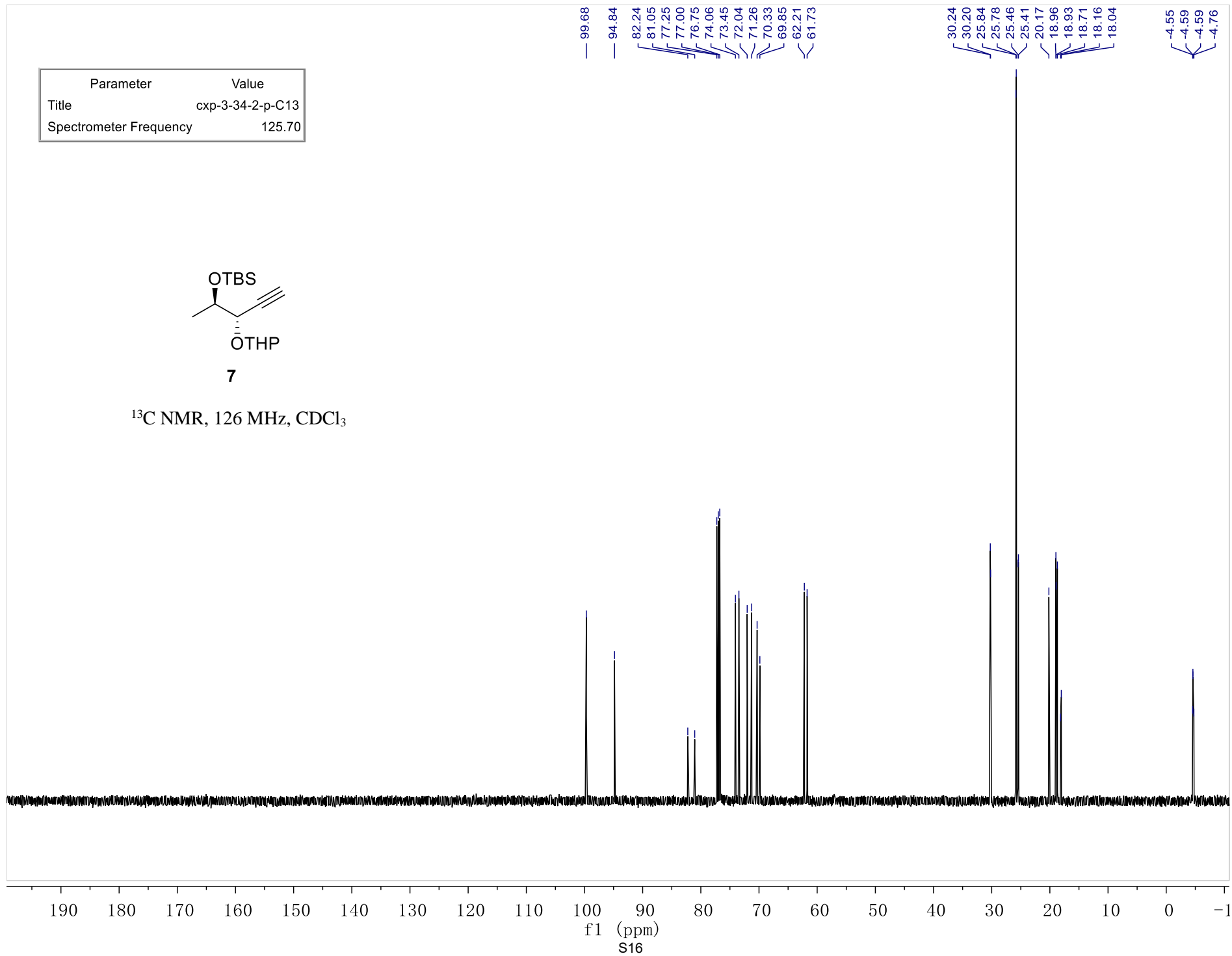
f1 (ppm)  
S14



| Parameter              | Value            |
|------------------------|------------------|
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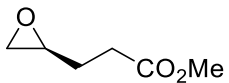


$^{13}\text{C}$  NMR, 126 MHz,  $\text{CDCl}_3$



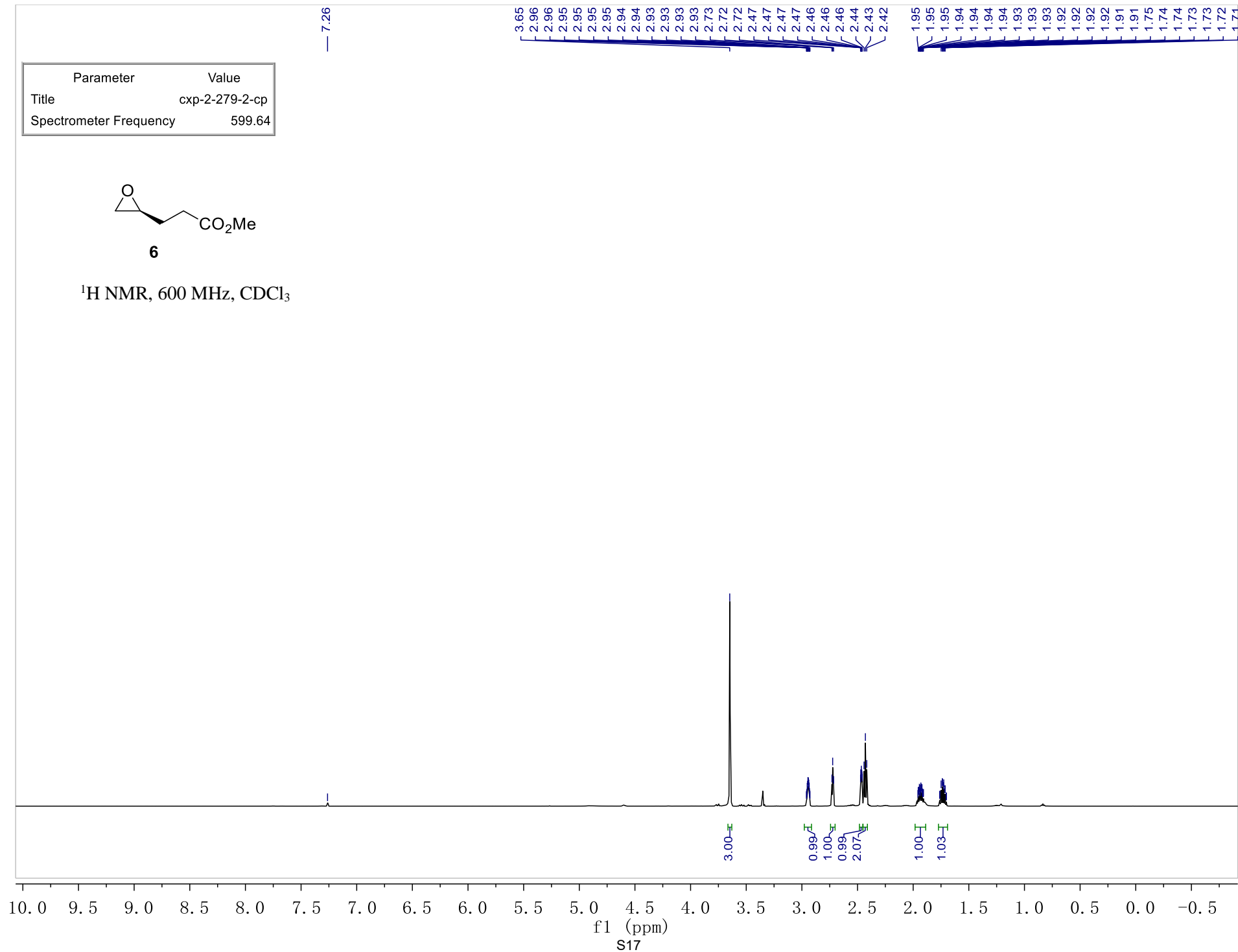


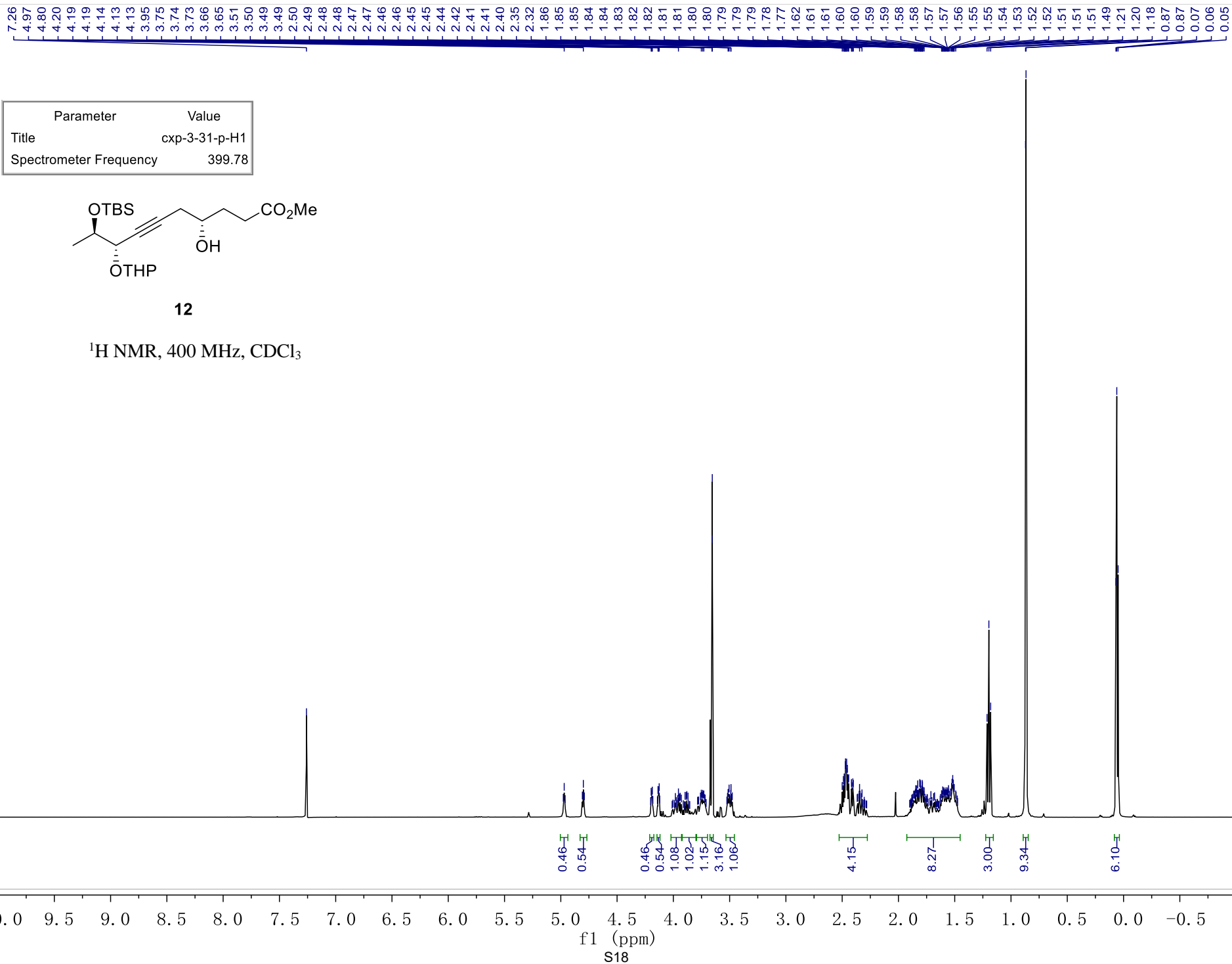
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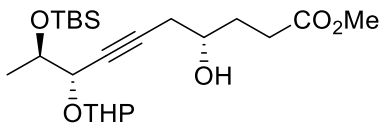
**6**

