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Supporting Information

Total Synthesis and Selective Activity of a New Class of Conformationally-Restrained Epothilones

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General methods.

All reactions were carried out under an argon or nitrogen atmosphere using dry solvents under anhydrous conditions, unless otherwise noted. Tetrahydrofuran (THF) and diethyl ether were distilled under nitrogen from sodium-benzophenone. The solvents used were ACS grade from Fisher. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise noted. Reagents were purchased from Aldrich and Acros, and used without further purification. Amano PS-D lipase was generously provided from Amano Enzyme USA. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.20 mm POLYGRAM® SIL silica gel plates (Art.-Nr. 805 023) with fluorescent indicator UV_{254} using UV light and 15% sulfuric acid in ethanol solution and heat as visualizing agents. Normal phase flash column chromatography was carried out using Davisil® silica gel (100-200 mesh, Fisher). Preparative thin-layer chromatography (PTLC) separations were carried out on 1 mm, or 2 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on Varian INOVA 600, Varian VXRS-400, Bruker AC-F 300 MHz, or Nicolet NM-500 MHz (modified with a Tecmag Libra interface) instruments and calibrated using residual undeuterated solvent as internal reference. Coupling constants (*J*) were expressed in Hertz. Attached proton tests (APT) were performed to distinguish between different carbons in the ^{13}C NMR spectra. The following abbreviations were used to explain the

multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and b = broad. Optical rotations were recorded on an AUTOPOL® III 589/546 polarimeter. High-resolution mass spectra (HRMS) were recorded on a Micromass LCT Electrospray mass spectrometer performed at the Mass Spectrometry & Proteomics Facility (The Ohio State University). (+)-Allyldiisopinocampheylborane solution in pentane was prepared by an adaptation of a procedure reported by Brown *et al*.[1] Allylmagnesium bromide (5.82 ml of 1 M solution in ether, 5.82 mmol) was added dropwise to a well-stirred solution of (-)-*B*-methoxydiisopinocampheylborane (1.92 g, 6.062 mmol) in ether (35 ml) at 0 °C. After addition was complete, the reaction mixture was stirred at room temperature for 1h, and the solvents were pumped off under reduced pressure. The residue was extracted with dry pentane (3 x 13 ml) under nitrogen, and the stirring was discontinued to allow the precipitation of the MgBr(OMe) salt. The clear pentane supernatant was cannulated into another flask through a filtering funnel, and used without further purification.

Zinc borohydride (0.3 M solution in dry ether) was prepared by addition of saturated solution of anhydrous zinc chloride (12 g, 88.05 mmol, oven dried at 130 °C for 8 h under vacuo) in ether (50 ml) to $NaBH_4$ (8.1 g) in ether (150 ml).[2,3]

General procedure for Mosher Ester: To a stirred solution of alcohol (1 equiv), DMAP (0.5 equiv), and triethylamine (3 equiv) in methylene chloride was added (*S*)-(+)- or (*R*)-(-)-a-methoxy-a-(trifluoromethyl)phenylacetyl chloride (MTPACl) (3 equiv) at room temperature. The resulting mixture was stirred overnight. The solution was diluted with ethyl acetate and washed with water, dried, and concentrated in vacuo. Purification by silica gel column chromatography will furnish the Mosher Ester.

6-Methyl-hept-6-enoic acid (7): *n*BuLi (10.8 ml of 2.5 M in hexanes, 27 mmol, 1.3 equiv) was added to a solution of methyltriphenylphosphonium bromide (9.7 g, 27 mmol, 1.3 equiv) in dimethyl sulfoxide (50 ml) at 0^{o}C, and the mixture was stirred at room temperature for 1 h. It was then added to a solution of 6-oxo-heptanoic acid **6** (3 g, 20.82 mmol, 1 equiv) and *n*BuLi (8.33 ml of 2.5 M in hexanes, 20.82 mmol, 1 equiv) in THF (30 ml). The mixture was stirred at room temperature for 48 hr. Water was added and the mixture was acidified with 2 N HCl and extracted with methylene chloride (3 x 50 ml). The organic layer was washed with 10% aqueous sodium hydroxide solution. The aqueous layer was acidified with 2 N HCl and extracted with ethyl acetate (3 x 60 ml). The organic extracts were dried over anhydrous sodium sulfate and concentrated in vacuo. Purification by flash column chromatography (10% EtOAc/hexanes) gave pure acid **7** (2.32 g, 78%) as a colorless oil: TLC R_f = 0.47 (silica gel, 25% EtOAc/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) d 4.69 (s, 1H), 4.65 (s, 1H), 2.34 (t, *J* = 7.8 Hz, 2H), 2.01 (t, *J* = 7.8 Hz, 2H), 1.69 (s, 3H), 1.64-1.58 (m, 2H), 1.50-1.44 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) d 180.7, 145.6, 110.4, 37.5, 34.2, 27.1, 24.4, 22.5.

6-Methyl-hept-6-enoyl chloride (8): To a solution of the carboxylic acid **7** (2.2 g, 15.5 mmol) in benzene (30 ml), was added oxalyl chloride (3 ml, 34.4 mmol, 2.22 equiv). A drying tube was placed on the flask and the reaction mixture was stirred for 90 min at room temperature before it was concentrated in vacuo. The crude acid chloride **8** was used in the next step without further purification: TLC R_f = 0.37 (silica gel, 25% EtOAc/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) d 4.69 (s, 1H), 4.67 (s, 1H), 2.88 (t, *J* = 7.8 Hz, 2H), 2.02 (t, *J* = 7.8 Hz, 2H), 1.74-1.66 (m, 2H), 1.69 (s, 3H), 1.58-1.46 (m, 2H); ^{13}C NMR

(100 MHz, $CDCl_3$) d 173.9, 145.1, 110.7, 46.7, 37.3, 26.4, 24.8, 22.4.

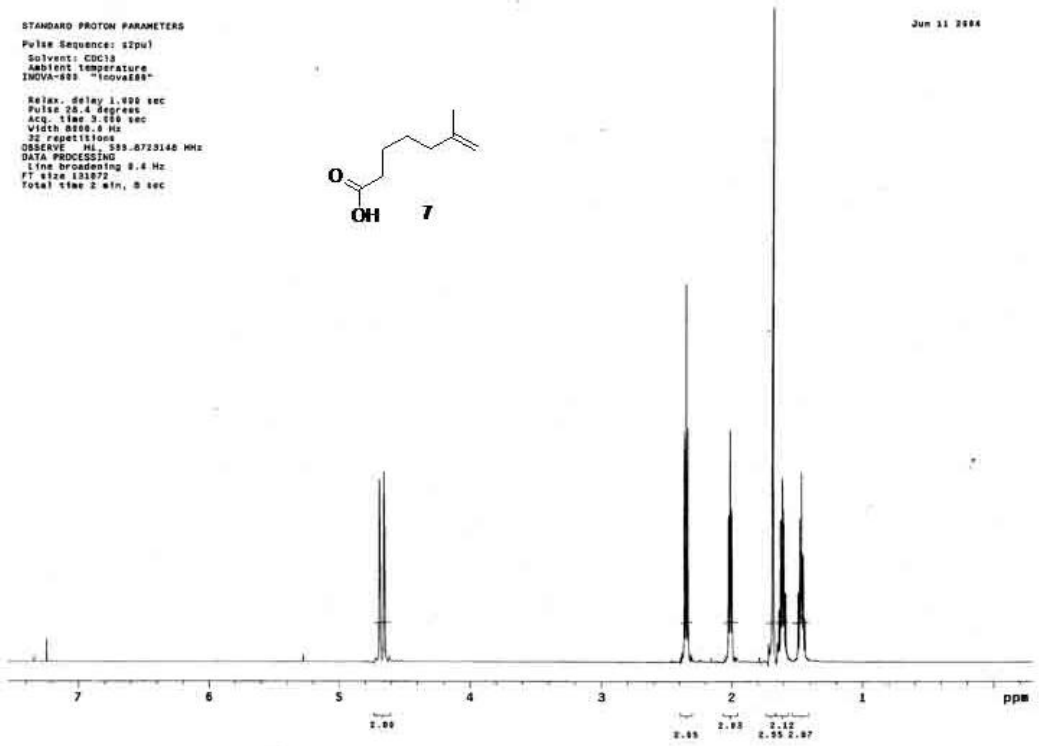
(4S)-4-Isopropyl-3-(6-methyl-hept-6-enoyl)-oxazolidin-2-one (9): To a solution of (*S*)-4-isopropyl-2-oxazolidonone (1.56 g, 12.1 mmol, 1 equiv) in THF (40 ml) at -78°C was added *n*BuLi (4.84 ml of a 2.5 M solution in hexanes, 12.1 mmol, 1 equiv). After 15 min acid chloride **8** (2.14 g, 13.3 mmol, 1.1 equiv) was added and the mixture was stirred for 30 min at -78°C and for 15 min at 0°C. Saturated aqueous ammonium chloride solution (10 ml) was added and the resulting slurry was concentrated in vacuo. The residue was diluted with ether and washed successively with saturated aqueous sodium bicarbonate and brine. The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. Purification by flash chromatography (10% EtOAc/hexanes) gave imide **9** (2.94 g, 96%) as a colorless oil: $[a]^{22}_D$ = +66.7 (c= 0.6, $CHCl_3$); TLC R_f = 0.40 (silica gel, 25% EtOAc/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) d 4.68 (s, 1H), 4.66 (s, 1H), 4.43-4.40 (m, 1H), 4.25 (t, *J* = 9.0 Hz, 1H), 4.19 (dd, *J* = 3.0 Hz, 9.0 Hz, 1H), 3.01-2.83 (m, 2H), 2.38-2.32 (m, 1H), 2.02 (t, *J* = 7.8 Hz, 2H), 1.69 (s, 3H), 1.67-1.61 (m, 2H), 1.51-1.46 (m, 2H), 0.90 (d, *J* = 7.2 Hz, 3H), 0.85 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) d 173.5, 154.3, 145.8, 110.2, 63.6, 58.6, 37.7, 35.6, 28.6, 27.2, 24.3, 22.6, 18.2, 14.9; HRMS (ESI): *m/z*: calcd for $C_{14}H_{23}NO_3$ + Na^+ 276.1576; found 276.1567 [M + Na^+].

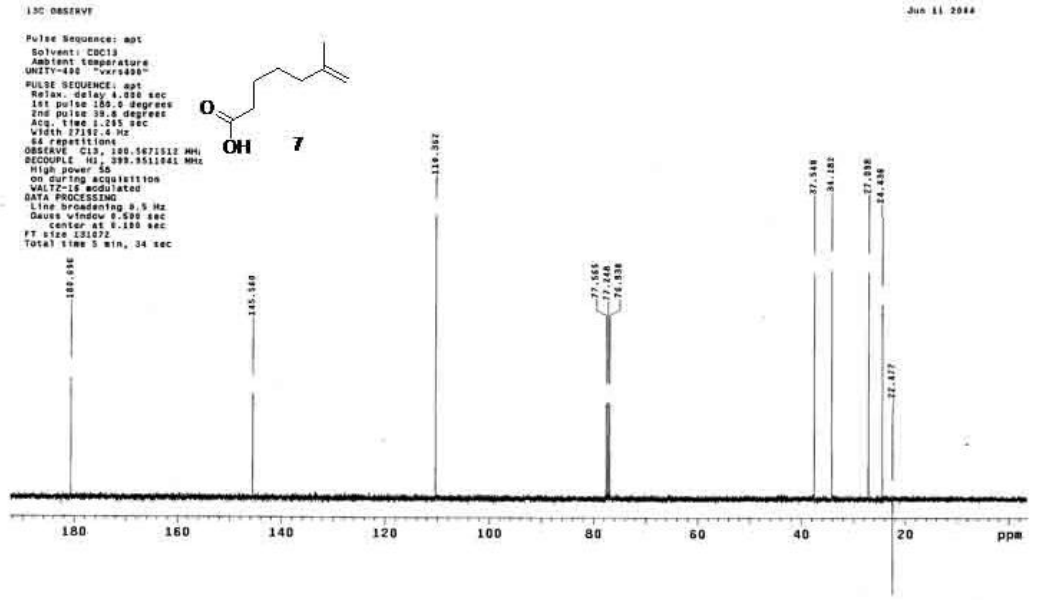
(2S)-2,6-Dimethyl-hept-6-enal (3): As reported by Schinzer *et al.*[4]: $[a]^{22}_D$ = +11.8 (c=0.5, $CHCl_3$); TLC R_f = 0.64 (silica gel, 25% EtOAc/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) d 9.56 (d, *J* = 1.8 Hz, 1H), 4.66 (s, 1H), 4.62 (s, 1H), 2.34-2.28 (m, 1H), 1.98 (t, *J* = 7.8 Hz, 2H), 1.69-1.62 (m, 4H), 1.48-1.27 (m, 3H), 1.05 (d,

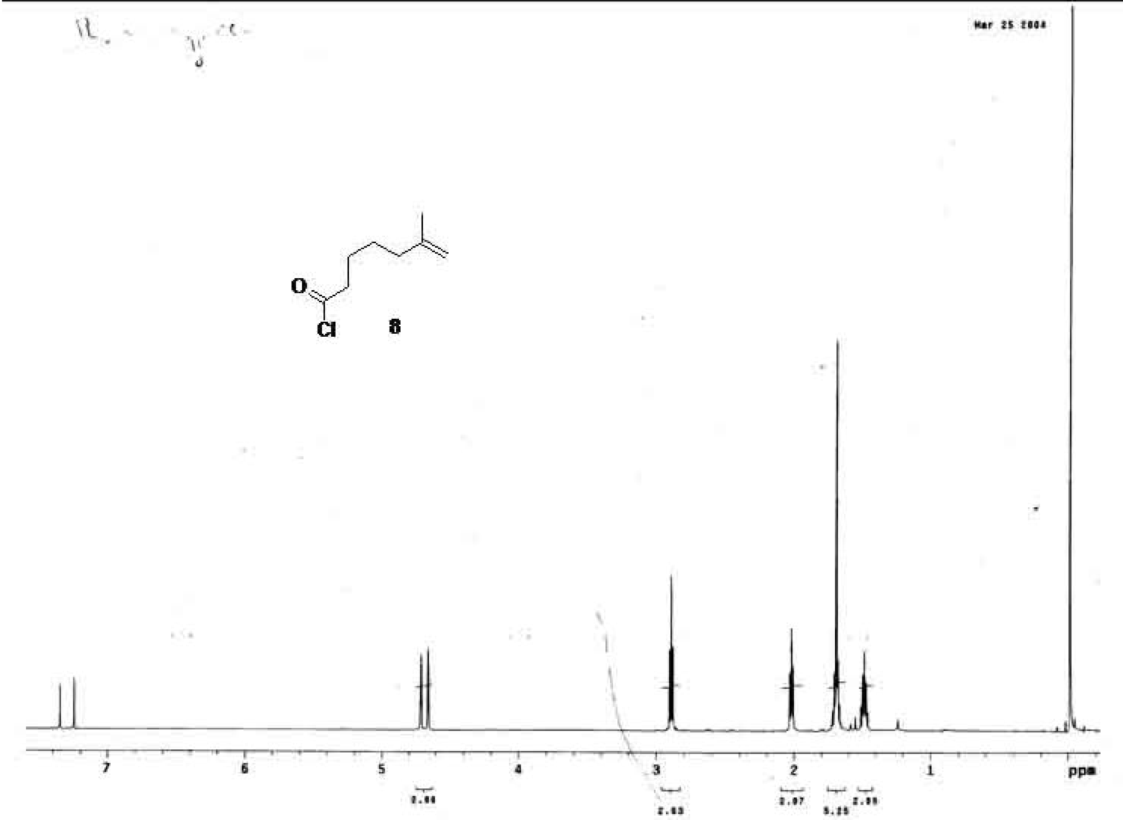
J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) d 205.3, 145.4, 110.4, 46.4, 37.8, 30.2, 24.9, 22.4, 13.5.

(5S)-5,7-Bis-(tert-butyl-dimethyl-silanyloxy)-4,4-dimethyl-heptan-3-one (4): Sodium borohydride (570 mg, 15.4 mmol, 2 equiv) was dissolved in methylene chloride (175 ml) and dry ethanol (75 ml). The mixture was cooled to -78^{o}C for 15 min after which a solution of aldehyde **10** [5] (2.2 g, 7.7 mmol, 1 equiv) in methylene chloride (5 ml) was added. After stirring for 1 h water (6 ml) was added and the reaction mixture was allowed to warm to room temperature. Methylene chloride (400 ml) was added and the mixture was washed with saturated aqueous sodium bicarbonate before it was dried over anhydrous sodium sulfate and concentrated in vacuo to give crude alcohol mixture **11** and **12**. The crude alcohol mixture was dissolved in methylene chloride (40 ml) and cooled to 0^{o}C. Imidazole (3.14 g, 46.15 mmol, 6 equiv) and *tert*-butyldimethylsilyl chloride (3.47 g, 23.1 mmol, 3 equiv) were added and the reaction mixture was stirred at room temperature for 16 hr. Saturated aqueous ammonium chloride (30 ml) was added and the layers were separated. The aqueous layer was further extracted with ethyl acetate (3 x 30) and combined organic extracts were dried over anhydrous sodium sulfate and concentrated in vacuo. Purification by flash chromatography (1% - 5% EtOAc/Hexanes) gave the bis(silylether) **4** (2.5 g, 81% over two steps) as a colorless oil: $[a]^{22}_{D}$ = -7.4 (c= 1.8, $CHCl_3$); TLC R_f = 0.70 (silica gel, 20% EtOAc/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) d 4.06 (dd, *J* = 7.6 Hz, 3.0 Hz, 1H), 3.62-3.54 (m, 2H), 2.57-2.41 (m, 2H), 1.56-1.42 (m, 2H), 1.09 (s, 3H), 1.02 (s, 3H), 0.99 (t, *J* = 7.0 Hz, 3H), 0.86 (s, 9H), 0.85 (s, 9H), 0.07 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H), 0.002 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) d 215.8, 73.6, 60.3, 53.2, 37.5, 31.8, 26.3, 26.1, 22.4, 20.2, 18.5, 18.4, 7.9, -3.8,

-5.1; HRMS (ESI): *m/z*: calcd for $C_{21}H_{46}O_3Si_2$ + Na^+ 425.2883; found 425.2885 [M + Na^+].



