Supplementary Material (ESI) for Organic & Biomolecular Chemistry

Supporting information

Synthesis of benzo-and naphtho-fused bicyclo[n.3.1]alkane frameworks with a bridgehead nitrogen function by palladium-catalyzed intramolecular α'-arylation of α-nitroketones

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Synthesis of halides 2

1. General procedure for benzylic bromination

To a solution of the suitable methylbenzene (20 mmol) in CCl_4 (80 ml) was added NBS (1.3 eq) and a catalytic amount of AIBN. The reaction was refluxed for 8-24 h, cooled, filtered and evaporated. The residue was crystallized from ethanol, affording the following benzylic bromides: 2-bromo-1-bromomethyl-5-chlorobenzene,[1] 2-bromo-1-bromomethyl-5-nitrobenzene,[2] 2-bromo-1-bromomethyl-5-methoxybenzene, methyl (4-bromo-3-bromomethyl)benzoate and 1-bromo-2-bromomethylnaphthalene.[3] 1-Bromo-2-bromomethylbenzene and 2-bromo-1-bromomethyl-4,5-methylenedioxybenzene were purchased from Aldrich.

2. General procedure for benzylic iodination

A solution of the suitable benzylic bromide (4 mmol) and potassium iodide (10 mmol) in 40 ml of dry acetone, freshly distilled over anhydrous calcium sulphate (“drierite”). The solution was refluxed for 6 h, under an argon atmosphere. After cooling, the reaction mixture was poured onto 10% aqueous sodium thiosulfate (25 ml) and extracted with dichloromethane (4 x 30 ml). The organic layer was dried over sodium sulphate and evaporated, giving the benzylic iodides with sufficient purity to be used for the next step without further purification

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1 B. Le Bourdonnec, L. K. Leister, C. A. Ajello, J. A. Cassel, P. R; Seida, H. O’Hare, M. Gu, G.-H. Chu, P. A. Tuthill, R. N. DeHaven, R. E. Dolle, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 336.

2 S. M. Tsang, A. P. Paul, M. P. DiGiaimo, *J. Org. Chem.* **1964**, *29*, 3387.

3 D. A. Hunt, *Org. Prep. Proc. Int.* **1989**, *21*, 360.

2-Bromobenzyl iodide. Yield, 87%. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 7.55 (dd, 1H, *J* = 7.9 and 1.1 Hz, H-3); 7.45 (dd, 1H, *J* = 7.6 and 1.7 Hz, H-6); 7.28 (td, 1H, *J* = 7.4 and 1.1 Hz, H-5); 7.14 (td, 1H, *J* = 7.7 and 1.7 Hz, H-4); 4.56 (s, 2H, H-α) ppm. ^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 138,8 (C-1); 133,9 (C-3); 131,1 (C-6); 130,1 (C-4); 128,5 (C-5); 124,6 (C-2); 6,8 (C-α) ppm.

2-Bromo-5-chlorobenzyl iodide. Yield, 90%. IR (KBr): 1461, 1388, 1158, 1029 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 7.45 (dd, 1H, *J* = 7.1 and 1.5 Hz, H-3); 7.42 (t, 1H, *J* = 1.9 Hz, H-6); 7,10 (td, 1H, *J* = 7.1 and 1.9 Hz, H-5); 4.46 (d, 2H, *J* = 1.5 Hz, H-α) ppm. ^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 139.9 (C-1); 134.4 (C-3); 133.5 (C-5); 130.2 (C-6); 129.4 (C-4); 121.7 (C-2); 4.1 (C-α) ppm.

2-Bromo-5-nitrobenzyl iodide. Yield, 48 %. IR (KBr): 3094, 1699, 1506 and 1345 (NO_2), 1162, 1031 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 8.30 (d, 1H, *J* = 2.4 Hz, H-6); 7.97 (dd, 1H, *J* = 8.7 and 2.5 Hz, H-4); 7.74 (td, 1H, *J* = 8.7 Hz, H-3); 4.58 (s, 2H, H-α) ppm. ^{13}C-RMN ($CDCl_3$, 63 MHz) δ: 147.1 (C-5); 140.3 (C-1); 134.4 (C-3); 131.1 (C-2); 124.8 (C-6); 123.7 (C-4); 3.0 (C-α) ppm.

1-Bromo-2-Iodomethyl-4-methoxybenzene. Yield, 92%. White solid, mp 84 °C. IR (neat) 2967, 2839, 1573, 1474, 1411, 1282, 1251, 1172, 1053, 1013, 871, 807 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 3.79 (s, 3H), 4.49 (s, 2H), 6.70 (dd, *J* = 3.0 and 8.8 Hz, 1H), 6.97 (d, *J* = 2.9 Hz, 1H), 7.40 (d, *J* = 8.8 Hz, 1H). ^{13}C-NMR ($CDCl_3$, 62.9 MHz) δ 6.6, 56.0, 114.8, 116.1, 116.2, 134.5, 139.5, 159.5.

4-Bromo-3-iodomomethylbenzoic acid methyl ester. Yield, 95%. White solid, mp 68 °C. IR (neat) 2949, 1727, 1714, 1434, 1386, 1289, 1116, 1040, 968, 763 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 3.87 (s, 3H), 4.48 (s, 2H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.82 (dd, *J* = 1.5 and 8.0 Hz, 1H), 8.10 (d, *J* = 1.5 Hz, 1H). ^{13}C-NMR ($CDCl_3$, 62.9 MHz) δ 5.0, 52.9, 124.3, 129.4, 130.9, 131.5, 134.8, 143.7, 165.5.

1-Bromo-2-iodomethylnaphthalene. Yield, 94 %. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 8.33 (d, 1H, *J* = 8.4 Hz, H-8); 7.83-7.76 (m, 2H, H-3,5); 7.66-7.49 (m, 3H, H-4,6,7); 4.82 (s, 2H, H-α) ppm. ^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 136.2 (C-2); 133.7 (C-4a); 132.6 (C-8a); 128.3 (C-5); 128.1 (C-7); 127.8 (C-4); 127.4 (C-8); 127.2 (C-3); 126.9 (C-6), 124.1 (C-1); 7.7 (C-α) ppm.

3. Synthesis of 2-Bromo-1-iodomethyl-4-methylbenzene

(a) 2-Bromo-4-methylbenzyl alcohol. To a solution of 2-bromo-4-methylbenzaldehyde (0,10 g; 0,50 mmol) in methanol (15 ml) was added $NaBH_4$ (0.03 g, 0.75 mmol) portionwise over 5 min. The reaction mixture was stirred at room temperature for 30 min and treated dropwise with HCl 2M until the effervescence ceases. After stirring at room temperature for 15 min, the reaction mixture was extracted with dichloromethane (3 x 20 ml). The combined organic layers were dried over sodium sulphate and evaporated, yielding 0,10 g (98 %) of the alcohol, as a white solid. IR (KBr): 3353 (OH), 3952, 1606, 1335 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 7.39 (d, 1H, *J* = 0.7 Hz, H-3); 7.34 (d, 1H, *J* = 7.7 Hz, H-6); 7.15 (dd, 1H, *J* = 7.7 and 0.8 Hz, H-5); 4.70 (s, 2H, H-α); 2.43 (br s, 1H, OH); 2.34 (s, 3H, CH_3) ppm. ^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 139.2 (C-4); 136.5 (C-1); 132.9 (C-3); 128.7 (C-6); 128.3 (C-5); 122.3 (C-2); 64.7 (C-α); 20.6 (CH_3) ppm. Anal. Calcd. for C_8H_9OBr: C, 47.79; H, 451. Found: C, 47.76; H, 4.46.

(b) 2-Bromo-1-iodomethyl-4-methylbenzene. To a solution of 2-bromo-4-methylbenzyl alcohol (0.92 g; 4.6 mmol) and NaI (2.70 g, 18.0 mmol) in acetonitrile (40 ml), under an argon atmosphere, was dropwise added chlorotrimethylsilane (2.3 ml; 18.0 mmol). After stirring at room temperature for 3 h, the reaction mixture was poured on water (25 ml) and extracted with dichloromethane (4 x 25 ml). The combined organic layers were washed with 10% aqueous sodium thiosulphate (25 ml) and brine (25 ml), dried over anhydrous sodium

sulphate and evaporated, yielding 1.30 g (91%) of the iodide, as a yellowish solid. Mp 62-63º C. IR (KBr): 2950, 1603, 1489, 1157 cm^{-1}. ^{1}H-RMN ($CDCl_3$, 250 MHz) δ: 7,38 (d, 1H, *J* = 0,9 Hz, H-3); 7,34 (d, 1H, *J* = 7,8 Hz, H-6); 7,09 (dd, 1H, *J* = 7,8 y 0,9 Hz, H-5); 4,55 (s, 2H, H-α); 2,32 (s, 3H, CH_3) ppm. ^{13}C-RMN ($CDCl_3$, 63 MHz) δ: 139,9 (C-4); 135,1 (C-1); 135,8 (C-3); 130,2 (C-6); 128,7 (C-5); 123,7 (C-2); 20,8 (CH_3); 6,1 (C-α) ppm. Anal. Calcd. for C_8H_8BrI: C, 30.90; H, 2.59. Found: C, 31.24; H, 2.39.

General procedure for the C-alkylation of α-nitroketones. Synthesis of compounds 3

To a solution of the suitable 2-nitrocycloalkanone **1** (0,64-3,50 mmol) in dry tetrahidrofuran (5-10 ml) was added DBU (0.13-0.65 ml, 0.83-4.15 mmol). After stirring for 5 min at room temperature and under an argon atmosphere, a solution of the suitable benzylic halide (0.83-4.55 mmol) in dry THF was added, and stirring at room temperature was maintained for 2-24 h, as specified in Table 1. The reaction mixture was diluted with dichloromethane (15 ml) and 2M aqueous HCl was added until the aqueous layer was acidic. The aqueous solution was extracted with dichloromethane (3 x 10 mL), and the combined organic layers were dried over anhydrous sodium sulfate and evaporated. The residue was identified as the essentially pure compunds **3**, which were employed for the next step without further purification. Analytical samples were obtained by chromatography on silica gel using a gradient from petroleum ether to dichloromethane.

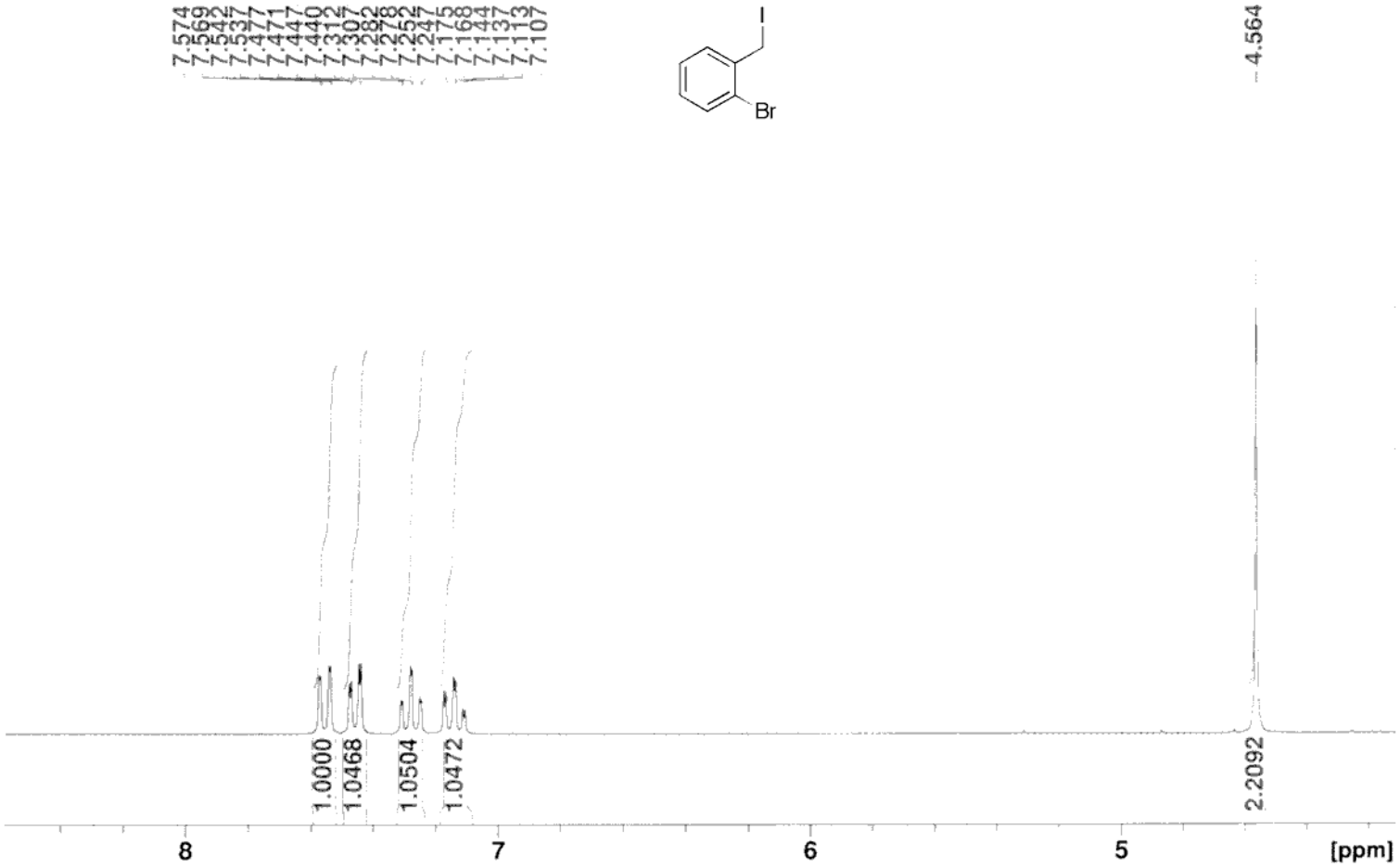
Table 1. Structures and reaction times for compounds **3**

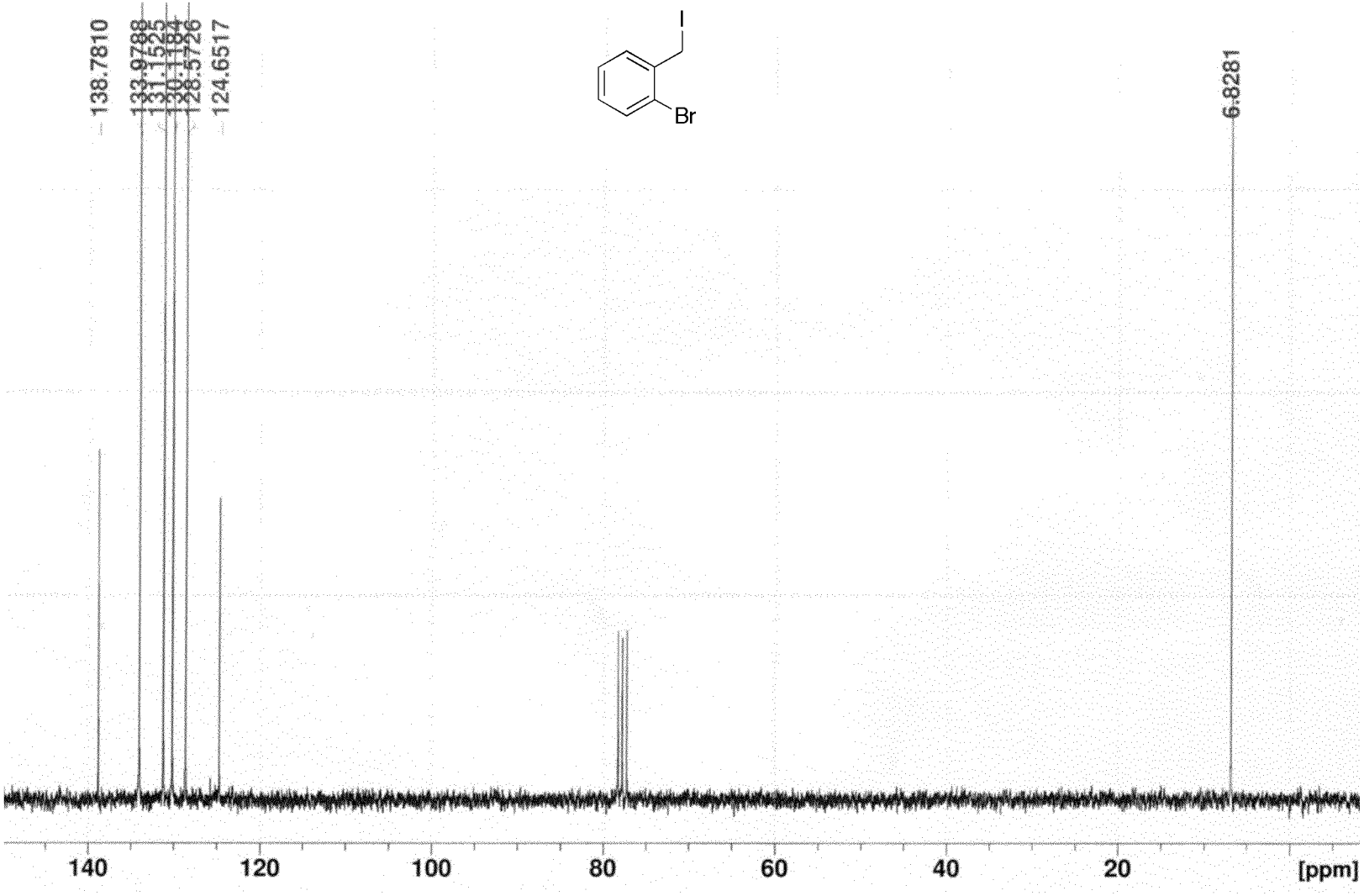
Cmpd.	n	X	R^3	R^4	R^5	Time, h
3a	1	Br	H	H	H	3
3b	1	I	H	CH_3	H	24
3c	1	I	-CH=CH-CH=CH-		H	19

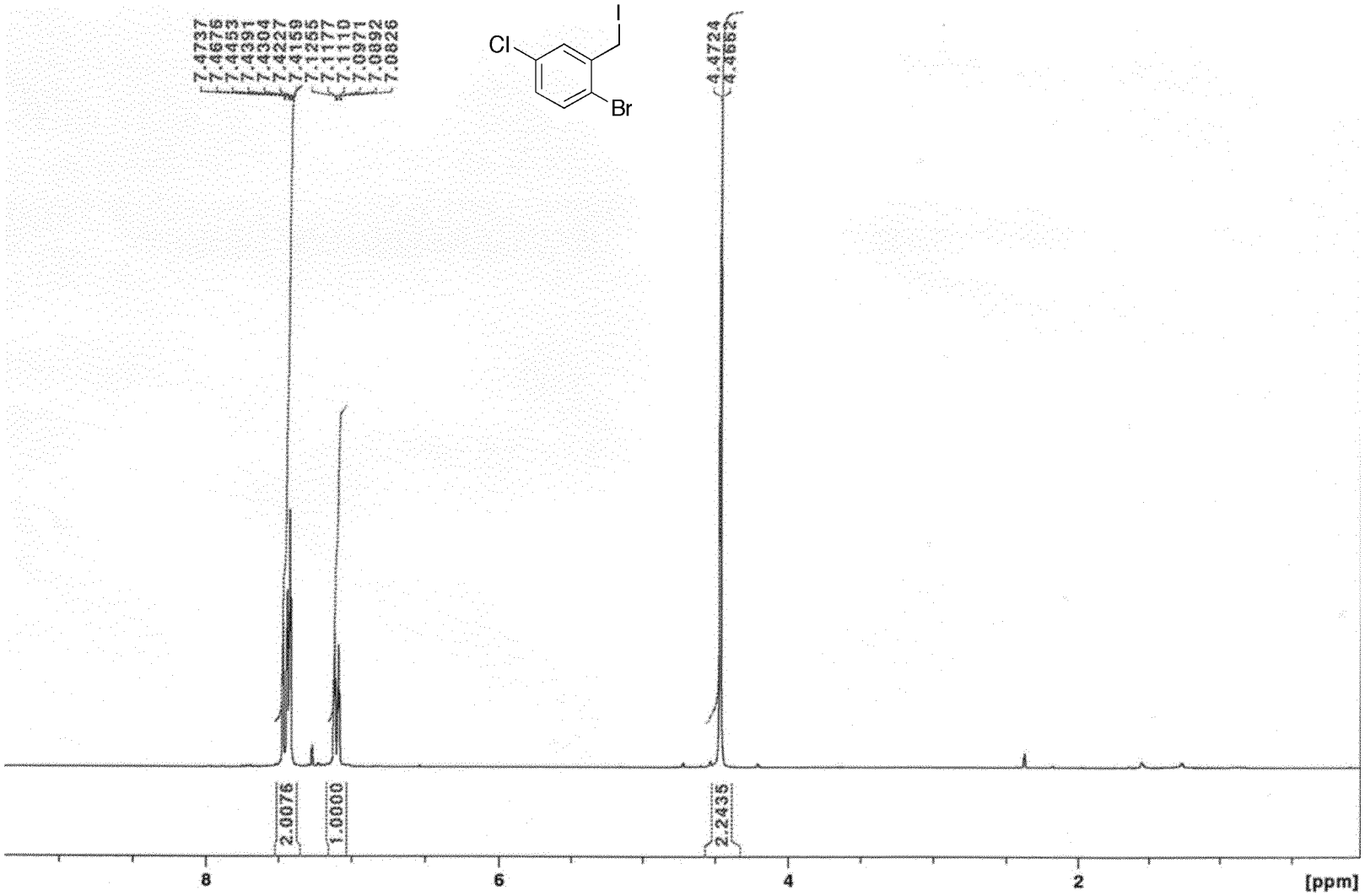
Cmpd.	n	X	R^3	R^4	R^5	Time, h
3d	2	Br	H	H	H	2
3e	2	Br	H	H	Cl	24
3f	2	Br	H	H	NO_2	7
3g	2	I	H	H	CO_2CH_3	24
3h	2	I	H	CH_3	H	24
3i	2	I	H	-O-CH_2-O-		24
3j	2	Br	-CH=CH-CH=CH-		H	24
3k	3	Br	H	H	H	4
3l	3	Br	H	H	Cl	24
3l	3	I	H	H	Cl	19

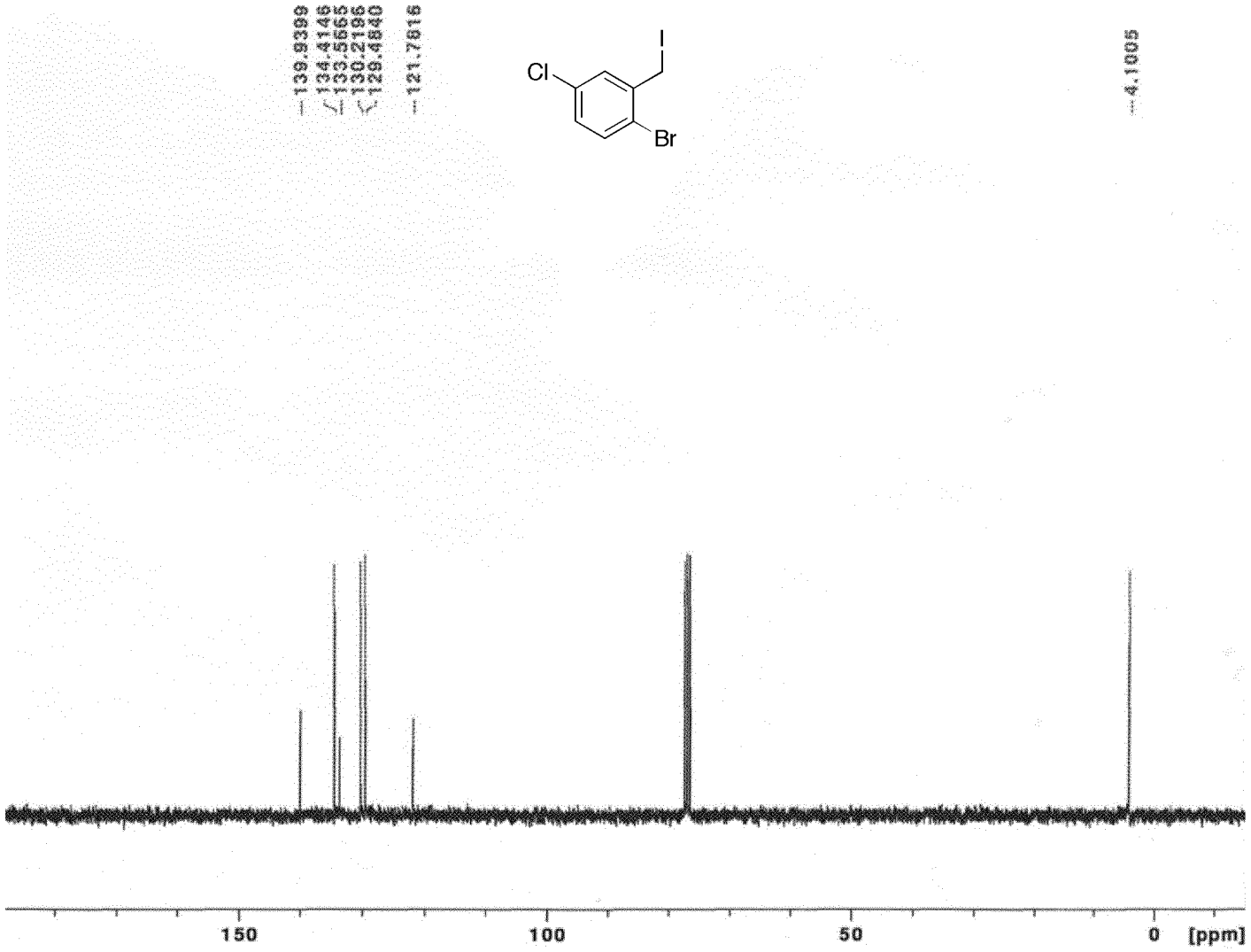
Cmpd.	n	X	R^3	R^4	R^5	Time, h
3m	3	Br	H	H	NO_2	10
3n	3	I	H	H	CO_2CH_3	24
3o	3	I	H	CH_3	H	24
3p	3	I	H	H	OCH_3	24
3q	3	I	-CH=CH-CH=CH-		H	19

