Supporting Information

Highly Regioselective Internal Heck Arylation of Hydroxyalkyl Vinyl Ethers by Aryl Halides in Water

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Contents

1. General Information and Materials

All small scale reactions were performed in sealed process vials (capable to withhold elevated pressure) under air with magnetic stirring. Microwave experiments were conducted using a Smith Synthesizer™ single mode cavity, producing controlled irradiation at 2450 MHz. In all microwave heated reactions, the temperature of the reaction mixture was measured using a built-in, on-line infrared temperature sensor. For column chromatography commercially available silica gel 60 (particle size: 0.040-0.063 mm) was used. GC-MS analyses were done with a CP-SIL 8 CB Low Bleed (30 m × 0.25 mm) or a CP-SIL 5 CB Low Bleed (30 m × 0.25 mm) capillary column using a 40-300 °C temperature gradient and EI ionization. ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, using $CDCl_3$ as a solvent. Chemical shifts for ^{1}H and ^{13}C are referenced to TMS via the solvent signal. Compounds **5a-e**[1], **5f**[2], **5g**[1], **5h**[3], **5i**[1] and **5j-k**[4] are known structures and spectroscopic data matched with the literature.

The aryl halides **1a-s**, olefins **2a-i**, K_2CO_3, $Pd(OAc)_2$, dppp and $(dippp)_2Pd$ were purchased from commercial suppliers and were used directly as received. $(dippp)_2Pd$ was stored at -20 ˚C under N_2. High quality ultrapure Millipore-water was used in reactions utilizing water as a reaction media.

2. General Experimental Procedure for Internal Heck Reactions using Aryl Bromides or Aryl Iodides (Tables 1, 2, 4 and 5)

A mixture of corresponding aryl bromide or aryl iodide (0.50 mmol), olefin (2.5 mmol), $Pd(OAc)_2$ (2.8 mg, 0.0125 mmol), dppp (10.3 mg, 0.025 mmol), K_2CO_3 (83-207 mg, 0.60-1.5 mmol) and 1.0 mL of water was stirred in a sealed vessel in a preheated oil bath at 90 ˚C for 80 min. In comparative arylations reported in Table 5, water was replaced with toluene or

reactions were run without any solvent. After cooling down, 2.0 mL of ethyl acetate was added to the reaction mixture which was stirred for 5 min before analysis of the organic layer with GC/MS. 0.5 mL of concentrated HCl (aq.) was added to the mixture followed by stirring at room temperature for 1-3 h. Completion of hydrolysis was verified with GC/MS. The reaction was worked up by extraction with ethyl acetate and 10 % K_2CO_3 (aq.). Products were purified by flash chromatography on silica gel. Eluents: isohexane/ethyl acetate.

3. Experimental Procedure for Large Scale Internal Heck Reaction using 4-Bromoanisole and Ethylene Glycol Vinyl Ether (Table 2, entry 1)

A mixture of 4-bromoanisole (9.35 g, 50 mmol), ethylene glycol vinyl ether (22.4 mL, 250 mmol), $Pd(OAc)_2$ (0.28 g, 1.25 mmol), dppp (1.03 g, 2.5 mmol), K_2CO_3 (8.29 g, 60 mmol) and 100 mL of water was stirred in a 250 mL round bottom flask at 90 ˚C for 80 min under reflux. After cooling down, 50 mL of ethyl acetate was added to the reaction mixture which was stirred for 5 min before analysis of the organic layer with GC/MS. Thereafter, 25 mL of concentrated HCl (aq.) was slowly added to the mixture followed by stirring at room temperature for 1 h. Completion of hydrolysis was verified with GC/MS. Reaction was worked up and purified as described above.

4. General Experimental Procedure for Microwave Assisted Internal Heck Reactions using Aryl Chlorides (Table 3)

A mixture of corresponding aryl chloride (0.25 mmol), $(dippp)_2Pd$ (8.2 mg, 0.0125 mmol), K_2CO_3 (104 mg, 0.75 mmol) and 1.0 mL of water was stirred in a sealed vessel suitable for microwave experiments in a preheated oil bath at 50 ˚C for 15 min. Ethylene glycol vinyl ether (112 μL, 1.25 mmol) was added, the vessel was sealed and the reaction mixture was

irradiated with microwaves at 130 ˚C for 90 min. Reactions were hydrolyzed, worked up and purified as previously described.

5. References

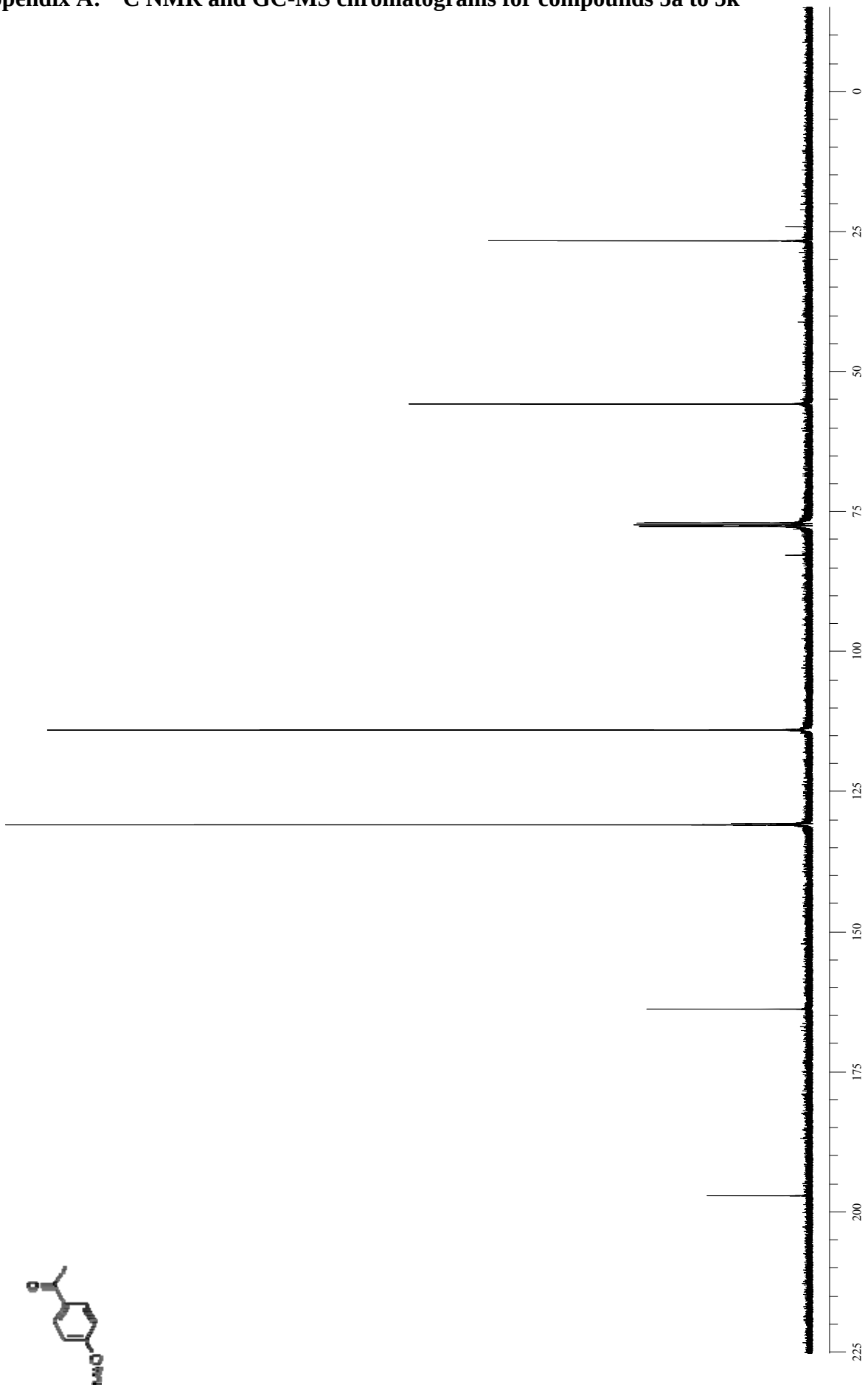
(1) Liu, S. F.; Berry, N.; Thomson, N.; Pettman, A.; Hyder, Z.; Mo, J.; Xiao, J. L. *J. Org. Chem.* **2006**, *71*, 7467.

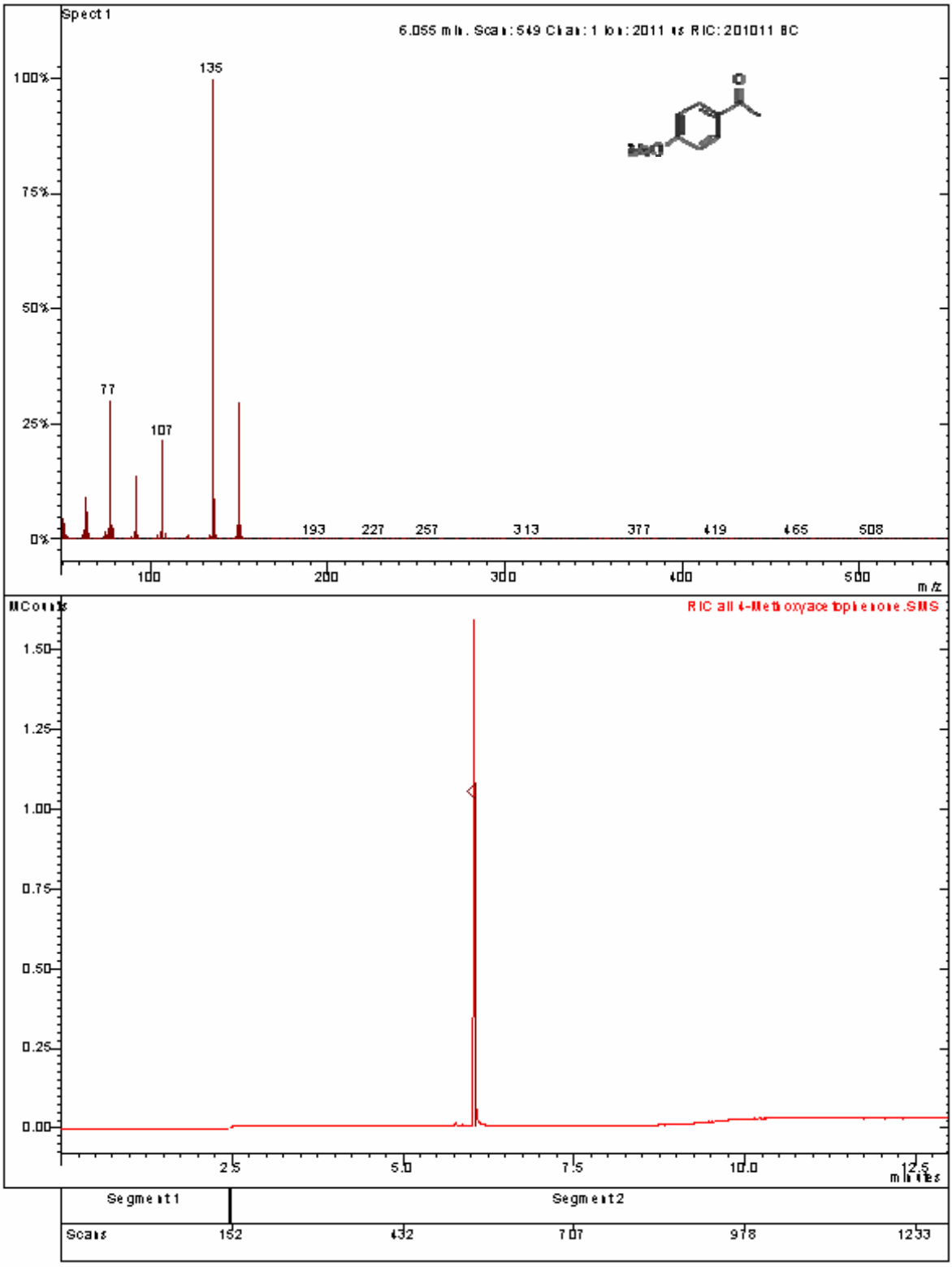
(2) Kazmierski, I.; Bastienne, M.; Gosmini, C.; Paris, J. M.; Perichon, J. *J. Org. Chem.* **2004**, *69*, 936.

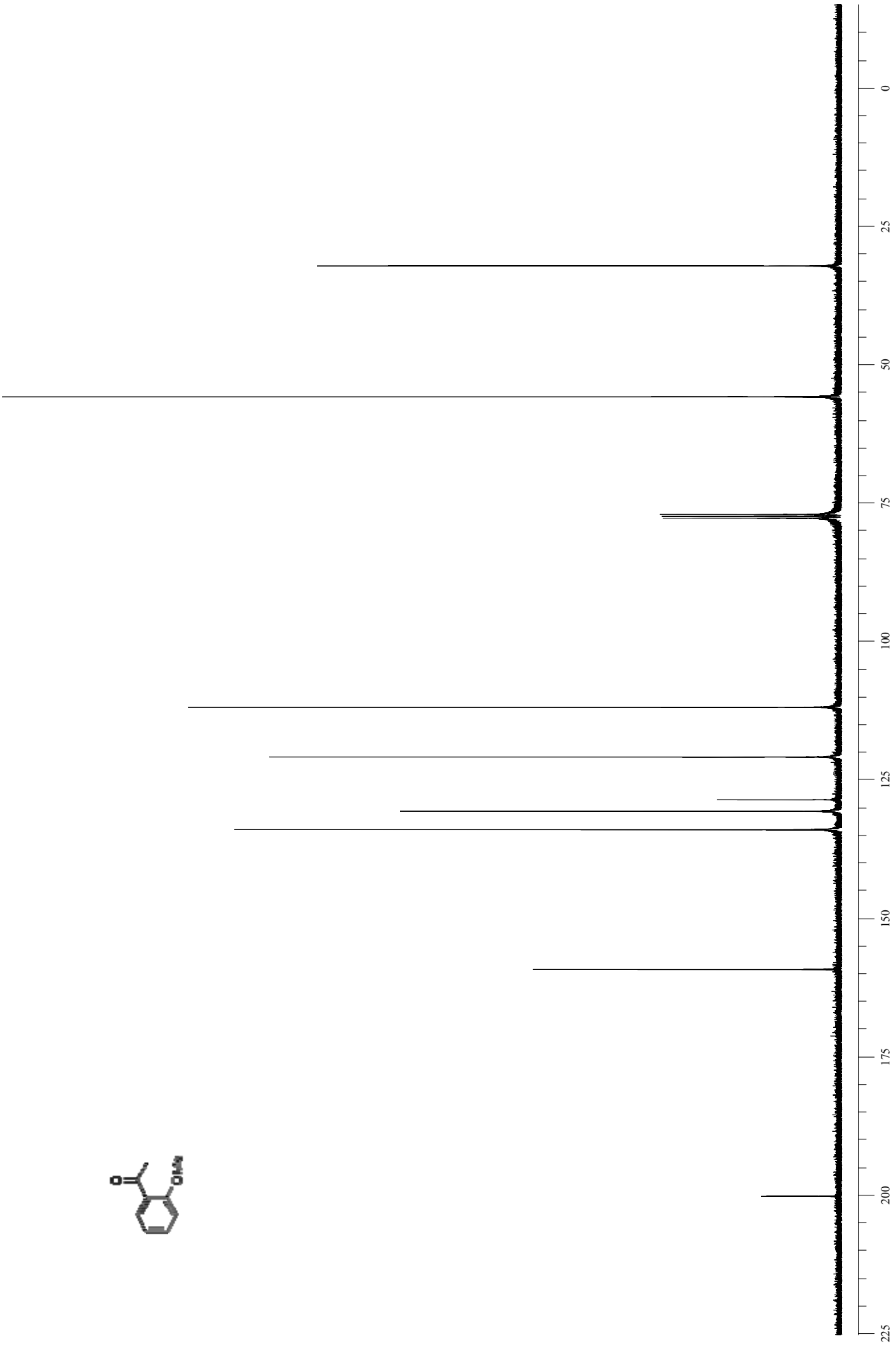
(3) Pena, M. A.; Sestelo, J. P.; Sarandeses, L. A. *Synthesis* **2003**, 780.

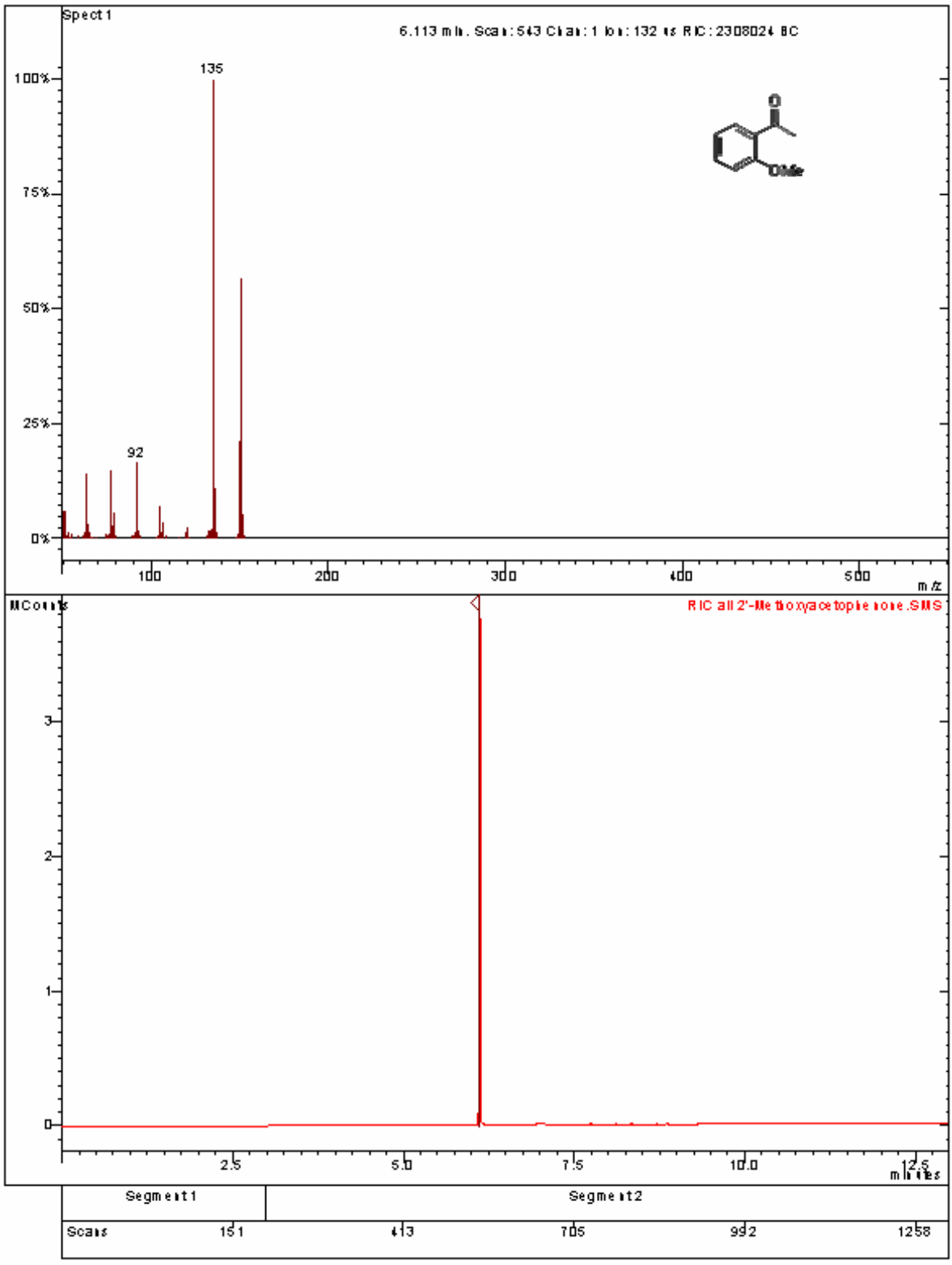
(4) Pei, W.; Mo, J.; Xiao, J. L. *J. Organomet. Chem.* **2005**, *690*, 3546.

