SUPPORTING INFORMATION

Title **Bio-inspired diastereoconvergent synthesis of the tricyclic core of palodesangrens via Diels-Alder reaction , $LiAlH_4$-mediated isomerization, and acid-mediated cyclization**

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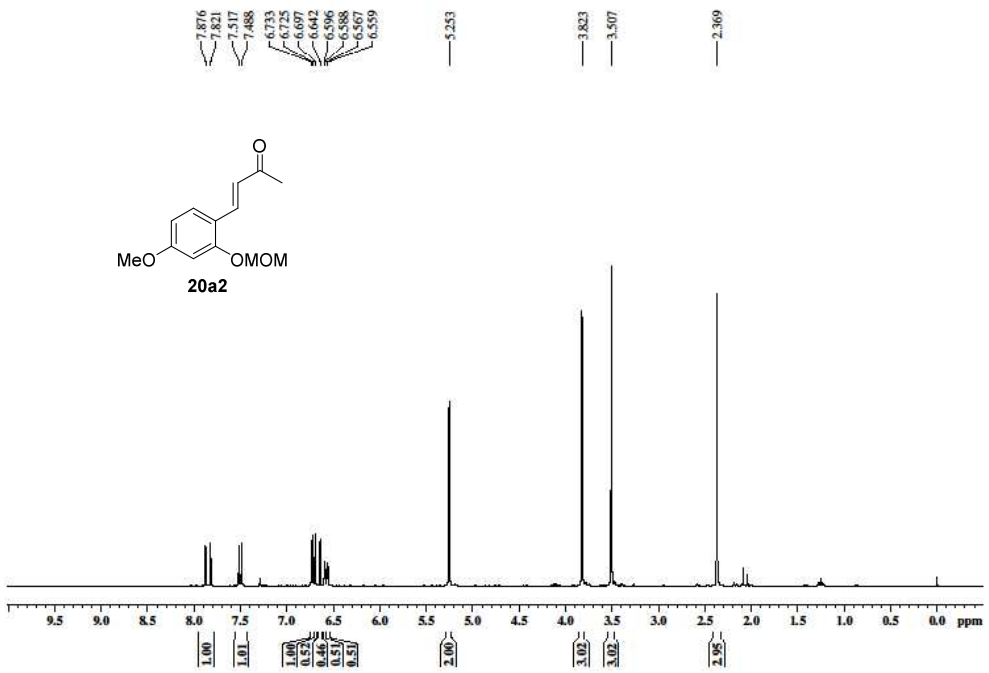

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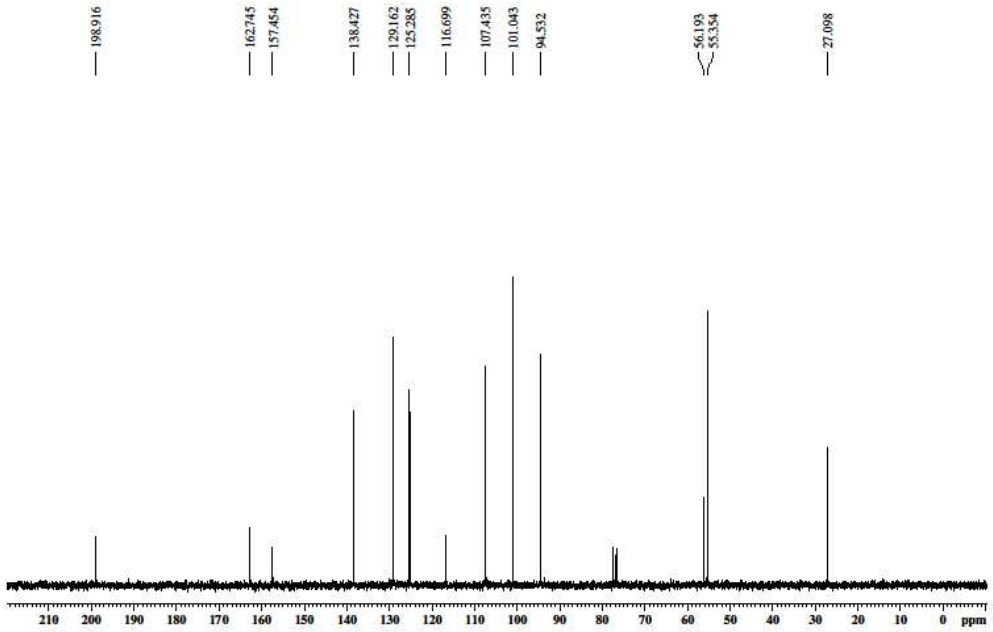

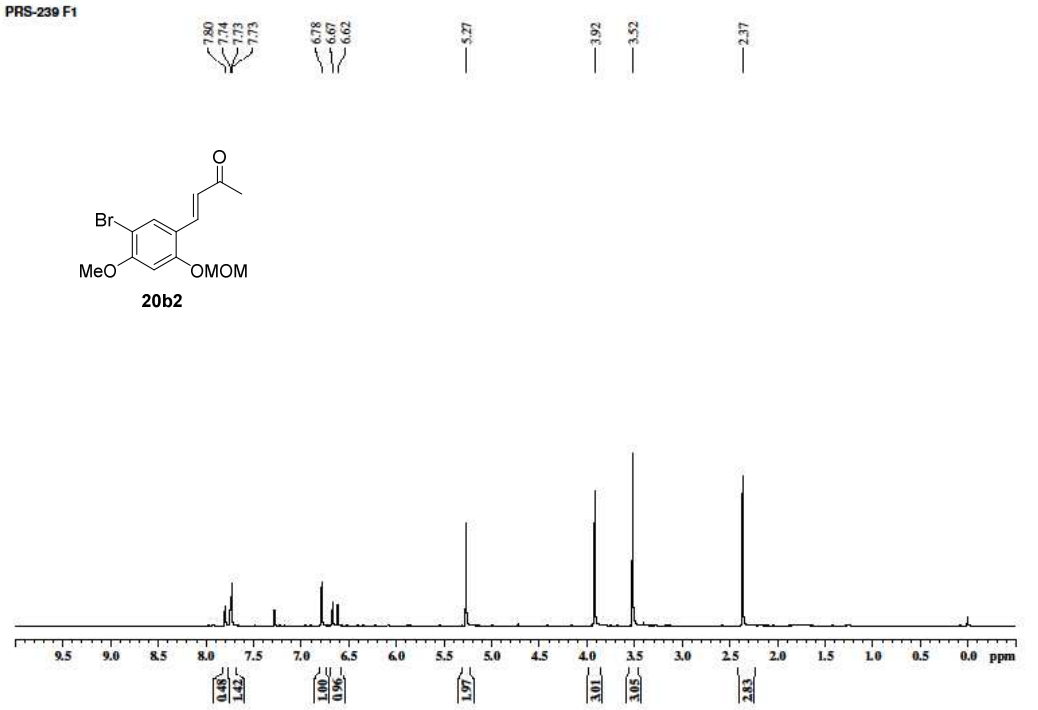
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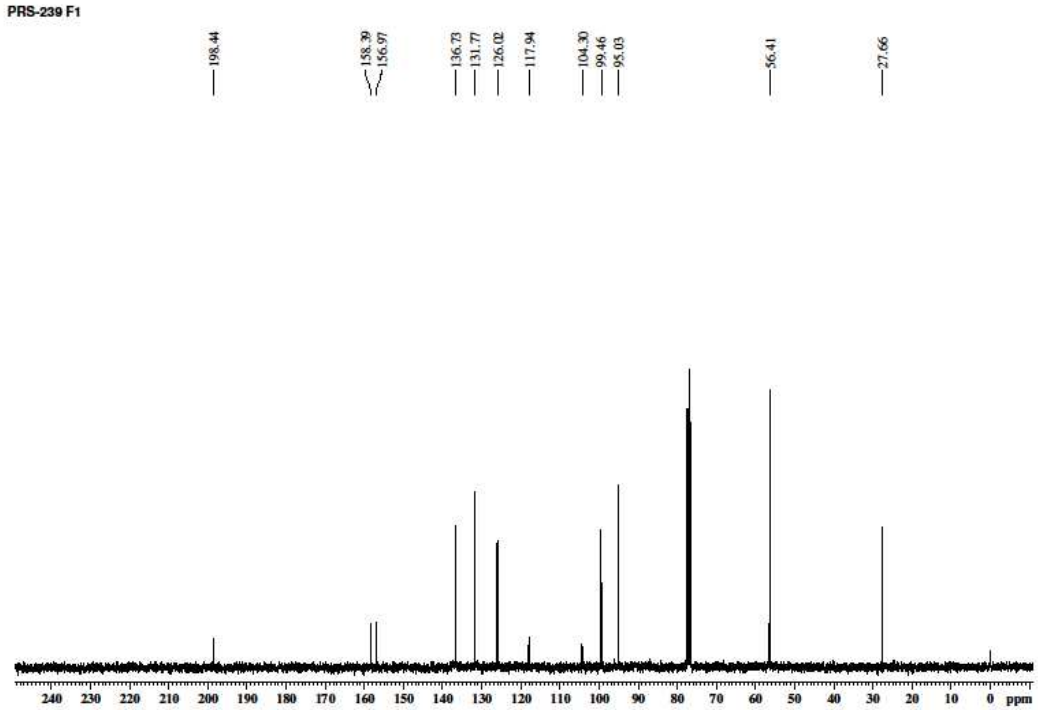
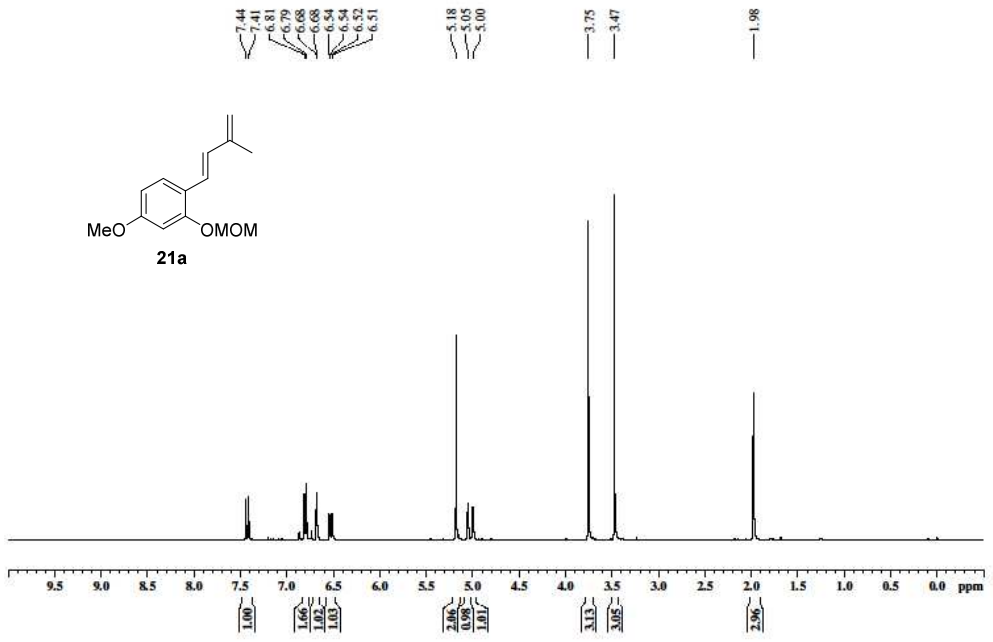
7.80
7.74
7.73
7.73
6.78
6.67
6.62
5.27
3.92
3.52
2.37
O
Br
MeO
OMOM
20b2
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
0.48
1.42
1.00
0.96
1.97
3.01
3.05
2.83


PRS-239 F1
198.44
158.39
156.97
136.73
131.77
126.02
117.94
104.30
99.46
95.03
56.41
27.66
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

PRS-211 F1



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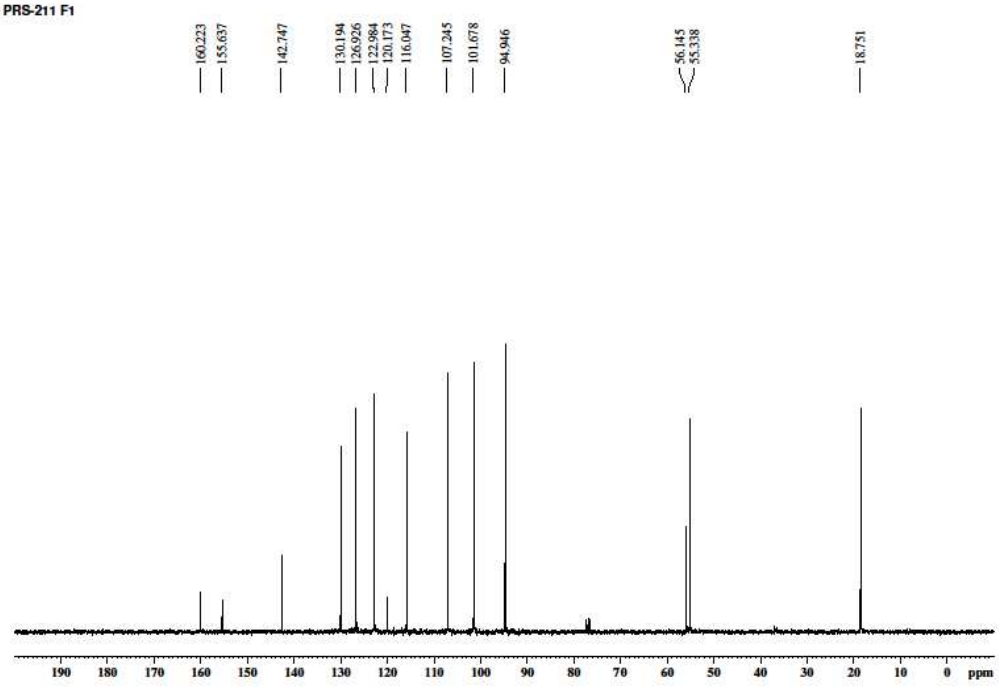
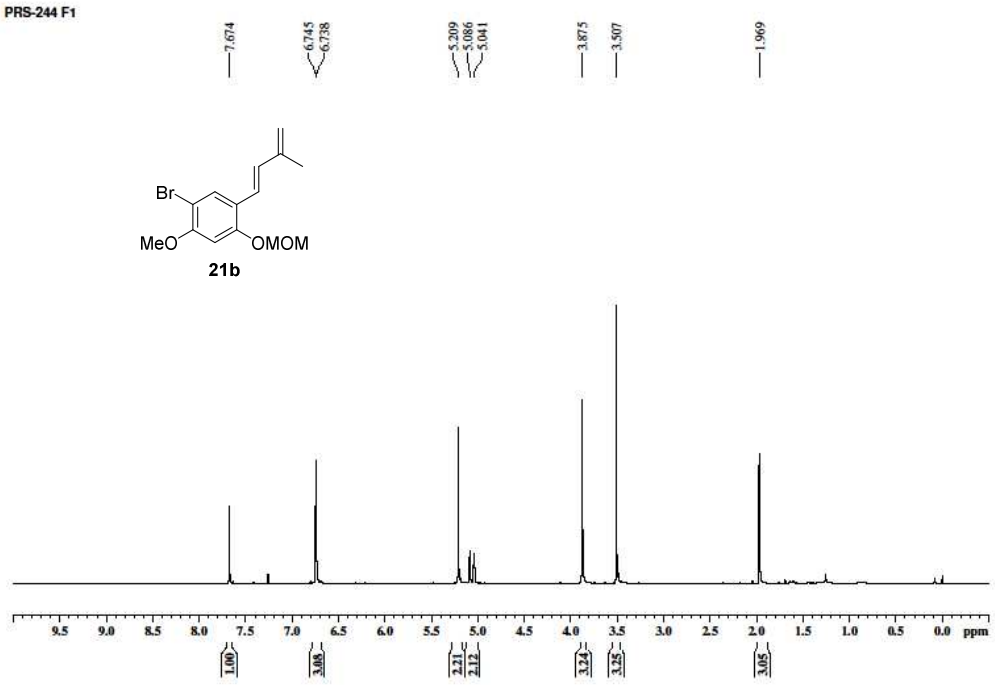
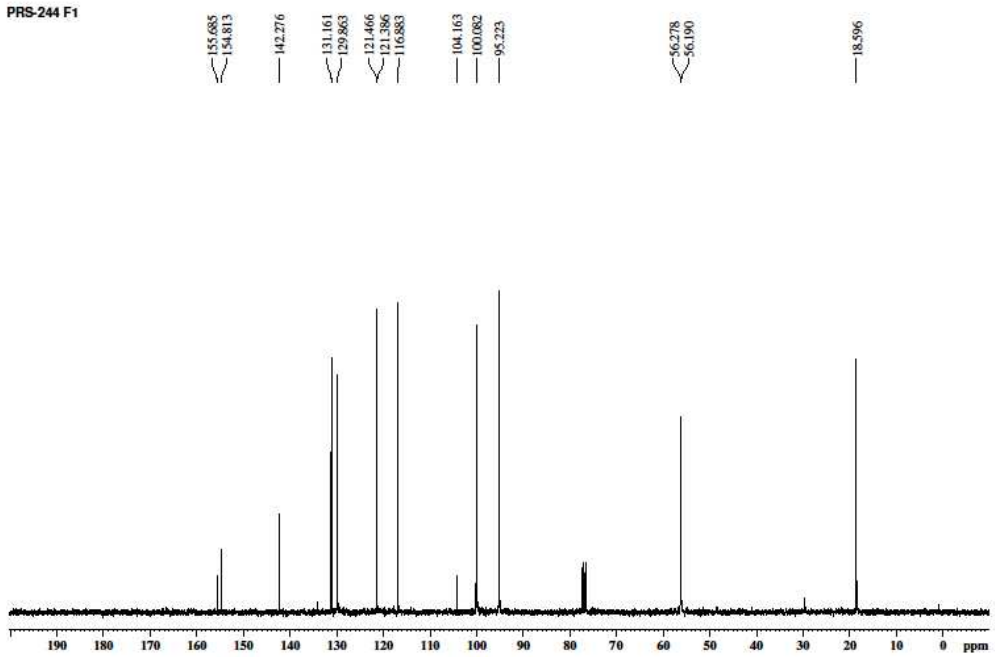
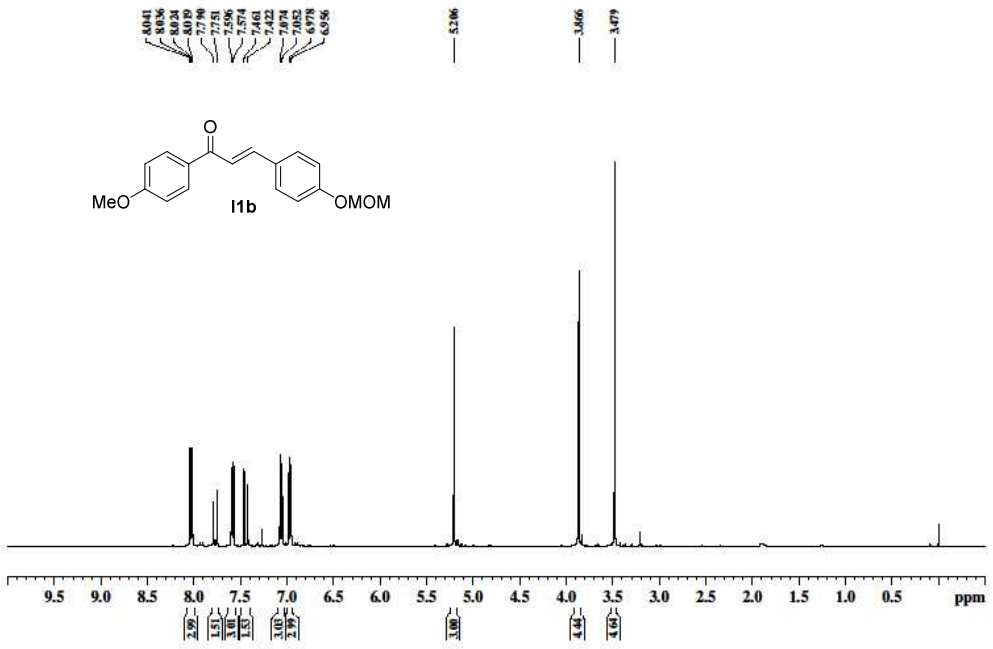



PRS-244 F1
7.674
6.745
6.738
5.209
5.086
5.041
3.875
3.507
1.969
Br
MeO
OMOM
21b
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
1.00
3.08
2.21
2.12
3.24
3.25
3.05


PRS-244 F1
155.685
154.813
142.276
131.161
129.863
121.466
121.386
116.883
104.163
100.082
95.223
56.278
56.190
18.596
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

PRS–275 F2 CDCl3 400MHz



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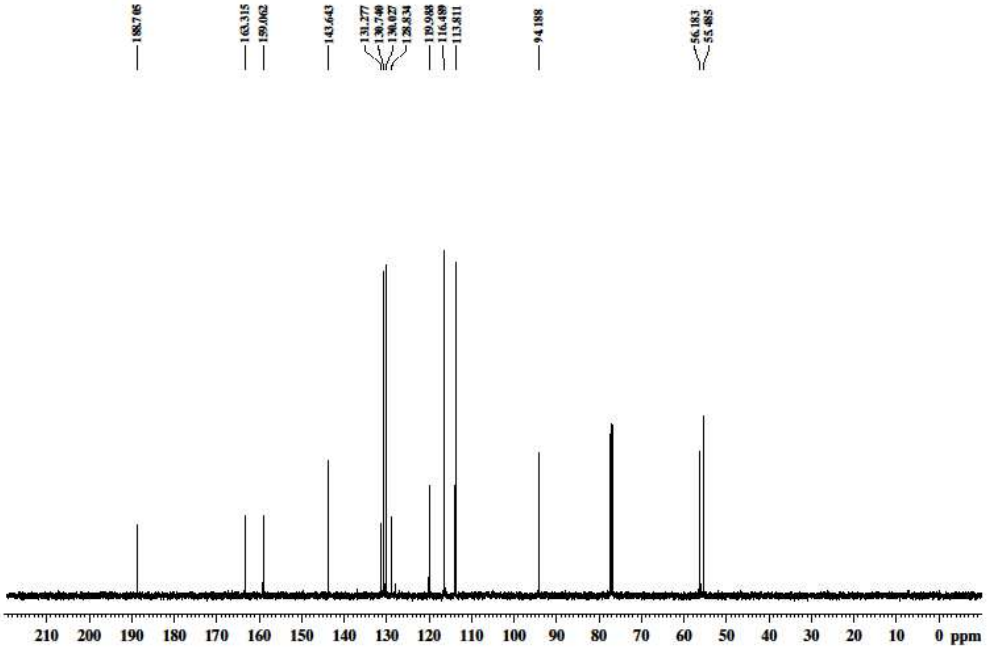
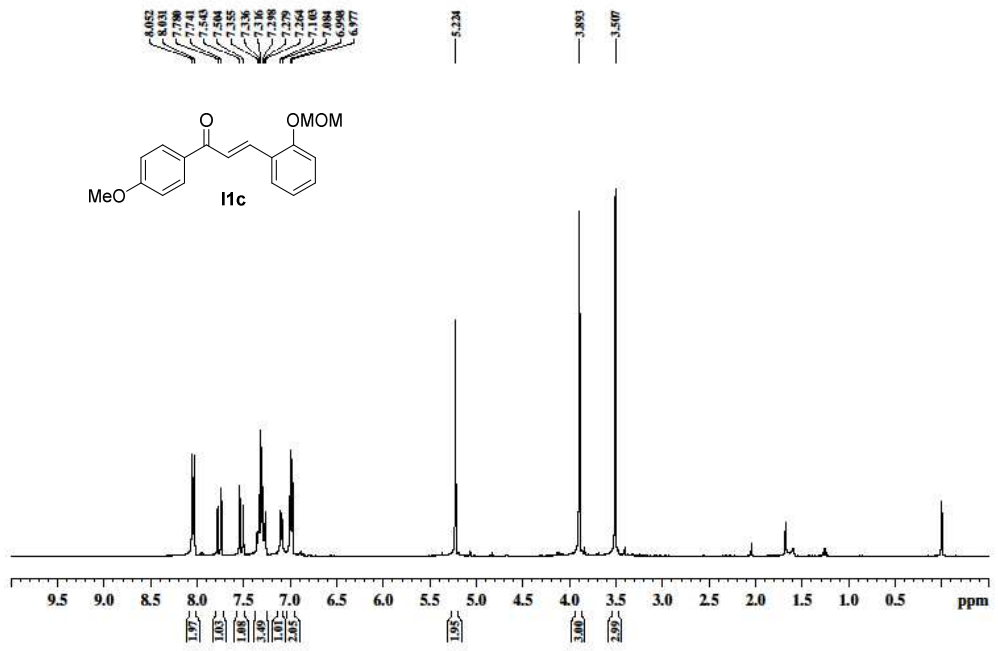
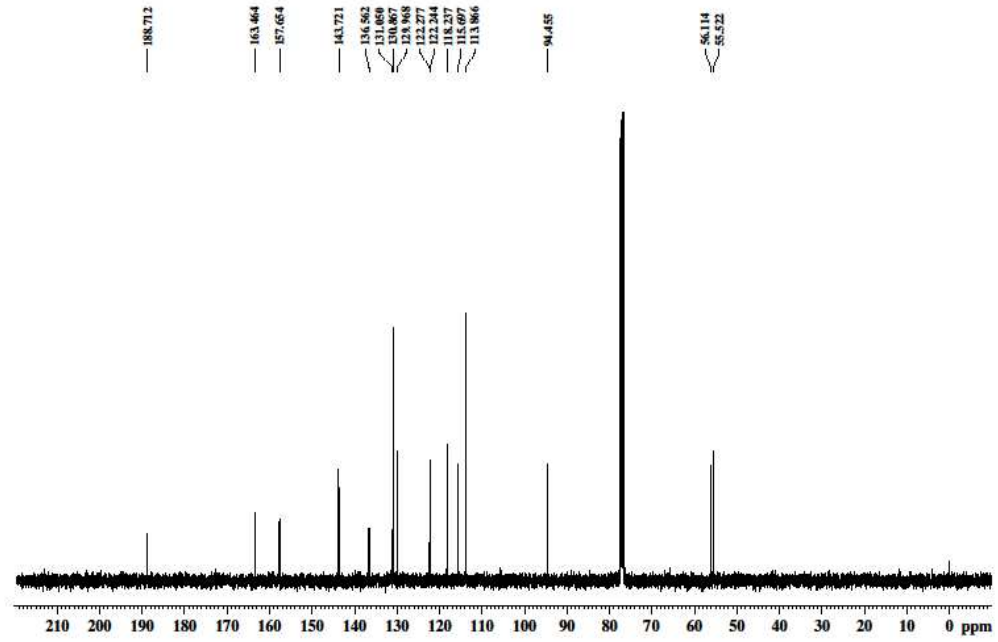
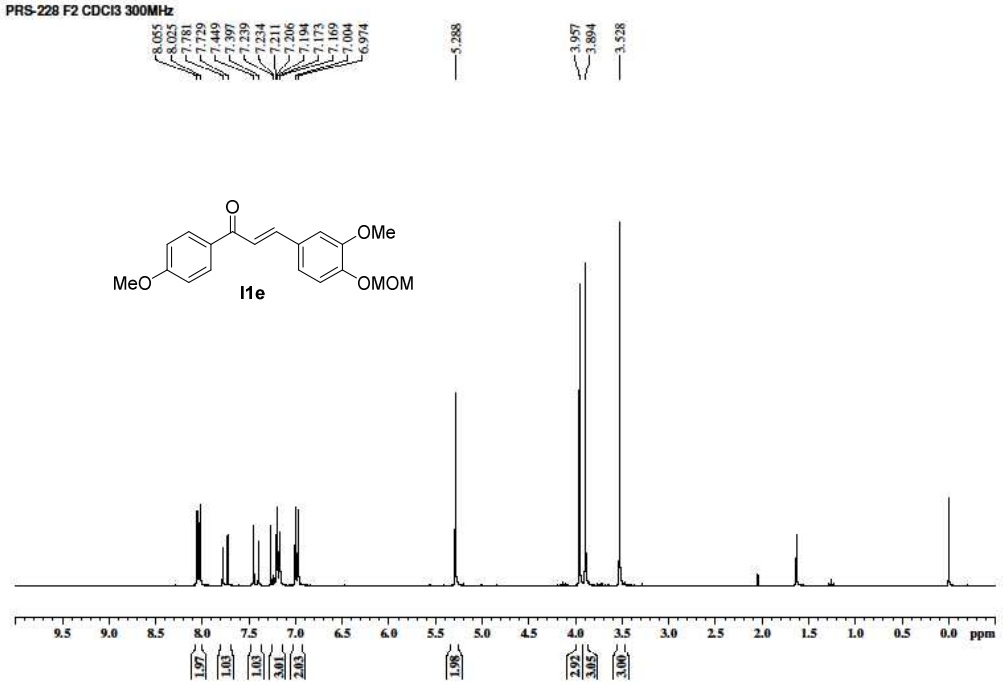


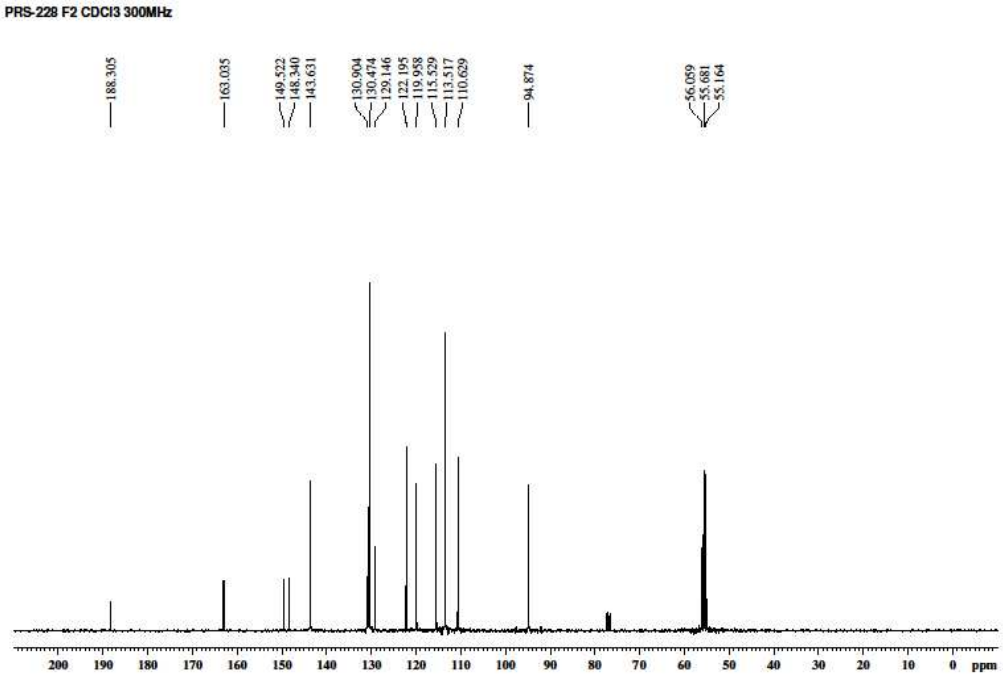
PRS–03–036F1 in CDCl3 NMR400



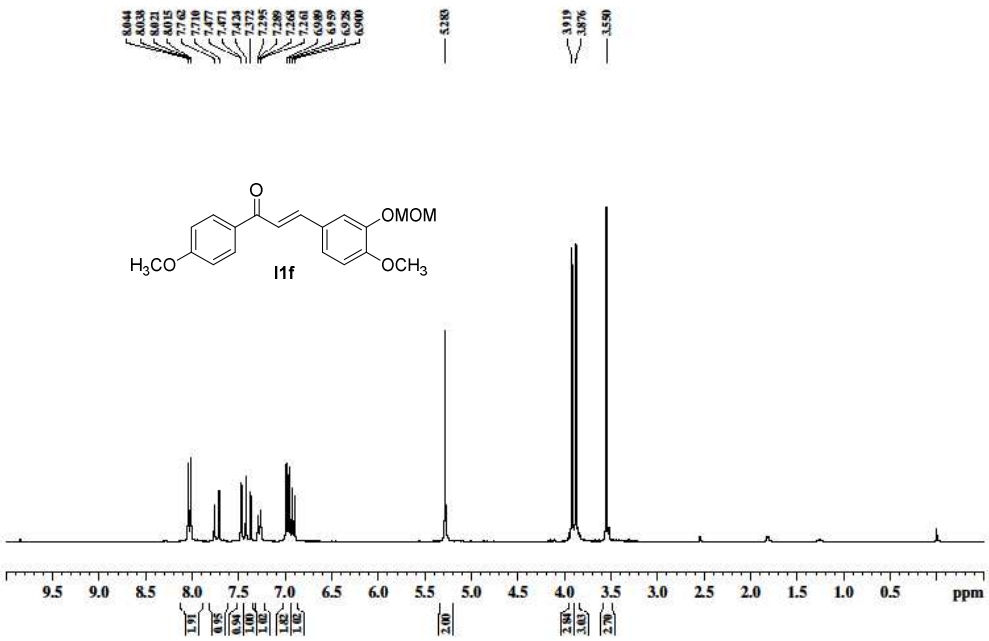
PRS–03–036F1 in CDCl3 NMR400



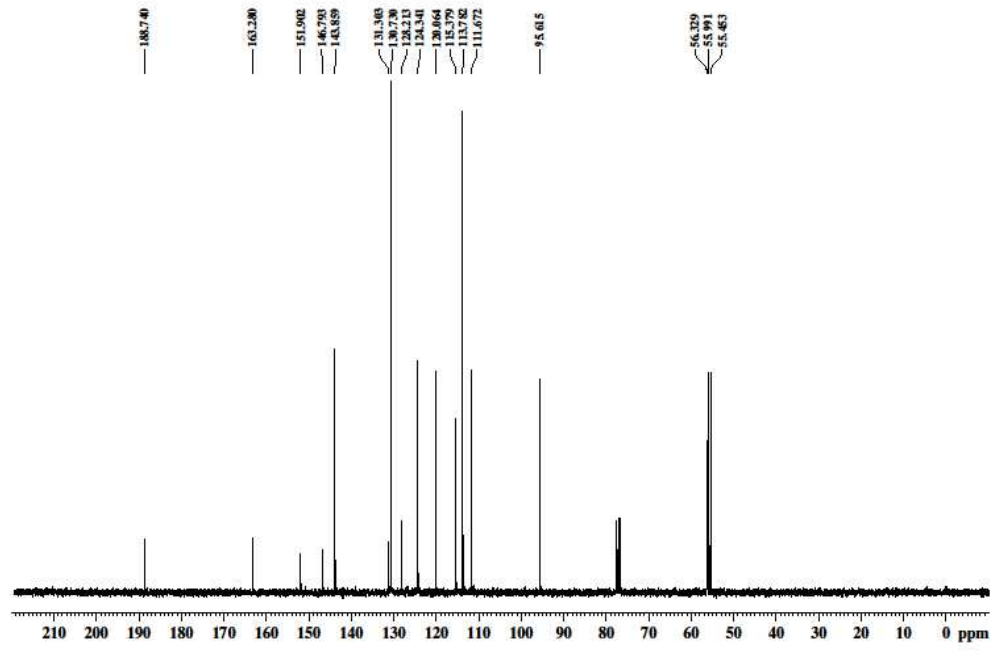

PRS-228 F2 CDCl3 300MHz
8.055
8.025
7.781
7.729
7.449
7.397
7.239
7.234
7.211
7.206
7.194
7.173
7.169
7.004
6.974
5.288
3.957
3.894
3.528
O
OMe
MeO
OMOM
I1e
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
1.97
1.03
1.00
3.01
2.03
1.98
2.92
3.05
3.00