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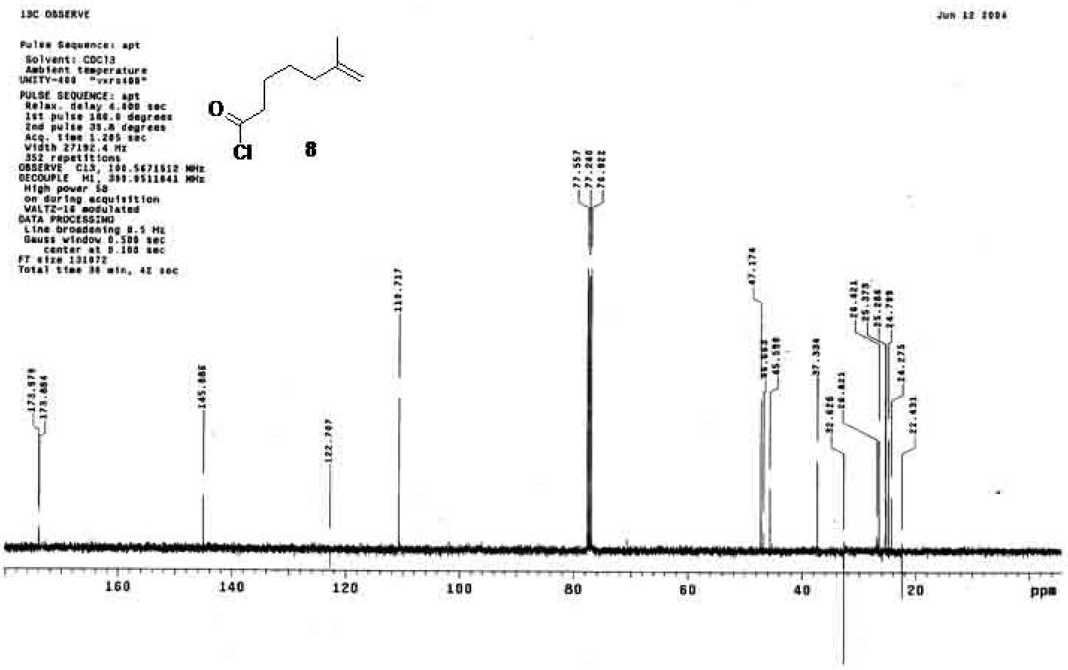
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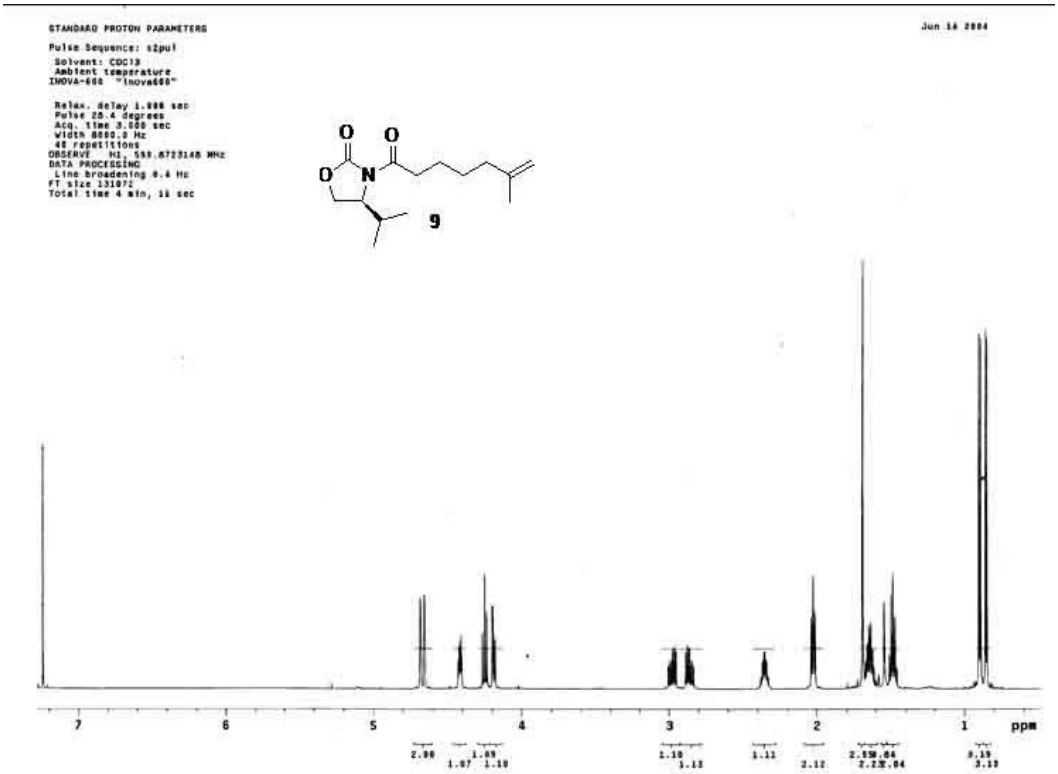
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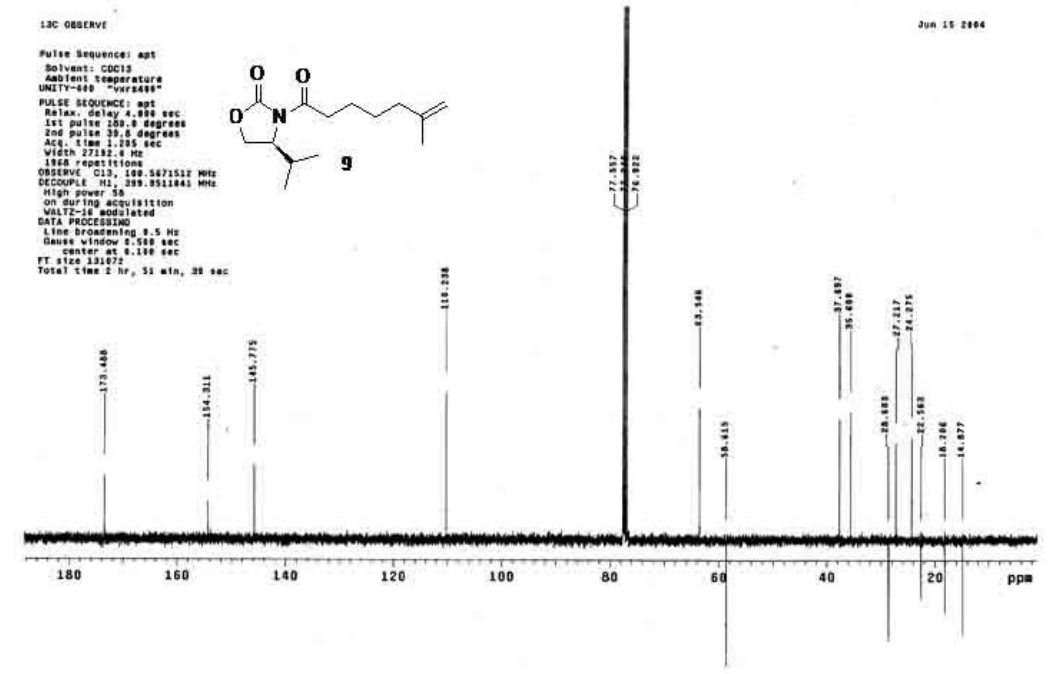
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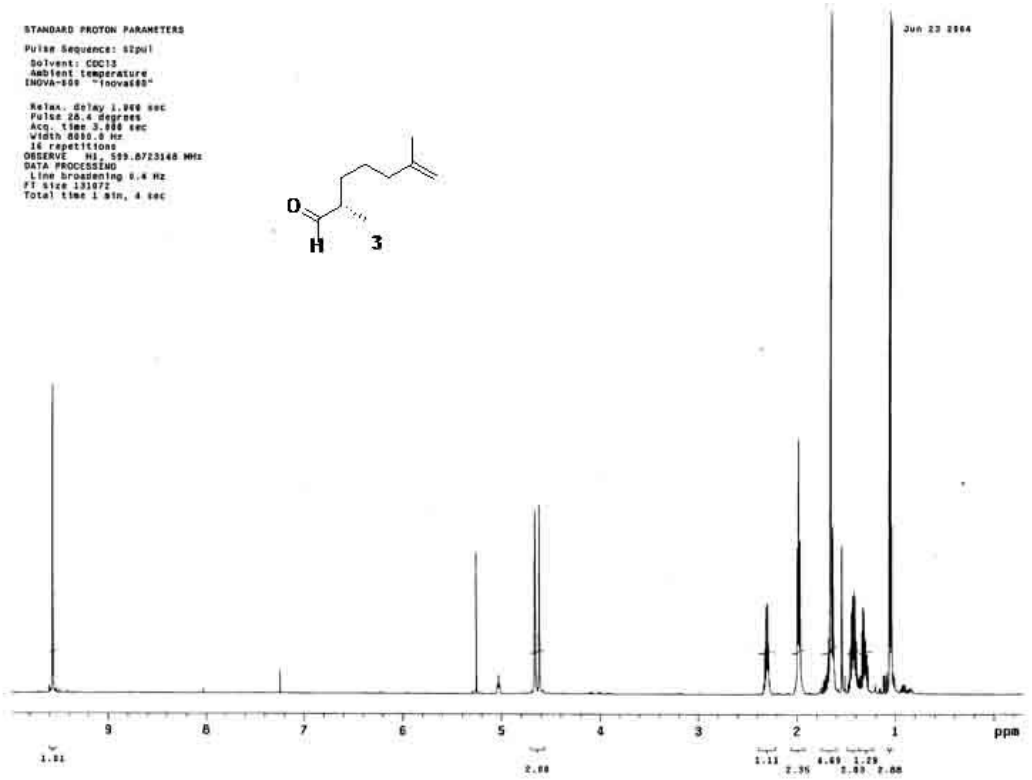
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Jun 23 2004
O
H
3
9
8
7
6
5
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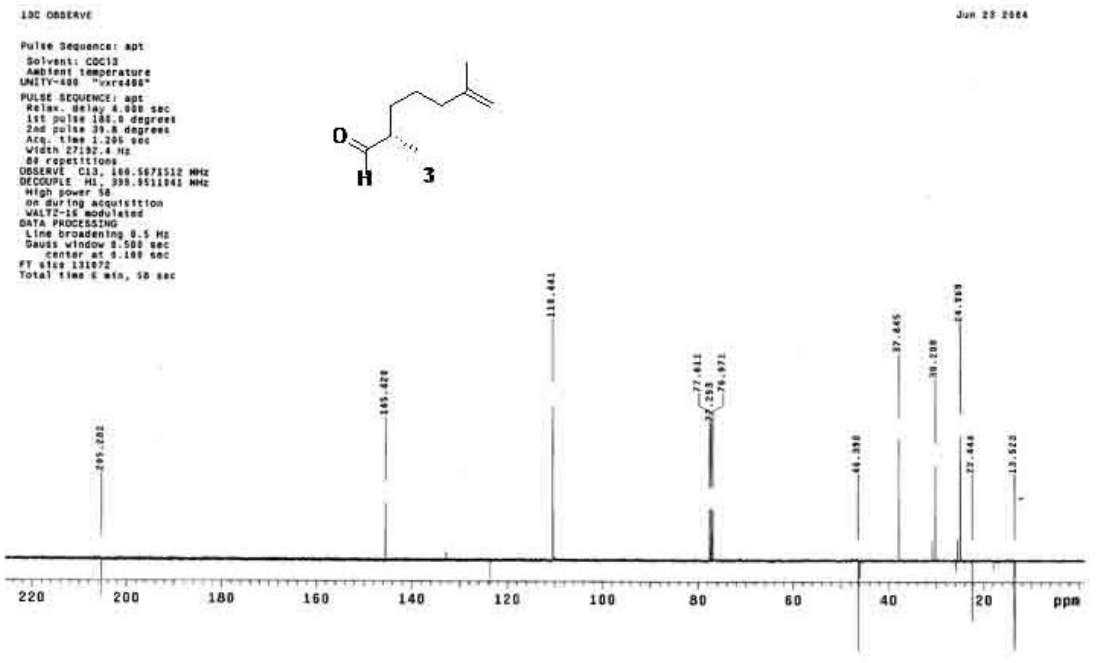
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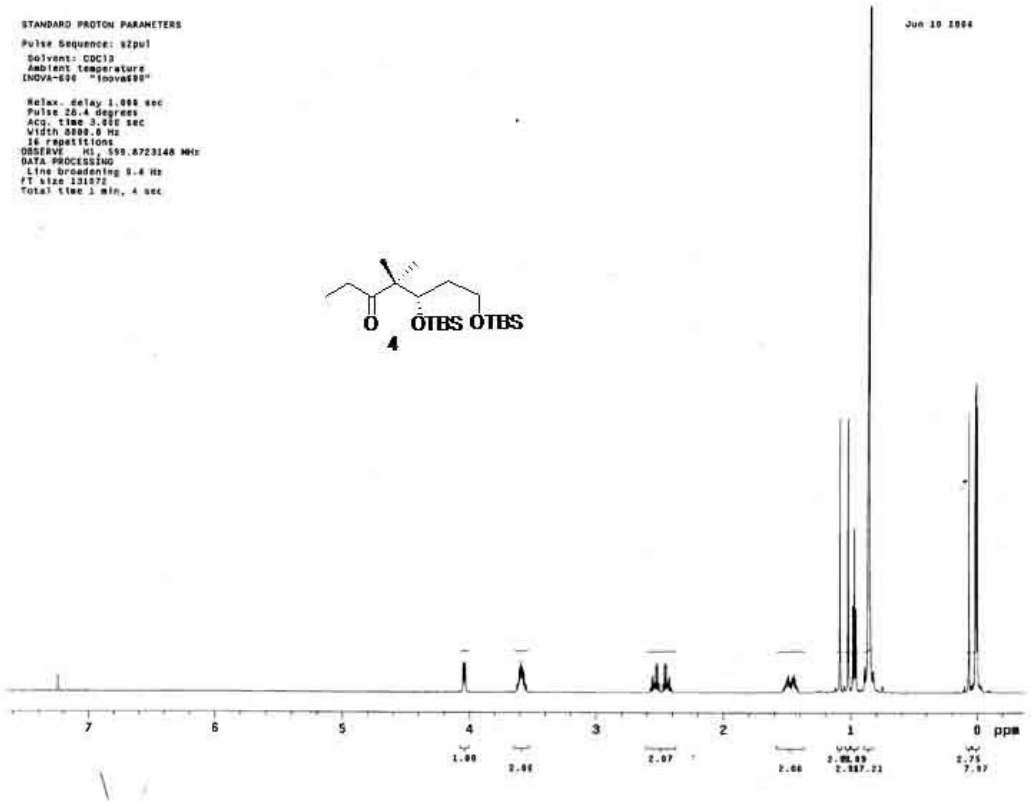
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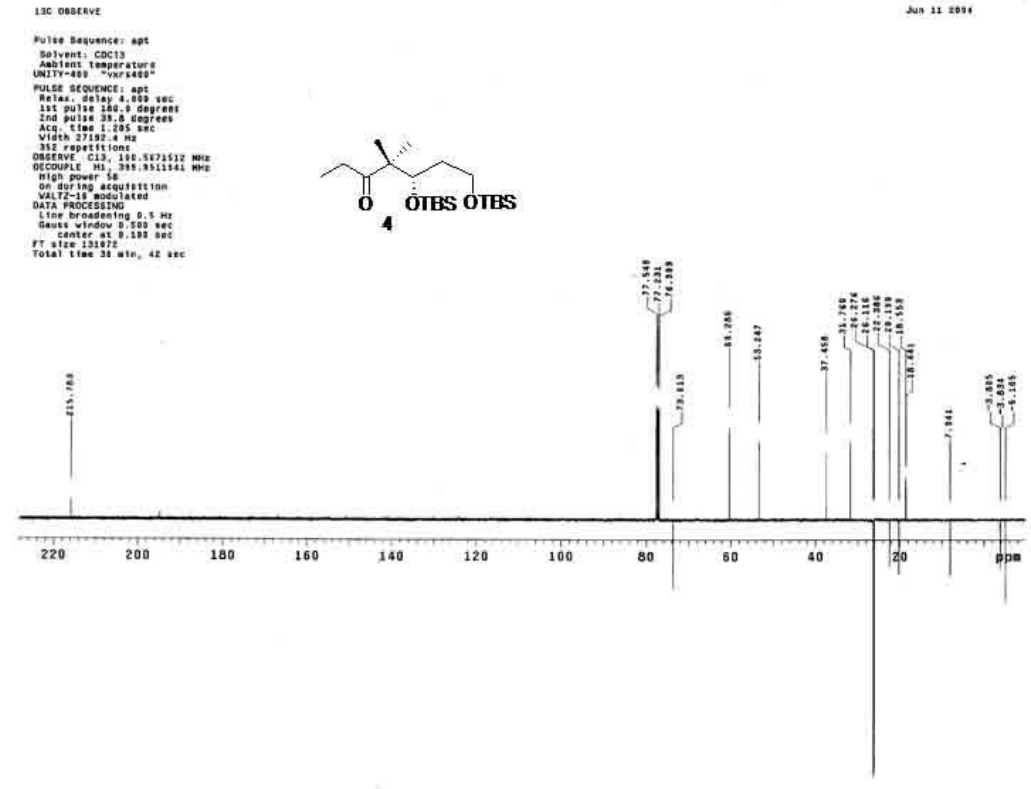
7.97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20
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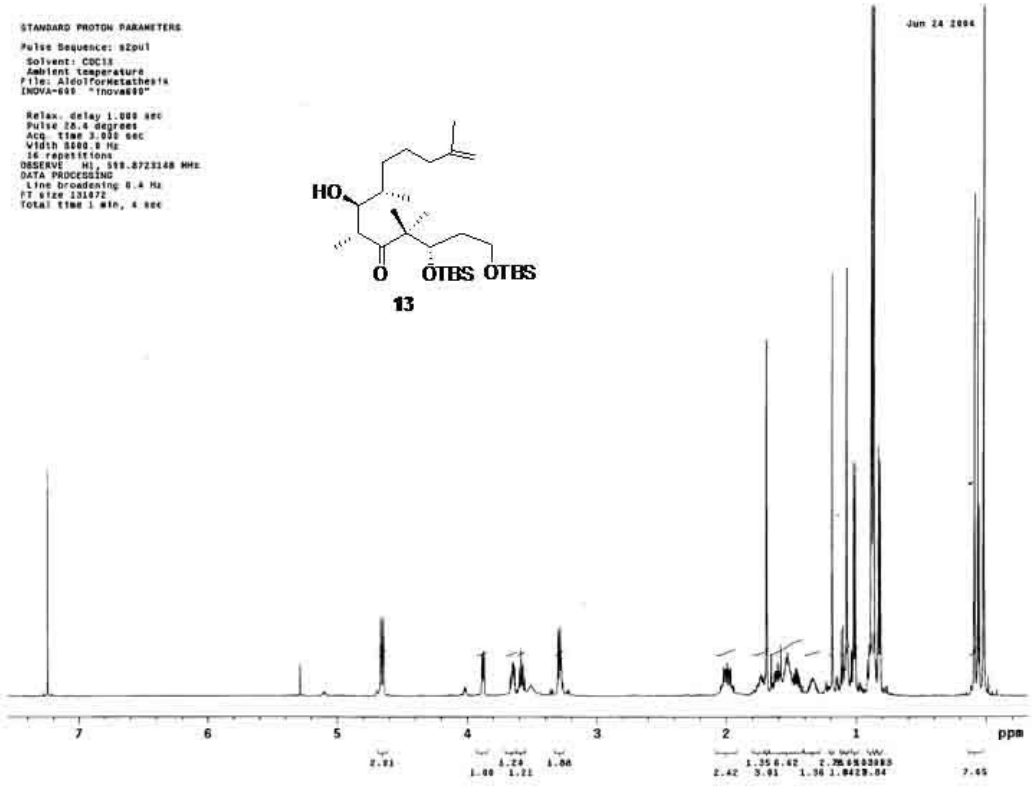
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Jun 24 2004
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7
6
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4
3
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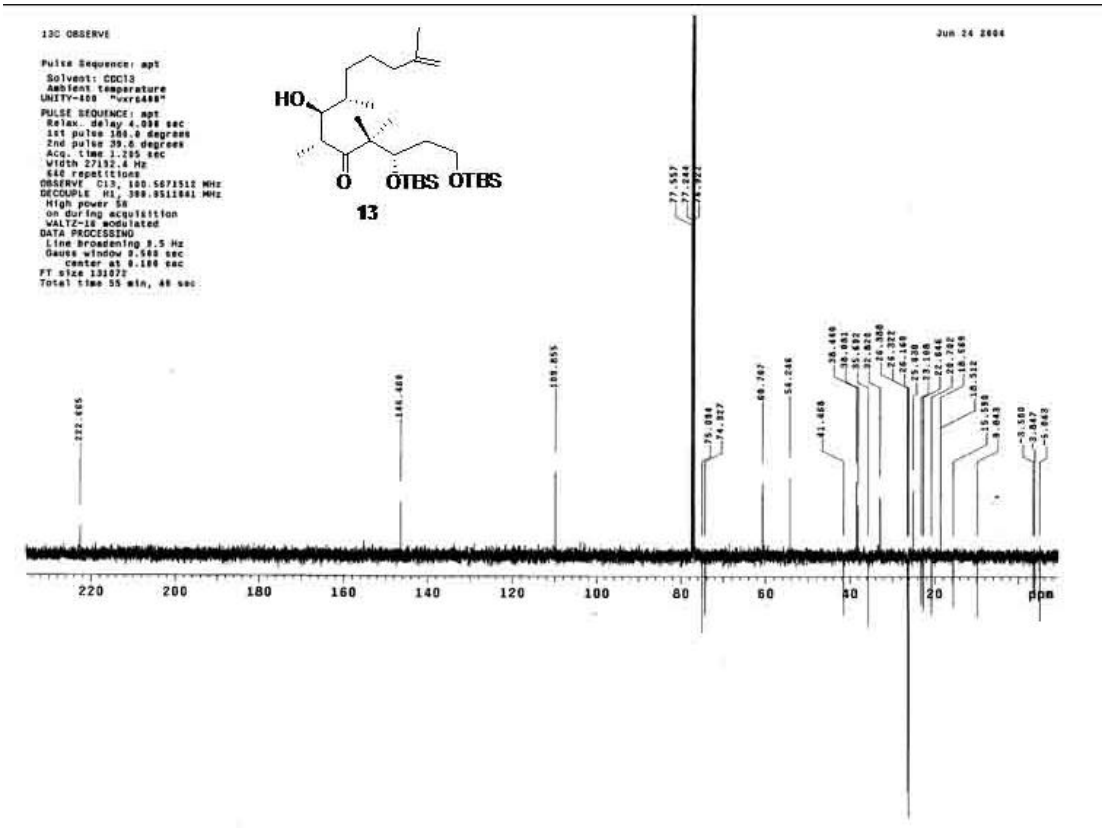
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Jun 24 2004
HO
O
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OTBS
13
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25.145
