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Epimerization of C5 of an *N*-hydroxypyrrolidine in the Synthesis of Swainsonine Related Iminosugars

Bao-Chen Qian,[a,e] Akiko Kamori,[b] Kyoko Kinami,[b] Atsushi Kato,*[b] Yi-Xian Li,[a] George W. J. Fleet[c,d] and Chu-Yi Yu*[a,d]

[a] *Beijing National Laboratory for Molecular Science (BNLMS), CAS Key Laboratory of Molecular Recognition and Function, Institute of Chemistry, Chinese Academy of Sciences, Beijing 100190, China. Email: yucy@iccas.ac.cn*
[b] *Department of Hospital Pharmacy, University of Toyama, 2630 Sugitani, Toyama 930-0194, Japan. E-mail: kato@med.u-toyama.ac.jp*
[c] *Chemistry Research Laboratory, Department of Chemistry, University of Oxford, Mansfield Road, Oxford, OX1 3TA, UK.*
[d] *National Engineering Research Center for Carbohydrate Synthesis, Jiangxi Normal University, Nanchang 330022, PR China*
[e] *University of Chinese Academy of Sciences, Beijing 100049, China.*

Supplementary Information

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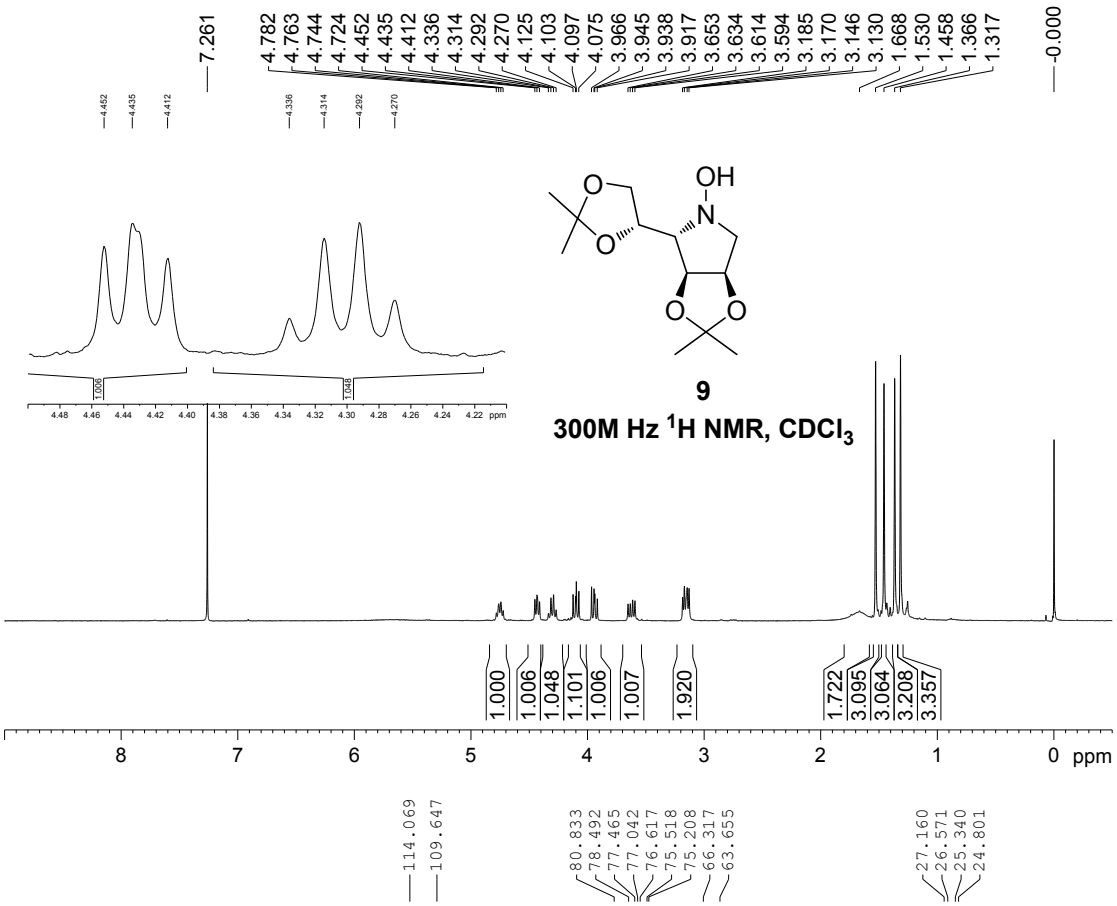
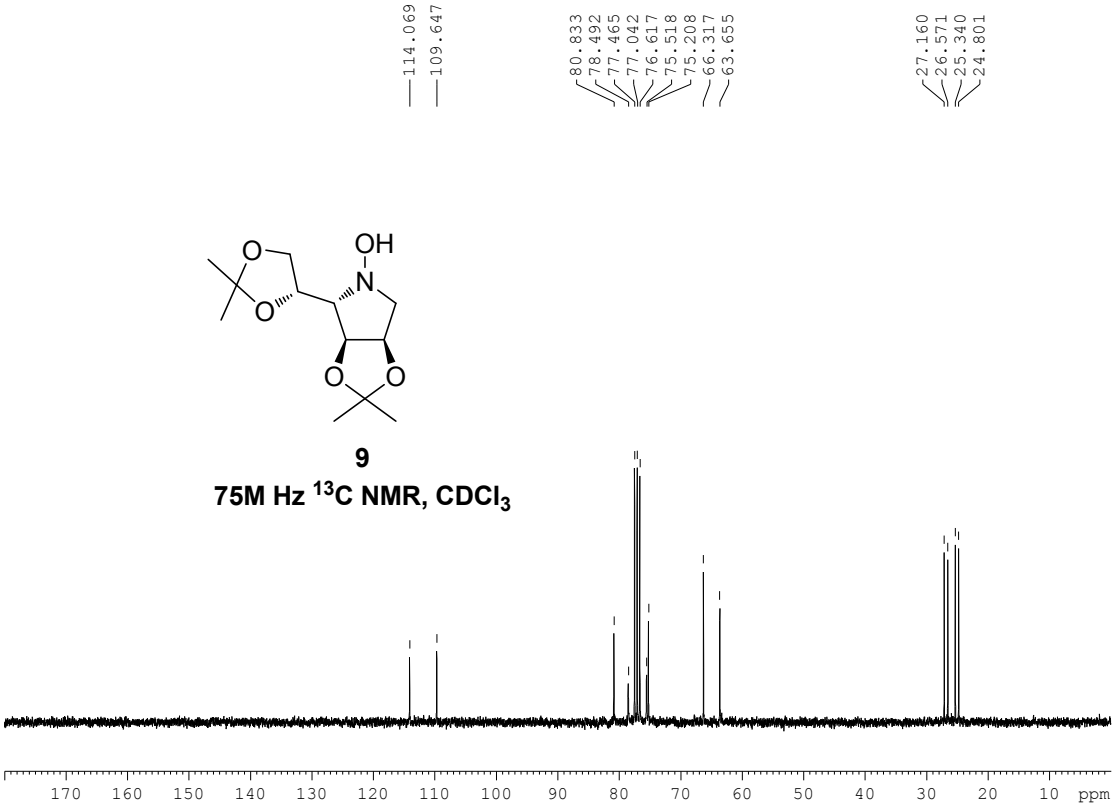
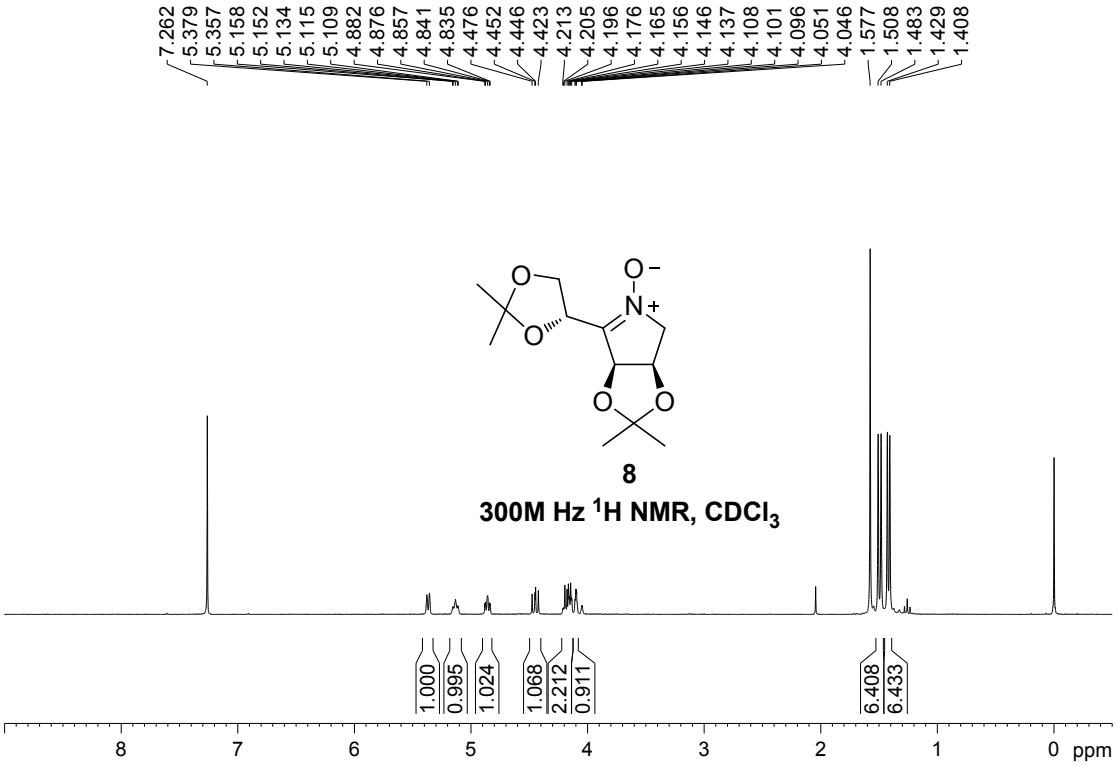
1. Copies of ^{1}H and ^{13}C NMR spectra for new compounds



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5.357
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4.876
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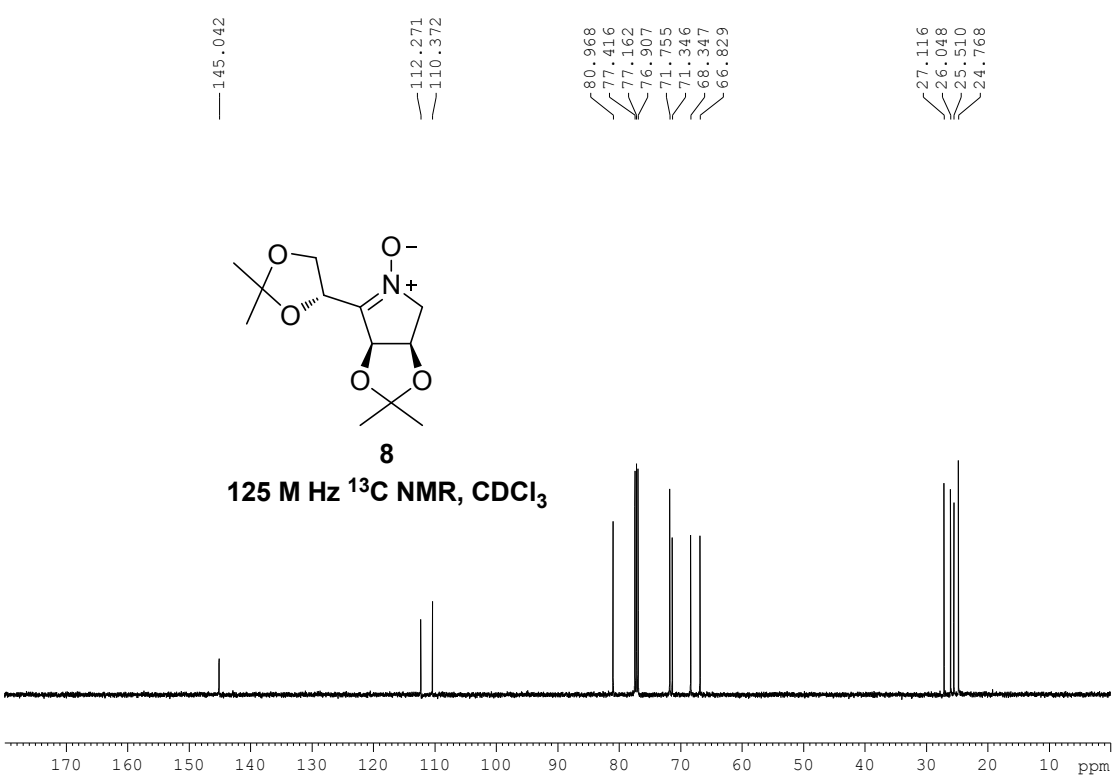
4.841
4.835
4.476
4.452
4.446
4.423
4.213
4.205
4.196
4.176
4.165
4.156
4.146
4.137
4.108
4.101
4.096
4.051
4.046
1.577
1.508
1.483
1.429
1.408
8
300M Hz 1H NMR, CDCl3
1.000
0.995
1.024
1.068
2.212
0.911
6.408
6.433
8
7
6
5
4
3
2
1
0 ppm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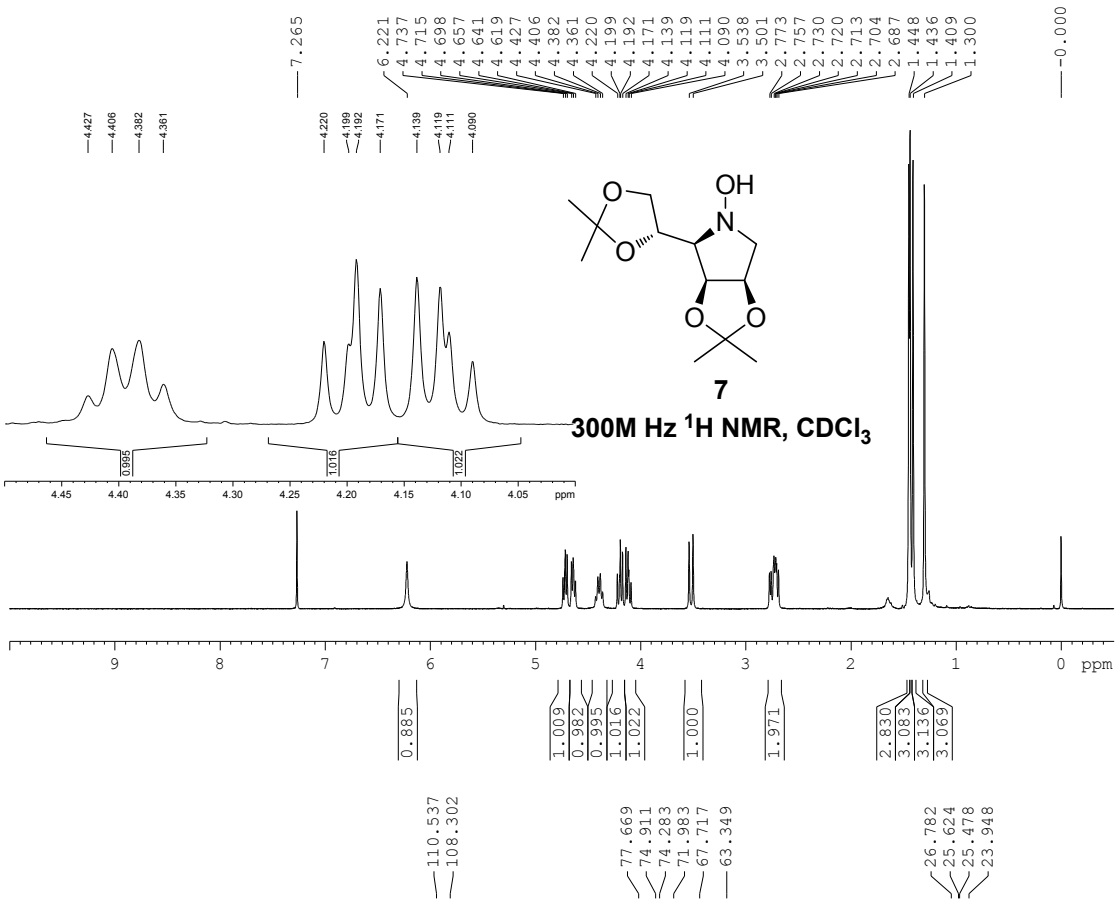
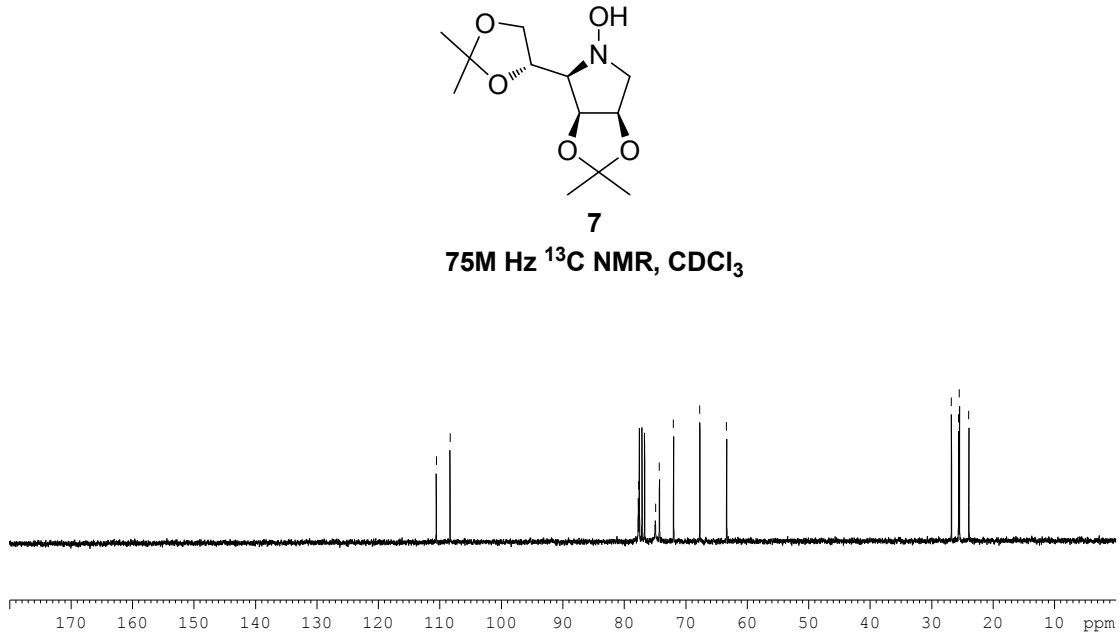
112.271
110.372
80.968
77.416
77.162
76.907
71.755
71.346
68.347
66.829
27.116
26.048
25.510
24.768
8
125 M Hz 13C NMR, CDCl3
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10 ppm