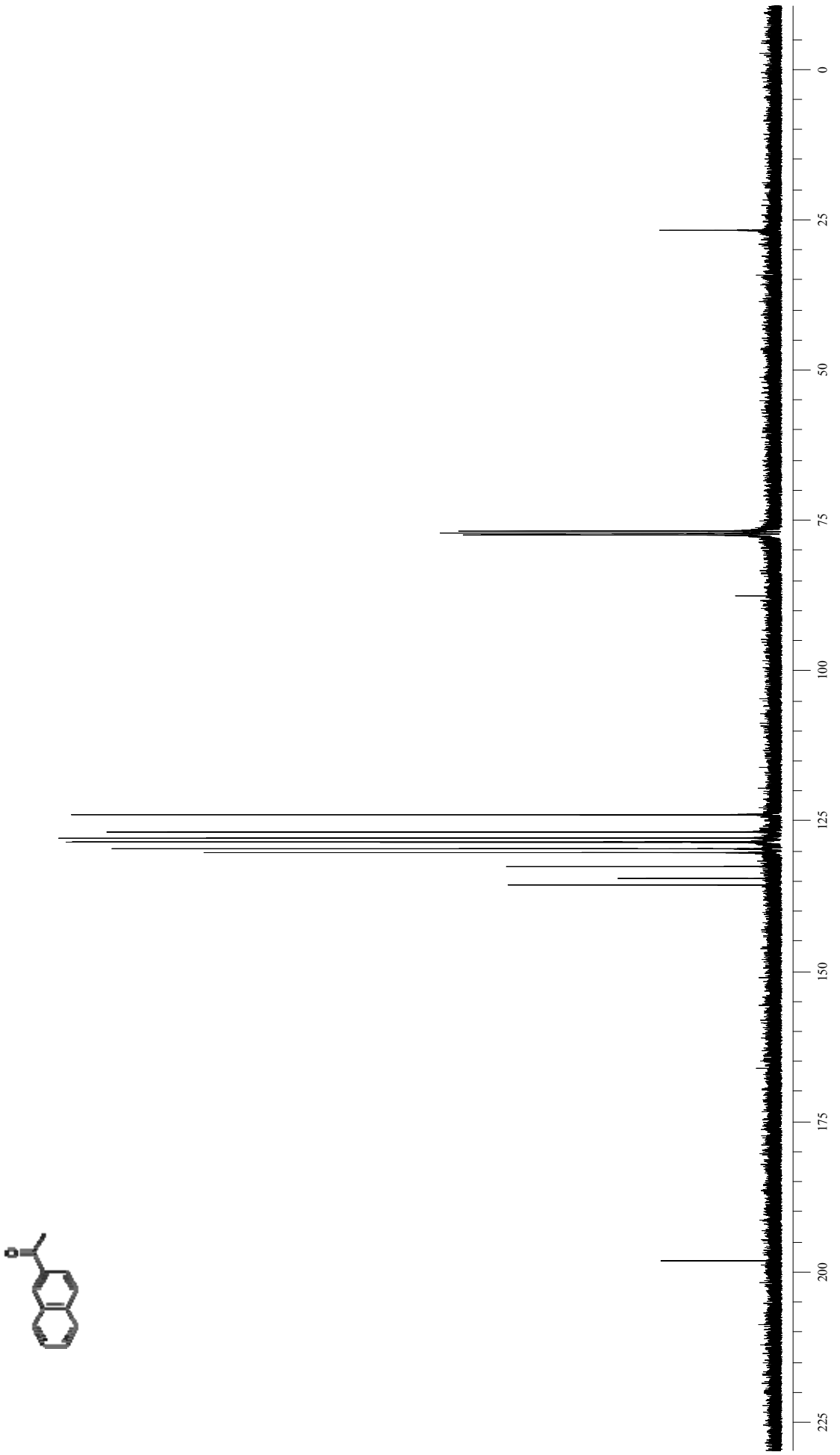
Appendix A: ^{13}C NMR and GC-MS chromatograms for compounds 5a to 5k

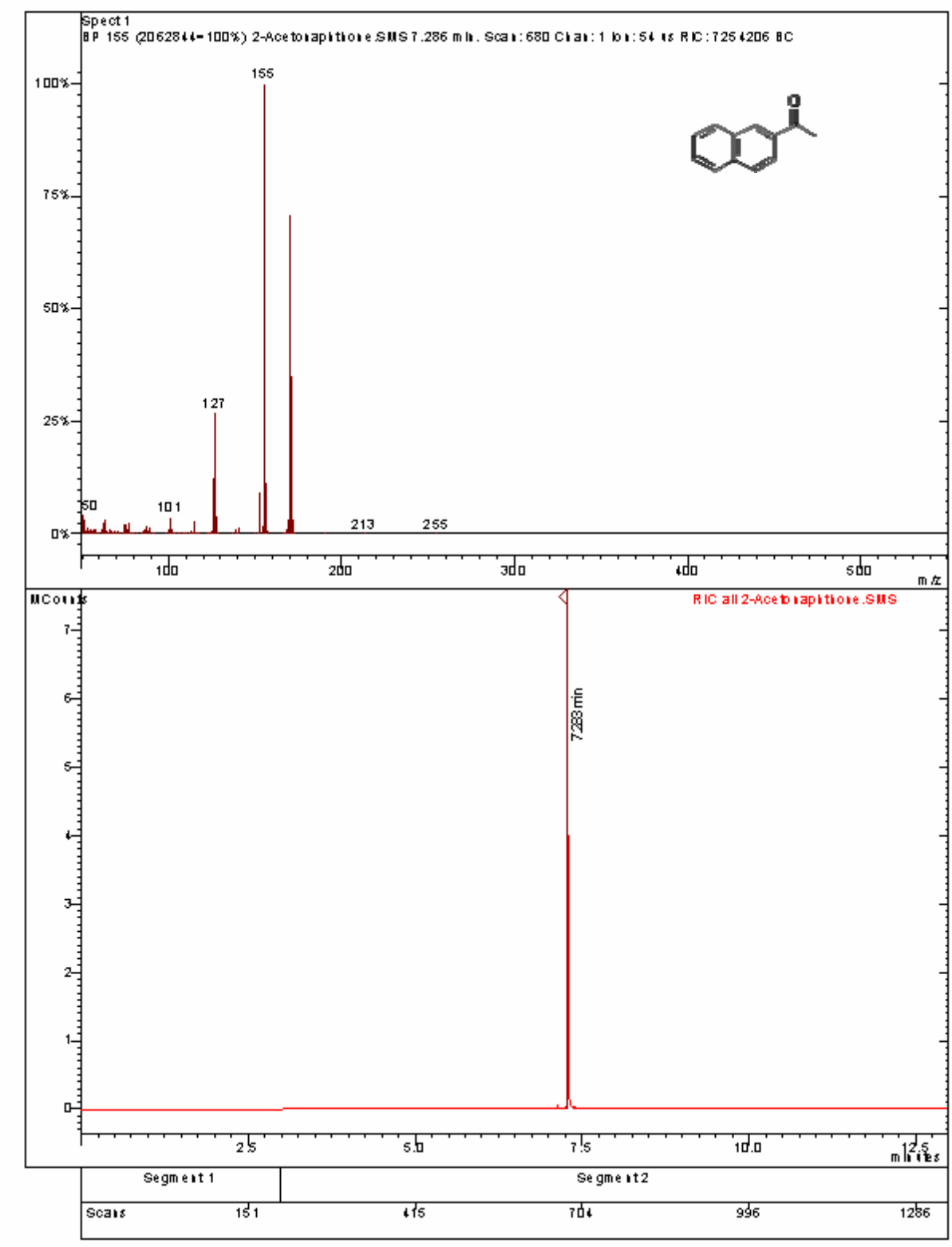


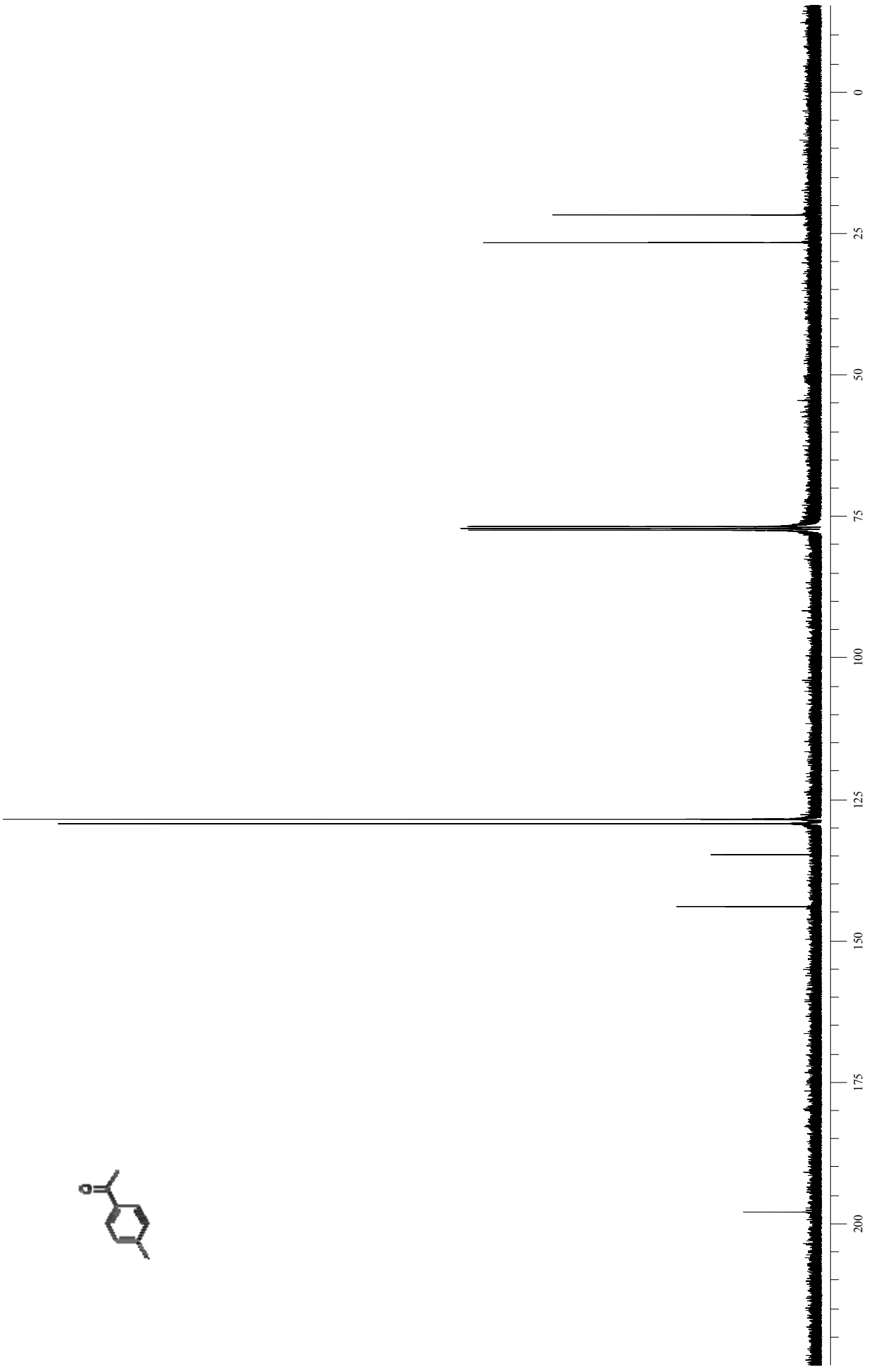

Spect 1
6.055 min, Scan: 549 Chan: 1 Ion: 2011 vs RIC: 201011 BC
135
77
107
193
227
257
313
377
419
465
508
100%
75%
50%
25%
0%
100
200
300
400
500
m/z
MCounts
RIC all 4-Methoxyacetophenone.SMS
1.50
1.25
1.00
0.75
0.50
0.25
0.00
2.5
5.0
7.5
10.0
12.5
minutes
Segment 1
Segment 2
Scans
152
432
707
978
1233

