

# Phosphodiester silybin dimers powerful radical scavengers: A antiproliferative activity on different cancer cell lines

*Valeria Romanucci<sup>1</sup>, Rita Pagano<sup>1</sup>, Antonio Lembo<sup>1</sup>, Domenica Capasso<sup>2,3</sup>, Sonia Di Gaetano<sup>2,4</sup>, Armando Zarrelli<sup>1</sup> and Giovanni Di Fabio<sup>1,5\*</sup>*

<sup>1</sup> Department of Chemical Sciences, University of Naples Federico II, Via Cintia 4, Napoli, 80126, Italy.

<sup>2</sup> CIRPEB, University of Naples "Federico II", Via Mezzocannone 16, Napoli, 80134, Italy.

<sup>3</sup> CESTEV, University of Naples "Federico II", Via De Amicis 95, Napoli, 80145, Italy.

<sup>4</sup> Institute of Biostructures and Bioimaging-CNR, Via Mezzocannone 16, Napoli, 80134, Italy.

<sup>5</sup> AIPRAS Onlus (Associazione Italiana per la Promozione delle Ricerche sull'Ambiente e la Salute umana Onlus) Via Campellone 50, Dugenta (BN), 82030, Italy.

\*corresponding author email: [difabio@unina.it](mailto:difabio@unina.it)

## ELECTRONIC SUPPLEMENTARY INFORMATION:

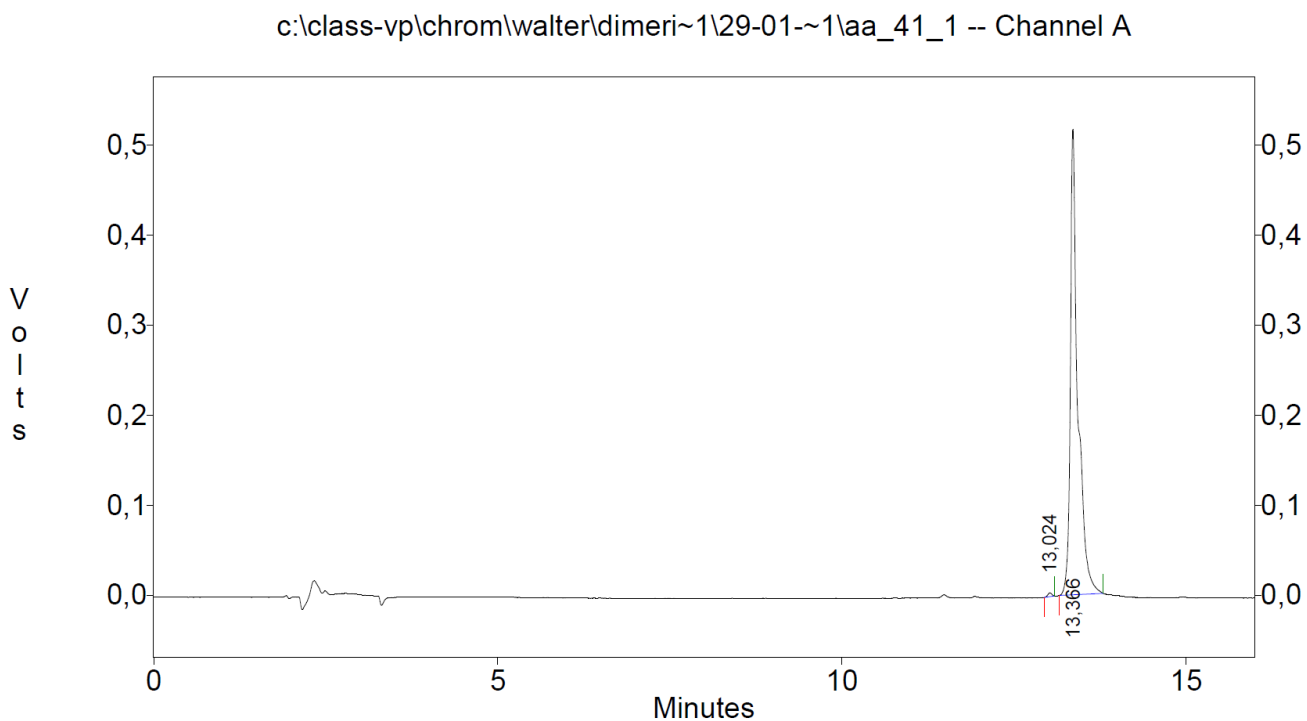
### Table of contents

<b>Figure S1</b>	RP-HPLC profile of dimer <b>6aa</b>	.....pag	2
<b>Figure S2</b>	RP-HPLC profile of dimer <b>6aa</b>	....."	3
<b>Figure S3</b>	RP-HPLC profile of dimer <b>6aa</b>	....."	4
<b>Figure S4 – S5:</b>	spectra of <b>2a</b>	....."	5-6
<b>Figure S6 – S7:</b>	spectra of <b>2b</b>	....."	7-8
<b>Figure S8 – S10:</b>	spectra of <b>4a</b>	....."	9-11
<b>Figure S11 – S13:</b>	spectra of <b>4b</b>	....."	12-14
<b>Figure S14 – S16:</b>	spectra of <b>5aa</b>	....."	15-17
<b>Figure S17 – S19:</b>	spectra of <b>5bb</b>	....."	18-20
<b>Figure S20 – S22:</b>	spectra of <b>5ab</b>	....."	21-23
<b>Figure S23 – S25:</b>	spectra of <b>6aa</b>	....."	24-26
<b>Figure S26 – S28:</b>	spectra of <b>6bb</b>	....."	27-29
<b>Figure S29 – S31:</b>	spectra of <b>6ab</b>	....."	30-32

**Figure S1** RP-HPLC analysis of dimer **6aa**

## Channel A Results

Name	Time	Area	Area %	Conc (mg/L)
	13,02	16352	0,41	0,000
	13,37	3938752	99,59	0,000
Totals :		3955104	100,00	0,000

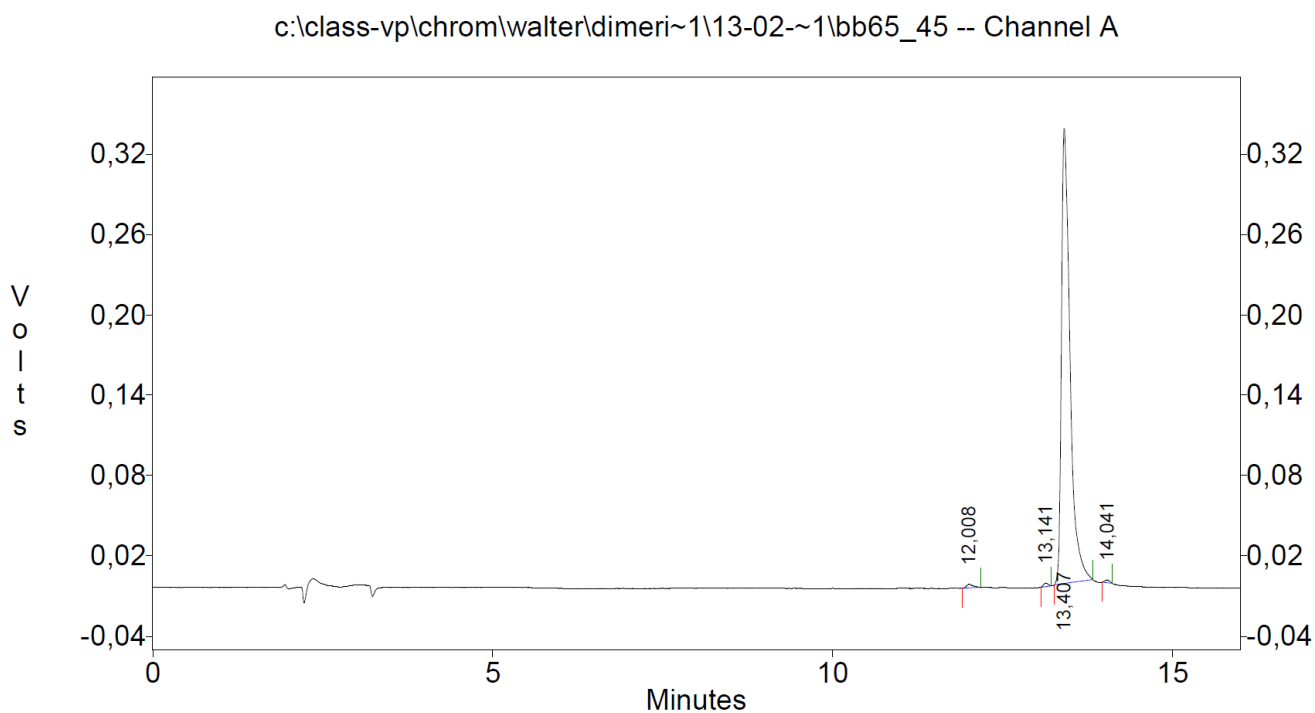


Linear gradient of MeCN in in 0.1 M ammonium acetate in H<sub>2</sub>O (pH 7.0) from 5% to 95% over 20 min at a flow rate of 0.8 mL/min with detection at 288 nm.

**Figure S2** RP-HPLC analysis of dimer **6bb**.

## Channel A Results

Name	Time	Area	Area %	Conc (mg/L)
	12,01	17289	0,58	0,000
	13,14	12082	0,41	0,000
	13,41	2937685	98,66	0,000
	14,04	10401	0,35	0,000
Totals :		2977457	100,00	0,000

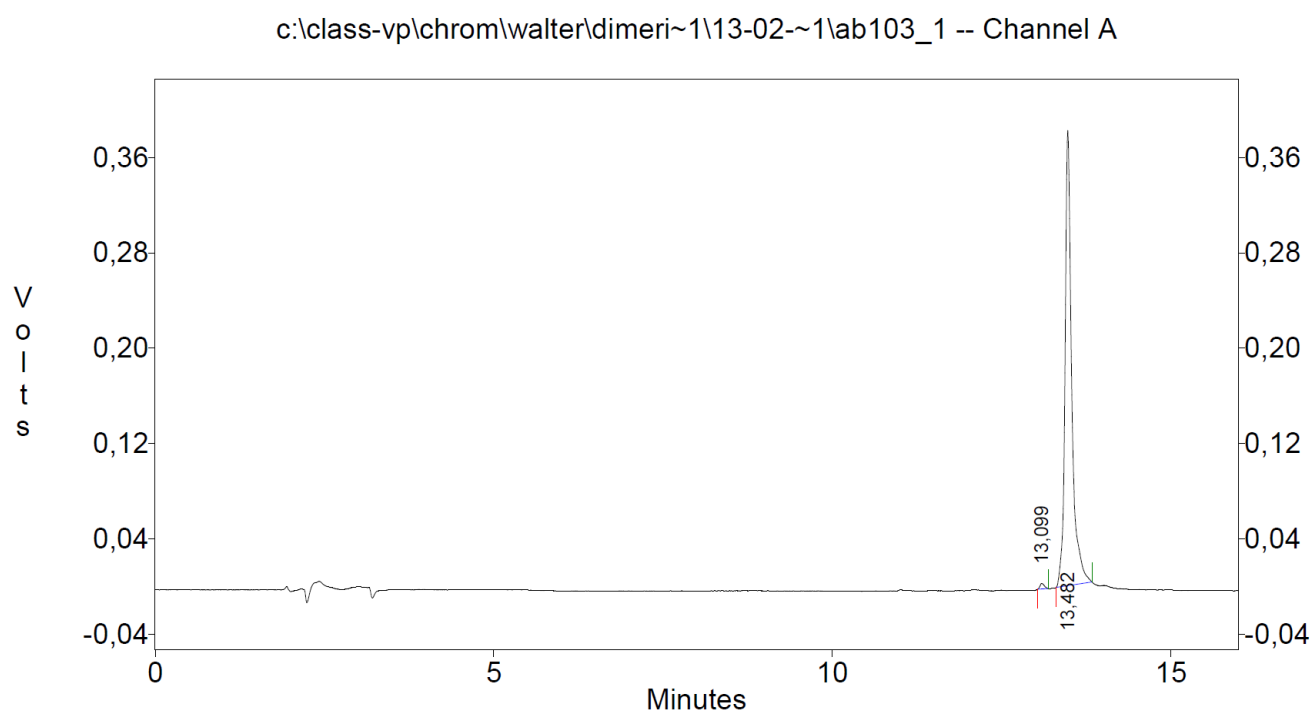


Linear gradient of MeCN in in 0.1 M ammonium acetate in H<sub>2</sub>O (pH 7.0) from 5% to 95% over 20 min at a flow rate of 0.8 mL/min with detection at 288 nm.

**Figure S3** RP-HPLC analysis of dimer **6ab**.

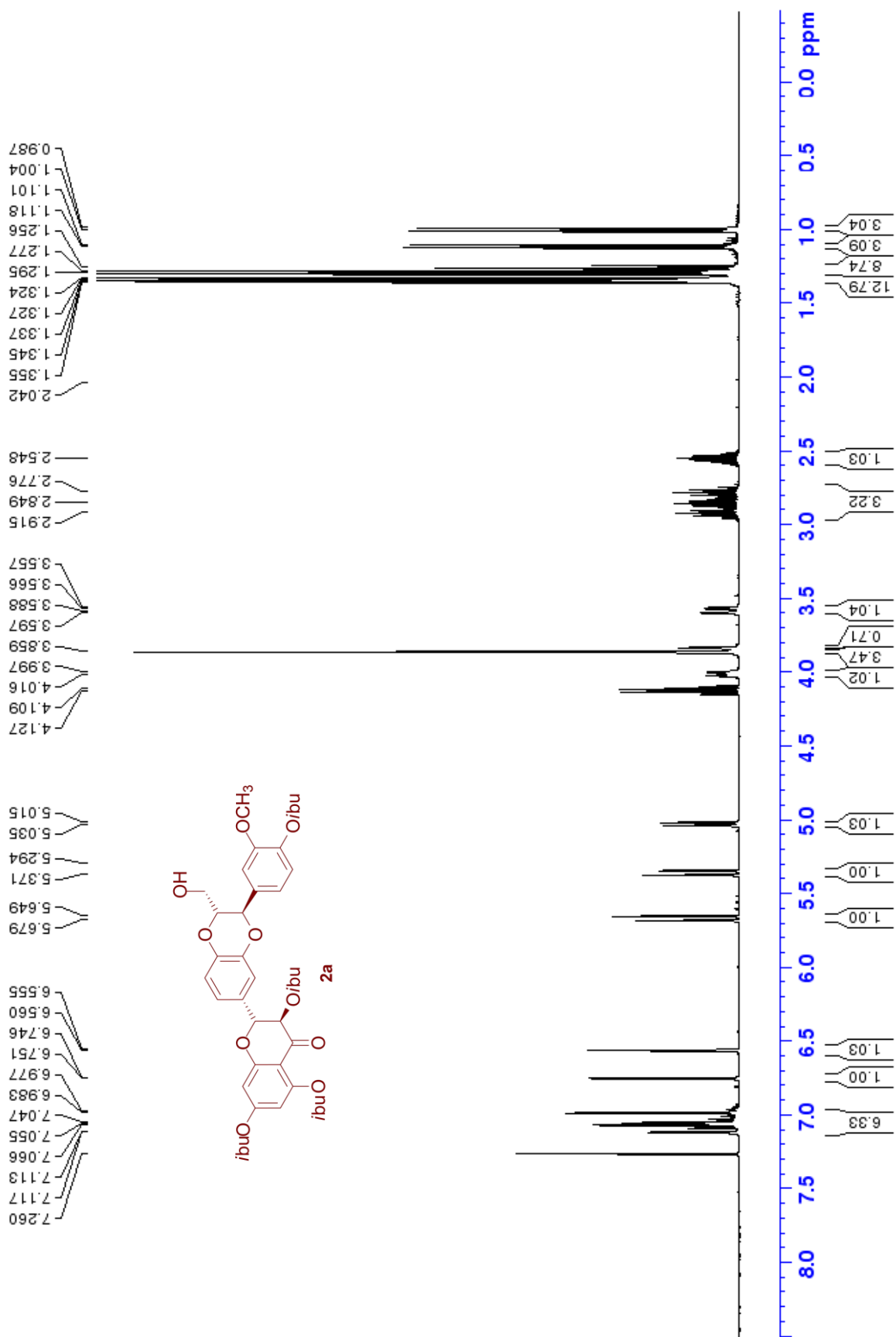
## Channel A Results

Name	Time	Area	Area %	Conc (mg/L)
	13,10	20922	0,80	0,000
	13,48	2594441	99,20	0,000
Totals :		2615363	100,00	0,000

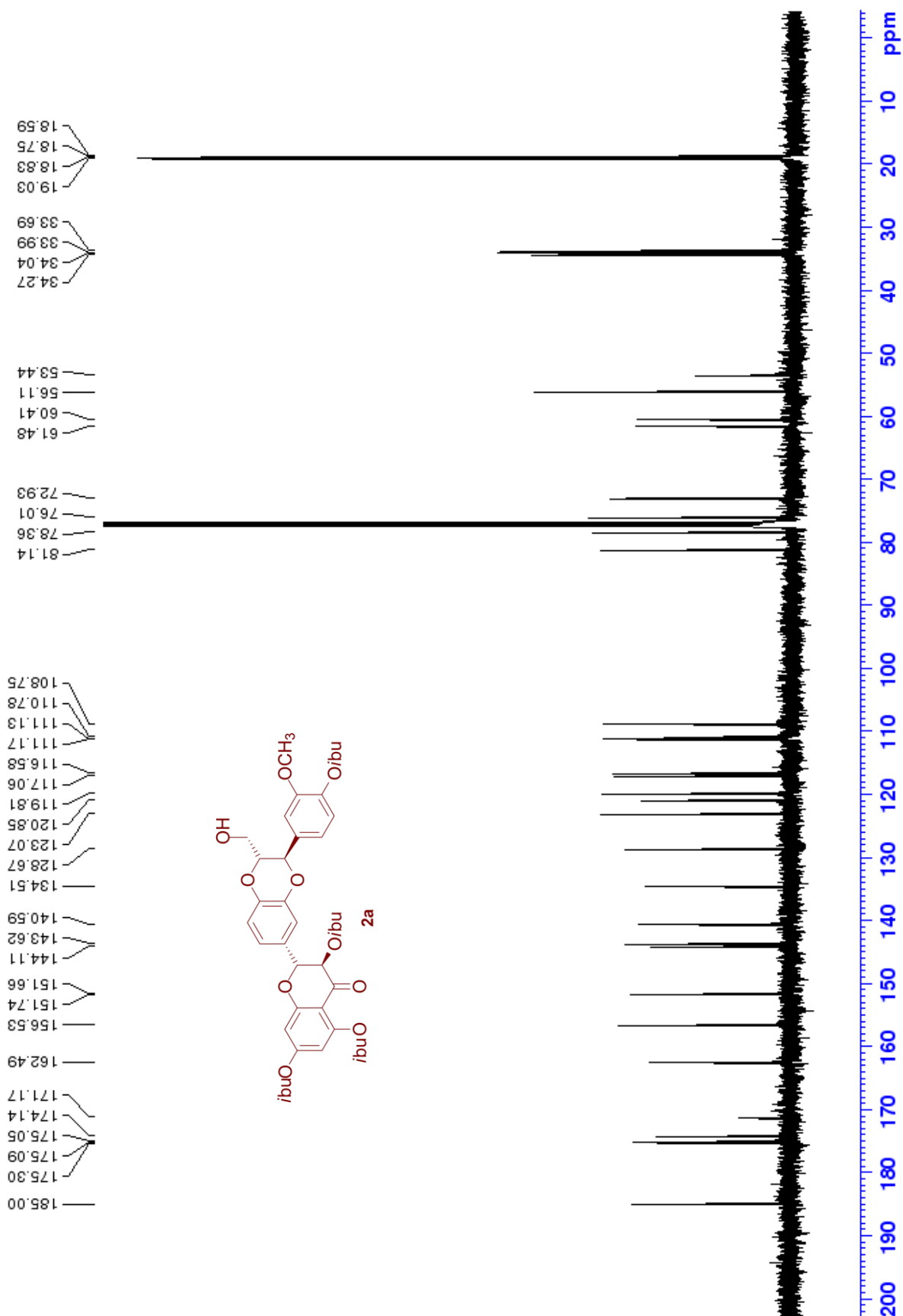


Linear gradient of MeCN in in 0.1 M ammonium acetate in H<sub>2</sub>O (pH 7.0) from 5% to 95% over 20 min at a flow rate of 0.8 mL/min with detection at 288 nm.

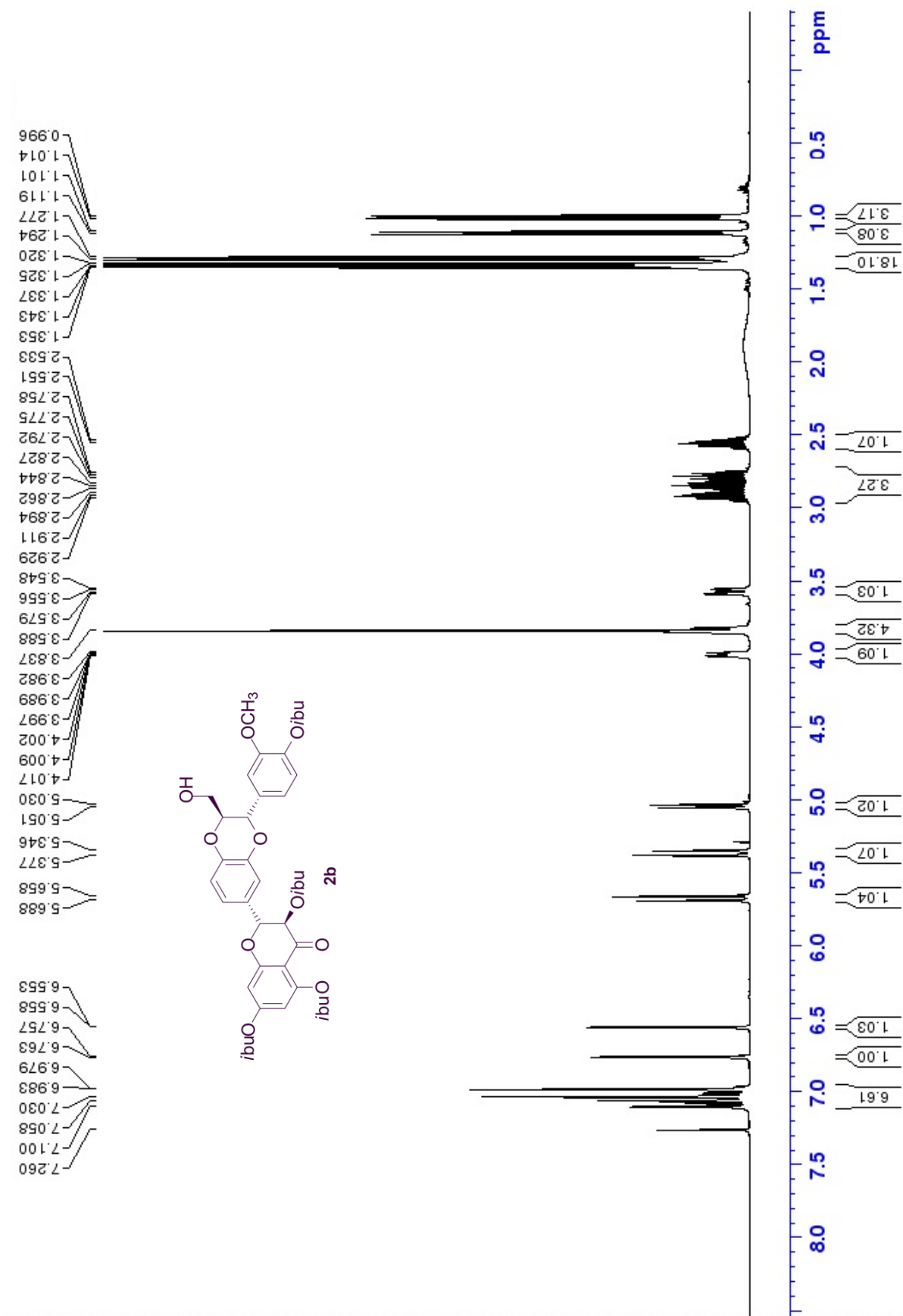
**Figure S4**  $^1\text{H}$  NMR spectrum of 3,5,7,4"-tetra-*O*-isobutyryl-silybinB **2a** (400 MHz,  $\text{CDCl}_3$ )



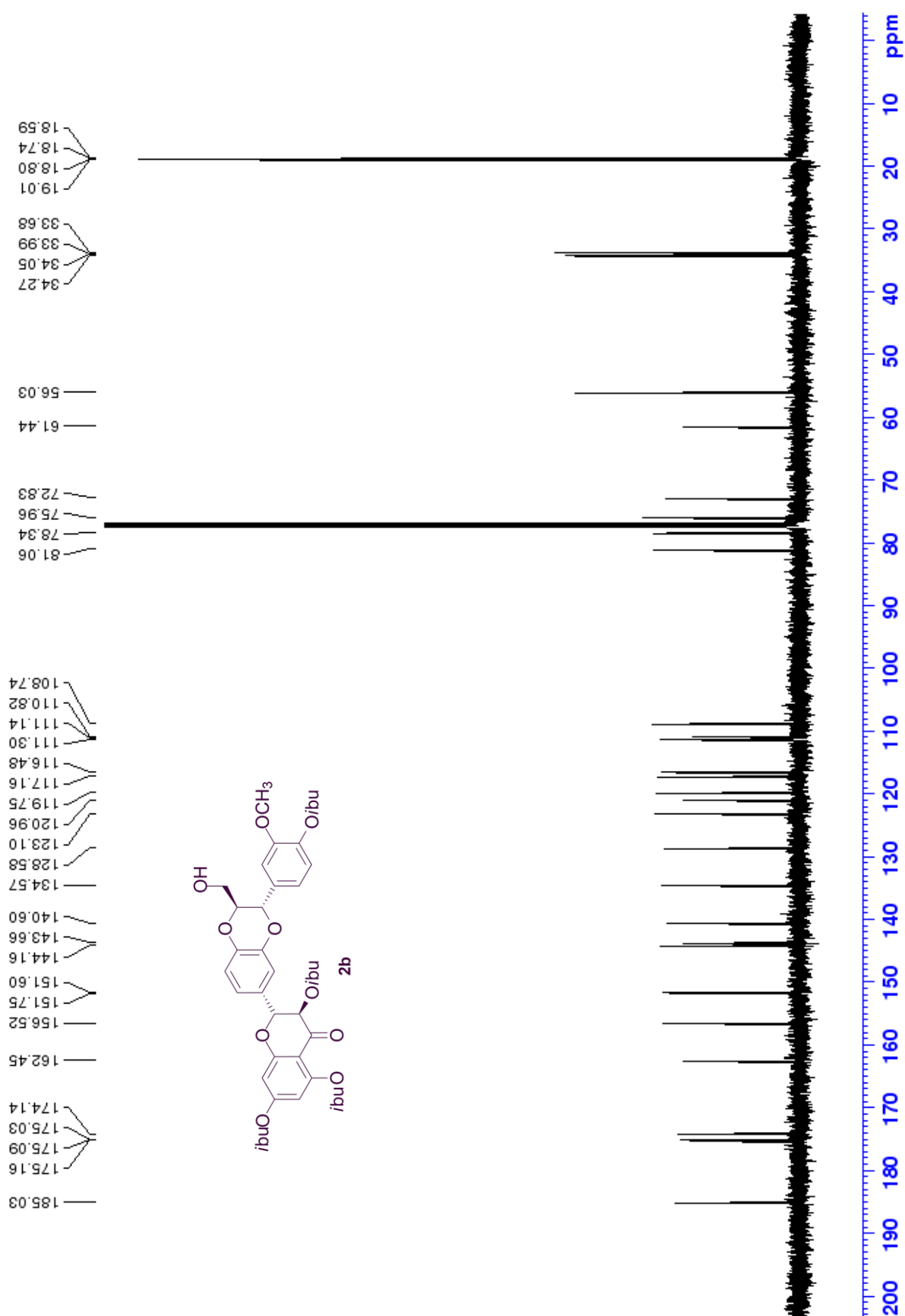
**Figure S5**  $^{13}\text{C}$  NMR spectrum of 3,5,7,4''-tetra-*O*-isobutyryl-silybinB **2a** (100 MHz,  $\text{CDCl}_3$ )



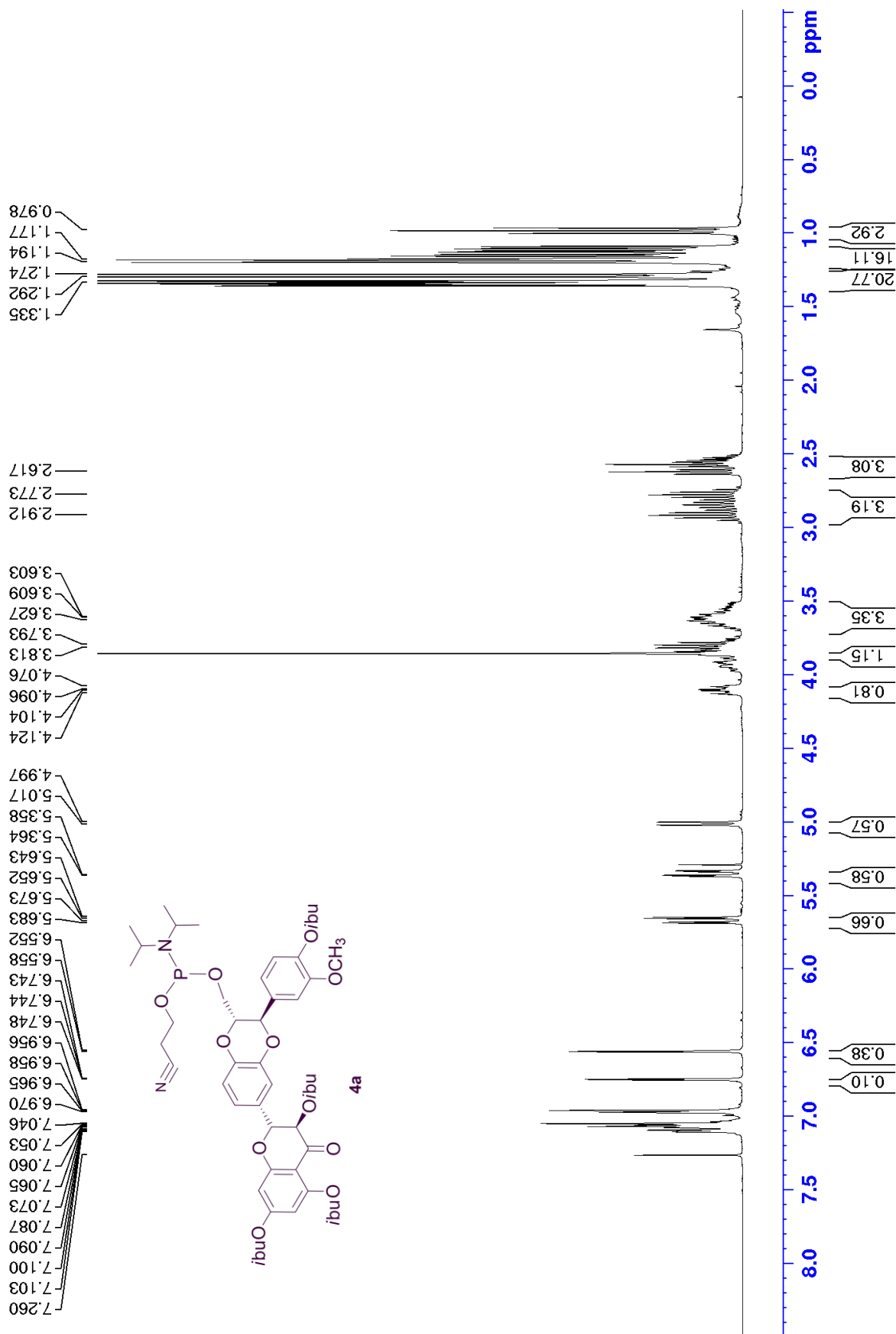
**Figure S6**  $^1\text{H}$  NMR spectrum of 3,5,7,4"-tetra-*O*-isobutyryl-silybinB **2b** (400 MHz,  $\text{CDCl}_3$ )

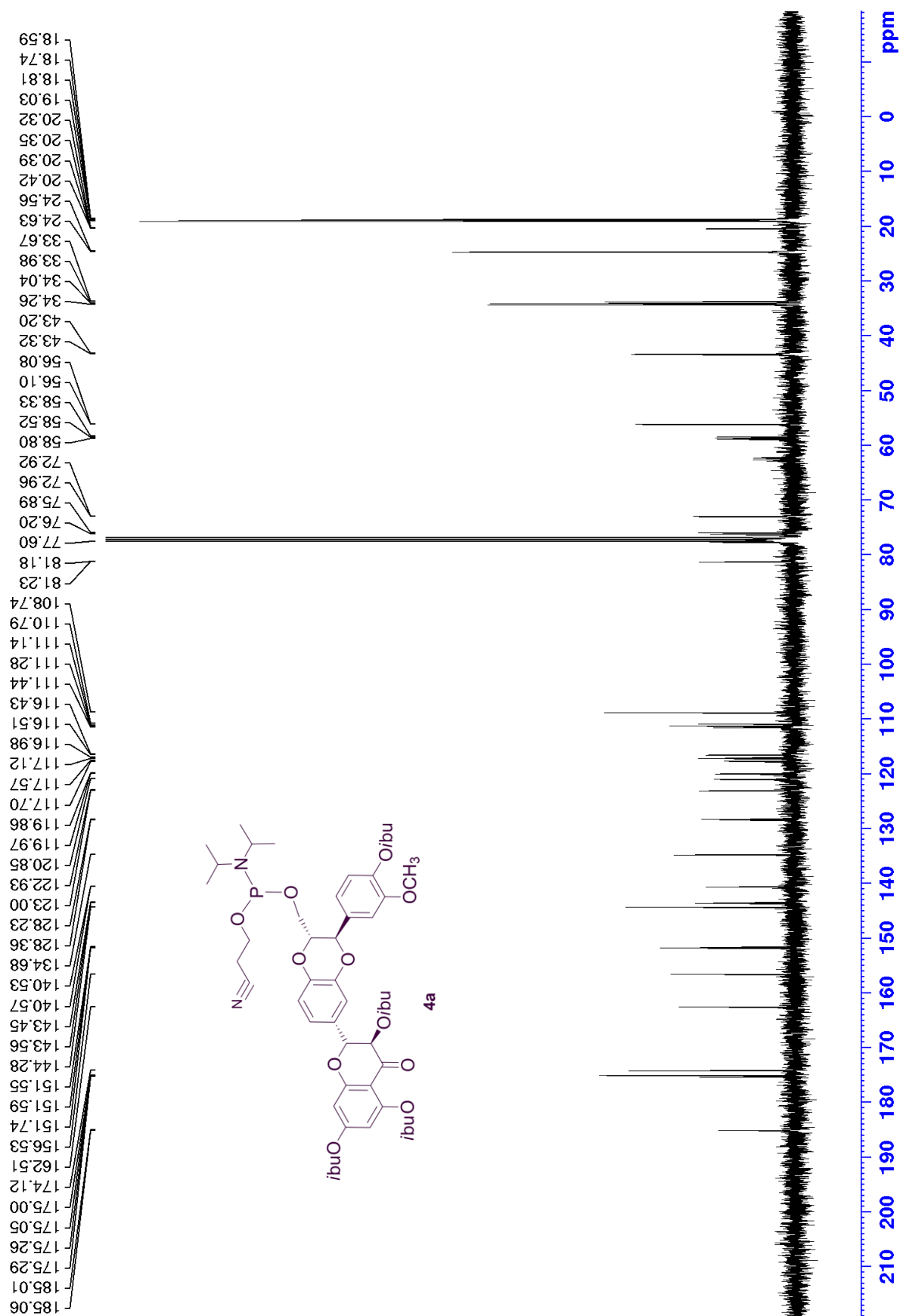


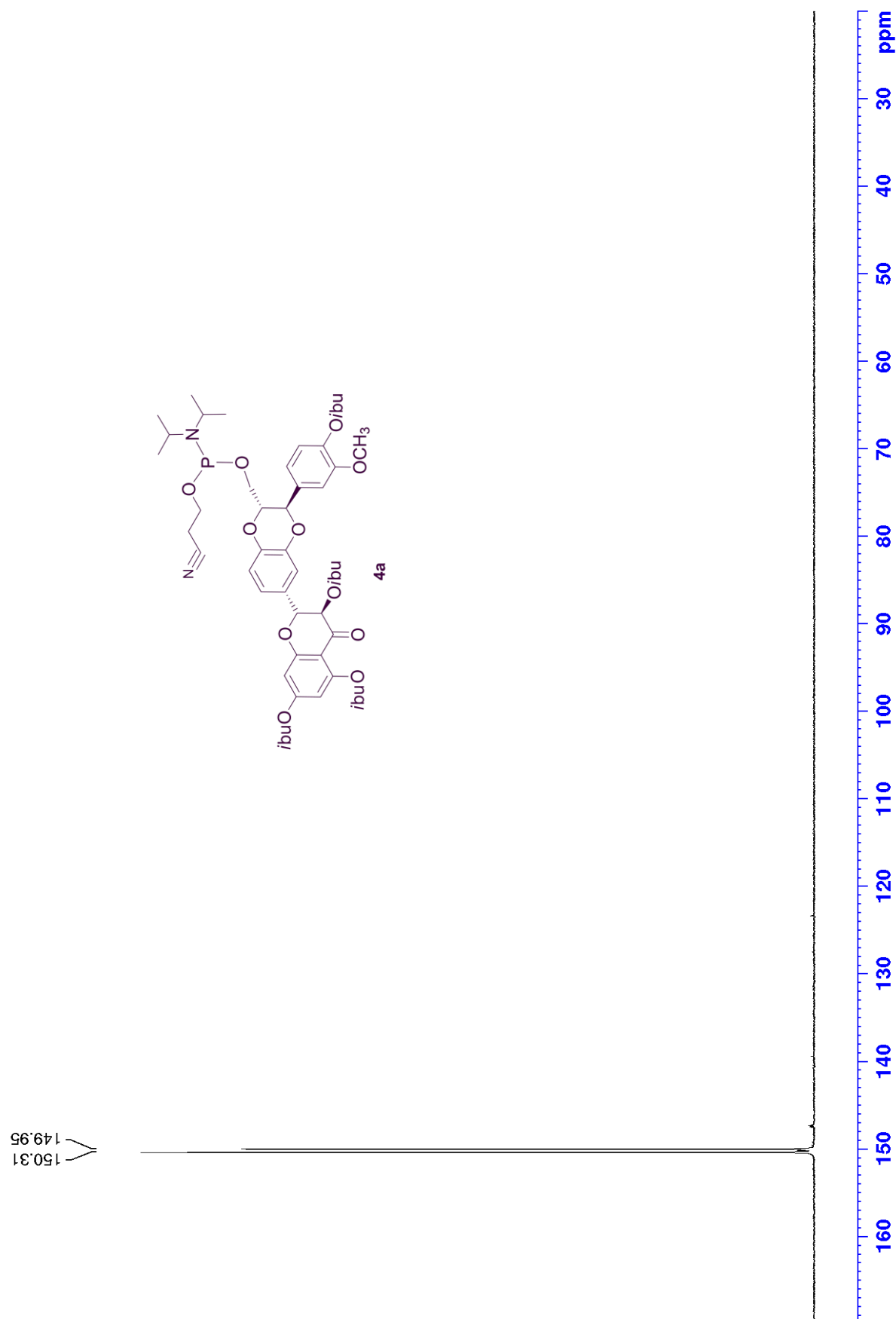
**Figure S7**  $^{13}\text{C}$  NMR spectrum of 3,5,7,4"-tetra-O-isobutyryl-silybinB **2b** (100 MHz,  $\text{CDCl}_3$ )

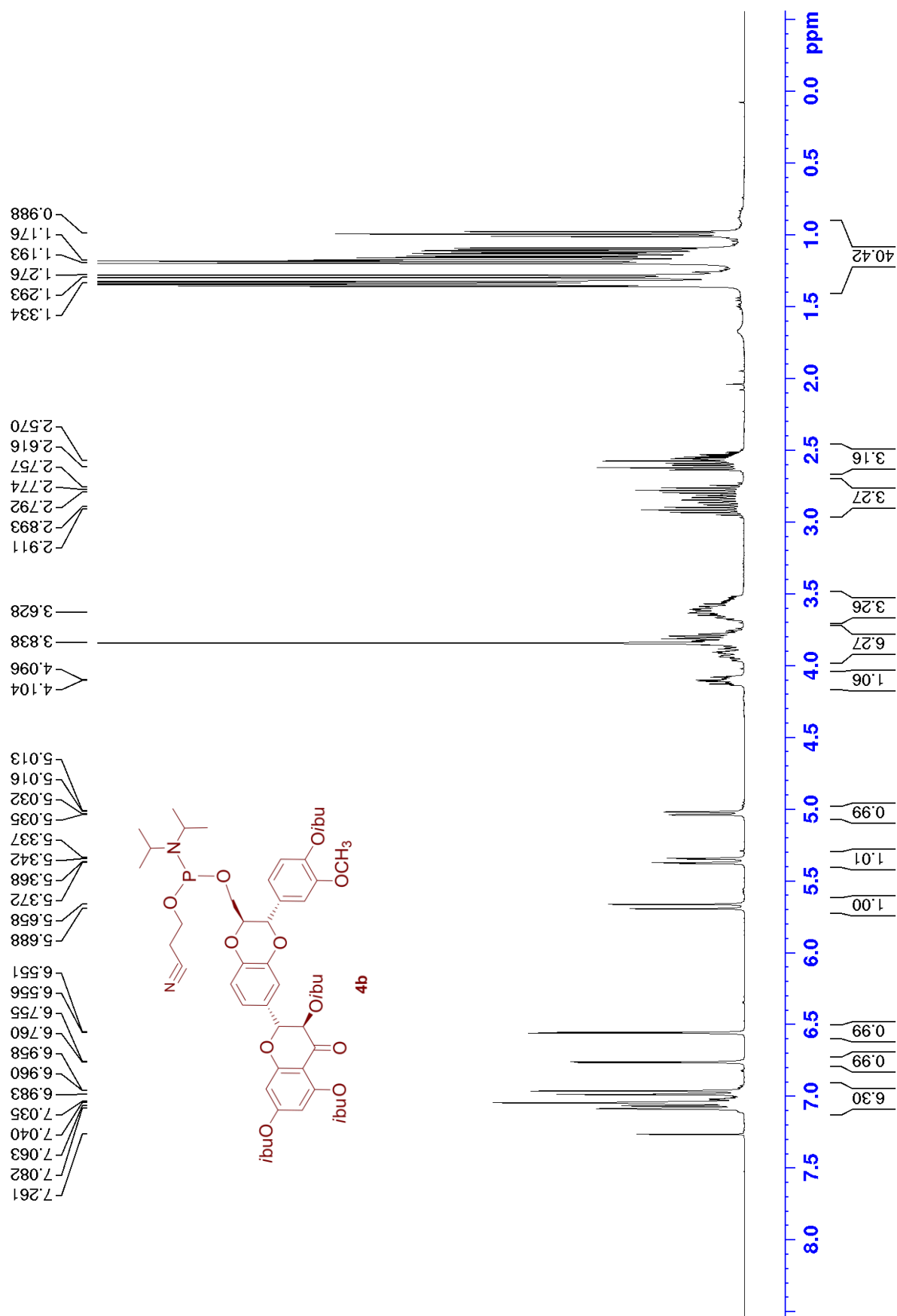


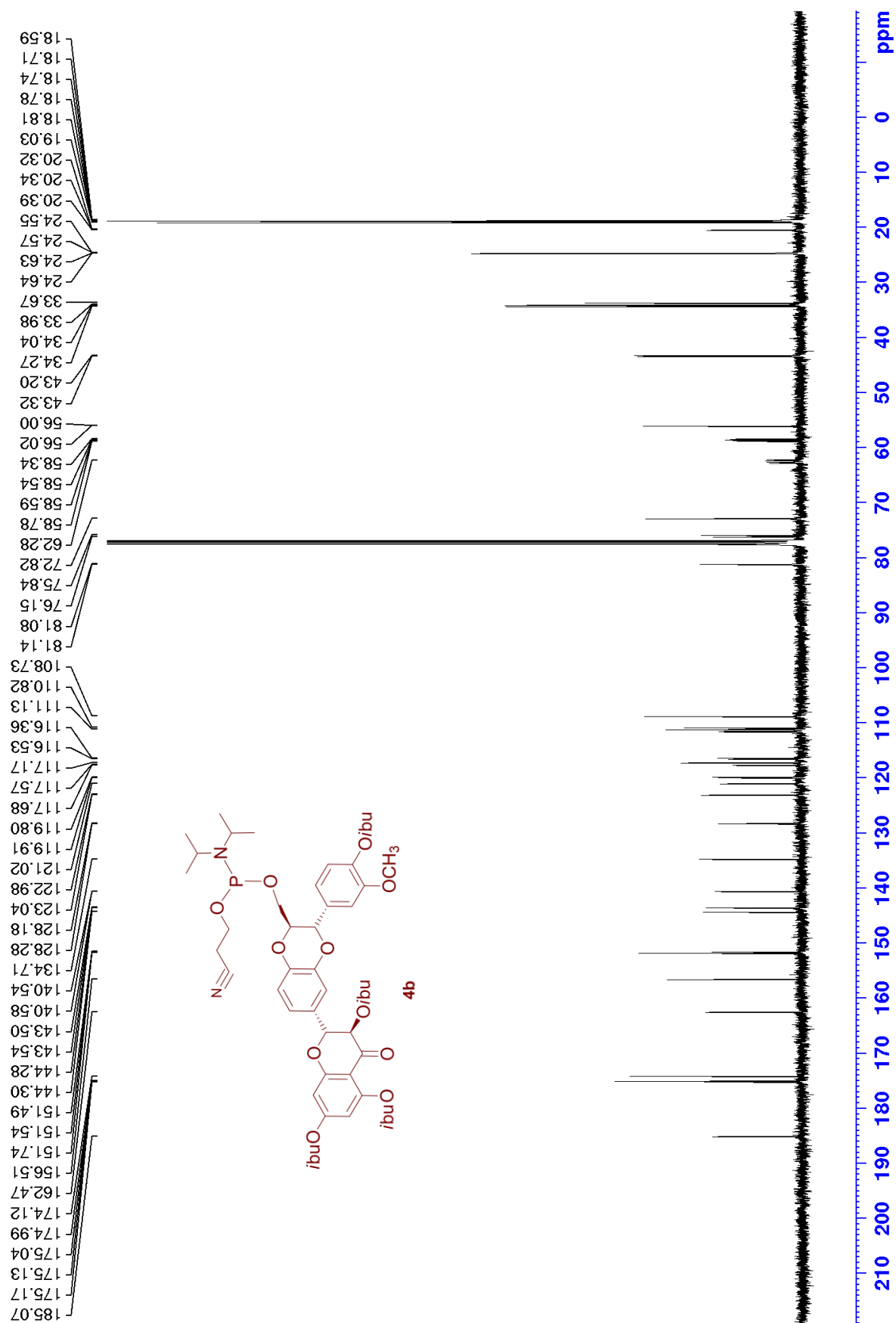


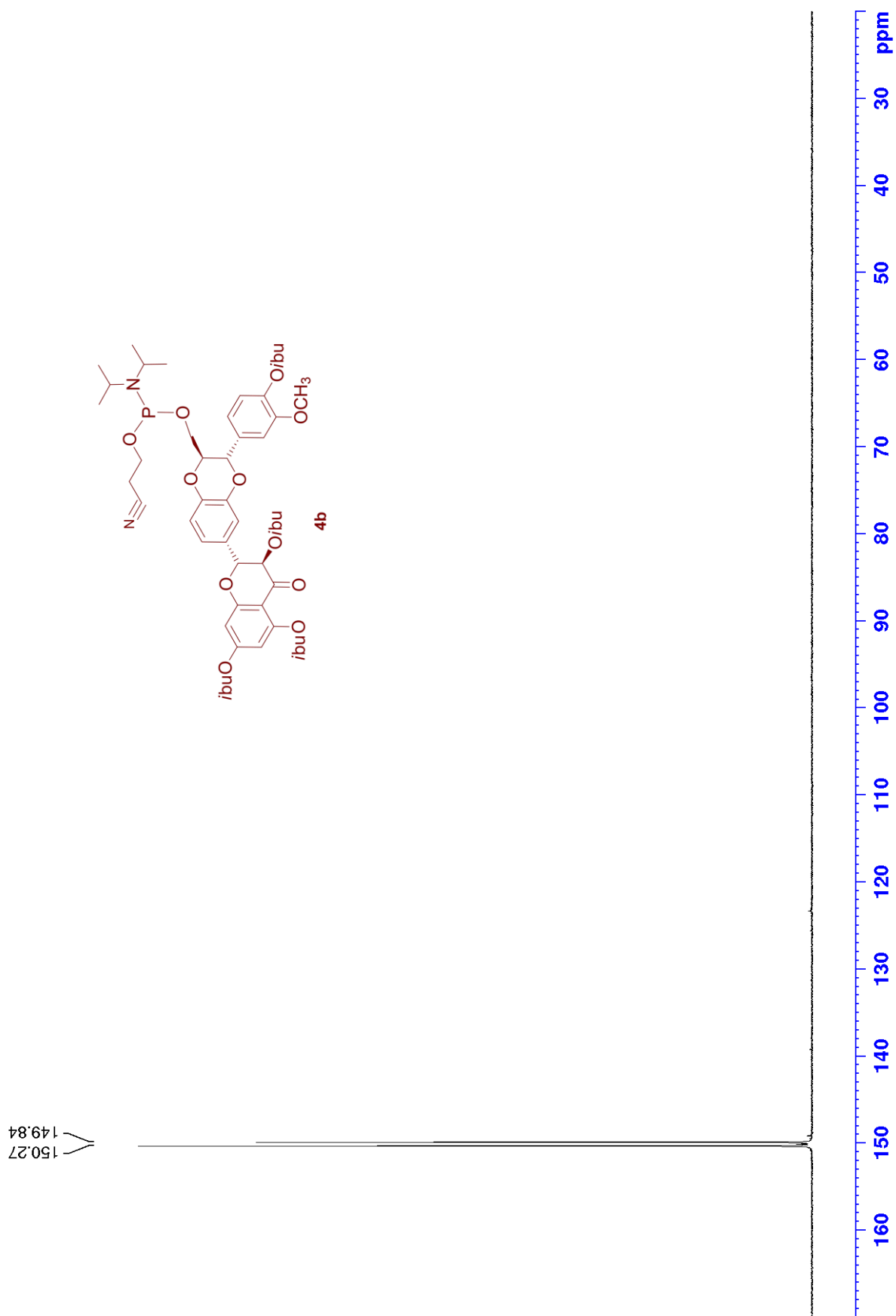
**Figure S8**  $^1\text{H}$  NMR spectrum of phosphoramidite derivative **4a** (400 MHz,  $\text{CDCl}_3$ )

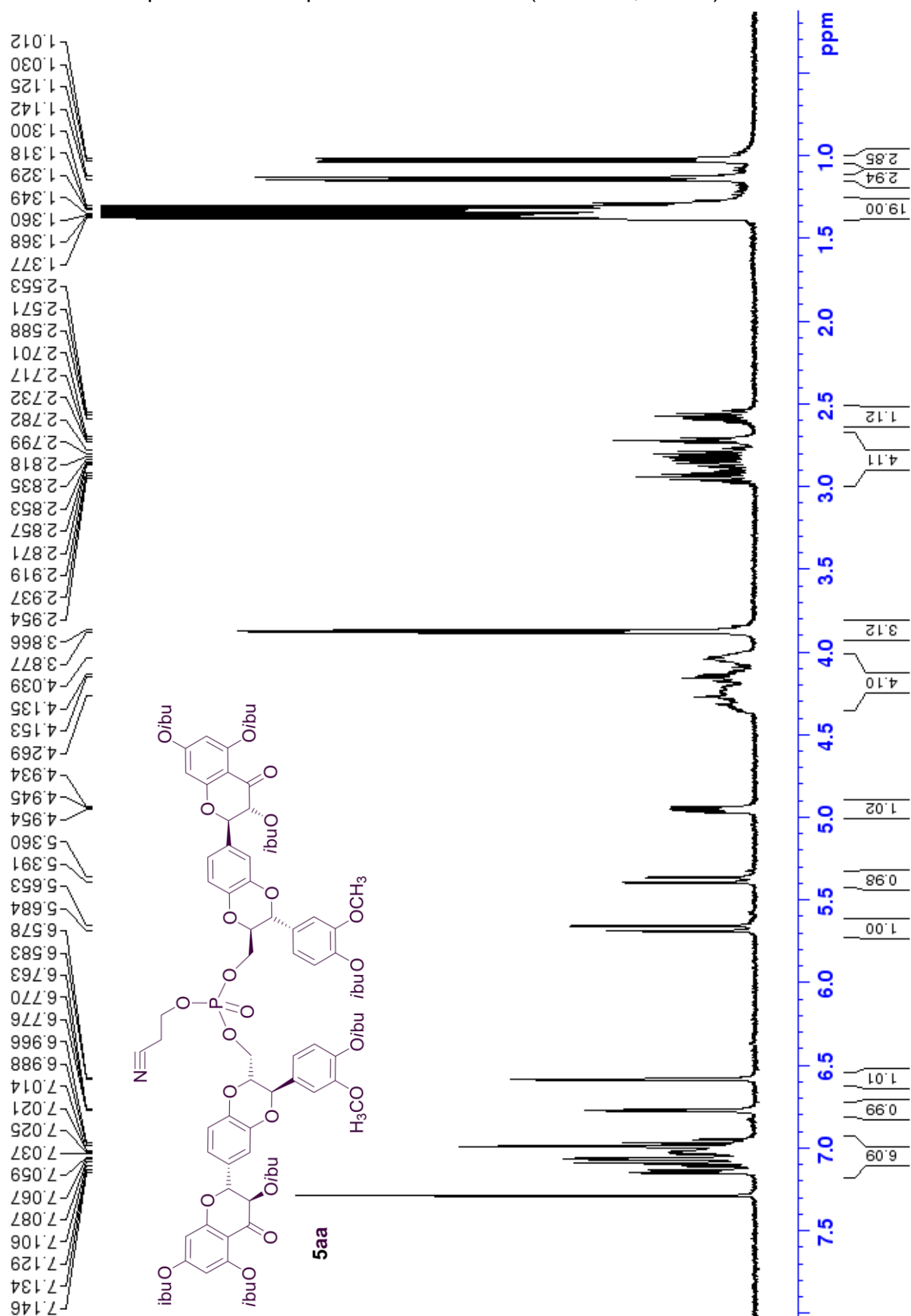
**Figure S9**  $^{13}\text{C}$  NMR spectrum of phosphoramidite derivative **4a** (100 MHz,  $\text{CDCl}_3$ )

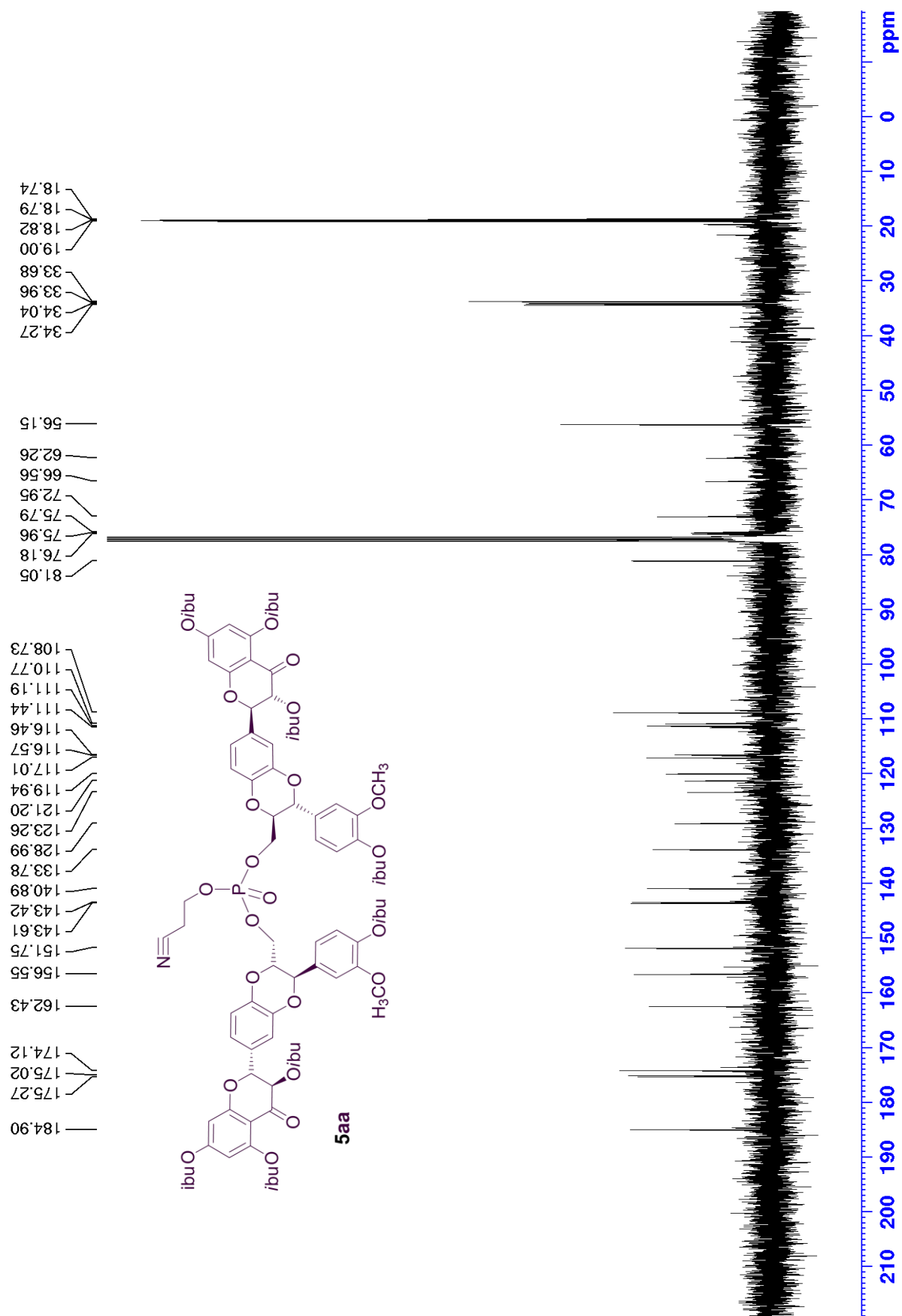
**Figure S10**  $^{31}\text{P}$  NMR spectrum of phosphoramidite derivative **4a** (168 MHz,  $\text{CDCl}_3$ )

**Figure S11**  $^1\text{H}$  NMR spectrum of phosphoramidite derivative **4b** (400 MHz,  $\text{CDCl}_3$ )

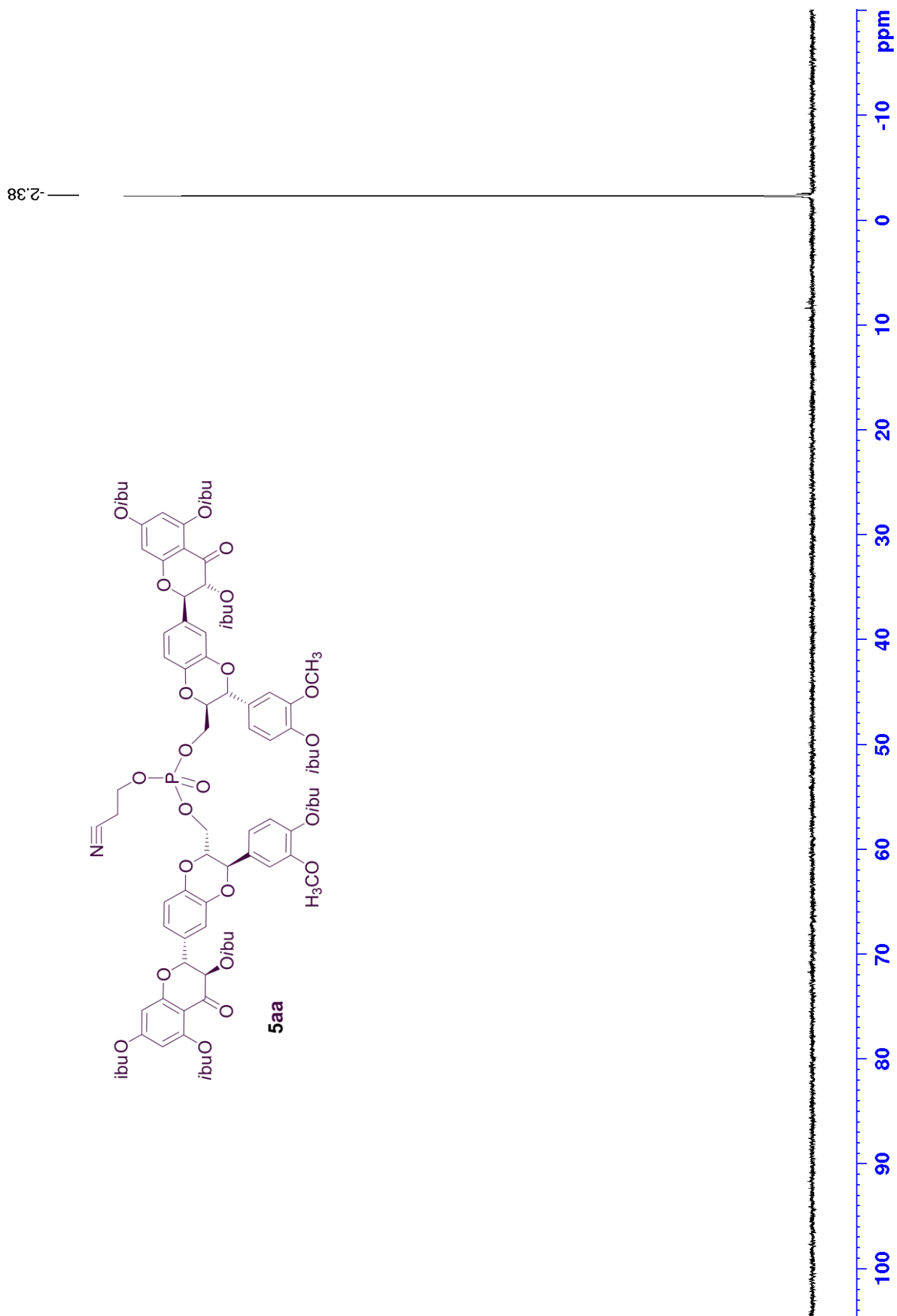
**Figure S12**  $^{13}\text{C}$  NMR spectrum of phosphoramidite derivative **4b** (400 MHz,  $\text{CDCl}_3$ )

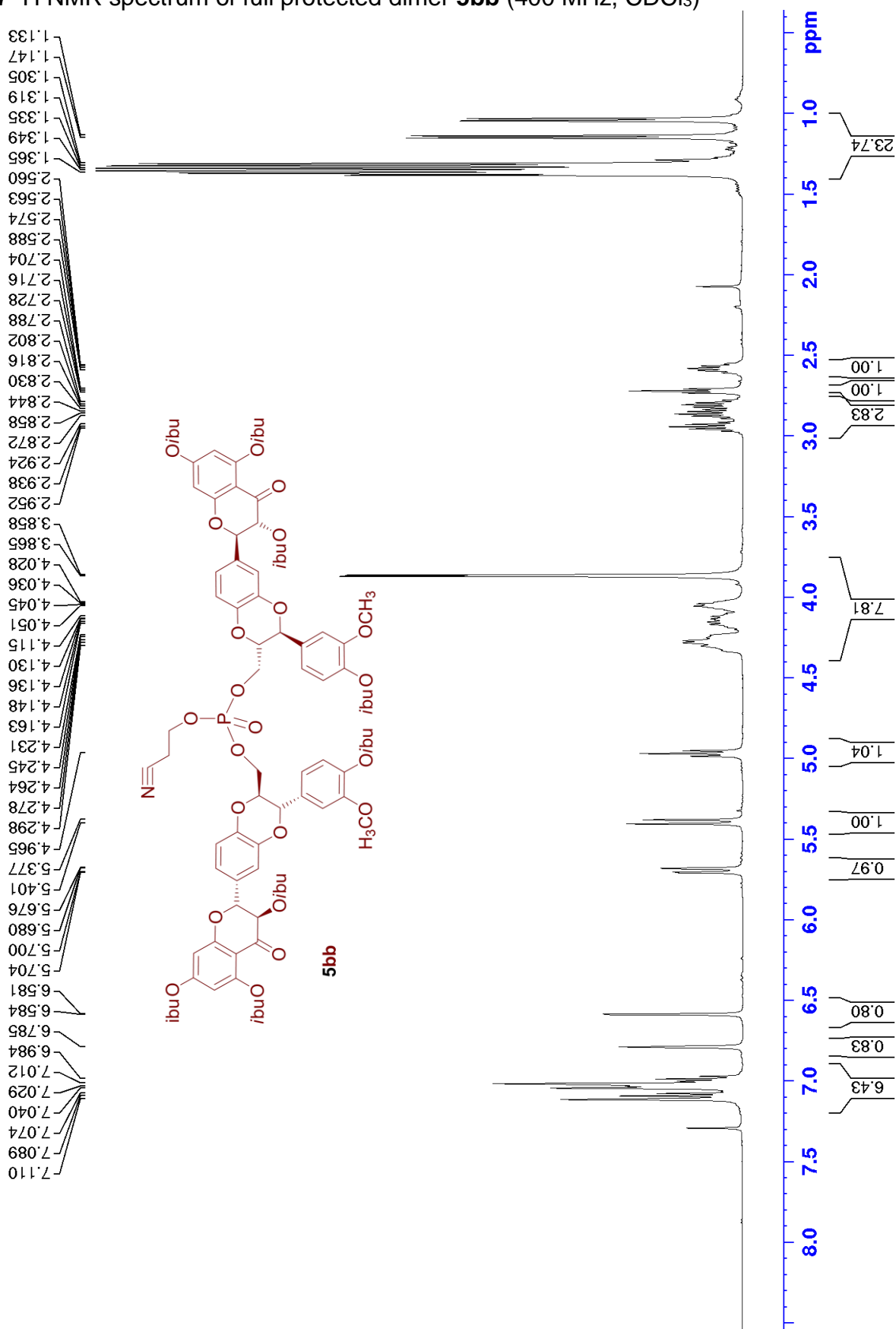




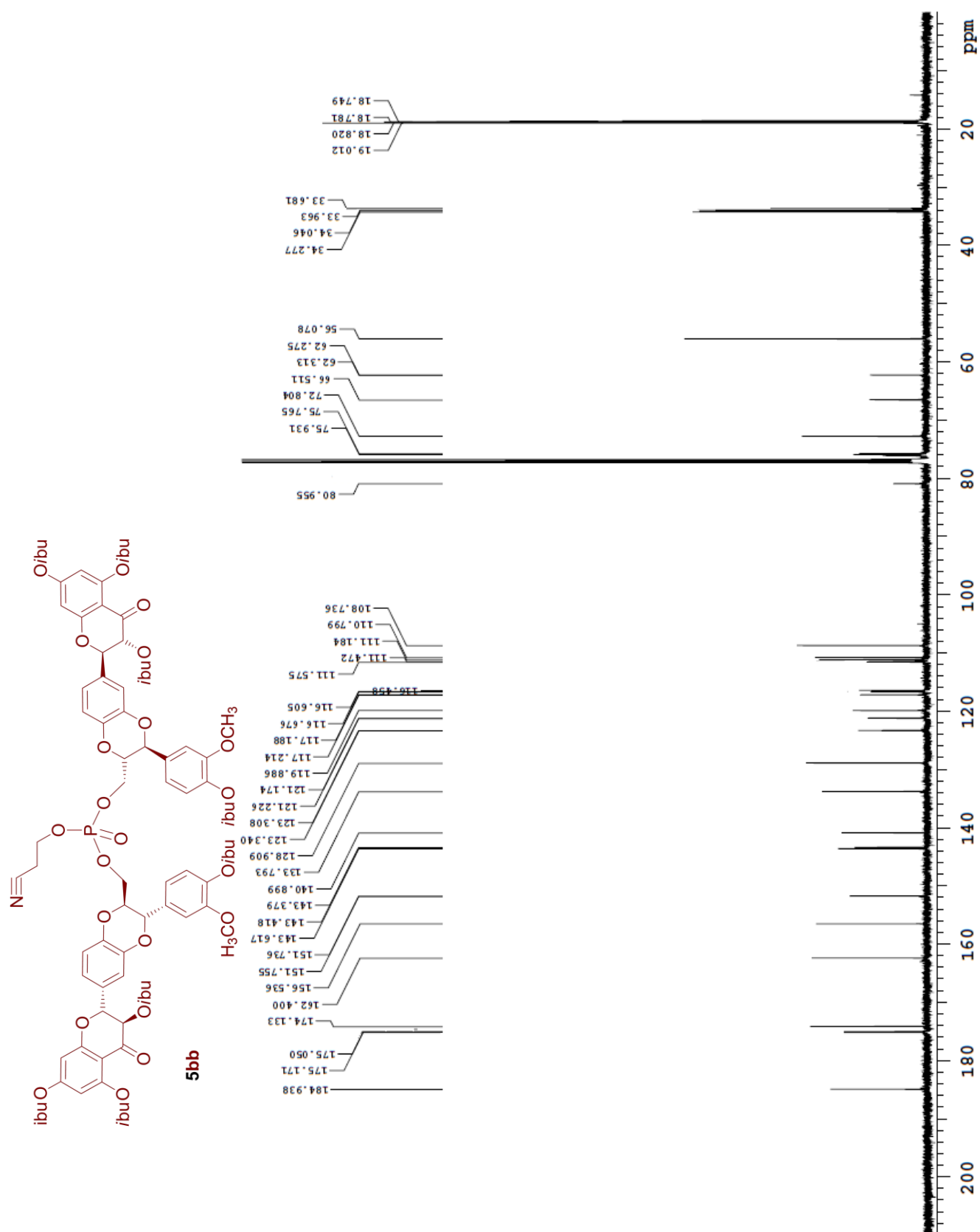
**Figure S15**  $^{13}\text{C}$  NMR spectrum of full protected dimer **5aa** (100 MHz,  $\text{CDCl}_3$ )

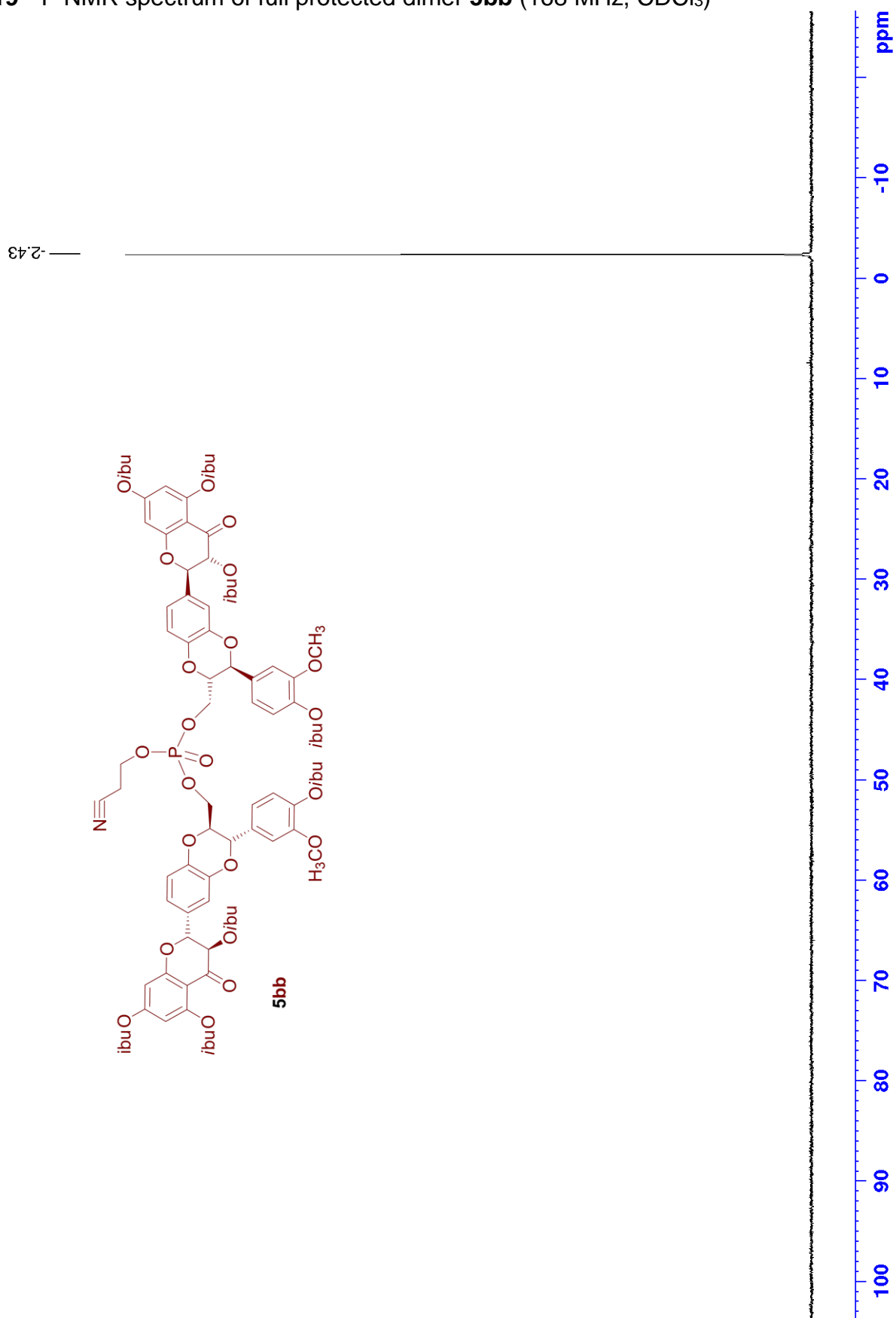


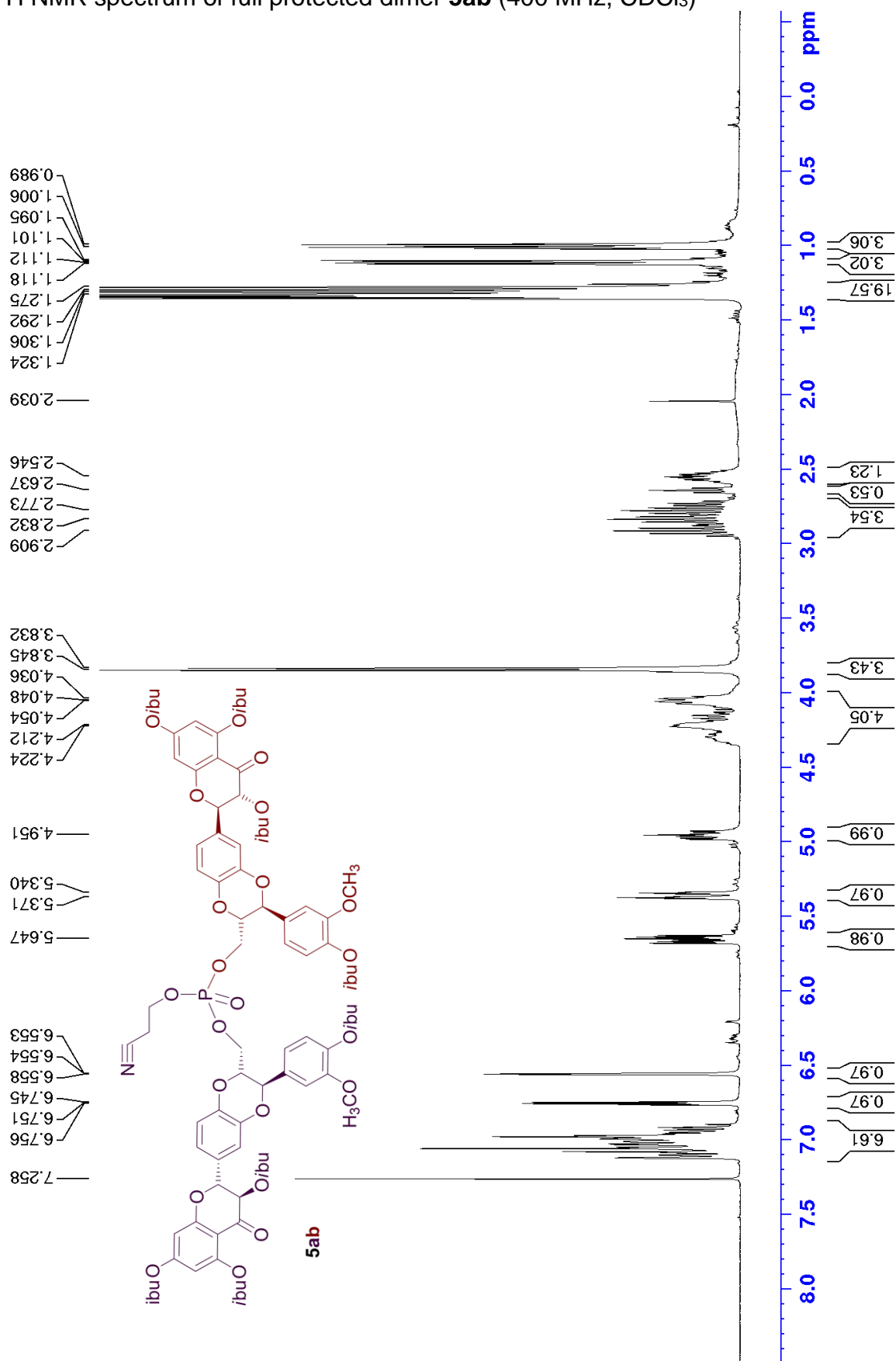
**Figure S16**  $^{31}\text{P}$  NMR spectrum of full protected dimer **5aa** (168 MHz,  $\text{CDCl}_3$ )

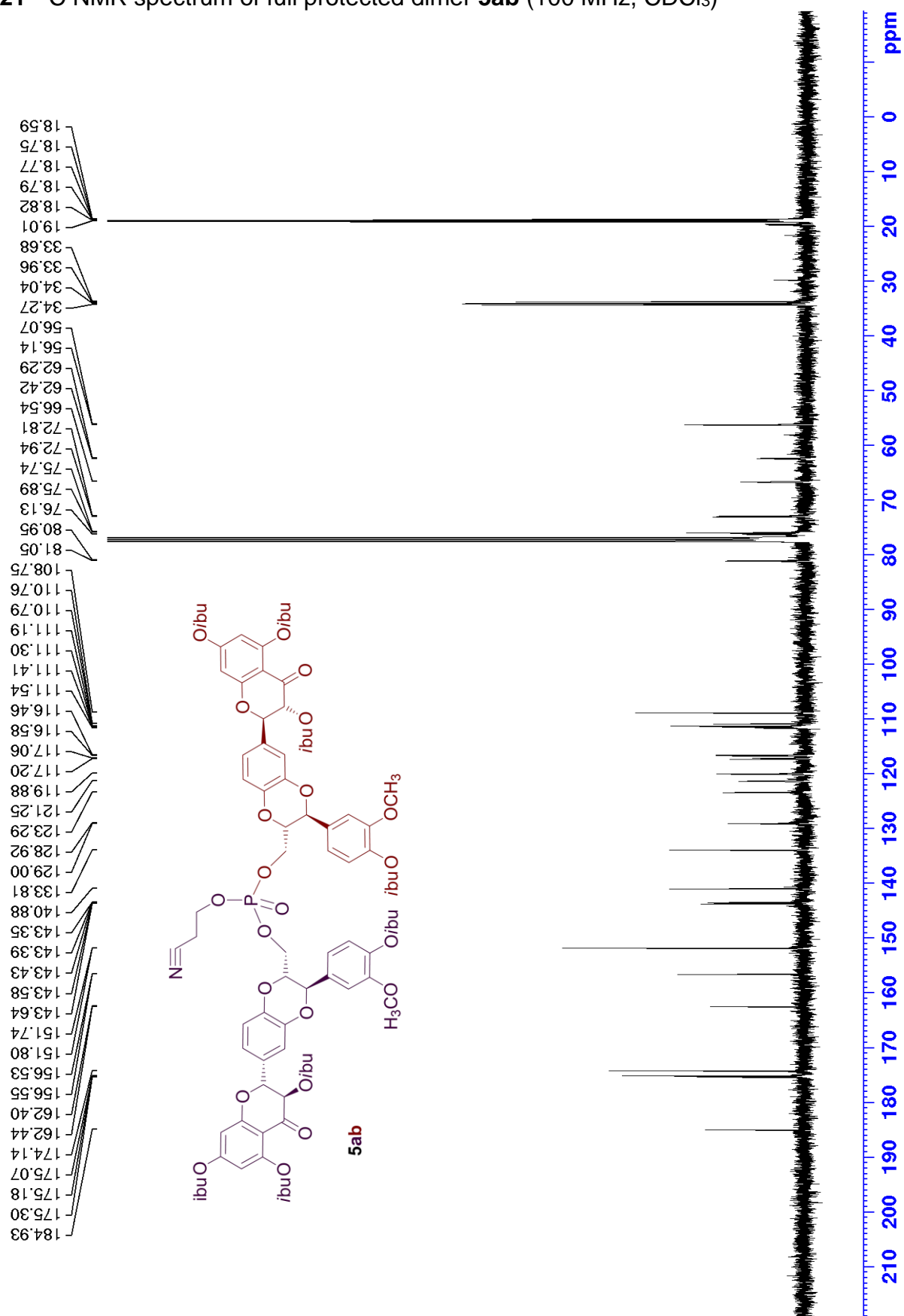


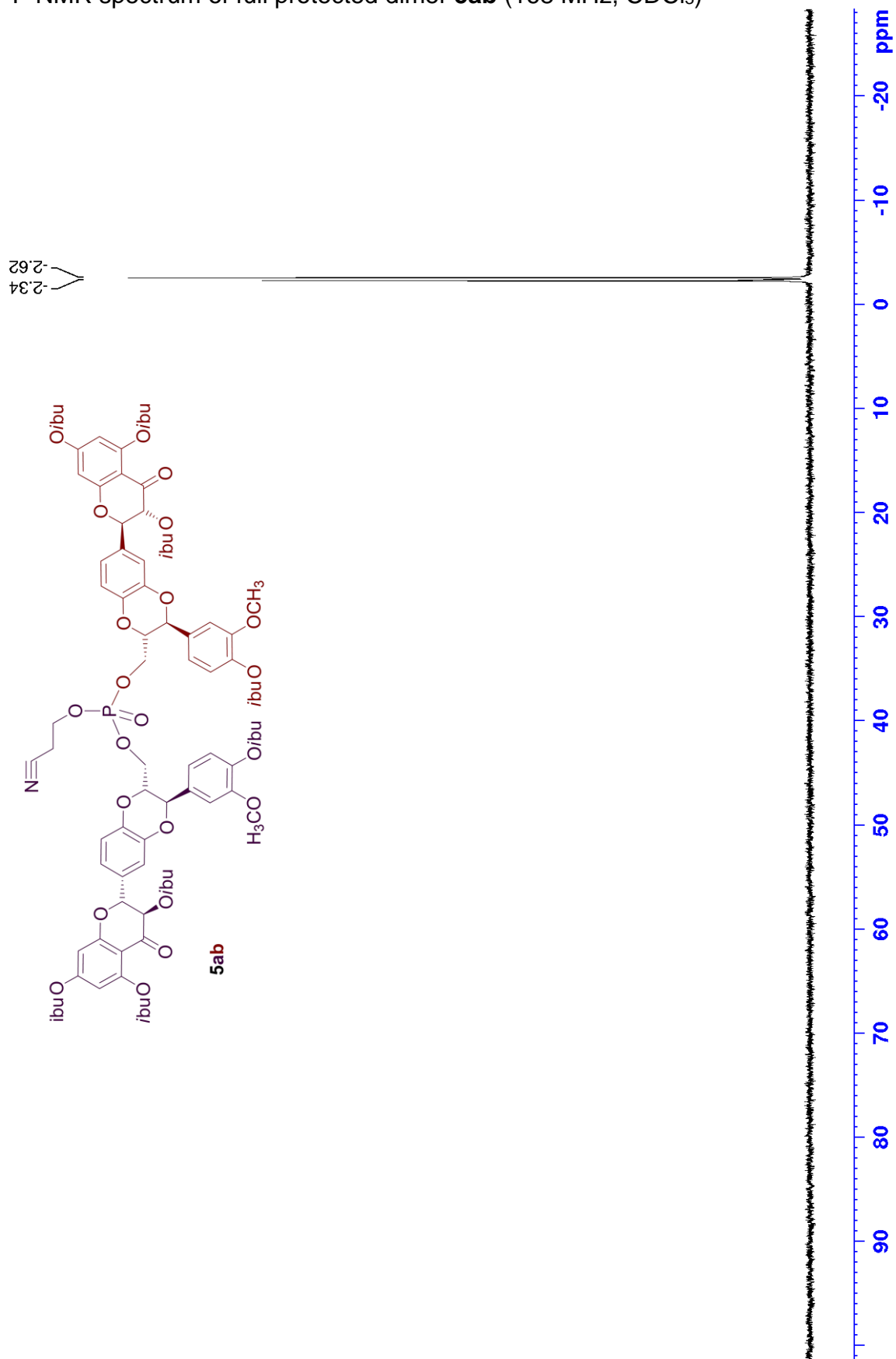
**Figure S18**  $^{13}\text{C}$  NMR spectrum of full protected dimer **5bb** (125 MHz,  $\text{CDCl}_3$ )

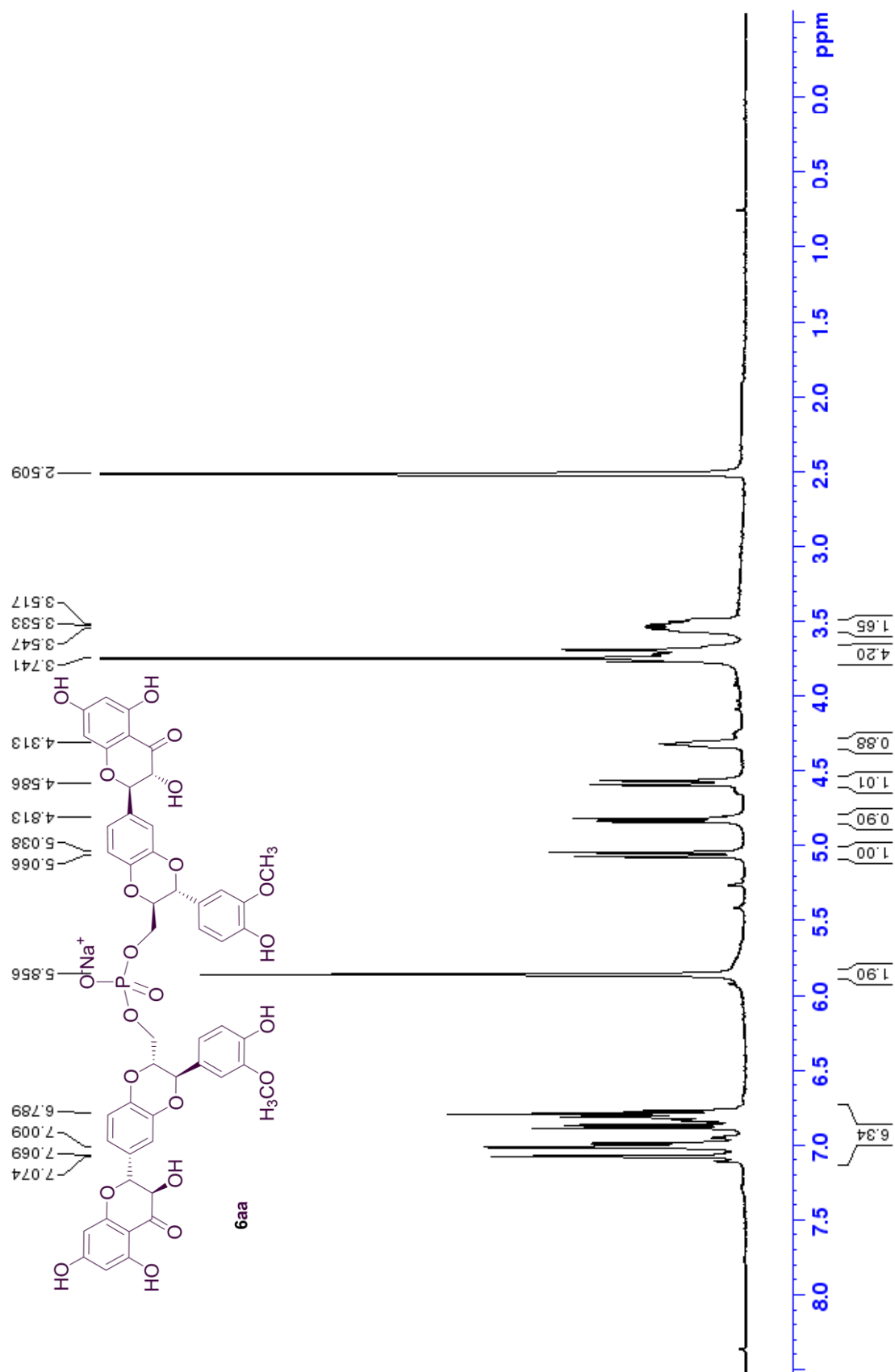


**Figure S19**  $^{31}\text{P}$  NMR spectrum of full protected dimer **5bb** (168 MHz,  $\text{CDCl}_3$ )

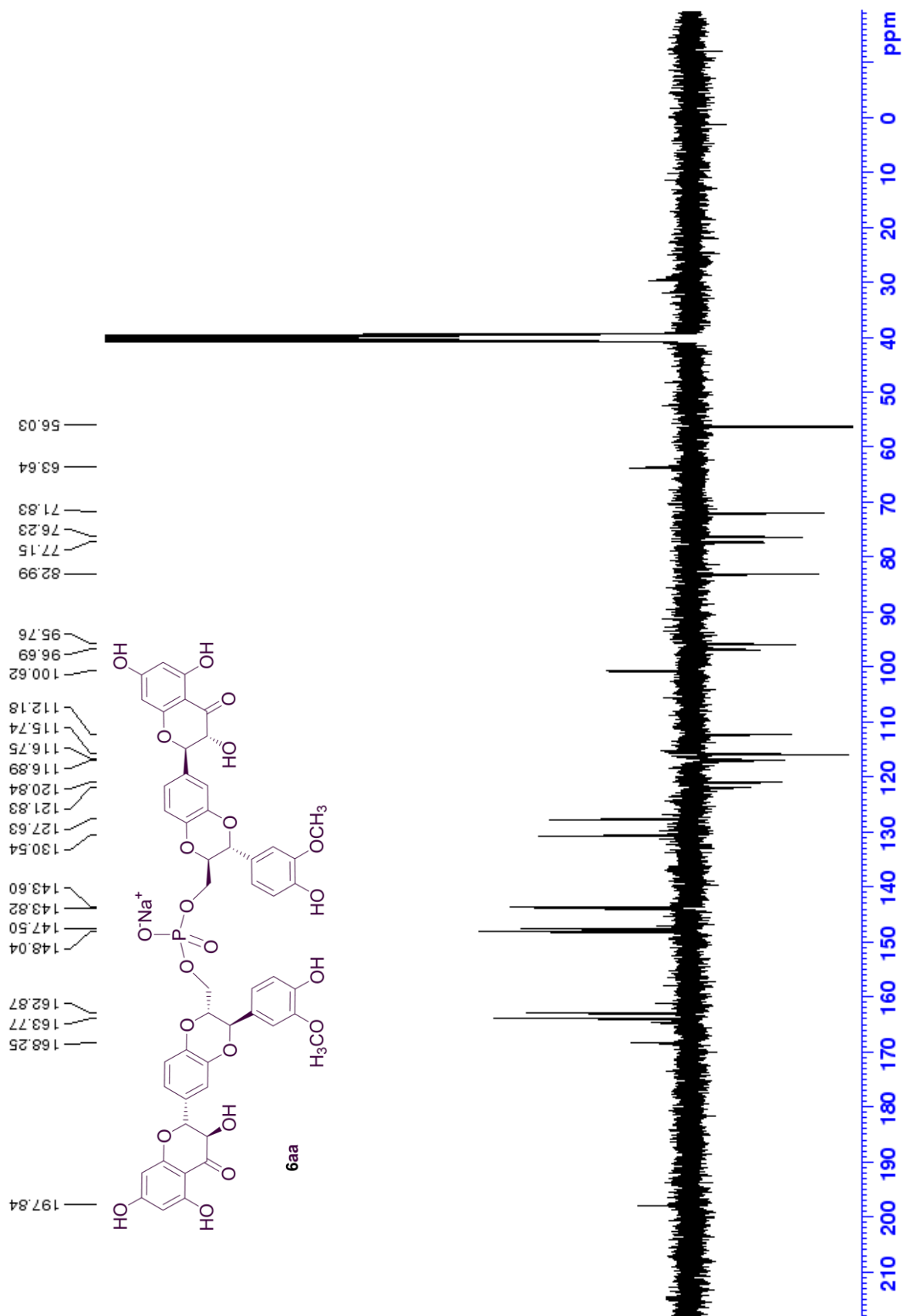




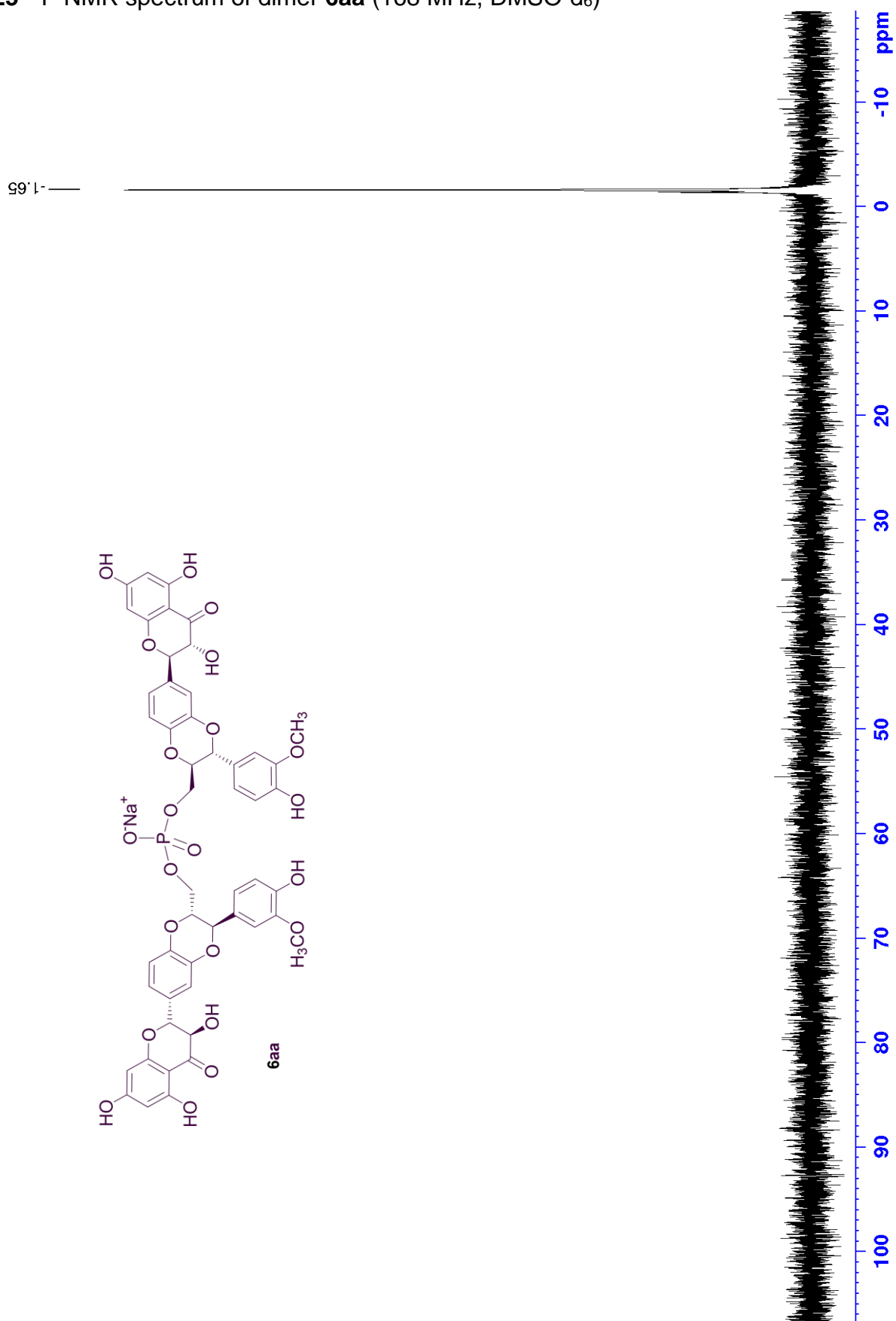
**Figure S22**  $^{31}\text{P}$  NMR spectrum of full protected dimer **5ab** (168 MHz,  $\text{CDCl}_3$ )

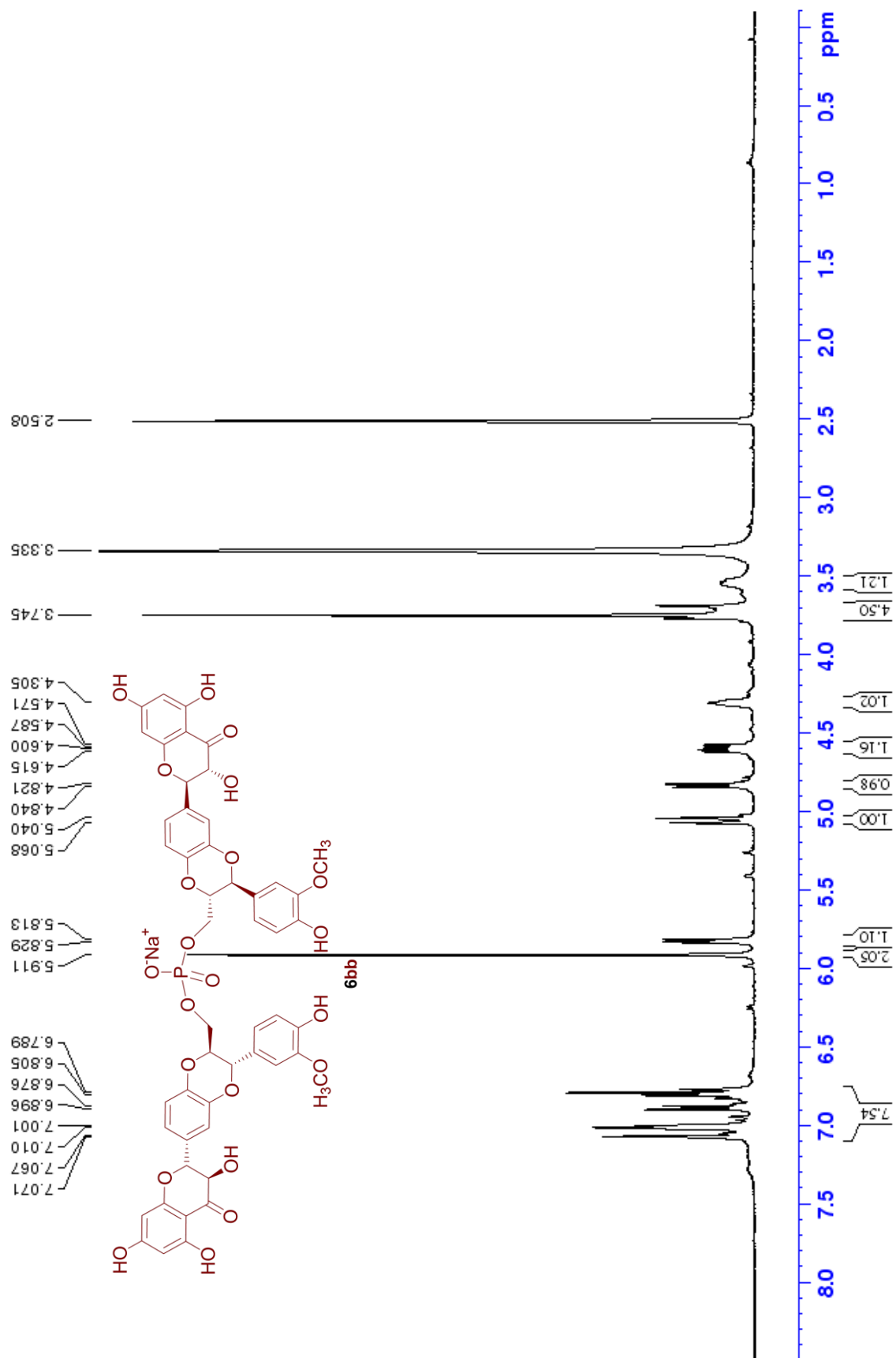
**Figure S23**  $^1\text{H}$  NMR spectrum of dimer **6aa** (400 MHz,  $\text{DMSO-d}_6$ )

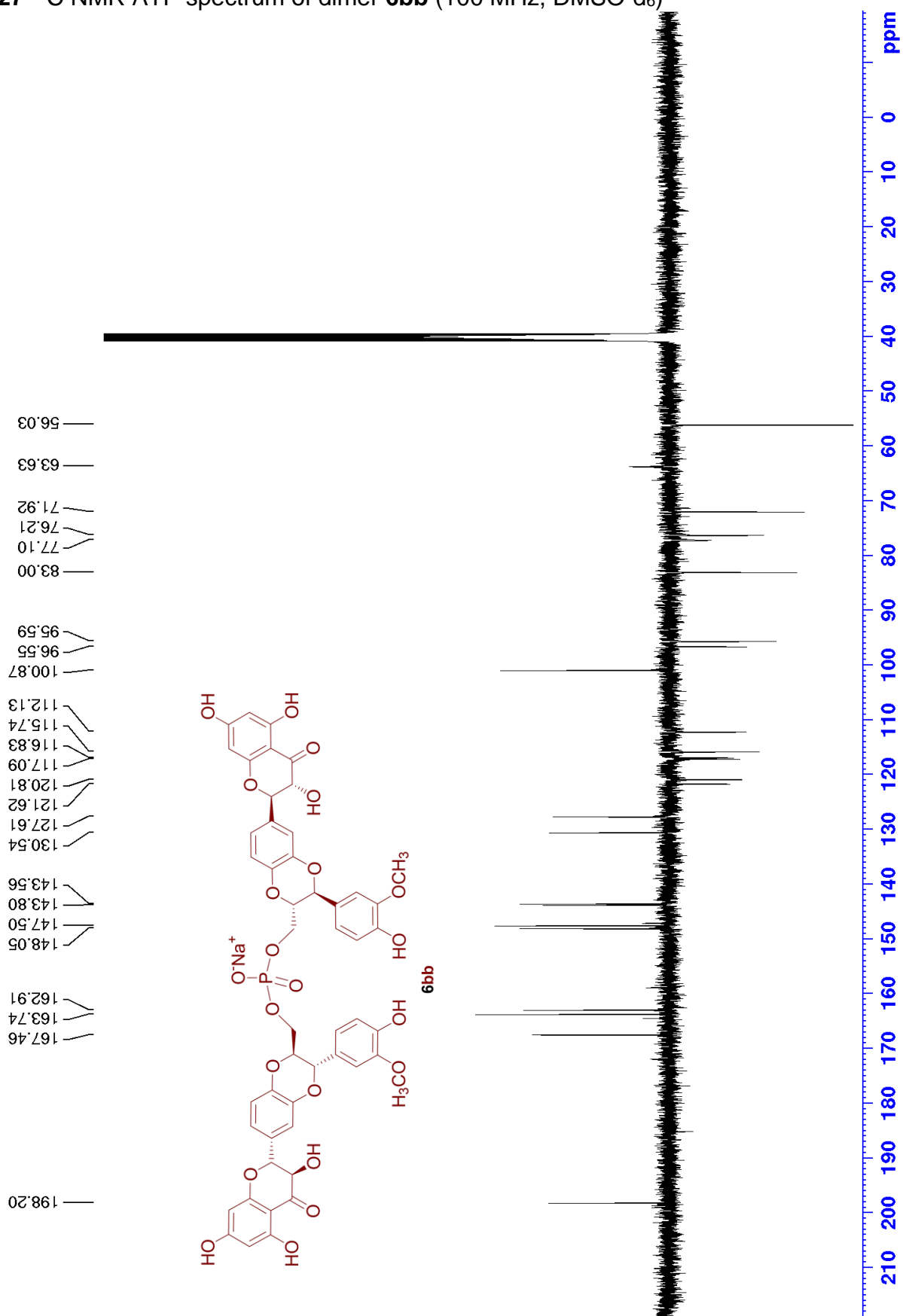


**Figure S24**  $^{13}\text{C}$  NMR ATP spectrum of dimer **6aa** (100 MHz, DMSO- $d_6$ )

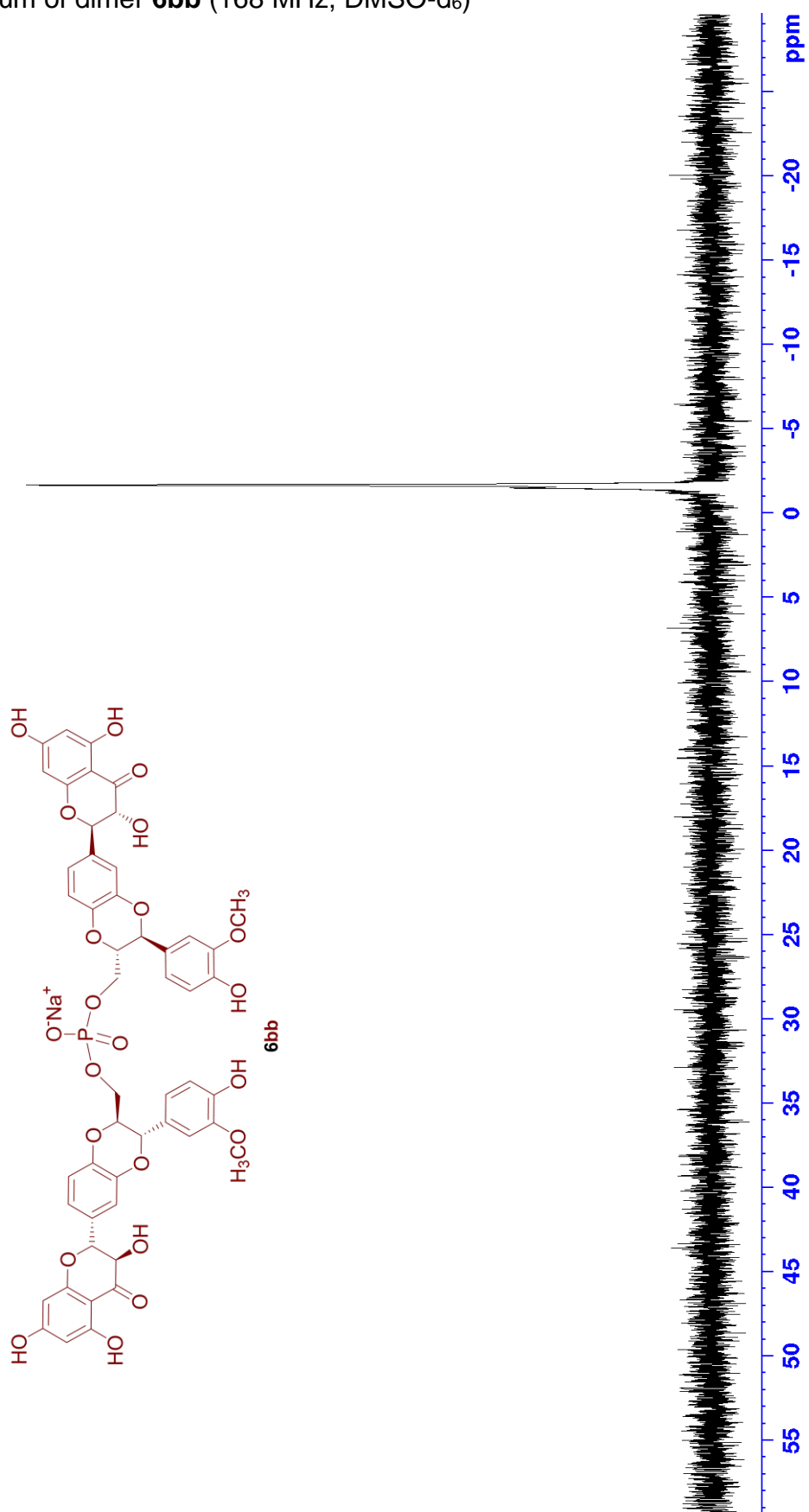
**Figure S25**  $^{31}\text{P}$  NMR spectrum of dimer **6aa** (168 MHz, DMSO- $\text{d}_6$ )

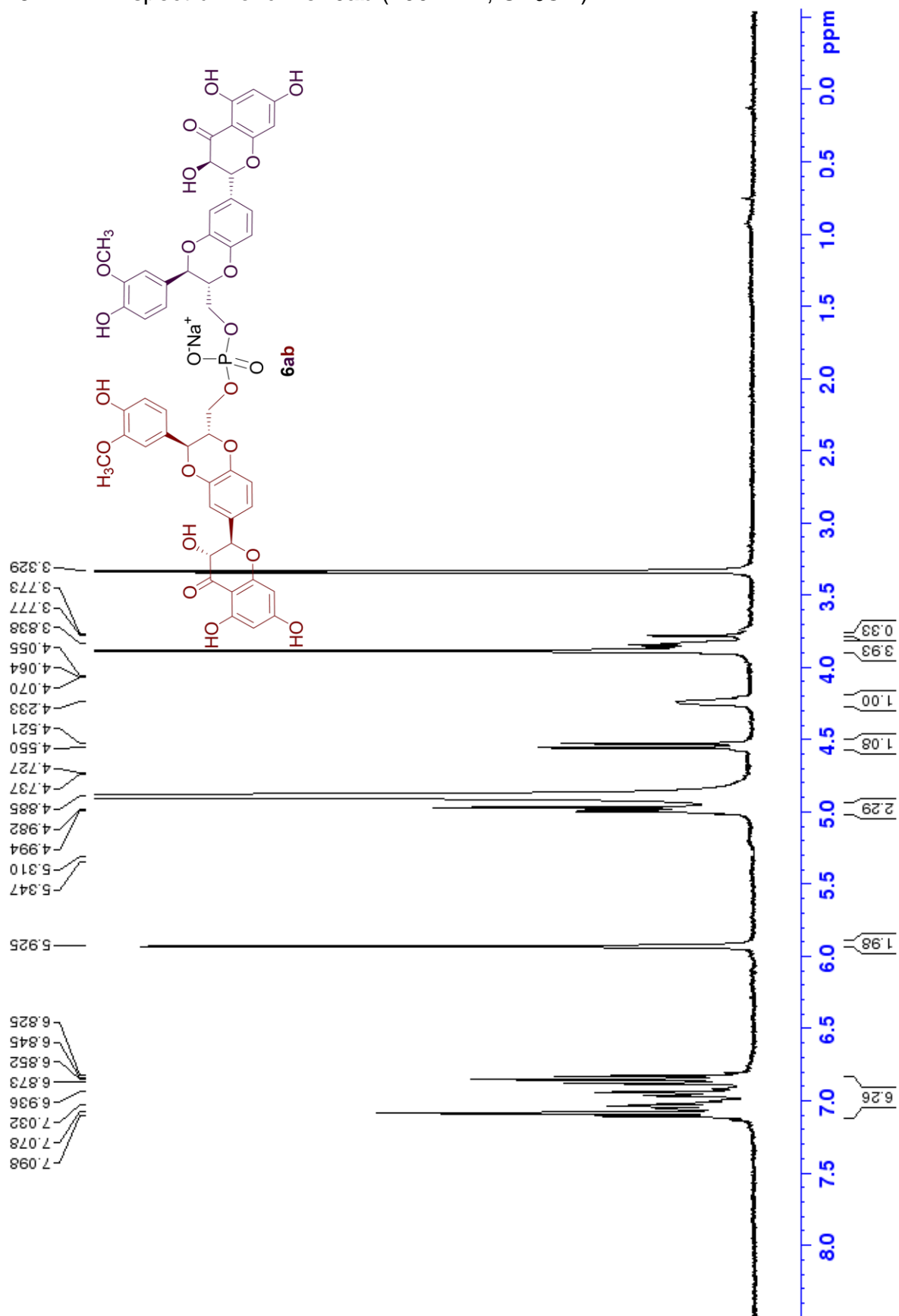


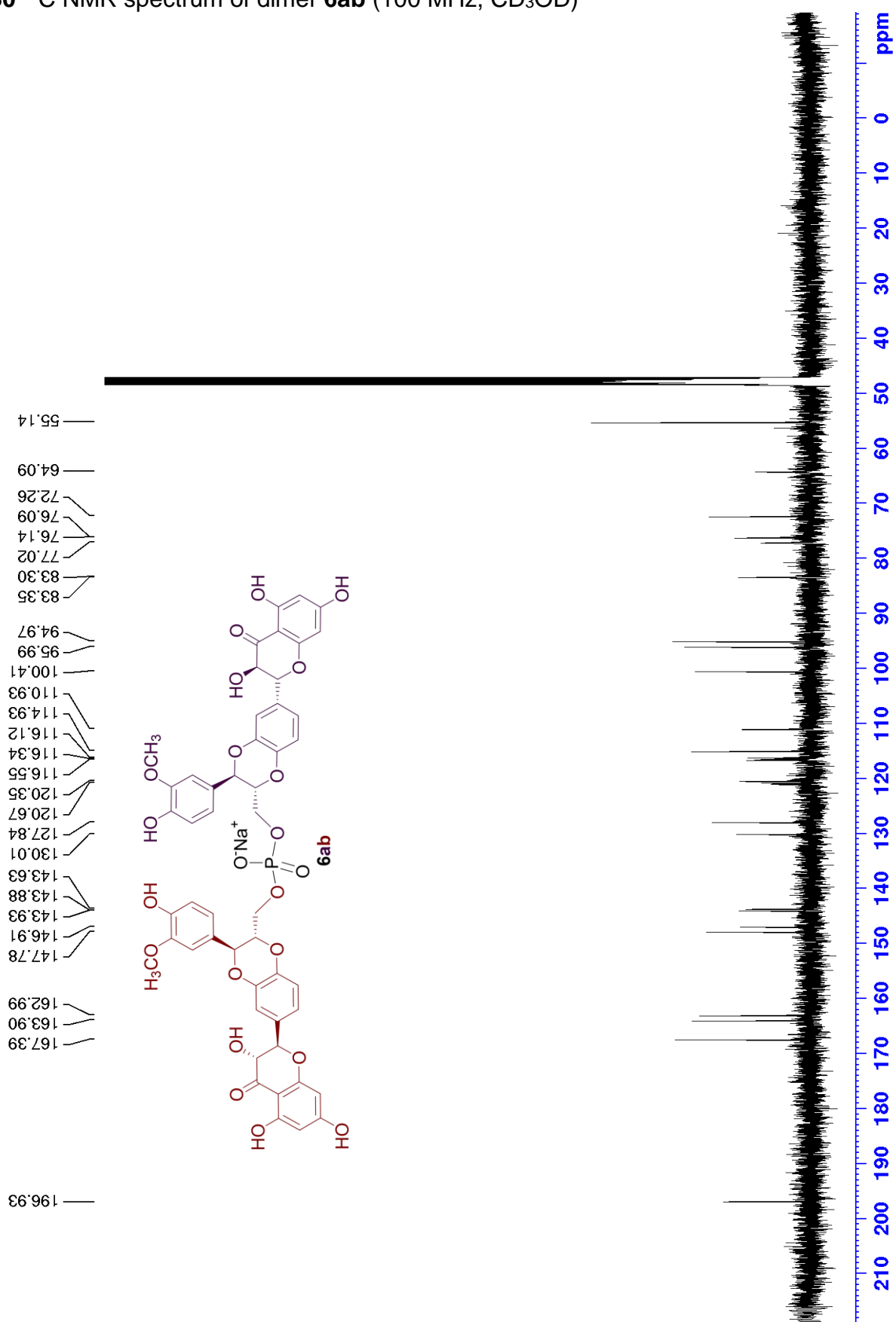
**Figure S26**  $^1\text{H}$  NMR spectrum of dimer **6bb** (400 MHz,  $\text{DMSO-d}_6$ )

**Figure S27**  $^{13}\text{C}$  NMR ATP spectrum of dimer **6bb** (100 MHz,  $\text{DMSO-d}_6$ )

—1.74



**Figure S29**  $^1\text{H}$  NMR spectrum of dimer **6ab** (400 MHz,  $\text{CD}_3\text{OD}$ )

**Figure S30**  $^{13}\text{C}$  NMR spectrum of dimer **6ab** (100 MHz,  $\text{CD}_3\text{OD}$ )

**Figure S31**  $^{31}\text{P}$  NMR spectrum of dimer **6ab** (168 MHz,  $\text{CD}_3\text{OD}$ )

