Pd-catalyzed dehydrogenative C–H activation of iminyl hydrogen with indole C3-H and C2-H bond: An elegant synthesis of indeno[1,2-*b*]indoles and indolo[1,2-*a*]indoles

*Somjit Hazra, Biplab Mondal, Rajendra Narayan De, and B Roy**

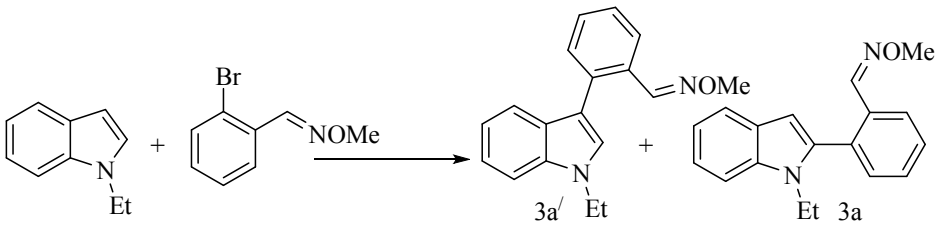
Supporting information

Contents

1. General:

Melting points were determined in open capillaries and are uncorrected. IR spectra (ν_{max} in cm^{-1}) were recorded on a Perkin-Elmer L 120-000A spectrometer on KBr disks. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DPX-400 spectrometer in $CDCl_3$ with TMS as internal standard (chemical shift in δ). Chemical shifts of common trace PMR impurities ($CDCl_3$, ppm) in some samples: H_2O, 1.56; solvent impurities: 1.26, 0.86; $CHCl_3$, 7.26. In some low polar samples ^{13}C peak was observed at 29.7 (δ_C) corresponding to solvent greasy impurities. CHN was recorded on 2400 series II CHN analyzer Perkin Elmer instrument. MS were recorded on a Q-TOF micro^{Tm} instrument. Silica gel [(60-120, 230-400 mesh), Rankem, India] was used for chromatographic separation. Silica gel G [CDH, (India)] was used for TLC. Petroleum ether refers to the fraction boiling between 60 °C and 80 °C.

2.a. Table 1: **Optimization of C2-arylations of *N*-ethyl indole**:

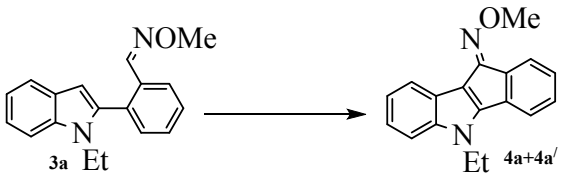


Entry	Catalyst (1mol%)	Ligand[a,b]	Solvent	Temp	Con(%)	Yield [%][c] 3a/	3a
1	$Pd(OAc)_2$	-	DMF	130 °C	71	30	40
2	$Pd(OAc)_2$	-	*o*-xylene	130 °C	20	25	41
3	$Pd(OAc)_2$	-	Dioxane	100 °C	45	29	34
4	$Pd(OAc)_2$	-	DMA	130 °C	81	28	42
5	$Pd(OAc)_2$	1	DMA	130 °C	100	27	52
6	$Pd(OAc)_2$	2	DMA	130 °C	84	31	37
7	$Pd(OAc)_2$	3	DMA	130 °C	72	23	41
8	$Pd(OAc)_2$	1	DMA	90 °C	61	32	43
9	$Pd(OAc)_2$	1	DMA	145 °C	100	22	41

[a] Ligands are 1=PPh_3,2=Xantphos,3=1,10-Phenanthroline, [b] CsOAc was used as base. [c] yield were calculated after collumn chromatography.

Starting from Sames *et. al.* procedure,[1] we tried to optimize the C2-arylation reaction by varying ligands, solvents and temperature. We found DMA as solvent, gave the best conversion. We tried 3 ligands, among them PPh_3 acted most proficiently (Table 1, entry 5). The optimum temperature was found to be 130 °C. When the reaction was carried out in 90 °C (Table 1, entry 8) the conversion and the ratio of 3a/3a/ is low. At higher temperature the yield reduced slightly (Table 1, entry 9).

2.b. Table 2. Optimization of intramolecular dehydrogenative cross coupling reaction



Entry	Catalyst[a]	Additive	Solvent	Yield[%][b]
1	$Pd(OAc)_2$	$Cu(OAc)_2$	DMF	70
2	$Pd(OAc)_2$	$PhI(OAc)_2$	DMF	65
3	$Pd(OAc)_2$	AgOAc	DMF	76
4	$Pd(OAc)_2$	$K_2S_2O_8$	DMF	82
5	$Pd(OAc)_2$	$K_2S_2O_8$	Toluuene	15
6	$Pd(OAc)_2$	$K_2S_2O_8$	o-xylene	36
7	$Pd(OAc)_2$	$K_2S_2O_8$	Dioxane	53
8	$Pd(OAc)_2$	$K_2S_2O_8$	DMA	85
9	$Pd_2(dba)_3$	$K_2S_2O_8$	DMA	NR
10	$PdCl_2$	$K_2S_2O_8$	DMA	80
11	$Pd(MeCN)_2Cl_2$	$K_2S_2O_8$	DMA	60
12	$Cu(OTf)_2$[c]	-	DMA	22

Reaction condition: 2-arylated indoloxime (1 equiv.), $Pd(OAc)_2$ (5 mol%), $K_2S_2O_8$ (1equiv.), stirred at 110 ^oC in DMA. a) Catalyst used 5 mol% b) Yields were calculated after flash chromatography. c) $Cu(OTf)_2$ was used in 1 equiv. N.R = no reaction. Reaction time =1.5-3h (reaction was monitored by TLC).

Initially the reaction was conducted in DMF using $Pd(OAc)_2$ (5 mol%) and $Cu(OAc)_2$ (1equiv.) as oxidizing agent at 110 ^oC. We observed the formation of the cross coupling product with a yield of 70% (Table 2, entry 1).Interestingly, both geometrical isomers (**4a** and **4a**/) was detected. However, only the major isomer was successfully purified. The minor isomer was obtained as a contaminant with the major isomer. Other oxidizing agents were also tried but the best yield (82%) was obtained with $K_2S_2O_8$ (Table

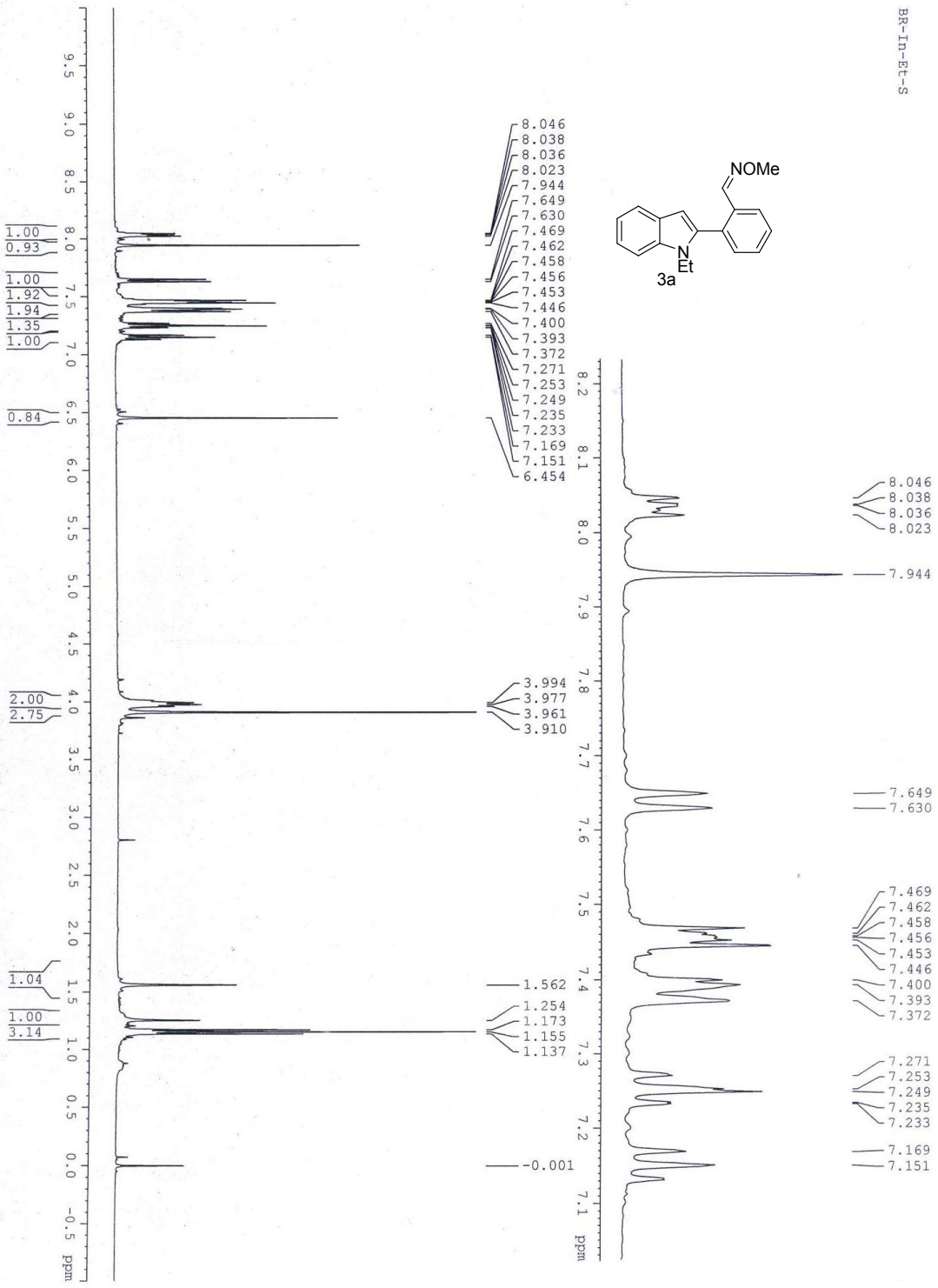
2, entry 4), although the yield with AgOAc (Table 2, entry 3) was also very good (76%).We then screened some other solvents for this transformation. We found the polar solvents to respond much better compared to the no polar ones. However, dioxane (Table 2, entry 7) gave only modest yield (53%) and the yields were very low with toluene and *o*-xylene (Table 2, entry 5, 6). Interestingly, DMA gave the best yield (85%) and the reaction was completed within 2 hours (Table 2, entry 8). As expected, Pd_2dba_3 [Pd (0)] was not effective (Table 2, entry 9) for the transformation while $PdCl_2$ gave very good yield (80%).The reaction was found to be less efficient with $PdCl_2(MeCN)_2$ giving a combined yield of 60%. Reasoning that, the reaction is probably proceeding *via* electrophilic palladation in C3-position, we performed the reaction with an electrophilic copper salt [$Cu(OTf)_2$]. Very interestingly, we observed the formation of the cross coupling product but instead of both geometrical isomers (**4a** and **4a'**), only a single isomer (the major isomer of previous reactions) was formed. However the yield was low in comparison with Pd salts (Table 2, entry 12) and the reaction was completed in 1.5 hours.

Reference:

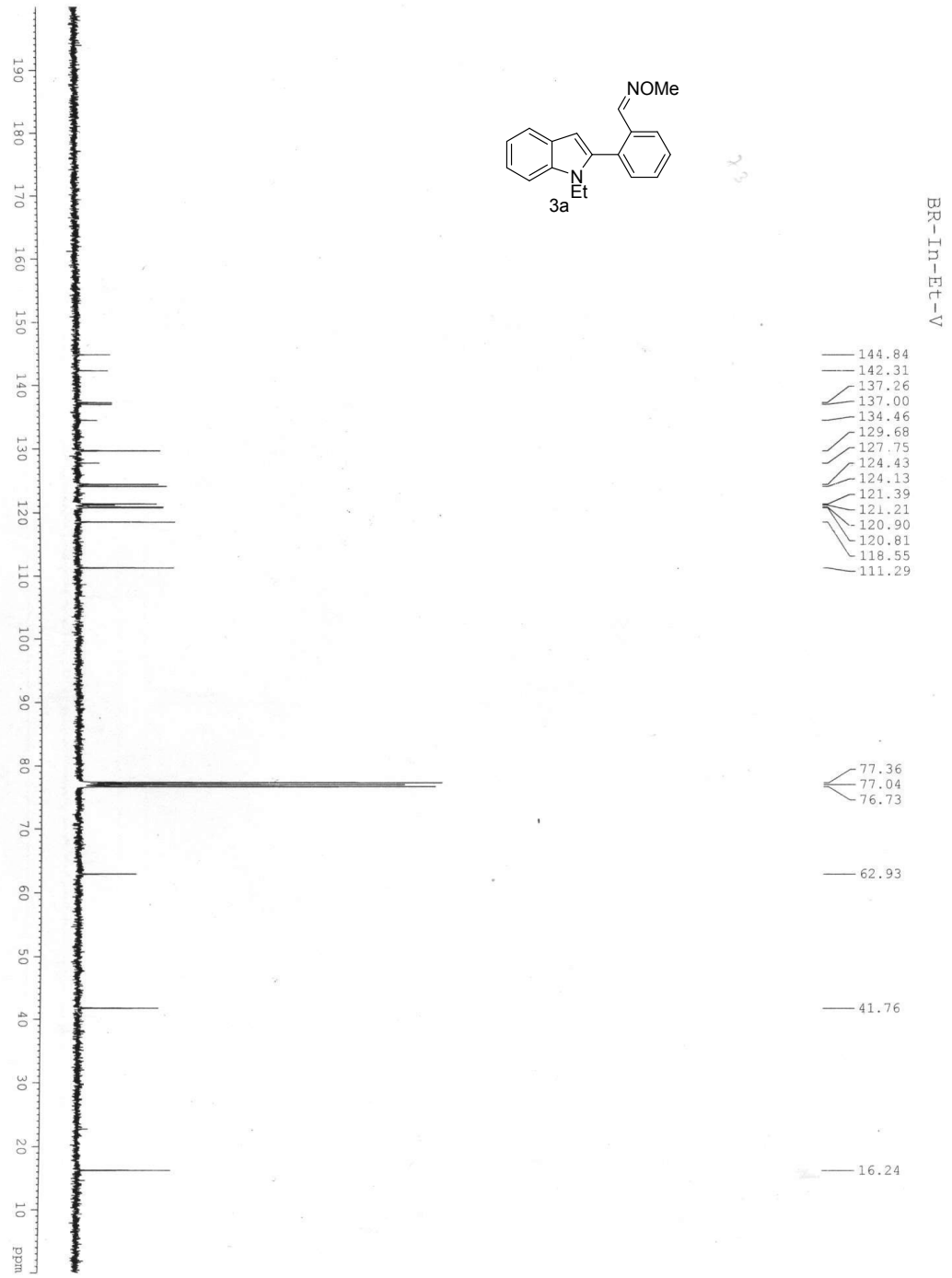
1. Lane, B. S.; Brown, M. A.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 8050.

1H and 13C NMR scan copies:

2-(1-ethyl-1H-indol-3-yl)benzaldehyde O-methyl oxime (3a) :



2-(1-ethyl-1H-indol-3-yl)benzaldehyde O-methyl oxime (3a):



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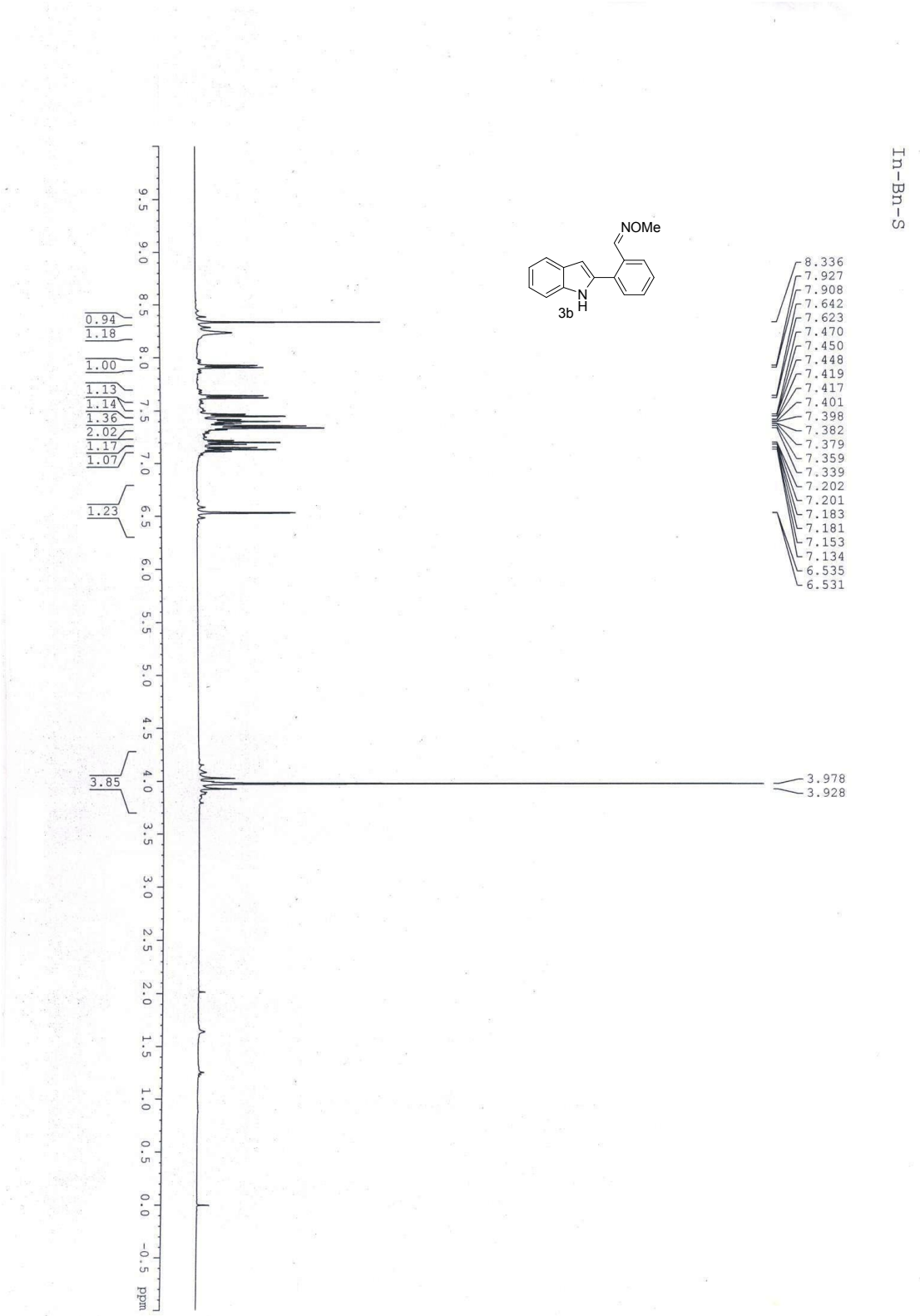
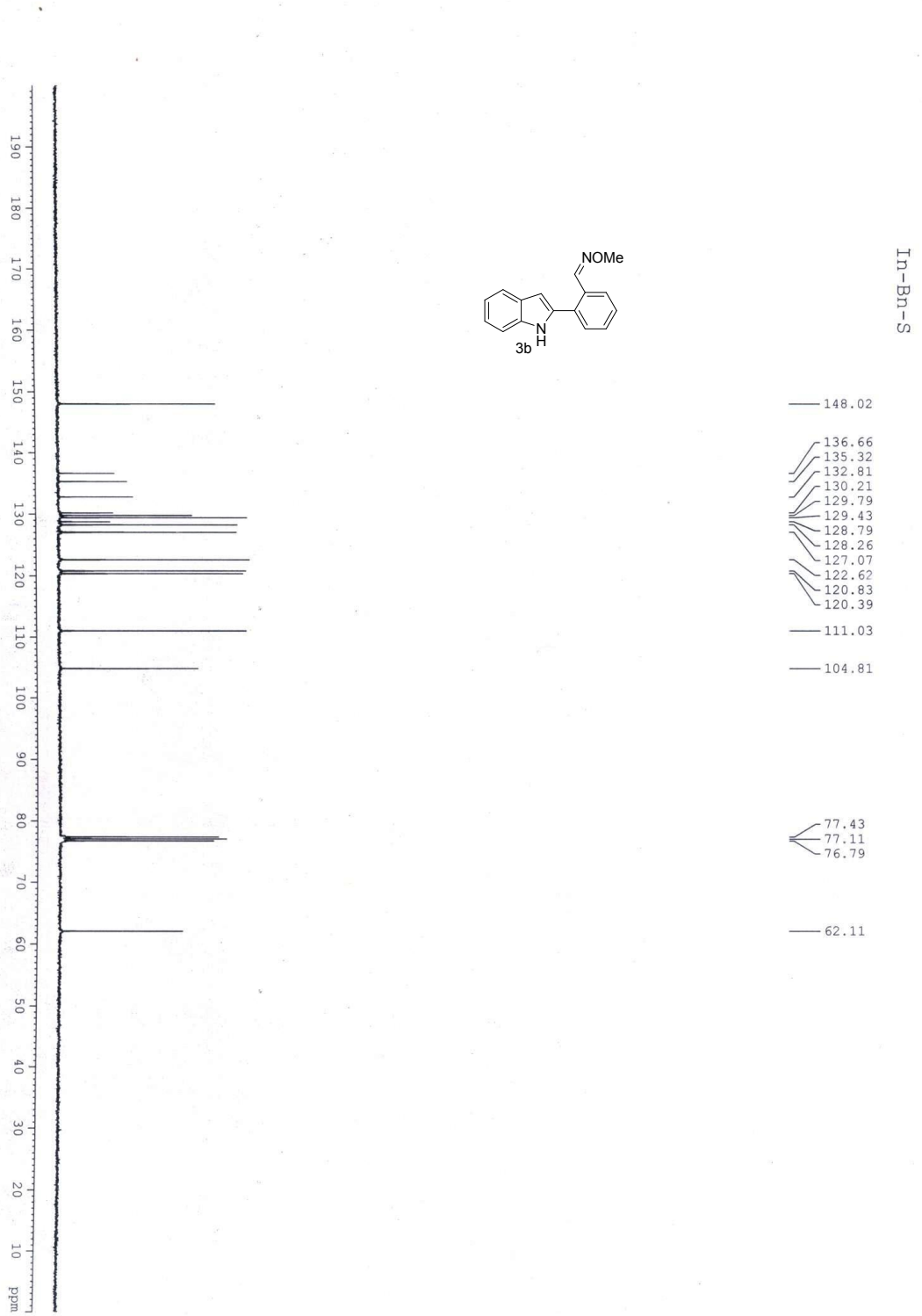
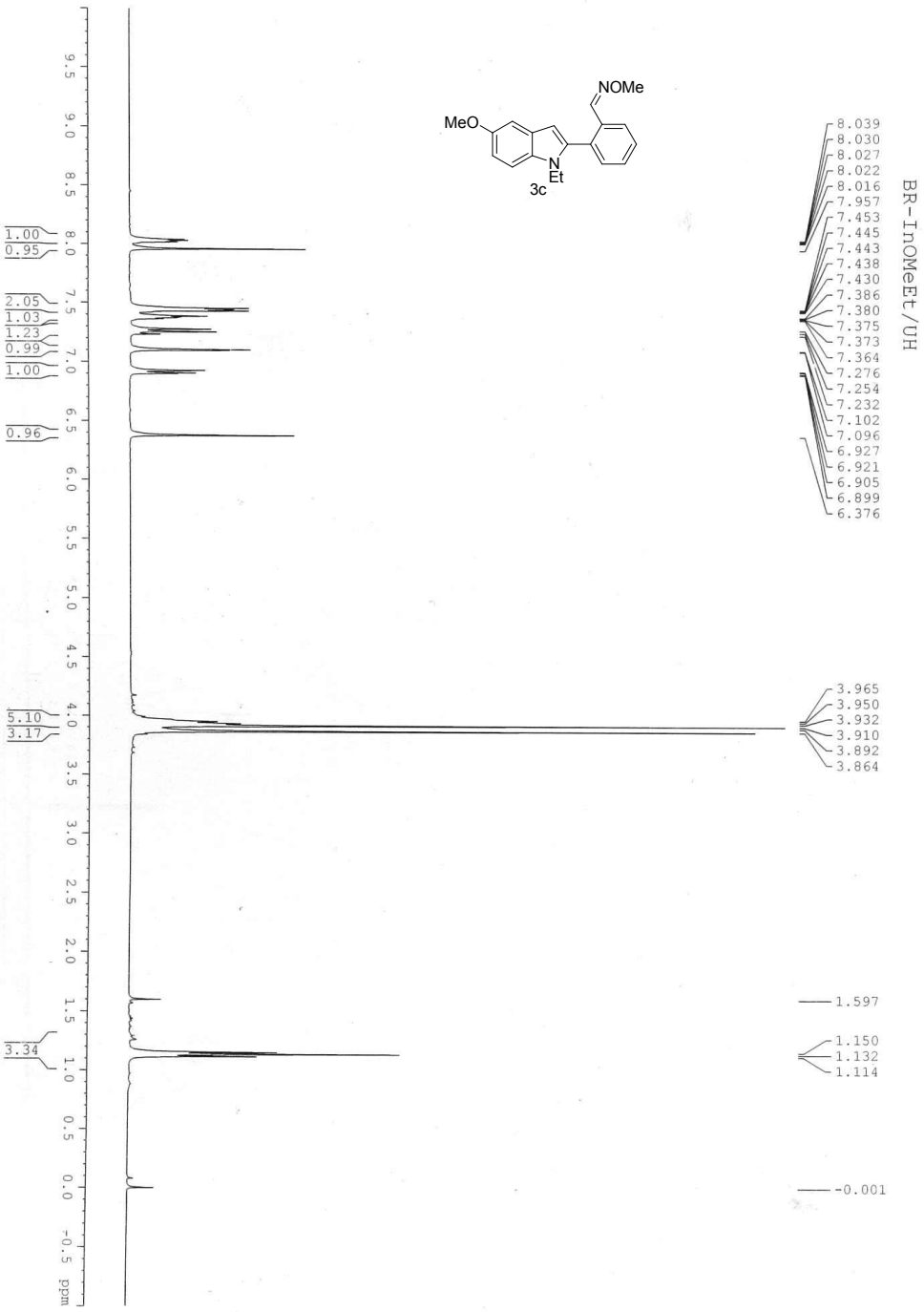


2-(1H-indol-2-yl)benzaldehyde O-methyl oxime (3b):



2-(1-ethyl-5-methoxy-1H-indol-2-yl)benzaldehyde O-methyl oxime (3c):



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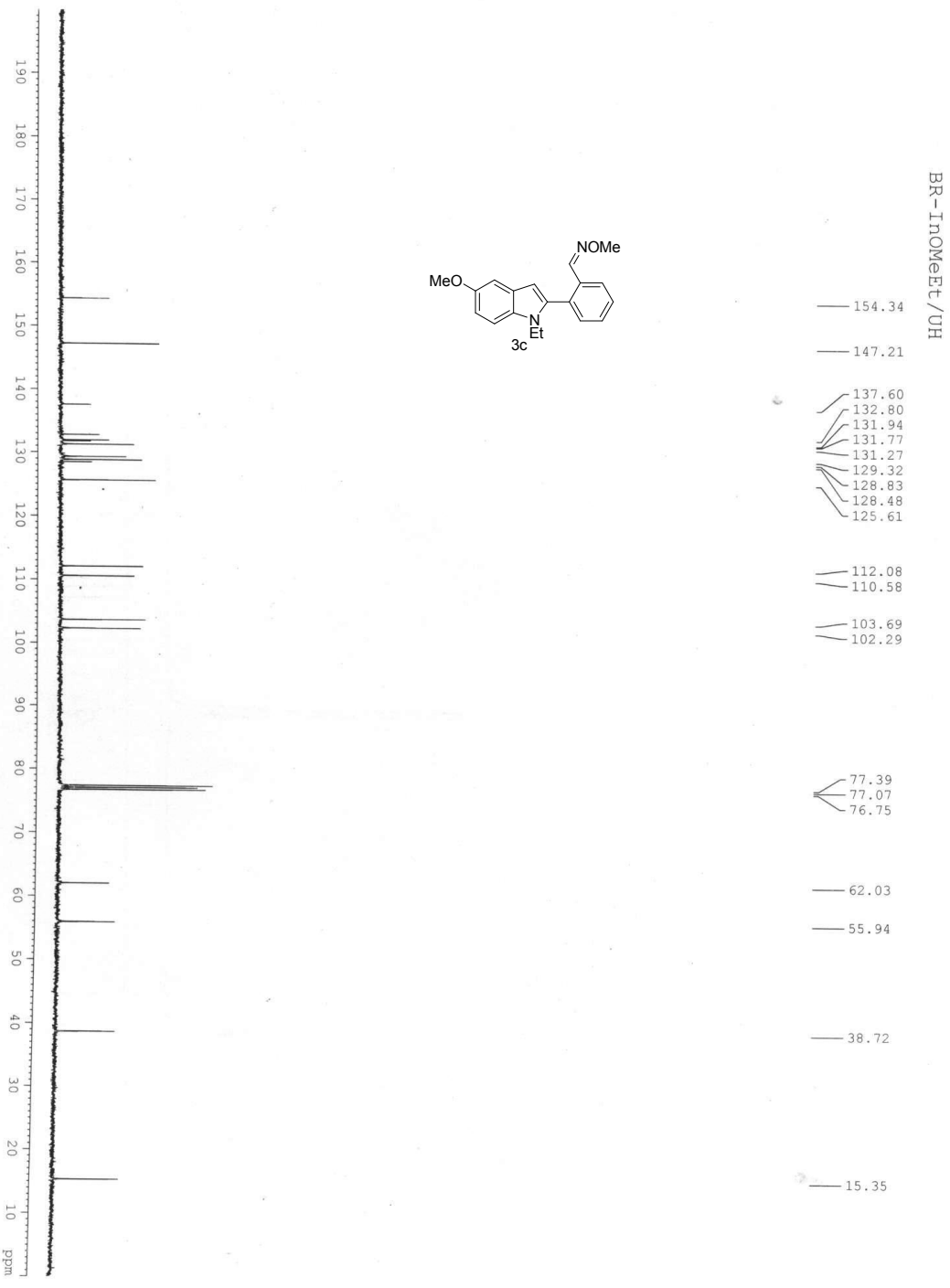