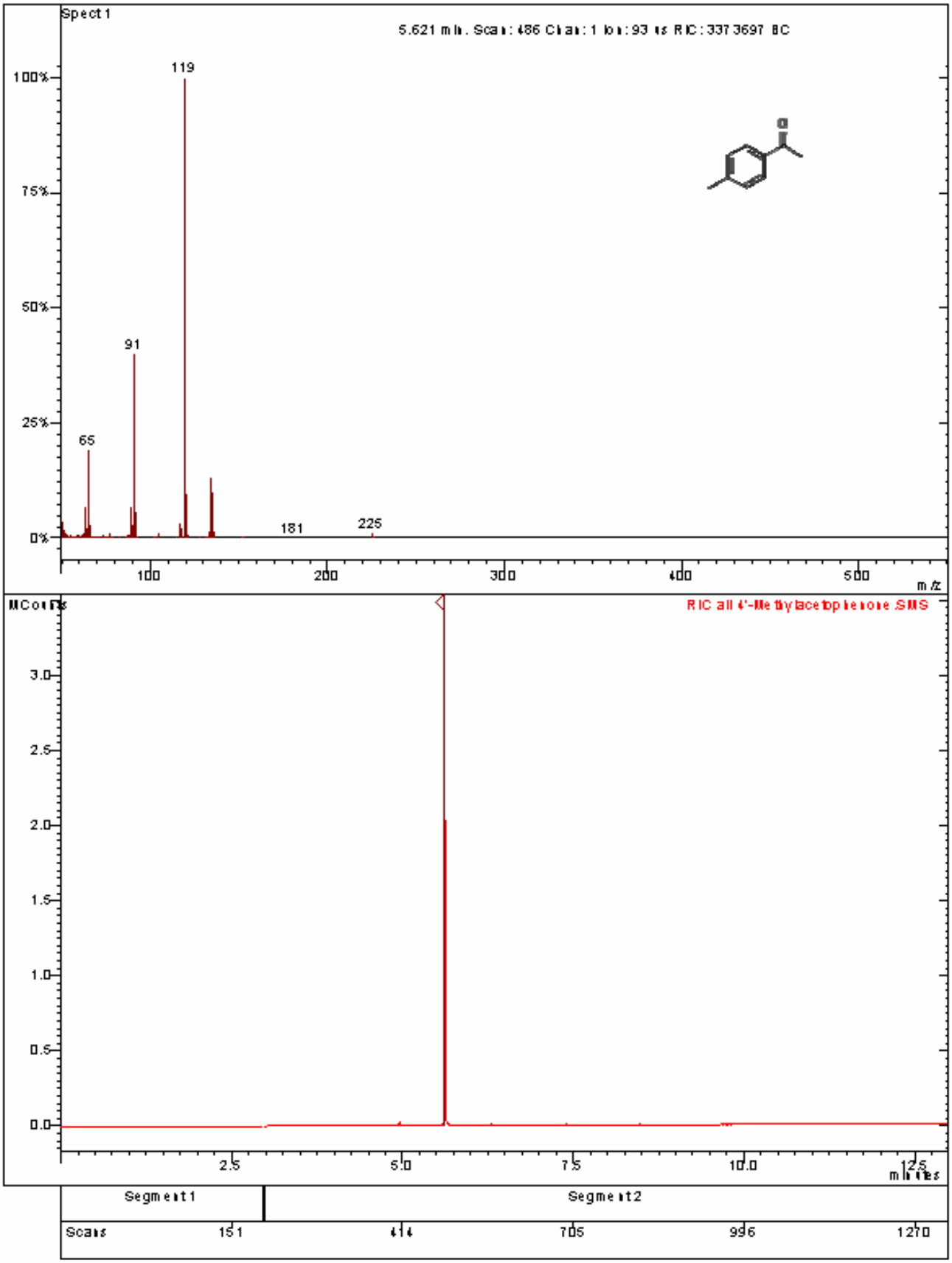

0
25
50
75
100
125
150
175
200
225

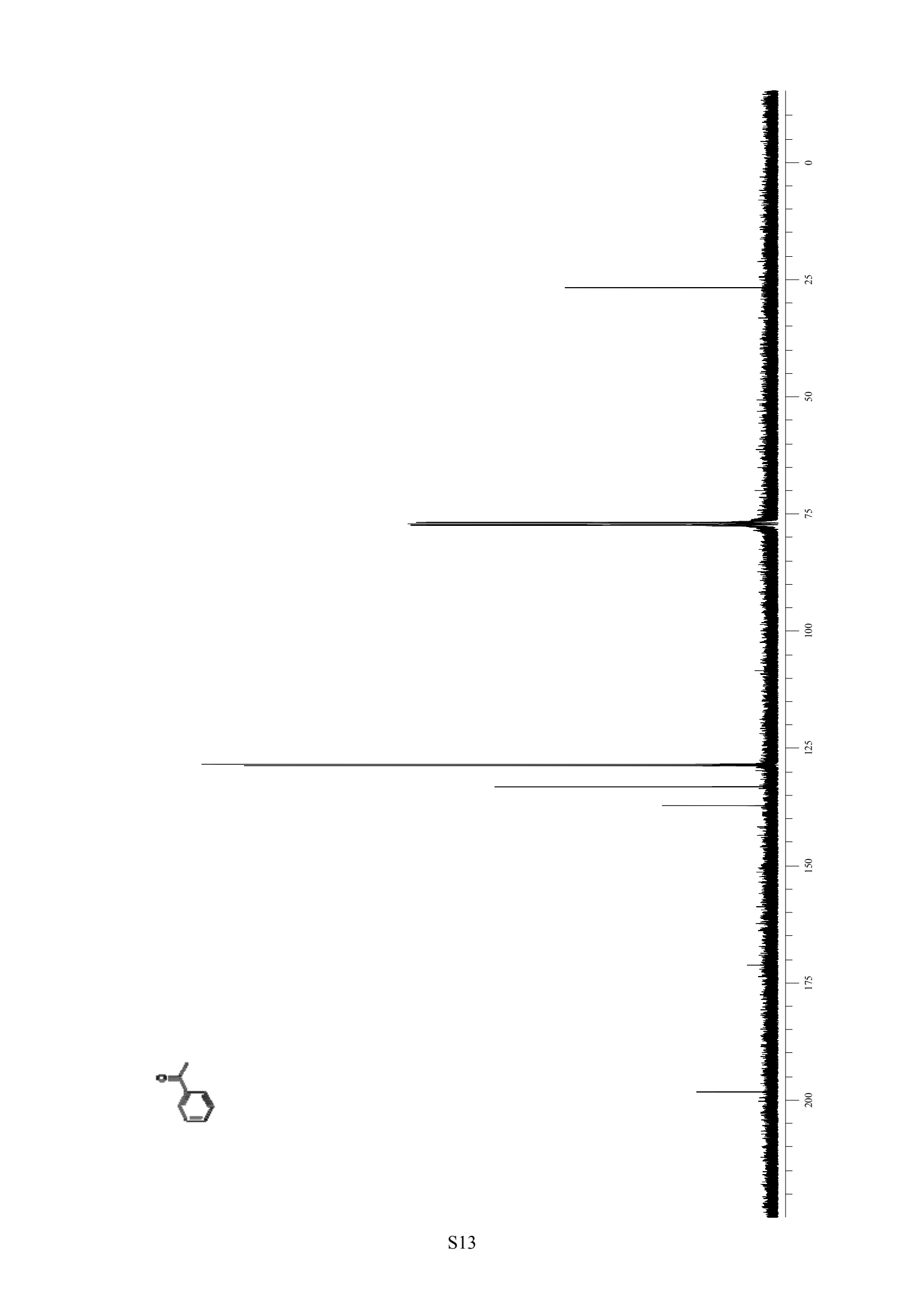

Spect 1
6.113 min, Scan: 543 Chan: 1 Ion: 132 vs RIC: 2308024 BC
135
92
100%
75%
50%
25%
0%
100
200
300
400
500
m/z
MCounts
RIC all 2'-Methoxyacetophenone.SMS
3
2
1
0
2.5
5.0
7.5
10.0
12.5
minutes
Segment 1
Segment 2
Scans
151
413
705
992
1258

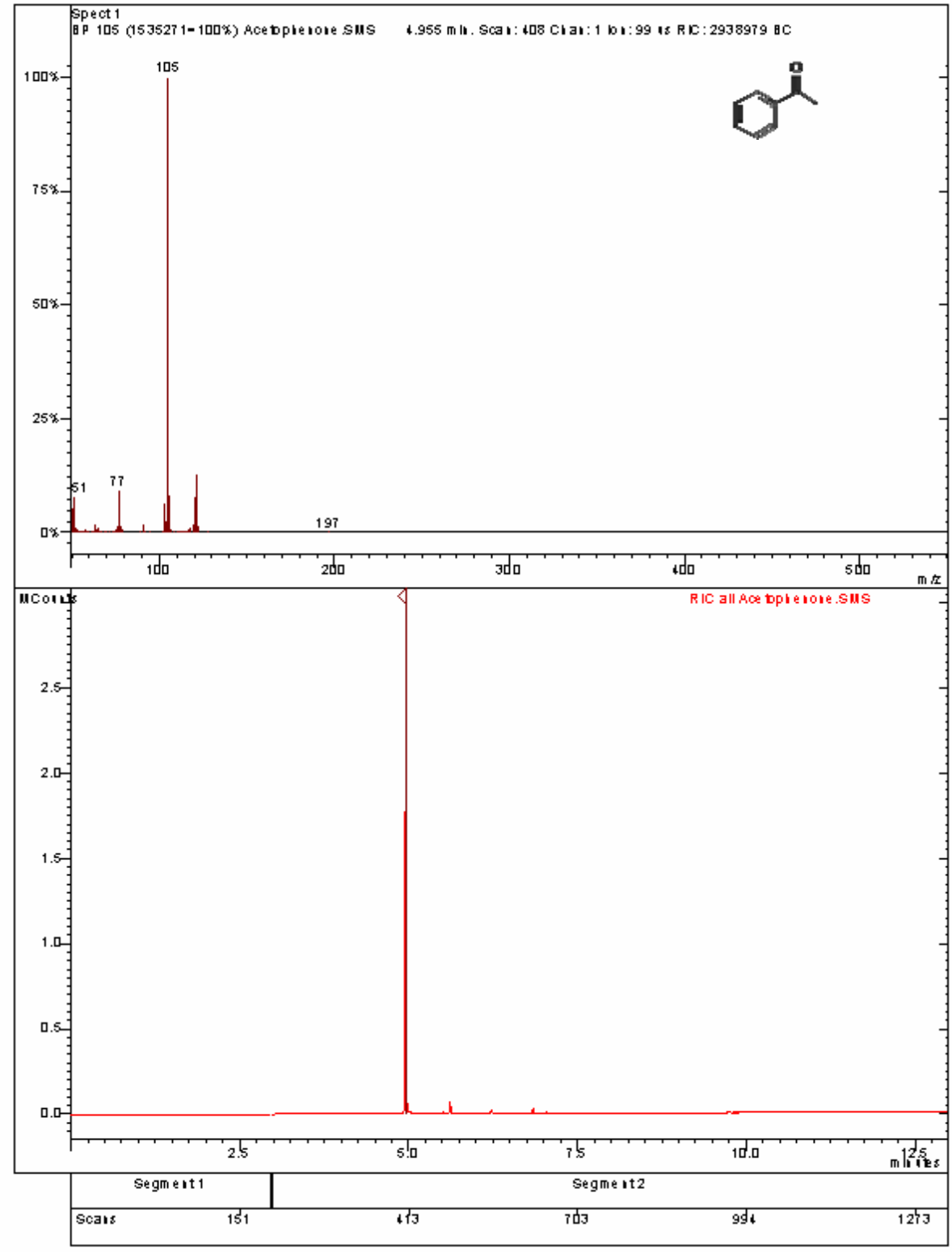

0
25
50
75
100
125
150
175
200
225

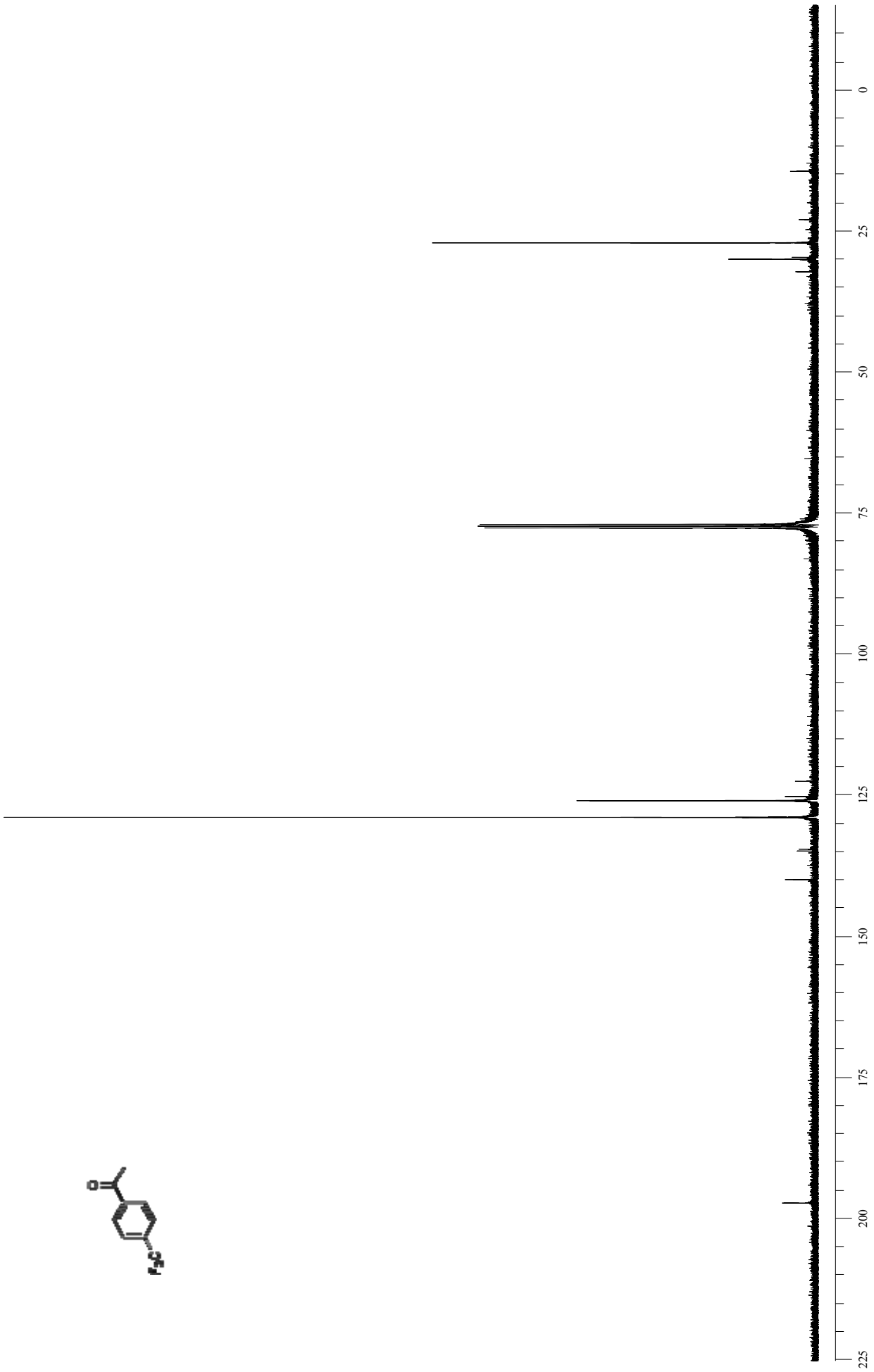

Spect 1
BP 155 (2062844=100%) 2-Acetonaphthone.SMS 7.286 min. Scan: 680 Chan: 1 Ion: 54 to RIC: 7254206 BC
100%
75%
50%
25%
0%
155
127
50
101
213
255
100
200
300
400
500
m/z
MCounts
RIC all 2-Acetonaphthone.SMS
7.283 min
2.5
5.0
7.5
10.0
12.5
minutes
Segment 1
Segment 2
Scans
151
415
704
996
1286

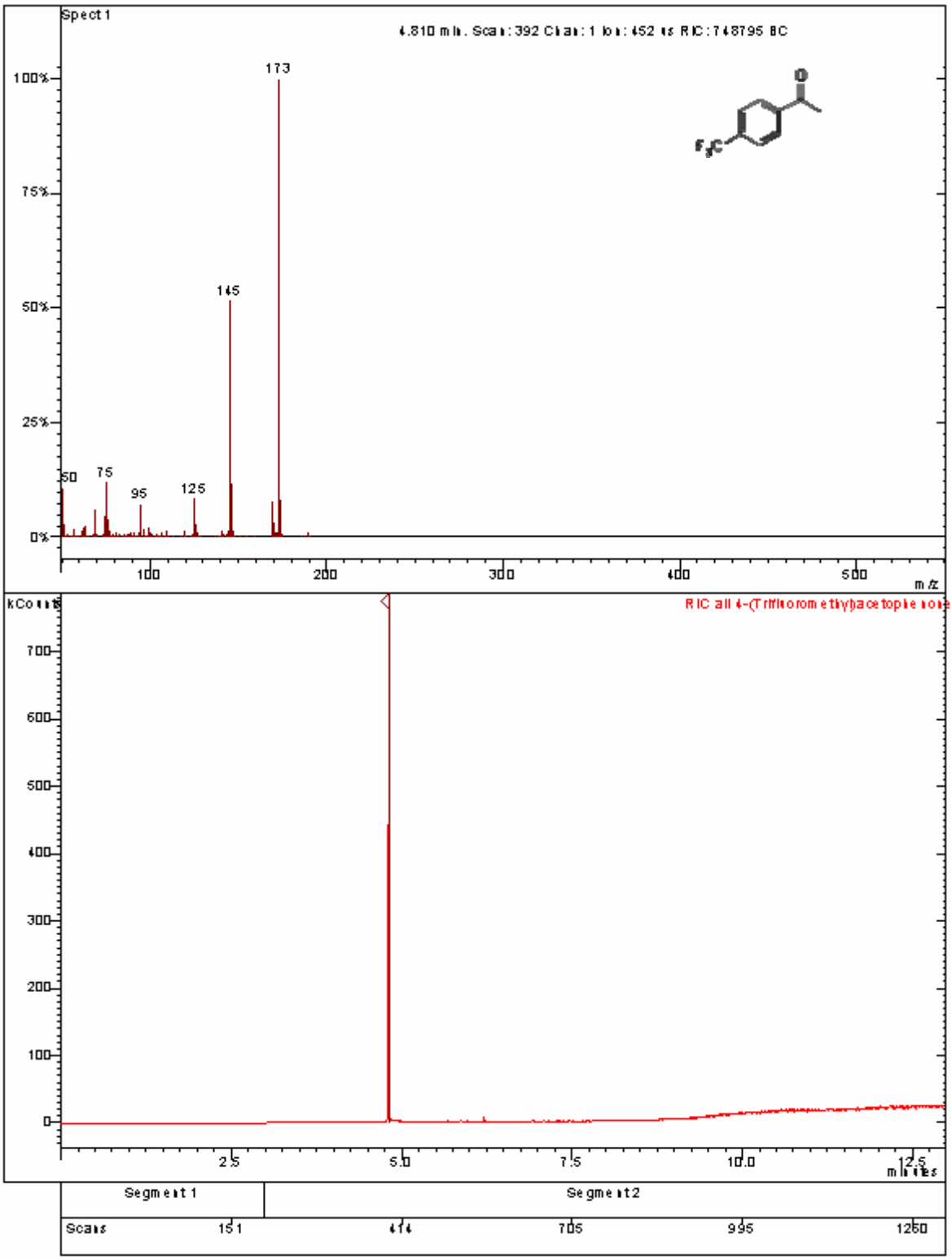

0
25
50
75
100
125
150
175
200

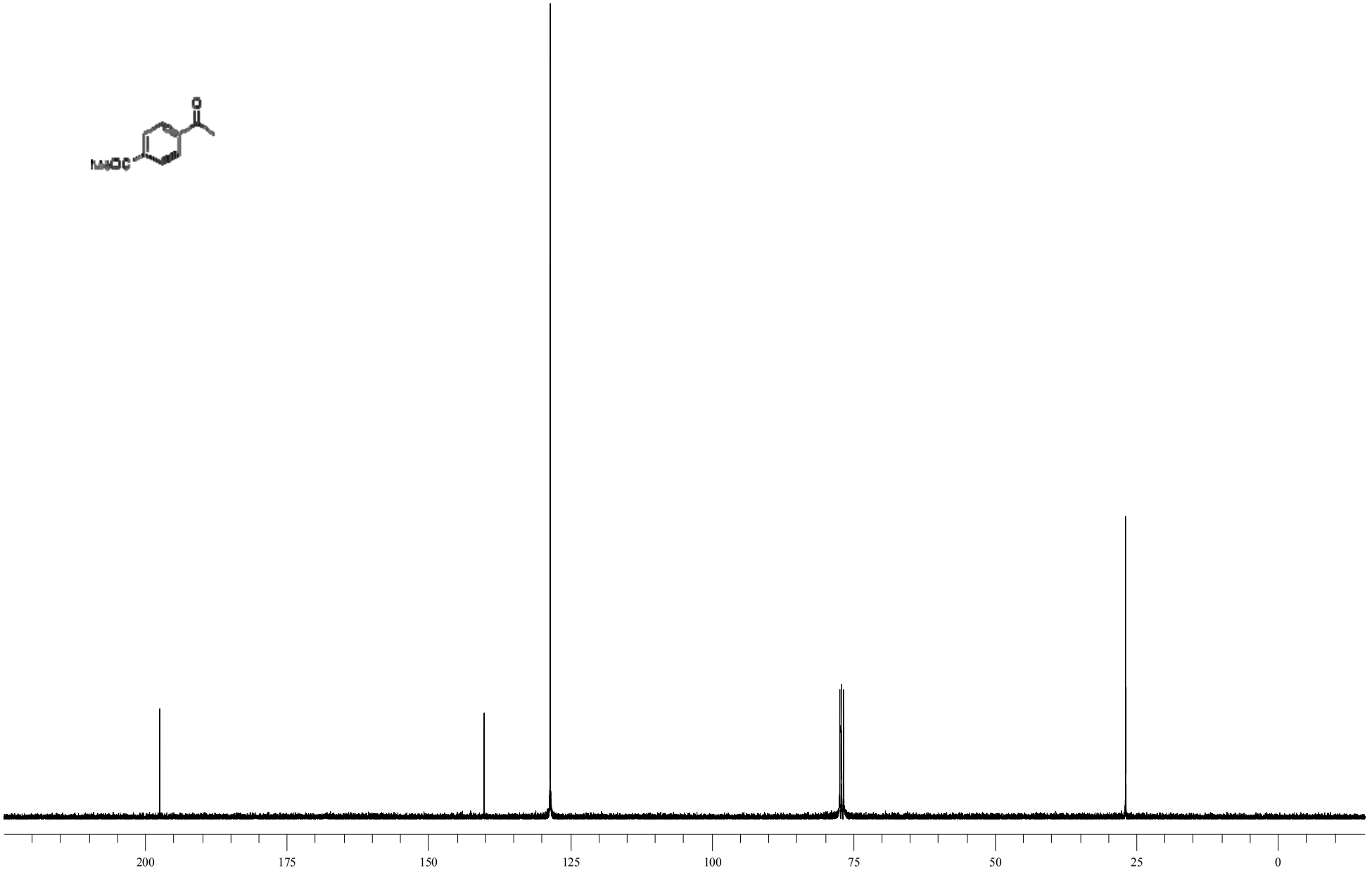

Spect 1
5.621 min, Scan: 486 Chan: 1 Ion: 93 vs RIC: 3373697 BC
100%
75%
50%
25%
0%
119
91
65
181
225
100
200
300
400
500
m/z
RIC all 4'-Methylacetophenone.SMS
3.0
2.5
2.0
1.5
1.0
0.5
0.0
2.5
5.0
7.5
10.0
12.5
minutes
Segment 1
Segment 2
Scans
151
414
705
996
1270

