Supporting Information

Nucleotide Analogues bearing a C2′ or C3′-Stereogenic All-Carbon Quaternary Center as SARS-CoV-2 RdRp Inhibitors

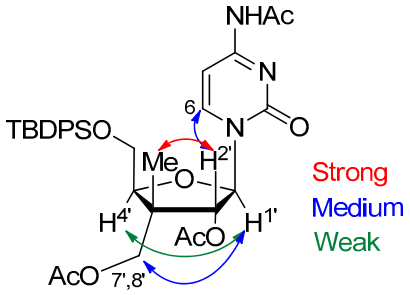
Amarender Manchoju[1], Renaud Zelli[1], Gang Wang[1], Carla Eymard[1], Adrian Oo[2], Mona Nemer[3]*, Michel Prévost[1]*, Baek Kim[2,4]*, and Yvan Guindon [1,3,5]*

[1]Bio-Organic Chemistry Laboratory, Institut de Recherches Cliniques de Montréal, Montréal, Québec H2W 1R7, Canada.
[2]Department of Pediatrics, School of Medicine, Emory University, Atlanta, Georgia, USA.
[3]Department of Biochemistry, Microbiology and Immunology, University of Ottawa, Ottawa, ON, K1N 6N5, Canada.
[4]Children's Healthcare of Atlanta, Atlanta, Georgia, USA.
[5]Department of Chemistry, Université de Montréal, Montréal, QC H3C 3J7
*Correspondence authors: mnemer@uottawa.ca (Mona Nemer), michel.prevost@ircm.qc.ca (Michel Prévost), baek.kim@emory.edu (Baek Kim), yvan.guindon@ircm.qc.ca (Yvan Guindon).

Stereochemical Proofs:

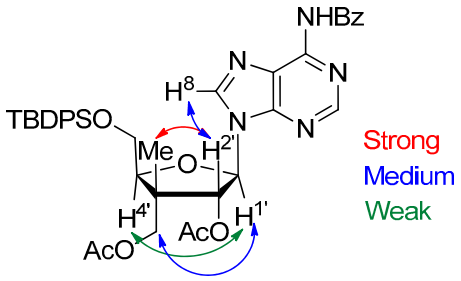
The relative β configurations of protected and deprotected nucleoside analogues **26-28** and **29** were determined by relevant nuclear Overhauser effect (nOe) enhancements (2D NOESY).

In addition, NOESY experiments further confirmed the 1',2'-trans stereochemistry.



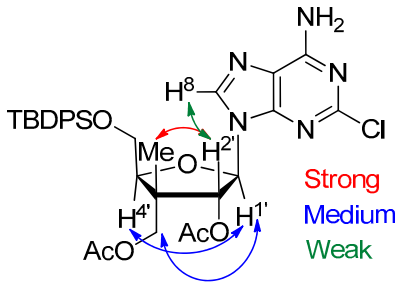
26

NOESY confirmed
β relative stereochemistry



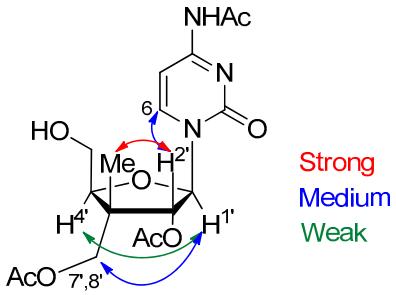
27

NOESY confirmed
β relative stereochemistry



28

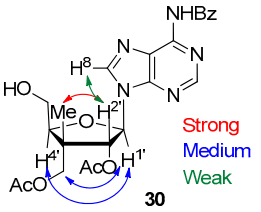
NOESY confirmed
β relative stereochemistry



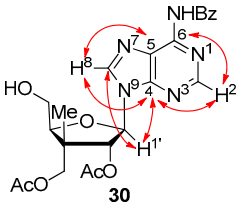
29

NOESY confirmed
β relative stereochemistry

The N^9 regiochemistry of the purine ring of compounds **30-31** and **33-34** was determined from HSQC and HMBC experiments. In addition, NOESY experiments further confirmed the 1',2'-*trans* stereochemistry.



NOESY confirmed
β relative stereochemistry

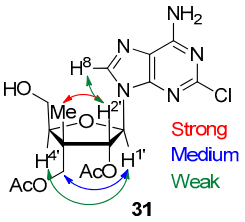


From HSQC

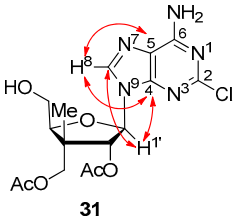
H^8 (8.82 ppm) ⟷ C^8 (144.5 ppm)
H^2 (8.70 ppm) ⟷ C^2 (153.1 ppm)
$H^{1'}$ (6.35 ppm) ⟷ $C^{1'}$ (88.4 ppm)

From HMBC

H^8 (8.82 ppm) ⟷ C^5 (125.2 ppm)
H^8 (8.82 ppm) ⟷ C^4 (153.4 ppm)
H^2 (8.70 ppm) ⟷ C^6 (151.2 ppm)
H^2 (8.70 ppm) ⟷ C^4 (153.4 ppm)
$H^{1'}$ (6.35 ppm) ⟷ C^4 (153.4 ppm)
$H^{1'}$ (6.35 ppm) ⟷ C^8 (144.5 ppm)



NOESY confirmed
β relative stereochemistry

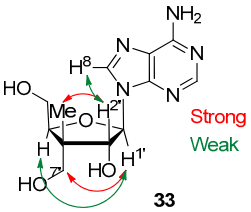


From HSQC

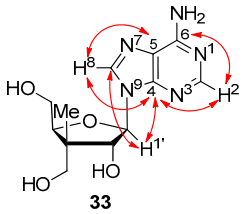
H^8 (8.41 ppm) ⟷ C^8 (141.6 ppm)
$H^{1'}$ (6.12 ppm) ⟷ $C^{1'}$ (151.7 ppm)

From HMBC

H^8 (8.41 ppm) ⟷ C^5 (119.4 ppm)
H^8 (8.41 ppm) ⟷ C^4 (151.7 ppm)
$H^{1'}$ (6.12 ppm) ⟷ C^8 (141.6 ppm)
$H^{1'}$ (6.12 ppm) ⟷ C^4 (151.7 ppm)



NOESY confirmed
β relative stereochemistry

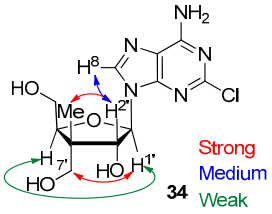


From HSQC

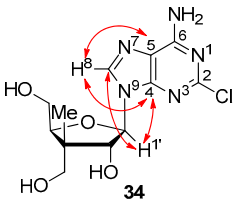
H^8 (8.30 ppm) ⟷ C^8 (142.4 ppm)
H^2 (8.18 ppm) ⟷ C^2 (153.3 ppm)
$H^{1'}$ (6.03 ppm) ⟷ $C^{1'}$ (91.4 ppm)

From HMBC

H^8 (8.30 ppm) ⟷ C^5 (121.1 ppm)
H^8 (8.30 ppm) ⟷ C^4 (149.9 ppm)
H^2 (8.18 ppm) ⟷ C^6 (157.6 ppm)
H^2 (8.18 ppm) ⟷ C^4 (149.9 ppm)
$H^{1'}$ (6.03 ppm) ⟷ C^4 (149.9 ppm)
$H^{1'}$ (6.03 ppm) ⟷ C^8 (142.4 ppm)



NOESY confirmed
β relative stereochemistry

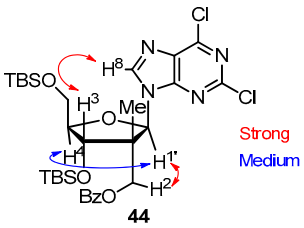


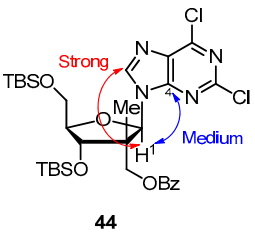
From HSQC

H^8 (8.30 ppm) ⟷ C^8 (142.4 ppm)
$H^{1'}$ (5.98 ppm) ⟷ $C^{1'}$ (91.1 ppm)

From HMBC

H^8 (8.30 ppm) ⟷ C^5 (119.9 ppm)
H^8 (8.30 ppm) ⟷ C^4 (151.4 ppm)
$H^{1'}$ (5.98 ppm) ⟷ C^8 (142.4 ppm)
$H^{1'}$ (5.98 ppm) ⟷ C^4 (151.4 ppm)





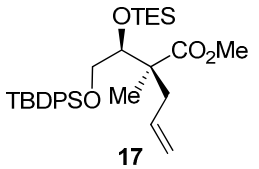
From HSQC

H^1 (6.61 ppm) ⟷ C^1 (88.16 ppm)
H^8 (8.90 ppm) ⟷ C^8 (145.00 ppm)

From HMBC

H^1 (6.60 ppm) ⟷ C^4 (152.83 ppm)
H^1 (6.60 ppm) ⟷ C^8 (145.00 ppm)

^{1}H-NMR (500 MHz, $CDCl_3$)



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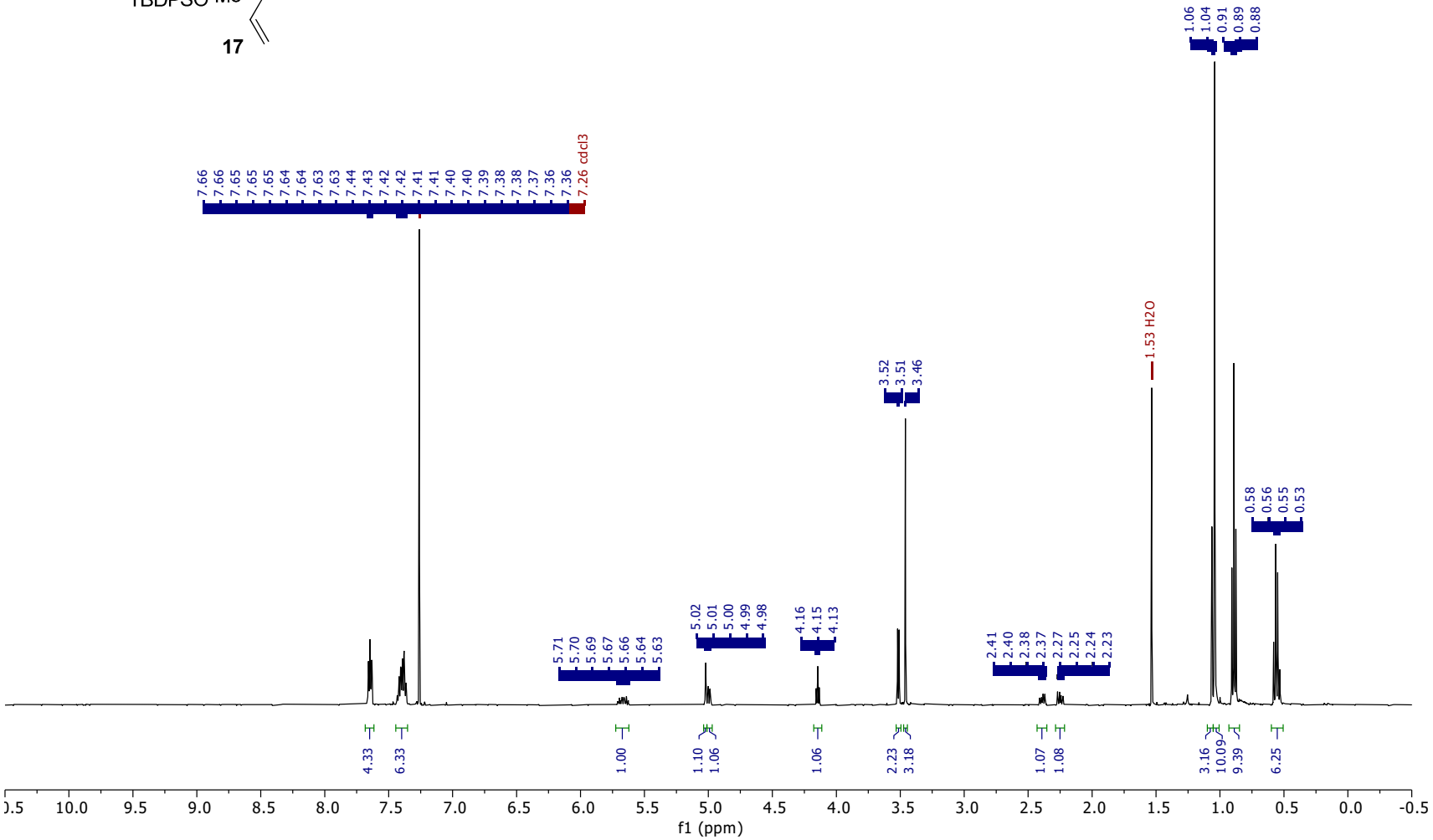
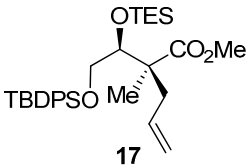
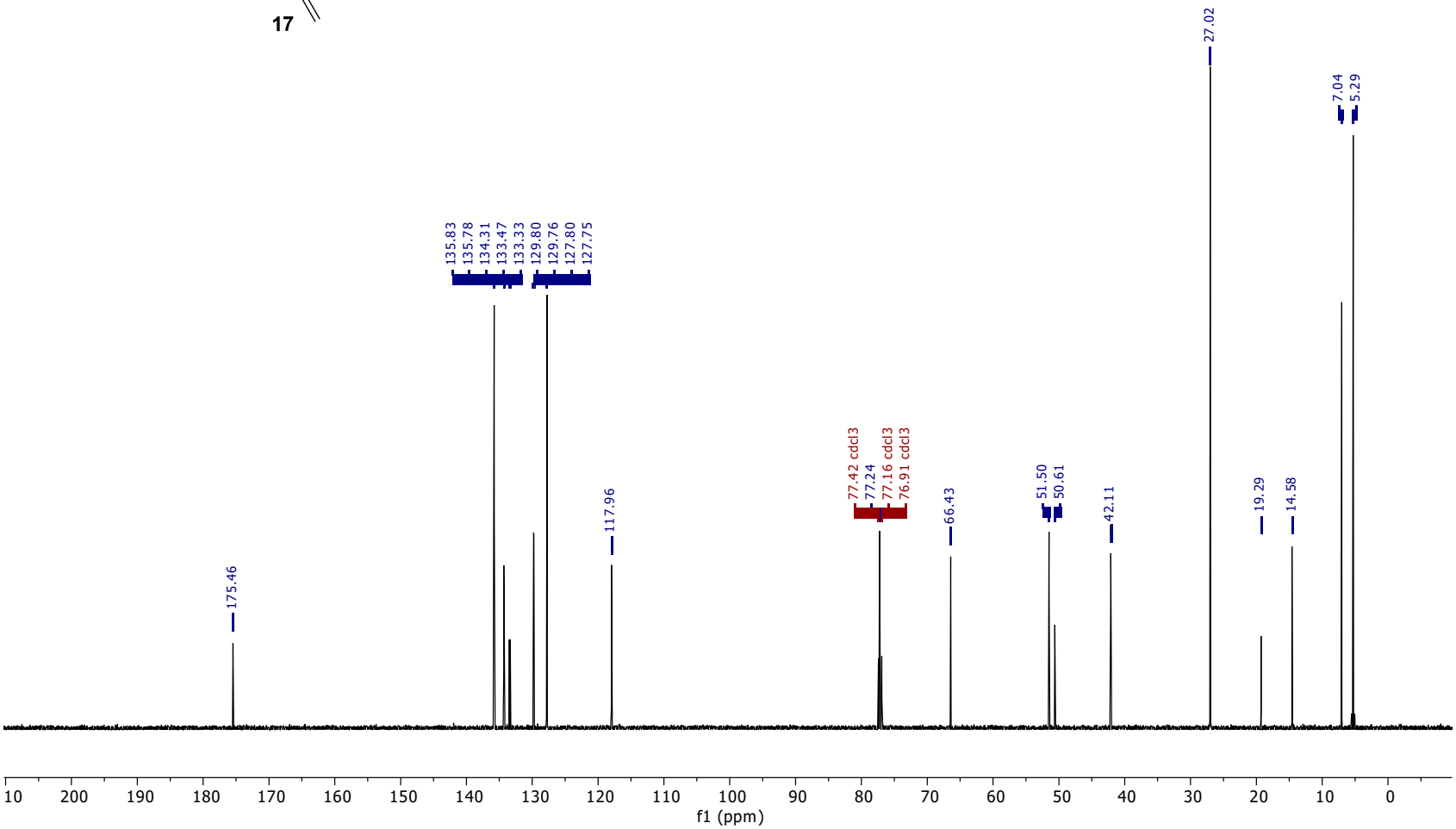
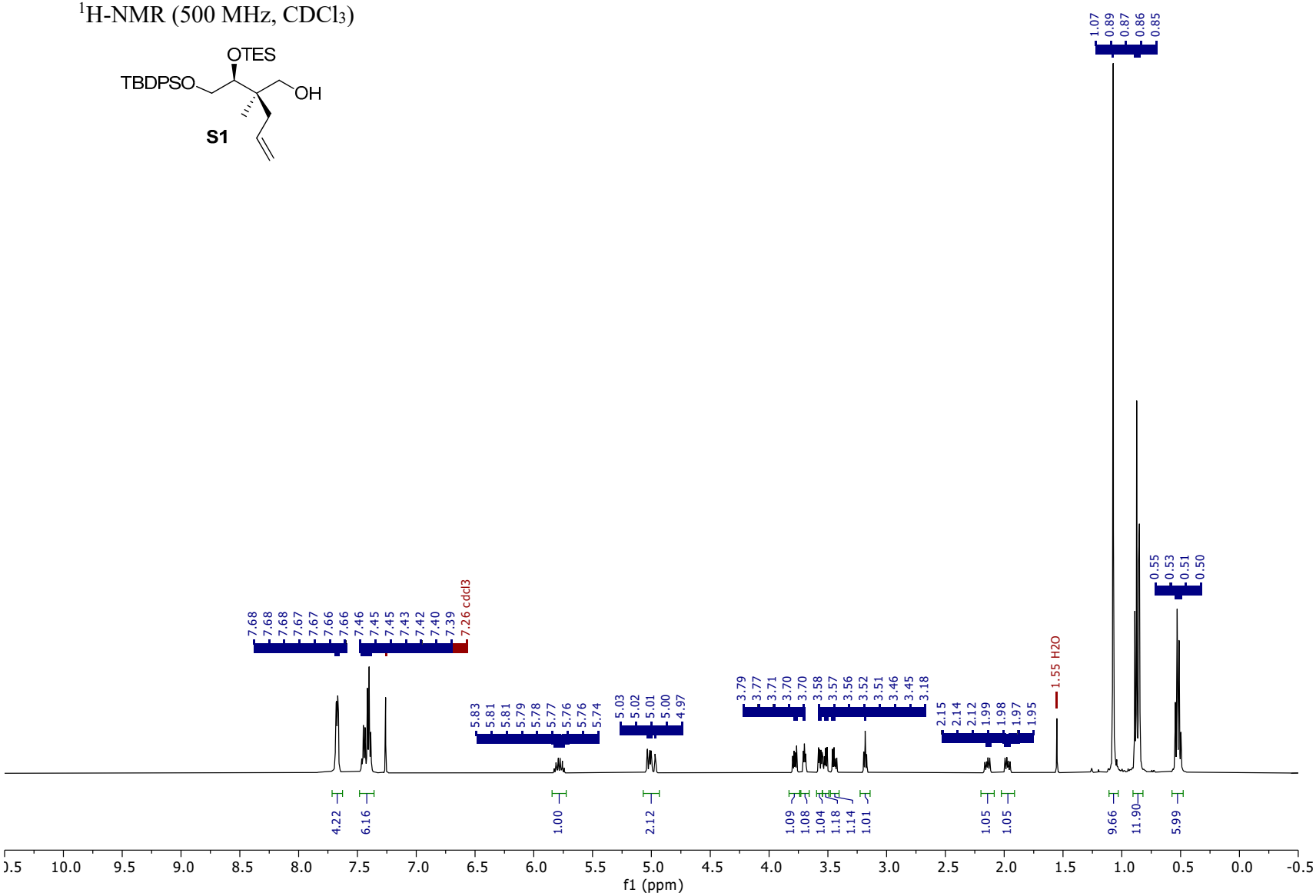


$^{13}C\{^{1}H\}$-NMR (126 MHz, $CDCl_3$)

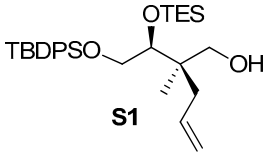


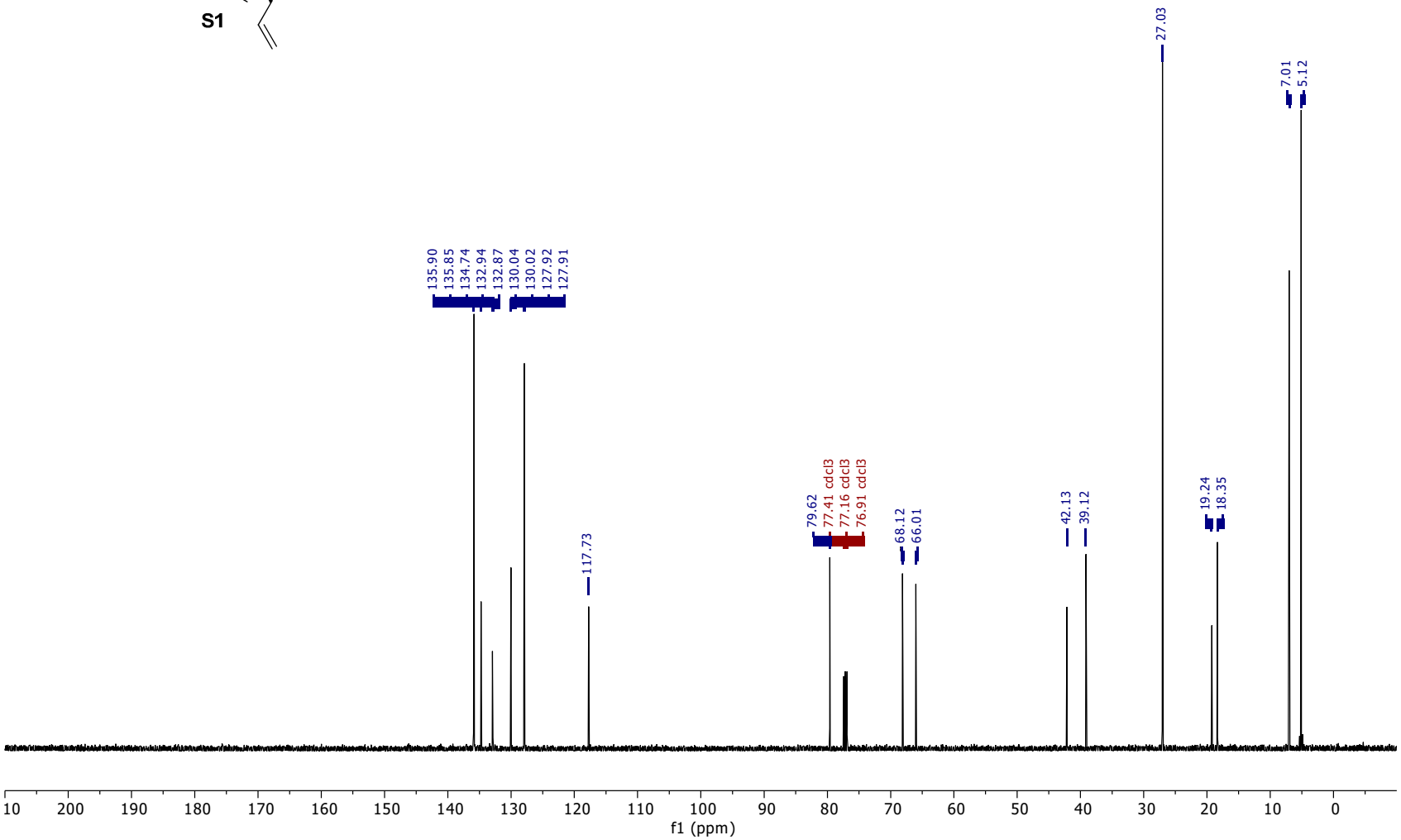


^{1}H-NMR (500 MHz, $CDCl_3$)



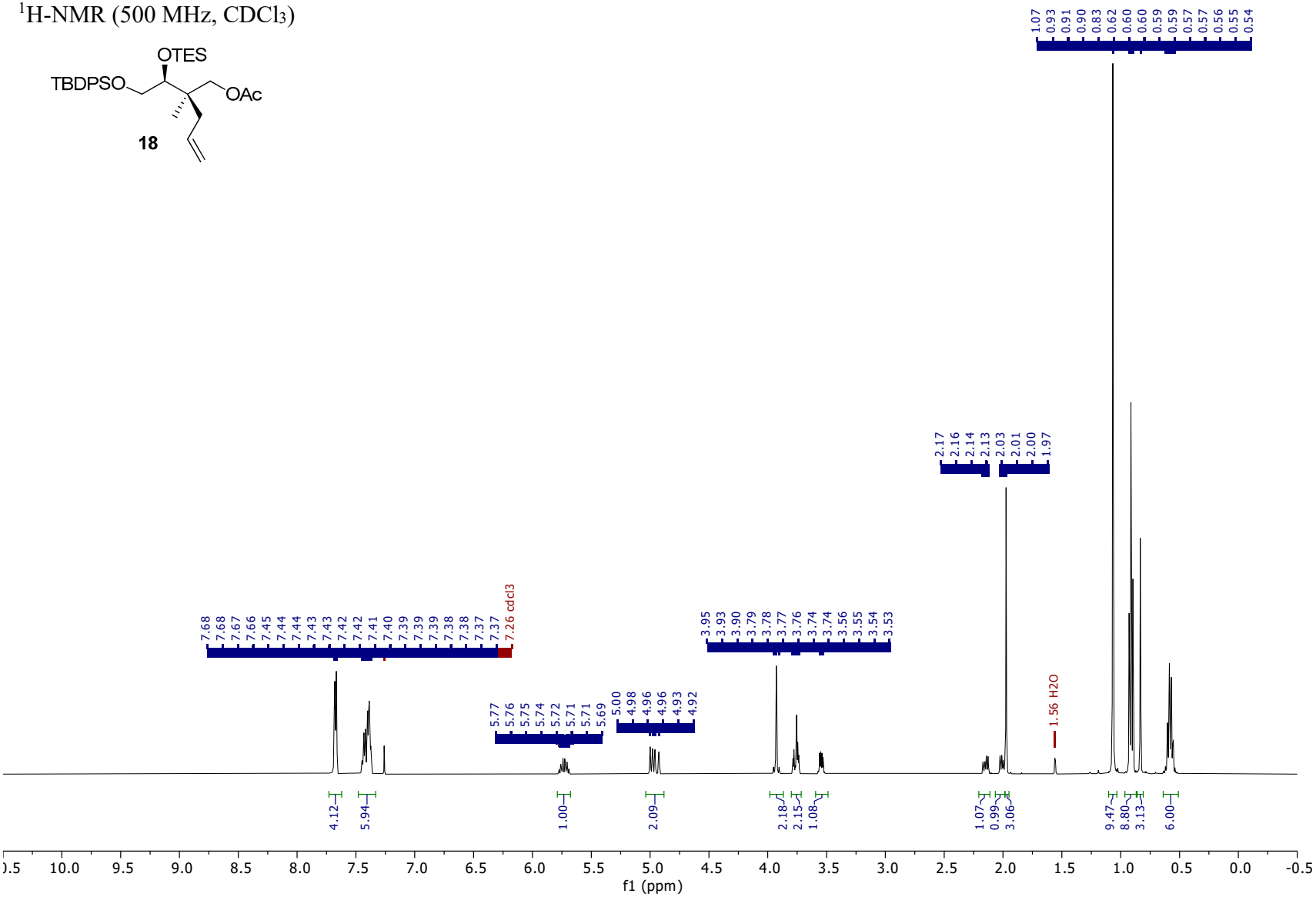
$^{13}C\{^{1}H\}$-NMR (126 MHz, $CDCl_3$)



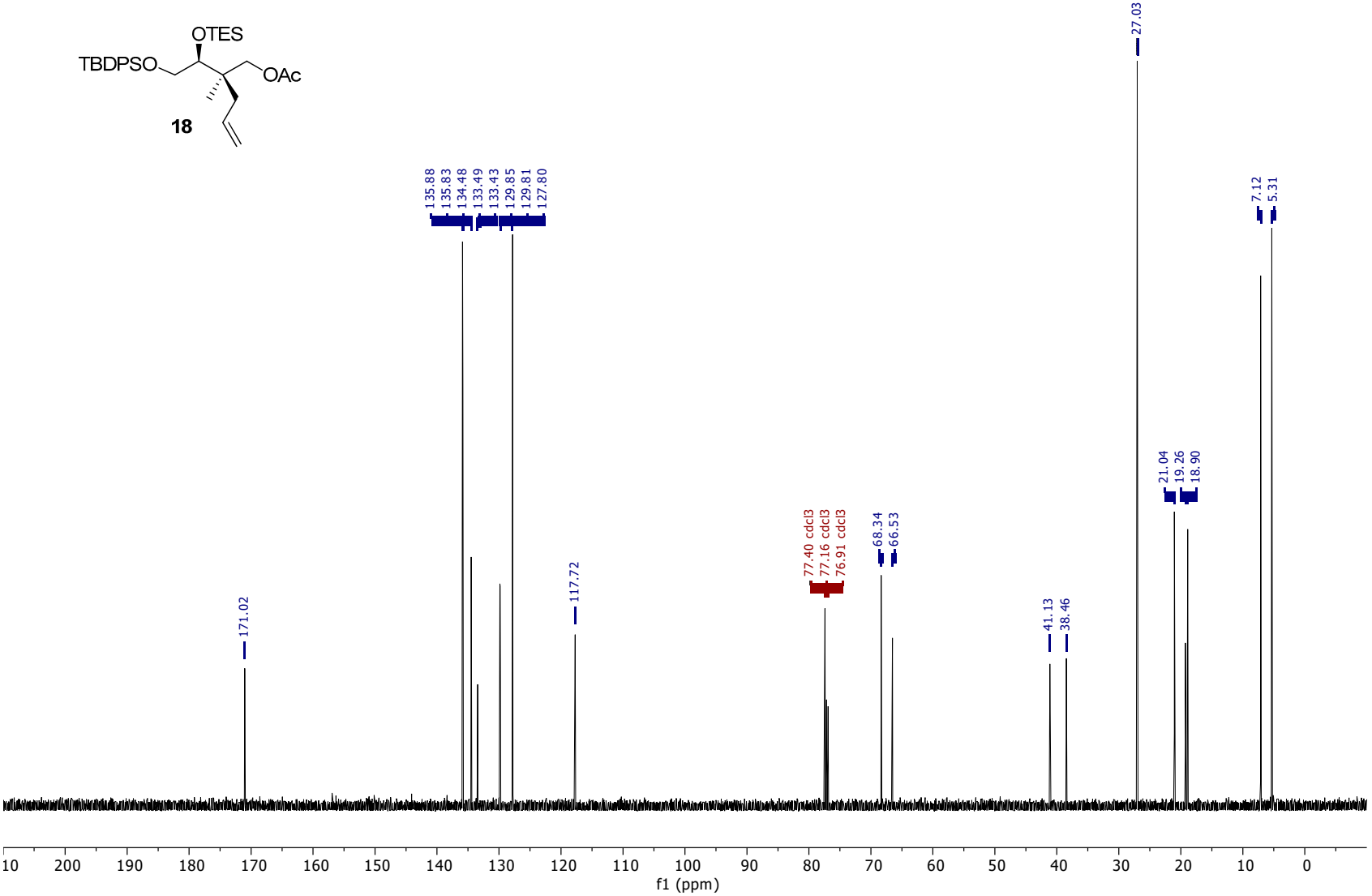


^{1}H-NMR (500 MHz, $CDCl_3$)

18

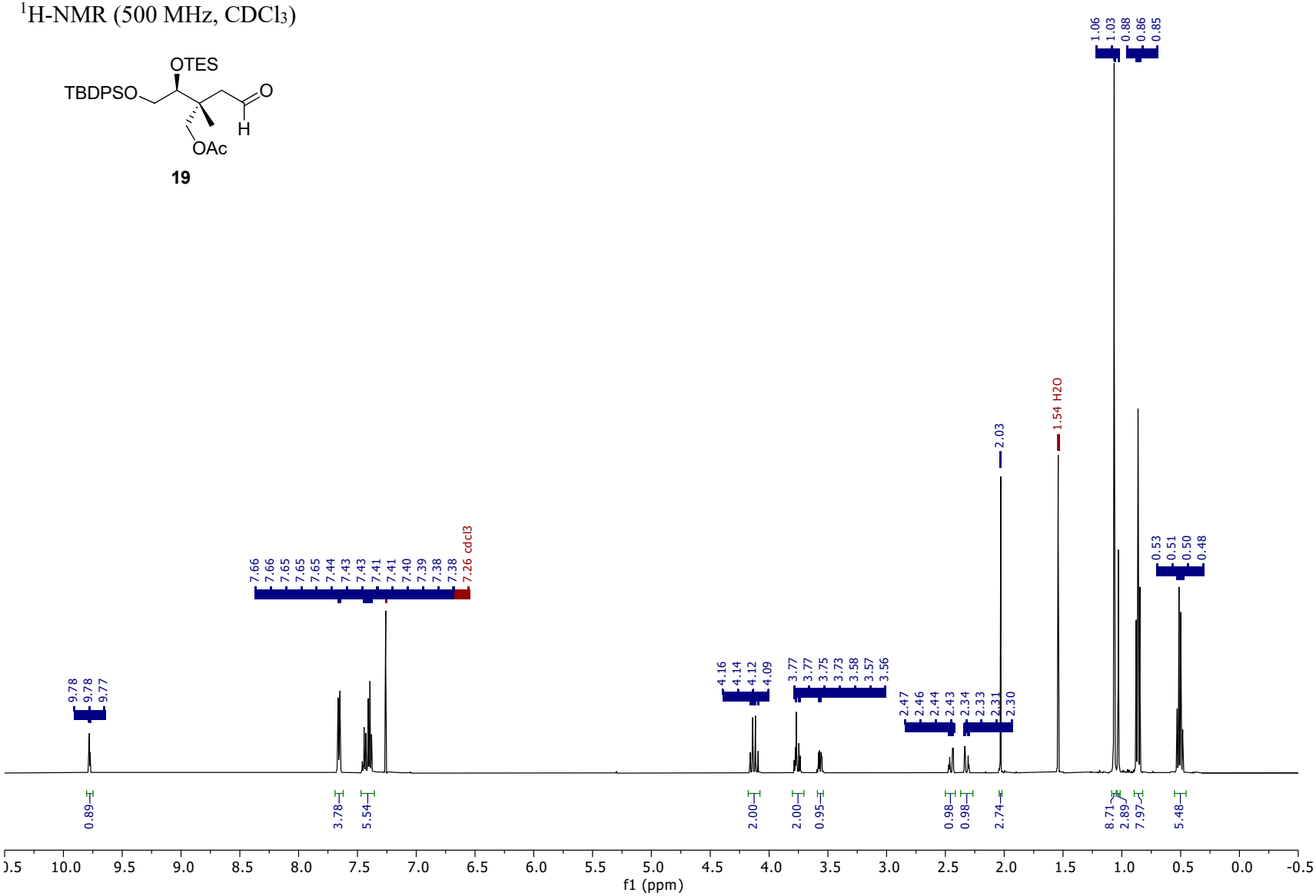


$^{13}C\{^{1}H\}$-NMR (126 MHz, $CDCl_3$)

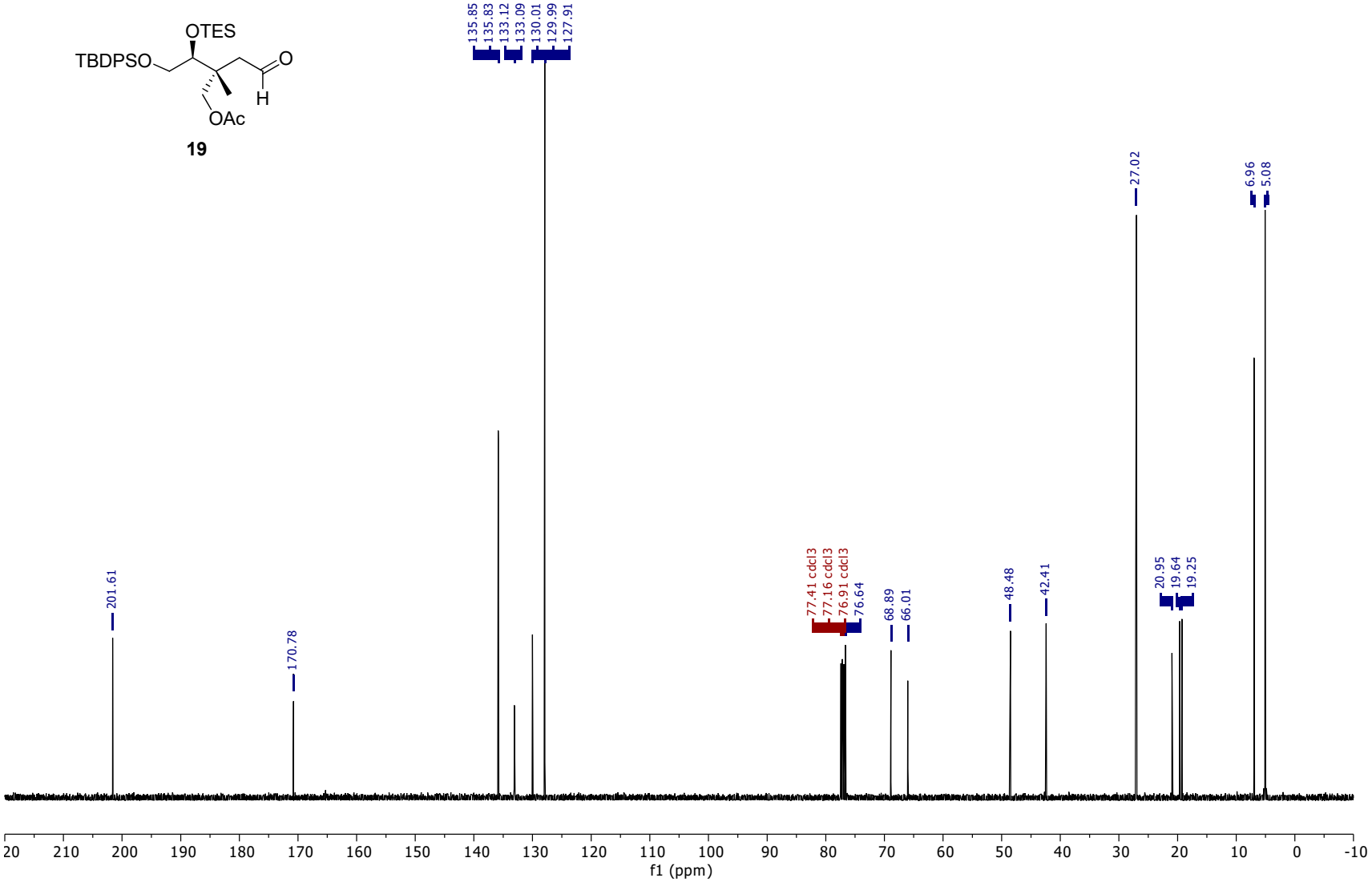


^{1}H-NMR (500 MHz, $CDCl_3$)

19



$^{13}C\{^{1}H\}$-NMR (126 MHz, $CDCl_3$)