<sup>1</sup>H NMR, 600 MHz, CDCl<sub>3</sub>



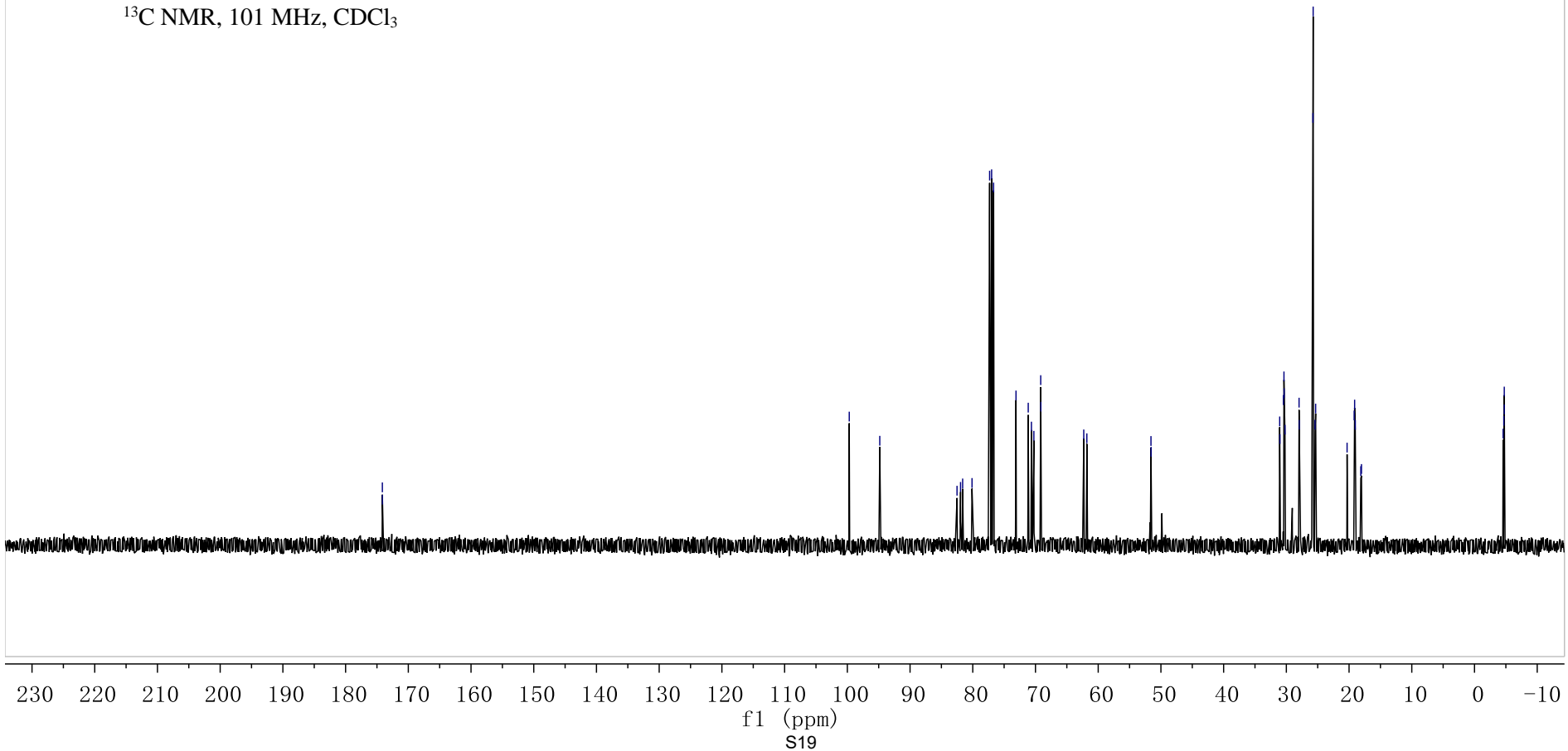


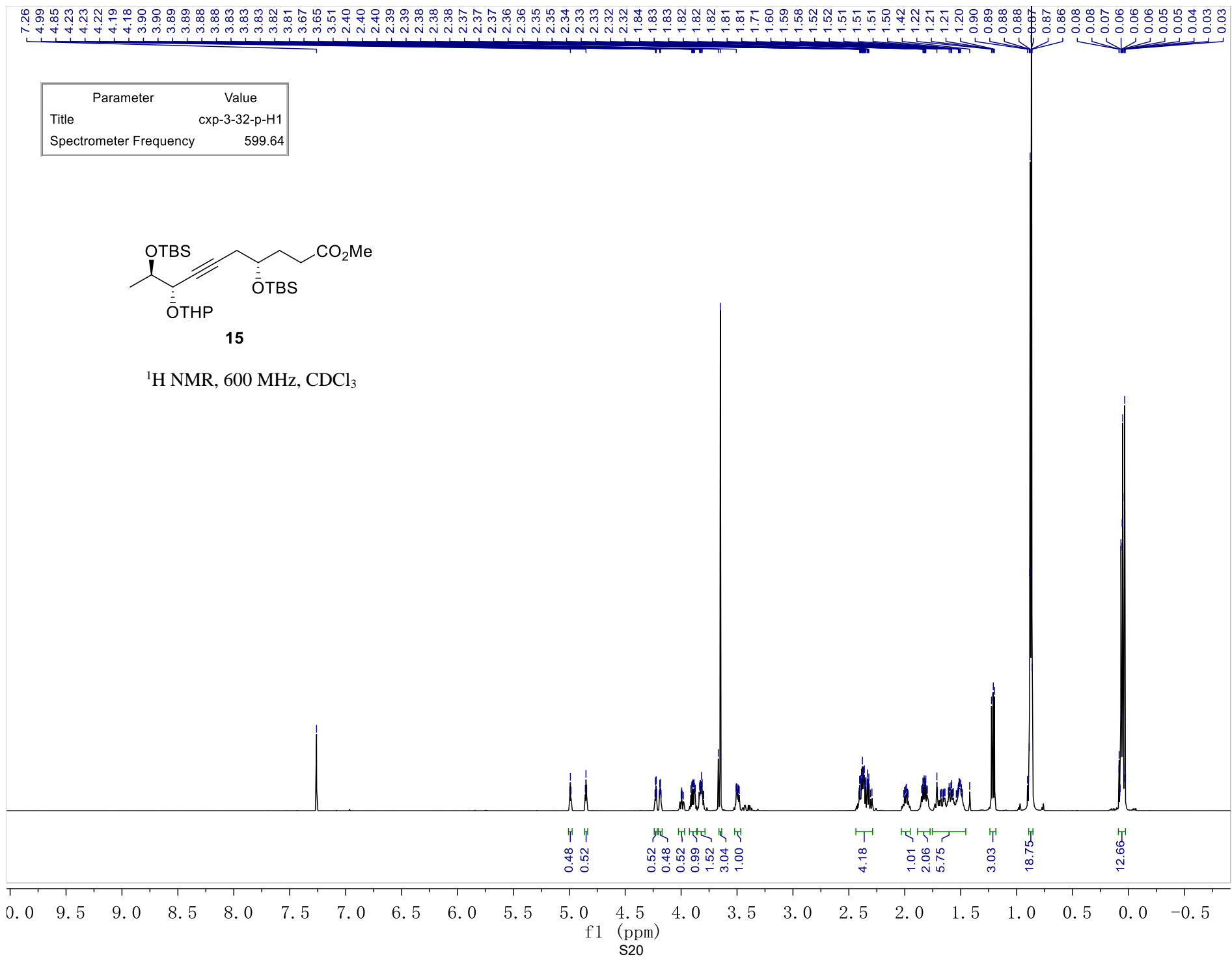
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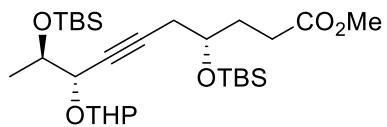
**12**

$^{13}\text{C}$  NMR, 101 MHz,  $\text{CDCl}_3$



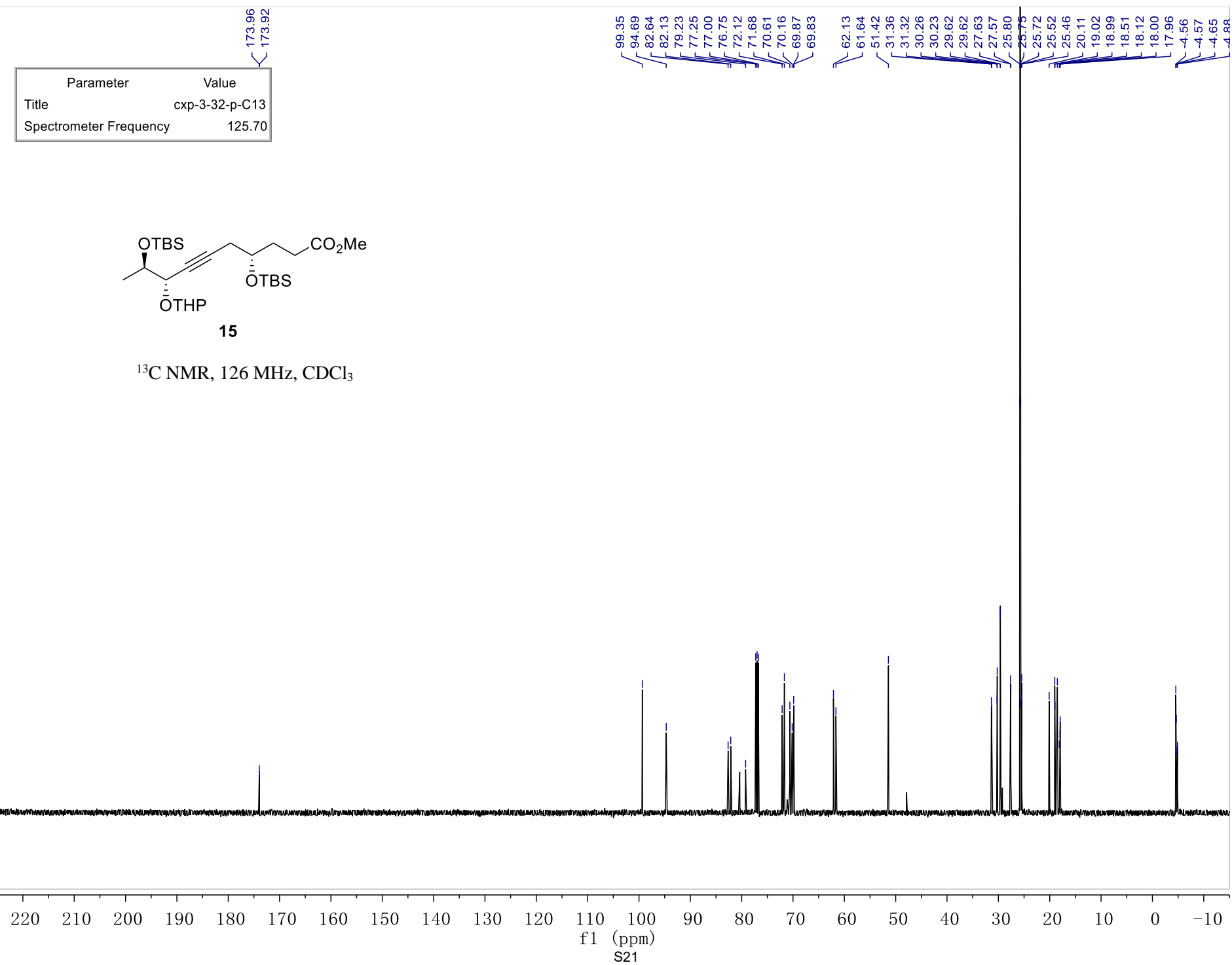


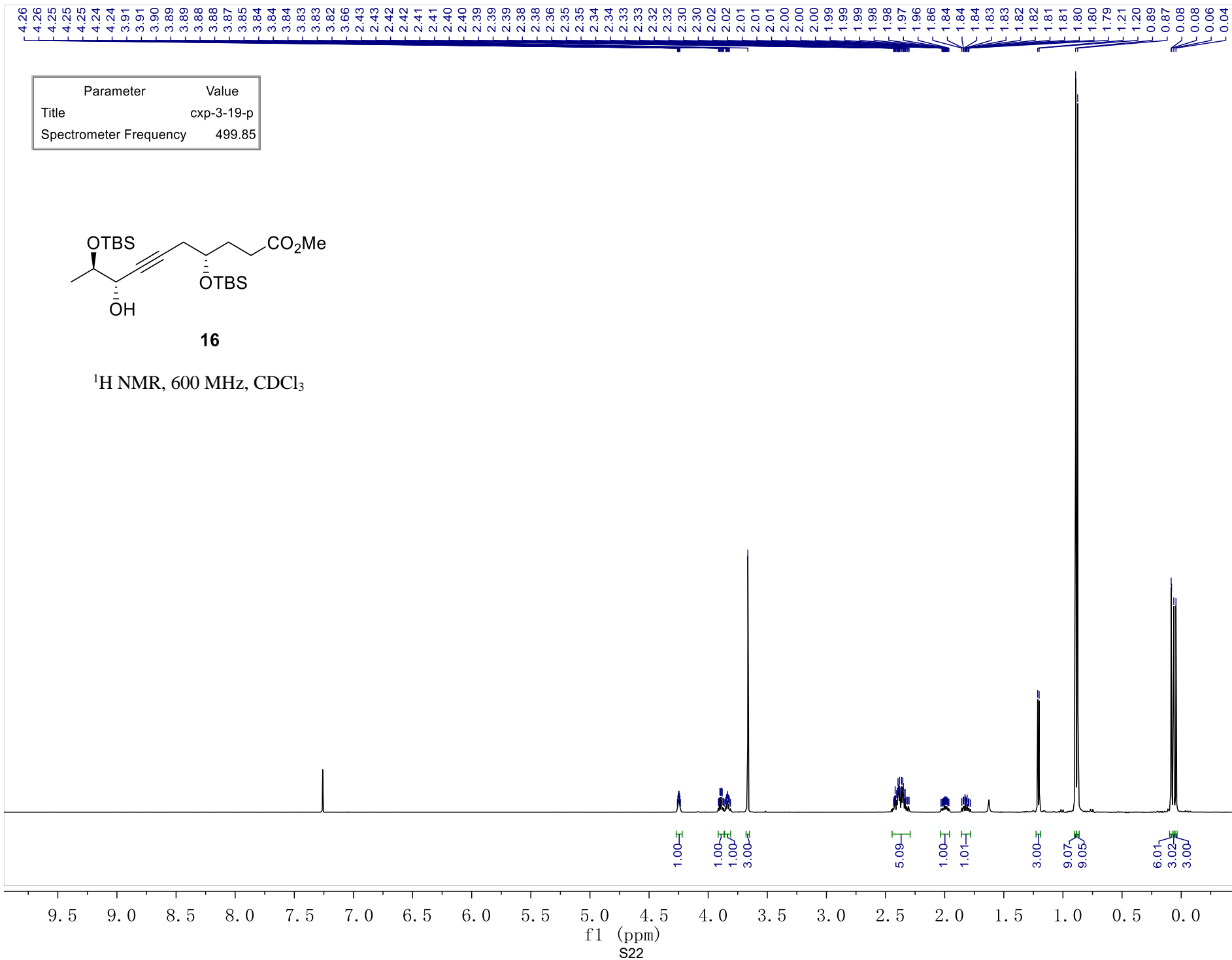
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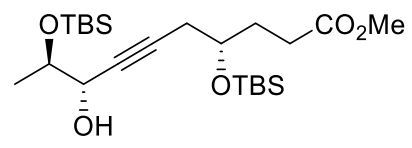
**15**

