Thermodynamic epimeric equilibration and crystallisation-induced dynamic resolution of lobelanine, norlobelanine and related analogues

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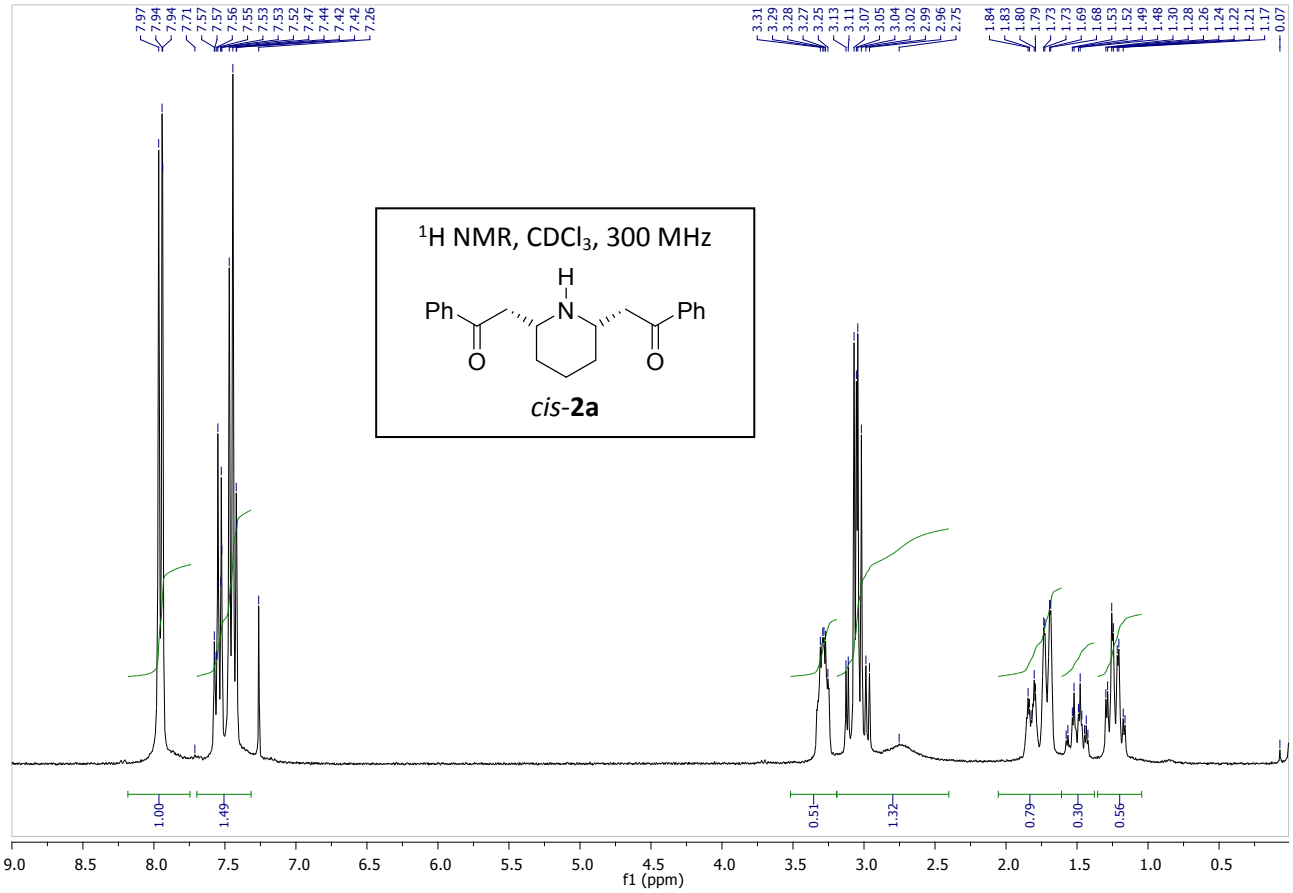
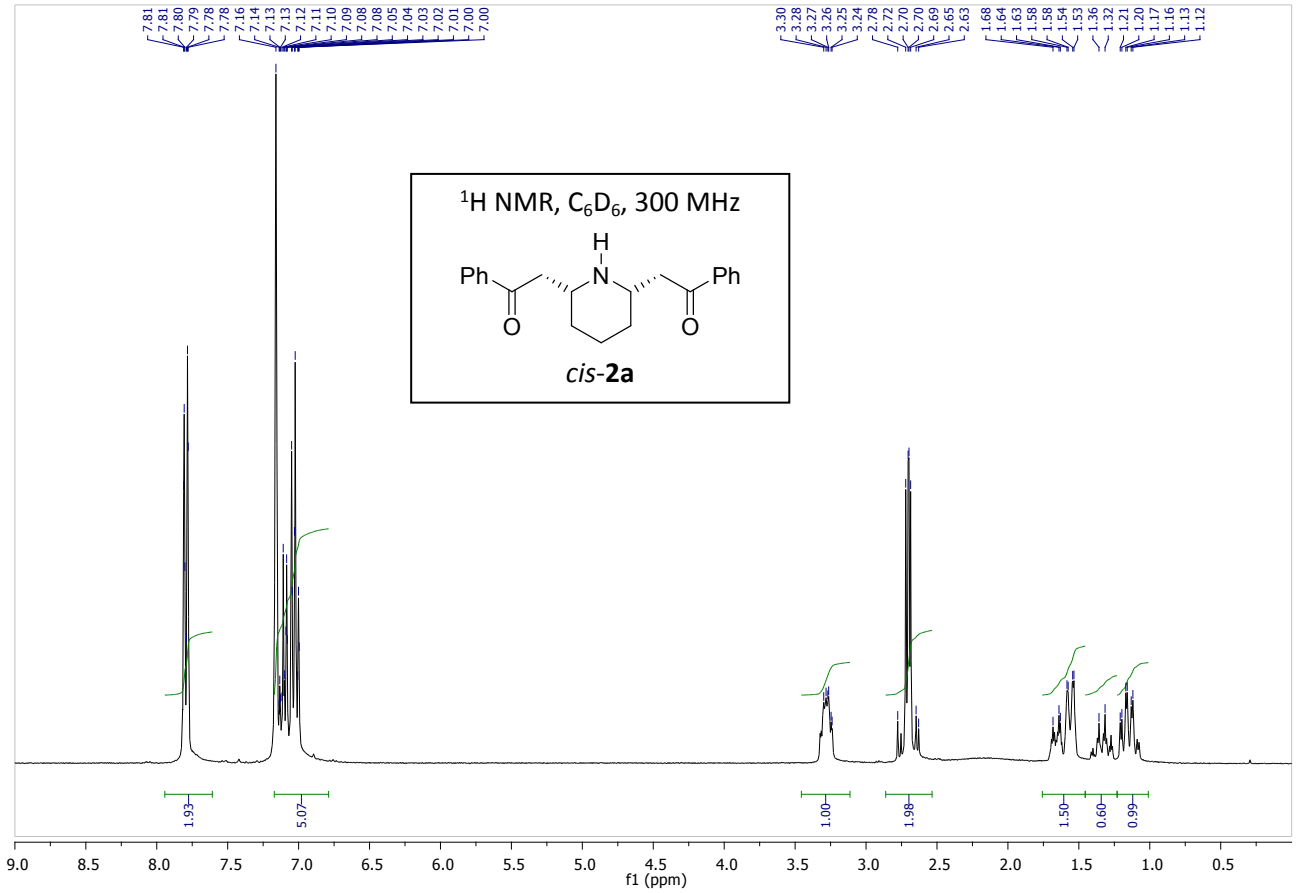
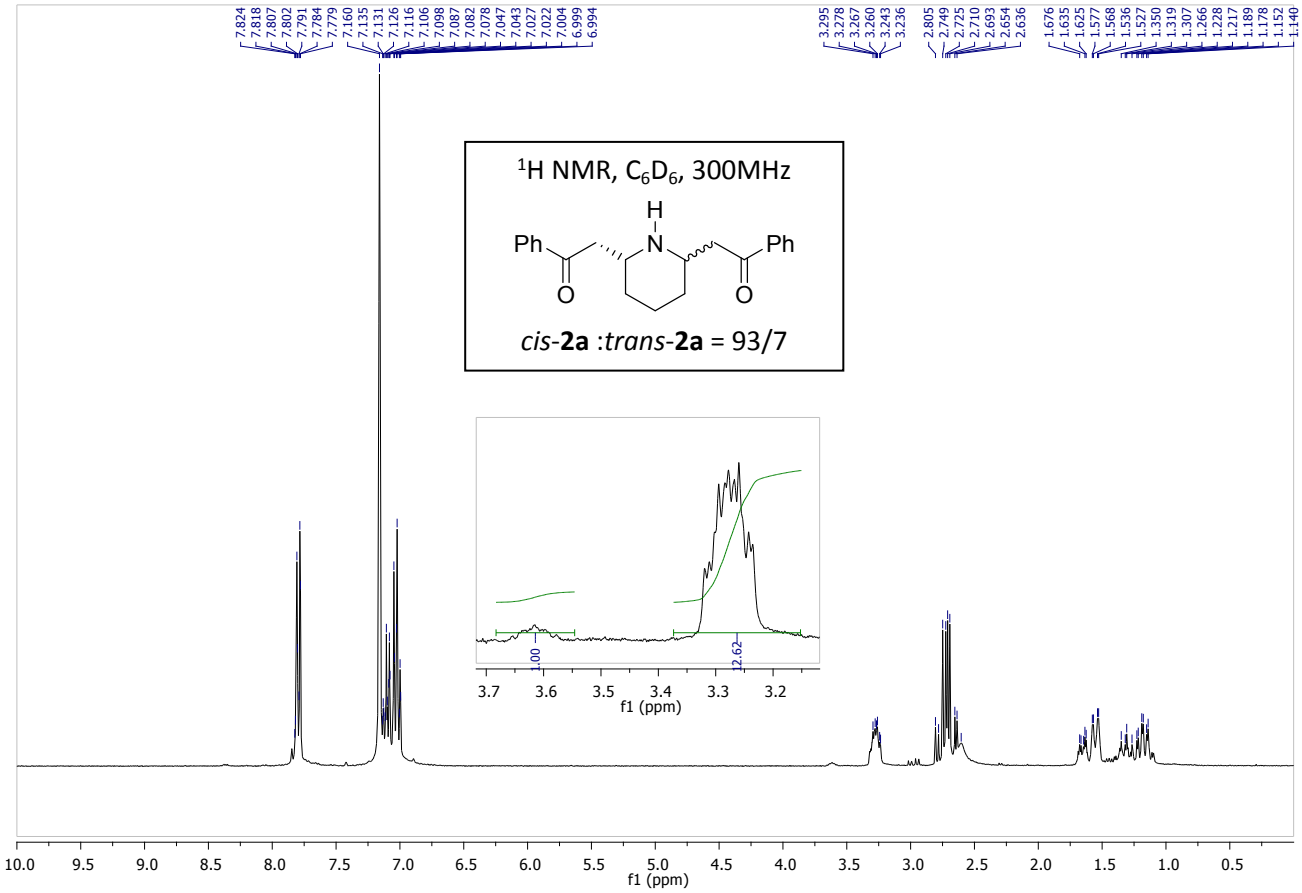
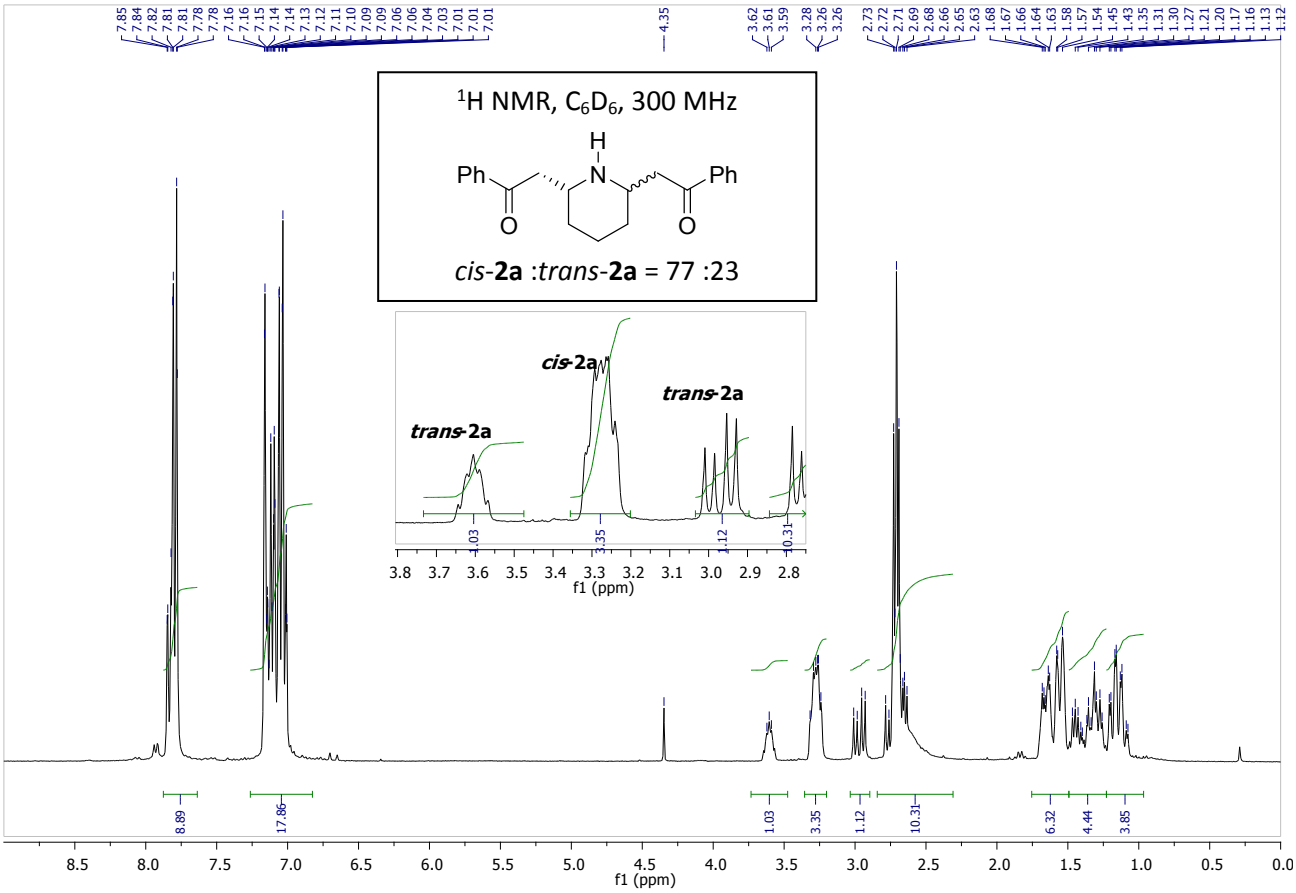
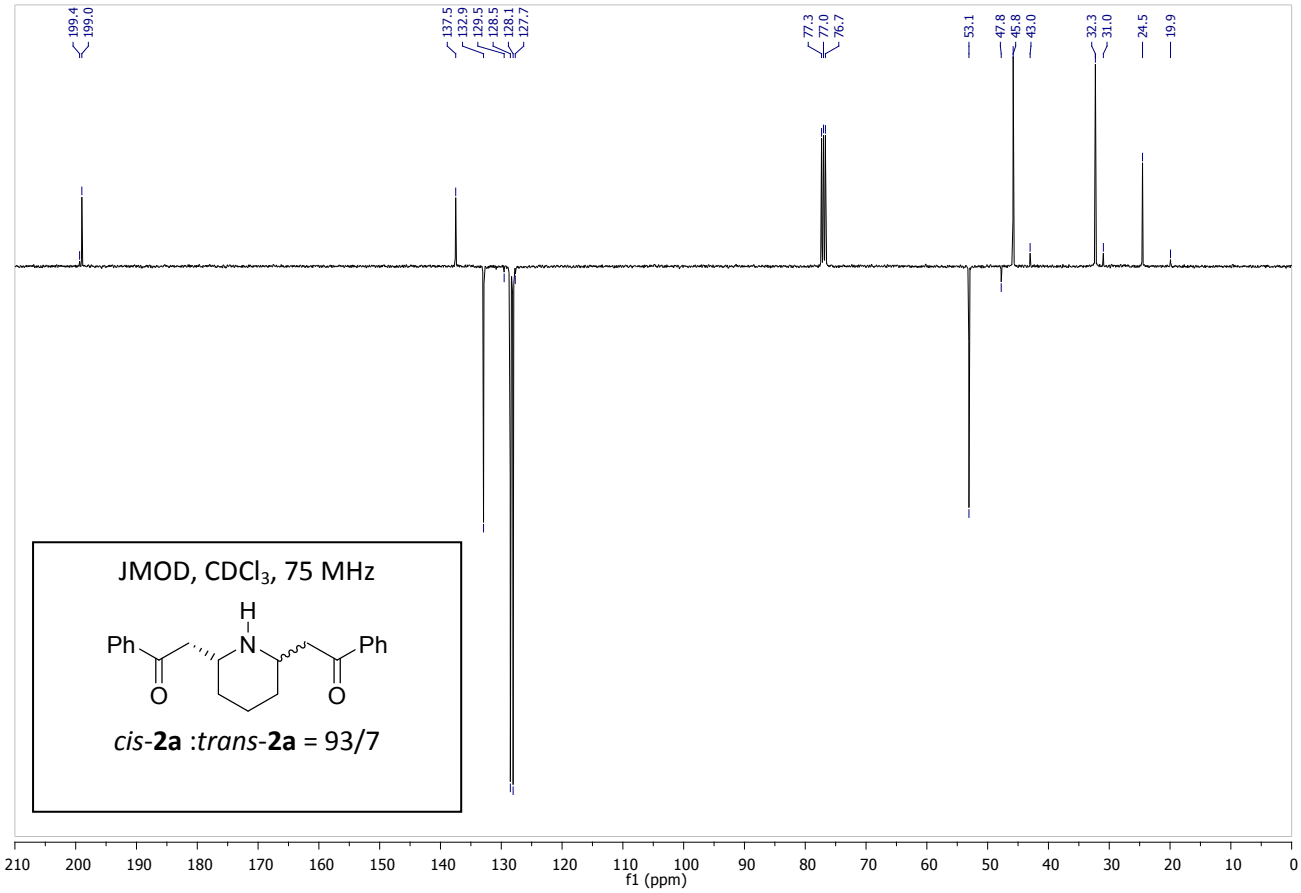

^{1}H NMR, $CDCl_3$, 300 MHz
Ph
H
N
O
O
Ph
cis-**2a**
f1 (ppm)

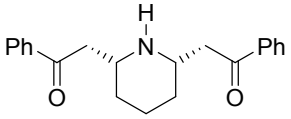

7.81
7.81
7.80
7.79
7.78
7.78
7.16
7.14
7.13
7.13
7.12
7.11
7.10
7.09
7.08
7.08
7.05
7.04
7.03
7.02
7.01
7.00
7.00
3.30
3.28
3.27
3.26
3.25
3.24
2.78
2.72
2.70
2.70
2.69
2.65
2.63
1.68
1.64
1.63
1.58
1.58
1.54
1.53
1.36
1.32
1.21
1.20
1.17
1.16
1.13
1.12
^{1}H NMR, C_6D_6, 300 MHz
Ph
H
N
Ph
O
O
cis-**2a**
1.93
5.07
1.00
1.98
1.50
0.60
0.99
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
f1 (ppm)


7.824
7.818
7.807
7.802
7.791
7.784
7.779
7.160
7.135
7.131
7.126
7.116
7.106
7.098
7.087
7.082
7.078
7.047
7.043
7.027
7.022
7.004
6.999
6.994
3.295
3.278
3.267
3.260
3.243
3.236
2.805
2.749
2.725
2.710
2.693
2.654
2.636
1.676
1.635
1.625
1.577
1.568
1.536
1.527
1.350
1.319
1.307
1.266
1.228
1.217
1.189
1.178
1.152
1.140
^{1}H NMR, C_6D_6, 300MHz
H
N
Ph
Ph
O
O
cis-**2a** :*trans*-**2a** = 93/7
1.00
12.62
3.7
3.6
3.5
3.4
3.3
3.2
f1 (ppm)
10.0
9.5
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
f1 (ppm)

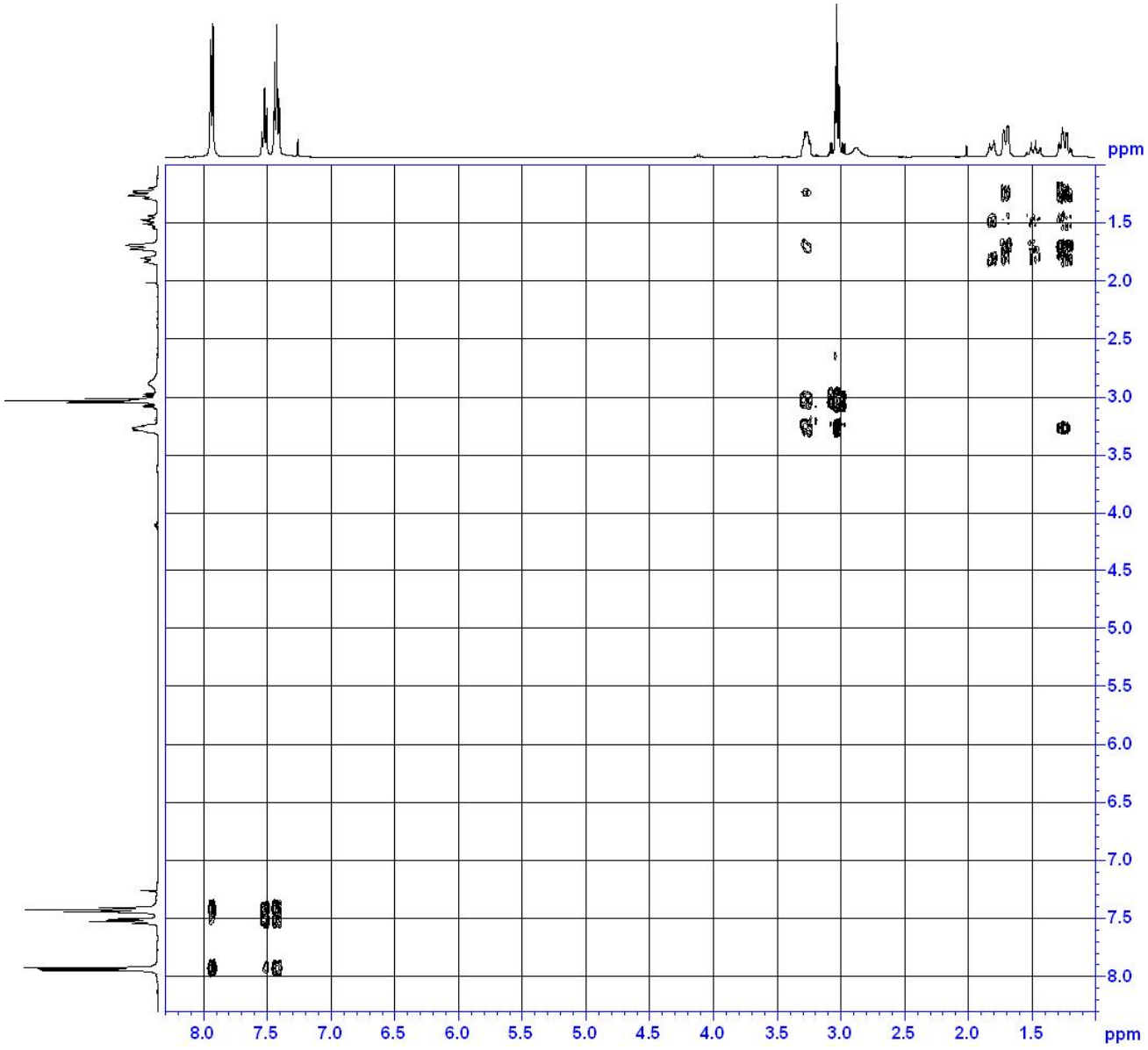

^{1}H NMR, C_6D_6, 300 MHz
Ph
N
H
Ph
O
O
cis-**2a** :*trans*-**2a** = 77 :23
cis-**2a**
trans-**2a**
trans-**2a**
f1 (ppm)
f1 (ppm)


199.4
199.0
137.5
132.9
129.5
128.5
128.1
127.7
77.3
77.0
76.7
53.1
47.8
45.8
43.0
32.3
31.0
24.5
19.9
JMOD, CDCl3, 75 MHz
H
N
Ph
Ph
O
O
cis-2a :trans-2a = 93/7
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