PRS-228 F2 CDCl3 300MHz
188.305
163.035
149.522
148.340
143.631
130.904
130.474
129.146
122.195
119.958
115.529
113.517
110.629
94.874
56.059
55.681
55.164
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

CD008 in CDCl3 300MHz



CD008 in CDCl3 300MHz



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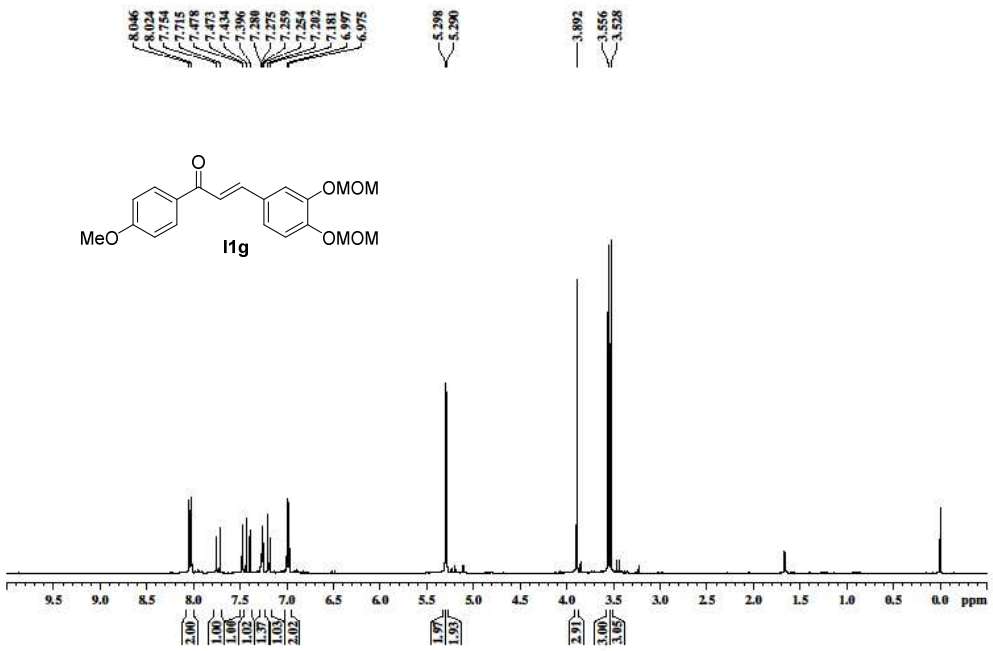
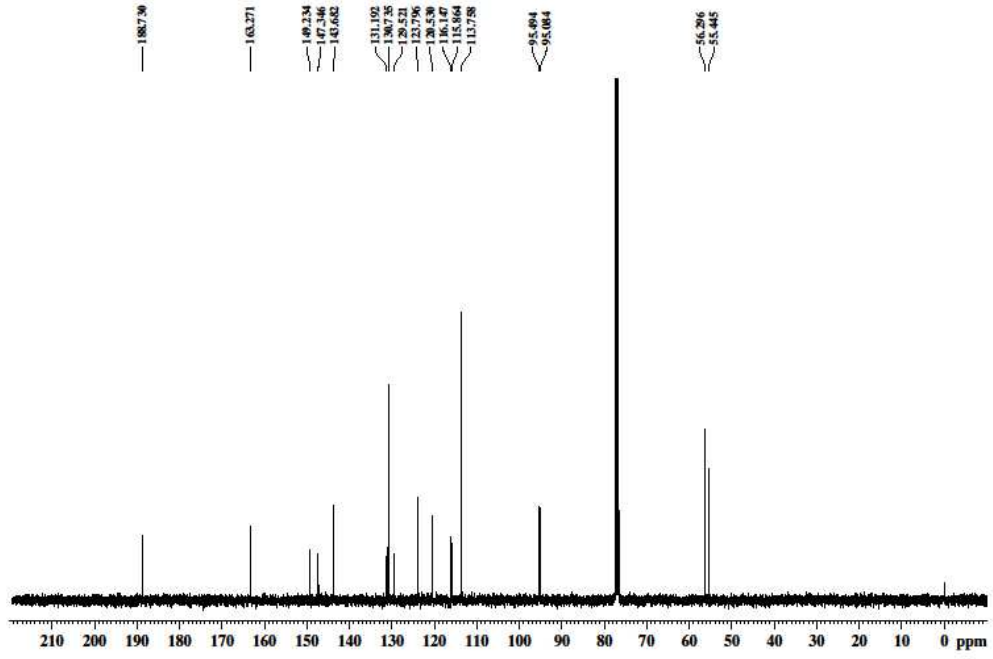


PRS–335 F2 CDCl3 400 MHz



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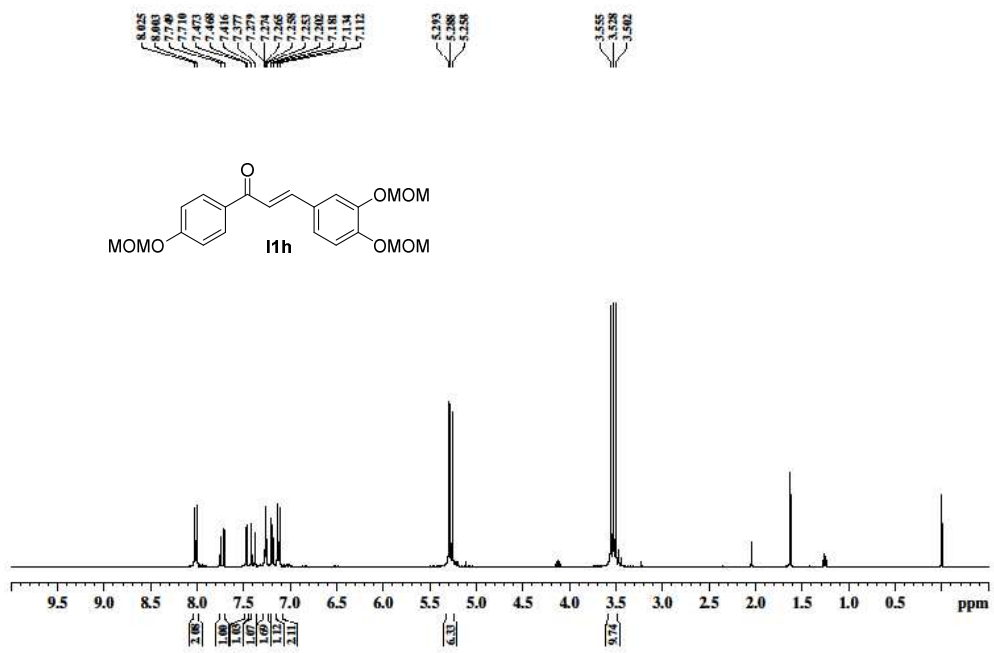

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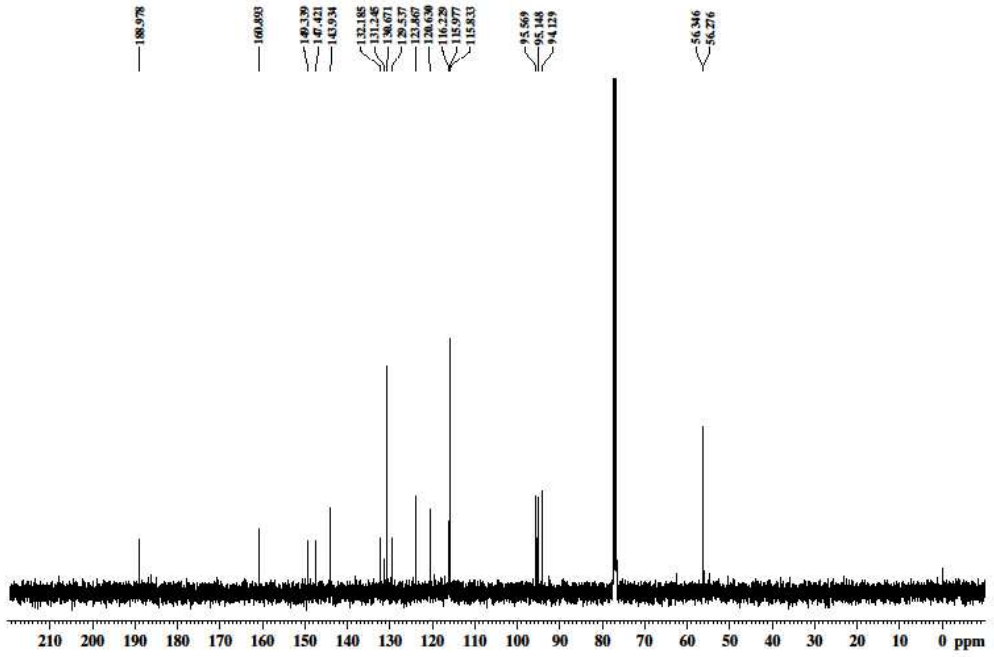
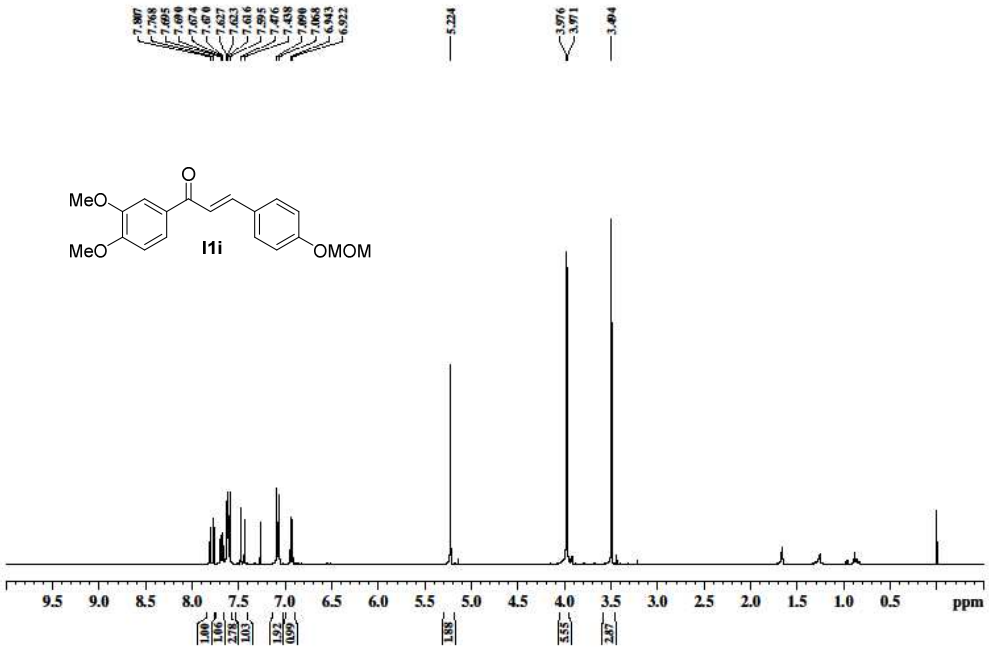
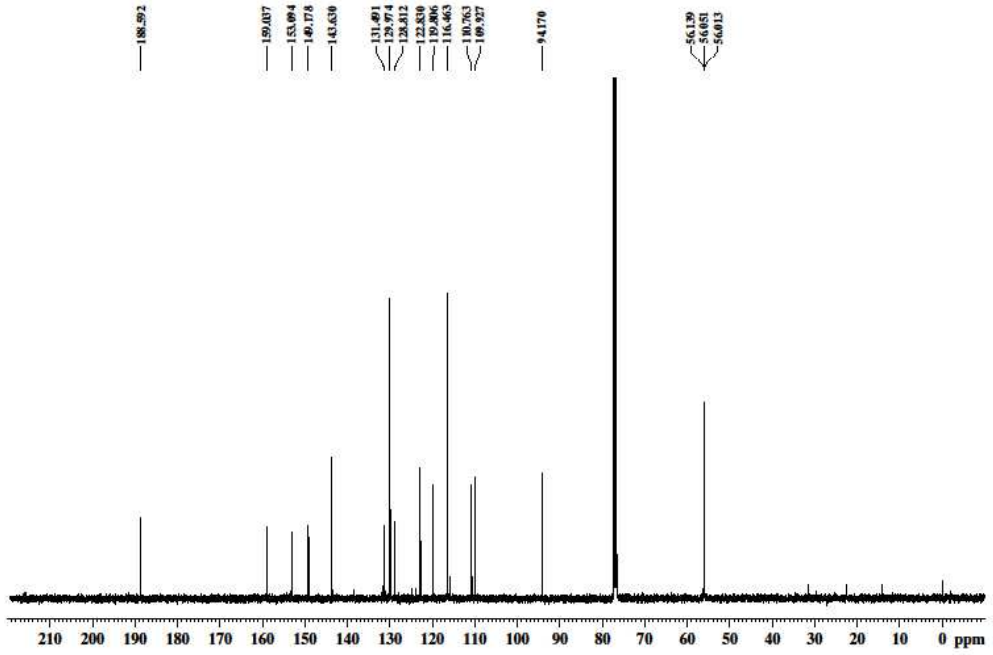


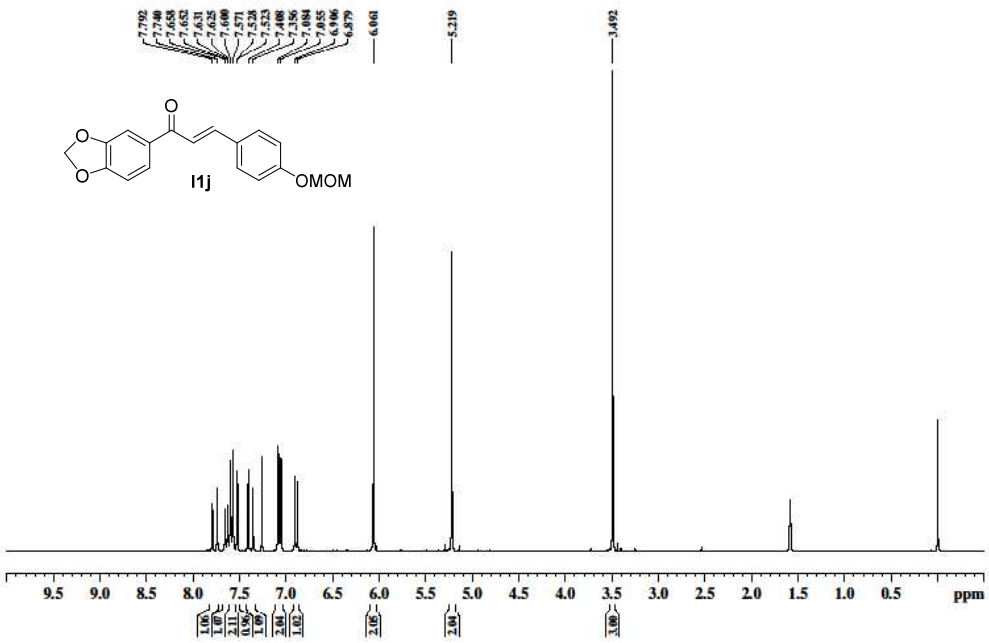
SW–002 in CDCl3 NMR400



SW–002 in CDCl3 400MHz



CD–006 CDCl3 300MHz



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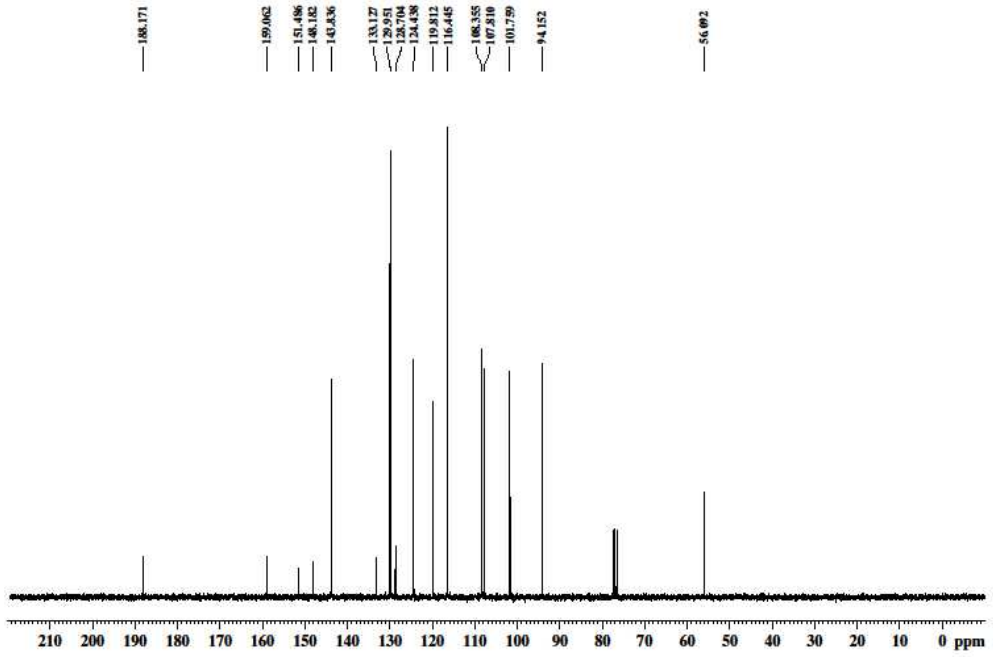
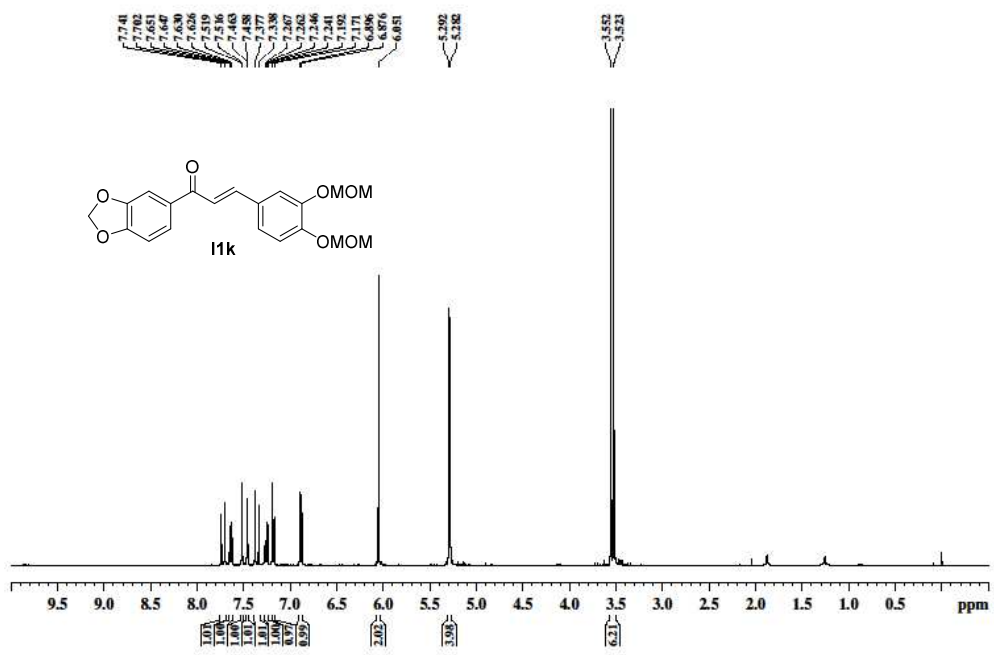
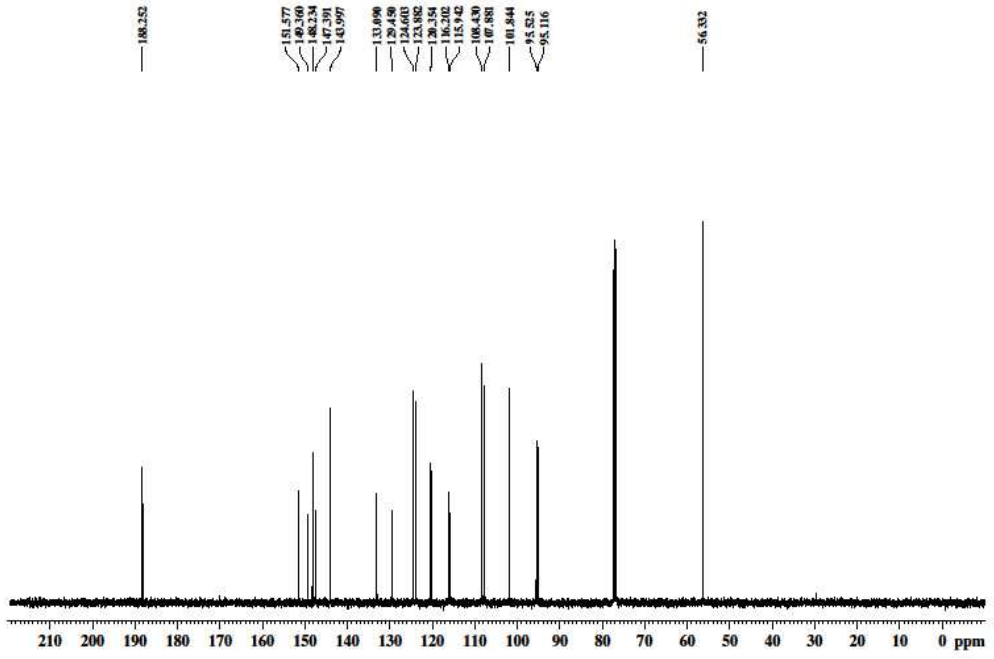


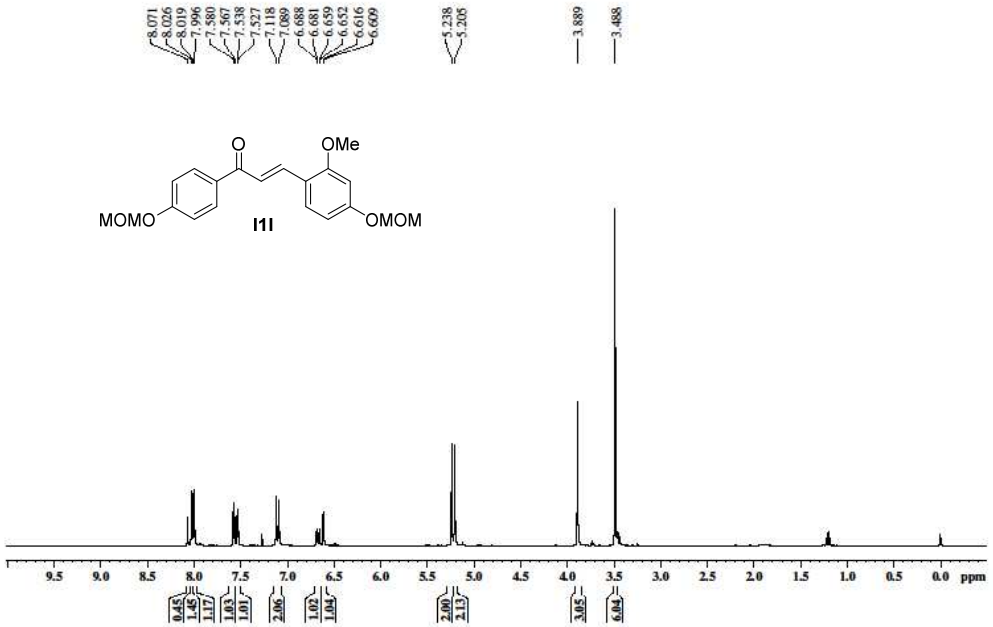
PRS–336–F1 CDCl3 400 MHz



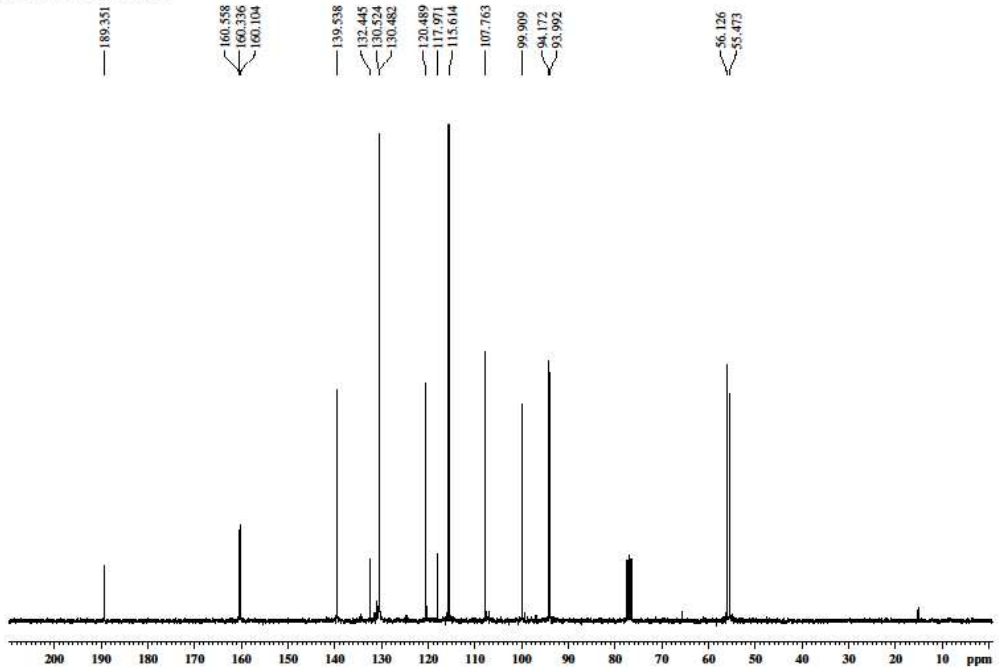
PRS–336–F1 CDCl3 400 MHz

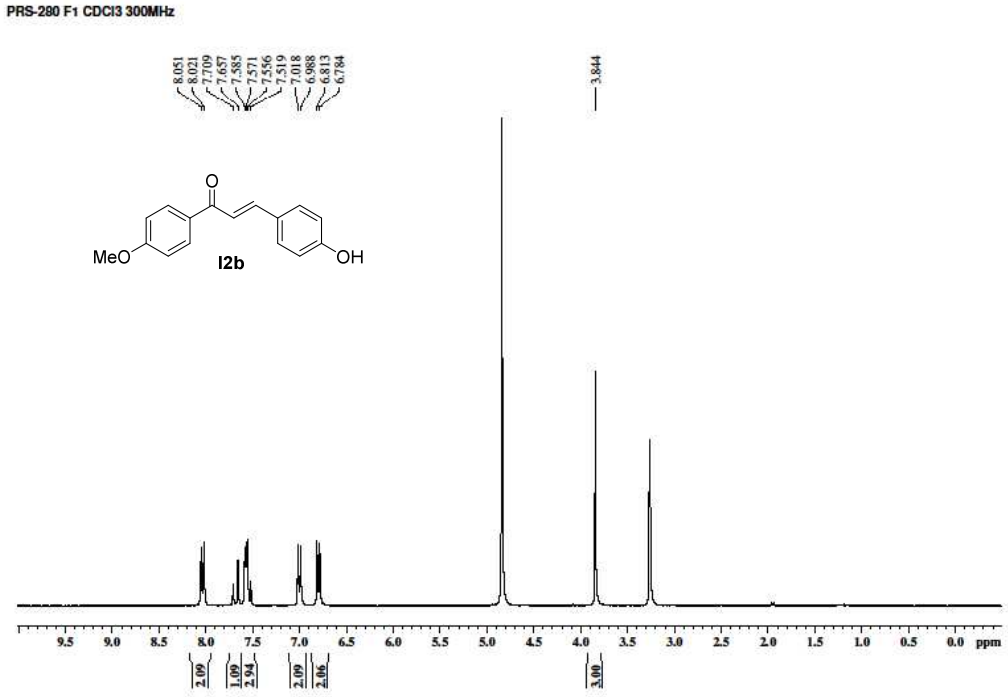


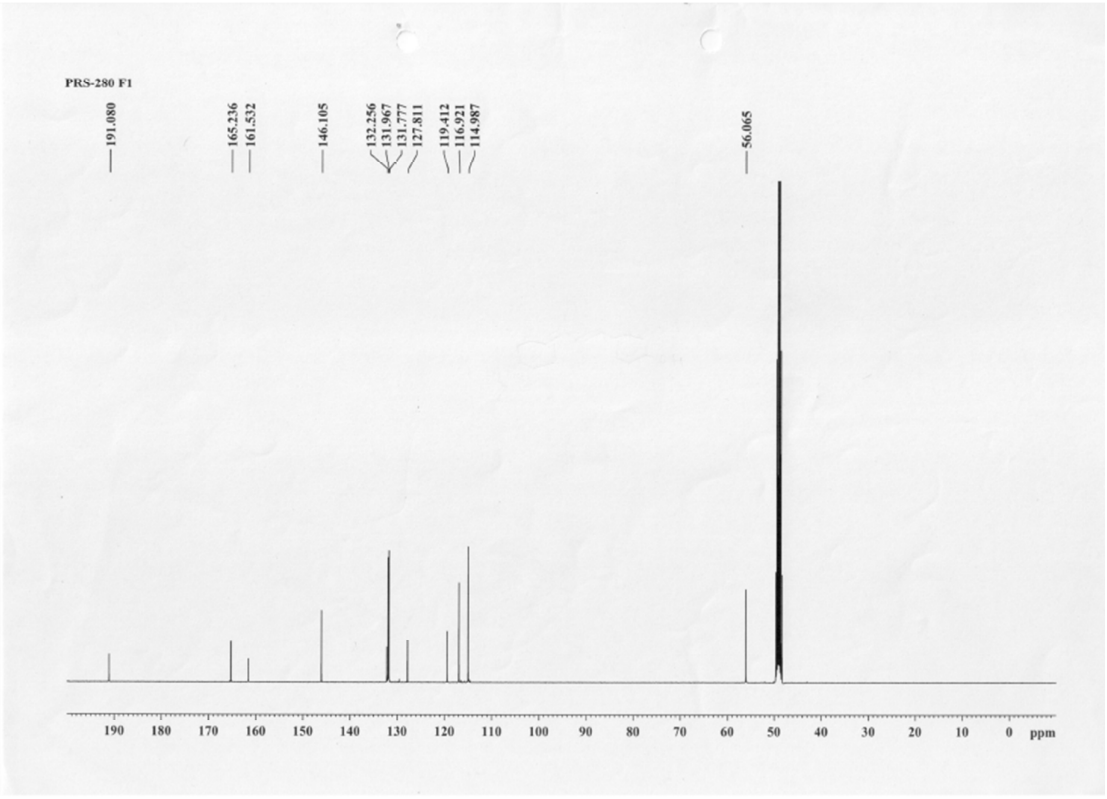
PRS-230 F2

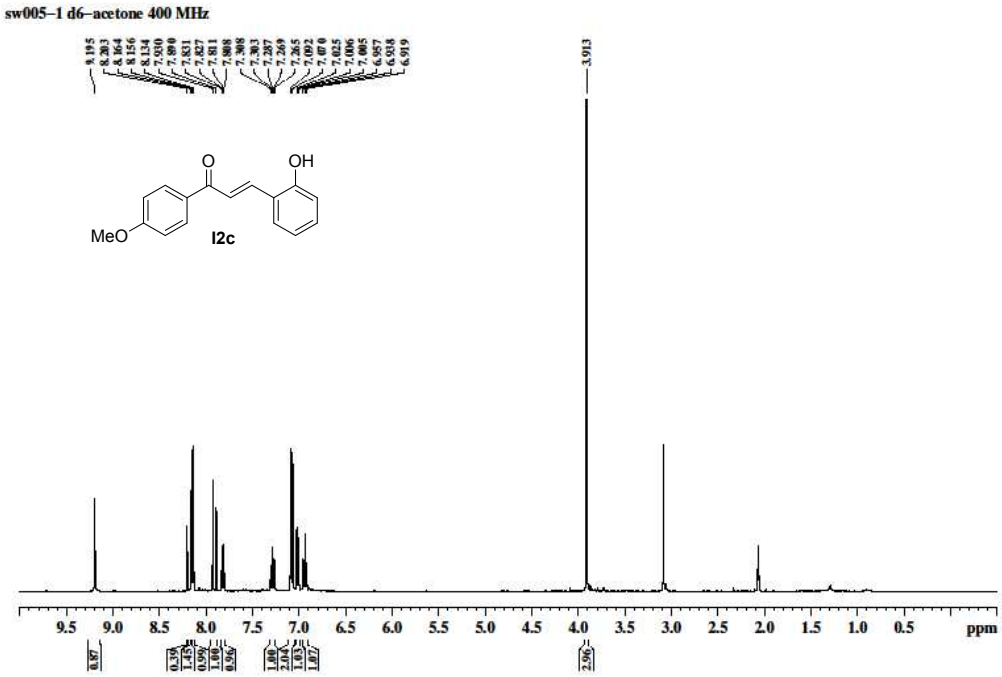


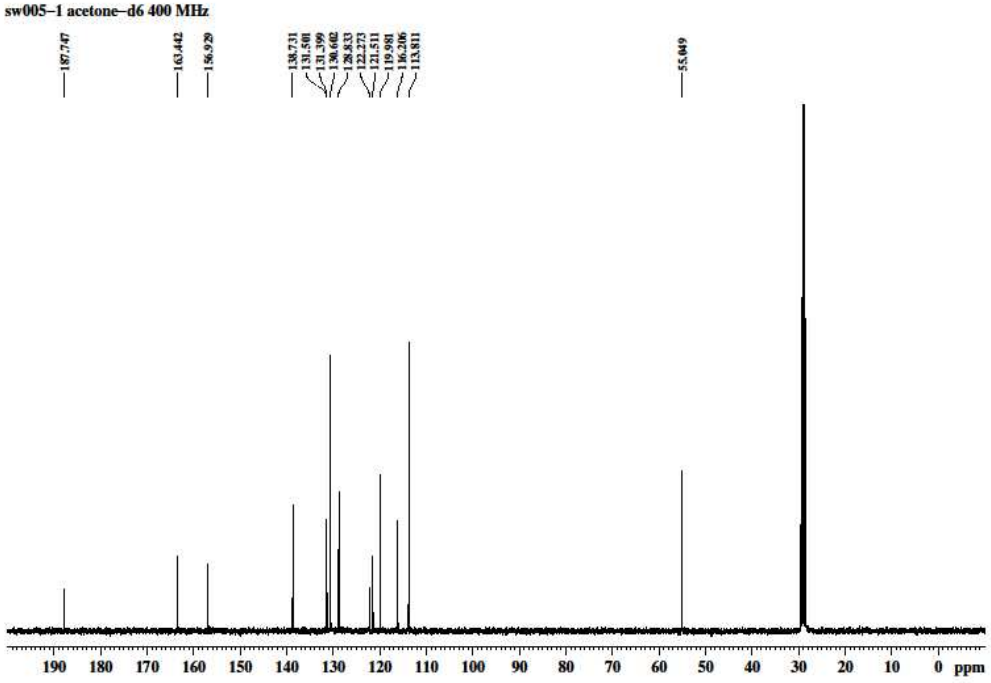
PRS-230 F2 CDCl3 300MHz



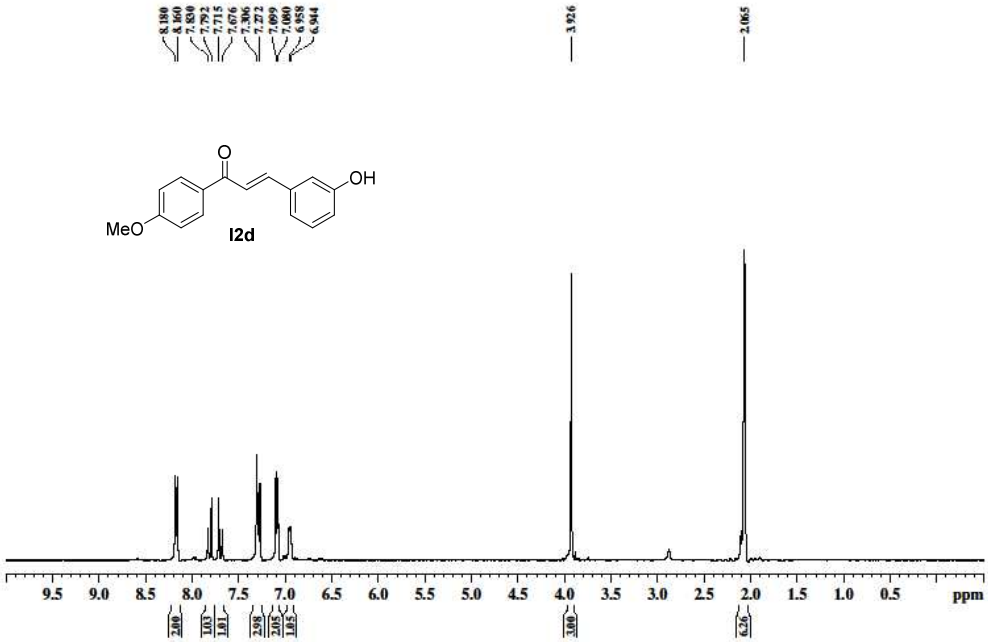

PRS-280 F1 CDCl3 300MHz
8.051
8.021
7.709
7.657
7.585
7.571
7.556
7.519
7.018
6.988
6.813
6.784
3.844
O
MeO
OH
I2b
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
2.09
1.09
2.94
2.09
2.06
3.00