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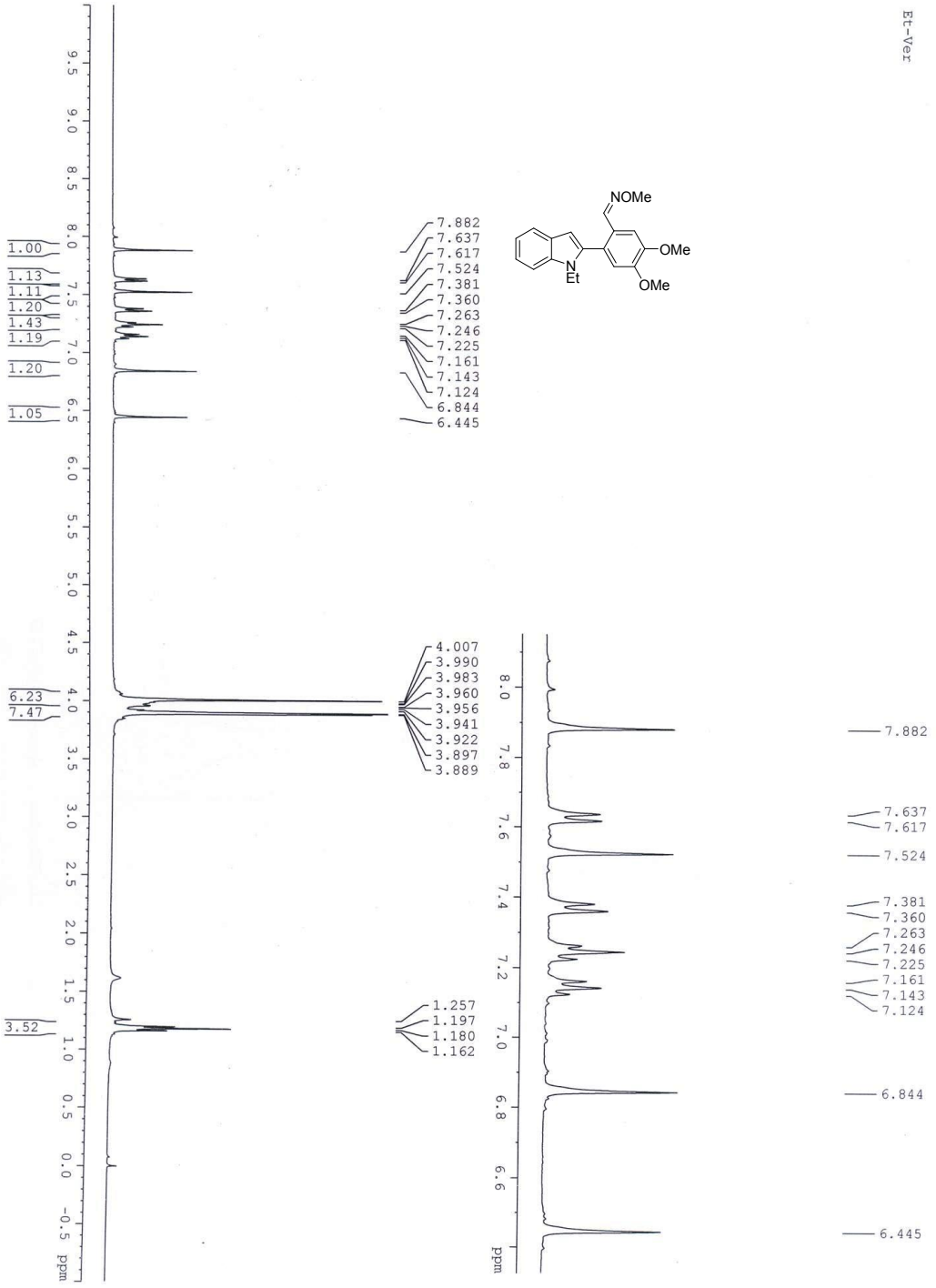
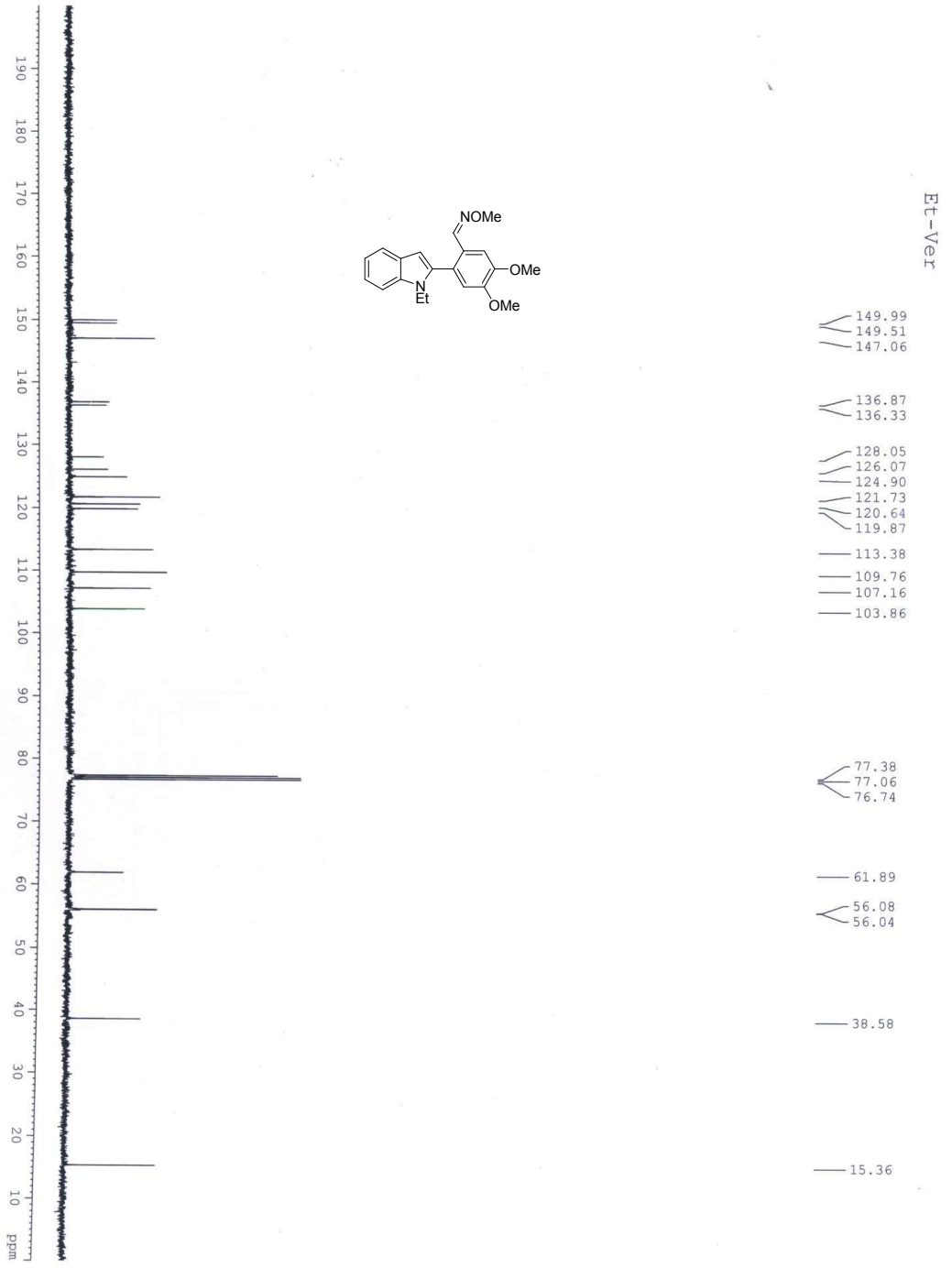


2-(1-ethyl-1H-indol-2-yl)-4,5-dimethoxybenzaldehyde O-methyl oxime (3d):



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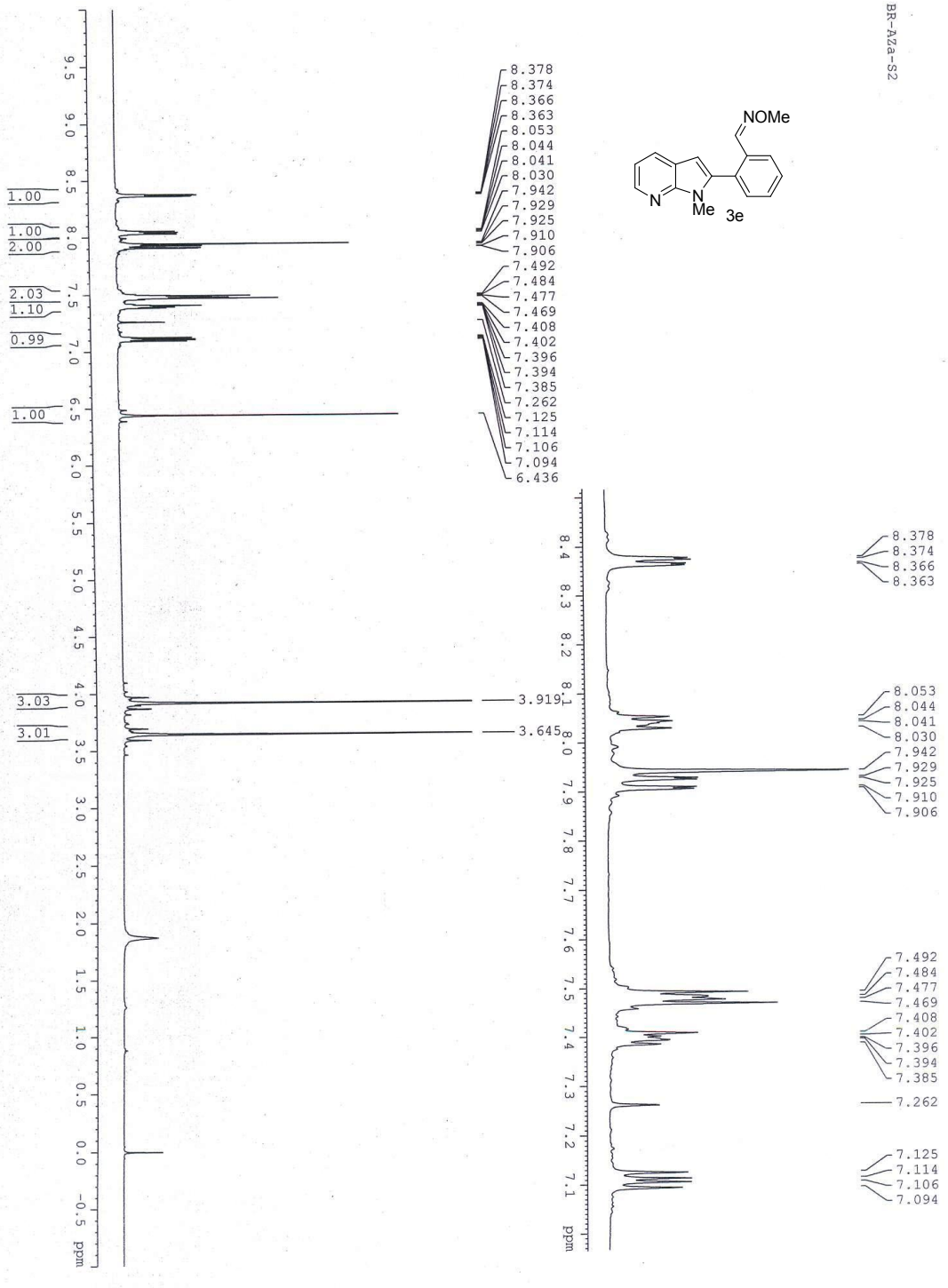
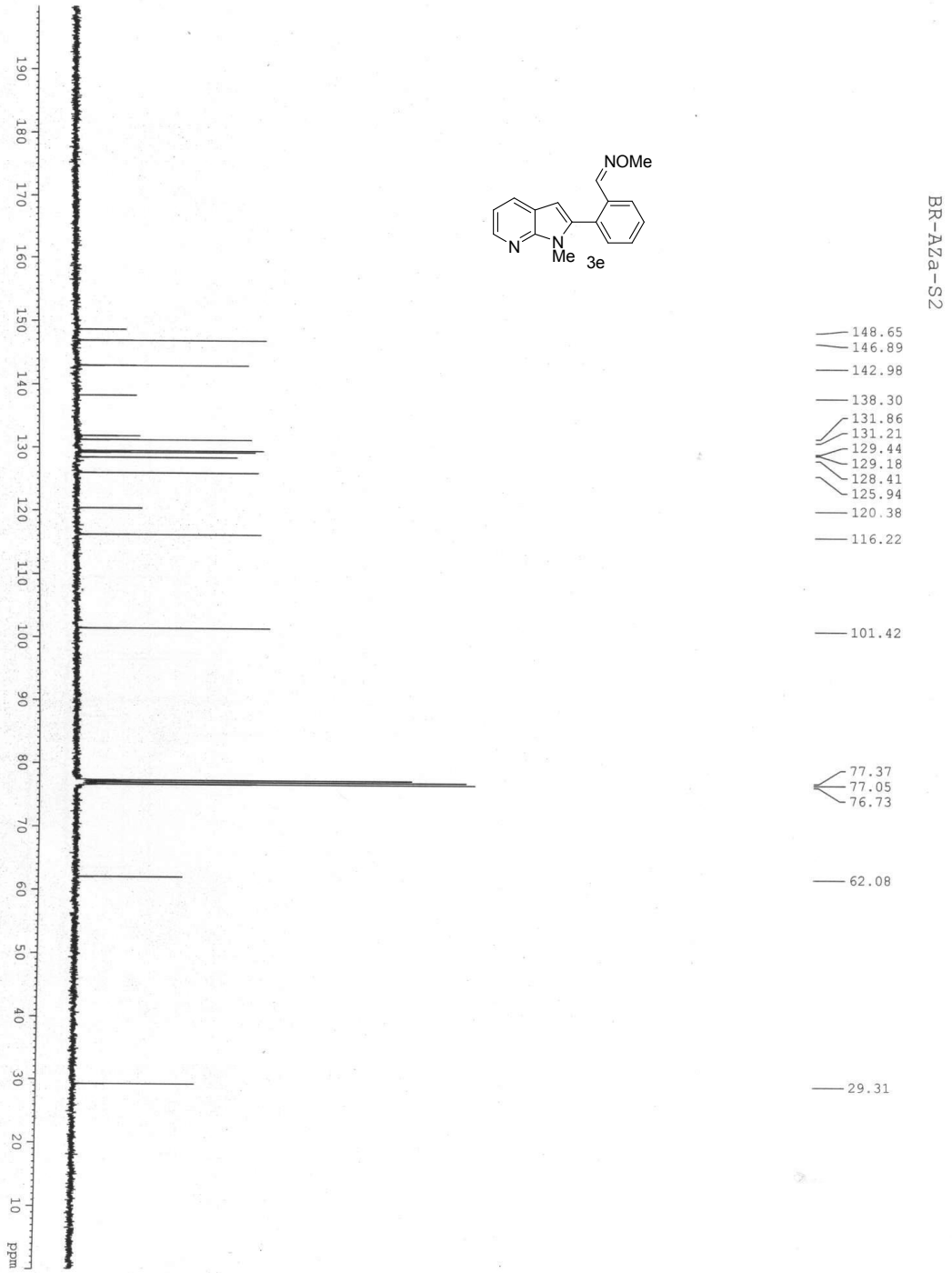
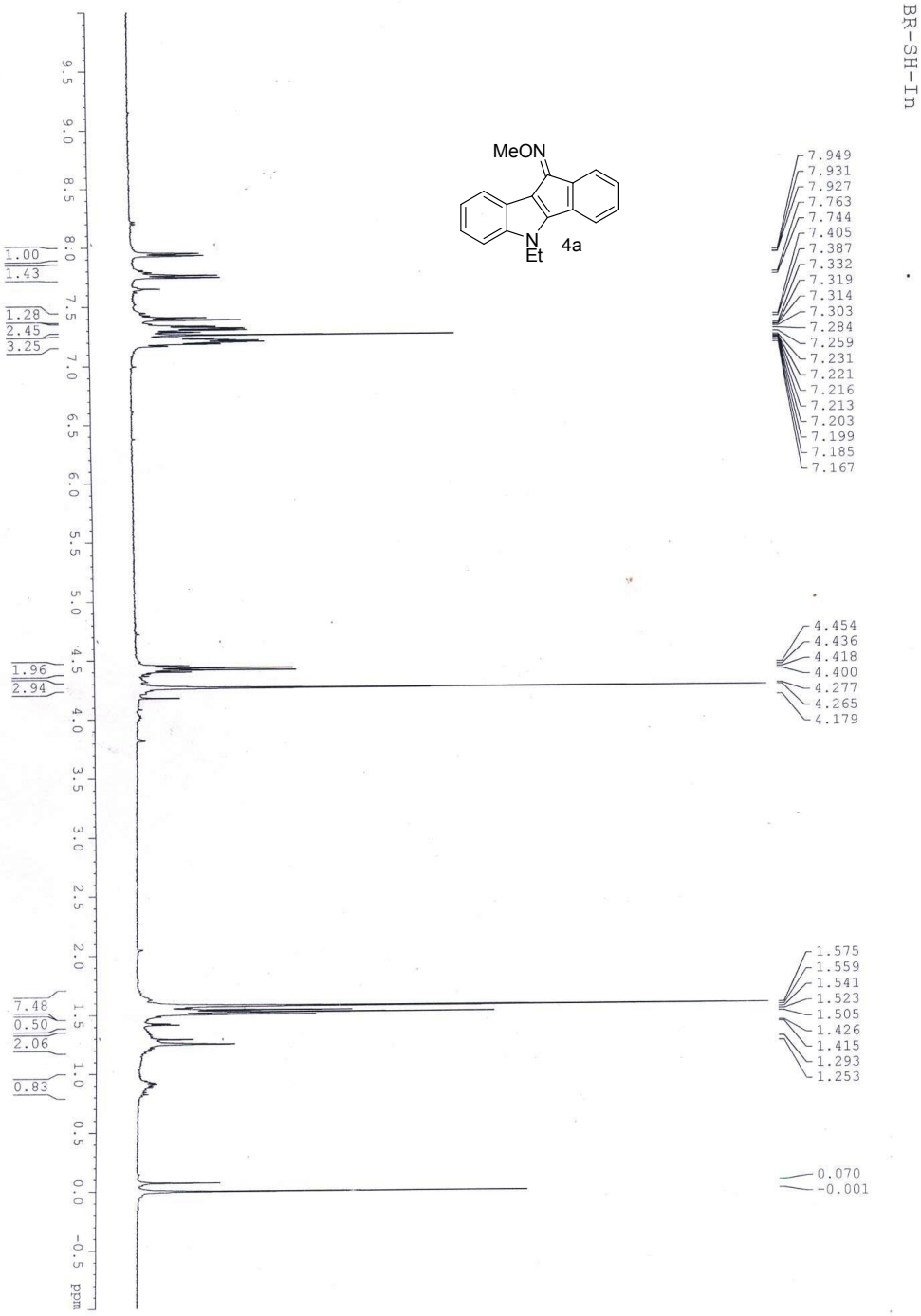


2-(1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)benzaldehyde O-methyl oxime (3e) :



5-ethylindeno[1,2-b]indol-10(5H)-one O-methyl oxime (4a) :



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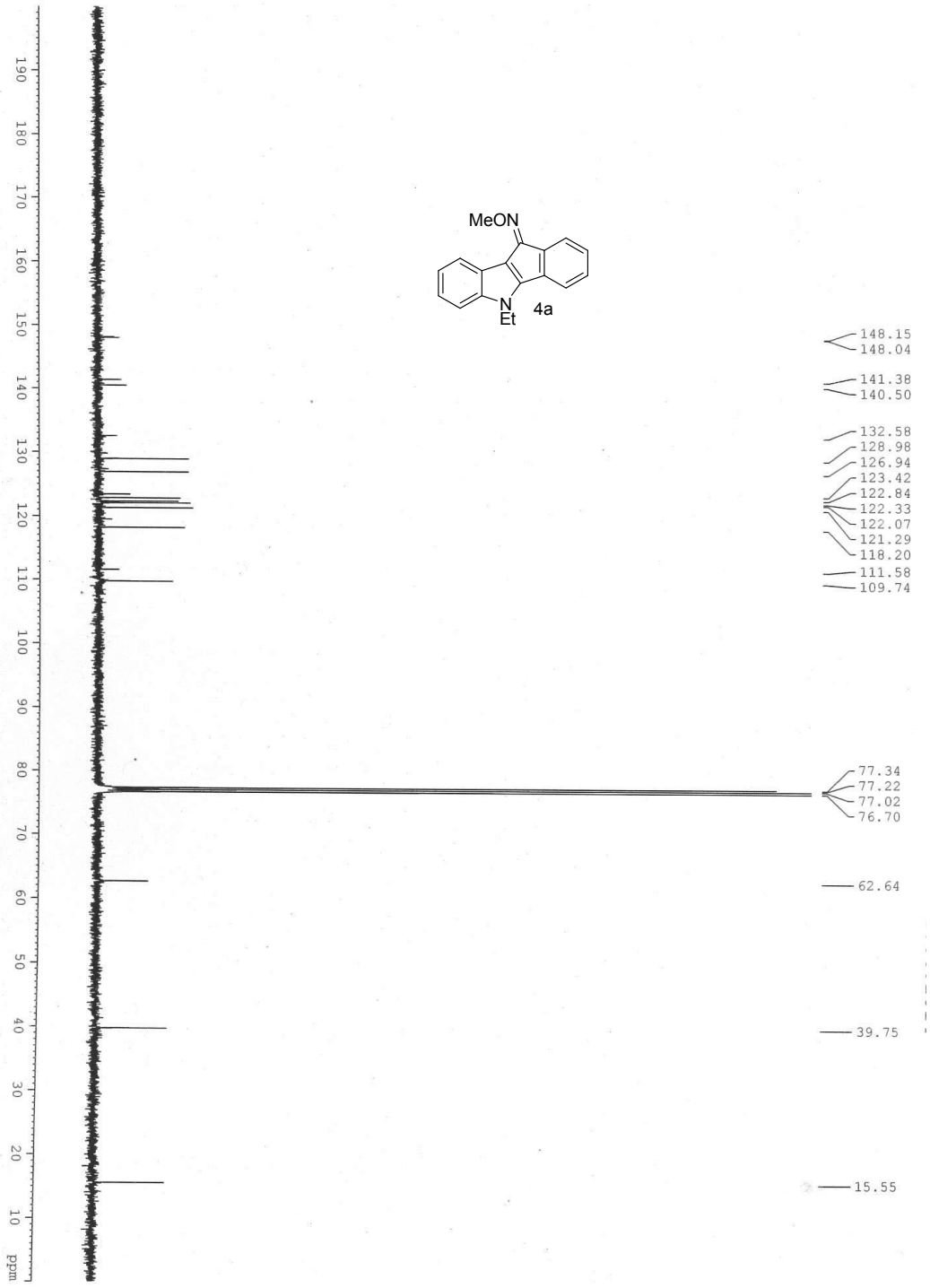

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7.176
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4.308
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+ 4a
N
Et
4a'
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1.00
0.50
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3.69
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ppm

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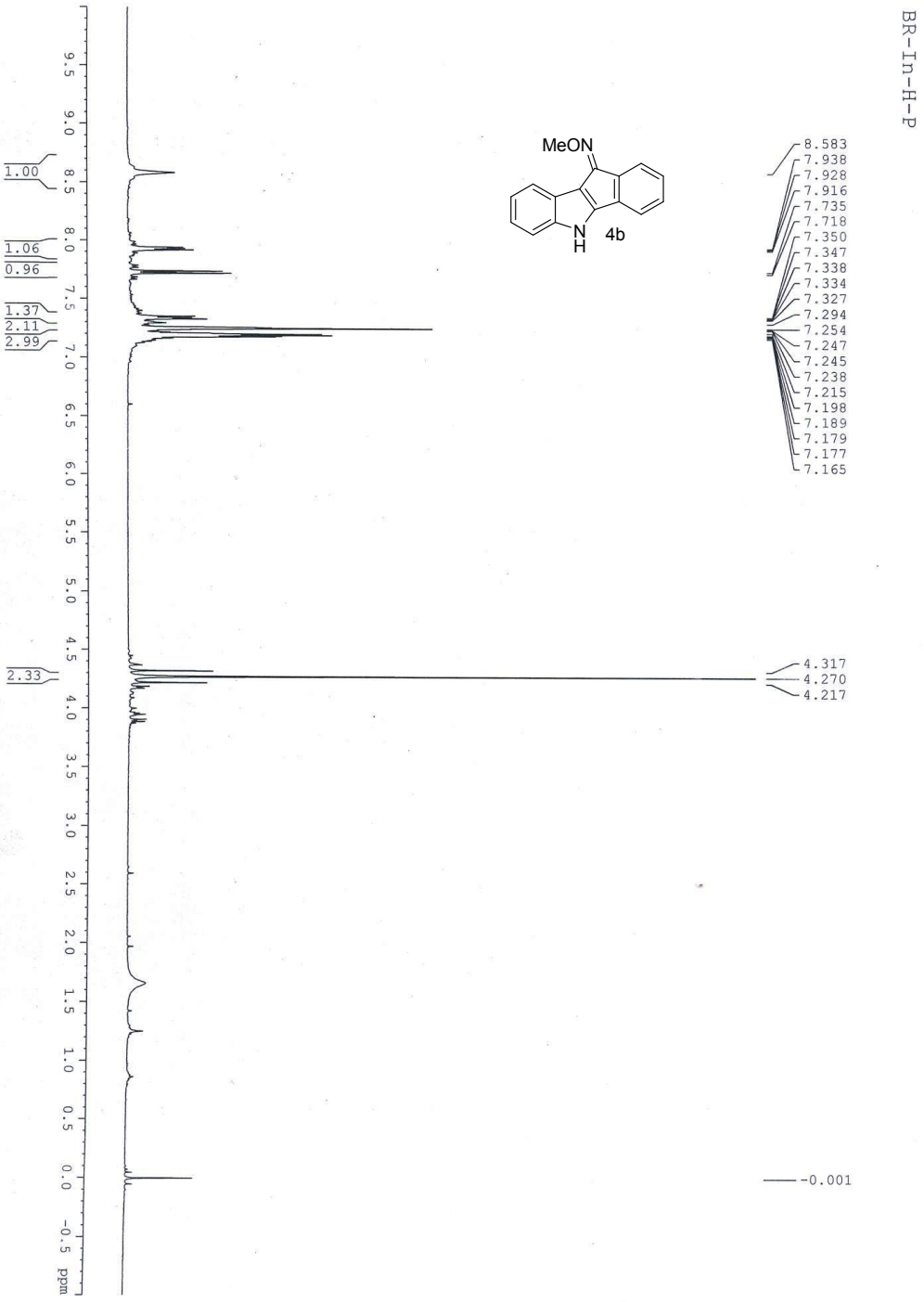
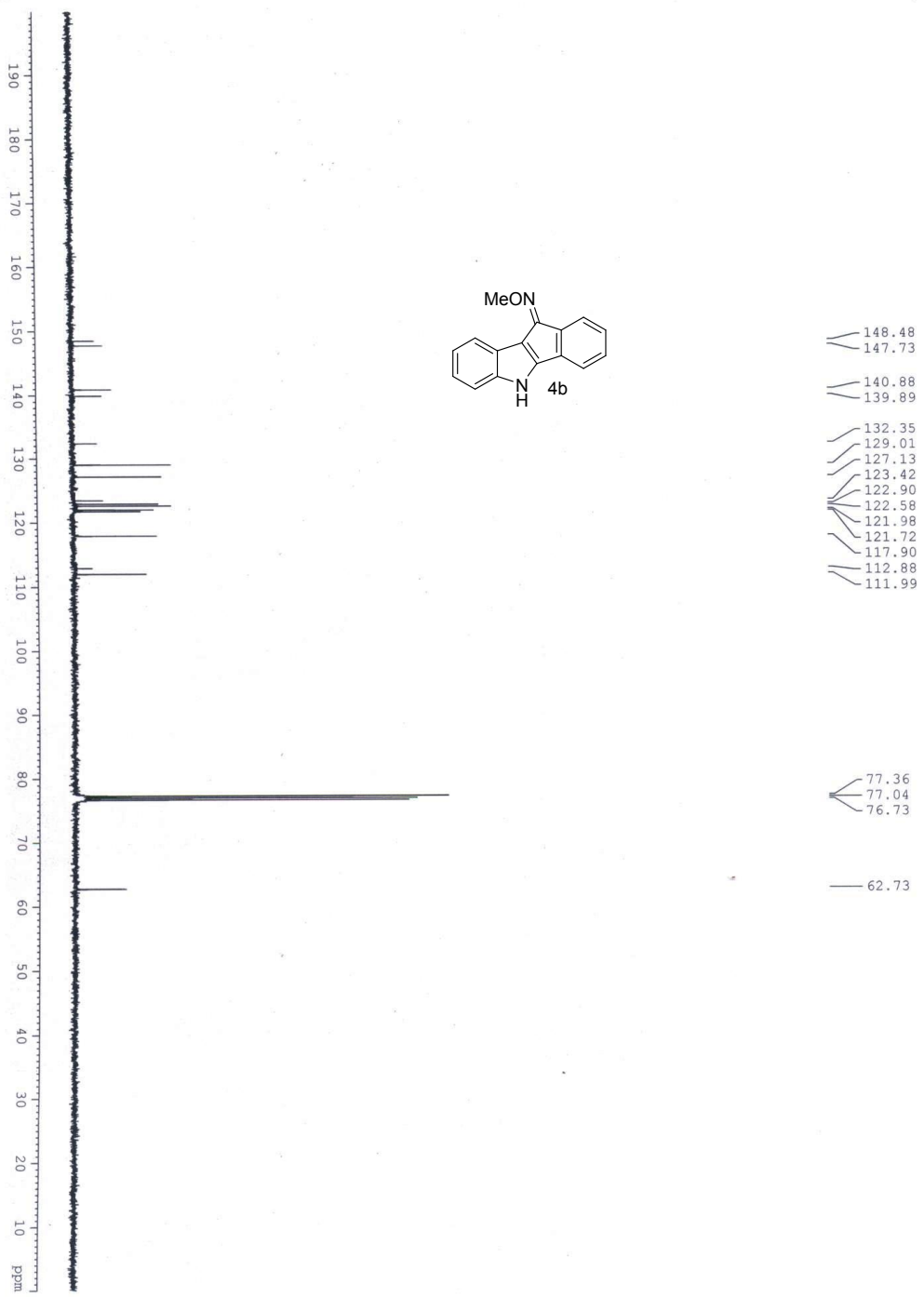
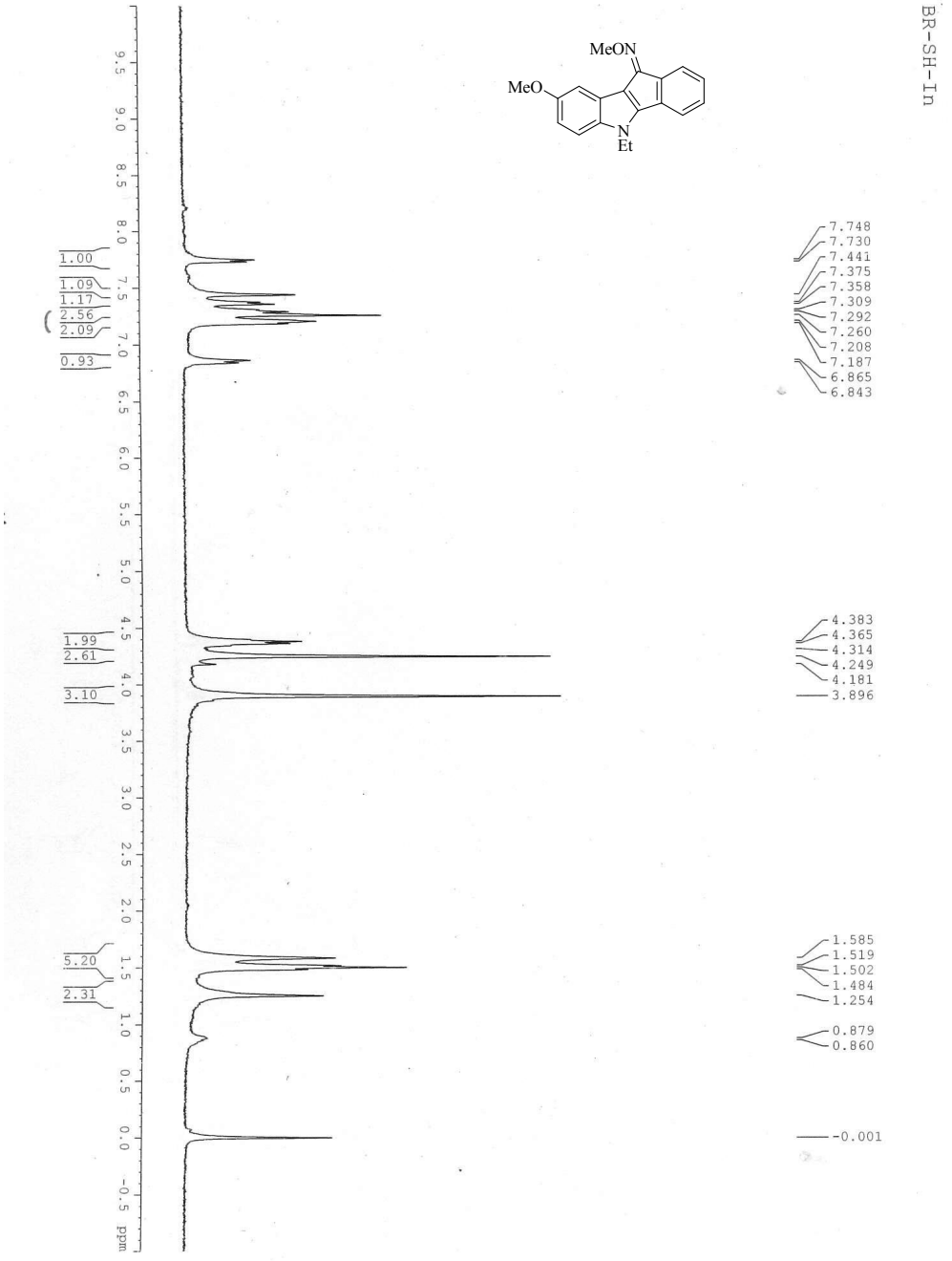


indeno[1,2-b]indol-10(5H)-one O-methyl oxime (4b):



