Partial reduction of electron deficient pyridines

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General Procedures and Supplementary Material

Method A: to a deep blue solution of freshly distilled ammonia (100mL), sodium (0.322g, 1.40mmol) and THF (10mL) was added the pyridine **4** (0.803g, 0.32mmol) in THF (20mL) and the reaction was stirred at -78ºC under an atmosphere of nitrogen for 30 mins. Addition of isoprene (0.5mL) followed by MeI (0.7mL, 1.12mmol) caused the reaction to turn light red in colour. Stirring was continued for 8 seconds (timed from the start of electophile addition) before rapid addition of saturated NH_4Cl solution (5mL) [colour change to light yellow]. The reaction was allowed to warm to room temperature overnight under an atmosphere of nitrogen. The organics were extracted with CH_2Cl_2 (4 x 30mL), dried (Na_2SO_4) and concentrated *in vacuo* to yield a yellow oil (0.9664g). Gradient column chromatography on silica eluting with 5:95 acetone/hexanes, followed by 10:90 acetone/hexanes isolated the title compound (**5**, R= Me) as a pale yellow oil (0.843g, 99%).

Method B: a solution of naphthalene (1.00g, 0.78mmol), sodium (0.172g, 0.75mmol) and THF (40mL) was sonicated at room temperature for 1 hour, by which time a deep green colour had been generated. The reaction was cooled to -78ºC before addition of the pyridine **4** (0.323g, 0.13mmol) in THF (20mL). Stirring was continued for 45 minutes before addition of $I(CH_2)_3Cl$ (0.55mL, 0.52mmol) over a period of 10 seconds. The reaction was stirred for a further 10 seconds before rapid addition of saturated NH_4Cl solution (5mL), on which the reaction turned light yellow/orange with a white precipitate. The reaction was allowed to warm to room temperature and was then absorbed on silica. Gradient column chromatography (with reaction dry-loaded) on silica eluting with neat hexanes (to remove the naphthalene), followed by 5:95 acetone/hexanes isolated the title compound (**5**, R= $(CH_2)_3Cl$) as a yellow oil (0.381g, 96%).

Cyclisation procedure 1: a solution of the substrate (**5**, n=1) (0.430g, 0.13mmol), DBU (0.22mL, 0.15mmol) and CH_2Cl_2 (25mL) were heated at reflux for 36 hours under an atmosphere of nitrogen. The reaction was allowed to cool before organics were extracted with CH_2Cl_2 (3 x 30mL), dried (Na_2SO_4) and concentrated *in vacuo* to yield a black oil (3.505g). Flash column chromatography on silica eluting with 10:90 acetone/hexanes isolated the cyclised compound (**6**, n=1) as an off-white solid (0.363g, 0.12mmol, 95%).

Cyclisation procedure 2: to a solution of the substrate (**5**, n=3) (0.202g, 0.56mmol) in THF (25mL) at -78°C was added KHMDS (0.213g, 1.07mmol) and 18-crown-6-ether (0.251g, 0.95mmol). The reaction was allowed to warm to room temperature and was stirred overnight before addition of saturated NH_4Cl solution (5mL). The organics were extracted with CH_2Cl_2 (4 x 30mL), dried (Na_2SO_4) and concentrated *in vacuo* to yield a brown oil (0.246g). Flash column chromatography on silica eluting with 10:90 acetone/hexanes isolated the cyclised compound (**6**, n=3) as an oil (0.083g, 0.26mmol, 46%).

Spectroscopic data:

Compound 2

R= Me

^{1}H NMR (300 MHz, $CDCl_3$)	δ 7.81 (s, br, 1H), 5.90 (d, br, 1H, J 9.9), 5.82 (dd, br, 1H, J 9.9, 1.8), 5.01 (sp, 1H, J 6.3), 4.15 (s, br, 2H), 1.38 (s, 3H), 1.23 (d, br, 6H, J 6.3).
^{13}C NMR (75 MHz, $CDCl_3$)	δ 171.55, 161.10, 125.44, 124.96, 68.79, 49.13, 43.92, 23.50, 21.52, 21.48.
MS (CI, *m/z*)	182 ($M+H^+$, 100%).
HRMS (CI, *m/z*)	$C_{10}H_{15}O_2N$ ($+H^+$) requires 182.1181, found 182.1179.
IR (film, cm^{-1})	2980, 2926, 2852, 1727, 1674, 1644, 1620, 1455, 1386, 1241, 1104, 911, 733.

Compound 2

R= Allyl

^{1}H NMR (300 MHz, $CDCl_3$)	δ 7.74 (dd, 1H, J 2.8, 1.8), 5.87 (ddd, 1H, J 10.6, 2.8, 0.8), 5.71 (ddd, 1H, J 10.6, 2.4, 1.8), 5.55 (m, 1H), 5.01 (m, 2H), 4.93 (sp, 1H, J 6.2), 4.03 (m, 2H), 2.43 (dt, 2H, J 7.4, 1.0), 1.15 (d, 6H, J 6.2).
^{13}C NMR (75 MHz, $CDCl_3$)	δ 170.53, 160.26, 131.58, 126.04, 123.67, 119.21, 68.87, 49.44, 41.47, 47.42, 21.54, 21.52.
MS (CI, *m/z*)	208 ($M+H^+$, 100%).
HRMS (CI, *m/z*)	$C_{12}H_{17}NO_2$ ($+H^+$) requires 208.1337, found 208.1330.
IR (film, cm^{-1})	2980, 2936, 1727, 1675, 1642, 1235, 1106.

Compound 2

R= Propargyl

^{1}H NMR (500 MHz, $CDCl_3$)	δ 7.90 (s, 1H), 6.06 (d, 1H, ^{3}J 10.2), 5.84 (dd, 1H, J 10.2, 2.2), 5.05 (sp, 1H, J 6.5), 4.21 (m, 2H), 2.70 and 2.63 (ABX, 2H, J_{A-B} 16.9, J_{AX} 2.8, J_{BX} 2.7), 2.04 (t, 1H, J 2.7), 1.26 (d, 3H, J 6.5), 1.25 (d, 3H, J 6.5).
^{13}C NMR (500MHz, $CDCl_3$)	δ 169.62, 158.86, 127.29, 123.04, 78.52, 71.48, 69.49, 49.75, 28.20, 27.03, 21.56 (2).
MS (CI, *m/z*)	206 ($M+H^+$, 100%).
HRMS (CI, *m/z*)	$C_{12}H_{15}NO_2$ ($+H^+$) required 206.1181, found 206.1181.
IR (film, cm^{-1})	3291, 2981, 2930, 1727, 1676, 1644, 1375, 1291, 1237, 1106, 1062.

Compound 5

R= Me

^{1}H NMR (300 MHz, $CDCl_3$)	δ 7.42 (dd, 1H, J 6.2, 1.7), 6.45 (dd, 1H, J 9.9, 1.7), 5.26 (d, br, 2H, J 9.9), 5.05 (sp, 2H, J 6.3), 1.41 (s, 3H), 1.27 (d, 6H, J 6.3), 1.24 (d, 6H, J 6.3).
^{13}C NMR (75 MHz, $CDCl_3$)	δ 173.13, 165.90, 141.75, 121.99, 113.28, 97.39, 69.20, 65.99, 58.80, 28.72, 21.82 (2), 21.42 (2).
MS (CI, *m/z*)	268 ($M+H^+$, 100%).
HRMS (CI, *m/z*)	$C_{14}H_{21}NO_4$ ($+H^+$) requires 268.1549, found 268.1552.
IR (film, cm^{-1})	3315, 2980, 1732, 1686, 1668, 1638, 1580, 1373, 1252, 1100.

Compound 5

R= Et

^{1}H NMR (300 MHz, $CDCl_3$)	δ 7.46 (dd, 1H, J 7.0, 1.7), 6.51 (dd, 1H, J 10.1, 1.7), 5.19 (d, br, 1H, J 10.1), 5.18 (s, br, 1H), 5.06 (sp, 1H, J 6.3), 5.05 (sp, 1H, J 6.3), 1.54 – 1.84 (m, 2H), 1.27 (d, 6H, J 6.3), 1.24 (d, 6H, J 6.3), 0.88 (t, 3H, J 7.4).
^{13}C NMR (75 MHz, $CDCl_3$)	δ 172.78, 165.90, 141.77, 122.87, 112.23, 97.85, 69.33, 66.13, 62.80, 34.34, 22.07 (2), 21.63 (2), 6.93.
MS (CI, *m/z*)	282 ($M+H^+$, 100%).
HRMS (CI, *m/z*)	$C_{15}H_{23}NO_4$ ($+H^+$) requires 282.1705, found 282.1704.

IR (film, cm^{-1})	3332, 2978, 1733, 1685, 1667, 1640, 1580, 1373, 1295, 1243, 1204, 1143, 1100.