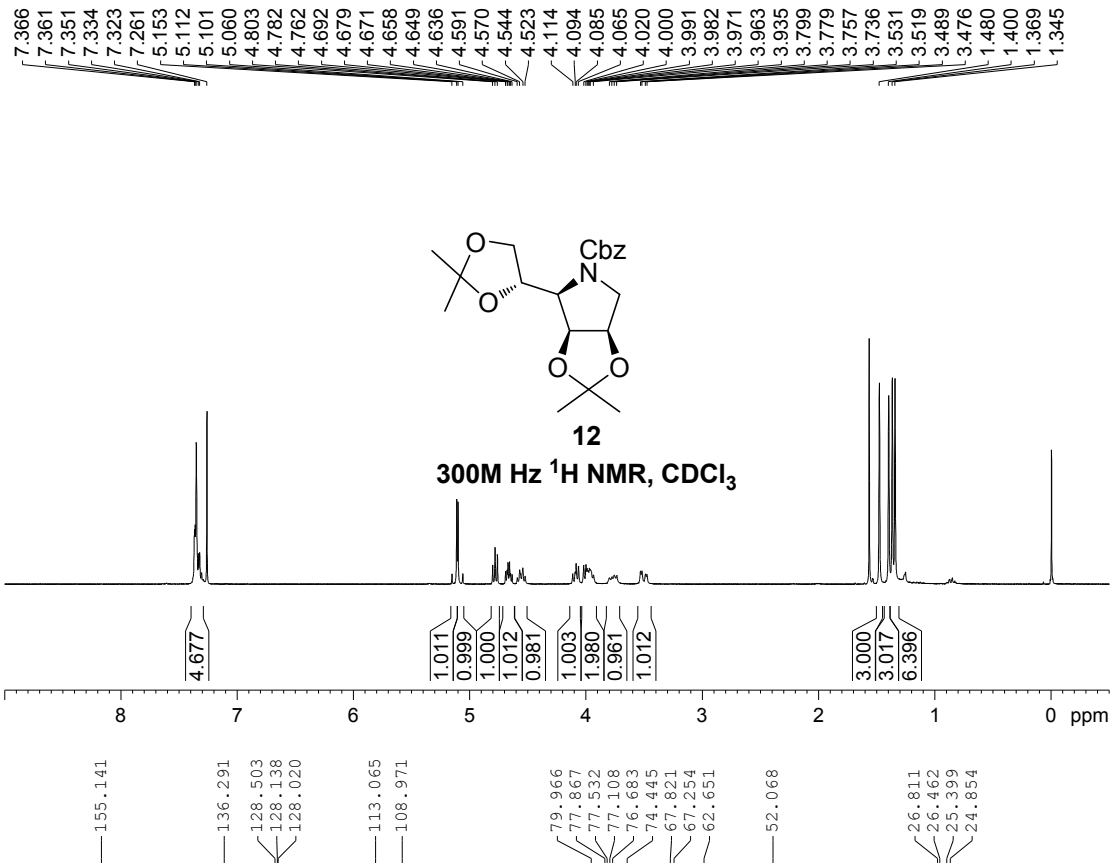
7

300M Hz ^{1}H NMR, $CDCl_3$



7

75M Hz ^{13}C NMR, $CDCl_3$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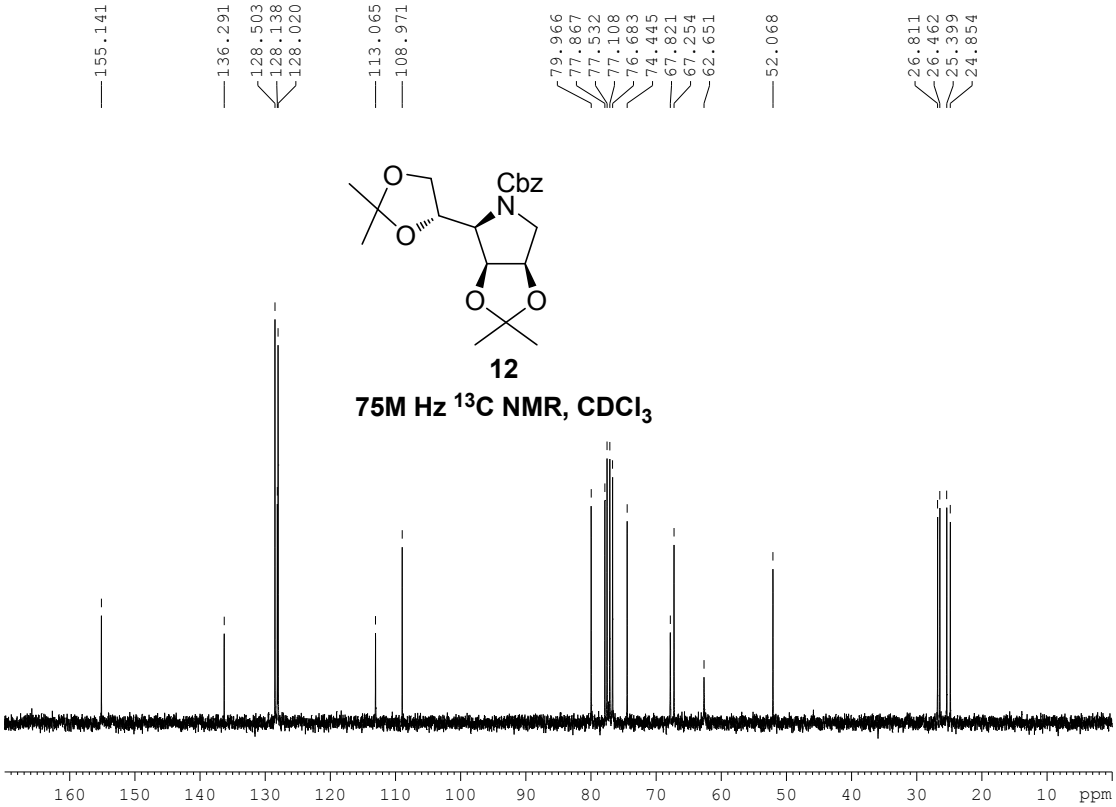
Cbz
N
O
O
O
O
12
300M Hz 1H NMR, CDCl3
4.677
1.011
0.999
1.000
1.012
0.981
1.003
1.980
0.961
1.012
3.000
3.017
6.396
8 7 6 5 4 3 2 1 0 ppm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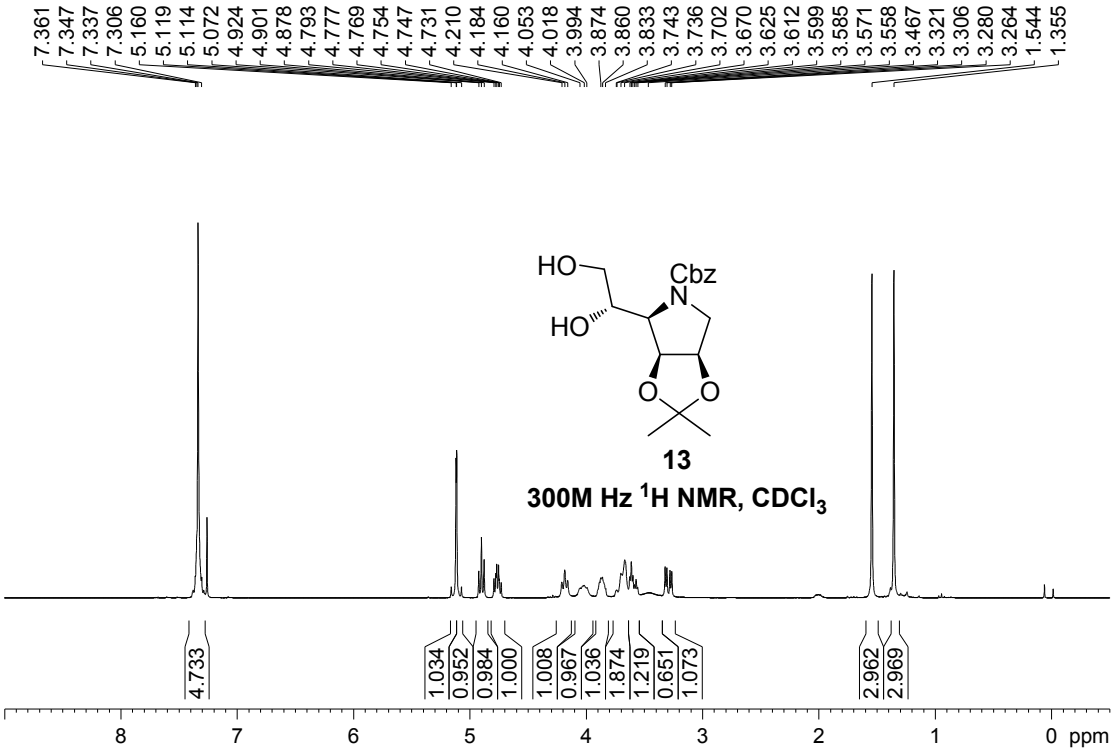
136.291
128.503
128.138
128.020
113.065
108.971
79.966
77.867
77.532
77.108
76.683
74.445
67.821
67.254
62.651
52.068
26.811
26.462
25.399
24.854
Cbz
N
O
O
O
O
12
75M Hz 13C NMR, CDCl3
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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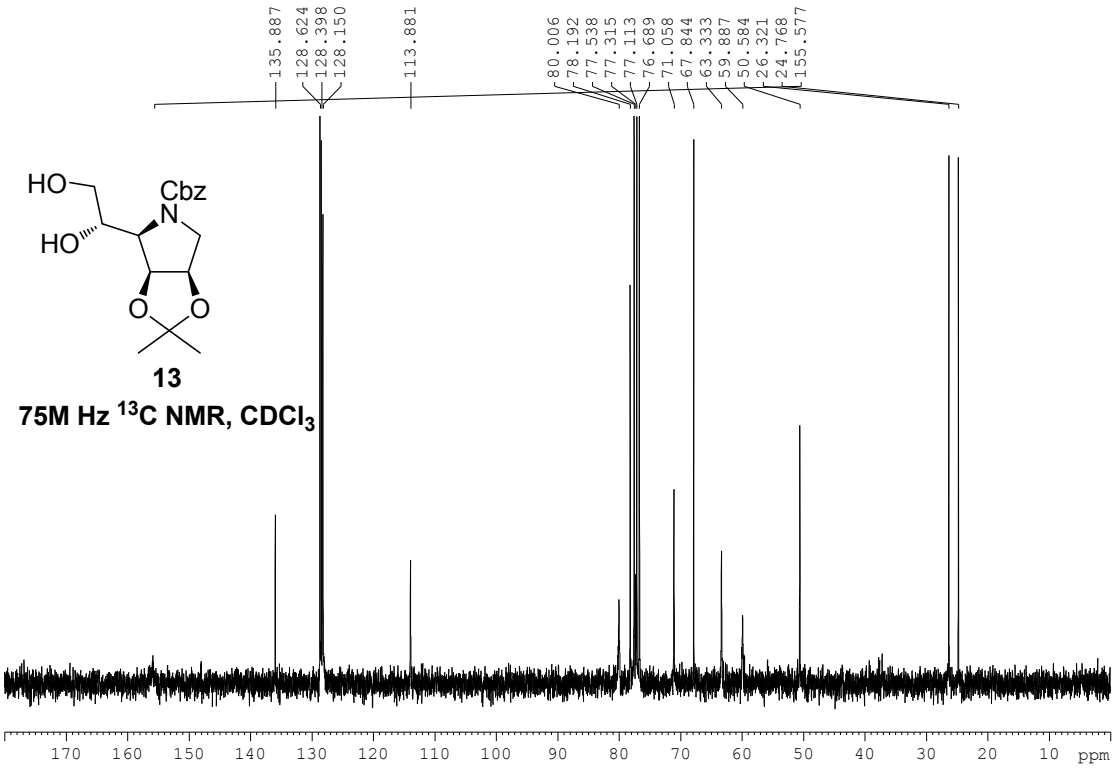
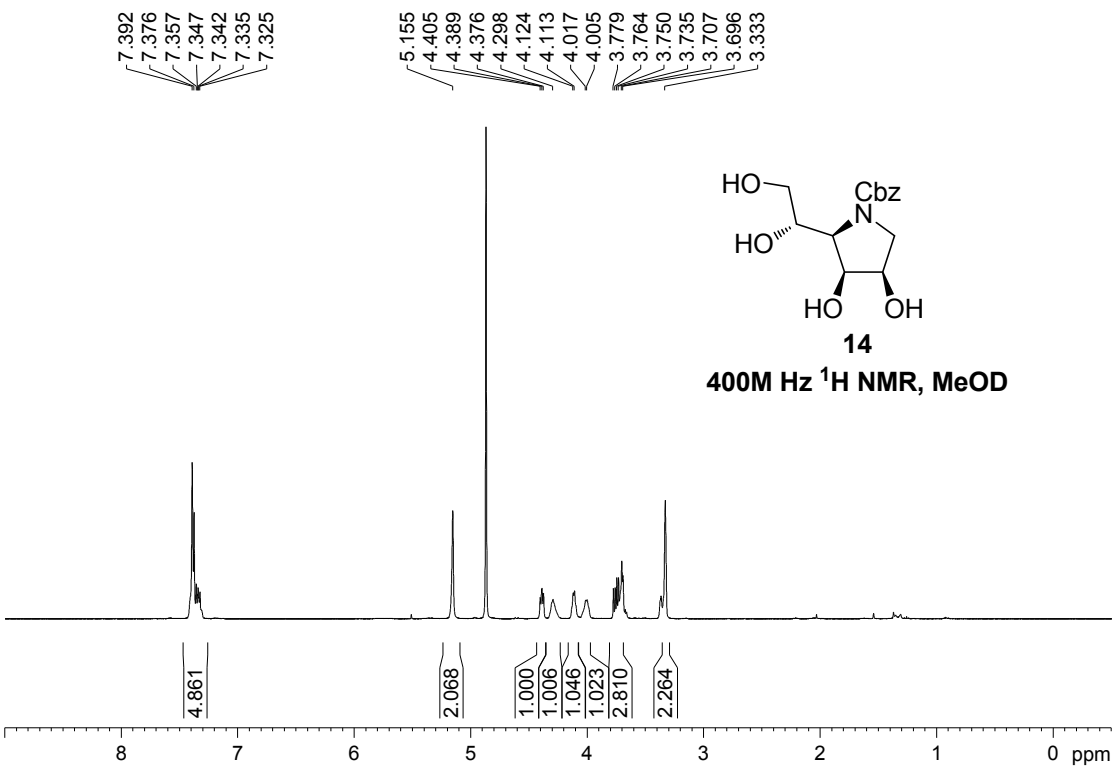
HO
Cbz
N
HO
O
O
13
300M Hz 1H NMR, CDCl3
4.733
1.034
0.952
0.984
1.000
1.008
0.967
1.036
1.874
1.219
0.651
1.073
2.962
2.969
8 7 6 5 4 3 2 1 0 ppm


135.887
128.624
128.398
128.150
113.881
80.006
78.192
77.538
77.315
77.113
76.689
71.058
67.844
63.333
59.887
50.584
26.321
24.768
155.577
HO
Cbz
N
HO
O
O
13
75M Hz 13C NMR, CDCl3
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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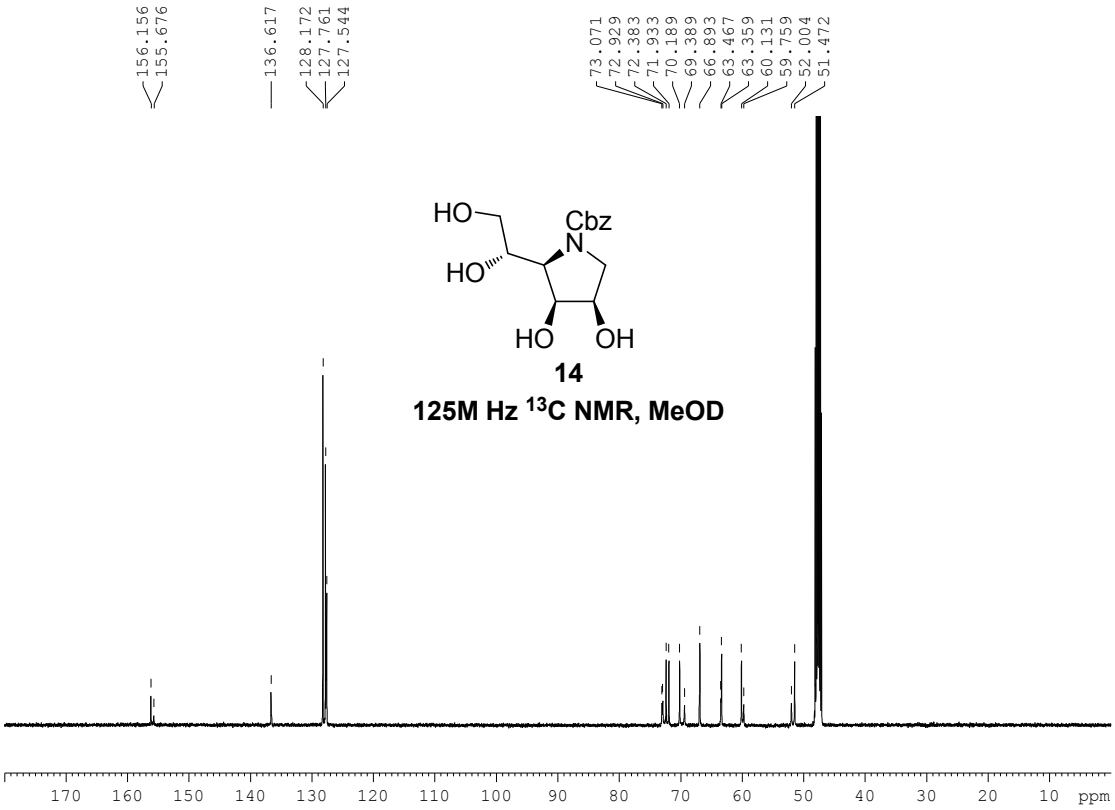
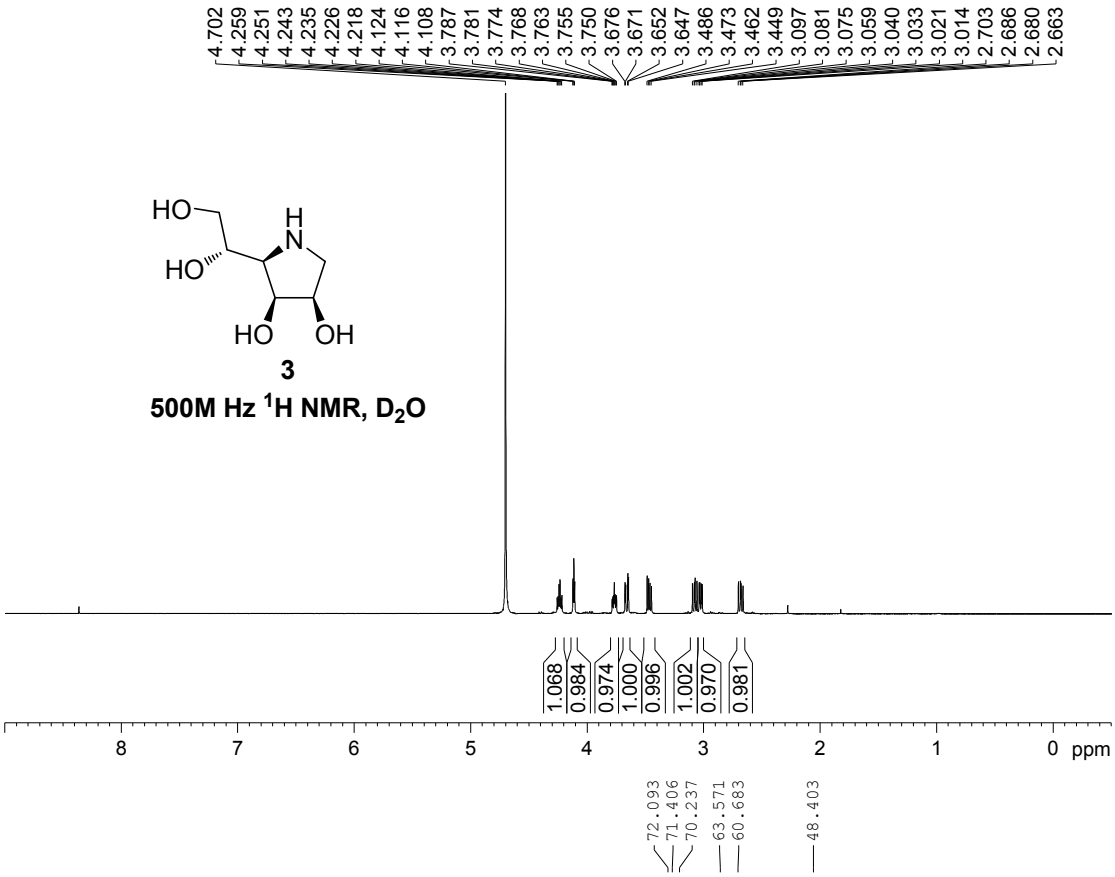
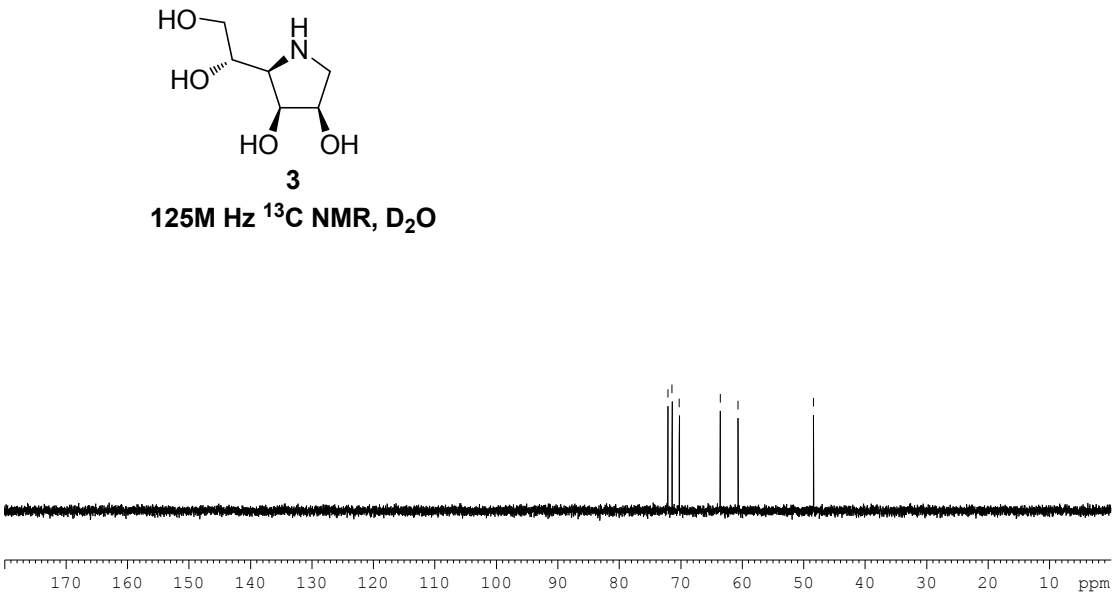
7.376
7.357
7.347
7.342
7.335
7.325
5.155
4.405
4.389
4.376
4.298
4.124
4.113
4.017
4.005
3.779
3.764
3.750
3.735
3.707
3.696
3.333
HO
Cbz
N
HO
HO
OH
14
400M Hz 1H NMR, MeOD
4.861
2.068
1.000
1.006
1.046
1.023
2.810
2.264
8
7
6
5
4
3
2
1
0 ppm