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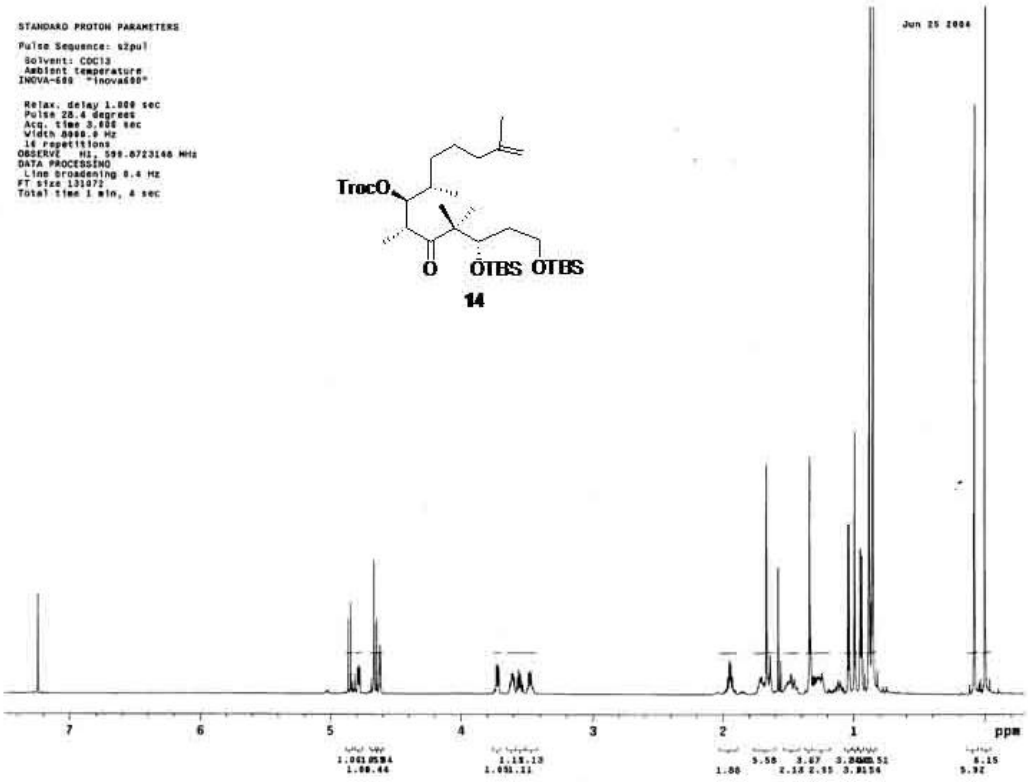
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Jun 25 2004
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O
OTBS
OTBS
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7
6
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3
2
1
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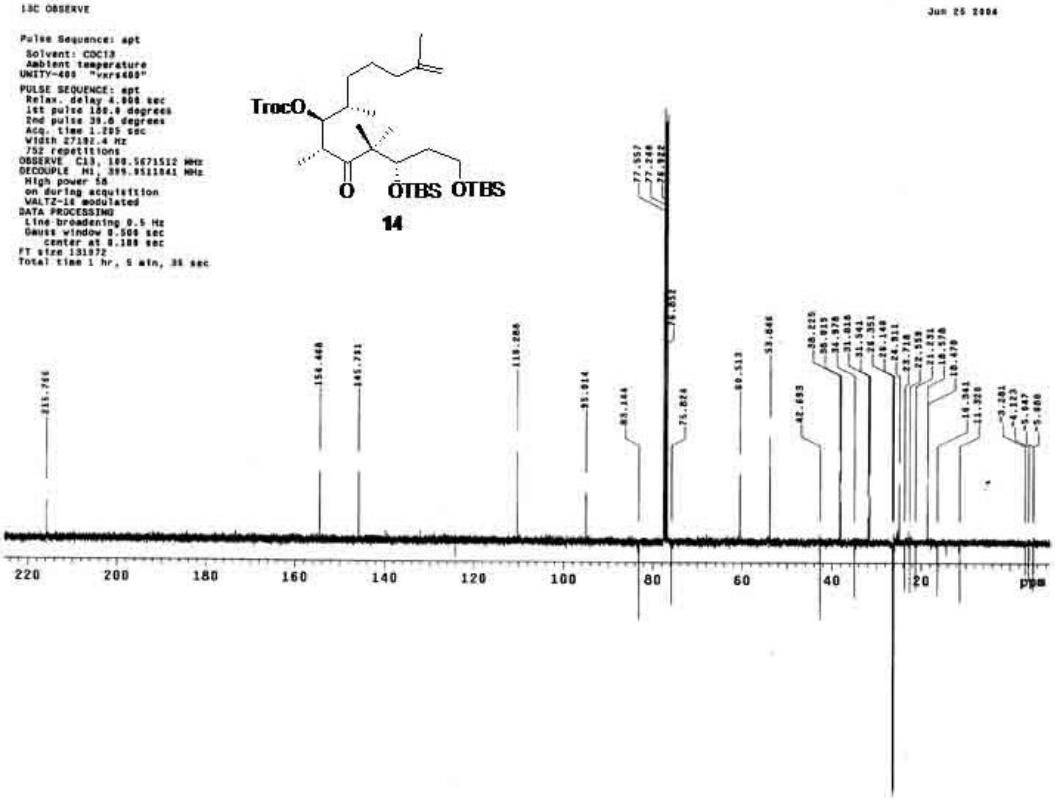
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OTBS
OTBS
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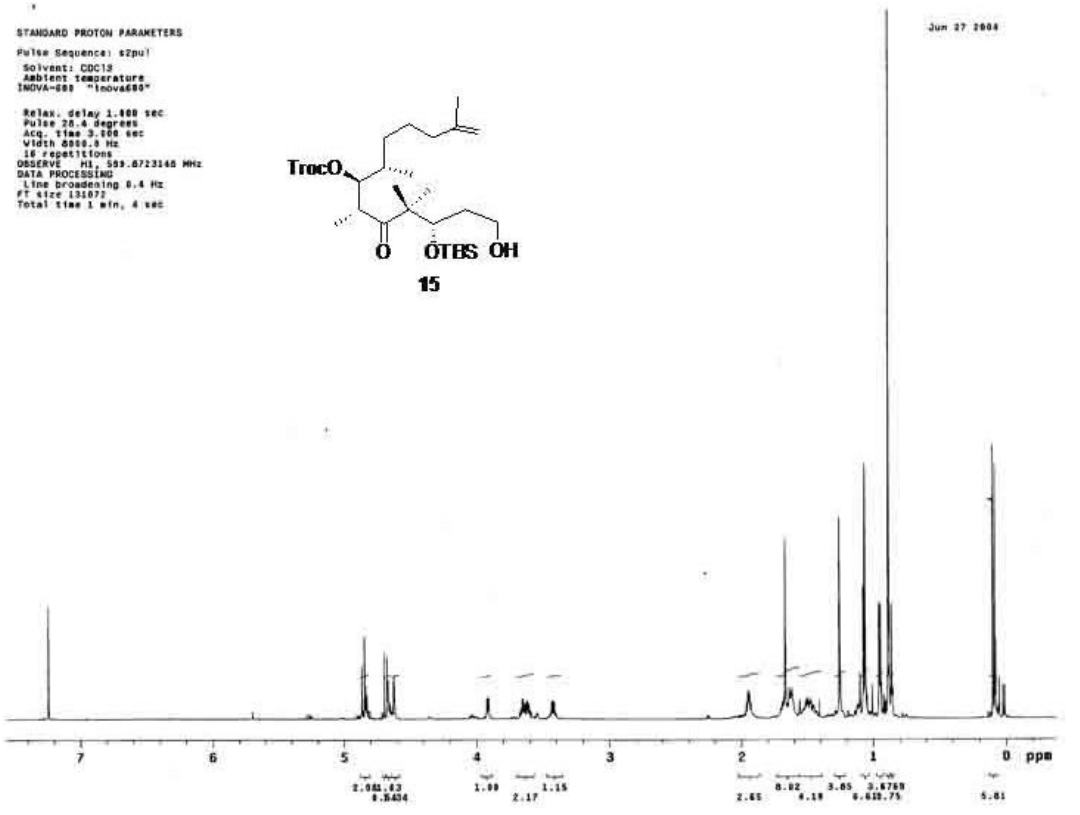
60
40
20
ppm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DATA PROCESSING
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Jun 27 2004
TrocO
O
OTBS
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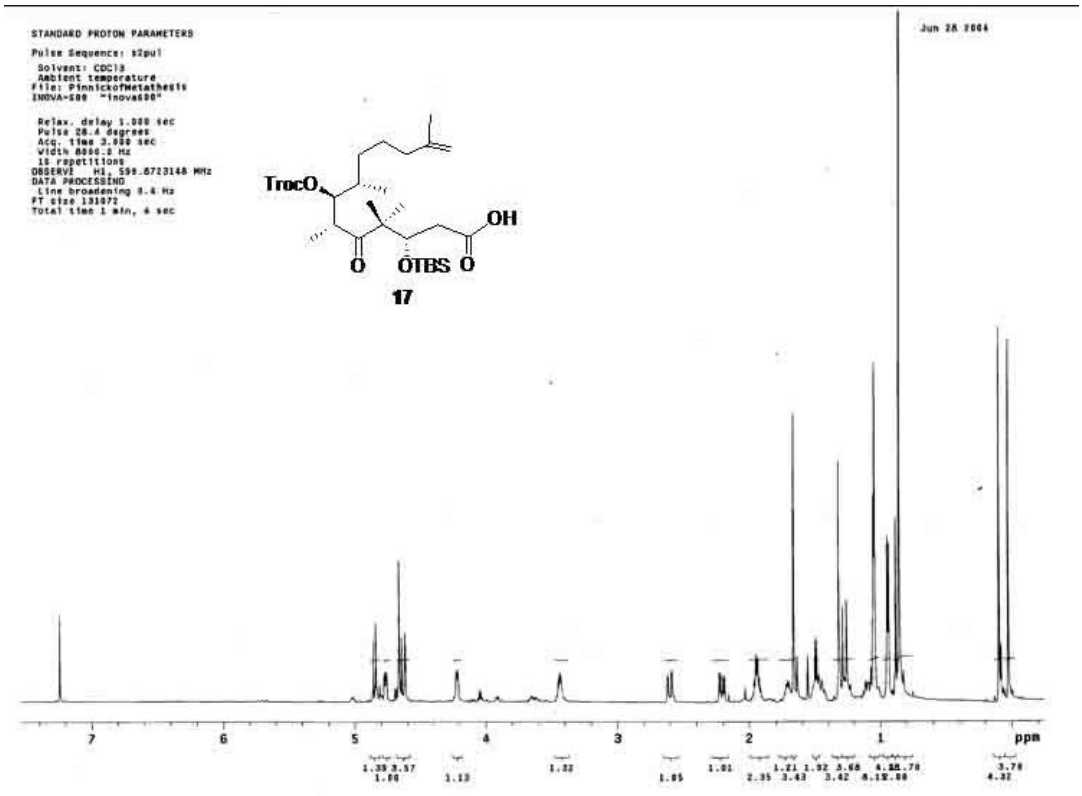
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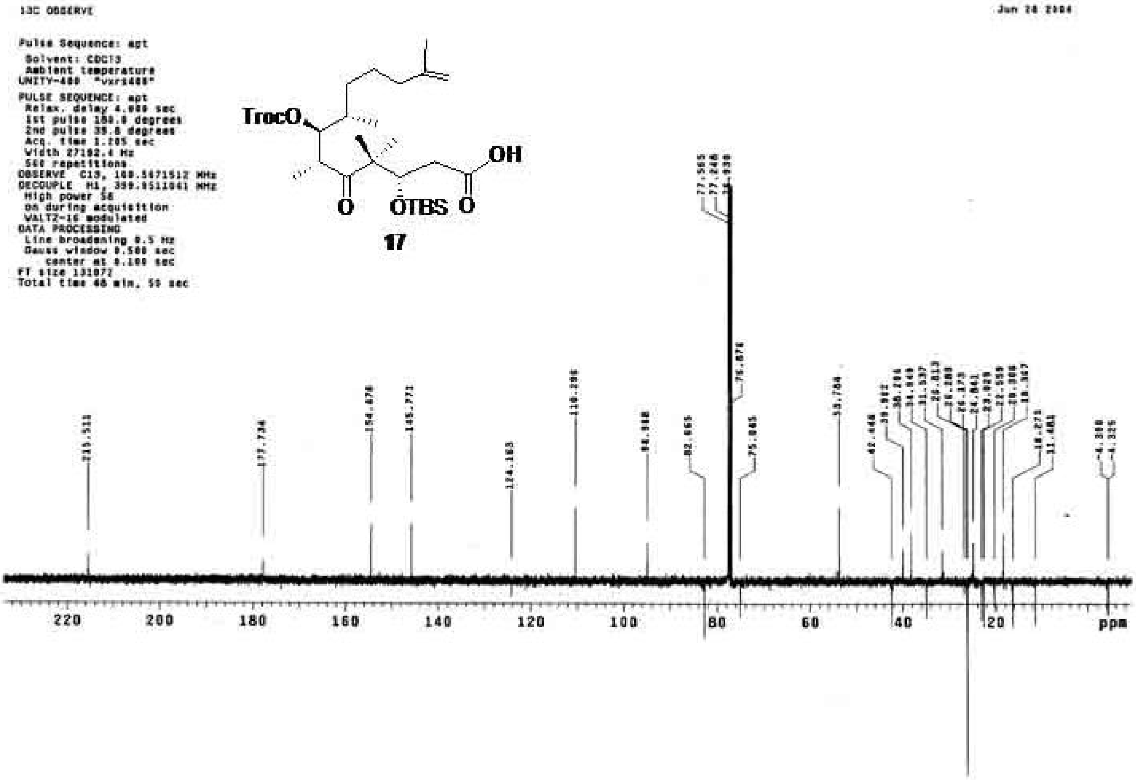
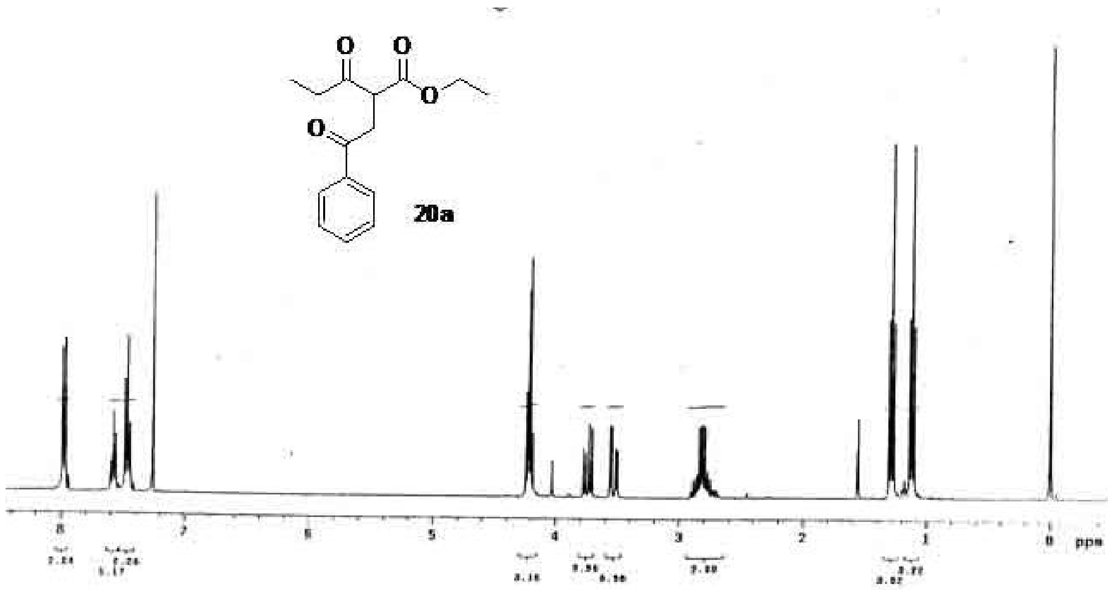
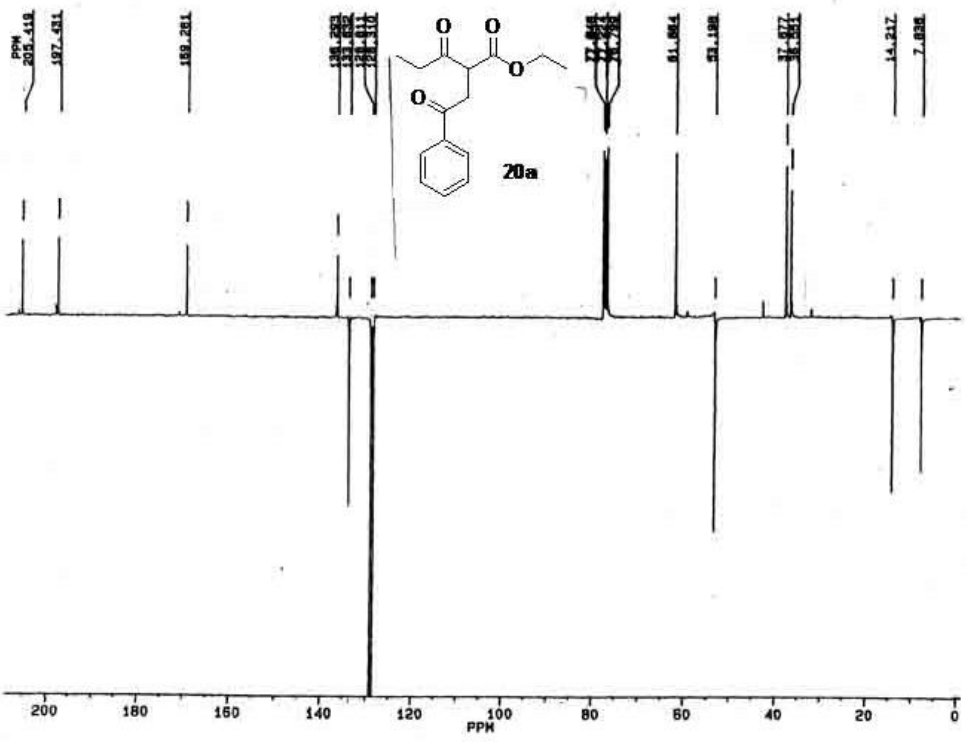
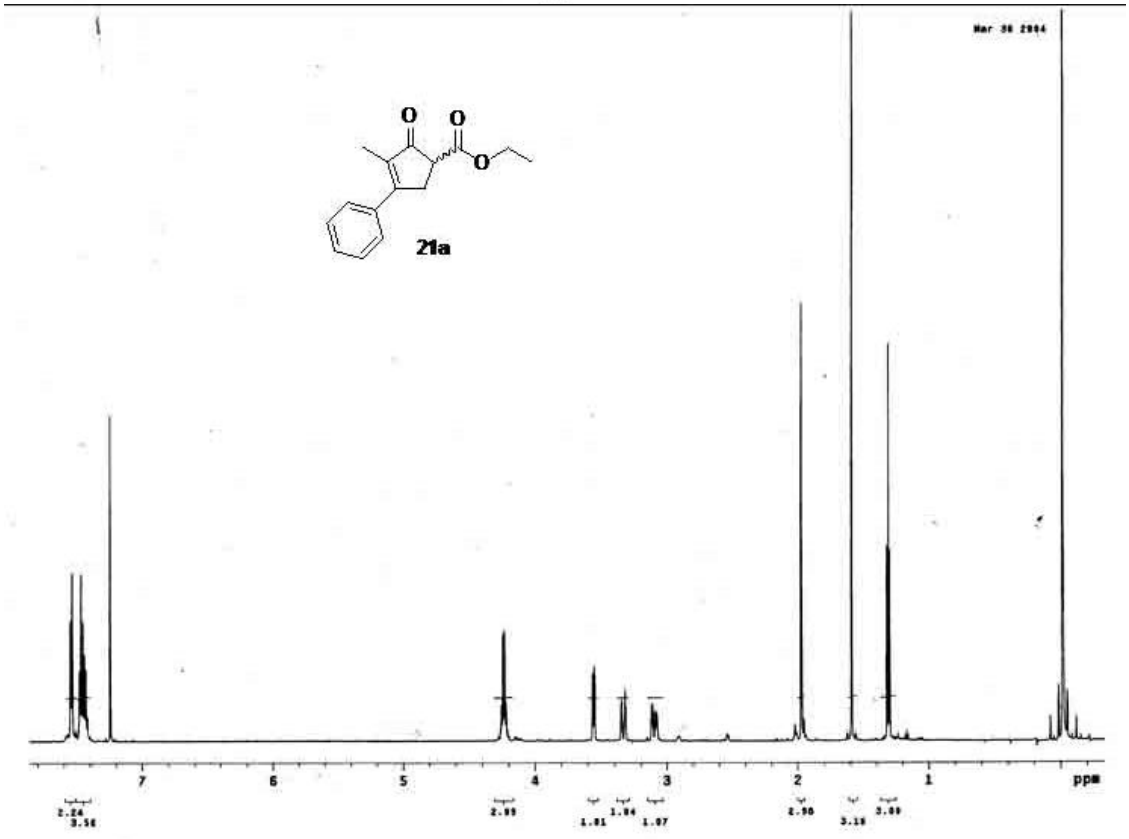
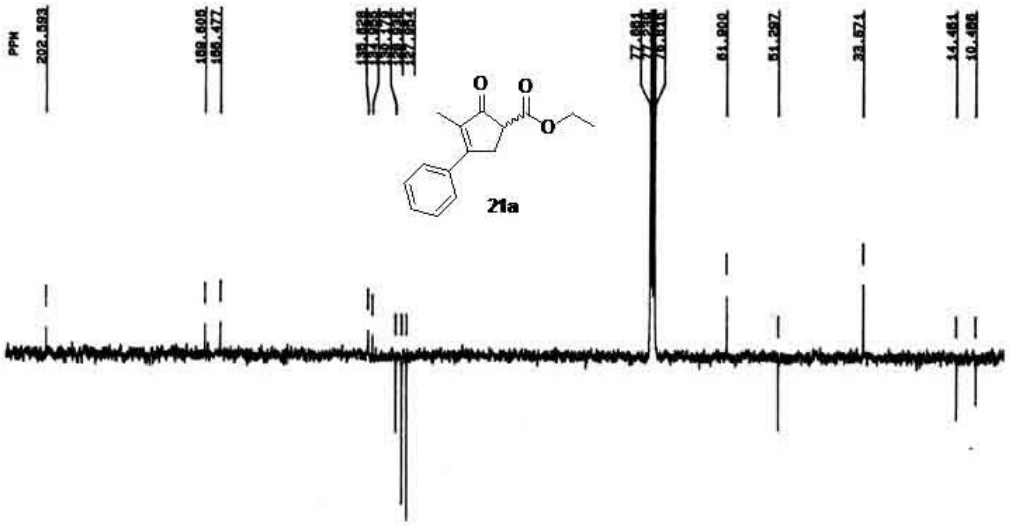
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 599.8723148 MHz
DATA PROCESSING
Line broadening 0.4 Hz
FT size 131072
Total time 1 min, 4 sec
Jun 28 2004
TrocO
OH
O
OTBS
O
17
7
6
5
4
3
2
1
ppm

