Quick and easy access to N-Mannich bases of 1-isoindolinones by catalytic electroactivation of primary and secondary amines and tandem reaction with 2-formylbenzonitriles

Laura Palombi,[*a] Antonia Di Mola[b] and Antonio Massa[a]

lpalombi@unisa.it

General remarks. All reactions were performed using commercially available compounds without further purification and technical grade solvents. All the reactions were monitored by thin layer chromatography (TLC) using *Merck Silica Gel 60 F254* plates and were visualized by fluorescence quenching at 254 nm. Column chromatographic purification of products was carried out using silica gel 60 (70–230 mesh, Merck). The NMR spectra were recorded on Bruker DRX 400, 300, 250 spectrometers (400 MHz, 300 MHz, 250 MHz, ^{1}H; 100 MHz, 75 MHz, 62,5 MHz ^{13}C). Spectra were referenced to residual $CHCl_3$ (7.26 ppm, ^{1}H; 77.00 ppm, ^{13}C) or $(CH_3)_2SO$ (2.5 ppm, ^{1}H; 39.52 ppm, ^{13}C) when indicated. Yields are given for isolated products showing one spot on a TLC plate and no impurities detectable in the NMR spectrum. Mass spectral analyses were carried out using an electrospray spectrometer, Waters 4 micro quadrupole. Elemental analyses were performed with FLASHEA 1112 series-Thermo Scientific for CHNS-O apparatus. Constant current electrolyses were performed using an Hewlett Packard DC Power Supply Mod. E3612A. The experiments were carried out in the cathodic compartment of a U-divided glass cell separated through a porous G-4 glass plug. Platinum spirals (apparent area 1 cm^2) were used as anode and cathode. In all the experiment the anolyte was constituted by a solution of $TEABF_4$ 0.05 M in CH_3CN.

Typical experimental procedure for electro-induced synthesis of isoindolinones 1 in CH_3CN: A solution of **2** (0.21 mmol) and **3** (0.2 mmol) in $CH_3CN/TEABF_4$ (0.4 ml/0.03 mmol) was electrolyzed at r.t., under galvanostatic conditions (8 mA, 0.025 electrons/molecule of **3**). At the end of the electrolysis, TLC analyses showed disappearance of **3** and the reaction was in any case prolonged at r.t. under magnetic stirring for 2h. The mixture was then concentrated *in vacuum* and directly purified by silica gel chromatography (hexane: AcEt= 2:1; CH_3Cl: AcEt = 9:1 or CH_3Cl: MeOH= 9:1).

Spectroscopic and analytical data for isoindolinone derivatives 1

3-(benzylamino)isoindolin-1-one (1aa): Amorphous solid; NMR ($CDCl_3$): 7.84-7.82 (2H, m); 7.82-7.47 (4H, m); 7.37-7.11 (4H, m); 5.55 (1H, s); 3.90 (1H, d, J= 13.2 Hz); 3.75 (1H, d, J= 13.2 Hz); 1.99 (1H, bs). C: 170.6; 145.4; 139.5; 132.2; 129.2; 128.5; 128.1; 127.2; 123.7; 123.4; 70.2; 48.6. MS (ESI): *m*/*z* = 261 (M + Na^+). Anal. Calcd for $C_{15}H_{14}N_2O$: C, 75.61; H, 5.92; N, 11.76; O, 6.71. Found: C, 75.63; H, 5.94; N, 11.75;

3-(benzylamino)-6-bromoisoindolin-1-one (1ba): Amorphous solid; NMR ($CDCl_3$): H: 7.95 (1H, d, J= 7.8 Hz); 7.70 (1H, d, J= 8.0 Hz); 7.50 (1H, d, J=8 Hz); 5.50 (1H, s); 3.90 (1H, d, J= 12 Hz); 3.75 (1H, d, J= 12 Hz); 1.78 (1H, bs). C: 168.6; 144.1; 139.3; 135.2; 134.1; 128.6 (2C); 128.1 (2C); 127.5; 126.7; 125.4; 123.4; 69.9; 48.76. MS (ESI): *m*/*z* = 318 (M + H^+). Anal. Calcd for $C_{15}H_{13}BrN_2O$: C, 56.80; H, 4.13; Br, 25.19; N, 8.83; O, 5.04. Found: C, 56.82; H, 4.15; N, 8.80;

3-((3,5-bis(trifluoromethyl)benzyl)amino)isoindolin-1-one (1ab): Amorphous solid; NMR ($(CD_3)_2SO$): H: 8.87 (1H, s); 7.99 (2H, s); 7.91 (1H, s); 7.63-7.45 (4H, m); 5.42 (1H, d, J=8.0 Hz); 3.87 (1H, m, dd, J_1=16.0 Hz; J_2=8.); 3.75 (1H, dd, J_1=16.0 Hz; J_2=8.0 Hz); 3.58-3.53 (1H, m). C: 169.3; 146.2, 145.0; 133.3; 132.1; 130.8; 130.5(2C, q, $^{1}J_{CF}$=270Hz); 129.3; 129.0; 125.3; 124.2; 122.9; 122.6; 120.7; 120.7; 69.8; 46.8. MS (ESI): *m*/*z* = 375 (M + H^+). Anal. Calcd for $C_{17}H_{12}F_6N_2O$: C, 54.55; H, 3.23; F, 30.46; N, 7.48; O, 4.27 Found: C, 54.55; H, 3.25; F, 30.43; N, 7.50.

3-((4-chlorobenzyl)amino)isoindolin-1-one (1ac): Amorphous solid; NMR ($(CD_3)_2SO$): H: 8.88 (1H, s); 7.65-7.35 (8H, m); 5.35 (1H, d, J= 8.0 Hz); 3.73-3.59 (2H, m); 3.20-3.17 (1H, m). C: 169.3; 146.4; 140.1;

133.3; 132.1; 131.5; 130.2; 129.2; 128.5; 128.4; 124.2; 122.9; 69.9; 47.4. (ESI): *m*/*z* = 273 (M + H^+). Anal. Calcd for $C_{15}H_{13}ClN_2O$: C, 66.06; H, 4.80; Cl, 13.00; N, 10.27; O, 5.87. Found: C, 66.07; H, 4.82; N, 10.28

3-(benzyl(methyl)amino)isoindolin-1-one (1ad): Amorphous solid; NMR ($CDCl_3$): H 7.86 (1H, d, J= 8.0 Hz); 7.77-7.24 (9H, m); 5.56 (1H, s); 3.63 (2H, s); 2.19 (3H, s). C: 170.96; 144.92; 138.48; 132.56; 132.24; 129.15; 128.65; 128.43; 127.27; 123.68; 123.47; 75.58; 56.73; 36.28. (ESI): *m*/*z* = 253 (M + H^+). Anal. Calcd for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10; O, 6.34. Found: C, 76.19; H, 6.41; N, 11.11.

3-(dibenzylamino)isoindolin-1-one (1ae): Amorphous solid; NMR ($CDCl_3$): H: 7.93 (1H, s); 7.88 (1H, d, J=8.0 Hz); 7.67 (1H, d, J=8.0 Hz); 7.60 (1H, t, J=8.0 Hz); 7.58-7.25 (11H, m); 5.56 (1H, s); 3.70 (2H, d, J=16.0 Hz); 3.58 (2H, d, J= 16.0 Hz). C: C: 171.0; 145.4; 138.6 (2C); 132.8; 132.3; 129.1; 128.8 (4C); 128.5 (4C); 128.2; 127.3; 123.5 (2C); 72.3; 53.0 (2C). (ESI): *m*/*z* = 329 (M + H^+). Anal. Calcd for $C_{22}H_{20}N_2O$: C, 80.46; H, 6.14; N, 8.53; O, 4.87. Found: C, 80.48; H, 6.15; N, 8.53.

3-(butylamino)isoindolin-1-one (1af): Amorphous solid; NMR ($CDCl_3$): H: 7.80 (1H, d, J= 7.6 Hz); 7.72 (1H, s); 7.58-7.47 (3H, m); 5.49 (1H, s); 2.73-2.67 (1H, m); 2.59-2.52 (1H, m); 1.50-1.43 (2H, m); 1.43-1.32 (2H, m); 0.87 (3H, t, J= 7.3 Hz). C: C: 170.6; 145.7; 132.2; 132.1; 129.1; 123.6; 123.3; 70.7; 44.1; 32.5; 20.3; 13.9. (ESI): *m*/*z* = 205 (M + H^+). Anal. Calcd for $C_{12}H_{16}N_2O$: C, 70.56; H, 7.90; N, 13.71; O, 7.83. Found: C, 70.55; H, 7.88; N, 13.73.

3-(cyclohexylamino)isoindolin-1-one (1ag): Amorphous solid; NMR ($CDCl_3$): H: 7.81 (1H, d, J=7.5Hz); 7.59-7.45 (3H, m); 6.83 (1H, s); 5.53 (1H, s); 2.74-2.65 (1H, m); 2.02-1.99 (1H, m); 1.75-1.63 (6H, m); 1.25-1.17 (5H, m). C: 170.2; 144.4; 132.1; 131.9; 129.0; 123.7; 123.4; 68.4; 53.3; 35.0; 33.5; 25.9; 24.8; 24.6. (ESI): *m*/*z* = 231 (M + H^+). Anal. Calcd for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.16; O, 6.95. Found: C, 73.04; H, 7.88; N, 12.17.

3-(pyrrolidin-1-yl)isoindolin-1-one (1ah): Amorphous solid; NMR ($CDCl_3$): H: 7.82 (1H, d, J=6 Hz); 7.60 (1H, s); 7.58-7.45 (3H, m); 5.70 (1H, s); 2.74-2.71 (2H, m); 2.51-2.48 (2H, m); 2.04 (1H, bs); 1.77-1.75 (4H, m). C: 171.2; 145.3; 132.1 (2C); 128.9; 123.7; 123.4; 72.4; 47.1 (2C); 23.8 (2C). (ESI): *m*/*z* = 203 (M + H^+). Anal. Calcd for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85; O, 7.91. Found: C, 71.27; H, 7.01; N, 13.84.

3-morpholinoisoindolin-1-one (1ai): Amorphous solid; NMR ($CDCl_3$): H: 7.83 (1H, d, J=7.3 Hz); 7.58-7.48 (3H, m); 6.99 (1H, bs); 5.41 (1H, s); 3.69 (4H, t, J=4.5 Hz); 2.71-2.63 (2H, m); 2.43-2.39 (2H, m). C: 170.8; 143.6; 132.6; 132.2; 129.3; 123.8; 123.6; 76.2; 66.9; 47.7. (ESI): *m*/*z* = 219 (M + H^+). Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84; O, 14.66. Found: C, 66.05; H, 6.49; N, 12.87.

3-(4-methylpiperazin-1-yl)isoindolin-1-one (1aj): Amorphous solid; NMR ($CDCl_3$): H: 7.82 (1H, d, J=8 MHz); 7.59-7.47 (4H, m); 5.43 (1H, s); 2.70 (2H, bs); 2.43 (6H, m); 2.27 (3H, s). C: 170.6; 144.0; 132.6; 132.1; 129.2; 123.8; 123.5; 76.0; 55.1; 46.0. (ESI): *m*/*z* = 232 (M + H^+). Anal. Calcd for $C_{13}H_{17}N_2O$: C, 67.51; H, 7.41; N, 18.17; O, 6.92. Found: C, 67.52; H, 7.40; N, 18.19.

3-((*(S)*-1-phenylethyl)amino)isoindolin-1-one (1la): *Less polar diastereoisomer:* Amorphous solid; NMR ($CDCl_3$): H: 7.93 (1H, s); 7.69 (1H, d, J= 7.98 Hz); 7.50-7.46 (3H, m); 7.41-7.37 (2H, m); 7.32-7.28 (2H, m); 5.09 (1H, s); 4.10-4.05 (2H, m); 1.80 (1H, bs); 1.38 (3H, d, J=6.4 Hz). C: C: 168.7 144.7; 143.8; 135.1; 133.8; 128.9 (2C); 127.9; 126.9 (2C); 126.6; 125.4; 123.3; 68.2; 55.4; 25.4 $[\alpha]_D^{28}$:-122.6 (*c* 0.47, $CHCl_3$). *More polar diastereoisomer:* Yellow pale oil; NMR ($CDCl_3$): H: 7.75 (1H, d, J=7.5 Hz); 7.53-7.30 (8H, m); 6.40 (1H, s); 5.45 (1H, s), 4.09 (1H, q, J= 7.5 Hz); 1.85 (1H, bs); 1.46 (3H, d, J= 7.5Hz). C: : 169.7; 146.0; 145.7; 132.0; 129.1; 128.9; 127.6; 126.4; 123.8; 123.3; 69.7; 56.2; 24.0. $[\alpha]_D^{26}$:+21.6 (*c* 0.5, $CHCl_3$). (ESI): *m*/*z* = 253 (M + H^+). Anal. Calcd for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10; O, 6.34; Found: C, 76.19; H, 6.41; N, 11.12.

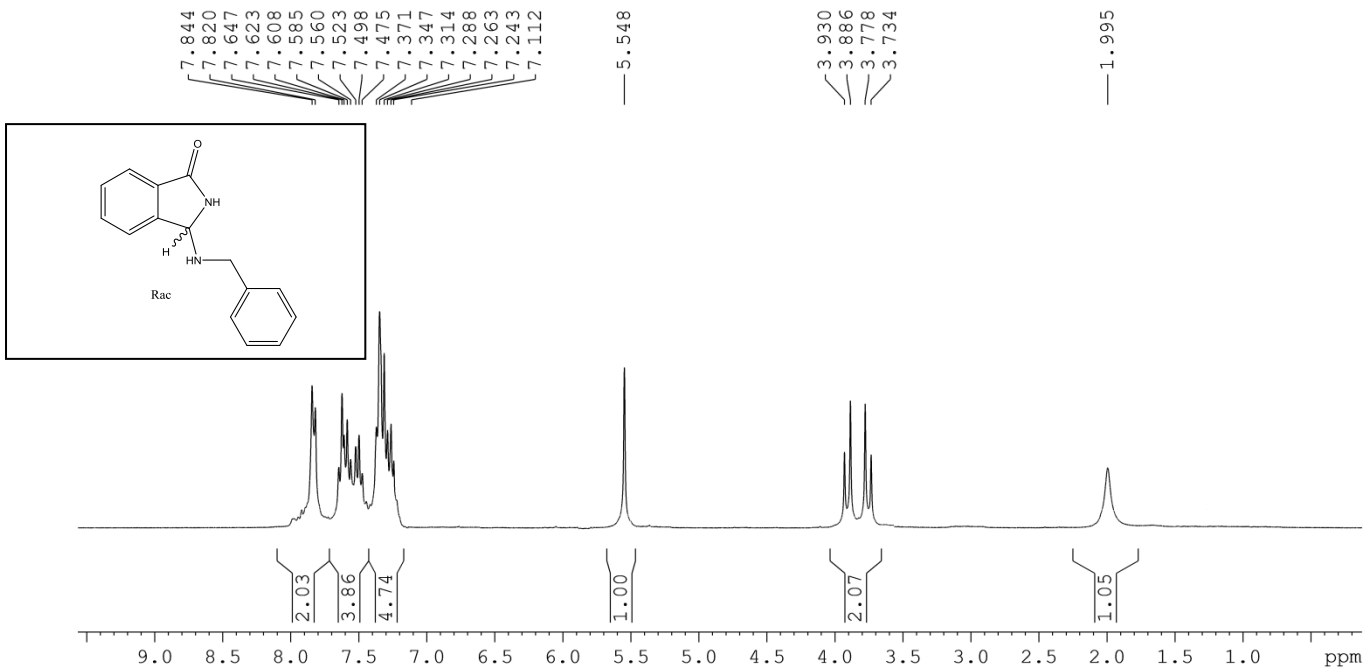
3-(((*(R)*-1-phenylethyl)amino)isoindolin-1-one (1ma): the two diastereoisomers gave spectral and analytical data identical to **1la**. *Less polar diastereoisomer*: $[\alpha]_D^{26}$:+156.6 (*c* 0.6, $CHCl_3$).