156.156
155.676
136.617
128.172
127.761
127.544
73.071
72.929
72.383
71.933
70.189
69.389
66.893
63.467
63.359
60.131
59.759
52.004
51.472
HO
Cbz
N
HO
HO
OH
14
125M Hz 13C NMR, MeOD
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10 ppm



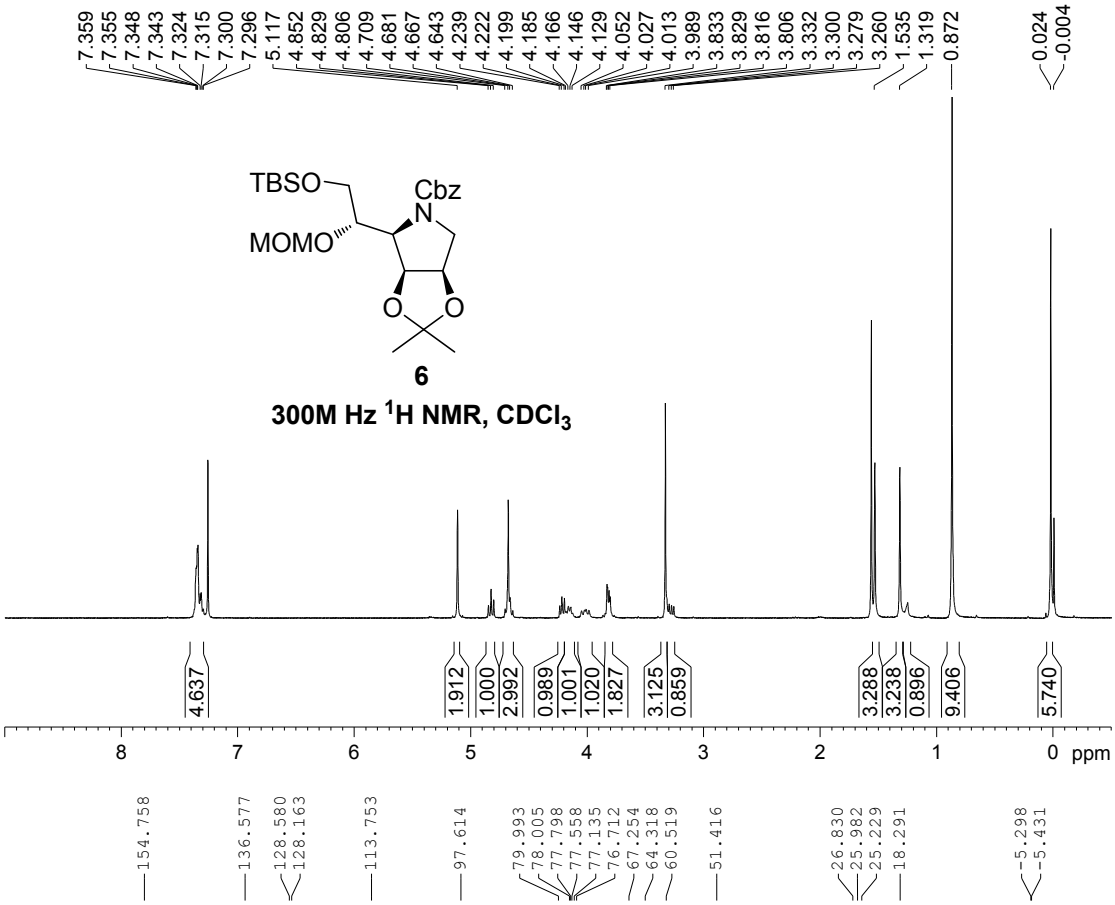
3

500M Hz ^{1}H NMR, D_2O



3

125M Hz ^{13}C NMR, D_2O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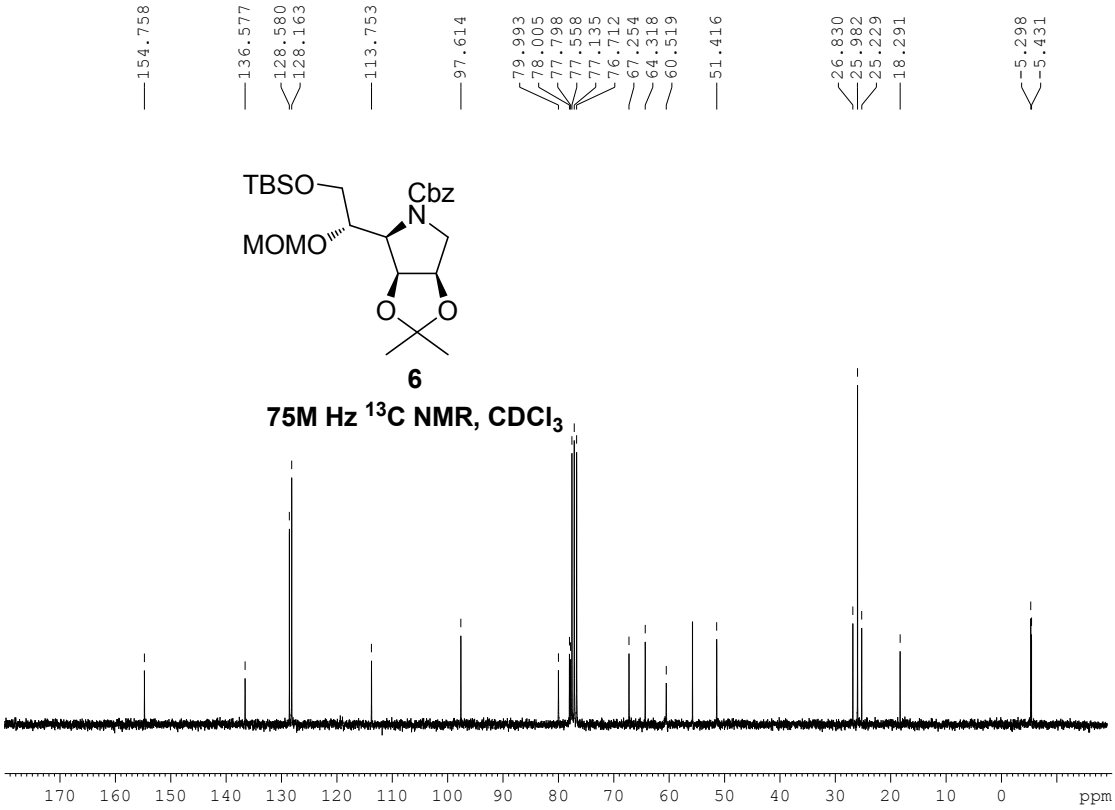
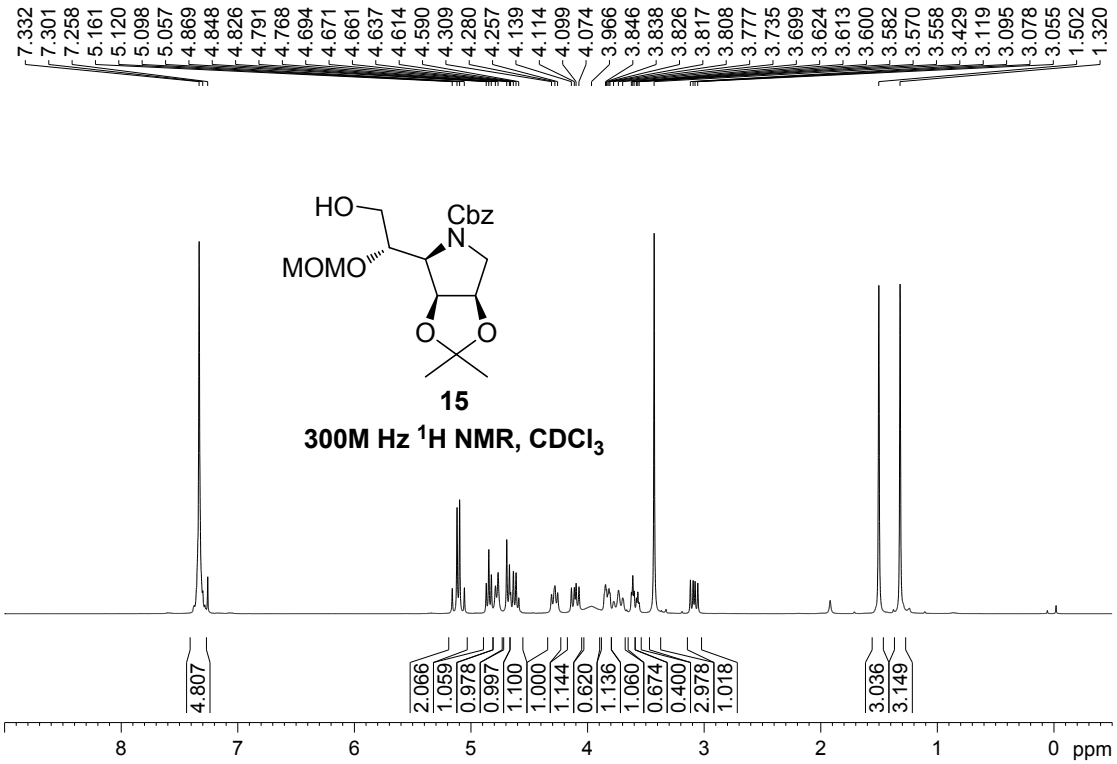
TBSO
Cbz
N
MOMO
O
O
6
300M Hz 1H NMR, CDCl3
4.637 1.912 1.000 2.992 0.989 1.001 1.020 1.827 3.125 0.859 3.288 3.238 0.896 9.406 5.740
8 7 6 5 4 3 2 1 0 ppm


154.758 136.577 128.580 128.163 113.753 97.614 79.993 78.005 77.798 77.558 77.135 76.712 67.254 64.318 60.519 51.416 26.830 25.982 25.229 18.291 -5.298 -5.431
TBSO
Cbz
N
MOMO
O
O
6
75M Hz 13C NMR, CDCl3
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


