Selective synthesis of 3-deoxy-5-hydroxy-1-amino-carbasugars as potential α-glucosidase inhibitors

Chunfeng Jiang,[a] Quan Liu, [b] Jiaming Liu,[a] Kaixuan Liu,[a] Liangliang Tian,[a] Mingfei Duan,[a] Ying Wang,[a] Zhufang Shen *[b] and Youjun Xu * [a]

[a]School of Pharmaceutical Engineering, and Key Laboratory of Structure-Based Drug Design & Discovery (Ministry of Education), Shenyang Pharmaceutical University, Shenyang 110016, P. R. of China. xuyoujun@syphu.edu.cn

[b]Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100050, P. R. of China. shenzhf@imm.ac.cn

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Single Crystal X–Ray Diffraction Analysis

Table 1 gives the crystallographic information for compound **16a** solved using single crystal X–ray diffraction. The structure has been given the CCDC number 1900790. A single crystal with crystal dimensions 0.22×0.20×0.18 mm^3, was mounted on a goniometer and diffraction data was collected using a single crystal X–ray diffractometer.

Table 1. Crystallographic information for $C_{36}H_{41}NO_4$

Sample	**$C_{36}H_{41}NO_4$**
Chemical formula	$C_{36}H_{41}NO_4$
Space group	$P2_1$
Temperature	296(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
a/Å	15.676(4)
b/Å	5.9027(13)
c/Å	16.875(4)
β/°	104.625(7)
Volume/$Å^3$	1510.8(6)
Z	2
Density (calculated)	1.213 Mg/m^3
Absorption coefficient	0.078 mm^{-1}
F(000)	592
Theta range for data collection	1.247° to 24.943°
Index ranges	–18<=h<=17, –6<=k<=6, –15<=l<=20
Reflections collected	7530
Independent reflections	4835 [R(int)=0.0433]
Absolute structure parameter	–3.2(10)
Final R indices [I>2sigma(I)]	R_1=0.0555, wR_2=0.1068
R indices (all data)	R_1=0.1060, wR_2=0.1326
Largest diff. peak and hole	0.134 and –0.172 e.$Å^{-3}$

α-glucosidase inhibition assays

Crude rat small intestinal α-glucosidase was prepared according to the reported procedure.[1] The reaction mixture consisted of 100 μL of crude α-glucosidase and 80 μL of a compound solutions (in 50 mM phosphate buffer at pH 6.8). After pre-incubation at 37 °C for 10 min, 20 μL of sucrose (100 mg/mL) was added and the solution was further incubated for 30 min at 37 °C. The reaction was stopped by incubation for 3 min at 80~85 °C. The amount of liberated glucose was determined by the glucose oxidase method. Voglibose, miglitol and acarbose were used as the positive control.

In vivo assay for hypoglycemic effect

Healthy male ICR mice (20-22 g) were purchased from Beijing Vital River Laboratory Animal Technology Co., Ltd (Beijing, China). All mice were acclimatized in a light and temperature controlled room for 3 days with food and water available ad libitum. The mice were divided into 9 groups. Each group consisted of 8 animals. Test compounds were given to each mouse by oral administration at a single dose (2.0 mg/kg). Voglibose, miglitol and acarbose (2.0 mg/kg) were used as the positive control. A sucrose solution was administered to each mouse (represented as 0 min). Mice in the control group were administered the same volume of distilled H_2O and sucrose solution. About 20μL of blood was collected from the tail vein at 0, 30, 60 and 120 min. The blood glucose level was measured using the glucose oxidase method. Data are expressed as the mean (mg/dL) ± SD.

Table 2. Hypoglycemic activity of the compounds (**17b** and **17h~k**) and the positive control in healthy male ICR mice after single oral administration of sucrose.

Groups	Dosage (mg/kg)	Glycemia(mg/dL)				AUC(mg.h/dL)
		0 min	30 min	60 min	120 min	
Nor	–	69.1±9.2	191.3±26.7	164.0±35.6	112.2±14.8	292.0±41.6
17b	2	75.7±13.1	108.1±19.5***	110.3±17.2**	94.8±8.7*	203.1±18.9***
17h	2	77.9±10.2	112.2±8.5***	104.7±9.8***	110.9±20.7	209.6±19.4***
17i	2	82.7±15.3	138.1±17.7***	120.9±17.6*	125.4±37.8	243.0±25.7*
17j	2	76.2±6.9	102.0±5.1***	104.5±9.5***	98.4±7.2*	197.6±12.1***
17k	2	74.9±7.2	128.5±17.2***	148.1±58.6	115.7±21.6	251.9±49.2
Voglibose	2	77.1±11.9	103.1±10.0***	101.4±12.3***	94.1±17.6	193.9±22.5***
Miglitol	2	68.2±8.0	115.0±13.5***	147.2±19.5	135.2±18.5	252.5±28.0
Acarbose	2	64.0±7.9	138.6±15.2***	137.3±16.0	114.8±13.9	245.7±26.3*

*P<0.05, **P<0.01, ***P<0.001 vs Nor group, n=8, means±SD.

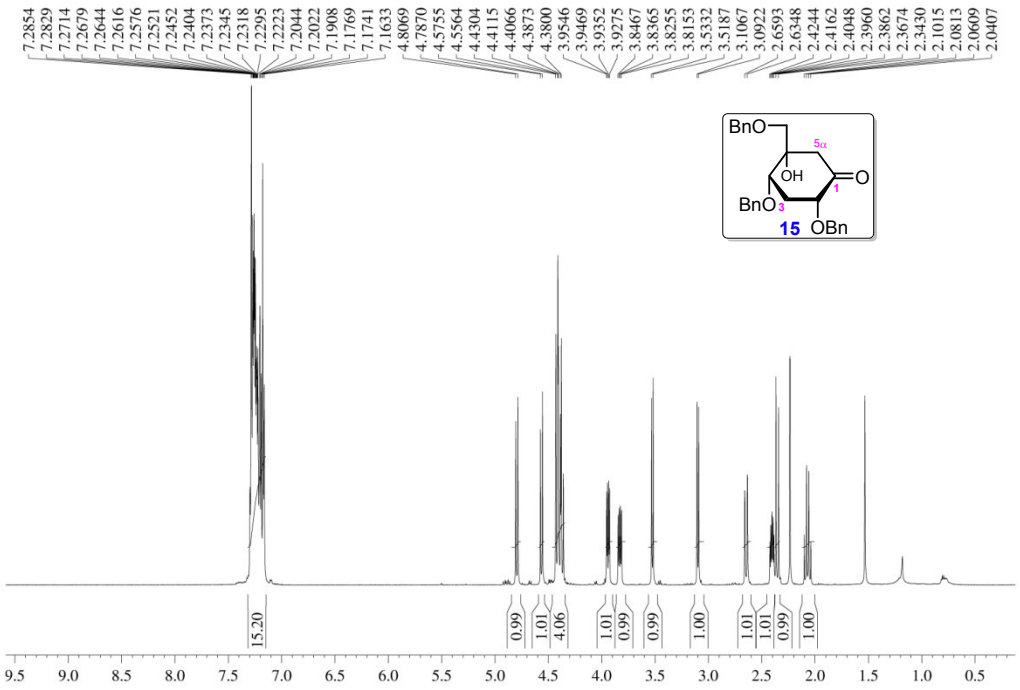
Docking study

Molecular docking study was carried out to investigate the binding mode of some compounds and the voglibose with the crystal structure of human sucrase (PDB: 3LPP)[2] using LigandFit embedded in Discovery Studio 3.0 software package. The protein structure was prepared by removing the water molecules, displaying hydrogen atoms and cleaning the protein. The chemical structures of small molecules were prepared by using Marvin Sketch. Finally, the compound with minimized conformational energy was docked into the protein binding pocket.

References

1. T. Nishioka, J. Kawabata, Y. Aoyama, *J. Nat. Prod.,* 1998, **61**, 1413–1415.

2. L. Sim, C. Willemsma, S. Mohan, H. Y. Naim, B. M. Pinto, D. R. Rose, *J. Biol. Chem.*, 2010, **285**, 17763–17770.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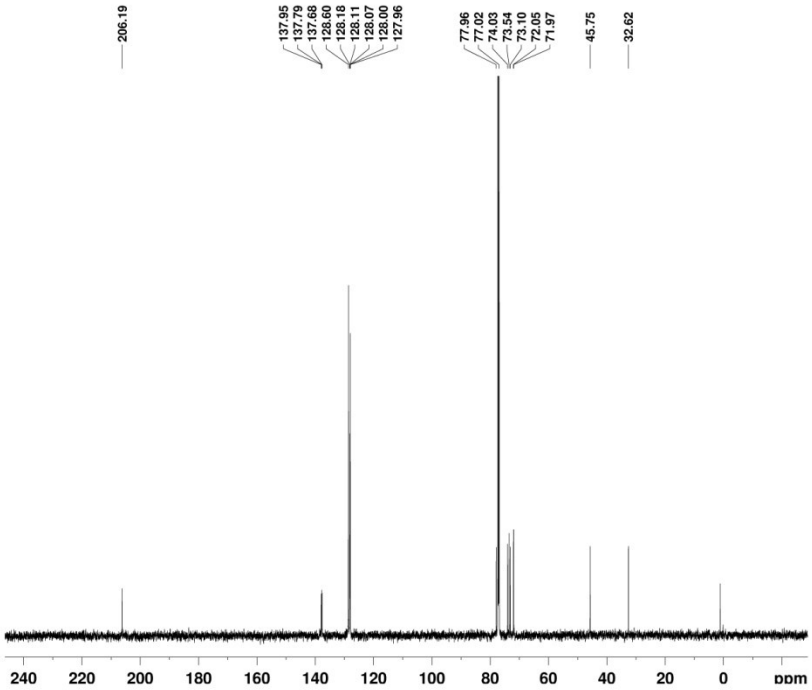
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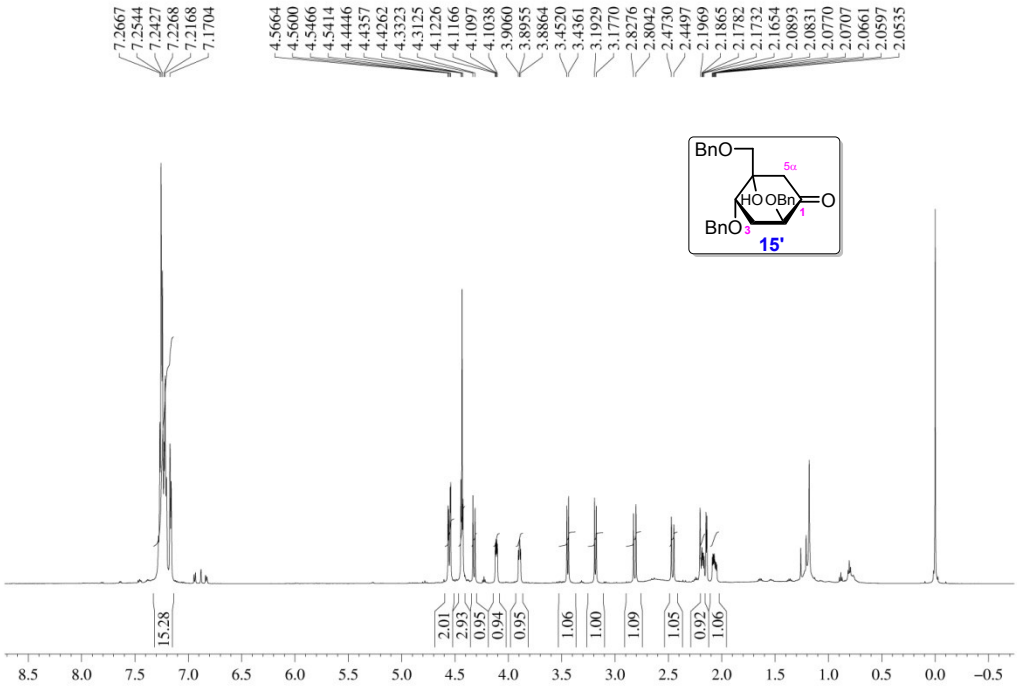
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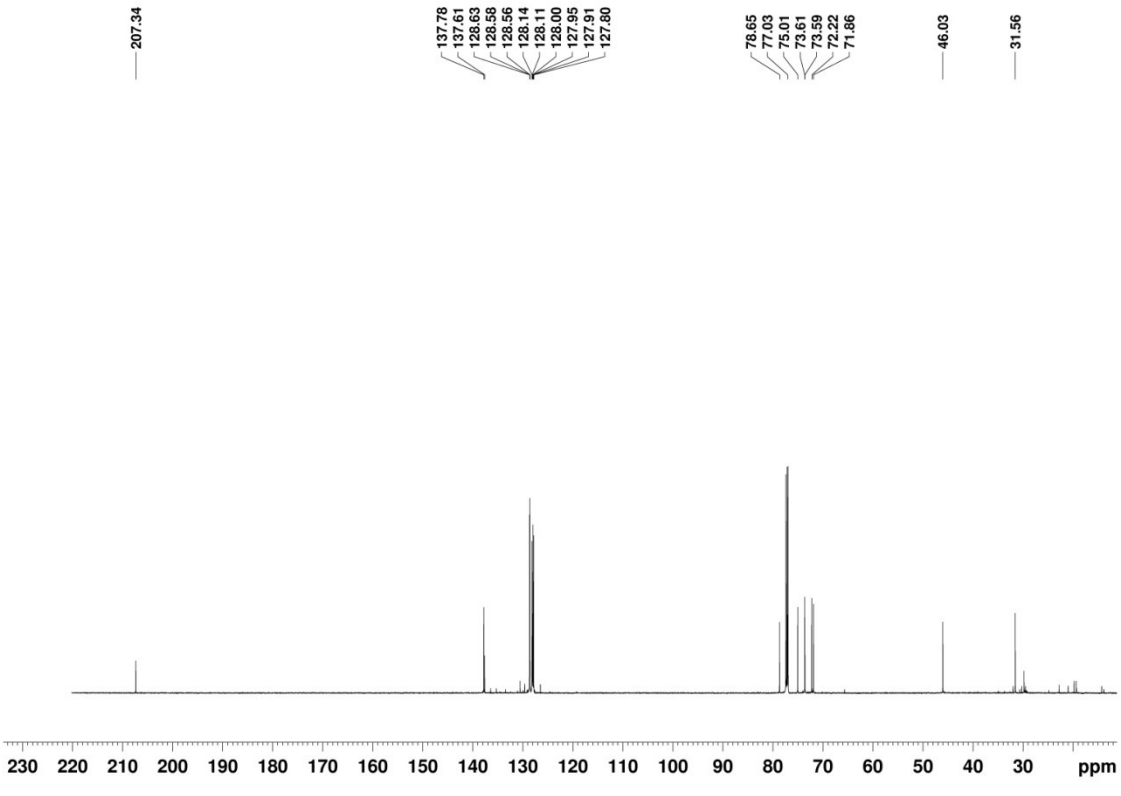
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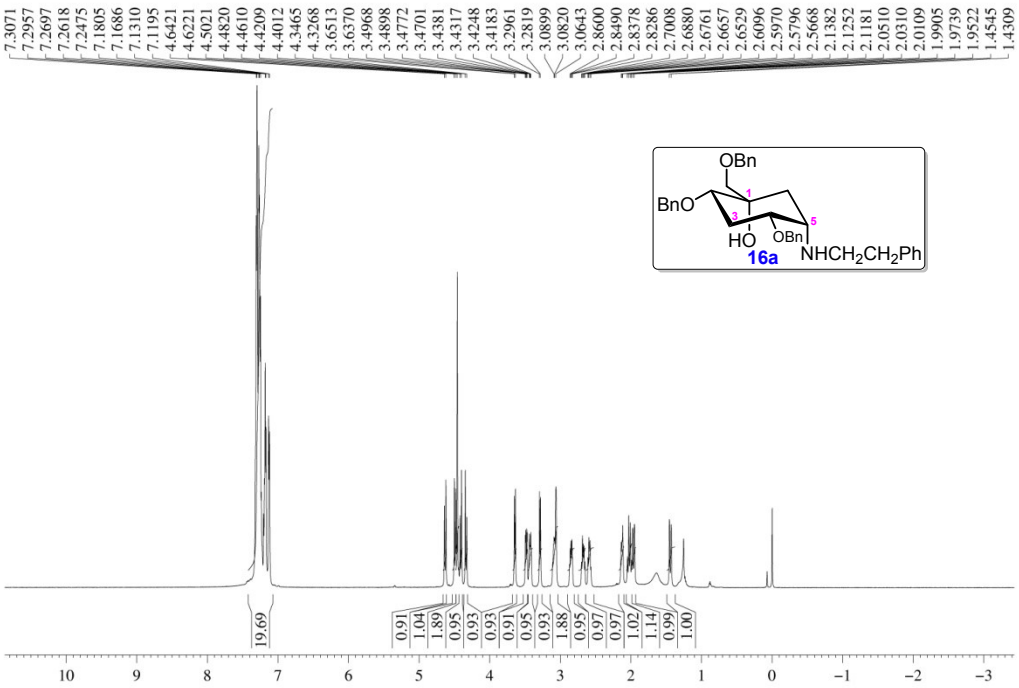
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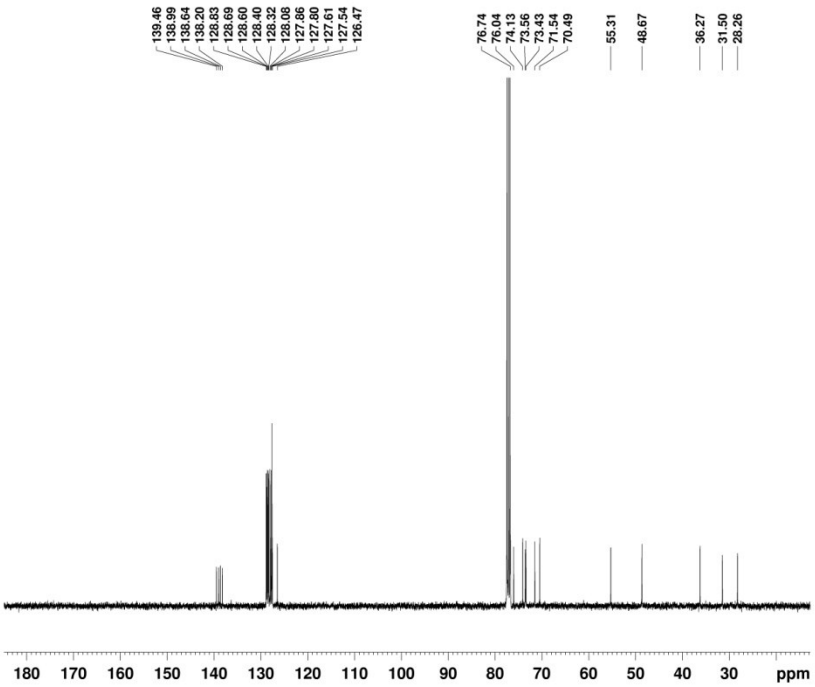