PRS-280 F1
191.080
165.236
161.532
146.105
132.256
131.967
131.777
127.811
119.412
116.921
114.987
56.065
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

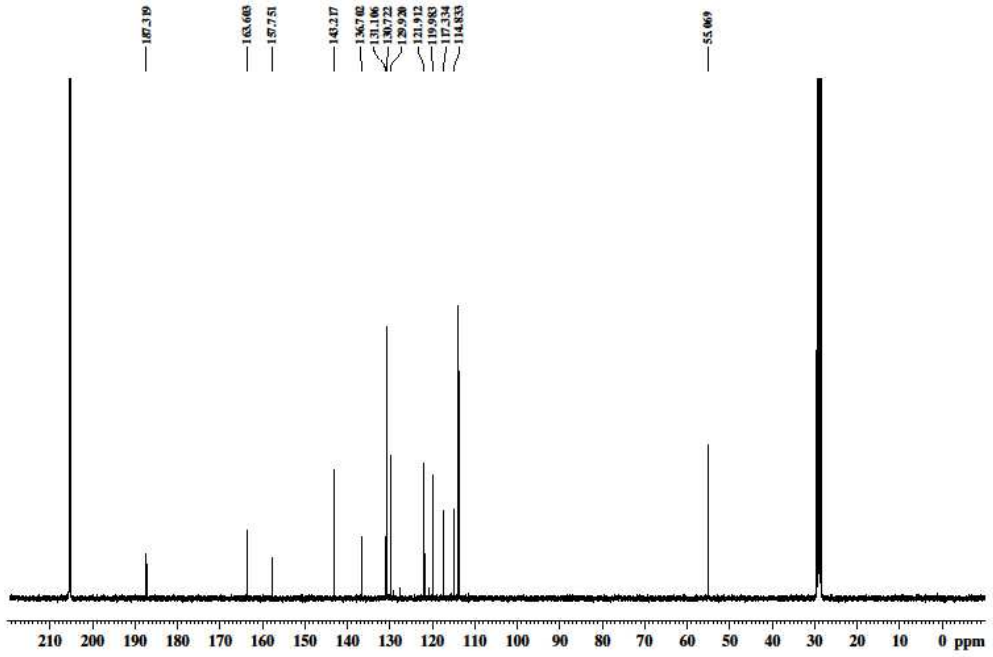

sw005–1 d6–acetone 400 MHz
O
OH
MeO
I2c
ppm


sw005–1 acetone–d6 400 MHz
ppm

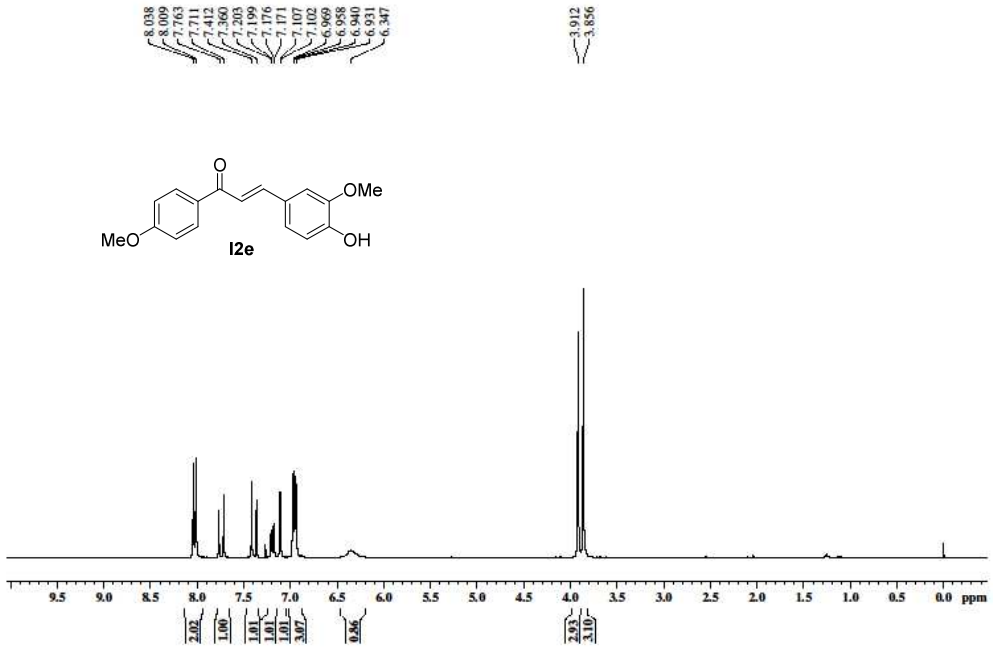
PRS–03–041F1 CDCl3 400 MHz



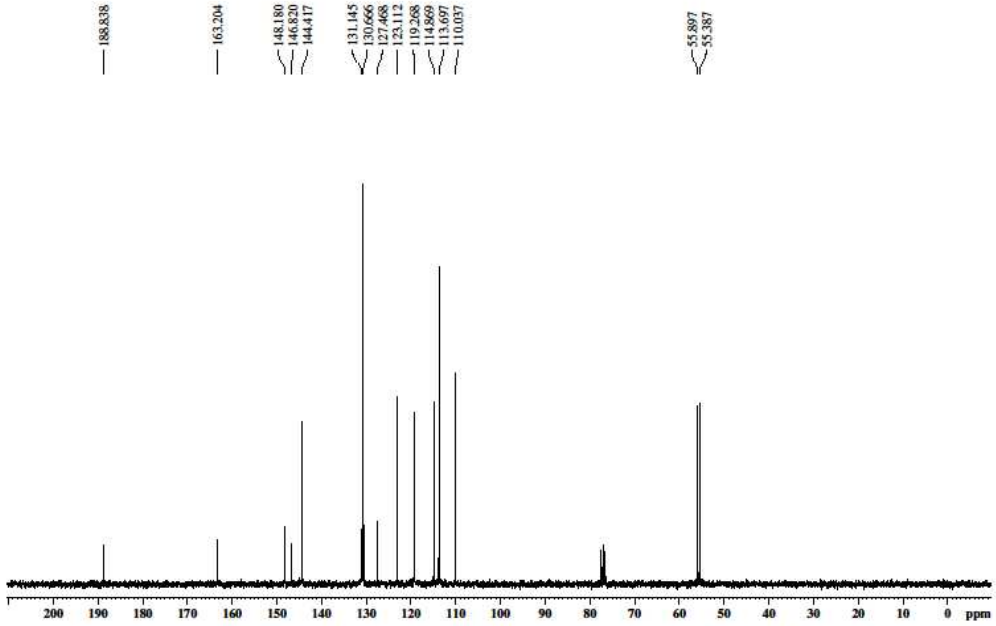
PRS–03–041F1 CDCl3 400 MHz

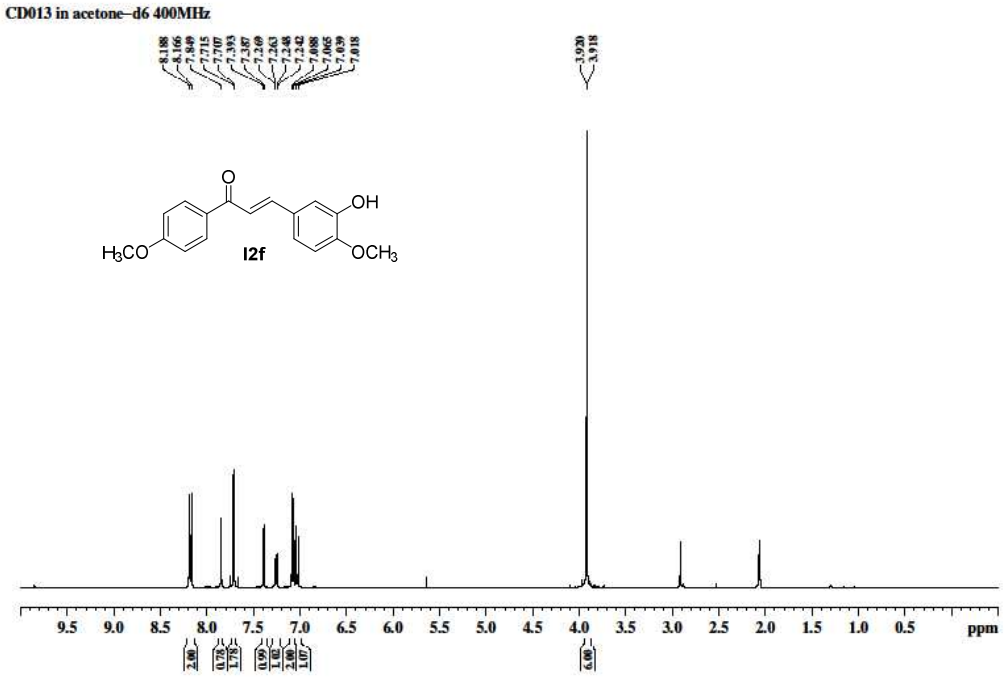


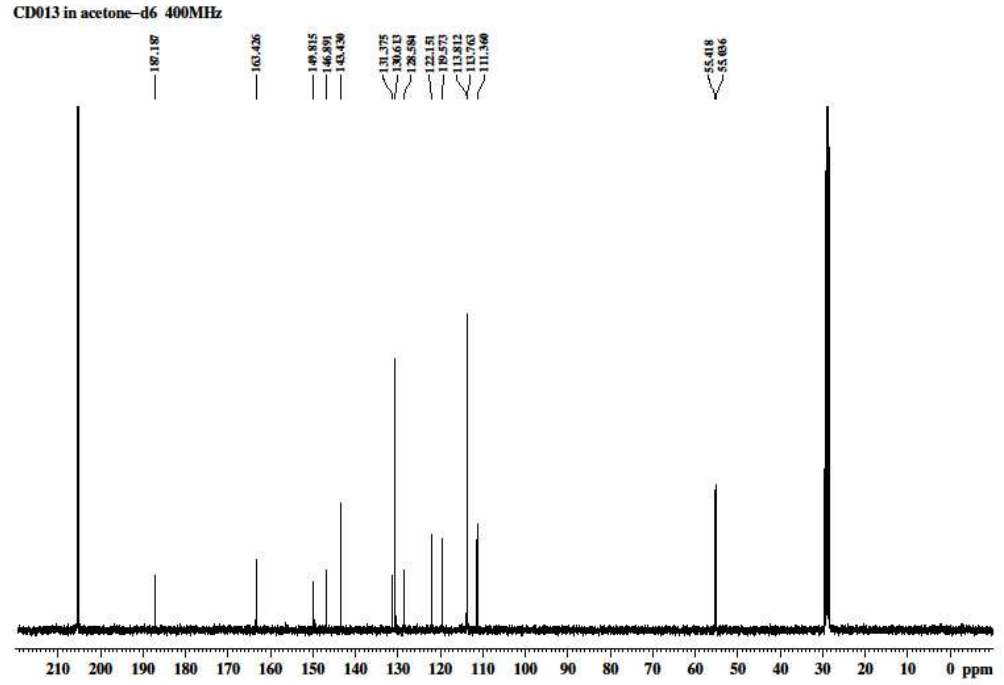
PRS-231 acetone-d6 300MHz



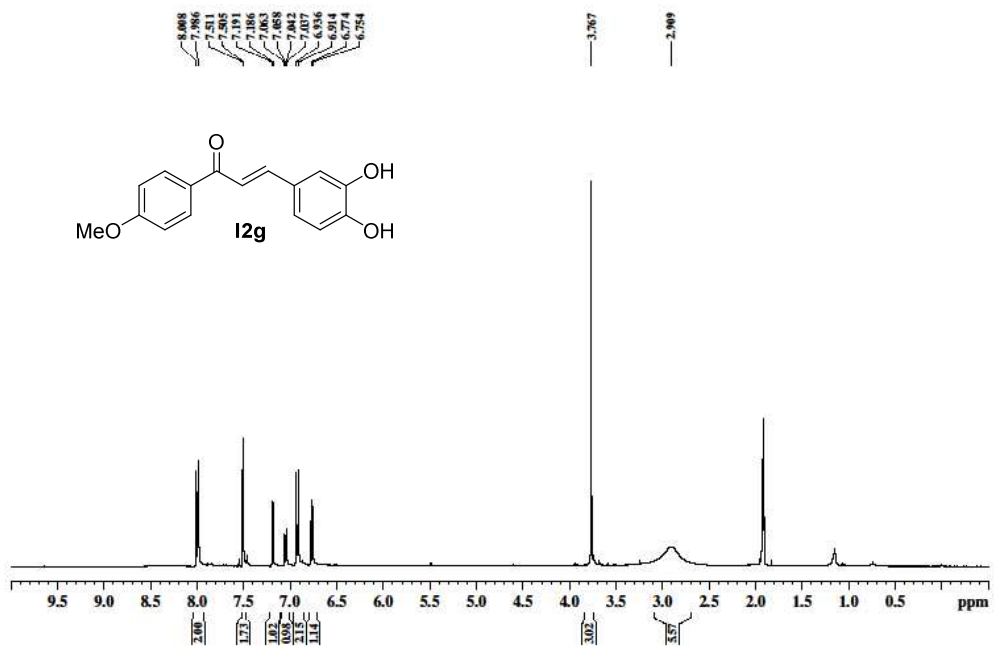
PRS-231 acetone-d6 300MHz



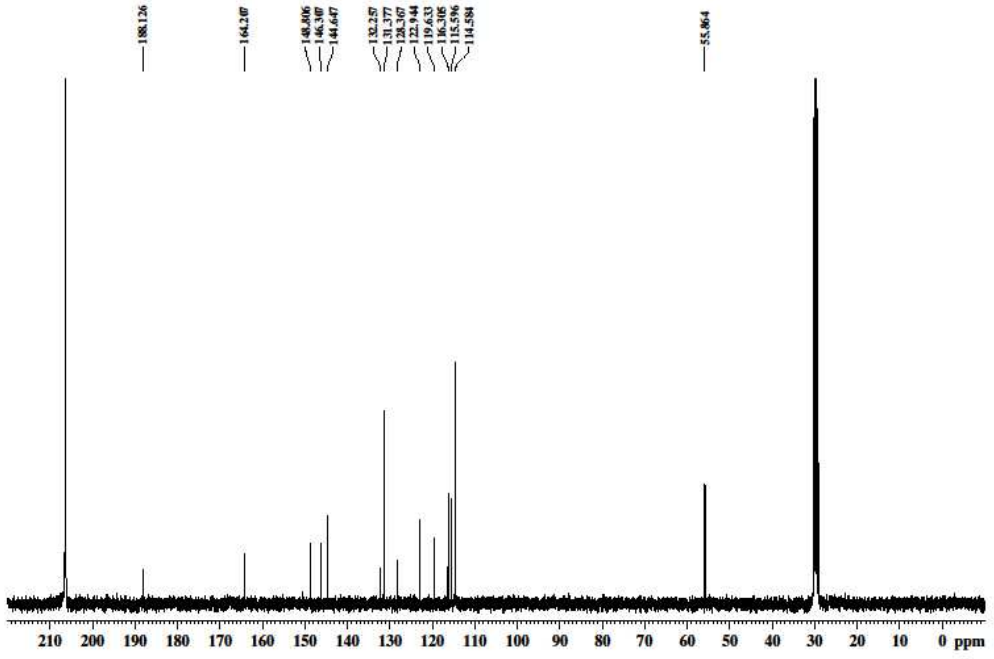

CD013 in acetone-d6 400MHz
8.188
8.166
7.949
7.715
7.707
7.395
7.385
7.269
7.263
7.248
7.242
7.088
7.065
7.039
7.018
3.920
3.918
O
OH
H3CO
OCH3
I2f
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
2.00
0.78
1.78
0.99
1.02
2.00
1.07
6.00


CD013 in acetone-d6 400MHz
180.187
163.426
149.815
146.891
143.430
131.375
130.613
128.584
122.151
119.573
113.812
113.763
111.360
55.418
55.406
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

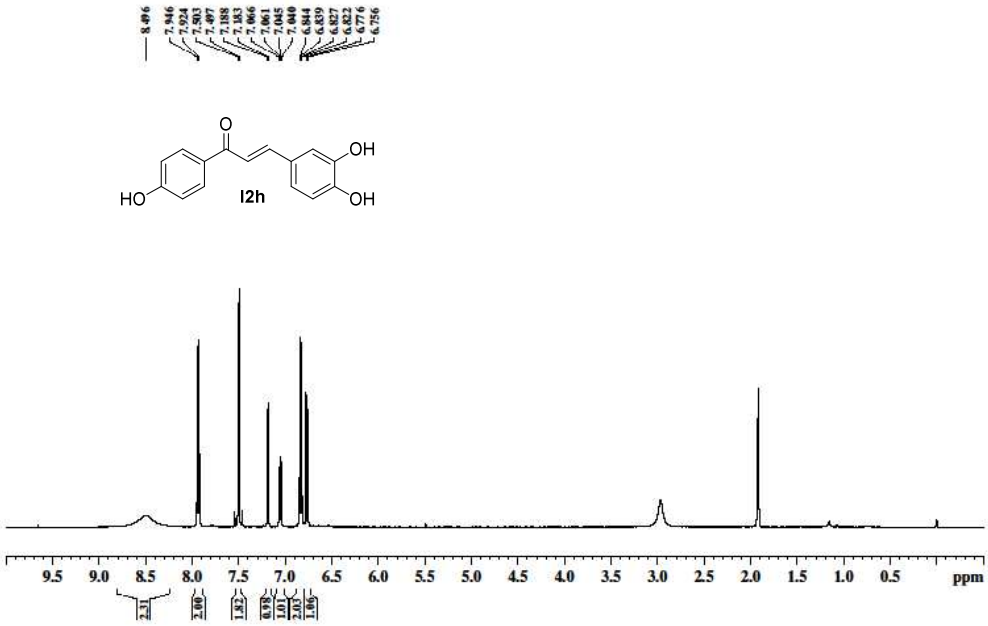
SW008 in acetone–d6 400MHz



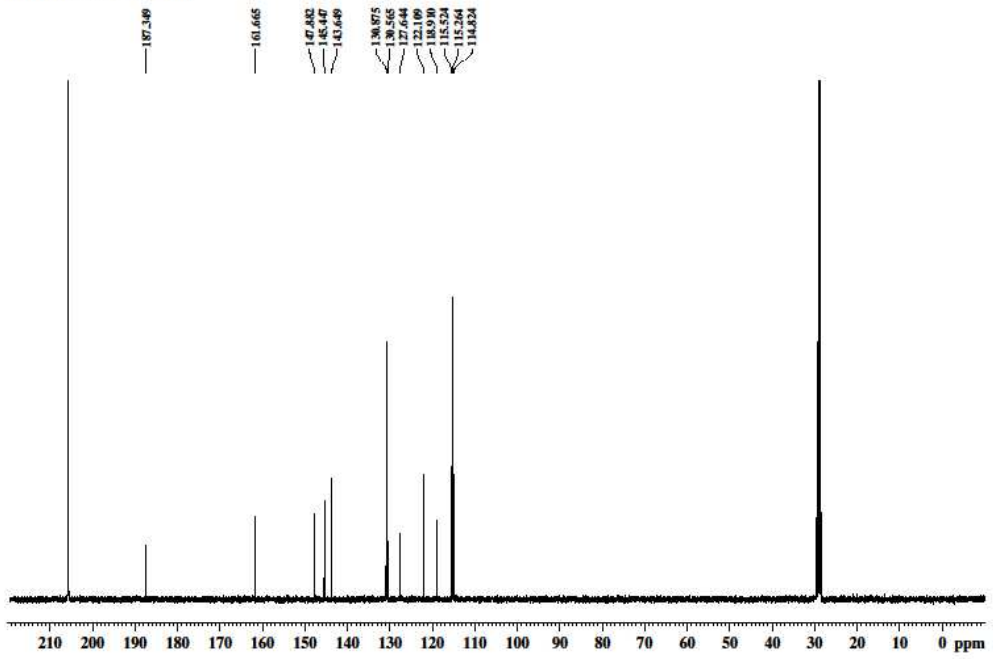
SW008 in acetone–d6 400MHz

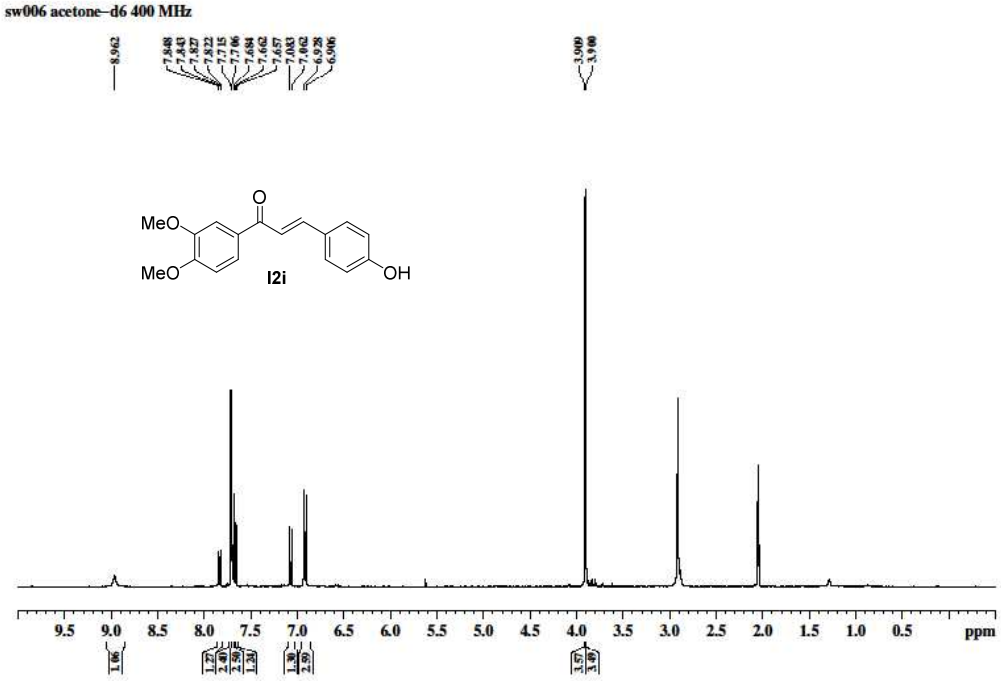


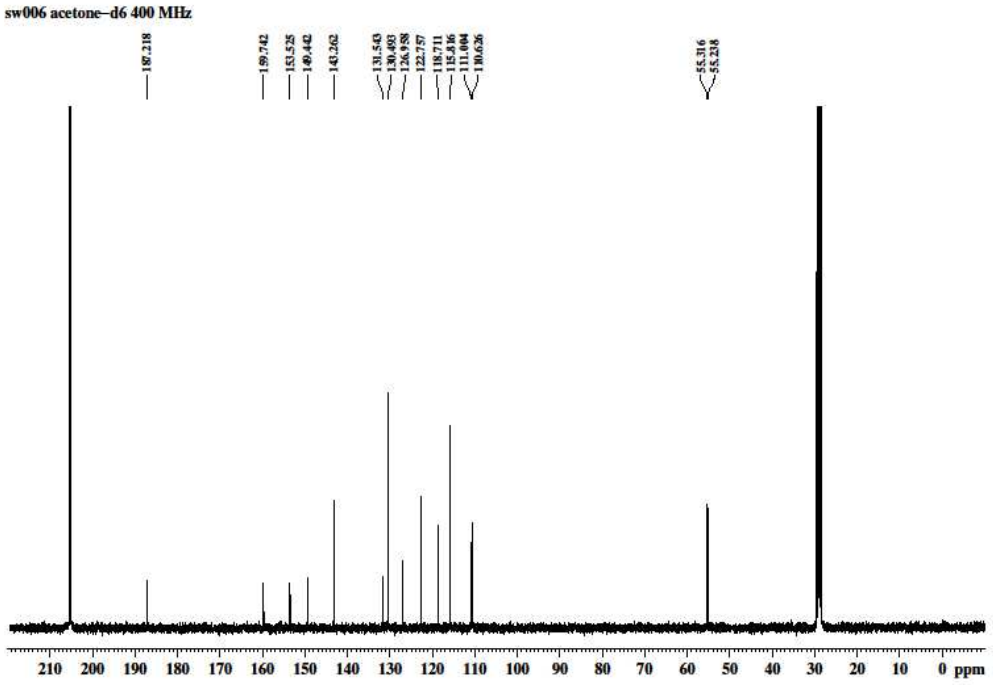
CD084 d6–acetone 400 MHz



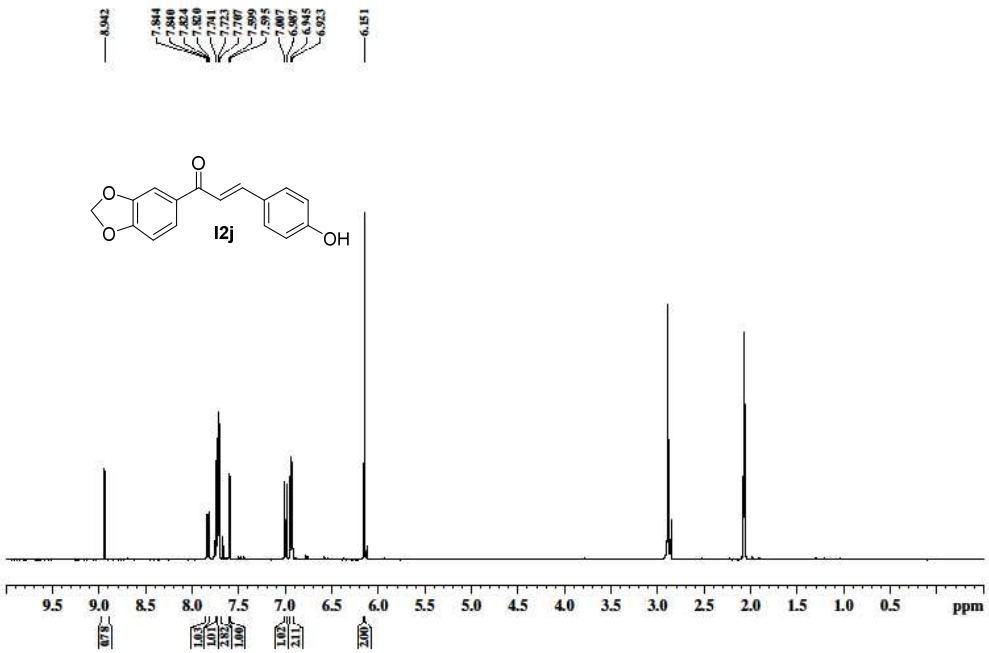
CD084 acetone–d6 400MHz



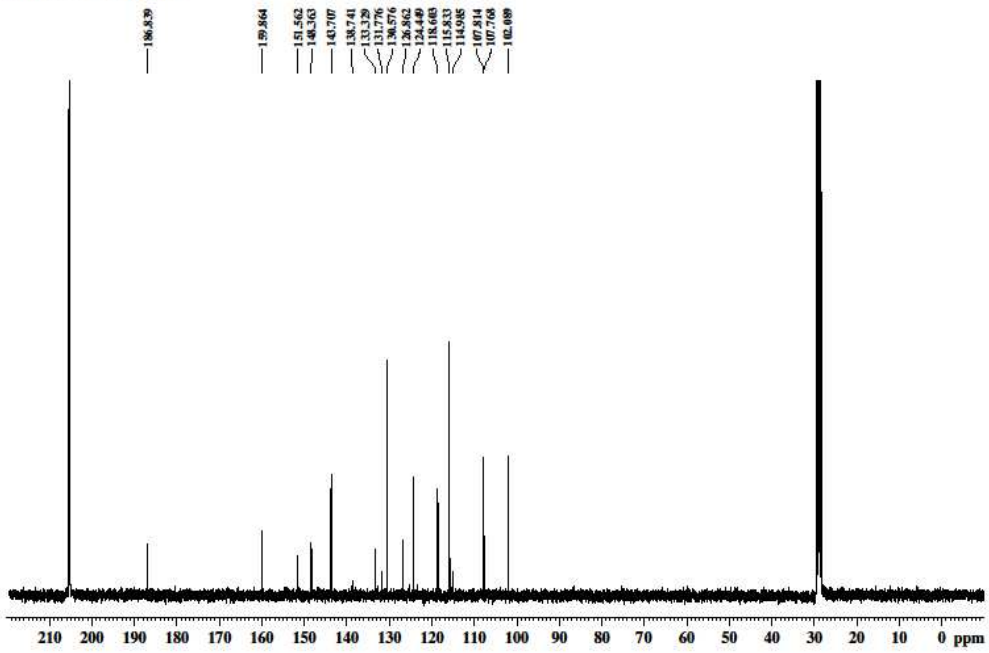

sw006 acetone–d6 400 MHz
8.962
7.848
7.843
7.827
7.822
7.715
7.706
7.684
7.662
7.657
7.033
7.062
6.928
6.906
3.909
3.900
MeO
MeO
O
OH
I2i
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.06
1.27
2.40
2.50
1.24
1.30
2.59
3.57
3.49


sw006 acetone–d6 400 MHz
187.218
159.742
153.525
149.442
143.262
130.543
130.403
126.958
122.757
118.711
115.816
111.004
100.626
55.316
55.218
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0 ppm