7.332
7.301
7.258
5.161
5.120
5.098
5.057
4.869
4.848
4.826
4.791
4.768
4.694
4.671
4.661
4.637
4.614
4.590
4.309
4.280
4.257
4.139
4.114
4.099
4.074
3.966
3.846
3.838
3.826
3.817
3.808
3.777
3.735
3.699
3.624
3.613
3.600
3.582
3.570
3.558
3.429
3.119
3.095
3.078
3.055
1.502
1.320
HO
Cbz
N
MOMO
O
O
15
300M Hz 1H NMR, CDCl3
4.807
2.066
1.059
0.978
0.997
1.100
1.000
1.144
0.620
1.136
1.060
0.674
0.400
2.978
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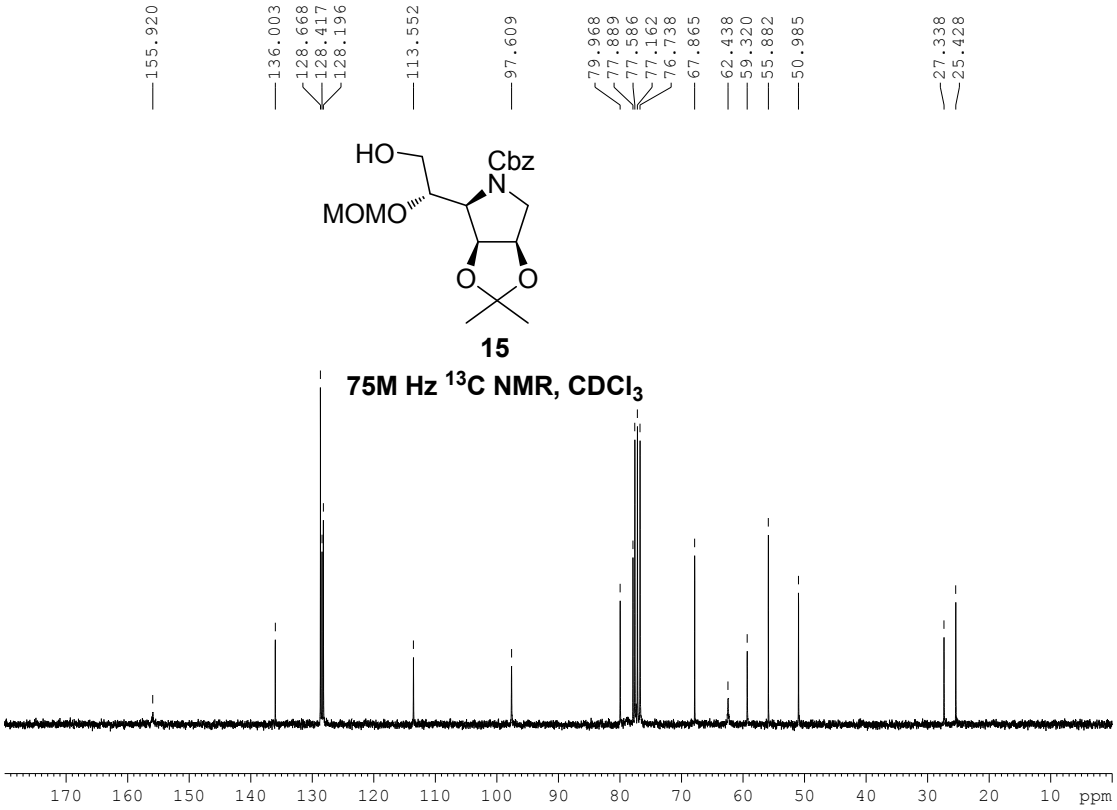
3.036
3.149
8
7
6
5
4
3
2
1
0 ppm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136.003
128.668
128.417
128.196
113.552
97.609
79.968
77.889
77.586
77.162
76.738
67.865
62.438
59.320
55.882
50.985
27.338
25.428
HO
Cbz
N
MOMO
O
O
15
75M Hz 13C NMR, CDCl3
170
160
150
140
130
120
110
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90
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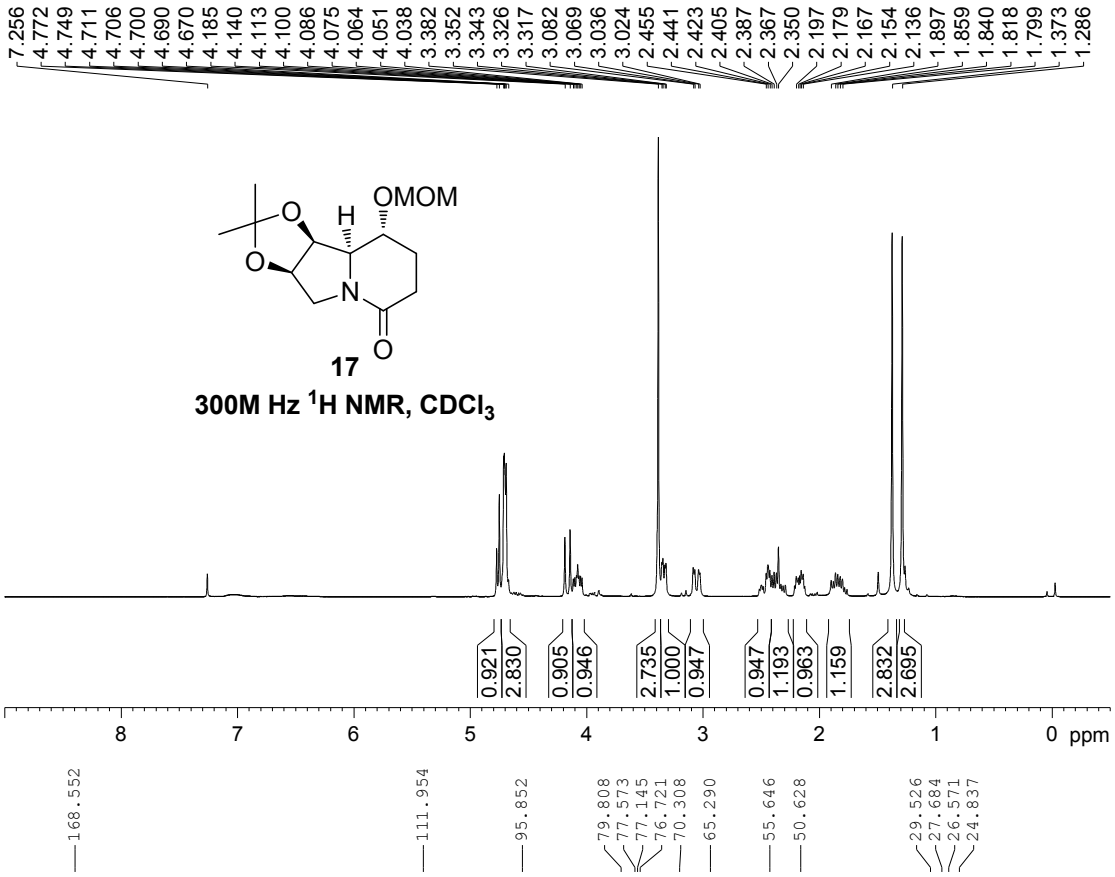
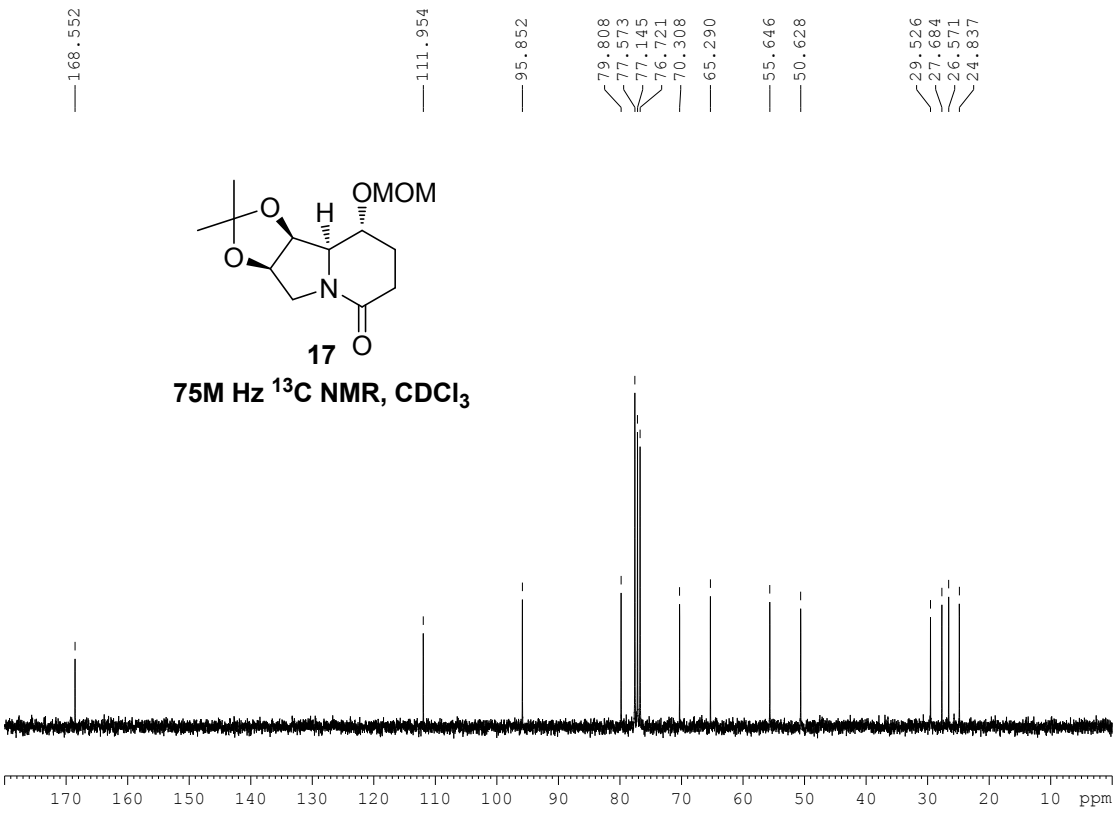
70
60
50
40
30
20
10 ppm


7.256 4.772 4.749 4.711 4.706 4.700 4.690 4.670 4.185 4.140 4.113 4.100 4.086 4.075 4.064 4.051 4.038 3.382 3.352 3.343 3.326 3.317 3.082 3.069 3.036 3.024 2.455 2.441 2.423 2.405 2.387 2.367 2.350 2.197 2.179 2.167 2.154 2.136 1.897 1.859 1.840 1.818 1.799 1.373 1.286
OMOM
H
O
O
N
O
17
300M Hz 1H NMR, CDCl3
0.921 2.830 0.905 0.946 2.735 1.000 0.947 0.947 1.193 0.963 1.159 2.832 2.695
8 7 6 5 4 3 2 1 0 ppm


168.552 111.954 95.852 79.808 77.573 77.145 76.721 70.308 65.290 55.646 50.628 29.526 27.684 26.571 24.837
OMOM
H
O
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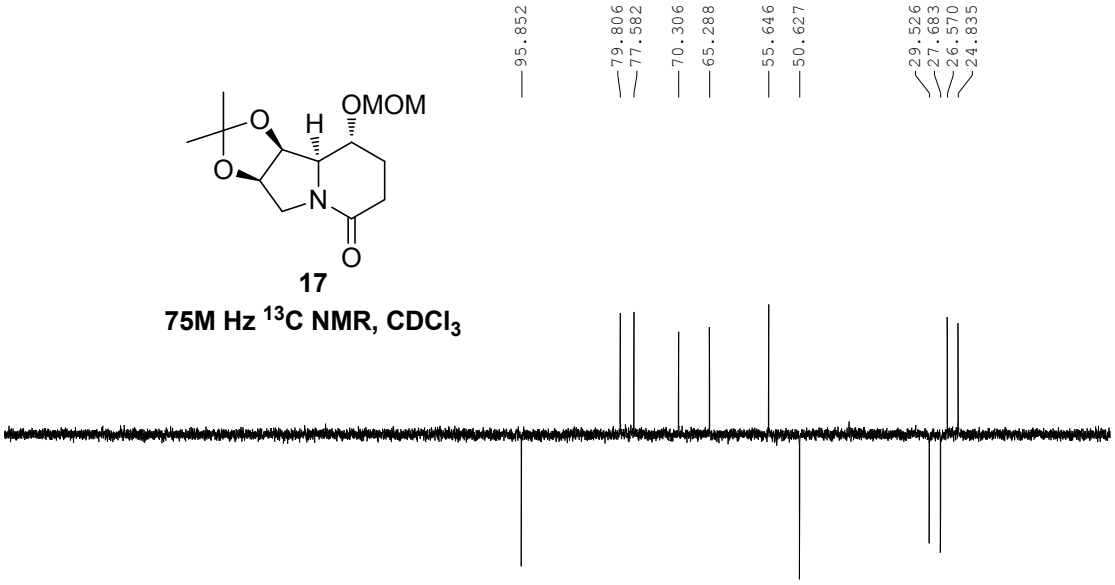
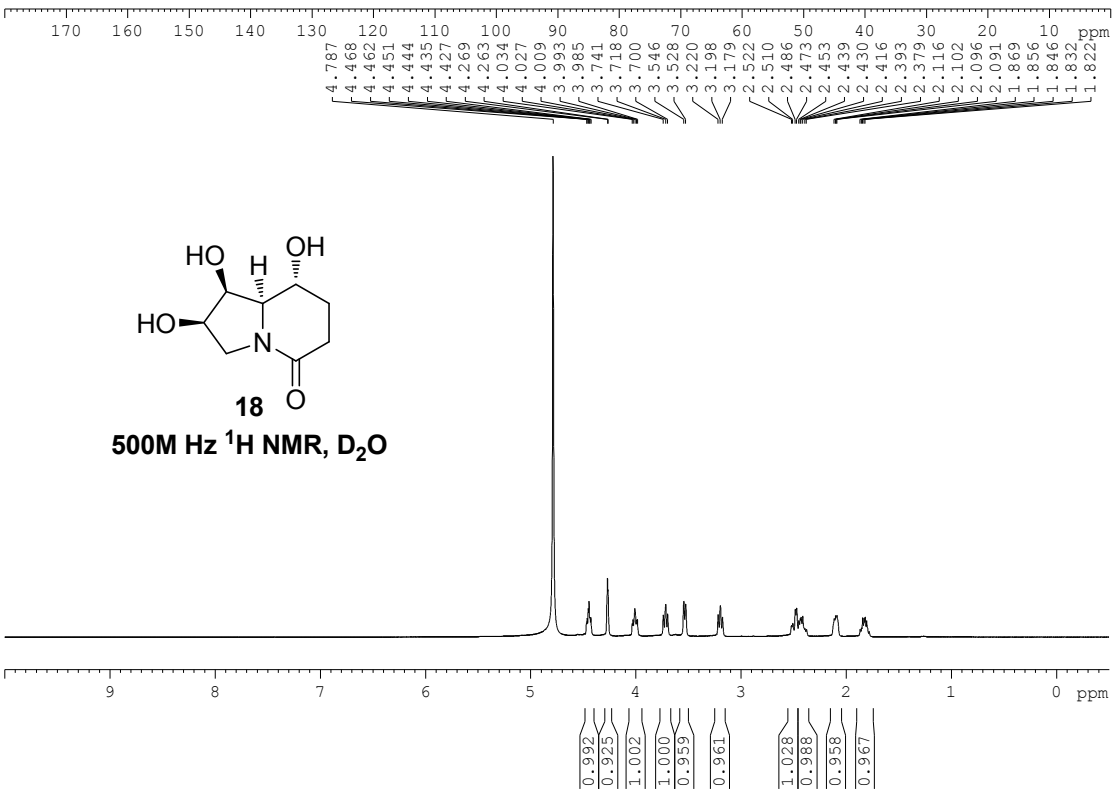
17
75M Hz 13C NMR, CDCl3
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


95.852
79.806
77.582
70.306
65.288
55.646
50.627
29.526
27.683
26.570
24.835
OMOM
H
O
O
N
O
17
75M Hz 13C NMR, CDCl3
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


4.787
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4.444
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4.427
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3.993
3.985
3.741
3.718
3.700
3.546
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3.220
3.198
3.179
2.522
2.510
2.486
2.473
2.453
2.439
2.430
2.416
2.393
2.379
2.116
2.102
2.096
2.091
1.869
1.856
1.846
1.832
1.822
HO
H
OH
HO
N
O
18
500M Hz 1H NMR, D2O
9 8 7 6 5 4 3 2 1 0 ppm
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0.925
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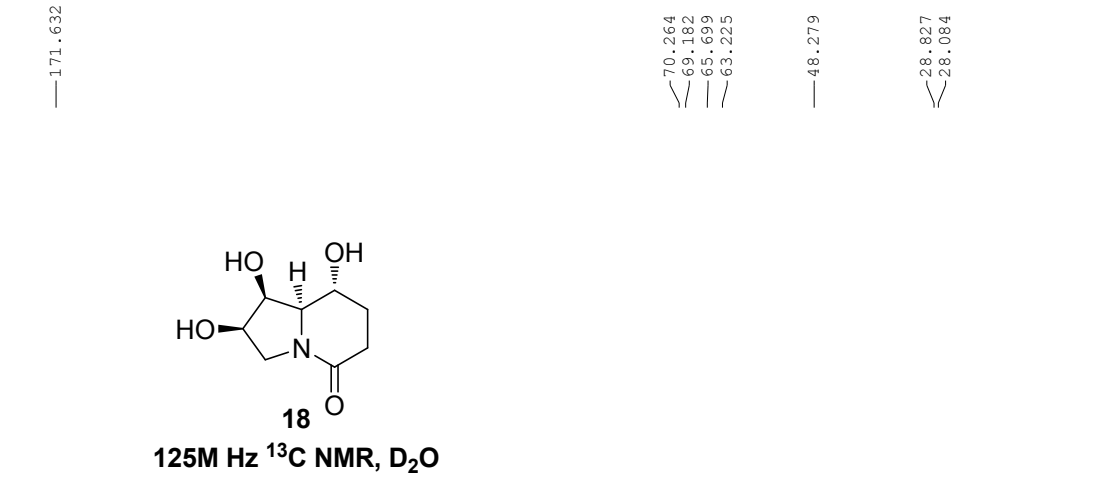
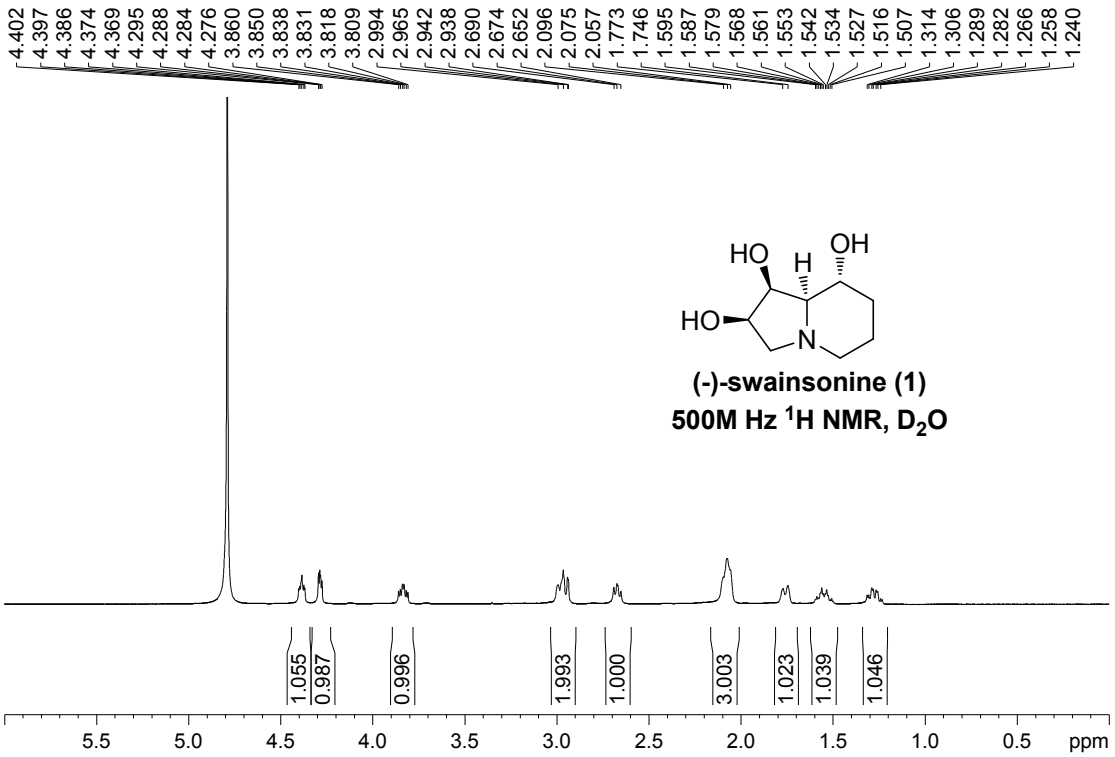
1.000
0.959
0.961
1.028
0.988
0.958
0.967



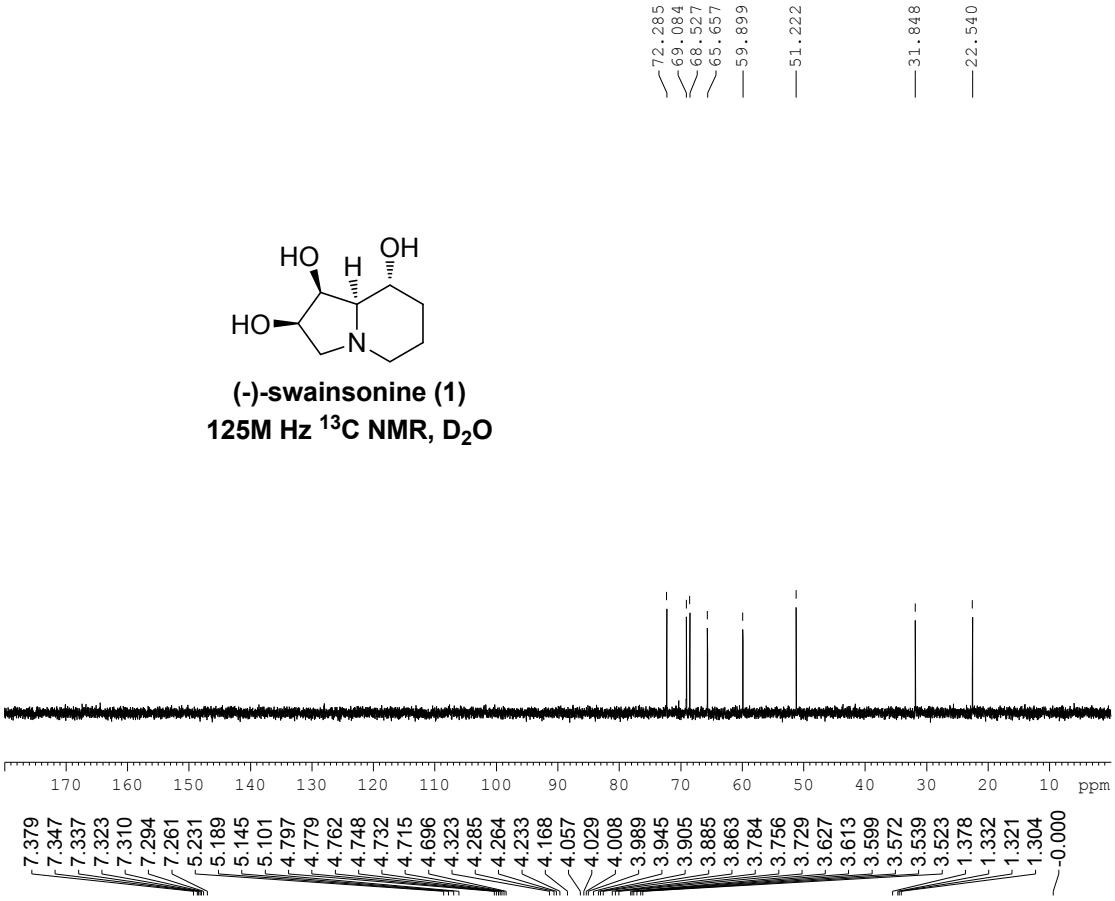
18

125M Hz ^{13}C NMR, D_2O

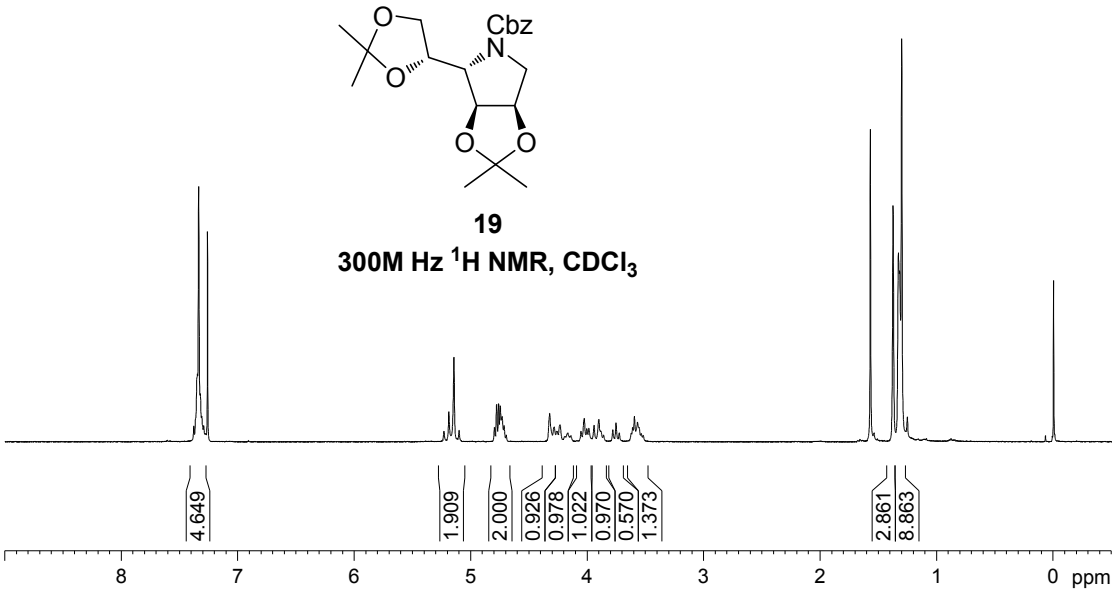


(-)-swainsonine (1)