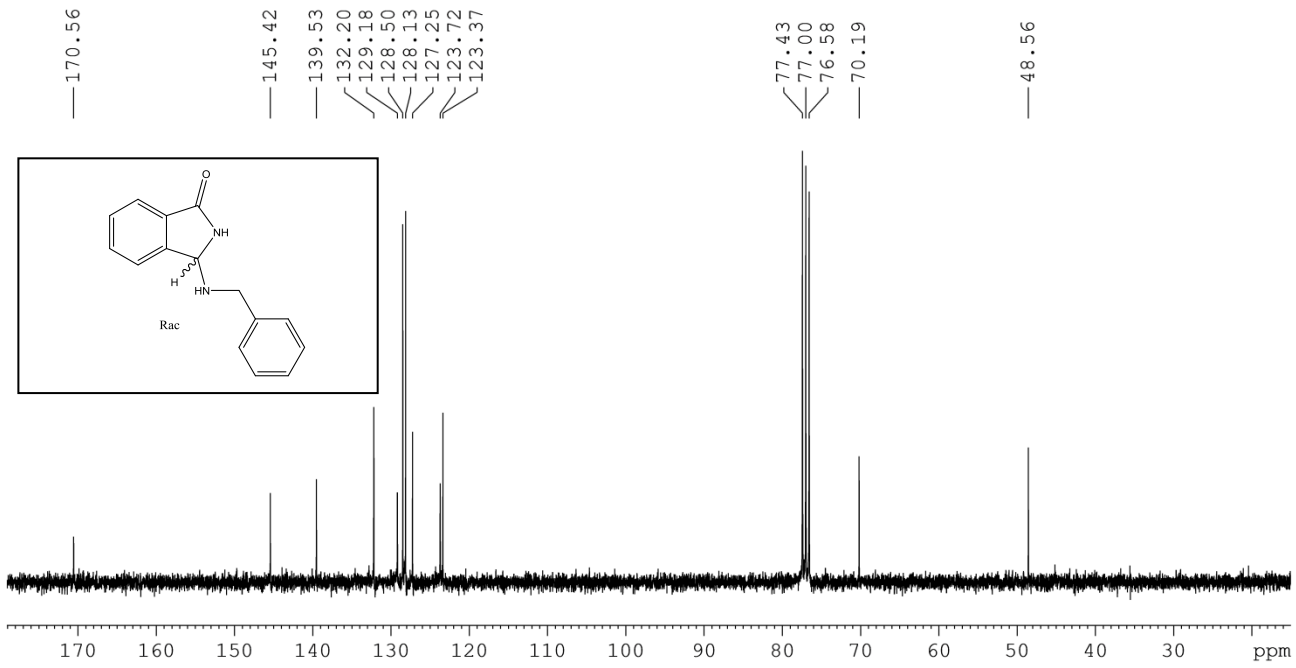
6-bromo-3-(((*(R)*-1-phenylethyl)amino)isoindolin-1-one (1mb): *Less polar diastereoisomer:* Amorphous solid; NMR ($CDCl_3$): H: 7.93 (1H, s); 7.69 (1H, d, J= 7.98 Hz); 7.50-7.46 (3H, m); 7.41-7.37 (2H, m); 7.32-7.28 (2H, m); 5.09 (1H, s); 4.10-4.05 (2H, m); 1.80 (1H, bs); 1.38 (3H, d, J=6.40 Hz). C: 168.7 144.7; 143.8; 135.1; 133.8; 128.9 (2C); 127.9; 126.9 (2C); 126.6; 125.4; 123.3; 68.2; 55.44; 25.4. $[\alpha]_D^{28}$:+82.9 (*c* 0.3, $CHCl_3$).). (ESI): *m*/*z* = 331 ($M + H^+$). Anal. Calcd for $C_{16}H_{15}BrN_2O$: C, 58.02; H, 4.57; Br, 24.12; N, 8.46; O, 4.83; Found: C, 58.05; H, 4.60; N, 8.47.

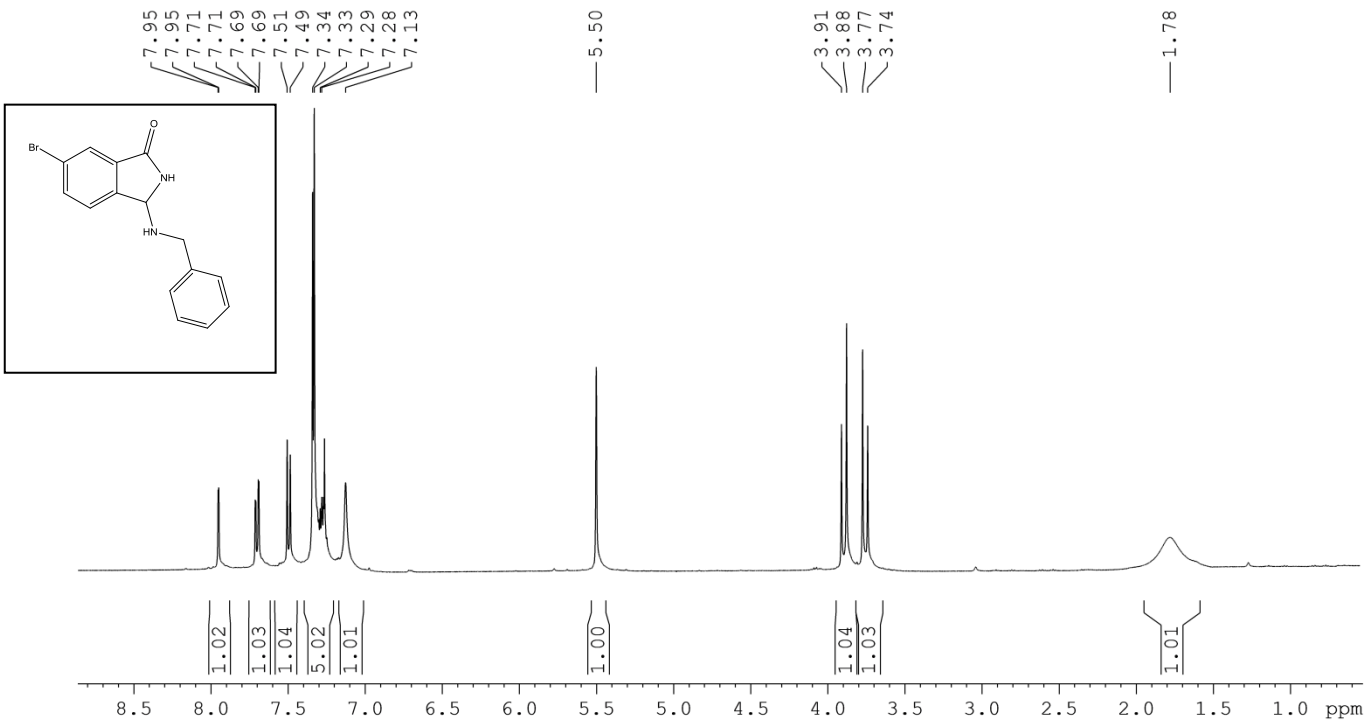
3-(((*(S)*-1-cyclohexylethyl)amino)isoindolin-1-one (1na): *mixture of diastereoisomers*: amorphous solid: NMR ($CDCl_3$): H: 7.81 (2H, m); 7.60-7.46 (6H, m); 7.25 (1H, bs); 7.16 (1H, bs); 5.52 (1H, s); 5.46 (1H, s); 2.78-2.72 (1H, m); 2.69-2.63 (1H,m); 1.43-0.90 (30H, m). C: 170.2; 170.1; 146.5; 146.3; 132.0; 129.0; 123.9; 123.8; 123.3; 123.3; 70.2; 68.9; 55.3; 54.3; 44.2; 43.42; 29.5; 29.2; 28.4; 28.0; 26.7, 26.6; 19.1; 17.8. (ESI): *m*/*z* = 259 ($M + H^+$). Anal. Calcd for $C_{16}H_{22}N_2O$ C, 74.38; H, 8.58; N, 10.84; O, 6.19. Found: C, 74.41; H, 8.59; N, 10.87.

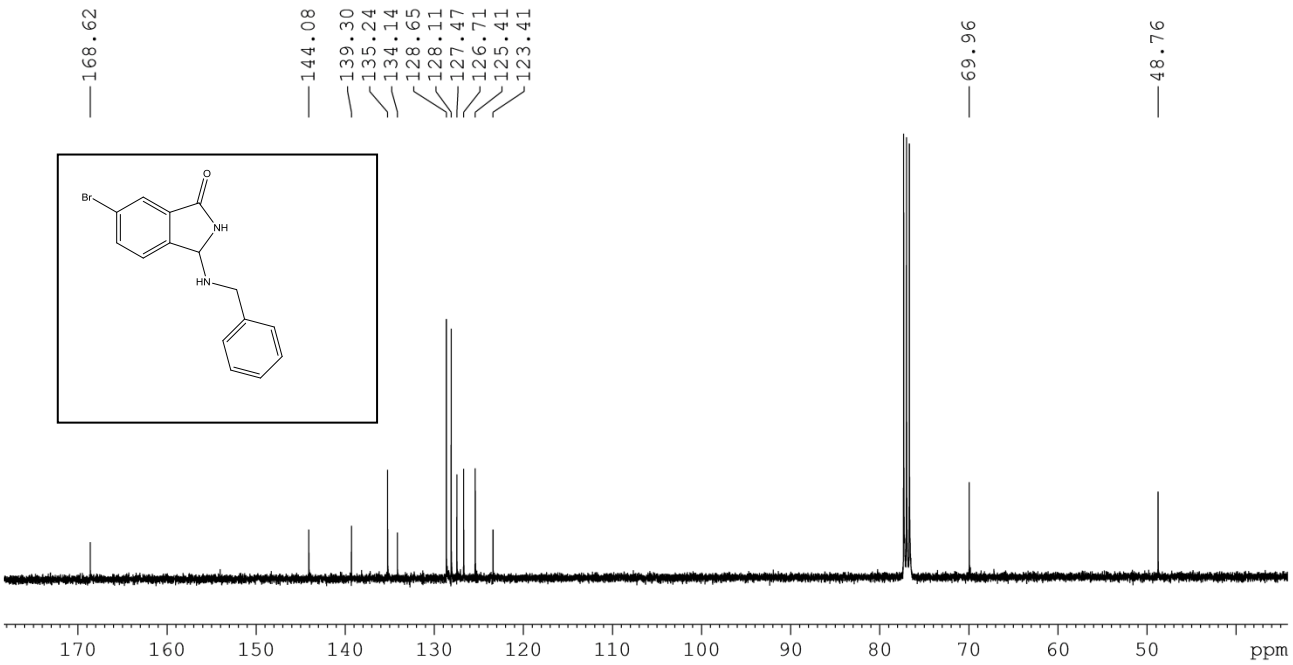
3-(((6,6-dimethylbicyclo[3.1.1]heptan-3-yl)methyl)amino)isoindolin-1-one (1oa): *mixture of diastereo isomers*: amorphous solid: NMR ($CDCl_3$): H: 7.81 (2H, d, J=9 Hz); 7.59-7.50 (63H, m): 6.98 (1H, s); 6.92 (1H, s); 5.50 (1H, s); 5.48 (1H, s); 2.75-2.61 (2H, m); 2.59-2.41 (2H, m); 2.43-2.39 (2H, m); 2.20-2.0 (2H, m); 1.98-1.79 (10H, m); 1.64 (2H, s); 1.47-1.38 (1H, m); 1.16 (3H, s); 1.13 (3H, s); 0.91-0.88 (1H, m); 0.90 (3H, s); 0.80 (3H, s). C: C: 170.19 (2C); 145.64 (2C); 1323.14 (2C); 129.10 (2C); 123.68 (2C); 123.62 (2C); 123.38(2C); 70.63(2C); 50.52; 49.79; 44.42; 43.73; 42.15; 42.07; 41.41(2C); 38.58 (2C); 33.37; 33.25; 27.95 (2C); 26.10 (2C); 23.24; 23.05; 20.47 (2C). (ESI): *m*/*z* = 285 ($M + H^+$). Anal. Calcd for $C_{18}H_{24}N_2O$: C, 76.02; H, 8.51; N, 9.85; O, 5.63. Found: C, 76.03; H, 8.52; N, 9.87.

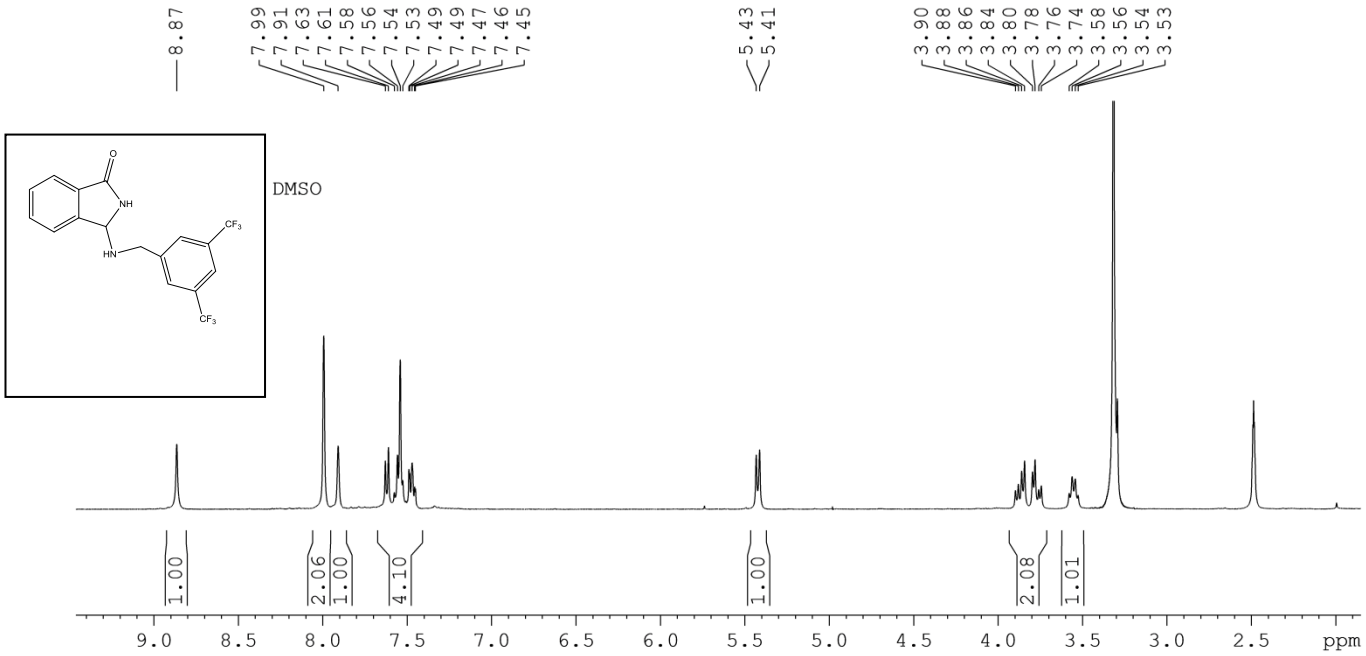
tert-butyl (3-oxoisoindolin-1-yl)-L-prolinate (1pa): *Major diastereoisomer*: Yellow pale oil; NMR ($CDCl_3$): H: 7.81 (1H, d, *J*=7.5 Hz); 7.62-7.48 (4H, m); 7.32 (1H, bs); 5.80 (1H, s); 3.50 (1H, t, *J*=7.5 Hz); 2.54-2.47 (2H, m); 2.07-1.99 (2H, m); 1.80-1.67 (2H, m); 1.50 (9H, s). C: 173.0; 170.9; 145.2; 132.2; 132.0; 129.1; 123.9; 123.4; 81.1; 71.7; 62.6; 44.7; 29.6; 29.6; 28.1; 23.5. $[\alpha]_D^{25}$:-130.6 (*c* 0.45, $CHCl_3$). *Minor diastereoisomer*: Yellow oil; NMR ($CDCl_3$): H: 7.81 (1H, d. 7.5 Hz); 7.52-7.49 (3H, m); 7.10 (1H, bs); 5.71 (1H, s); 3.55-3.52 (1H, m); 3.20-3.13 (1H, m); 2.66-2.57 (1H, m); 2.12-2.08 (1H, m); 2.00-1.82 (3H, m); 1.32 (9H, s). C: 174.9; 170.1; 144.7; 132.2; 131.9; 129.1; 124.3; 123.4; 80.8; 71.9; 60.5; 47.7; 31.1; 27.9; 24.1. $[\alpha]_D^{25}$:+53.5 (*c* 0.40, $CHCl_3$). (ESI): *m*/*z* = 303 ($M + H^+$). Anal. Calcd for $C_{17}H_{22}N_2O_3$: C, 67.53; H, 7.33; N, 9.26; O, 15.87: Found: C, 67.55; H, 7.35; N, 9.27