Compound 5

R= *i*Bu

^1H NMR (300 MHz, $CDCl_3$)	δ 7.44 (dd, 1H, J 6.4, 1.6), 6.45 (dd, 1H, J 10.3, 1.6), 5.22 (s, br, 1H), 5.18 (d, 1H, J 10.3), 5.05 (sp, 1H, J 6.3), 5.04 (sp, 1H, J 6.3), 1.84 (sp, 1H, J 6.5), 1.77 - 1.67 (m, 1H), 1.54 – 1.44 (m, 1H), 1.27 + 1.26 (2 x d, 6H, J 6.3), 1.23 (d, 6H, J 6.3), 0.94 + 0.89 (2 x d, 6H, J 6.5).
^{13}C NMR (75 MHz, $CDCl_3$)	δ 173.13, 165.90, 141.54, 122.28, 113.38, 97.71, 69.38, 66.14, 62.39, 49.52, 24.22, 23.62, 23.58, 22.06 (2) 21.57 (2).
MS (CI, *m/z*)	310 ($M+H^+$, 100%).
HRMS (CI, *m/z*)	$C_{17}H_{27}NO_4$ ($+H^+$) requires 310.2018, found 310.2020.
IR (film, cm^{-1})	3320, 2979, 1732, 1665, 1638, 1580, 1468, 1370, 1305, 1281, 1236, 1137, 1100.

Compound 5

R= $CH_2CH(O)CH_2$ (mixture of diastereoisomers) * corresponds to peaks for the major isomer

^1H NMR (400 MHz, $CDCl_3$)	δ 7.49* + 7.46 (2 x dd, 1H, J 6.9, 1.6), 6.55* + 6.52 (2 x dd, 1H, J 10.1, 1.6), 5.53 + 5.41* (2 x s, br, 1H), 5.21 (dd, 1H, J 10.1, 1.9), 5.08 (sp, 1H, J 6.2), 5.05 (sp, 1H, J 6.2), 3.11 – 3.06* + 3.00 – 2.94 (2 x m, 1H), 2.77 + 2.75* (2 x d, J 4.1) 2.47 + 2.46* (2 x d, J 2.7), (2.10 + 2.03*) + 1.69 (ABX, 2H, J_{A-B} 14.8, J_{A-X} 4.0, J_{B-X} 7.1), 1.28 (d, 6H, J 6.2), 1.24 (d, 6H, J 6.2).
^{13}C NMR (100 MHz, $CDCl_3$)	δ 171.91 + 171.77, 165.70 , 141.66 + 141.56, 123.61 + 123.45, 111.99 + 111.74, 98.29 + 98.15, 69.87, 69.83, 66.31, 66.25, 61.98 + 61.35, 47.87 + 47.35, 46.15, 44.05 + 43.89, 22.05, 21.60, 21.58, 21.55, 21.52.
MS (CI, *m/z*)	310 ($M+H^+$, 100%).
HRMS (CI, *m/z*)	$C_{16}H_{23}NO_5$ ($+H^+$) requires 310.1654, found 310.1651.
IR (film, cm^{-1})	3412, 2982, 2938, 2824, 1721, 1677, 1637, 1456, 1387, 1277, 1203, 1102, 916, 746.

Compound 5

R= Allyl

^{1}H NMR (400 MHz, $CDCl_3$)	δ 7.43 (dd, 1H, J 6.6, 1.4), 6.47 (dd, 1H, J 10.1, 1.4), 5.67 – 5.55 (m, 1H), 5.46 (s, br, 1H), 5.21 – 4.96 (m, 5H), 2.44 (ABX, 2H, J_{A-B} 13.8, J_{A-X} 7.8, J_{B-X} 6.9), 1.25 (d, 6H, J 6.2), 1.21 (d, 6H, J 6.2).
^{13}C NMR (100 MHz, $CDCl_3$)	δ 171.84, 165.90, 141.77, 130.15, 122.97, 120.30, 112.31, 97.94, 69.54, 66.20, 62.08, 45.85, 22.09 (2), 21.69, 21.62.
MS (CI, *m/z*)	294 ($M+H^+$, 100%).
HRMS (CI, *m/z*)	$C_{16}H_{23}NO_4$ ($+H^+$) requires 294.1705, found 294.1705.
IR (film, cm^{-1})	3341, 2980, 1735, 1686, 1671, 1638, 1579, 1495, 1470, 1422, 1372, 1305, 1233, 1181, 1100, 1022, 995, 919, 835, 733.

Compound 5

R= $(CH_2)_3Cl$

^{1}H NMR (400 MHz, $CDCl_3$)	δ 7.45 (d, 1H, J 6.0), 6.52 (d, 1H, J 10.0), 5.22 (s, br, 1H), 5.18 (d, 1H, J 10.0), 5.06 (sp, 1H, J 6.3), 5.05 (sp, 1H, J 6.3), 3.61 – 3.49 (m, 2H), 2.00 – 1.62 (m, 4H), 1.28 (d, 6H, J 6.3), 1.24 (d, 6H, J 6.3).
^{13}C NMR (100 MHz, $CDCl_3$)	δ 172.49, 165.81, 142.05, 123.30, 111.59, 97.40, 69.58, 66.15, 62.07, 44.54, 38.62, 26.31, 21.99 (2), 21.53, 21.46.
MS (CI, *m/z*)	330 ($M+H^+$, 100%).
HRMS (CI, *m/z*)	$C_{16}H_{24}NO_4Cl$ ($+H^+$) requires 330.1472, found 330.1480.
IR (film, cm^{-1})	3319, 2981, 2936, 2875, 1733, 1683, 1639, 1581, 1513, 1451, 1370, 1303, 1249, 1100, 960, 915, 835, 733, 651.

Compound 5

R= $(CH_2)_4Cl$

^{1}H NMR (300 MHz, $CDCl_3$)	δ 7.44 (d, 1H, J 6.6), 6.48 (d, 1H, J 10.2), 5.36 (d, br, 1H), 5.16 (d, 1H, J 10.2), 5.04 (sp, 1H, J 6.3), 5.03 (sp, 1H, J 6.3), 3.50 (t, 2H, J 6.6), 1.81 – 1.65 (m, 3H), 1.62 – 1.48 (m, 2H), 1.43 – 1.31 (m, 1H), 1.26 (d, 6H, J 6.3), 1.22 (d, 6H, J 6.3).
^{13}C NMR (75 MHz, $CDCl_3$)	δ 172.62, 165.87, 141.78, 123.00, 112.16, 97.84, 69.57, 66.23, 62.34, 44.47, 40.55, 32.20, 22.08 (2), 21.64, 21.59, 20.14.
MS (CI, *m/z*)	344 ($M+H^+$, 100%).
HRMS (CI, *m/z*)	$C_{17}H_{26}NO_4Cl$ ($+H^+$) requires 344.1628, found 344.1628.

IR (film, cm^{-1})	3322, 2980, 2938, 2872, 1732, 1682, 1638, 1580, 1513, 1457, 1372, 1304, 1275, 1245, 1180, 1145, 1098, 916, 836, 734.

Compound 5

R= $(CH_2)_5Cl$

^{1}H NMR (400 MHz, $CDCl_3$)	δ 7.45 (dd, 1H, J 7.5, 1.5), 6.50 (dd, 1H, J 9.9, 1.5), 5.18 (dd, 1H, J 9.9, 1.8), 5.18 (s, br, 1H), 5.06 (sp, 1H, J 6.2), 5.05 (sp, 1H, J 6.2), 3.53 (t, 2H, J 6.6), 1.81 – 1.71 (m, 3H), 1.60 – 1.36 (m, 5H), 1.28 (d, 6H, J 6.2), 1.24 (d, 6H, J 6.2).
^{13}C NMR (100 MHz, $CDCl_3$)	δ 172.78, 165.90, 141.94, 122.84, 112.20, 97.52, 69.39, 66.13, 62.40, 44.71, 41.21, 32.23, 26.57, 22.06, 22.05 (2), 21.59, 21.54.
MS (CI, *m/z*)	358 ($M+H^+$, 30%).
HRMS (CI, *m/z*)	$C_{18}H_{28}NO_4Cl$ ($+H^+$) requires 358.1785, found 358.1776.
IR (film, cm^{-1})	3322, 2980, 2938, 2866, 1734, 1685, 1642, 1582, 1504, 1465, 1372, 1304, 1261, 1245, 1098, 836, 734.

