Short Access to Pyrimidine Derivates by the $S_{RN}1$ Mechanism. Synthesis of Substituted Uracil by Nucleophiles Through a One-pot Procedure

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Experimental Section

Reaction of 11 with 6-halo-2,4-dimethoxypyrimidines.

Reactions in liquid ammonia were performed as indicated in the typical procedure. When DMSO was used, it was added into a two-necked 20 mL round-bottomed flask, a nitrogen inlet and a magnetic stirrer. After degasification by vacuum, potassium *t*-butoxide (117.0 mg, 1.04 mmol) was added and stirred for 5 min. Then acetophenone was added (117 µL, 1.00 mmol) and the mixture was stirred for 15 min. The irradiation was started and then 6-chloro-2,4-dimethoxypyrimidine (43.6 mg, 0.25 mmol) was added to the solution. The reaction mixture was irradiated for the time indicated and ammonium nitrate was added to quench the reaction.

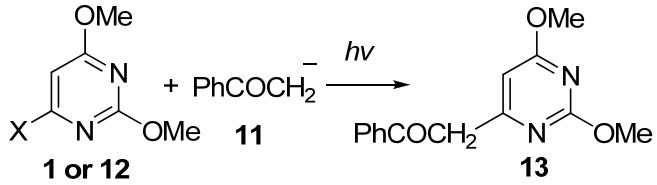


Table S1. Reaction of **11** with 6-halo-2,4-dimethoxypyrimidines.[a]

Expt	Substrate	Conditions	Product (yield %)[b]	Cl^-, %[c]
1	**12**	~150 mL NH_3, *hν*, 30 min	**13** (traces)	<5
2	**12**	~150 mL NH_3, *hν*, 180 min[d]	**13** (10-20%)[e]	87
3	**12**	~150 mL NH_3, *hν*, 140 min[f]	**13** (traces)	<5
4	**1**	~150 mL NH_3, *hν*, 15 min[d]	[g]	<9
5	**12**	10 mL DMSO *hν*, 180 min	**13** (14-28%)[e]	70
6	**1**	10 mL DMSO *hν*, 120 min	[g]	68

[a] All reactions were performed with 0.25 x 10^{-3} mol of substrate and 1.0 x 10^{-3} mol of **11**. Substrate was added in 1 mL of Et_2O. Photostimulated reactions employed two water-cooled metalic iodure. [b] Yield. [c] Determined potentiometrically. [d] 0.25 x 10^{-3} mol of pinacolona was added. [e] Quantified by ^{1}H NMR. [f] Potassium *t*-butoxide 0.25 x 10^{-3} mol was added. [g] Product not quantified. Distribution of products was similar to expt 3.

Hydrolysis of 6-substituted-2,4-dimethoxypyrimidines.

In addition to the results presented in the text other conditions were studied. Table S2 resume all of them. There are examples in the literature of esters and amides deprotection reactions in the absence of water, by the use of trifluorocetic acid in organic solvent. However the results obtained in our case highlight that the present of water is necessary in this deprotection reaction (Expt 4-5 , Table S2). The concentration of the pyrimidine was important in the yield of products (Expt 1 vs 2, 12 vs 13 Table S2).

Table S2. Hydrolysis of 6-substituted-2,4-dimethoxypyrimidines.

Expt	Substrate, 10^{-3} M	Conditions	Product (yield %)	Heating
1	**6**, 125	HCl(36%)/MeOH (1:10) reflux 24 h	**19** (40)[a]	CH
2	**6**, 16.7	HCl 0.2 M reflux 48 h	**19** (85)[a]	CH
3	**6**, 6 (17)[b,c]	HCl 0.2 M 120 C 80 min, sealed tube	**19** (37)[c]	CH
4	**6**, 100	CF_3COOH/MeOH reflux	-	CH
5	**6**, 100	CF_3COOH/CCl_4 reflux	-	CH
6	**8**, 12	HCl 0.2 M reflux 48 h	**20** (75)	CH
7	**18**, 10.7	HCl 0.2 M reflux 48 h	**21** (69)	CH
8	**6**, 6 (7%)[b,c]	HCl 0.2 M 120 C 40 min, sealed tube	**19** (58)[c]	MW
9	**6**, 6 (1%) [b,c]	HCl 0.1 M 120 C 40 min, sealed tube	**19** (81)[c]	MW
10	**6**, 6 (30%) [b,c]	HCl 0.01 M 120 C 40 min, sealed tube	**19** (51)[c]	MW
11	**6**, 6 (85%) [b,c]	Water 120 C 80 min, sealed tube	-	MW
12	**6**, 16.7	HCl 0.1 M 120 C 40 min, sealed tube	**19** (78)[d]	MW
13	**6**, 50	HCl 0.1 M 120 C 40 min, sealed tube	**19** (55)[d]	MW
14	**6**, 16.7	HCl 0.1 M 120 C 20 min, sealed tube	**19** (81)[d]	MW
15	**6**, 16.7	HCl 0.1 M 120 C 10 min, sealed tube	**19** (81)[d]	MW

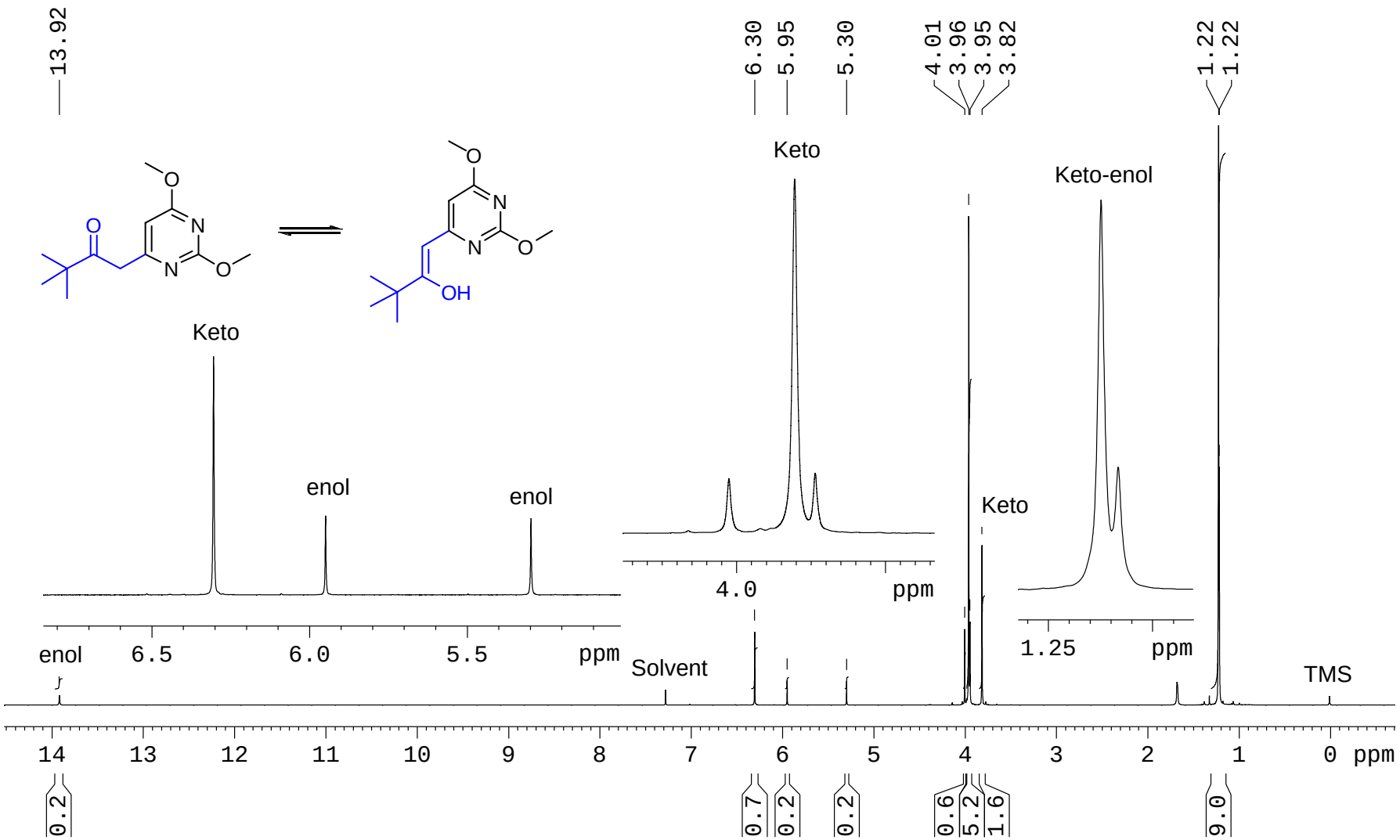
16	**6**, 16.7	HCl 0.01 M 120 C 60 min, sealed tube	**19** (85)[d]	MW
17	**6**, 16.7	HCl 0.1 M Constant Power 70 W (100-103 C) 20’ open tube	**19** (~12) min,	MW

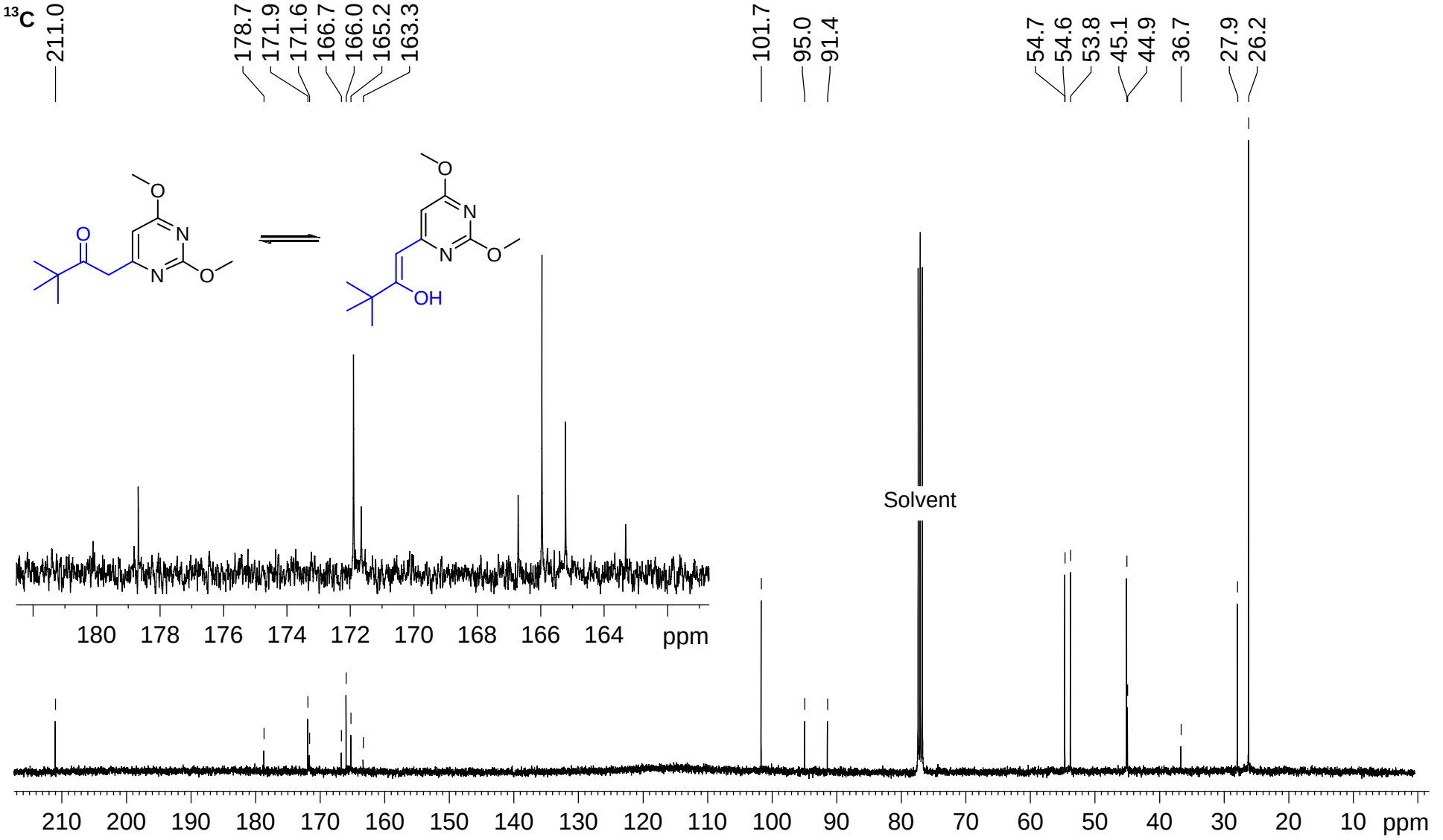
[a] Yield. [b] Remaining substrate. [c] Quantified by ^{1}H NMR. [d] Quantified by HPLC.