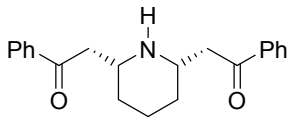
COSY, $CDCl_3$, 400 MHz



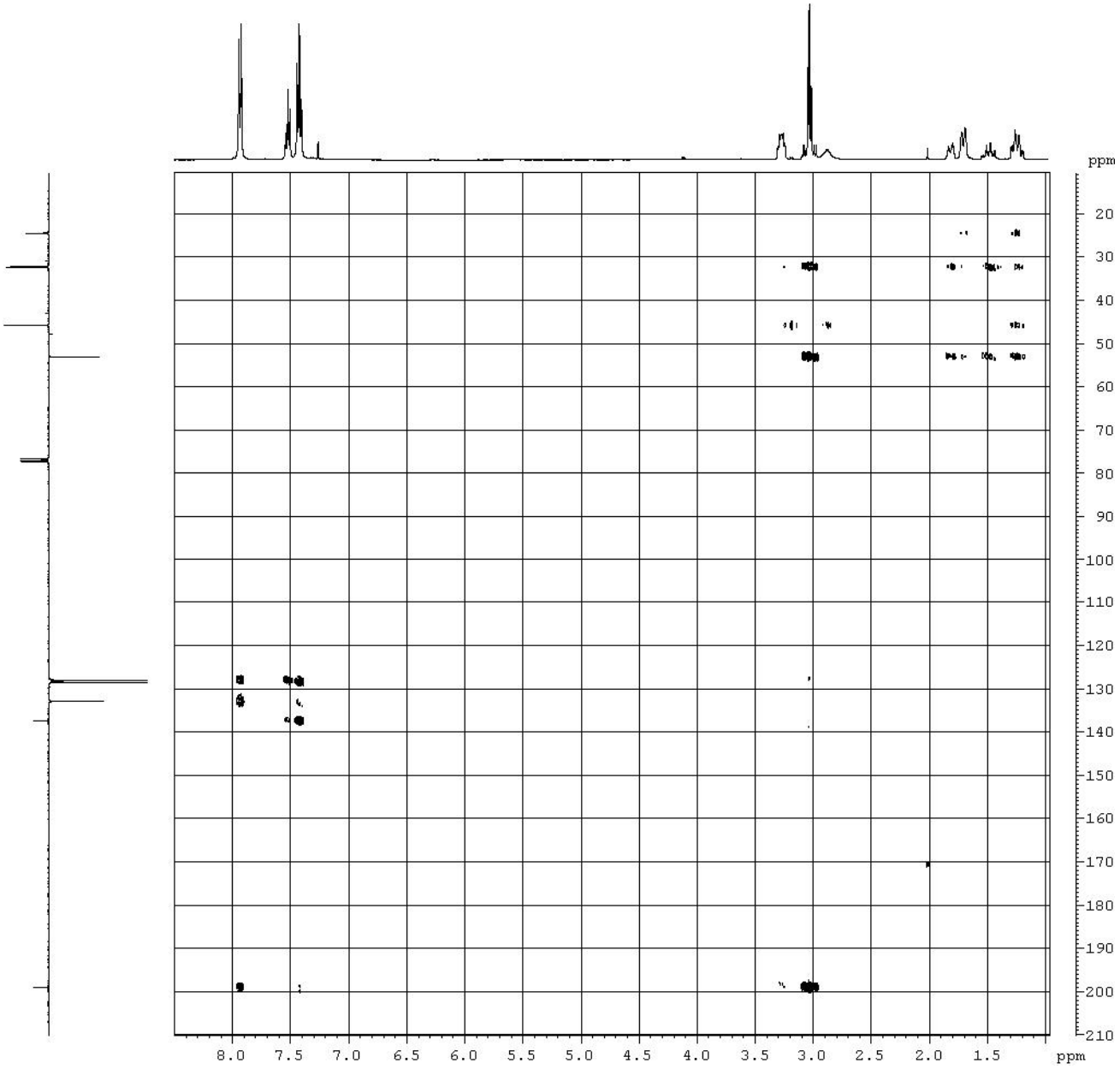
cis-**2a**



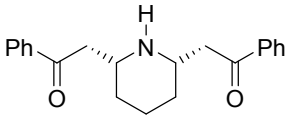
HMBC, $CDCl_3$, 400 MHz



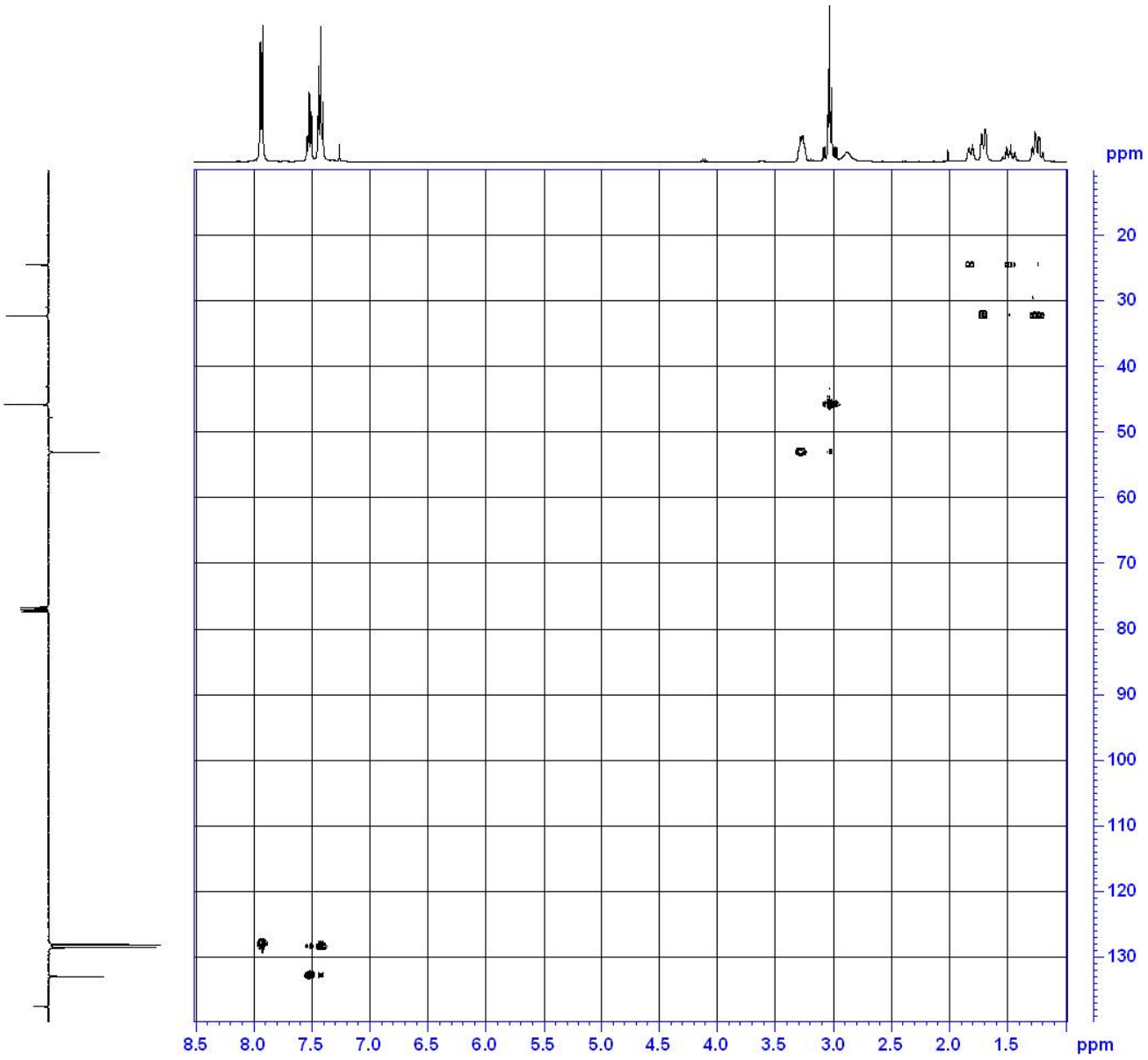
cis-**2a**



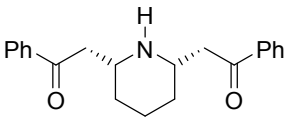
HSQC, $CDCl_3$, 400 MHz



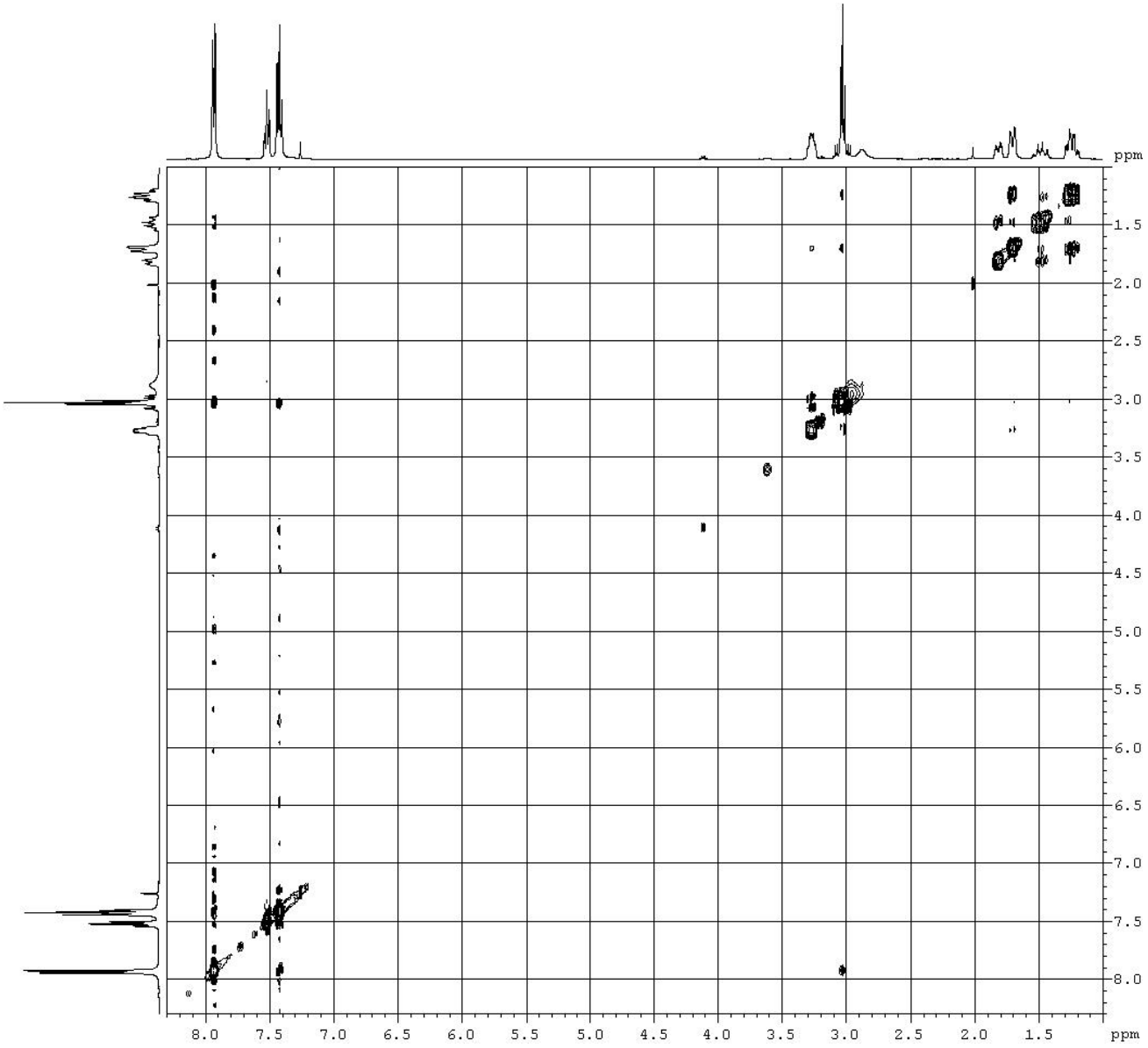
cis-**2a**

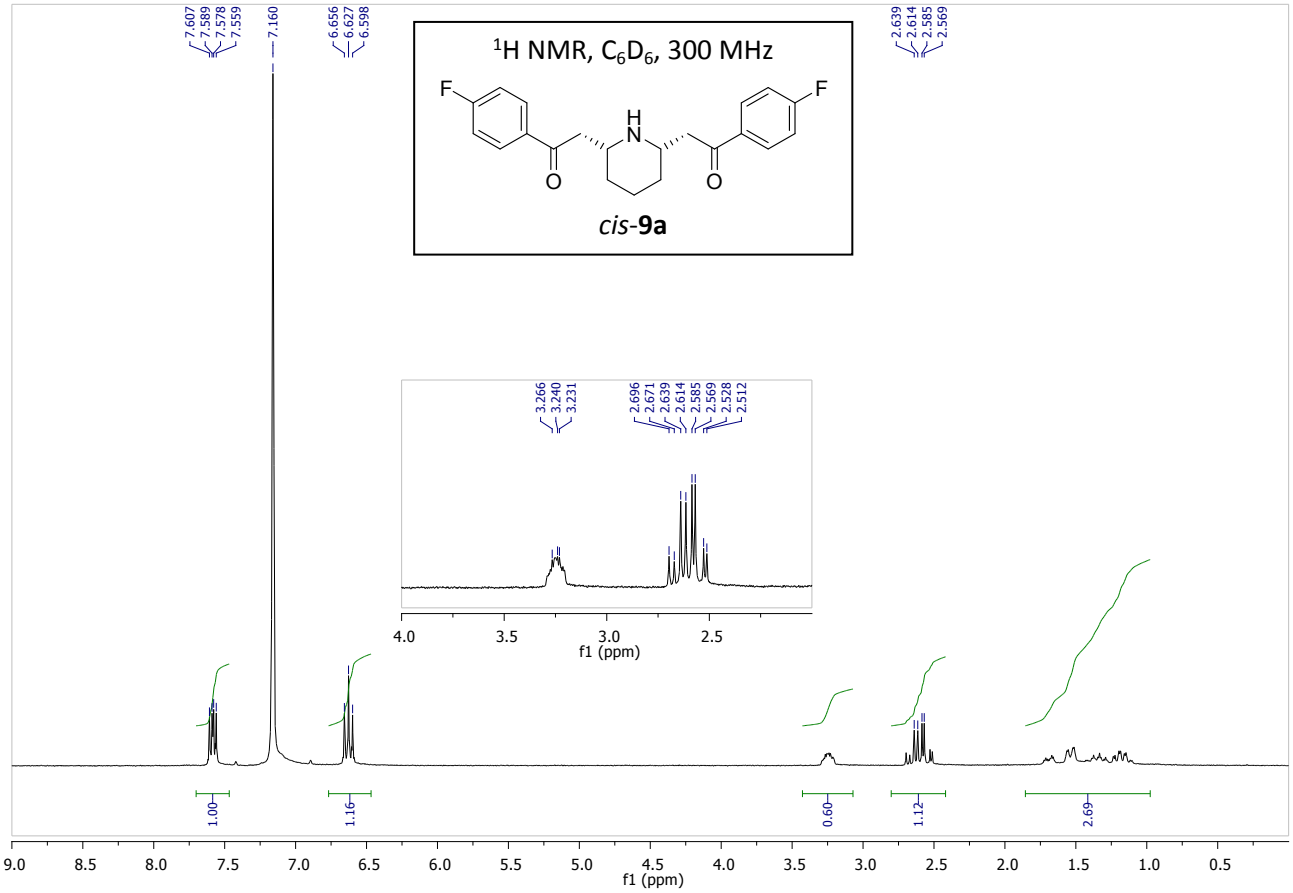


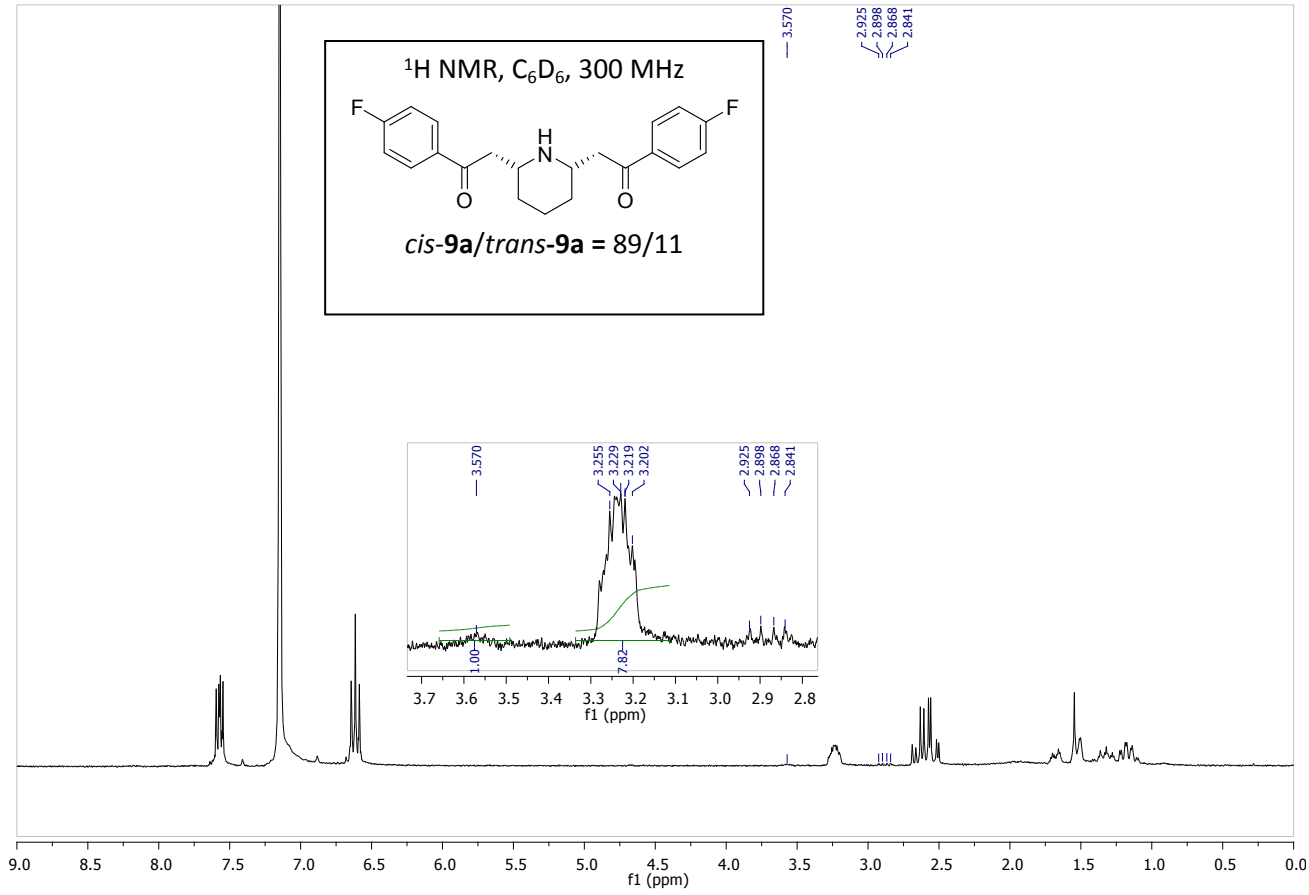
NOESY, $CDCl_3$, 400 MHz

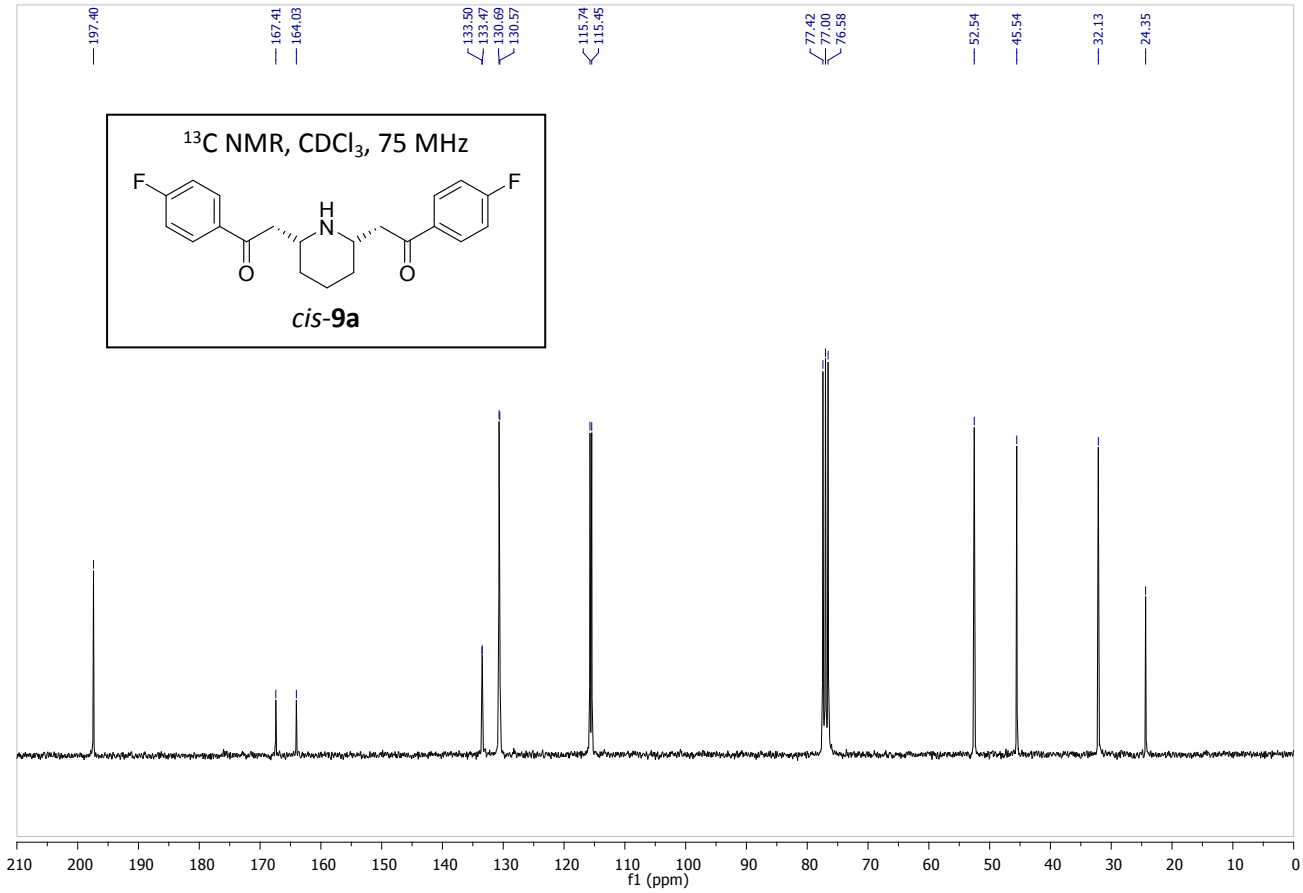


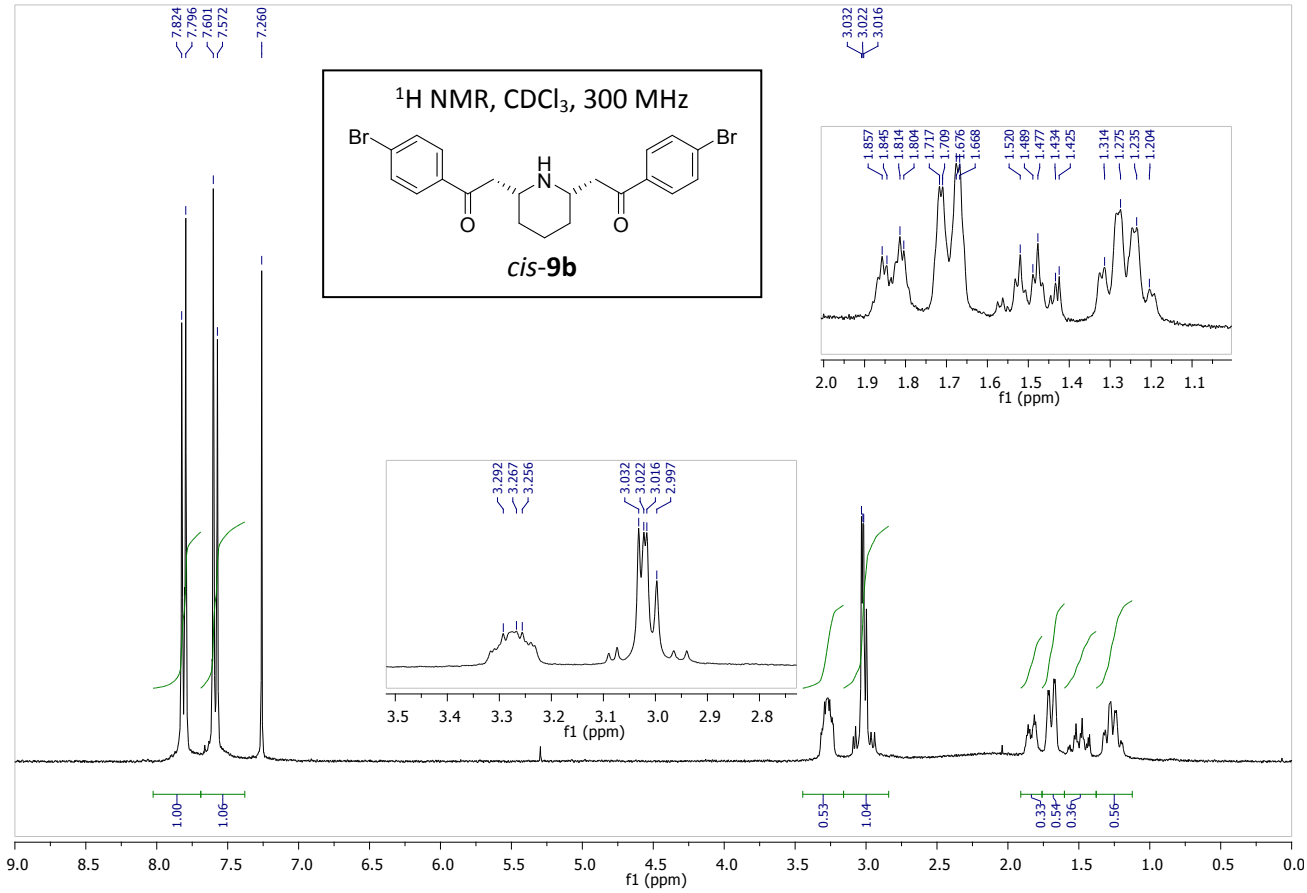
cis-**2a**

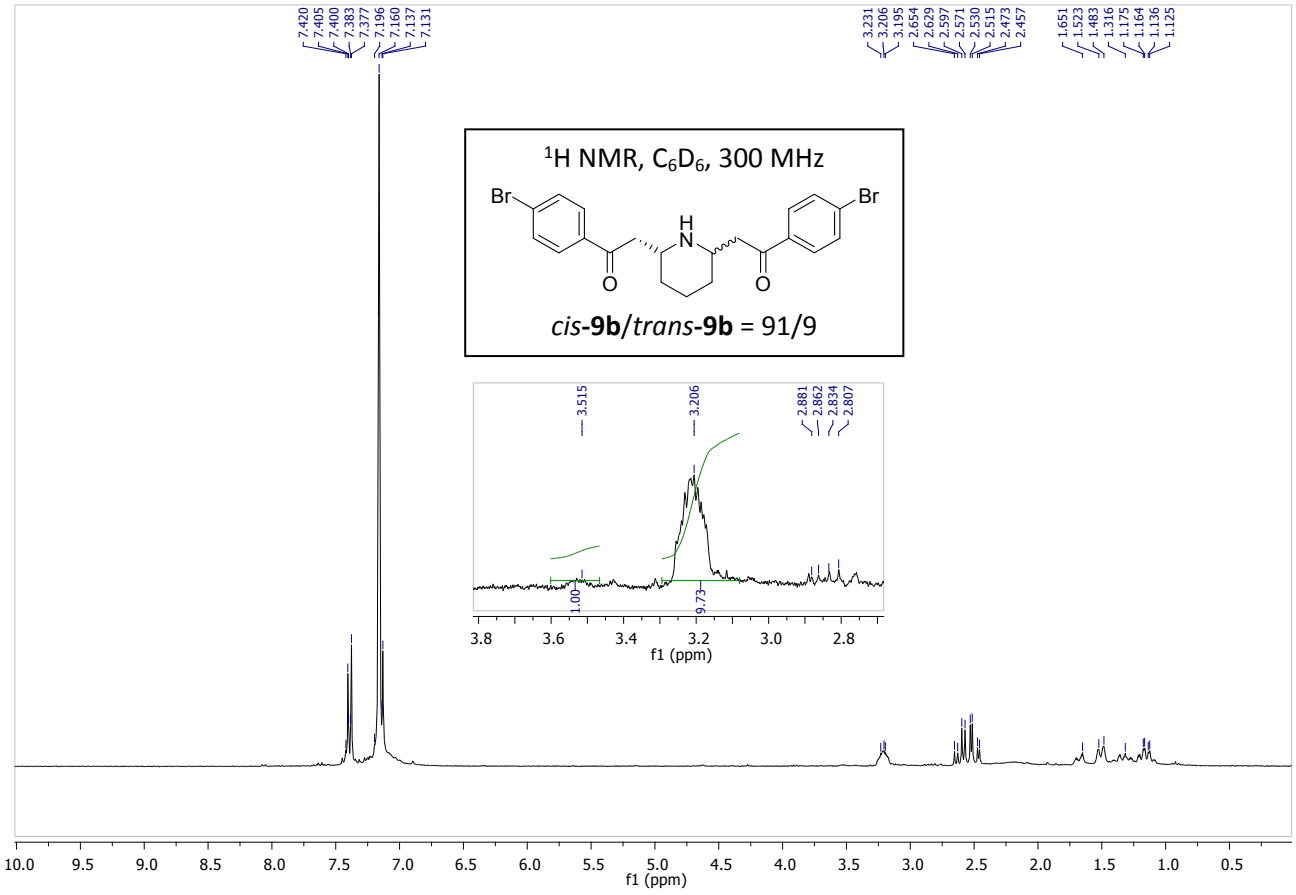


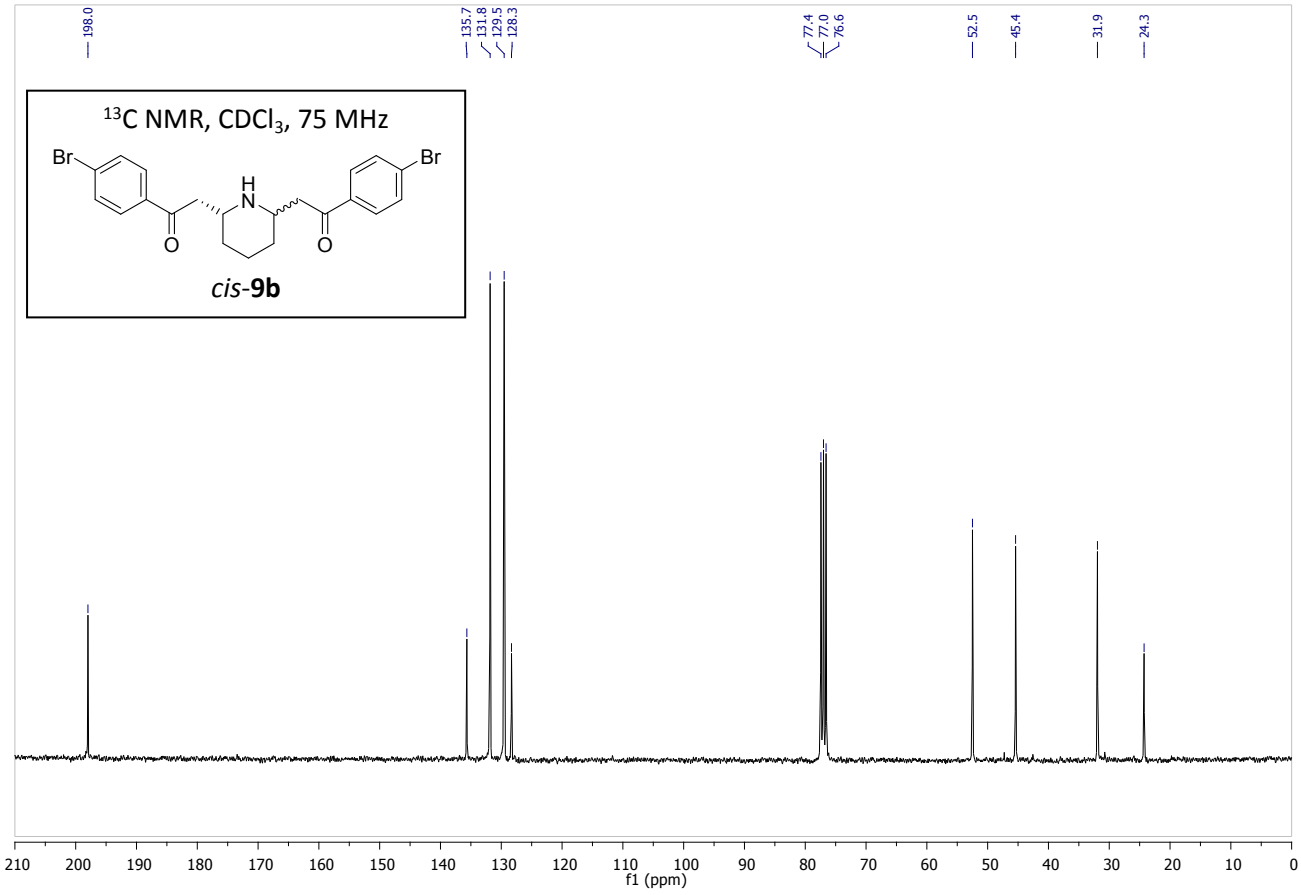

7.607
7.589
7.578
7.559
7.160
6.656
6.627
6.598
2.639
2.614
2.585
2.569
^{1}H NMR, C_6D_6, 300 MHz
F
F
H
N
O
O
cis-**9a**
3.266
3.240
3.231
2.696
2.671
2.639
2.614
2.585
2.569
2.528
2.512
4.0
3.5
3.0
2.5
f1 (ppm)
1.00
1.16
0.60
1.12
2.69
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

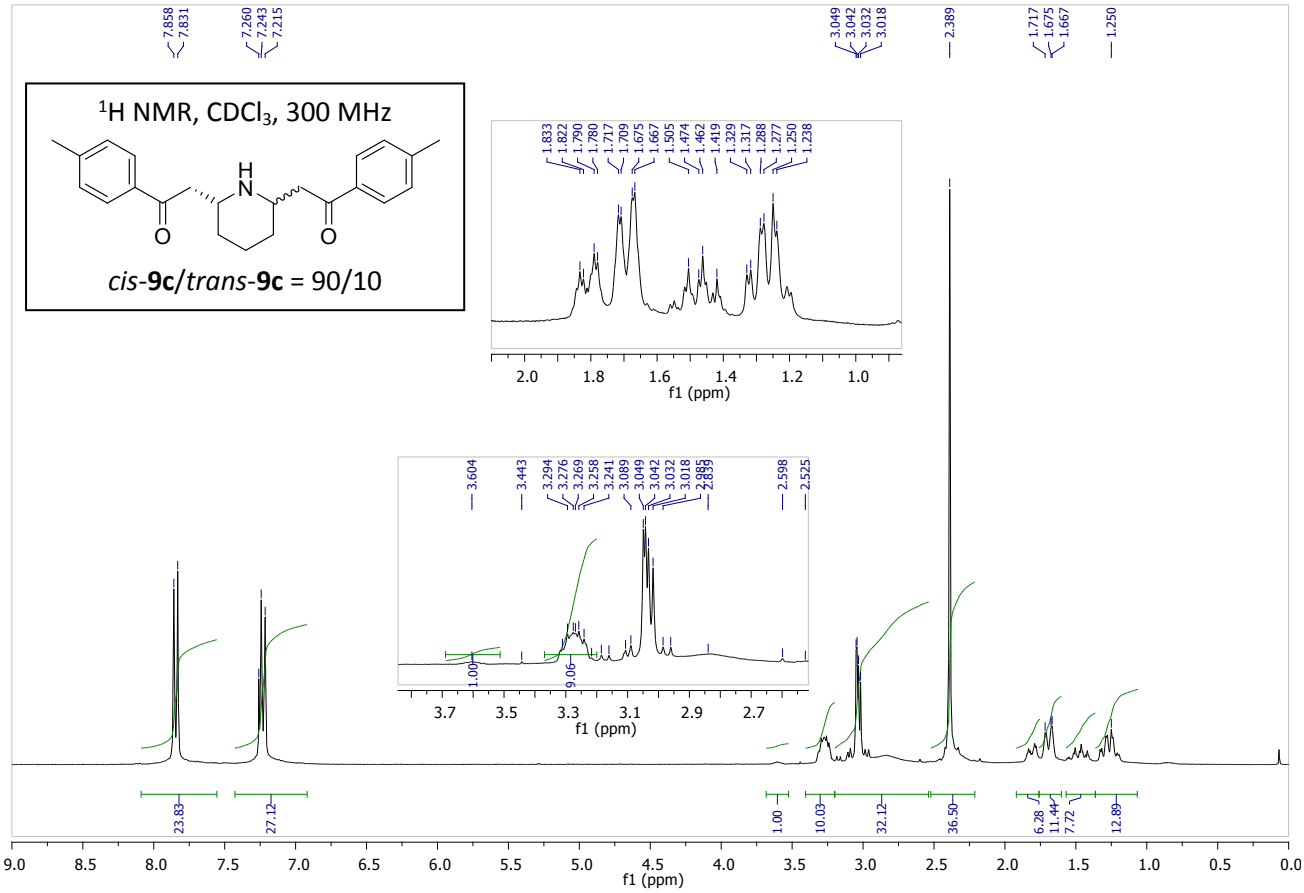

^{1}H NMR, C_6D_6, 300 MHz
F
F
H
N
O
O
cis-**9a**/*trans*-**9a** = 89/11
3.570
2.925
2.898
2.868
2.841
3.255
3.229
3.219
3.202
1.00
7.82
f1 (ppm)
f1 (ppm)

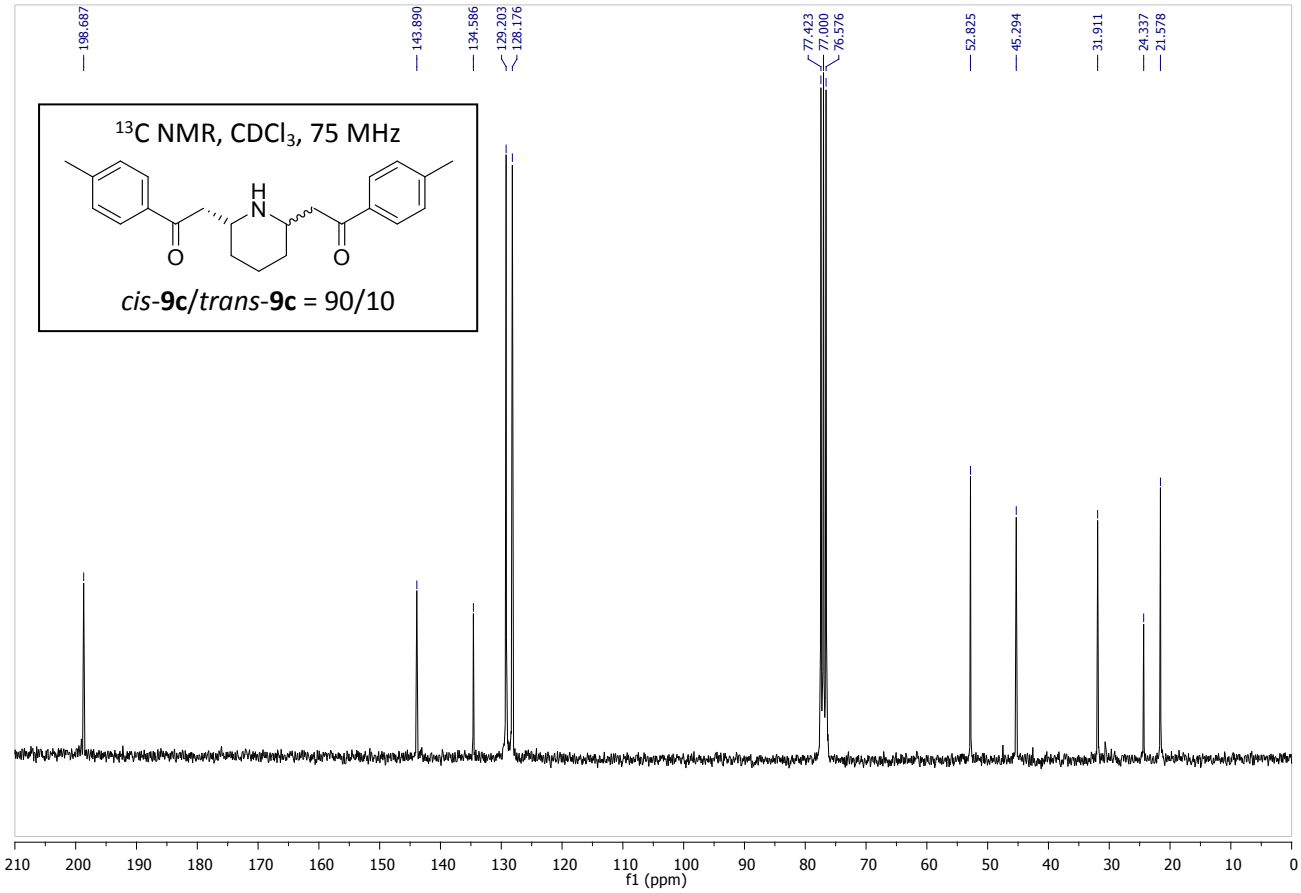

197.40
167.41
164.03
133.50
133.47
130.69
130.57
115.74
115.45
77.42
77.00
76.58
52.54
45.54
32.13
24.35
13C NMR, CDCl3, 75 MHz
F
F
H
N
O
O
cis-9a
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

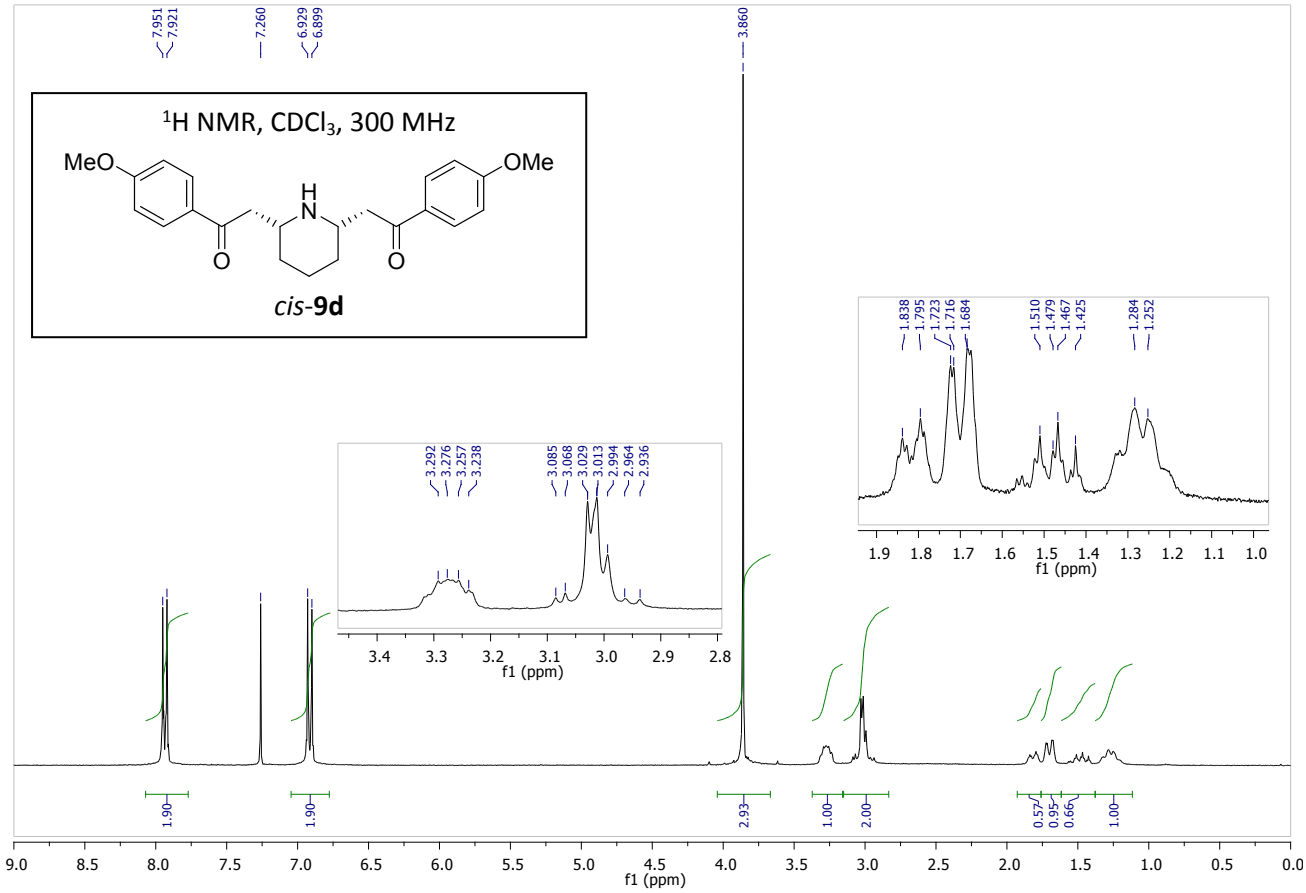

7.824
7.796
7.601
7.572
7.260
3.032
3.022
3.016
^{1}H NMR, CDCl$_3$, 300 MHz
Br
Br
H
N
O
O
cis-**9b**
1.857
1.845
1.814
1.804
1.717
1.709
1.676
1.668
1.520
1.489
1.477
1.434
1.425
1.314
1.275
1.235
1.204
2.0 1.9 1.8 1.7 1.6 1.5 1.4 1.3 1.2 1.1
f1 (ppm)
3.292
3.267
3.256
3.032
3.022
3.016
2.997
3.5 3.4 3.3 3.2 3.1 3.0 2.9 2.8
f1 (ppm)
1.00
1.06
0.53
1.04
0.33
0.54
0.36
0.56
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 0.0
f1 (ppm)

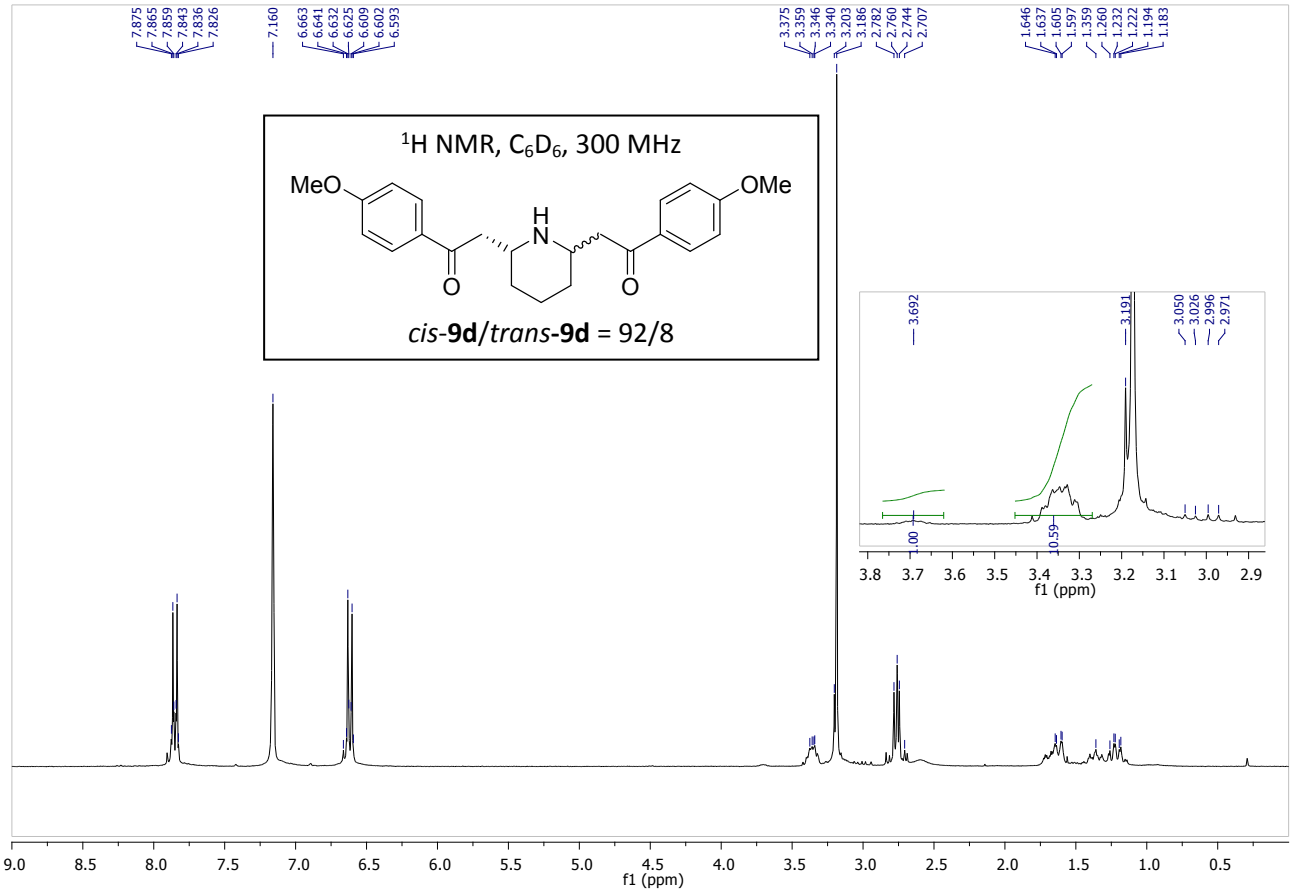

7.420
7.405
7.400
7.383
7.377
7.196
7.160
7.137
7.131
3.231
3.206
3.195
2.654
2.629
2.597
2.571
2.530
2.515
2.473
2.457
1.651
1.523
1.483
1.316
1.175
1.164
1.136
1.125
1H NMR, C6D6, 300 MHz
Br
Br
H
N
O
O
cis-9b/trans-9b = 91/9
3.515
3.206
2.881
2.862
2.834
2.807
1.00
9.73
3.8
3.6
3.4
3.2
3.0
2.8
f1 (ppm)
10.0
9.5
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
f1 (ppm)

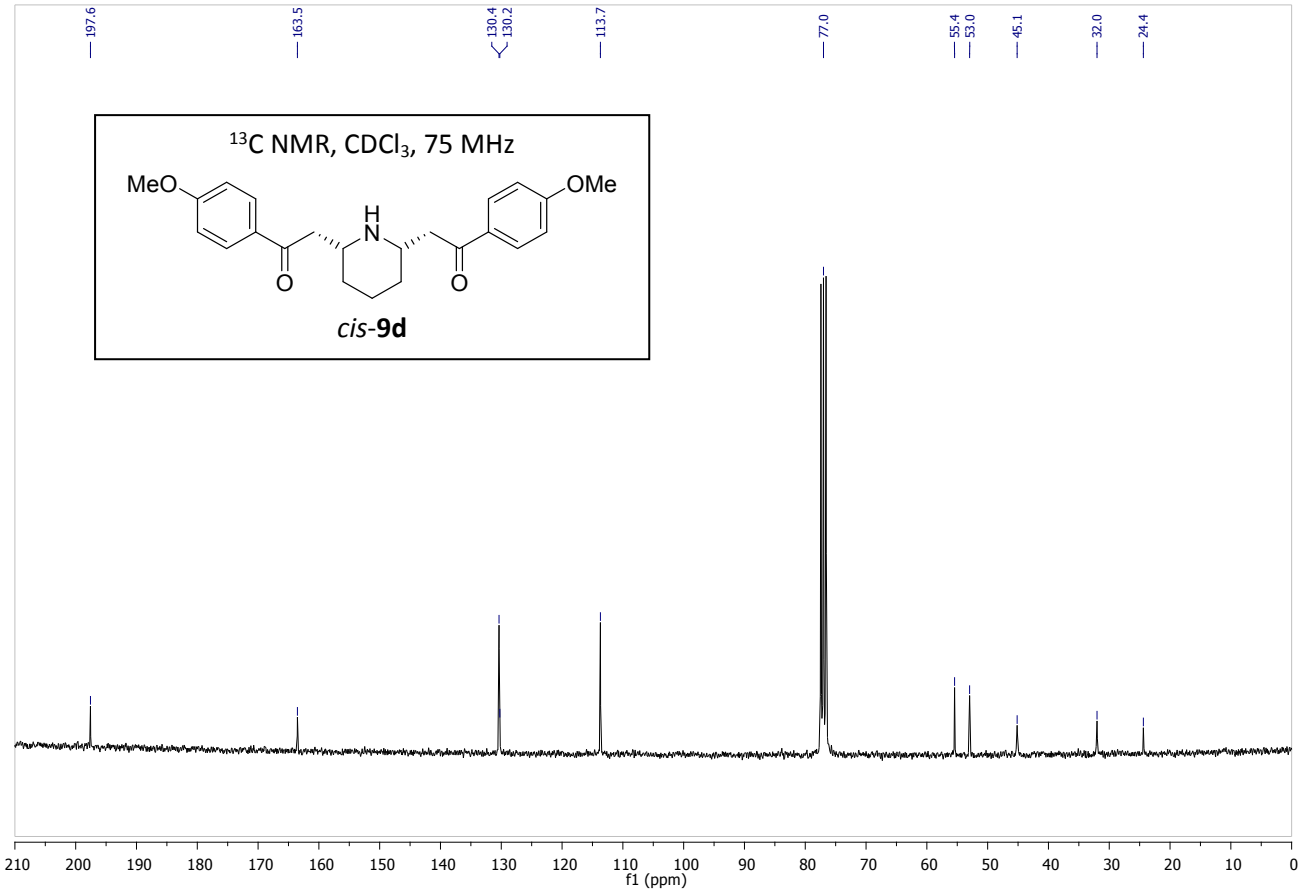

198.0
135.7
131.8
129.5
128.3
77.4
77.0
76.6
52.5
45.4
31.9
24.3
^{13}C NMR, $CDCl_3$, 75 MHz
Br
Br
H
N
O
O
cis-**9b**
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