Compound 6

n= 1

^{1}H NMR (300 MHz, $CDCl_3$)	δ 7.54 (s, br, 1H), 6.51 (dd, 1H, J 9.6, 1.1), 5.14 (d, 1H, J 9.6), 5.06 (sp, 1H, J 6.1), 4.98 (sp, 1H, J 6.1), 3.83 – 3.53 (m, 2H), 2.51 – 2.39 + 2.16 – 2.02 (m, 2H), 1.91 – 1.76 (m, 2H), 1.24 (d, 6H, J 6.1,), 1.24 + 1.23 (2 x d, 6H, J 6.1).
^{13}C NMR (75 MHz, $CDCl_3$)	δ 172.50, 165.87, 142.83, 122.99, 109.78, 99.16, 68.68, 68.48 , 65.91, 51.01, 37.84, 22.10, 22.08, 21.59, 21.50, 20.69.
MS (CI, *m/z*)	294 ($M+H^+$, 60%).
HRMS (CI, *m/z*)	$C_{16}H_{23}NO_4$ ($+H^+$) requires 294.1705, found 294.1702.
IR (film, cm^{-1})	2978, 1731, 1683, 1623, 1554, 1276, 1177, 1105, 1085.
Mpt (°C)	62-63°C

Compound 6

n= 2

^{1}H NMR (300 MHz, $CDCl_3$)	δ 7.26 (s, br, 1H), 6.36 (dd, 1H, J 9.8, 1.4), 5.06-5.04 (m, 2H) 4.81 (d, 1H, J 9.8), 3.67 – 3.59 (m, 1H), 3.34 – 3.26 (m, 1H), 2.38 – 2.27

	(m, 1H), 1.93 – 1.78 (m, 2H), 1.73 – 1.57 (m, 2H,), 1.43 – 1.29 (m, 1H), 1.28 + 1.26 (2 x d, 6H, J 6.3), 1.23 (d, 6H, J 6.3).
^{13}C NMR (75 MHz, $CDCl_3$)	δ 170.28, 165.73, 147.81, 122.56, 113.98, 95.90, 68.83, 65.85 (2), 52.42, 35.65, 25.19, 22.07 (2), 21.65, 21.50, 21.45.
MS (CI, *m/z*)	308 ($M+H^+$, 100%).
HRMS (CI, *m/z*)	$C_{17}H_{25}NO_4$ ($+H^+$) requires 308.1862, found 308.1869.
IR (film, cm^{-1})	2981, 2937, 2876, 1727, 1680, 1635, 1580, 1458, 1374, 1253, 1177, 1099, 914, 837, 734.

Compound 6

n= 3

^{1}H NMR (400 MHz, $CDCl_3$)	δ 7.37 (s, br, 1H), 6.50 (dd, 1H, J 9.6, 1.4), 5.03 (sp, 1H, J 6.3), 4.97 (sp, 1H, J 6.3), 4.79 (d, 1H, J 9.6,), 3.51 – 3.29 (m, 2H), 2.23 – 2.14 (m, 1H), 1.91 – 1.71, 1.60 – 1.40 and 1.31 – 1.24 (3 x m, 7H), 1.22 (d, 6H, J 6.3), 1.20 (d, 6H, J 6.3).
^{13}C NMR (100 MHz, $CDCl_3$)	δ 172.81, 165.78, 146.89, 124.24, 113.76, 97.61, 68.60, 67.57, 65.93, 53.21, 40.74, 31.06, 29.09, 22.39, 22.10, 22.09, 21.63, 21.48.
MS (CI, *m/z*)	322 ($M+H^+$, 70%).
HRMS (CI, *m/z*)	$C_{18}H_{27}NO_4$ ($+H^+$) requires 322.2018, found 322.2020.
IR (film, cm^{-1})	2978, 2930, 2858, 1731, 1683, 1637, 1568, 1425, 1354, 1298, 1242, 1163, 1107, 997, 969, 832, 769, 725.

AJM1/40 f42-64
STANDARD 1H OBSERVE

Solvent: CDCL3
Ambient temperature
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File: 1801
Queue name Dec22a
DATE Dec 22 97
INOVA-300 "porthos"