Graphical NMR Spectral Data of Compounds Synthesized

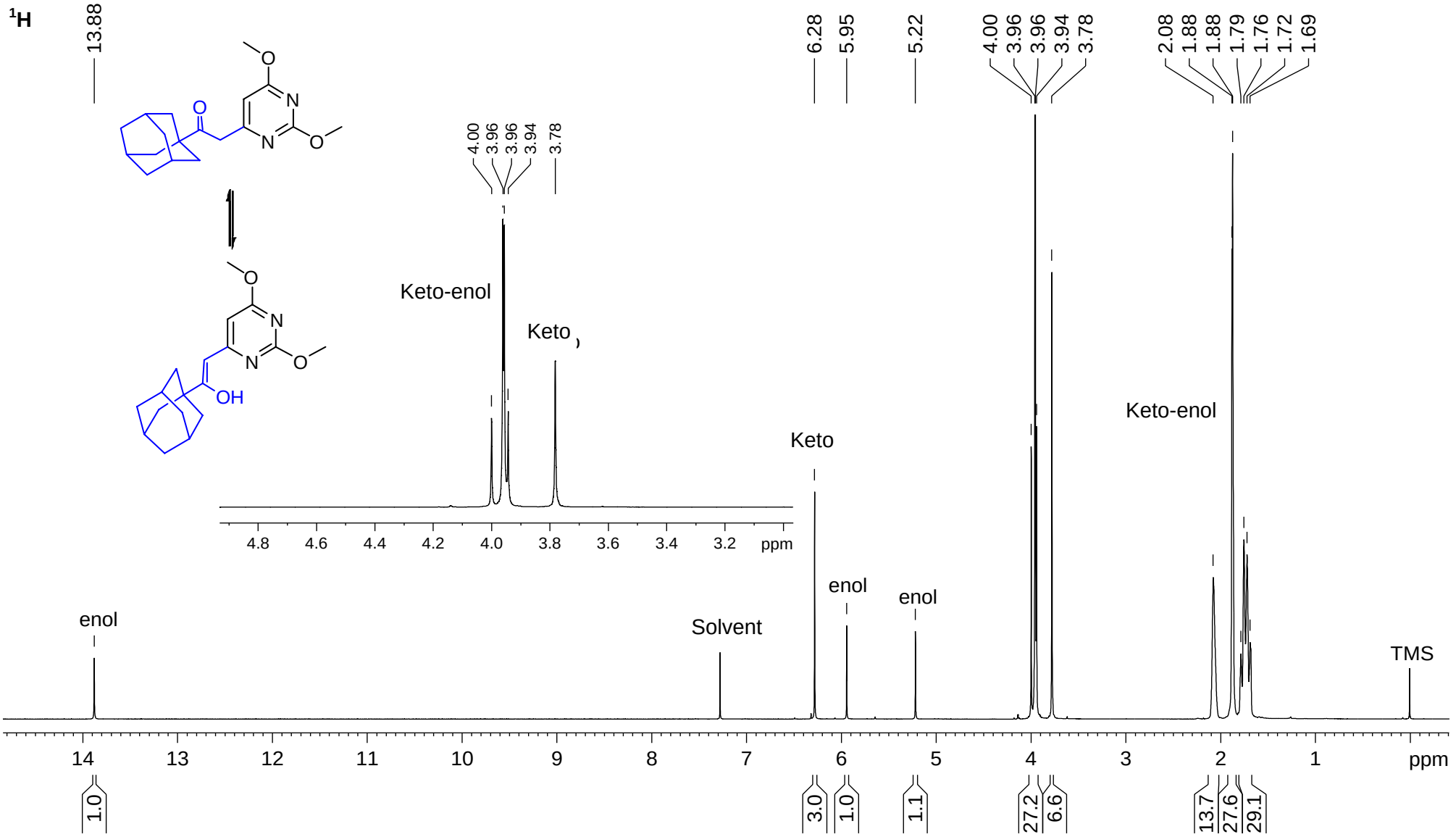
1-(2,6-Dimethoxypyrimidin-4-yl)-3,3-dimethylbutan-2-one (6) in CCl_3D.

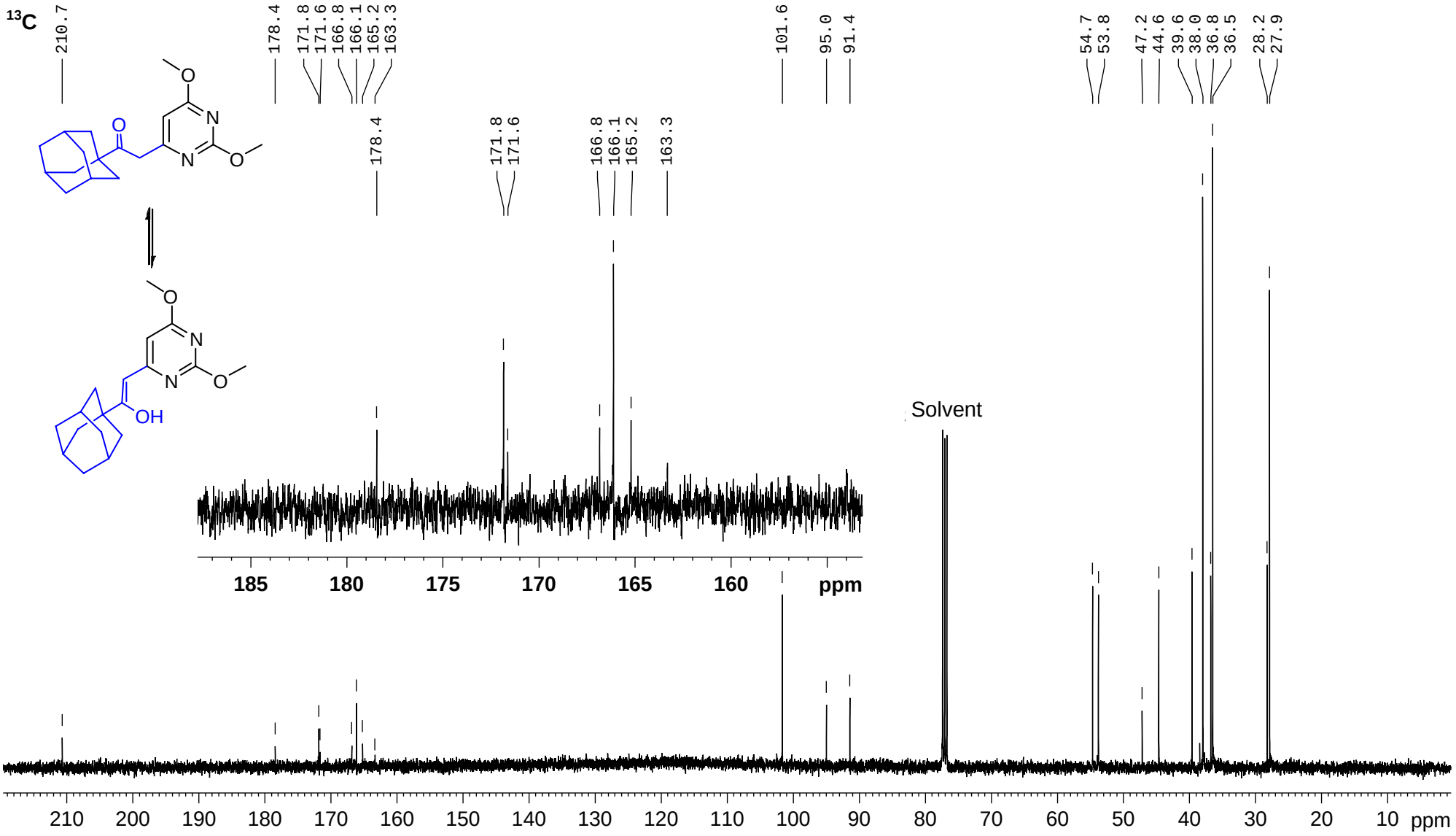
^1H



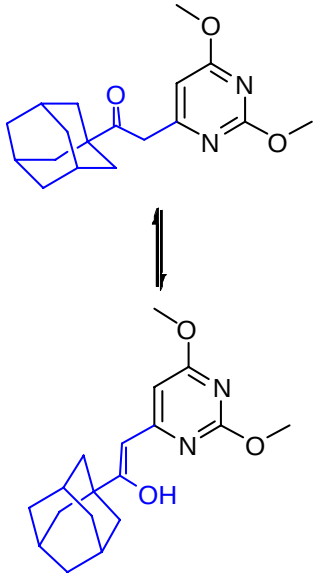

13C
211.0
178.7
171.9
171.6
166.7
166.0
165.2
163.3
101.7
95.0
91.4
54.7
54.6
53.8
45.1
44.9
36.7
27.9
26.2
O
N
N
O
O
N
N
O
OH
Solvent
180 178 176 174 172 170 168 166 164 ppm
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

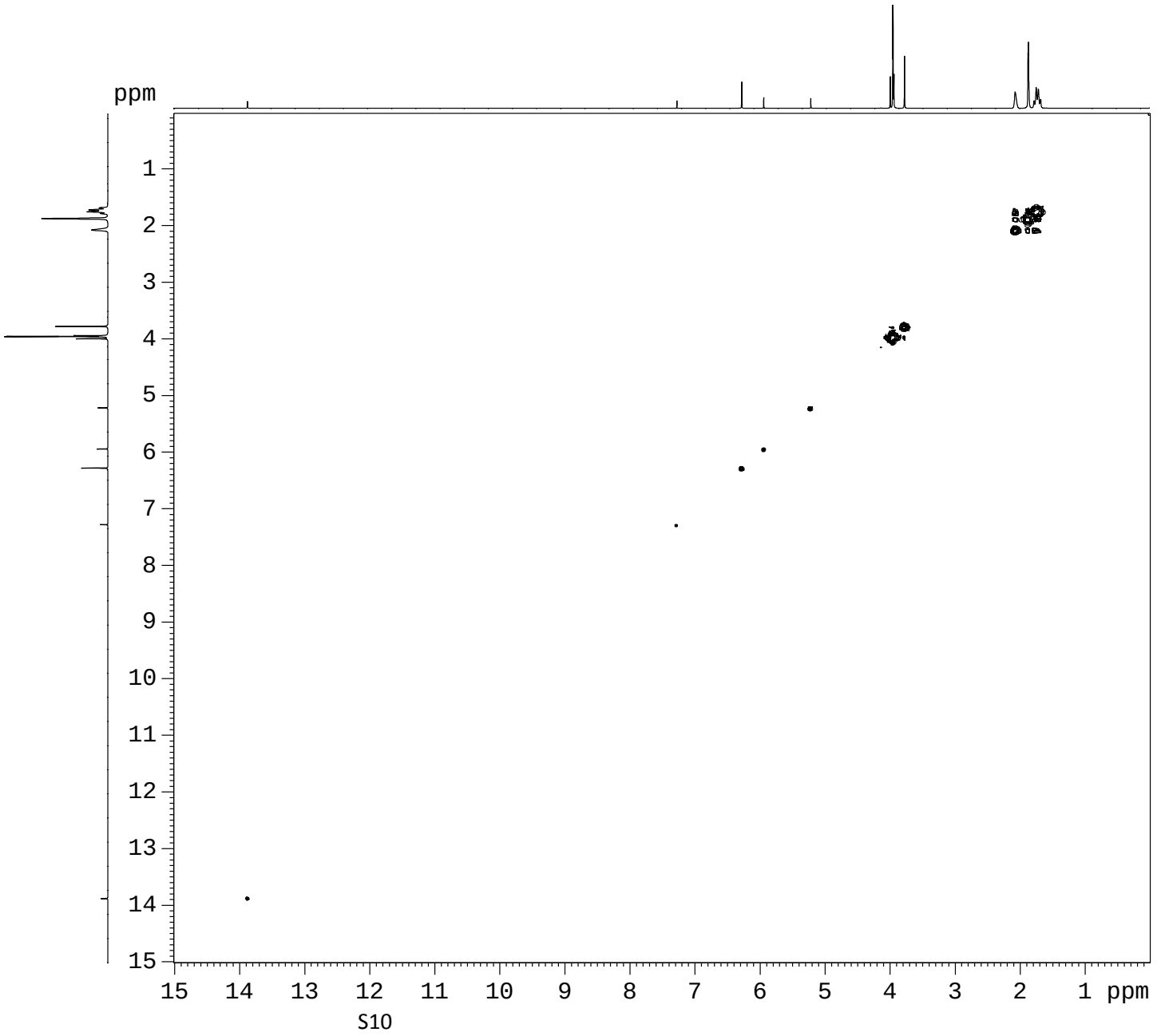
1-(1-Adamantyl)-2-(2,6-dimethoxypyrimidin-4-yl)ethanone (8) in CCl_3D.