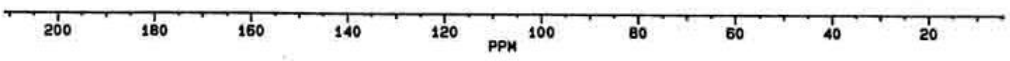

13C OBSERVE
Pulse Sequence: apt
Solvent: CDCl3
Ambient temperature
PULSE SEQUENCE: apt
Width 27192.4 Hz
High power 56
on during acquisition
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
TrocO
OH
OTBS
17
220
200
180
160
140
120
100
80
60
40
20
ppm

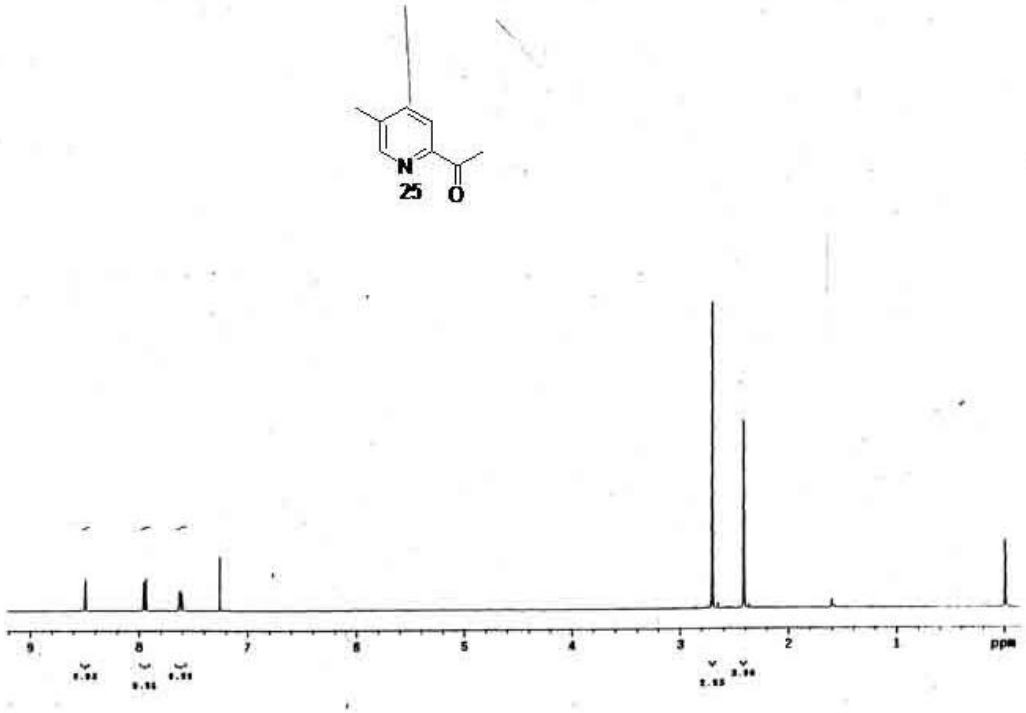

20a
8
7
6
5
4
3
2
1
0
ppm

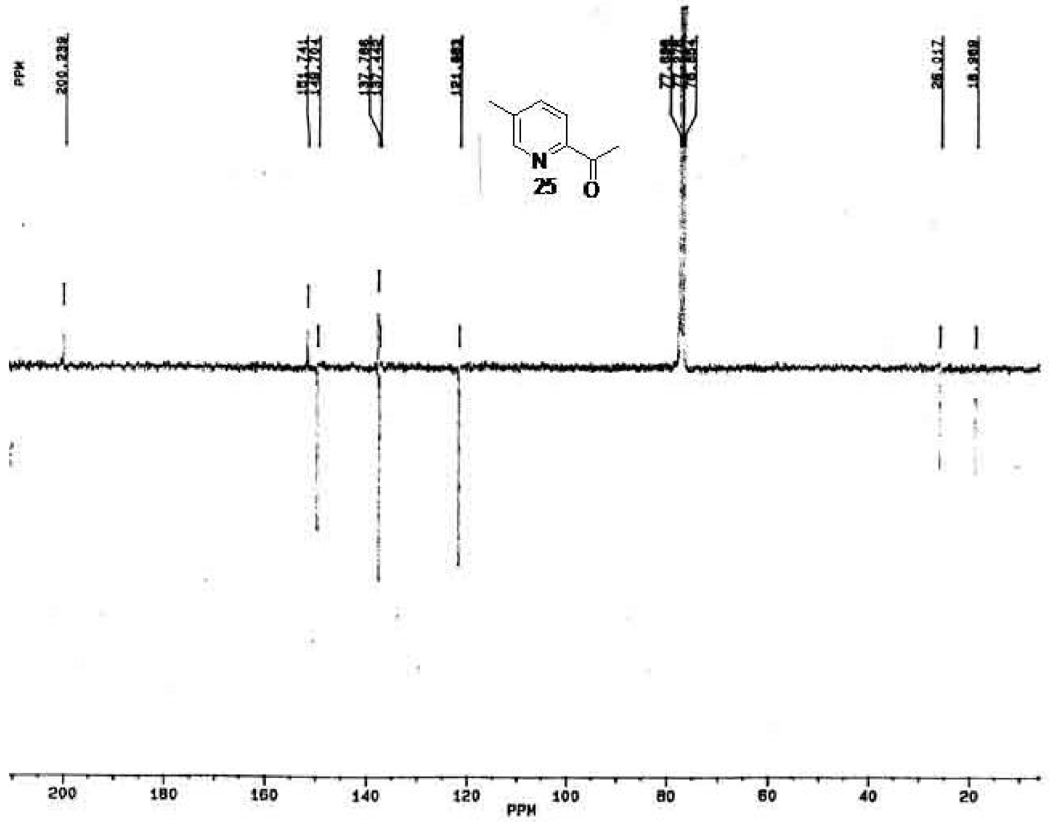

20a
200
180
160
140
120
100
80
60
40
20
0
PPM

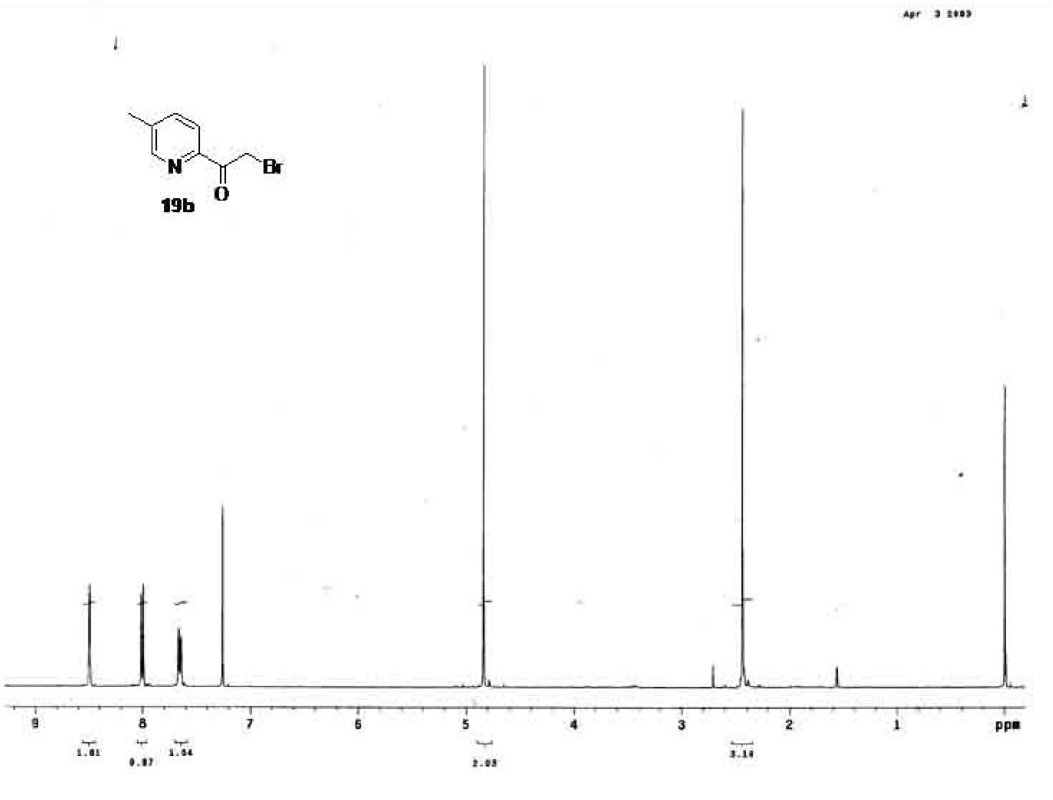

21a
7
6
5
4
3
2
1
ppm

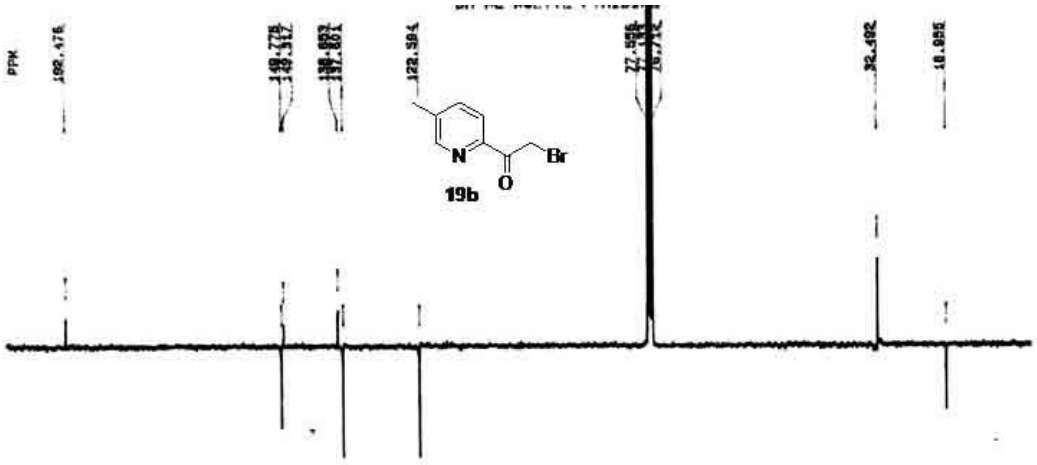

PPM
202.593
169.605
166.477
77.681
61.800
51.287
33.671
14.481
10.488
21a

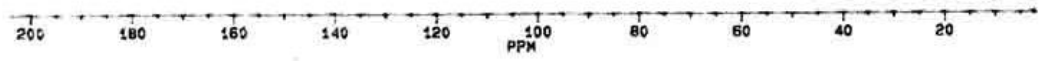

200
180
160
140
120
PPM
100
80
60
40
20

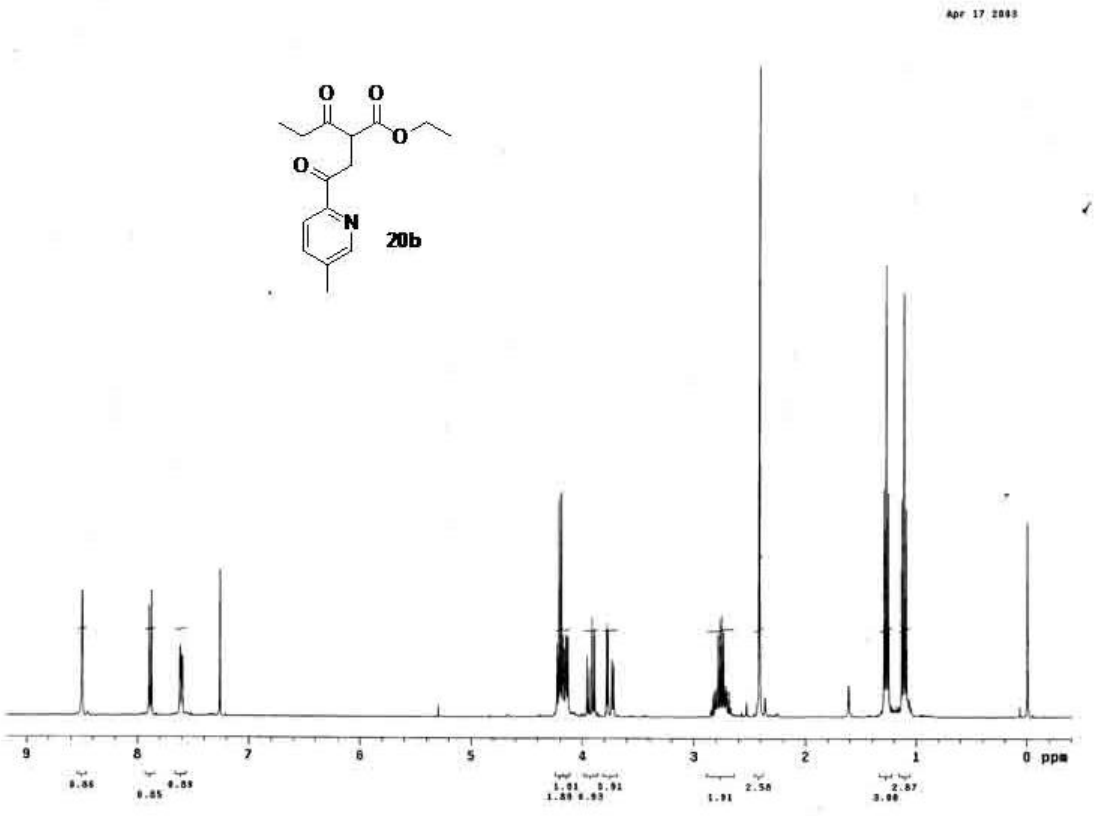

N
25
O
9
8
7
6
5
4
3
2
1
ppm

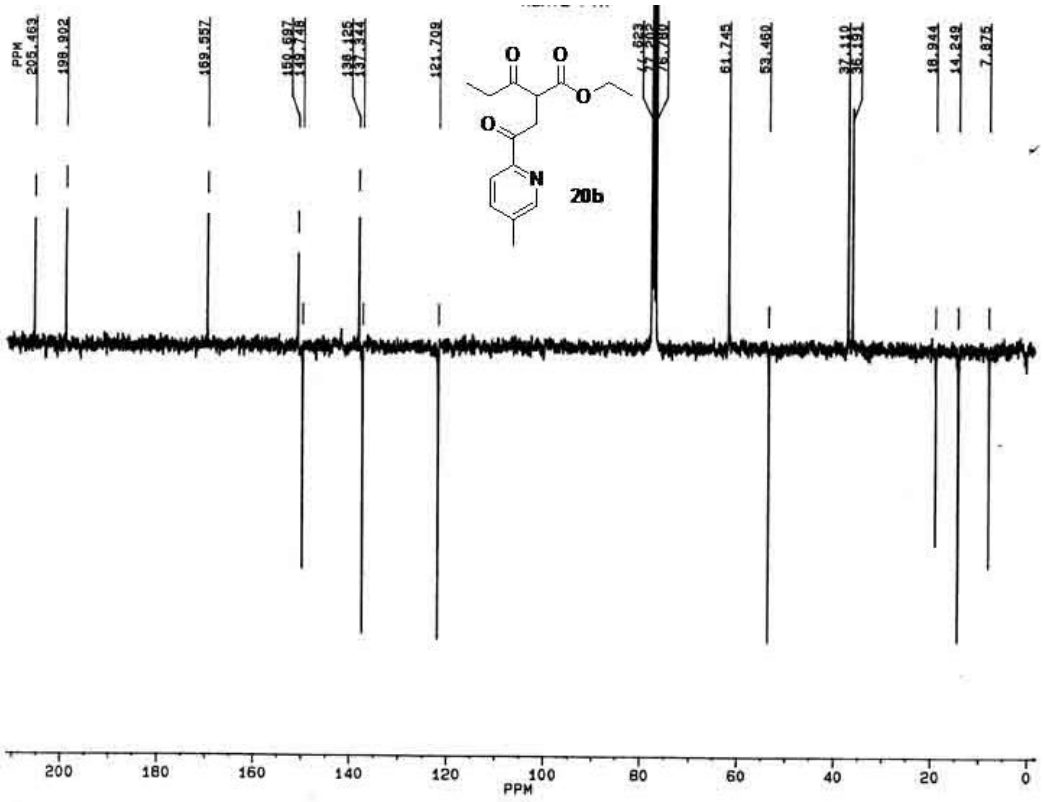

PPM
N
25
O
200
180
160
140
120
PPM
100
80
60
40
20

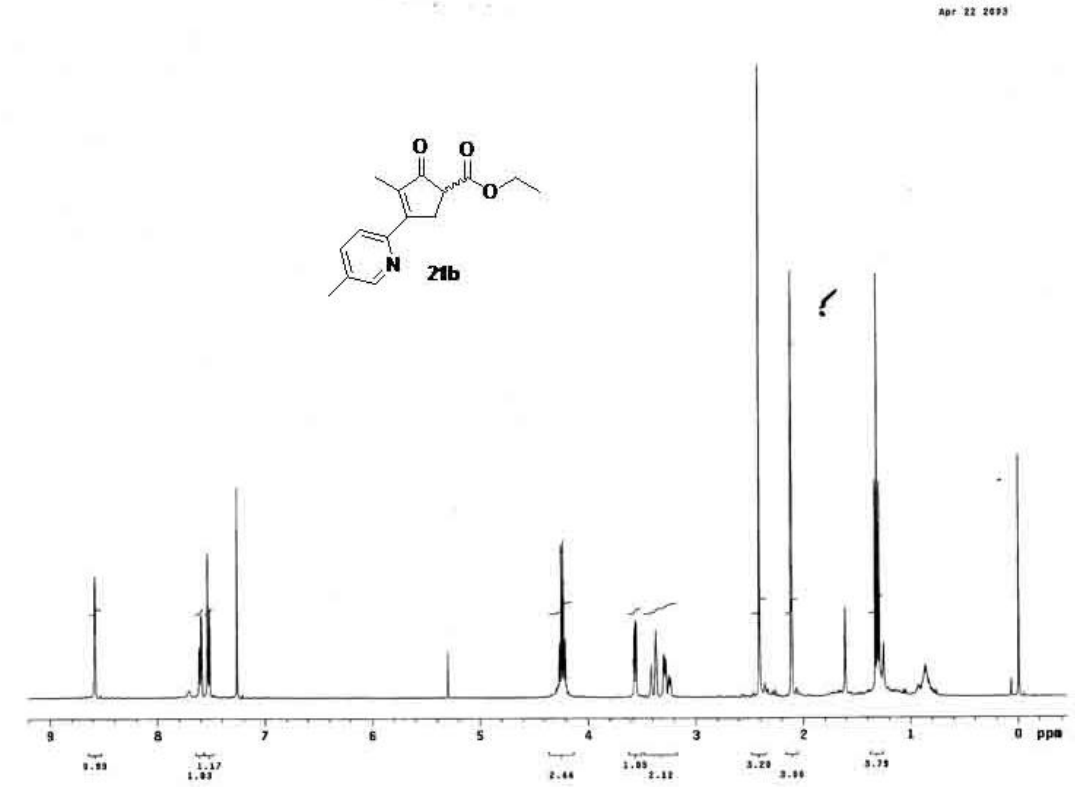

N
O
Br
19b
9
8
7
6
5
4
3
2
1
ppm

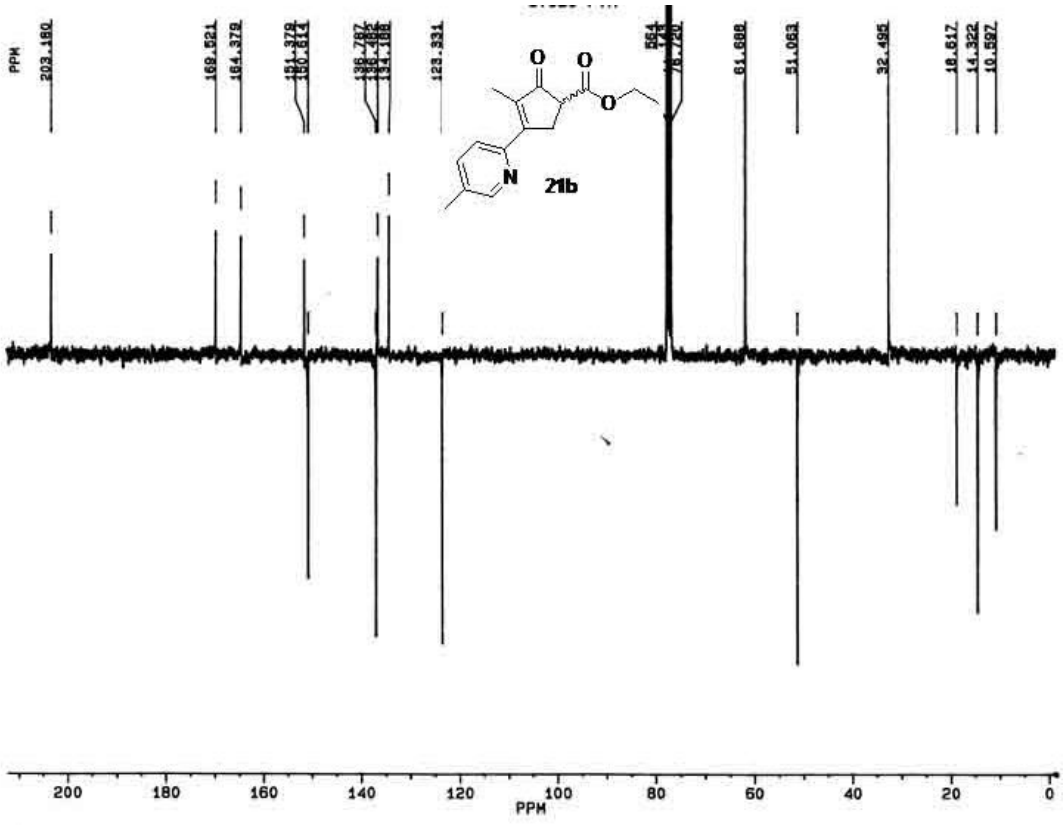

PPM
N
Br
O
19b

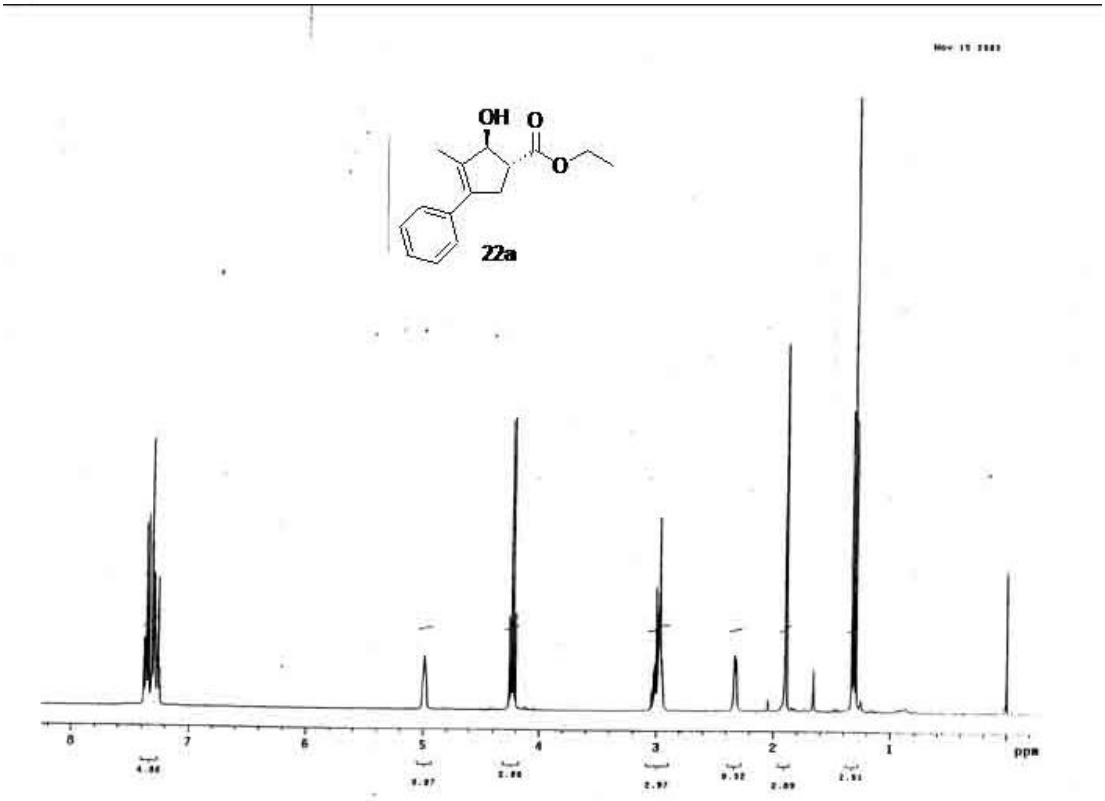

200
180
160
140
120
100
80
60
40
20
PPM

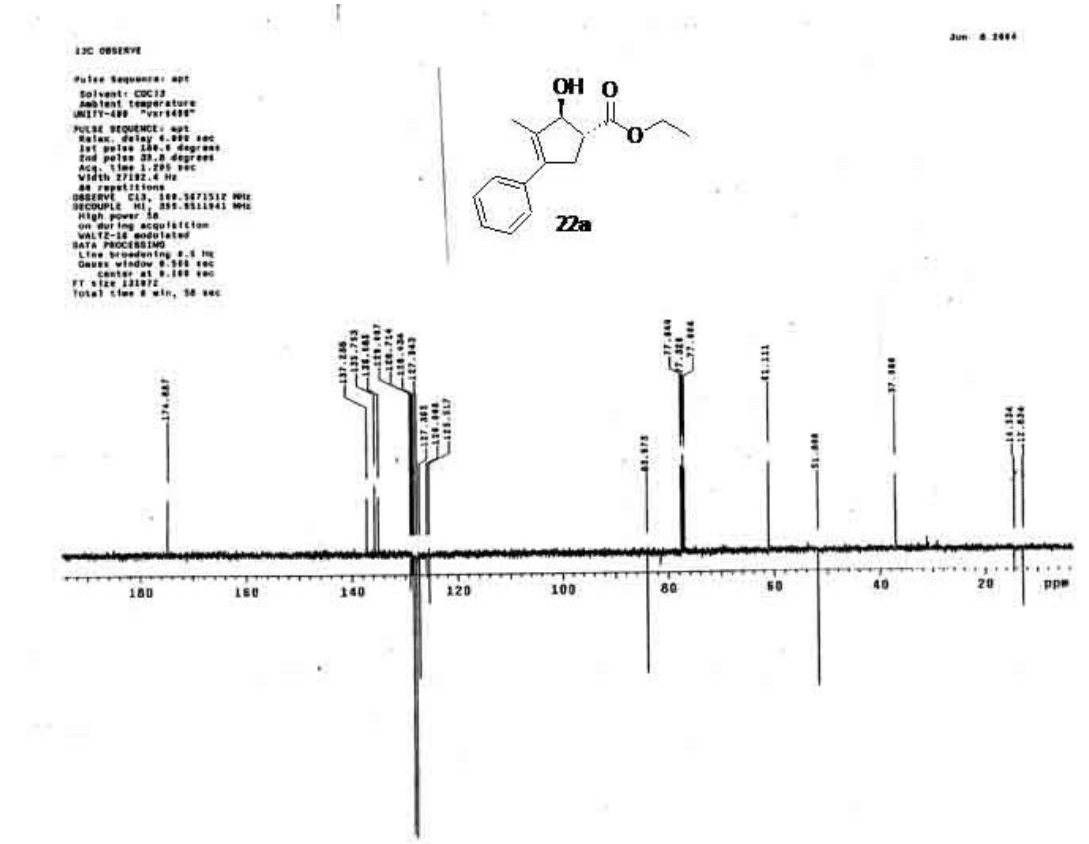

Apr 17 2003
O
O
O
O
N
20b
9
8
7
6
5
4
3
2
1
0 ppm

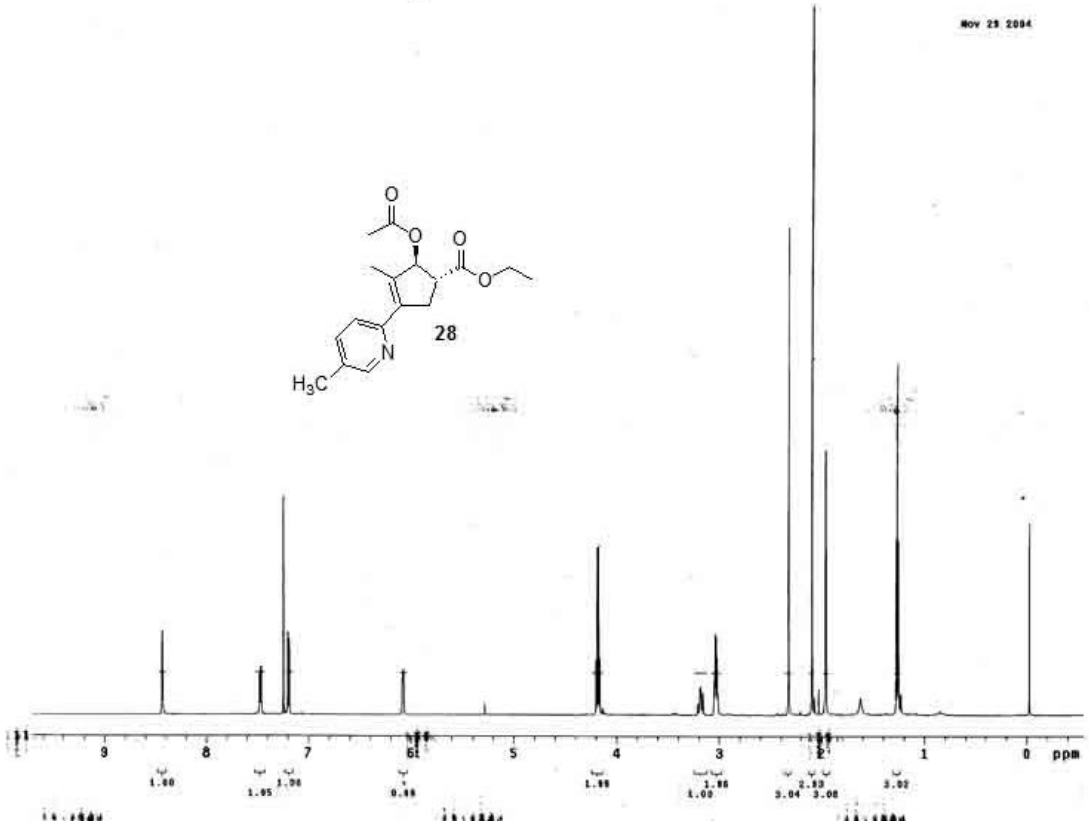

PPM
205.463
198.902
169.567
150.697
149.718
138.125
137.414
121.709
77.623
77.305
76.780
61.745
53.460
37.110
36.191
18.944
14.249
7.875
20b
200
180
160
140
120
100
80
60
40
20
0
PPM

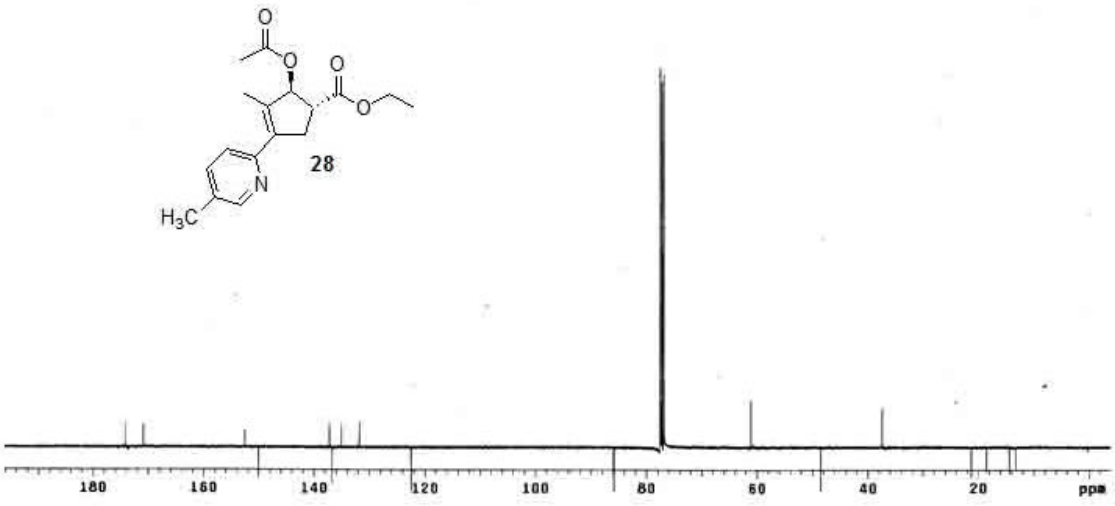

Apr 22 2003
21b
9
8
7
6
5
4
3
2
1
0 ppm
0.93
1.17
1.03
2.44
1.05
2.12
3.20
3.00
3.79