5-ethyl-8-methoxyindeno[1,2-b]indol-10(5H)-one O-methyl oxime (4c):



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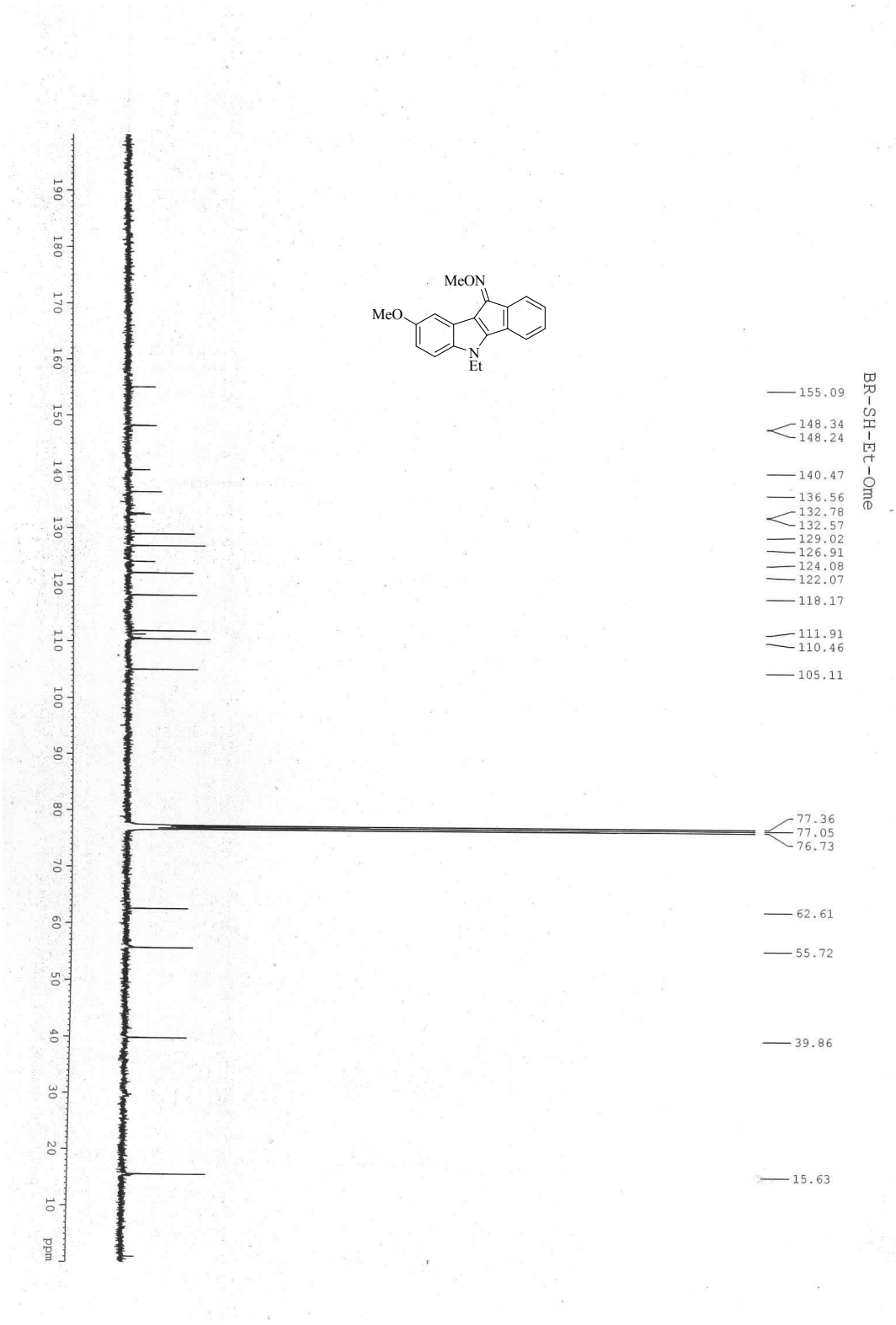

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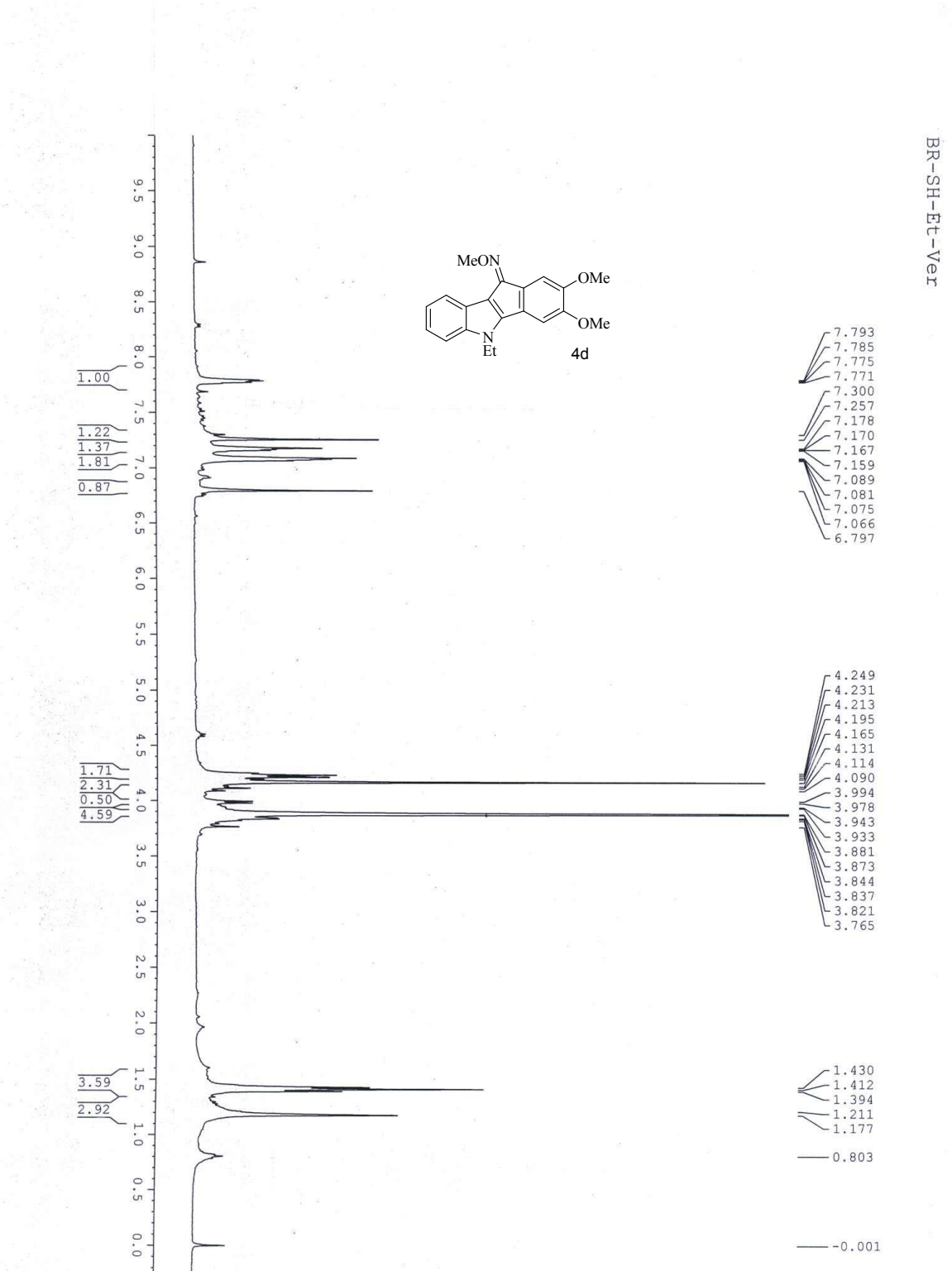

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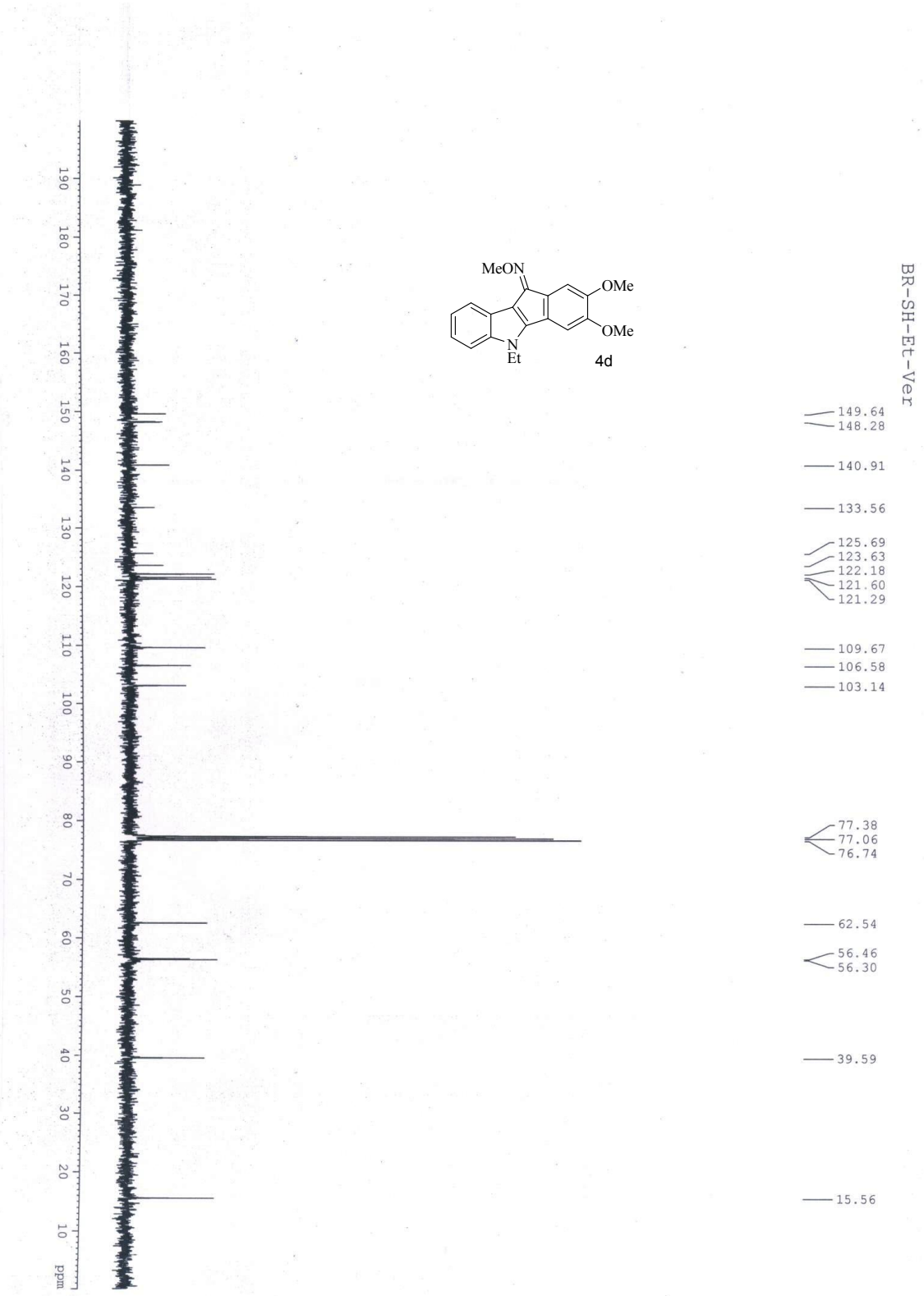

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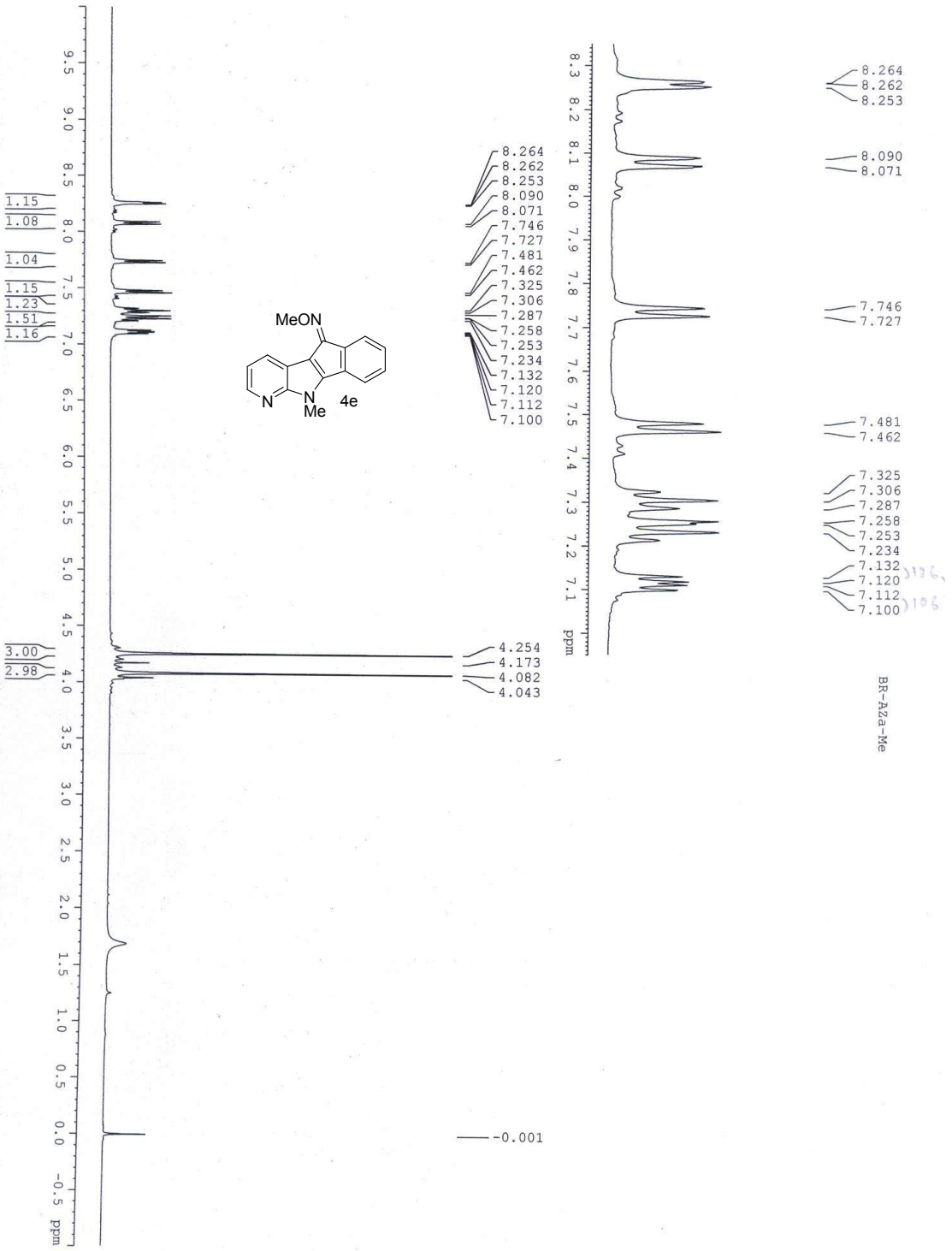
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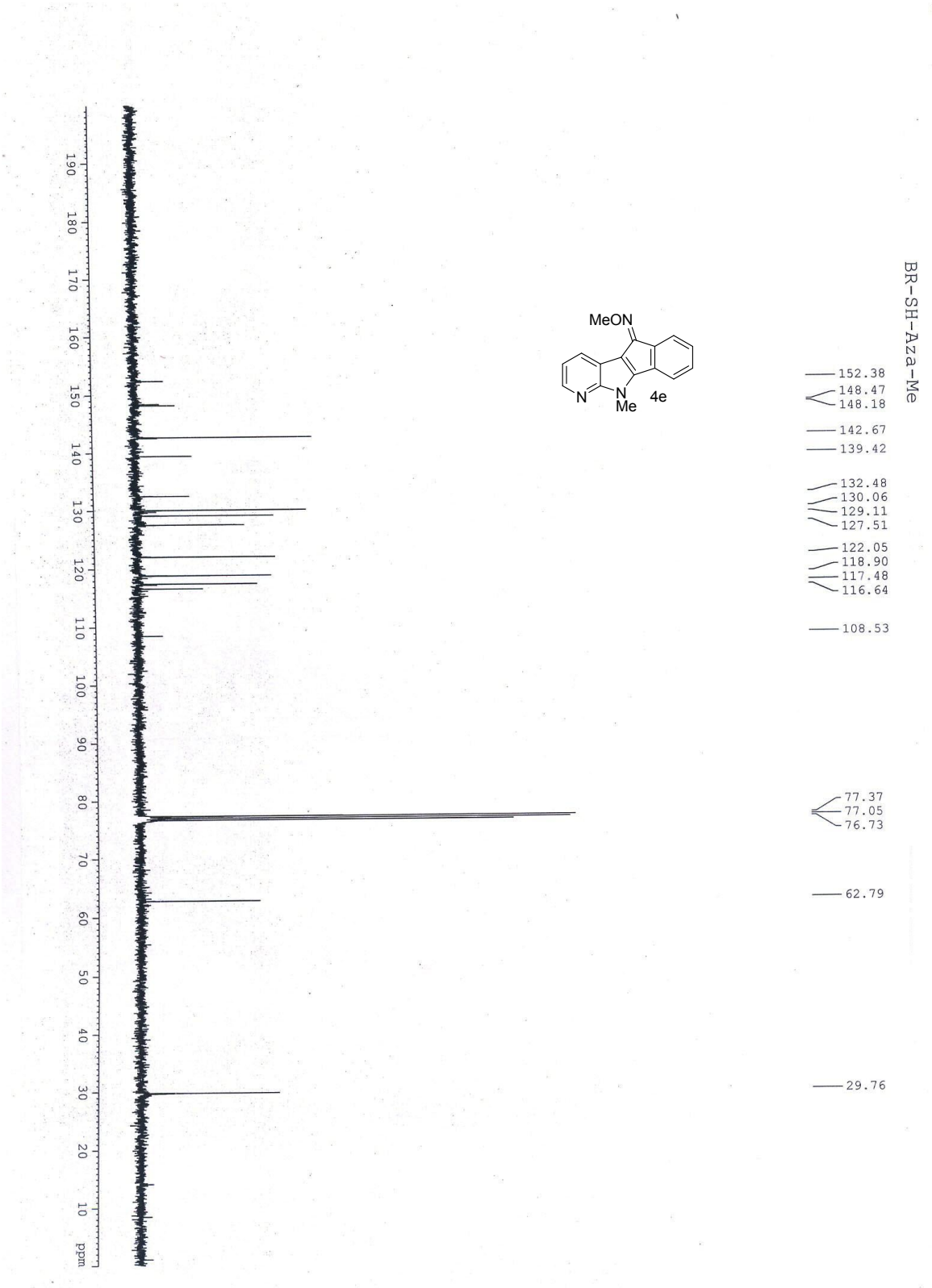
BR-Aza-Me

Compound (4e):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160
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120
110
100
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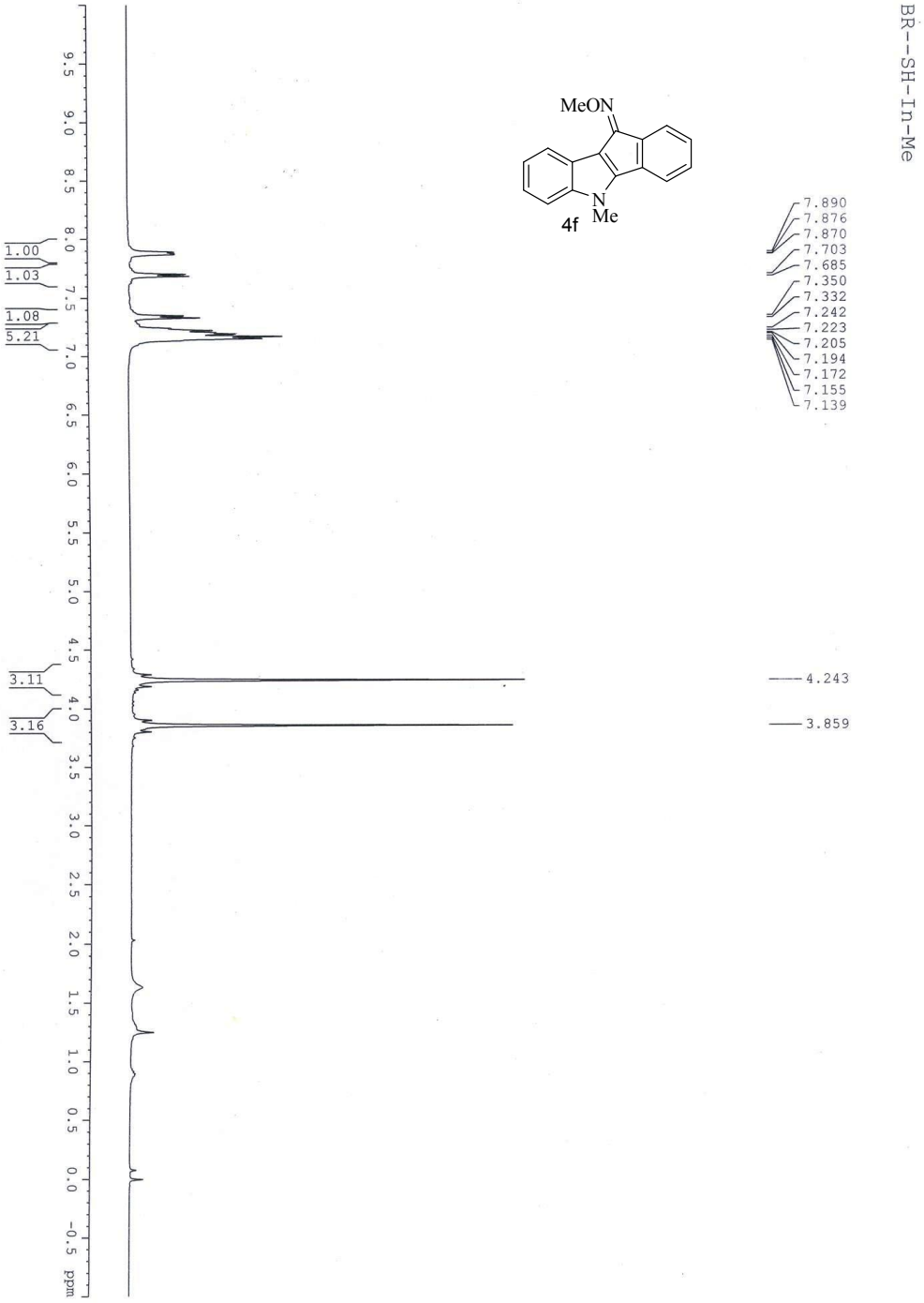
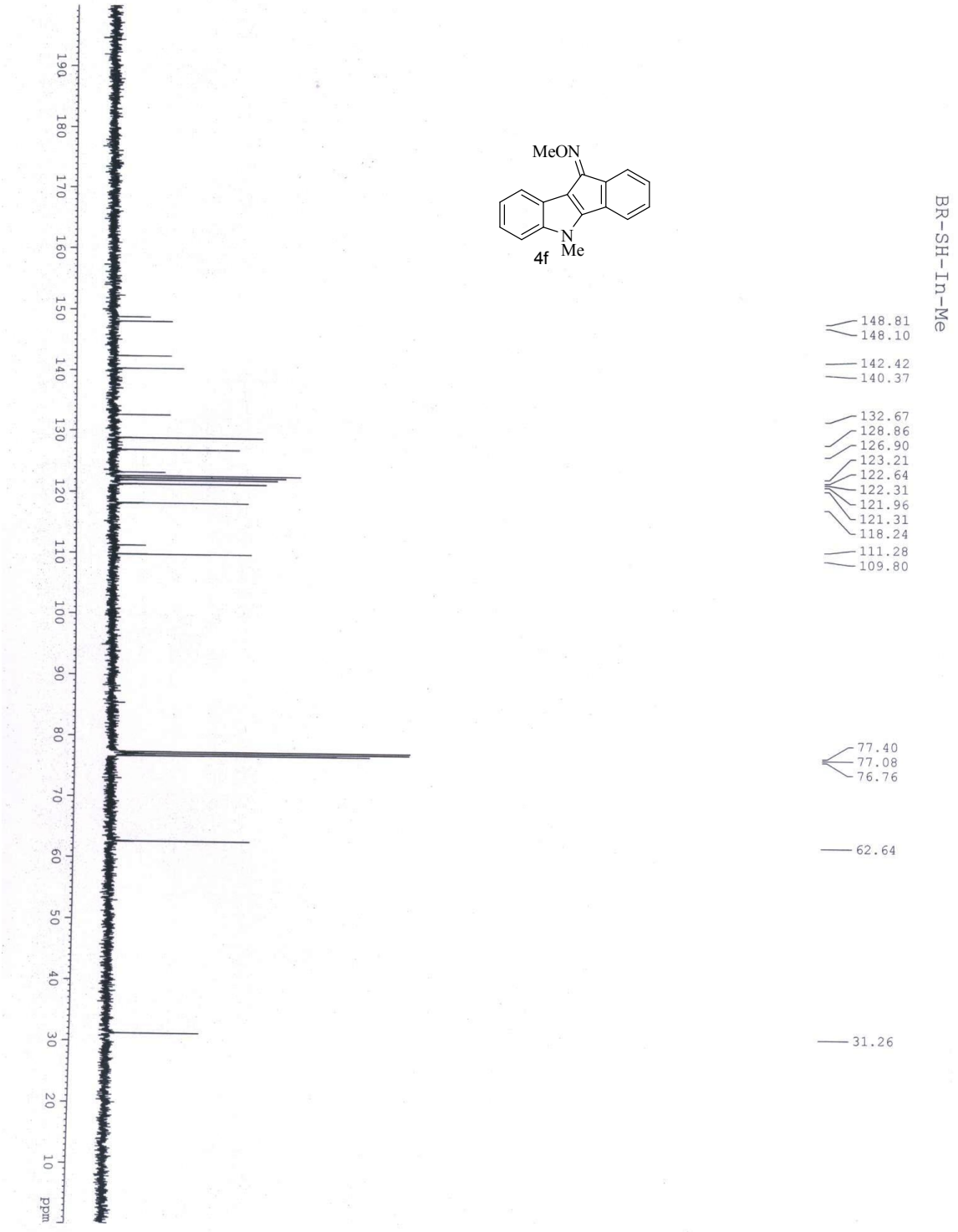
5-methylindeno[1,2-b]indol-10(5H)-one O-methyl oxime (4f):



5-methylindeno[1,2-b]indol-10(5H)-one O-methyl oxime (4f):



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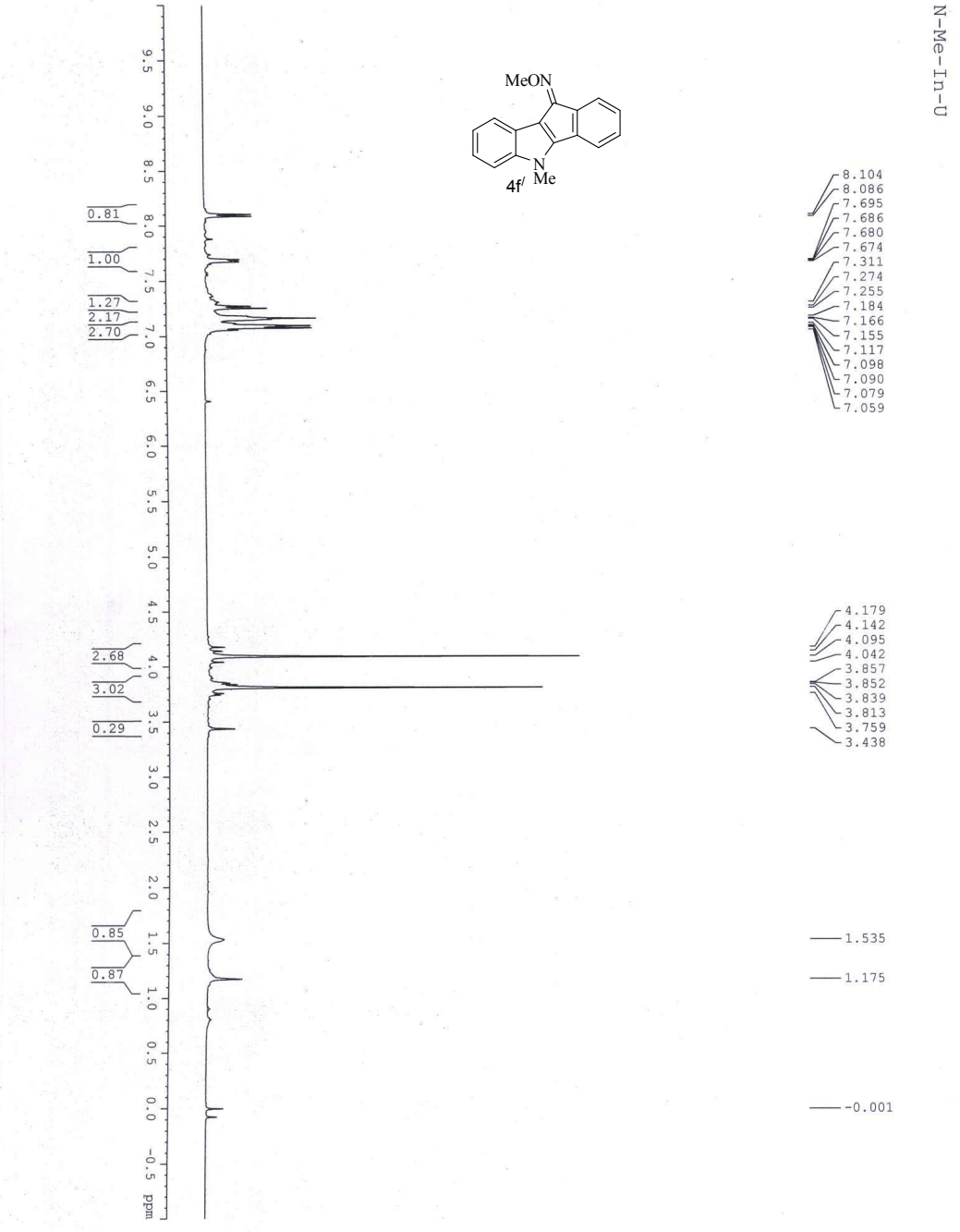
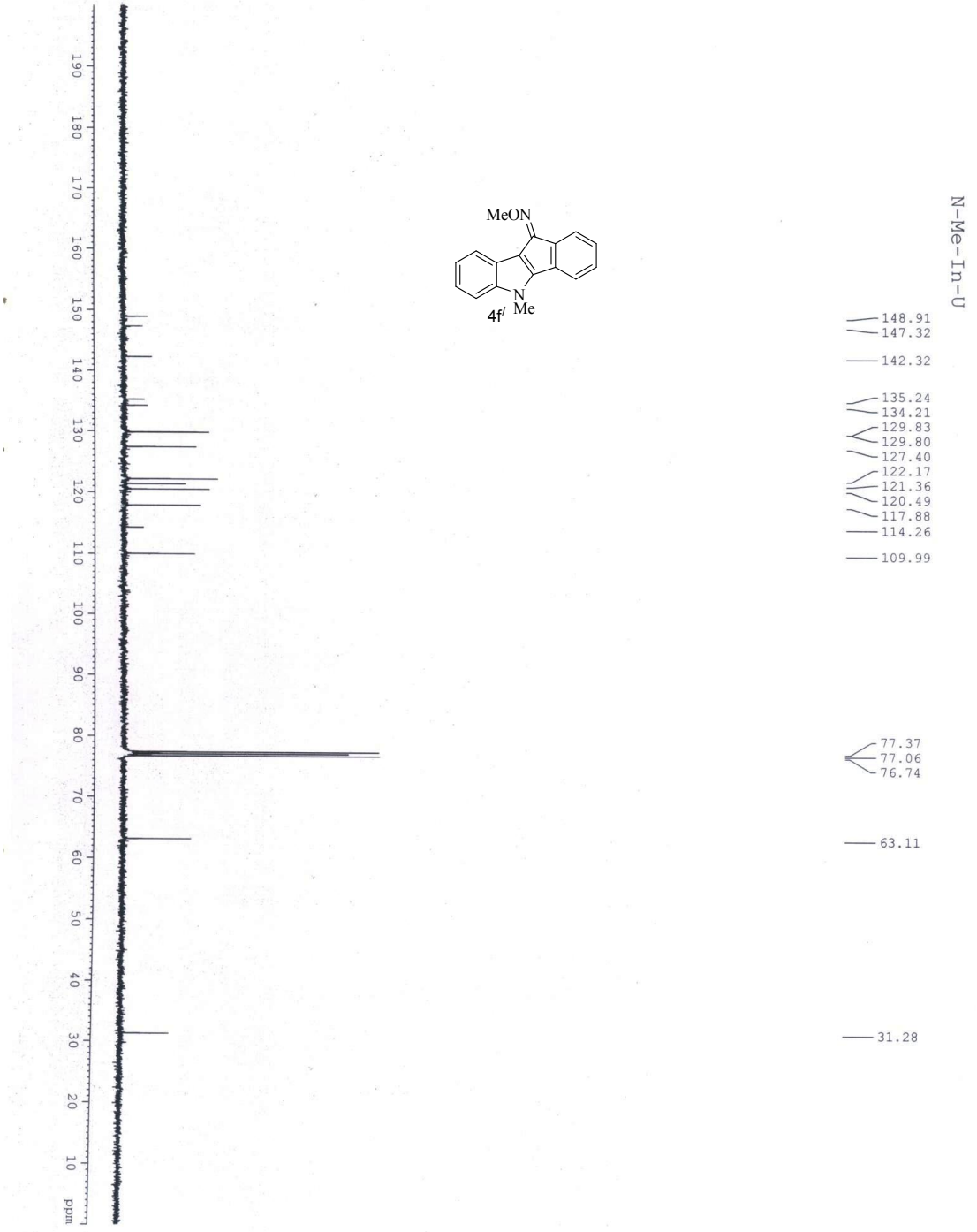


