Enantioselective Halolactonizations Using Amino-acid-derived Phthalazine Catalysts

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GENERAL METHODS

General Procedures

All reactions were generally performed open air or in dried glassware under an atmosphere of dry N_2. Reaction mixtures were stirred magnetically unless otherwise indicated and monitored by thin layer chromatography (TLC) on Merck precoated glass-backed silica gel 60 F-254 0.25 mm plates with visualization by fluorescence quenching at 254 nm. TLC plates were stained using potassium permanganate. Chromatography purification of products (flash column chromatography) was performed on silica gel 60 (70-230 mesh, Merck) using a forced flow of eluent at 0.3-0.5 bar. Concentration of reaction product solutions and chromatography fractions under reduced pressure was performed by rotary evaporation at 35-45^{o}C at the appropriate pressure and then at rt, ca. 10 mmHg (vacuum pump) unless otherwise indicated.

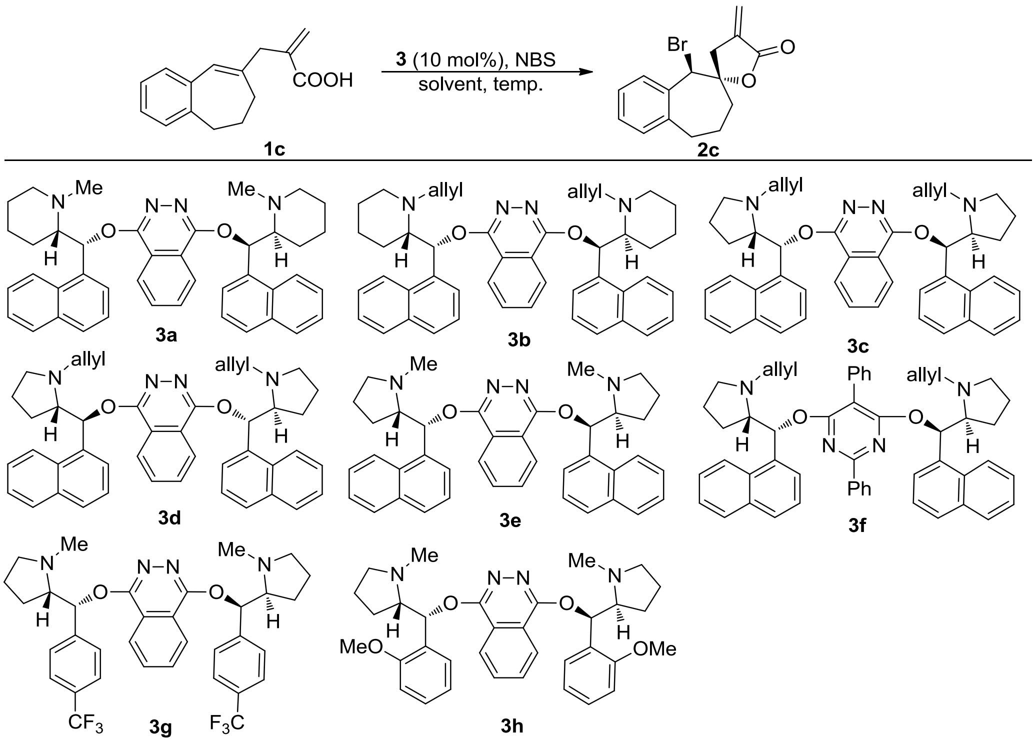
Materials

All chemicals, including dry solvents were purchased from Aldrich, Fluka, Acros, TCI, Merck, Strem, or Alfa Aesar and used as such unless stated otherwise. Yields given refer to chromatographically purified compounds unless otherwise demonstrated.

Instrumentation

Melting points were determined on a Sinoinstructment melting point apparatus. ^{1}H NMR spectra were recorded on Bruker 300 MHz or Bruker 400 MHz spectrometer. ^{13}C NMR spectra were recorded on Bruker 75 MHz or Bruker 100 MHz spectrometer. ^{13}C NMR chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane (with the central peak of $CHCl_3$ at 77.16 ppm used as standard). ^{1}H NMR chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane (with the peak of $CHCl_3$ at 7.26 ppm used as standard; with the peak of benzene at 7. 36 ppm used as standard). ^{19}F NMR spectra are referenced relative to C_6F_6 (with the peak of −162.85 ppm) in $CDCl_3$. All ^{13}C spectra were measured with complete proton decoupling. NMR coupling constants (J) are reported in Hertz (Hz), and splitting patterns are indicated as follows: br, broad; s, singlet; d, doublet; dd, doublet of doublet; ddd, doublet of doublet of doublet; dt, doublet of triplet; t, triplet; q, quartet; m, multiplet. High resolution mass spectrometric measurements (HRMS) were performed by the AB SCIEX, Triple TOF 5600+. Enantiomeric excesses were determined by HPLC analysis on Shimadzu HPLC units, including the following instruments: pump, LC-16; detector, SPD-16; column, Daicel Chiralpak AD-H, OD-H or OJ-H.

Table 1. Optimization of the Bromolactonization[a]

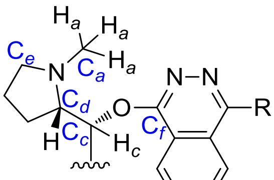


entry	3	solvent	temp. (°C)	Yield % (ee %)
1	**3a**	toluene	−40	94 (17)
2	**3b**	toluene	−40	95 (12)
3	**3c**	toluene	−40	96 (90)
4	**3d**	toluene	−40	95 (62)
5	**3e**	toluene	−40	95 (87)
6	**3f**	toluene	−40	93 (10)
7	**3g**	toluene	−40	94 (71)
8	**3h**	toluene	−40	93 (76)
9	**3c**	toluene	−20	95 (73)
10	**3c**	toluene	−60	96 (94)
11	**3c**	**toluene**	**−78**	**97 (96)**
12	**3c**	CH_2Cl_2	−78	90 (82)
13[b]	**3c**	Hexane/CH_2Cl_2	−78	89 (85)
14[c]	**3c**	Hexane/ toluene	−78	90 (88)
15[d]	**3c**	toluene	−78	94 (92)
16[e]	**3c**	toluene	−78	92 (87)
17[f]	**3c**	toluene	−78	97 (95)

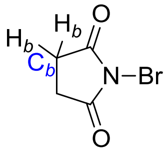
[a] Reactions were carried out with substrate **1c** (0.1 mmol), **3** (0.01 mmol), and NBS (0.12 mmol) in solvent (4 mL). The yield was isolated yield and the ee was determined by chiral HPLC. [b] The reaction was conducted in Hexane/CH_2Cl_2 (1/1). [c] The reaction was conducted in Hexane/toluene (1/1). [d] BzOH (0.1 mmol) was used as additive. [e] $NsNH_2$ (0.1 mmol) was used as additive. [f] The ammount of **3c** was 0.015 mmol.

NMR study of 1b, 3e and NBS

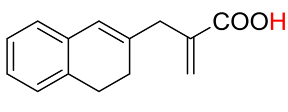
Upon mixing 1:1 of **3e** and NBS in CD_2Cl_2 at room temperature, the protons of H_a in **3e** shifted downfield (~0.2 ppm) while the methylene protons of H_b in NBS shifted upfield (~0.3 ppm).[11] Also, the ^{13}C-NMR indicated that C_a, C_d and C_e in **3e** exhibited significant upfield shift (0.2−1.2 ppm) while C_b in NBS exhibited a downfield shift (~0.8 ppm). These phenomena suggesting an interaction between the pyrrolidine and NBS as depicted in species **9** (Figure 1).[12a] For the ^{13}C-NMR study of a mixture of **3e**/**1b** at a 1:1 ratio, C_a and C_e in **3e** exhibited upfield shift (~0.5 ppm), indicating that a proton transfer from carboxylic acid to pyrrolidine might occur (Figure 1, species **10a**). Alternatively, we observed considerable upfield shift of C_c (~1.1 ppm) and C_f (~0.7 ppm) in **3e**, indicating that proton transfer could also happen in the phthalazine moiety as shown in species **10b**.[12b] Also, we speculated that the positive charge of oxonium ion might lead to a downfield shift of H_c.



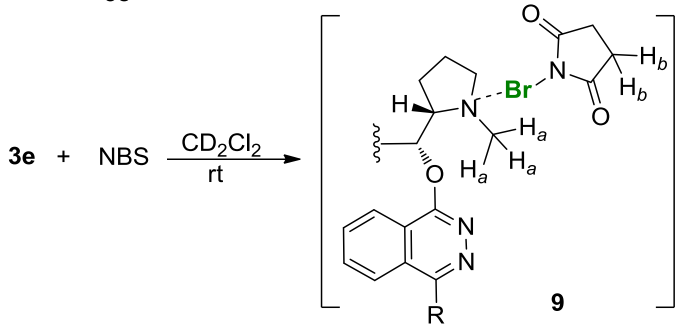
3e

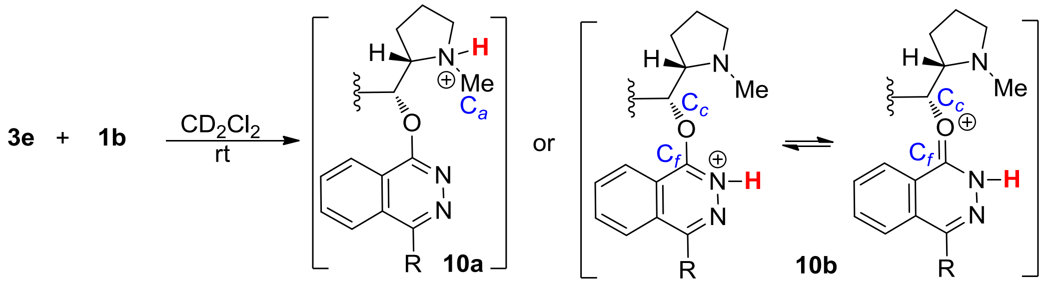


NBS

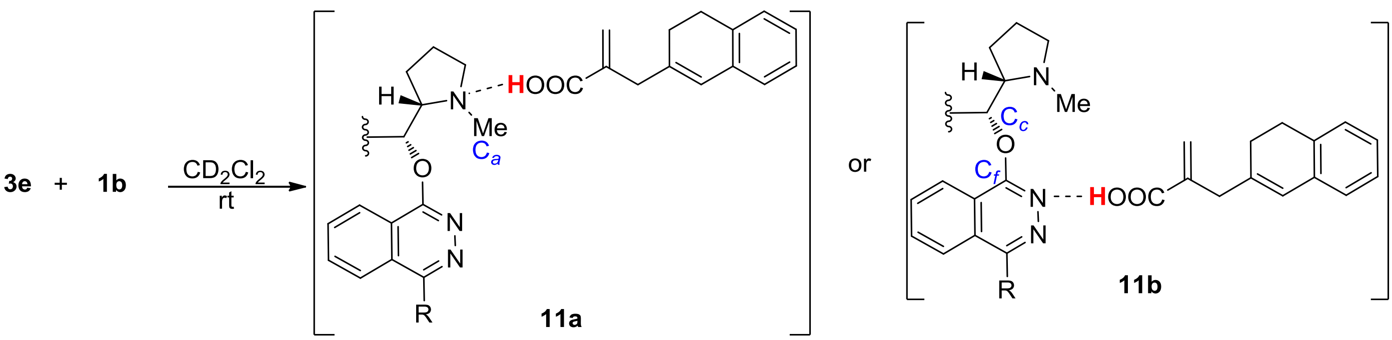


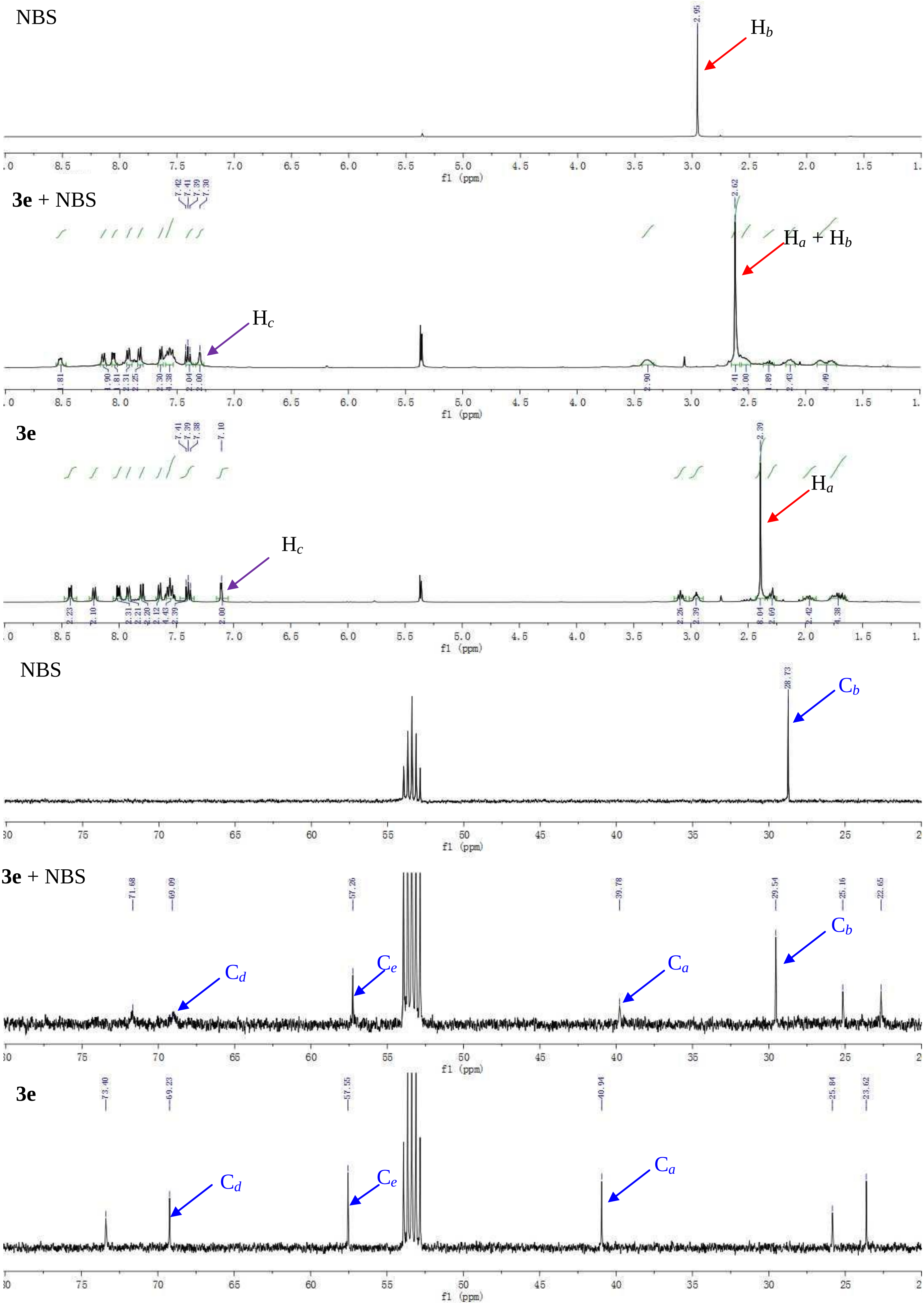
1b



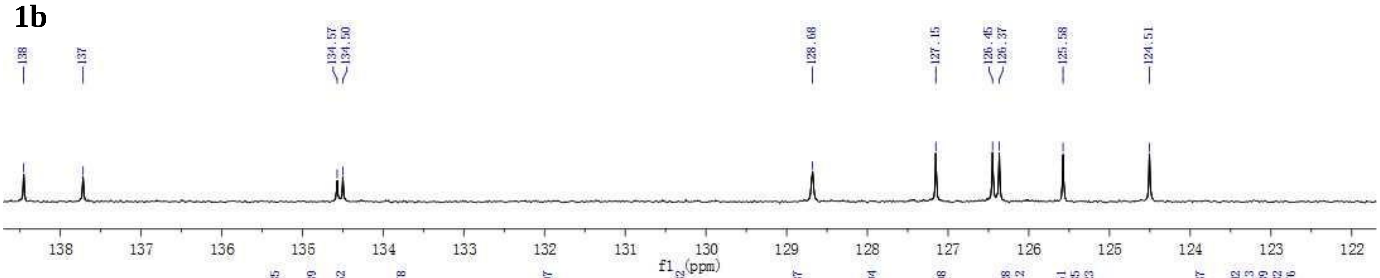


It is noteworthy to mention that hydrogen bond might display equal effect as proton transfer.

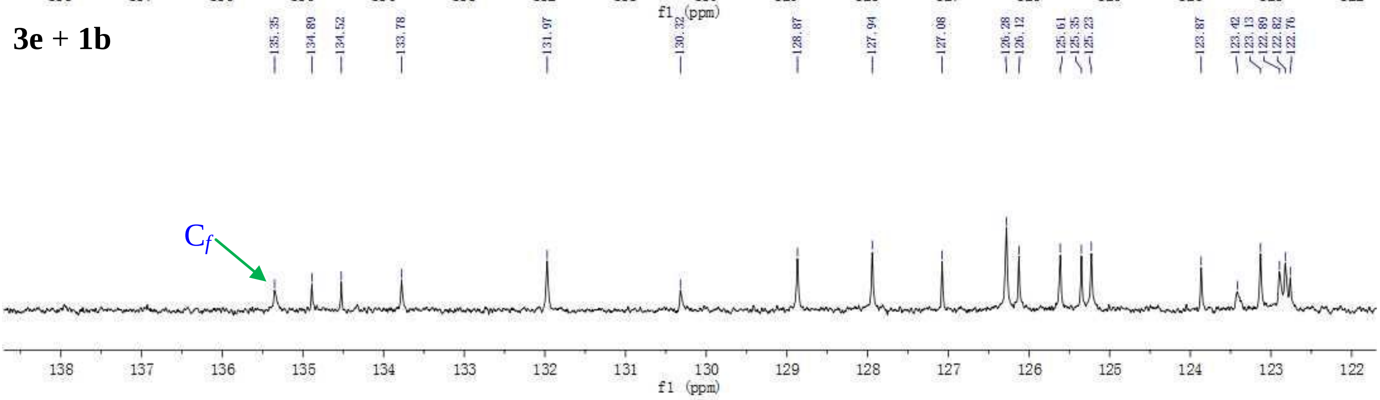



NBS
H b
3e + NBS
H a + H b
H c
3e
H a
H c
NBS
C b
3e + NBS
C d
C e
C a
C b
3e
C d
C e
C a
f1 (ppm)

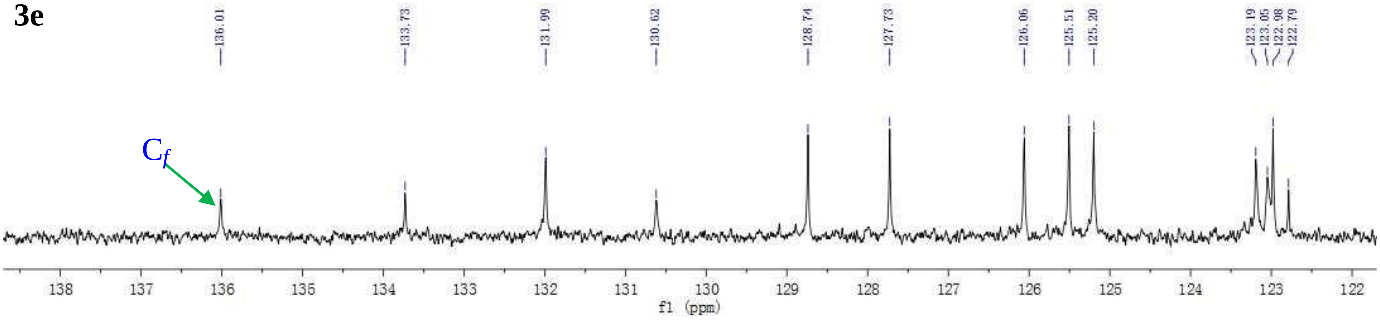
1b



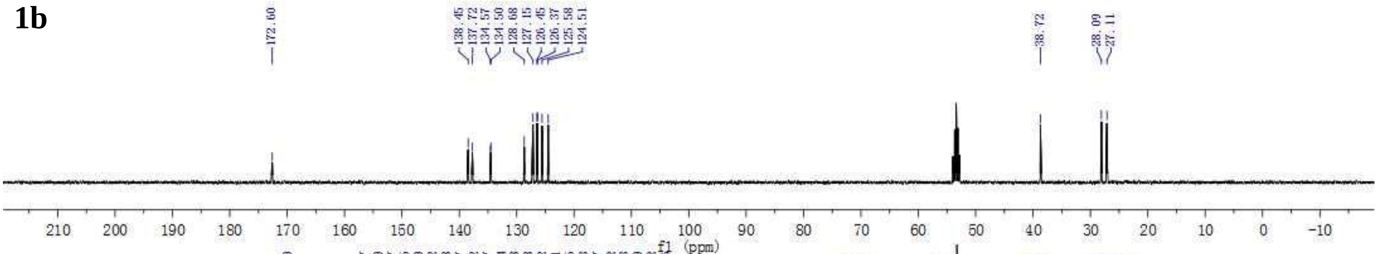
3e + 1b



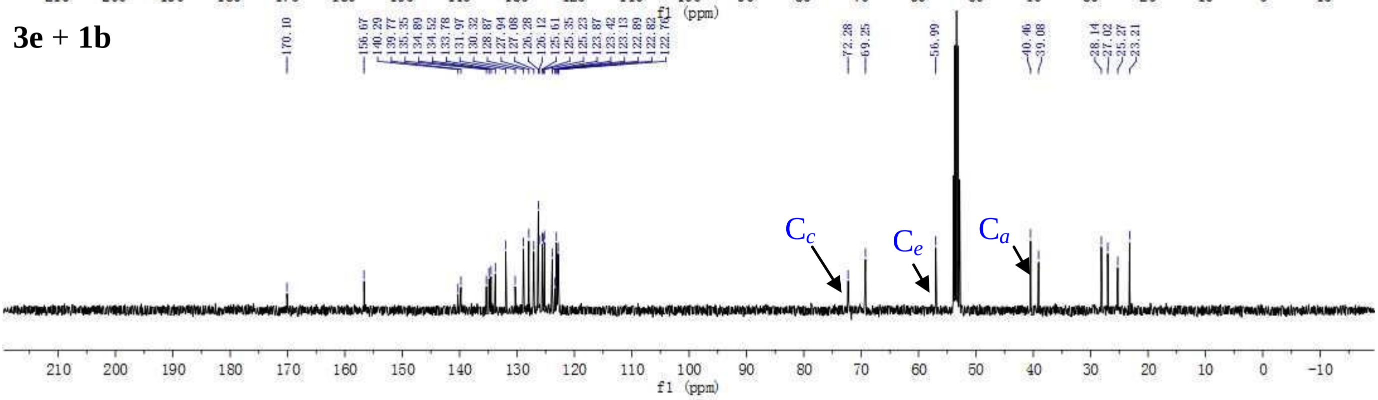
3e



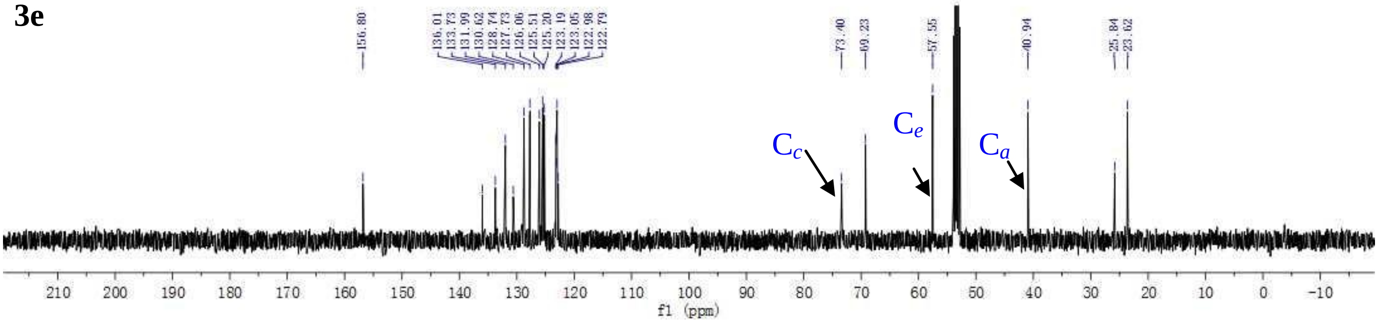
1b



3e + 1b

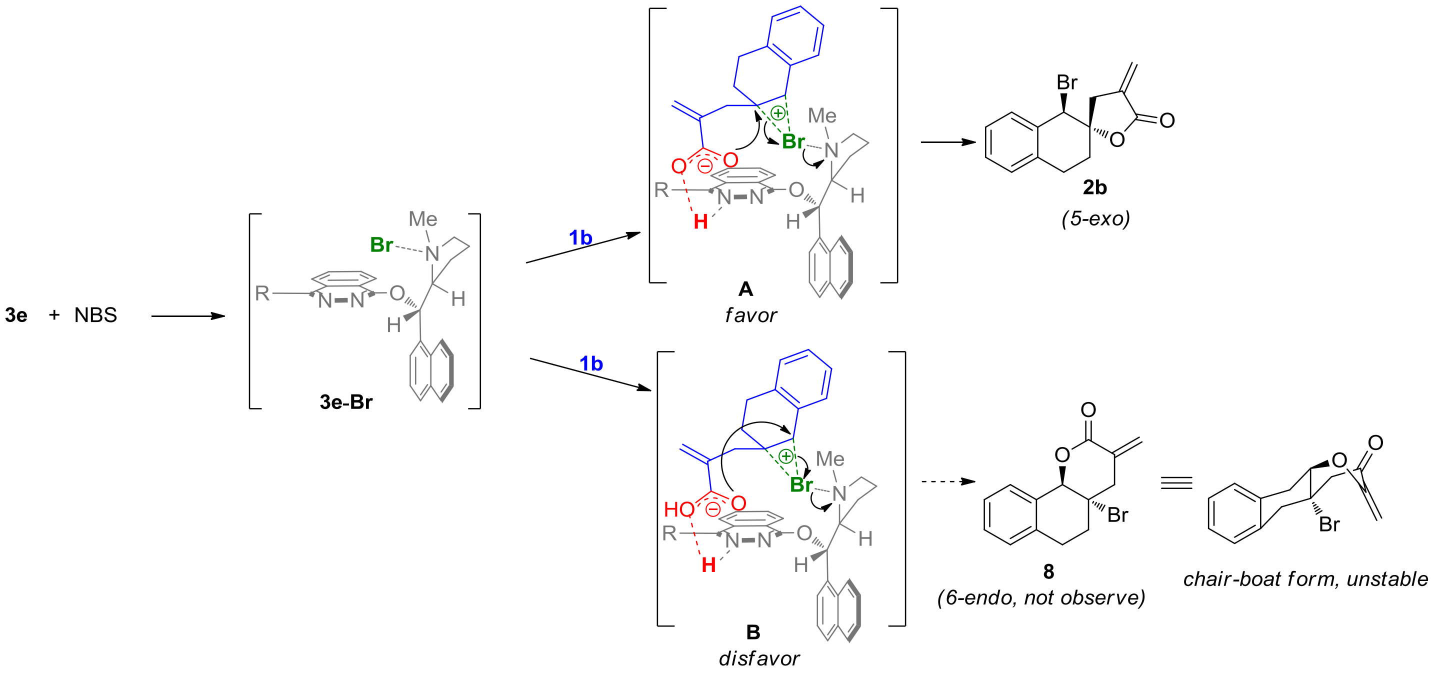


3e



Mechanistic study of 5-*exo*-cyclization

Theoretically, both 5-exo-cyclization and 6-endo-cyclization are possible according to the Baldwin's Rules. The high selectivity of 5-exo-cyclization might contribute to the more stable tertiary carbocation in transition state A, while the corresponding secondary carbocation in B was less stable. In addition, as shown in scheme the resulting product **8** which processes a *cis*-fused ring system might not be stable. Therefore, 5-exo-cyclization is strongly favored over 6-endo-cyclization, and provides the spiro halolactone **2b** exclusively.



Sulforhodamine B Assay[1]: The cell proliferation of adherent cells was determined by sulforhodamine B assay (SRB). Cells were seeded in 96-well plates and then treated with different concentrations of drugs. After 72 hr of incubation, cells were fixed with 10% trichloroacetic acid for 1 hr at 4°C, washed 5 times with tap water and air-dried. Cells that survived were stained with 0.4% (w/v) sulforhodamine B (SRB) for 20 min at room temperature and washed 5 times with 1% acetic acid. Bound SRB was solubilized with 10 mM Tris and absorbance was measured at 540 nm.

Cell code	Cell culture conditions
H1975(L858R/T790M)	Medium 1640 with 1.5 mM L-glutamine adjusted to contain 2.2 g/L sodium bicarbonate, 90%; fetal bovine serum, 10%
A431	DMEM with 1.5 mM L-glutamine adjusted to contain 2.2 g/L sodium bicarbonate, 90%; fetal bovine serum, 10%

H1975 (L858R/T790M) cell IC_{50} results

Compound	Repeat 1 (uM)	Repeat 2 (uM)	Average (uM)	SD
2a *(rac)*	4.87	5.10	4.98	0.95

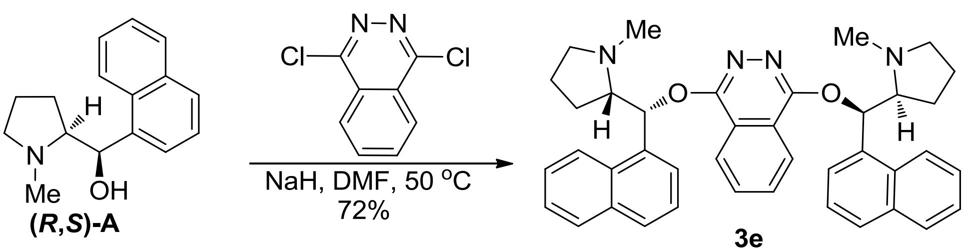
2b *(rac)*	1.68	1.83	1.76	0.26
2c *(rac)*	0.80	1.36	1.08	0.4
2c *(96% ee)*	1.2	1.19	1.2	0.1
***ent*-2c** *(96% ee)*	0.95	1.04	1.0	0.15
parthenolide	1.31	1.54	1.43	0.16

A431 cell IC_{50} results

Compound	**Repeat 1 (uM)**	**Repeat 2 (uM)**	**Average (uM)**	**SD**
2a *(rac)*	2.63	2.94	2.79	0.51
2b *(rac)*	4.63	4.81	4.72	0.8
2c *(rac)*	1.33	1.20	1.27	0.09
2c *(96% ee)*	3.1	3.4	3.3	0.4
***ent*-2c** *(96% ee)*	2.2	2.8	2.5	0.5
parthenolide	3.18	1.95	2.57	0.87

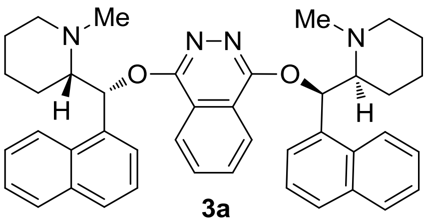
SYNTHESIS OF AMINO-ACID-DERIVED PHTHALAZINE CATALYSTS

Representative Procedure for the Preparation of Amino-acid-derived Phthalazine Catalyst.[2]



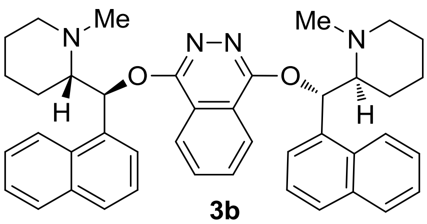
To a solution of (***R***, ***S***)-**A**[2](482 mg, 2 mmol, 2.0 eq) in DMF (6 mL) was added NaH (dispersion in mineral oil, 120 mg, 3 mmol) in one portion at room temperature. After stirring for 15 min, 1,4-dichlorophthalazine (239 mg, 1.2 mmol, 0.6 eq) was added to the reaction. The reaction was stirred for 24 h at 50 ^{o}C. After evaporation of DMF, the residue was purified by flash column chromatography (MeOH/EtOAc 1:10) to afford amino-acid-derived phthalazine catalyst **3e** in 72% yield.

1,4-bis((*R*)-((*S*)-1-methylpyrrolidin-2-yl)(naphthalen-1-yl)methoxy)phthalazine, **3e**
438 mg, 72%, yellow solid; MP 90–91 ℃; $[\alpha]_D^{25}$= 15.5 (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.45-7.33 (m, 20H), 3.15-3.10 (m, 2H), 3.03-2.98 (m, 2H), 2.51 (s, 6H), 2.45-2.24 (m, 4H), 2.02-1.93 (m, 2H), 1.78-1.58 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 156.8, 135.6, 133.8, 131.9, 130.6, 128.8, 127.9, 125.9, 125.5, 125.3, 123.5, 123.2, 123.1, 122.9; HRMS (TOF$^+$) calcd. for $C_{40}H_{40}N_4O_2$ $[M+H]^+$ 609.3579, found 609.3577.



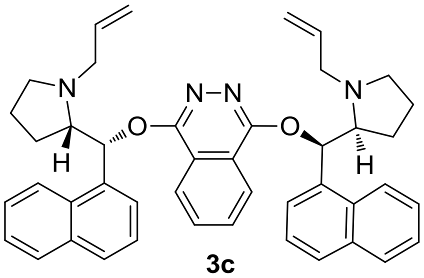
3a

1,4-bis((*R*)-((*S*)-1-methylpiperidin-2-yl)(naphthalen-1-yl)methoxy)phthalazine
509 mg, 80%, yellow solid; MP 91–92 ℃; $[\alpha]_D^{25}$= 15.4 (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.53-7.28 (m, 20H), 3.01-2.88 (m, 3H), 2.66 (s, 6H), 2.57-2.53 (m, 2H), 2.19-2.12 (m, 2H), 2.05-1.95 (m, 1H), 1.78-1.54 (m, 6H), 1.10-0.97 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 156.7, 134.9, 133.9, 132.0, 128.9, 127.9, 125.9, 125.5, 125.0, 123.8, 123.6, 123.5, 123.1, 71.7, 62.3, 58.2, 43.7, 25.8, 24.7, 24.5; HRMS (TOF$^+$) calcd. for $C_{42}H_{44}N_4O_2$ $[M+H]^+$ 637.5579, found 637.5590.



3b

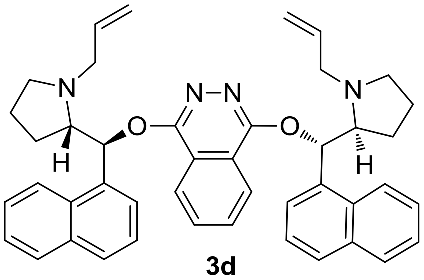
1,4-bis((*S*)-((*S*)-1-methylpiperidin-2-yl)(naphthalen-1-yl)methoxy)phthalazine
477 mg, 75%, yellow solid; MP 93–94 ℃; $[\alpha]_D^{25}$= –36.9 (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.66-7.11 (m, 20H), 3.41-3.35 (m, 2H), 2.95-2.91 (m, 2H), 2.43 (s, 6H), 2.49-2.39 (m, 2H), 1.56-1.51 (m, 6H), 1.18-1.03 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 156.1, 135.7, 134.0, 131.8, 131.6, 128.7, 128.4, 127.1, 125.9, 125.4, 125.3, 123.1, 122.8, 78.4, 66.3, 55.6, 42.9, 27.3, 24.2, 23.5; HRMS (TOF$^+$) calcd. for $C_{42}H_{44}N_4O_2$ $[M+H]^+$ 637.5579, found 637.5584.



3c

1,4-bis((*R*)-((*S*)-1-allylpyrrolidin-2-yl)(naphthalen-1-yl)methoxy)phthalazine

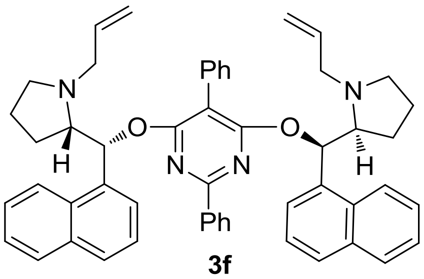
449 mg, 68%, yellow solid; MP 94-95 ℃; $[\alpha]_D^{25}$=18.6 (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.93-7.48 (m, 16H), 6.15-6.02(m, 2H), 5.69 (s, broad, 2H), 5.42-5.25 (m, 4H), 3.83-3.77 (m, 2H), 3.29-3.10 (m, 6H), 2.48-2.39 (m, 2H), 1.81-1.60 (m, 8H), 1.19-1.12 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 136.7, 135.6, 133.6, 130.1, 129.0, 127.4, 125.7, 125.6, 125.3, 123.3, 122.6, 117.6, 67.3, 67.1, 57.0, 54.8, 24.4, 23.4; HRMS (TOF$^+$) calcd. for $C_{44}H_{44}N_4O_2$ $[M+H]^+$ 661.3534, found 661.3537.



3d

1,4-bis((*S*)-((*S*)-1-allylpyrrolidin-2-yl)(naphthalen-1-yl)methoxy)phthalazine

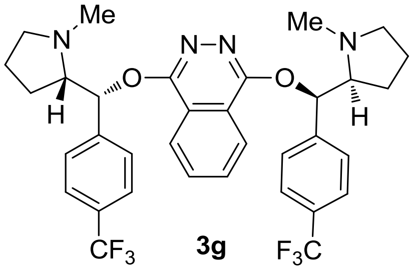
437 mg, 66%, yellow solid; MP 93-94 ℃; $[\alpha]_D^{25}$= –20.7 (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.58-7.09 (m, 21H), 5.81-5.68 (m, 2H), 5.00-4.92 (m, 4H), 3.65-3.59 (m, 2H), 3.40-3.33 (m, 2H), 3.15-3.10 (m, 2H), 3.00-2.92 (m, 2H), 2.45-2.36 (m, 2H), 1.82-1.61 (m, 7H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 156.9, 136.4, 136.0, 133.9, 131.7, 131.5, 128.7, 128.1, 125.8, 125.4, 125.2, 124.8, 123.1, 122.9, 116.2, 78.7, 66.6, 59.5, 54.6, 29.0, 24.4; HRMS (TOF$^+$) calcd. for $C_{44}H_{44}N_4O_2$ $[M+H]^+$ 661.3534, found 661.3532.



3f

4,6-bis((*R*)-((*S*)-1-allylpyrrolidin-2-yl)(naphthalen-1-yl)methoxy)-2,5-diphenylpyrimidine

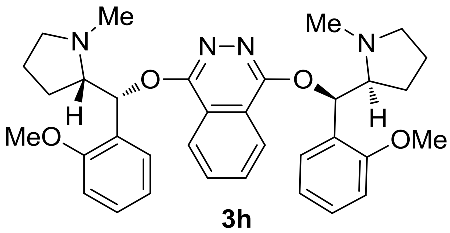
465.4 mg, 61%, yellow solid; MP 149-150 ℃; $[\alpha]_D^{25}$= 17.4 (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.39-7.09 (m, 26H), 5.73-5.60 (m, 2H), 5.05-4.95 (m 4H), 3.25-3.19 (m, 4H), 3.08-3.04 (m, 2H), 2.95-2.88 (m, 2H), 2.40-2.32 (m, 2H), 2.11-2.04 (m, 2H), 1.75-1.59 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.8, 153.5, 130.2, 129.3, 126.6, 124.0, 123.9, 122.9, 121.7, 120.9, 120.7, 120.6, 120.2, 118.6, 118.3, 118.2, 117.4, 116.8, 109.2, 97.5, 68.7, 59.7, 50.8, 47.5, 19.7, 16.3; HRMS (TOF$^+$) calcd. for $C_{52}H_{50}N_4O_2$ $[M+H]^+$ 763.4007, found 763.4039.



3g

1,4-bis((*R*)-((*S*)-1-methylpyrrolidin-2-yl)(4-(trifluoromethyl)phenyl)methoxy)phthalazine

405 mg, 63%, yellow solid; MP 86-87 ℃; $[\alpha]_D^{25}$= 24.9 (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.32-6.51 (m, 14H), 3.12-3.06 (m, 2H), 2.36 (s, 6H), 2.33-2.26 (m, 2H), 2.22-2.15 (m, 2H), 1.88-1.72 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 156.8, 143.8, 132.1, 129.8, 129.3, 127.0, 125.2 (q, J = 3.8 Hz), 123.1, 122.8, 76.1, 70.6, 57.5, 41.6, 25.9, 23.5; HRMS (TOF$^+$) calcd. for $C_{34}H_{34}F_6N_4O_2$ $[M+H]^+$ 645.3755, found 645.3764.