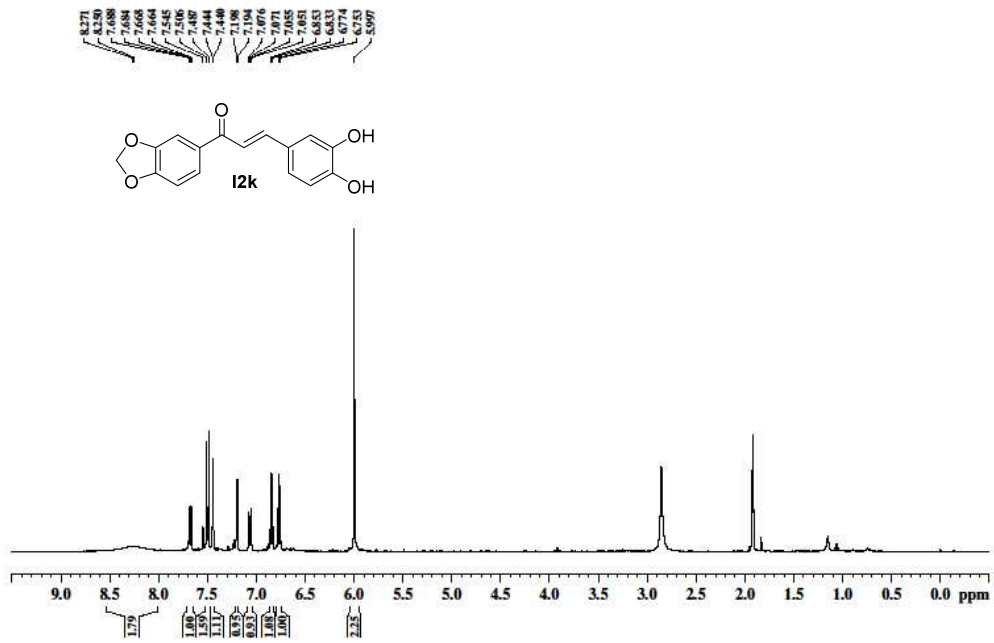
CD012 in acetone 400MHz



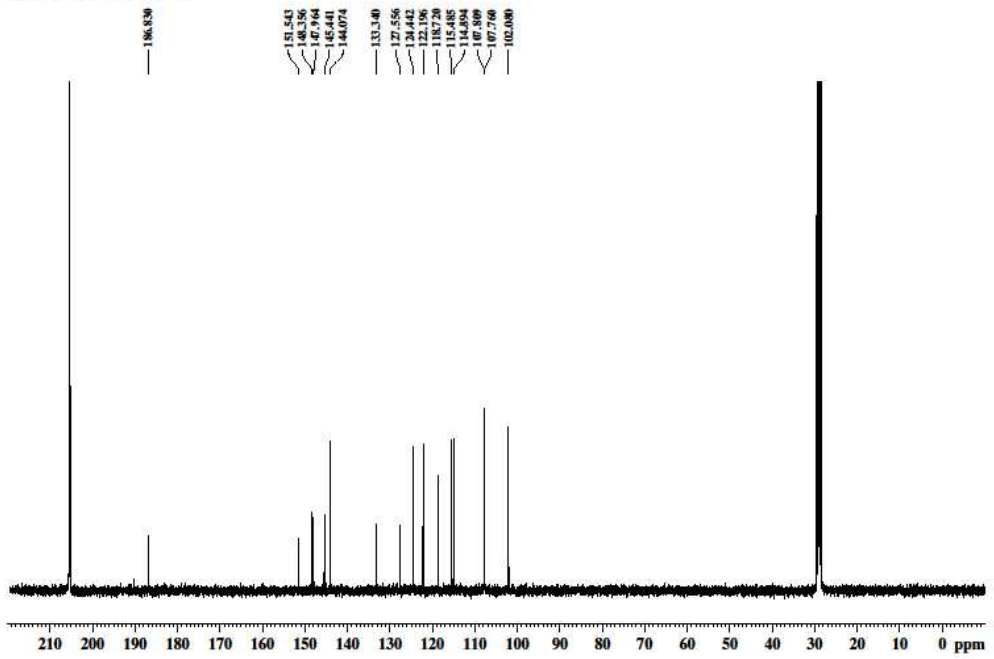
CD012 acetone–d6 400MHz



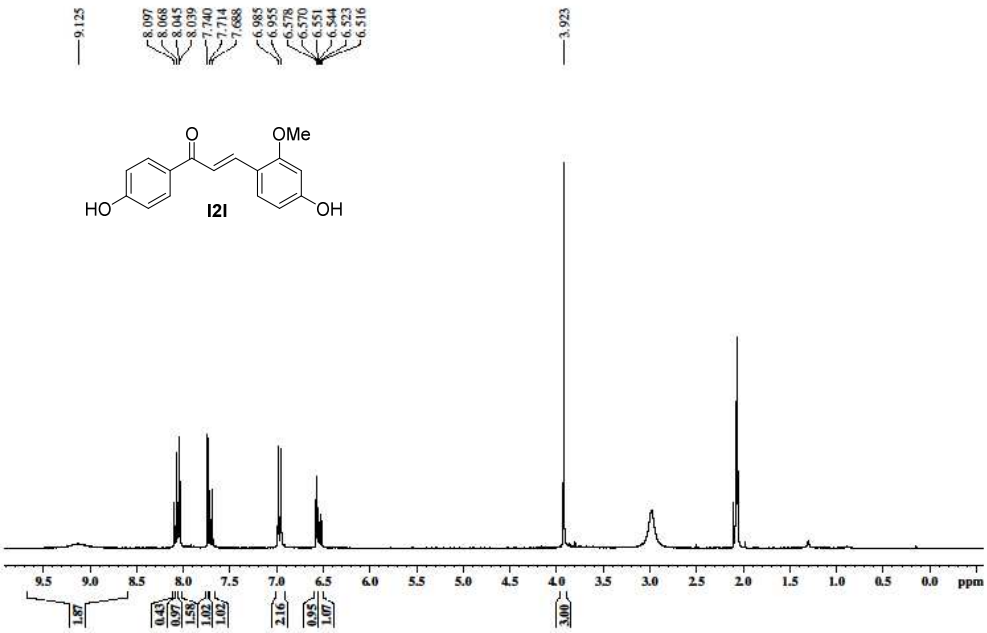
sw007 acetone–d6 400 MHz



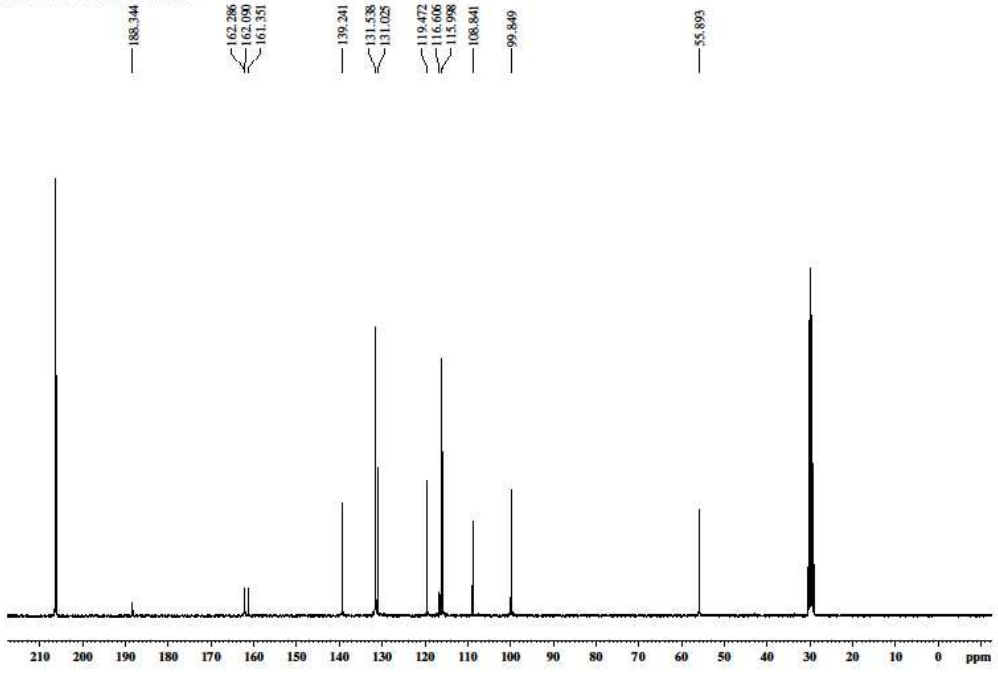
sw007 acetone–d6 400 MHz



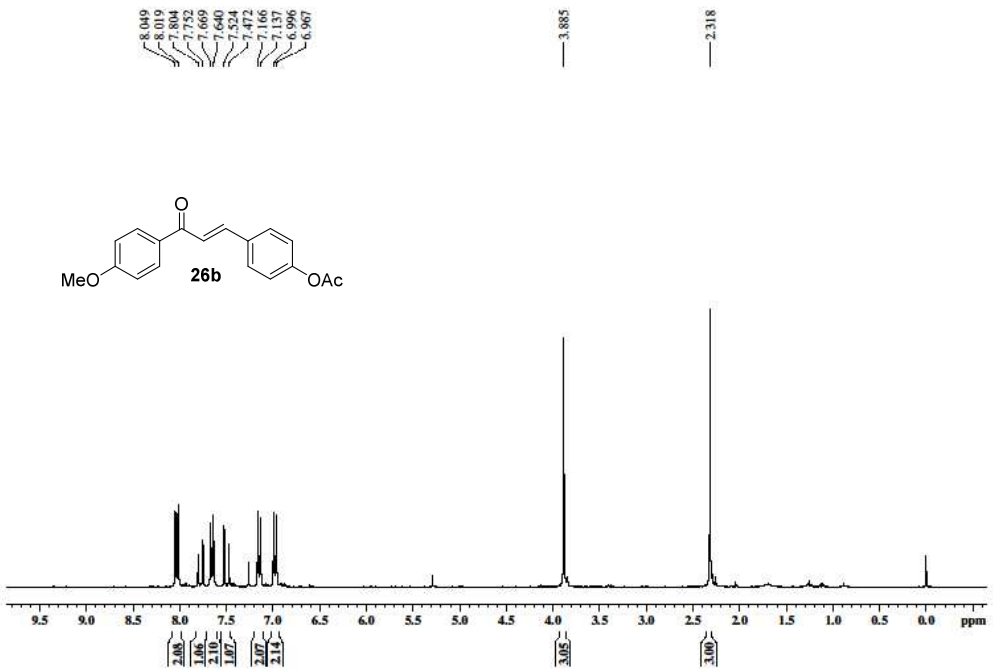
PRS-232 F1 in d6-acetone



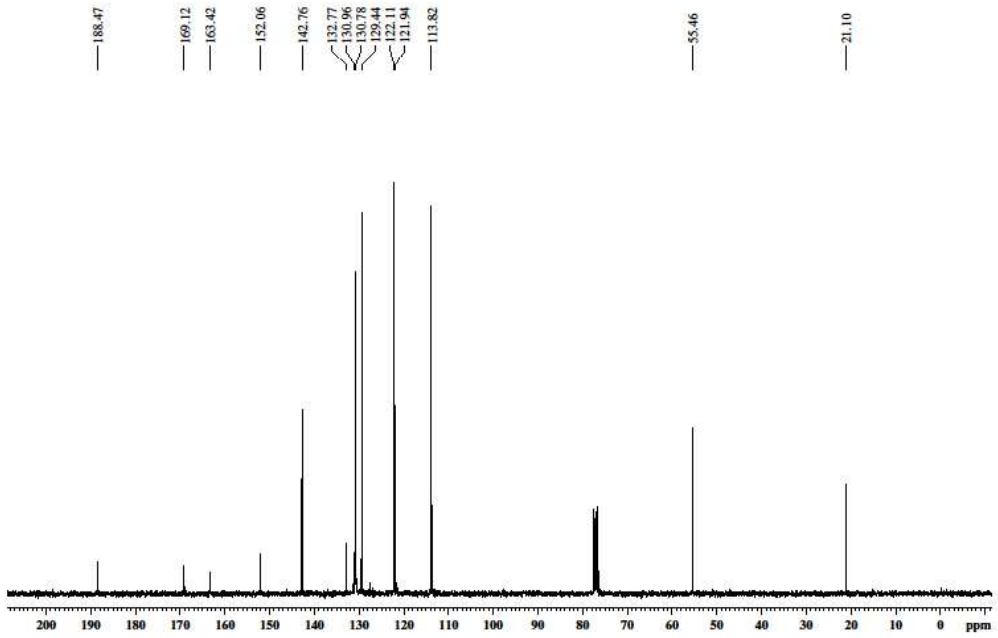
PRS-232 F1 acetone-d6 300MHz

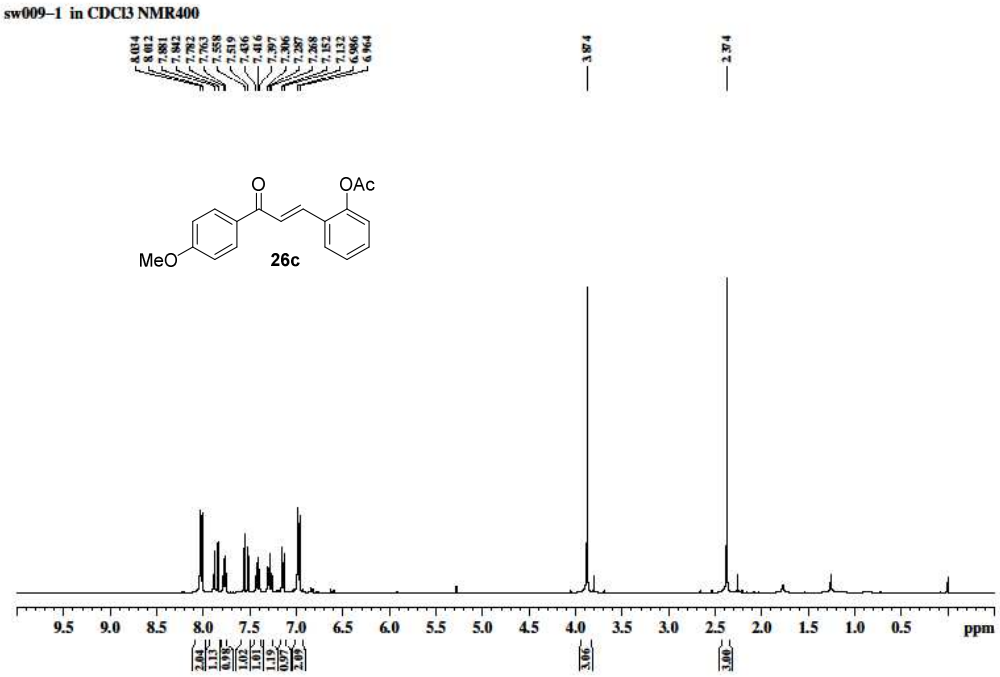


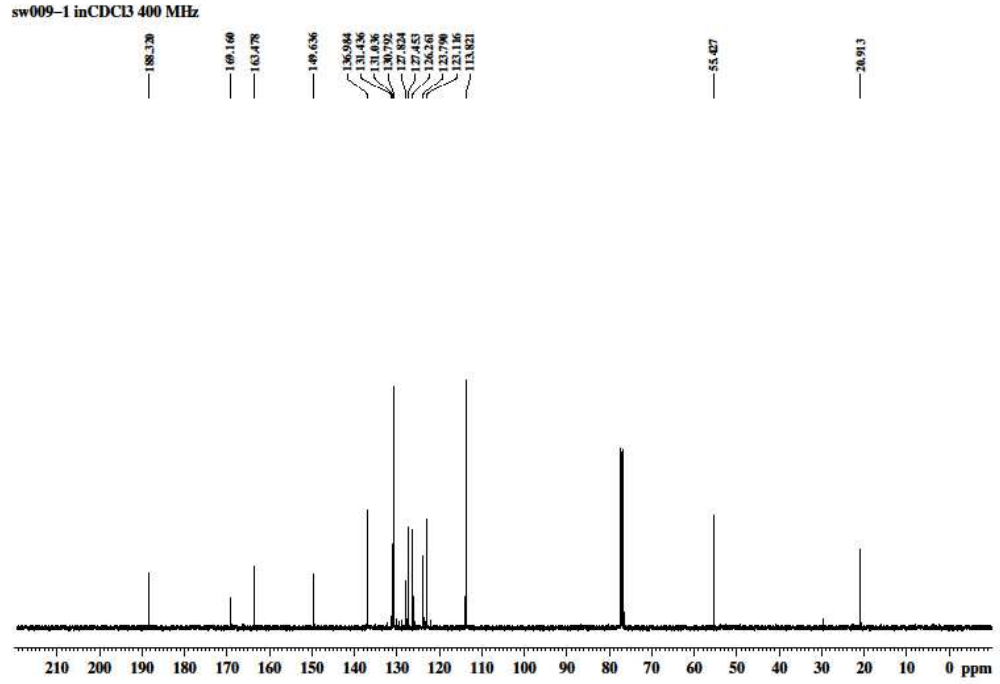
PRS-282 F1 CDCl3 300MHz



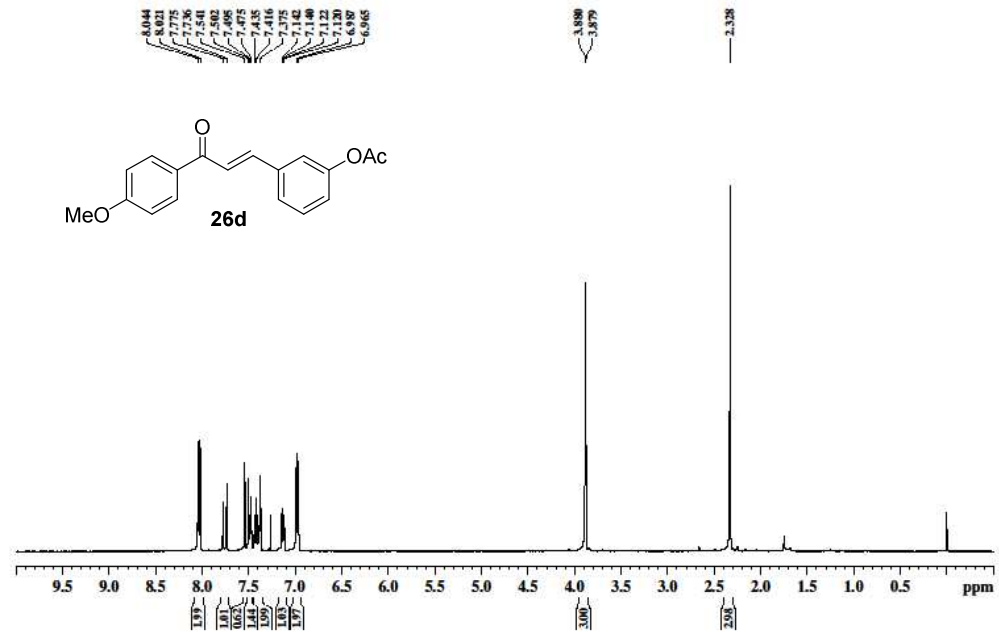
PRS-282 F1 CDCl3 300MHz



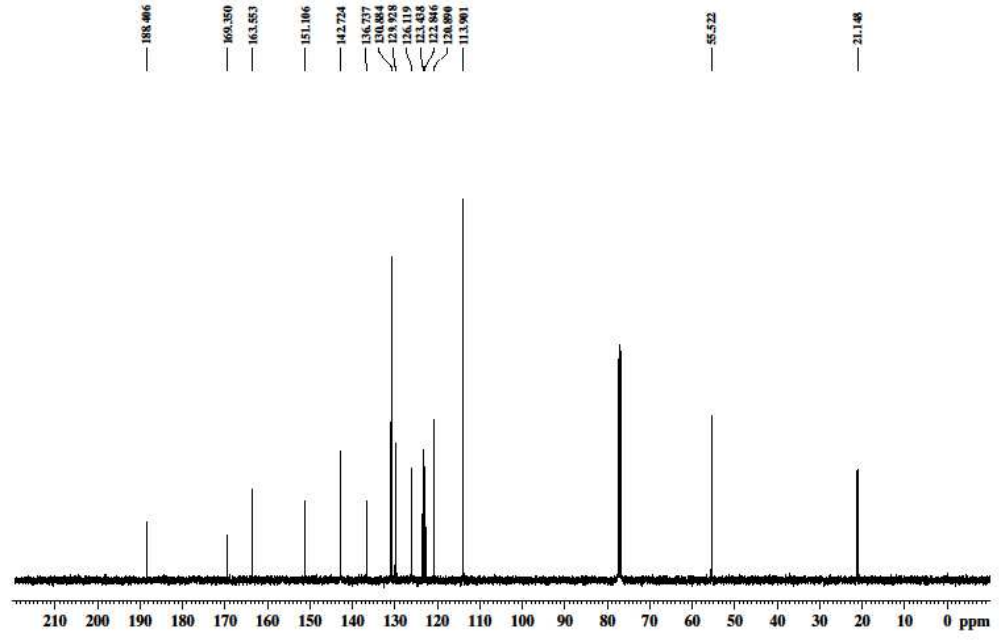

sw009–1 in CDCl3 NMR400
8.034
8.012
7.881
7.842
7.782
7.763
7.558
7.519
7.456
7.416
7.397
7.306
7.287
7.268
7.152
7.132
6.986
6.964
3.874
2.374
O
OAc
MeO
26c
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
2.04
1.13
0.98
1.02
1.01
1.19
0.97
2.00
3.06
3.00


sw009–1 inCDCl3 400 MHz
188.320
169.160
163.478
149.636
136.984
131.436
131.036
130.792
127.824
127.453
126.261
123.790
123.116
113.821
55.427
26.913
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

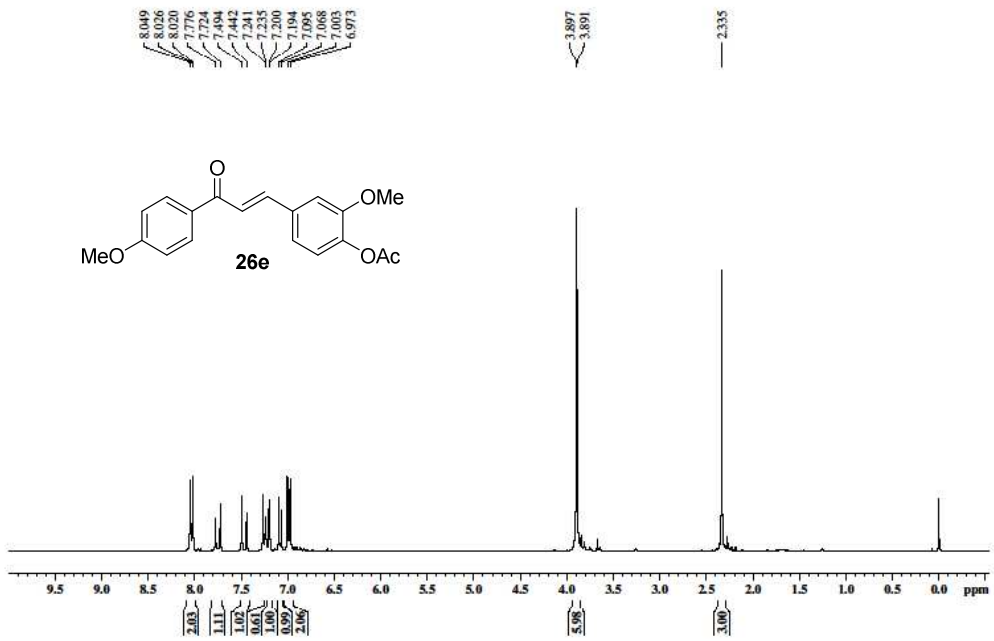
PRS–03–043F1 in CDCl3 NMR400



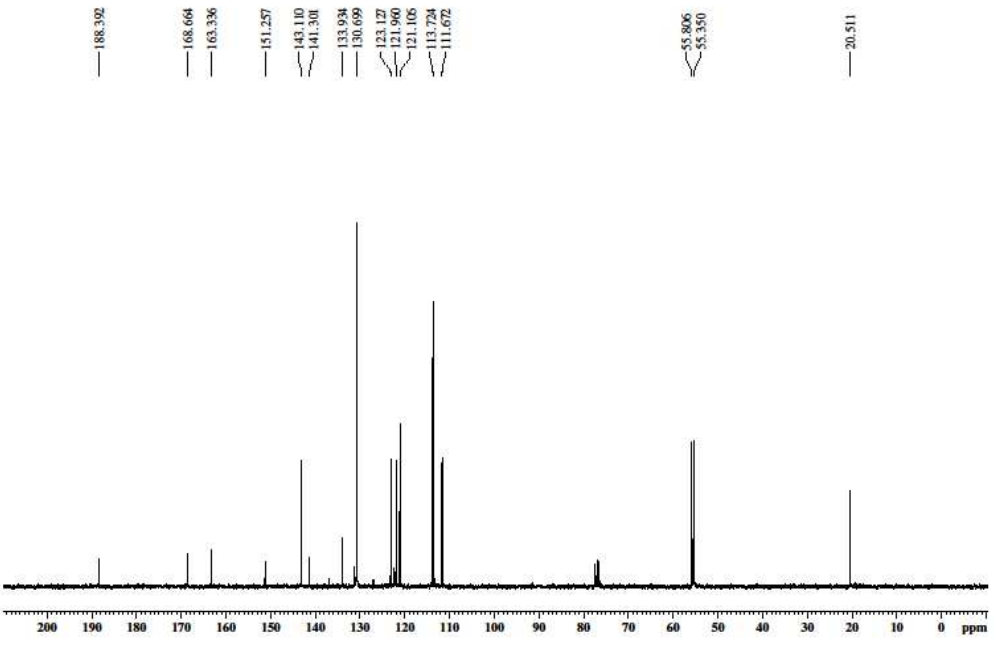
PRS–03–043F1 in CDCl3 NMR400

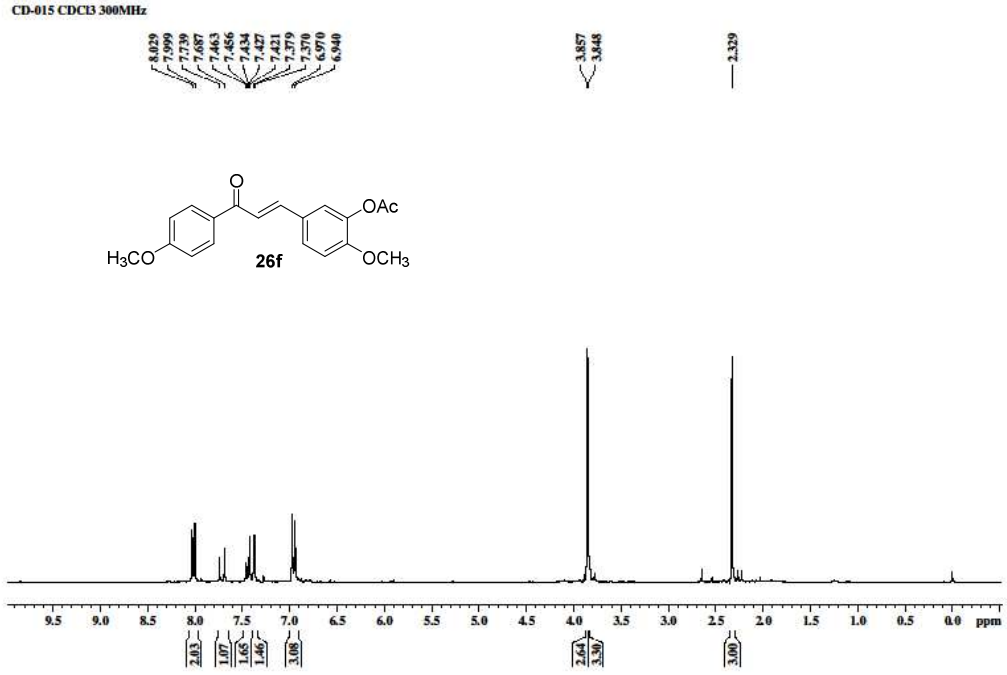


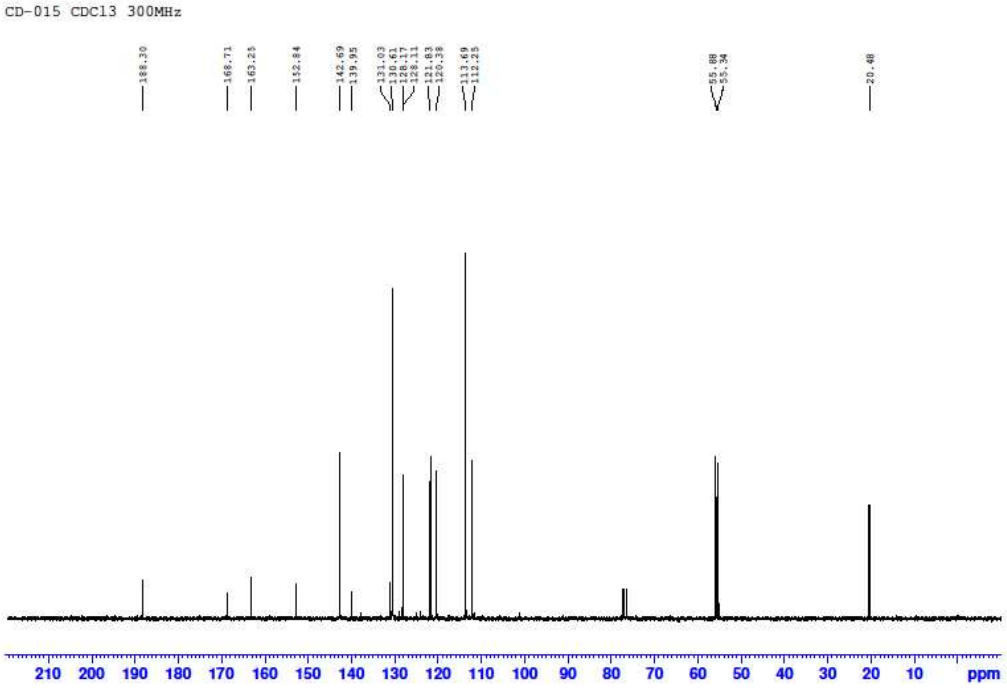
PRS-168 F2 CDCl3 300MHz

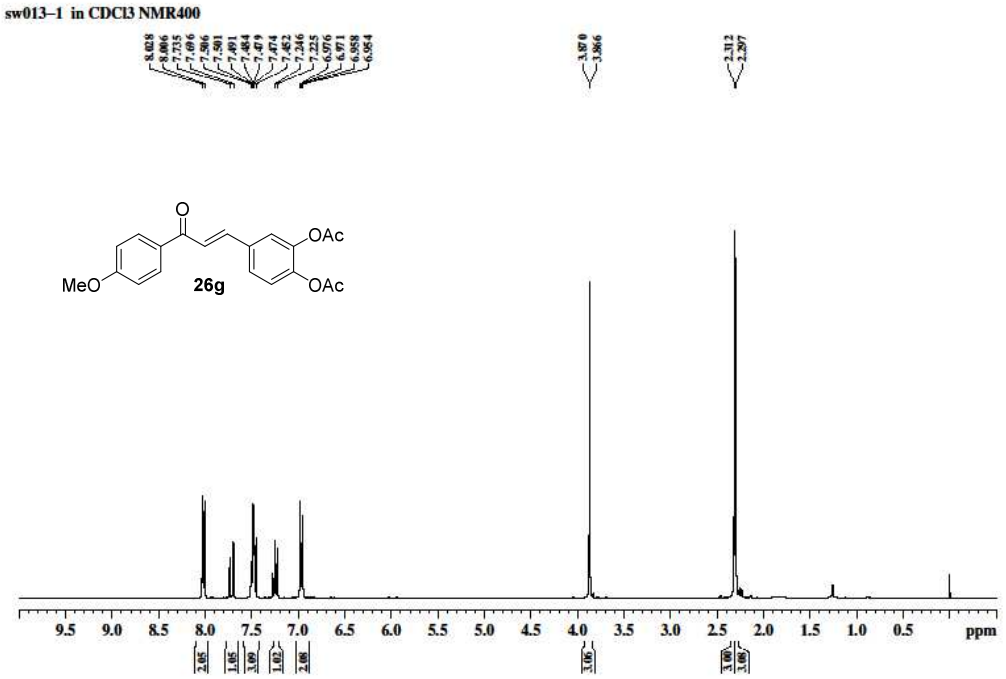


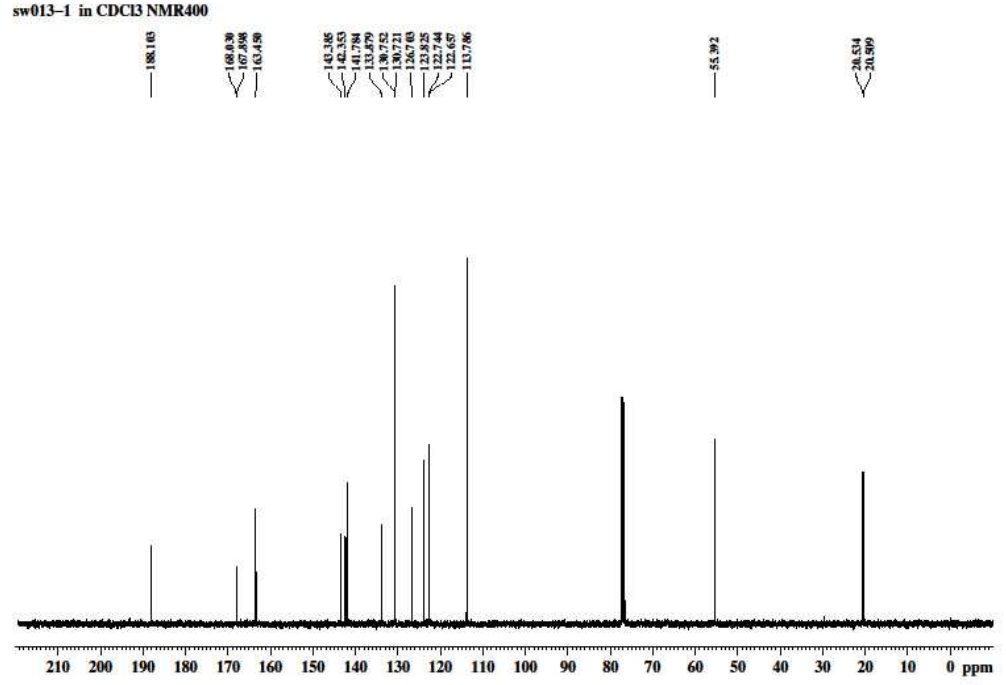
PRS-168 F2 CDCl3 300MHz



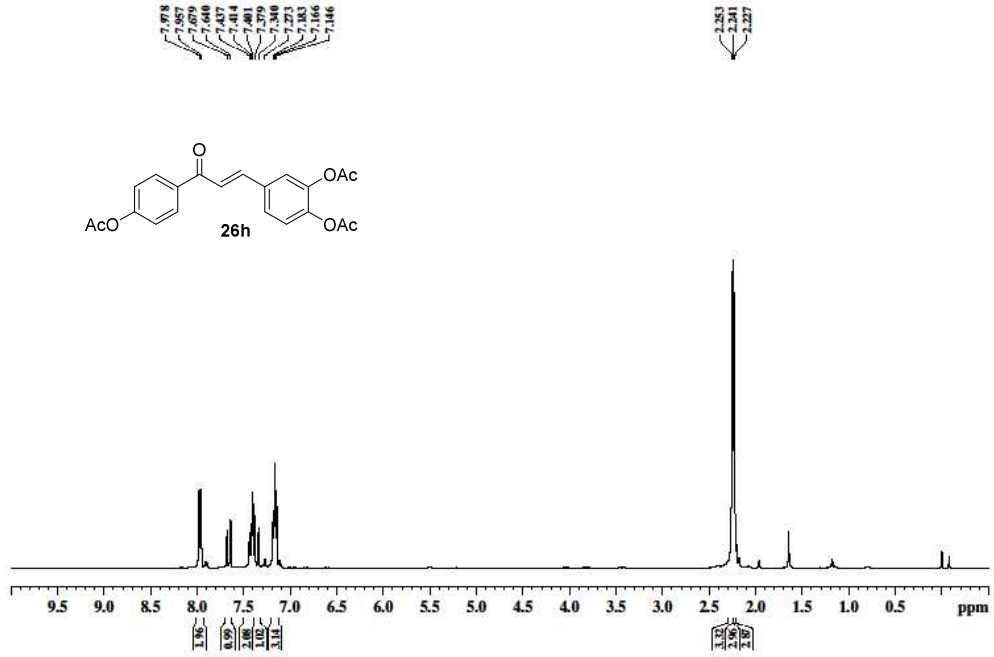

CD-015 CDCl3 300MHz
8.029
7.999
7.739
7.687
7.463
7.456
7.434
7.427
7.421
7.379
7.370
6.970
6.940
3.857
3.848
2.329
O
OAc
H3CO
OCH3
26f
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
2.03
1.07
1.65
1.46
3.08
2.64
3.30
3.00


