

Novel Pd^{II}-Mediated Cascade Carboxylative Annulation to Construct Benzo[*b*]furan-3-Carboxylic Acids

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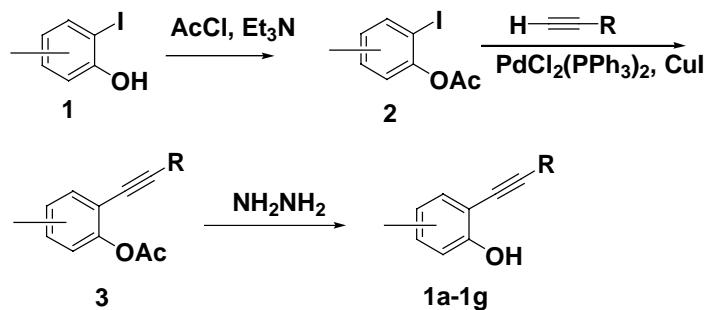
I. General Methods

Materials: Reaction solvents were commercially purchased from *Acros* and *Aldrich* without further purification and reagents were used as received. Reactions for the synthesis of the starting material were monitored by thin-layer chromatography (TLC) on 0.25 mm precoated Merck Silica Gel 60 F₂₅₄, visualizing with ultraviolet light or phosphomolybdic acid stain. Flash column chromatography was performed on Merck Silica Gel 60 (230-400 mesh) using reagent grade hexanes, dichloromethane, methanol and ethyl acetate.

Analysis: ¹H NMR spectra were recorded on a INOVA plus Varian 500 MHz spectrometer and are referenced to residual solvents peaks (DMSO-d₆; ¹H: δ 2.50 ppm (DMSO-d₆)). Other peaks shown in the blank: δ 3.31 ppm (H₂O in DMSO-d₆) and δ 1.22 ppm (poly/oligopropylene dissolved in DMSO-d₆ from polypropylene 96-well plate). ¹H-¹H couplings are assumed to be first order, and peak multiplicity is reported as s (single), d (doublet), t (triplet), q (quartet), m (multiplet), or b (broad). In regards to the products cleaved from the beads (10 macrobeads), their ¹H NMR spectra were recorded after 16 scans. All LC-MS spectra were obtained on a Micromass

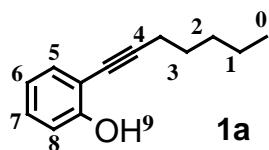
ZQ mass spectrometer in electrospray positive ionization (ES+) mode in line with a Waters 2790 HPLC system (Separations Module, AllianceTM). LC-MS chromatography was performed on a Waters Symmetry C18 Column (3.5 μ m, 2.1X 50 mm, W93491F 26) using a flow rate of 0.4 mL/min in a gradient of 15-100% CH₃CN in H₂O in 9 min with 1 min wash. Column temperature: 30 $^{\circ}$ C. [ES⁺]: Capillary (kV): 3.5; Cone (V): 70; Extractor (V): 5; RF Lens (V): 0.3; Source temperature ($^{\circ}$ C): 150; Cone temperature ($^{\circ}$ C): 20; Desolvation temperature ($^{\circ}$ C): 400; Cone gas flow (L/Hr): 114; Desolvation gas flow (L/Hr): 466. Injection Volume: 10 μ l. Software: Masslynx. Normally, product cleaved from one bead is sufficient for LC-MS analysis. After the product was dried completely, it was dissolved in 0.15 mL THF (HPLC grade) for LC-MS test, which was reported as: LC-MS (retention time, [M+1]⁺/ [M+Na]⁺ (ES+)).

II. Starting materials synthesis.

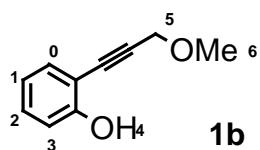


General synthetic procedures for making the starting materials

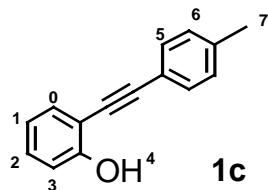
Please see the supporting information from *Org. Lett.* **2000**, 2, 297-299.



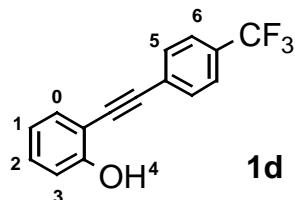
2-Hept-1-ynyl-phenol (**1a**) $^{\text{H}}$ NMR (500 MHz, d6-DMSO): δ 9.64 (s, 1 H₉), 7.19 (d, 1 H₅, J = 7.5 Hz), 7.09 (t, 1 H₆, J = 5.75 Hz), 6.84 (d, 1 H₈, J = 8.0 Hz), 6.71 (t, 1 H₇, J = 8.5 Hz), 2.40-2.37 (m, 2 H₄), 1.53-1.50 (m, 2 H₃), 1.40-1.36 (m, 2 H₂), 1.32-1.28 (m, 2 H₁), 0.89-0.85 (m, 3 H₀).



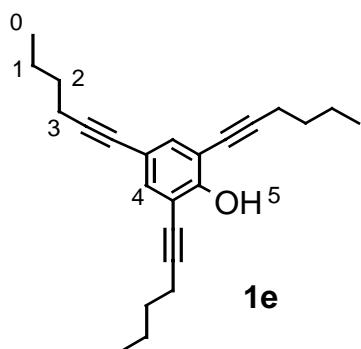
2-(3-Methoxy-prop-1-ynyl)-phenol (**1b**) $^{\text{H}}$ NMR (500 MHz, d6-DMSO): δ 7.36 (d, 1 H₀, J = 5.0 Hz), 7.25 (t, 1 H₁, J = 7.5 Hz), 6.95 (d, 1 H₃, J = 8.5 Hz), 6.87 (t, 1 H₂, J = 7.5 Hz), 5.92 (s, 1 H₄), 4.39 (s, 2 H₅), 3.47 (s, 3 H₆).



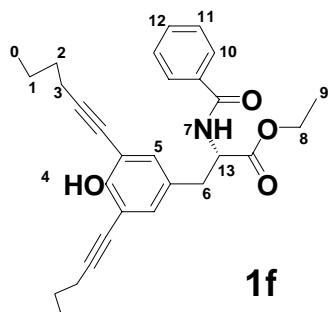
2-p-Tolylethynyl-phenol (**1c**) H^1 NMR (500 MHz, d6-DMSO): δ 7.49-7.47 (m, 2 H₅ & 2 H₆), 7.30 (t, 1 H₁, J = 8.0 Hz), 7.21 (d, 1 H₀, J = 8.0 Hz), 7.05 (d, 1 H₃, J = 8.0 Hz), 6.95 (t, 1 H₂, J = 7.5 Hz), 5.98 (s, 1 H₄), 2.42 (s, 3 H₇).



2-(4-Trifluoromethyl-phenylethynyl)-phenol (**1d**) H^1 NMR (500 MHz, d6-DMSO): δ 7.66-7.62 (m, 2 H₅ & 2 H₆), 7.45 (d, 1 H₀, J = 7.5 Hz), 7.32 (t, 1 H₁, J = 7.0 Hz), 7.01 (d, 1 H₃, J = 8.5 Hz), 6.94 (t, 1 H₂, J = 7.5 Hz), 5.82 (s, 1 H₄).

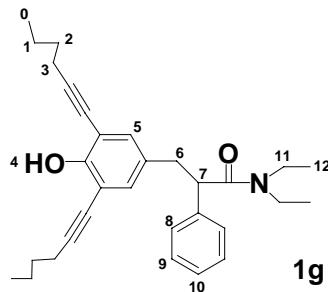


2,4,6-Tri-hex-1-ynyl-phenol (**1e**) H^1 NMR (500 MHz, d6-DMSO): δ 9.44 (s, 1 H₅), 7.14 (s, 2 H₄), 2.41 (t, 6 H₃, J = 6.0 Hz), 2.34 (t, 6 H₂, J = 6.0 Hz), 1.51-1.40 (m, 6 H₁), 0.89 (t, 9 H₀, J = 6.0 Hz).



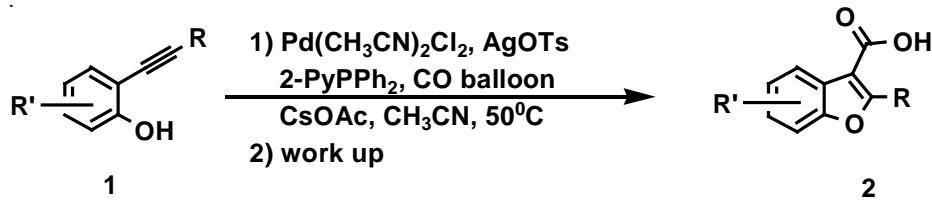
2-Benzoylamino-3-(3,5-di-hex-1-ynyl-4-hydroxy-phenyl)-propionic acid ethyl ester (**1f**) H^1 NMR (500 MHz, d6-DMSO): δ 8.92 (s, 1 H₄), 8.75 (d, 2 H₇, J = 8.0 Hz), 7.78 (d, 1 H₁₀, J = 7.5 Hz) 7.53 (t, 2 H₁₂, J = 7.5 Hz), 7.44 (t, 2 H₁₁, J = 7.5 Hz), 7.12 (s, 1 H₅), 4.56-4.50 (m, 1 H₁₃), 4.10-

4.05 (m, 2 H₈), 3.00-2.88 (m, 2 H₆), 2.4 (t, 4 H₃, *J* = 7.0 Hz), 1.52-1.47 (m, 4 H₂), 1.44-1.37 (m, 4 H₁), 1.13 (t, 3 H₉, *J* = 7.5 Hz), 0.89 (t, 6 H₀, *J* = 7.5 Hz).

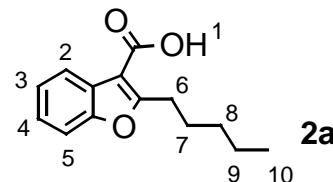


3-(3,5-Di-hex-1-ynyl-4-hydroxy-phenyl)-N,N-diethyl-2-phenyl-propionamide (**1g**) ¹H NMR (500 MHz, d6-DMSO): δ 8.81 (s, 1 H₄), 7.35 (d, 2 H₈, *J* = 7.5 Hz), 7.28 (t, 2 H₉, *J* = 7.5 Hz), 7.20 (t, 1 H₁₀, *J* = 7.5 Hz), 7.01 (s, 2 H₅), 4.09-4.06 (m, 1 H₇), 3.23-3.09 (m, 4 H₁₁), 2.50-2.48 (m, 2 H₆), 2.40 (t, 4 H₃, *J* = 7.0 Hz), 1.53-1.47 (m, 2 H₂), 1.45-1.39 (m, 4 H₁), 0.91-0.88 (m, 6 H₀ & 6 H₁₂).

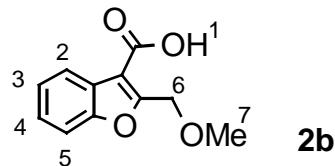
III. Carboxylative Annulation (general stoichiometric method).



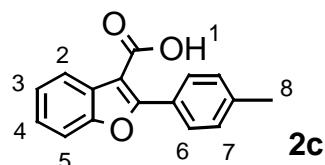
To proceed with carbonylative annulation reaction, Pd(CH₃CN)₂Cl₂ (1.1 equiv), 2-Py-PPh₃ (1.1 equiv), AgOTs (4 equiv) and CsOAc (20 equiv) were mixed and degassed under high vacuum, and then charged with CO followed by addition of the dry CH₃CN. The mixtures were then stirred at 50 °C under balloon pressure of CO for 10 min before the deprotected starting materials (**1a-1g**) (1 equiv) dissolved in CH₃CN was added. After 2 hrs, the mixtures were filtered through a short plug of silica gel with CH₃CN washings, followed by chromatographic purification to give the product (**2a-2g**).



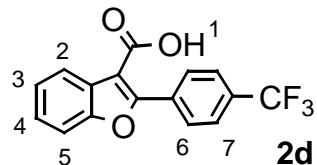
2-Pentyl-benzofuran-3-carboxylic acid (2a**):** ¹H NMR (500 MHz, d6-DMSO): δ 12.90 (s, br, 1 H₁), 7.90 (m, 1 H₂), 7.57 (m, 1 H₅), 7.29 (m, 1 H₃ & 1 H₄), 3.13 (t, 2 H₆, *J* = 7.5 Hz), 1.70 (m, 2 H₇), 1.29 (m, 2 H₈ & 1 H₉), 0.84 (t, 3 H₁₀, *J* = 6.5 Hz). ¹³C NMR (500 MHz, d6-DMSO): δ (ppm) 167.17, 165.66, 153.73, 126.81, 125.14, 124.49, 122.19, 111.67, 109.42, 31.46, 27.88, 27.76, 22.41, 14.48. LC-MS: 5.97 min, [M-H₂O+]⁺ 215 (ES+). Melting Point: 78-80 °C.



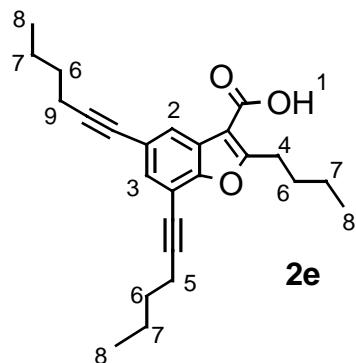
2-Methoxymethyl-benzofuran-3-carboxylic acid (2b): ^1H NMR (500 MHz, d6-DMSO): δ 13.28 (s, br, 1H₁), 7.98 (d, 1H₂, J = 7.5 Hz), 7.64 (d, 1H₅, J = 8.5 Hz), 7.37 (m, 1H₃ & 1H₄), 4.88 (s, 2H₆), 3.33 (s, 3H₇). ^{13}C NMR (500 MHz, d6-DMSO): δ (ppm) 165.19, 160.86, 154.24, 129.95, 129.23, 126.18, 124.77, 122.79, 112.12, 65.26, 58.69. LC-MS: 3.97 min, [M+1]⁺ 207 (ES+). Melting Point: 96-98 $^{\circ}\text{C}$.



2-p-Tolyl-benzofuran-3-carboxylic acid (2c): ^1H NMR (500 MHz, d6-DMSO): δ 13.40 (s, br, 1H₁), 7.99 (dd, 1H₂, J_1 = 2.0 Hz, J_2 = 7.0 Hz), 7.89 (d, 2H₆, J = 8.0 Hz), 7.66 (d, 1H₅, J = 7.5 Hz), 7.30-7.40 (m, 1H₃ & 1H₄ & 2H₇), 2.38 (s, 3H₈). ^{13}C NMR (500 MHz, d6-DMSO): δ (ppm) 165.33, 160.40, 153.73, 140.95, 129.90, 129.51, 127.78, 127.02, 126.00, 124.79, 122.98, 111.91, 109.48, 21.75. LC-MS: 5.31 min, [M-H₂O+1]⁺ 235 (ES+). Melting Point: 183-185 $^{\circ}\text{C}$.

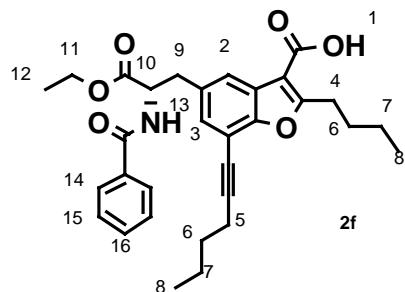


2-(4-Trifluoromethyl-phenyl)-benzofuran-3-carboxylic acid (2d): ^1H NMR (500 MHz, d6-DMSO): δ 13.10 (s, br, 1H₁), 8.21 (d, 2H₇, J = 8.0 Hz), 8.00 (d, 1H₂, J = 8.0 Hz), 7.89 (d, 2H₇, J = 8.0 Hz), 7.89 (d, 1H₅, J = 8.0 Hz), 7.35-7.50 (m, 1H₃ & 1H₄). ^{13}C NMR (500 MHz, d6-DMSO): δ (ppm) 165.00, 158.12, 154.14, 133.71, 130.80, 127.40, 126.73, 125.82, 125.79, 125.76, 125.10, 123.31, 112.18, 111.58. LC-MS: 5.57 min, [M-H₂O+1]⁺ 289 (ES+). Melting Point: 103-105 $^{\circ}\text{C}$.

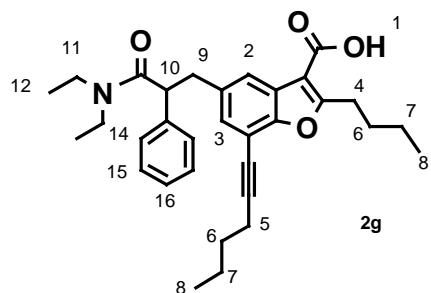


2-Butyl-5,7-di-hex-1-ynyl-benzofuran-3-carboxylic acid (2e): ^1H NMR (500 MHz, d6-DMSO): δ 13.20 (s, br, 1H₁), 7.82 (s, 1H₂), 7.27 (s, 1H₃), 3.15 (t, 2H₄, J = 8.0 Hz), 2.51 (t, 2H₅, J = 7.0 Hz), 2.40 (t, 2H₉, J = 7.0 Hz), 1.30-1.80 (m, 6H₆ & 6H₇), 0.88-0.95 (m, 9H₈). ^{13}C NMR (500 MHz, d6-DMSO): δ (ppm) 168.32, 165.18, 152.71, 130.75, 127.43, 124.78, 119.90, 109.66, 108.31, 97.42,

90.59, 80.45, 74.50, 30.92, 30.70, 30.03, 27.61, 22.47, 22.14, 21.98, 19.22, 18.94, 14.23, 14.16. LC-MS: 7.78 min, $[M+1]^+$. 379 (ES+). Melting Point: 122-124 $^{\circ}\text{C}$.



5-(2-Benzoylamino-2-ethoxycarbonyl-ethyl)-2-butyl-7-hex-1-ynyl-benzofuran-3-carboxylic acid (2f): ^1H NMR (500 MHz, d6-DMSO): δ 13.04 (s, br, 1H₁), 8.83 (d, , J = 7.5 Hz), 7.82 (s, 1H₂), 7.78 (d, 2H₁₄, J = 7.0 Hz), 7.30-7.60 (m, 1H₁₆ & 2H₁₅), 7.29 (s, 1H₃), 4.61 (m, 1H₁₀), 4.08 (m, 2H₁₁), 3.20 (m, 2H₉), 3.13 (t, 2H₄, J = 8.0 Hz), 2.49 (m, 2H₅), 1.10-1.70 (m & m & m & m, 4H₆ & 4H₇), 1.12 (t, 2H₁₂, J = 7.0 Hz), 0.88-0.95 (m, 6H₈). ^{13}C NMR (500 MHz, d6-DMSO): δ (ppm) 172.17, 167.62, 167.28, 165.47, 152.44, 134.54, 134.25, 132.11, 129.94, 129.42, 129.22, 128.92, 128.08, 127.07, 122.69, 107.36, 96.43, 75.35, 61.28, 55.41, 41.41, 41.37, 36.74, 30.79, 30.15, 27.63, 22.46, 21.97, 19.20, 14.67, 14.23, 14.16. LC-MS: 6.45 min, $[M+1]^+$. 518 (ES+). Melting Point: 166-168 $^{\circ}\text{C}$.



2-Butyl-5-(2-diethylcarbamoyl-2-phenyl-ethyl)-7-hex-1-ynyl-benzofuran-3-carboxylic acid (2g): ^1H NMR (500 MHz, d6-DMSO): δ 12.97 (s, br, 1H₁), 7.68 (s, 1H₂), 7.38 (d, 2H₁₄, J = 7.0 Hz), 7.29 (m, 1H₁₆ & 2H₁₅), 7.20 (s, 1H₃), 4.65 (m, 1H₁₀), 2.80-3.40 (m, 4H₁₁ & 2H₉ & 2H₄), 2.49 (t, 2H₅, J = 6.5 Hz), 1.10-1.70 (m & m & m & m, 4H₆ & 4H₇), 0.80-1.00 (m, 6H₅ & 3H₈), 0.71 (t, 3H₈, J = 7.0 Hz). ^{13}C NMR (500 MHz, d6-DMSO): δ (ppm) 171.30, 167.36, 165.50, 152.20, 141.19, 136.42, 129.94, 129.26, 129.21, 129.14, 128.48, 127.41, 126.82, 122.51, 109.74, 107.11, 96.10, 75.53, 49.87, 41.90, 40.72, 30.92, 30.84, 30.28, 30.18, 27.65, 22.49, 22.00, 19.21, 14.97, 14.27, 14.24, 14.18, 14.16, 14.08, 13.39. LC-MS: 6.87 min, $[M+\text{Na}]^+$. 524 (ES+).