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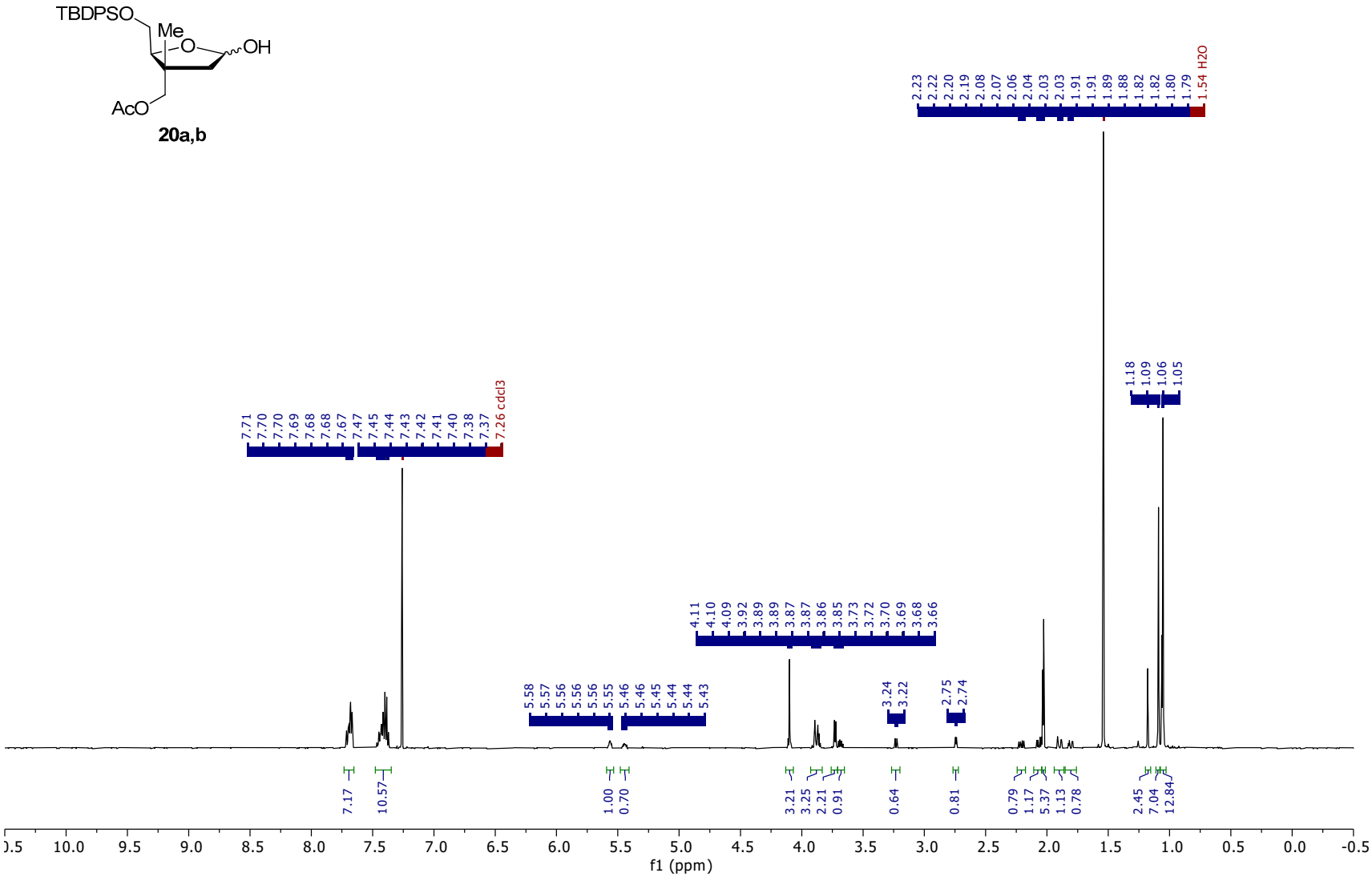
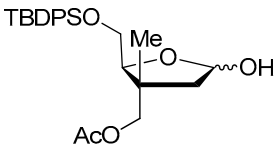
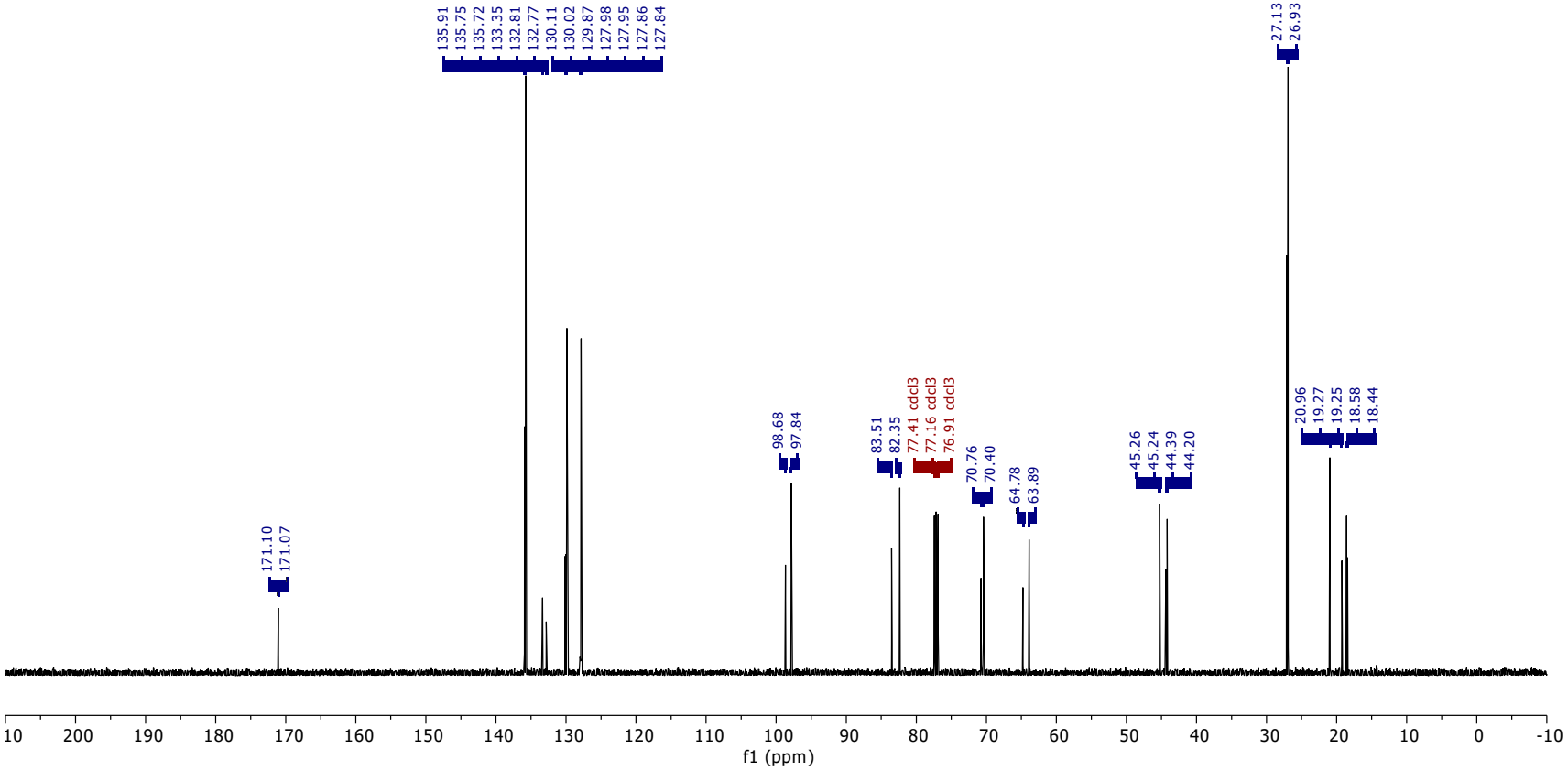


$^{13}C\{^{1}H\}$-NMR (126 MHz, $CDCl_3$)



20a,b



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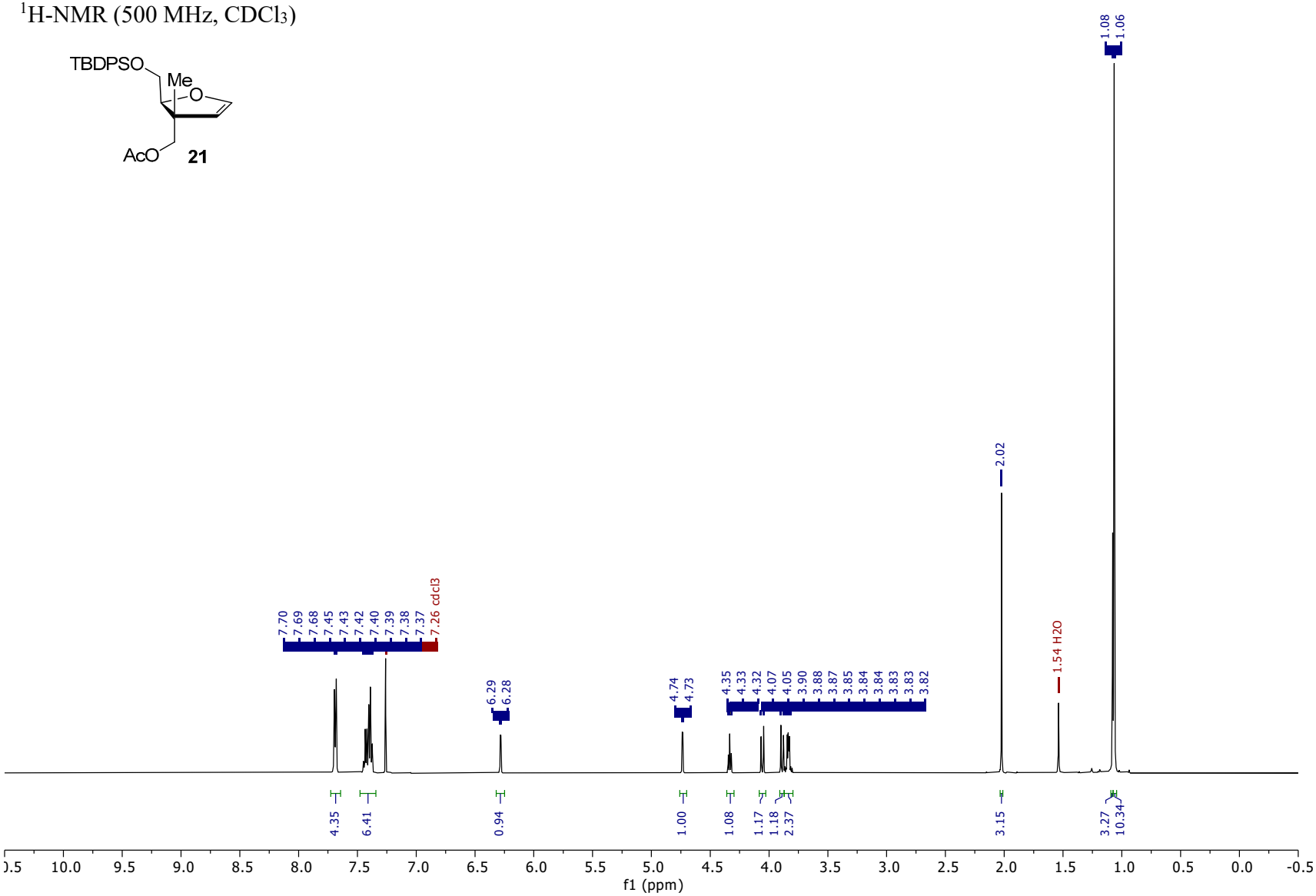
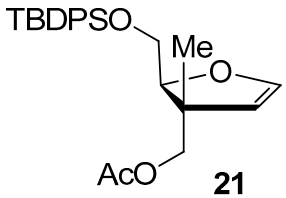
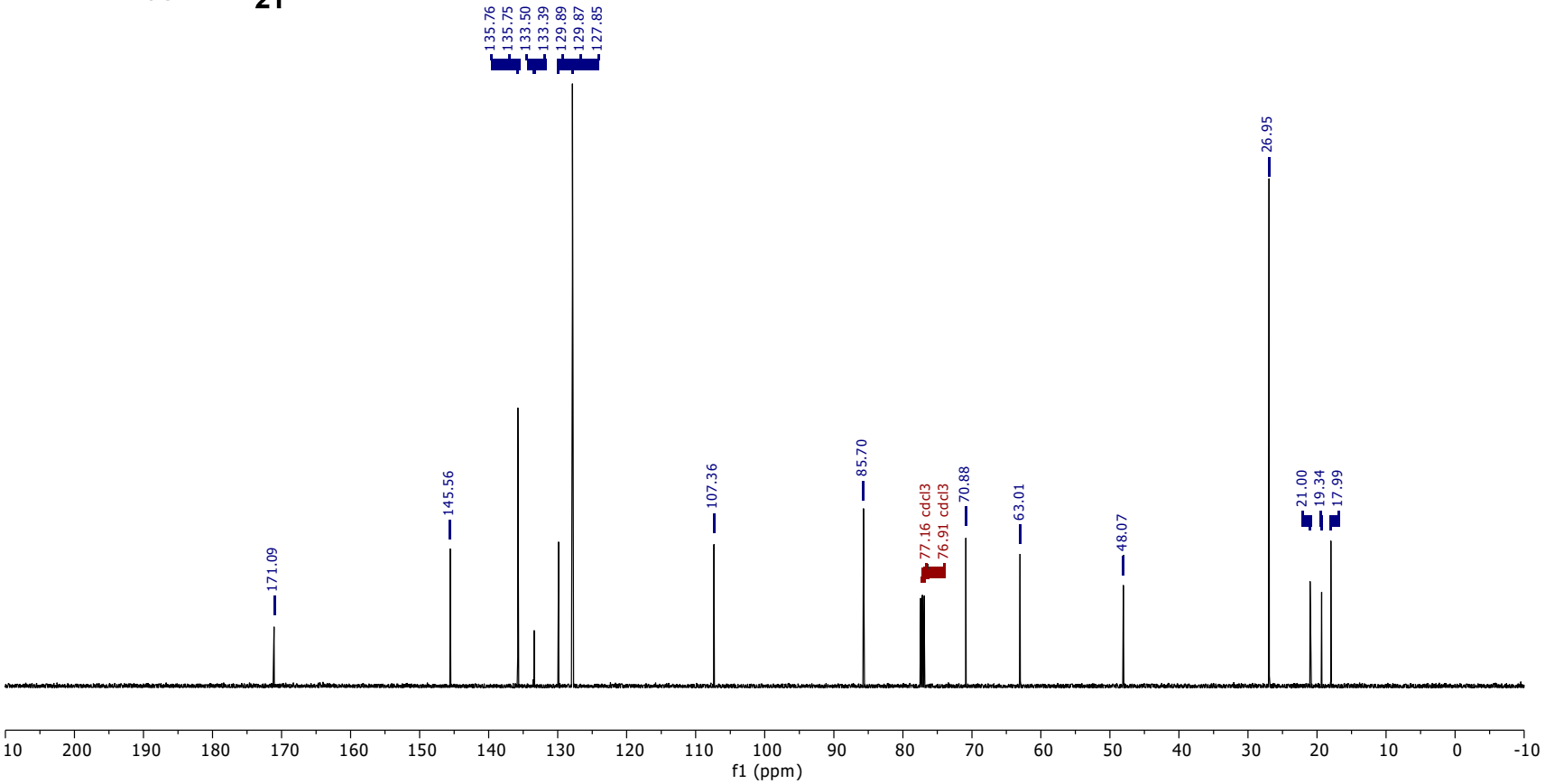


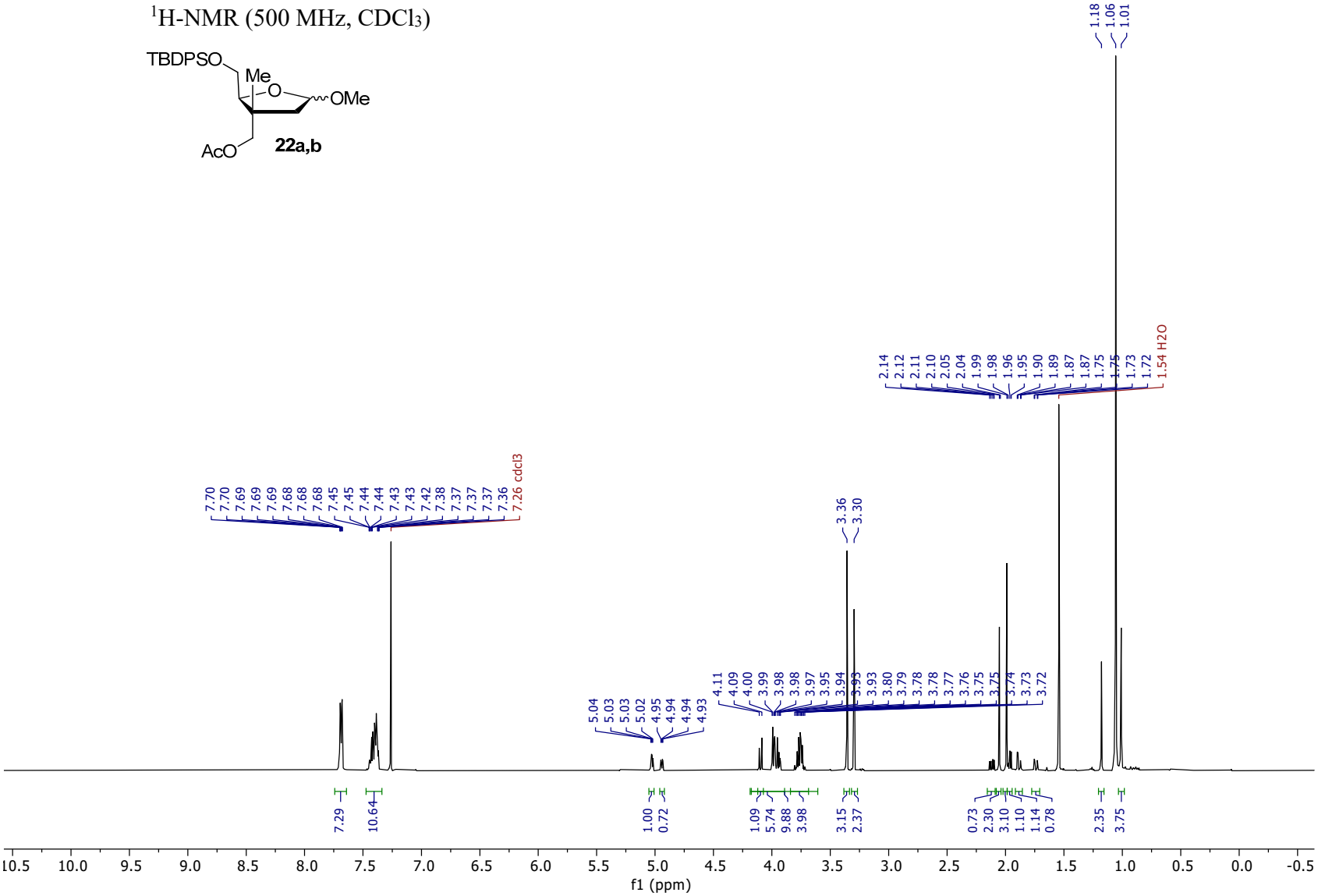
$^{13}C\{^{1}H\}$-NMR (126 MHz, $CDCl_3$)





^{1}H-NMR (500 MHz, $CDCl_3$)

22a,b



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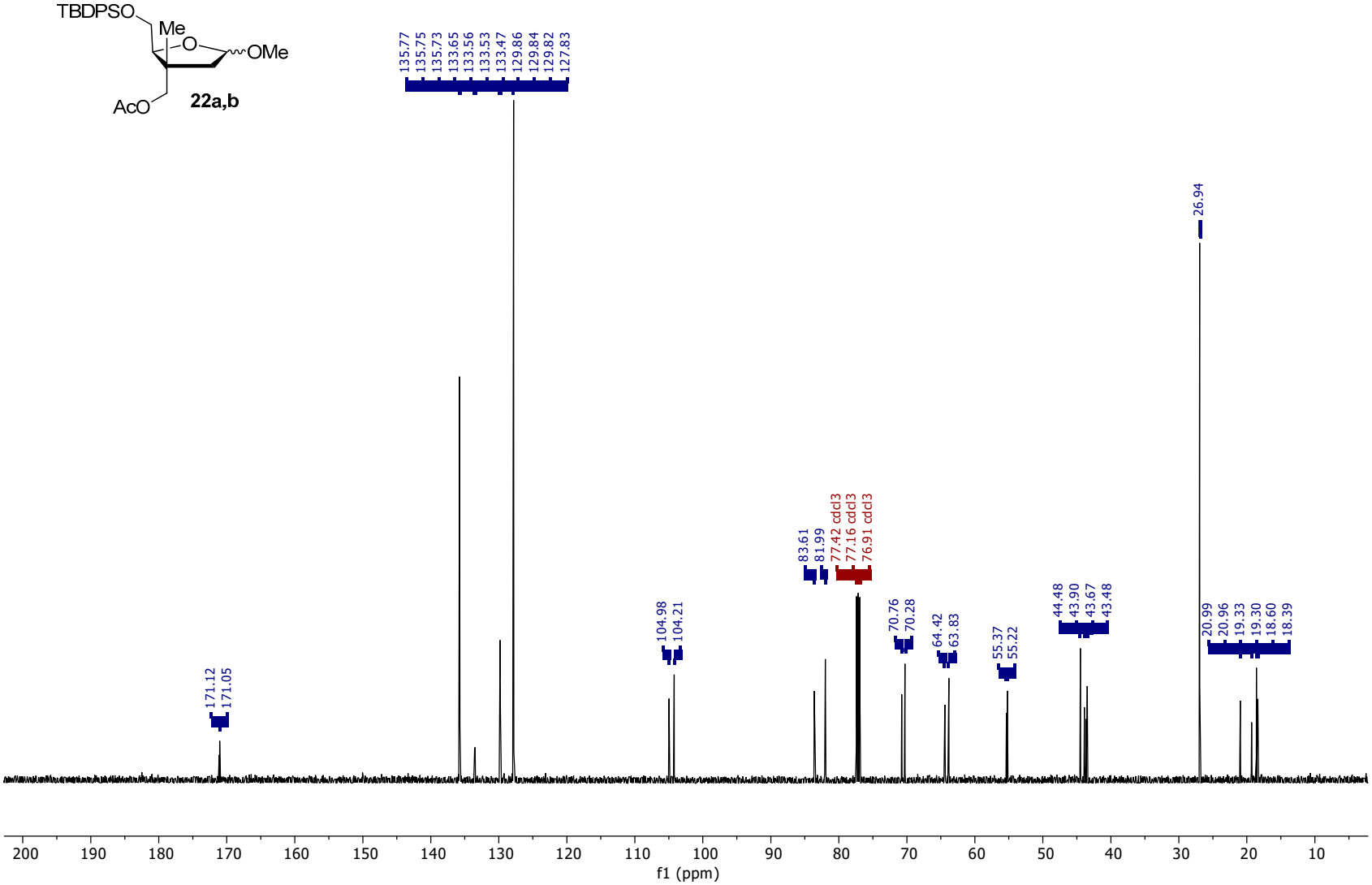
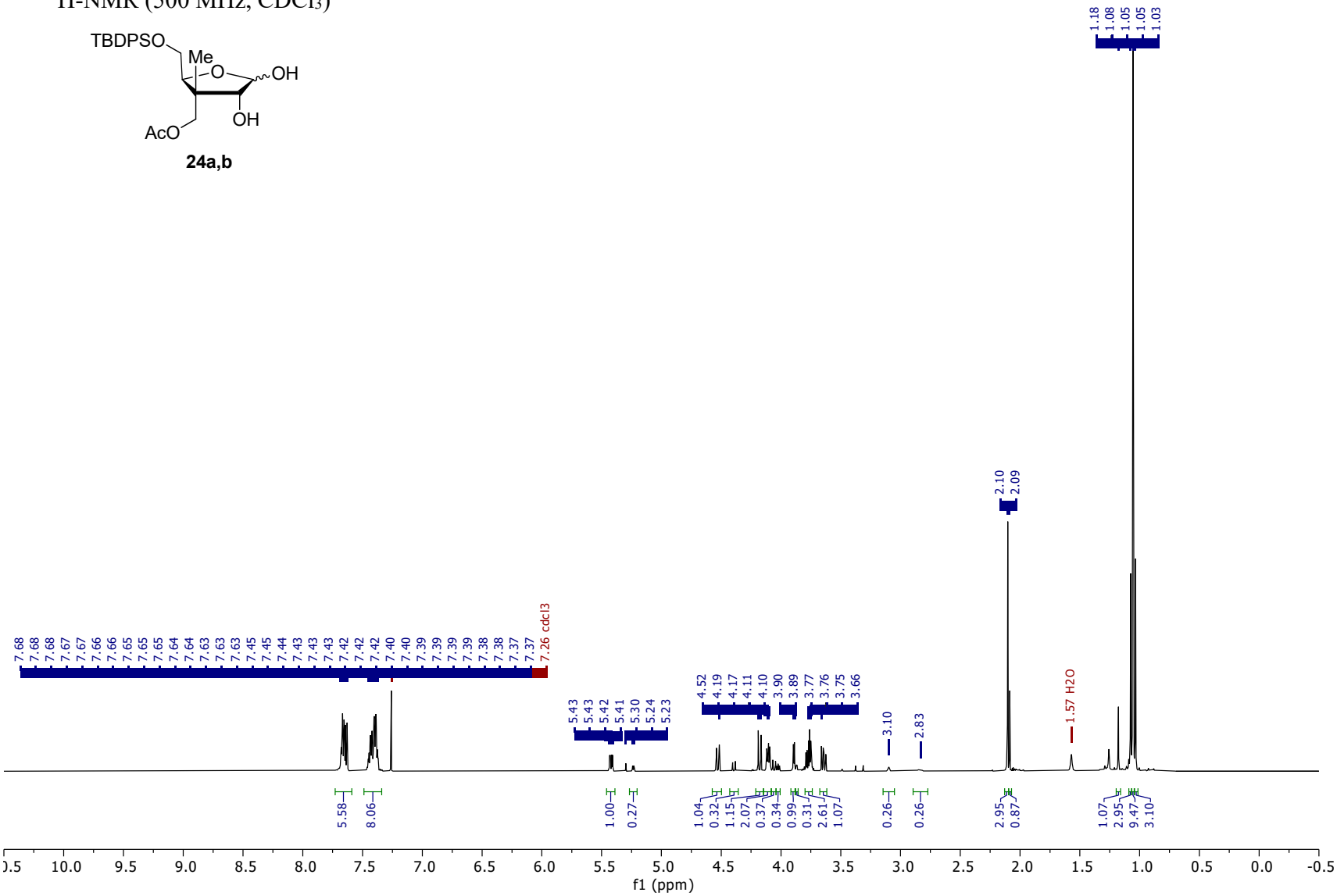


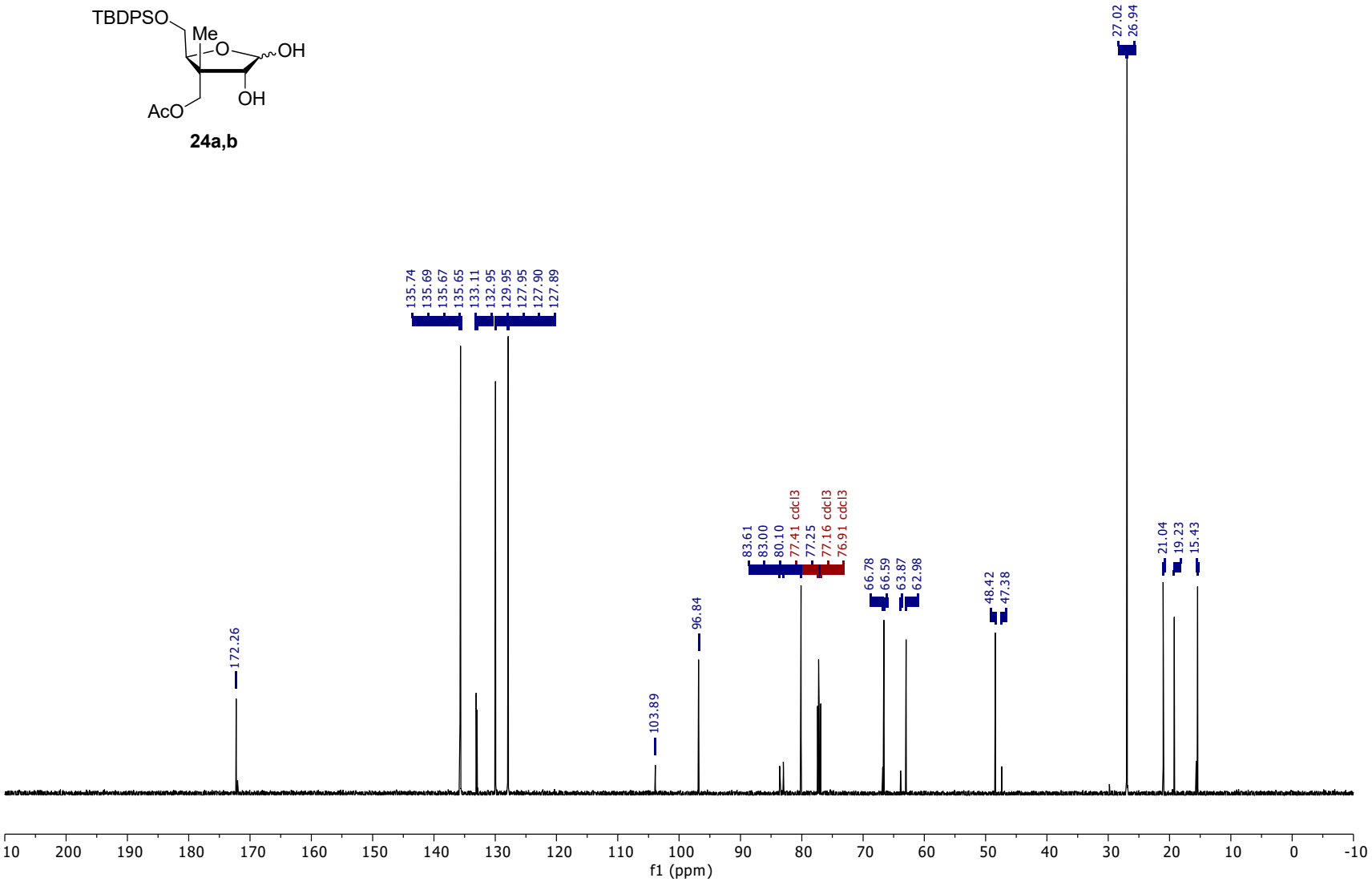
^{1}H-NMR (500 MHz, $CDCl_3$)

24a,b



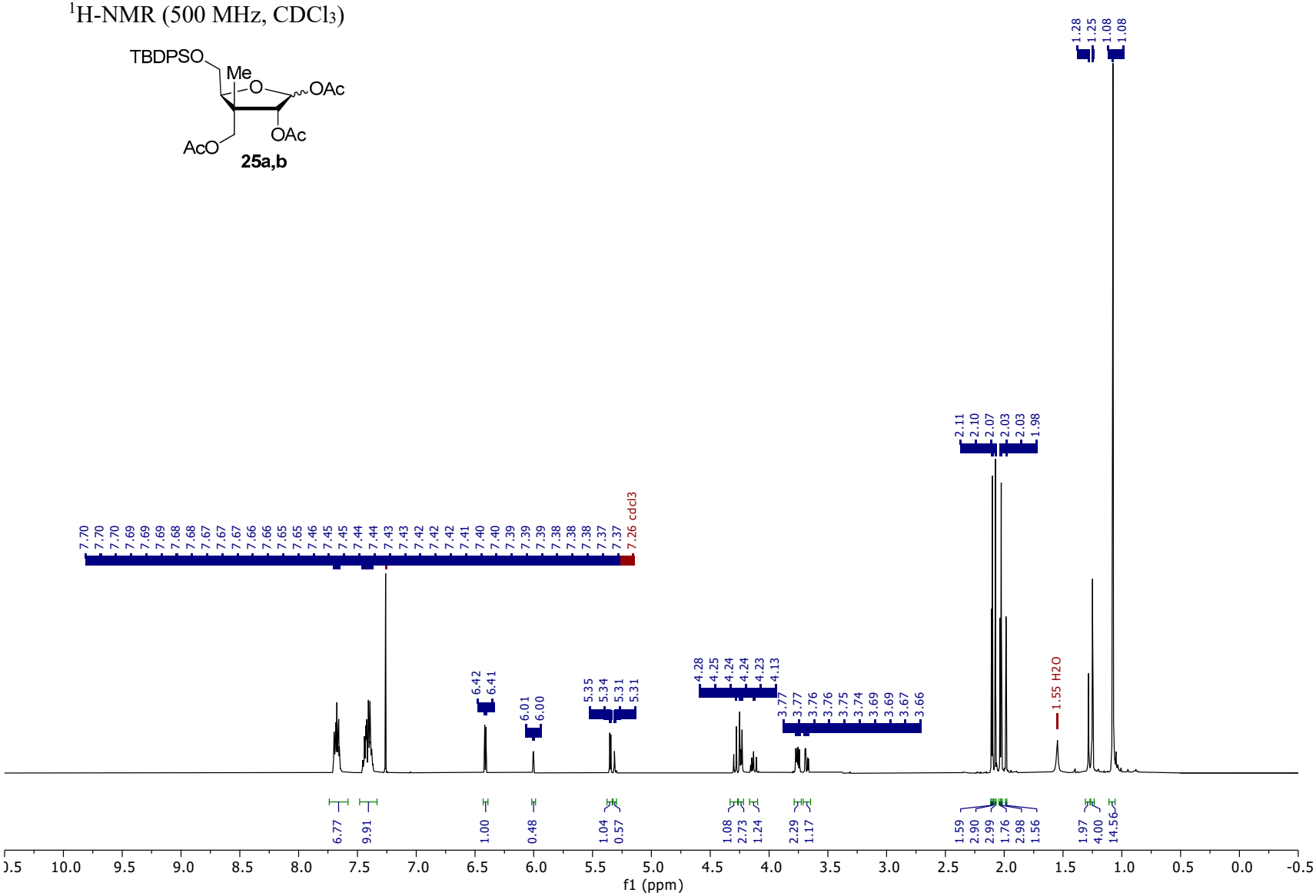
$^{13}C\{^{1}H\}$-NMR (126 MHz, $CDCl_3$)

24a,b



^{1}H-NMR (500 MHz, $CDCl_3$)

25a,b



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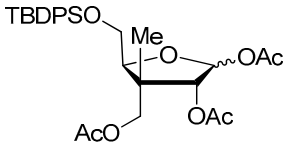
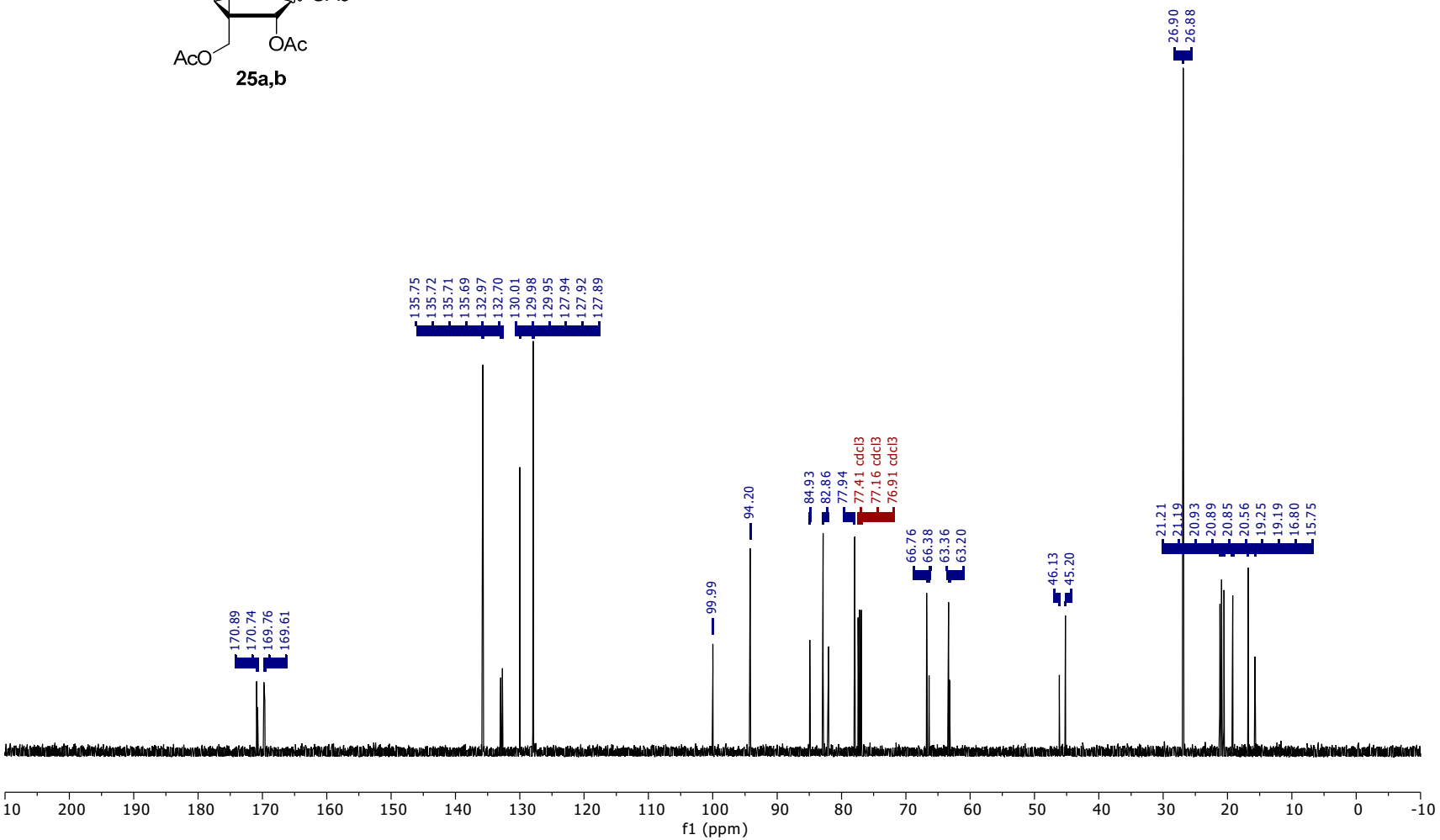
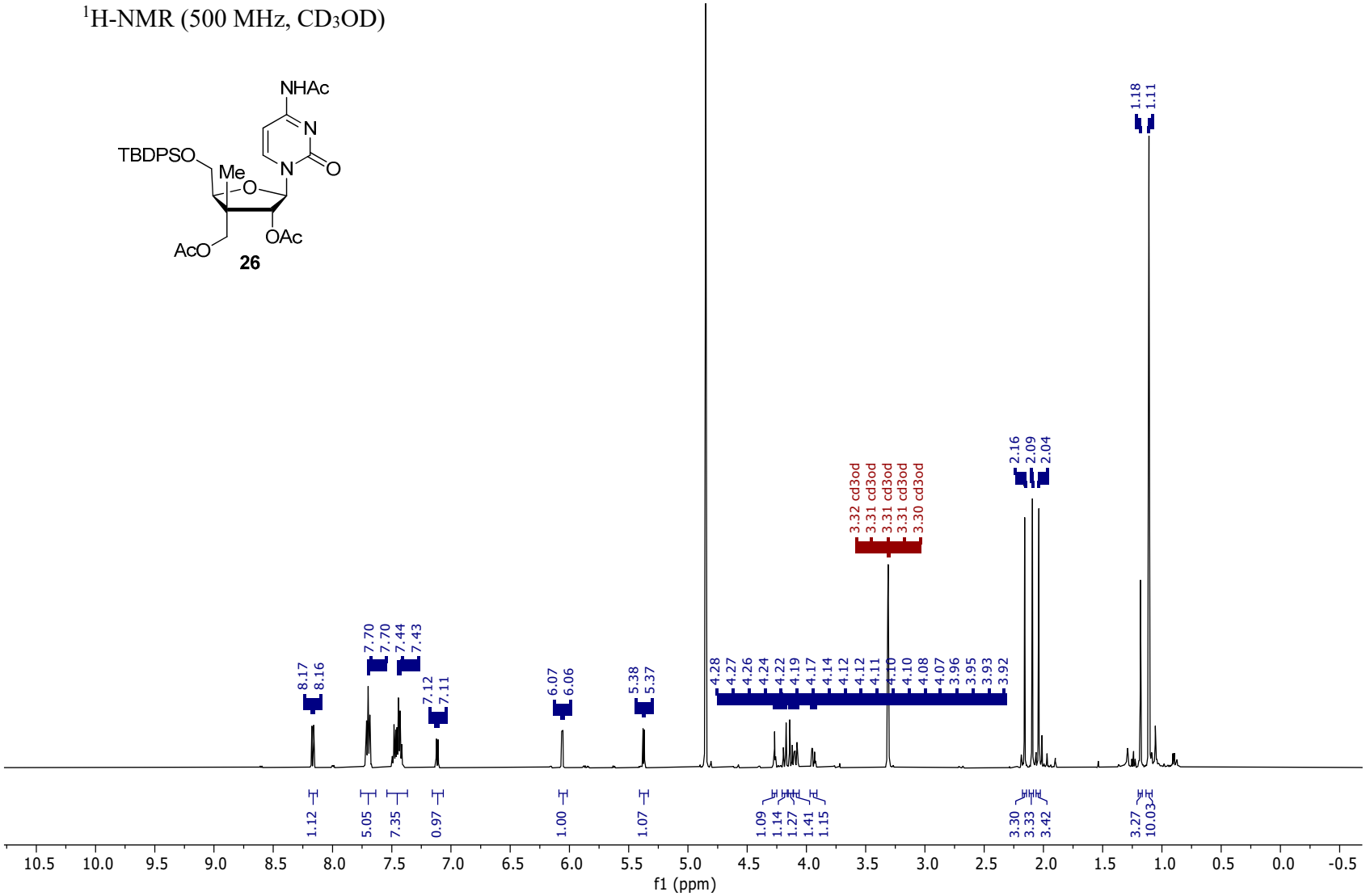


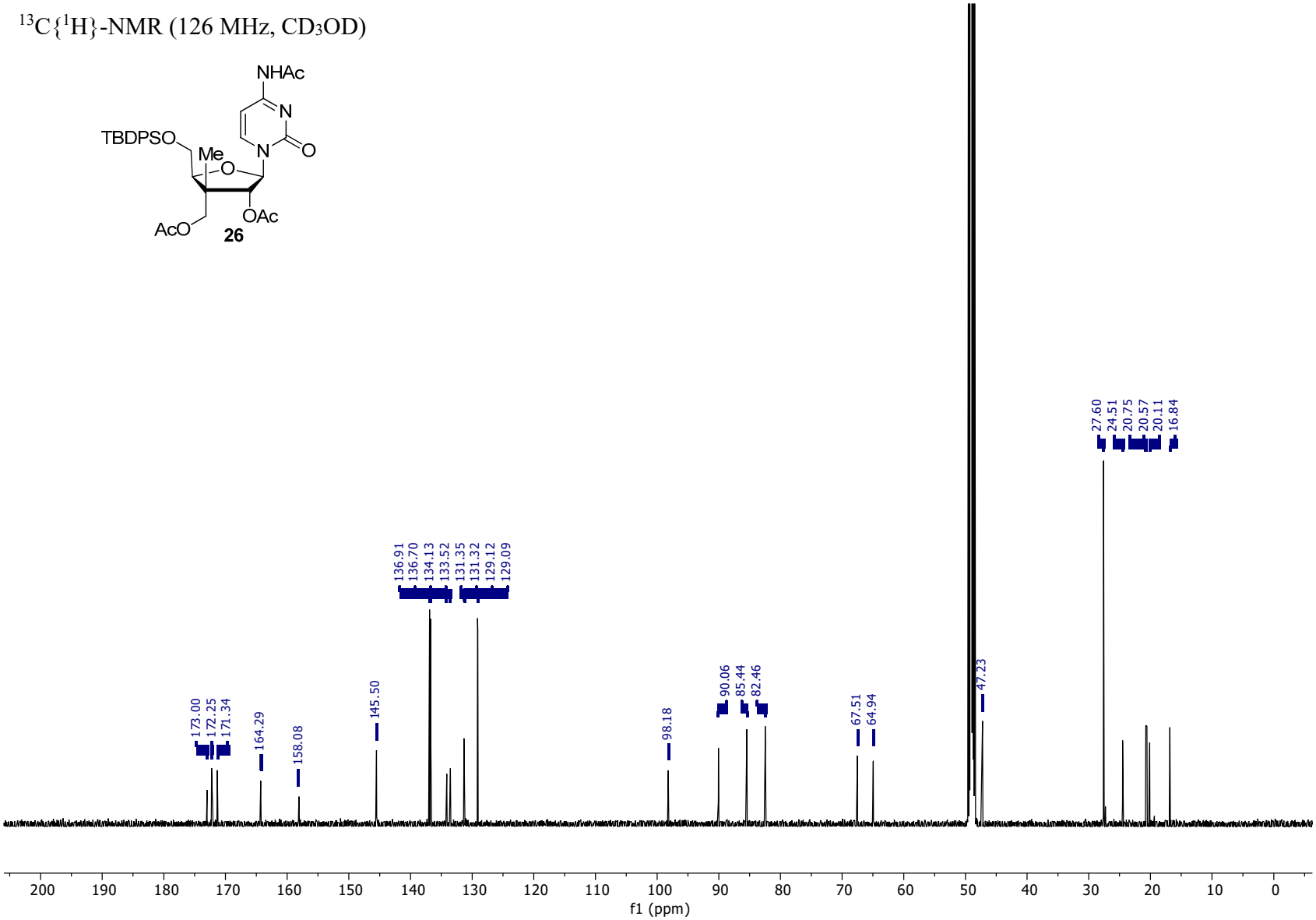
25a,b



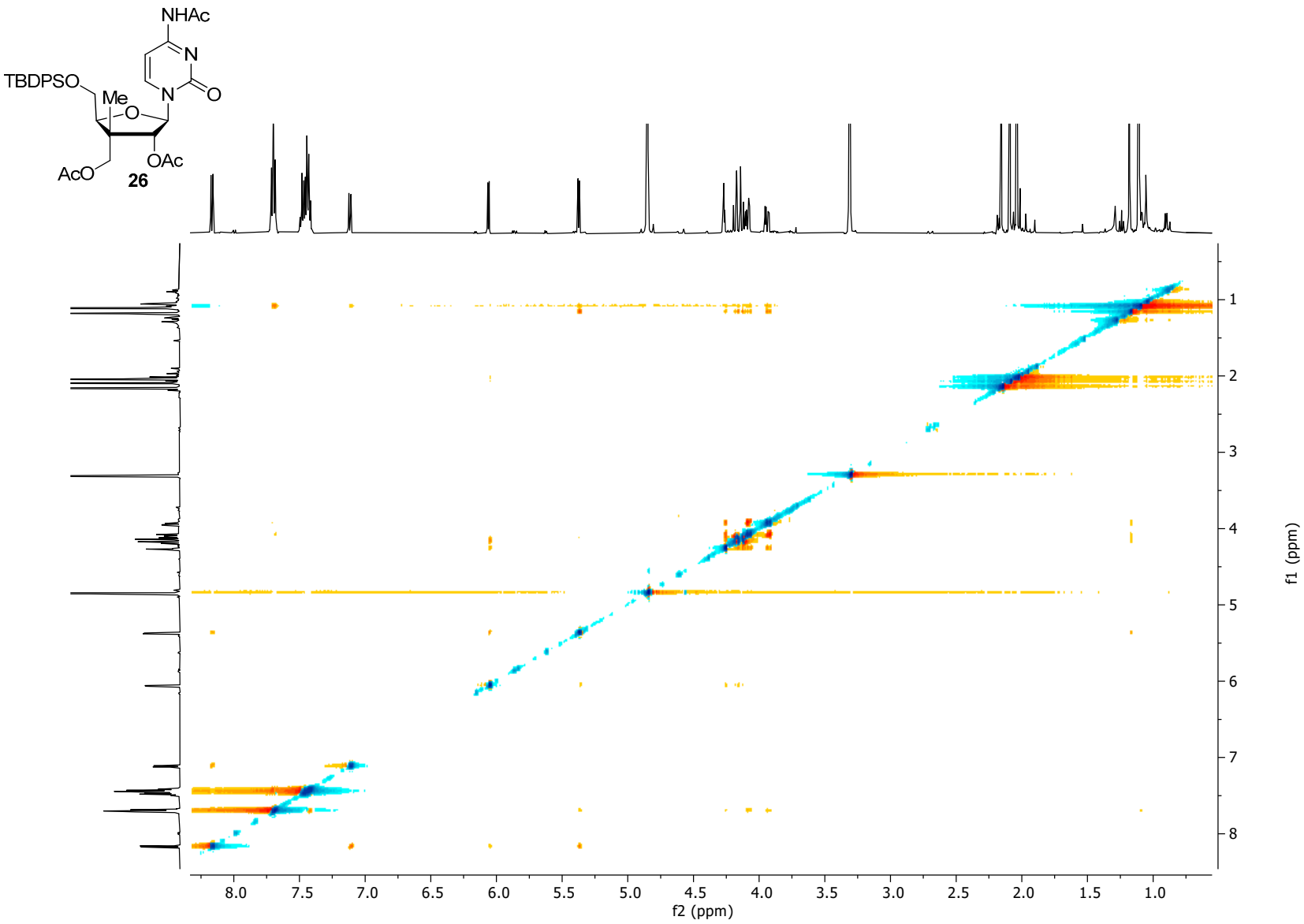
^{1}H-NMR (500 MHz, CD_3OD)