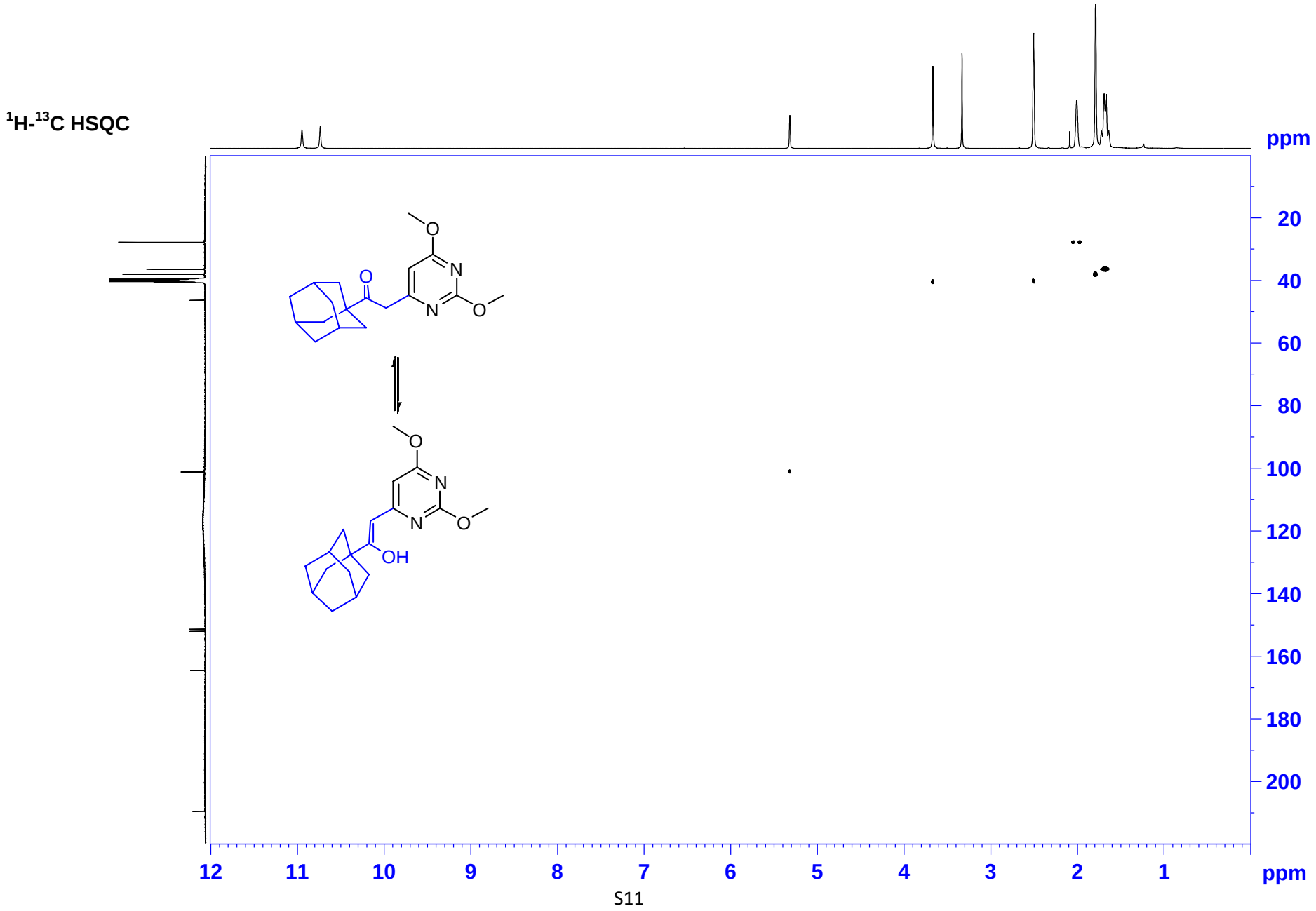



^{13}C
210.7
178.4
171.8
171.6
166.8
166.1
165.2
163.3
101.6
95.0
91.4
54.7
53.8
47.2
44.6
39.6
38.0
36.8
36.5
28.2
27.9
Solvent
185
180
175
170
165
160
ppm
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

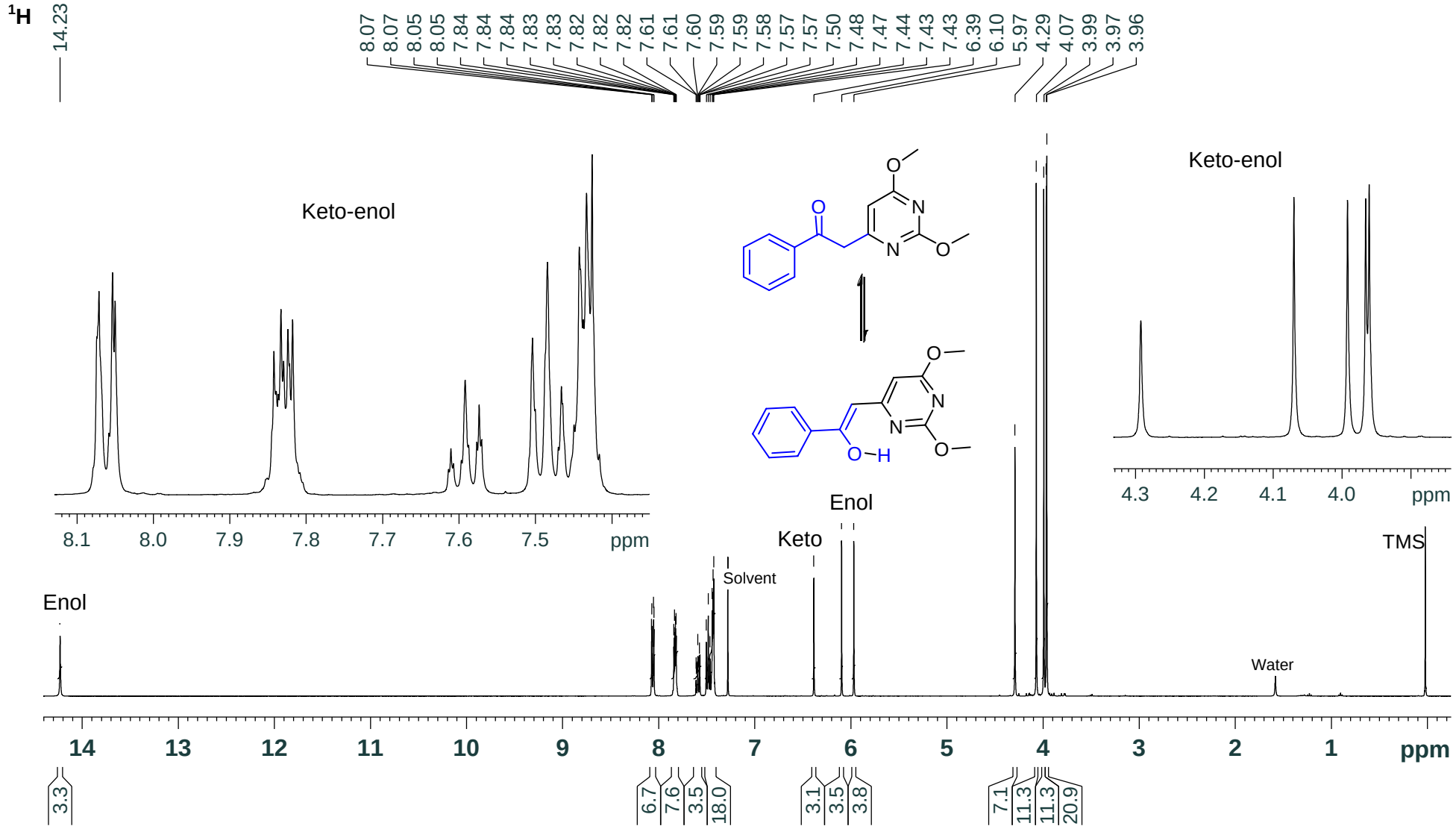
^{1}H-^{1}H COSY


O
N
N
O
O
N
N
O
OH

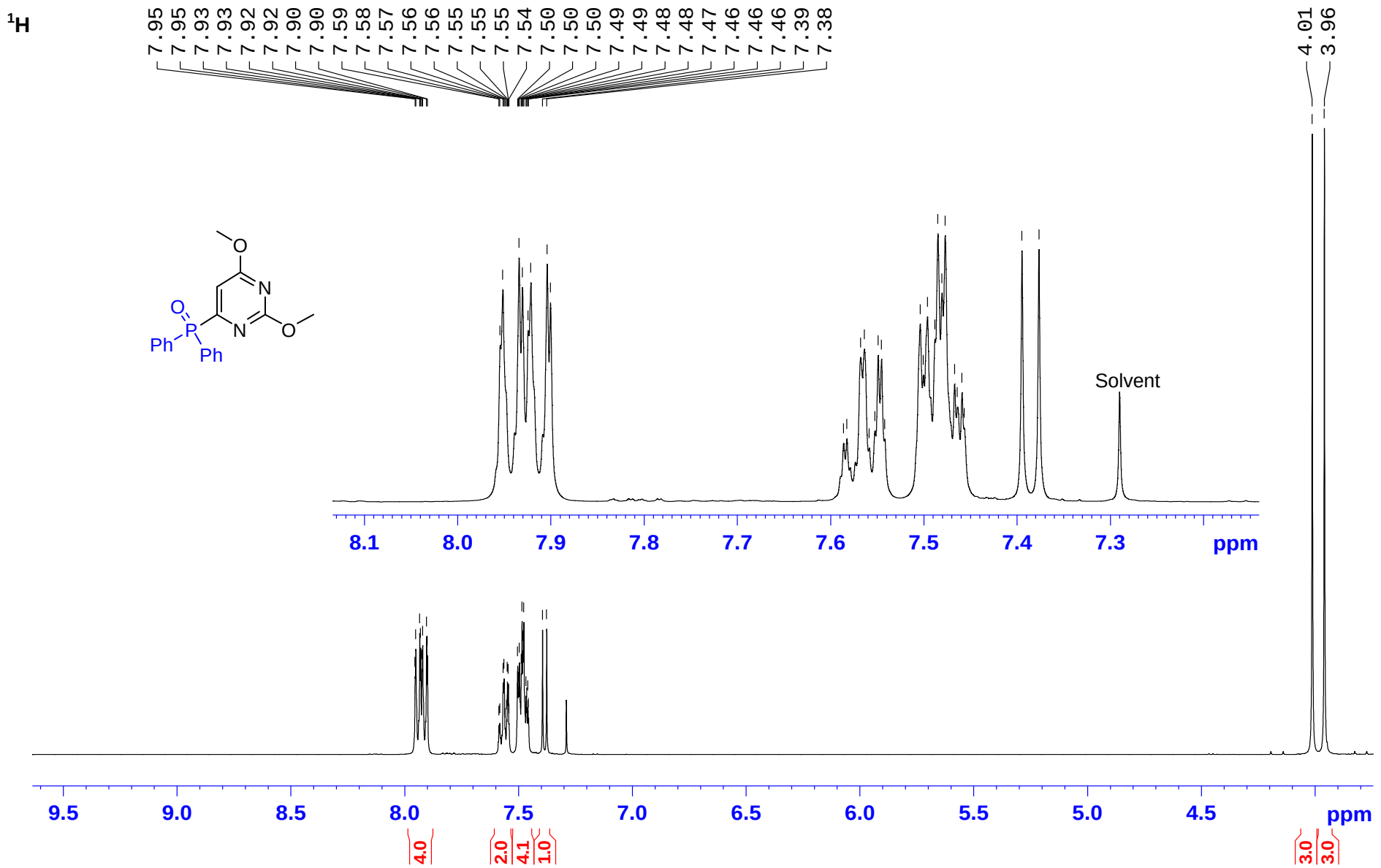

ppm
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 ppm


^{1}H-^{13}C HSQC
ppm
20
40
60
80
100
120
140
160
180
200
12
11
10
9
8
7
6
5
4
3
2
1
ppm
O
N
N
O
O
O
N
N
O
OH

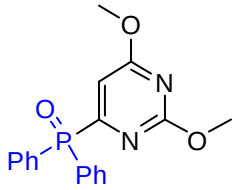
2-(2,6-Dimethoxypyrimidin-4-yl)-1-phenylethanone (13) in CCl_3D.