IV. Table of Spectra

1. **^1H NMR and ^{13}C NMR spectra of compound 1a.** (Page 1-2) (S8-S9)
2. **^1H NMR and ^{13}C NMR spectra of compound 1b.** (Page 3-4) (S10-S11)
3. **^1H NMR of compound 1c.** (Page 5) (S12)
4. **^1H NMR of compound 1d.** (Page 6) (S13)
5. **^1H NMR and ^{13}C NMR spectra of compound 1e.** (Page 7-8) (S14-S15)
6. **^1H NMR and ^{13}C NMR spectra of compound 1f.** (Page 9-10) (S16-S17)
7. **^1H NMR and ^{13}C NMR spectra of compound 1g.** (Page 11-12) (S18-S19)
8. **^1H NMR, ^{13}C NMR and LC-MS spectra of compound 2a.** (Page 13-16) (S20-S23)
9. **^1H NMR, ^{13}C NMR and LC-MS spectra of compound 2b.** (Page 17-20) (S24-S27)
10. **^1H NMR, ^{13}C NMR and LC-MS spectra of compound 2c.** (Page 21-24) (S28-S31)
11. **^1H NMR, ^{13}C NMR and LC-MS spectra of compound 2d.** (Page 25-28) (S32-S35)
12. **^1H NMR, ^{13}C NMR and LC-MS spectra of compound 2e.** (Page 29-32) (S36-S39)
13. **^1H NMR, ^{13}C NMR and LC-MS spectra of compound 2f.** (Page 33-36) (S40-S43)
14. **^1H NMR, ^{13}C NMR and LC-MS spectra of compound 2g.** (Page 37-40) (S44-S47)
15. **^1H NMR, ^{13}C NMR and LC-MS spectra of ^{18}O -labeled compound 2.** (Page 41-43) (S48-S50)

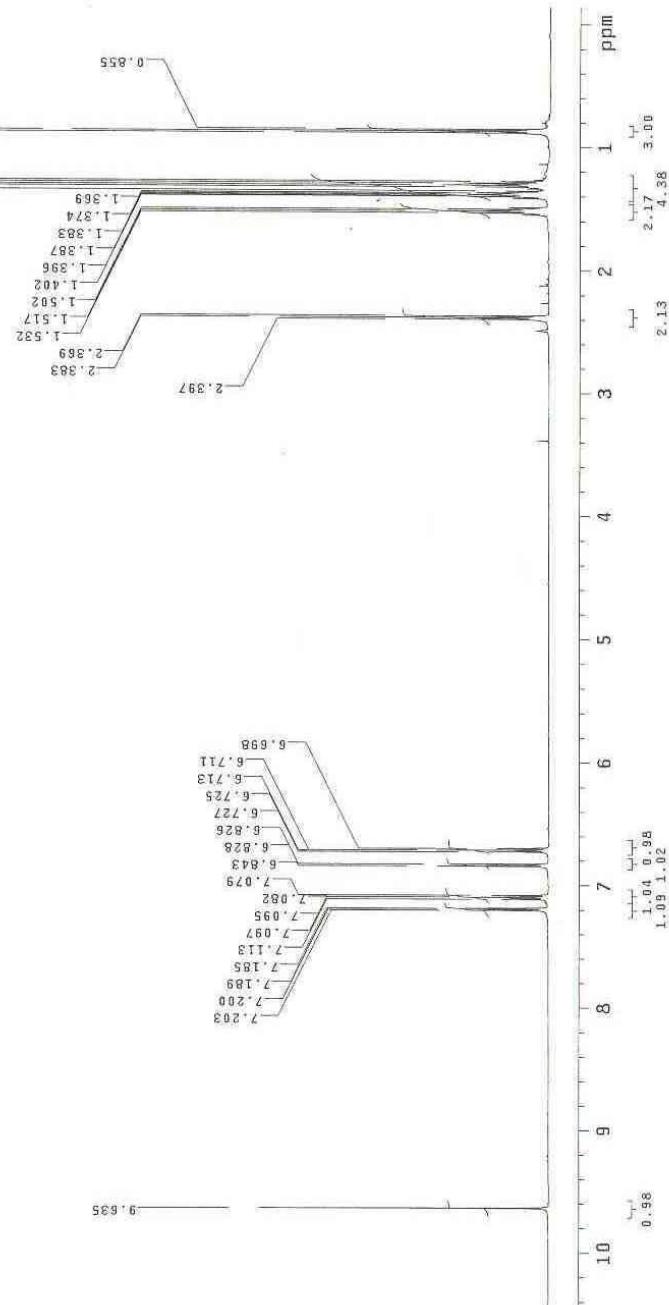
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DATA PROCESSING
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Time 0 min, 23 se

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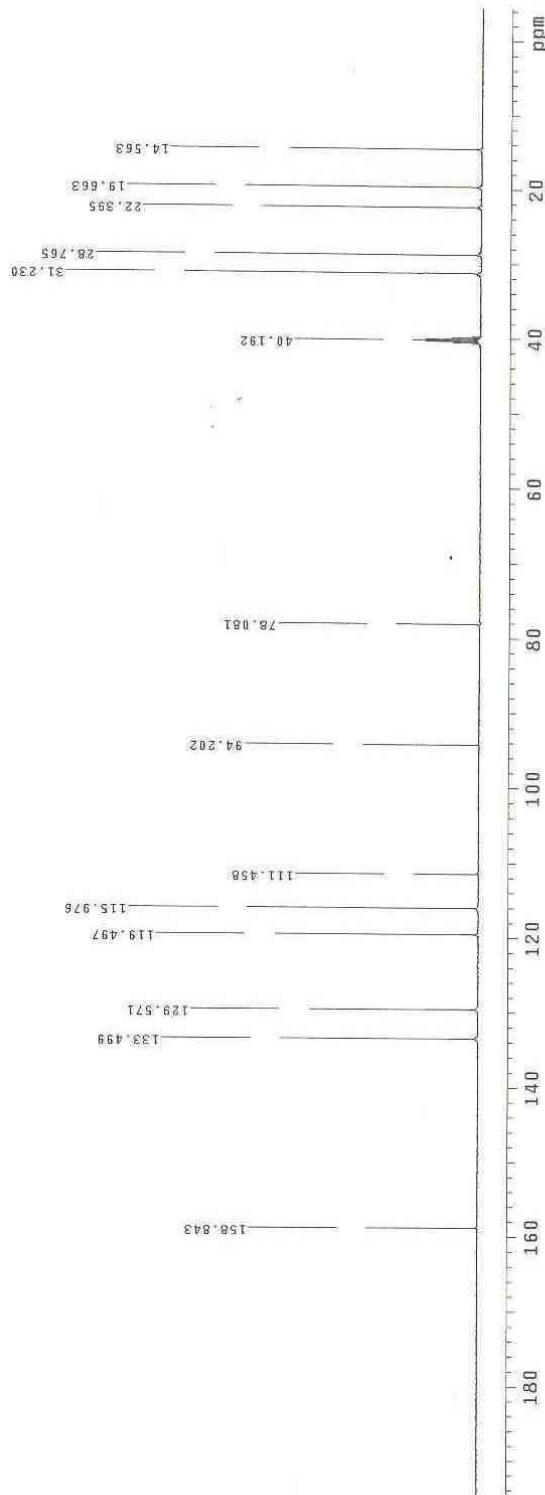
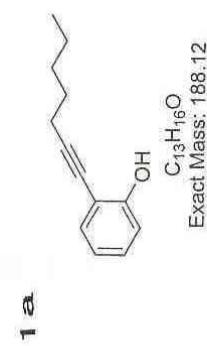
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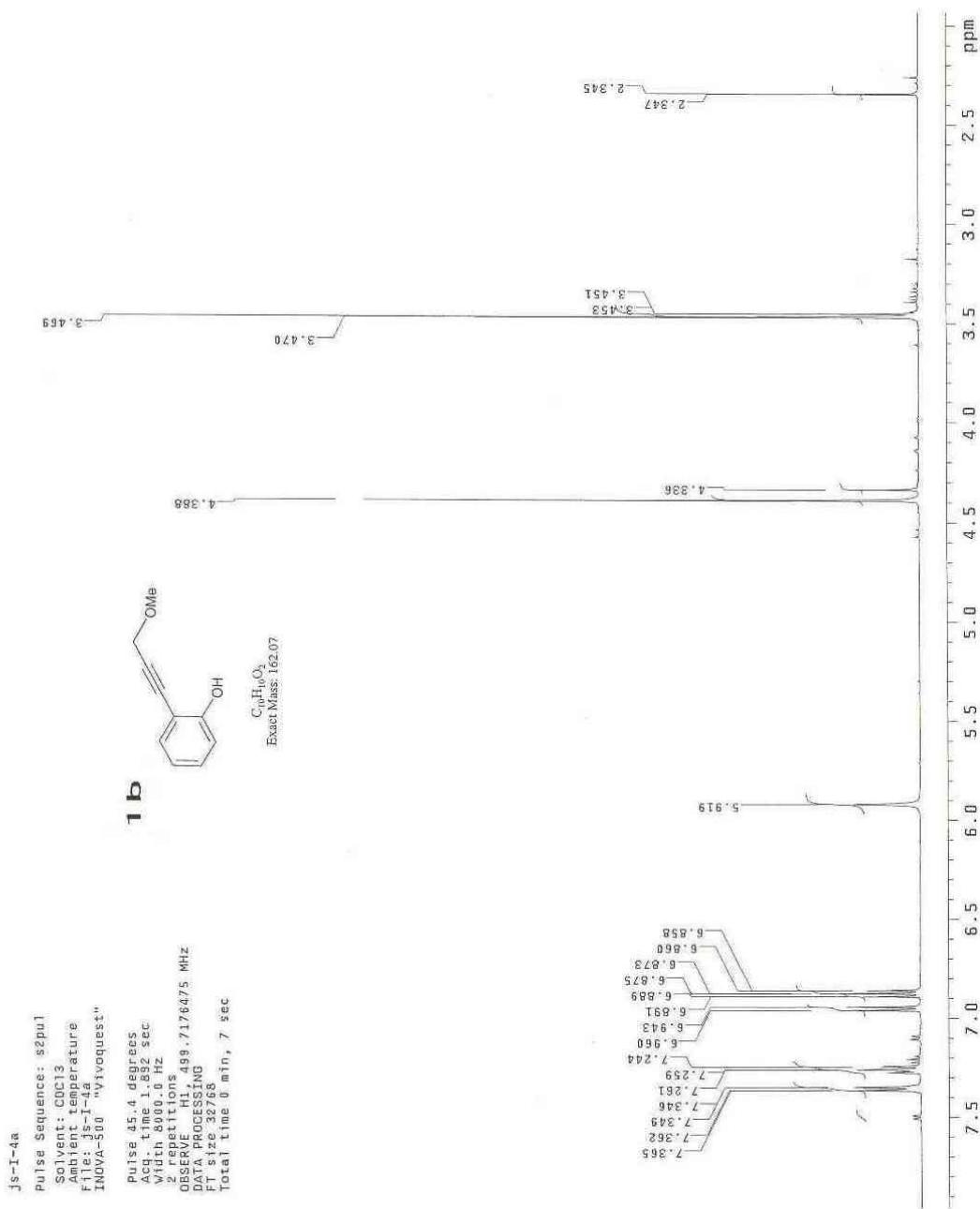


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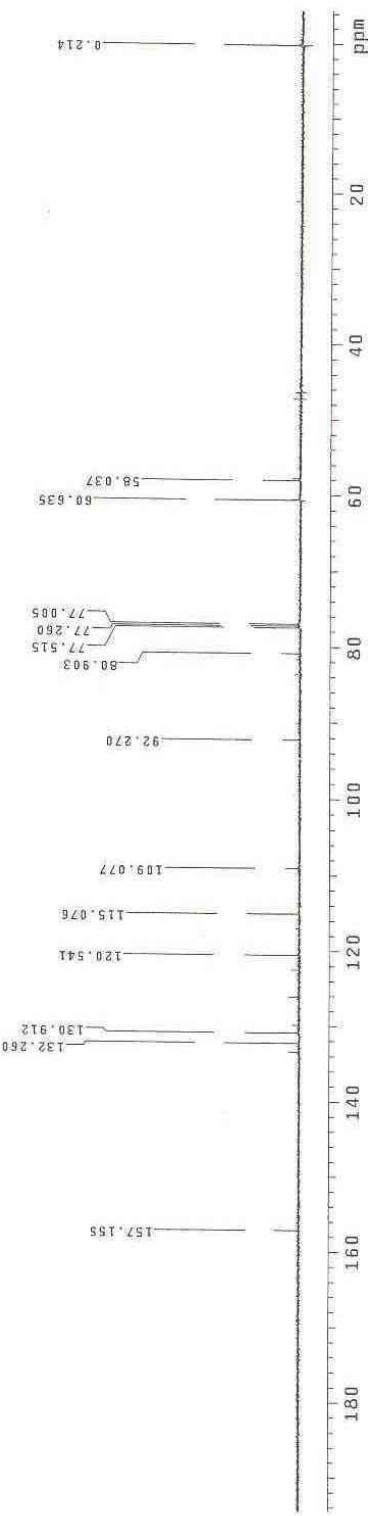
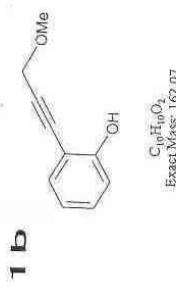
B36-2
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Ambient temperature
User: 1-14-87
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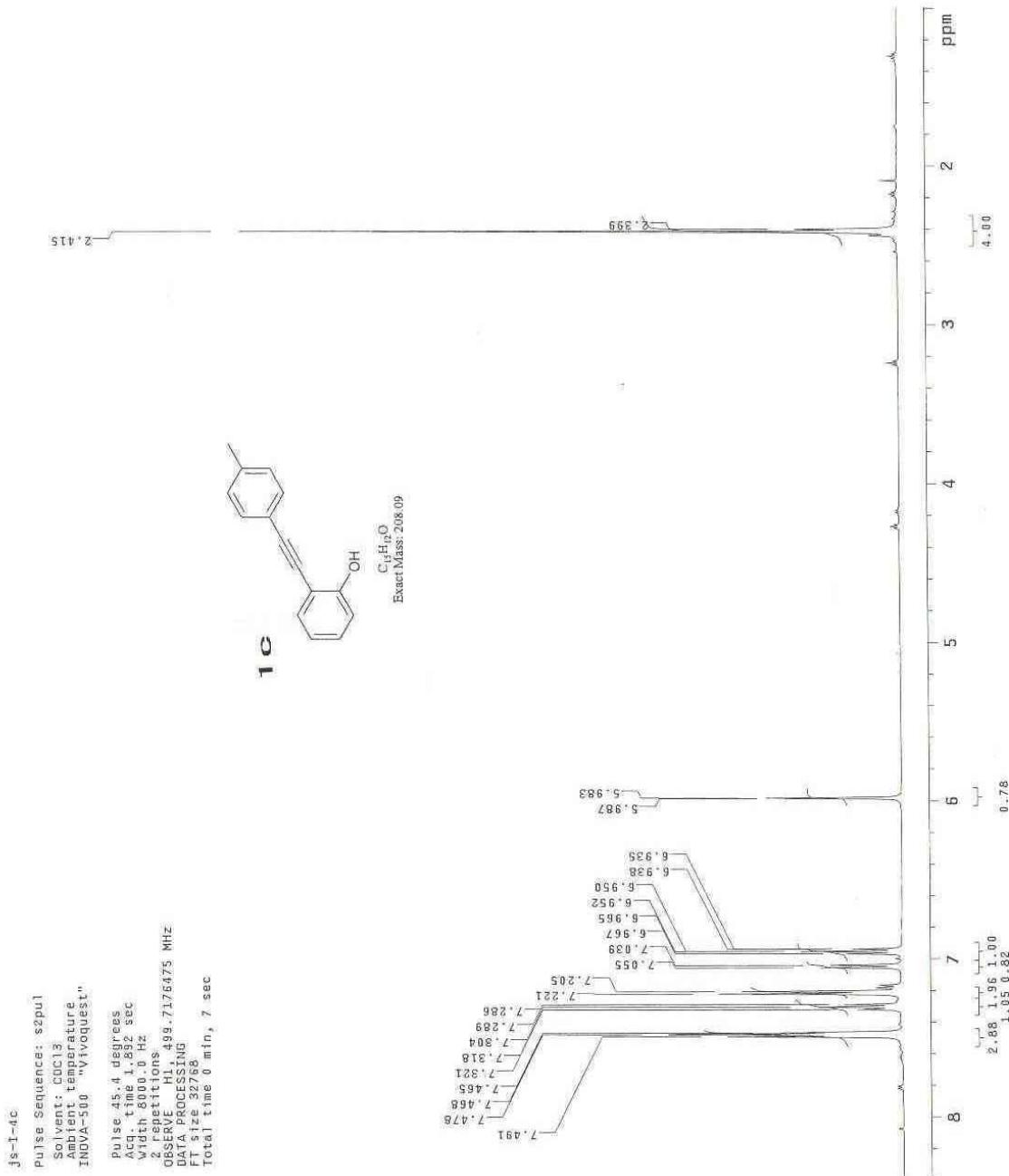
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Width 2500.0 Hz
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power 41 dB
continuously on
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Total time 3 hr, 38 min, 16 sec