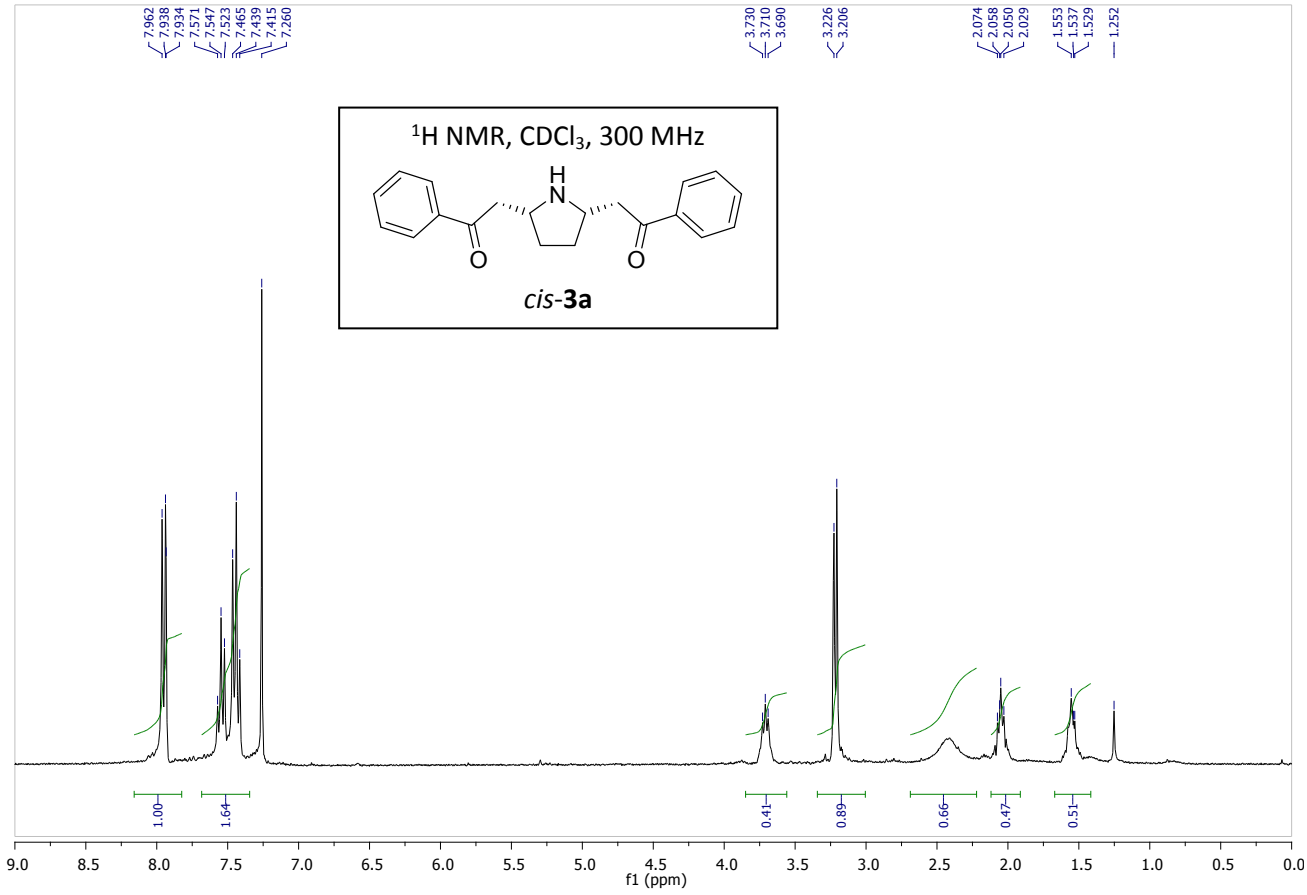

^{1}H NMR, $CDCl_3$, 300 MHz
cis-**9c**/*trans*-**9c** = 90/10
f1 (ppm)

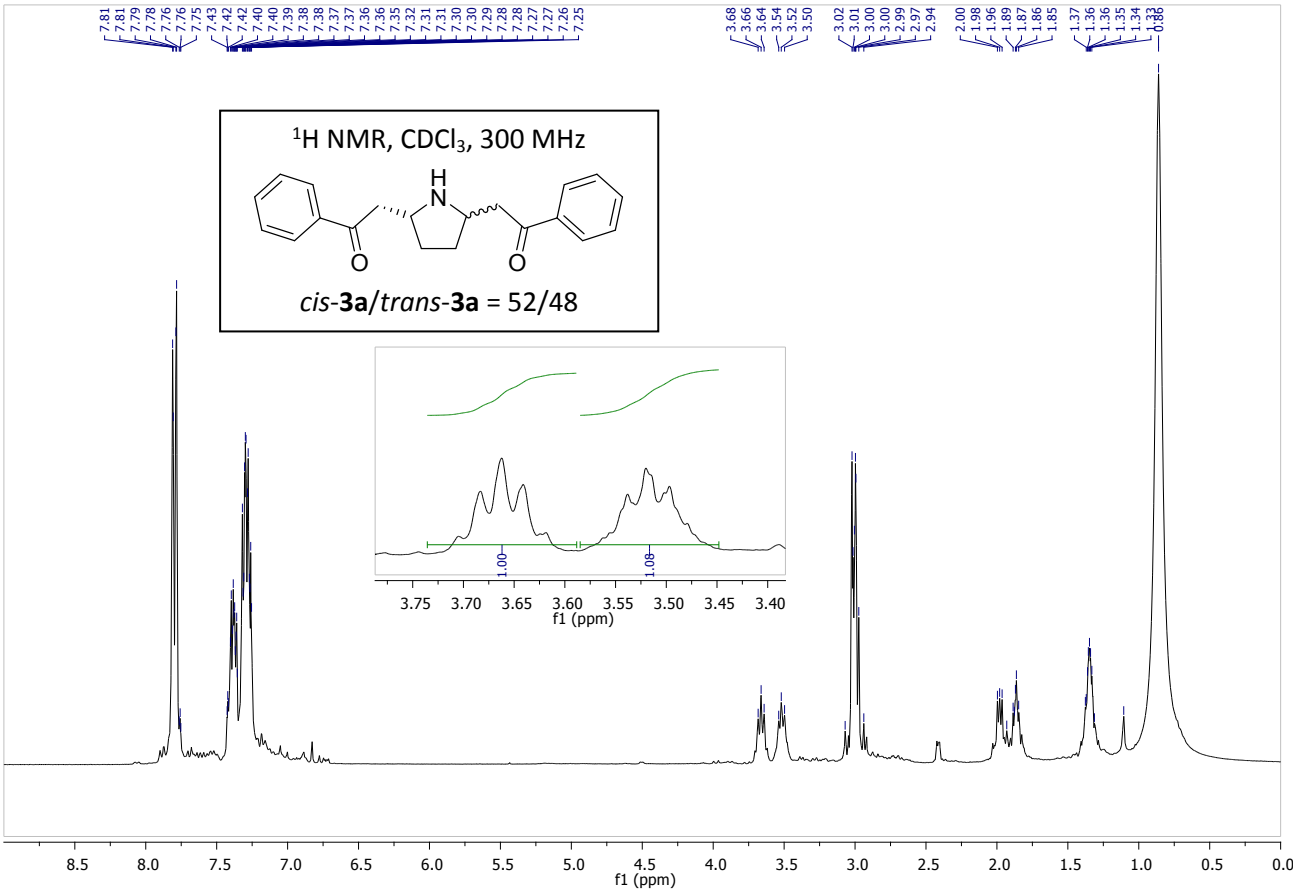

198.687
143.890
134.586
129.203
128.176
77.423
77.000
76.576
52.825
45.294
31.911
24.337
21.578
^{13}C NMR, $CDCl_3$, 75 MHz
H
N
O
O
cis-**9c**/*trans*-**9c** = 90/10
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

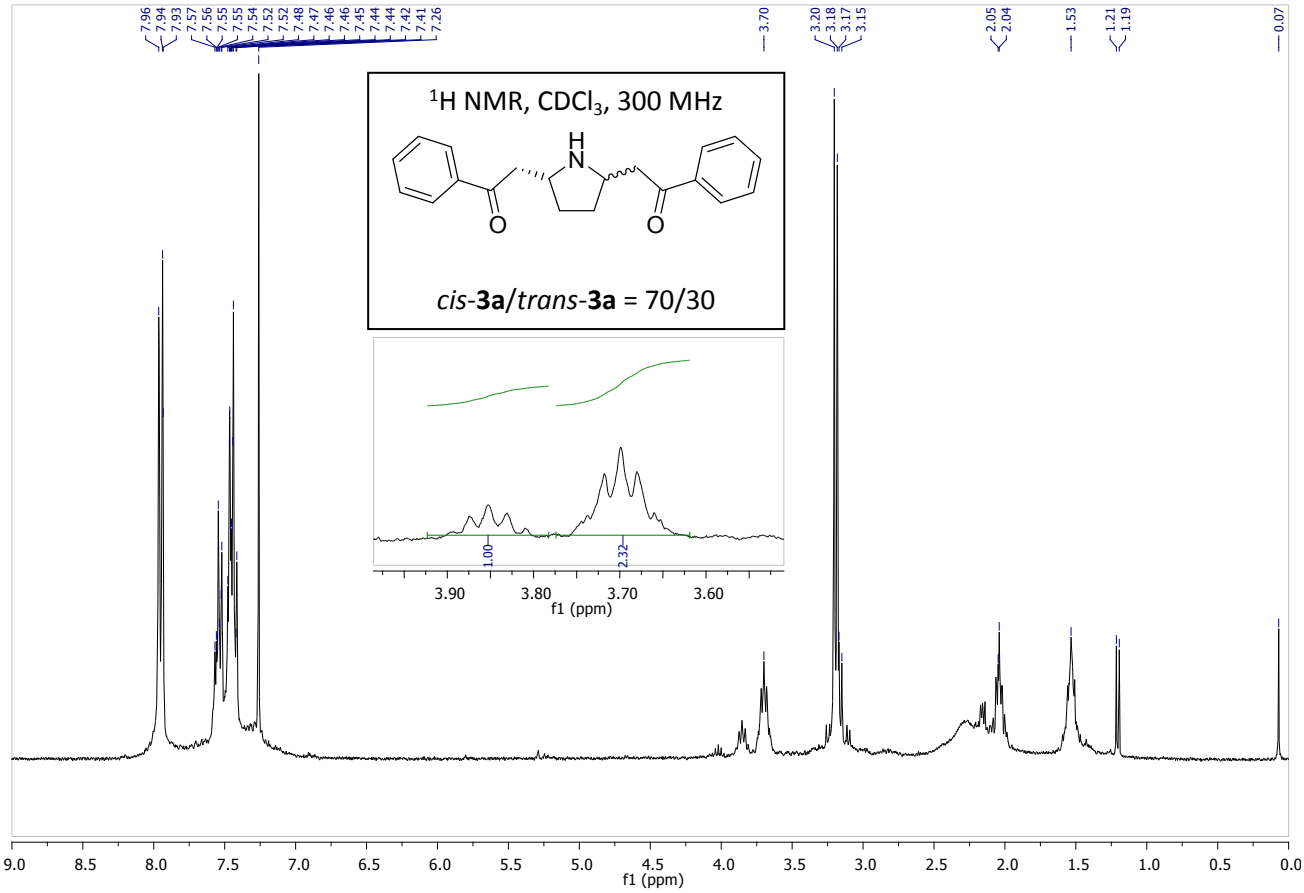

7.951
7.921
7.260
6.929
6.899
3.860
1H NMR, CDCl3, 300 MHz
MeO
OMe
H
N
O
O
cis-9d
3.292
3.276
3.257
3.238
3.085
3.068
3.029
3.013
2.994
2.964
2.936
1.838
1.795
1.723
1.716
1.684
1.510
1.479
1.467
1.425
1.284
1.252
1.90
1.90
2.93
1.00
2.00
0.57
0.95
0.66
1.00
f1 (ppm)

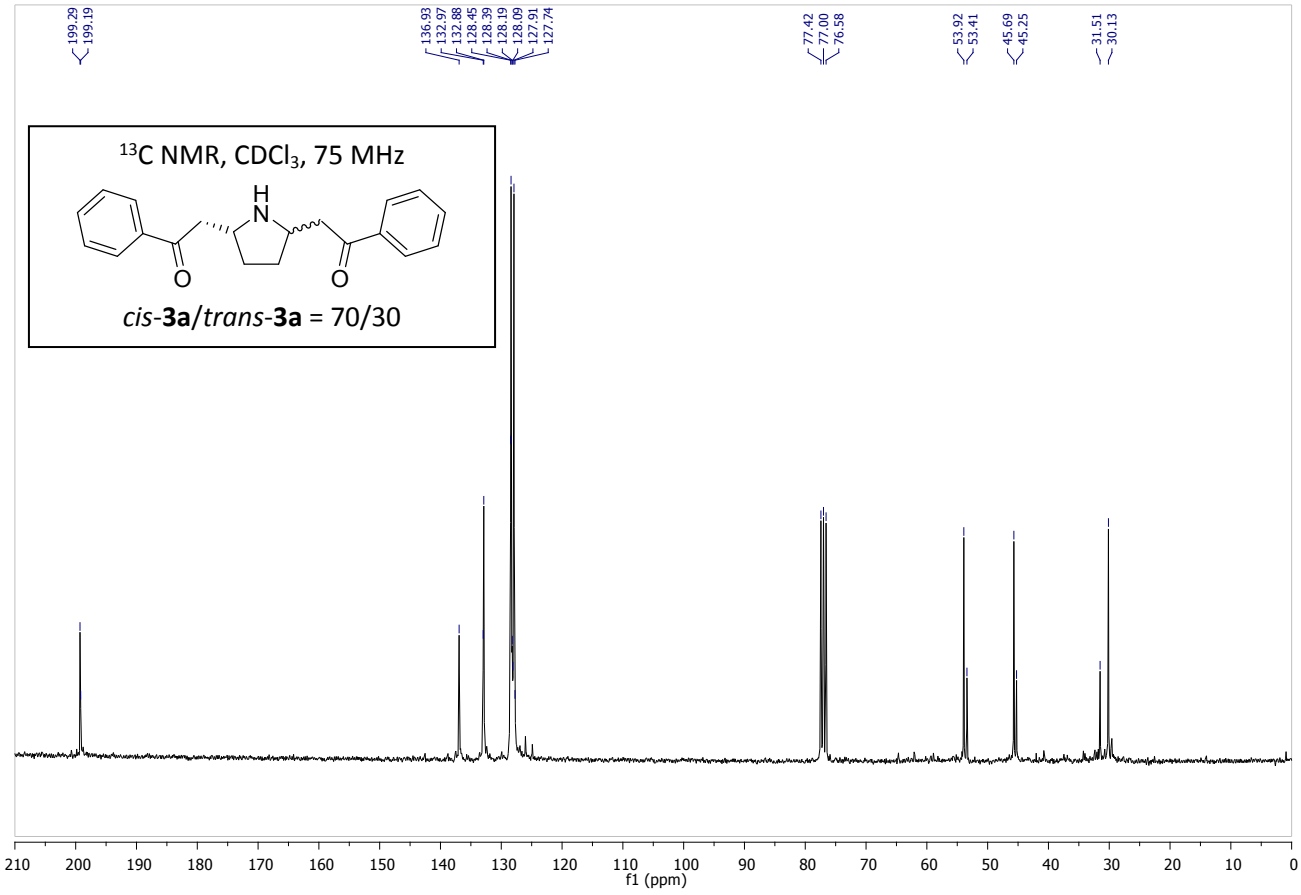

7.875
7.865
7.859
7.843
7.836
7.826
7.160
6.663
6.641
6.632
6.625
6.609
6.602
6.593
3.375
3.359
3.346
3.340
3.203
3.186
2.782
2.760
2.744
2.707
1.646
1.637
1.605
1.597
1.359
1.260
1.232
1.222
1.194
1.183
^{1}H NMR, C_6D_6, 300 MHz
MeO
OMe
H
N
O
O
cis-**9d**/*trans*-**9d** = 92/8
3.692
3.191
3.050
3.026
2.996
2.971
1.00
0.59
3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1 3.0 2.9
f1 (ppm)
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
f1 (ppm)

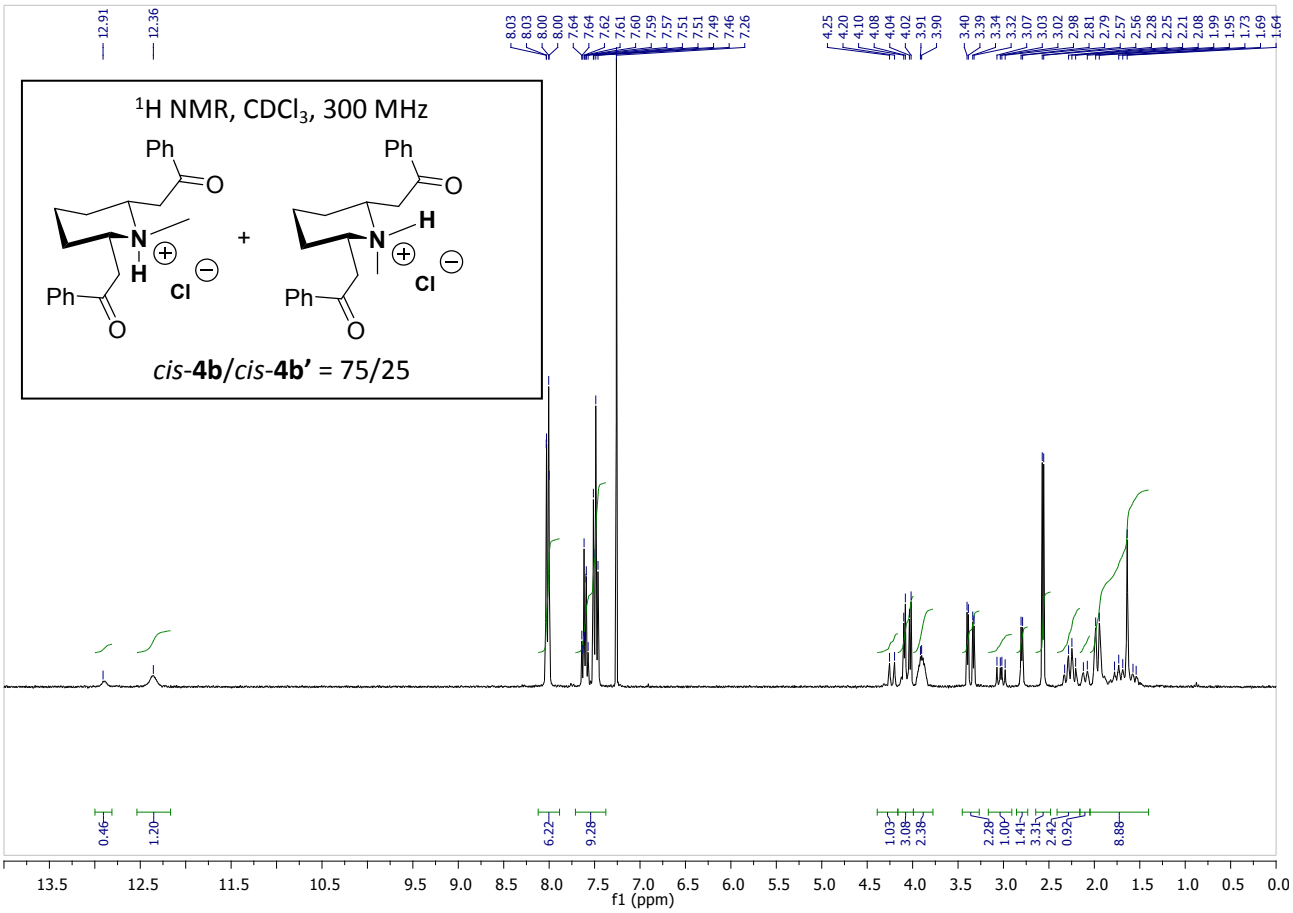

197.6
163.5
130.4
130.2
113.7
77.0
55.4
53.0
45.1
32.0
24.4
^{13}C NMR, $CDCl_3$, 75 MHz
MeO
OMe
H
N
O
O
cis-**9d**
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

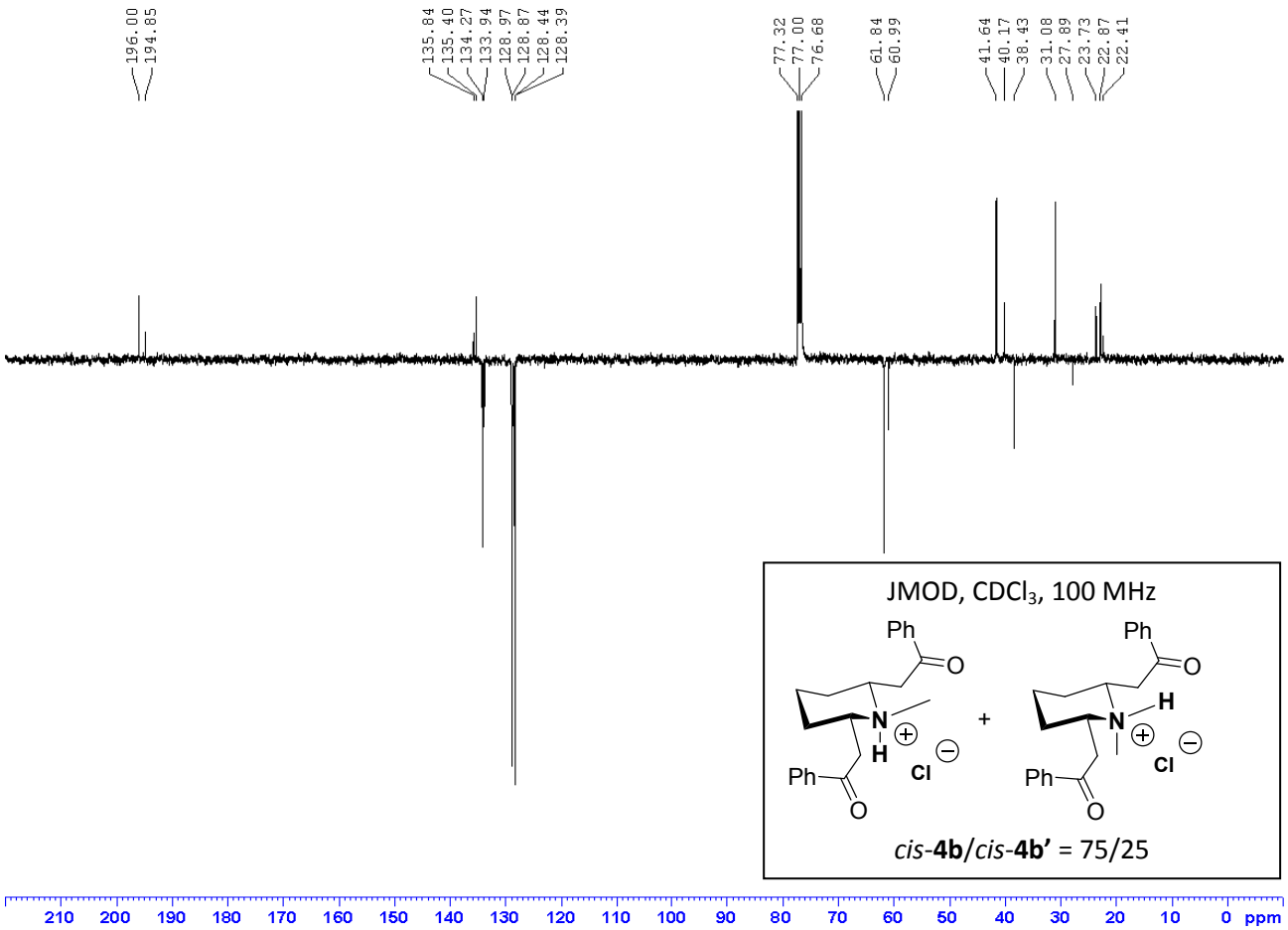

7.962
7.938
7.934
7.571
7.547
7.523
7.465
7.439
7.415
7.260
3.730
3.710
3.690
3.226
3.206
2.074
2.058
2.050
2.029
1.553
1.537
1.529
1.252
^{1}H NMR, $CDCl_3$, 300 MHz
H
N
O
O
cis-**3a**
1.00
1.64
0.41
0.89
0.66
0.47
0.51
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


^{1}H NMR, $CDCl_3$, 300 MHz
H
N
O
O
cis-**3a**/*trans*-**3a** = 52/48
1.00
1.09
3.75 3.70 3.65 3.60 3.55 3.50 3.45 3.40
f1 (ppm)
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 0.0
f1 (ppm)

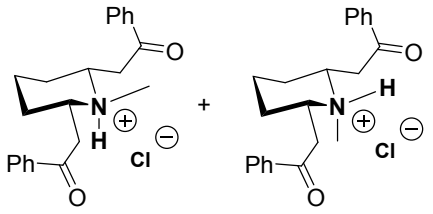

7.96
7.94
7.93
7.57
7.56
7.55
7.55
7.54
7.52
7.52
7.48
7.47
7.46
7.46
7.45
7.44
7.44
7.42
7.41
7.26
3.70
3.20
3.18
3.17
3.15
2.05
2.04
1.53
1.21
1.19
0.07
^{1}H NMR, $CDCl_3$, 300 MHz
H
N
O
O
cis-**3a**/*trans*-**3a** = 70/30
1.00
2.32
3.90
3.80
3.70
3.60
f1 (ppm)
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


199.29
199.19
136.93
132.97
132.88
128.45
128.39
128.19
128.09
127.91
127.74
77.42
77.00
76.58
53.92
53.41
45.69
45.25
31.51
30.13
^{13}C NMR, $CDCl_3$, 75 MHz
H
N
O
O
cis-**3a**/*trans*-**3a** = 70/30
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

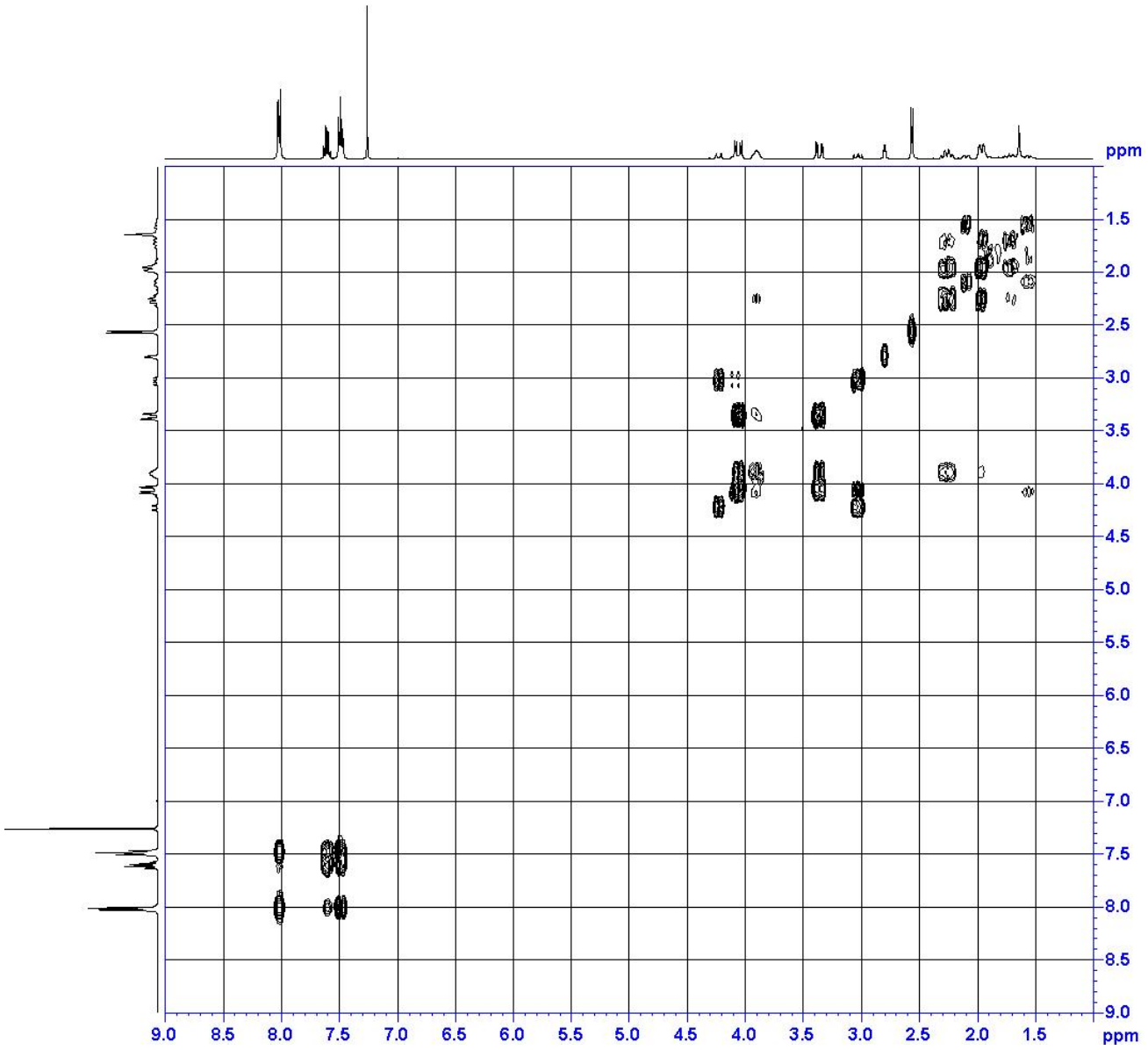

^{1}H NMR, $CDCl_3$, 300 MHz
Ph
O
N
H
Cl
+
cis-4b/cis-4b' = 75/25
f1 (ppm)