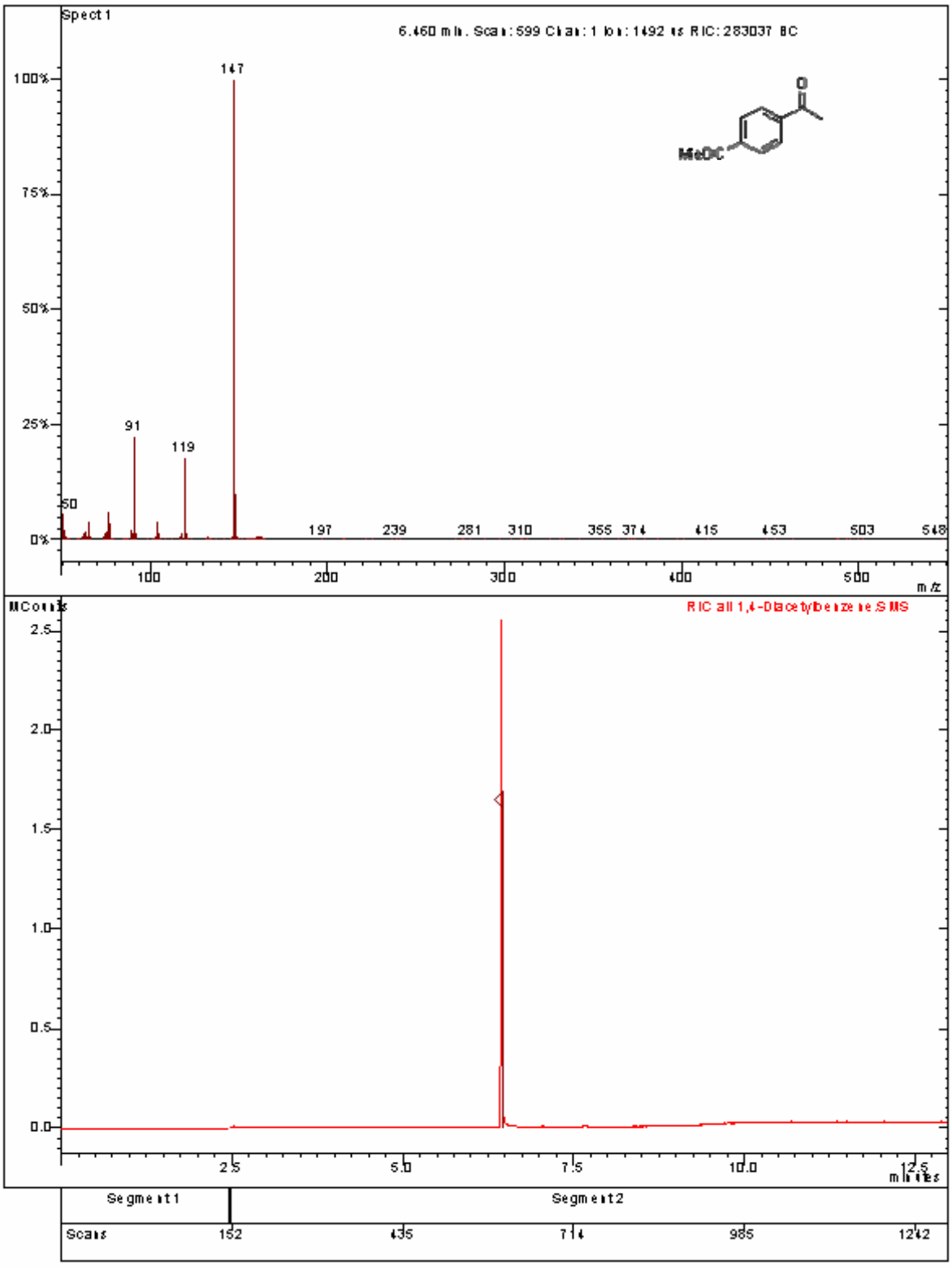

0
25
50
75
100
125
150
175
200

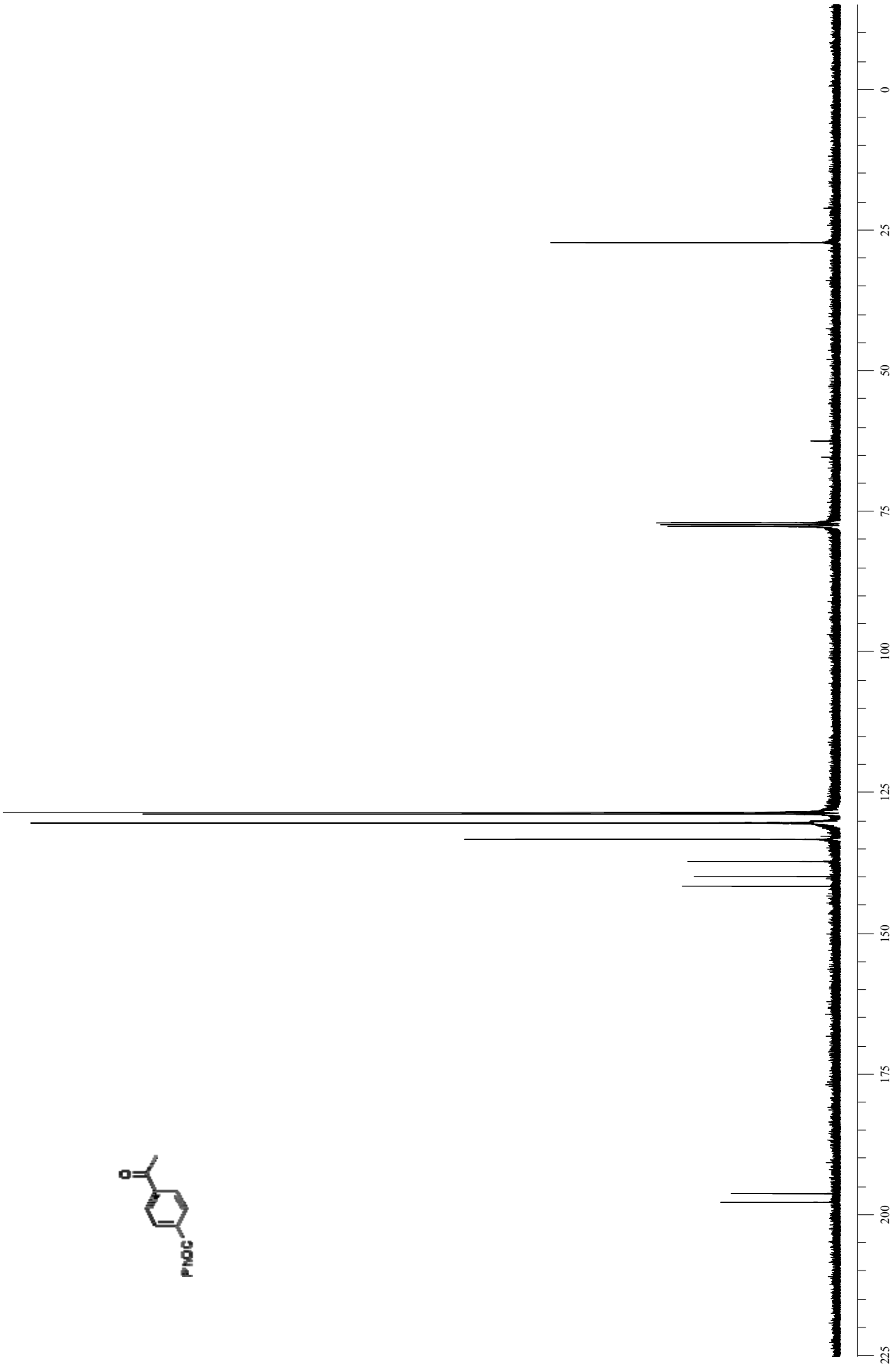

Spect 1
BP 105 (1535271=100%) Acetophenone.SMS
4.955 min. Scan: 408 Chan: 1 Ion: 99 to RIC: 2938979 BC
105
77
51
197
100%
75%
50%
25%
0%
100
200
300
400
500
m/z
MCounts
RIC all Acetophenone.SMS
2.5
2.0
1.5
1.0
0.5
0.0
2.5
5.0
7.5
10.0
12.5
minutes
Segment 1
Segment 2
Scans
151
413
703
994
1273

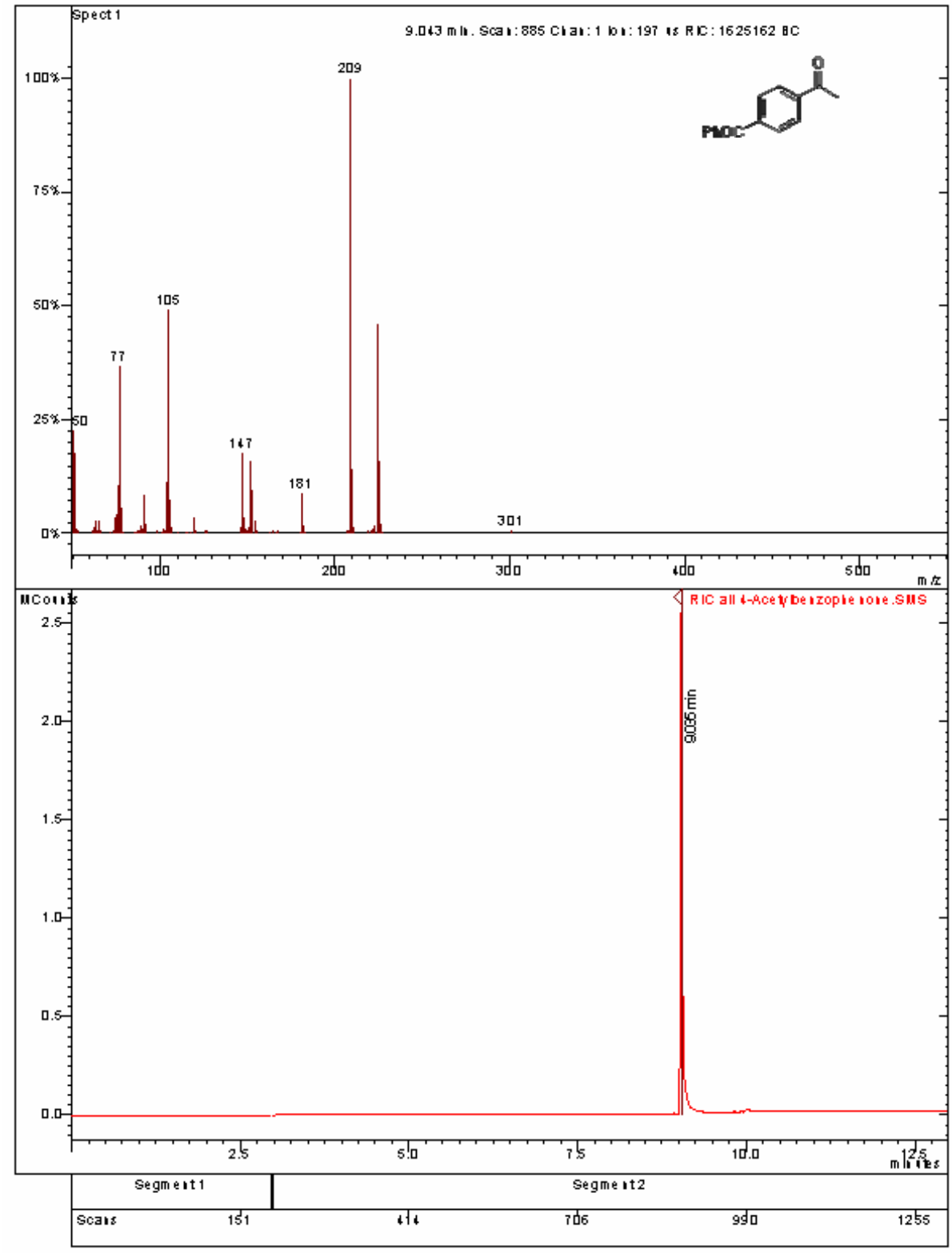

O
Br
225
200
175
150
125
100
75
50
25
0

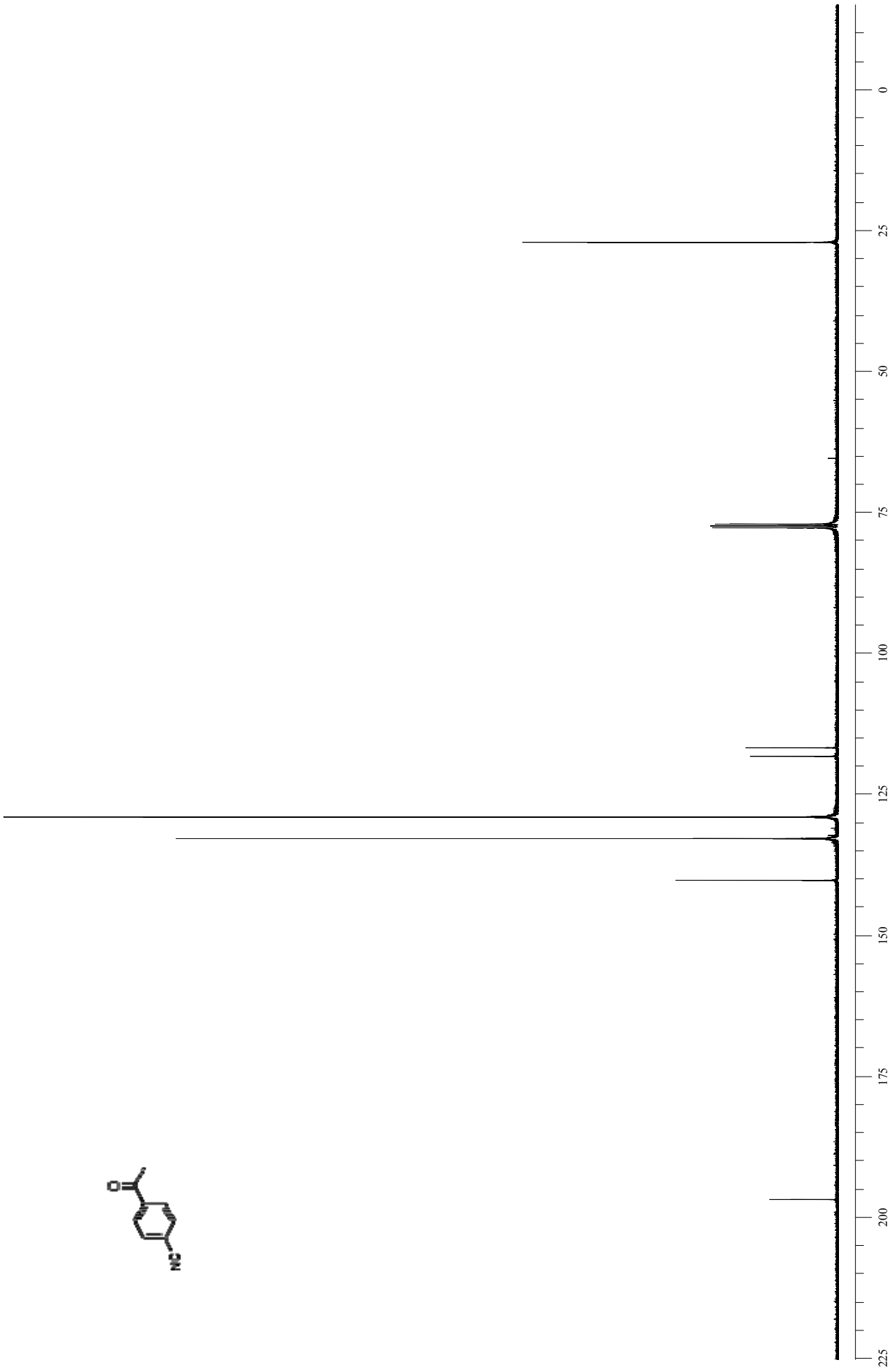

Spect 1
4.810 min, Scan: 392 Chan: 1 Ion: 452 vs RIC: 748795 BC
100%
75%
50%
25%
0%
173
145
50
75
95
125
100
200
300
400
500
m/z
kCounts
700
600
500
400
300
200
100
0
RIC all 4-(Trifluoromethyl)acetophenone
2.5
5.0
7.5
10.0
12.5
minutes
Segment 1
Segment 2
Scans
151
474
705
995
1250