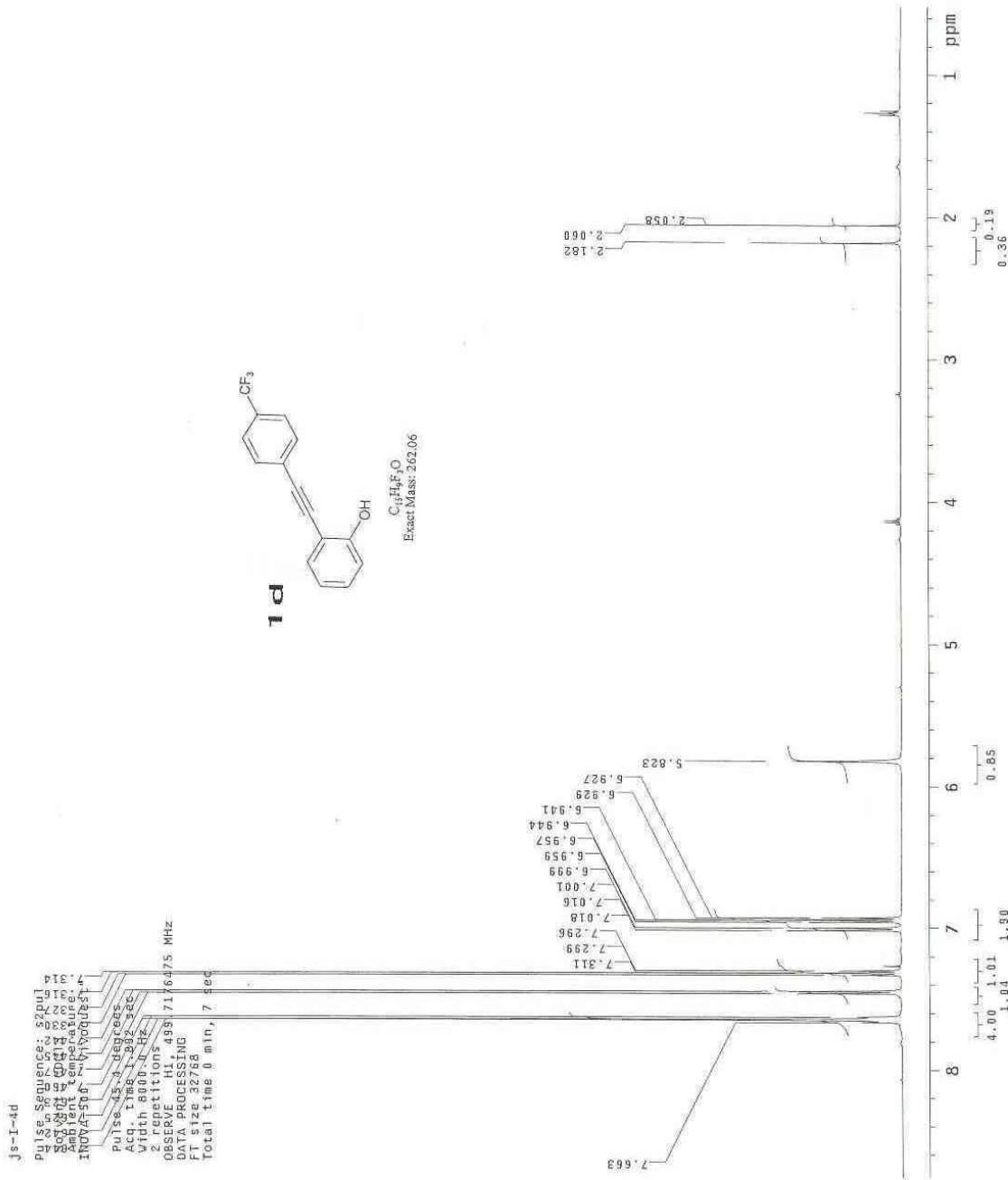


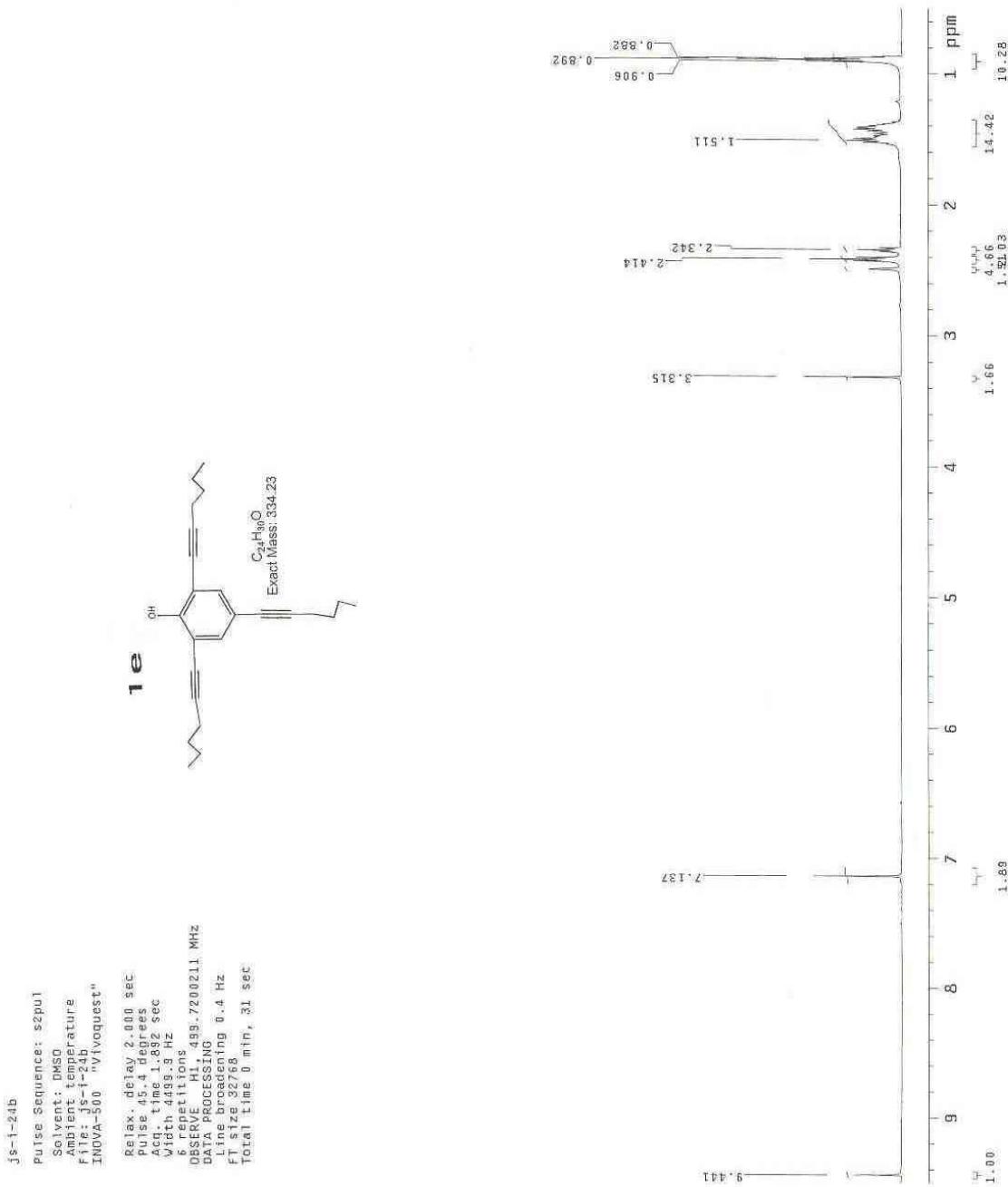


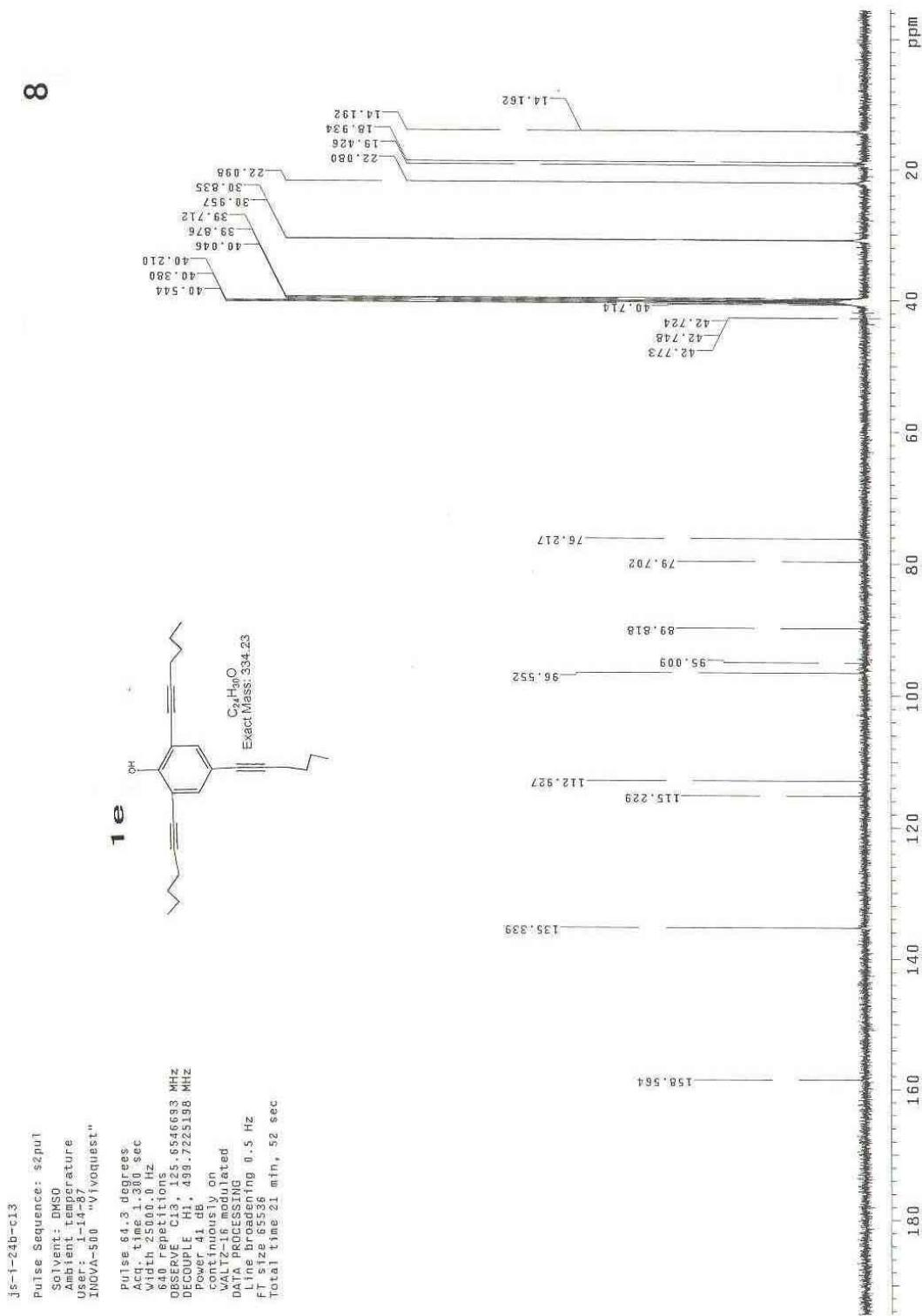
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 User: 1-4-87
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 DECOUPLE H1, 199.7201462 MHz
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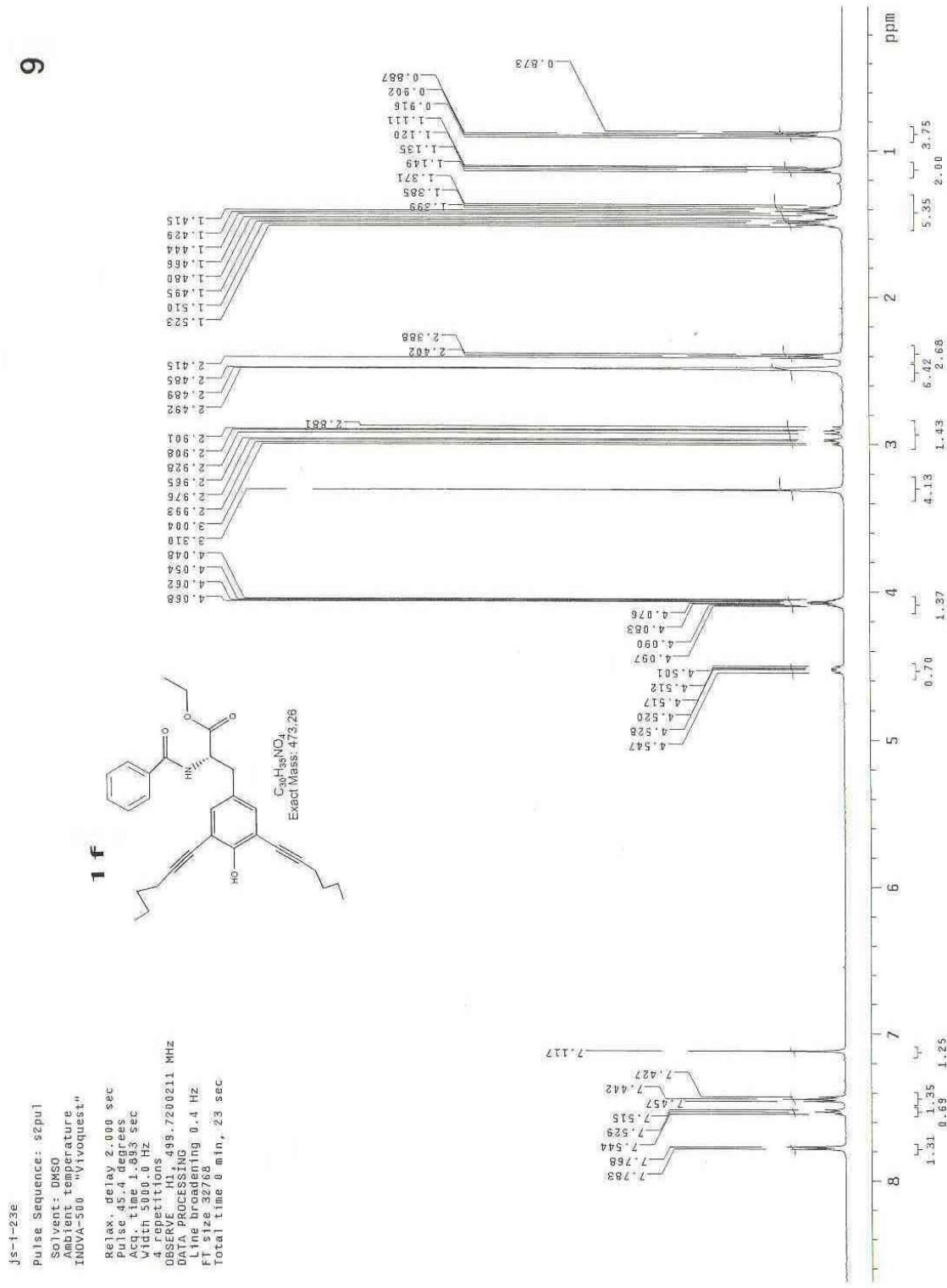


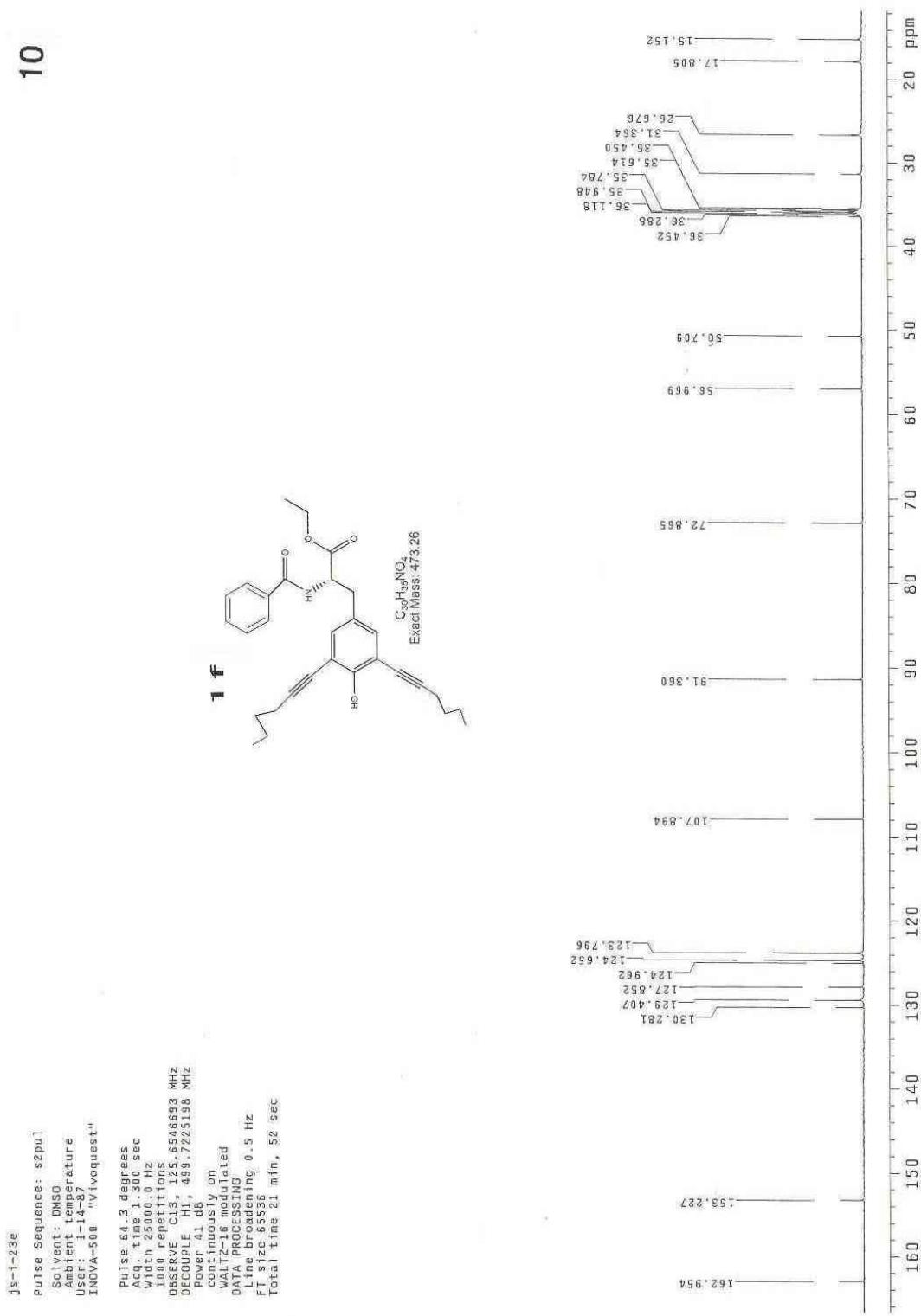


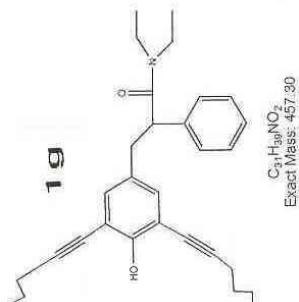




9







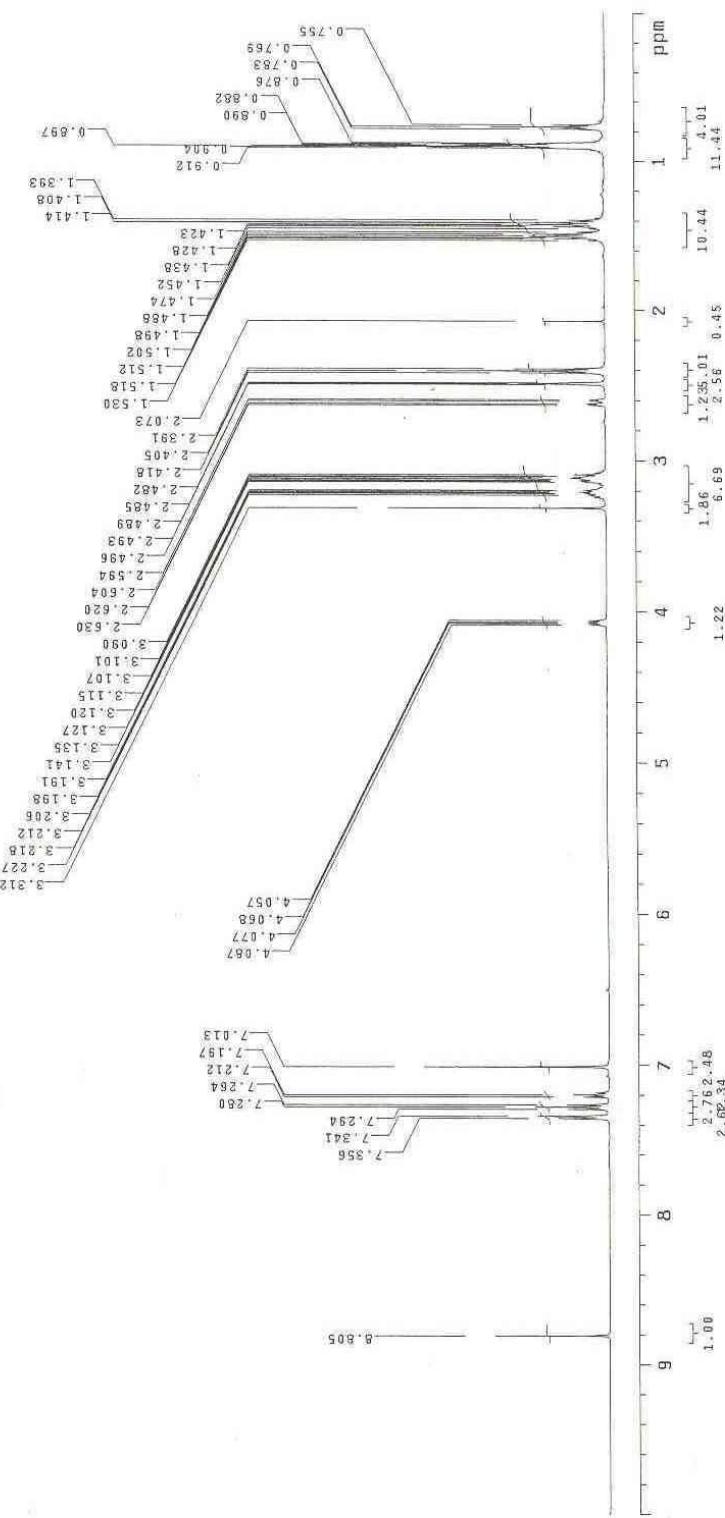
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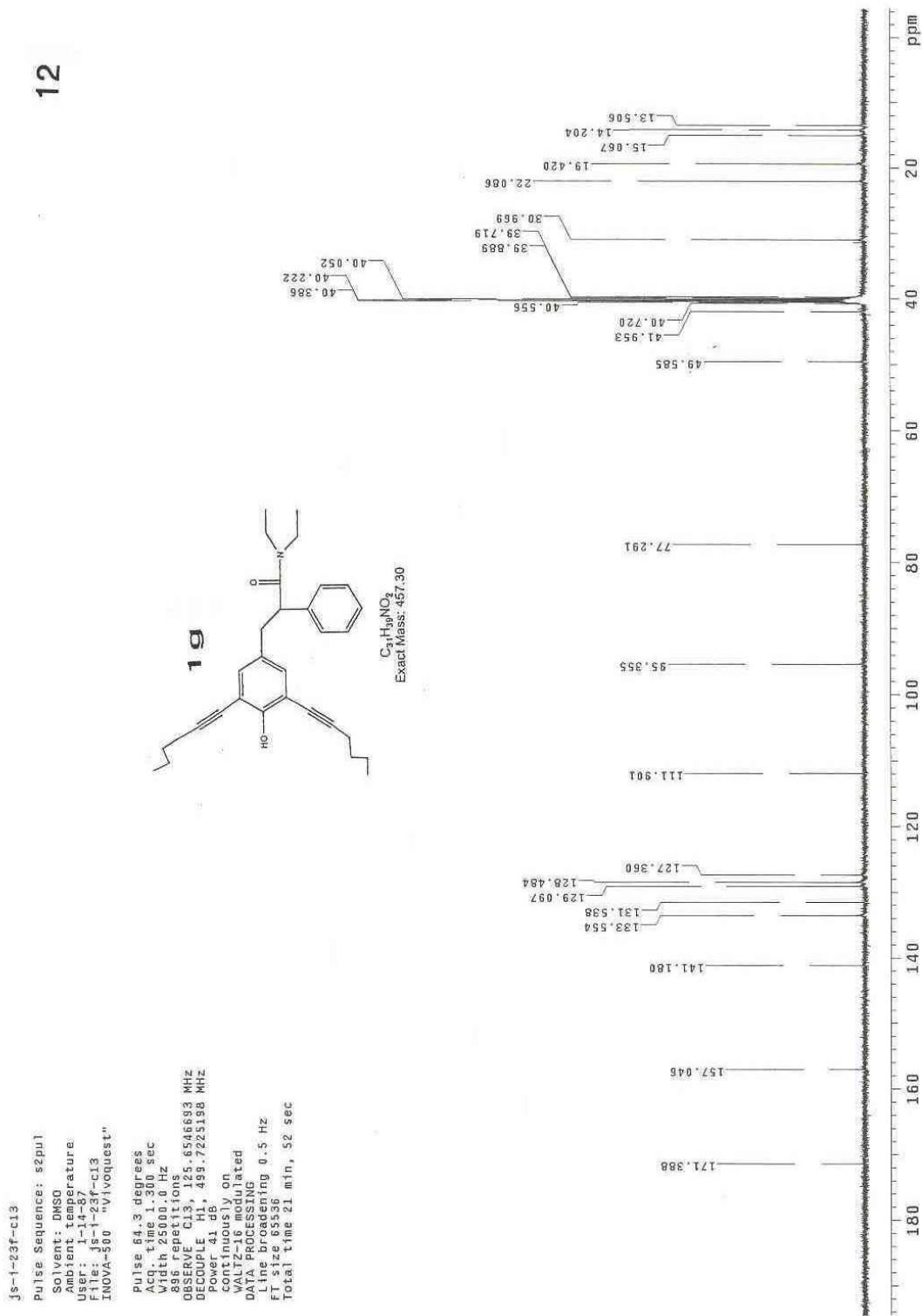
S2p1
Sequence: S2p1
Sovient: DRSO
Ambient temperature
INDIV-A-500 "Inquest"