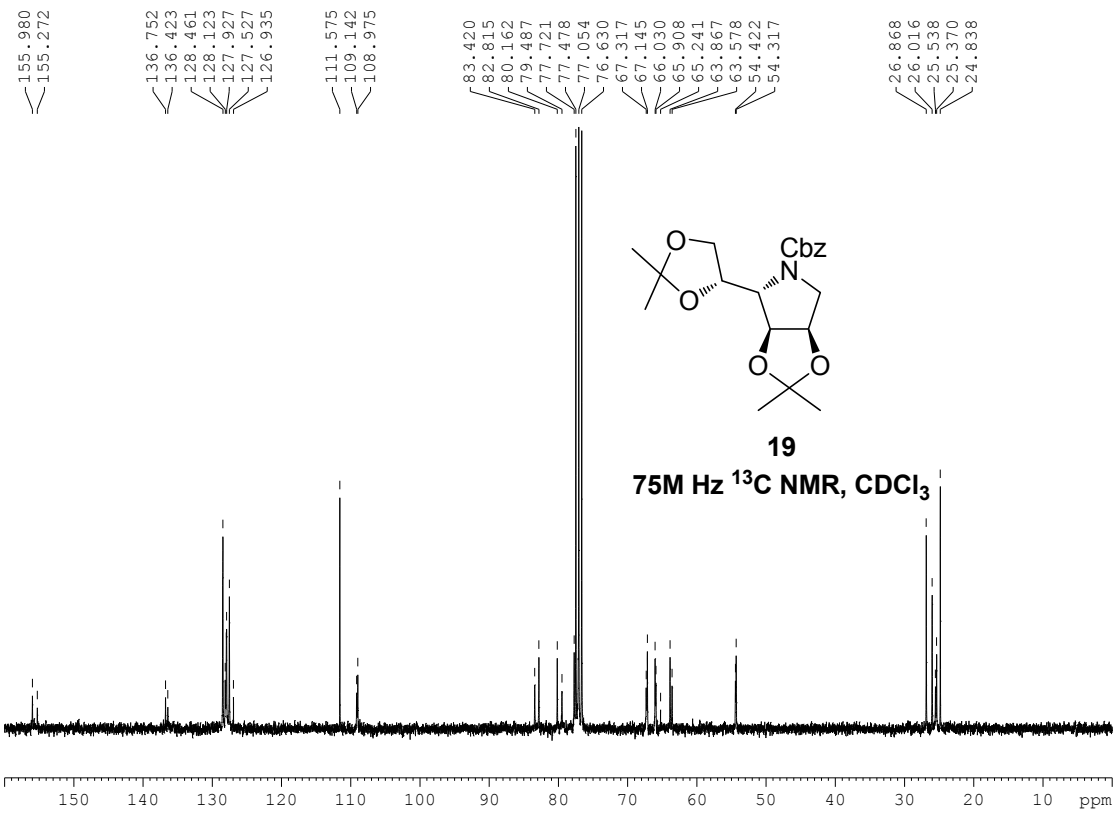
500M Hz ^{1}H NMR, D_2O



(-)-swainsonine (1)
125M Hz ^{13}C NMR, D_2O

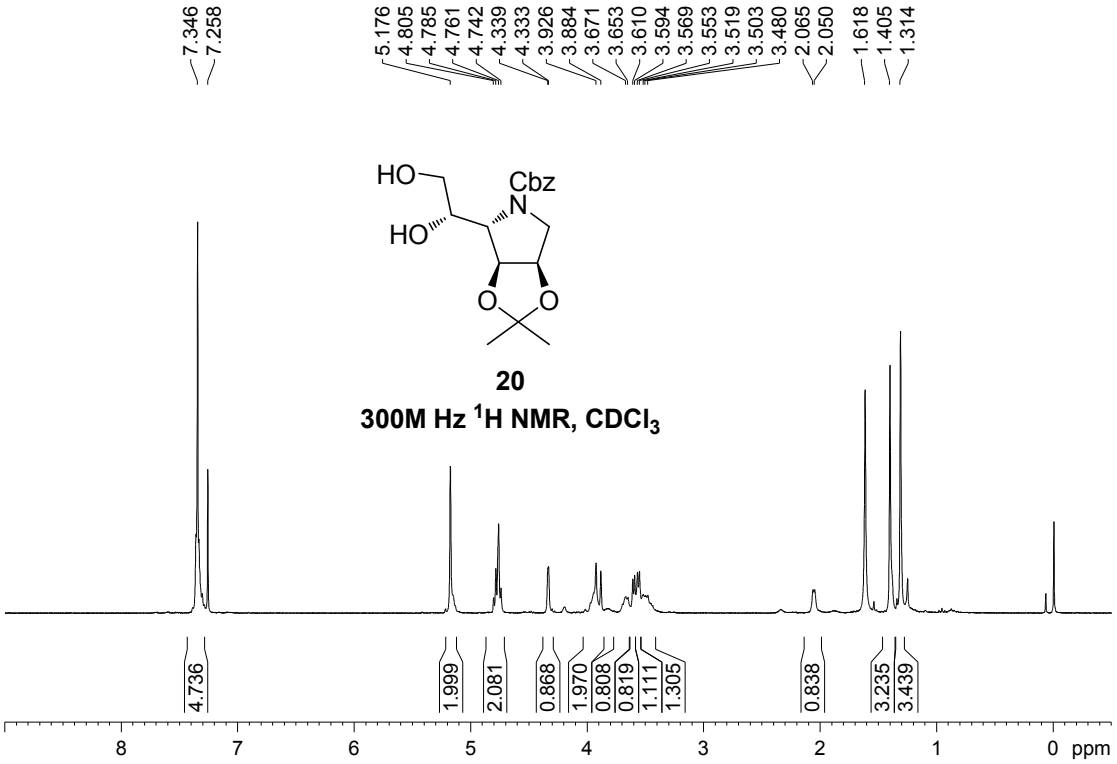


19
300M Hz ^{1}H NMR, $CDCl_3$



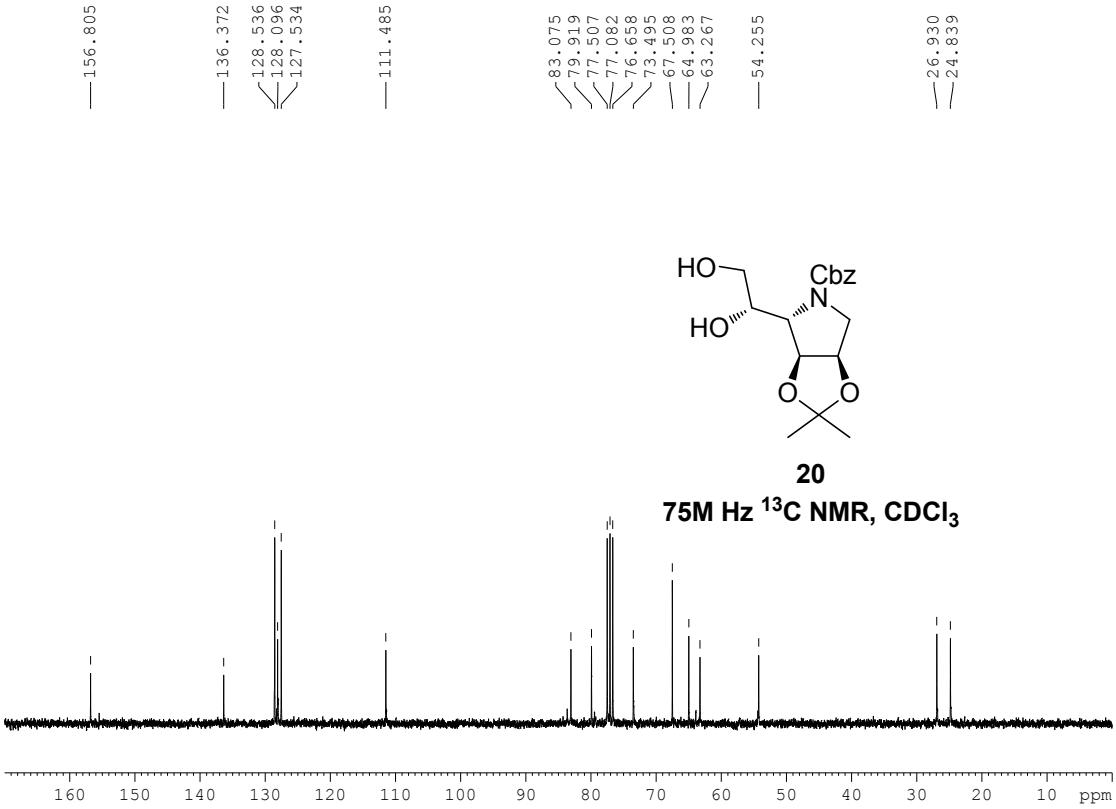
19

75M Hz ^{13}C NMR, $CDCl_3$



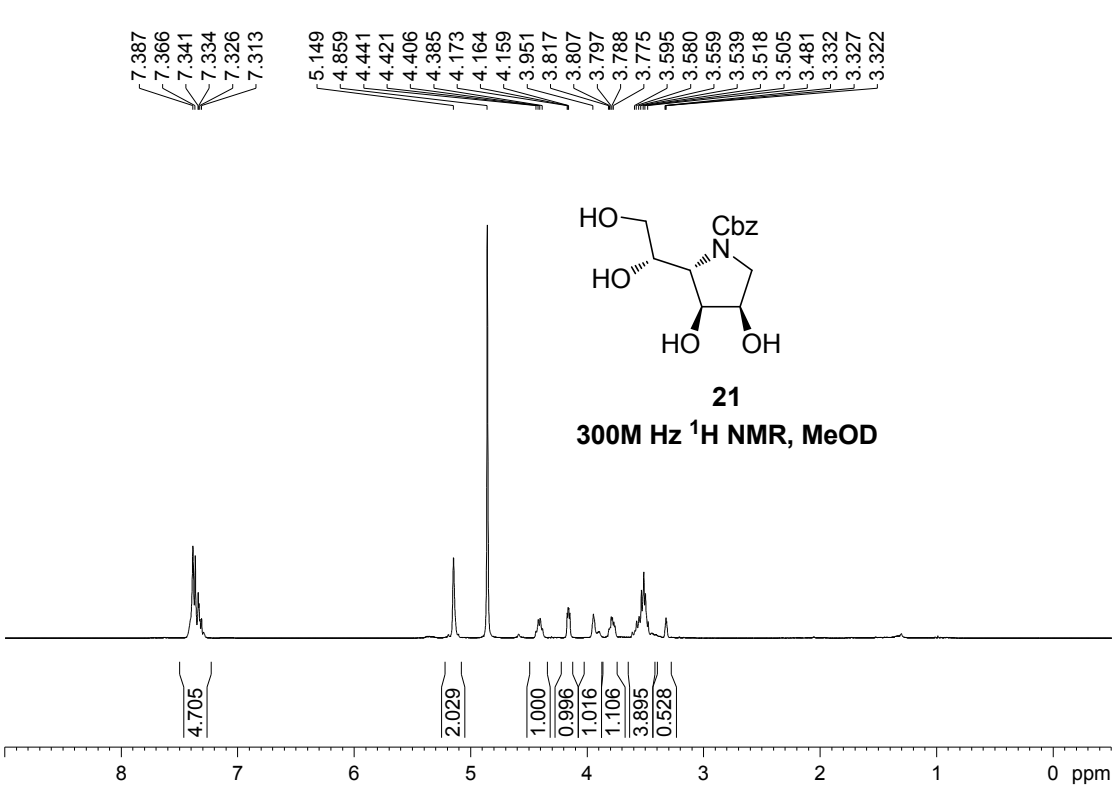
20

300M Hz ^{1}H NMR, $CDCl_3$



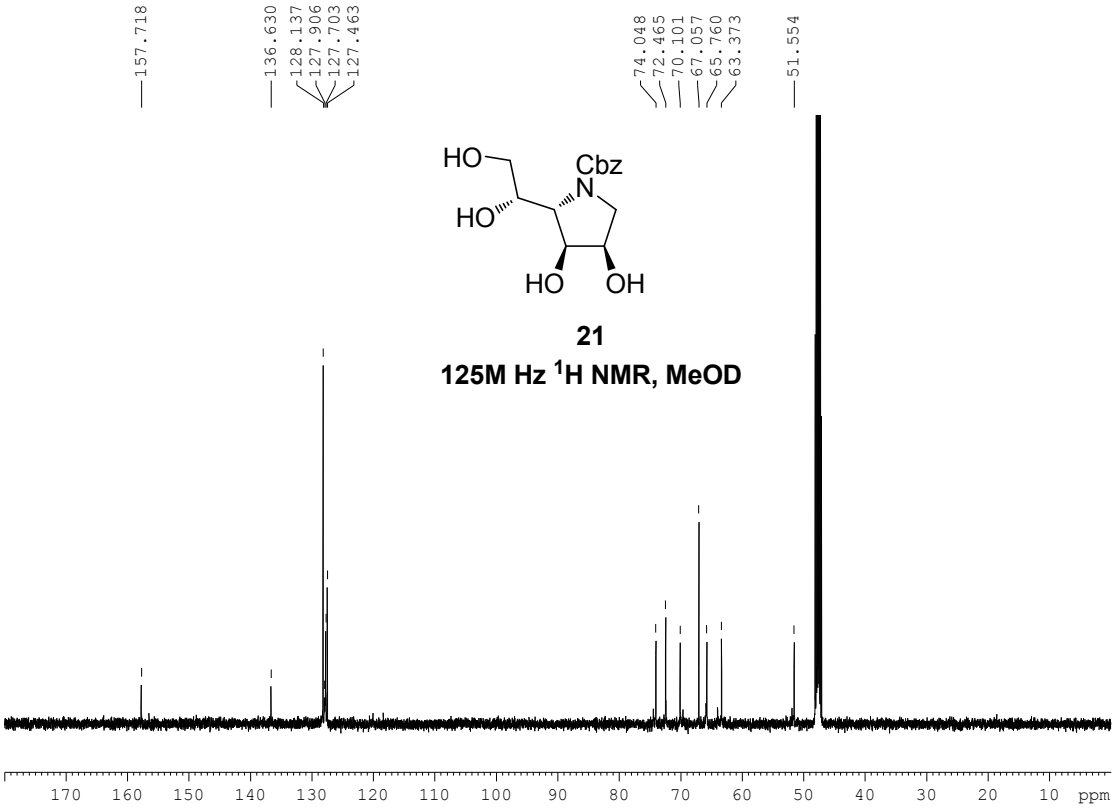
20

75M Hz ^{13}C NMR, $CDCl_3$



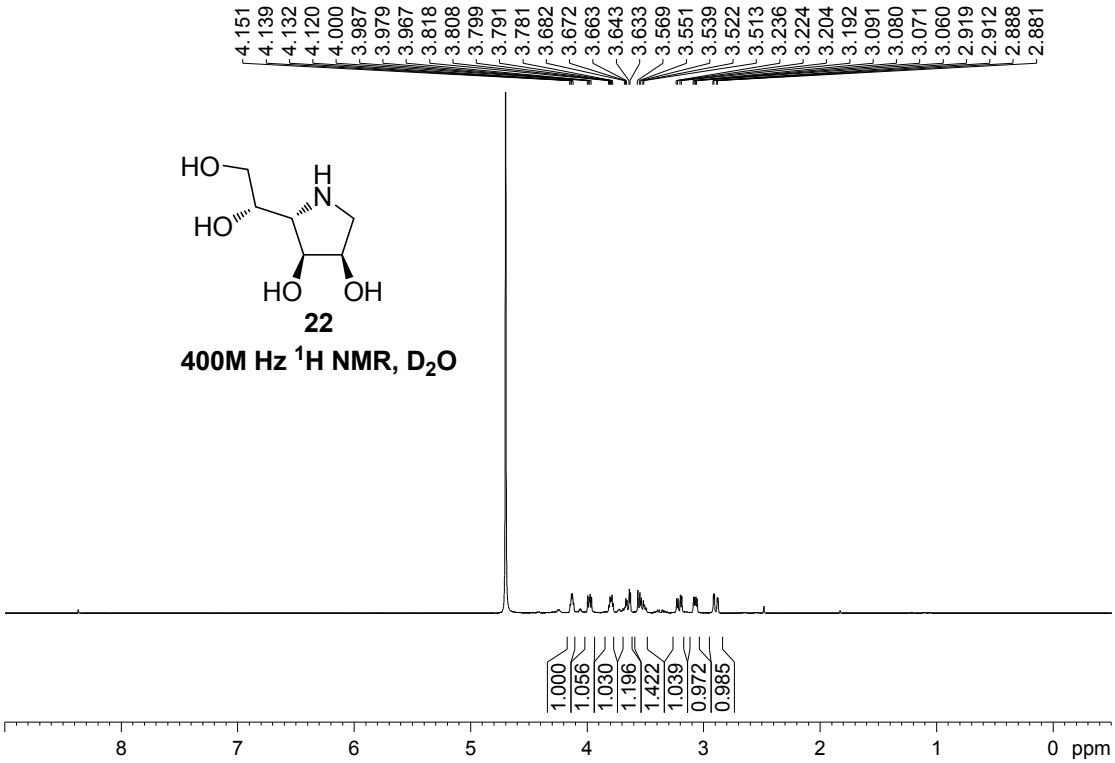
21

300M Hz ^{1}H NMR, MeOD



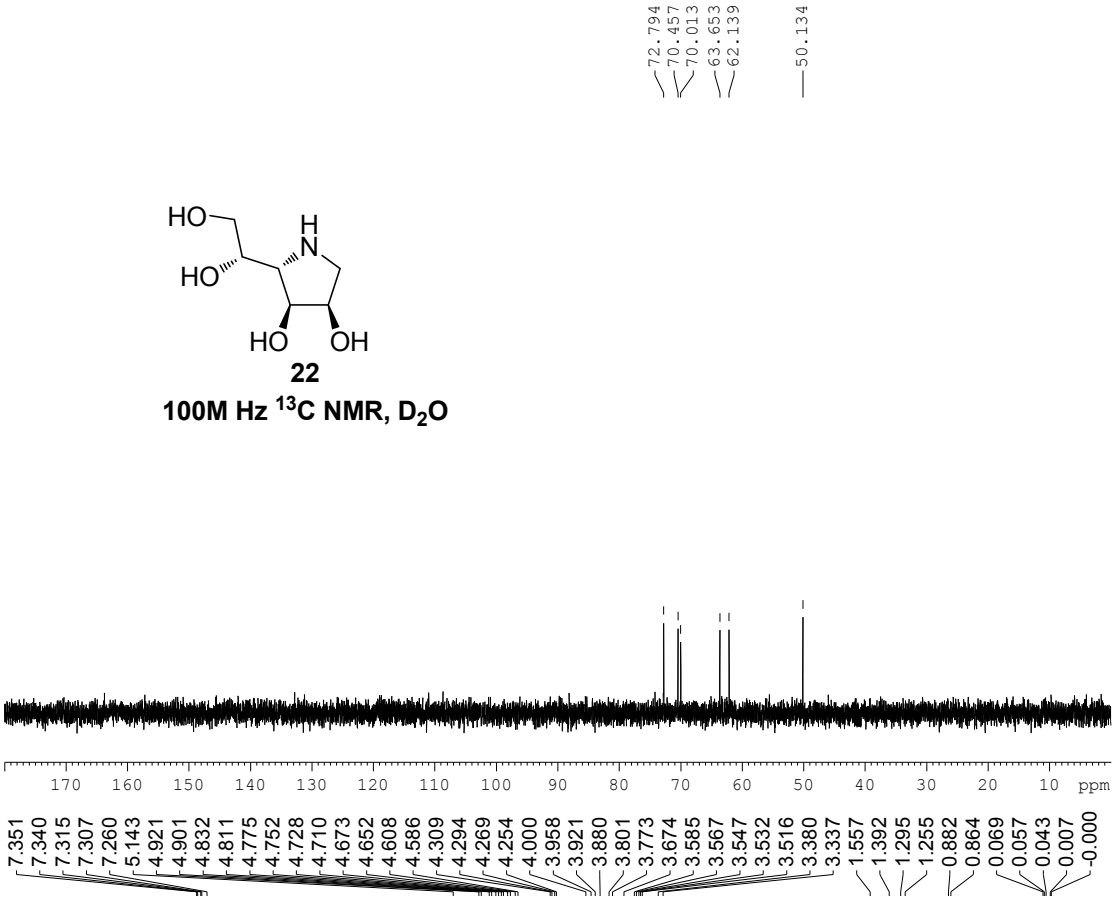
21

125M Hz ^{1}H NMR, MeOD



22

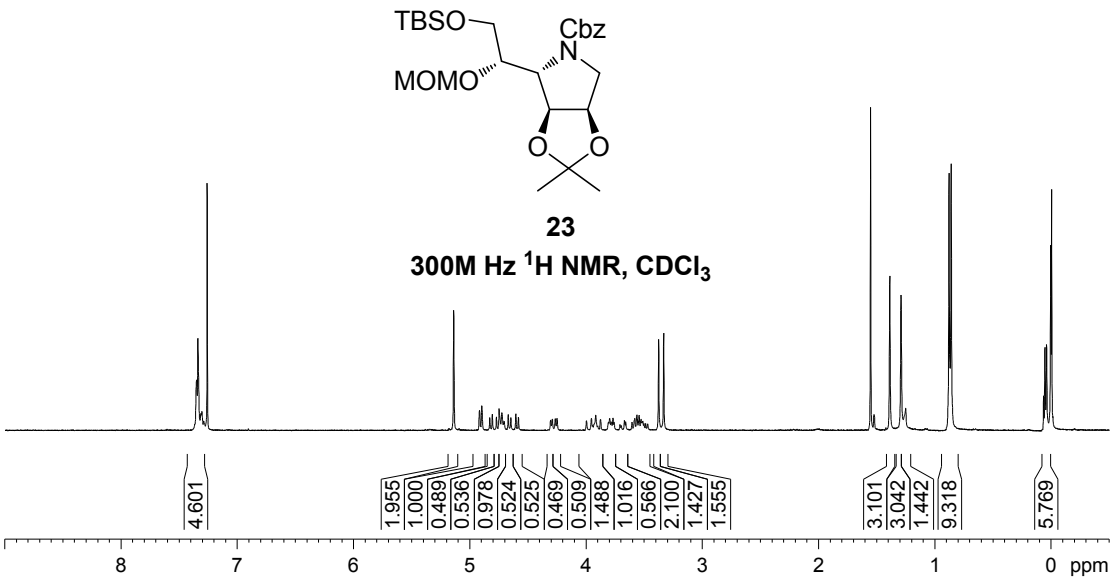
400M Hz ^{1}H NMR, D_2O



HO
HO
H
N
HO
OH

22

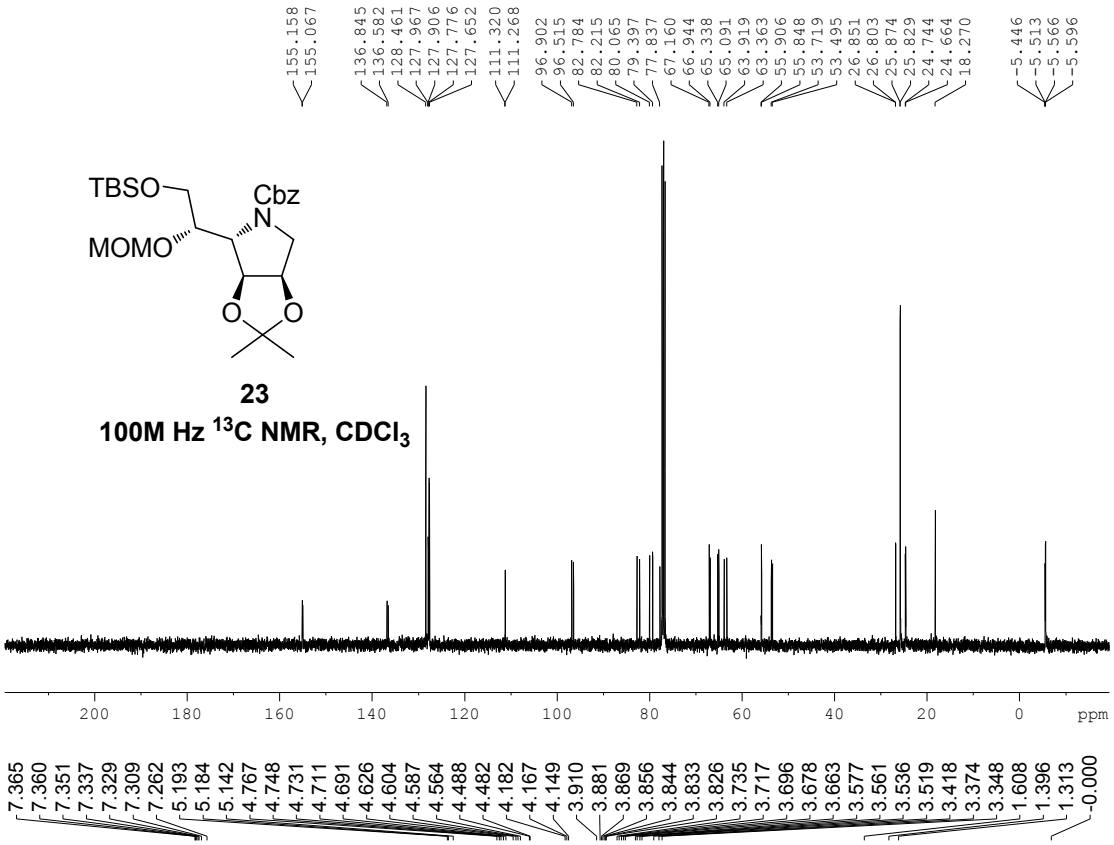
100M Hz ^{13}C NMR, D_2O



TBSO
Cbz
N
MOMO
O
O

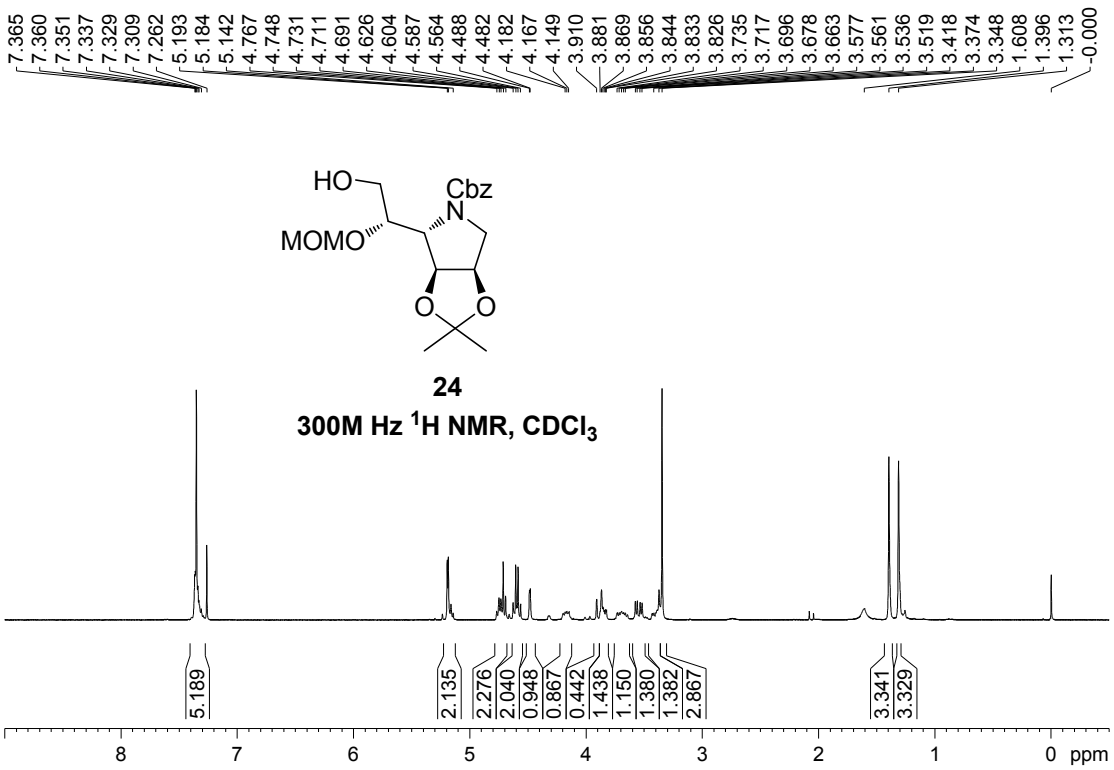
23

300M Hz ^{1}H NMR, $CDCl_3$



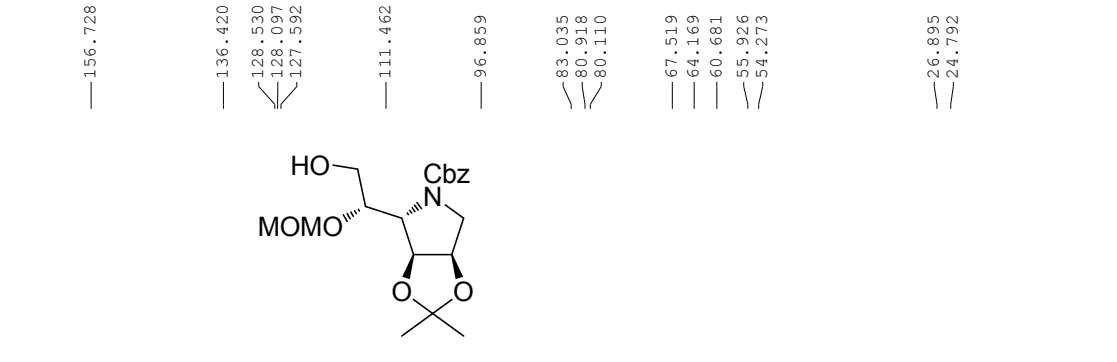
23

100M Hz ^{13}C NMR, $CDCl_3$



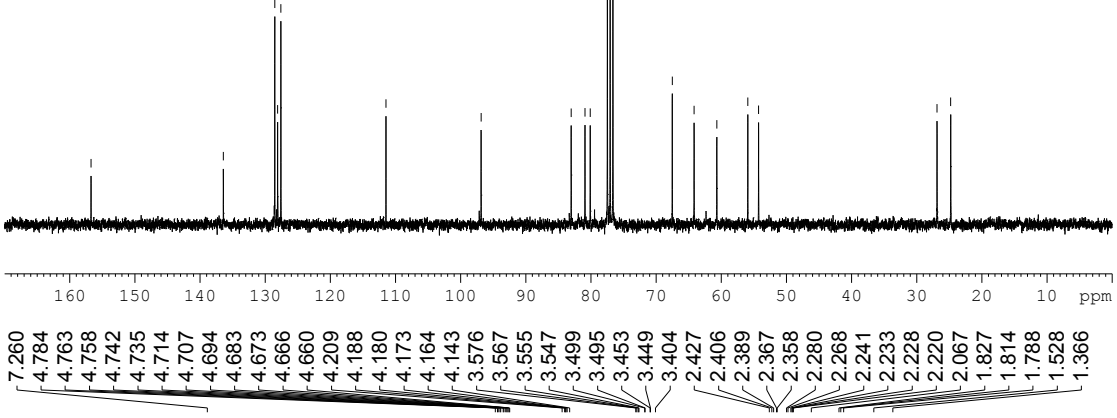
24

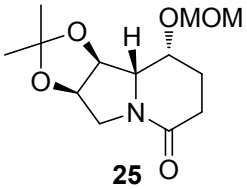
300M Hz ^{1}H NMR, $CDCl_3$



24

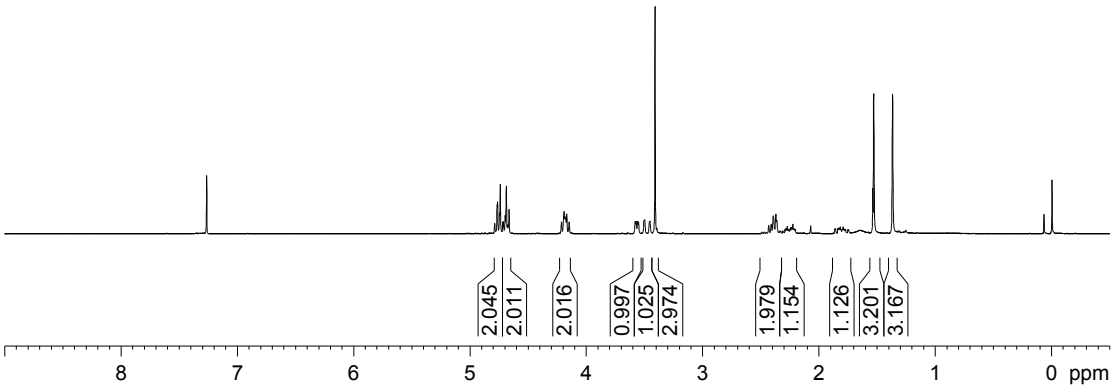
75M Hz ^{13}C NMR, $CDCl_3$

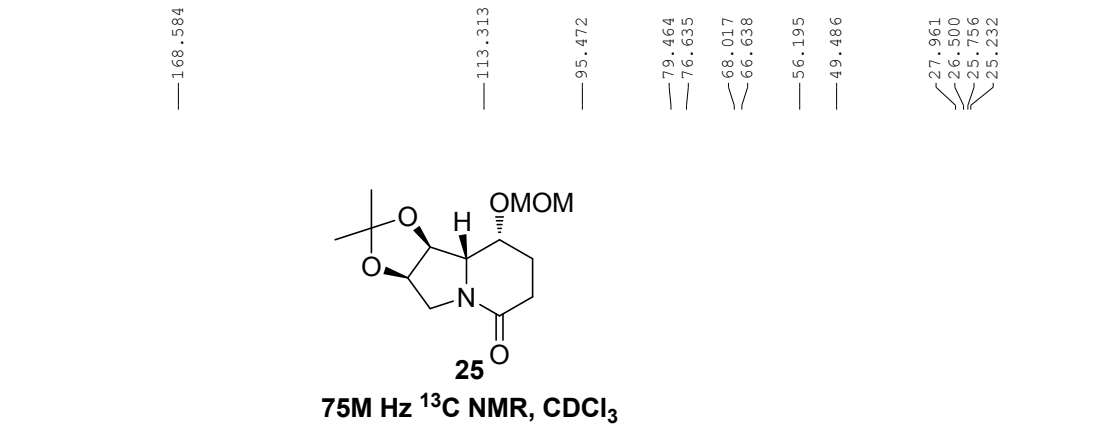




25

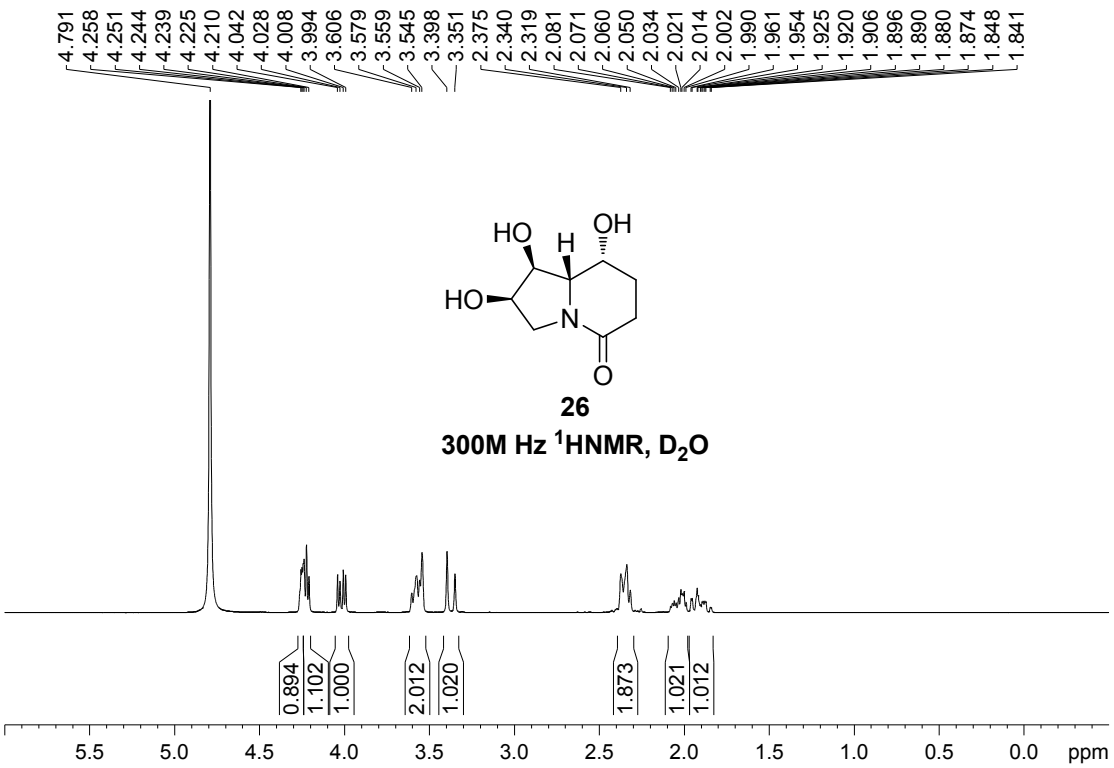