JMOD, $CDCl_3$, 100 MHz
Ph
O
N
H
Cl
+
cis-4b/cis-4b' = 75/25
ppm

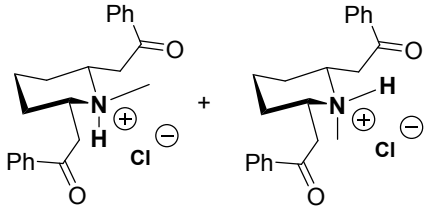
COSY, $CDCl_3$, 400 MHz



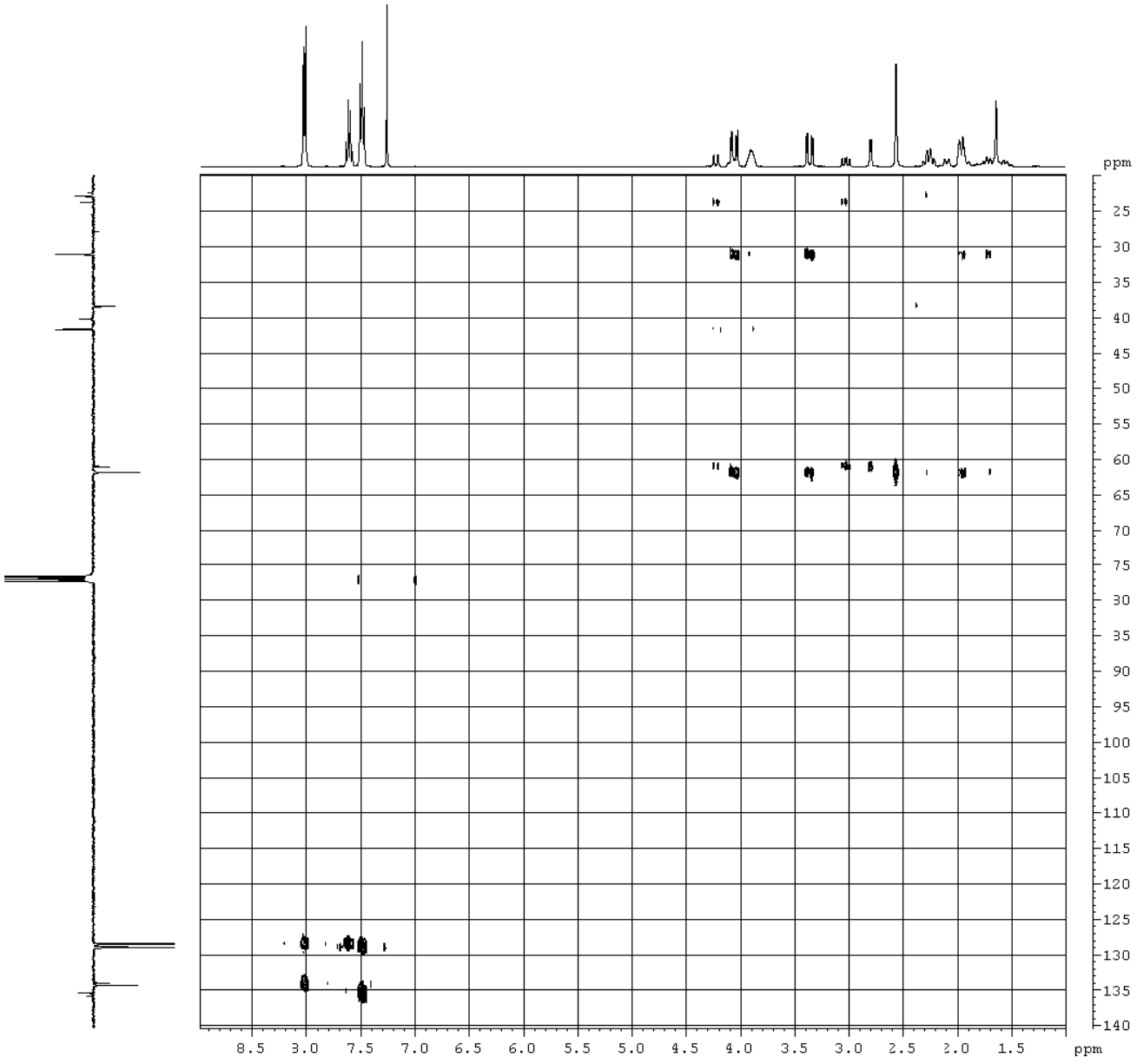
cis-**4b**/*cis*-**4b'** = 75/25



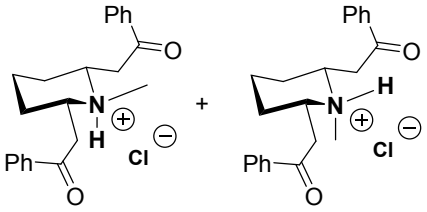
HMBC, $CDCl_3$, 400 MHz



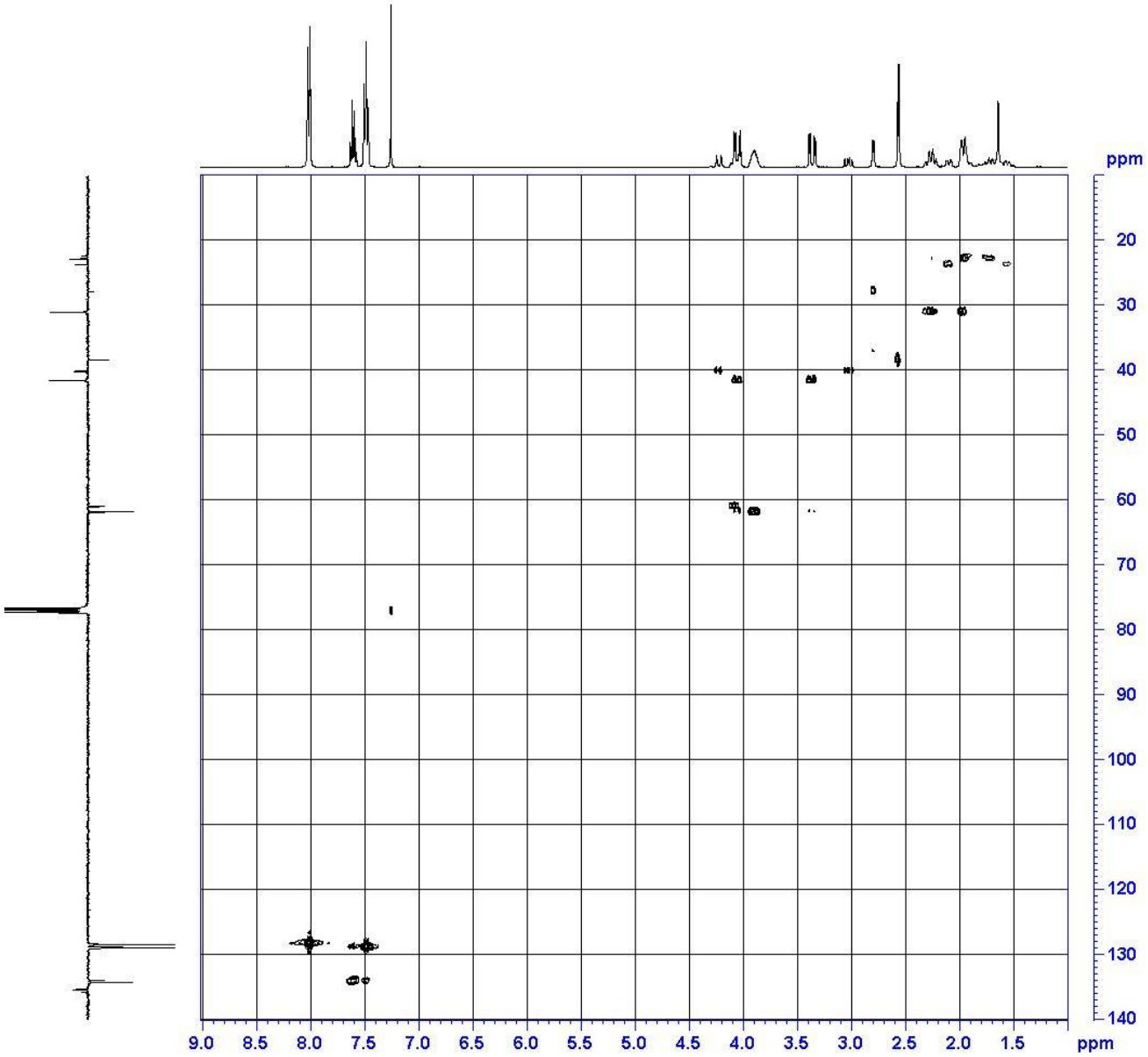
cis-**4b**/*cis*-**4b'** = 75/25



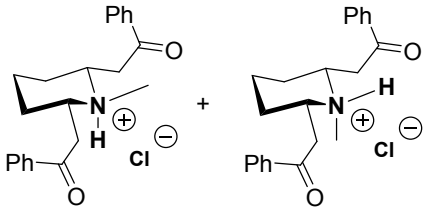
HSQC, $CDCl_3$, 400 MHz



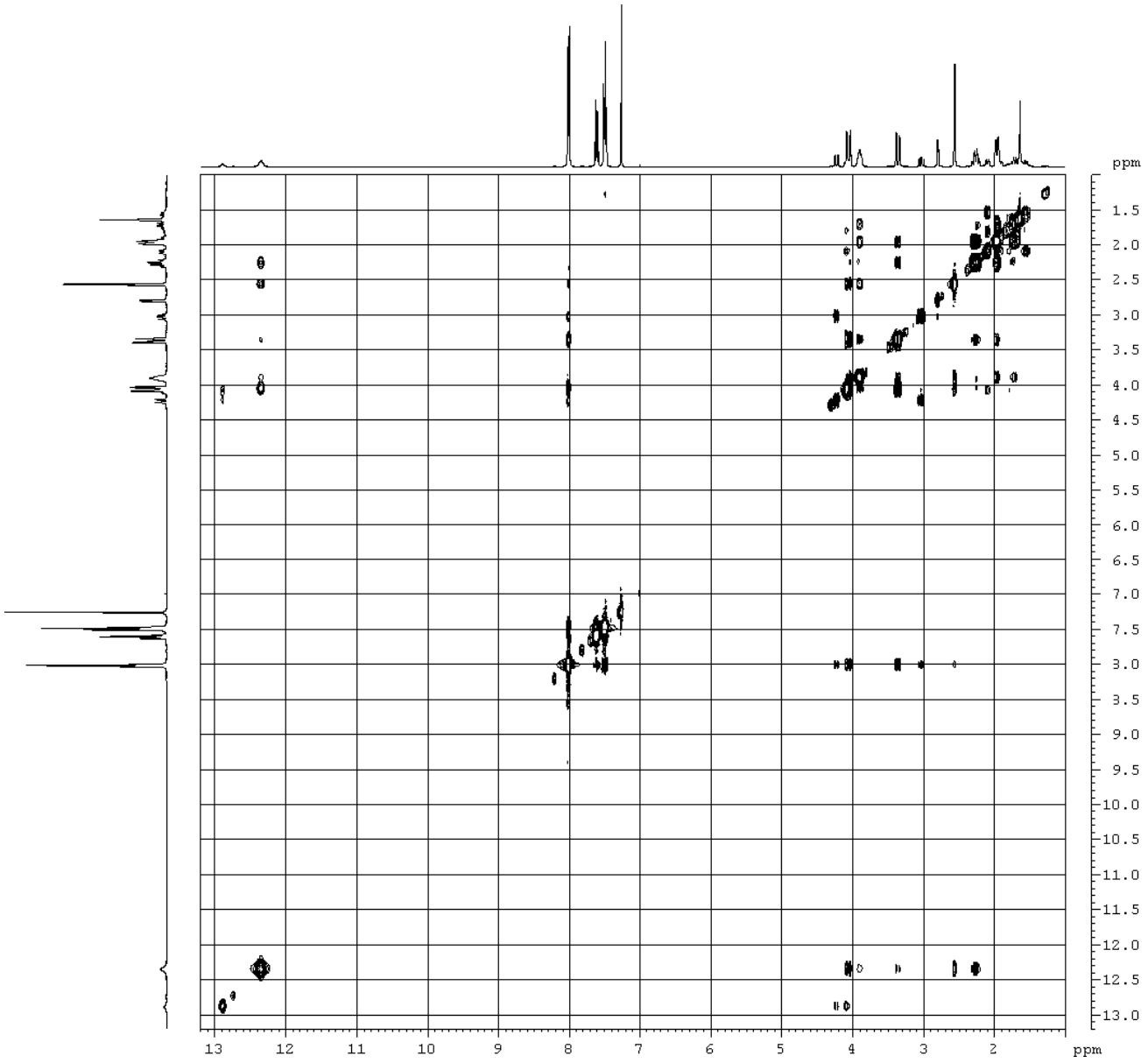
cis-**4b**/*cis*-**4b'** = 75/25

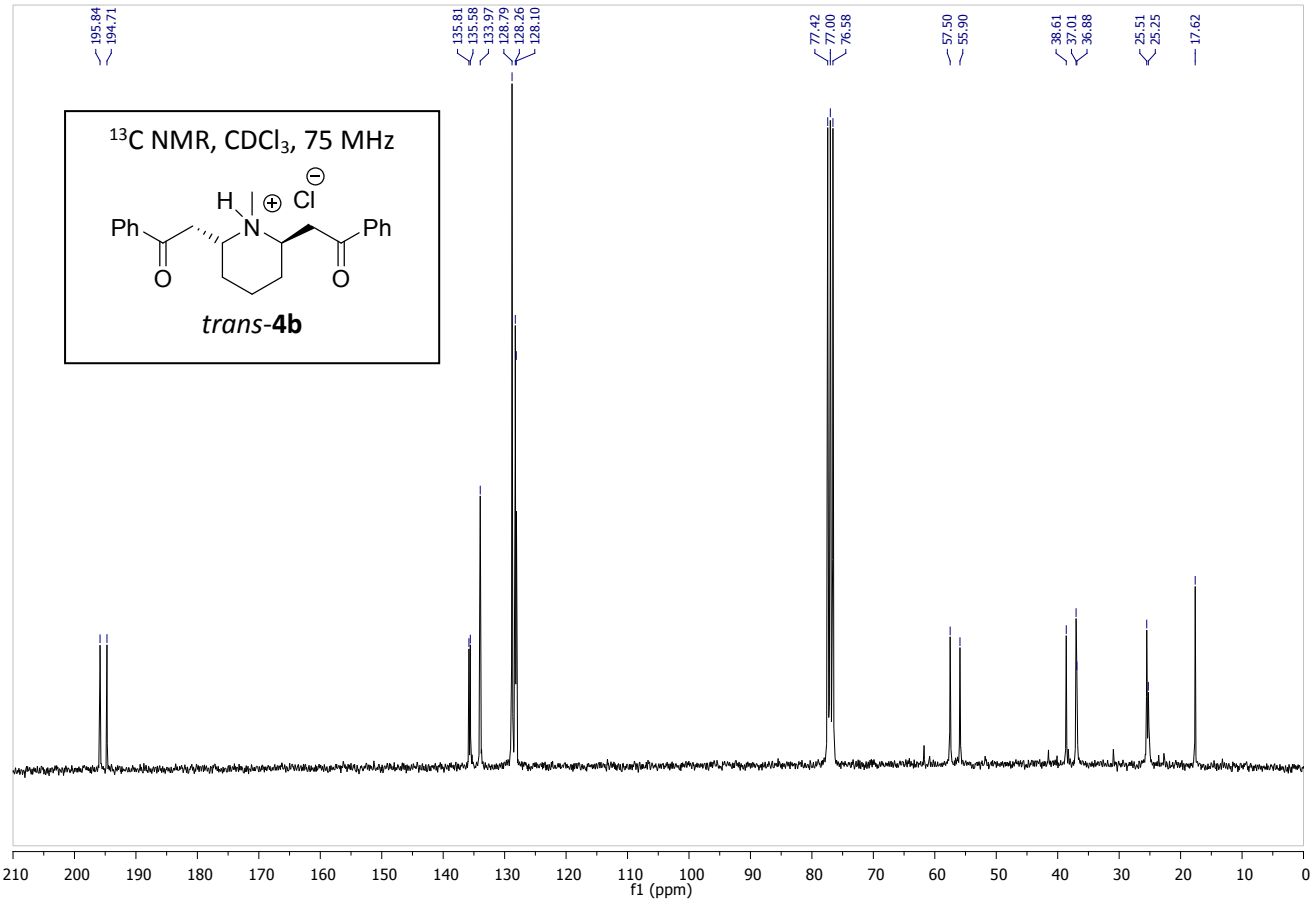


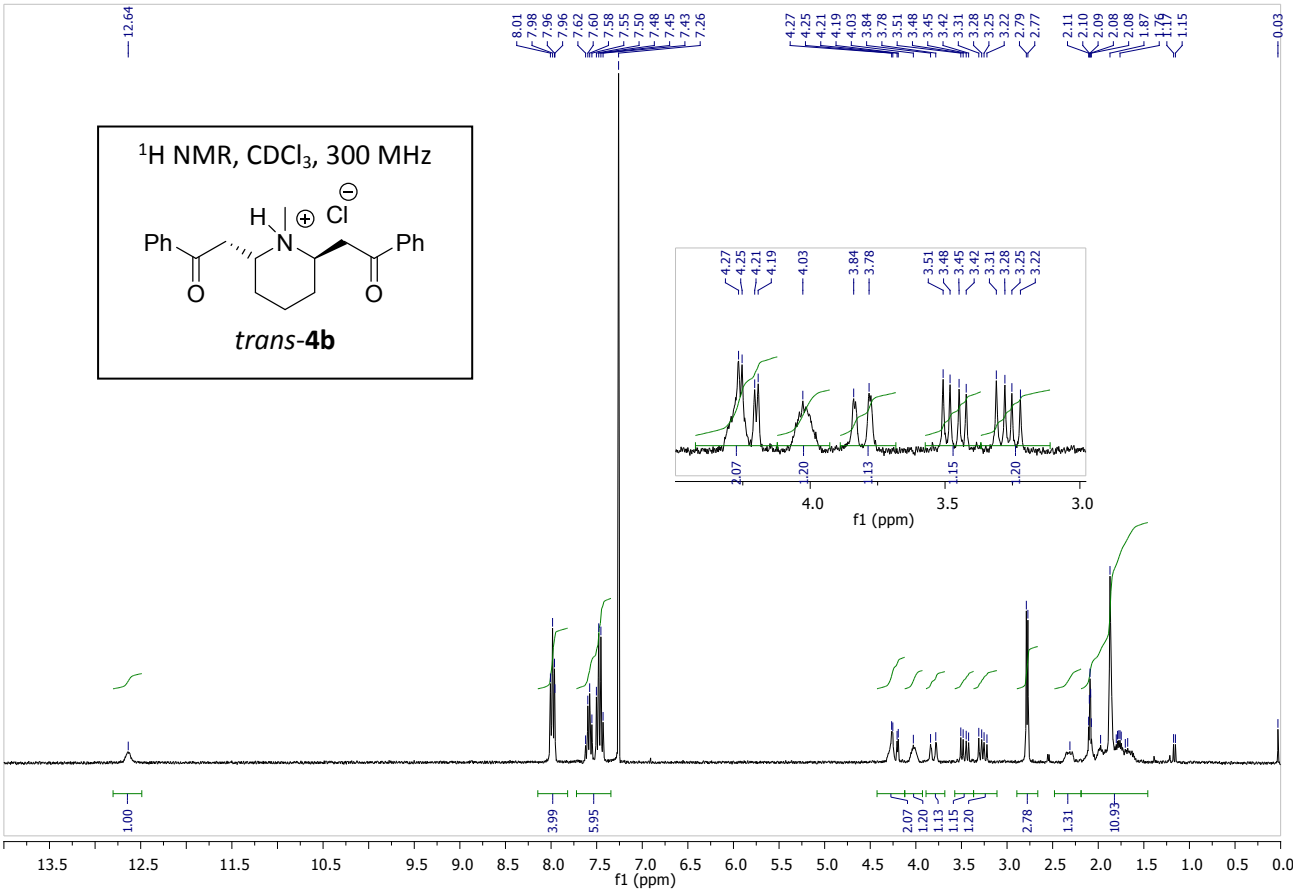
NOESY, $CDCl_3$, 400 MHz

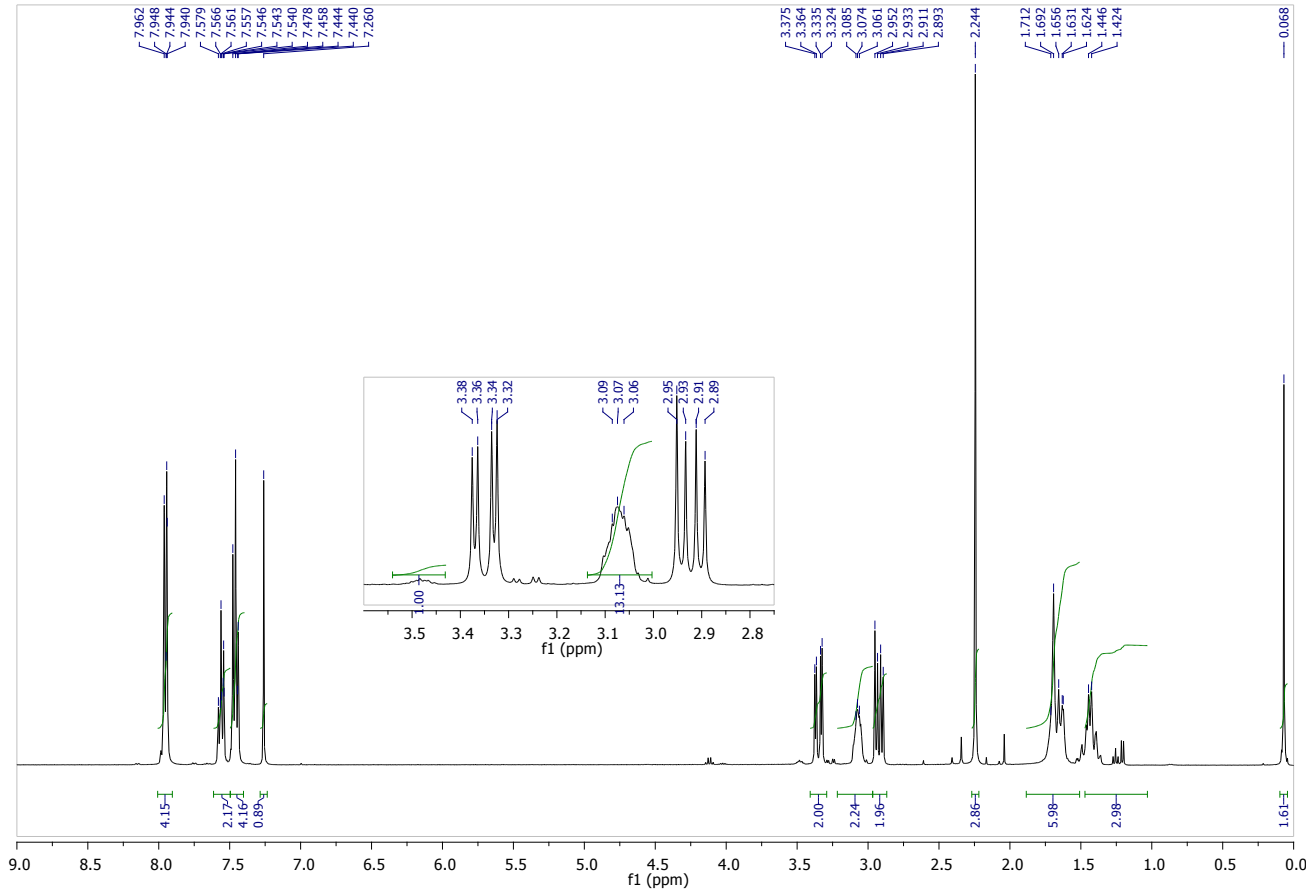


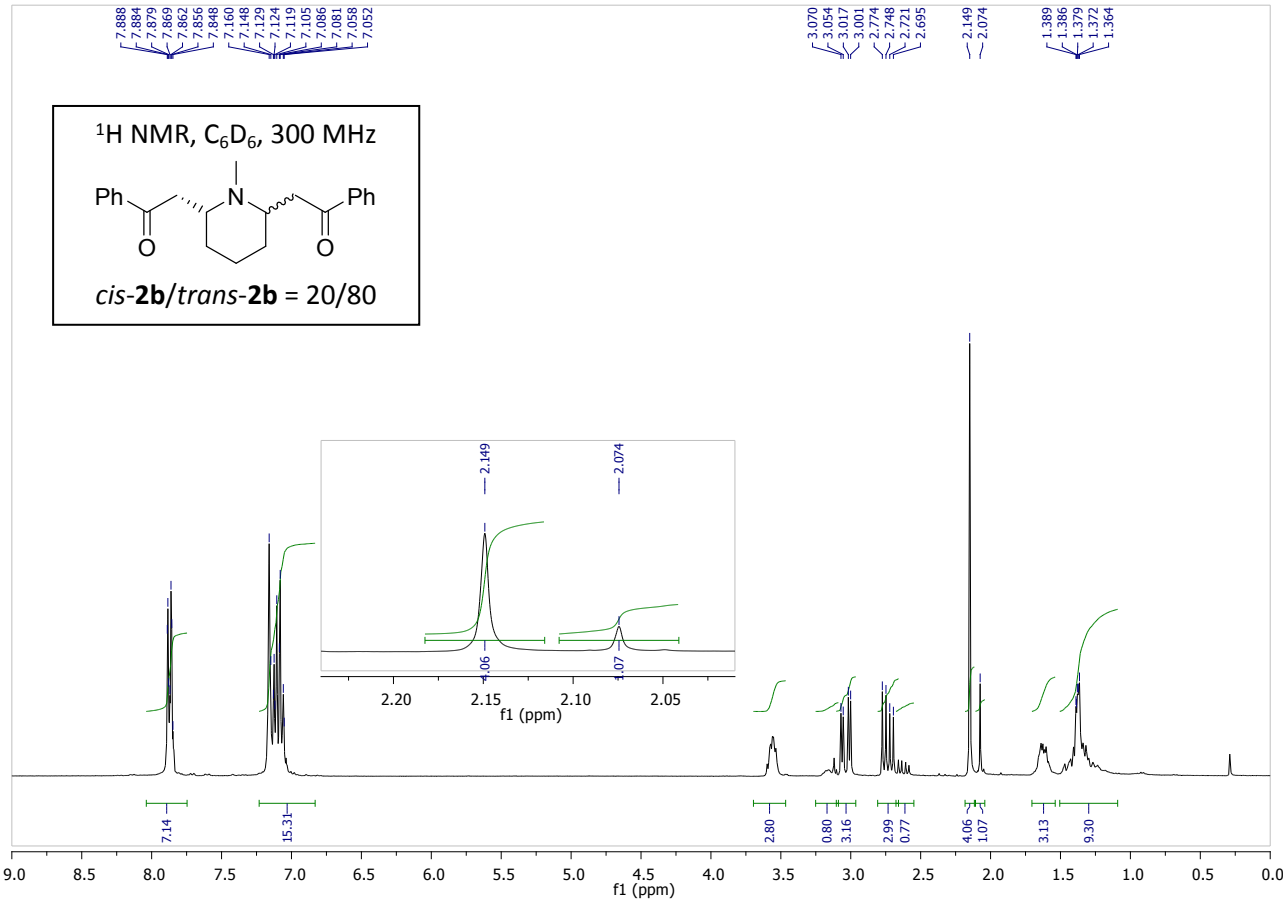
cis-**4b**/*cis*-**4b'** = 75/25

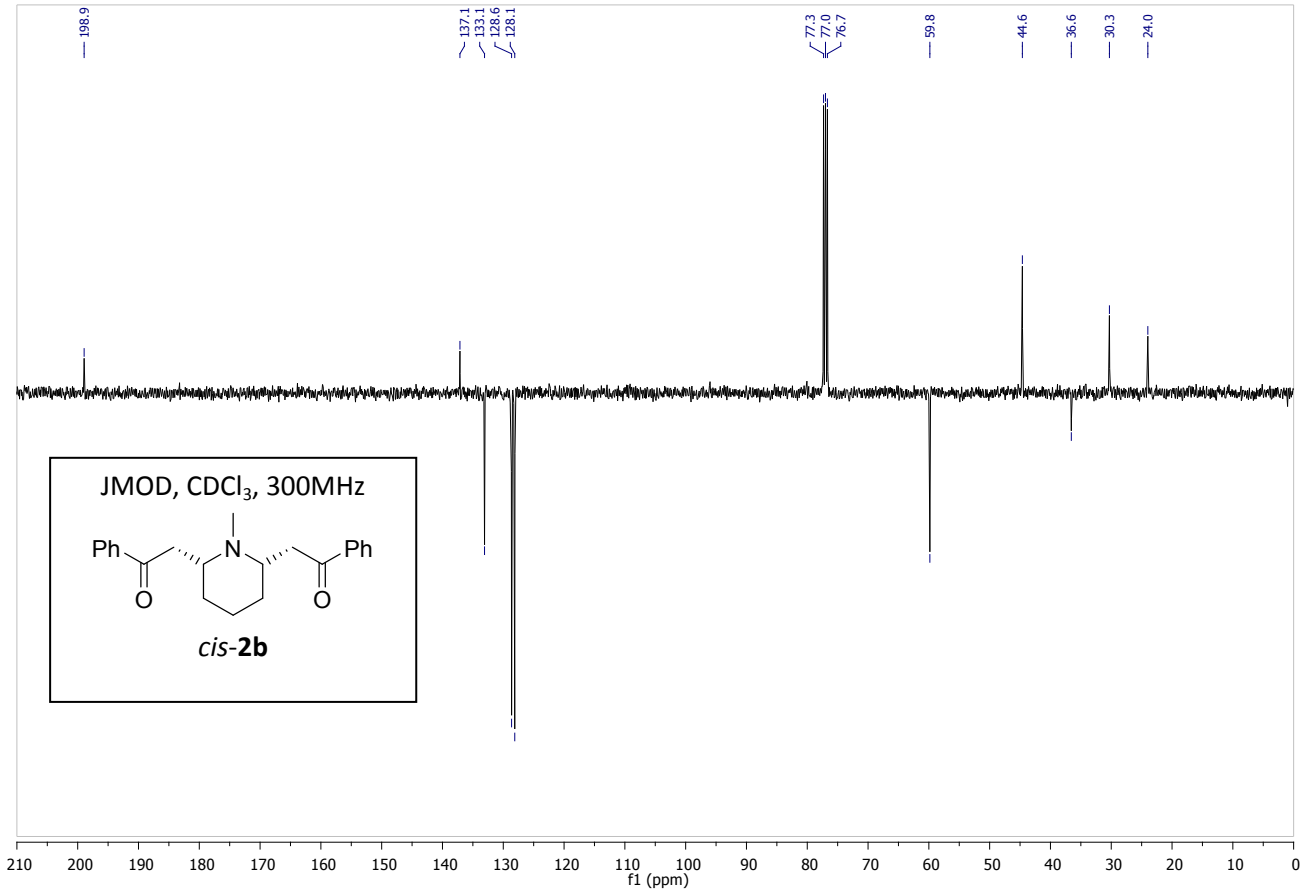


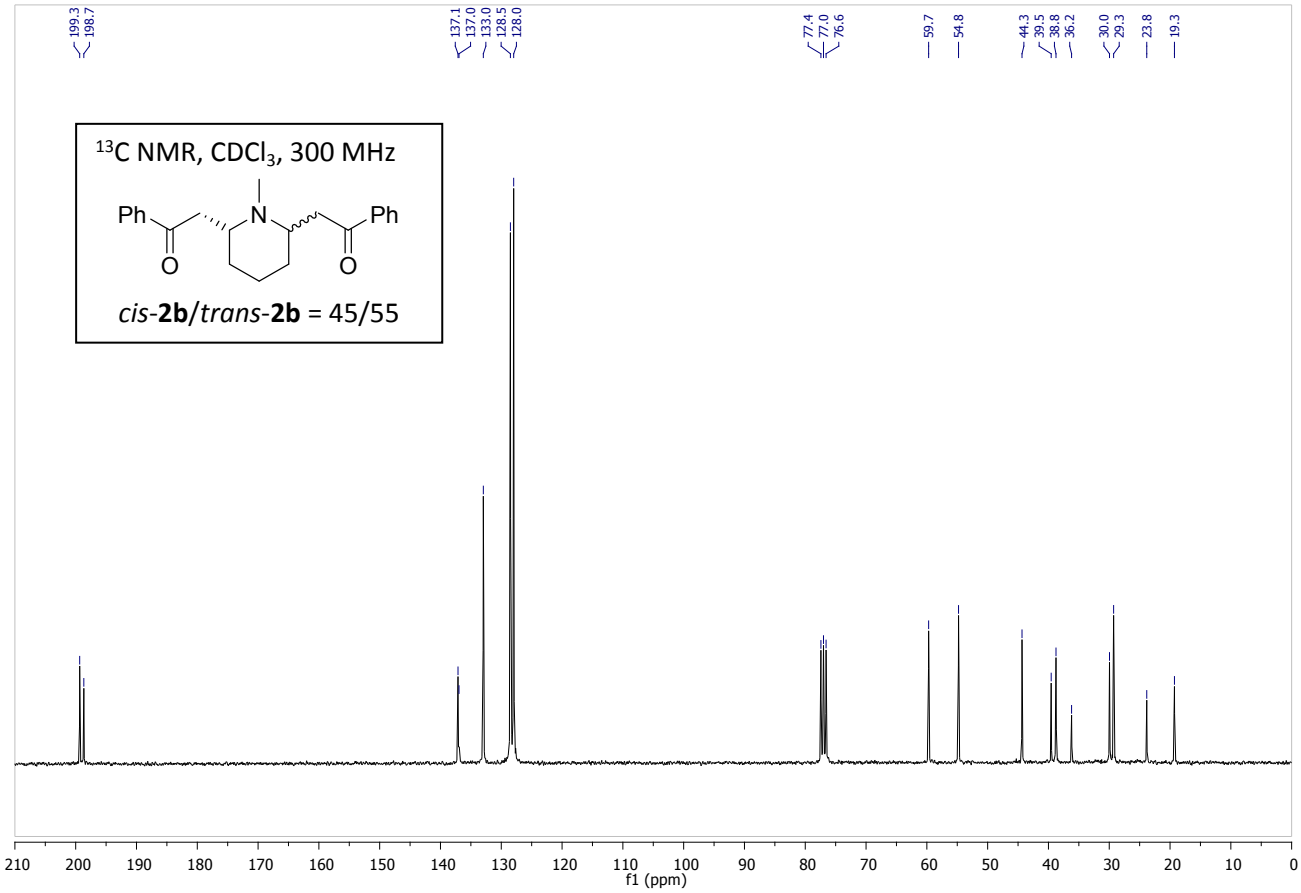

195.84
194.71
135.81
135.58
133.97
128.79
128.26
128.10
77.42
77.00
76.58
57.50
55.90
38.61
37.01
36.88
25.51
25.25
17.62
13C NMR, CDCl3, 75 MHz
H
N
Cl
Ph
Ph
O
O
trans-4b
f1 (ppm)

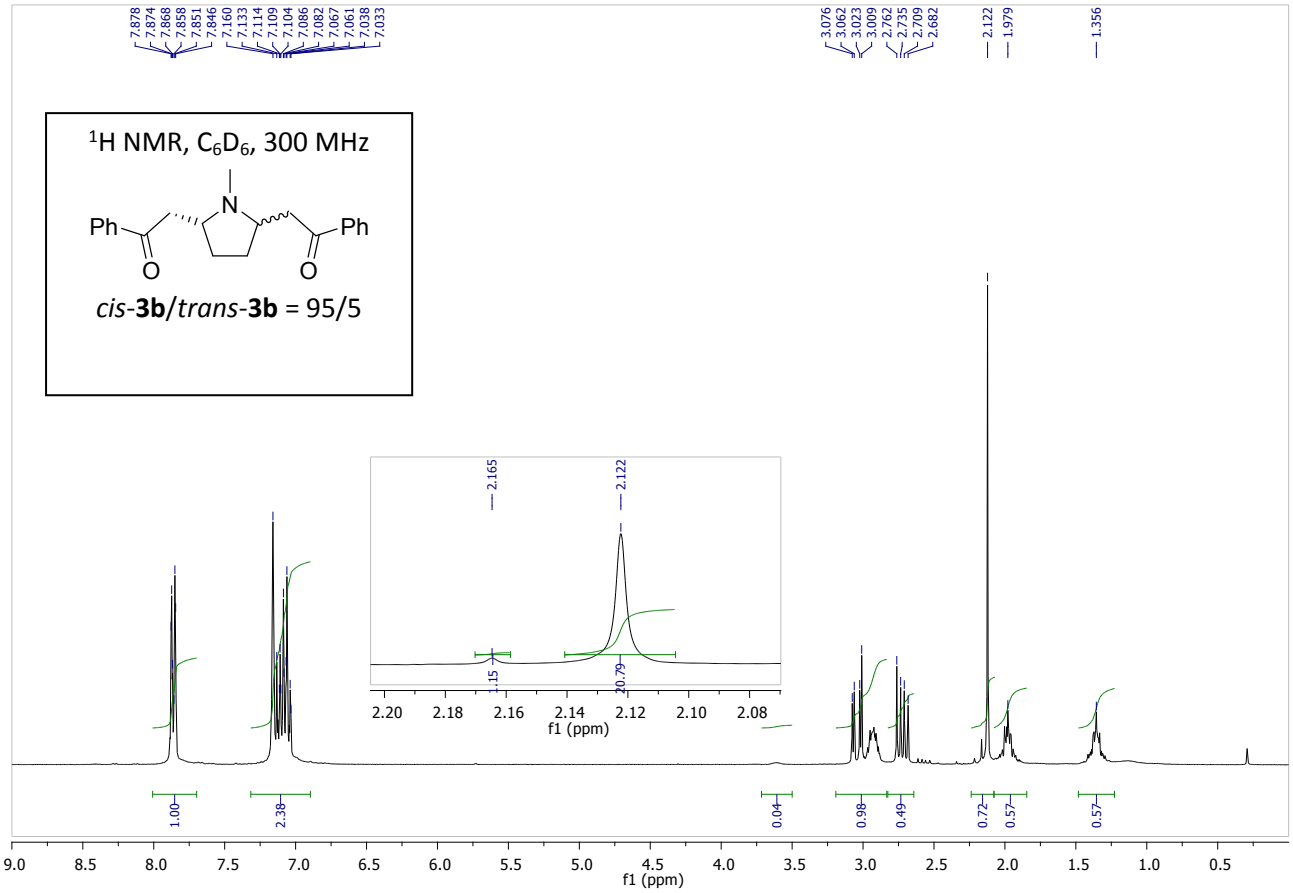

12.64
8.01
7.98
7.96
7.96
7.62
7.60
7.58
7.55
7.50
7.48
7.45
7.43
7.26
4.27
4.25
4.21
4.19
4.03
3.84
3.78
3.51
3.48
3.45
3.42
3.31
3.28
3.25
3.22
2.79
2.77
2.11
2.10
2.09
2.08
2.08
1.87
1.76
1.17
1.15
0.03
1H NMR, CDCl3, 300 MHz
H
N
Cl
Ph
Ph
O
O
trans-4b
2.07
1.20
1.13
1.15
1.20
f1 (ppm)
1.00
3.99
5.95
2.07
1.20
1.13
1.15
1.20
2.78
1.31
10.93
f1 (ppm)

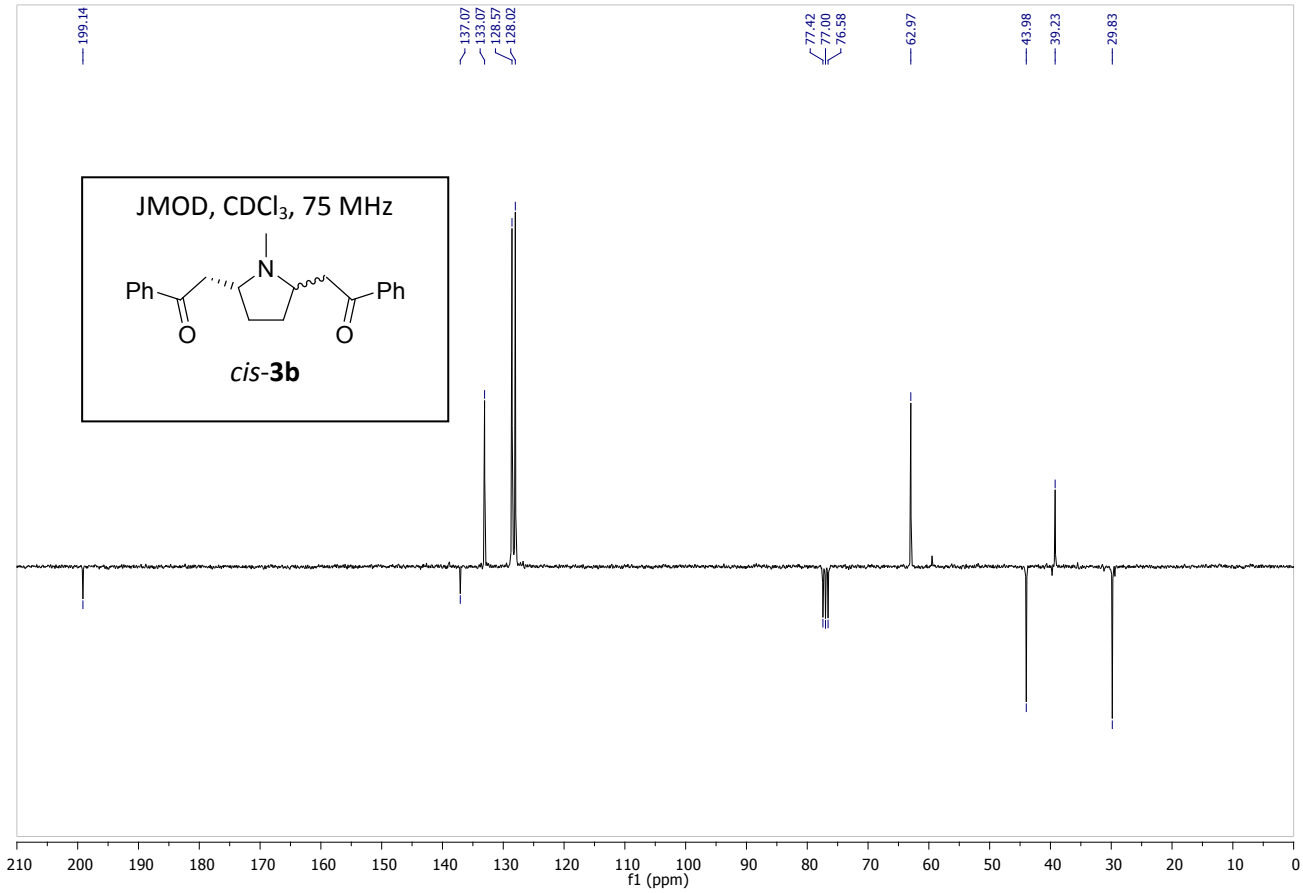

7.962
7.948
7.944
7.940
7.579
7.566
7.561
7.557
7.546
7.543
7.540
7.478
7.458
7.444
7.440
7.260
3.375
3.364
3.335
3.324
3.085
3.074
3.061
2.952
2.933
2.911
2.893
2.244
1.712
1.692
1.656
1.631
1.624
1.446
1.424
0.068
3.38
3.36
3.34
3.32
3.09
3.07
3.06
2.95
2.93
2.91
2.89
1.00
3.13
3.5
3.4
3.3
3.2
3.1
3.0
2.9
2.8
f1 (ppm)
4.15
2.17
4.16
0.89
2.00
2.24
1.96
2.86
5.98
2.98
1.61
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
0.0
f1 (ppm)

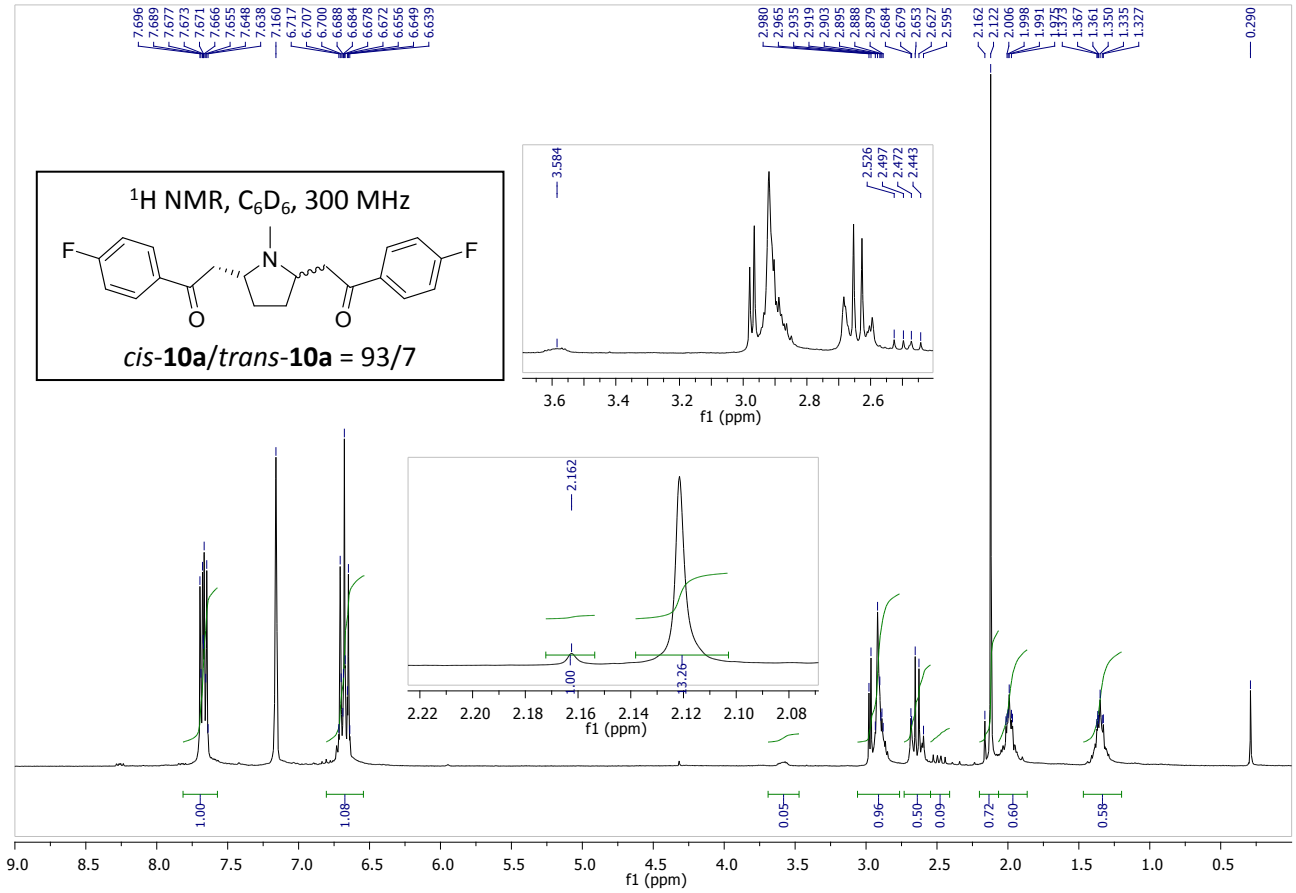

7.888
7.884
7.879
7.869
7.862
7.856
7.848
7.160
7.148
7.129
7.124
7.119
7.105
7.086
7.081
7.058
7.052
3.070
3.054
3.017
3.001
2.774
2.748
2.721
2.695
2.149
2.074
1.389
1.386
1.379
1.372
1.364
^{1}H NMR, C_6D_6, 300 MHz
Ph
N
Ph
O
O
cis-**2b**/*trans*-**2b** = 20/80
2.149
2.074
4.06
1.07
2.20
2.15
2.10
2.05
f1 (ppm)
7.14
15.31
2.80
0.80
3.16
2.99
0.77
4.06
1.07
3.13
9.30
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
0.0
f1 (ppm)