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Pulse 15.0 degrees
Acq. time 3.641 sec
Width 4499.9 Hz
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DATA PROCESSING
Line broadening 0.3 Hz
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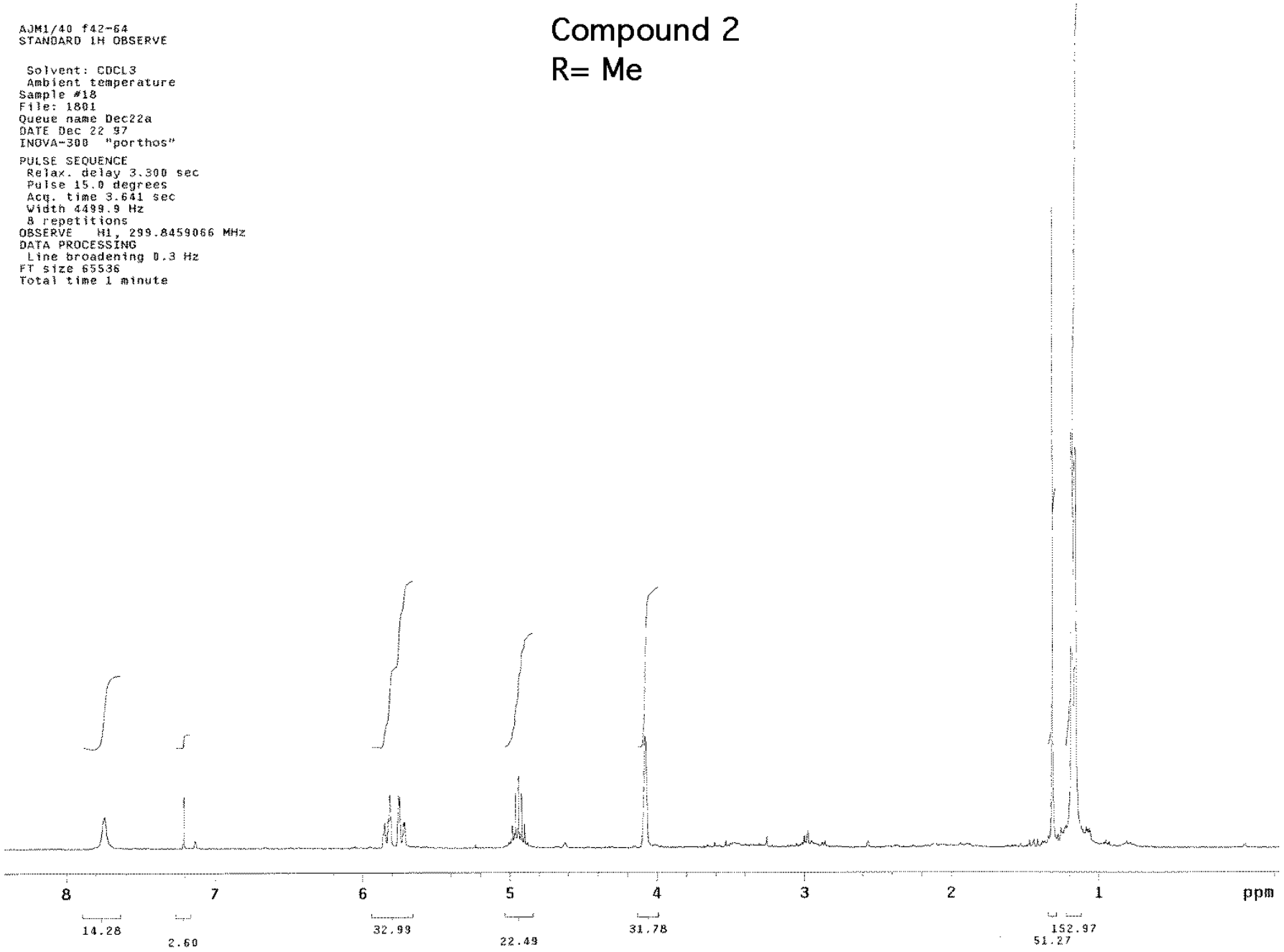
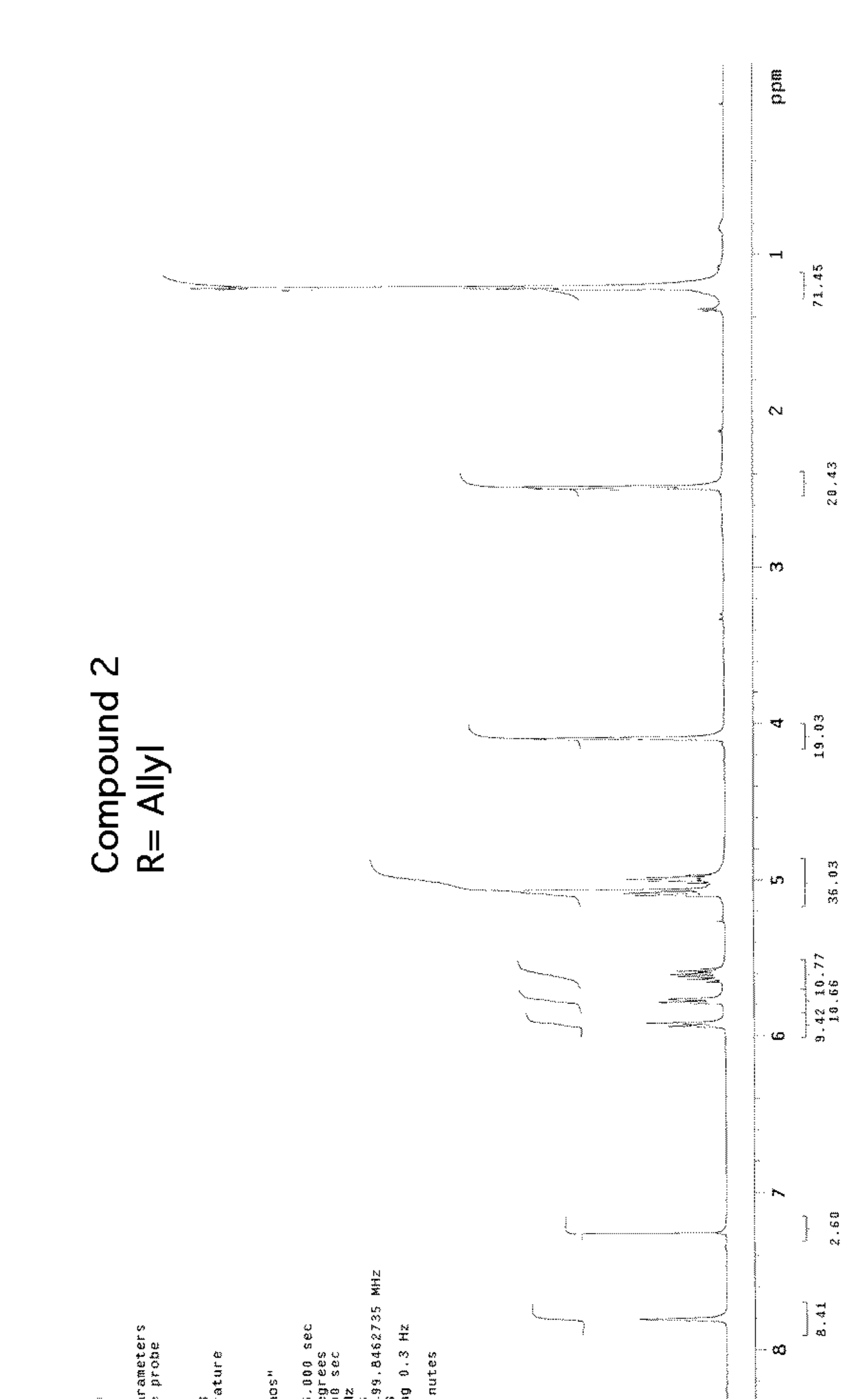
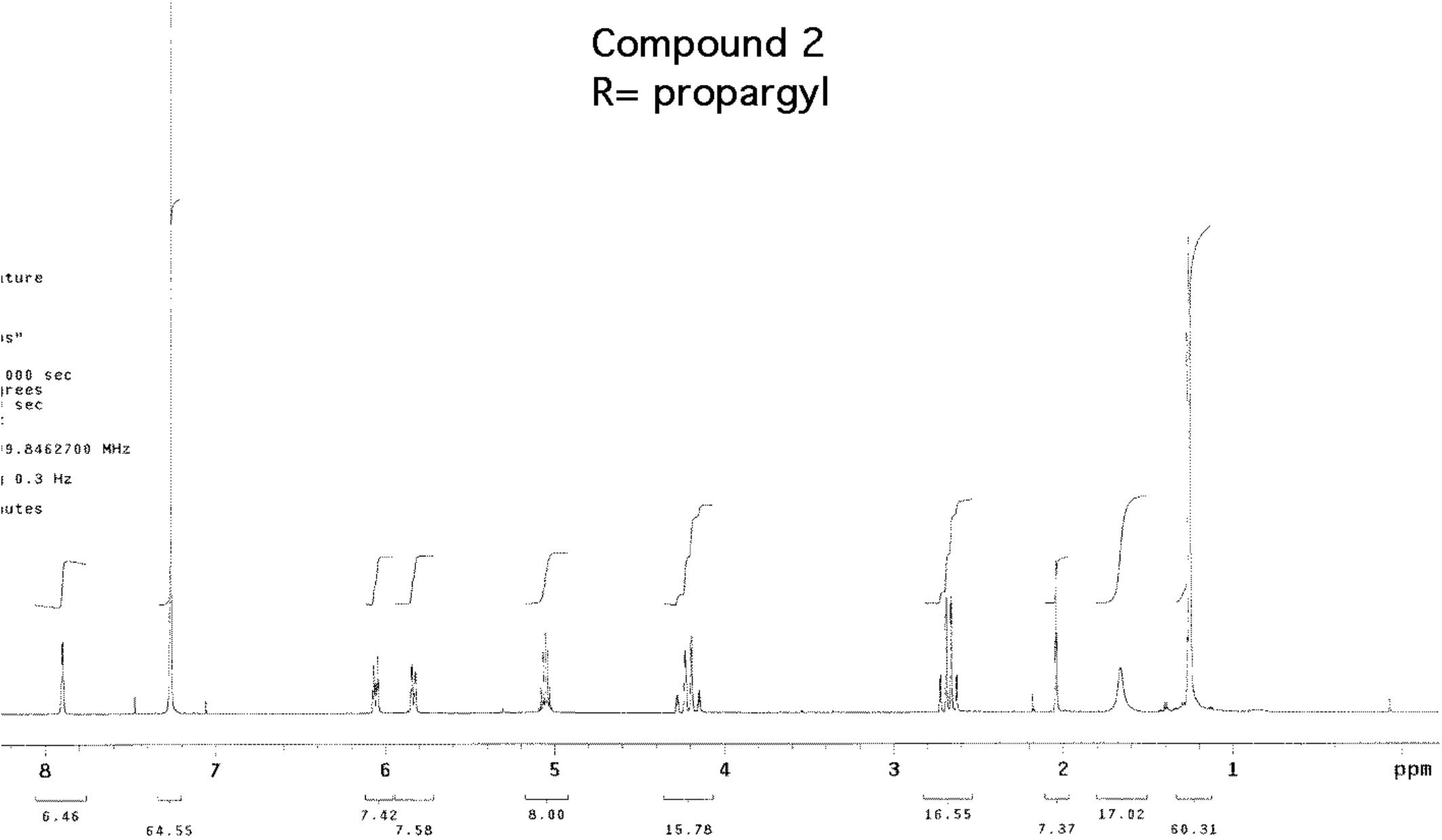
Compound 2
R= Me