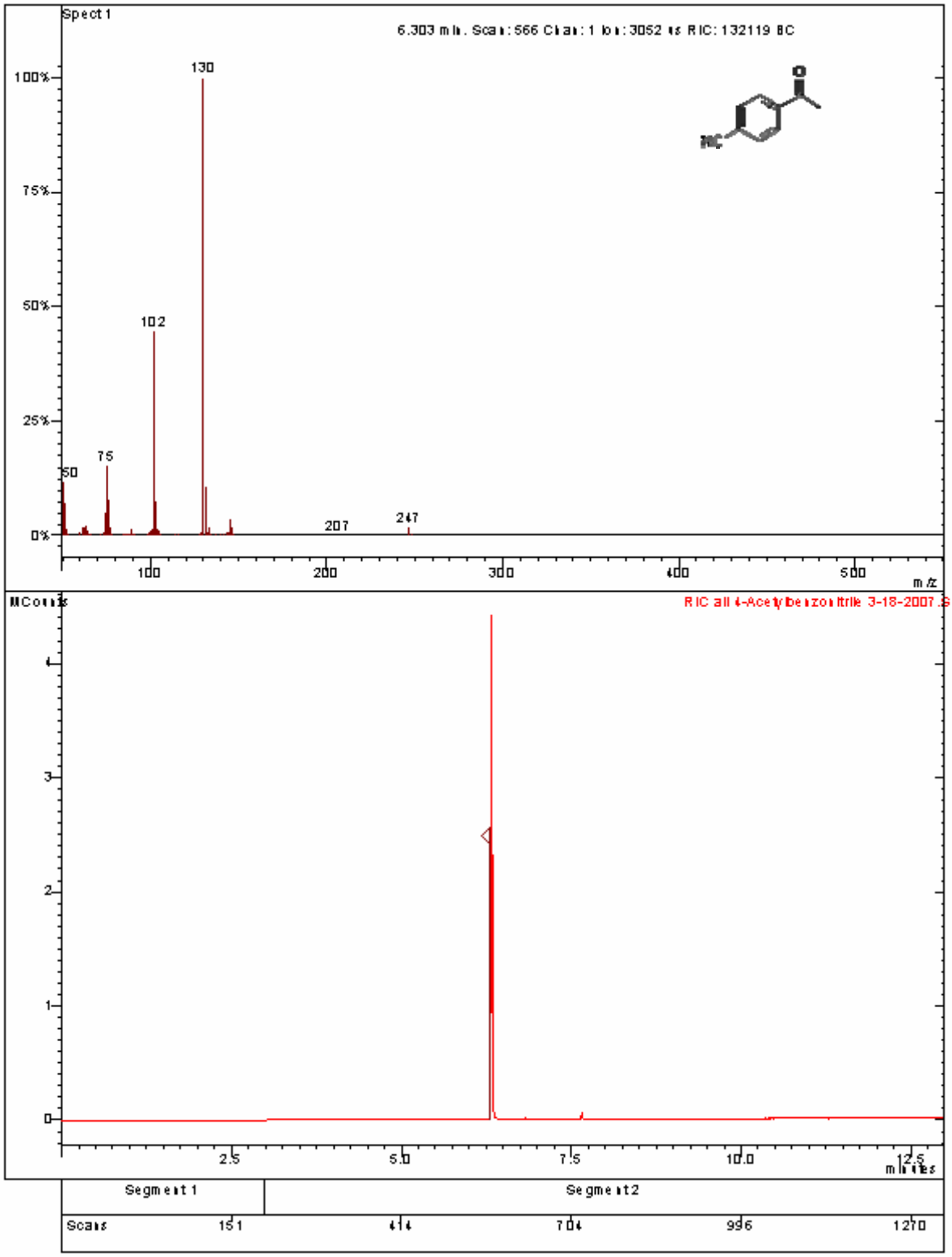

O
H3CO
200
175
150
125
100
75
50
25
0

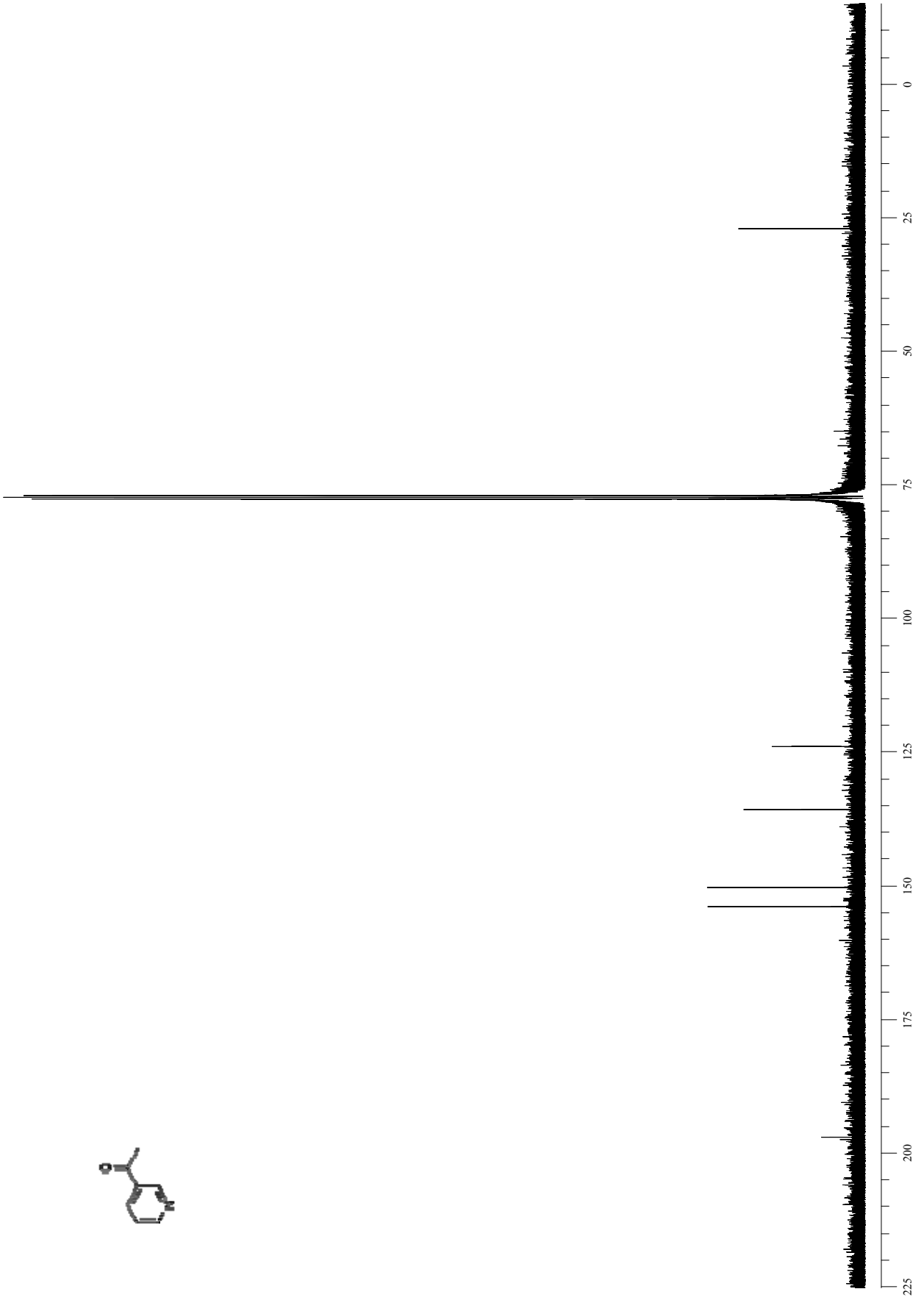

Spect 1
6.460 min, Scan: 599 Chan: 1 Ion: 1492 vs RIC: 283037 BC
147
91
119
50
197
239
281
310
355 374
415
453
503
548
100%
75%
50%
25%
0%
100
200
300
400
500
m/z
MeOC
O
MCons
RIC all 1,4-Diacetylbenzene.SMS
2.5
2.0
1.5
1.0
0.5
0.0
2.5
5.0
7.5
10.0
12.5
minutes
Segment 1
Segment 2
Scans
152
435
714
985
1242

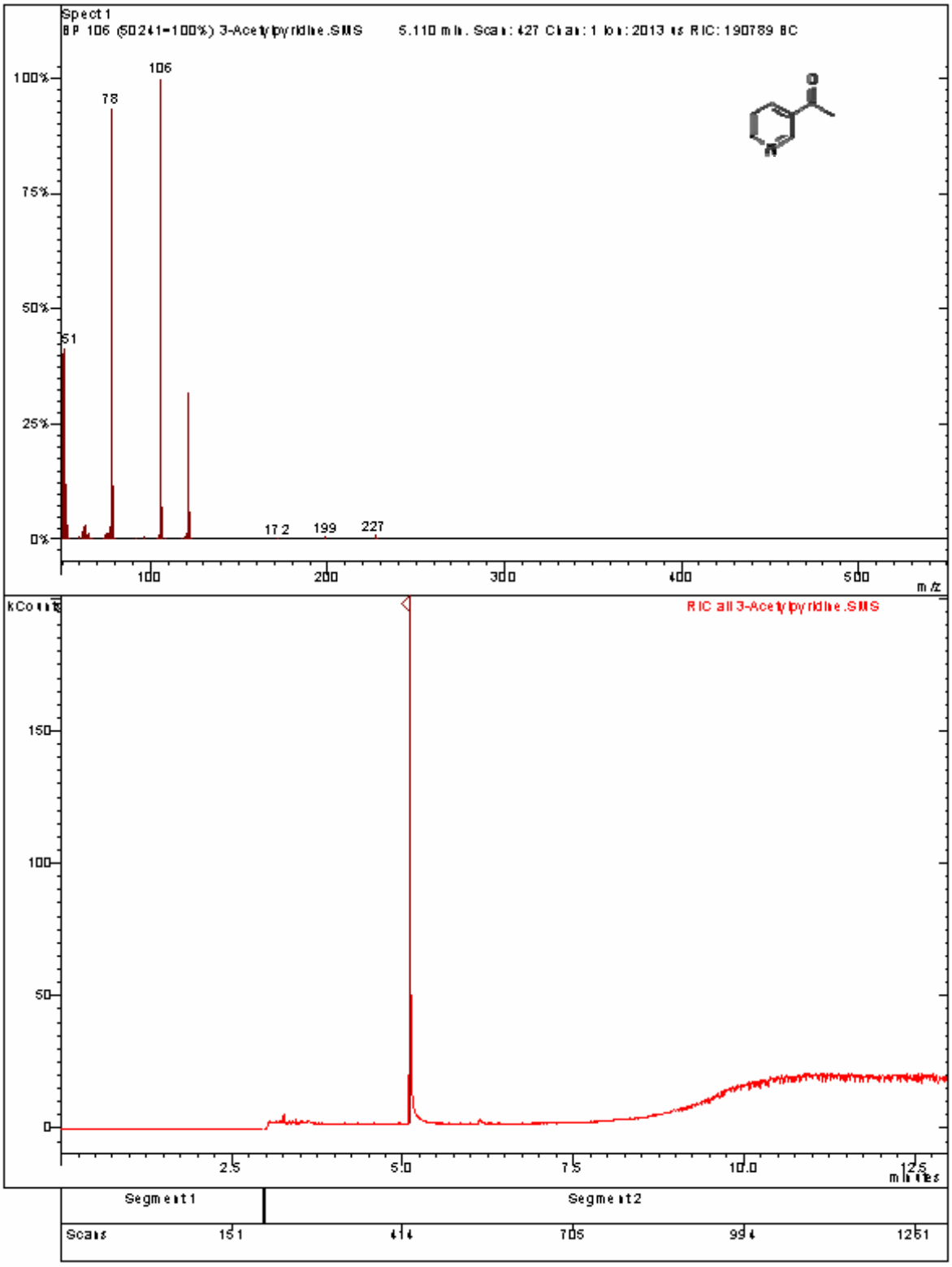

O
PhOC
0
25
50
75
100
125
150
175
200
225

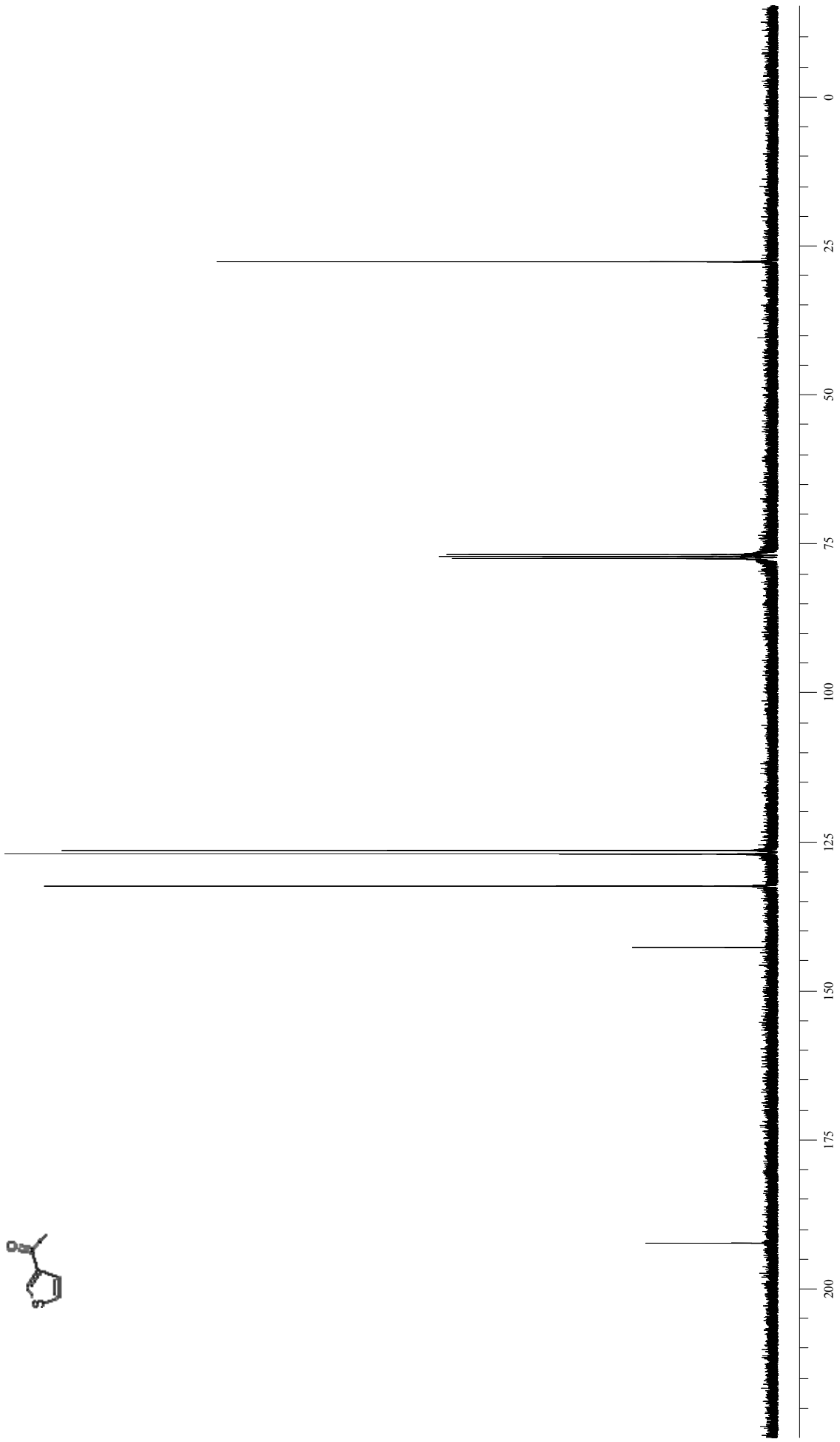

Spect 1
9.043 min, Scan: 885 Chan: 1 Ion: 197 vs RIC: 1625162 BC
100%
75%
50%
25%
0%
209
105
77
50
147
181
301
100
200
300
400
500
m/z
MCounts
2.5
2.0
1.5
1.0
0.5
0.0
RIC all 4-Acetylbenzophenone.SMS
9.035 min
2.5
5.0
7.5
10.0
12.5
minutes
Segment 1
Segment 2
Scans
151
414
706
990
1255

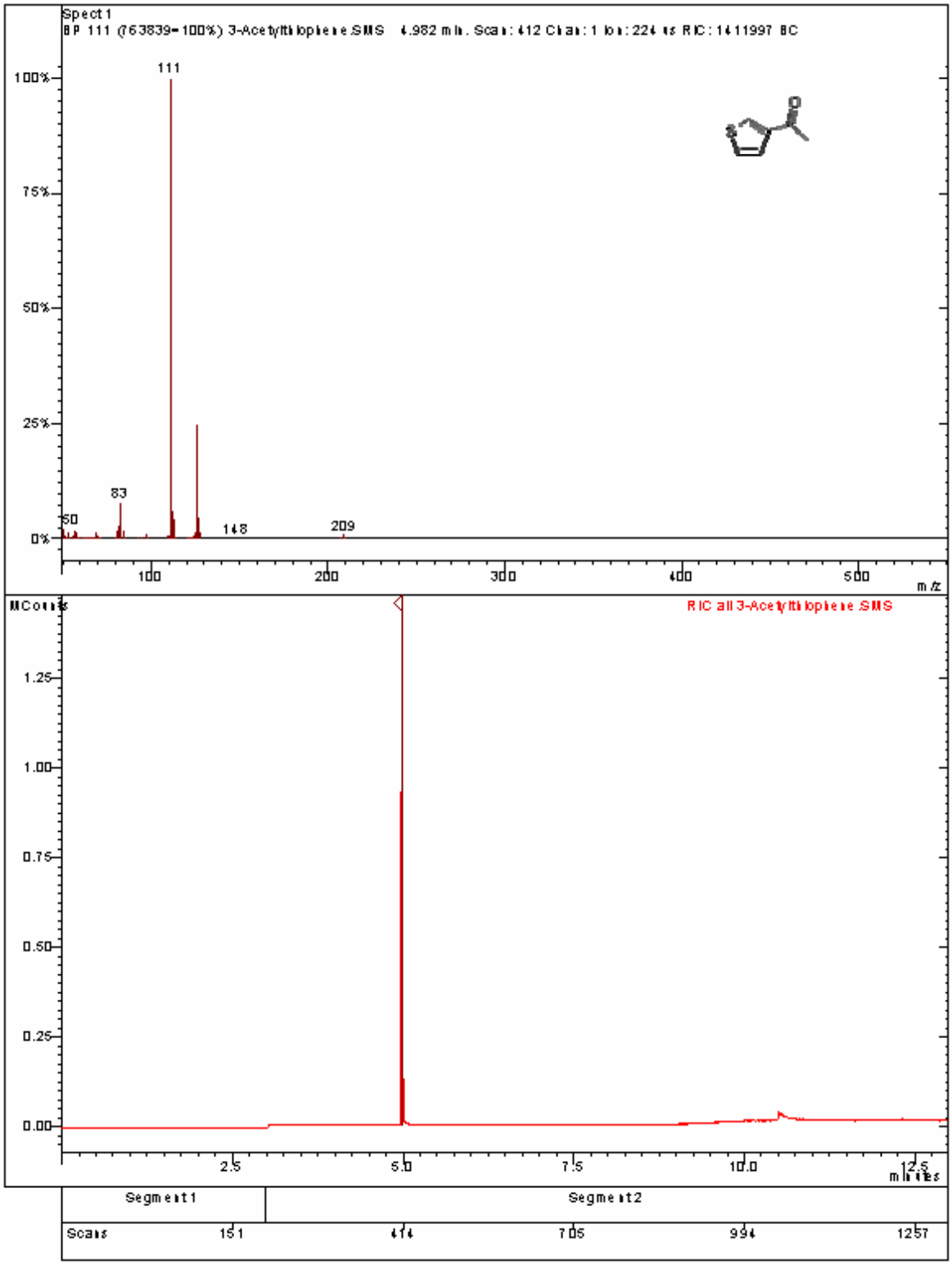

O
N
0
25
50
75
100
125
150
175
200
225


Spect 1
6.303 min, Scan: 566 Chan: 1 Ion: 3052 vs RIC: 132119 BC
100%
75%
50%
25%
0%
130
102
75
50
207
247
100
200
300
400
500
m/z
MCounts
RIC all 4-Acetylbenzonitrile 3-18-2007.SI
4
3
2
1
0
2.5
5.0
7.5
10.0
12.5
minutes
Segment 1
Segment 2
Scans
151
414
704
996
1270