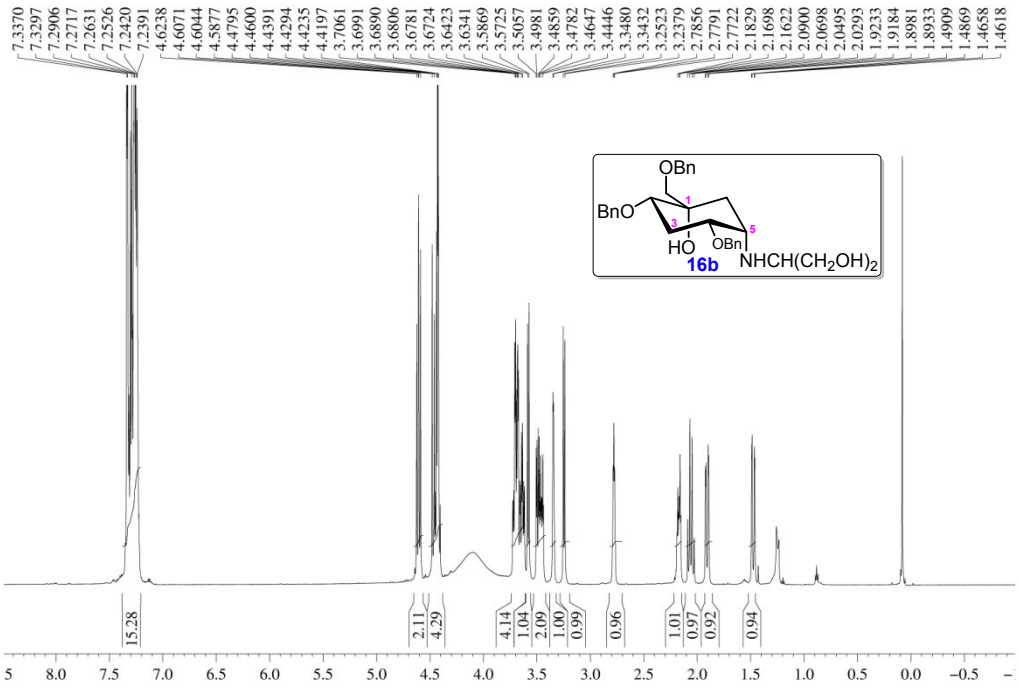
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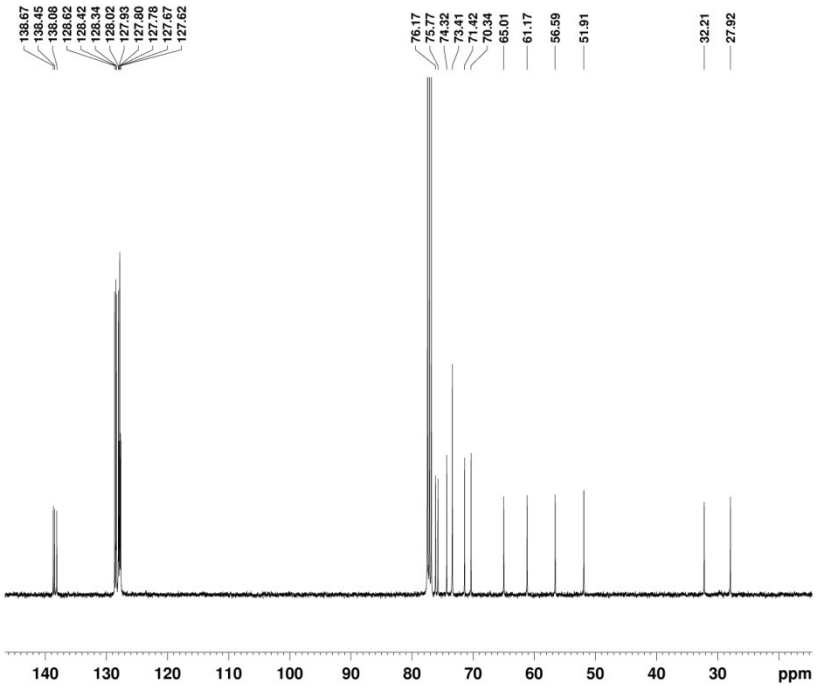

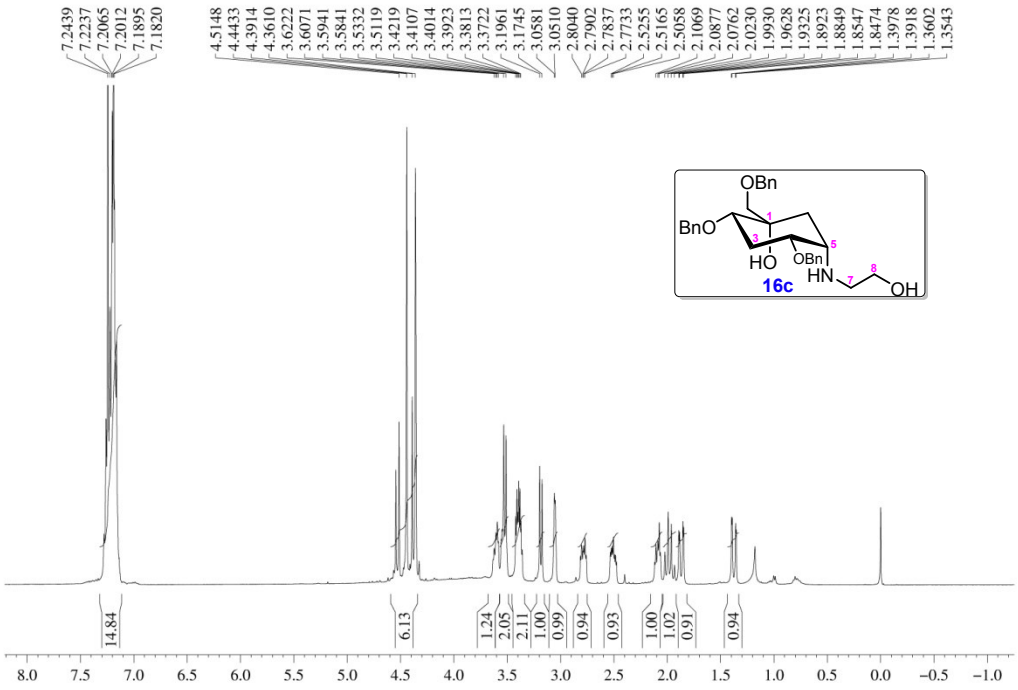
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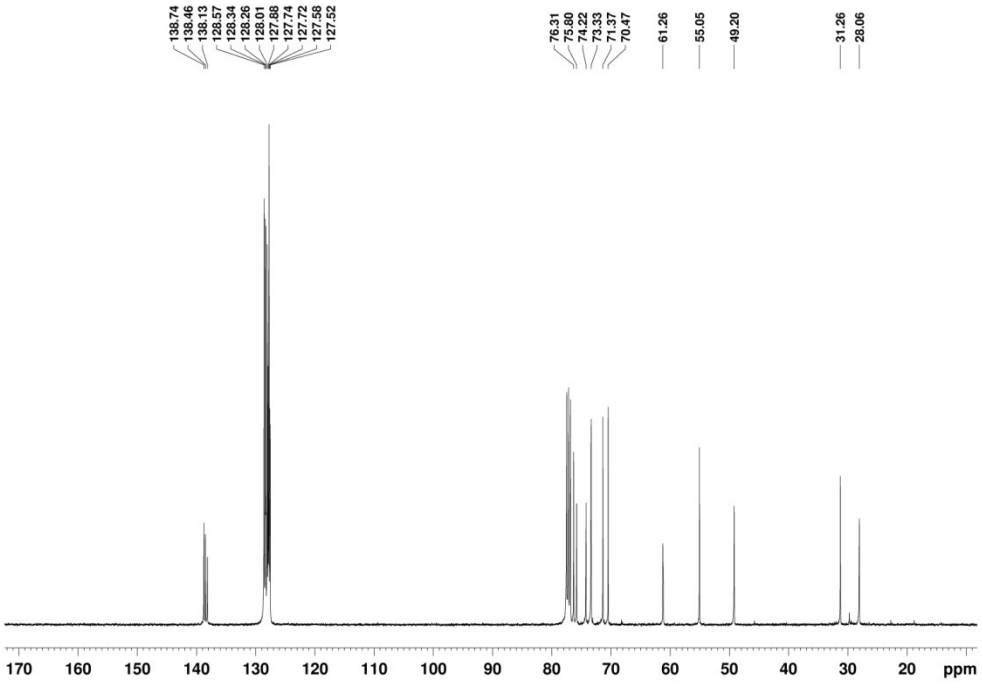
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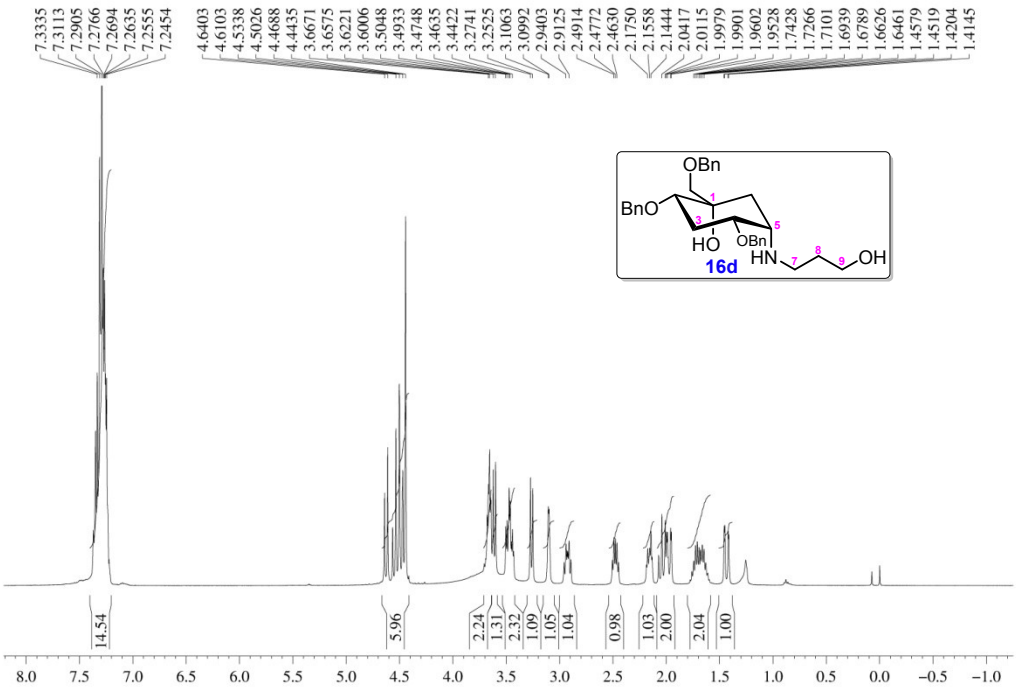
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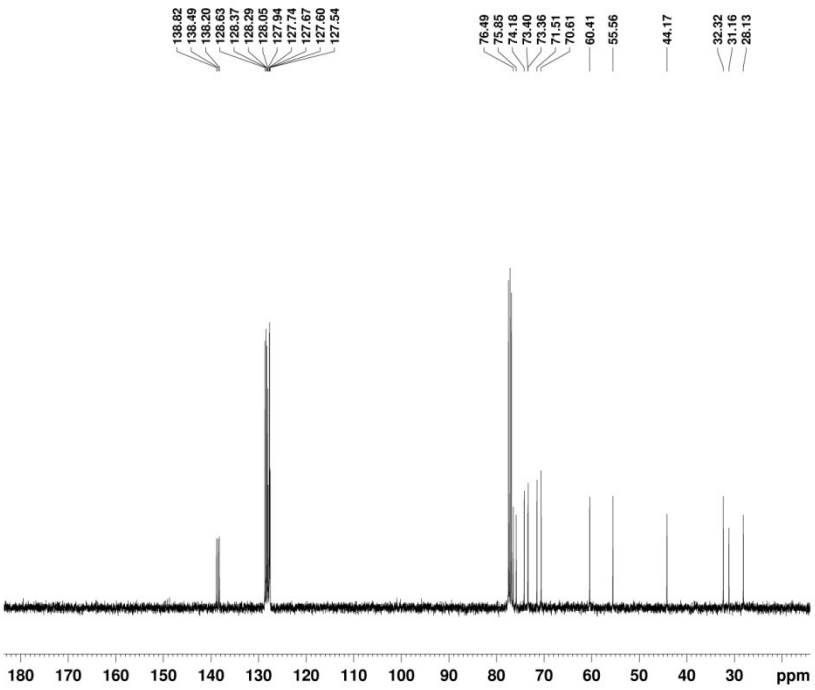
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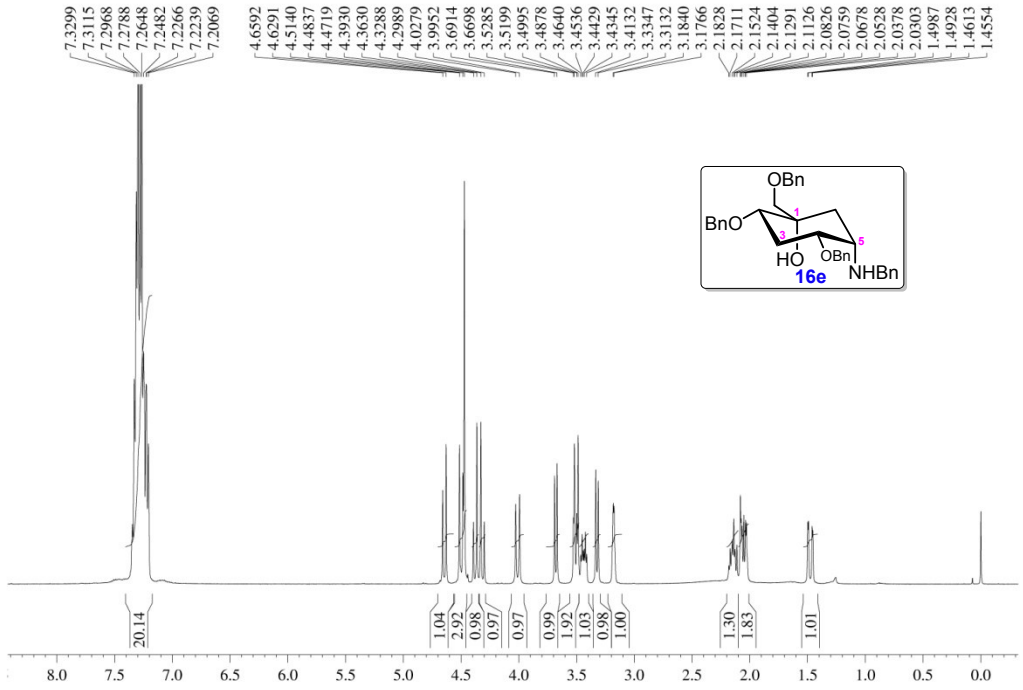
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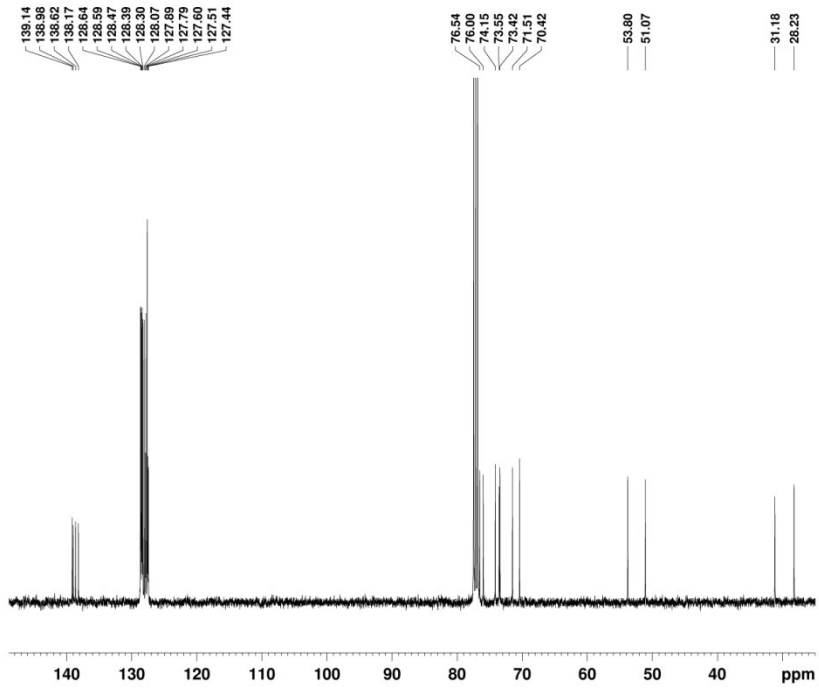
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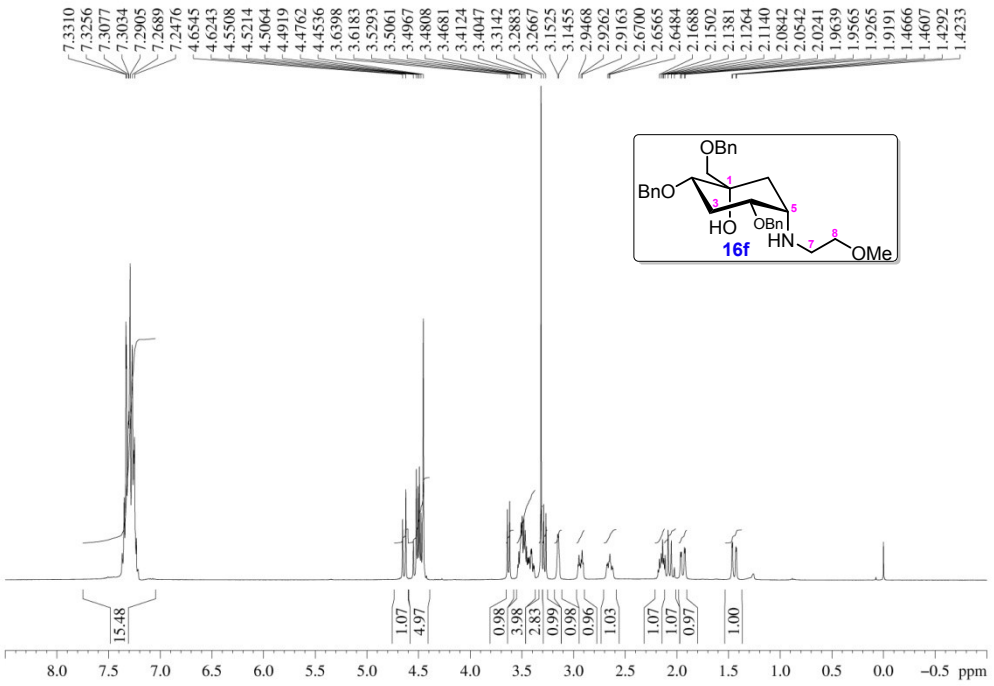
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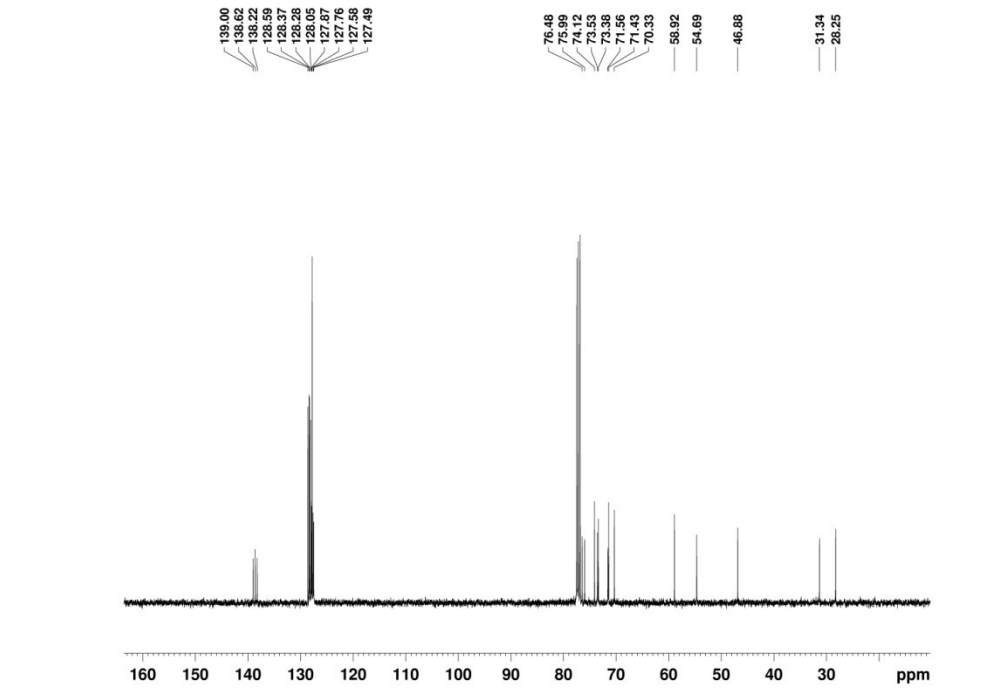
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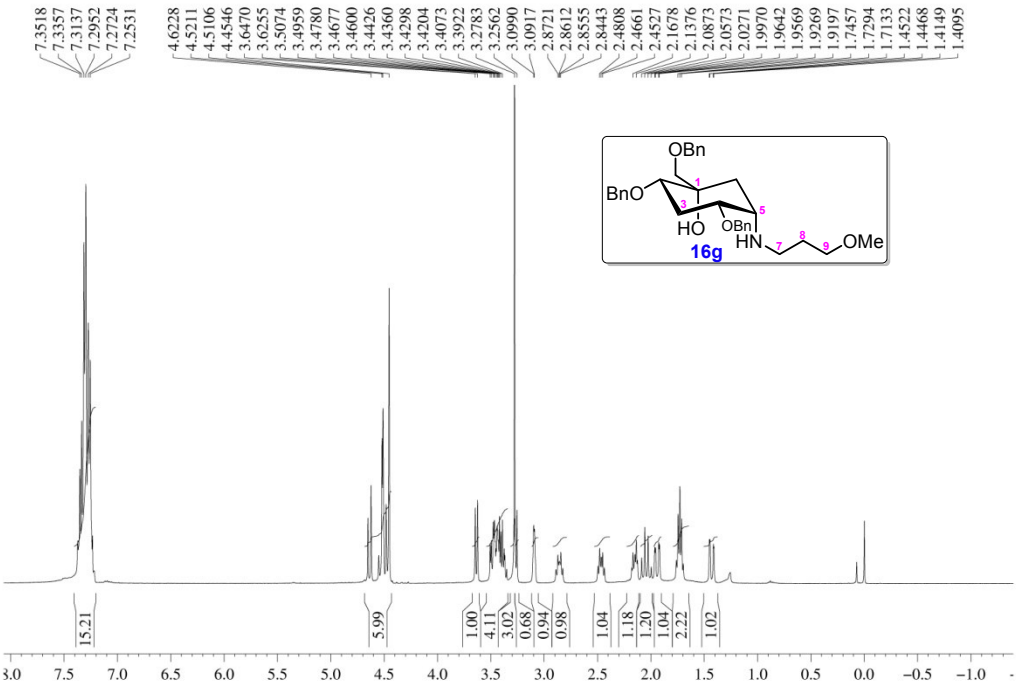
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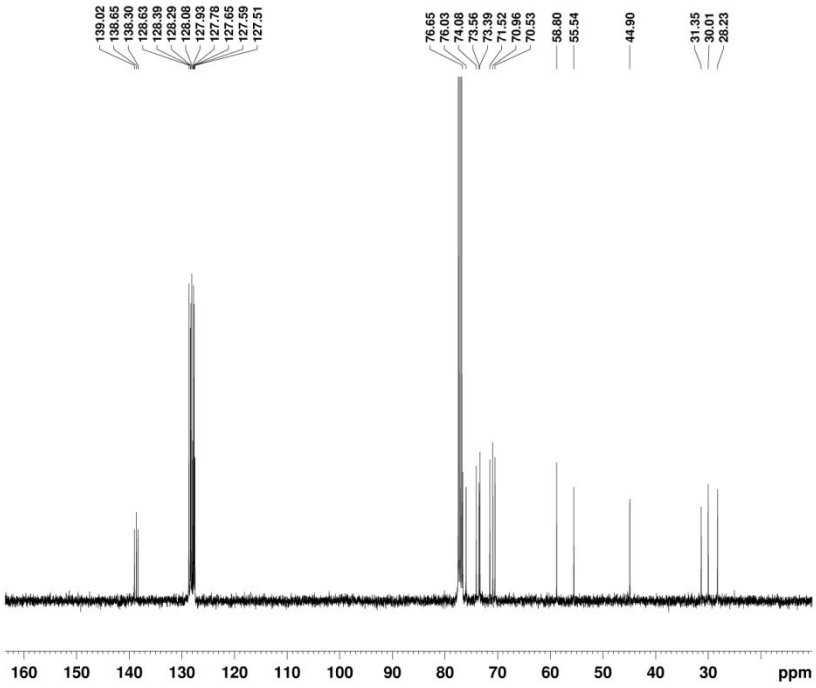