300M Hz ^{1}H NMR, $CDCl_3$





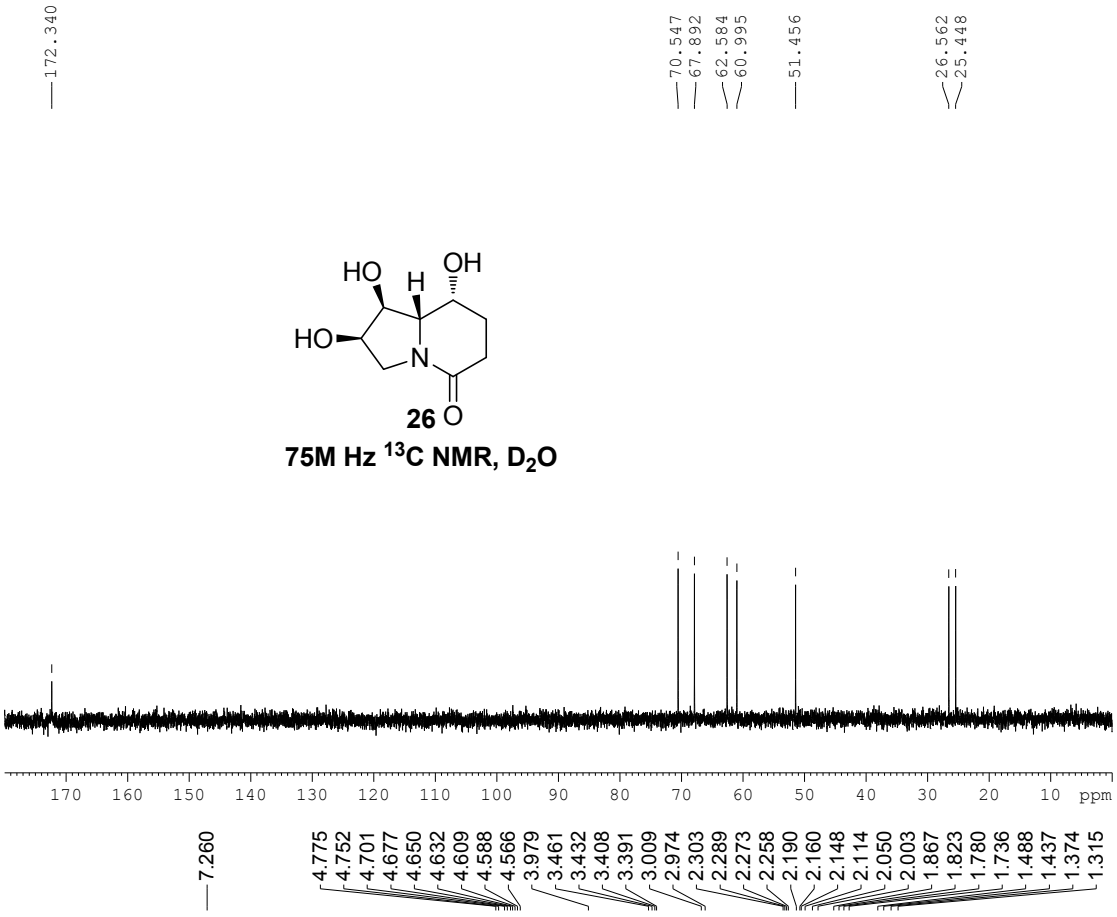
25

75M Hz ^{13}C NMR, $CDCl_3$

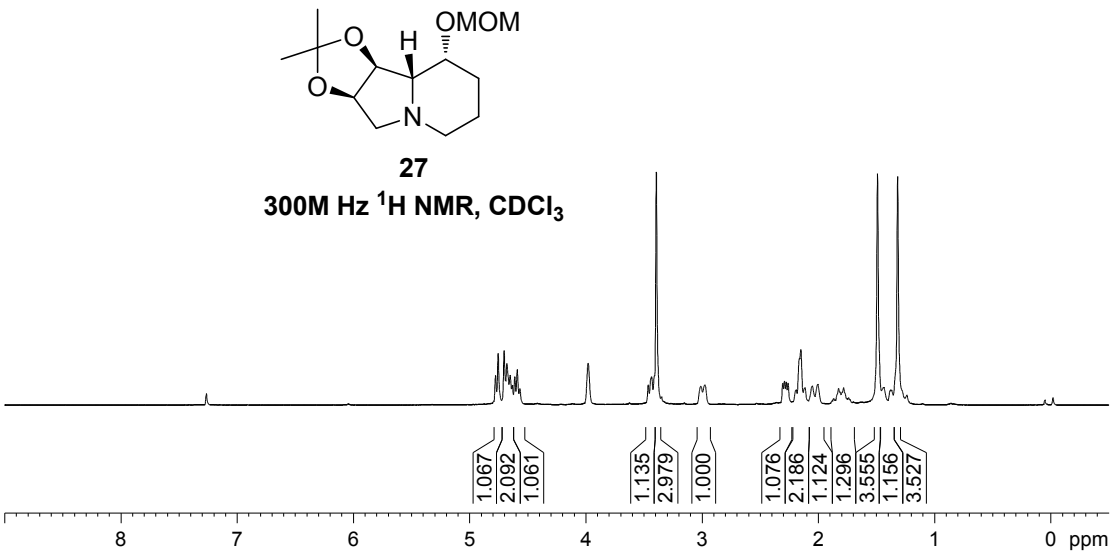


26

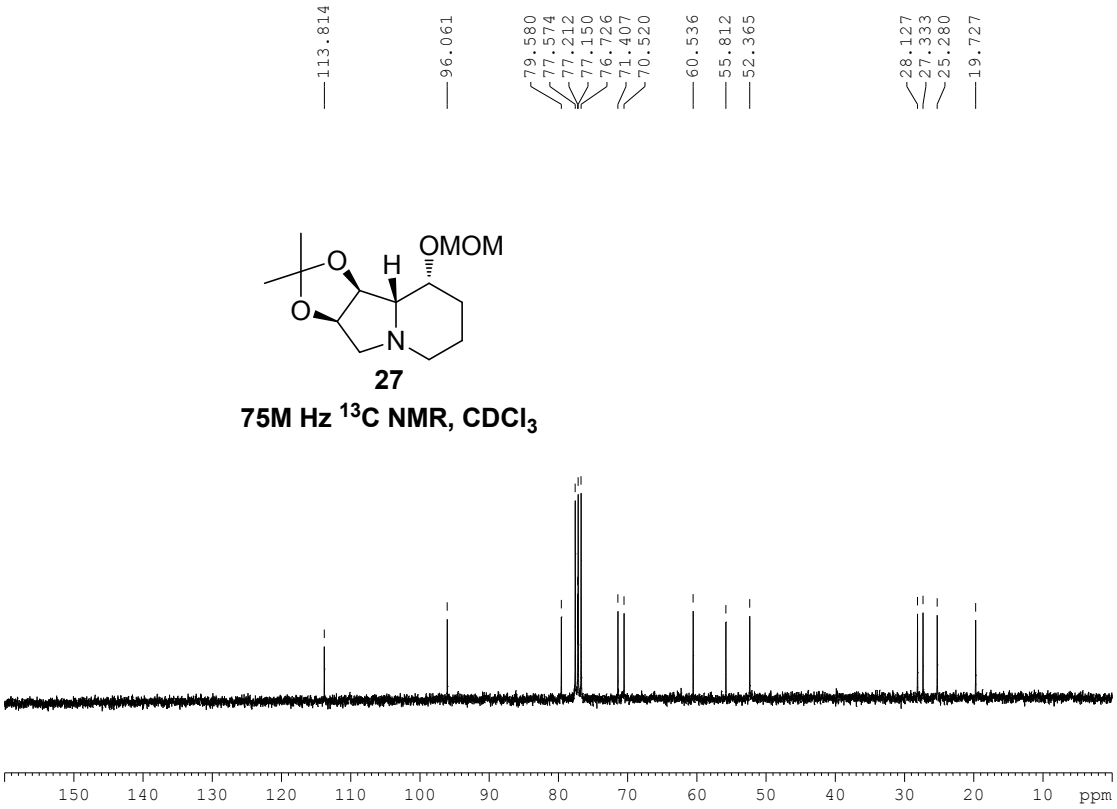
300M Hz ^{1}HNMR, D_2O

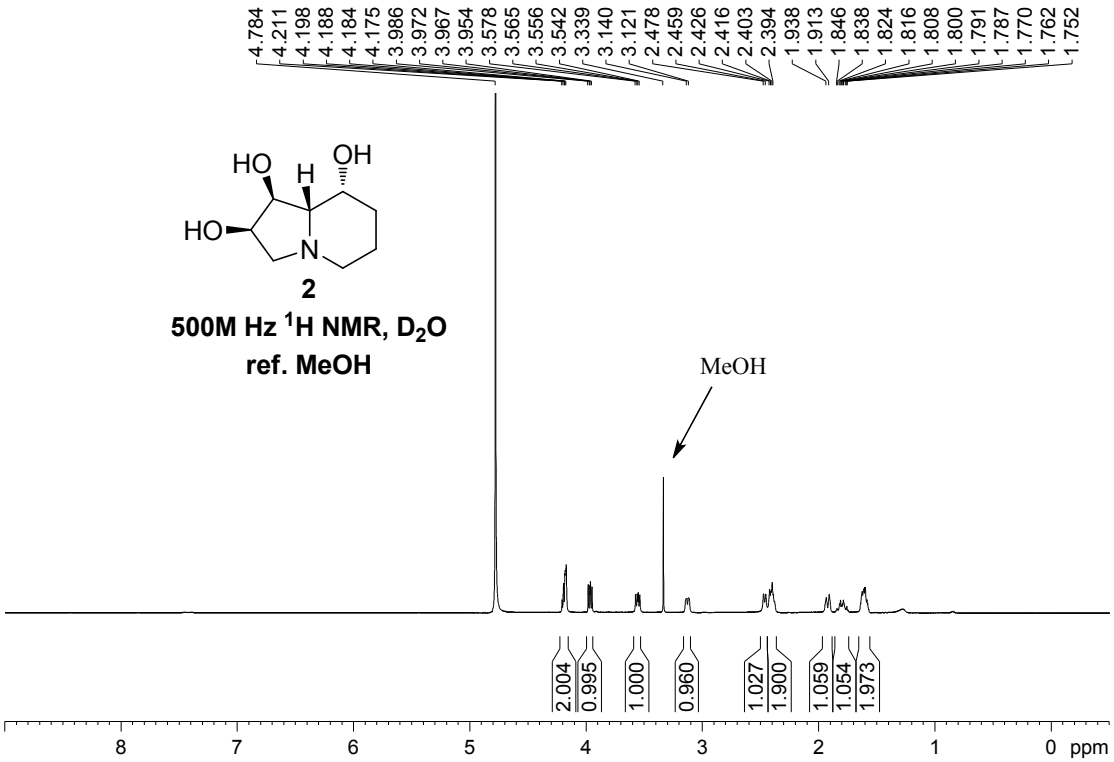


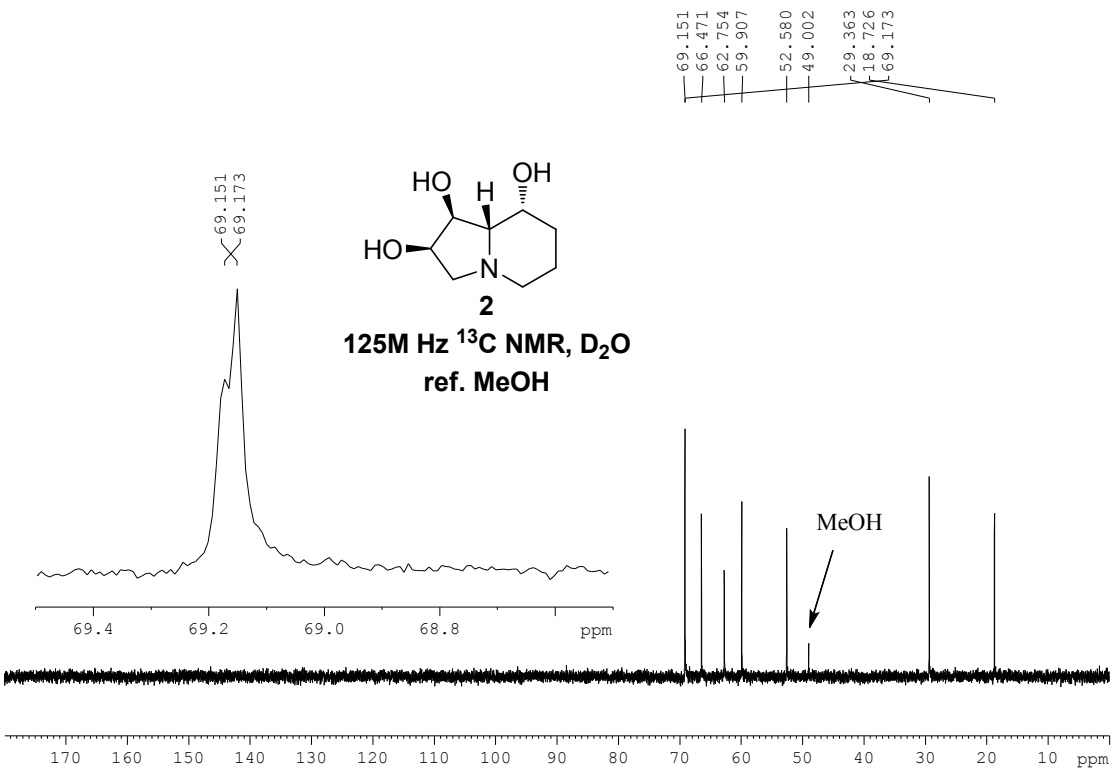
75M Hz ^{13}C NMR, D_2O



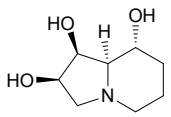
300M Hz ^{1}H NMR, $CDCl_3$


113.814
96.061
79.580
77.574
77.212
77.150
76.726
71.407
70.520
60.536
55.812
52.365
28.127
27.333
25.280
19.727
OMOM
H
O
O
N
27
75M Hz 13C NMR, CDCl3
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


4.784
4.211
4.198
4.188
4.184
4.175
3.986
3.972
3.967
3.954
3.578
3.565
3.556
3.542
3.339
3.140
3.121
2.478
2.459
2.426
2.416
2.403
2.394
1.938
1.913
1.846
1.838
1.824
1.816
1.808
1.800
1.791
1.787
1.770
1.762
1.752
HO
H
OH
HO
N
2
500M Hz 1H NMR, D2O
ref. MeOH
MeOH
2.004
0.995
1.000
0.960
1.027
1.900
1.059
1.054
1.973
8 7 6 5 4 3 2 1 0 ppm



2. Comparison of the synthetic samples with literature



(-)-swainsonine
1

Table 1 Comparison of the synthetic (-)-swainsonine (**1**) with natural product (^{1}H NMR)

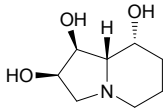