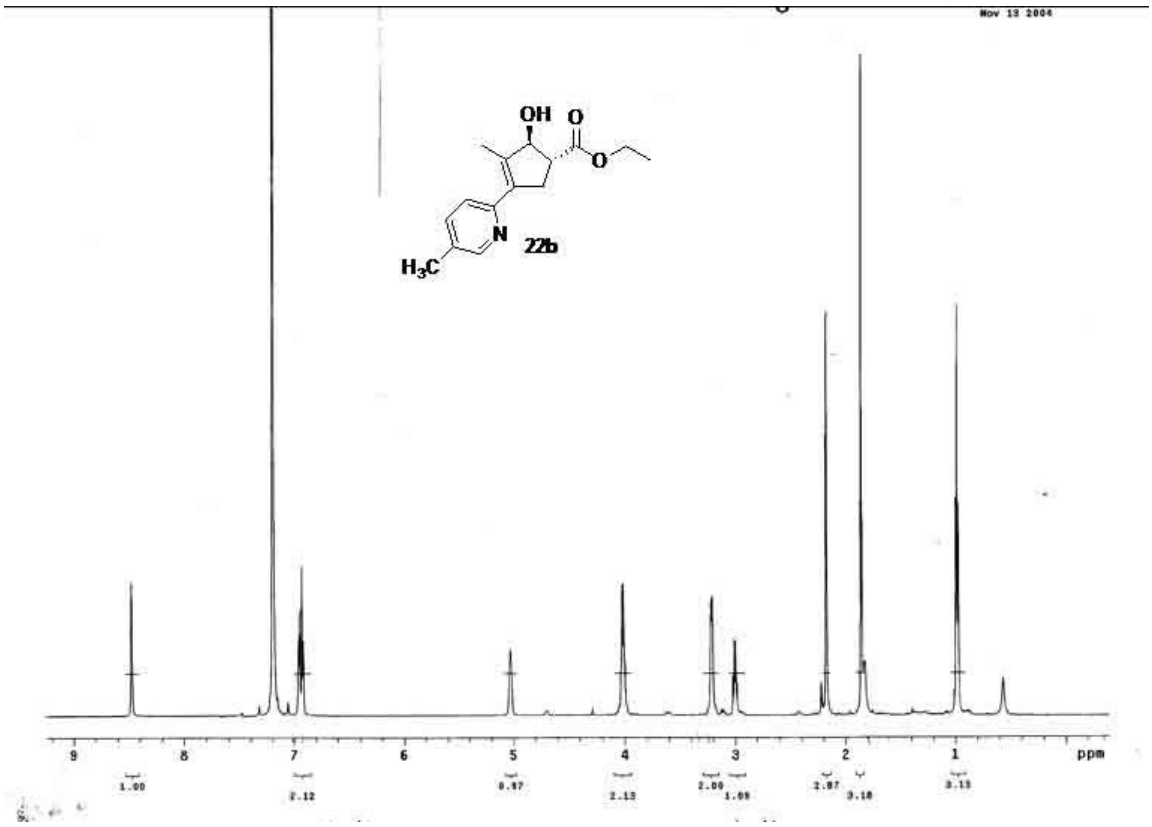

PPM
203.180
169.621
164.372
151.378
150.811
136.787
123.331
61.688
51.063
32.495
18.617
14.322
10.592
O
O
O
N
21b
200
180
160
140
120
100
80
60
40
20
0
PPM

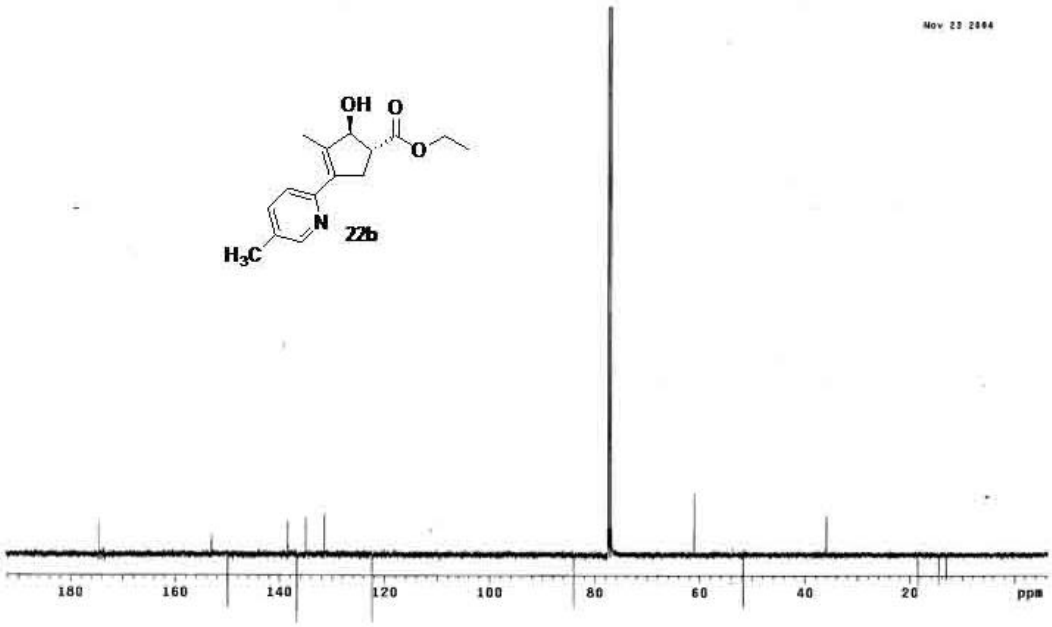

OH
O
O
22a
8
7
6
5
4
3
2
1
ppm

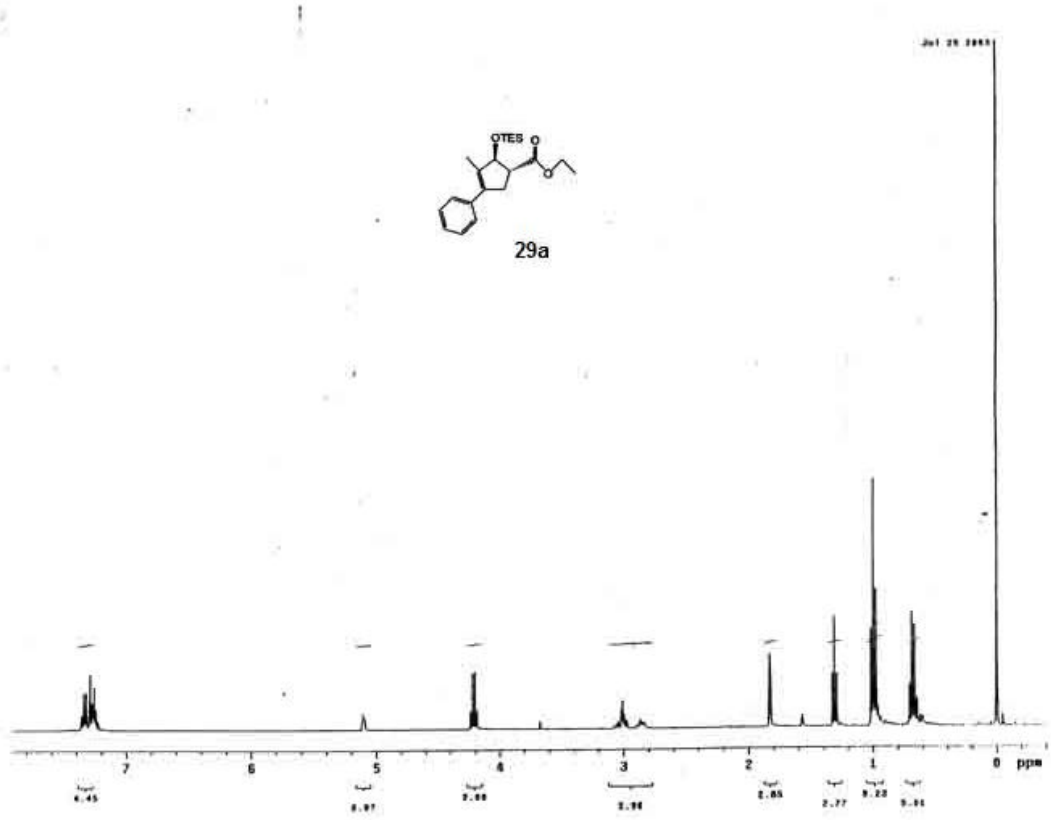

OH
O
O
22a
ppm

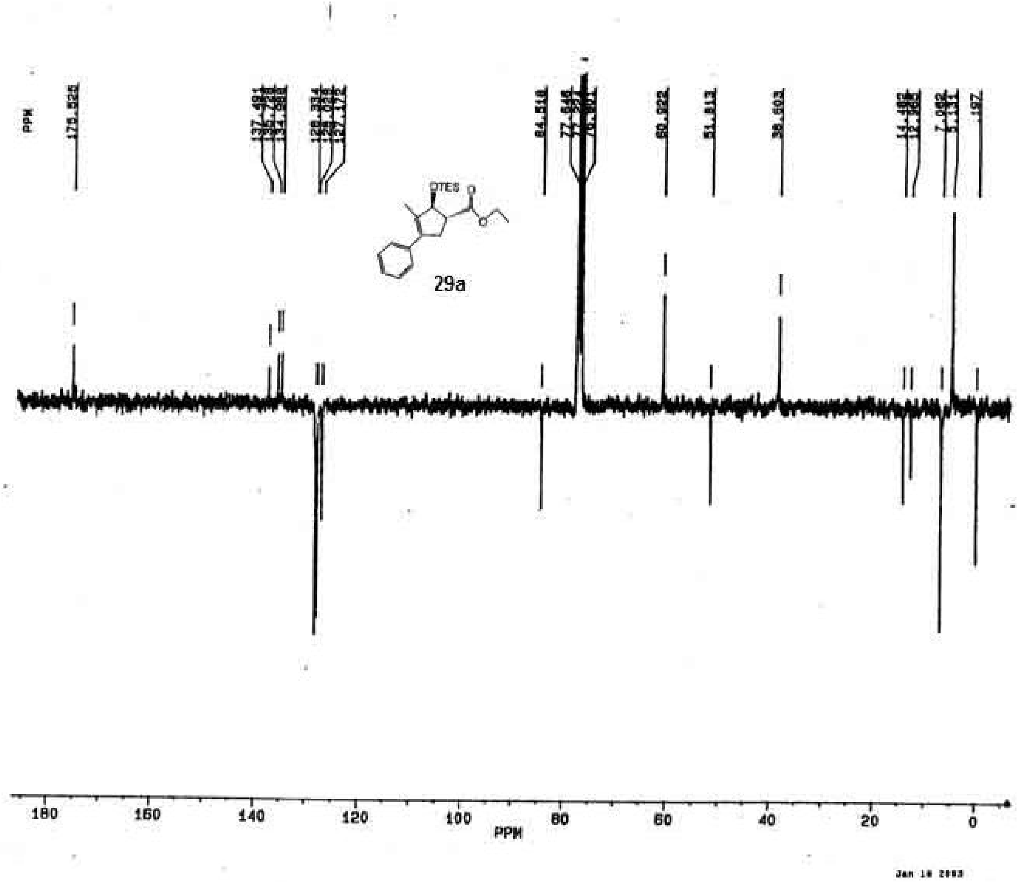

O
O
O
O
N
H3C
28
ppm

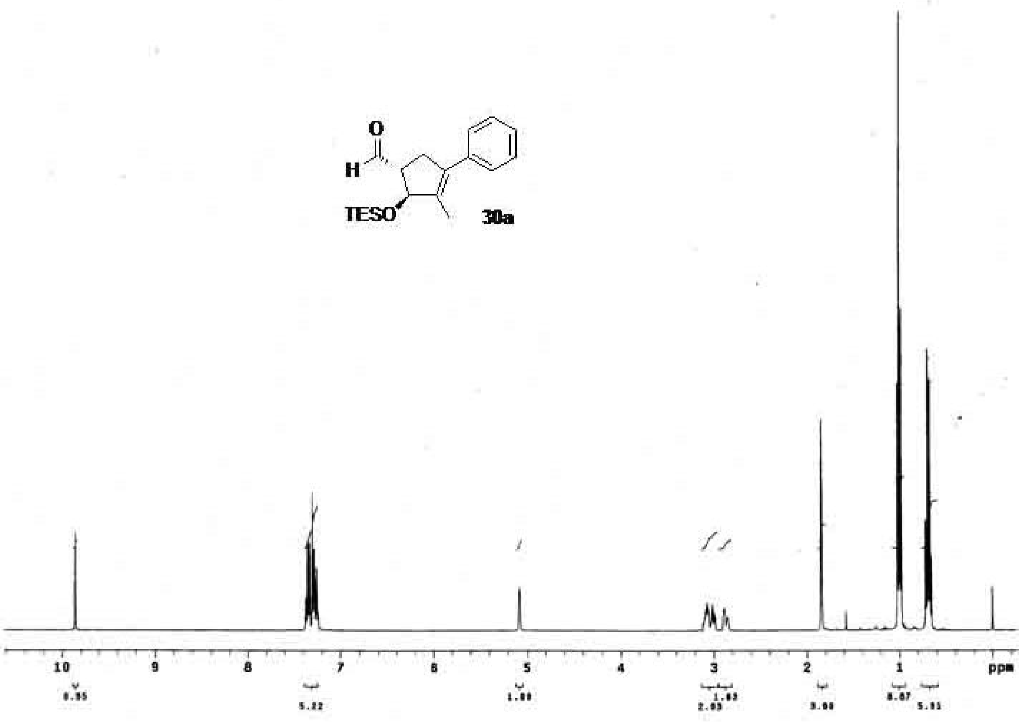

O
O
O
O
N
H3C
28
180
160
140
120
100
80
60
40
20
ppm

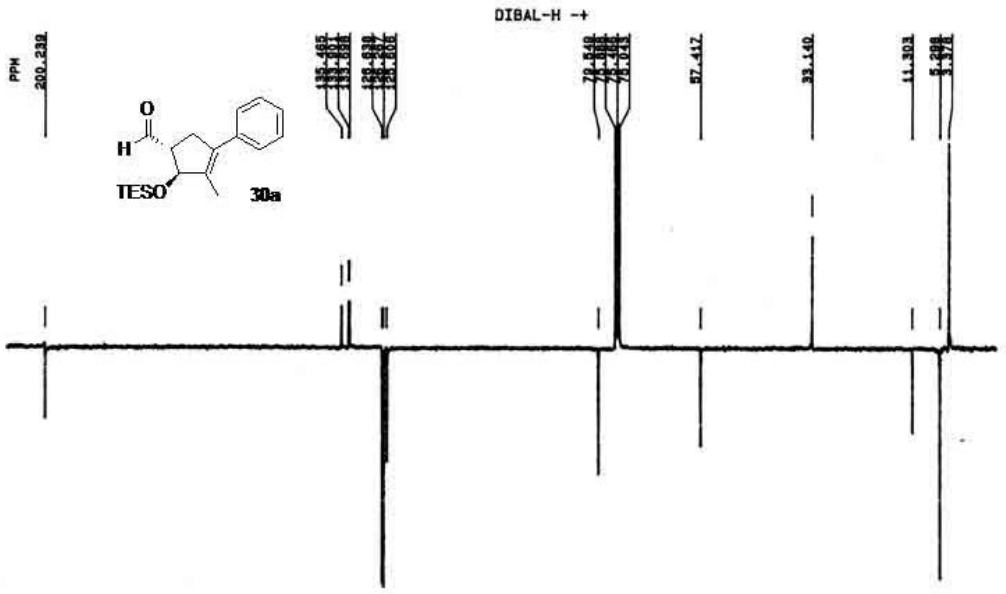

Nov 13 2004
OH
O
O
N
H3C
22b
9
8
7
6
5
4
3
2
1
ppm
1.00
2.12
0.97
2.13
2.09
1.09
2.87
3.18
3.15