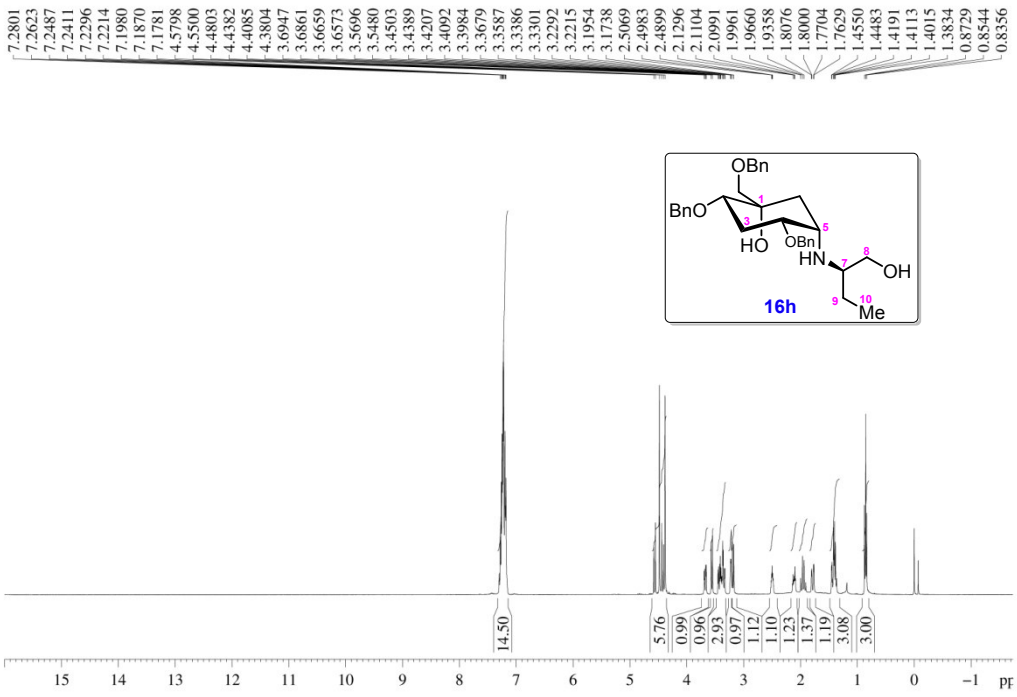
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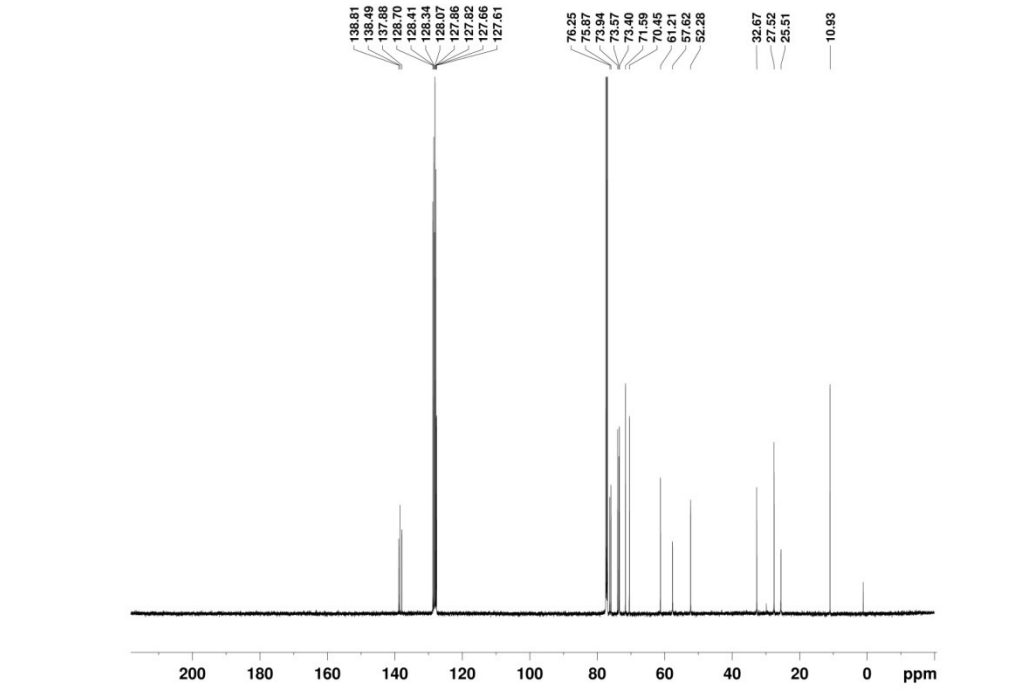
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61.21
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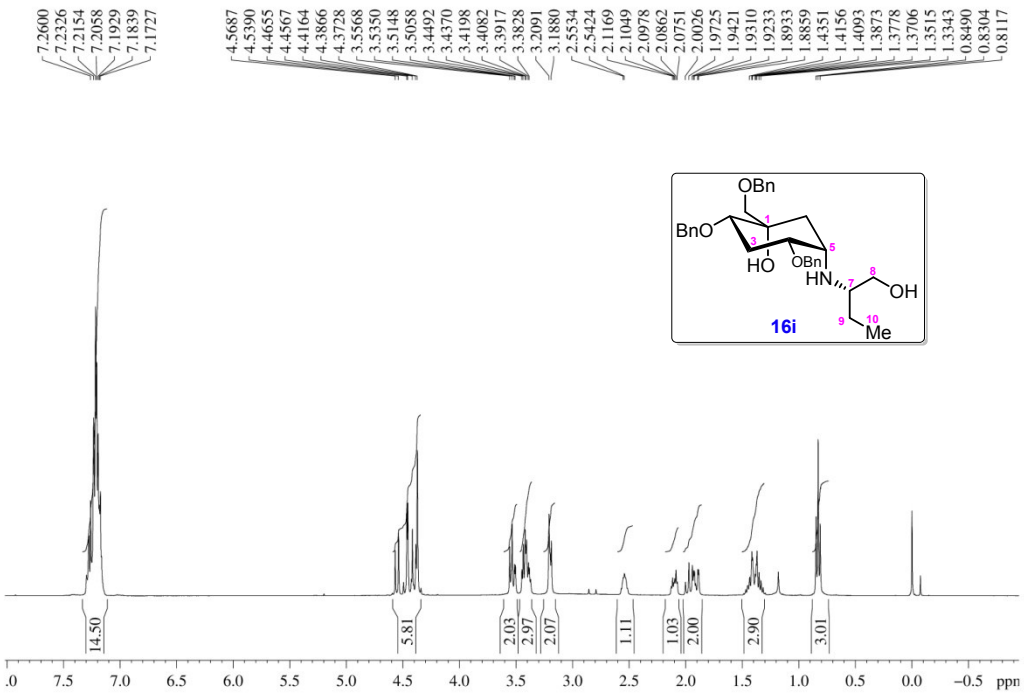
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3.5568
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3.4370
3.4198
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2.5424
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2.0751
2.0026
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1.9421
1.9310
1.9233
1.8933
1.8859
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1.3873
1.3778
1.3706
1.3515
1.3343
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0.8304
0.8117
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BnO
HO
OBn
HN
OH
Me
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1.03
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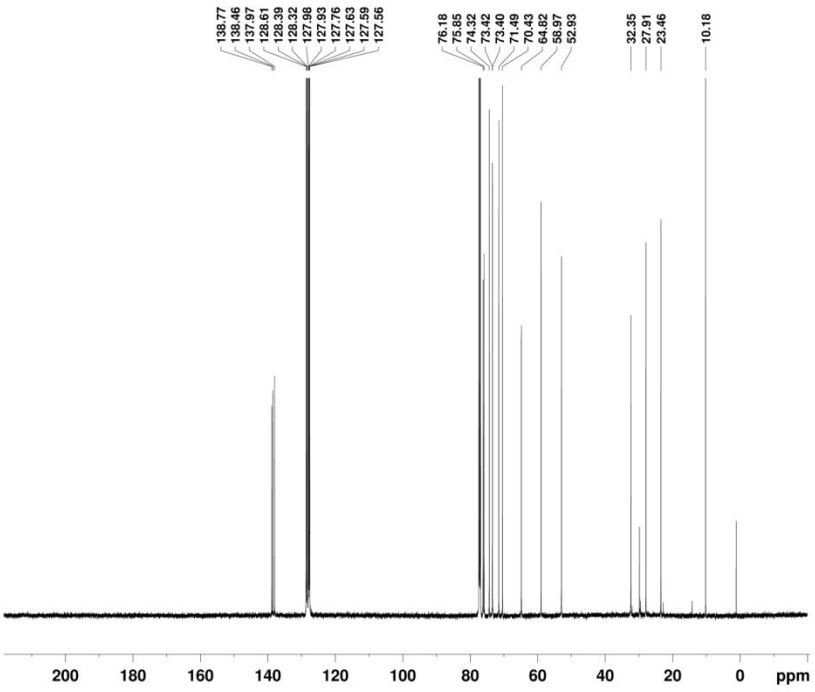
3.01
ppm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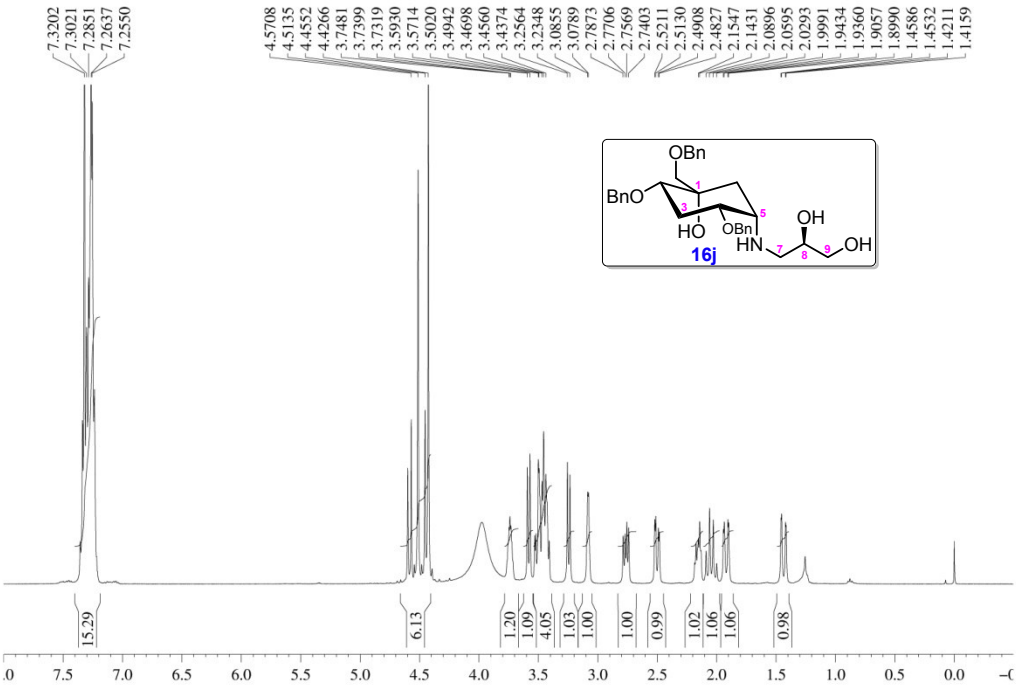
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3.7319
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3.5020
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3.2348
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3.0789
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2.7706
2.7569
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2.0896
2.0595
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1.9360
1.9057
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1.4586
1.4532
1.4211
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OBn
BnO
HO
OBn
HN
OH
OH
16j
15.29
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4.05
1.03
1.00
1.00
0.99
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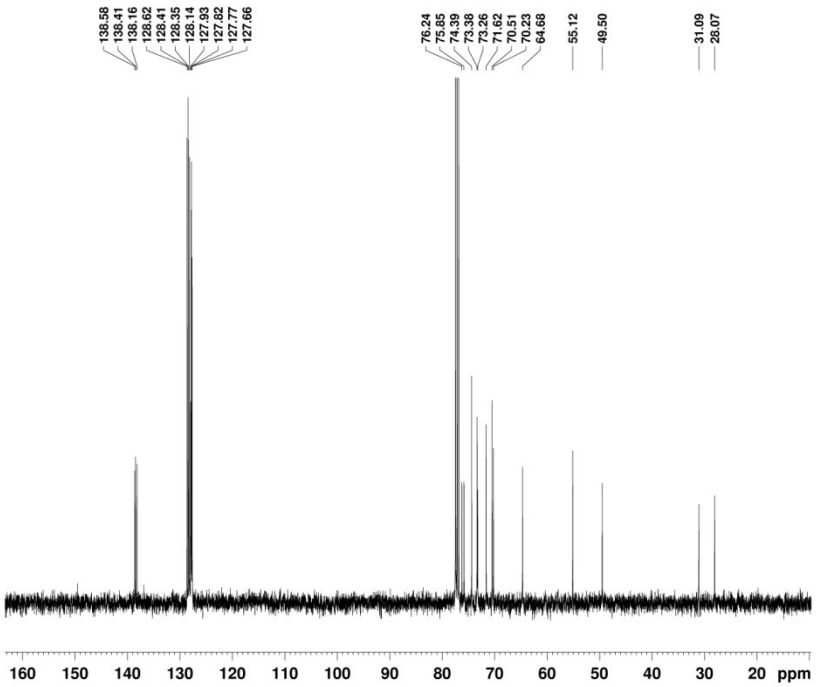
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74.39
73.38
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28.07
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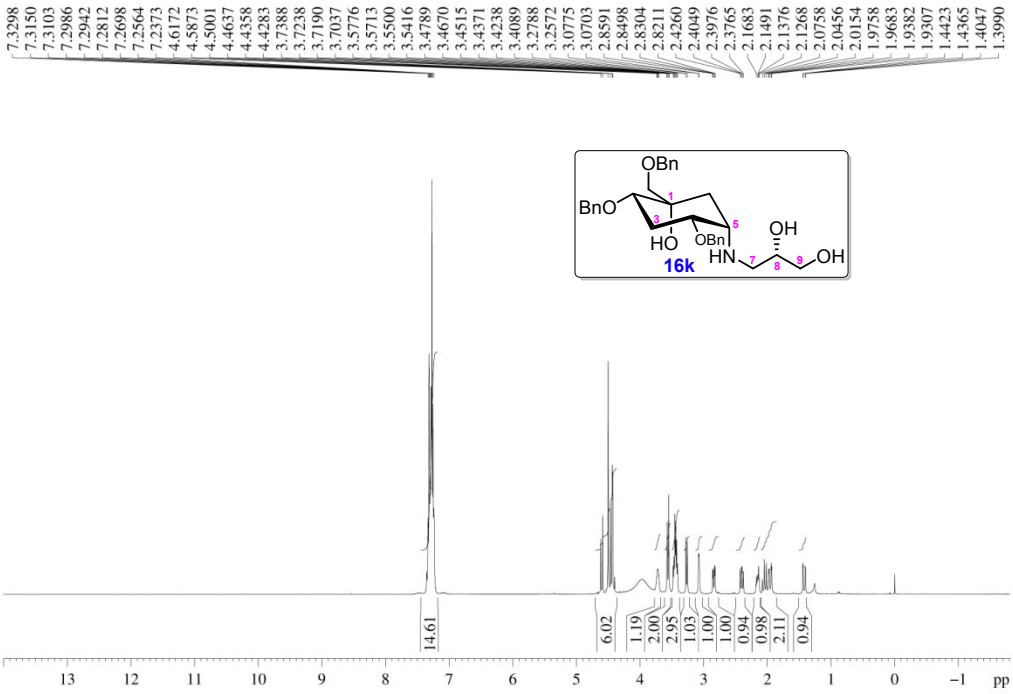
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4.4283
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3.7238
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3.5500
3.5416
3.4789
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3.4515
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3.4238
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3.0775
3.0703
2.8591
2.8498
2.8304
2.8211
2.4260
2.4049
2.3976
2.3765
2.1683
2.1491
2.1376
2.1268
2.0758
2.0456
2.0154
1.9758
1.9683
1.9382
1.9307
1.4423
1.4365
1.4047
1.3990
OBn
BnO
HO
OBn
HN
OH
OH
16k
14.61
6.02
1.19
2.00
2.95
1.03
1.00
1.00
0.94
0.98
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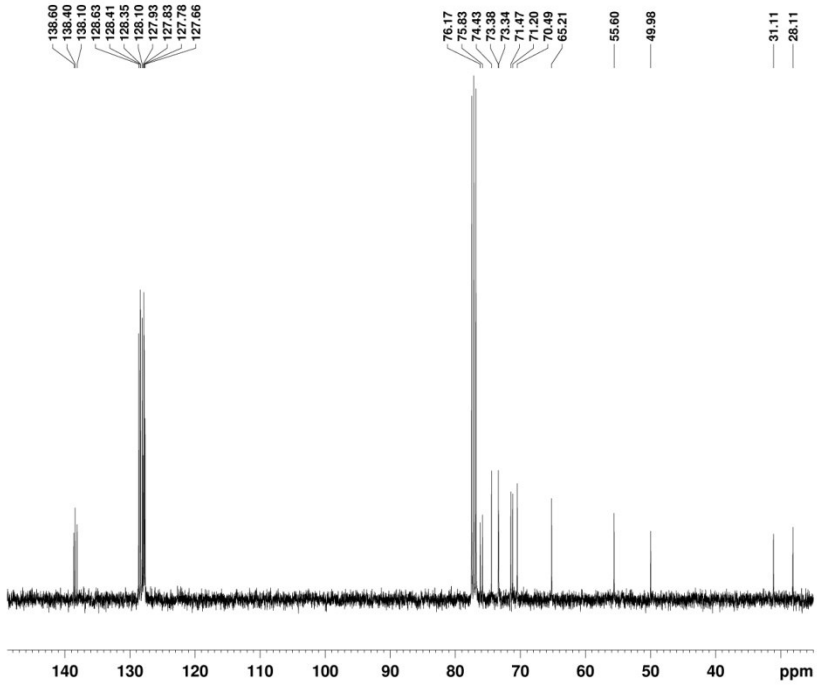
12
11
10
9
8
7
6
5
4
3
2
1
0
−1
pp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76.17
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70.49
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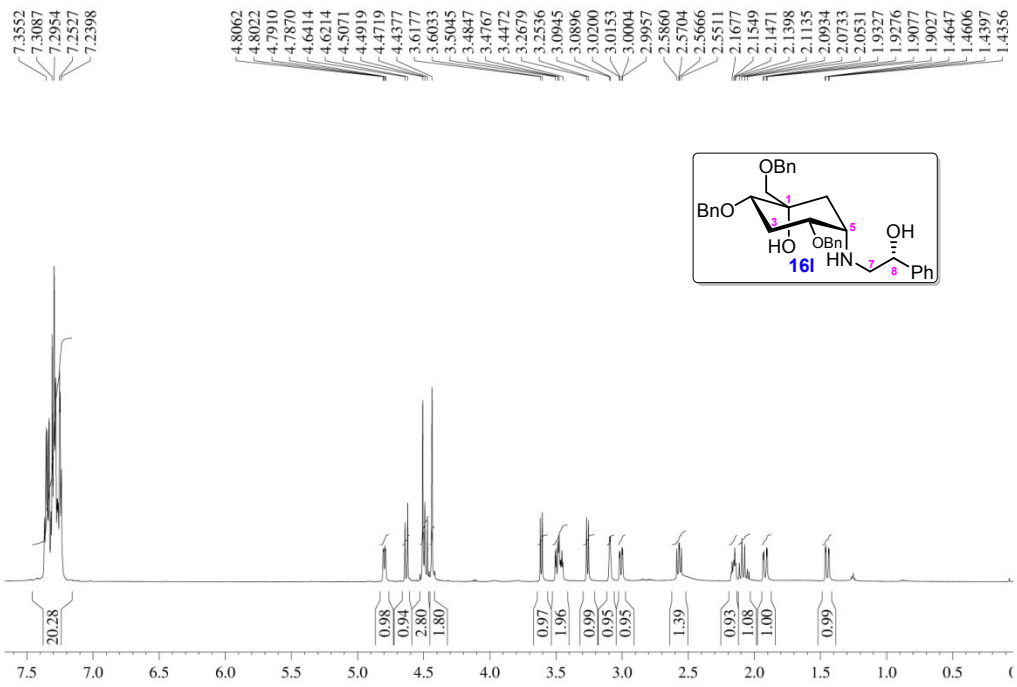
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4.5071
4.4919
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3.6033
3.5045
3.4847
3.4767
3.4472
3.2679
3.2536
3.0945
3.0896
3.0200
3.0153
3.0004
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2.5860
2.5704
2.5666
2.5511
2.1677
2.1549
2.1471
2.1398
2.1135
2.0934
2.0733
2.0531
1.9327
1.9276
1.9077
1.9027
1.4647
1.4606
1.4397
1.4356
OBn
BnO
HO
OBn
HN
OH
Ph
16l
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1.80
0.97
1.96
0.99
0.95
0.95
1.39
0.93
1.08
1.00
0.99
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7.0
6.5
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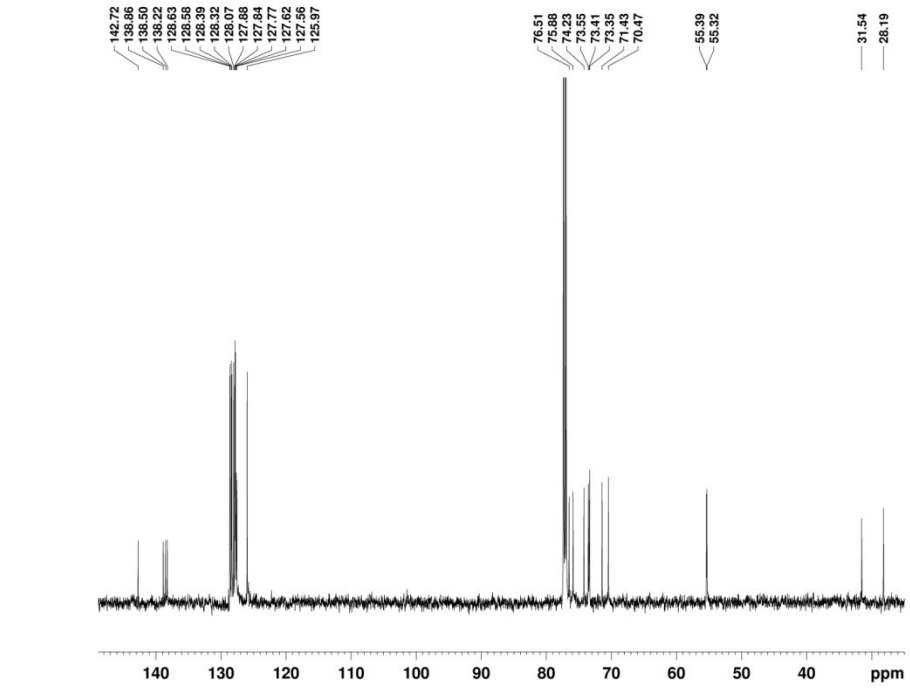
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127.56
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76.51
75.88
74.23
73.55
73.41
73.35
71.43
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55.39
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31.54
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140
130
120
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100
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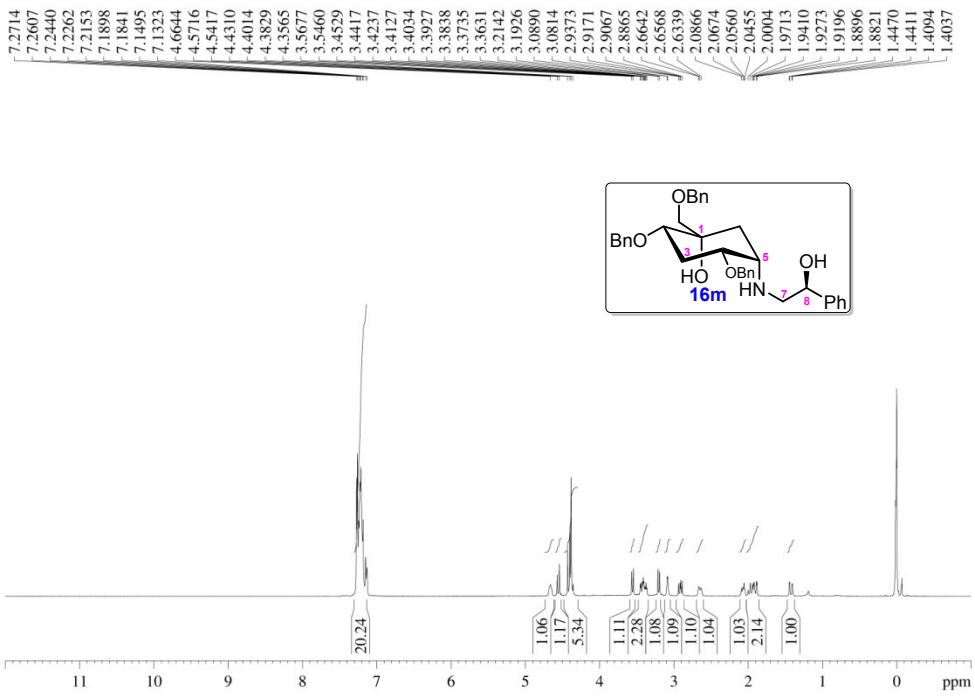
60
50
40
ppm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3.3735
3.3631
3.2142
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3.0814
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2.6568
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2.0866
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1.9273
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1.8821
1.4470
1.4411
1.4094
1.4037
OBn
BnO
HO
OBn
HN
OH
Ph
16m
20.24
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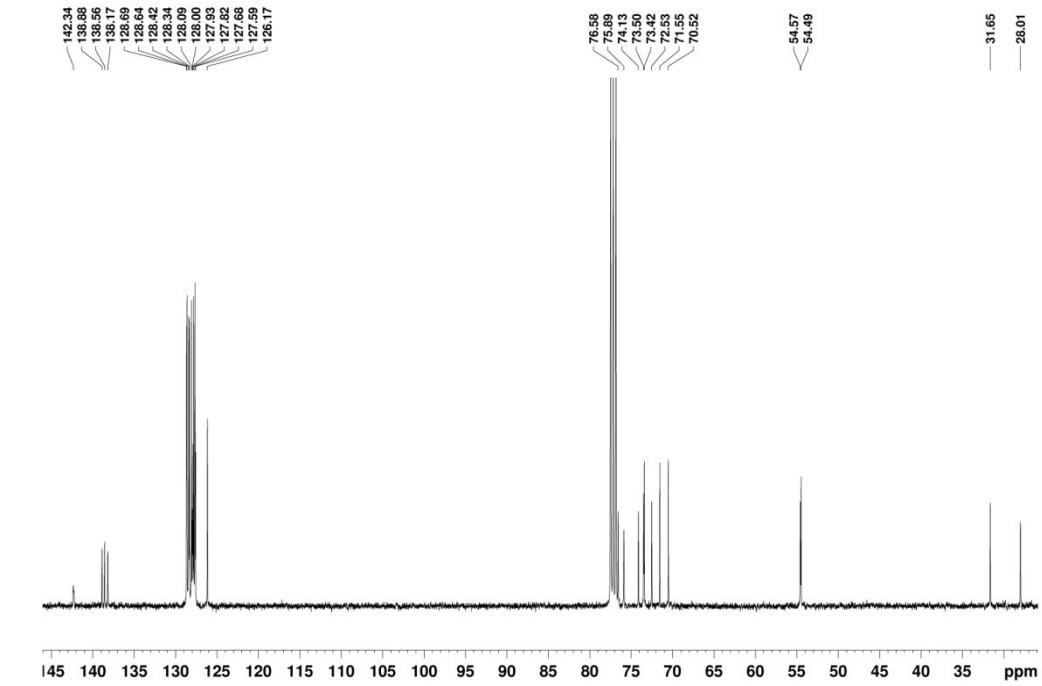
1.11
2.28
1.08
1.09
1.10
1.04
1.03
2.14
1.00
ppm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127.68
127.59
126.17
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73.50
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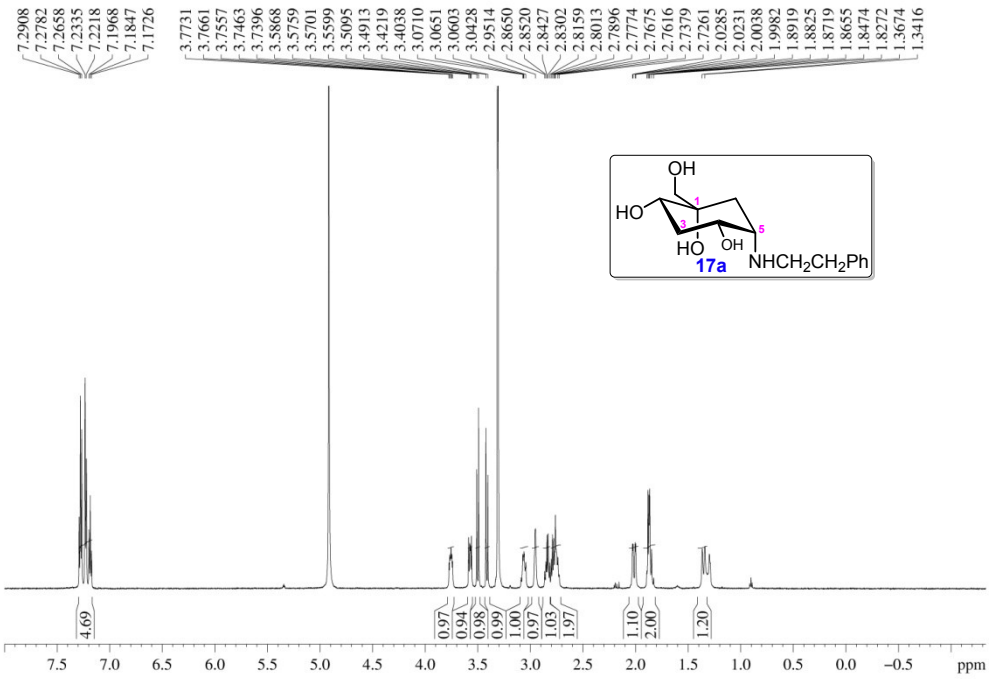
72.53
71.55
70.52
54.57
54.49
31.65
28.01
ppm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3.5701
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3.4219