$^{13}C\{^{1}H\}$-NMR (126 MHz, CD_3OD)

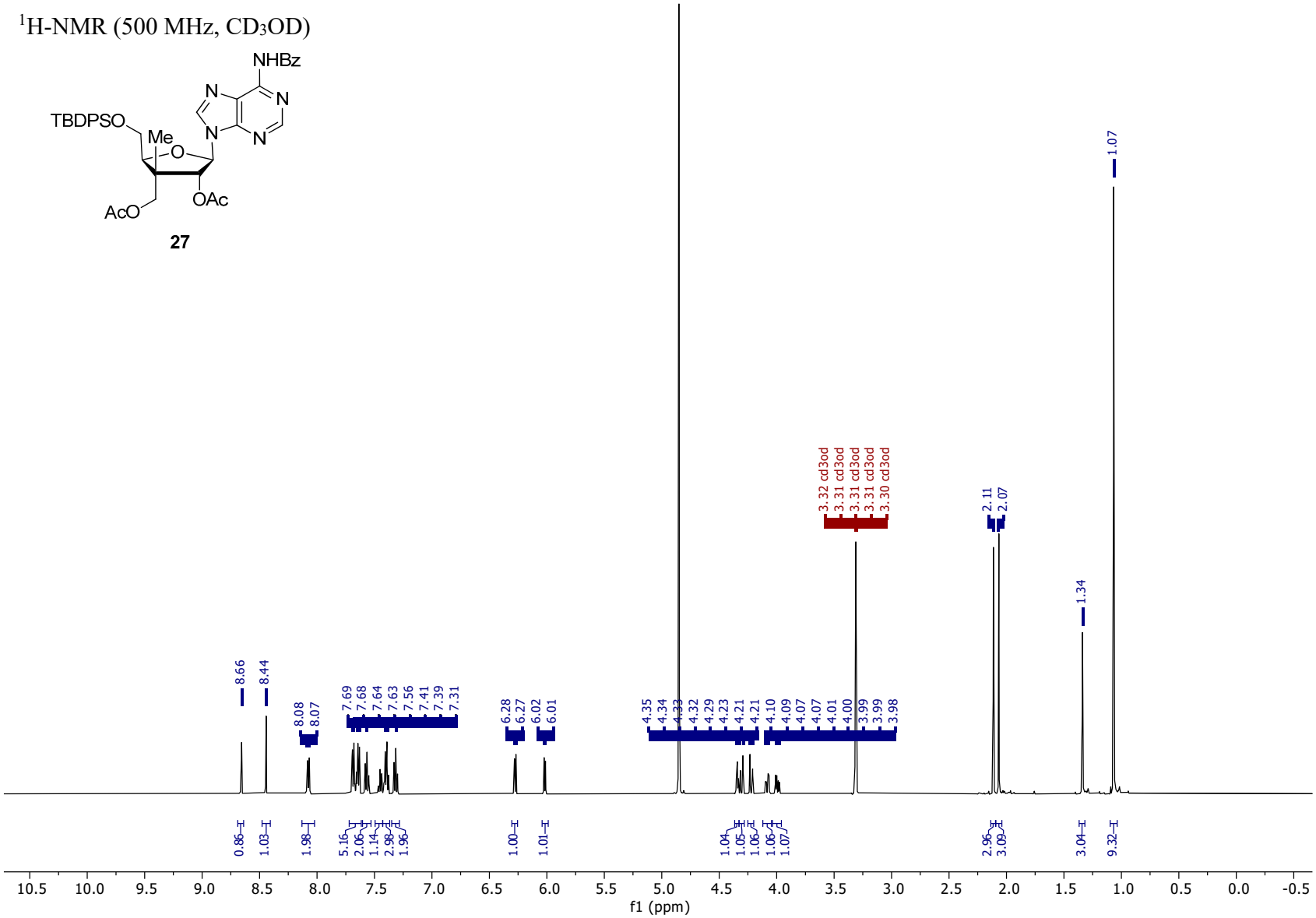


NOESY (500 MHz, CD_3OD)



^{1}H-NMR (500 MHz, CD_3OD)

27



$^{13}C\{^{1}H\}$-NMR (126 MHz, CD_3OD)

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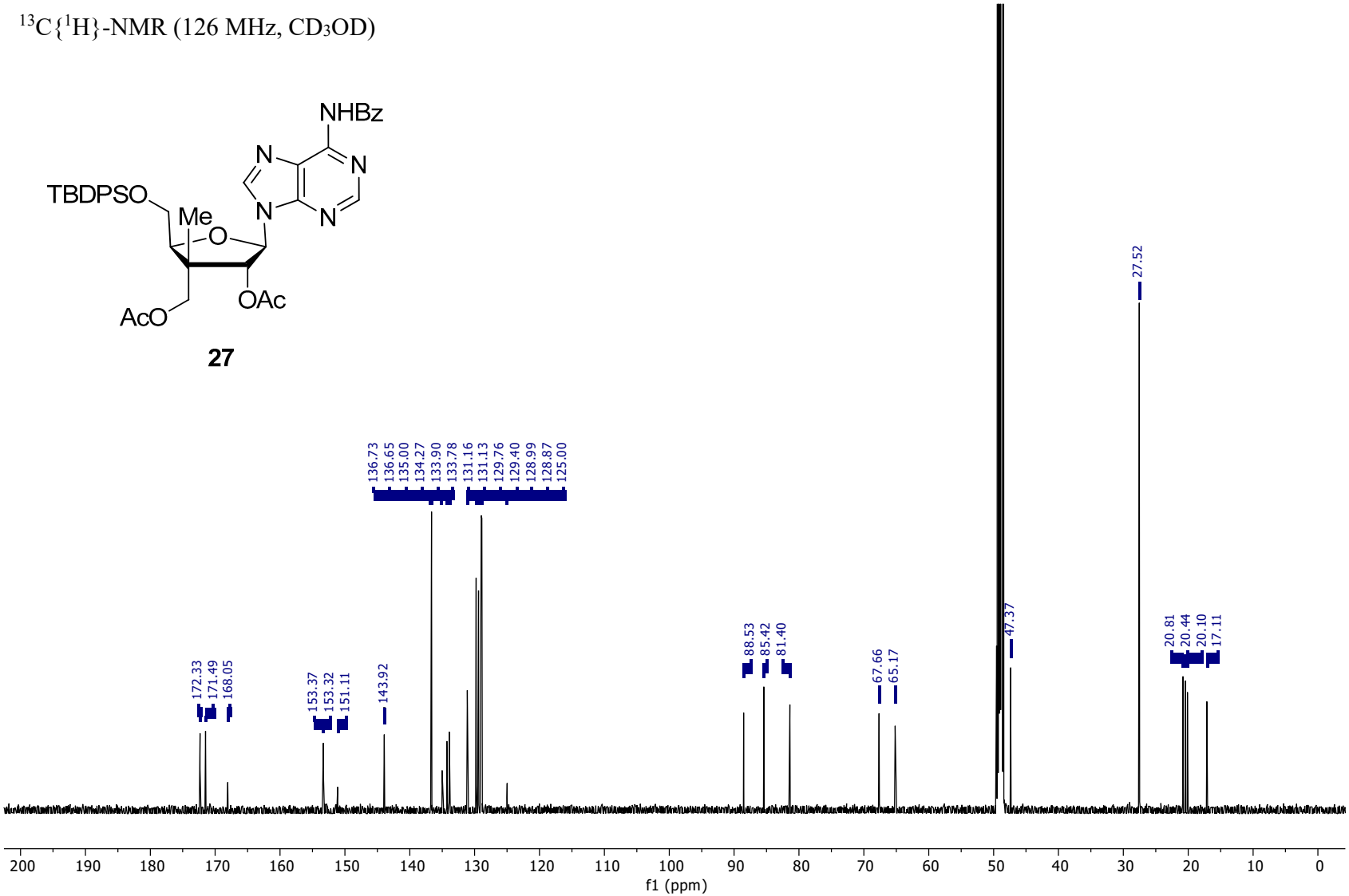

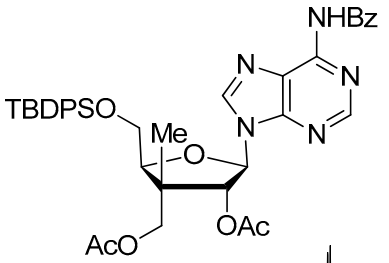

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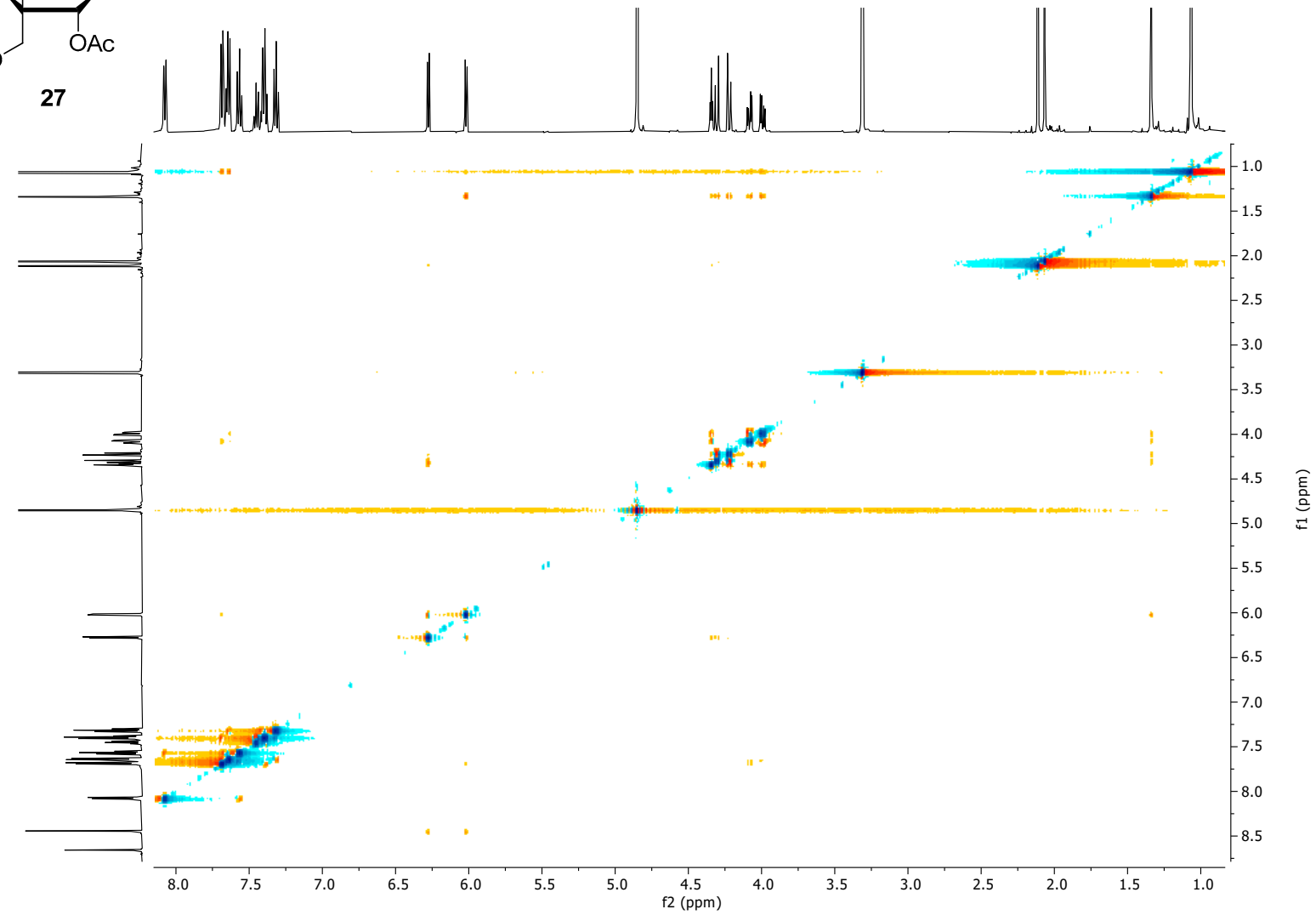
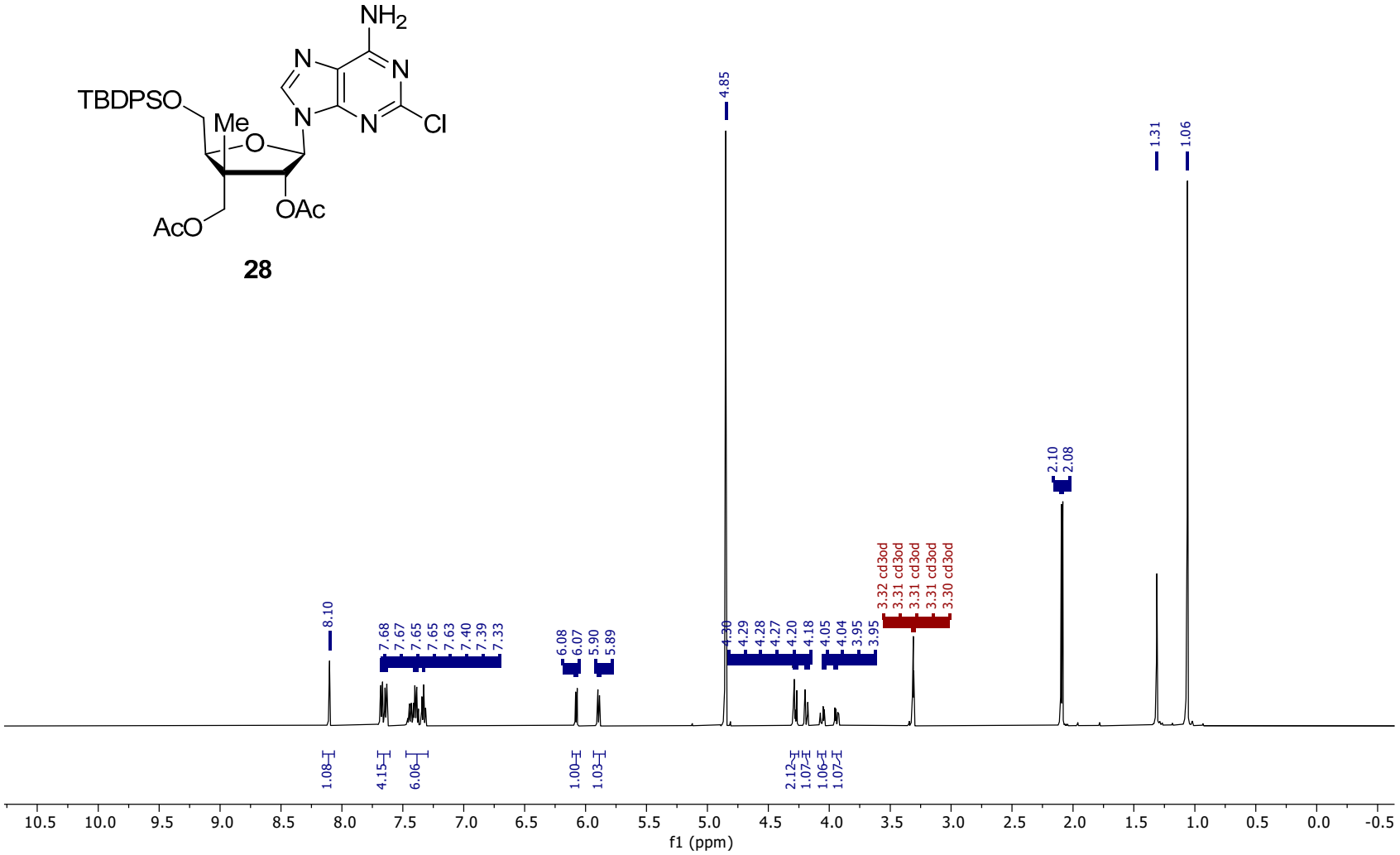
NOESY (500 MHz, CD_3OD)



^{1}H-NMR (500 MHz, CD_3OD)



$^{13}C\{^{1}H\}$-NMR (126 MHz, CD_3OD)

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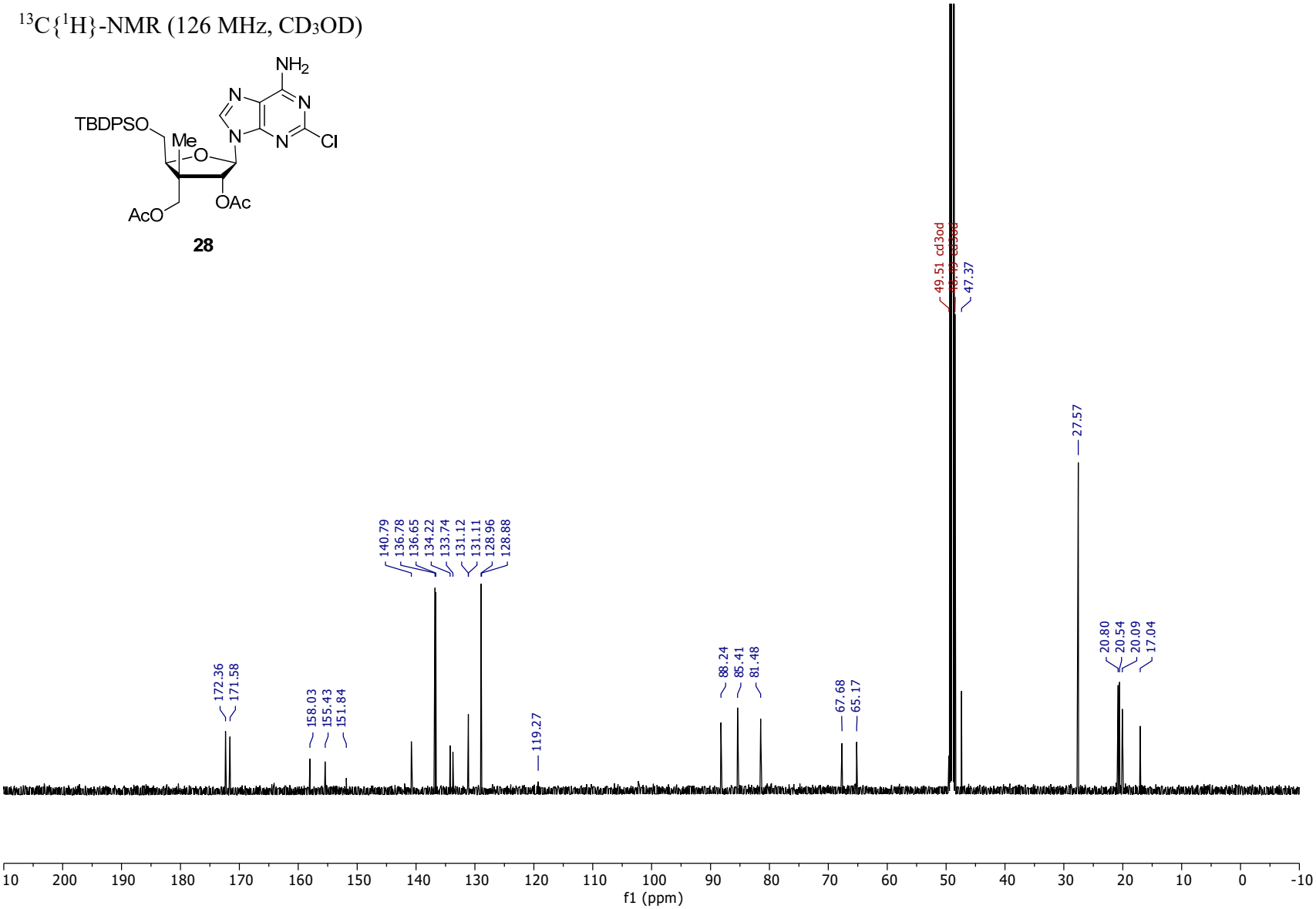
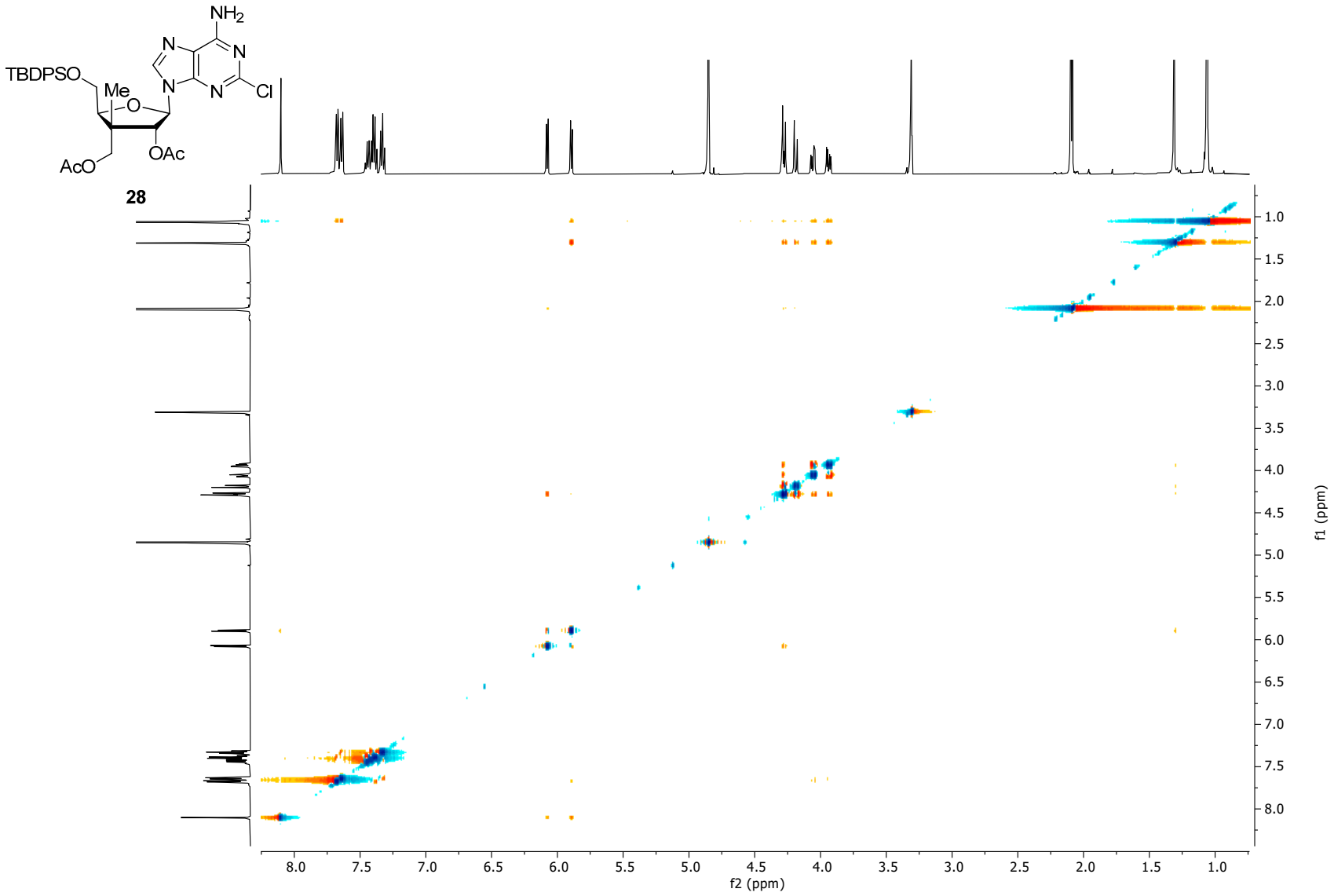
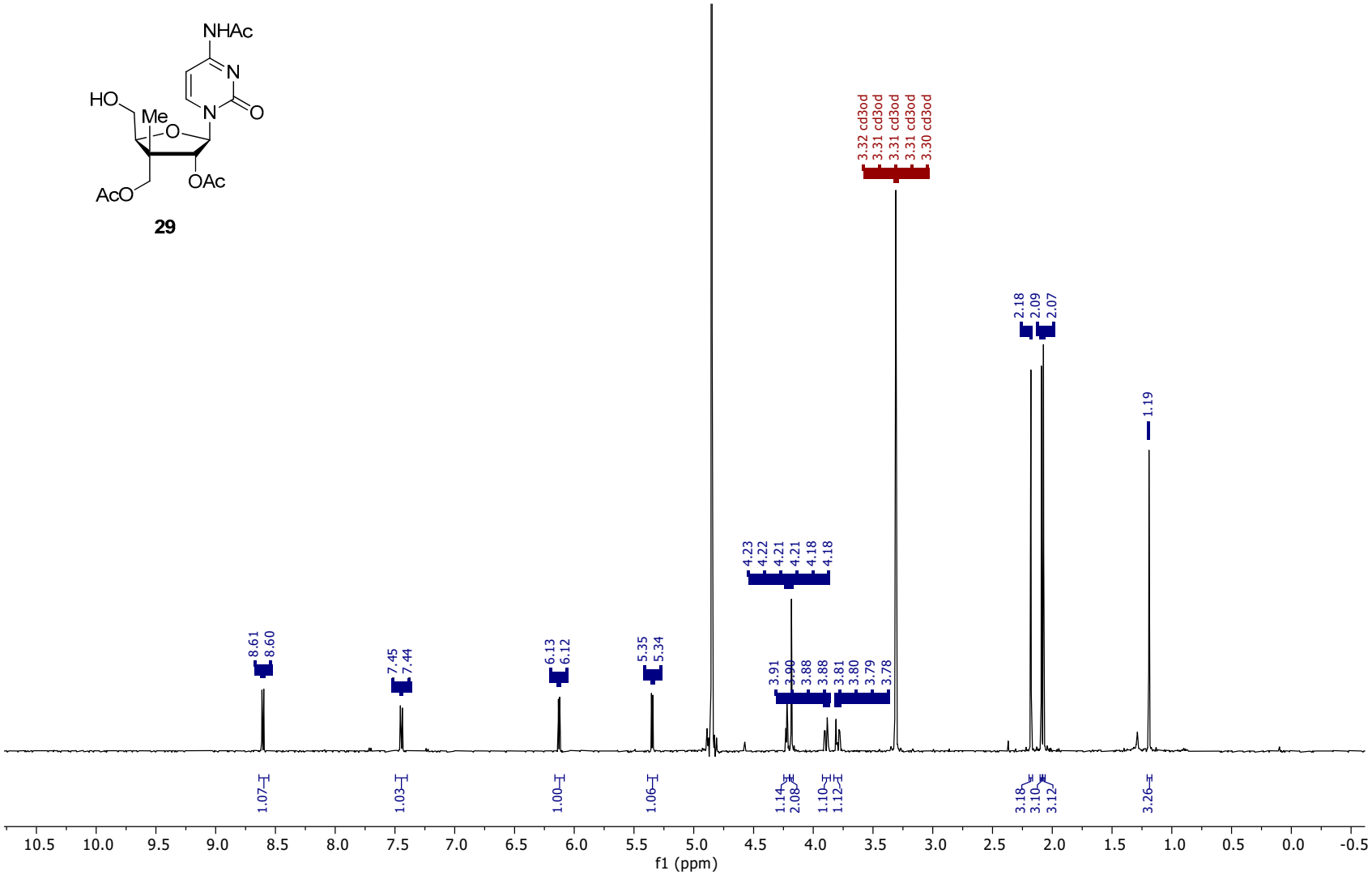


NOESY (500 MHz, CD_3OD)

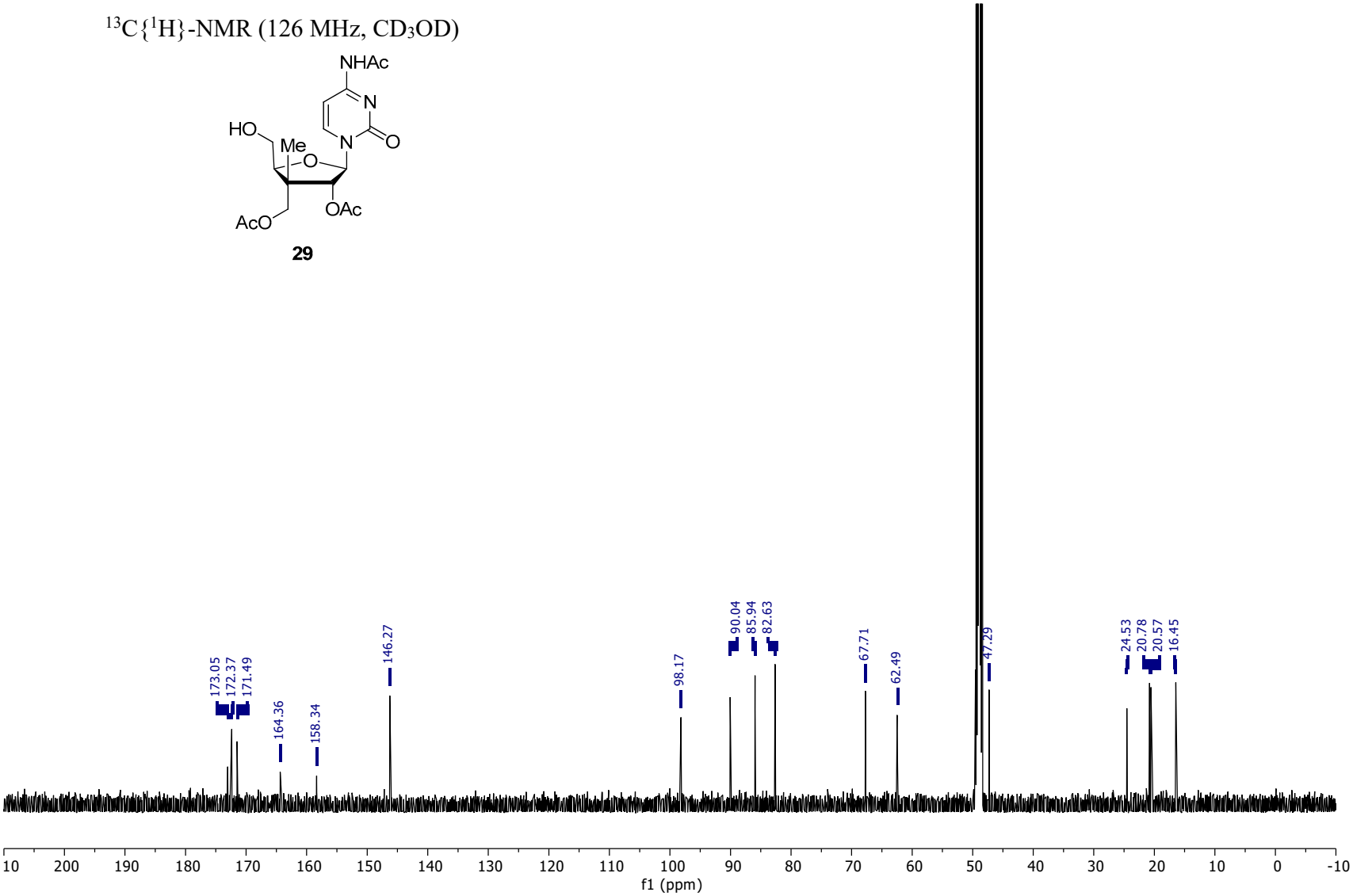


^{1}H-NMR (500 MHz, CD_3OD)

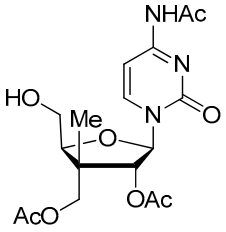


$^{13}C\{^{1}H\}$-NMR (126 MHz, CD_3OD)

29



NOESY (500 MHz, CD_3OD)



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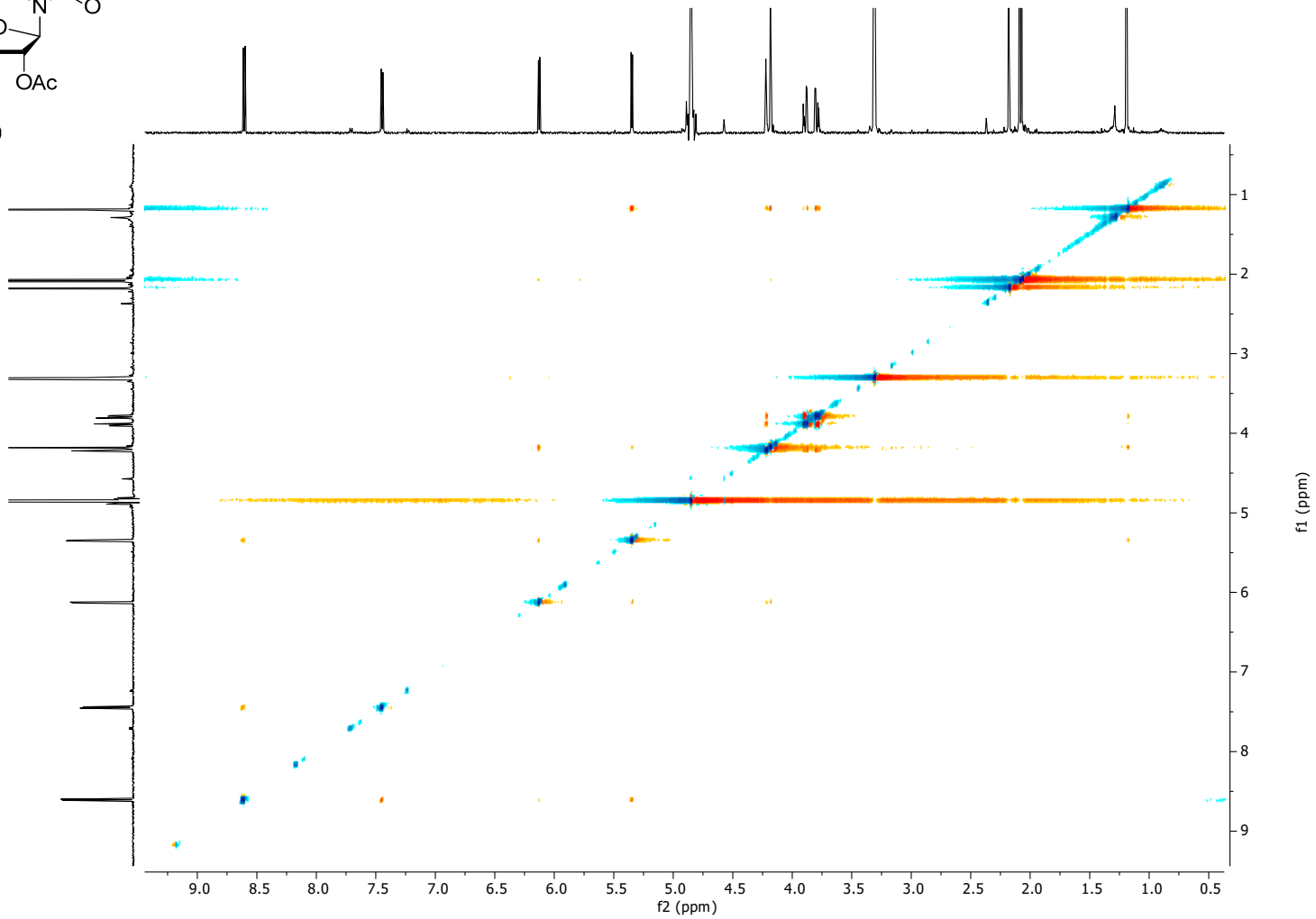
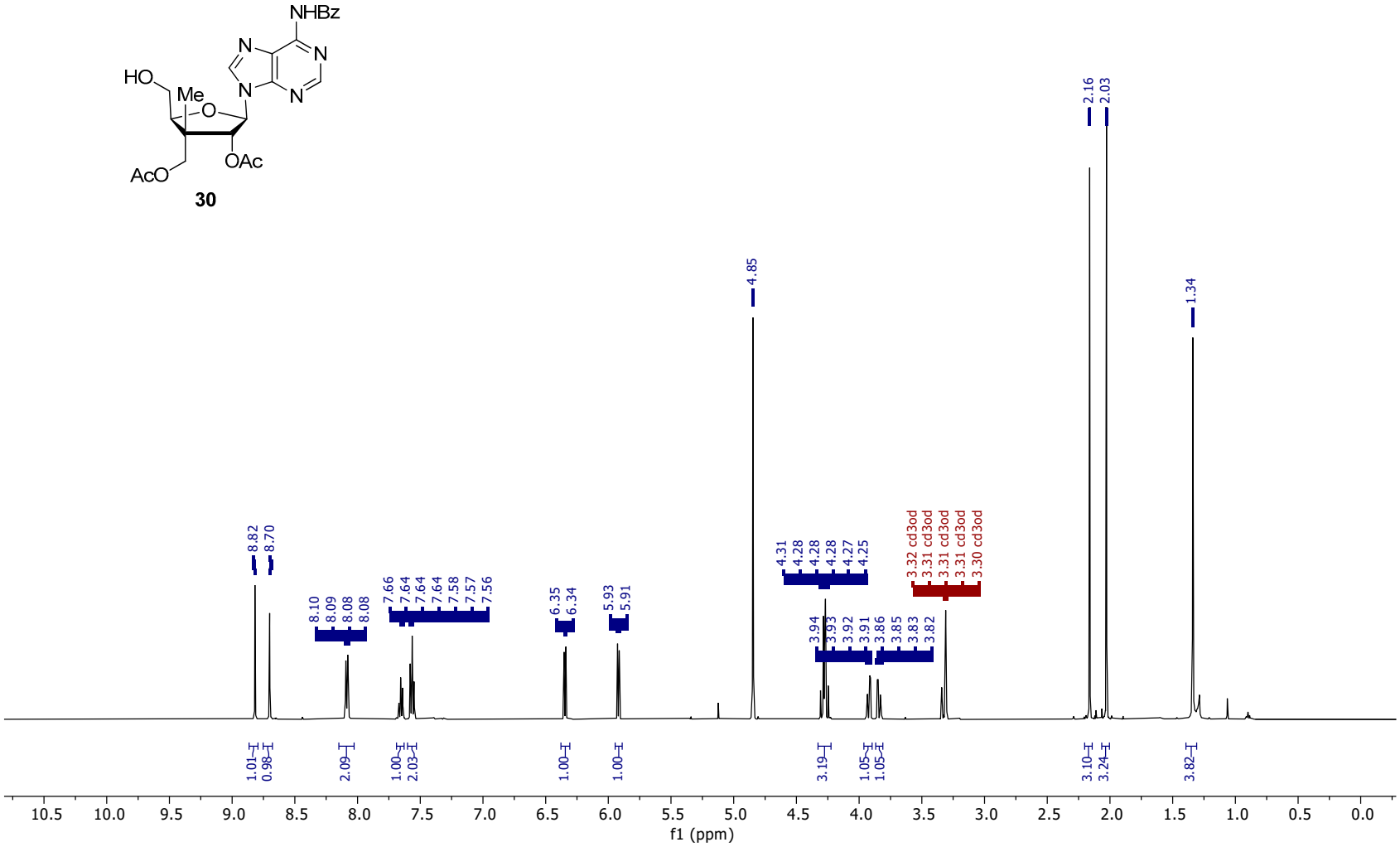
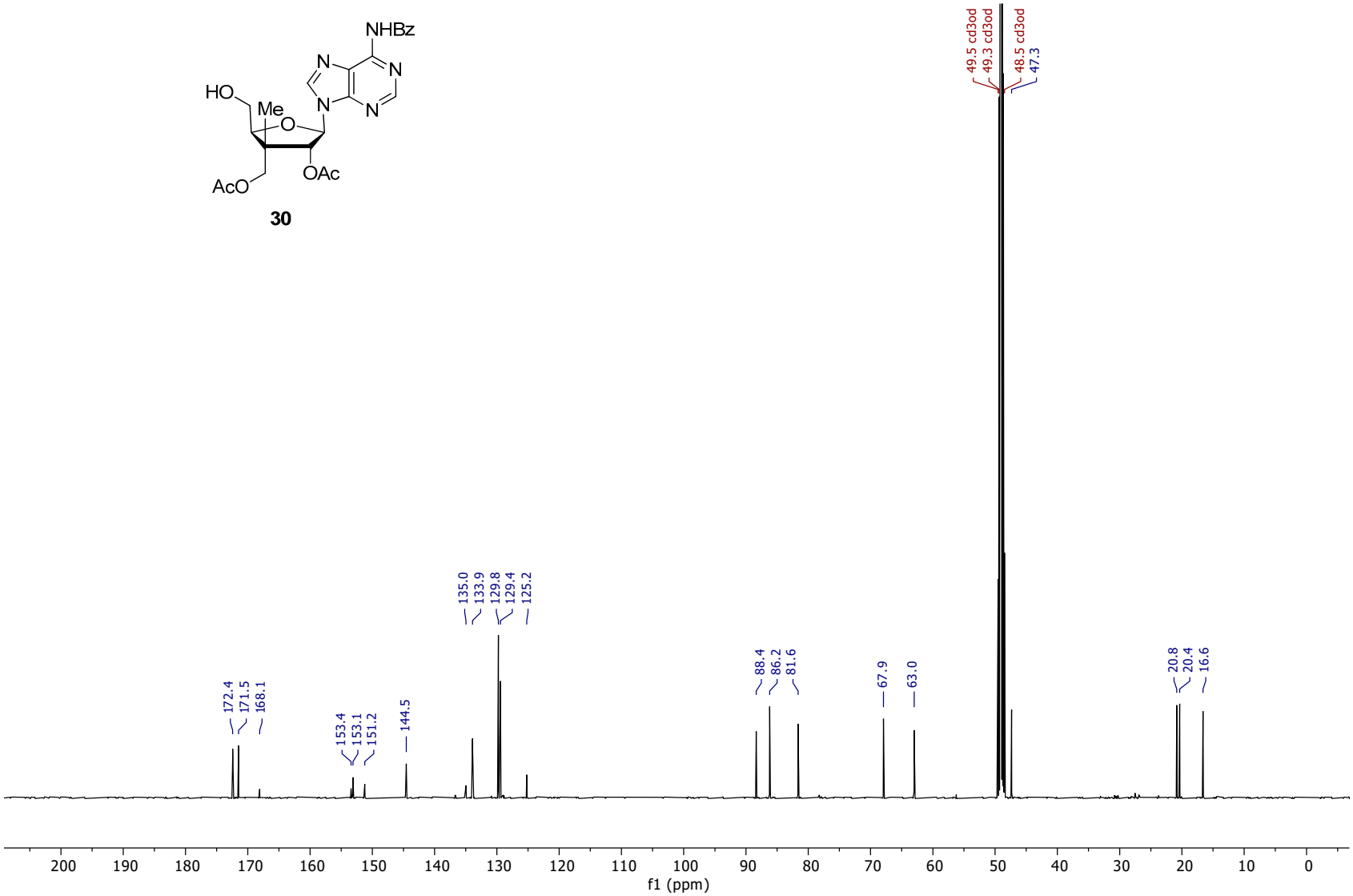