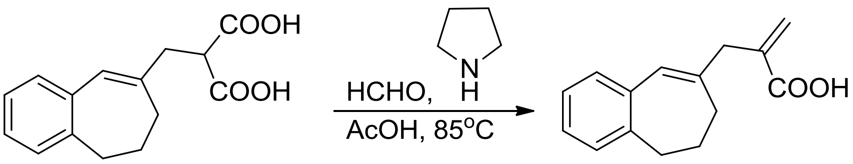
3h

1,4-bis((*R*)-(2-methoxyphenyl)((*S*)-1-methylpyrrolidin-2-yl)methoxy)phthalazine

364 mg, 64%, yellow solid; MP 82-83 ℃; $[\alpha]_D^{25}$= 25.8 (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.39-6.72 (m, 14H), 3.90 (s, 6H), 3.15-3.12 (m, 2H), 3.35-3.33 (m, 2H), 2.26 (s, 6H), 1.88-1.63 (m, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 156.9, 156.6, 131.6, 128.6, 128.2, 127.2, 123.2, 122.8, 120.4, 110.7, 74.9, 68.4, 58.6, 55.6, 43.6, 28.3, 24.1; HRMS (TOF$^+$) calcd. for $C_{34}H_{40}N_4O_4$ $[M+H]^+$ 569.6761, found 569.6759.

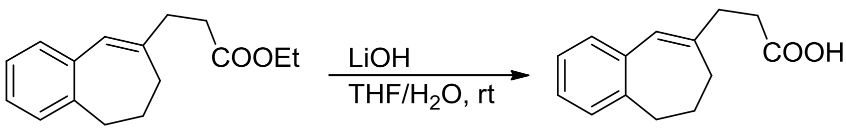
SYNTHESIS OF DIENOIC ACID SUBSTRATES AND ASYMMETRIC HALOLACTONIZATION REACTIONS

Representative Procedure for the Synthesis of Dienoic Acid Substrate.[3]



1c

Prepared from the di-acid according to the reported procedure.[3] To a solution of di-acid (780 mg, 3.0 mmol, 1.0 eq.) in acetic acid (6 mL) was added pyrrolidine (0.1 mL, 1.2 mmol, 0.4 eq.) and formaldehyde solution (36.5-38% in H_2O, 1mL, 13.2 mmol, 4.4 eq.) at room temperature. The mixture was then stirred for 24 h at 85°C. After evaporation of acetic acid, water and EtOAc were added. The organic layer was washed with water, and dried over magnesium sulfate. Concentration of the organic layer offered the crude product that was further purified by flash column chromatography (hexane/EtOAc) to give the corresponding enoic acid **1c** 478.9 mg, 70%, ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.24-7.17 (m, 4H), 6.52 (s, 1H), 6.44 (s, 1H), 5.85 (s, 1H), 3.28 (s, 2H), 2.87-2.84 (m, 2H), 2.39 (t, J = 8.0 Hz, 2H), 2.11-2.05 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 173.0, 141.3, 140.5, 138.7, 136.5, 130.5, 129.0, 128.6, 126.4, 126.0, 41.8, 35.5, 34.3, 28.3.

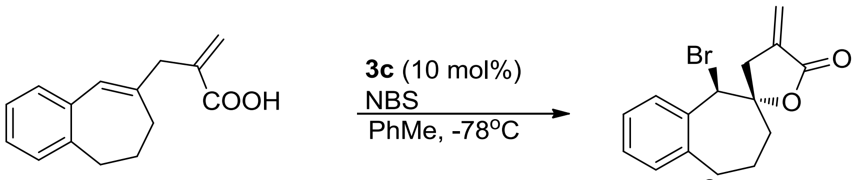


7b

Representative Procedure for the Synthesis of Alkenoic Acid Substrates.[4]

Prepared from the ester according to the reported procedure.[4] To a solution of ester (244 mg, 1.0 mmol, 1.0 eq.) in THF/H2O (v/v = 1:1, 4 mL) was added LiOH (2.0 mmol, 2 eq.) at room temperature. The mixture was then stirred for 24 h. After evaporation of THF, HCl (1M, 3 mL), water and EtOAc were added. The organic layer was washed with water, and dried over magnesium sulfate. Concentration of the organic layer offered the crude product that was further purified by flash column chromatography (hexane/EtOAc) to give the corresponding alkenoic acid **7b** 194.4 mg, 90%, white solid; MP 120-121 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.18-7.13 (m, 4H), 6.36 (s, 1H), 2.79-2.55 (m, 6H), 2.31 (t, J = 8.0 Hz, 2H), 2.09-2.05 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 179.5, 141.8, 141.2, 136.7, 130.2, 128.9, 126.8, 126.3, 125.9, 35.2, 34.9, 33.7, 33.6, 28.8; HRMS (TOF^{-}) calcd. for $C_{14}H_{16}O_2$ $[M-H]^+$ 215.7044, found 215.7043.

Representative Procedure for Asymmtric Bromolactionization.

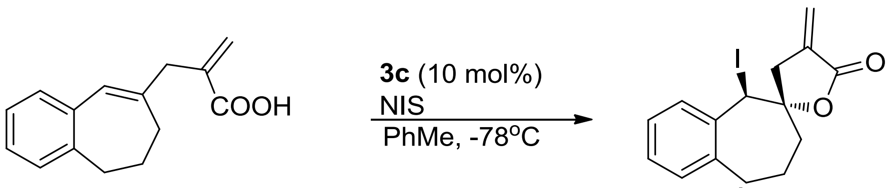


1c 2c

To a PhMe (4 mL) solution of dienoic acid **1c** (22.8 mg, 0.1 mmol, 1.0 equiv), and catalyst **3c** (6.7 mg, 0.01 mmol, 0.1 equiv), at −78 °C, in dark under nitrogen was added NBS (21.2 mg, 0.12 mmol, 1.2 equiv). The resulting mixture was stirred at −78 °C and monitored by TLC. The reaction was quenched with saturated Na_2SO_3 (1 mL) at −78 °C and then was warm to room temperature. The solution was diluted with water (3 mL) and extrated with EtOAc, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc) to yield the corresponding lactone **2c**.

1 mmol scale procedure of 2c

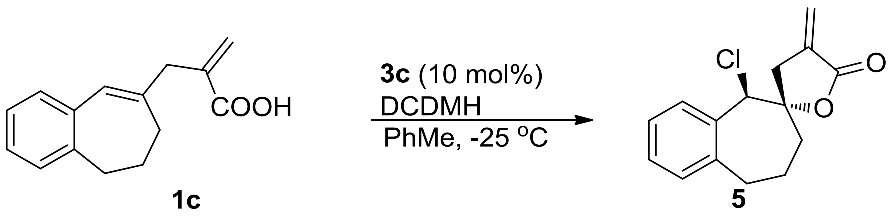
To a PhMe (40 mL) solution of dienoic acid **1c** (228 mg, 1 mmol, 1.0 equiv), and catalyst **3c** (67 mg, 0.1 mmol, 0.1 equiv), at −78 °C, in dark under nitrogen was added NBS (212 mg, 1.2 mmol, 1.2 equiv). The resulting mixture was stirred at −78 °C and monitored by TLC. The reaction was quenched with saturated Na_2SO_3 (10 mL) at −78 °C and then was warm to room temperature. The solution was diluted with water (30 mL) and extrated with EtOAc, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc) to yield the corresponding lactone **2c** 302.6 mg, 99% yeild.



1c 4a

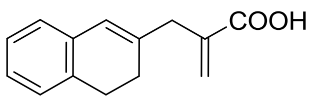
Representative Procedure for Asymmtric Iodolactionization.

To a PhMe (4 mL) solution of dienoic acid **1c** (22.8 mg, 0.1 mmol, 1.0 equiv), and catalyst **3c** (6.7 mg, 0.01 mmol, 0.1 equiv), at −78 °C, in dark under nitrogen was added NIS (26.9 mg, 0.12 mmol, 1.2 equiv). The resulting mixture was stirred at −78 °C and monitored by TLC. The reaction was quenched with saturated Na_2SO_3 (1 mL) at −78 °C and then was warm to room temperature. The solution was diluted with water (3 mL) and extrated with EtOAc, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc) to yield the corresponding lactone **4a**.



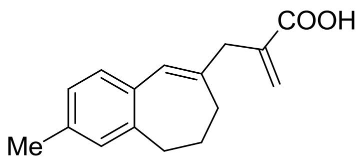
Representative Procedure for Asymmtric Chlorolactionization.

To a PhMe (4 mL) solution of dienoic acid **1c** (22.8 mg, 0.1 mmol, 1.0 equiv), and catalyst **3c** (6.7 mg, 0.01 mmol, 0.1 equiv), at −25 °C, in dark under nitrogen was added DCDMH (23.6 mg, 0.12 mmol, 1.2 equiv). The resulting mixture was stirred at −25 °C and monitored by TLC. The reaction was quenched with saturated Na_2SO_3 (1 mL) at −25 °C and then was warm to room temperature. The solution was diluted with water (3 mL) and extrated with EtOAc, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc) to yield the corresponding lactone **4**.



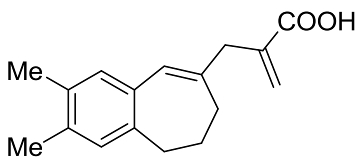
1b

449.4 mg, 70%; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.20-7.04 (m, 4H), 6.48 (s, 1H), 6.33 (s, 1H), 5.82 (s, 1H), 3.24 (s, 2H), 2.89 (t, J = 8.0 Hz, 2H), 2.33 (t, J = 9.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 172.8, 138.2, 137.7, 134.5, 134.4, 128.8, 127.3, 126.6, 126.5, 125.8, 124.8, 38.8, 28.2, 27.1.



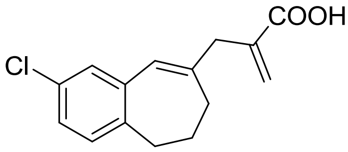
1d

515.5 mg, 71%, white solid; MP 131-132 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.01-6.91 (m, 3H), 6.43 (s, 1H), 6.32 (s, 1H), 5.78 (s, 1H), 3.20 (s, 2H), 2.77-2.75 (m, 2H), 2.35-2.29 (m, 5H), 2.03-1.97 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.9, 140.3, 138.6, 138.3, 136.2, 135.2, 131.2, 128.9, 128.5, 128.3, 127.0, 41.8, 34.7, 34.3, 28.3, 20.8; HRMS (TOF$^+$) calcd. for $C_{16}H_{18}O_2$ $[M+H]^+$ 243.5077, found 243.5076.



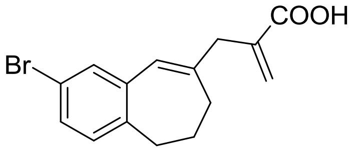
1e

529.9 mg, 69%, white solid; MP 139-140 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.94 (s, 1H), 6.90 (s, 1H), 6.44 (s, 1H), 6.31 (s, 1H), 5.79 (s, 1H), 3.20 (s, 2H), 2.78-2.75 (m, 2H), 2.34 (t, J = 8.0 Hz, 2H), 2.25 (s, 6H), 2.03-1.97 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.7, 139.2, 138.8, 138.7, 134.5, 133.8, 132.1, 130.5, 128.4, 128.2, 41.8, 34.9, 34.5, 28.0, 19.2, 19.0; HRMS (TOF$^+$) calcd. for $C_{17}H_{20}O_2$ $[M+H]^+$ 257.2894, found 257.2895.



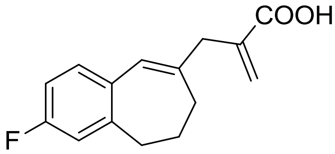
1f

534.5 mg, 68%, yellow solid; MP 129-130 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.14-7.04 (m, 3H), 6.44 (s, 1H), 6.30 (s, 1H), 5.78 (s, 1H), 3.20 (s, 2H), 2.75-2.73 (m, 2H), 2.31 (t, J = 8.0 Hz, 2H), 2.03-1.97 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.4, 143.0, 141.1, 138.3, 135.0, 131.6, 128.8, 128.7, 127.3, 125.9, 41.7, 34.9, 34.2, 28.0; HRMS (TOF$^+$) calcd. for $C_{15}H_{15}ClO_2$ $[M+H]^+$ 263.1962, found 263.1961.



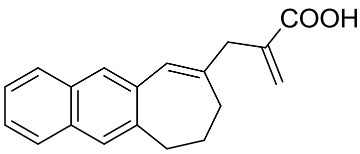
1g

615.1 mg, 67%, yellow solid; MP 144-145 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.29-6.98 (m, 3H), 6.44 (s, 1H), 6.29 (s, 1H), 5.79 (s, 1H), 3.20 (s, 2H), 2.75-2.72 (m, 2H), 2.31 (t, J = 8.0 Hz, 2H), 2.03-1.97 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.5, 143.3, 141.3, 138.3, 135.5, 131.9, 131.7, 128.8, 127.3, 119.8, 41.7, 34.8, 34.2, 28.1; HRMS (TOF$^+$) calcd. for $C_{15}H_{15}BrO_2$ $[M+H]^+$ 307.5022, found 307.5024.



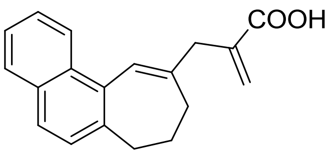
1h

524.0 mg, 71%, yellow solid; MP 137-138 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.06-6.76 (m, 3H), 6.45 (s, 1H), 6.29 (s, 1H), 5.79 (s, 1H), 3.21 (s, 2H), 2.75-2.72 (m, 2H), 2.31 (t, J = 8.0 Hz, 2H), 2.03-1.97 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.3, 162.5 (d, J = 244.0 Hz), 142.1, 138.4 (d, J = 7.0 Hz), 138.3, 137.0 (d, J = 3.0 Hz), 130.2 (d, J = 8.0 Hz), 128.7, 127.4 (d, J = 2.0 Hz), 116.6 (d, J = 21.0 Hz), 112.8 (d, J = 21.0 Hz), 41.6, 34.2, 34.0, 28.5; HRMS (TOF$^+$) calcd. for $C_{15}H_{15}FO_2$ $[M+H]^+$ 247.3908, found 247.3909.



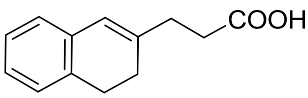
1i

600.5 mg, 72%, white solid; MP 131-132 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.05-7.37 (m, 6H), 7.04 (s, 1H), 6.53 (s, 1H), 5.91 (s, 1H), 3.47 (s, 2H), 2.79 (t, J = 8.0 Hz, 2H), 2.33-2.26 (m, 2H), 2.10 (t, J = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.7, 142.7, 138.6, 133.8, 132.3, 131.8, 128.9, 128.2, 126.6, 125.7, 124.8, 124.6, 124.0, 40.9, 35.3, 33.2, 29.8; HRMS (TOF$^+$) calcd. for $C_{19}H_{18}O_2$ $[M+H]^+$ 279.6127, found 279.6128.



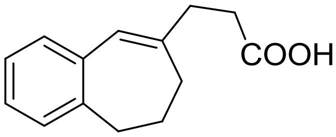
1j

583.8 mg, 70%, white solid; MP 129-130 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.16-7.27 (m, 6H), 6.59 (s, 1H), 6.49 (s, 1H), 5.86 (s, 1H), 3.35 (s, 2H), 3.20-3.17 (m, 2H), 2.32-2.18 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.6, 142.3, 138.6, 136.9, 135.2, 132.5, 132.0, 128.9, 128.7, 128.6, 127.7, 125.9, 125.7, 124.9, 123.8, 41.2, 32.9, 32.0, 27.2; HRMS (TOF$^+$) calcd. for $C_{19}H_{18}O_2$ $[M+H]^+$ 279.6124, found 279.6125.



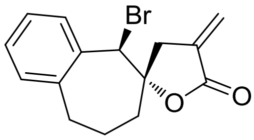
6a

185.8 mg, 92%, white solid; MP 114-115 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.18-7.04 (m, 4H), 6.30 (s, 1H), 2.89 (t, J = 8.0 Hz, 2H), 2.67-2.59 (m, 4H), 2.33 (t, J = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 179.7, 139.6, 134.5, 134.4, 127.3, 126.5, 125.7, 122.9, 32.4, 32.0, 28.1, 27.3; HRMS (TOF$^-$) calcd. for $C_{13}H_{14}O_2$ $[M-H]^+$ 201.3985, found 201.3984.



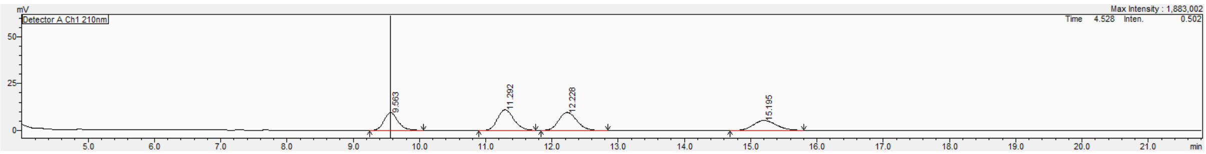
6b

200.8 mg, 93%, white solid; MP 120-121 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.18-7.13 (m, 4H), 6.36 (s, 1H), 2.79-2.55 (m, 6H), 2.31 (t, J = 4.0 Hz, 2H), 2.09-2.05 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 179.5, 141.8, 141.2, 136.7, 130.2, 128.9, 126.8, 126.3, 125.9, 35.2, 34.9, 33.7, 33.6, 28.8; HRMS (TOF$^-$) calcd. for $C_{14}H_{16}O_2$ $[M-H]^+$ 215.2472, found 215.2474.

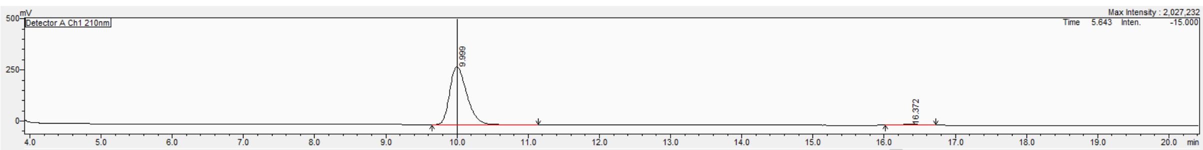


2c

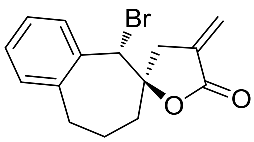
30.3 mg, 99%; white solid; MP 138-139 ℃; $[\alpha]_D^{25}$=−33.0 (c 1.0, MeOH, 96% ee); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.26-7.13 (m, 4H) 6.33 (t, J = 3.0 Hz, 1H), 5.76 (t, J = 3.0 Hz, 1H), 4.95 (s, 1H), 3.33-2.71 (m, 5H), 2.03-1.87 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 169.1, 142.9, 135.4, 134.4, 131.0, 130.8, 129.4, 126.5, 123.8, 84.5, 61.9, 42.3, 38.6, 34.5, 23.0; HPLC (Daicel Chiralcel OD-H, i-PrOH/Hexane = 10/90, 1.0 mL/min, 210 nm) t_1 = 10.0 min (major), t_2 = 16.4 min (minor).



Peak#	Ret. Time	Area	Height	Conc.	Area%
1	9.563	140748	9466	21.916	21.916
2	11.292	187752	10972	29.234	29.234
3	12.228	184083	9683	28.663	28.663
4	15.195	129646	5299	20.187	20.187
Total		642229	35419	100.000	100.000

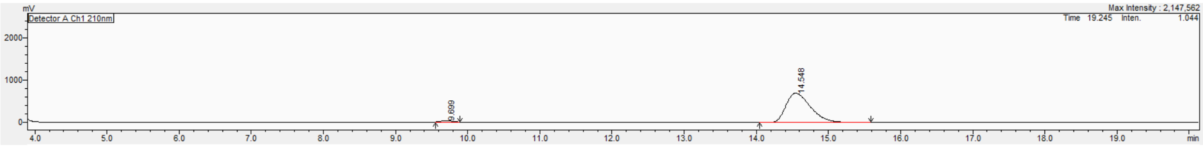


Peak#	Ret. Time	Area	Height	Conc.	Area%
1	9.999	4741793	283967	98.175	98.175
2	16.372	88154	3768	1.825	1.825
Total		4829946	287735	100.000	100.000

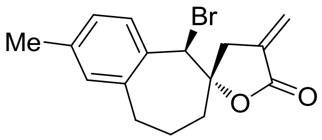


ent-**2c**

30.3 mg, 99%; colorless oil; $[\alpha]_D^{25}$=+33.2 (c 1.0, MeOH, −96% ee); HPLC (Daicel Chiralcel OD-H, i-PrOH/Hexane = 10/90, 1.0 mL/min, 210 nm) t_1 = 9.7 min (minor), t_2 = 14.6 min (major).

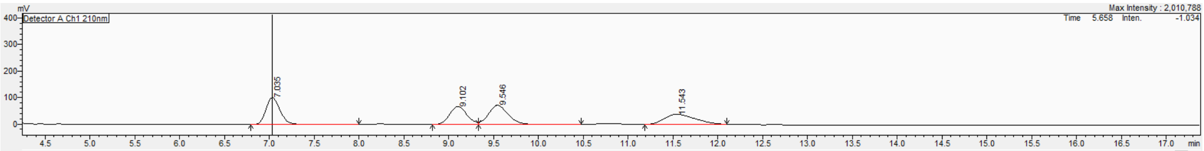


Peak#	Ret. Time	Area	Height	Conc.	Area%
1	9.699	350115	31677	2.100	2.100
2	14.548	16319532	690548	97.900	97.900
Total		16669647	722226	100.000	100.000

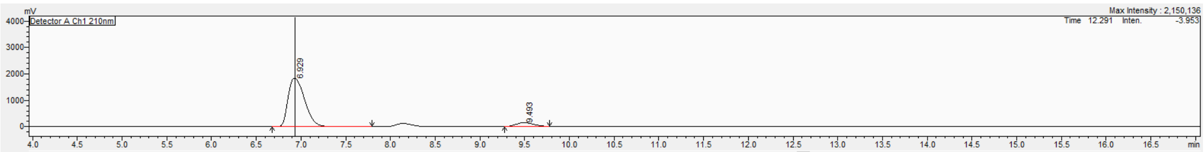


2d

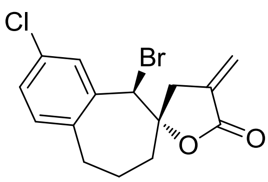
31.4 mg, 98%; yellow oil; $[\alpha]_D^{25}$=−17.0 (*c* 1.0, MeOH, 84% ee); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.06-6.98 (m, 3H), 6.32 (s, 1H), 5.74 (s, 1H), 4.90 (s, 1H), 3.25-2.71 (m, 5H), 2.30 (s, 3H), 2.03-1.86 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.0, 139.9, 136.0, 135.1, 134.5, 131.7, 130.7, 130.0, 123.6, 84.5, 62.2, 42.4, 38.7, 34.1, 21.2, 20.7; HRMS (TOF$^+$) calcd. for $C_{16}H_{17}BrO_2$ $[M+H]^+$ 321.4708, found 321.4709; HPLC (Daicel Chiralcel OD-H, *i*-PrOH/Hexane = 10/90, 1.0 mL/min, 210 nm) t_1 = 6.9 min (major), t_2 = 9.5 min (minor).



Peak#	Ret. Time	Area	Height	Conc.	Area%
1	7.035	1093580	101449	27.150	27.150
2	9.102	906161	67556	22.497	22.497
3	9.546	1108971	73035	27.532	27.532
4	11.543	919153	38531	22.820	22.820
Total		4027866	280571	100.000	100.000

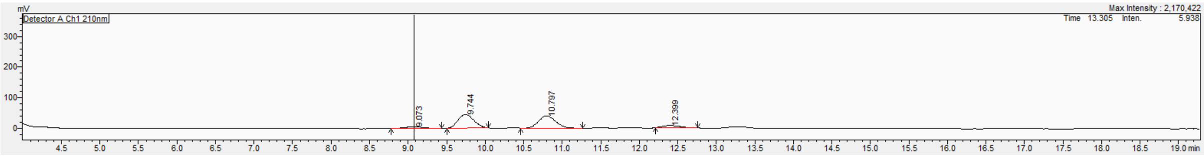


Peak#	Ret. Time	Area	Height	Conc.	Area%
1	6.929	23414647	1842372	91.861	91.861
2	9.493	2074479	148225	8.139	8.139
Total		25489126	1990596	100.000	100.000

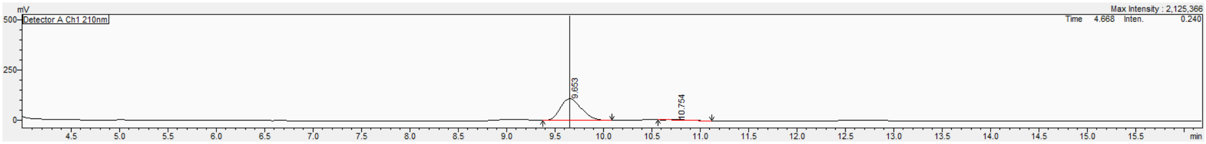


2e

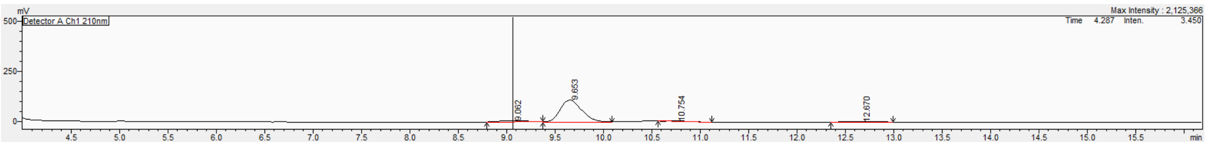
32.6 mg, 96%; yellow oil; $[\alpha]_D^{25}$=−41.0 (*c* 1.0, MeOH, 97% ee), dr = 90:10; the main peaks of NMR were assigned: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.16-7.11 (m, 3H), 6.33 (s, 1H), 5.76 (s, 1H), 4.90 (s, 1H), 3.29-2.73 (m, 5H), 2.03-1.89 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.8， 144.8， 135.0， 134.1， 132.2， 130.7， 126.4， 124.0， 84.2， 60.7， 42.2， 38.4， 34.2， 22.7; HRMS (TOF$^+$) calcd. for $C_{15}H_{14}ClBrO_2$ $[M+H]^+$ 341.0963, found 341.0964; HPLC (Daicel Chiralcel OD-H, *i*-PrOH/Hexane = 10/90, 1.0 mL/min, 210 nm) t_1 = 9.7 min (major), t_2 = 10.8 min (minor).



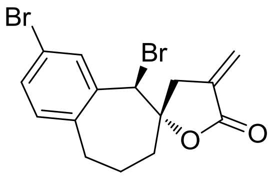
Peak#	Ret. Time	Area	Height	Conc.	Area%
1	9.073	109471	5940	7.427	7.427
2	9.744	640080	44570	43.428	43.428
3	10.797	605618	39603	41.090	41.090
4	12.399	118713	7242	8.054	8.054
Total		1473883	97355	100.000	100.000



Peak#	Ret. Time	Area	Height	Conc.	Area%
1	9.653	1733285	110532	98.474	98.474
2	10.754	26865	2569	1.526	1.526
Total		1760151	113101	100.000	100.000

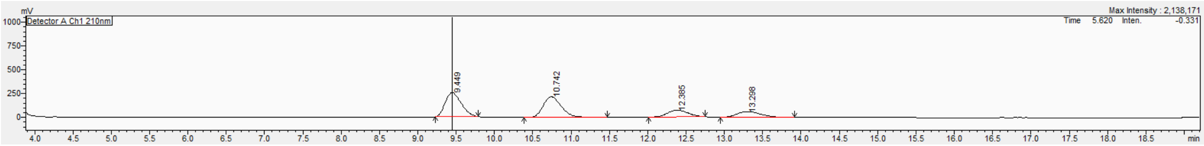


Peak#	Ret. Time	Area	Height	Conc.	Area%
1	9.062	128978	6941	6.630	6.630
2	9.653	1733285	110532	89.095	89.095
3	10.754	26865	2569	1.381	1.381
4	12.670	56309	2511	2.894	2.894
Total		1945439	122553	100.000	100.000

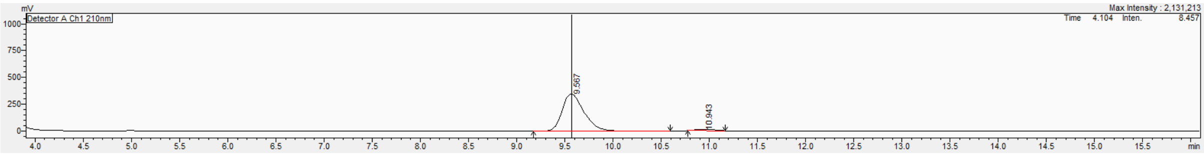


2f

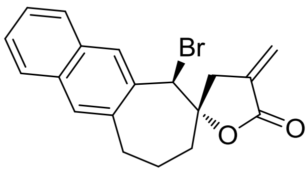
37.2 mg, 97%; yellow oil; $[\alpha]_D^{25}$=−38.5 (*c* 1.0, MeOH, 94% ee), dr > 99:1; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.32-7.03 (m, 3H), 6.33 (s, 1H), 5.75 (s, 1H), 4.91-4.88 (m, 1H), 3.30-2.71 (m, 5H), 2.03-1.88 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.7, 145.0, 134.5, 134.1, 133.6, 132.4, 129.5, 123.9, 123.4, 84.1, 60.7, 42.2, 38.4, 34.2, 22.7; HRMS (TOF$^+$) calcd. for $C_{15}H_{14}Br_2O_2$ $[M+H]^+$ 385.1546, found 385.1547; HPLC (Daicel Chiralcel OD-H, *i*-PrOH/Hexane = 10/90, 1.0 mL/min, 210 nm) t_1 = 9.6 min (major), t_2 = 10.9 min (minor).



Peak#	Ret. Time	Area	Height	Conc.	Area%
1	9.449	3672324	252156	37.111	37.111
2	10.742	3653222	218000	36.918	36.918
3	12.385	1293357	70244	13.070	13.070
4	13.298	1276722	59885	12.902	12.902
Total		9895625	600285	100.000	100.000

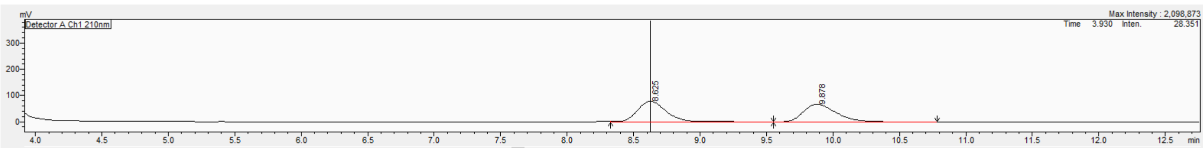


Peak#	Ret. Time	Area	Height	Conc.	Area%
1	9.567	5434597	343272	96.951	96.951
2	10.943	170898	13269	3.049	3.049
Total		5605495	356541	100.000	100.000

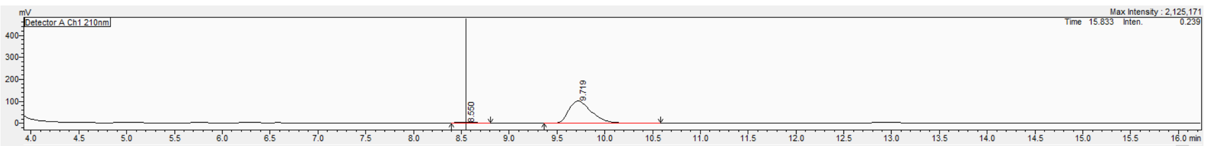


2g

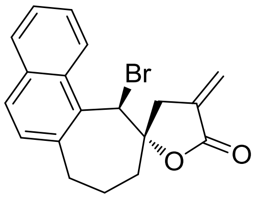
36.1 mg, 99%; white solid; MP 167-168 ℃; $[\alpha]_D^{25}$=−77.5 (*c* 1.0, MeOH, -95% ee), dr > 99:1; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.97-7.28 (m, 6H), 6.35 (s, 1H), 6.05 (s, 1H), 5.81 (s, 1H), 3.53-2.85 (m, 5H), 2.13-2.01 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.8, 142.5, 134.4, 132.8, 132.0, 129.9, 129.7, 129.1, 127.2, 125.0, 123.8, 121.4, 84.6, 53.7, 43.2, 38.9, 35.4, 22.7; HRMS (TOF$^+$) calcd. for $C_{19}H_{17}BrO_2$ $[M+H]^+$ 357.4826, found 357.4826; HPLC (Daicel Chiralcel OD-H, *i*-PrOH/Hexane = 10/90, 1.0 mL/min, 210 nm) t_1 = 8.6 min (minor), t_2 = 9.7 min (major).



Peak#	Ret. Time	Area	Height	Conc.	Area%
1	8.625	1199062	78541	50.807	50.807
2	9.878	1160986	67658	49.193	49.193
Total		2360048	146199	100.000	100.000

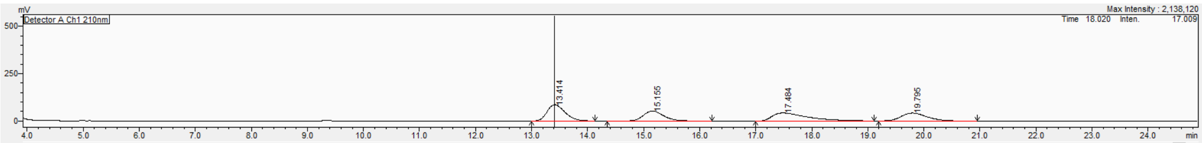


Peak#	Ret. Time	Area	Height	Conc.	Area%
1	8.550	45801	3788	2.687	2.687
2	9.719	1658875	100663	97.313	97.313
Total		1704676	104451	100.000	100.000

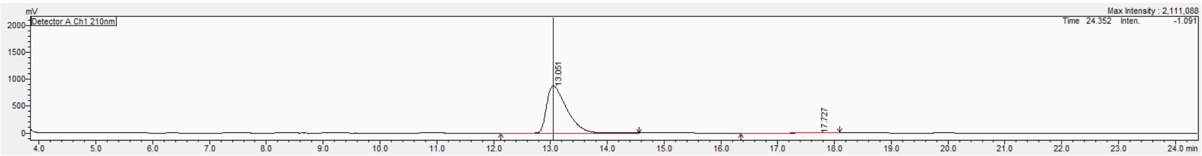


2h

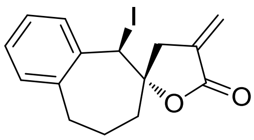
36.1 mg, 99%; yellow oil; $[\alpha]_D^{25}$=+63.0 (c 1.0, MeOH, 99.8% ee), dr > 99:1; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.23-7.31 (m, 6H), 6.33 (s, 1H), 5.76 (s, 1H), 5.19 (s, 1H), 3.83-2.73 (m, 5H), 2.10-1.91 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.8, 134.5, 134.0, 132.4, 132.0, 128.7, 128.4, 126.8, 126.4, 126.2, 123.7, 123.5, 84.3, 62.0, 41.9, 38.8, 25.6, 22.2; HRMS (TOF$^+$) calcd. for $C_{19}H_{17}BrO_2$ $[M+H]^+$ 357.4826, found 357.4826; HPLC (Daicel Chiralcel OD-H, *i*-PrOH/Hexane = 10/90, 1.0 mL/min, 210 nm) t_1 = 13.1 min (major), t_2 = 17.7 min (minor).



Peak#	Ret. Time	Area	Height	Conc.	Area%
1	13.414	1915035	86077	29.176	29.176
2	15.155	1357826	52711	20.687	20.687
3	17.484	1904466	42535	29.015	29.015
4	19.795	1386412	42161	21.122	21.122
Total		6563739	223484	100.000	100.000

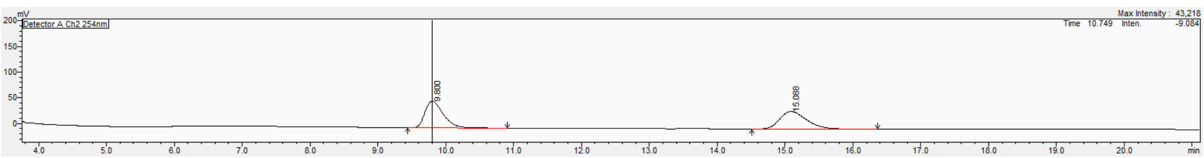


Peak#	Ret. Time	Area	Height	Conc.	Area%
1	13.051	21537111	880225	99.915	99.915
2	17.727	18369	6797	0.085	0.085
Total		21555480	887022	100.000	100.000

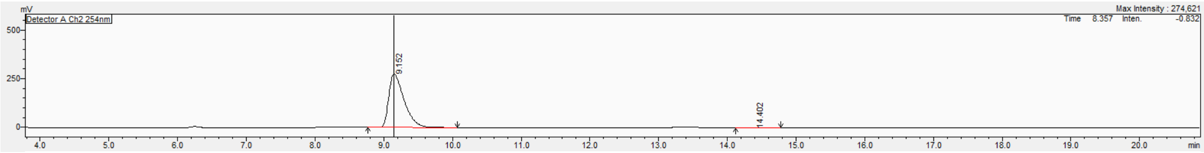


4a

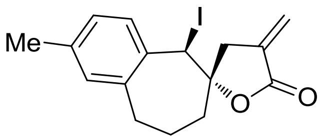
35.0 mg, 99%; yellow oil; $[\alpha]_D^{25}$=−63.5 (c 1.0, MeOH, 99.6% ee); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.24-7.11 (m, 4H), 6.31 (s, 1H), 5.75 (s, 1H), 5.25 (s, 1H), 3.19-2.89 (m, 5H), 2.07-1.90 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.1, 143.0, 137.2, 134.8, 130.9, 129.8, 129.0, 126.5, 123.6, 84.4, 43.9, 42.1, 39.7, 34.9, 22.7; HRMS (TOF$^+$) calcd. for $C_{15}H_{15}IO_2$ $[M+H]^+$ 355.3910, found 355.3908; HPLC (Daicel Chiralcel OD-H, *i*-PrOH/Hexane = 10/90, 1.0 mL/min, 210 nm) t_1 = 9.2 min (major), t_2 = 14.4 min (minor).



Peak#	Ret. Time	Area	Height	Conc.	Area%
1	9.800	955362	51624	50.178	50.178
2	15.088	948583	34060	49.822	49.822
Total		1903946	85684	100.000	100.000

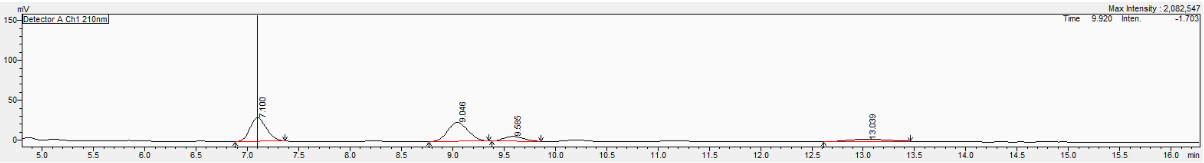


Peak#	Ret. Time	Area	Height	Conc.	Area%
1	9.152	4252146	275530	99.800	99.800
2	14.402	8520	411	0.200	0.200
Total		4260667	275941	100.000	100.000

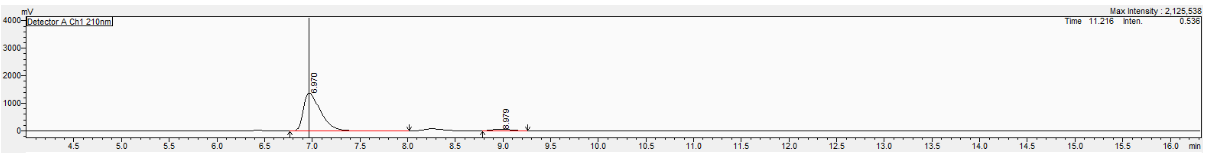


4b

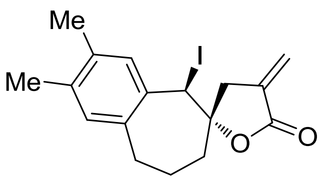
35.7 mg, 97%; yellow oil; $[\alpha]_D^{25}$=−56.0 (*c* 1.0, MeOH, 92% ee); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.01-6.95 (m, 3H), 6.32 (s, 1H), 5.74 (s, 1H), 5.20 (s, 1H), 3.14-2.84 (m, 5H), 2.29 (s, 3H), 2.06-1.87 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.2, 139.9, 137.0, 135.9, 134.9, 130.9, 130.5, 129.7, 123.4, 84.5, 43.9, 42.5, 39.7, 34.4, 22.9, 20.7; HRMS (TOF^+) calcd. for $C_{16}H_{17}IO_2$ $[M+H]^+$ 369.4175, found 369.4176; HPLC (Daicel Chiralcel OD-H, *i*-PrOH/Hexane = 10/90, 1.0 mL/min, 210 nm) t_1 = 7.0 min (major), t_2 = 9.0 min (minor).



