Electronic Supplementary Information for *Chemical Communications*

A Highly Efficient Access to Enantiopure Tetrahydropyridines: Dual-organocatalyst-promoted Asymmetric Cascade Reaction

Hua Lin, Yu Tan, Wen-Jie Liu, Zhi-Cheng Zhang, Xing-Wen Sun* and Guo-Qiang Lin*

Department of Chemistry, Fudan University, 220 Handan Road, Shanghai, 200433, P.R.China

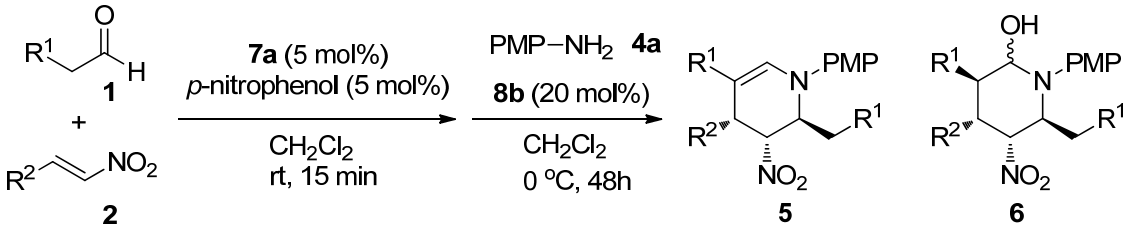
Email: sunxingwen@fudan.edu.cn; lingq@sioc.ac.cn

Contents

General experimental methods:

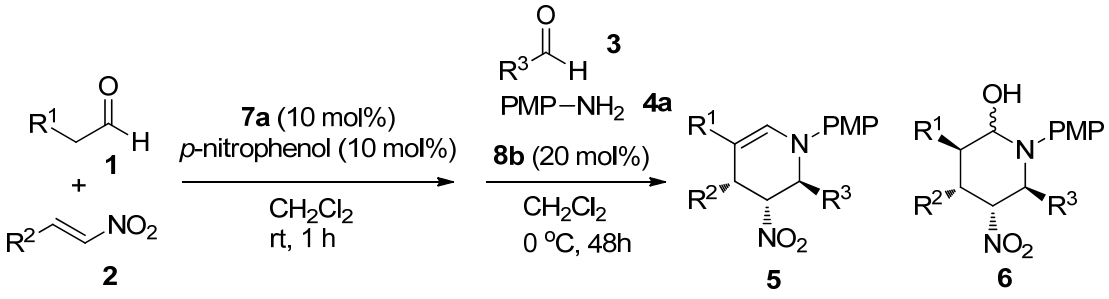
NMR spectra were all recorded on a ECA (400 MHz) spectrometer. Chemical shifts are reported in δ ppm referenced to an internal $SiMe_4$ standard for ^1H NMR and chloroform-*d* (δ 77.0) for ^{13}C NMR. Optical rotations were measured in $CHCl_3$ on a Rudolph research analytical, Auto pol ® LV, automatic polarimeter. HPLC was performed on an Agilent 1100 series instrument or a Jasco uv-2075 plus intelligent uv/ivs detector by using Daicel Chiracel AS-H column or Phenomenex Lux 5u Amylose-2 column. Flash column chromatography was performed using silica gel (300–400 mesh). Analytical thin–layer chromatography was performed using glass plates pre-coated with 0.25 mm 300–400 mesh silica gel impregnated with a fluorescent indicator (254 nm). Thin layer chromatography plates were visualized by exposure to ultraviolet light. Commercial reagents and solvents were used as received. Dichloromethane was fractionally distilled.

General procedure for the synthesis of tetrahydropyridine derivates **5a-5l**:



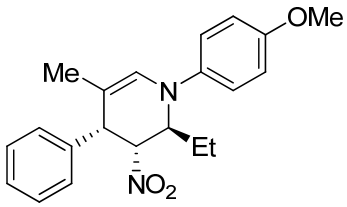
A solution of nitroalkene **2** (0.25 mmol), *p*-nitrophenol (5 mol%) and catalyst **7a** (5 mol%) in CH_2Cl_2 (0.25 mL) was added with aldehyade 1 (1.25 mmol). The result mixture was stirred at room temperature until all the nitroalkene was consumed, then cooled to 0 °C, added with catalyst **8b** (20 mol%), $PMPNH_2$ (1.25 mmol) and 4Å MS (100 mg). The mixture was kept at 0 °C for 48 hours before diluted with CH_2Cl_2, filtered through a short pad of celite. The filtrate was concentrated and purified on silica gel to afford the desired product.

General procedure for the synthesis of tetrahydropyridine derivates **5m-5o**:



A solution of nitroalkene **2** (0.25 mmol), *p*-nitrophenol (10 mol%) and catalyst **7a** (10 mol%) in CH_2Cl_2 (0.25 mL) was added with aldehyade 1 (0.3 mmol). The result mixture was stirred at room temperature until all the nitroalkene was consumed, then cooled to 0 °C, added with aldehyde **3** (1 mmol), catalyst 8**b** (20 mol%), $PMPNH_2$ (1 mmol) and 4Å MS

(100 mg). The mixture was kept at 0 °C for 48 hours before diluted with CH_2Cl_2, filtered through a short pad of celite. The filtrate was concentrated and purified on silica gel to afford the desired product.



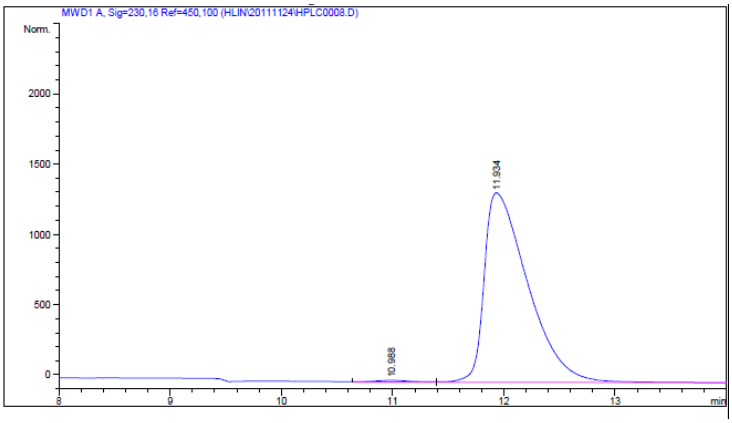
(2*S*,3*R*,4*R*)-2-ethyl-1-(4-methoxyphenyl)-5-methyl-3-nitro-4-phenyl-1,2,3,4-tetrahydropyridine (5a)

Purified by FC (PE:EtOAc = 30:1). Orange solid. The ee was determined by chiral HPLC using a Phenomenex Lux 5u Amylose-2 column (hexane/*i*-PrOH = 90/10); flow rate 1 mL/min; λ = 230 nm; τ_{major} = 12.0 min, τ_{minor} = 11.0 min, 99% ee.

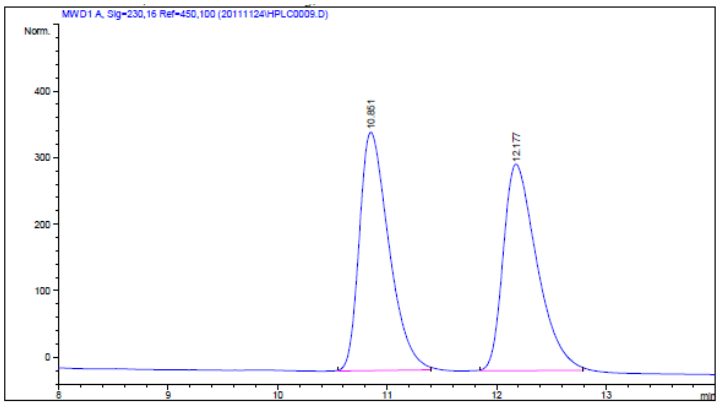
$[\alpha]_D^{15}$ = + 381.7 (c = 1.0, CH_3Cl).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.21-7.31 (m, 5H), 6.98 (d, *J*=8.4 Hz, 2H), 6.86 (d, *J*=8.8 Hz, 2H), 6.35 (s, 1H), 5.09 (t, *J*=4.8 Hz, 1H), 4.04-4.09 (m, 1H), 3.77 (s, 3H), 3.76 (d, *J*=6.4 Hz, 1H), 1.71-1.76 (m, 2H), 1.63 (s, 3H), 1.07 (t, *J*=7.6, Hz, 3H) **^{13}C-NMR ($CDCl_3$, 100 MHz):** δ 154.7, 140.5, 136.3, 129.3, 128.5, 128.2, 127.7, 119.9, 114.5, 105.6, 87.0, 57.9, 55.6, 44.3, 24.3, 18.6, 9.7

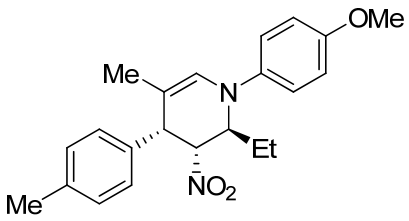
HRMS (APCI) *m/z* calcd for $C_{21}H_{25}N_2O_3$ $[M+H]^+$ 353.1865 , found: 353.1864



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.988	VV	0.3121	272.87451	12.62987	0.7383
2	11.934	VV	0.4114	3.66849e4	1348.49402	99.2617
Totals :				3.69578e4	1361.12389	



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.851	BB	0.2864	6702.11963	358.09979	50.2106
2	12.177	BB	0.3261	6645.90088	310.02689	49.7894
Totals :				1.33480e4	668.12668	

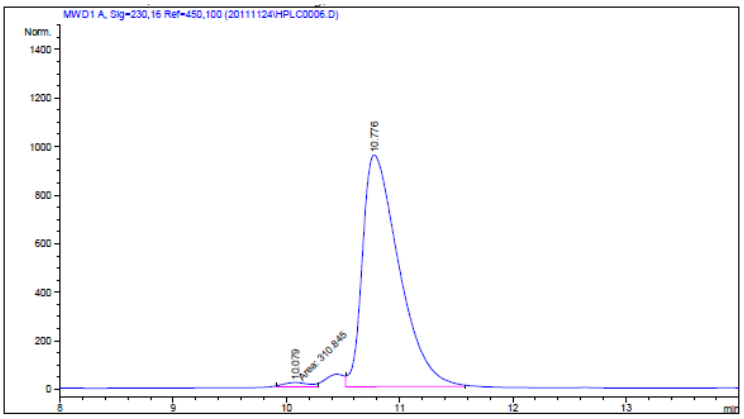


(2*S*,3*R*,4*R*)-2-ethyl-1-(4-methoxyphenyl)-5-methyl-3-nitro-4-(p-tolyl)-1,2,3,4-tetrahydropyridine (5b)

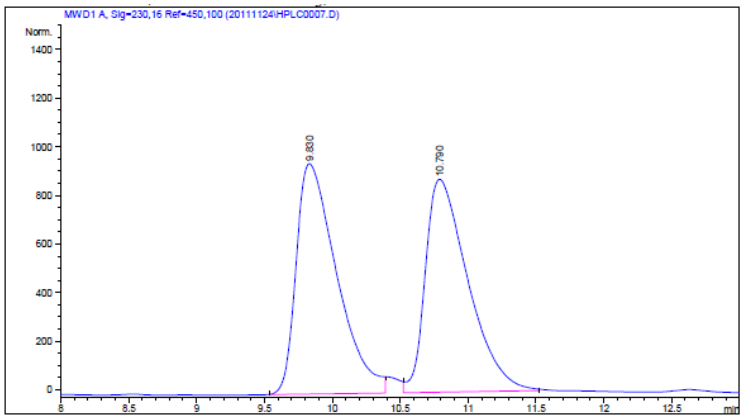
Purified by FC (PE:EtOAc = 30:1). Orange solid. The ee was determined by chiral HPLC using a Phenomenex Lux 5u Amylose-2 column (hexane/*i*-PrOH = 90/10); flow rate 1 mL/min; λ = 230 nm; τ_{major} = 10.8 min, τ_{minor} = 10.1 min, 97% ee. $[\alpha]_D^{15}$ = + 338.7 (c = 1.0, CH_3Cl).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.10-7.12 (m, 4H), 6.99 (d, *J*=8.8 Hz, 2H), 6.87 (d, *J*=8.8 Hz, 2H), 6.35 (s, 1H), 5.09 (t, *J*= 4.8 Hz, 1H), 4.06-4.10 (m, 1H), 3.78 (s, 3H), 3.76 (d, *J*=6.4 Hz, 1H), 2.32 (s, 3H),1.67-1.78 (m, 2H), 1.63 (s, 3H), 1.07 (t, *J*= 7.6 Hz, 3H) **^{13}C-NMR ($CDCl_3$, 100 MHz):** δ 154.7, 140.5, 137.3, 133.1, 129.2, 129.2, 128.0, 119.9, 114.5, 105.8, 87.0, 57.8, 55.5, 44.0, 24.3, 21.1, 18.6, 9.7

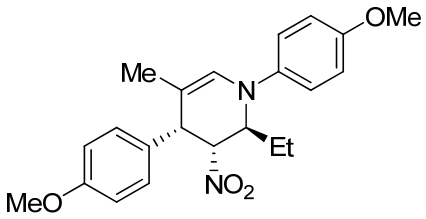
HRMS (APCI) *m/z* calcd for $C_{22}H_{27}N_2O_3$ $[M+H]^+$ 367.2022, found: 367.2023



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.079	MF	0.2759	310.84454	18.78014	1.4337
2	10.776	VB	0.3348	2.13700e4	955.85840	98.5663
Totals :				2.16809e4	974.63854	



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.830	BB	0.3157	1.96615e4	948.97809	50.7105
2	10.790	BB	0.3265	1.91105e4	875.90771	49.2895
Totals :				3.87720e4	1824.88580	

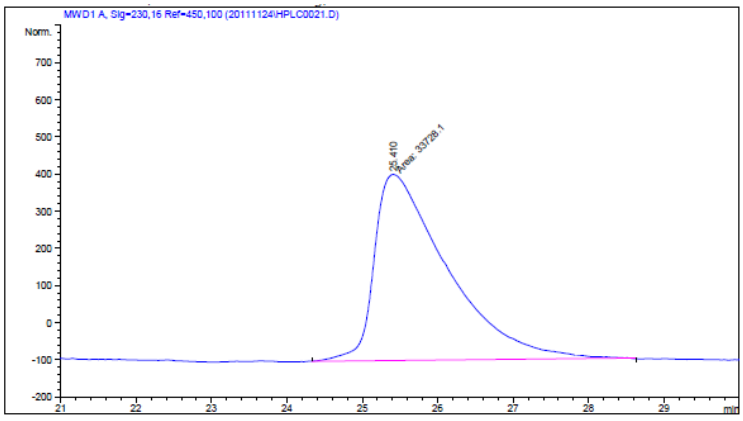


(2*S*,3*R*,4*R*)-2-ethyl-1,4-bis(4-methoxyphenyl)-5-methyl-3-nitro-1,2,3,4-tetrahydropyridine (5c)

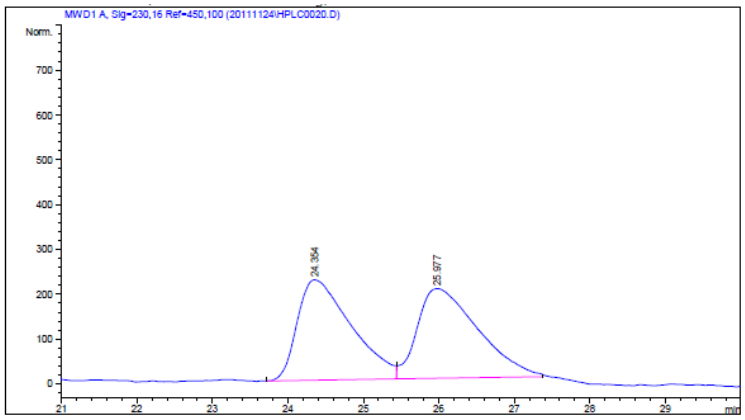
Purified by FC (PE:EtOAc = 30:1). Orange solid. The ee was determined by chiral HPLC using a Phenomenex Lux 5u Amylose-2 column (hexane/*i*-PrOH = 90/10); flow rate 1 mL/min; λ = 230 nm; τ_{major} = 25.4 min, τ_{minor} = 23.9 min, >99% ee. $[\alpha]_D^{15}$ = + 275.2 (c = 1.0, CH_3Cl).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.15 (d, *J*=8.0 Hz, 2H), 6.98 (d, *J*=8.4 Hz, 2H), 6.86 (d, *J*=8.4 Hz, 4H), 6.33 (s, 1H), 5.07 (t, *J*= 4.8 Hz, 1H), 4.04-4.07 (m, 1H), 3.78 (s, 6H), 3.75 (d, *J*=6.8 Hz, 1H), 1.69-1.76 (m, 2H), 1.63 (s, 3H), 1.07 (t, *J*=7.6 Hz, 3H) **^{13}C-NMR ($CDCl_3$, 100 MHz):** δ 159.2, 154.8, 140.6, 130.5, 130.2, 128.2, 120.1, 114.6, 114.0, 106.1, 87.2, 57.9, 55.7, 55.3, 43.7, 29.8, 24.4, 18.7, 9.8

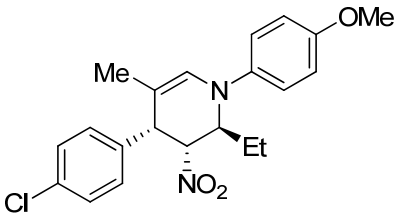
HRMS (APCI) *m/z* calcd for $C_{22}H_{27}N_2O_4$ $[M+H]^+$ 383.1971, found: 383.1972



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	25.410	MM	1.1218	3.37281e4	501.09595	100.0000
Totals :				3.37281e4	501.09595	



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	24.354	PV	0.7022	1.11026e4	224.02725	49.8601
2	25.977	VB	0.7522	1.11649e4	200.34044	50.1399
Totals :				2.22676e4	424.36769	

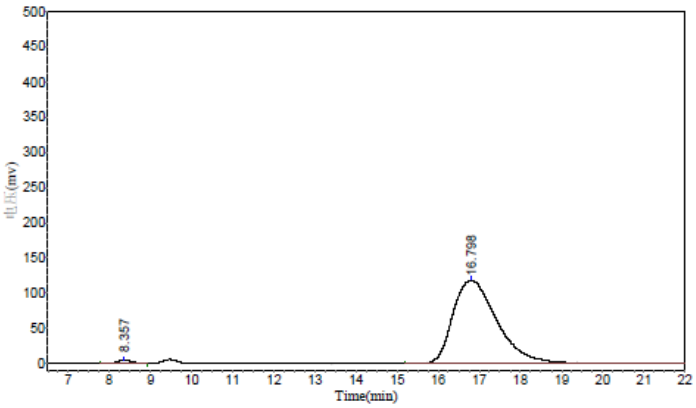


(2*S*,3*R*,4*R*)-4-(4-chlorophenyl)-2-ethyl-1-(4-methoxyphenyl)-5-methyl-3-nitro-1,2,3,4-tetrahydropyridine (5d)

Purified by FC (PE:EtOAc = 30:1). Orange solid. The ee was determined by chiral HPLC using a Daicel Chiracel AS-H column (hexane/*i*-PrOH = 90/10); flow rate 1 mL/min; λ = 230 nm; τ_{major} = 16.8 min, τ_{minor} = 8.4 min, 98% ee. $[\alpha]_D^{15}$ = + 290.8 (c = 1.0, CH_3Cl).