CD-015 CDCl3 300MHz
188.30
168.71
163.25
152.84
142.69
139.95
131.03
130.61
128.17
128.11
121.83
120.38
113.69
112.25
55.88
55.34
20.48
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

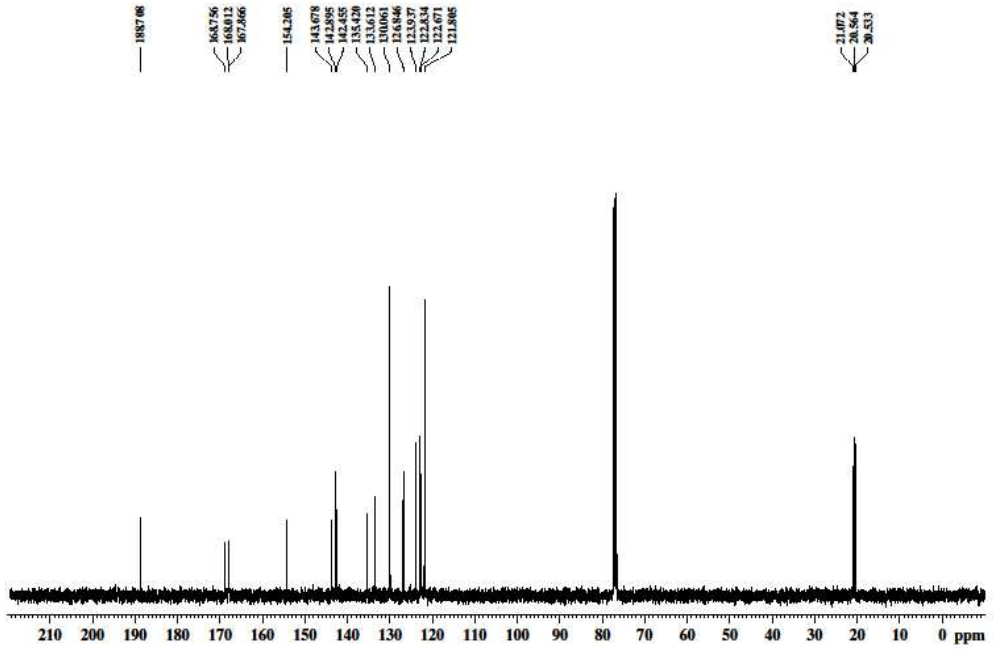

sw013–1 in CDCl3 NMR400
8.028
8.006
7.735
7.696
7.506
7.501
7.491
7.484
7.474
7.452
7.246
7.225
6.976
6.971
6.958
6.954
3.870
3.866
2.312
2.297
O
OAc
MeO
OAc
26g
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
2.05
1.05
3.09
1.02
2.00
3.06
3.00
3.00


sw013–1 in CDCl3 NMR400
168.103
168.030
167.898
163.450
143.385
142.353
141.784
133.879
130.752
130.721
126.703
123.825
122.744
122.657
113.786
55.392
20.534
20.509
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