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3.0710
3.0651
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3.0428
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1.8272
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1.3416
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HO
HO
OH
NHCH2CH2Ph
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0.94
0.98
0.99
1.00
0.97
1.03
1.97
1.10
2.00
1.20
7.5
7.0
6.5
6.0
5.5
5.0
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2.5
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1.0
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0.0
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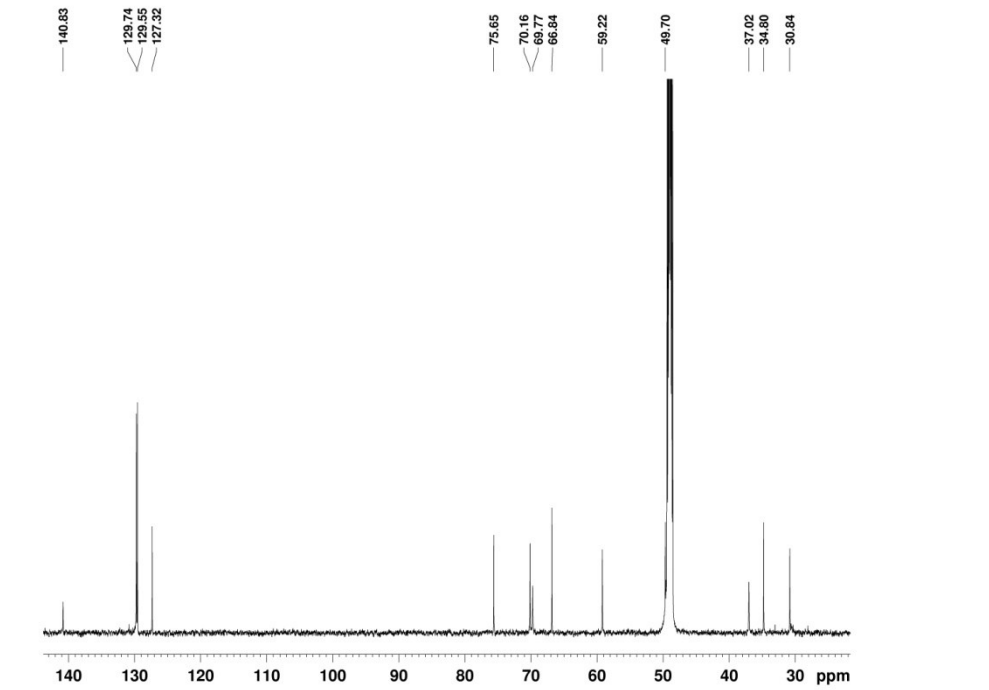
ppm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130
120
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90
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50
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30
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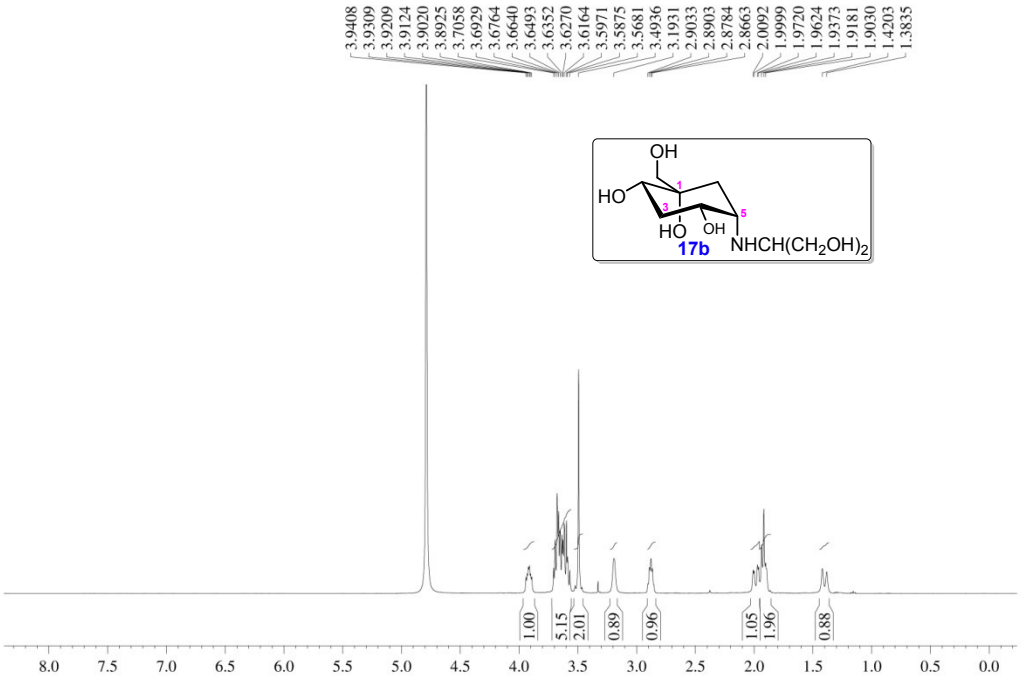
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3.6352
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3.5681
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3.1931
2.9033
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2.8663
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1.9720
1.9624
1.9373
1.9181
1.9030
1.4203
1.3835
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HO
HO
OH
NHCH(CH2OH)2
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2.01
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1.05
1.96
0.88
8.0
7.5
7.0
6.5
6.0
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4.0
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2.0
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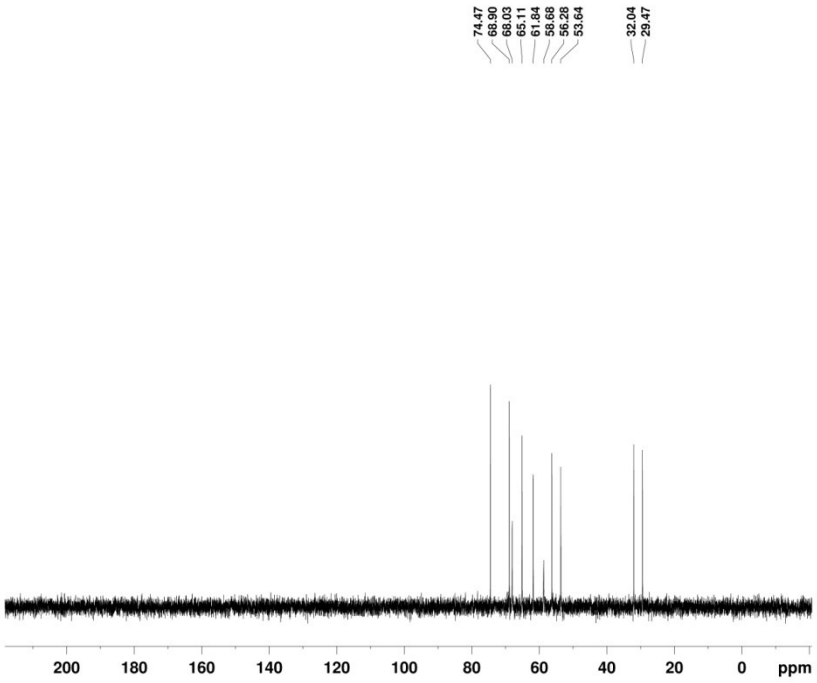
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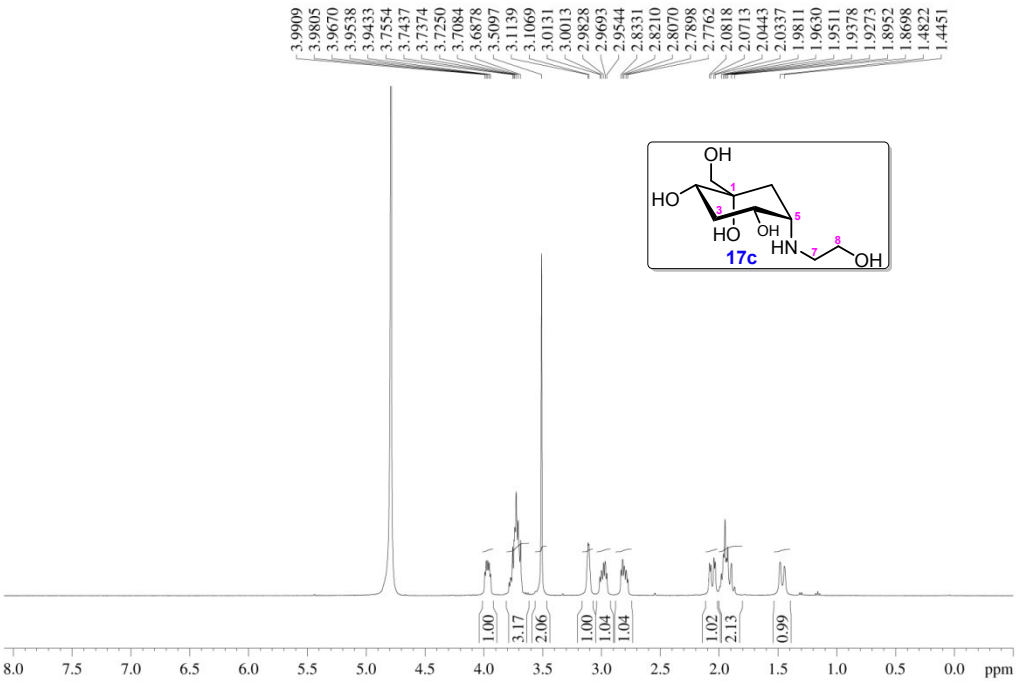
32.04
29.47
200
180
160
140
120
100
80
60
40
20
0
ppm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3.1139
3.1069
3.0131
3.0013
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2.0443
2.0337
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1.9630
1.9511
1.9378
1.9273
1.8952
1.8698
1.4822
1.4451
OH
HO
HO
OH
HN
OH
17c
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3.17
2.06
1.00
1.04
1.04
1.02
2.13
0.99
8.0
7.5
7.0
6.5
6.0
5.5
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4.0
3.5
3.0
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1.5
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0.0
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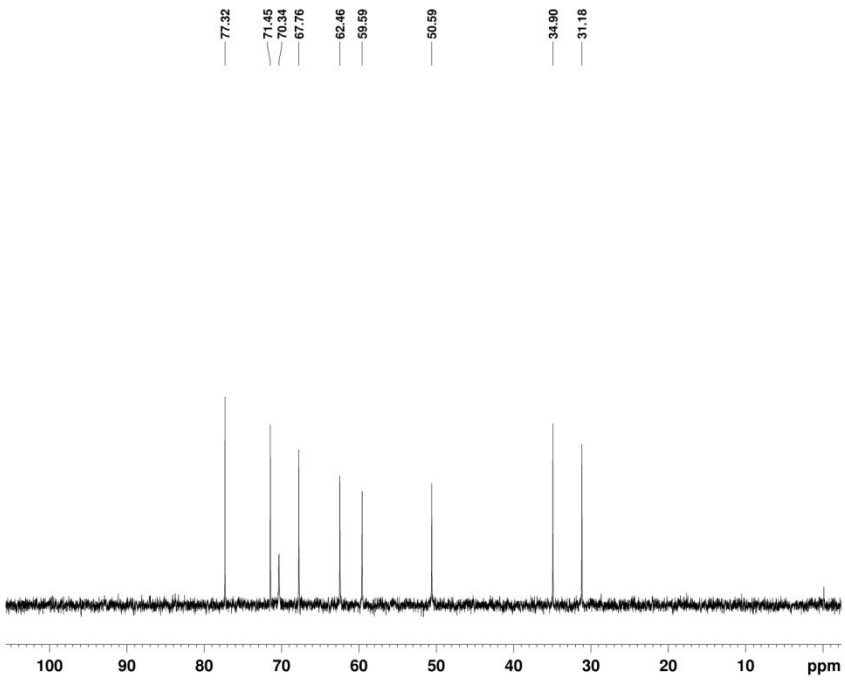
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90
80
70
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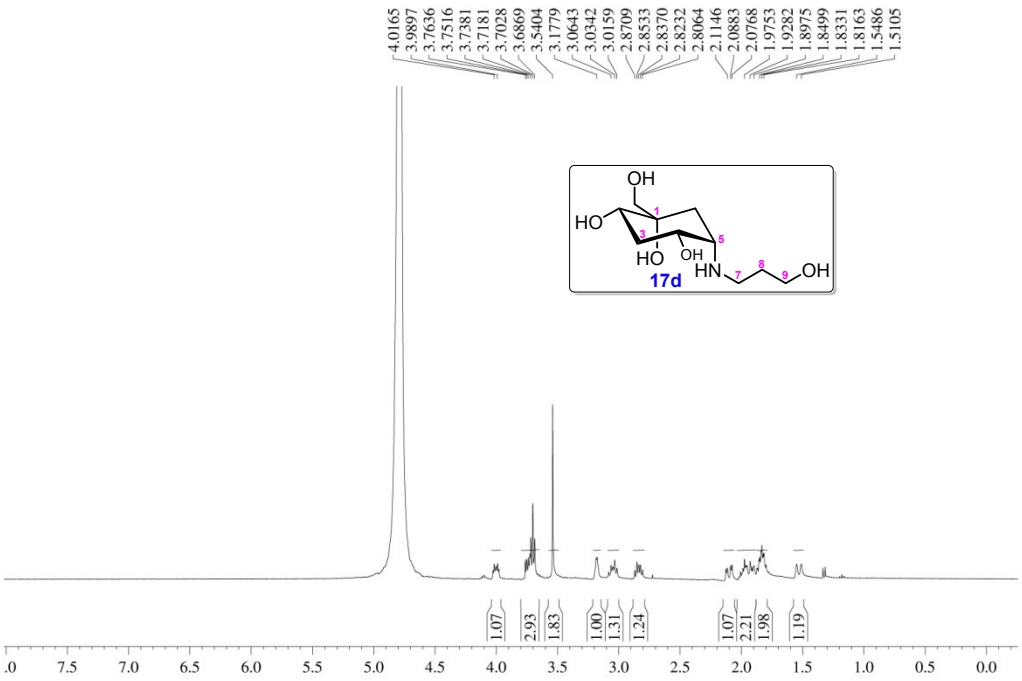
40
30
20
10
ppm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3.7181
3.7028
3.6869
3.5404
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3.0643
3.0342
3.0159
2.8709
2.8533
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2.8232
2.8064
2.1146
2.0883
2.0768
1.9753
1.9282
1.8975
1.8499
1.8331
1.8163
1.5486
1.5105
OH
HO
HO
OH
HN
OH
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1.00
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1.24
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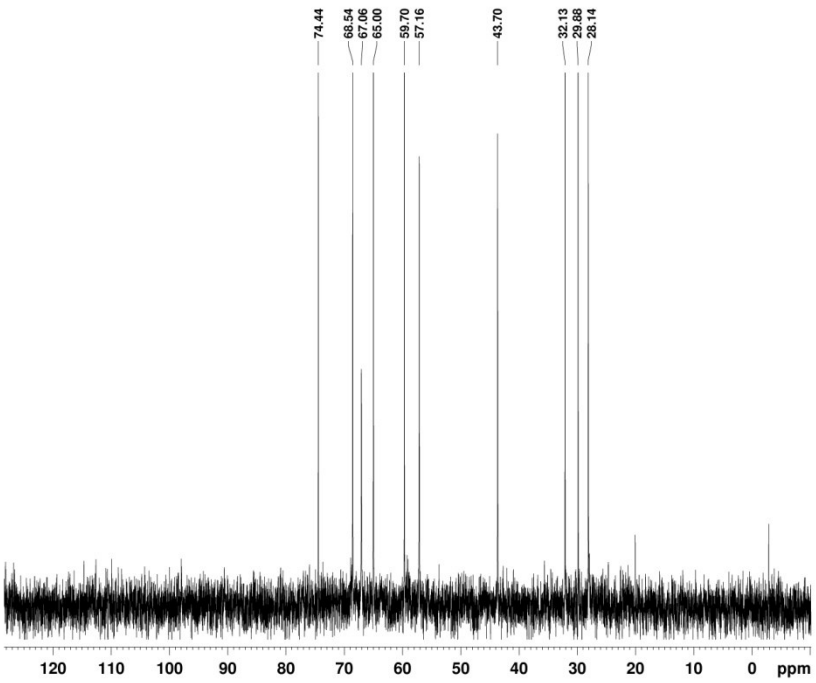
2.21
1.98
1.19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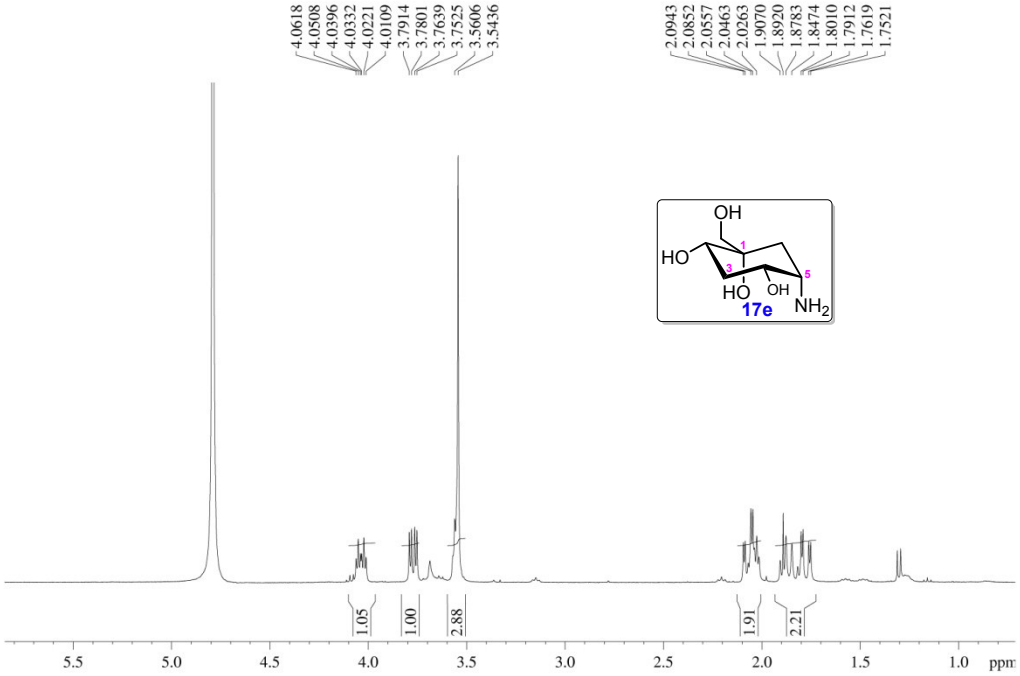
ppm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3.5436
2.0943
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1.8783
1.8474
1.8010
1.7912
1.7619
1.7521
OH
HO
HO
OH
NH2
17e
1.05
1.00
2.88
1.91
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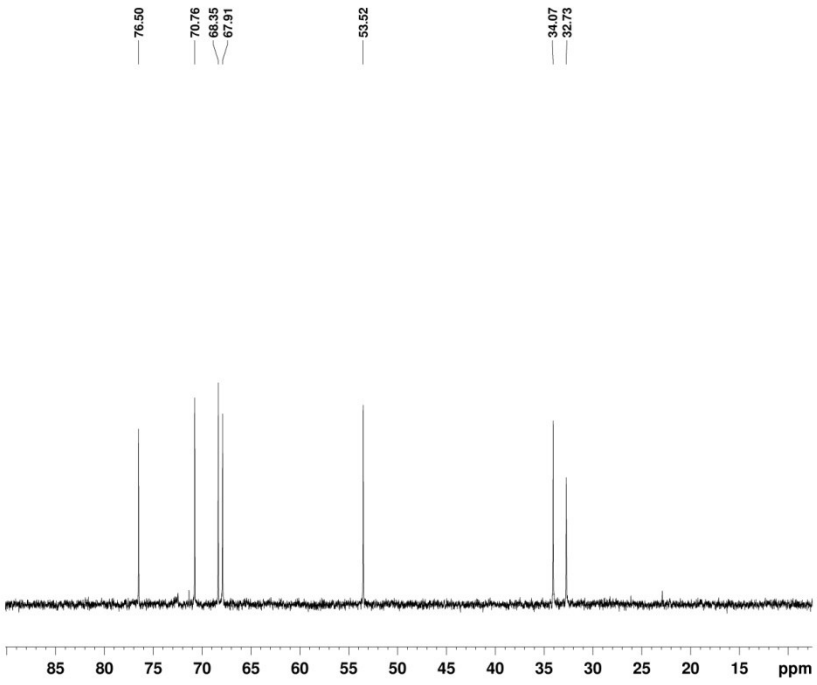
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm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80
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45
40
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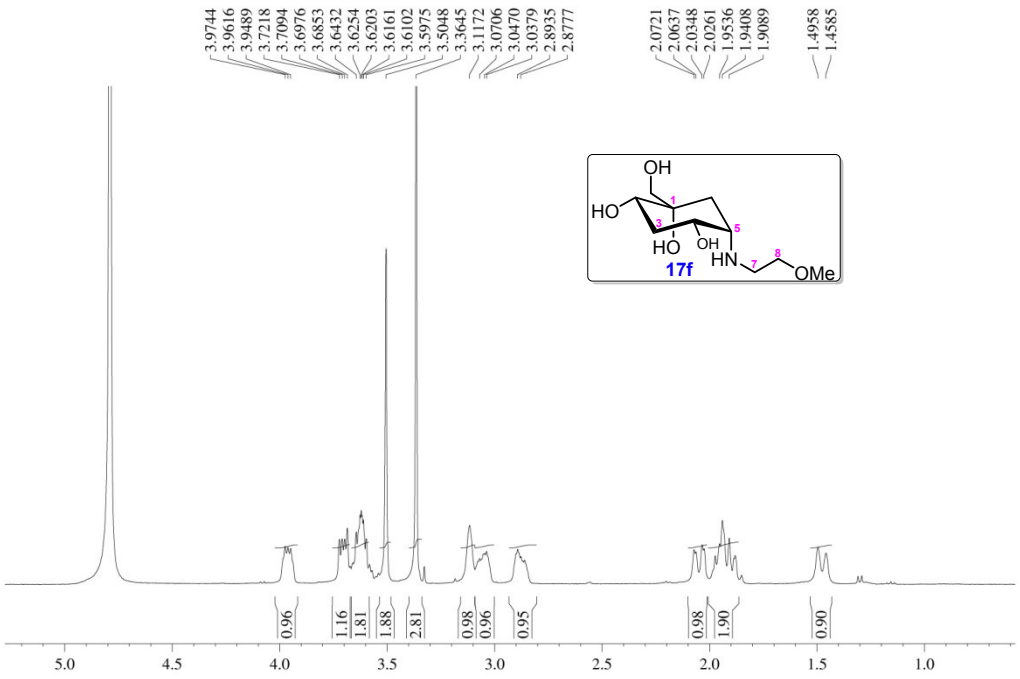
30
25
20
15
ppm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3.6161
3.6102
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3.5048
3.3645
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2.0721
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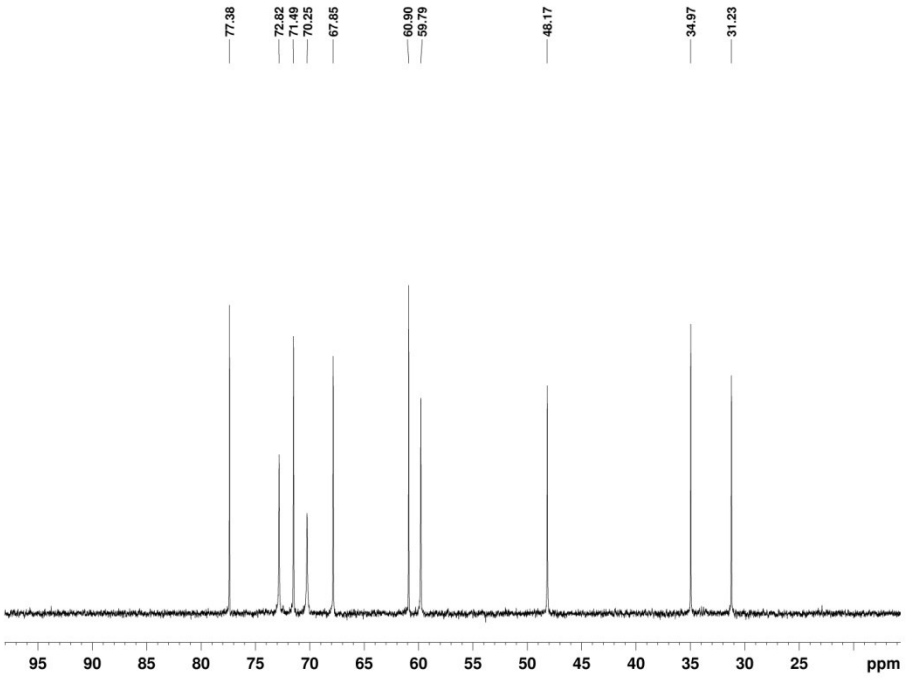
1.4585
OH
HO
HO
OH
HN
OMe
17f
0.96
1.16
1.81
1.88
2.81
0.98
0.96
0.95
0.98
1.90
0.90
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0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72.82
71.49
70.25
67.85
60.90
59.79
48.17
34.97
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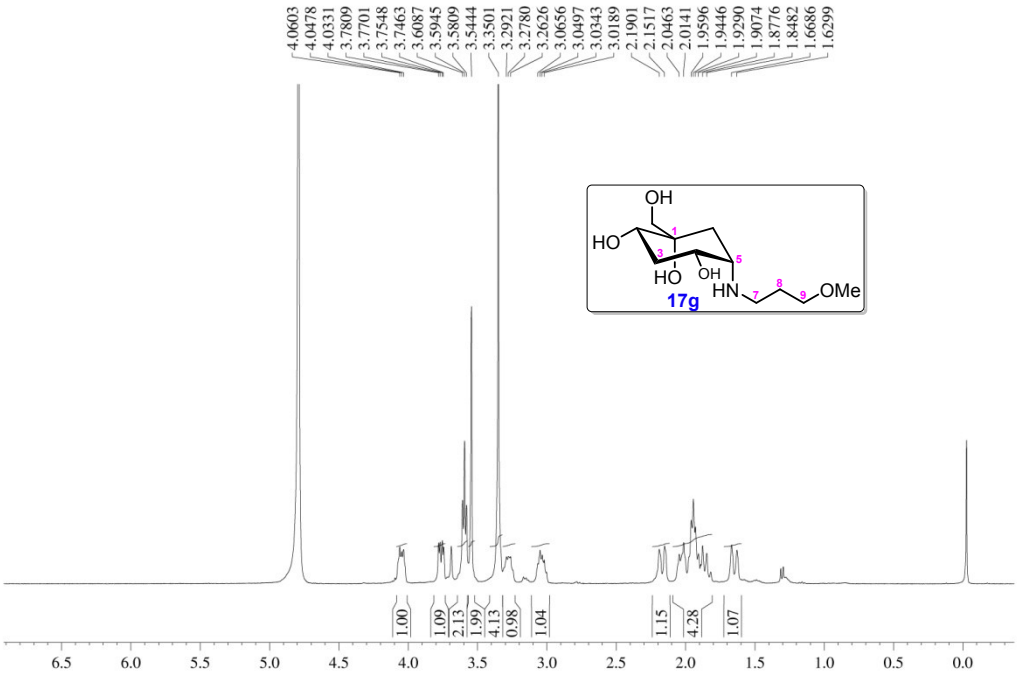
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
ppm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4.0331
3.7809
3.7701
3.7548
3.7463
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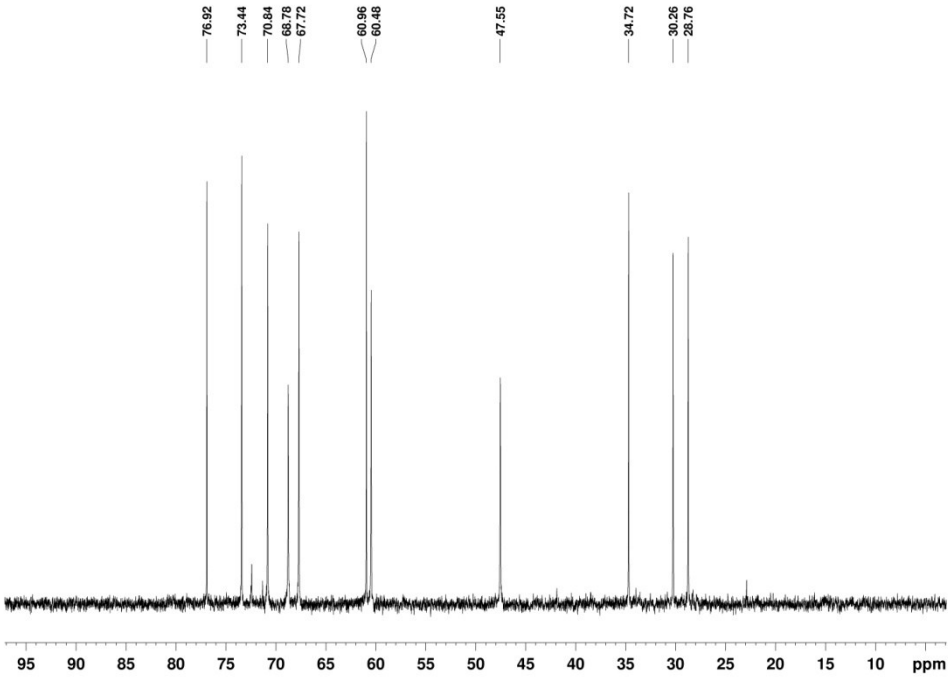
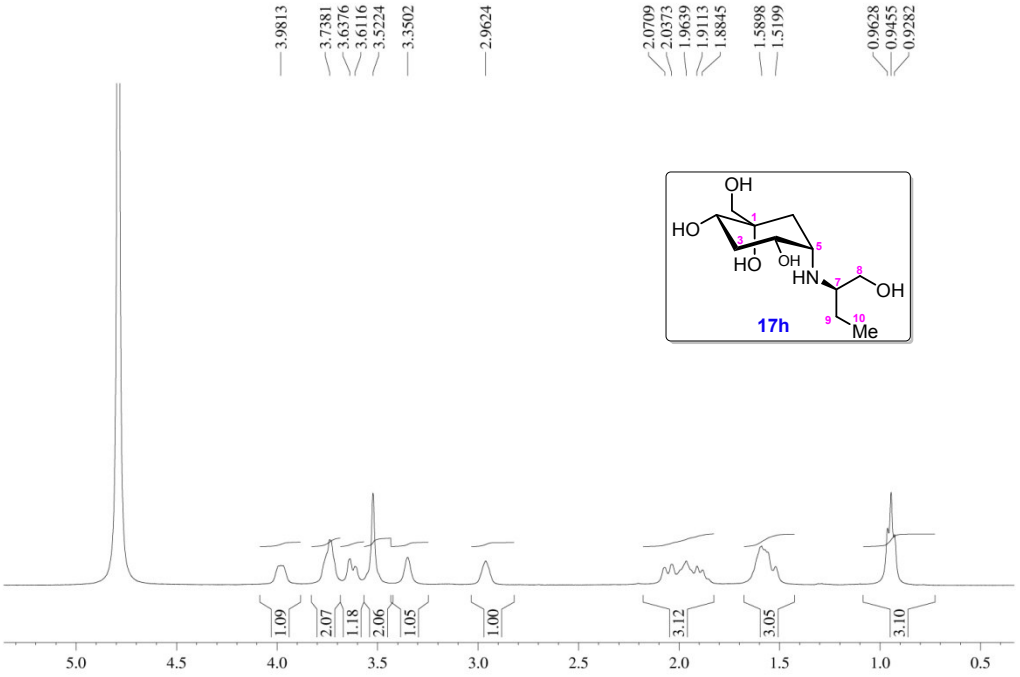
3.5945
3.5809
3.5444
3.3501
3.2921
3.2780
3.2626
3.0656
3.0497
3.0343
3.0189
2.1901
2.1517
2.0463
2.0141
1.9596
1.9446
1.9290
1.9074
1.8776
1.8482
1.6686
1.6299
OH
HO
HO
OH
HN
OMe
17g
1.00
1.09
2.13
1.99
4.13
0.98
1.04
1.15
4.28
1.07
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