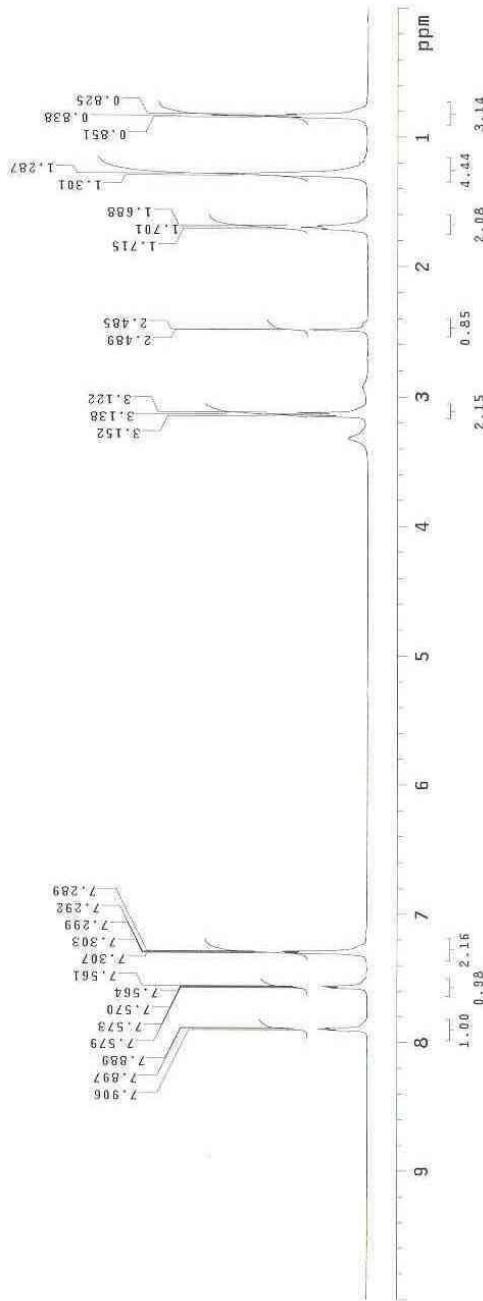
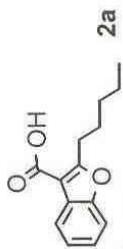
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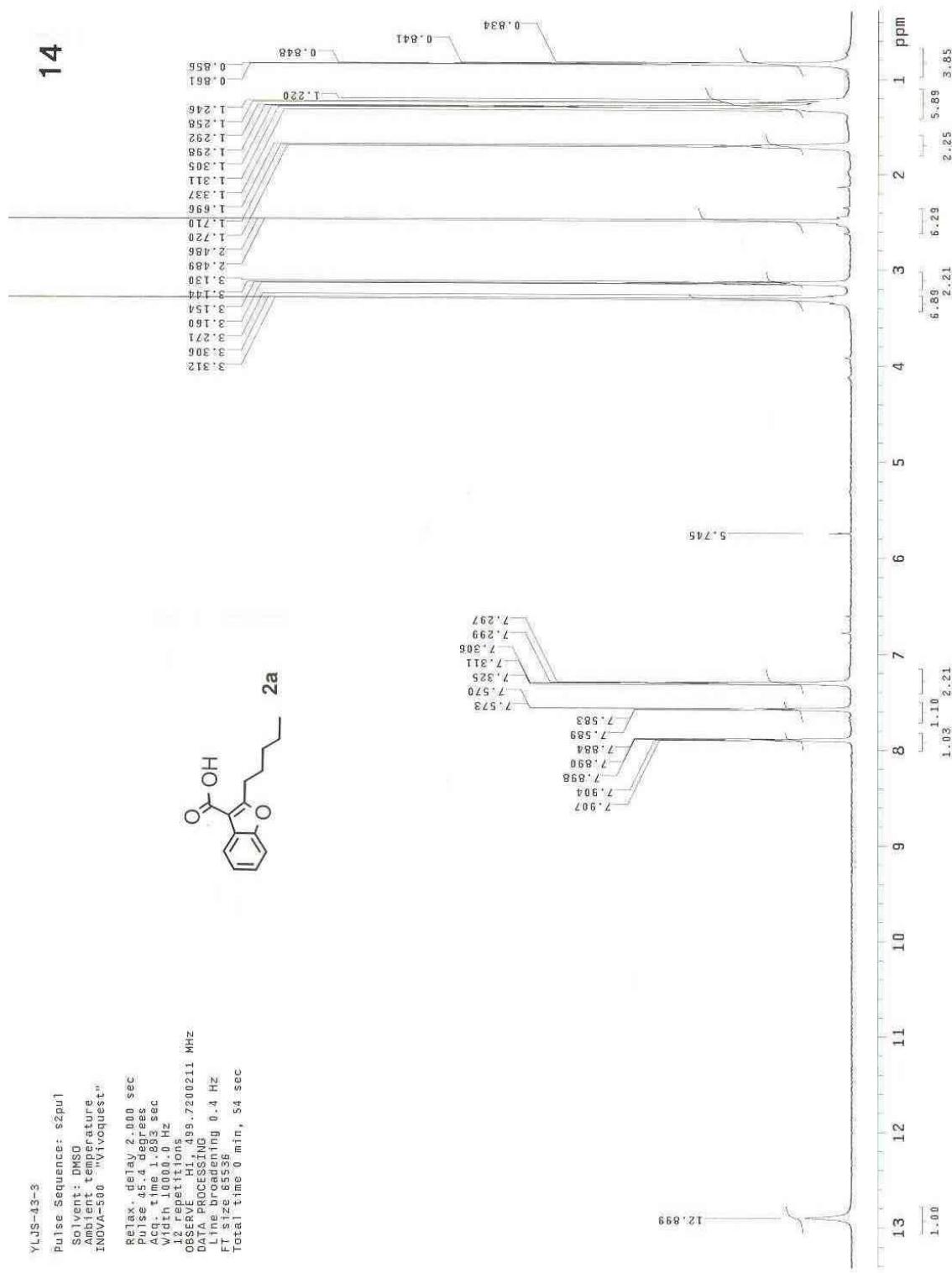
Relax. delay 2.000 sec
 Pulse 45.4 degrees
 ACH. Time 1.833 sec
 With 5000.0 Hz
 4 repetitions

OBSEERVE H1. 499.7200211 MHz
 A PROCESSING
 LINE broadening 0.4 Hz
 FFT size 3788
 23 sec









STANDARD CARBON PARAMETERS

Pulse Sequence: \$2p1

Scans: DMSO

Ambient temperature

User file: 141-87

File: b13-1-3-13

INIVA-500 "Vivionquest"

Pulse: 64.3 degrees

Acq. time: 1.30 sec

Width: 5000.0 Hz

156 repetitions

OBERVE: C13, 125.6546693 Hz

DEBOUCLE: HI, 49.725198 Hz

POWER: 41 dB

continuously on

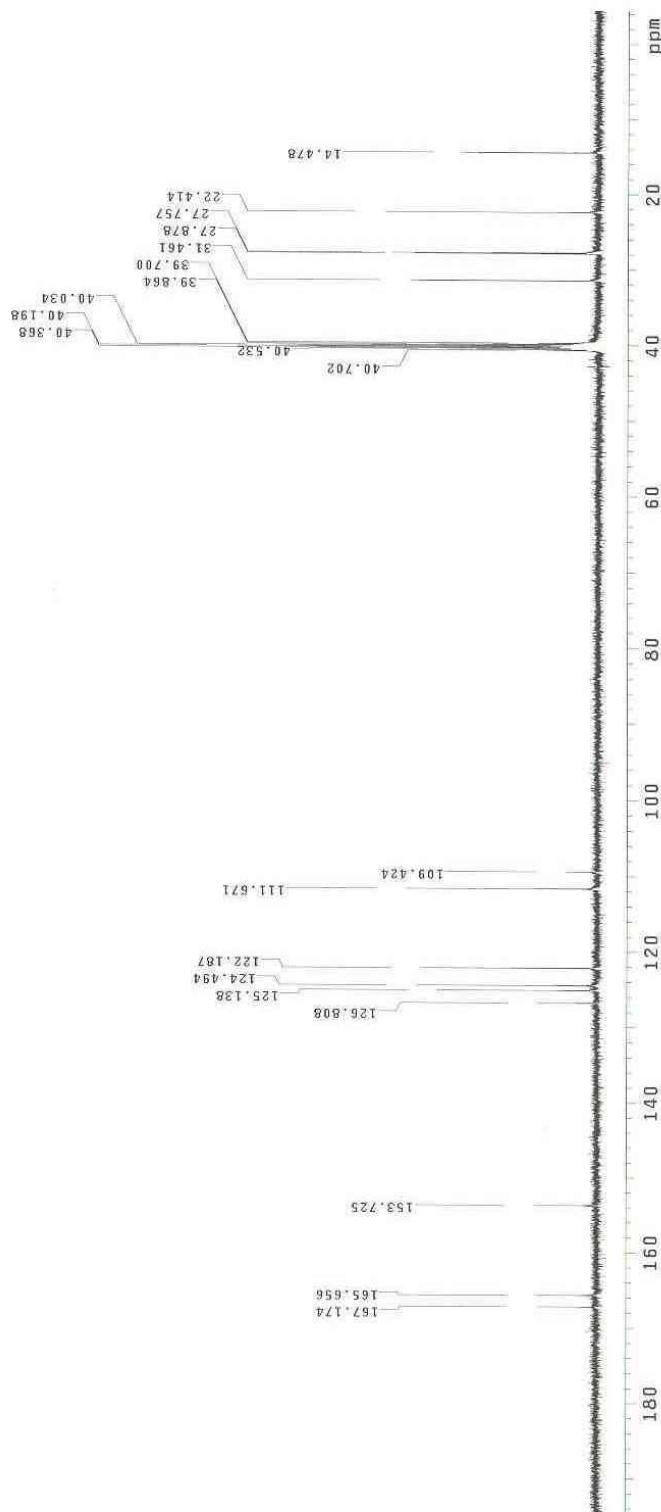
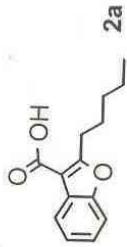
WAVL: 16 modulated