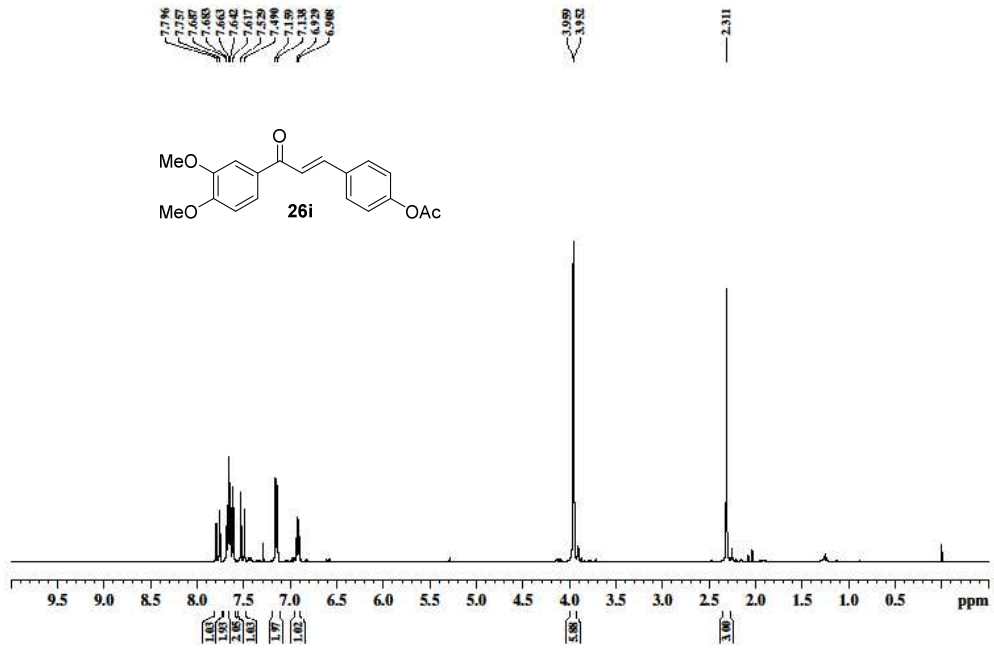
CD085 in CDCl3 NMR400



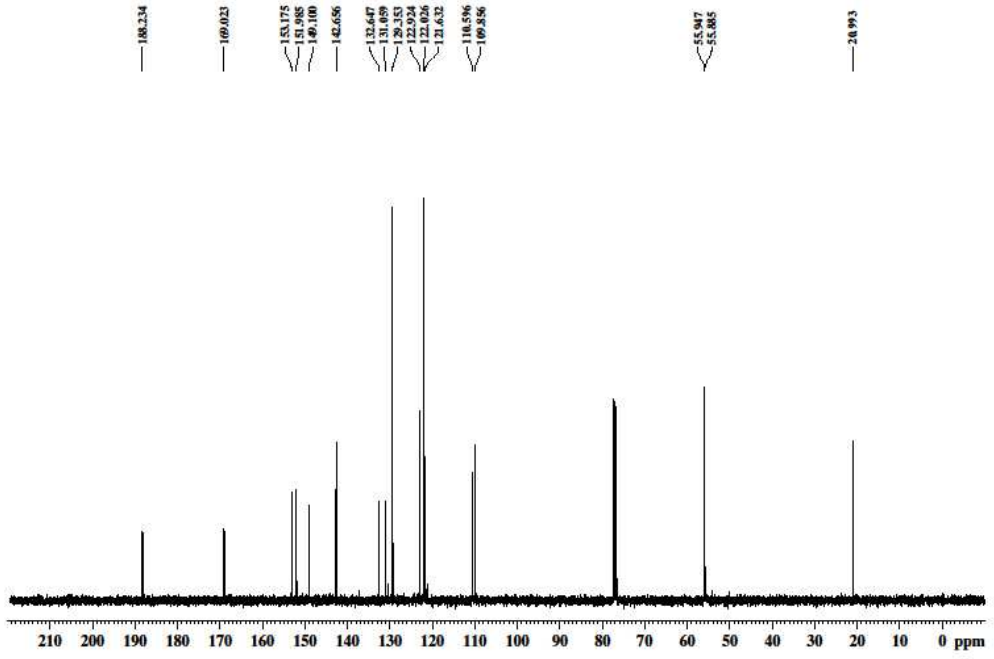
CD085 CDCl3 400 MHz



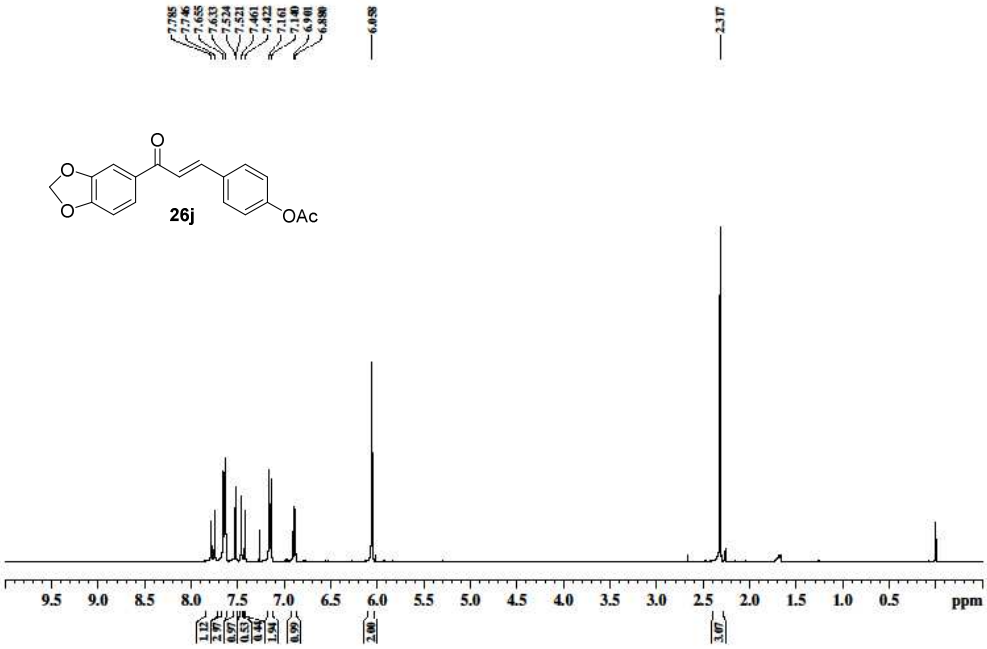
SW–011 in CDCl3 NMR400



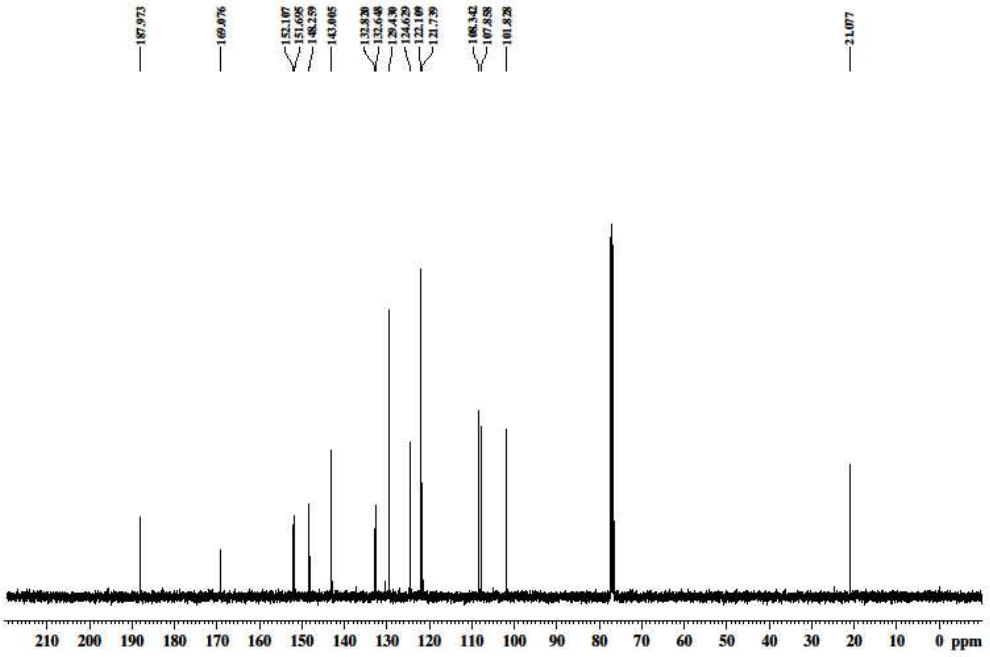
SW–011 in CDCl3 400MHz



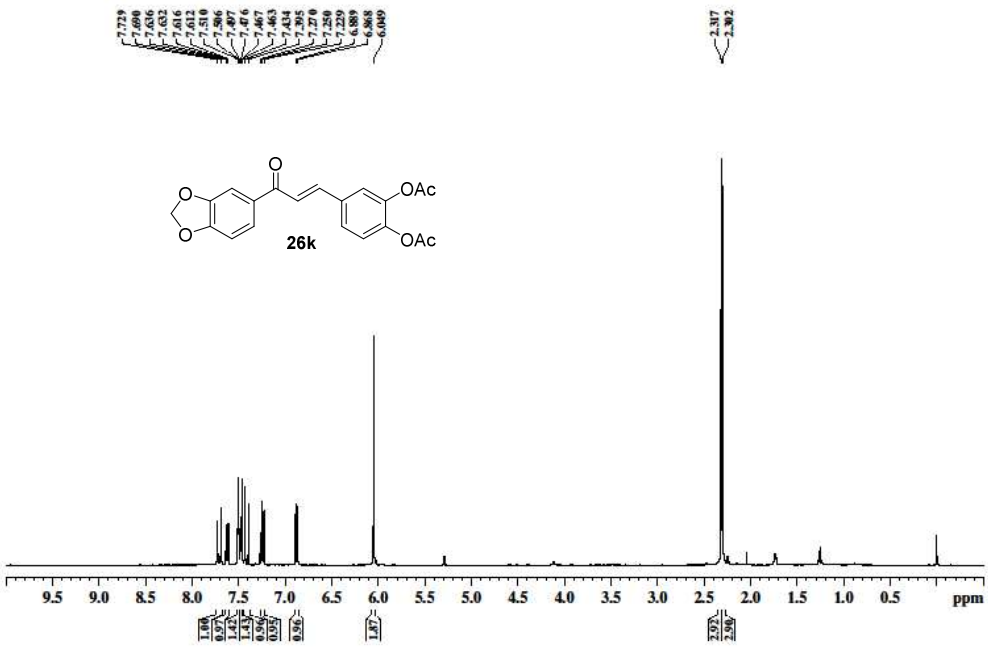
CD–014 in CDCl3 NMR400



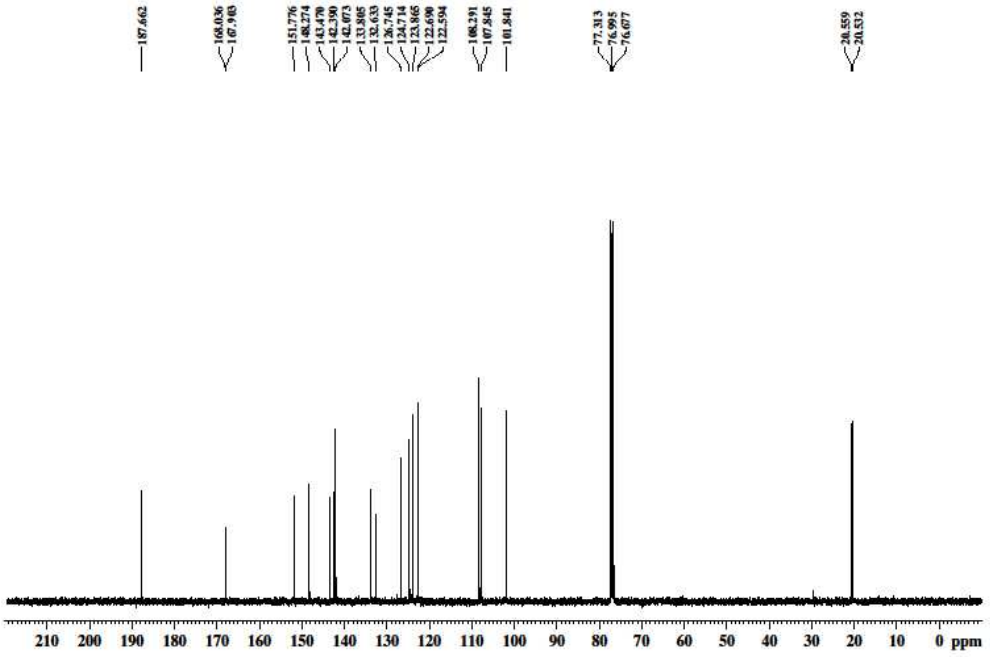
CD–014 CDCl3 400MHz



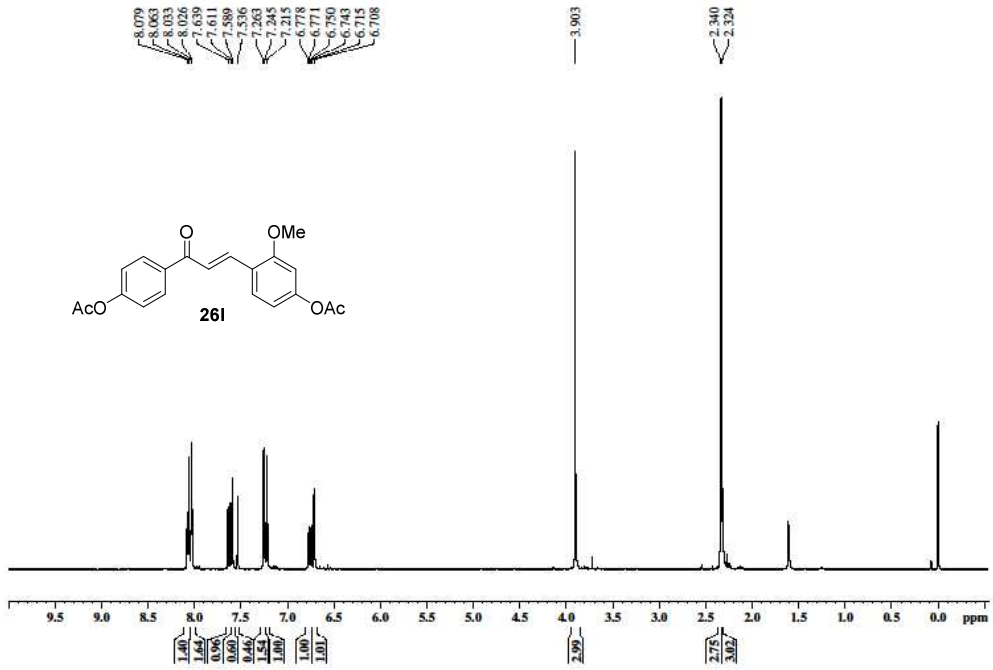
sw012–1 CDCl3 400 MHz



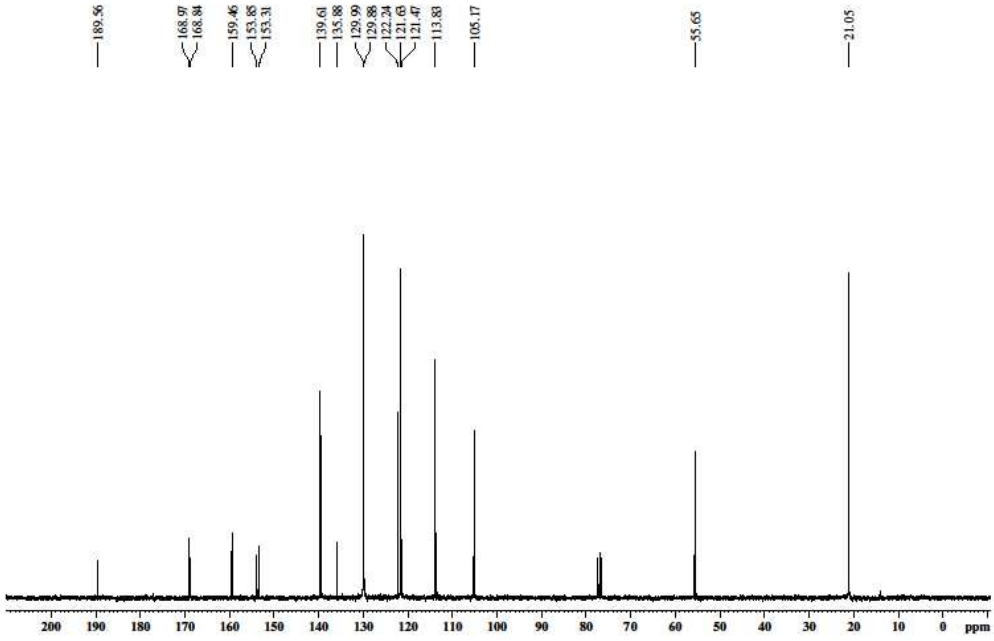
SW012–1 in CDCl3 400MHz



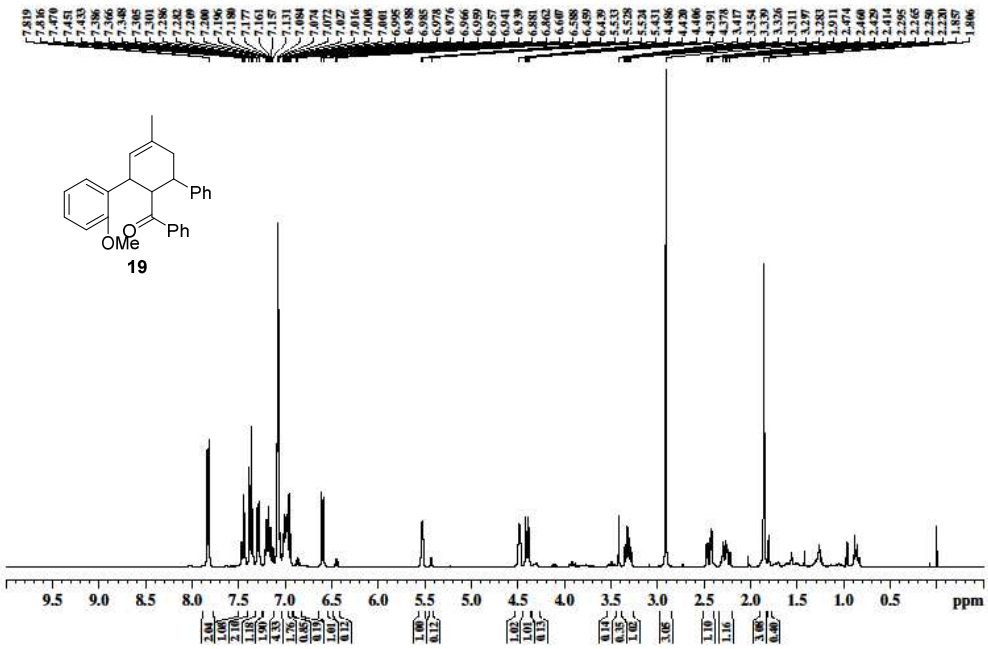
PRS-234 F1 CDCl3 300MHz



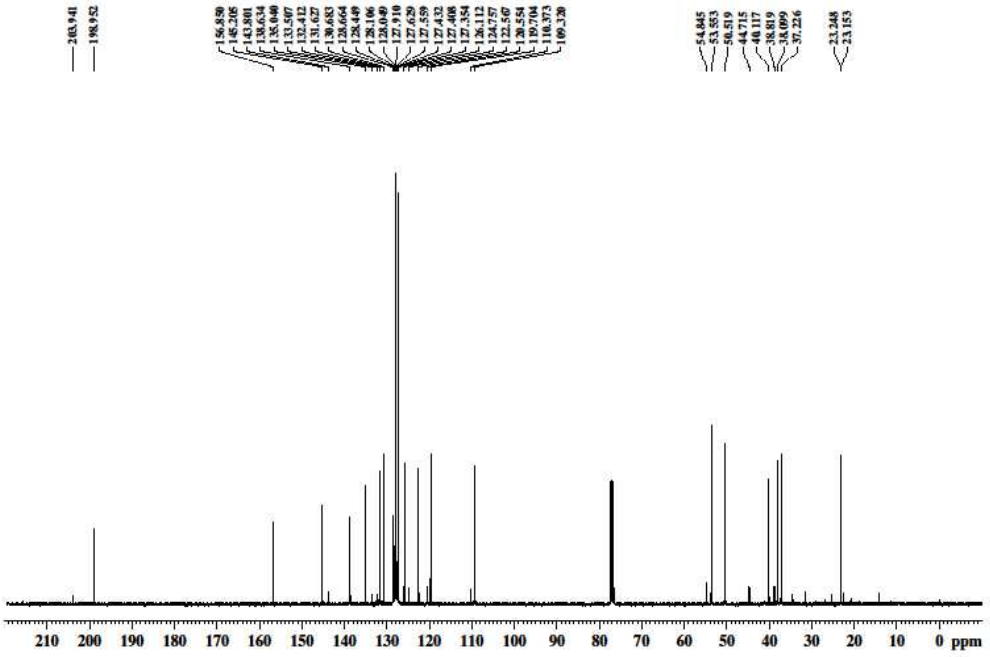
PRS-234 F1 CDCl3 300MHz



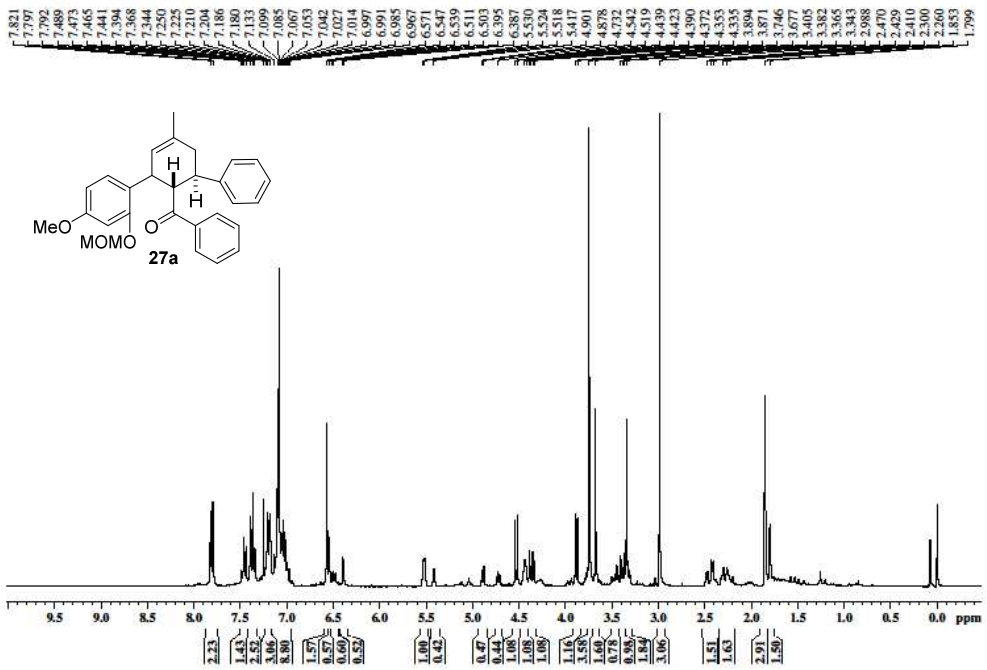
PRS–157F2 CDCl3 NMR400



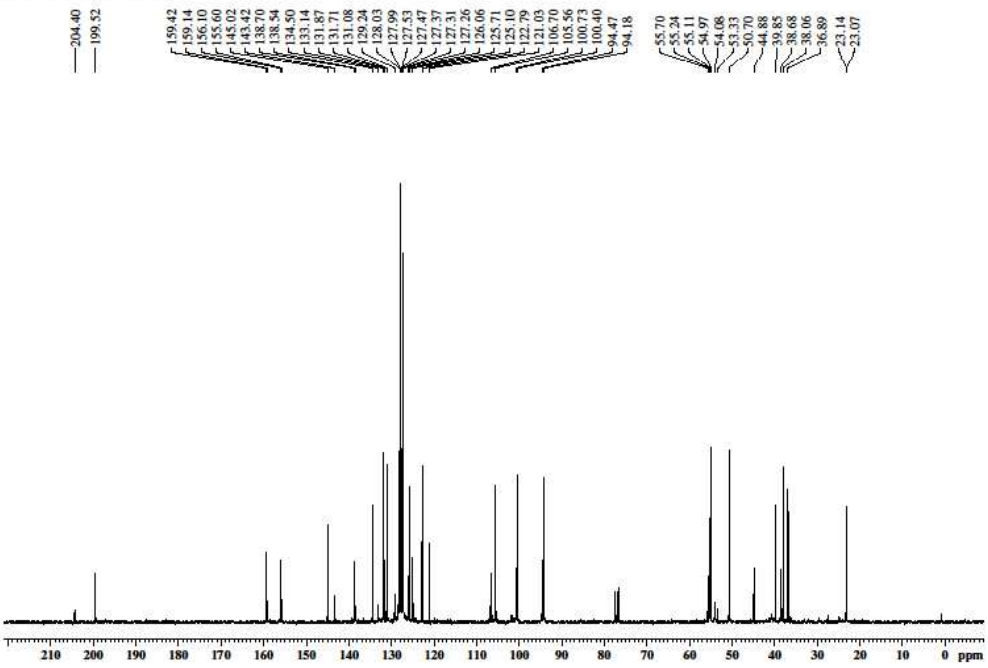
PRS–157F2 in CDCl3 NMR400



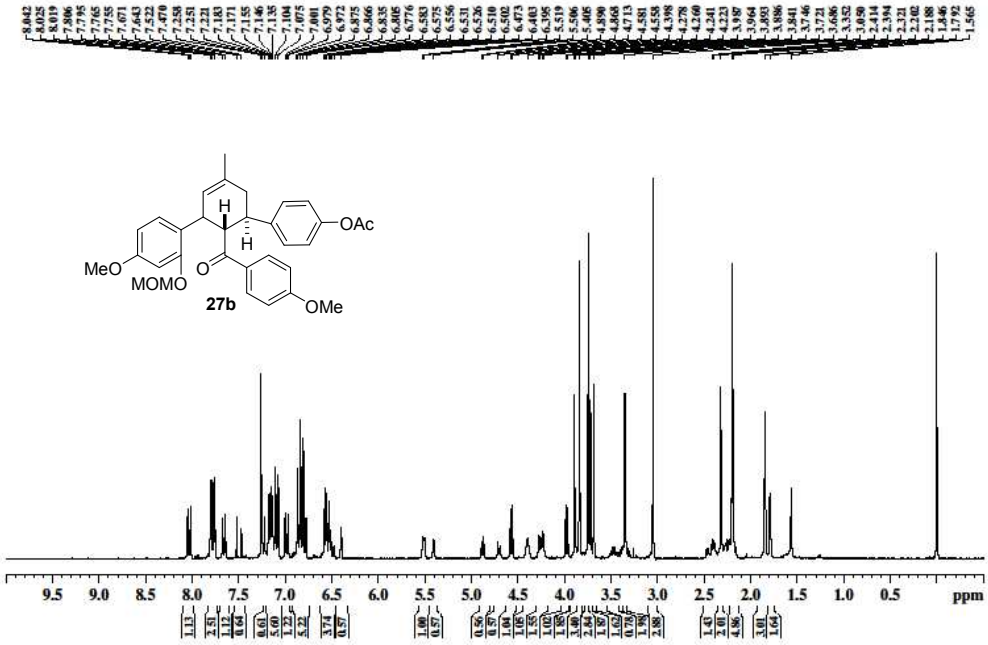
PRS-193 F3



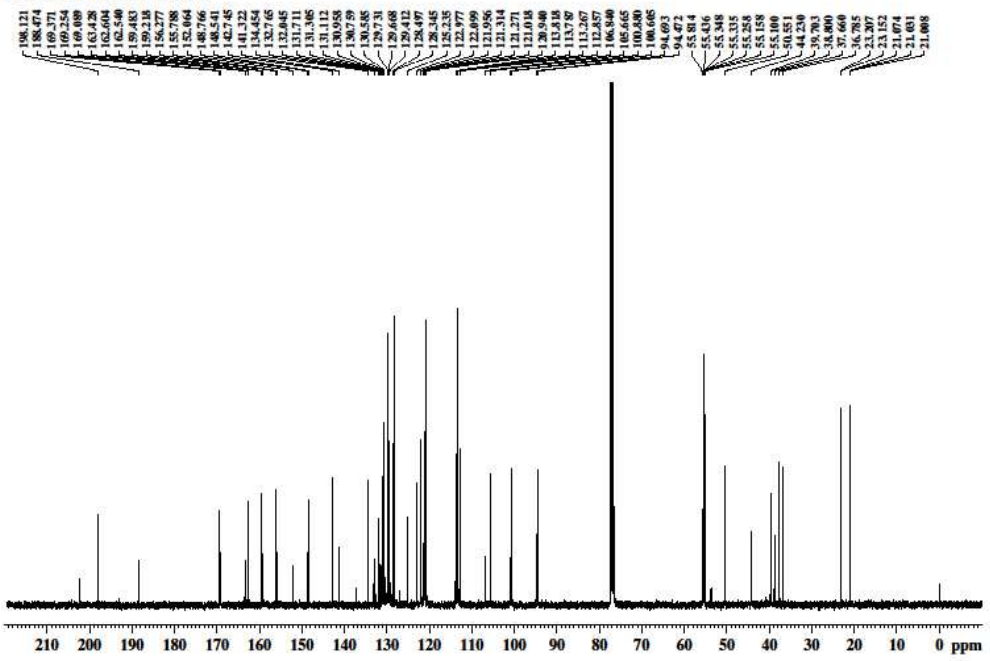
PRS-193 F3 CDCl3 300MHz



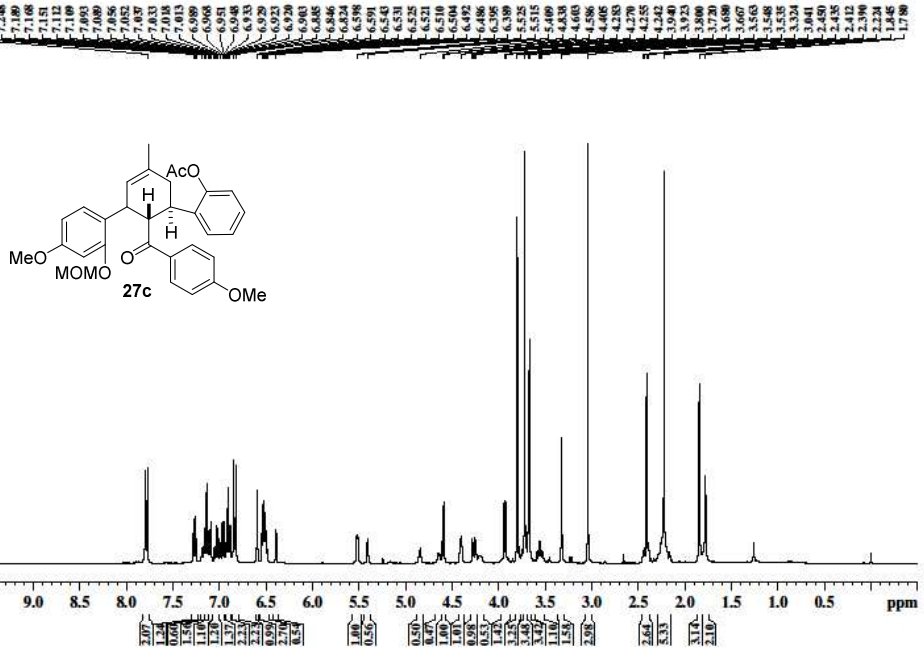
PRS–284 F4 CDCl3 400MHz



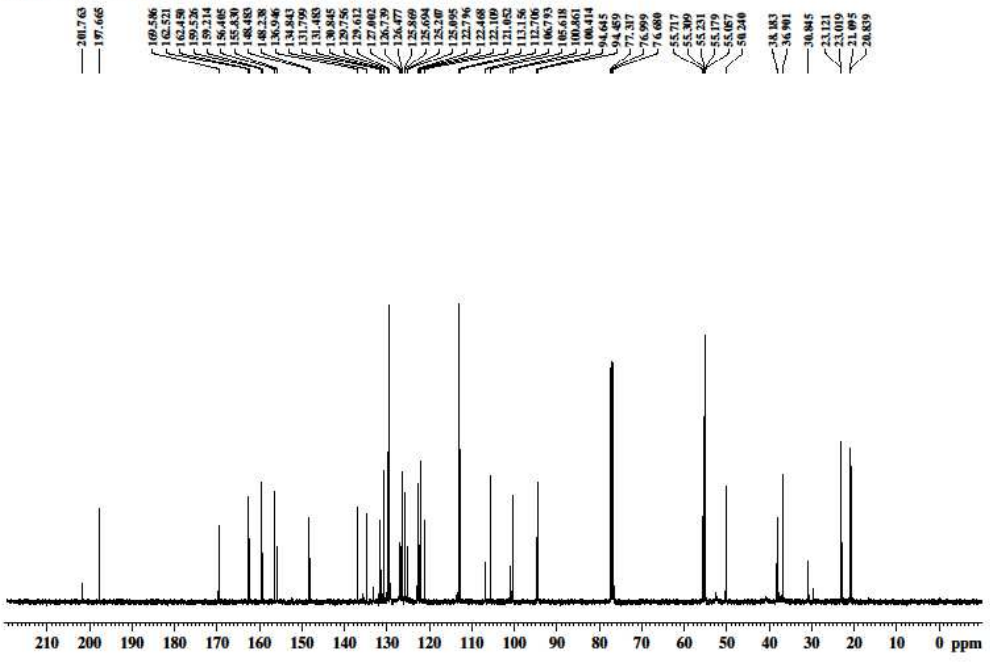
PRS–284F4 in CDCl3 400MHz



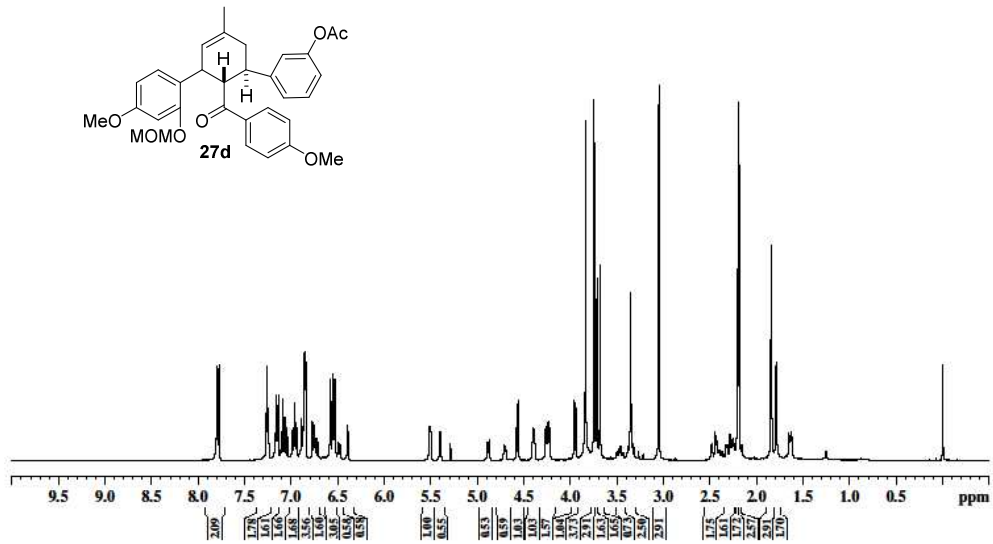
sw021–3 CDCl3 400 MHz



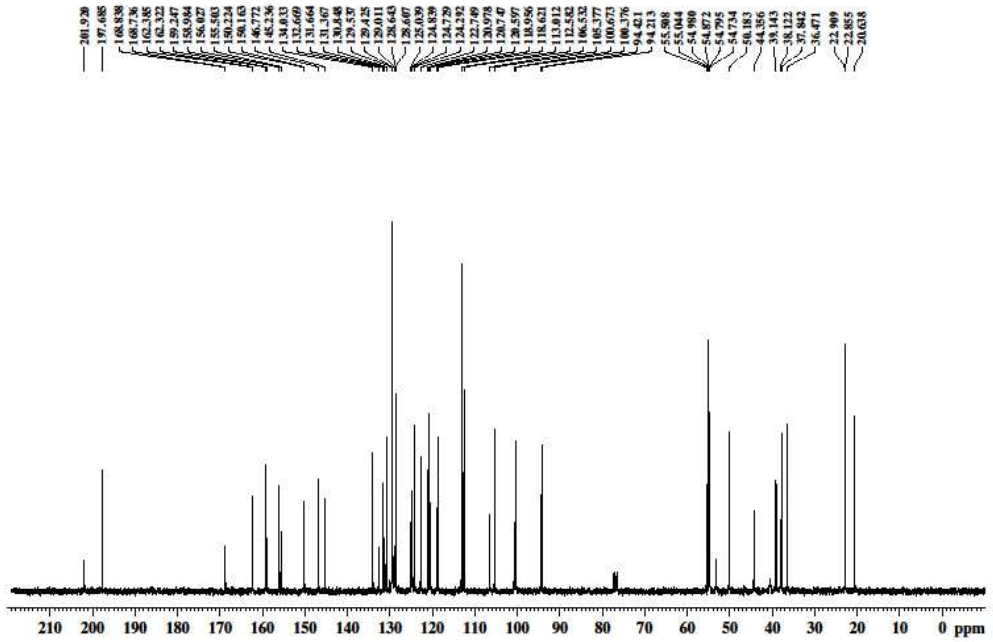
sw021–3 CDCl3 400 MHz



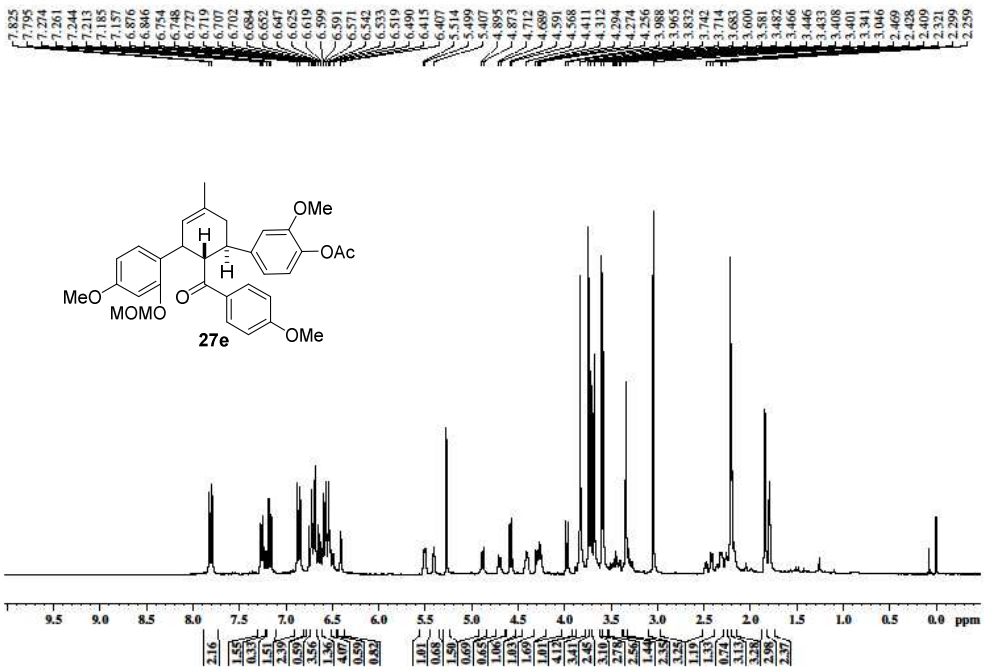
PRS–03–046F4 in CDCl3 300MHz



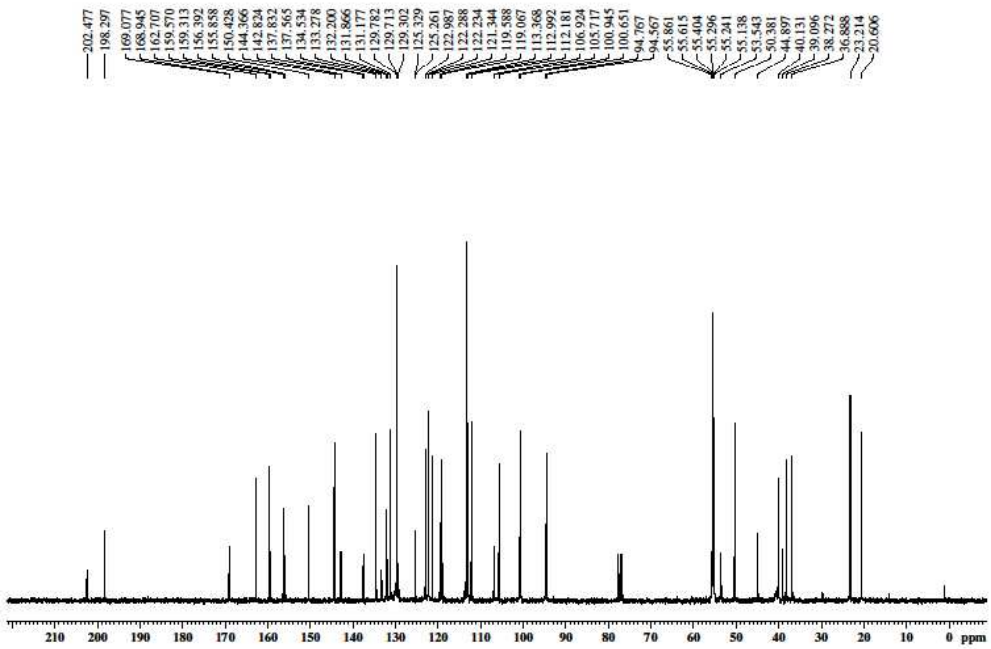
PRS–03–046F4 in CDCl3 300MHz



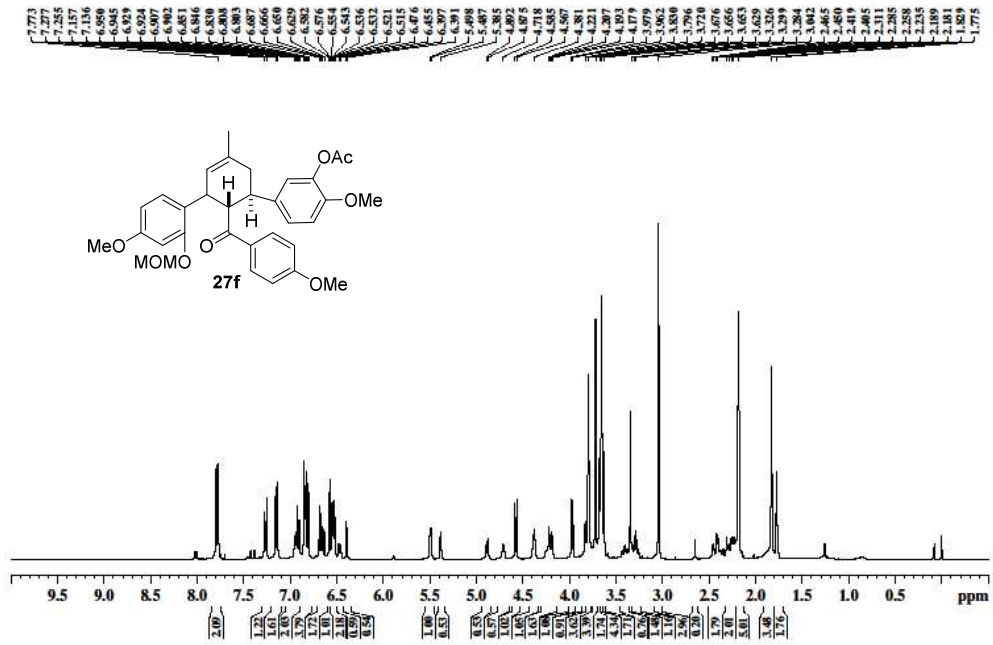
PRS-192 F5 CDCl3 300MHz



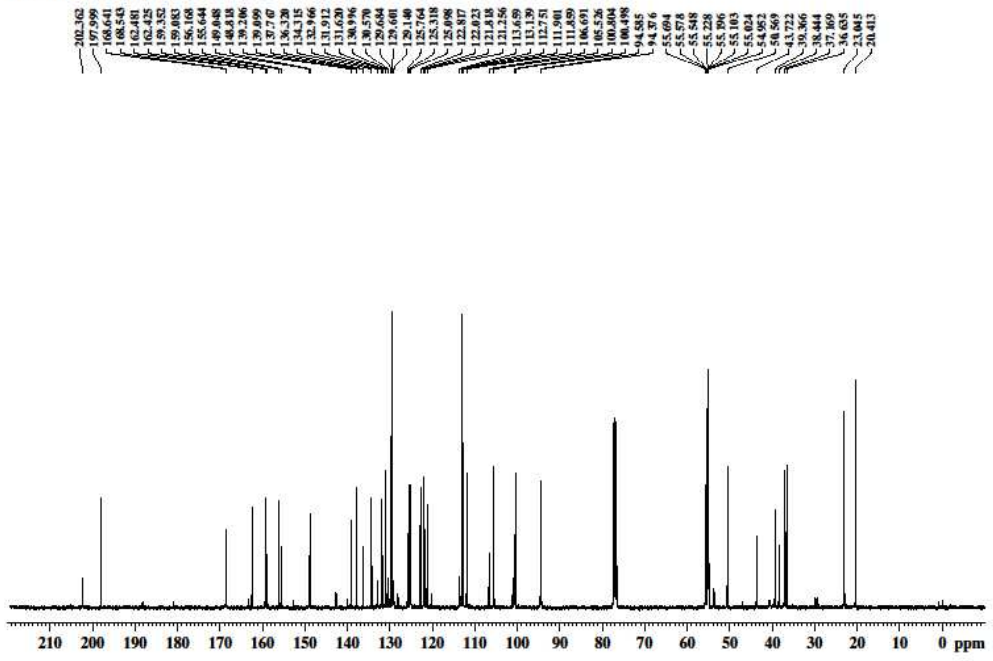
PRS-192 F5 CDCl3 300MHz



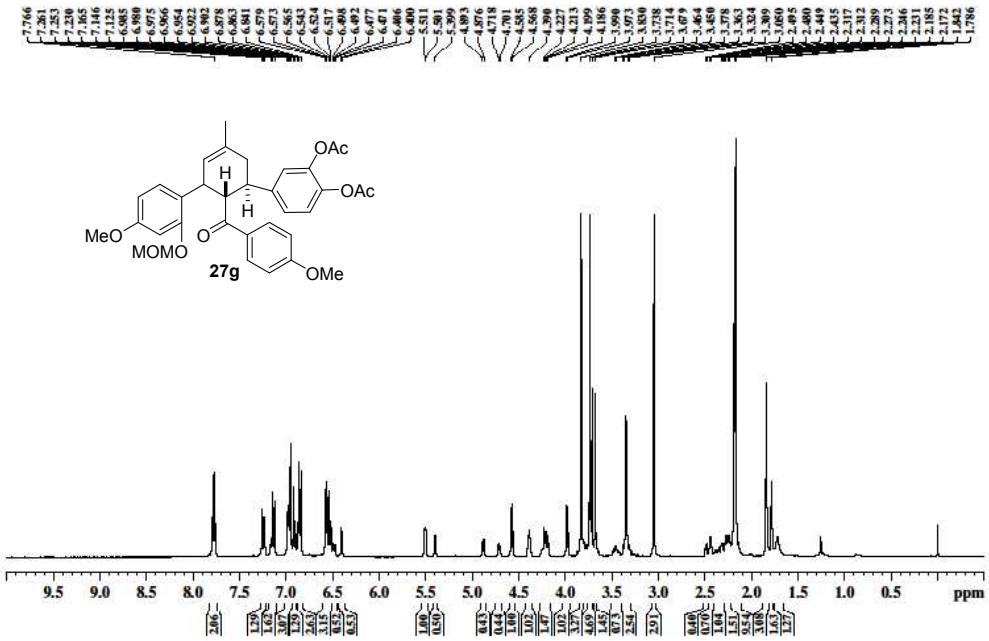
PRS–345 F3 in CDCl3 400MHz



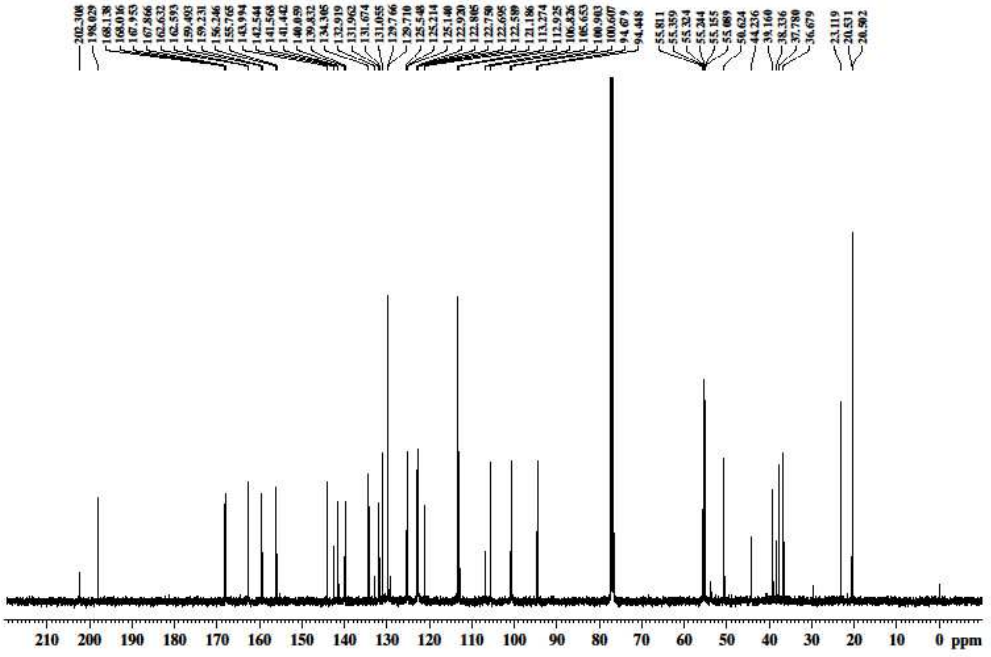
PRS–345 F3 in CDCl3 400MHz



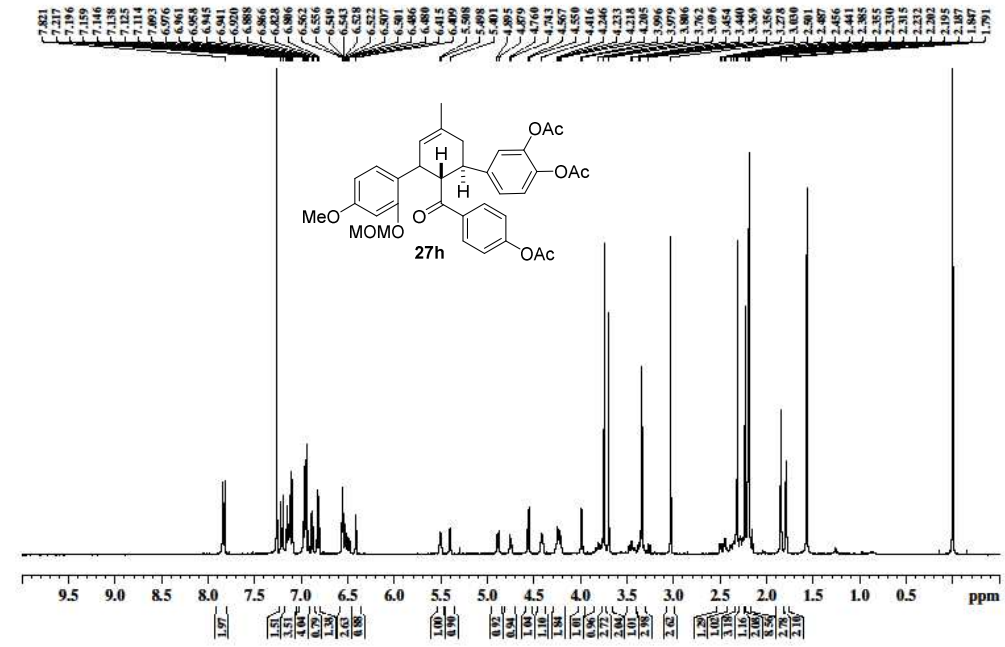
sw020–1 CDCl3 400 Mz



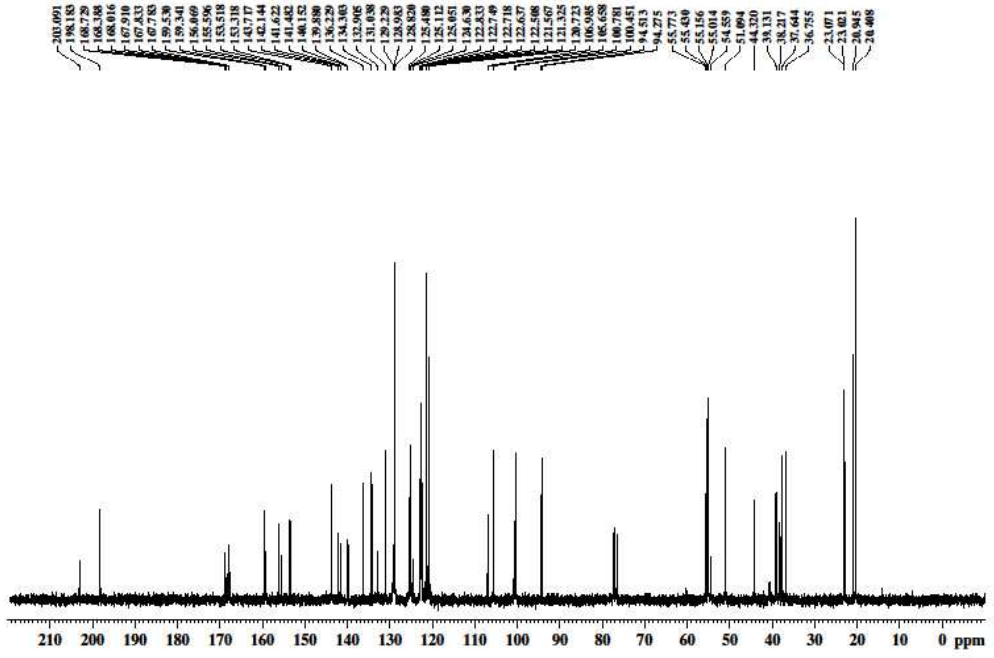
sw020–1 CDCl3 400 Mz



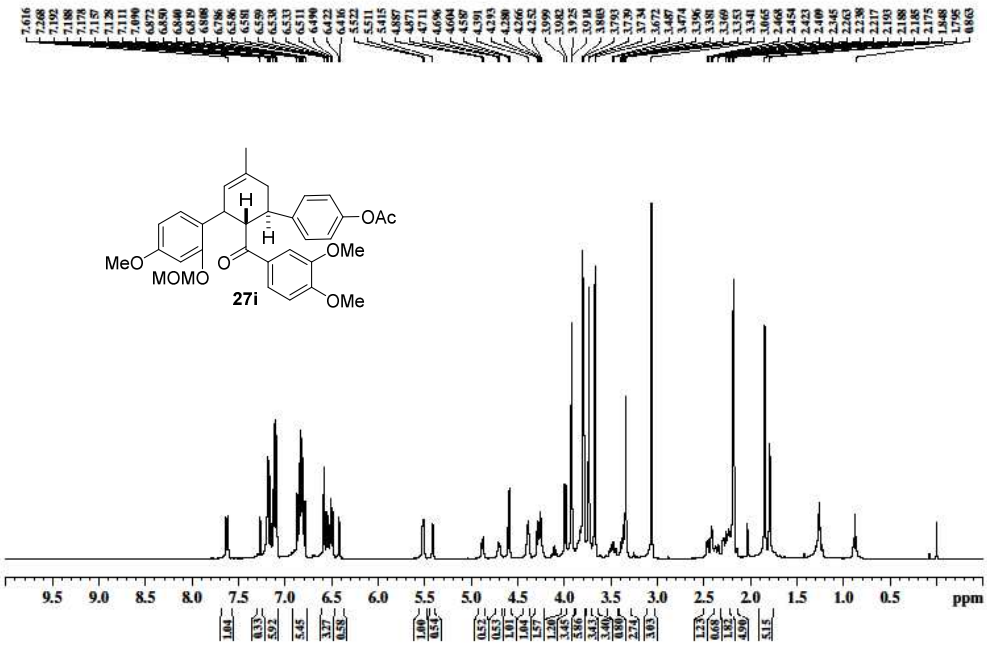
PRS–03–045F4 CDCl3 300MHz



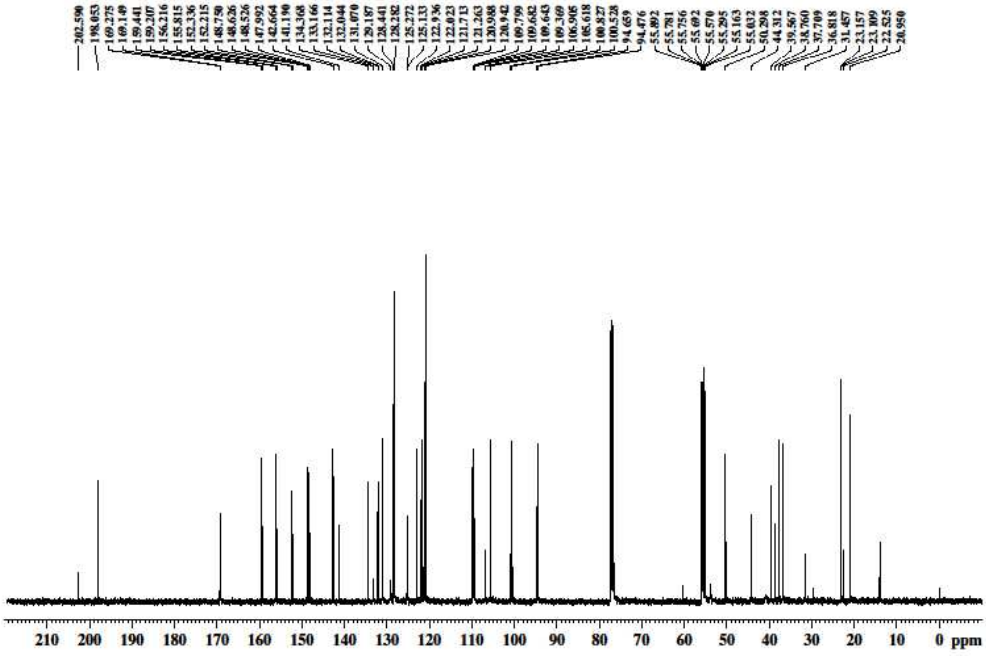