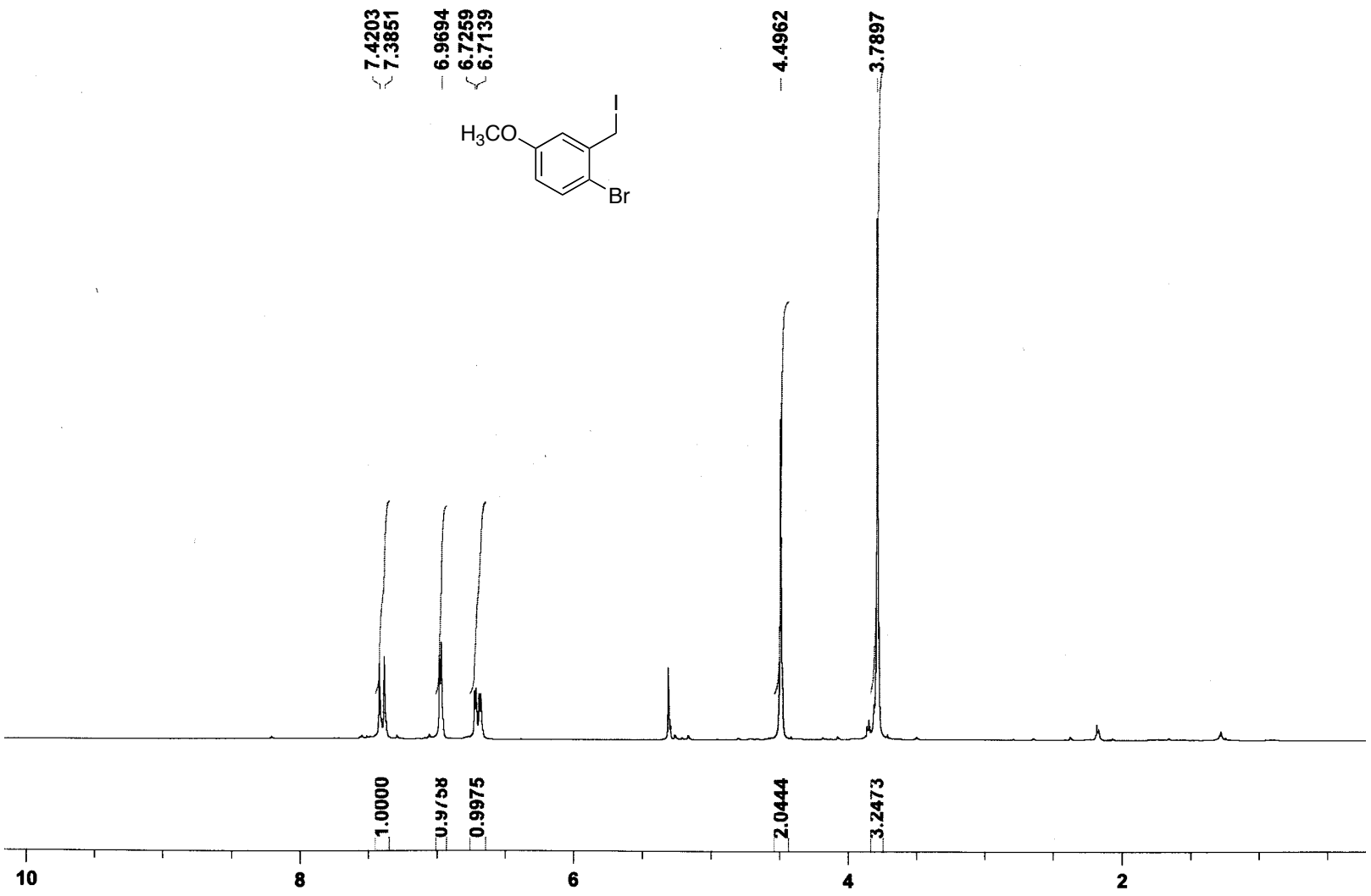
Spectra of representative compounds

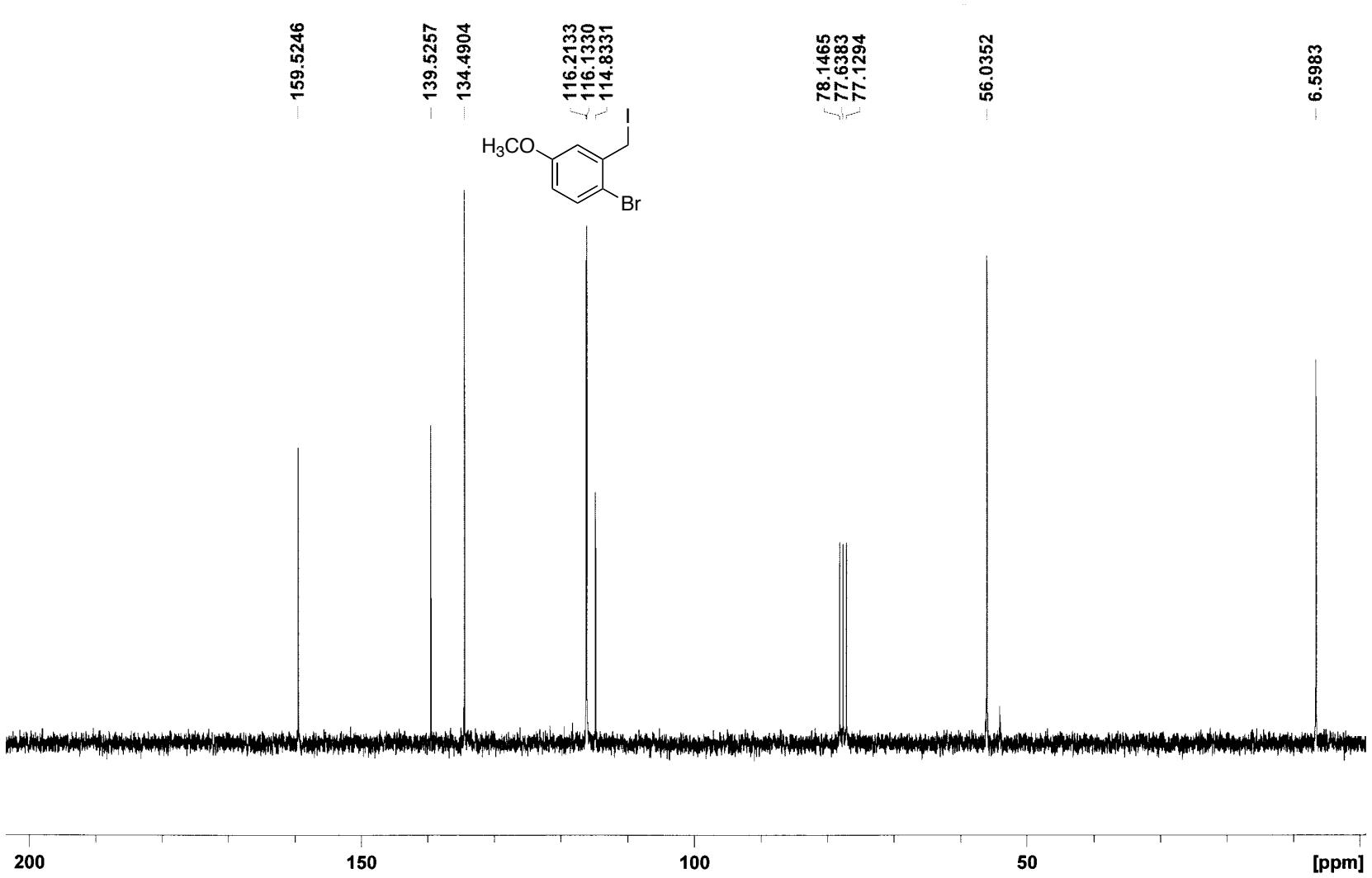


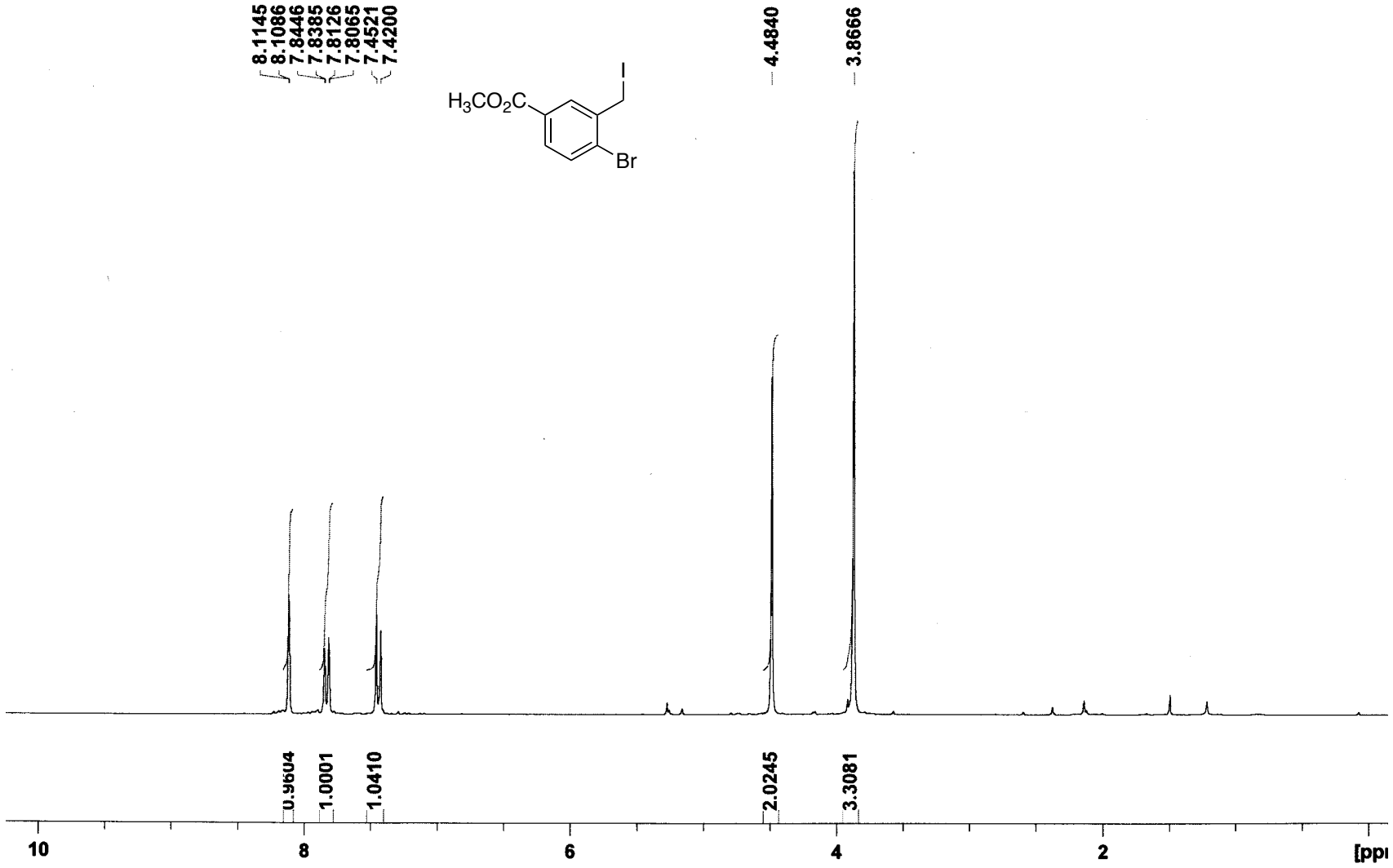


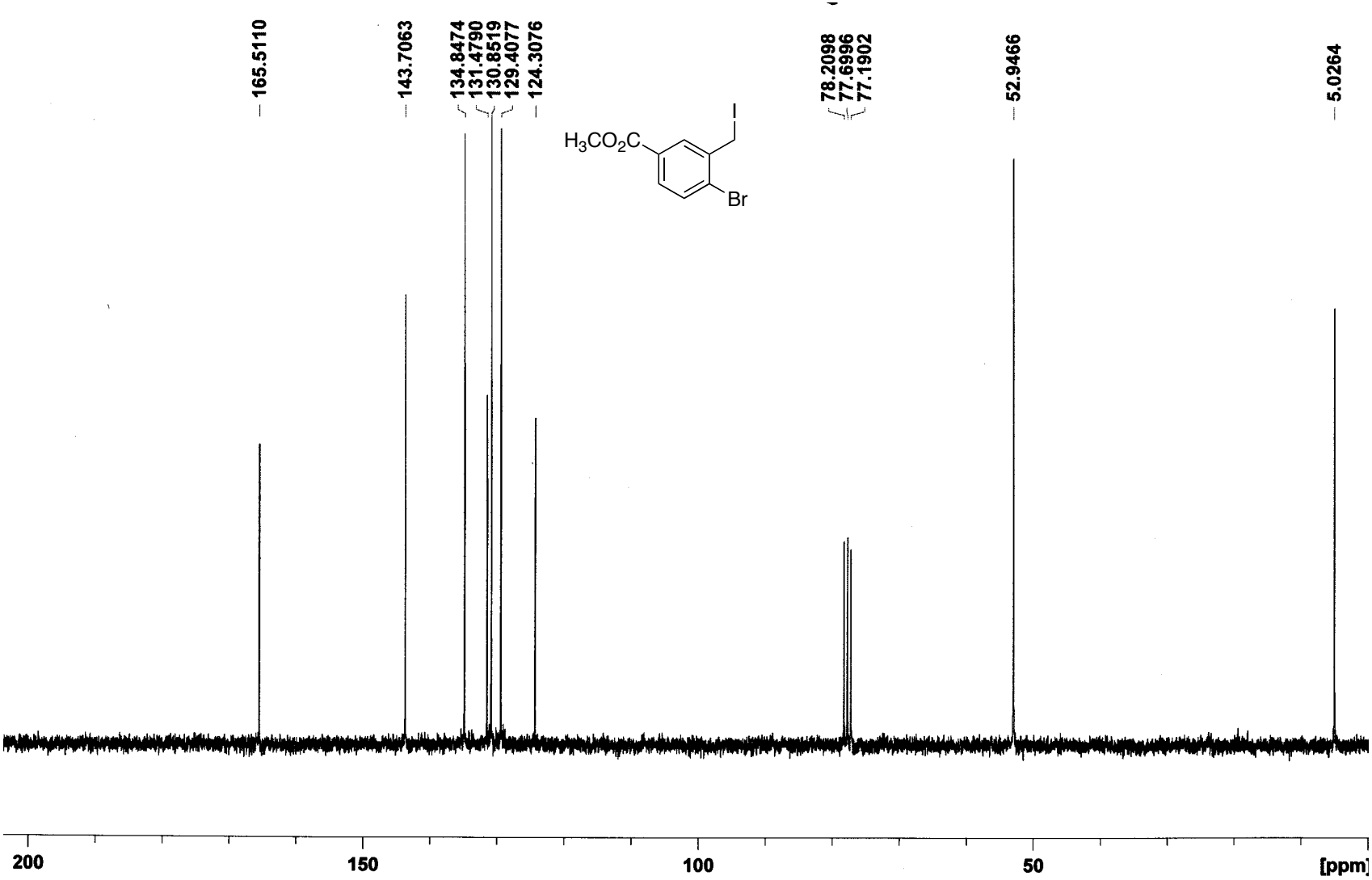


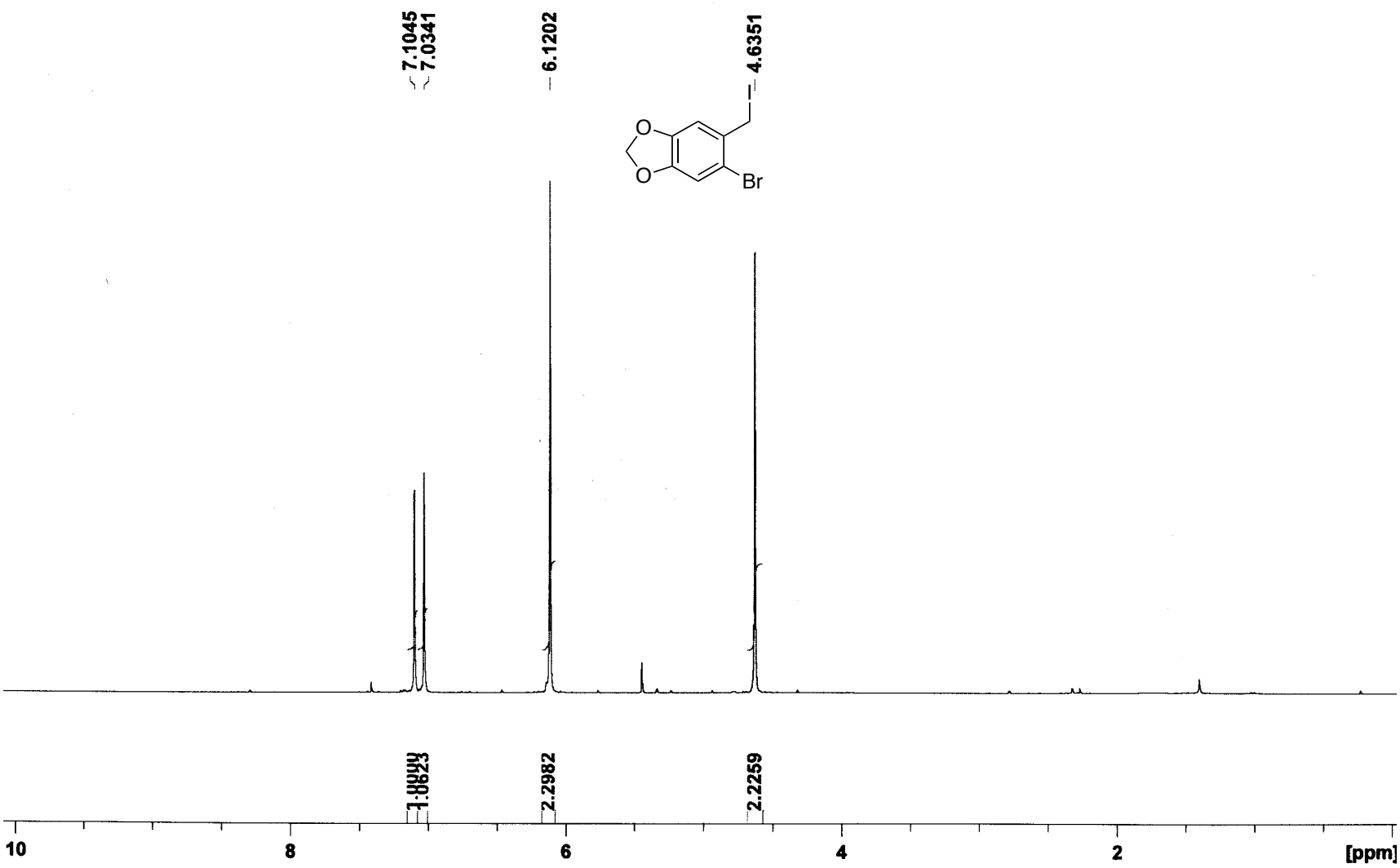


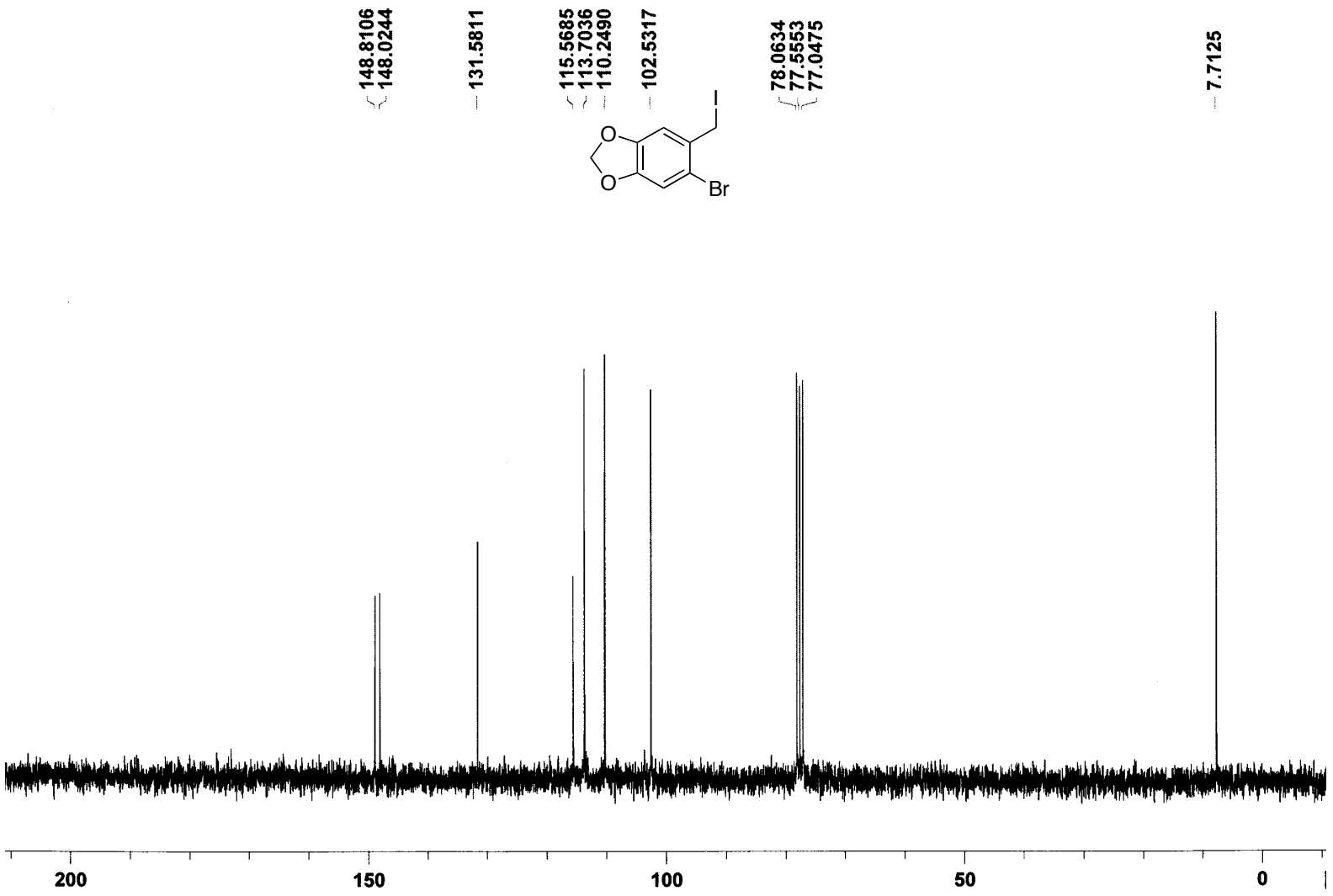


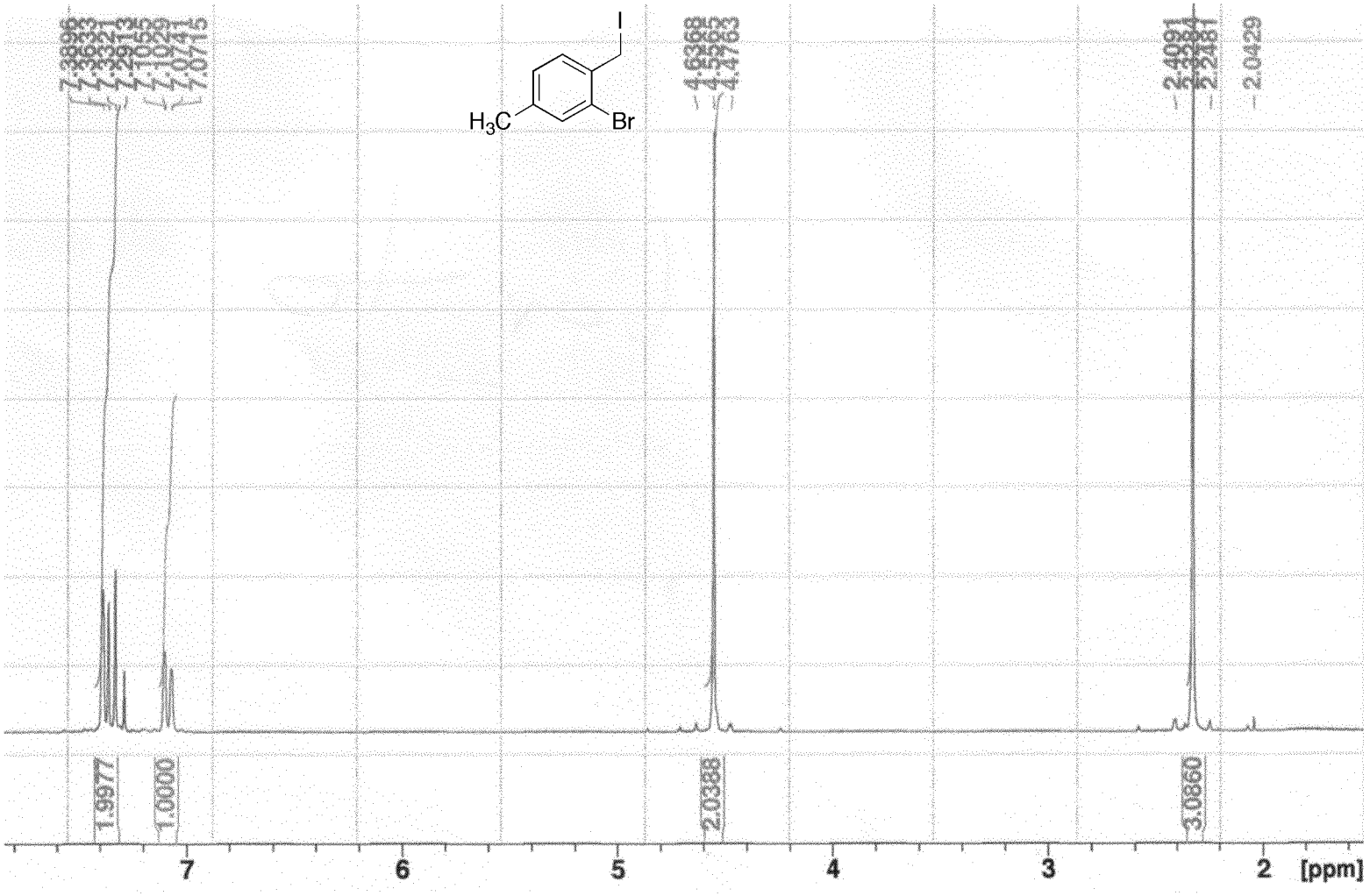