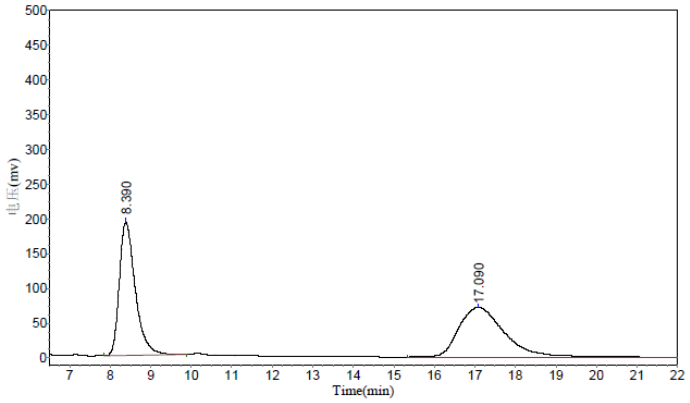
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.30 (d, *J*=8.4 Hz, 2H), 7.17 (d, *J*=8.0 Hz, 2H), 6.98 (d, *J*=8.8 Hz, 2H), 6.86 (d, *J*=8.8 Hz, 2H), 6.35 (s, 1H), 5.07 (t, *J*= 4.8 Hz, 1H), 4.04-4.07 (m, 1H), 3.78 (s, 3H), 3.75 (d, *J*=5.6 Hz, 1H), 1.69-1.76 (m, 2H), 1.61 (s, 3H), 1.07 (t, *J*= 7.6 Hz, 3H) **^{13}C-NMR ($CDCl_3$, 100 MHz):** δ 154.8, 140.3, 134.9, 133.6, 130.7, 128.7, 128.5, 119.9, 114.5, 105.0, 86.8, 57.9, 55.6, 43.7, 24.2, 18.5, 9.7

HRMS (APCI) *m/z* calcd for $C_{21}H_{24}ClN_2O_3$ $[M+H]^+$ 387.1475, found: 387.1482



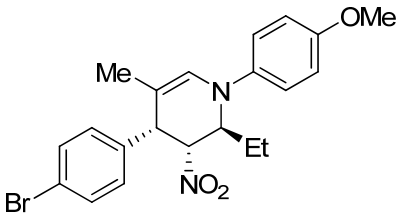
Results

Peak No.	Peak ID	Ret Time	Height	Area	Conc.
1		8.357	4054.716	104914.844	1.1627
2		16.798	118725.109	8918574.000	98.8373
Total			122779.825	9023488.844	100.0000



Results

Peak No.	Peak ID	Ret Time	Height	Area	Conc.
1		8.390	194554.719	5541365.500	50.2083
2		17.090	71155.078	5495385.500	49.7917
Total			265709.797	11036751.000	100.0000

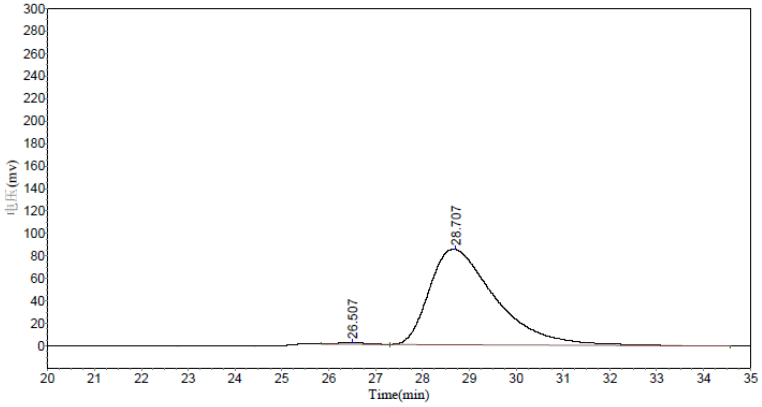


(2*S*,3*R*,4*R*)-4-(4-bromophenyl)-2-ethyl-1-(4-methoxyphenyl)-5-methyl-3-nitro-1,2,3,4-tetrahydropyridine (5e)

Purified by FC (PE:EA=30:1). Orange solid. The ee was determined by chiral HPLC using a Daicel Chiracel AS-H column (hexane/*i*-PrOH = 99/1); flow rate 0.5 mL/min; λ = 230 nm; τ_{major} = 28.7 min, τ_{minor} = 26.5 min, 96% ee. $[\alpha]_D^{15}$ = + 129.1 (c = 0.5, CH_3Cl).

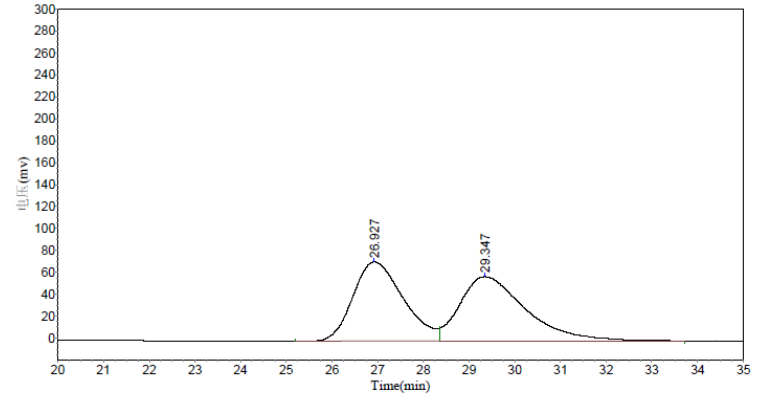
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.30 (d, *J*=7.6 Hz, 2H), 7.17 (d, *J*=7.6 Hz, 2H), 6.97 (d, *J*=8.0 Hz, 2H), 6.86 (d, *J*=8.4 Hz, 2H), 6.35 (s, 1H), 5.07 (t, *J*= 4.8 Hz, 1H), 4.04-4.07 (m, 1H), 3.78 (s, 3H), 3.75 (d, *J*=6.4 Hz, 1H), 1.65-1.78 (m, 2H), 1.61 (s, 3H), 1.07 (t, *J*= 7.6 Hz, 3H) **^{13}C-NMR ($CDCl_3$, 100 MHz):** δ 154.8, 140.3, 134.9, 133.6, 130.7, 128.7, 128.5, 120.0, 114.5, 105.0, 86.8, 57.8, 55.6, 43.7, 29.7, 24.2, 18.5, 9.7

HRMS (APCI) *m/z* calcd for $C_{21}H_{24}BrN_2O_3$ $[M+H]^+$ 431.0970, found: 431.0972



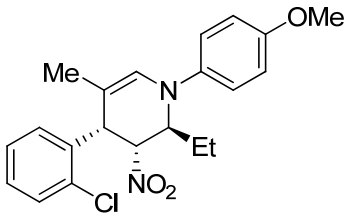
Results

Peak No.	Peak ID	Ret Time	Height	Area	Conc.
1		26.507	2899.361	190897.063	2.1828
2		28.707	85969.539	8554718.000	97.8172
Total			88868.900	8745615.063	100.0000



Results

Peak No.	Peak ID	Ret Time	Height	Area	Conc.
1		26.927	72188.094	5521151.000	48.5967
2		29.347	58765.578	5840011.500	51.4033
Total			130953.672	11361162.500	100.0000



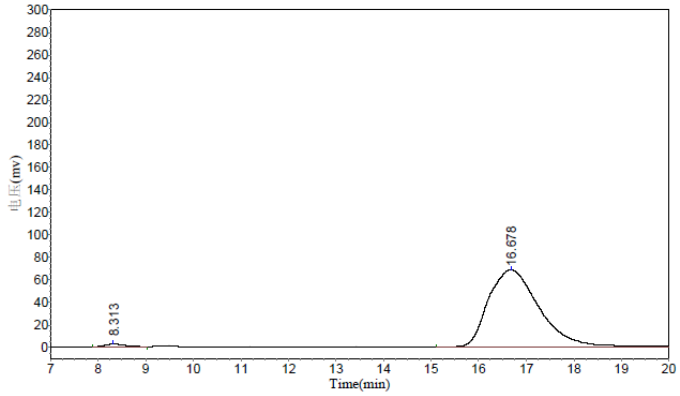
(2*S*,3*R*,4*R*)-4-(2-chlorophenyl)-2-ethyl-1-(4-methoxyphenyl)-5-methyl-3-nitro-1,2,3,4-tetrahydropyridine (5f)

Purified by FC (PE:EA=30:1). Orange solid. The ee was determined by chiral HPLC using a Daicel Chiracel AS-H column (hexane/*i*-PrOH = 90/10); flow rate 1 mL/min; λ = 230 nm; τ_{major} = 16.7 min, τ_{minor} = 8.3 min, 97% ee.

$[\alpha]_D^{15}$ = + 590.7 (c = 1.0, CH_3Cl).

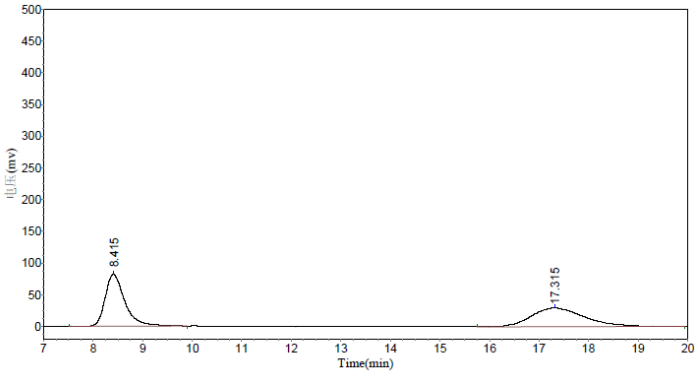
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.49 (d, *J*=7.6 Hz, 1H), 7.18 (d, *J*=8.8 Hz, 2H), 7.06 (d, *J*=6.8 Hz, 1H), 6.84 (d, *J*=8.4 Hz, 2H), 6.76 (d, *J*=8.0Hz, 2H), 6.33 (s, 1H), 5.28 (d, *J*=4.8 Hz, 1H), 4.19 (d, *J*=5.2 Hz, 1H), 4.02-4.07 (m, 1H), 3.68 (s, 3H), 1.81-1.89 (m, 1H), 1.69-1.76(m, 1H), 1.58 (s, 3H), 1.13 (t, *J*= 7.6 Hz, 3H) **^{13}C-NMR ($CDCl_3$, 100 MHz):** δ 154.1, 140.7, 134.6, 132.7, 131.6, 129.2, 127.5, 127.3, 125.7, 118.0, 114.5, 106.0, 83.7, 60.4, 55.6, 41.9, 25.3, 18.4, 10.7,

HRMS (APCI) *m/z* calcd for $C_{21}H_{24}ClN_2O_3$ $[M+H]^+$ 387.1475, found: 387.1477



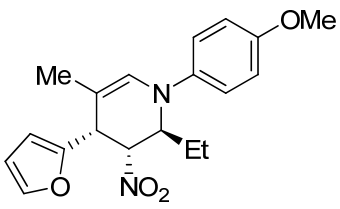
Results

Peak No.	Peak ID	Ret Time	Height	Area	Conc.
1		8.313	2729.280	78489.398	1.4934
2		16.678	68672.453	5177363.500	98.5066
Total			71401.733	5255852.898	100.0000



Results

Peak No.	Peak ID	Ret Time	Height	Area	Conc.
1		8.415	81662.250	2288705.000	51.0535
2		17.315	29417.785	2194249.500	48.9465
Total			111080.035	4482954.500	100.0000

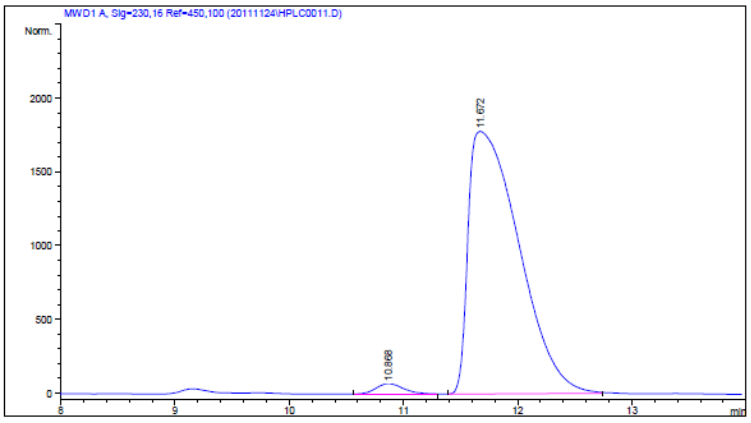


(2*S*,3*R*,4*R*)-2-ethyl-4-(furan-2-yl)-1-(4-methoxyphenyl)-5-methyl-3-nitro-1,2,3,4-tetrahydropyridine (5g)

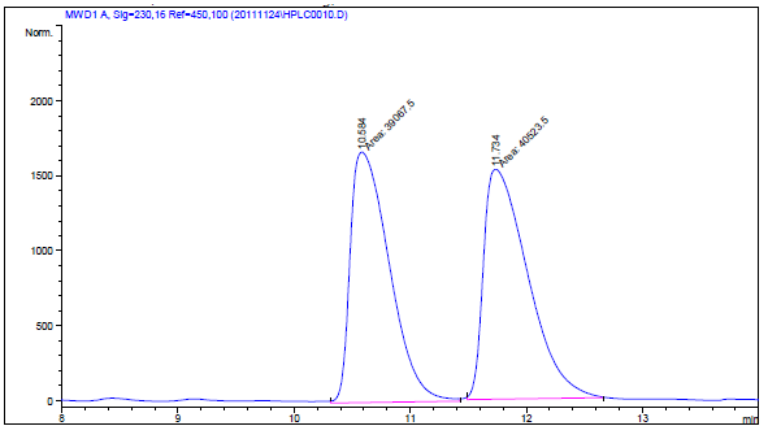
Purified by FC (PE:EtOAc = 30:1). Orange solid. The ee was determined by chiral HPLC using a Phenomenex Lux 5u Amylose-2 column (hexane/*i*-PrOH = 90/10); flow rate 1 mL/min; λ = 230 nm; τ_{major} = 11.7 min, τ_{minor} = 10.9 min, 96% ee. $[\alpha]_D^{15}$ = + 145.1 (c = 0.5, CH_3Cl).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.36 (s, 1H), 6.97 (d, *J*=8.8 Hz, 2H), 6.85 (d, *J*=8.8 Hz, 2H), 6.34 (s, 1H), 6.24 (d, *J*=10.4 Hz, 2H), 5.11 (t, *J*= 4.8 Hz, 1H), 4.10-4.14 (m, 1H), 3.95 (d, *J*=5.2 Hz, 1H), 3.77 (s, 3H), 1.71-1.78 (m, 2H), 1.68 (s, 3H), 1.06 (t, *J*= 7.6 Hz, 3H) **^{13}C-NMR ($CDCl_3$, 100 MHz):** δ 155.0, 150.4, 142.2, 140.3, 127.9, 120.5, 114.5, 110.6, 109.4, 103.6, 84.5, 58.3, 55.5, 38.4, 24.2, 18.3, 9.5

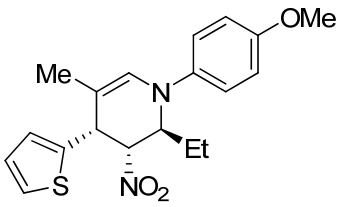
HRMS (APCI) *m/z* calcd for $C_{19}H_{23}N_2O_4$ $[M+H]^+$ 343.1658, found: 343.1668



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.868	BB	0.2615	1206.62231	71.29272	2.1502
2	11.672	PB	0.4158	5.49096e4	1780.40613	97.8498
Totals :				5.61162e4	1851.69884	



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.584	MM	0.3896	3.90675e4	1671.11499	49.0853
2	11.734	MM	0.4405	4.05235e4	1533.09668	50.9147
Totals :				7.95910e4	3204.21167	



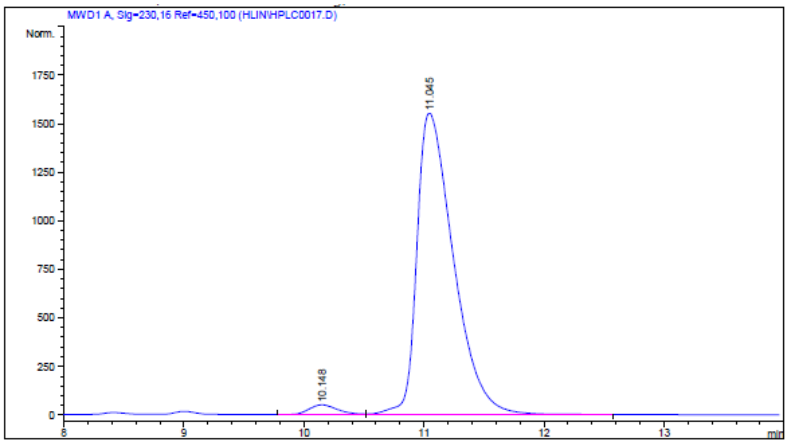
(2*S*,3*R*,4*R*)-2-ethyl-1-(4-methoxyphenyl)-5-methyl-3-nitro-4-(thiophen-2-yl)-1,2,3,4-tetrahydropyridine (5h)

Purified by FC (PE:EtOAc = 30:1). Orange solid. The ee was determined by chiral HPLC using a Phenomenex Lux 5u Amylose-2 column (hexane/*i*-PrOH = 90/10); flow rate 1 mL/min; λ = 230 nm; τ_{major} = 11.0 min, τ_{minor} = 10.1 min, 94% ee.