(-)-swainsonine(lit.[a])	(-)-swainsonine(lit.[b])	Synthetic sample(**1**)
4.42-4.17 (m, 2H)	4.44-4.18 (m, 2H)	4.42 – 4.35 (m, 1H)
3.79 (ddd, *J* = 9-10, 10, 4-5Hz, 1H)	3.80 (ddd, 1H)	4.29 (dd, J = 5.7, 3.6 Hz, 1H)
		3.83 (dt, *J* = 10.7, 4.6 Hz, 1H)
2.85 (m, 2H)	2.89 (dd, 2H)	2.99-2.94 (m, 2H)
2.50 (dd, *J* = 11, 6Hz, 1H)	2.53 (dd, 1H)	2.67 (dd, *J* = 10.9,8.25 Hz, 1H)
		2.14 – 2.02 (m, 3H)
2.13-0.94 (m, 6H)	2.14-0.98 (m, 6H)	1.76 (d, *J* = 13.8 Hz, 1H)
		1.55 (qt, *J* = 5.7, 3.6 Hz, 1H)
		1.31-1.23 (m, 1H)

Table 2 Comparison of the synthetic (-)-swainsonine (**1**) with natural product (^{13}C NMR)

(-)-swainsonine(lit.[a])	(-)-swainsonine(lit.[b])	Synthetic sample(**1**)	$\Delta\delta_1$ (relative to lit[a])	$\Delta\delta_2$ (relative to lit[b])
72.55	72.56	72.29	0.26	0.27
69.42	69.42	69.08	0.34	0.34
68.74	68.77	68.53	0.21	0.24
66.07	66.06	65.66	0.41	0.40
60.38	60.38	59.90	0.48	0.48
51.33	51.38	51.22	0.11	0.16
32.16	32.21	31.85	0.31	0.36
22.89	22.89	22.54	0.35	0.35

(a) S. M. Colegate, P. R. Dorling and C. R. Huxtable, *Aust. J. Chem.*, 1979, **32**, 2257-2264.

(b) M. J. Schneider, F. S. Ungemach, H. P. Broquist and T. M. Harris, *Tetrahedron*, 1983, **39**, 29-32.