<sup>13</sup>C NMR, 126 MHz, CDCl<sub>3</sub>



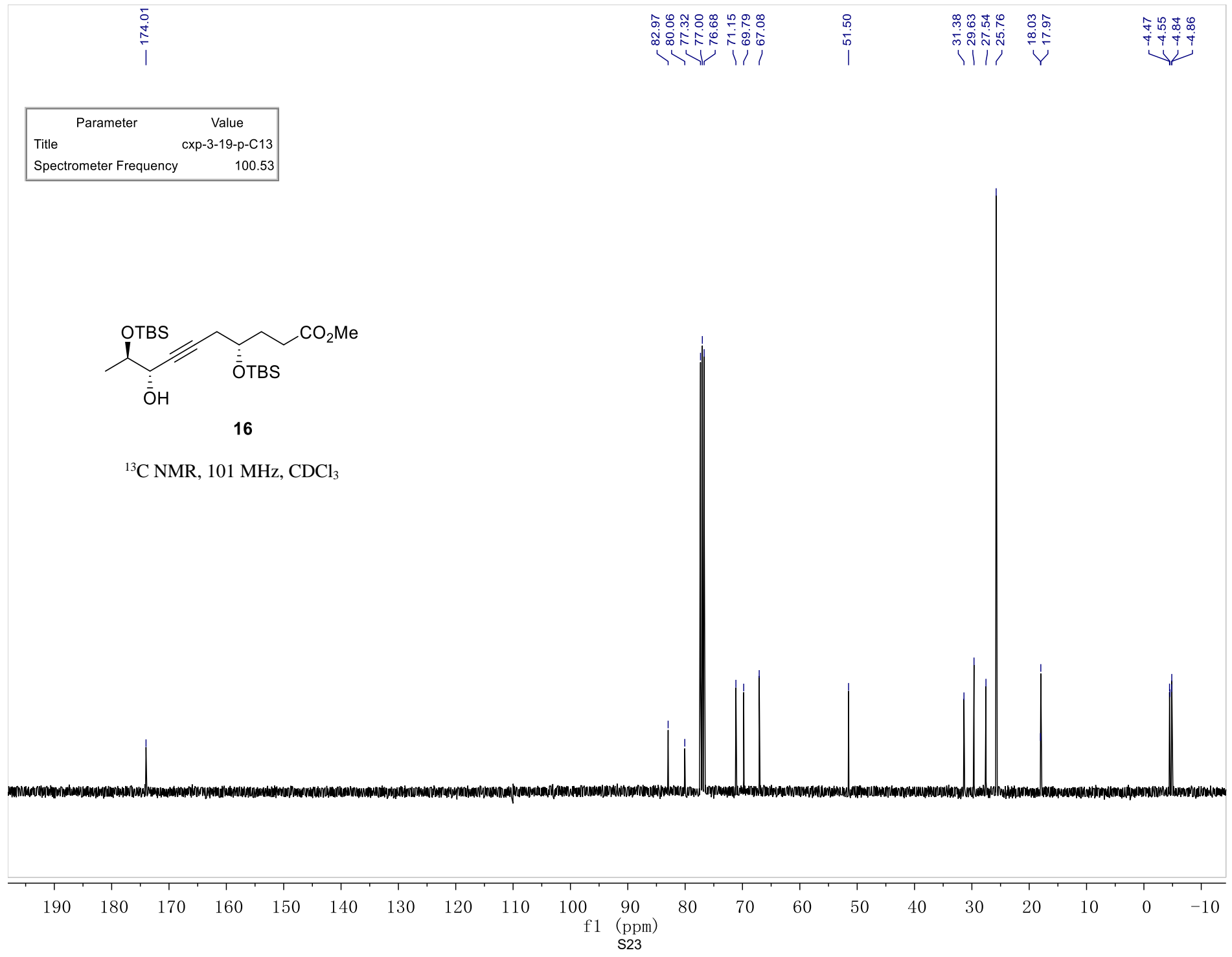


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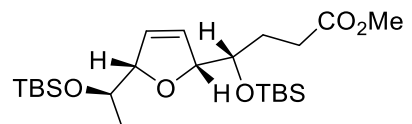
**16**

<sup>13</sup>C NMR, 101 MHz, CDCl<sub>3</sub>



5.99  
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1.90  
1.90  
1.59  
1.21  
1.20  
1.20  
1.19  
0.89  
0.89  
0.89  
0.06  
0.05  
0.04  
0.03

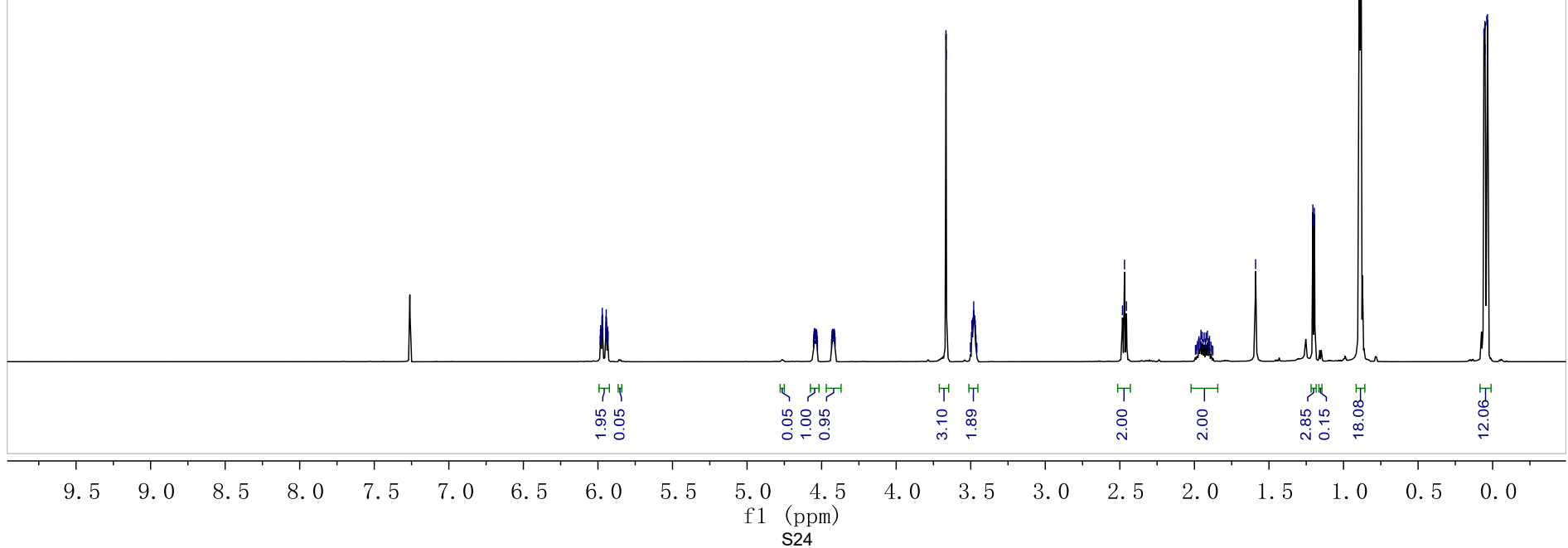
| Parameter              | Value         |
|------------------------|---------------|
| Title                  | cxp-3-41-p-H1 |
| Spectrometer Frequency | 599.64        |



**17**

*d.r.* = 95/5

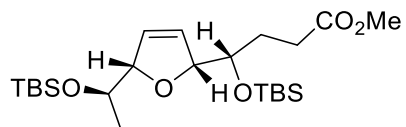
<sup>1</sup>H NMR, 600 MHz, CDCl<sub>3</sub>



f1 (ppm)  
S24

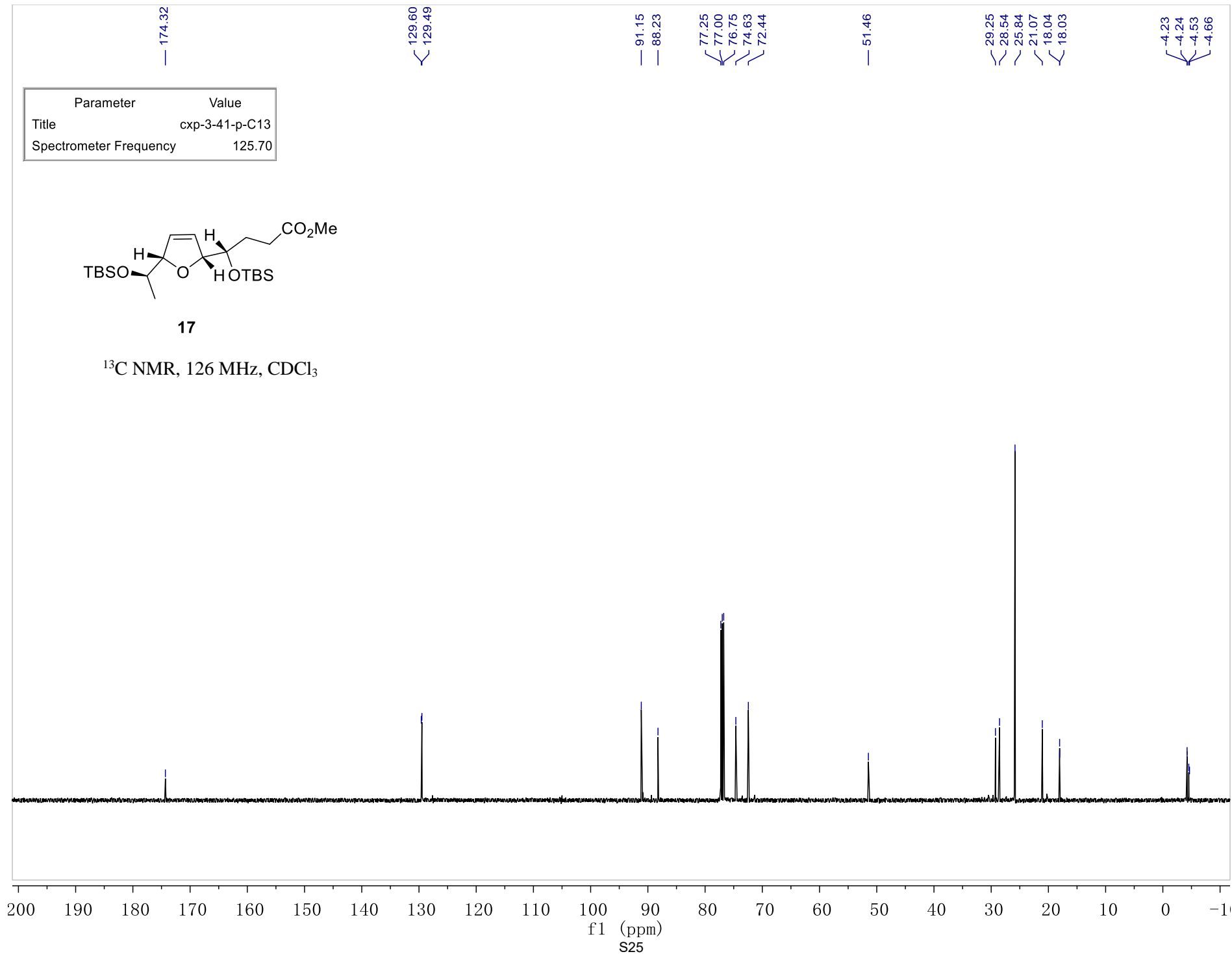


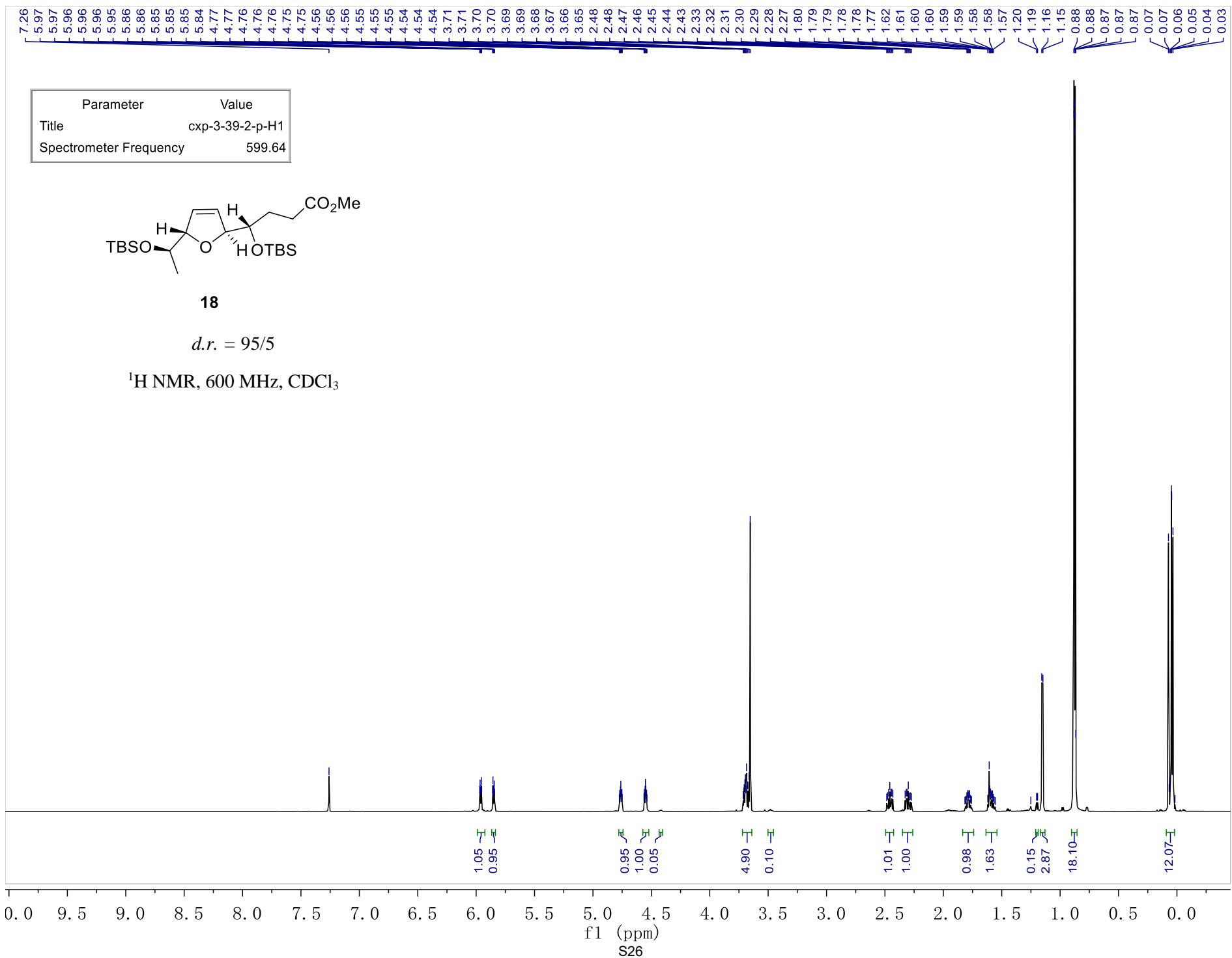
| Parameter              | Value          |
|------------------------|----------------|
| Title                  | cxp-3-41-p-C13 |
| Spectrometer Frequency | 125.70         |

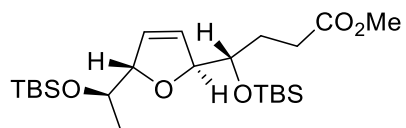


17

<sup>13</sup>C NMR, 126 MHz, CDCl<sub>3</sub>



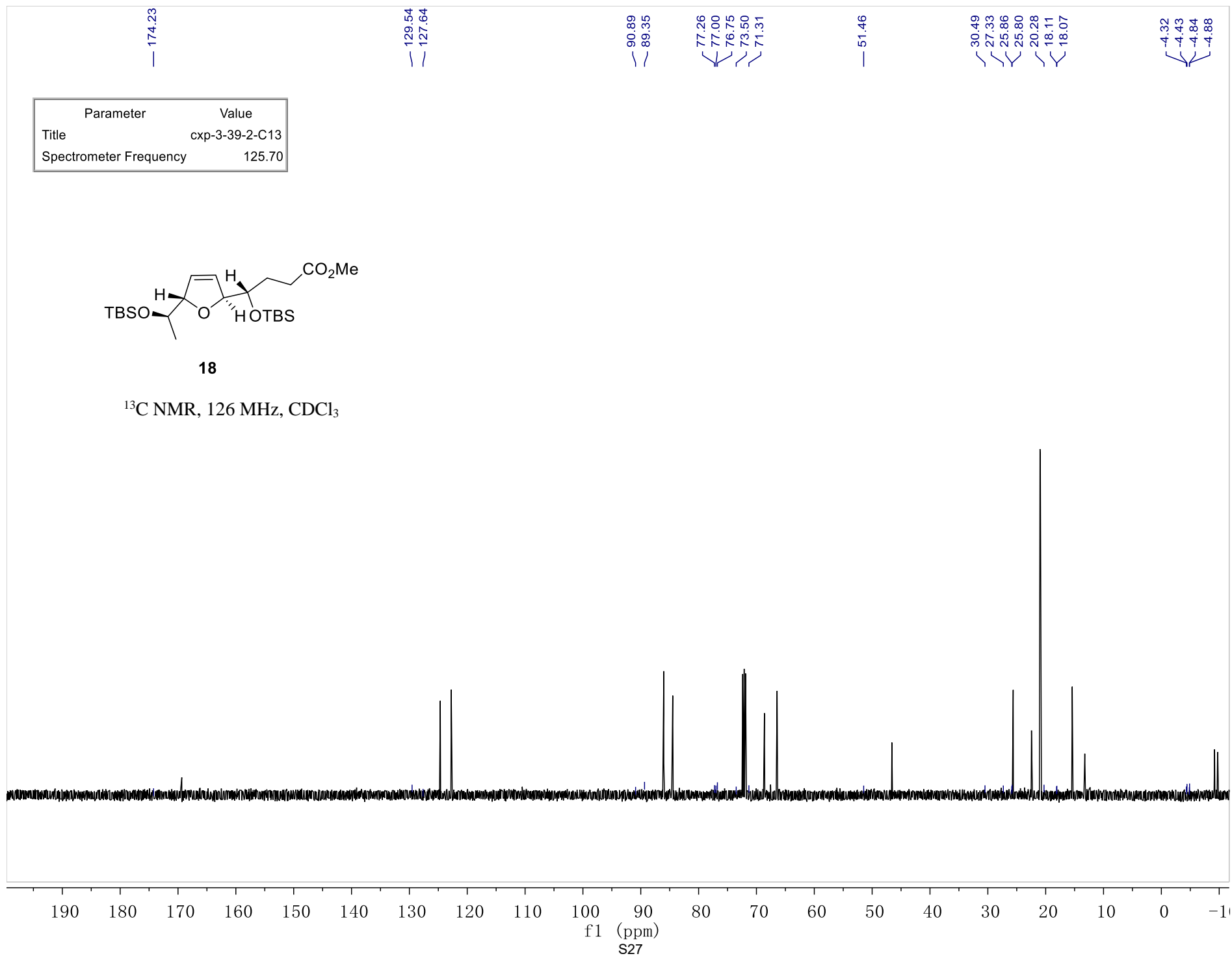


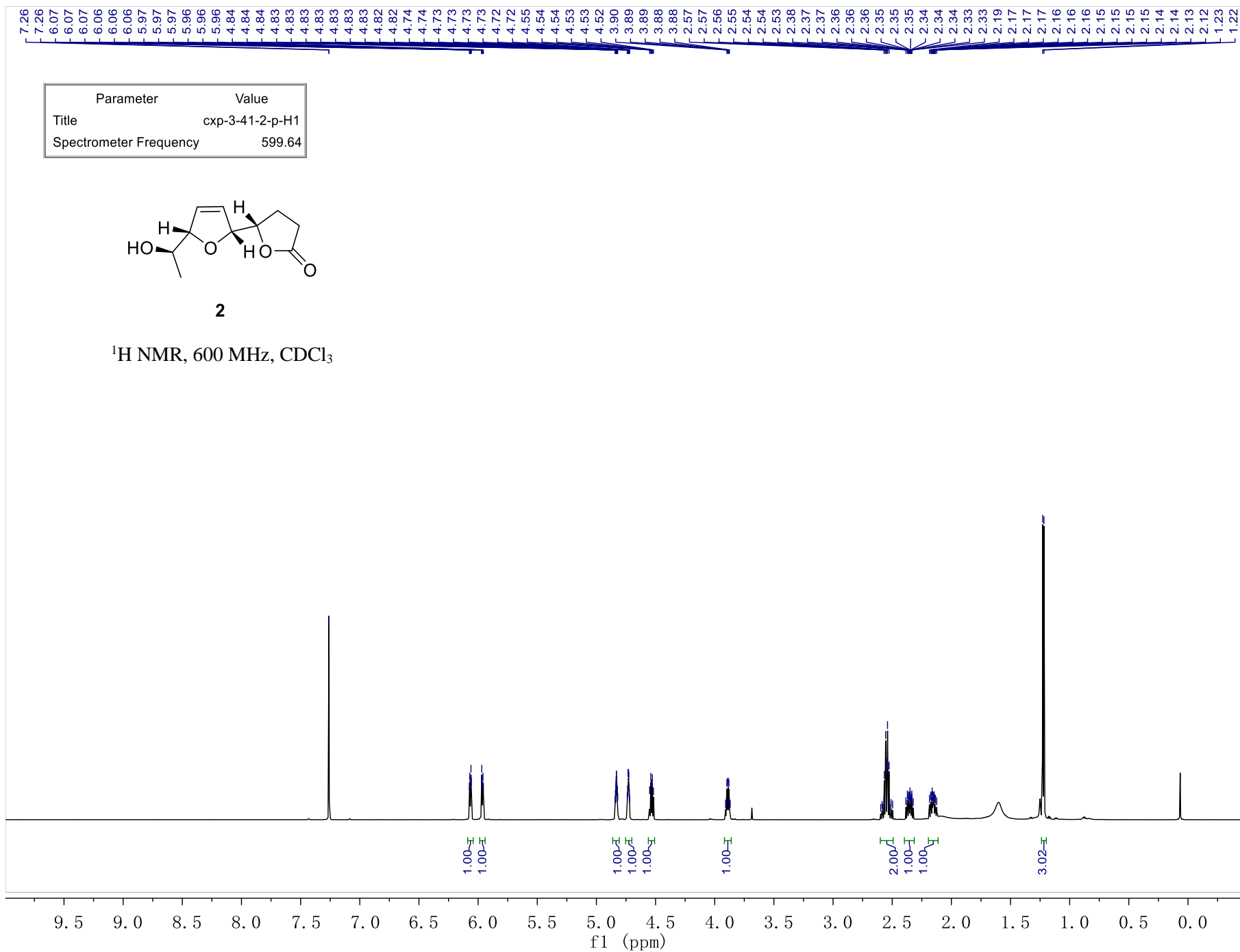


**18**

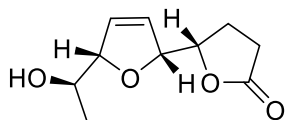
<sup>13</sup>C NMR, 126 MHz, CDCl<sub>3</sub>

| Parameter              | Value          |
|------------------------|----------------|
| Title                  | cxp-3-39-2-C13 |
| Spectrometer Frequency | 125.70         |



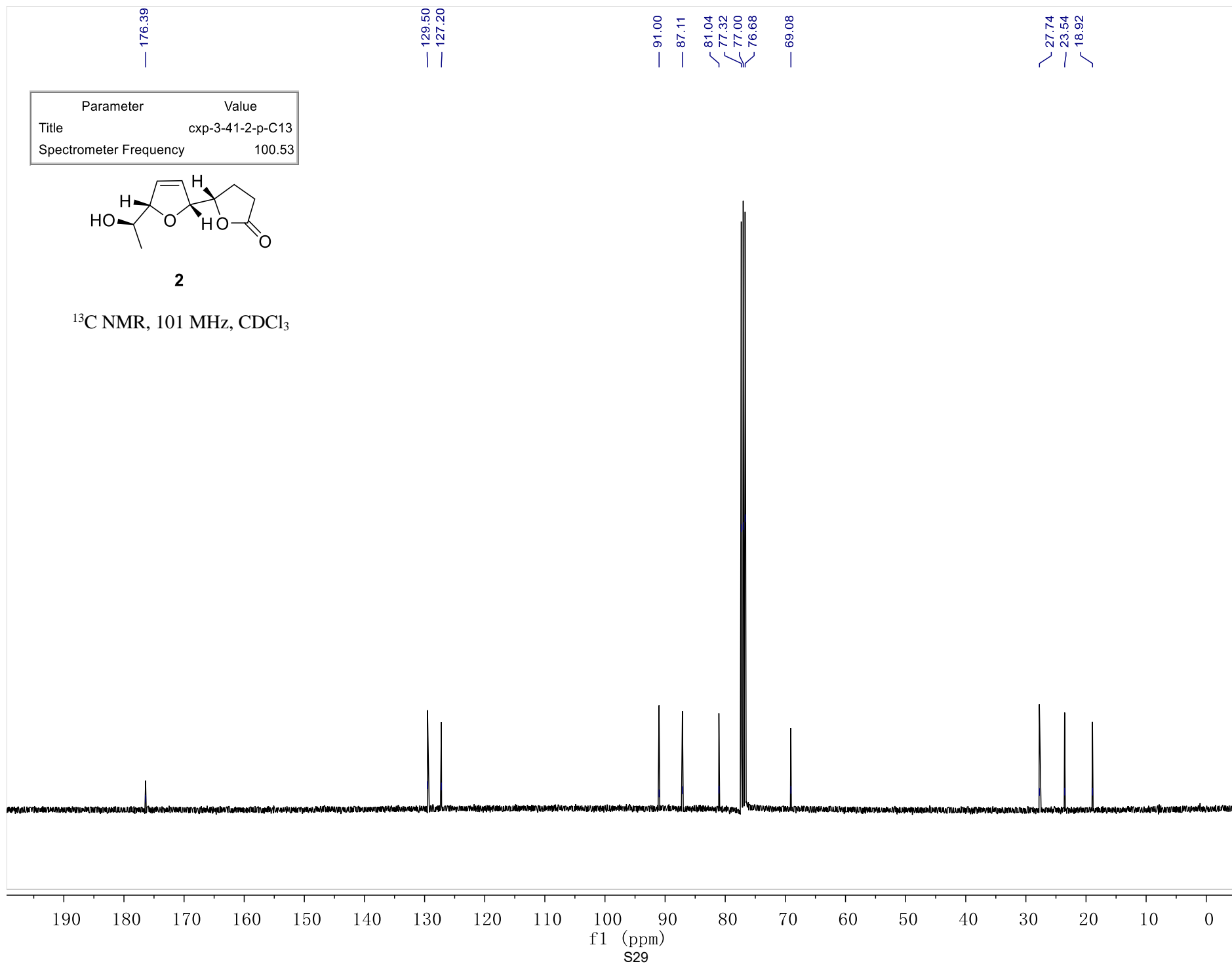


| Parameter              | Value            |
|------------------------|------------------|
| Title                  | cxp-3-41-2-p-C13 |
| Spectrometer Frequency | 100.53           |