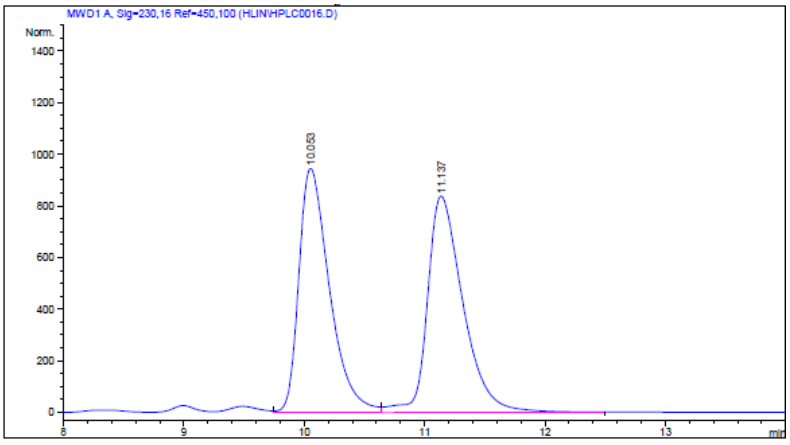
$[\alpha]_D^{15}$ = + 159.3 (c = 1.0, CH_3Cl).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.24 (d, *J*=8.0 Hz, 2H), 7.03 (d, *J*=7.6 Hz, 2H), 6.88-6.96 (m, 2H), 6.86 (d, *J*=8.0 Hz, 2H), 6.20 (s, 1H), , 5.02 (t, *J*= 4.8 Hz, 1H), 4.14 (d, *J*=5.2 Hz, 1H), 4.11 (d, *J*=4.8 Hz, 1H), 3.78 (s, 3H), 1.68 (s, 3H), 1.60-1.68 (m, 2H), 0.99 (t, *J*=6.8 Hz, 3H) **^{13}C-NMR ($CDCl_3$, 100 MHz):** δ 155.5, 140.0, 139.9, 129.1, 127.5, 127.0, 125.3, 122.0, 114.5, 105.1, 86.4, 56.3, 55.5, 40.7, 23.2, 18.5, 8.8

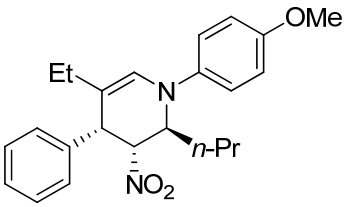
HRMS (ESI) *m/z* calcd for $C_{19}H_{23}N_2O_3S$ $[M+H]^+$ 359.1429, found: 359.1416



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.148	VV	0.2725	954.40869	52.90302	2.7876
2	11.045	VV	0.3256	3.32834e4	1555.69836	97.2124
Totals :				3.42378e4	1608.60138	



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.053	VV	0.2679	1.67136e4	946.91968	49.2302
2	11.137	VB	0.3099	1.72363e4	838.14673	50.7698
Totals :				3.39498e4	1785.06641	

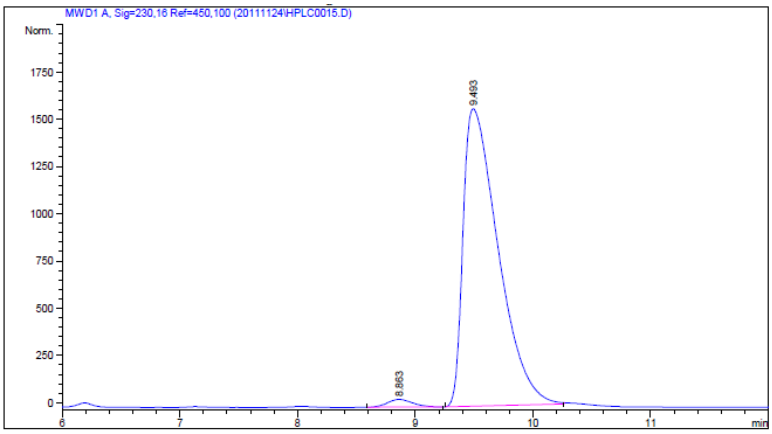


(2*S*,3*R*,4*R*)-5-ethyl-1-(4-methoxyphenyl)-3-nitro-4-phenyl-2-propyl-1,2,3,4-tetrahydropyridine (5i)

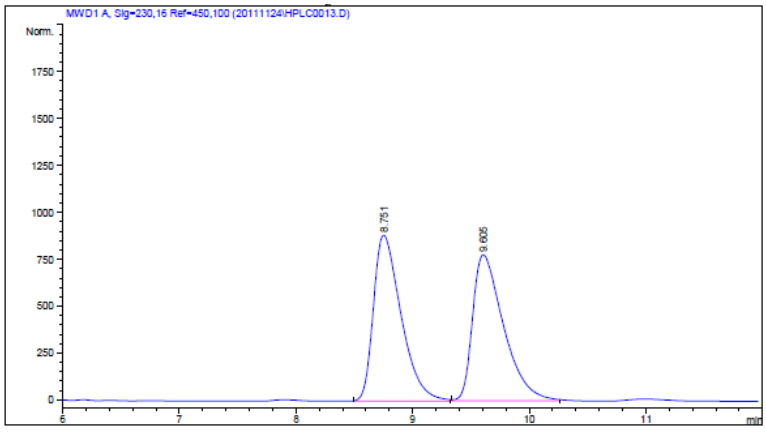
Purified by FC (PE:EtOAc = 100:1). Orange solid. The ee was determined by chiral HPLC using a Phenomenex Lux 5u Amylose-2 column (hexane/*i*-PrOH = 90/10); flow rate 1 mL/min; λ = 230 nm; τ_{major} = 9.5 min, τ_{minor} = 8.9 min, 96% ee. $[\alpha]_D^{15}$ = + 345.9 (c = 1.0, CH_3Cl).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.21-7.31 (m, 5H), 6.97 (d, *J*=8.0 Hz, 2H), 6.85 (d, *J*=8.4 Hz, 2H), 6.37 (s, 1H), 5.06 (t, *J*= 4.8 Hz, 1H), 4.11-4.16 (m, 1H), 3.87 (d, *J*=5.2 Hz, 1H), 3.77 (s, 3H), 1.95-2.07 (m, 2H), 1.60-1.71 (m, 2H), 1.52-1.60 (m, 2H), 0.92-0.98 (m, 6H) **^{13}C-NMR ($CDCl_3$, 100 MHz):** δ 154.7, 140.6, 136.4, 129.4, 128.4, 127.7, 126.9, 119.7, 114.5, 111.7, 87.4, 57.0, 55.6, 42.5, 33.6, 25.5, 18.6, 14.1, 13.2

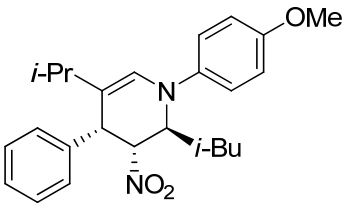
HRMS (APCI) *m/z* calcd for $C_{23}H_{29}N_2O_3$ $[M+H]^+$ 381.2178, found: 381.2185



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.863	BP	0.2302	603.71576	40.43468	1.8200
2	9.493	BB	0.3194	3.25675e4	1574.13989	98.1800
Totals :				3.31712e4	1614.57457	



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.751	BB	0.2503	1.45769e4	884.42712	50.3976
2	9.605	BB	0.2791	1.43469e4	777.97723	49.6024
Totals :				2.89238e4	1662.40436	

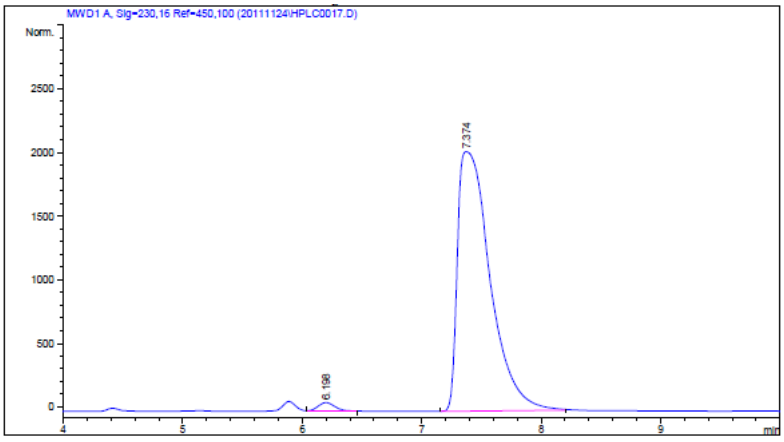


(2*S*,3*R*,4*R*)-2-isobutyl-5-isopropyl-1-(4-methoxyphenyl)-3-nitro-4-phenyl-1,2,3,4-tetrahydropyridine (5j)

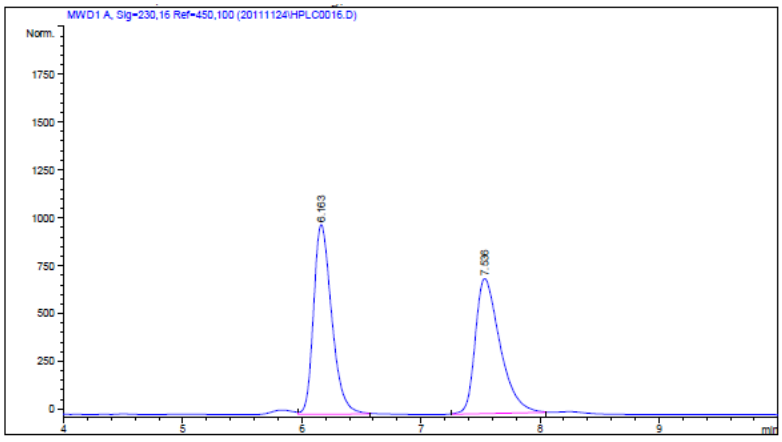
Purified by FC (PE:EtOAc = 200:1). Orange solid. The ee was determined by chiral HPLC using a Phenomenex Lux 5u Amylose-2 column (hexane/*i*-PrOH = 90/10); flow rate 1 mL/min; λ = 230 nm; τ_{major} = 7.4 min, τ_{minor} = 6.4 min, 96% ee. $[\alpha]_D^{15}$ = + 415.5 (c = 1.0, CH_3Cl).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.21-7.30 (m, 5H), 6.93 (d, *J*=7.6 Hz, 2H), 6.85 (d, *J*=8.0 Hz, 2H), 6.38 (s, 1H), 5.00-5.04 (m, 1H), 4.19-4.22 (m, 1H), 3.89 (d, *J*=5.6 Hz, 1H), 3.76 (s, 3H), 2.23-2.26 (m, 1H), 1.81-1.84 (m, 1H), 1.67-1.73 (m, 1H), 1.56-1.59 (m, 1H), 0.89-1.17 (m, 12H) **^{13}C-NMR ($CDCl_3$, 100 MHz):** δ 154.3, 141.0, 136.6, 129.4, 128.5, 127.6, 124.8, 118.6, 116.6, 114.6, 87.7, 56.4, 55.6, 41.8, 40.9, 28.8, 24.5, 23.3, 22.5, 20.0

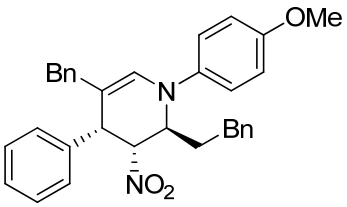
HRMS (APCI) *m/z* calcd for $C_{25}H_{33}N_2O_3$ $[M+H]^+$ 409.2491, found: 409.2489



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.198	VB	0.1571	702.90070	68.83579	1.7858
2	7.374	PB	0.2914	3.86584e4	2037.26709	98.2142
Totals :				3.93613e4	2106.10288	



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.163	VB	0.1634	1.04913e4	991.61261	50.7101
2	7.536	BB	0.2184	1.01975e4	706.48645	49.2899
Totals :				2.06888e4	1698.09906	

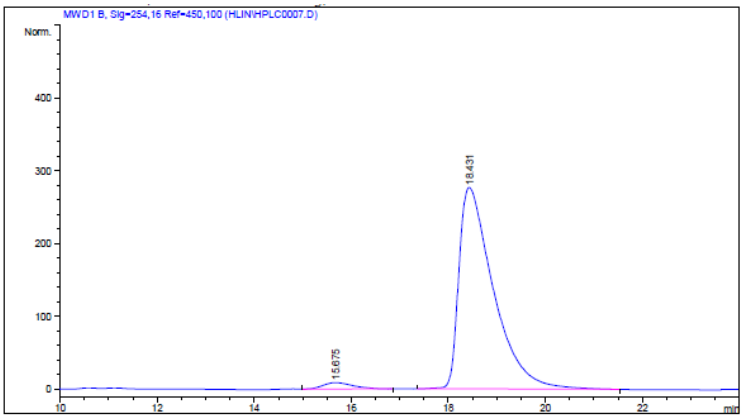


(2*S*,3*R*,4*R*)-5-benzyl-1-(4-methoxyphenyl)-3-nitro-2-phenethyl-4-phenyl-1,2,3,4-tetrahydropyridine (5k)

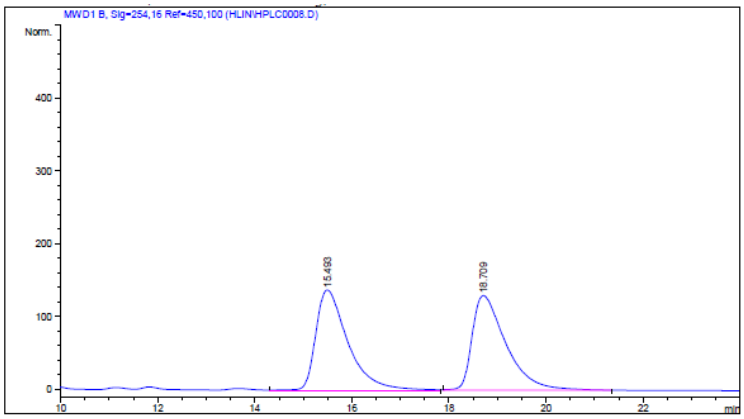
Purified by FC (PE:EtOAc = 20:1). Orange solid. The ee was determined by chiral HPLC using a Phenomenex Lux 5u Amylose-2 column (hexane/*i*-PrOH = 90/10); flow rate 1 mL/min; λ = 230 nm; τ_{major} = 18.4 min, τ_{minor} = 15.7 min, 94% ee. $[\alpha]_D^{15}$ = + 173.7 (c = 1.0, CH_3Cl).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.05-7.28 (m, 13H), 6.82-6.95 (m, 6H), 6.58 (s, 1H), 4.95-5.00 (m, 1H), 4.15-4.22 (m, 1H), 3.75 (s, 3H), 3.47 (d, *J*=5.6 Hz, 1H), 3.38 (d, *J*=14.4 Hz, 1H), 3.22 (d, *J*=14.4 Hz, 1H), 2.76 (t, *J*=7.2Hz, 2H), 1.81-1.95 (m, 2H) **^{13}C-NMR ($CDCl_3$, 100 MHz):** δ 154.8, 140.7, 140.2, 140.0, 135.6, 129.6, 128.6, 128.5, 128.4, 128.2, 127.7, 126.3, 126.1, 119.3, 114.6, 110.9, 87.1, 57.3, 55.6, 41.6, 39.1, 33.6, 31.8

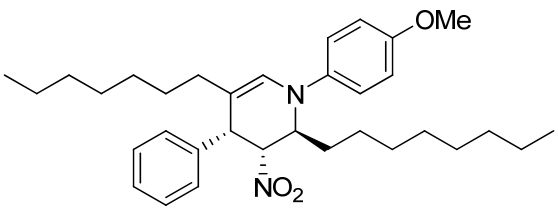
HRMS (APCI) *m/z* calcd for $C_{33}H_{33}N_2O_3$ $[M+H]^+$ 505.2491, found: 505.2494



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.675	VB	0.6354	388.48734	8.89664	2.7601
2	18.431	BB	0.7370	1.36866e4	276.71490	97.2399
Totals :				1.40751e4	285.61154	



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.493	VB	0.6938	6349.24072	137.74077	50.1580
2	18.709	BB	0.7244	6309.23340	129.96367	49.8420
Totals :				1.26585e4	267.70444	

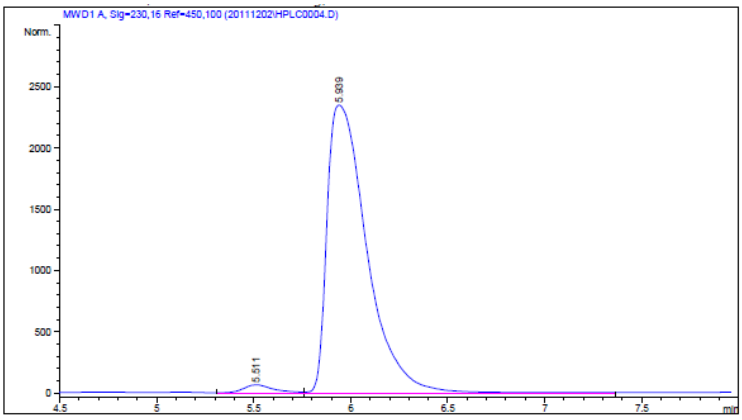


(2*S*,3*R*,4*R*)-5-heptyl-1-(4-methoxyphenyl)-3-nitro-2-octyl-4-phenyl-1,2,3,4-tetrahydropyridine (5l)

Purified by FC (PE:EtOAc = 20:1). Orange solid. The ee was determined by chiral HPLC using a Phenomenex Lux 5u Amylose-2 column (hexane/*i*-PrOH = 90/10); flow rate 1 mL/min; λ = 230 nm; τ_{major} = 5.9 min, τ_{minor} = 5.5 min, 96% ee. $[\alpha]_D^{15}$ = + 263.4 (c = 1.0, CH_3Cl).

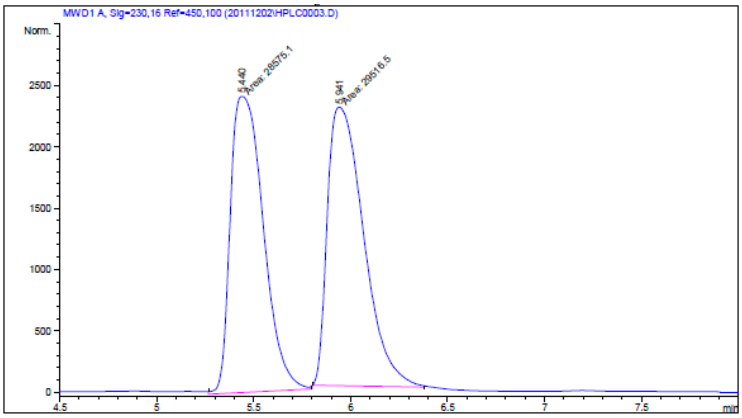
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.24-7.33 (m, 5H), 6.99 (d, *J*=8.4 Hz, 2H), 6.88 (d, *J*=8.8 Hz, 2H), 6.40 (s, 1H), 5.07 (t, *J*= 1.2 Hz, 1H), 4.13-4.19 (m, 1H), 3.86 (d, *J*=5.6 Hz, 1H), 3.79 (s, 3H), 1.95-2.09 (m, 2H), 1.62-1.82 (m, 2H), 1.45-1.57 (m, 2H), 1.15-1.42 (m, 20H), 0.86-0.94 (m, 6H) **^{13}C-NMR ($CDCl_3$, 100 MHz):** δ 154.7, 140.7, 136.5, 129.5, 128.6, 127.8, 127.7, 119.7, 114.7, 110.2, 87.5, 57.4, 55.7, 42.6, 32.5, 31.9, 31.7, 29.7, 29.5, 29.3, 29.2, 28.3, 25.4, 22.7, 14.2

HRMS (APCI) *m/z* calcd for $C_{33}H_{49}N_2O_3$ $[M+H]^+$ 521.3743, found: 521.3737



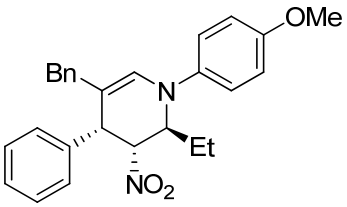
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.511	VV	0.1621	741.54010	67.51435	2.1612
2	5.939	VV	0.2207	3.35703e4	2349.82397	97.8388

Totals : 3.43118e4 2417.33833



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.440	MM	0.1973	2.85751e4	2414.32471	49.1897
2	5.941	MM	0.2166	2.95165e4	2271.05347	50.8103

Totals : 5.80916e4 4685.37817

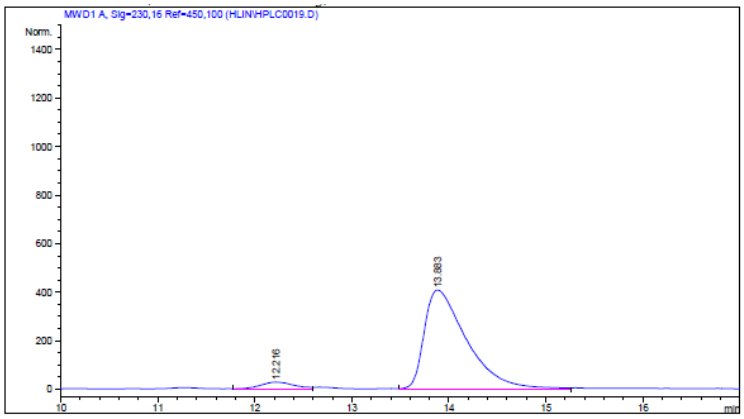


(2*S*,3*R*,4*R*)-5-benzyl-2-ethyl-1-(4-methoxyphenyl)-3-nitro-4-phenyl-1,2,3,4-tetrahydropyridine (5m)