5-methylindeno[1,2-b]indol-10(5H)-one O-methyl oxime (4f/):



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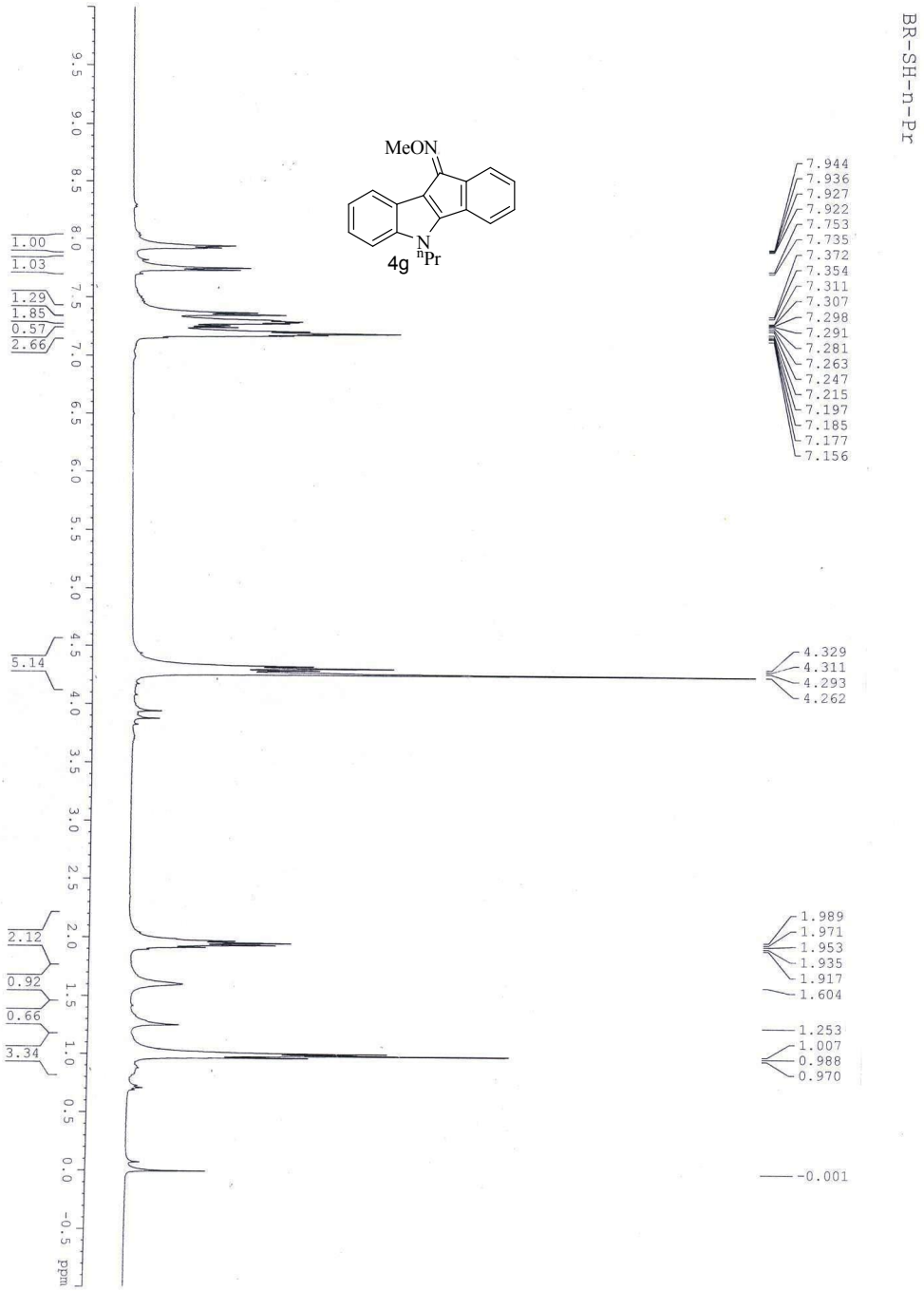

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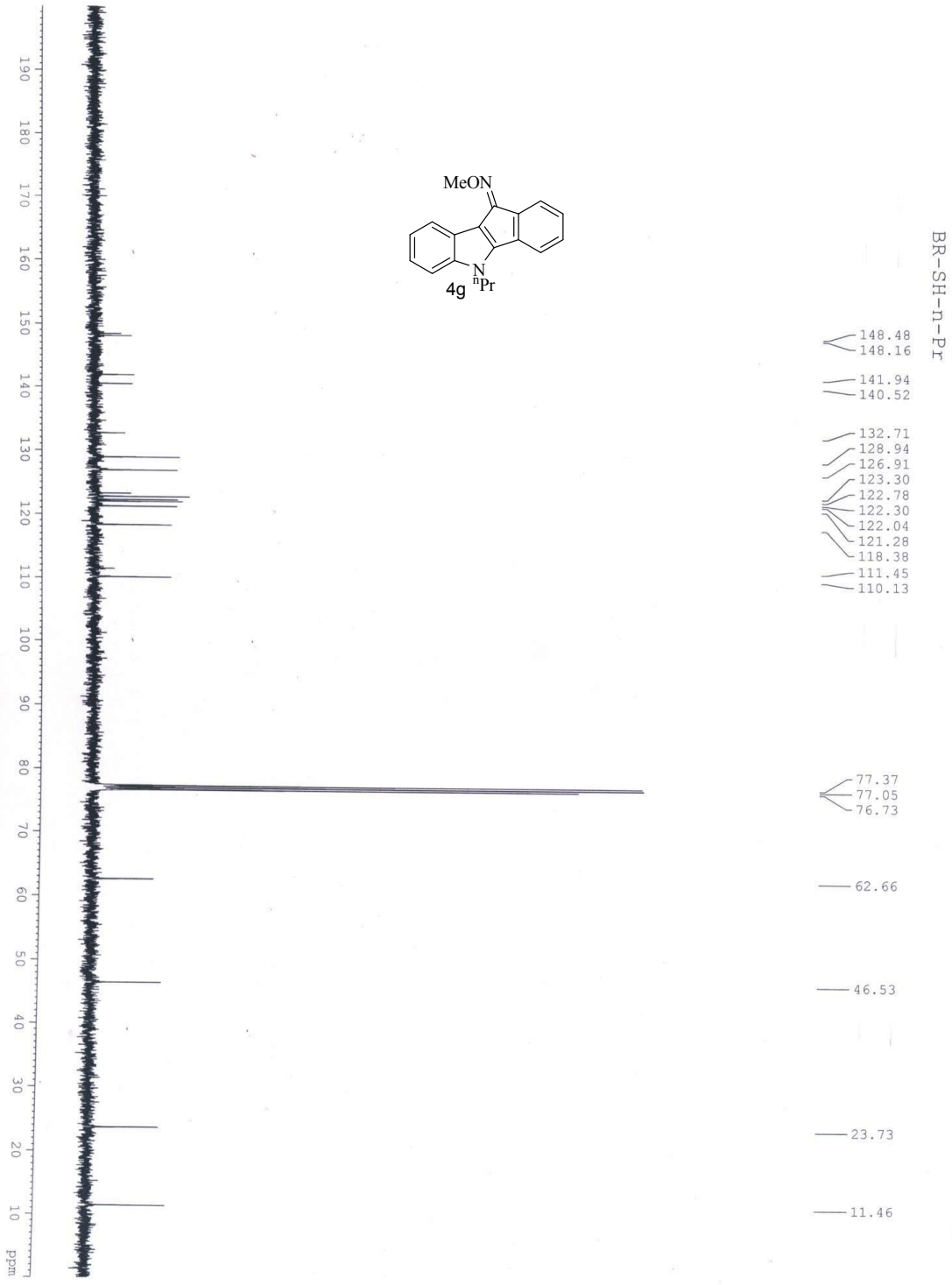

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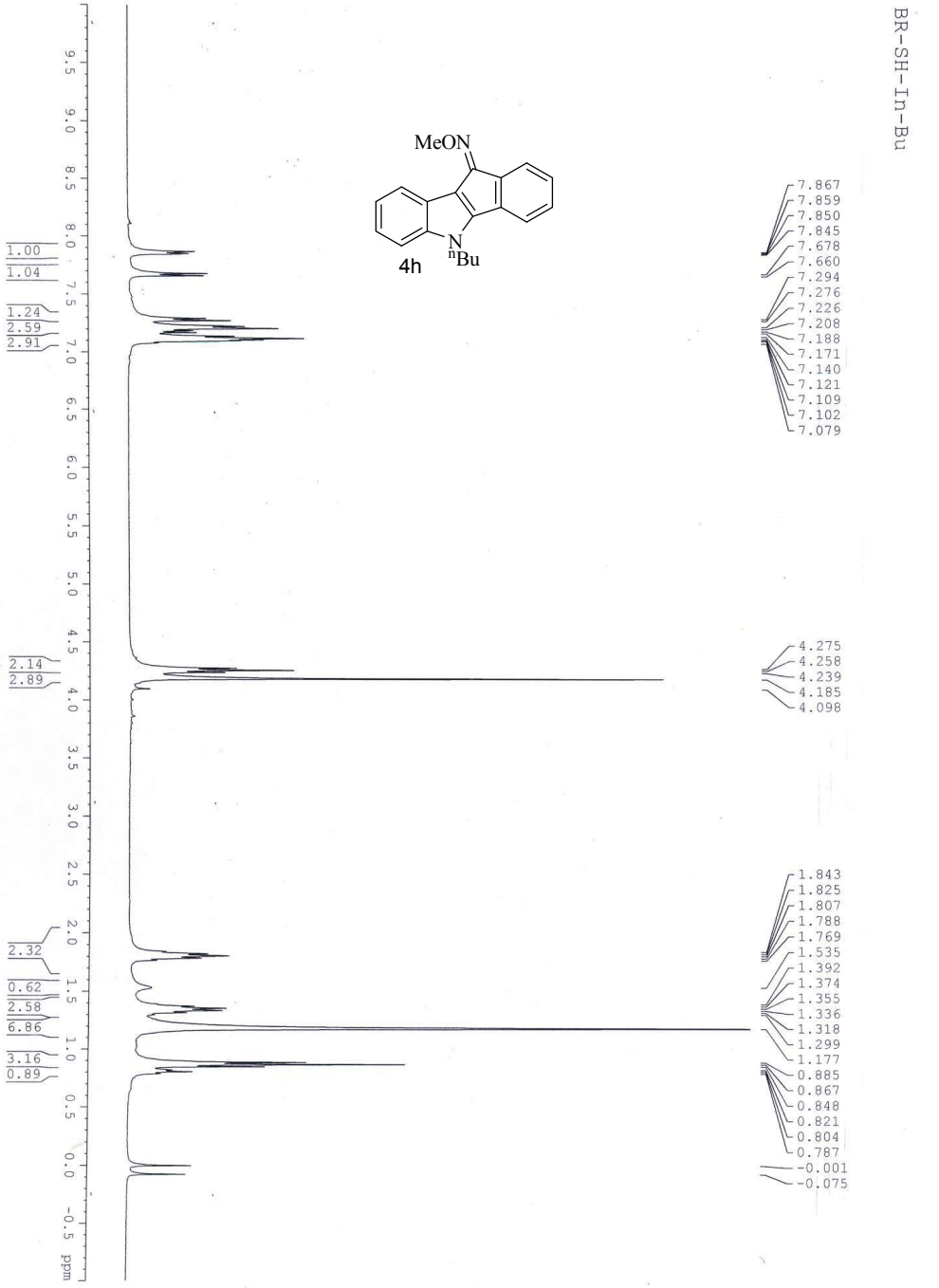
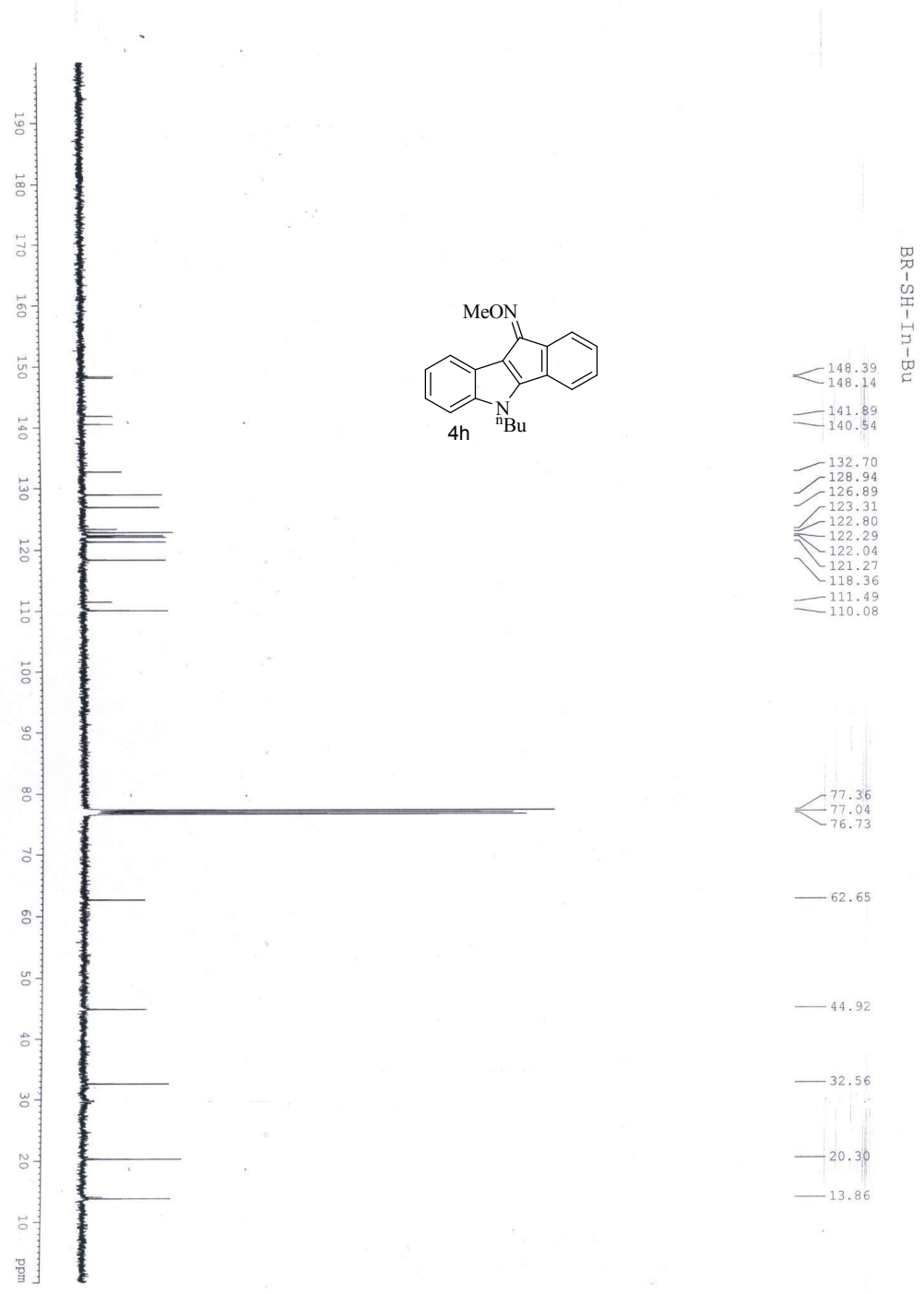


5-butylindeno[1,2-b]indol-10(5H)-one O-methyl oxime (4h):



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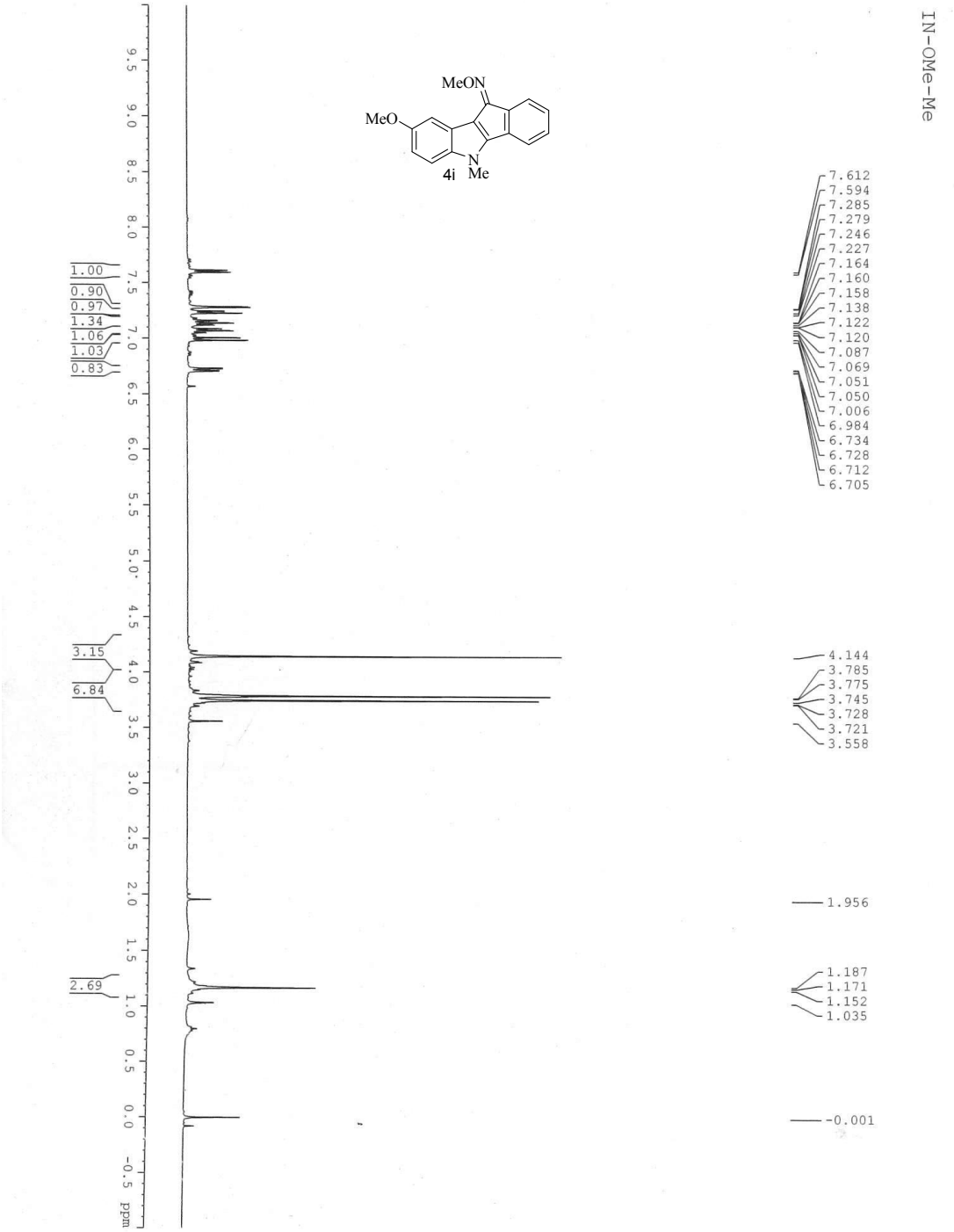
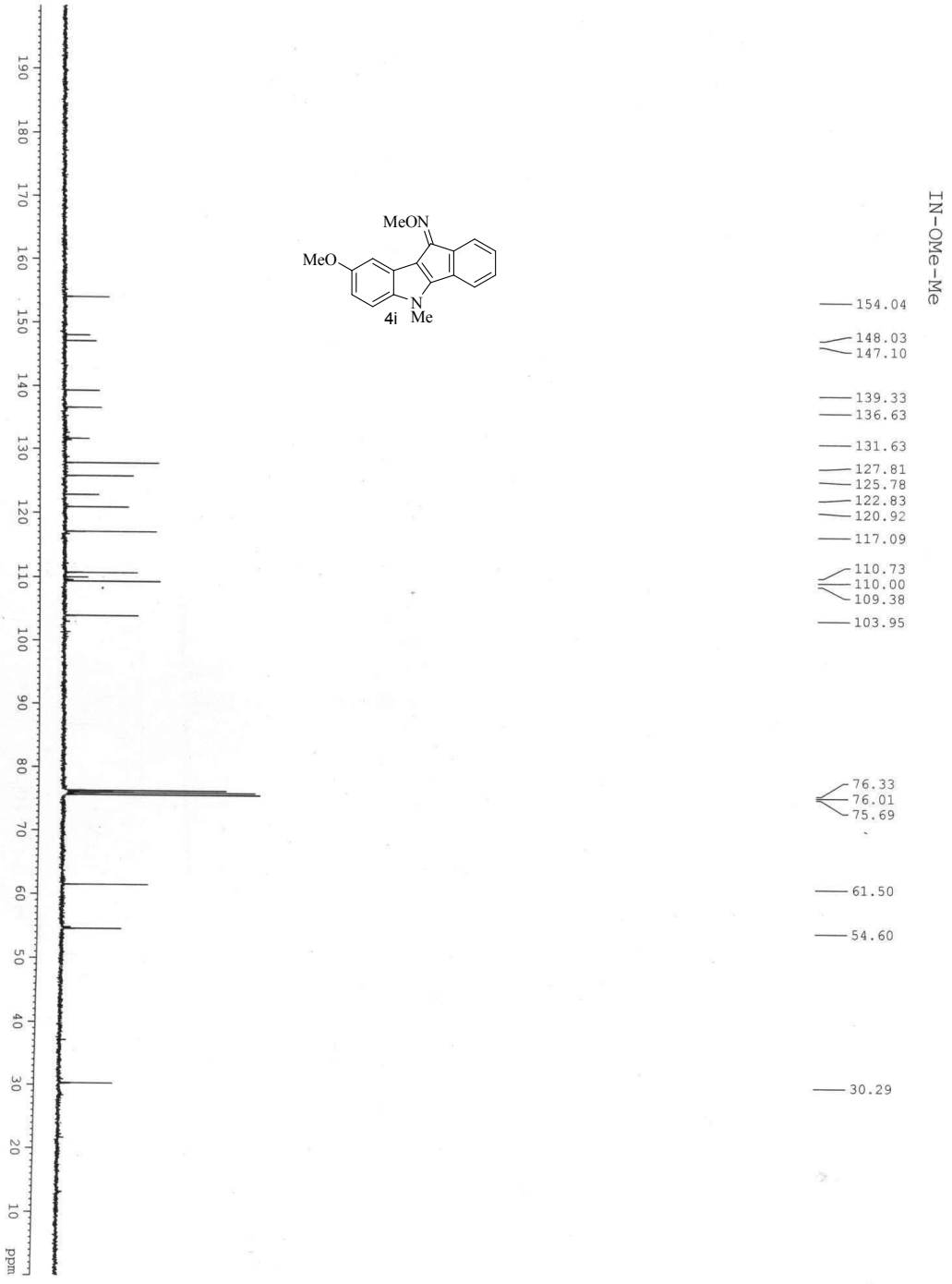
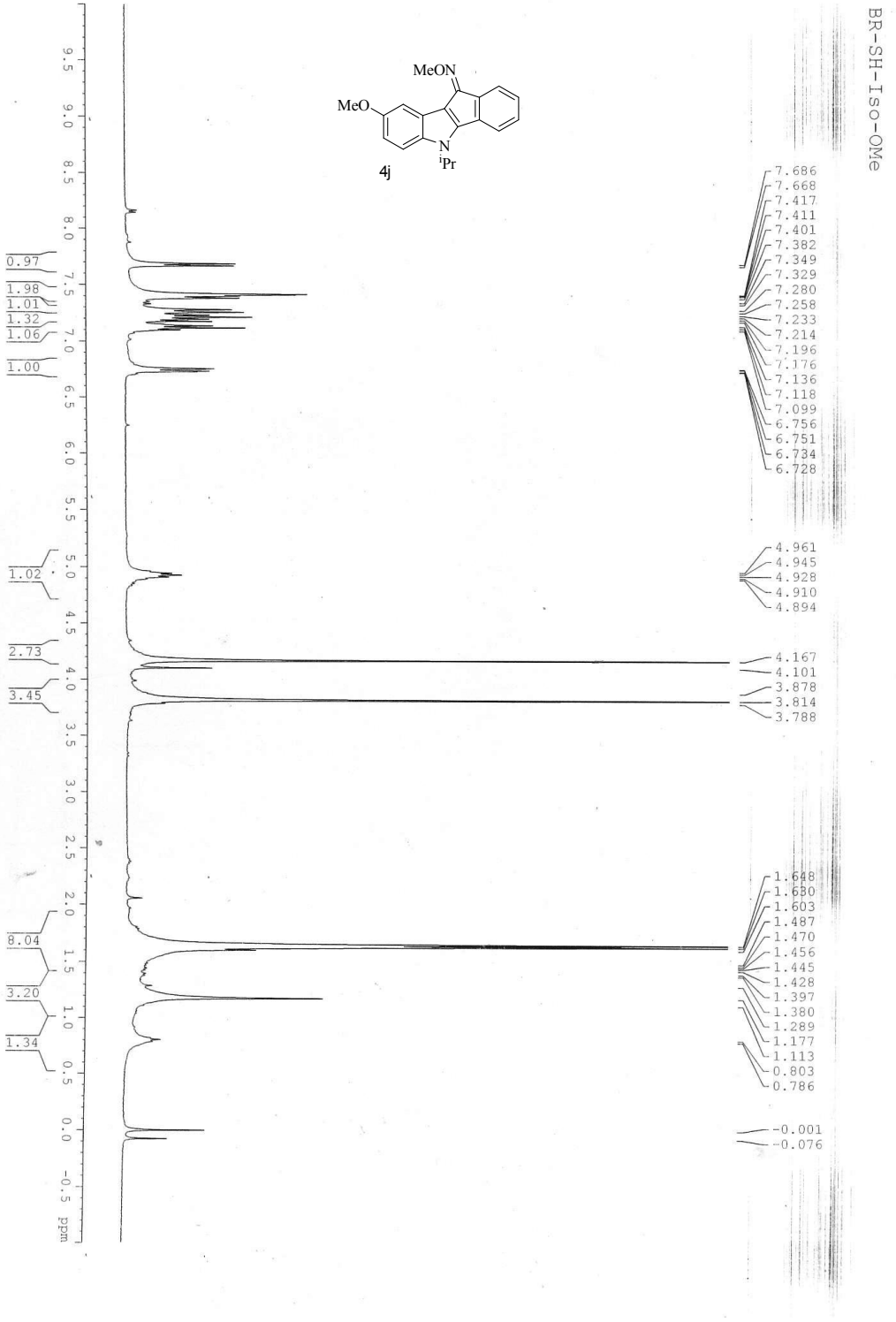