Peak#	Ret. Time	Area	Height	Conc.	Area%
1	7.100	325816	29276	40.948	40.948
2	9.046	318503	23533	40.029	40.029
3	9.585	77392	5859	9.726	9.726
4	13.039	73973	2942	9.297	9.297
Total		795683	61610	100.000	100.000

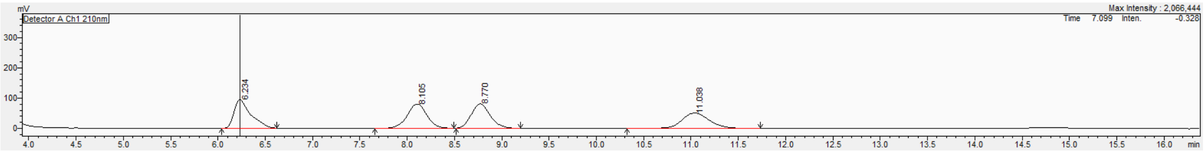


Peak#	Ret. Time	Area	Height	Conc.	Area%
1	6.970	17336068	1366761	95.782	95.782
2	8.979	763507	58520	4.218	4.218
Total		18099575	1425281	100.000	100.000

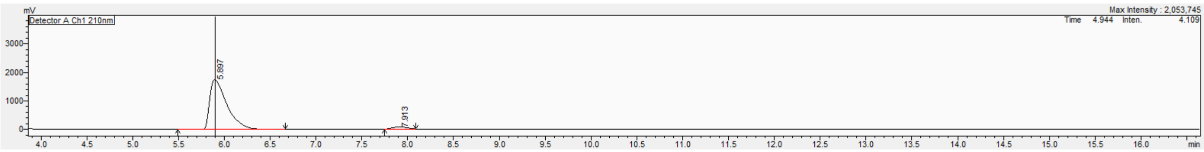


4c

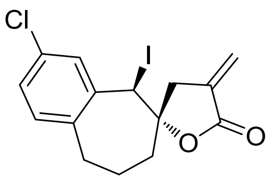
36.7 mg, 96%; yellow oil; $[\alpha]_D^{25}$=−39.5 (c 1.0, MeOH, 93% ee); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.93 (s, 1H), 6.92 (s, 1H), 6.32 (s, 1H), 5.74 (s, 1H), 4.91 (s, 1H), 3.22-2.71 (m, 5H), 2.22 (s, 3H), 2.20 (s, 3H), 2.02-1.85 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 169.1, 140.2, 137.9, 134.5, 134.4, 132.6, 132.4, 132.3, 123.6, 84.6, 62.4, 42.5, 38.6, 34.0, 23.3, 19.3, 19.0; HRMS (TOF$^+$) calcd. for $C_{17}H_{19}IO_2$ $[M+H]^+$ 383.2956, found 383.2957; HPLC (Daicel Chiralcel OD-H, *i*-PrOH/Hexane = 10/90, 1.0 mL/min, 210 nm) t_1 = 5.9 min (major), t_2 = 7.9 min (minor).



Peak#	Ret. Time	Area	Height	Conc.	Area%
1	6.234	1173132	93592	25.818	25.818
2	8.105	1160006	80022	25.529	25.529
3	8.770	1124182	80070	24.741	24.741
4	11.038	1086565	51994	23.913	23.913
Total		4543886	305678	100.000	100.000

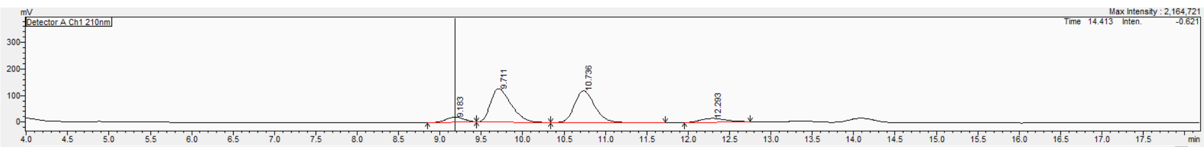


Peak#	Ret. Time	Area	Height	Conc.	Area%
1	5.897	22653627	1734487	96.368	96.368
2	7.913	853709	78697	3.632	3.632
Total		23507336	1813184	100.000	100.000

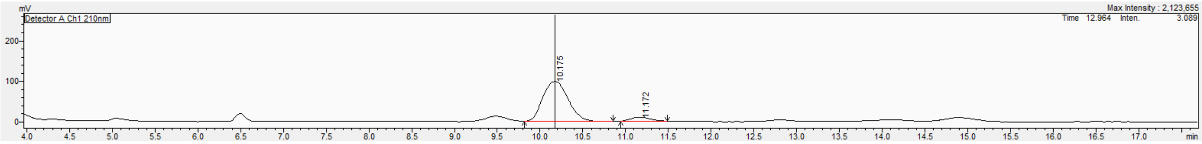


4d

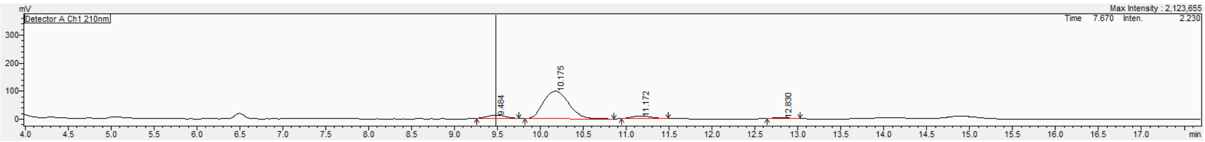
38.0 mg, 98%; yellow oil; $[\alpha]_D^{25}$=−22.0 (c 1.0, MeOH, 85% ee), dr = 91:9; the main peaks of NMR were assigned: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.18-7.06 (m, 3H), 6.32 (s, 1H), 5.75 (s, 1H), 5.19 (s, 1H), 3.16-2.84 (m, 5H), 2.07-1.93 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.0, 144.8, 135.9, 134.5, 131.0, 130.9, 126.5, 123.9, 84.2, 43.7, 40.6, 39.5, 34.6, 22.5; HRMS (TOF$^+$) calcd. for $C_{15}H_{14}ClIO_2$ $[M+H]^+$ 389.1762, found 389.1763; HPLC (Daicel Chiralcel OD-H, *i*-PrOH/Hexane = 10/90, 1.0 mL/min, 210 nm) t_1 = 10.2 min (major), t_2 = 11.2 min (minor).



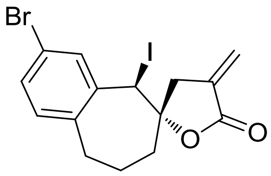
Peak#	Ret. Time	Area	Height	Conc.	Area%
1	9.183	278754	18556	5.849	5.849
2	9.711	2153319	125729	45.184	45.184
3	10.736	2036080	119763	42.724	42.724
4	12.293	297528	14351	6.243	6.243
Total		4765680	278399	100.000	100.000



Peak#	Ret. Time	Area	Height	Conc.	Area%
1	10.175	2010247	98010	92.435	92.435
2	11.172	164530	10158	7.565	7.565
Total		2174778	108168	100.000	100.000

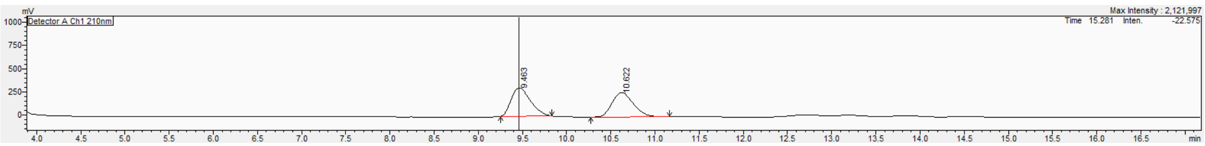


Peak#	Ret. Time	Area	Height	Conc.	Area%
1	9.484	171962	11568	7.207	7.207
2	10.175	2010247	98010	84.249	84.249
3	11.172	164530	10158	6.895	6.895
4	12.830	39327	3245	1.648	1.648
Total		2386067	122982	100.000	100.000

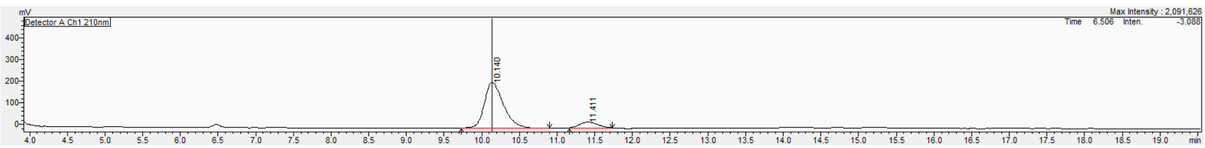


4e

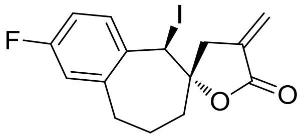
42.8 mg, 99%; yellow oil; $[\alpha]_D^{25}$=−31.5 (*c* 1.0, MeOH, 80% ee), dr > 99:1; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.30-7.00 (m, 3H), 6.33 (s, 1H), 5.76 (s, 1H), 5.17 (s, 1H), 3.17-2.83 (m, 5H), 2.06-1.89 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.0, 145.0, 136.4, 134.5, 133.8, 131.2, 129.5, 123.9, 122.9, 84.2, 43.7, 40.5, 39.5, 34.6, 22.5; HRMS (TOF$^+$) calcd. for $C_{15}H_{14}BrIO_2$ $[M+H]^+$ 433.1954, found 433.1953; HPLC (Daicel Chiralcel OD-H, *i*-PrOH/Hexane = 10/90, 1.0 mL/min, 210 nm) t_1 = 10.1 min (major), t_2 = 11.4 min (minor).



Peak#	Ret. Time	Area	Height	Conc.	Area%
1	9.463	4606928	304113	51.289	51.289
2	10.622	4375406	263347	48.711	48.711
Total		8982334	567460	100.000	100.000

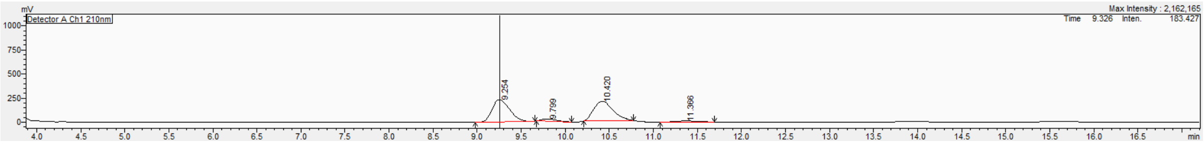


Peak#	Ret. Time	Area	Height	Conc.	Area%
1	10.140	3836267	213670	89.775	89.775
2	11.411	436951	26472	10.225	10.225
Total		4273218	240142	100.000	100.000

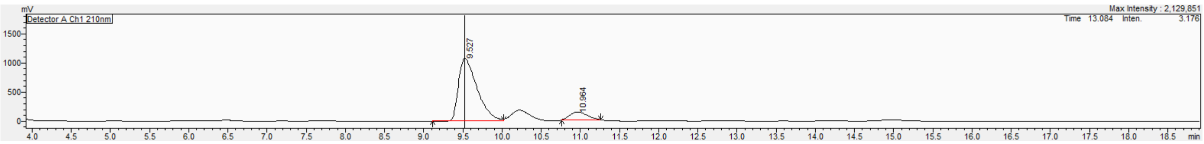


4f

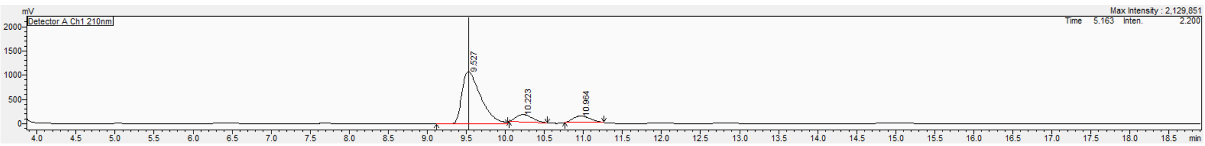
36.1 mg, 97%; yellow oil; $[\alpha]_D^{25}$=−33.0 (*c* 1.0, MeOH, 80% ee), dr = 90:10; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.14-6.85(m, 3H), 6.34 (t, *J* = 3 Hz, 1H), 5.76 (t, *J* = 3 Hz, 1H), 5.12 (s, 1H), 3.15-2.80 (m, 5H), 2.08-1.86 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 169.7, 162.4 (d, *J* = 243.8 Hz), 139.0 (d, *J* = 25.5 Hz), 134.5, 132.5 (d, *J* = 7.5 Hz), 123.9, 116.7 (d, *J* = 22.5 Hz), 115.5(d, *J* = 20.3 Hz), 84.4, 43.7, 40.2, 39.5, 34.1, 22.7; HRMS (TOF$^+$) calcd. for $C_{15}H_{14}FIO_2$ $[M+H]^+$ 373.0840, found 373.0841; HPLC (Daicel Chiralcel OD-H, *i*-PrOH/Hexane = 10/90, 1.0 mL/min, 210 nm) t_1 = 9.5 min (major), t_2 = 10.9 min (minor).



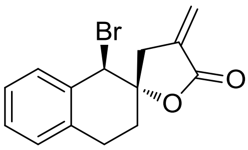
Peak#	Ret. Time	Area	Height	Conc.	Area%
1	9.254	3131874	229858	47.009	47.009
2	9.799	261301	23013	3.922	3.922
3	10.420	3049307	201628	45.770	45.770
4	11.366	219772	12082	3.299	3.299
Total		6662253	466581	100.000	100.000



Peak#	Ret. Time	Area	Height	Conc.	Area%
1	9.527	17740860	1070708	89.779	89.779
2	10.964	2019770	133706	10.221	10.221
Total		19760630	1204415	100.000	100.000

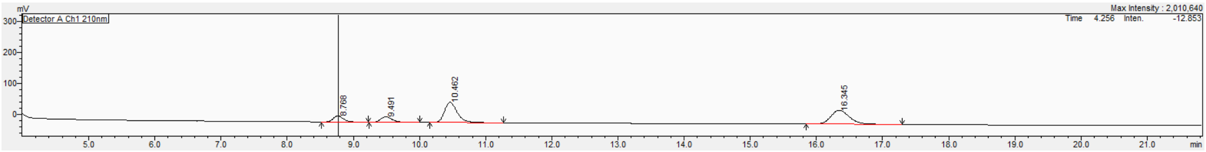


Peak#	Ret. Time	Area	Height	Conc.	Area%
1	9.527	17740860	1070708	80.769	80.769
2	10.223	2204210	153136	10.035	10.035
3	10.964	2019770	133706	9.195	9.195
Total		21964840	1357551	100.000	100.000

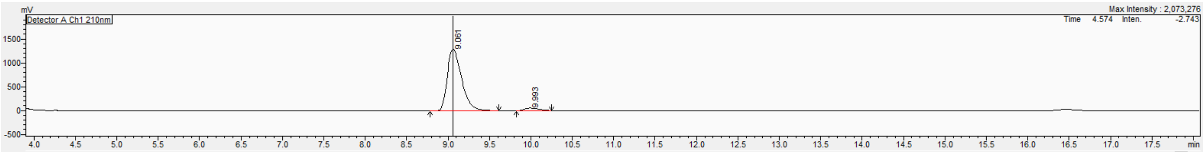


2b

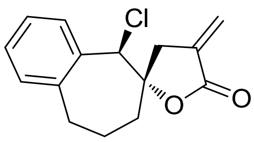
28.3 mg, 97%; white solid; MP 130-132 ℃; $[\alpha]_D^{25}$= −17.5 (*c* 1.0, MeOH, 92% ee), dr > 99:1; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.37-7.13 (m, 4H), 6.34 (s, 1H), 5.76 (s, 1H), 5.25 (s, 1H), 3.37-2.95 (m, 4H), 2.69-2.61 (m, 1H), 2.07-2.00 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.1, 134.6, 134.5, 134.1, 130.9, 128.9, 128.8, 126.6, 123.3, 82.9, 54.8, 39.8, 29.3, 25.3; HPLC (Daicel Chiralcel IB, *i*-PrOH/Hexane = 10/90, 1.0 mL/min, 210 nm) t_1 = 9.0 min (major), t_2 = 10.0 min (minor).



Peak#	Ret. Time	Area	Height	Conc.	Area%
1	8.768	218369	19856	9.901	9.901
2	9.491	222423	18018	10.085	10.085
3	10.462	881399	65287	39.965	39.965
4	16.345	883229	44824	40.048	40.048
Total		2205419	147984	100.000	100.000

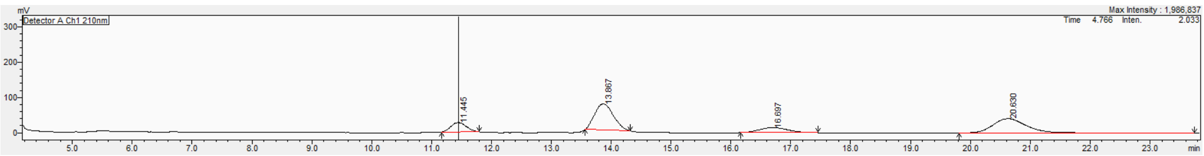


Peak#	Ret. Time	Area	Height	Conc.	Area%
1	9.061	15518687	1289950	95.957	95.957
2	9.993	653855	54091	4.043	4.043
Total		16172542	1344041	100.000	100.000

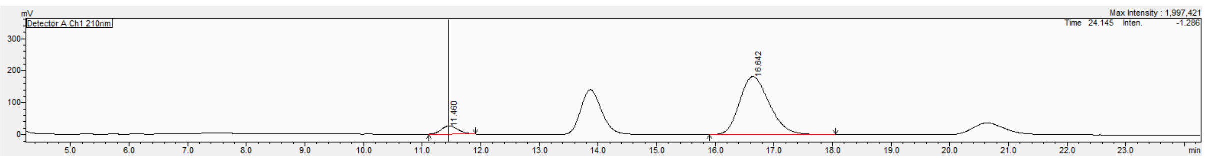


5

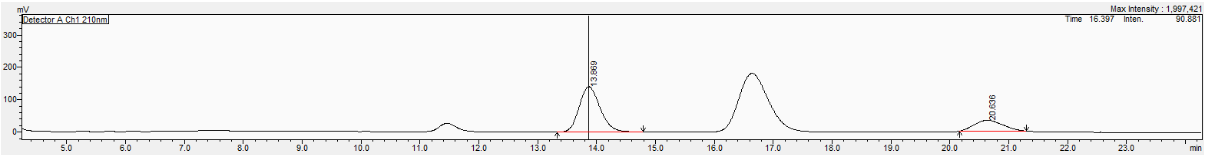
25.2 mg, 96%; yellow oil; $[\alpha]^{25}_{D}$= +12.0 (c 1.0, MeOH, −85% ee); dr = 60:40, the main peaks of NMR were assigned: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.32-7.14 (m, 4H), 6.63-6.31 (m, 1H), 5.74-4.88 (m, 2H), 3.29-2.52 (m, 4H), 2.09-1.88 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.9, 130.6, 130.5, 130.1, 129.4, 129.3, 126.5, 126.4, 123.5, 84.4, 69.5, 39.1, 38.3, 34.1, 22.9; HRMS (TOF^{+}) calcd. for $C_{15}H_{15}ClO_2$ $[M+H]^{+}$ 263.5124, found 263.5125; HPLC (Daicel Chiralcel OJ-H, *i*-PrOH/Hexane = 20/80, 1.0 mL/min, 210 nm) t_1 = 11.4 min (minor), t_2 = 16.6 min (major).



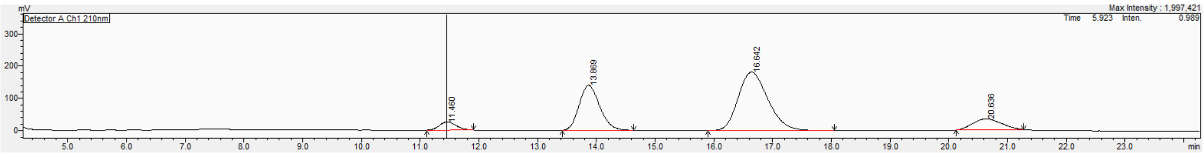
Peak#	Ret. Time	Area	Height	Conc.	Area%
1	11.445	479668	26524	11.596	11.596
2	13.867	1605851	73835	38.821	38.821
3	16.697	469819	14023	11.358	11.358
4	20.630	1581171	40381	38.225	38.225
Total		4136510	154763	100.000	100.000



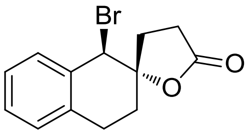
Peak#	Ret. Time	Area	Height	Conc.	Area%
1	11.460	510102	25806	7.391	7.391
2	16.642	6391981	181401	92.609	92.609
Total		6902083	207207	100.000	100.000



Peak#	Ret. Time	Area	Height	Conc.	Area%
1	13.869	3447807	140100	75.520	75.520
2	20.636	1117617	33236	24.480	24.480
Total		4565424	173336	100.000	100.000

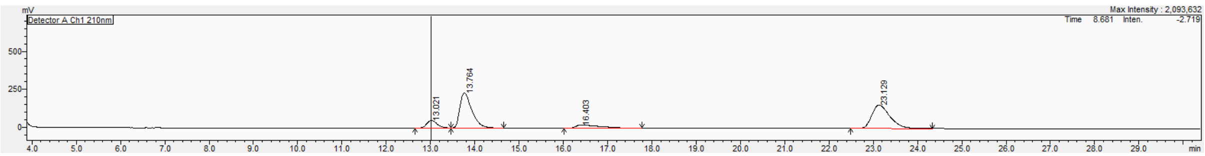


Peak#	Ret. Time	Area	Height	Conc.	Area%
1	11.460	510102	25806	4.457	4.457
2	13.869	3394219	139401	29.655	29.655
3	16.642	6391981	181401	55.845	55.845
4	20.636	1149573	33829	10.044	10.044
Total		11445875	380437	100.000	100.000

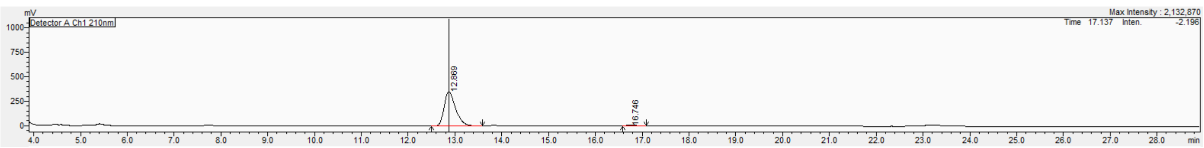


7a

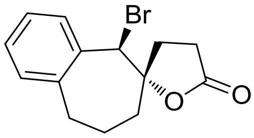
27.2 mg, 97%; yellow oil; $[\alpha]_D^{25}$= +29.5 (*c* 1.0, MeOH, 97% ee), dr > 99:1; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.37-7.12 (m, 4H), 5.24 (s, 1H), 3.23-2.06 (m, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 175.9, 134.6, 134.4, 130.9, 128.9, 128.7, 126.6, 85.7, 54.8, 33.3, 28.8, 28.3, 25.3; HRMS (TOF$^+$) calcd. for $C_{13}H_{13}BrO_2$ $[M+H]^+$ 281.3607, found 281.3608; HPLC (Daicel Chiralcel IB, *i*-PrOH/Hexane = 10/90, 1.0 mL/min, 210 nm) t_1 = 12.9 min (major), t_2 = 16.7 min (minor).



Peak#	Ret. Time	Area	Height	Conc.	Area%
1	13.021	818723	49856	7.921	7.921
2	13.764	4318413	229664	41.781	41.781
3	16.403	833617	22156	8.065	8.065
4	23.129	4365119	154030	42.233	42.233
Total		10335873	455706	100.000	100.000

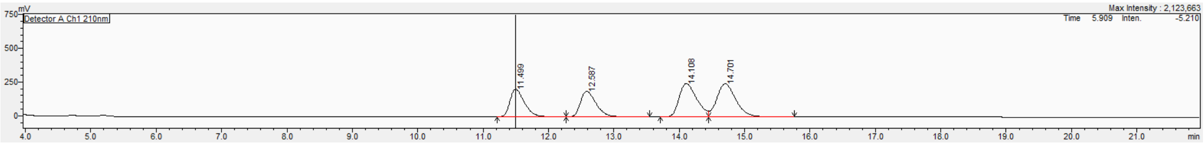


Peak#	Ret. Time	Area	Height	Conc.	Area%
1	12.869	6040497	352788	98.465	98.465
2	16.746	94153	5343	1.535	1.535
Total		6134651	358131	100.000	100.000

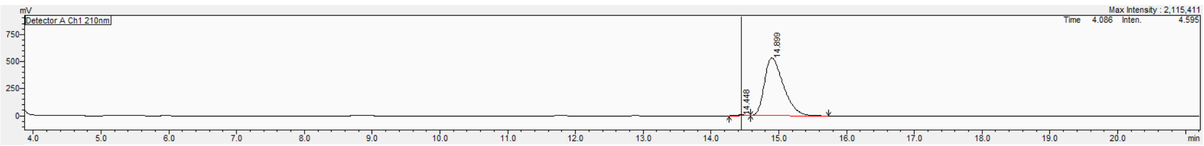


7b

29.1 mg, 98%; yellow oil; $[\alpha]_D^{25}$= +47 (*c* 1.0, MeOH, 99% ee), dr > 99:1; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.26-7.13 (m, 4H), 5.00 (s, 1H), 3.30-1.81 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 175.8, 142.8, 135.7, 130.9, 130.7, 129.4, 126.5, 87.4, 61.9, 37.8, 35.5, 34.6, 28.5, 23.1; HRMS (TOF$^+$) calcd. for $C_{14}H_{15}BrO_2$ $[M+H]^+$ 295.3976, found 295.3975; HPLC (Daicel Chiralcel IB, *i*-PrOH/Hexane = 10/90, 1.0 mL/min, 210 nm) t_1 = 14.4 min (minor), t_2 = 14.9 min (major).



Peak#	Ret. Time	Area	Height	Conc.	Area%
1	11.499	3118443	204188	19.798	19.798
2	12.587	3117887	189135	19.795	19.795
3	14.108	4592791	246642	29.158	29.158
4	14.701	4922015	245442	31.249	31.249
Total		15751136	885406	100.000	100.000



Peak#	Ret. Time	Area	Height	Conc.	Area%
1	14.448	56902	5034	0.551	0.551
2	14.899	10268609	529413	99.449	99.449
Total		10325511	534446	100.000	100.000

REFERENCES

1. Quan, H.; Liu, H.; Li, C.; Lou, L. *J. Pharmacol. Exp. Ther.* **2009**, *330*, 326.
2. Jiang, X.; Tan, C. K.; Zhou, L. Yeung, Y.-Y. *Angew. Chem. Int. Ed.* **2012**, *51*, 7771.
3. Wang, W.; He, H.; Gan, M.; Wang, H.; Wang, Y.; Jiang, X. *Adv. Synth. Catal.* **2019**, 10.1002/adsc.201900728.
4. Zhou, L.; Tan, C. K.; Jiang, X.; Chen, F.; Yeung, Y.-Y. *J. Am. Chem. Soc.* **2010**, *132*, 15474.

X-ray of 2b

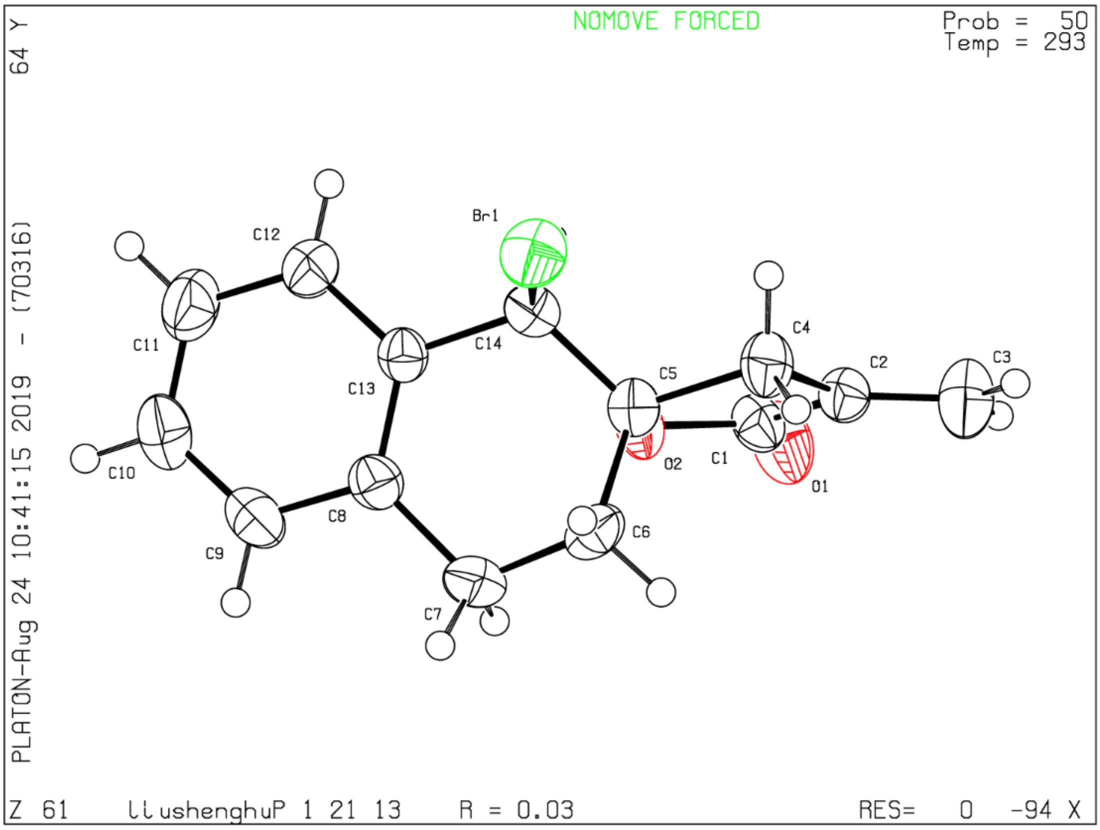
Bond precision:	C-C = 0.0042 A	Wavelength=0.71073
Cell:	a=9.1440(3) b=7.0069(2) c=9.8897(4)	
	alpha=90 beta=99.952(4) gamma=90	
Temperature:	293 K	
	Calculated	Reported
Volume	624.11(4)	624.11(4)
Space group	P 21	P 1 21 1
Hall group	P 2yb	P 2yb
Moiety formula	C14 H13 Br O2	C14 H13 Br O2
Sum formula	C14 H13 Br O2	C14 H13 Br O2
Mr	293.14	293.16
Dx,g cm-3	1.560	1.560
Z	2	2
Mu (mm-1)	3.280	3.279
F000	296.0	295.6
F000'	295.56	
h,k,lmax	11,8,12	11,8,12
Nref	2561[1391]	2469
Tmin,Tmax	0.330,0.362	0.754,1.000
Tmin'	0.305	

Correction method= # Reported T Limits: Tmin=0.754 Tmax=1.000
AbsCorr = MULTI-SCAN

Data completeness= 1.77/0.96 Theta(max)= 26.350

R(reflections)= 0.0270(2238) wR2(reflections)= 0.0523(2469)

S = 1.055 Npar= 162



X-ray of 2c

Bond precision: C-C = 0.0101 A Wavelength=0.71073

Cell: a=7.3086(5) b=10.6430(6) c=17.7938(12)
alpha=90 beta=90 gamma=90

Temperature: 293 K

	Calculated	Reported
Volume	1384.10(15)	1384.10(15)
Space group	P 21 21 21	P 21 21 21
Hall group	P 2ac 2ab	P 2ac 2ab
Moiety formula	C15 H15 Br O2	C15 H15 Br O2
Sum formula	C15 H15 Br O2	C15 H15 Br O2
Mr	307.17	307.19
Dx,g cm-3	1.474	1.474
Z	4	4
Mu (mm-1)	2.961	2.961
F000	624.0	623.2
F000'	623.12	
h,k,lmax	9,13,22	9,13,22
Nref	2828[1646]	2663
Tmin,Tmax	0.496,0.744	0.298,1.000
Tmin'	0.472	

Correction method= # Reported T Limits: Tmin=0.298 Tmax=1.000
AbsCorr = MULTI-SCAN

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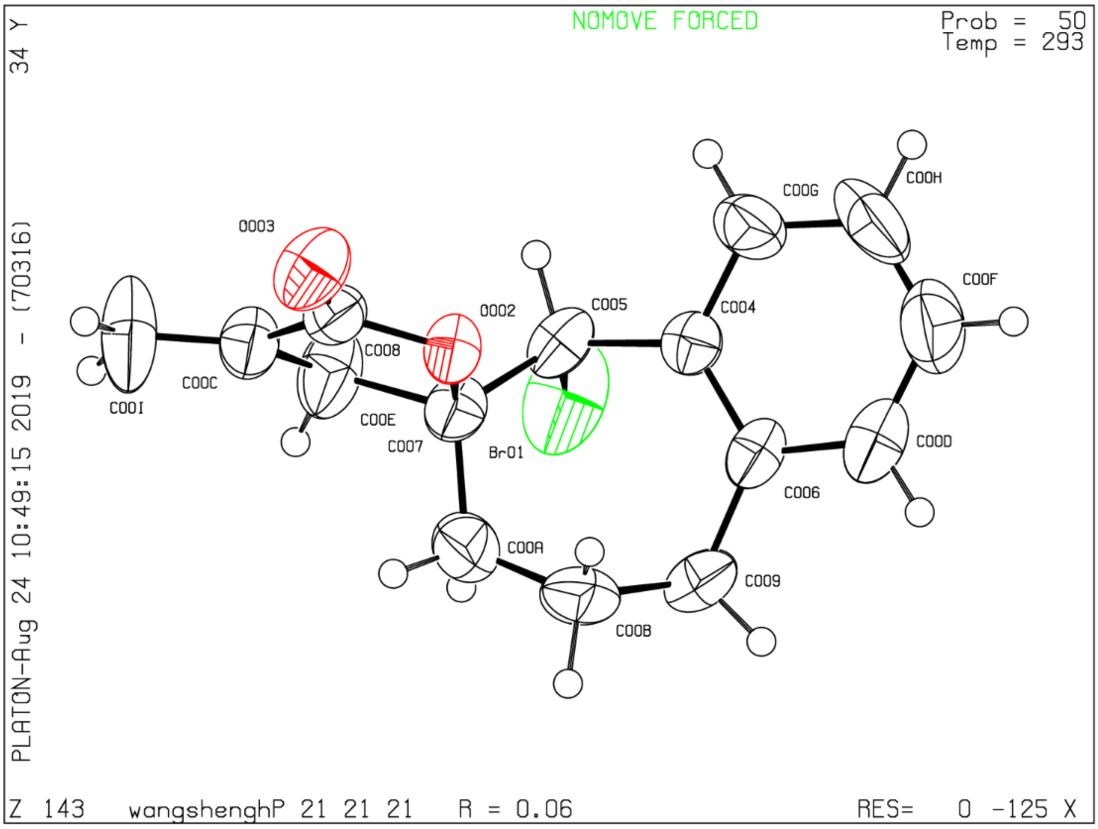
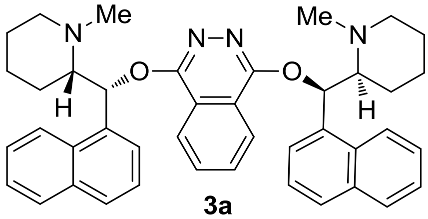
S = 1.045 Npar= 171

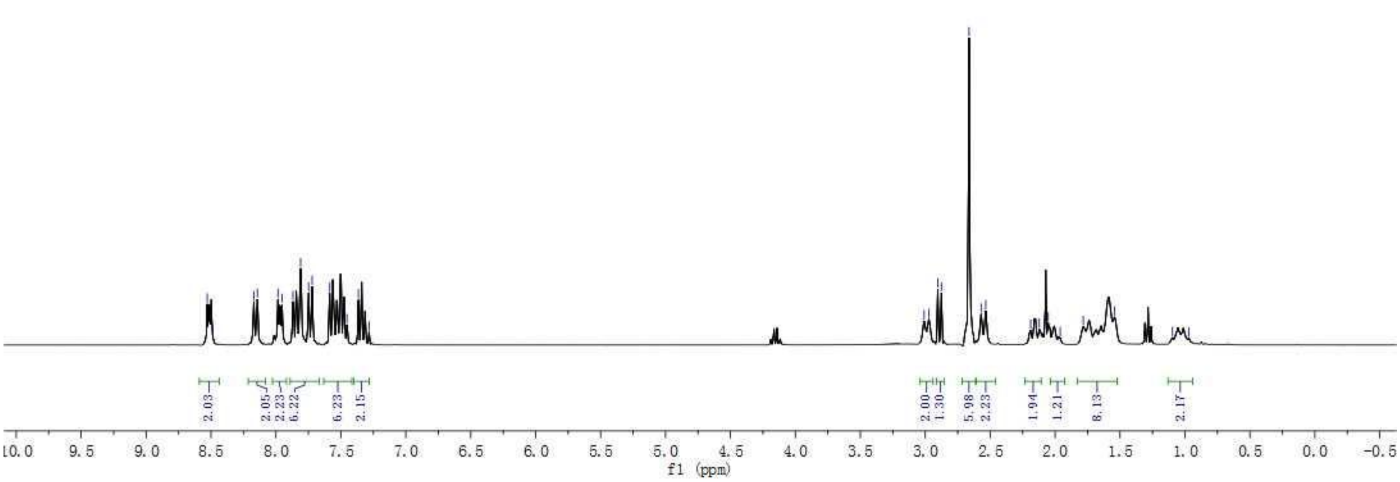


$^{1}H/^{13}C$-NMR



N
Me
N–N
O
H

3a



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11110a
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3.01 2.97 2.90 2.88 2.66 2.57 2.53 2.19 2.12 2.05 1.96 1.78 1.54 1.10 0.97
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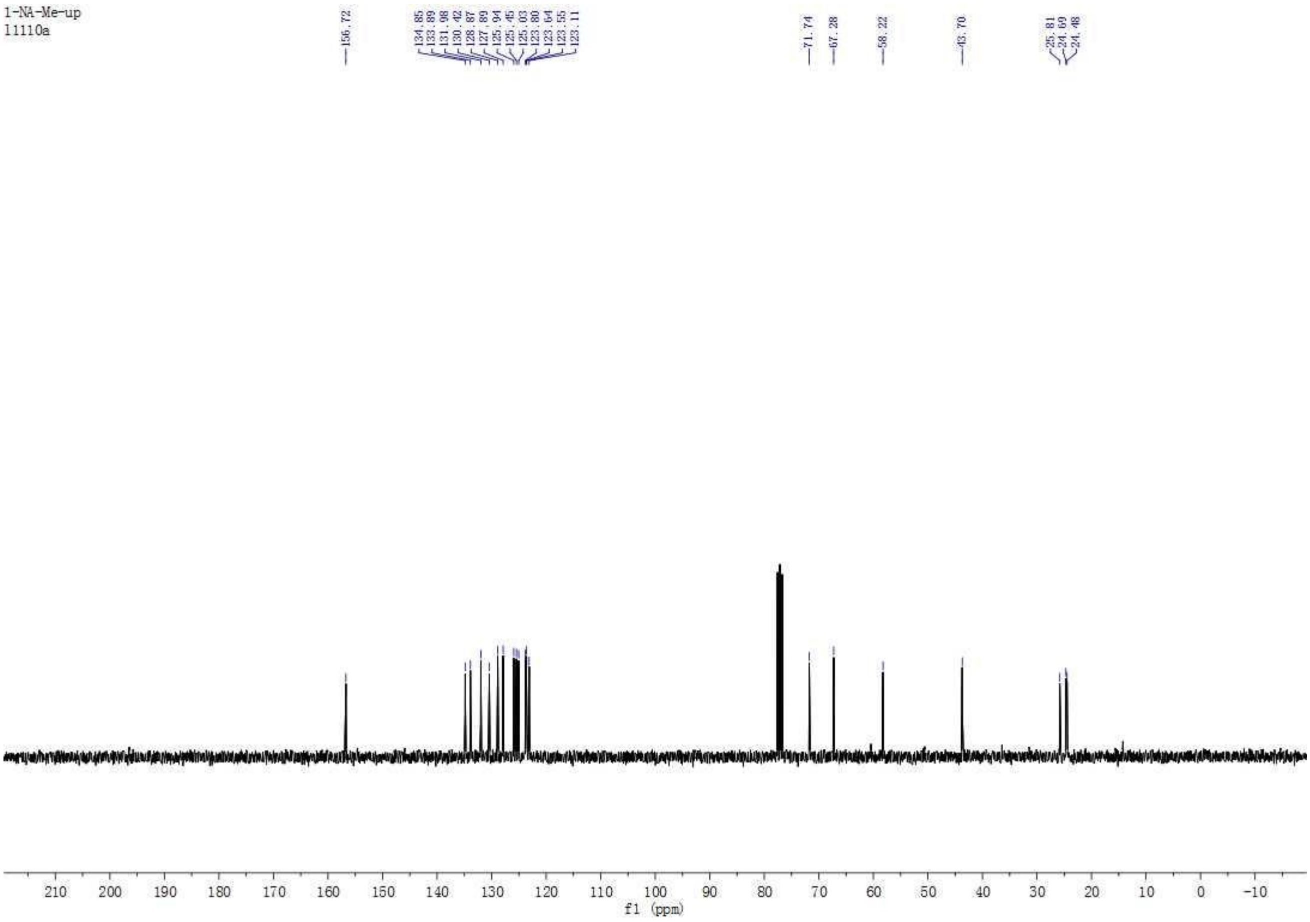
f1 (ppm)