^{1}H-NMR (500 MHz, CD_3OD)

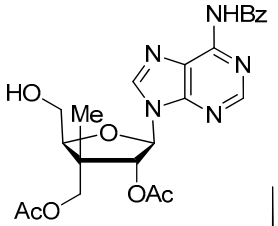


$^{13}C\{^{1}H\}$-NMR (126 MHz, CD_3OD)

30



NOESY (500 MHz, CD_3OD)



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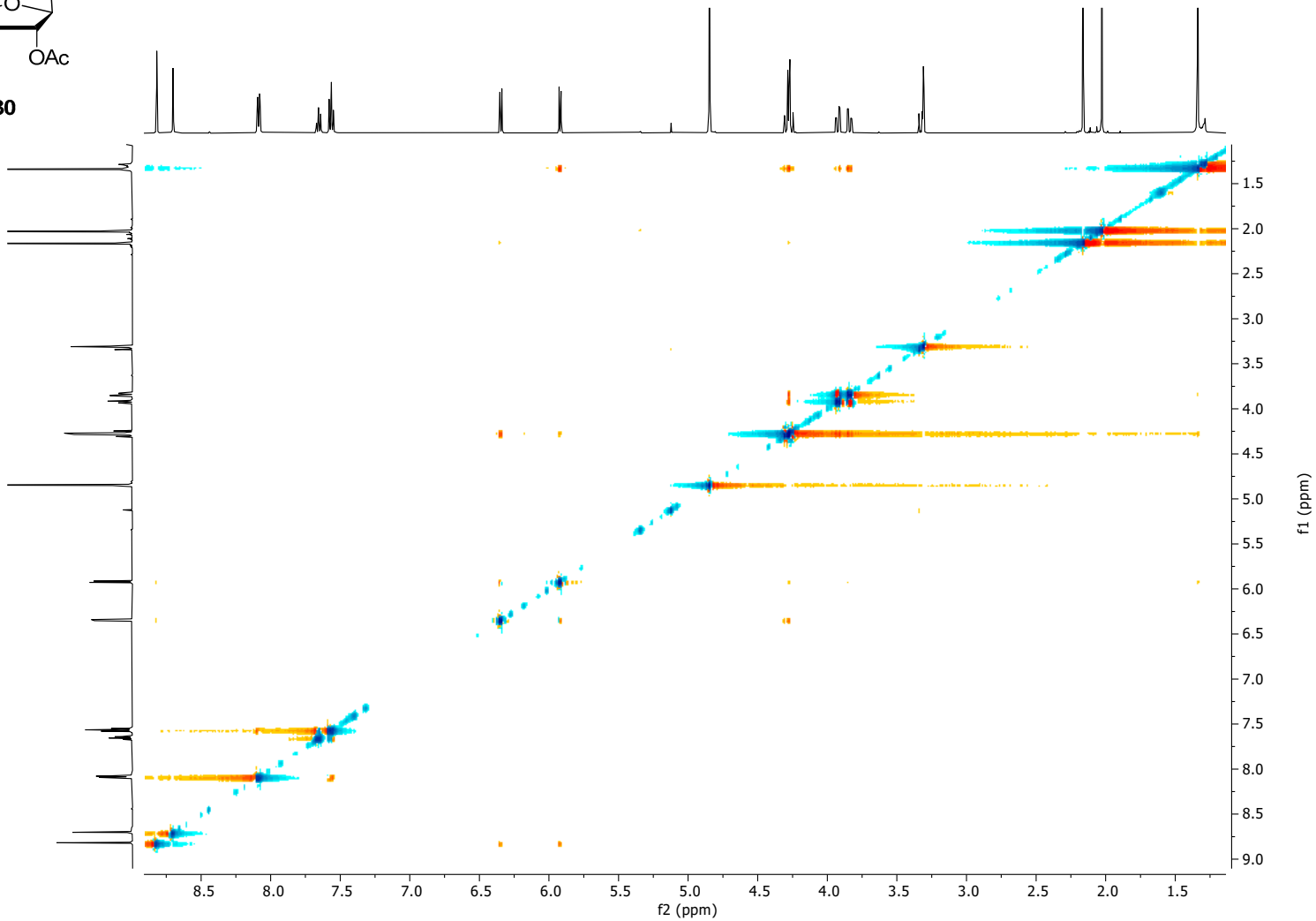
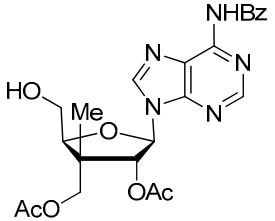


HMBC (500 MHz, CD_3OD)



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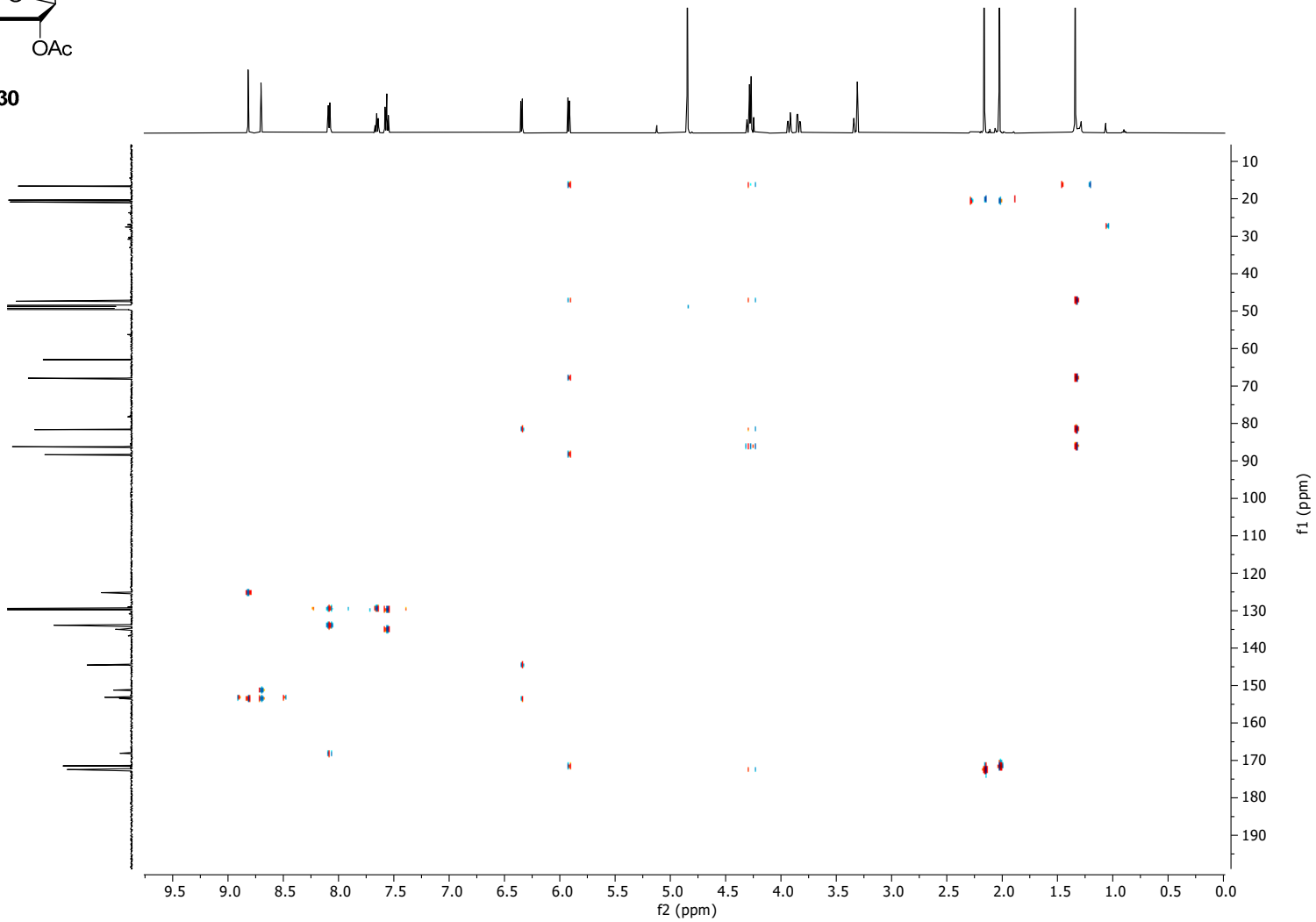
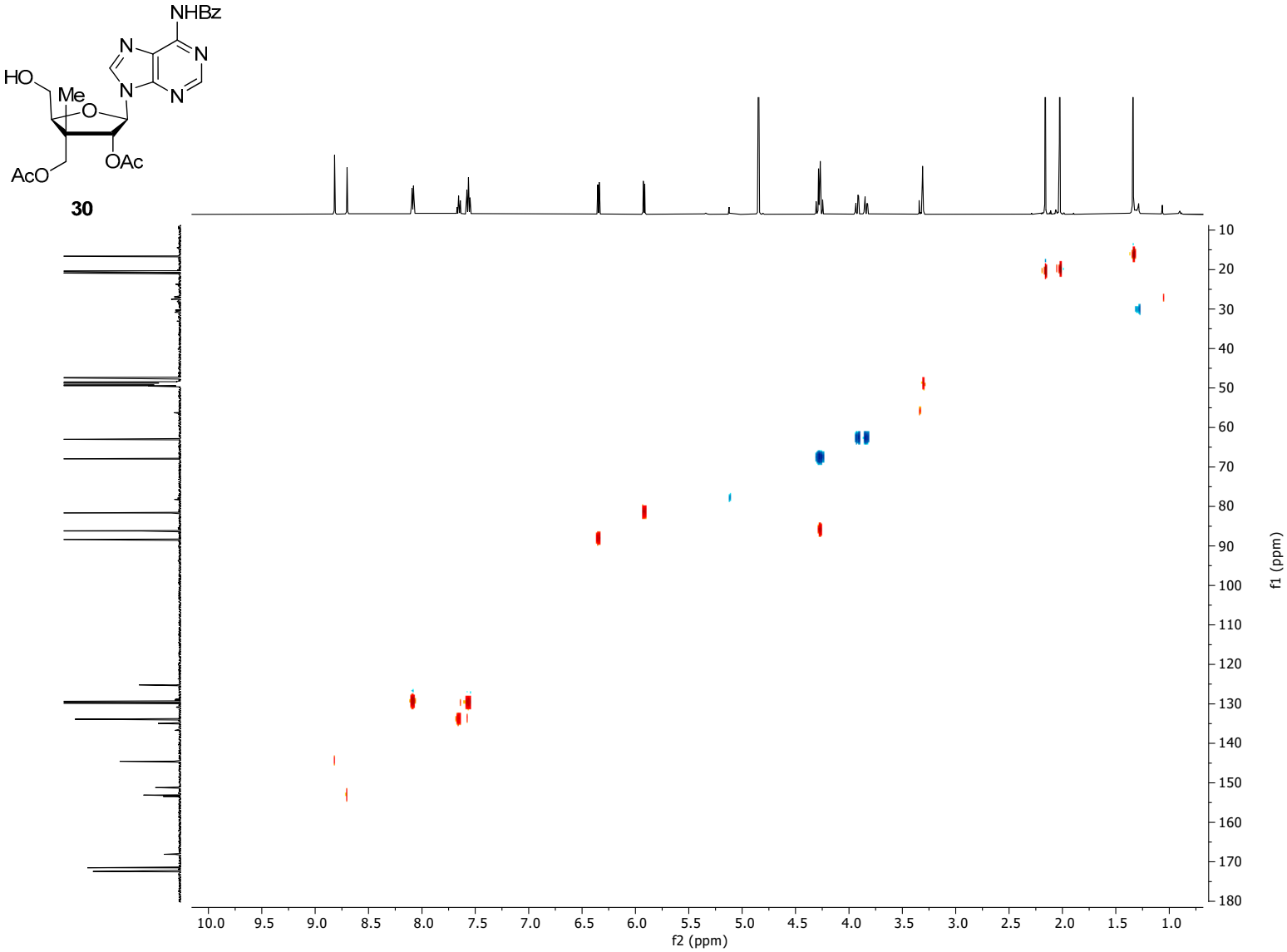
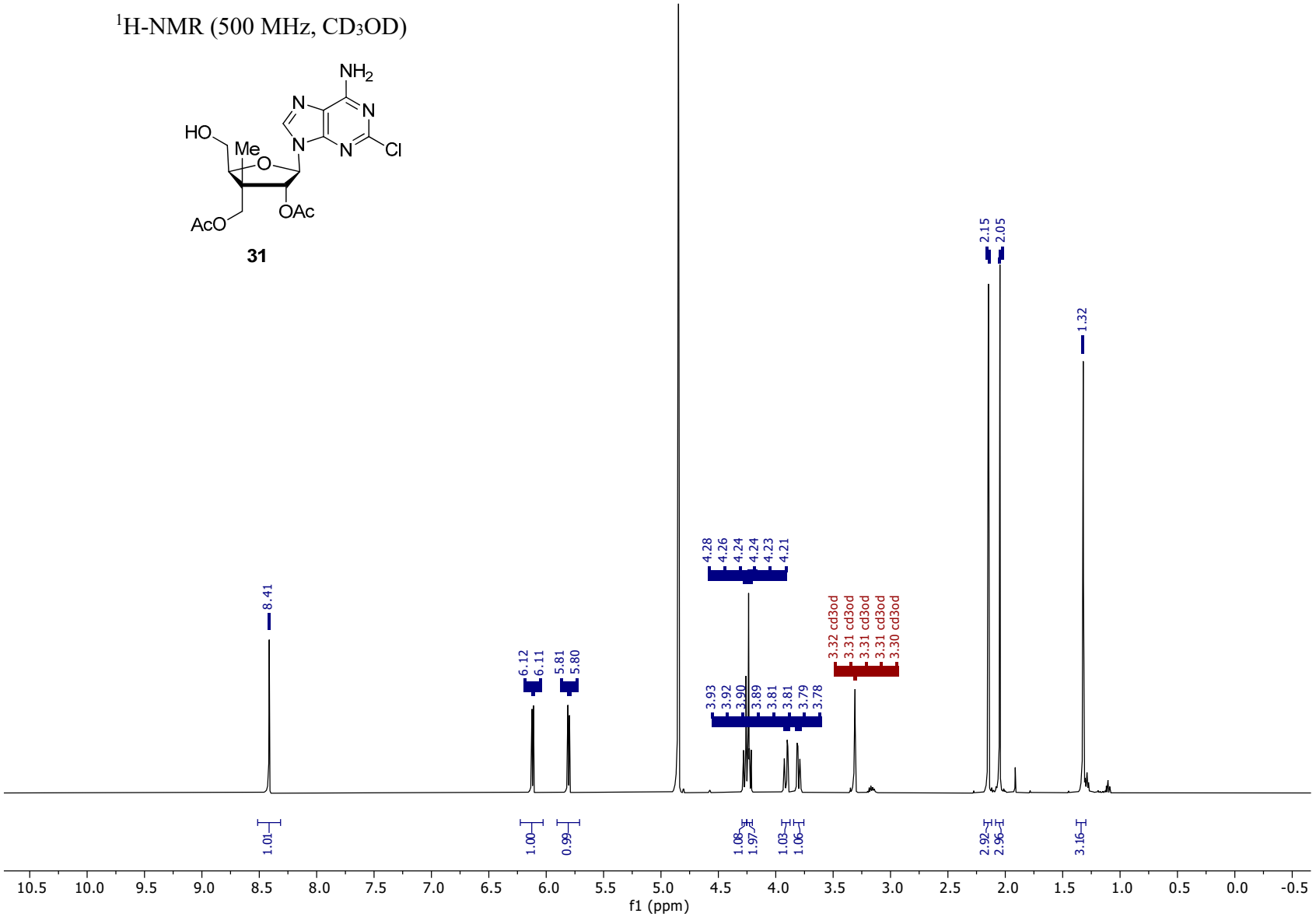


HSQC (500 MHz, CD_3OD)



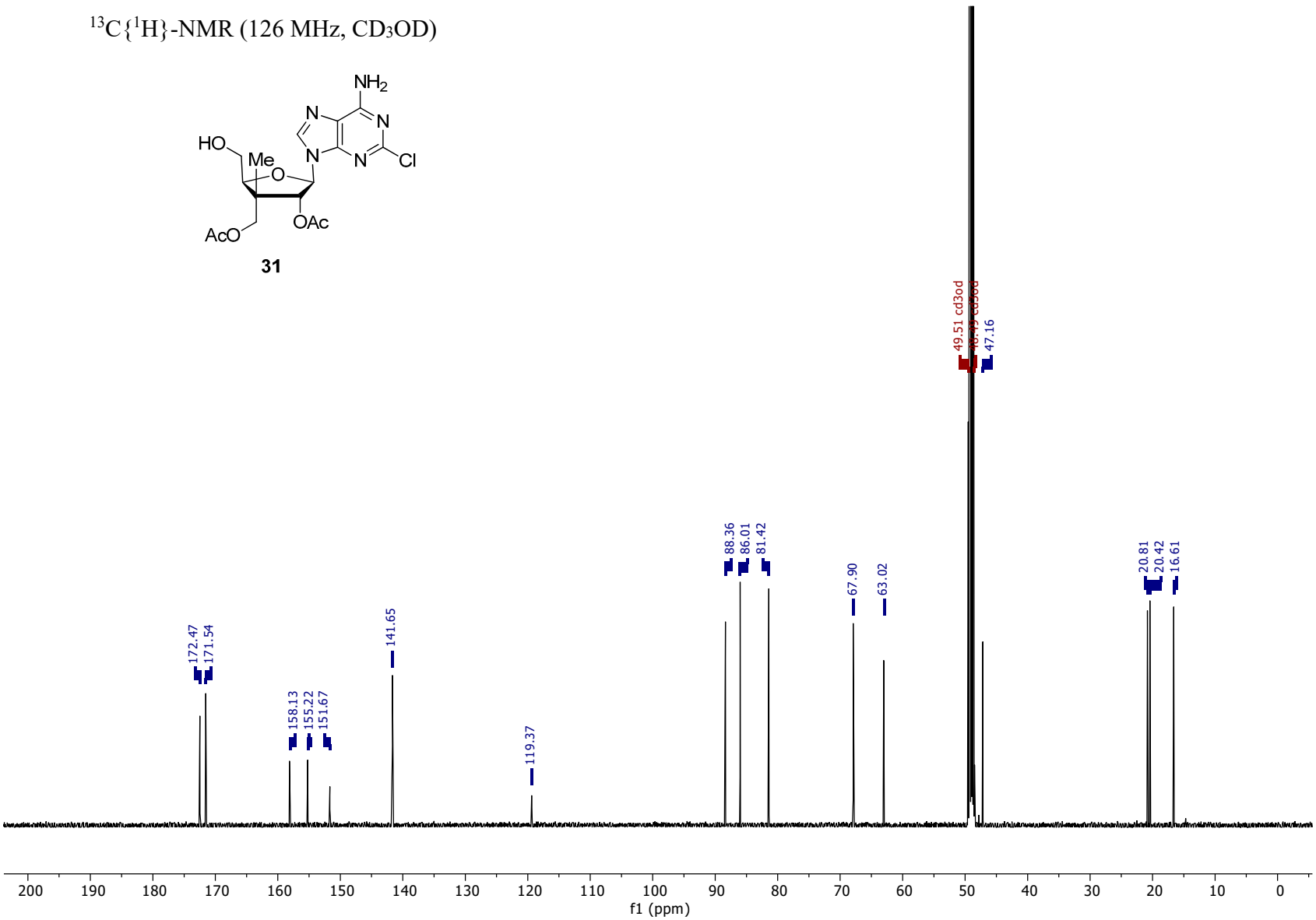
^{1}H-NMR (500 MHz, CD_3OD)

31

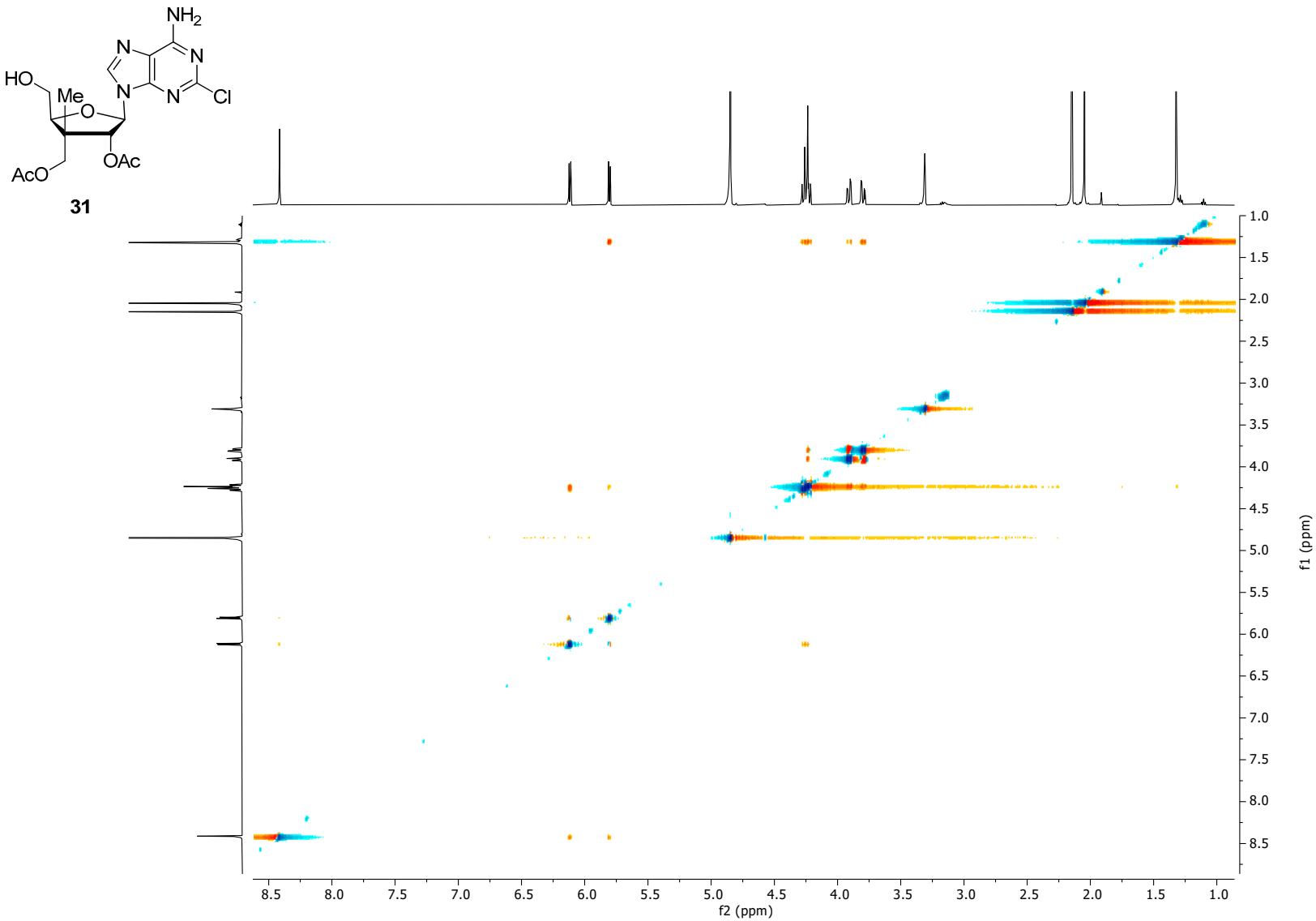


$^{13}C\{^{1}H\}$-NMR (126 MHz, CD_3OD)

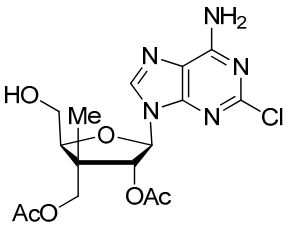
31



NOESY (500 MHz, CD_3OD)



HMBC (500 MHz, CD_3OD)



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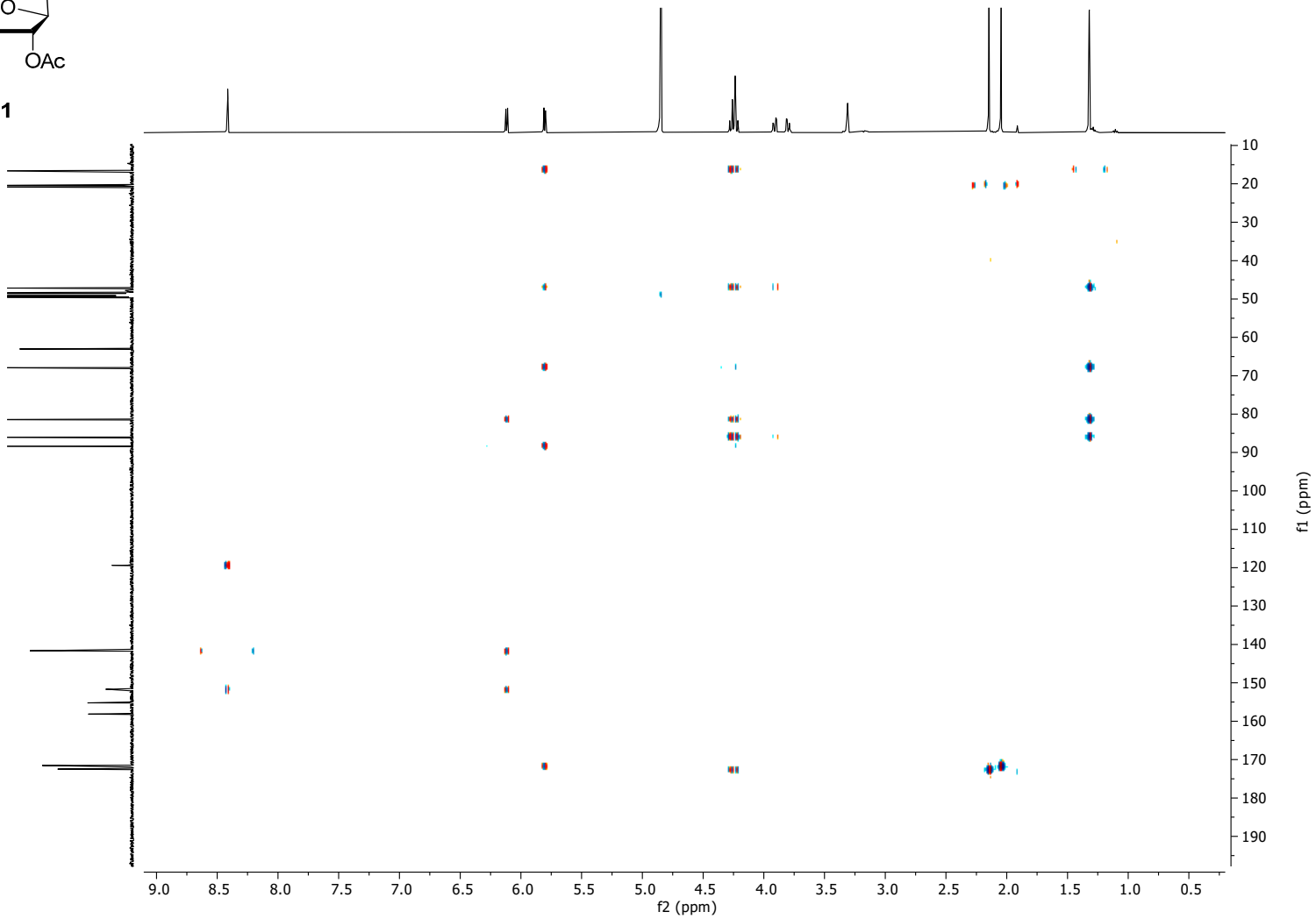
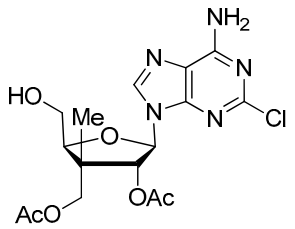


HSQC (500 MHz, CD_3OD)



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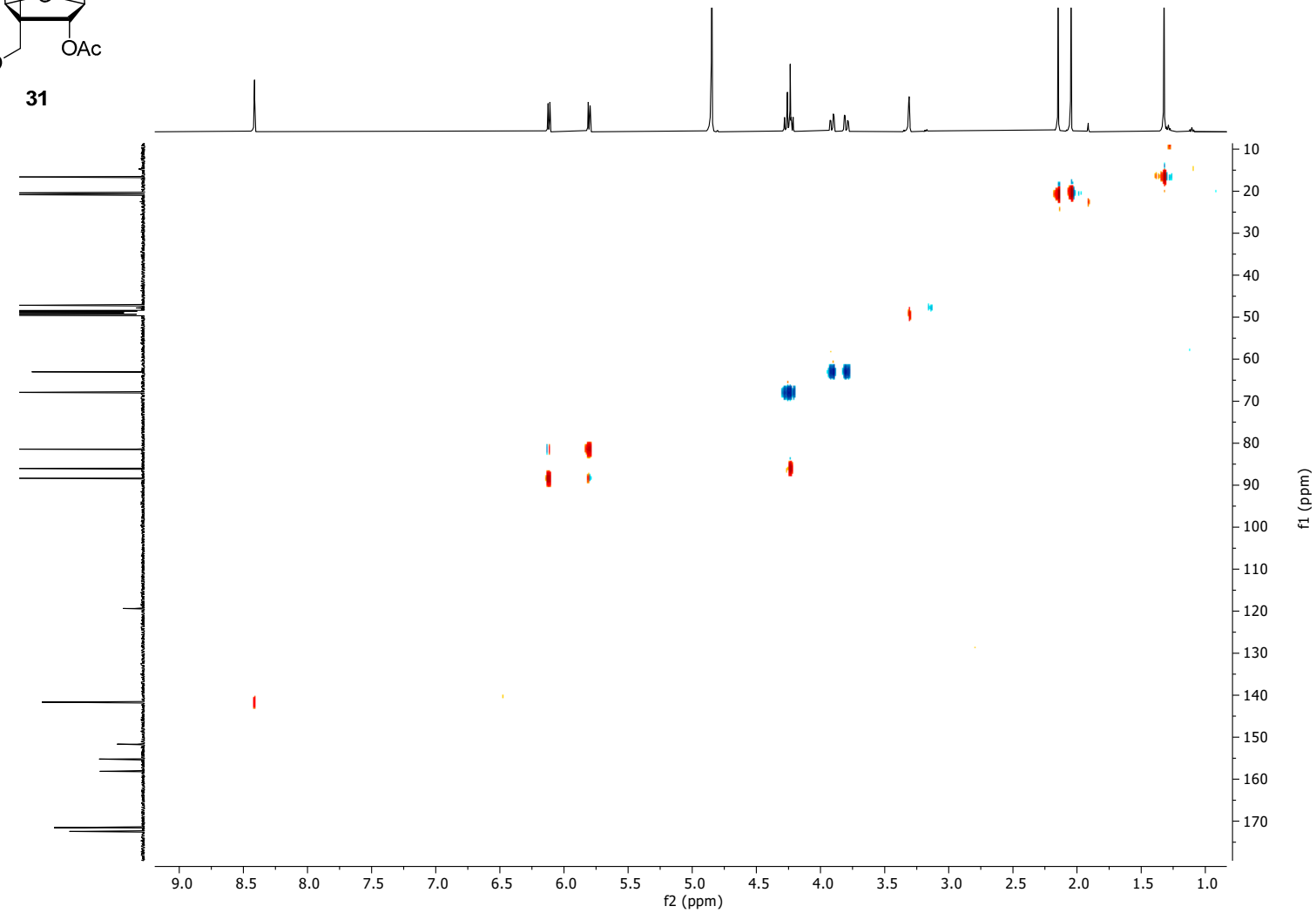
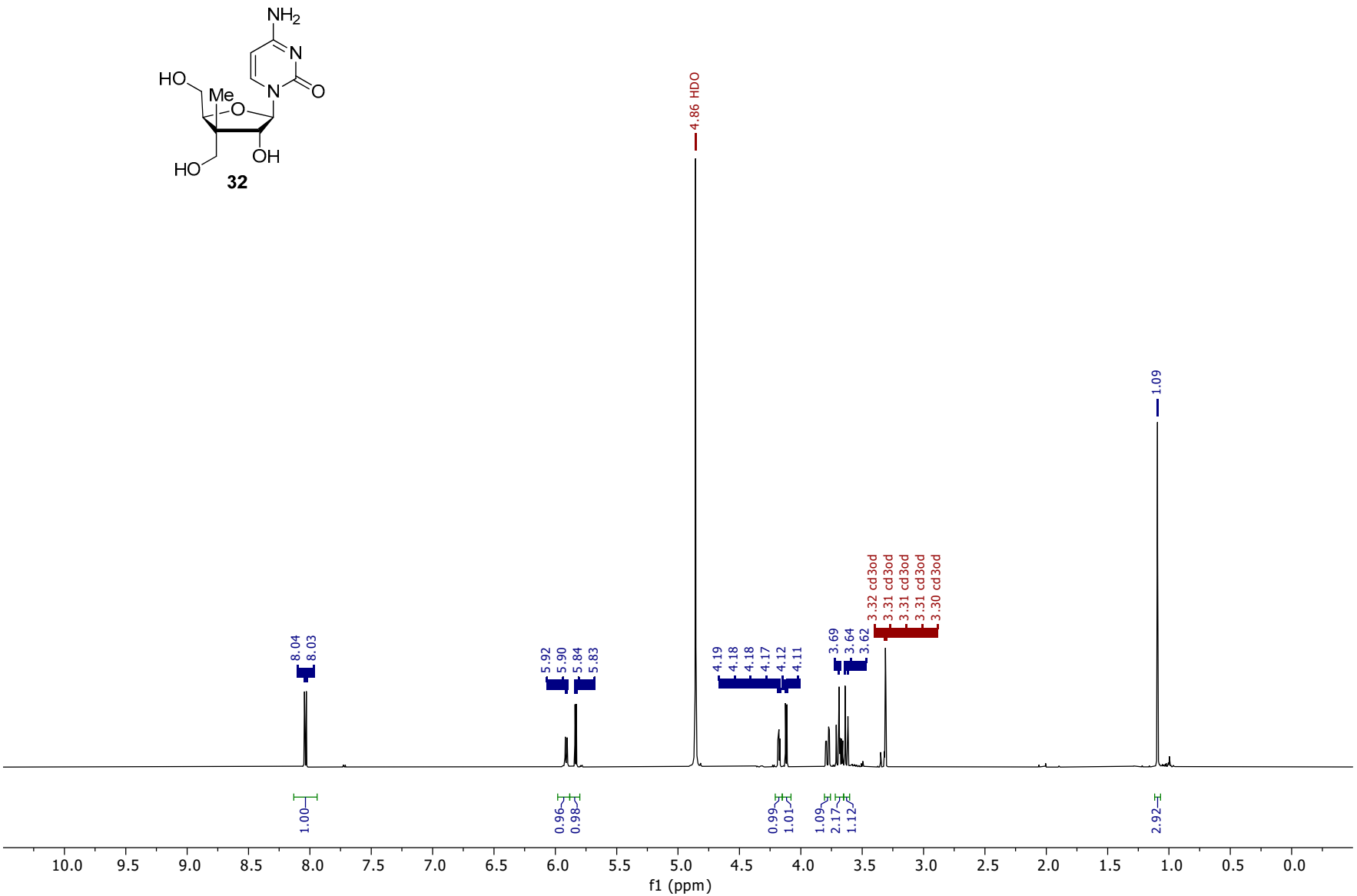
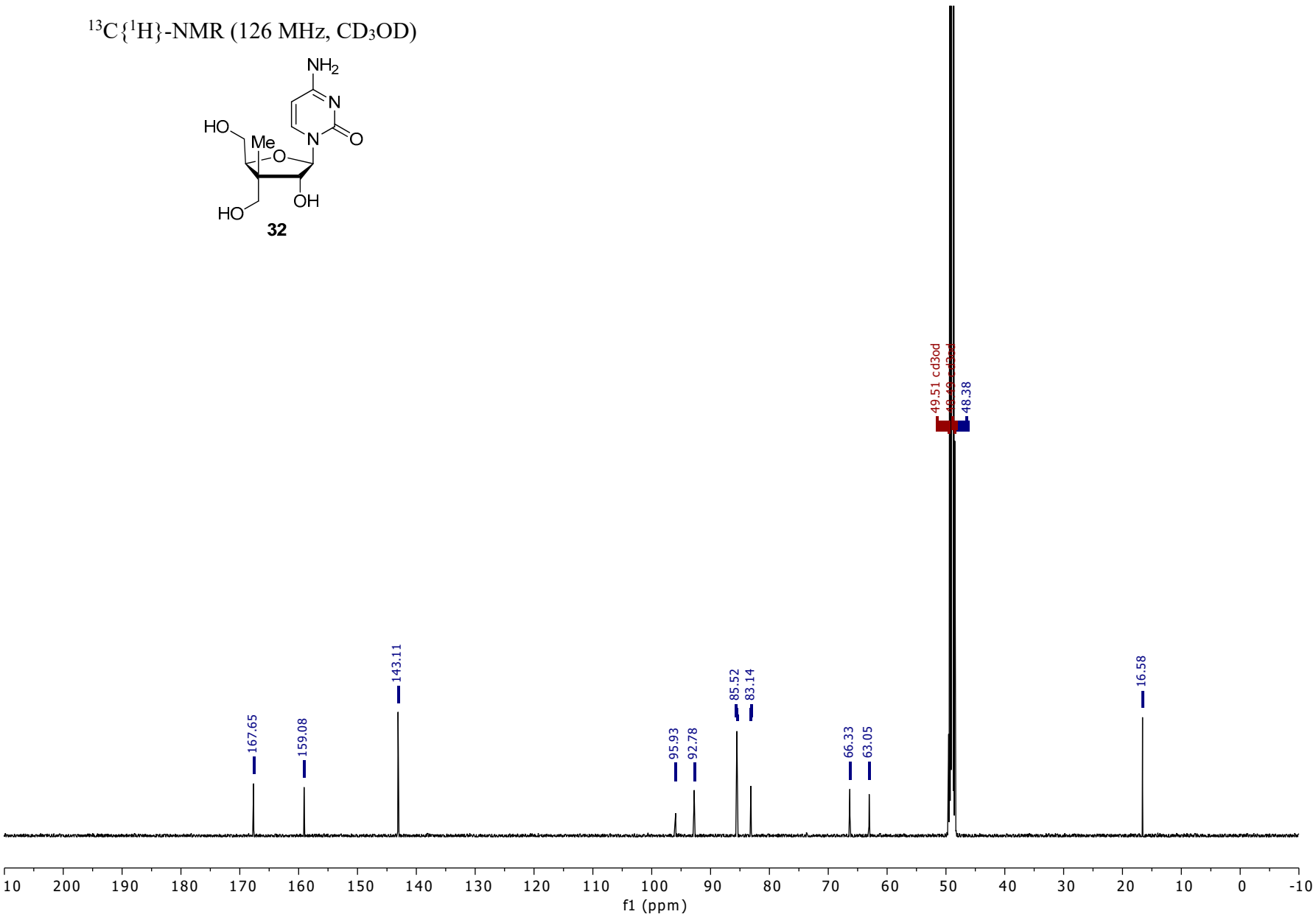


^{1}H-NMR (500 MHz, CD_3OD)