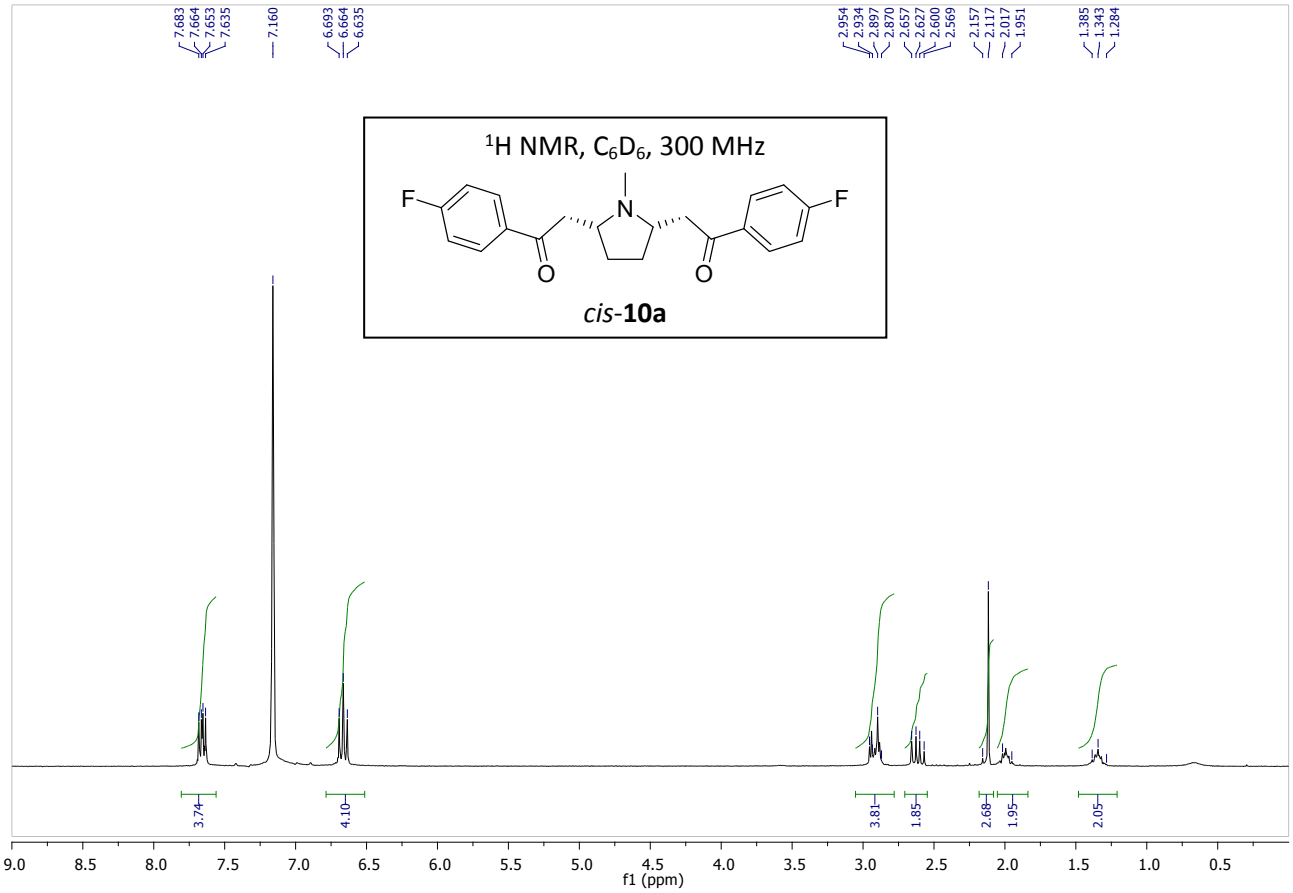

198.9
137.1
133.1
128.6
128.1
77.3
77.0
76.7
59.8
44.6
36.6
30.3
24.0
JMOD, CDCl3, 300MHz
Ph
N
Ph
O
O
cis-2b
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

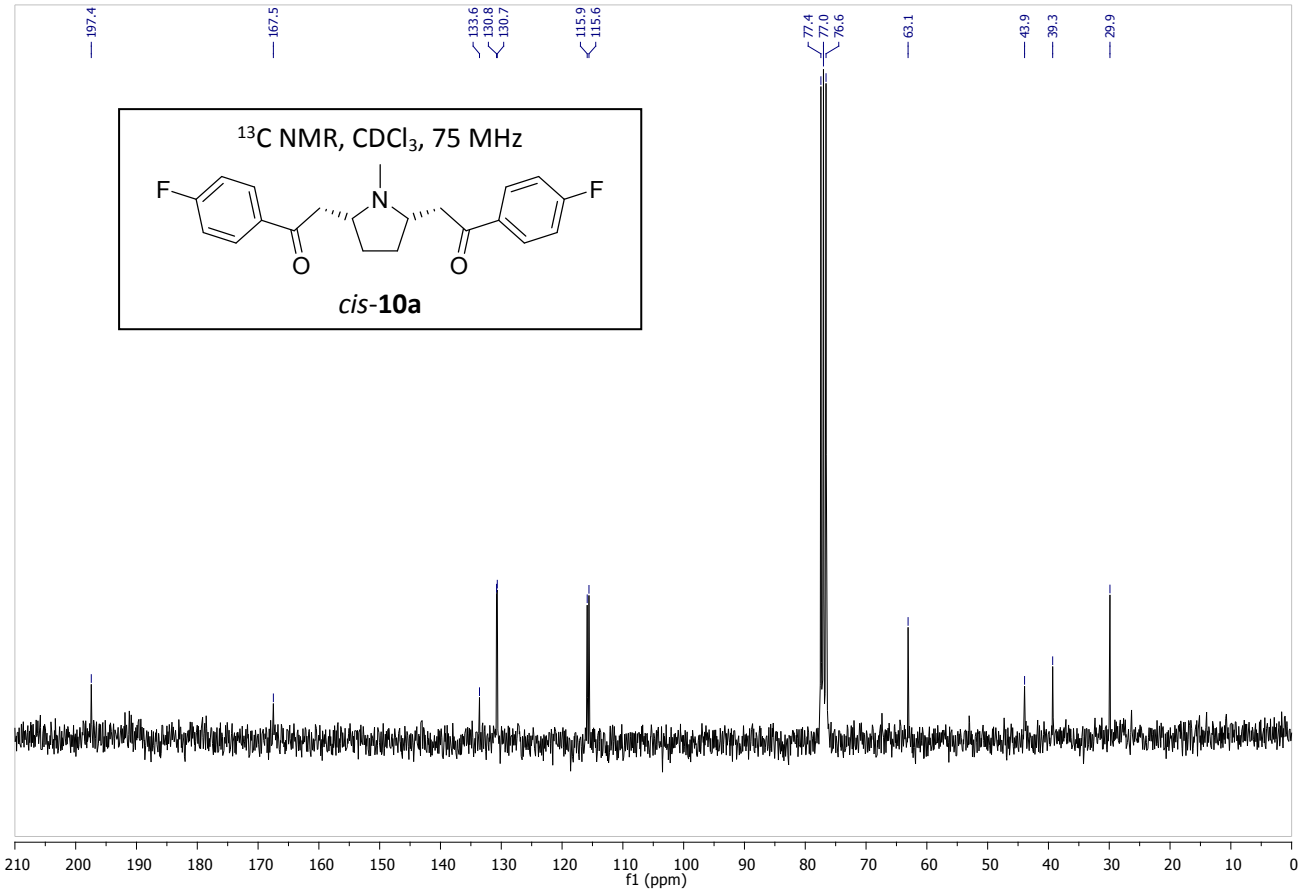

199.3
198.7
137.1
137.0
133.0
128.5
128.0
77.4
77.0
76.6
59.7
54.8
44.3
39.5
38.8
36.2
30.0
29.3
23.8
19.3
^{13}C NMR, $CDCl_3$, 300 MHz
Ph
N
Ph
O
O
cis-**2b**/*trans*-**2b** = 45/55
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

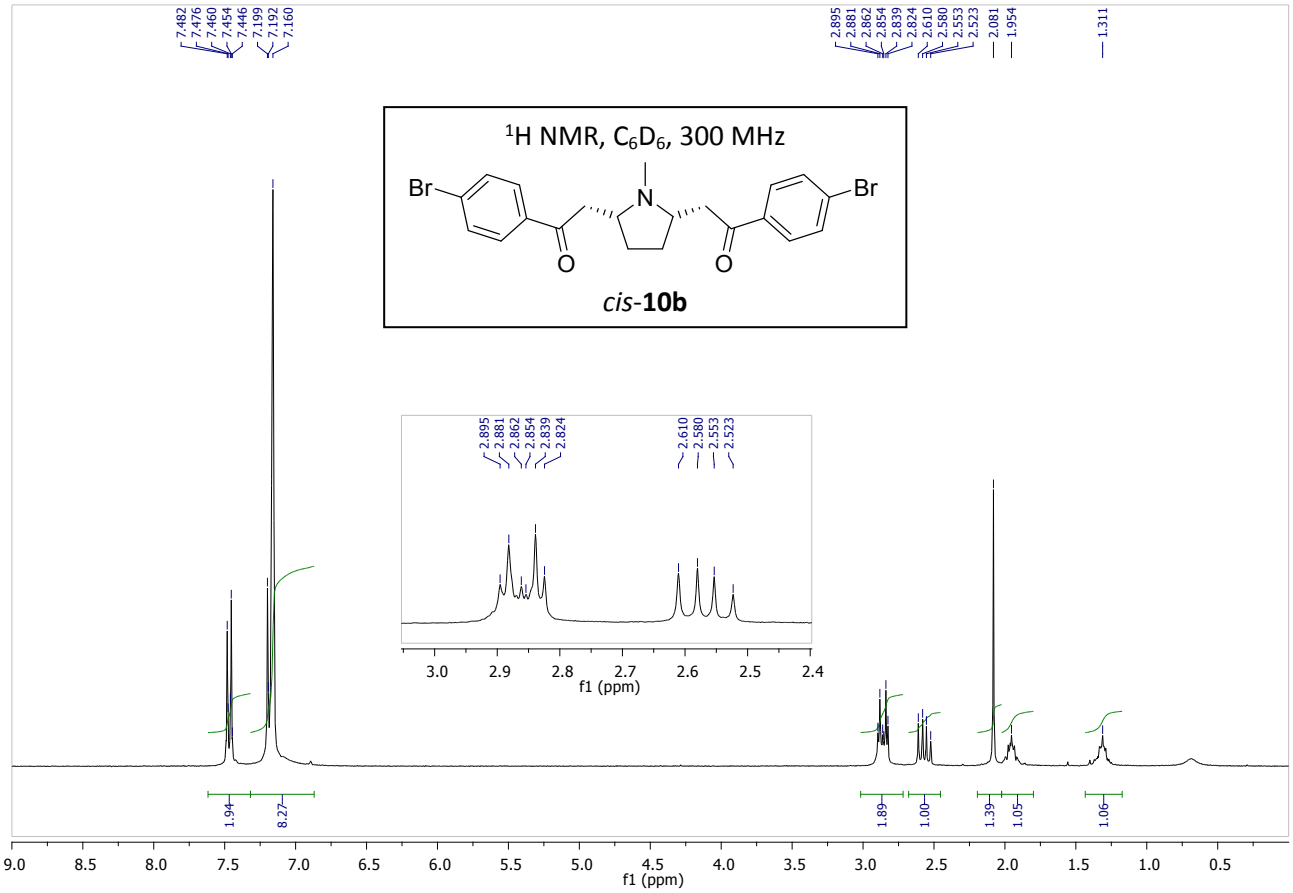

7.878
7.874
7.868
7.858
7.851
7.846
7.160
7.133
7.114
7.109
7.104
7.086
7.082
7.067
7.061
7.038
7.033
3.076
3.062
3.023
3.009
2.762
2.735
2.709
2.682
2.122
1.979
1.356
1H NMR, C6D6, 300 MHz
Ph
N
Ph
O
O
cis-3b/trans-3b = 95/5
2.165
2.122
1.15
20.79
2.20
2.18
2.16
2.14
2.12
2.10
2.08
f1 (ppm)
1.00
2.38
0.04
0.98
0.49
0.72
0.57
0.57
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
f1 (ppm)

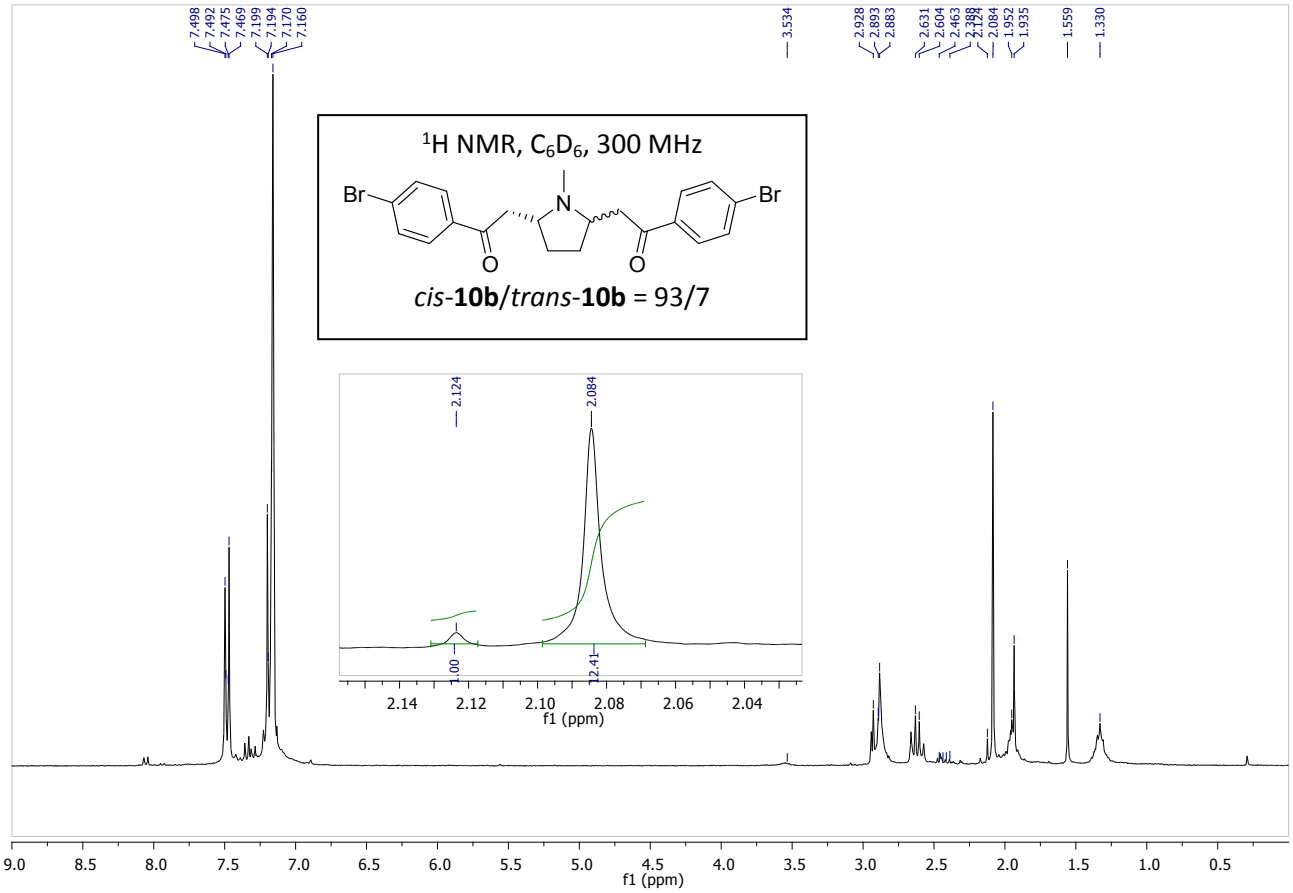

199.14
137.07
133.07
128.57
128.02
77.42
77.00
76.58
62.97
43.98
39.23
29.83
JMOD, CDCl3, 75 MHz
Ph
N
Ph
O
O
cis-3b
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

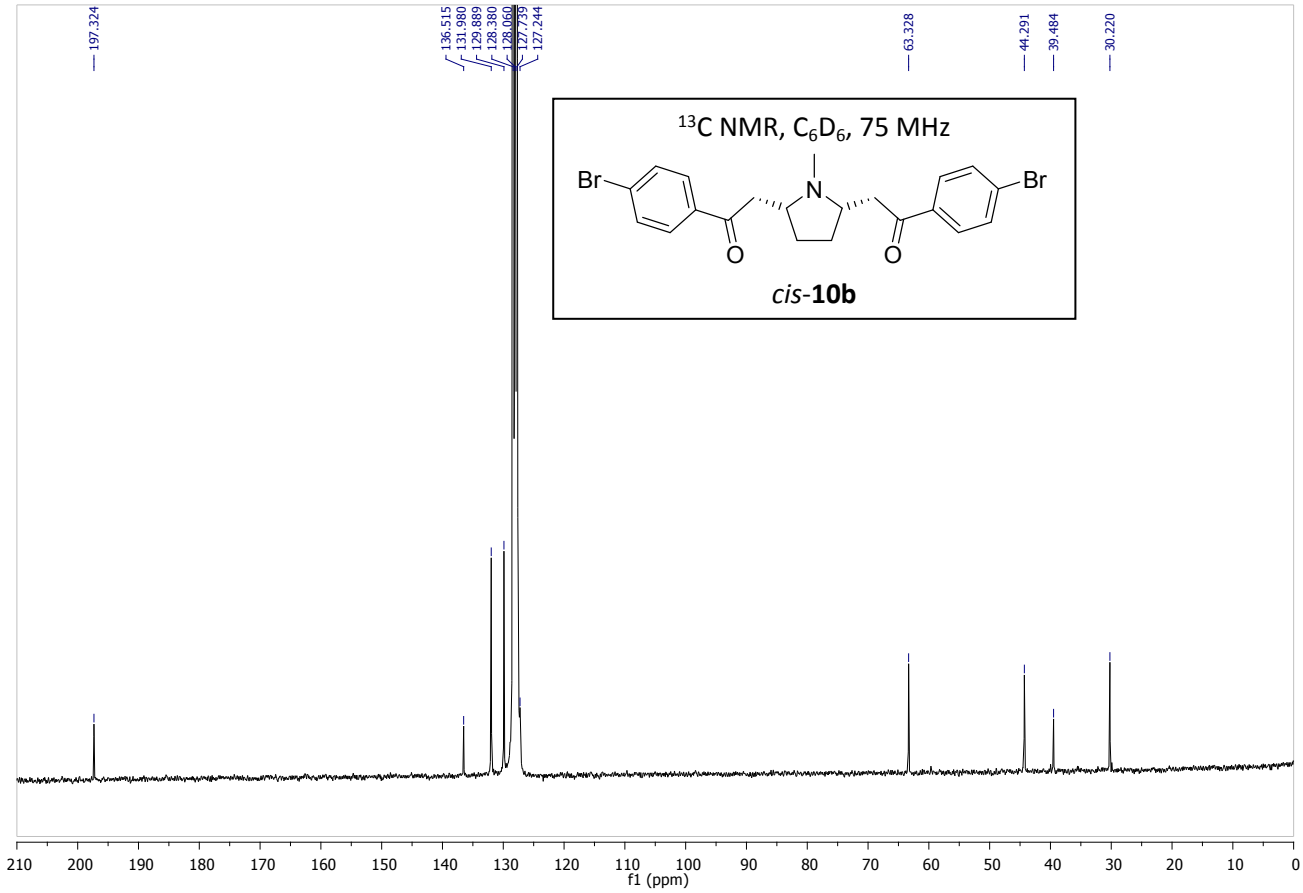

^{1}H NMR, C_6D_6, 300 MHz
F
N
O
O
F
cis-**10a**/*trans*-**10a** = 93/7
f1 (ppm)
f1 (ppm)
f1 (ppm)

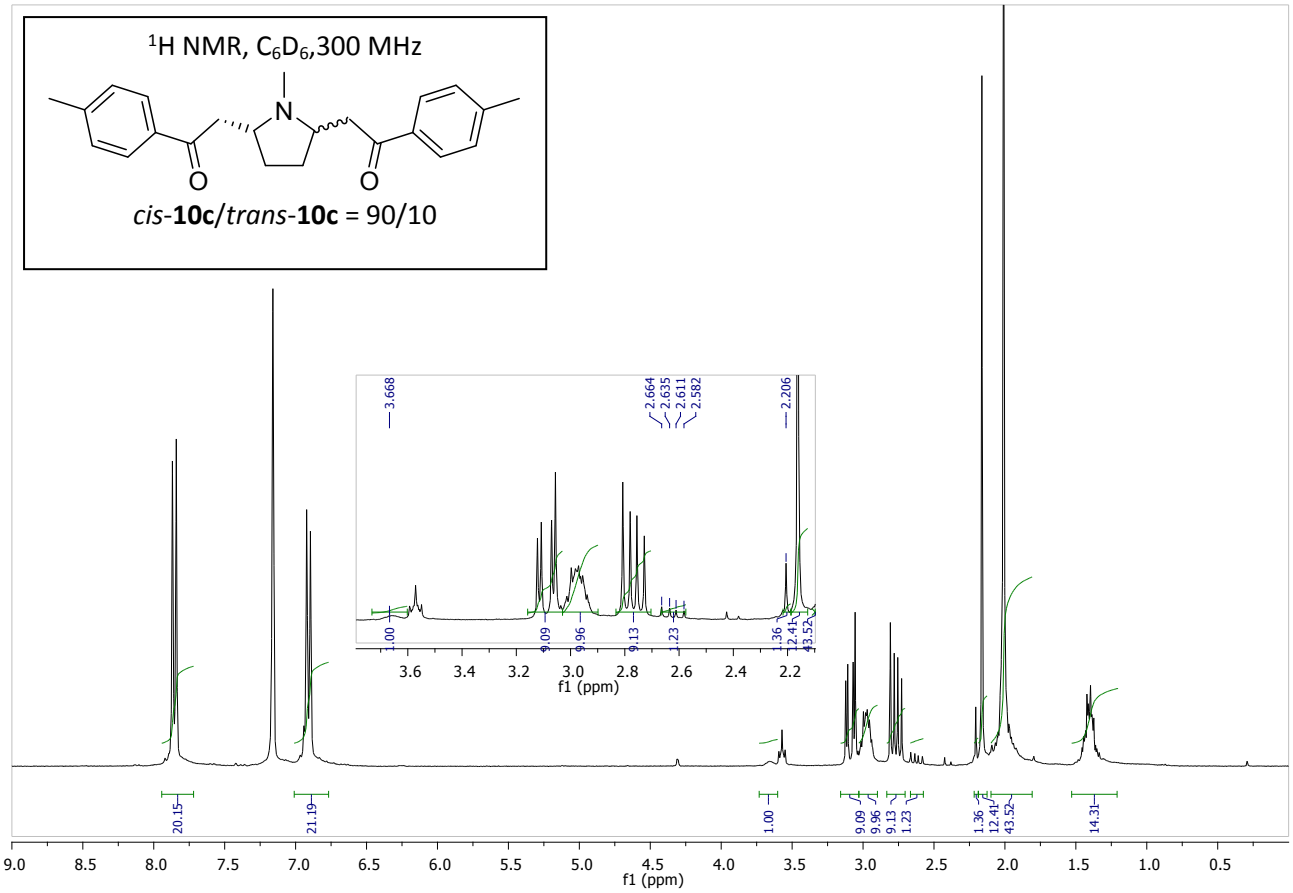

7.683
7.664
7.653
7.635
7.160
6.693
6.664
6.635
2.954
2.934
2.897
2.870
2.657
2.627
2.600
2.569
2.157
2.117
2.017
1.951
1.385
1.343
1.284
^{1}H NMR, C_6D_6, 300 MHz
F
N
O
O
F
cis-**10a**
3.74
4.10
3.81
1.85
2.68
1.95
2.05
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

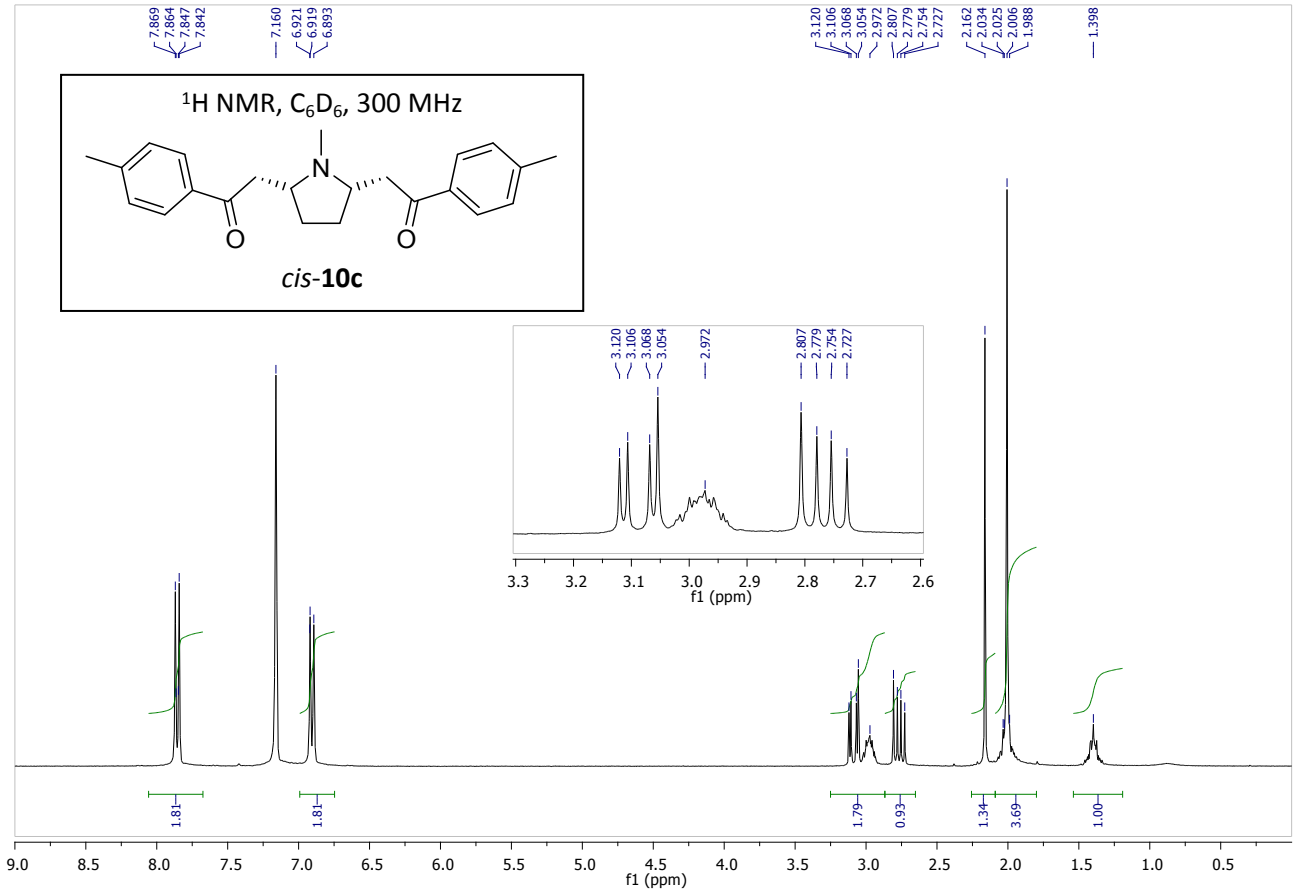

197.4
167.5
133.6
130.8
130.7
115.9
115.6
77.4
77.0
76.6
63.1
43.9
39.3
29.9
^{13}C NMR, $CDCl_3$, 75 MHz
F
N
O
O
F
cis-**10a**
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

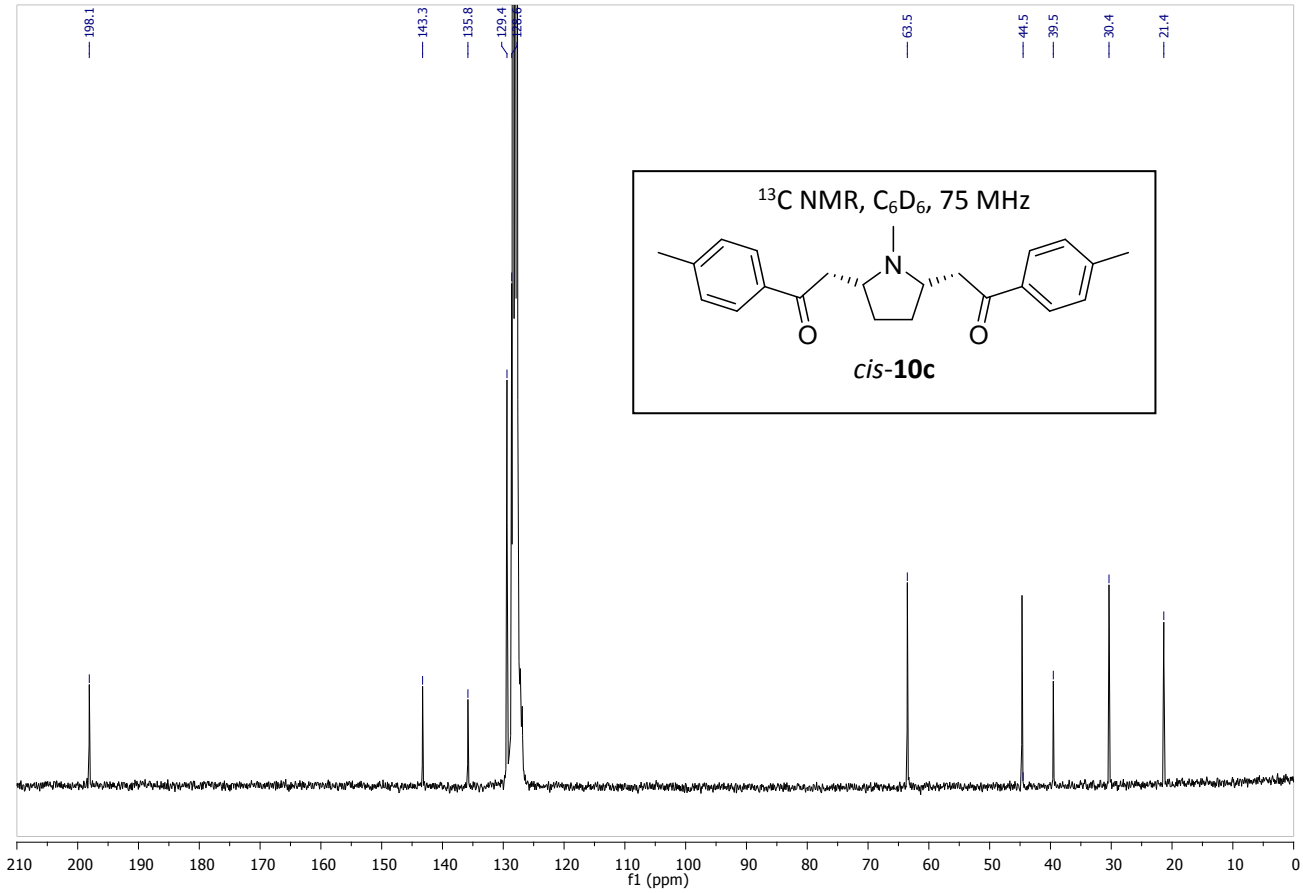

7.482
7.476
7.460
7.454
7.446
7.199
7.192
7.160
2.895
2.881
2.862
2.854
2.839
2.824
2.610
2.580
2.553
2.523
2.081
1.954
1.311
^{1}H NMR, C_6D_6, 300 MHz
Br
N
Br
O
O
cis-**10b**
f1 (ppm)
1.94
8.27
1.89
1.00
1.39
1.05
1.06
f1 (ppm)

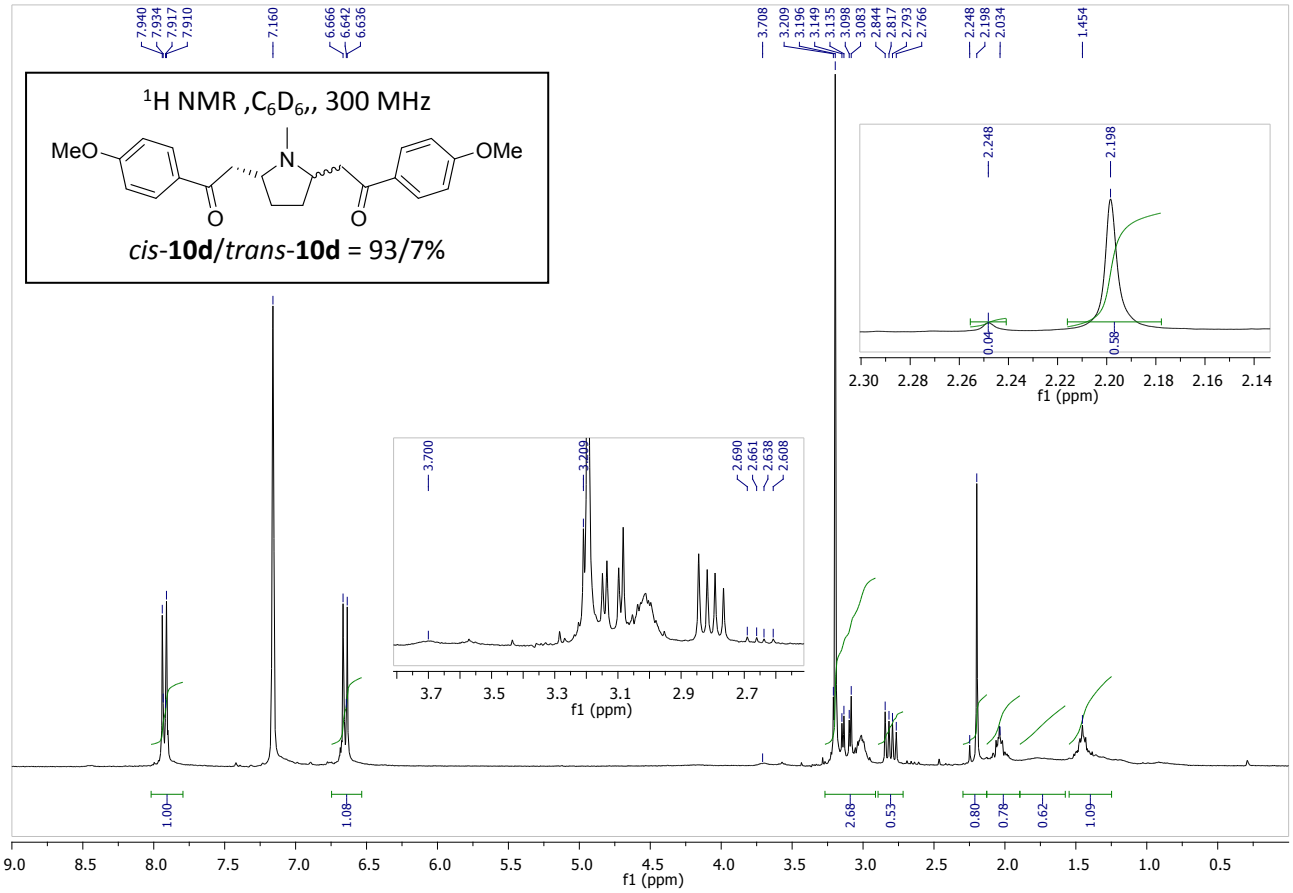

7.498
7.492
7.475
7.469
7.199
7.194
7.170
7.160
3.534
2.928
2.893
2.883
2.631
2.604
2.463
2.388
2.124
2.084
1.952
1.935
1.559
1.330
^{1}H NMR, C_6D_6, 300 MHz
Br
N
O
O
Br
cis-**10b**/*trans*-**10b** = 93/7
2.124
2.084
1.00
2.41
2.14
2.12
2.10
2.08
2.06
2.04
f1 (ppm)
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

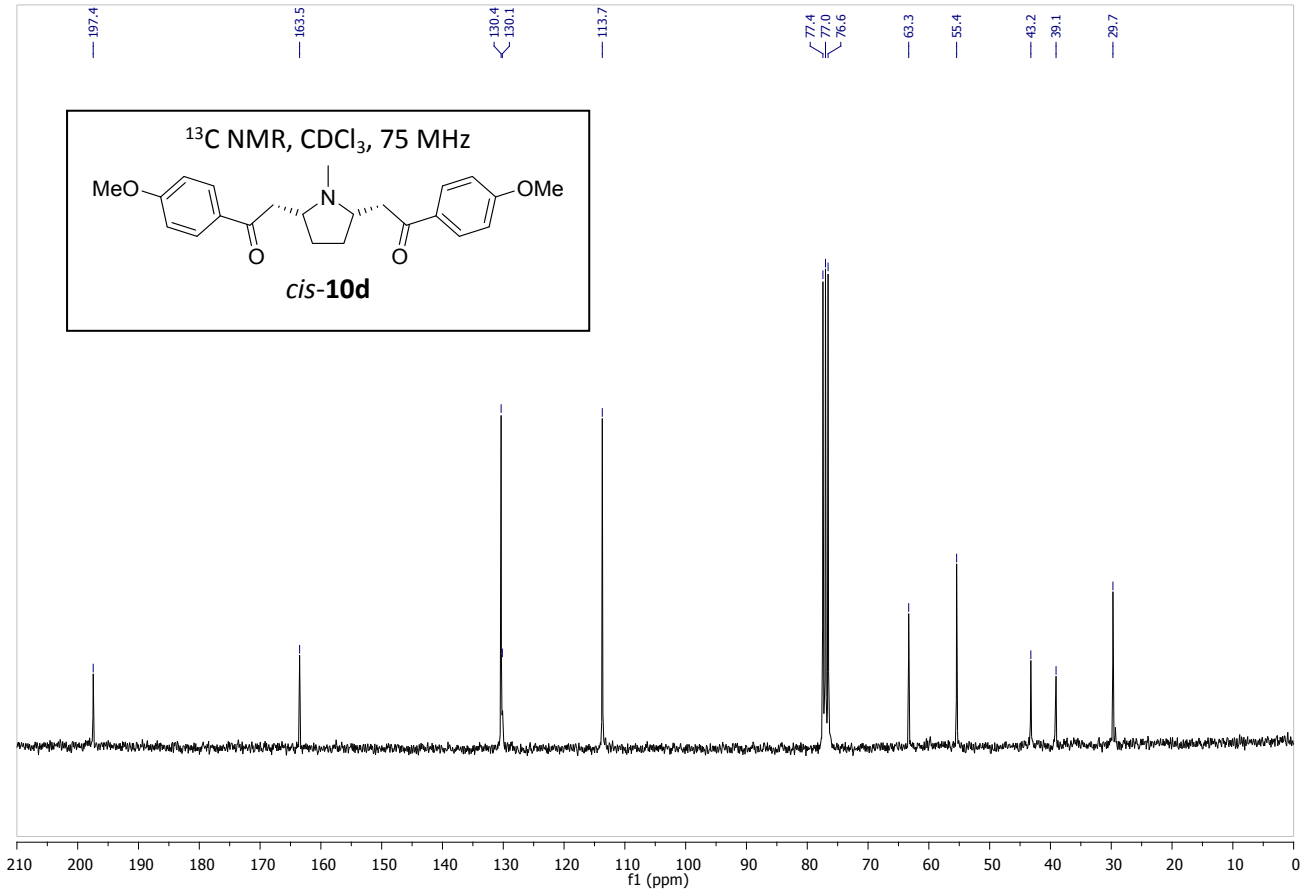

197.324
136.515
131.980
129.889
128.380
128.060
127.739
127.244
63.328
44.291
39.484
30.220
^{13}C NMR, C_6D_6, 75 MHz
Br
N
Br
O
O
cis-**10b**
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