1-NA-Me-up
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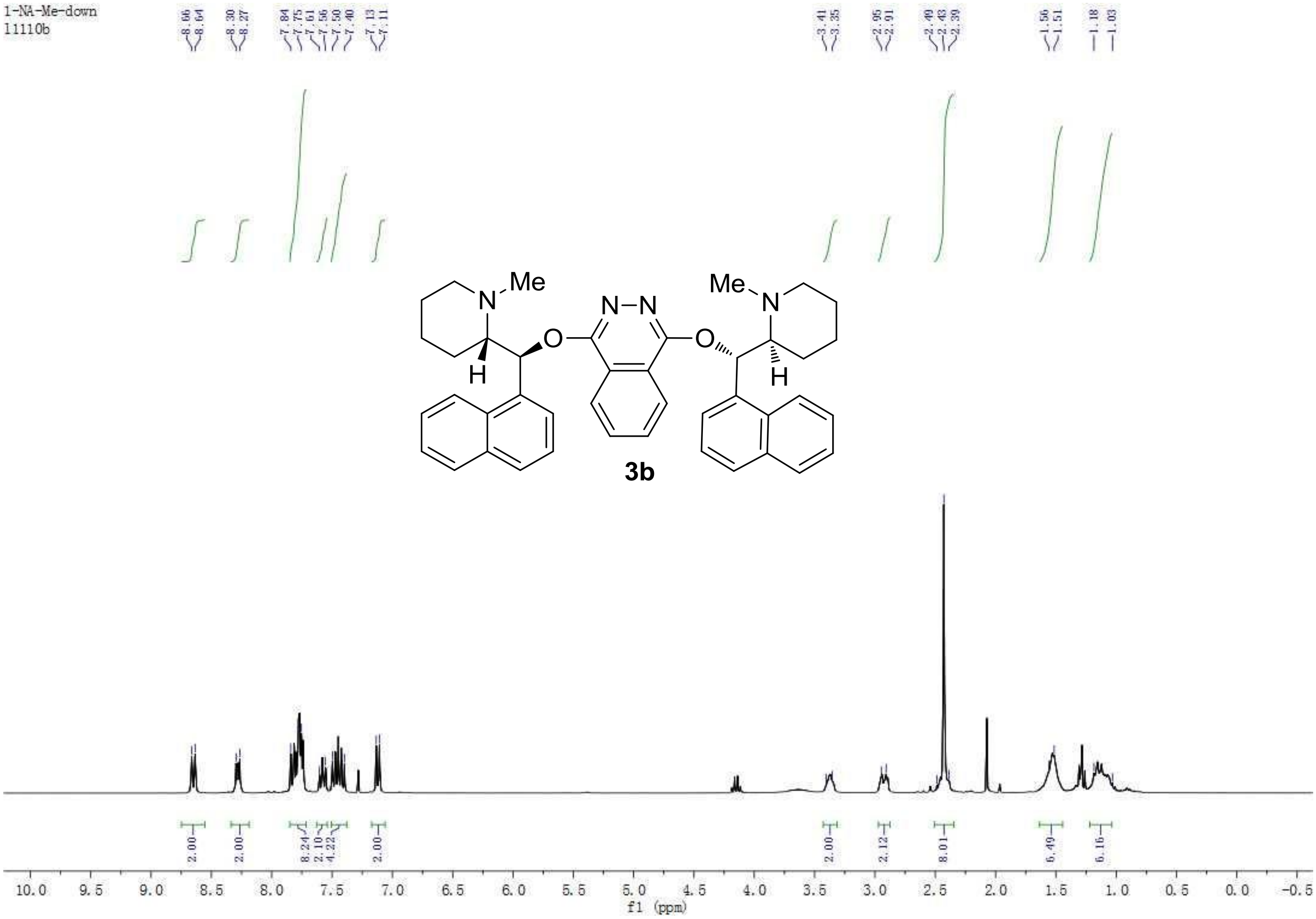
134.85 133.89 131.98 130.42 128.87 127.89 125.94 125.45 125.03 123.80 123.64 123.55 123.11
71.74 67.28 58.22 43.70 25.81 24.69 24.48
f1 (ppm)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7.11
3.41
3.35
2.95
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2.43
2.39
1.56
1.51
1.18
1.03
Me
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N–N
O
H
3b
2.00
2.00
8.24
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4.22
2.00
2.00
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8.01
6.49
6.16
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
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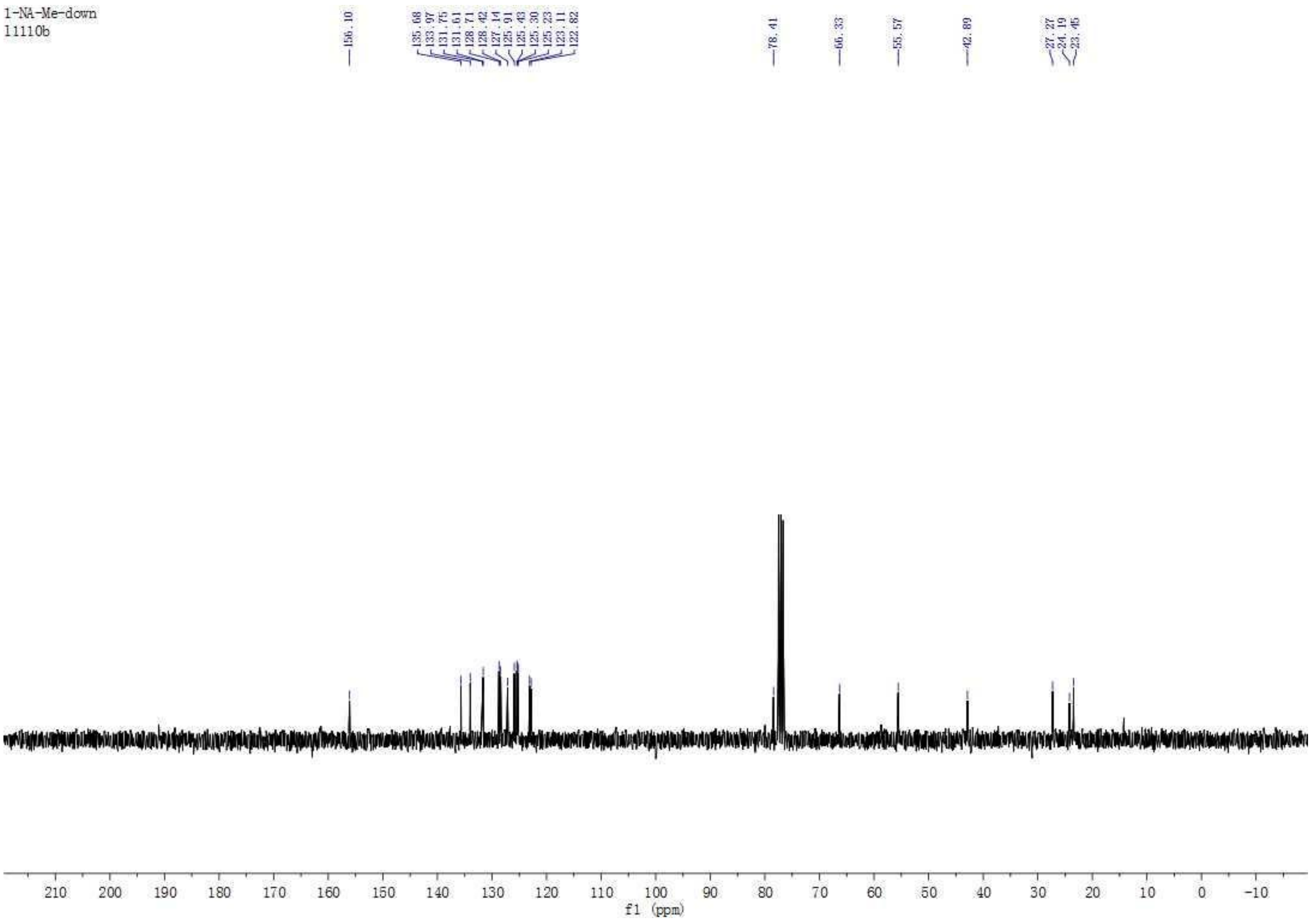
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125.30
125.23
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122.82
78.41
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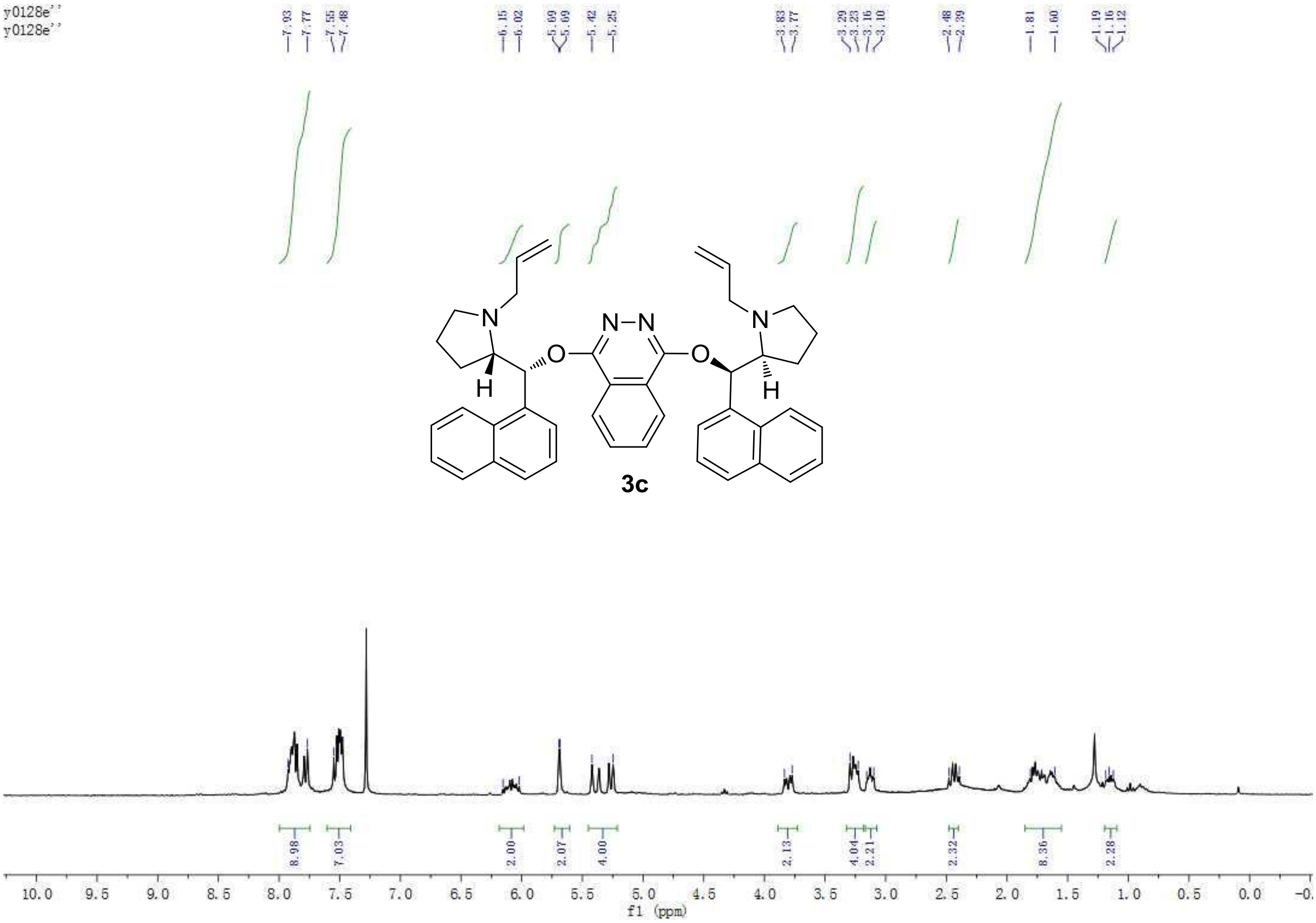
f1 (ppm)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y0128e''
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7.55
7.48
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6.02
5.69
5.69
5.42
5.25
3.83
3.77
3.29
3.23
3.16
3.10
2.48
2.39
1.81
1.60
1.19
1.16
1.12
N
N–N
O
O
N
H
H
3c
8.98
7.03
2.00
2.07
4.00
2.13
4.04
2.21
2.32
8.36
2.28
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
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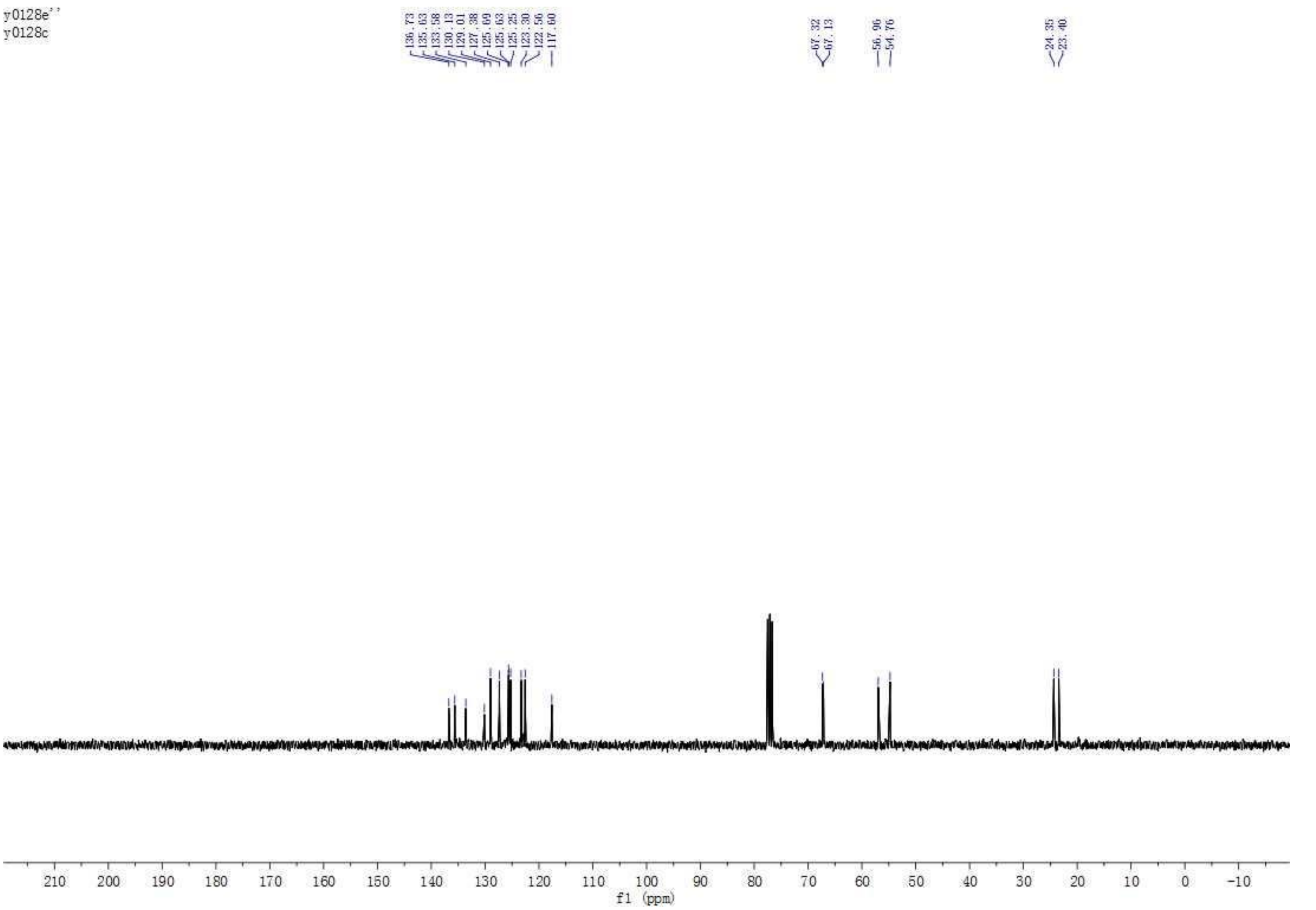
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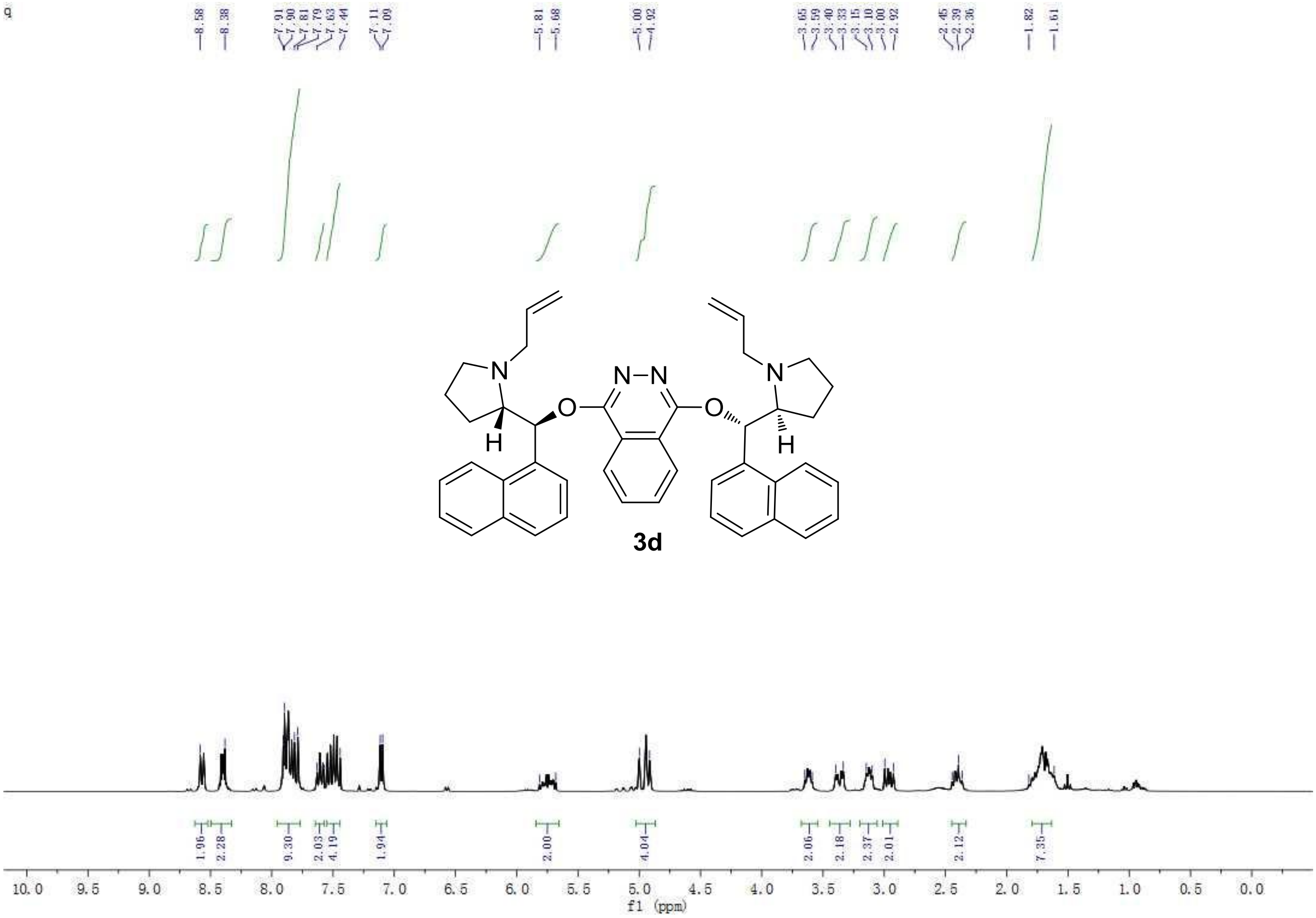
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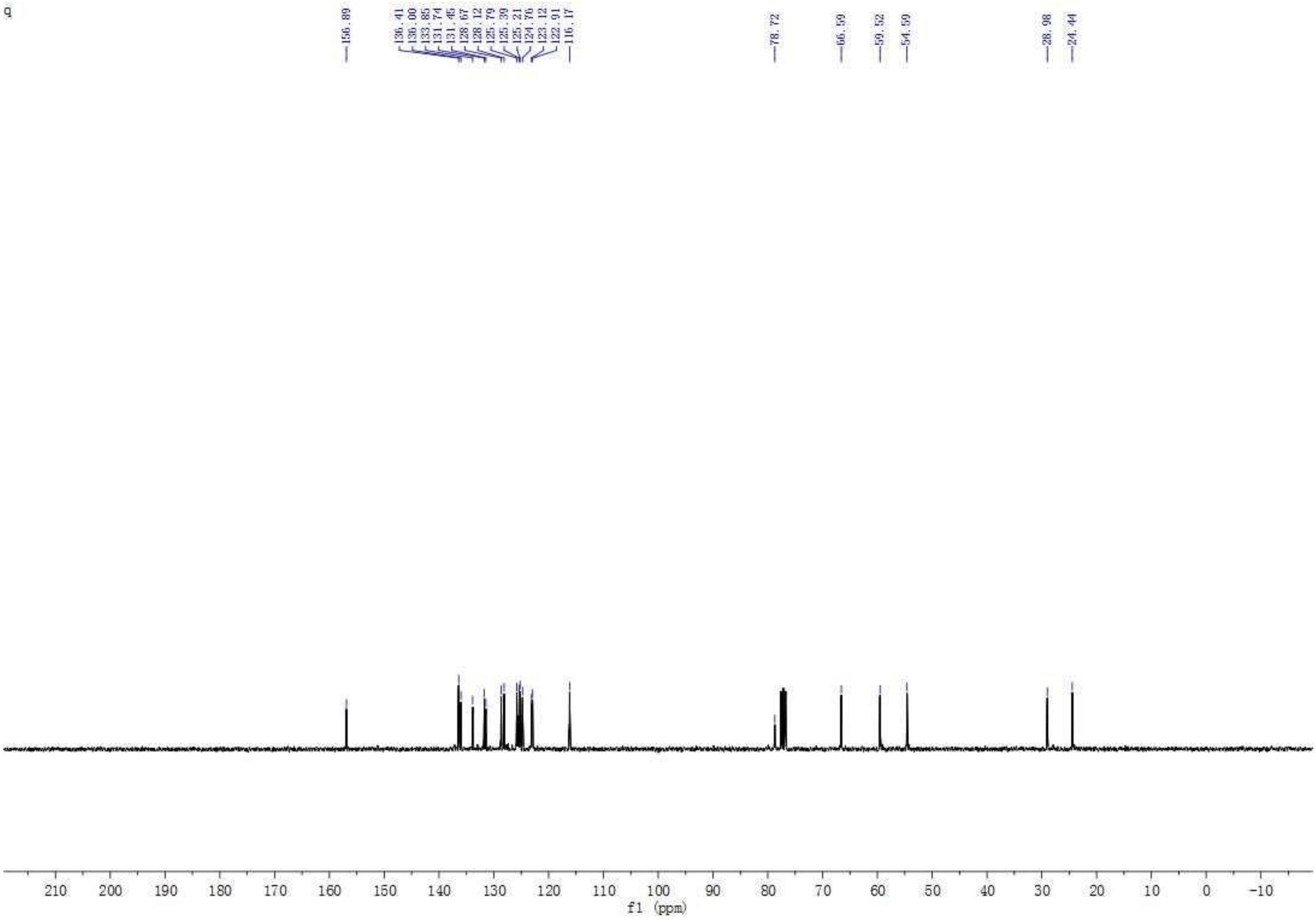
1.96 2.28 9.30 2.03 4.19 1.94 2.00 4.04 2.06 2.18 2.37 2.01 2.12 7.35
3d
f1 (ppm)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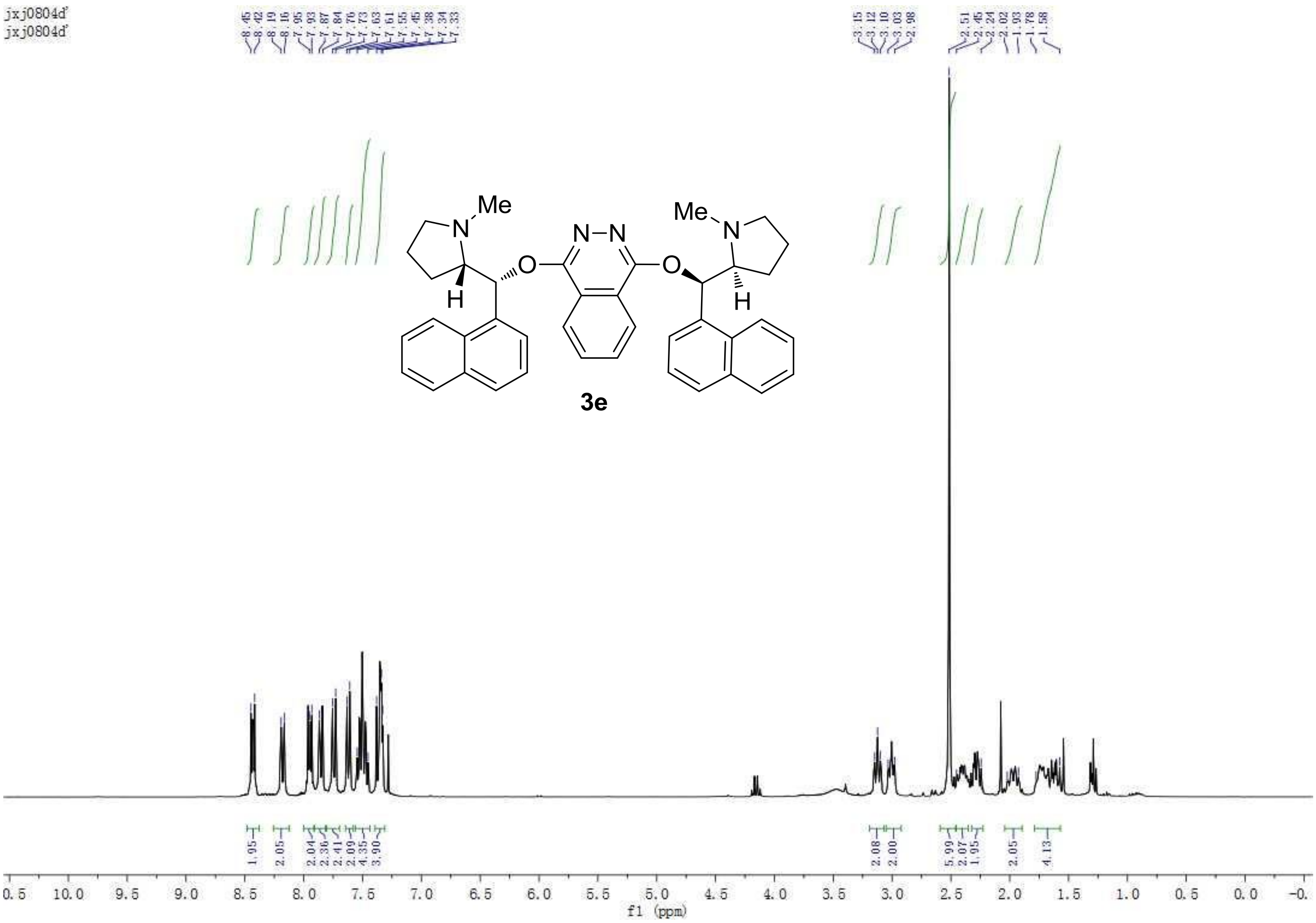
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3.15 3.12 3.10 3.03 2.98
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Me
N–N
O
H
Me
N
3e
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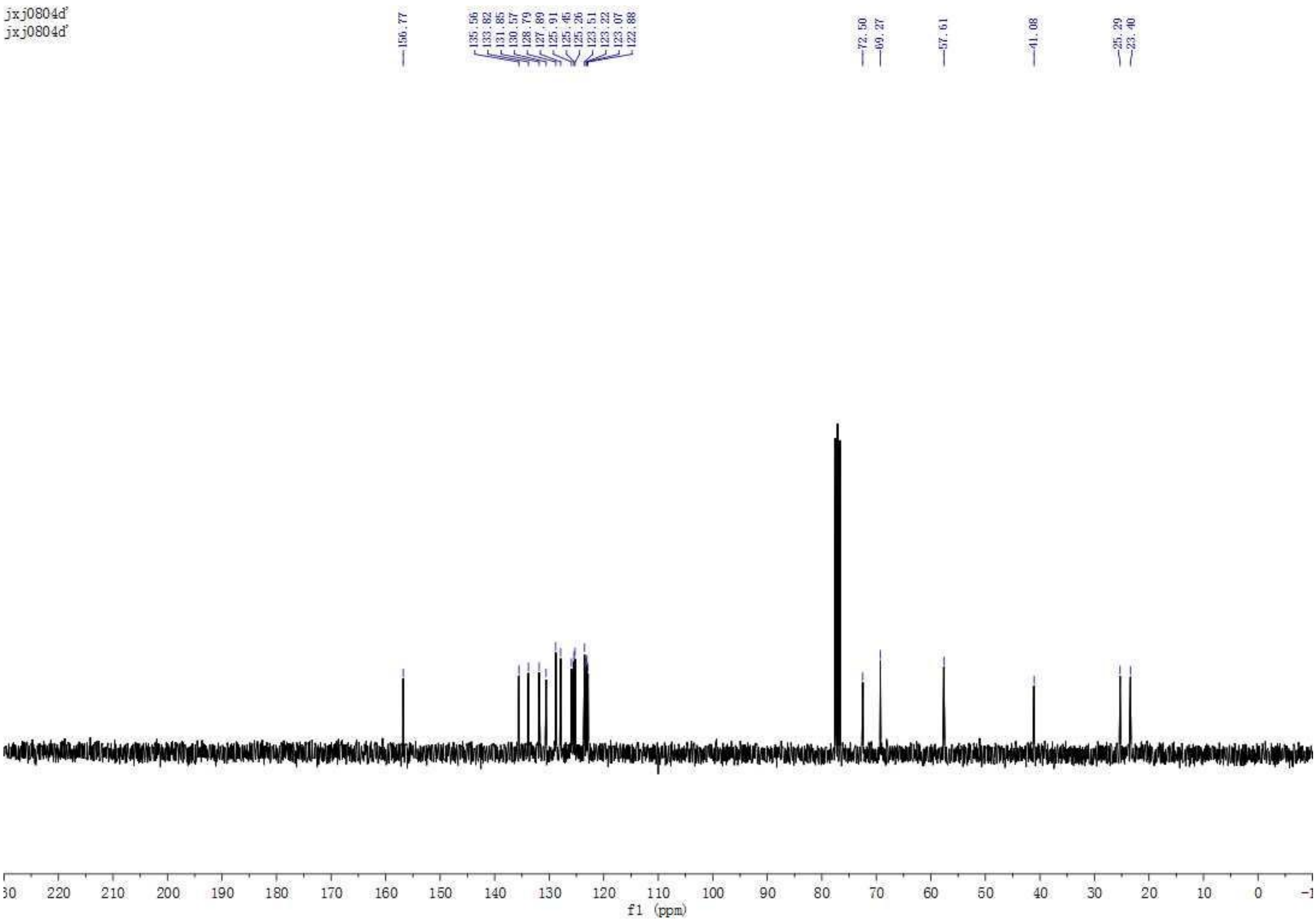
2.05
4.13
f1 (ppm)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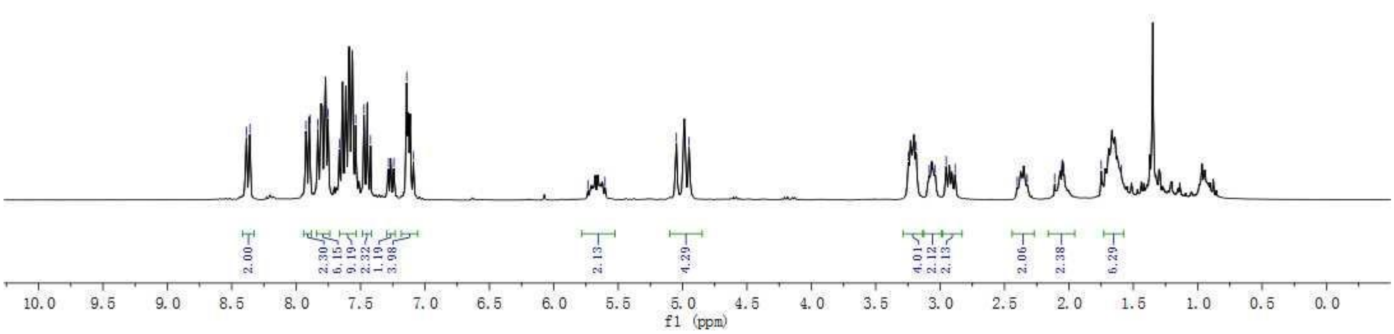
57.61
41.08
25.29 23.40
f1 (ppm)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jxj0917c
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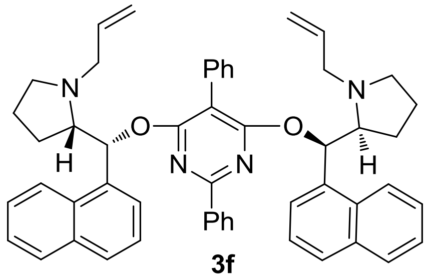
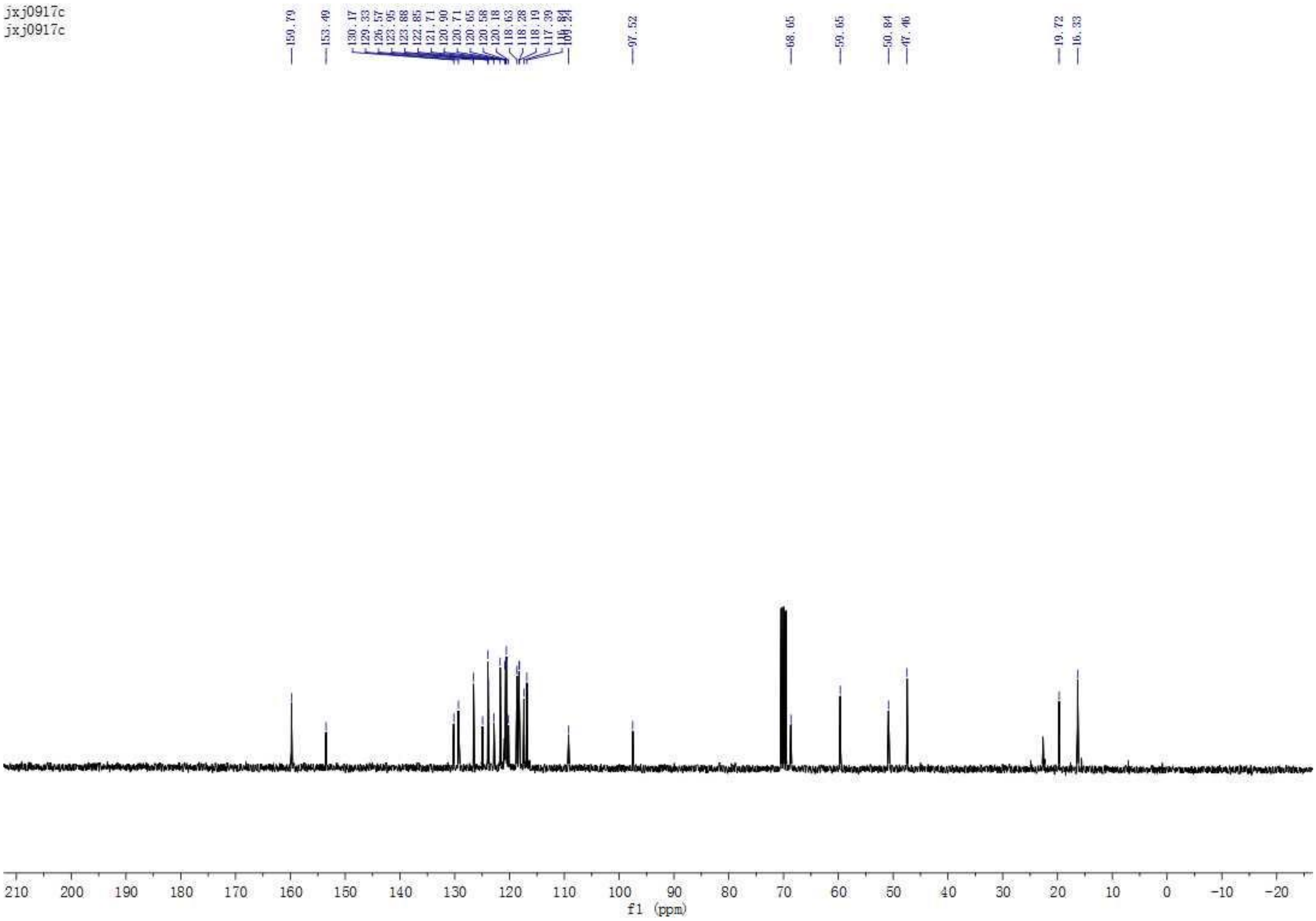
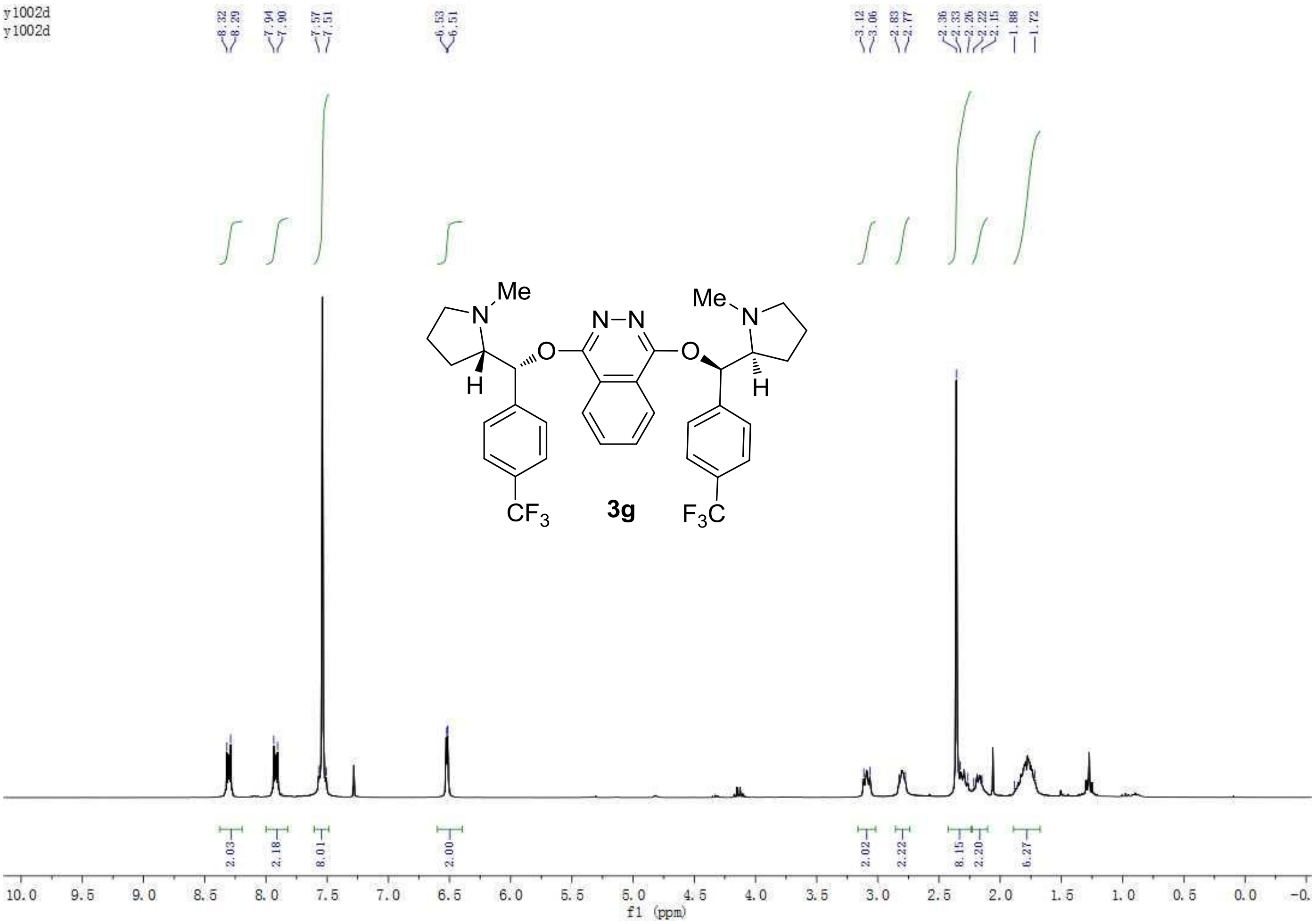
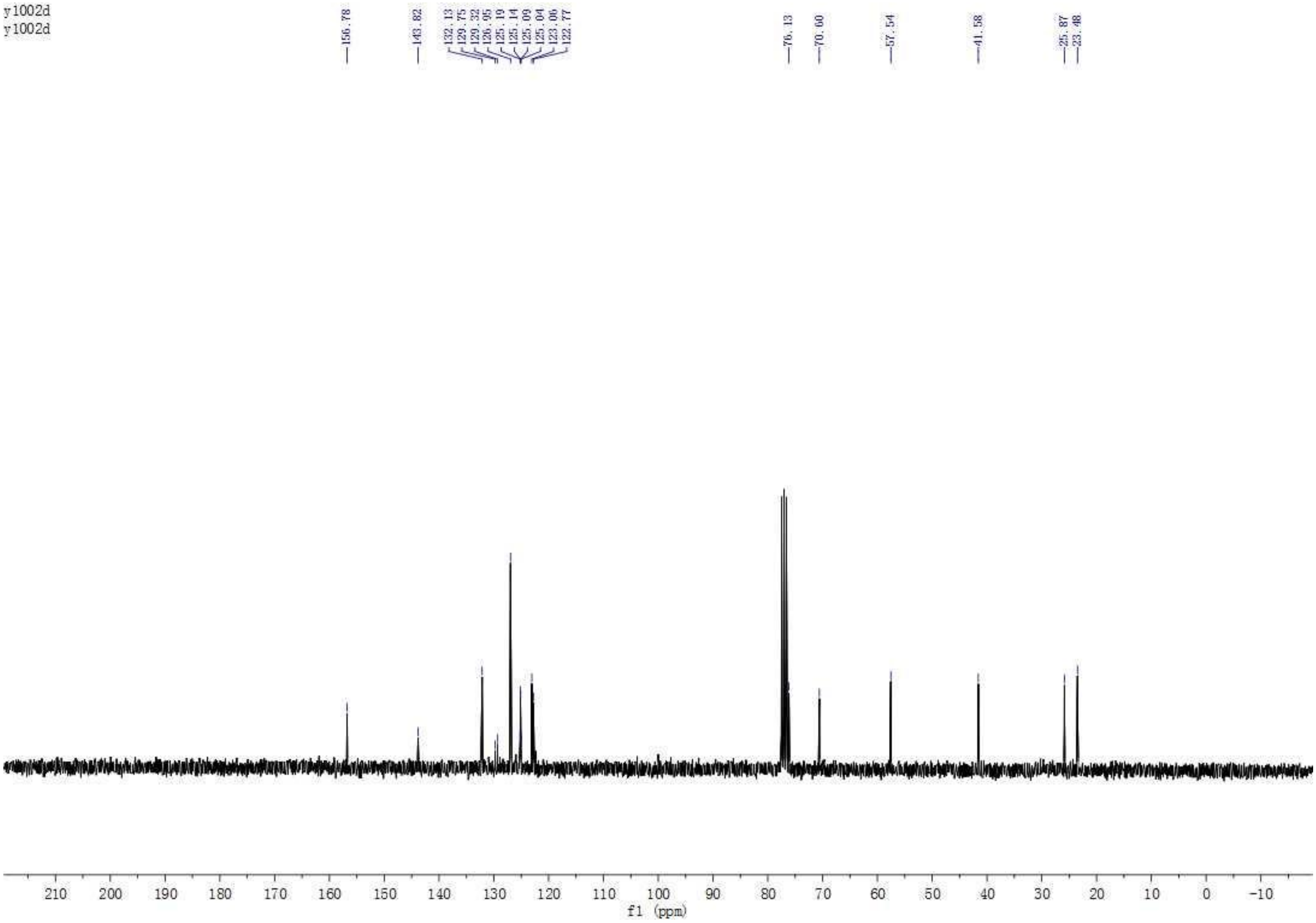
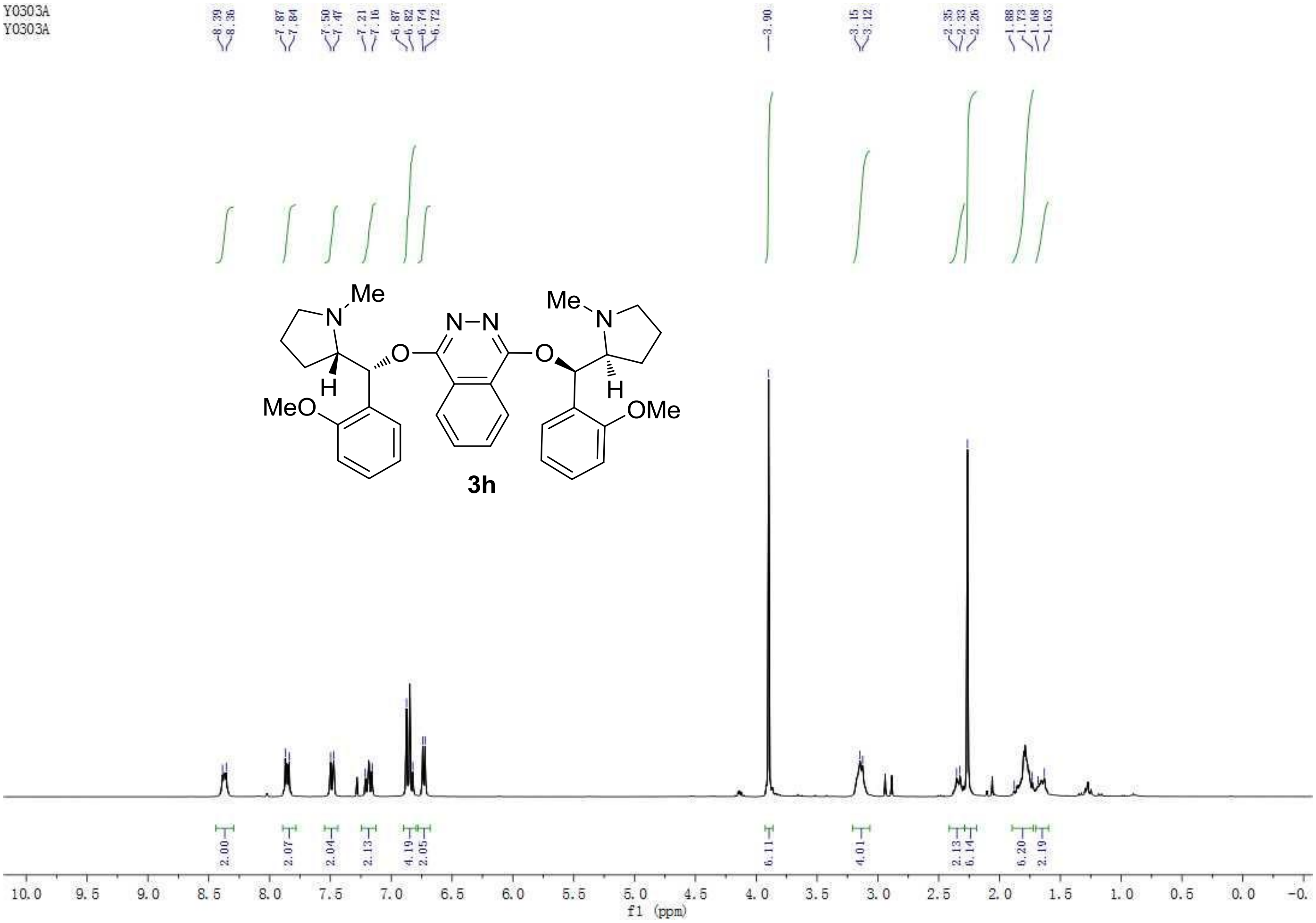
5.73 5.60
5.05 4.95
3.25 3.19 3.08 3.04 2.95 2.88
2.40 2.32 2.11 2.04
1.75 1.59
2.00 2.30 6.15 9.19 2.32 1.19 3.98 2.13 4.29 4.01 2.12 2.13 2.06 2.38 6.29
f1 (ppm)