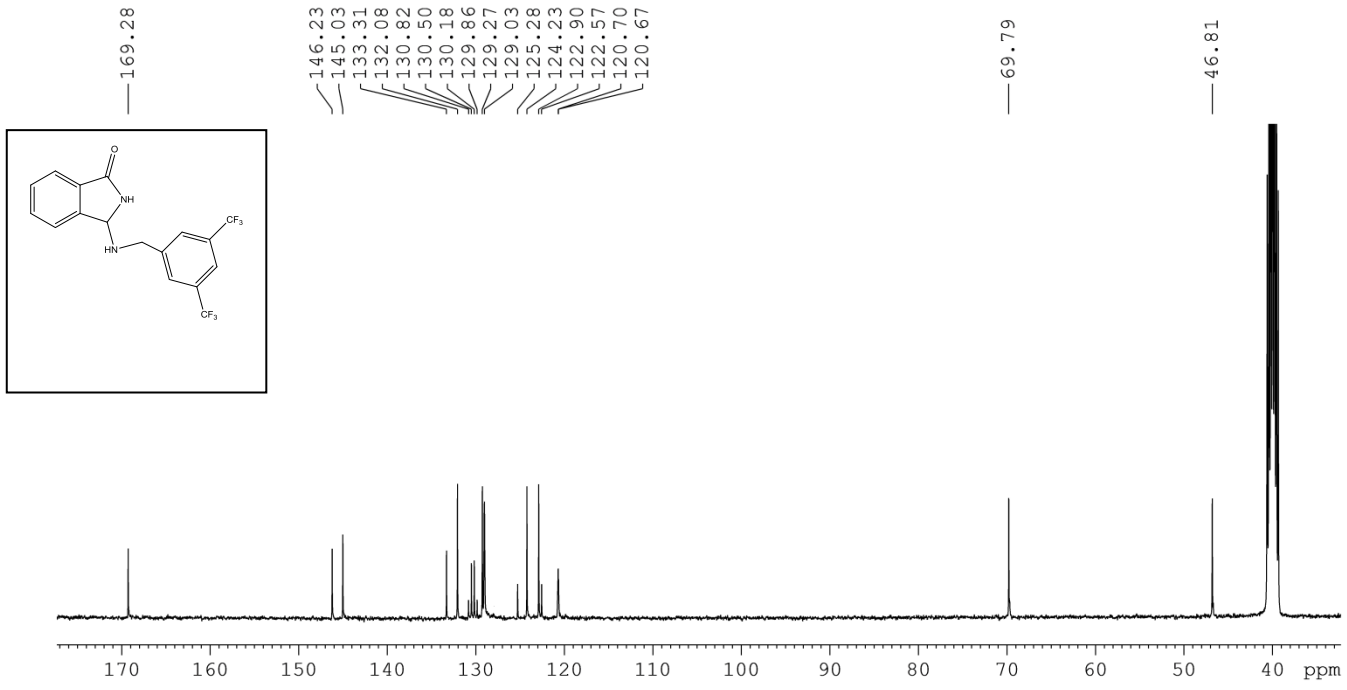

7.844
7.820
7.647
7.623
7.608
7.585
7.560
7.523
7.498
7.475
7.371
7.347
7.314
7.288
7.263
7.243
7.112
5.548
3.930
3.886
3.778
3.734
1.995
O
NH
H
HN
Rac
2.03
3.86
4.74
1.00
2.07
1.05
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

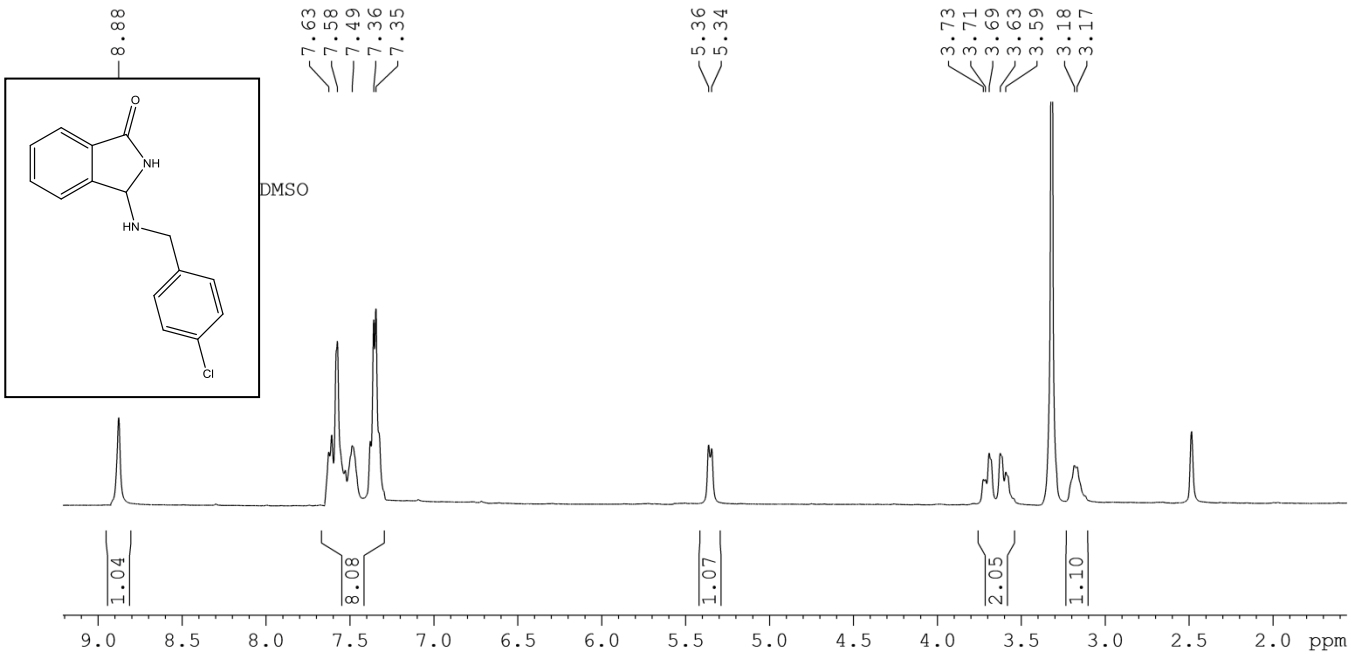

170.56
145.42
139.53
132.20
129.18
128.50
128.13
127.25
123.72
123.37
77.43
77.00
76.58
70.19
48.56
O
NH
H
HN
Rac
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm

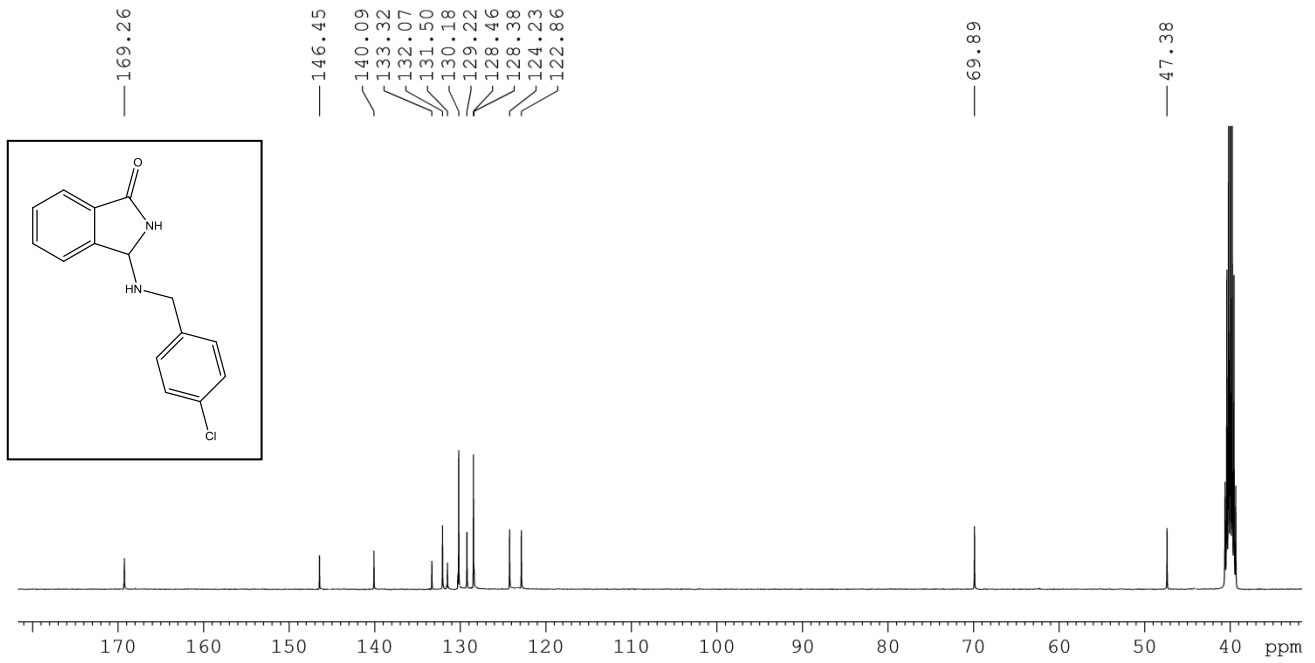

7.95
7.95
7.71
7.71
7.69
7.69
7.51
7.49
7.34
7.33
7.29
7.28
7.13
5.50
3.91
3.88
3.77
3.74
1.78
Br
O
NH
HN
1.02
1.03
1.04
5.02
1.01
1.00
1.04
1.03
1.01
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

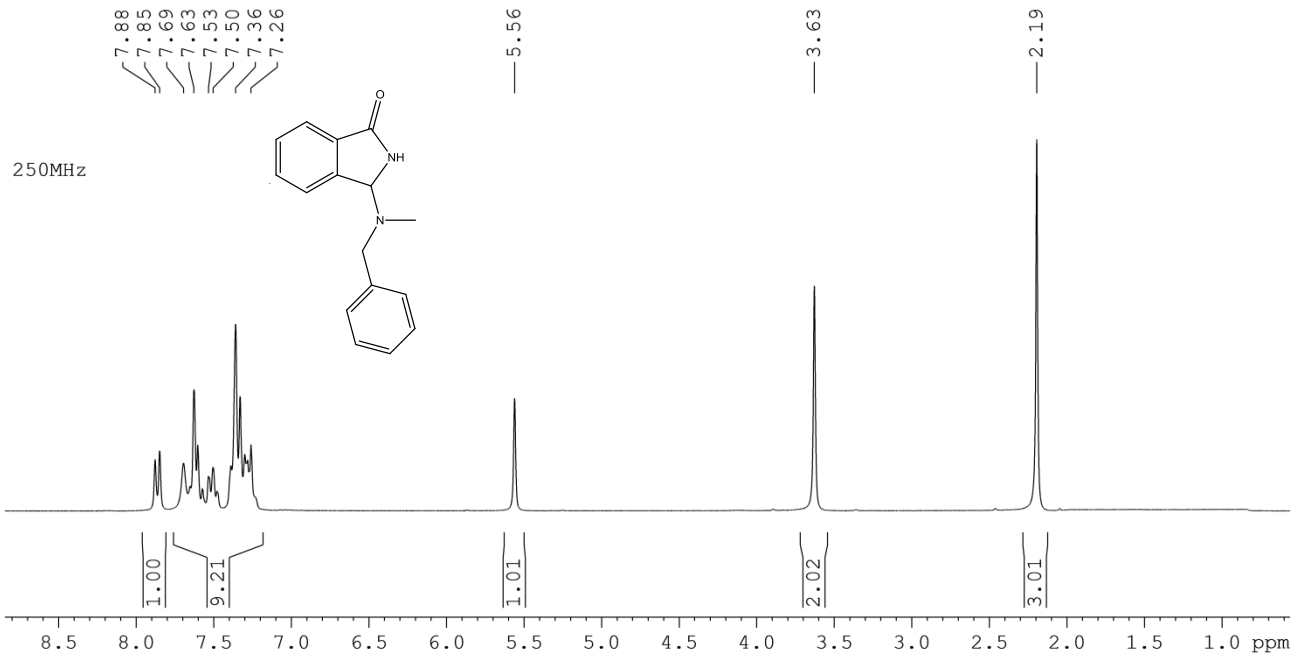

168.62
144.08
139.30
135.24
134.14
128.65
128.11
127.47
126.71
125.41
123.41
69.96
48.76
Br
O
NH
HN
170
160
150
140
130
120
110
100
90
80
70
60
50
ppm

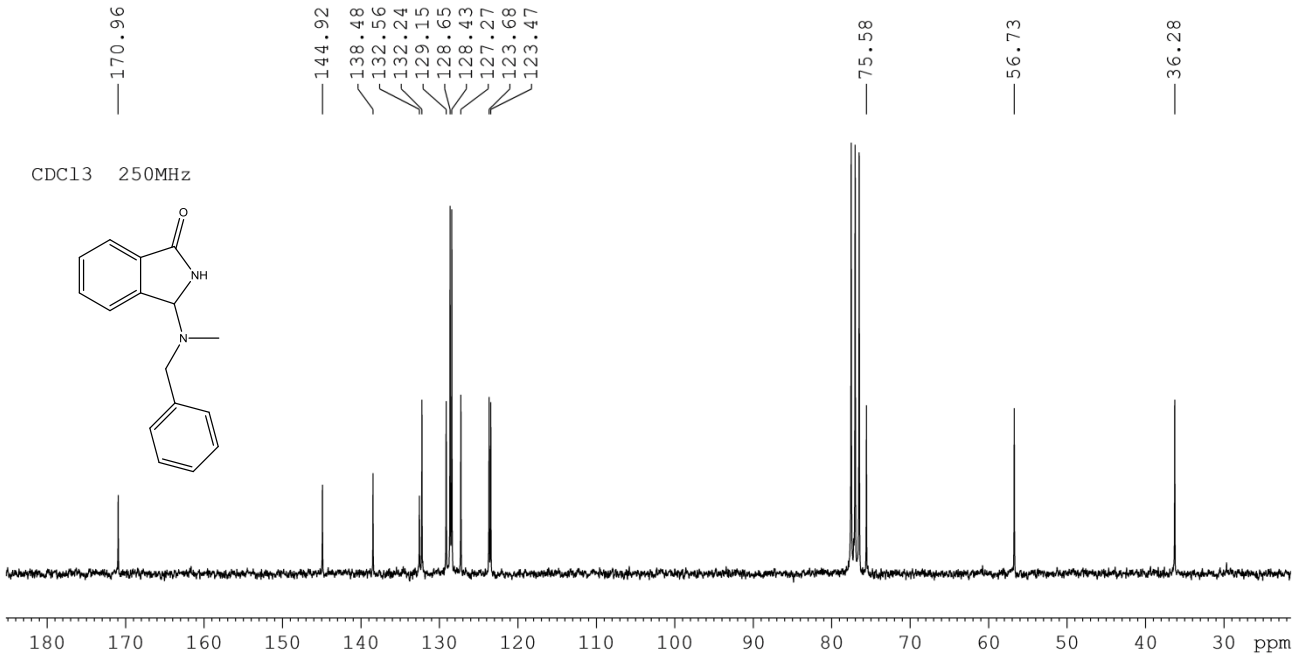

8.87
7.99
7.91
7.63
7.61
7.58
7.56
7.54
7.53
7.49
7.49
7.47
7.46
7.45
5.43
5.41
3.90
3.88
3.86
3.84
3.80
3.78
3.76
3.74
3.58
3.56
3.54
3.53
DMSO
1.00
2.06
1.00
4.10
1.00
2.08
1.01
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
ppm