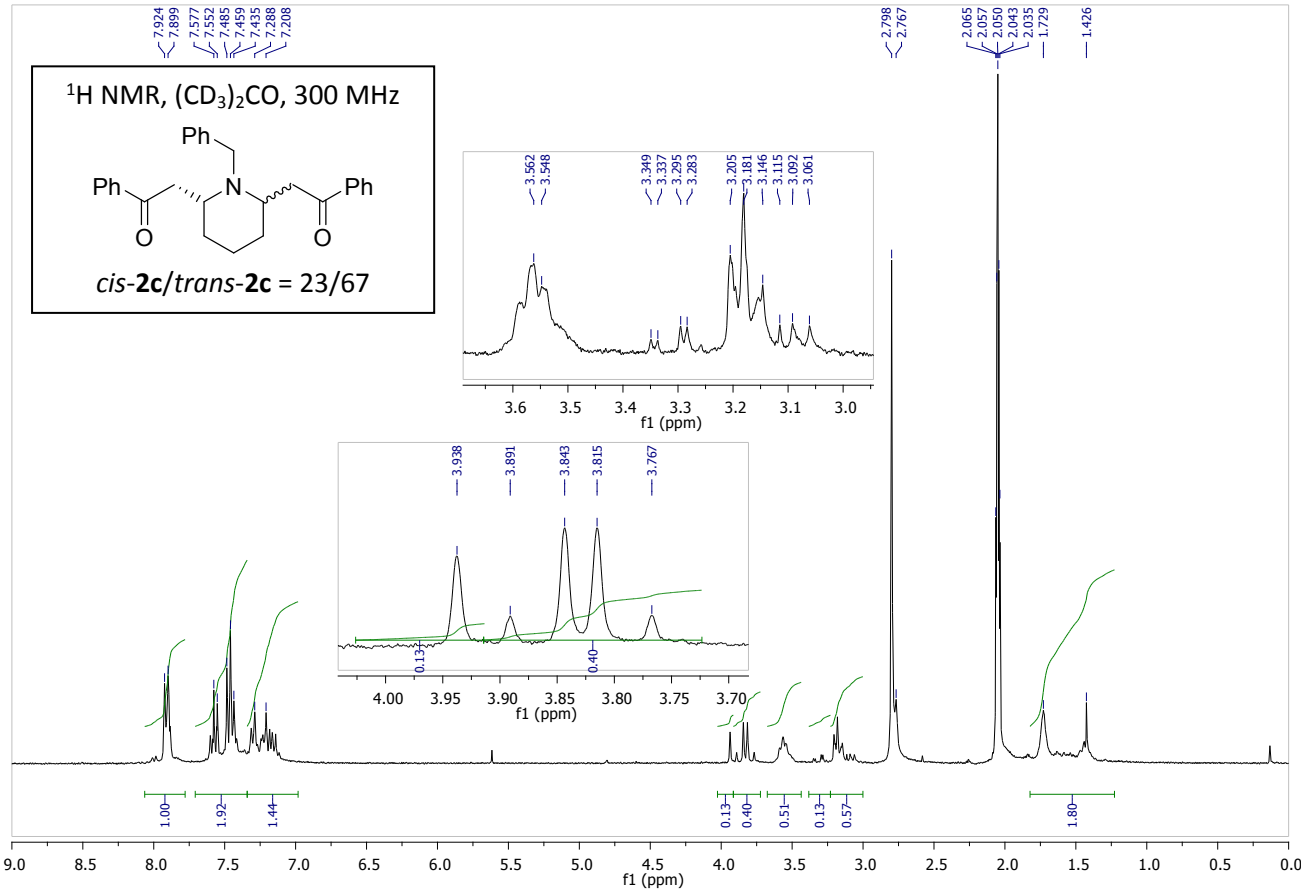

1H NMR, C6D6,300 MHz
N
O
O
cis-10c/trans-10c = 90/10
3.668
2.664
2.635
2.611
2.582
2.206
1.00
9.09
9.96
9.13
1.23
1.36
12.41
43.52
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
f1 (ppm)
20.15
21.19
1.00
9.09
9.96
9.13
1.23
1.36
12.41
43.52
14.31
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

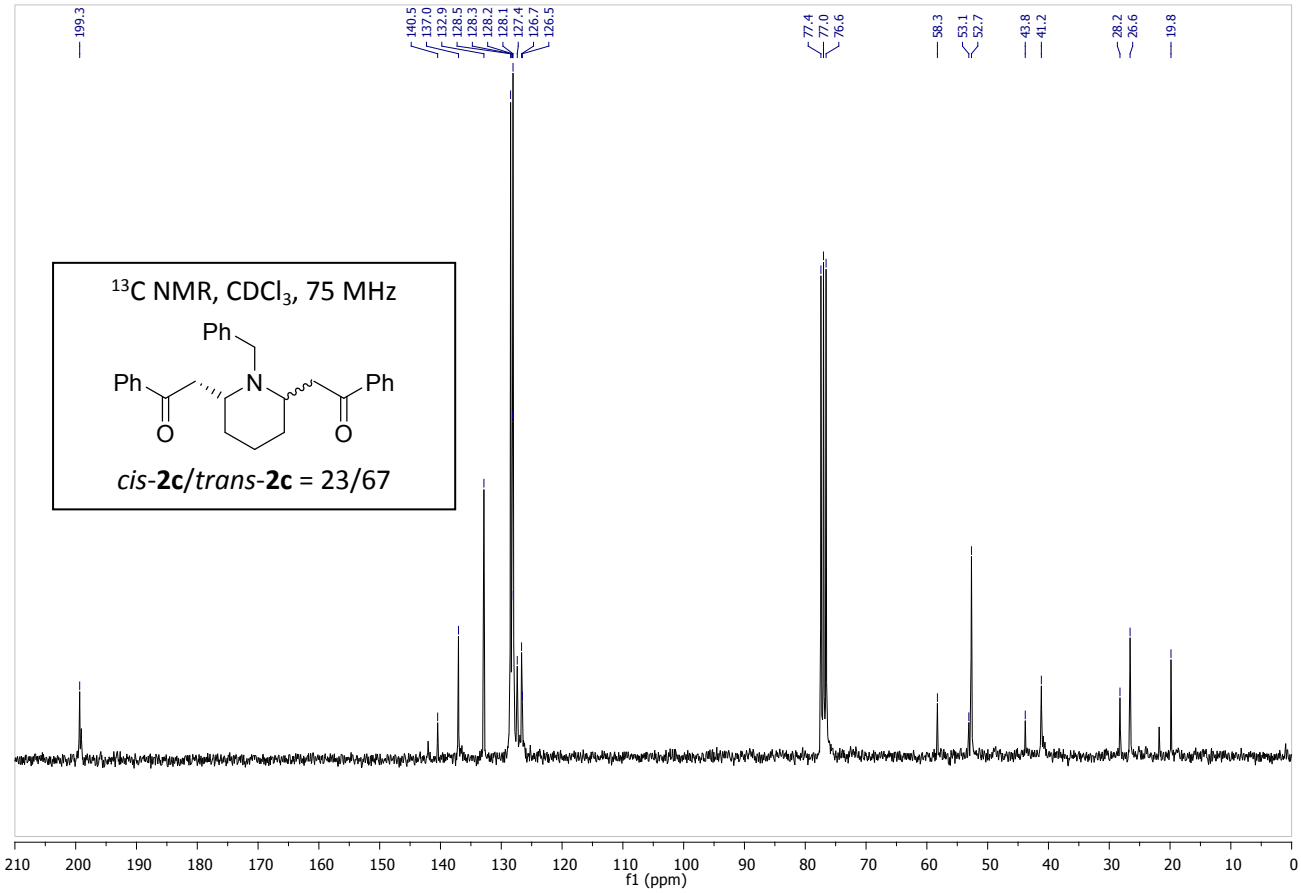

7.869
7.864
7.847
7.842
7.160
6.921
6.919
6.893
3.120
3.106
3.068
3.054
2.972
2.807
2.779
2.754
2.727
2.162
2.034
2.025
2.006
1.988
1.398
^{1}H NMR, C_6D_6, 300 MHz
N
O
O
cis-**10c**
f1 (ppm)
1.81
1.81
1.79
0.93
1.34
3.69
1.00
f1 (ppm)

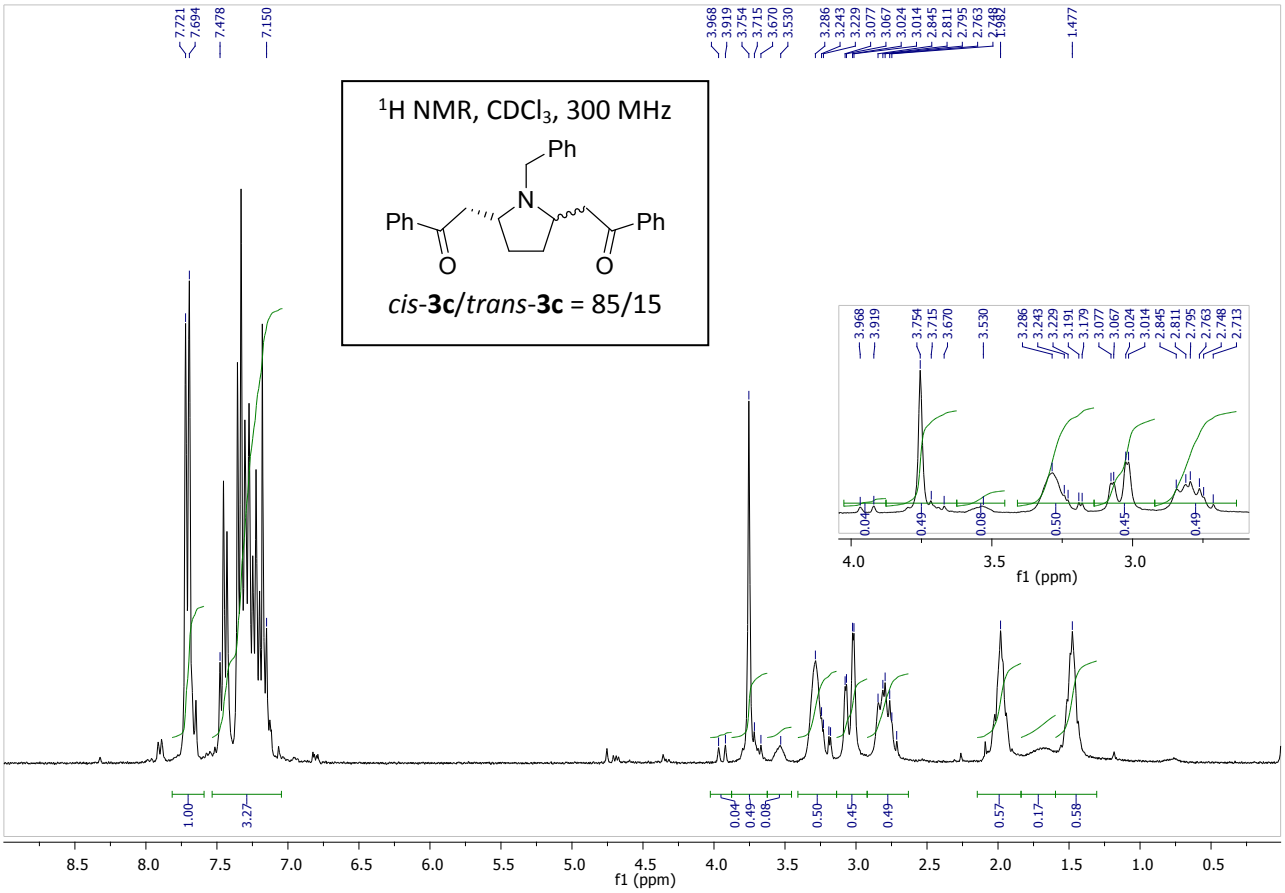

198.1
143.3
135.8
129.4
63.5
44.5
39.5
30.4
21.4
^{13}C NMR, C_6D_6, 75 MHz
N
O
O
cis-**10c**
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

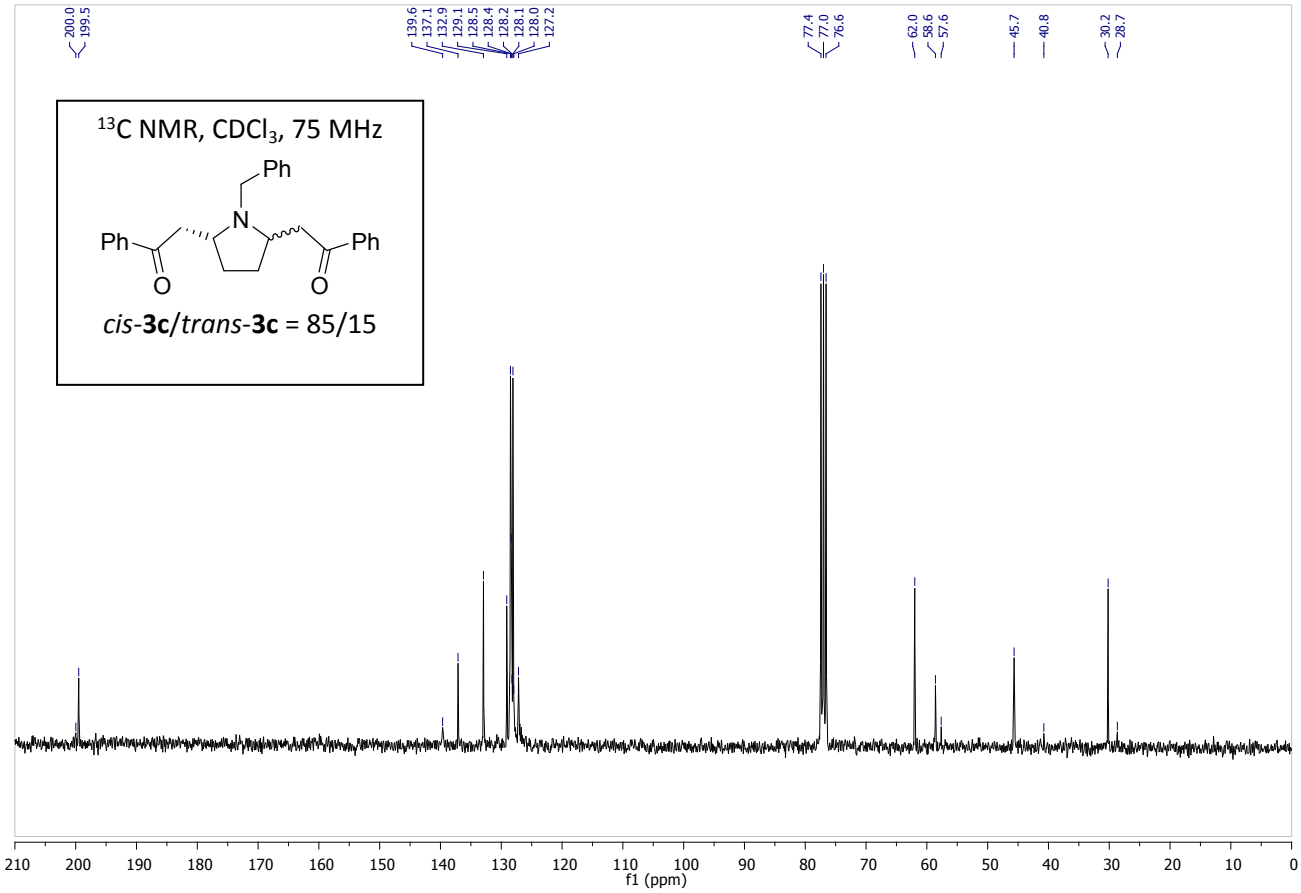

^{1}H NMR ,C_6D_6,, 300 MHz
MeO
OMe
N
O
O
cis-**10d**/*trans*-**10d** = 93/7%
f1 (ppm)

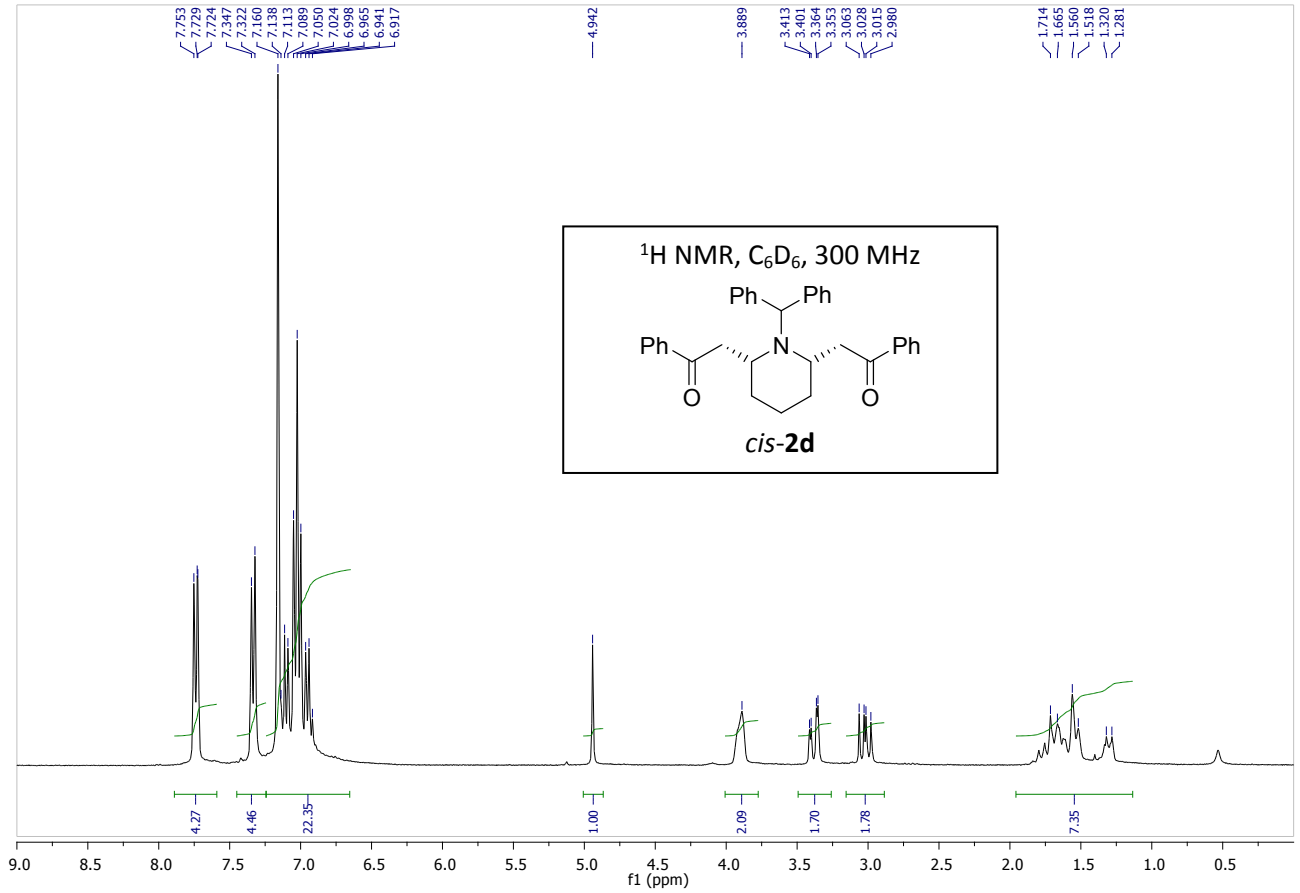

197.4
163.5
130.4
130.1
113.7
77.4
77.0
76.6
63.3
55.4
43.2
39.1
29.7
^{13}C NMR, $CDCl_3$, 75 MHz
MeO
OMe
N
O
O
cis-**10d**
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

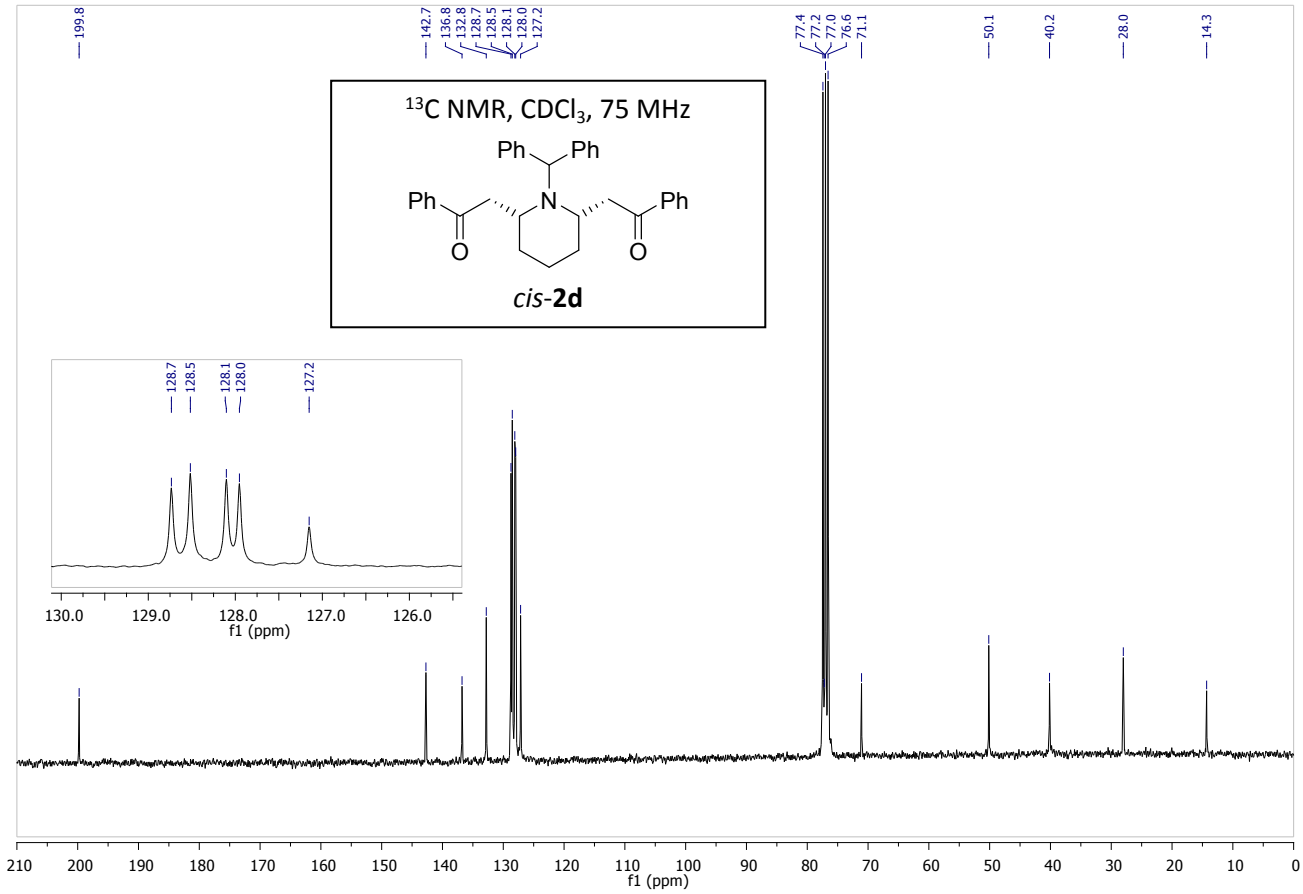

^{1}H NMR, $(CD_3)_2CO$, 300 MHz
Ph
Ph
N
Ph
O
O
cis-**2c**/*trans*-**2c** = 23/67
f1 (ppm)

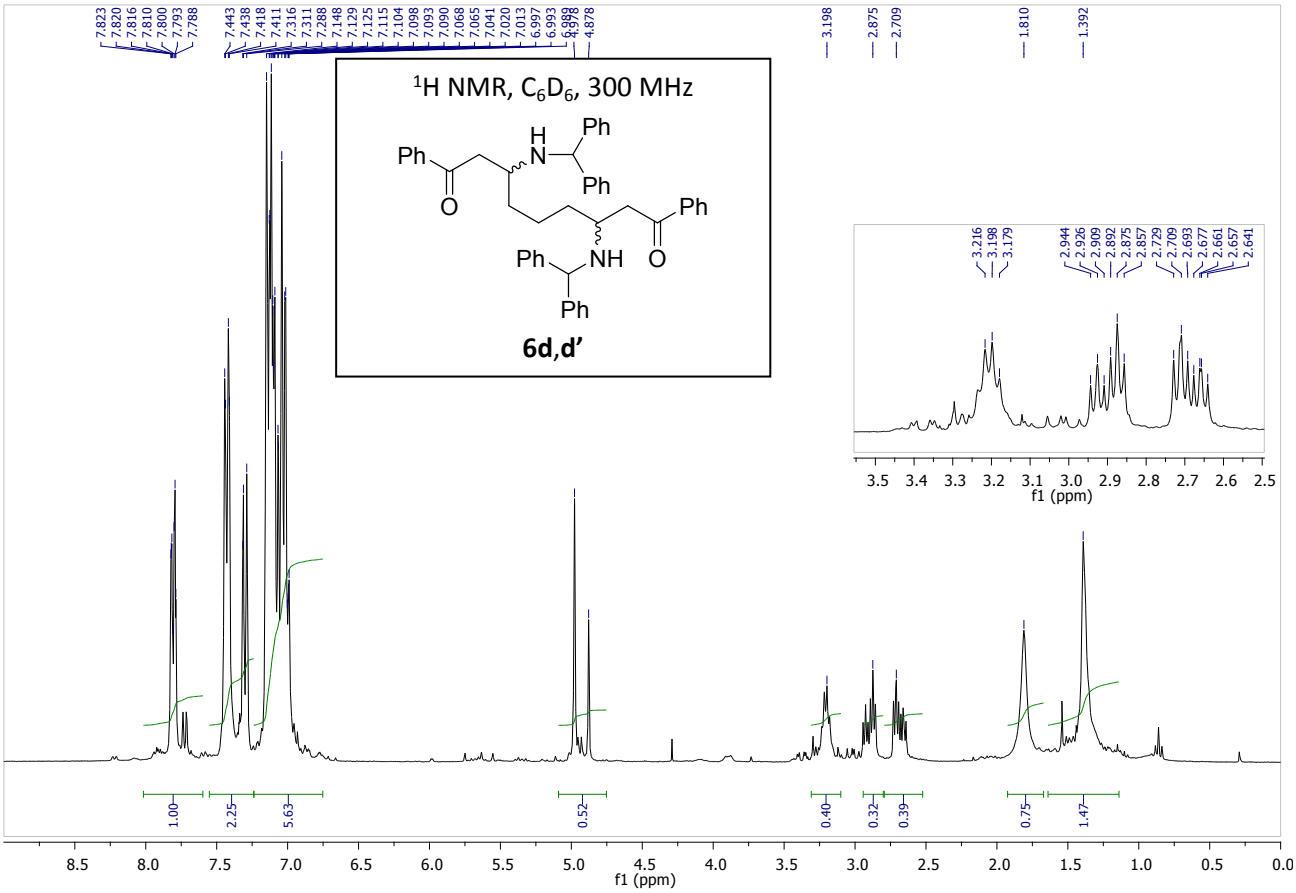

199.3
140.5
137.0
132.9
128.5
128.3
128.2
128.1
127.4
126.7
126.5
77.4
77.0
76.6
58.3
53.1
52.7
43.8
41.2
28.2
26.6
19.8
13C NMR, CDCl3, 75 MHz
Ph
Ph
N
Ph
O
O
cis-2c/trans-2c = 23/67
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

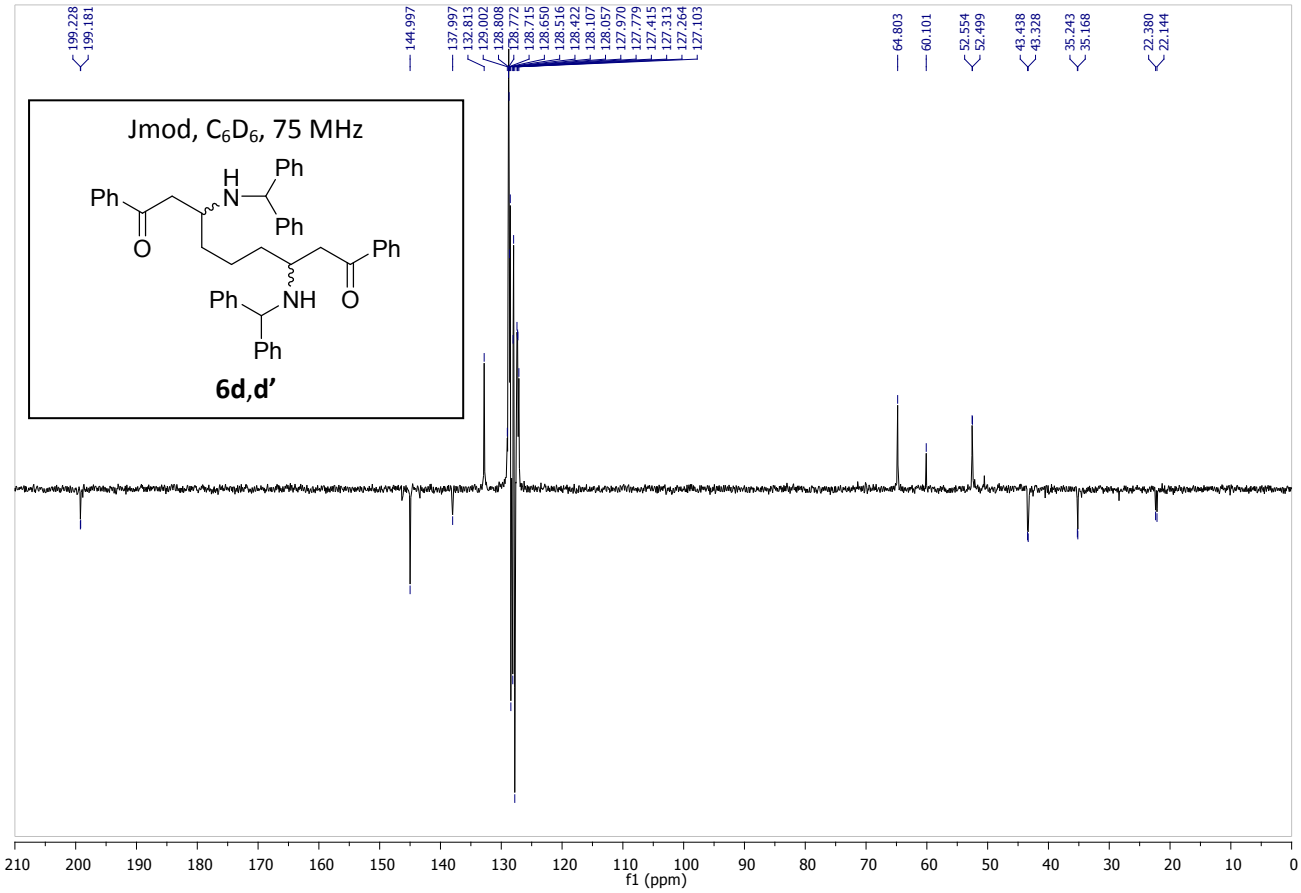

^{1}H NMR, $CDCl_3$, 300 MHz
Ph
N
Ph
Ph
O
O
cis-**3c**/*trans*-**3c** = 85/15
f1 (ppm)

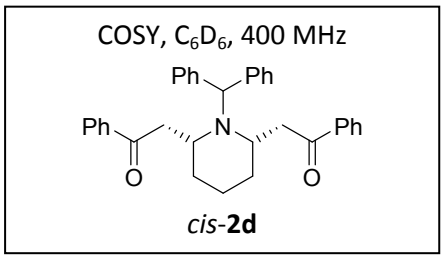

200.0
199.5
139.6
137.1
132.9
129.1
128.5
128.4
128.2
128.1
128.0
127.2
77.4
77.0
76.6
62.0
58.6
57.6
45.7
40.8
30.2
28.7
^{13}C NMR, $CDCl_3$, 75 MHz
Ph
N
Ph
Ph
O
O
cis-**3c**/*trans*-**3c** = 85/15
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

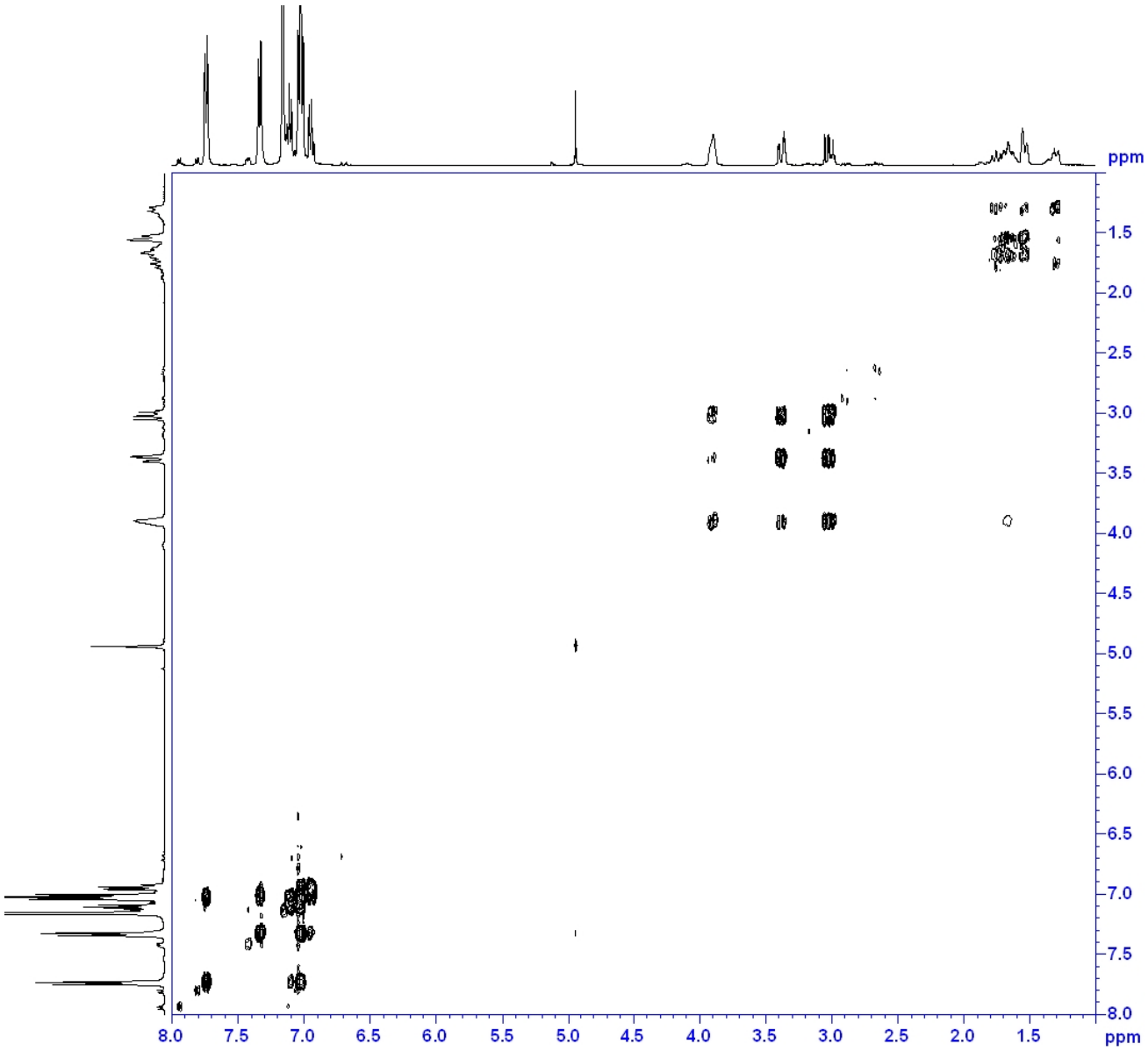

7.753
7.729
7.724
7.347
7.322
7.160
7.138
7.113
7.089
7.050
7.024
6.998
6.965
6.941
6.917
4.942
3.889
3.413
3.401
3.364
3.353
3.063
3.028
3.015
2.980
1.714
1.665
1.560
1.518
1.320
1.281
4.27
4.46
22.35
1.00
2.09
1.70
1.78
7.35
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)
^{1}H NMR, C_6D_6, 300 MHz
Ph
Ph
Ph
N
Ph
O
O
cis-**2d**


199.8
142.7
136.8
132.8
128.7
128.5
128.1
128.0
127.2
77.4
77.2
77.0
76.6
71.1
50.1
40.2
28.0
14.3
128.7
128.5
128.1
128.0
127.2
130.0
129.0
128.0
127.0
126.0
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)
^{13}C NMR, $CDCl_3$, 75 MHz
Ph
Ph
Ph
N
Ph
O
O
cis-**2d**

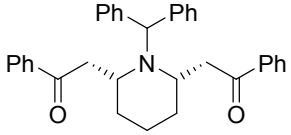

^{1}H NMR, C_6D_6, 300 MHz
6d,d'
f1 (ppm)


199.228
199.181
144.997
137.997
132.813
129.002
128.808
128.772
128.715
128.650
128.516
128.422
128.107
128.057
127.970
127.779
127.415
127.313
127.264
127.103
64.803
60.101
52.554
52.499
43.438
43.328
35.243
35.168
22.380
22.144
Jmod, C6D6, 75 MHz
Ph
H
N
Ph
Ph
O
Ph
Ph
NH
O
Ph
6d,d'
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