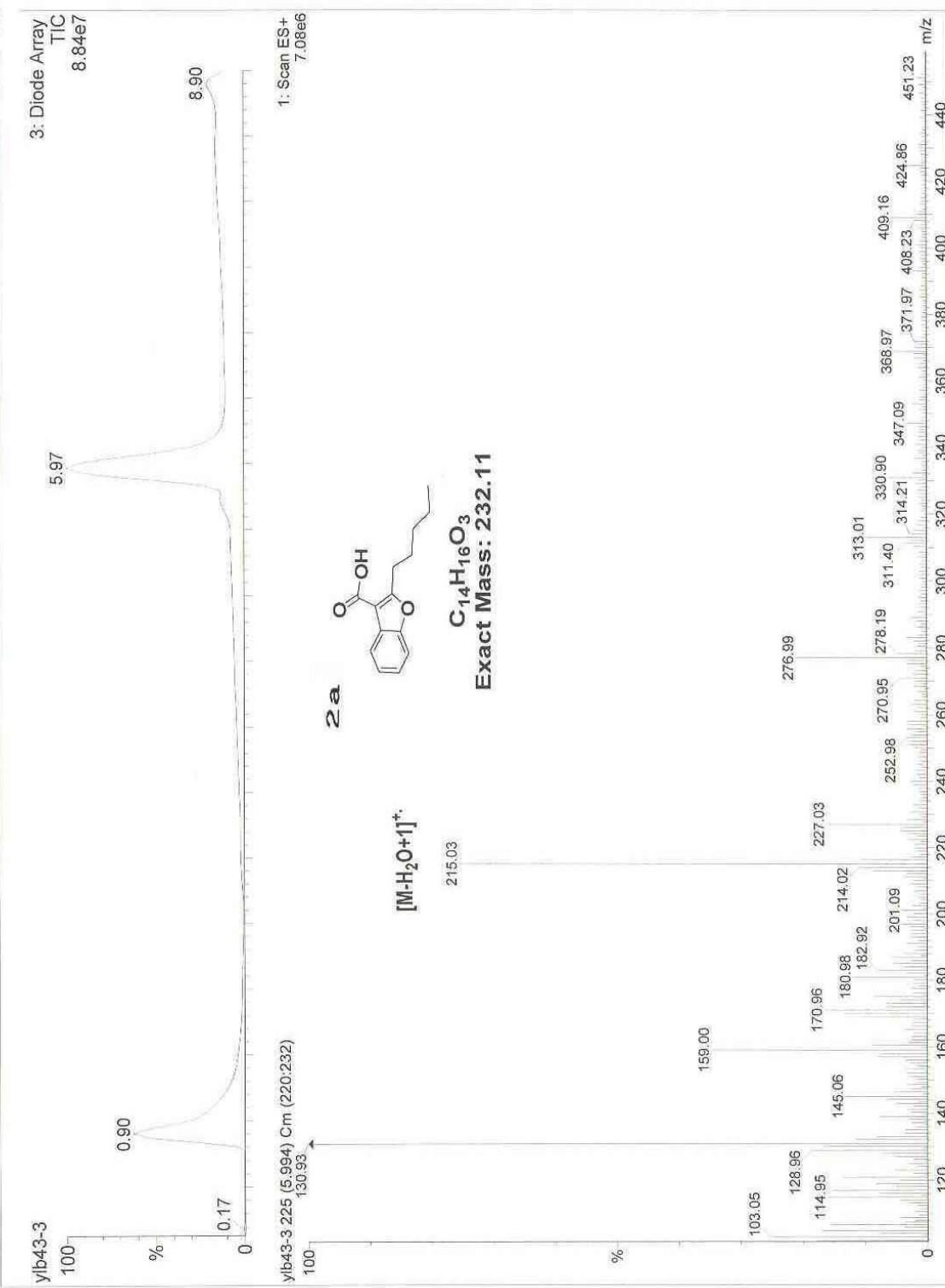
DATA PROCESSING

LINE broadening: 0.5 Hz

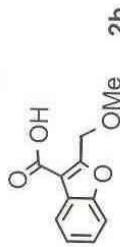
FS: 1e 6536

Total time: 21 min, 52 sec





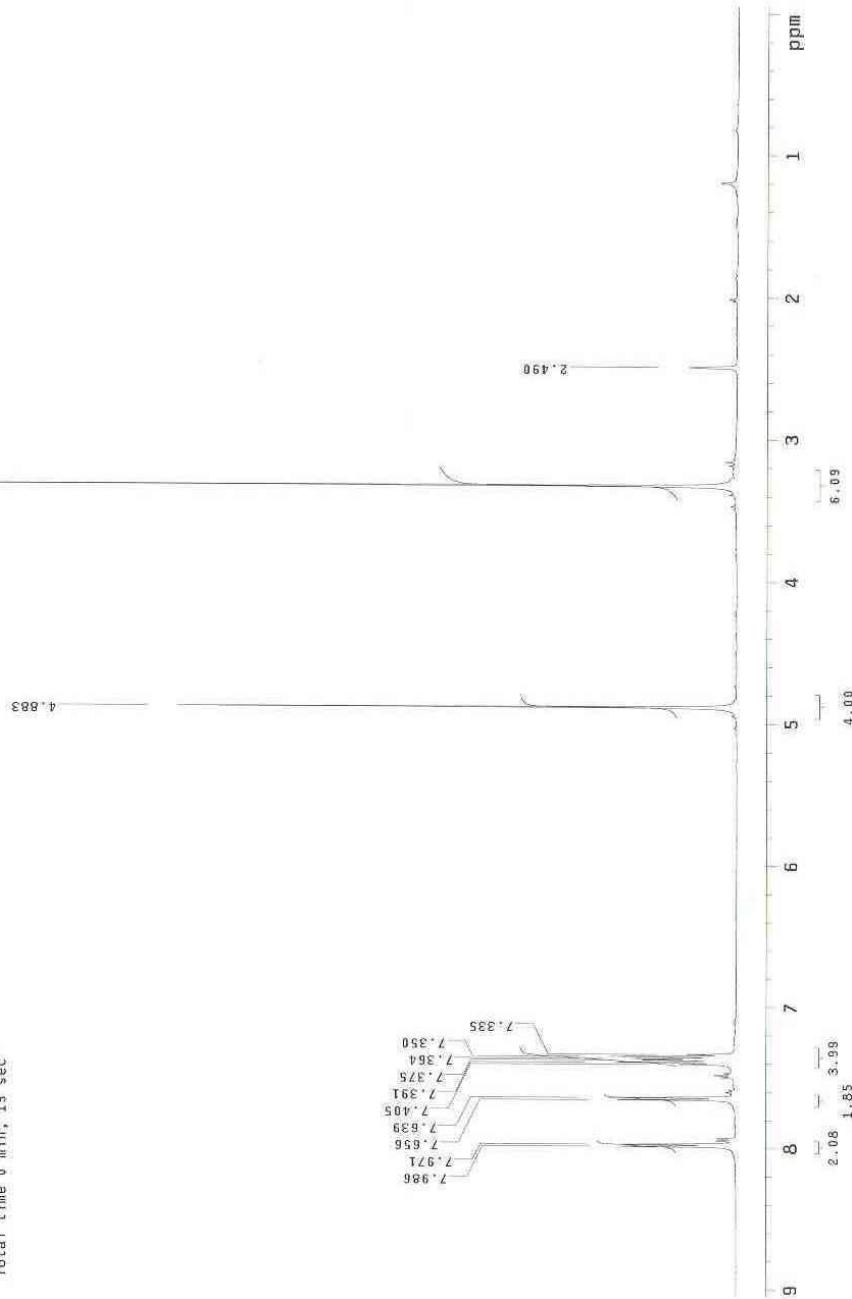
1

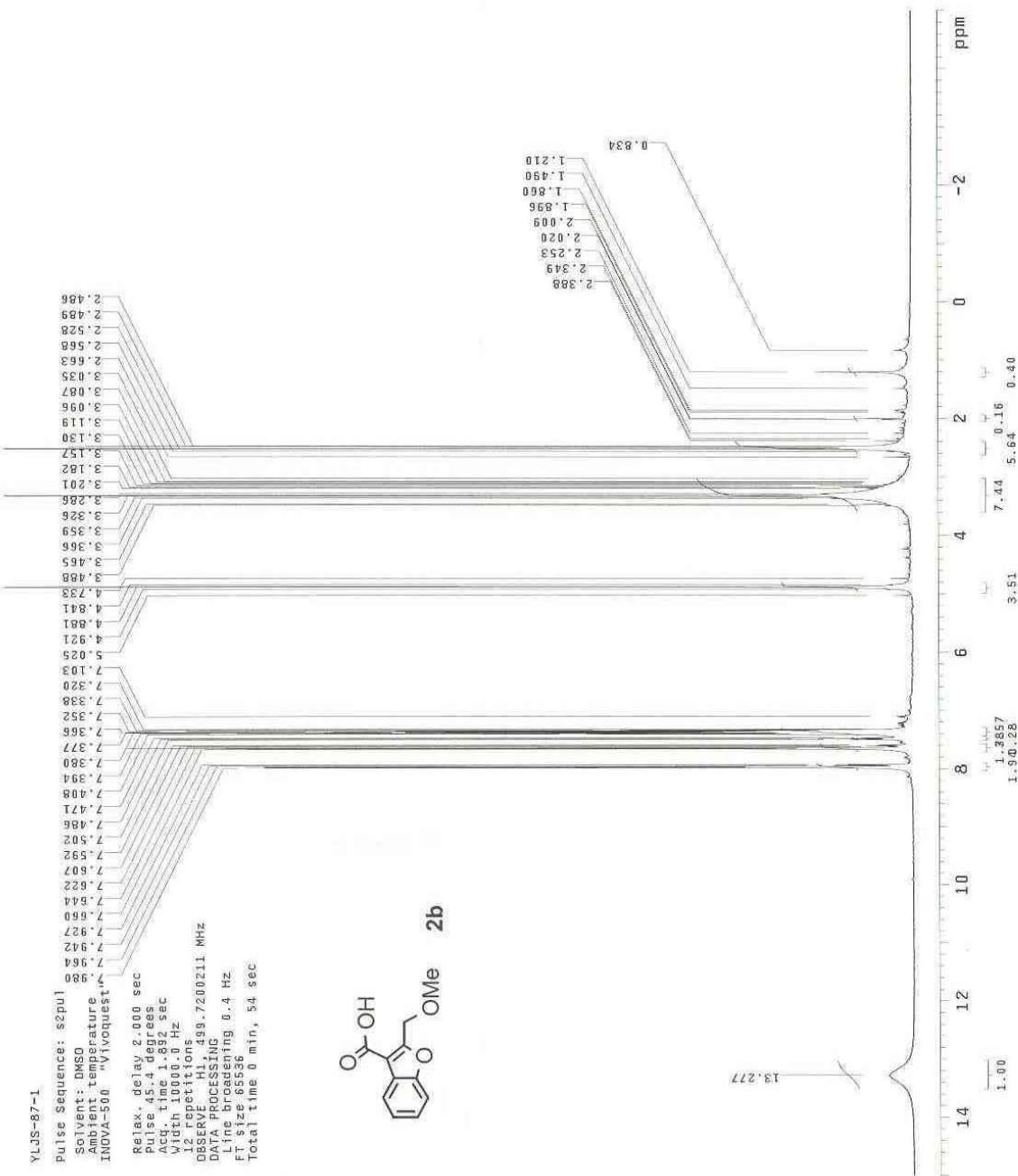


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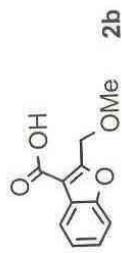
y\hb7-7

Pulse Sequence: s2p1
Solvent: DMSO
Ambient temperature
INNOVA-500 "Vivoxust"
```

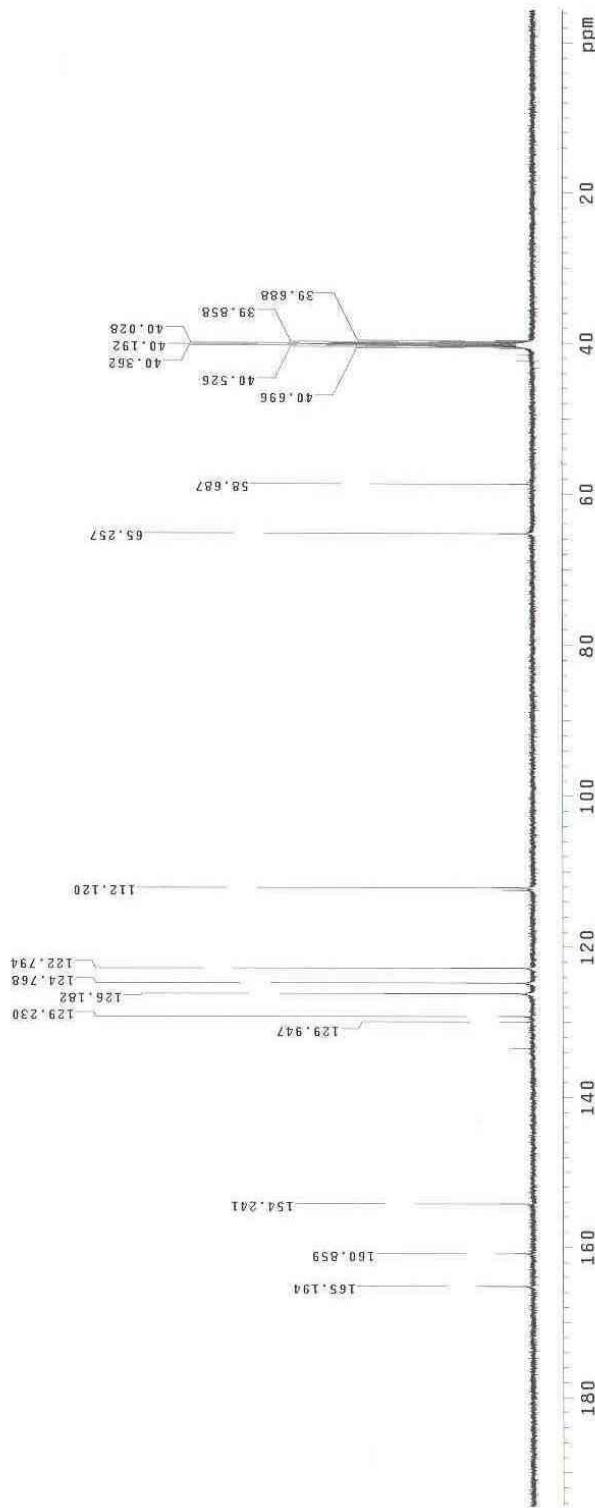


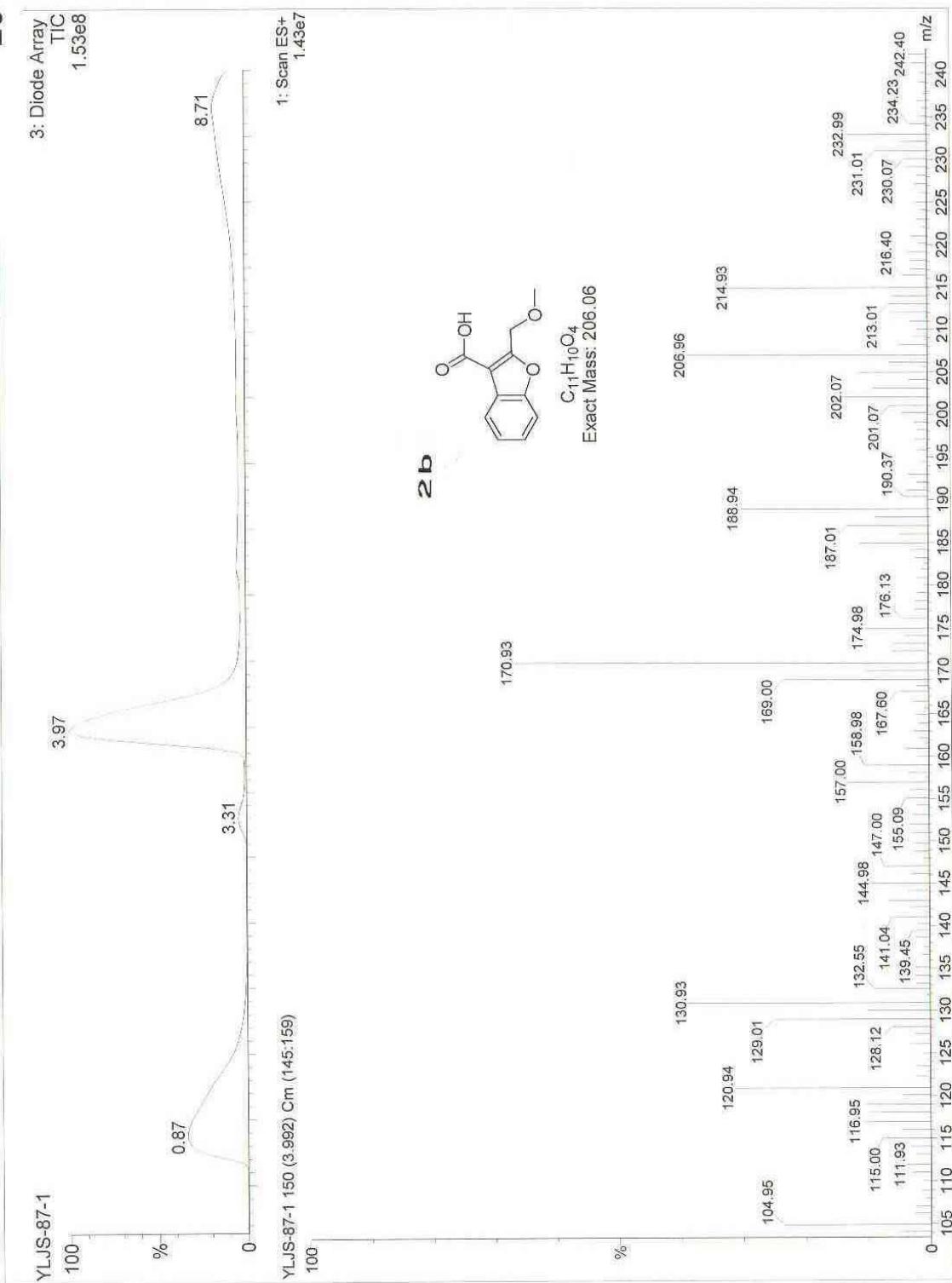


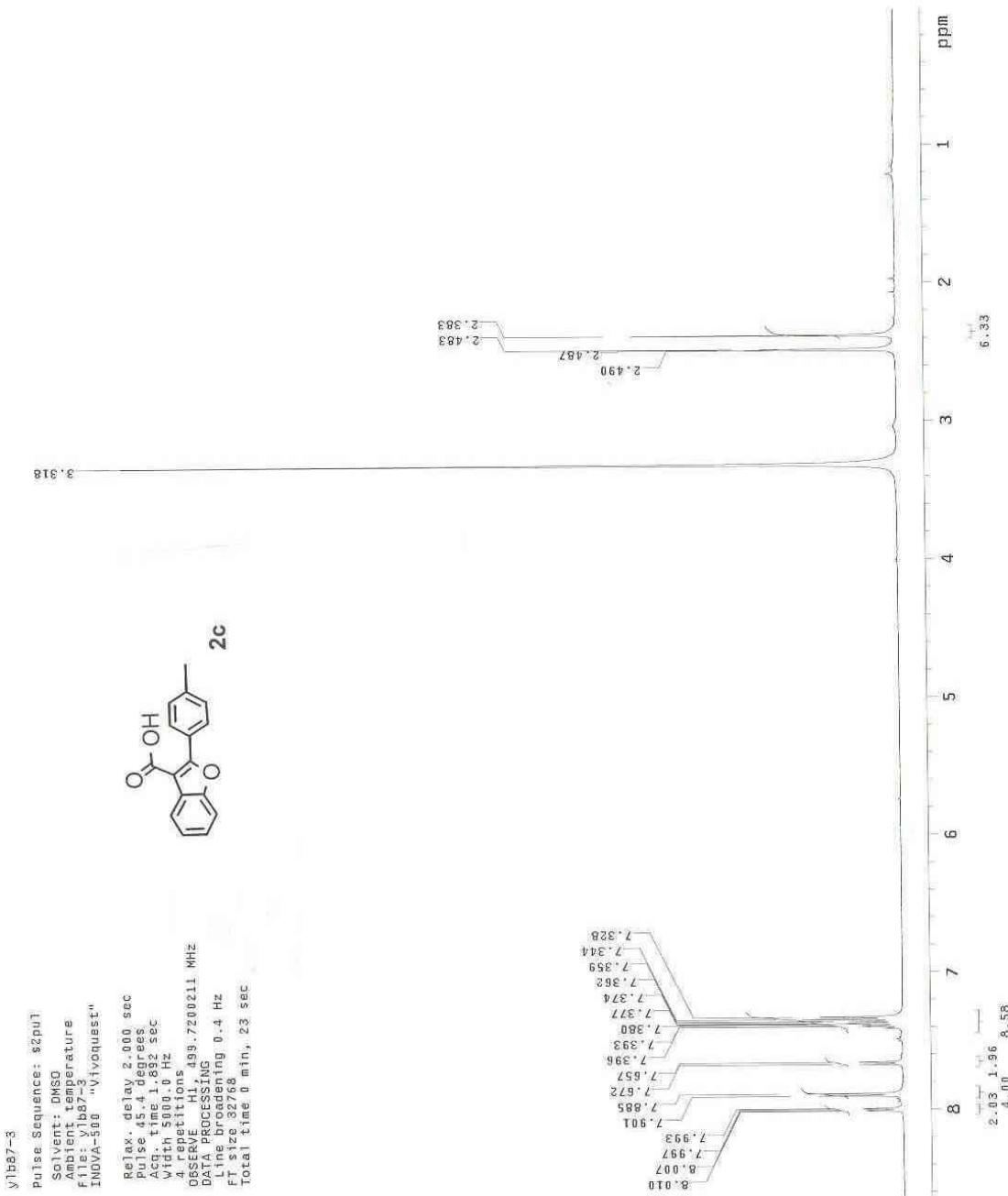
y1b87-1
 Pulse Sequence: s2pu1
 Solvent: DMSO
 Ambient temperature
 User: 1-14-87
 INOVA-500 "Vivoduest"
 Pulse: 64.3 degrees
 Acq. time 1.300 sec
 Width 25000 Hz
 384 repetitions
 QSPRF1C13, 125, 6546693 MHz
 DECODE1, H1, 453, 725198 MHz
 Power 11, da
 Continuously on
 WALT-16 decimated
 DATA PROCESSING
 Line broadening 0.5 Hz
 FT size 65536
 Total time 21 min, 52 sec

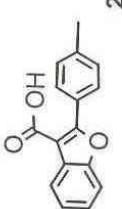
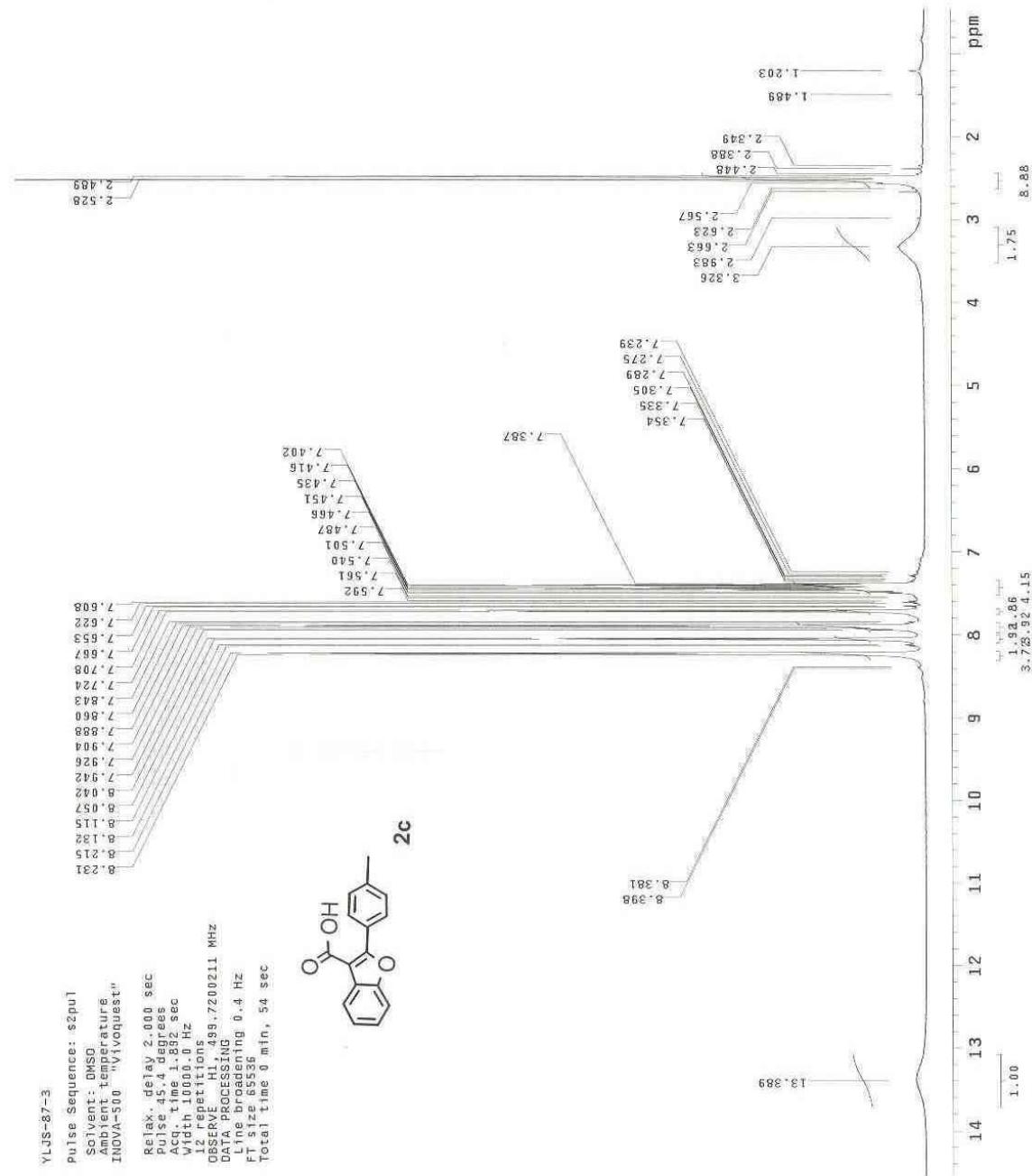


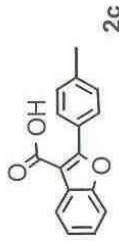
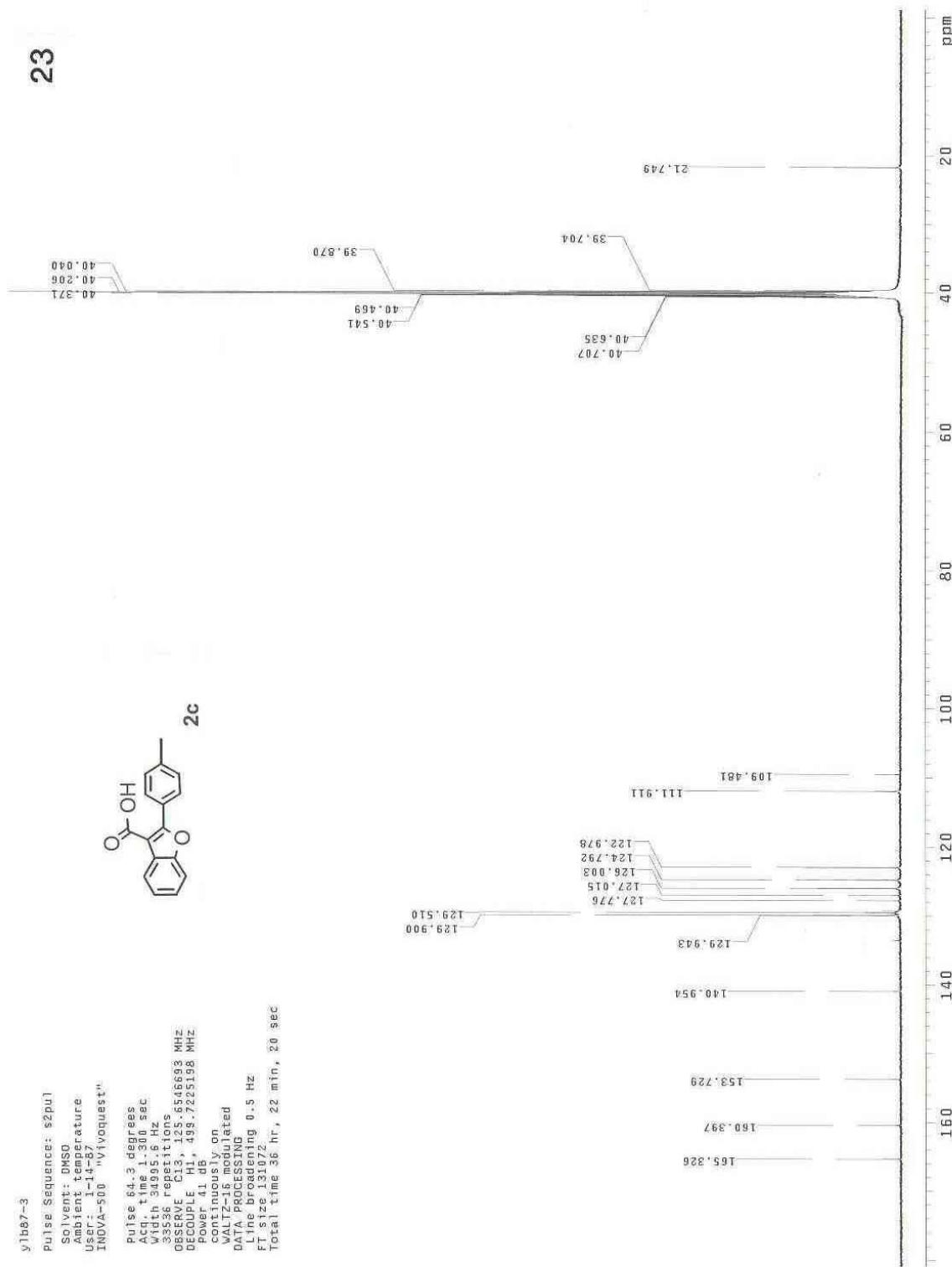
2b