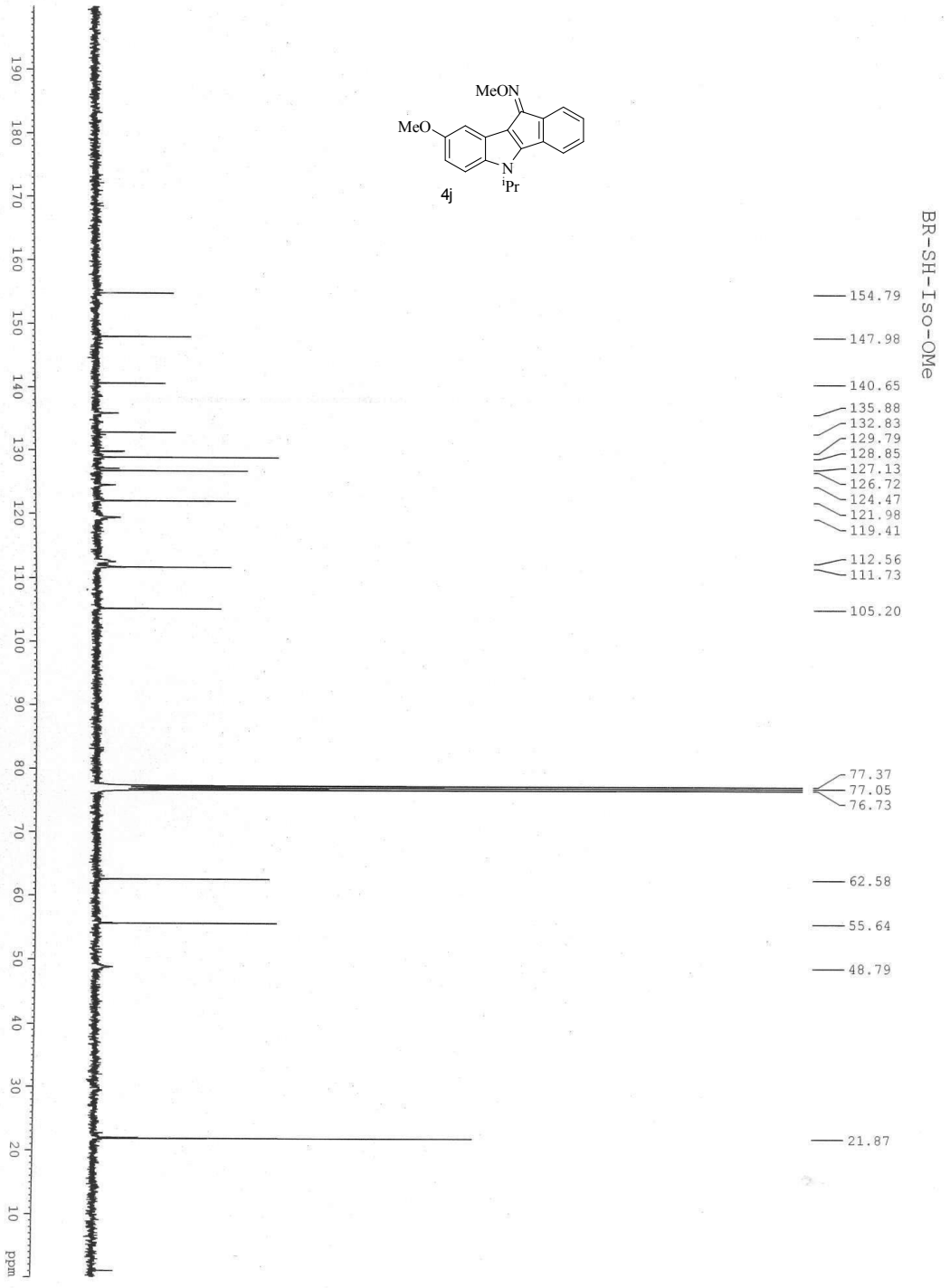
8-methoxy-5-methylindeno[1,2-b]indol-10(5H)-one O-methyl oxime (4i):



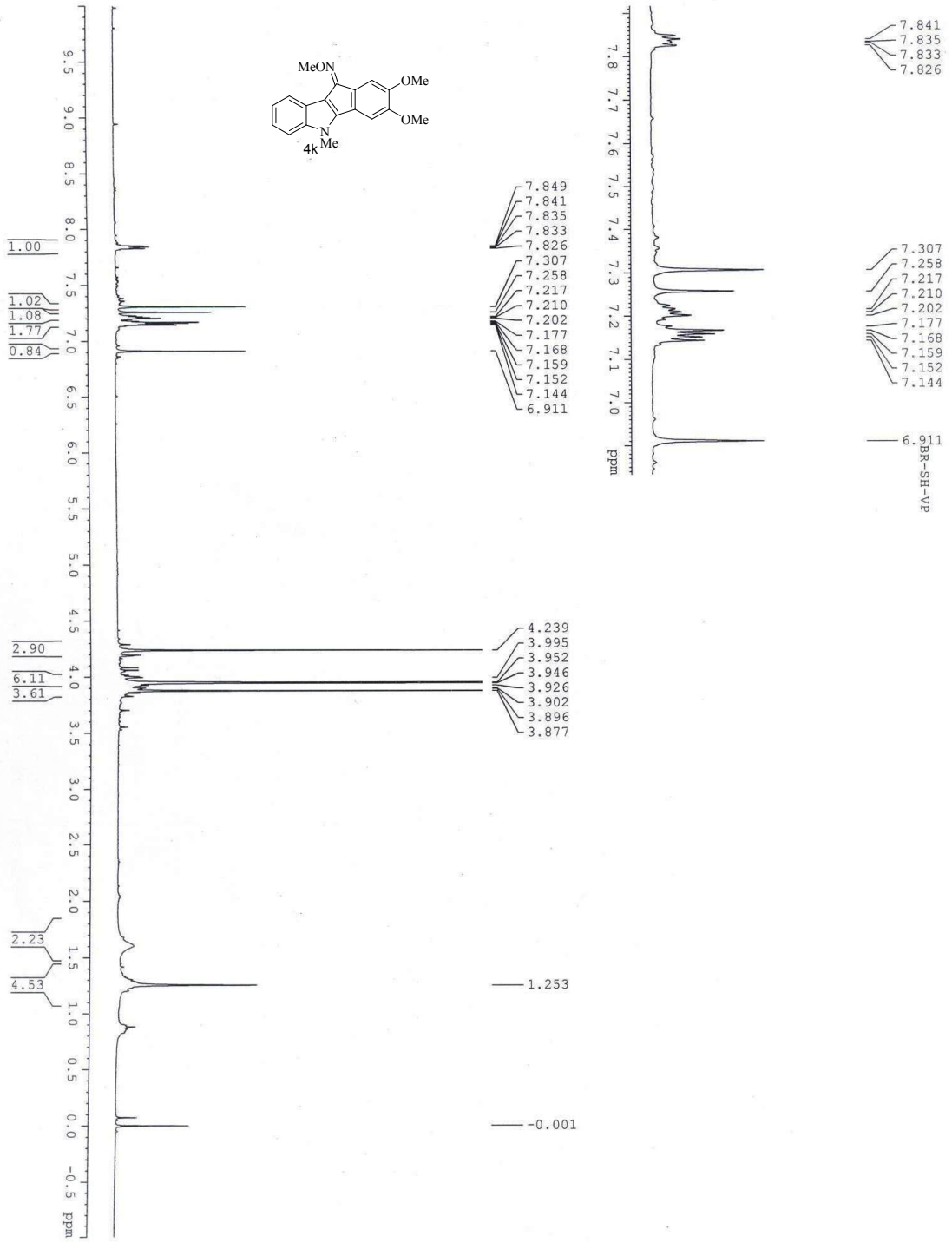
5-isopropyl-8-methoxyindeno[1,2-b]indol-10(5H)-one O-methyl oxime (4j):



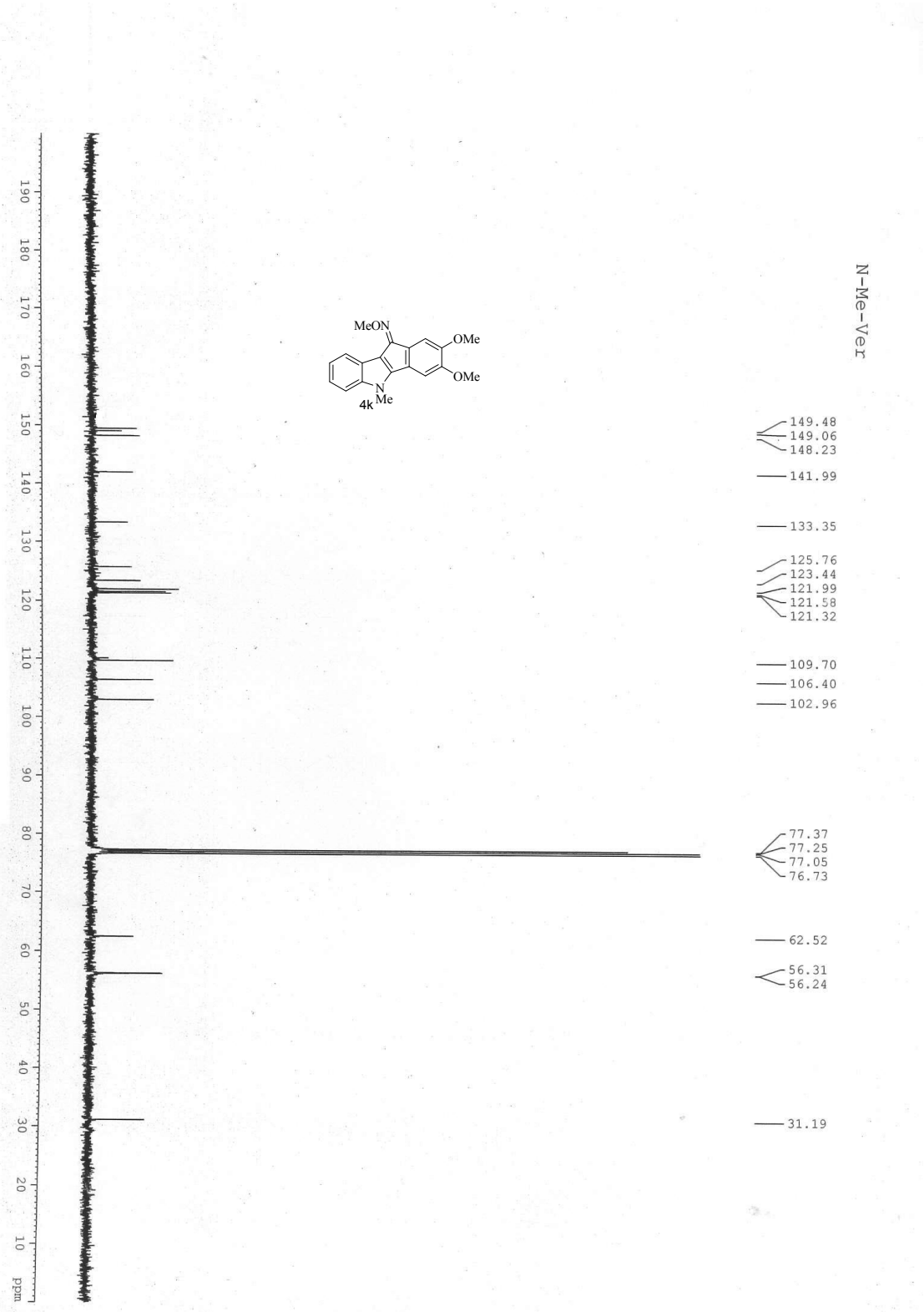
5-isopropyl-8-methoxyindeno[1,2-b]indol-10(5H)-one O-methyl oxime (4j):



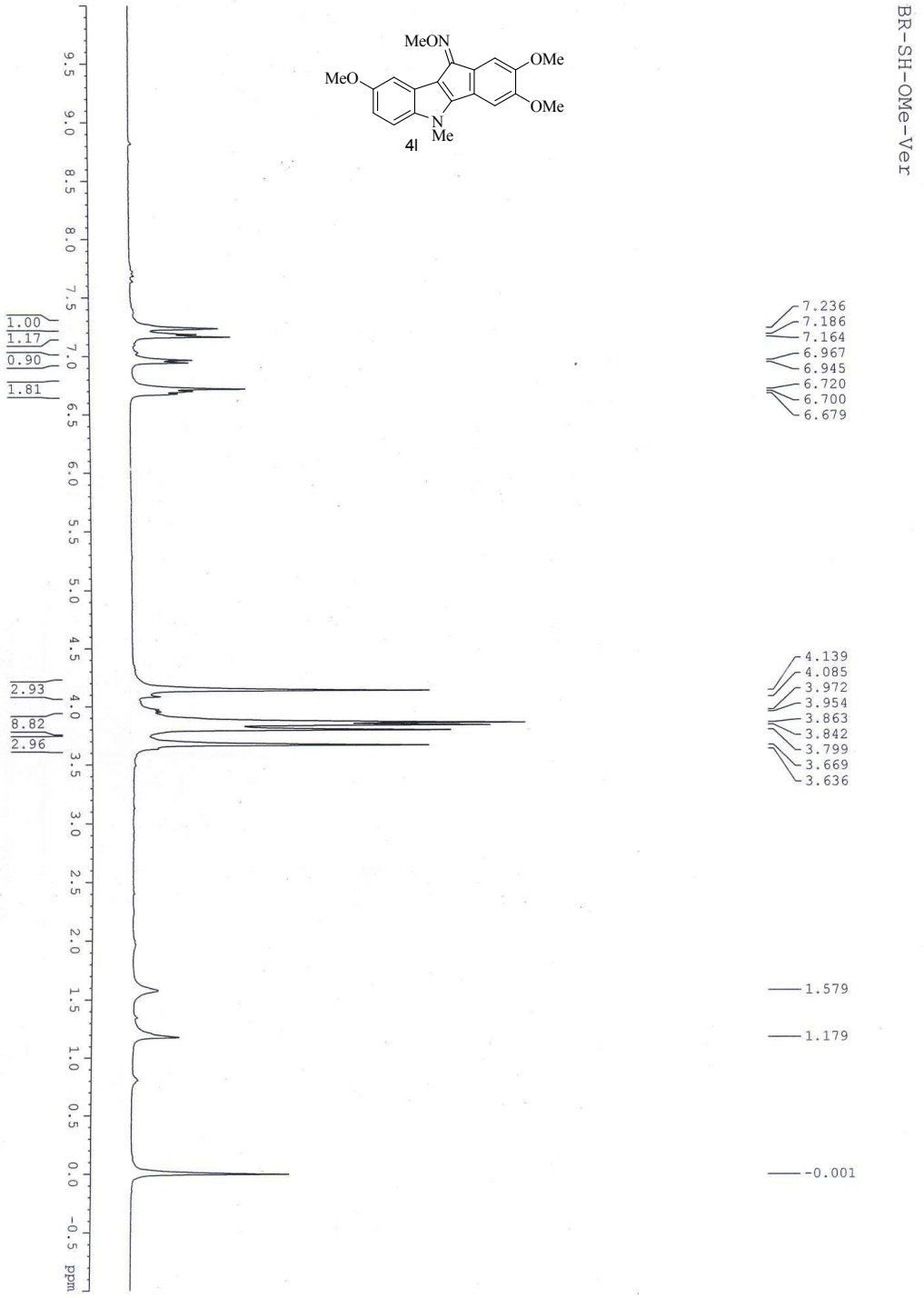
2,3-dimethoxy-5-methylindeno[1,2-b]indol-10(5H)-one O-methyl oxime (4k):



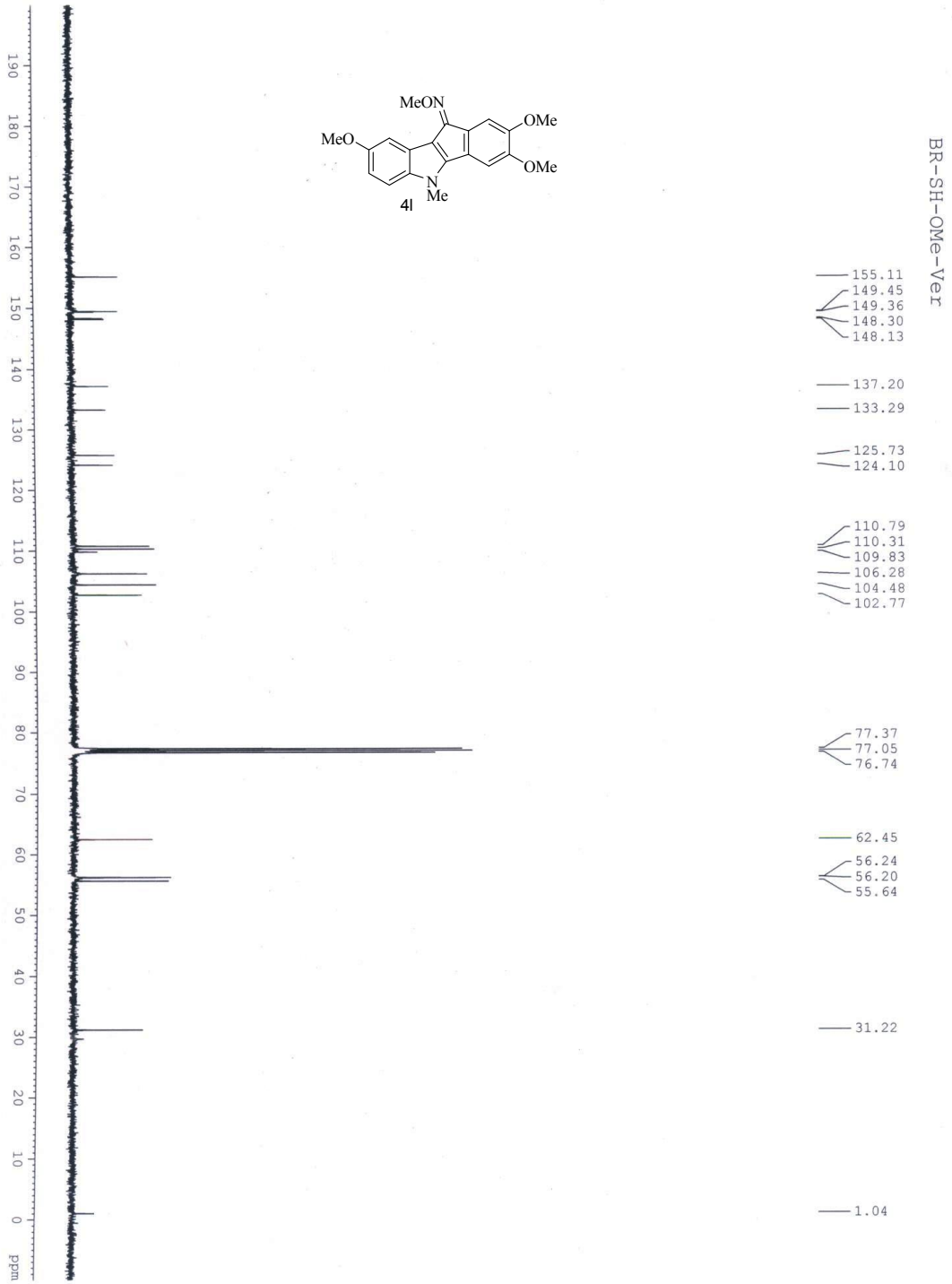
2,3-dimethoxy-5-methylindeno[1,2-b]indol-10(5H)-one O-methyl oxime (4k):



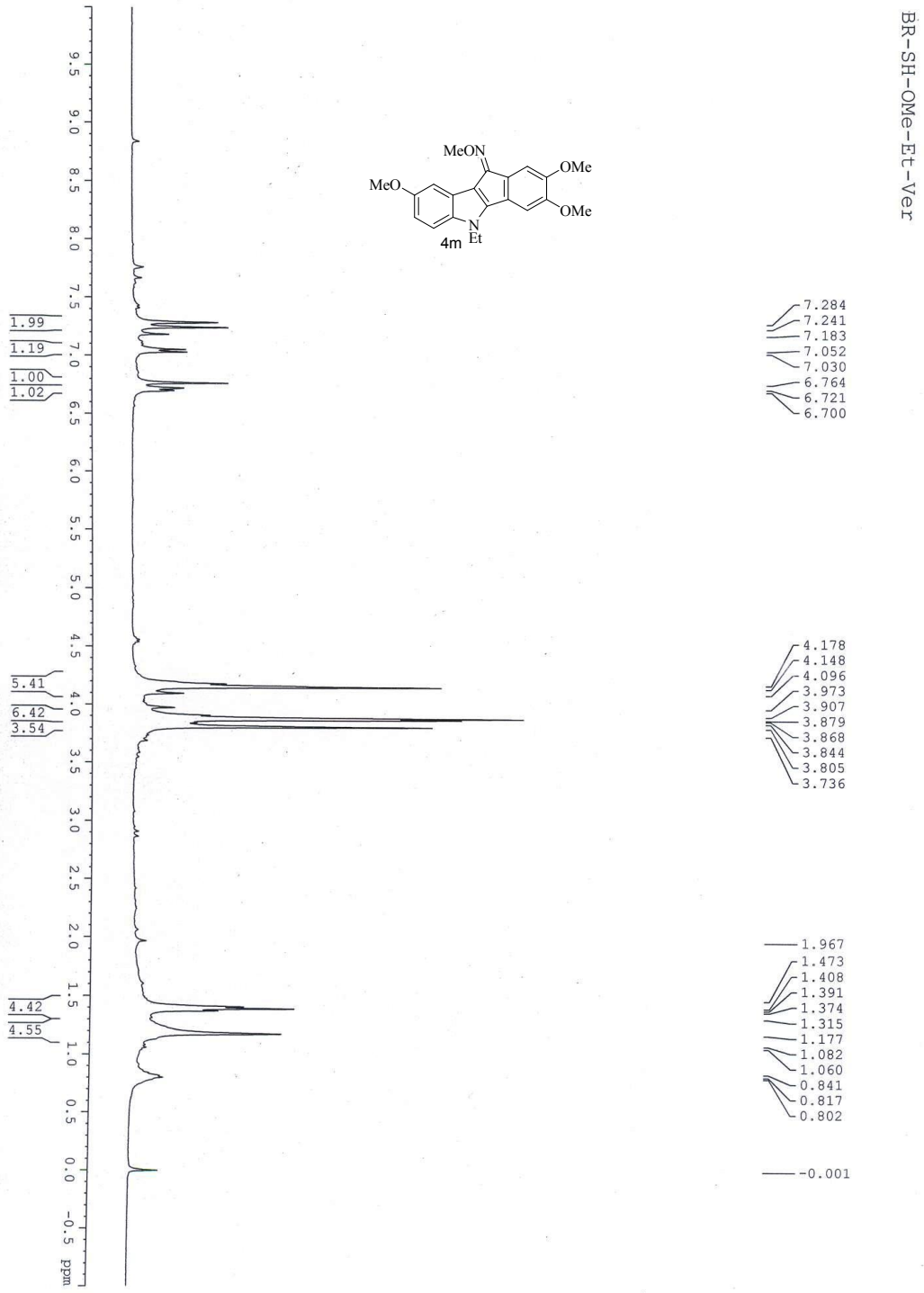
2,3,8-trimethoxy-5-methylindeno[1,2-b]indol-10(5H)-one O-methyl oxime (4l) :



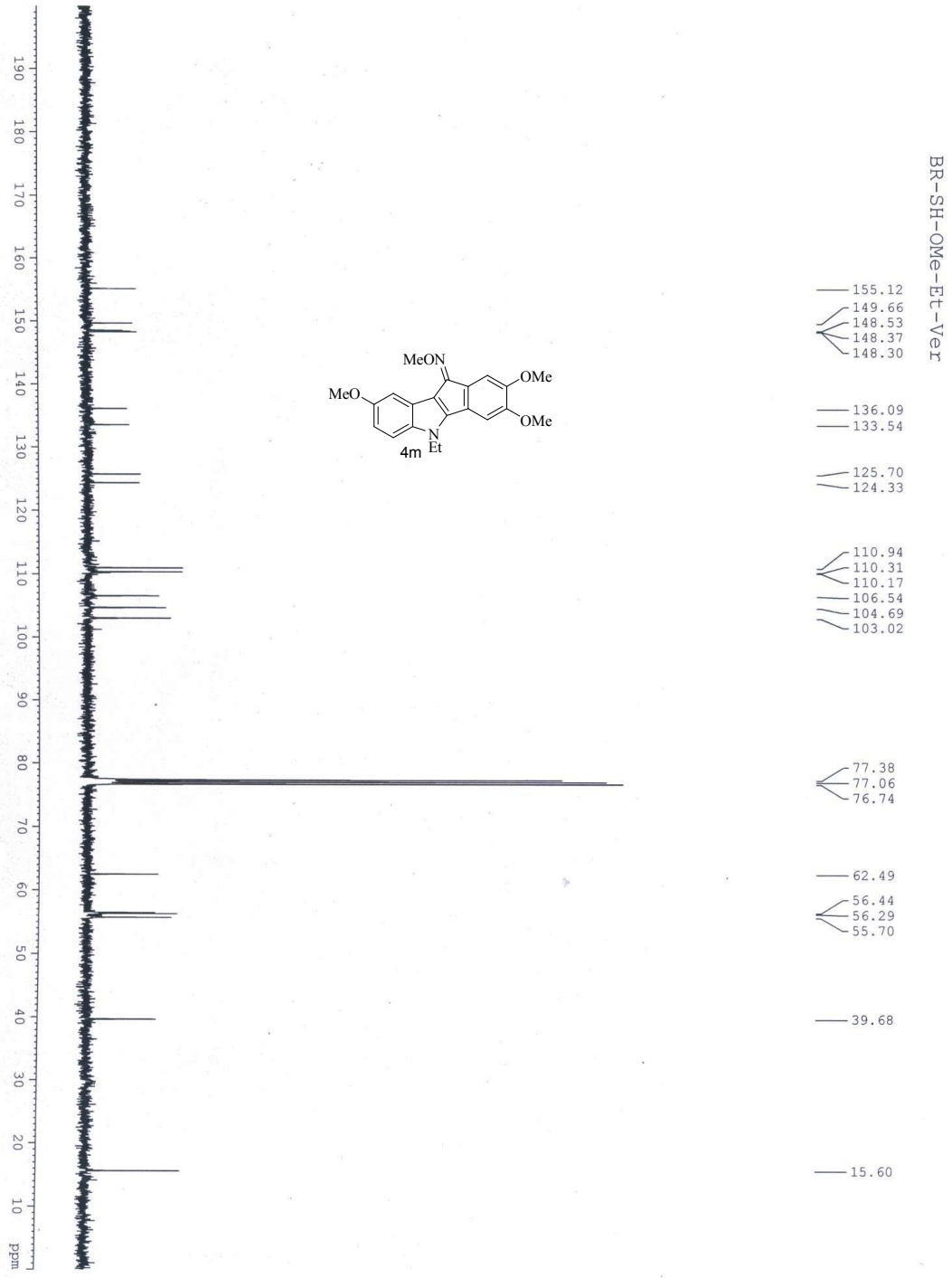
2,3,8-trimethoxy-5-methylindeno[1,2-b]indol-10(5H)-one O-methyl oxime (4l) :



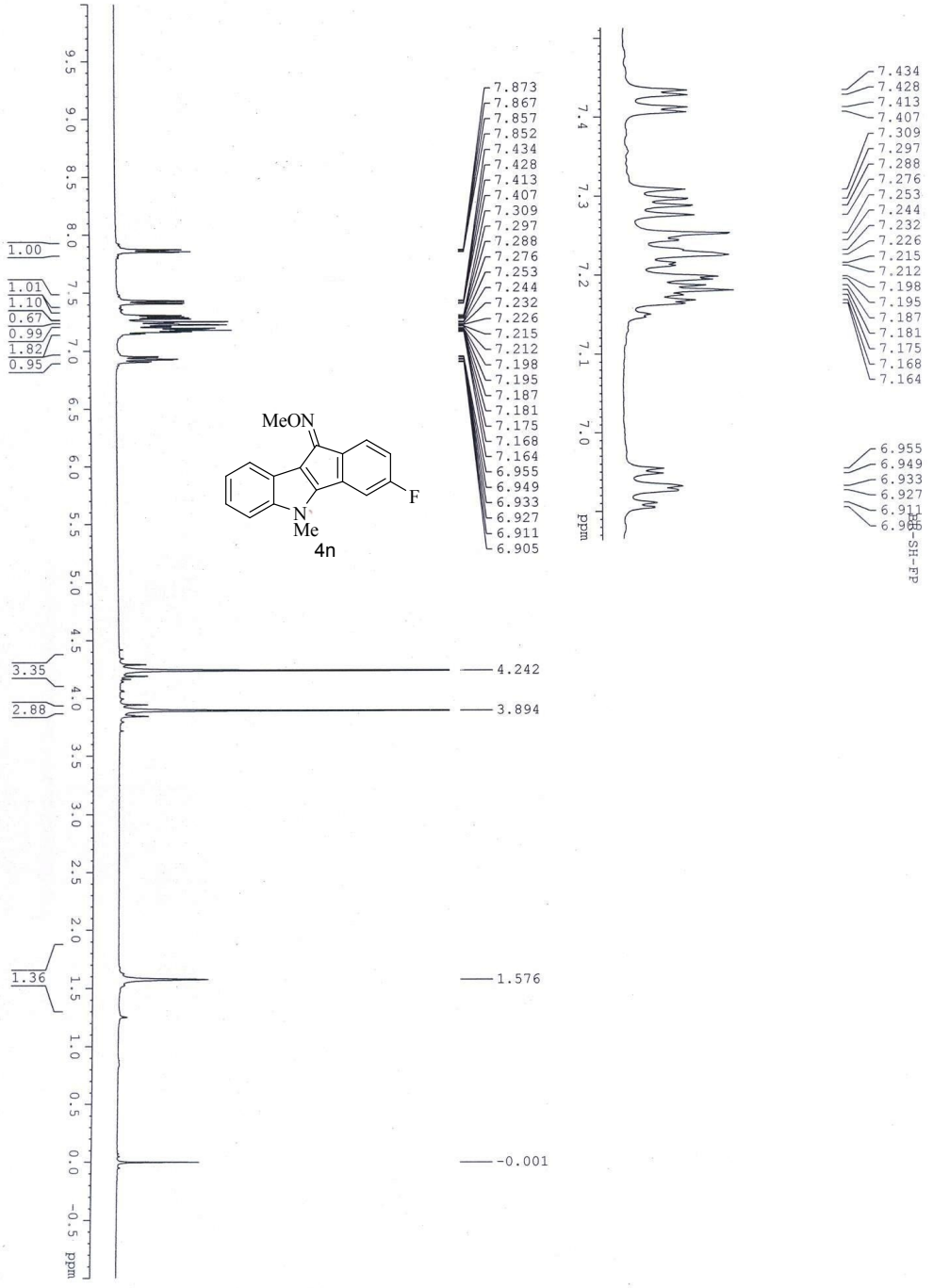
5-ethyl-2,3,8-trimethoxyindeno[1,2-b]indol-10(5H)-one O-methyl oxime (4m):



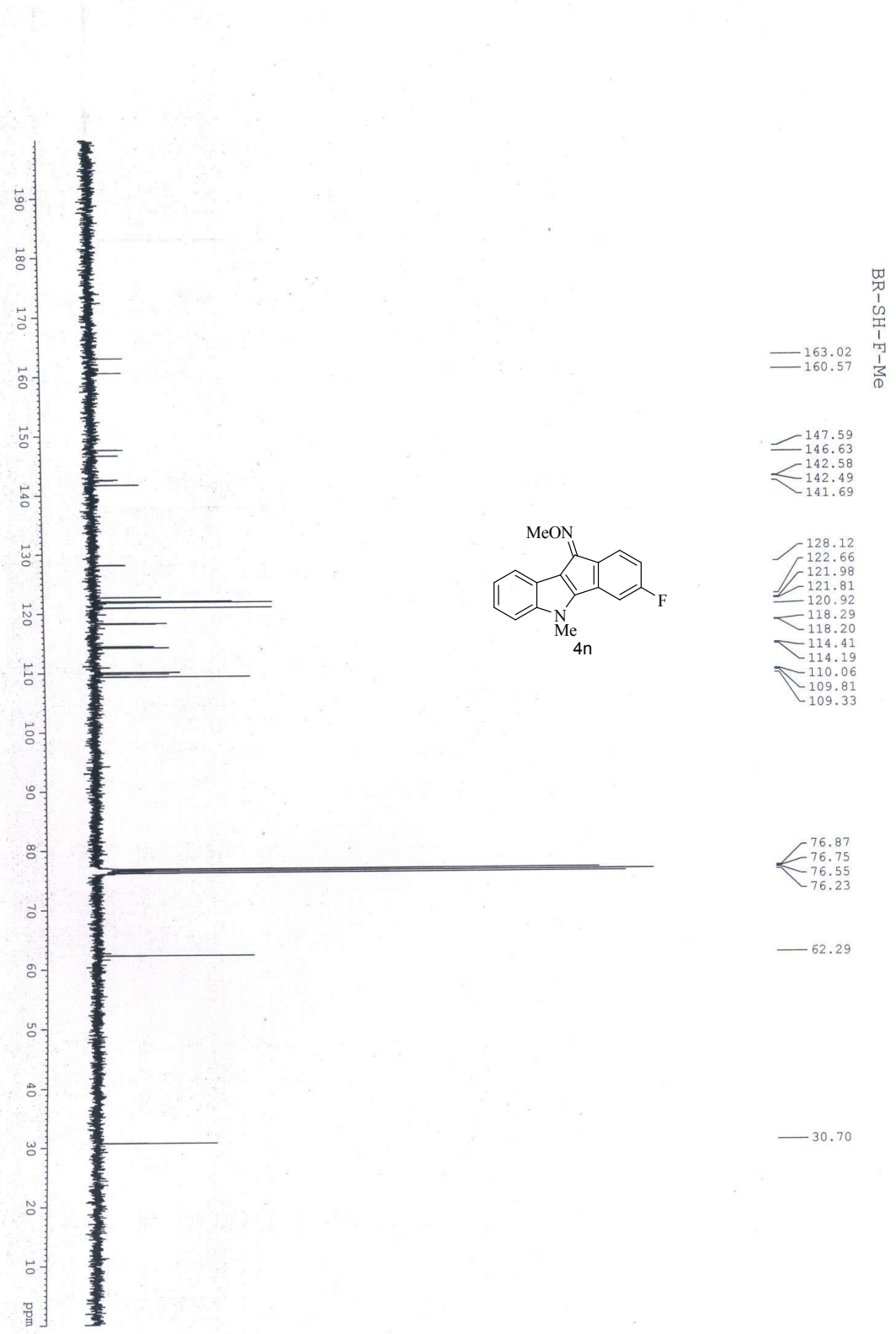
5-ethyl-2,3,8-trimethoxyindeno[1,2-b]indol-10(5H)-one O-methyl oxime (4m):