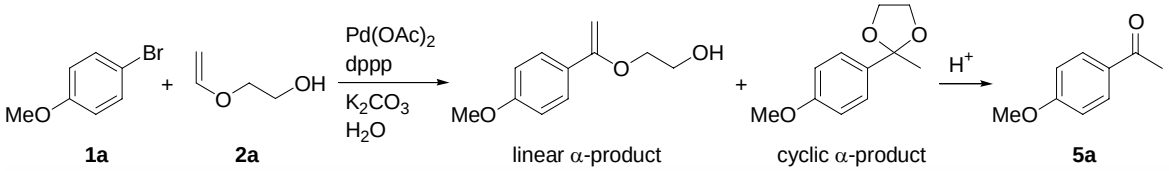

0
25
50
75
100
125
150
175
200
225
O
N


Spect 1
BP 106 (50241=100%) 3-Acetylpyridine.SMS
5.110 min. Scan: 427 Chan: 1 Ion: 2013 vs RIC: 190789 BC
100%
75%
50%
25%
0%
106
78
51
172
199
227
100
200
300
400
500
m/z
kCounts
RIC all 3-Acetylpyridine.SMS
150
100
50
0
2.5
5.0
7.5
10.0
12.5
minutes
Segment 1
Segment 2
Scans
151
414
705
994
1251

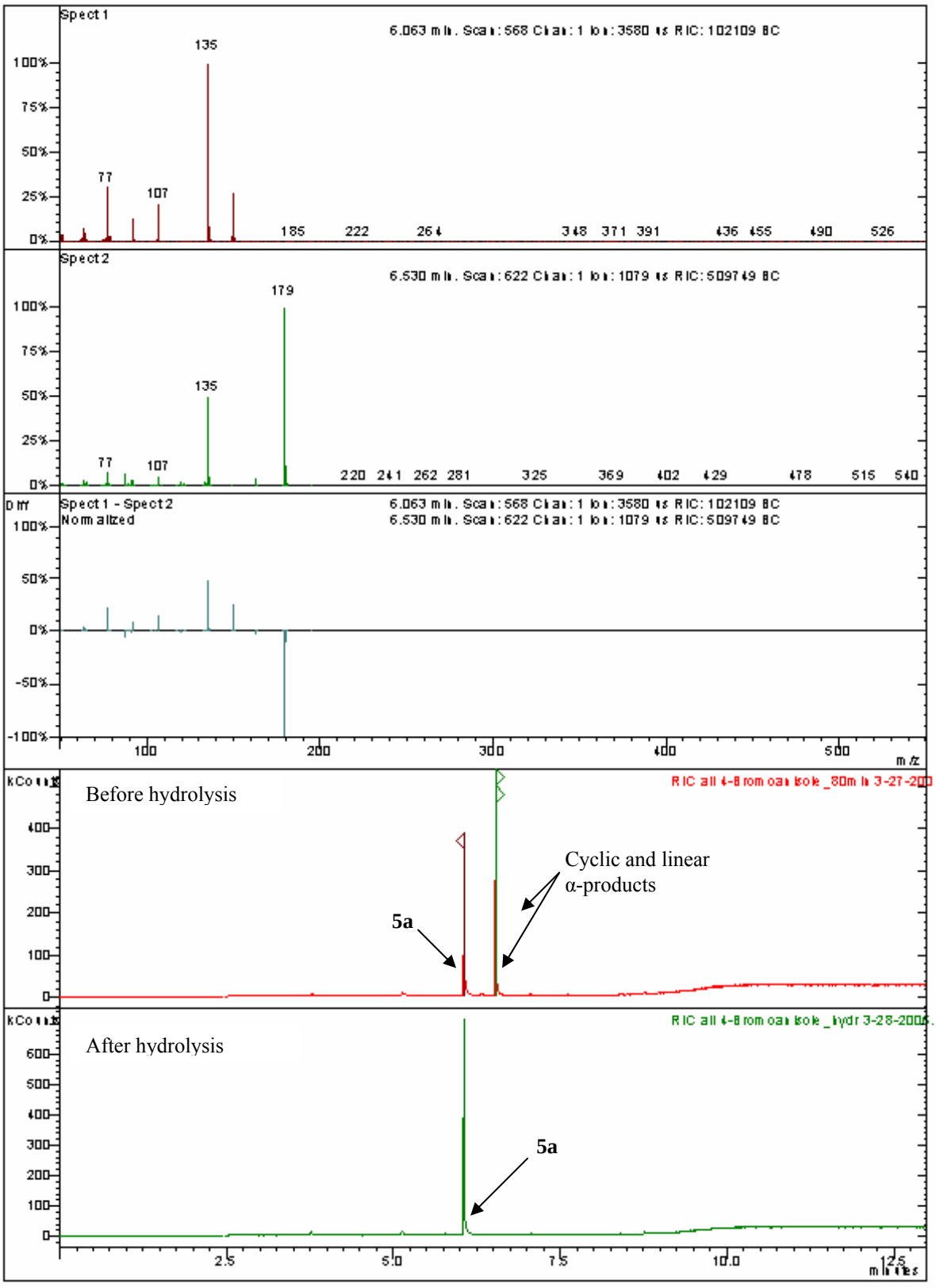

0
25
50
75
100
125
150
175
200

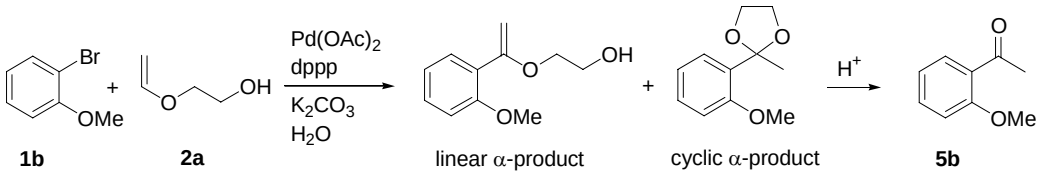

Spect 1
BP 111 (763839=100%) 3-Acetylthiophene.SMS 4.982 min. Scan: 412 Chan: 1 Ion: 224 vs RIC: 1411997 BC
111
83
50
148
209
100%
75%
50%
25%
0%
100
200
300
400
500
m/z
MCounts
RIC all 3-Acetylthiophene.SMS
1.25
1.00
0.75
0.50
0.25
0.00
2.5
5.0
7.5
10.0
12.5
minutes
Segment 1
Segment 2
Scans
151
414
705
994
1257

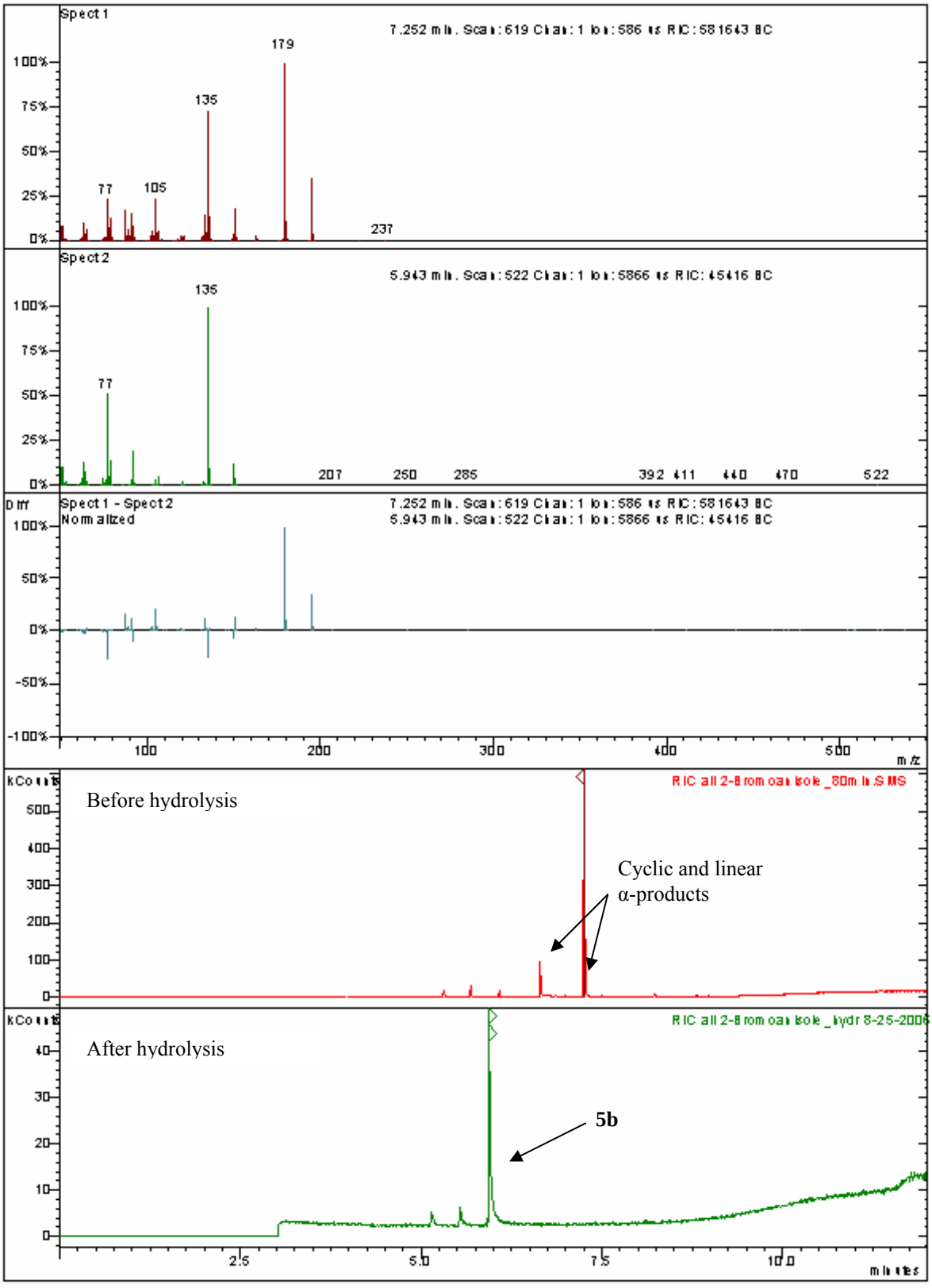
B: GC-MS chromatograms for reaction mixtures before and after hydrolysis

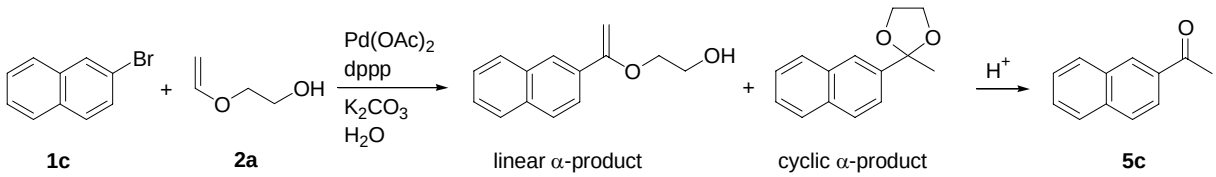


1a **2a** linear α-product cyclic α-product **5a**

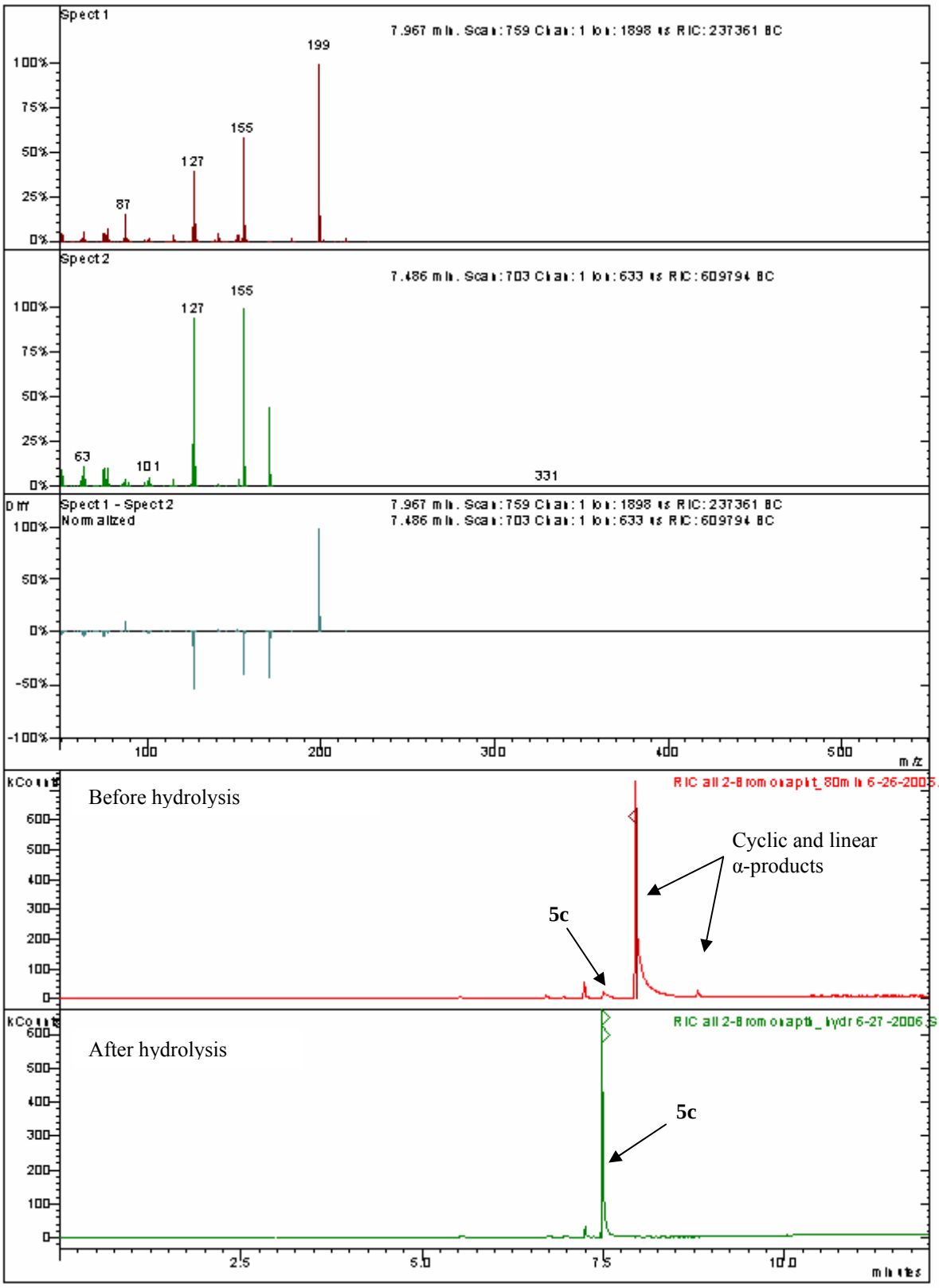


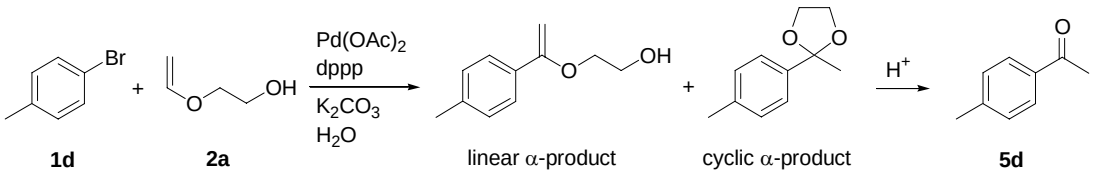

Br
OMe
1b
+
OH
O
2a
Pd(OAc)2
dppp
K2CO3
H2O
OH
O
OMe
linear α-product
+
O
O
OMe
cyclic α-product
H+
O
OMe
5b