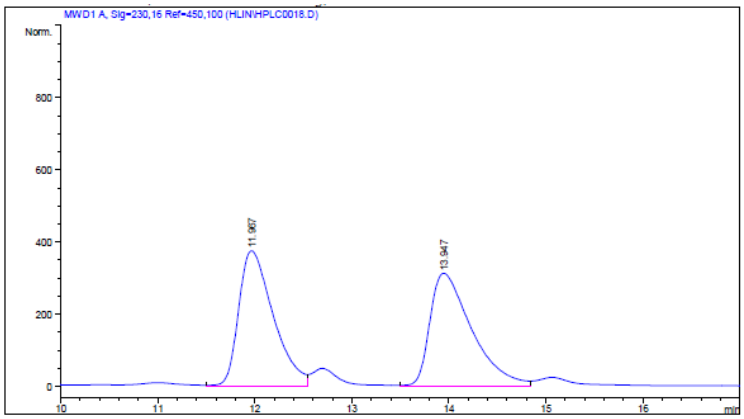
Purified by FC (PE:EtOAc = 30:1). Orange solid. The ee was determined by chiral HPLC using a Phenomenex Lux 5u Amylose-2 column (hexane/*i*-PrOH = 90/10); flow rate 1 mL/min; λ = 230 nm; τ_{major} = 13.9 min, τ_{minor} = 12.2 min, 90% ee. $[\alpha]_D^{15}$ = + 281.8 (c = 1.17, CH_3Cl).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.16-7.30 (m, 8H), 7.00 (d, *J*=8.0 Hz, 2H), 6.93 (d, *J*=6.4 Hz, 2H), 6.87 (d, *J*=8.0 Hz, 2H), 6.52 (s, 1H), 4.99 (t, *J*= 4.8 Hz, 1H), 4.03-4.09 (m, 1H), 3.78 (s, 3H), 3.54 (d, *J*=5.2 Hz, 1H), 3.37 (d, *J*=14.4 Hz, 1H), 3.22 (d, *J*=14.4 Hz, 1H), 1.56-1.68 (m, 2H), 1.03 (t, *J*= 6.8Hz, 3H) **^{13}C-NMR ($CDCl_3$, 100 MHz):** δ 154.8, 140.3, 140.0, 135.9, 129.6, 128.8, 128.5, 128.2, 127.8, 126.1, 119.8, 114.5, 110.0, 86.9, 58.3, 55.6, 41.8, 39.1, 24.6, 9.8

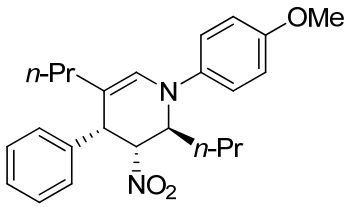
HRMS (ESI) *m/z* calcd for $C_{27}H_{29}N_2O_3$ $[M+H]^+$ 428.2178, found: 429.2177



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.216	VV	0.3345	655.06610	27.44516	5.0482
2	13.883	VV	0.4509	1.23213e4	407.31335	94.9518
Totals :				1.29763e4	434.75852	



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.967	VV	0.3762	9246.95898	374.37997	49.9404
2	13.947	VV	0.4470	9269.04785	311.61481	50.0596
Totals :				1.85160e4	685.99478	

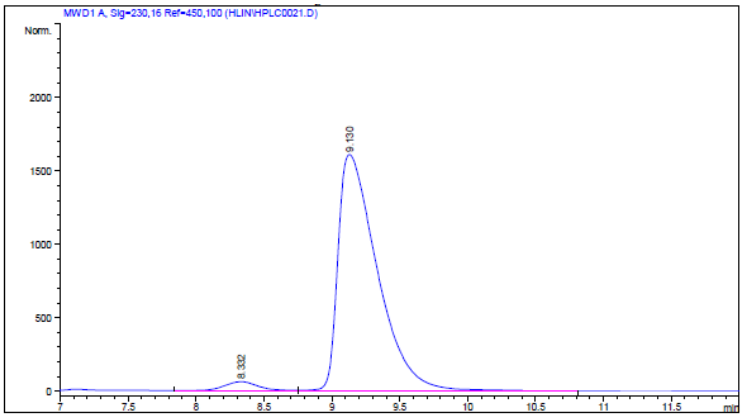


(2*S*,3*R*,4*R*)-1-(4-methoxyphenyl)-3-nitro-4-phenyl-2,5-dipropyl-1,2,3,4-tetrahydropyridine (5n)

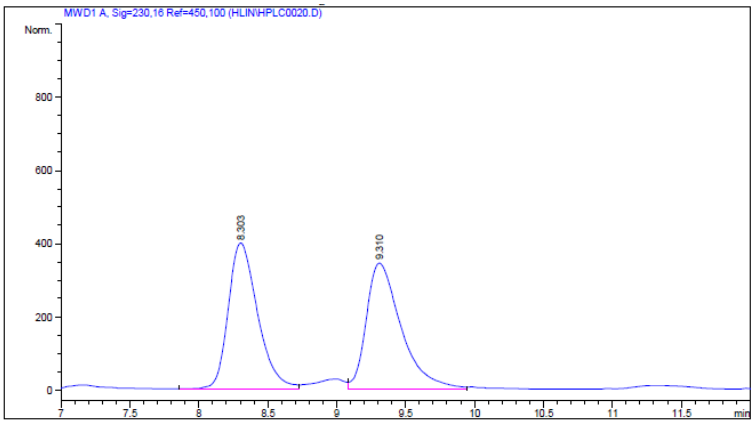
Purified by FC (PE:EtOAc = 30:1). Orange solid. The ee was determined by chiral HPLC using a Phenomenex Lux 5u Amylose-2 column (hexane/*i*-PrOH = 90/10); flow rate 1 mL/min; λ = 230 nm; τ_{major} = 9.1 min, τ_{minor} = 8.3 min, 94% ee. $[\alpha]_D^{15}$ = + 375.1 (c = 1.0, CH_3Cl).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.24-7.33 (m, 5H), 6.97 (d, *J*=8.0 Hz, 2H), 6.85 (d, *J*=8.0 Hz, 2H), 6.38 (s, 1H), 5.05 (t, *J*= 4.8 Hz, 1H), 4.11-4.19 (m, 1H), 3.83 (d, *J*=6.4 Hz, 1H), 3.76 (s, 3H), 2.02-2.10 (m, 1H), 1.88-1.95 (m, 1H), 1.60-1.78 (m, 2H), 1.48-1.58 (m, 2H), 1.17-1.41 (m, 2H), 0.98 (t, *J*= 6.4Hz, 3H), 0.82 (t, *J*= 6.4Hz, 3H) **^{13}C-NMR ($CDCl_3$, 100 MHz):** δ 154.5, 140.5, 136.3, 129.4, 128.4, 127.6, 127.6, 119.5, 114.5, 109.7, 87.3, 57.1, 55.5, 42.3, 34.5, 33.8, 21.3, 18.7, 14.1, 13.6

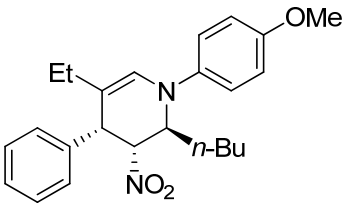
HRMS (ESI) *m/z* calcd for $C_{24}H_{31}N_2O_3$ $[M+H]^+$ 395.2335, found: 395.2320



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.332	VV	0.2624	1038.67151	61.07146	3.1313
2	9.130	VB	0.3032	3.21319e4	1607.57861	96.8687
Totals :				3.31706e4	1668.65008	



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.303	VV	0.2286	5996.38428	400.69403	49.5138
2	9.310	VV	0.2663	6114.13818	345.78717	50.4862
Totals :				1.21105e4	746.48120	

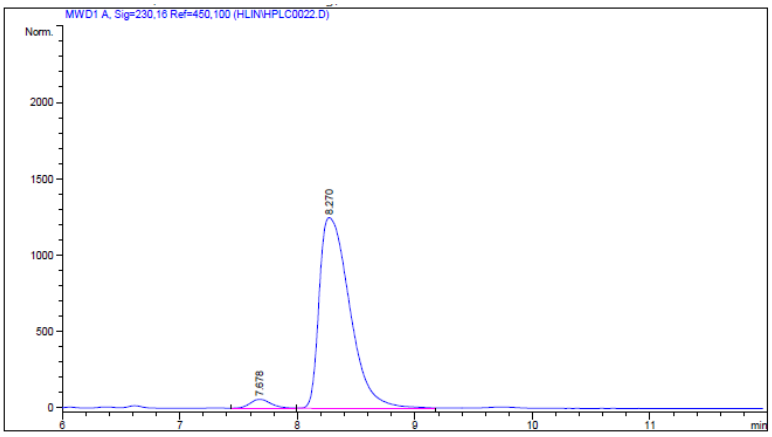


(2S,3R,4R)-2-butyl-5-ethyl-1-(4-methoxyphenyl)-3-nitro-4-phenyl-1,2,3,4-tetrahydropyridine (5o)

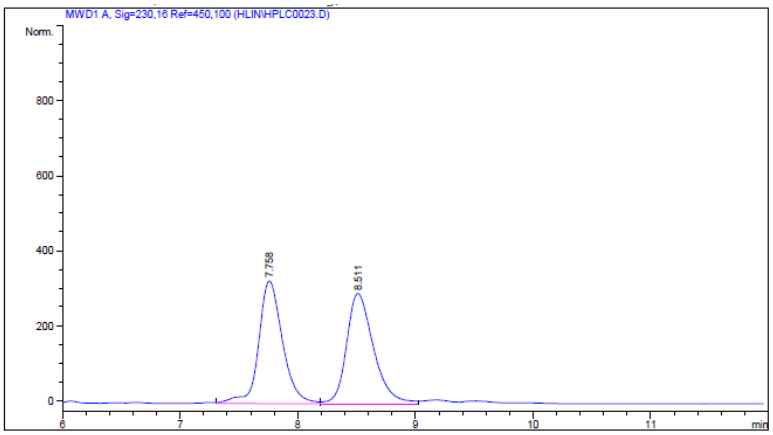
Purified by FC (PE:EtOAc = 50:1). Orange solid. The ee was determined by chiral HPLC using a Phenomenex Lux 5u Amylose-2 column (hexane/*i*-PrOH = 90/10); flow rate 1 mL/min; λ = 230 nm; τ_{major} = 8.3 min, τ_{minor} = 7.7 min, 93% ee. $[\alpha]_D^{15}$ = + 318.3 (c = 1.0, CH_3Cl).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.22-7.30 (m, 5H), 6.97 (d, *J*=7.6 Hz, 2H), 6.86 (d, *J*=7.6 Hz, 2H), 6.37 (s, 1H), 5.08 (t, *J*= 4.8 Hz, 1H), 4.11-4.17 (m, 1H), 3.87 (d, *J*=4.8 Hz, 1H), 3.77 (s, 3H), 1.91-2.10 (m, 2H), 1.56-1.77 (m, 2H), 1.28-1.51 (m,4H), 0.89-0.96 (m, 6H) **^{13}C-NMR ($CDCl_3$, 100 MHz):** δ 154.6, 140.5, 136.4, 129.3, 128.4, 127.7, 126.9, 119.7, 114.5, 111.7, 87.3, 57.0, 55.5, 42.5, 31.0, 27.3, 25.5, 22.7, 13.9, 13.2

HRMS (ESI) *m/z* calcd for $C_{24}H_{31}N_2O_3$ $[M+H]^+$ 395.2335, found: 395.2331

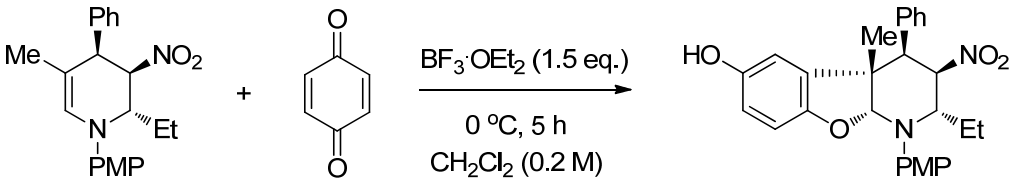


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.678	VV	0.1960	770.26239	59.92337	3.2984
2	8.270	VV	0.2828	2.25827e4	1249.98364	96.7016
Totals :				2.33529e4	1309.90701	



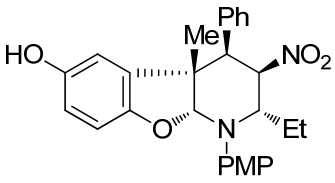
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.758	VV	0.2130	4639.56006	327.95761	49.7442
2	8.511	VV	0.2437	4687.27930	294.45123	50.2558
Totals :				9326.83936	622.40884	

Procedure for the synthesis of pyridine derivates 10:



5a **9** 5 eq. **10** 61% yield >99:1 dr

A solution of **5a** (0.1 mmol) in CH_2Cl_2 (0.5 mL) was cooled to 0 °C, then added with benzoquinone (0.5 mmol) and BF_3·OEt (0.15 mmol). The result mixture was stirred at 0 °C for 5 hours before quenched with $NaHCO_3$ (sat. aq.), extracted with CH_2Cl_2, dried over Na_2SO_4, filtered and concentrated, purified on silica gel to afford the desired product.



(2S,3R,4R,4aS,9aR)-2-ethyl-1-(4-methoxyphenyl)-4a-methyl-3-nitro-4-phenyl-1,2,3,4,4a,9a-hexahydrobenzofuro[2,3-b]pyridin-6-ol (10)

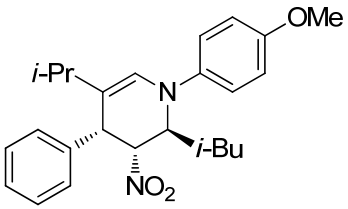
Purified by FC (PE:EtOAc = 8:1). Orange solid. $[\alpha]_D^{25}$ = -247.98 (c = 1.0, CH_3Cl).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.31-7.33 (m, 7H), 6.95 (d, *J*=9.2 Hz, 2H), 6.82 (d, *J*=2.4 Hz, 1H), 6.89-6.75 (m, 2H), 4.77 (s, 1H), 4.61-4.65 (m, 1H), 4.50-4.55 (m, 1H), 3.84 (s, 3H), 3.78 (d, *J*=8.8 Hz, 1H), 1.41-1.55 (m, 1H), 1.26 (s, 3H), 0.56 (t, *J*=7.8 Hz, 3H) **^{13}C-NMR ($CDCl_3$, 100 MHz):** δ 155.1, 151.4, 150.1, 140.5, 134.3, 130.6, 128.8, 128.3, 121.0, 116.4, 114.8, 110.1, 109.7, 100.7, 87.8, 55.6, 54.8, 53.0, 49.1, 29.7, 27.7, 25.7, 9.4

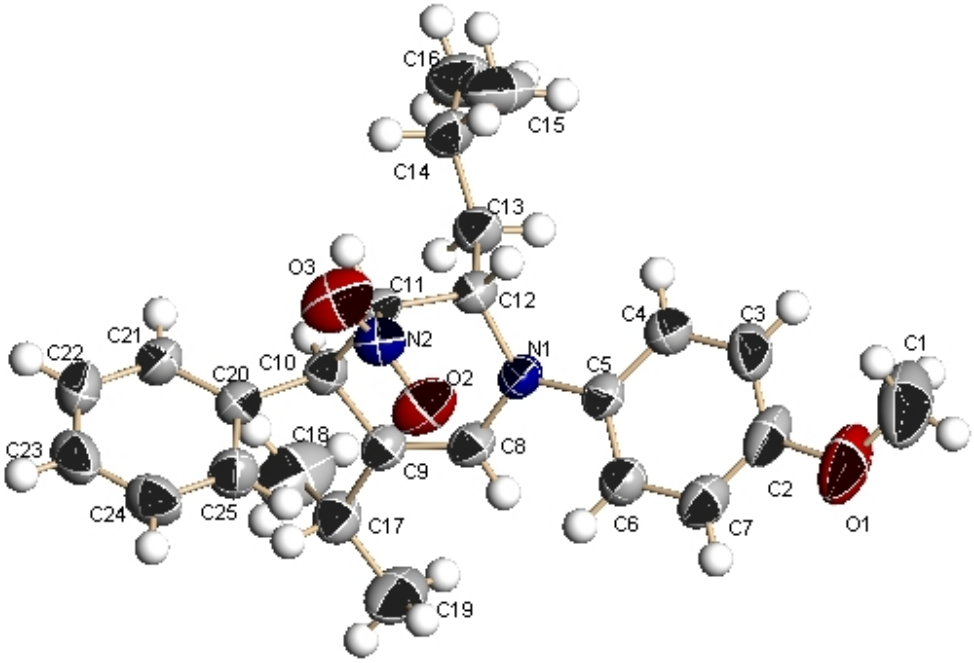
HRMS (EI) *m/z* calcd for $C_{27}H_{28}N_2O_5$ $[M]^+$ 460.1998 , found: 460.2000.

X-ray crystal structure of compound 5j

The absolute configurations of all synthetic tetrahydropyridines **5a-o** were assigned based on the known stereochemistry of Michael addition in the first step together with the determination of relative configuration of the tetrahydropyridine product **5j** through X-ray crystallography.

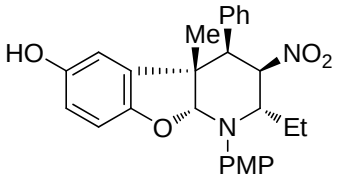


5j

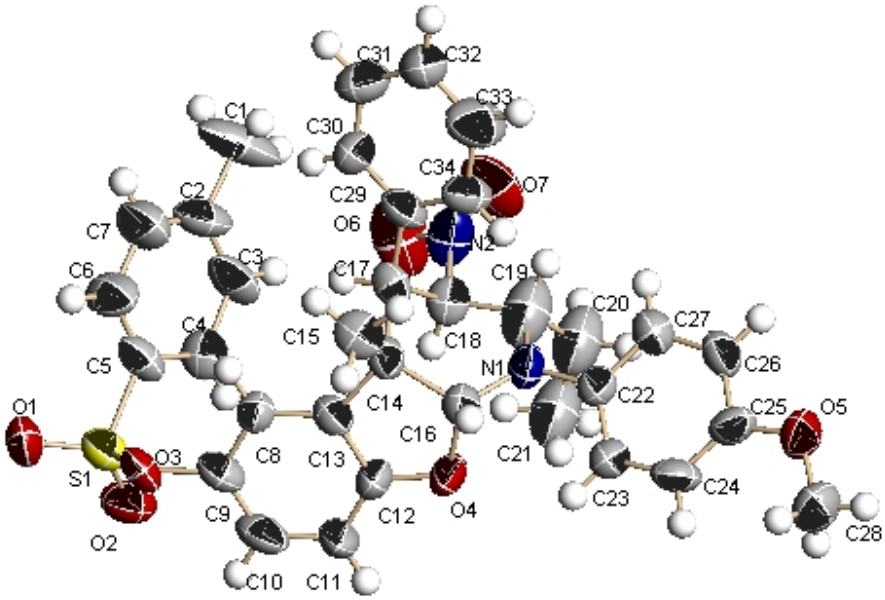


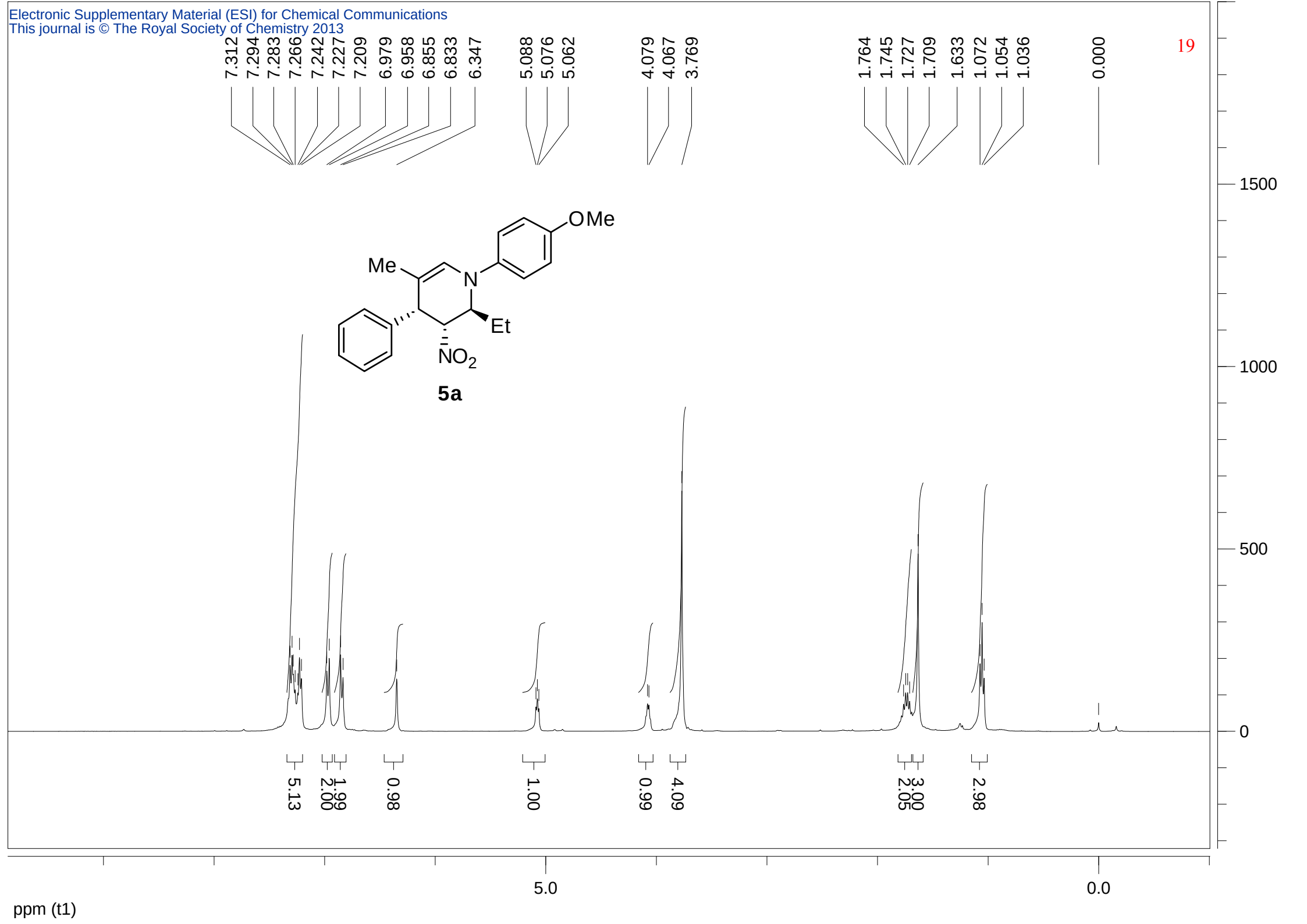
X-ray crystal structure of compound 10

The absolute configurations of two new formed stereocenters in compound **10** were determined based on its crystal structure.