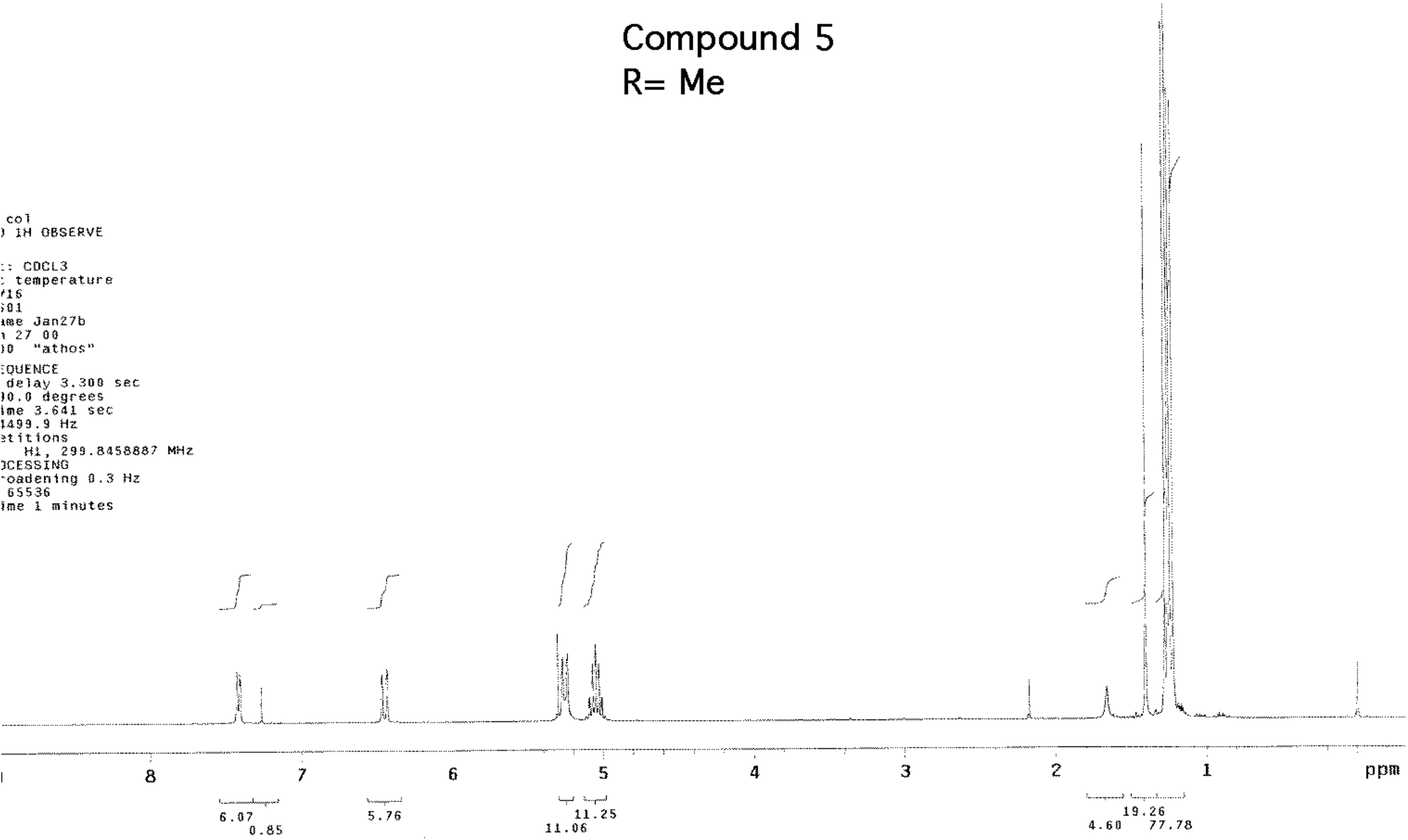
Compound 2
R= Allyl



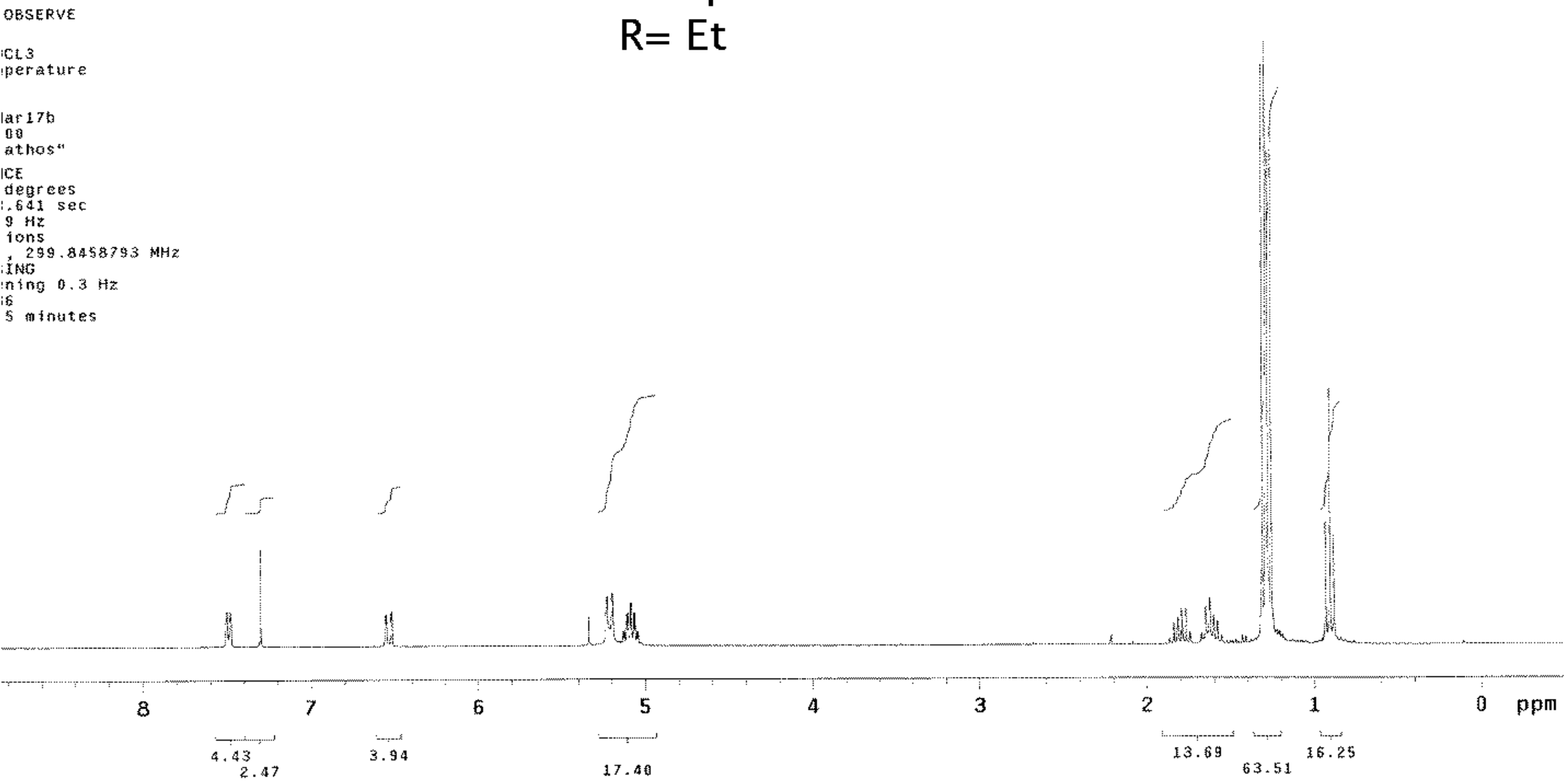
Compound 2
R= propargyl



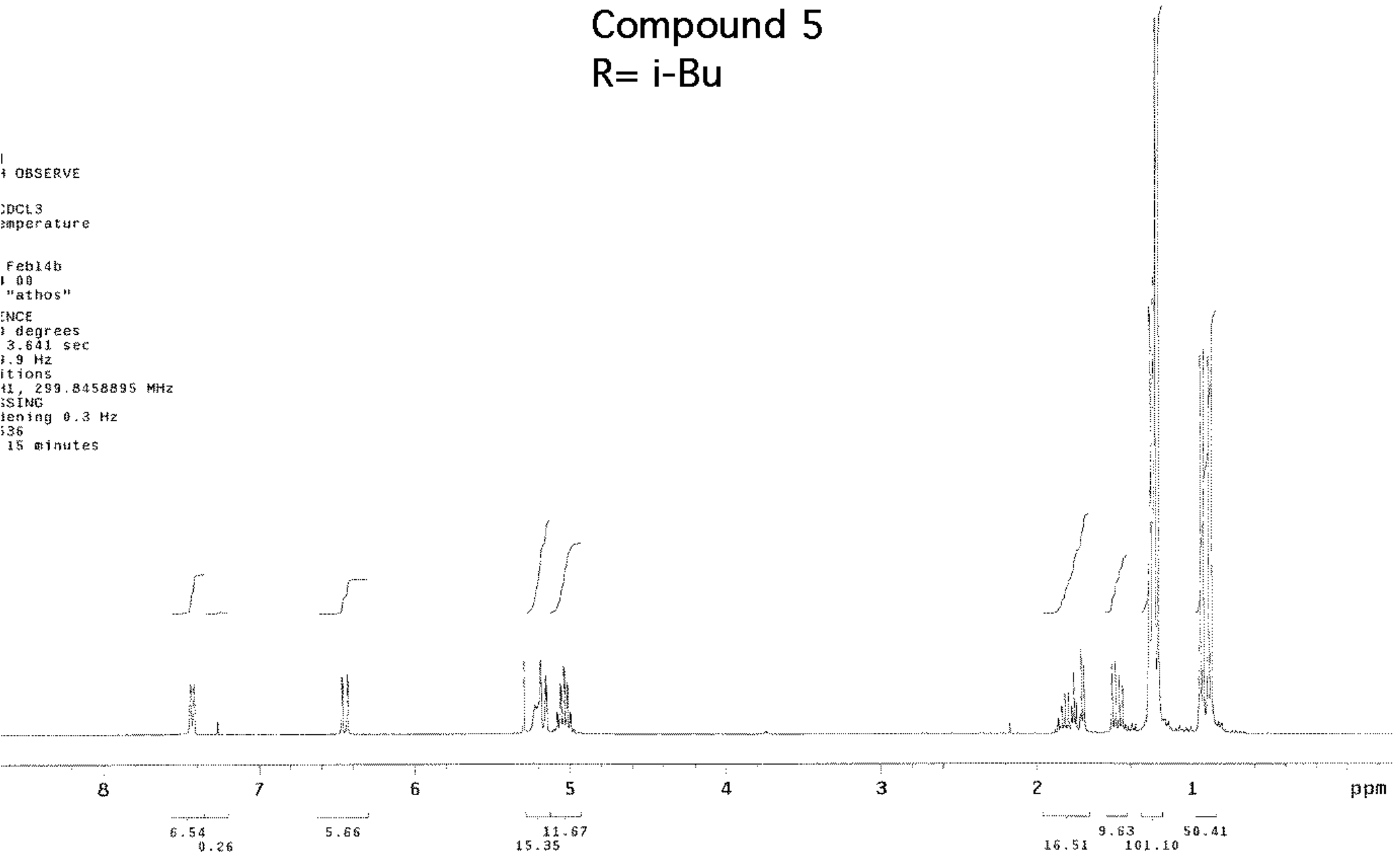
Compound 5
R= Me



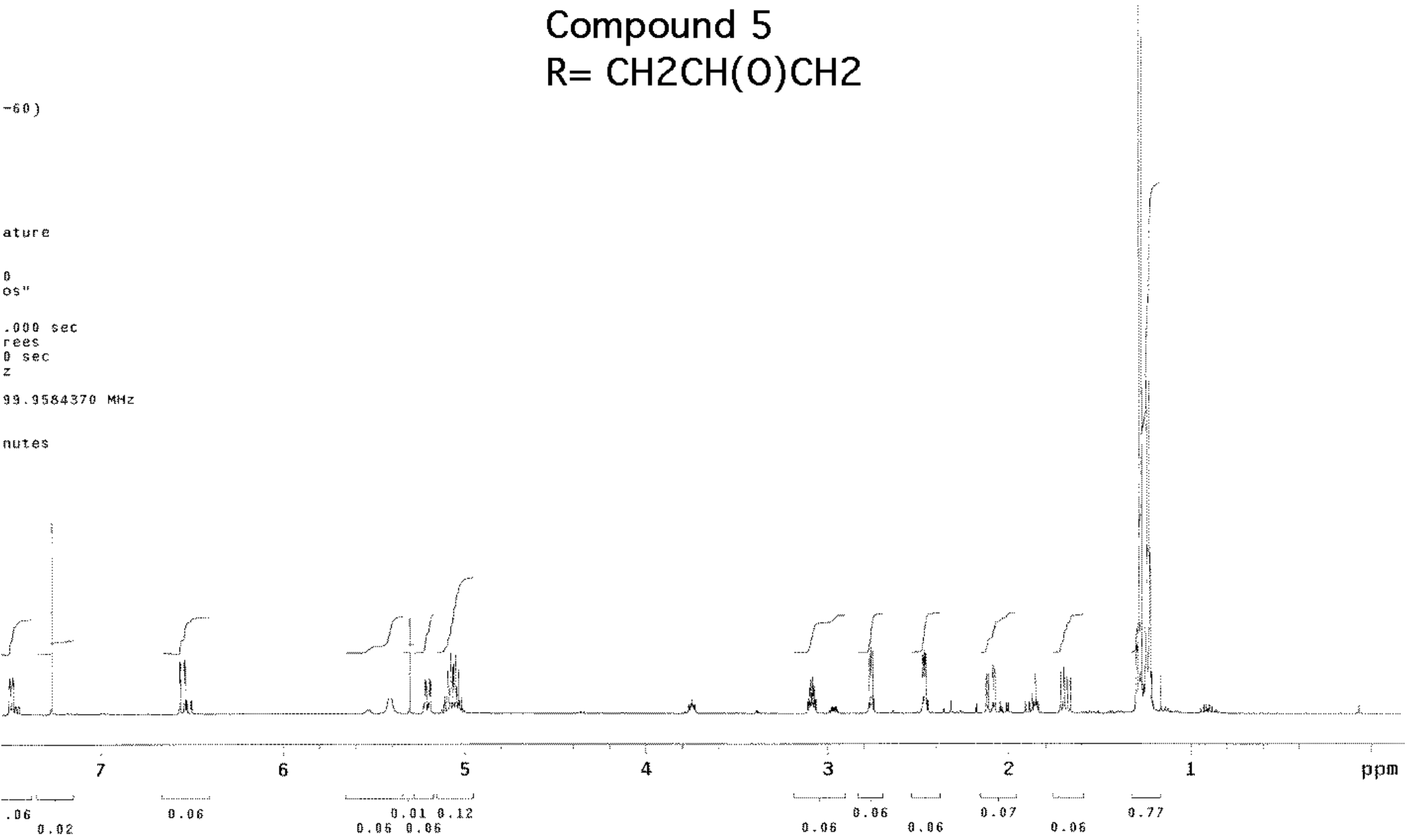