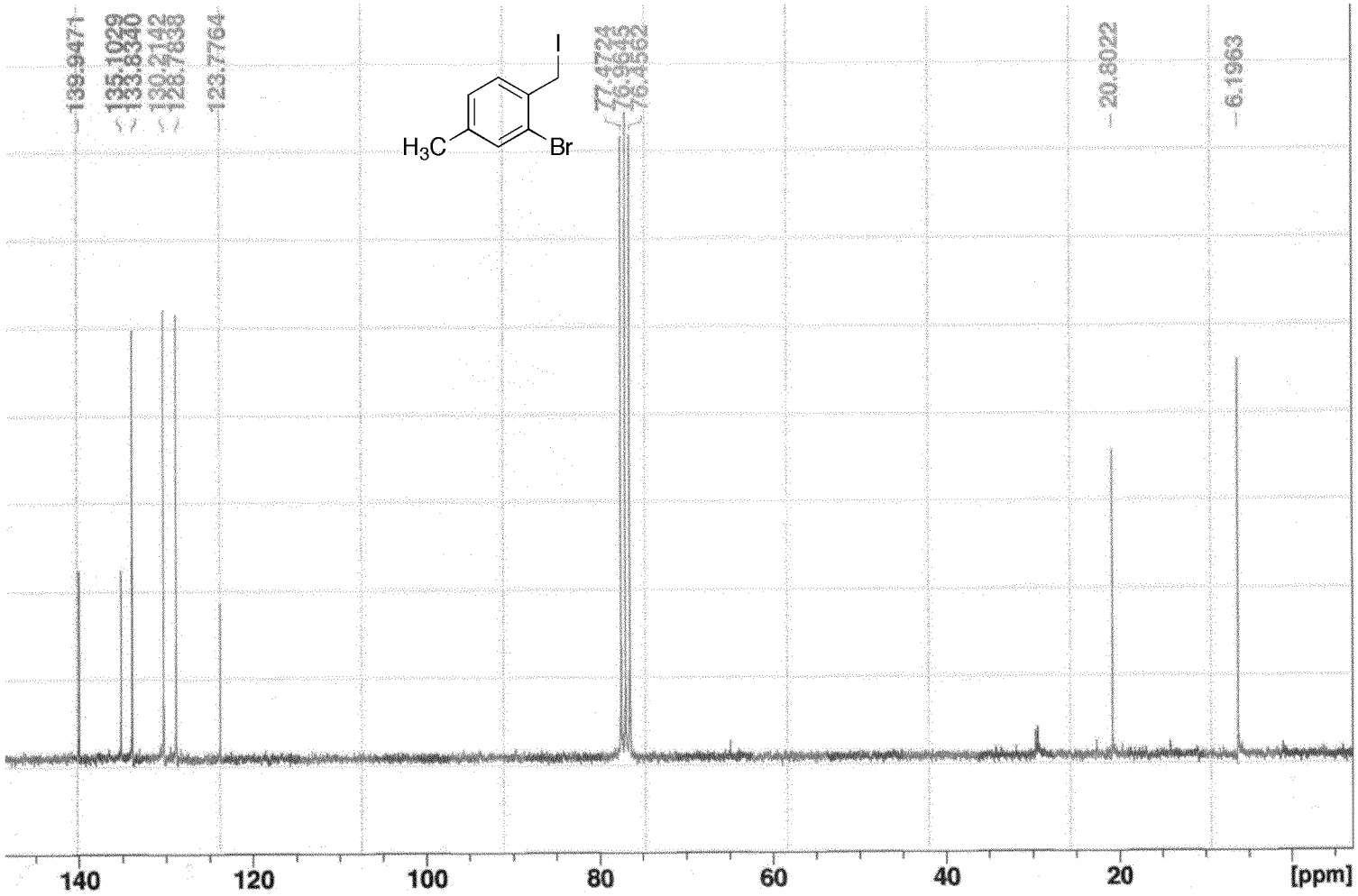


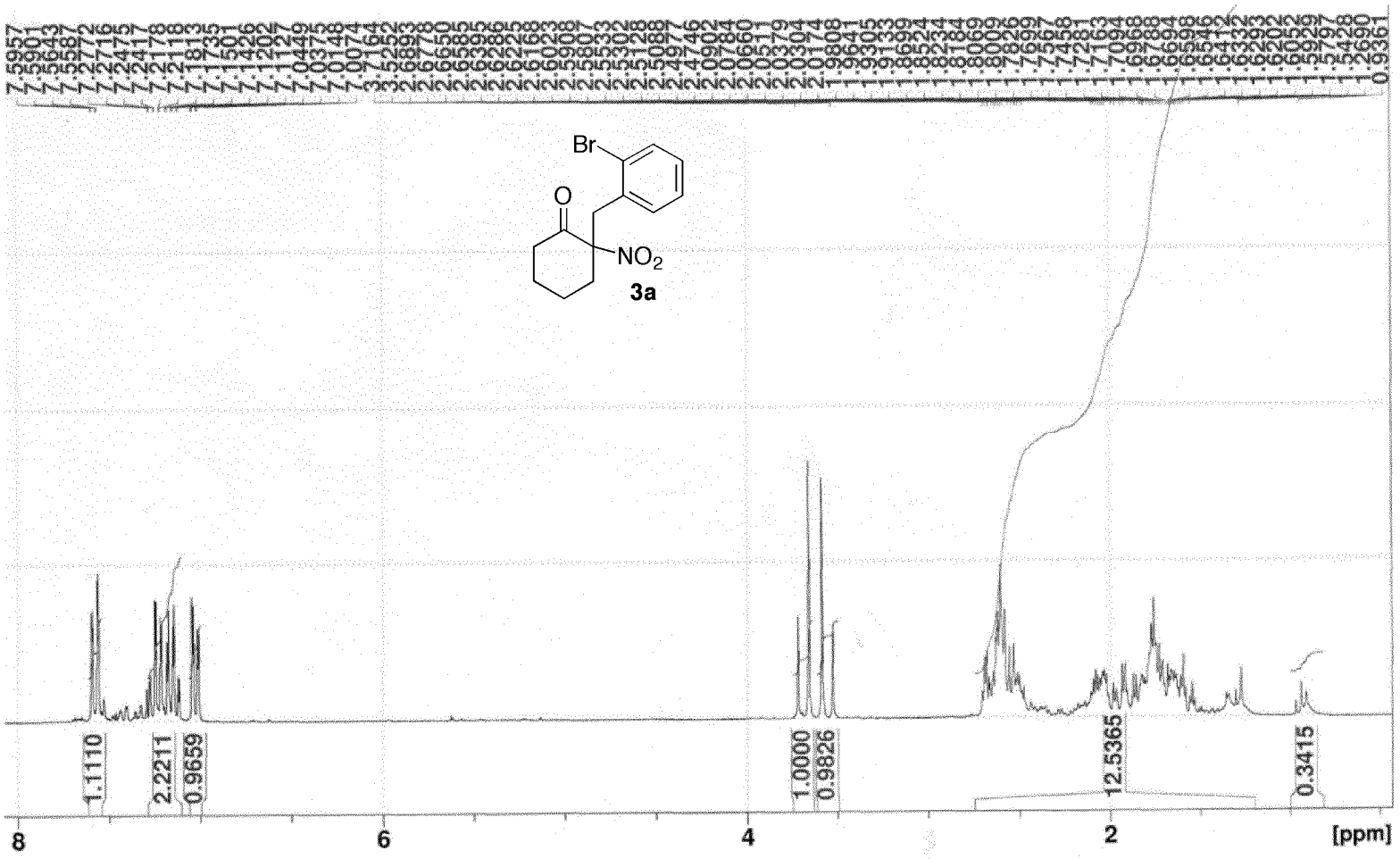


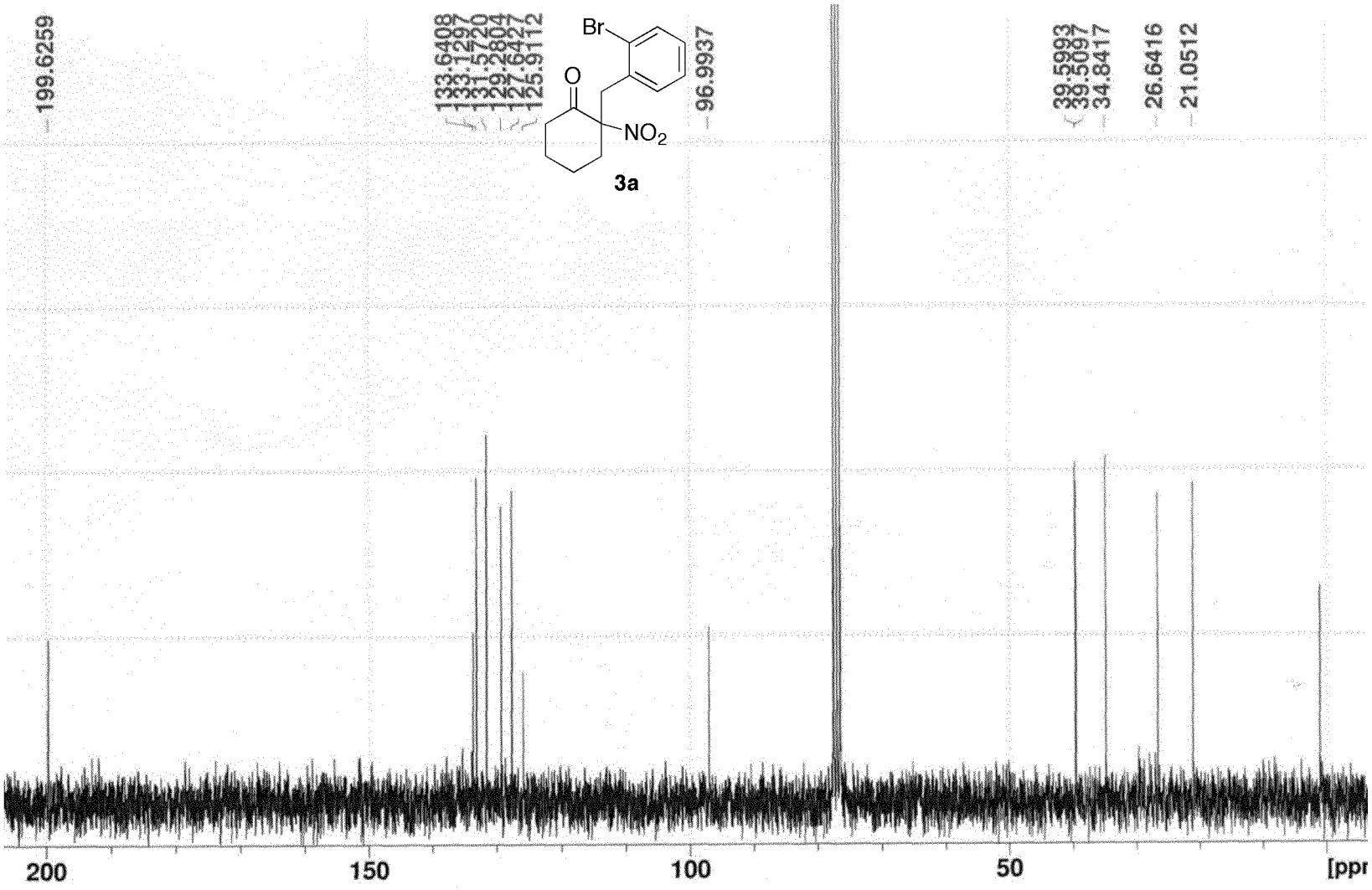


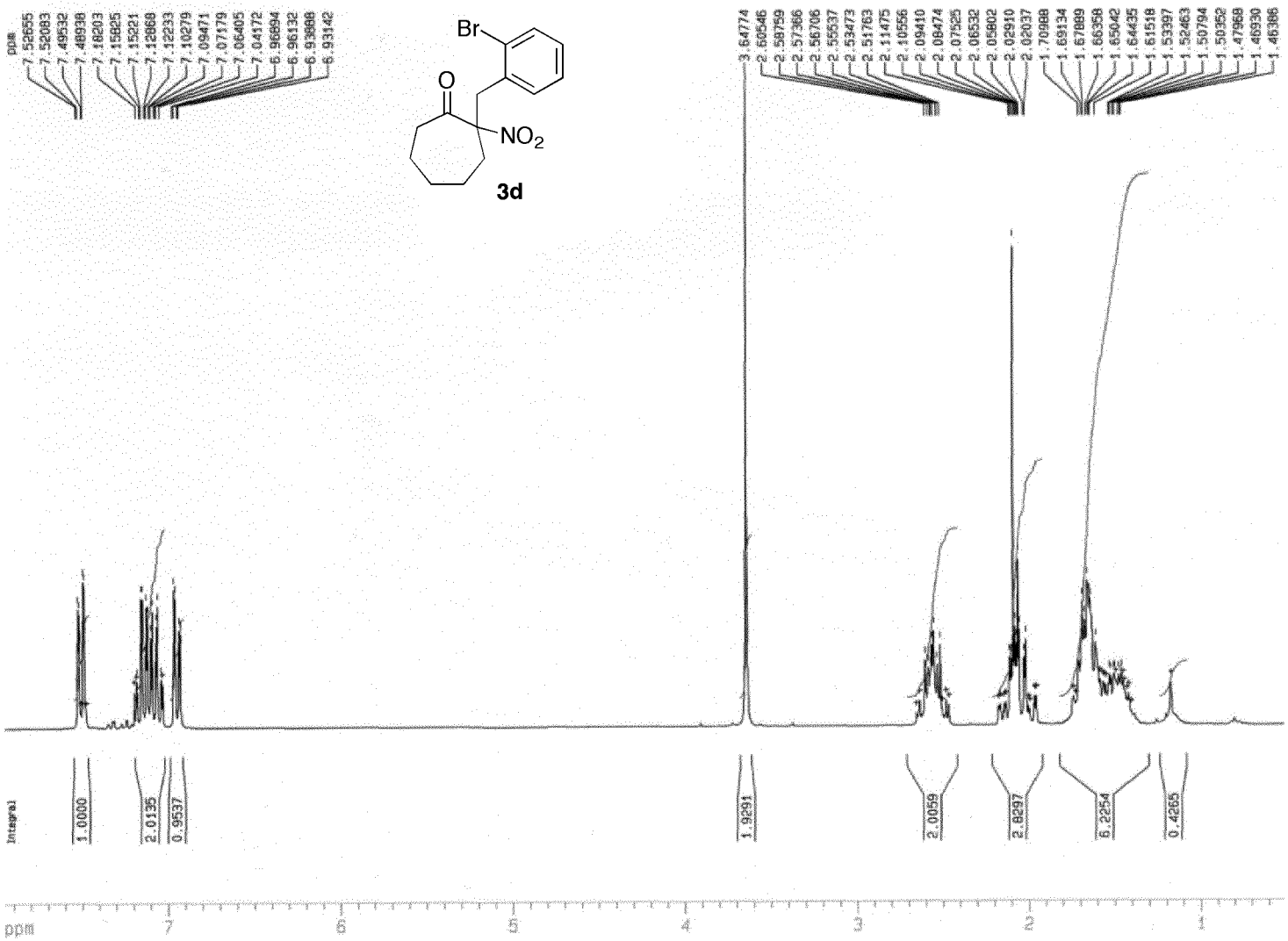








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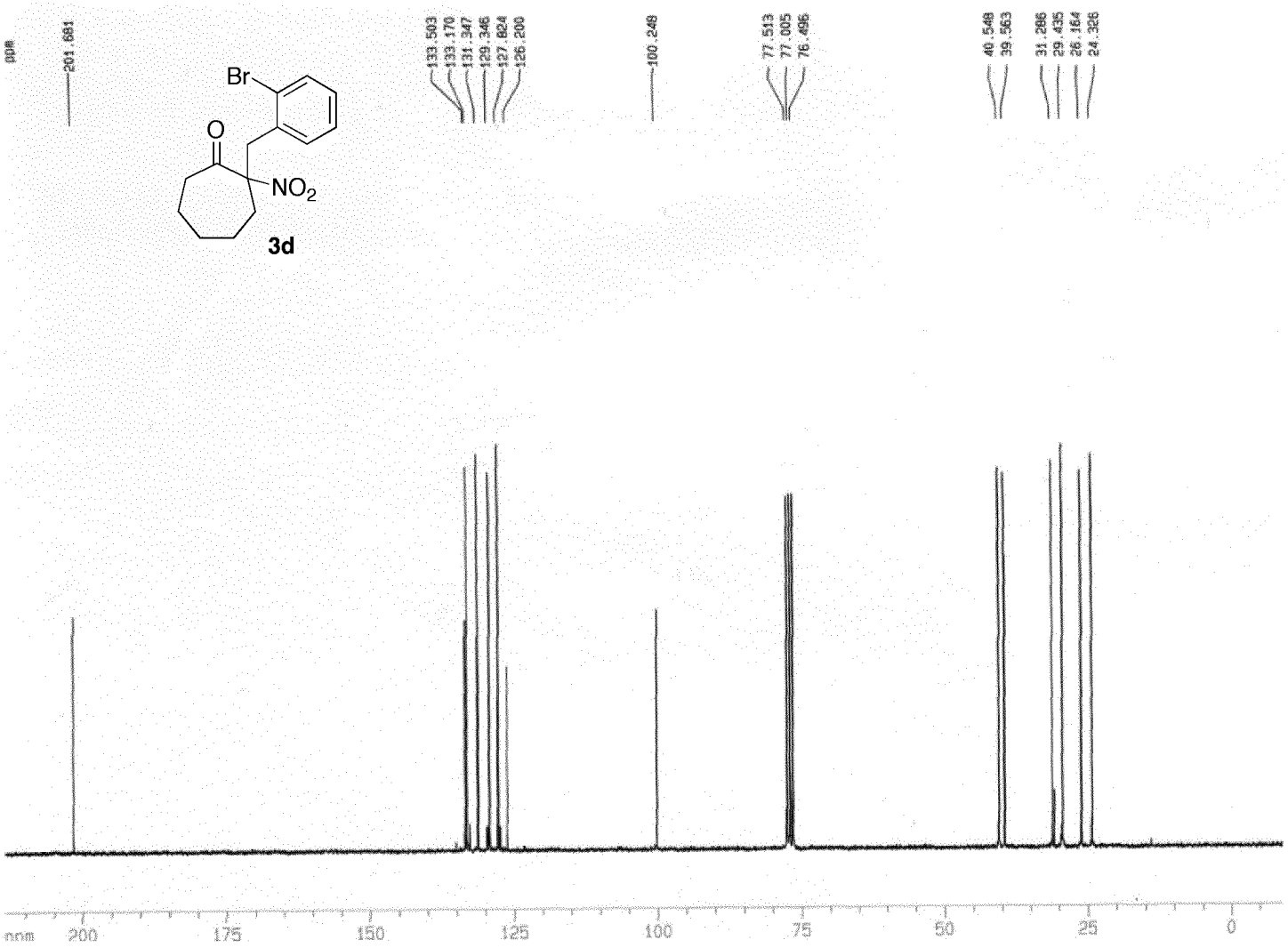
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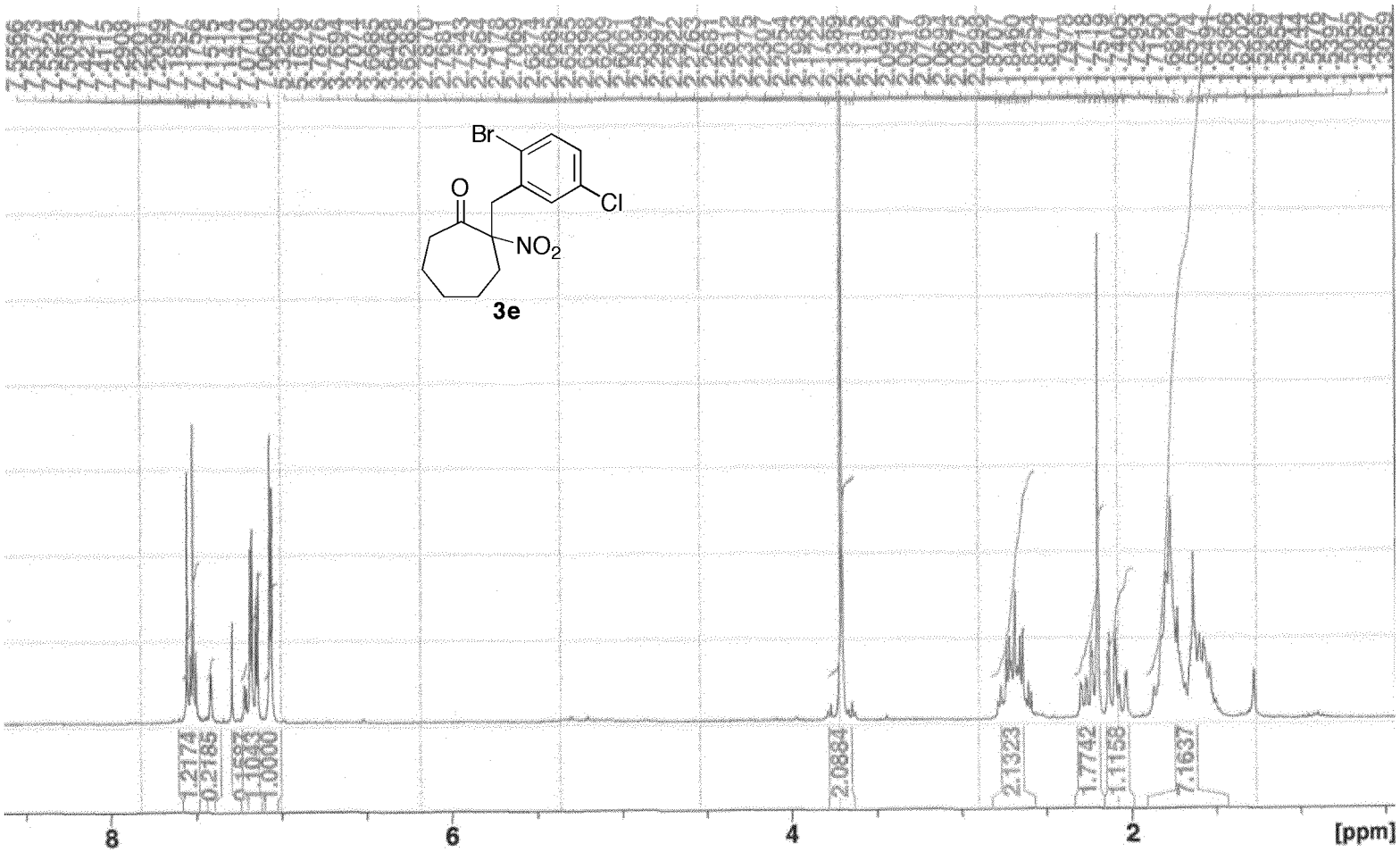