10





154.696
140.417
136.268
129.335
128.466
128.153
127.705
119.870
114.487
105.592
86.988
77.318
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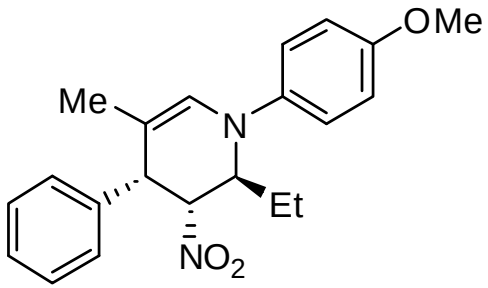
55.555
44.316
24.282
18.588
9.683

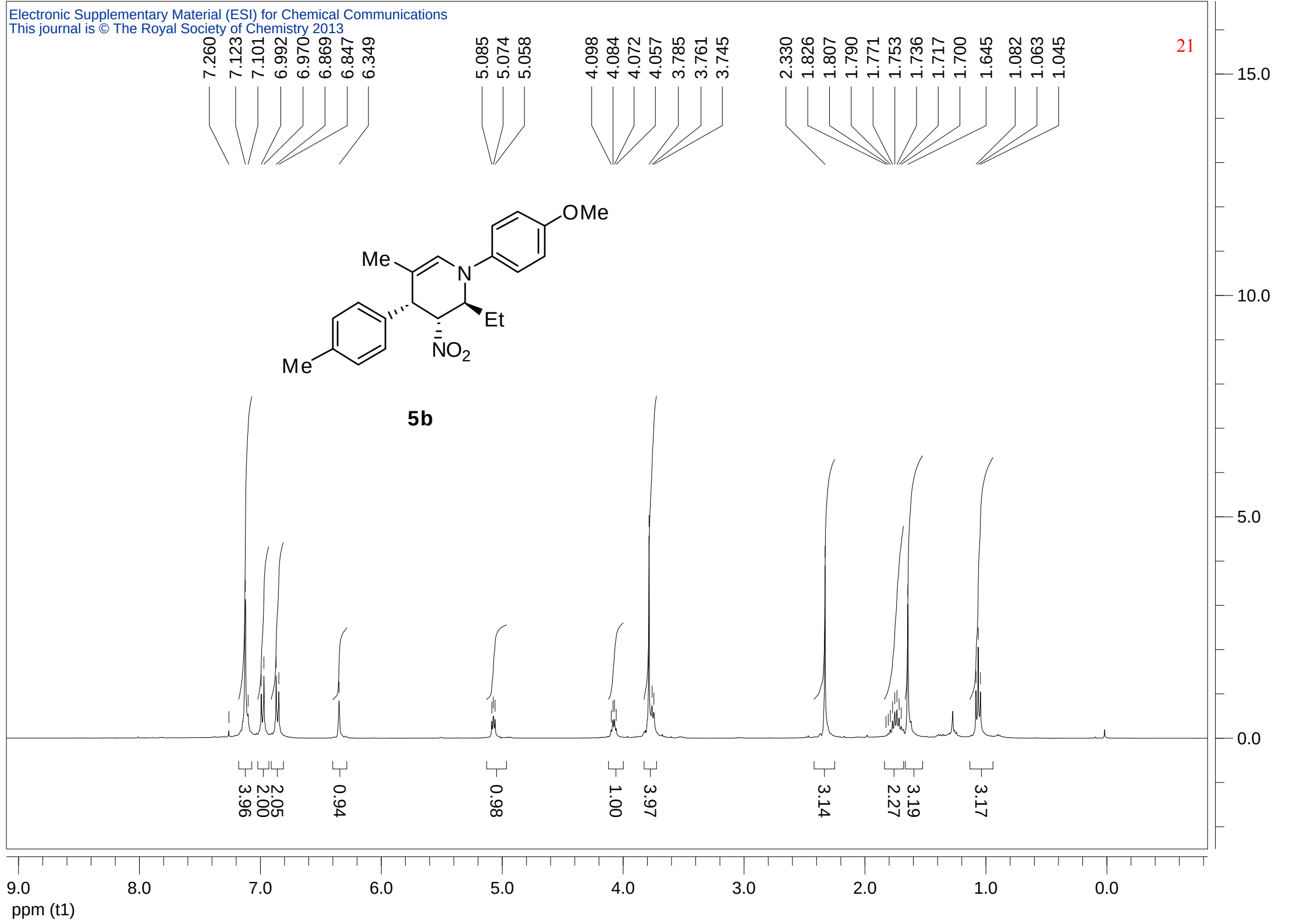


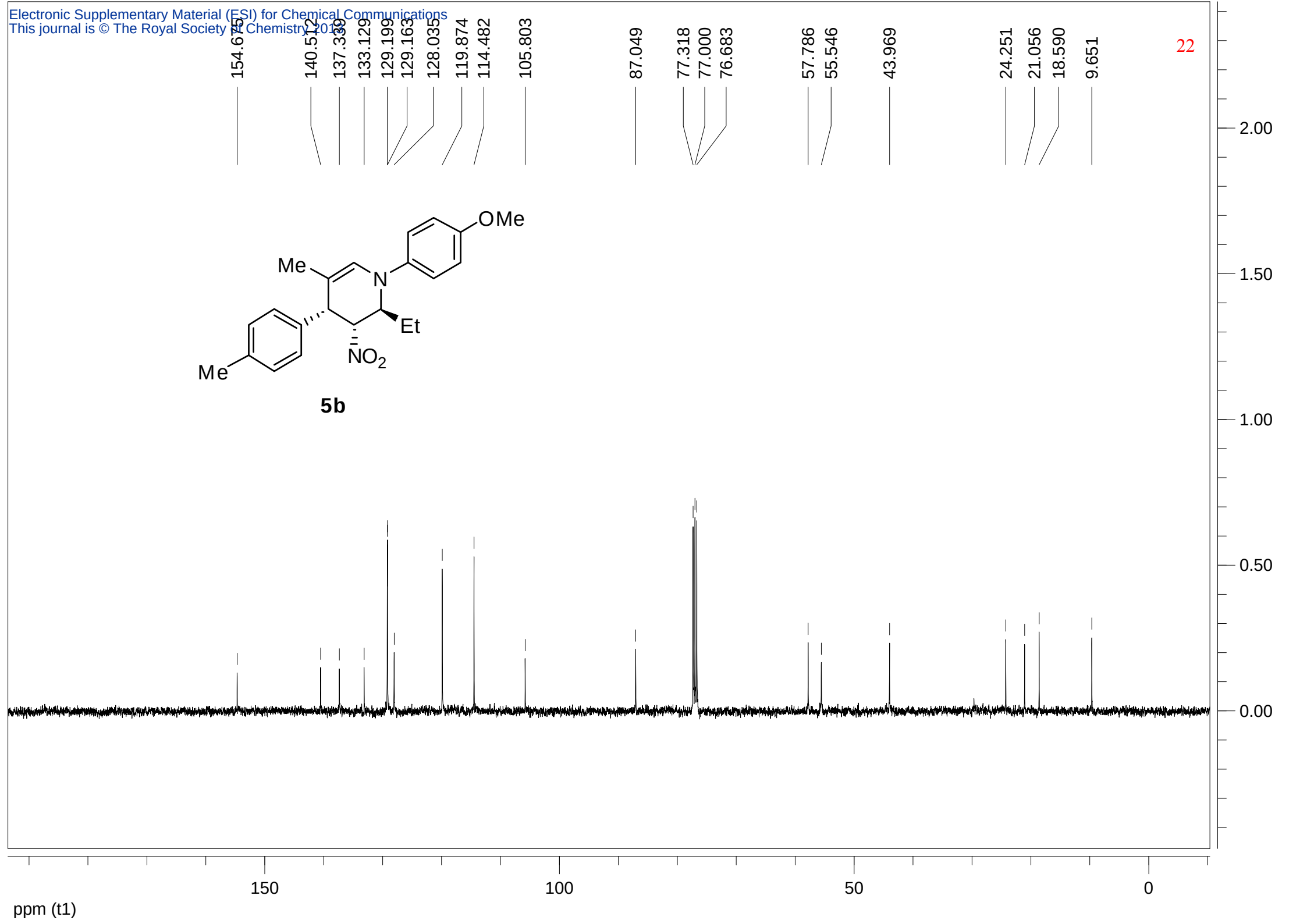
5a

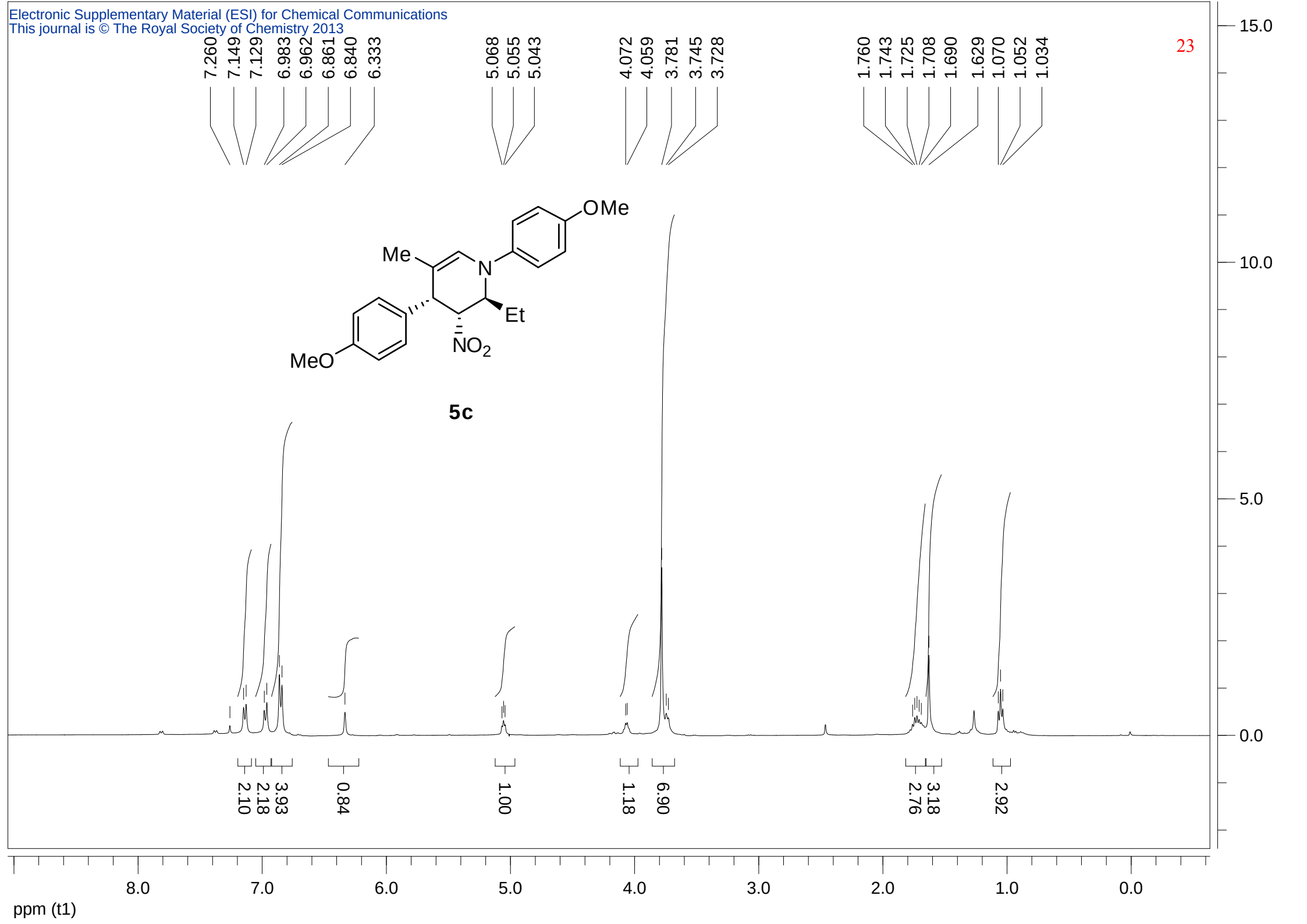
5000
4000
3000
2000
1000
0

150
100
50
0

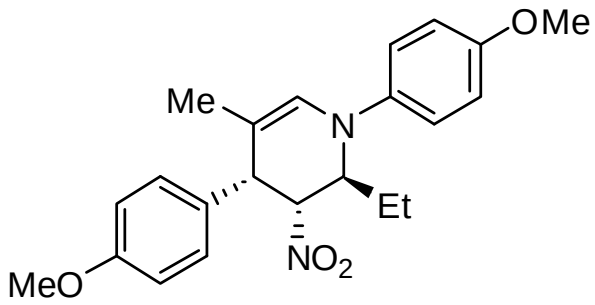
ppm (t1)







159.178
154.835
140.645
130.466
130.196
128.183
120.059
114.633
114.016
106.070
87.212
77.463
77.145
76.827
57.888
55.684
55.251
43.749
29.788
24.365
18.719
9.780