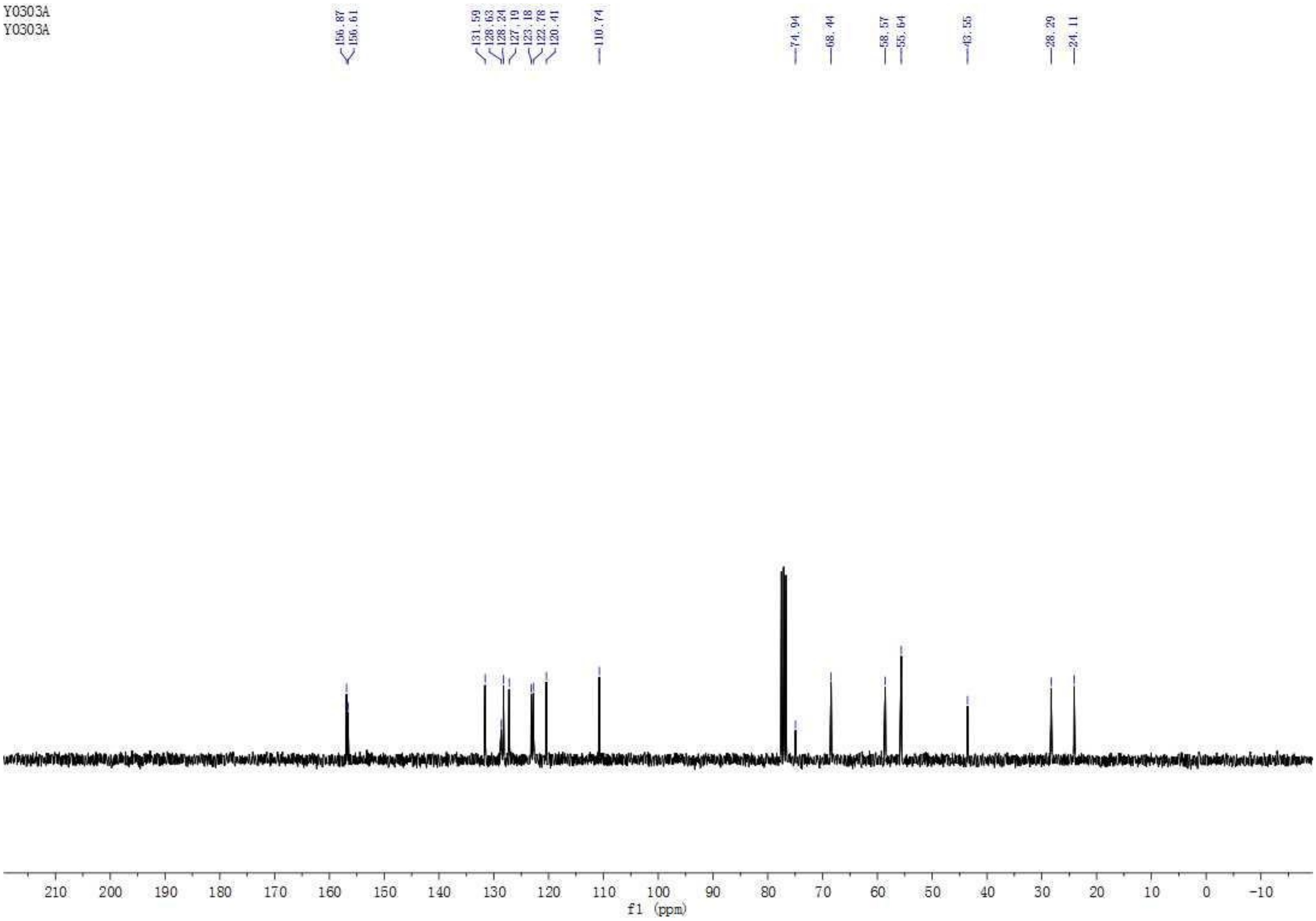

Ph
N
O
O
N
H
N
N
H
Ph
3f

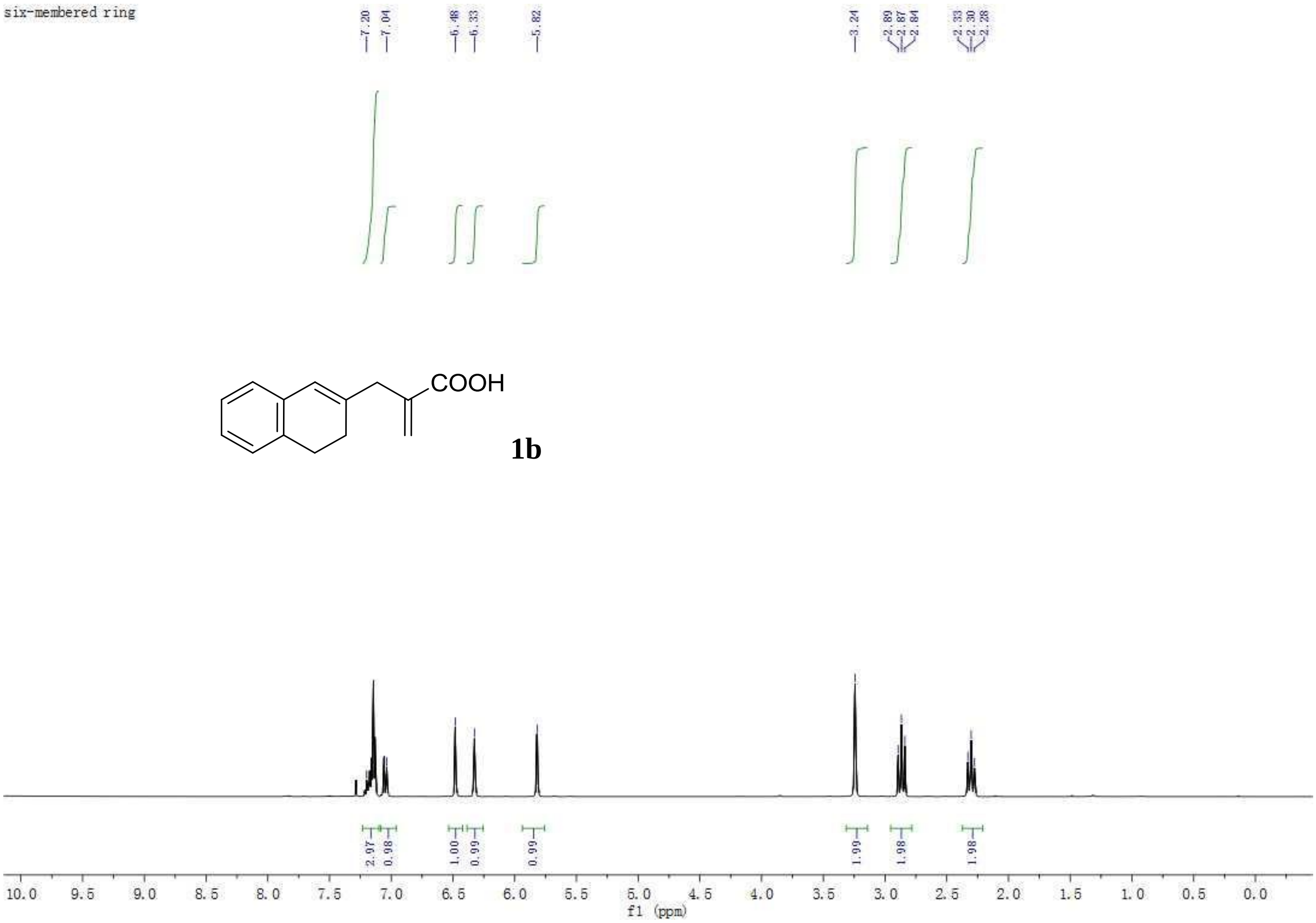

jxj0917c
jxj0917c
159.79 153.49 130.17 129.33 126.57 123.95 123.88 122.85 121.71 120.90 120.71 120.65 120.58 120.18 118.63 118.28 118.19 117.39 109.24
97.52
68.65
59.65
50.84 47.46
19.72 16.33
f1 (ppm)

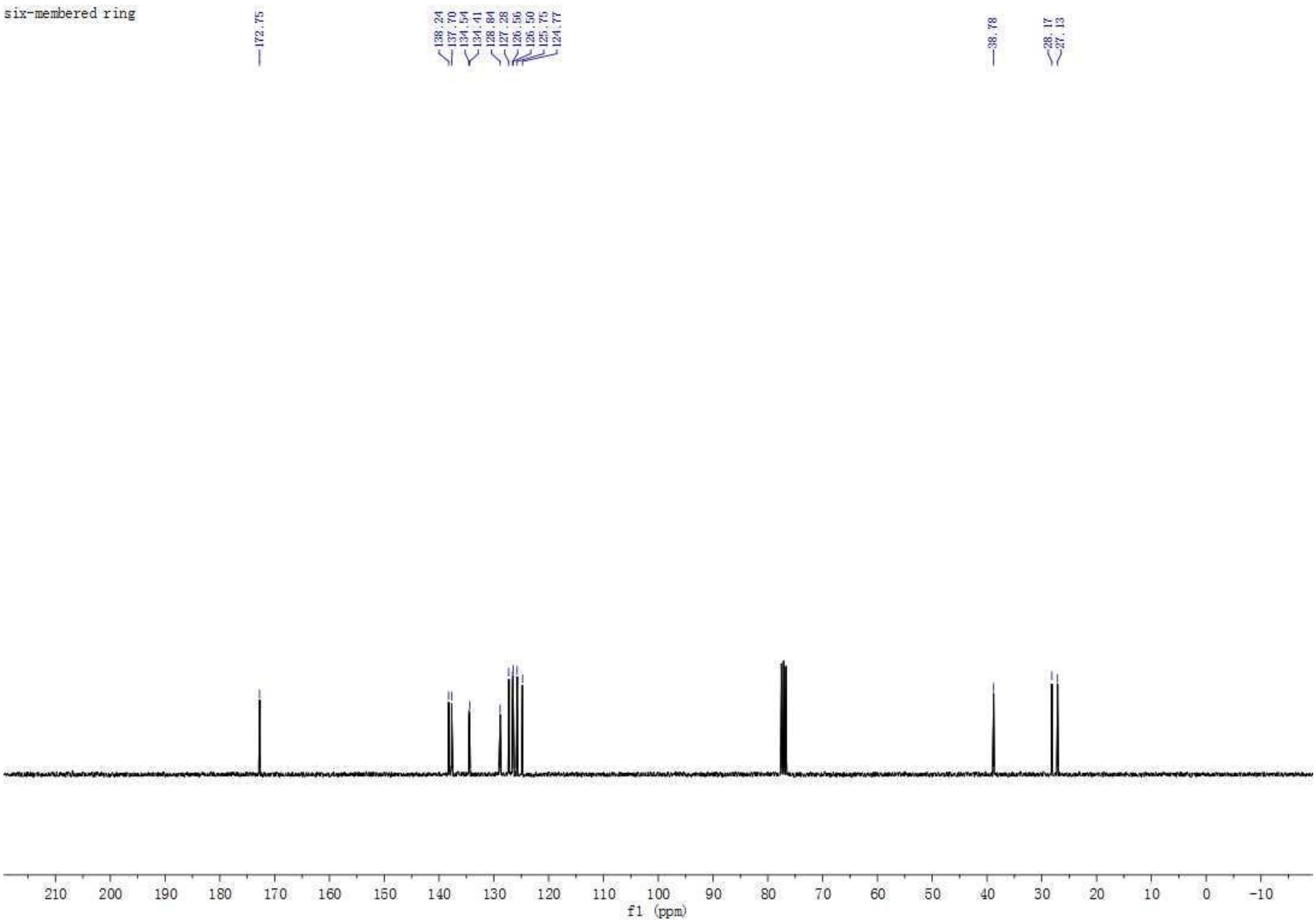

y1002d
y1002d
8.32
8.29
7.94
7.90
7.57
7.51
6.53
6.51
3.12
3.06
2.83
2.77
2.36
2.33
2.26
2.22
2.15
1.88
1.72
Me
N–N
O
H
CF3
3g
F3C
2.03
2.18
8.01
2.00
2.02
2.22
8.15
2.20
6.27
f1 (ppm)

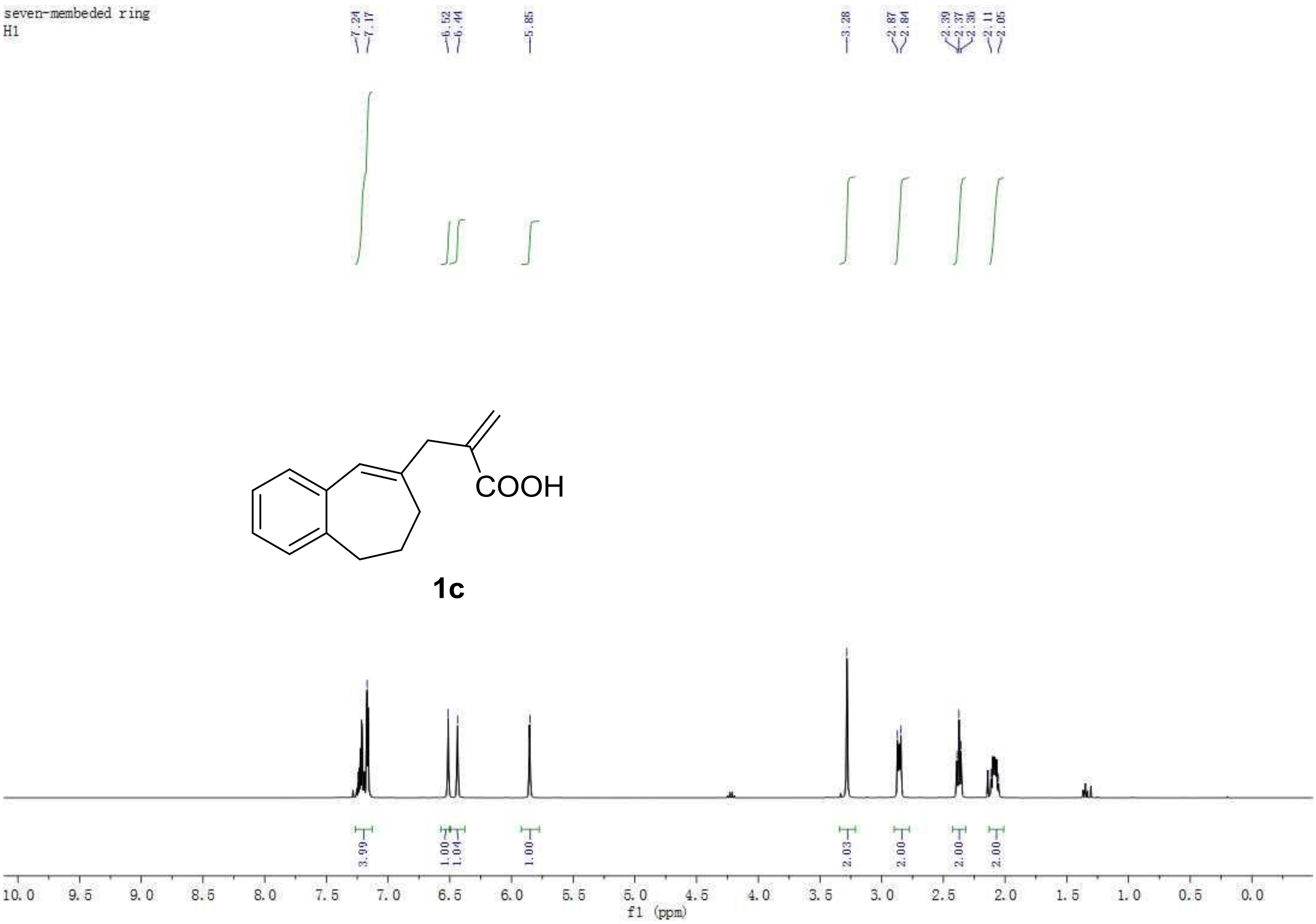

y1002d
y1002d
156.78
143.82
132.13
129.75
129.32
126.95
125.19
125.14
125.09
125.04
123.06
122.77
76.13
70.60
57.54
41.58
25.87
23.48
f1 (ppm)

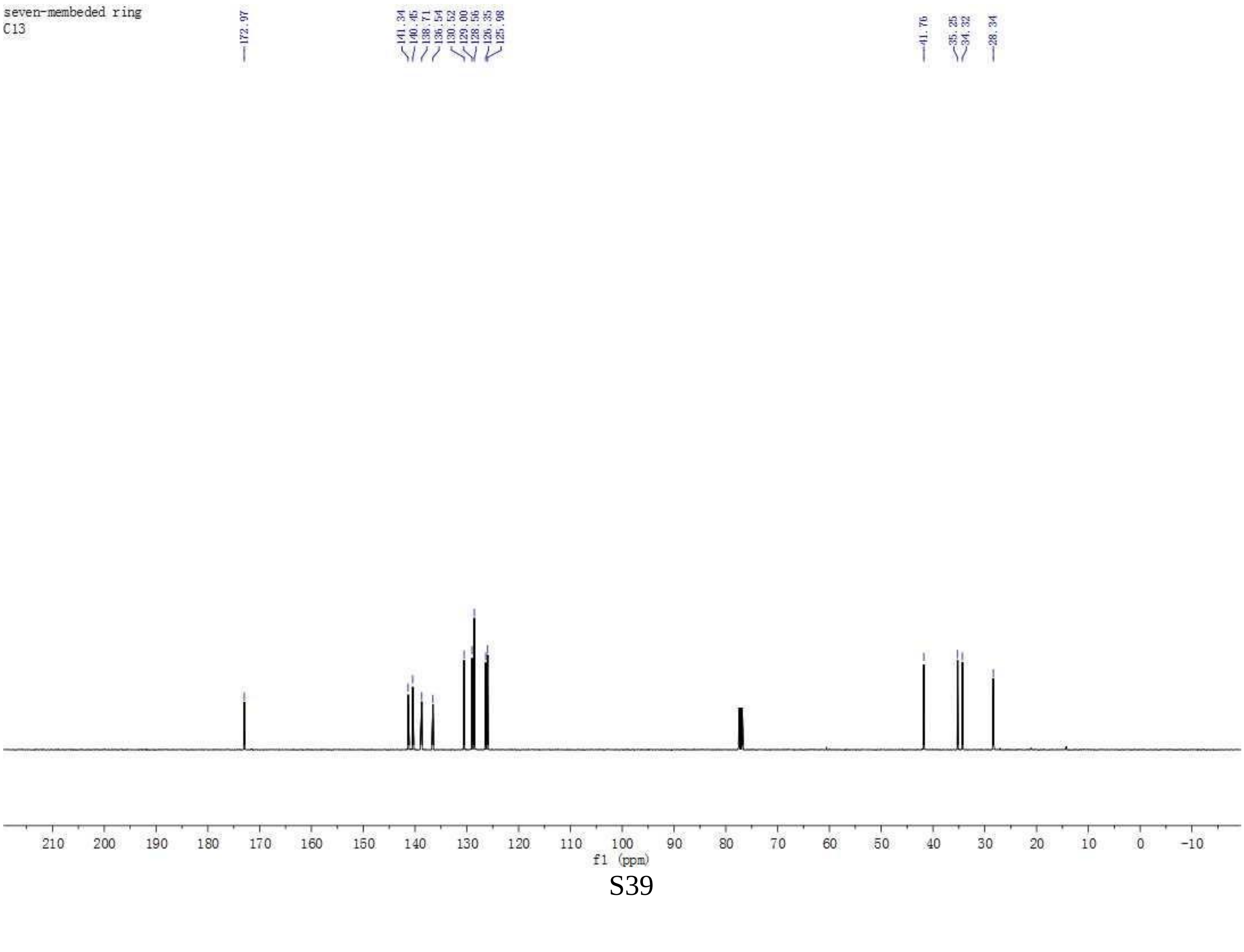

Y0303A
Y0303A
8.39
8.36
7.87
7.84
7.50
7.47
7.21
7.16
6.87
6.82
6.74
6.72
3.90
3.15
3.12
2.35
2.33
2.26
1.88
1.73
1.68
1.63
Me
N
H
MeO
O
N–N
O
Me
N
H
OMe
3h
2.00
2.07
2.04
2.13
4.19
2.05
6.11
4.01
2.13
6.14
6.20
2.19
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.
f1 (ppm)

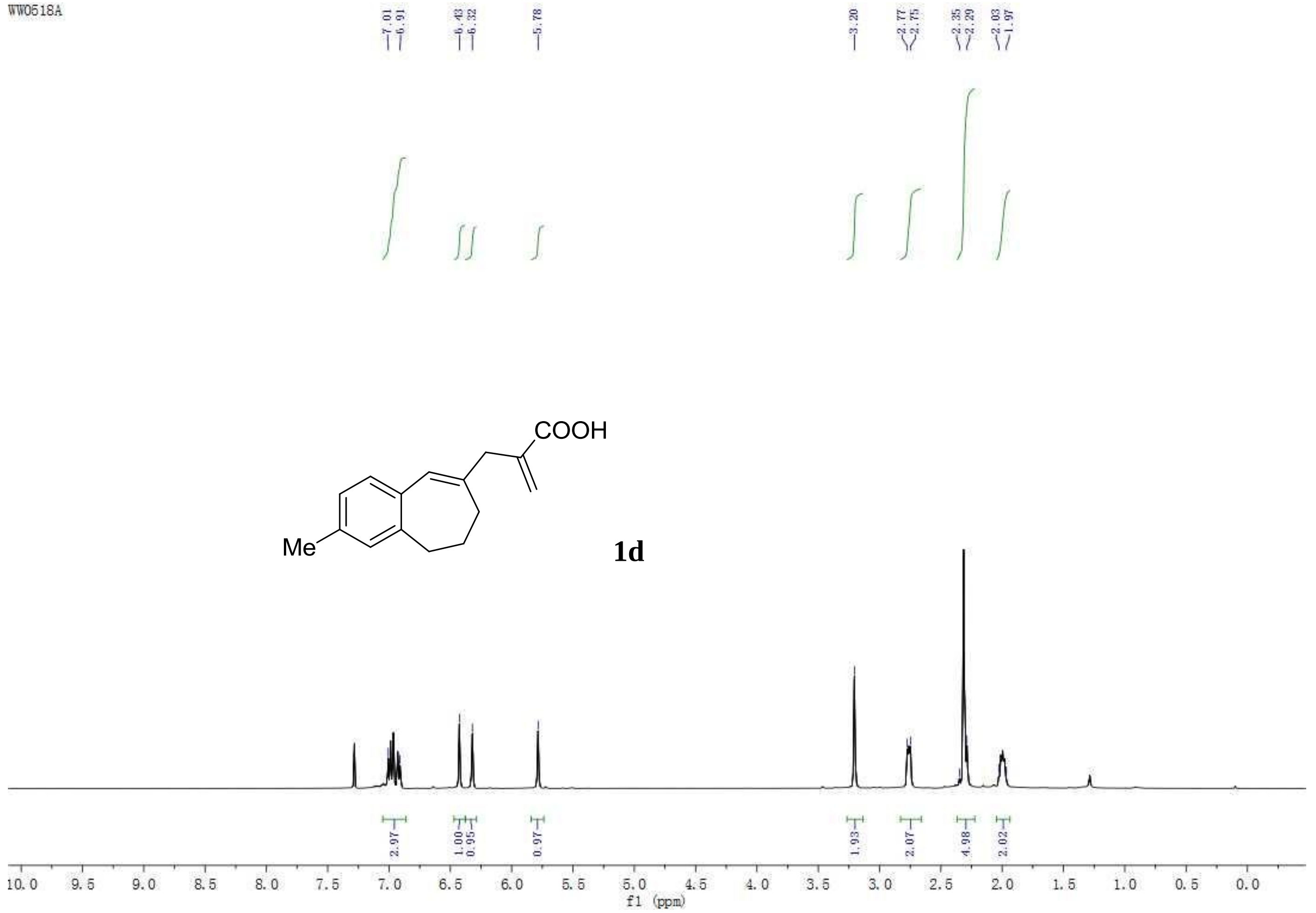

Y0303A
Y0303A
156.87
156.61
131.59
128.63
128.24
127.19
123.18
122.78
120.41
110.74
74.94
68.44
58.57
55.64
43.55
28.29
24.11
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

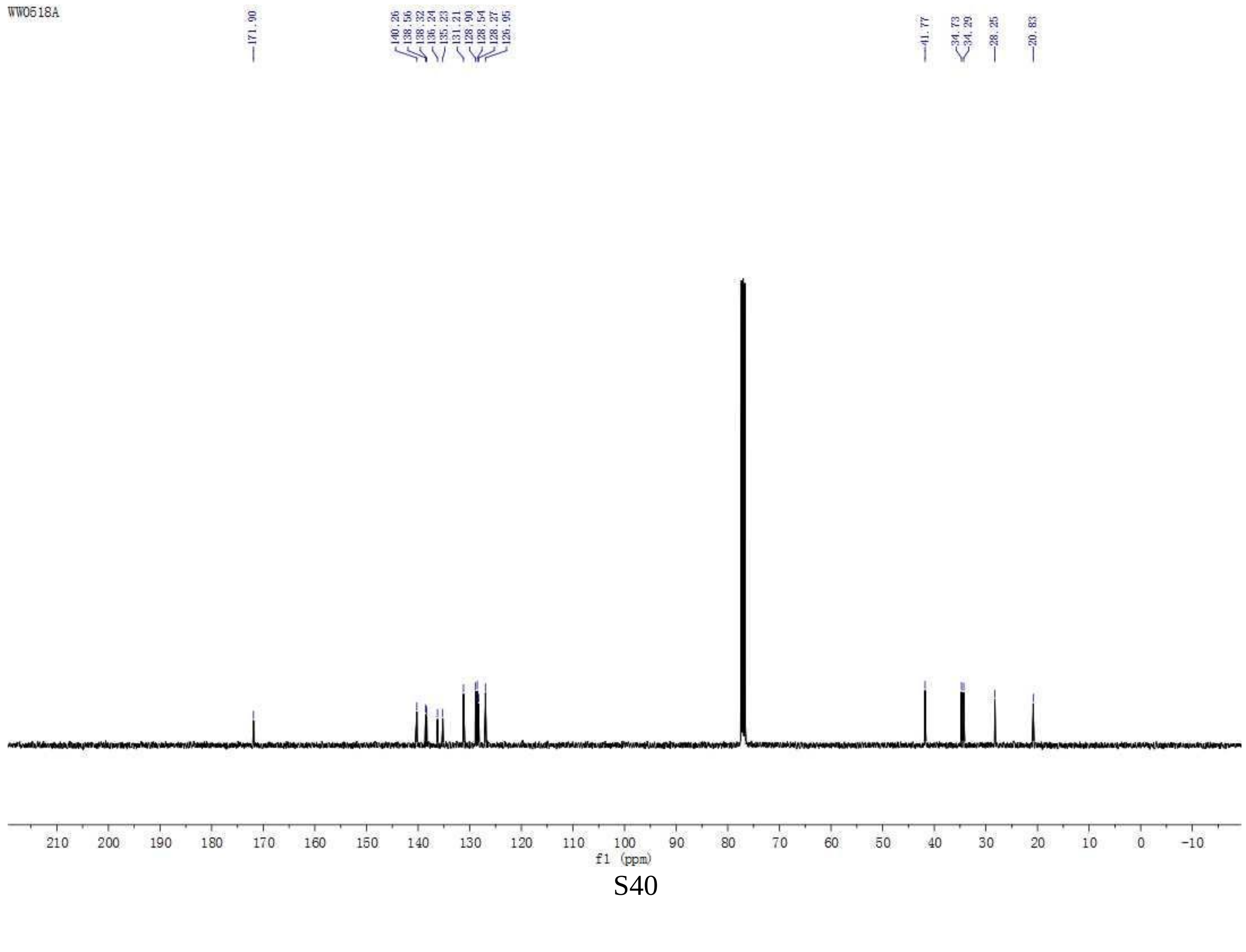

six-membered ring
7.20
7.04
6.48
6.33
5.82
3.24
2.89
2.87
2.84
2.33
2.30
2.28
COOH
1b
2.97
0.98
1.00
0.99
0.99
1.99
1.98
1.98
f1 (ppm)