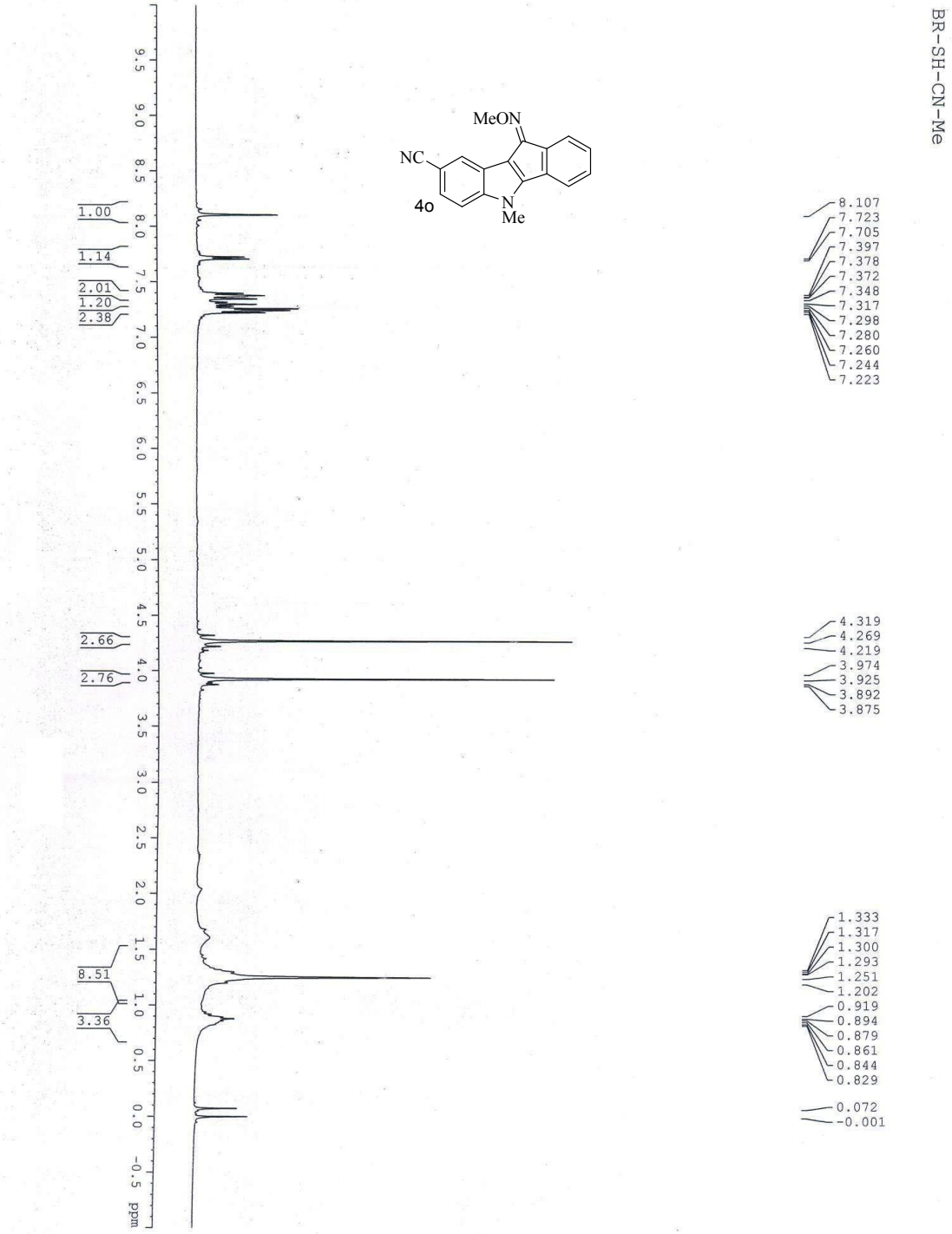
3-fluoro-5-methylindeno[1,2-b]indol-10(5H)-one O-methyl oxime (4n):



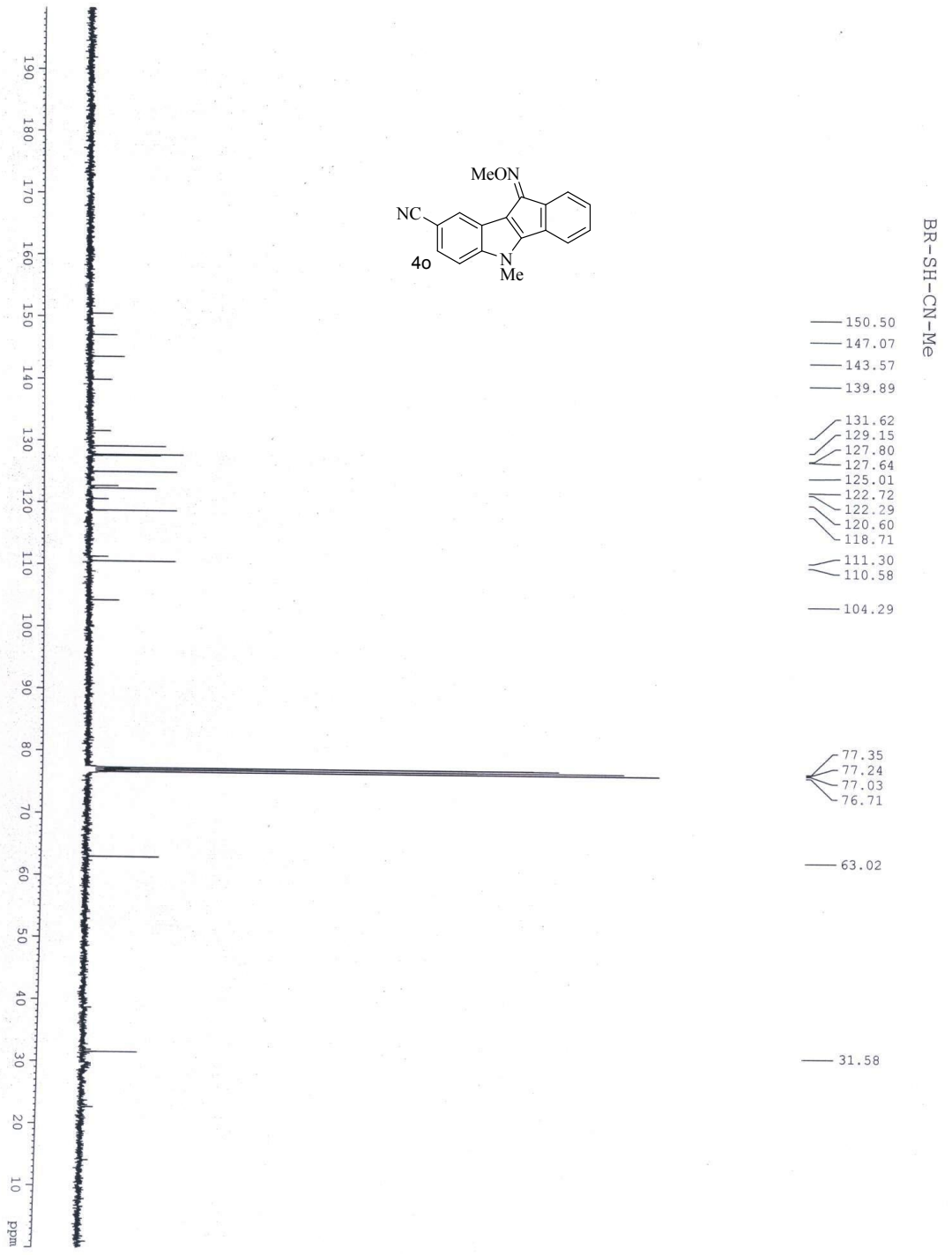
3-fluoro-5-methylindeno[1,2-b]indol-10(5H)-one O-methyl oxime (4n):



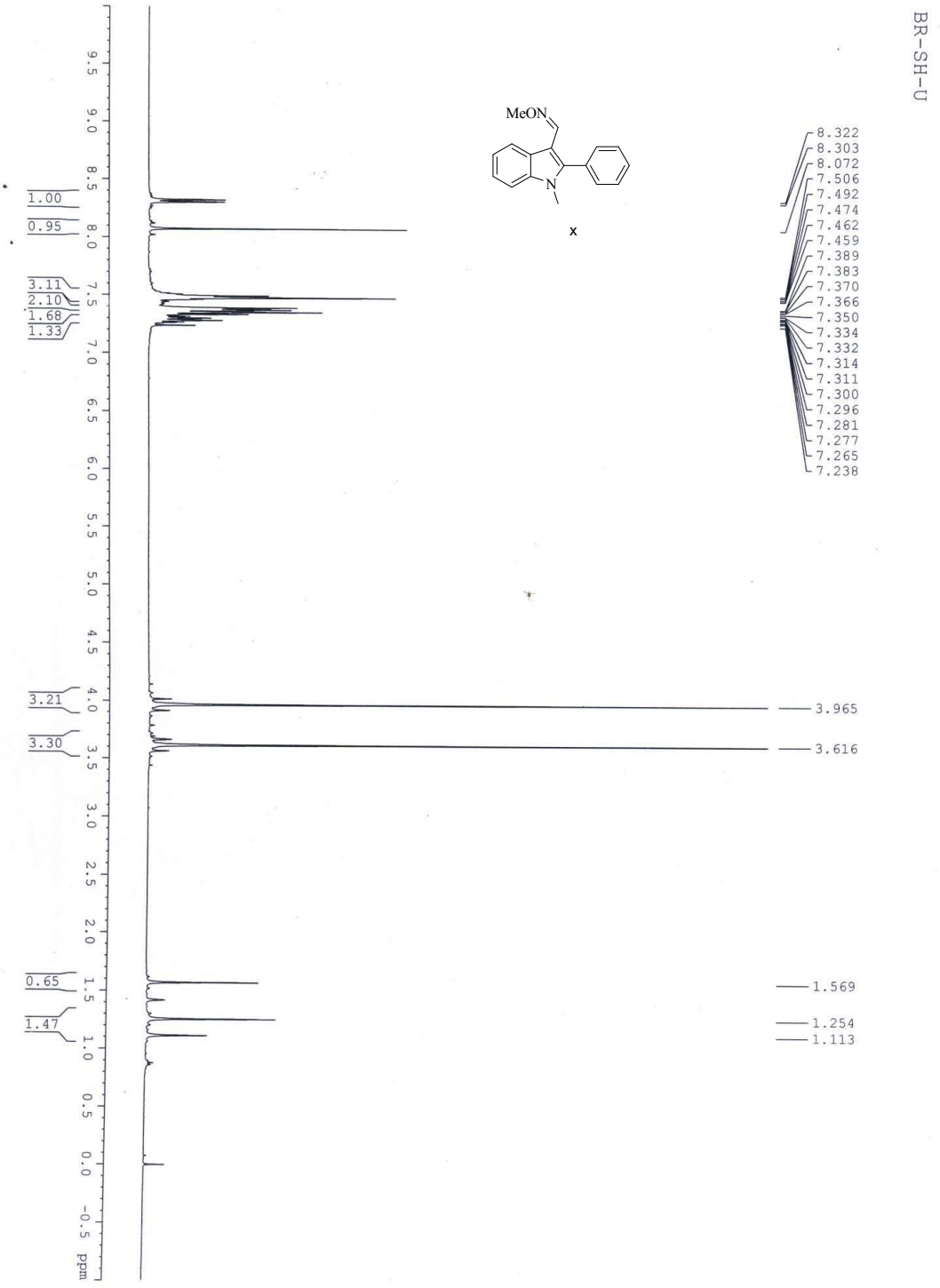
10-(methoxyimino)-5-methyl-5,10-dihydroindeno[1,2-b]indole-8-carbonitrile (4o):



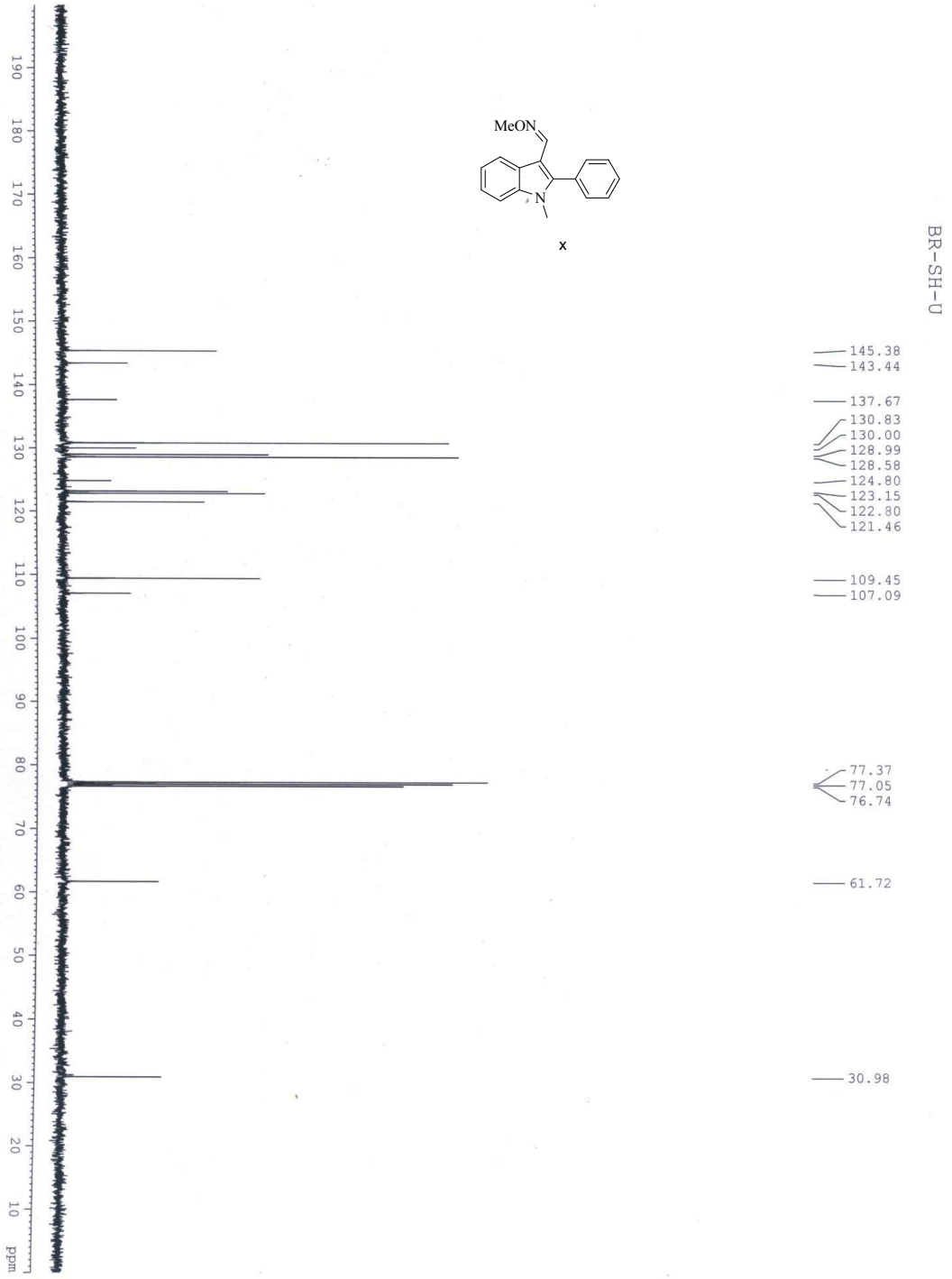
10-(methoxyimino)-5-methyl-5,10-dihydroindeno[1,2-b]indole-8-carbonitrile (4o):



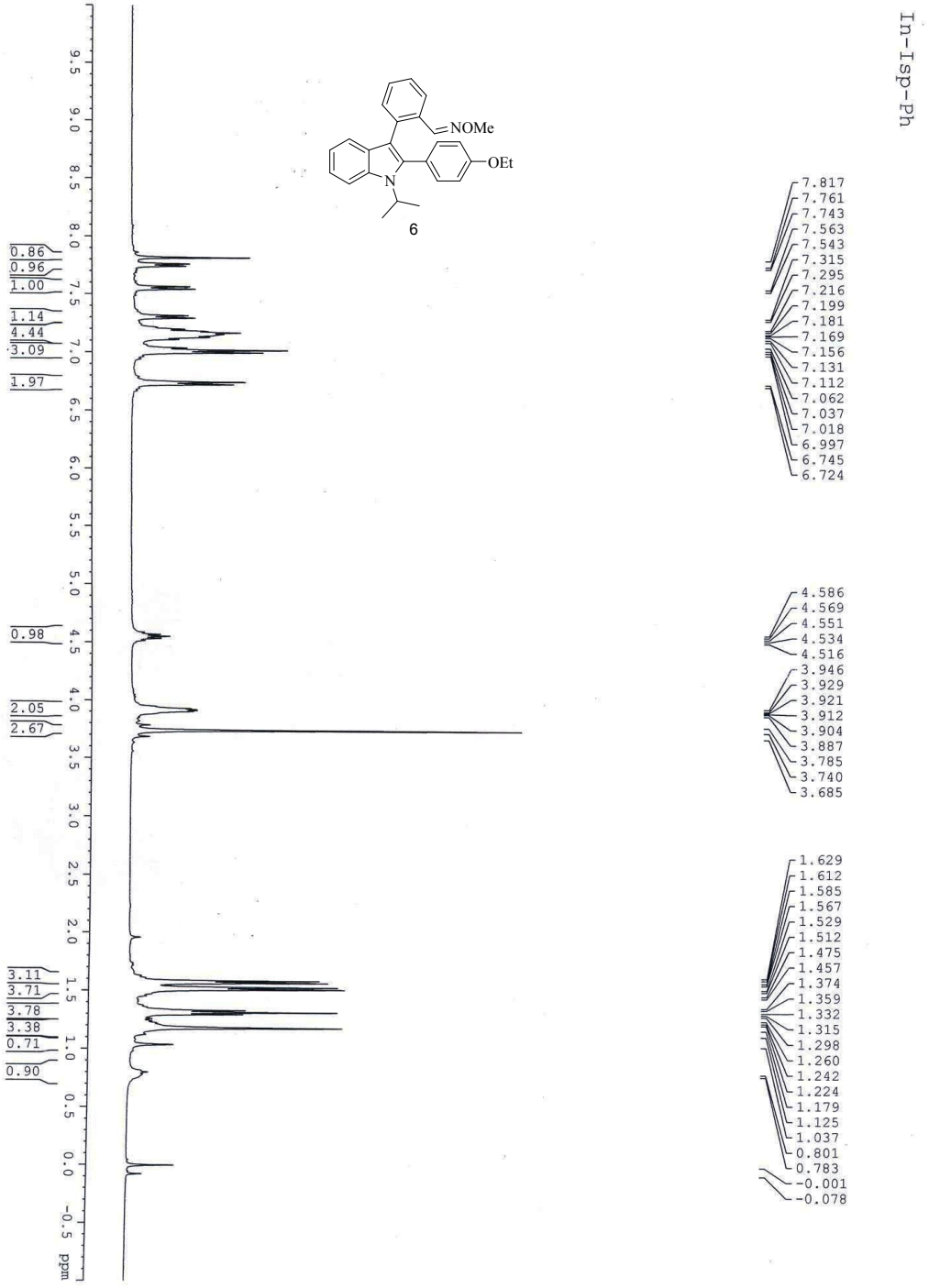
1-methyl-2-phenyl-1H-indole-3-carbaldehyde O-methyl oxime (x):



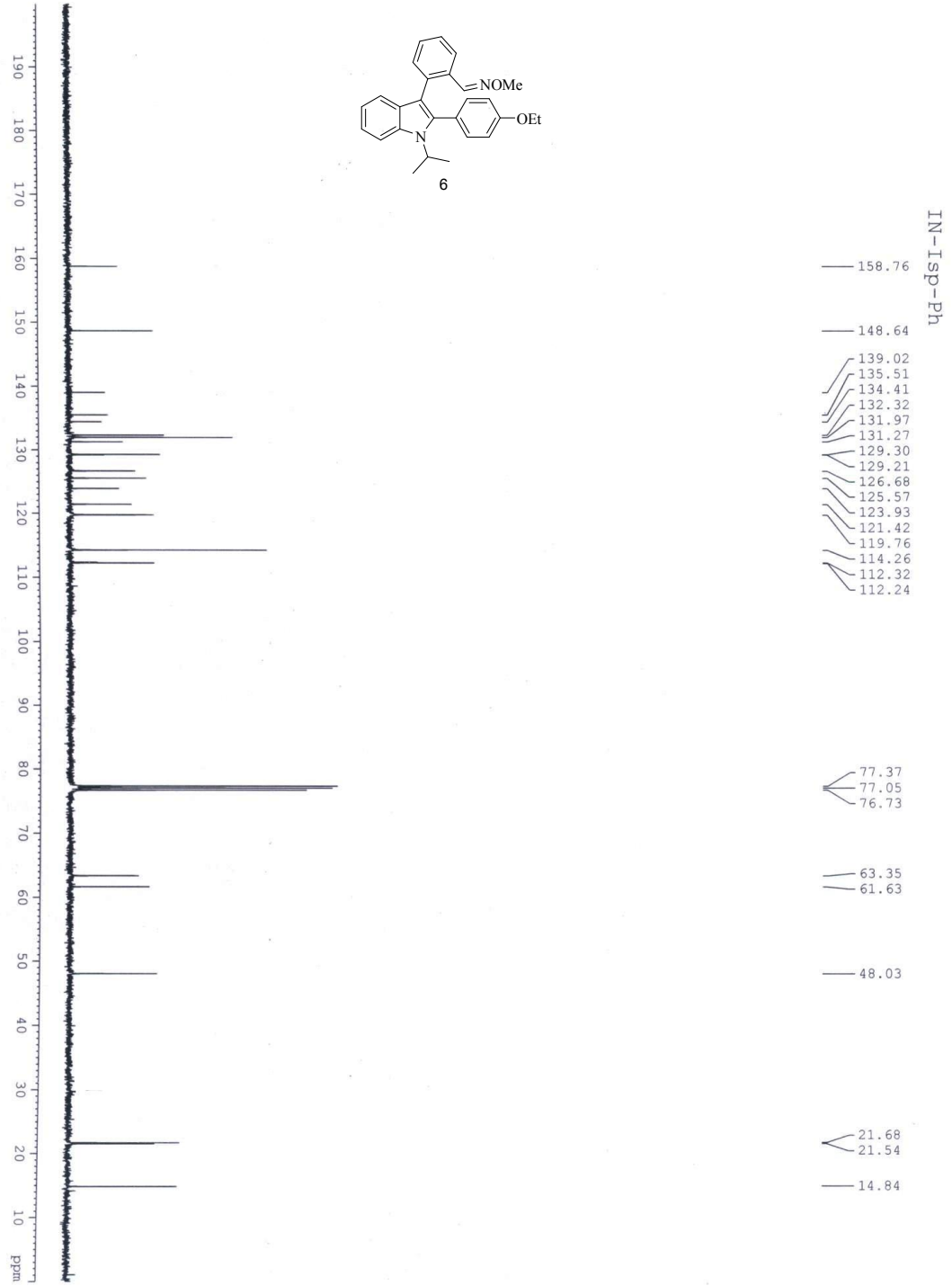
1-methyl-2-phenyl-1H-indole-3-carbaldehyde O-methyl oxime (x):



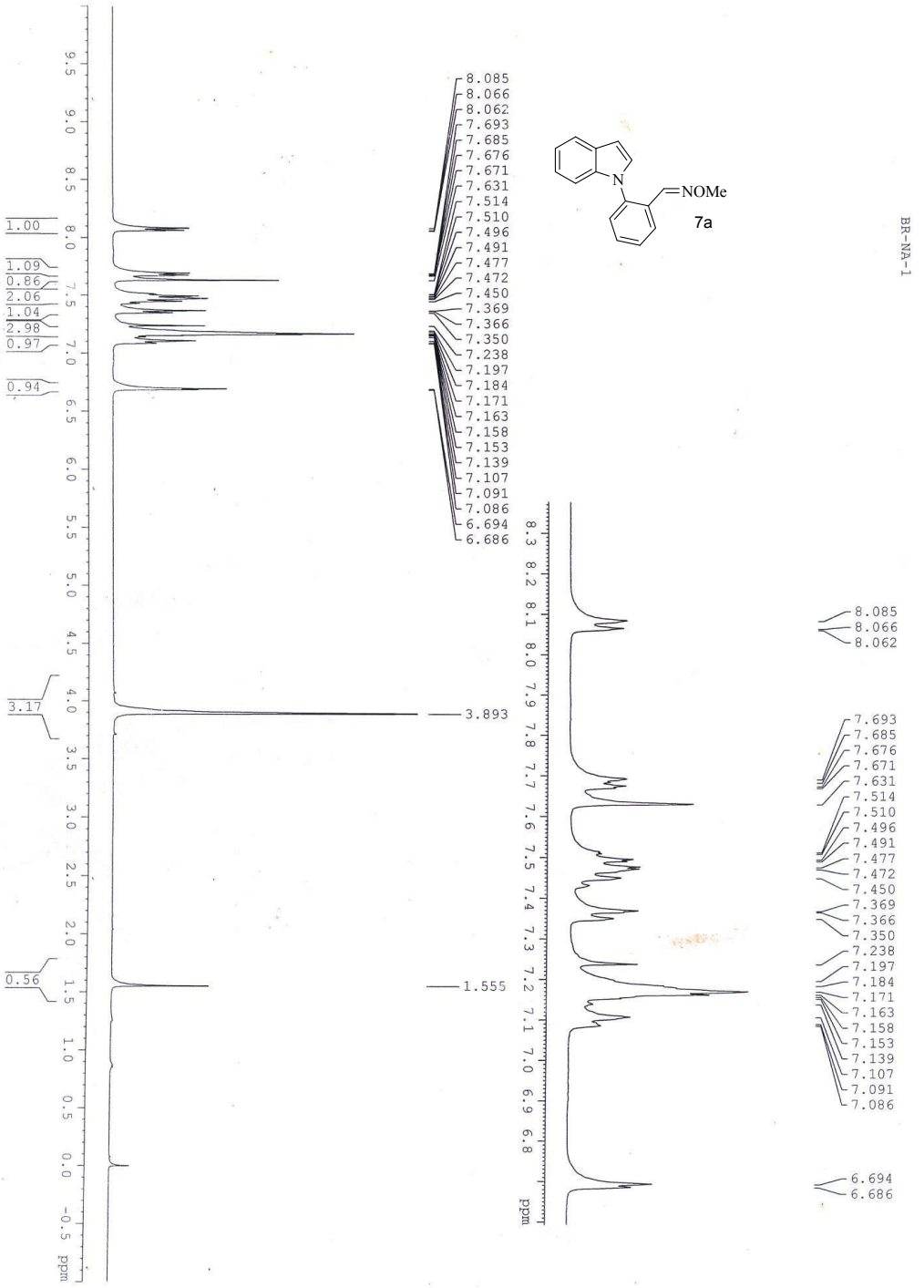
2-(2-(4-ethoxyphenyl)-1-isopropyl-1H-indol-3-yl)benzaldehyde O-methyl oxime (6):



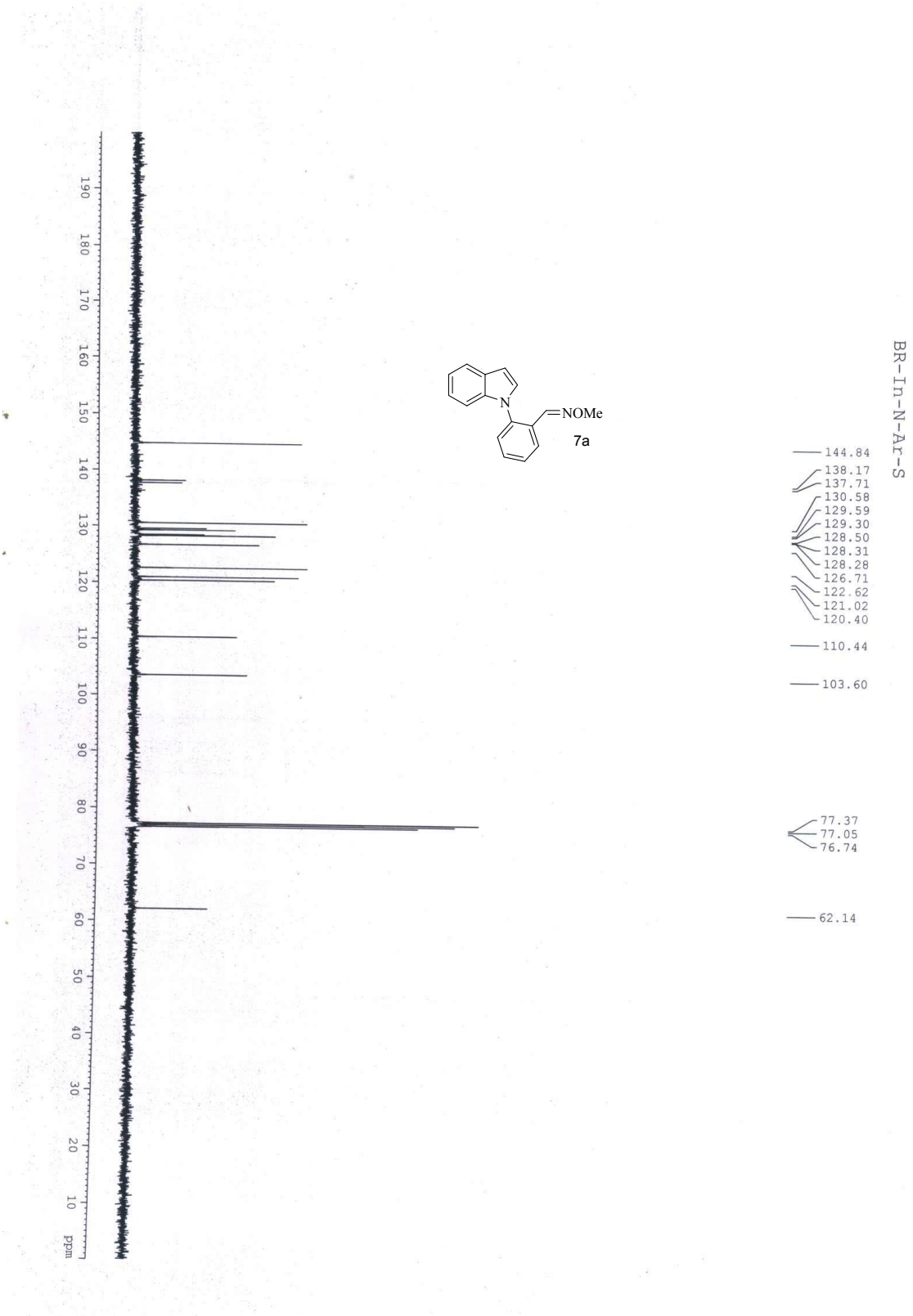
2-(2-(4-ethoxyphenyl)-1-isopropyl-1H-indol-3-yl)benzaldehyde O-methyl oxime (6):