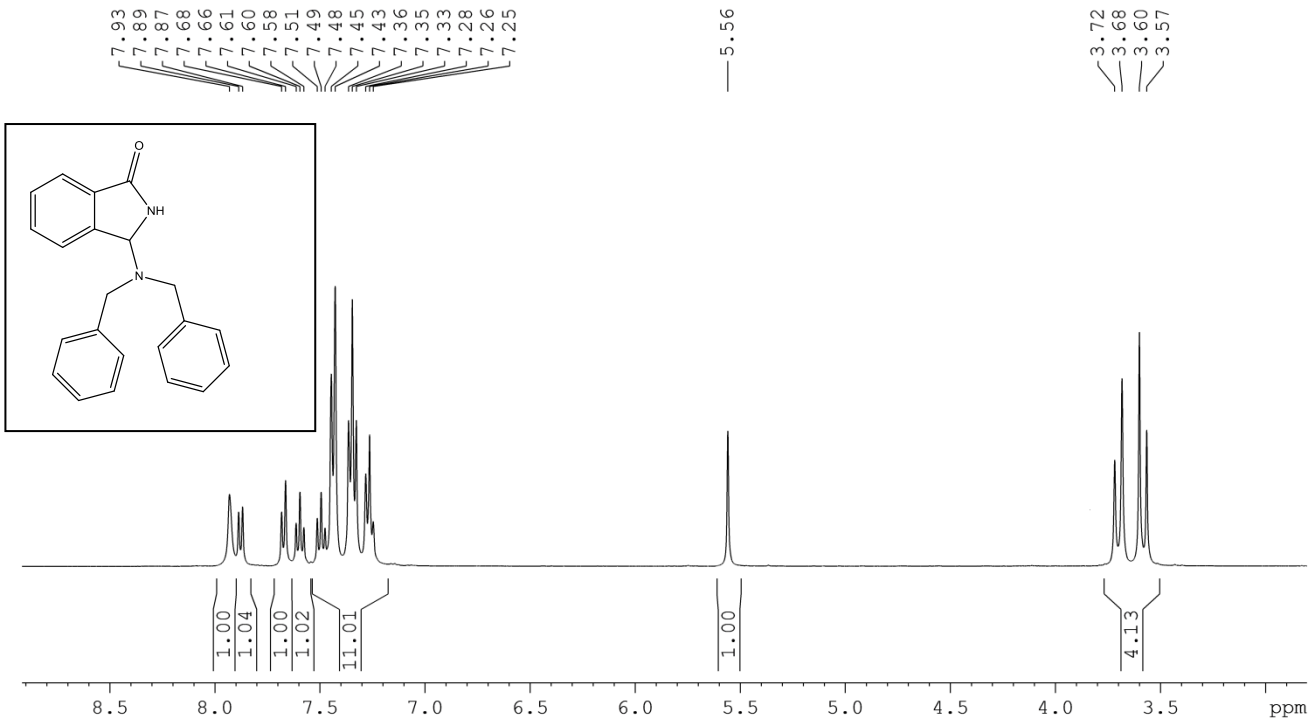

169.28
146.23
145.03
133.31
132.08
130.82
130.50
130.18
129.86
129.27
129.03
125.28
124.23
122.90
122.57
120.70
120.67
69.79
46.81
170
160
150
140
130
120
110
100
90
80
70
60
50
40
ppm

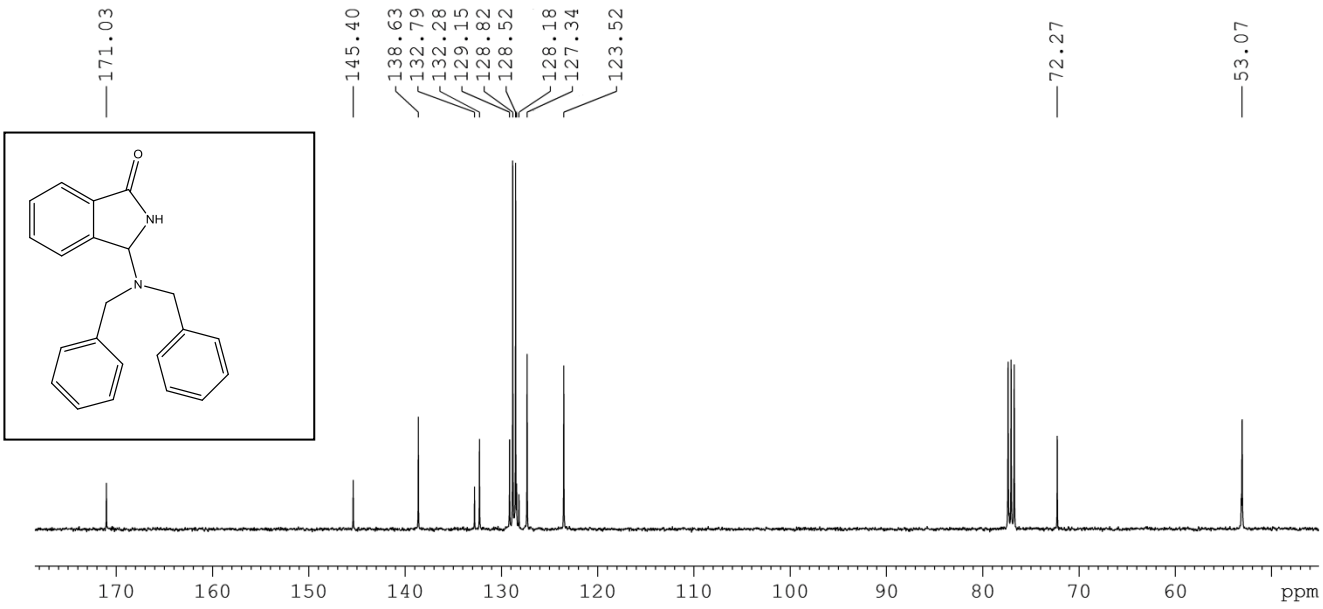

8.88
7.63
7.58
7.49
7.36
7.35
5.36
5.34
3.73
3.71
3.69
3.63
3.59
3.18
3.17
DMSO
O
NH
HN
Cl
1.04
8.08
1.07
2.05
1.10
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
ppm

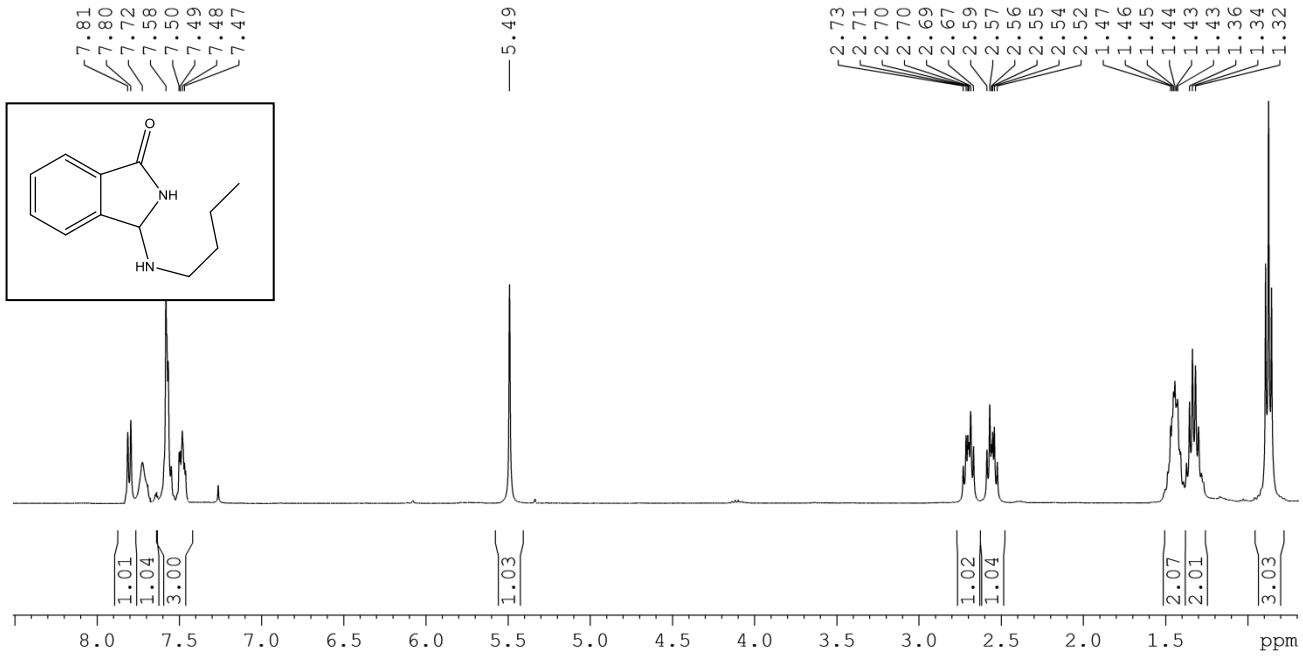

169.26
146.45
140.09
133.32
132.07
131.50
130.18
129.22
128.46
128.38
124.23
122.86
69.89
47.38
O
NH
HN
Cl
170
160
150
140
130
120
110
100
90
80
70
60
50
40
ppm

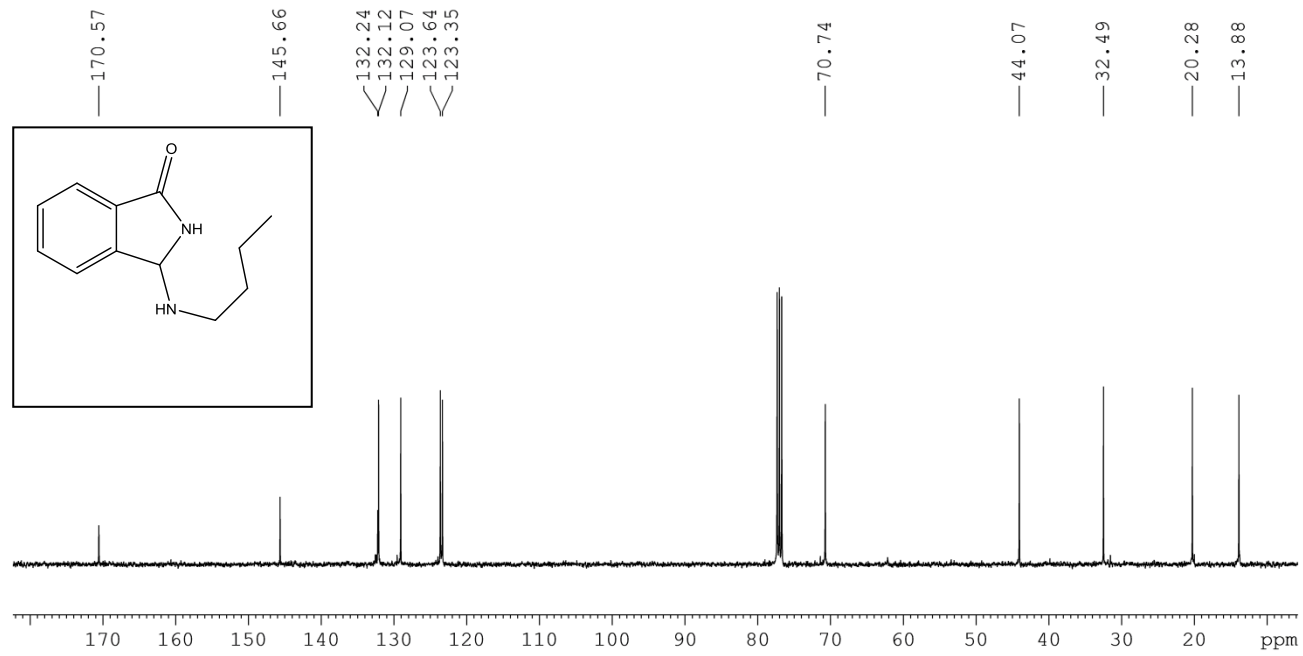

7.88
7.85
7.69
7.63
7.53
7.50
7.36
7.26
5.56
3.63
2.19
250MHz
O
NH
N
1.00
9.21
1.01
2.02
3.01
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0 ppm

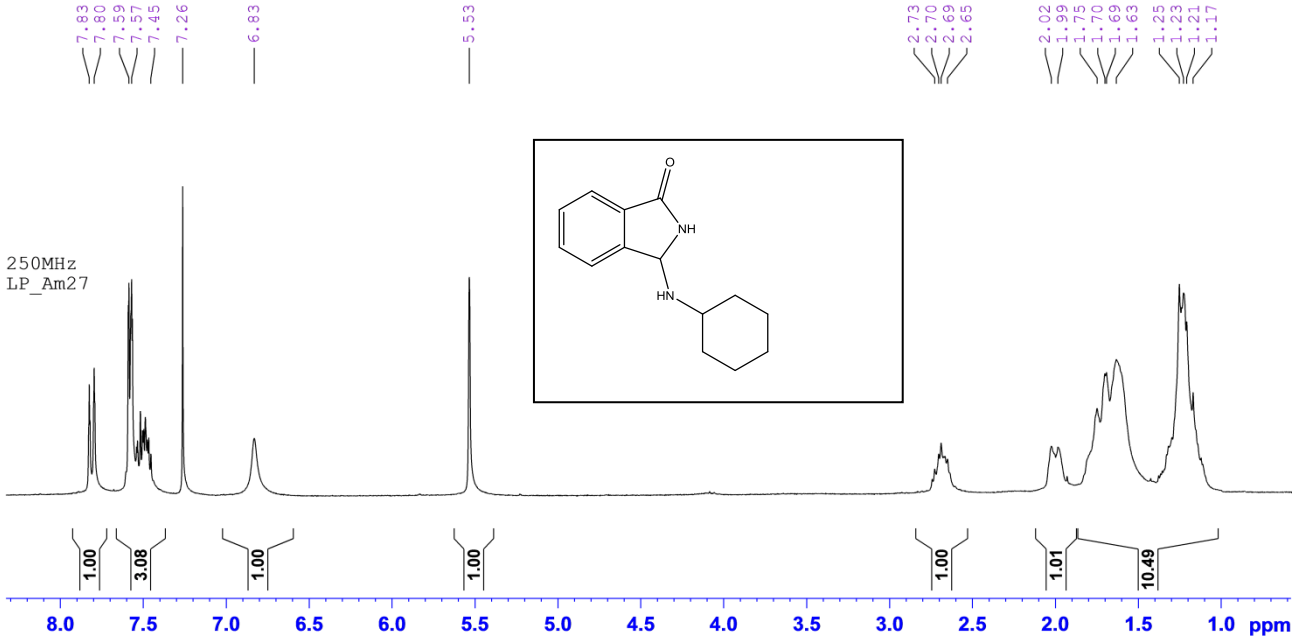

170.96
144.92
138.48
132.56
132.24
129.15
128.65
128.43
127.27
123.68
123.47
75.58
56.73
36.28
CDCl3 250MHz
O
NH
N
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30 ppm

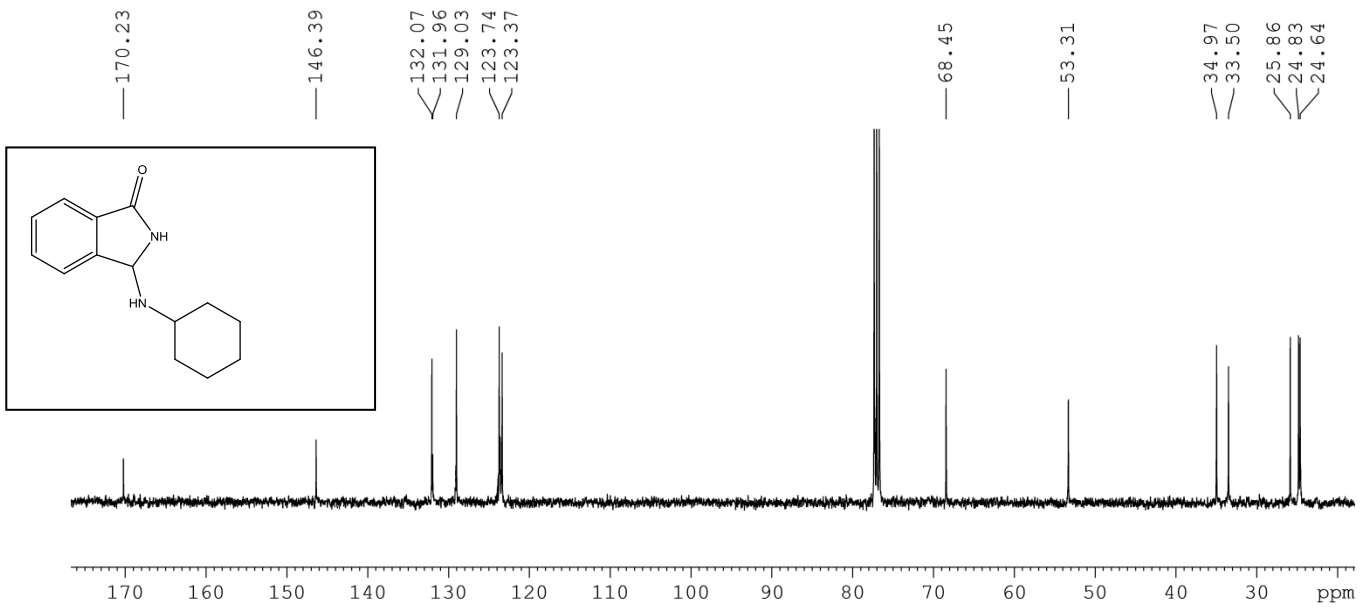

7.93
7.89
7.87
7.68
7.66
7.61
7.60
7.58
7.51
7.49
7.48
7.45
7.43
7.36
7.35
7.33
7.28
7.26
7.25
5.56
3.72
3.68
3.60
3.57
O
NH
N
1.00
1.04
1.00
1.02
11.01
1.00
4.13
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
ppm