76.92
73.44
70.84
68.78
67.72
60.96
60.48
47.55
34.72
30.26
28.76
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
ppm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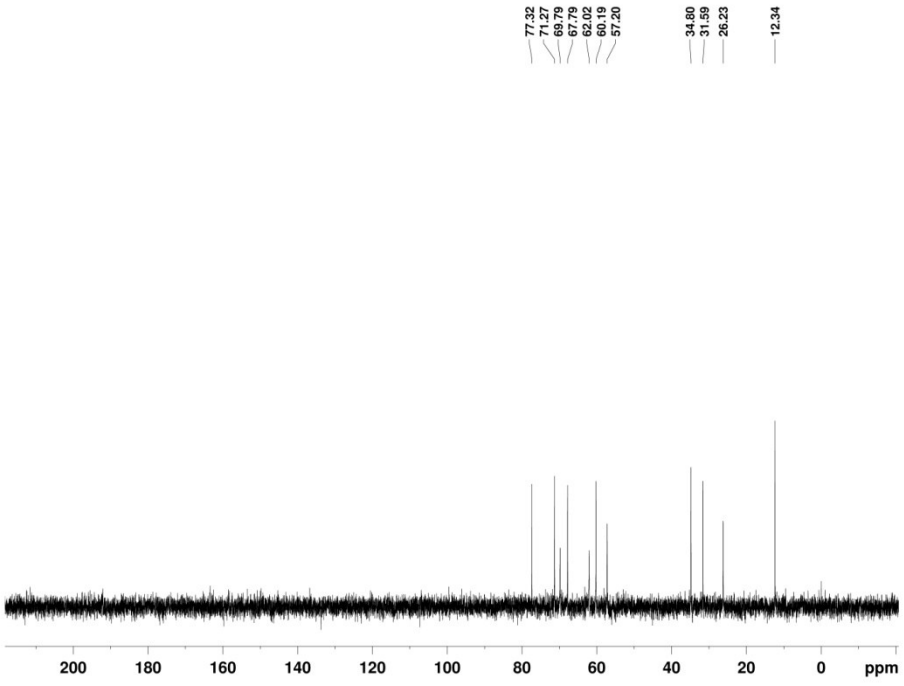
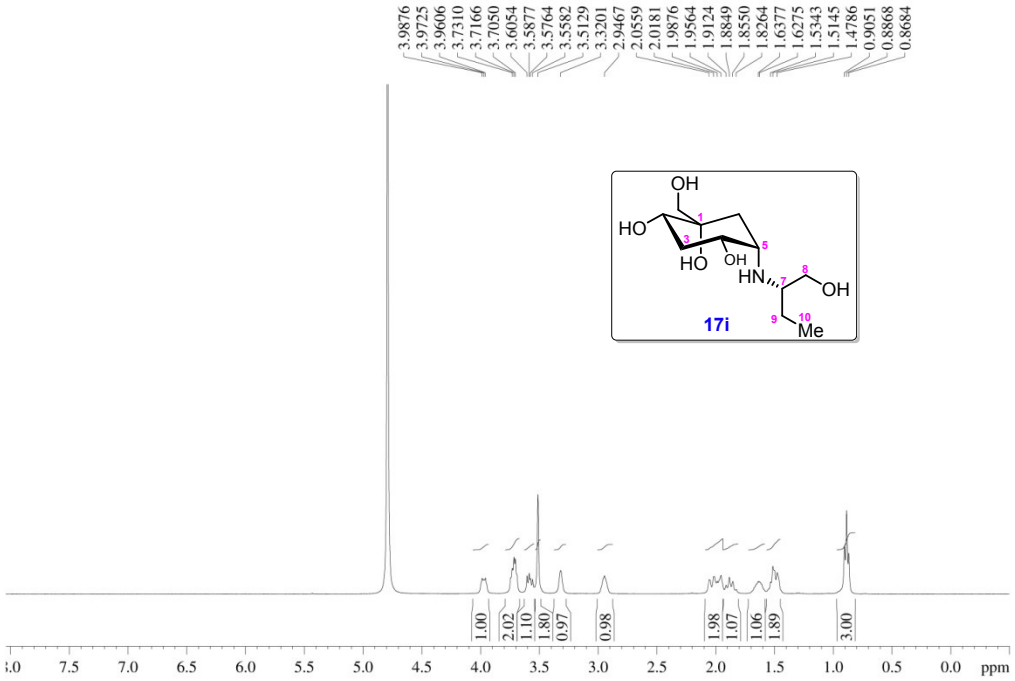
3.7381
3.6376
3.6116
3.5224
3.3502
2.9624
2.0709
2.0373
1.9639
1.9113
1.8845
1.5898
1.5199
0.9628
0.9455
0.9282
OH
HO
HO
OH
HN
OH
Me
17h
1.09
2.07
1.18
2.06
1.05
1.00
3.12
3.05
3.10
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5