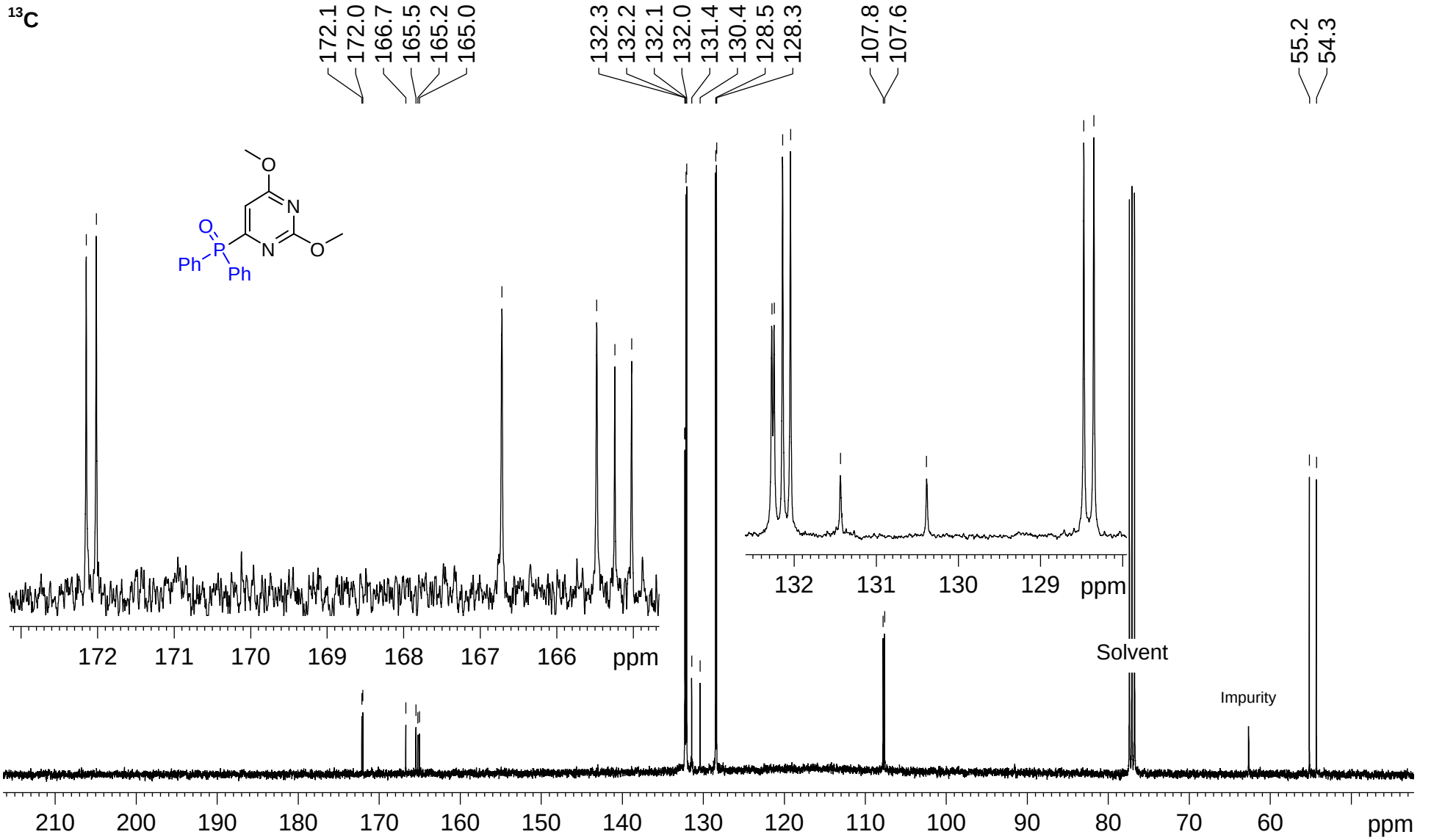


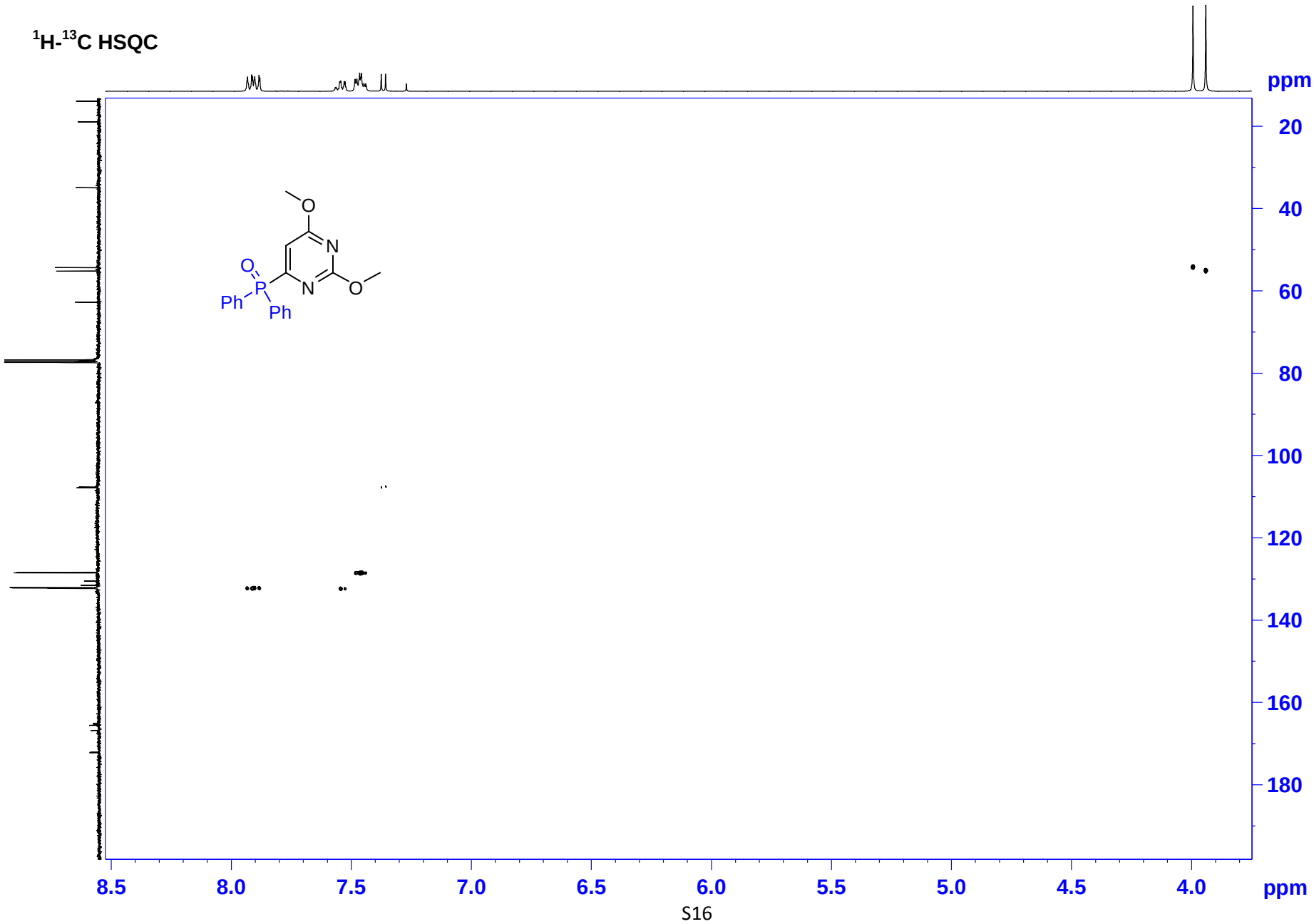
Diphenyl(2,4-dimethoxy-6-pyrimidyl)phosphane oxide (17) in CCl_3D.