2

8a-*epi*-swainsonine

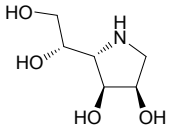
Table 3 Comparison of the synthetic (-)-8a-*epi*-swainsonine (**2**) with literature (^{1}H NMR)

(-)-8a-*epi*-swainsonine (lit[a])	Synthetic sample(**2**)
4.32 (q, J = 6.6 Hz, 1H)	4.25-4.12 (m, 2H)
4.10 (m, 1H)	3.97 (dd, J = 9.4, 6.7 Hz, 1H)
3.91 (dd, J = 9.0, 6.6 Hz, 1H)	3.56 (dd, J = 11.2, 6.7 Hz, 1H)
3.39 (dd, J = 10.2, 6.6 Hz, 1H)	3.18 – 3.03 (m, 1H)
2.95 (dd, J = 10.2, 1.8 Hz, 1H)	2.47 (d, J = 9.2 Hz, 1H)
2.14 (dd, J = 10.2, 6.6 Hz, 1H)	2.42 (d, J = 5.0 Hz, 1H)
2.10 (m, 2H)	2.41 – 2.35 (m, 1H)
1.87-1.90 (m, 1H)	1.99 – 1.88 (m, 1H)
1.69-1.77 (m, 1H)	1.85-1.75 (m, 1H)
1.50-1.58 (m, 2H)	1.68 – 1.51 (m, 2H)

Table 4 Comparison of the synthetic (-)-8a-swainsonine (**2**) with literature (^{13}C NMR)

(-)-8a-swainsonine (lit[a])	Synthetic sample(**2**)	$\Delta\delta$
70.7	69.2	-1.5
70.5	69.15	-1.4
67.7	66.5	-1.2
64.4	62.8	-1.6
61.4	59.9	-1.5
53.4	52.6	-0.8
30.9	29.4	-1.5
20.1	18.7	-1.4

(a) J. N. Abrams, R. S. Babu, H. Guo, D. Le, J. Le, J. M. Osbourn and G. A. O'Doherty, *J. Org. Chem.*, 2008, **73**, 1935-1940



22

Table 5 Comparison of the synthetic compound (**22**) with literature (^{1}H NMR)

Literature	Synthetic sample(**22**)
3.95 (dt, H-2, 1H)	4.14 (dd, J = 7.7, 4.7 Hz, 1H)
3.78 (dd, H-3, $J_{2,3}$ = 5.2 Hz, 1H)	3.98 (dd, J = 8.2, 4.9 Hz, 1H)
3.62 (m, H-5, 1H)	3.85 – 3.76 (m, 1H)
3.57 (dd, H-6', $J_{5,6'}$ =4.1 Hz, 1H)	3.65 (dd, J = 11.8, 3.9 Hz, 1H)
3.40 (dd, H-6, $J_{6,6'}$ = 11.8 Hz**,** $J_{5,6}$ = 7.7Hz, 1H)	3.55 (dd, J = 11.8, 7.0 Hz, 1H)
3.02 (dd, H-1', $J_{1',2}$ = 5.1 Hz, 1H)	3.21 (dd, J = 12.6, 4.8 Hz, 1H)
2.78 (dd, H-4, $J_{3,4}$ = 7.9 Hz, $J_{4,5}$ = 4.2 Hz, 1H)	3.08 (dd, J = 8.2, 4.2 Hz, 1H)
2.62 (dd, H-1, $J_{1,1'}$ = 12.5 Hz, $J_{1,2}$ = 3.4 Hz, 1H)	2.90 (dd, J = 12.6, 2.8 Hz, 1H)

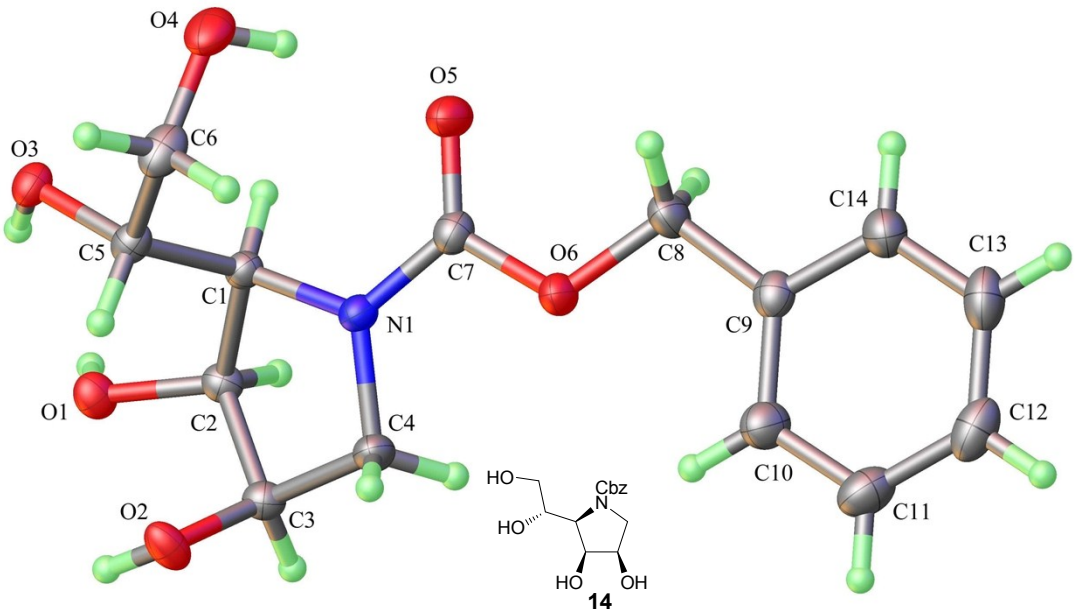
G. W. J. Fleet, J. C. Son, D. S. C. Green, I. C. di Bello and B. Winchester, *Tetrahedron*, 1988, **44**, 2649-2655.

Table 6 Comparison of the synthetic compound (**22**) with literature (^{13}C NMR)

Literature	Synthetic sample(**2**)	Δδ
72.2	72.8	0.6
69.3	70.5	1.2
67.8	70.0	2.2
63.1	63.7	0.6
61.9	62.1	0.2
49.9	50.1	0.2

B. Chandrasekhar, A. Madhan and B. V. Rao, *Tetrahedron*, 2007, **63**, 8746-8751

3. X-Ray ellipsoid plots of 14



Single-crystal X-ray diffraction data on compounds **14** was collected using MoKα radiation (λ =0.71073 Å) and a Bruker APEX 2 CCD area detector. Crystals were prepared for data collectionby coating with high viscosity microscope oil (Paratone-N, Hampton Research). The oil-coated crystal was placed on a MicroMesh mount (MiTeGen, Ithaca, NY) and transferred immediately to the diffractometer. Data collection temperature is as indicated in the followed information. Corrections were applied for Lorentz polarization, and absorption effects.

Table 7. Crystal data and structure refinement for **14**.

Identification code	sa4435	
Empirical formula	C14 H19 N O6	
Formula weight	297.30	
Temperature	173.1500 K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 5.6525(14) Å	α= 90°.
	b = 7.679(2) Å	β= 90°.
	c = 32.488(9) Å	γ = 90°.
Volume	1410.1(6) $Å^3$	
Z	4	
Density (calculated)	1.400 Mg/m^3	
Absorption coefficient	0.110 mm^{-1}	

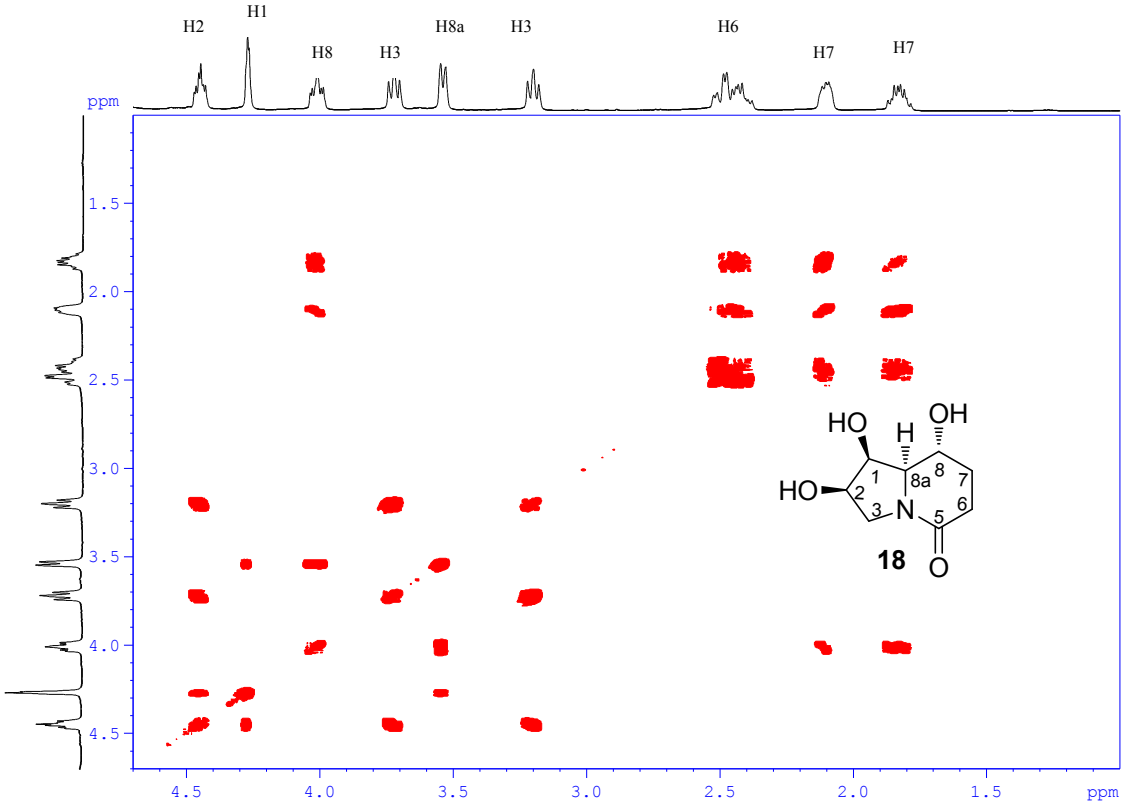
F (000)	632
Crystal size	0.37 x 0.31 x 0.07 mm^3
Theta range for data collection	3.252 to 27.472°.
Index ranges	-6<=h<=7, -9<=k<=9, -41<=l<=42
Reflections collected	9818
Independent reflections	3185 [R (int) = 0.0296]
Completeness to theta = 26.000°	98.2 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.0000 and 0.8182
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3185 / 0 / 206
Goodness-of-fit on F^2	1.117
Final R indices [I>2sigma (I)]	R1 = 0.0337, wR2 = 0.0726
R indices (all data)	R1 = 0.0350, wR2 = 0.0733
Absolute structure parameter	-0.1(4)
Extinction coefficient	n/a
Largest diff. peak and hole	0.187 and -0.161 e.$Å^{-3}$

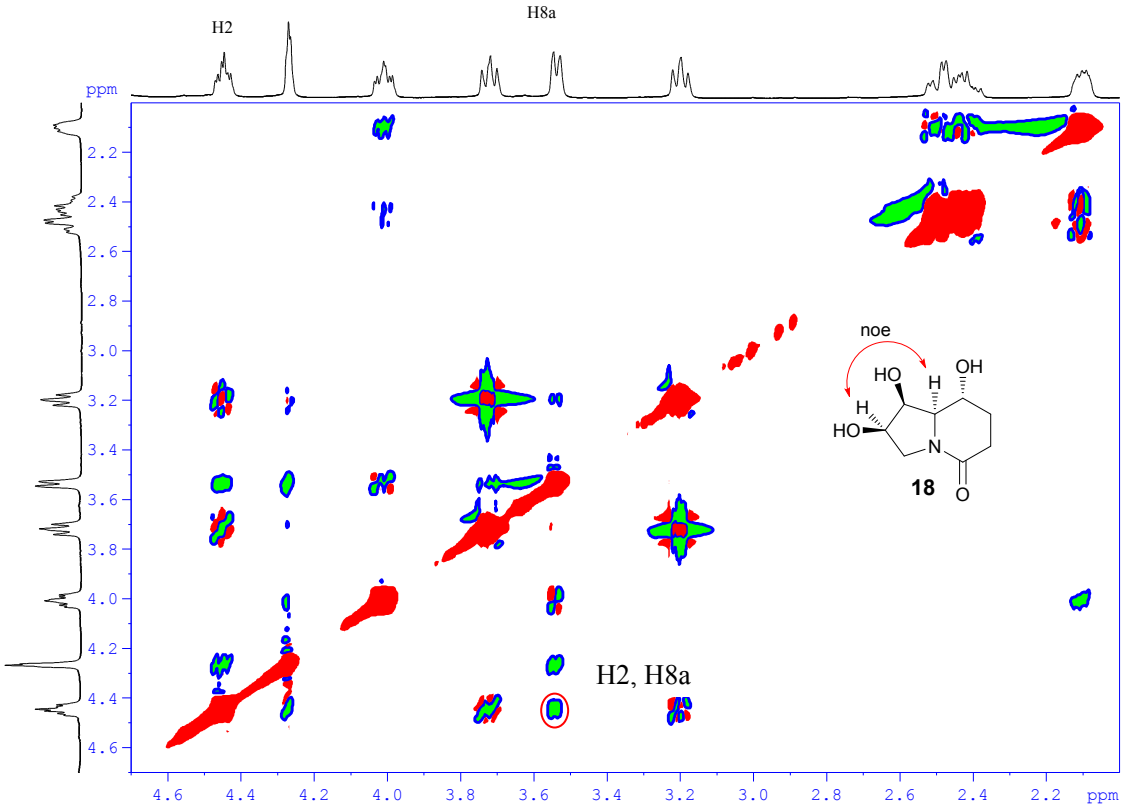
Table 8. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **14**. U (eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O1	7385(2)	1851(2)	2675(1)	23(1)
O2	3504(2)	2424(2)	3156(1)	25(1)
O3	8221(2)	5357(2)	2499(1)	22(1)
O4	9771(3)	7897(2)	3083(1)	36(1)
O5	10800(3)	6064(2)	3801(1)	31(1)
O6	8409(2)	4848(2)	4279(1)	26(1)
N1	7743(3)	4282(2)	3617(1)	20(1)
C1	8444(3)	4140(2)	3182(1)	18(1)
C2	7810(3)	2220(2)	3096(1)	19(1)
C3	5594(3)	1867(2)	3355(1)	21(1)
C4	5959(3)	2976(3)	3739(1)	24(1)
C5	7163(3)	5450(2)	2901(1)	20(1)
C6	7399(4)	7323(2)	3043(1)	29(1)
C7	9121(3)	5130(2)	3887(1)	22(1)
C8	9937(4)	5571(3)	4590(1)	28(1)
C9	8822(3)	5286(2)	5006(1)	24(1)

C10	6801(4)	4295(3)	5065(1)	31(1)
C11	5867(4)	4102(3)	5460(1)	36(1)
C12	6919(4)	4897(3)	5794(1)	36(1)
C13	8929(4)	5889(3)	5736(1)	36(1)
C14	9874(4)	6082(3)	5346(1)	31(1)

4. COSY & NOESY analysis of compound 18

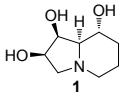
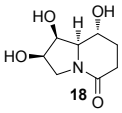
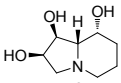
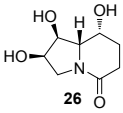
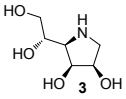
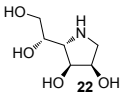




5. Results of the bioassay

The enzymes *α*-glucosidases (from yeast, rice and rat intestinal maltase), *β*-glucosidases (from almond and bovine liver), *α*-galactosidase (from coffee beans), *β*-galactosidase (from bovine liver), *α*-mannosidase (from jack beans), *β*-mannosidase (from snail), *α*-L-fucosidase (from bovine kidney), *α*,*α*-trehalase (from porcine kidney), amyloglucosidase (from Aspergillus niger), *α*-L-rhamnosidase (from Penicillium decumbens) and β-glucronidase (from *E. coli* and Bovine liver) were purchased from Sigma-Aldrich Chemical Co. (St. Louis, Mo. USA). Brush border membranes prepared from rat small intestine according to the method of Kessler *et al.*[1] were assayed at pH 5.8 for rat intestinal maltase using maltose. The released D-glucose was determined colorimetrically using the Glucose CII-test Wako (Wako Pure Chemical Ind.; Osaka, Japan). Other glycosidase activities were determined using an appropriate p-nitrophenyl glycoside as substrate. The reaction was stopped by adding 400 mM Na_2CO_3. The released p-nitrophenol was measured spectrometrically at 400 nm. The assay results are summarized in the following Table.

Table 9. Concentration of iminosugars giving 50% inhibition of various glycosidase

	 1	 18	 2	 26	 3	 22
α-Glucosidase						
Yeast	NIa (0.3%)b	NI (5.4%)	NI (13.4%)	NI (5.6%)	68.4	NI (4.9%)
Rice	NI (45.3%)	NI (0%)	NI (3.7%)	NI (3.4%)	NI (38.7%)	NI (17%)
Rat intestinal maltase	NI (42.9%)	NI (6.8%)	NI (17.4%)	NI (4.2%)	NI (31.6%)	NI (28.1%)
β-Glucosidase						
Almond	NI (1.2%)	NI (6.6%)	NI (0%)	NI (6.2%)	NI (20.2%)	NI (40.8%)
Bovine liver	NI (30.3%)	595	NI (36.8%)	NI (0%)	NI (20.5%)	NI (37.2%)
α-Galactosidase						
Coffee beans	NI (1.8%)	NI (0%)	NI (0%)	NI (0%)	NI (35.7%)	NI (7.4%)
β-Galactosidase						
Bovine liver	546	491	1000	NI (17.9%)	NI (46.8%)	NI (14.6%)
α-Mannosidase						
Jack bean	0.73	NI(3.8%)	71	625	3.87	213
β-Mannosidase						
Snail	NI (0%)	NI (0%)	NI (0%)	NI (2.2%)	NI (6.4%)	NI (1.2%)
α-L-Fucosidase						
Bovine kidney	NI (0%)	NI (2.4%)	NI (16.3%)	NI (8.3%)	NI (33.2%)	NI (29.4%)
α, α-Trehalase						
Porcine kidney	NI (4.3%)	NI (2.9%)	NI (4.8%)	NI (3.9%)	NI (2.8%)	NI (9.6%)
Amyloglucosidase						
Aspergillus niger	NI (9.3%)	NI (0%)	NI (0%)	NI (0%)	NI (0%)	NI (3.8%)
α-L-Rhamnosidase						
Penicillium decumbens	NI (4.9%)	NI (0%)	NI (26.1%)	NI (3.6%)	NI (19.1%)	NI (1.6%)
β-Glucuronidase						
E. coli	NI (0.7%)	NI (11.5%)	NI (17.7%)	NI (0.4%)	542	NI (0%)
Bovine liver	NI (6.5%)	NI (0%)	NI (0%)	NI (13.8%)	NI (22.3%)	NI (23.8%)

[a] NI : no inhibition (less than 50% inhibition at 1000 μM).

[b] ( ) : inhibition at 1000 μM.

(1) Kessler, M.; Acuto, O.; Storelli, C.; Murer, H.; Semenza, G. A. *Biochim. Biophys. Acta*, **1978**, *506*, 136.