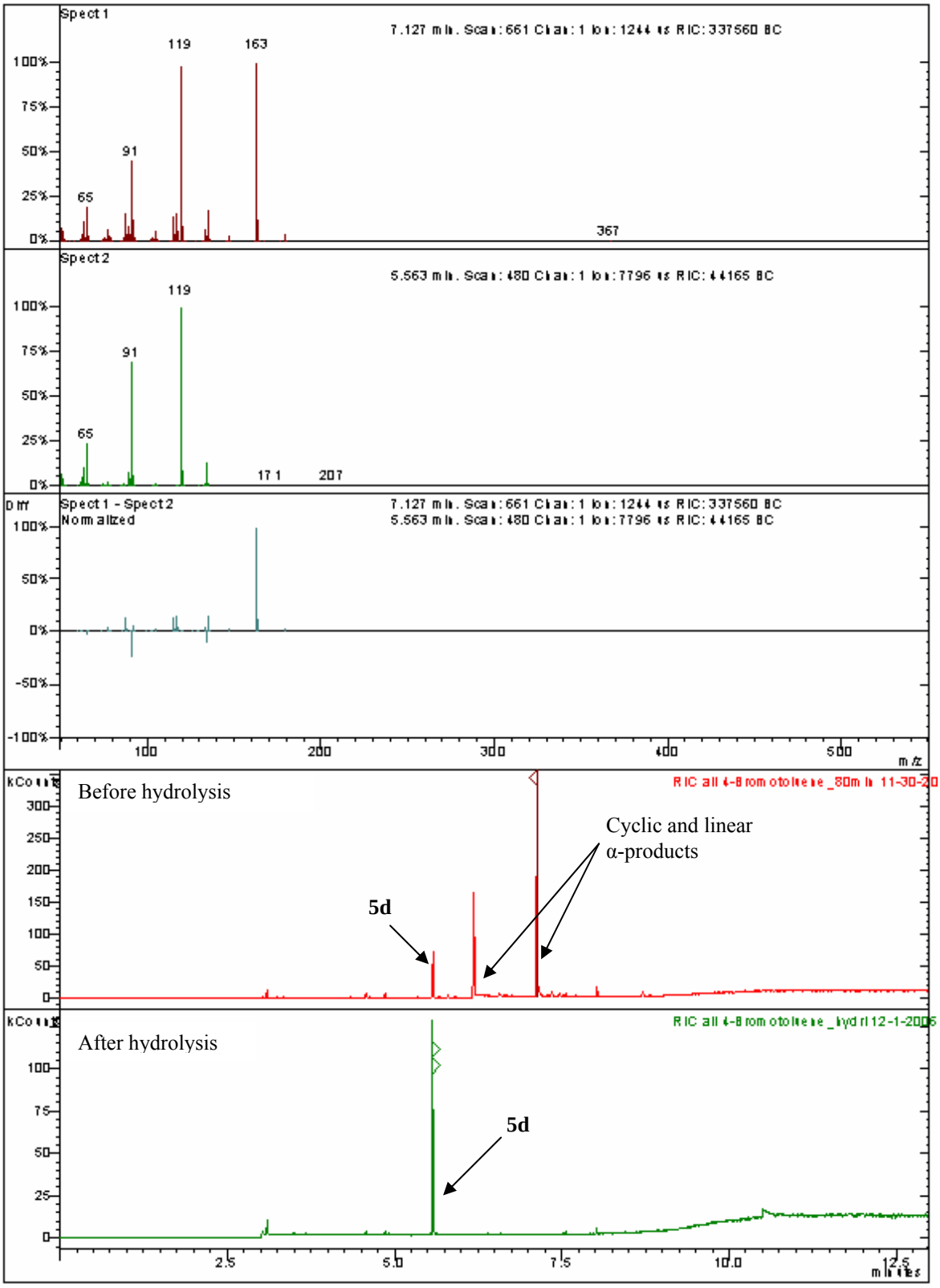

Spect 1
7.252 min. Scan:619 Chan:1 Ion:586 vs RIC:581643 BC
179
135
77
105
237
Spect 2
5.943 min. Scan:522 Chan:1 Ion:5866 vs RIC:45416 BC
135
77
207
250
285
392
411
440
470
522
Diff
Spect 1 - Spect 2
Normalized
7.252 min. Scan:619 Chan:1 Ion:586 vs RIC:581643 BC
5.943 min. Scan:522 Chan:1 Ion:5866 vs RIC:45416 BC
m/z
Before hydrolysis
Cyclic and linear
α-products
After hydrolysis
5b
minutes

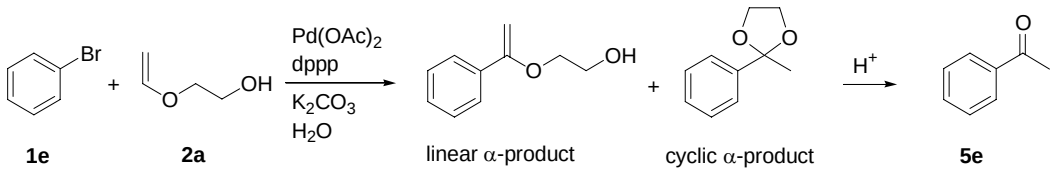


1c **2a** linear α-product cyclic α-product **5c**

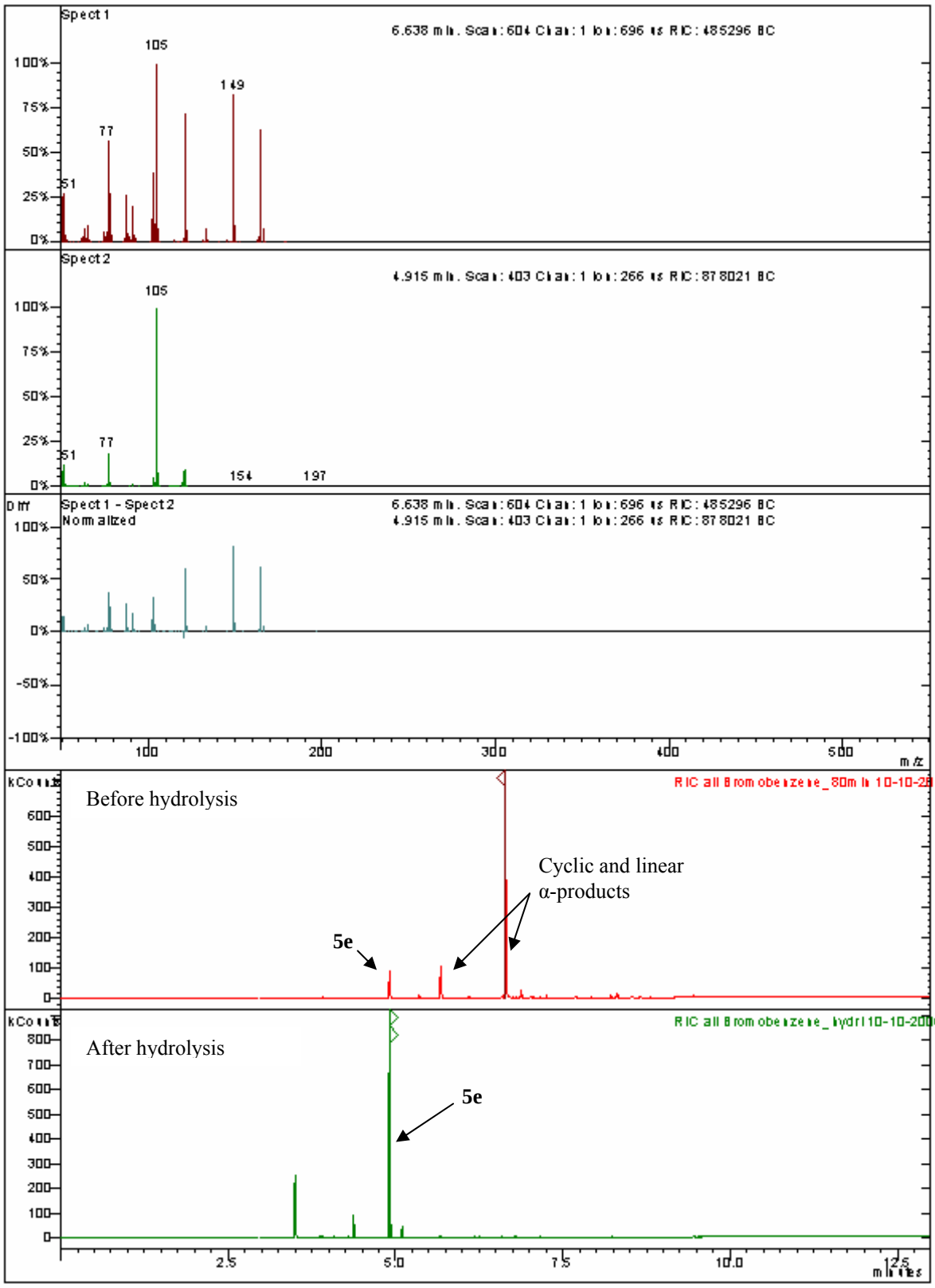


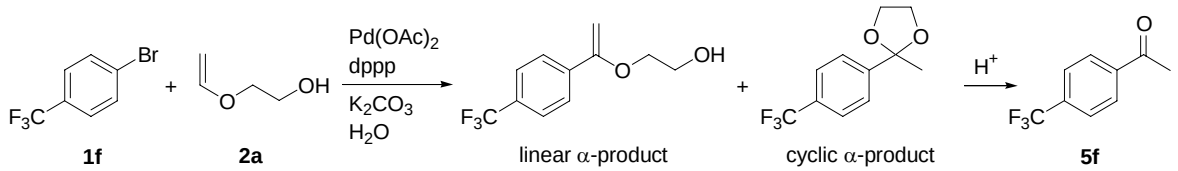

Br
OH
O
Pd(OAc)2
dppp
K2CO3
H2O
OH
O
O
O
H+
O
1d
2a
linear α-product
cyclic α-product
5d


Spect 1
7.127 min. Scan: 661 Chan: 1 Ion: 1244 as RIC: 337560 BC
119
163
91
65
367
Spect 2
5.563 min. Scan: 480 Chan: 1 Ion: 7796 as RIC: 44165 BC
119
91
65
171
207
Diff
Spect 1 - Spect 2
Normalized
7.127 min. Scan: 661 Chan: 1 Ion: 1244 as RIC: 337560 BC
5.563 min. Scan: 480 Chan: 1 Ion: 7796 as RIC: 44165 BC
m/z
Before hydrolysis
Cyclic and linear
α-products
5d
After hydrolysis
5d
minutes

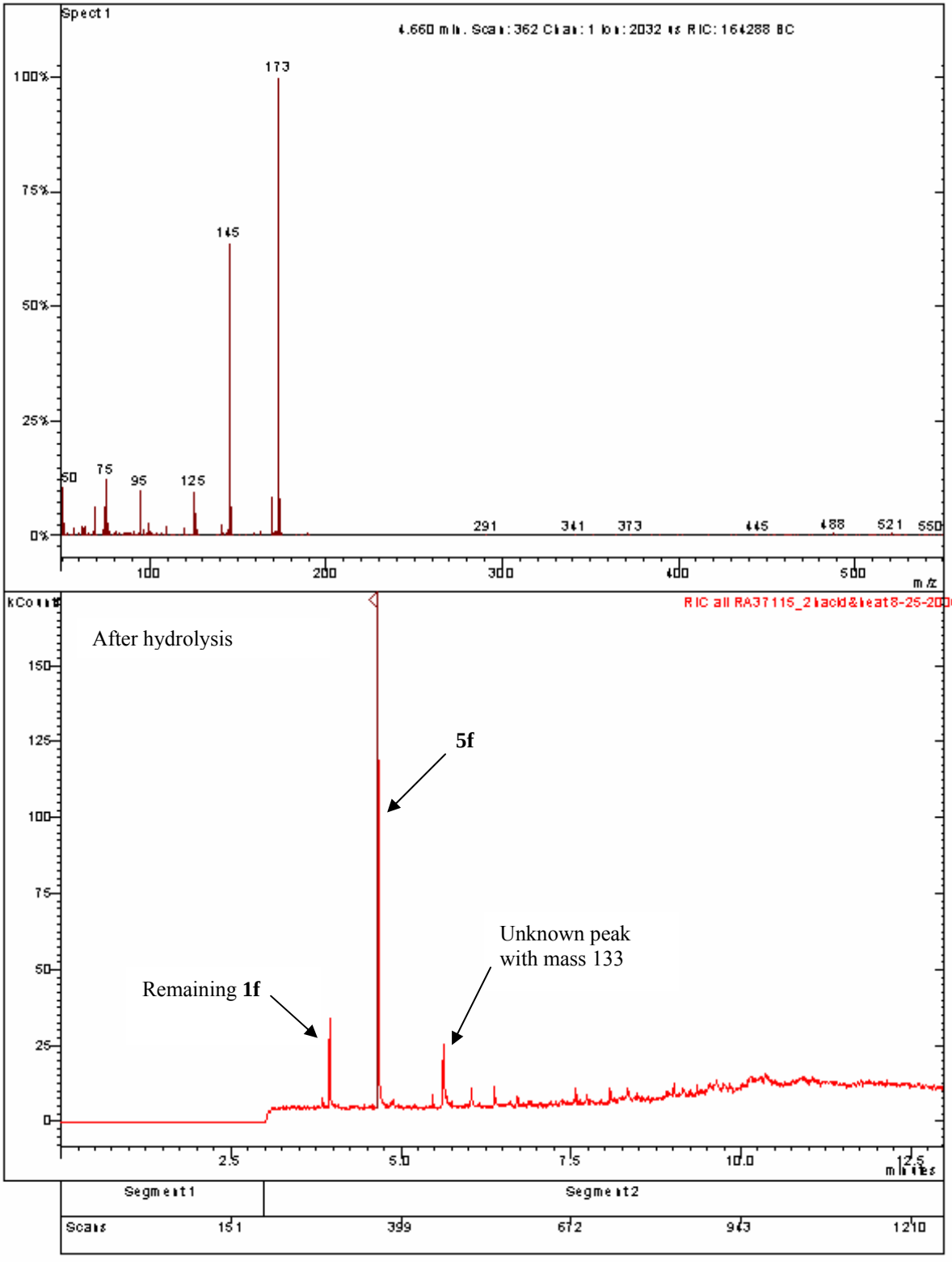


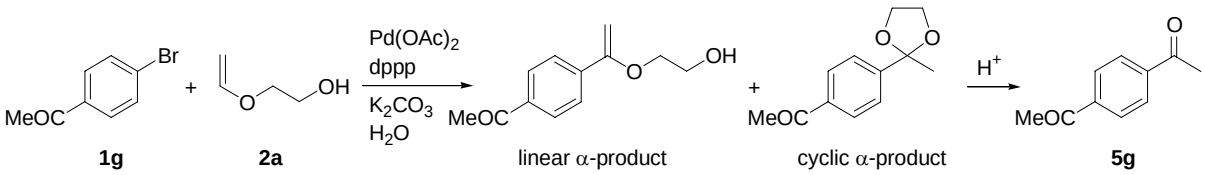
1e **2a** linear α-product cyclic α-product **5e**



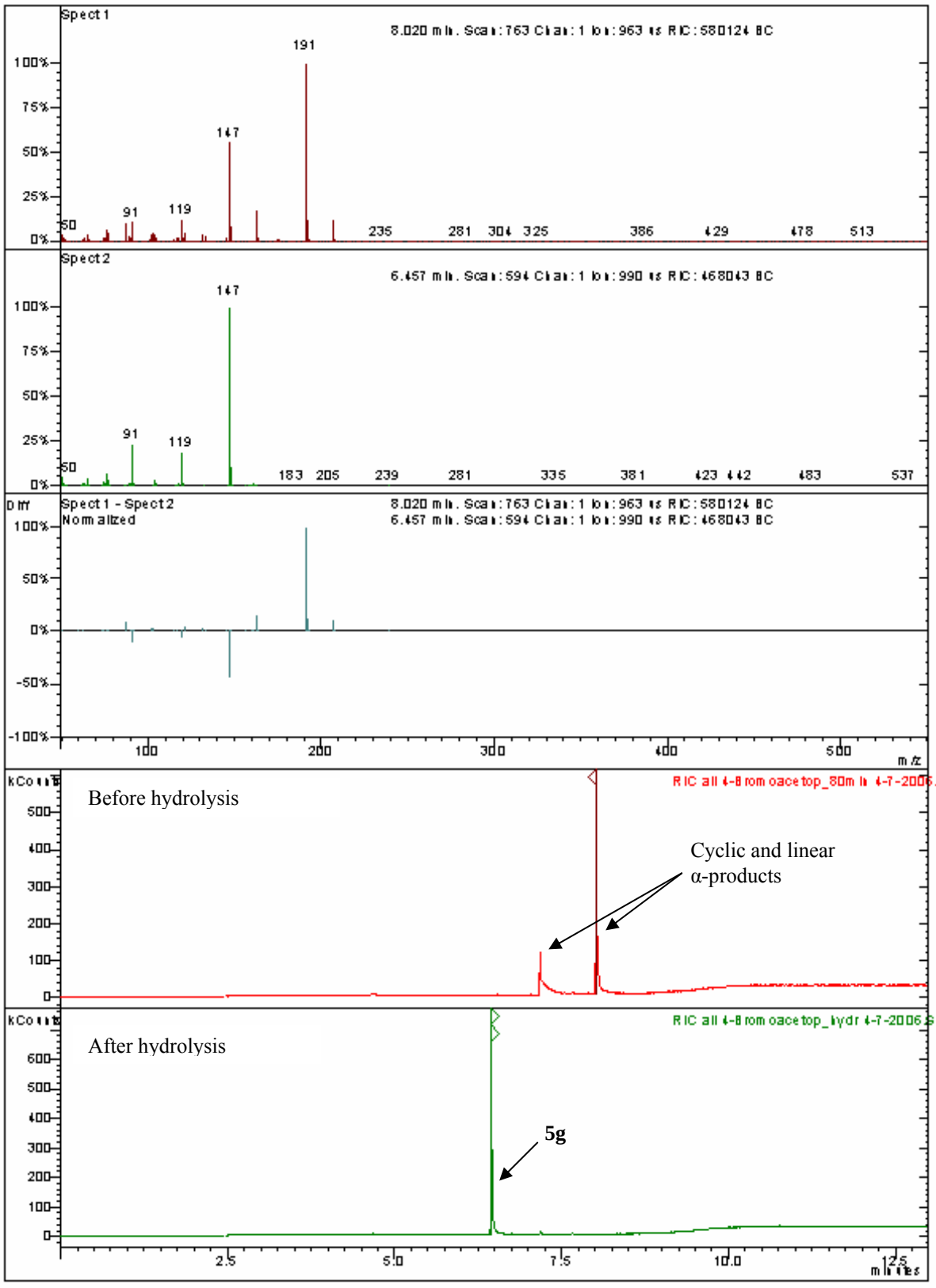


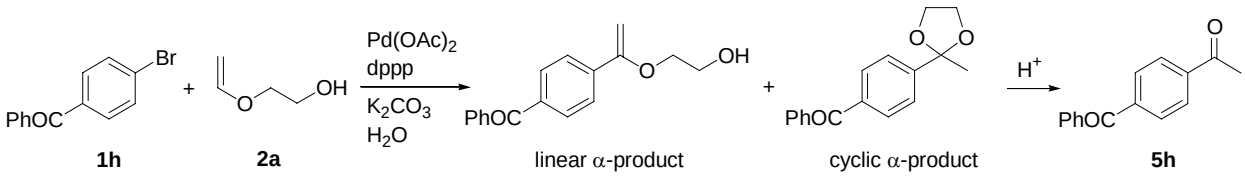
As the formed internal product seems to prefer alkaline water instead of ethyl acetate, there is no good spectrum available for reaction mixture before hydrolysis.