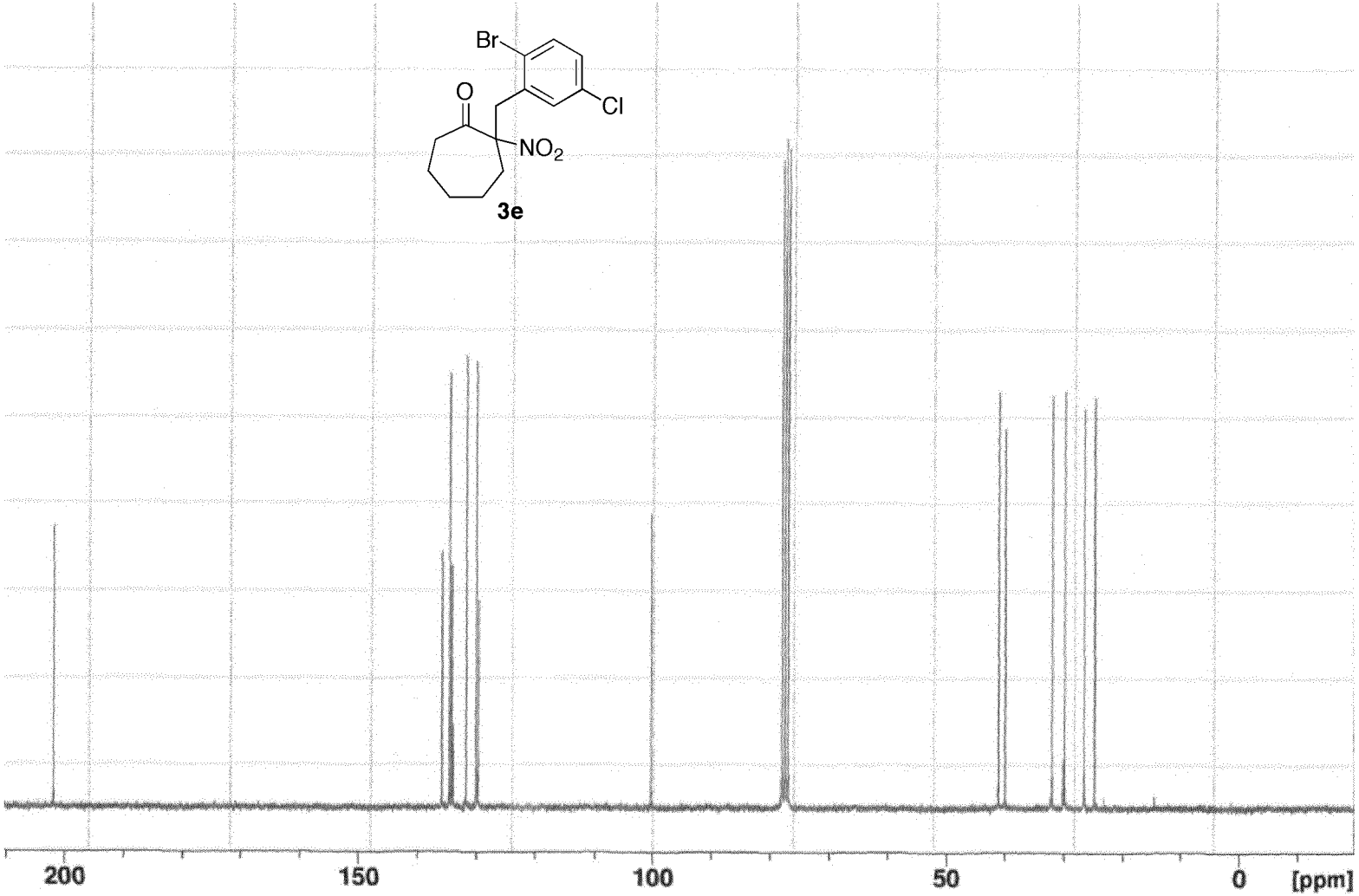

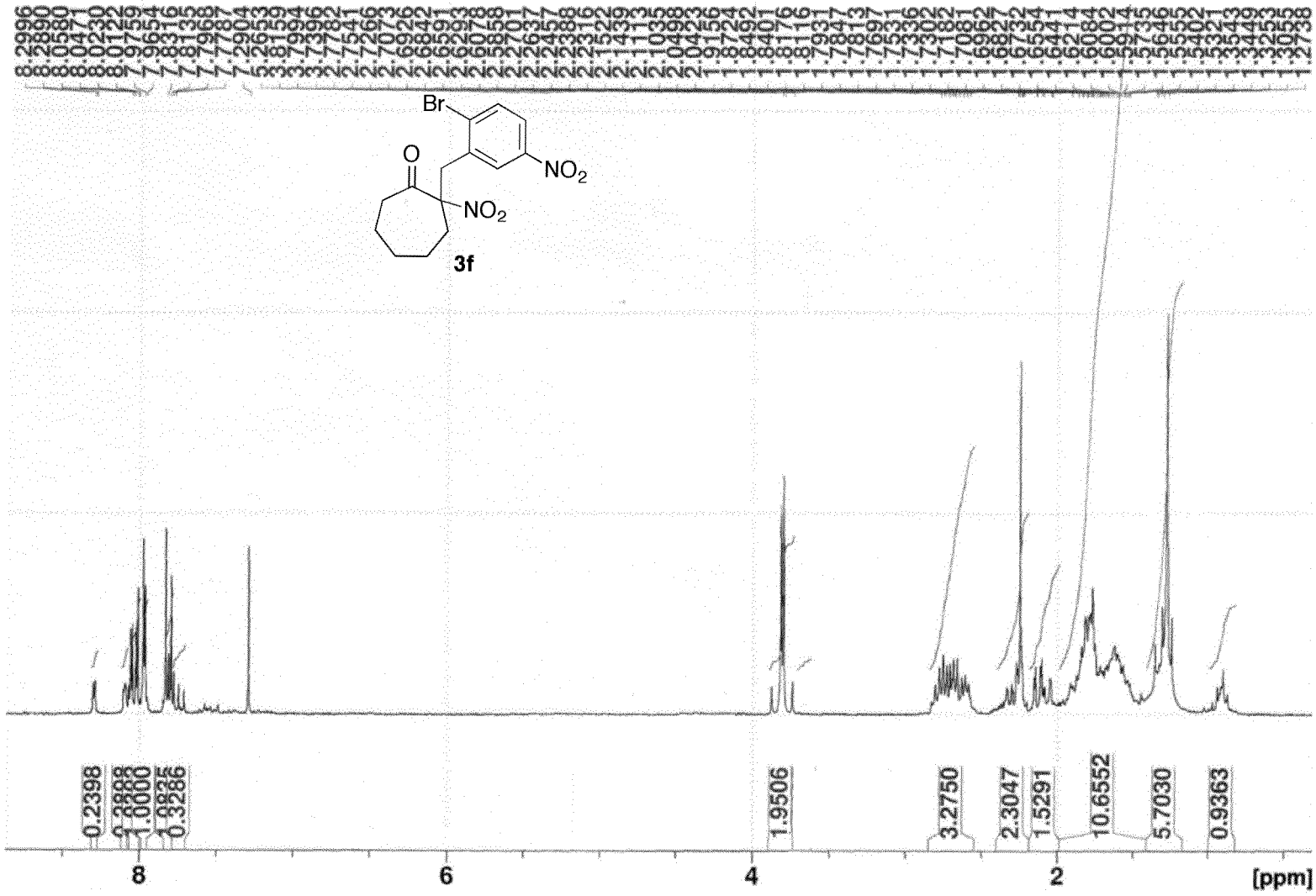

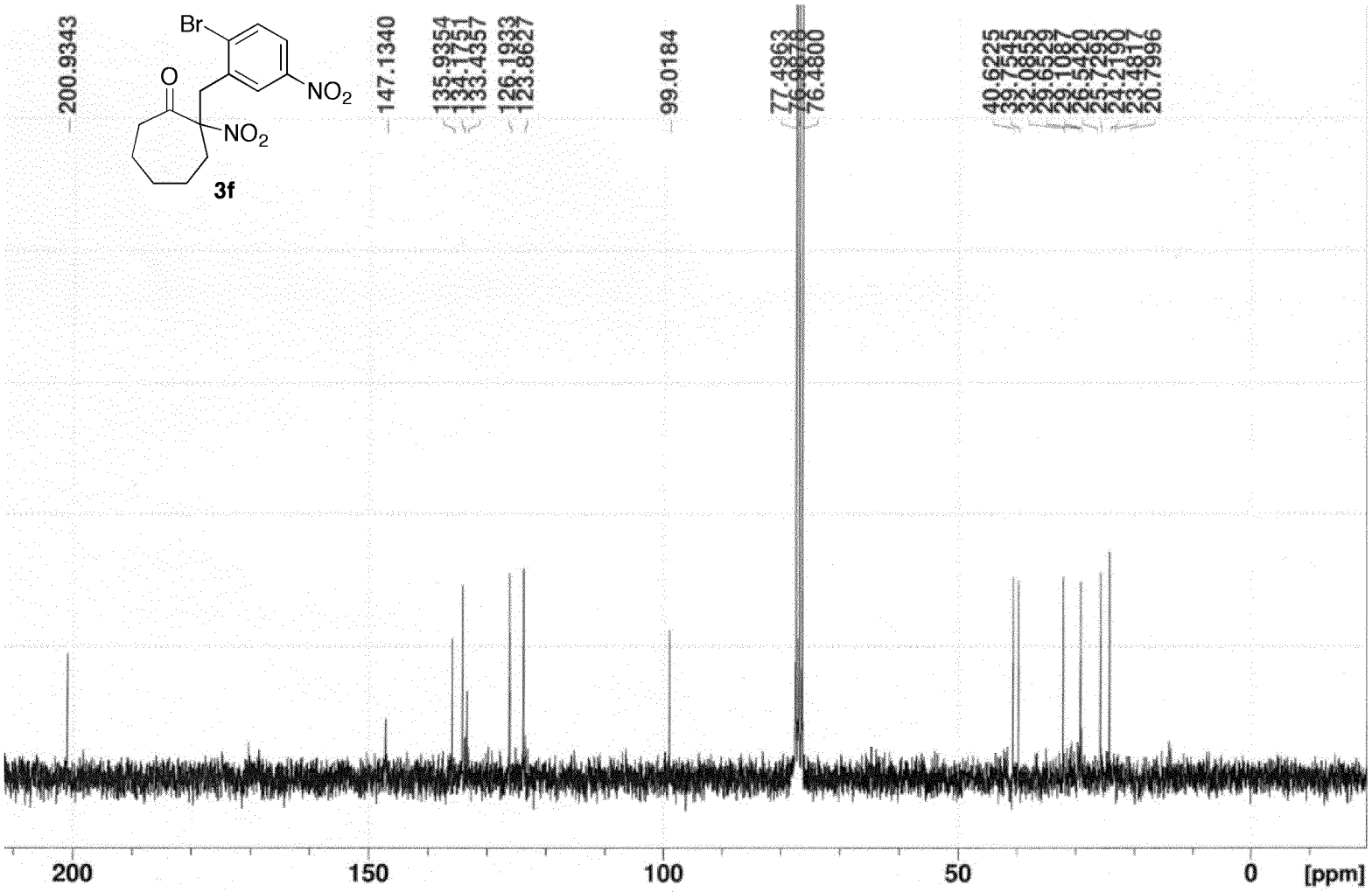

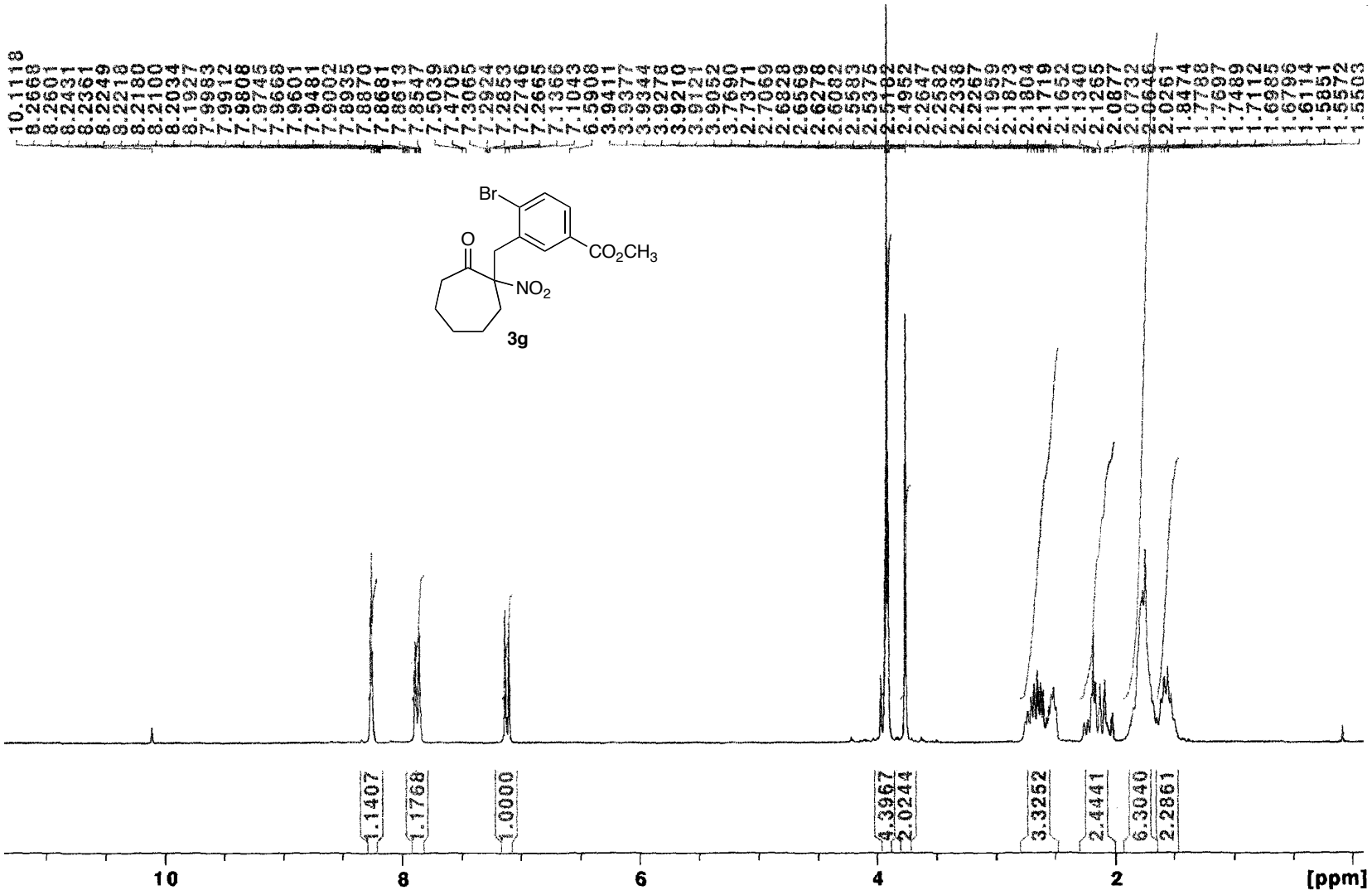
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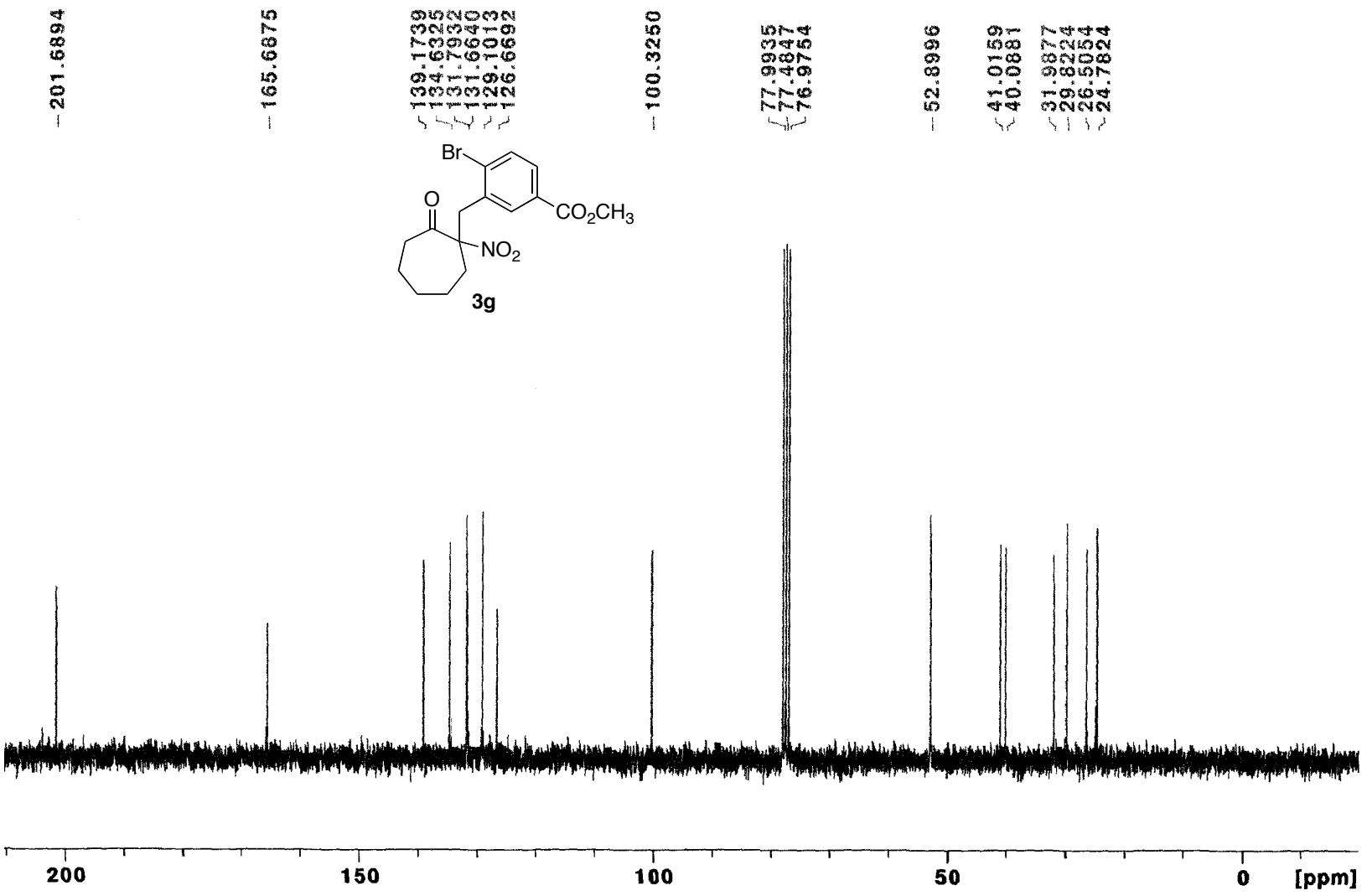