```

y\hb@-3 Pulse Sequence: $pup
      Solvent: DMSO
      Ambient temperature
      User: "1-14-87"
      INSTRUM="500-MX/1V0quest"

```

Pulse 64.3 degrees

Acc 1.30 sec

Width 3495.6 Hz

33536 repetitions

DESYEVE 113, 125, 6546

DCOUPLE 11, 49, 7225

Power 41 dB

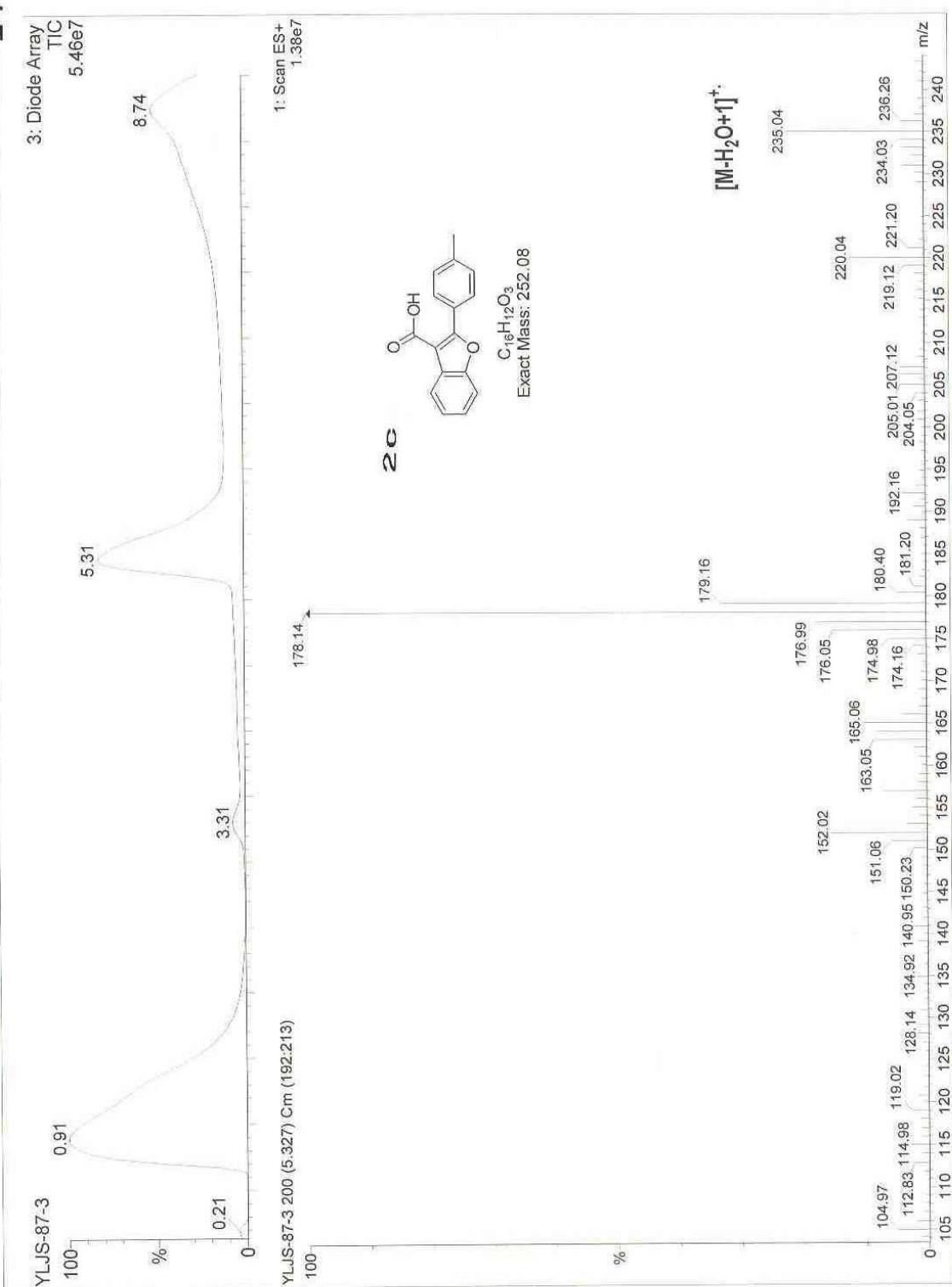
WALTZ-16 modulated

DATA PROCESSING

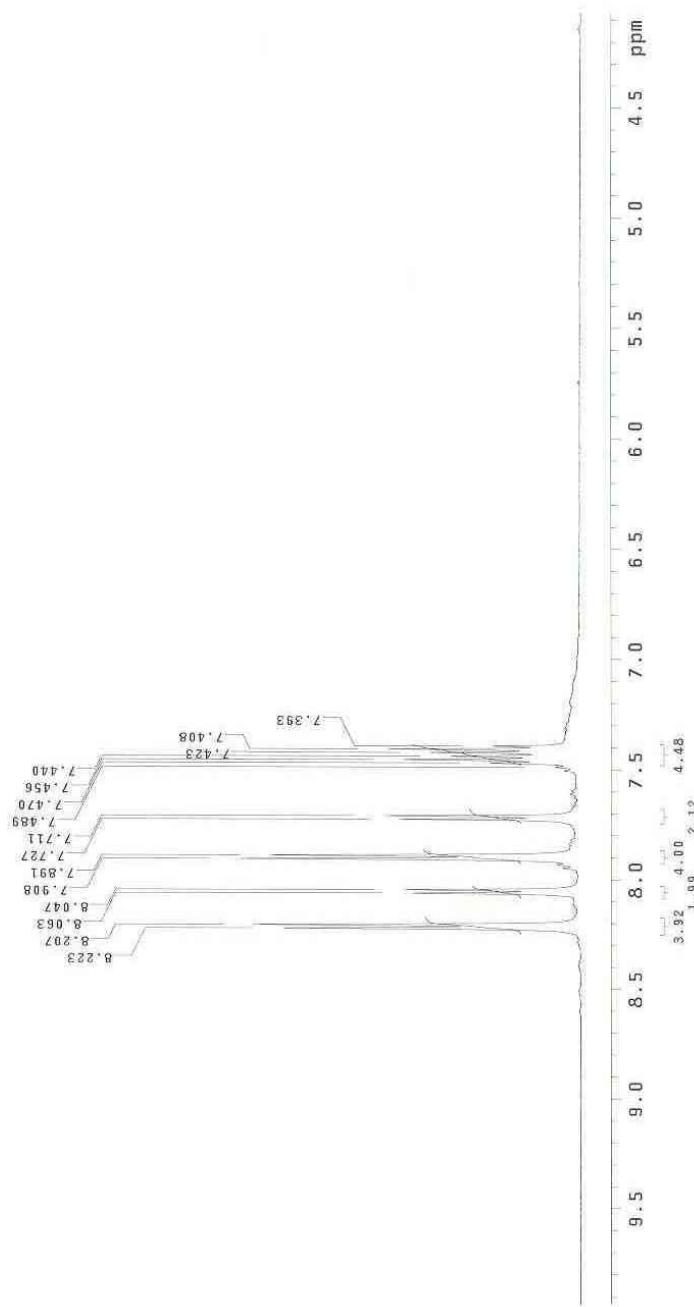
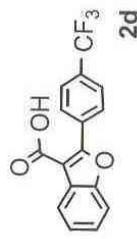
LINE BROADENING .5 Hz

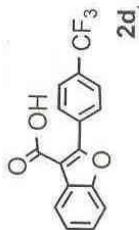
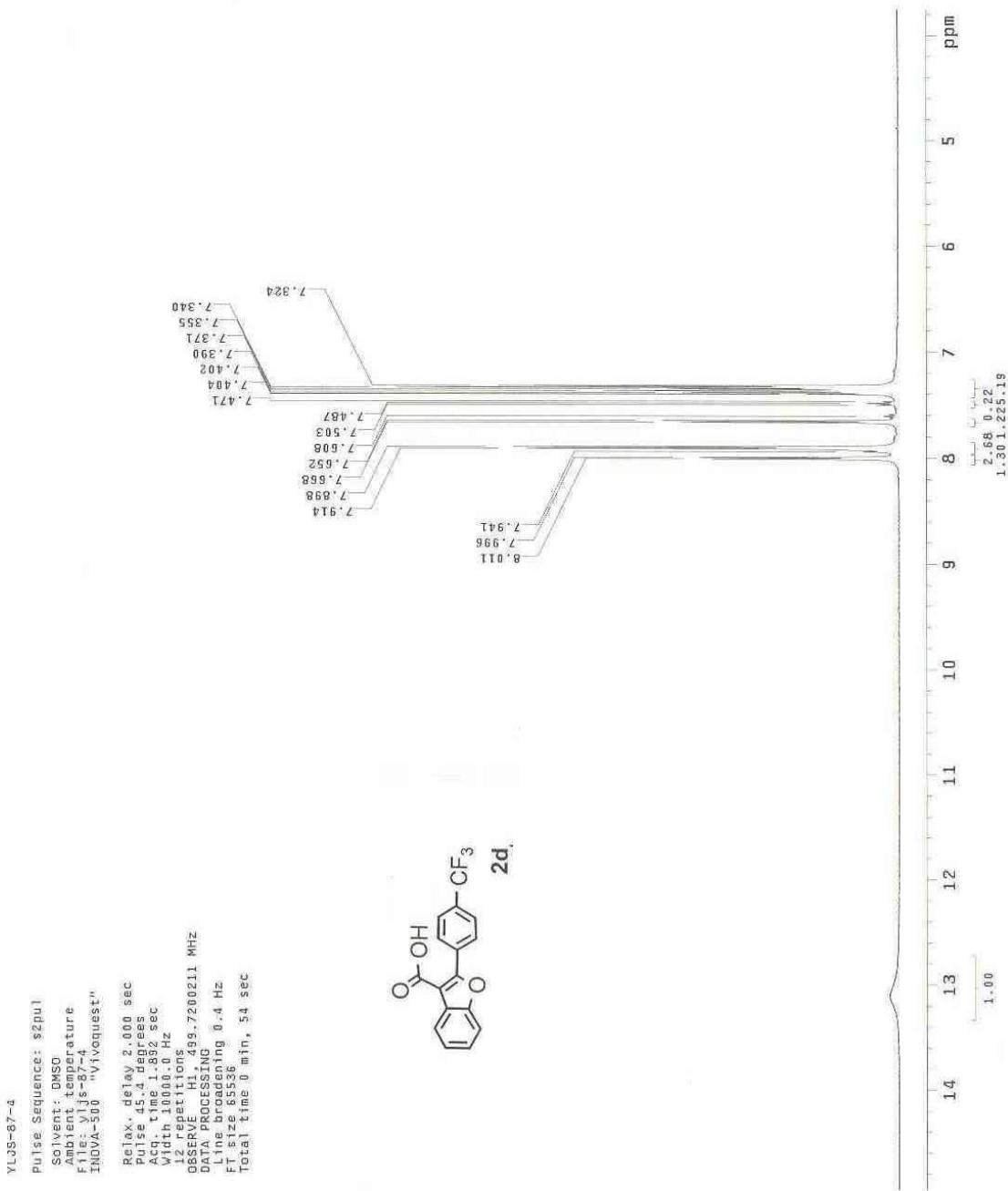
FT size 11000

FT Total time 36 hr, 22 m

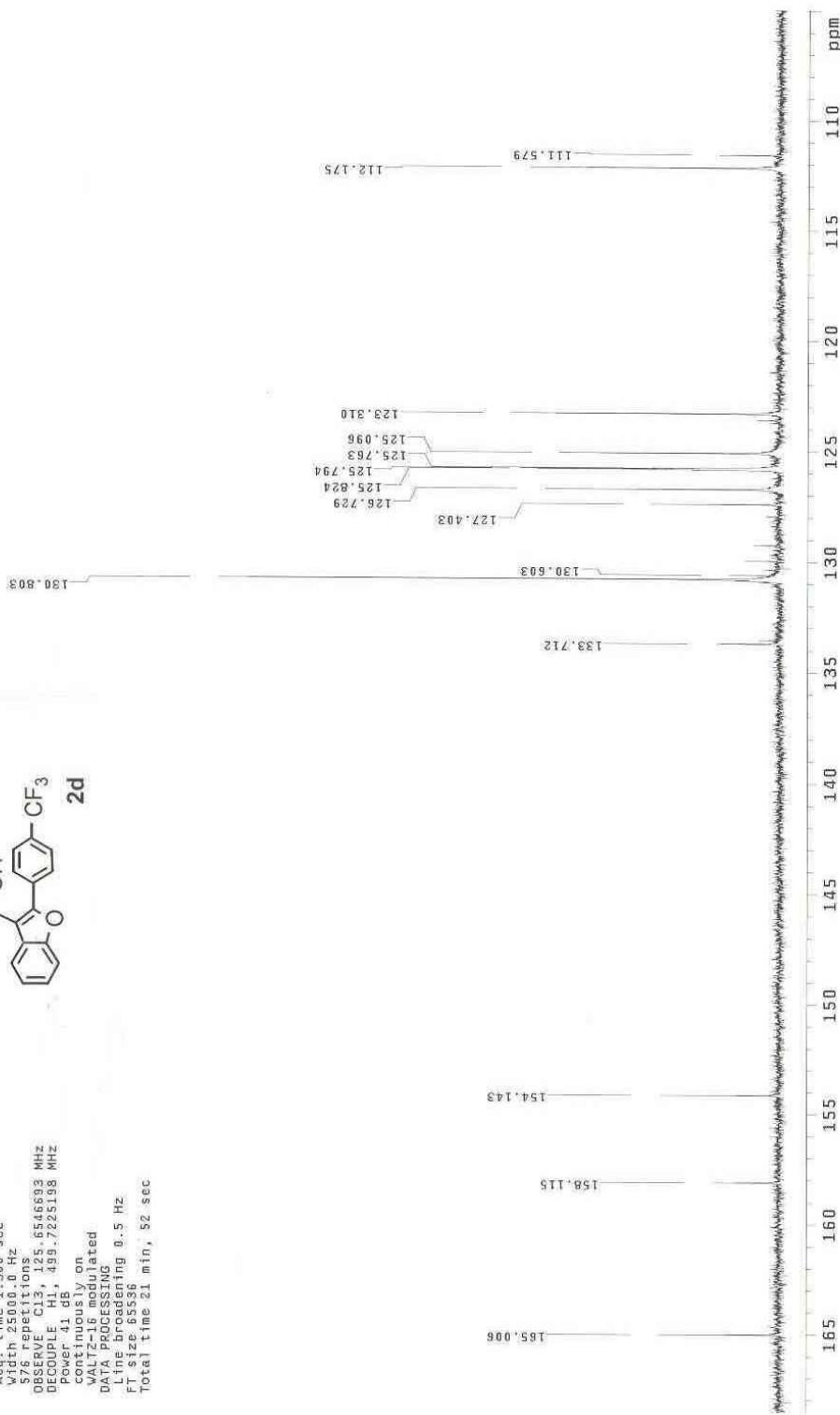
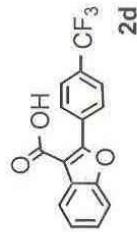


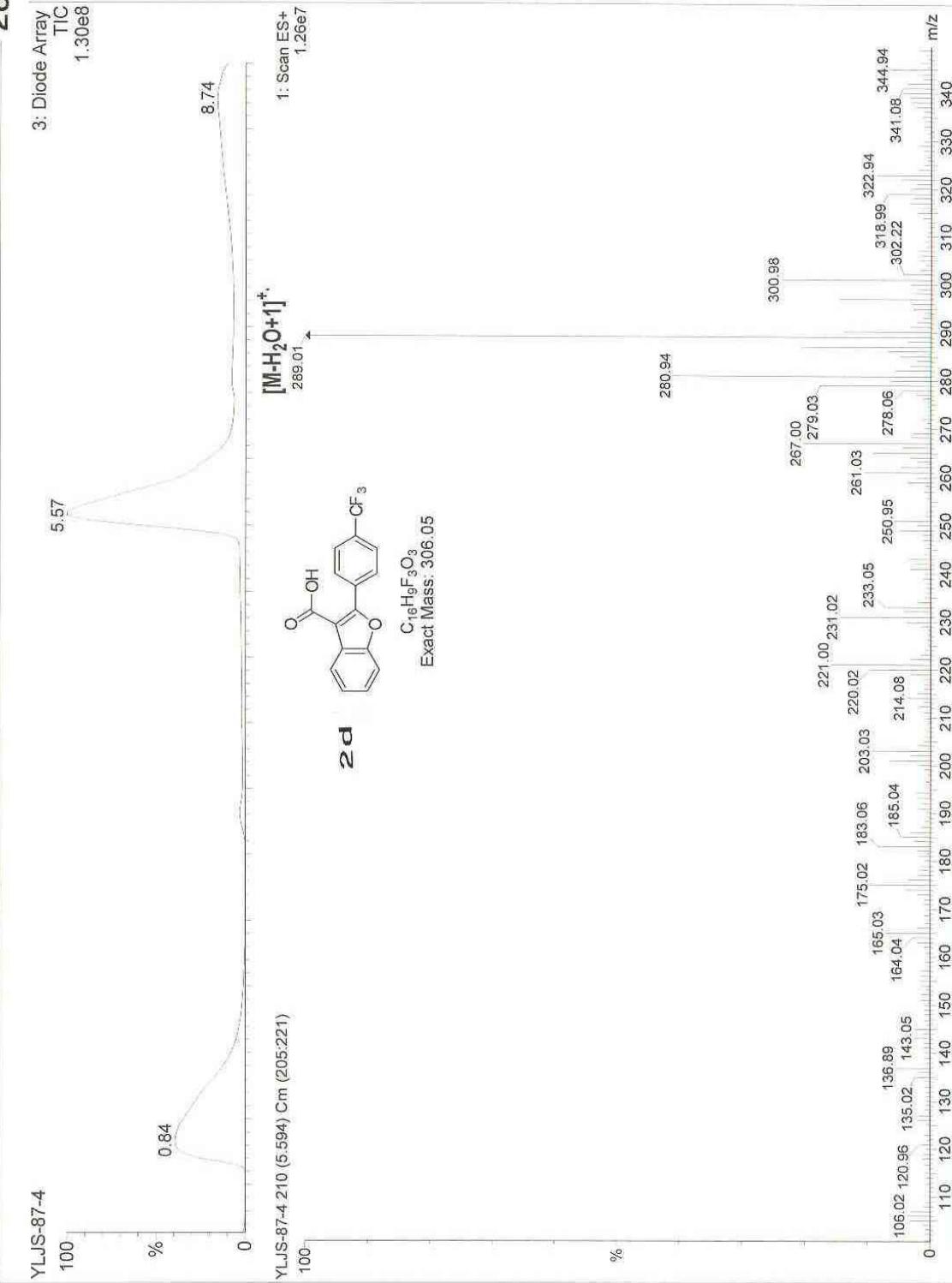
y1b37-4
 Pulse Sequence: s2pul
 Solvent: DMSO
 Ambient temperature
 INOVA-500 "Nyivquest"
 Relax. delay 2.000 sec
 Pulse 45.4 degrees
 Acc. time 1.892 sec
 Width 5000.0 Hz
 4 repetitions
 OBSERVE H1, 499.720211 MHz
 DATA PROCESSING
 Line broadening 0.4 Hz
 FT size 32768
 Total time 0 min, 23 sec

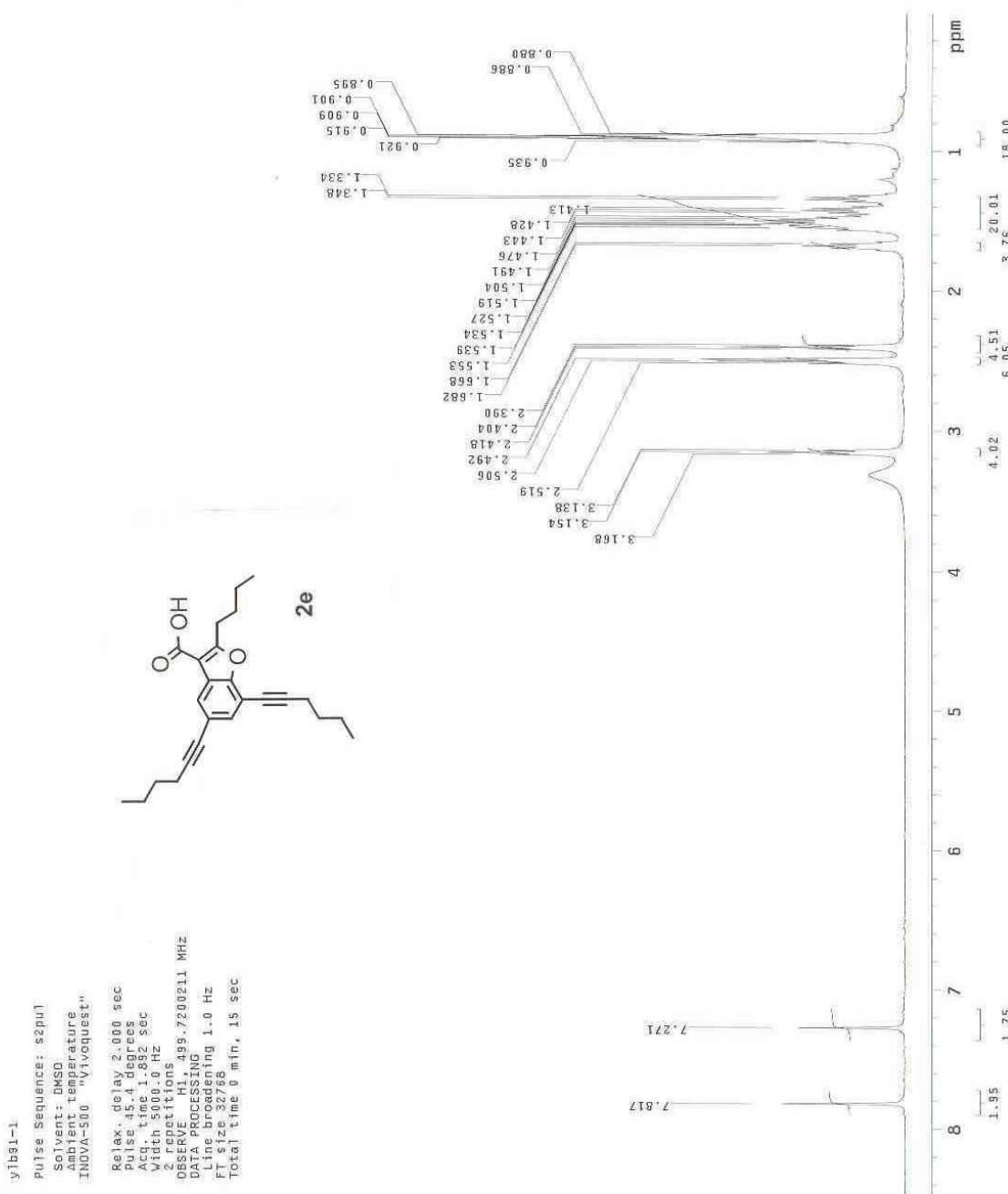


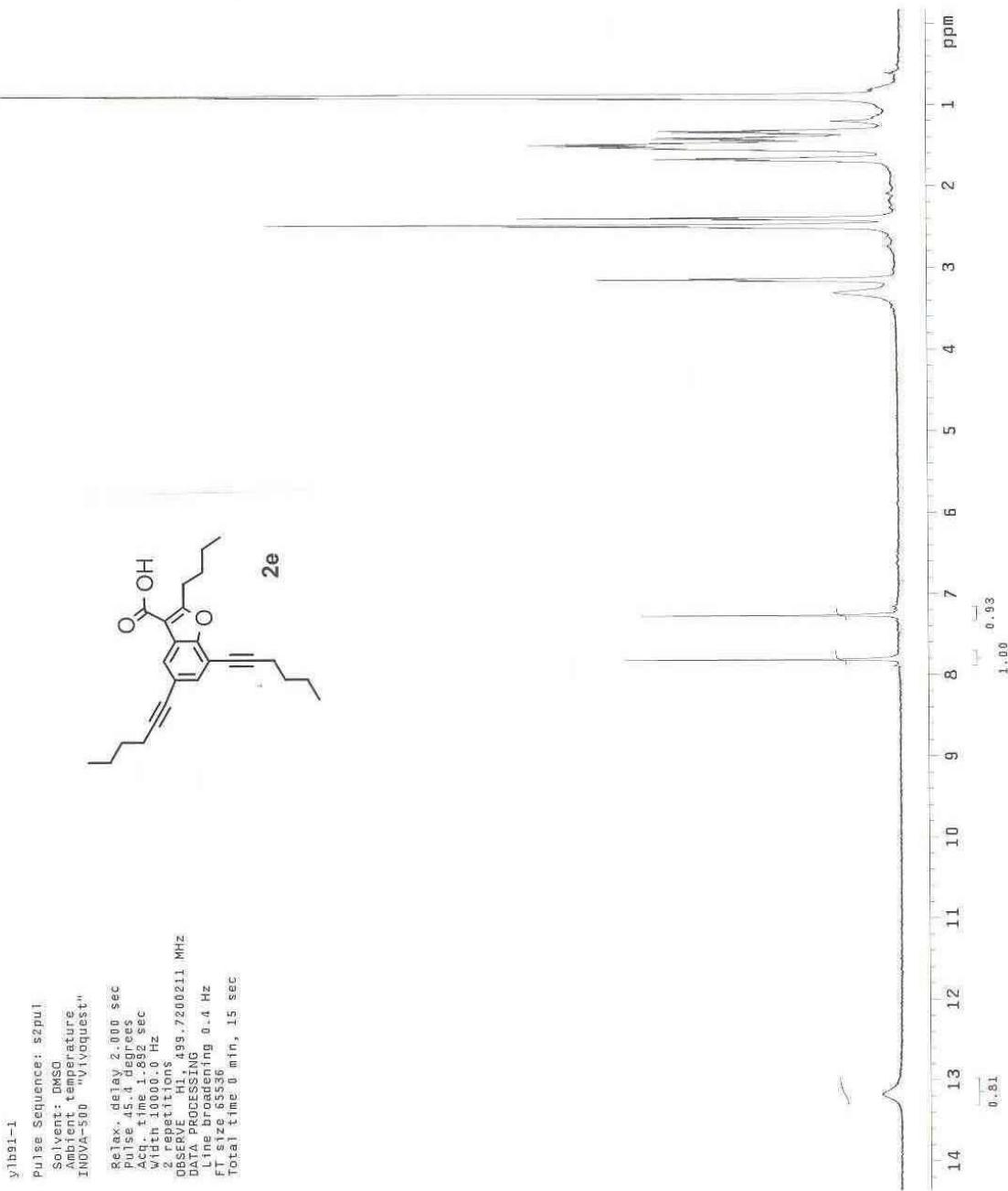


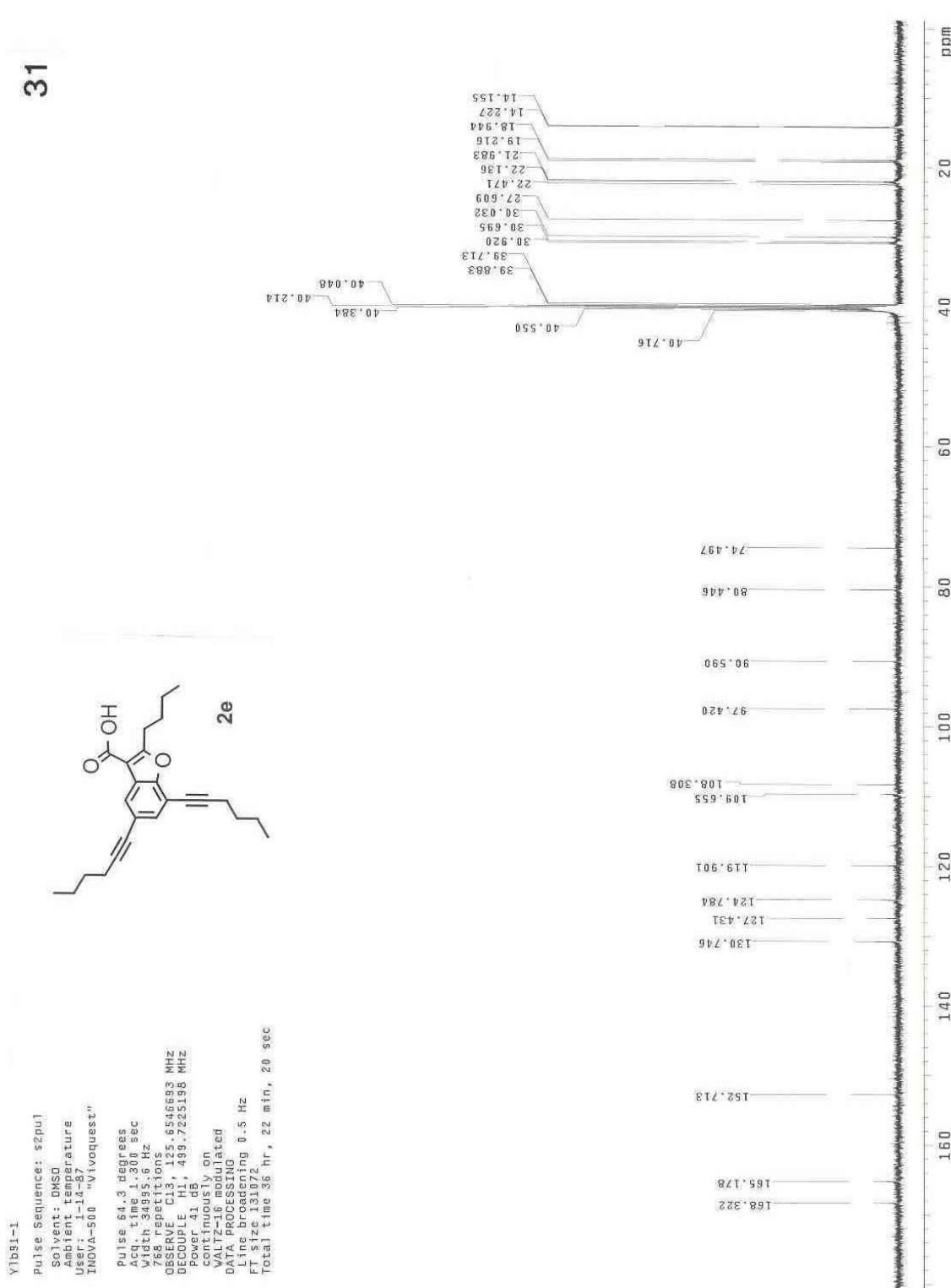
ylb87-4
 Pulse Sequence: \$2pu1
 Solvent: DMSO
 Ambient temperature
 User: I-14-87
 INIVA-500 - "Vivavquest"
 Pulse 64.3 degrees
 Acq. time 1.300 sec
 Width 2000.0 Hz
 576 repetitions
 OBSERVE Cl3, 125.654693 MHz
 DECOUPLE H1, 49.7225198 MHz
 Power 41 dB
 continuosly on
 WALT-16 modulated
 DATA PROCESSING
 Line broadening 0.5 Hz
 FT size 65536
 Total time 21 min, 52 sec



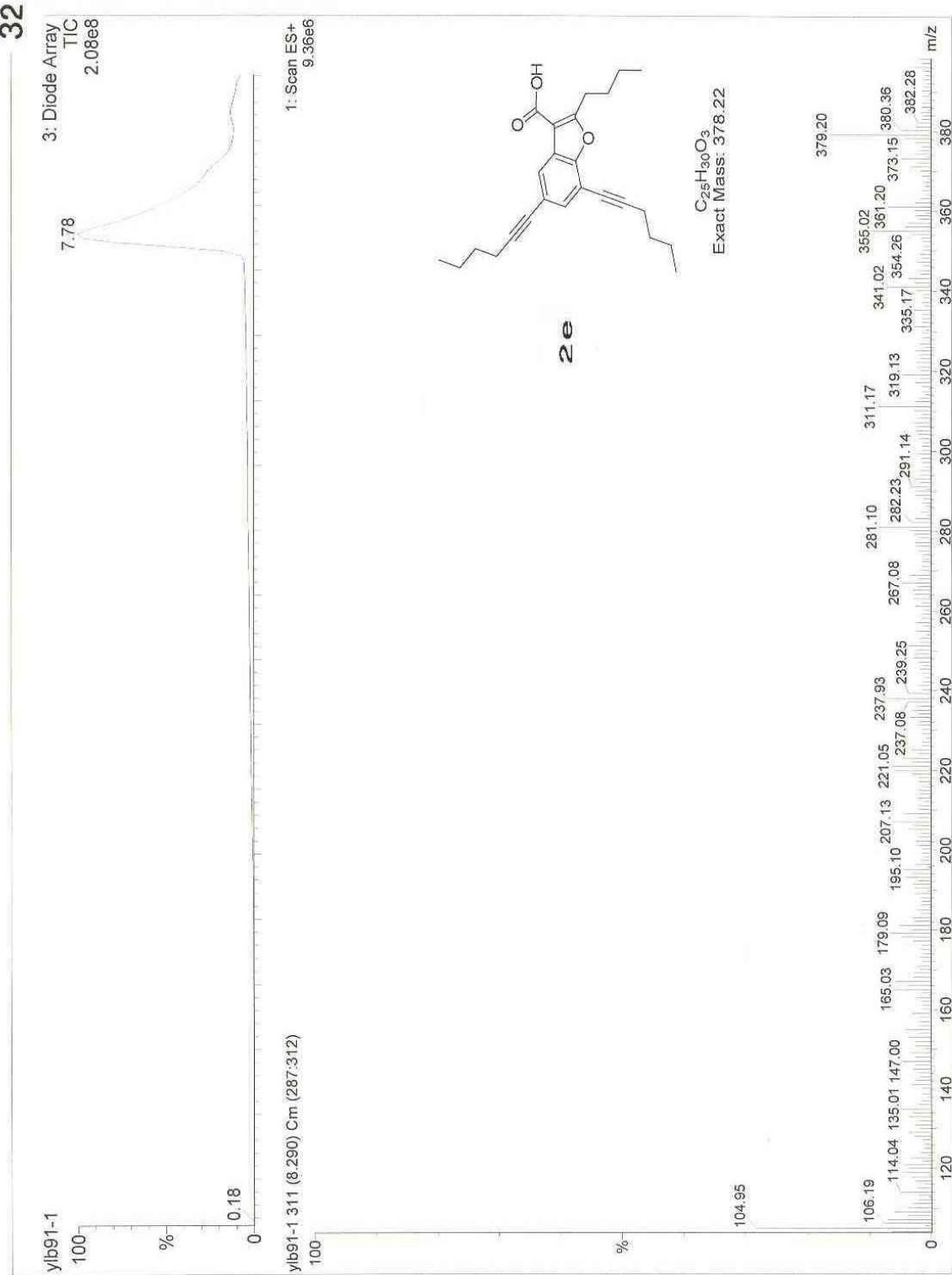






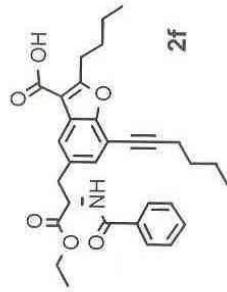


32



S

39

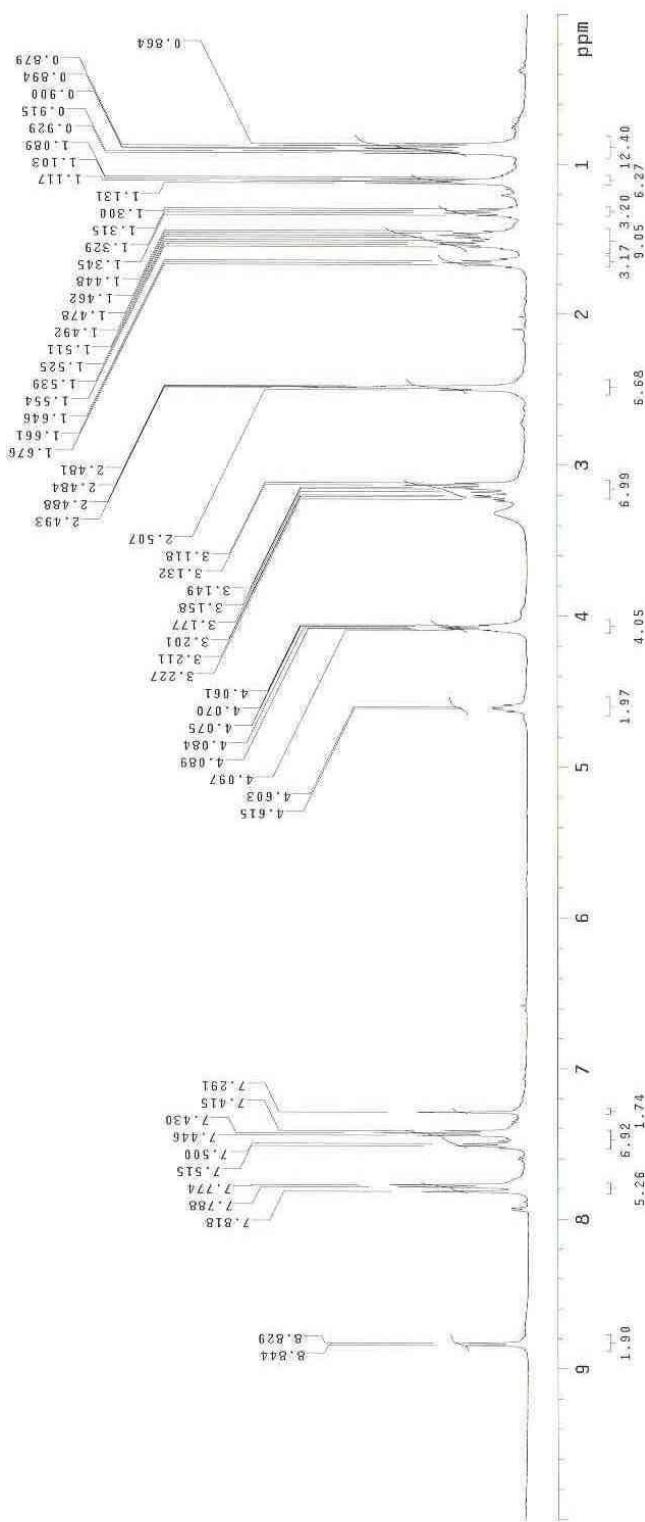


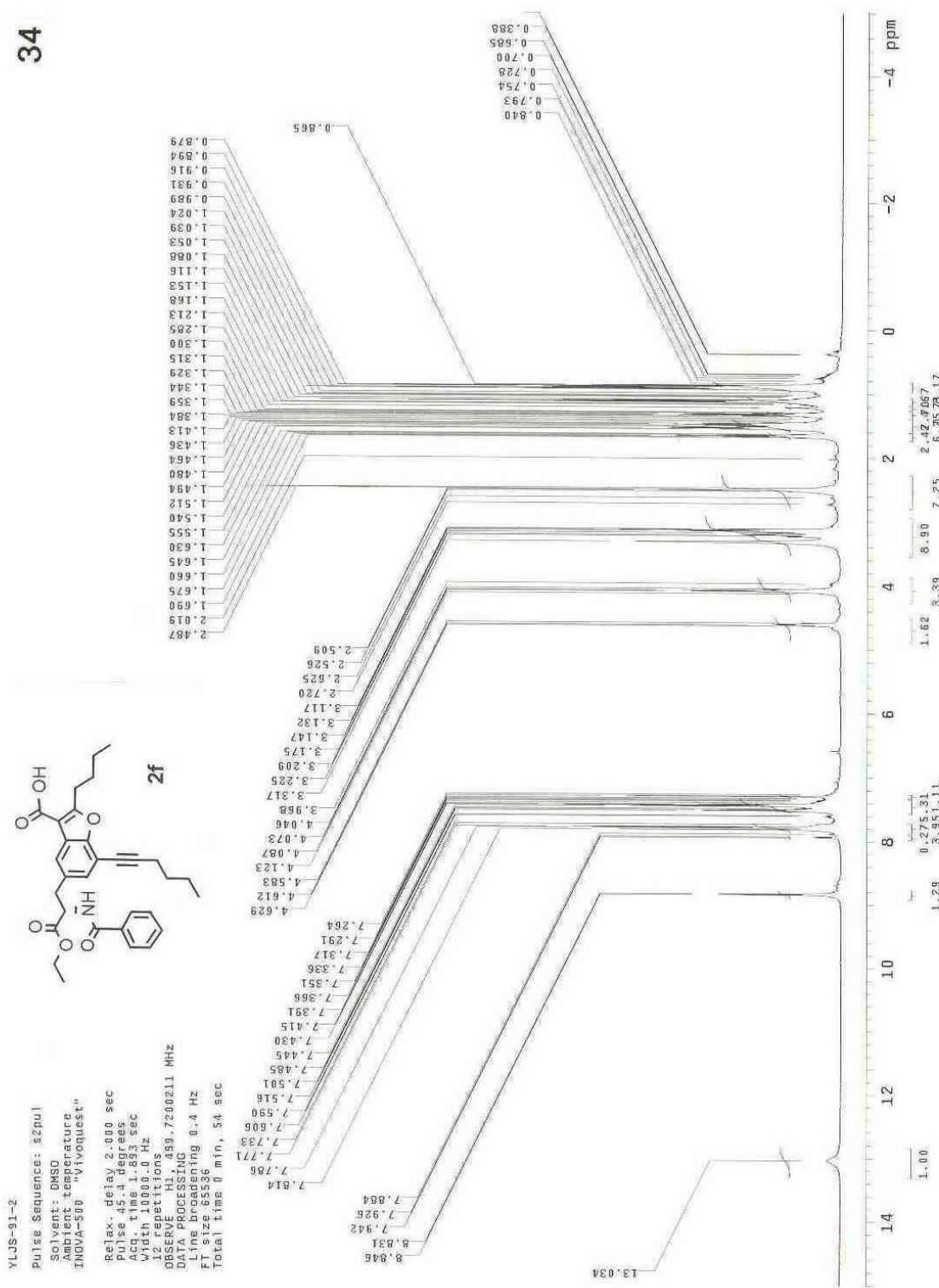
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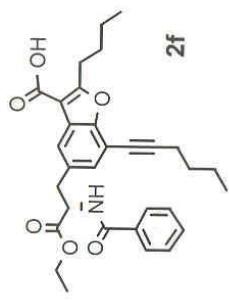
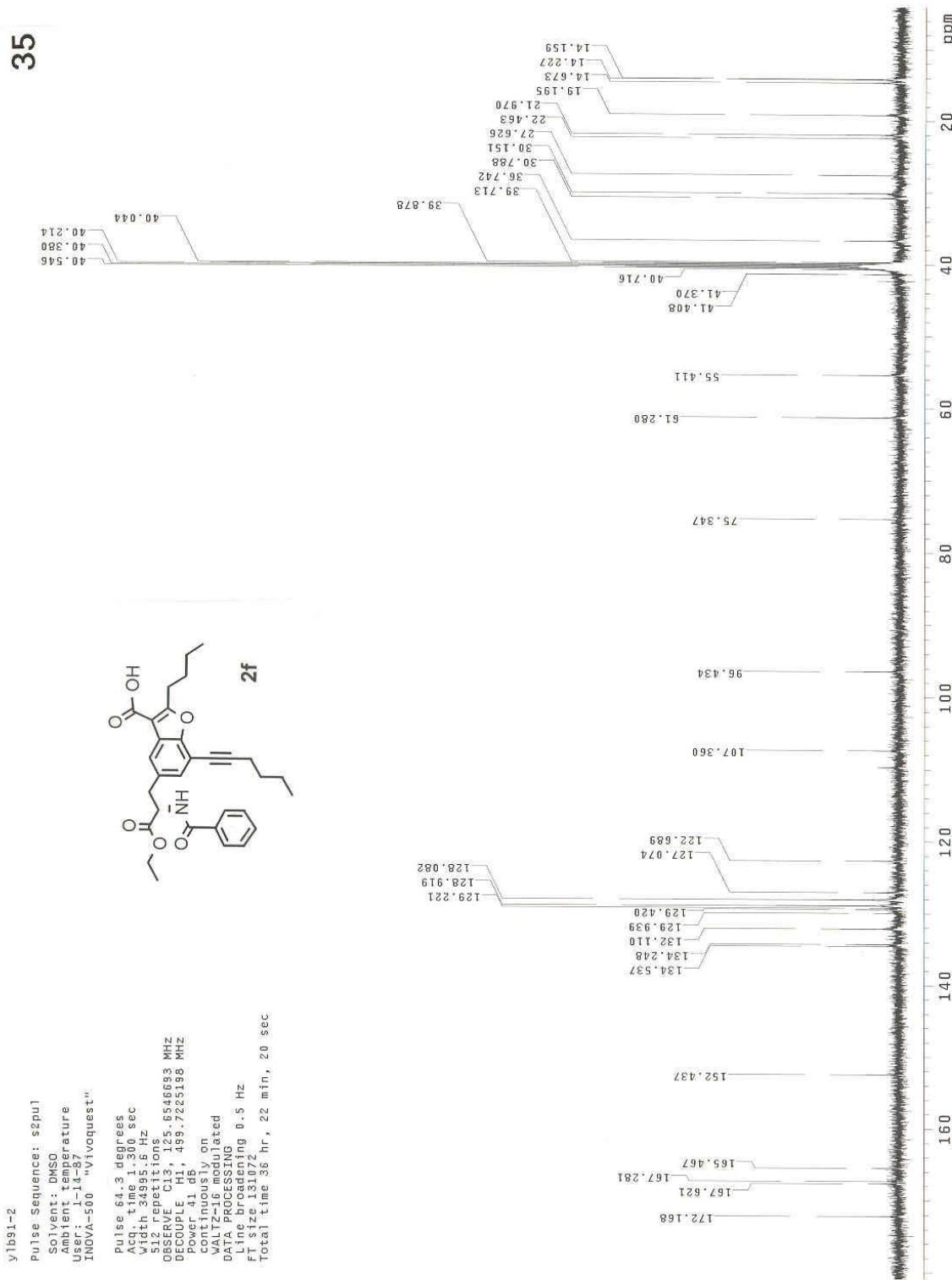
y1b1g1-2

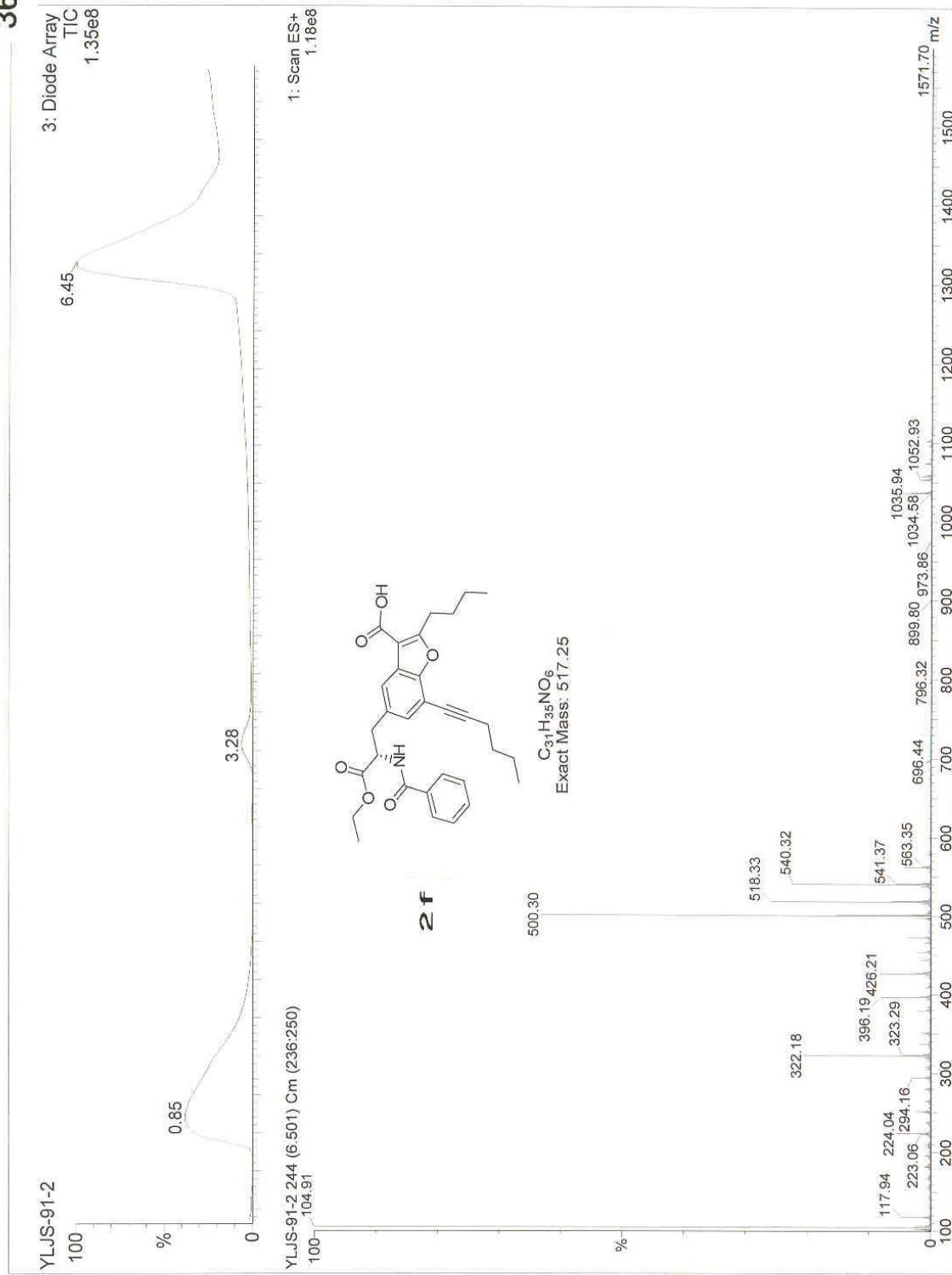
Pulse Sequence: $2pul
Source: DMSO
Ambient temperature
INOVA-500 "vivogenesis"
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 1.893 sec