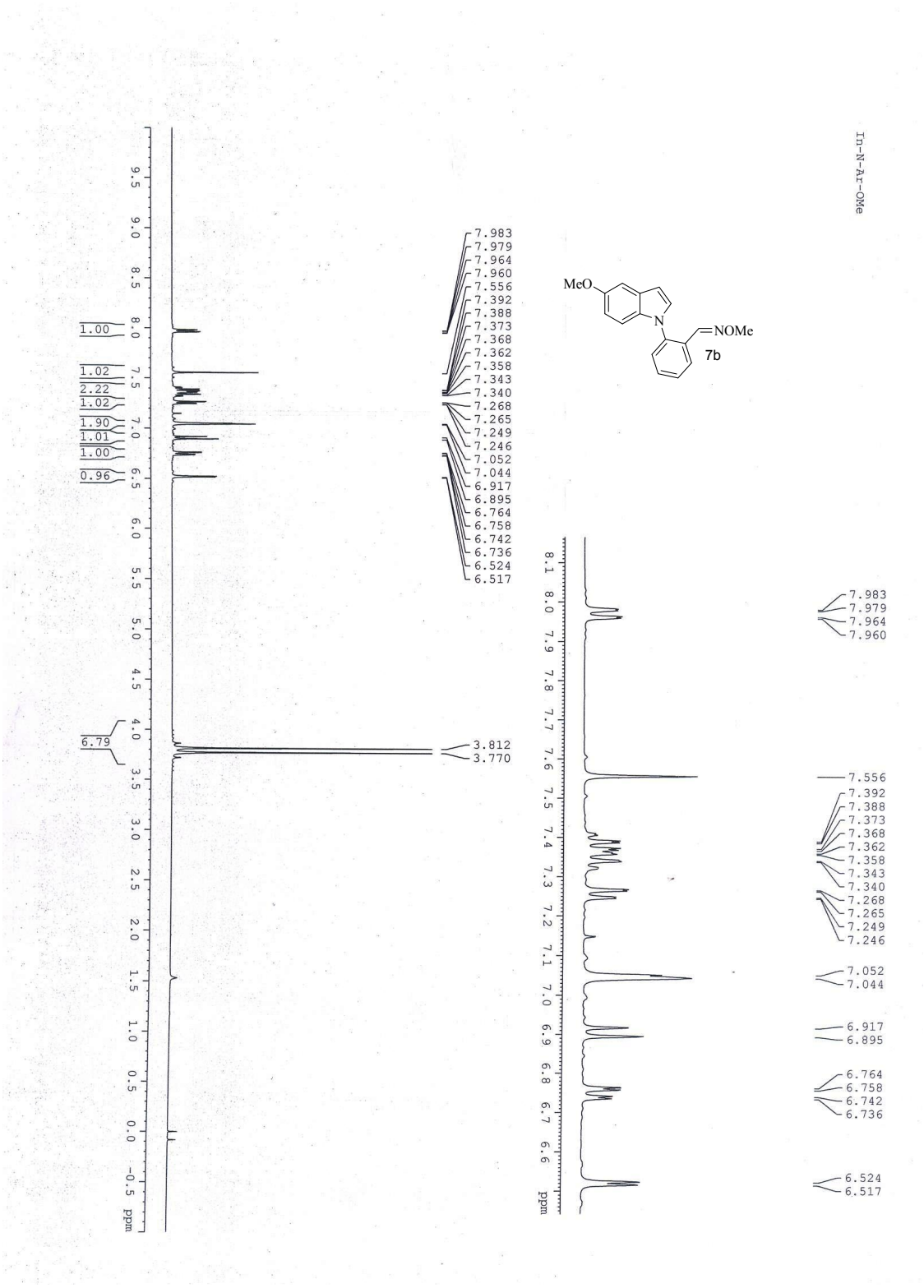
2-(1H-indol-1-yl)benzaldehyde O-methyl oxime (7a):



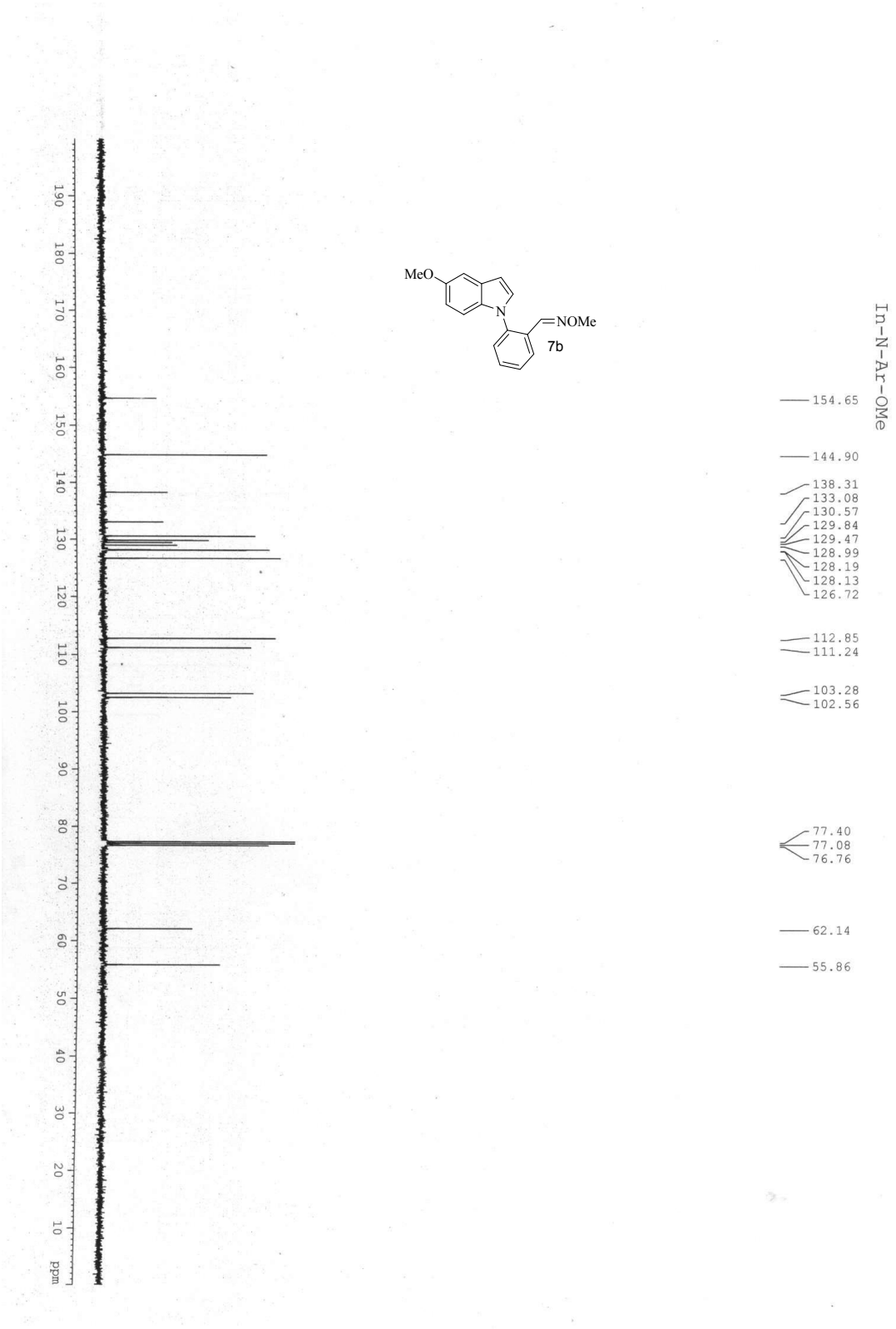
2-(1H-indol-1-yl)benzaldehyde O-methyl oxime (7a):



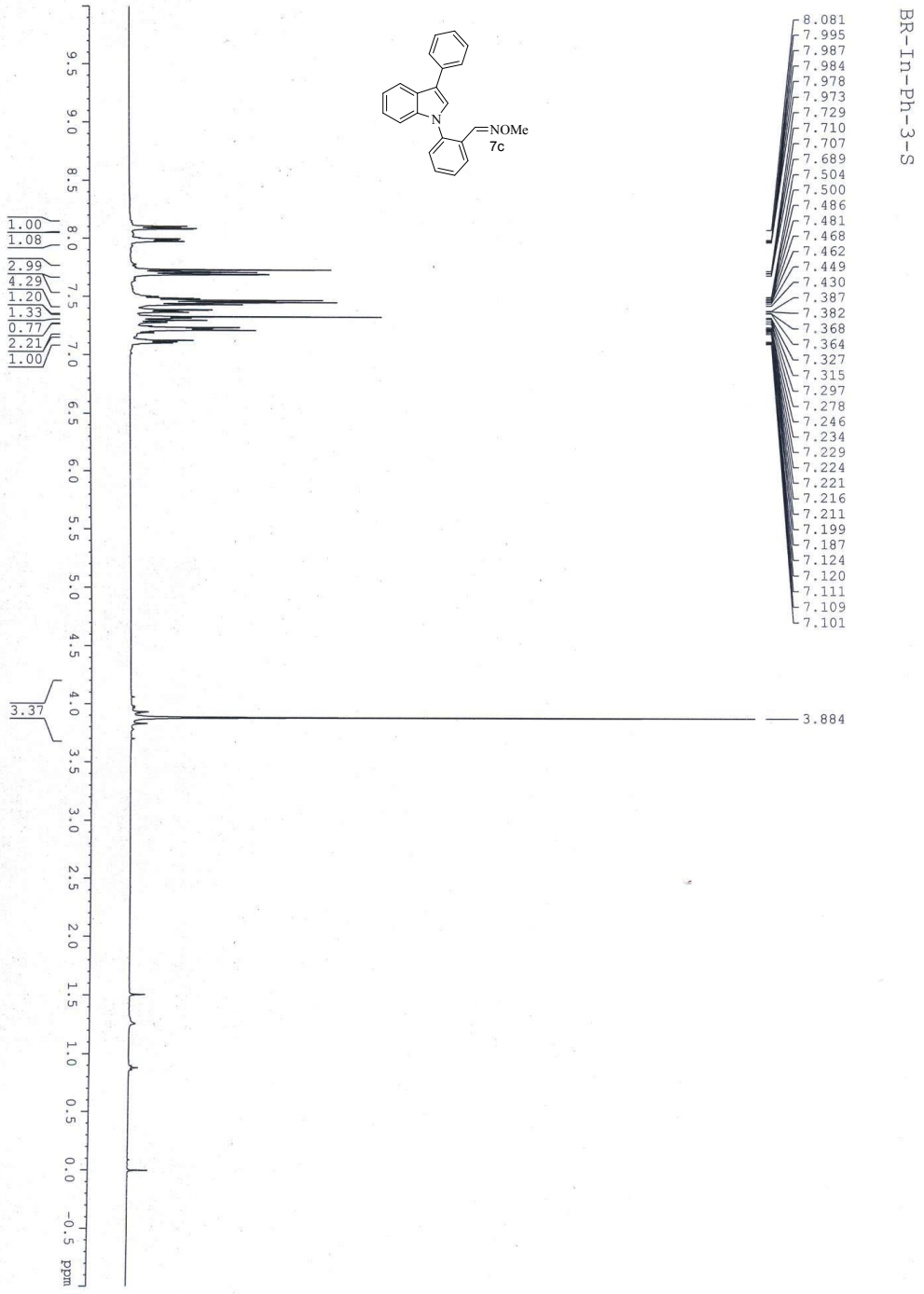
2-(5-methoxy-1H-indol-1-yl)benzaldehyde O-methyl oxime (7b):



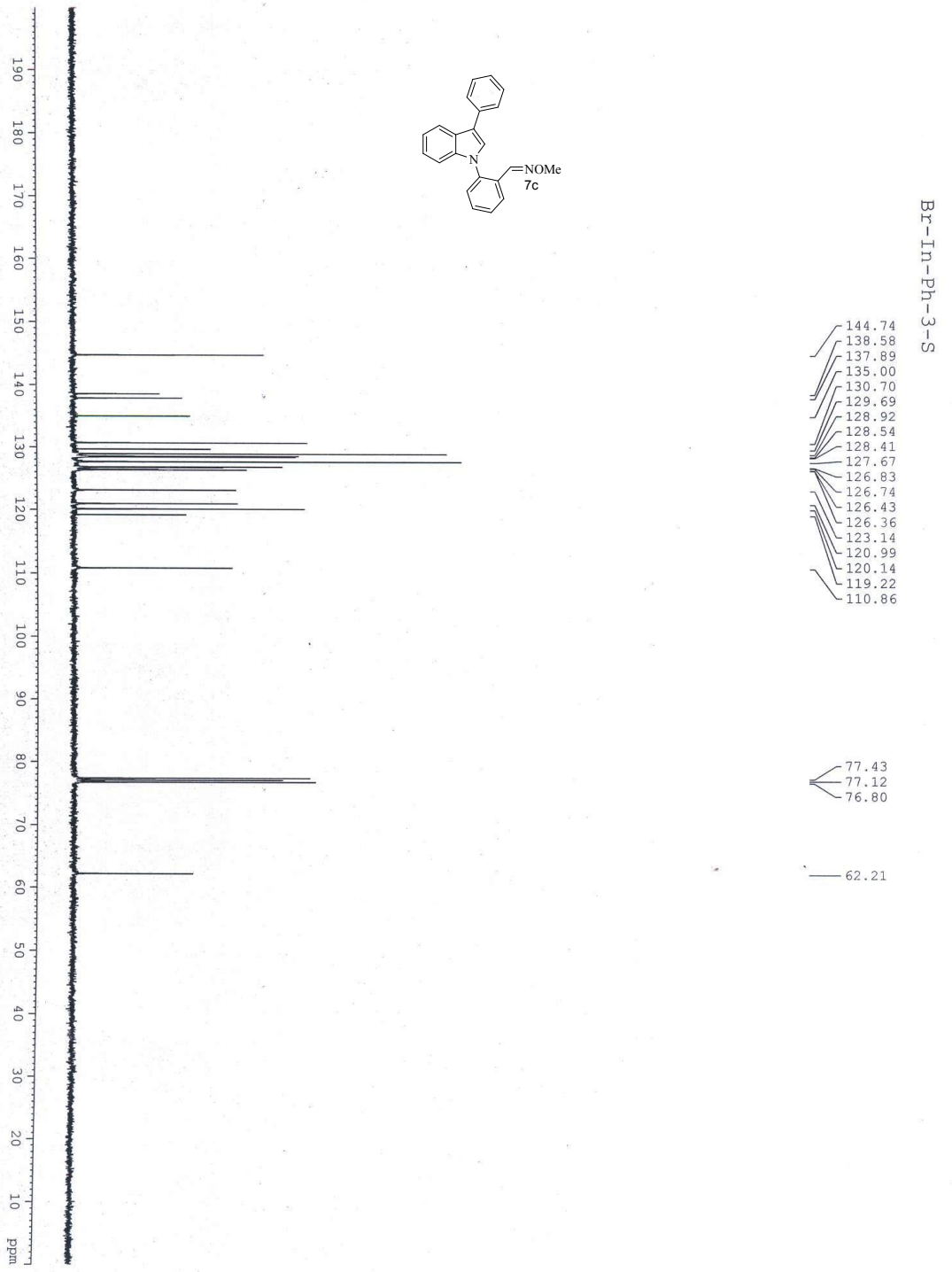
2-(5-methoxy-1H-indol-1-yl)benzaldehyde O-methyl oxime (7b):



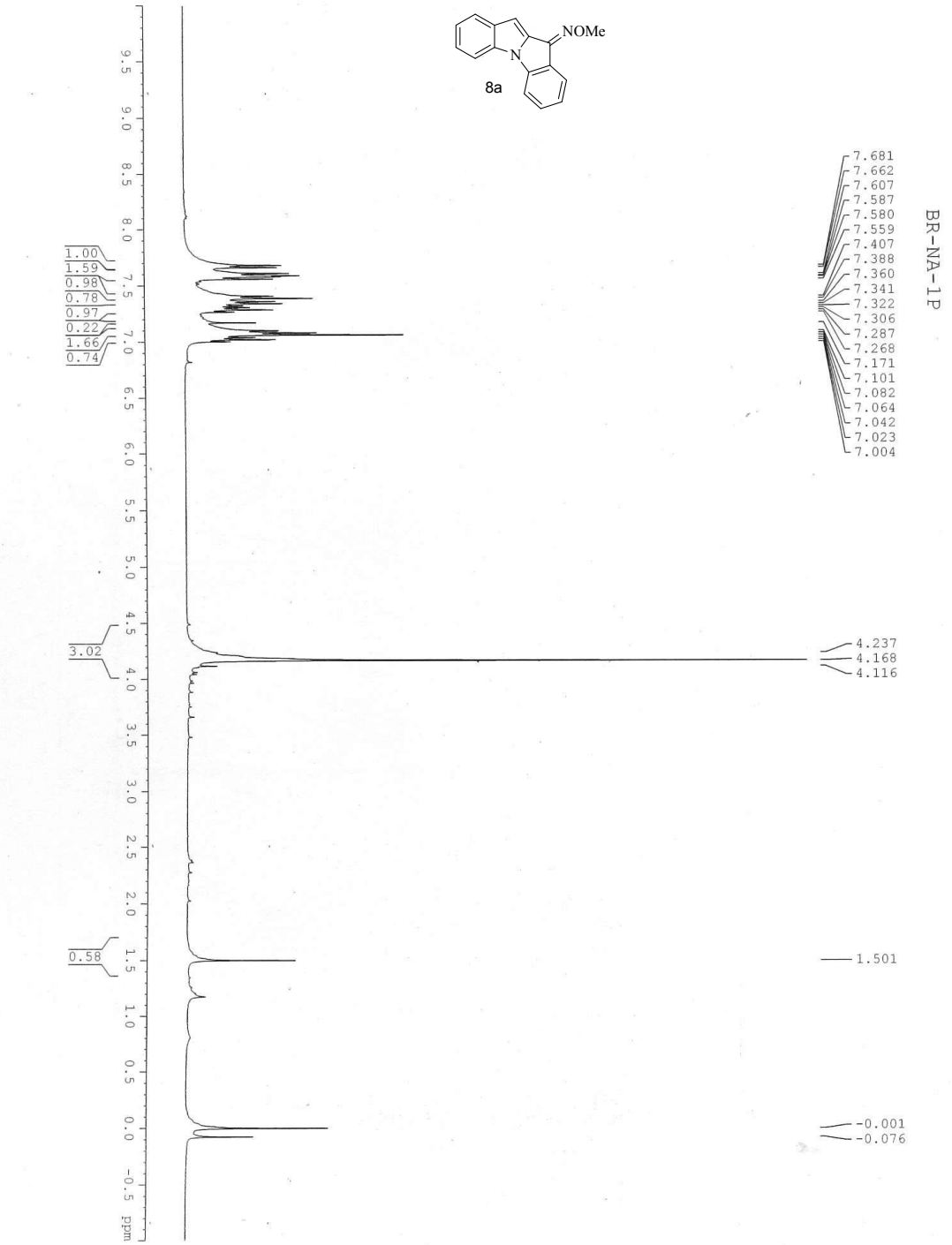
2-(3-phenyl-1H-indol-1-yl)benzaldehyde O-methyl oxime (7c):



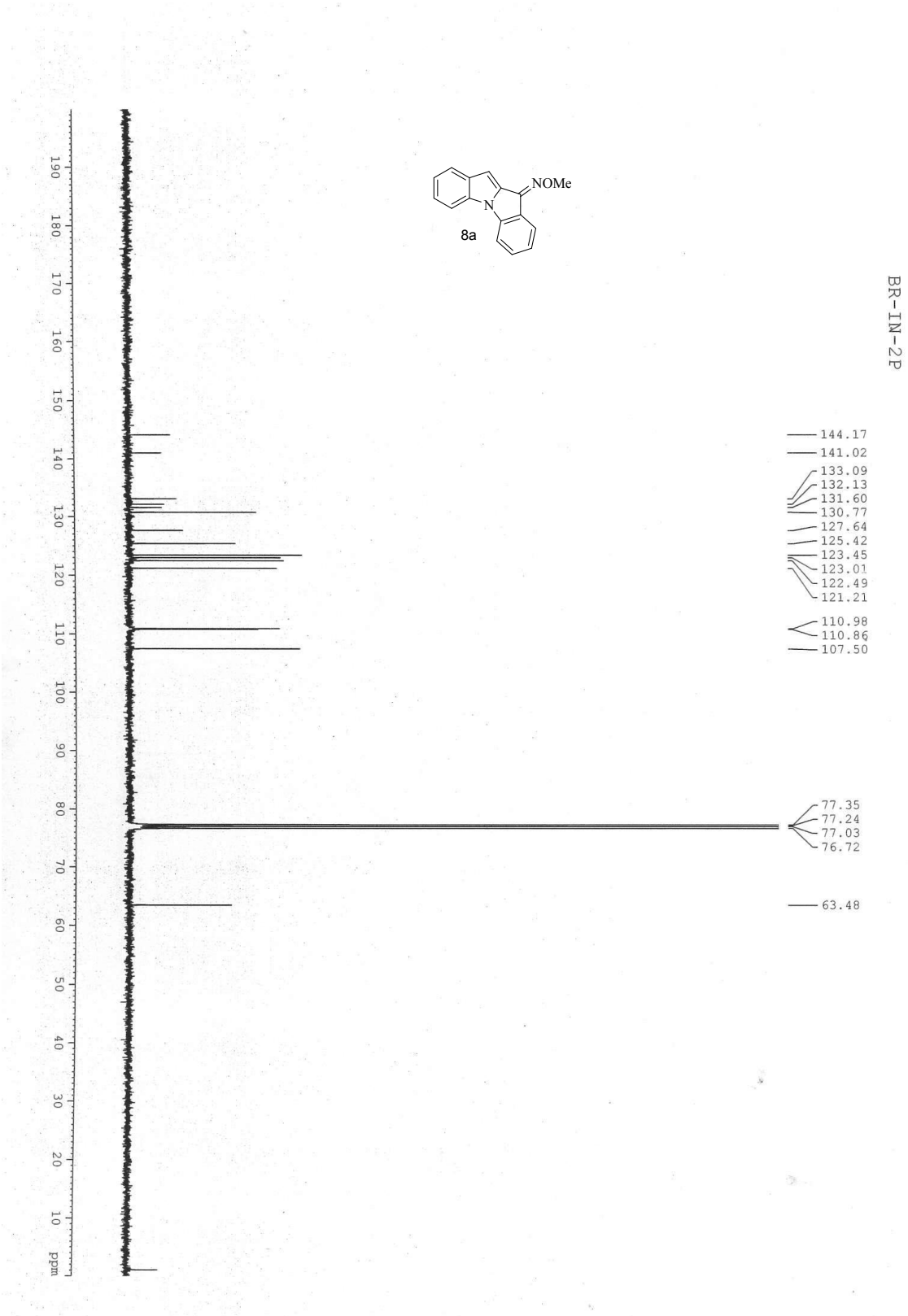
2-(3-phenyl-1H-indol-1-yl)benzaldehyde O-methyl oxime (7c):



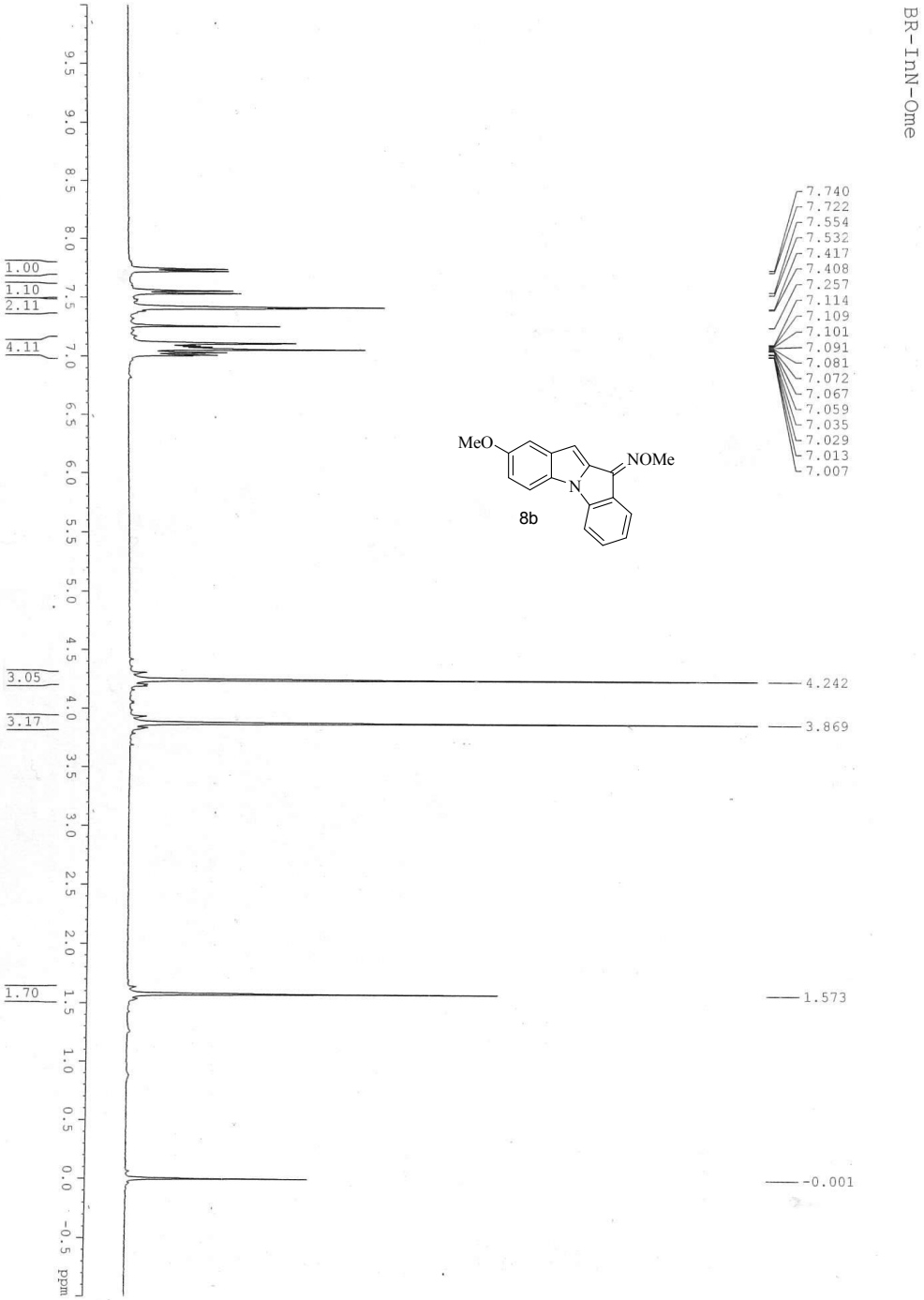
10H-indolo[1,2-a]indol-10-one O-methyl oxime (8a):



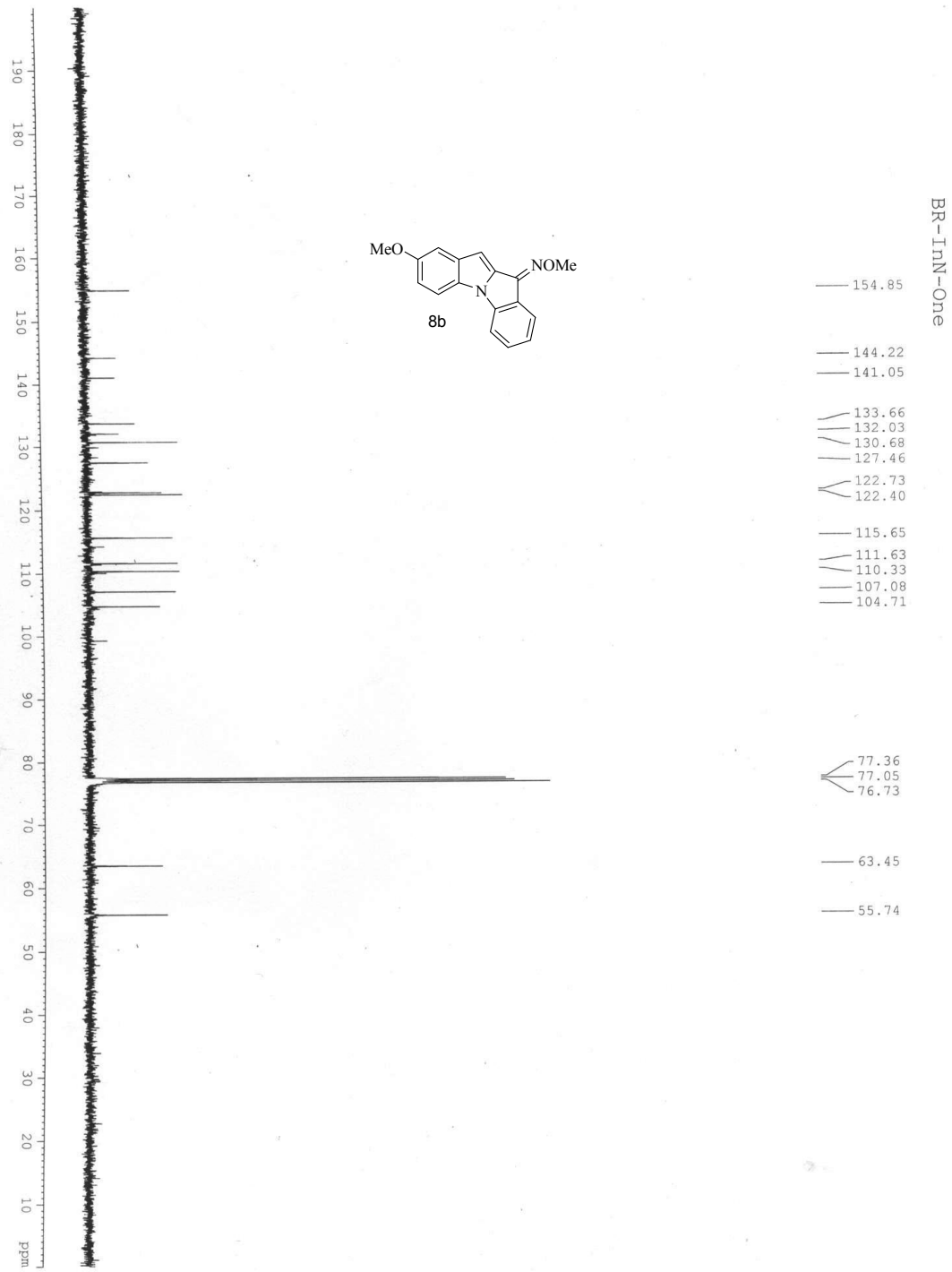
10H-indolo[1,2-a]indol-10-one O-methyl oxime (8a):