77.32
71.27
69.79
67.79
62.02
60.19
57.20
34.80
31.59
26.23
12.34
200
180
160
140
120
100
80
60
40
20
0
ppm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3.9606
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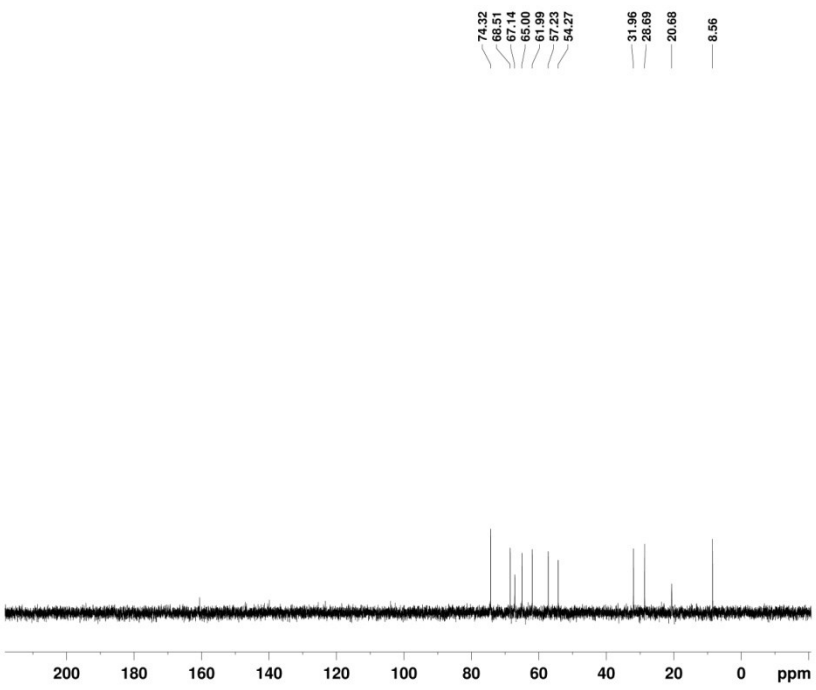
3.7166
3.7050
3.6054
3.5877
3.5764
3.5582
3.5129
3.3201
2.9467
2.0559
2.0181
1.9876
1.9564
1.9124
1.8849
1.8550
1.8264
1.6377
1.6275
1.5343
1.5145
1.4786
0.9051
0.8868
0.8684
OH
HO
HO
OH
HN
OH
Me
17i
1.00
2.02
1.10
1.80
0.97
0.98
1.98
1.07
1.06
1.89
3.00
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm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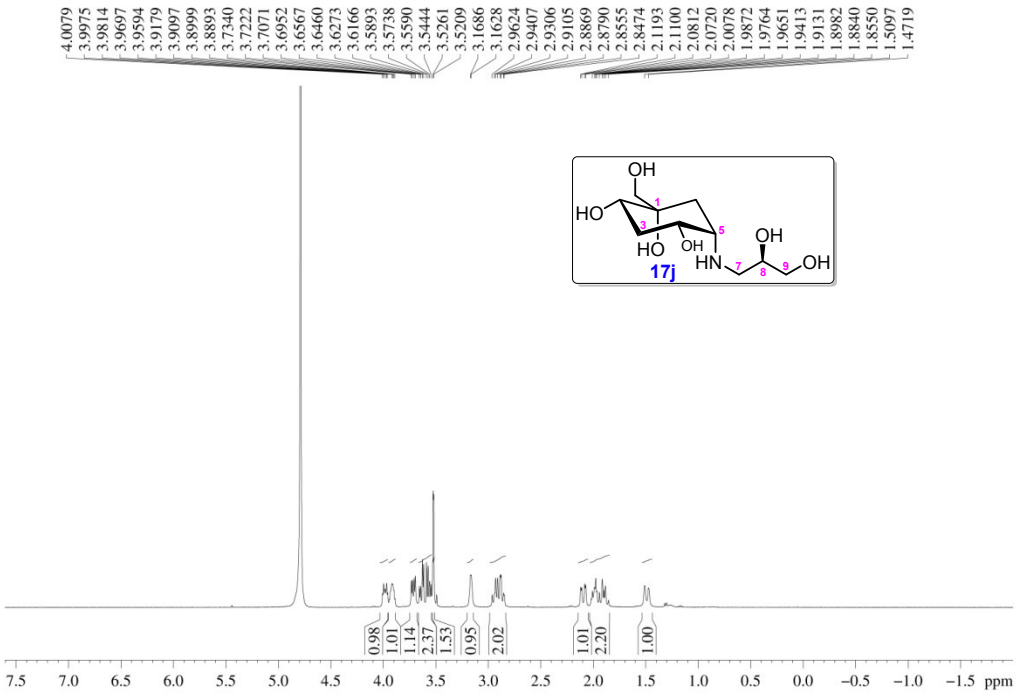
68.51
67.14
65.00
61.99
57.23
54.27
31.96
28.69
20.68
8.56
200
180
160
140
120
100
80
60
40
20
0
ppm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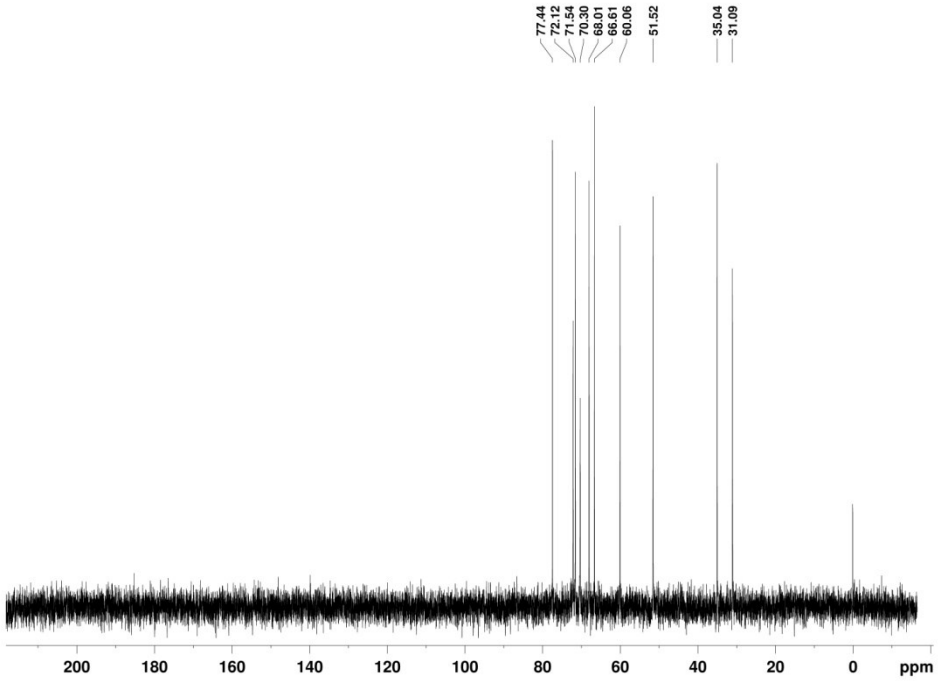
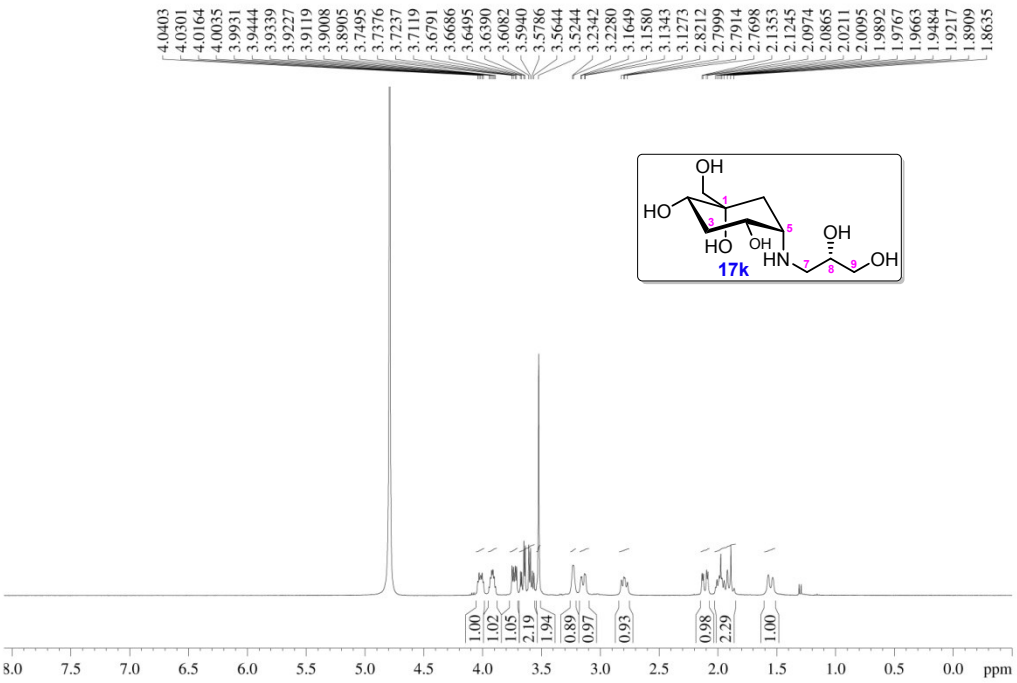
3.9814
3.9697
3.9594
3.9179
3.9097
3.8999
3.8893
3.7340
3.7222
3.7071
3.6952
3.6567
3.6460
3.6273
3.6166
3.5893
3.5738
3.5590
3.5444
3.5261
3.5209
3.1686
3.1628
2.9624
2.9407
2.9306
2.9105
2.8869
2.8790
2.8555
2.8474
2.1193
2.1100
2.0812
2.0720
2.0078
1.9872
1.9764
1.9651
1.9413
1.9131
1.8982
1.8840
1.8550
1.5097
1.4719
OH
HO
HO
OH
HN
OH
OH
17j
0.98
1.01
1.14
2.37
1.53
0.95
2.02
1.01
2.20
1.00
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5 −1.0 −1.5 ppm