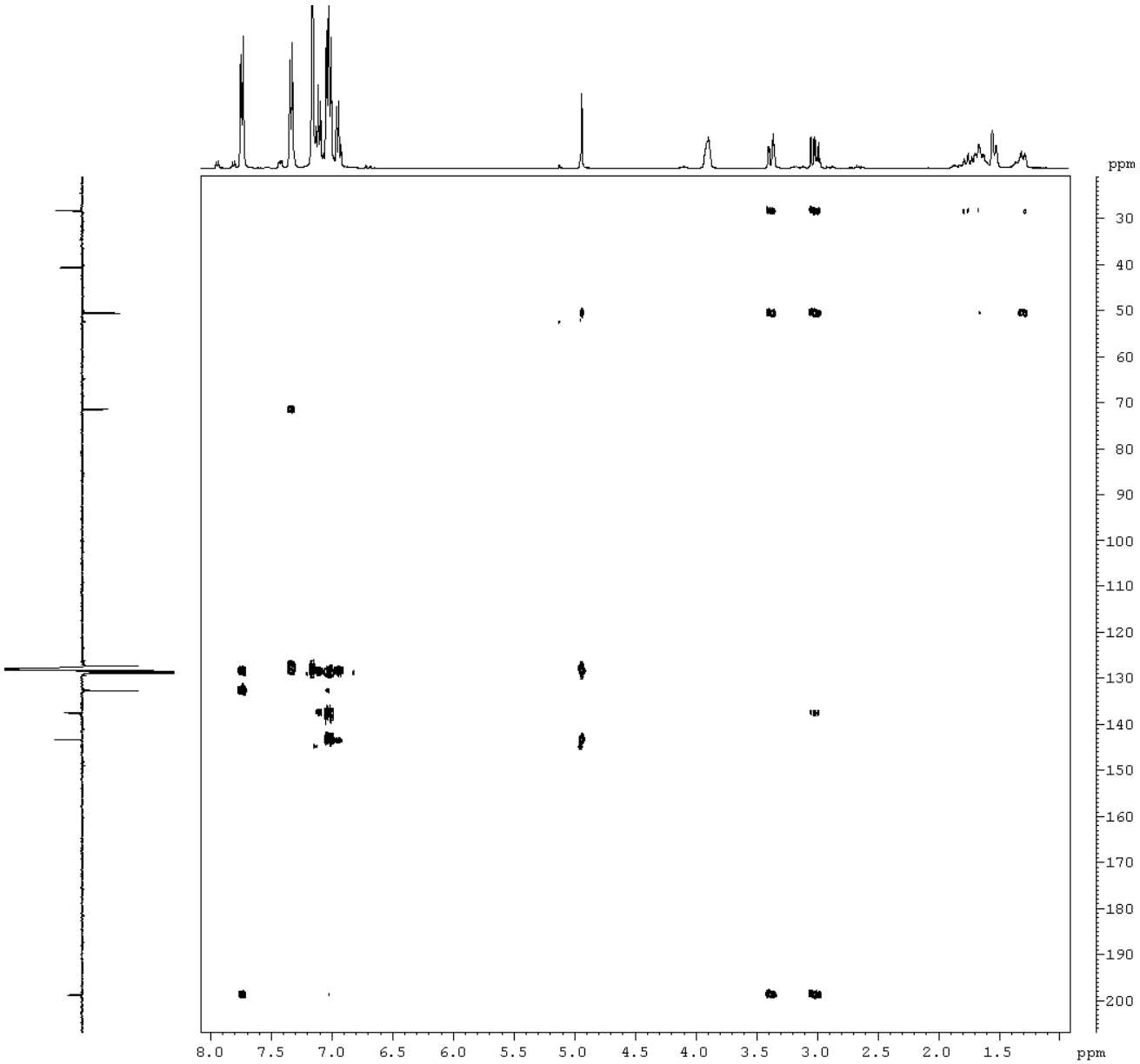

COSY, C6D6, 400 MHz
Ph
Ph
Ph
N
Ph
O
O
cis-2d



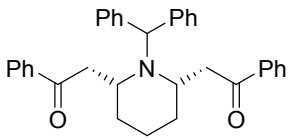
HMBC, C_6D_6, 400 MHz



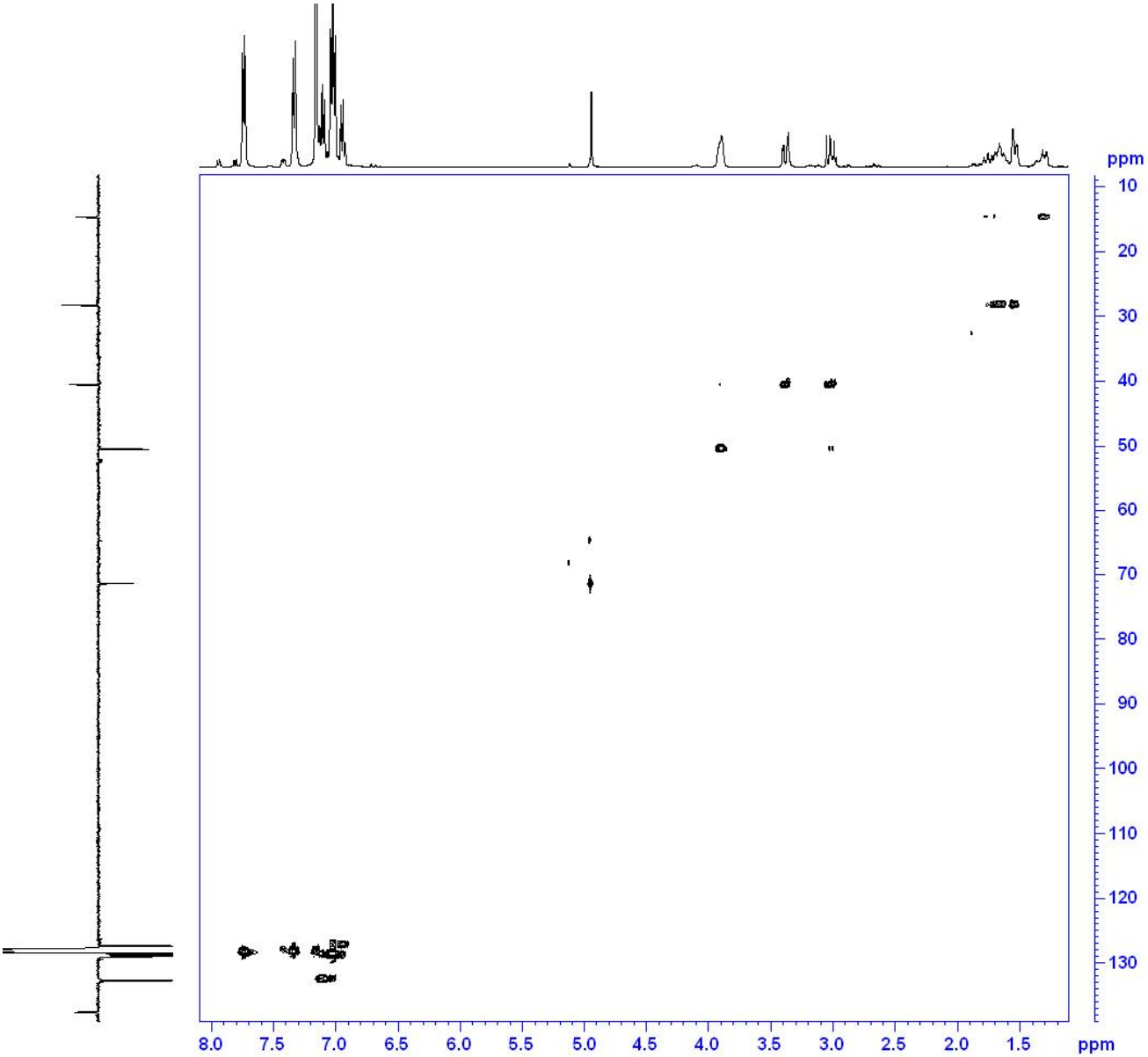
cis-**2d**



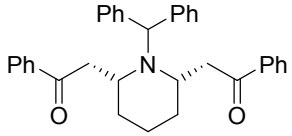
HSQC, C_6D_6, 400 MHz



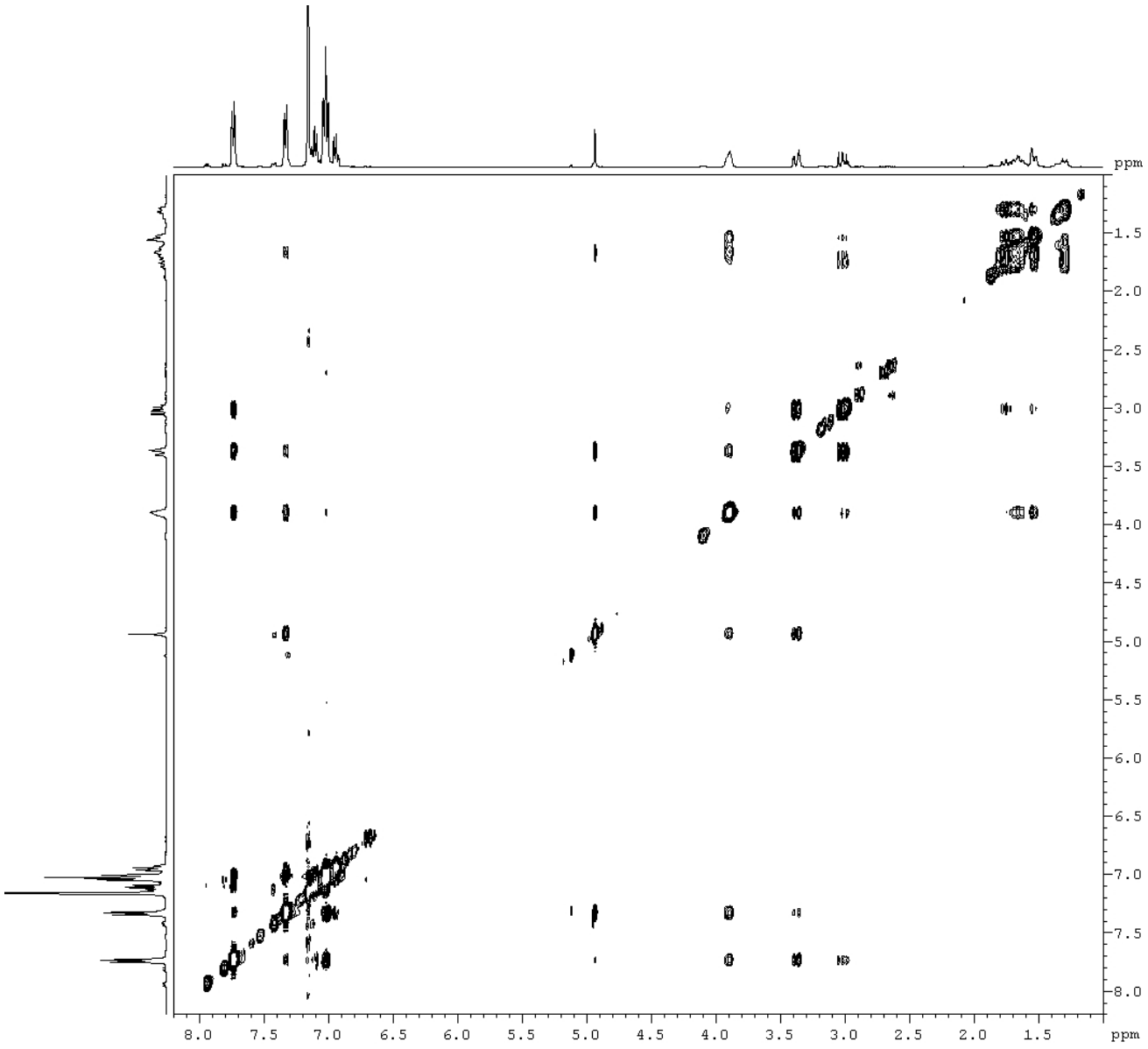
cis-**2d**

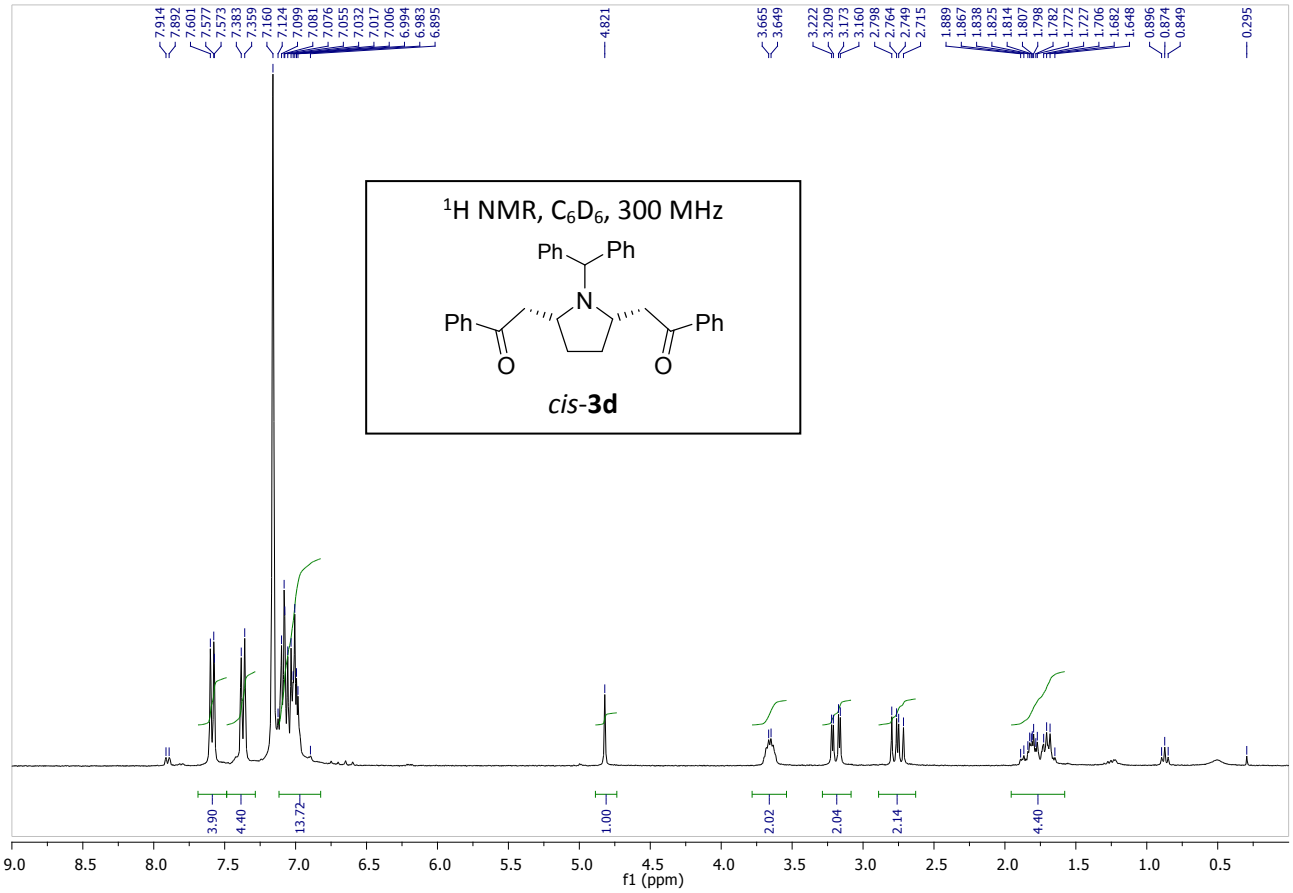


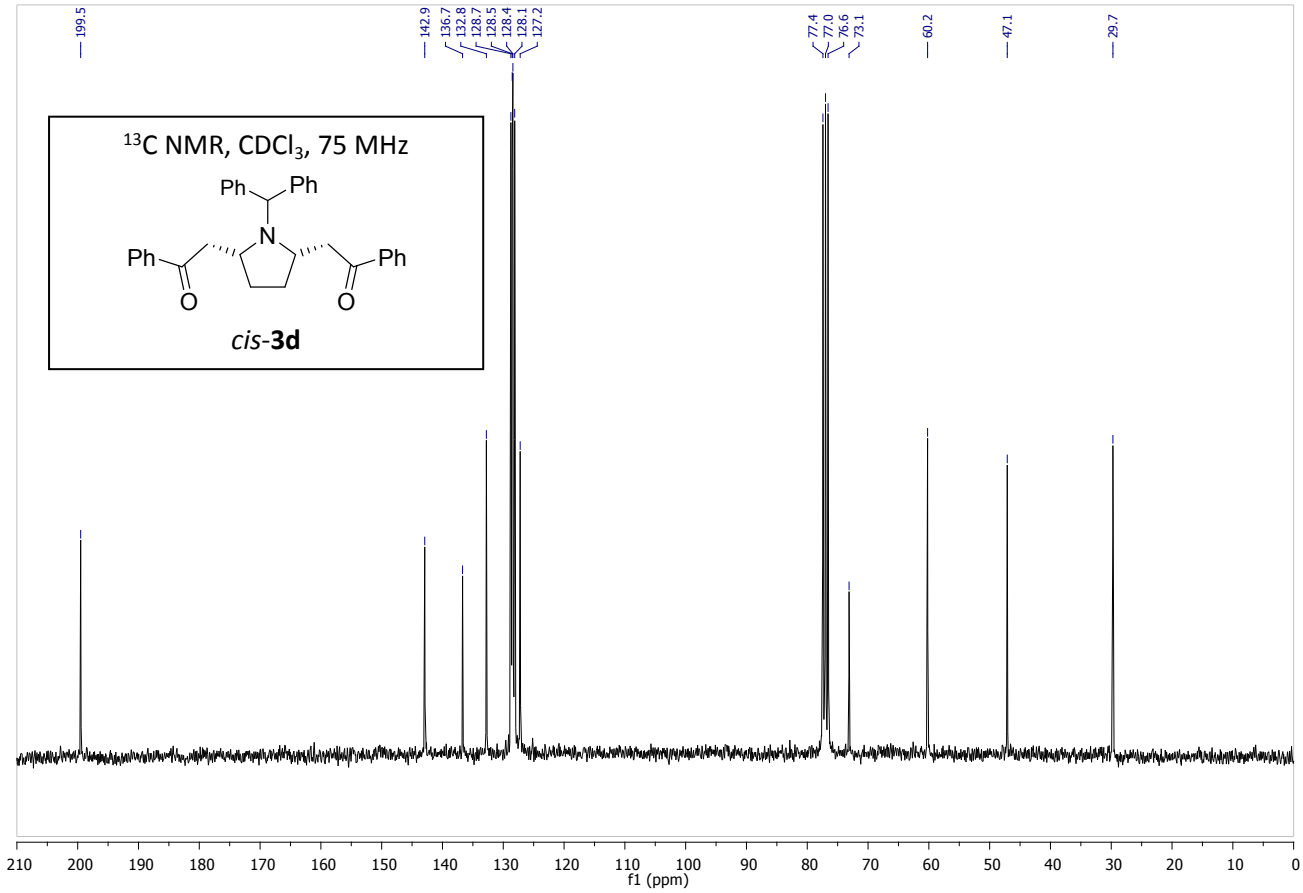
NOESY, C_6D_6, 400 MHz

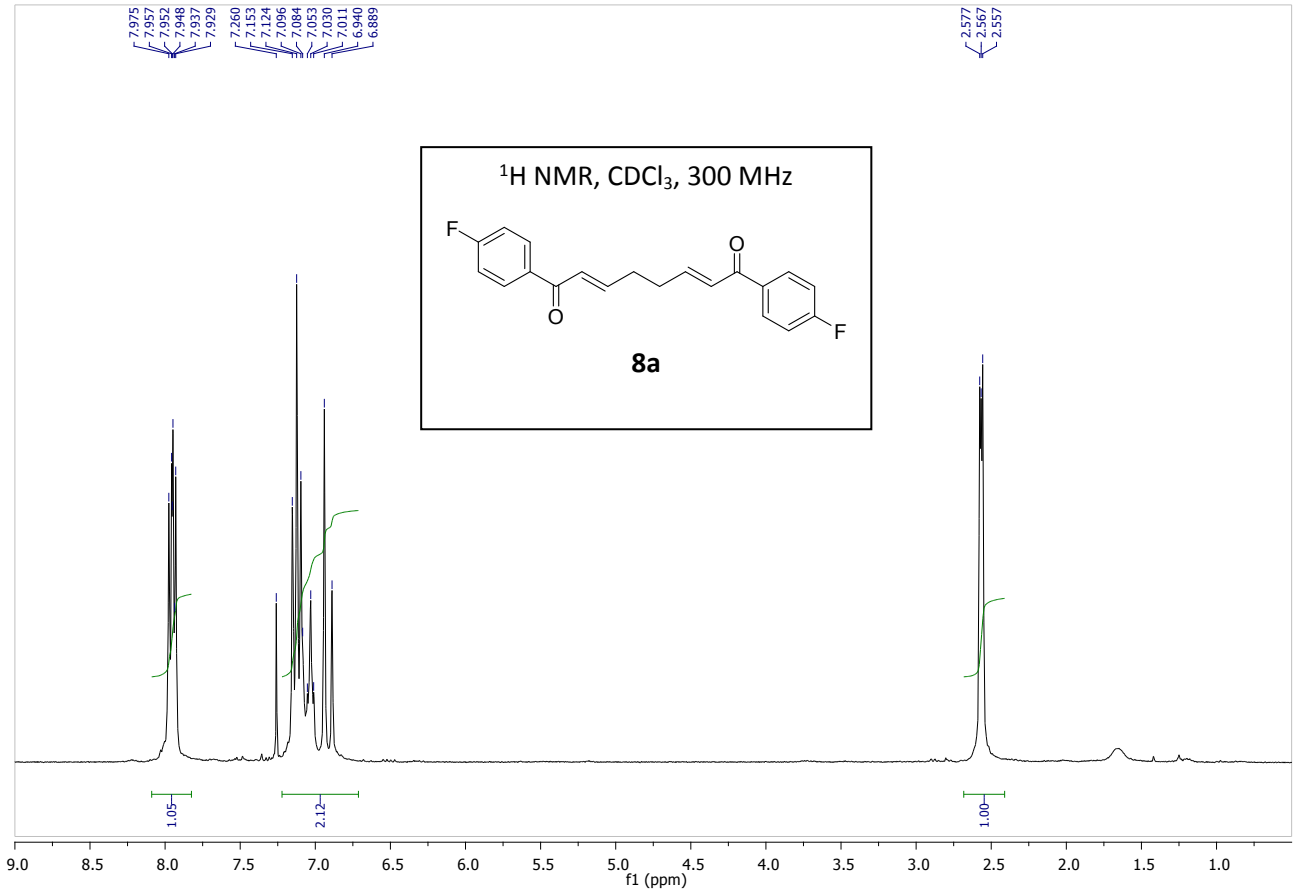


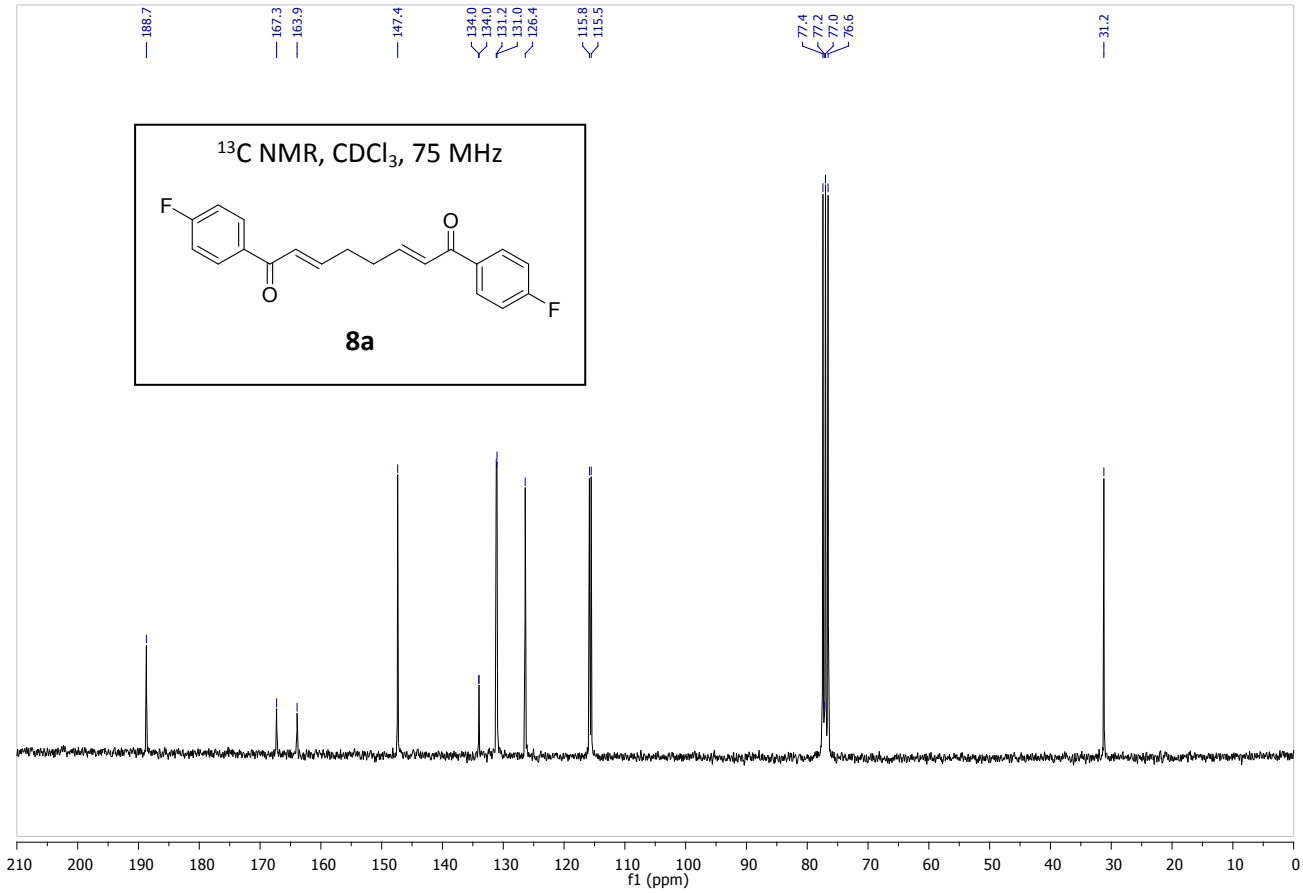
cis-**2d**

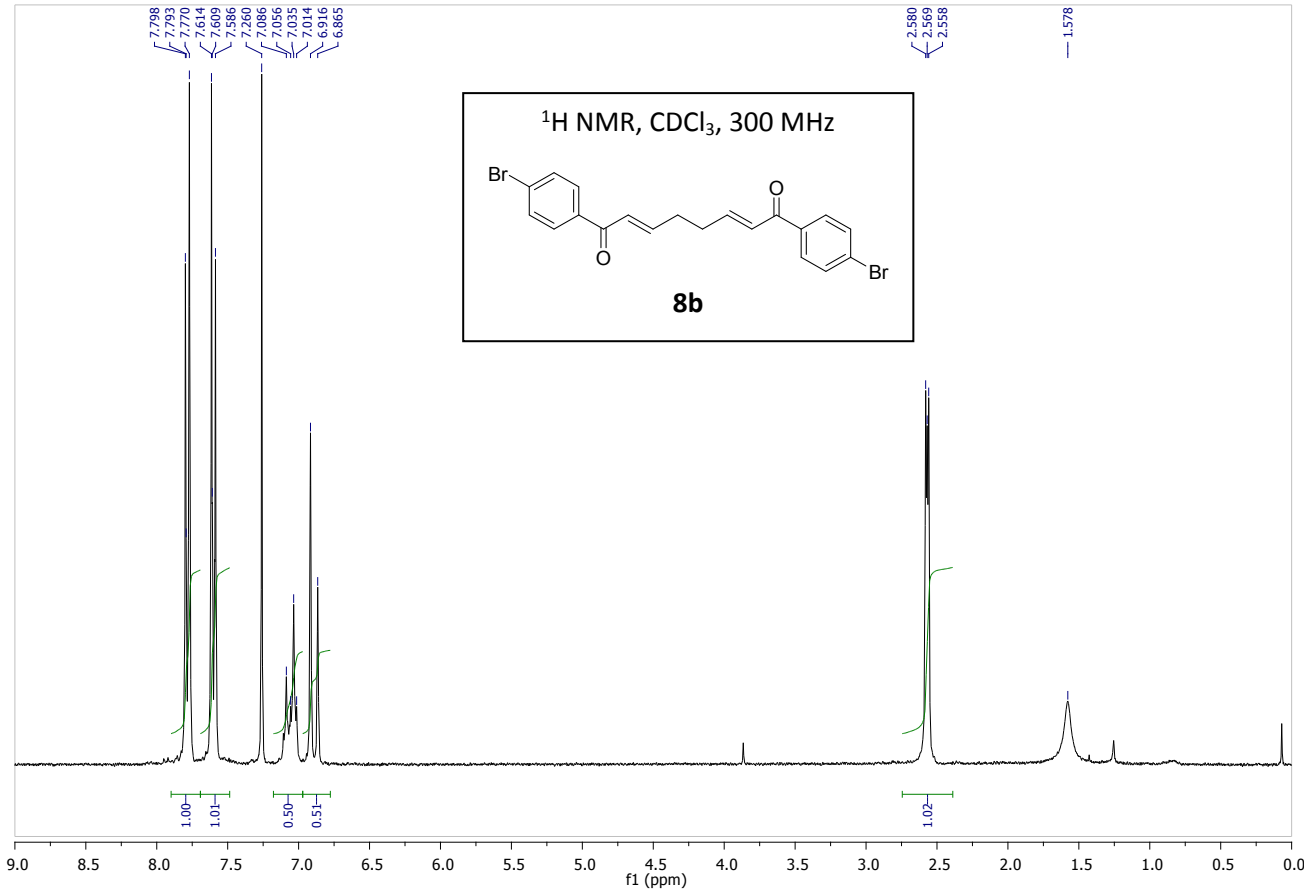

ppm
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm

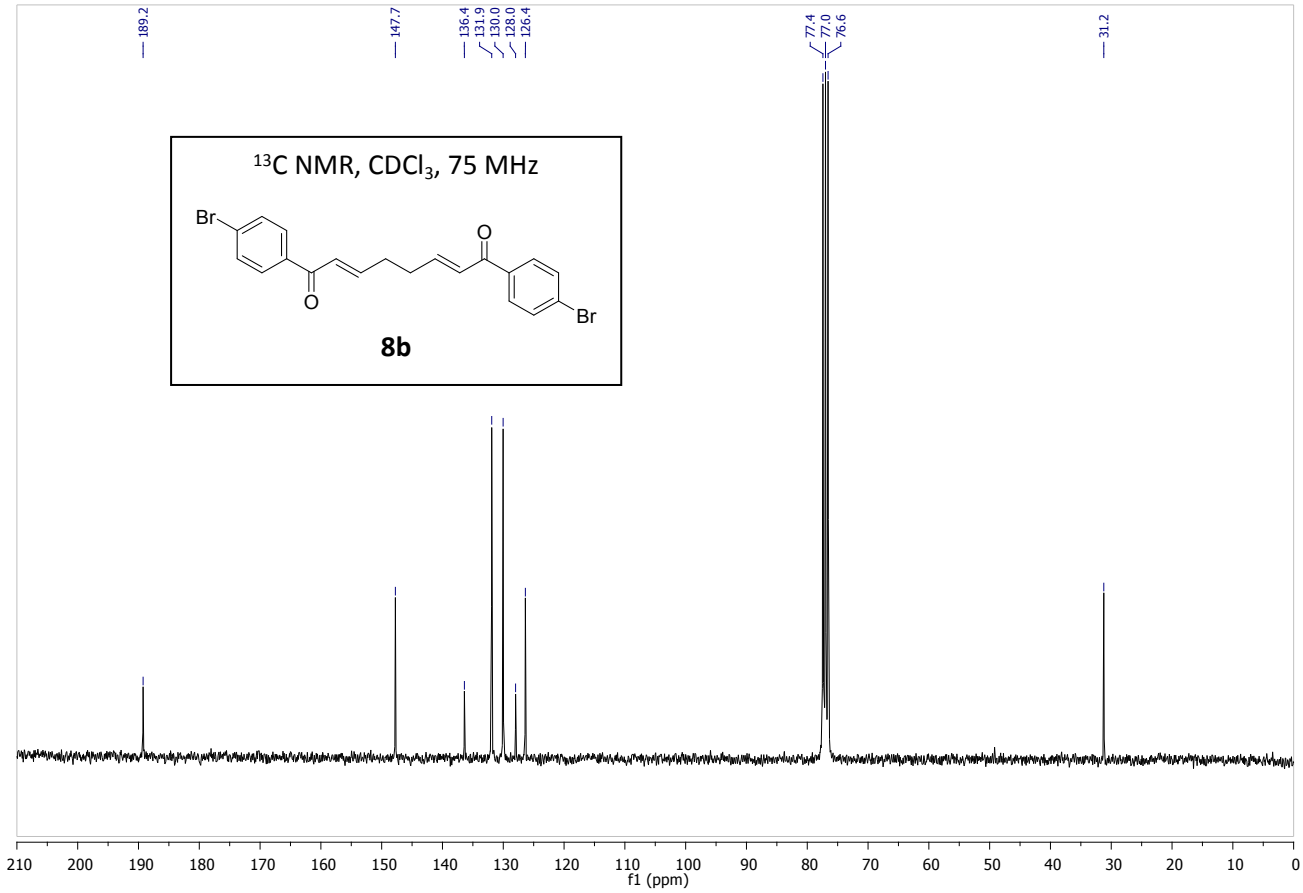

7.914
7.892
7.601
7.577
7.573
7.383
7.359
7.160
7.124
7.099
7.081
7.076
7.055
7.032
7.017
7.006
6.994
6.983
6.895
4.821
3.665
3.649
3.222
3.209
3.173
3.160
2.798
2.764
2.749
2.715
1.889
1.867
1.838
1.825
1.814
1.807
1.798
1.782
1.772
1.727
1.706
1.682
1.648
0.896
0.874
0.849
0.295
^{1}H NMR, C_6D_6, 300 MHz
Ph
Ph
N
Ph
Ph
O
O
cis-**3d**
3.90
4.40
13.72
1.00
2.02
2.04
2.14
4.40
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
f1 (ppm)

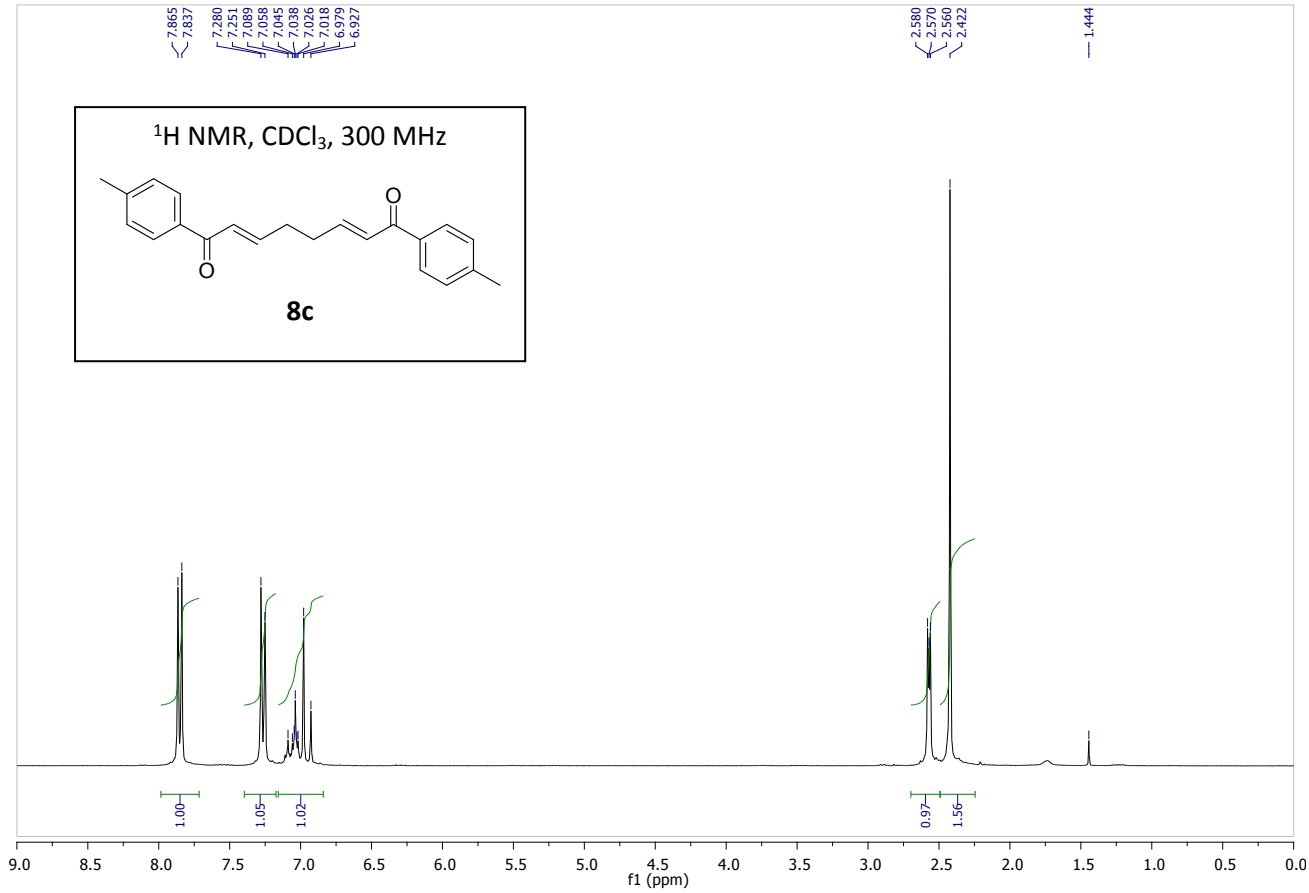

199.5
142.9
136.7
132.8
128.7
128.5
128.4
128.1
127.2
77.4
77.0
76.6
73.1
60.2
47.1
29.7
13C NMR, CDCl3, 75 MHz
Ph
Ph
N
Ph
Ph
O
O
cis-3d
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

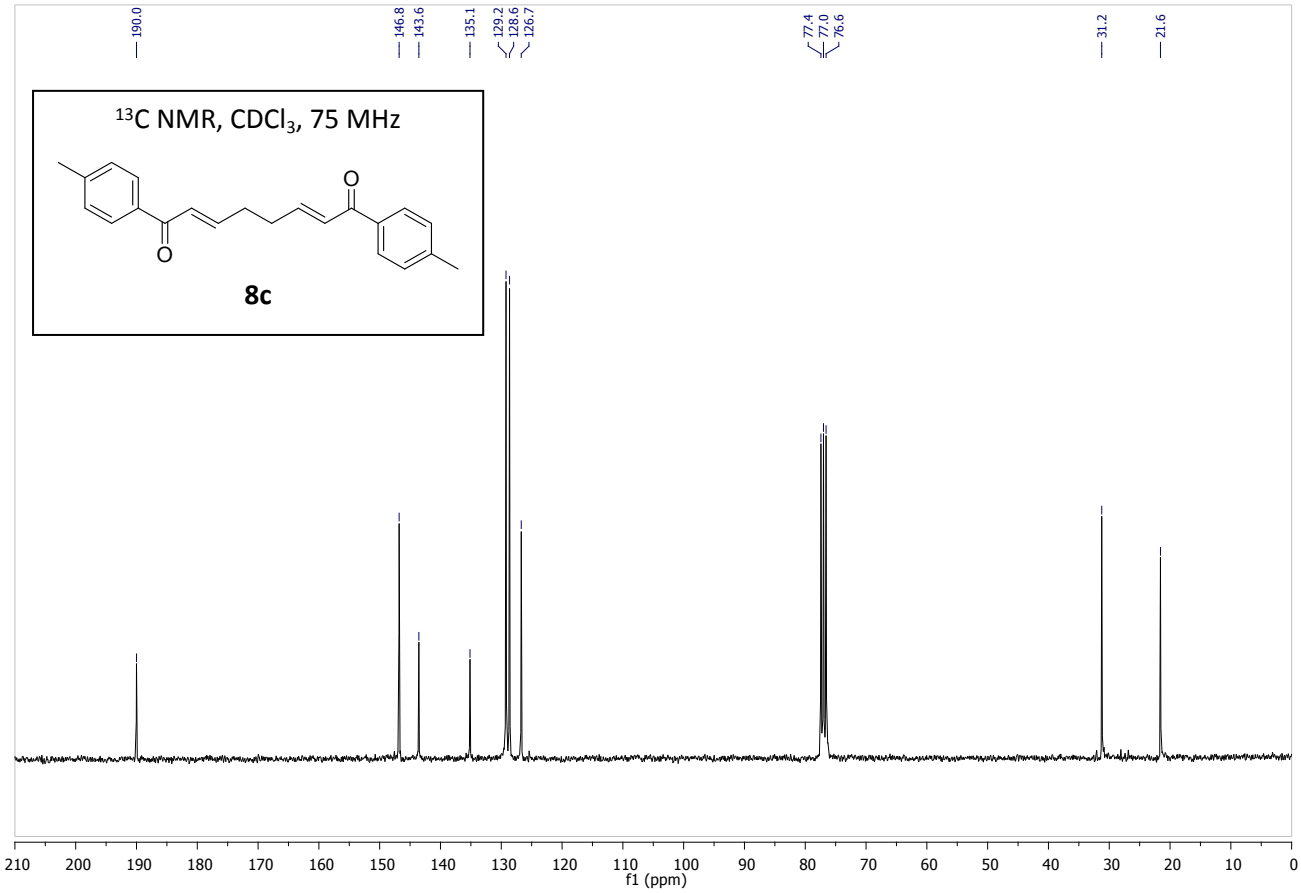

7.975
7.957
7.952
7.948
7.937
7.929
7.260
7.153
7.124
7.096
7.084
7.053
7.030
7.011
6.940
6.889
2.577
2.567
2.557
^{1}H NMR, $CDCl_3$, 300 MHz
F
O
O
F
8a
1.05
2.12
1.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)