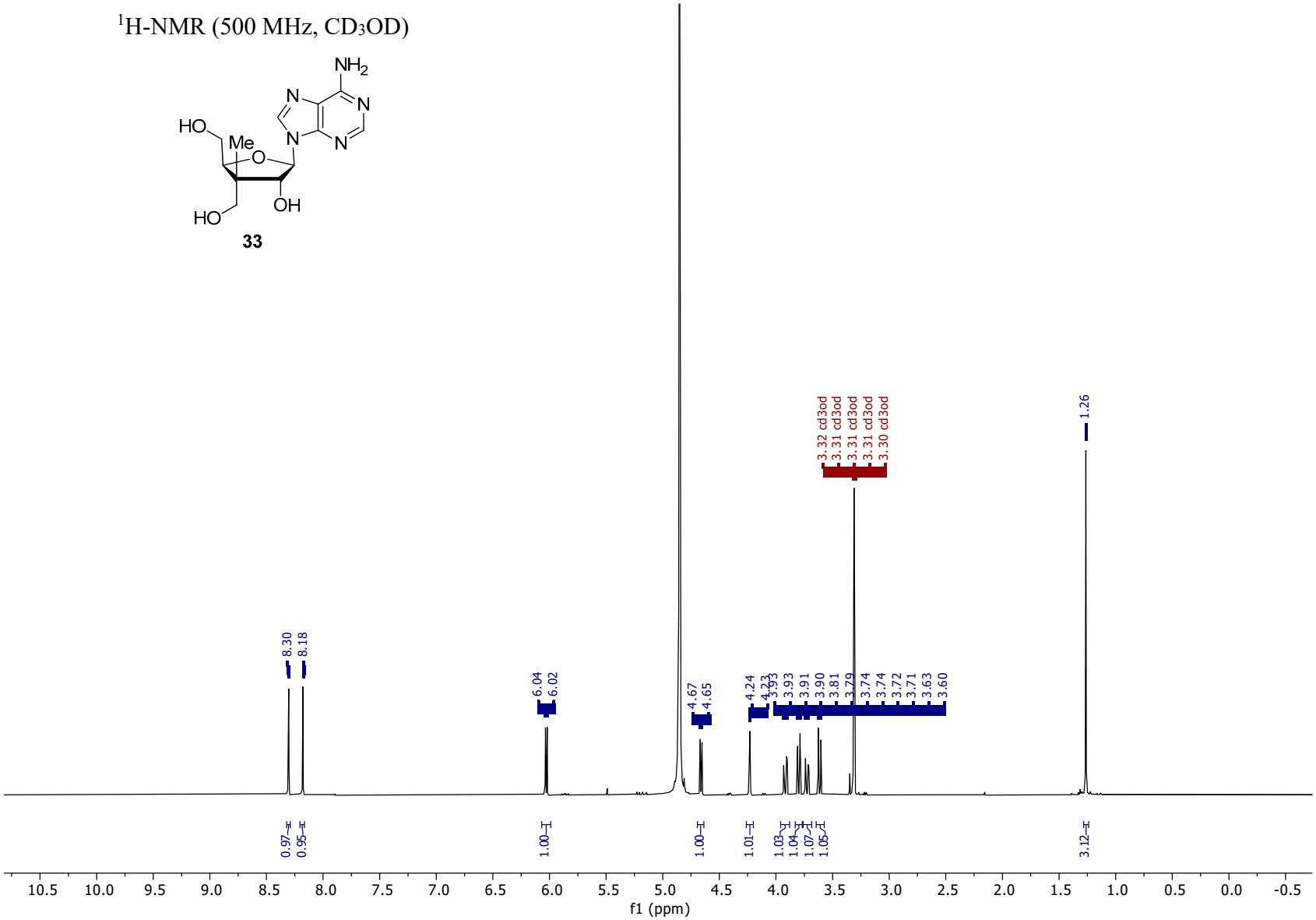
$^{13}C\{^{1}H\}$-NMR (126 MHz, CD_3OD)

32



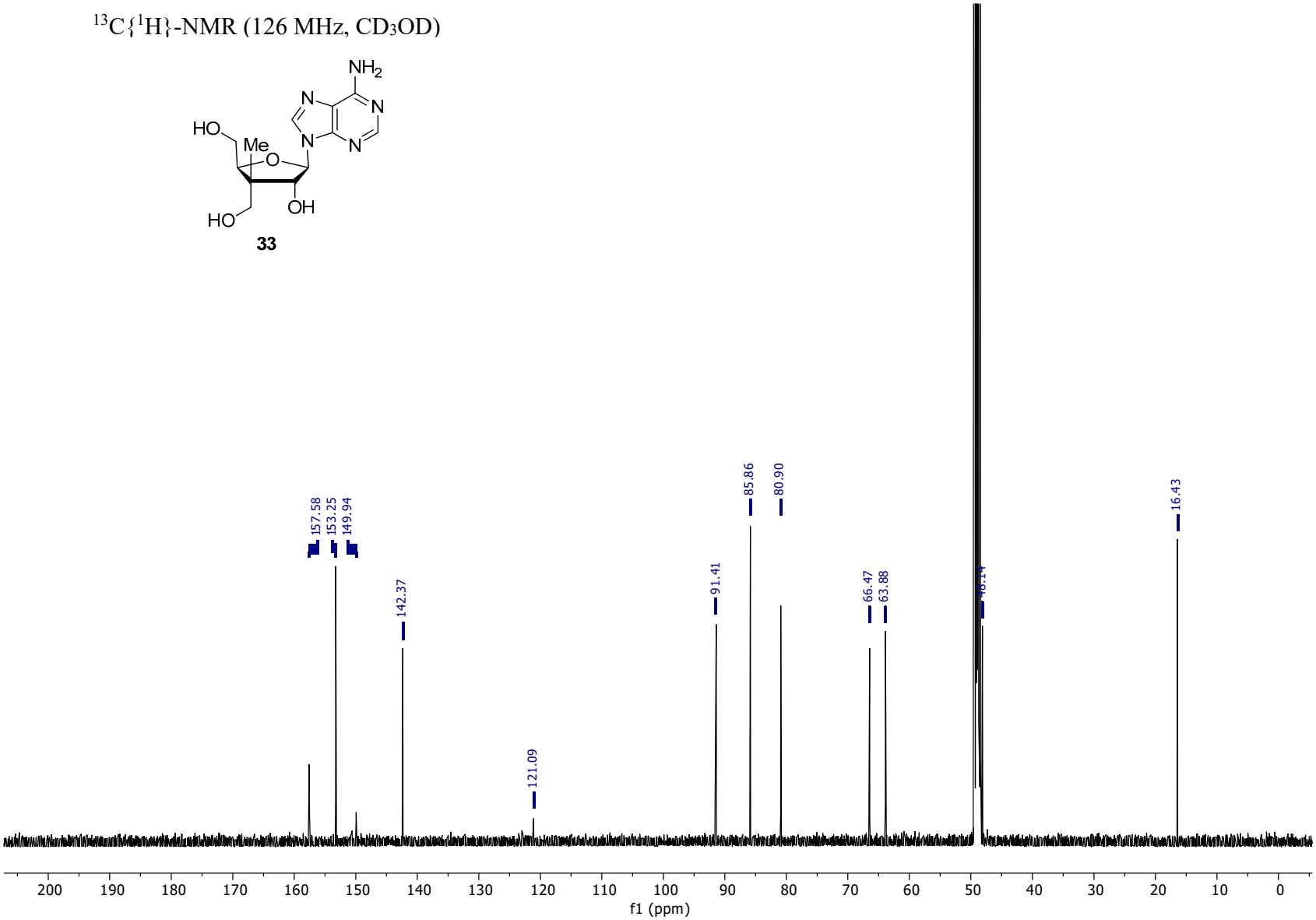
^{1}H-NMR (500 MHz, CD_3OD)

33

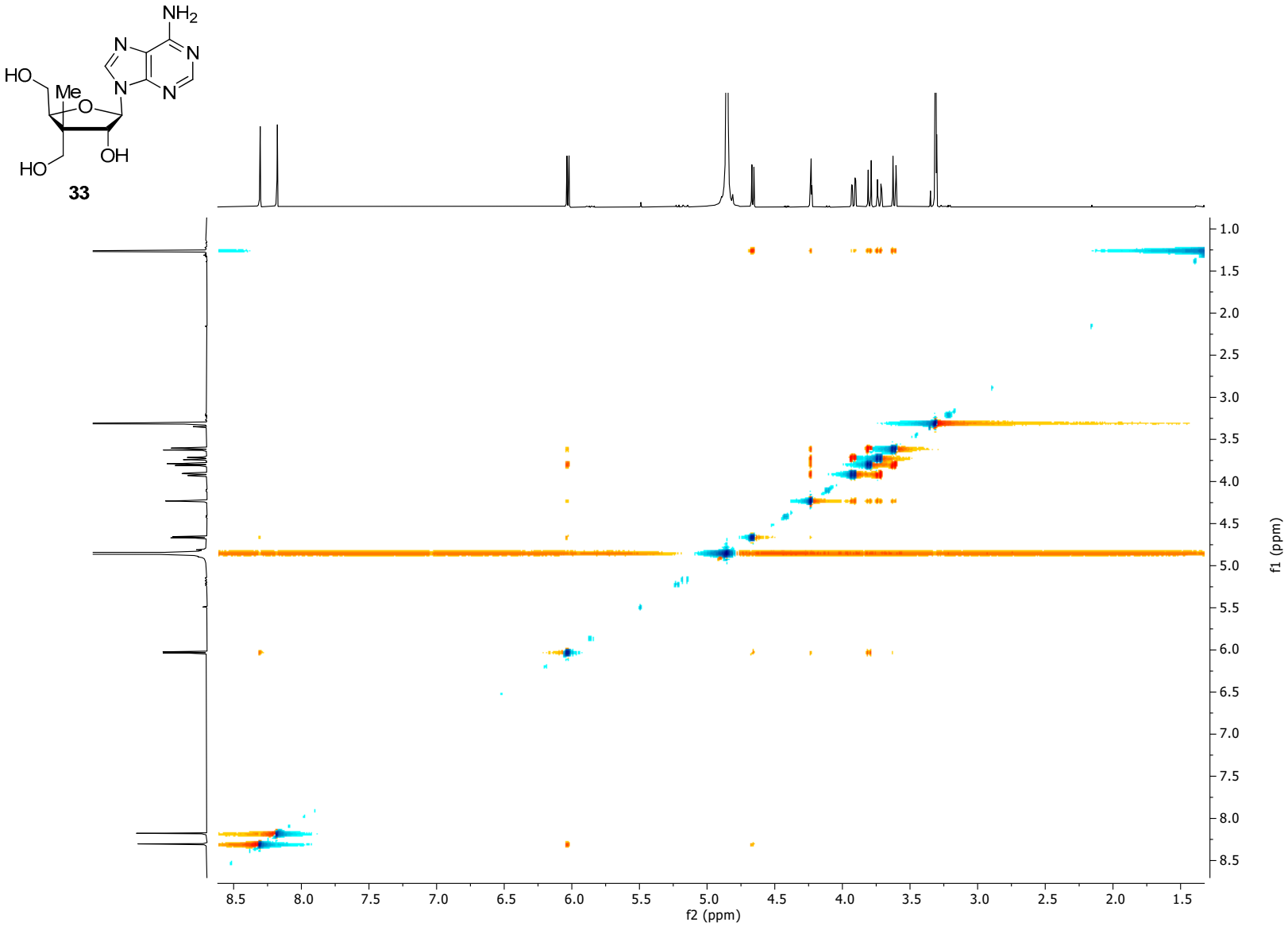


$^{13}C\{^{1}H\}$-NMR (126 MHz, CD_3OD)

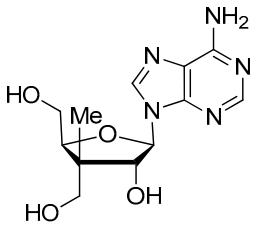
33



NOESY (500 MHz, CD_3OD)



HMBC (500 MHz, CD_3OD)



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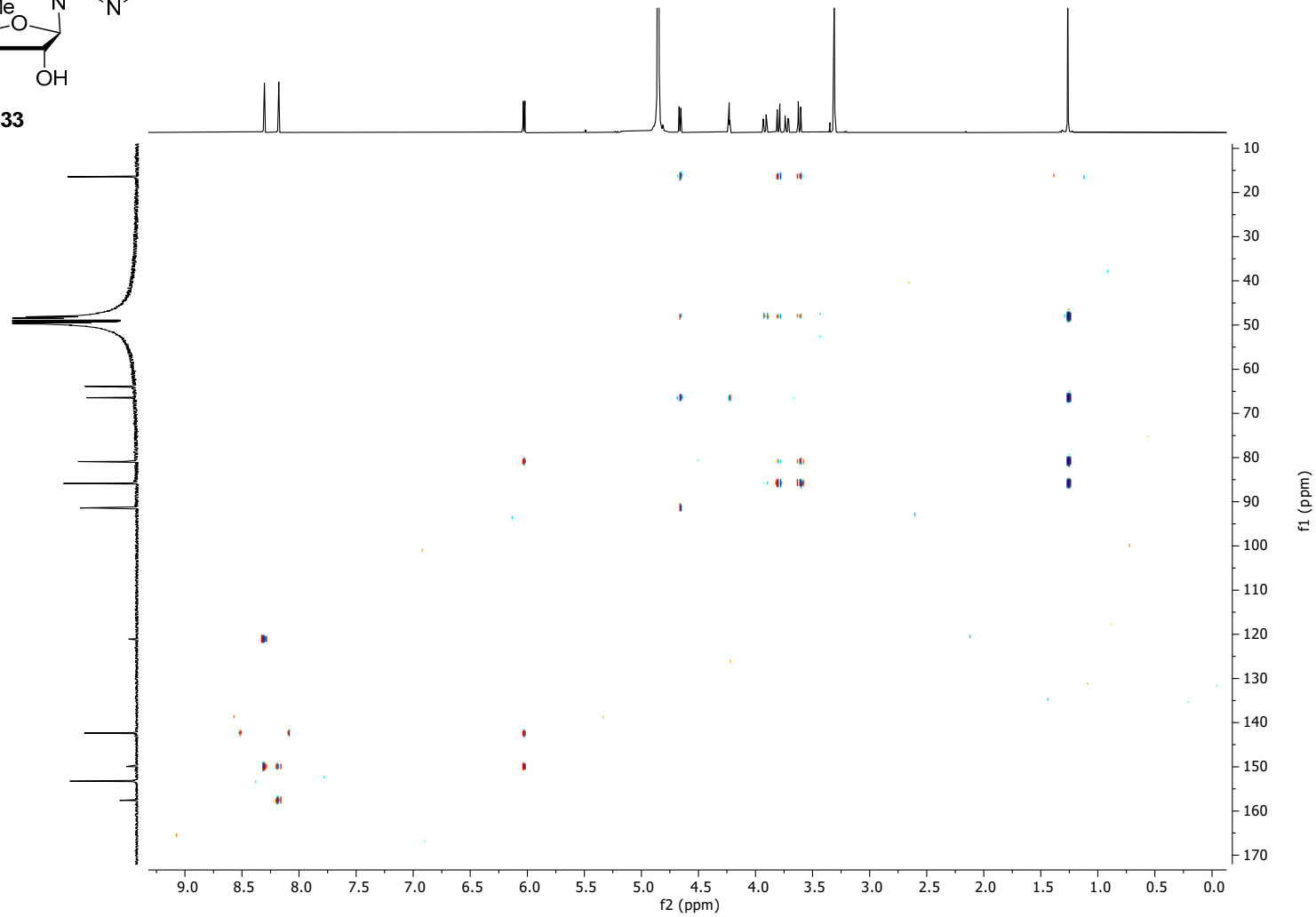
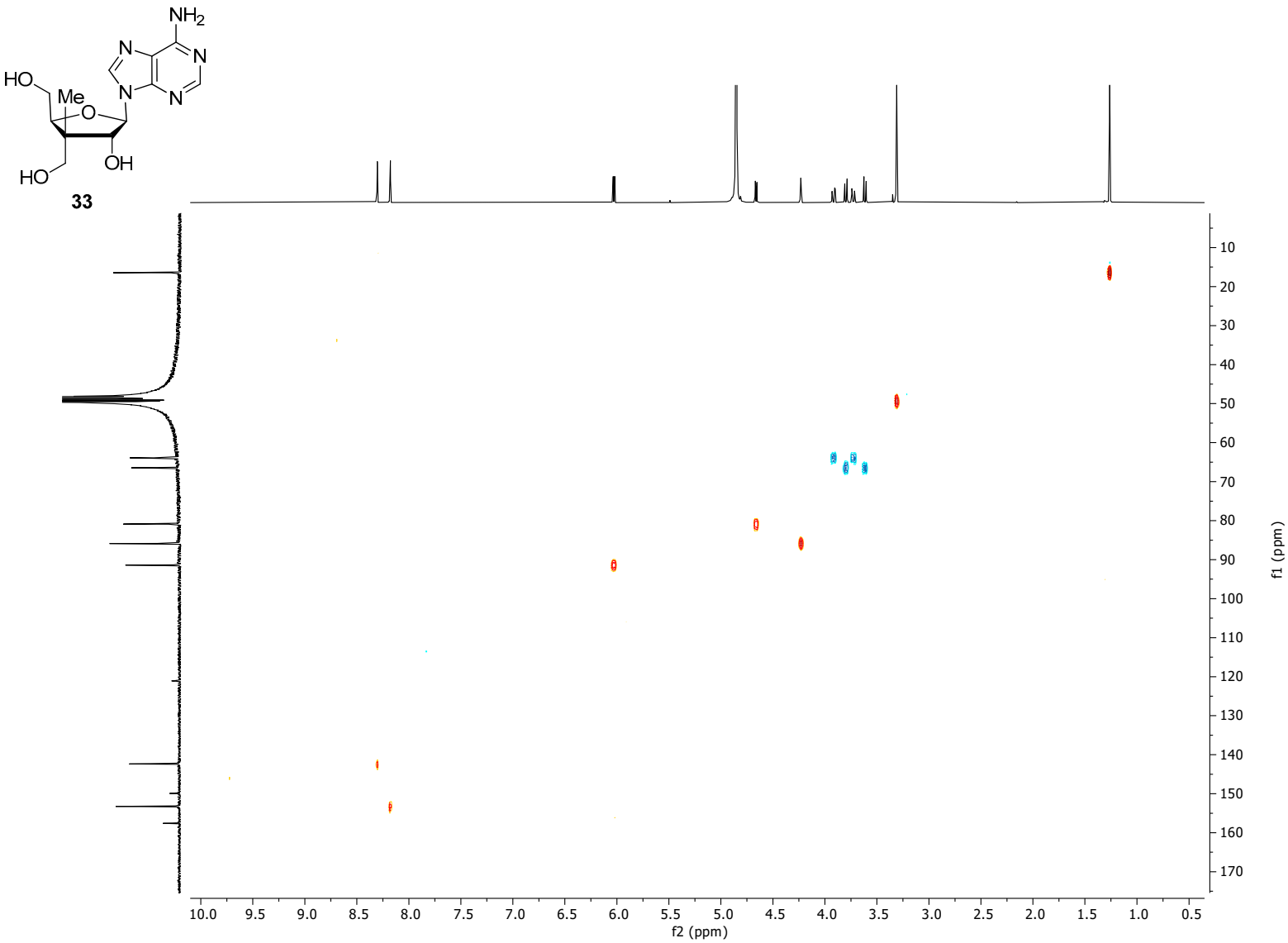
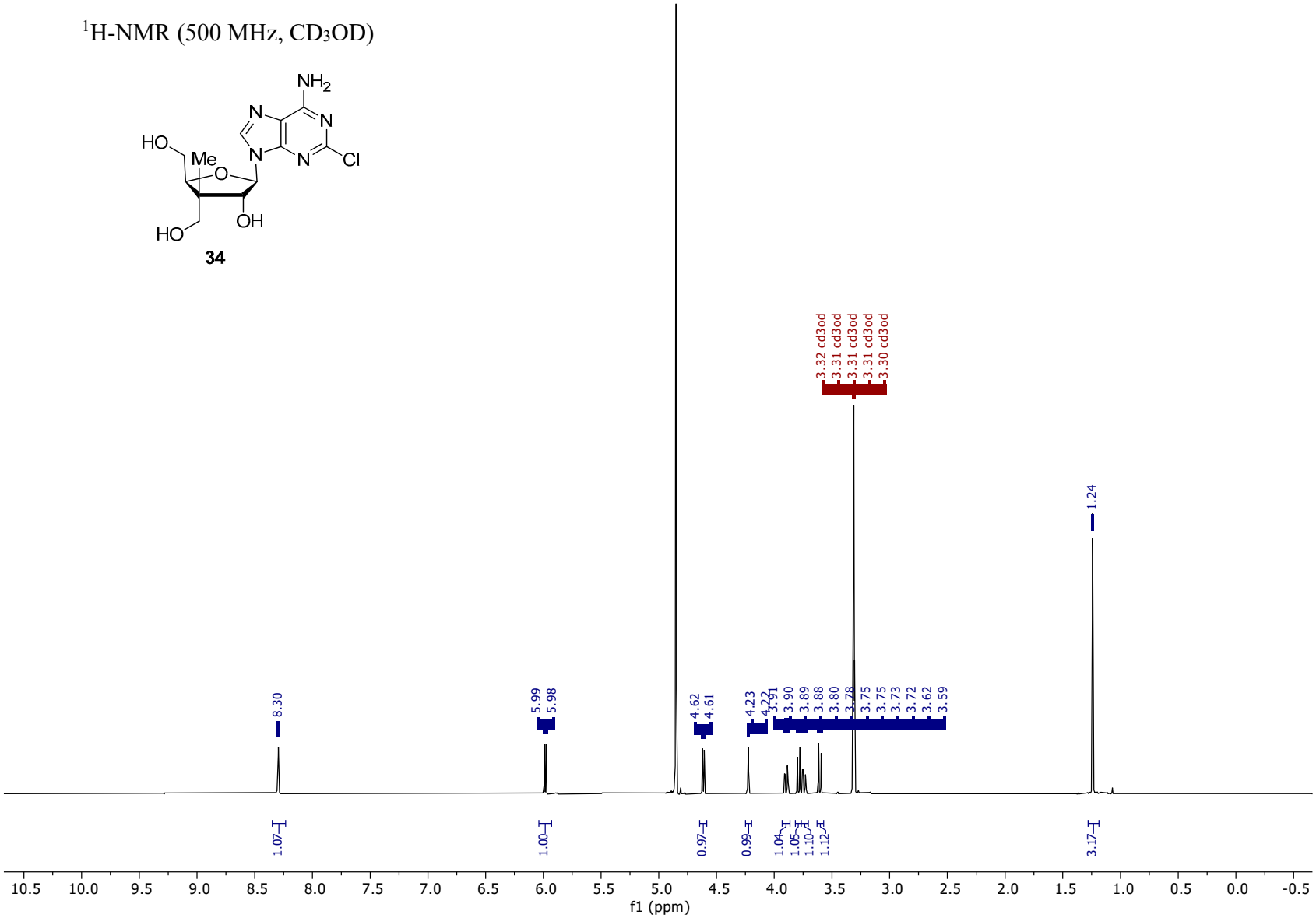


HSQC (500 MHz, CD_3OD)



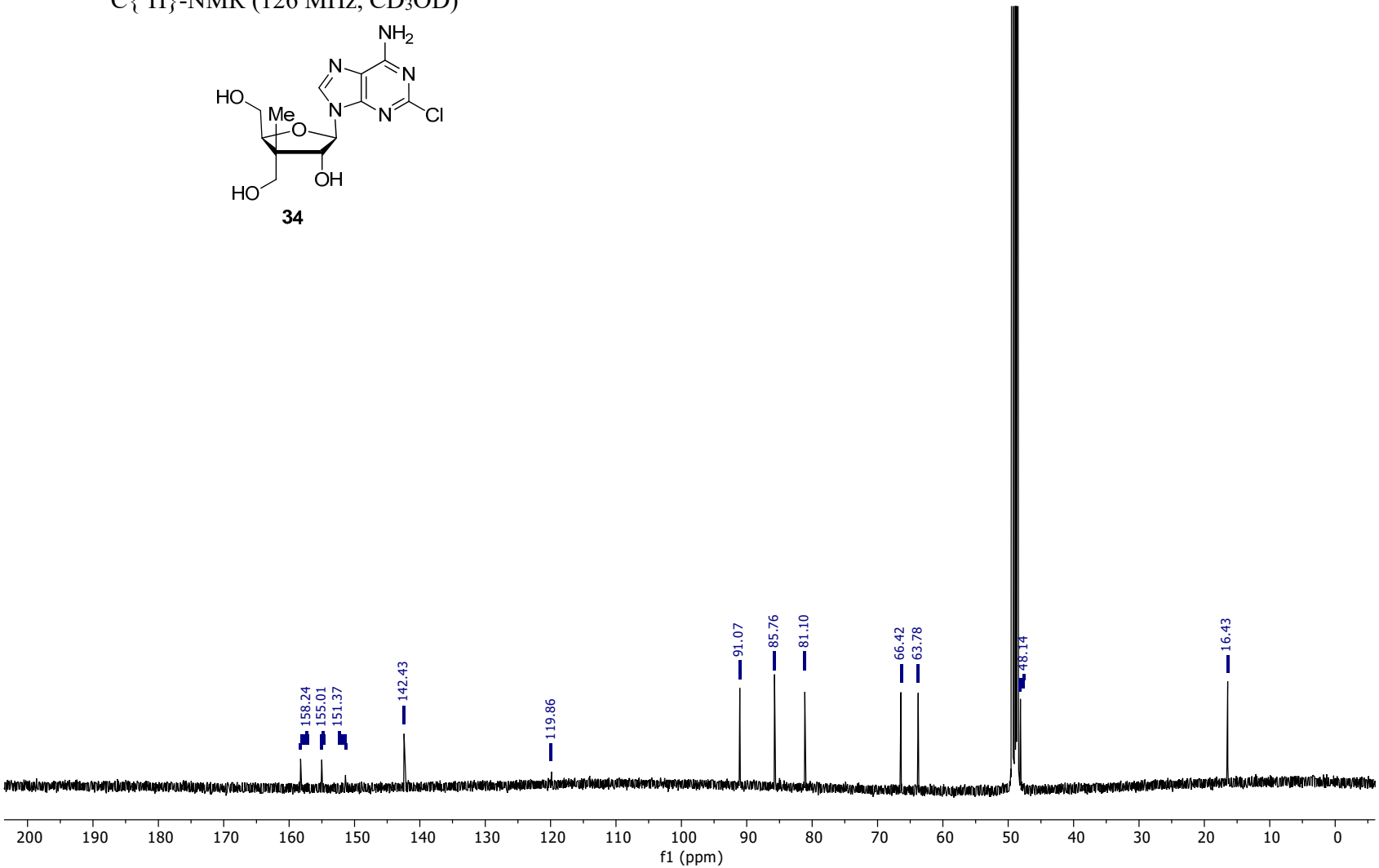
^{1}H-NMR (500 MHz, CD_3OD)

34

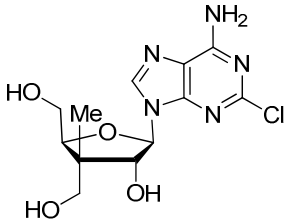


$^{13}C\{^{1}H\}$-NMR (126 MHz, CD_3OD)

34



NOESY (500 MHz, CD_3OD)



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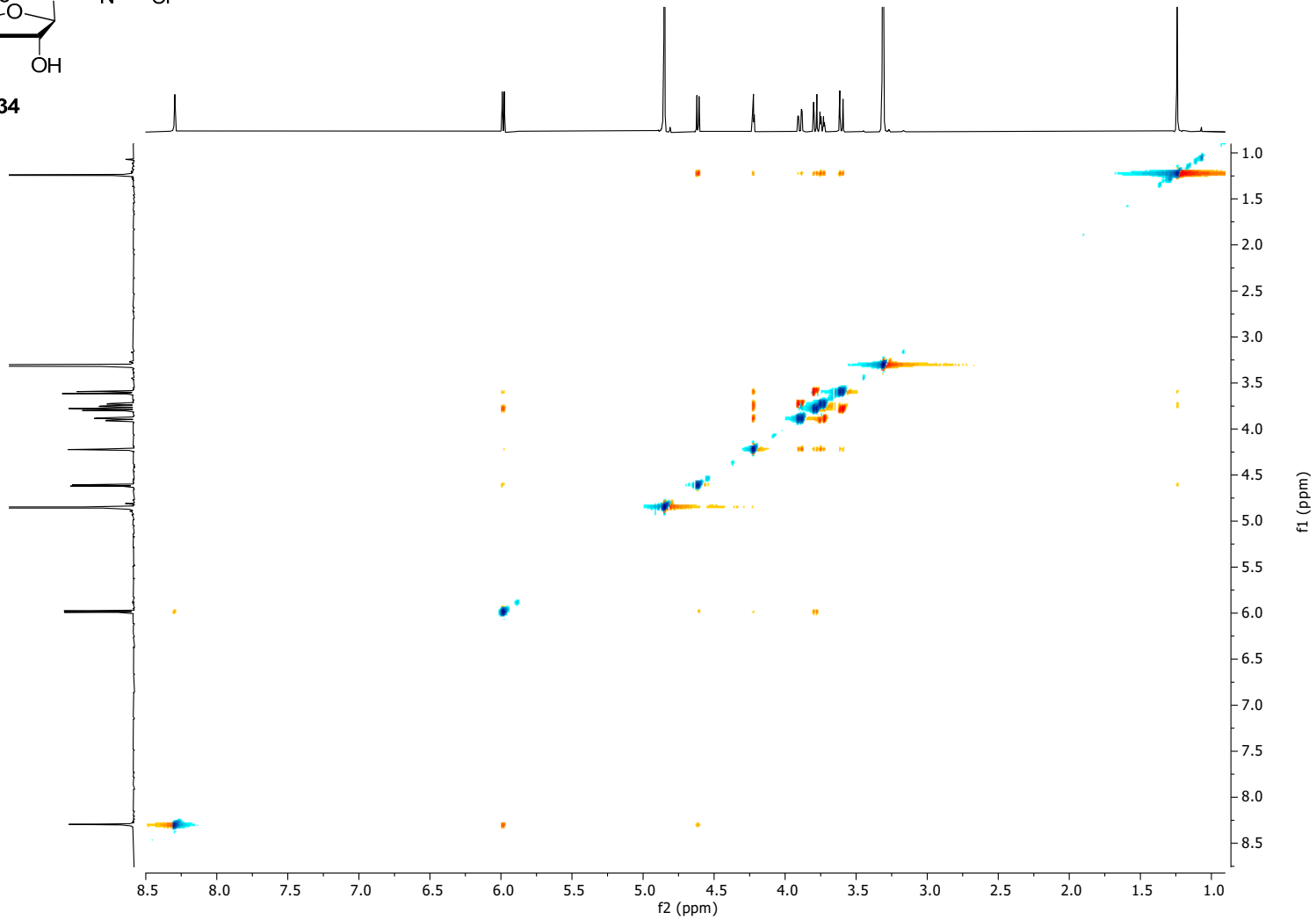
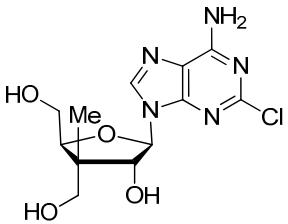


HMBC (500 MHz, CD_3OD)



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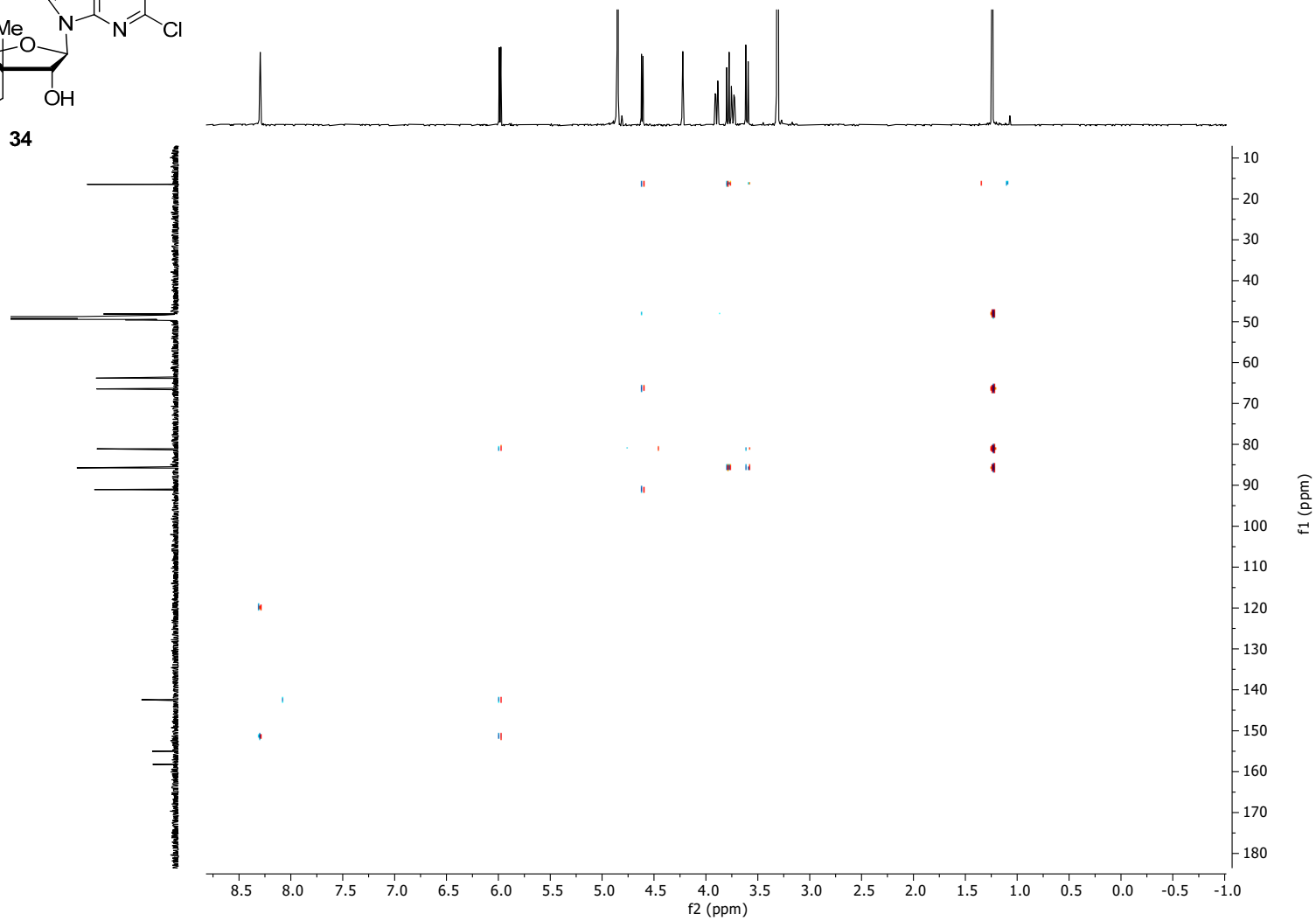
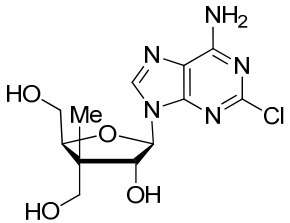


HSQC (500 MHz, CD_3OD)



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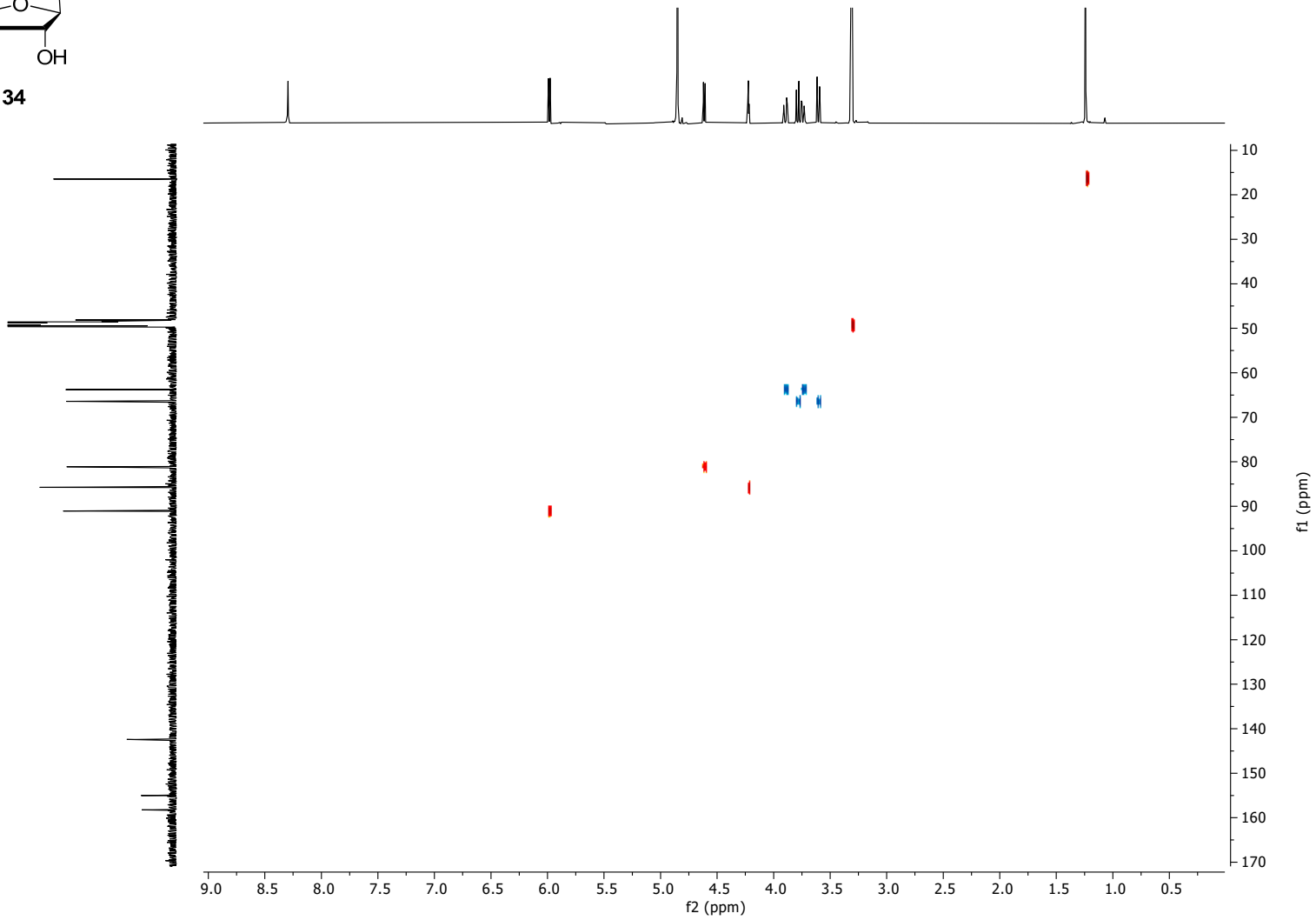
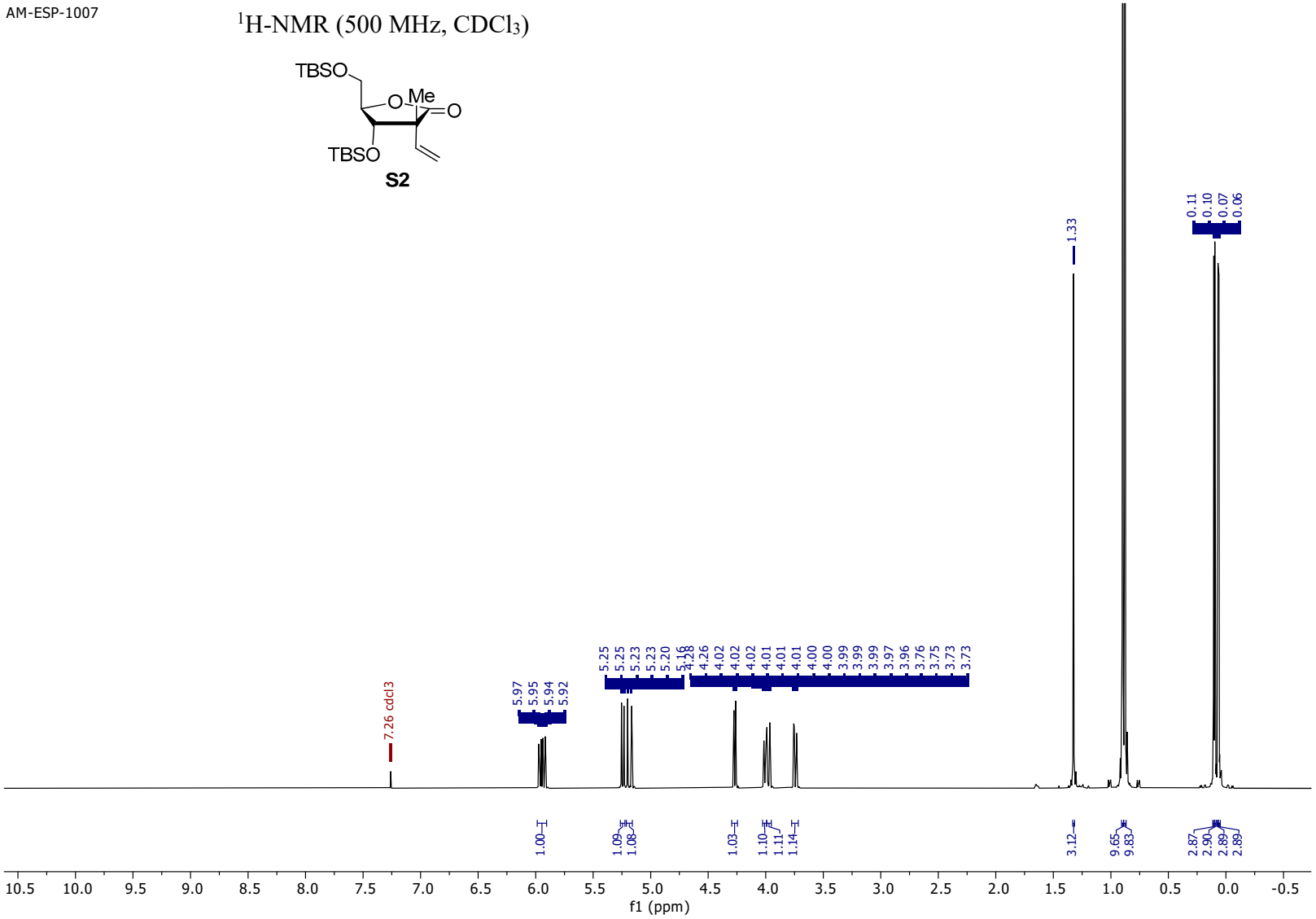


AM-ESP-1007

^{1}H-NMR (500 MHz, $CDCl_3$)