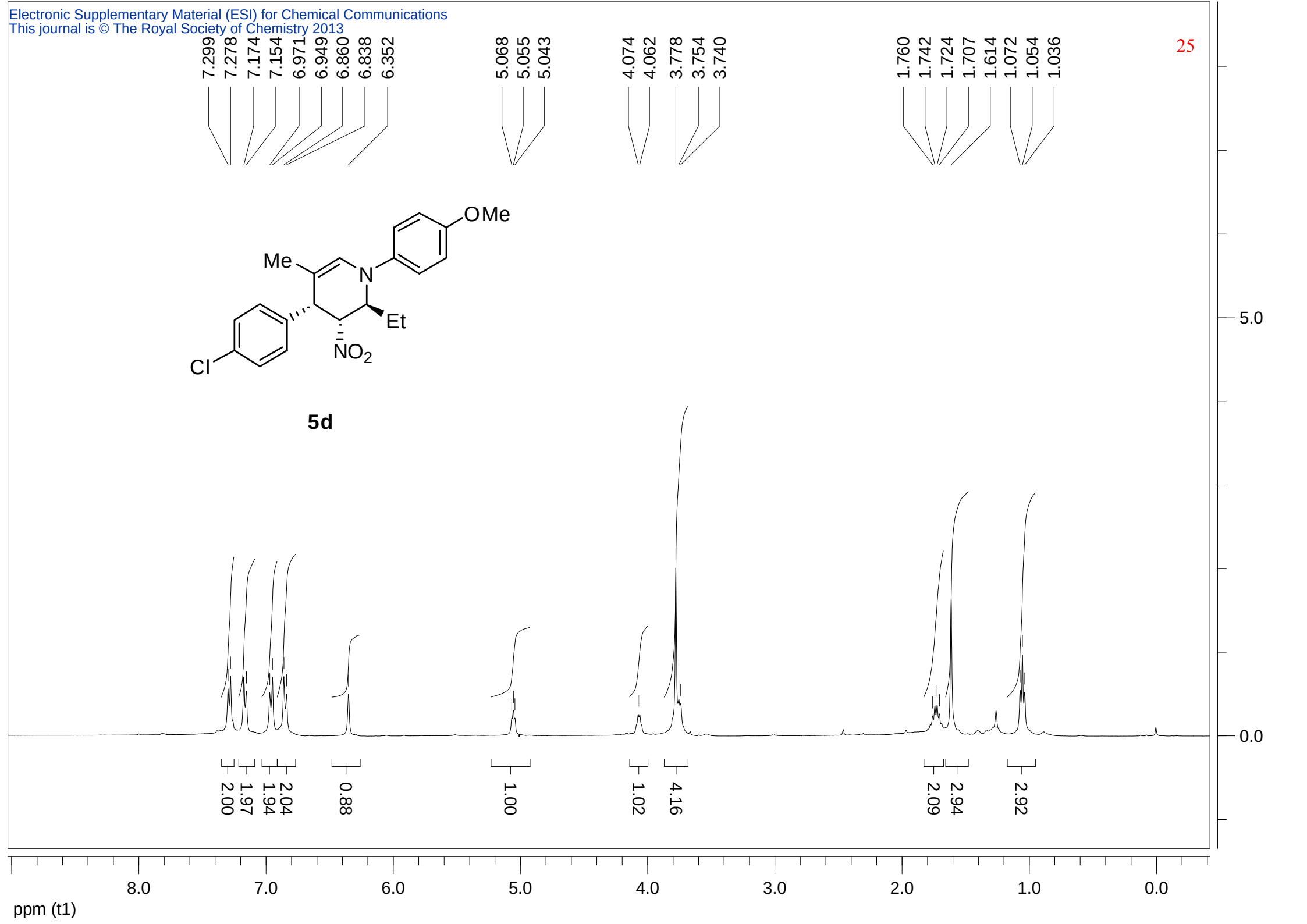


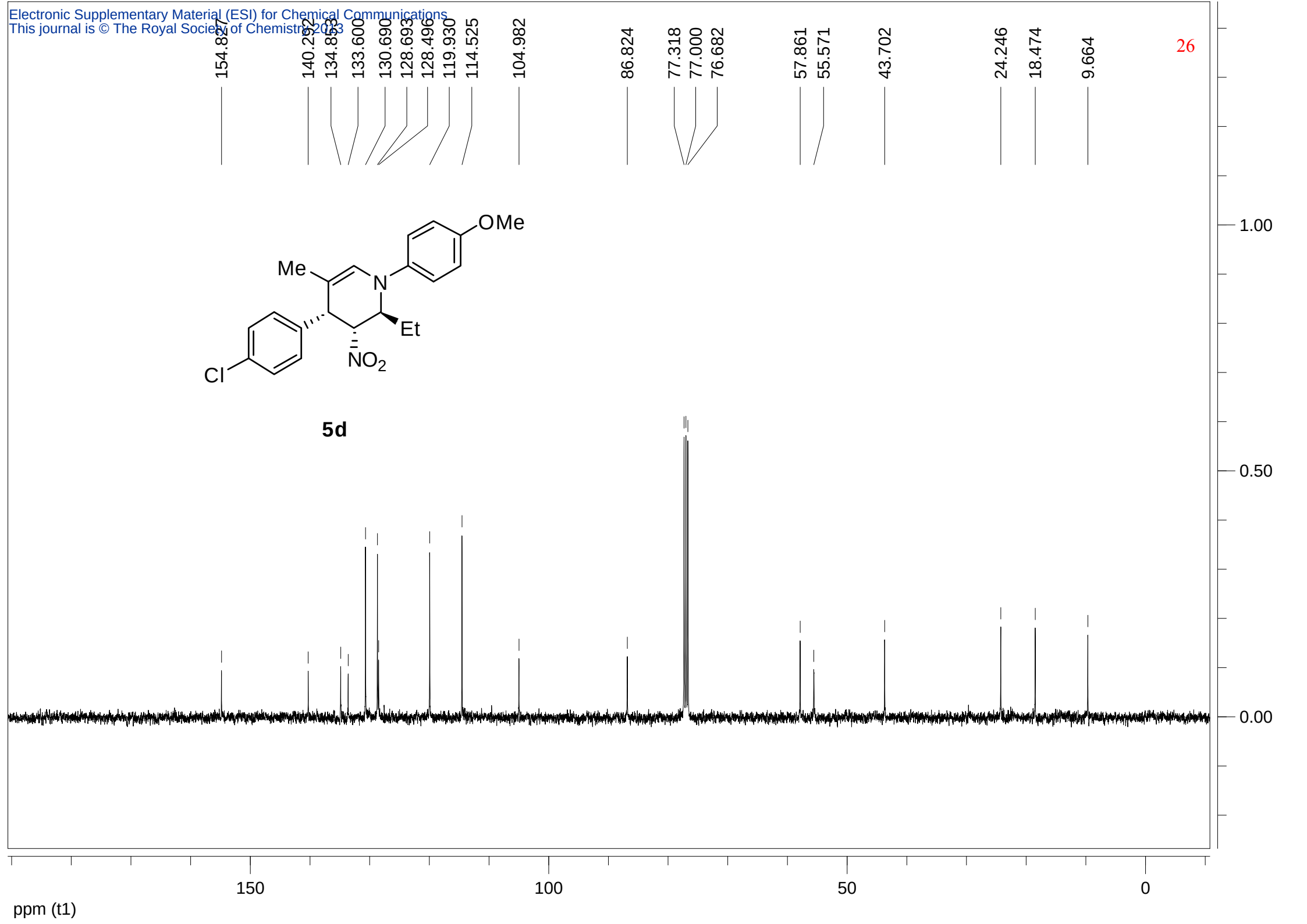
5c

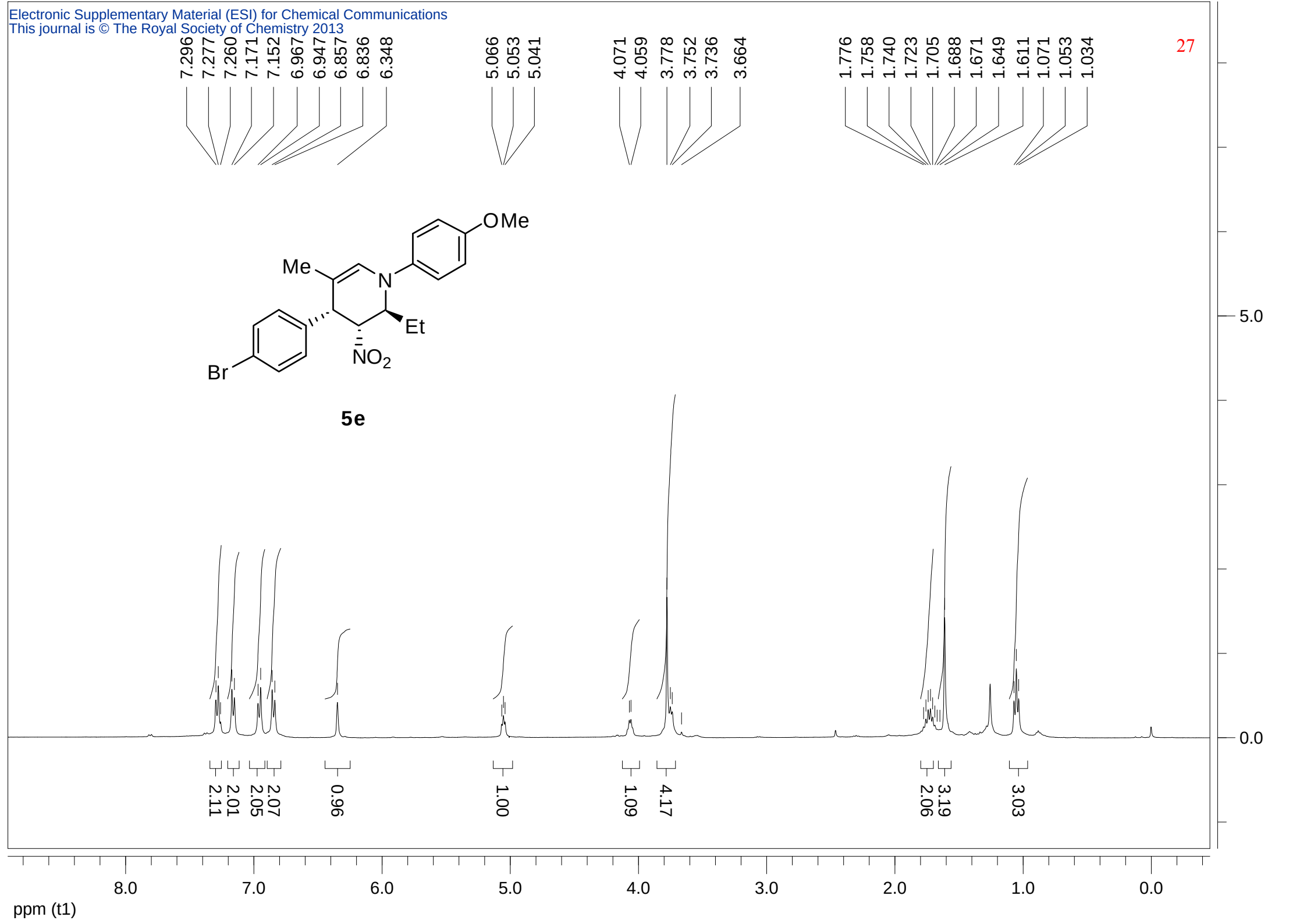
1.00
0.50
0.00

150
100
50
0

ppm (f1)







154.846
140.297
134.860
133.620
130.694
128.706
128.543
119.962
114.536
104.978
86.831
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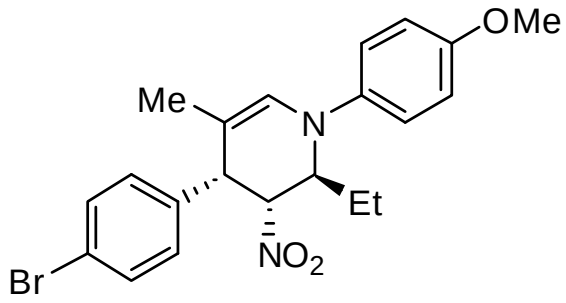
55.561
43.726
29.663
24.249
18.482
9.662

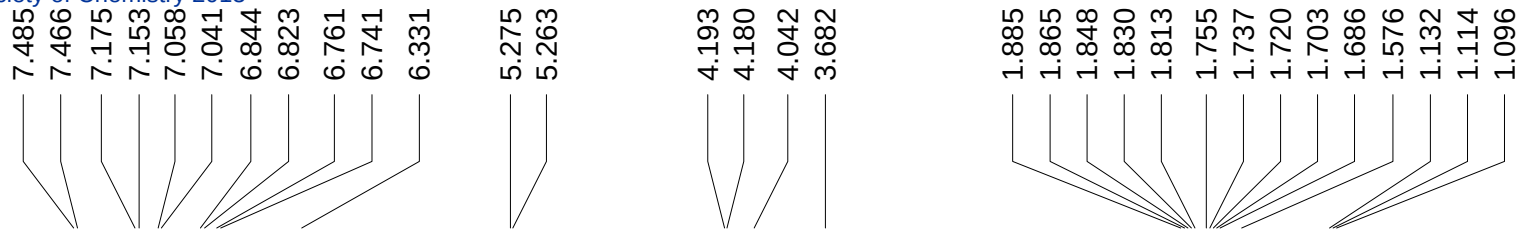


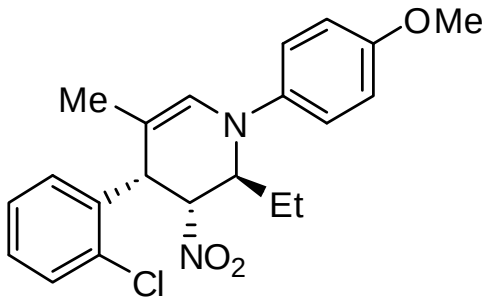
5e

1.00
0.50
0.00

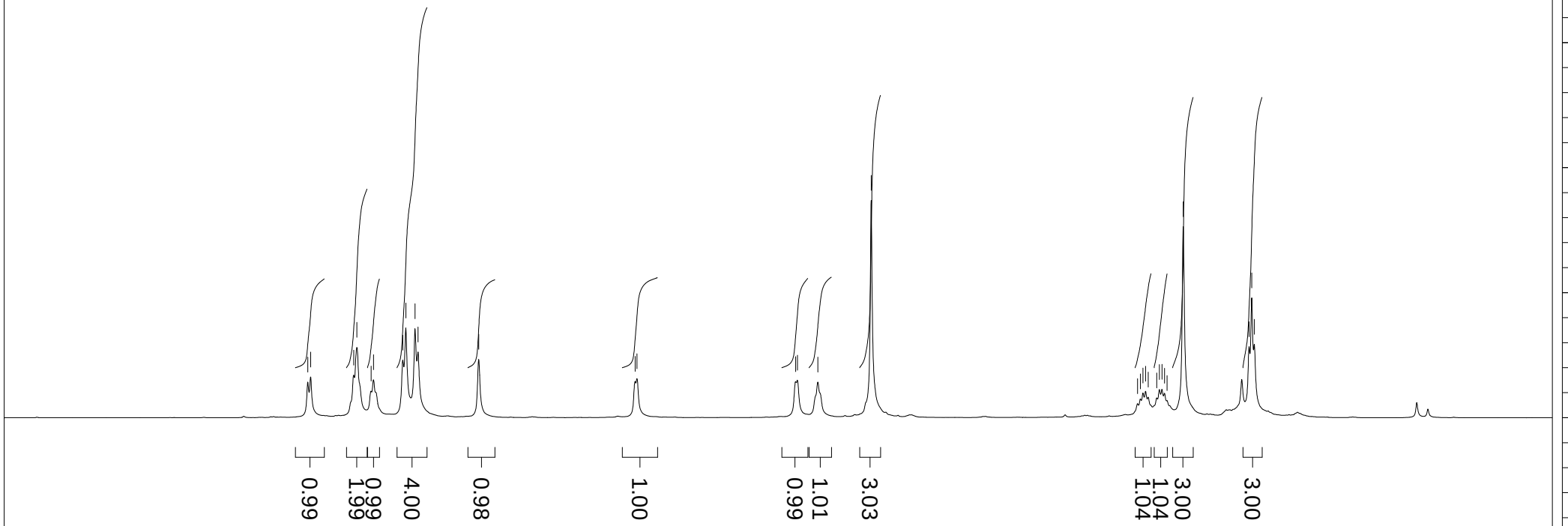
150
100
50
0

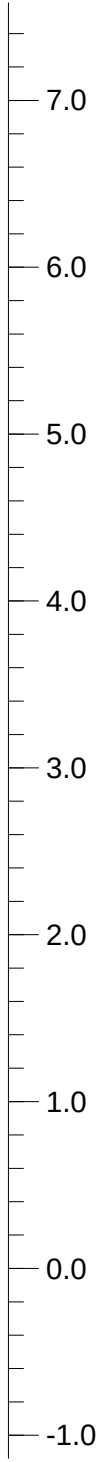
ppm (t1)





5f





154.142
140.655
134.553
132.679
131.567
129.224
127.527
127.254
125.659
117.980
114.521
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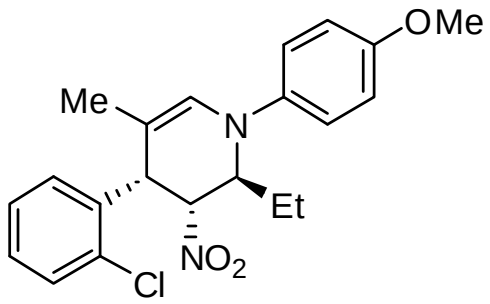
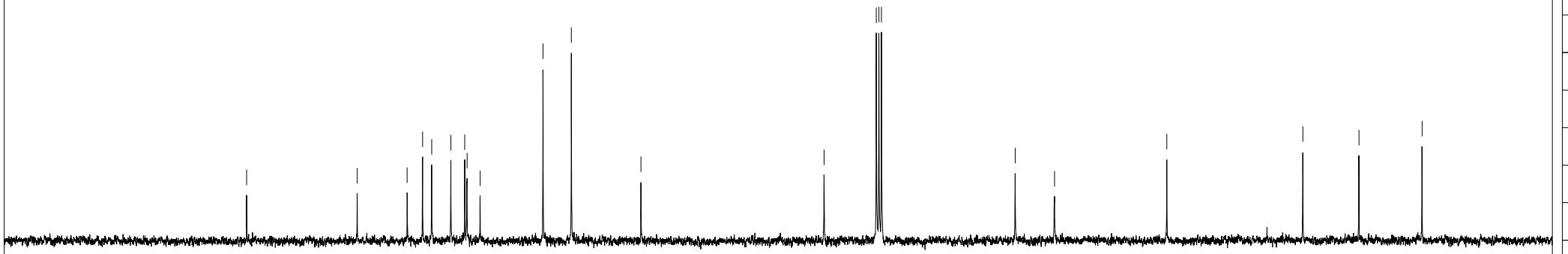
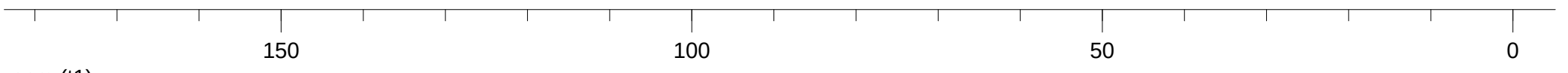
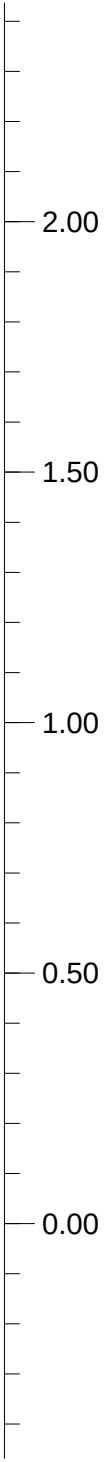
60.371
55.571
41.865
25.274
18.426
10.731

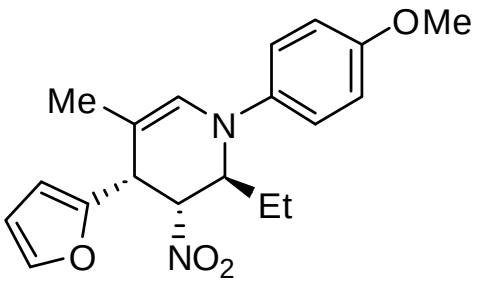


5f









5g

155.010
150.416
142.237
140.331
127.866
120.488
114.486
110.591
109.377
103.621
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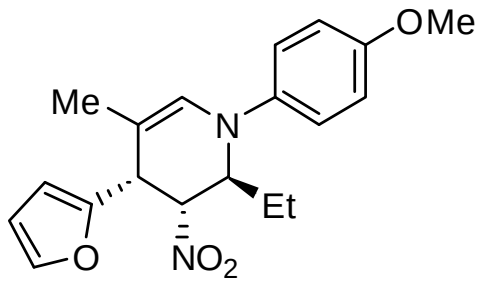
55.541
38.364
24.183
18.277
9.498



5g

2.00
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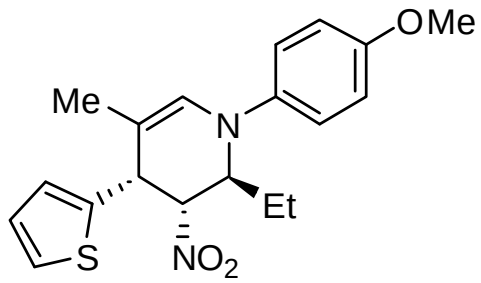
1.00
0.50
0.00

150
100
50
0

ppm (t1)



5h

155.518
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127.479
127.019
125.335
121.976
114.463
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77.318
77.000
76.681
56.338
55.495
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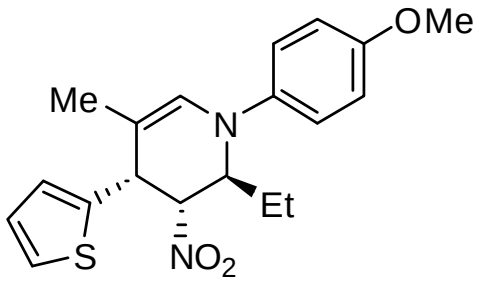
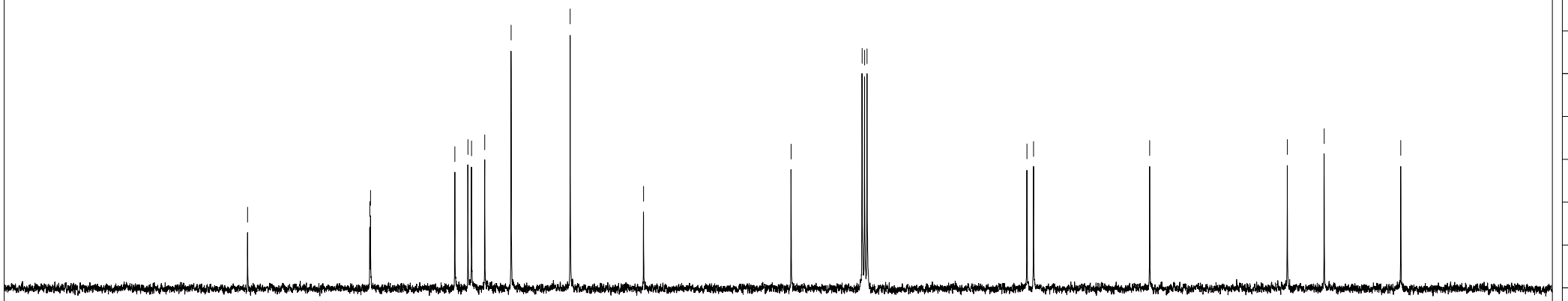
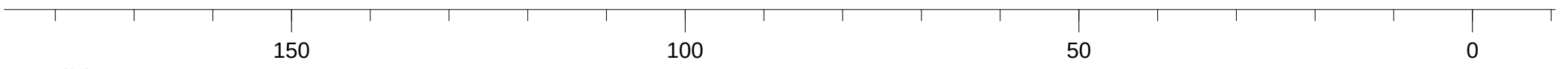
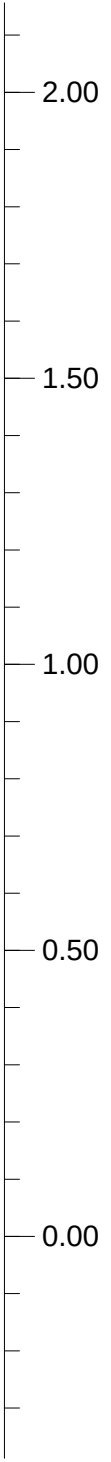
23.197
18.509
8.760