PRS–03–045F4 in CDCl3 300MHz



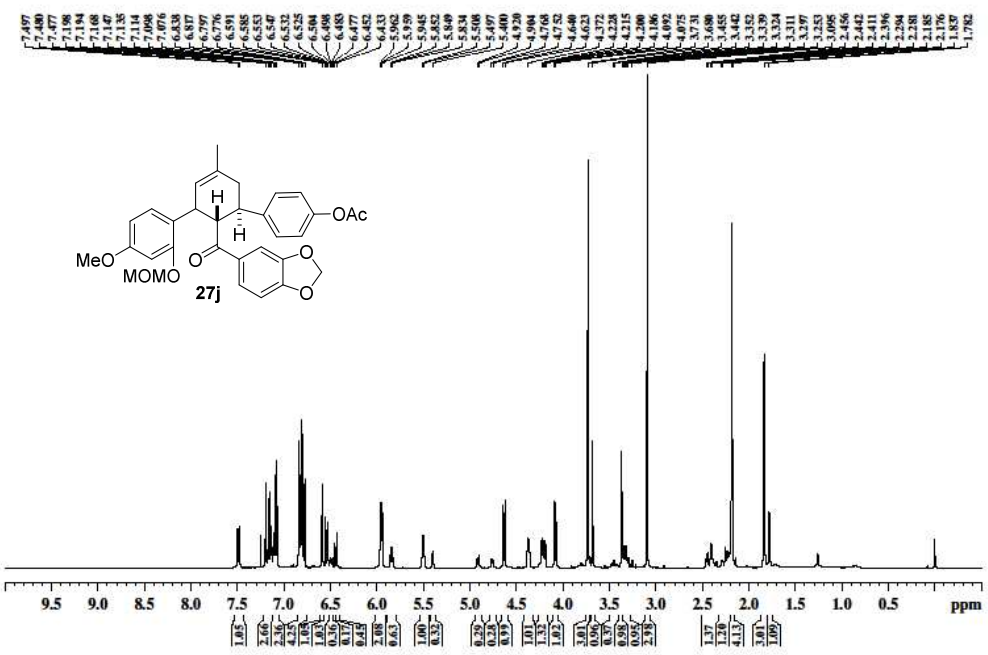
PRS–346–F3 in CDCl3 NMR400



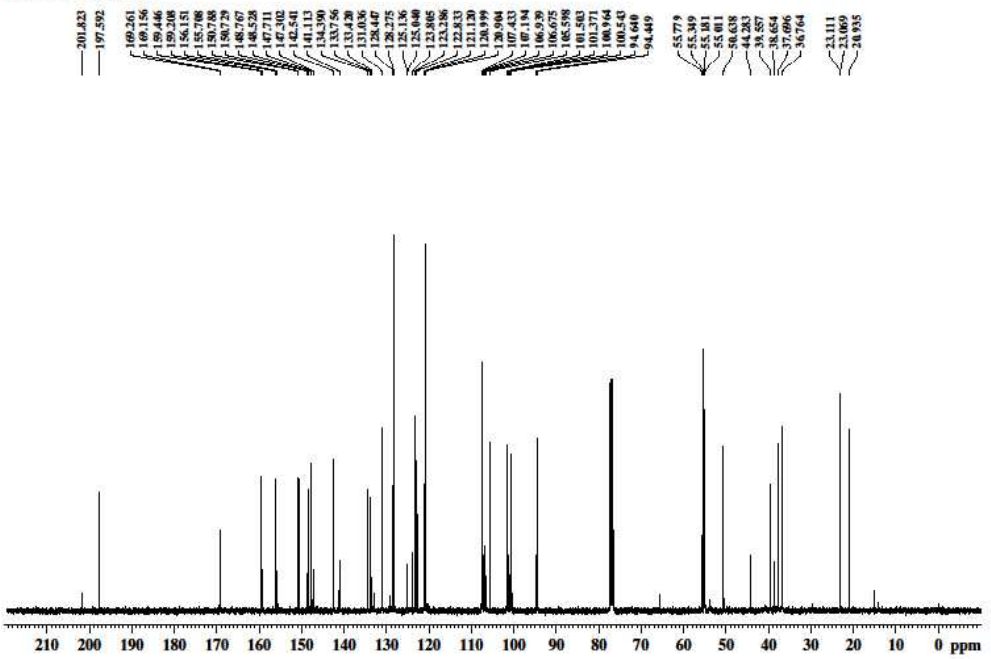
PRS–346 F3 in CDC3 400 MHz



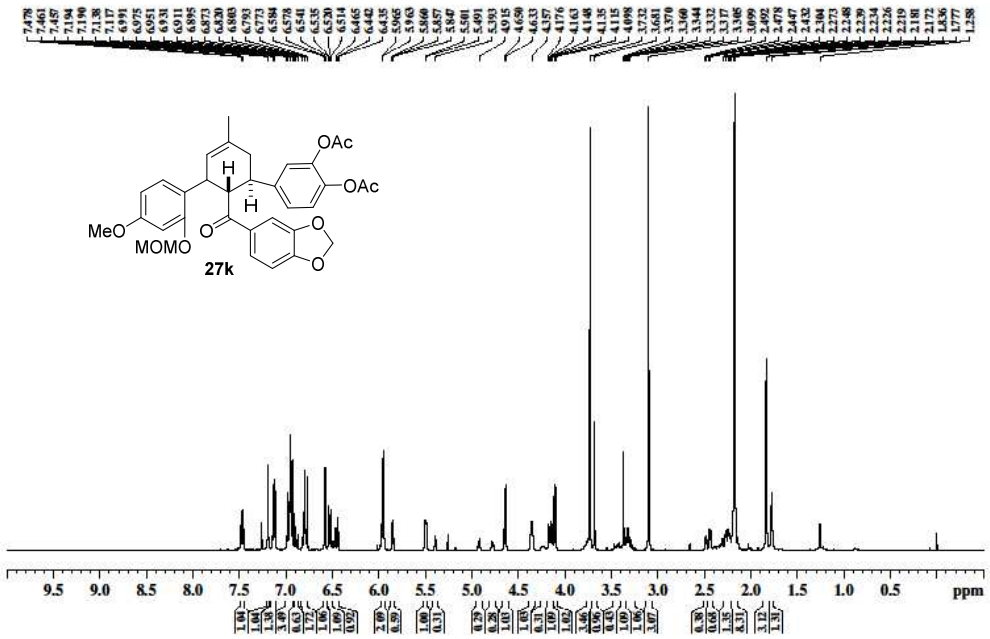
PRS–344 F3 400 MHz



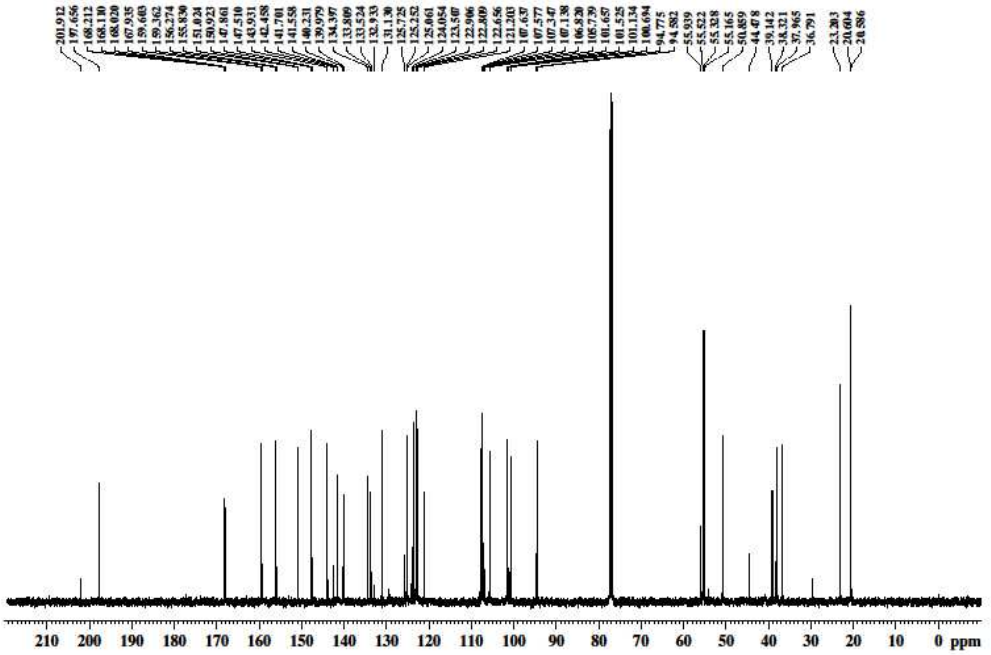
PRS–344 F3 400 MHz



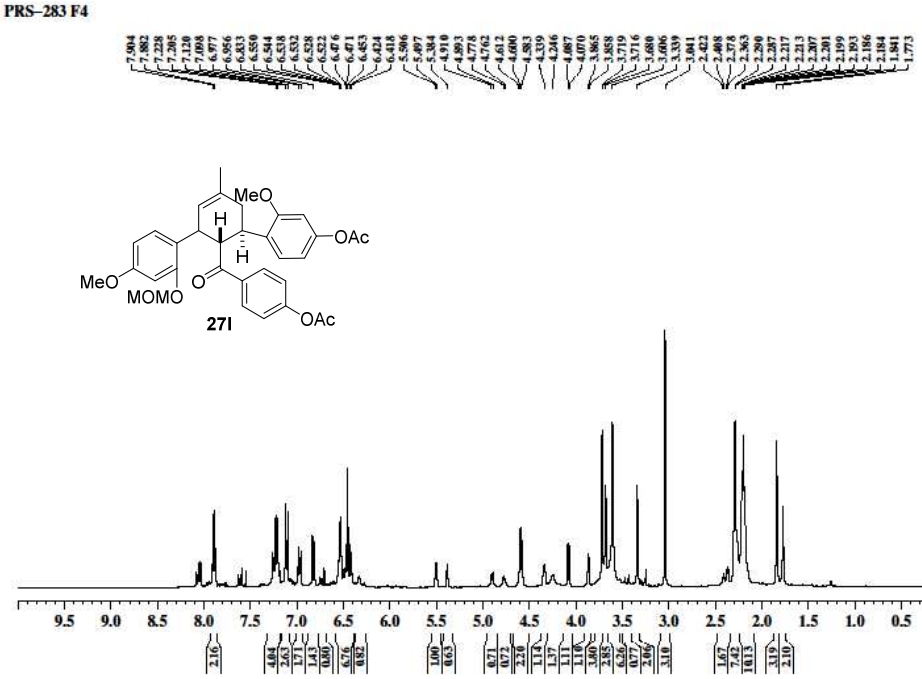
sw025–1 CDCl3 400 MHz



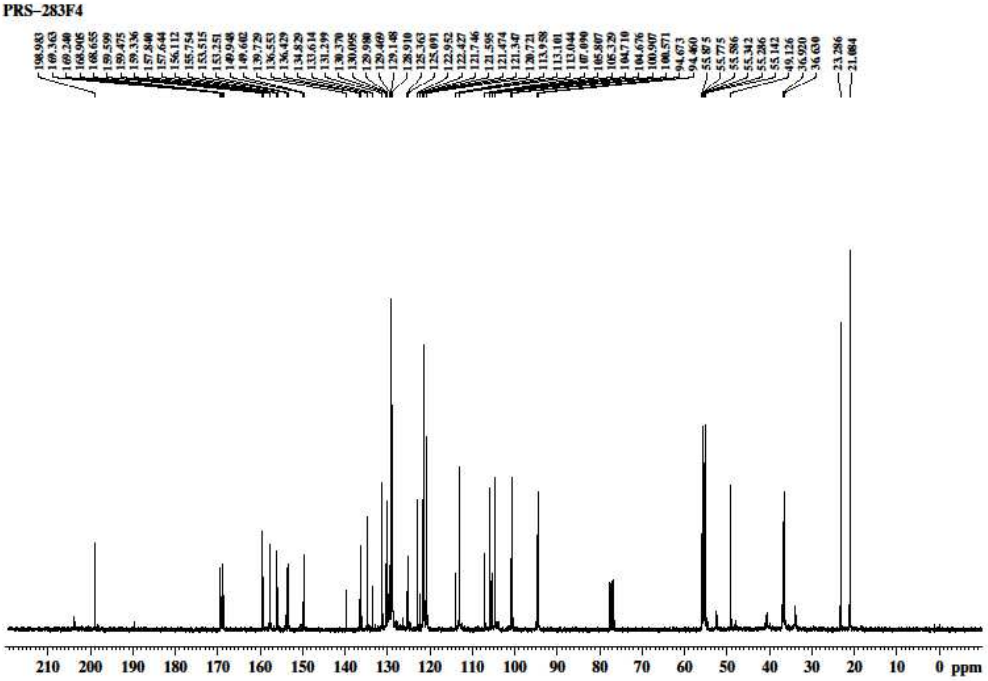
SW025_1 in CDCl3 NMR400



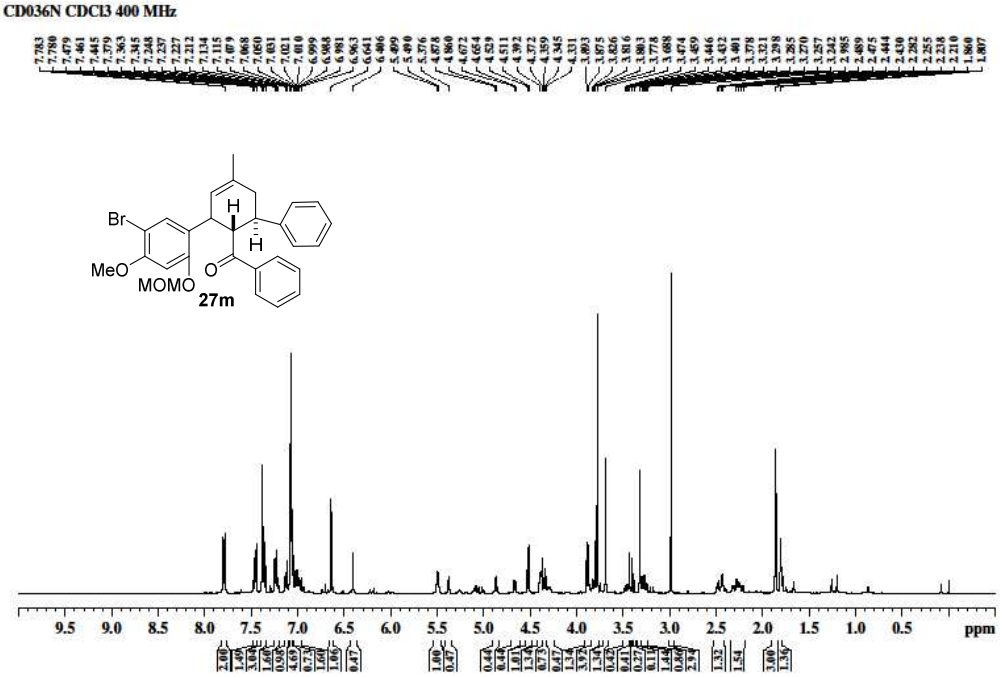
PRS–283 F4



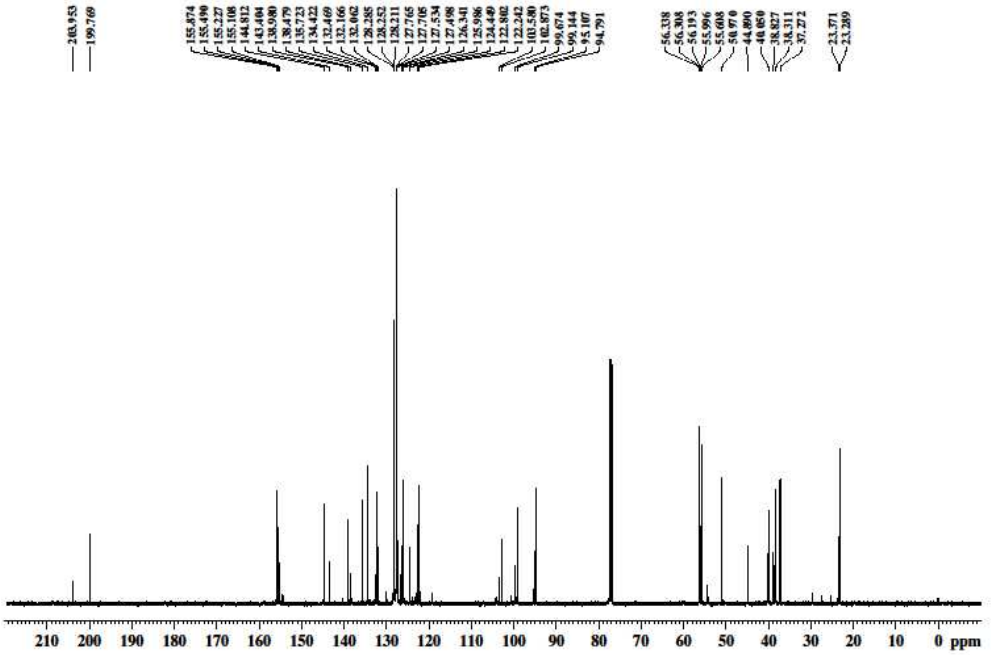
PRS–283F4



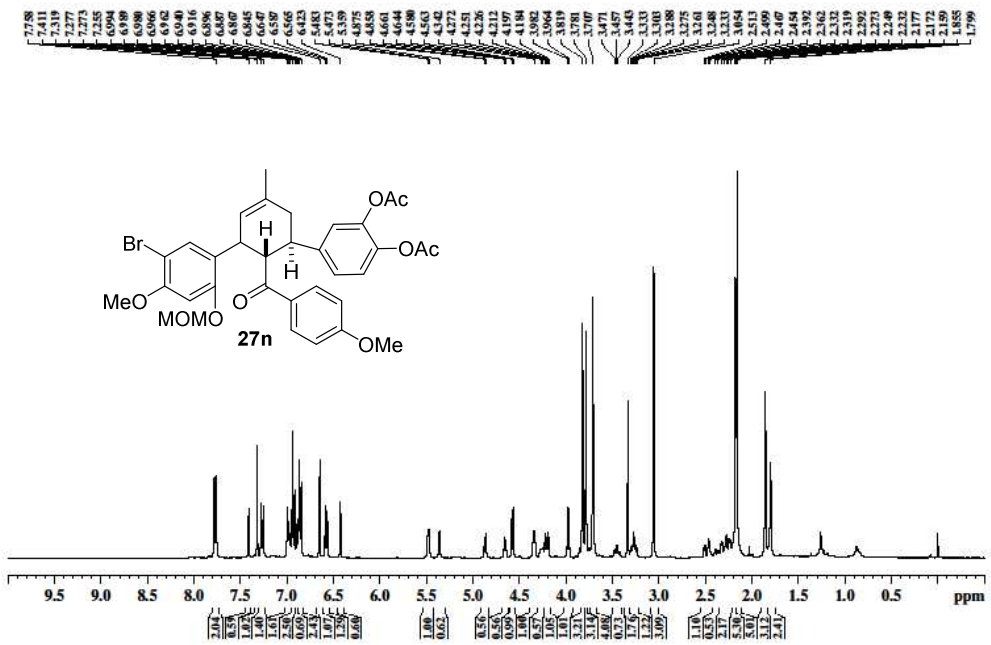
CD036N CDCl3 400 MHz



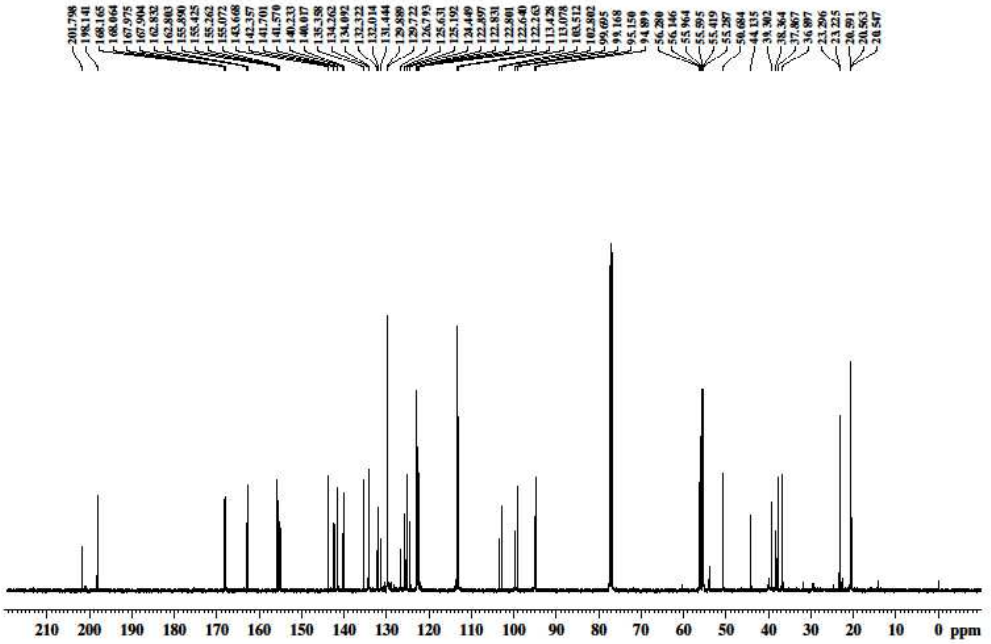
CD036N CDCl3 400 MHz



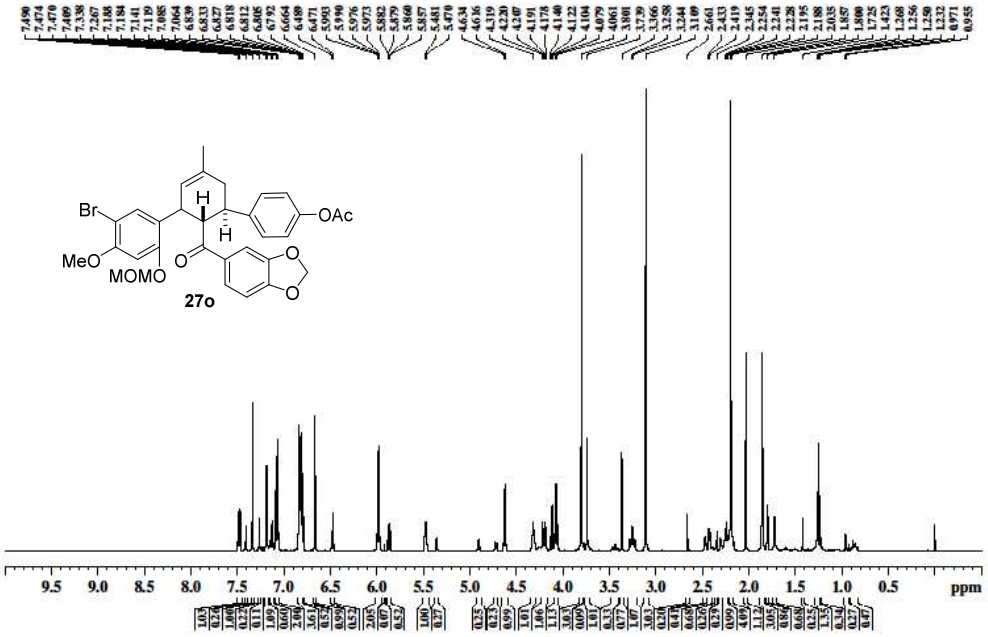
PRS–03–038F4 CDCl3 400 MHz



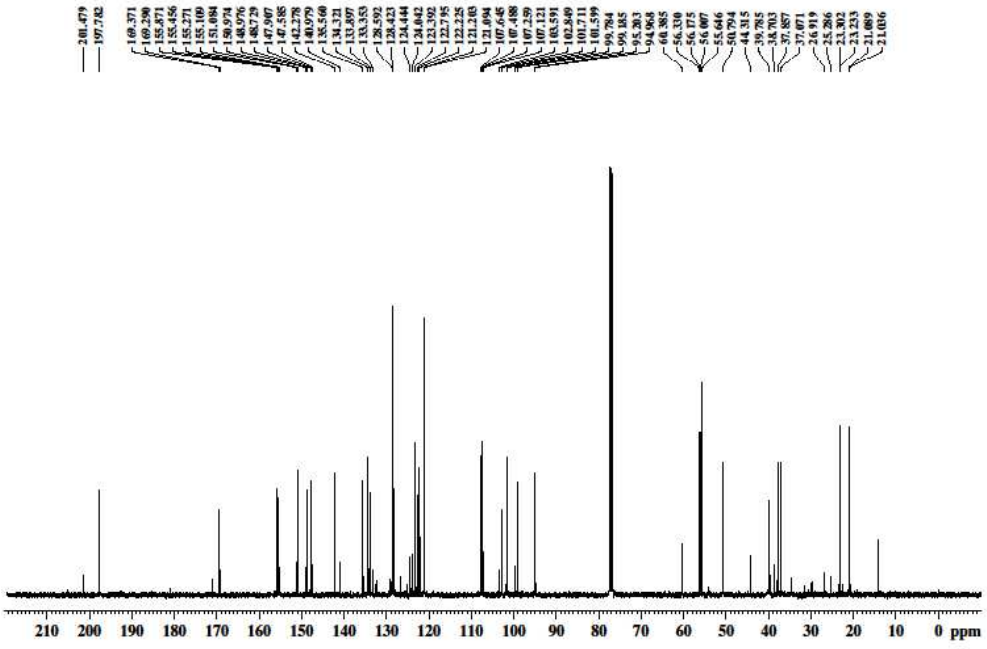
PRS–03–038F4 CDCl3 400MHz



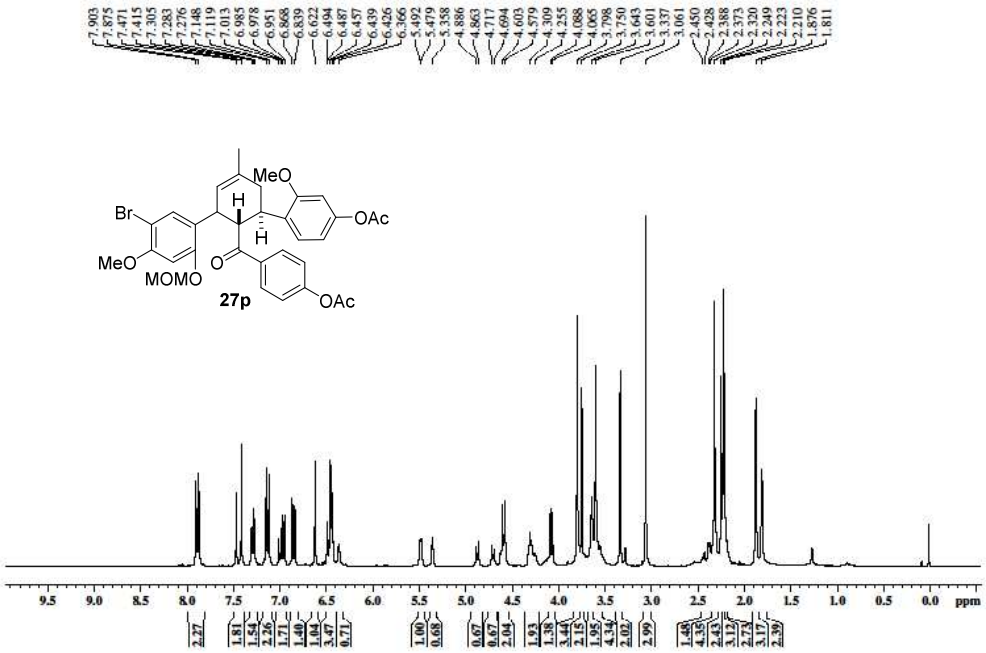
CD042 CDCl3 400MHz



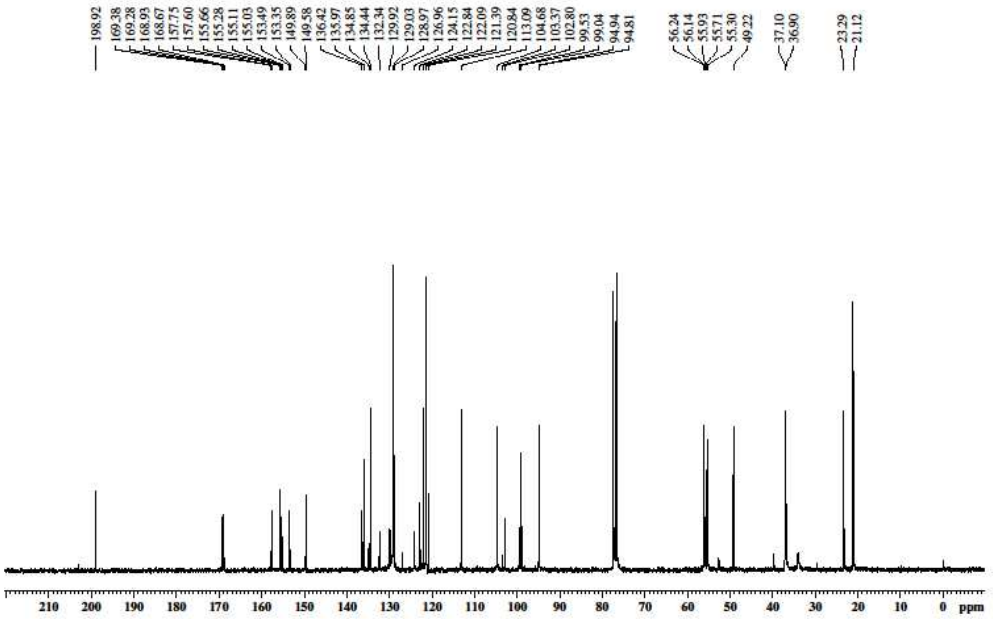
CD042 CDCl3 400MHz

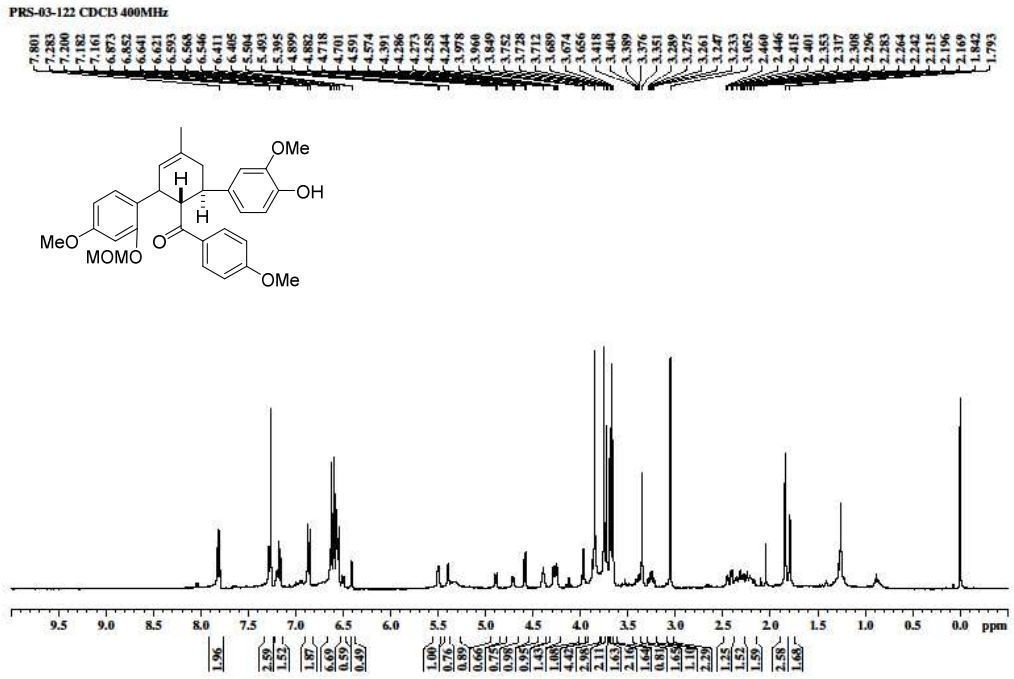


PRS-257 F1 CDCl3 300MHz



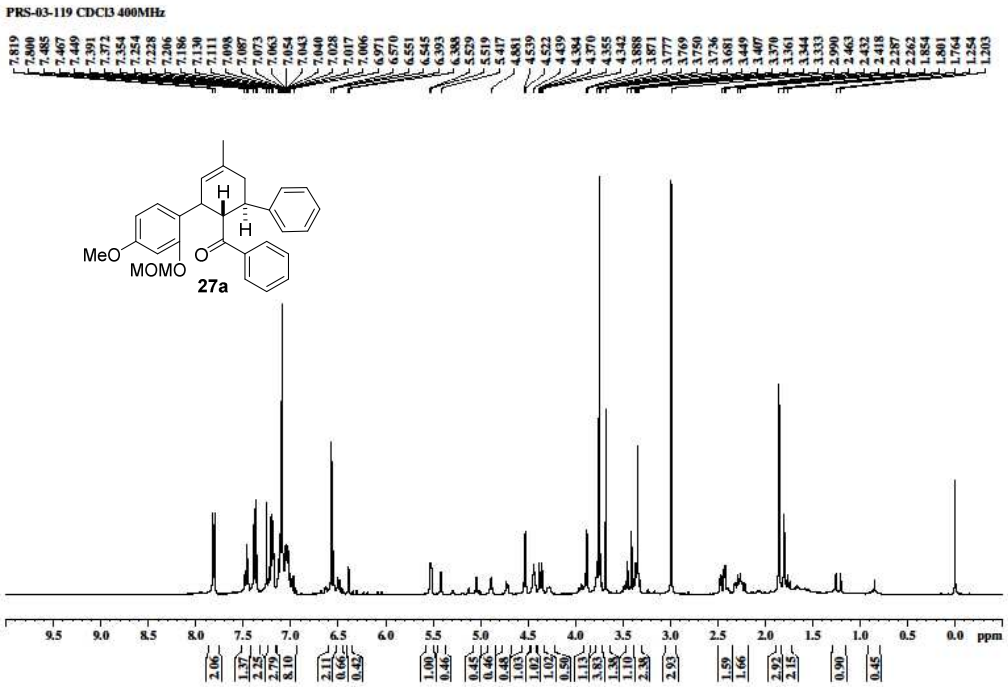
PRS-257 F1 CDCl3 300MHz





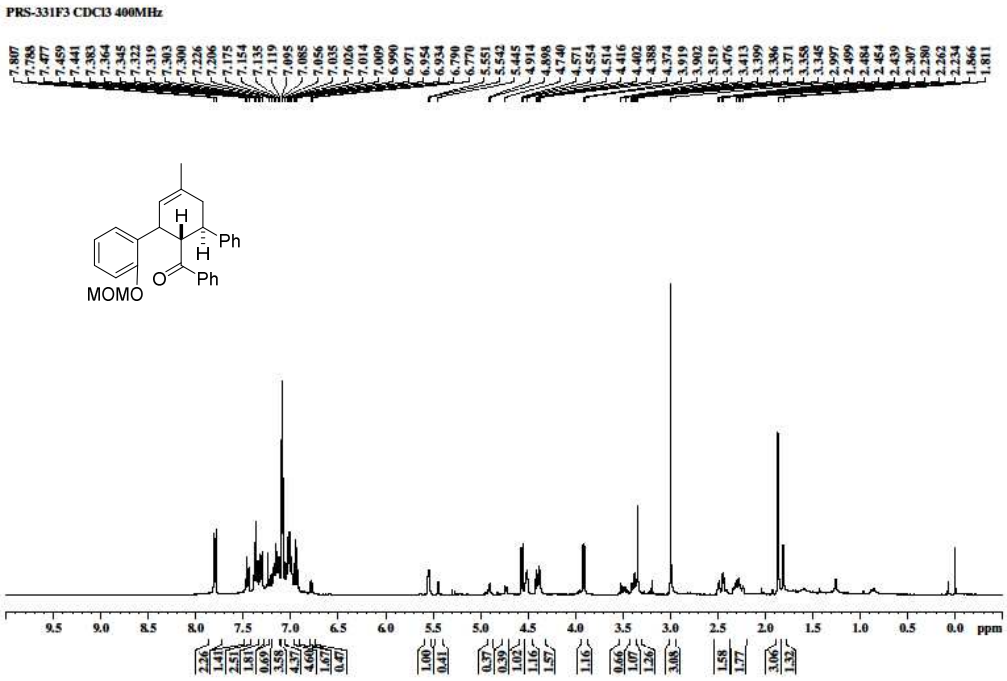
Crude ^{1}H NMR of treating **27e** with 1.0 equivalent of $LiAlH_4$, showing that only the acetate underwent reduction while the ketone was left intact (δ 7.80 (d, *J* = 12.0 Hz, 2H). There was NO C10a isomerization (2 sets of broad singlets at δ 5.50 and 5.49 of ca. 1.3:1 similar to the ratio of *endo*:*exo* of **27a** (1.2:1)).

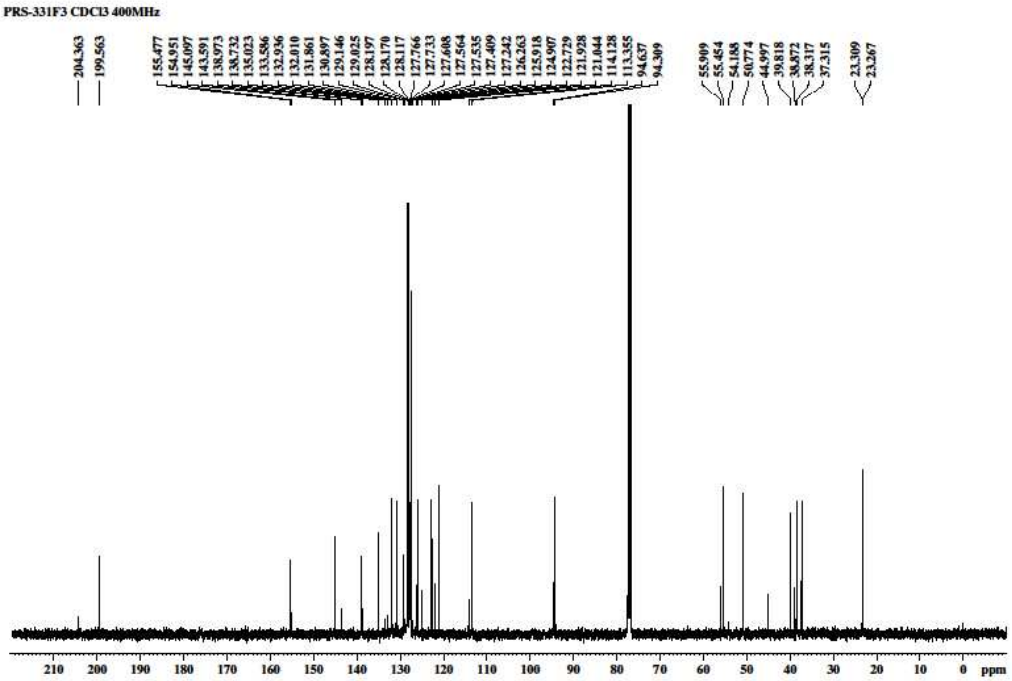
The spectra proved the existence of the intermediate **A (A1** and **A2)** proposed in Scheme 5 of the manuscript.



Crude ^{1}H NMR showed that NO C10a isomerization was detected when **27a** was treated under basic conditions (Cs_2CO_3 or NaOH in EtOH).

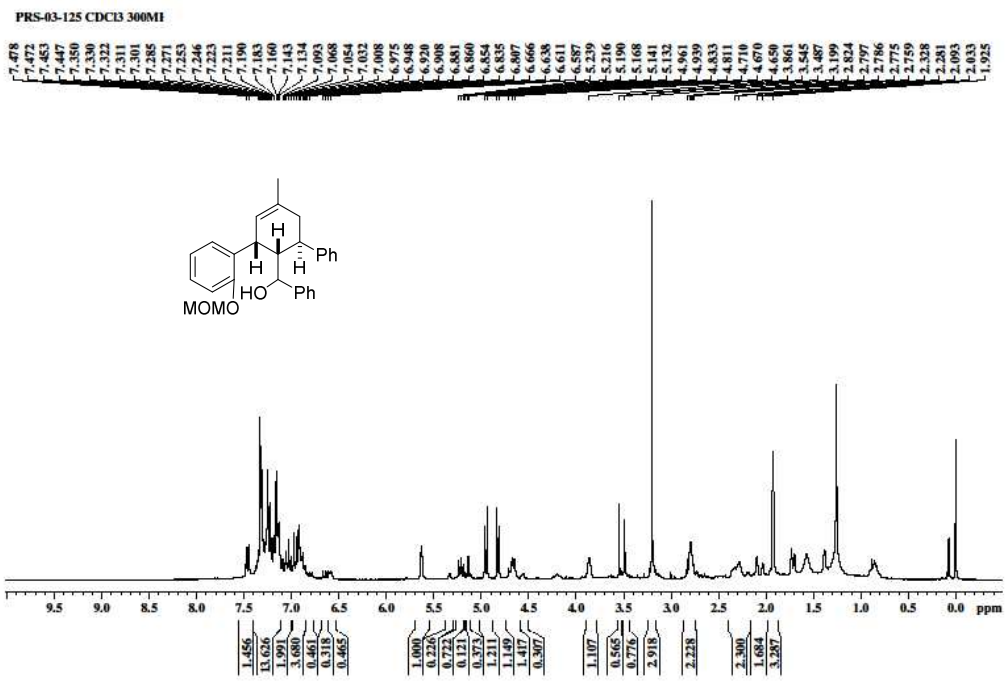
The spectra provided a proof that $LiAlH_4$ was required for the C10a isomerization.





Following the General Procedure for the Diels-Alder reaction described in the Experimental Section of the manuscript, the desired product was obtained as a white gummy solid (95.7 mg, 0.22 mmol, 50.0%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.80 (s, 3H, major), 1.87 (s, 3H,

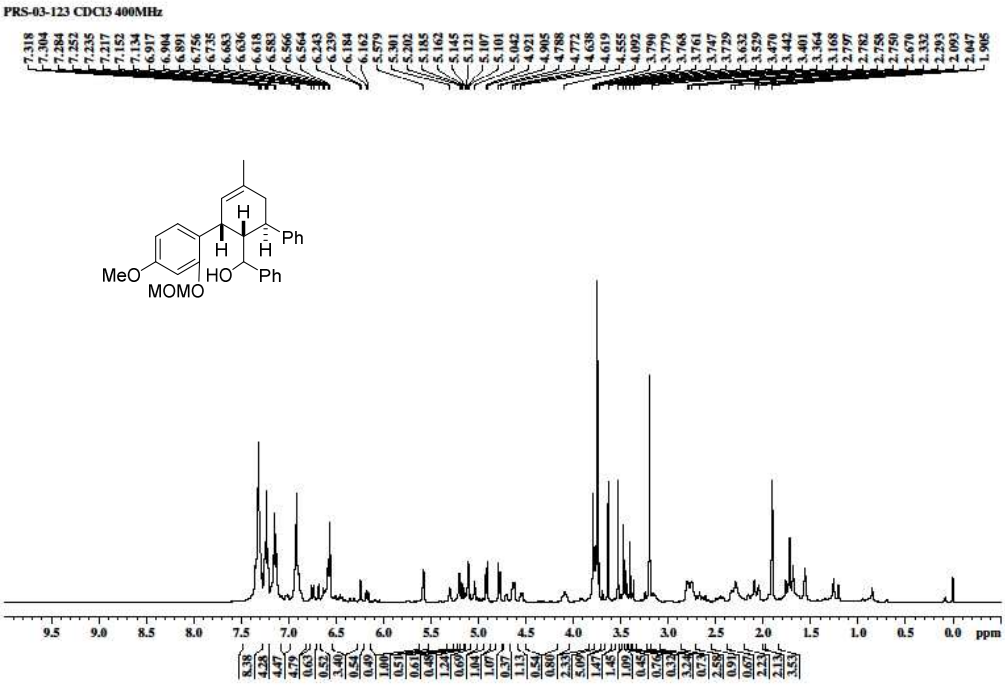
minor), 2.23−2.33 (m, 1H, major), 2.23−2.33 (m, 1H, minor), 2.47 (dd, *J* = 18.0, 6.0 Hz, 1H, major), 2.43−2.49 (m, 1H, minor), 2.99 (S, 3H, major), 3.35 (S, 3H, minor), 3.36−3.41 (m, 1H, major), 3.45−3.52 (m, 1H, minor), 3.91 (d, *J* = 6.8 Hz, 1H, major), 4.39 (dd, *J* = 11.2, 5.6, Hz, 1H, major), 4.37−4.41 (m, 1H, minor), 4.51 (br s, 1H, major), 4.56 (d, *J* = 6.7 Hz, 1H, major), 4.72 (d, *J* = 6.7 Hz, 1H, minor), 4.91 (d, *J* = 9.2 Hz, 1H, minor), 5.45 (br s, 1H, minor), 5.54 (br d, *J* = 3.8 Hz, 1H, major), 6.78 (d, *J* = 8.0 Hz, 1H, minor), 6.94 (d, *J* =8.0 Hz, 2H, major), 6.97−7.06 (m, 4H) ,7.08 (d, *J* = 4 Hz, 4H), 7.12−7.23 (m, 4H), 7.30 (dd, *J* = 7.6, 1.2, Hz, 2H), 7.36 (t, *J* = 7.6 Hz, 2H), 7.46 (t, *J* = 7.2 Hz, 1H), 7.79 (d, *J* = 7.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.3 (major), 23.3 (minor), 37.3 (major), 38.3 (major), 38.9 (major), 39.8 (minor), 44.9 (major), 50.8 (major), 55.5 (major), 55.9 (minor), 94.3 (major), 94.6 (minor), 113.4 (major), 114.1 (minor), 121.0 (major), 121.9 (minor), 122.7 (major), 124.9 (minor), 125.9 (major), 126.3 (minor), 127.2 (minor), 127.4 (major), 127.5 (major), 127.6 (major), 127.6 (minor), 127.7 (minor), 127.8 (minor), 128.1 (minor), 128.2 (major), 128.2 (major), 129.1 (minor), 130.8 (major), 131.9 (minor), 130.9 (major), 131.9 (minor), 132.0 (major), 132.9 (minor), 133.6 (minor), 135.0 (major), 138.7 (minor), 138.9 (major), 143.6 (minor), 145.1 (major), 154.9 (minor), 155.5 (major), 199.6 (major), 204.4 (minor). IR (UATR): ν_{max} 2930, 2908, 2828, 1681, 1598, 1486 cm^{-1}. LRMS (EI): m/z (rel intensity) 105 (100), 247 (21), 263 (36), 367 (22), 412 (M^+, 6). TOF-HRMS: calcd for $C_{28}H_{28}O_3Na$ (M + Na^+) 435.1931, found 435.1936.



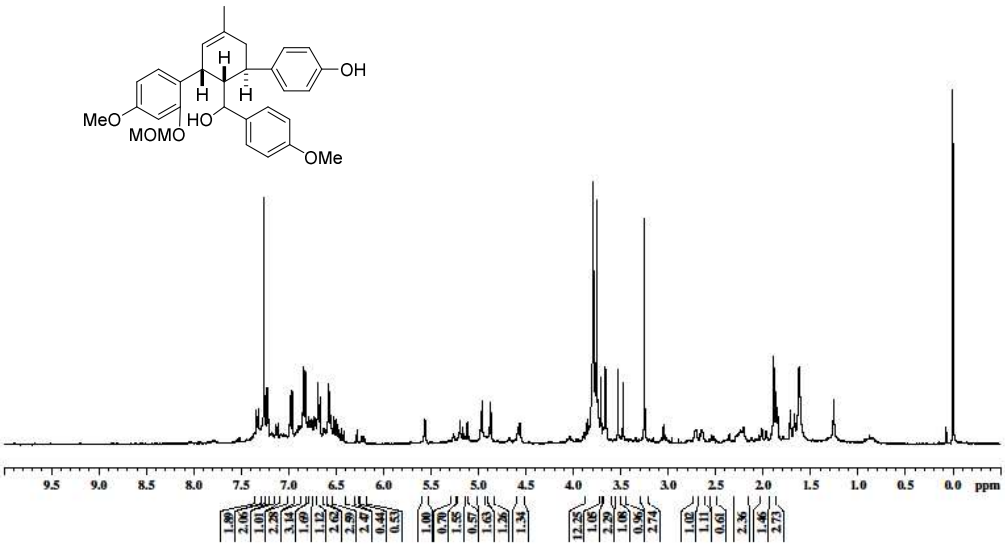
Crude ^{1}H NMR showed that the $LiAlH_4$ of this substrate provided the structure drawn as the major product. This was demonstrated by the presence of peaks at δ 5.63 (br s, 1H), 4.95 (d, *J* = 6.6 Hz, 1H), 4.82 (d, *J* = 6.6 Hz, 1H), 3.86 (br s, 1H), 3.20 (s, 3H).

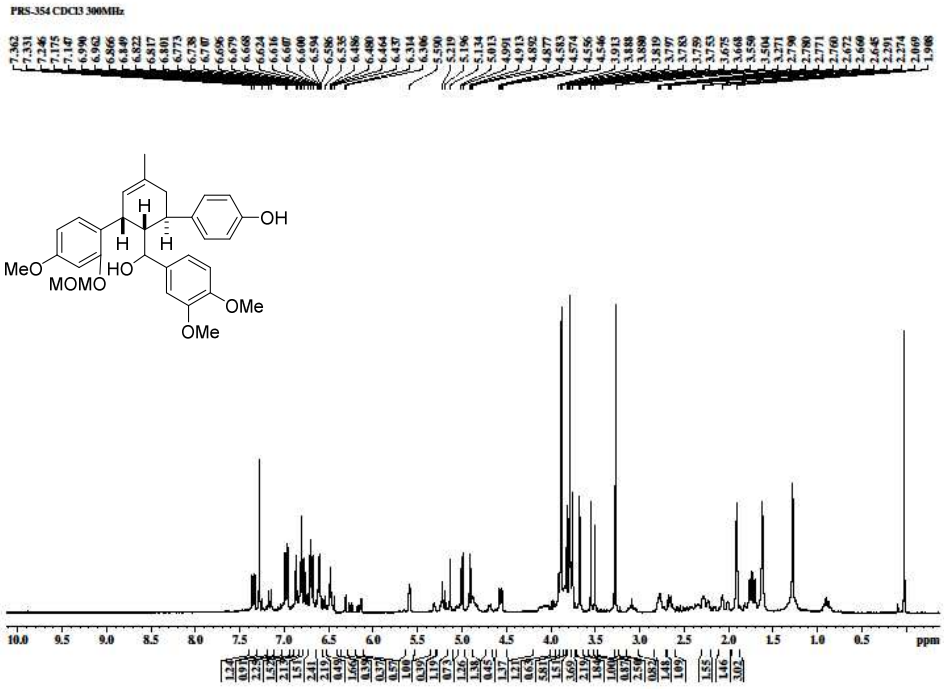
This provided a proof that during this step, both keto-carbonyl reduction and C10a isomerization took place. In addition, it supported the existence of the intermediate **A1** over **A2**.

PRS-03-123 CDCl3 400MHz

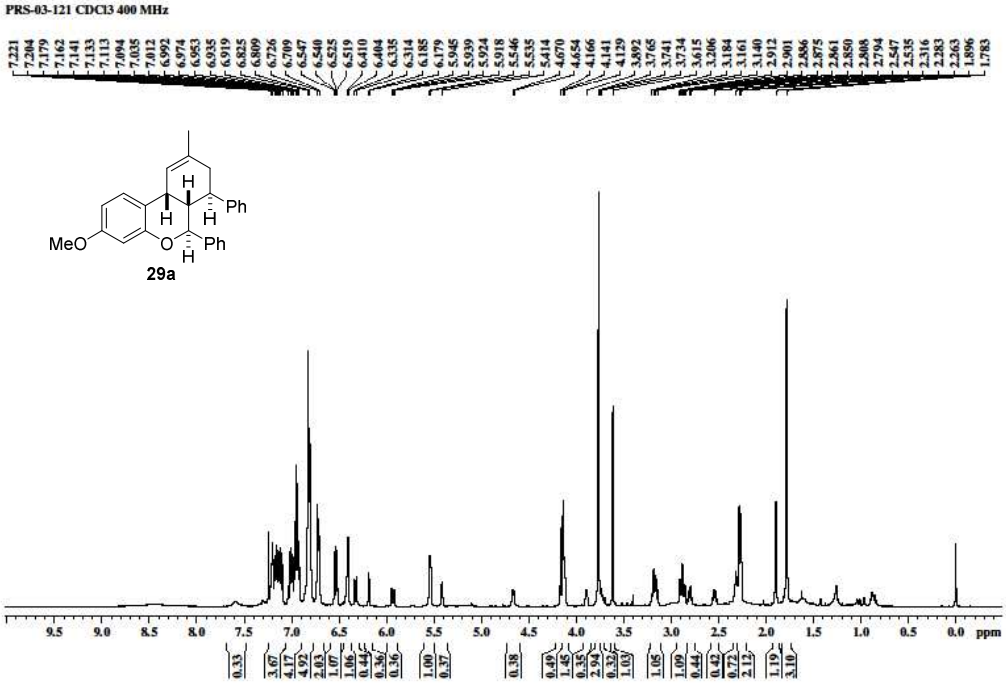


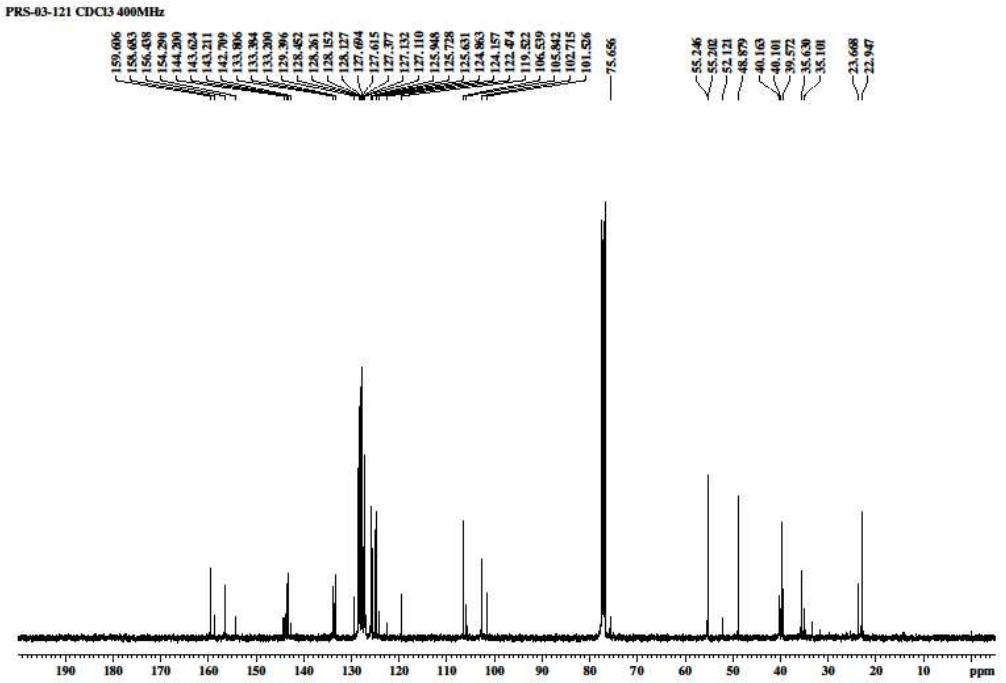
PRS-03-124 CDCl3 400MHz



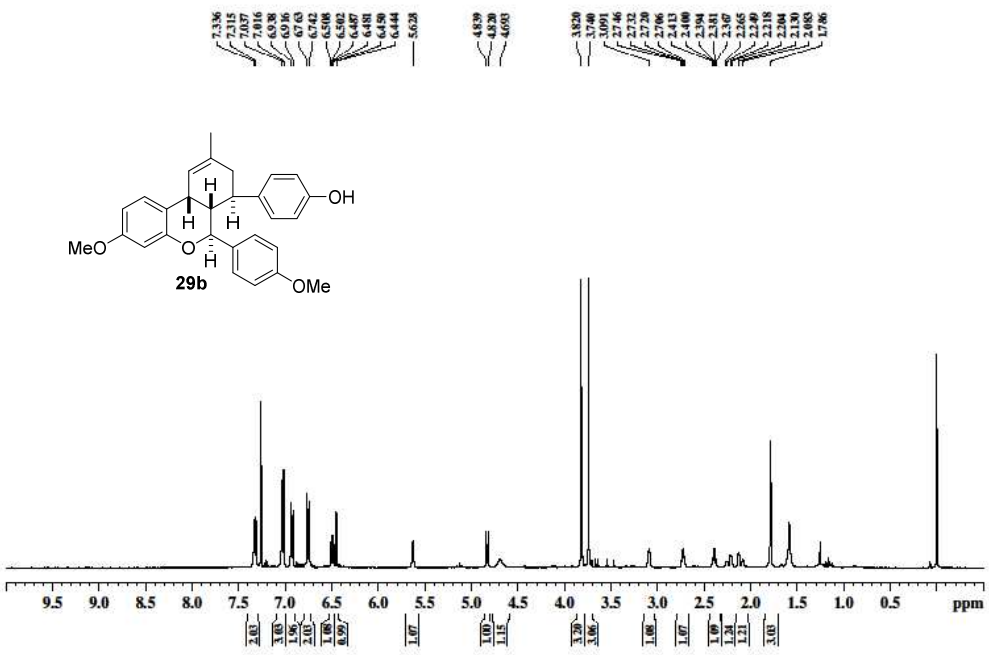


Similarly, crude ^{1}H NMR of **27a**, **27b**, and **27i** all demonstrated the existence of the intermediate **A1** as the major products during the $LiAlH_4$ reduction/C10a isomerization to furnish the corresponding alcohols with all three stereocenters at C6a, C7, and C10a matching those in the natural palodesangrens.

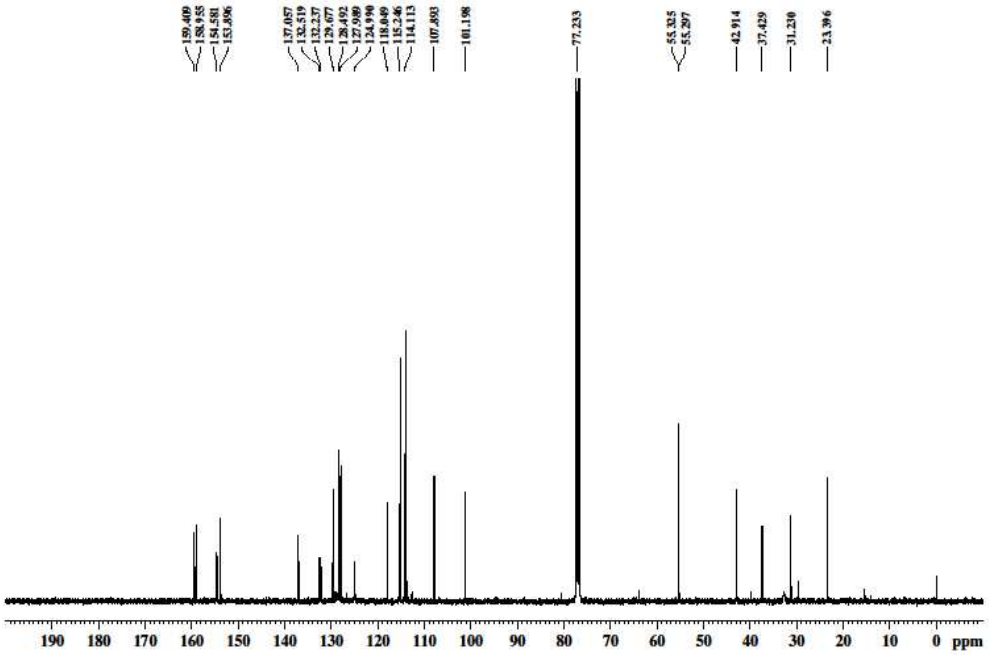

PRS-03-121 CDCl3 400 MHz
MeO
Ph
Ph
H
H
H
O
29a
ppm


PRS-03-121 CDCl3 400MHz
ppm

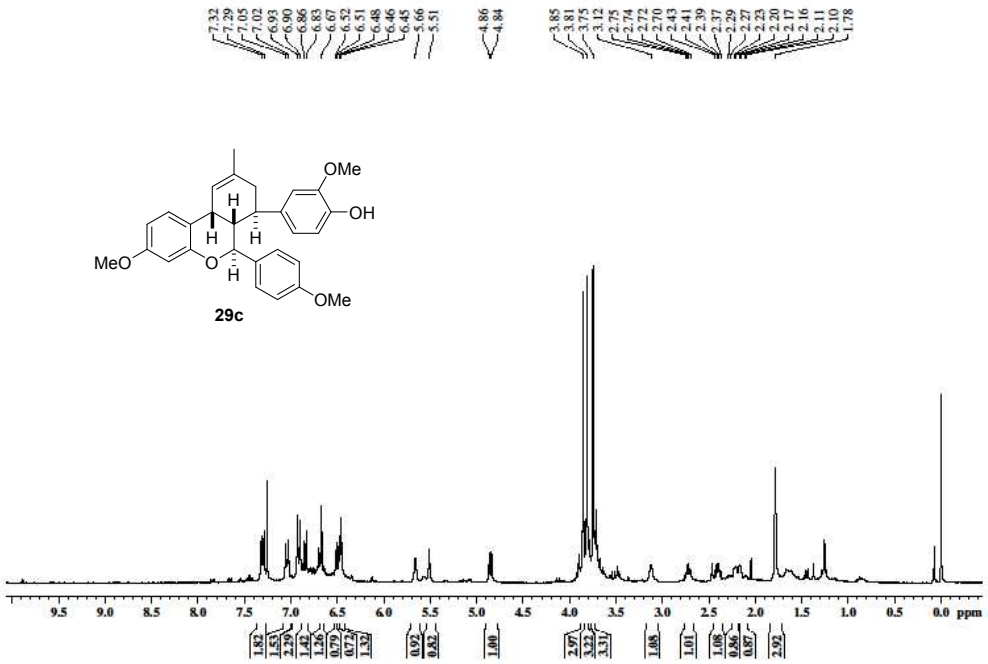
PRS–299 F2 CDCl3 400MHz



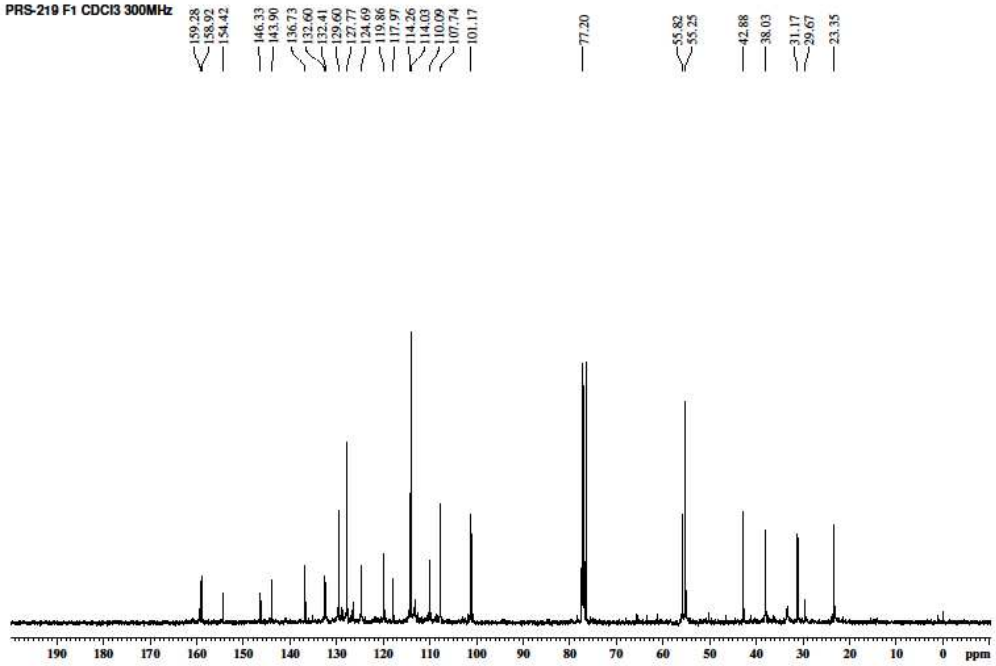
PRS–299F2 400MHz CDCl3



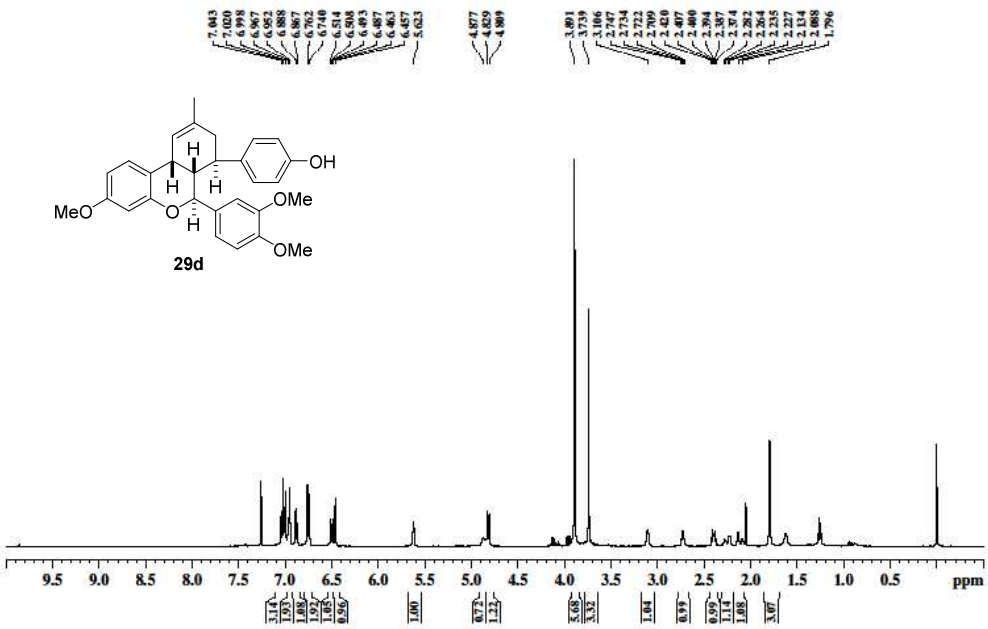
PRS-219 F1 CDCl3 300MHz



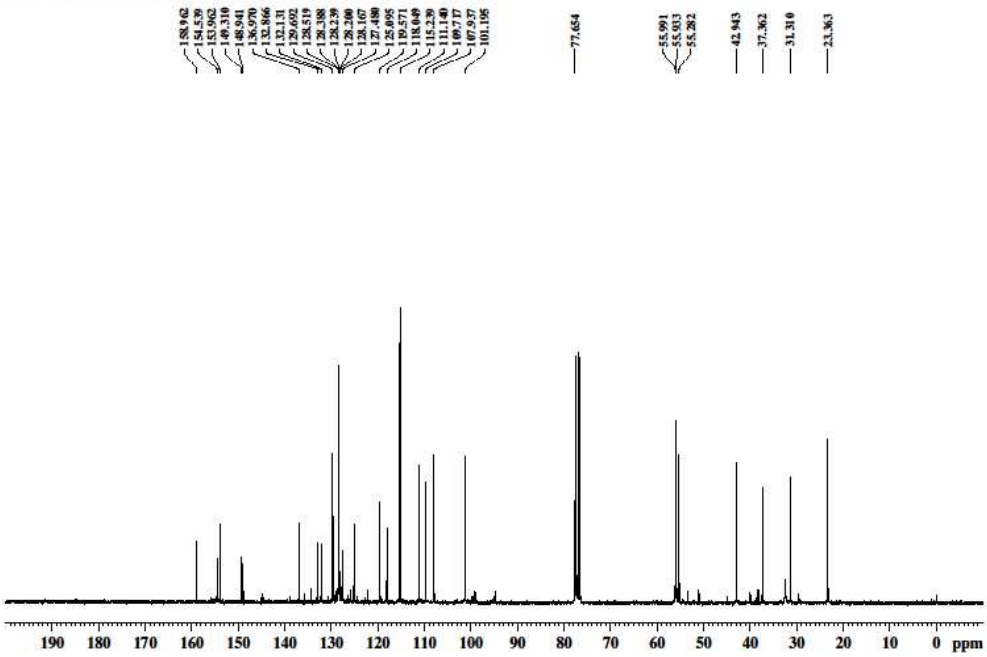
PRS-219 F1 CDCl3 300MHz

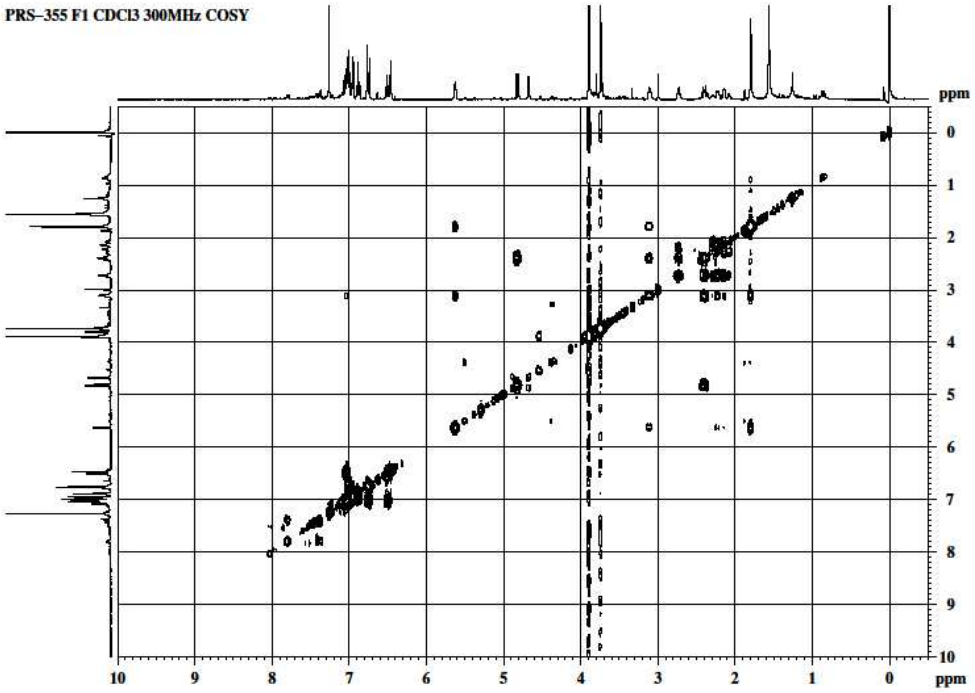


PRS–355–F1 in CDCl3 NMR400

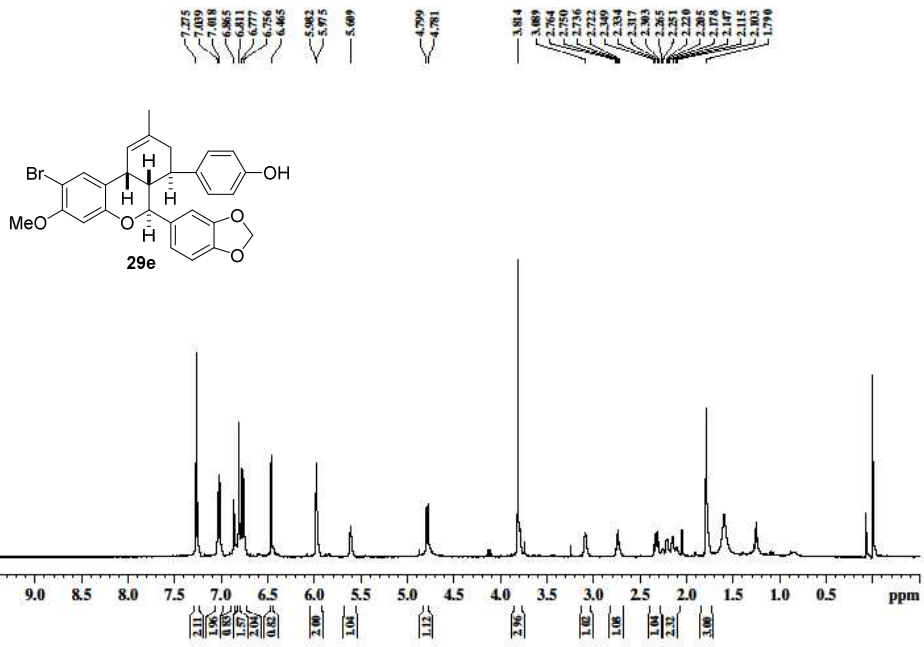


PRS–355 F1 CDCl3 400 MHz

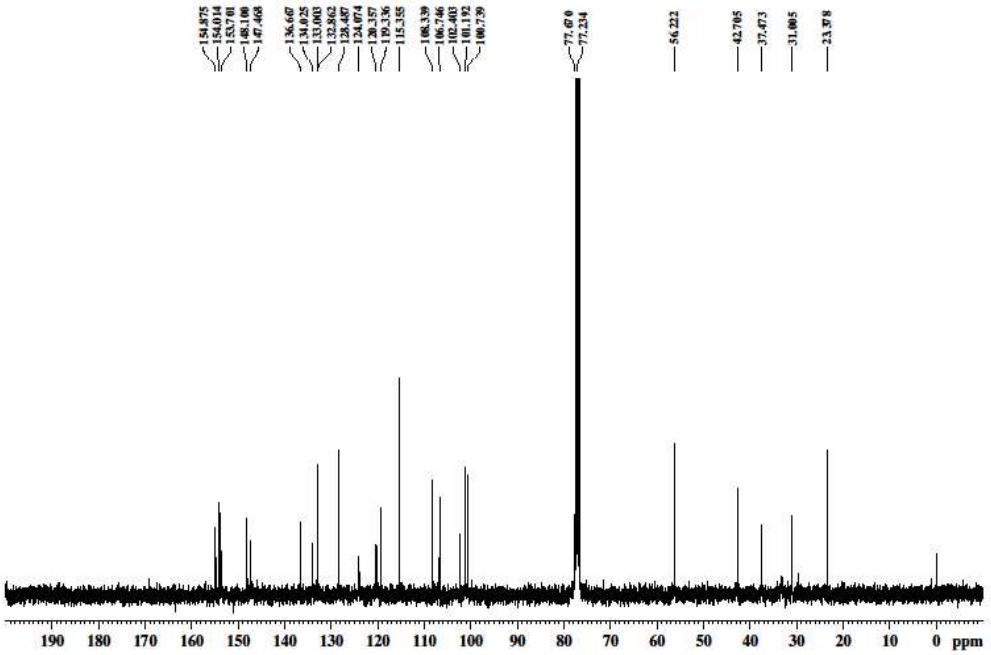



PRS–355 F1 CDCl3 300MHz COSY
ppm
0
1
2
3
4
5
6
7
8
9
10
10
9
8
7
6
5
4
3
2
1
0
ppm

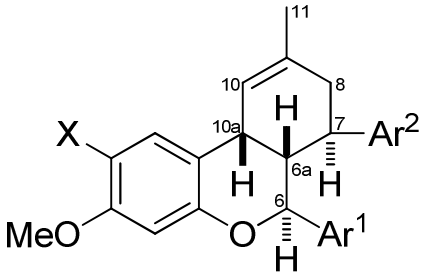
PRS359 F1 CDCl3 400MHz



PRS–359 F1 CDCl3 400MHz



Comparison of spectral assignments for 29a-e



comp	H_6	C_6	H_{10}	H_{10a}	H_{11}
29a	4.80 (d, *J* = 7.4 Hz, 1H)	77.5	5.43 (br s, 1H)	3.80 (br s, 1H)	1.79 (s, 3H)
29b	4.83 (d, *J* = 7.6 Hz, 1H)	77.2	5.63 (br s, 1H)	3.09 (br s, 1H)	1.79 (s, 3H)
29c	4.85 (d, *J* = 7.2 Hz, 1H)	77.2	5.66 (br s, 1H)	3.12 (br s, 1H)	1.78 (s, 3H)
29d	4.82 (d, *J* = 8.0 Hz, 1H)	77.7	5.62 (s, 1H)	3.11, (br s, 1H)	1.79 (s, 3H)
29e	4.79 (d, *J* = 7.2 Hz, 1H)	77.7	5.61 (br s, 1H)	3.09 (br s, 1H)	1.79 (s, 3H)

From the above table, the stereochemistry of **29a** at C6, C6a, and C7 could be established to follow those of **29b-e**. The stereochemistry at C10a was established as shown based on the fact that during $LiAlH_4$ step, **27a** underwent both reduction and C10a isomerization and thus would have the stereocenters at C6a, C7, and C10a as shown although the chemical shift value of H_{10a} at δ 3.80 was significantly different from H_{10a} of **29b-e**. The stereochemistry at C6 of **29a** was established based on the *J* value of approximately 7.2-8.0 Hz.