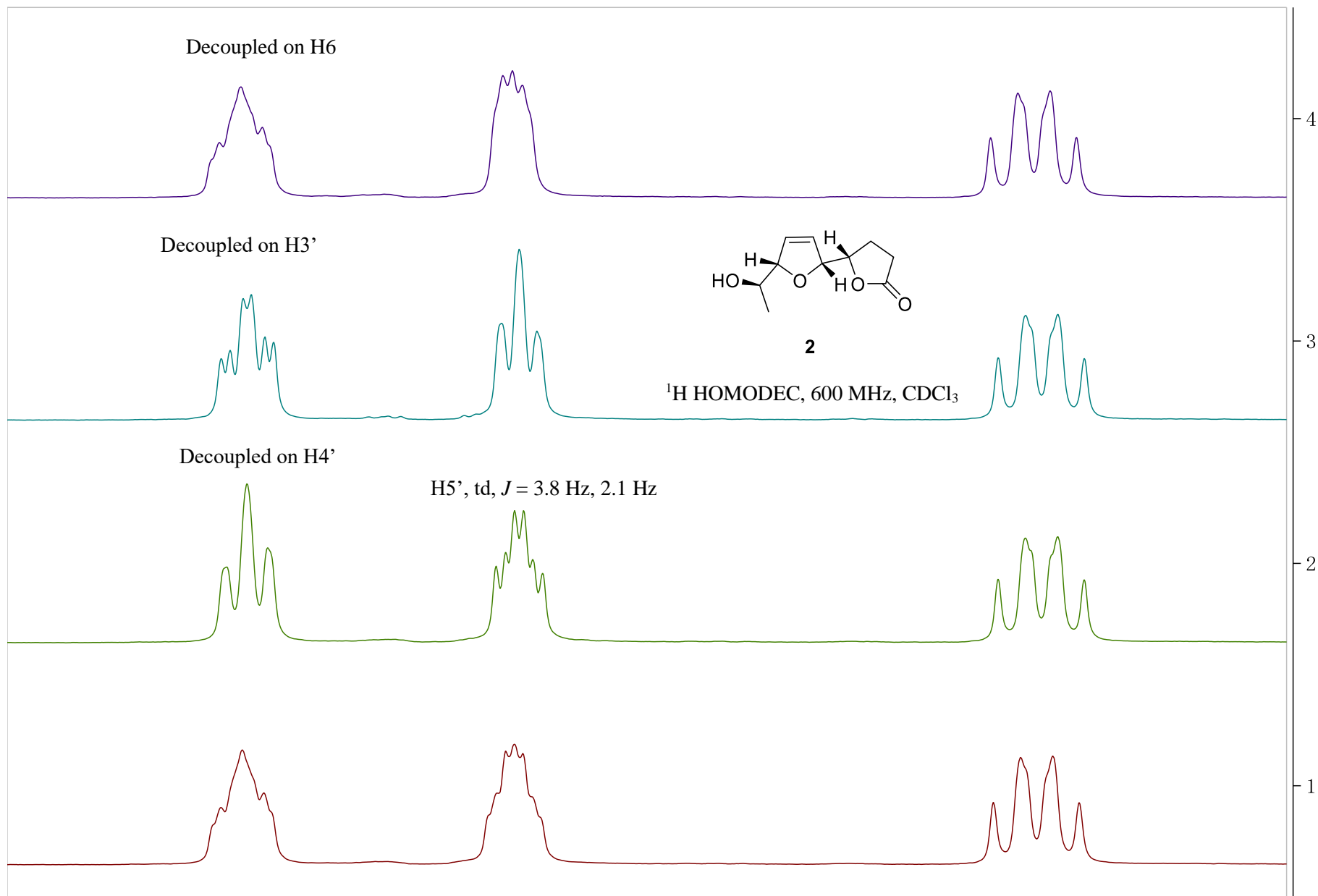


**2**

<sup>13</sup>C NMR, 101 MHz, CDCl<sub>3</sub>

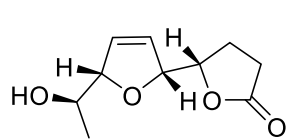


f1 (ppm)  
S29



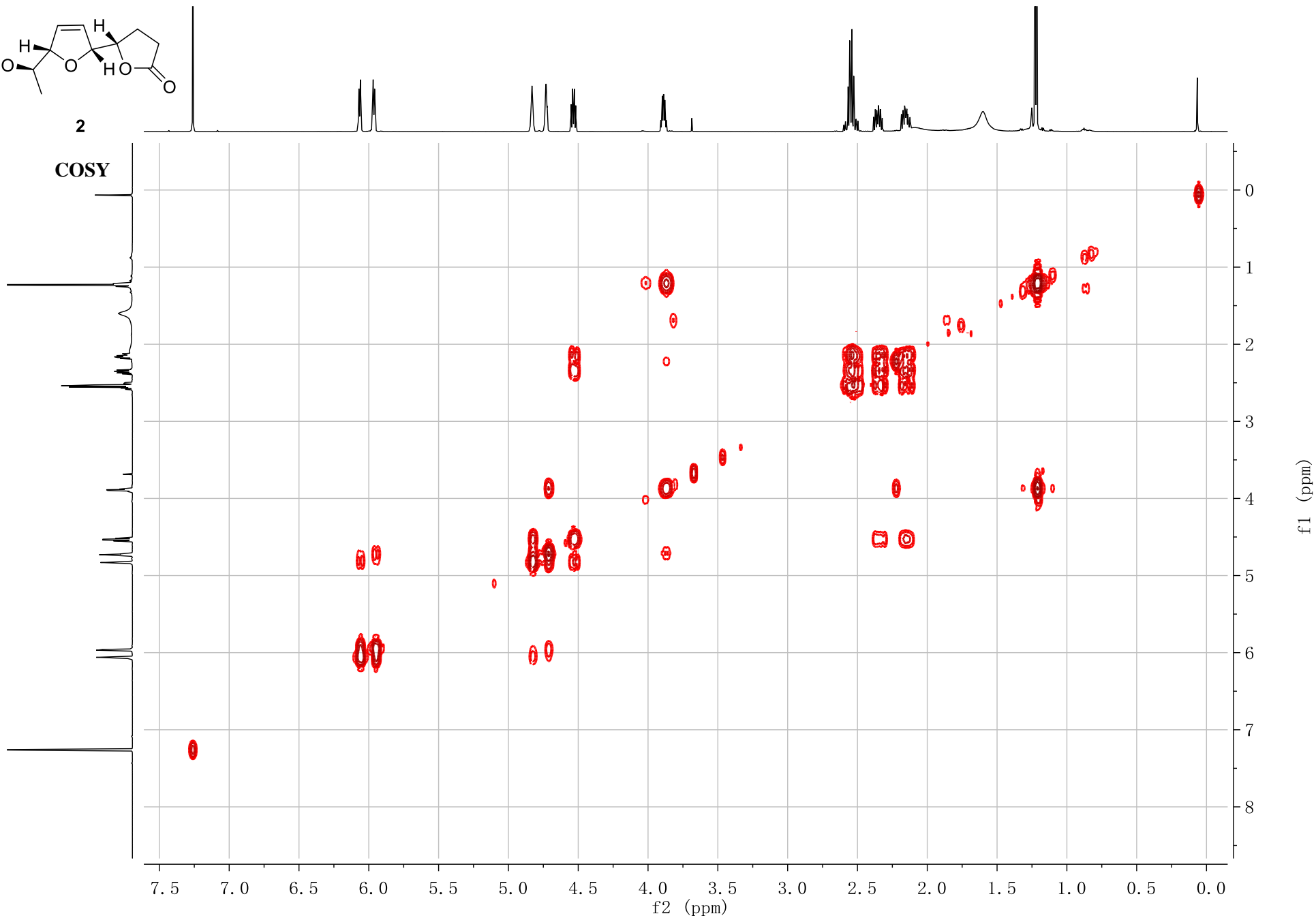
4.84 4.82 4.80 4.78 4.76 4.74 4.72 4.70 4.68 4.66 4.64 4.62 4.60 4.58 4.56 4.54 4.52 4.50 4.48 4.46 4.44 4.42 4.40 4.38

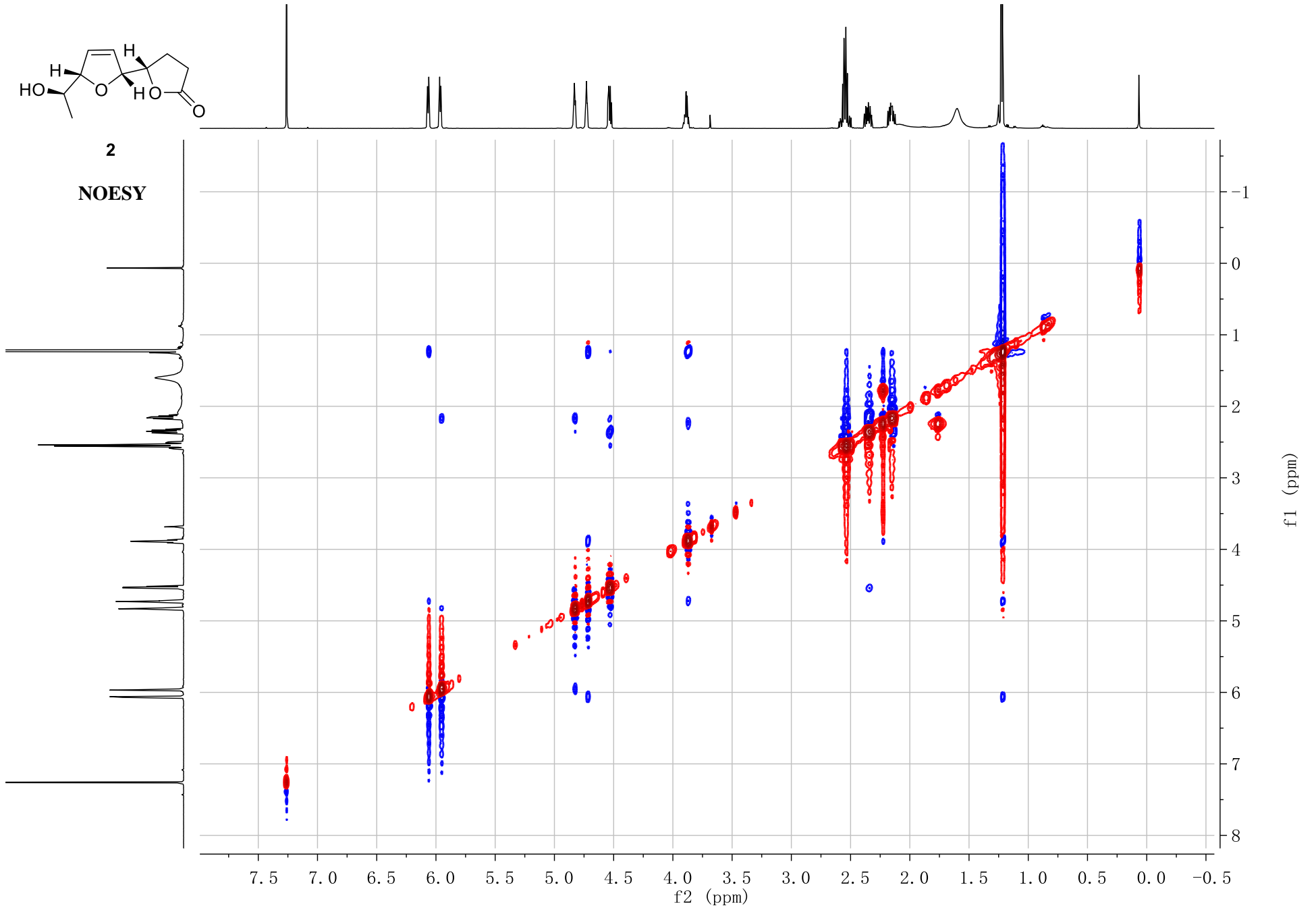
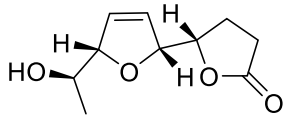
f1 (ppm)<sub>S30</sub>