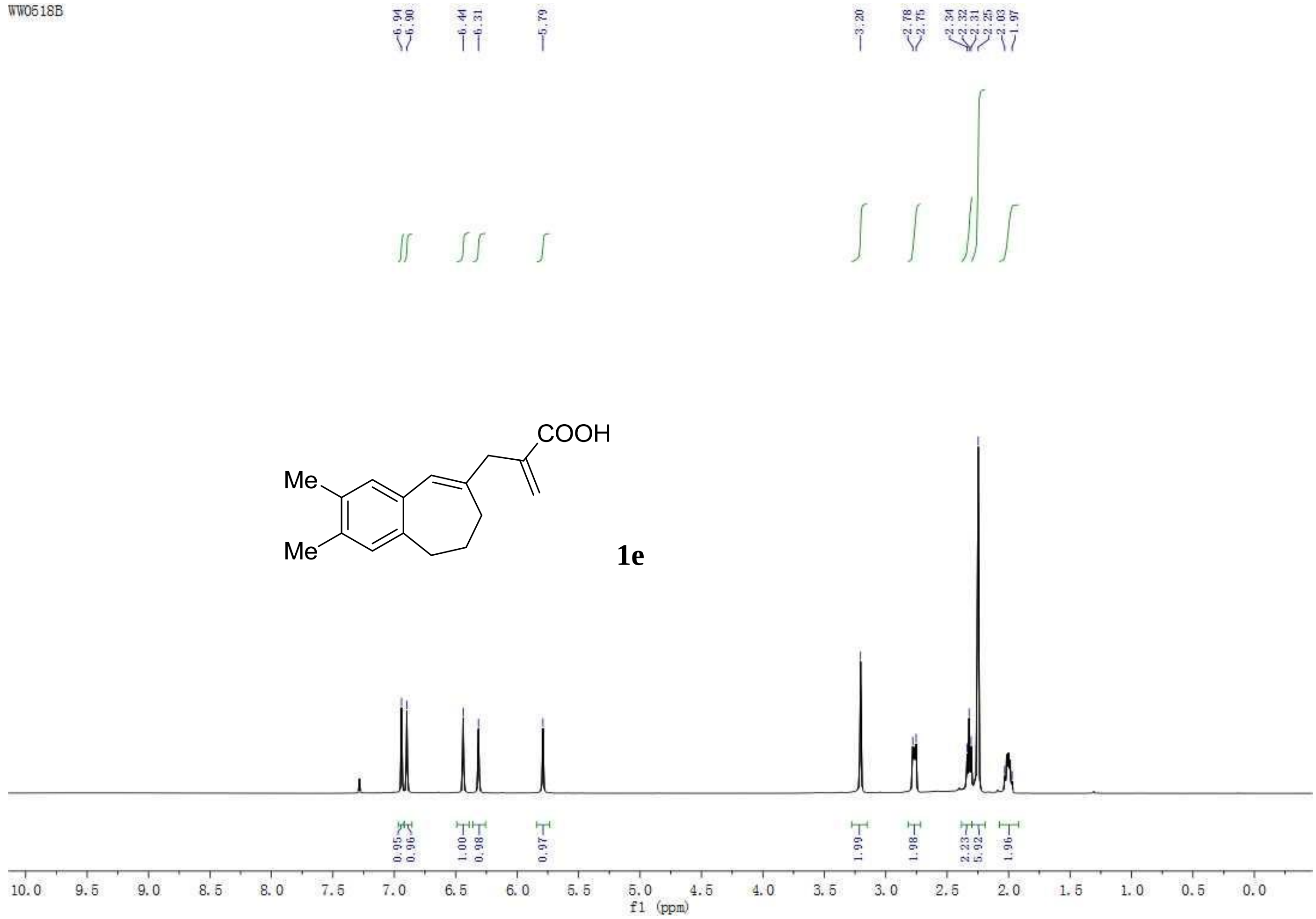

six-membered ring
172.75
138.24
137.70
134.54
134.41
128.84
127.28
126.56
126.50
125.75
124.77
38.78
28.17
27.13
f1 (ppm)

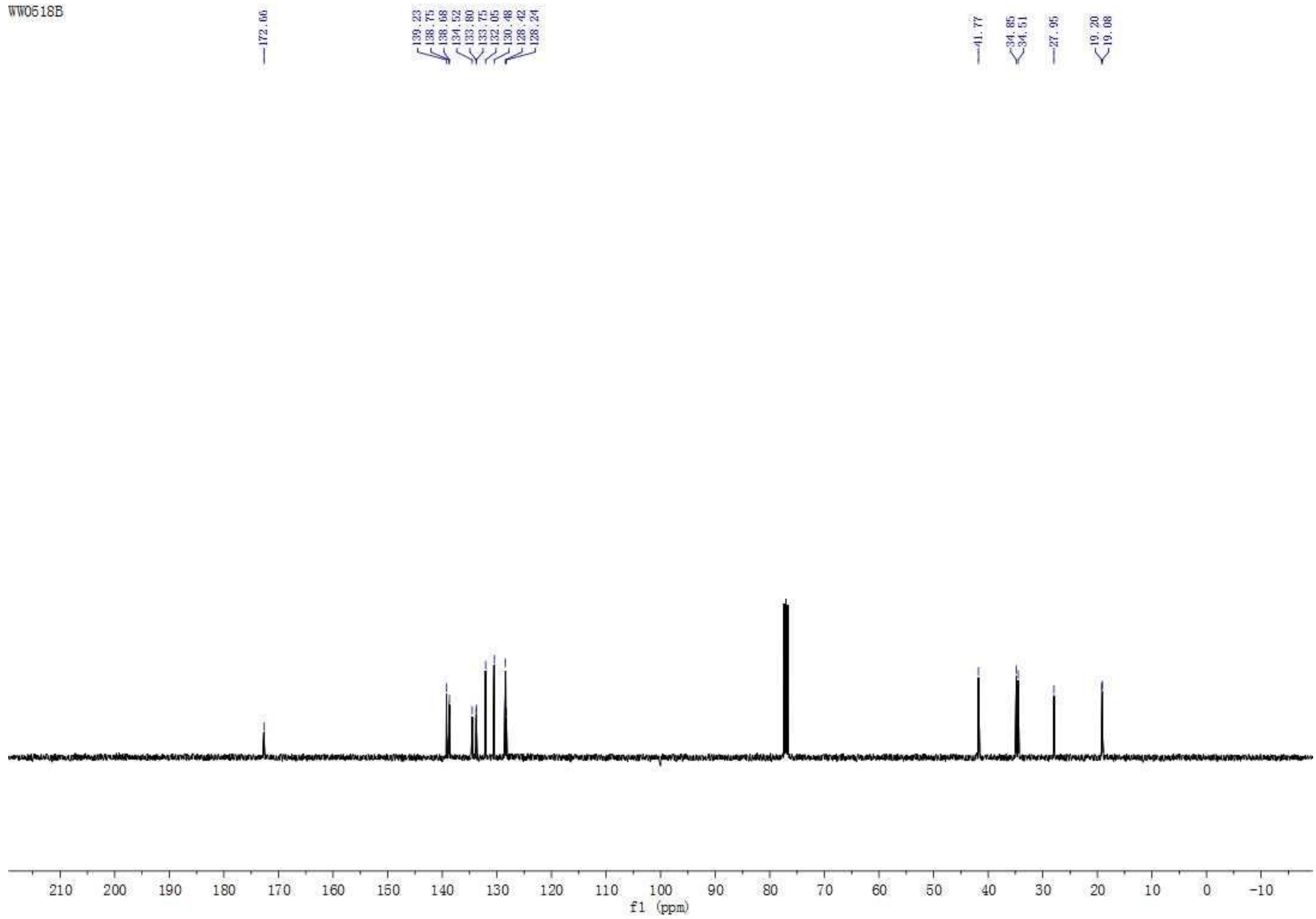

seven-membeded ring
H1
7.24
7.17
6.52
6.44
5.85
3.28
2.87
2.84
2.39
2.37
2.36
2.11
2.05
COOH
1c
3.99
1.00
1.04
1.00
2.03
2.00
2.00
2.00
f1 (ppm)


seven-membeded ring
C13
172.97
141.34
140.45
138.71
136.54
130.52
129.00
128.56
126.35
125.98
41.76
35.25
34.32
28.34
f1 (ppm)

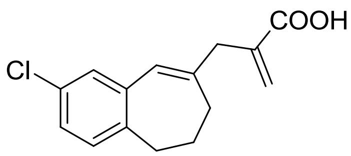

WW0518A
7.01
6.91
6.43
6.32
5.78
3.20
2.77
2.75
2.35
2.29
2.03
1.97
COOH
Me
1d
2.97
1.00
0.95
0.97
1.93
2.07
4.98
2.02
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


WW0518A
171.90
140.26
138.56
138.32
136.24
135.23
131.21
128.90
128.54
128.27
126.95
41.77
34.73
34.29
28.25
20.83
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

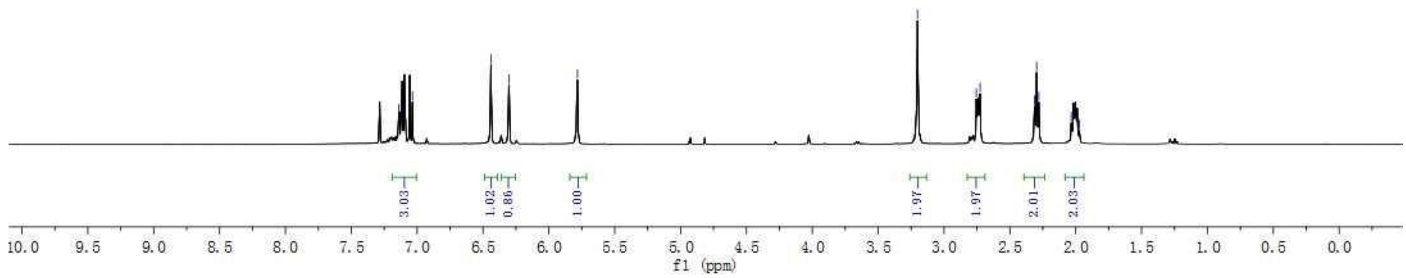

WW0518B
6.94
6.90
6.44
6.31
5.79
3.20
2.78
2.75
2.34
2.32
2.31
2.25
2.03
1.97
COOH
Me
Me
1e
0.95
0.96
1.00
0.98
0.97
1.99
1.98
2.23
5.92
1.96
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

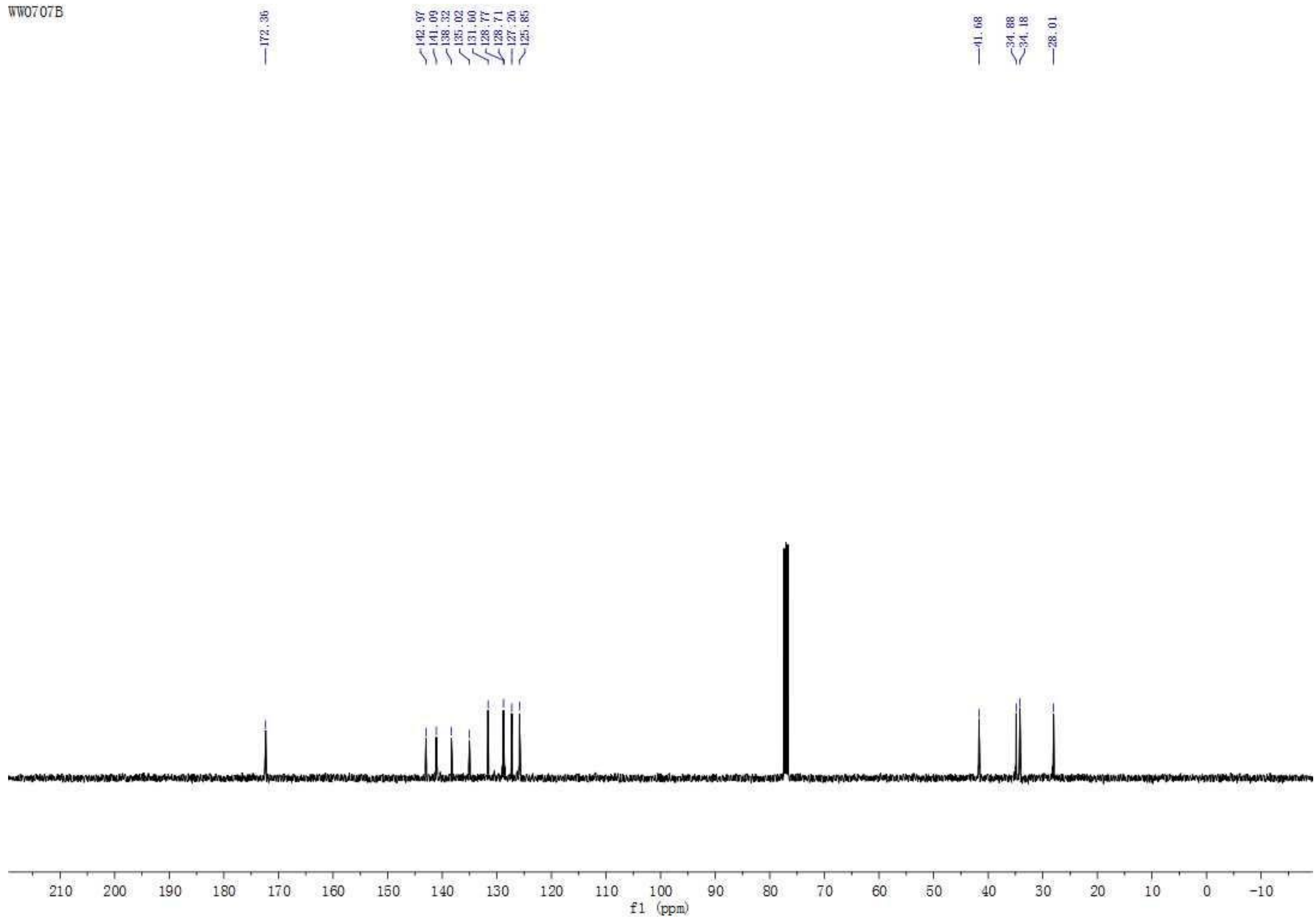

WW0518B
172.66
139.23
138.75
138.68
134.52
133.80
133.75
132.05
130.48
128.42
128.24
41.77
34.85
34.51
27.95
19.20
19.08
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

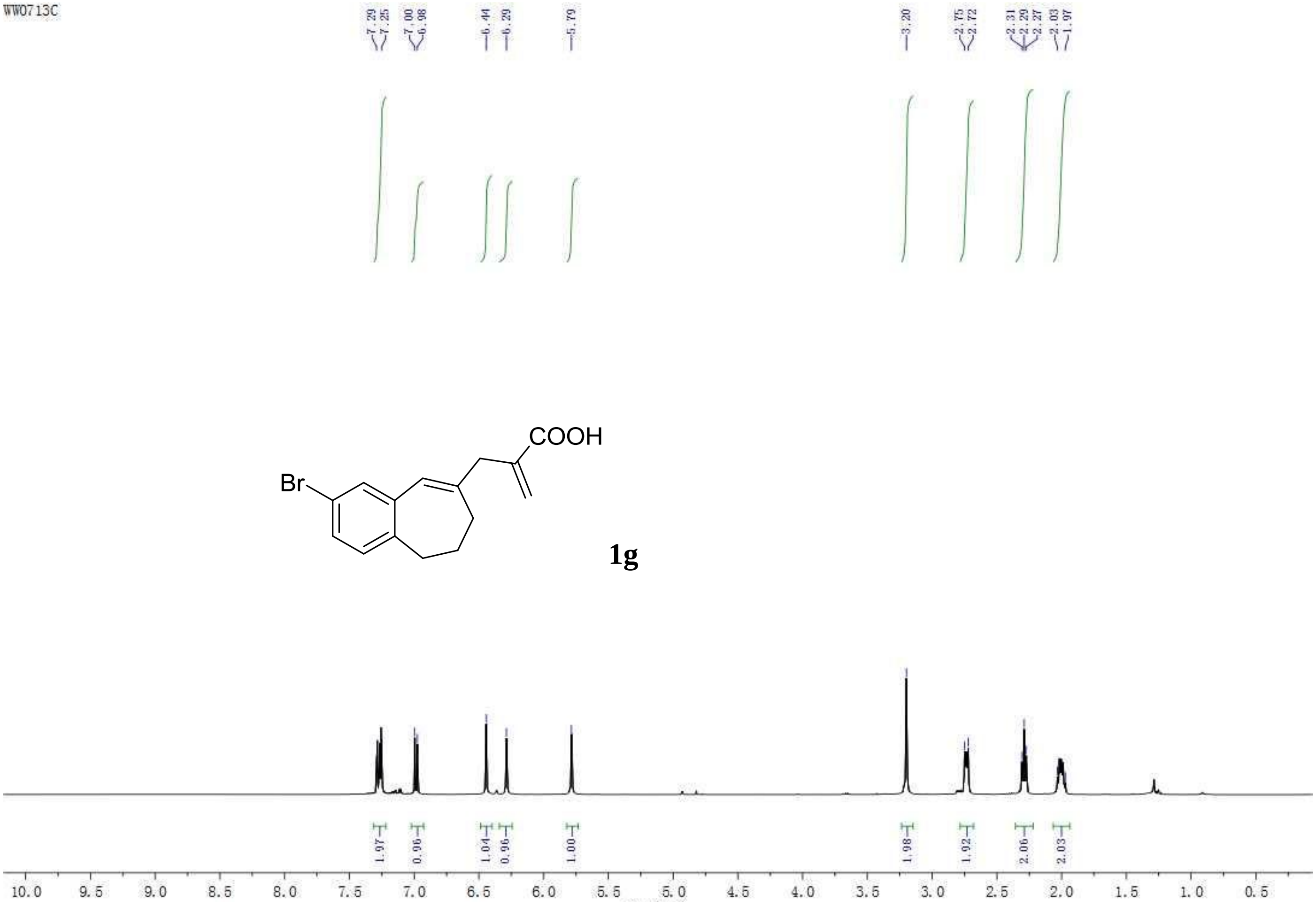

WW0707B
7.14
7.04
6.44
6.30
5.78
3.20
2.75
2.73
2.31
2.30
2.28
2.03
1.97


COOH
Cl

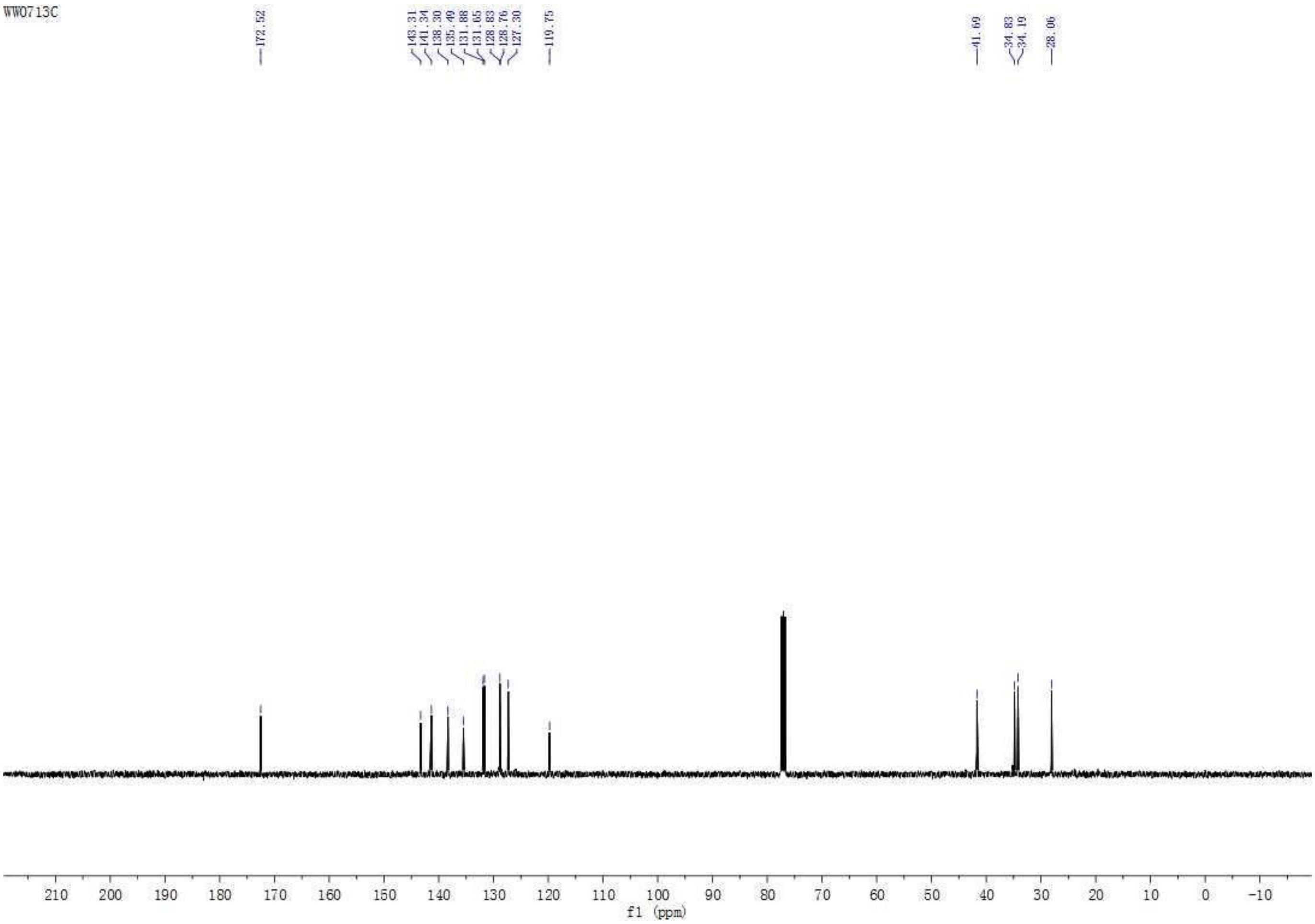
1f

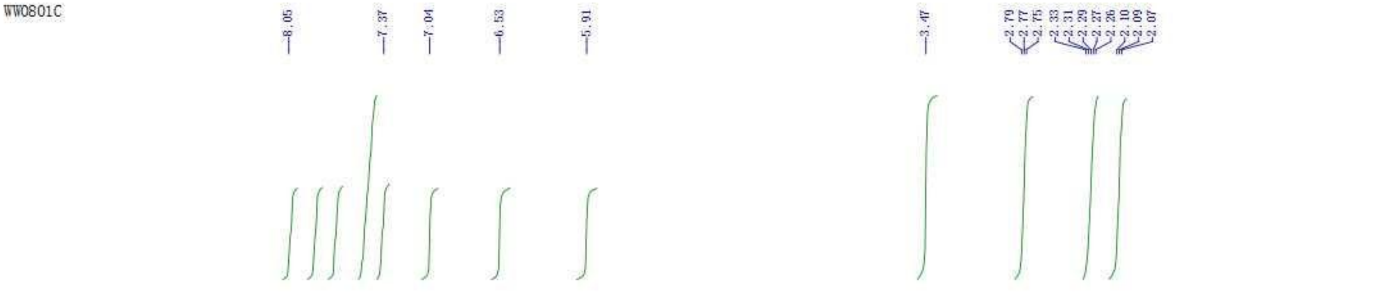

3.03
1.02
0.86
1.00
1.97
1.97
2.01
2.03
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

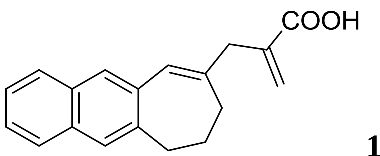

WW0707B
172.36
142.97
141.09
138.32
135.02
131.60
128.77
128.71
127.26
125.85
41.68
34.88
34.18
28.01
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


WW0713C
7.29
7.25
7.00
6.98
6.44
6.29
5.79
3.20
2.75
2.72
2.31
2.29
2.27
2.03
1.97
1.97
0.96
1.04
0.96
1.00
1.98
1.92
2.06
2.03
f1 (ppm)
COOH
Br

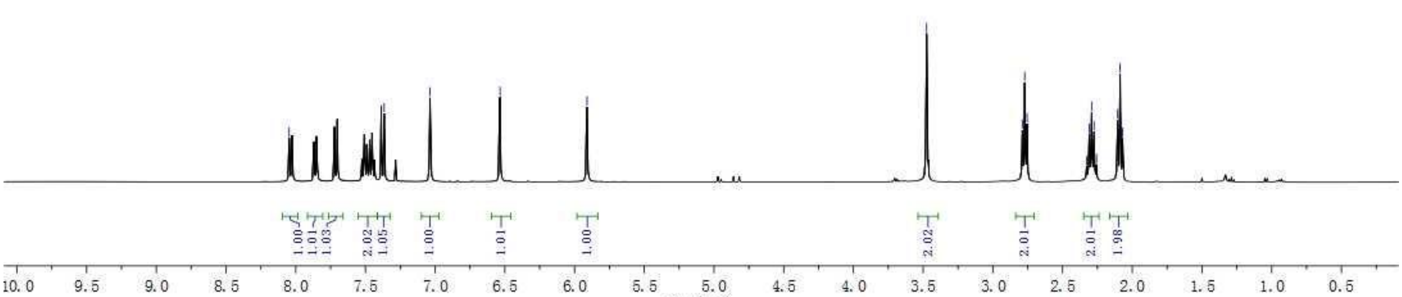
1g

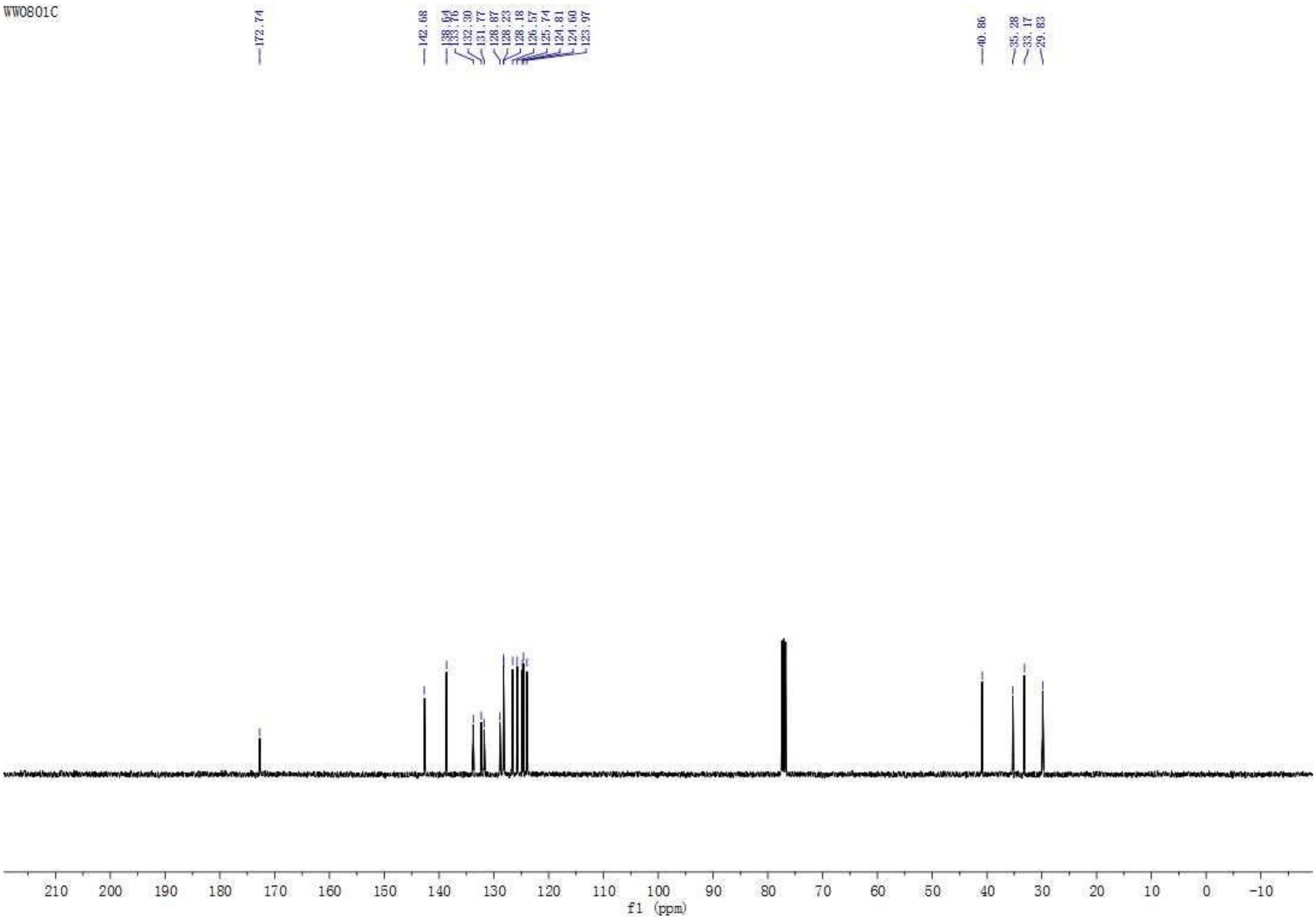

WW0713C
172.52
143.31
141.34
138.30
135.49
131.88
131.65
128.83
128.76
127.30
119.75
41.69
34.83
34.19
28.06
f1 (ppm)

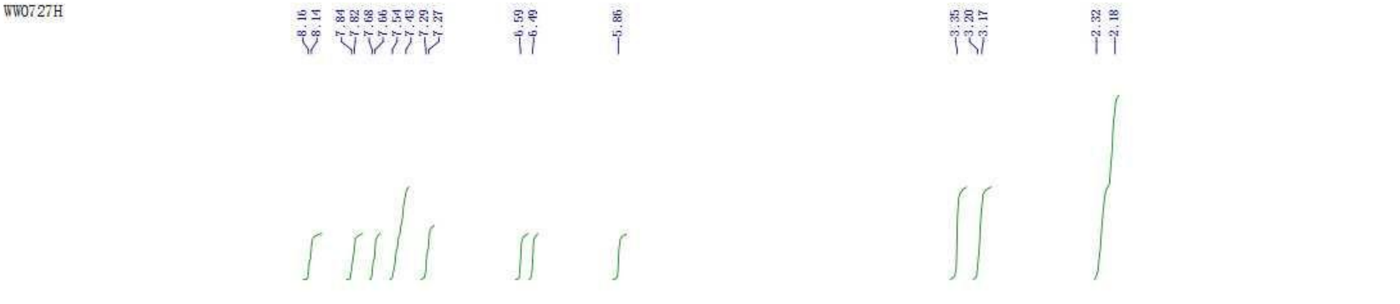

WW0801C

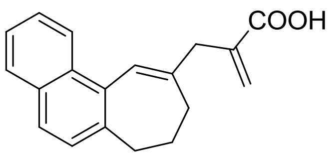

COOH

1h

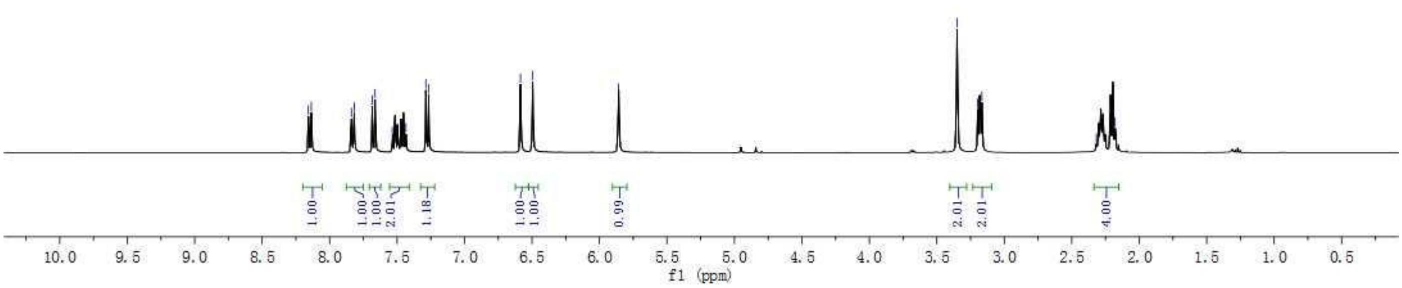

1.00
1.01
1.03
2.02
1.05
1.00
1.01
1.00
2.02
2.01
2.01
1.98
f1 (ppm)

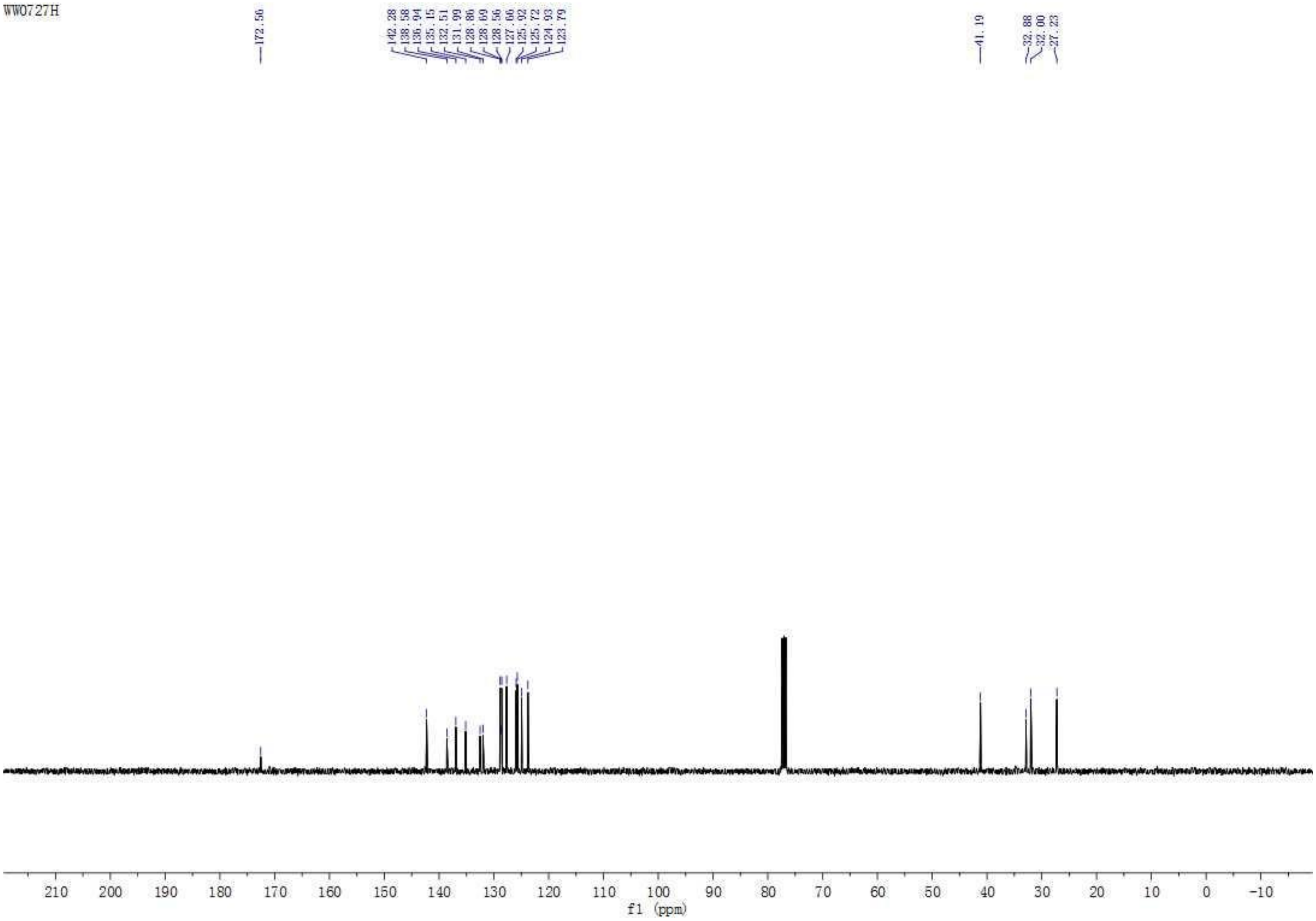

WW0801C
f1 (ppm)

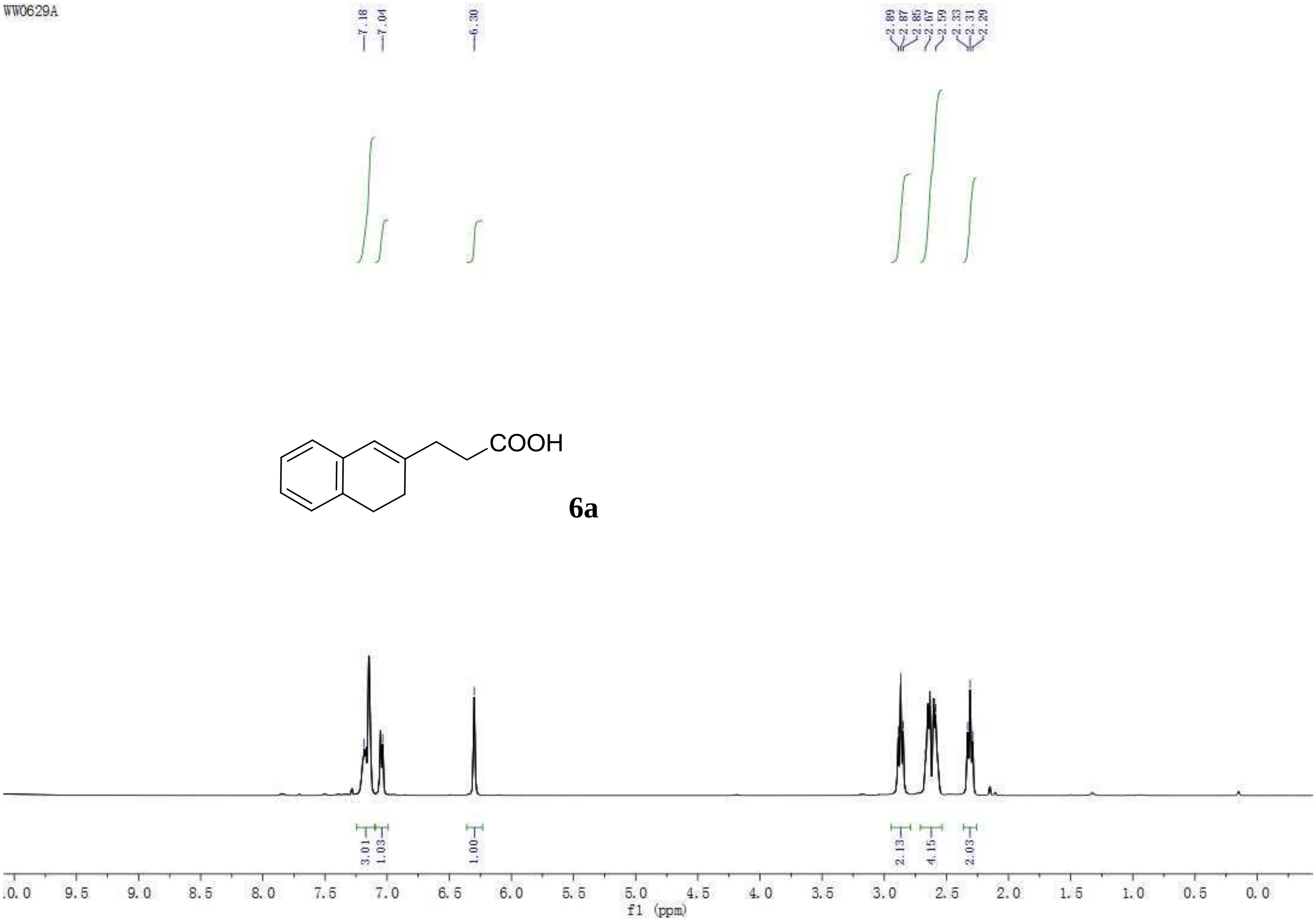

WW0727H
8.16
8.14
7.84
7.82
7.68
7.66
7.54
7.43
7.29
7.27
6.59
6.49
5.86
3.35
3.20
3.17
2.32
2.18

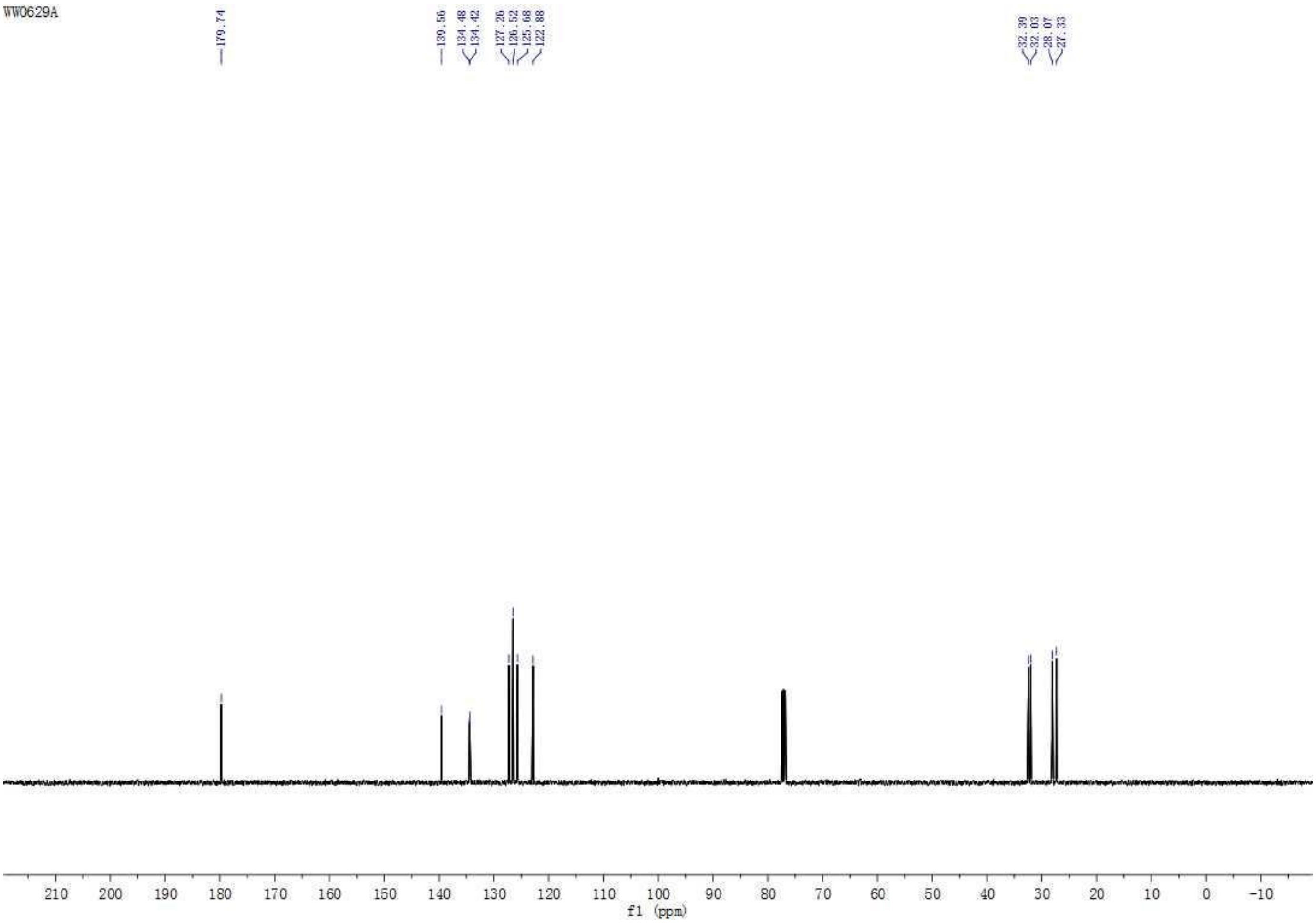

COOH

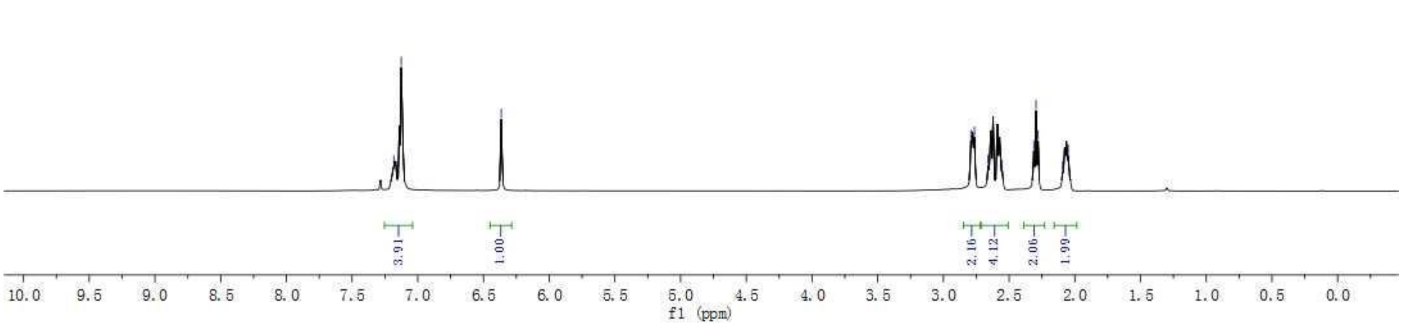
1i

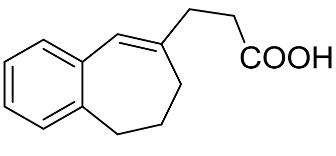

1.00
1.00
1.00
2.01
1.18
1.00
1.00
0.99
2.01
2.01
4.00
f1 (ppm)