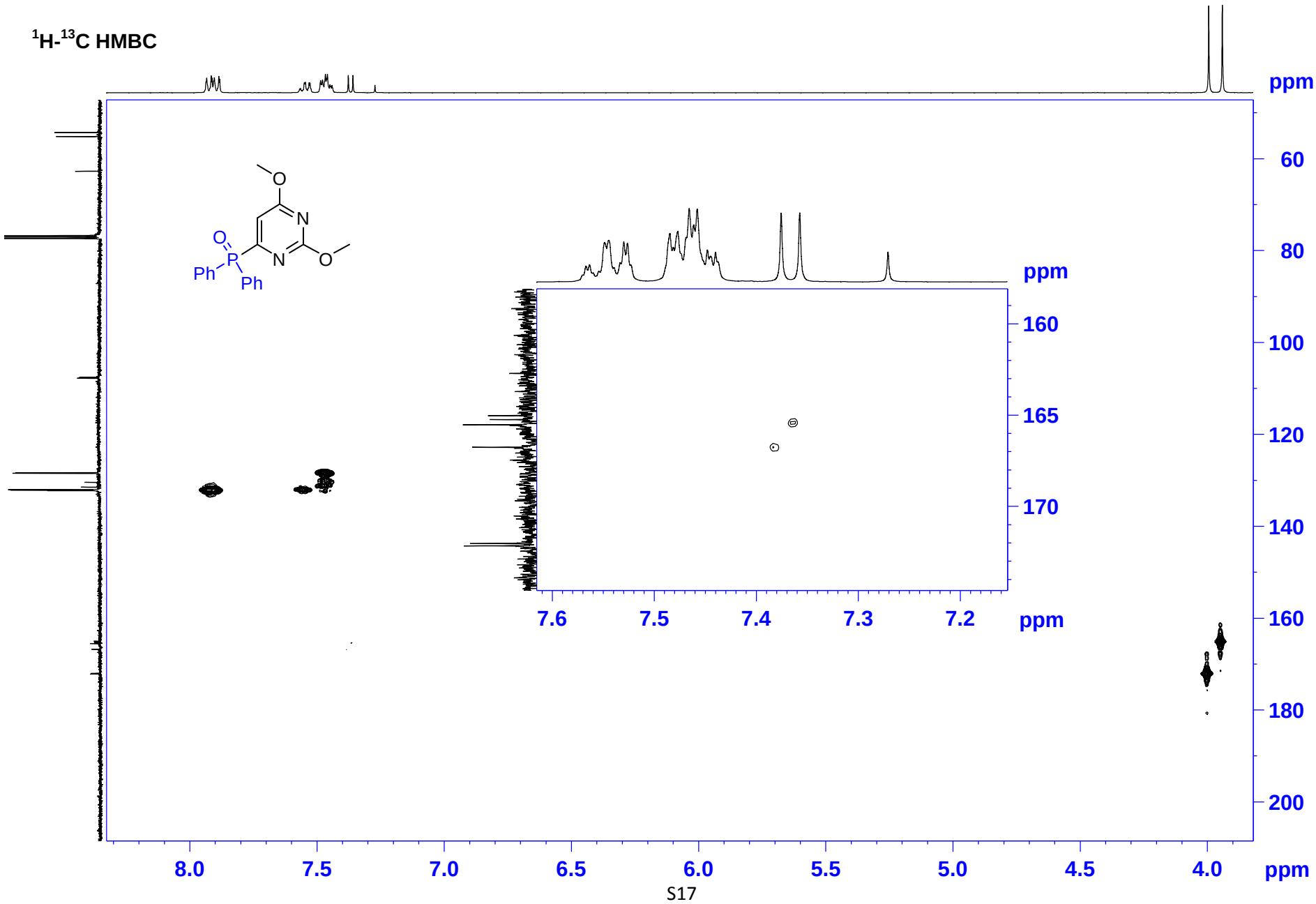


^{31}P

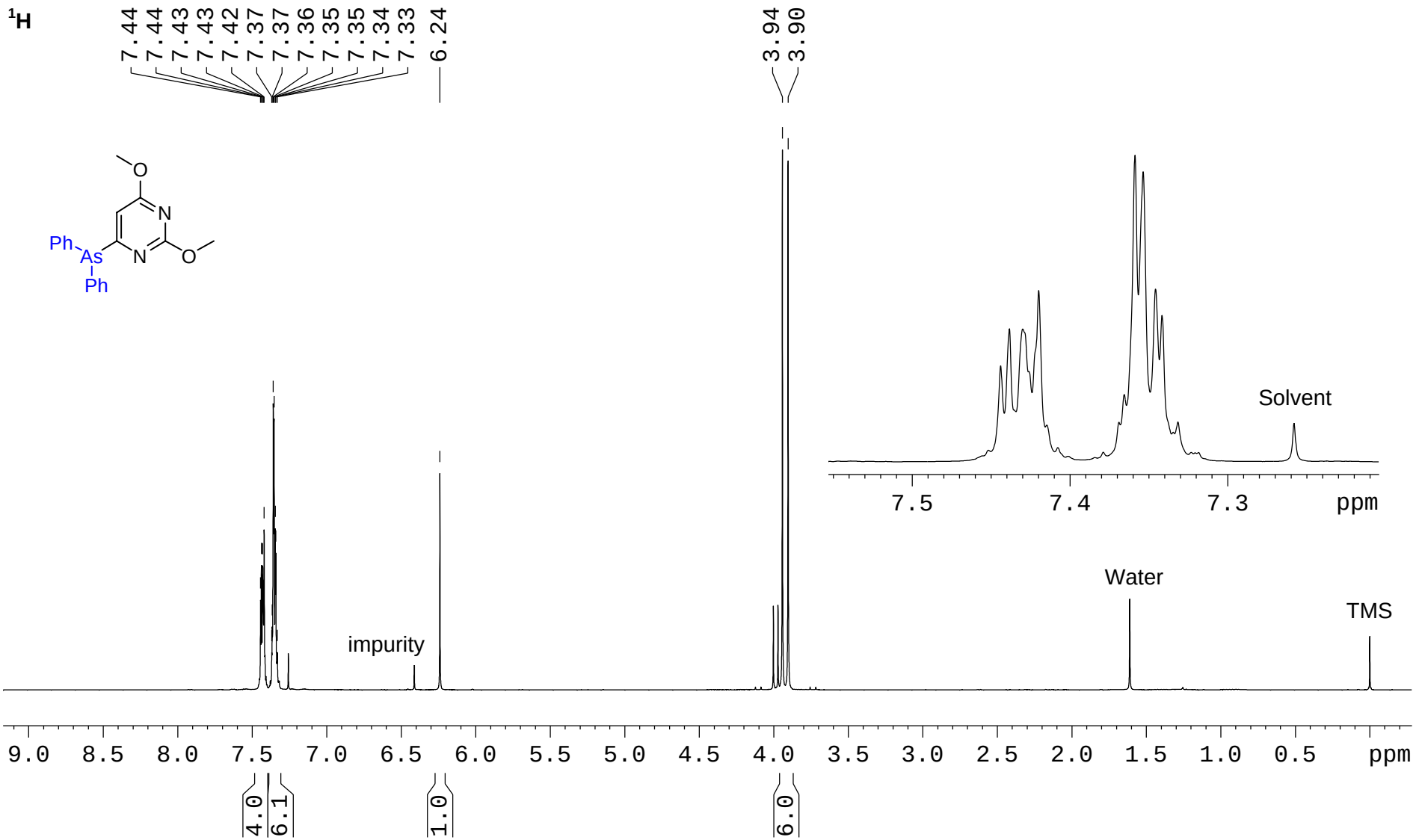


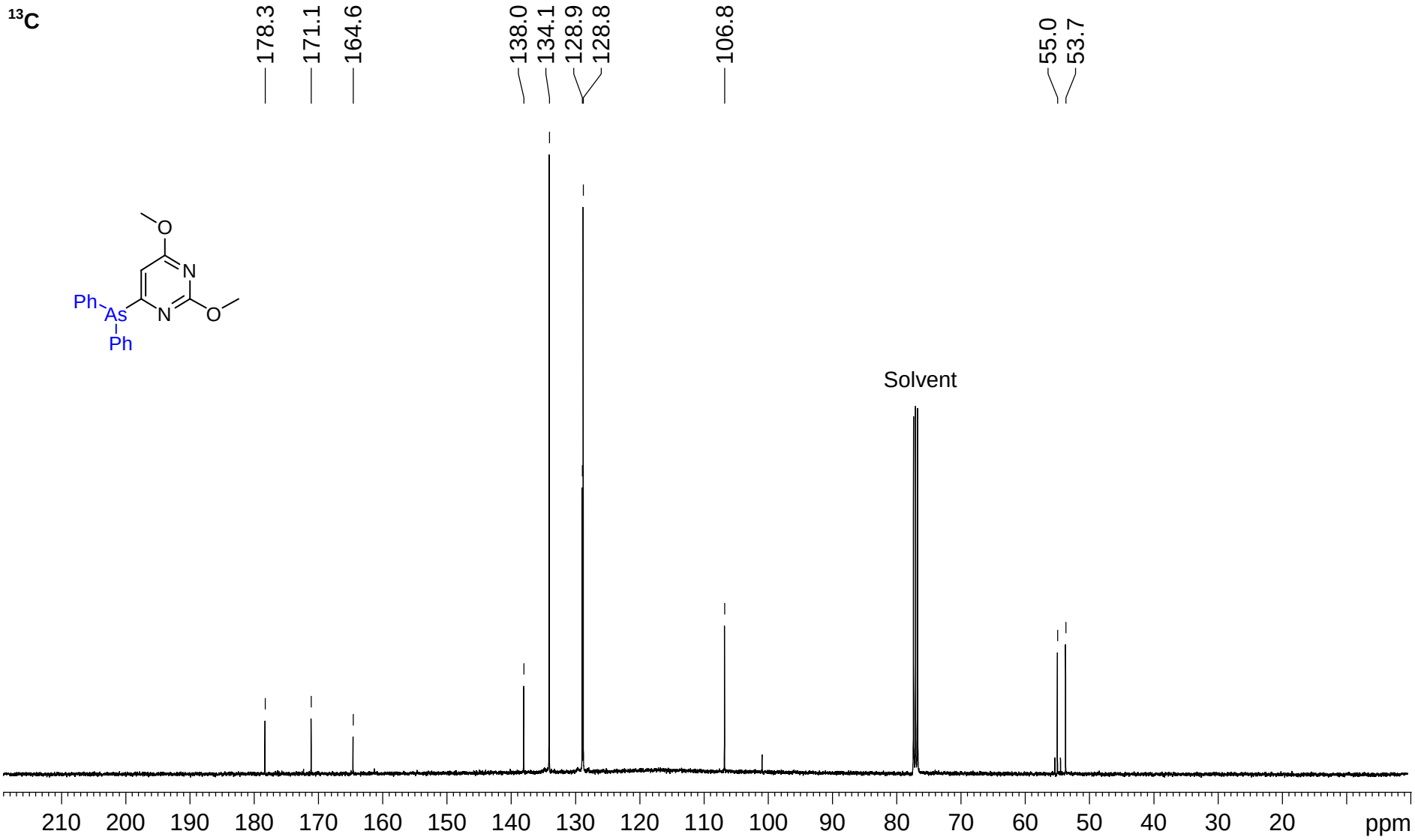

13C
172.1
172.0
166.7
165.5
165.2
165.0
132.3
132.2
132.1
132.0
131.4
130.4
128.5
128.3
107.8
107.6
55.2
54.3
O
N
O
P
Ph
Ph
N
O
172 171 170 169 168 167 166 ppm
132 131 130 129 ppm
Solvent
Impurity
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 ppm


^{1}H-^{13}C HSQC
ppm
20
40
60
80
100
120
140
160
180
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
ppm
O
N
O
P
Ph
Ph
N
O

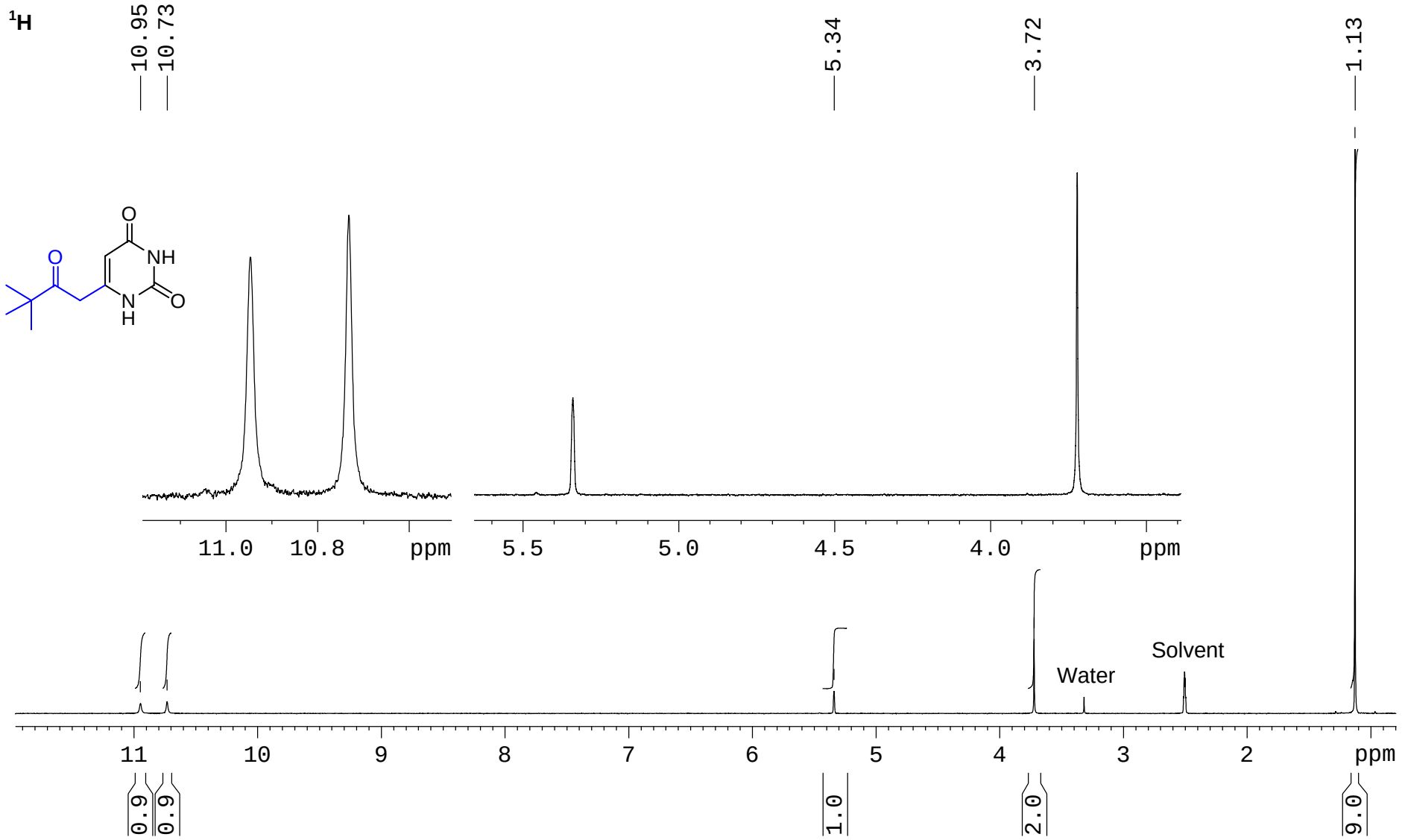

^{1}H-^{13}C HMBC
ppm
60
80
100
120
140
160
180
200
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
ppm
O
N
N
O
O
P
Ph
Ph
ppm
160
165
170
7.6
7.5
7.4
7.3
7.2
ppm

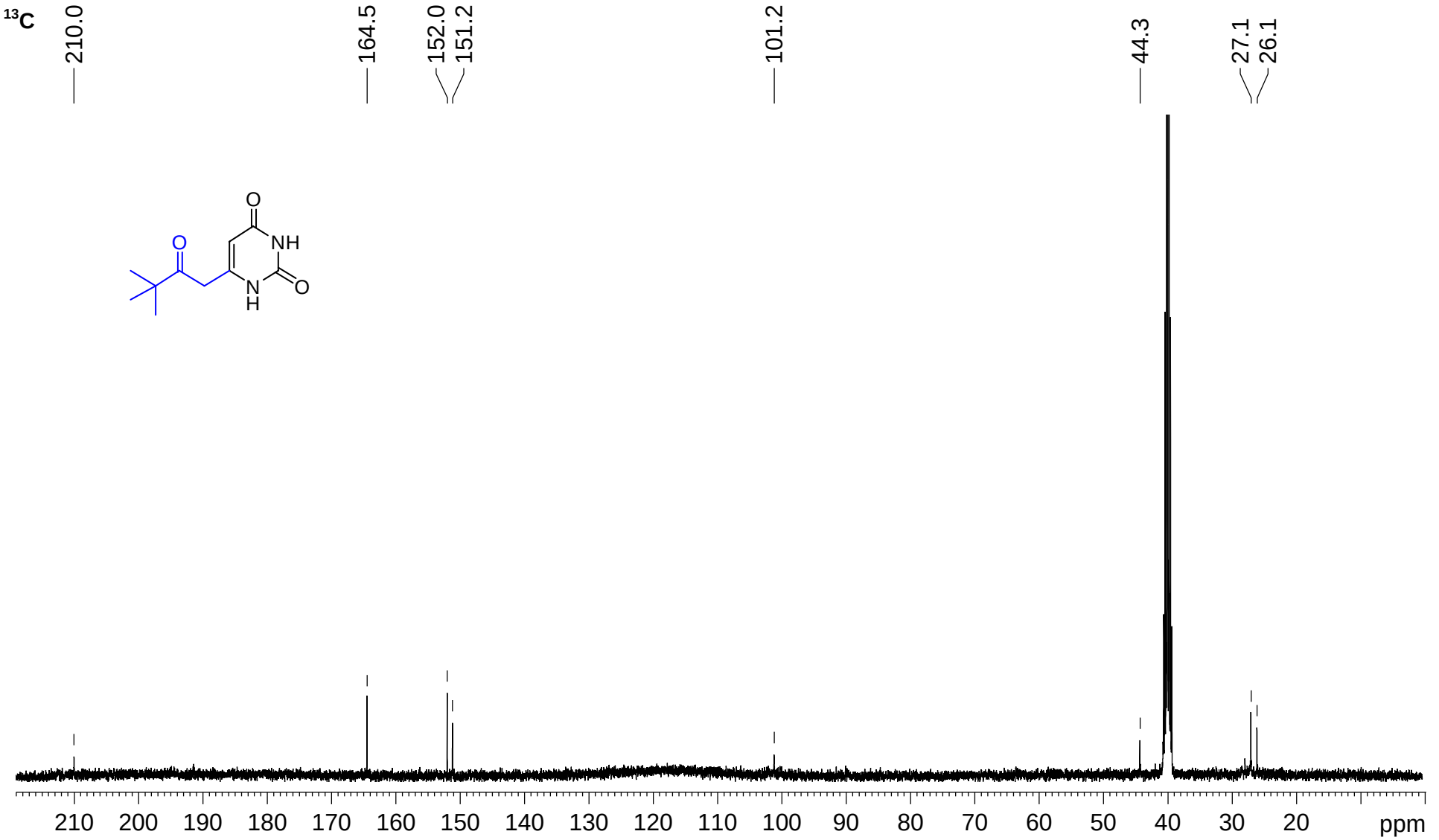
Diphenyl(2,4-dimethoxy-6-pyrimidyl)arsane (18) in CCl_3D.




13C
178.3
171.1
164.6
138.0
134.1
128.9
128.8
106.8
55.0
53.7
O
N
Ph
As
N
O
Ph
Solvent
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

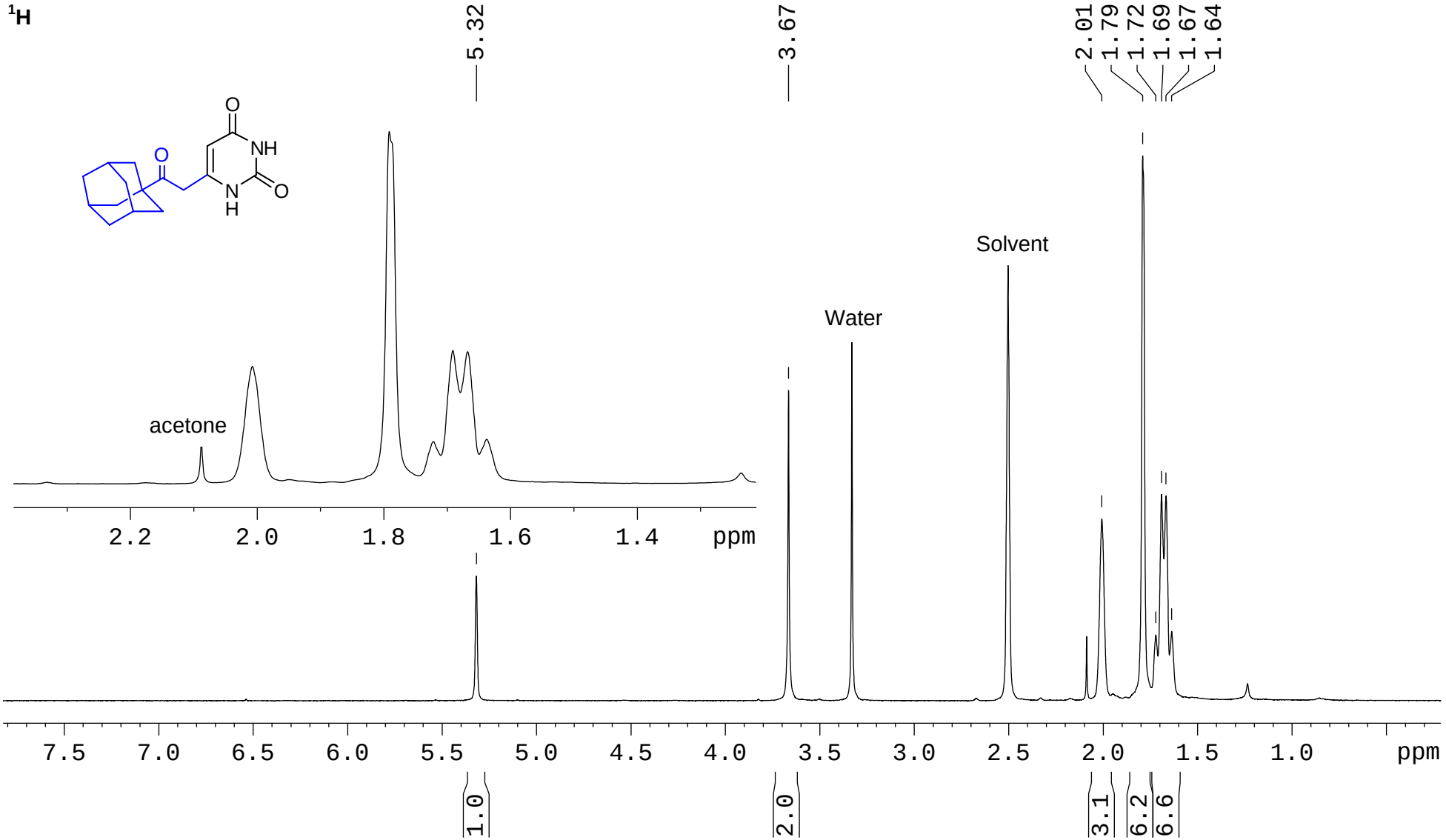
6-(3,3-Dimethyl-2-oxobutyl)uracil (19) in DMSO-d_6.