Compound 5
R= Et



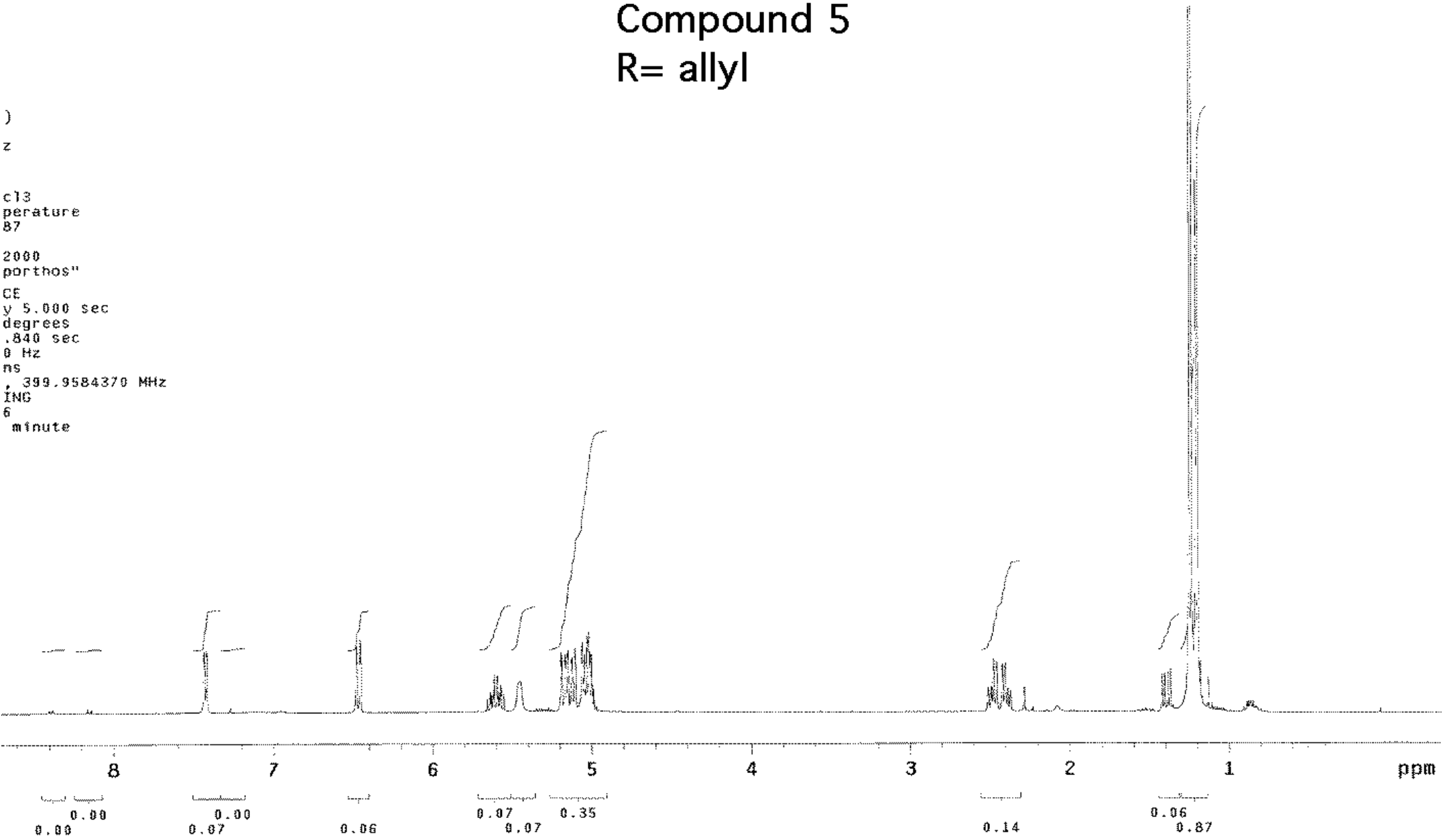
Compound 5
R= i-Bu



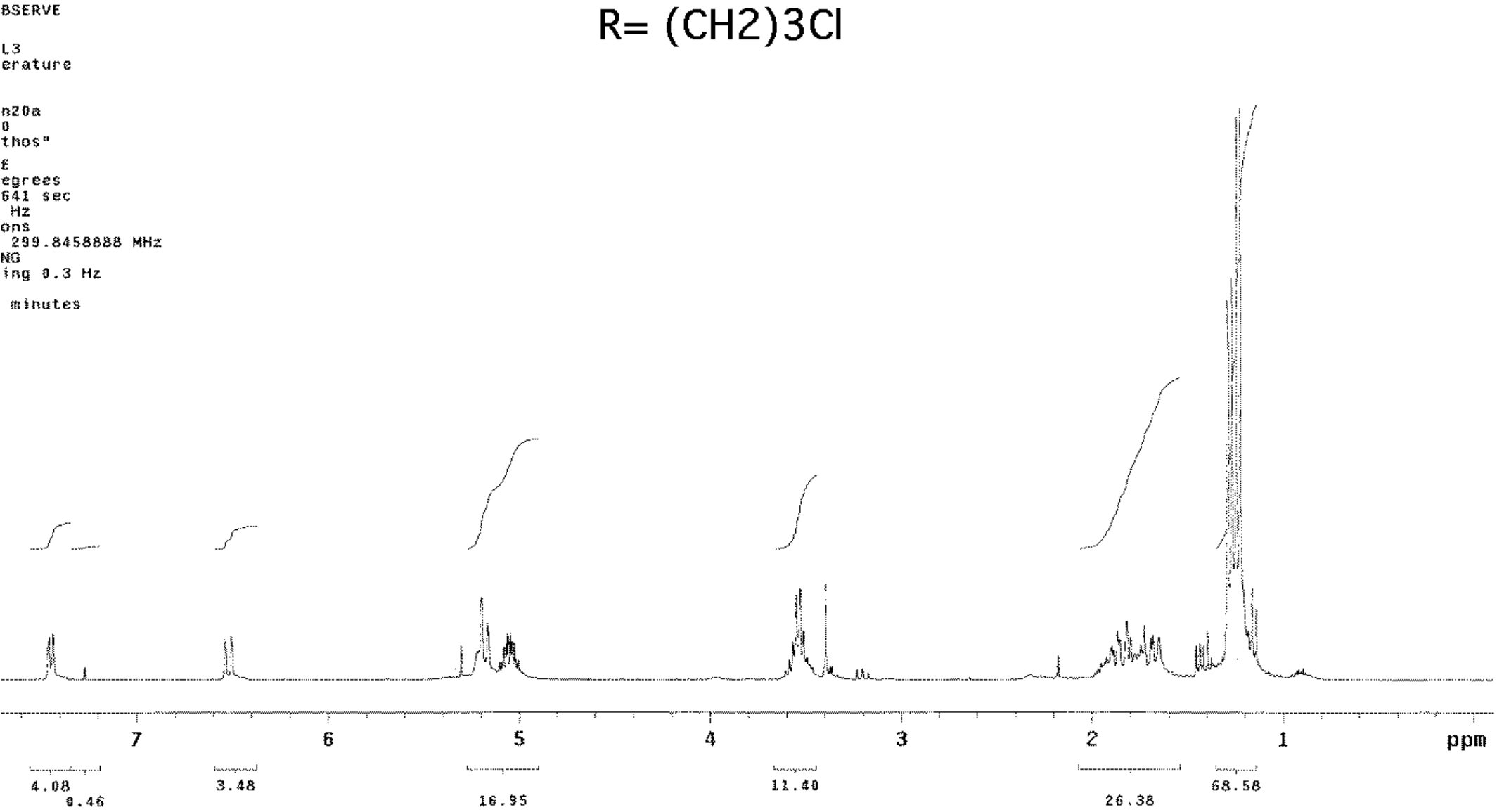
Compound 5
R= CH2CH(O)CH2



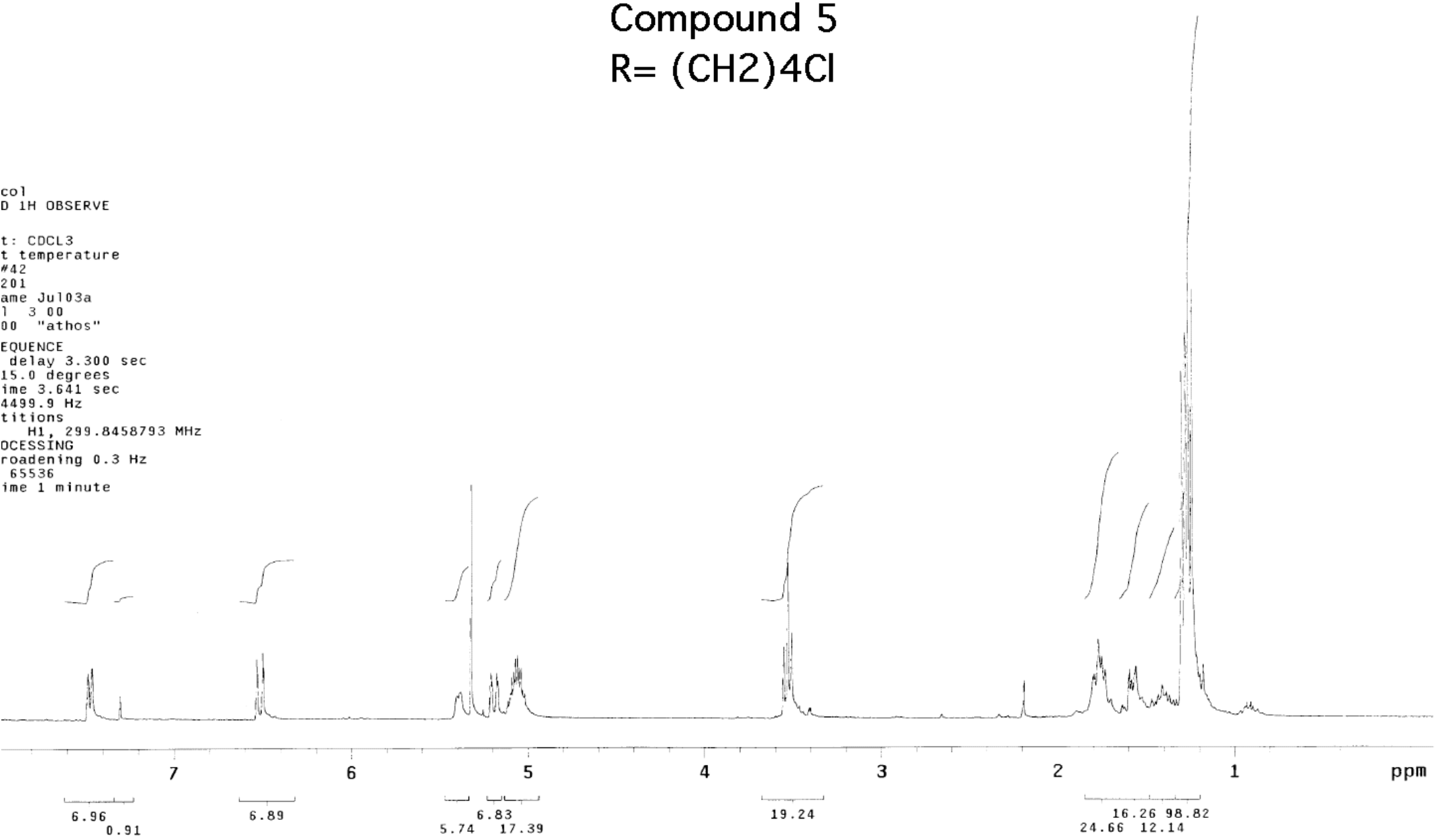
Compound 5
R= allyl



Compound 5
R= (CH2)3Cl



Compound 5
R= (CH2)4Cl



Andy McRiner
AJM6/73 col
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Aramis
Proton 400MHz
23.08.00
169

Solvent: cdcl3
Ambient temperature
User: 1-12-87
File: 169
DATE Aug 23 2000
INOVA-300 "athos"