77.44
72.12
71.54
70.30
68.01
66.61
60.06
51.52
35.04
31.09
200 180 160 140 120 100 80 60 40 20 0 ppm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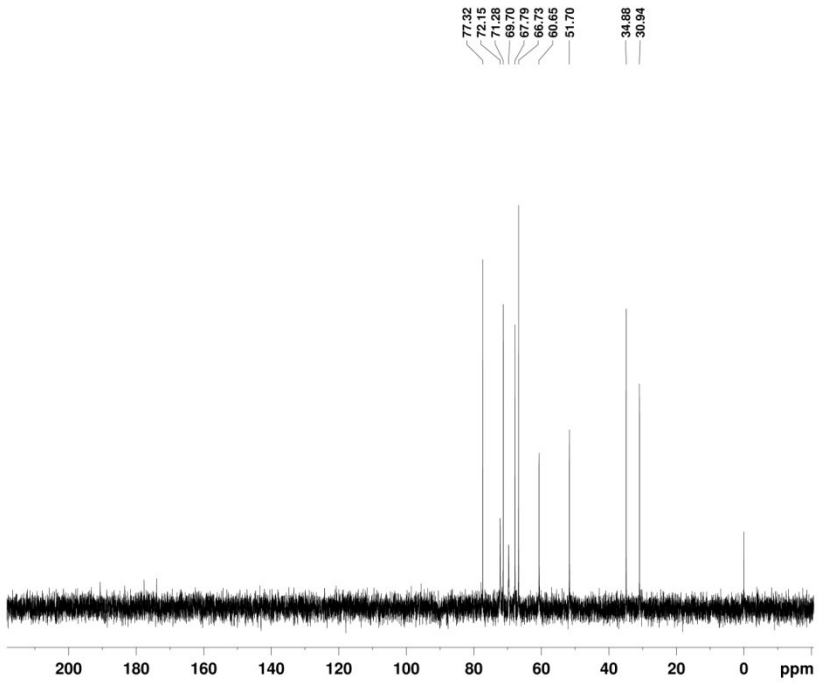
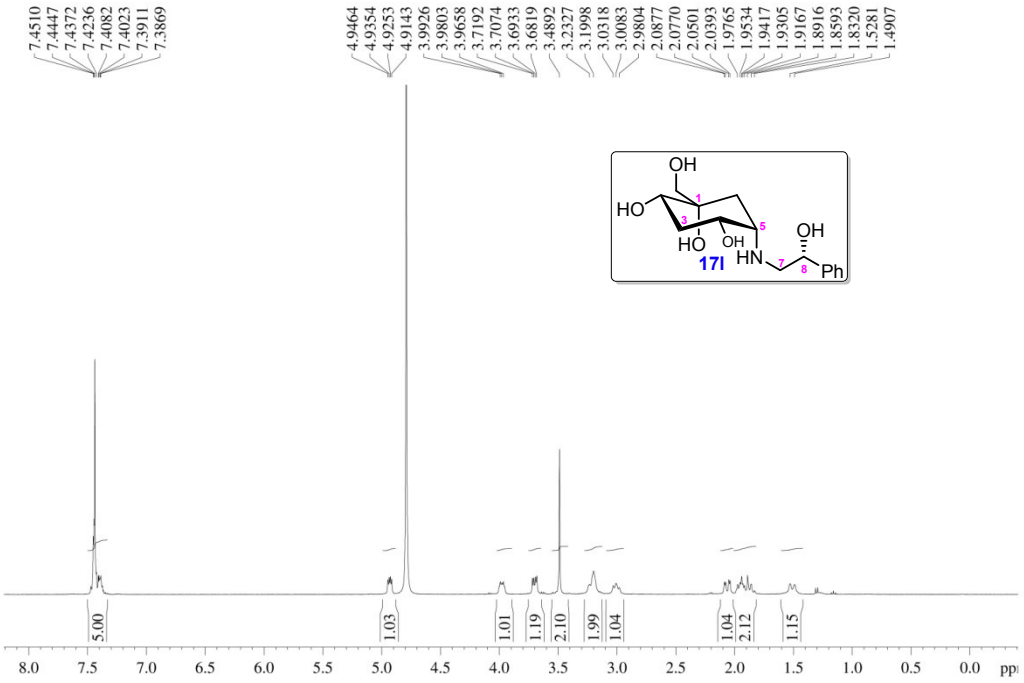
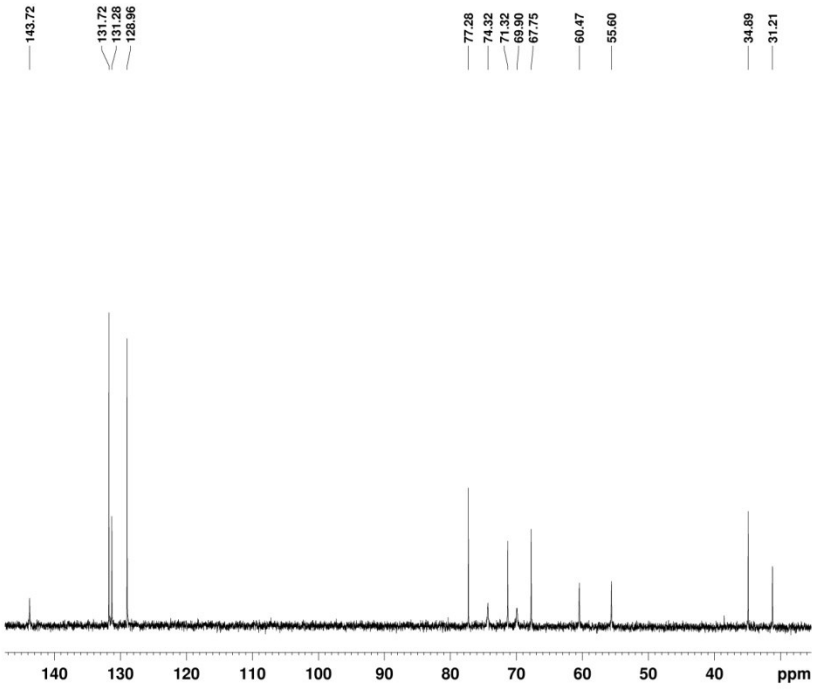
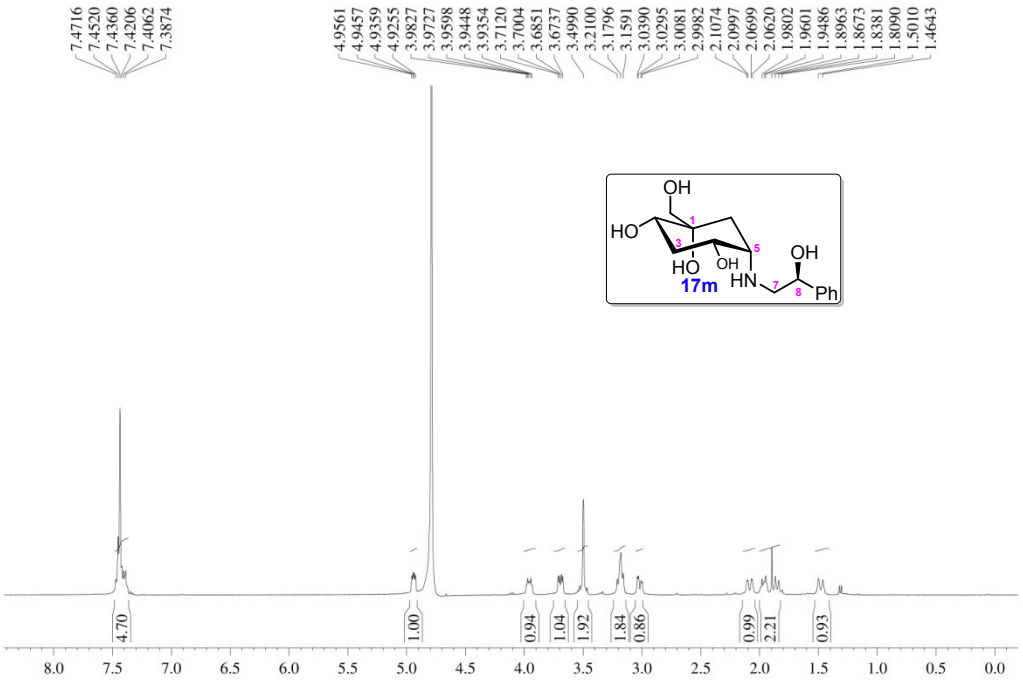
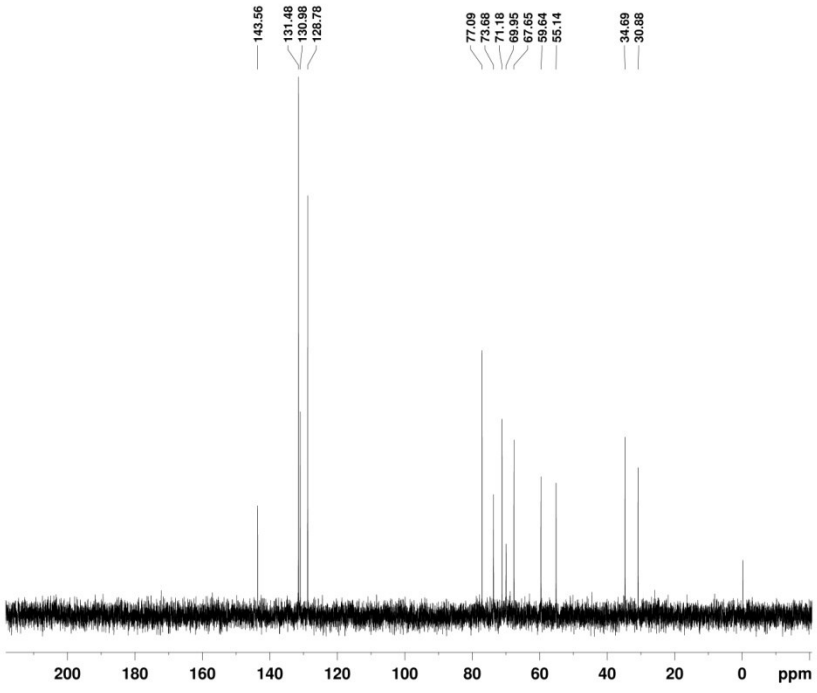
4.0301
4.0164
4.0035
3.9931
3.9444
3.9339
3.9227
3.9119
3.9008
3.8905
3.7495
3.7376
3.7237
3.7119
3.6791
3.6686
3.6495
3.6390
3.6082
3.5940
3.5786
3.5644
3.5244
3.2342
3.2280
3.1649
3.1580
3.1343
3.1273
2.8212
2.7999
2.7914
2.7698
2.1353
2.1245
2.0974
2.0865
2.0211
2.0095
1.9892
1.9767
1.9663
1.9484
1.9217
1.8909
1.8635
OH
HO
HO
OH
HN
OH
OH
17k
1.00
1.02
1.05
2.19
1.94
0.89
0.97
0.93
0.98
2.29
1.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