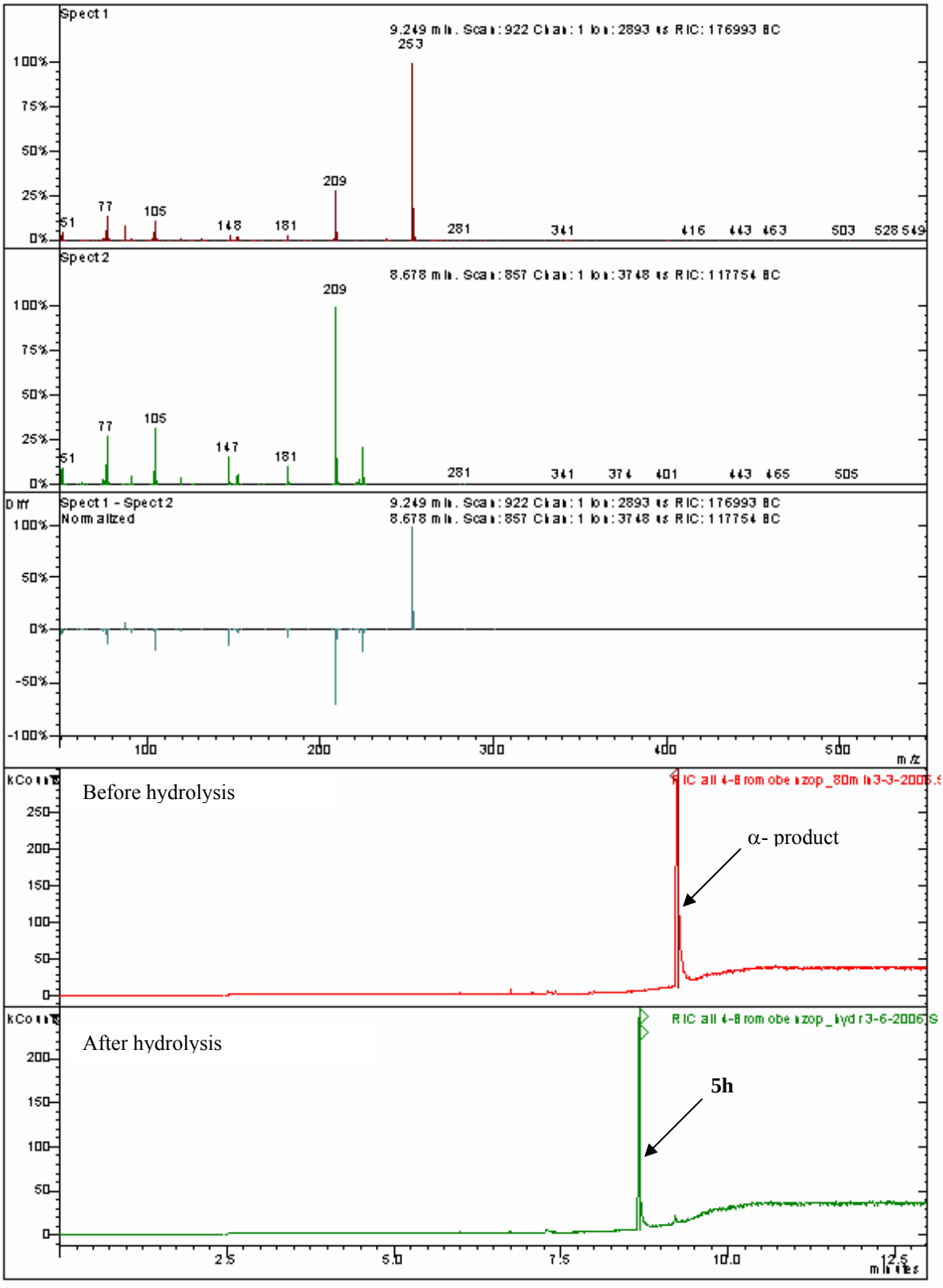


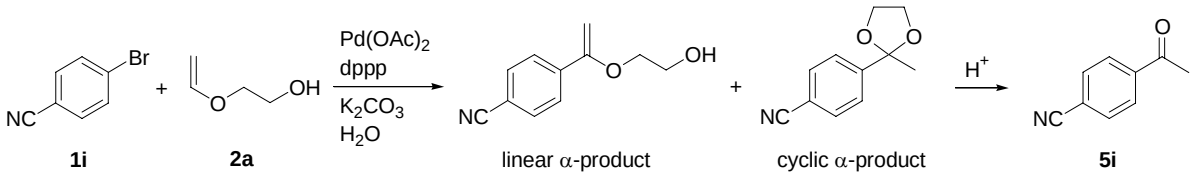
1g **2a** linear α-product cyclic α-product **5g**



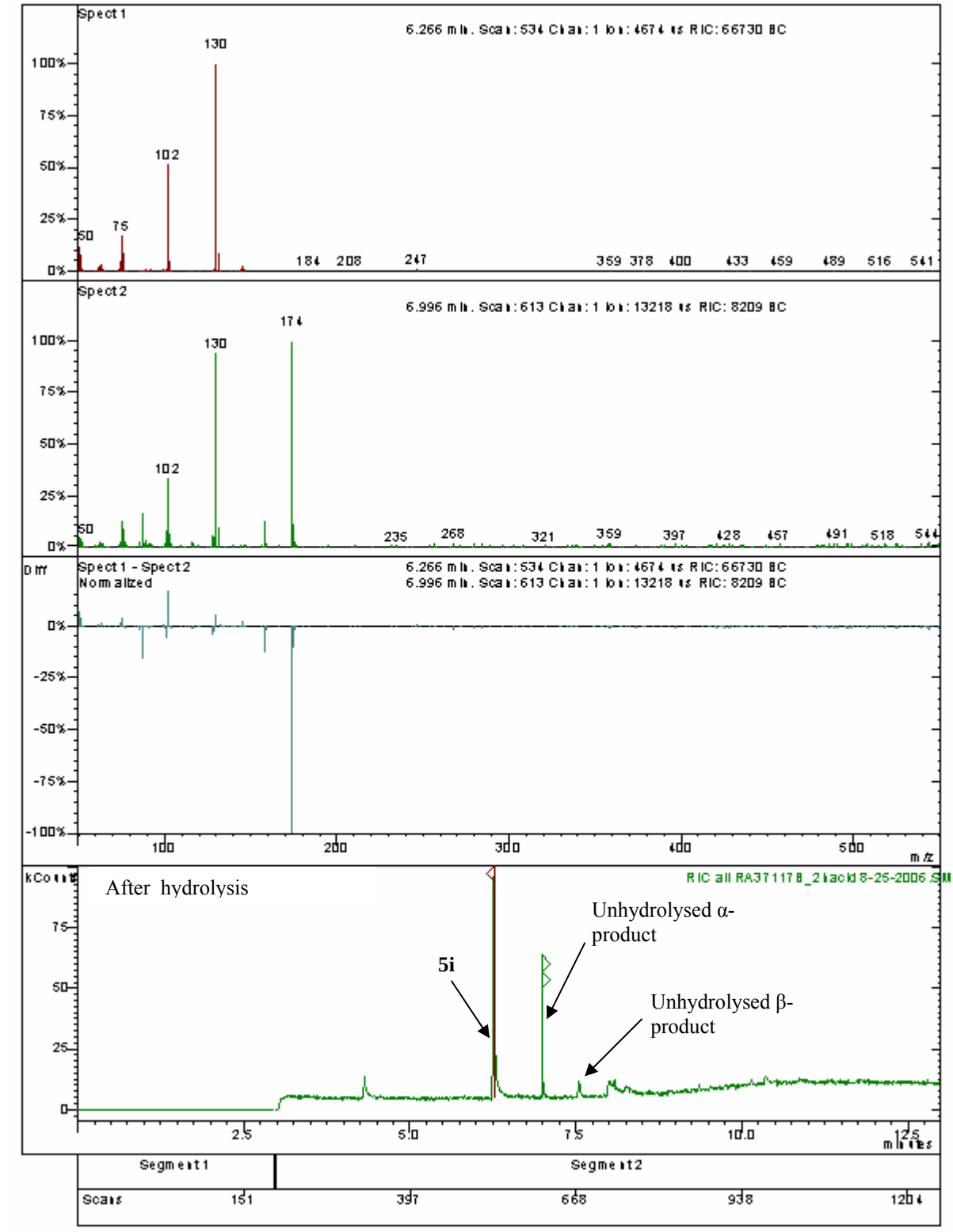


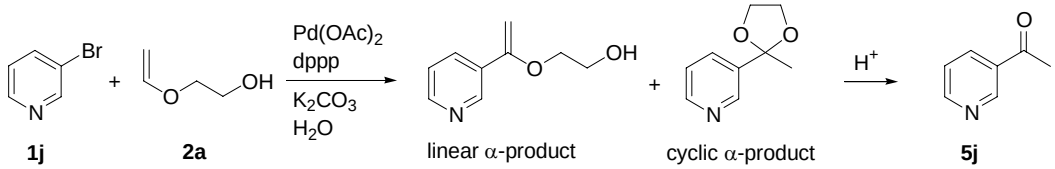
1h **2a** linear α-product cyclic α-product **5h**



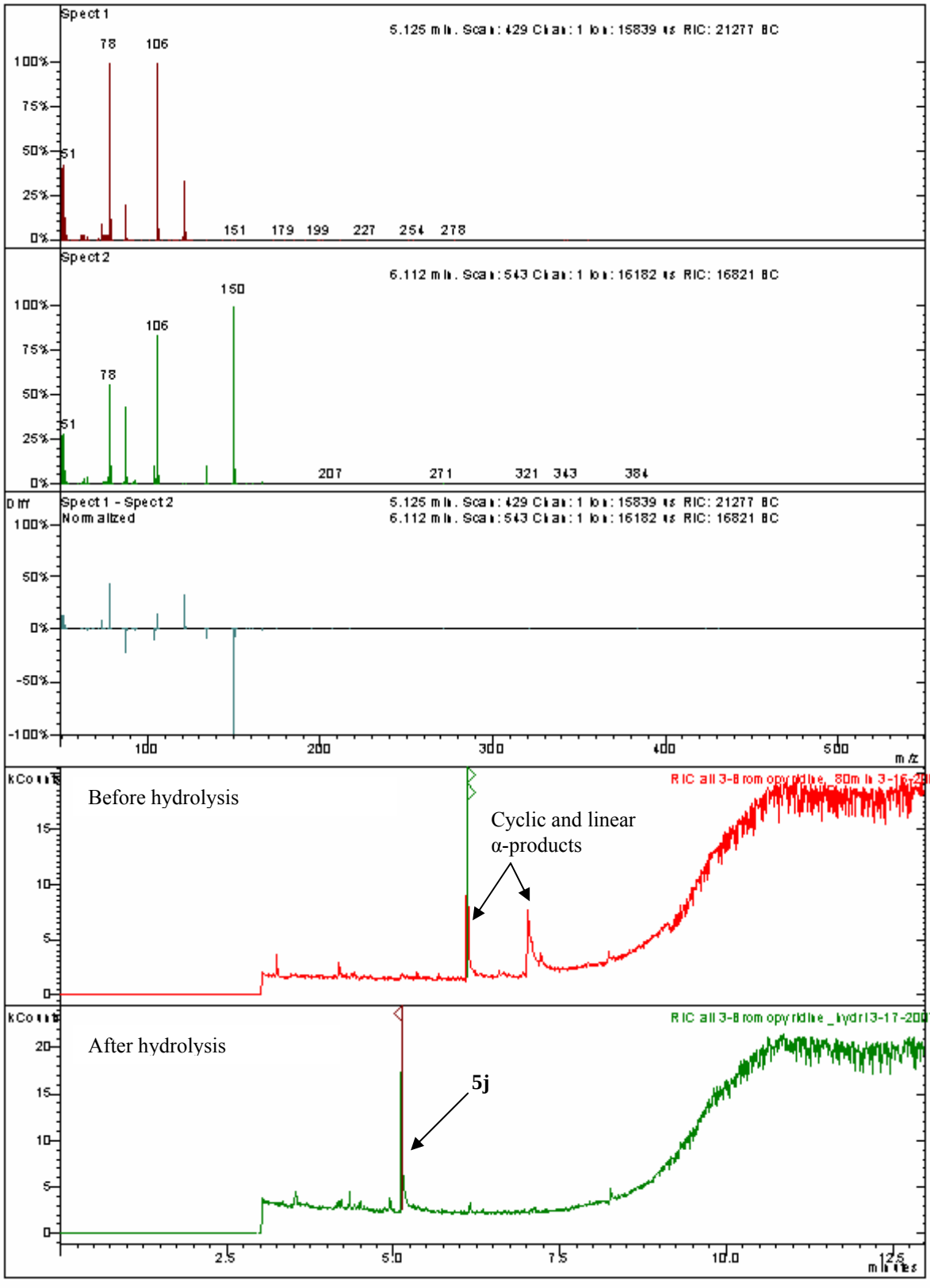


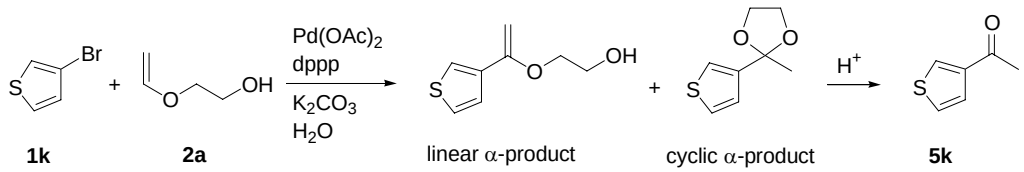
As the formed internal product seems to prefer alkaline water instead of ethyl acetate, there is no good spectrum available for reaction mixture before hydrolysis.

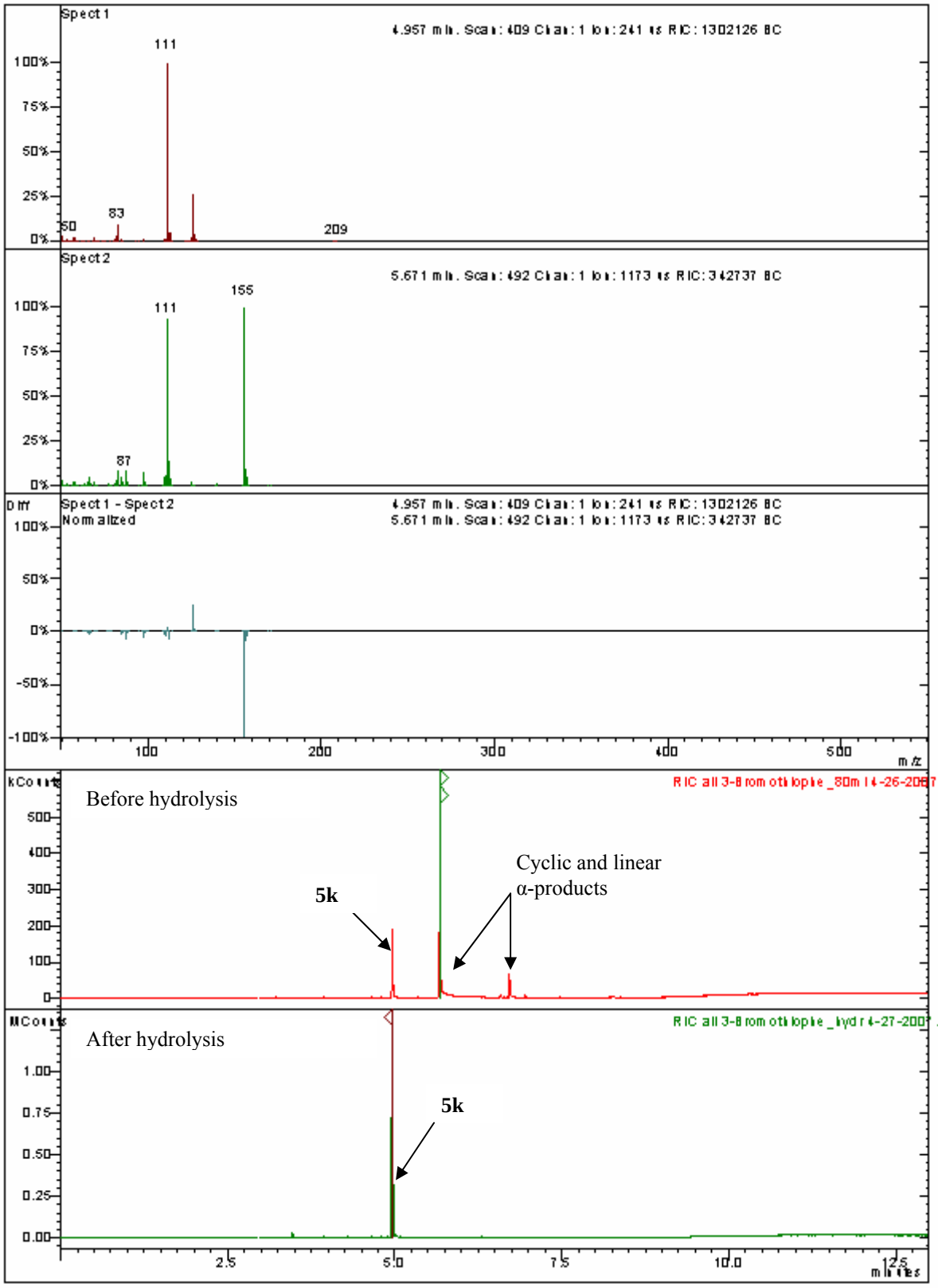




Weak GC-MS chromatogram due to high water solubility.




Br
S
+
OH
O
Pd(OAc)2
dppp
K2CO3
H2O
OH
O
S
+
O
O
S
H+
O
S
1k
2a
linear α-product
cyclic α-product
5k


Spect 1
111
100%
75%
50%
25%
0%
50
83
209
Spect 2
111
155
87
Spect 1 - Spect 2
Normalized
100
200
300
400
500
m/z
Before hydrolysis
5k
Cyclic and linear
α-products
After hydrolysis
5k
2.5
5.0
7.5
10.0
12.5