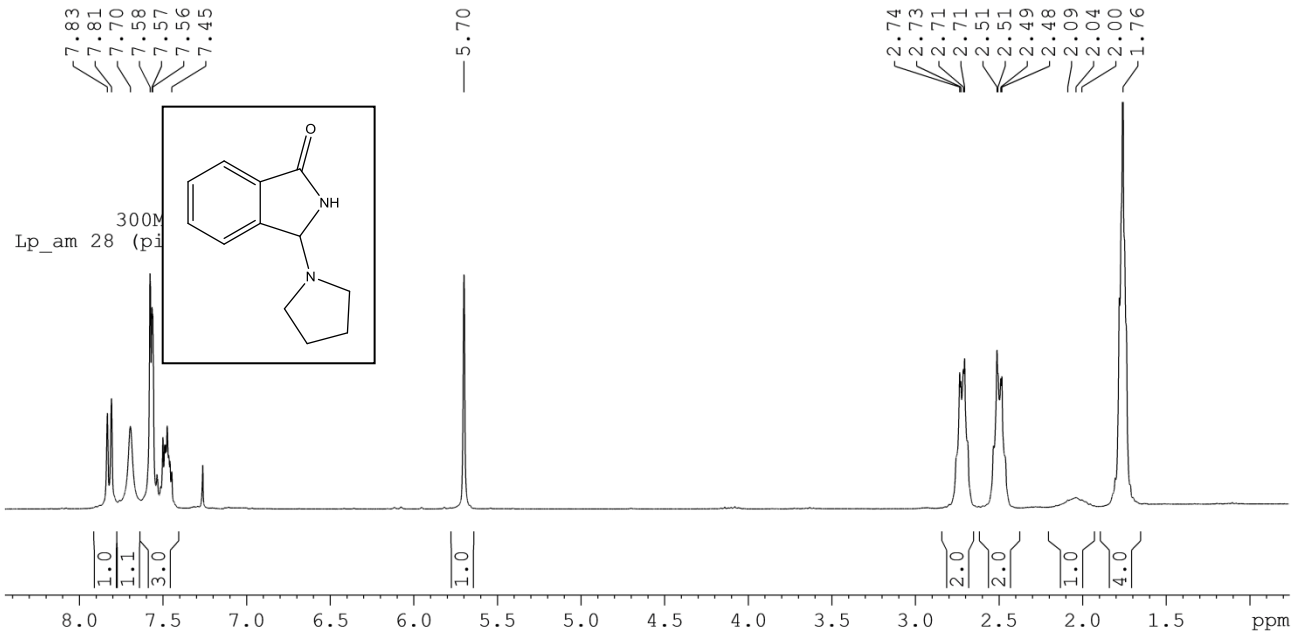

171.03
145.40
138.63
132.79
132.28
129.15
128.82
128.52
128.18
127.34
123.52
72.27
53.07
O
NH
N
170
160
150
140
130
120
110
100
90
80
70
60
ppm

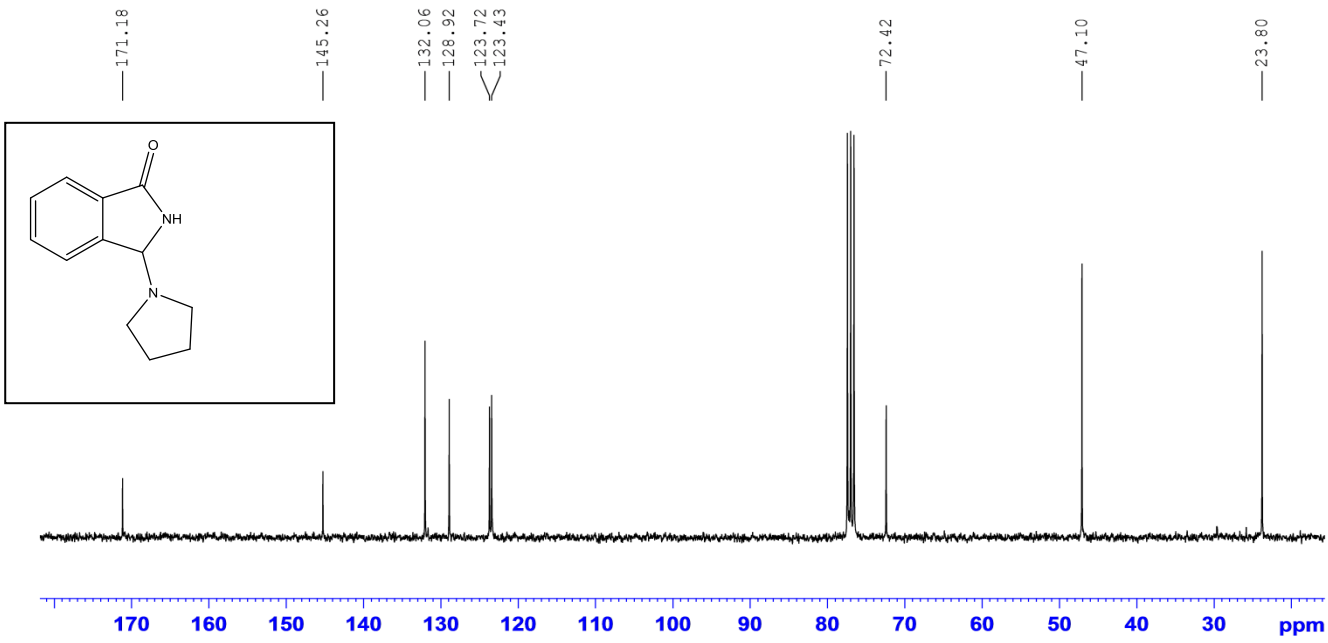

7.81
7.80
7.72
7.58
7.50
7.49
7.48
7.47
5.49
2.73
2.71
2.70
2.70
2.69
2.67
2.59
2.57
2.56
2.55
2.54
2.52
1.47
1.46
1.45
1.44
1.43
1.43
1.36
1.34
1.32
O
NH
HN
1.01
1.04
3.00
1.03
1.02
1.04
2.07
2.01
3.03
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm

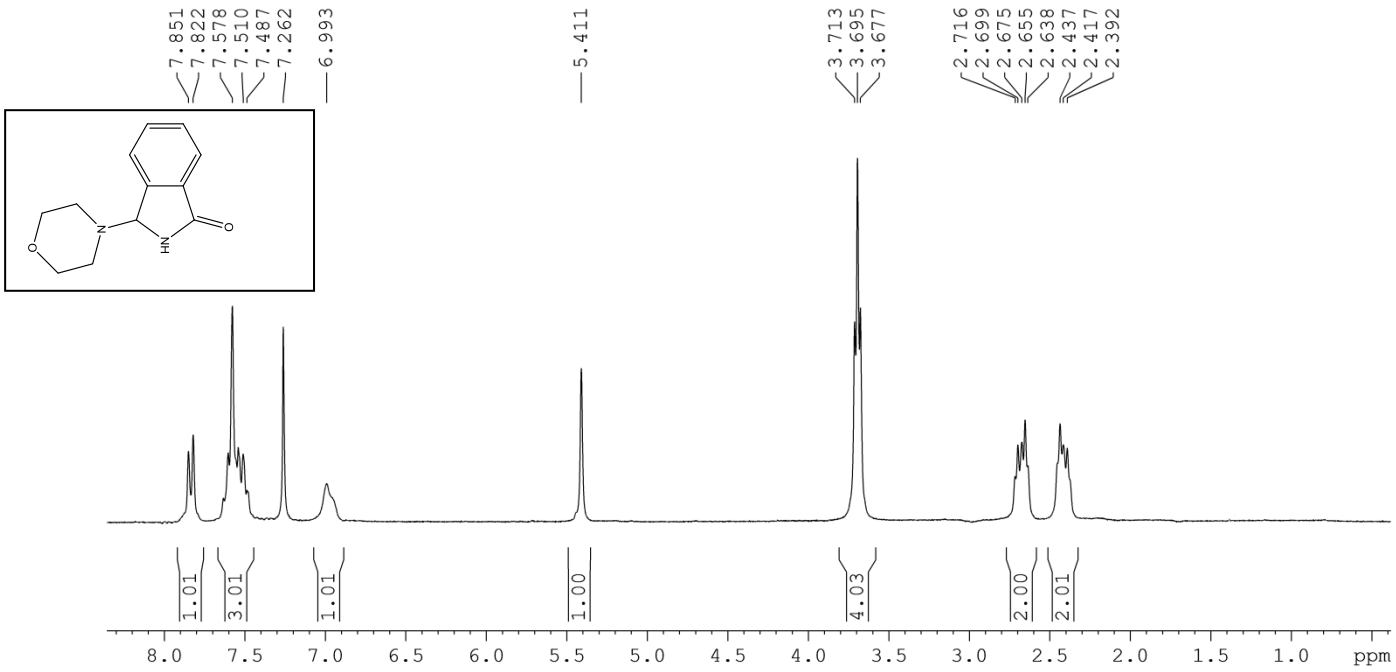

170.57
145.66
132.24
132.12
129.07
123.64
123.35
70.74
44.07
32.49
20.28
13.88
O
NH
HN
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

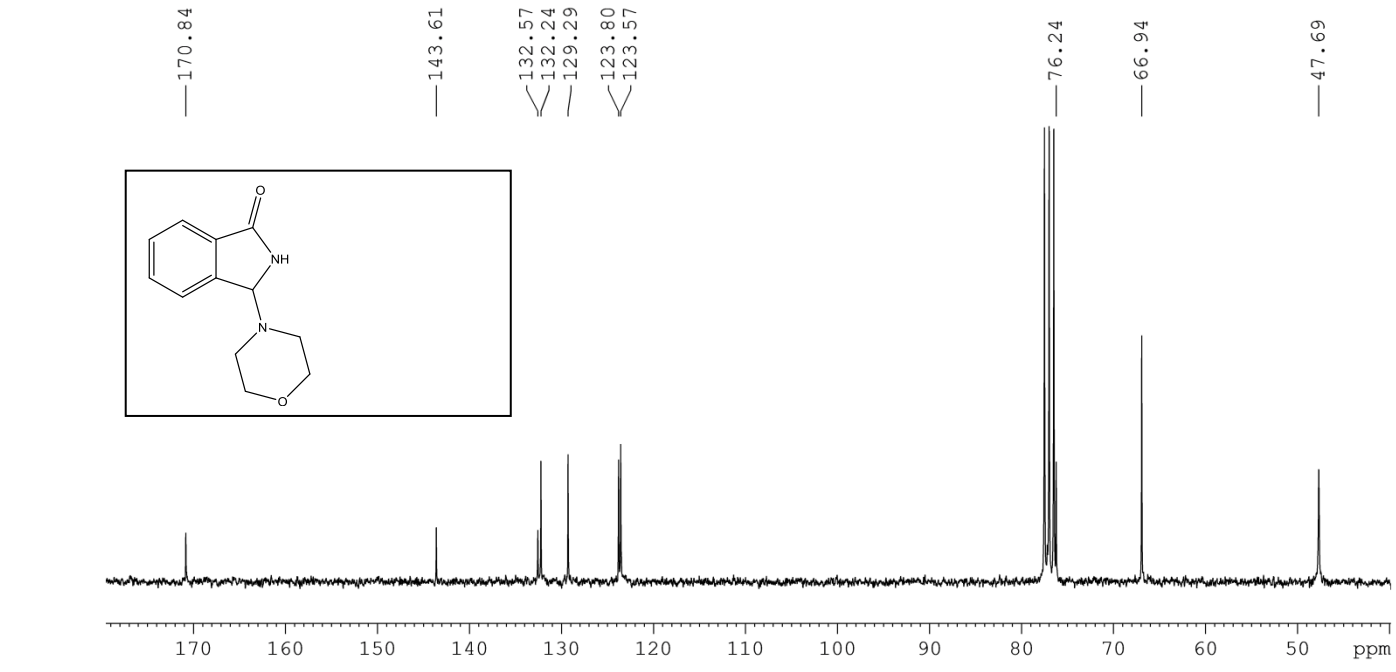

7.83
7.80
7.59
7.57
7.45
7.26
6.83
5.53
2.73
2.70
2.69
2.65
2.02
1.99
1.75
1.70
1.69
1.63
1.25
1.23
1.21
1.17
250MHz
LP_Am27
O
NH
HN
1.00
3.08
1.00
1.00
1.00
1.01
10.49
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

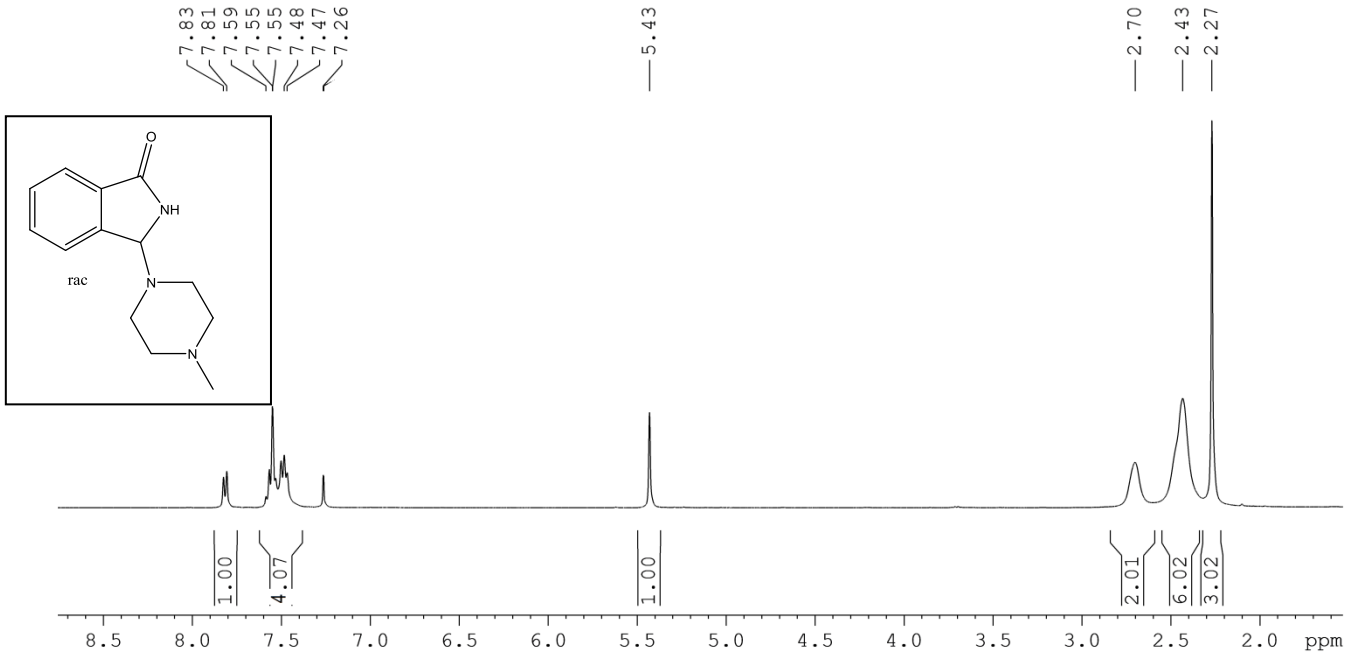

170.23
146.39
132.07
131.96
129.03
123.74
123.37
68.45
53.31
34.97
33.50
25.86
24.83
24.64
O
NH
HN
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm

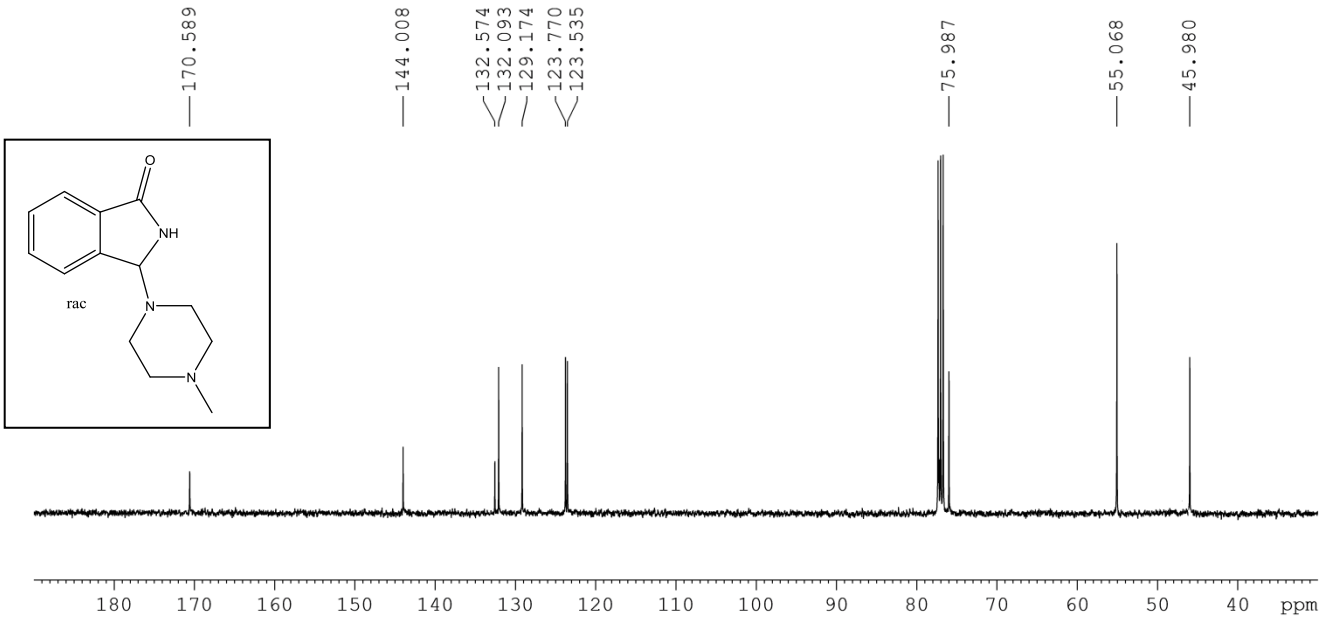

7.83
7.81
7.70
7.58
7.57
7.56
7.45
5.70
2.74
2.73
2.71
2.71
2.51
2.51
2.49
2.48
2.09
2.04
2.00
1.76
300M
Lp_am 28 (pi
O
NH
N
1.0
1.1
3.0
1.0
2.0
2.0
1.0
4.0
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm

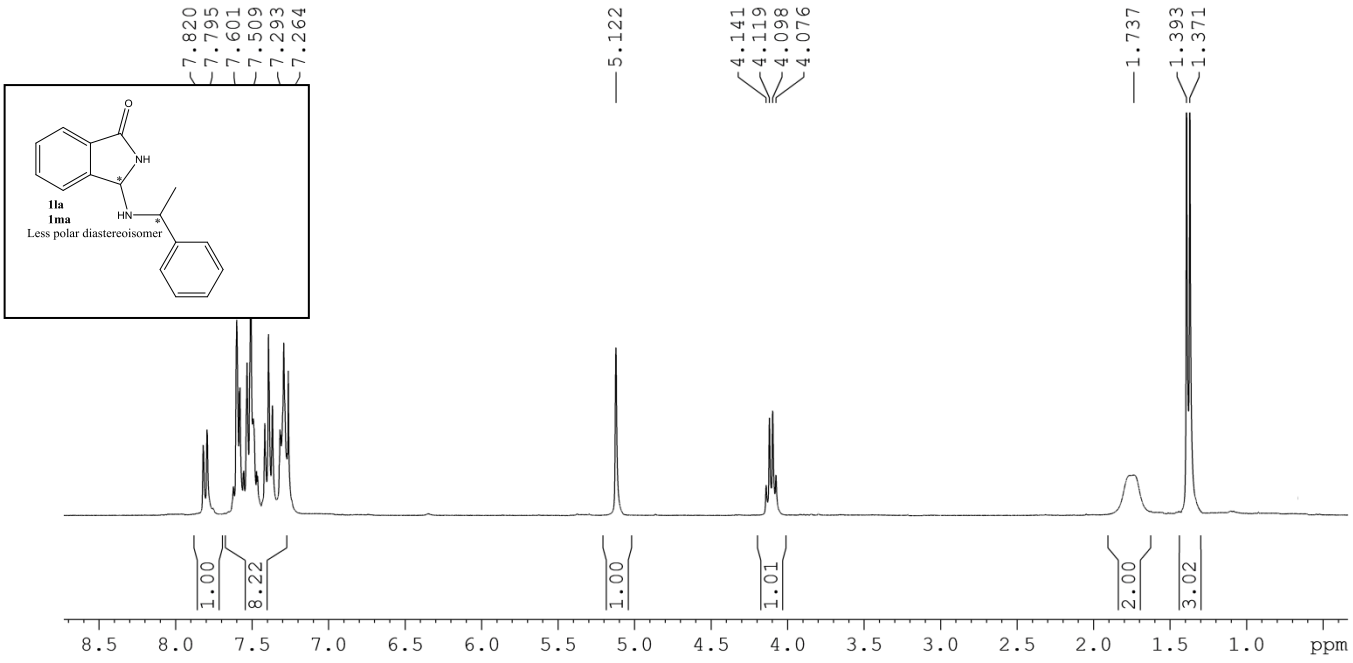

171.18
145.26
132.06
128.92
123.72
123.43
72.42
47.10
23.80
O
NH
N
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm

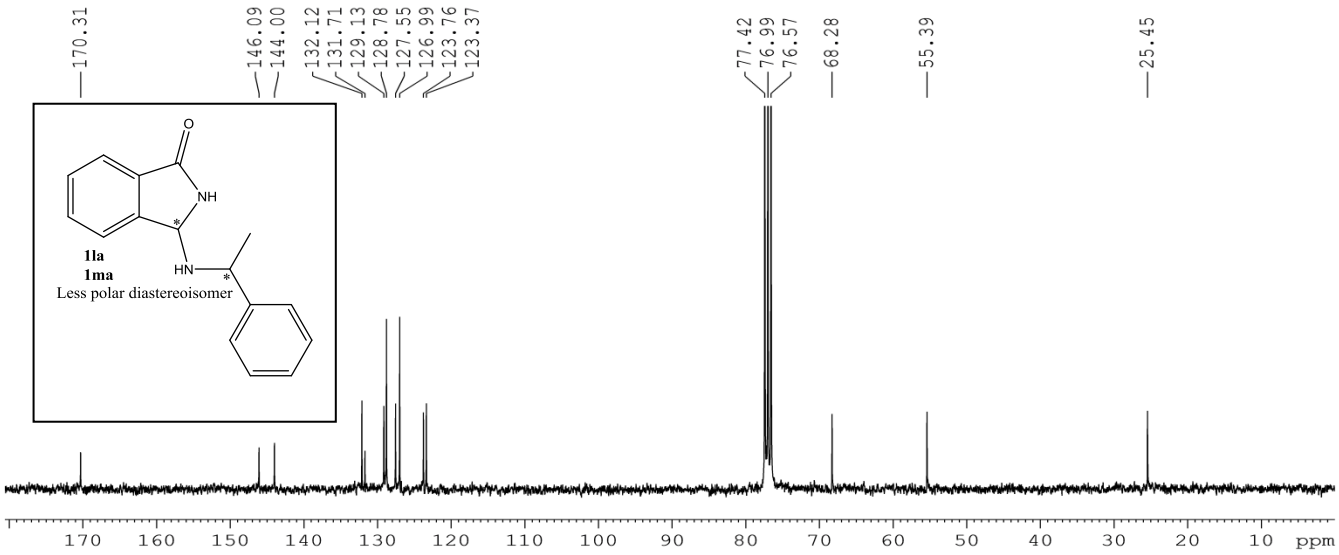

7.851
7.822
7.578
7.510
7.487
7.262
6.993
5.411
3.713
3.695
3.677
2.716
2.699
2.675
2.655
2.638
2.437
2.417
2.392
1.01
3.01
1.01
1.00
4.03
2.00
2.01
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

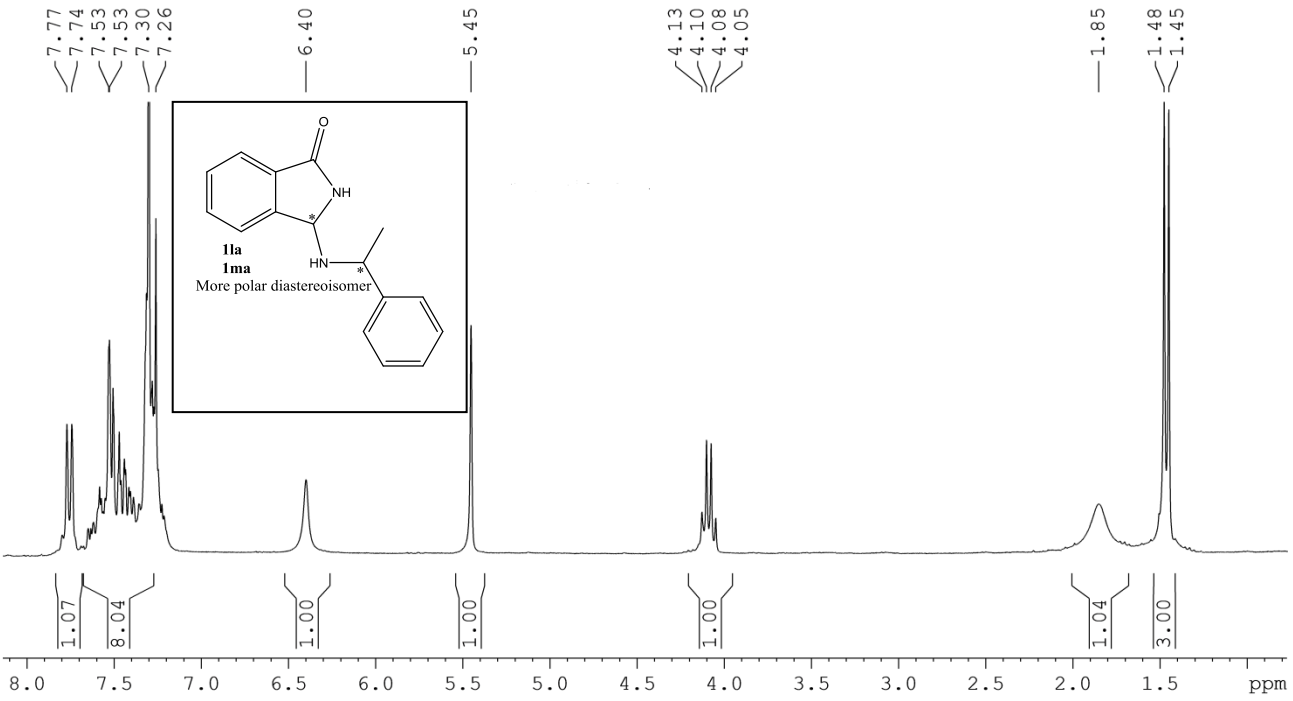

170.84
143.61
132.57
132.24
129.29
123.80
123.57
76.24
66.94
47.69
170
160
150
140
130
120
110
100
90
80
70
60
50
ppm

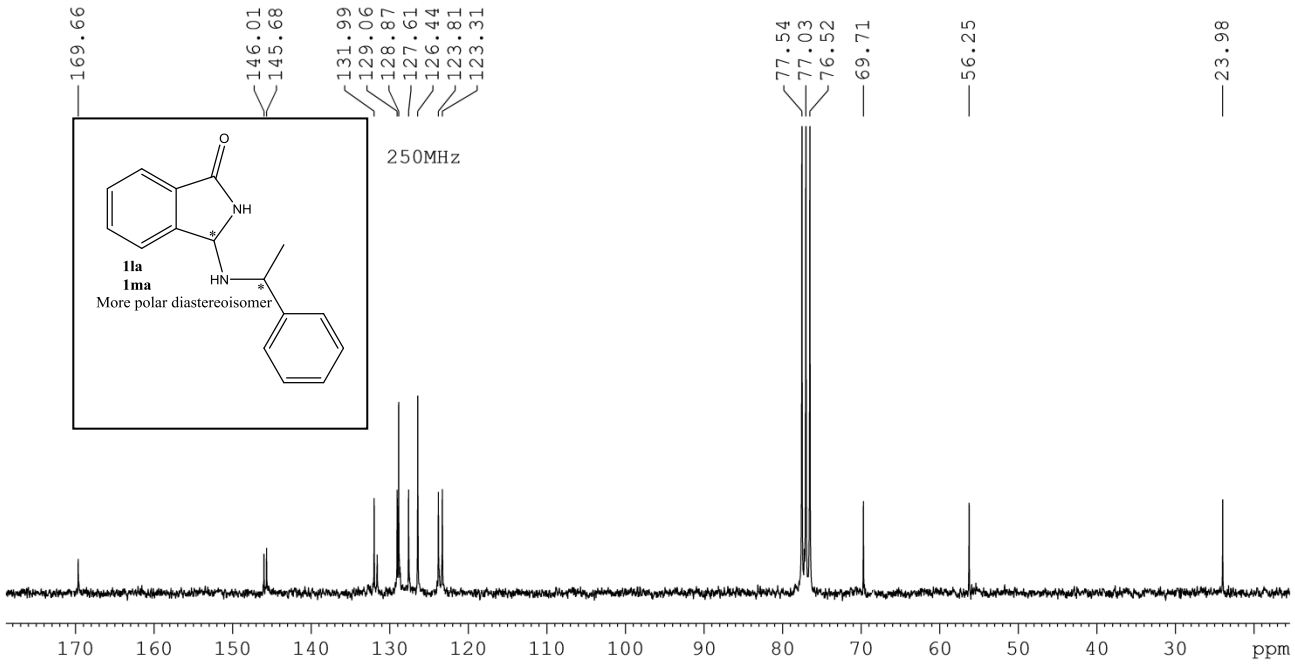

7.83
7.81
7.59
7.55
7.55
7.48
7.47
7.26
5.43
2.70
2.43
2.27
O
NH
rac
N
N
1.00
4.07
1.00
2.01
6.02
3.02
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
ppm

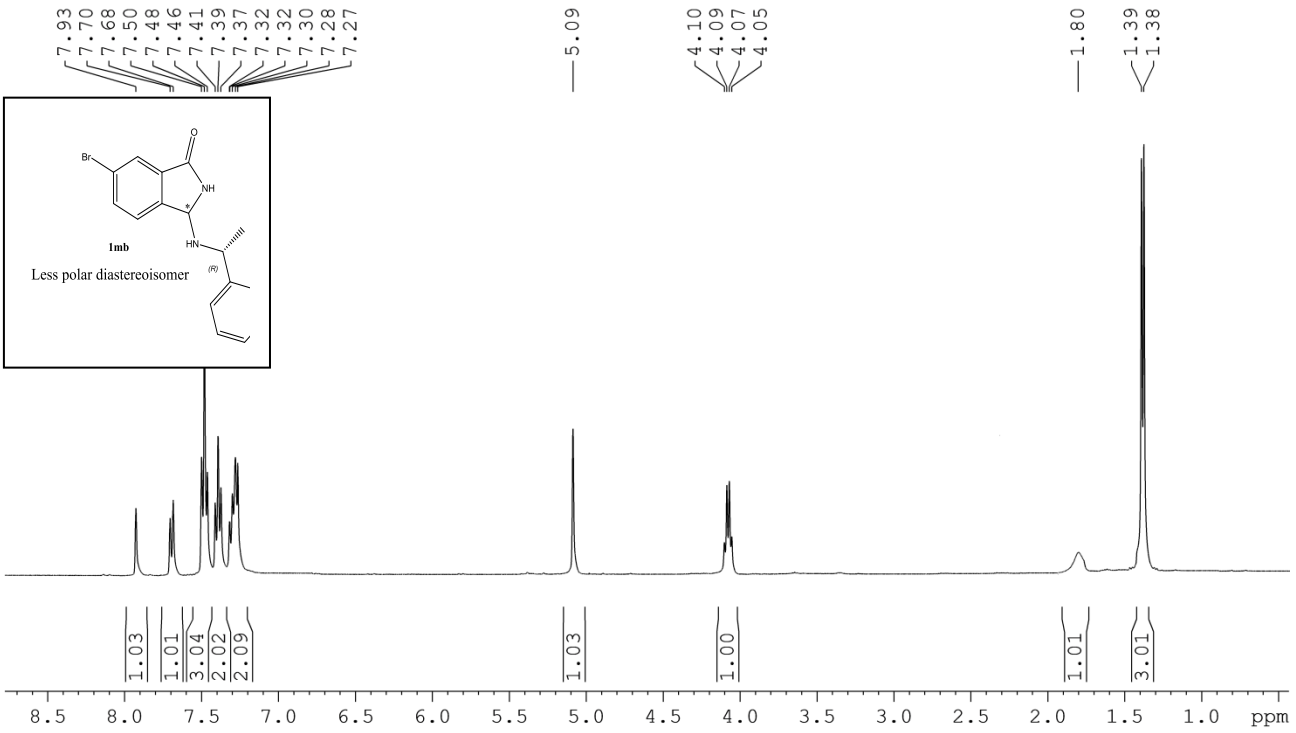

170.589
144.008
132.574
132.093
129.174
123.770
123.535
75.987
55.068
45.980
O
NH
rac
N
N
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
ppm

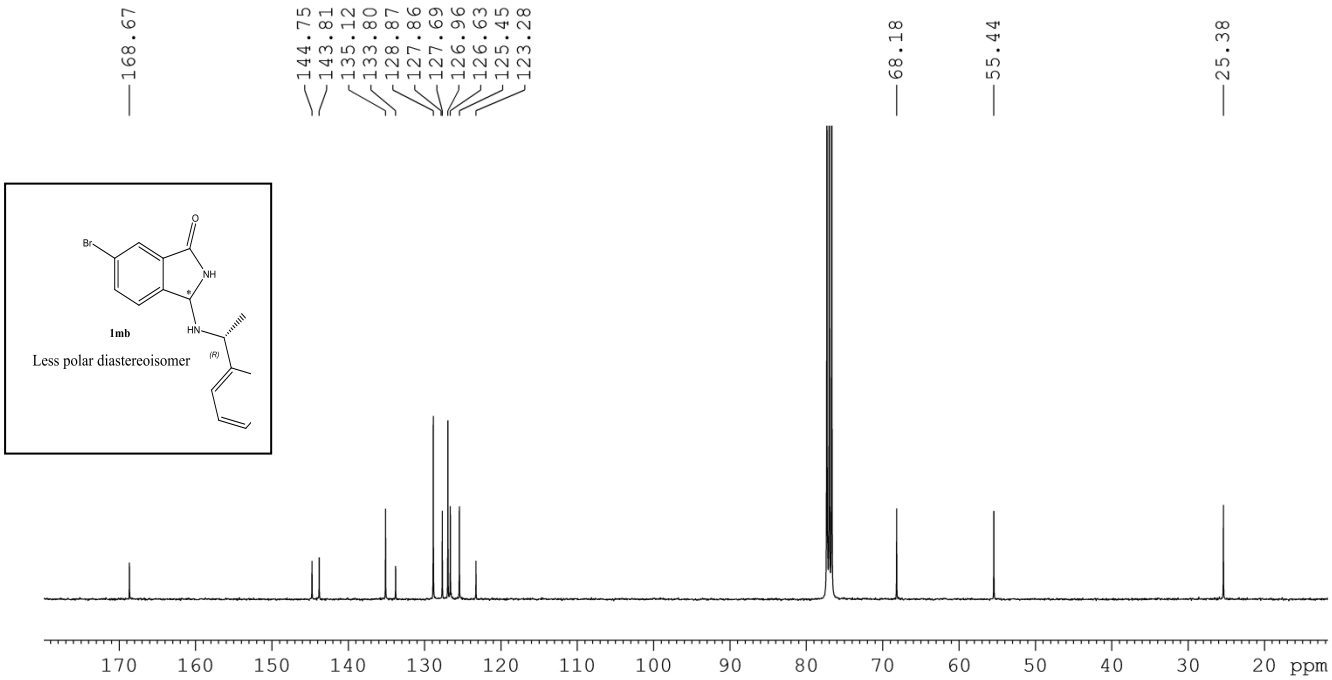

7.820
7.795
7.601
7.509
7.293
7.264
5.122
4.141
4.119
4.098
4.076
1.737
1.393
1.371
1.00
8.22
1.00
1.01
2.00
3.02
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
O
NH
HN
1la
1ma
Less polar diastereoisomer

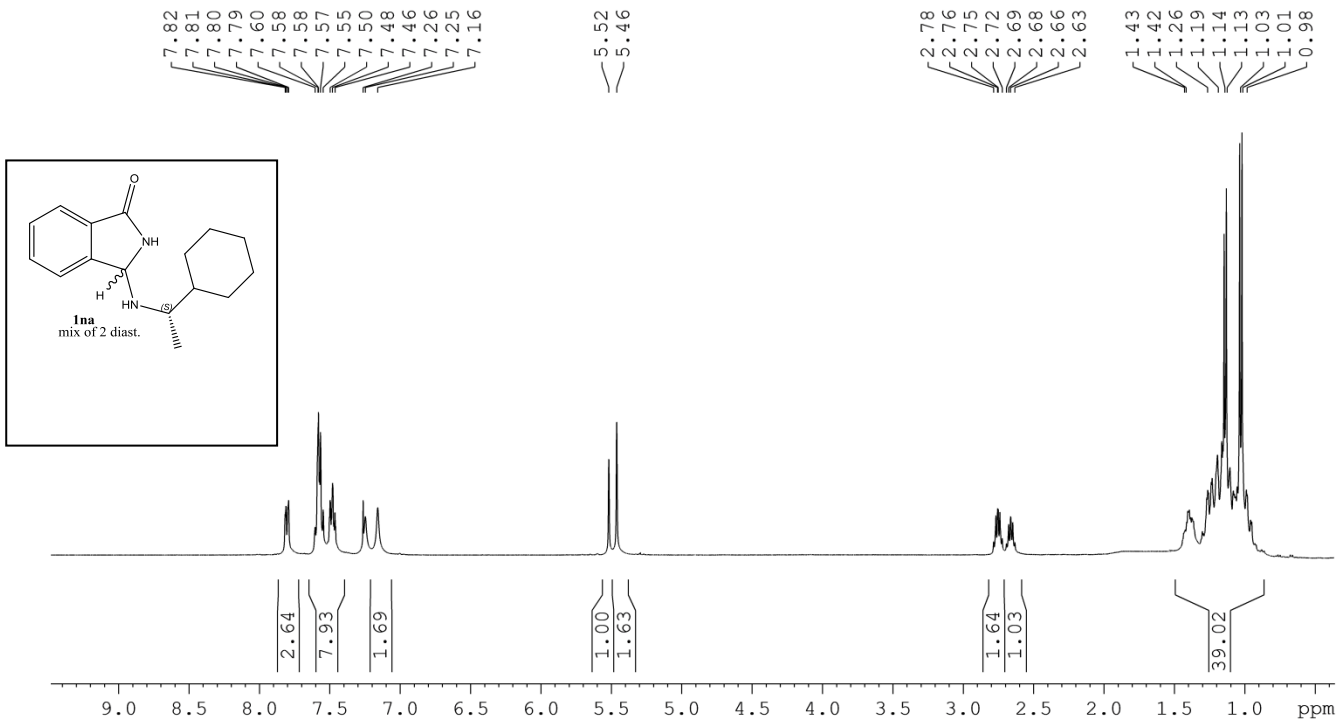

170.31
146.09
144.00
132.12
131.71
129.13
128.78
127.55
126.99
123.76
123.37
77.42
76.99
76.57
68.28
55.39
25.45
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm
O
NH
HN
1la
1ma
Less polar diastereoisomer

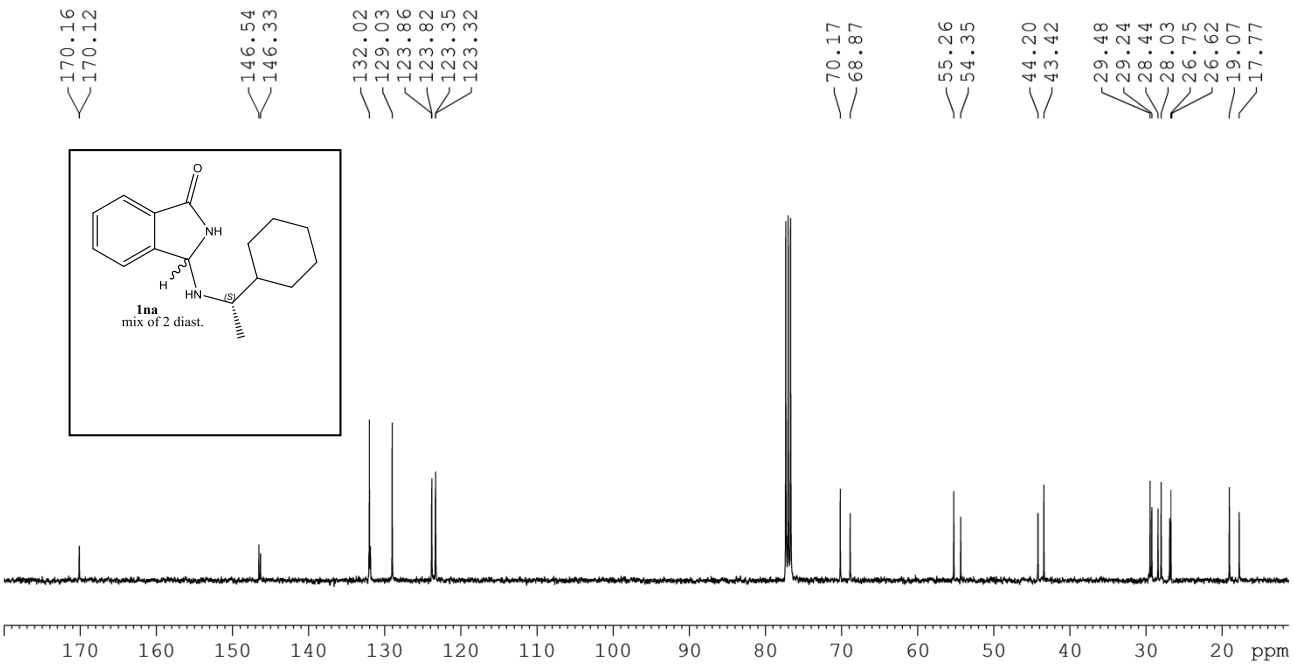

7.77
7.74
7.53
7.53
7.30
7.26
6.40
5.45
4.13
4.10
4.08
4.05
1.85
1.48
1.45
1.07
8.04
1.00
1.00
1.00
1.04
3.00
1la
1ma
More polar diastereoisomer
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm

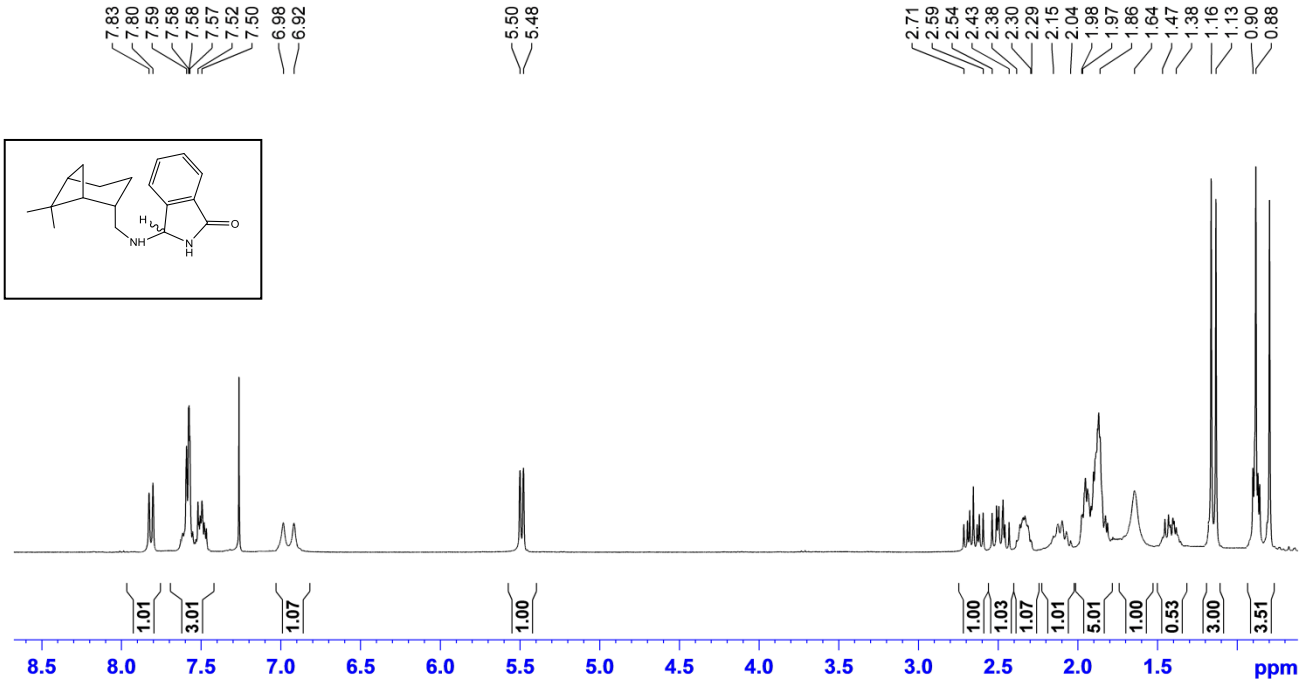

169.66
146.01
145.68
131.99
129.06
128.87
127.61
126.44
123.81
123.31
77.54
77.03
76.52
69.71
56.25
23.98
250MHz
1la
1ma
More polar diastereoisomer
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm

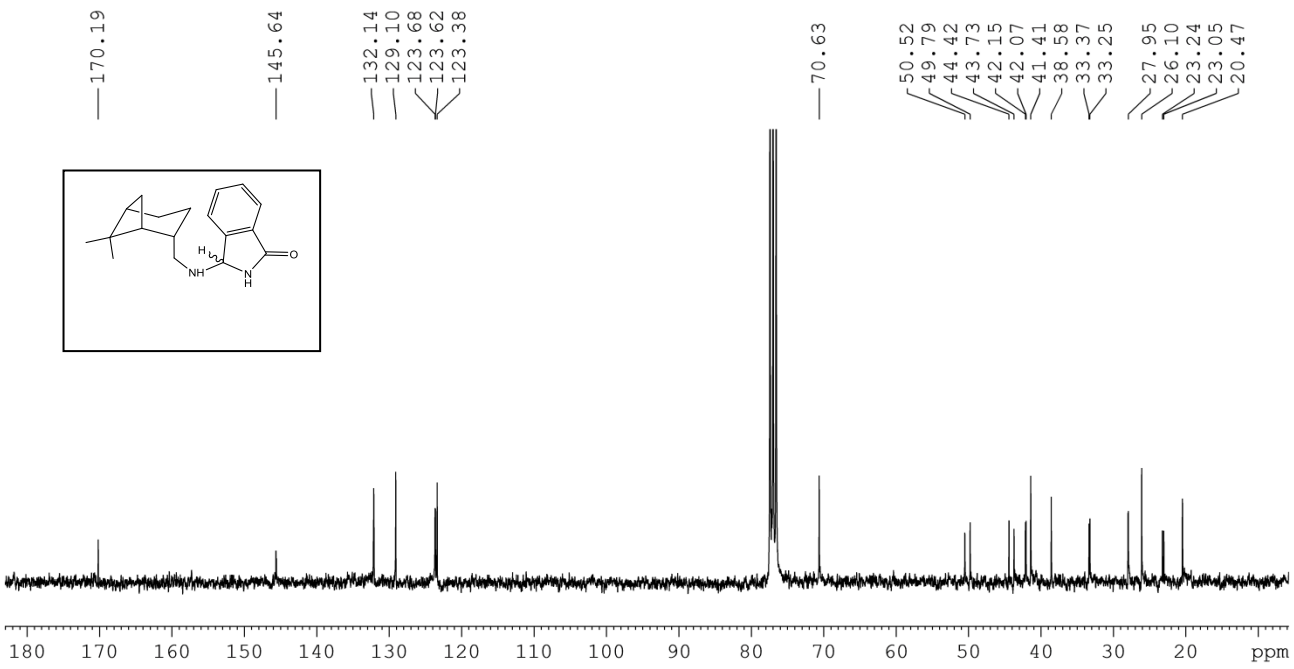

7.93
7.70
7.68
7.50
7.48
7.46
7.41
7.39
7.37
7.32
7.30
7.28
7.27
5.09
4.10
4.09
4.07
4.05
1.80
1.39
1.38
Br
O
NH
HN
*
(R)
1mb
Less polar diastereoisomer
1.03
1.01
3.04
2.02
2.09
1.03
1.00
1.01
3.01
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

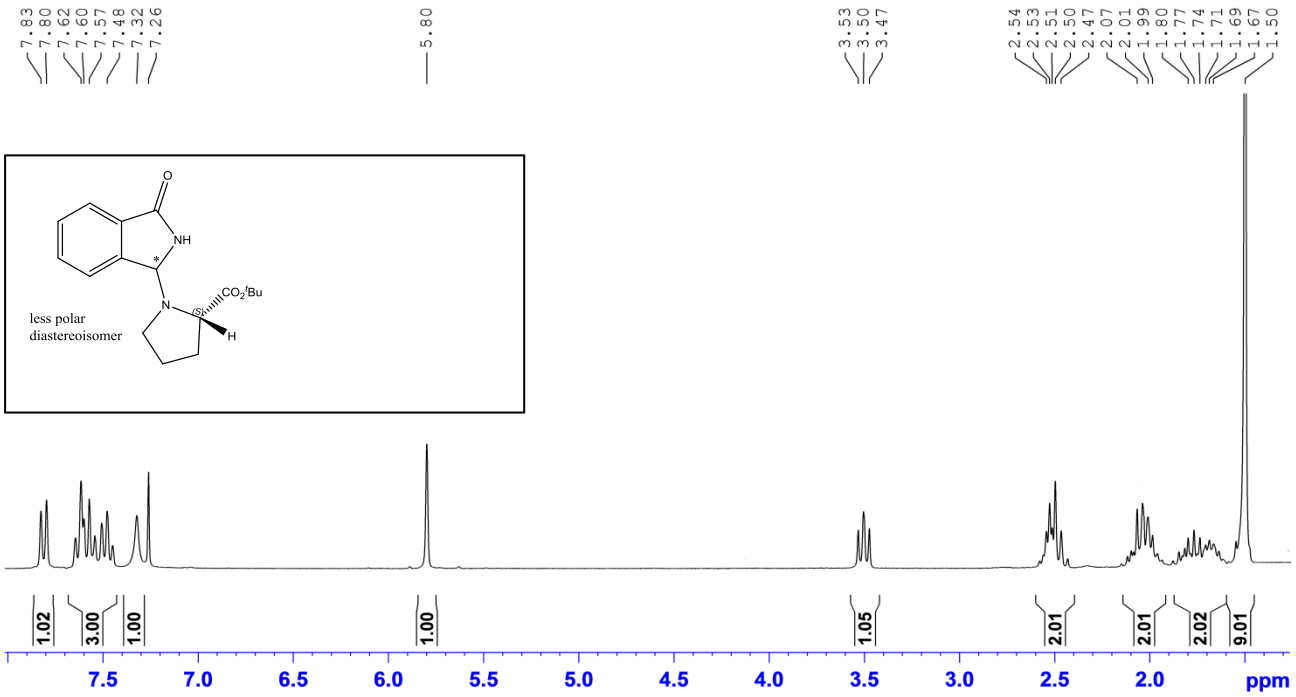

168.67
144.75
143.81
135.12
133.80
128.87
127.86
127.69
126.96
126.63
125.45
123.28
68.18
55.44
25.38
Br
O
NH
HN
*
(R)
1mb
Less polar diastereoisomer
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

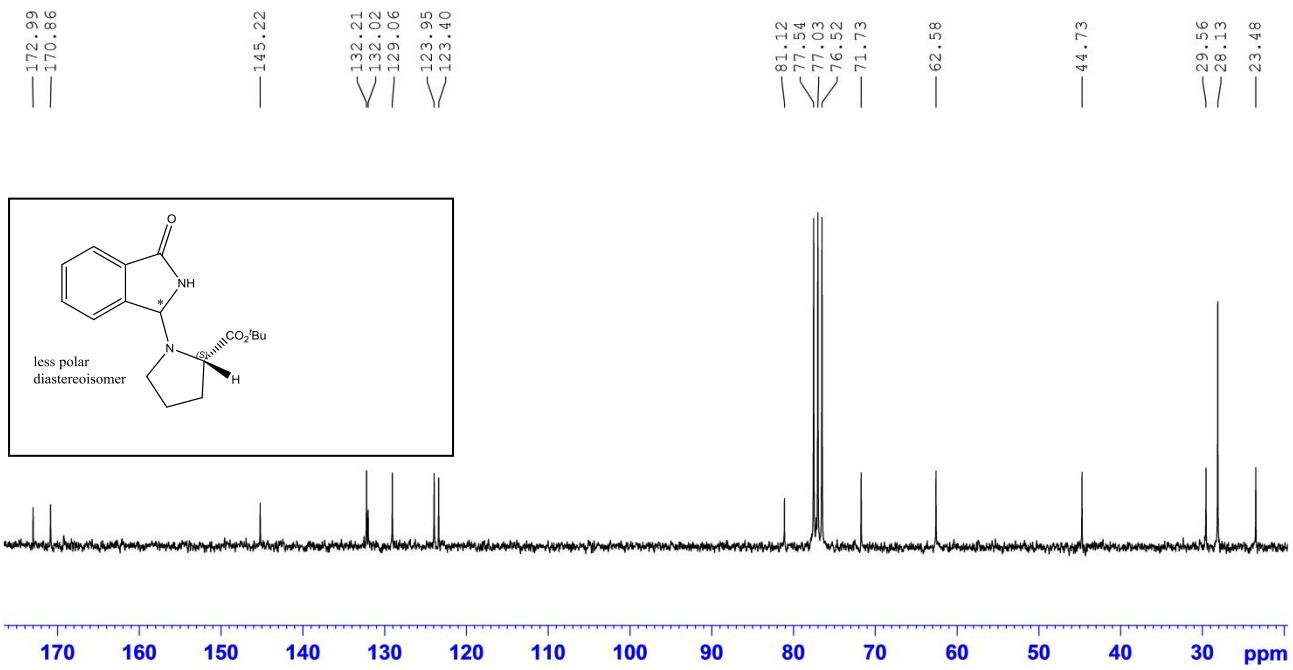

7.82
7.81
7.80
7.79
7.60
7.58
7.58
7.57
7.55
7.50
7.48
7.46
7.26
7.25
7.16
5.52
5.46
2.78
2.76
2.75
2.72
2.69
2.68
2.66
2.63
1.43
1.42
1.26
1.19
1.14
1.13
1.03
1.01
0.98
O
NH
H
HN
(S)
1na
mix of 2 diast.
2.64
7.93
1.69
1.00
1.63
1.64
1.03
39.02
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

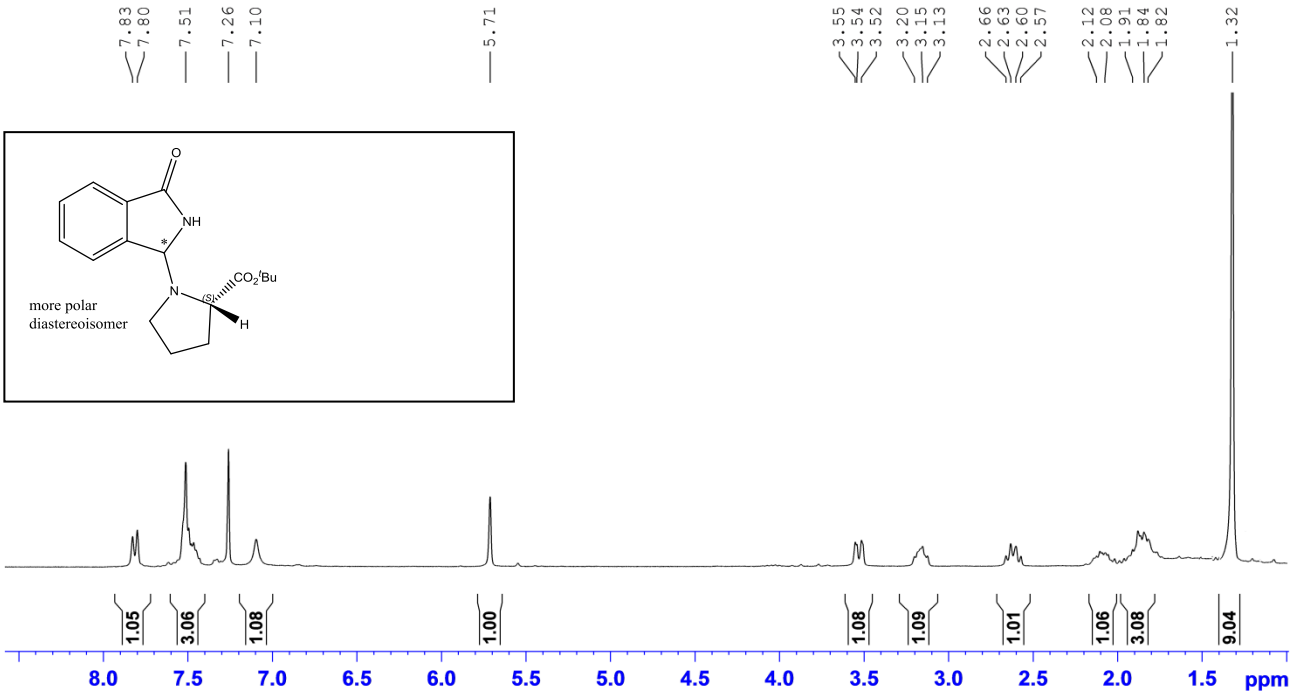

170.16
170.12
146.54
146.33
132.02
129.03
123.86
123.82
123.35
123.32
70.17
68.87
55.26
54.35
44.20
43.42
29.48
29.24
28.44
28.03
26.75
26.62
19.07
17.77
O
NH
H
HN
(S)
1na
mix of 2 diast.
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

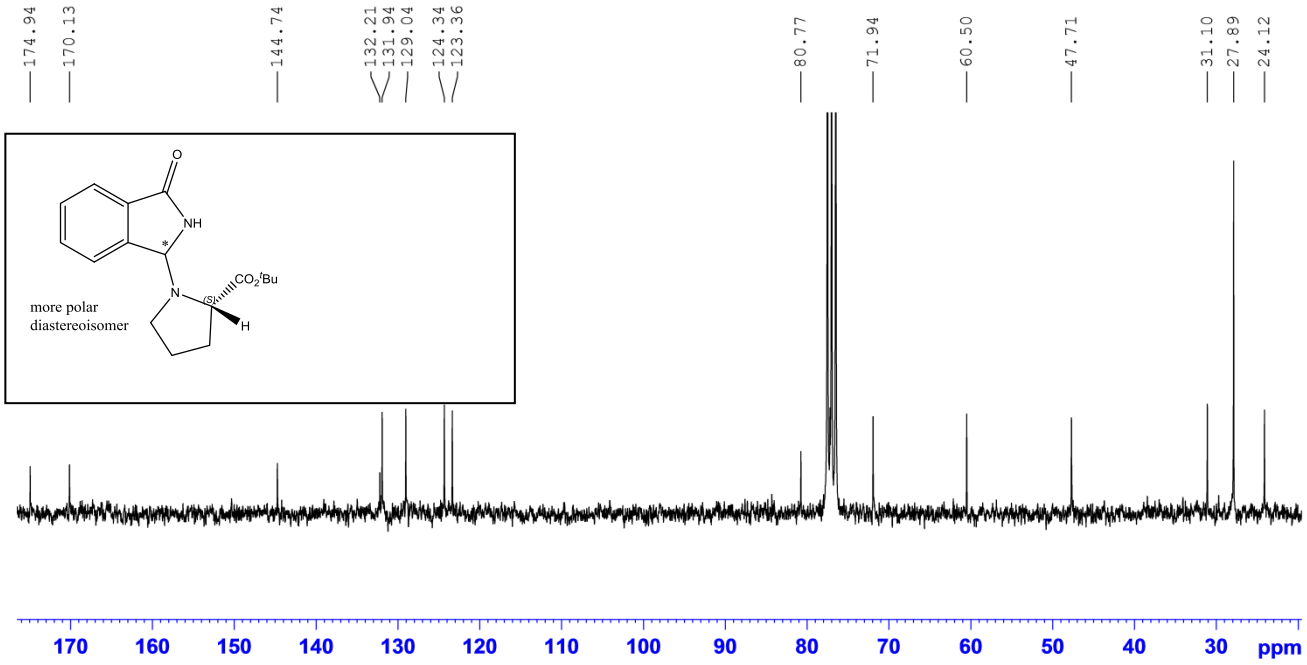

7.83
7.80
7.59
7.58
7.58
7.57
7.52
7.50
6.98
6.92
5.50
5.48
2.71
2.59
2.54
2.43
2.38
2.30
2.29
2.15
2.04
1.98
1.97
1.86
1.64
1.47
1.38
1.16
1.13
0.90
0.88
1.01
3.01
1.07
1.00
1.00
1.03
1.07
1.01
5.01
1.00
0.53
3.00
3.51
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm


170.19
145.64
132.14
129.10
123.68
123.62
123.38
70.63
50.52
49.79
44.42
43.73
42.15
42.07
41.41
38.58
33.37
33.25
27.95
26.10
23.24
23.05
20.47
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


7.83
7.80
7.62
7.60
7.57
7.48
7.32
7.26
5.80
3.53
3.50
3.47
2.54
2.53
2.51
2.50
2.47
2.07
2.01
1.99
1.80
1.77
1.74
1.71
1.69
1.67
1.50
O
NH
*
N
(S)
CO2tBu
H
less polar
diastereoisomer
1.02
3.00
1.00
1.00
1.05
2.01
2.01
2.02
9.01
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
ppm


172.99
170.86
145.22
132.21
132.02
129.06
123.95
123.40
81.12
77.54
77.03
76.52
71.73
62.58
44.73
29.56
28.13
23.48
O
NH
*
N
(S)
CO2tBu
H
less polar
diastereoisomer
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm


7.83
7.80
7.51
7.26
7.10
5.71
3.55
3.54
3.52
3.20
3.15
3.13
2.66
2.63
2.60
2.57
2.12
2.08
1.91
1.84
1.82
1.32
O
NH
*
N
(S)
CO2tBu
H
more polar
diastereoisomer
1.05
3.06
1.08
1.00
1.08
1.09
1.01
1.06
3.08
9.04
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


174.94
170.13
144.74
132.21
131.94
129.04
124.34
123.36
80.77
71.94
60.50
47.71
31.10
27.89
24.12
O
NH
*
N
(S)
CO2tBu
H
more polar
diastereoisomer
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm