

## Supporting Information

### Prodrug Strategies for the Development of $\beta$ -L-5-((E)-2-bromovinyl)-1-((2S,4S)-2-(hydroxymethyl)-1,3-(dioxolane-4-yl)uracil (L-BH DU) Against Varicella Zoster Virus (VZV)

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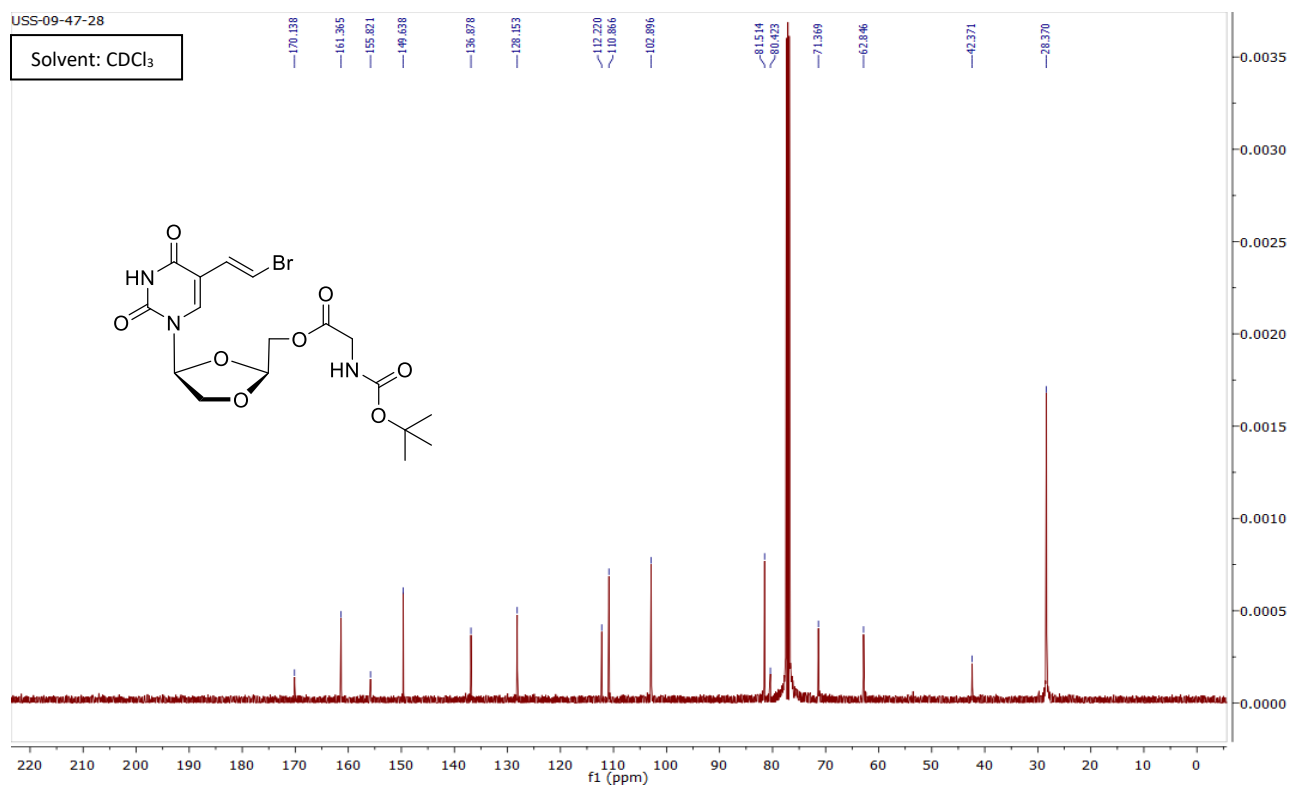
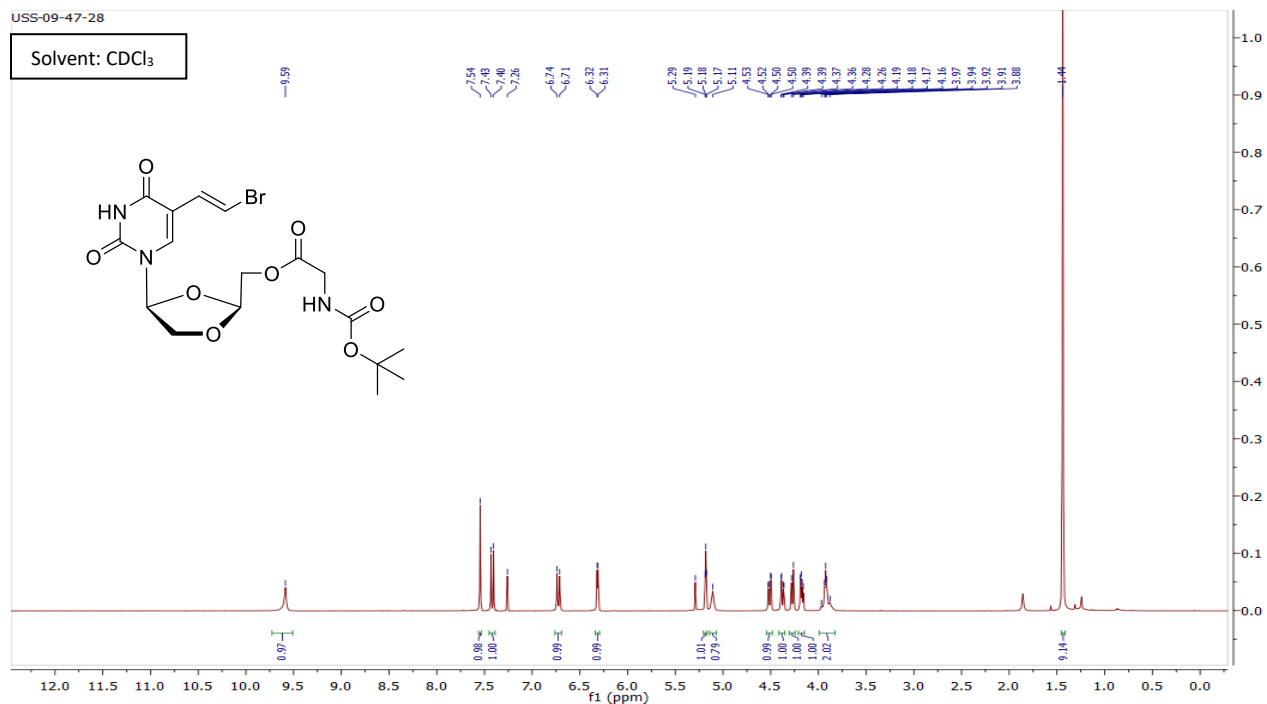
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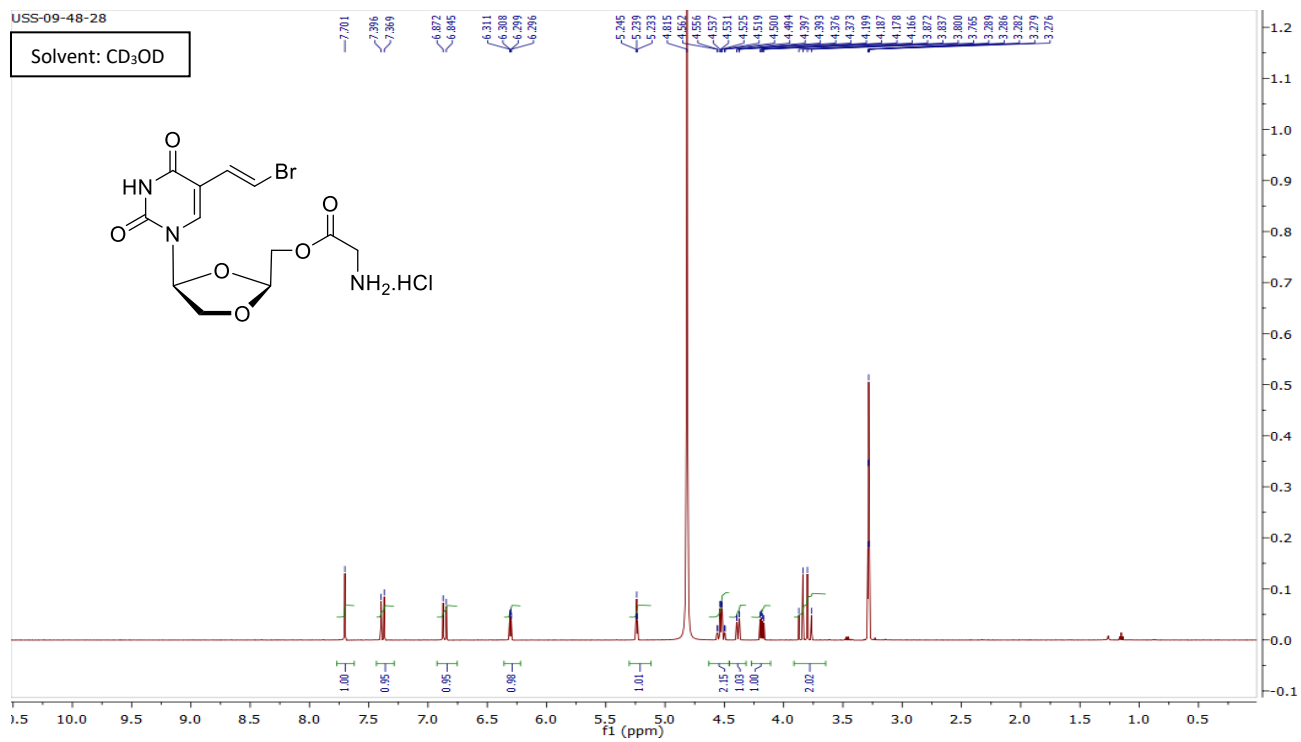
Corresponding author: Uma S. Singh, [ussingh@uga.edu](mailto:ussingh@uga.edu)

Corresponding author: Chung K. Chu, [dchu@uga.edu](mailto:dchu@uga.edu)

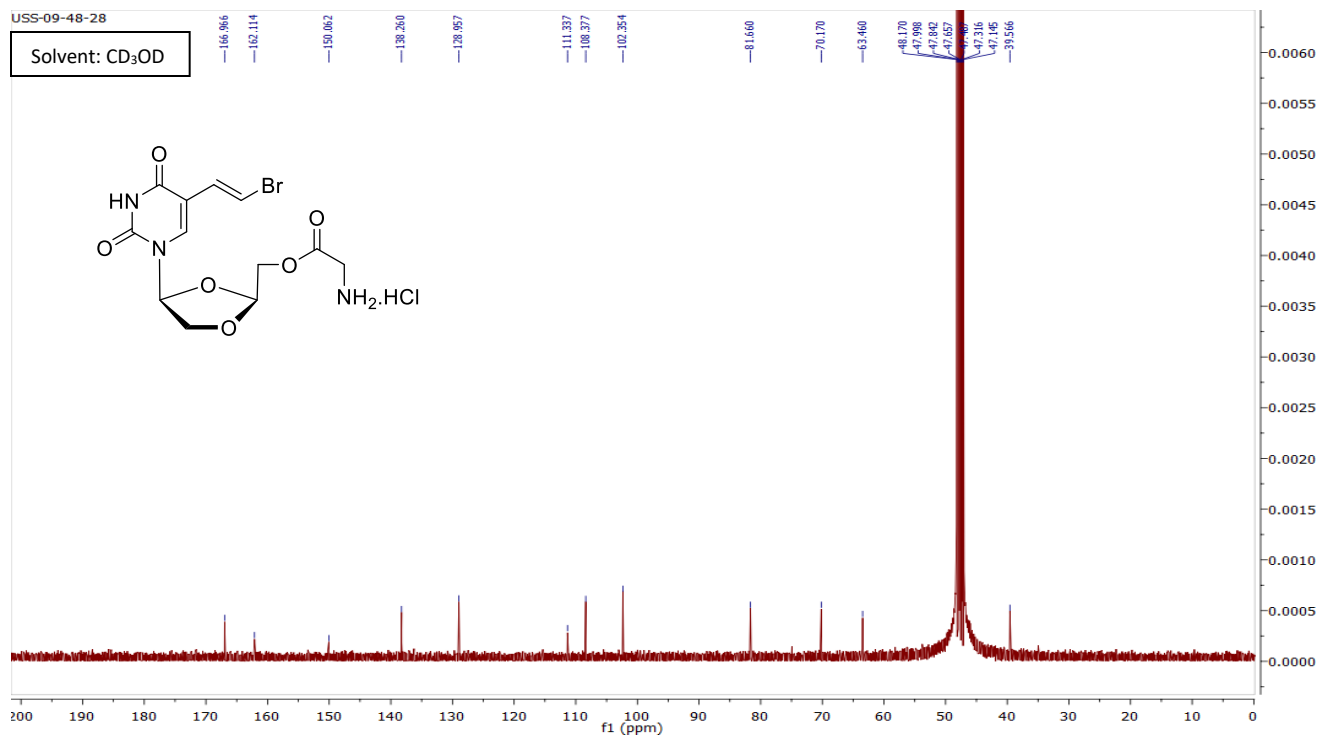
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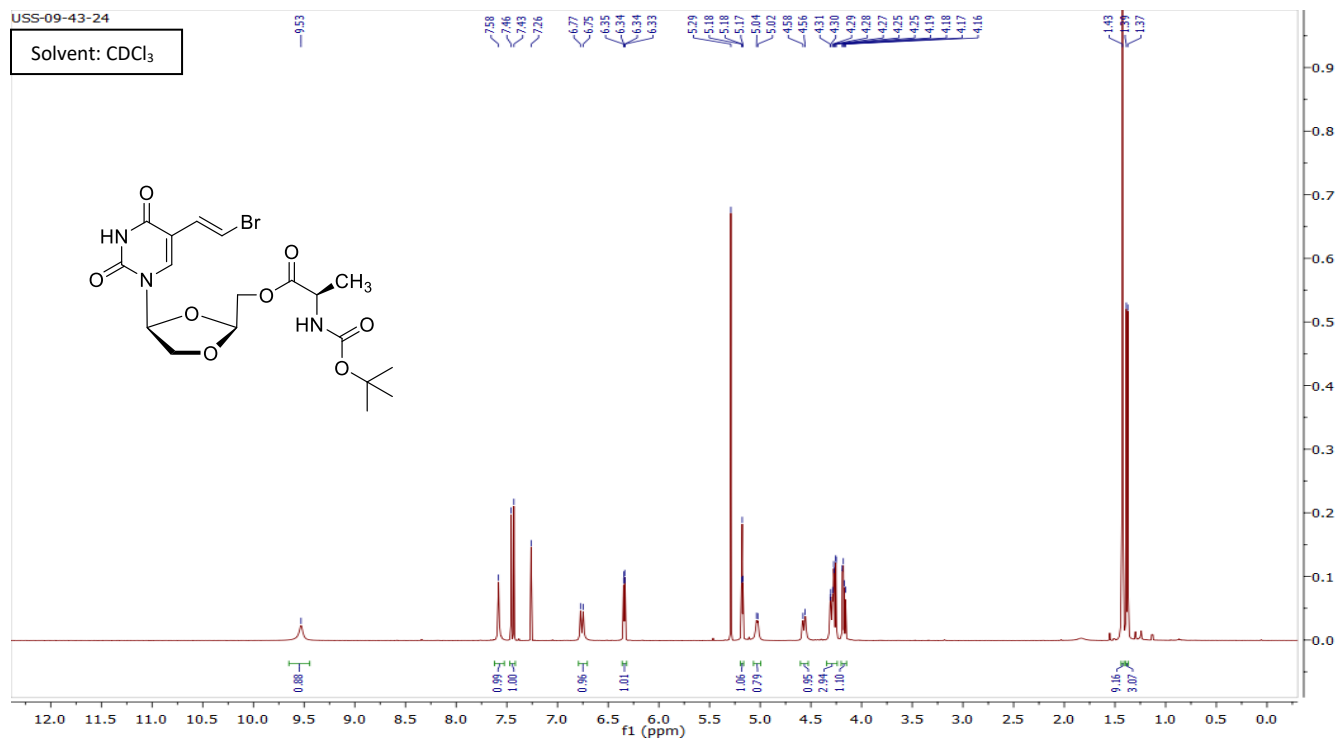




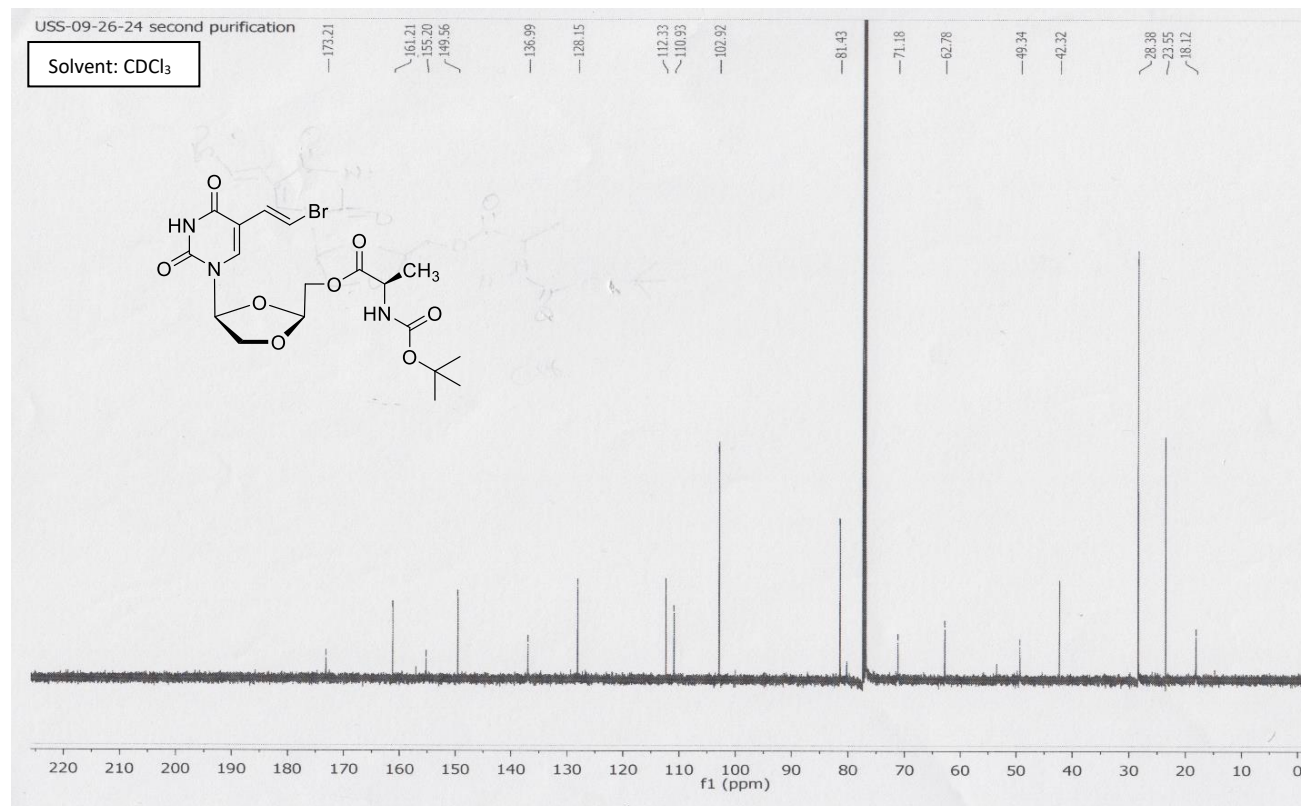
<sup>1</sup>H NMR of L-BH DU-5'-O-glycyl ester hydrochloride (**14**)



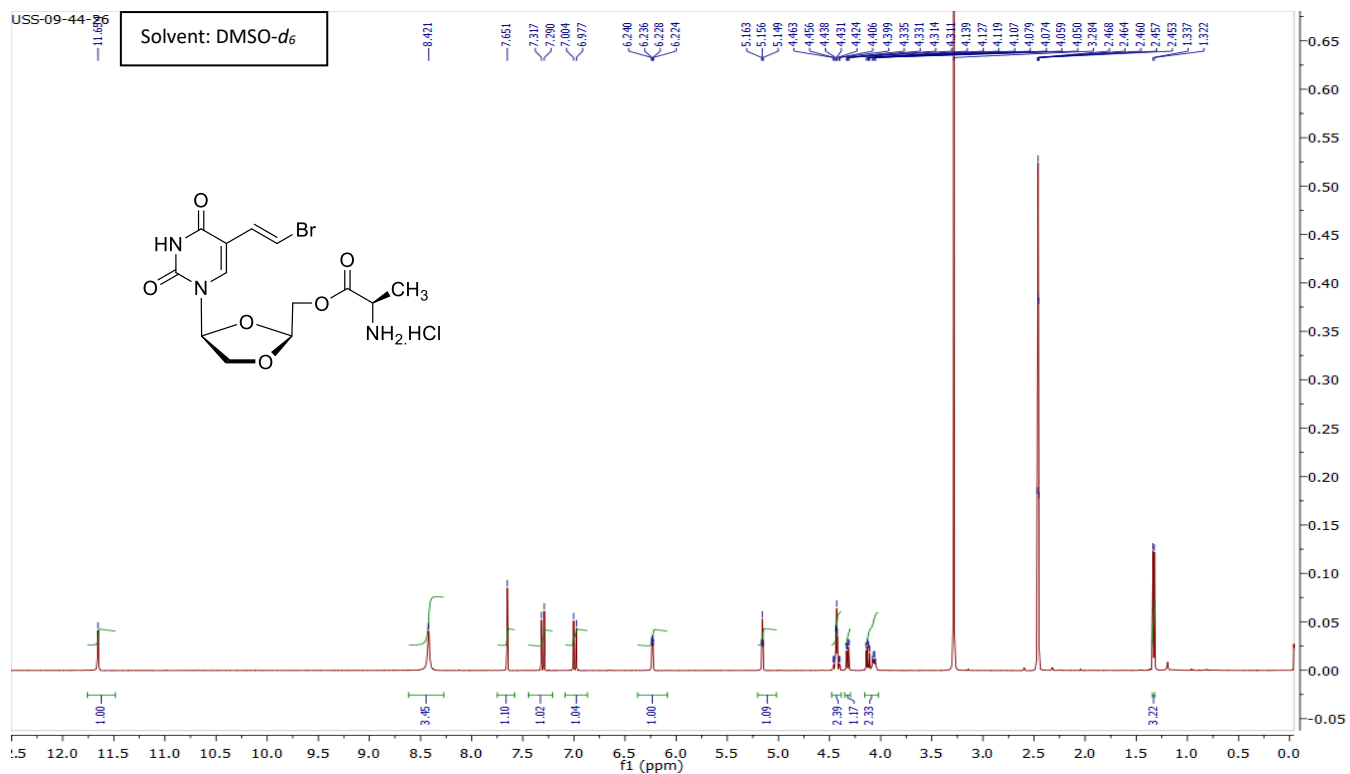
<sup>13</sup>C NMR of L-BH DU-5'-O-glycyl ester hydrochloride (**14**)



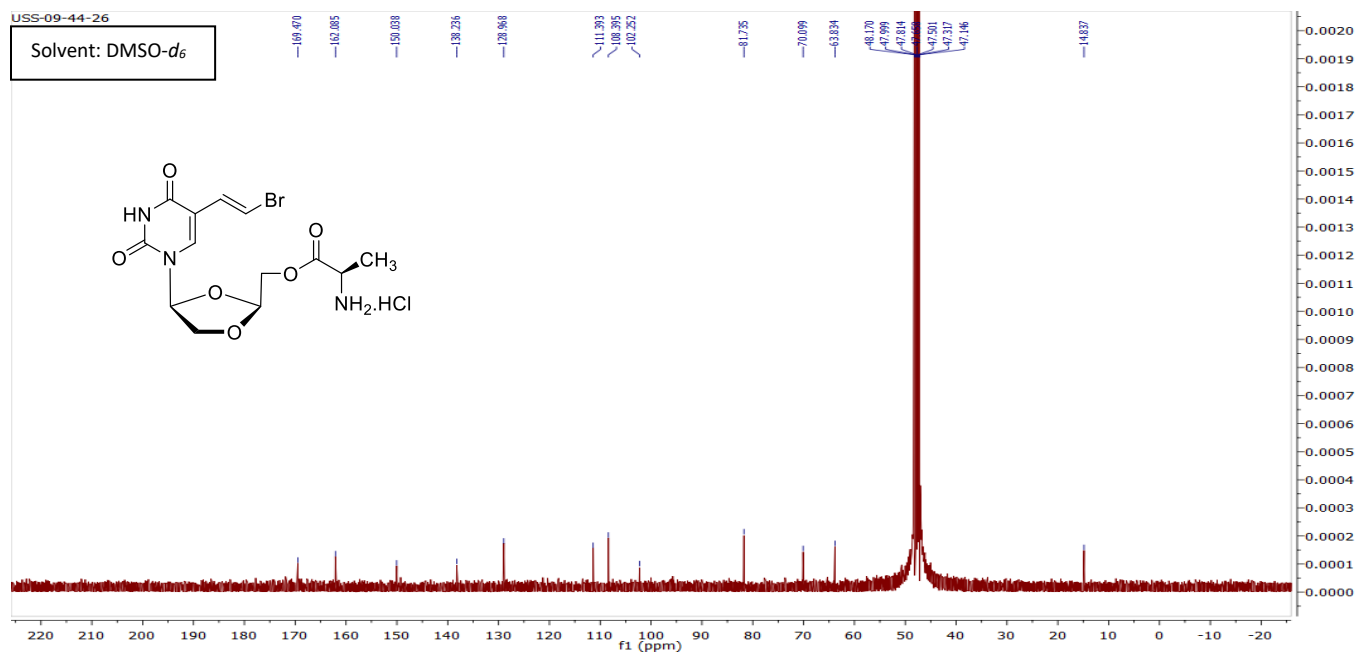
<sup>1</sup>H NMR of L-BH DU-5'-O-L- Boc-alanine ester (**3**)



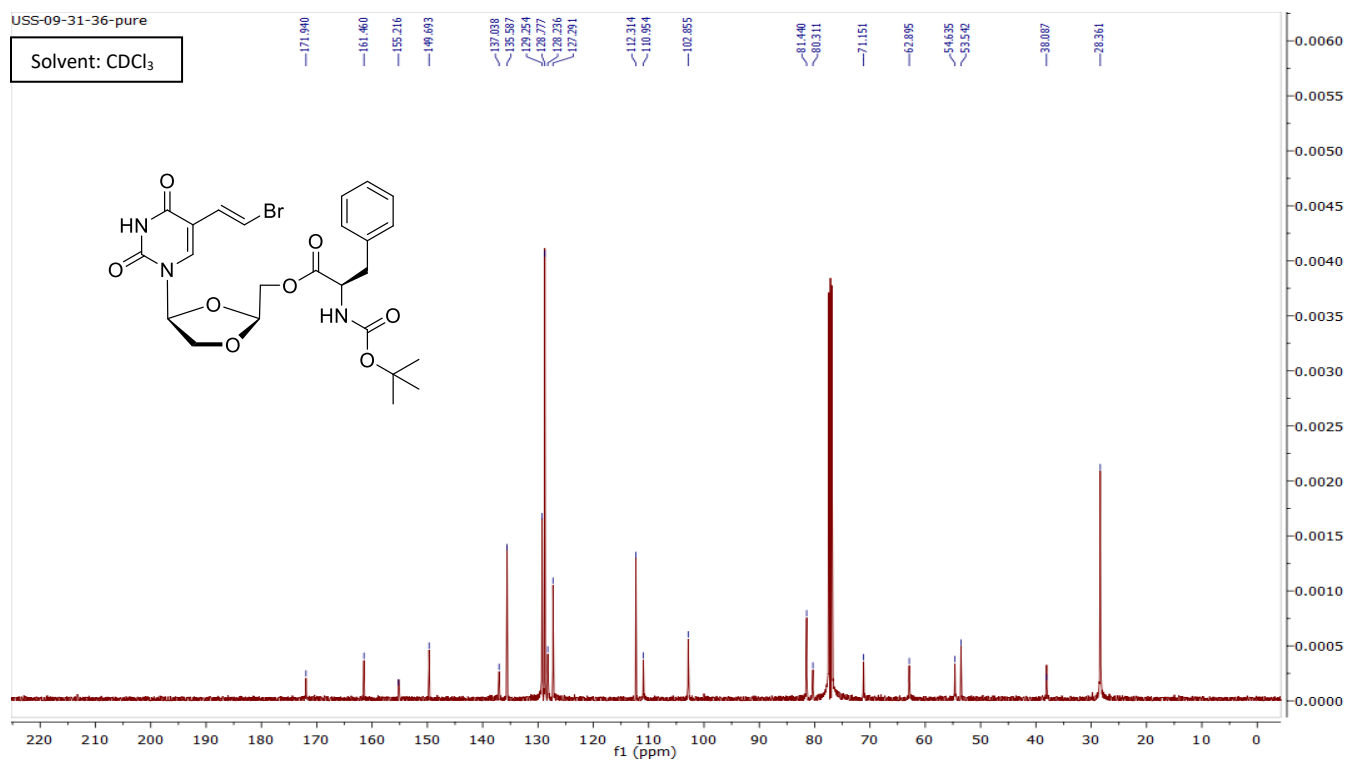
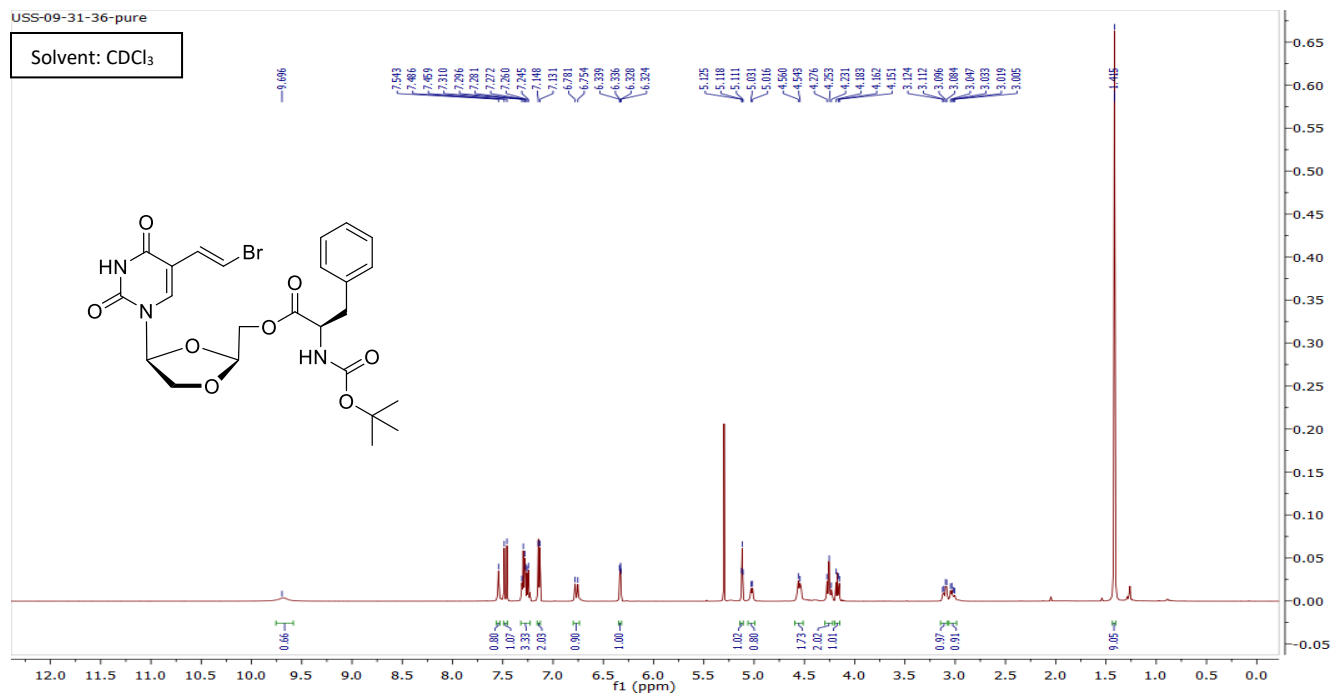
<sup>13</sup>C NMR of L-BH DU-5'-O-L- Boc-alanine ester (**3**)

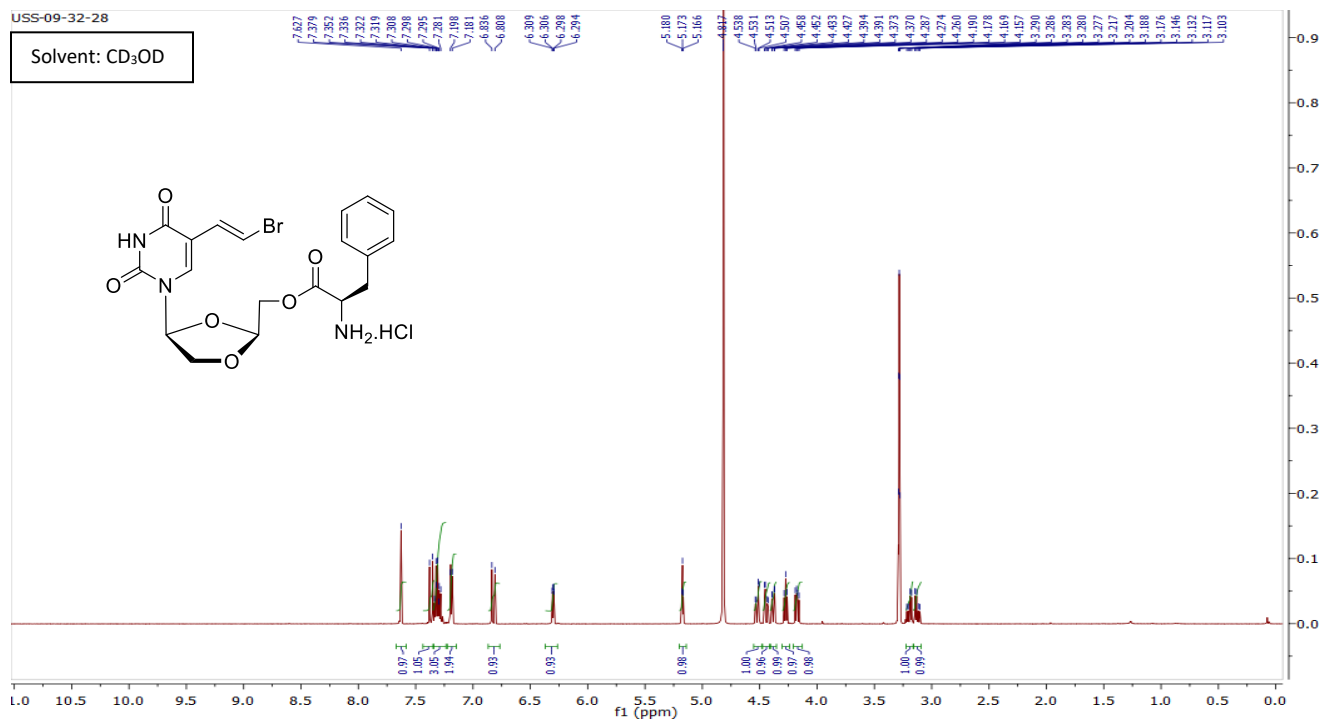


<sup>1</sup>H NMR of L-BH DU-5'-O-L-alanyl ester hydrochloride (15)

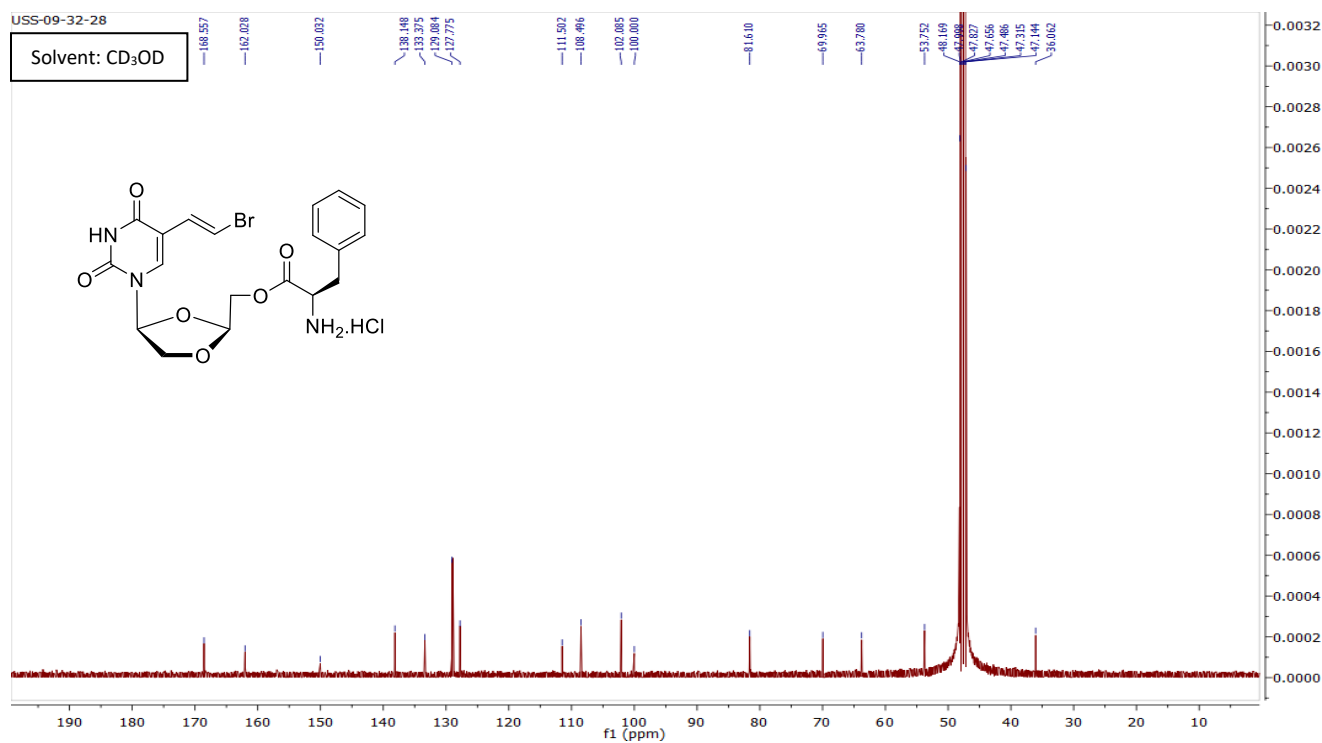


<sup>13</sup>C NMR of L-BH DU-5'-O-L-alanyl ester hydrochloride (15)

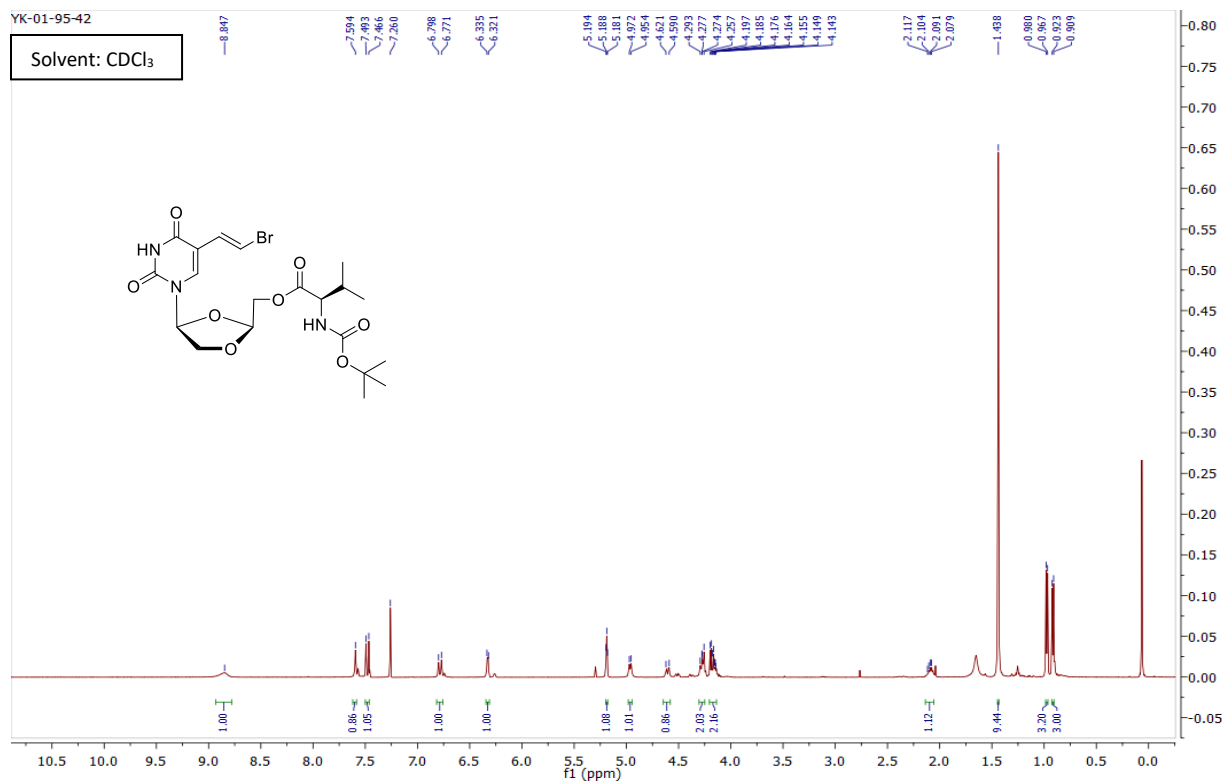




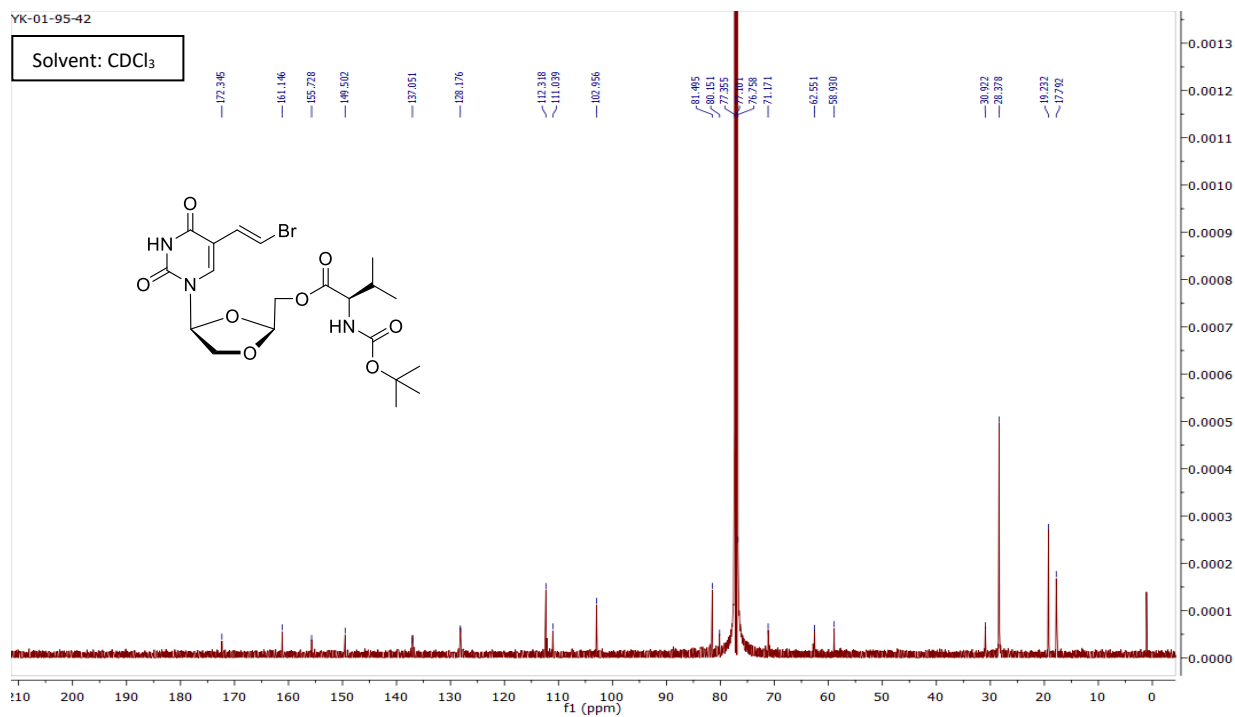
$^1\text{H}$  NMR of L-BH DU-5'-O-L-phenylalanyl ester hydrochloride (16)



$^{13}\text{C}$  NMR of L-BH DU-5'-O-L-phenylalanyl ester hydrochloride (16)

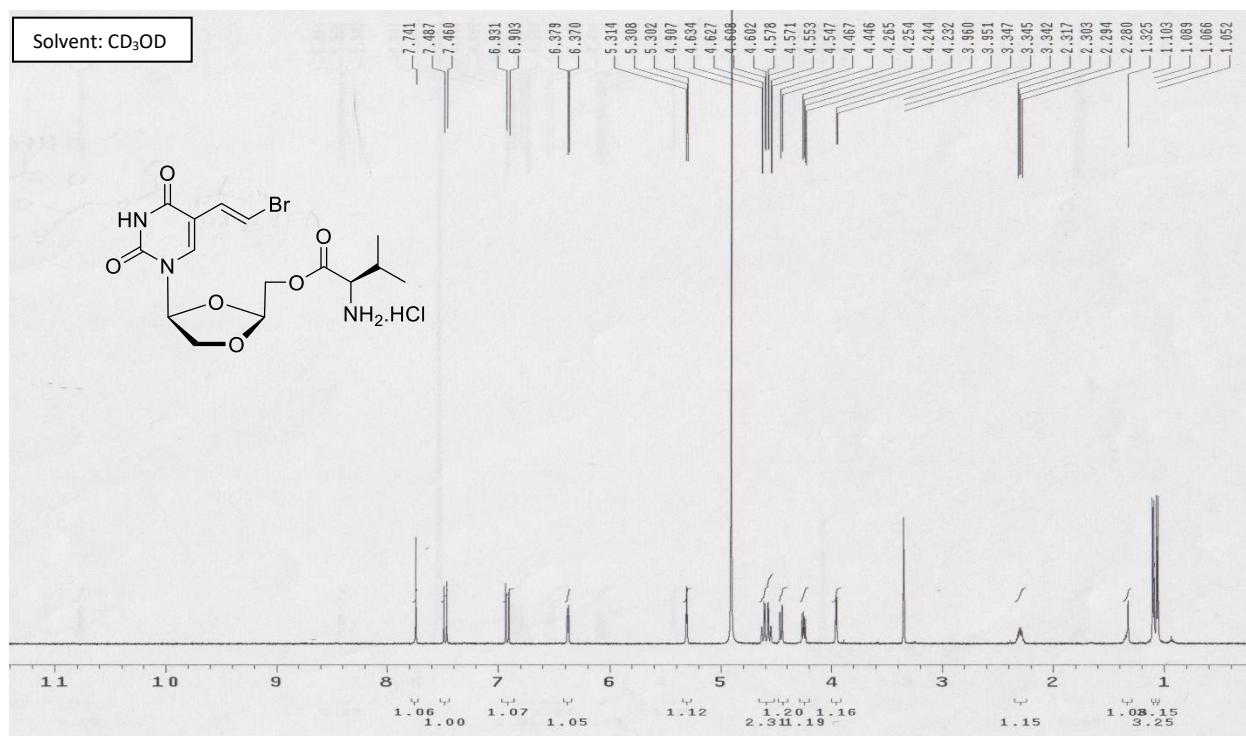


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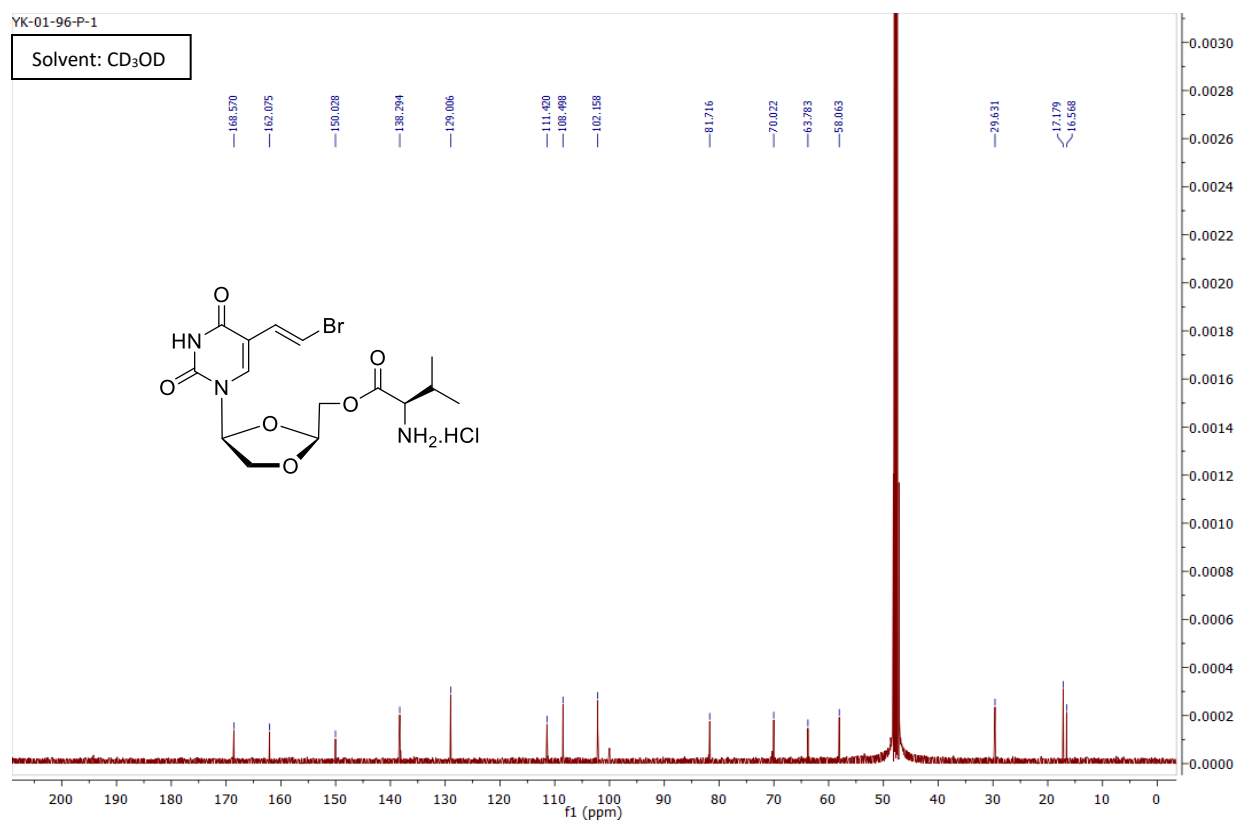


<sup>13</sup>C NMR of L-BH DU-5'-O-L-Boc-valine ester (5)

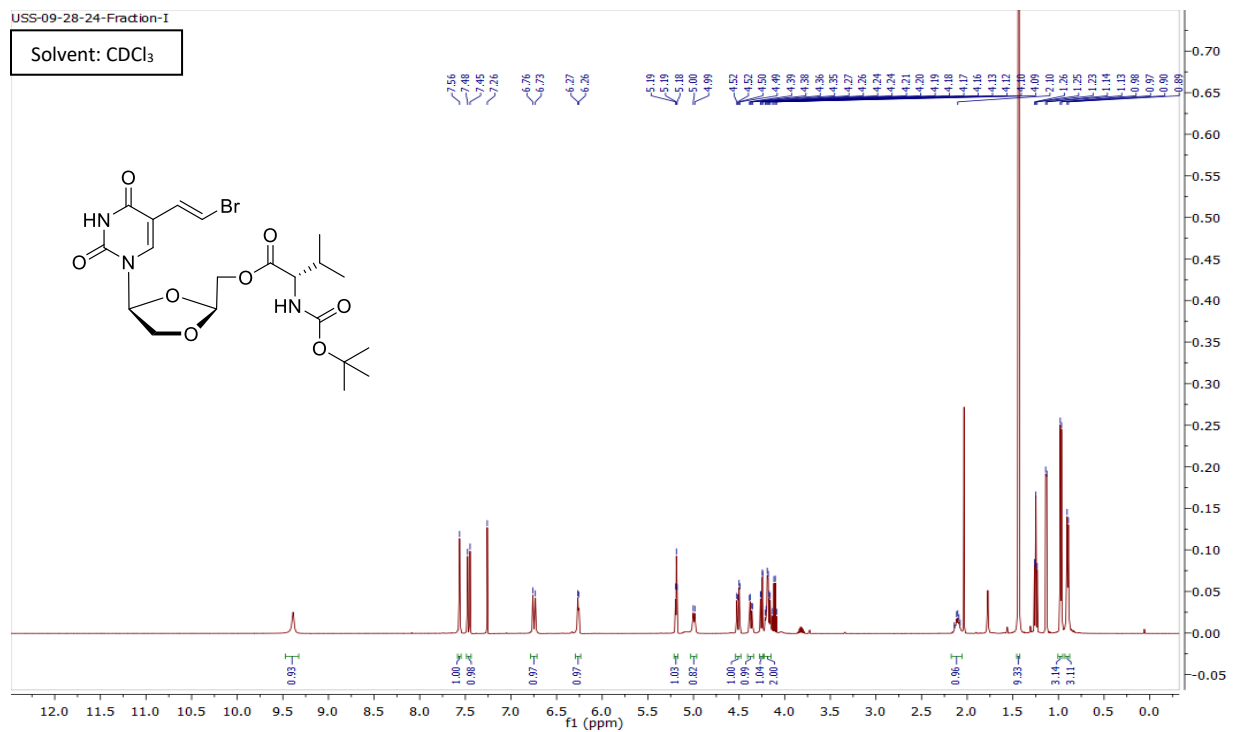




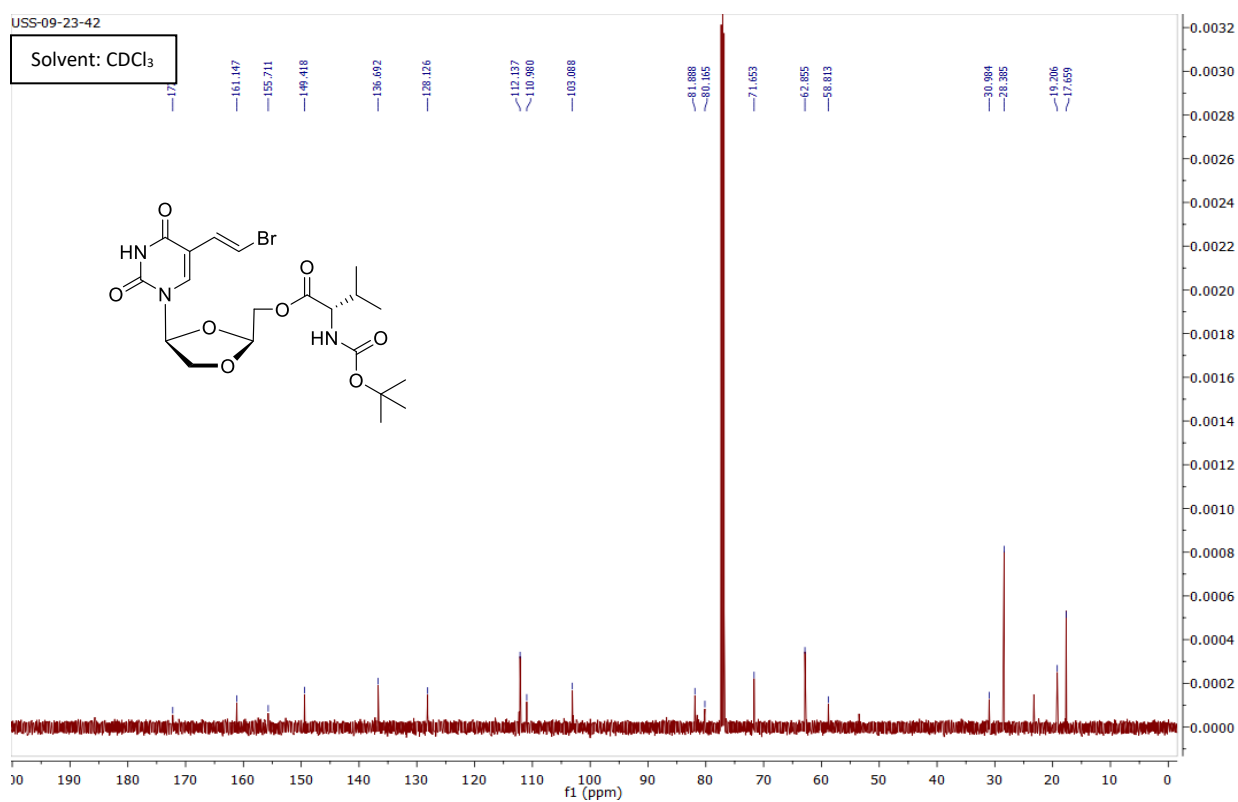
<sup>1</sup>H NMR of L-BH DU-5'-O-L-valyl ester hydrochloride (17)



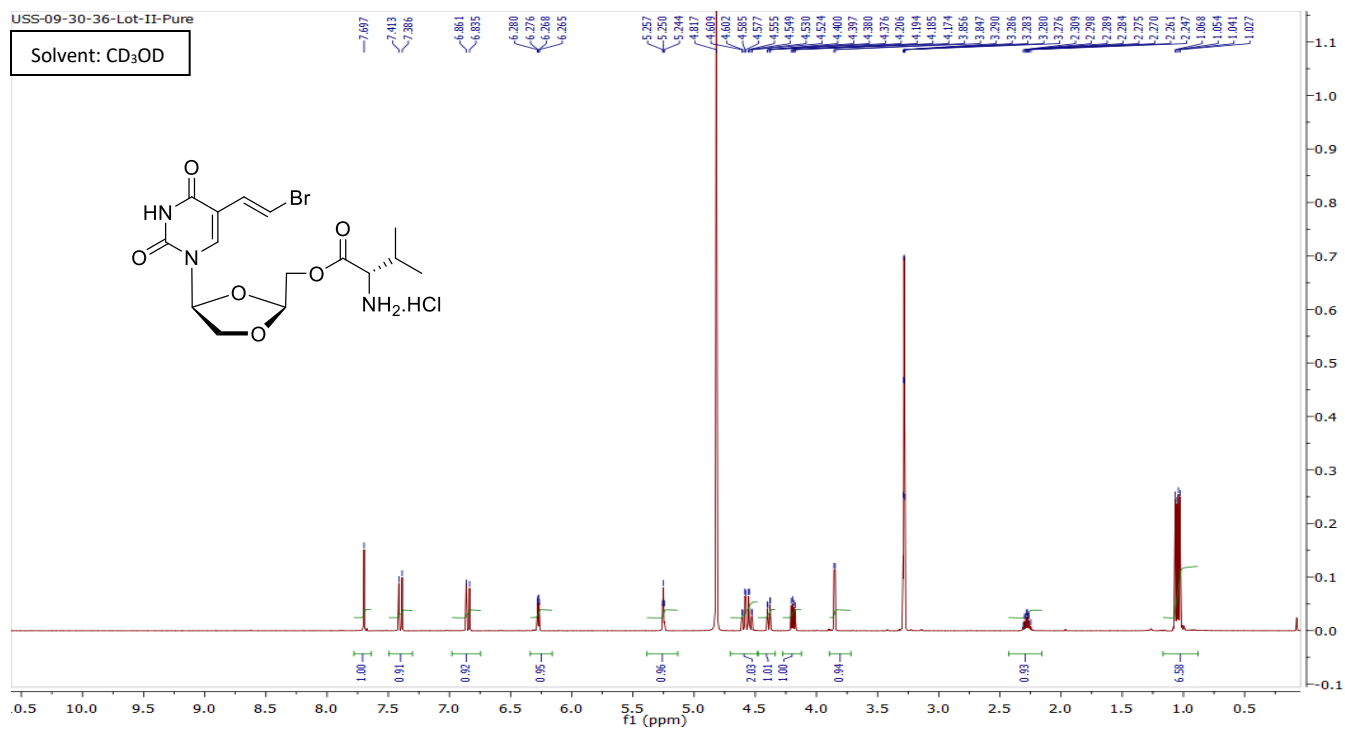
<sup>13</sup>C NMR of L-BH DU-5'-O-L-valyl ester hydrochloride (17)



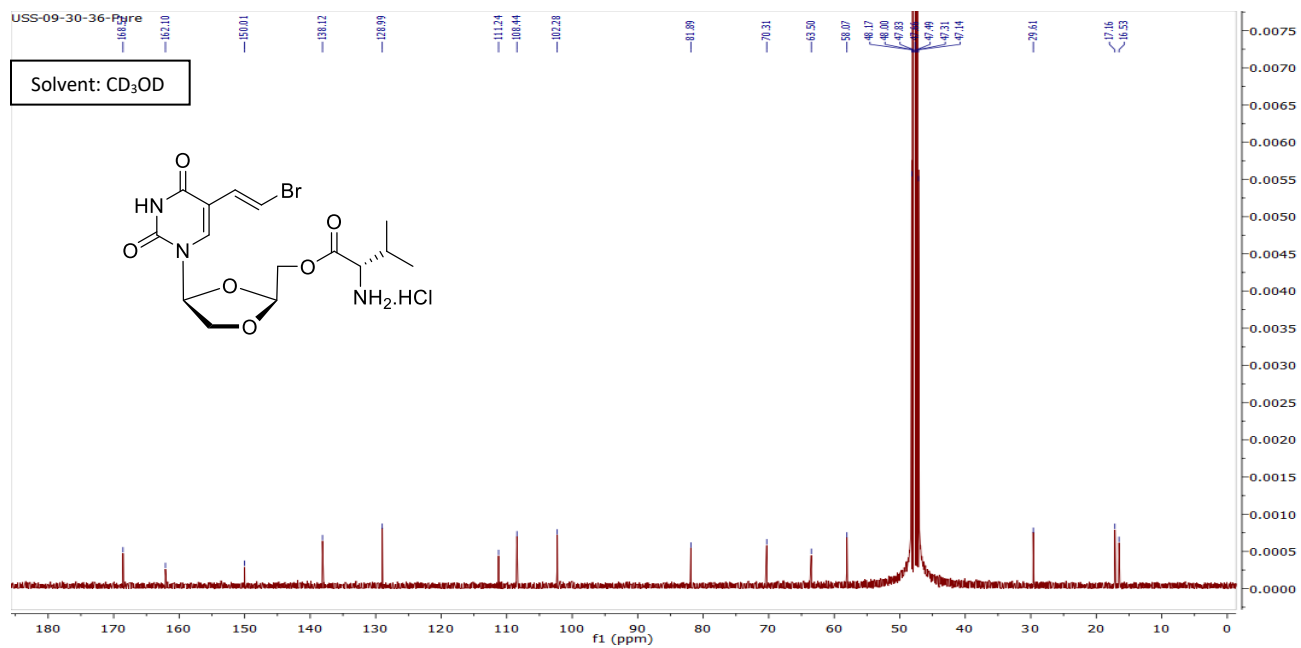
<sup>1</sup>H NMR of L-BH DU-5'-O-D-Boc-valine ester (6)



<sup>13</sup>C NMR of L-BH DU-5'-O-D-Boc-valine ester (6)

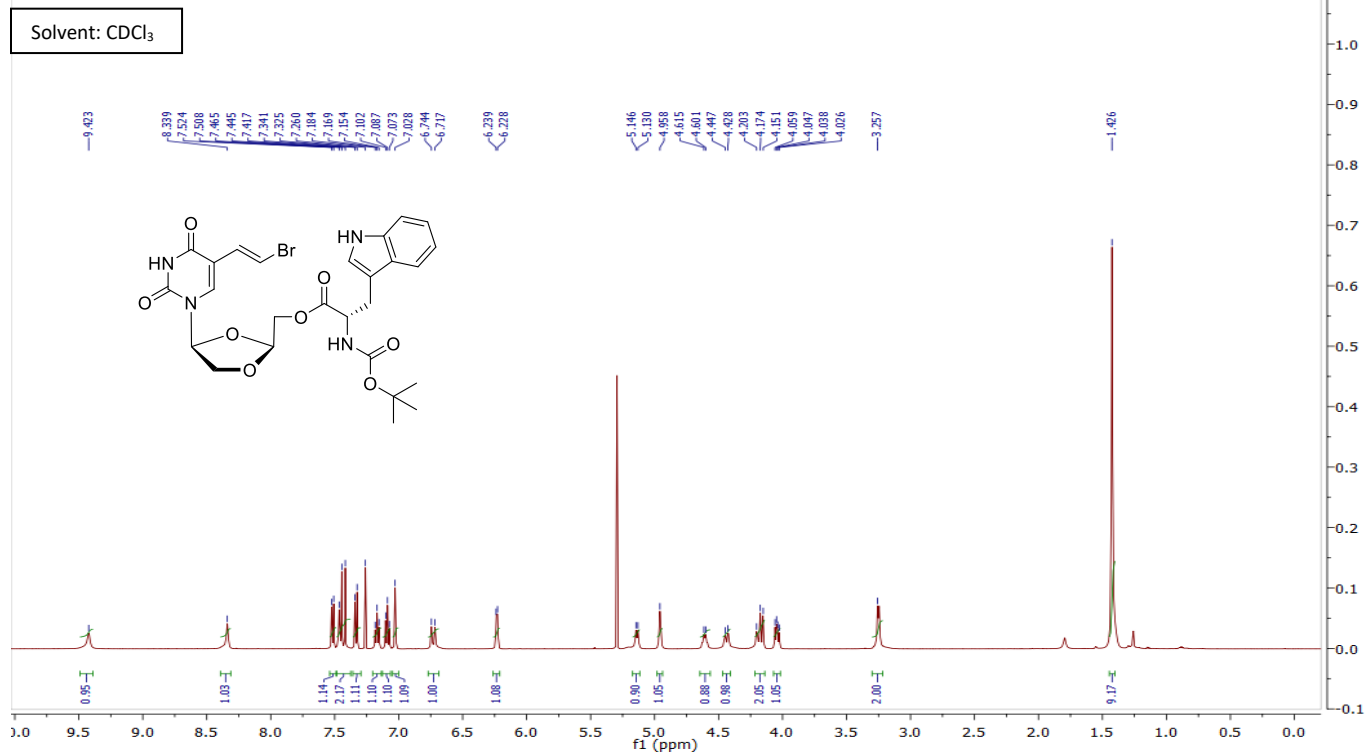


<sup>1</sup>H NMR of L-BH DU-5'-O-D-valyl ester hydrochloride (18)

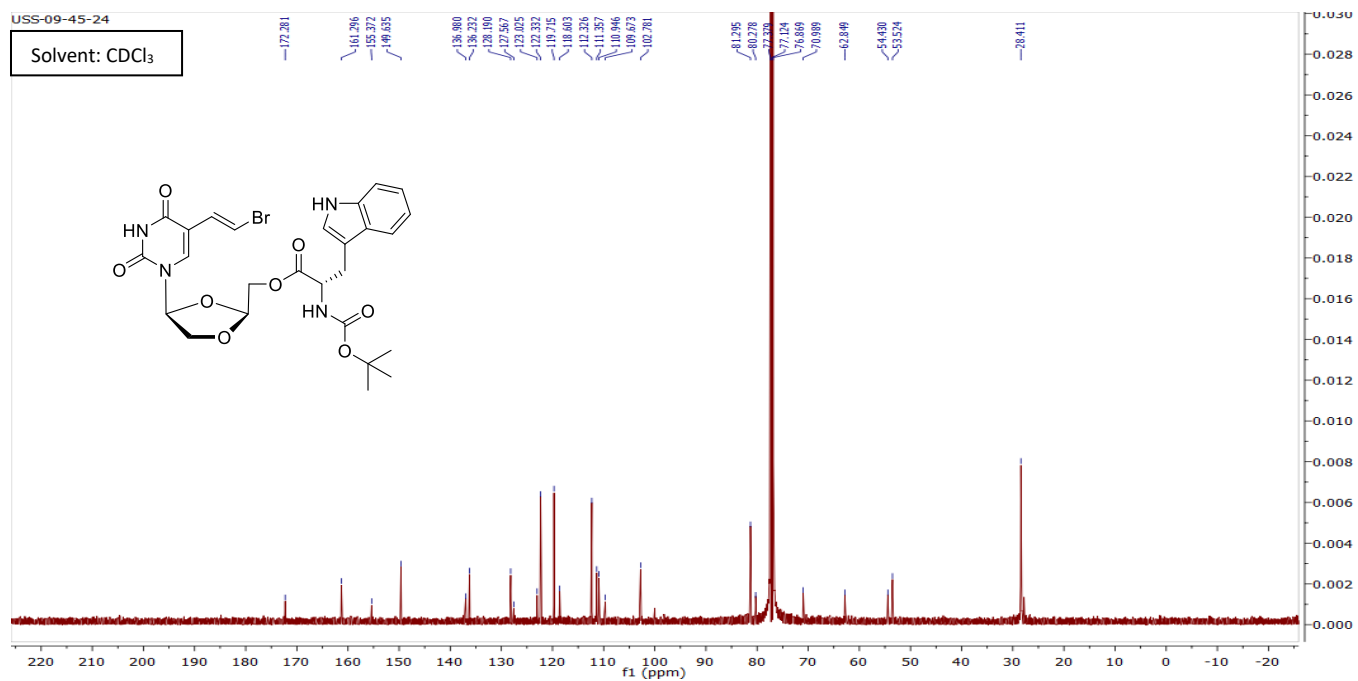


<sup>13</sup>C NMR of L-BH DU-5'-O-D-valyl ester hydrochloride (18)

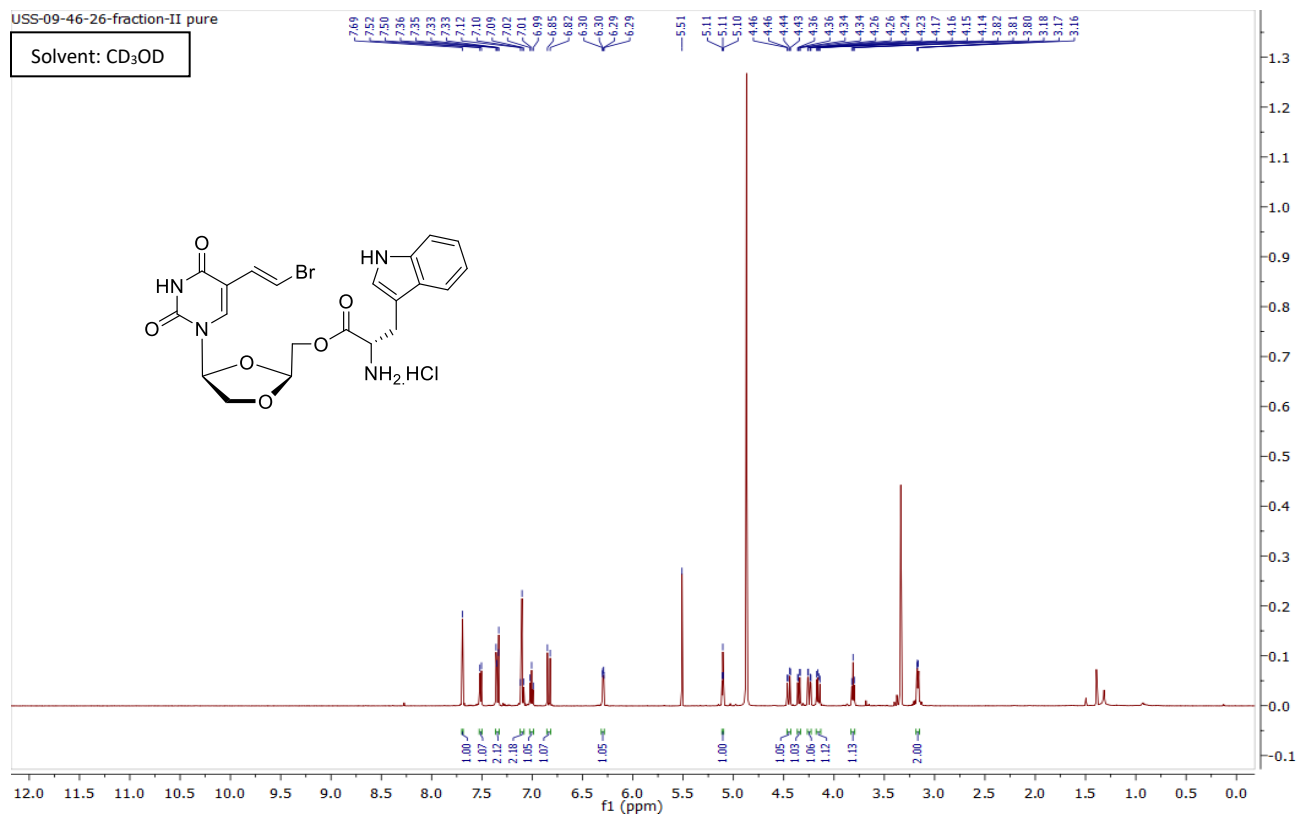
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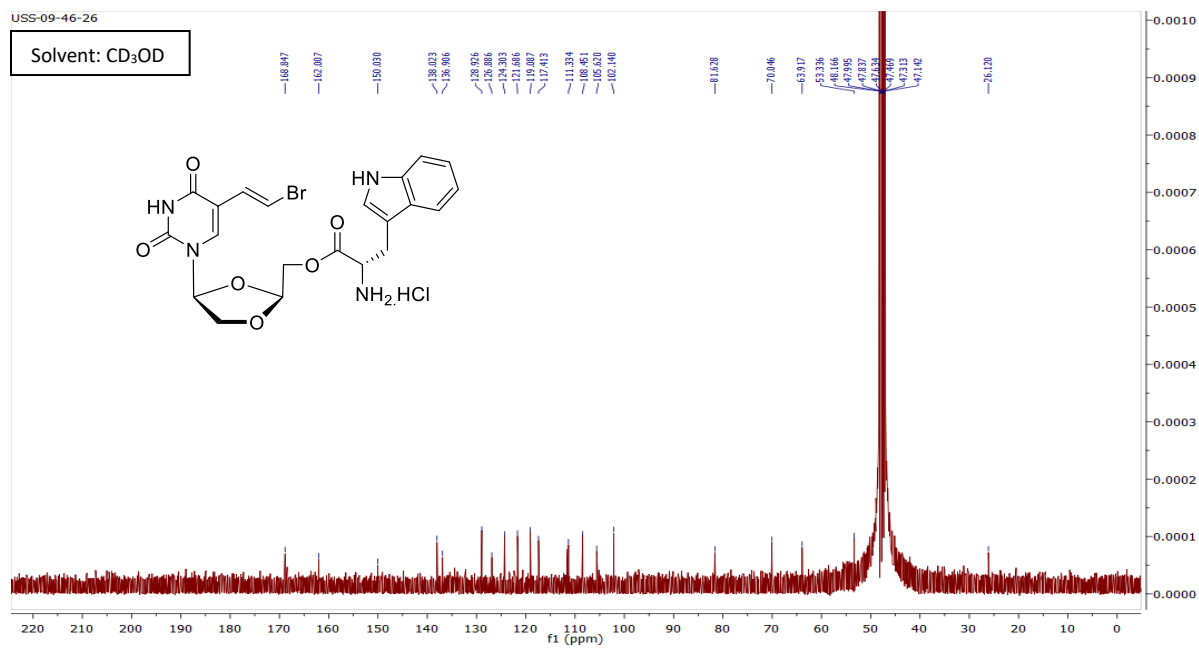
<sup>1</sup>H NMR of L-BH DU-5'-O-L-Boc-tryptophan ester (7)



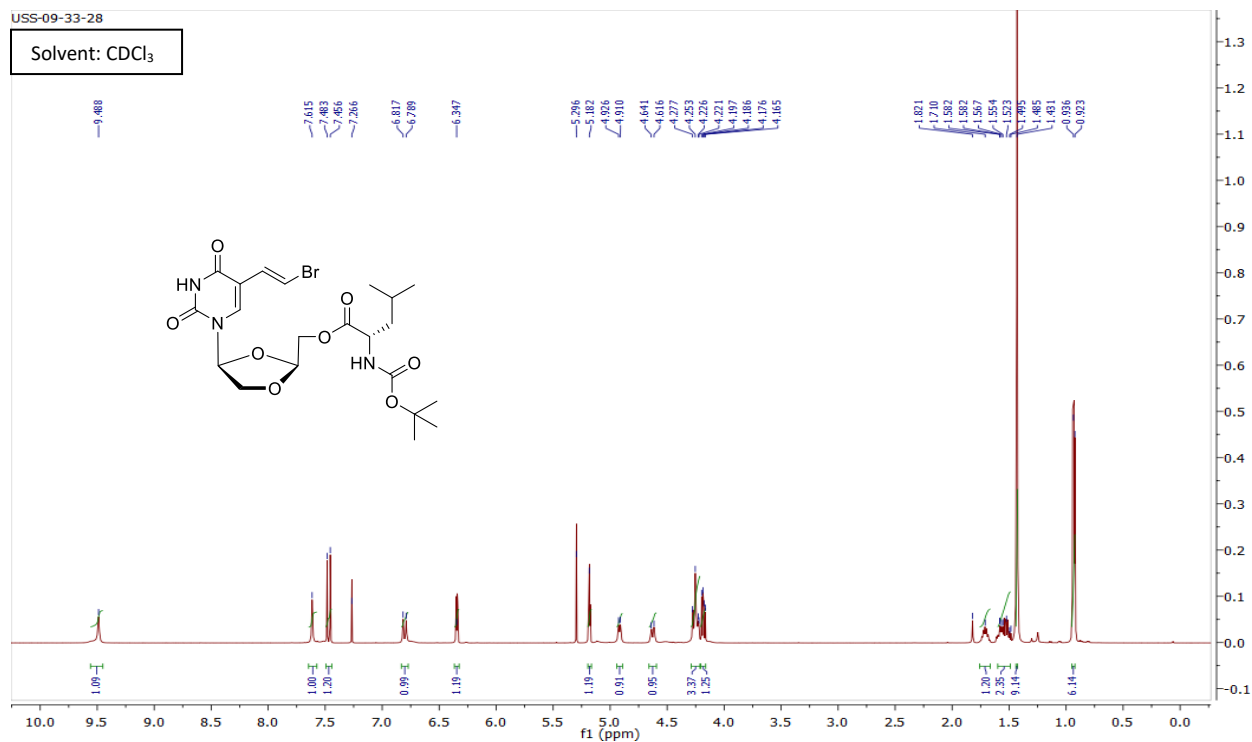
<sup>13</sup>C NMR of L-BH DU-5'-O-L-Boc-tryptophan ester (7)



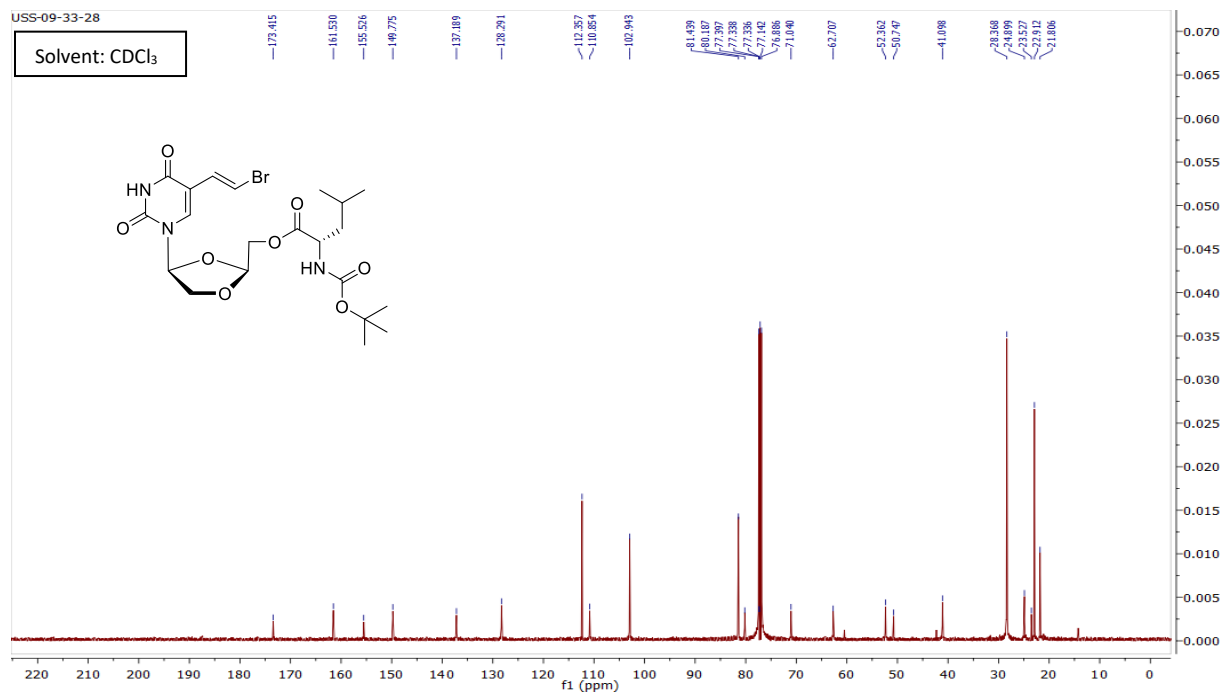
<sup>1</sup>H NMR of L-BH DU-5'-O-L-tryptophan ester hydrochloride (19)



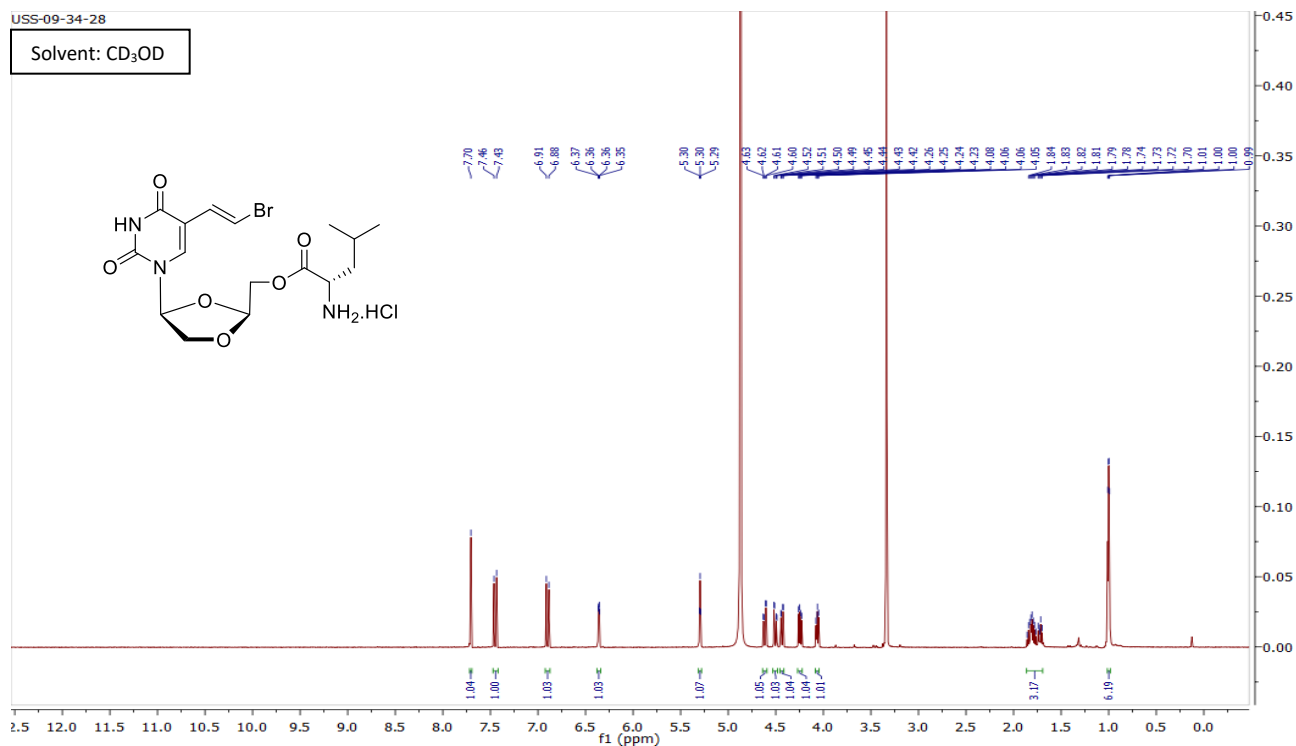
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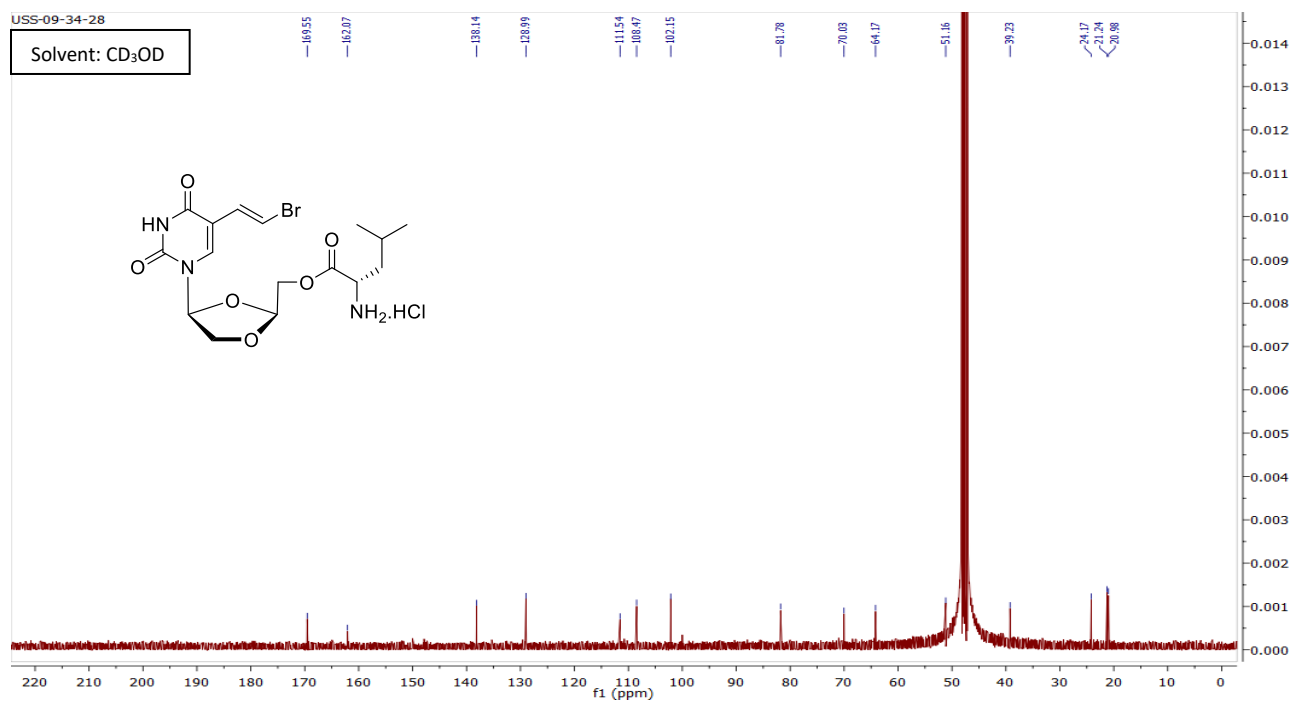
<sup>1</sup>H NMR of L-BH DU-5'-O-L-Boc-leucine ester (8)