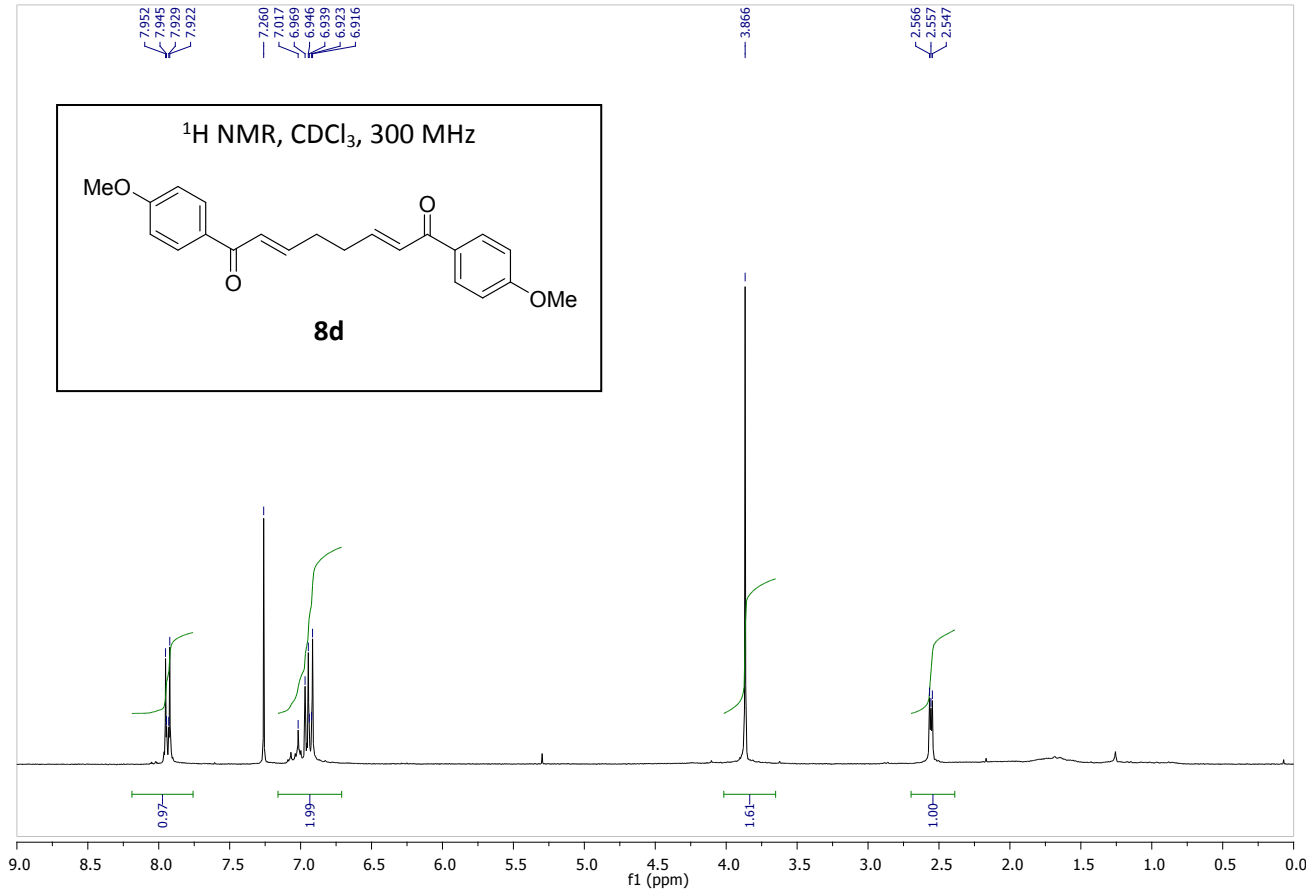

188.7
167.3
163.9
147.4
134.0
134.0
131.2
131.0
126.4
115.8
115.5
77.4
77.2
77.0
76.6
31.2
13C NMR, CDCl3, 75 MHz
F
O
O
F
8a
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

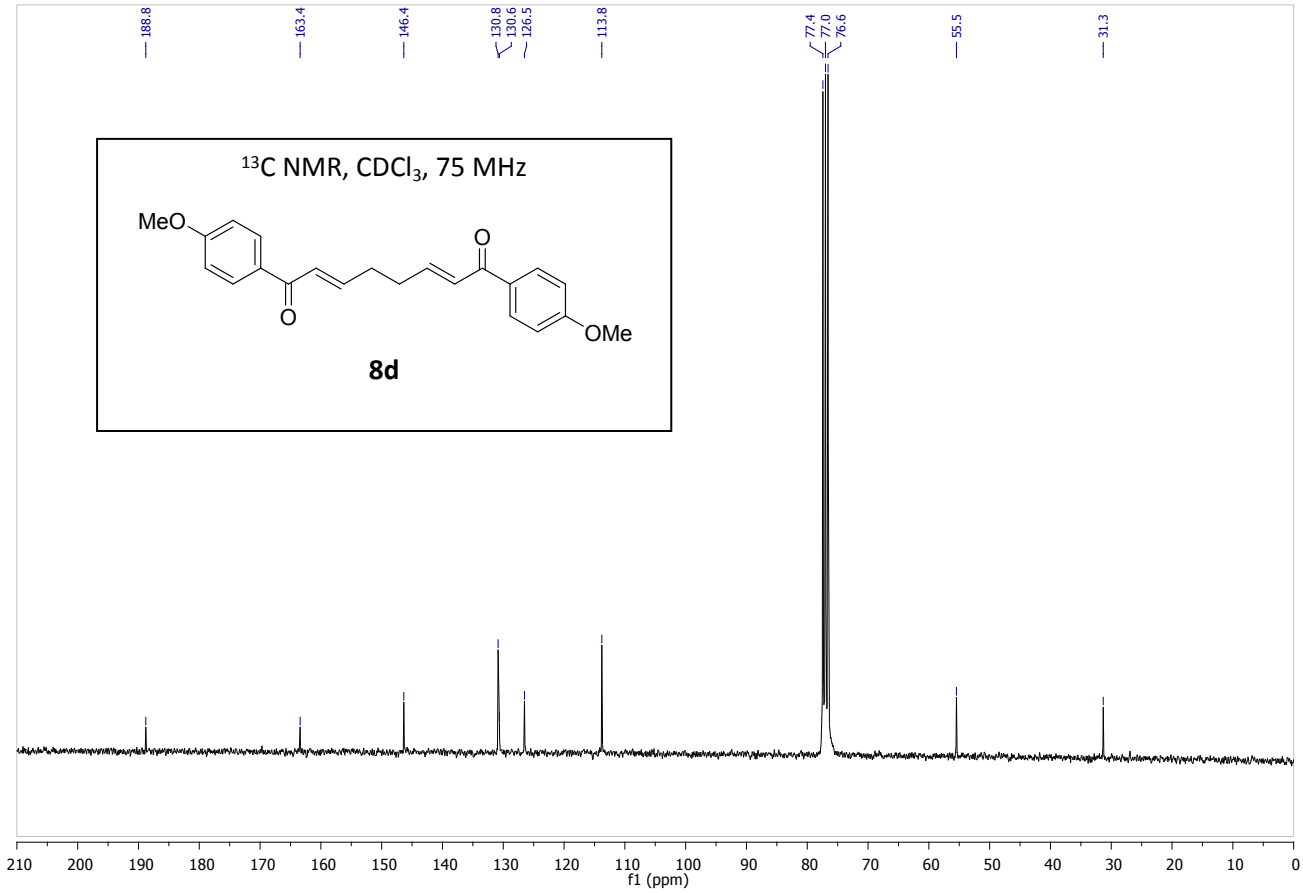

7.798
7.793
7.770
7.614
7.609
7.586
7.260
7.086
7.056
7.035
7.014
6.916
6.865
2.580
2.569
2.558
1.578
1H NMR, CDCl3, 300 MHz
Br
O
O
Br
8b
1.00
1.01
0.50
0.51
1.02
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


189.2
147.7
136.4
131.9
130.0
128.0
126.4
77.4
77.0
76.6
31.2
13C NMR, CDCl3, 75 MHz
Br
O
O
Br
8b
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

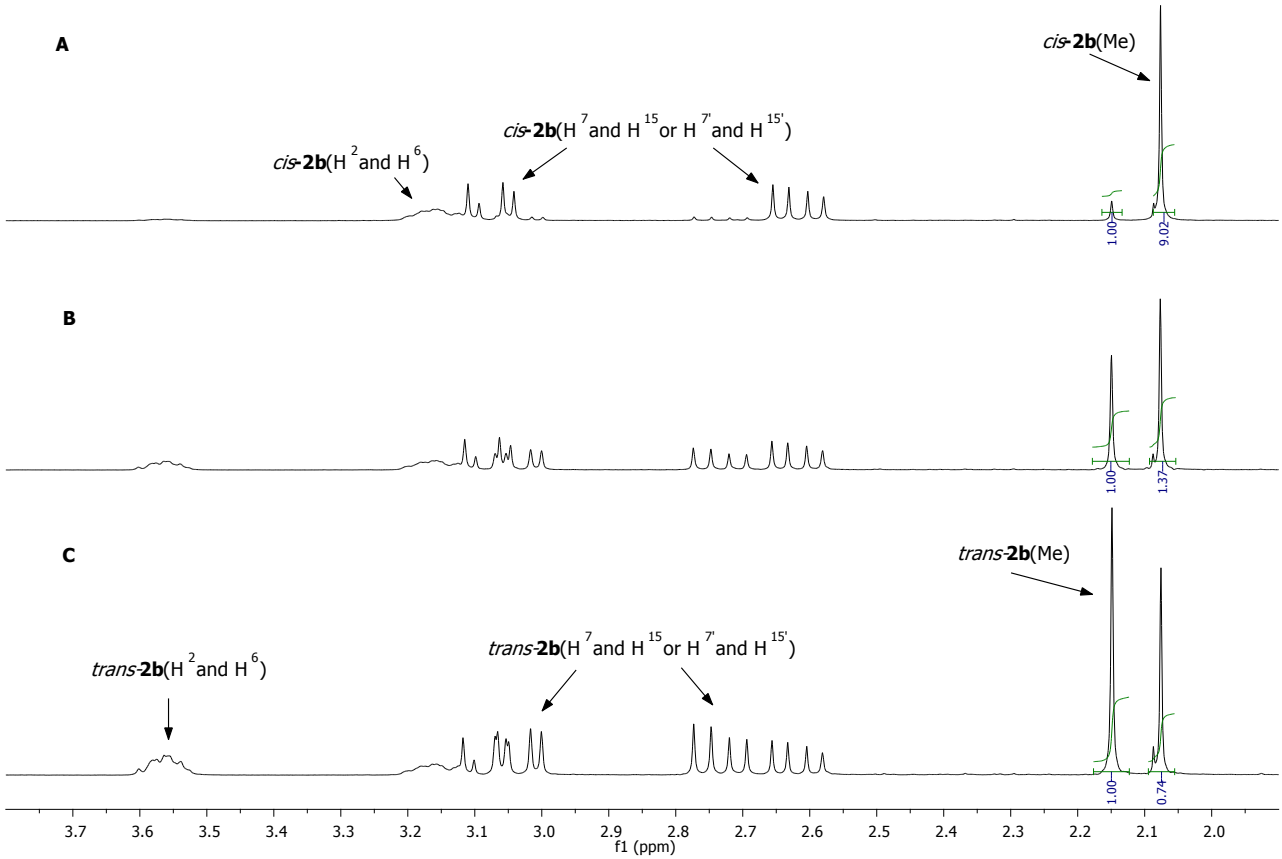

7.865
7.837
7.280
7.251
7.089
7.058
7.045
7.038
7.026
7.018
6.979
6.927
2.580
2.570
2.560
2.422
1.444
^{1}H NMR, $CDCl_3$, 300 MHz
O
O
8c
1.00
1.05
1.02
0.97
1.56
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


190.0
146.8
143.6
135.1
129.2
128.6
126.7
77.4
77.0
76.6
31.2
21.6
13C NMR, CDCl3, 75 MHz
O
O
8c
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


7.952
7.945
7.929
7.922
7.260
7.017
6.969
6.946
6.939
6.923
6.916
3.866
2.566
2.557
2.547
^{1}H NMR, $CDCl_3$, 300 MHz
MeO
O
O
OMe
8d
0.97
1.99
1.61
1.00
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
0.0
f1 (ppm)

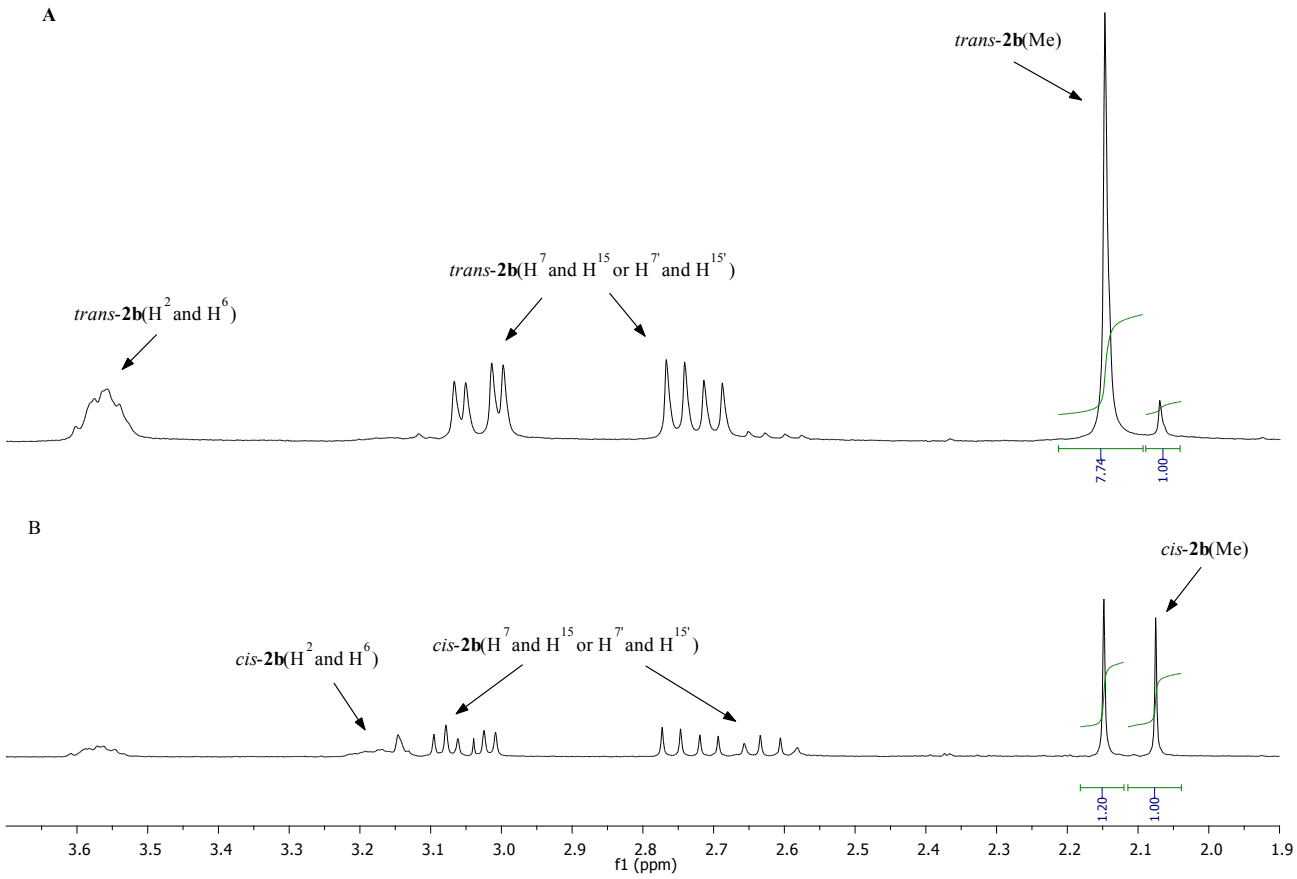


Isomerization of *cis*-2b in *trans*-2b:



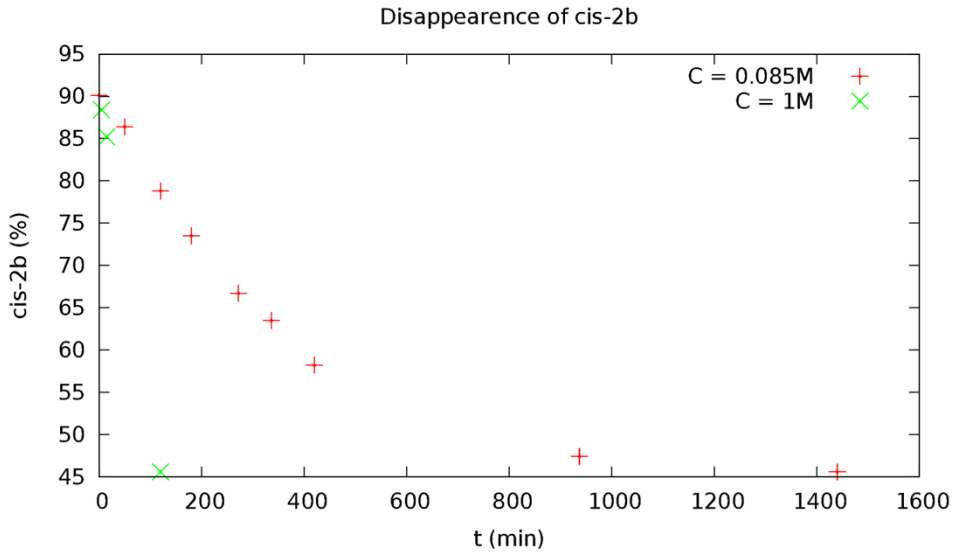
^{1}H NMR spectra (300 MHz) of A) C_6D_6 solution (0.085 M) of compound *cis*-**2b** containing 10% of *trans*-**2b**. B) same solution after 5 hours at room temperature and containing 42% of *trans*-**2b** C) same solution after 23 hours at room temperature and total equilibration, containing 55% of *trans*-**2b**.

Isomerization of *trans*-2b in *cis*-2b:

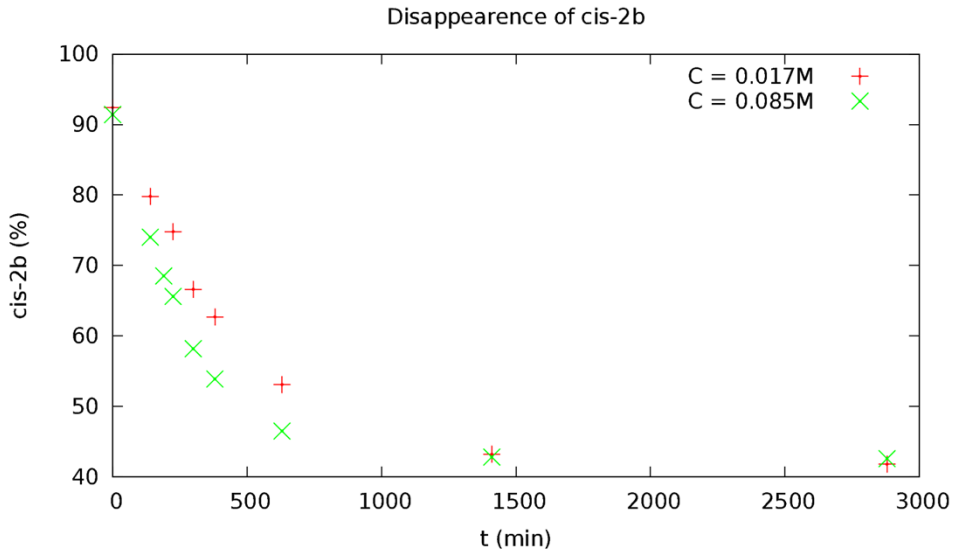


^{1}H NMR spectra (300 MHz) of A) C_6D_6 solution of compound *trans*-**2b** containing 11% of *cis*-**2b**. B) same solution after total equilibration containing 55% of *trans*-**2b**.

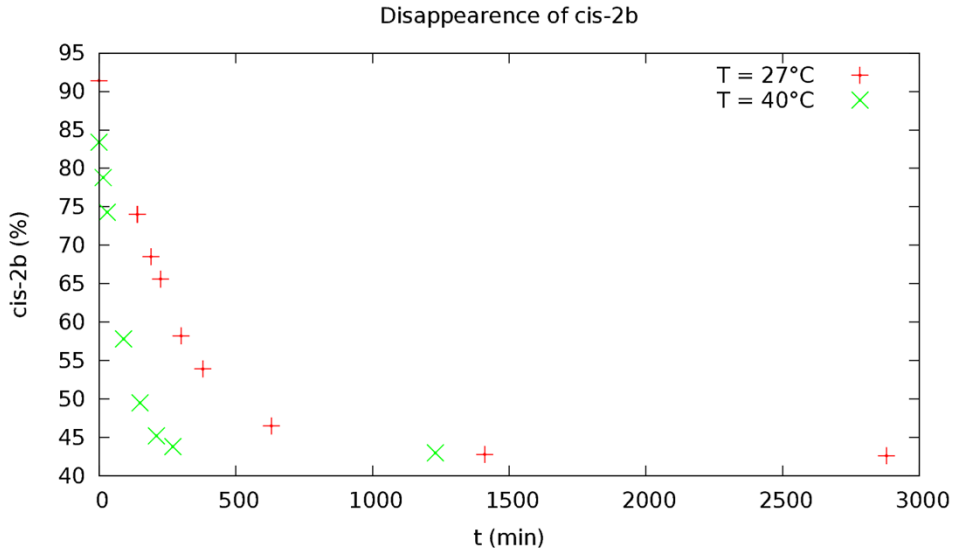
Kinetic studies: progress curves:



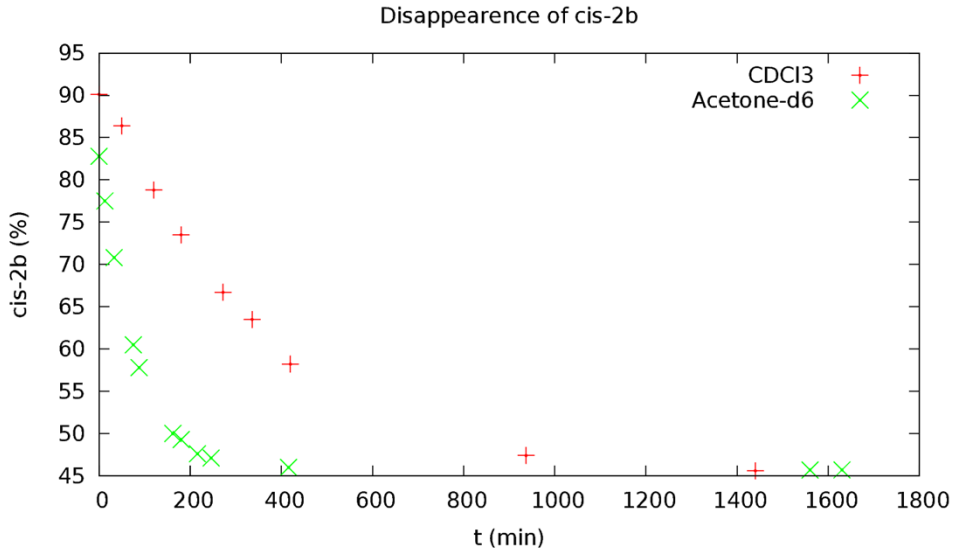
↑ Rate of disappearence of *cis*-**2b** at various concentrations in C_6D_6.



↑ Rate of disappearence of *cis*-**2b** at various concentrations in $CDCl_3$.



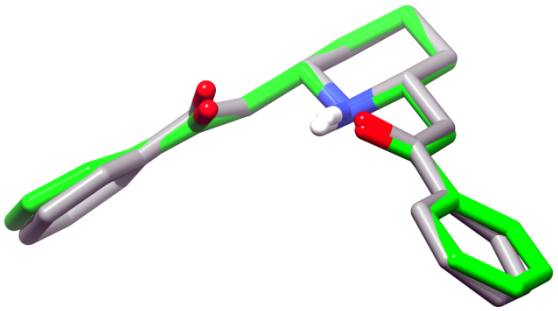
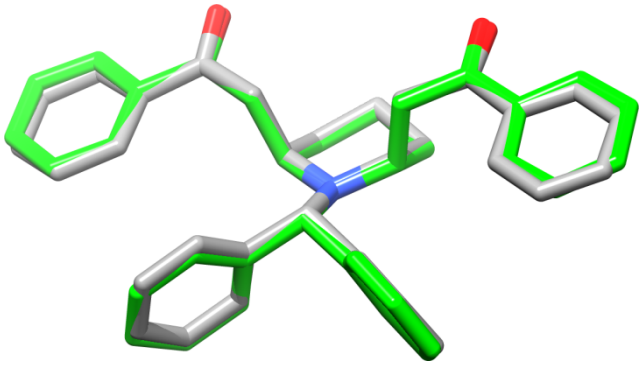
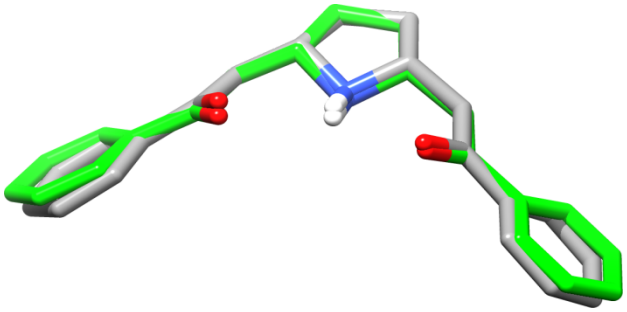
↑ Rate of disappearence of *cis*-**2b** at various temperatures in C_6D_6.



↑ Rate of disappearence of *cis*-**2b** in various solvents.

RMSD for superimposition of theoretical models with X-ray structures:

Alignment based on heavy atoms and depiction of the result were performed with UCSF Chimera [1,2].

Compound	**Superimposition**	**RMSD (Å)**
Cis-**2a**		0.264
Cis-**2d**		0.191
Cis-**3a**		0.288

Model coordinates for DFT calculations:

Compound *cis*-**2a** (E(RB3LYP) = −1019.29973521 Ha, Lowest Frequency: 14.0494 cm^{-1}, Sum of electronic and thermal Free Energies = −1018.954641 Ha):

C	1.23360	2.06179	-0.33164
C	1.25658	3.50020	0.20596
C	0.00000	4.26899	-0.21618
C	-1.25659	3.50021	0.20595
C	-1.23361	2.06180	-0.33166
N	-0.00001	1.38638	0.09882
C	2.44855	1.28287	0.18682
C	-2.44856	1.28288	0.18679
C	2.65512	-0.08248	-0.45909
O	1.87598	-0.50618	-1.30213
C	-2.65515	-0.08246	-0.45913
O	-1.87598	-0.50618	-1.30214
C	-3.84249	-0.90441	-0.04808
C	-4.02627	-2.15177	-0.66615
C	-5.10905	-2.95653	-0.32609
C	-6.02413	-2.52596	0.63942
C	-5.85028	-1.28860	1.26196
C	-4.76553	-0.48107	0.92040
C	3.84248	-0.90442	-0.04806
C	4.02627	-2.15177	-0.66614
C	5.10906	-2.95652	-0.32610
C	6.02416	-2.52594	0.63939
C	5.85030	-1.28859	1.26194
C	4.76554	-0.48107	0.92040
H	1.30107	2.10758	-1.43529
H	1.31325	3.46679	1.30329
H	2.16013	4.01115	-0.15185
H	0.00000	5.27599	0.21964
H	0.00001	4.39778	-1.30832
H	-1.31326	3.46679	1.30328
H	-2.16013	4.01116	-0.15188
H	-1.30106	2.10758	-1.43531
H	-0.00001	0.46466	-0.33745
H	3.36113	1.87574	0.03072
H	2.34929	1.14889	1.27309
H	-2.34931	1.14889	1.27306
H	-3.36113	1.87576	0.03069
H	-3.30218	-2.46521	-1.41108
H	-5.24224	-3.91991	-0.81092
H	-6.87018	-3.15404	0.90594
H	-6.55906	-0.95207	2.01368
H	-4.64265	0.47746	1.41460
H	3.30217	-2.46522	-1.41106
H	5.24226	-3.91989	-0.81095

H	6.87022	-3.15401	0.90589
H	6.55910	-0.95205	2.01364
H	4.64265	0.47746	1.41461

Compound *cis*-**2d** (E(RB3LYP) = −1520.68535899 Ha, Lowest Frequency: 7.1884 cm^{-1}, Sum of electronic and thermal Free Energies = −1520.161661 Ha):

C	-1.69598	-1.50375	-0.62007
C	-3.00320	-2.28414	-0.52855
O	-2.96437	-3.50395	-0.41889
C	-4.32428	-1.57445	-0.54568
C	-5.48653	-2.35105	-0.39760
C	-6.74223	-1.75391	-0.40636
C	-6.85647	-0.36819	-0.56166
C	-5.70963	0.41263	-0.70881
C	-4.44916	-0.18619	-0.70282
H	-2.04985	-0.11144	0.96812
H	-1.76590	-0.72614	-1.38932
H	-0.95536	-2.23314	-0.94580
H	-5.37290	-3.42351	-0.27846
H	-7.63417	-2.36412	-0.29169
H	-7.83774	0.09946	-0.56757
H	-5.78927	1.48966	-0.82612
H	-3.57159	0.43978	-0.82112
C	-1.26927	-0.83976	0.73689
C	-1.24260	-1.83989	1.90787
C	-0.00060	-2.73077	1.89593
C	1.24194	-1.84064	1.90784
C	1.26914	-0.84045	0.73692
N	0.00013	-0.07159	0.69642
C	1.69556	-1.50469	-0.62001
C	3.00292	-2.28488	-0.52863
O	2.96429	-3.50465	-0.41845
C	4.32390	-1.57502	-0.54654
C	5.48632	-2.35144	-0.39880
C	6.74194	-1.75414	-0.40825
C	6.85594	-0.36844	-0.56390
C	5.70893	0.41220	-0.71071
C	4.44855	-0.18679	-0.70406
H	-1.25261	-1.25954	2.84030
H	-2.15590	-2.44219	1.89517
H	-0.00078	-3.38963	2.77270
H	-0.00083	-3.38731	1.01743
H	1.25238	-1.26038	2.84032
H	2.15486	-2.44351	1.89502
H	2.05008	-0.11252	0.96818
H	0.95495	-2.23427	-0.94534
H	1.76521	-0.72731	-1.38952
H	5.37288	-3.42389	-0.27934

H	7.63401	-2.36421	-0.29383
H	7.83714	0.09933	-0.57033
H	5.78839	1.48922	-0.82826
H	3.57085	0.43906	-0.82208
C	0.00064	1.09638	-0.20187
H	0.00143	0.78561	-1.26210
C	2.76869	3.24869	1.38430
H	3.12469	3.51430	2.37624
C	1.70167	2.36232	1.24927
H	1.23366	1.93619	2.13179
C	1.23116	1.99582	-0.02003
C	1.85231	2.54743	-1.14658
H	1.49665	2.27910	-2.13920
C	2.91556	3.44508	-1.01499
H	3.37902	3.86545	-1.90375
C	3.37854	3.79736	0.25263
H	4.20567	4.49385	0.36025
C	-2.76879	3.25013	1.37987
H	-3.12542	3.51695	2.37125
C	-1.70155	2.36377	1.24660
H	-1.23394	1.93899	2.12998
C	-1.23020	1.99574	-0.02195
C	-1.85077	2.54582	-1.14957
H	-1.49450	2.27626	-2.14164
C	-2.91424	3.44349	-1.01976
H	-3.37722	3.86265	-1.90933
C	-3.37804	3.79728	0.24713
H	-4.20531	4.49382	0.35337

Compound *cis*-**3a** (E(RB3LYP) = −979.980587405 Ha, Lowest Frequency: 9.0140 cm^{-1}, Sum of electronic and thermal Free Energies = −979.665233 Ha):

O	2.21803	-0.51732	-1.36058
C	2.88974	0.02537	-0.49334
C	4.16577	-0.60762	-0.02032
C	4.97001	-0.04342	0.98154
C	6.14671	-0.67650	1.38157
C	6.53173	-1.87827	0.78456
C	5.73606	-2.44844	-0.21392
C	4.56174	-1.81771	-0.61222
C	2.45114	1.35149	0.12021
C	1.16849	1.91317	-0.49079
C	0.77607	3.30347	0.06241
C	-0.77621	3.30350	0.06229
C	-1.16860	1.91316	-0.49086
C	-2.45126	1.35150	0.12013
C	-2.88953	0.02509	-0.49303
C	-4.16570	-0.60778	-0.02025

C	-4.97046	-0.04311	0.98094
C	-6.14727	-0.67609	1.38078
C	-6.53191	-1.87823	0.78425
C	-5.73572	-2.44886	-0.21356
C	-4.56129	-1.81823	-0.61167
O	-2.21743	-0.51792	-1.35977
N	-0.00006	1.09132	-0.16262
H	4.68117	0.88926	1.45558
H	6.76226	-0.23211	2.15895
H	7.44922	-2.37026	1.09672
H	6.03389	-3.38427	-0.67909
H	3.92756	-2.24155	-1.38397
H	2.30239	1.21013	1.19993
H	3.27068	2.07628	0.01002
H	1.31371	1.99107	-1.58353
H	1.15923	3.43002	1.08139
H	1.20045	4.10877	-0.54579
H	-1.15953	3.43018	1.08118
H	-1.20045	4.10875	-0.54607
H	-1.31378	1.99099	-1.58361
H	-2.30266	1.21054	1.19992
H	-3.27091	2.07612	0.00955
H	-4.68193	0.88986	1.45460
H	-6.76322	-0.23133	2.15764
H	-7.44949	-2.37013	1.09626
H	-6.03325	-3.38497	-0.67836
H	-3.92671	-2.24242	-1.38290
H	-0.00003	0.23286	-0.70968

X-Ray crystal structure determination:

Crystals were grown by recrystallization (*cis*-**2a**) in toluene, (*cis*-**2d**) in C_6D_6 and (*cis*-**3a**) in ethyl acetate.

Crystals were mounted on a nylon loop with some Paratone® oil. Regarding *cis*-**2a**, X-ray crystallographic data were collected at a low temperature (193(2) K) on a Rigaku diffractometer constituted by a MM007 HF copper rotating-anode generator, equipped with Osmic confocal optics, and a Rapid II curved Image Plate using filtered Cu-Kα radiation (λ =1.54187 Å). A total of 72 oscillation images were collected, from four sweeps of data using ω oscillations in 5.0° steps. The exposure rate was 120.0 sec per °. Regarding the two other structures, a full hemisphere of data completed by three ω scans for a total of 109° *wrt cis*-**2d** (one for a total of 97.3° *wrt cis*-**3a**) were collected at room temperature with 37.5s frames (120s frames) on a Enraf-Nonius Kappa diffractometer fitted with a CCD based detector using MoKα radiation (0.71073 Å). Data reduction

and scaling were carried out using *Fs_Process*[3] *wrt cis*-**2a** or *Scalepack*[4] *wrt* the two other structures. The space group assignment, for each case was based upon systematic absences, *E*-statistics, agreement factors for equivalent reflections, and successful refinement of the structure. The structures were solved by direct methods (*SHELXS-97*),[5] completed by subsequent Fourier syntheses and refined with full-matrix least-squares methods against $|F^2|$ data (*SHELXL-2012*).[5] All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were treated as idealized contributions except for those borne by a nitrogen atom with *Uiso* = 1.2*Ueq*(N) and N–H = 0.87(1) Å *wrt cis*-**3a**.

Crystal structure data for *cis*-**2a**: $C_{21}H_{23}NO_2$, M = 321.40, monoclinic, a = 6.377 (1), b = 10.614 (1), c = 26.405 (2) Å, β = 103.339(6) °, V = 1739.1 (2) Å^3, T = 193(2) K, space group P21/c, Z = 4, D_c = 1.228 gcm^{-3}, μ(Cu-Kα) = 0.617 mm^{-1}, F(000)= 688, λ = 1.54187 Å, 2 θ_{max} = 136.5 ° (d_{min} = 0.83Å), -5 ≤ h ≤ 7, -8 ≤ k ≤ 12, -31 ≤ l ≤ 31, 8145 measured reflections, 3103 independent, R(int)= 0.040, 221 parameters were refined against 3103 reflections, R1 = 0.0512 for 1792 $F_o > 4\sigma F_o$ and 0.1039 for all data, wR2 = 0.1894, $\Delta\rho_{min}$ and $\Delta\rho_{max}$= -0.292 and 0.255 e.Å^{-3} , GOF = 1.131.

Crystal structure data for *cis*-**2d**: $C_{34}H_{33}NO_2$, M = 487.61, monoclinic, a = 23.678(6), b = 14.550(2), c = 19.515(4) Å, β = 126.678(5) °, V = 5392.0(19) Å^3, T = 293(2) K, space group C2/c, Z = 8, D_c = 1.201 gcm^{-3}, μ(Mo-Kα) = 0.074 mm^{-1}, F(000) = 2080, λ = 0.71073 Å, 2θ_{max}= 41.5 °(d_{min} = 1.00 Å), -23 ≤ h ≤ 23, -14 ≤ k ≤ 14, -19 ≤ l ≤ 19, 29604 measured reflections, 2782 independent, R(int)= 0.044, 335 parameters were refined against 2776 reflections, R1 = 0.0486 for 2048 $F_o > 4\sigma F_o$ and 0.0705 for all data, wR2 = 0.1384, $\Delta\rho_{min}$ and $\Delta\rho_{max}$= -0.140 and 0.134 e.Å^{-3} , GOF = 1.045.

Crystal structure data for *cis*-**3a**: $C_{20}H_{21}NO_2$, M = 307.38, monoclinic, a = 5.421(2), b = 11.015(3), c = 28.258(6) Å, β = 100.740(4) °, V = 1657.8(8) Å^3, T = 293(2) K, space group P21/c, Z = 4, D_c = 1.232 gcm^{-3}, μ(Mo-Kα) = 0.079 mm^{-1}, F(000) = 656, λ = 0.71073 Å, 2θ_{max}= 52.7 °(d_{min} = 0.80 Å), -6 ≤ h ≤ 6, -12 ≤ k ≤ 13, -35 ≤ l ≤ 35, 9647 measured reflections, 3336 independent, R(int)= 0.031, 211 parameters were refined against 3332 reflections, R1 = 0.0466 for 2141 $F_o > 4\sigma F_o$ and 0.0832 for all data, wR2 = 0.1301, $\Delta\rho_{min}$ and $\Delta\rho_{max}$= -0.179 and 0.120 e.Å^{-3} , GOF = 1.035.

CCDC- 964826 *cis*-**2a**, 964827 *cis*-**2d** and 964828 *cis*-**3a** contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via http://www.ccdc.cam.ac.uk/data_request/cif.

References:

[1] Chimera is developed by the Resource for Biocomputing, Visualization, and Informatics at the University of California, San Francisco, with support from the National Institutes of Health (National Center for Research Resources grant 2P41RR001081, National Institute of General Medical Sciences grant 9P41GM103311).

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[3] Rigaku. (2009) CrystalClear-SM Expert 2.0 r4 Rigaku Corporation, Tokyo, Japan.

[4] Otwinowski, Z. & Minor, W. (1997). Methods in Enzymology, Volume 276, Macromolecular Crystallography, part A, edited by C.W. Carter, Jr. & R.M. Sweet, 307-326, 1997, New York: Academic Press.

[5] G.M. Sheldrick, *Acta Cryst.*, 2008, **A64**, 112-122.