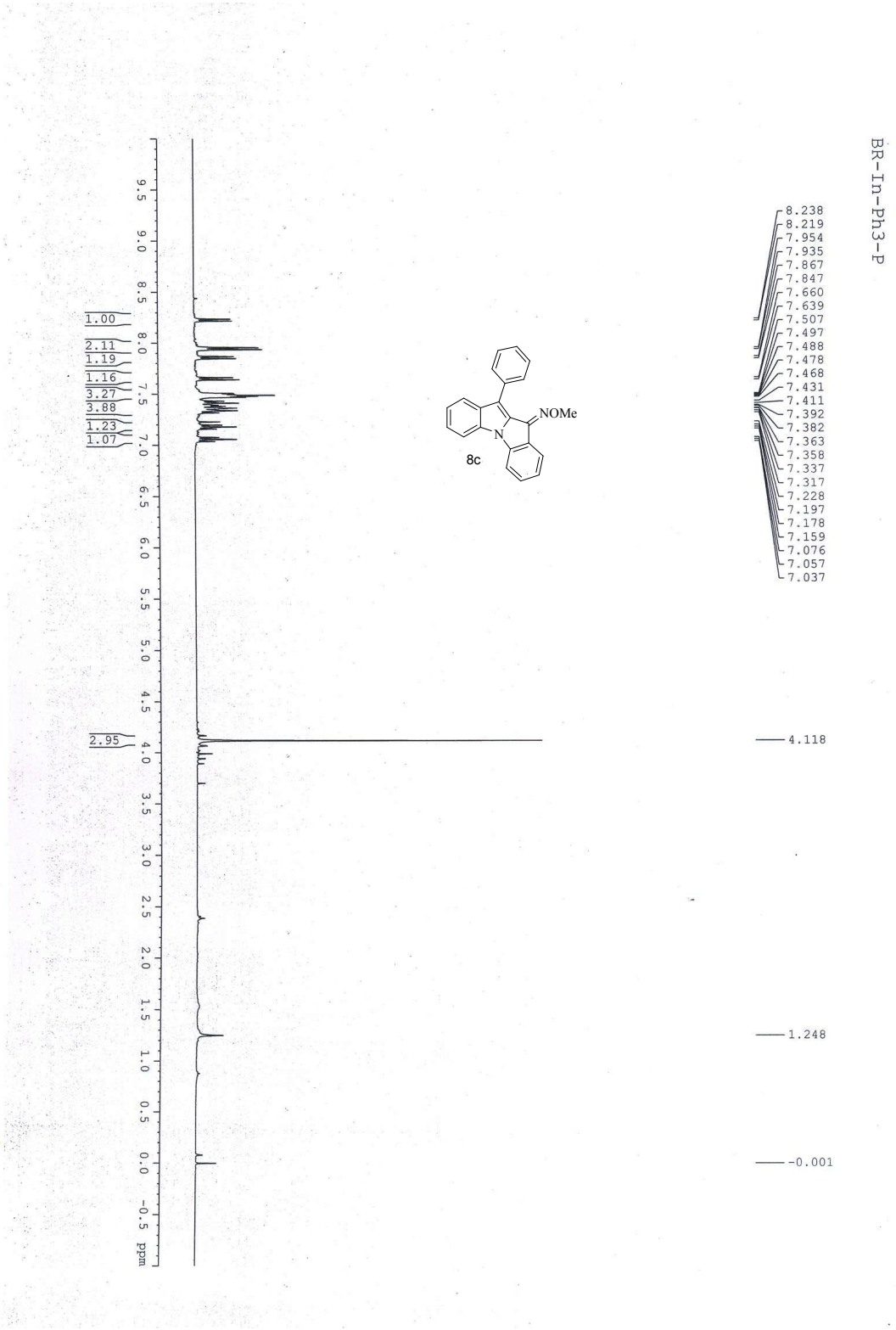
2-methoxy-10H-indolo[1,2-a]indol-10-one O-methyl oxime (8b):



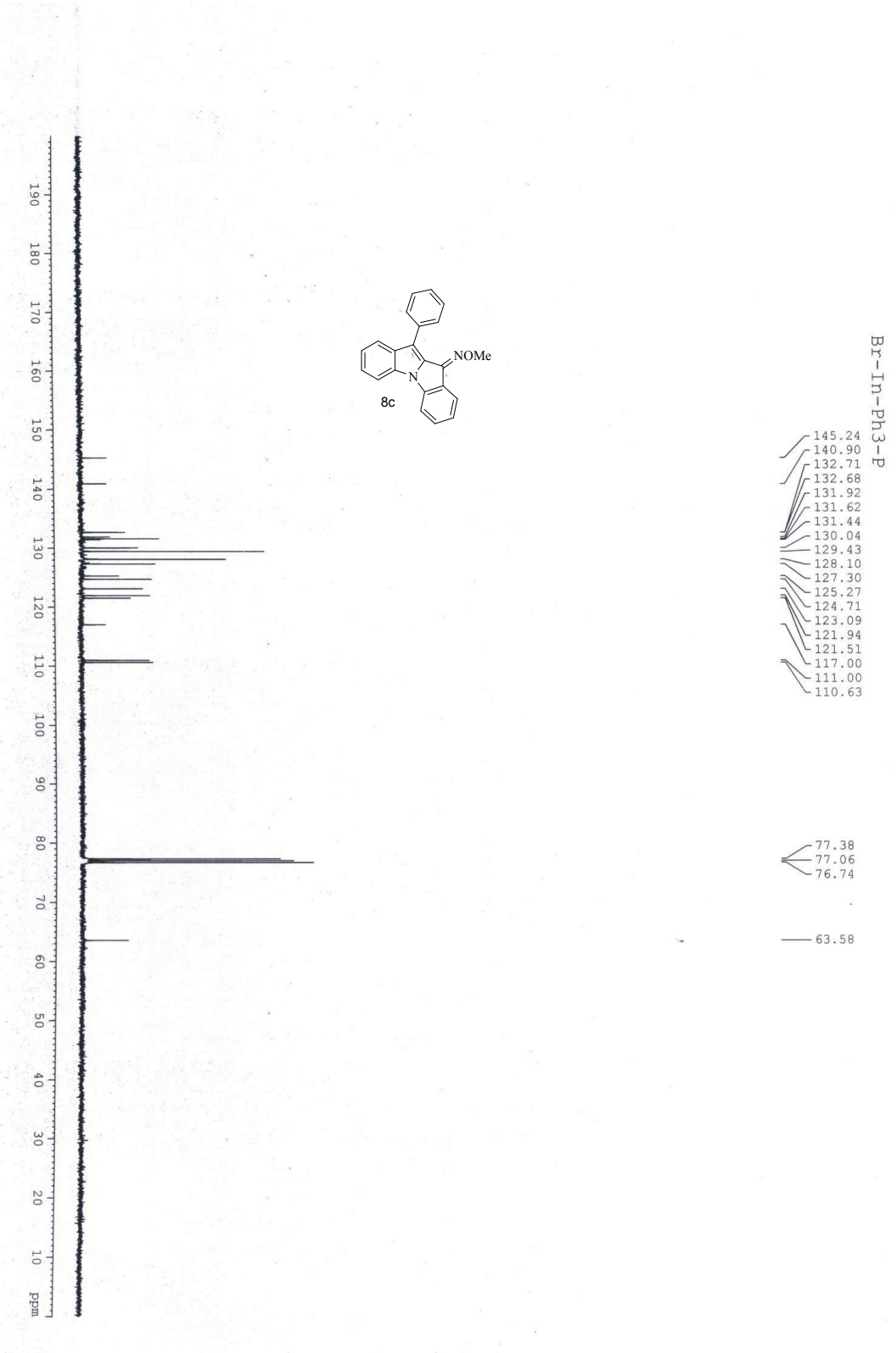
2-methoxy-10H-indolo[1,2-a]indol-10-one O-methyl oxime (8b):



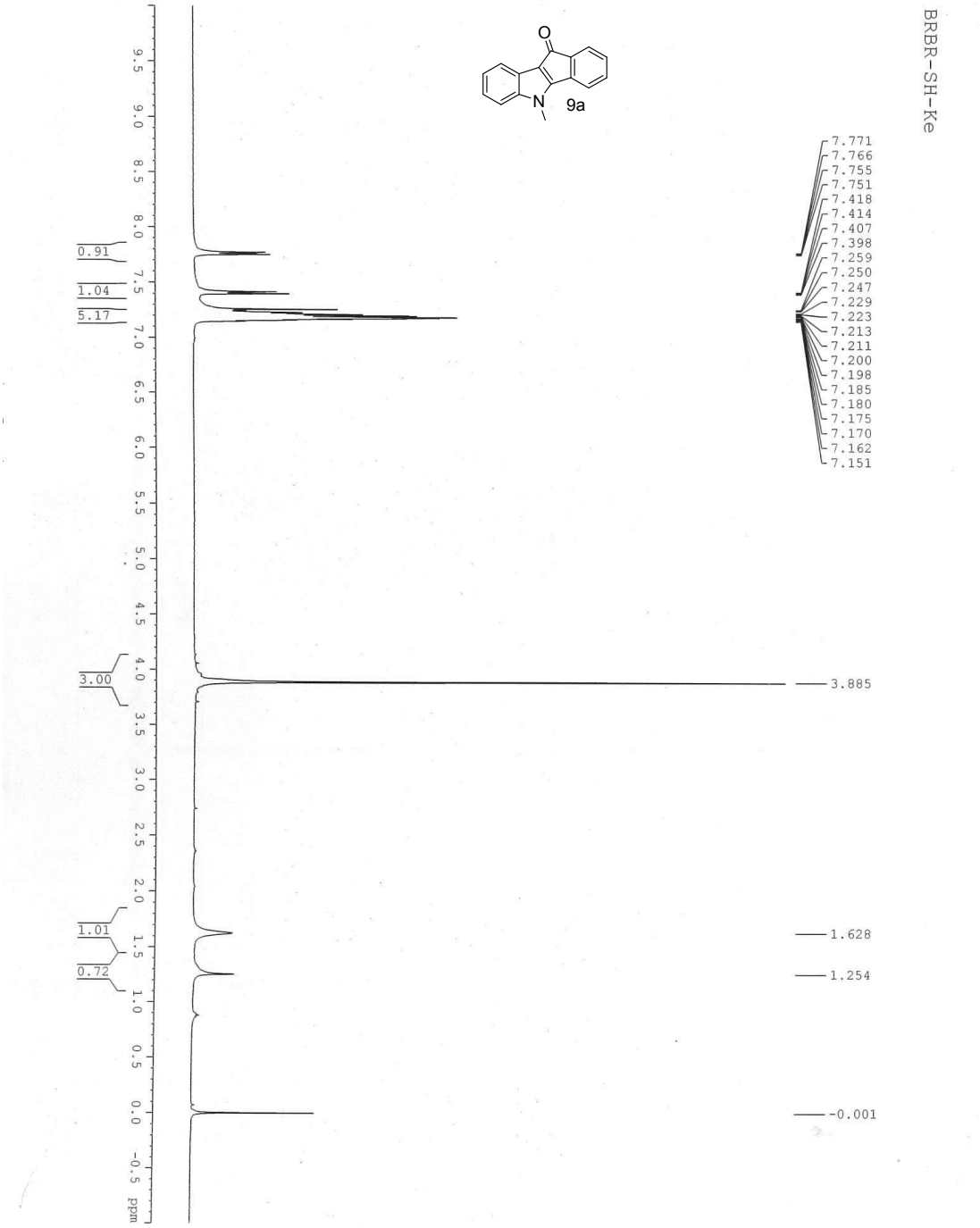
11-phenyl-10H-indolo[1,2-a]indol-10-one O-methyl oxime (8c):



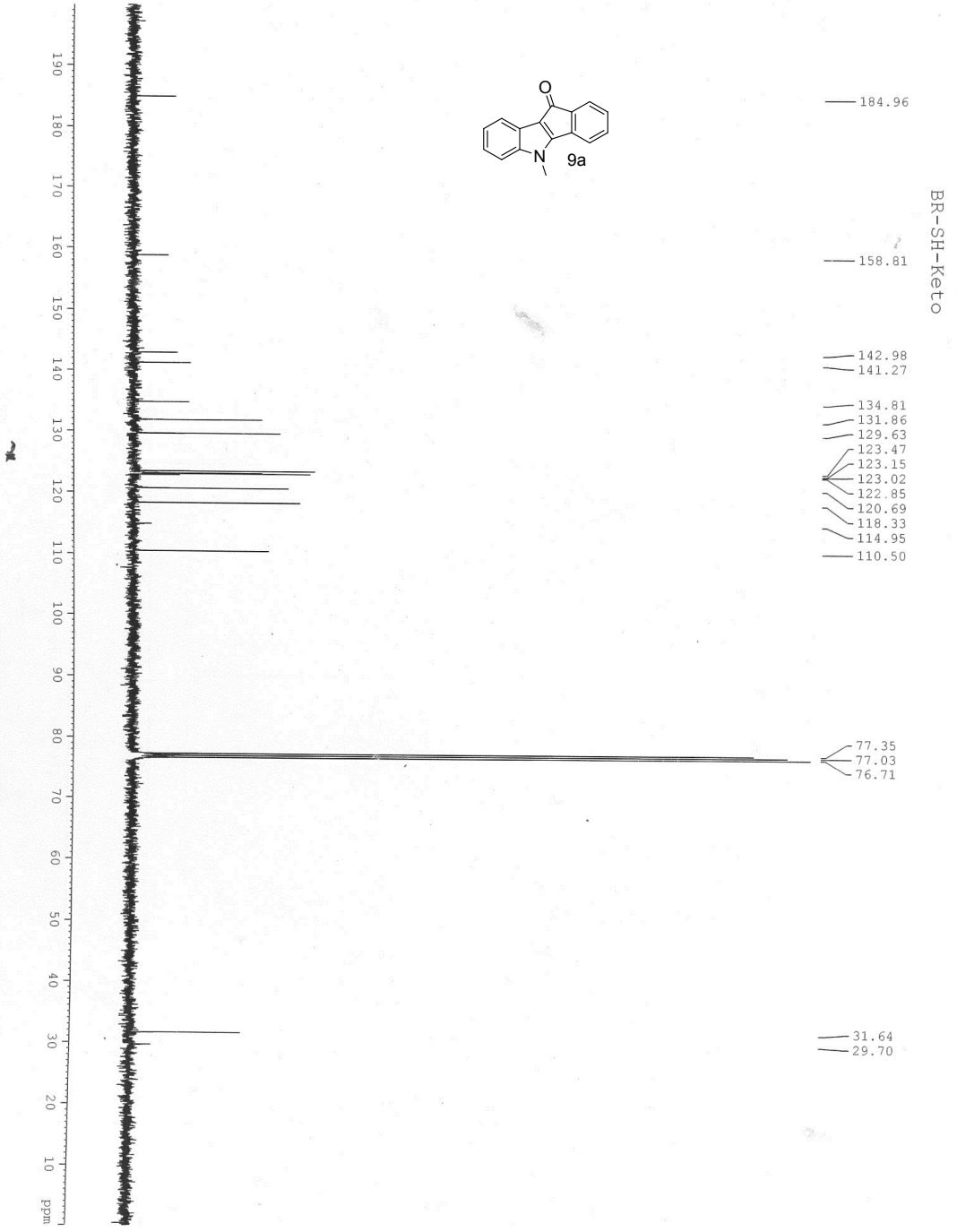
11-phenyl-10H-indolo[1,2-a]indol-10-one O-methyl oxime (8c):



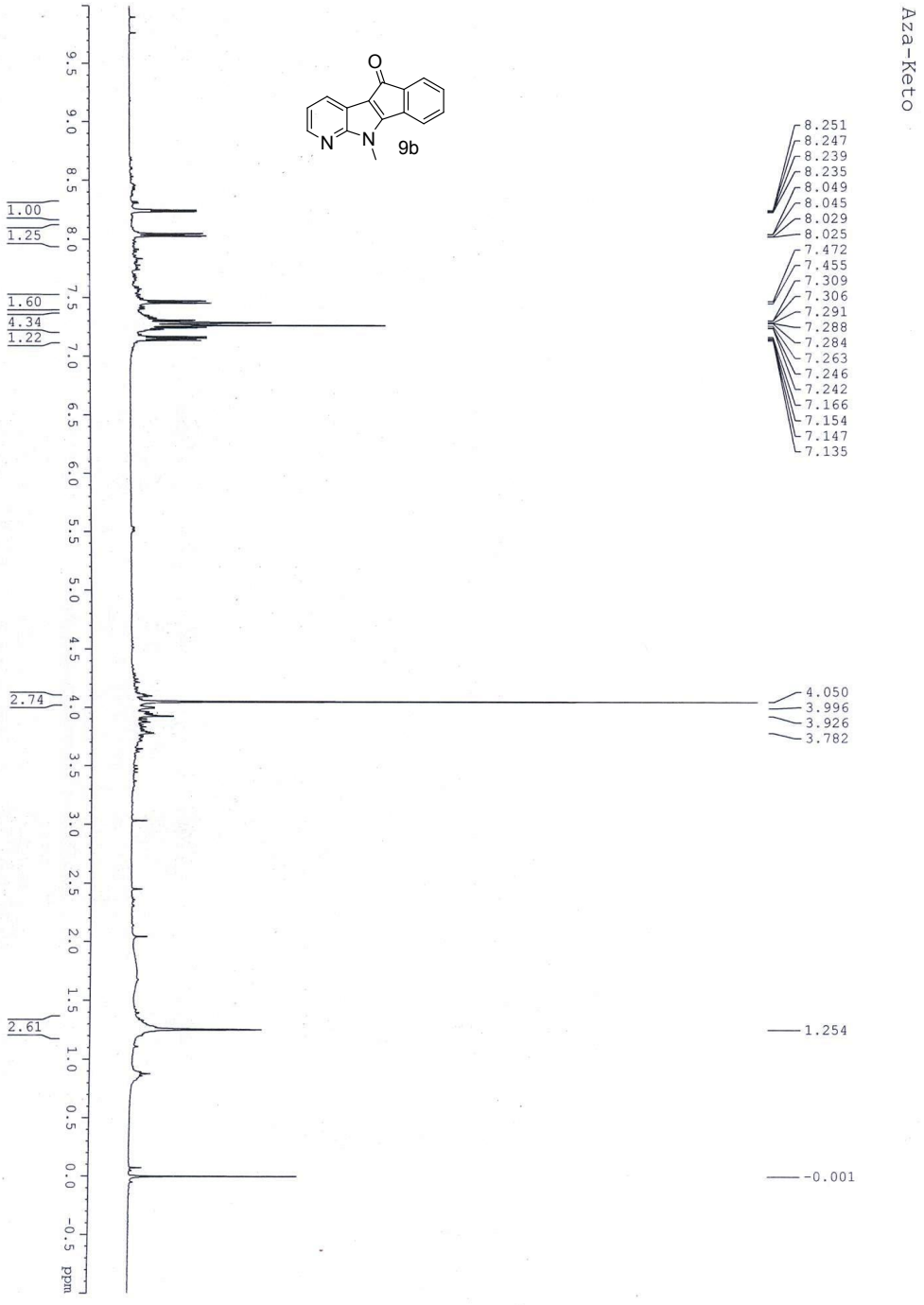
5-methylindeno[1,2-b]indol-10(5H)-one (9a):



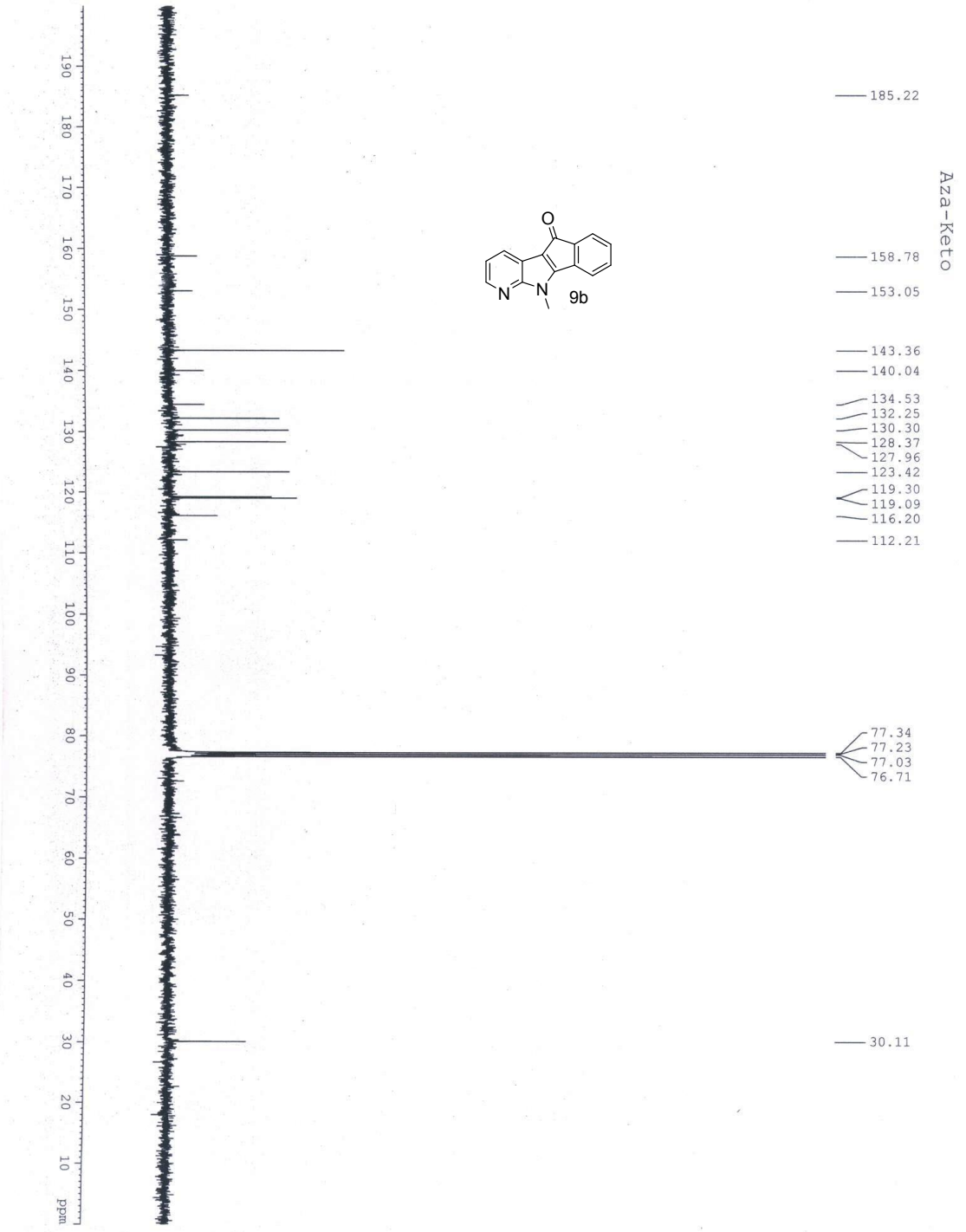
5-methylindeno[1,2-b]indol-10(5H)-one (9a):



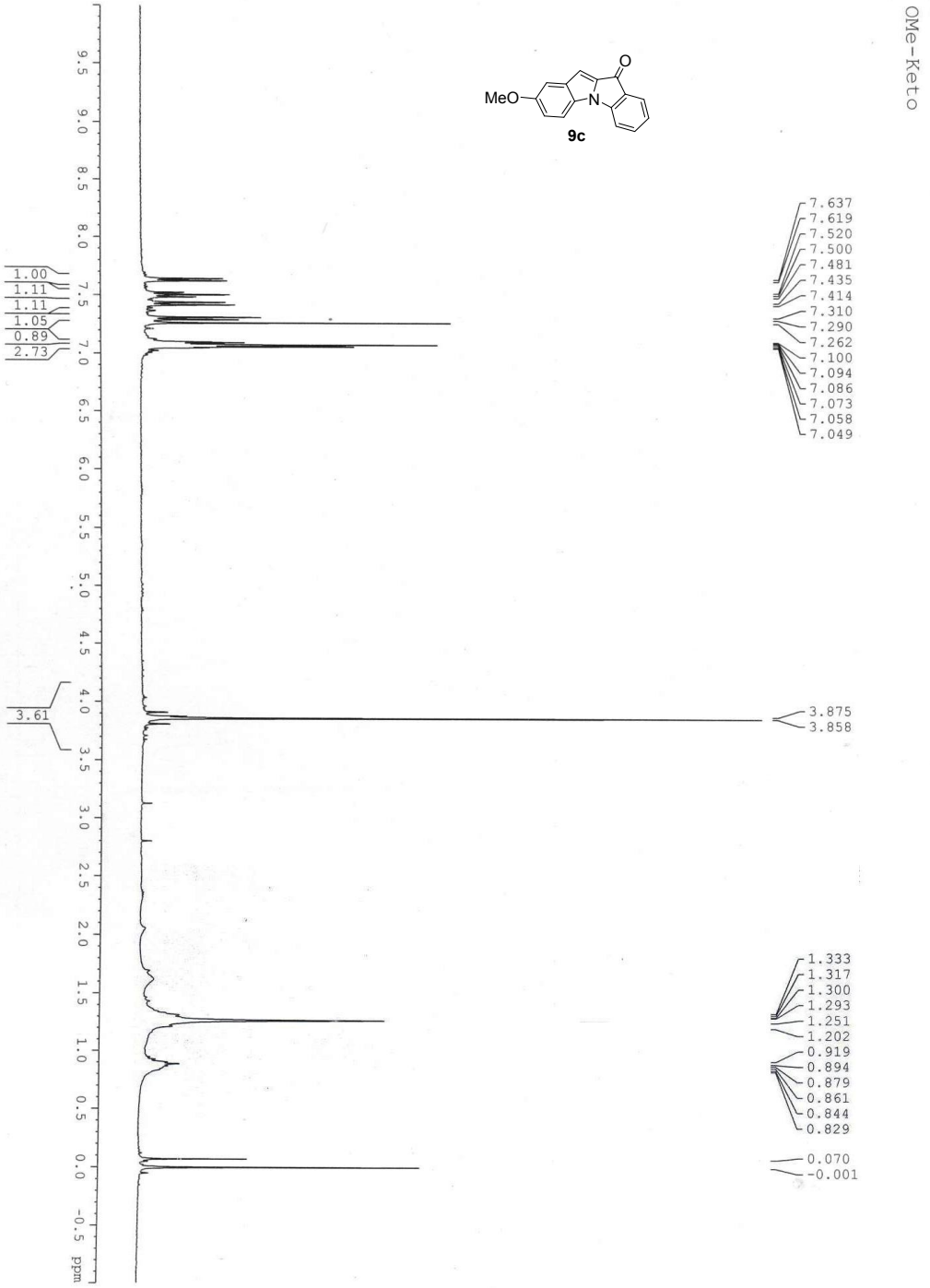
10-methylindeno[2',1':4,5]pyrrolo[2,3-b]pyridin-5(10H)-one (9b):



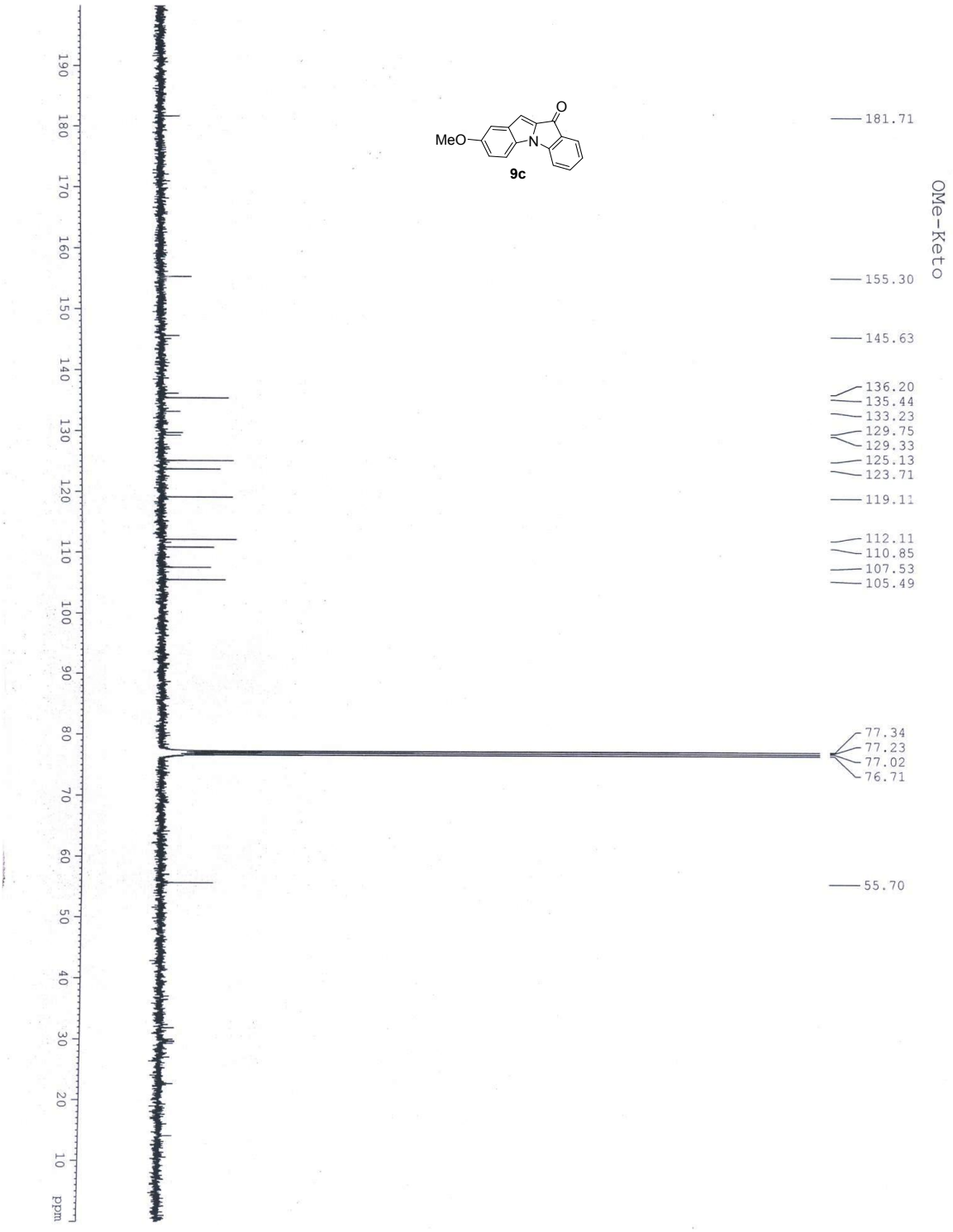
10-methylindeno[2',1':4,5]pyrrolo[2,3-b]pyridin-5(10H)-one (9b):



2-methoxy-10H-indolo[1,2-a]indol-10-one (9c):



2-methoxy-10H-indolo[1,2-a]indol-10-one (9c):



Mass spectra of compound 3a and 4a:

Elemental Composition

File Edit View Process Help

Single Mass Analysis
Tolerance = 10.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3
Monoisotopic Mass, Even Electron Ions
3544 formula(e) evaluated with 12 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:

Mass	Calc. Mass	mDa	PPM	DBE	Formula	i-FIT	i-FIT Norm	Fit Conf %	C	H	N	O	Na	Cl	Br	I
277.1335	277.1341	-0.6	-2.2	11.5	C18 H17 N2 O	232.2	0.355	70.15	18	17	2	1				
	277.1317	1.8	6.5	8.5	C16 H18 N2 O Na	233.1	1.319	26.75	16	18	2	1	1			
	277.1359	-2.4	-8.7	-1.5	C6 H21 N4 O8	236.4	4.558	1.05	6	21	4	8				
	277.1349	-1.4	-5.1	0.5	C5 H18 N8 O4 Na	236.7	4.920	0.73	5	18	8	4	1			
	277.1333	0.2	0.7	-0.5	C2 H17 N10 O6	237.2	5.410	0.45	2	17	10	6				
	277.1362	-2.7	-9.7	5.5	C6 H14 N12 Na	237.3	5.533	0.40	6	14	12		1			
	277.1346	-1.1	-4.0	4.5	C3 H13 N14 O2	237.6	5.806	0.30	3	13	14	2				
	277.1327	1.8	6.7	1.5	C H14 N14 O3 Na	238.2	6.377	0.17	1	14	14	3	1			