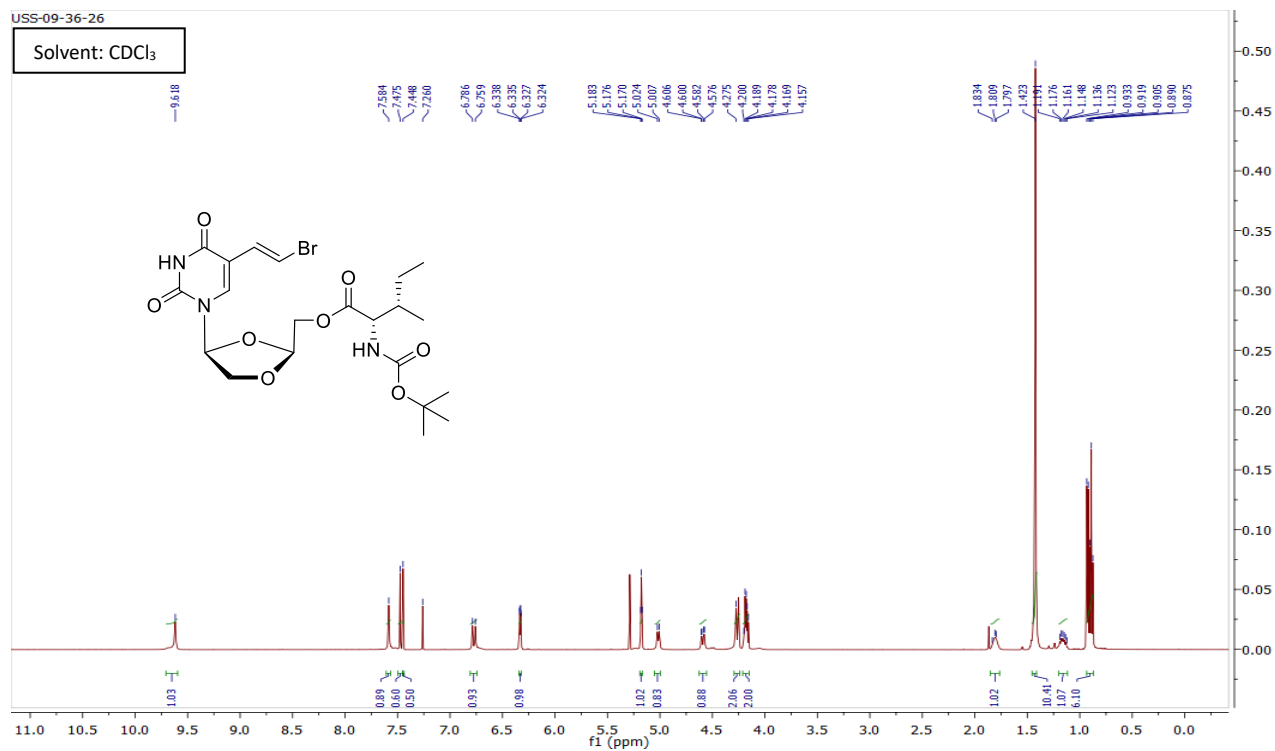
<sup>13</sup>C NMR of L-BH DU-5'-O-L-Boc-leucine ester (8)



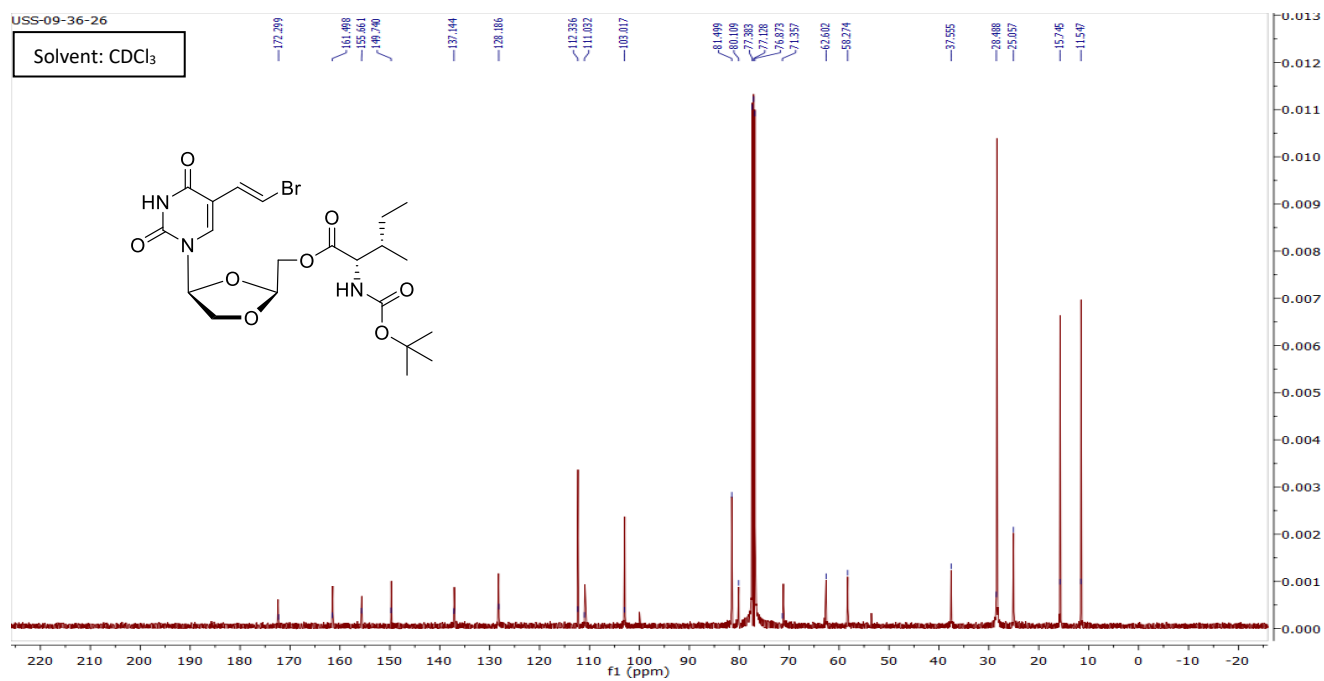
$^1\text{H}$  NMR of L-BH DU-5'-O-L-leucine ester hydrochloride (20)



$^{13}\text{C}$  NMR of L-BH DU-5'-O-L-leucine ester hydrochloride (20)

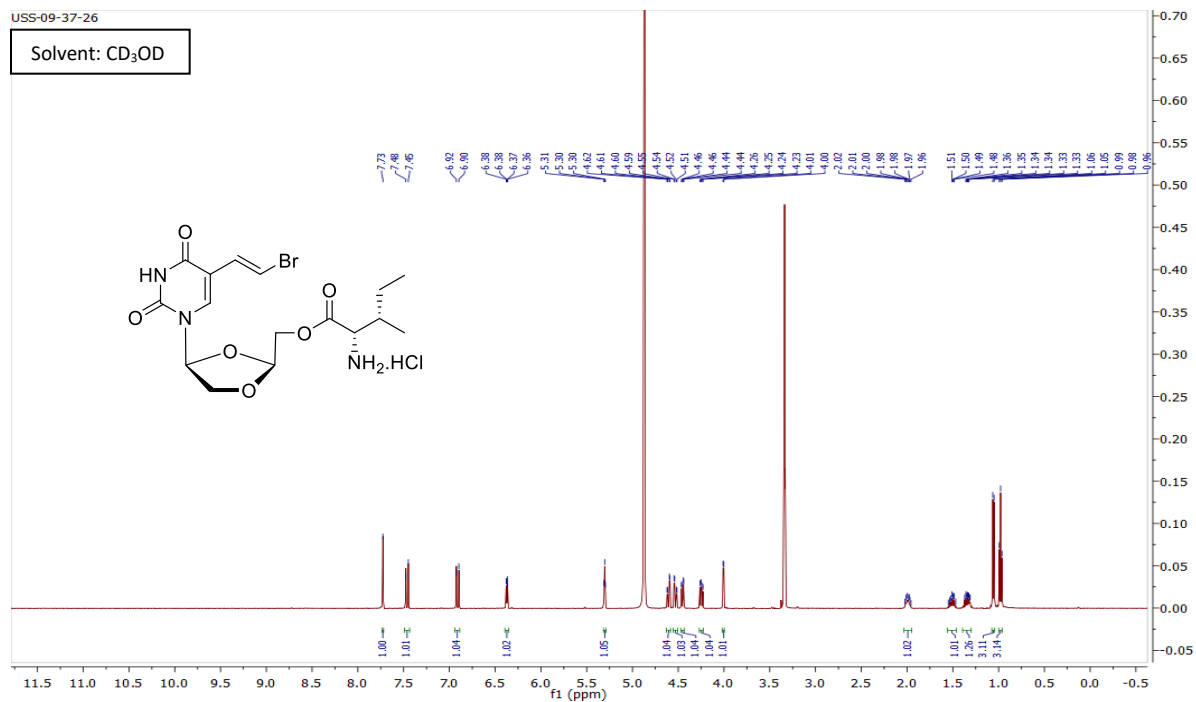


<sup>1</sup>H NMR of L-BH DU-5'-O-L-Boc-iso-leucine ester (9)

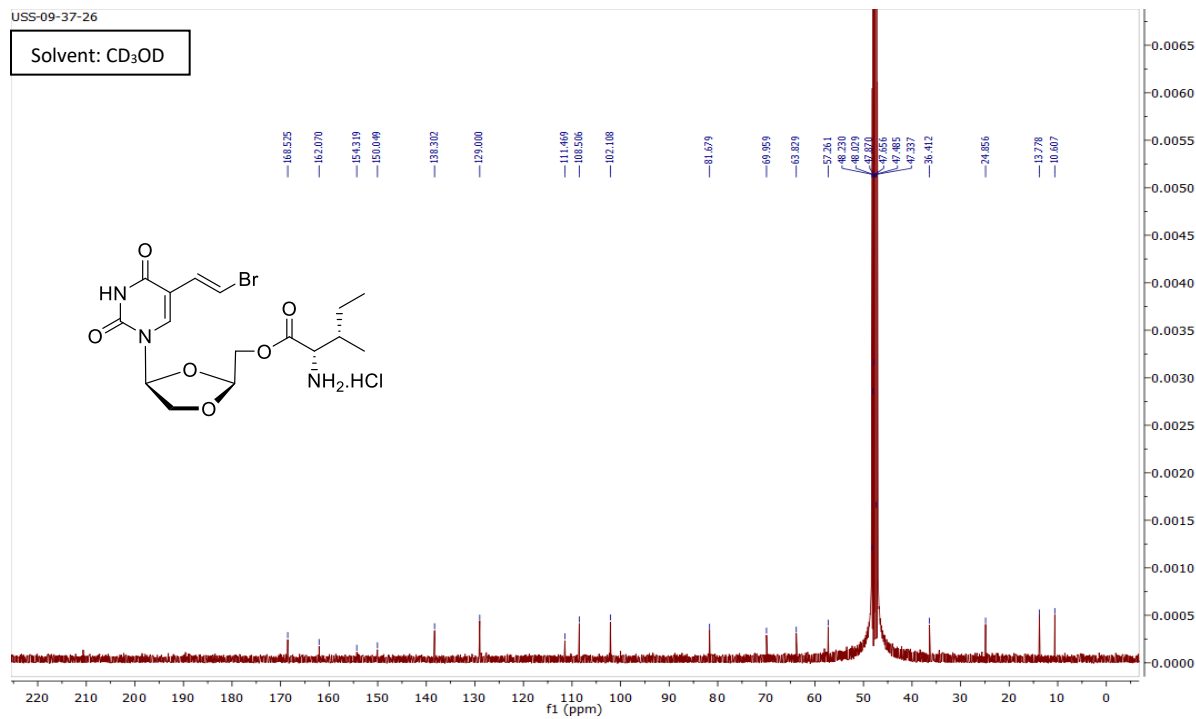


<sup>13</sup>C NMR of L-BH DU-5'-O-L-Boc-iso-leucine ester (9)

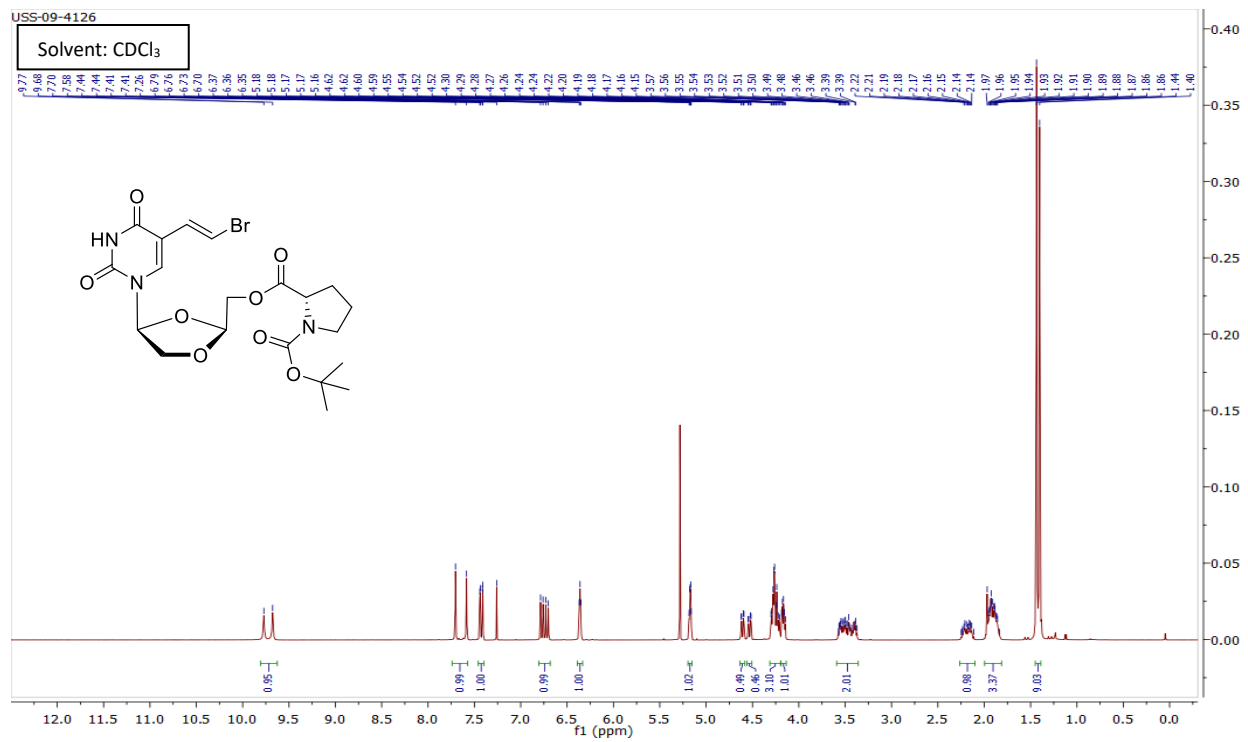




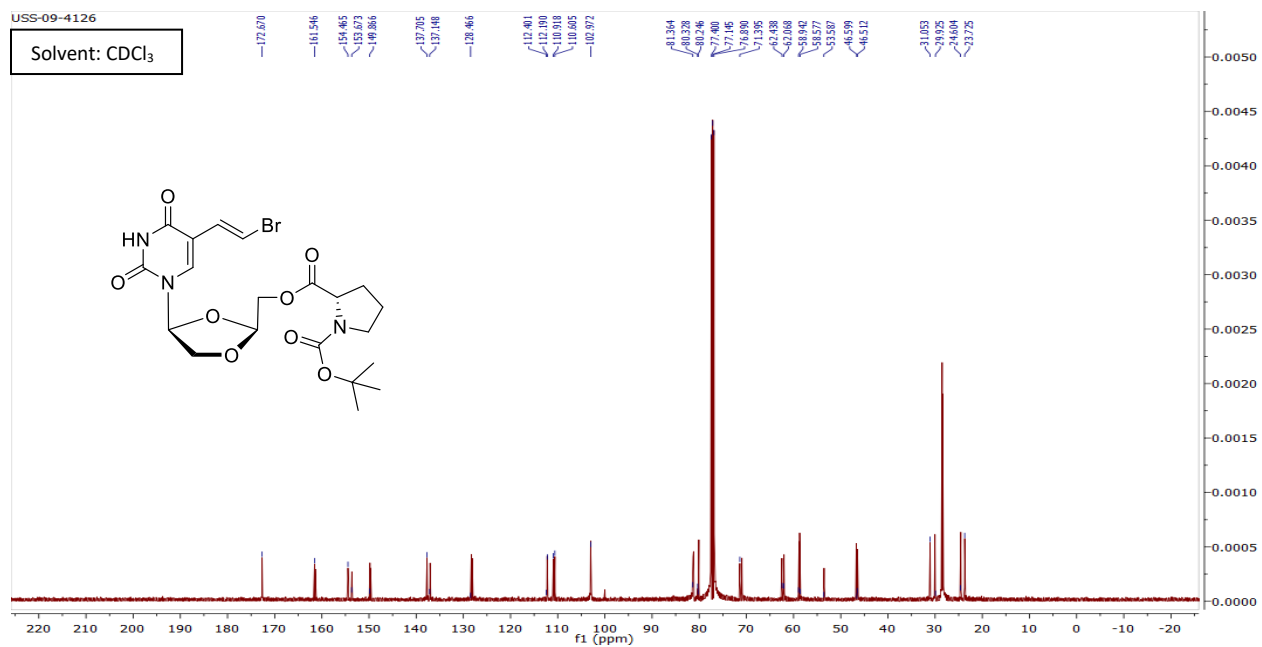
<sup>1</sup>H NMR of L-BH DU-5'-O-L-iso-leucine ester hydrochloride (21)



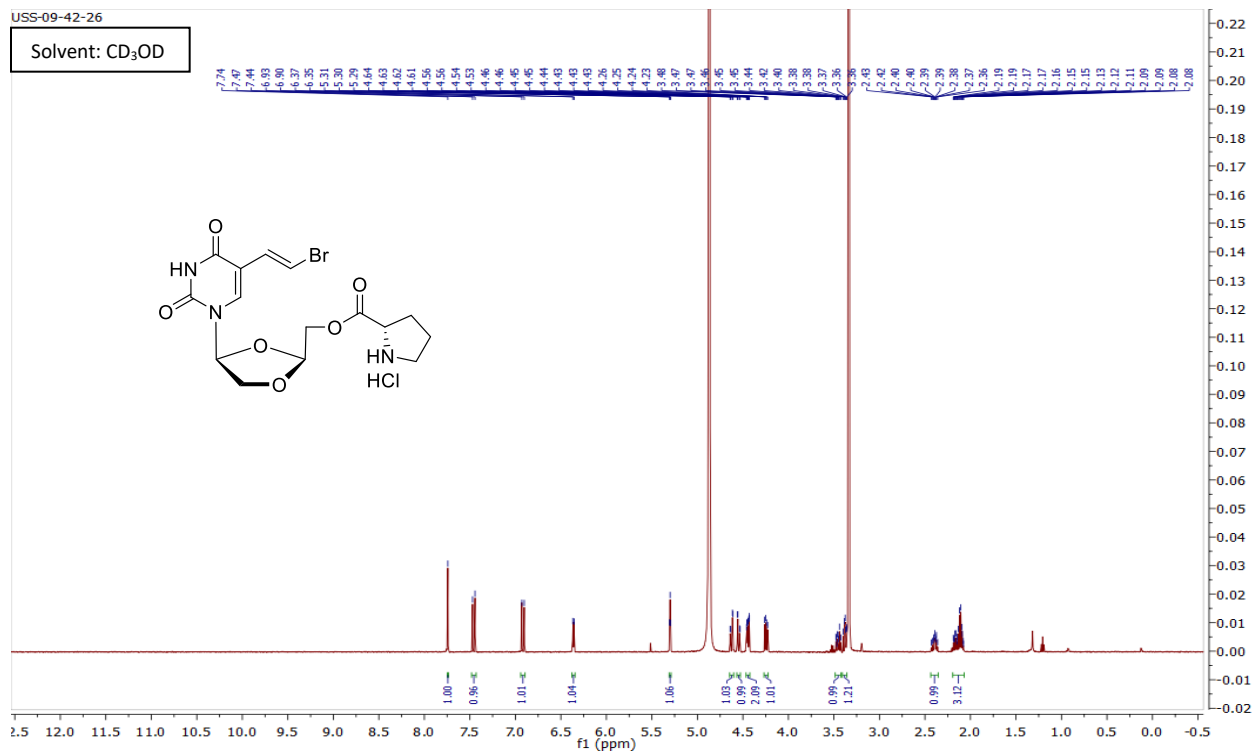
<sup>13</sup>C NMR of L-BH DU-5'-O-L-iso-leucine ester hydrochloride (21)



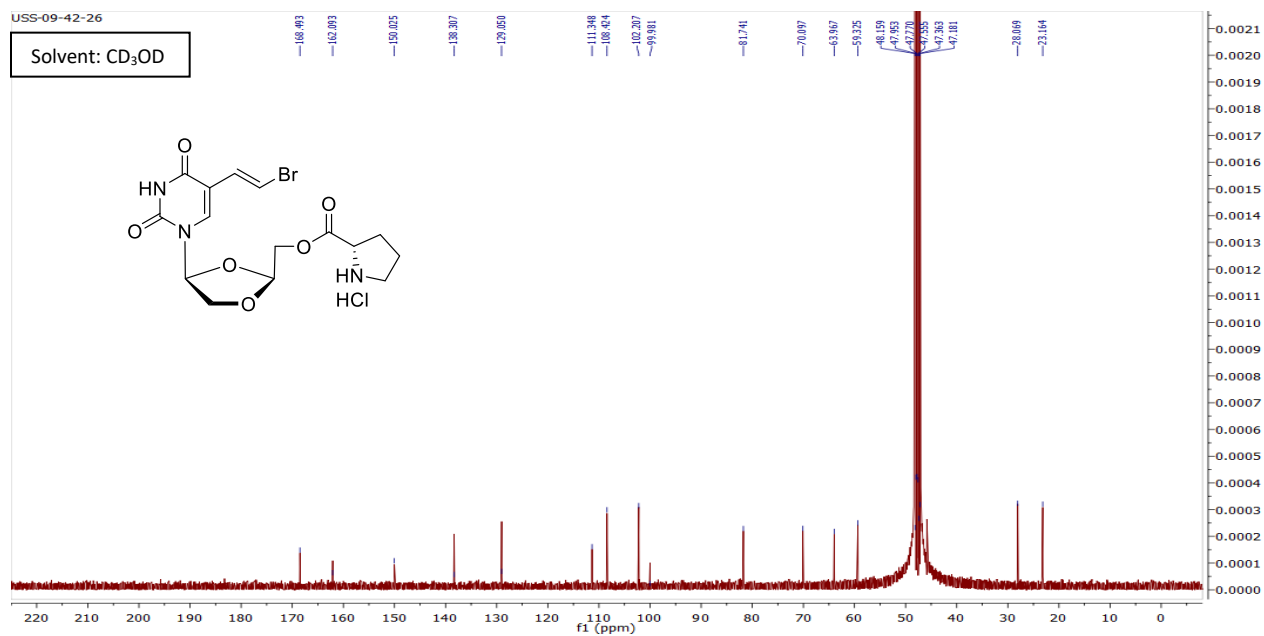
<sup>1</sup>H NMR of L-BH DU-5'-O-L-Boc-proline ester (10)



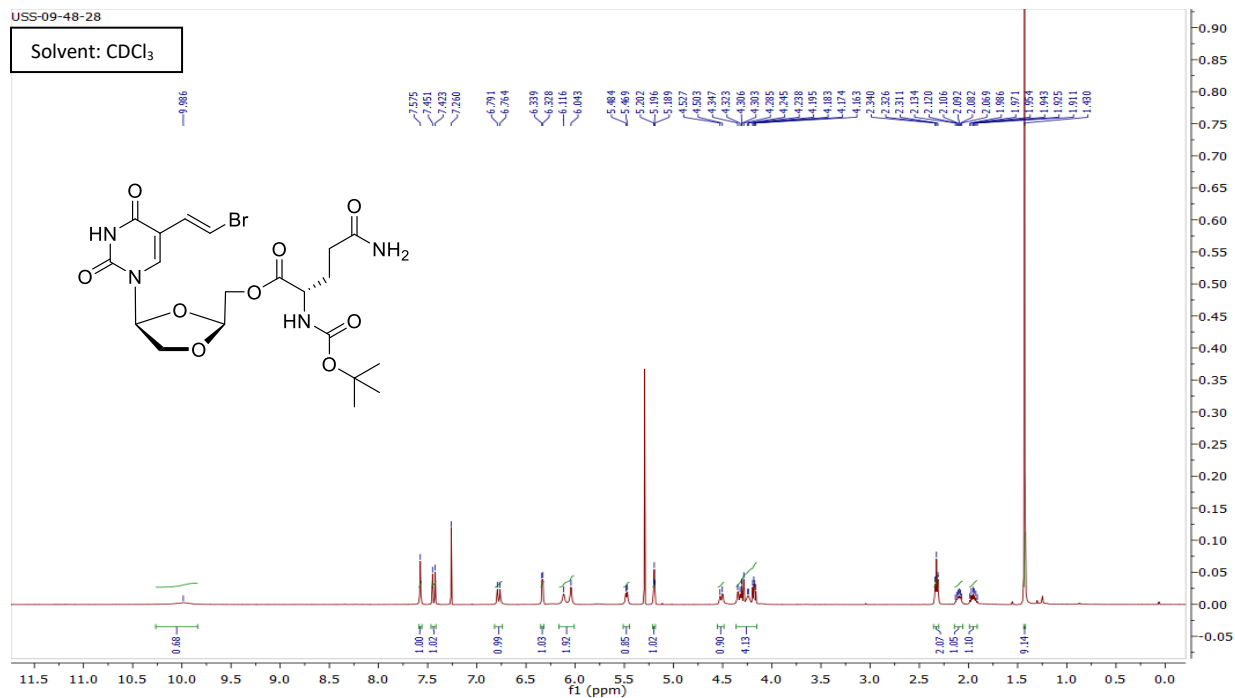
<sup>13</sup>C NMR of L-BH DU-5'-O-L-Boc-proline ester (10)