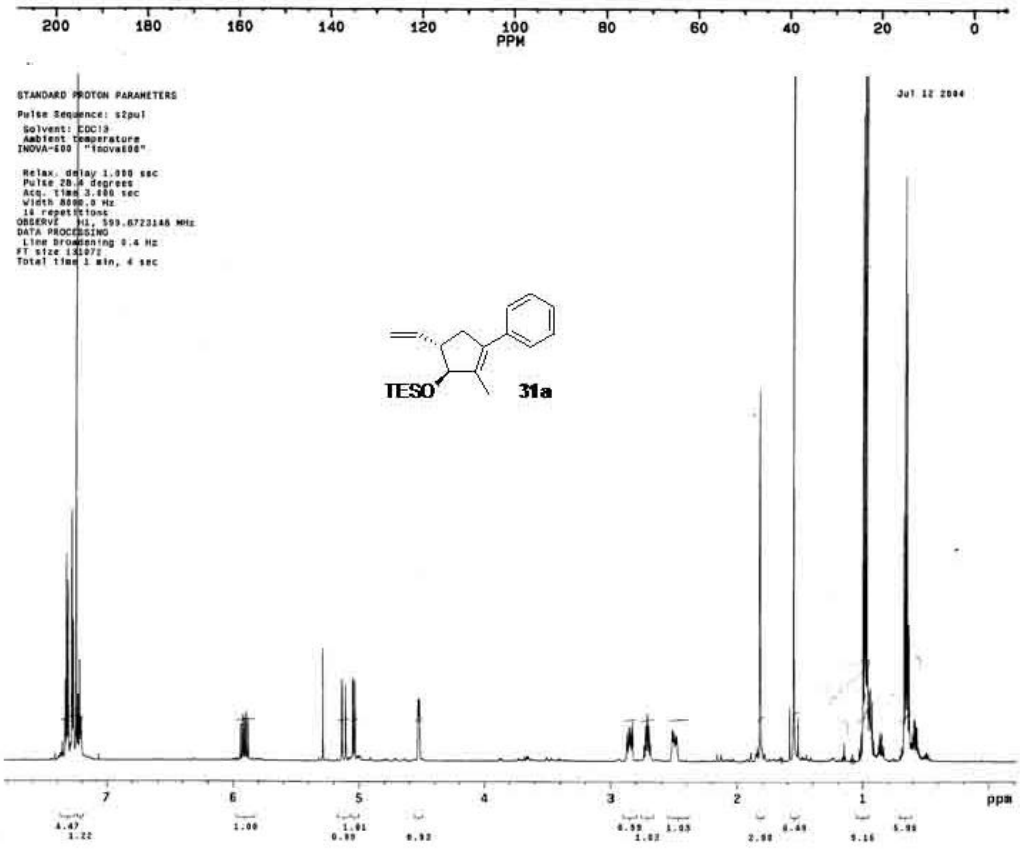

OH
O
O
N
H_3C
22b
180
160
140
120
100
80
60
40
20
ppm

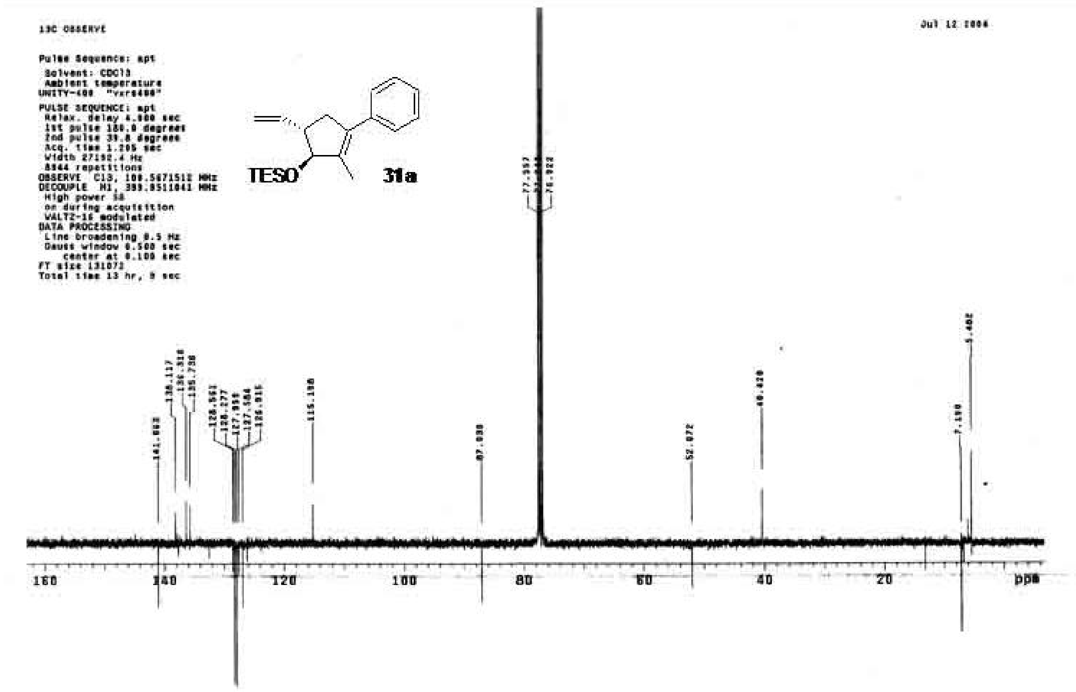

OTES
O
O
29a
7
6
5
4
3
2
1
0
ppm

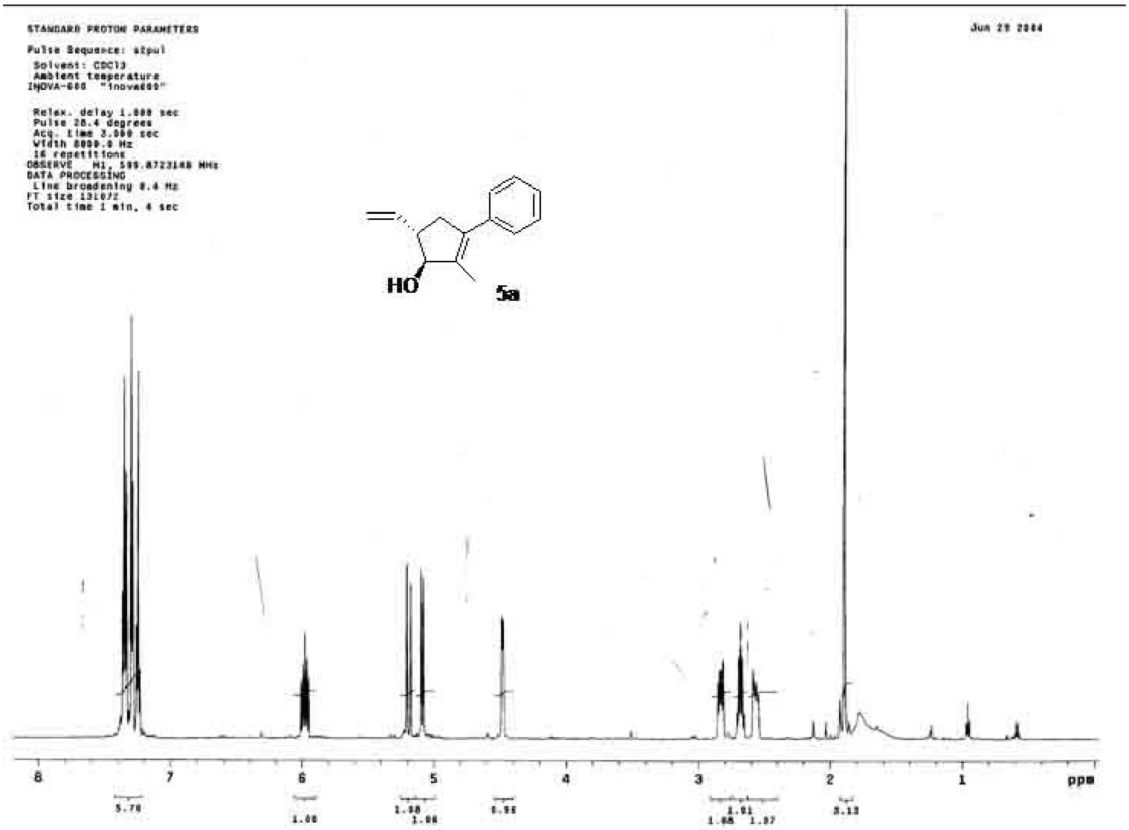

PPM
175.526
84.518
60.922
51.813
38.603
.197
OTES
29a
180 160 140 120 100 PPM 80 60 40 20 0

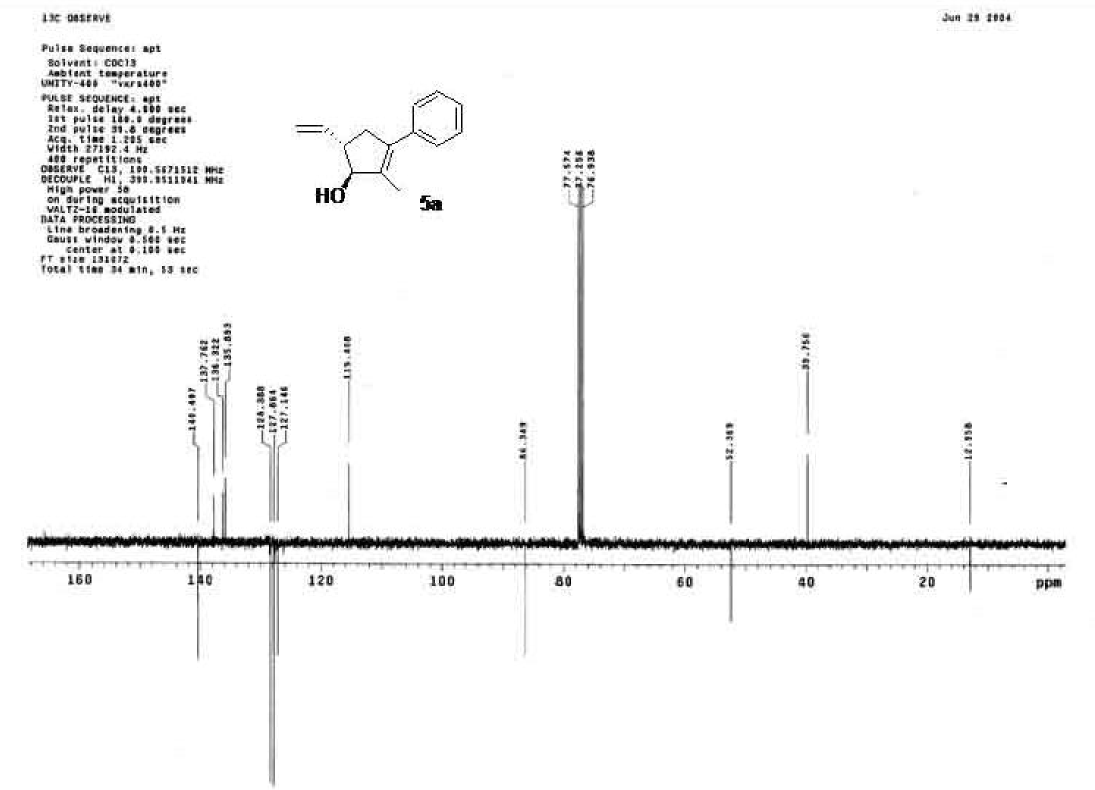

O
H
TESO
30a
10 9 8 7 6 5 4 3 2 1 ppm

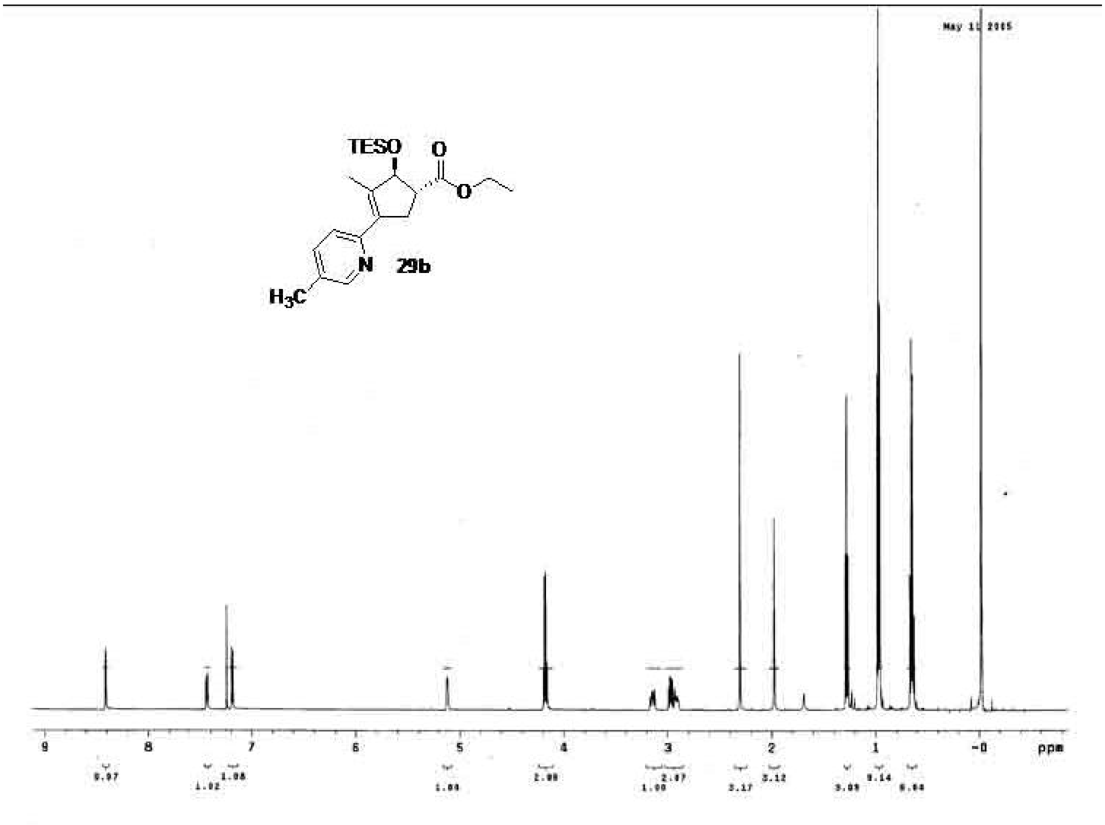

DIBAL-H -+
PPM
200.230
57.417
33.140
11.303
TESO
30a

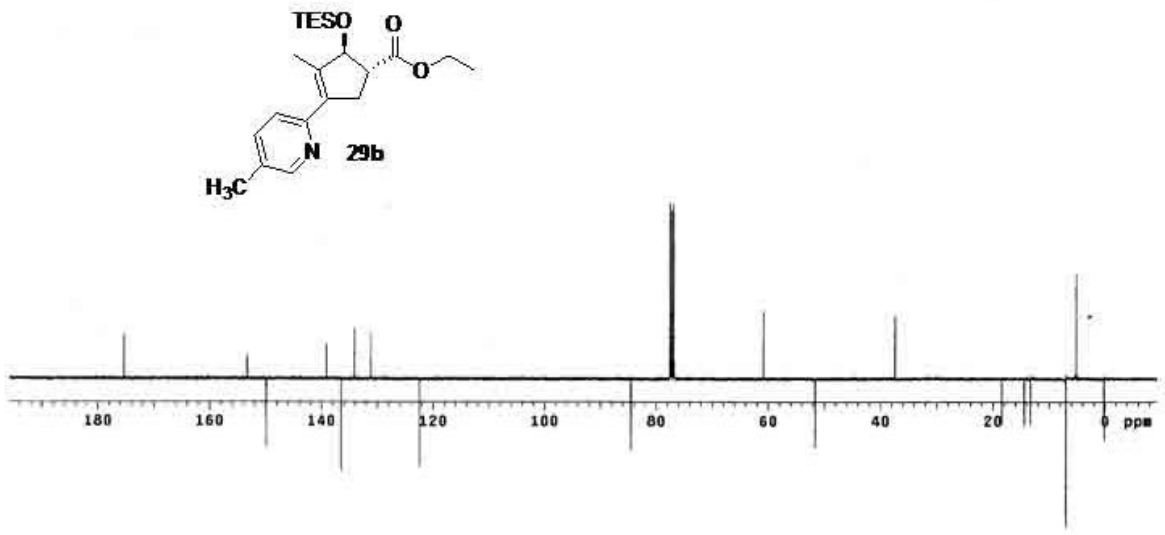

200
180
160
140
120
100
80
60
40
20
0
PPM
STANDARD PROTON PARAMETERS
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
INOVA-600 | "inova600"
Relax. delay 1.000 sec
Pulse 28.4 degrees
Acq. time 3.000 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 599.8723148 MHz
DATA PROCESSING
Line Broadening 0.4 Hz
FT size 131072
Total time 1 min, 4 sec
Jul 12 2004
TESO
31a
7
6
5
4
3
2
1
ppm
4.47
1.22
1.00
1.01
0.99
0.93
0.59
1.02
1.05
2.00
0.49
9.16
5.99

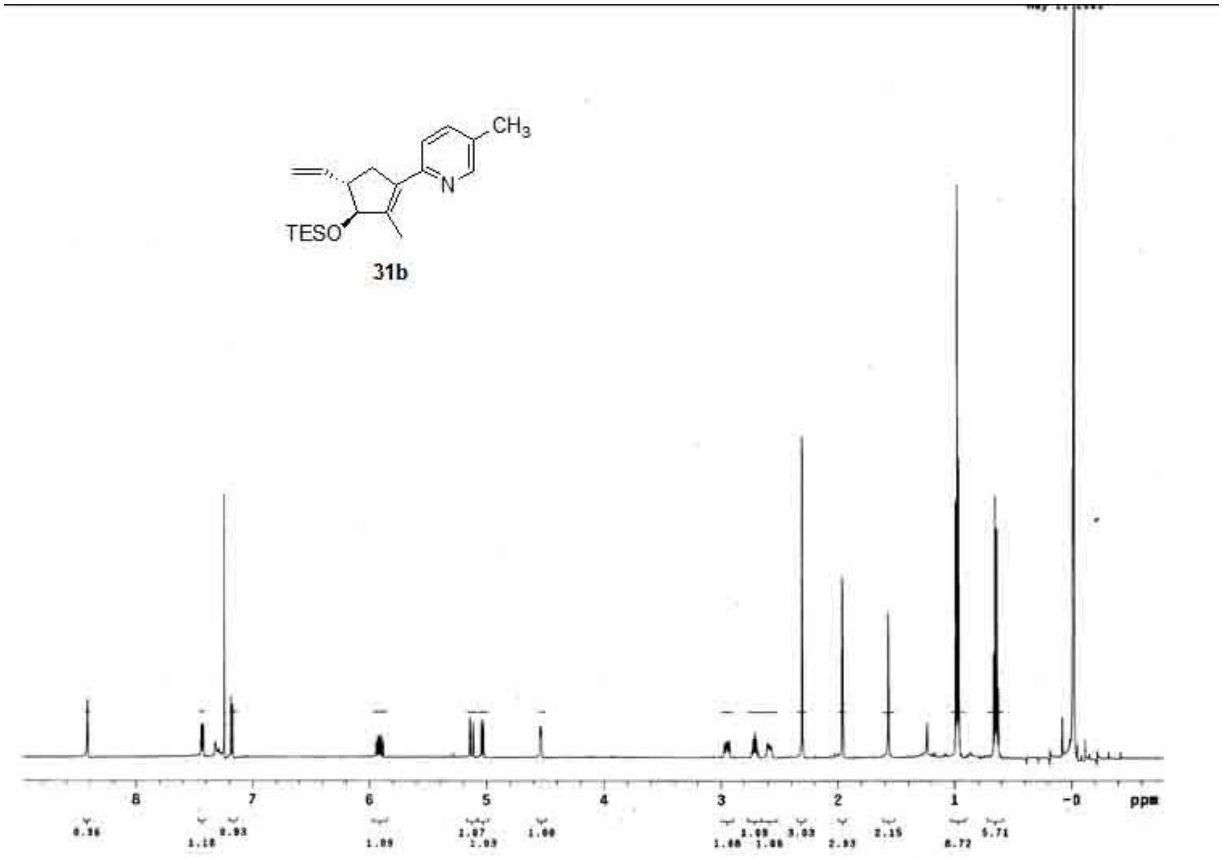

13C OBSERVE
Pulse Sequence: apt
Solvent: CDCl3
Ambient temperature
31a
TESO
Jul 12 2004
ppm

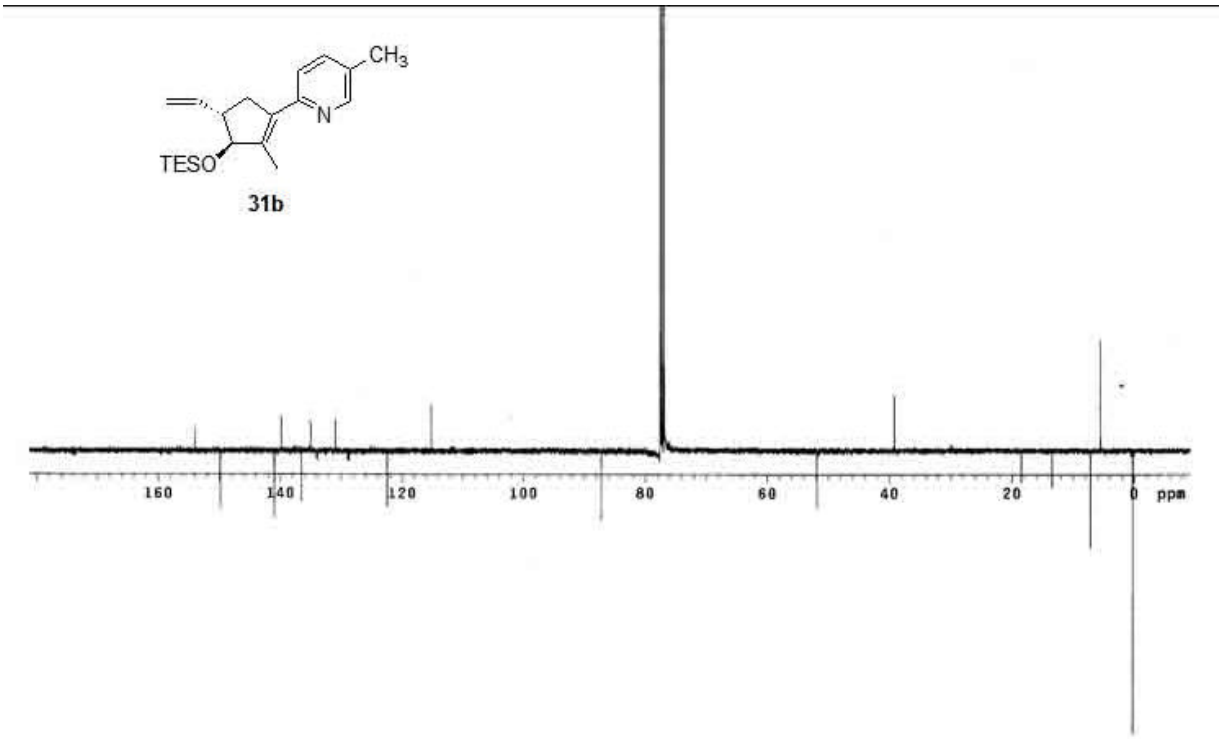

STANDARD PROTON PARAMETERS
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
HO
5a
Jun 29 2004
ppm

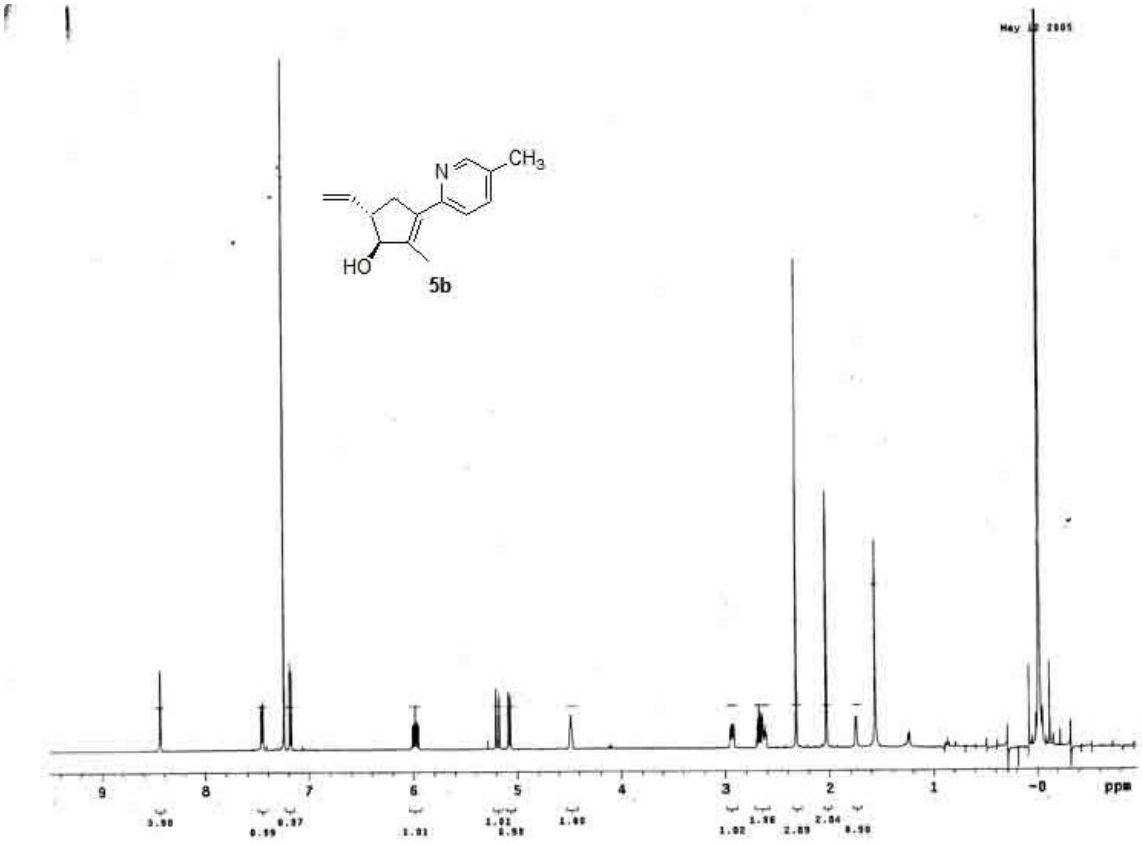

13C OBSERVE
Jun 29 2004
Pulse Sequence: apt
Solvent: CDCl3
Ambient temperature
HO
5a
140.497
137.762
136.322
135.893
128.880
127.864
127.146
115.408
86.349
77.574
77.256
76.938
52.369
39.756
12.938
160
140
120
100
80
60
40
20
ppm