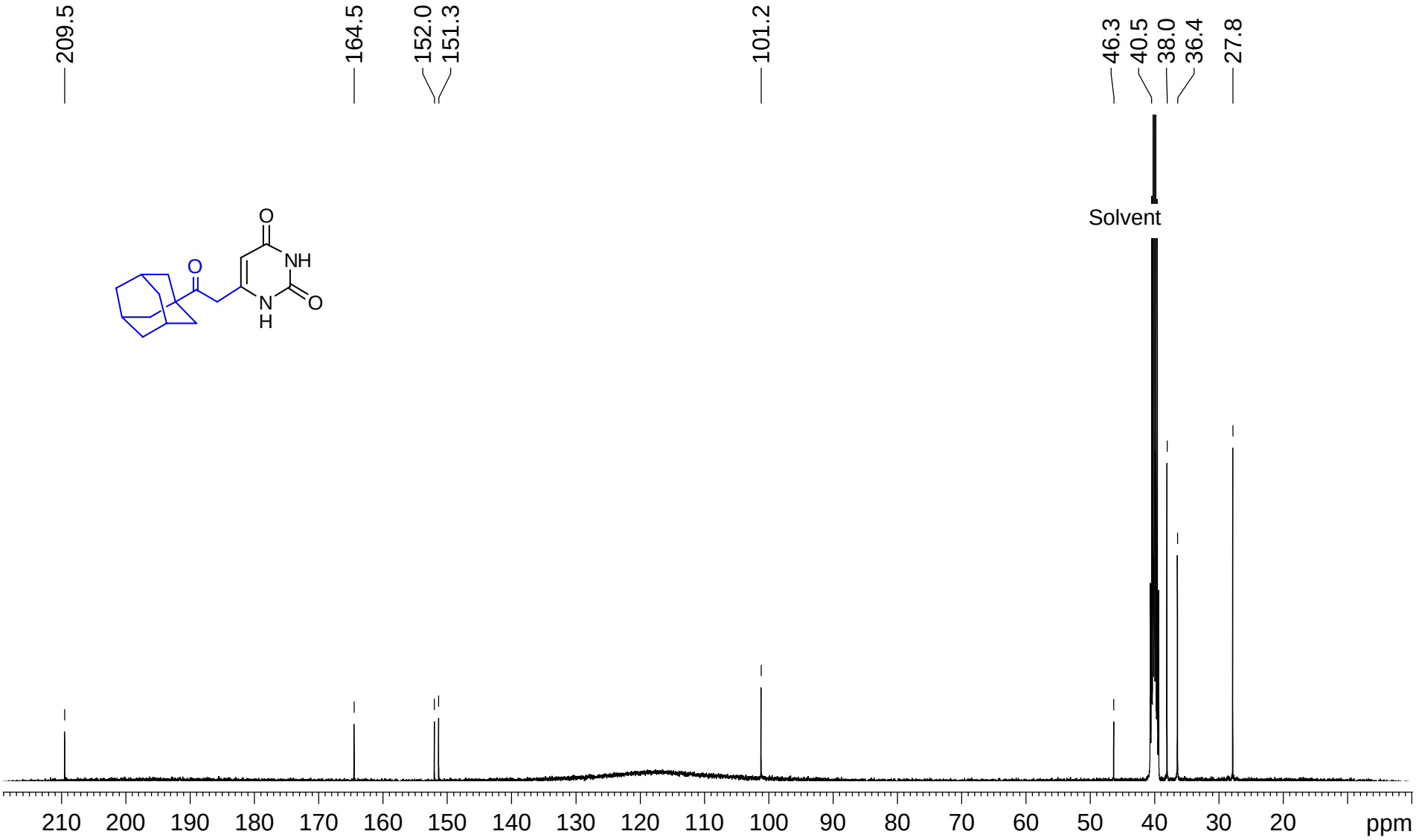

13C
210.0
164.5
152.0
151.2
101.2
44.3
27.1
26.1
O
NH
O
O
N
H
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

6-(2-Oxo-2-(1-adamantyl)ethyl)uracil (20) in DMSO-d_6.