WW0727H
172.56
142.28
138.58
136.94
135.15
132.51
131.99
128.86
128.69
128.56
127.66
125.92
125.72
124.93
123.79
41.19
32.88
32.00
27.23
f1 (ppm)

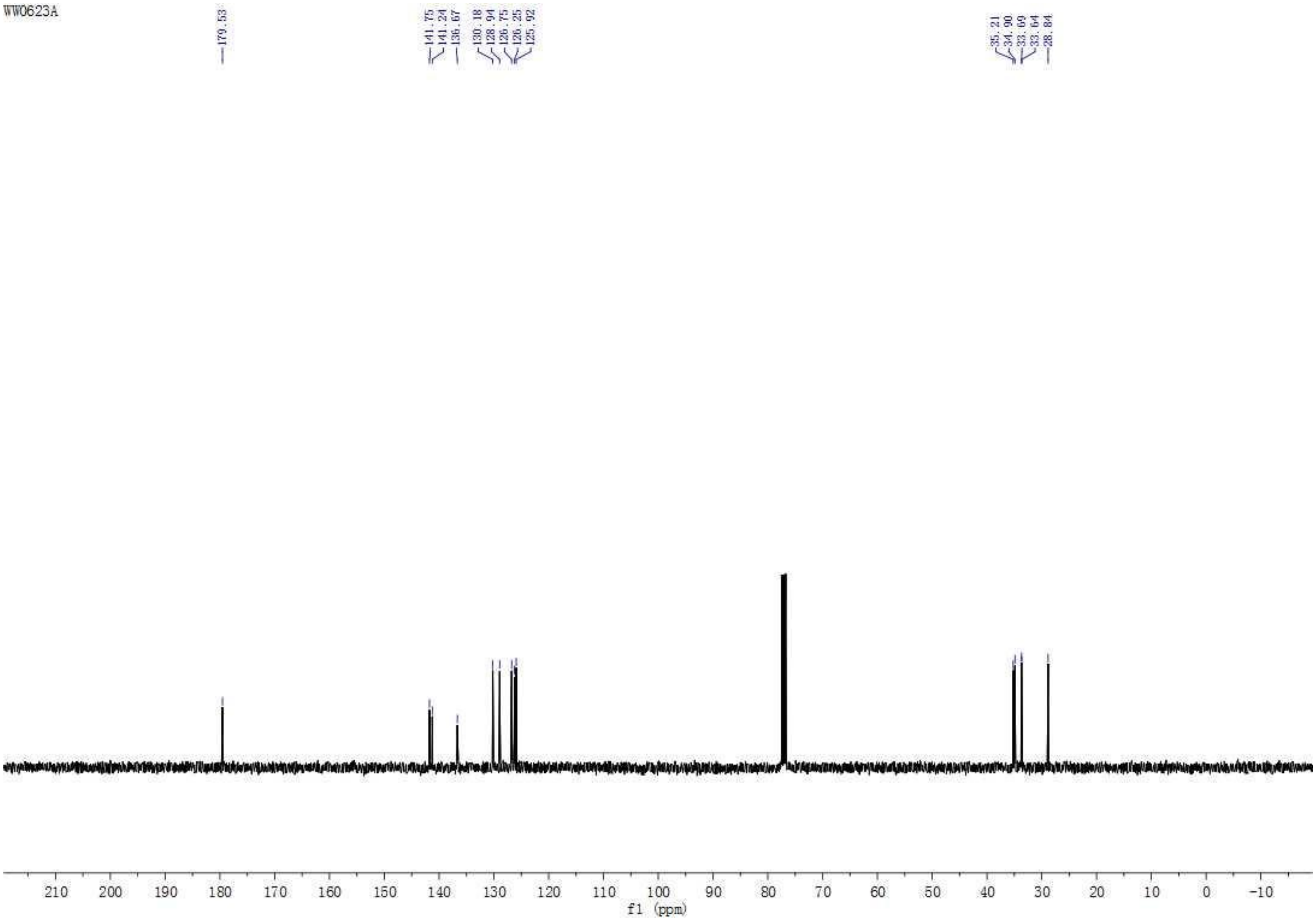

WW0629A
7.18
7.04
6.30
2.89
2.87
2.85
2.67
2.59
2.33
2.31
2.29
COOH
6a
3.01
1.03
1.00
2.13
4.15
2.03
f1 (ppm)

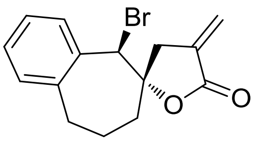

WW0629A
179.74
139.56
134.48
134.42
127.26
126.52
125.68
122.88
32.39
32.03
28.07
27.33
f1 (ppm)



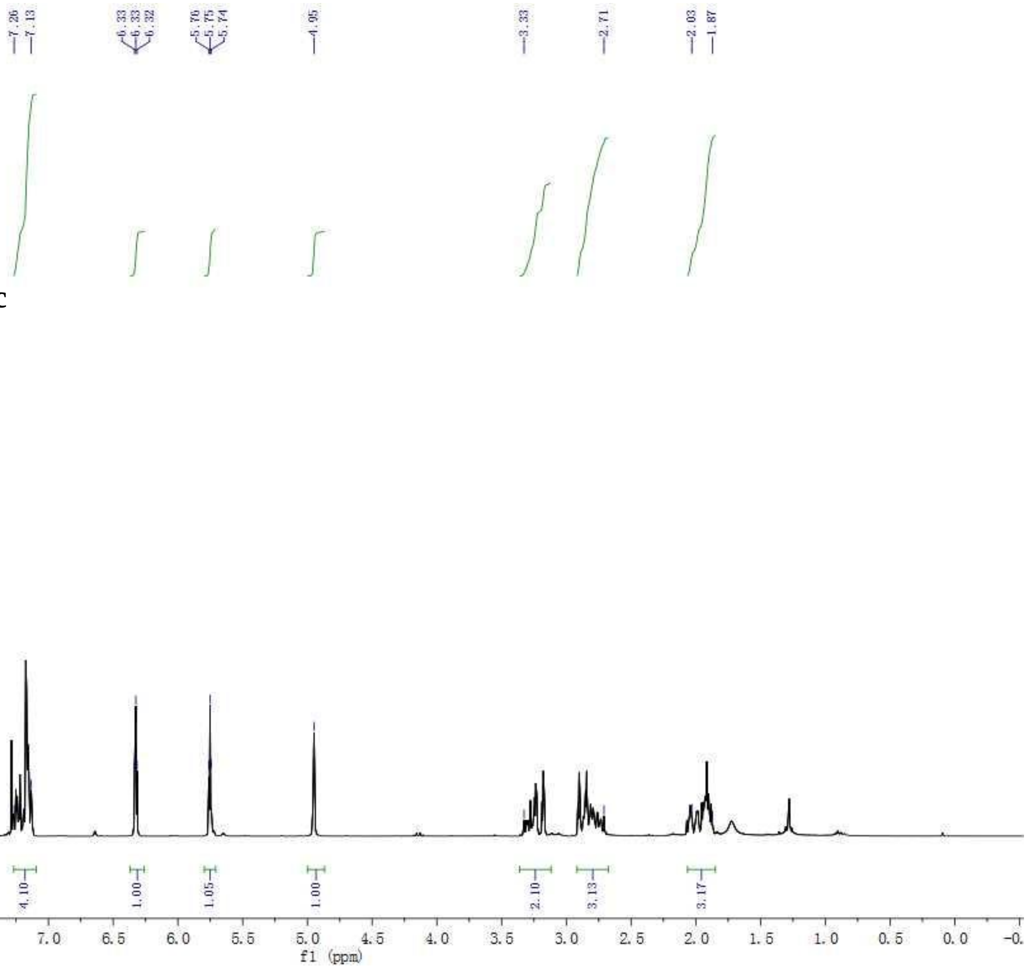


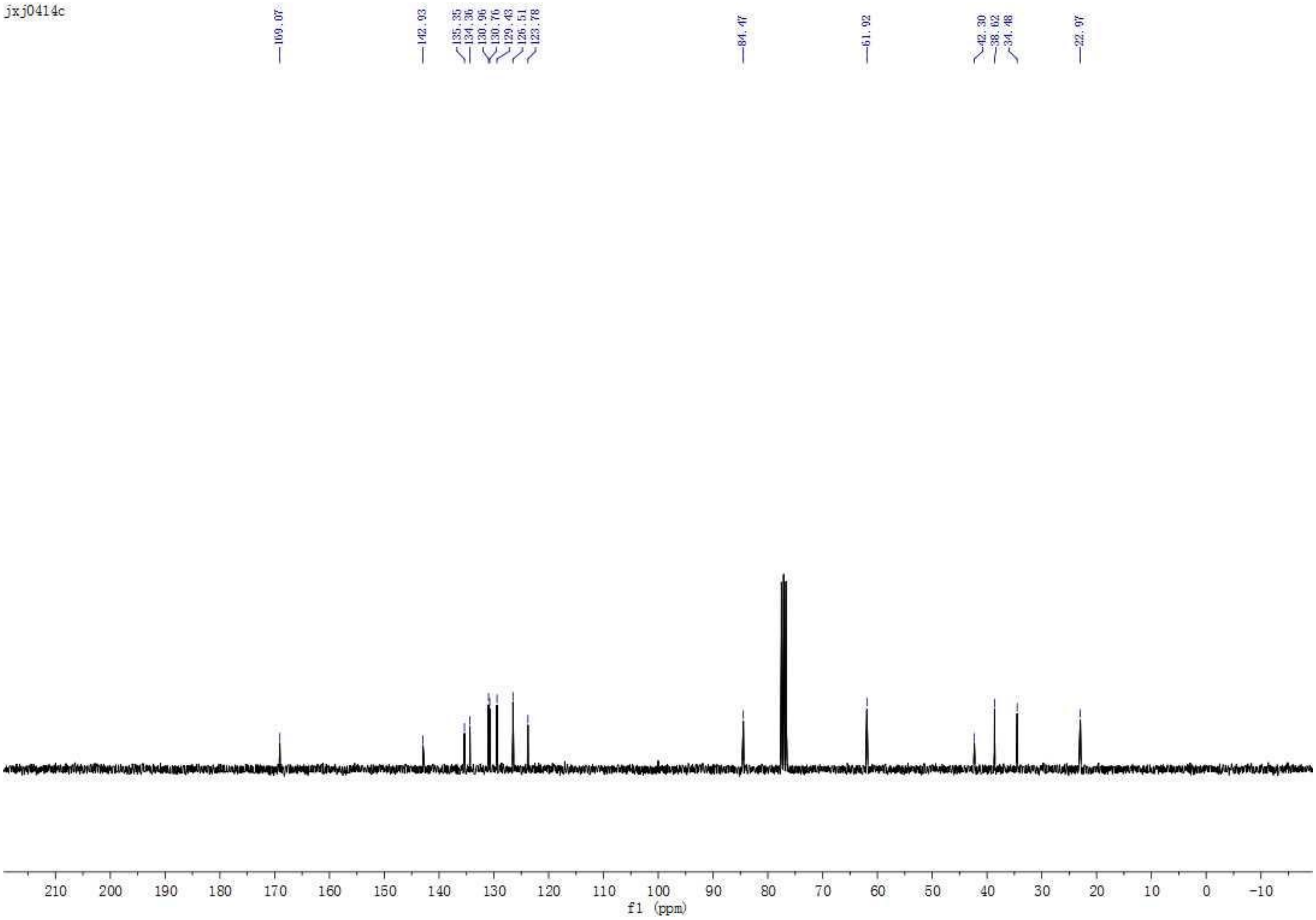
6b

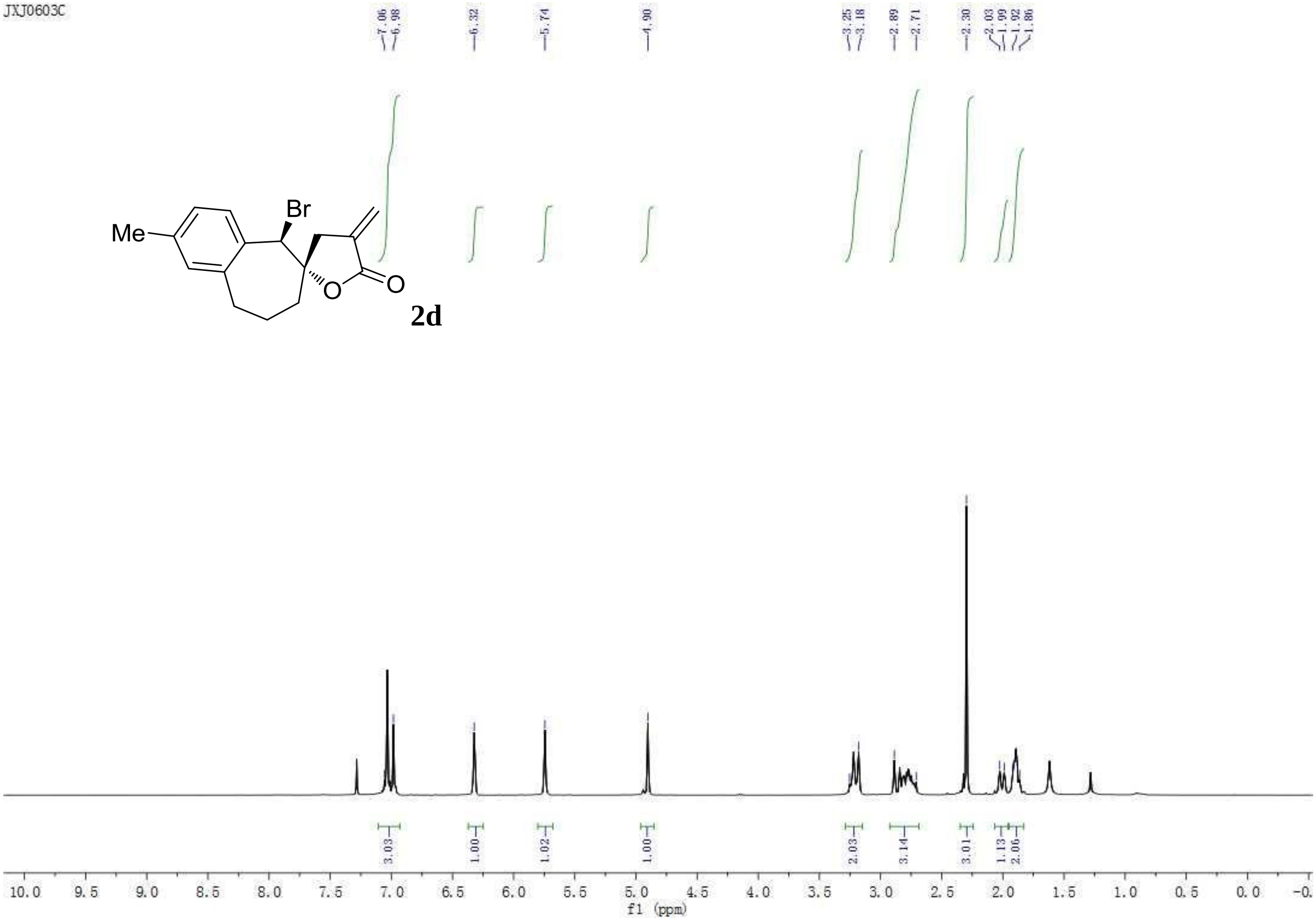



Br
O
O

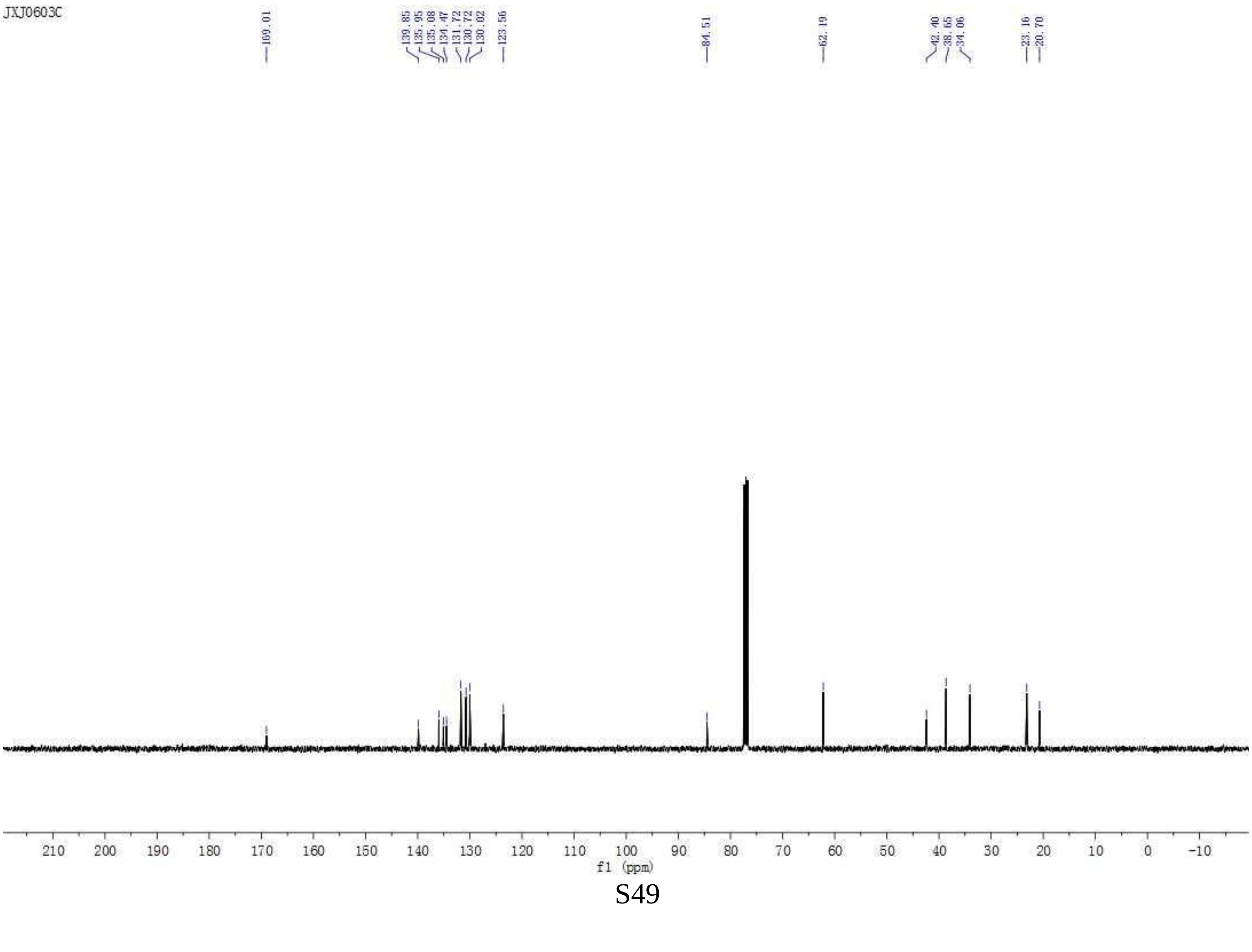
2c


jxj0414a
7.26
7.13
6.33
6.33
6.32
5.76
5.75
5.74
4.95
3.33
2.71
2.03
1.87
4.10
1.00
1.05
1.00
2.10
3.13
3.17
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.
f1 (ppm)

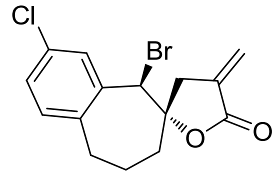

jxj0414c
169.07
142.93
135.35
134.36
130.96
130.76
129.43
126.51
123.78
84.47
61.92
42.30
38.62
34.48
22.97
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