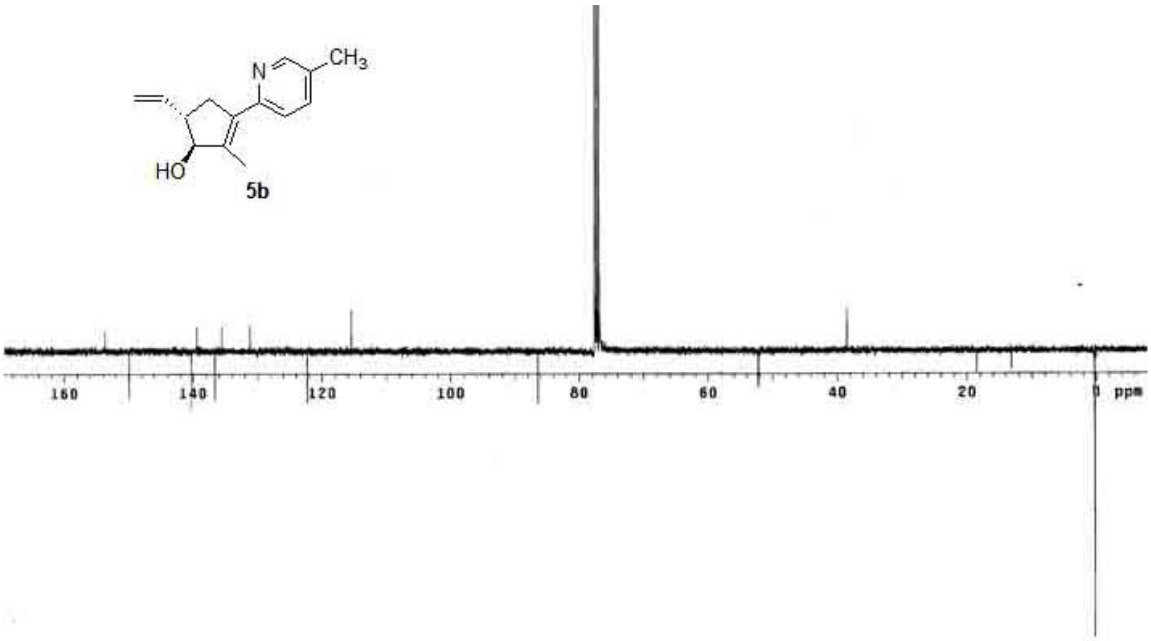

May 11 2005
TESO
O
O
N
29b
H3C
9
8
7
6
5
4
3
2
1
-0
ppm

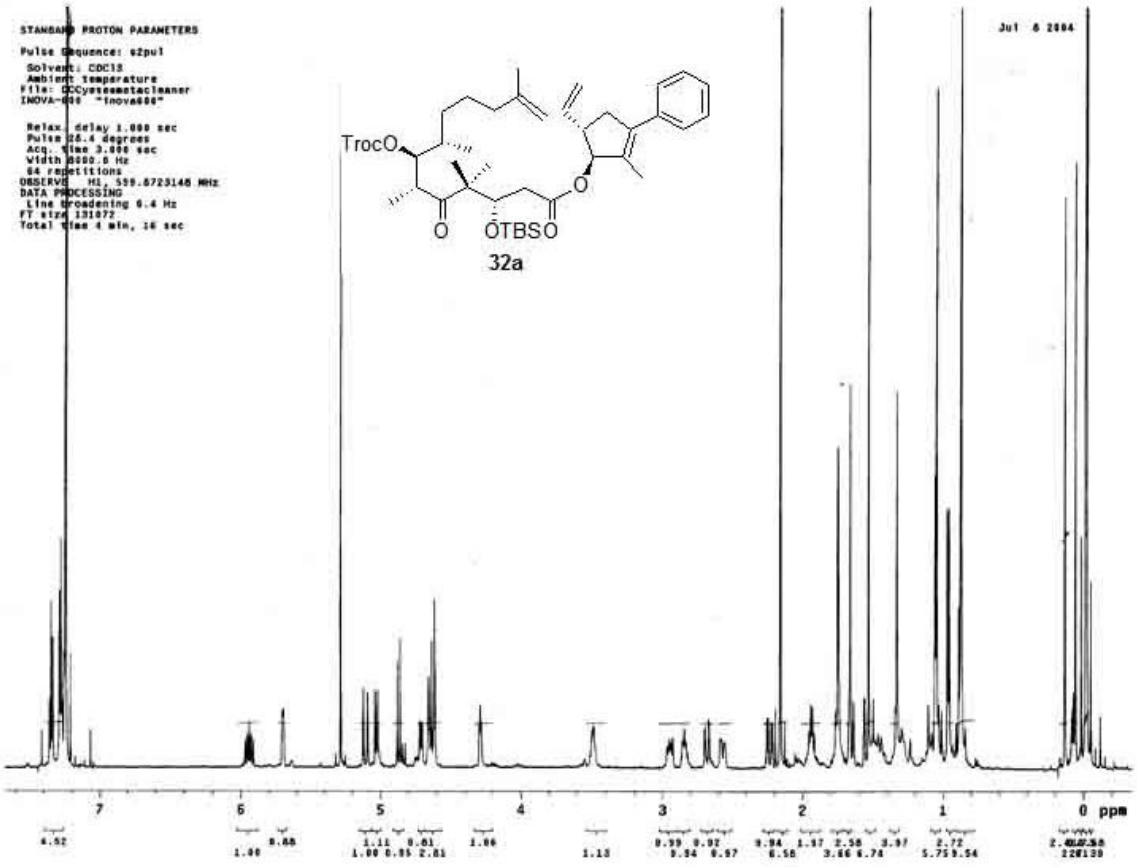

TESO
O
O
N
29b
H3C
180
160
140
120
100
80
60
40
20
0 ppm

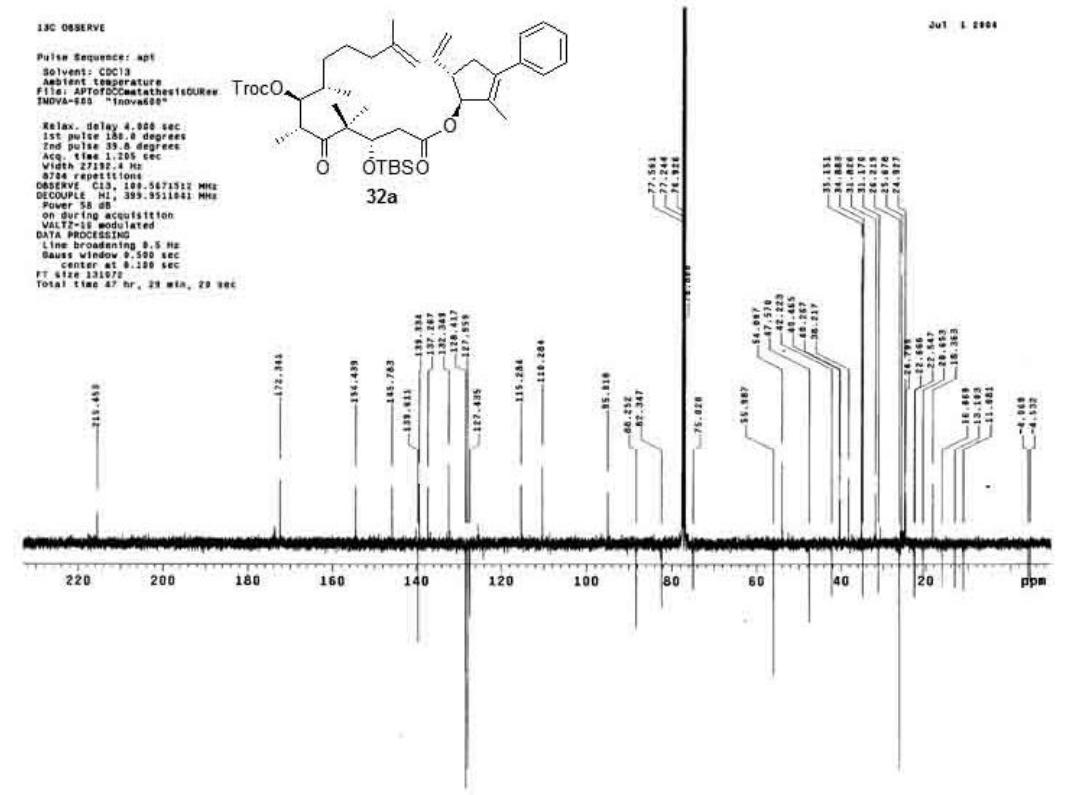

CH3
N
TESO
31b
8
7
6
5
4
3
2
1
-0
ppm

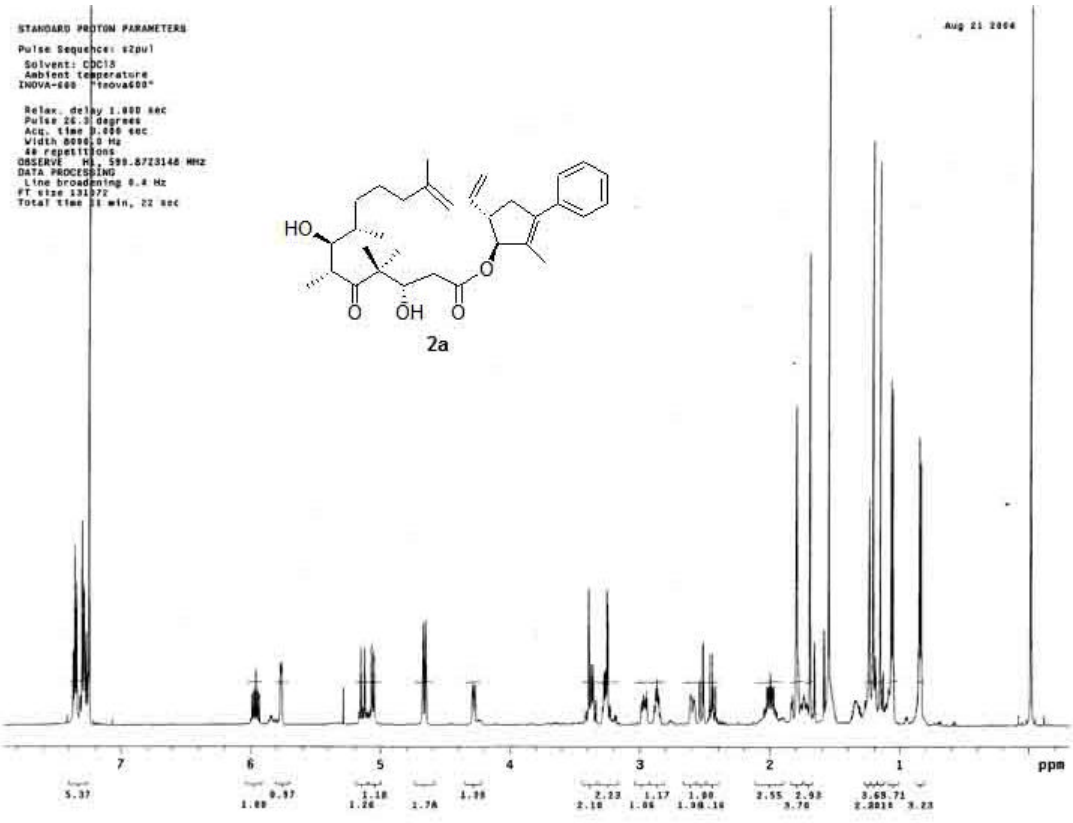

CH3
N
TESO
31b
160
140
120
100
80
60
40
20
0
ppm

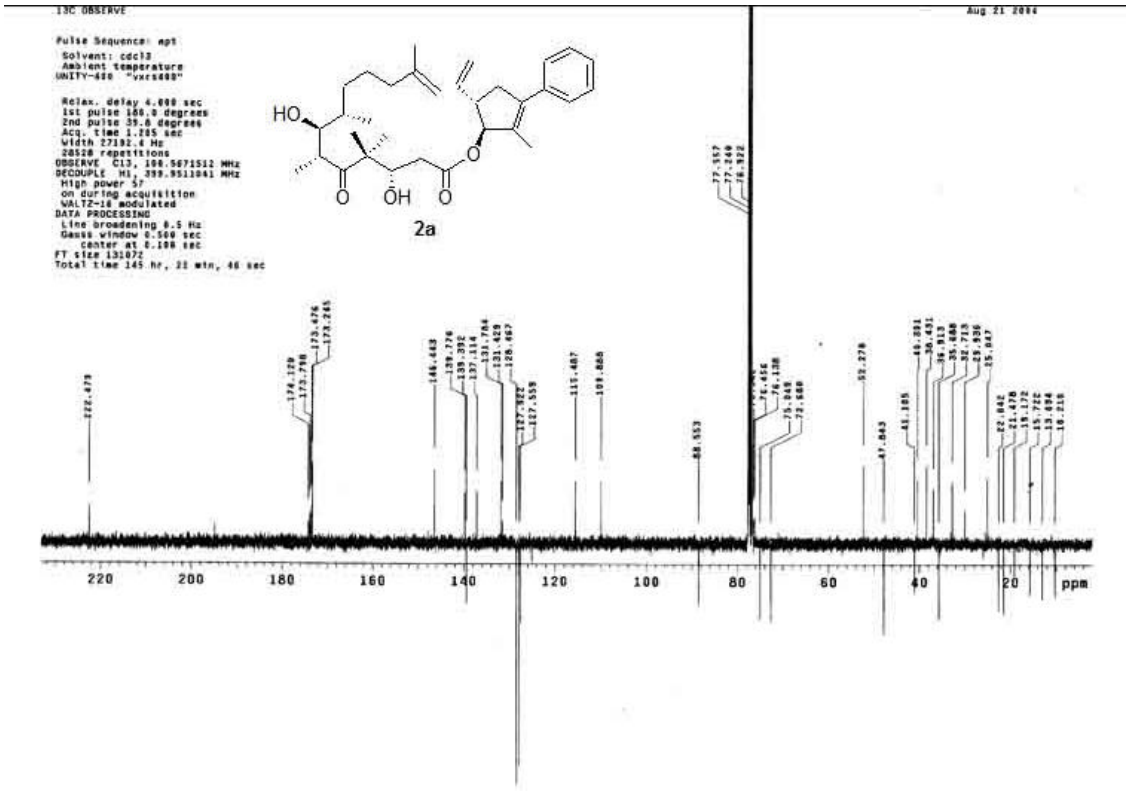

CH3
N
HO
5b
9
8
7
6
5
4
3
2
1
-0
ppm

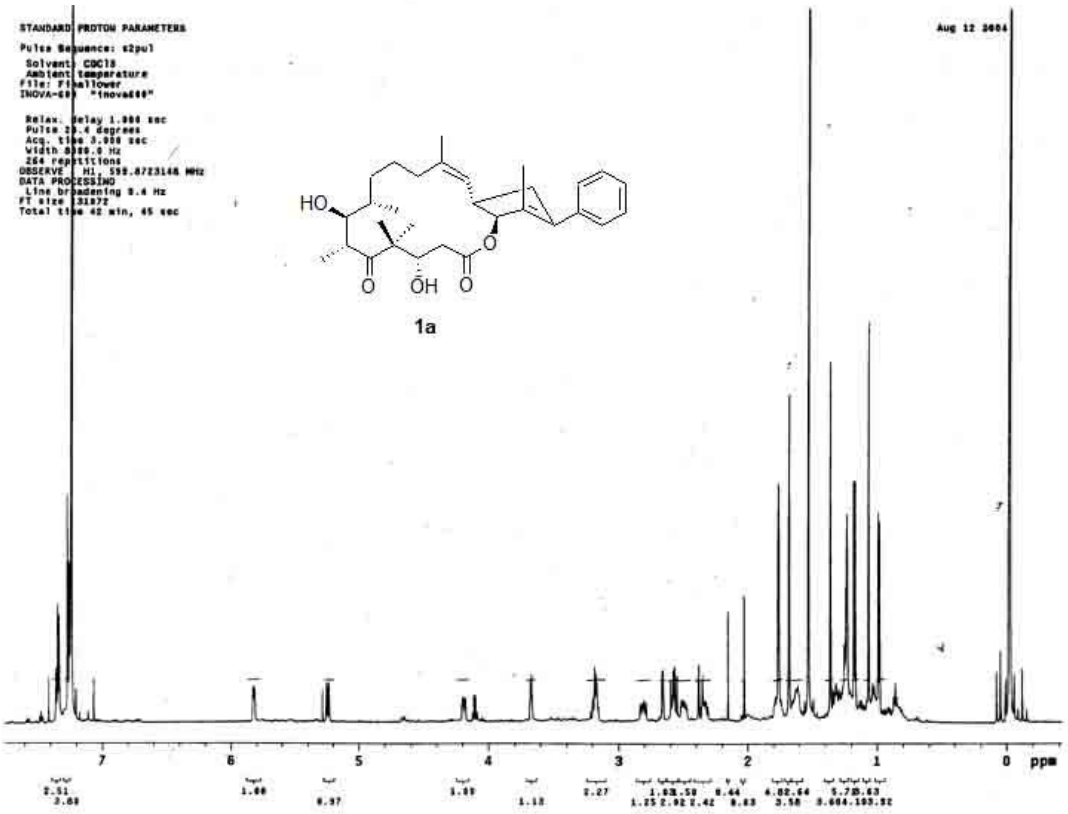

N
CH3
HO
5b
160
140
120
100
80
60
40
20
0 ppm


STANDARD PROTON PARAMETERS
Jul 6 2004
TrocO
O
O
OTBSO
32a
7
6
5
4
3
2
1
0 ppm


13C OBSERVE
Pulse Sequence: apt
Solvent: CDCl3
Ambient temperature
INOVA-600 "inova600"
Relax. delay 4.000 sec
1st pulse 180.0 degrees
2nd pulse 39.8 degrees
Acq. time 1.205 sec
Width 27192.4 Hz
8704 repetitions
OBSERVE C13, 100.5671512 MHz
DECOUPLE H1, 399.9511041 MHz
Power 58 dB
on during acquisition
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
Gauss window 0.500 sec
center at 0.180 sec
FT size 131072
Total time 47 hr, 29 min, 29 sec
TrocO
OTBSO
32a
Jul 1 2004
ppm


STANDARD PROTON PARAMETERS
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
INOVA-600 "inova600"
Relax. delay 1.000 sec
Pulse 26.3 degrees
Acq. time 3.000 sec
Width 6096.8 Hz
48 repetitions
OBSERVE H1, 599.8723148 MHz
DATA PROCESSING
Line broadening 0.4 Hz
FT size 131072
Total time 11 min, 22 sec
HO
OH
2a
Aug 21 2004
ppm


13C OBSERVE
Aug 21 2004
Pulse Sequence: apt
Solvent: cdcl3
Ambient temperature
UNITY-600 "vxrs600"
Relax. delay 4.000 sec
1st pulse 180.0 degrees
2nd pulse 35.0 degrees
Acq. time 1.285 sec
Width 27192.4 Hz
28528 repetitions
OBSERVE C13, 100.5671512 MHz
DECOUPLE H1, 399.9511041 MHz
High power 57
on during acquisition
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
Gauss window 0.500 sec
center at 0.100 sec
FT size 131072
Total time 145 hr, 21 min, 46 sec
HO
O
OH
O
O
2a
222.473
174.129
173.798
173.476
173.245
146.443
139.776
139.392
137.114
133.794
133.429
126.467
127.822
127.559
117.487
109.888
80.553
77.157
77.249
76.922
76.456
76.138
75.848
72.680
52.278
47.643
41.385
41.201
36.431
36.013
35.488
32.723
31.936
31.457
22.842
21.478
19.172
15.722
13.684
10.218
220
200
180
160
140
120
100
80
60
40
20
ppm


STANDARD PROTON PARAMETERS
Aug 12 2004
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
File: Fthallower
INOVA-600 "inova600"
Relax. delay 1.000 sec
Pulse 23.4 degrees
Acq. time 3.000 sec
Width 8000.0 Hz
264 repetitions
OBSERVE H1, 599.8723146 MHz
DATA PROCESSING
Line broadening 0.4 Hz
FT size 131072
Total time 42 min, 45 sec
HO
O
OH
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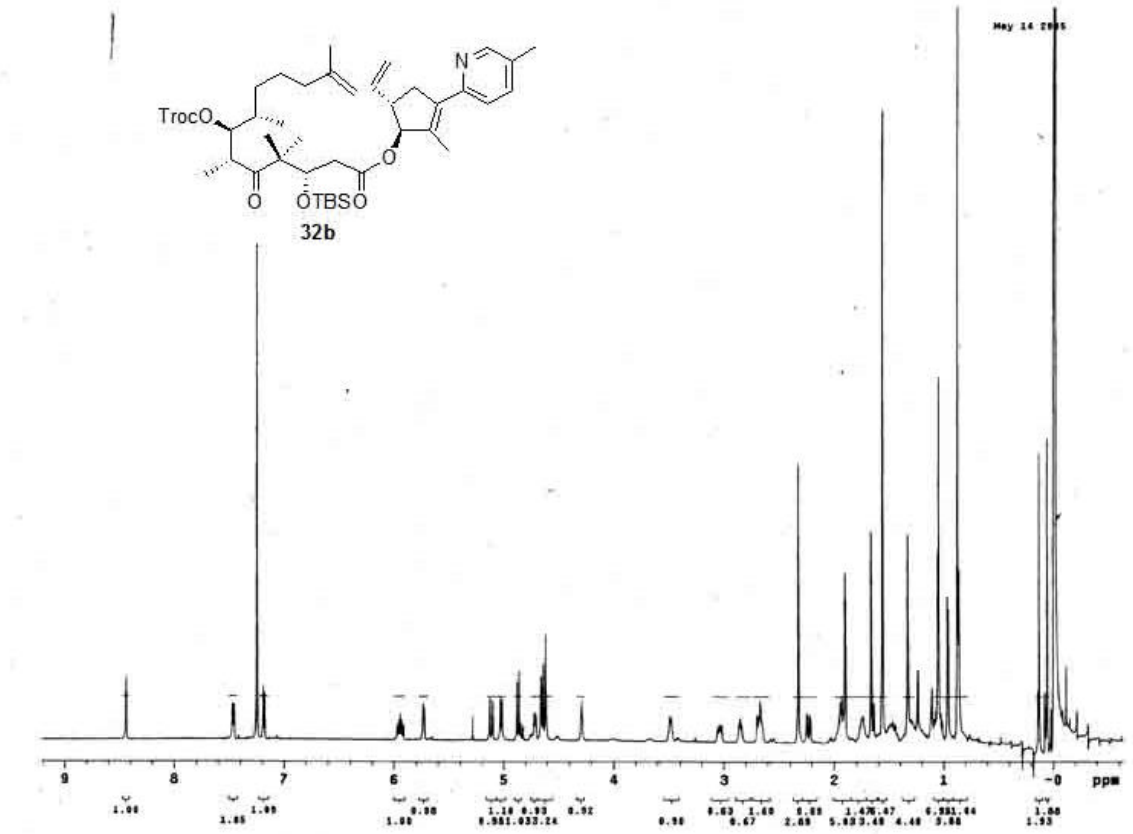
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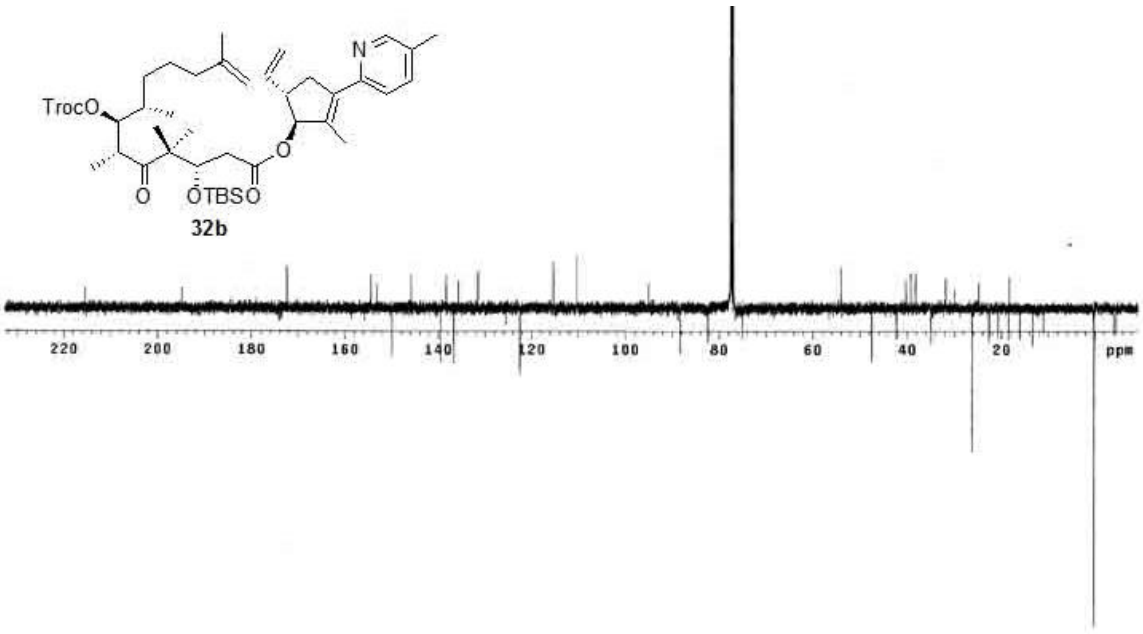
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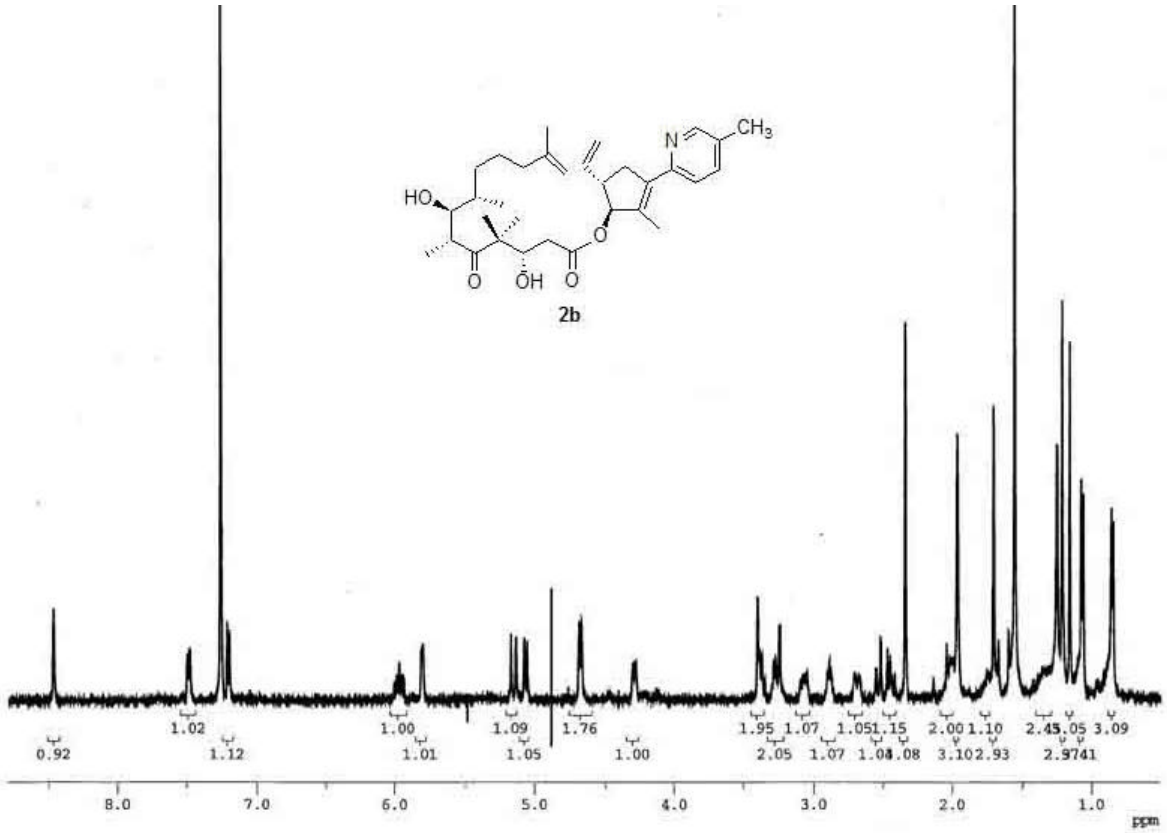
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1.95
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1.07
1.07
1.05
1.04
1.15
1.08
2.00
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1.10
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2.45
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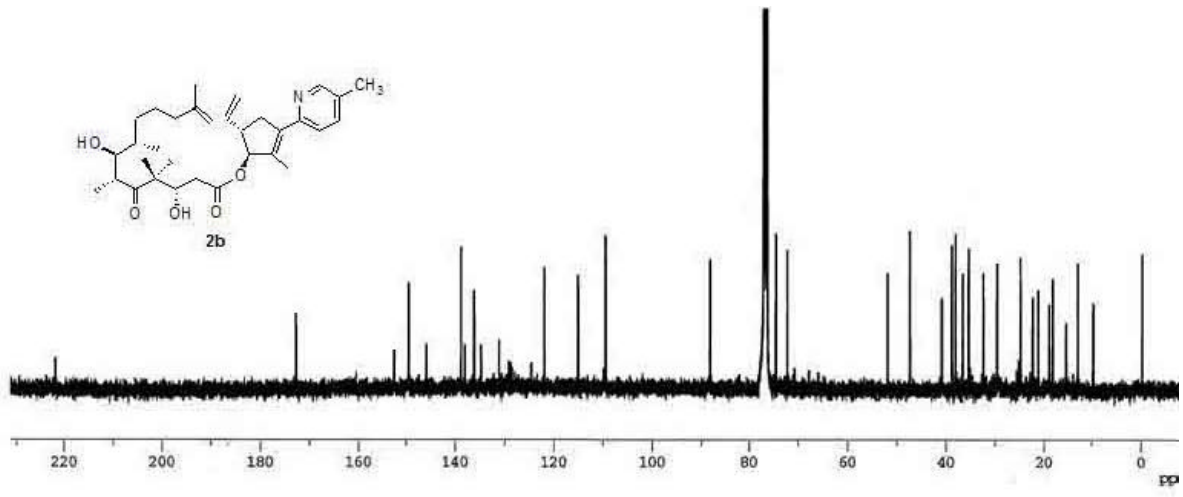
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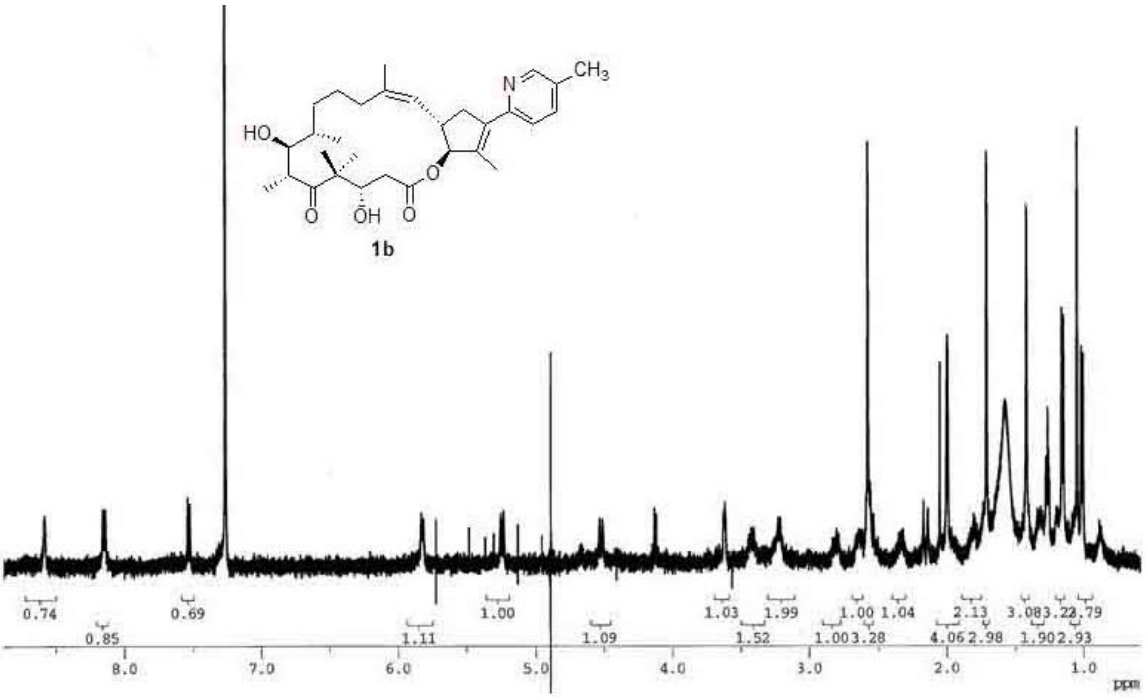
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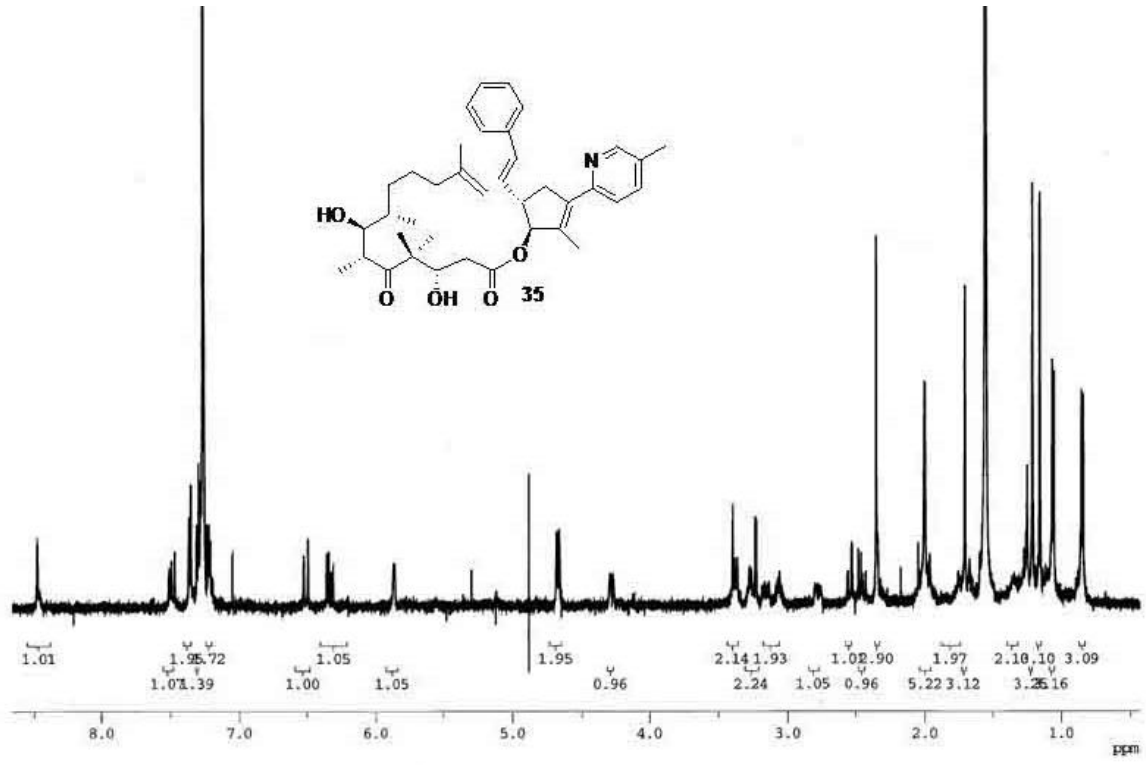
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ppm