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Acq. time 3.840 sec
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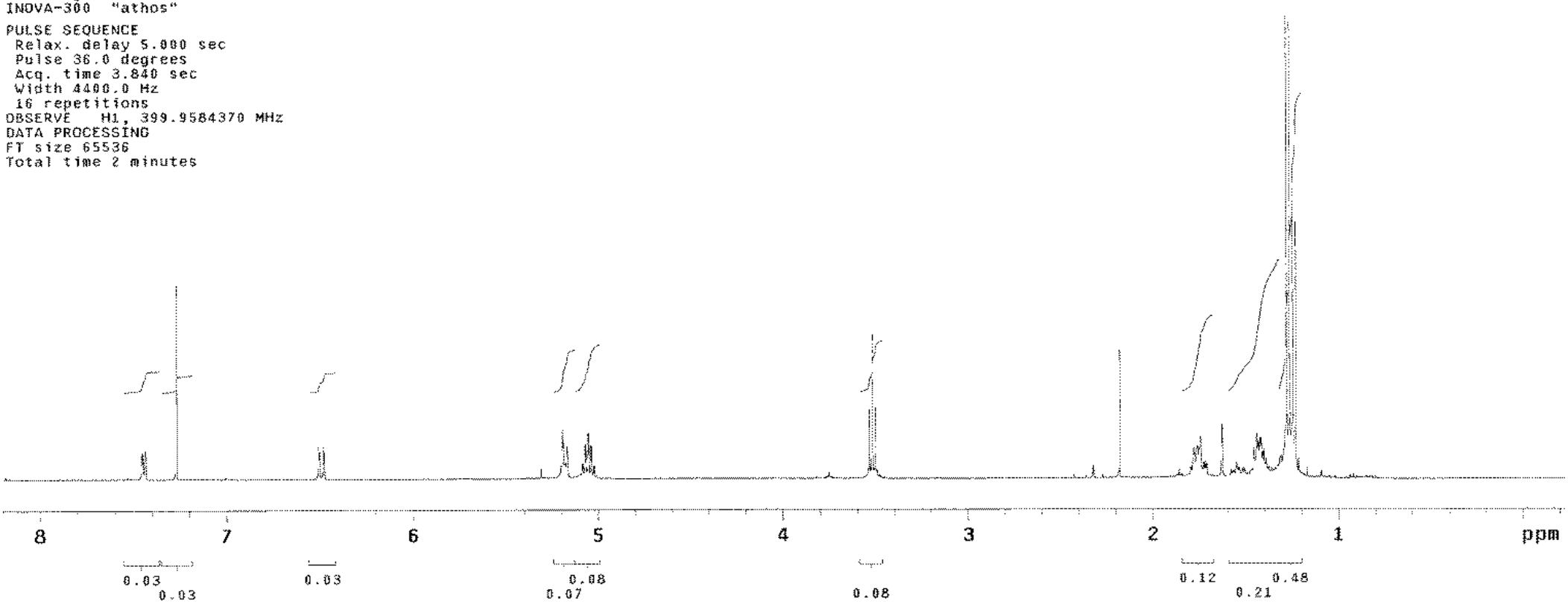
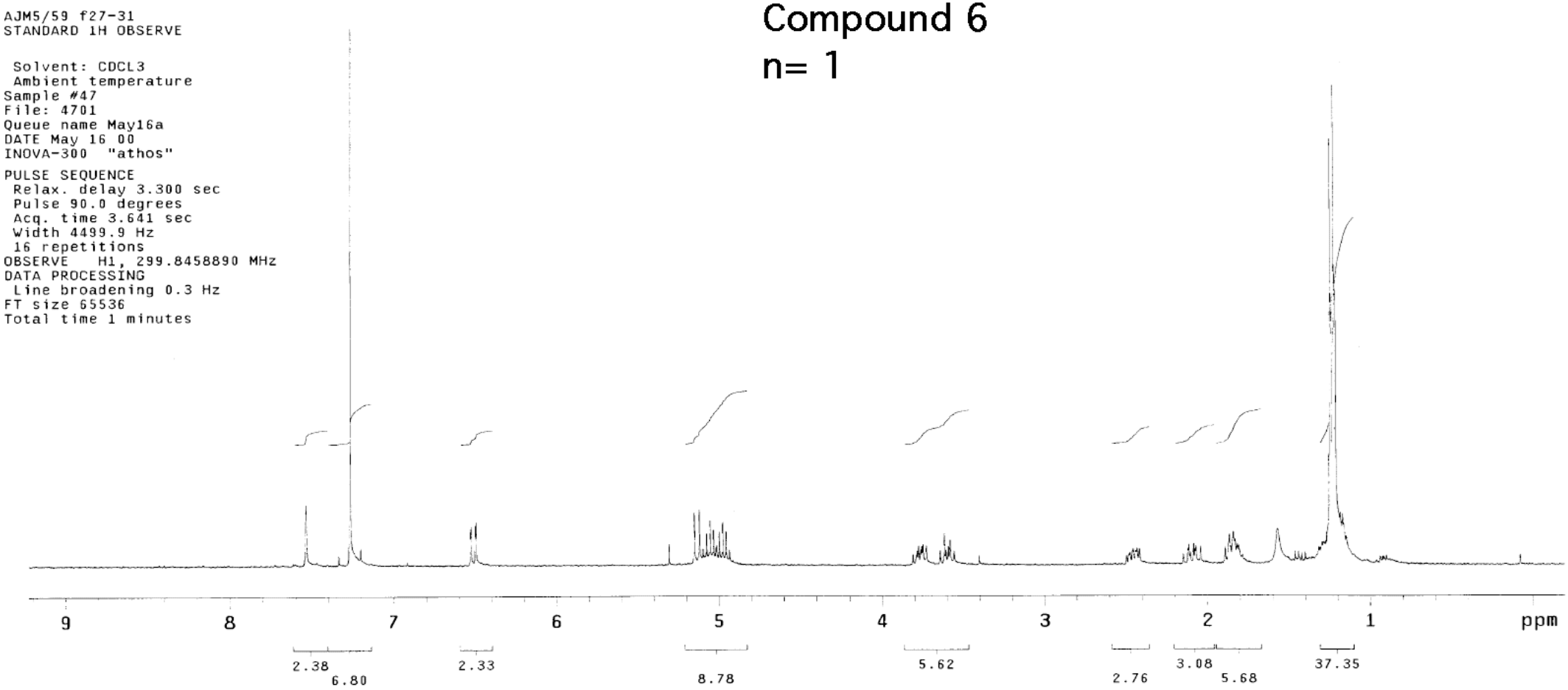
DATA PROCESSING
FT size 65536
Total time 2 minutes

Compound 5
R= (CH2)5Cl



Compound 6
n= 1

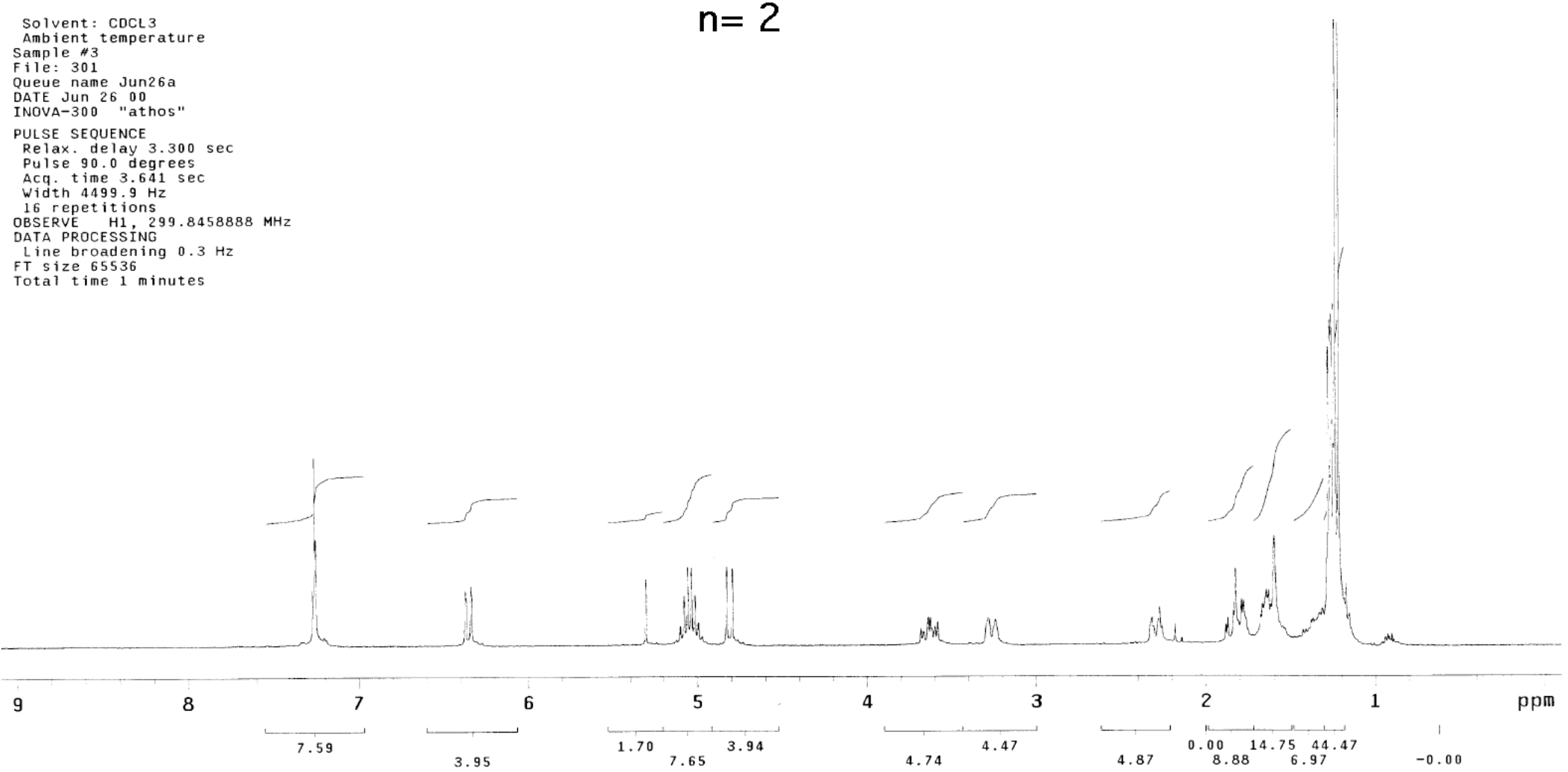


Compound 6
n= 2

AJM6/11 col
STANDARD 1H OBSERVE

Solvent: CDCL3
Ambient temperature
Sample #3
File: 301
Queue name Jun26a
DATE Jun 26 00
INOVA-300 "athos"

PULSE SEQUENCE
Relax. delay 3.300 sec
Pulse 90.0 degrees
Acq. time 3.641 sec
Width 4499.9 Hz
16 repetitions
OBSERVE H1, 299.8458888 MHz
DATA PROCESSING
Line broadening 0.3 Hz
FT size 65536
Total time 1 minutes



Compound 6
n=3