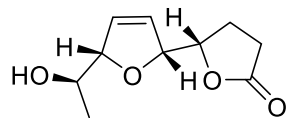
2

COSY

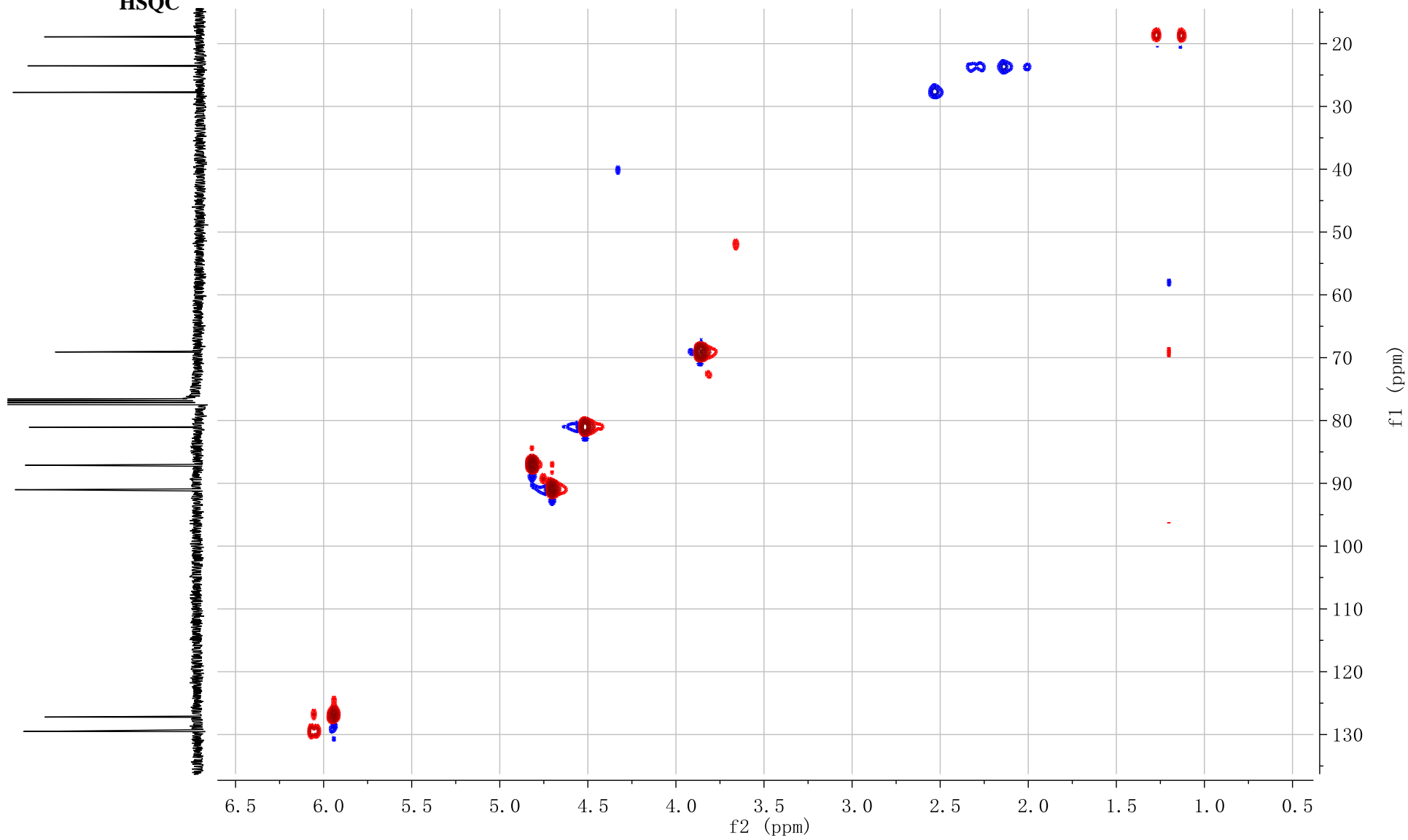


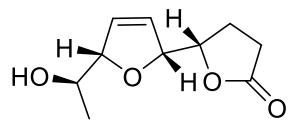






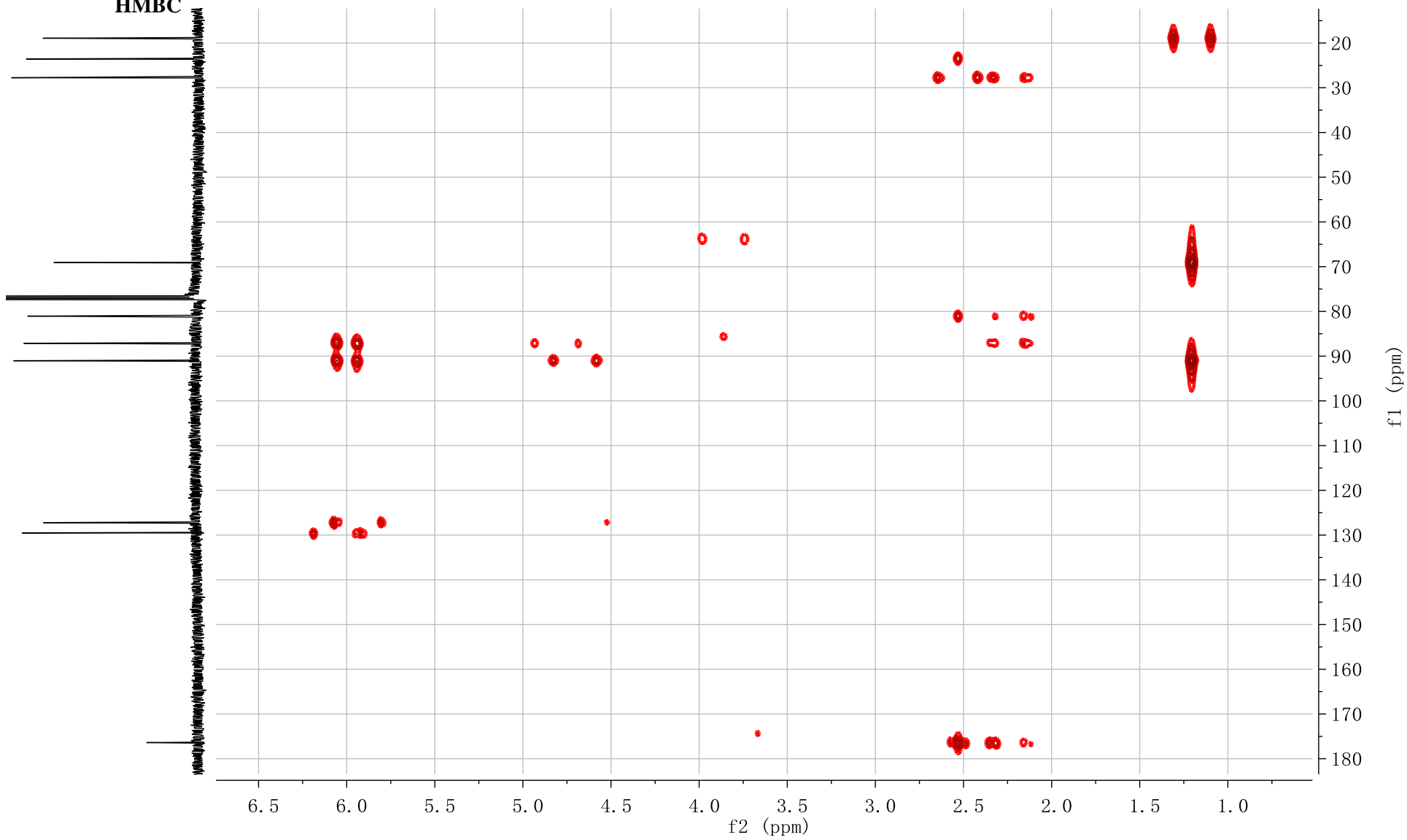
2  
HSQC

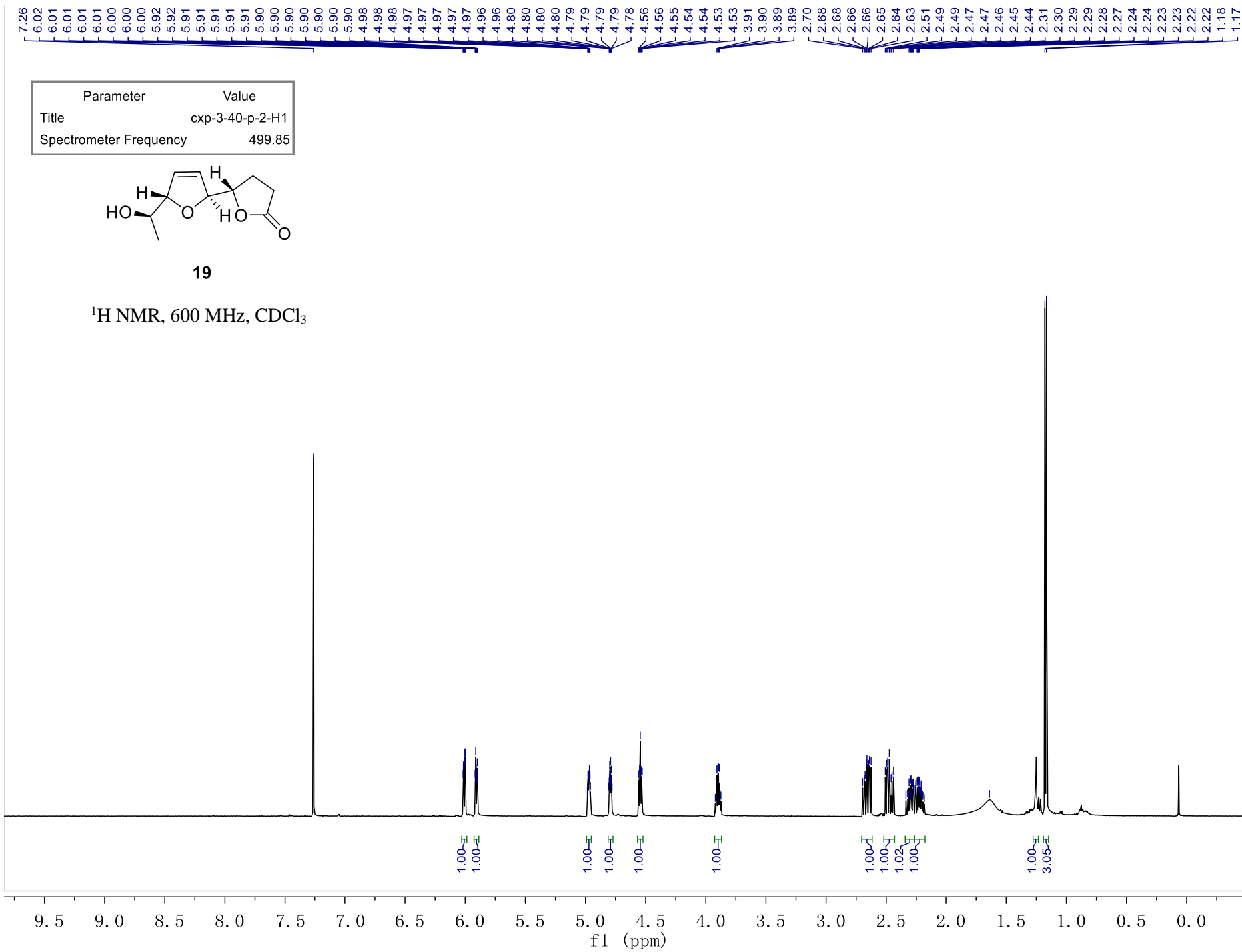




2

HMBC





— 177.24

— 128.79  
— 127.33

— 91.01

— 87.97

— 80.12

— 77.25

— 77.00

— 76.75

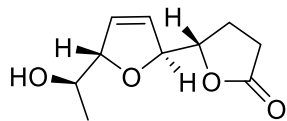
— 69.09

— 27.97

— 23.75

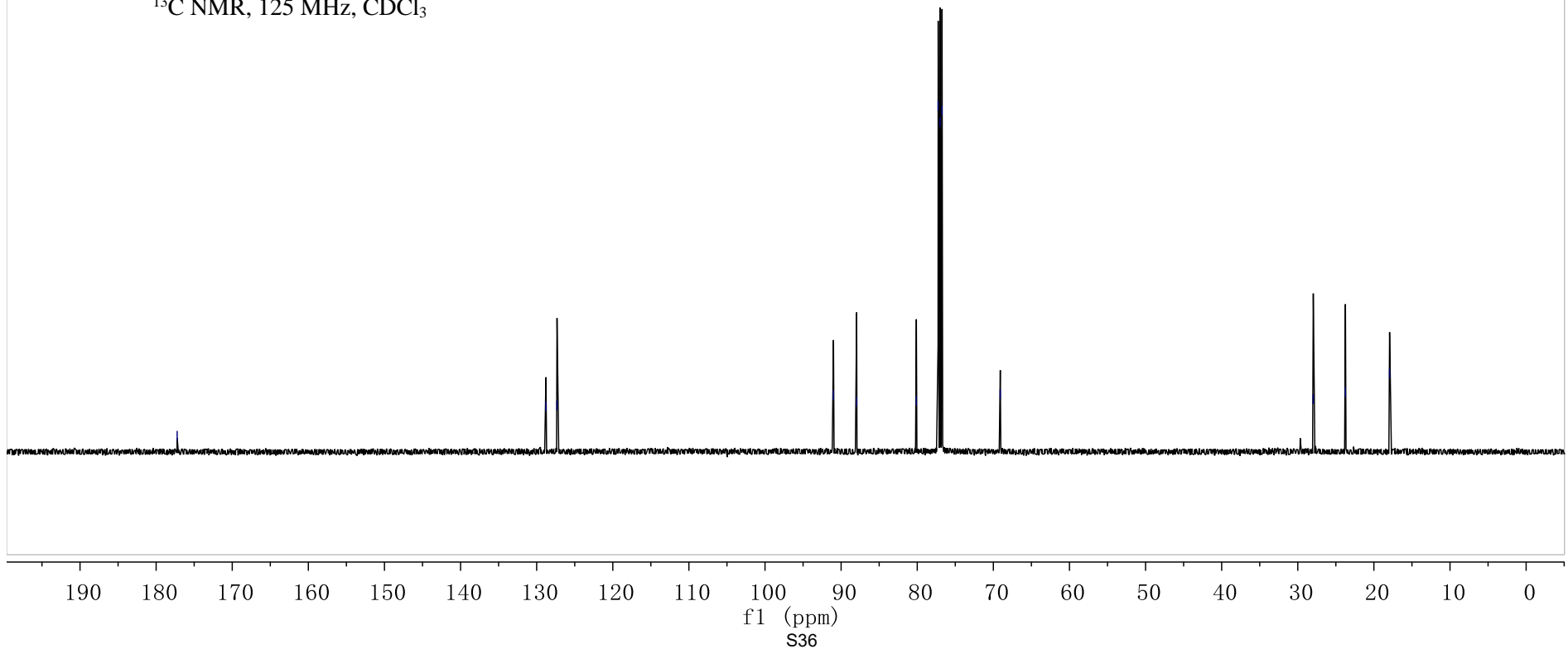
— 17.94

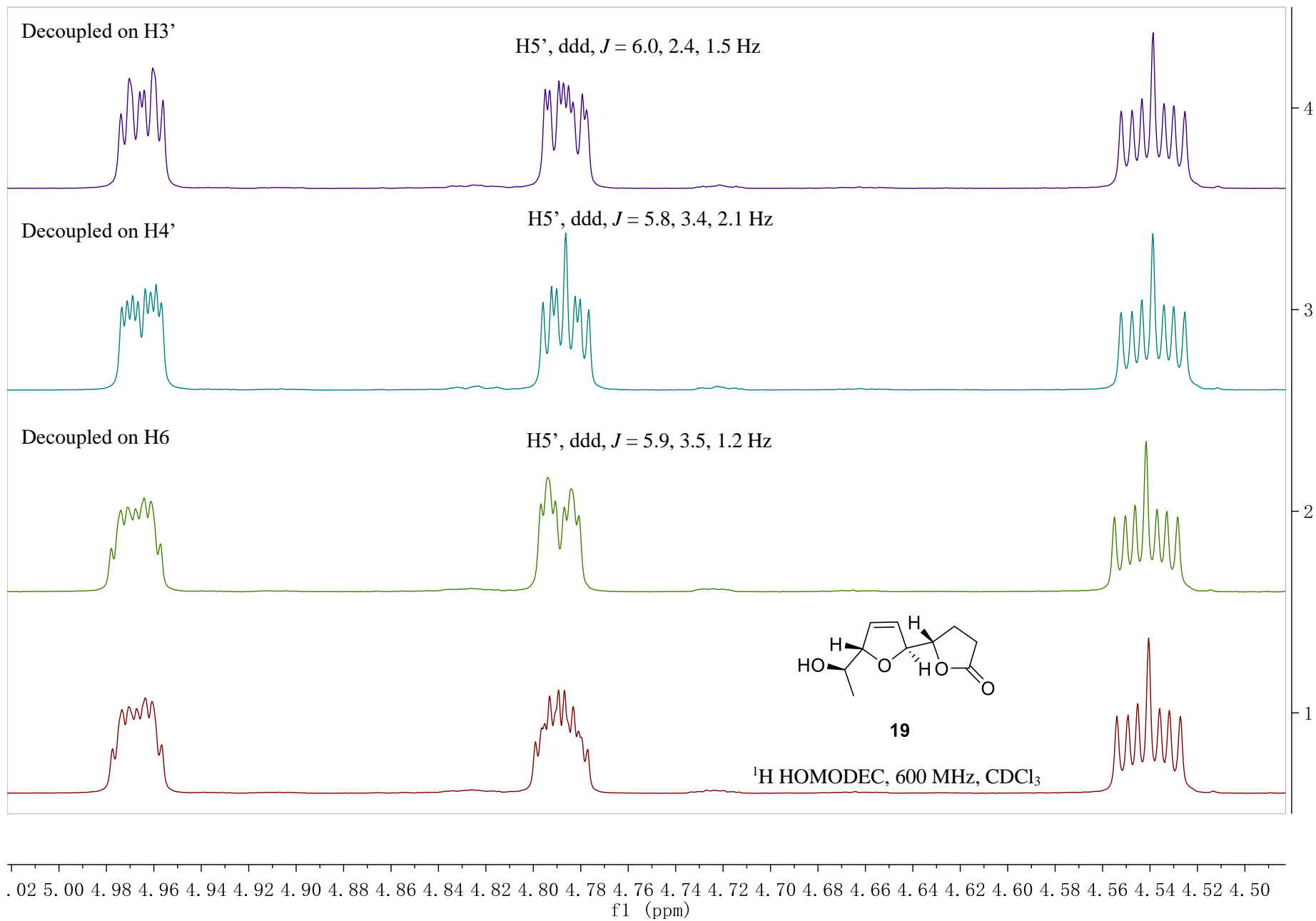
| Parameter              | Value            |
|------------------------|------------------|
| Title                  | cxp-3-40-p-2-C13 |
| Spectrometer Frequency | 125.70           |

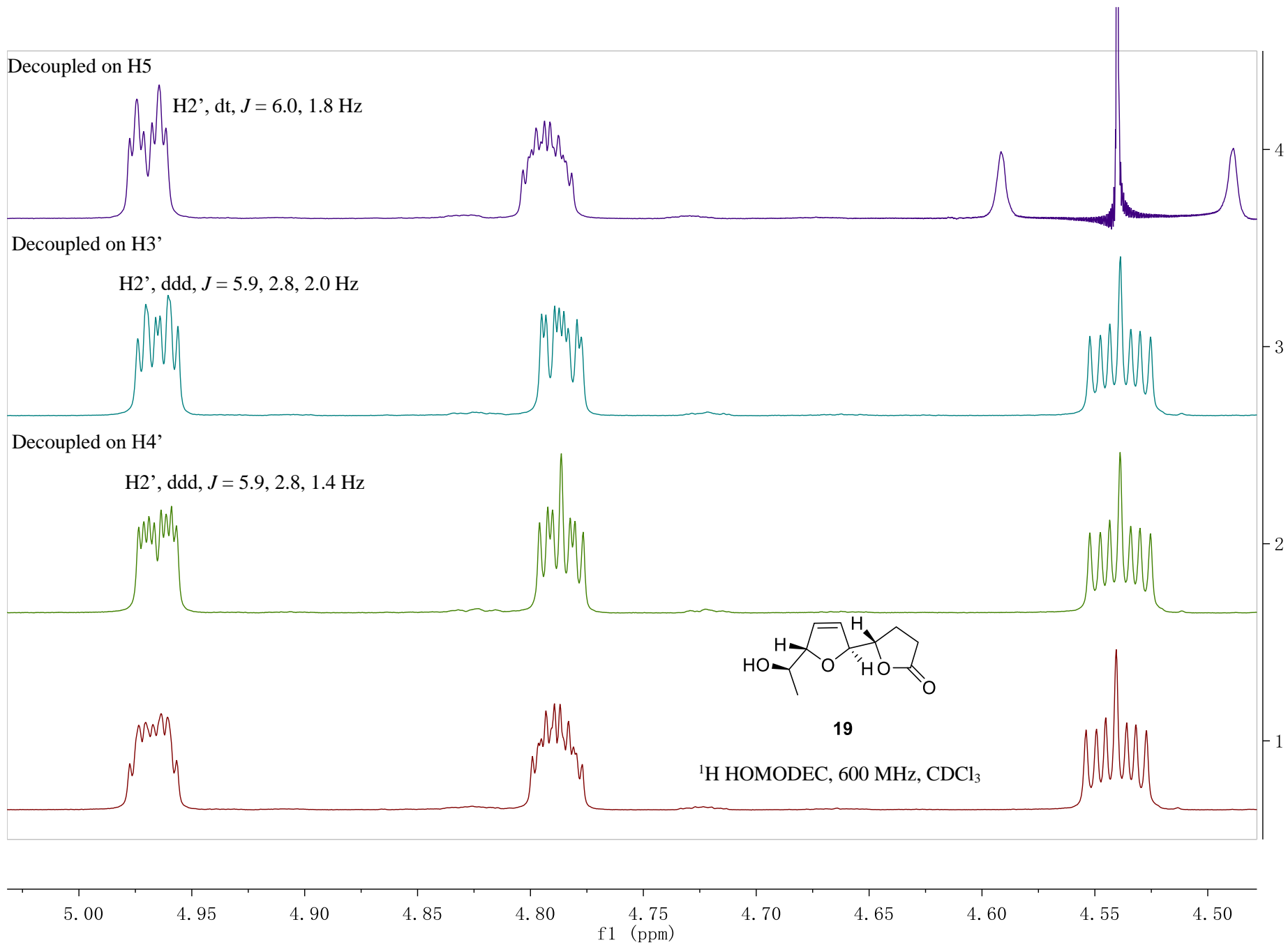


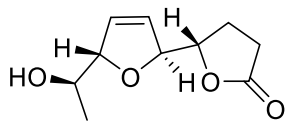
**19**

<sup>13</sup>C NMR, 125 MHz, CDCl<sub>3</sub>



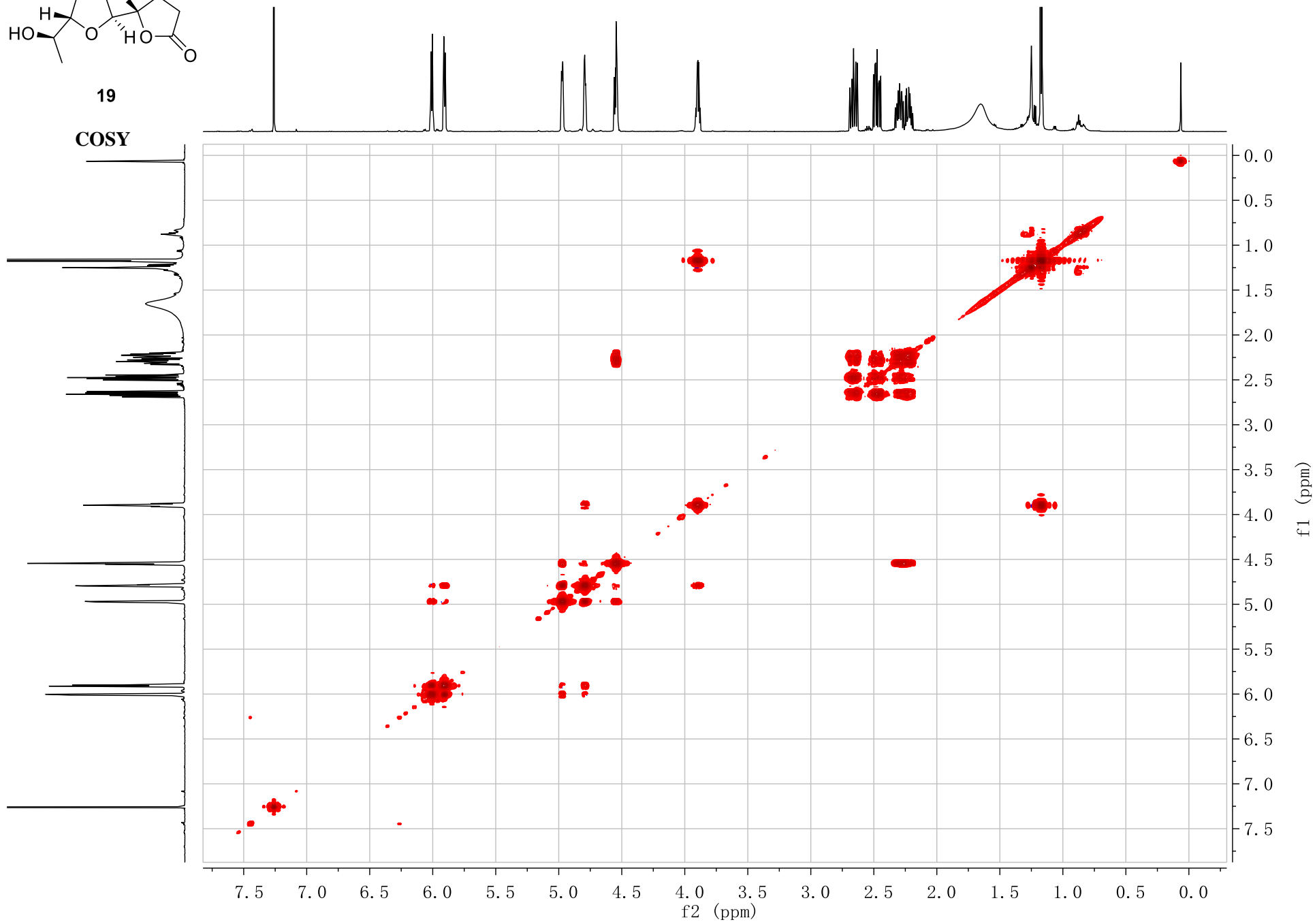


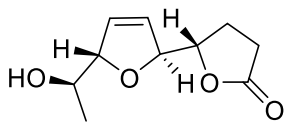




19

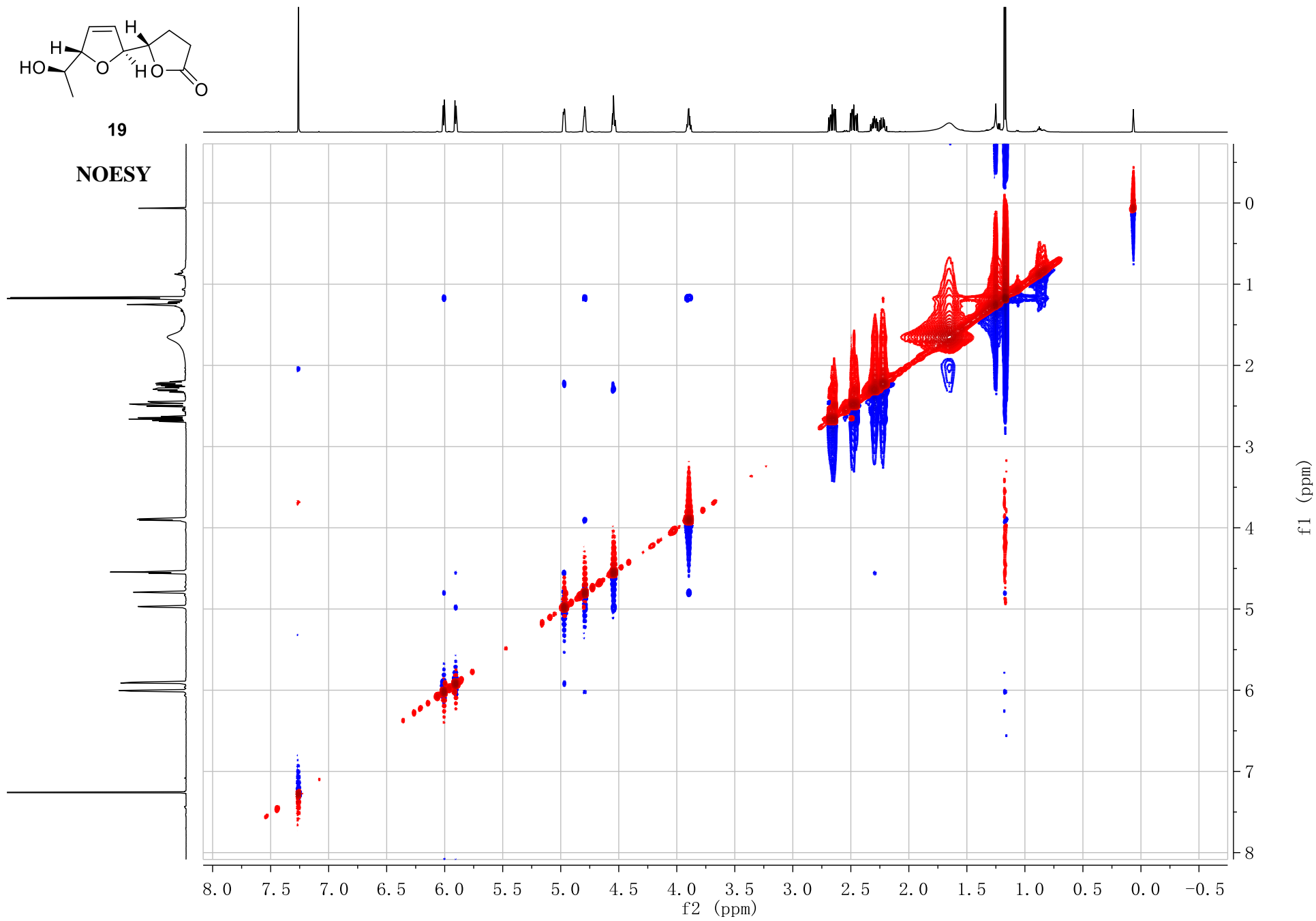
COSY



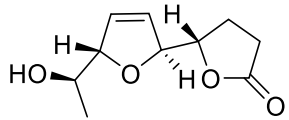


19

NOESY

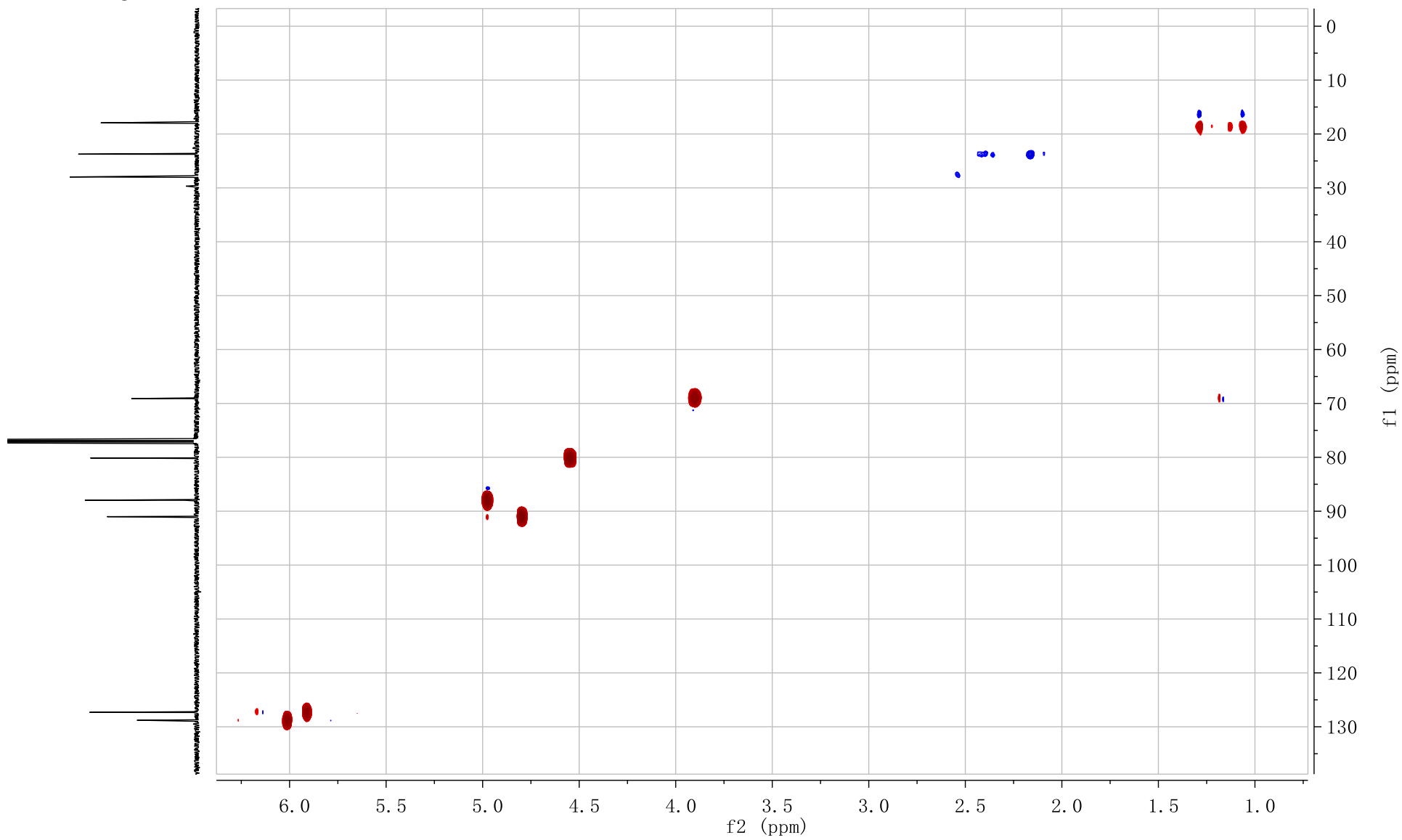


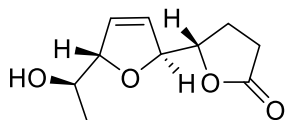




19

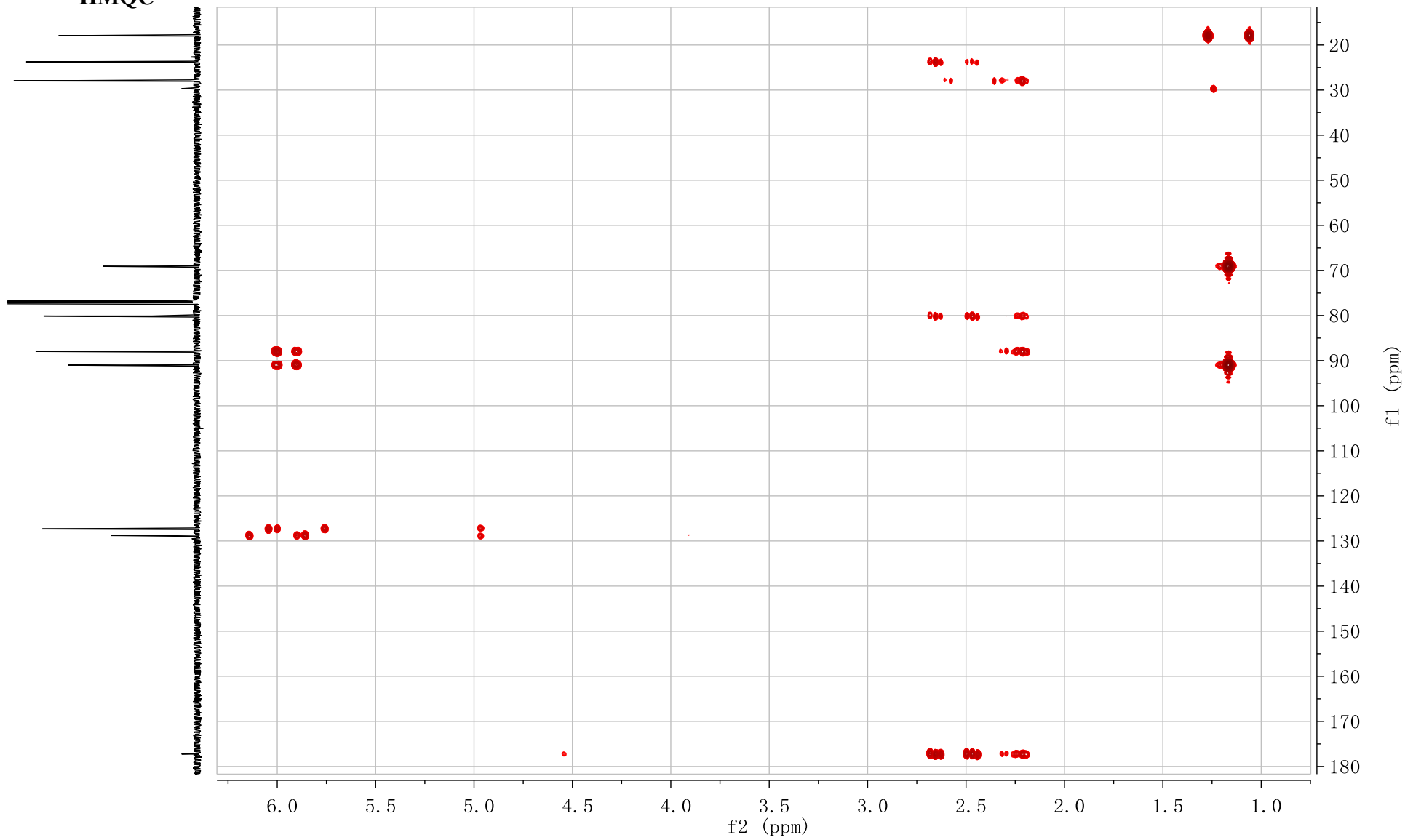
HSQC





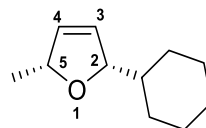
19

HMQC



4.88  
4.87  
4.87  
4.86  
4.86  
4.85  
4.85  
4.84

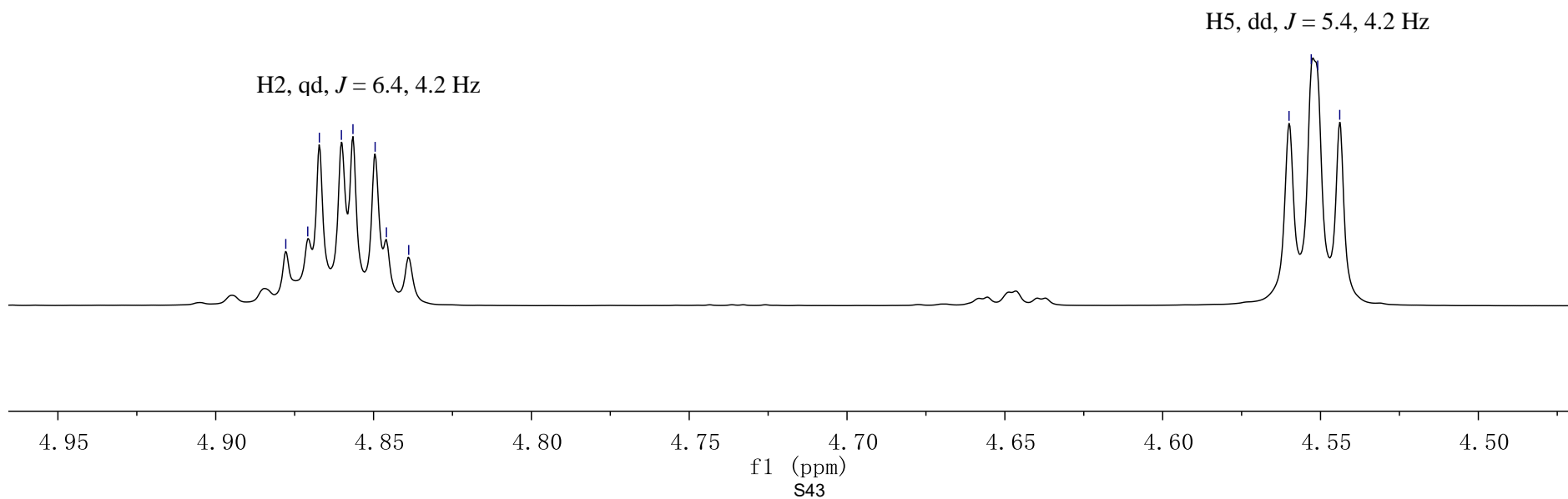
4.56  
4.55  
4.55  
4.54



$^1\text{H}$  HOMODEC, 600 MHz,  $\text{CDCl}_3$

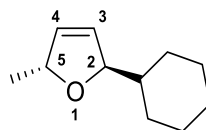
Decoupled on H3 and H4

$J(\text{H2-H5}) = 4.2 \text{ Hz}$



4.91  
4.91  
4.90  
4.90  
4.89  
4.89  
4.88  
4.88  
4.87  
4.87

4.67  
4.66  
4.65



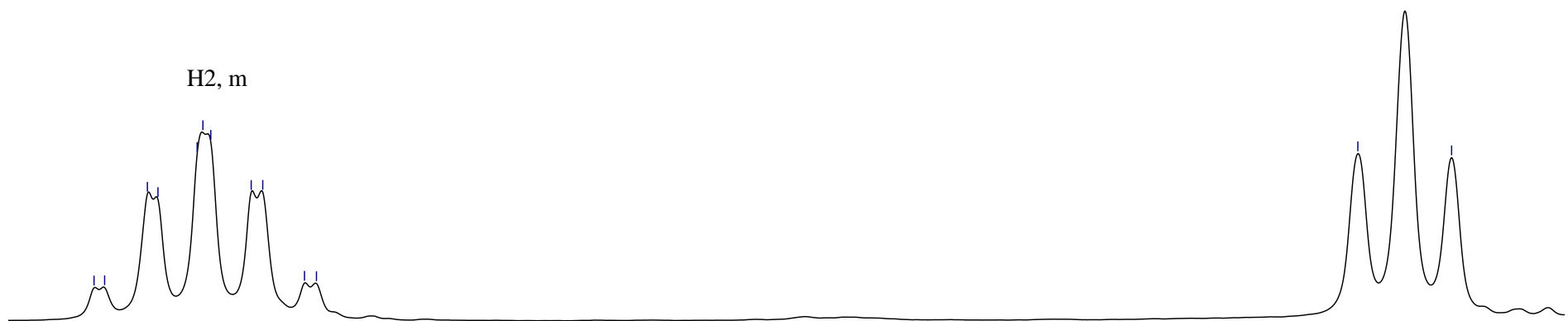
$^1\text{H}$  HOMODEC, 600 MHz,  $\text{CDCl}_3$

Decoupled on H3 and H4

$J(\text{H2-H5}) = 5.5 \text{ Hz}$

H5, t,  $J = 5.5 \text{ Hz}$

H2, m



93 4.91 4.89 4.87 4.85 4.83 4.81 4.79 4.77 4.75 4.73 4.71 4.69 4.67 4.65 4.63  
f1 (ppm)  
S44