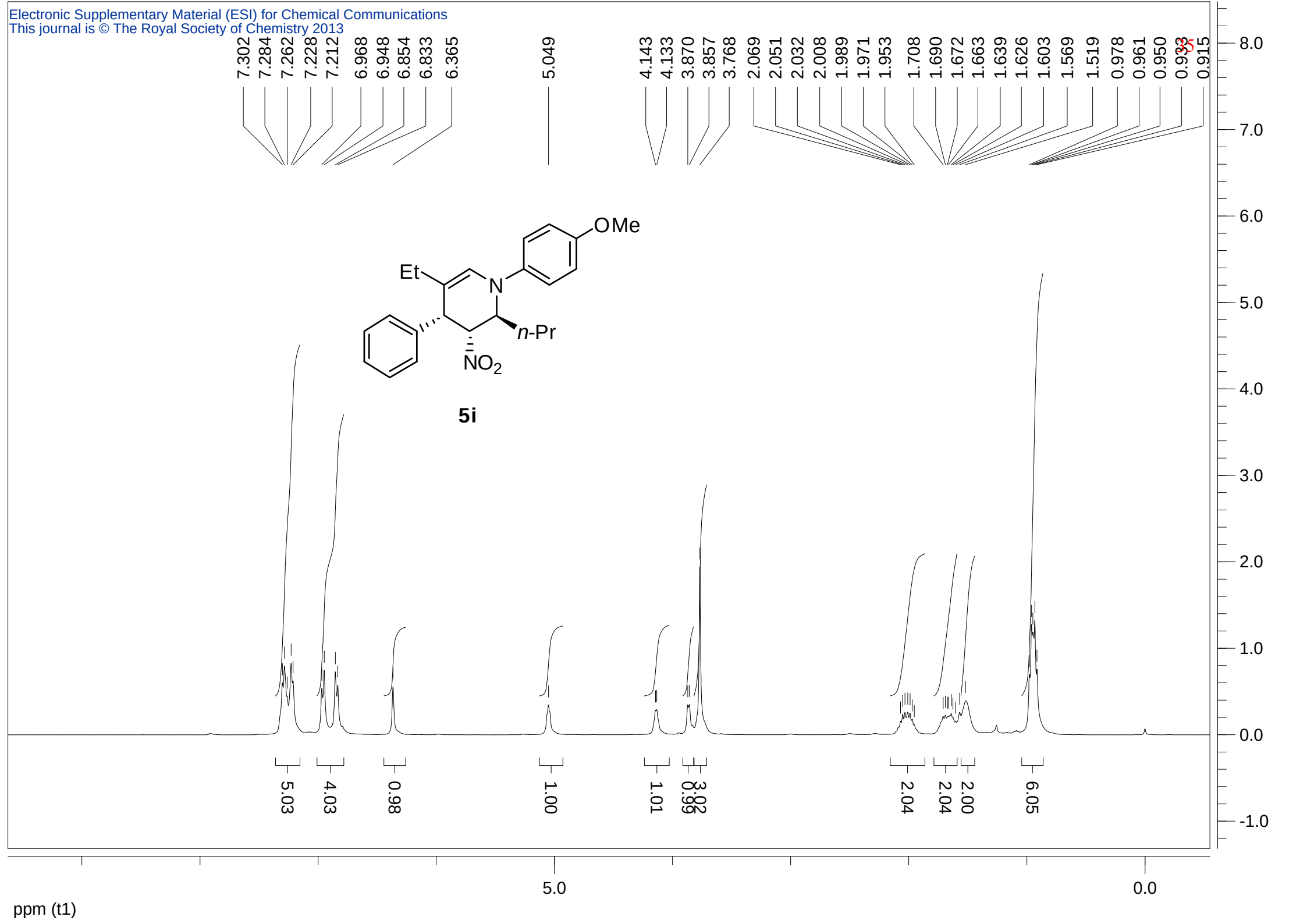


5h









154.659
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119.746
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111.663
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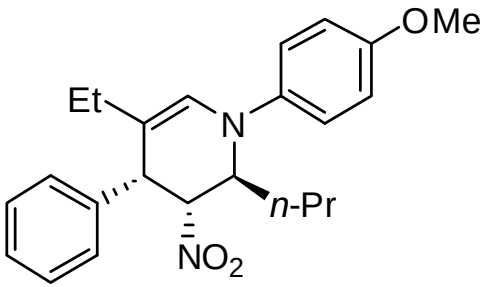
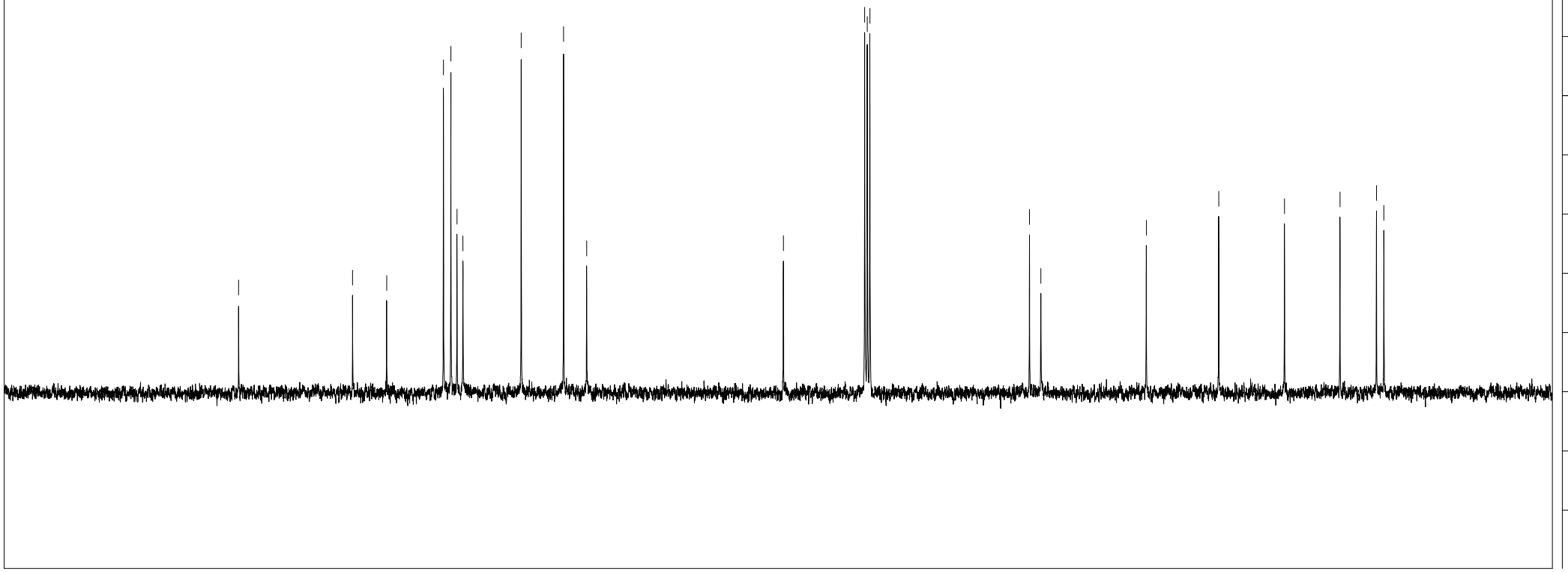
14.098
13.180



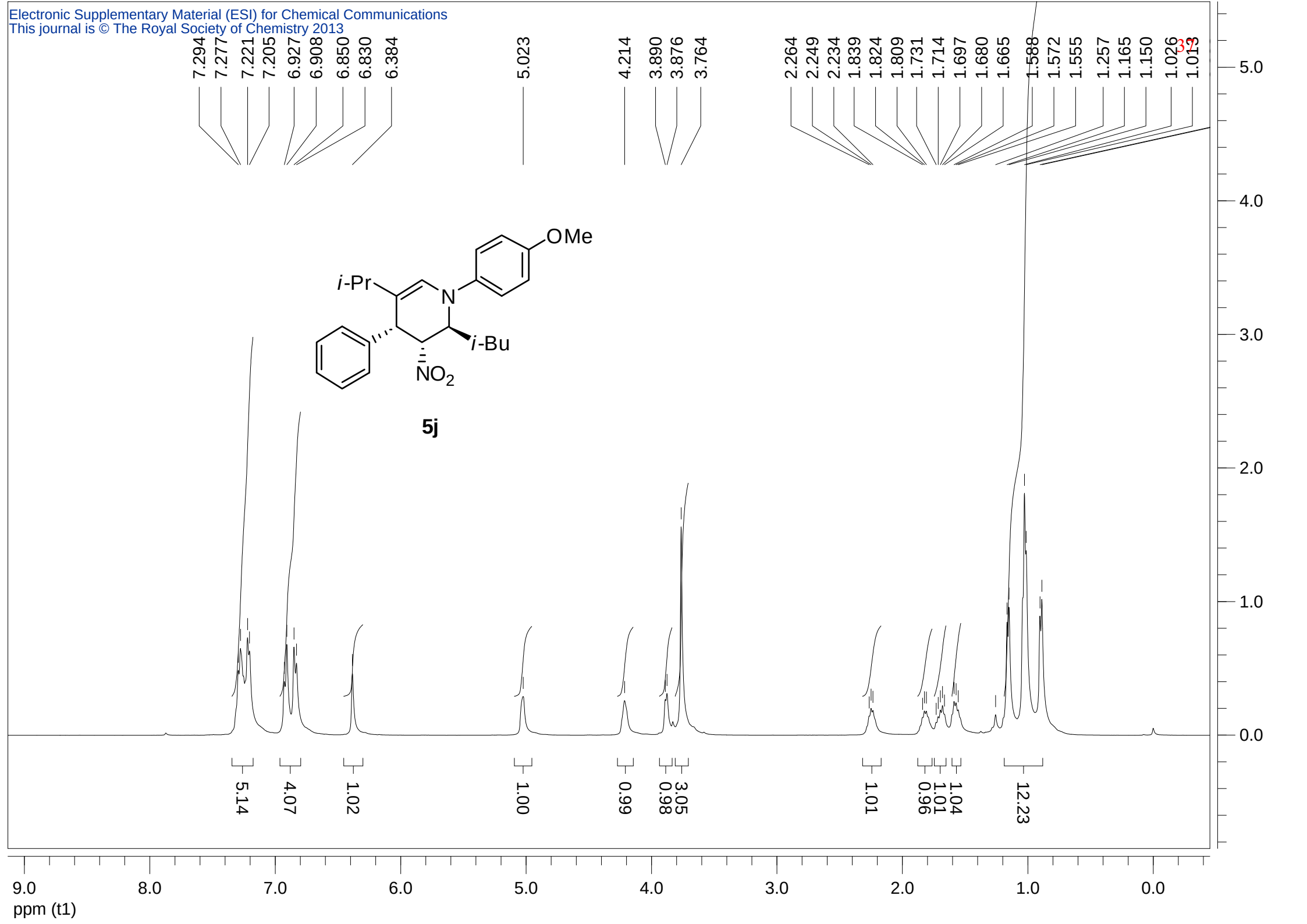
5i



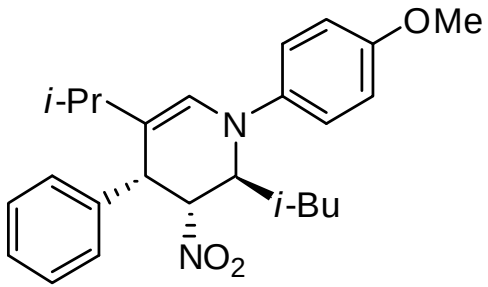
1.50
1.00
0.50
0.00

150
100
50
0

ppm (t1)



154.323
140.974
136.596
129.448
128.468
127.612
124.777
118.648
116.579
114.575
87.700
77.318
77.213
77.000
76.683
56.433
55.578
41.787
40.870
28.766
24.464
23.305
22.507
19.953

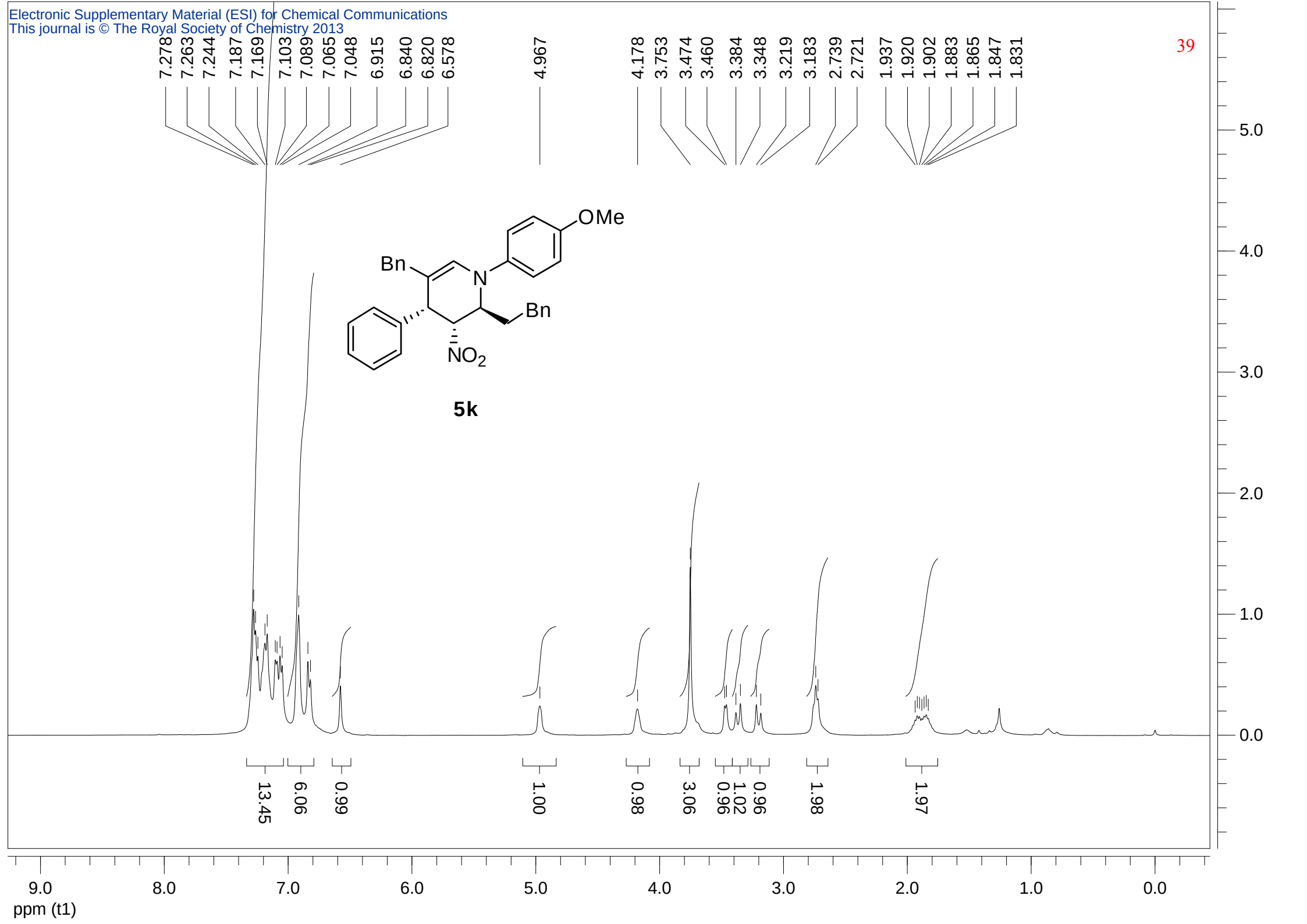


5j

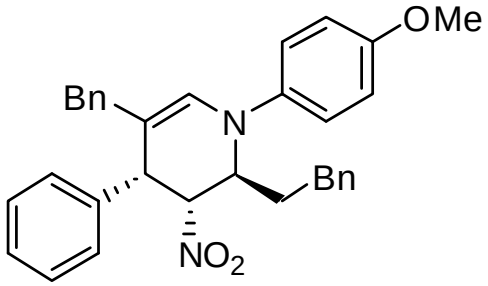
1.50
1.00
0.50
0.00

150
100
50
0

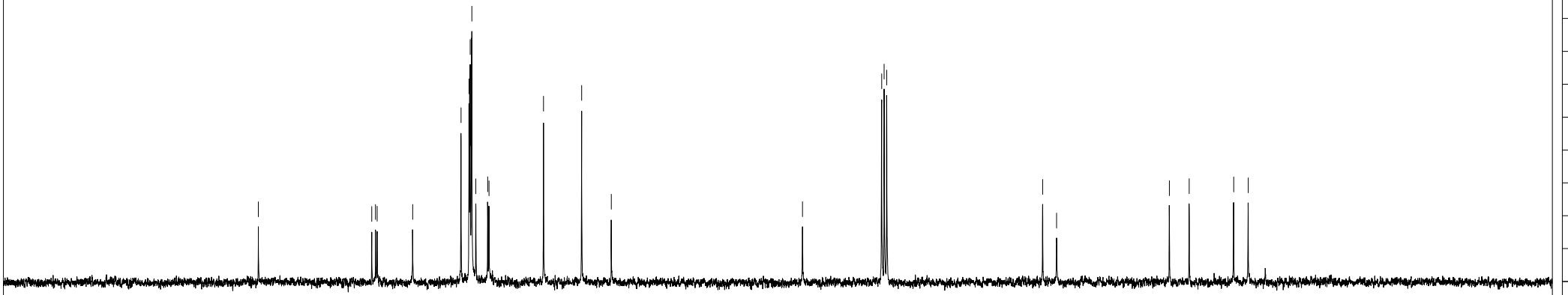
ppm (t1)



154.764
140.617
140.207
140.007
135.595
129.589
128.591
128.499
128.447
128.240
127.741
126.271
126.109
119.328
114.592
110.910
87.147
77.318
77.000
76.683
57.303
55.574
41.560
39.098
33.574
31.769



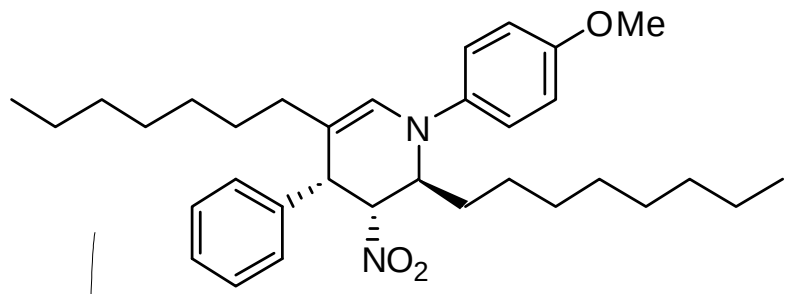
5k



2.50
2.00
1.50
1.00
0.50
0.00

150
100
50
0

ppm (t1)