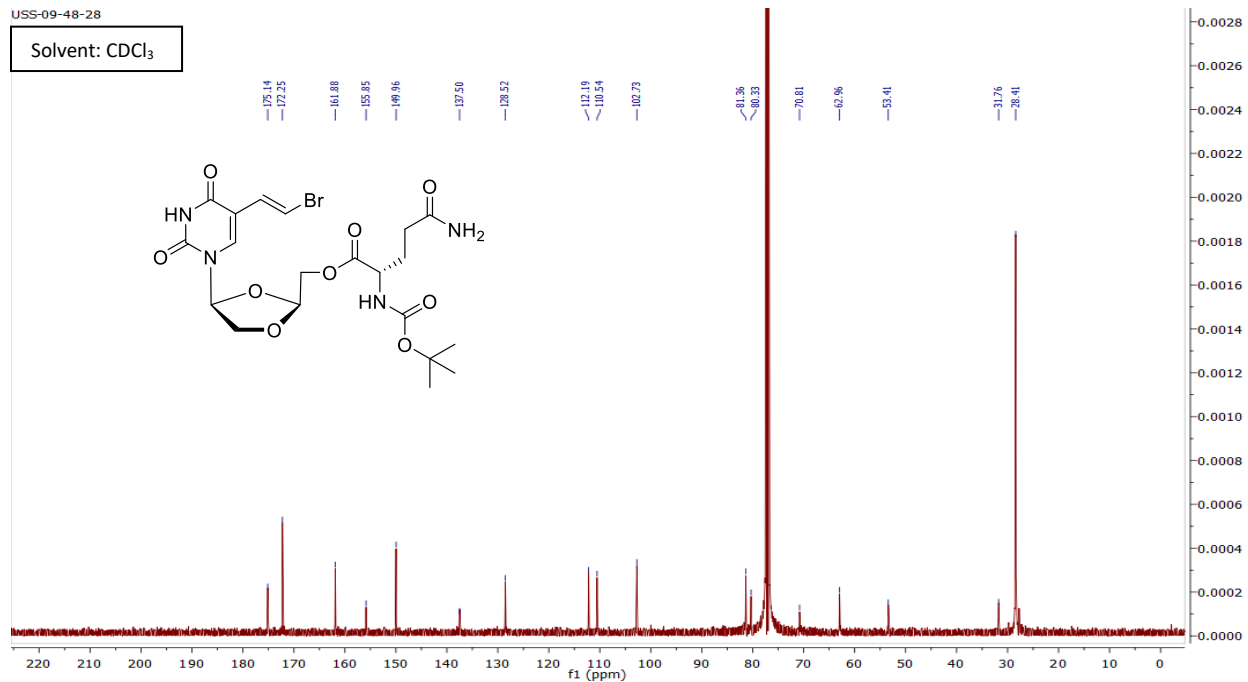
<sup>1</sup>H NMR of L-BH DU-5'-O-L-proline ester hydrochloride (22)



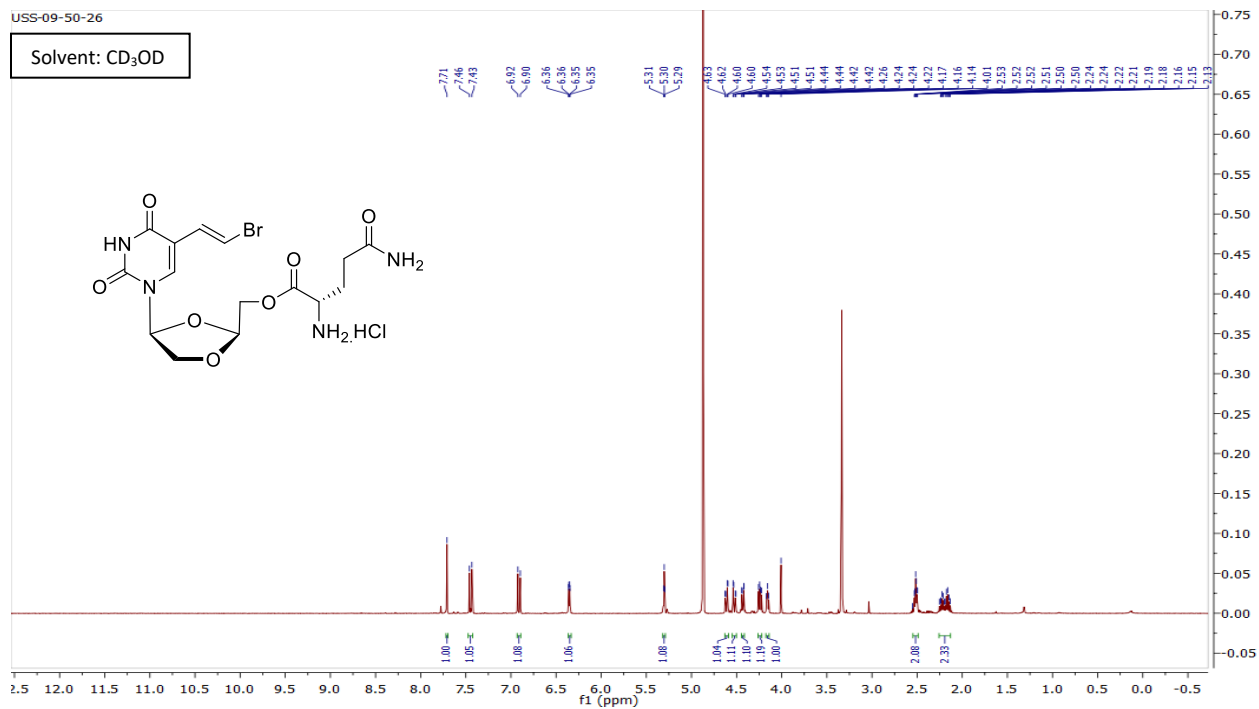
<sup>13</sup>C NMR of L-BH DU-5'-O-L-proline ester hydrochloride (22)



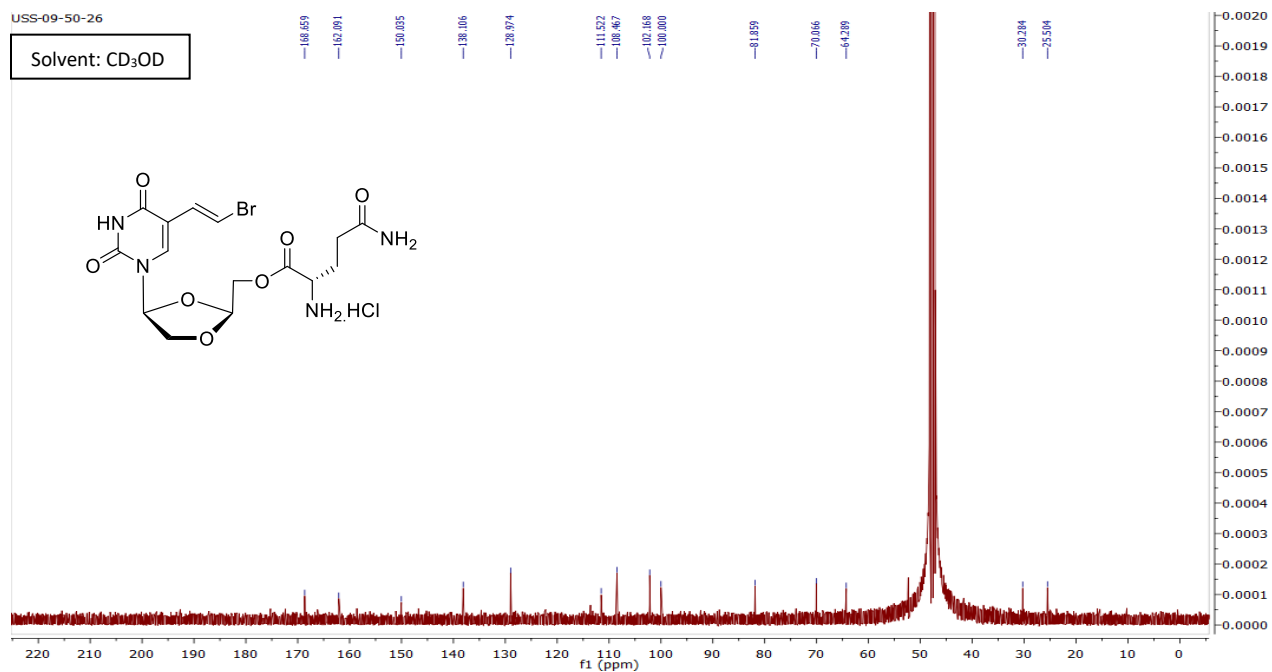
<sup>1</sup>H NMR of L-BH DU-5'-O-L-Boc-glutamine amide ester (11)



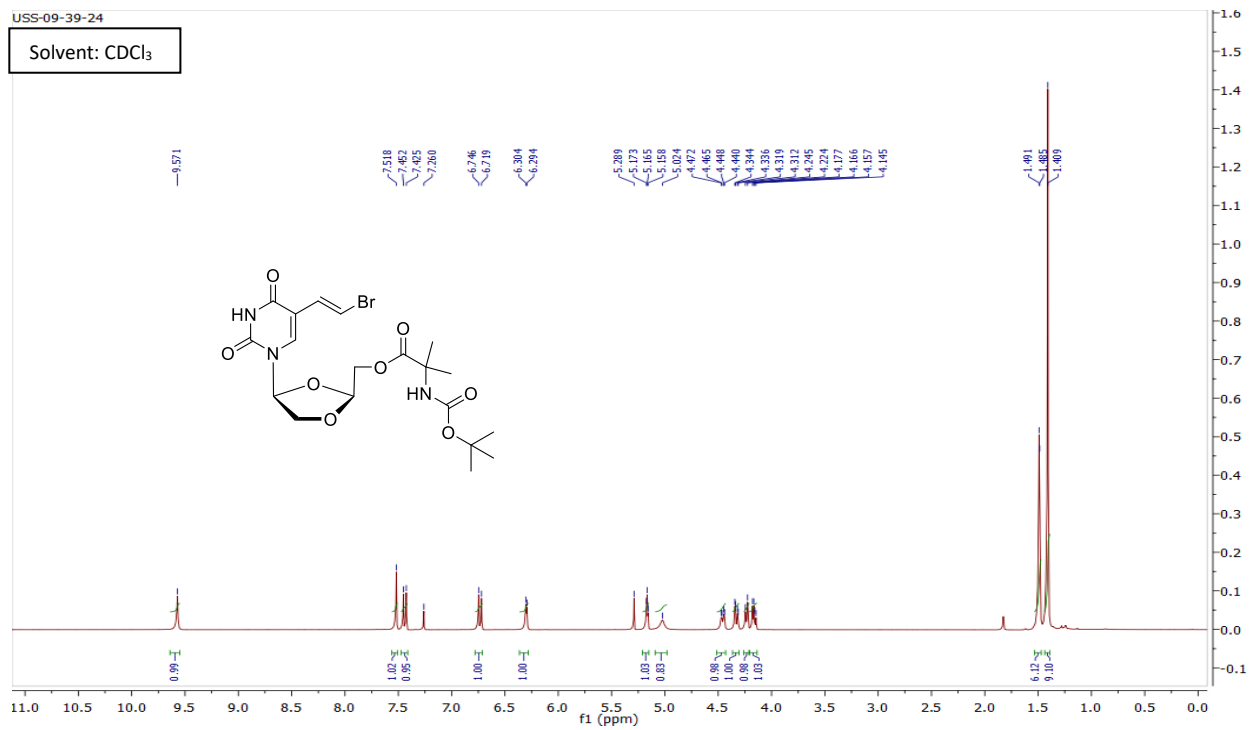
<sup>13</sup>C NMR of L-BH DU-5'-O-L-Boc-glutamine amide ester (11)



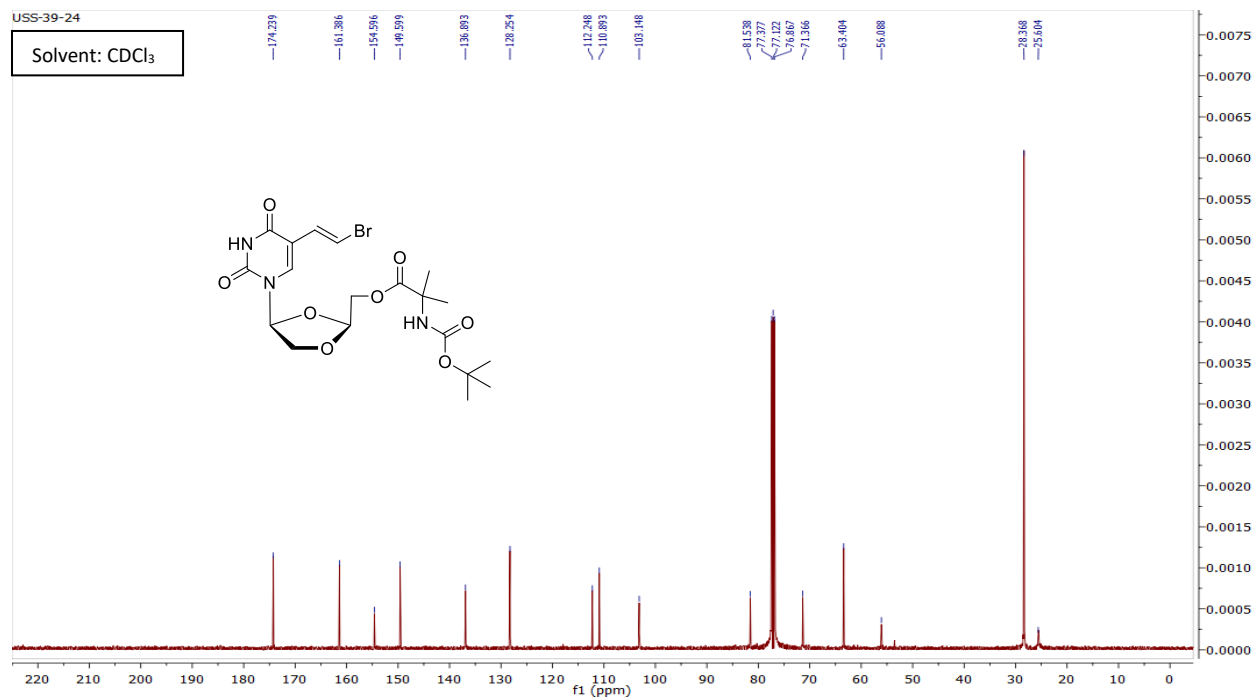
<sup>1</sup>H NMR of L-BH DU-5'-O-L-glutamine ester hydrochloride (**23**)



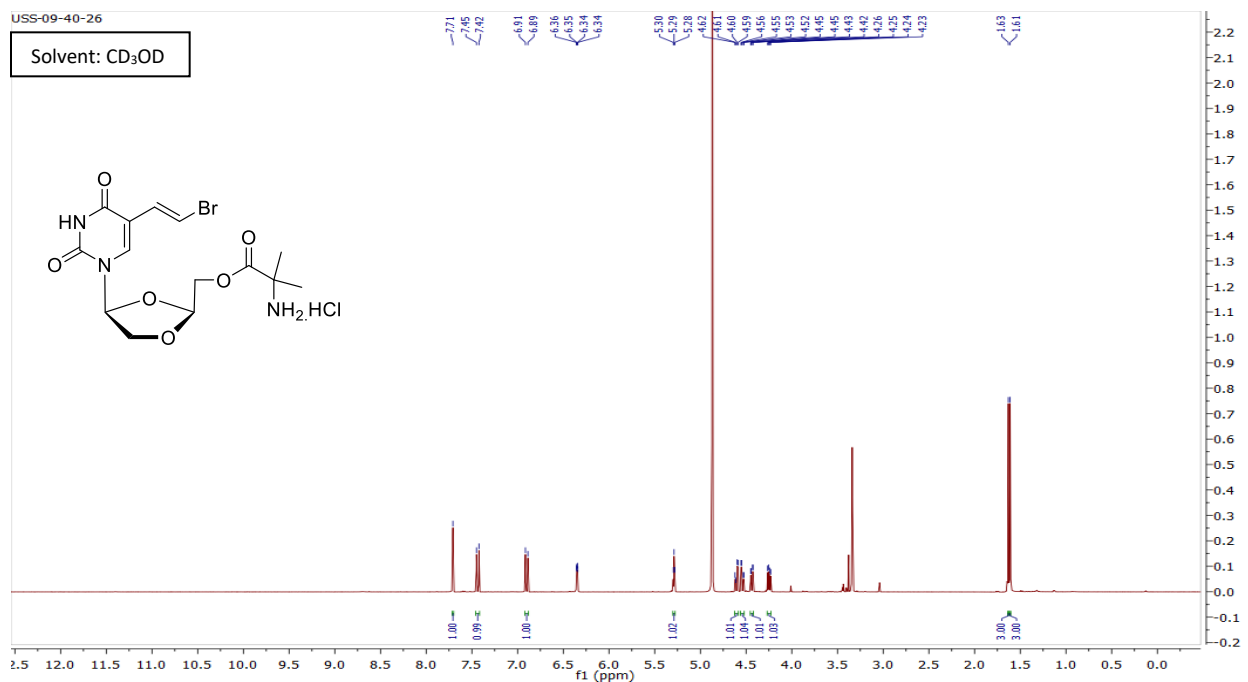
<sup>13</sup>C NMR of L-BH DU-5'-O-L-glutamine ester hydrochloride (**23**)



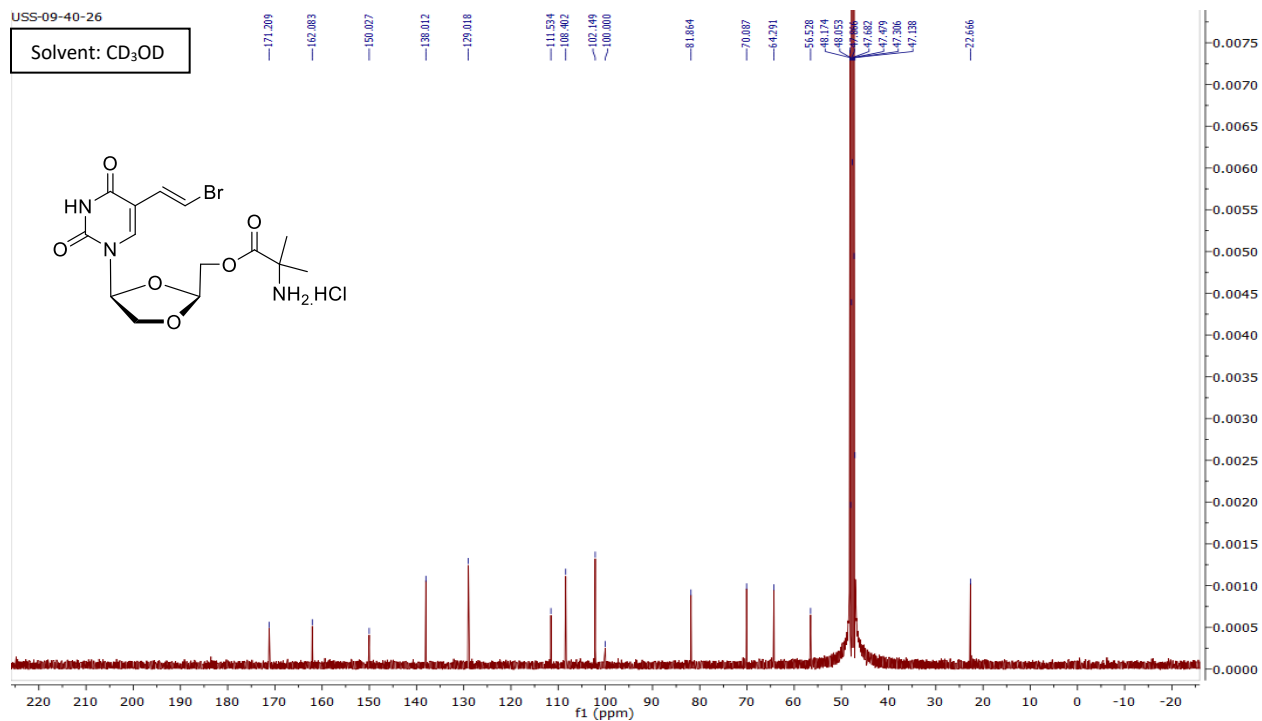
<sup>1</sup>H NMR of L-BH DU-5'-O-Boc-2-Aminoisobutyric ester (12)



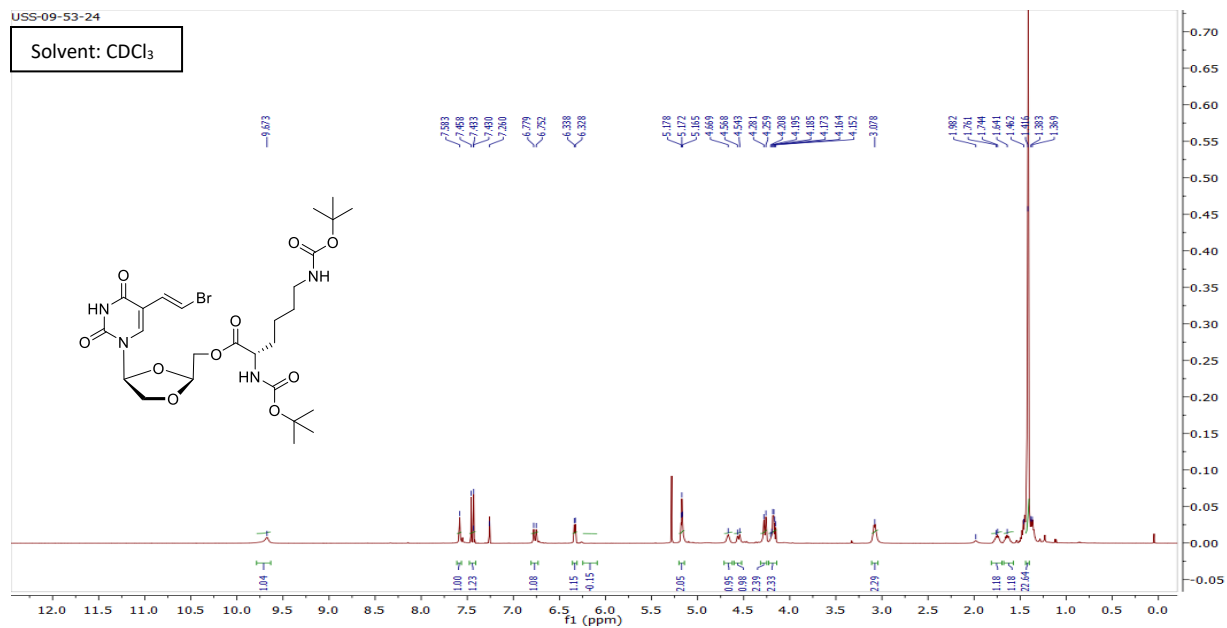
<sup>13</sup>C NMR of L-BH DU-5'-O-Boc-2-Aminoisobutyric ester (12)



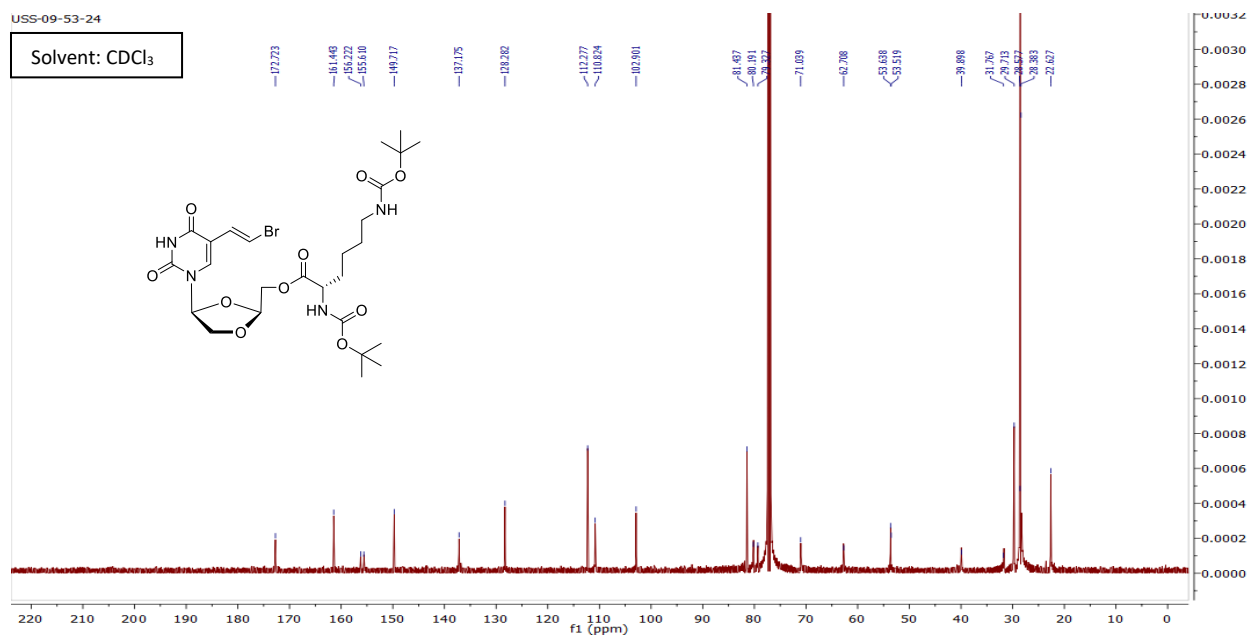
$^1\text{H}$  NMR of L-BHDU-5'-O-2-Aminoisobutyric acid ester hydrochloride (24)



$^{13}\text{C}$  NMR of L-BHDU-5'-O-2-Aminoisobutyric acid ester hydrochloride (24)

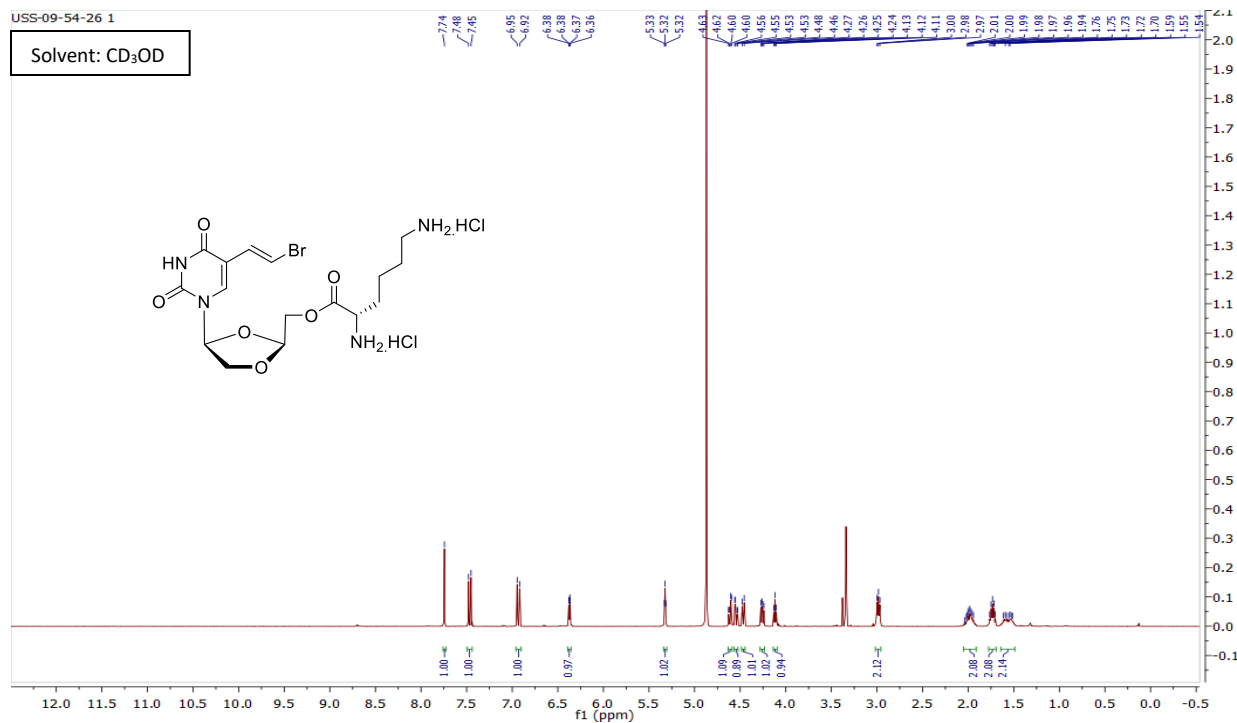


<sup>1</sup>H NMR of L-BH DU-5'-O-L-Boc-lysine Boc-amide ester (**13**)