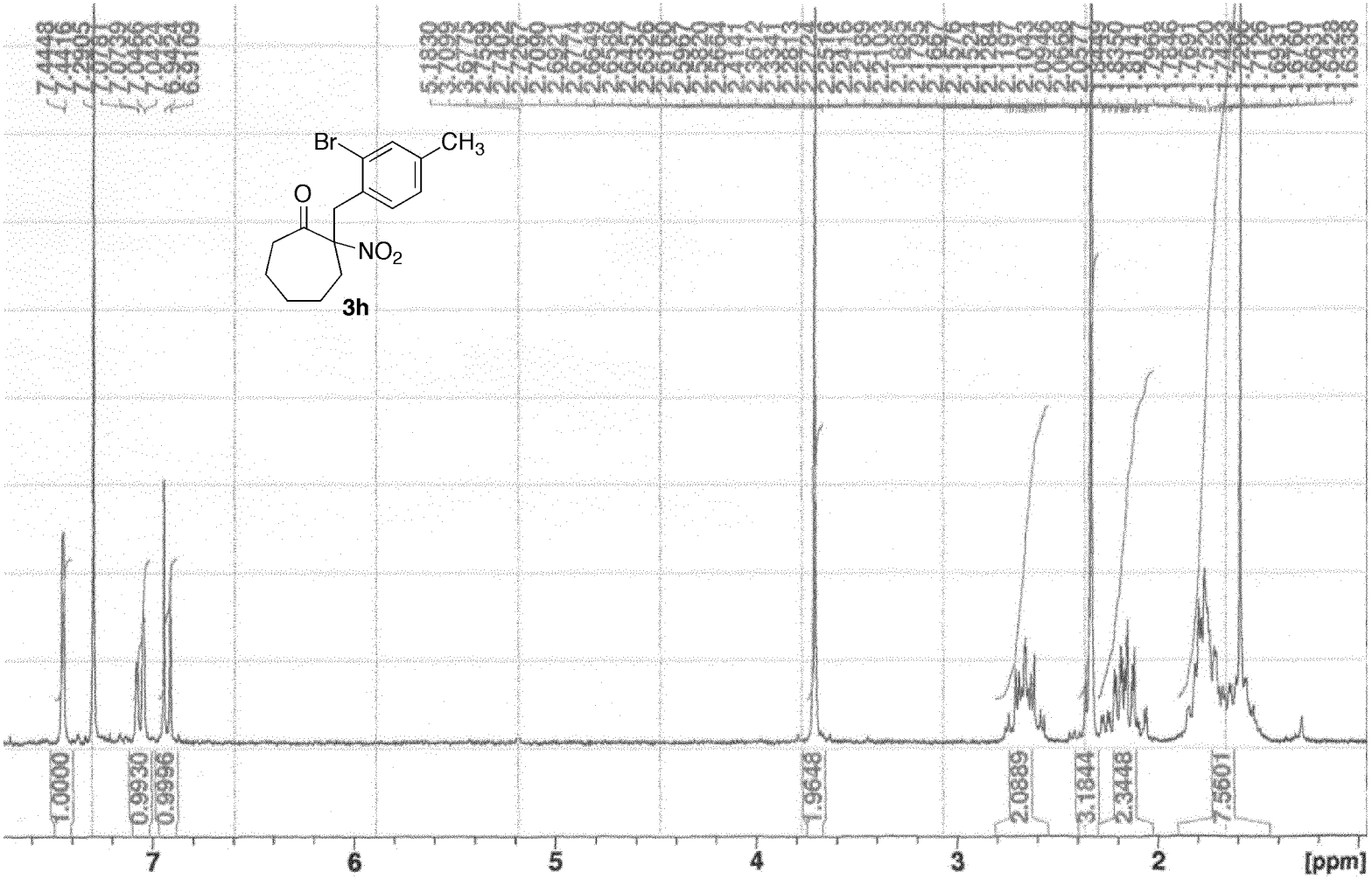

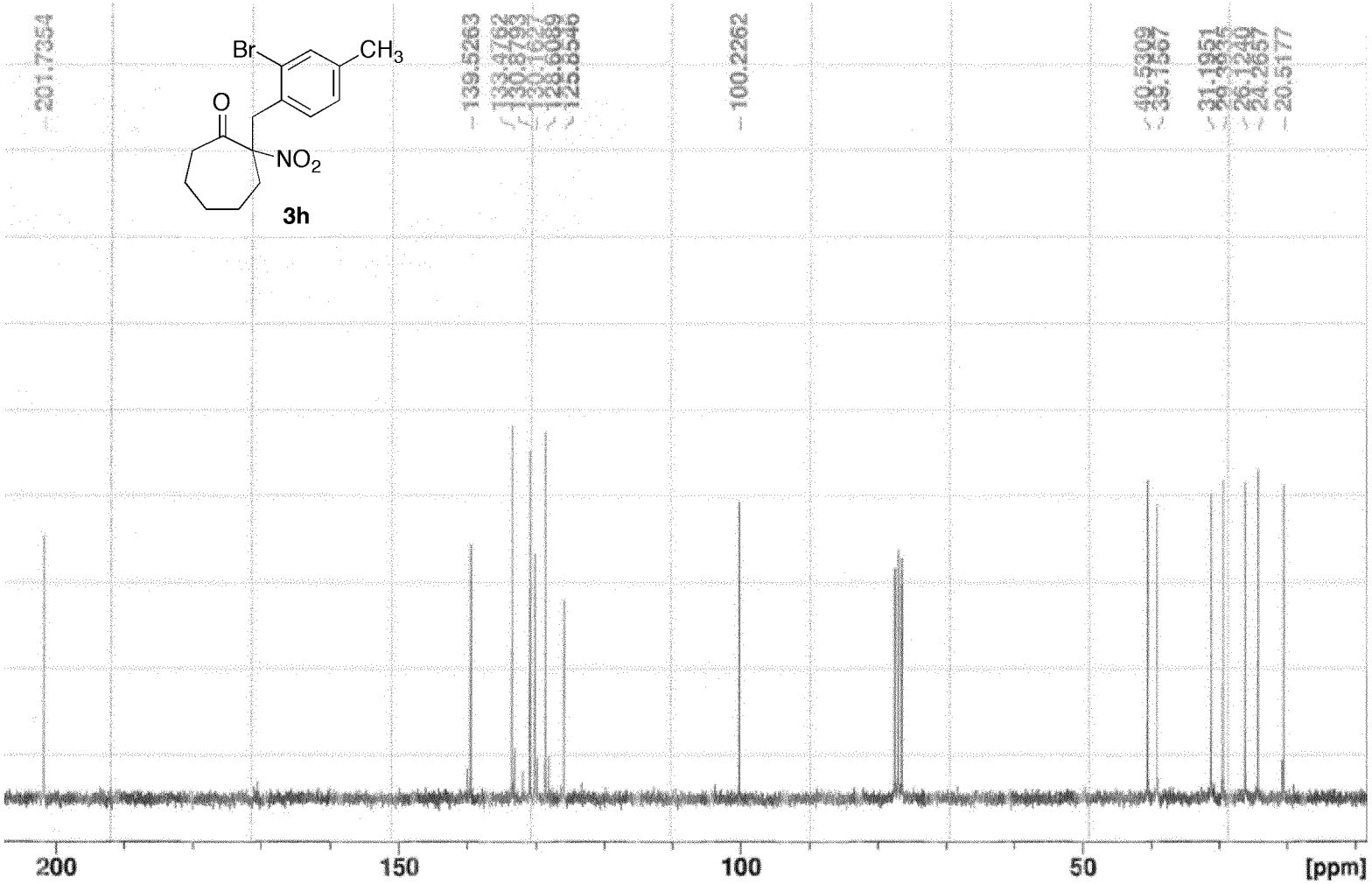

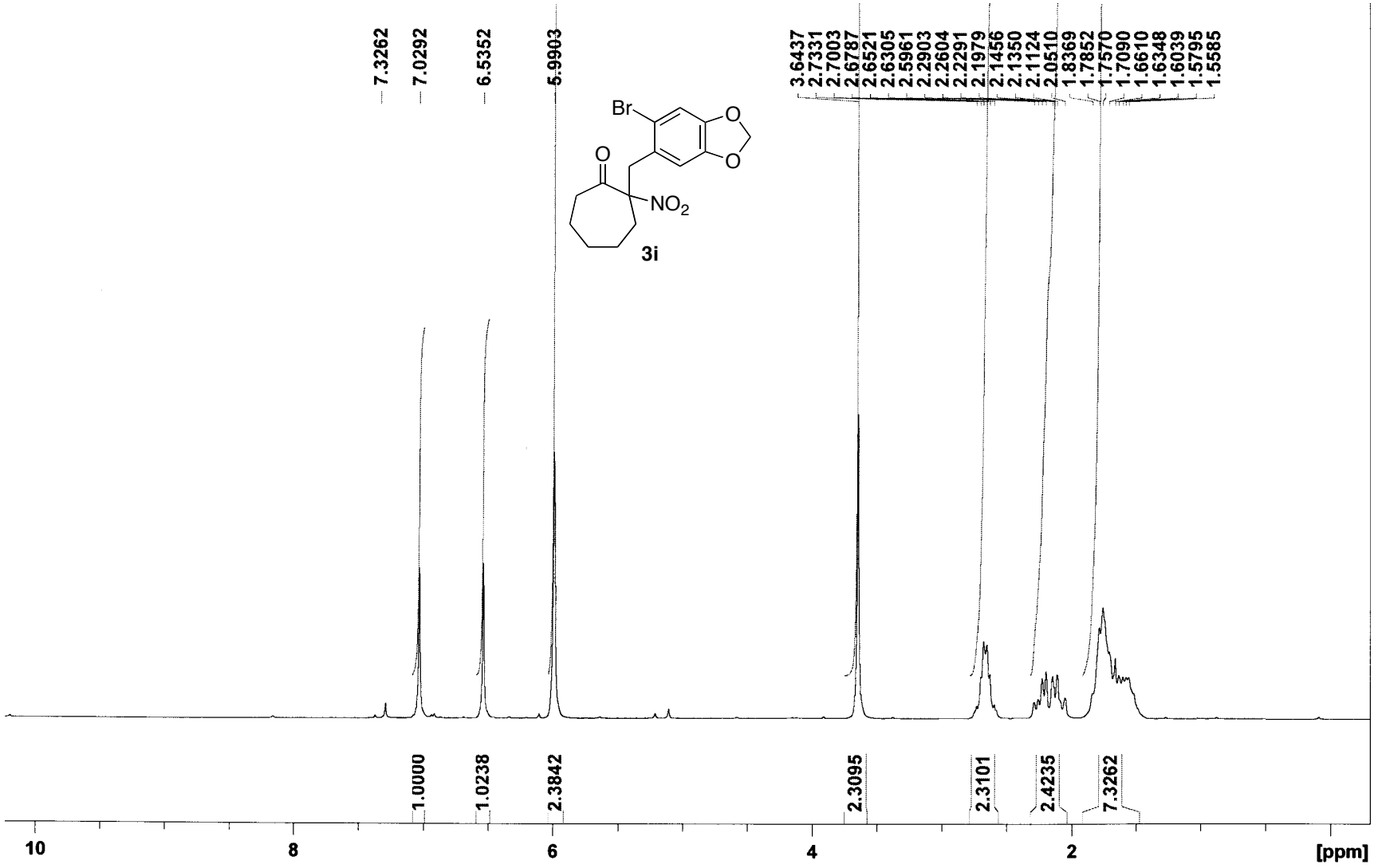

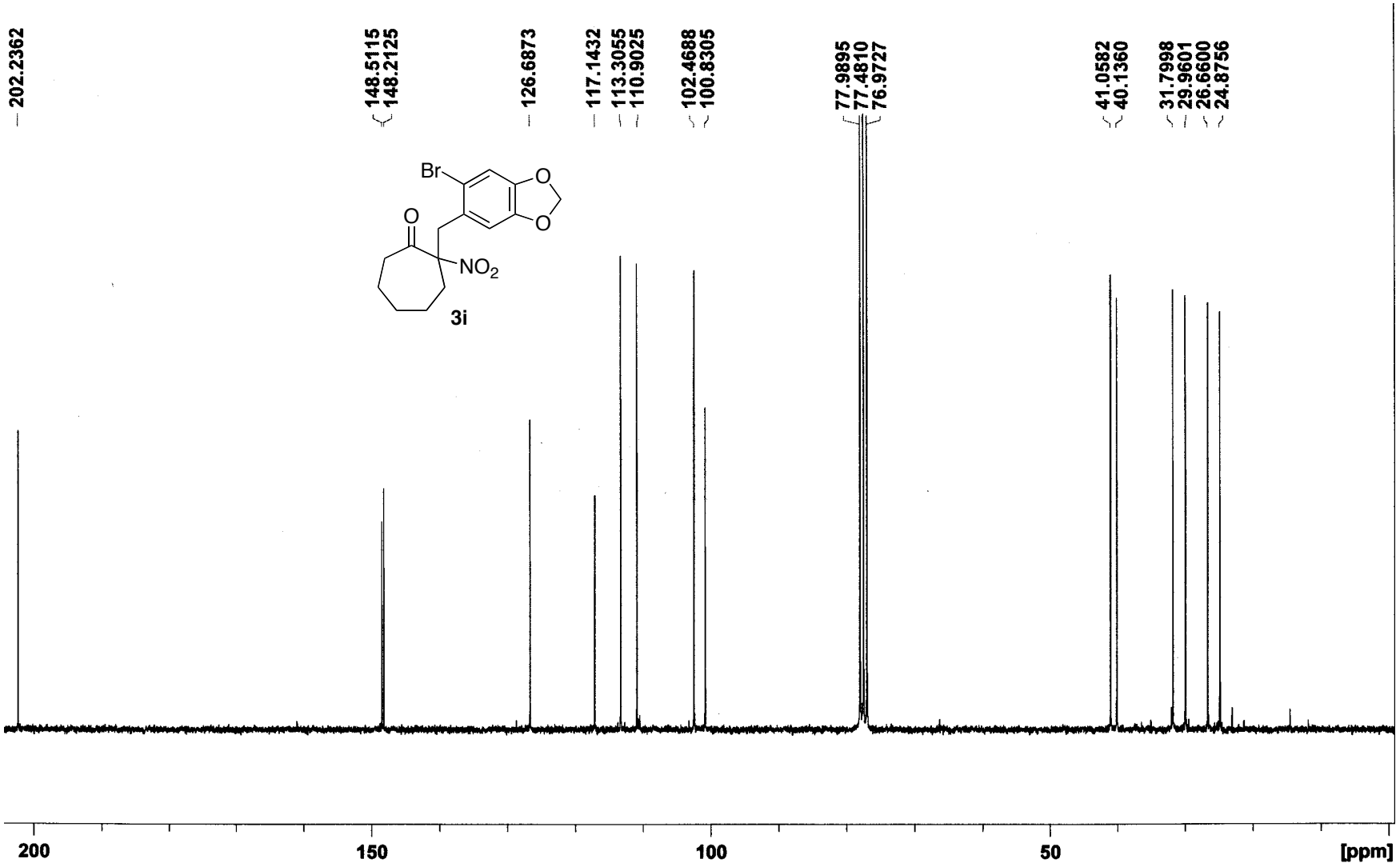

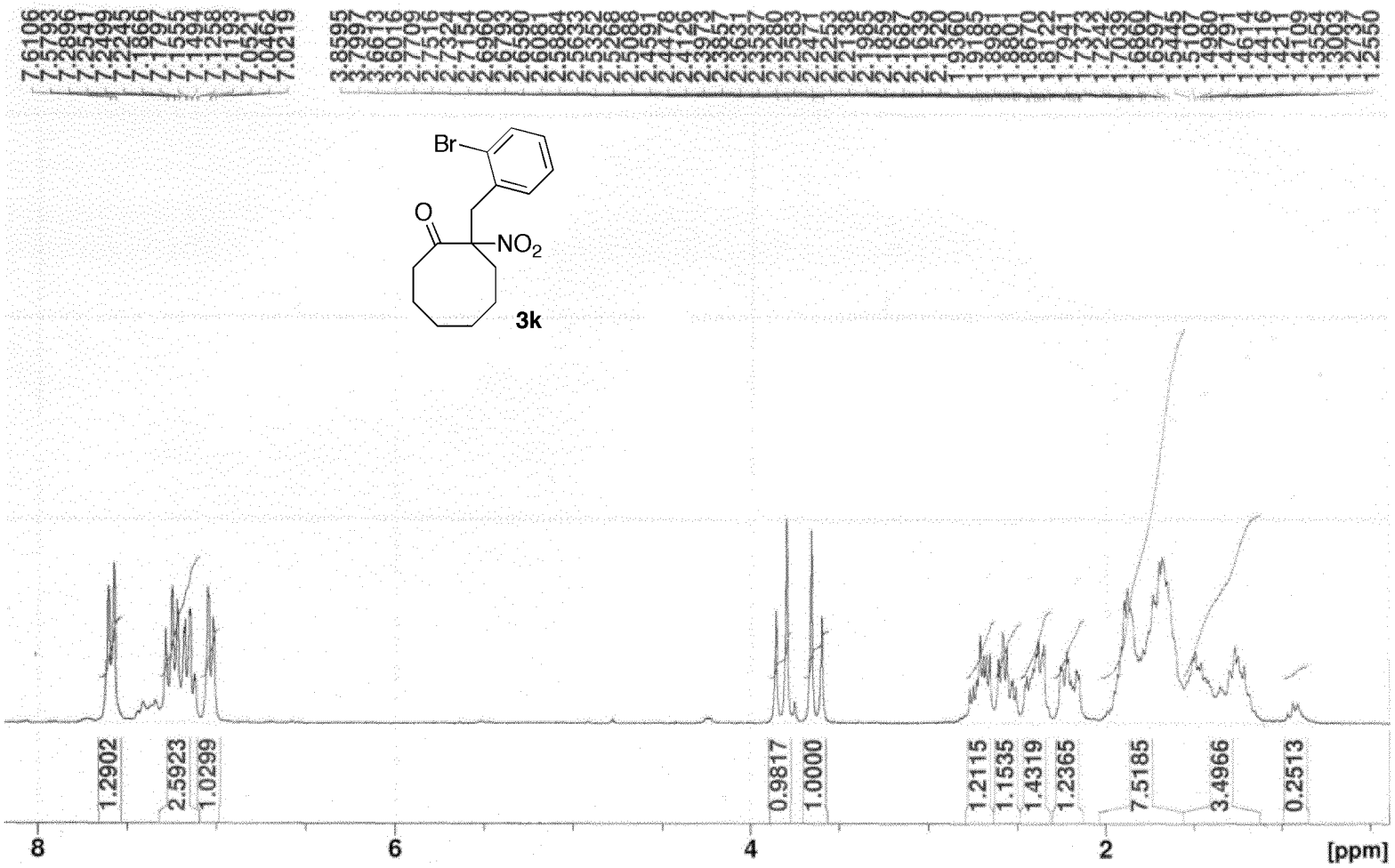

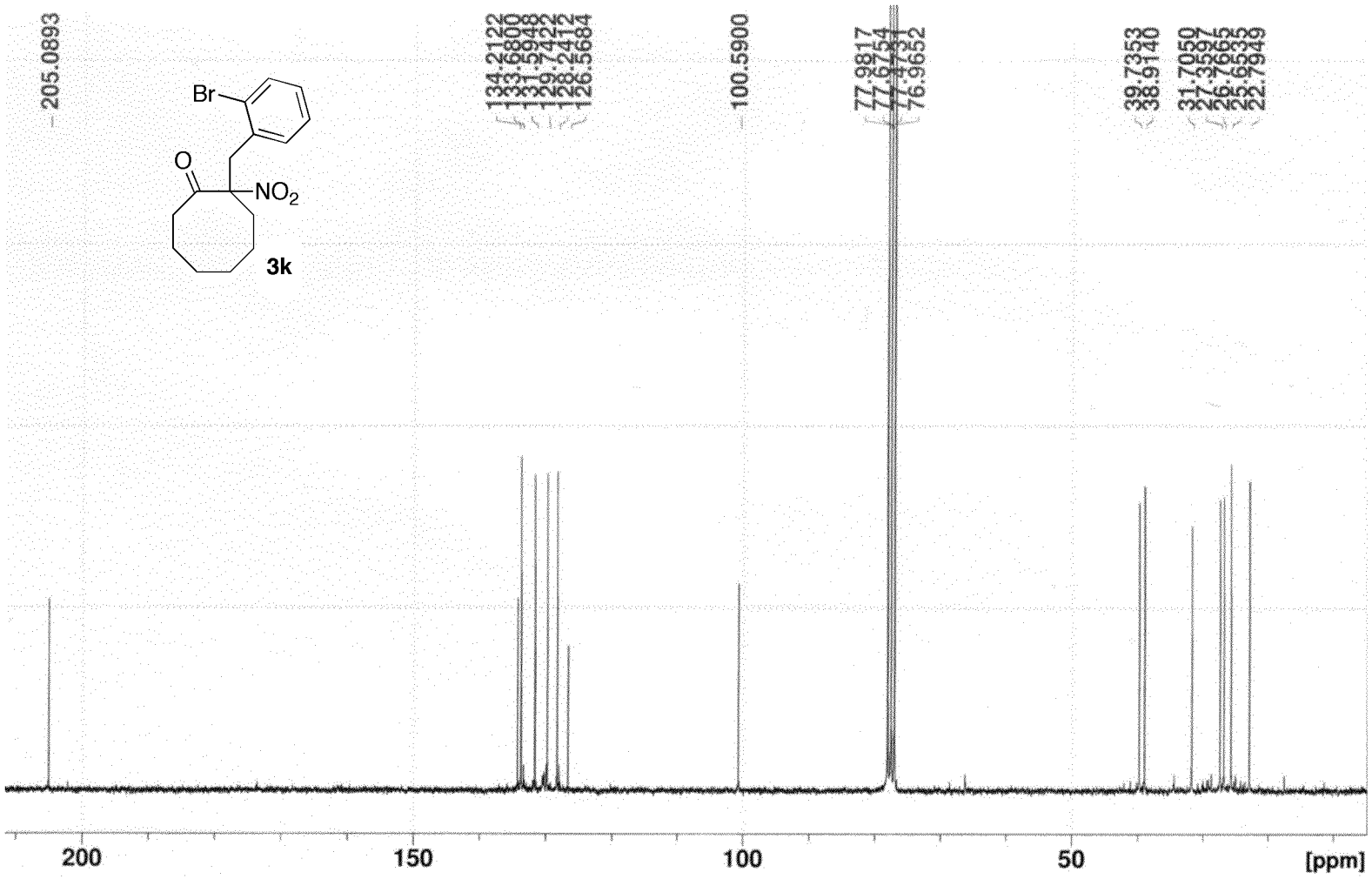

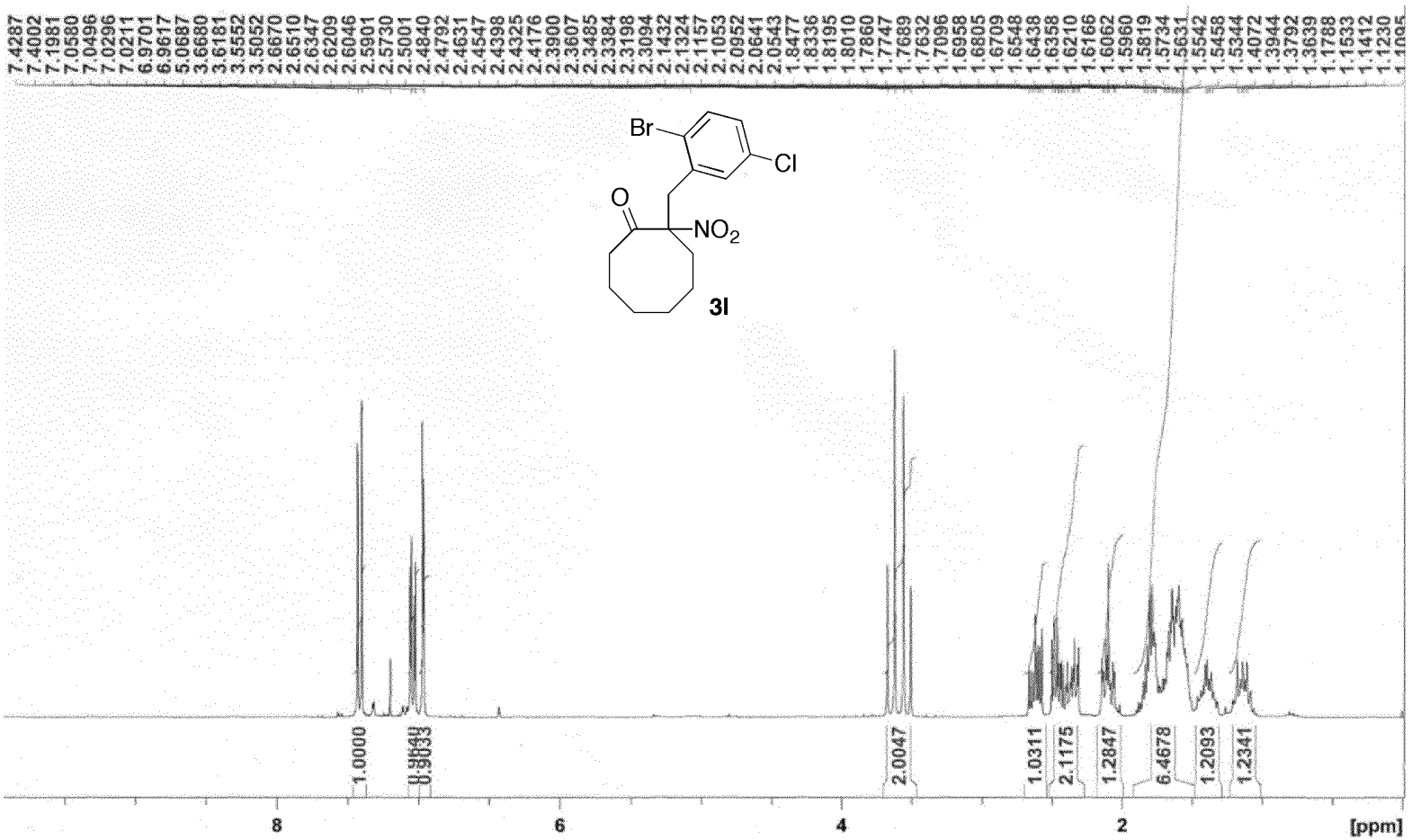

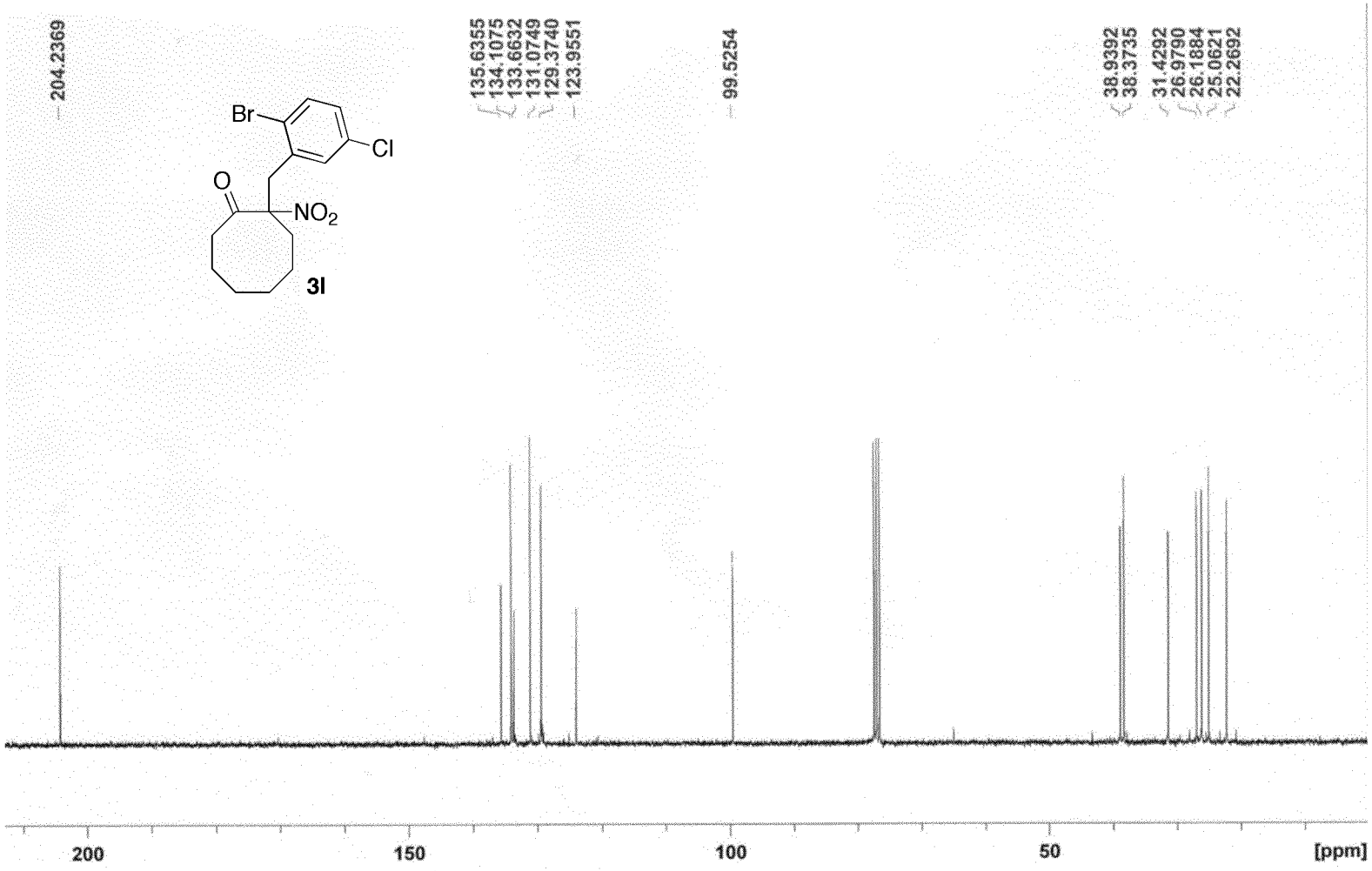

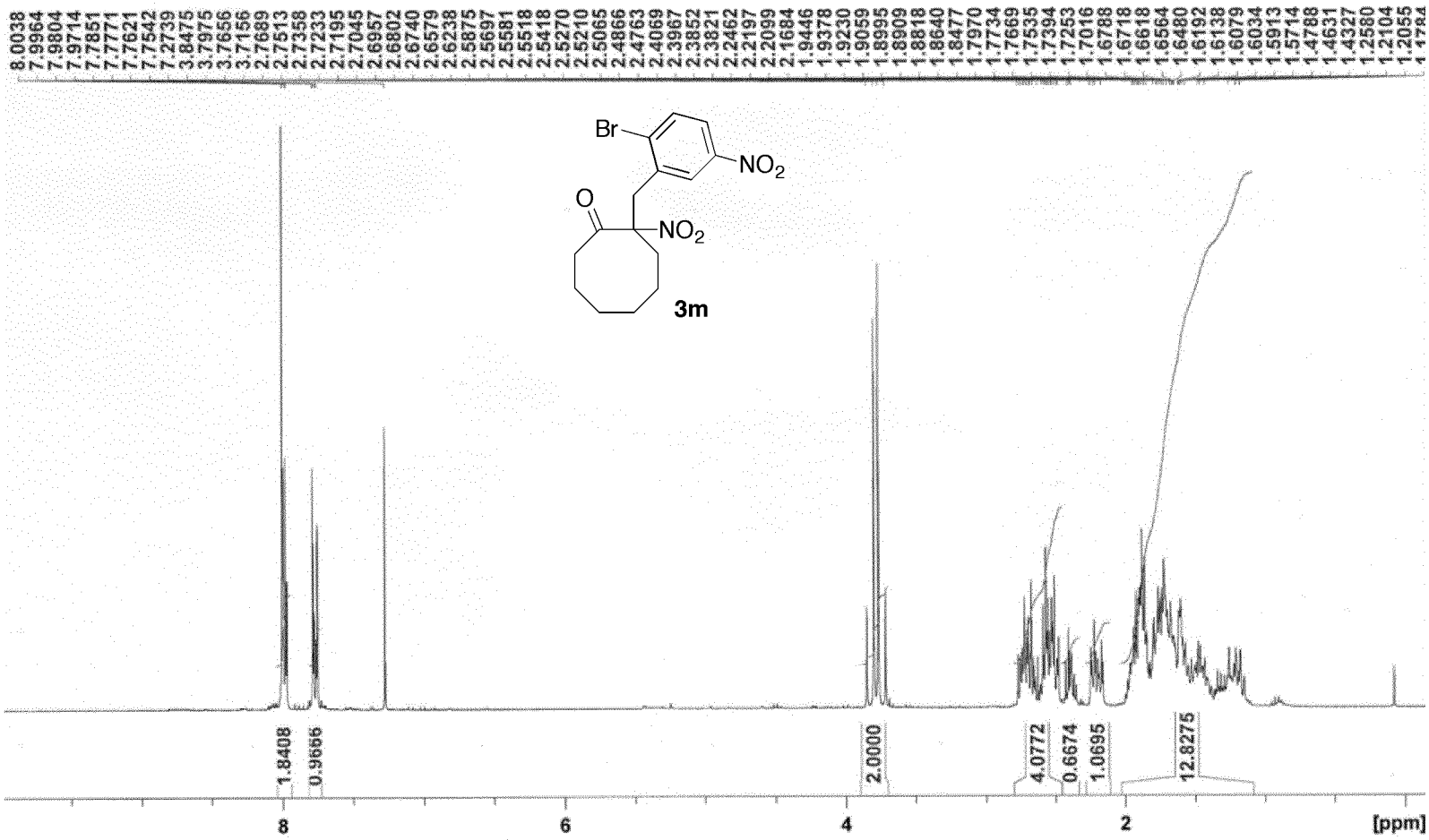

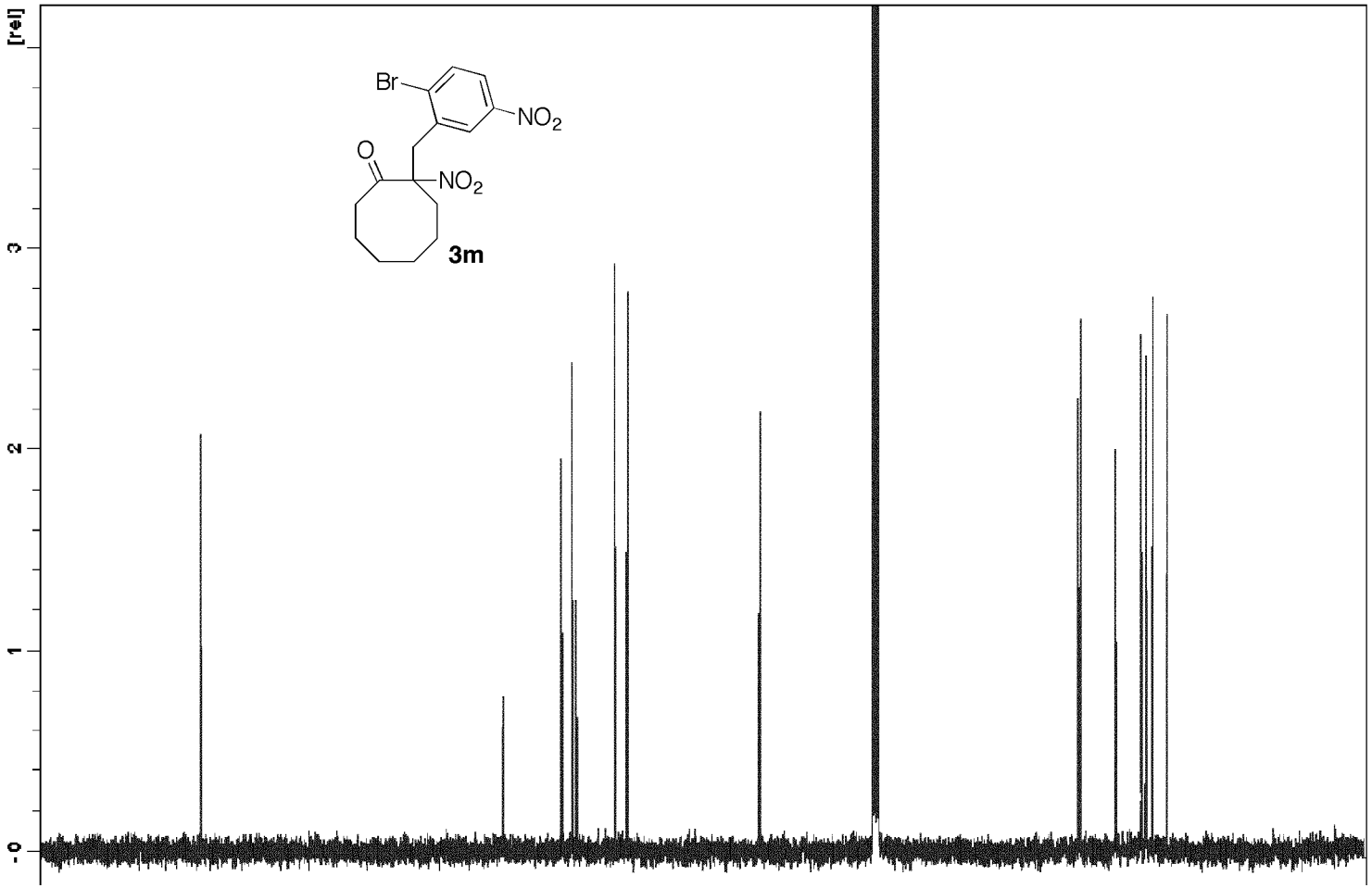

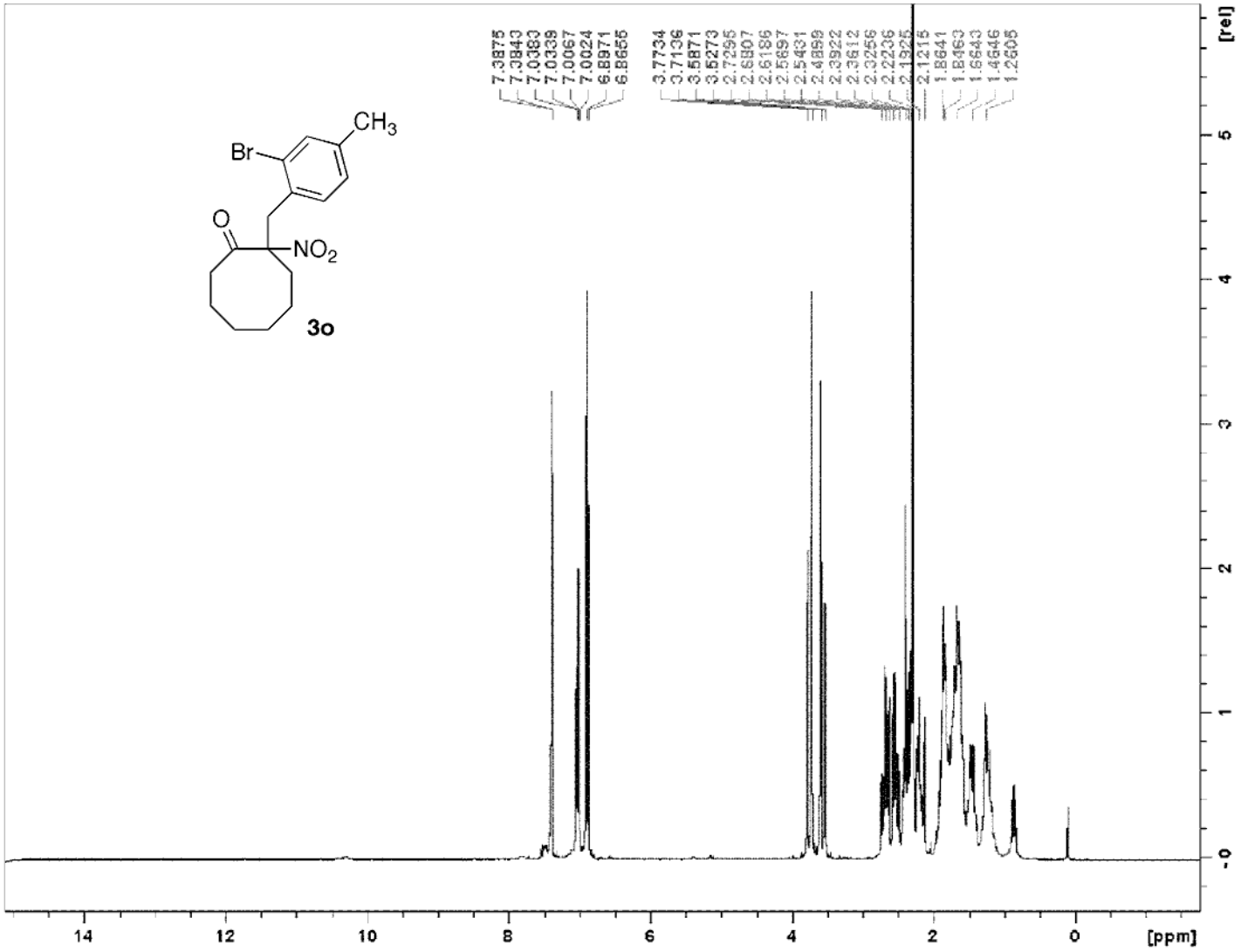