5l

7.329 7.311 7.286 7.260 7.241 6.991 6.970 6.883 6.862 6.399 5.069 5.015 4.164 4.155 3.860 3.846 3.794 2.050 2.033 2.012 1.994 1.978 1.779 1.761 1.743 1.725 1.707 1.689 1.672 1.653 1.638 1.513 1.300 1.220 0.918 0.895 0.876 0.859

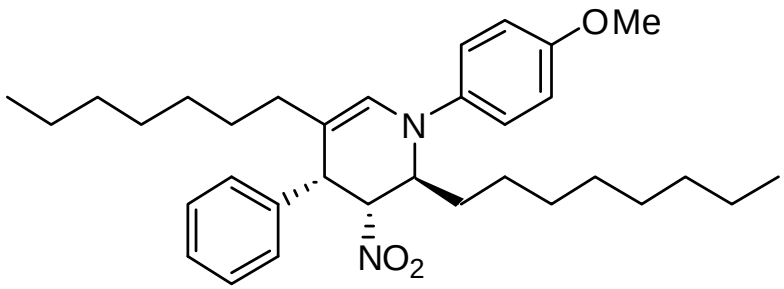
5.16 1.98 2.11 1.00 1.00 1.00 4.12 1.99 2.04 2.01 20.21 6.12

6.0 5.0 4.0 3.0 2.0 1.0 0.0

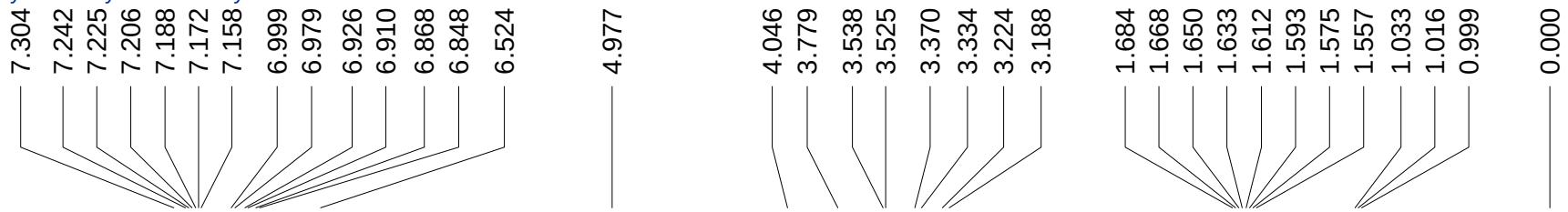
5.0 0.0

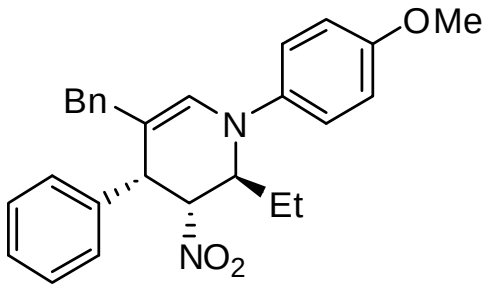
ppm (t1)

154.749
140.717
136.469
129.538
128.569
127.806
127.712
119.706
114.658
110.193
87.496
77.477
77.159
76.841
57.404
55.703
42.603
32.505
31.903
31.669
29.712
29.480
29.293
29.151
28.321
25.419
22.725
14.182

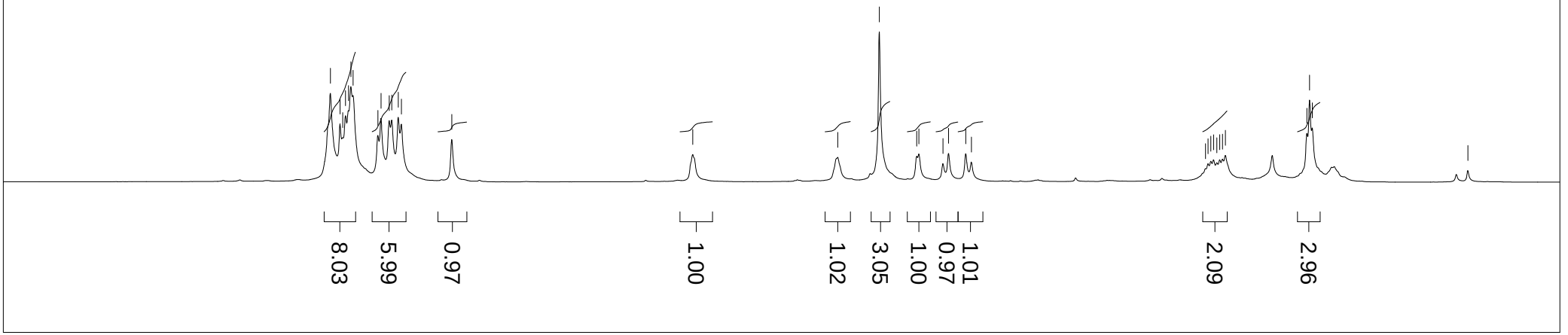


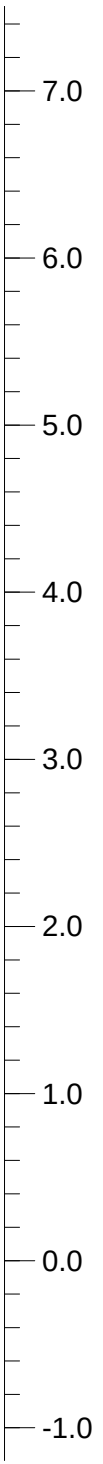
5l



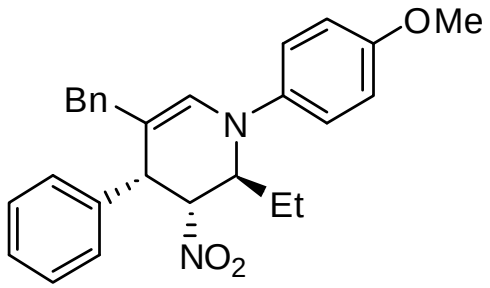


5m





154.838
140.316
139.965
135.926
129.554
128.855
128.519
128.248
127.779
126.073
119.824
114.534
109.973
86.858
77.317
77.000
76.682
58.314
55.575
41.828
39.111
24.553
9.803

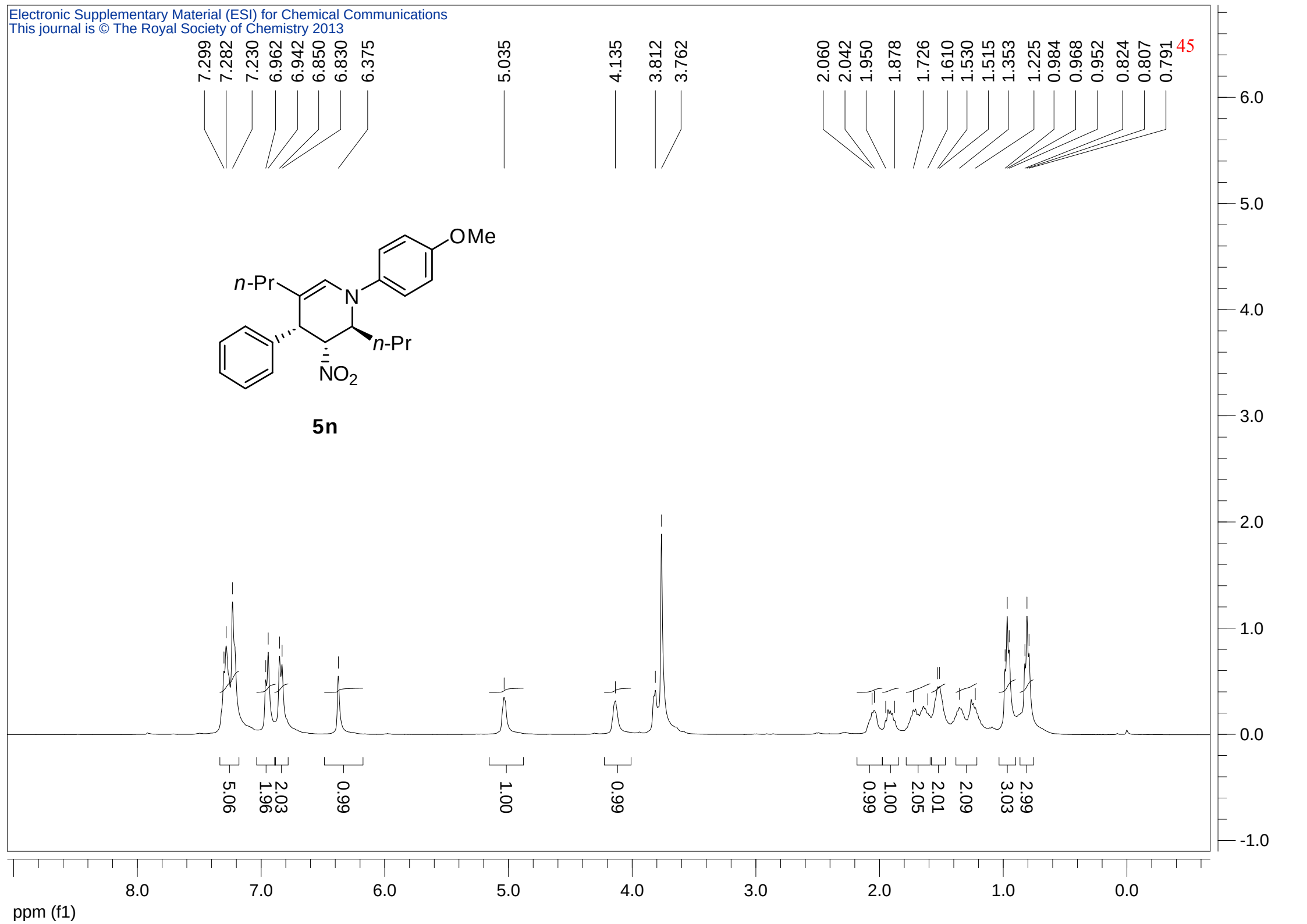


5m

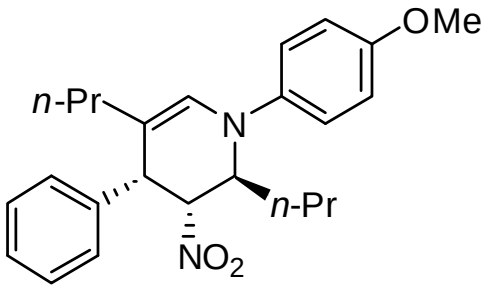
1.00
0.50
0.00

150
100
50
0

ppm (f1)



154.538
140.542
136.285
129.358
128.416
127.646
127.597
119.462
114.468
109.724
87.291
77.319
77.000
76.682
57.139
55.527
42.288
34.485
33.757
21.283
18.693
14.105
13.554

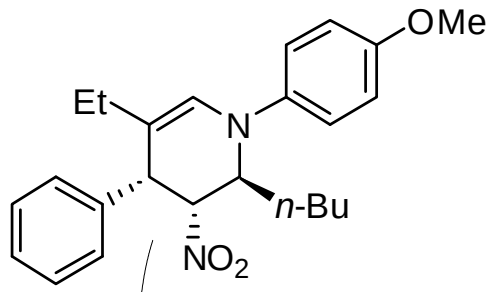


5n

2.50
2.00
1.50
1.00
0.50
0.00
-0.50

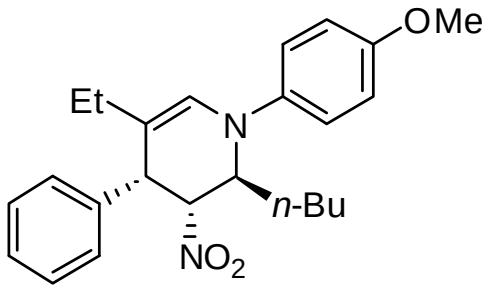
150
100
50
0

ppm (f1)



5o

154.609
140.516
136.355
129.337
128.423
127.672
126.925
119.709
114.468
111.686
87.322
77.317
77.000
76.681
56.977
55.531
42.500
30.982
27.346
25.459
22.654
13.916
13.195

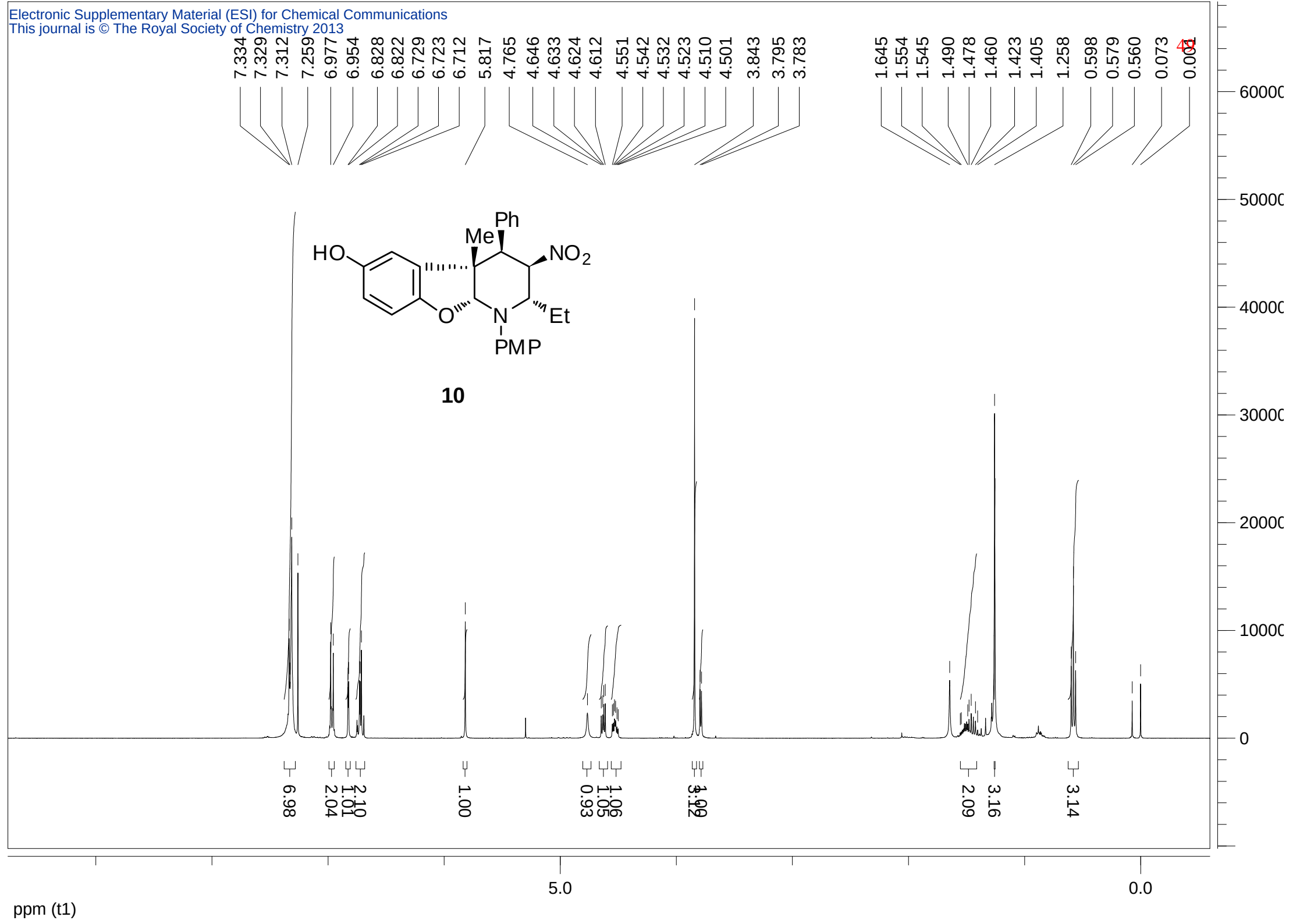


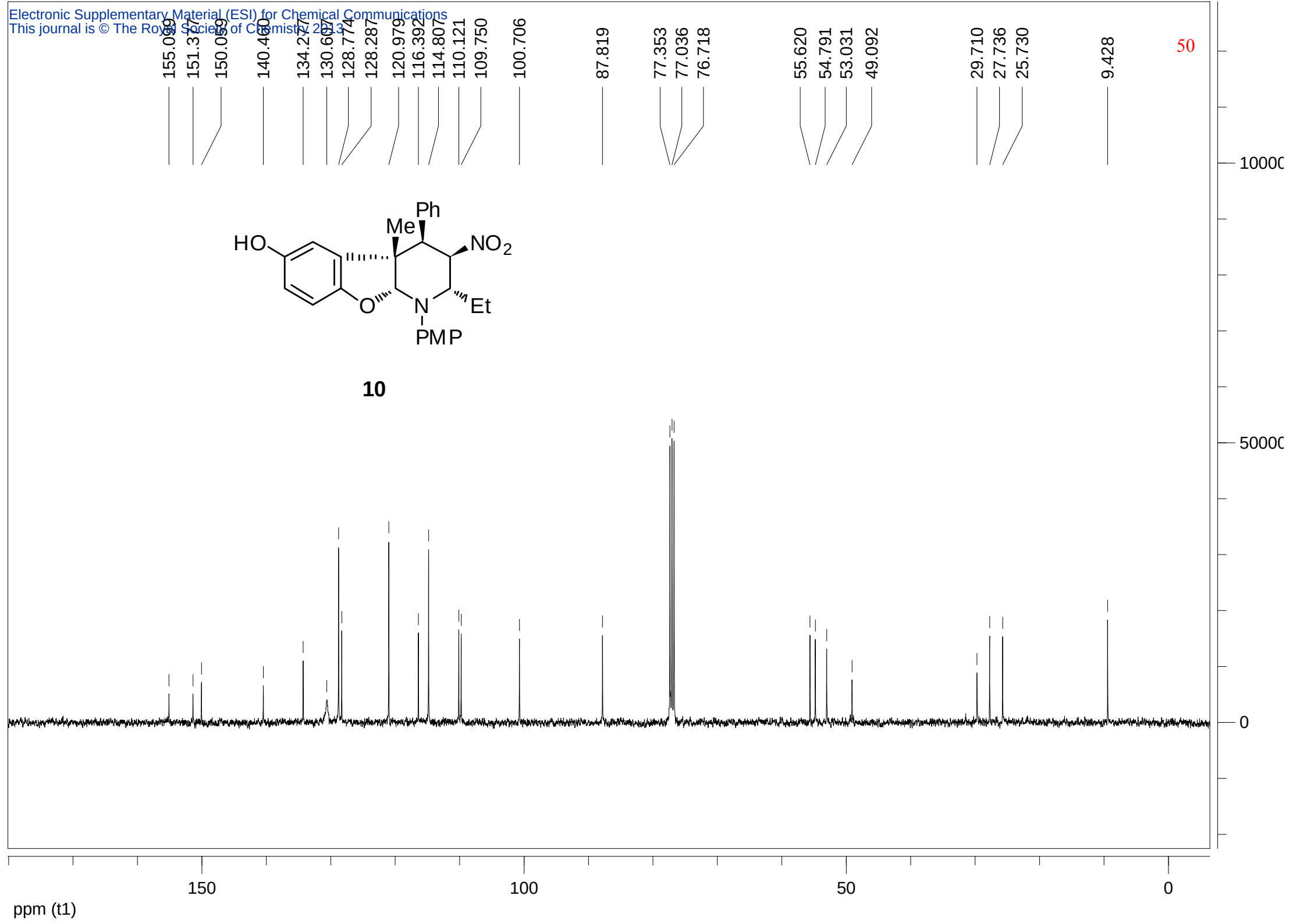
5o

2.50
2.00
1.50
1.00
0.50
0.00

150
100
50
0

ppm (f1)





10