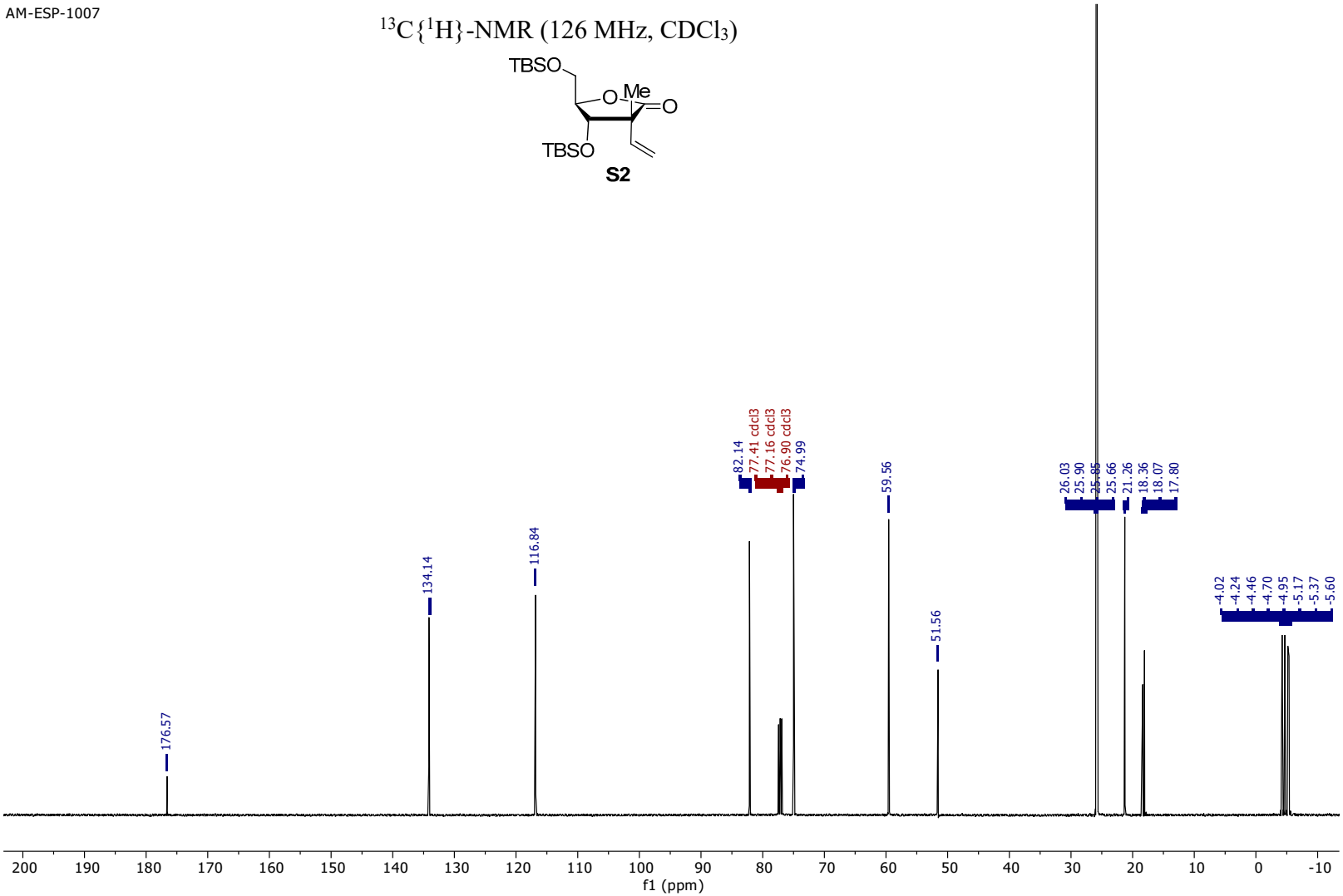
S2



AM-ESP-1007

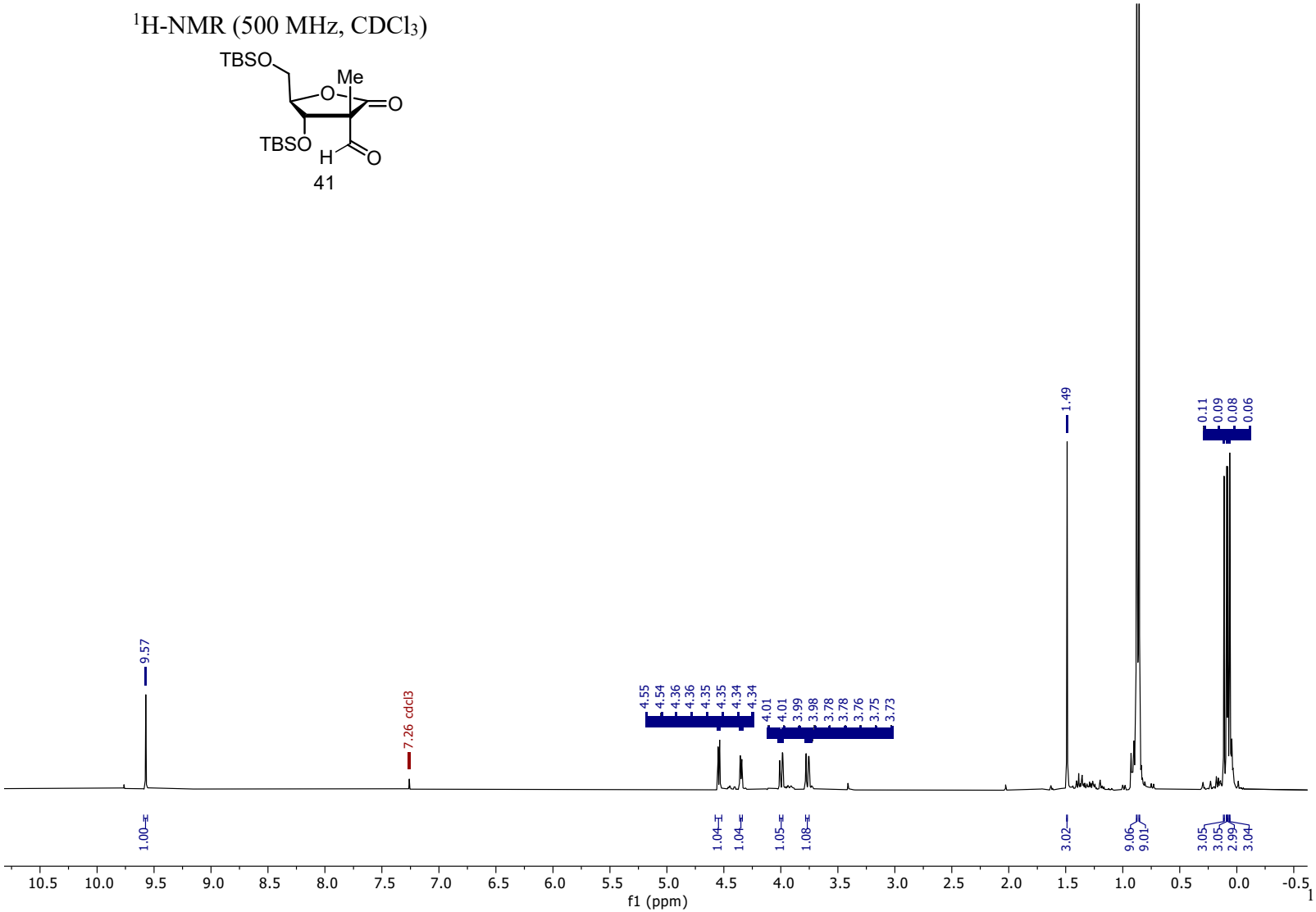
$^{13}C\{^{1}H\}$-NMR (126 MHz, $CDCl_3$)

S2



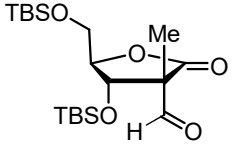
^{1}H-NMR (500 MHz, $CDCl_3$)

41

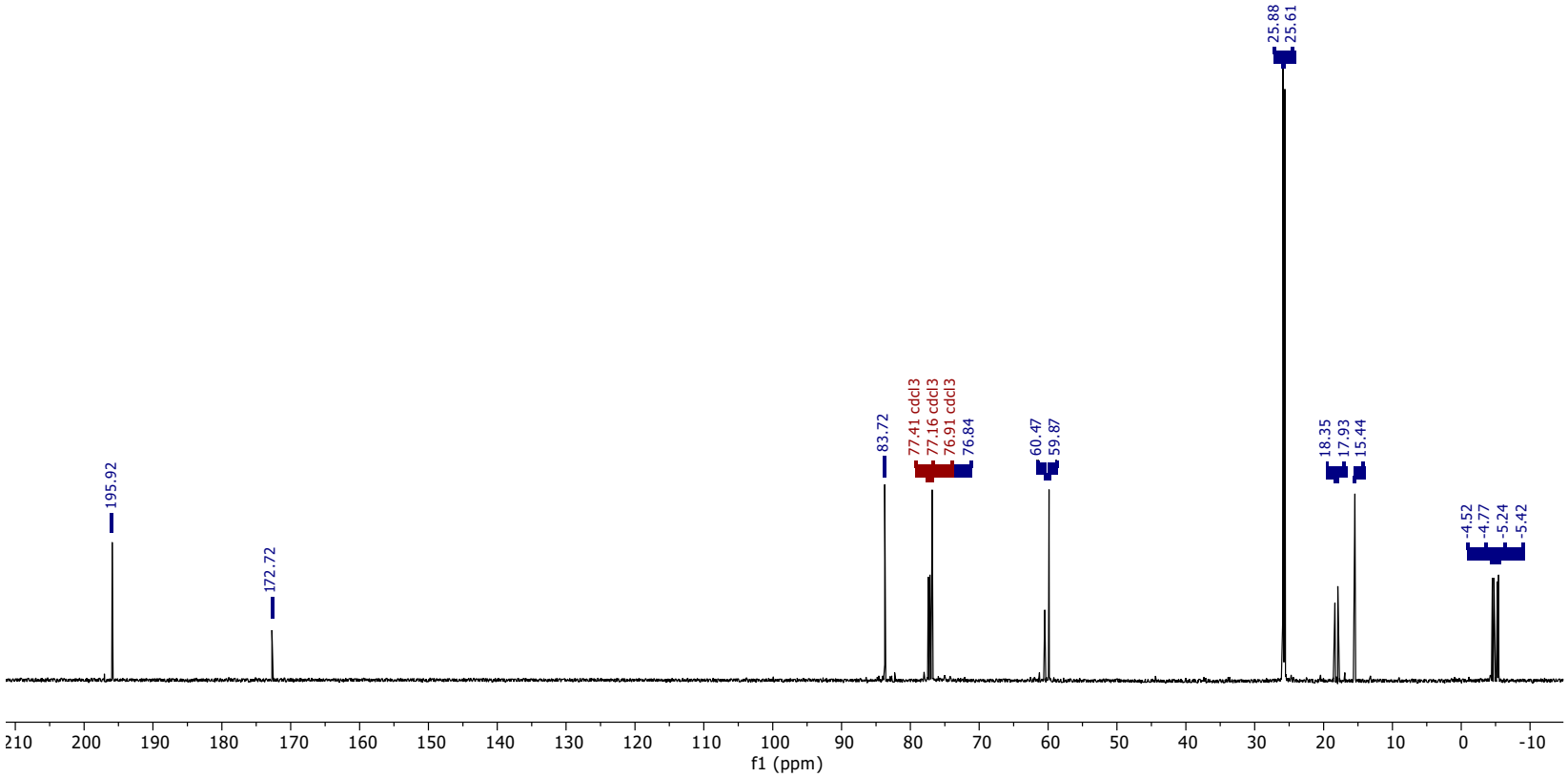


AM-ESP-873

$^{13}C\{^{1}H\}$-NMR (126 MHz, $CDCl_3$)



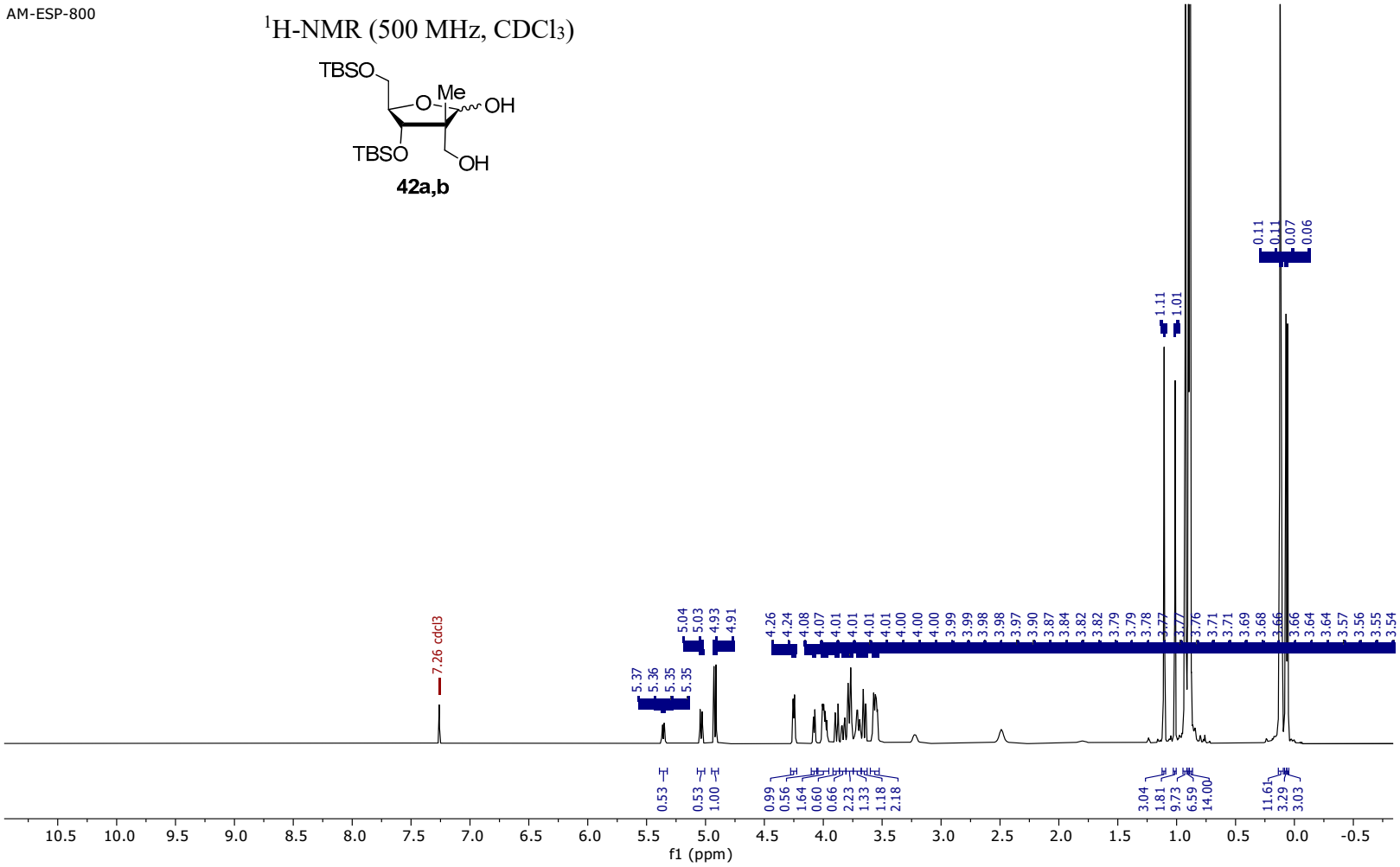
41



AM-ESP-800

^{1}H-NMR (500 MHz, $CDCl_3$)

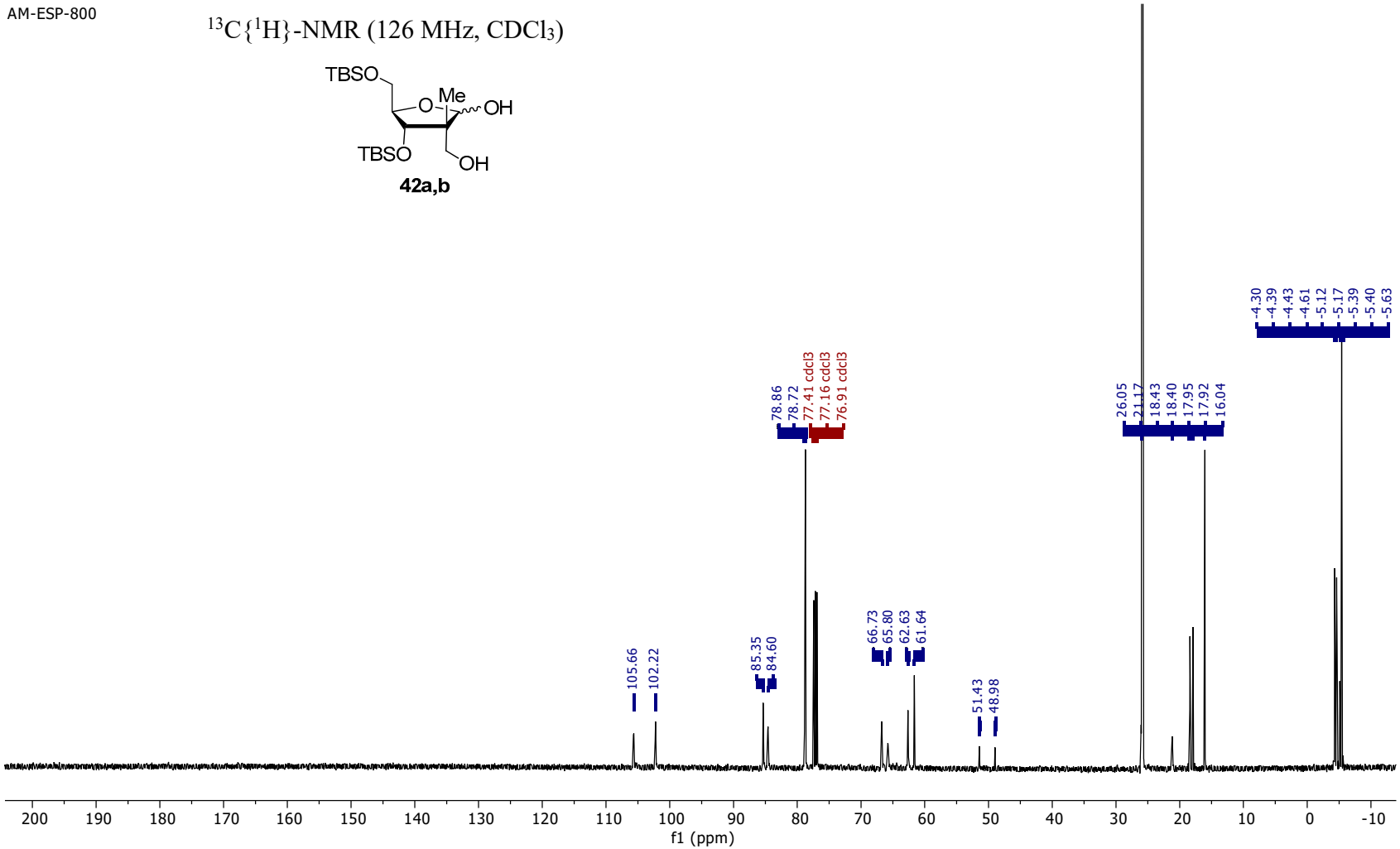
42a,b



AM-ESP-800

$^{13}C\{^{1}H\}$-NMR (126 MHz, $CDCl_3$)

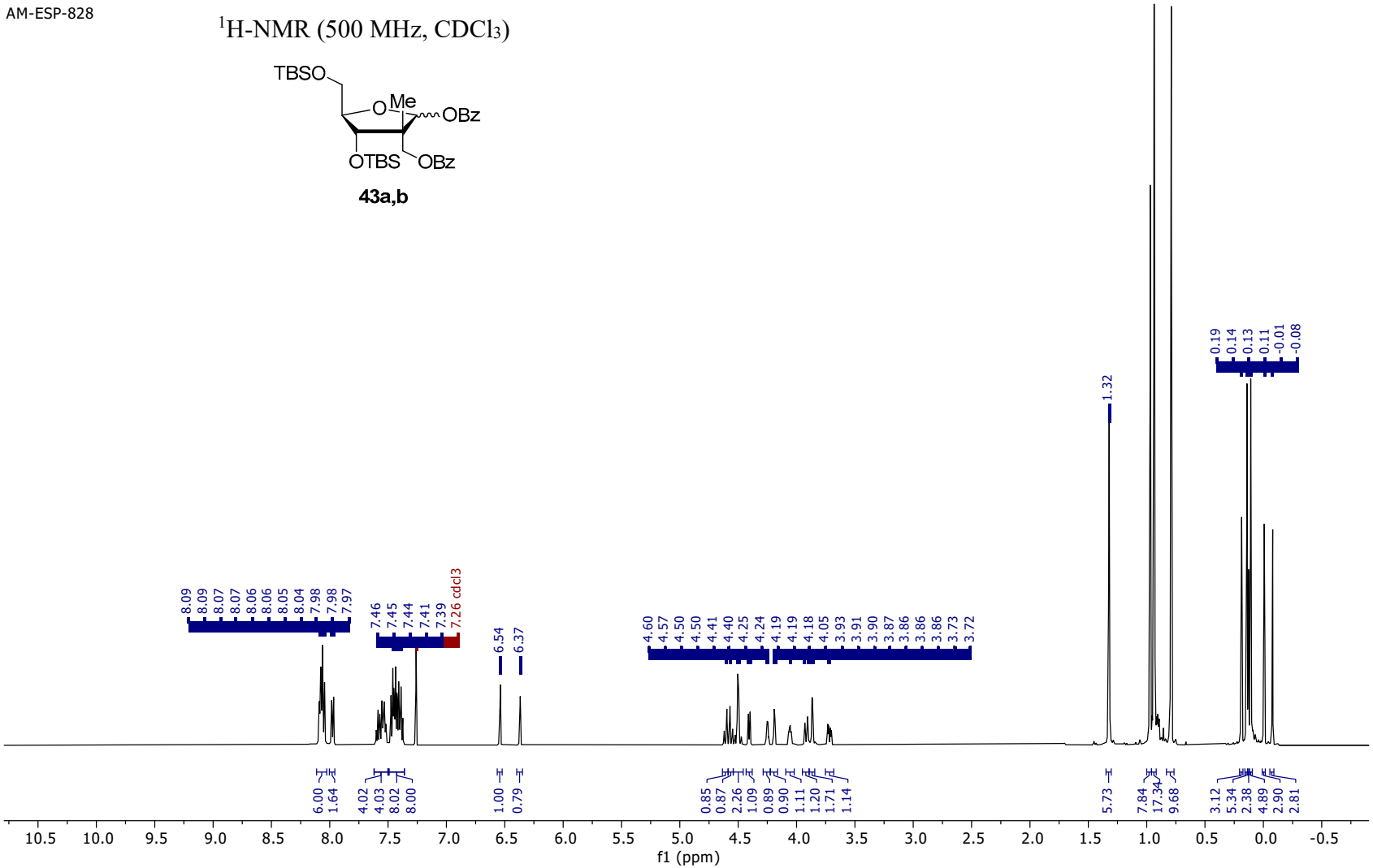
42a,b



AM-ESP-828

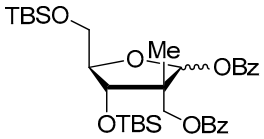
^{1}H-NMR (500 MHz, $CDCl_3$)

43a,b

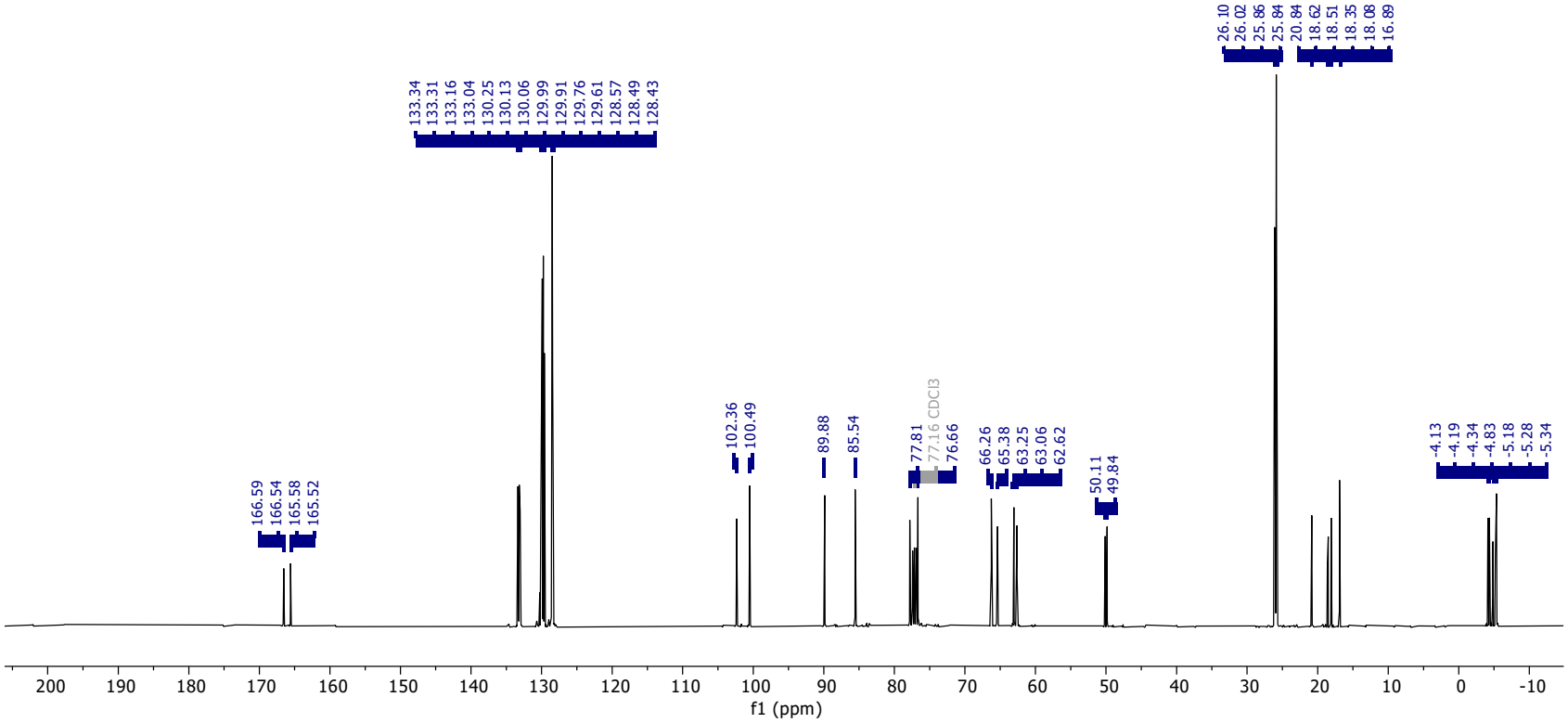


AM-ESP-828

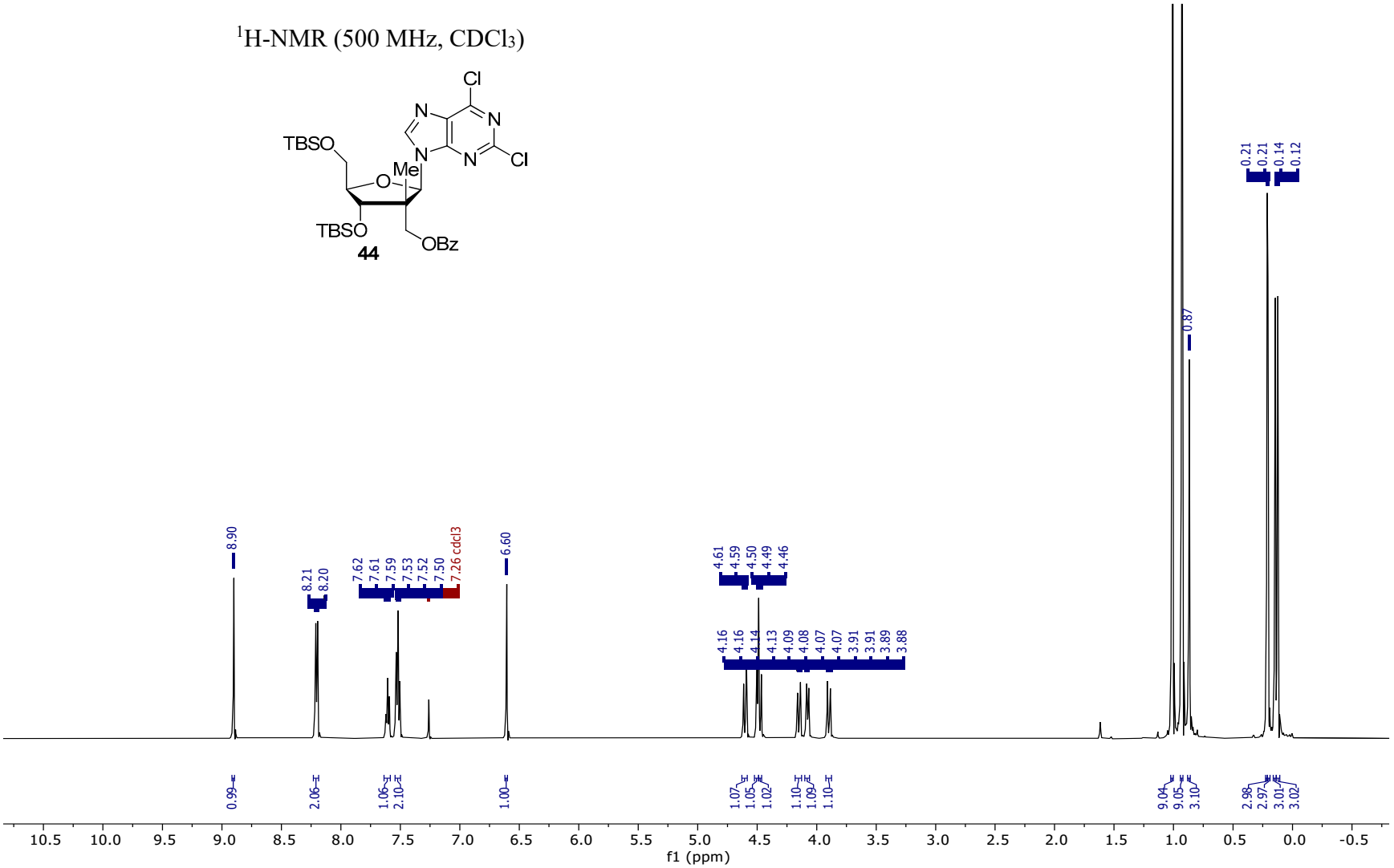
$^{13}C\{^{1}H\}$-NMR (126 MHz, $CDCl_3$)



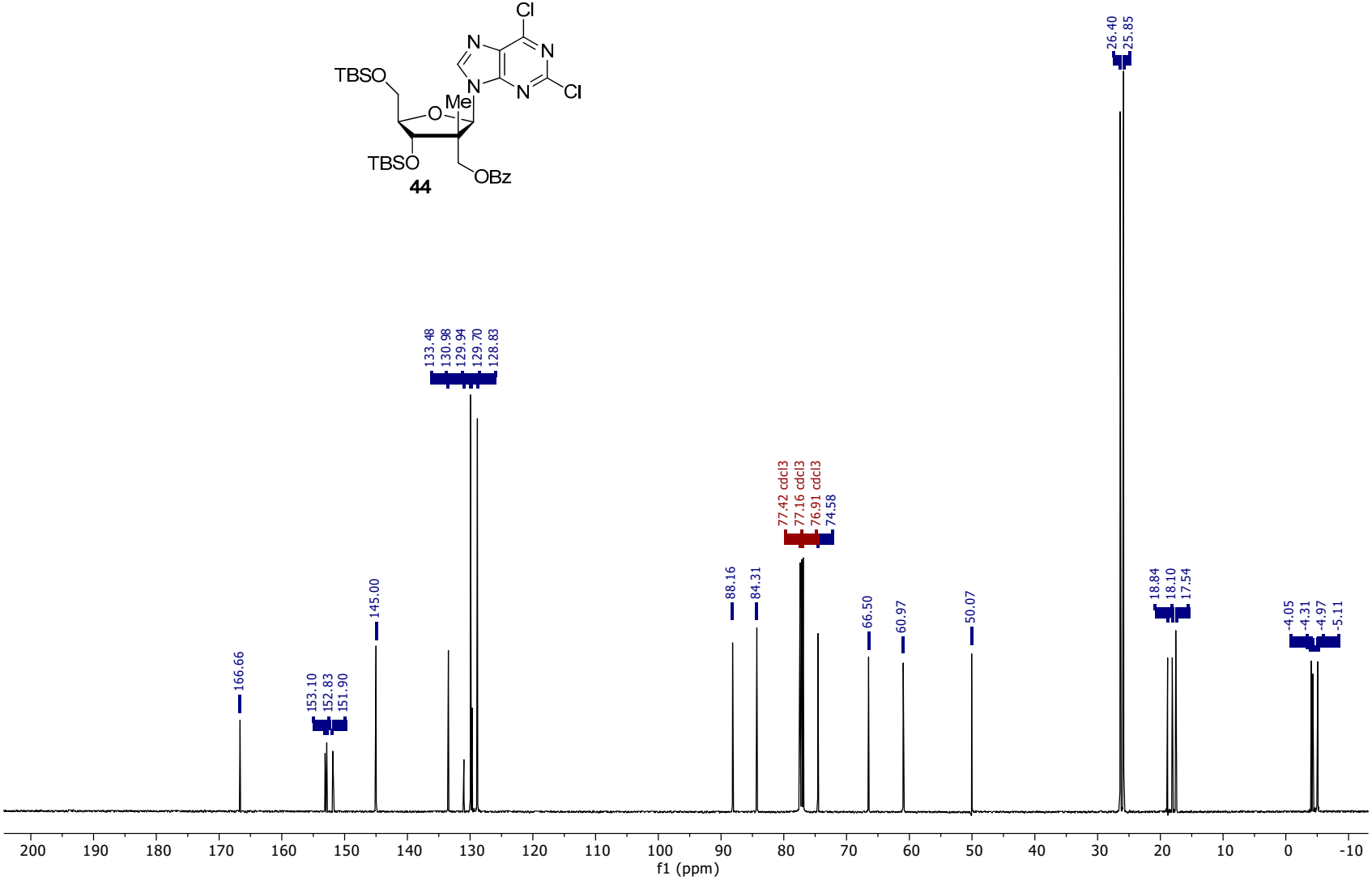
43a,b



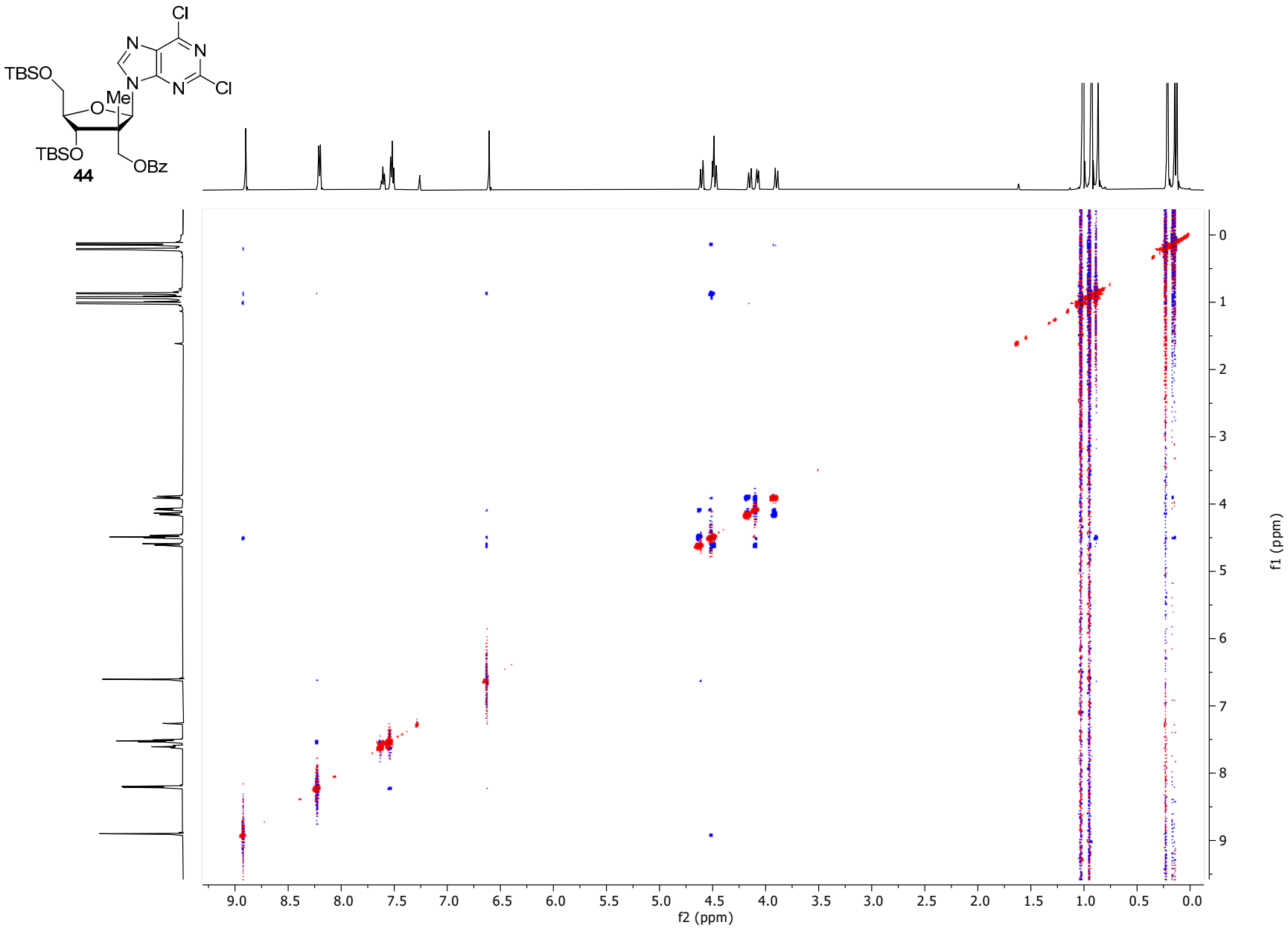
^{1}H-NMR (500 MHz, $CDCl_3$)



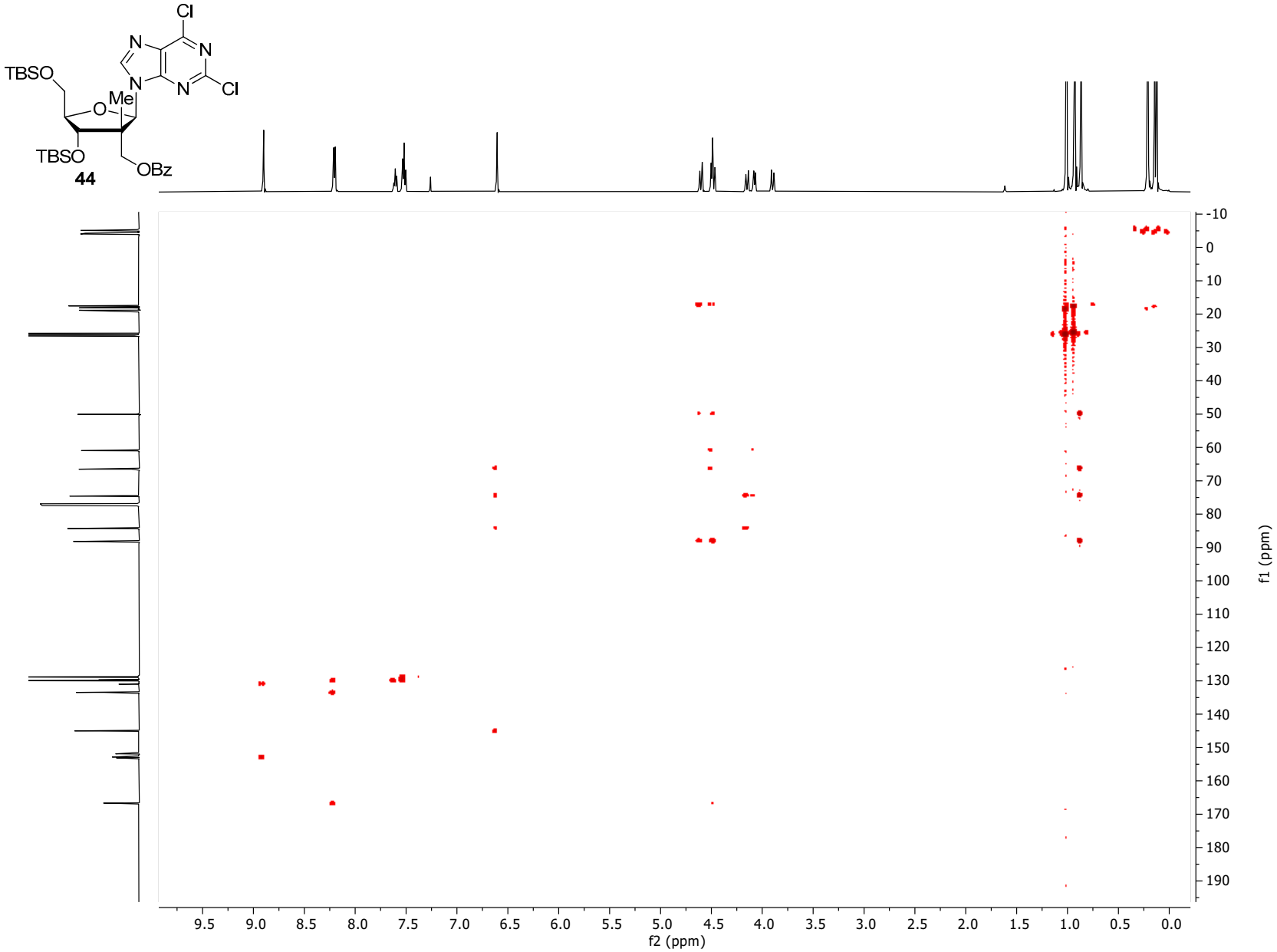
$^{13}C\{^{1}H\}$-NMR (126 MHz, $CDCl_3$)



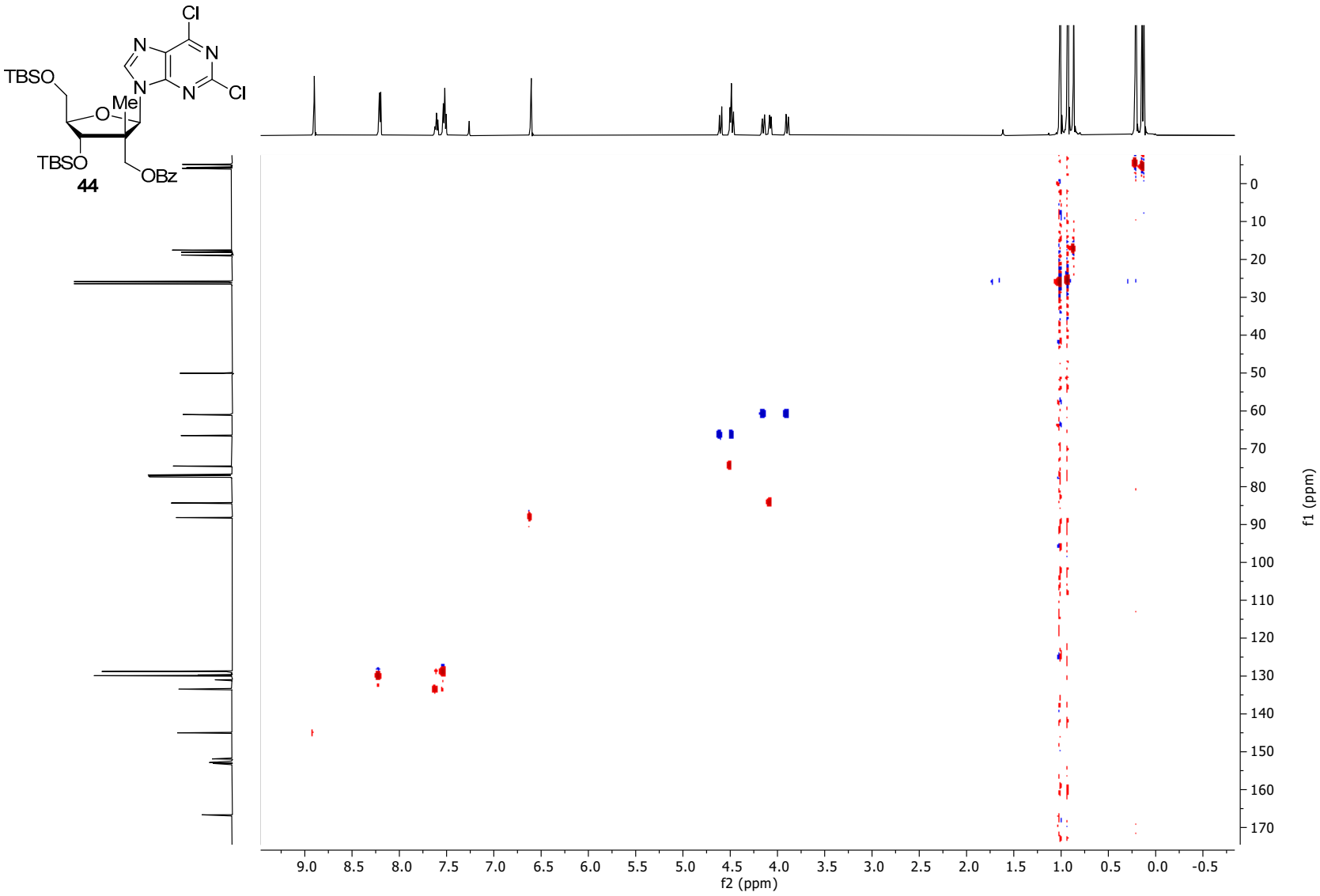
NOESY (500 MHz, $CDCl_3$)