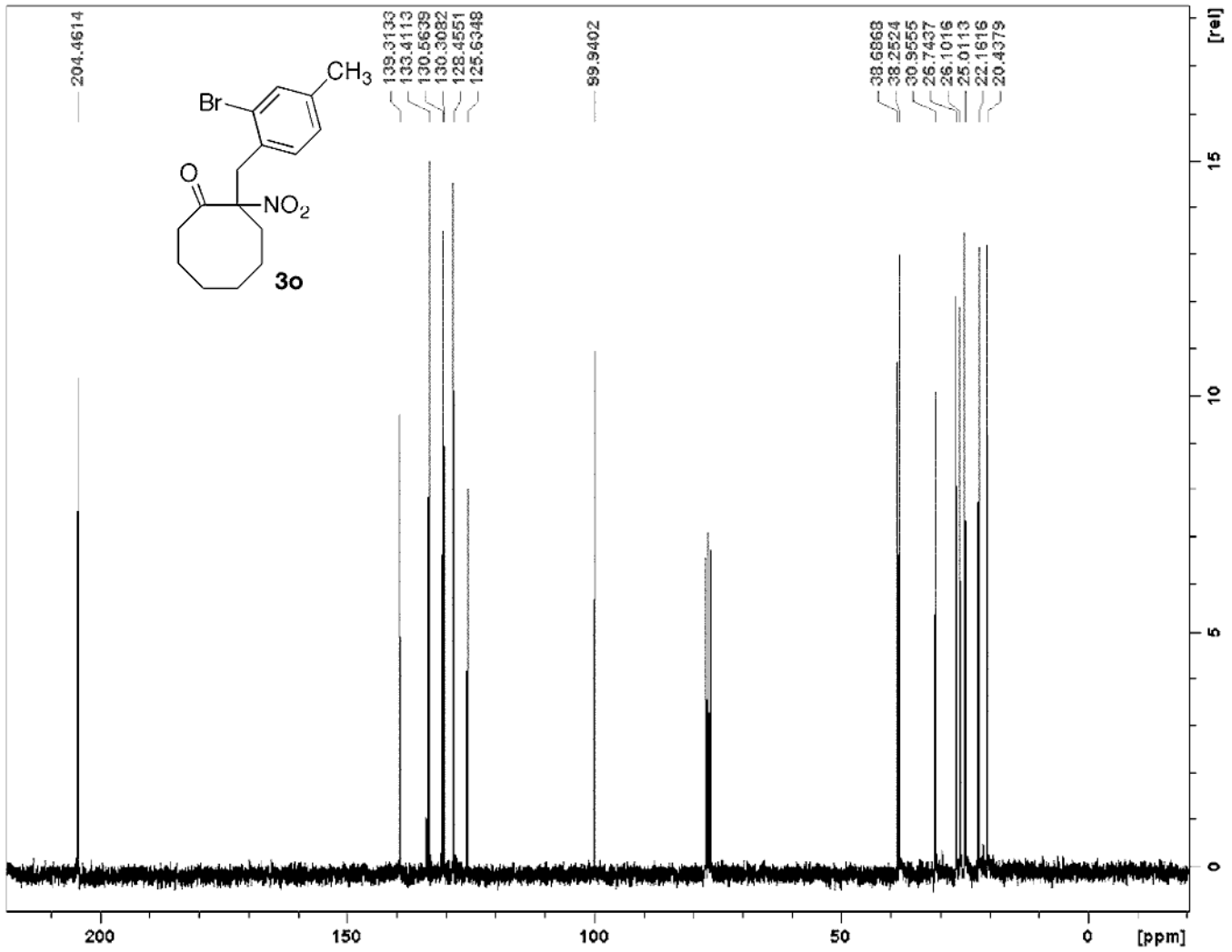

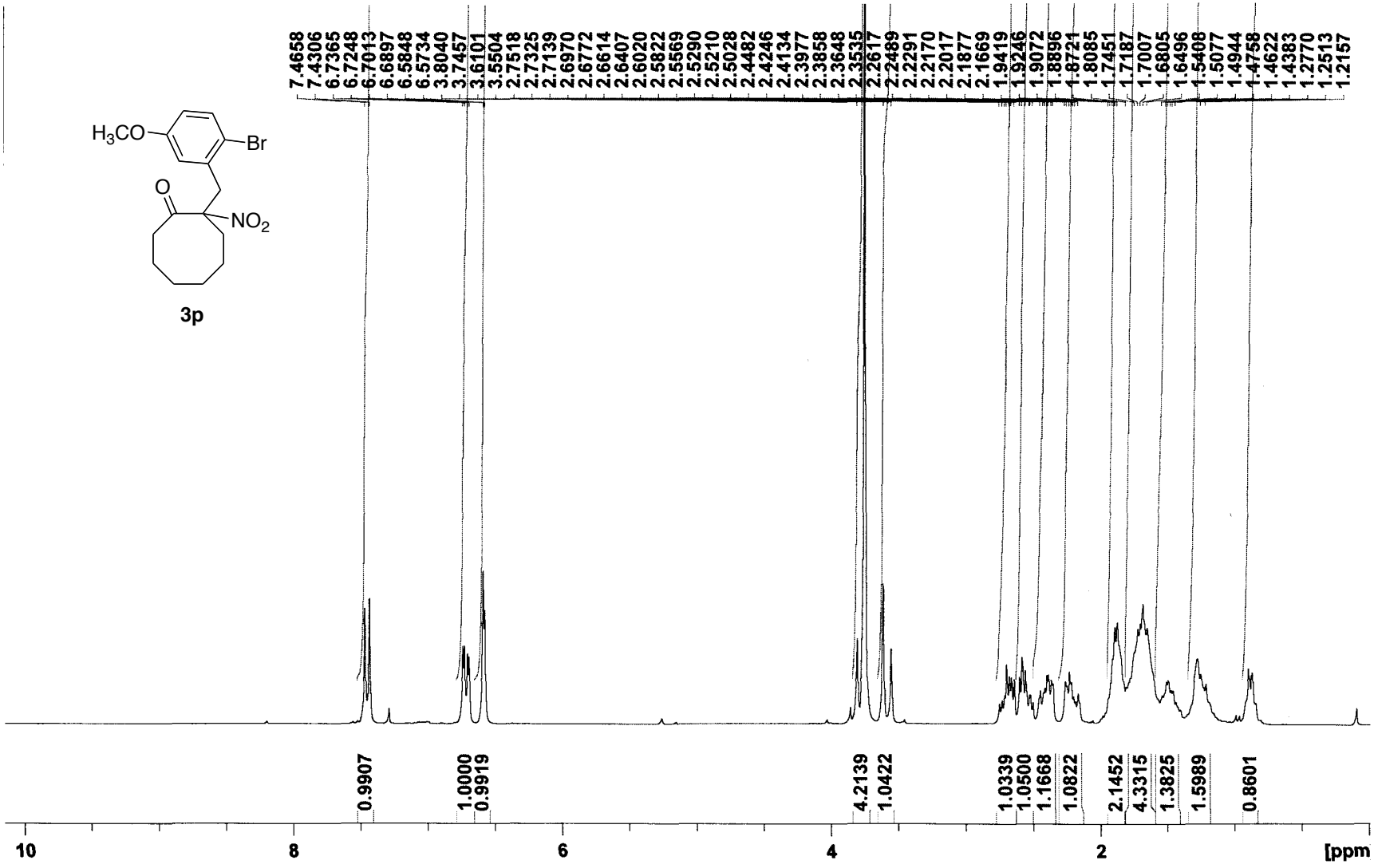

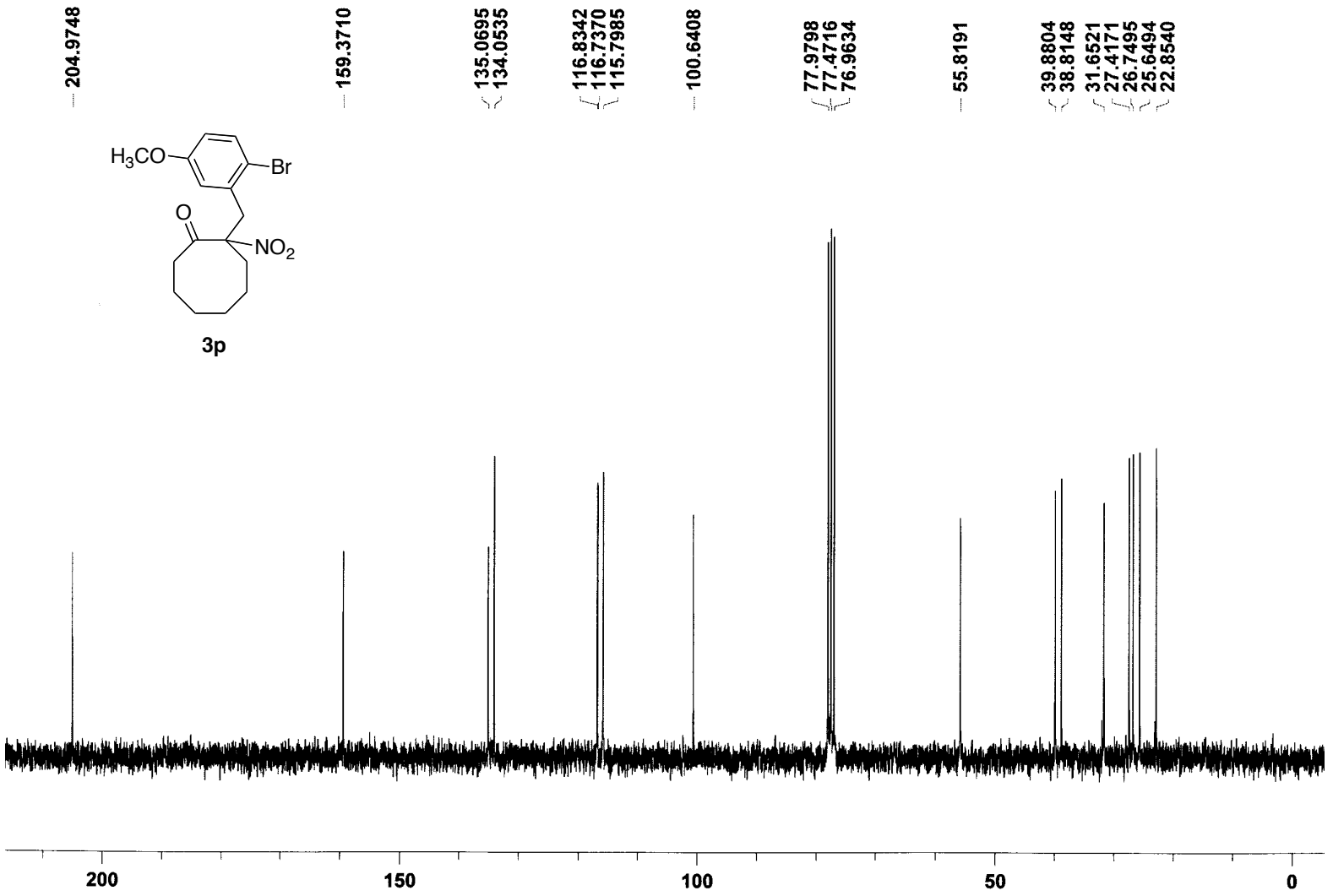

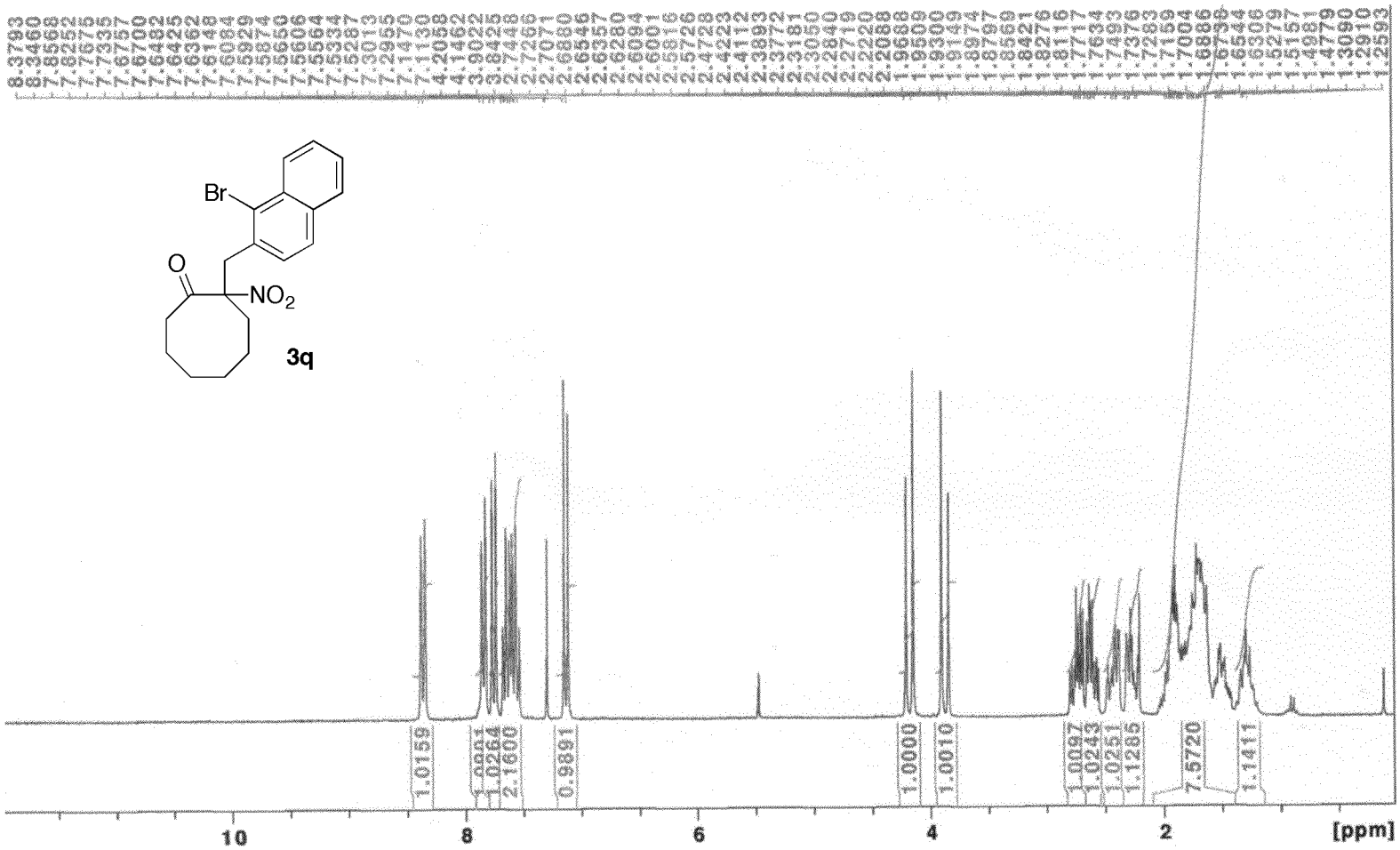

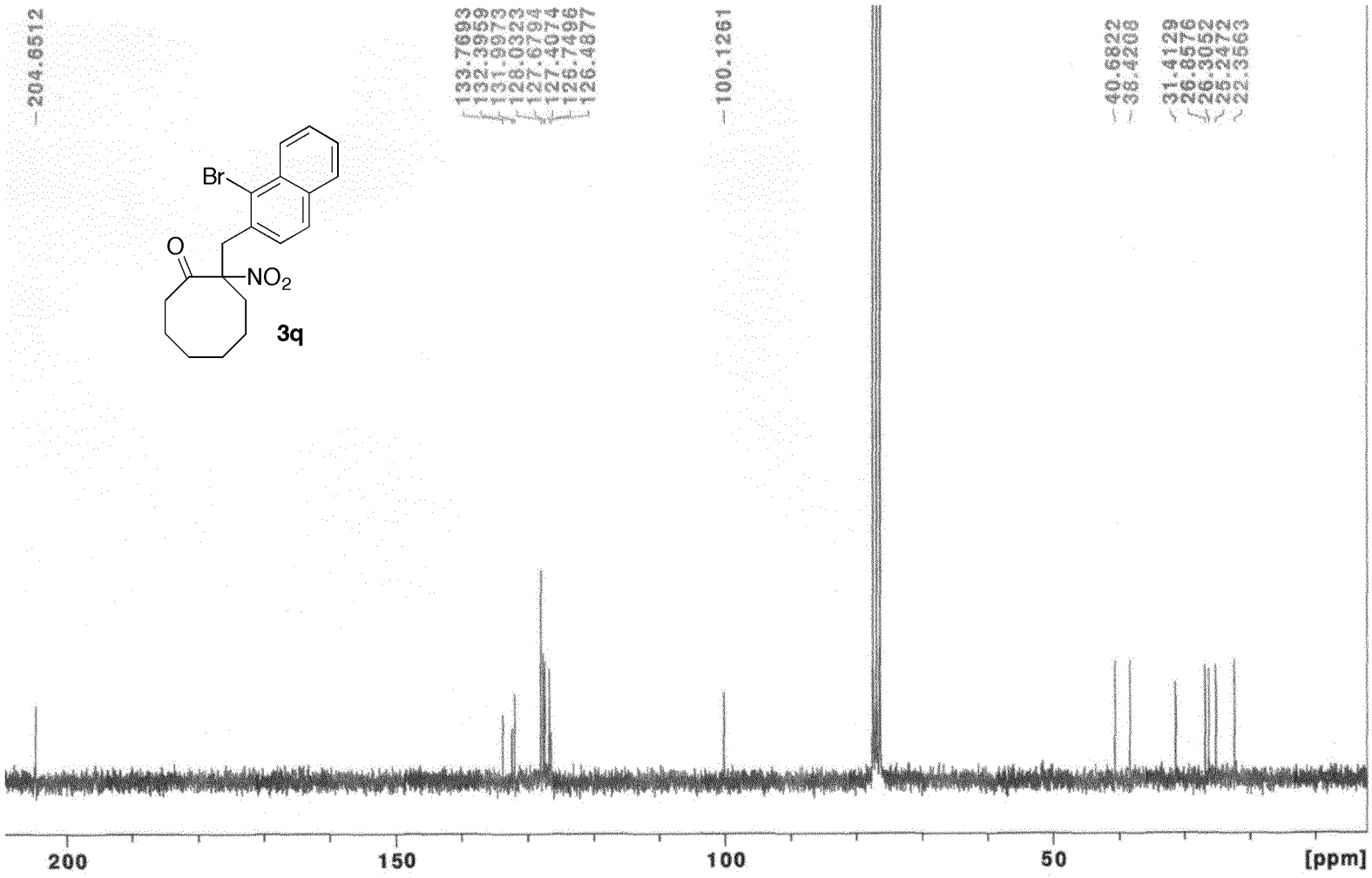

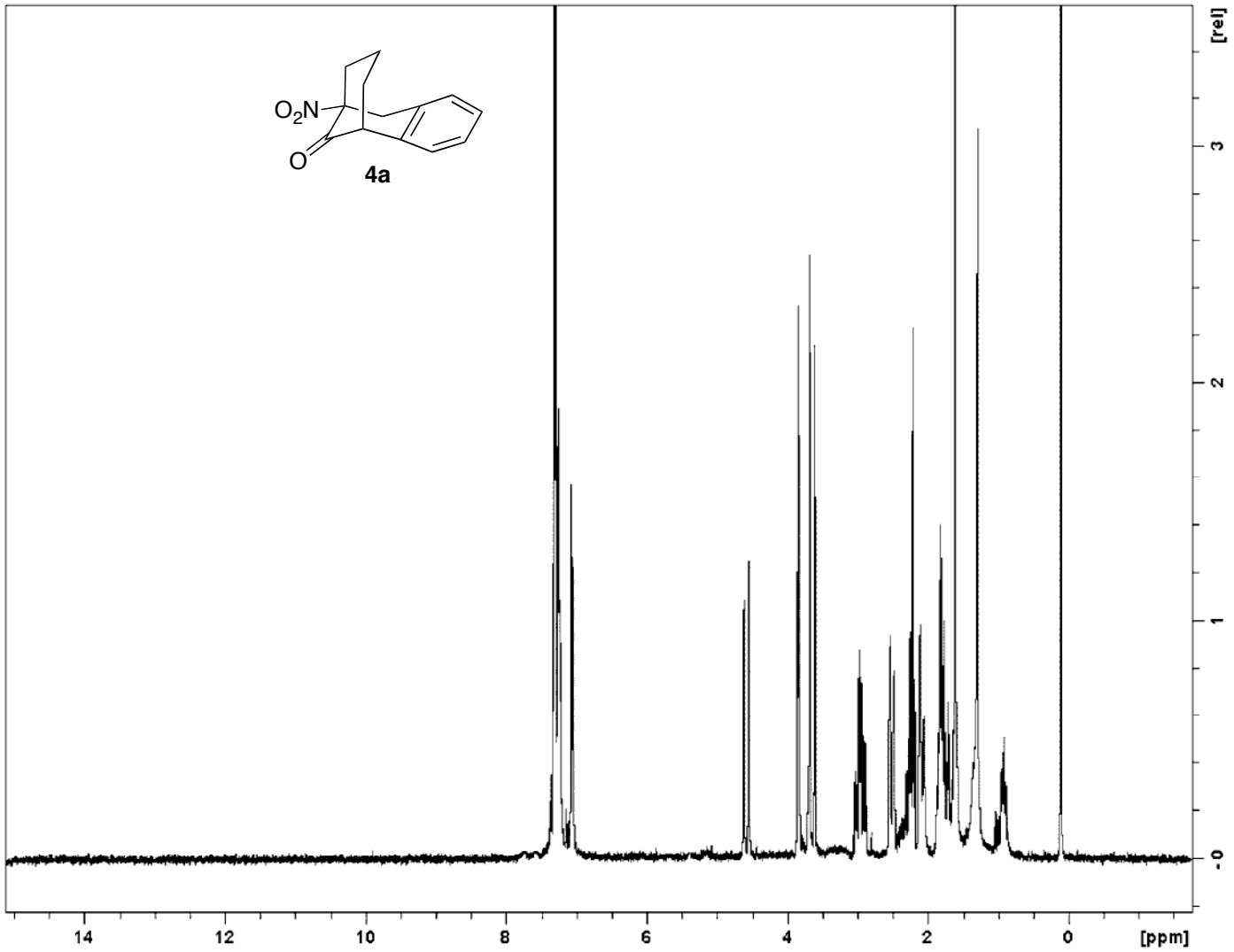

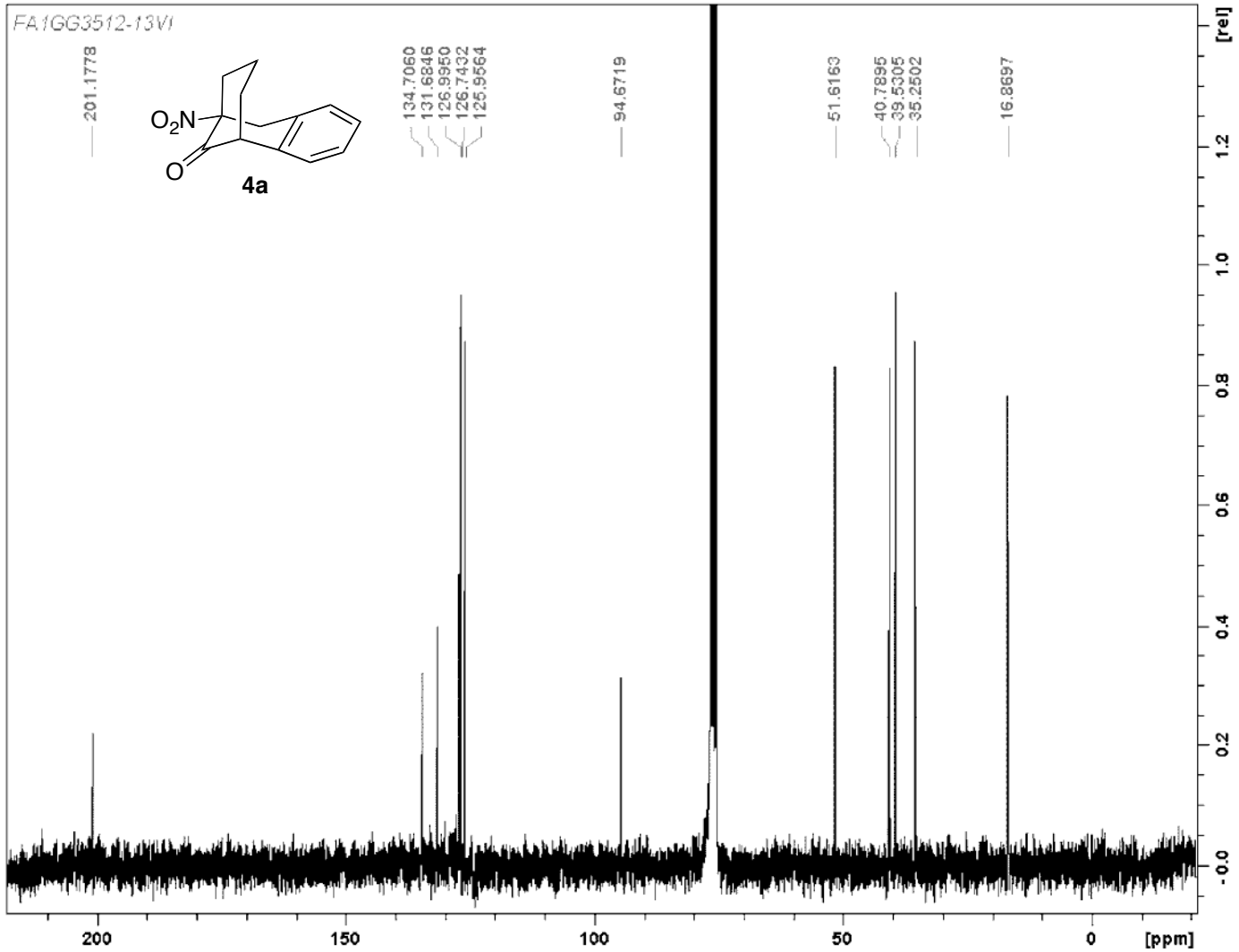
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O2N
O
4a
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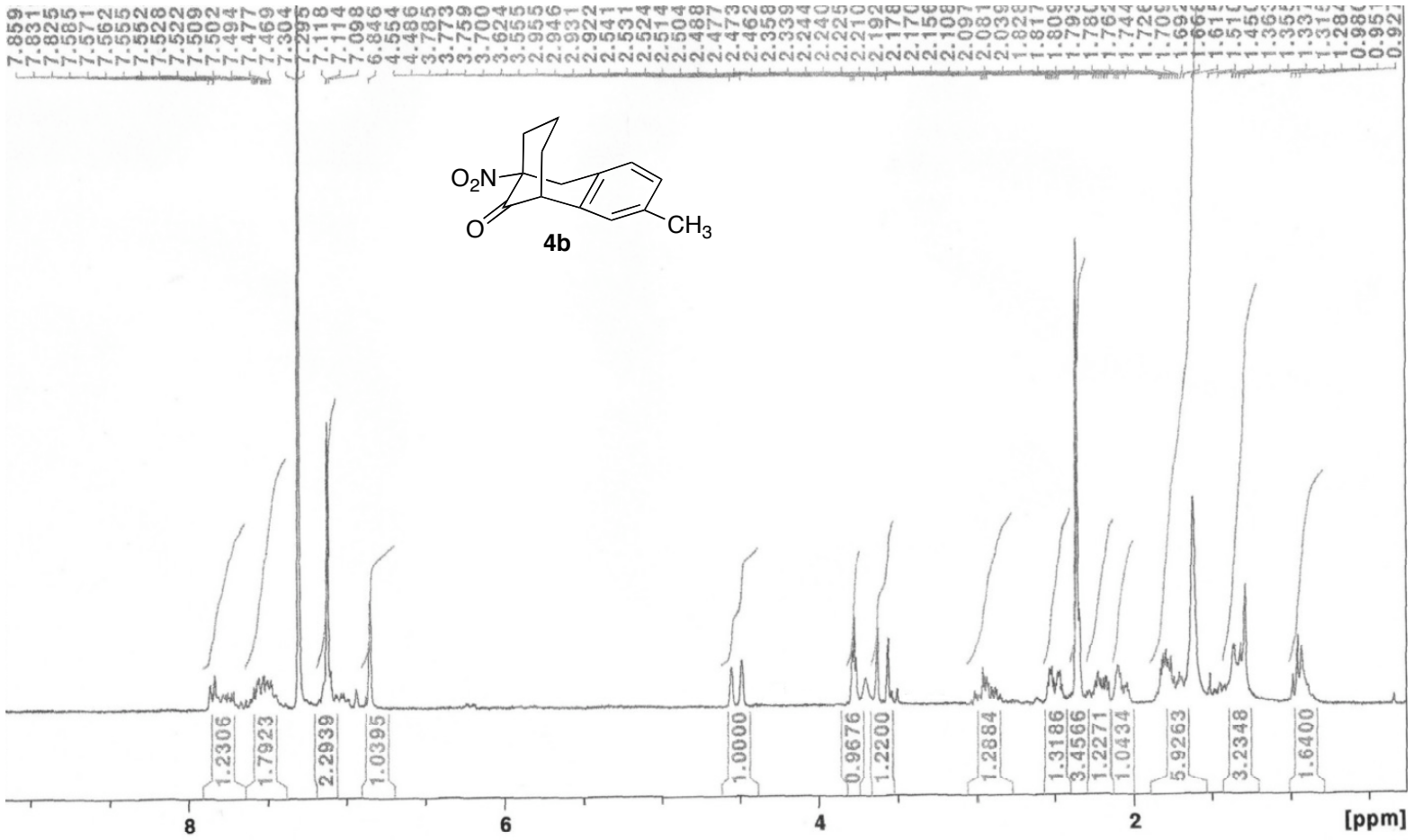