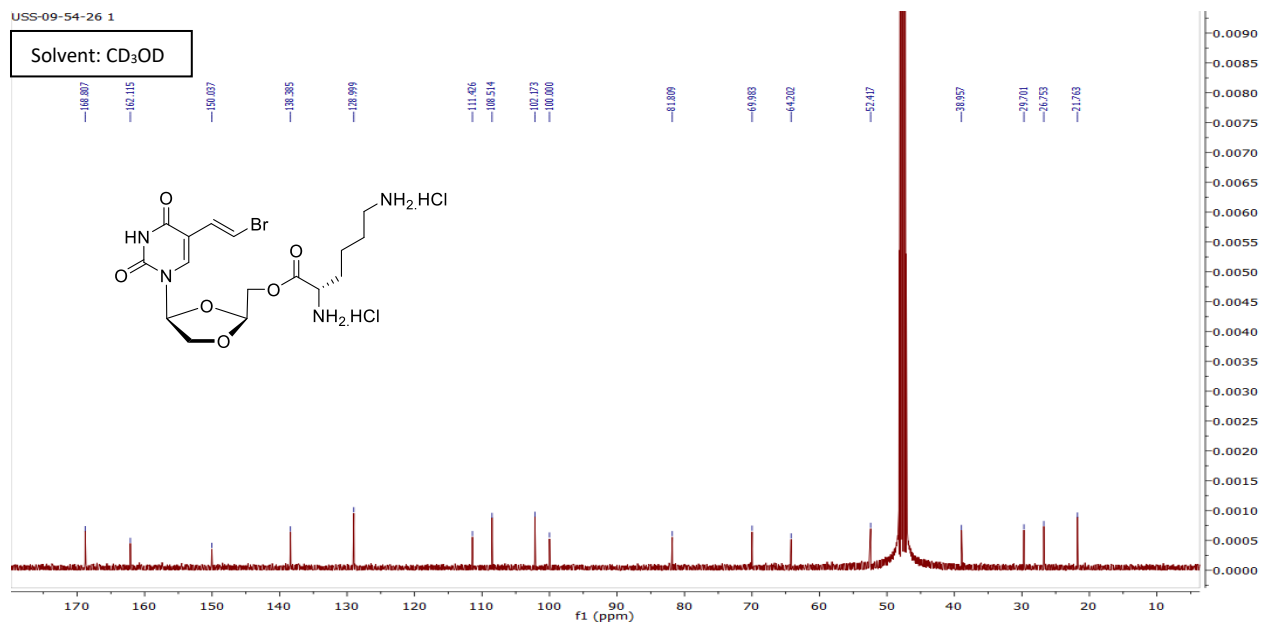


<sup>13</sup>C NMR of L-BH DU-5'-O-L-Boc-lysine Boc-amide ester (**13**)

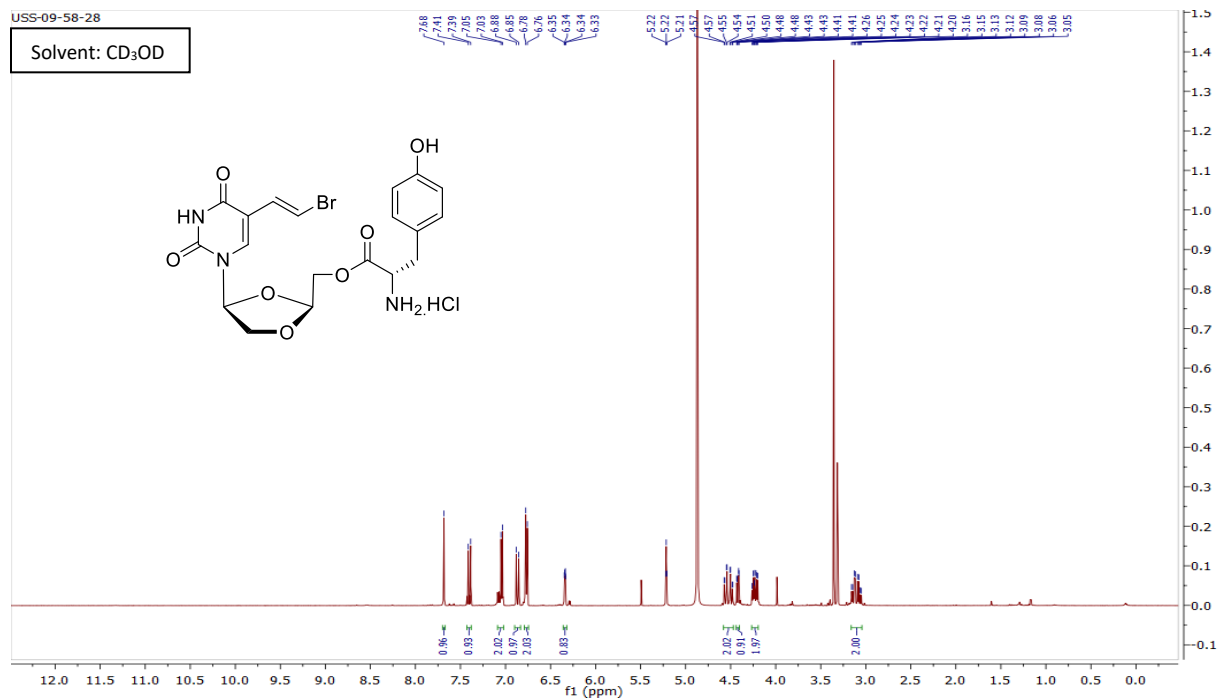




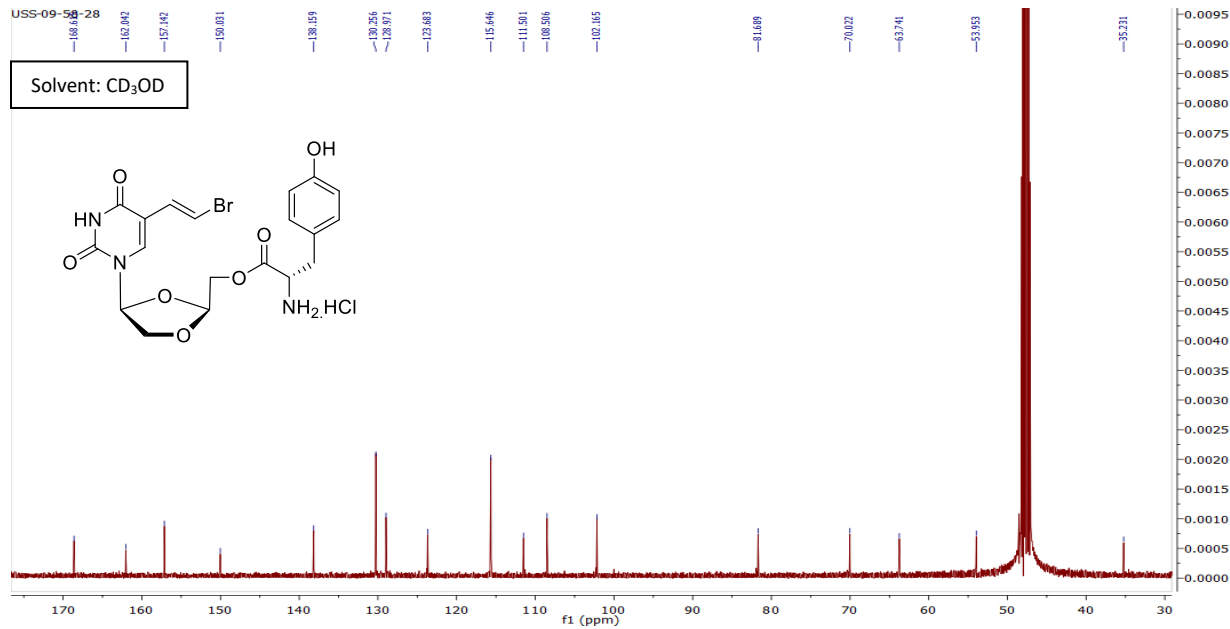
<sup>1</sup>H NMR of L-BH DU-5'-O-L-lysine ester hydrochloride (25)



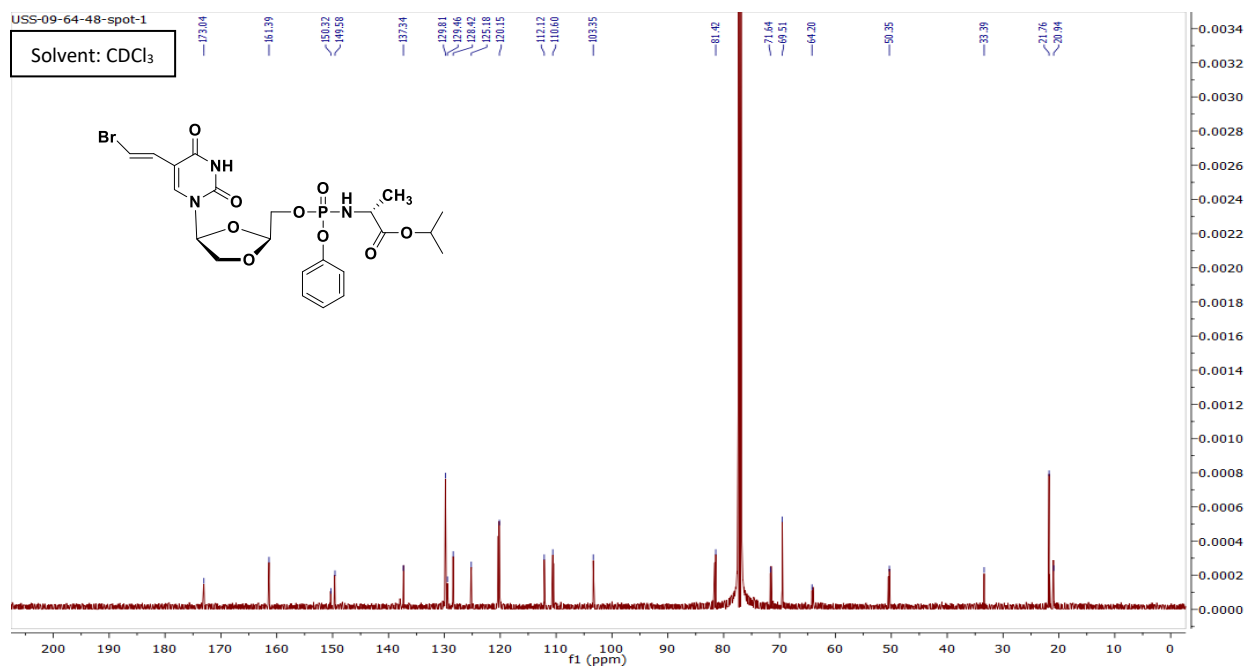
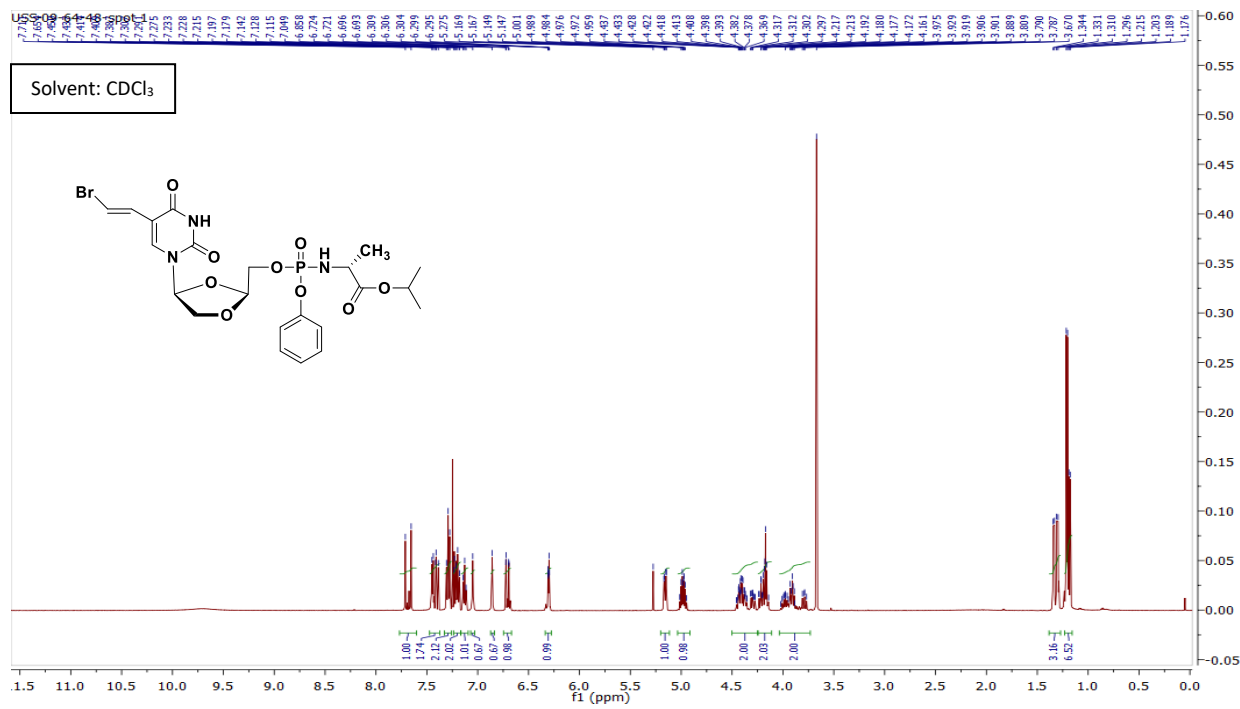
<sup>13</sup>C NMR of L-BH DU-5'-O-L-lysine ester hydrochloride (25)

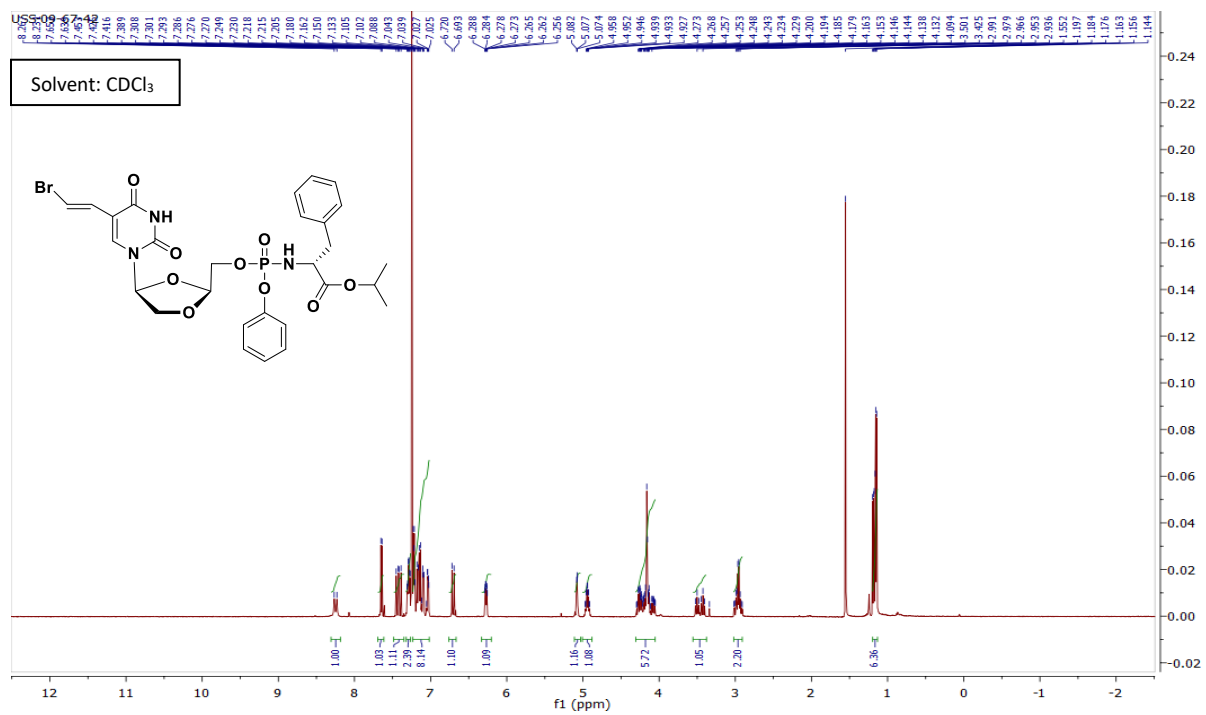
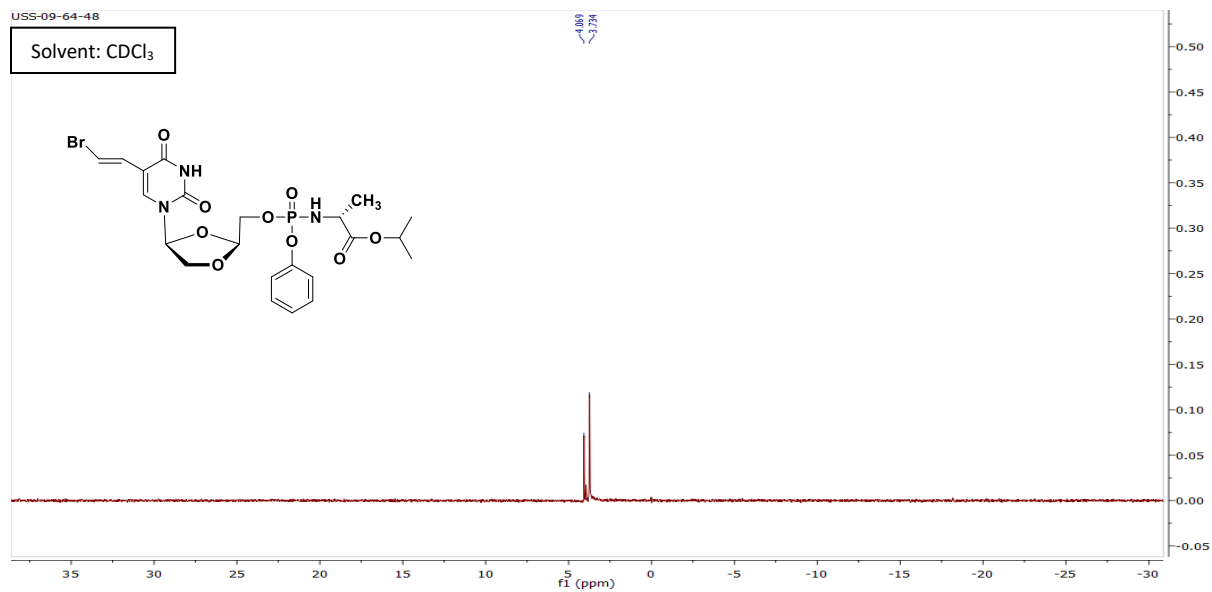


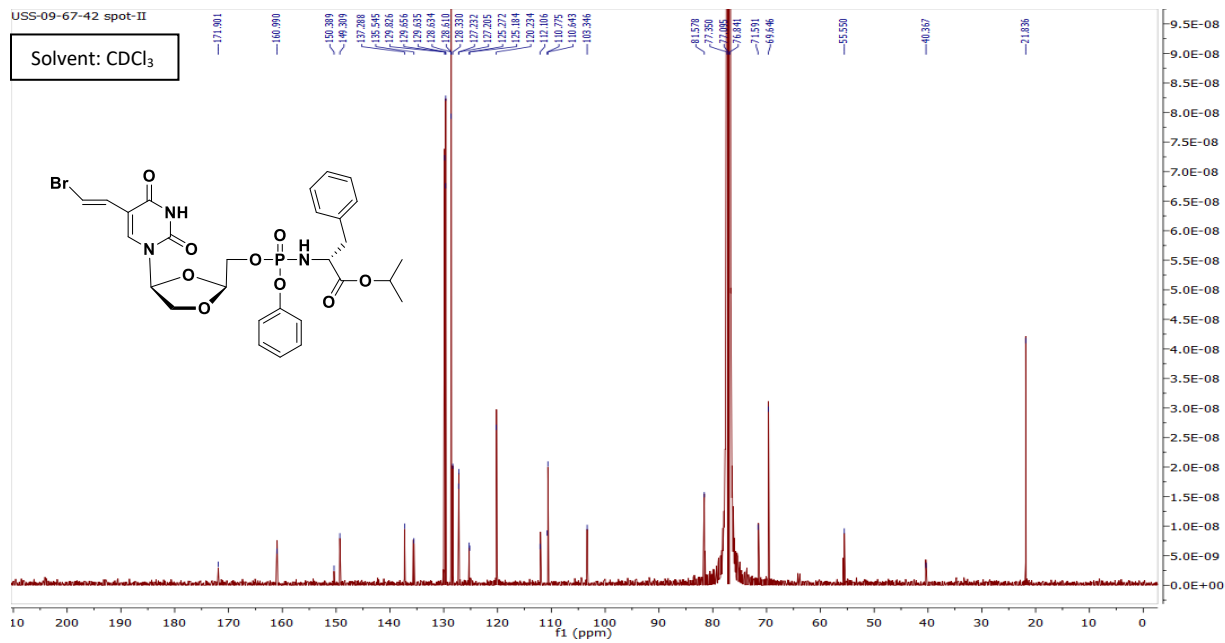
<sup>1</sup>H NMR of L-BH DU-5'-O-L-tyrosine ester hydrochloride (**26**)



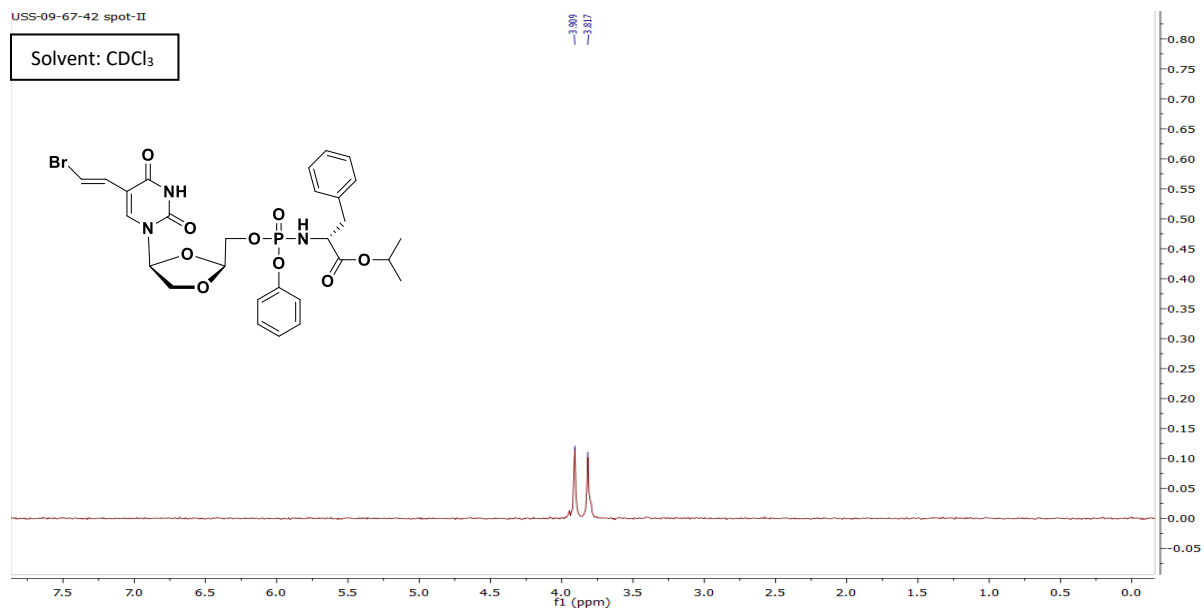
<sup>13</sup>C NMR of L-BH DU-5'-O-L-tyrosine ester hydrochloride (**26**)



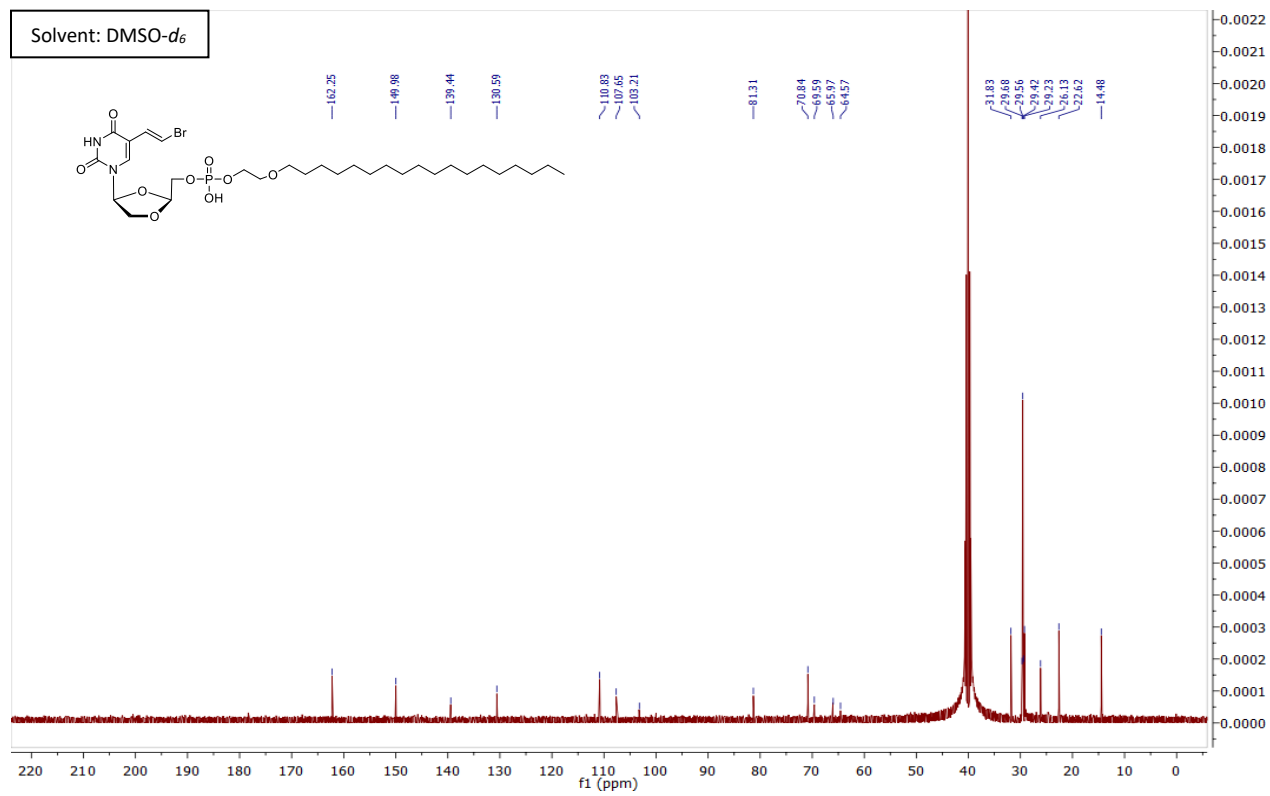
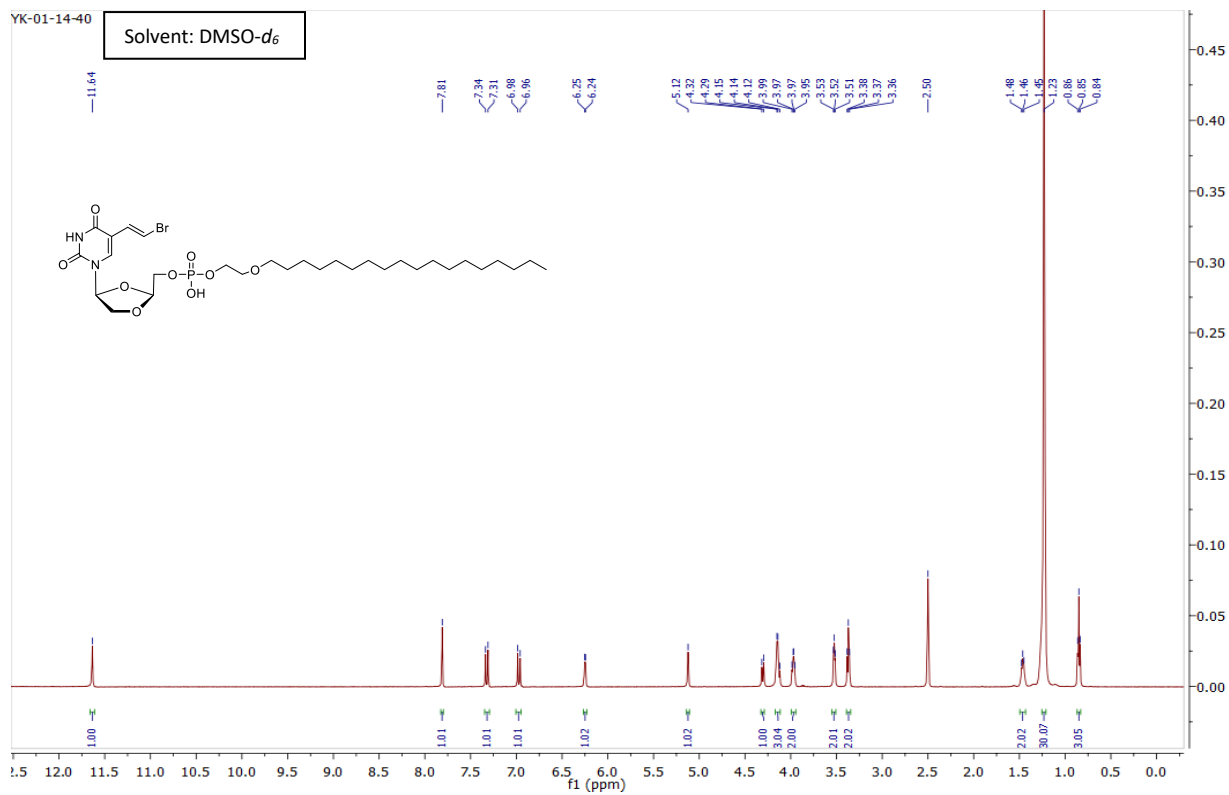


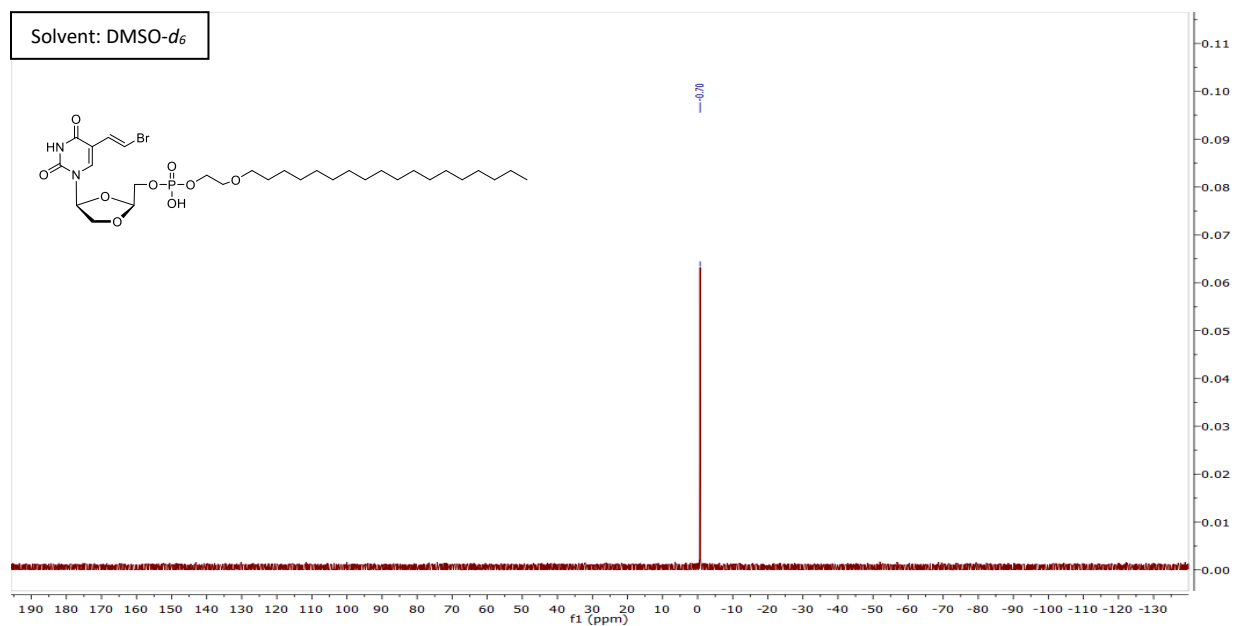


<sup>13</sup>C NMR of compound 34.