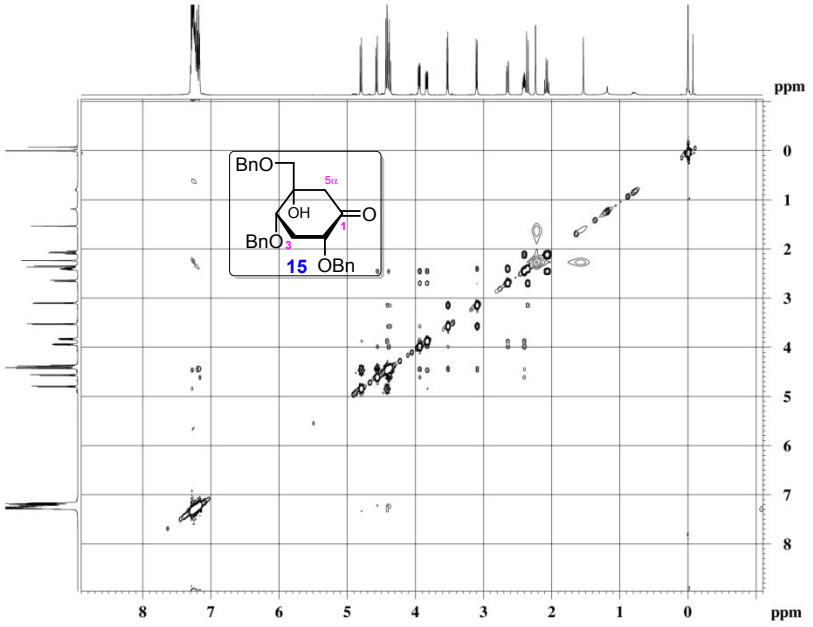

77.32
72.15
71.28
69.70
67.79
66.73
60.65
51.70
34.88
30.94
200
180
160
140
120
100
80
60
40
20
0
ppm

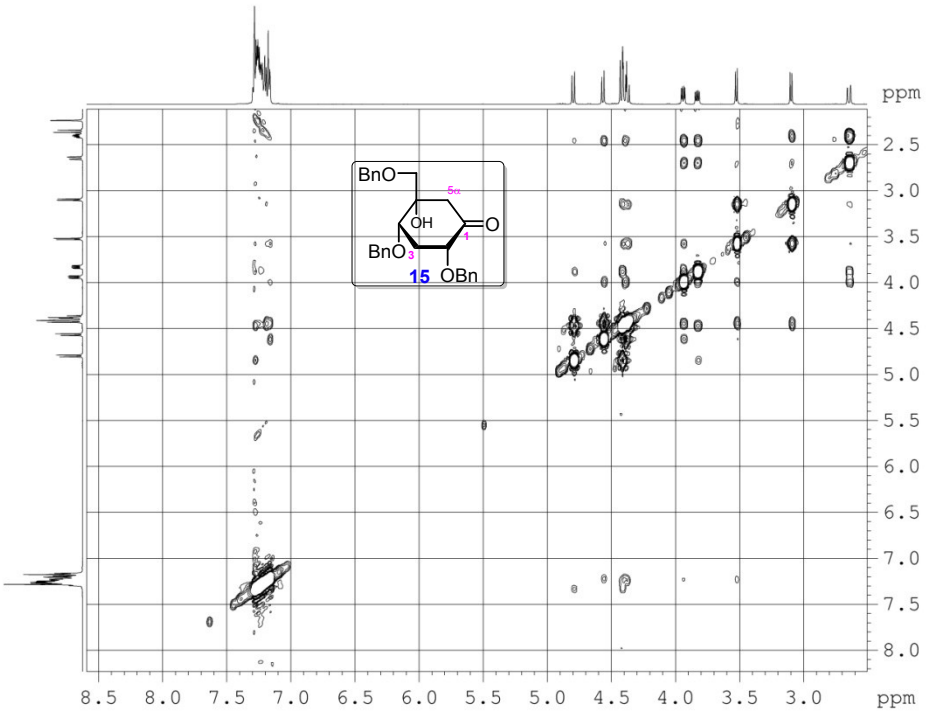

7.4510
7.4447
7.4372
7.4236
7.4082
7.4023
7.3911
7.3869
4.9464
4.9354
4.9253
4.9143
3.9926
3.9803
3.9658
3.7192
3.7074
3.6933
3.6819
3.4892
3.2327
3.1998
3.0318
3.0083
2.9804
2.0877
2.0770
2.0501
2.0393
1.9765
1.9534
1.9417
1.9305
1.9167
1.8916
1.8593
1.8320
1.5281
1.4907
OH
HO
HO
OH
HN
OH
Ph
17l
5.00
1.03
1.01
1.19
2.10
1.99
1.04
1.04
2.12
1.15
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

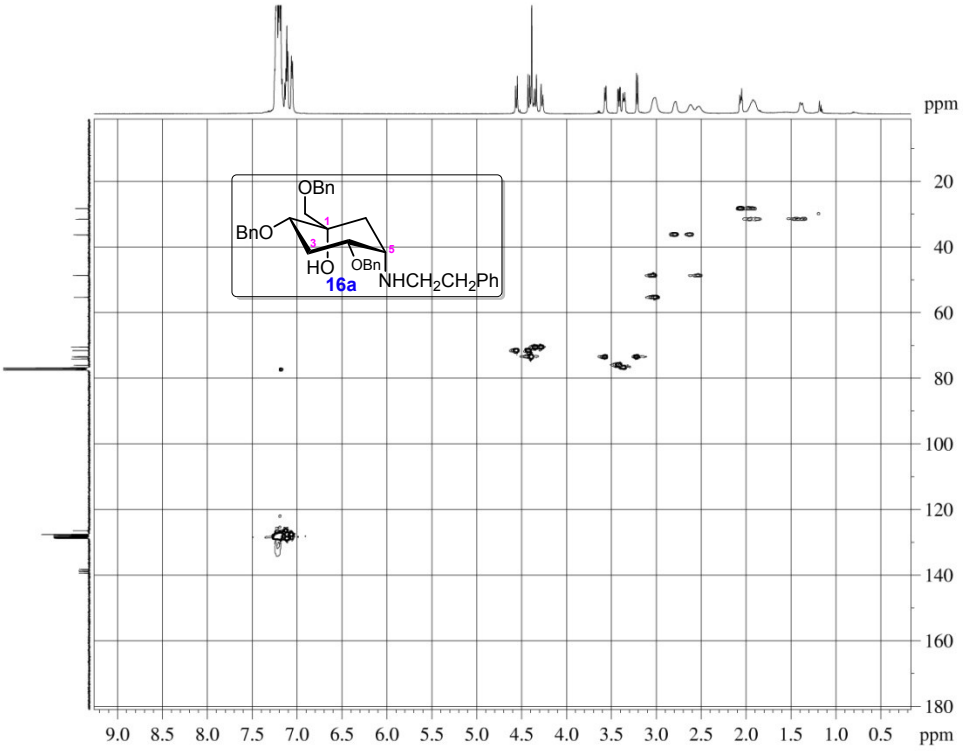

143.72
131.72
131.28
128.96
77.28
74.32
71.32
69.90
67.75
60.47
55.60
34.89
31.21
140
130
120
110
100
90
80
70
60
50
40
ppm

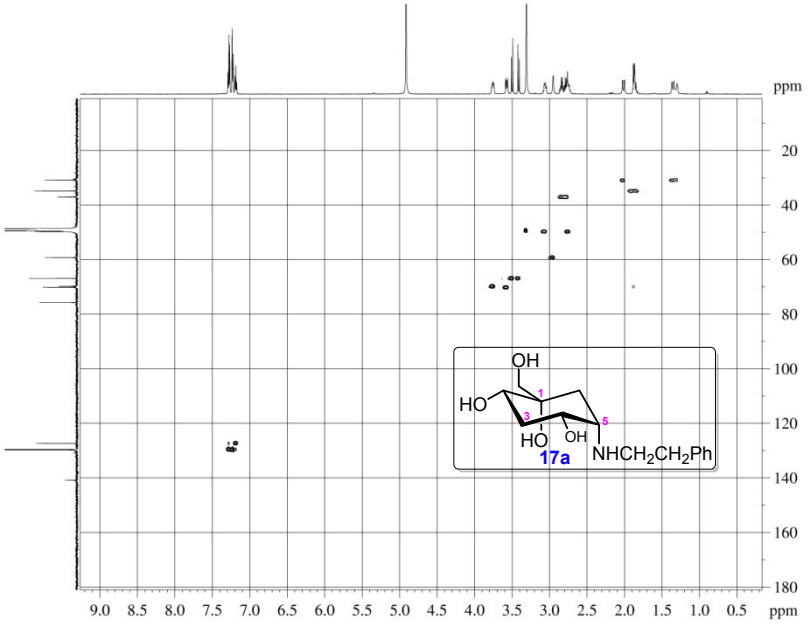

7.4716
7.4520
7.4360
7.4206
7.4062
7.3874
4.9561
4.9457
4.9359
4.9255
3.9827
3.9727
3.9598
3.9448
3.9354
3.7120
3.7004
3.6851
3.6737
3.4990
3.2100
3.1796
3.1591
3.0390
3.0295
3.0081
2.9982
2.1074
2.0997
2.0699
2.0620
1.9802
1.9601
1.9486
1.8963
1.8673
1.8381
1.8090
1.5010
1.4643
OH
HO
HO
OH
HN
OH
Ph
17m
4.70
1.00
0.94
1.04
1.92
1.84
0.86
0.99
2.21
0.93
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

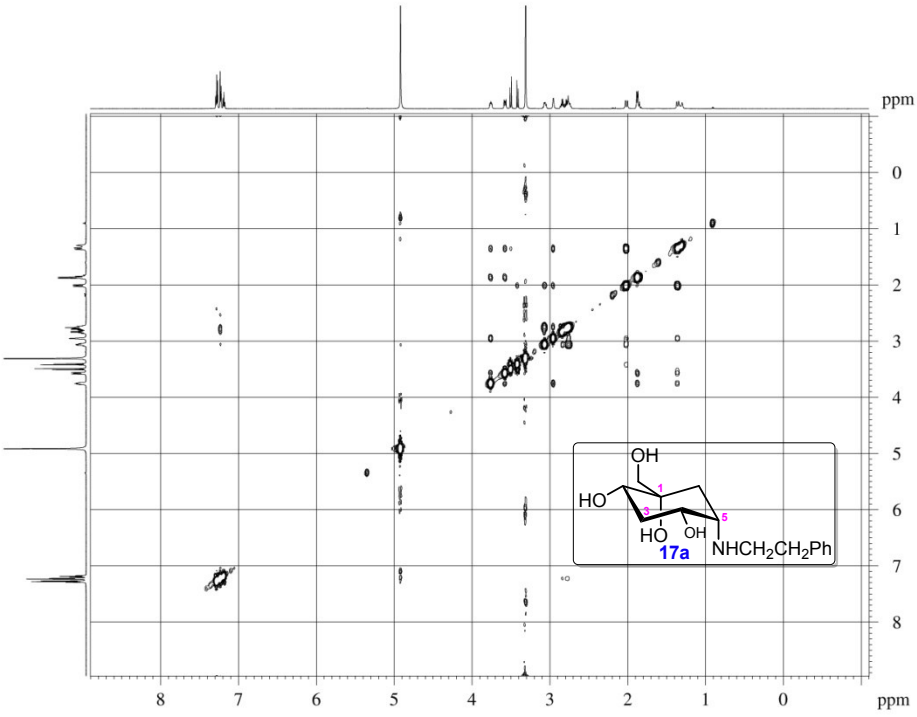

143.56
131.48
130.98
128.78
77.09
73.68
71.18
69.95
67.65
59.64
55.14
34.69
30.88
200
180
160
140
120
100
80
60
40
20
0
ppm


BnO
5α
OH
O
1
BnO 3
15 OBn
ppm
0
1
2
3
4
5
6
7
8
8 7 6 5 4 3 2 1 0
ppm


BnO
5α
OH
O
1
BnO 3
15 OBn
ppm
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0
ppm


OBn
BnO
HO
OBn
NHCH2CH2Ph
16a
ppm
20
40
60
80
100
120
140
160
180
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
ppm

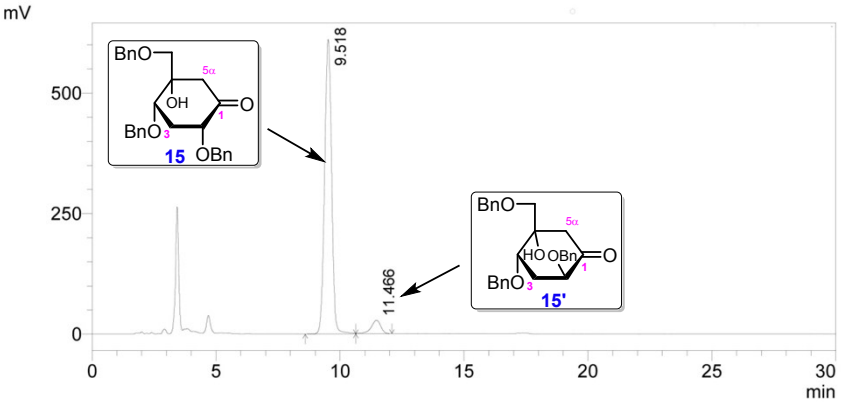

ppm
20
40
60
80
100
120
140
160
180
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
OH
HO
1
3
5
HO
OH
17a
NHCH2CH2Ph


ppm
0
1
2
3
4
5
6
7
8
8 7 6 5 4 3 2 1 0 ppm
OH
HO
1
3
5
HO
OH
17a
NHCH2CH2Ph

==== Shimadzu LCsolution ====

Operator	: Admin
Tray	: 1
Vial#	: 9
Inj. Volume	: 10 uL
Data Name	: 22
Method Name	: Method 0102-1.lcm
Batch Name	: 20190102.lcb
Report Name	: report.lcr

Chromatogram



Peak#	Time	Area	High	Area %	Resolution	PN#	Trailing factor
1	9.518	12099806	610888	94.136	0.000	5395	0.996
2	11.466	753795	28015	5.864	3.275	4670	0.768
		12853600	638903	100.000			