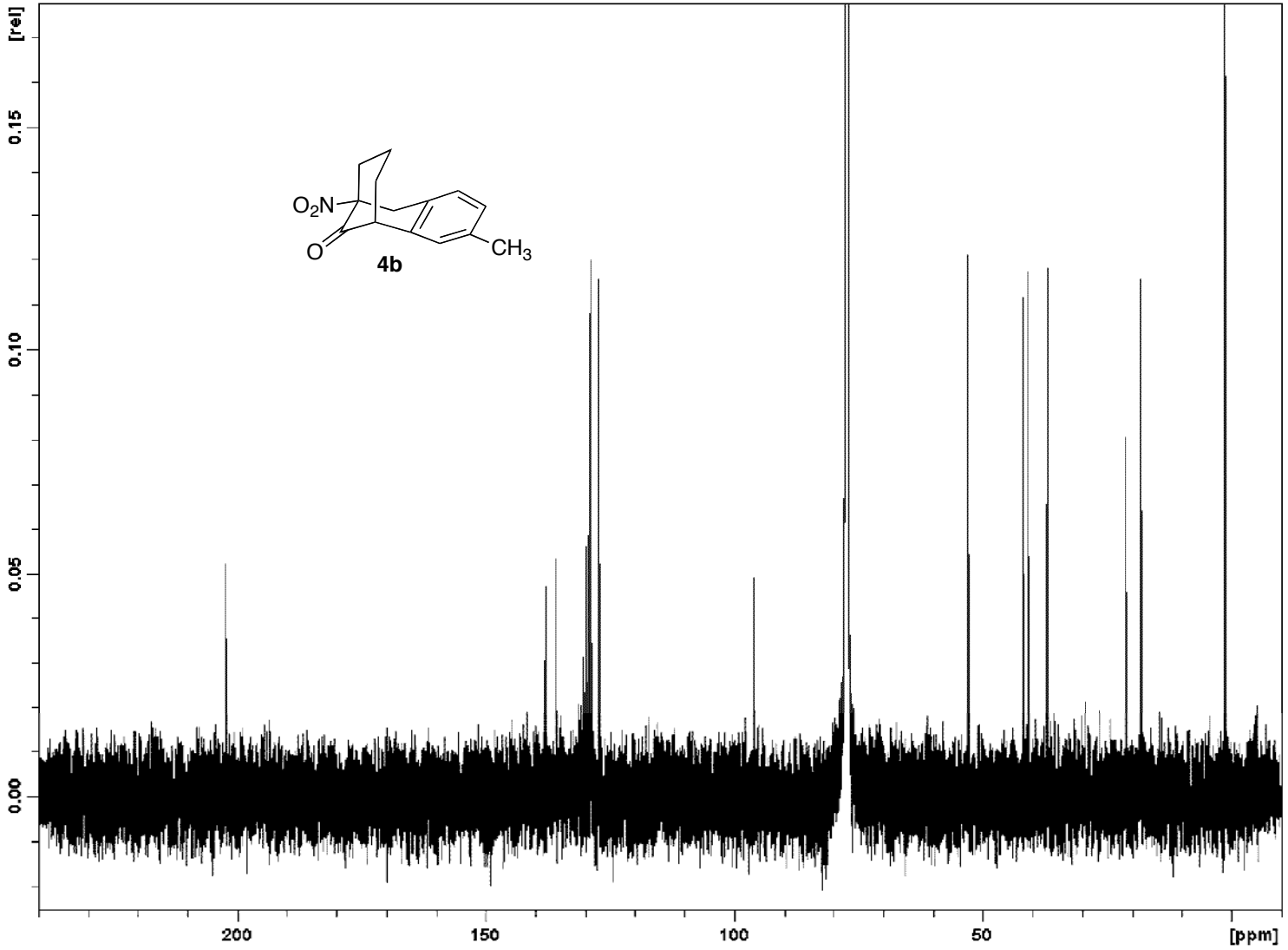

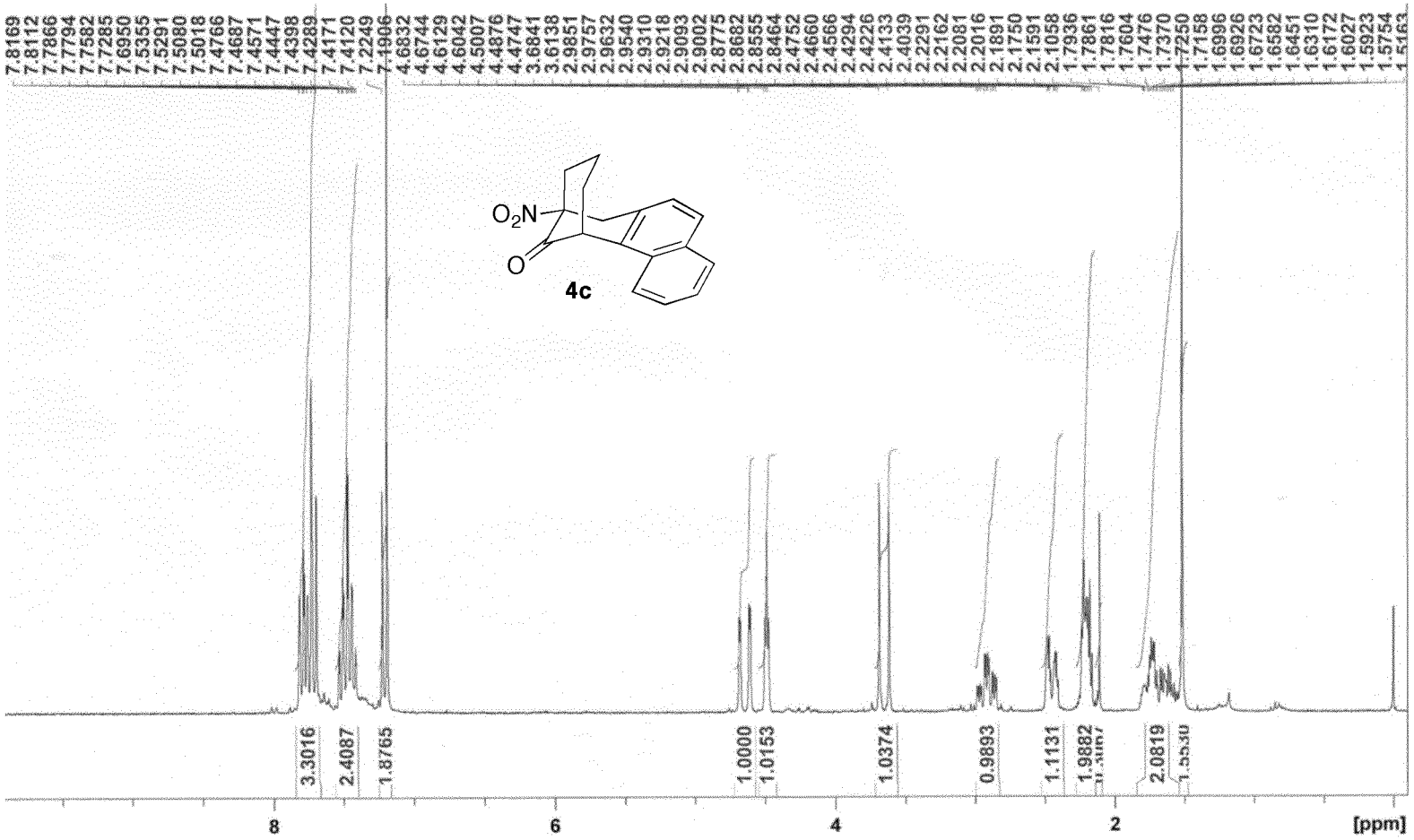

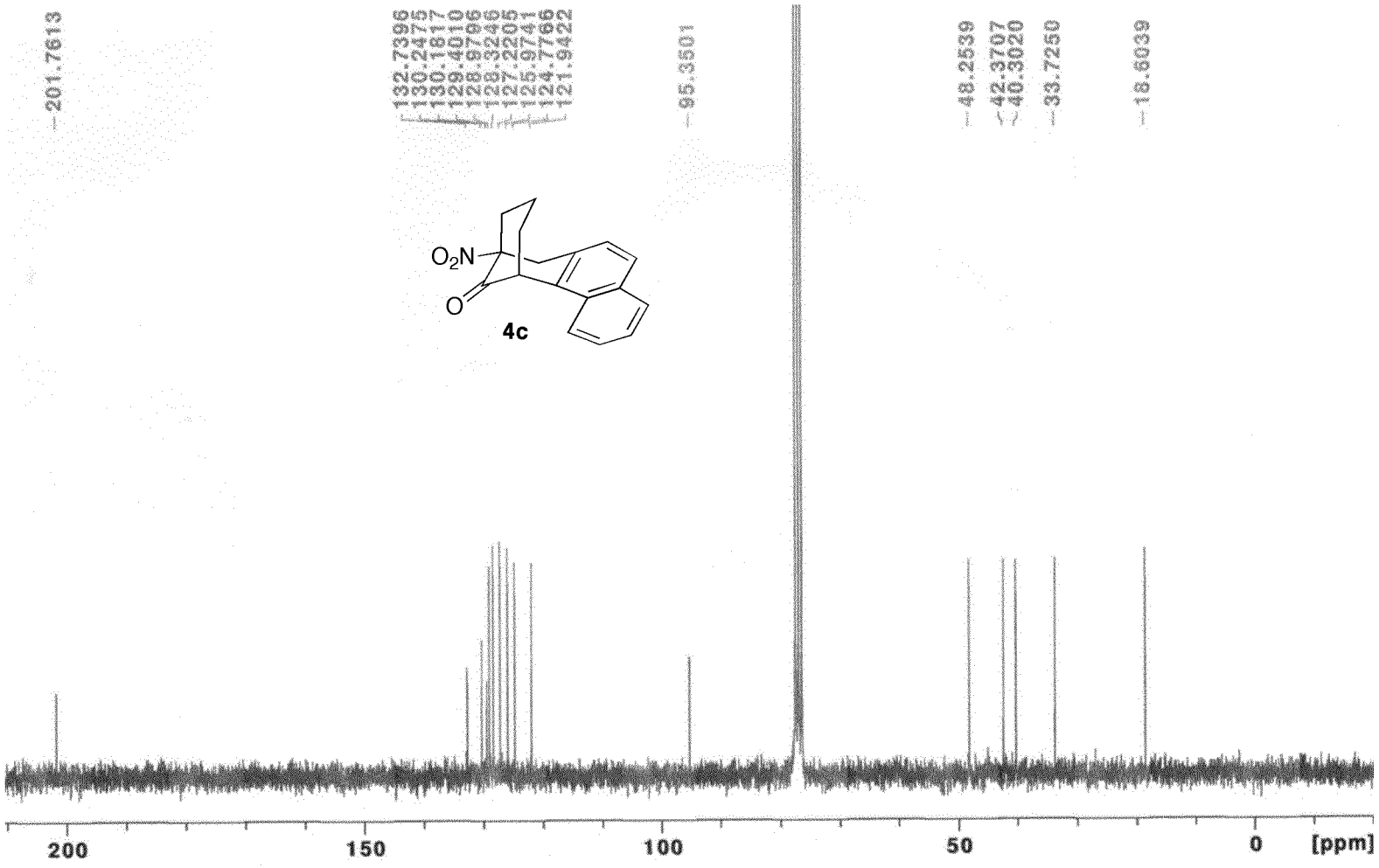

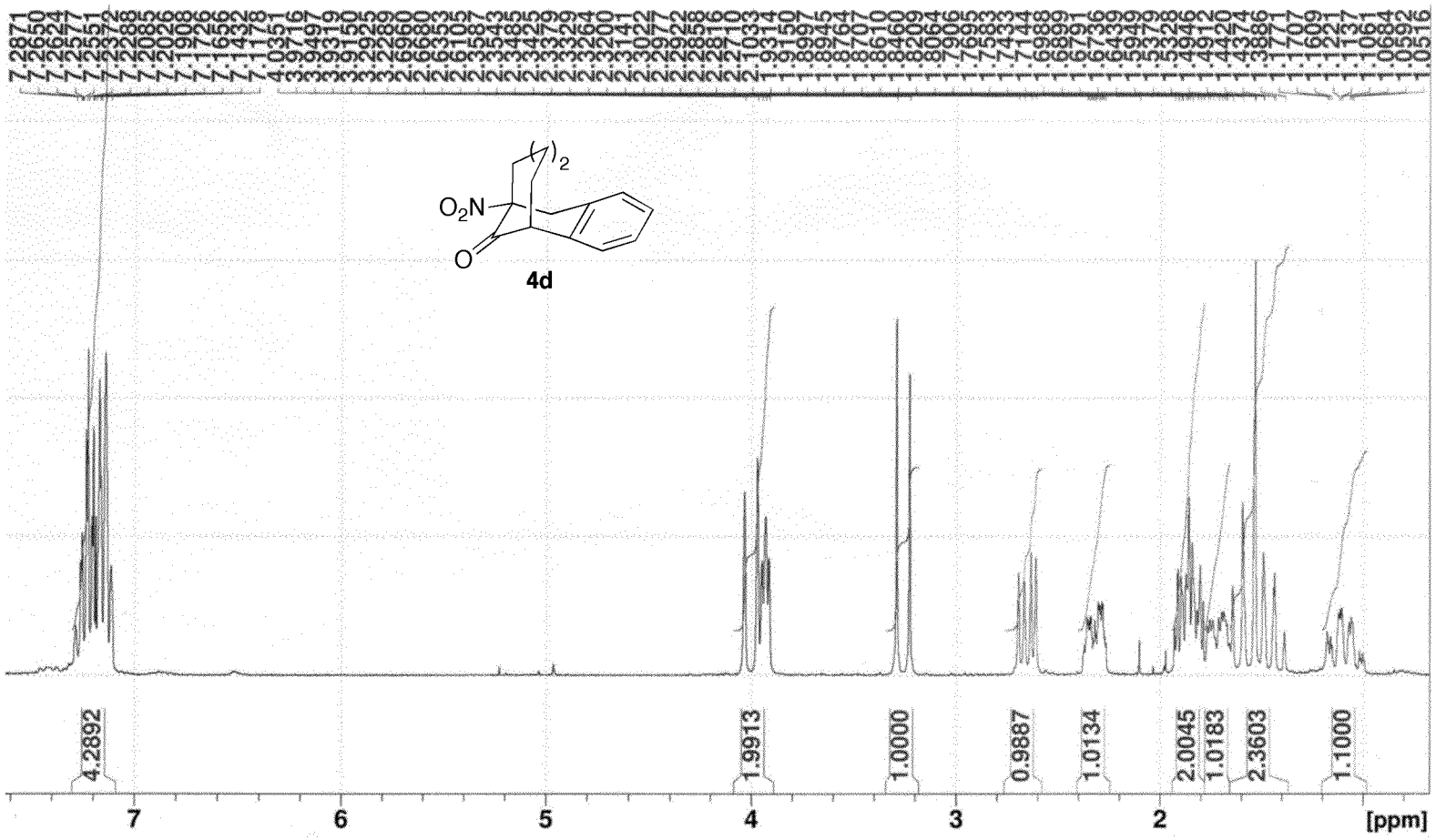

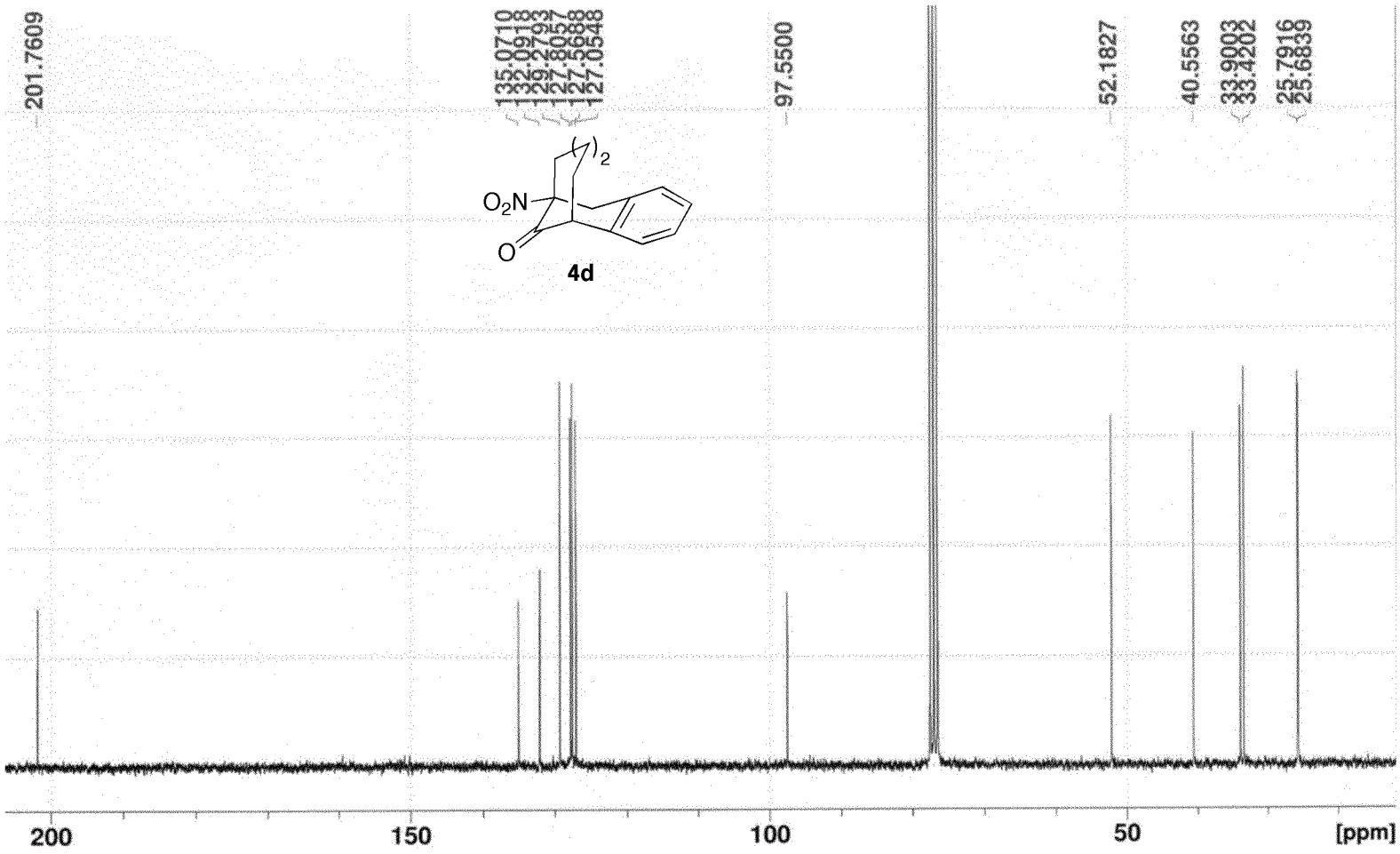

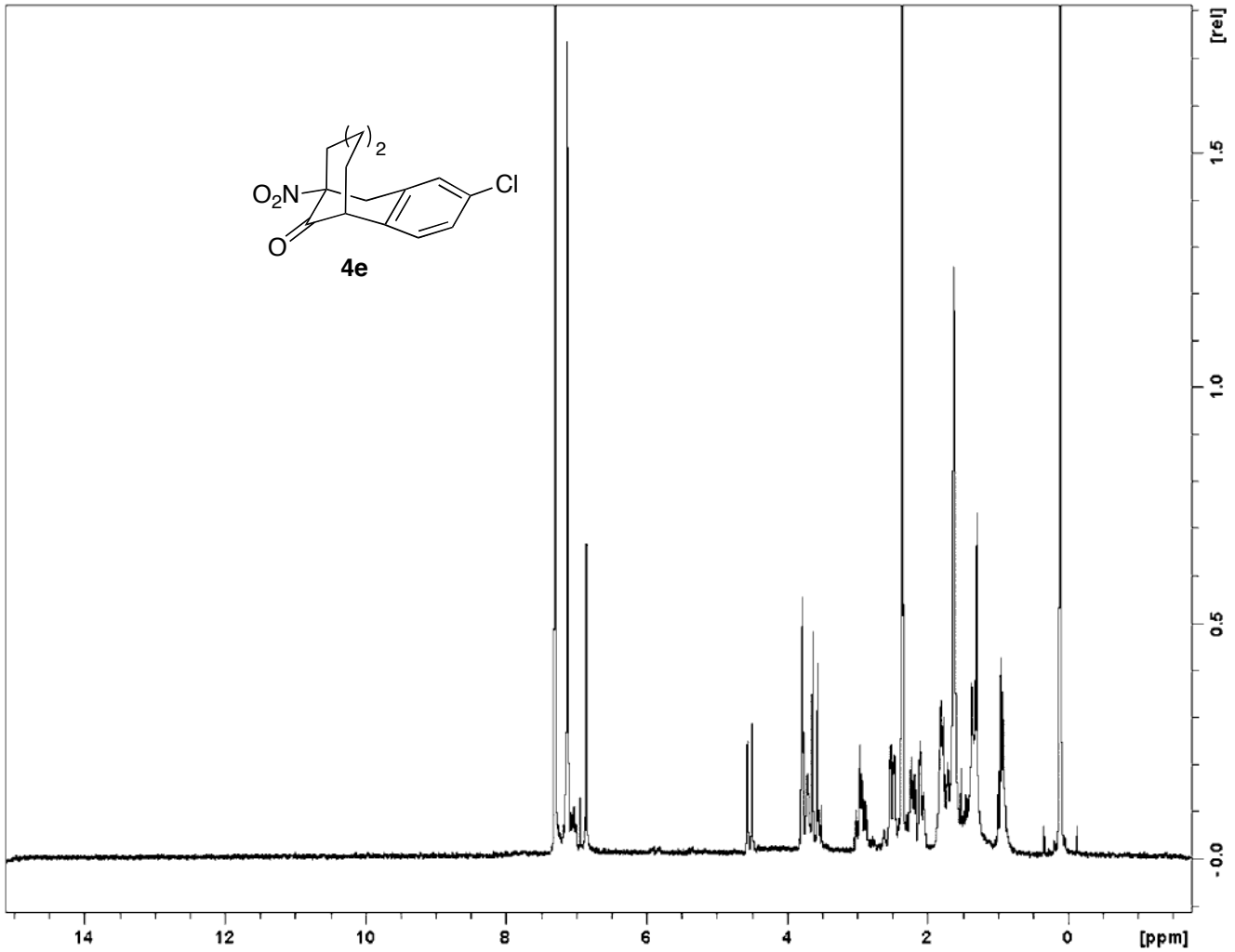

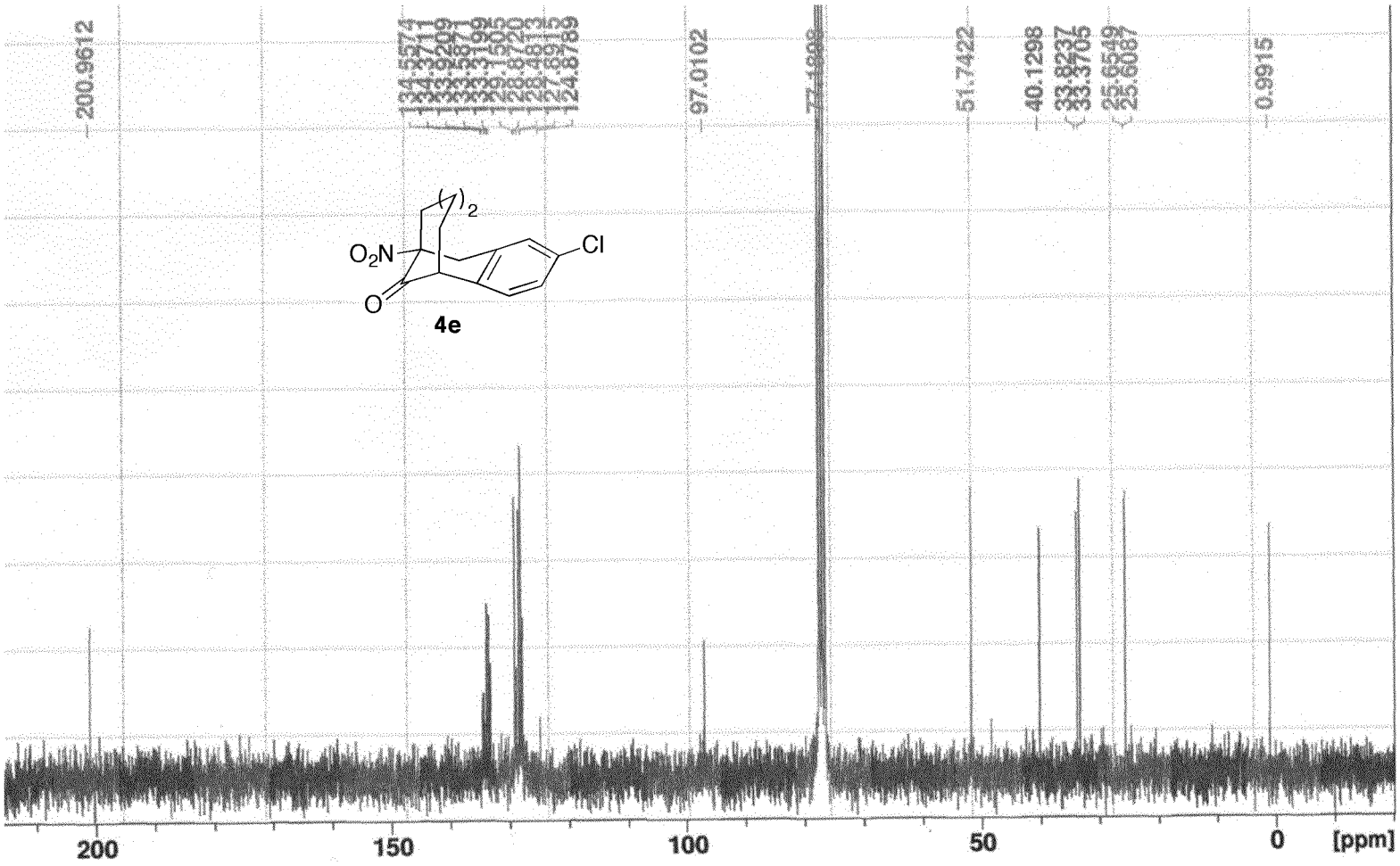

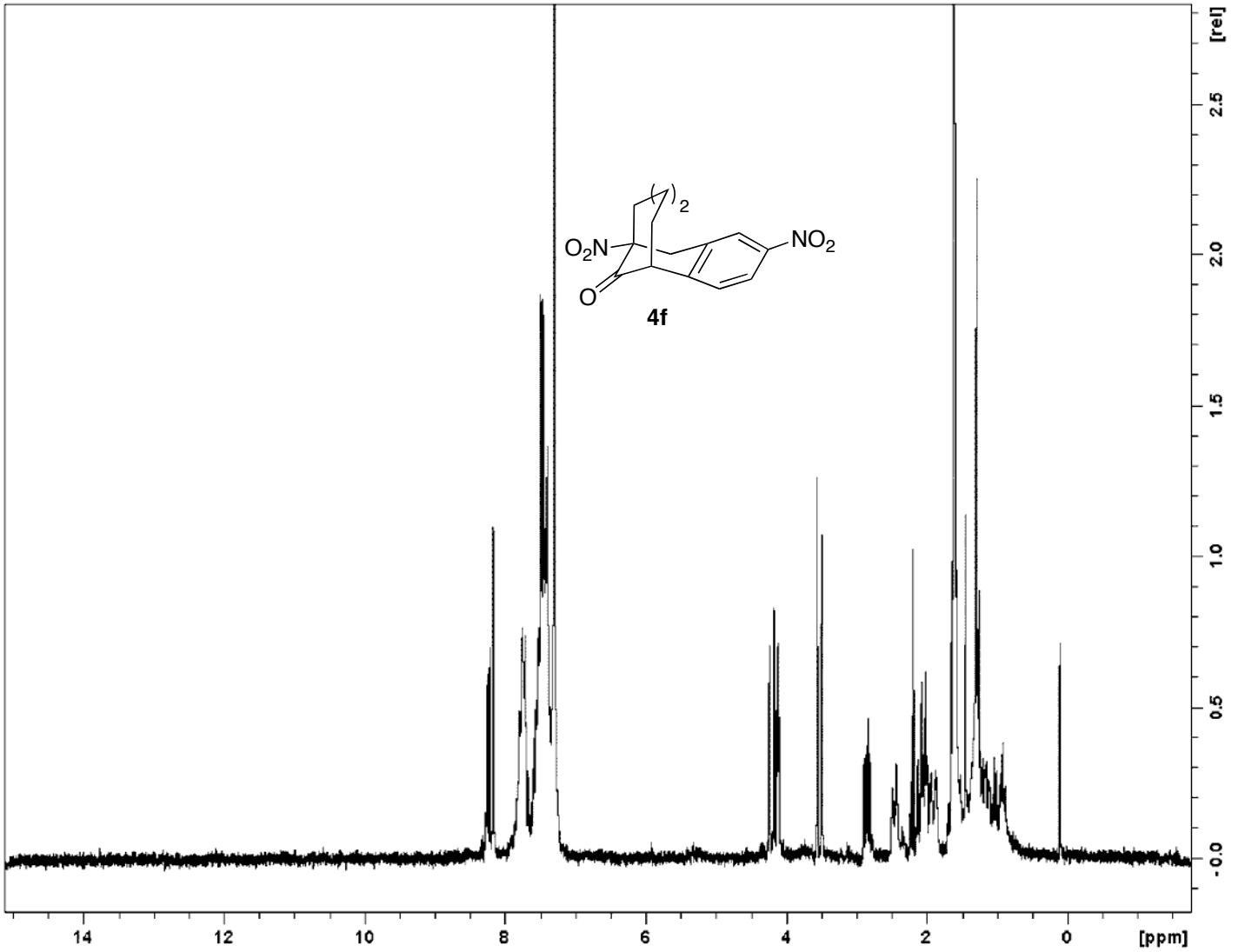

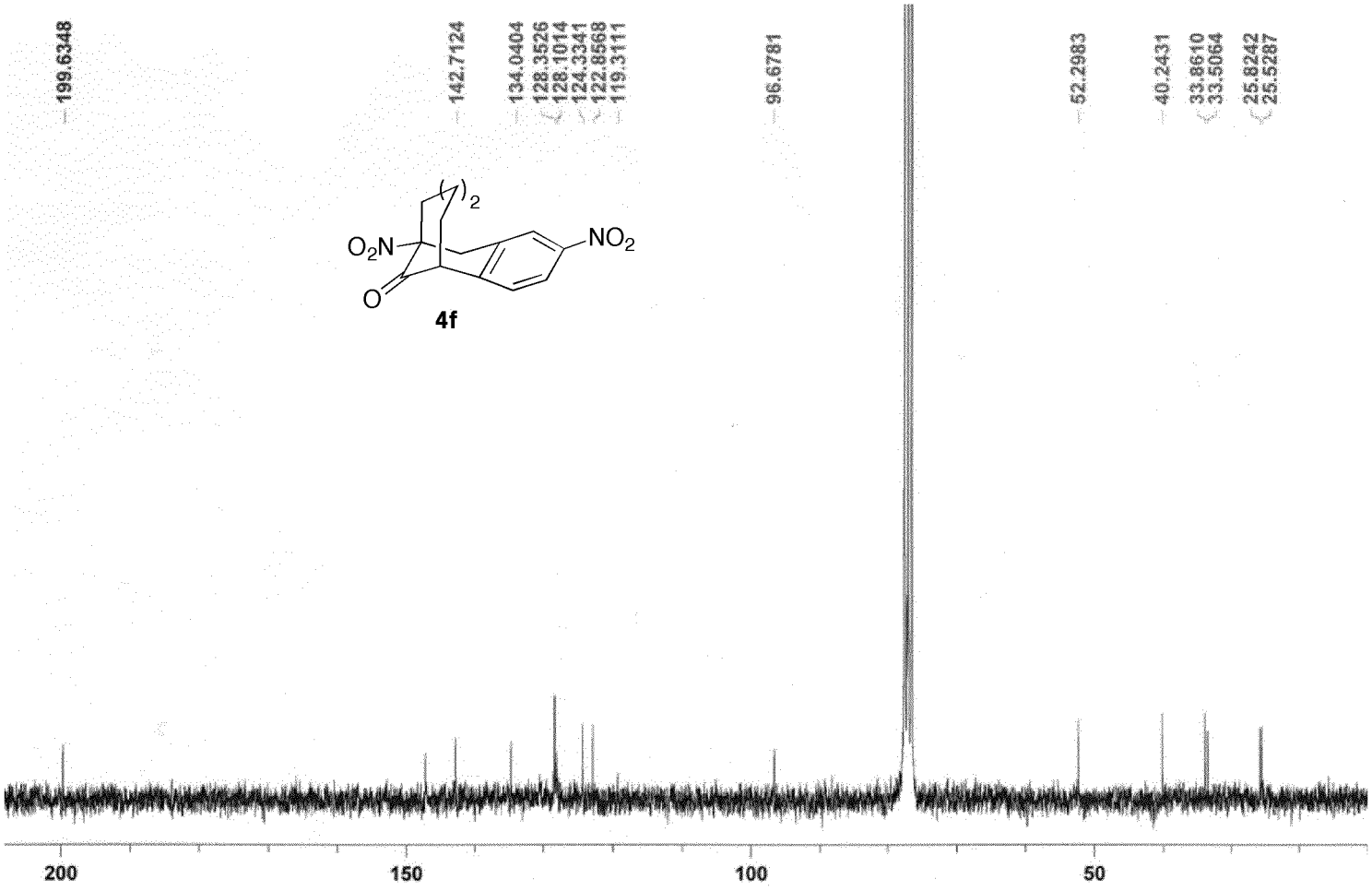

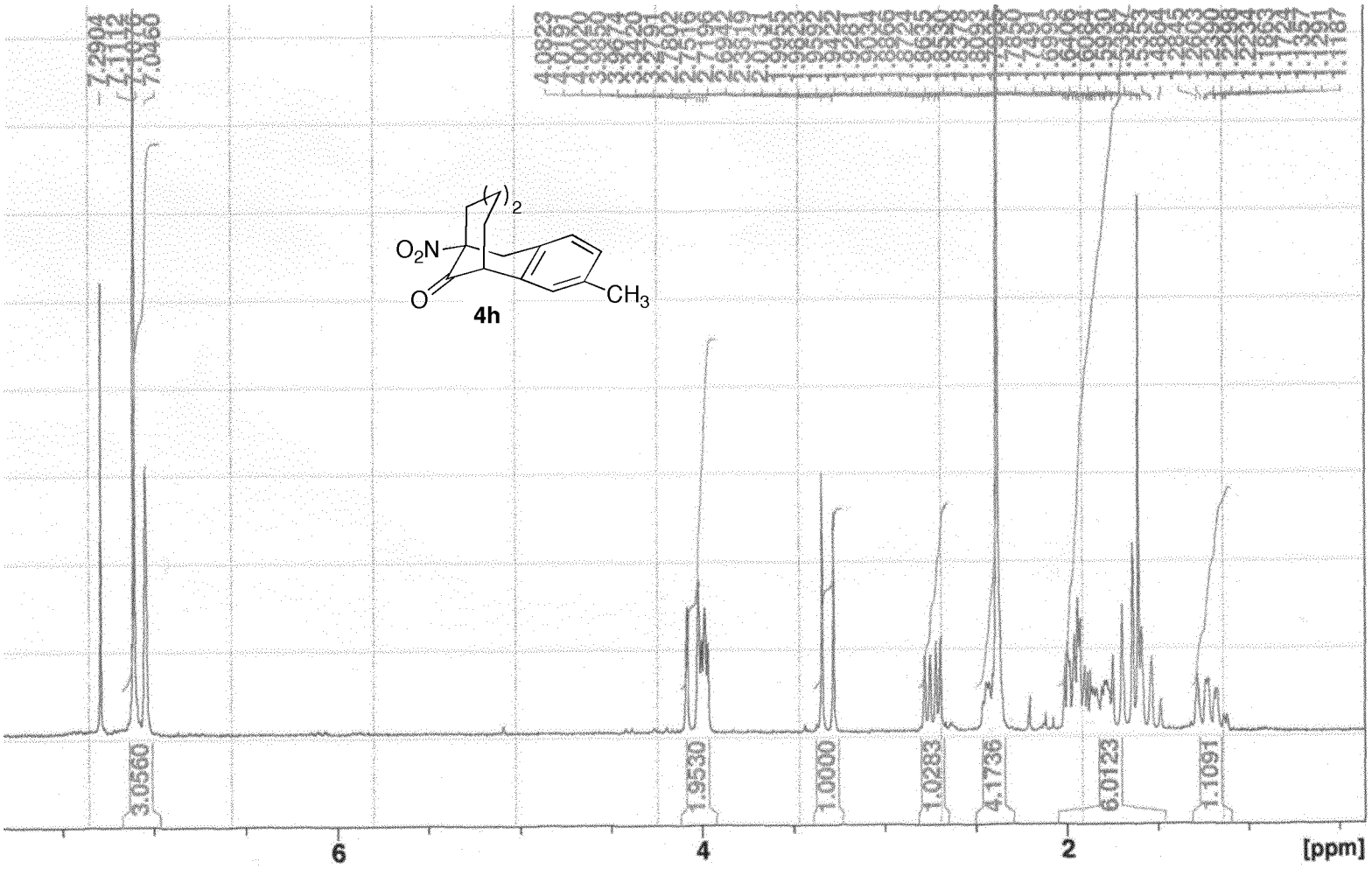
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7.0460
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O
CH3
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4
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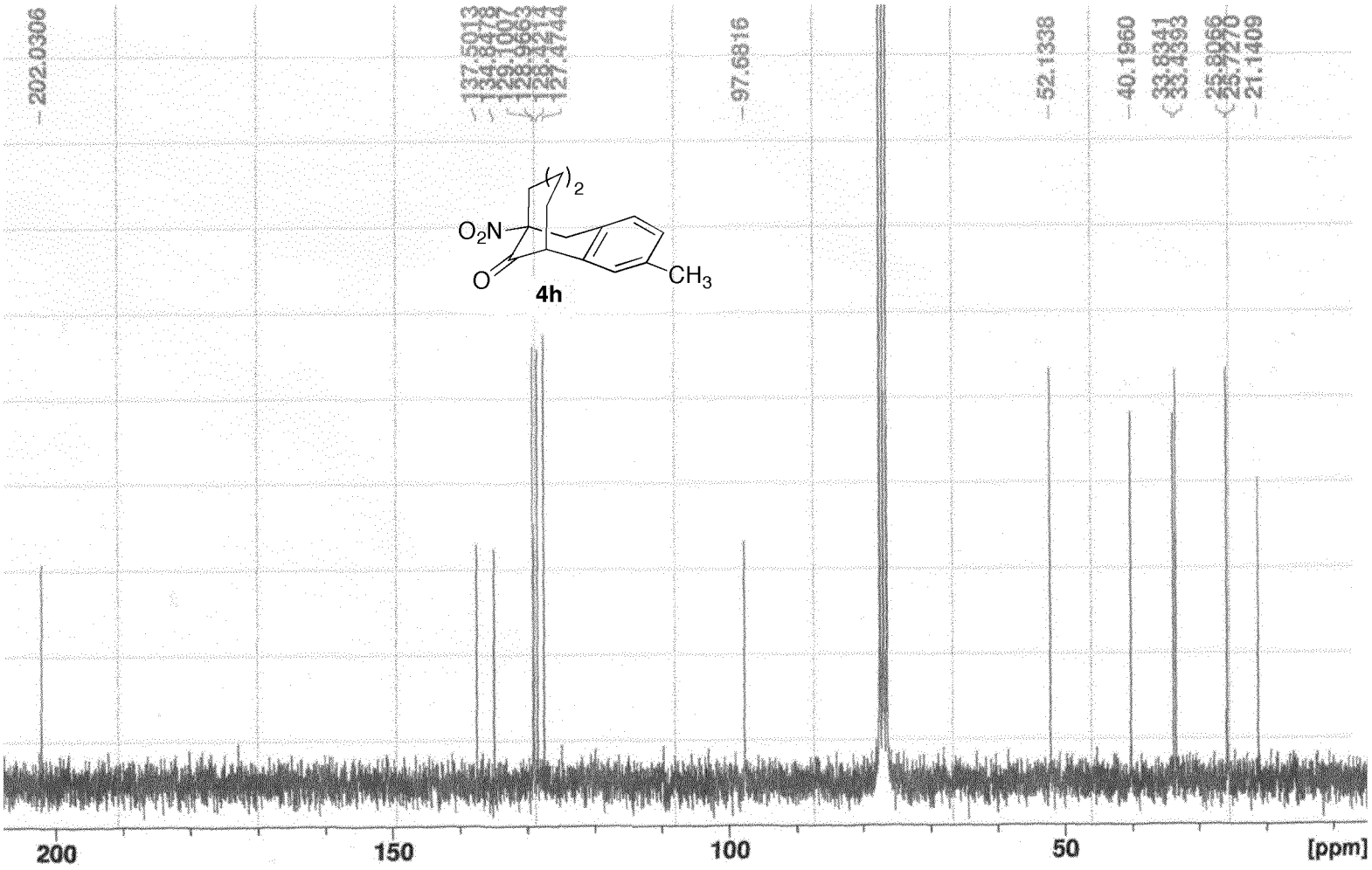

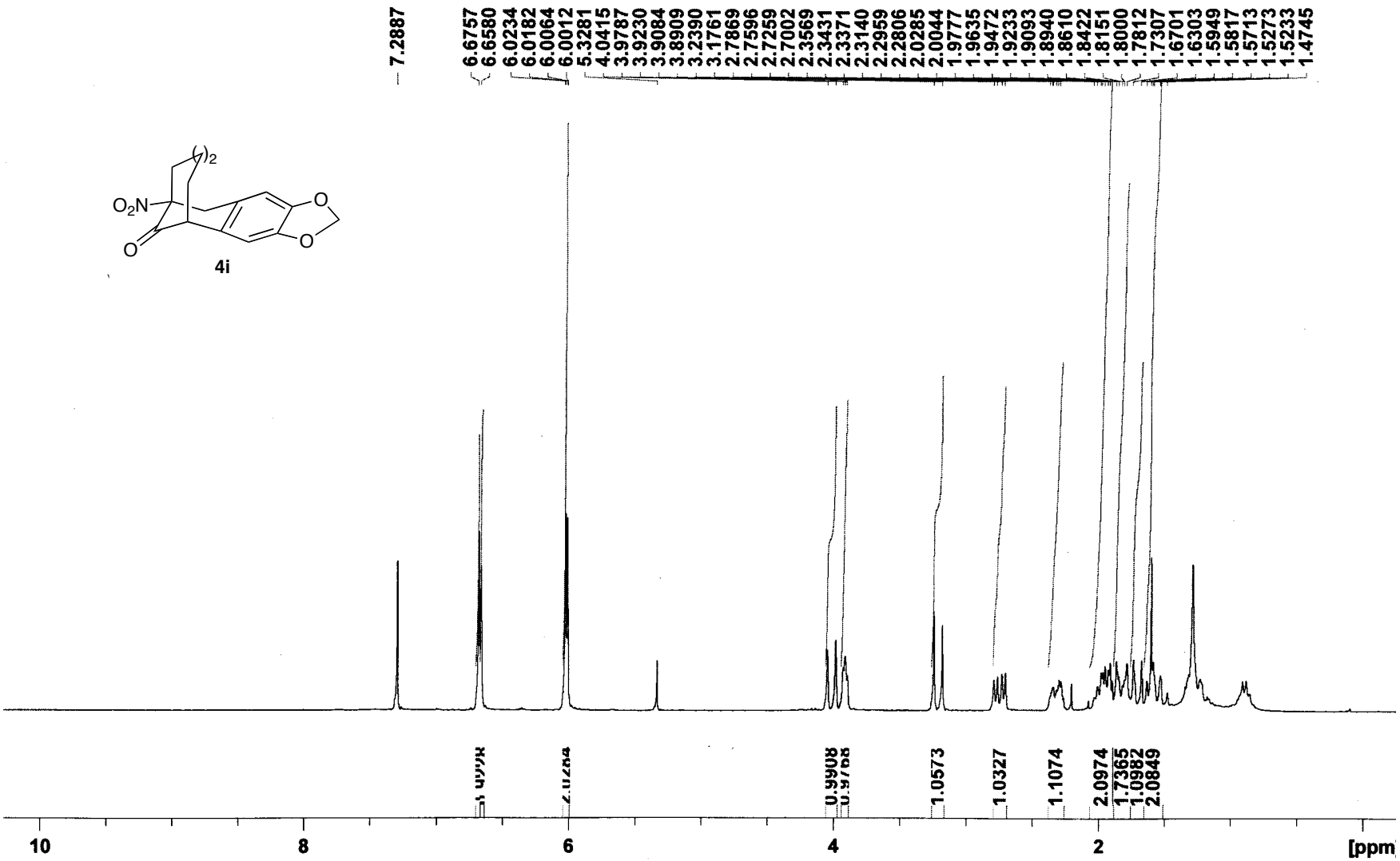

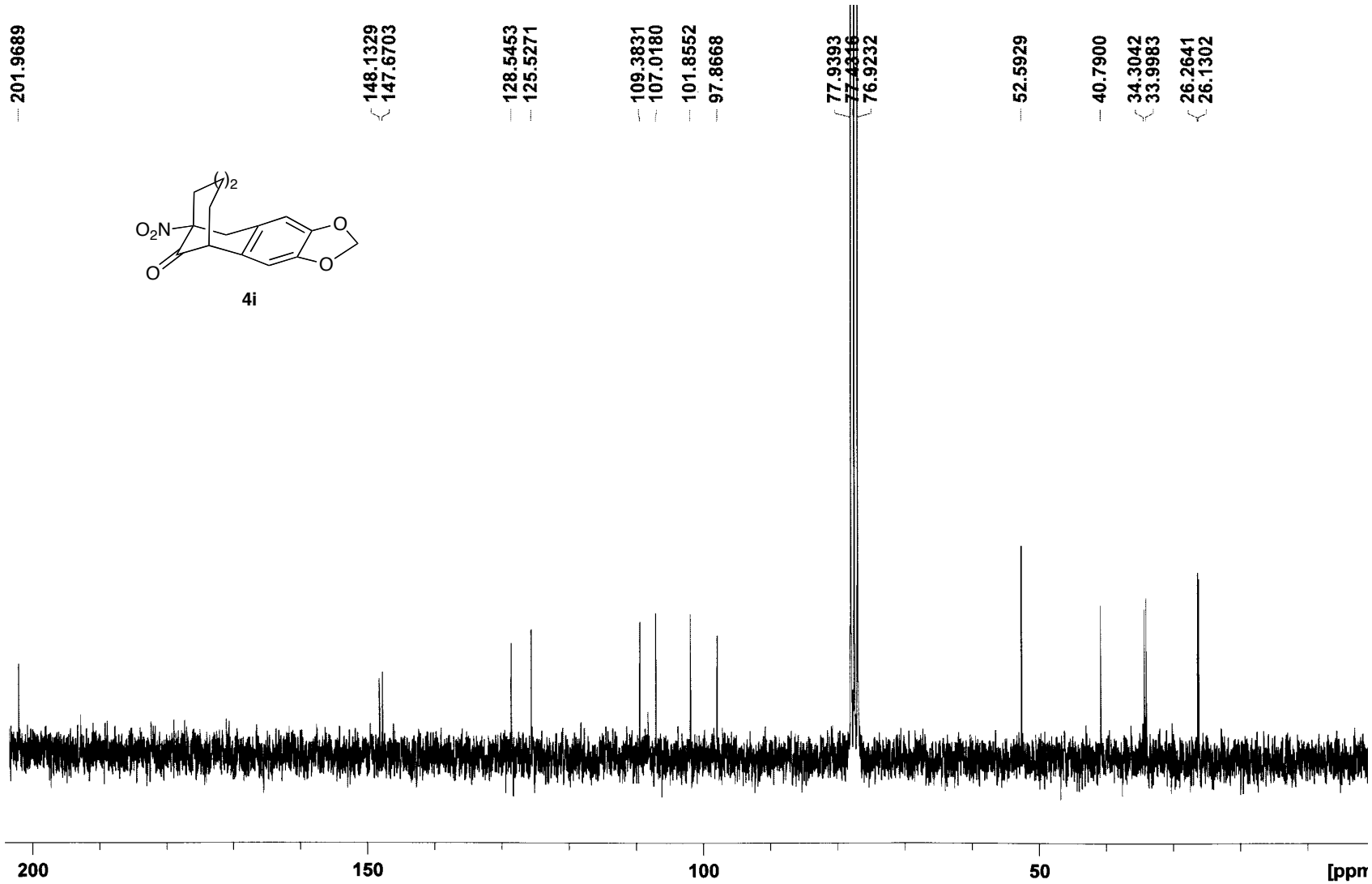
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O
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50
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