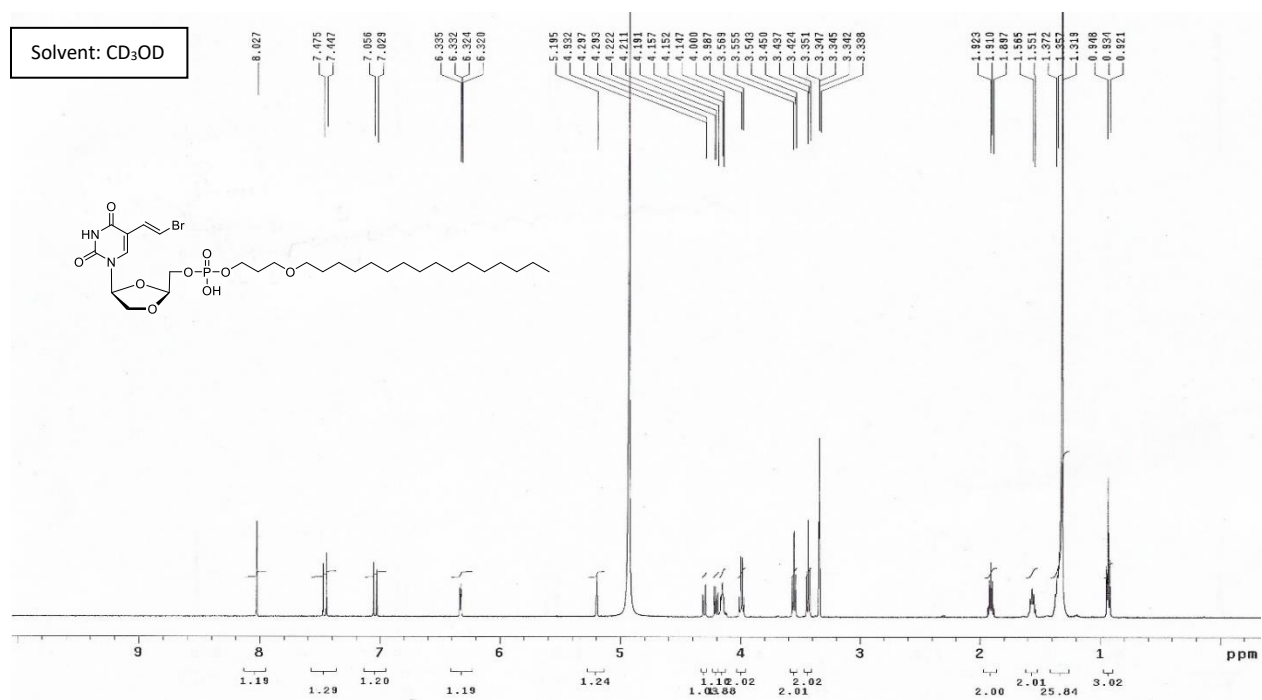


<sup>31</sup>P NMR of compound 34.

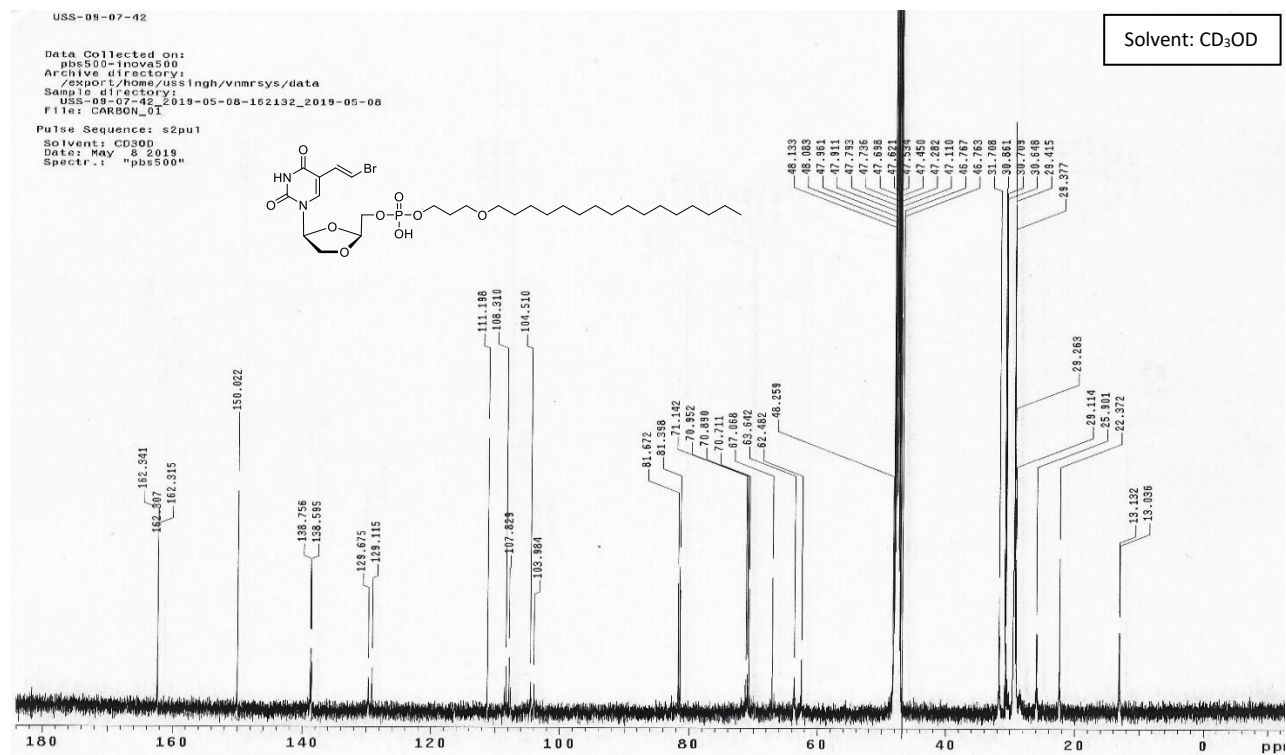




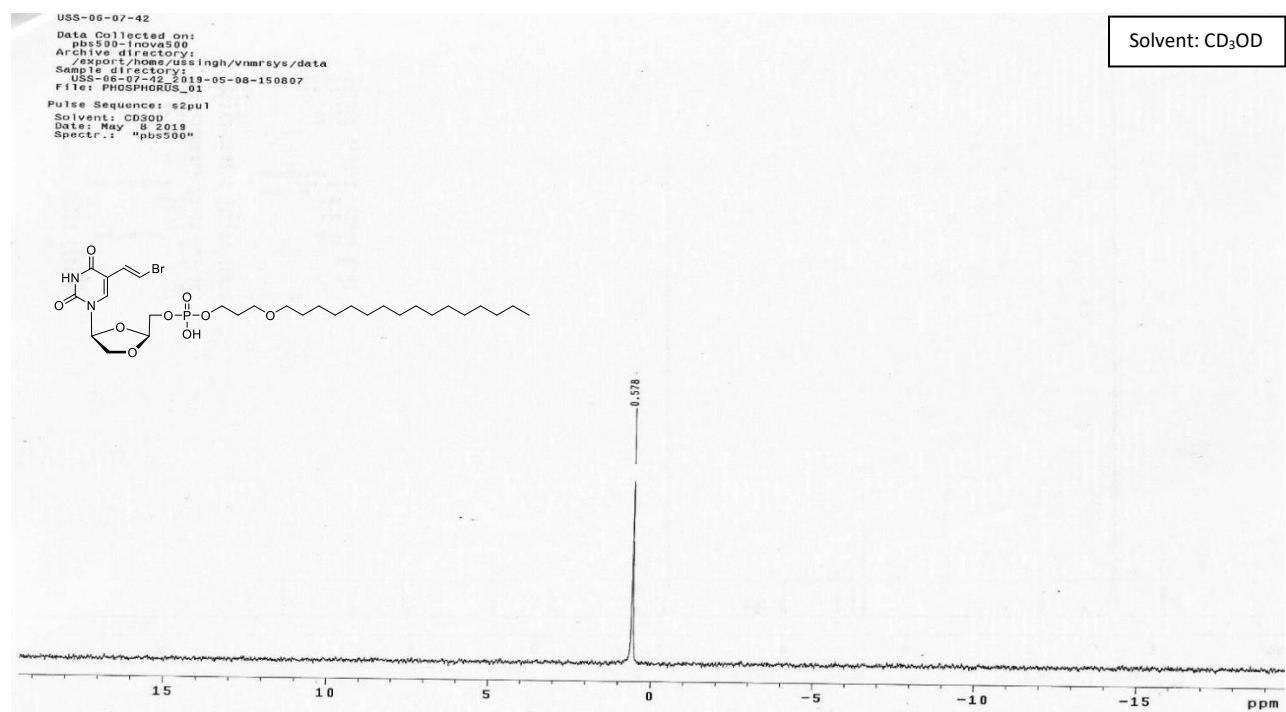
<sup>31</sup>P NMR of ODE-L-BH DU-MP (38).



<sup>1</sup>H NMR of HDP-L-BH DU-MP (39).

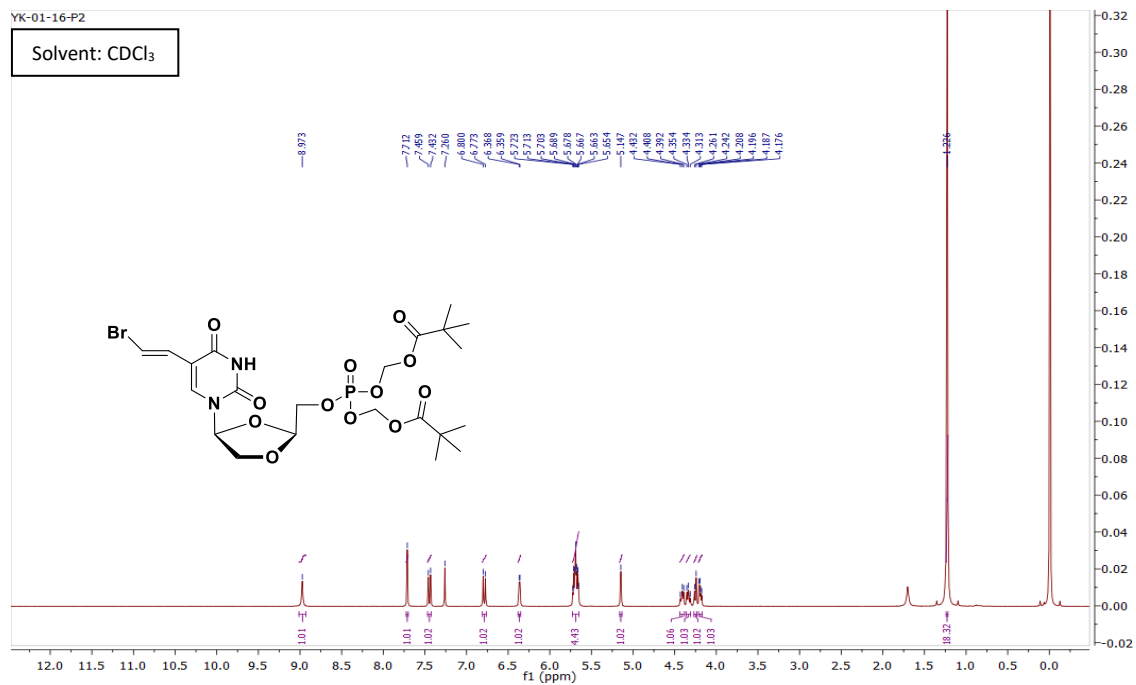


<sup>13</sup>C NMR of HDP-L-BH DU-MP (39).

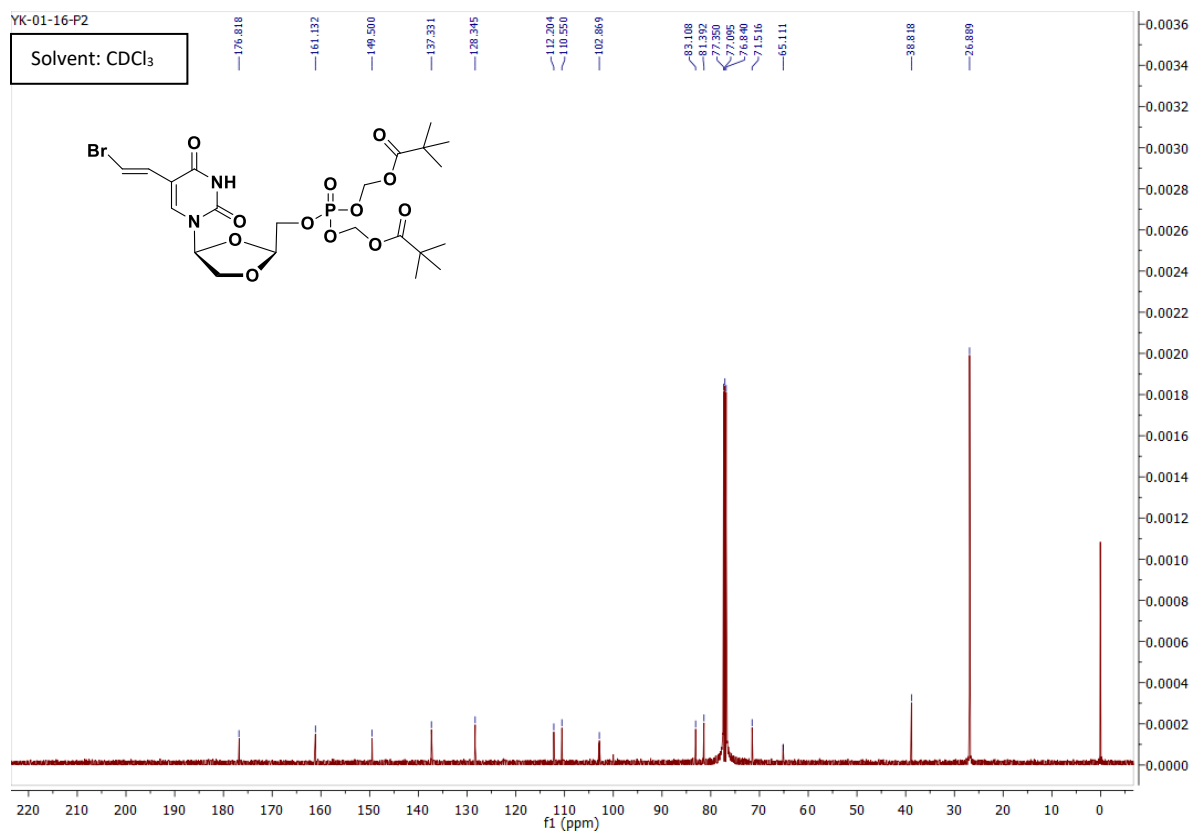


<sup>31</sup>P NMR of HDP-L-BH DU-MP (39).

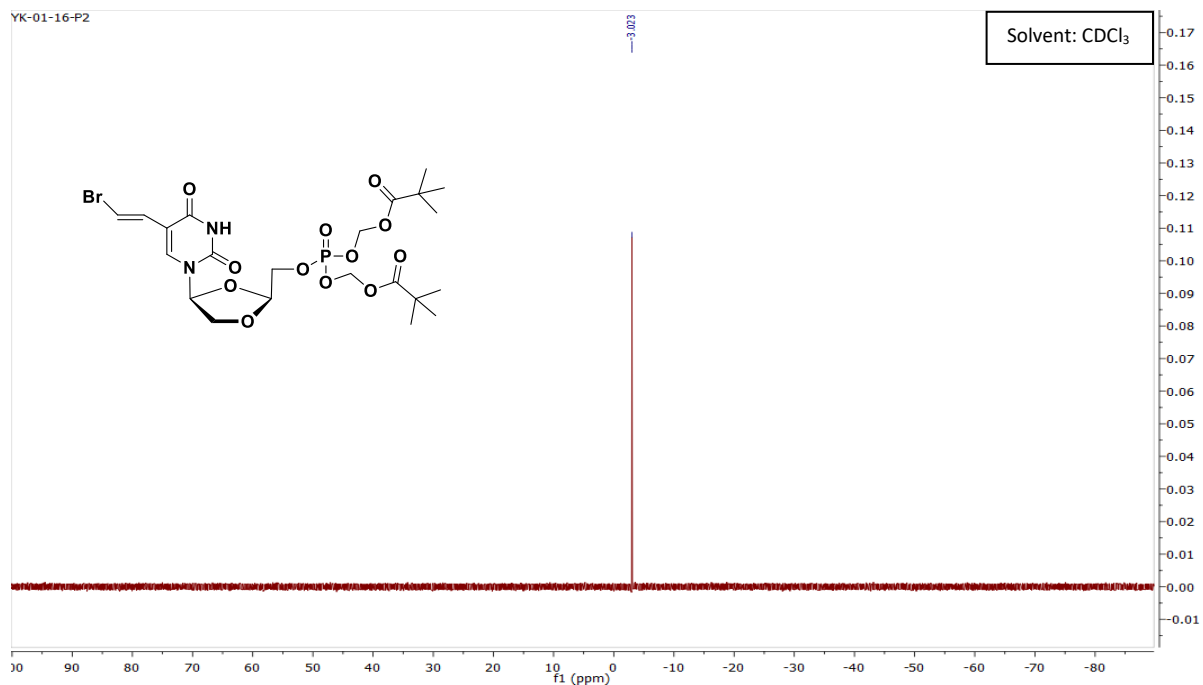




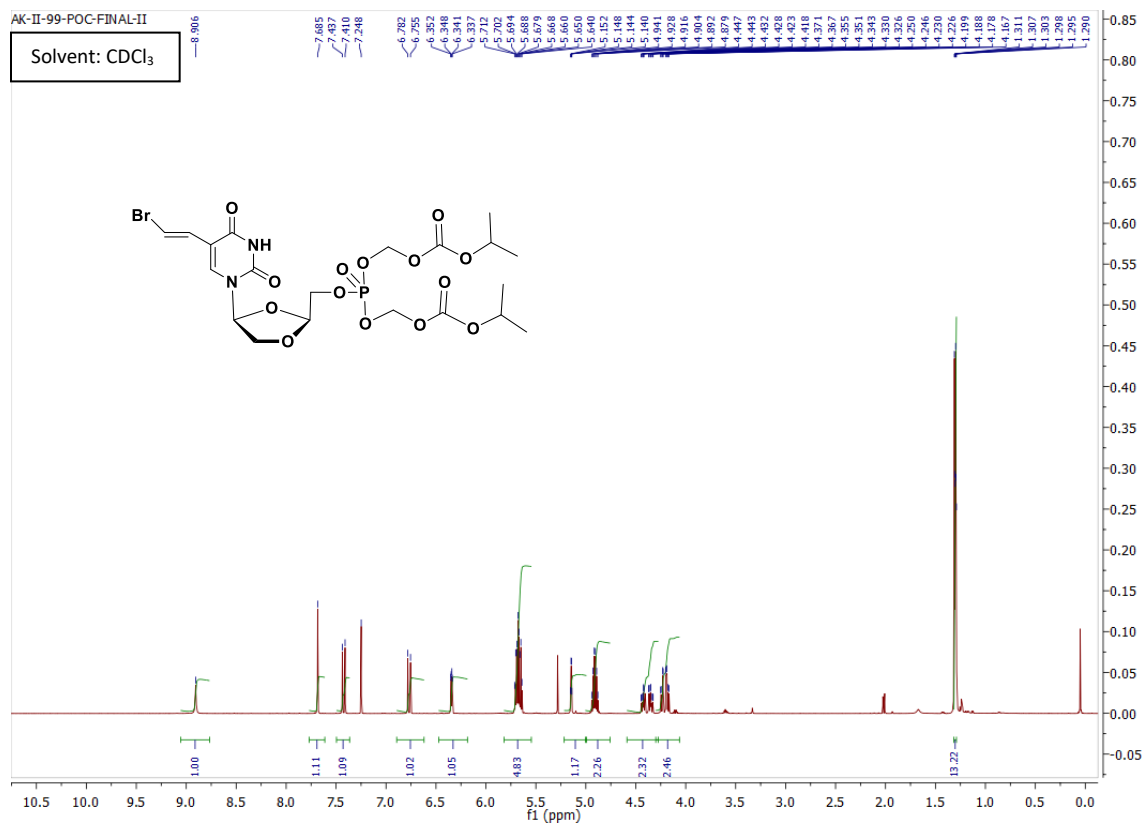
<sup>1</sup>H NMR of POM-L-BH DU-MP (41).



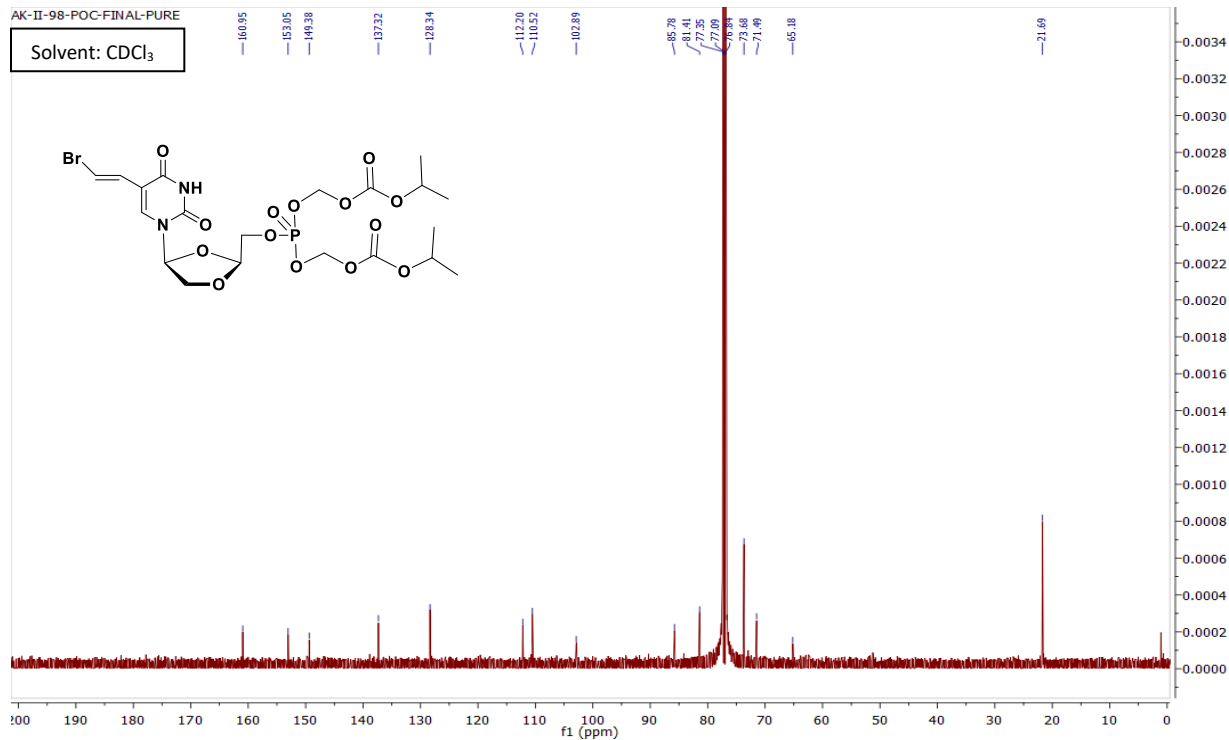
<sup>13</sup>C NMR of POM-L-BH DU-MP (41).



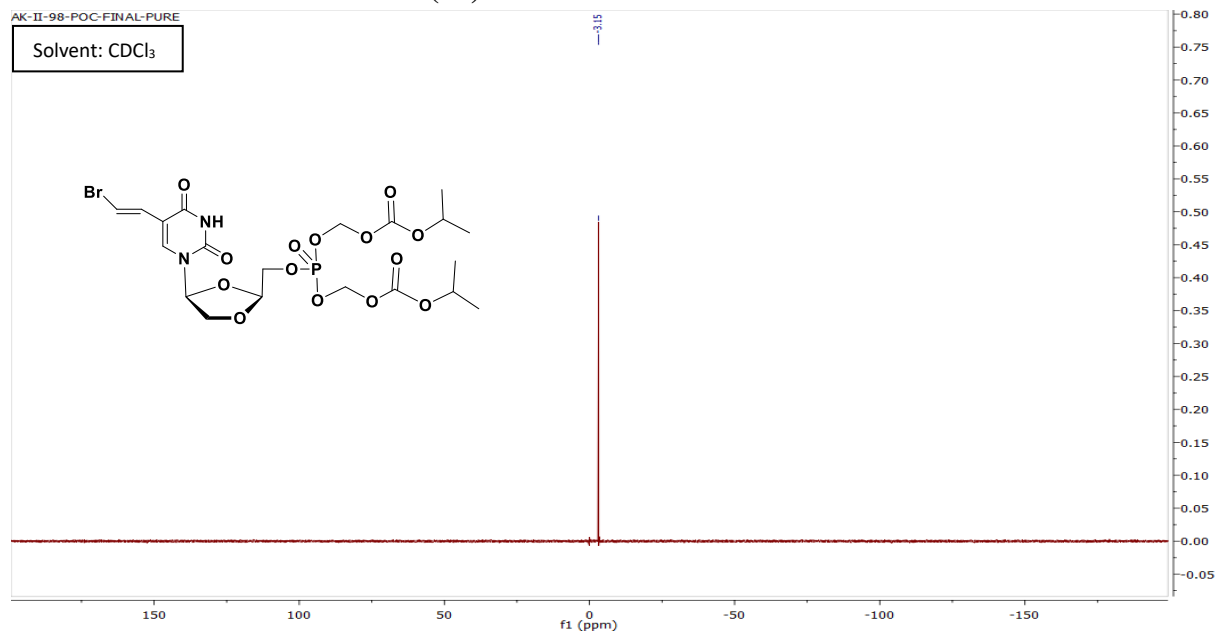
<sup>31</sup>P NMR of POM-L-BH DU-MP (41).



<sup>1</sup>H NMR of POC-L-BH DU-MP (47).



<sup>13</sup>C NMR of POC-L-BH DU-MP (47).



<sup>31</sup>P NMR of POC-L-BH DU-MP (47).

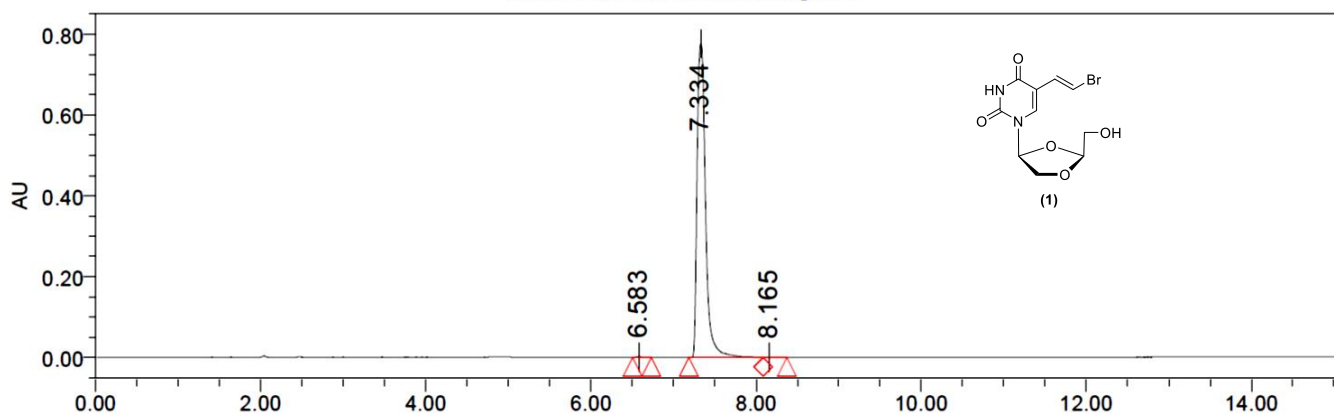
**Table S1:** elemental analysis of final compounds

Compound	Molecular Formula	Calculated			Found		
		C	H	N	C	H	N
14.	C <sub>12</sub> H <sub>15</sub> BrClN <sub>3</sub> O <sub>6</sub> . 1.5 H <sub>2</sub> O	32.78	4.13	9.56	32.39	3.90	9.23
15.	C <sub>13</sub> H <sub>17</sub> BrClN <sub>3</sub> O <sub>6</sub> . 1.0 H <sub>2</sub> O	35.11	4.31	9.45	35.05	4.32	9.28
16.	C <sub>19</sub> H <sub>21</sub> BrClN <sub>3</sub> O <sub>6</sub> . 1.0 H <sub>2</sub> O	43.82	4.45	8.07	43.75	4.51	7.98
17.	C <sub>15</sub> H <sub>21</sub> BrClN <sub>3</sub> O <sub>6</sub> . 0.5 H <sub>2</sub> O	38.85	4.78	9.06	38.82	4.85	8.96
18.	C <sub>15</sub> H <sub>21</sub> BrClN <sub>3</sub> O <sub>6</sub> . 1.2 H <sub>2</sub> O	37.82	4.95	8.82	37.69	5.12	8.65
19.	C <sub>21</sub> H <sub>22</sub> BrClN <sub>4</sub> O <sub>6</sub> . 1.0 H <sub>2</sub> O	45.06	4.32	10.0	44.75	4.46	9.78
20.	C <sub>16</sub> H <sub>23</sub> BrClN <sub>3</sub> O <sub>6</sub> . 1.0 H <sub>2</sub> O	39.48	5.18	8.63	39.29	5.31	8.41
21.	C <sub>16</sub> H <sub>23</sub> BrClN <sub>3</sub> O <sub>6</sub>	41.00	4.95	8.96	40.82	4.93	8.74
22.	C <sub>15</sub> H <sub>19</sub> BrClN <sub>3</sub> O <sub>6</sub> . 1.0 H <sub>2</sub> O	38.28	4.50	8.93	38.30	4.50	8.82
23.	C <sub>15</sub> H <sub>20</sub> BrClN <sub>4</sub> O <sub>7</sub> . 1.5 H <sub>2</sub> O	35.28	4.54	10.97	35.43	4.63	10.63
24.	C <sub>14</sub> H <sub>19</sub> BrClN <sub>3</sub> O <sub>6</sub> . 1.0 H <sub>2</sub> O	36.66	4.61	9.16	36.94	4.64	8.77
25.	C <sub>16</sub> H <sub>25</sub> BrCl <sub>2</sub> N <sub>4</sub> O <sub>6</sub> . 1.5 H <sub>2</sub> O	35.12	5.16	10.24	35.26	5.28	9.87
26.	C <sub>19</sub> H <sub>21</sub> BrClN <sub>3</sub> O <sub>7</sub> . 1.0 H <sub>2</sub> O	42.52	4.32	7.83	42.54	4.42	7.68
33.	C <sub>22</sub> H <sub>27</sub> BrN <sub>3</sub> O <sub>9</sub> P	44.91	4.63	7.14	45.23	4.92	6.85
34.	C <sub>28</sub> H <sub>31</sub> BrN <sub>3</sub> O <sub>9</sub> P	50.61	4.70	6.32	50.92	4.95	6.11
38.	C <sub>30</sub> H <sub>52</sub> BrN <sub>2</sub> O <sub>9</sub> P. 0.5 H <sub>2</sub> O	51.14	7.58	3.98	51.20	7.55	3.92
39.	C <sub>29</sub> H <sub>50</sub> BrN <sub>2</sub> O <sub>9</sub> P. 0.9 H <sub>2</sub> O	49.92	7.48	4.01	49.65	7.62	3.69
41.	C <sub>22</sub> H <sub>32</sub> BrN <sub>3</sub> O <sub>12</sub> P	42.12	5.14	4.47	42.34	5.23	4.26

## HPLC method and trace for compound (1)

HPLC Method Conditions			
Column	XBridge C18 (4.6x150), mm, 3.5µm	Sample	YK-02-22-P
Mobile Phase-A	10mM Ammonium Acetate in Water	Vial	1:F
Mobile Phase-B	100% Acetonitrile	Injection Volume	0.5 µL
Gradient (T% B)	0/10,1/10,10/95,15/95,15.1/10	Run Time	20 minutes
Flow Rate	0.8 mL/min	Proc. Chnl. Descr.:	2998 PDA MaxPlot (190.0 nm to 800.0 nm) (2998(210-400)nm) Subtracted from blank
Column oven Temp	Ambient	Acq. Method Set:	Method_1_COL-2
Diluent: MeOH			

### Auto-Scaled Chromatogram

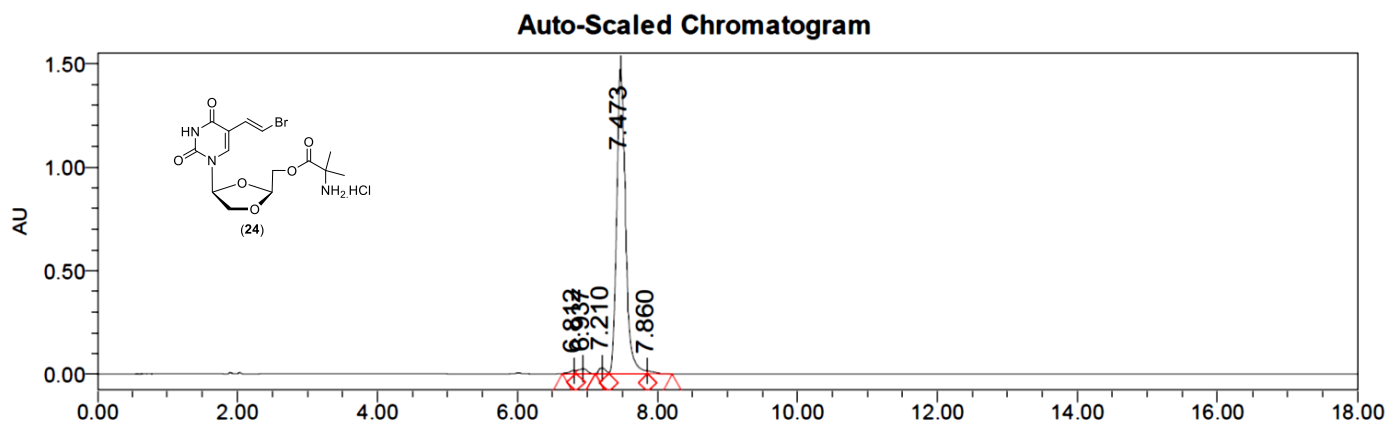


#### Peak Results

	RT	Area	% Area
1	6.583	3900	0.07
2	7.334	5515706	99.85
3	8.165	4112	0.07

## HPLC method and trace for compound (24)

HPLC Method Conditions			
Column	XBridge C18 (4.6x150), mm, 3.5 $\mu$ m	Sample	USS-09-40-26
Mobile Phase-A	10mM Ammonium Acetate in Water	Vial	1:F
Mobile Phase-B	100% Acetonitrile	Injection Volume	0.5 $\mu$ L
Gradient (T% B)	0/10,1/10,10/95,15/95,15.1/10	Run Time	20 minutes
Flow Rate	0.8 mL/min	Proc. Chnl. Descr.:	2998 PDA MaxPlot (190.0 nm to 800.0 nm) (2998(210-400)nm) Subtracted from blank
Column oven Temp	Ambient	Acq. Method Set:	Method_1_COL-2
Diluent: MeOH			

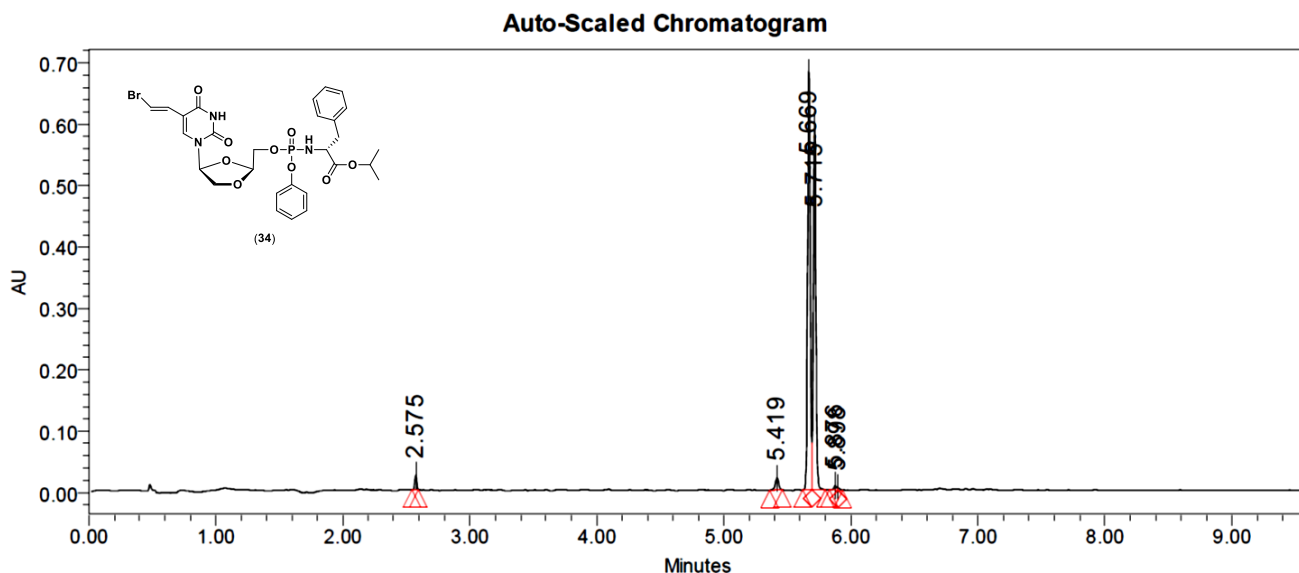


### Peak Results

	RT	Area	% Area
1	6.812	89312	0.66
2	6.937	215246	1.60
3	7.210	179665	1.34
4	7.473	12863074	95.63
5	7.860	103434	0.77

## HPLC method and trace for compound (34)

HPLC Method Conditions			
Column	UPLC BEH C18 (100x2.1), mm, 1.7 $\mu$ m	Sample	USS-09-67-42
Mobile Phase-A	0.05% FA in water	Vial	2:C,8
Mobile Phase-B	0.05% FA in ACN	Injection Volume	0.5 $\mu$ L
Gradient (T% B)	0/3, 0.5/3, 3/15, 5/100, 8/100, 8.10/3, 10/3	Run Time	10 minutes
Flow Rate	0.8 mL/min	Proc. Chnl. Descr.:	2998 PDA MaxPlot (190.0 nm to 800.0 nm) (2998(210-400) nm) Subtracted from Blank
Column oven Temp	50 $^{\circ}$ C	Acq. Method Set:	Method_1_COL-2
Diluent: Acetonitrile (ACN)			



### Peak Results

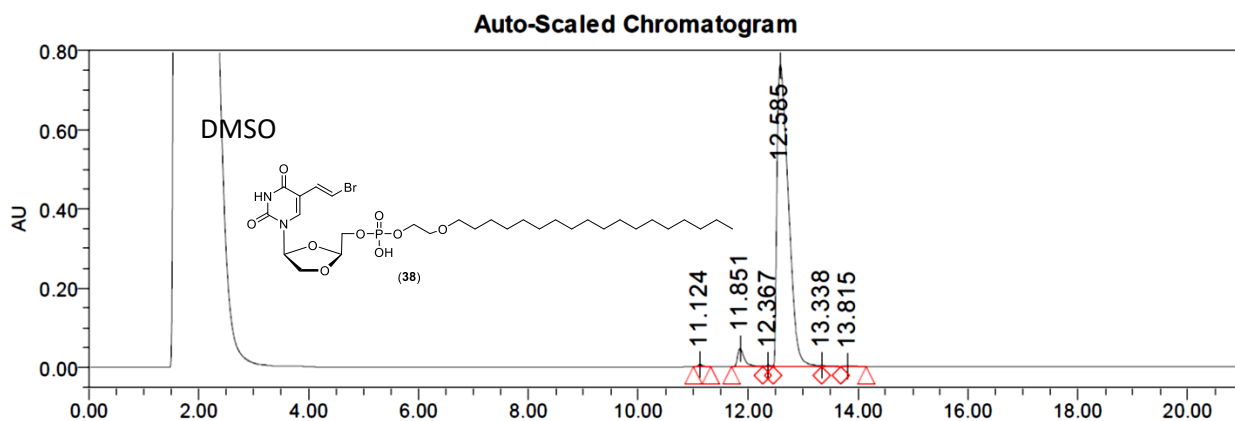
	RT	Area	Height	% Area
1	2.575	24554	23527	1.30
2	5.419	37276	19381	1.97
3	5.669	970842	683177	51.31
4	5.715	844265	596844	44.62
5	5.876	11377	7188	0.60

	RT	Area	Height	% Area
6	5.898	3622	3512	0.19

Mixture of two diastereomers  
 Diastereomer 1 = 51.31  
 Diastereomer 2 = 44.62  
 Total HPLC purity = 95.93

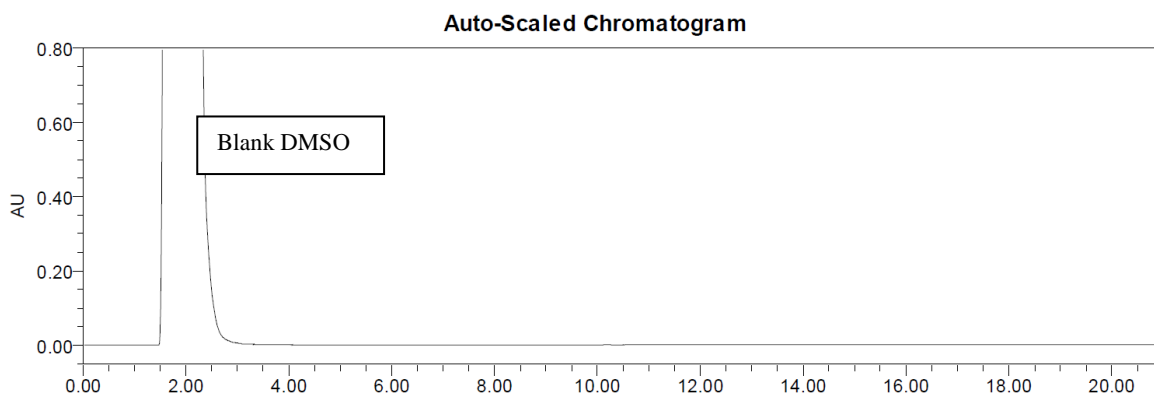
## HPLC method and trace for compound (38)

HPLC Method Conditions			
Column	XBridge C18 (4.6x150), mm, 3.5 $\mu$ m	Sample	YK-01-14-40
Mobile Phase-A	10mM Ammonium Acetate in Water	Vial	1:F
Mobile Phase-B	100% Acetonitrile	Injection Volume	0.5 $\mu$ L
Gradient (T% B)	0/50,1/50,10/95,20/95, 21/50	Run Time	20 minutes
Flow Rate	0.8 mL/min	Proc. Chnl.	2998 PDA MaxPlot (190.0 nm to 800.0 nm) (2998(210-400) nm)
Column oven Temp	Ambient	Acq. Method Set:	Method_1_COL-2
Diluent: MeOH+DMSO			



### Peak Results

	RT	Area	% Area
1	11.124	32548	0.28
2	11.851	411117	3.58
3	12.367	26936	0.23
4	12.585	10970267	95.52
5	13.338	26873	0.23
6	13.815	17312	0.15



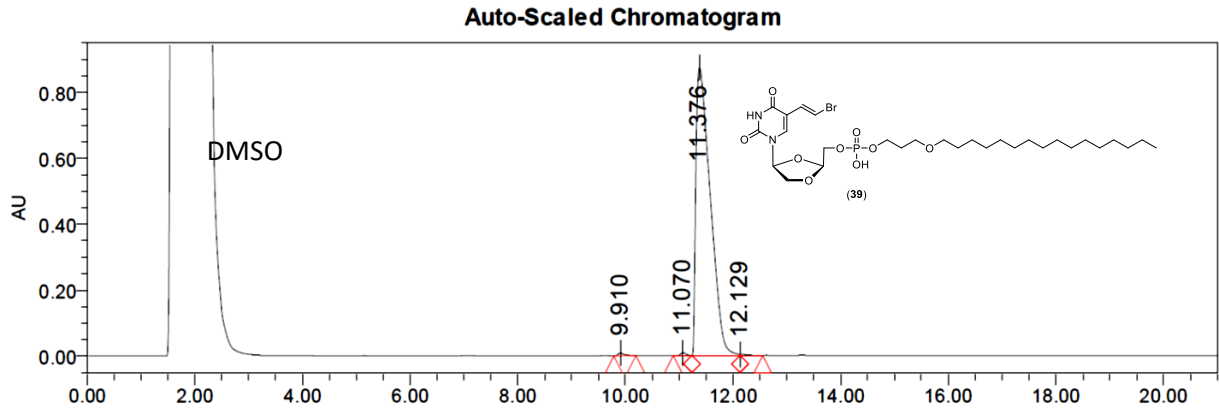
### Peak Results

	RT	Area	% Area
1			



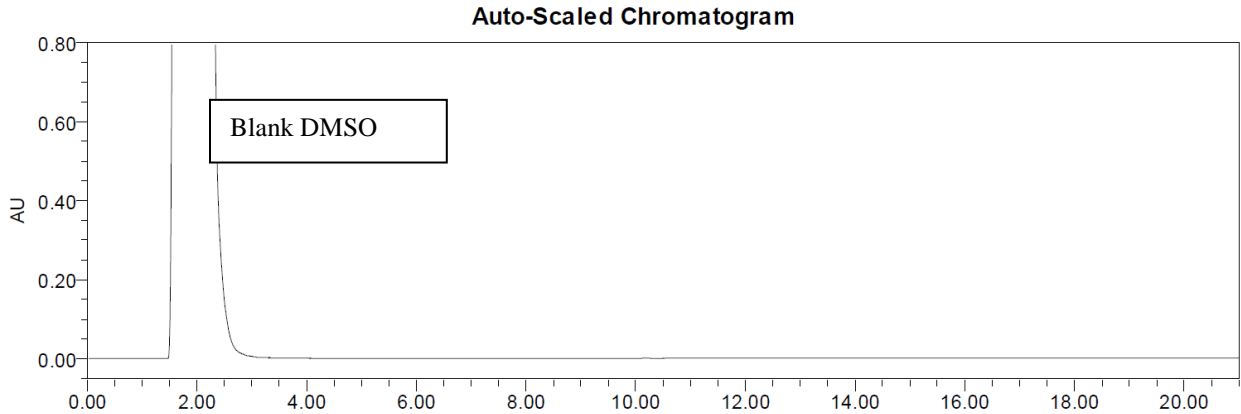
### HPLC method and trace for compound (39)

HPLC Method Conditions			
Column	XBridge C18 (4.6x150), mm, 3.5µm	Sample	USS-09-07-42
Mobile Phase-A	10mM Ammonium Acetate in Water	Vial	1:F
Mobile Phase-B	100% Acetonitrile	Injection Volume	0.5 µL
Gradient (T% B)	0/50,1/50,10/95,20/95, 21/50	Run Time	20 minute
Flow Rate	0.8 mL/min	Proc. Chnl.	2998 PDA MaxPlot (190.0 nm to 800.0 nm) (2998(210-400)nm)
Column oven Temp	Ambient	Acq. Method Set:	Method_1_COL-2
Diluent: MeOH+DMSO			



**Peak Results**

	RT	Area	% Area
1	9.910	70920	0.43
2	11.070	67562	0.41
3	11.376	16151477	98.97
4	12.129	29648	0.18

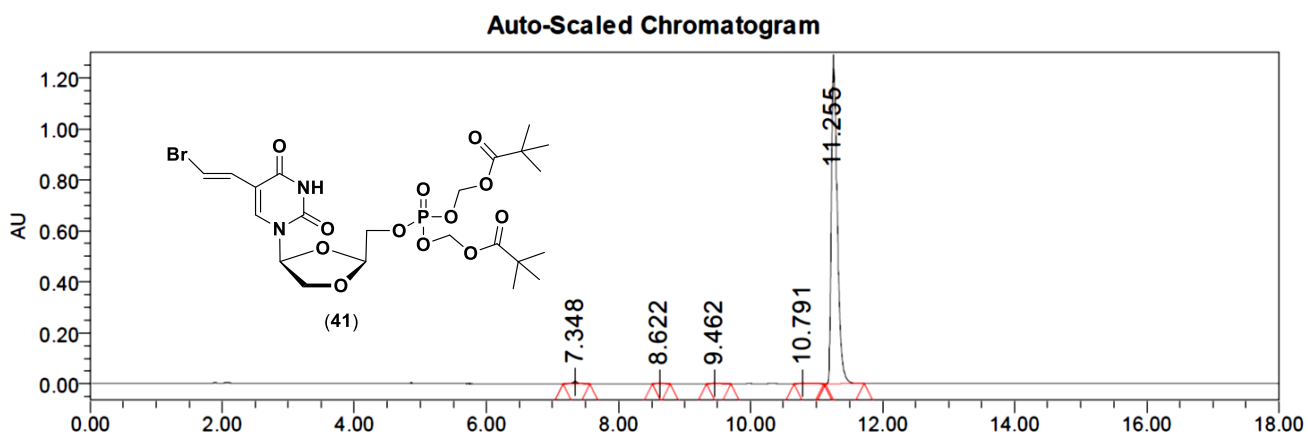


**Peak Results**

	RT	Area	% Area
1			

## HPLC method and trace for compound (41)

HPLC Method Conditions			
Column	XBridge C18 (4.6x150), mm, 3.5 $\mu$ m	Sample	YK-01-16-P-2
Mobile Phase-A	10mM Ammonium Acetate in Water	Vial	1:F
Mobile Phase-B	100% Acetonitrile	Injection Volume	0.5 $\mu$ L
Gradient (T% B)	0/10,1/10,10/95,15/95. 15. 1/10	Run Time	20 minute
Flow Rate	0.8 mL/min	Proc. Chnl. Descr.:	2998 PDA MaxPlot (190.0 nm to 800.0 nm) (2998(210-400) nm) Subtracted from blank
Column oven Temp	Ambient	Acq. Method Set:	Method_1_COL-2
Diluent: MeOH			



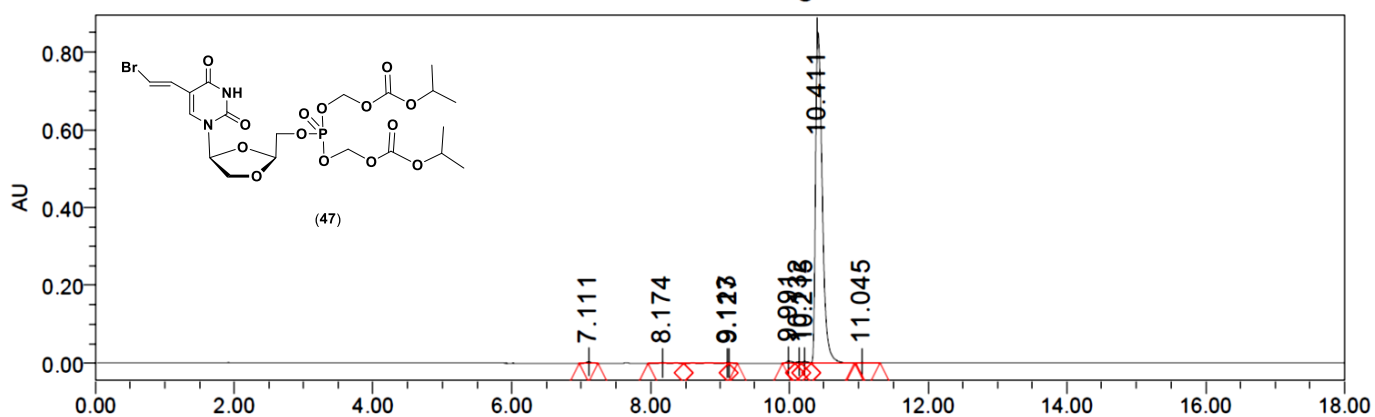
**Peak Results**

	RT	Area	% Area
1	7.348	44197	0.55
2	8.622	11801	0.15
3	9.462	17042	0.21
4	10.791	24910	0.31
5	11.255	7996494	98.79

## HPLC method and trace for compound (47)

HPLC Method Conditions			
Column	XBridge C18 (4.6x150), mm, 3.5µm	Sample	YK-02-26-P
Mobile Phase-A	10mM Ammonium Acetate in water	Vial	1:F
Mobile Phase-B	100% Acetonitrile	Injection Volume	0.5 µL
Gradient (T% B)	0/10,1/10,10/95,15/95. 15. 1/10	Rum Time	20 minute
Flow Rate	0.8 mL/min	Proc. Chnl. Descr.:	2998 PDA MaxPlot (190.0 nm to 800.0 nm) (2998(210-400) nm) Subtracted from blank
Column oven Temp	Ambient	Acq. Method Set:	Method_1_COL-2
Diluent: MeOH			

### Auto-Scaled Chromatogram



#### Peak Results

	RT	Area	% Area
1	7.111	16180	0.28
2	8.174	8653	0.15
3	9.113	13805	0.24
4	9.127	3178	0.05
5	9.991	30861	0.53
6	10.132	15077	0.26
7	10.215	24301	0.42
8	10.411	5694194	97.91

	RT	Area	% Area
9	11.045	9239	0.16