Width 5000.0 Hz
2 repetitions
DOSSEY PROCESSING
D1D1A -processing
D1D1A -broadening 0.4 Hz
FFTI size 32768
FFT size 1024
Time 0 min, 15 sec

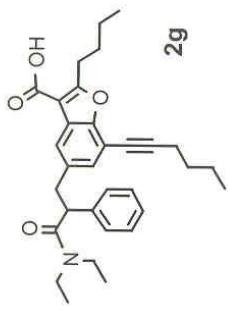
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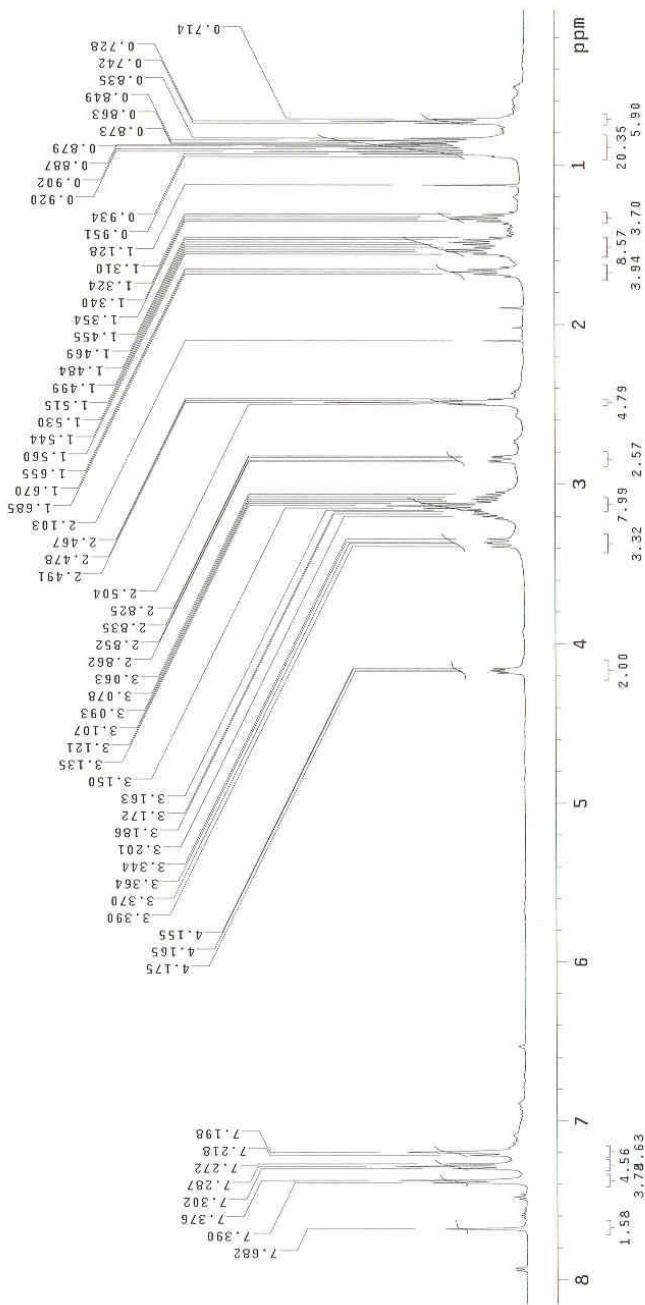


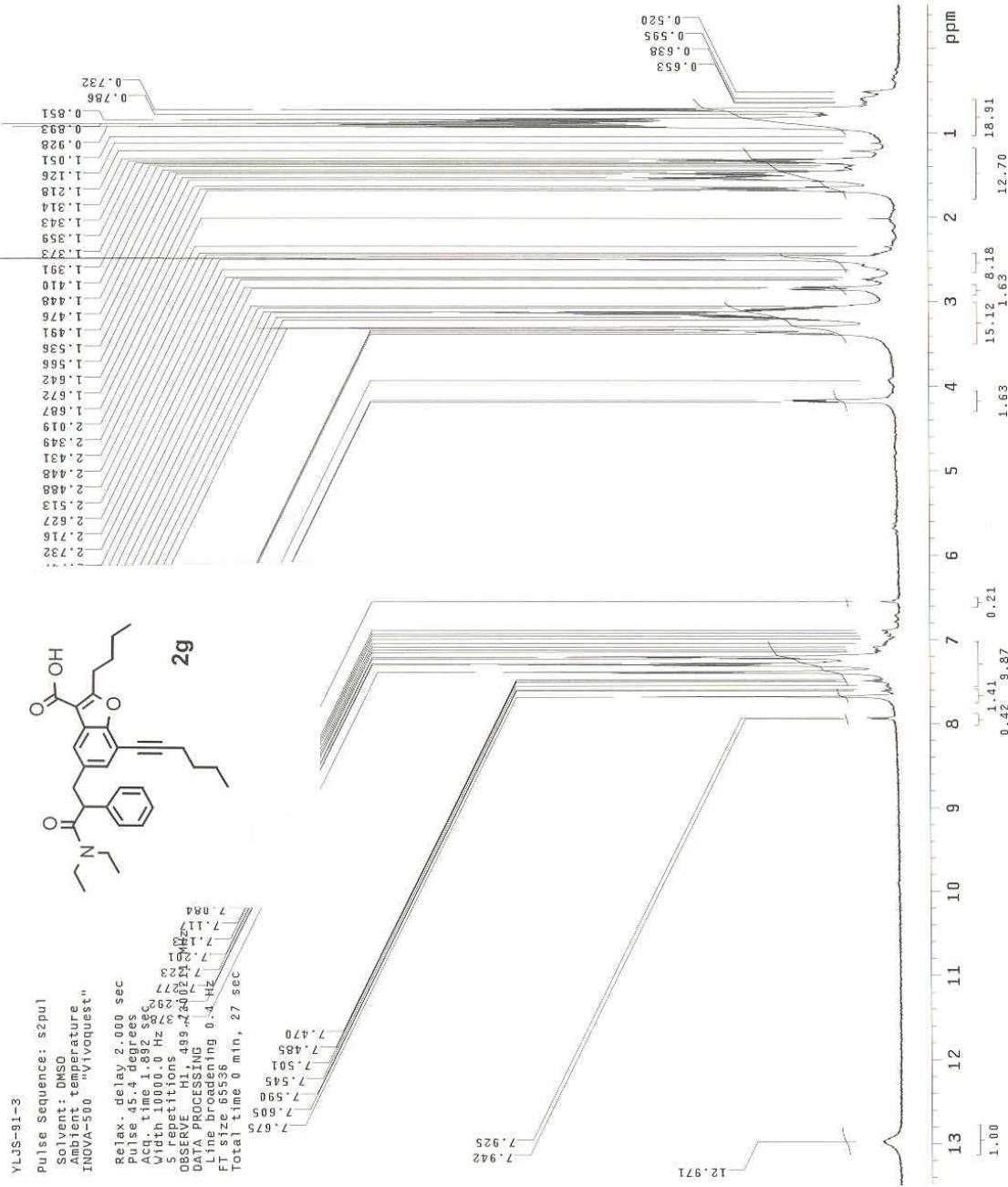


```

ybb91-3
Pulse Sequence: $2pu1
Solvent: D2SO
Ambient temperature
INOVATION="Hydroquest"
Relax. delay 2.000 sec
Pulse 45.4 degrees
Acq. time 1.822 sec
Width 5000.0 Hz
2 repetitions
OBSERVE H1, 499, 7200211 MHz
DATA PROCESSING
Line broadening 0.4 Hz
FT size 32768
total time 0 min, 15 sec

```





39

Y1b91-3
 Pulse Sequence: s2pu
 Solvent: DMSO
 Ambient temperature
 User: 1-147
 INOVA-500 "Vivowest"
 Pulse 64.3 degrees
 Acq. time 1.310 sec
 Width 3.995.6 Hz
 3840 repetitions
 OBSERVE: C13 : 125.6546693 MHz
 DECOUPLE: H1 : 49.7225198 MHz
 Power 41 dB
 continuously on
 VAWT-16 modulated
 DATA PROCESSING
 line broadening 0.5 Hz
 FT size 131072
 Total time 36 hr, 22 min, 20 sec