HMBC (500 MHz, $CDCl_3$)

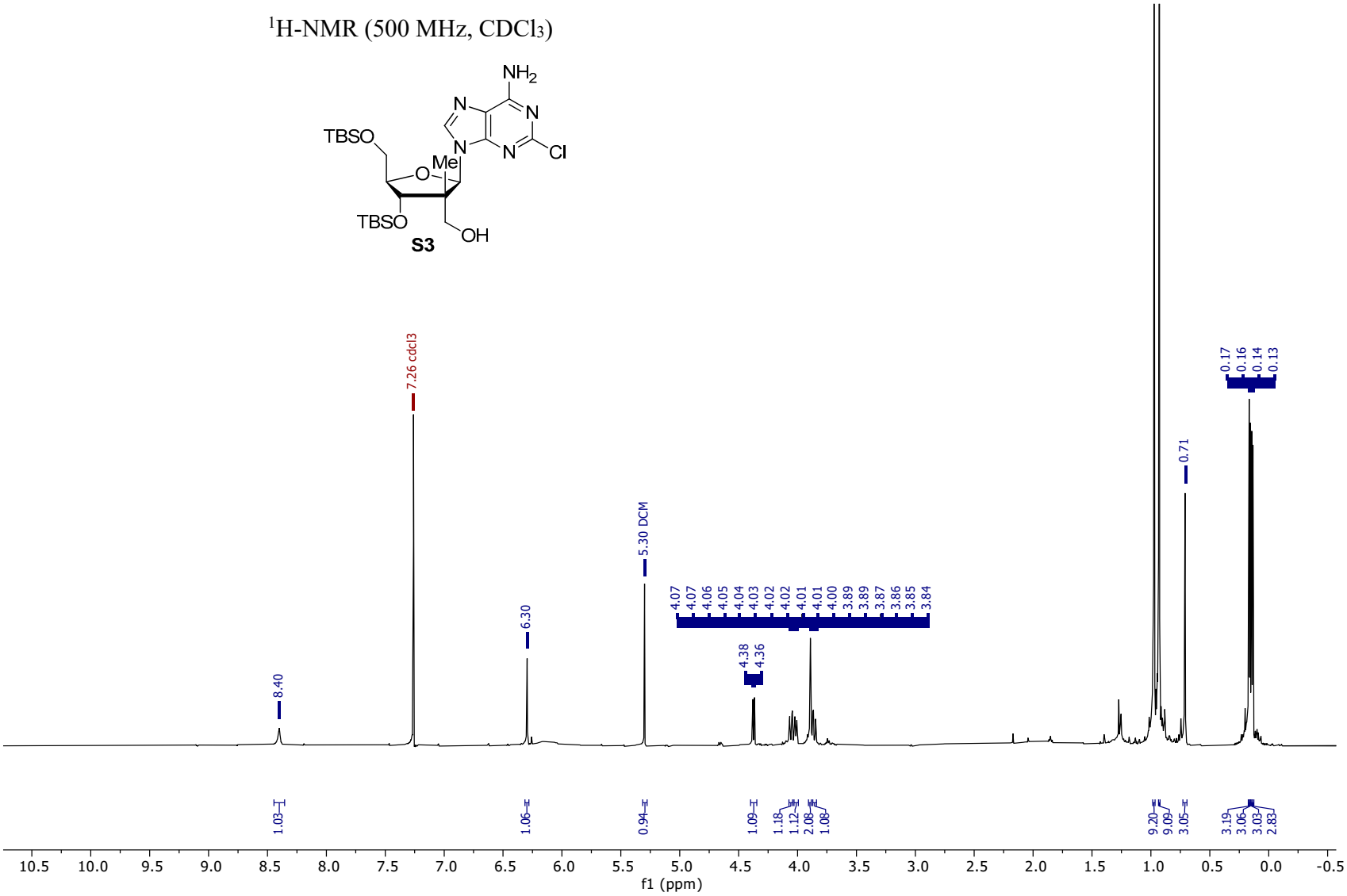


HSQC (500 MHz, $CDCl_3$)

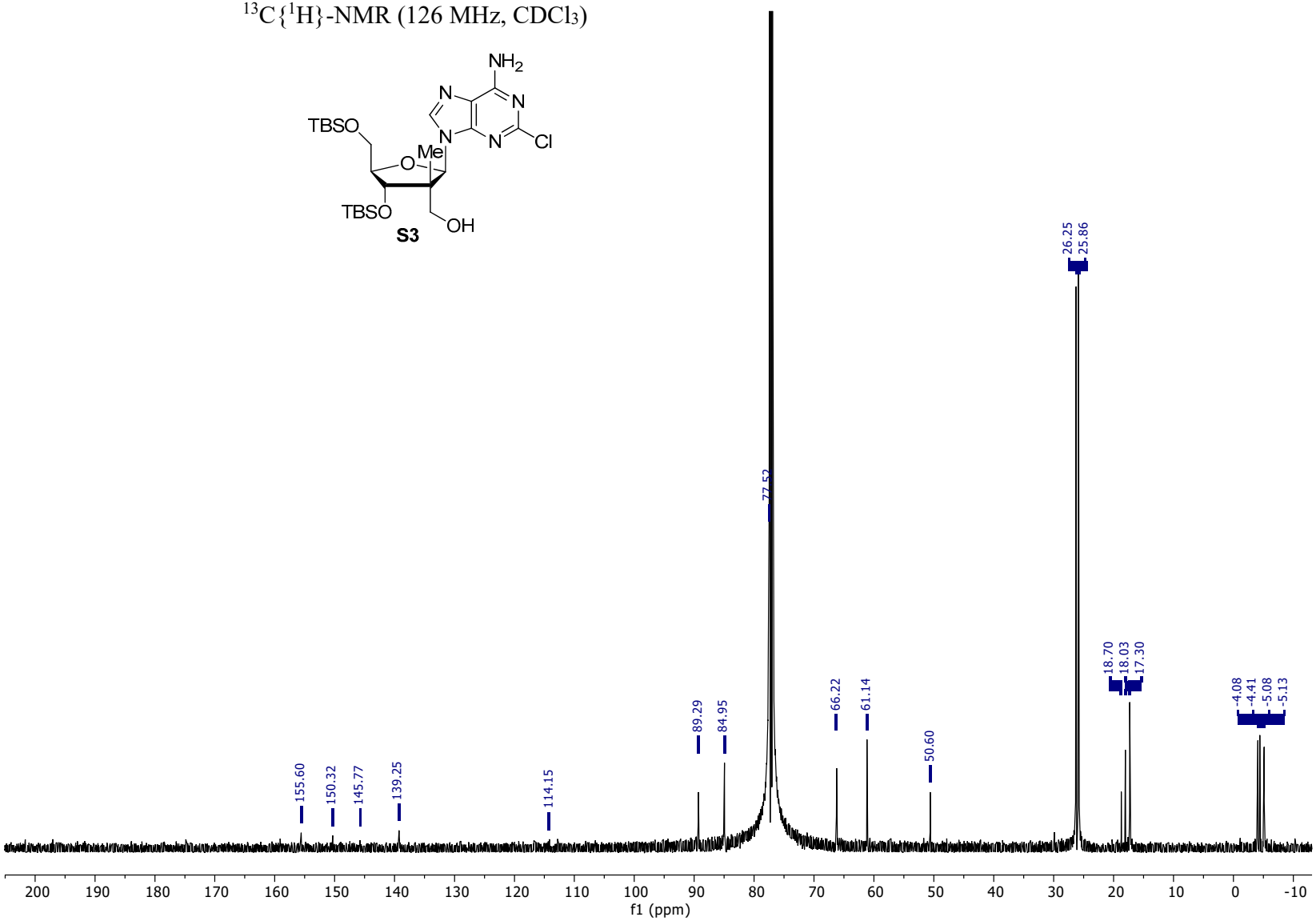


^{1}H-NMR (500 MHz, $CDCl_3$)

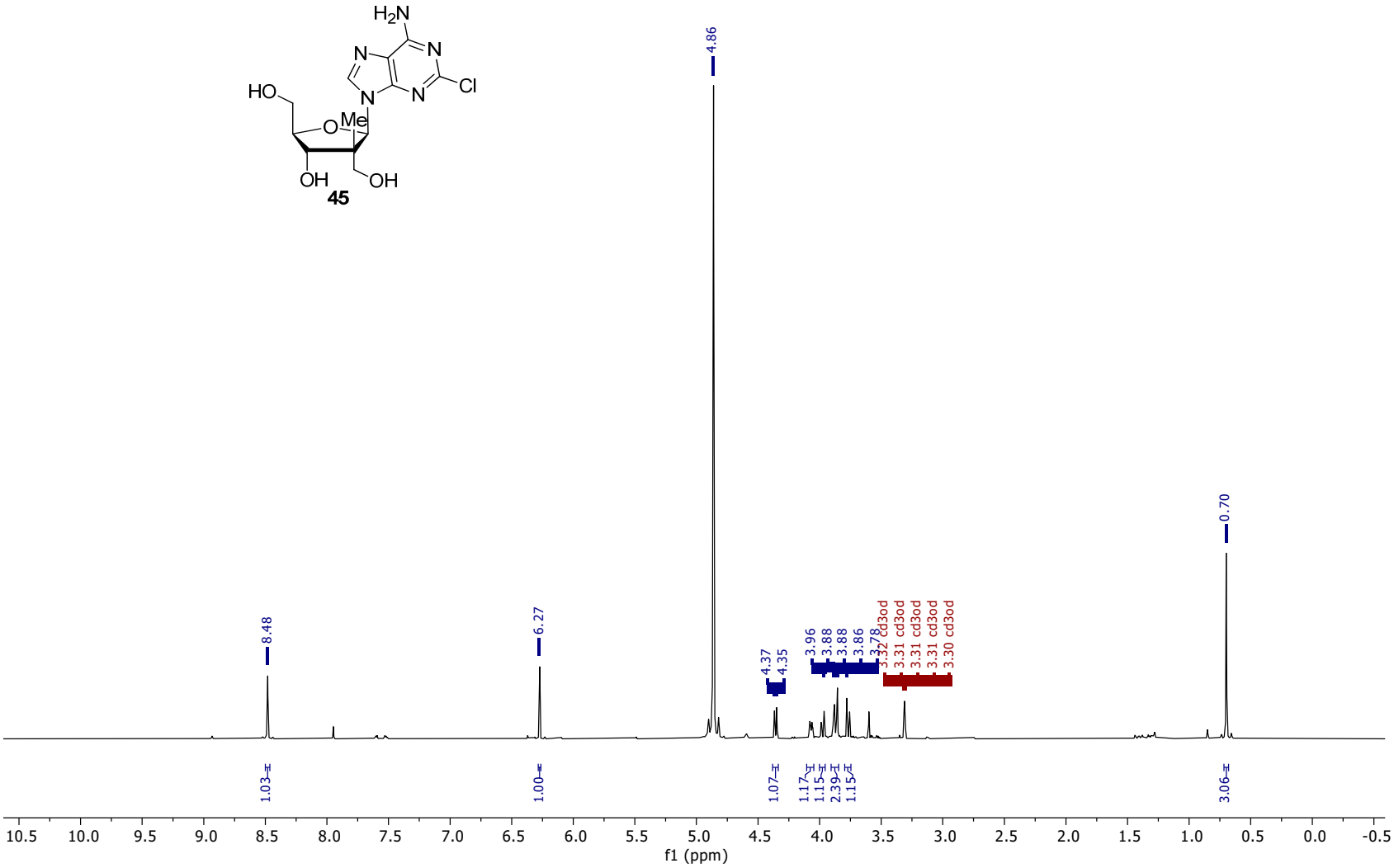
S3



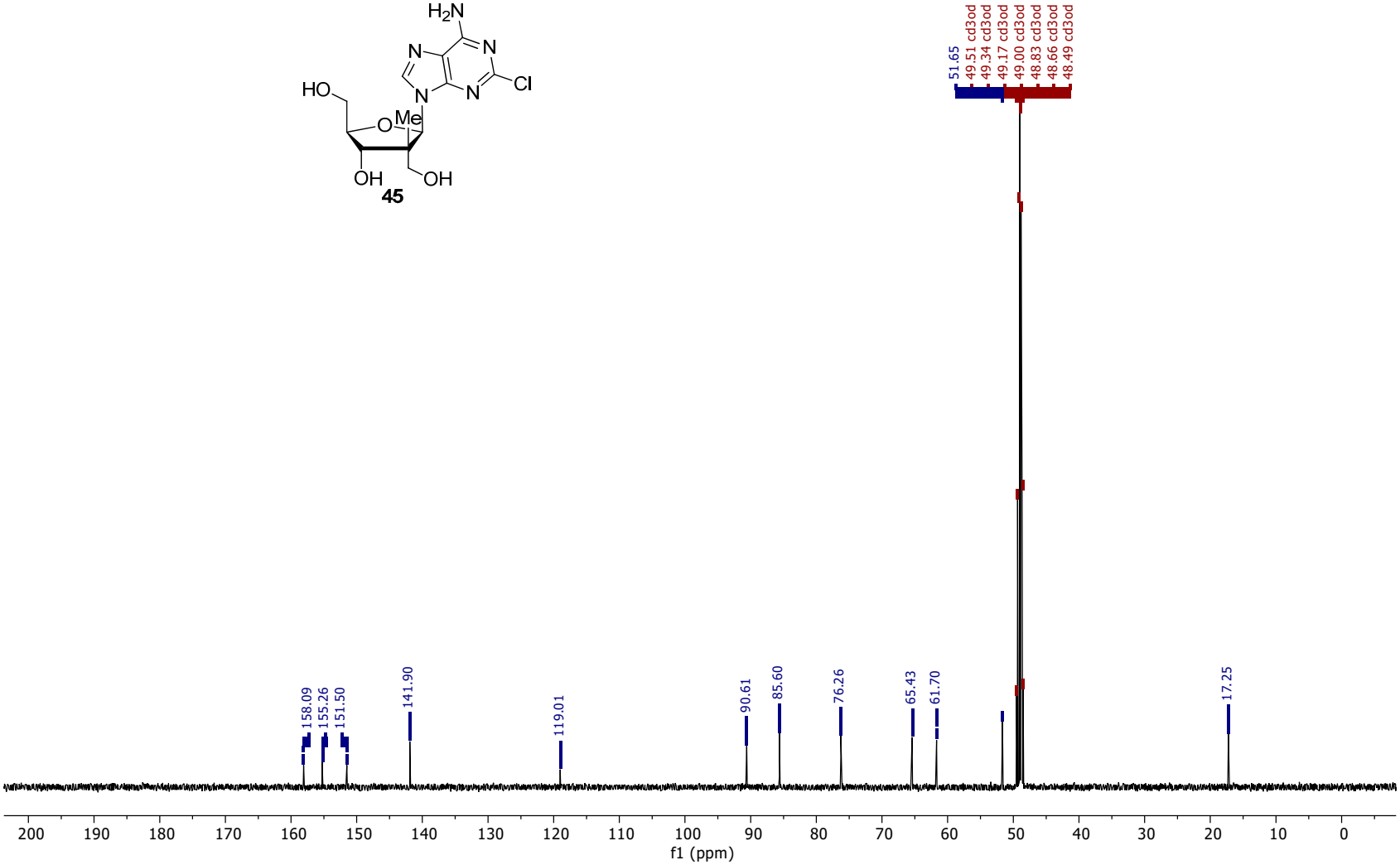
$^{13}C\{^{1}H\}$-NMR (126 MHz, $CDCl_3$)



^{1}H-NMR (500 MHz, CD_3OD)



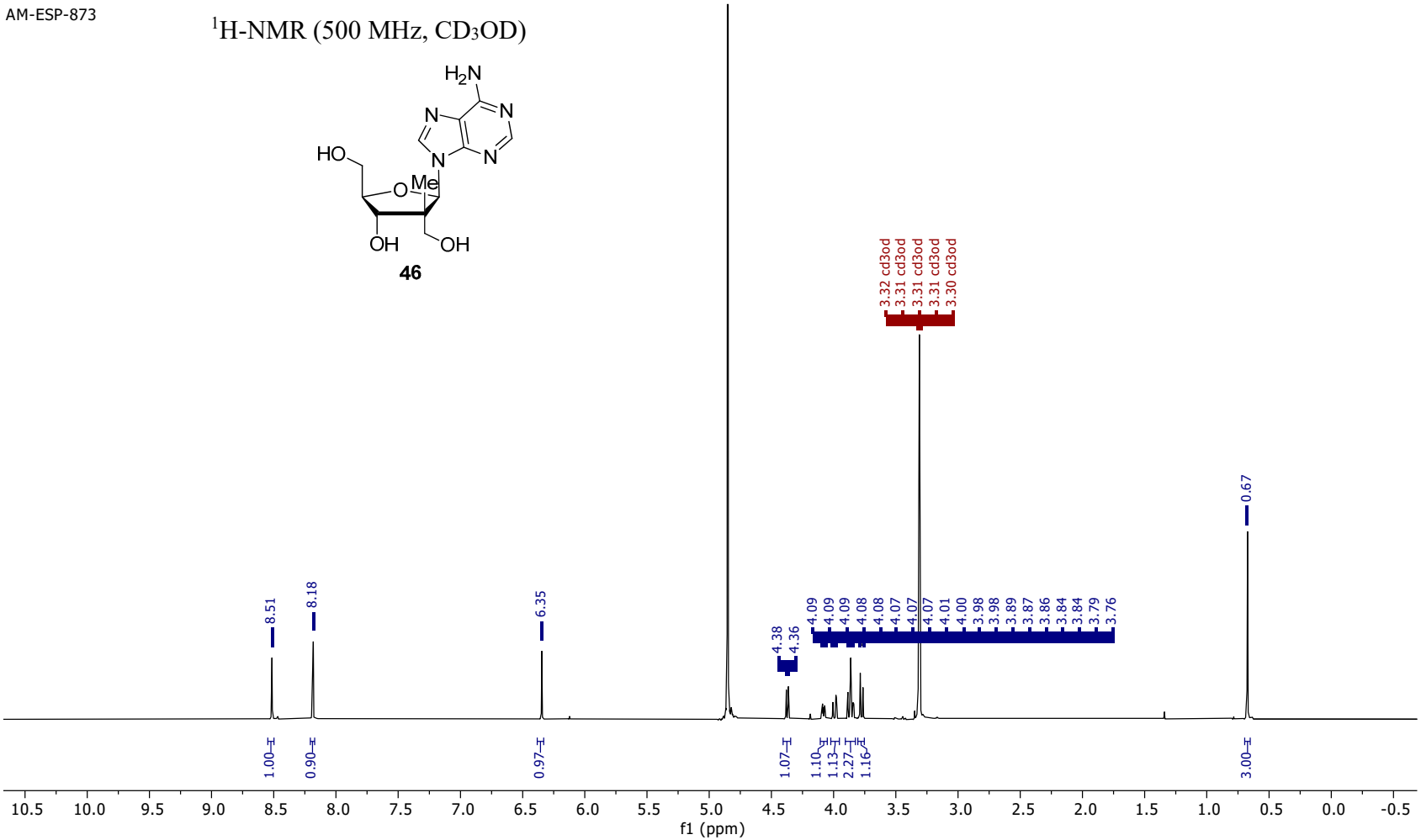
$^{13}C\{^{1}H\}$-NMR (126 MHz, CD_3OD)



AM-ESP-873

^{1}H-NMR (500 MHz, CD_3OD)

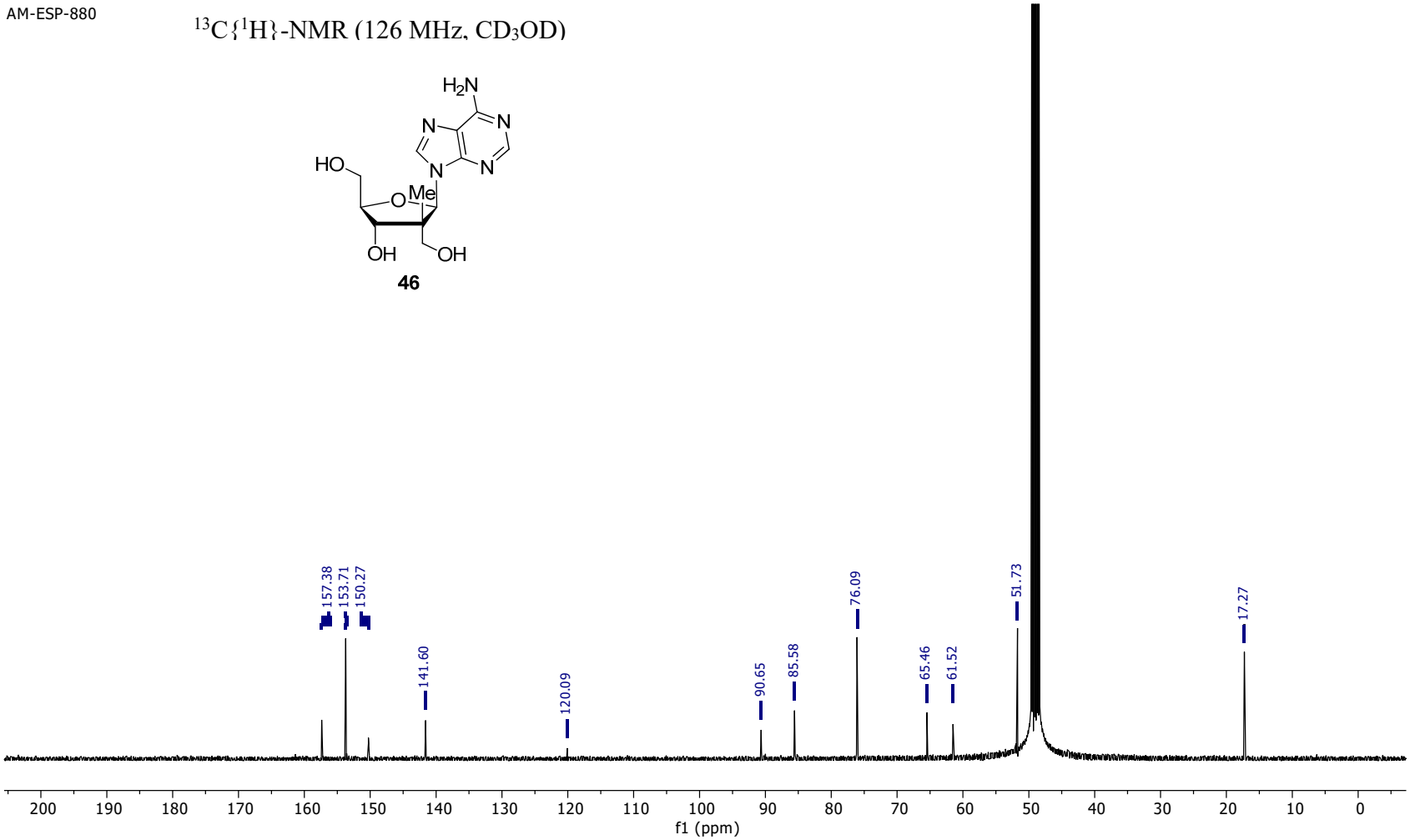
46



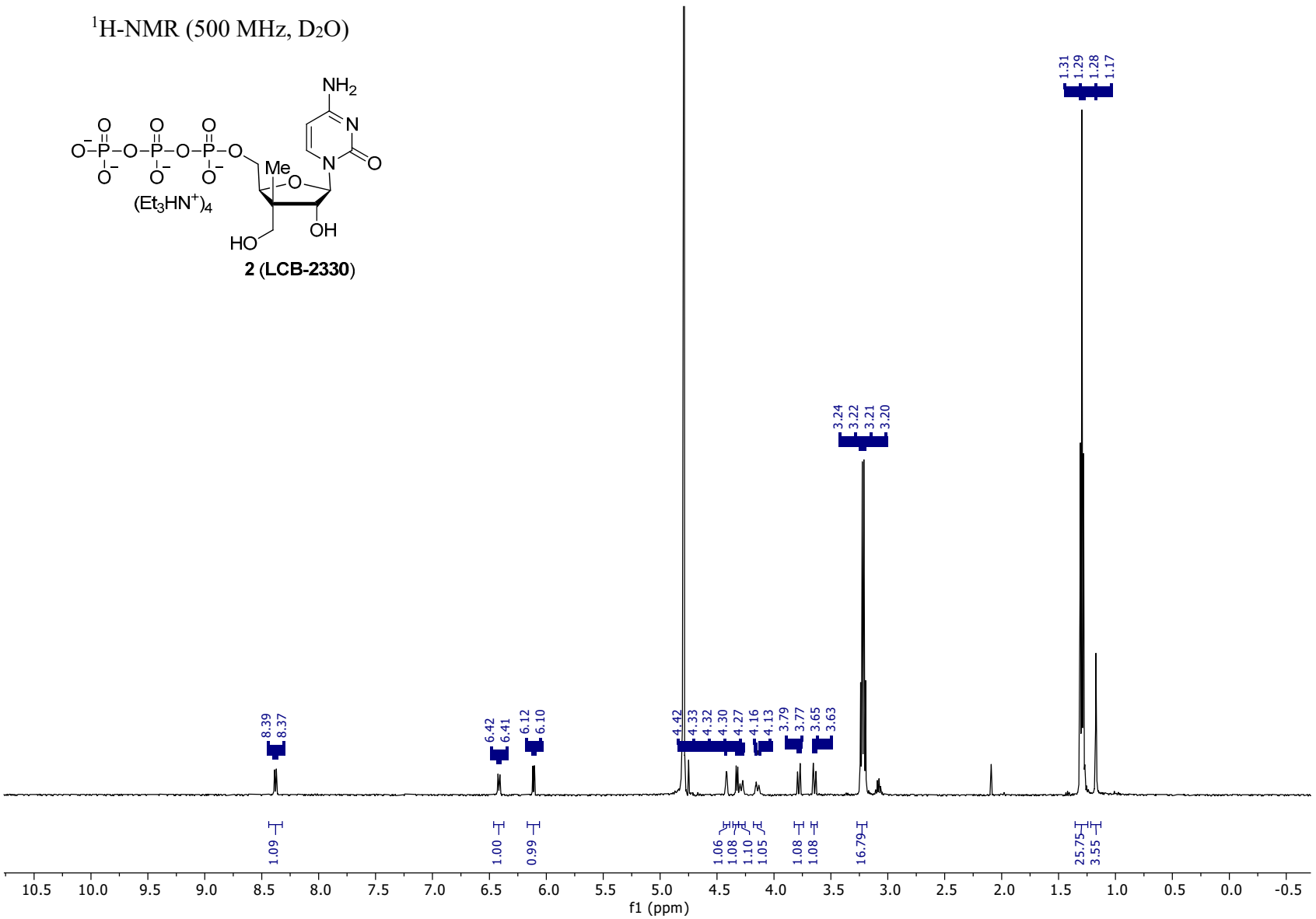
AM-ESP-880

$^{13}C\{^{1}H\}$-NMR (126 MHz, CD_3OD)

46

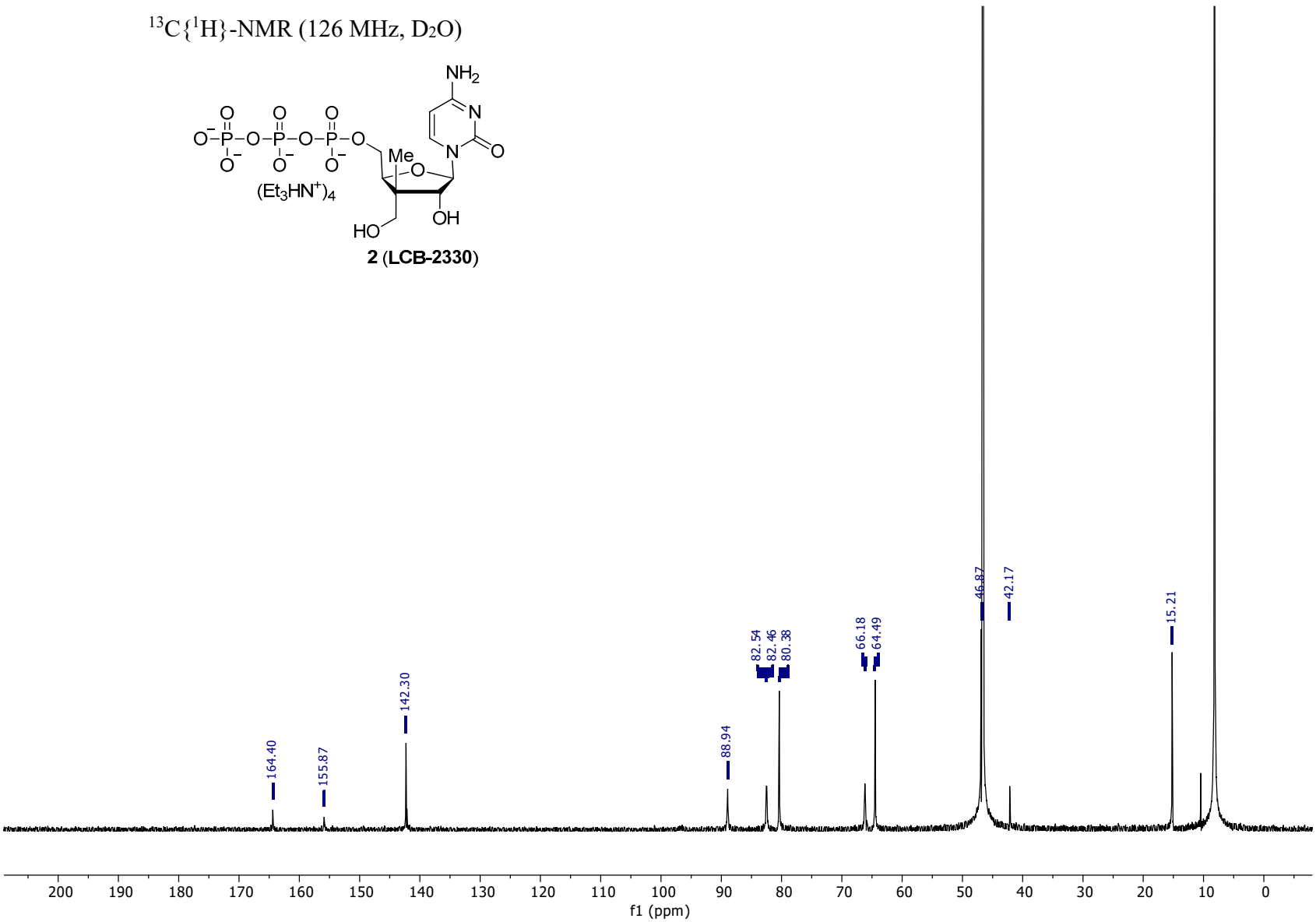


^{1}H-NMR (500 MHz, D_2O)

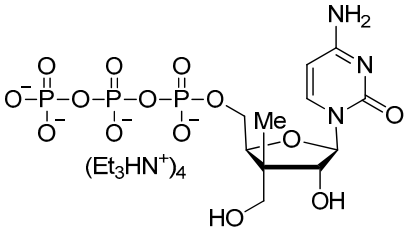


$^{13}C\{^{1}H\}$-NMR (126 MHz, D_2O)

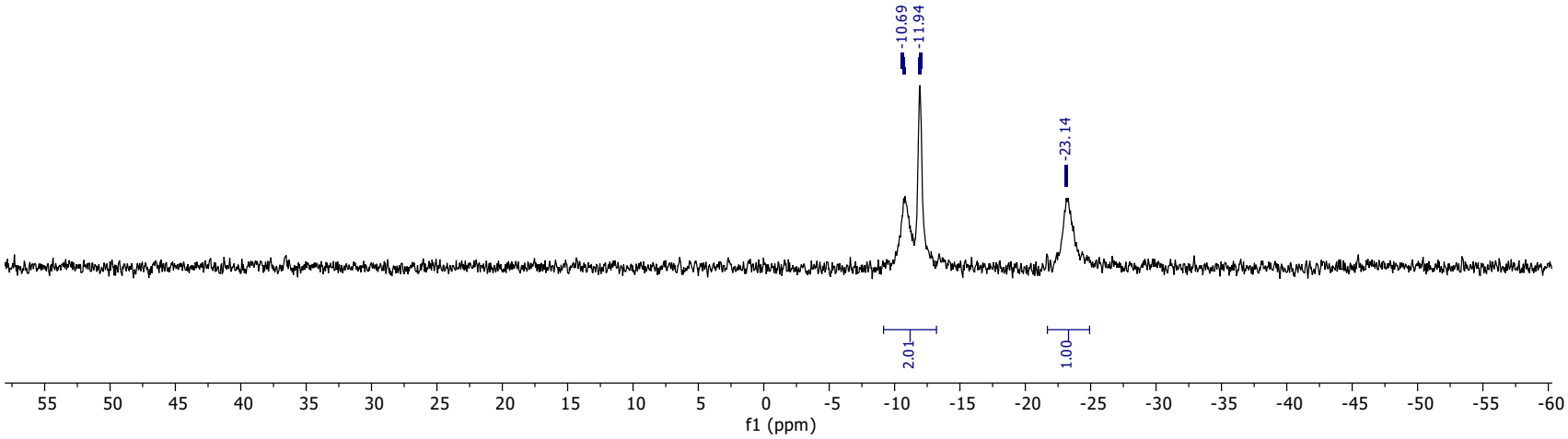
2 (**LCB-2330**)



^{31}PNMR (162 MHz, D_2O)

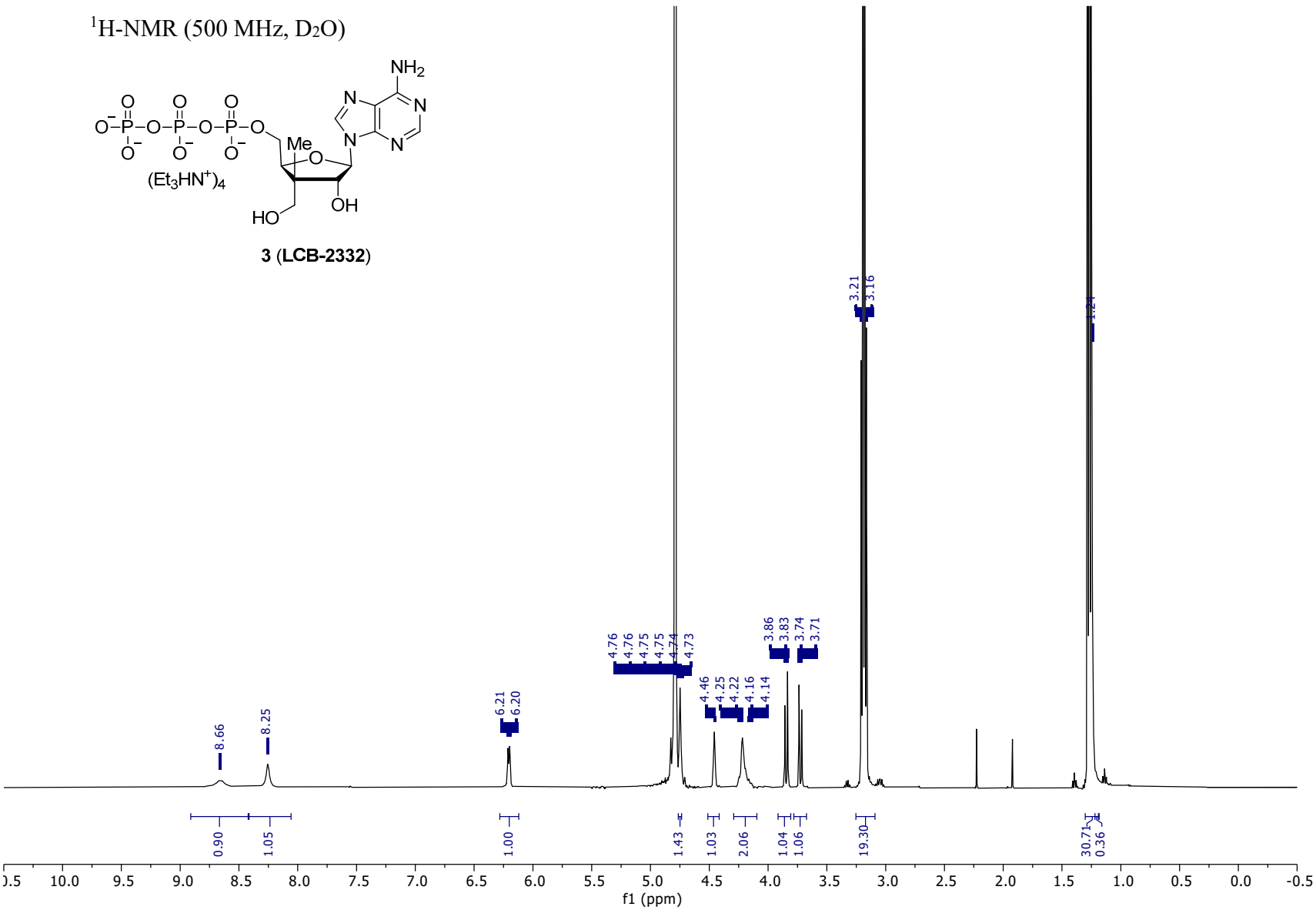


2 (**LCB-2330**)



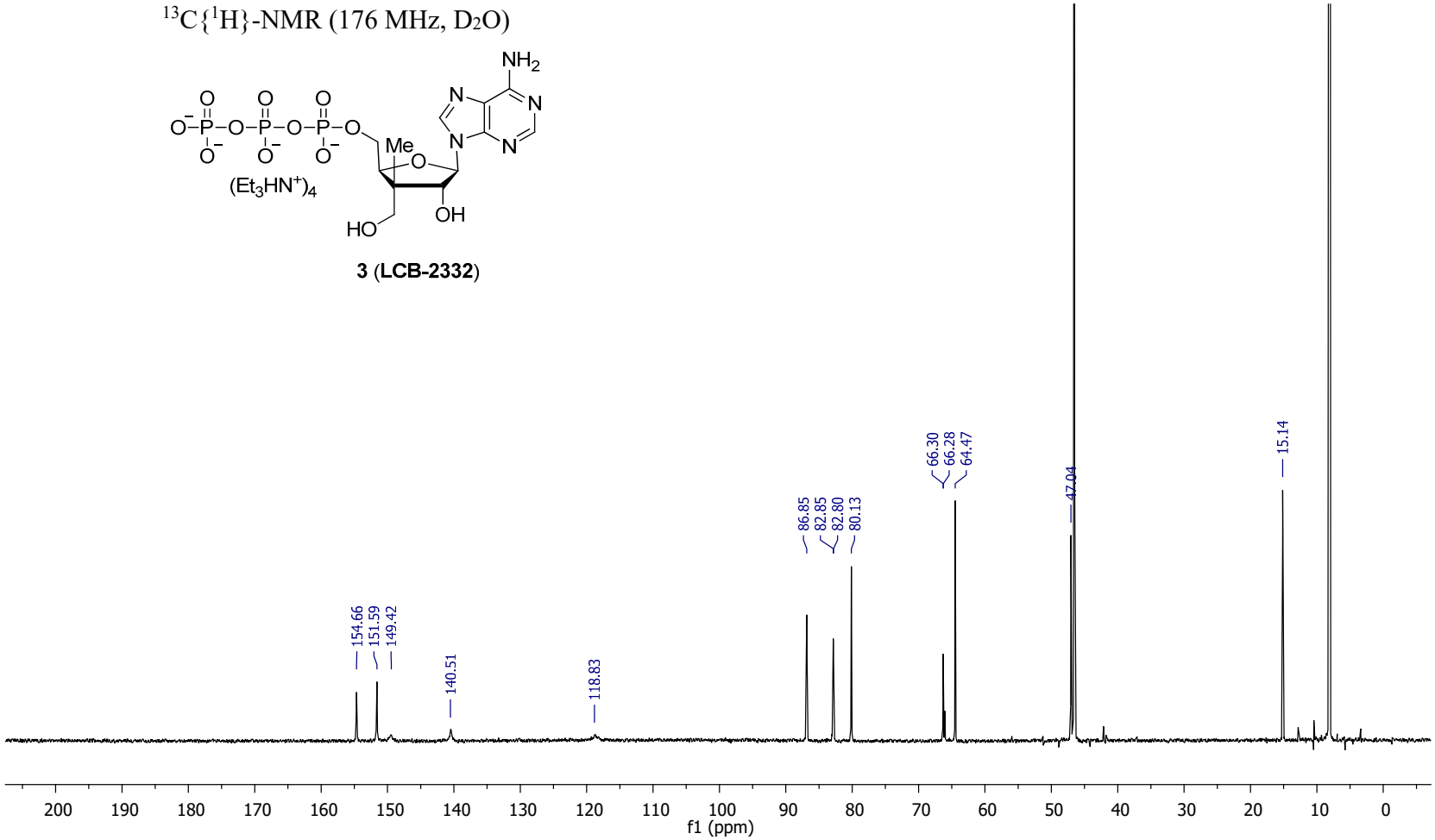
^{1}H-NMR (500 MHz, D_2O)

3 (**LCB-2332**)

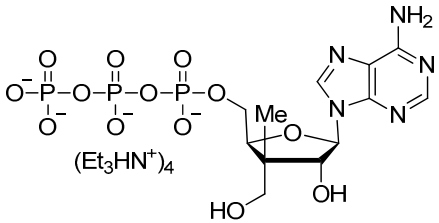


$^{13}C\{^{1}H\}$-NMR (176 MHz, D_2O)