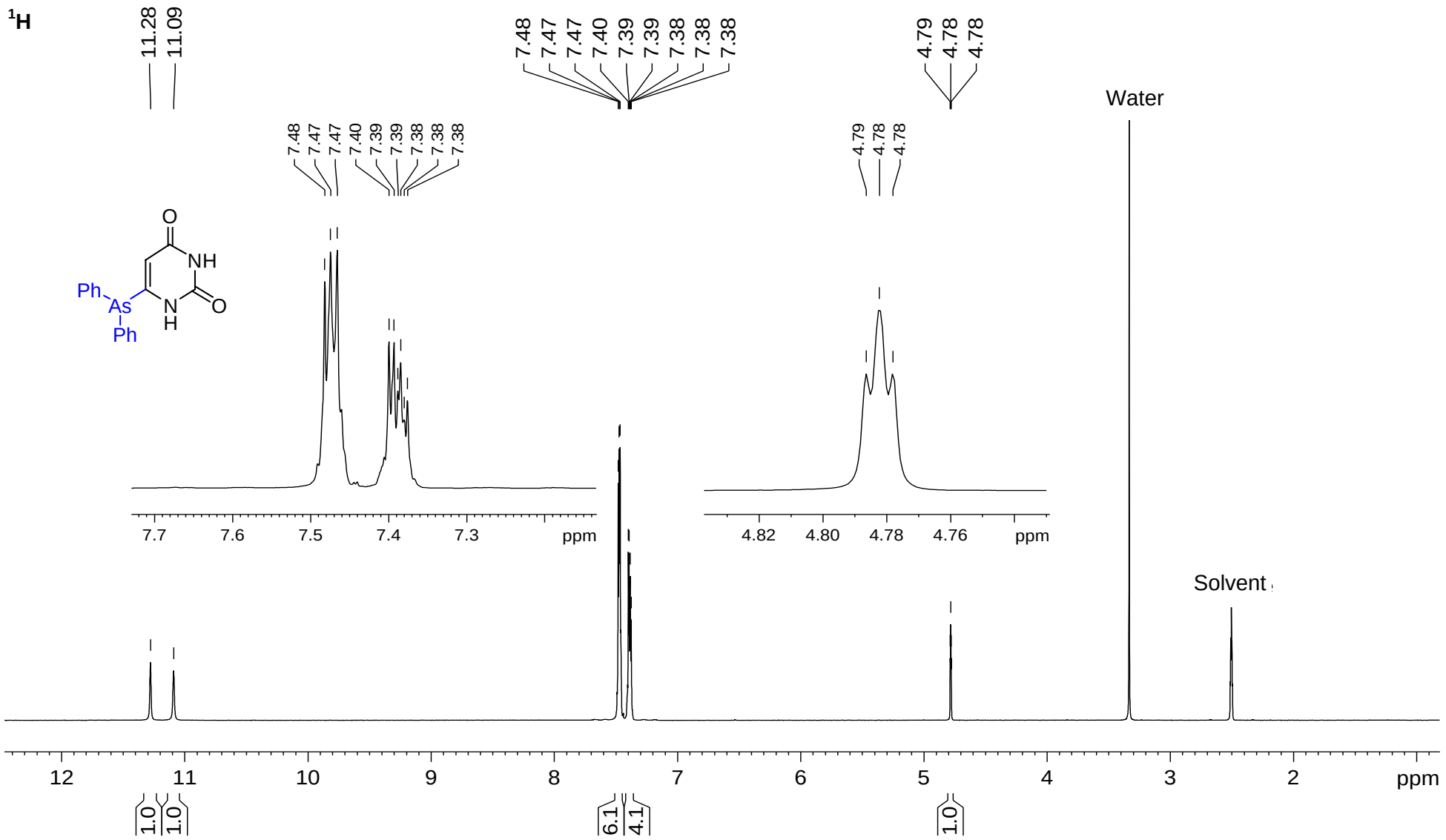
^{1}H

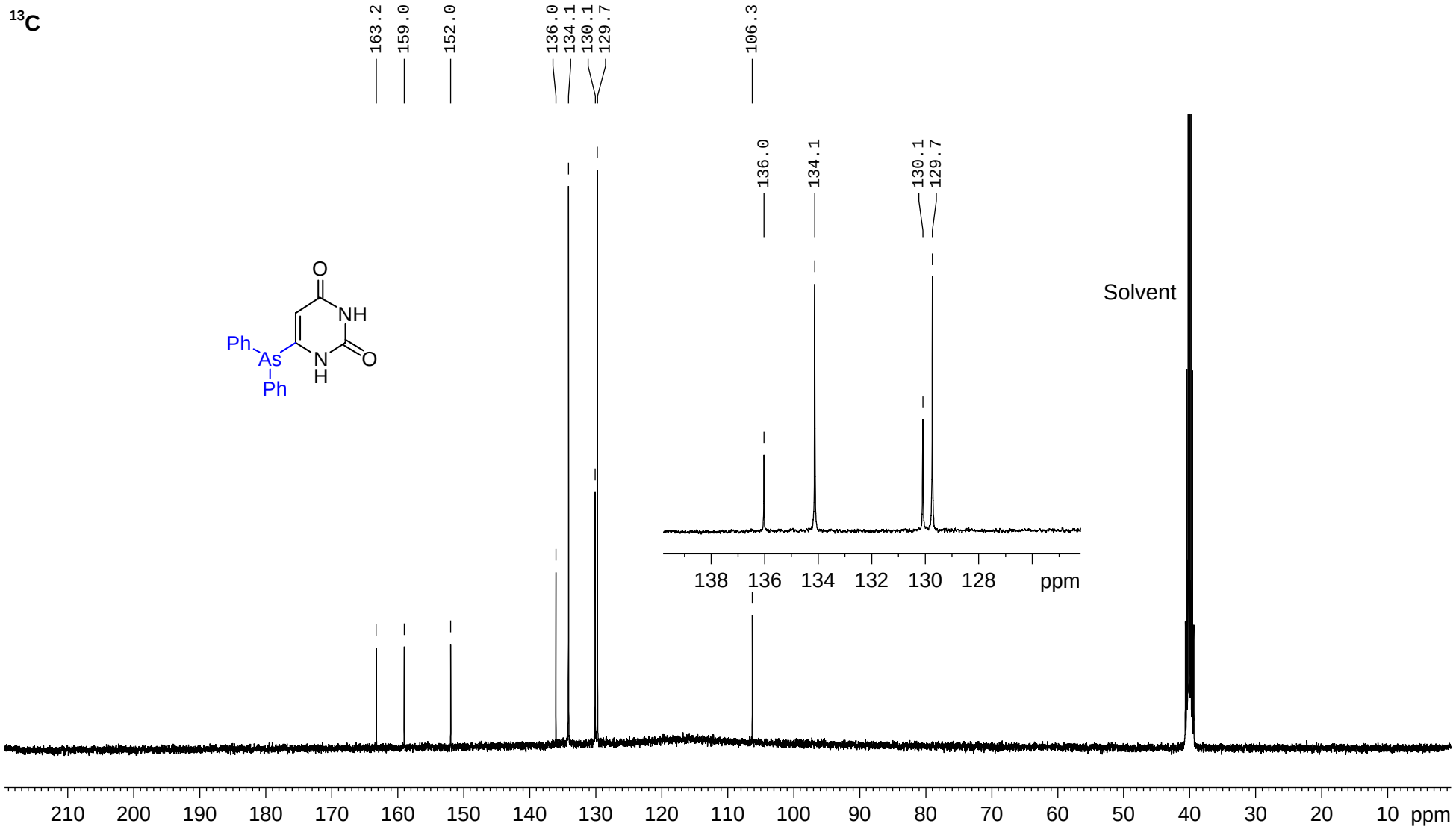


^{13}C

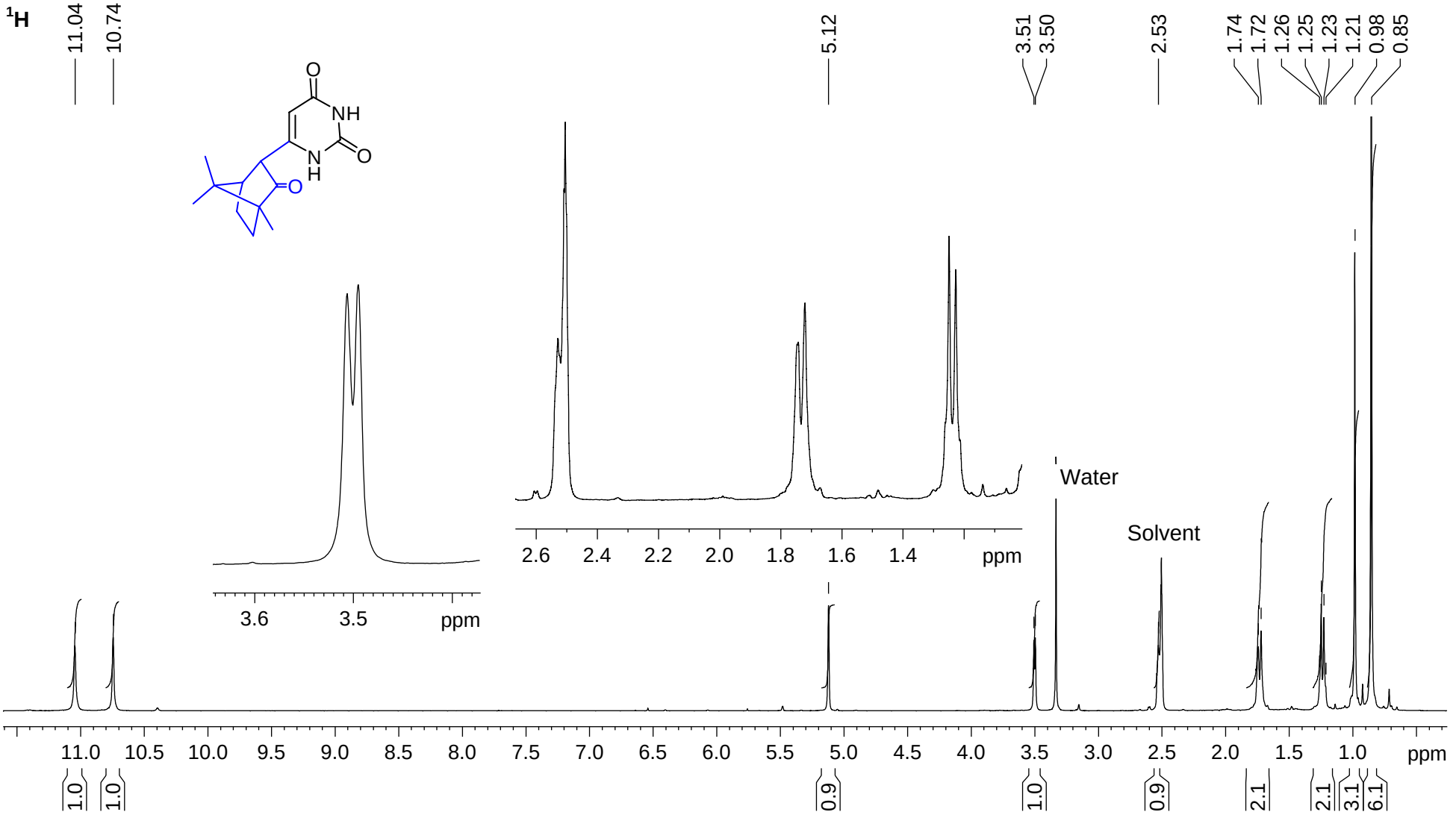

209.5
164.5
152.0
151.3
101.2
46.3
40.5
38.0
36.4
27.8
Solvent
O
NH
O
N
H
O
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

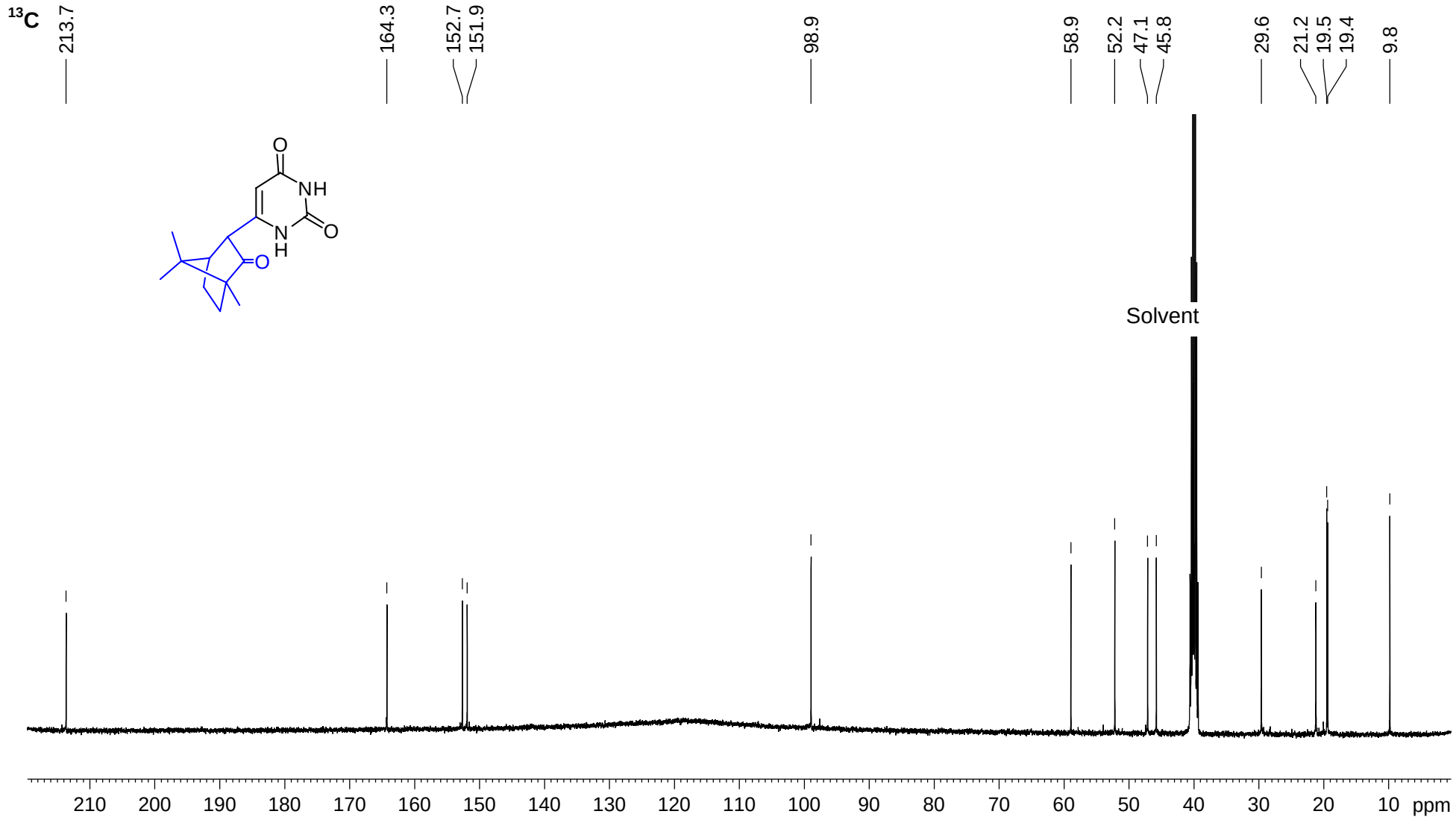
6-(Diphenylarsino)uracil (21) in DMSO-d_6



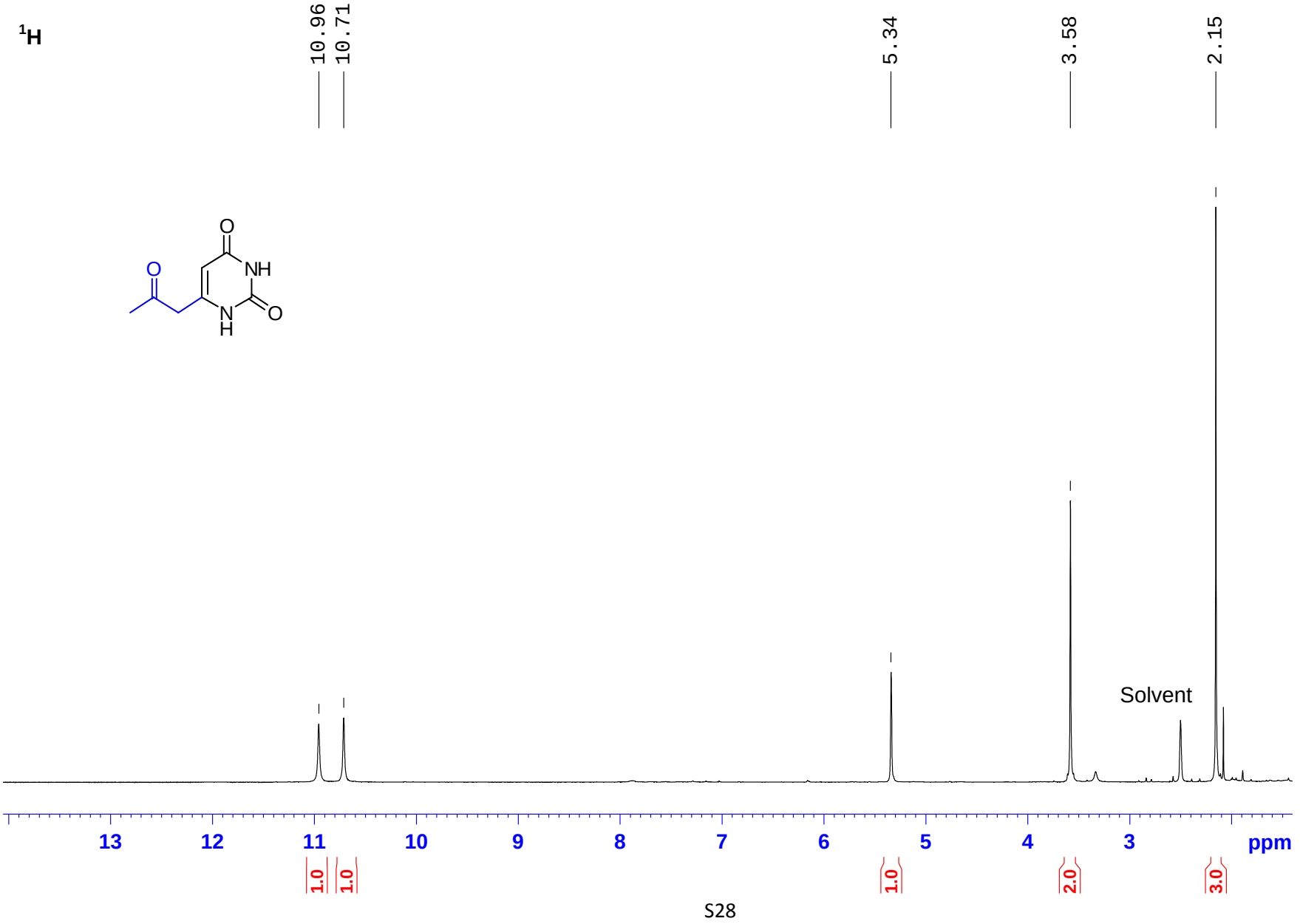

13C
163.2
159.0
152.0
136.0
134.1
130.1
129.7
106.3
Solvent
O
NH
Ph
As
N
H
O
Ph
138
136
134
132
130
128
ppm
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

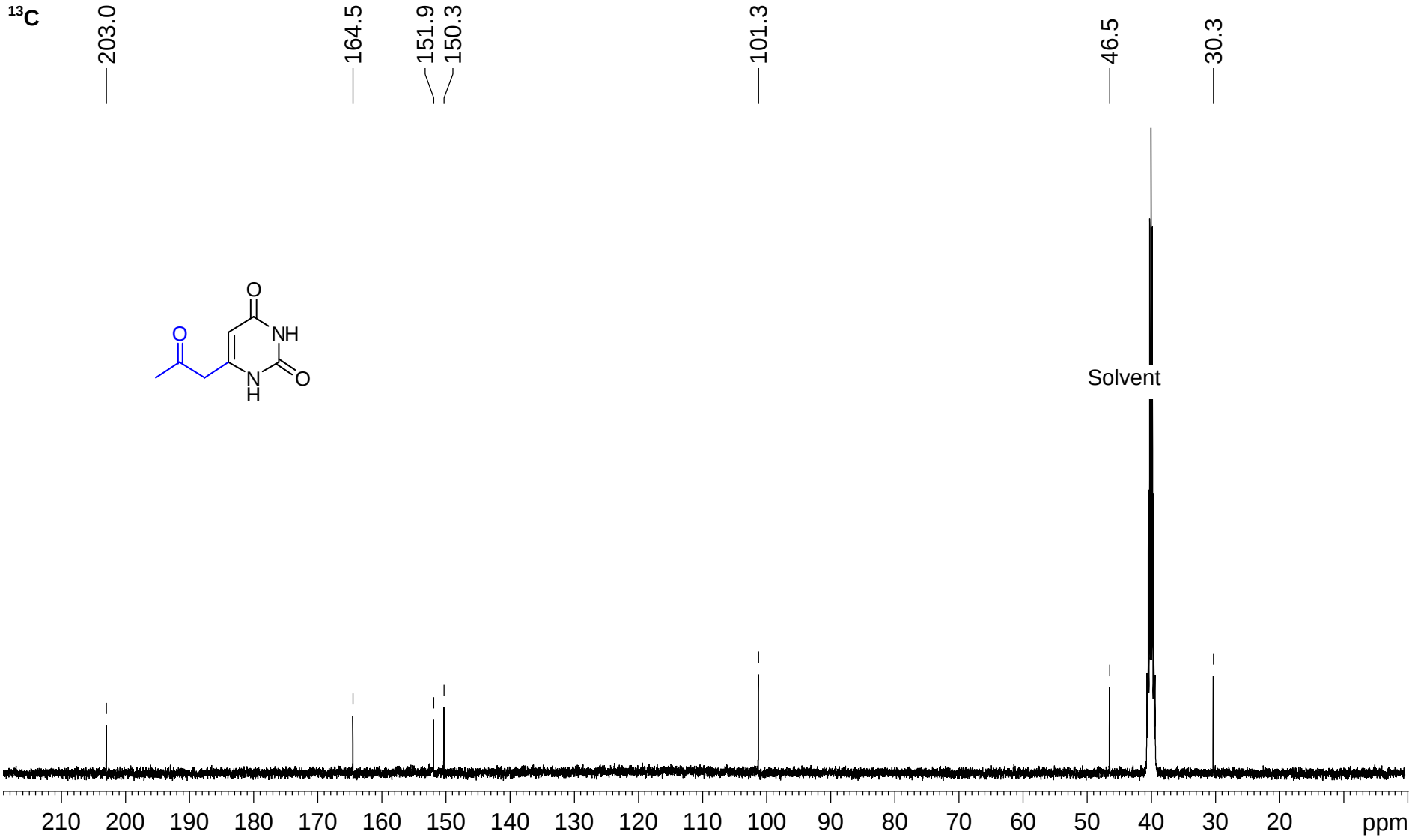
6-(4,7,7-Trimethyl-3-oxobicyclo[2.2.1]heptan-2-yl)uracil (22) in DMSO-d_6.



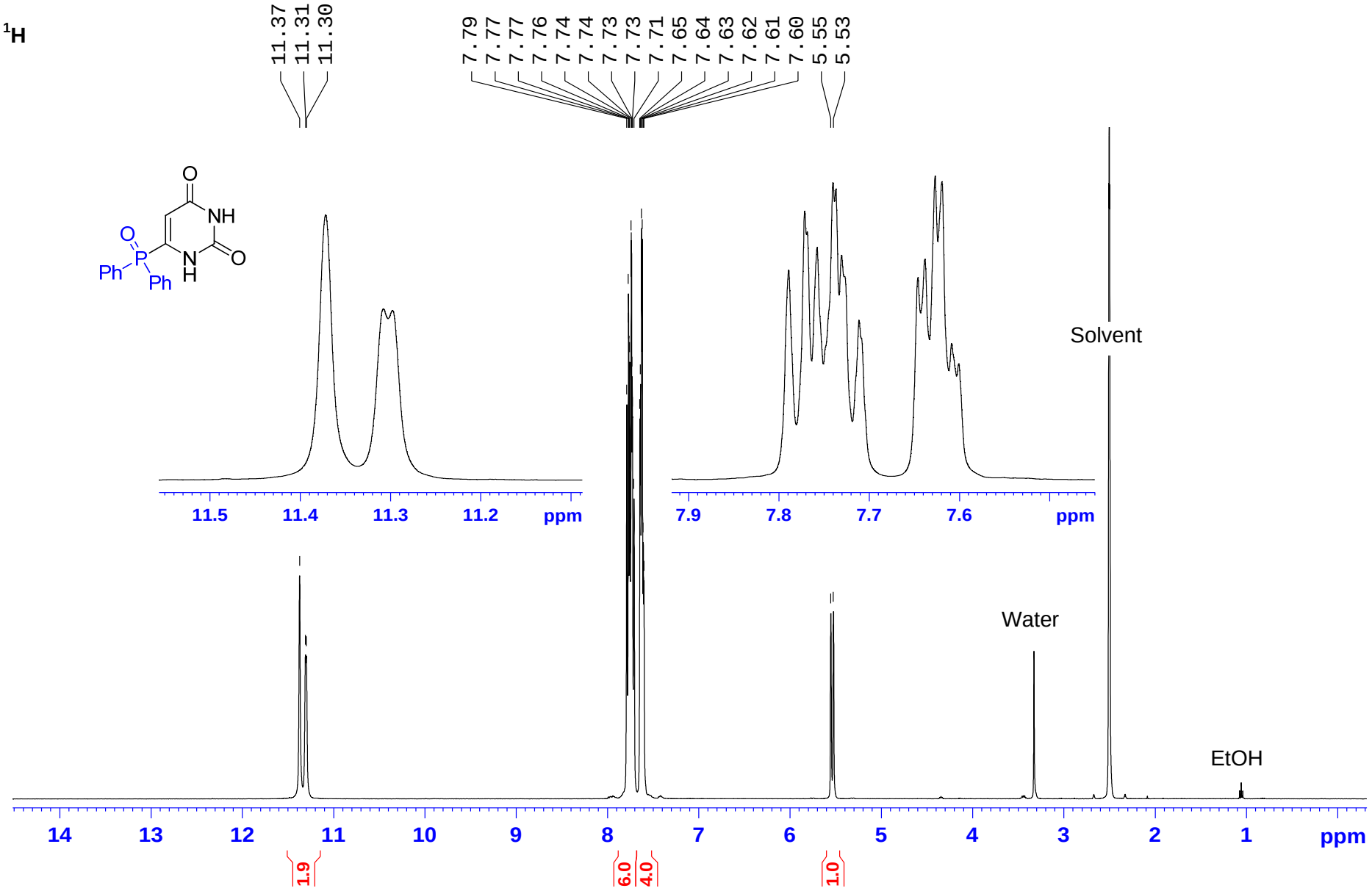

13C
213.7
164.3
152.7
151.9
98.9
58.9
52.2
47.1
45.8
29.6
21.2
19.5
19.4
9.8
O
NH
N
H
O
O
Solvent
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

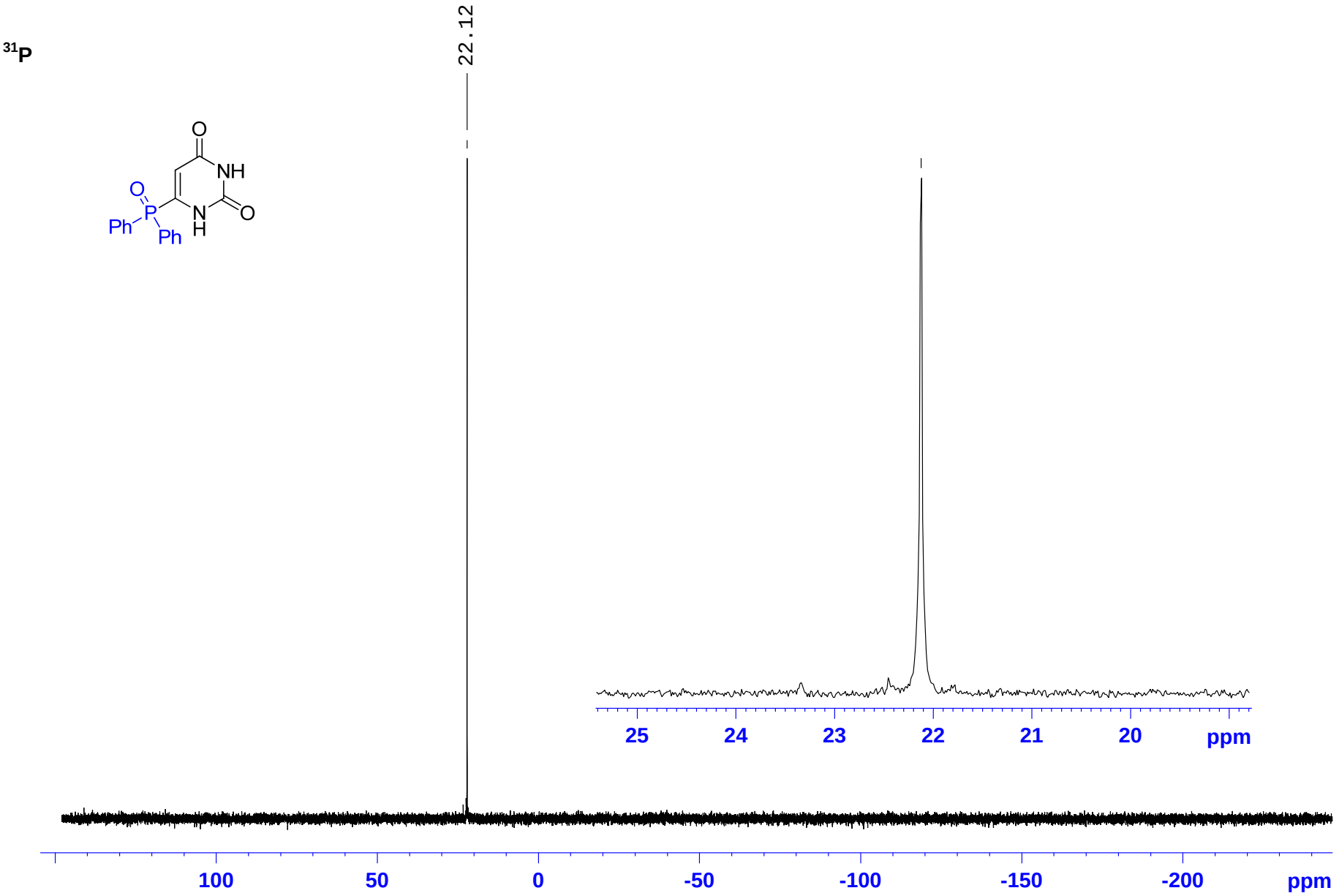
6-(2-Oxopropyl)uracil (24) in DMSO-d_6.




13C
203.0
164.5
151.9
150.3
101.3
46.5
30.3
O
NH
O
N
H
O
Solvent
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

6-(Diphenylphosphoryl)uracil (25) in DMSO-d_6.




31P
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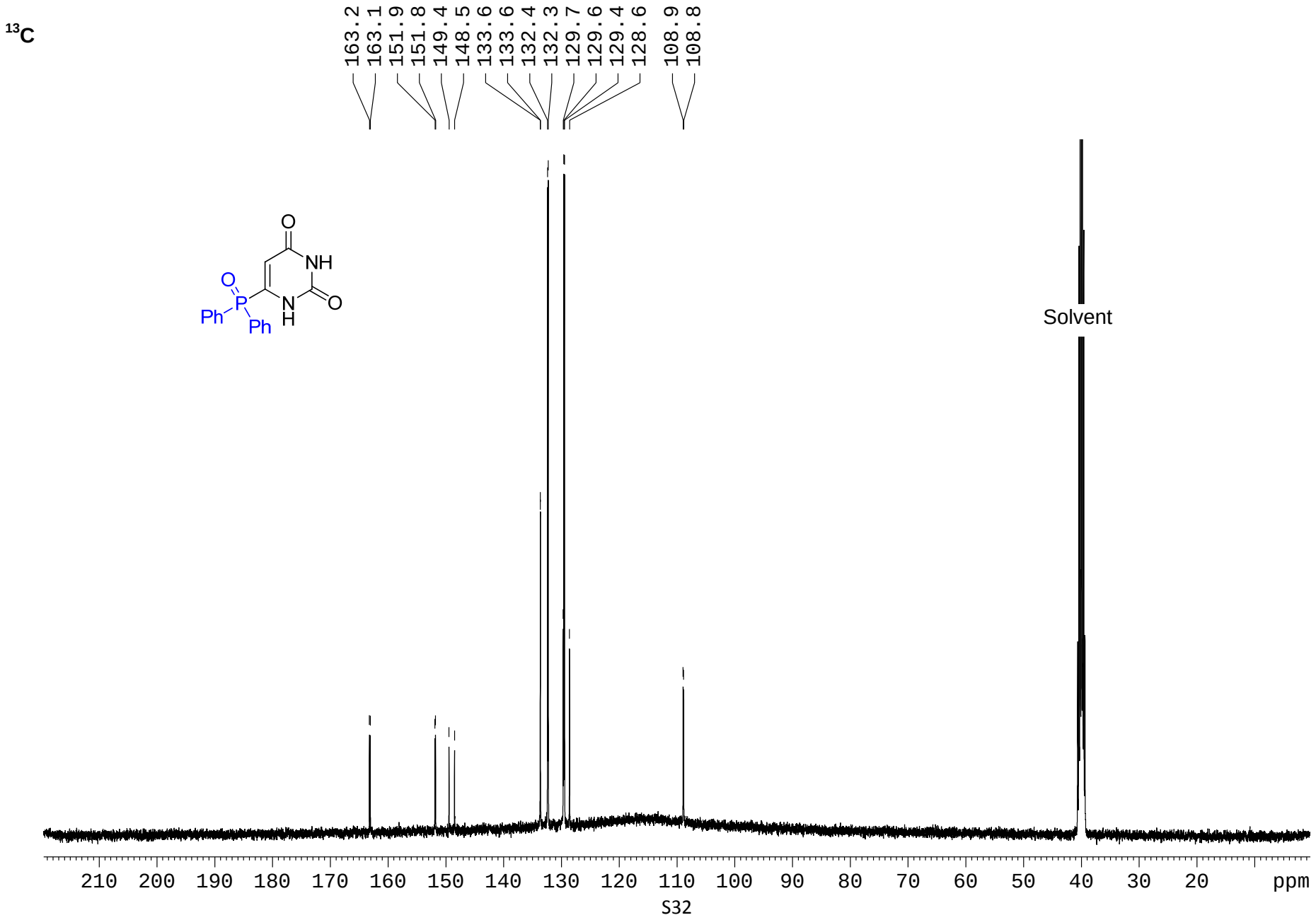
O
NH
O
P
N
H
Ph
Ph
25
24
23
22
21
20
ppm
100
50
0
-50
-100
-150
-200
ppm


13C
163.2
163.1
151.9
151.8
149.4
148.5
133.6
133.6
132.4
132.3
129.7
129.6
129.4
128.6
108.9
108.8
O
NH
O
P
N
H
O
Ph
Ph
Solvent
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm