Organocatalytic C3-Selective Friedel-Crafts Alkylations of Indoles with α,β-Unsaturated Ketones

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Electronic Supplementary Information(ESI)

Gerneral Information. Material were purchased from commercial suppliers and used without further purification. Solvents were dried according to standard procedures. Reactions were monitored by thin-layer chromatography (TLC) analysis. Flash column chromatography was performed using 200-300 mesh silica gel. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. ^{1}HNMR spectra were recorded on Varian Mercury 400 (400 MHz) spectrophotometers. Chemical shifts are reported in ppm from the solvent resonance as the internal standard ($CDCl_3$: 7.26 ppm). Data are reported as follows: chemical shift, multiplicity (s=single, d=doublet, t=triplet, q=quartet, m=multiplet, bs=broad single), coupling constants (Hz) and integration. ^{13}CNMR spectra were recorded on Varian Mercury 400 (100 MHz) with complete proton decoupling spectrophotometers ($CDCl_3$: 77.0 pm). Mass spectra analysis was performed on API 200 LC/MS system. Elementary analysis was taken on a Vario EL III elementary analysis instrument. 1-methylindole, 1,2-dimethylindole were prepared as described in the literature.[1]

General Procedure: To a round bottom flask equipped with a magnetic stir bar and charged with pyrrolidine was added the solvent, and the approrite acid , then placed in room temperature. The solution was stirred for 10 min before addition of enone. After stirring for an additional 10 min the indole substrate was added in one portion. The resulting suspension was stirred at room temperature until complete consumption of the indole substrate as determined by TLC. The reaction mixture was diluted with ether and washed with brine. The organic layer was dried with

$MgSO_4$ and concentrated in vacuo. The resulting residue was purified by silica gel chromatography to afford the title compounds.

4-(3-Indolyl)-5-methyl-2-hexanone (Table 2, entry 1). Prepared according to the general procedure from indole (58.6 mg, 0.50 mmol), 5-methyl-3-hexene-2-one (198 μL, 1.50 mmol), pyrrolidine (12.5 μL, 0.15 mmol), and $HClO_4$ (12 μL, 0.15 mmol) in CH_2Cl_2 (1.00 mL) at room tempetature for 6h and worked up in the general procedure, after silica gel chromatography, the title compound as a pale yellow oil (92% yield). ^{1}HNMR(400MHz, $CDCl_3$) δ: 0.87 (d, J=6.8Hz, 3H), 0.92 (d, J=6.4Hz, 3H), 1.97 (s, 3H), 2.02-2.09 (m, 1H), 2.82-2.92 (m, 2H), 3.31-3.36 (m, 1H), 6.94 (s, 1H), 7.08 - 7.19 (m, 2H), 7.33 - 7.37 (m,1H), 7.65(dm, J=7.6Hz, 1H), 8.01(bs,1H). ^{13}CNMR (100 MHz, $CDCl_3$) δ:20.3, 20.5, 30.0, 32.6, 39.3, 47.0, 111.2, 117.3, 119.0, 119.3, 121.7, 121.9, 127.1, 136.2, 209.6. MS(EI)m/z: 229(M^+),215,186,172,142. Anal calcd for $C_{15}H_{19}NO$: C,78.56; H,8.35; N,6.11; Found: C,78.71; H,8.31; N,6.21.

4-(3-(2-Methylindolyl))-5-methyl-2-hexanone(Table2,entry2). Prepared according to the general procedure from 2-methylindole (65.6 mg,0.50 mmol), 5-methyl-3-hexene-2-one (198 μL,1.50 mmol), pyrrolidine (12.5 μL,0.15 mmol), $HClO_4$ (12 μL,0.15 mmol) in CH_2Cl_2 (1.00 mL) at room tempetature for 10h and worked up in the general procedure, after silica gel chromatography, the title compound as a pale yellow oil (90% yield). ^{1}HNMR(400MHz, $CDCl_3$) δ: 0.71 (d, J=6.8Hz, 3H), 1.02 (d, J=6.4Hz, 3H), 1.84 (s, 3H), 2.13 (m, 1H), 2.28 (s, 3H), 2.87 (dd, J=14, 3.6Hz, 1H), 3.04(dd, J=9.6, 4.0Hz, 1H), 3.10 (m, 1H), 7.01-7.07 (m,2H), 7.16-7.19 (m,1H), 7.55 (dm, J=8.0Hz, 1H), 7.95 (bs, 1H). ^{13}CNMR(100MHz,$CDCl_3$) δ:12.0, 21.3, 21.4, 30.7, 32.4, 40.0, 46.6, 110.4, 112.8, 118.6, 119.0, 120.3, 127.2, 131.9,135.5,209.7. MS(EI)m/z:243(M^+),214,200,171. Anal calcd for $C_{16}H_{21}NO$: C,78.97; H,8.70; N,5.76; Found:C,78.93; H,8.79; N,5.80.

4-(3-(1,2-Dimethylindolyl))-5-methyl-2-hexanone (Table 2, entry 3). Prepared according to the general procedure from 1,2-Dimethylindole (72.6 mg,0.50 mmol),5-methyl-3-hexene-2-one (198 μL,1.50 mmol), pyrrolidine (12.5 μL,0.15 mmol), and $HClO_4$ (12 μL,0.15 mmol) in CH_2Cl_2 (1.00 mL) at room tempetature for 15h and worked up in the general procedure, after silica gel chromatography, the title compound as a pale yellow solid (87% yield). ^{1}HNMR (400MHz,$CDCl_3$) δ: 0.71(d,J=6.8Hz,3H),1.03(d,J=6.8Hz,3H), 1.86(s,3H), 2.17(m,1H), 2.36(s,3H), 2.88-2.91(m,1H), 3.07-3.13(m,2H), 3.63(s,3H), 7.02-7.26(m,3H), 7.58(dm,J=8.0Hz,1H). ^{13}CNMR(100MHz,$CDCl_3$) δ: 10.5, 21.4, 21.5, 29.5, 30.7, 32.5, 40.2, 46.9, 108.6, 112.4, 118.2,119.1,120.0,126.3, 133.8, 136.9, 209.3.

MS(EI)m/z:257(M^+), 214, 198, 184, 170. Anal calcd for $C_{17}H_{23}NO$: C,79.33; H,9.01; N,5.44; Found:C,79.69; H,9.04; N,5.12.

4-(3(1-Methylindolyl))-5-methyl-2-hexanone(Table2,entry4). Prepared according to the general procedure from 1-methylindole (65.6 mg,0.50 mmol), 5-methyl-3-hexene-2-one (198 μL,1.50 mmol), pyrrolidine (12.5 μL, 0.15 mmol), and $HClO_4$ (12 μL,0.15 mmol) in CH_2Cl_2 (1.00 mL) at room tempetature for 20h and worked up in the general procedure, after silica gel chromatography, the title compound as a yellow oil (83%yield). ^{1}HNMR(400MHz,$CDCl_3$) δ : 0.86(d, J=6.4 Hz, 3H), 0.91(d, J=6.8 Hz, 3H), 1.96(s, 3H), 2.05(m, 1H), 2.82-2.85(m, 2H), 3.30-3.32(m, 1H), 3.71(s,1H), 7.08(tm, J=7.4 Hz, 1H), 7.17-7.26(m, 2H), 7.62(dm, J=8.0 Hz, 1H). ^{13}CNMR (100MHz, $CDCl_3$) δ :20.1, 20.3 30.0, 32.4, 32.6, 39.0 47.0 109.2, 116.0, 118.6, 119.5, 121.3, 126.7, 127.7, 137.0, 209.4. MS(EI) m/z: 243(M^+), 200, 186, 157, 143. Anal calcd for $C_{16}H_{21}NO$: C,78.97; H,8.70; N,5.76; Found: C, 78.75; H, 8.76; N, 5.75.

4-(3-Indolyl)-4-phenyl-2-butanone (Table 2, entry 5). Prepared according to the general procedure from indole (58.6 mg,0.50 mmol), benzalacetone (219 mg, 1.50 mmol), pyrrolidine (12.5 μL,0.15 mmol), $HClO_4$ (12 μL, 0.15 mmol) in CH_2Cl_2 (1.00mL) at room tempetature for 12h and worked up in the general procedure, after silica gel chromatography, the title compound as a pale brown oil (80% yield). ^{1}HNMR(400MHz,$CDCl_3$) δ : 2.07(s,3H), 3.18(dd, J=16.0,7.6Hz, 1H), 3.23(dd, J=16.1,7.2Hz, 1H), 4.83(t, J=7.6Hz, 1H), 6.98-7.33(m,9H), 7.42(dm, J=8.4Hz, 1H) , 8.05(bs,1H). ^{13}CNMR(100MHz,$CDCl_3$) δ :30.3, 38.4, 50.3, 111.1, 118.8, 119.4, 121.3, 122.2, 126.3, 136.5, 127.7, 128.4, 136.5, 144.0, 207.7. MS(EI) m/z: 263(M^+), 221, 206,143. Anal calcd for $C_{18}H_{17}NO$: C,82.10; H,6.51; N,5.32; Found: C,82.19; H,6.52; N,5.27.

4-(3-(2-Methylindolyl))-4-phenyl-2-butanone(Table2.entry6). Prepared according to the general procedure from 2-methylindole(65.6 mg,0.50 mmol), benzalacetone (219 mg,1.50 mmol), pyrrolidine (12.5 μL,0.15 mmol), $HClO_4$(12 μL,0.15 mmol) in CH_2Cl_2 (1.00 mL) at room tempetature for 12h and worked up in the general procedure, after silica gel chromatography, the title compound as a yellow solid (87% yield). ^{1}HNMR(400MHz, $CDCl_3$) δ : 1.95(s, 3H), 2.35(s, 3H), 3.26(dd, J=16.8, 6.4 Hz, 1H), 3.38(dd, J=16.0, 8.4 Hz, 1H), 4.80(t, J=7.6 Hz, 1H), 6.92-7.25(m, 8H), 7.40(dm, J=7.6 Hz, 1H), 7.74(bs, 1H). ^{13}CNMR(100MHz,$CDCl_3$) δ :12.1, 30.8, 36.8, 48.2, 110.4, 113.1, 119.1, 119.2, 120.8, 125.9, 127.3, 128.3, 131.8, 135.4, 144.0, 207.9. MS(EI) m/z 277(M^+), 234,218,204,157. Anal calcd for $C_{19}H_{19}NO$: C, 82.28; H, 6.90, N, 5.05; Found: C, 82.08; H, 7.00; N, 5.36.

4-(3-(1,2-Dimethylindolyl))-4-phenyl-2-butanone (Table 2, entry 7). Prepared according to the general procedure from 1,2-dimethylindole(72.6 mg,0.50 mmol), benzalacetone (219 mg,1.50 mmol), pyrrolidine (12.5 µL,0.15 mmol), $HClO_4$ (12 µL,0.15 mmol) in CH_2Cl_2 (1.00 mL) at room tempetature for 4day and worked up in the general procedure, after silica gel chromatography, the title compound as a yellow solid (69% yield). ^{1}HNMR(400MHz, $CDCl_3$) δ : 1.98(s,3H), 2.40(s,3H), 3.33(dd, J=16, 6.4 Hz, 1H), 3.44(dd, J=16.0, 8.0 Hz, 1H), 3.60(s, 3H), 4.89(t, J=7.2 Hz, 1H), 6.97(tm, J=8.0 Hz, 1H), 7.10-7.14(m, 2H), 7.20-7.24(m, 3H), 7.29(dm, J=7.2 Hz, 2H), 7.47(dm, J=7.6 Hz, 1H). ^{13}CNMR(100MHz,$CDCl_3$) δ :10.5, 29.5 30.7, 37.0, 48.4, 108.8, 112.4, 118.7, 119.0, 120.3, 125.8, 126.3, 127.3, 128.2, 133.6, 136.8, 144.3, 207.8. MS(EI) m/z:291(M^+), 248, 232, 217, 144. Anal calcd for $C_{20}H_{21}NO$:C,82.44; H,7.26; N,4.81; Found: C,82.61: H,7.23; N,4.87.

4-(3-(1-Methylindolyl))-4-phenyl-2-butanone(Table2,entry8). Prepared according to the general procedure from 1-methylindole (65.6 mg,0.50 mmol),benzalacetone (219 mg,1.50 mmol), pyrrolidine (12.5 µL,0.15 mmol), $HClO_4$ (12 µL,0.15 mmol) in CH_2Cl_2 (1.00 mL) at room tempetature for 2day and worked up in the general procedure, after silica gel chromatography, the title compound as a brown oil (79% yield). ^{1}HNMR(400MHz,$CDCl_3$) δ :2.07(s,3H), 3.15(dd, J=16.0, 7.6 Hz, 1H), 3.24(dd, J=16.0, 7.6 Hz, 1H), 3.73(s, 3H), 4.82(t, J=7.6 Hz, 3H), 6.82(s,1H), 7.00(tm,J=7.5Hz,1H),7.12-7.41(m,7H),7.42(dm,J=8.0Hz,1H). ^{13}CNMR(100MHz,$CDCl_3$) δ :30.3, 32.6, 38.3, 50.4,109.2, 117.2, 118.8,119.4, 121.6, 126.1, 126.3, 126.8, 127.6, 128.4, 137.2, 144.1, 207.6. MS(EI)m/z : 277(M^+), 220, 217, 202, 158. Anal calcd for $C_{19}H_{19}NO$: C,82.28; H,6.90; N,5.05; Found: C,82.43;H,6.80;N,5.00.

4-(3-(1-Methylindolyl))-2-pentanone(Table3,entry9). Prepared according to the general procedure from 1-methylindole (65.6 mg,0.50 mmol), 3-penten-2-one (146 µL,1.50 mmol), pyrrolidine (12.5 µL, 0.15 mmol), and $HClO_4$ (12 µL,0.15 mmol) in CH_2Cl_2 (1.00 mL) at room tempetature for 20h and worked up in the general procedure, after silica gel chromatography,the title compound as a yellow oil (90% yield), ^{1}HNMR(400MHz,$CDCl_3$) δ : 1.37 (d, J=6.8 Hz, 3H), 2.10(s,3H), 2.70(dd, J=16.4, 8.4 Hz, 1H), 2.93(dd, J=16.0, 6.0 Hz, 1H), 3.64(m, 1H), 3.74(s, 3H), 6.84(s, 1H), 7.11(tm, 7.8 Hz, 1H), 7.21-7.31(m, 2H), 7.64(dm, J=8.4 Hz, 1H). ^{13}CNMR(100MHz,$CDCl_3$) δ :21.4, 27.0, 30.4, 32.6, 51.6, 109.3, 118.6, 119.2, 119.4, 121.6, 125, 126.5, 137.1, 208.7. MS(EI) m/z: 216(M^+),172,157,143,115. Anal calcd for $C_{14}H_{17}NO$: C,78.10; H,7.96; N,6.51; Found: C,78.39; H,7.90; N,6.55.

4-(3-indolyl) -2-pentanone(Table3,entry10). Prepared according to the general procedure from indole (58.6 mg,0.50 mmol), 3-penten-2-one (146 µL,1.50 mmol), pyrrolidine (12.5 µL, 0.15 mmol), and $HClO_4$ (12 µL,0.15

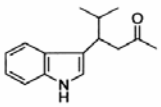
mmol) in CH_2Cl_2 (1.00 mL) at room tempetature for10h and worked up in the general procedure, after silica gel chromatography,the title compound as a yellow oil (82% yield), ^{1}HNMR(400MHz,$CDCl_3$) δ:1.37 (d, J=1.37Hz, 3H), 2.08(s, 3H), 2.71(dd,J=16.4, 8.4Hz), 2.93(dd,J=16.0, 6.0Hz), 3.64(m, 3H), 6.90(S,1H), 7.11-7.64(m,4H),8.14(s,1H). ^{13}CNMR(100MHz,$CDCl_3$) δ:21.0, 26.7,30.2,51.3,111.4,119.0,119.2,120.3,120.7,122.0,126.6,136.5,209.4.MS(EI) m/z:201(M^+),158,144,116,85. Anal calcd for $C_{13}H_{15}NO$: C,77.58;H,7.51;N,6.96; Found: C,77.51; H,7.52; N,6.99.

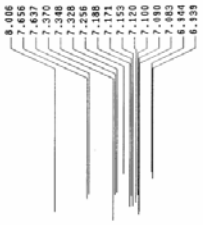
4-(3-(2-Methylindolyl))-2-pentanone(Table3,entry11). Prepared according to the general procedure from 2-methylindole(65.6 mg,0.50 mmol), 3-penten-2-one (146 μL,1.50 mmol), pyrrolidine (12.5 μL, 0.15 mmol), and $HClO_4$ (12 μL,0.15 mmol) in CH_2Cl_2 (1.00 mL) at room tempetature for14h and worked up in the general procedure, after silica gel chromatography,the title compound as a yellow oil 89% yield), ^{1}HNMR(400MHz,$CDCl_3$) δ: 0.82(d,3H), 1.53(s, 3H), 1.92(s, 3H), 2.39(dd, J=16.4,6.4Hz, 1H), 2.55(dd, J=16.0, 6.0Hz,1H), 3.1(m, 1H), 6.61-6.77(m,3H),7.17(m,1H),7.64(s,1H). ^{13}CNMR(100MHz,$CDCl_3$) δ:11.6, 20.8, 26.8, 30.4, 50.2, 110.5, 114.6, 118.7, 118.8, 120.5, 126.8, 130.5, 135.5, 209.6. MS(EI) m/z: 215(M^+),172,158,130,115. Anal calcd for$C_{14}H_{17}NO$: C,78.1;H,7.96;N,6.51: Found: C,78.5;H,7.92:N,6.53.

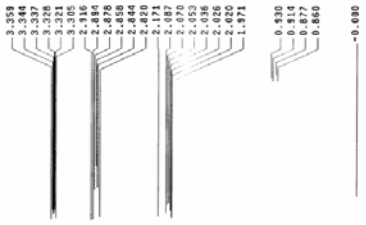
Reference:

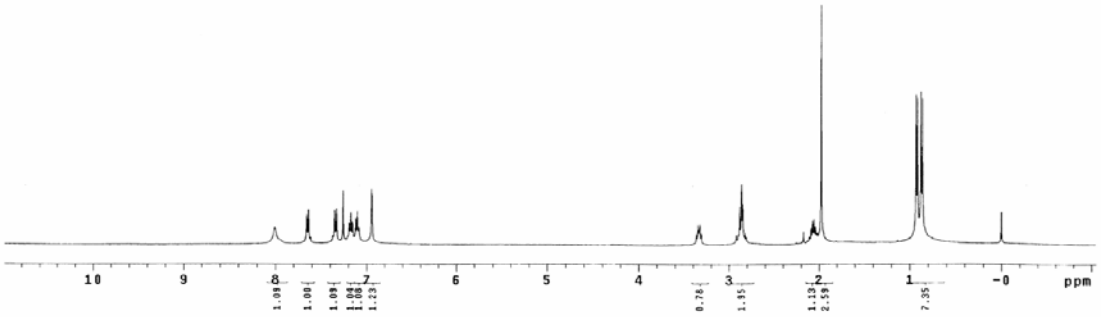
1. Yasuo KZKUGAWA; Yuko MIKAKE. *Synthesis* 1981,461.

ldp22 cdcl3









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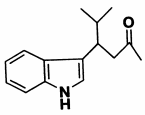

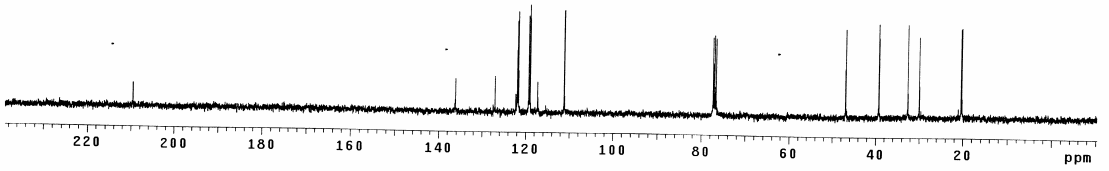

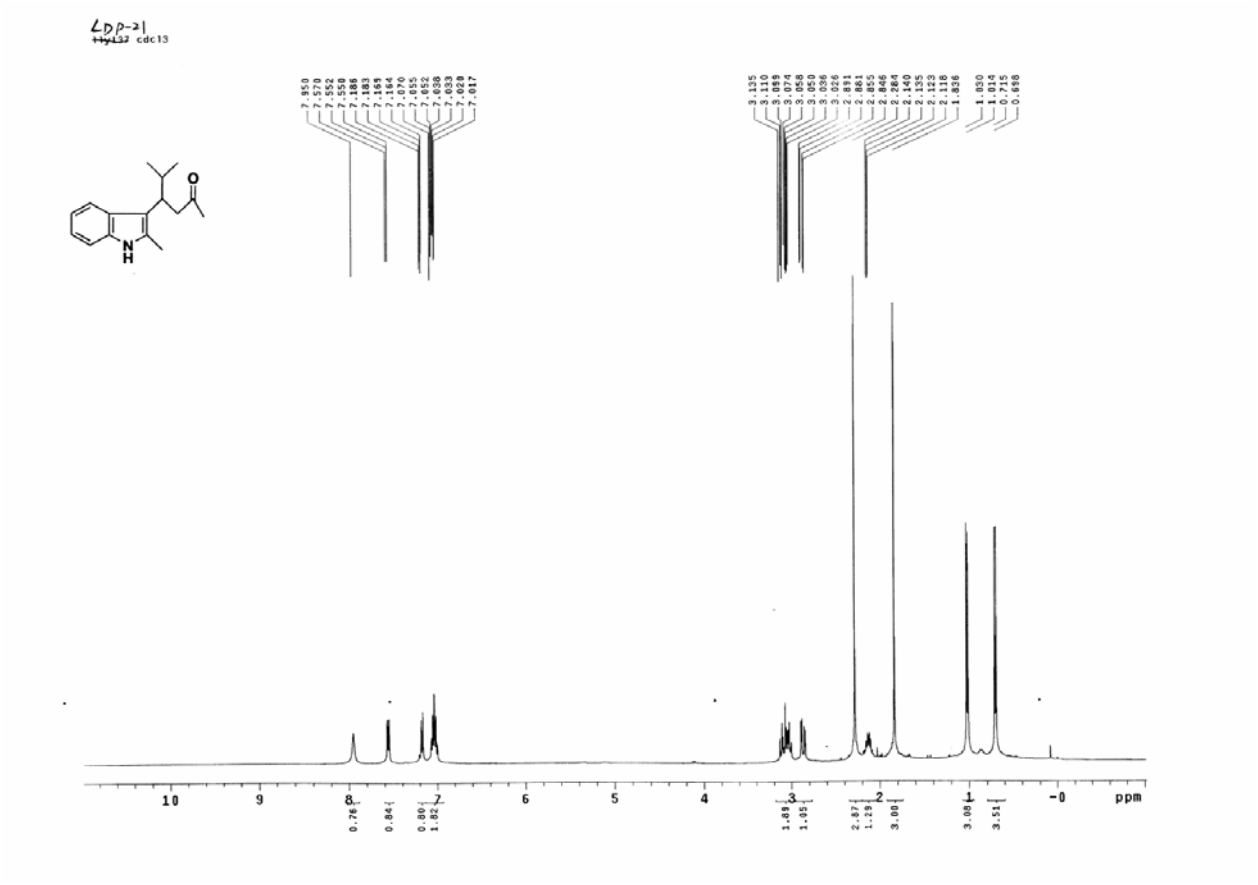
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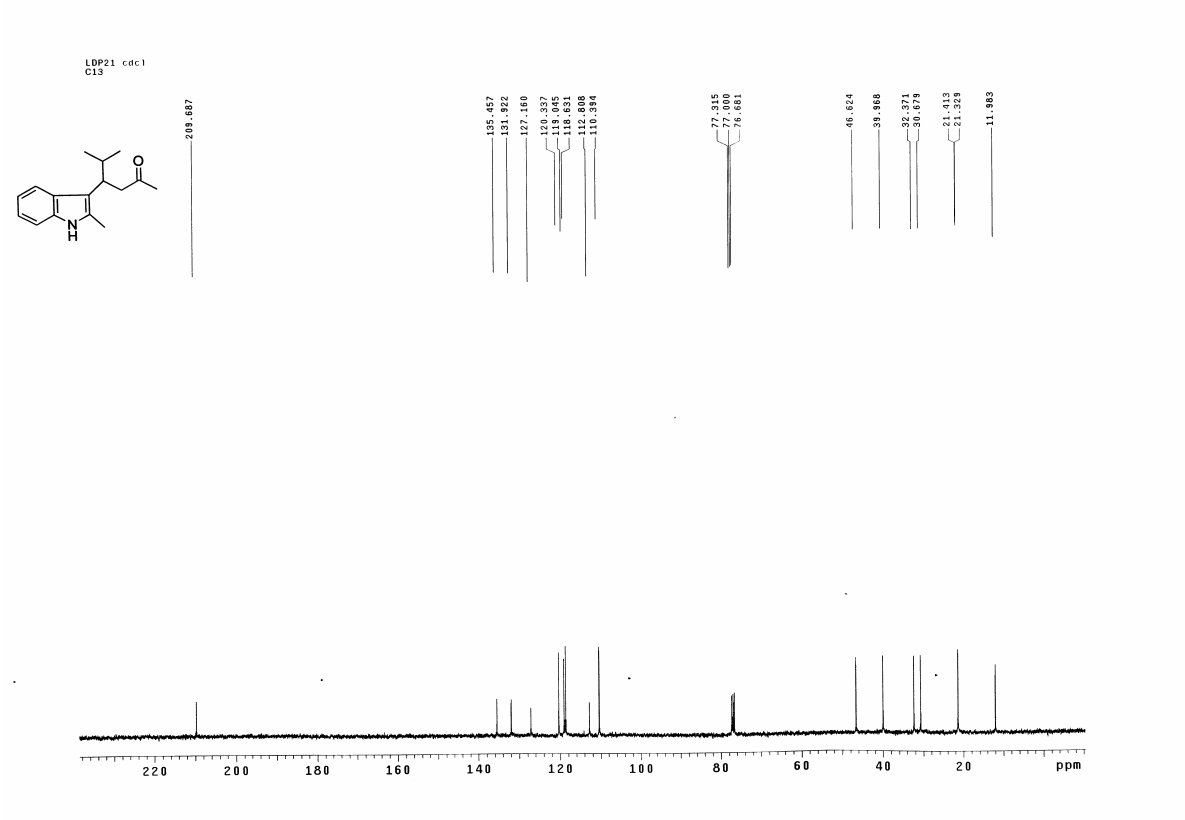
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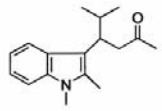

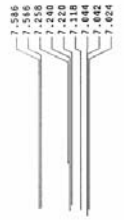

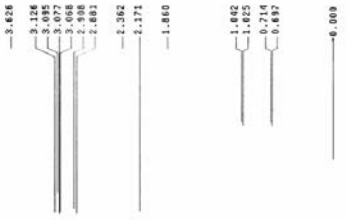

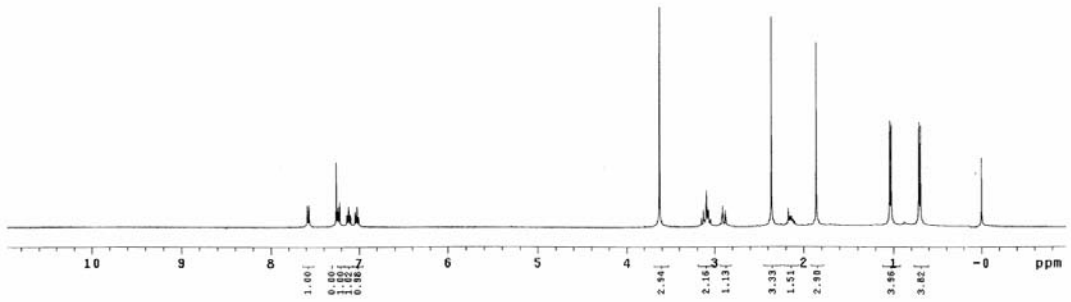

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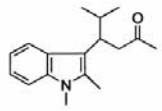

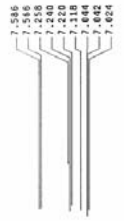

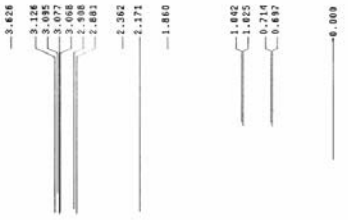

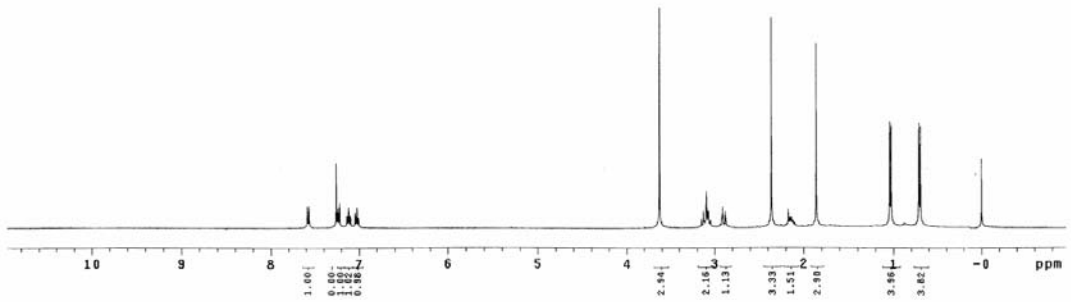

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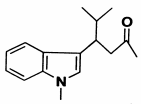
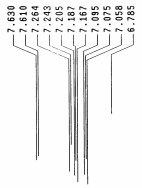
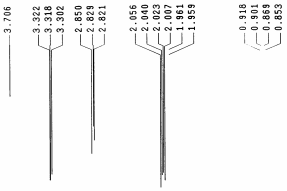
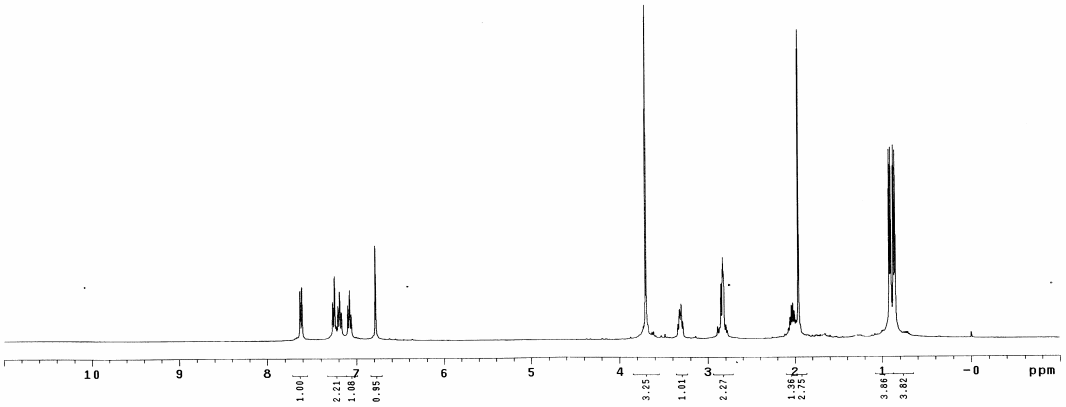
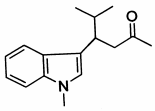


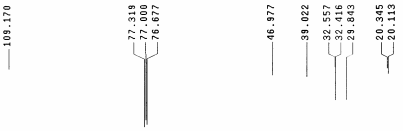


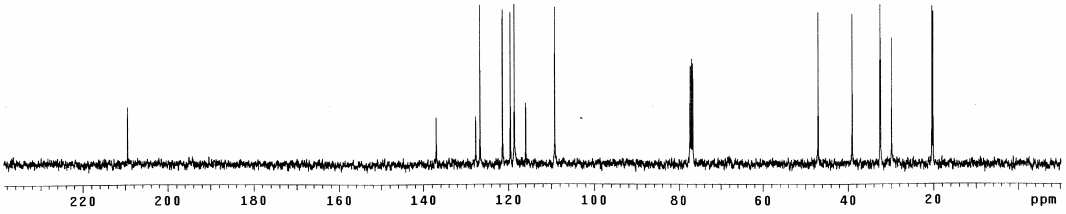


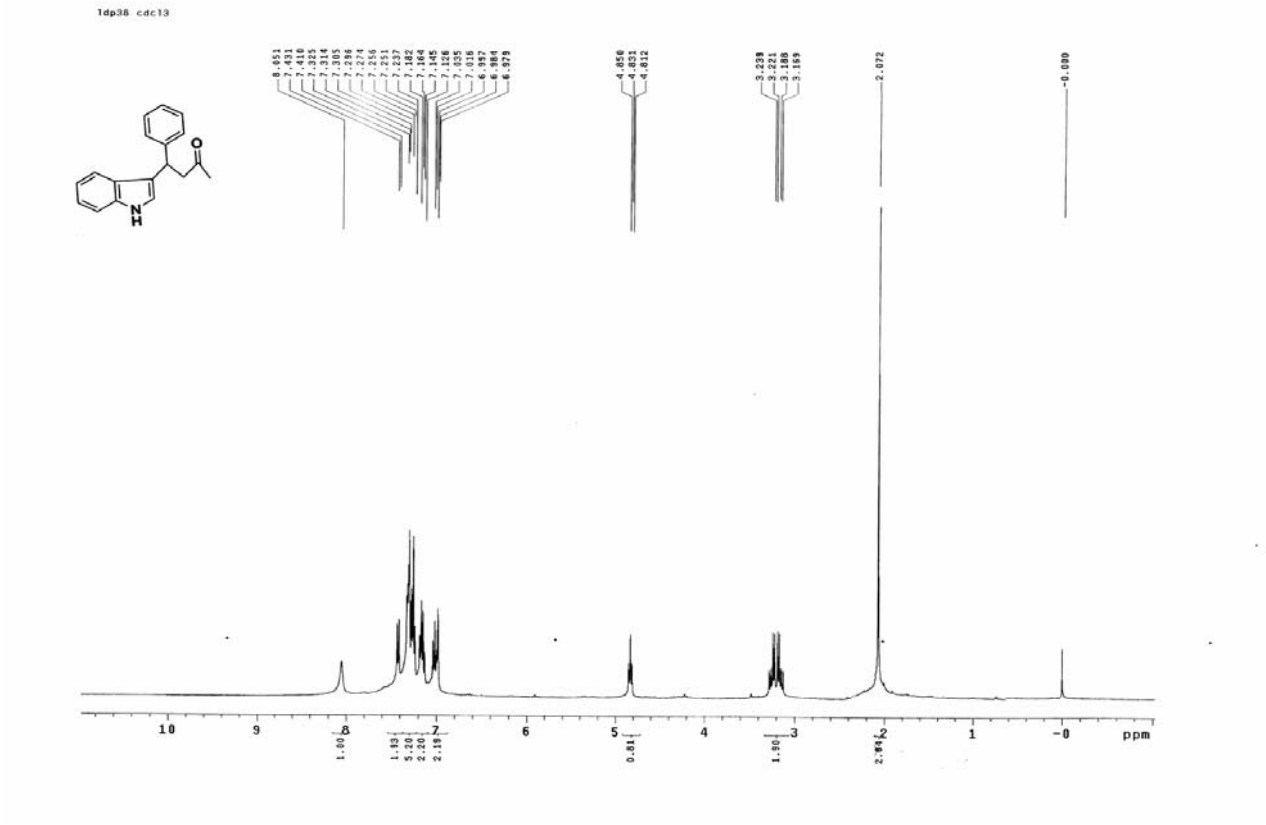


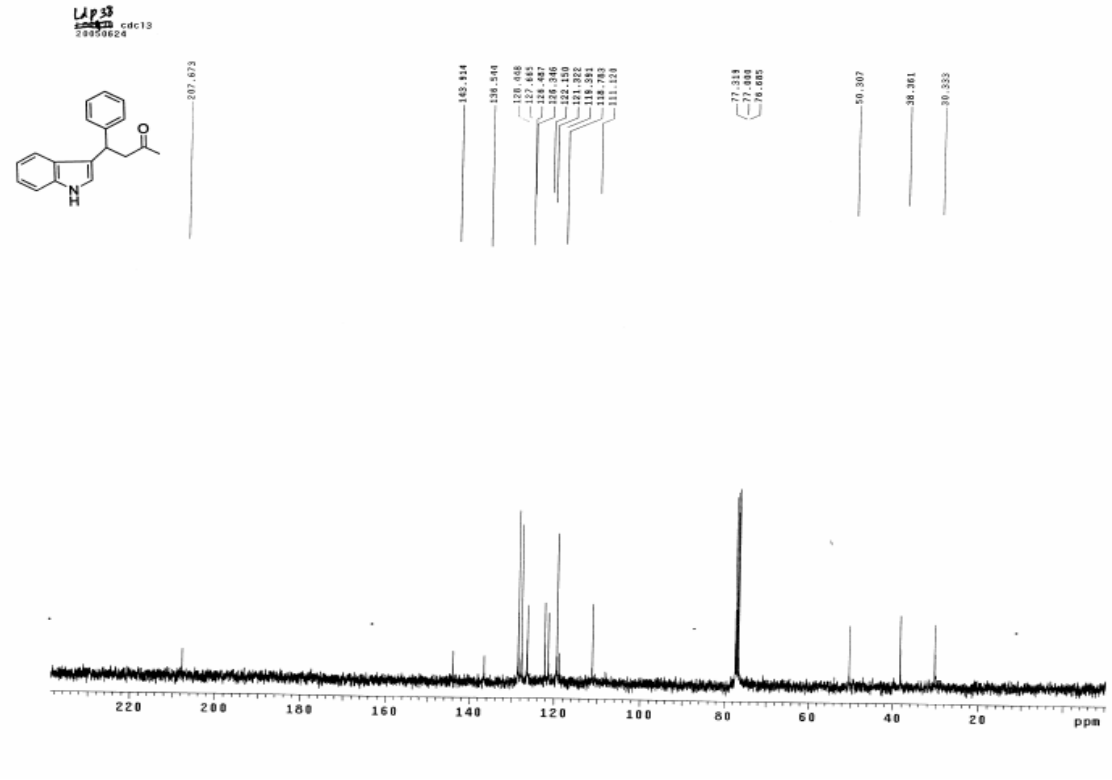
Li038
rdp38 c13

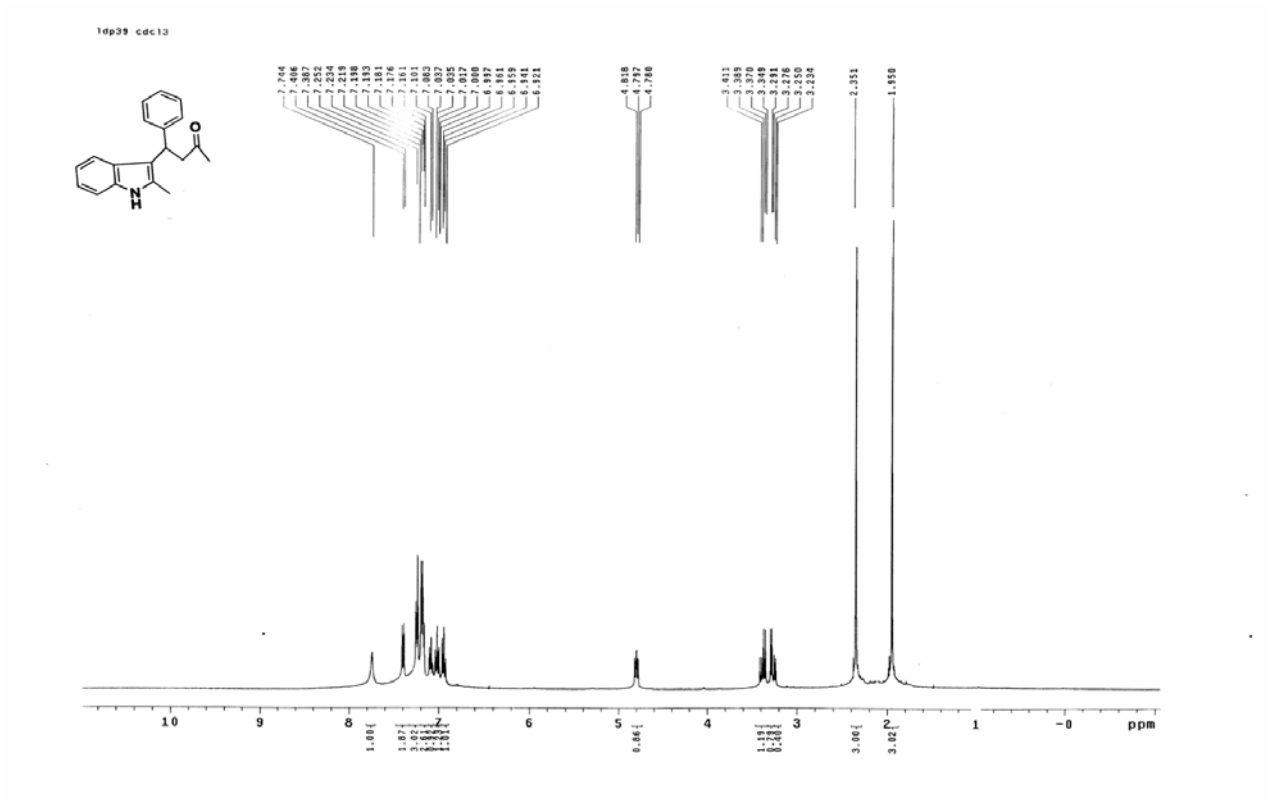


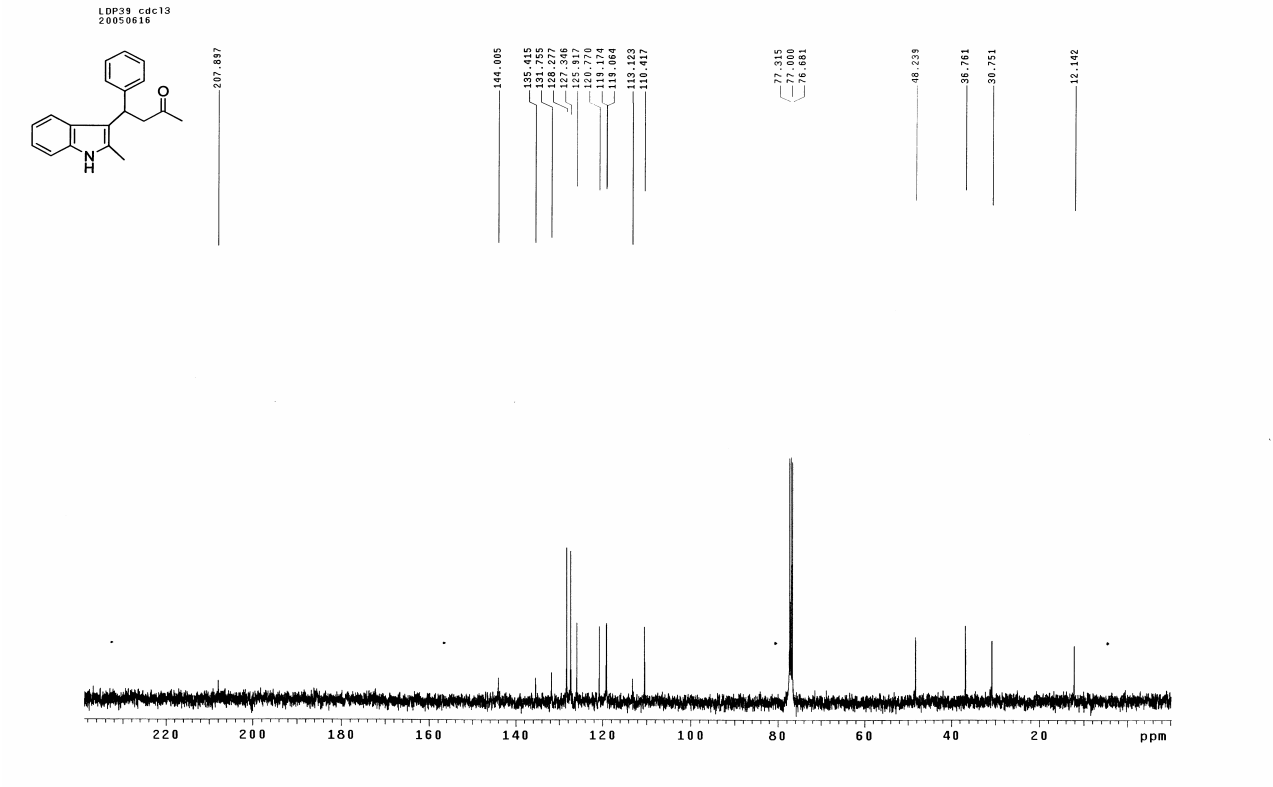




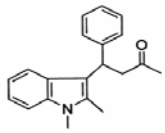

1dp38 cdcl3
8.651
7.431
7.410
7.325
7.314
7.305
7.296
7.274
7.256
7.251
7.237
7.182
7.164
7.145
7.126
7.035
7.016
6.957
6.884
6.879
4.650
4.631
4.612
3.239
3.221
3.188
3.169
2.072
-0.000
10
9
8
7
6
5
4
3
2
1
-0
ppm

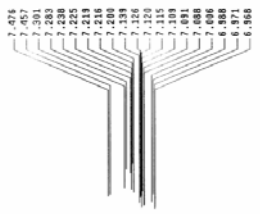

cdcl3
20050624
207.673
143.414
136.544
128.468
127.665
126.487
126.346
123.150
121.322
119.591
118.783
111.128
77.319
77.000
76.680
50.307
30.361
30.333
220
200
180
160
140
120
100
80
60
40
20
ppm

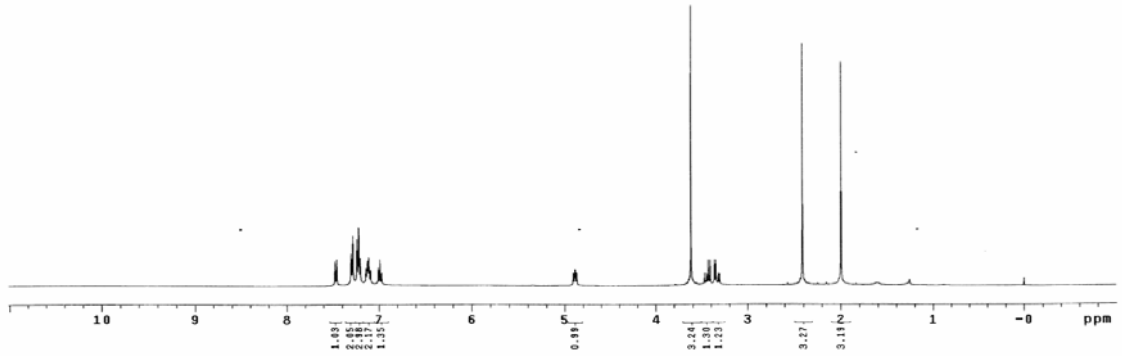

ldp39 cdcl3
ppm


LDP39 cdcl3
20050616
ppm

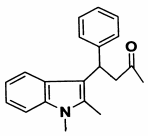
LDP40 cdc13

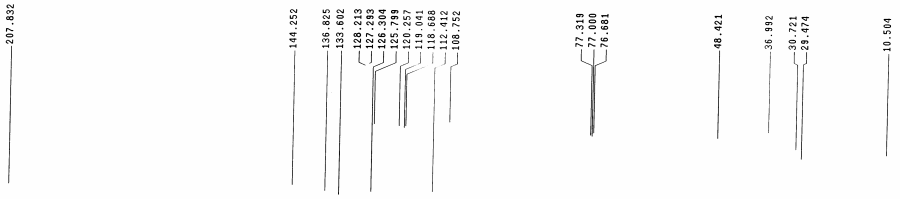


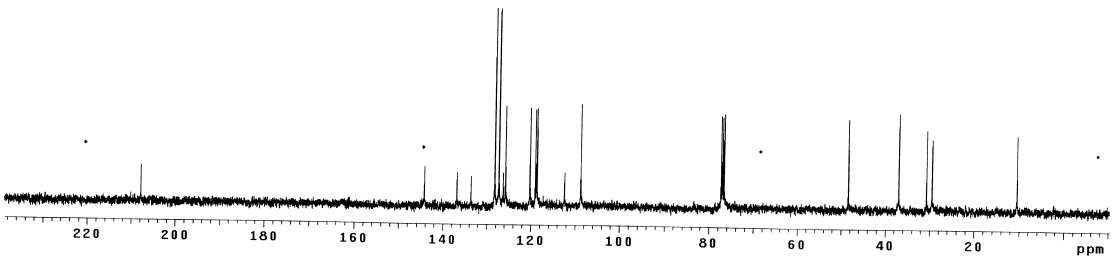


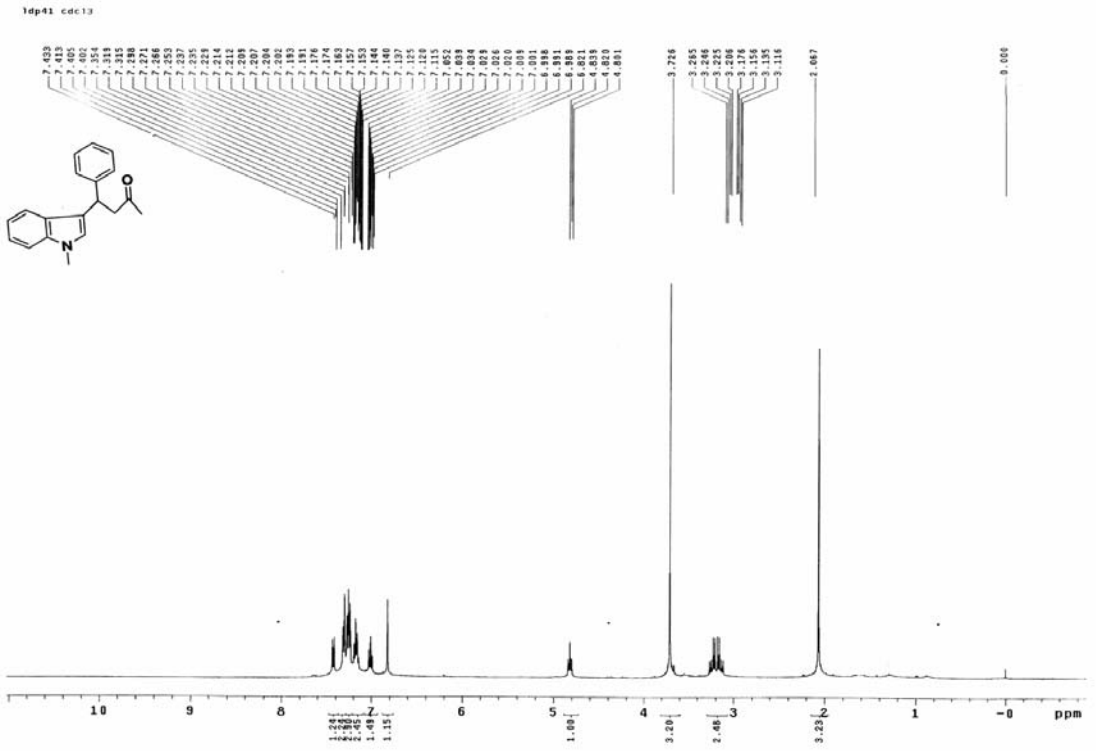


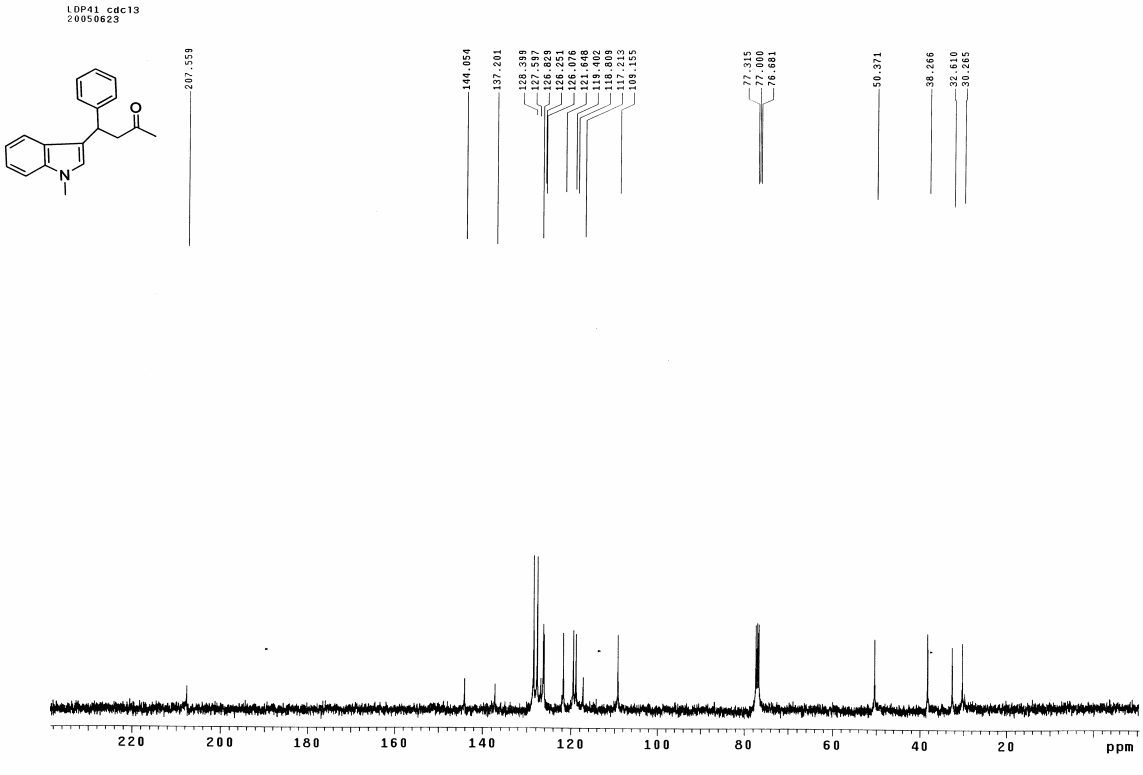
LDP40 cdc13
20050620

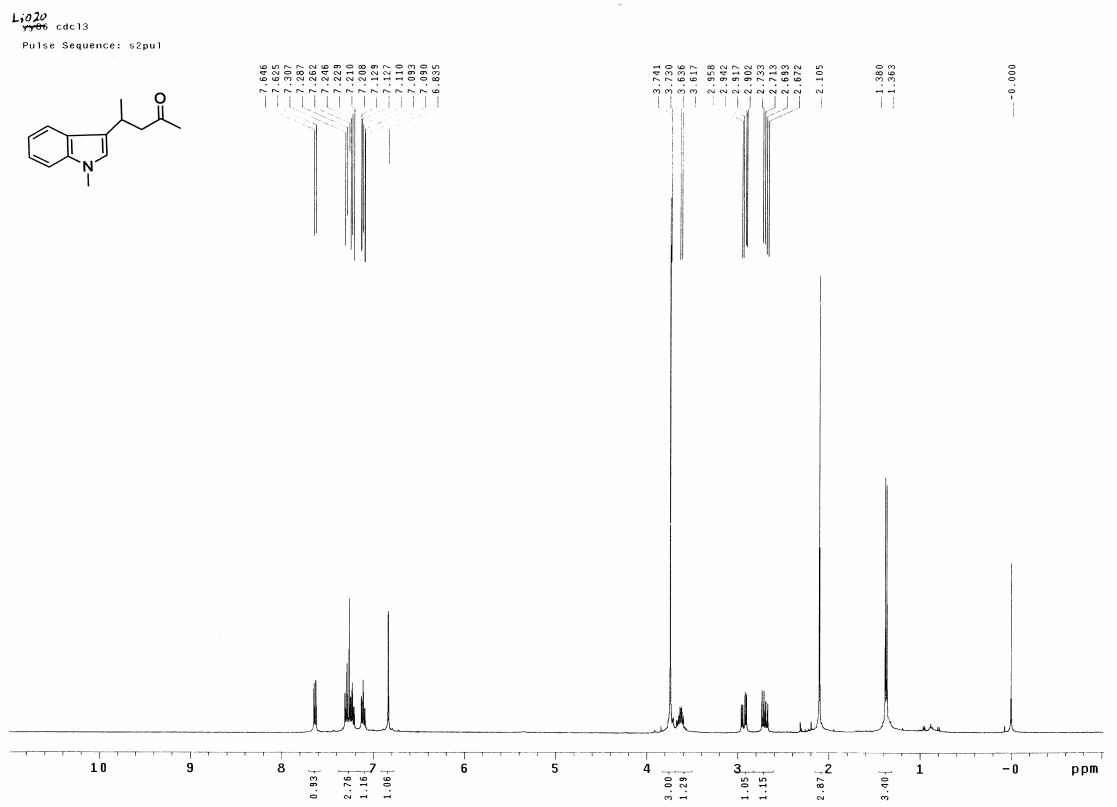


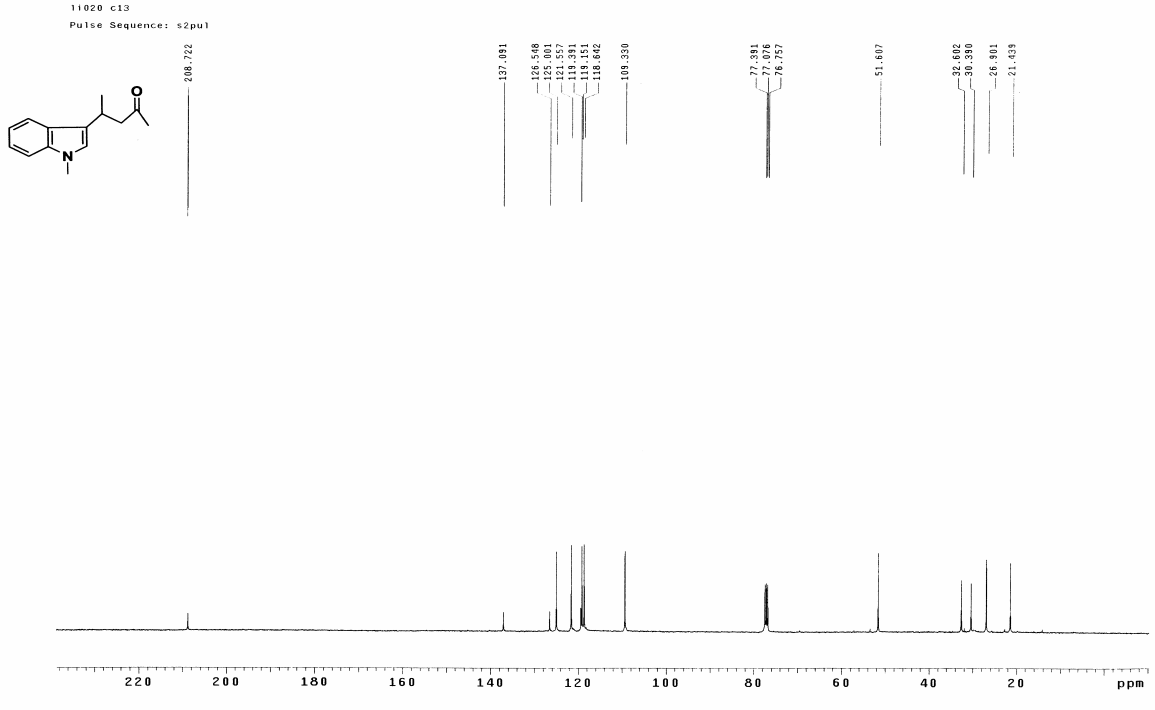


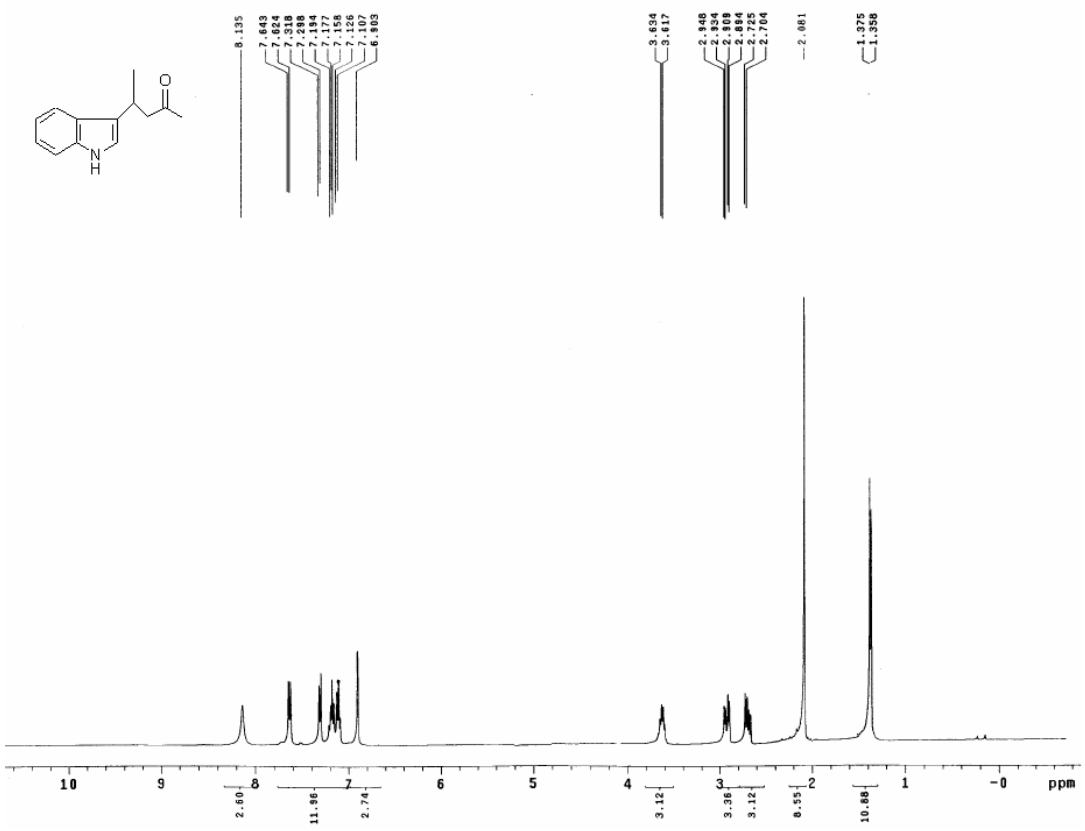


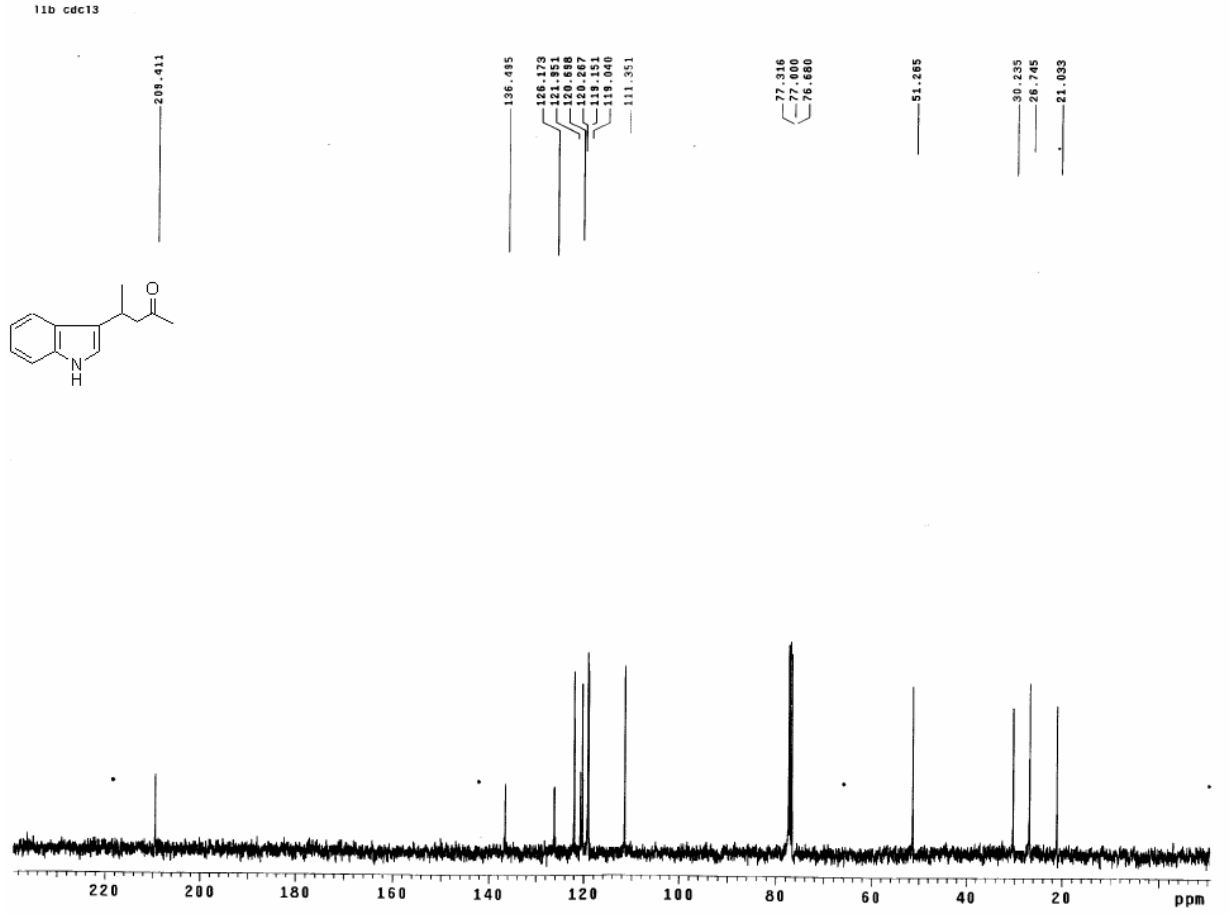

ldp41 cdcl3
7.433
7.413
7.405
7.402
7.354
7.318
7.315
7.298
7.271
7.266
7.253
7.237
7.235
7.224
7.214
7.212
7.205
7.207
7.204
7.202
7.193
7.191
7.176
7.174
7.163
7.157
7.153
7.144
7.140
7.137
7.125
7.120
7.115
7.052
7.039
7.034
7.031
7.026
7.020
7.009
7.001
6.998
6.991
6.986
6.821
6.819
4.835
4.820
4.801
3.726
3.265
3.246
3.225
3.206
3.176
3.156
3.135
3.116
2.067
0.000
O
N
10
9
8
7
6
5
4
3
2
1
-0
ppm
1.00
3.20
2.46
3.23


LDP41 cdcl3
20050623
207.559
144.054
137.201
128.399
127.597
126.829
126.671
126.076
121.648
119.402
118.809
117.213
109.155
77.315
77.000
76.681
50.371
38.266
32.610
30.265
O
N
220
200
180
160
140
120
100
80
60
40
20
ppm

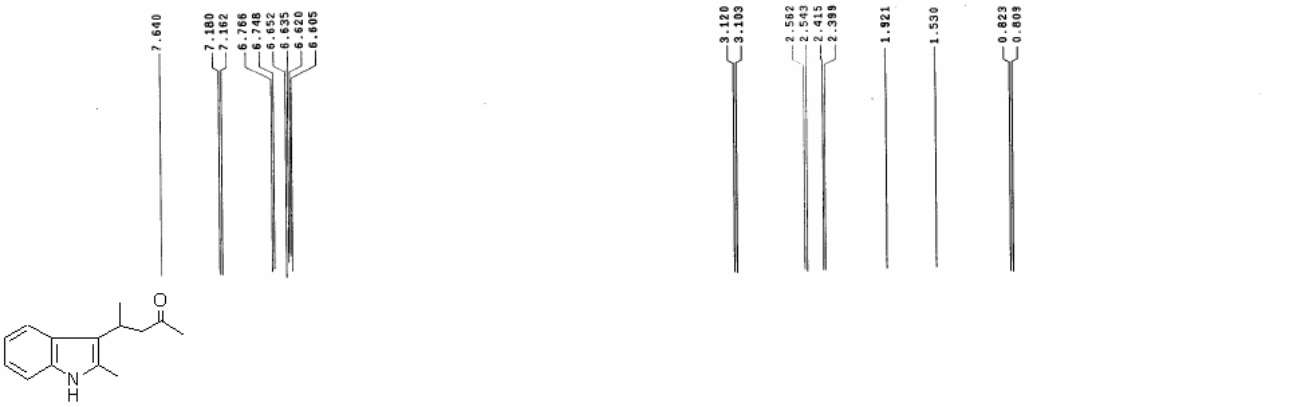

L1020
cdcl3
Pulse Sequence: s2pul
7.646
7.635
7.307
7.287
7.262
7.246
7.229
7.210
7.208
7.129
7.107
7.110
7.093
7.090
6.835
3.741
3.730
3.656
3.617
2.958
2.902
2.733
2.713
2.693
2.672
2.105
1.380
1.363
-0.000
0.93
2.76
1.16
1.06
3.00
1.29
1.05
1.15
2.87
3.40
10
9
8
7
6
5
4
3
2
1
-0
ppm

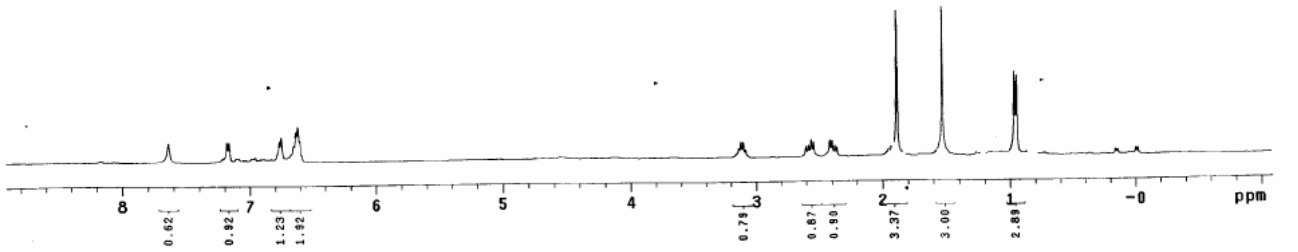

11020 c13
Pulse Sequence: s2pul
208.722
137.091
126.548
125.001
121.557
119.391
119.151
118.642
109.330
77.391
77.076
76.757
51.607
32.602
30.390
26.901
21.439
220
200
180
160
140
120
100
80
60
40
20
ppm


8.135
7.643
7.624
7.318
7.298
7.194
7.177
7.158
7.126
7.107
6.903
3.634
3.617
2.948
2.934
2.919
2.884
2.725
2.704
2.081
1.375
1.358
10
9
8
7
6
5
4
3
2
1
-0
ppm
2.60
11.98
2.74
3.12
3.36
3.12
8.55
10.88

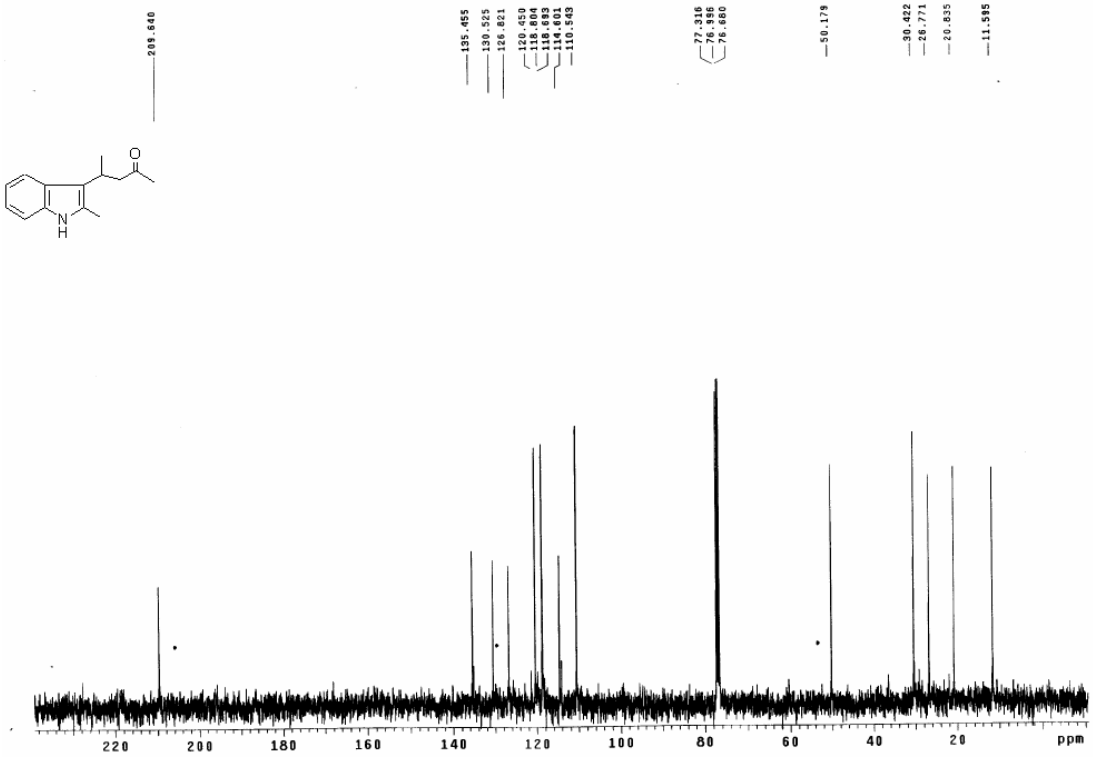

11b cdcl3
209.411
136.495
126.173
121.951
120.688
120.267
119.151
119.040
111.351
77.316
77.000
76.680
51.285
30.235
26.745
21.033
220
200
180
160
140
120
100
80
60
40
20
ppm

12 cdc13

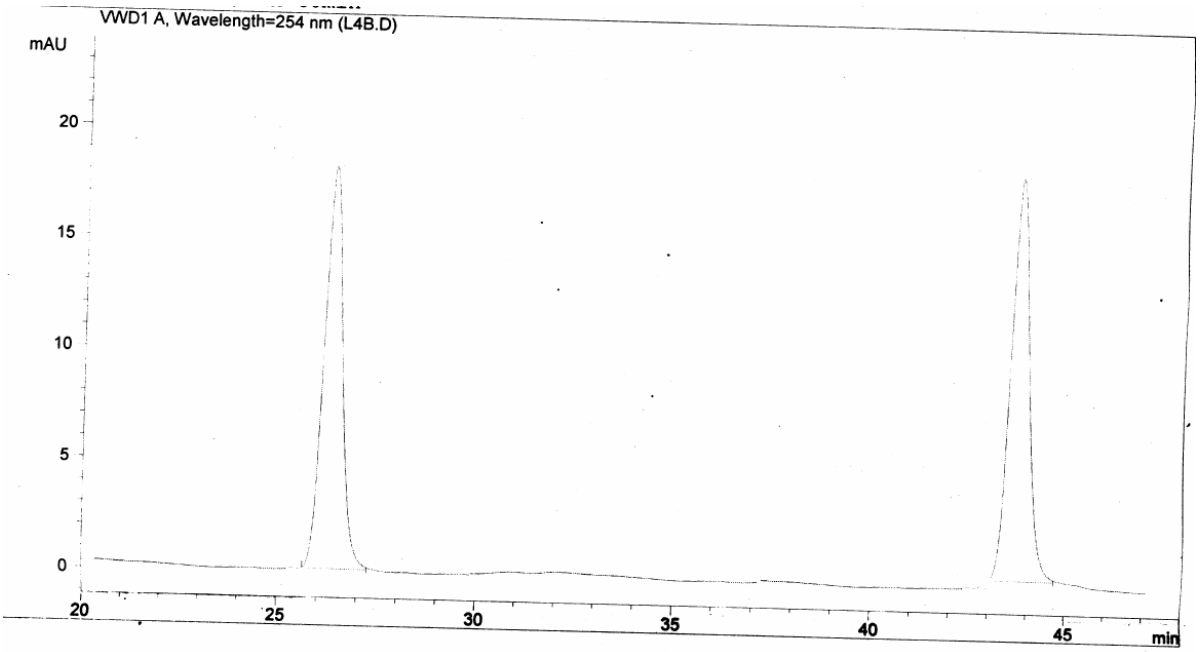


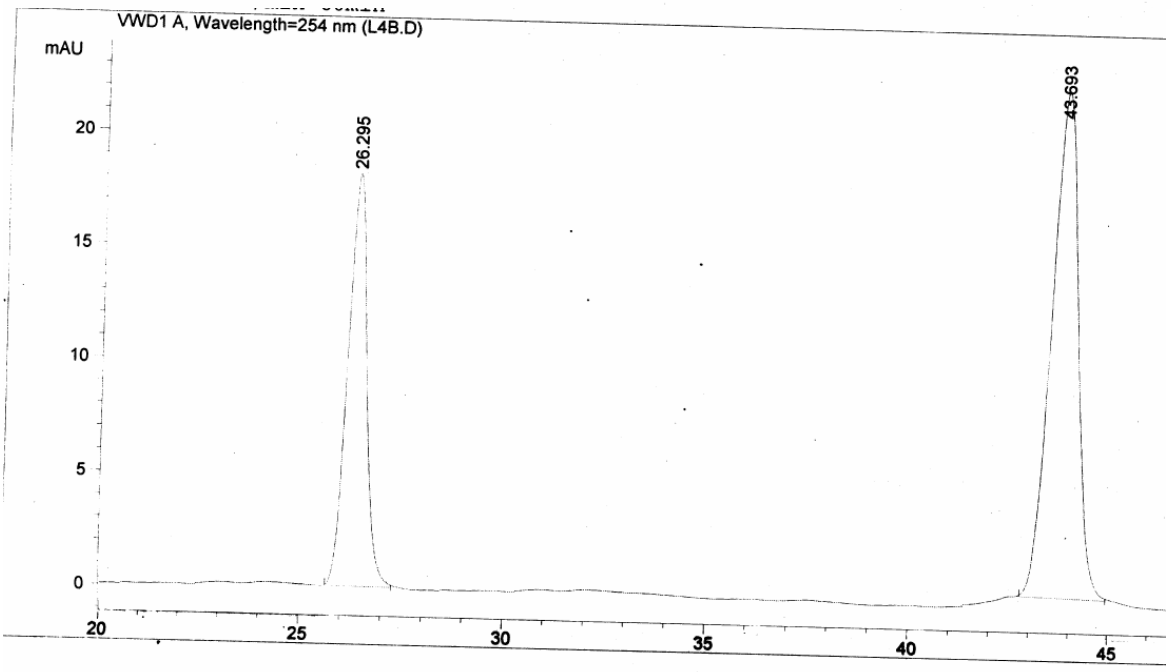


12 cdc13



3a racemic





Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	26.295	BB	0.4990	587.41498	18.12235	35.9552
2	43.693	BB	0.7263	1046.32727	22.36775	64.0448