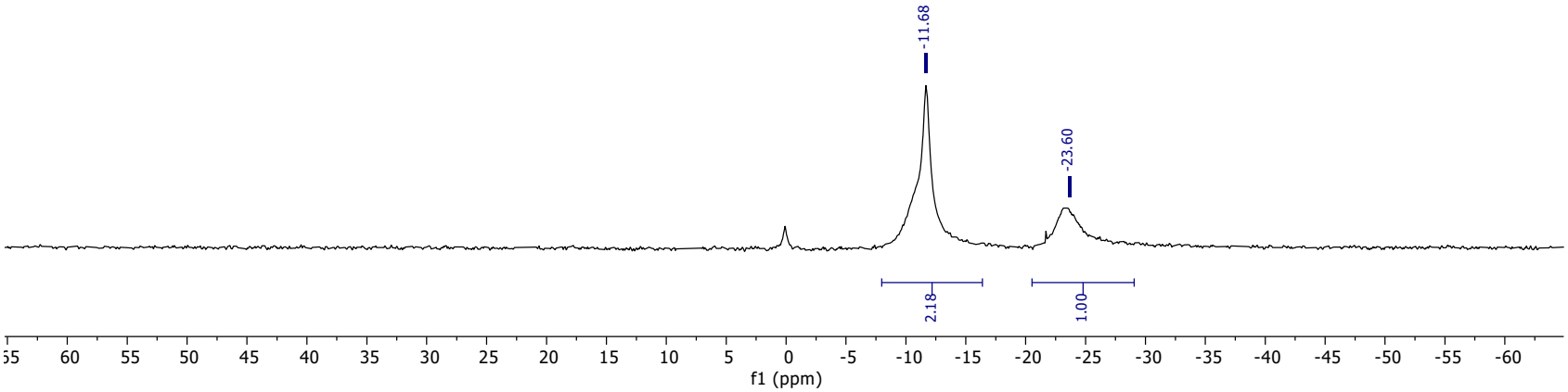
3 (**LCB-2332**)



^{31}P NMR (162 MHz, D_2O)



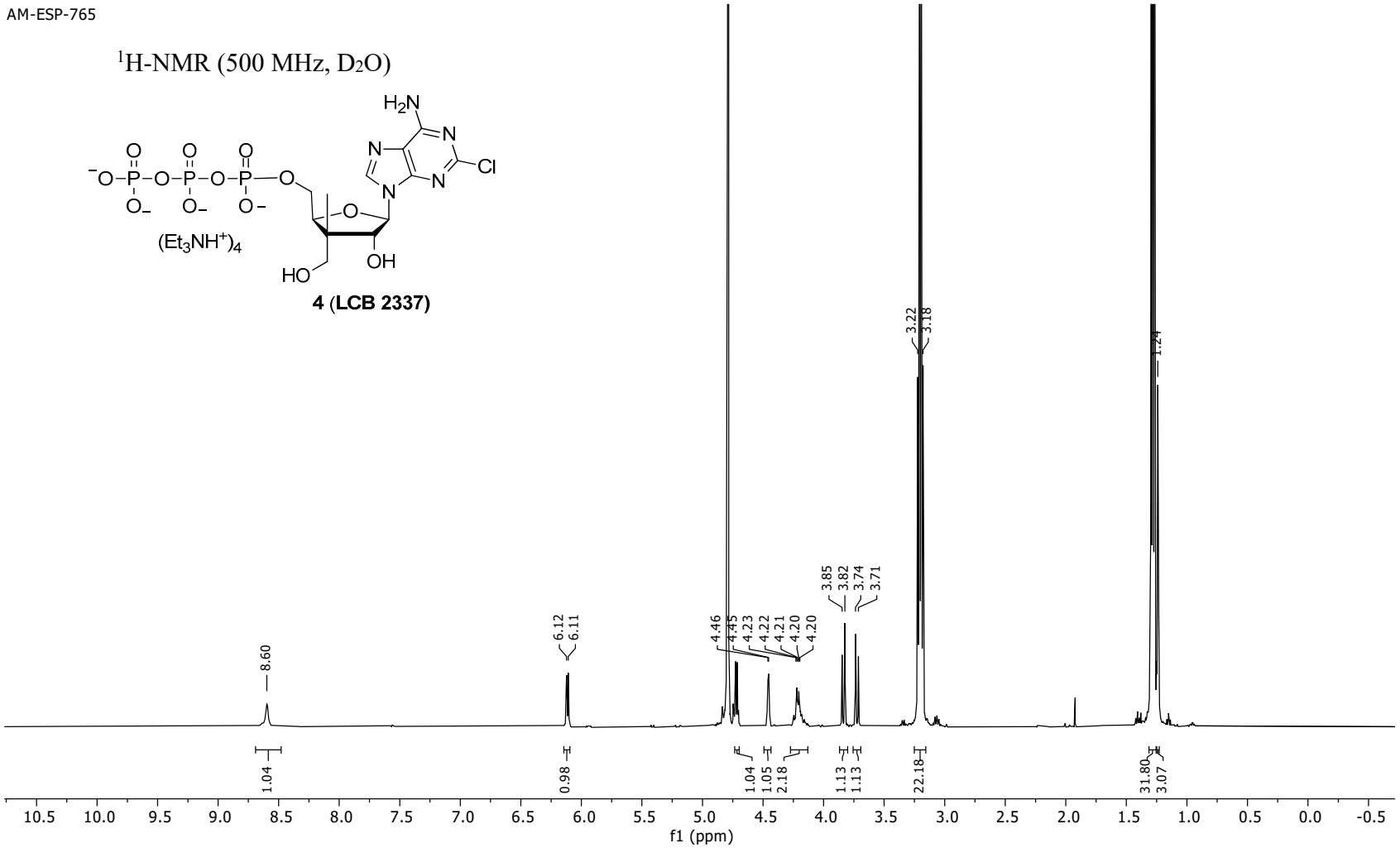
3 (**LCB-2332**)



AM-ESP-765

^{1}H-NMR (500 MHz, D_2O)

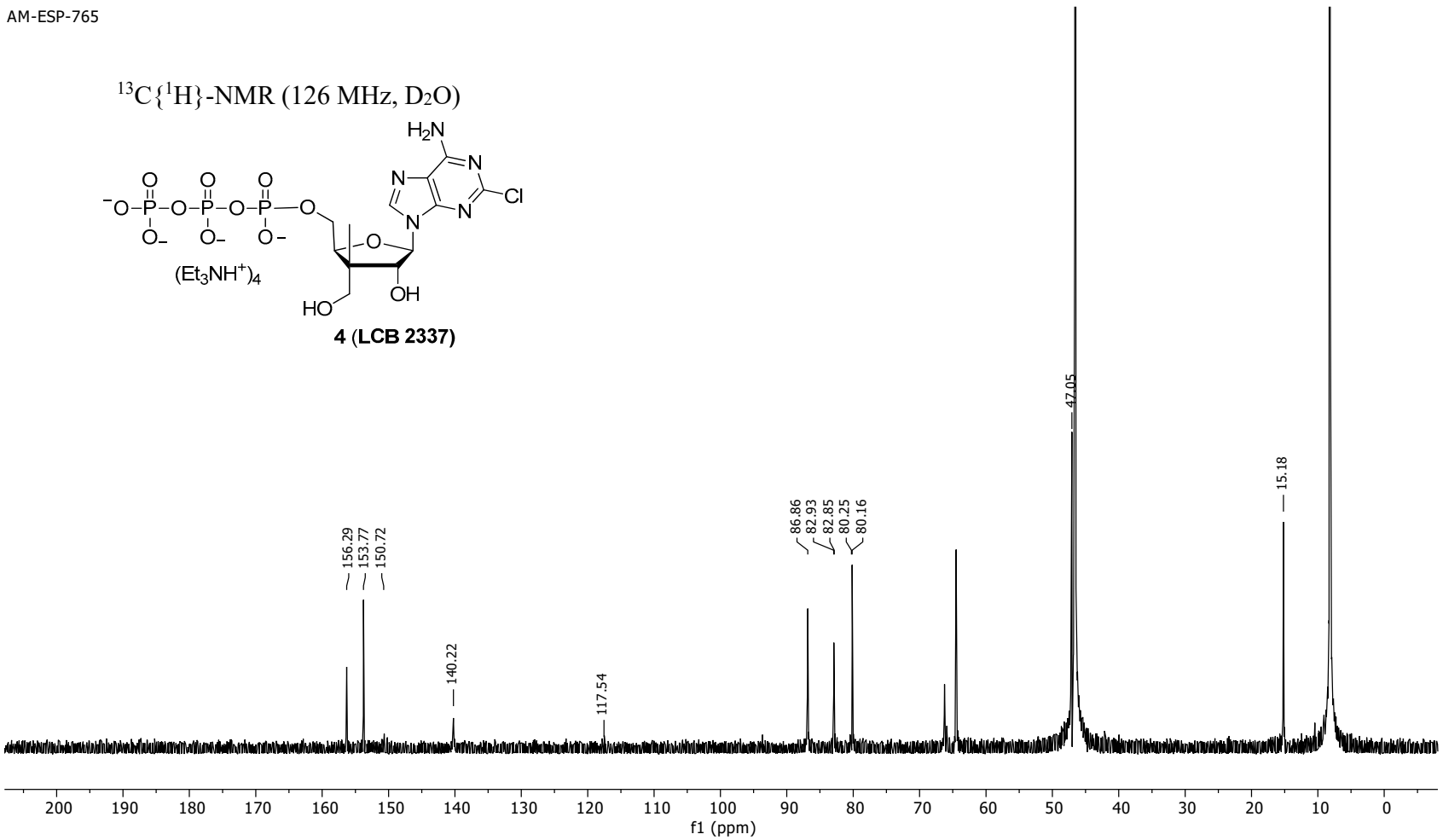
4 (LCB 2337)



AM-ESP-765

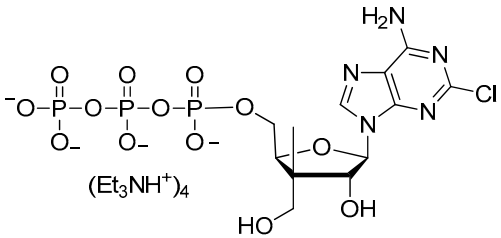
$^{13}C\{^{1}H\}$-NMR (126 MHz, D_2O)

4 (LCB 2337)

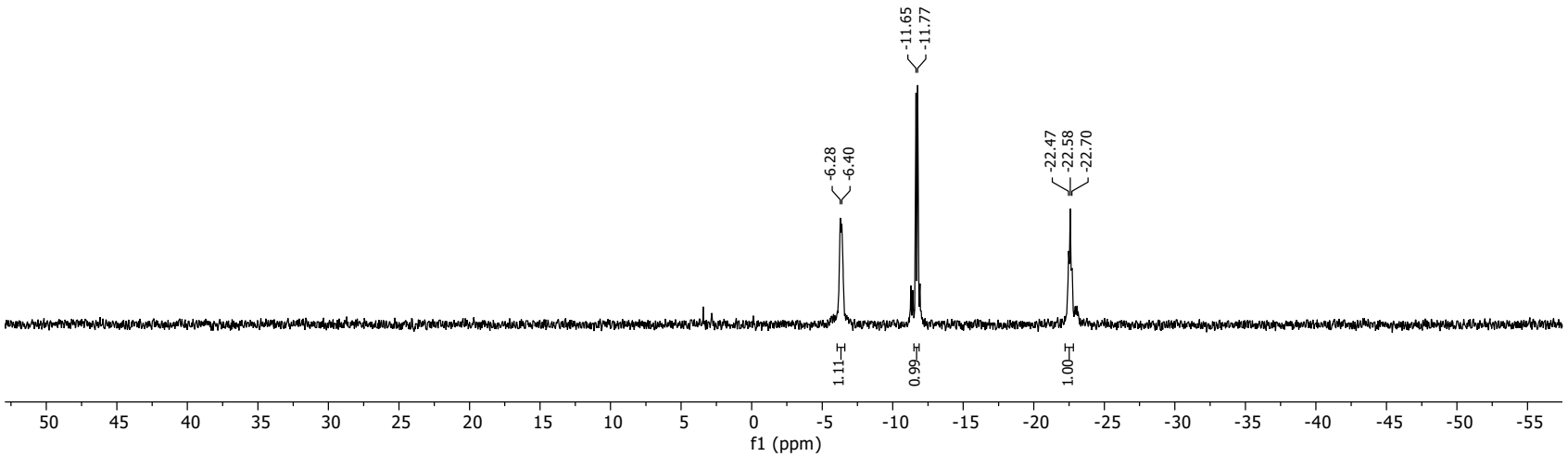


AM-ESP-765

^{31}P-NMR (162 MHz, D_2O)



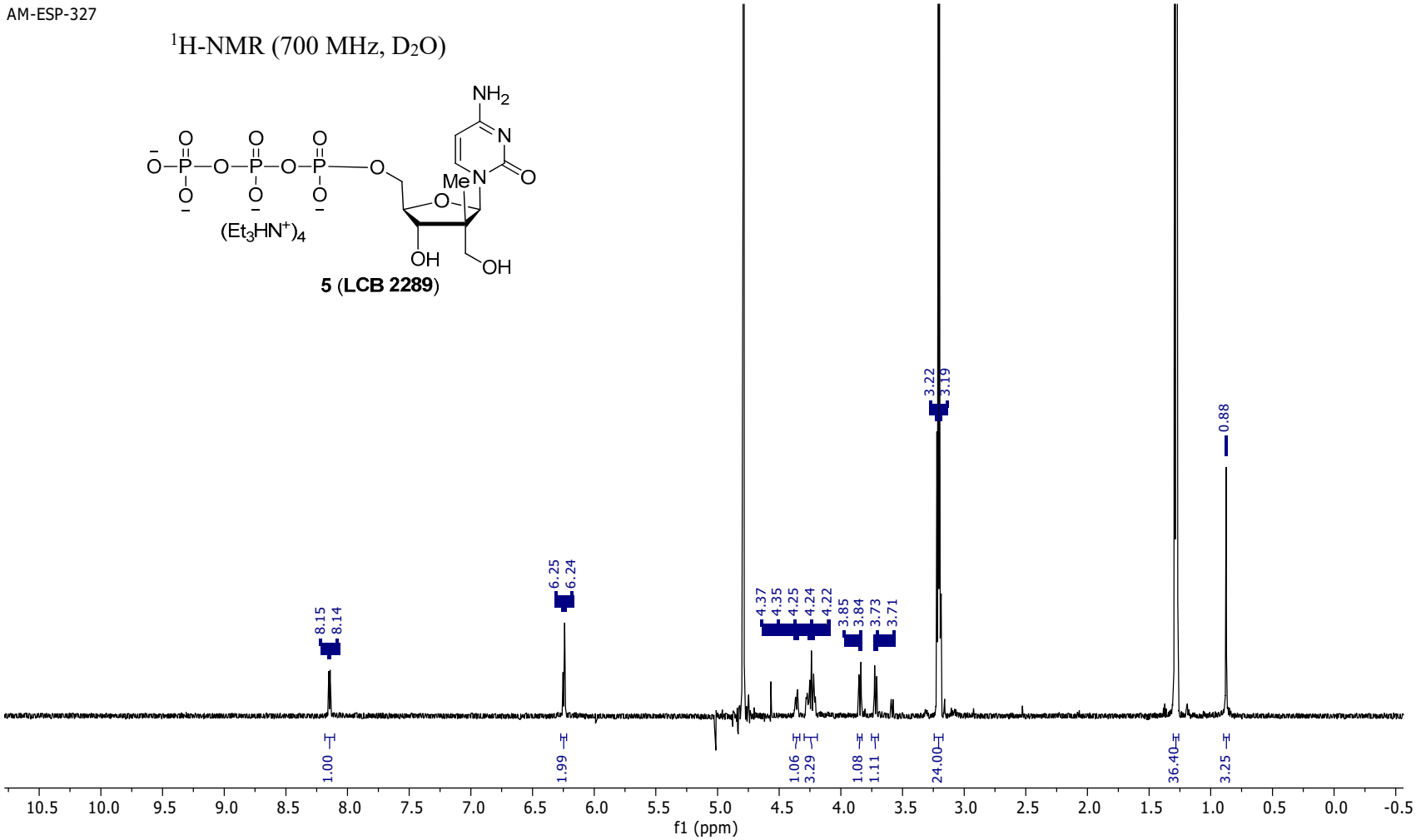
4 (LCB 2337)



AM-ESP-327

^{1}H-NMR (700 MHz, D_2O)

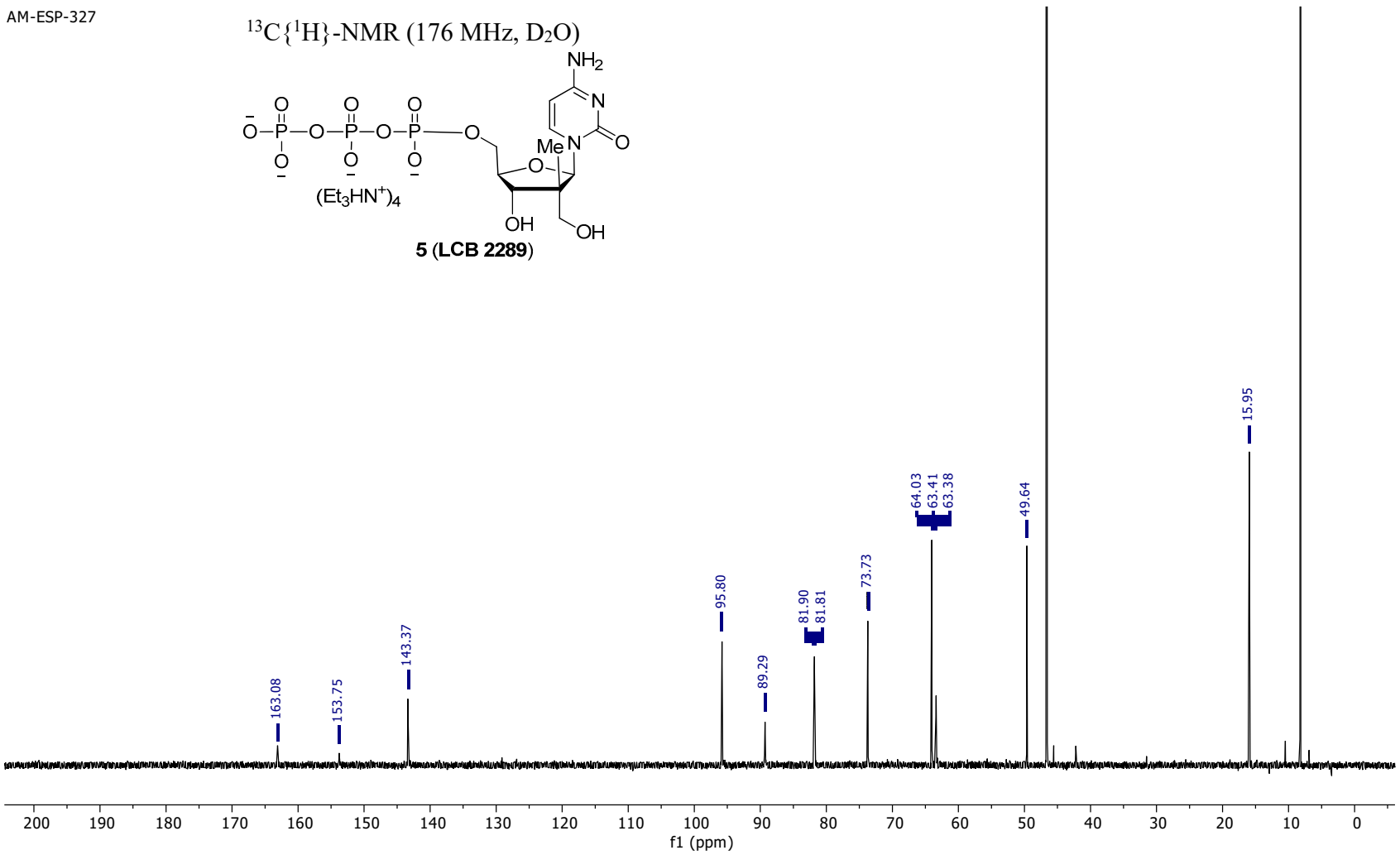
5 (**LCB 2289**)



AM-ESP-327

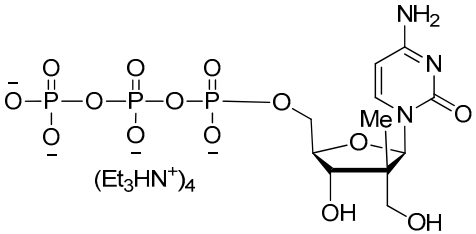
$^{13}C\{^{1}H\}$-NMR (176 MHz, D_2O)

5 (**LCB 2289**)

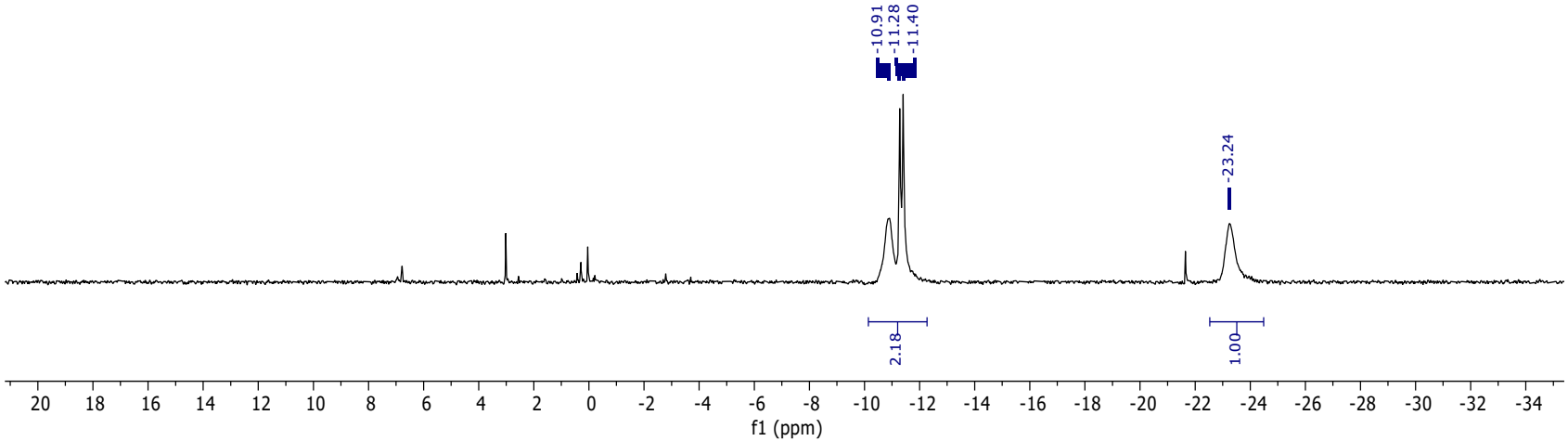


AM-ESP-327

^{31}P-NMR (162 MHz, D_2O)



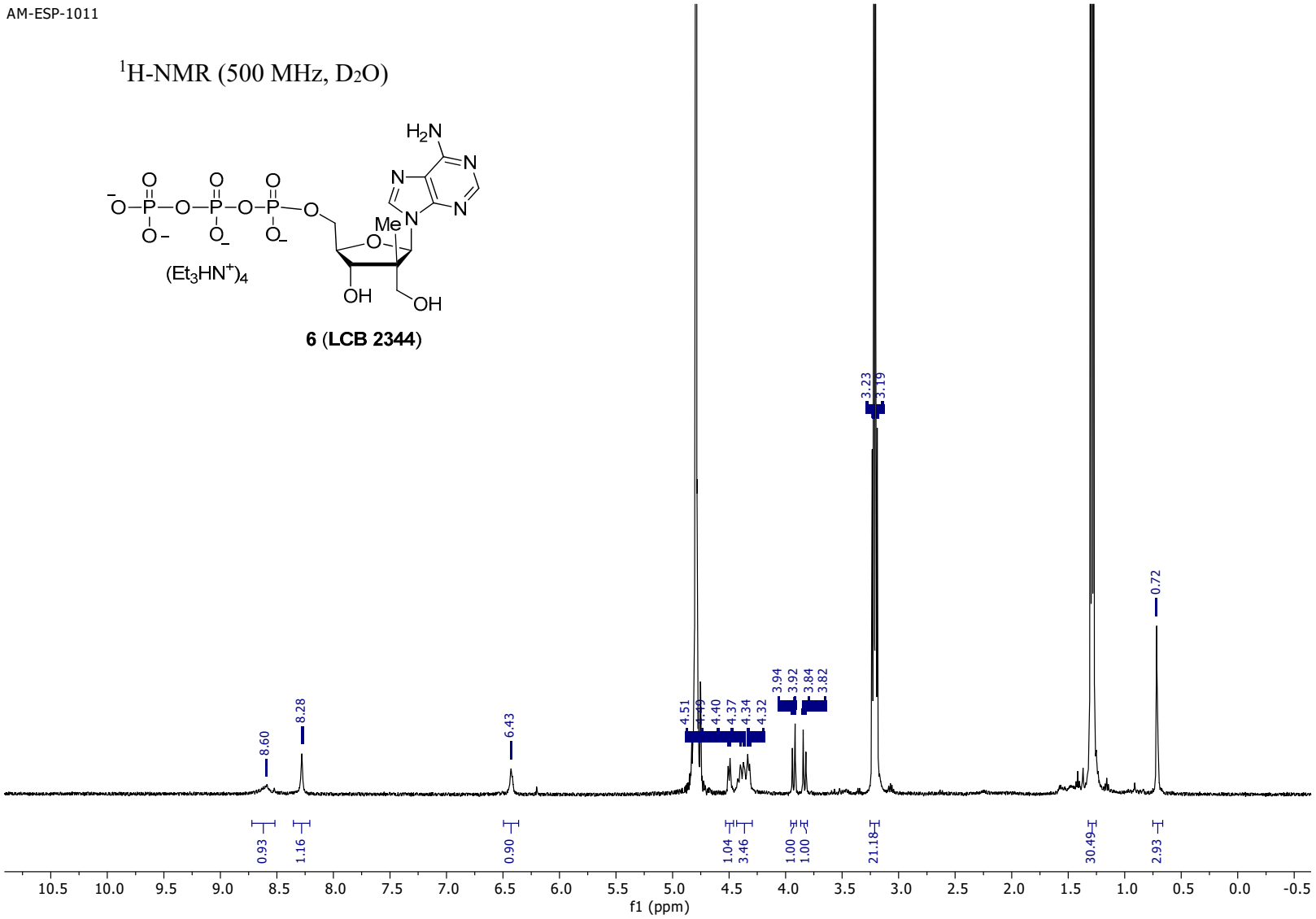
5 (**LCB 2289**)



AM-ESP-1011

^{1}H-NMR (500 MHz, D_2O)

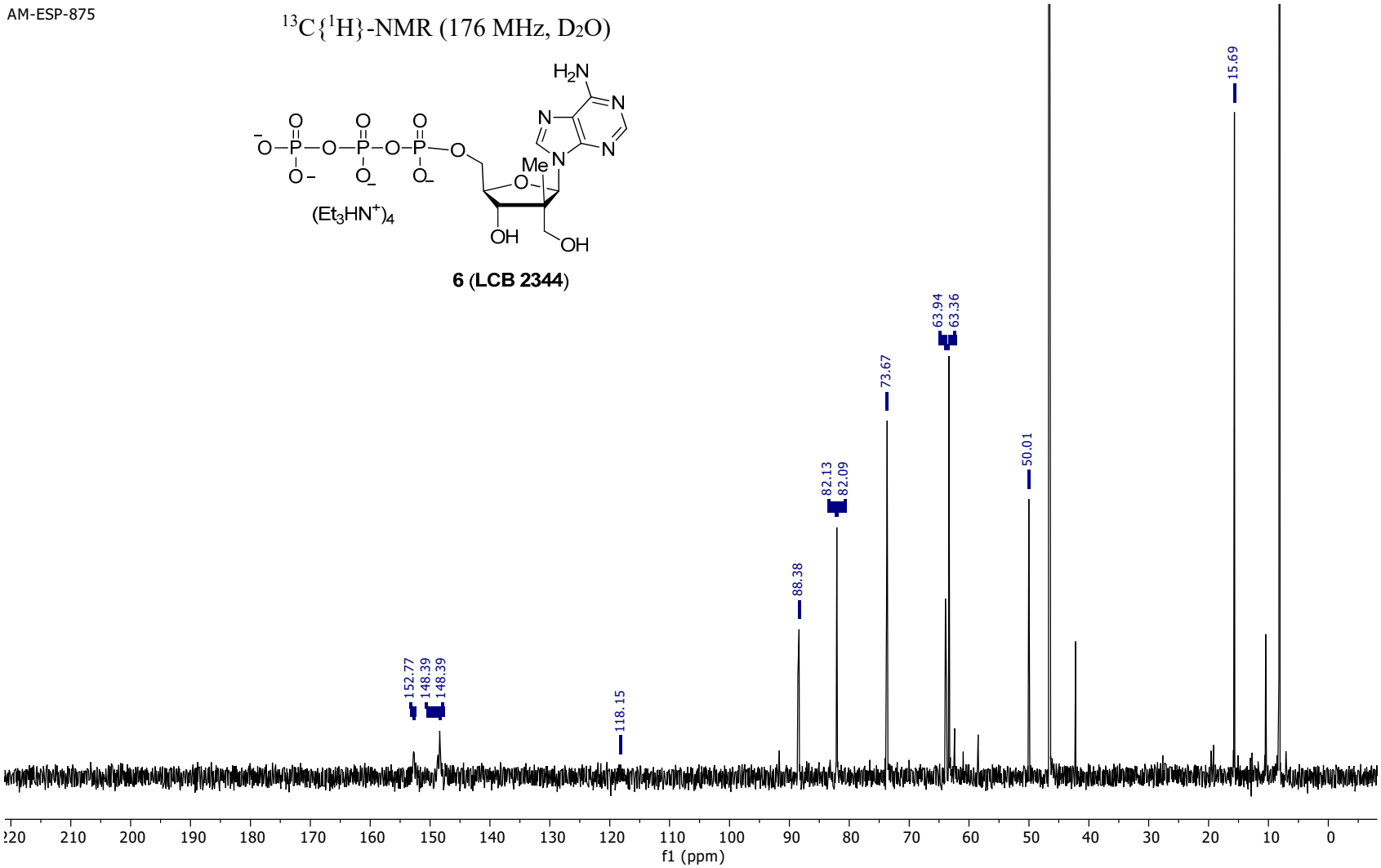
6 (**LCB 2344**)



AM-ESP-875

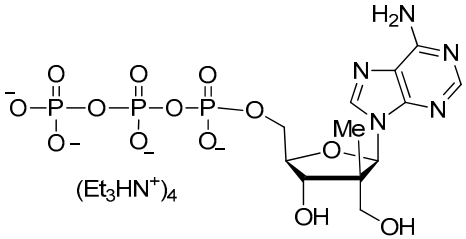
$^{13}C\{^{1}H\}$-NMR (176 MHz, D_2O)

6 (**LCB 2344**)

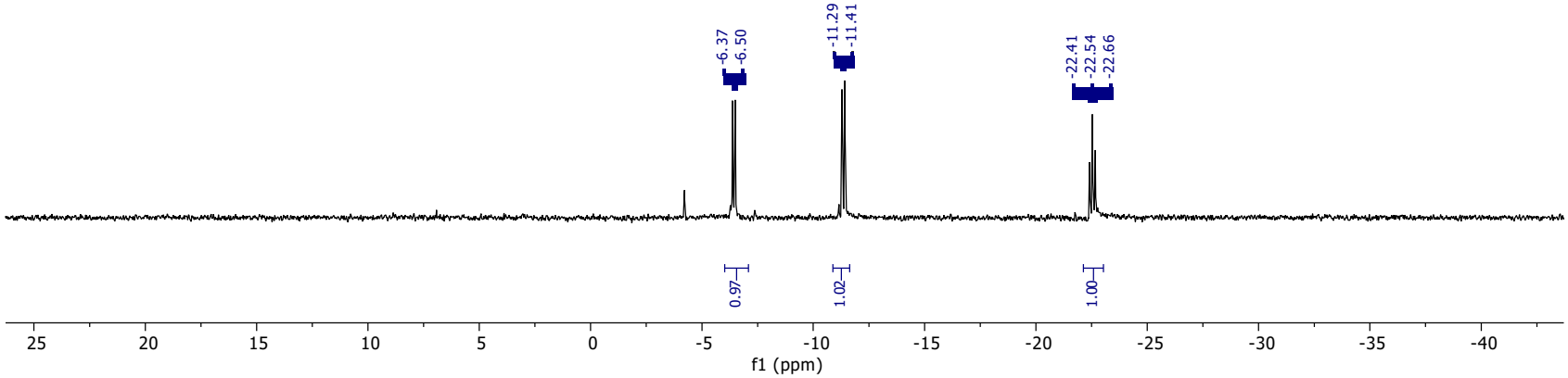


AM-ESP-878

^{31}P-NMR (162 MHz, D_2O)



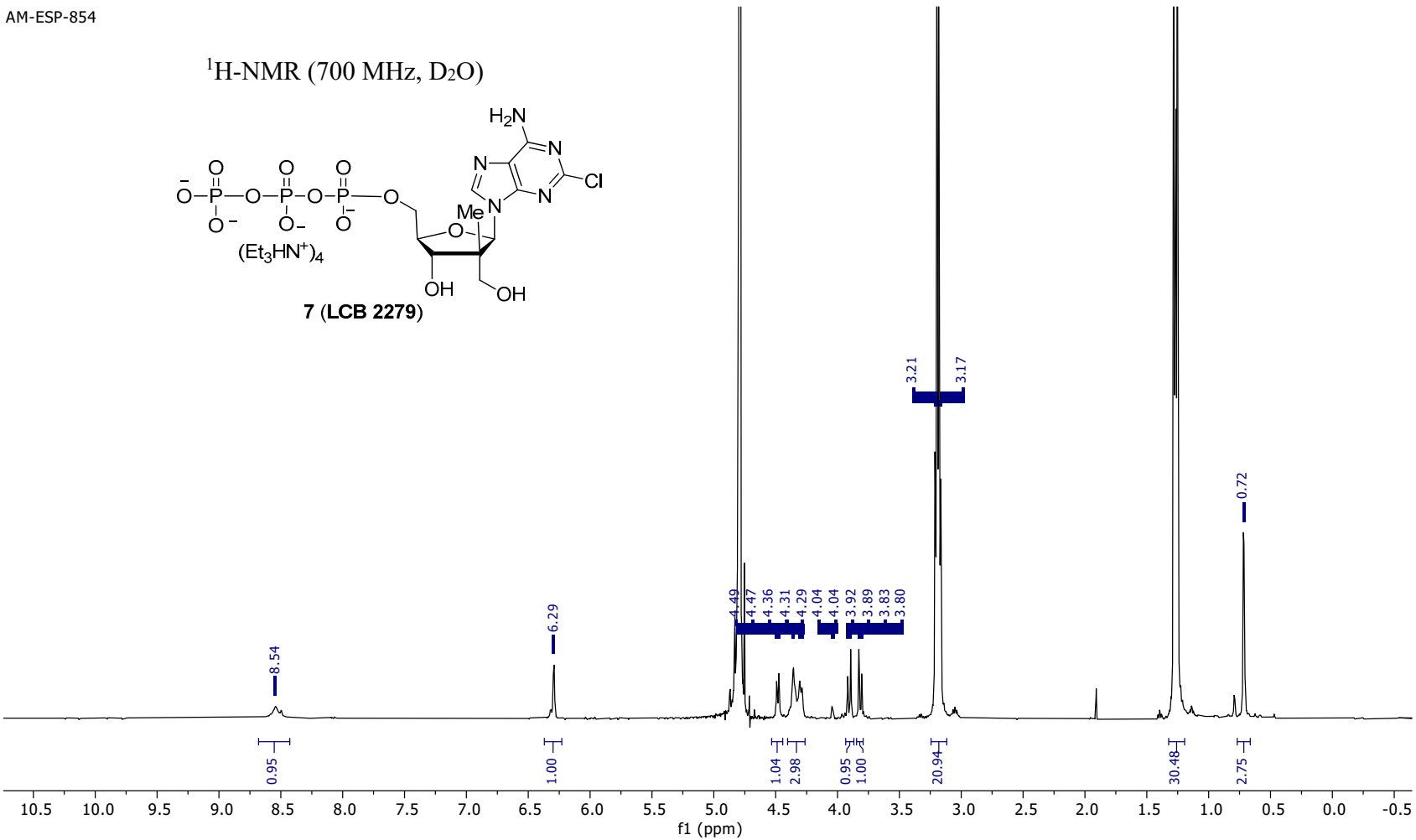
6 (**LCB 2344**)



AM-ESP-854

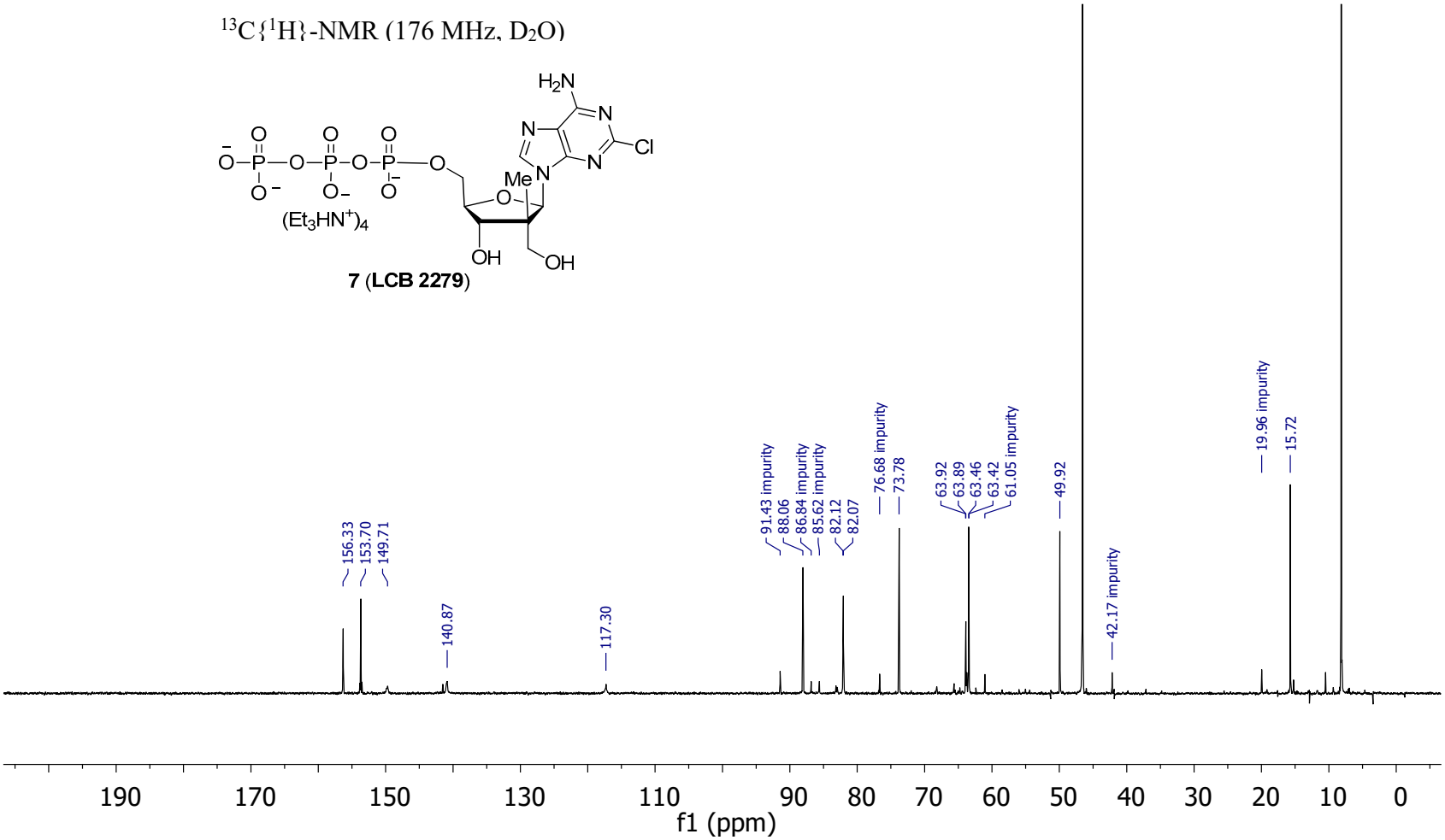
^{1}H-NMR (700 MHz, D_2O)

7 (**LCB 2279**)



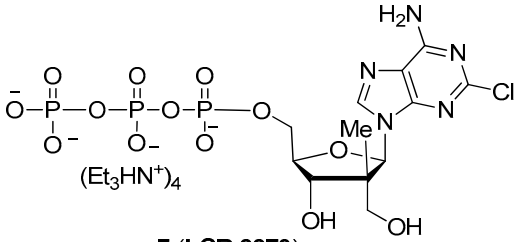
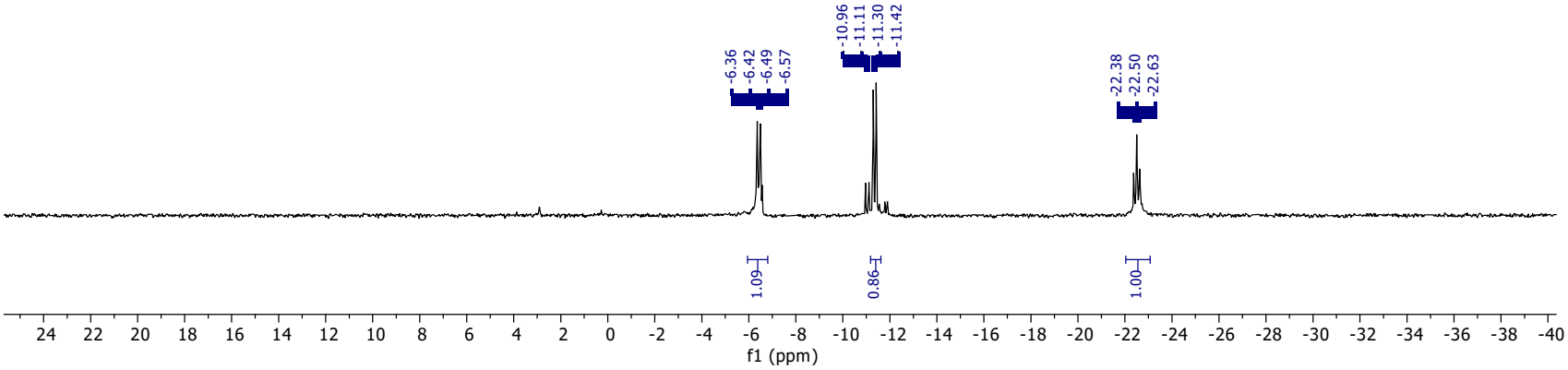
$^{13}C\{^{1}H\}$-NMR (176 MHz, D_2O)

7 (**LCB 2279**)



AM-ESP-854

^{31}P-NMR (162 MHz, D_2O)



7 (**LCB 2279**)