Figure 1S. Cytotoxicity data for compound **1b** against the NCI in vitro 60 cell line human tumor screen (Dose Response curves).

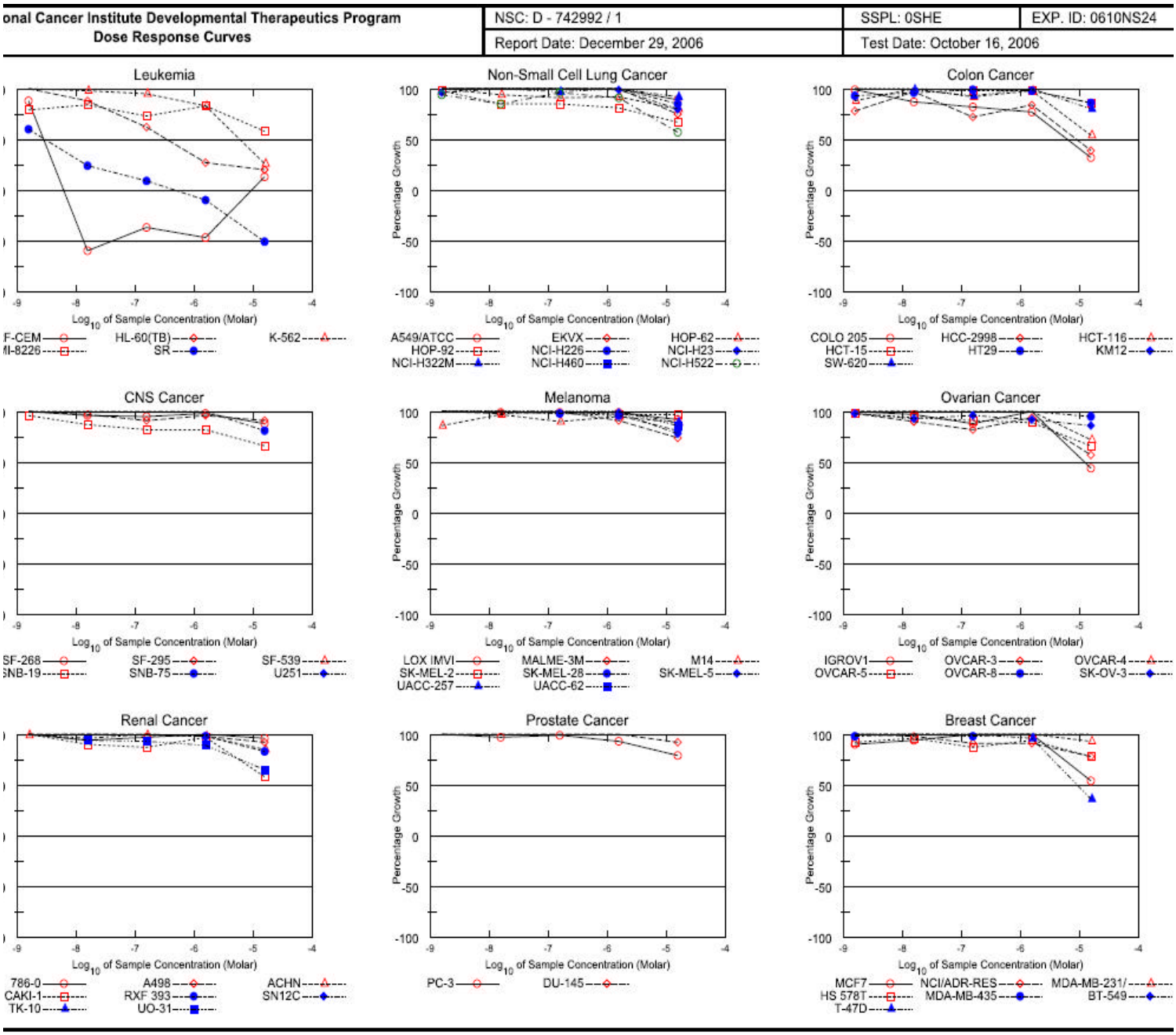


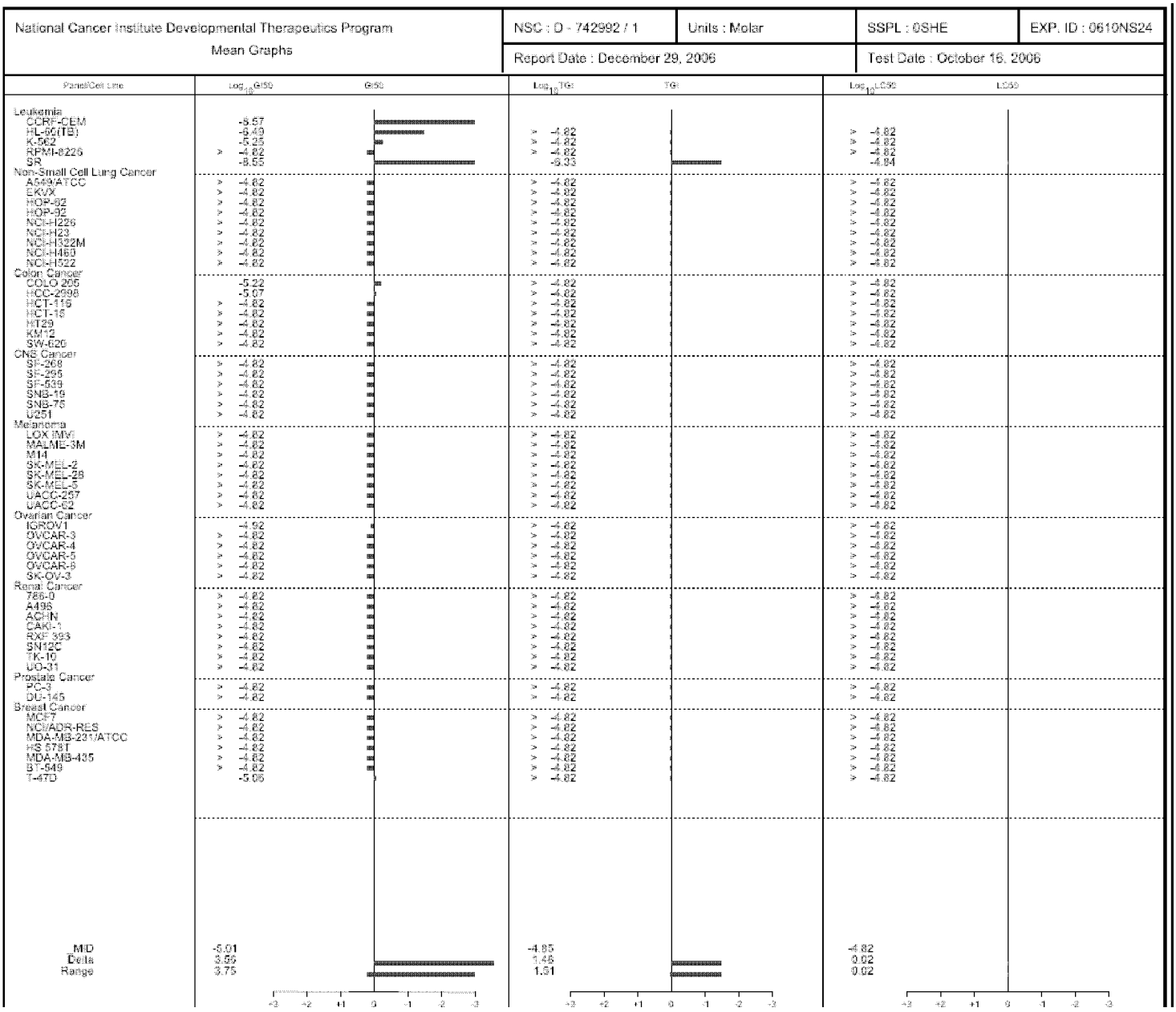
Figure 2S. Cytotoxicity data for compound **1b** against the NCI in vitro 60 cell line human tumor screen (In-Vitro Activity).

National Cancer Institute Developmental Therapeutics Program
In-Vitro Testing Results

NSC : D - 742992 / 1	Experiment ID : 0610NS24	Test Type : 08	Units : Molar
Report Date : December 29, 2006	Test Date : October 16, 2006	QNS :	MC :
COMI : MA-3 (54947)	Stain Reagent : SRB Dual-Pass Related	SSPL : 0SHE	

			Log10 Concentration											
	Time		Mean Optical Densities					Percent Growth						
Panel/Cell Line	Zero	Ctrl	-8.8	-7.8	-6.8	-5.8	-4.8	-8.8	-7.8	-6.8	-5.8	-4.8	GI50	TGI	LC50
Leukemia															
CCRF-CEM	0.207	0.904	0.819	0.082	0.131	0.111	0.299	88	-60	-37	-47	13	2.70E-9	.	.
HL-60(TB)	0.331	1.505	1.539	1.361	1.054	0.652	0.571	103	88	62	27	20	3.27E-7	> 1.50E-5	> 1.50E-5
K-562	0.154	1.069	1.095	1.054	1.023	0.913	0.388	103	98	95	83	26	5.62E-6	> 1.50E-5	> 1.50E-5
RPMI-8226	0.889	2.412	2.098	2.176	2.005	2.154	1.769	79	84	73	83	58	> 1.50E-5	> 1.50E-5	> 1.50E-5
SR	0.149	0.443	0.326	0.219	0.177	0.135	0.074	60	24	9	-10	-51	2.85E-9	4.64E-7	1.44E-5
Non-Small Cell Lung Cancer															
A549/ATCC	0.472	2.076	2.199	2.251	2.211	2.208	1.906	108	111	108	108	89	> 1.50E-5	> 1.50E-5	> 1.50E-5
EKVX	0.446	1.187	1.198	1.250	1.275	1.282	1.004	102	109	112	113	75	> 1.50E-5	> 1.50E-5	> 1.50E-5
HOP-62	0.534	1.631	1.649	1.568	1.527	1.539	1.417	102	94	91	92	80	> 1.50E-5	> 1.50E-5	> 1.50E-5
HOP-92	0.626	0.934	0.928	0.889	0.888	0.874	0.833	98	85	85	81	67	> 1.50E-5	> 1.50E-5	> 1.50E-5
NCI-H226	0.841	1.926	1.983	2.011	1.997	2.073	1.763	105	108	107	114	85	> 1.50E-5	> 1.50E-5	> 1.50E-5
NCI-H23	0.442	1.183	1.154	1.208	1.375	1.177	1.035	96	103	126	99	80	> 1.50E-5	> 1.50E-5	> 1.50E-5
NCI-H322M	0.521	1.213	1.215	1.239	1.193	1.270	1.160	100	104	97	108	92	> 1.50E-5	> 1.50E-5	> 1.50E-5
NCI-H460	0.309	2.133	2.208	2.210	2.238	2.276	2.163	104	104	106	108	102	> 1.50E-5	> 1.50E-5	> 1.50E-5
NCI-H522	0.716	1.624	1.568	1.490	1.588	1.543	1.232	94	85	96	91	57	> 1.50E-5	> 1.50E-5	> 1.50E-5
Colon Cancer															
COLO 205	0.290	0.741	0.735	0.683	0.658	0.638	0.436	99	87	82	77	32	6.04E-6	> 1.50E-5	> 1.50E-5
HCC-2998	0.639	0.997	0.919	0.988	0.899	0.939	0.780	78	97	72	84	39	8.59E-6	> 1.50E-5	> 1.50E-5
HCT-116	0.148	1.472	1.318	1.472	1.369	1.445	0.867	88	100	92	98	54	> 1.50E-5	> 1.50E-5	> 1.50E-5
HCT-15	0.214	1.956	2.011	1.959	1.916	1.920	1.720	103	100	98	98	86	> 1.50E-5	> 1.50E-5	> 1.50E-5
HT29	0.213	1.227	1.157	1.191	1.219	1.211	1.083	93	96	99	98	86	> 1.50E-5	> 1.50E-5	> 1.50E-5
KM12	0.447	1.511	1.567	1.587	1.709	1.601	1.577	105	107	119	109	106	> 1.50E-5	> 1.50E-5	> 1.50E-5
SW-620	0.202	1.415	1.474	1.403	1.332	1.839	1.175	105	99	93	135	80	> 1.50E-5	> 1.50E-5	> 1.50E-5
CNS Cancer															
SF-268	0.466	1.504	1.542	1.465	1.456	1.482	1.382	104	96	95	98	88	> 1.50E-5	> 1.50E-5	> 1.50E-5
SF-295	0.605	2.223	2.276	2.178	2.074	2.152	2.079	103	97	91	96	91	> 1.50E-5	> 1.50E-5	> 1.50E-5
SF-539	0.542	1.561	1.617	1.679	1.593	1.644	1.699	106	112	103	108	114	> 1.50E-5	> 1.50E-5	> 1.50E-5
SNB-19	0.795	2.866	2.782	2.607	2.487	2.503	2.167	96	87	82	82	66	> 1.50E-5	> 1.50E-5	> 1.50E-5
SNB-75	0.270	0.561	0.571	0.584	0.562	0.563	0.506	103	108	100	101	81	> 1.50E-5	> 1.50E-5	> 1.50E-5
U251	0.332	1.811	1.899	1.897	1.860	1.893	1.818	106	106	103	106	100	> 1.50E-5	> 1.50E-5	> 1.50E-5
Melanoma															
LOX IMVI	0.301	2.263	2.343	2.235	2.236	2.249	2.104	104	99	99	99	92	> 1.50E-5	> 1.50E-5	> 1.50E-5
MALME-3M	0.528	0.862	0.862	0.856	0.895	0.832	0.777	100	98	110	91	74	> 1.50E-5	> 1.50E-5	> 1.50E-5
M14	0.348	1.374	1.229	1.341	1.270	1.324	1.259	86	97	90	95	89	> 1.50E-5	> 1.50E-5	> 1.50E-5
SK-MEL-2	0.581	1.134	1.181	1.148	1.159	1.116	1.116	108	103	104	97	97	> 1.50E-5	> 1.50E-5	> 1.50E-5
SK-MEL-28	0.373	1.118	1.138	1.132	1.101	1.086	0.975	103	102	98	96	81	> 1.50E-5	> 1.50E-5	> 1.50E-5
SK-MEL-5	0.290	1.310	1.378	1.416	1.286	1.304	1.084	107	110	98	99	78	> 1.50E-5	> 1.50E-5	> 1.50E-5
UACC-257	0.929	1.958	2.021	2.098	2.014	2.006	1.840	106	114	105	105	89	> 1.50E-5	> 1.50E-5	> 1.50E-5
UACC-62	0.720	2.330	2.359	2.465	2.424	2.530	2.104	102	108	106	112	86	> 1.50E-5	> 1.50E-5	> 1.50E-5
Ovarian Cancer															
IGROV1	0.287	1.016	1.054	0.994	0.929	1.026	0.611	105	97	88	101	44	1.20E-5	> 1.50E-5	> 1.50E-5
OVCAR-3	0.373	1.555	1.529	1.442	1.343	1.479	1.042	98	90	82	94	57	> 1.50E-5	> 1.50E-5	> 1.50E-5
OVCAR-4	0.362	0.861	0.881	0.918	0.901	0.915	0.719	104	111	108	111	72	> 1.50E-5	> 1.50E-5	> 1.50E-5
OVCAR-5	0.771	2.104	2.084	2.022	1.989	1.955	1.652	98	94	91	89	66	> 1.50E-5	> 1.50E-5	> 1.50E-5
OVCAR-8	0.429	1.713	1.762	1.842	1.852	1.808	1.651	104	110	111	107	95	> 1.50E-5	> 1.50E-5	> 1.50E-5
SK-OV-3	0.753	1.202	1.192	1.170	1.184	1.168	1.139	98	93	96	92	86	> 1.50E-5	> 1.50E-5	> 1.50E-5
Renal Cancer															
786-0	0.659	2.611	2.633	2.489	2.553	2.625	2.526	101	94	97	101	96	> 1.50E-5	> 1.50E-5	> 1.50E-5
A498	0.845	1.453	1.454	1.466	1.457	1.442	1.403	100	102	101	98	92	> 1.50E-5	> 1.50E-5	> 1.50E-5
ACHN	0.332	1.741	1.726	1.741	1.726	1.713	1.528	99	100	99	98	85	> 1.50E-5	> 1.50E-5	> 1.50E-5
CAKI-1	0.640	1.769	1.820	1.655	1.617	1.732	1.294	104	90	87	97	58	> 1.50E-5	> 1.50E-5	> 1.50E-5
RXF 393	0.828	1.403	1.429	1.378	1.436	1.393	1.303	105	96	106	98	83	> 1.50E-5	> 1.50E-5	> 1.50E-5
SN12C	0.445	1.524	1.621	1.640	1.692	1.659	1.524	109	111	115	112	100	> 1.50E-5	> 1.50E-5	> 1.50E-5
TK-10	0.609	1.096	1.163	1.191	1.195	1.209	1.134	114	120	120	123	108	> 1.50E-5	> 1.50E-5	> 1.50E-5
UO-31	0.288	1.336	1.344	1.269	1.264	1.218	0.973	101	94	93	89	65	> 1.50E-5	> 1.50E-5	> 1.50E-5
Prostate Cancer															
PC-3	0.265	1.012	1.078	0.994	1.006	0.961	0.855	109	97	99	93	79	> 1.50E-5	> 1.50E-5	> 1.50E-5
DU-145	0.190	0.782	0.809	0.815	0.792	0.805	0.733	105	106	102	104	92	> 1.50E-5	> 1.50E-5	> 1.50E-5
Breast Cancer															
MCF7	0.386	1.418	1.319	1.353	1.426	1.537	0.939	90	94	101	112	54	> 1.50E-5	> 1.50E-5	> 1.50E-5
NCI/ADR-RES	0.366	1.174	1.201	1.157	1.105	1.102	0.995	103	98	91	91	78	> 1.50E-5	> 1.50E-5	> 1.50E-5
MDA-MB-231/ATCC	0.644	1.435	1.494	1.446	1.453	1.524	1.382	107	101	102	111	93	> 1.50E-5	> 1.50E-5	> 1.50E-5
HS 578T	0.381	0.819	0.784	0.799	0.762	0.793	0.722	92	96	87	94	78	> 1.50E-5	> 1.50E-5	> 1.50E-5
MDA-MB-435	0.481	2.297	2.260	2.383	2.259	2.512	2.303	98	105	98	112	100	> 1.50E-5	> 1.50E-5	> 1.50E-5
BT-549	0.635	1.222	1.293	1.315	1.321	1.322	1.229	112	116	117	117	101	> 1.50E-5	> 1.50E-5	> 1.50E-5
T-47D	0.609	1.055	1.123	1.081	1.055	1.035	0.768	115	106	100	96	36	8.65E-6	> 1.50E-5	> 1.50E-5

Figure 3S. Cytotoxicity data for compound **1b** against the NCI in vitro 60 cell line human tumor screen (Mean Graphs).



SI References:

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