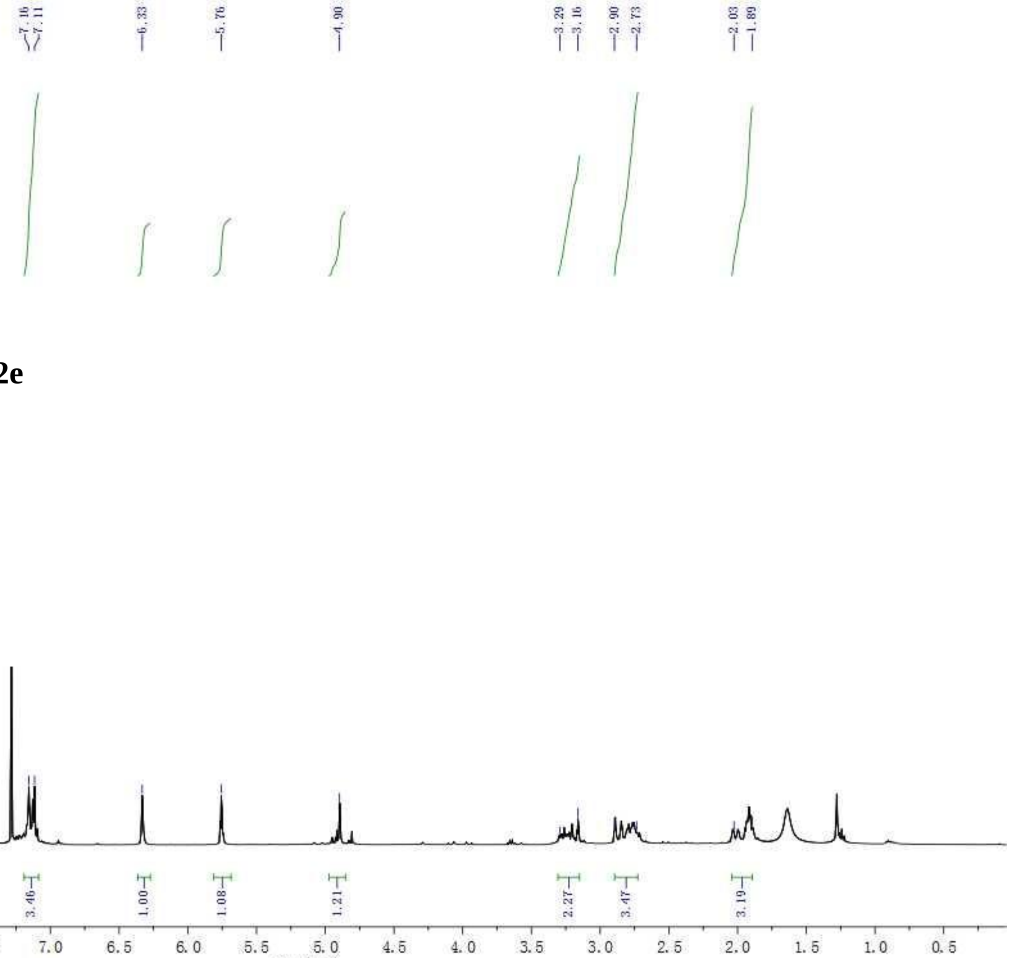
2d



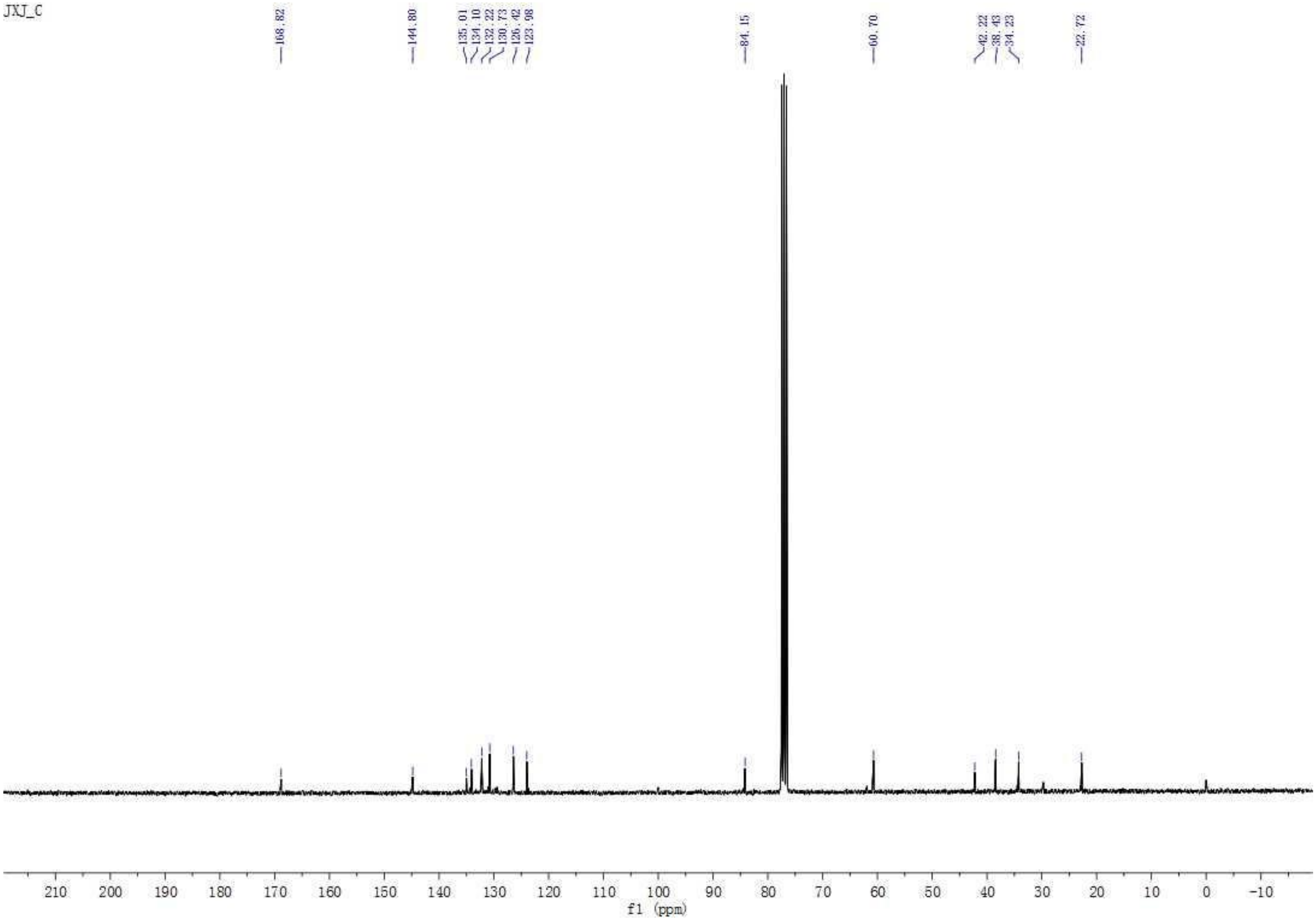
JXJ190810F



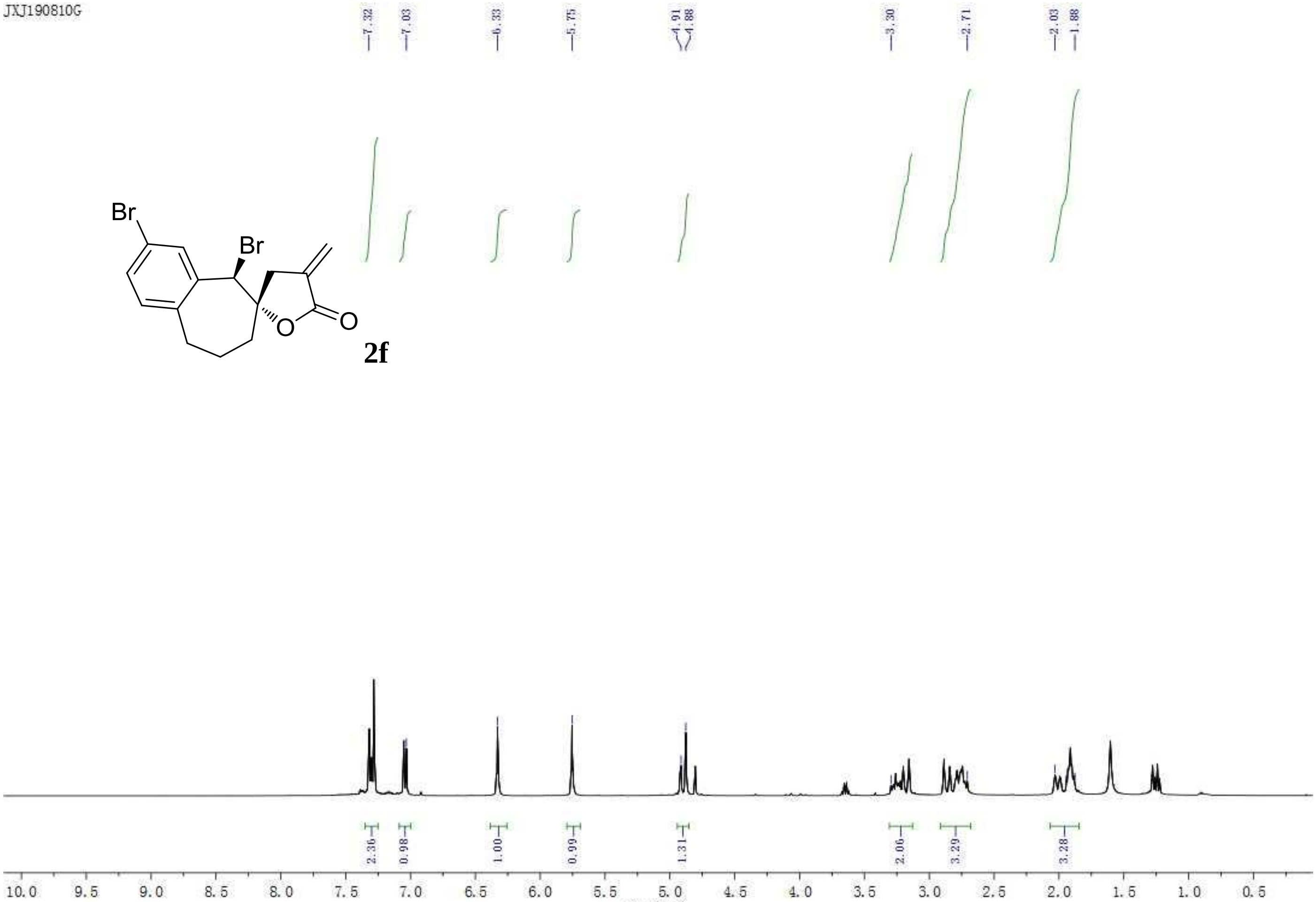
2e



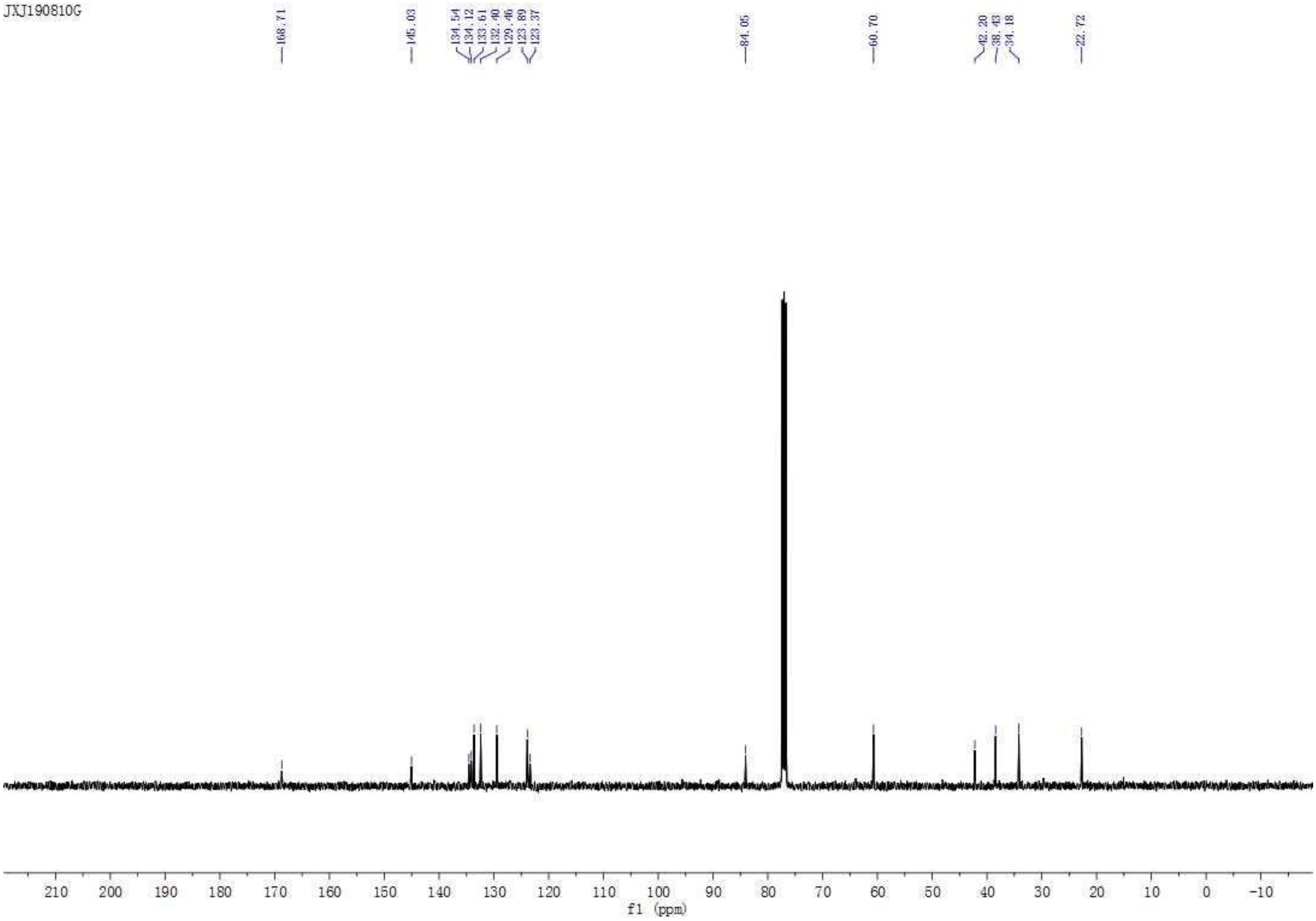
JXJ_C

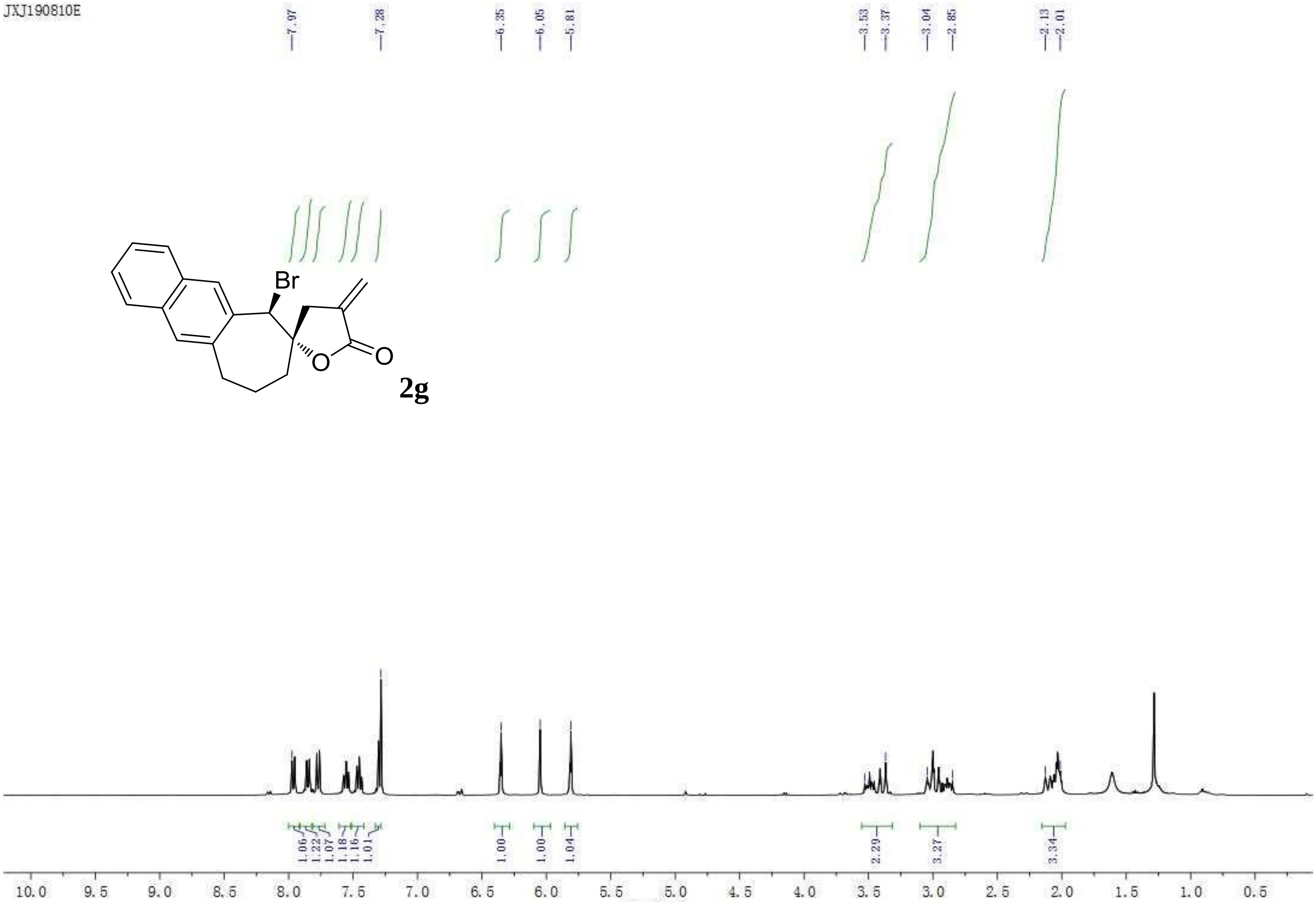


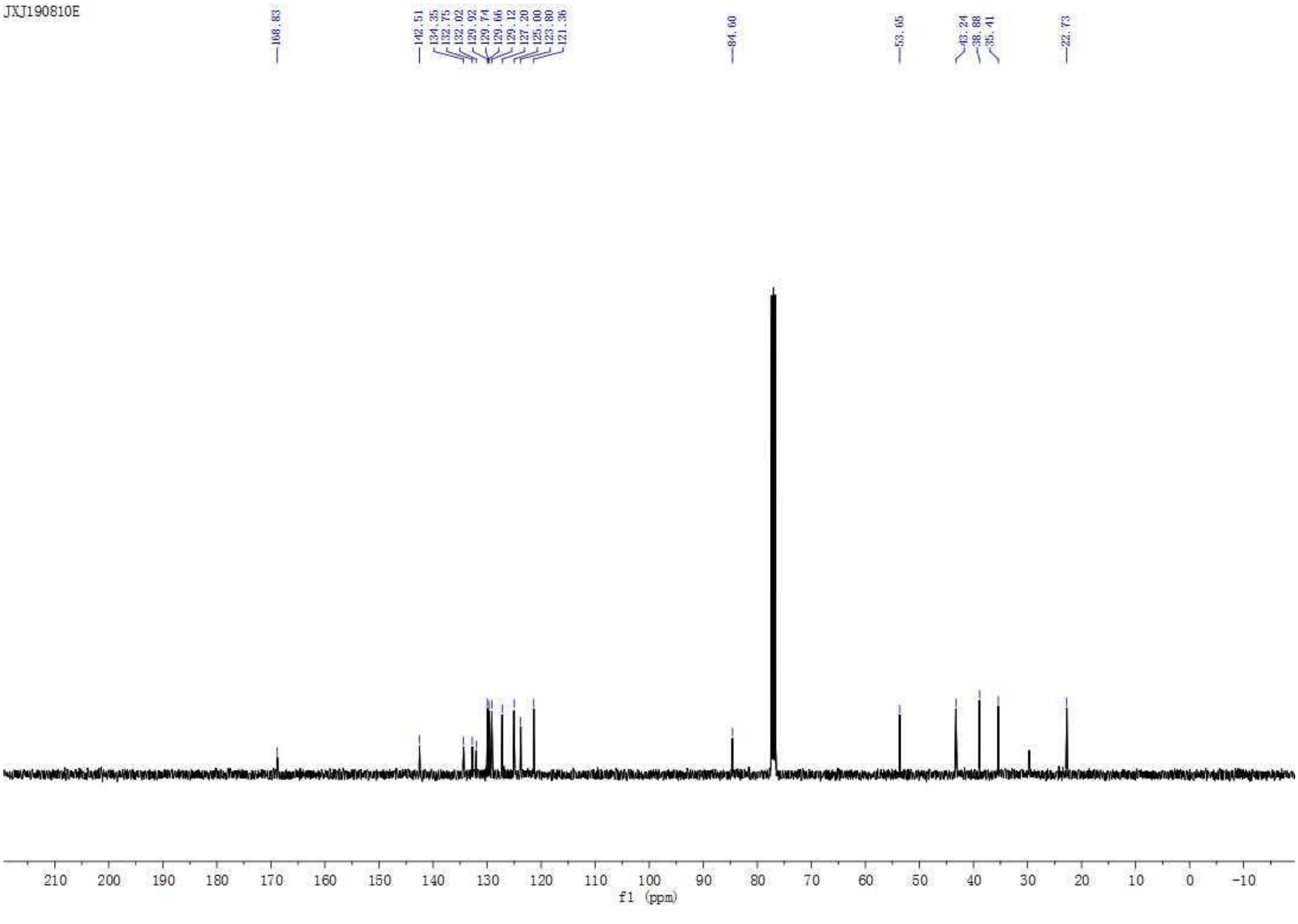
JXJ190810G

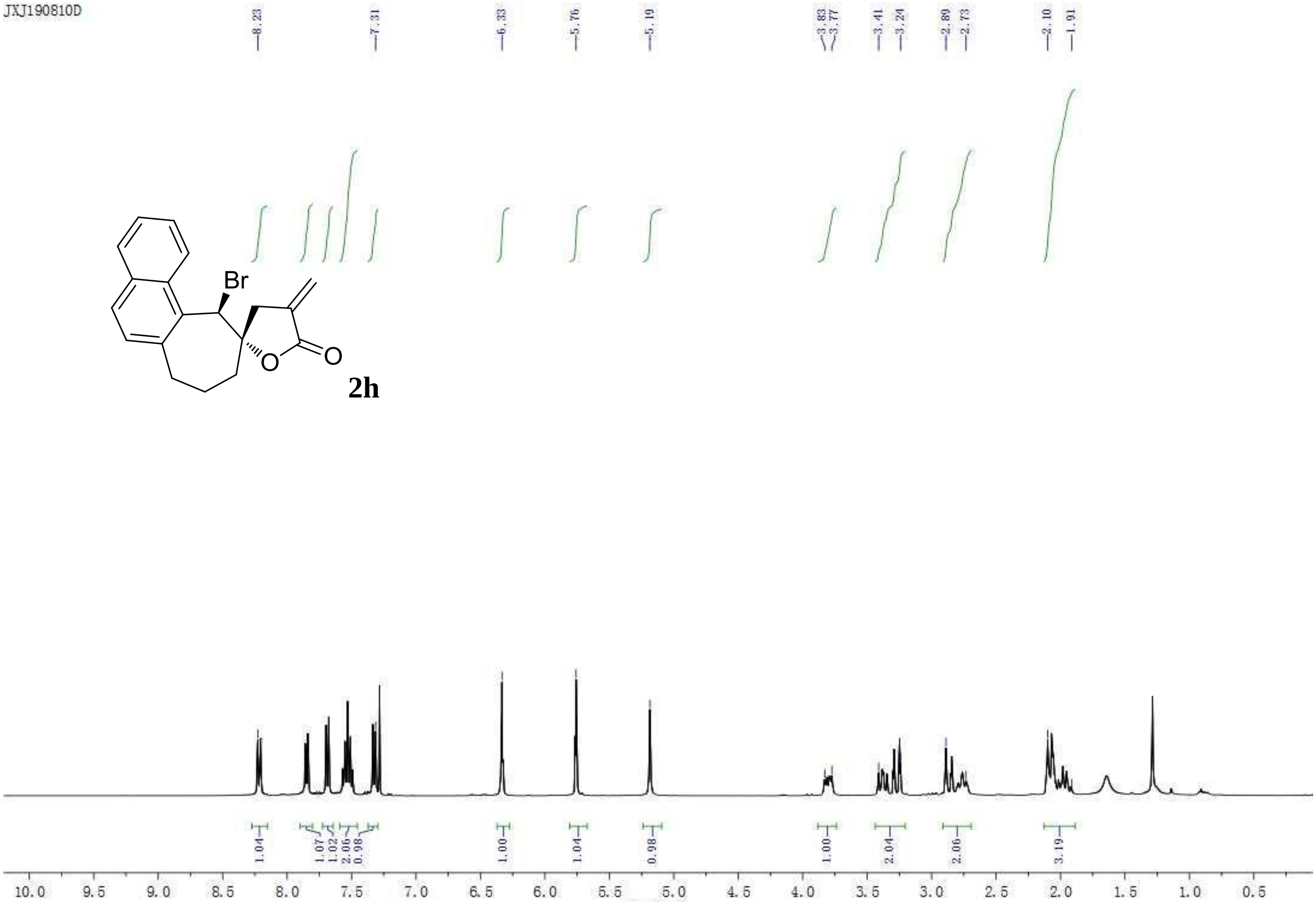


JXJ190810G

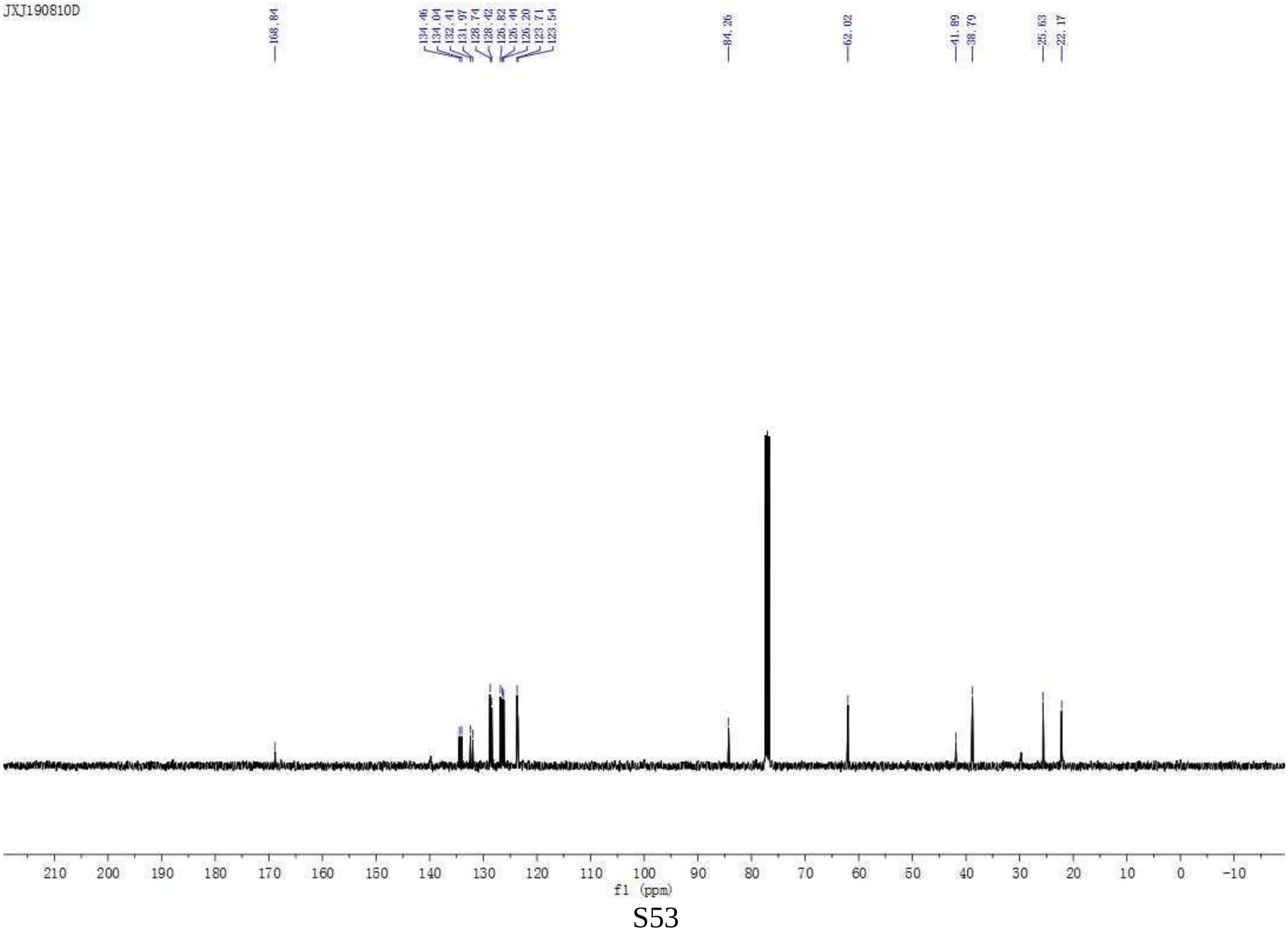


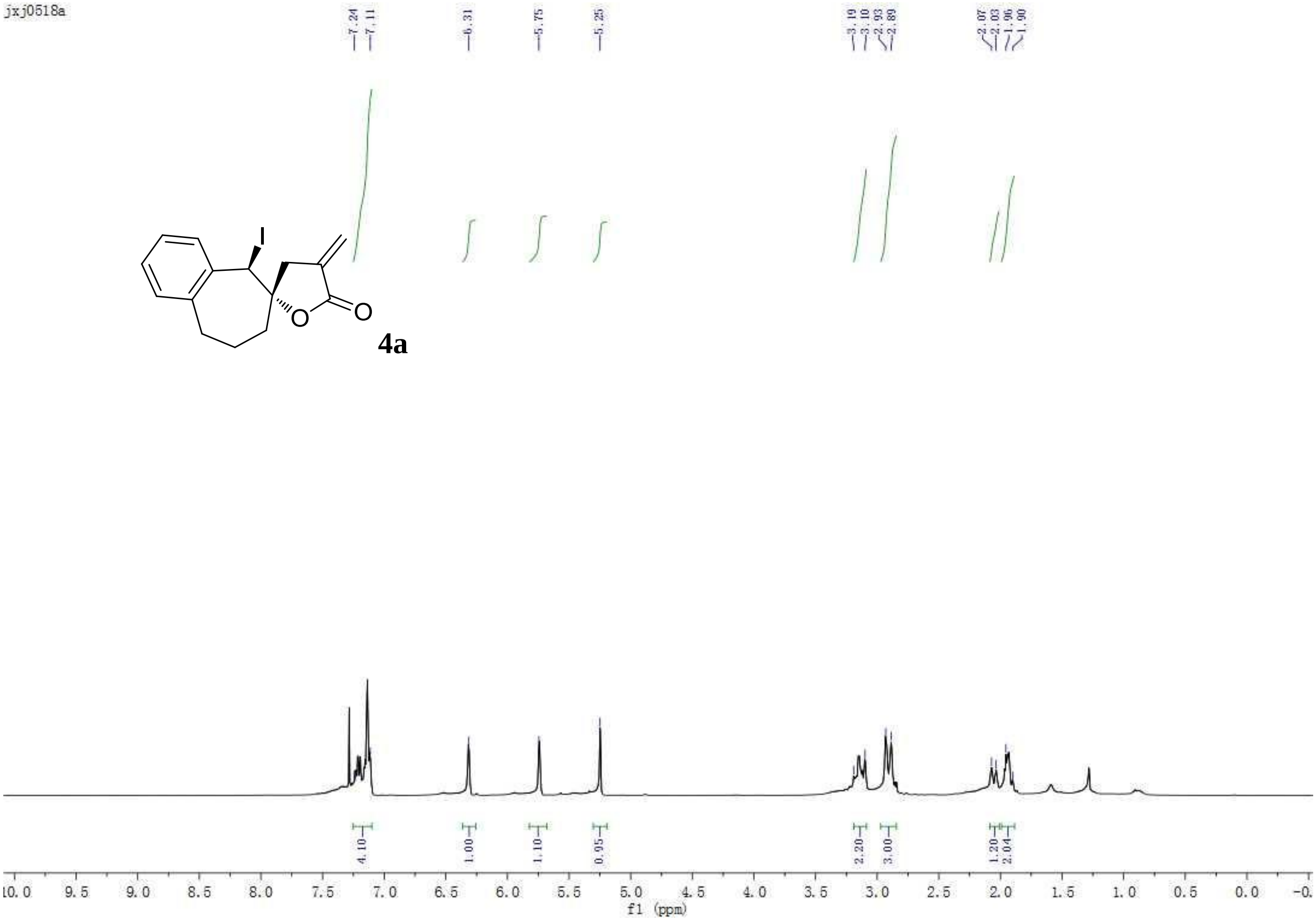

JXJ190810E
7.97
7.28
6.35
6.05
5.81
3.53
3.37
3.04
2.85
2.13
2.01
Br
O
O
2g
1.06
1.22
1.07
1.18
1.16
1.01
1.00
1.00
1.04
2.29
3.27
3.34
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

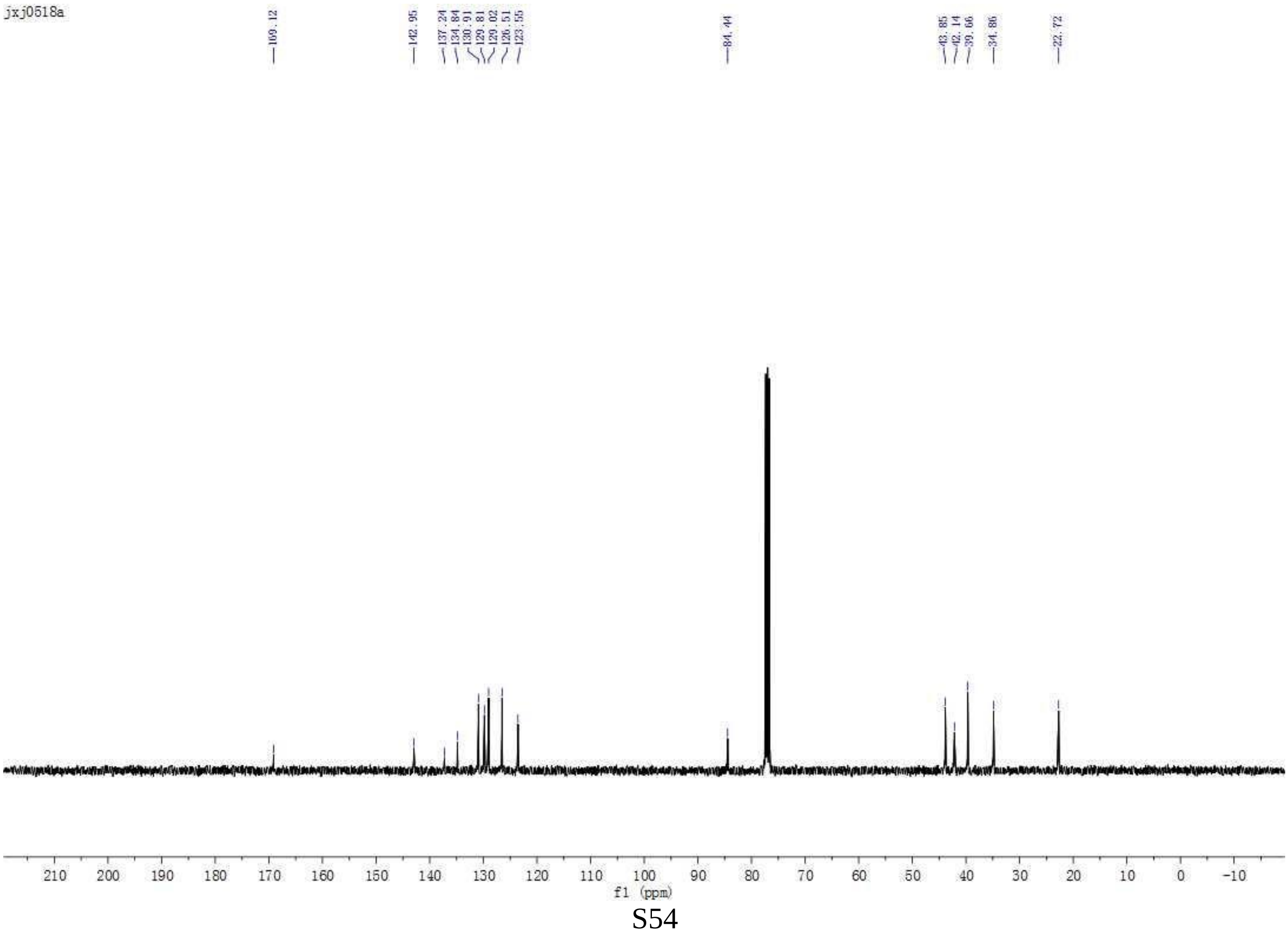

JXJ190810E
168.83
142.51
134.35
132.75
132.02
129.92
129.74
129.66
129.12
127.20
125.00
123.80
121.36
84.60
53.65
43.24
38.88
35.41
22.73
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

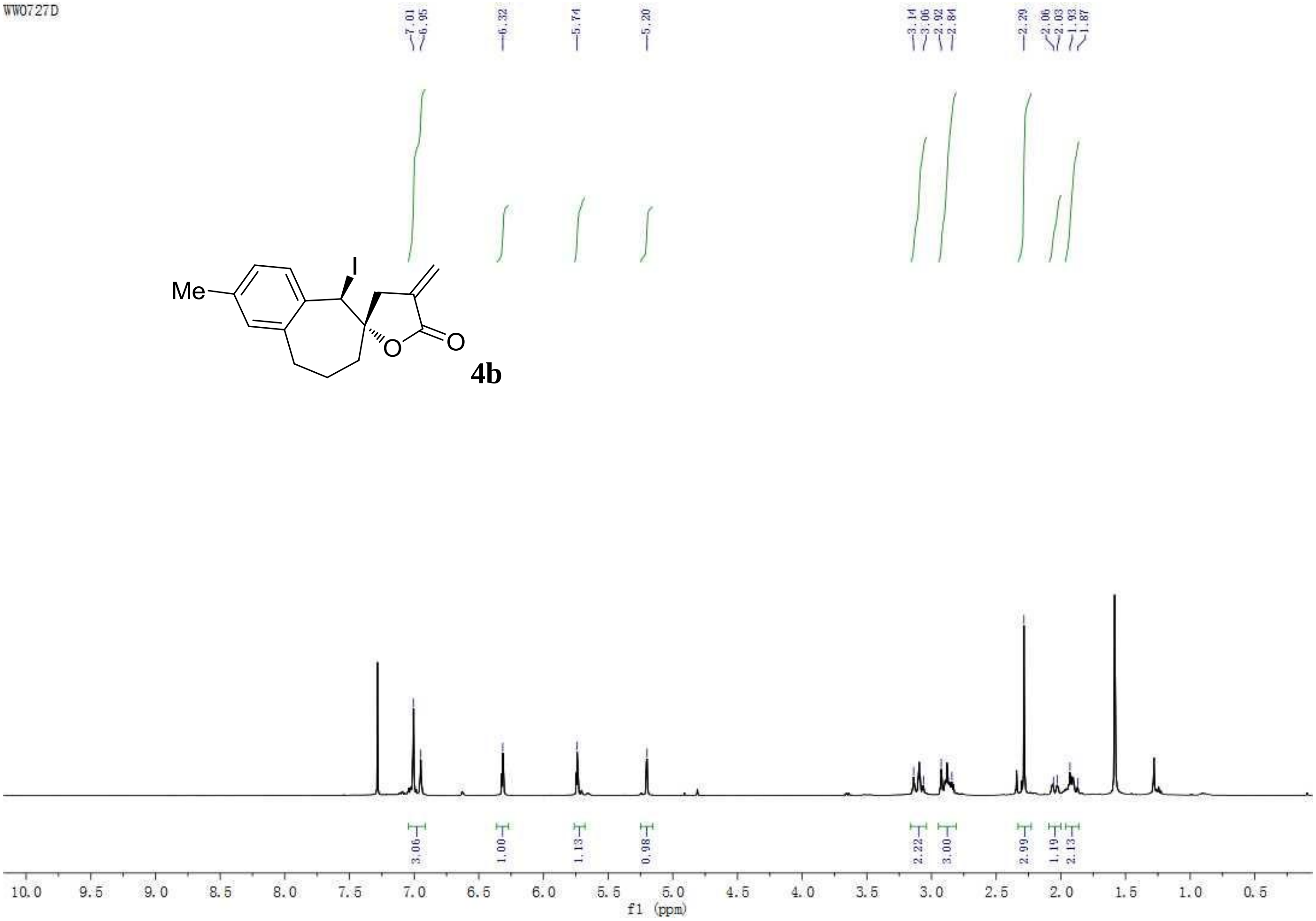

JXJ190810D
8.23
7.31
6.33
5.76
5.19
3.83
3.77
3.41
3.24
2.89
2.73
2.10
1.91
1.04
1.07
1.02
2.06
0.98
1.00
1.04
0.98
1.00
2.04
2.06
3.19
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)
Br
O
O

2h

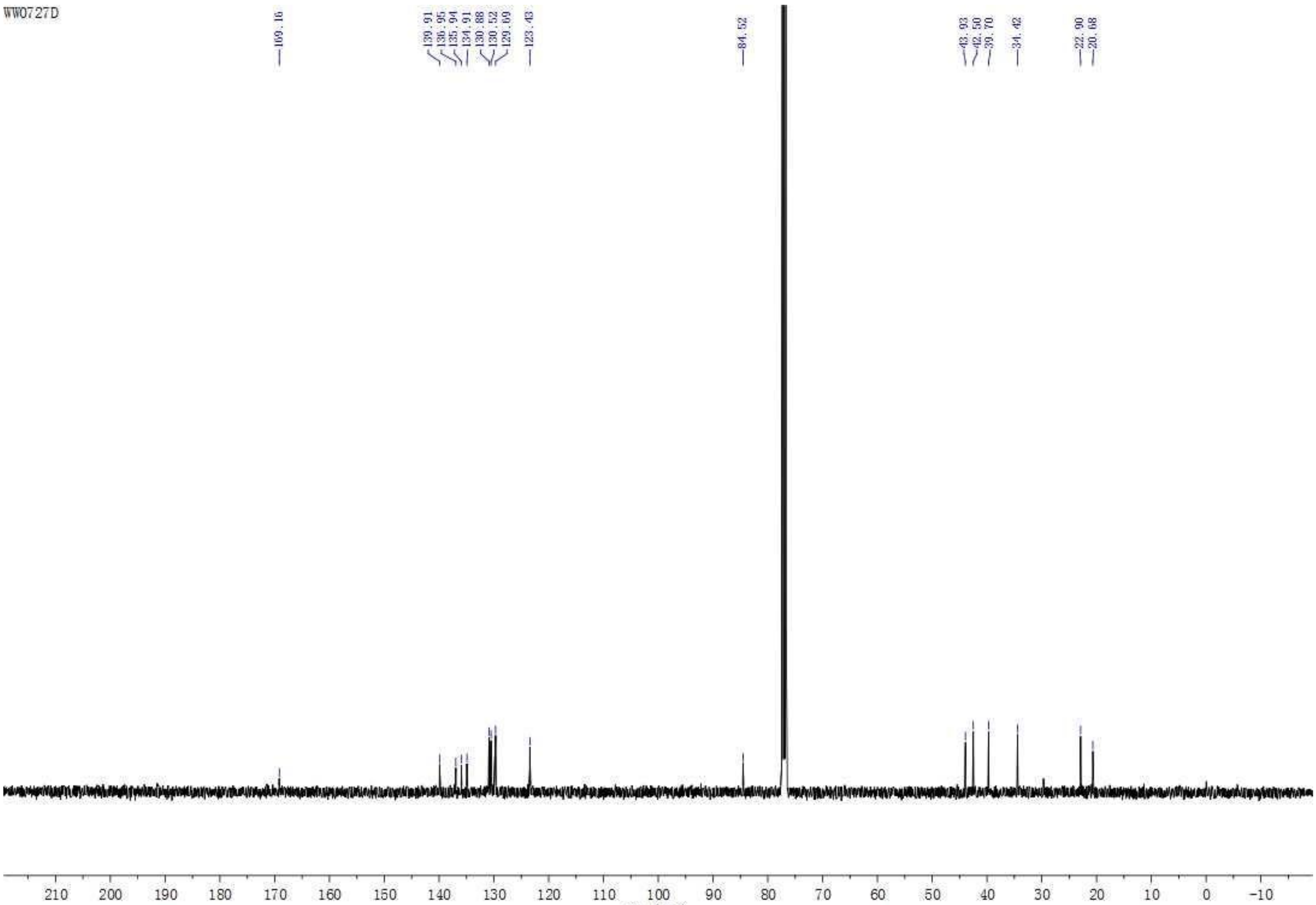

JXJ190810D
168.84
134.46
134.04
132.41
131.97
128.74
128.42
126.82
126.44
126.20
123.71
123.54
84.26
62.02
41.89
38.79
25.63
22.17
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


jxj0518a
7.24
7.11
6.31
5.75
5.25
3.19
3.10
2.93
2.89
2.07
2.03
1.96
1.90
I
O
O
4a
4.10
1.00
1.10
0.95
2.20
3.00
1.20
2.04
f1 (ppm)

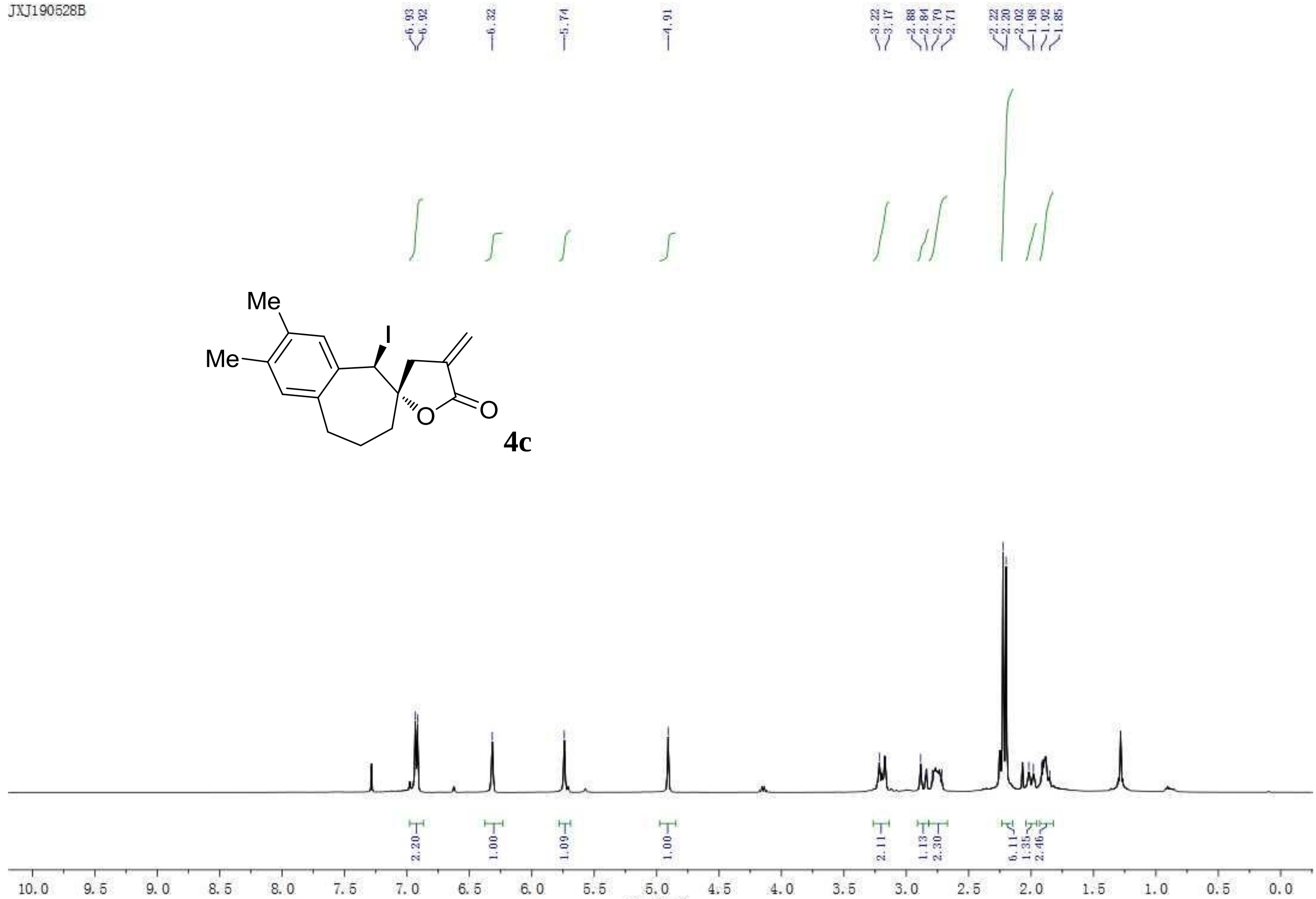

jxj0518a
169.12
142.95
137.24
134.84
130.91
129.81
129.02
126.51
123.55
84.44
43.85
42.14
39.66
34.86
22.72
f1 (ppm)

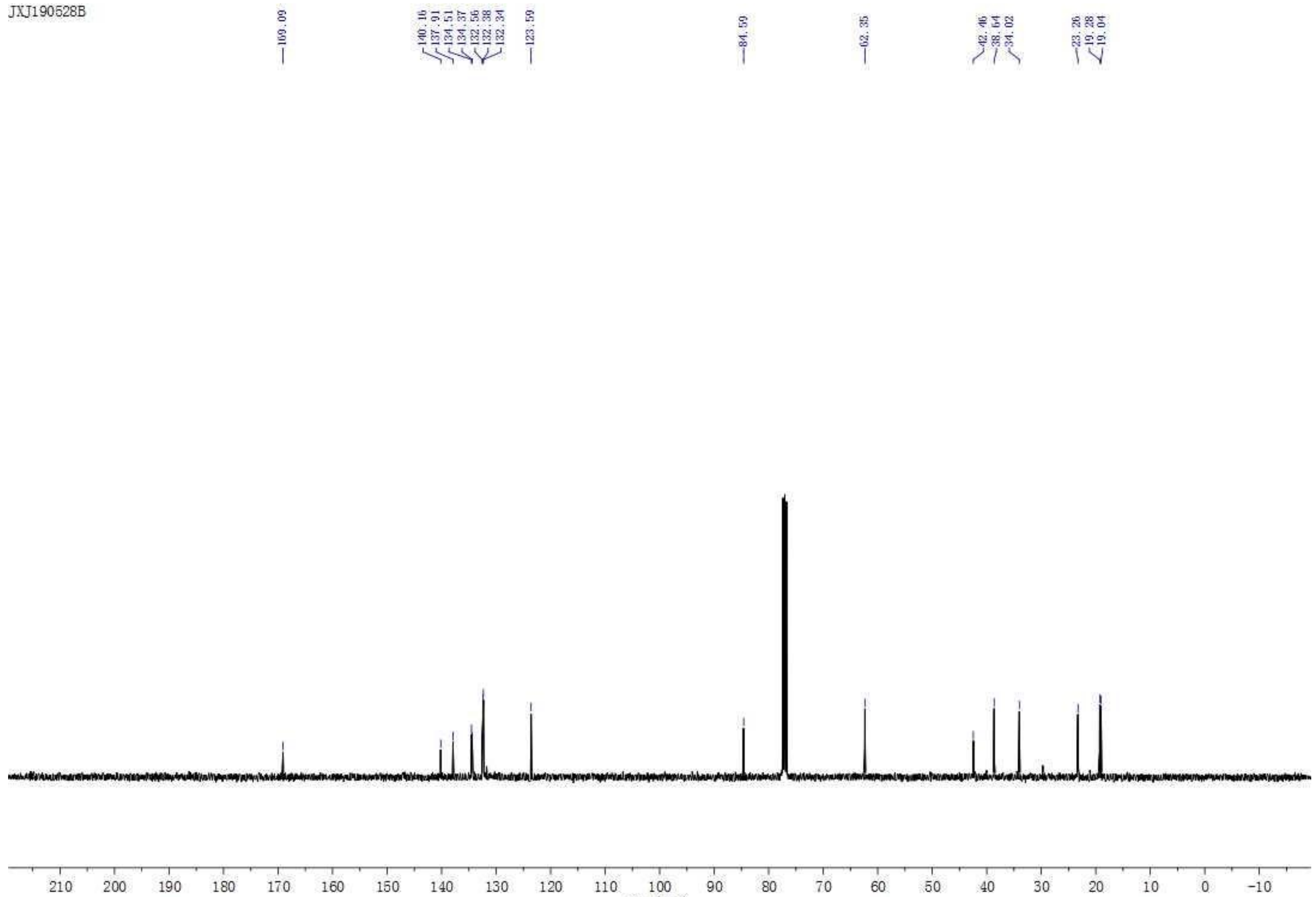


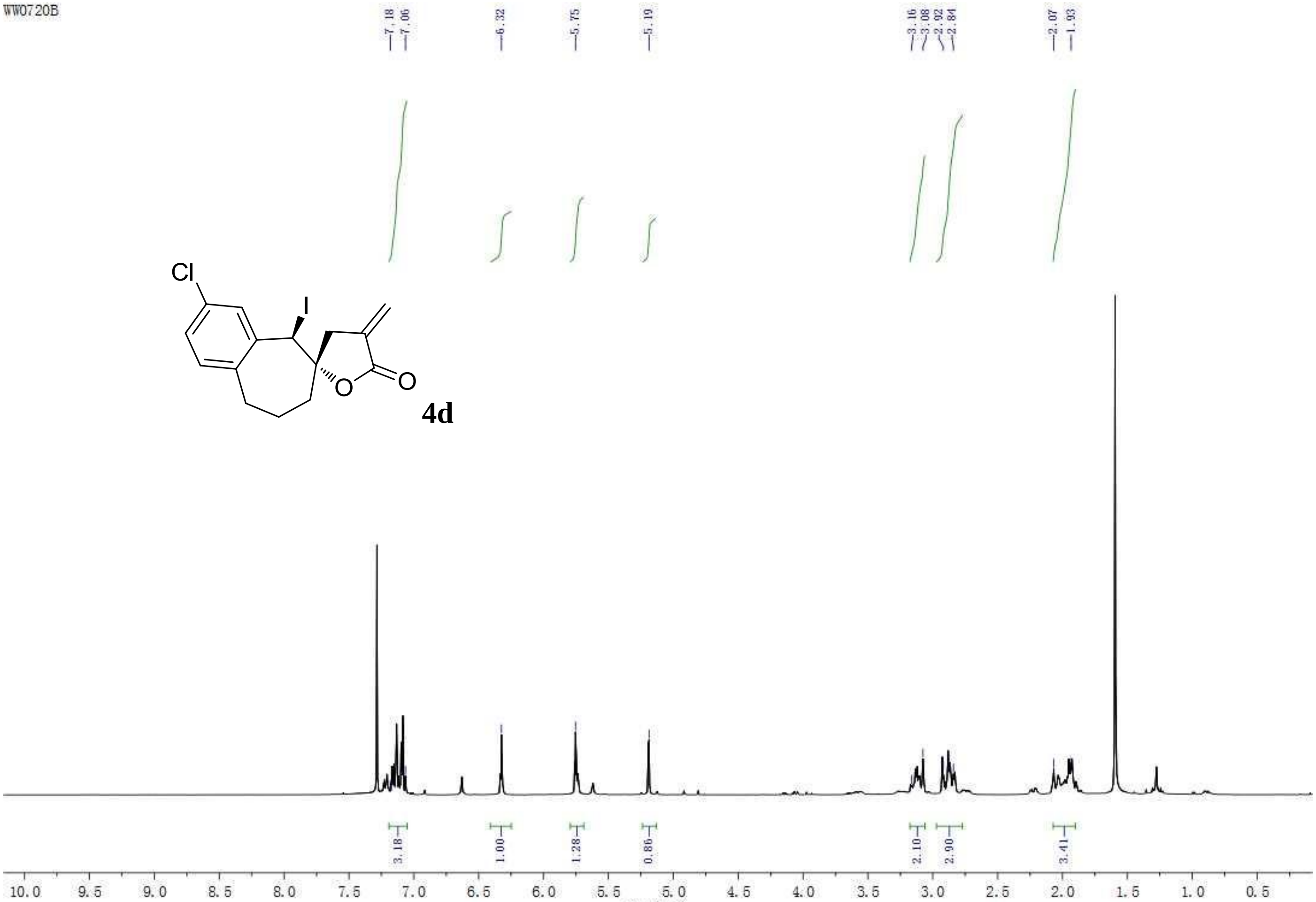
4b
WW0727D
7.01
6.95
6.32
5.74
5.20
3.14
3.06
2.92
2.84
2.29
2.06
2.03
1.93
1.87
3.06
1.00
1.13
0.98
2.22
3.00
2.99
1.19
2.13
f1 (ppm)



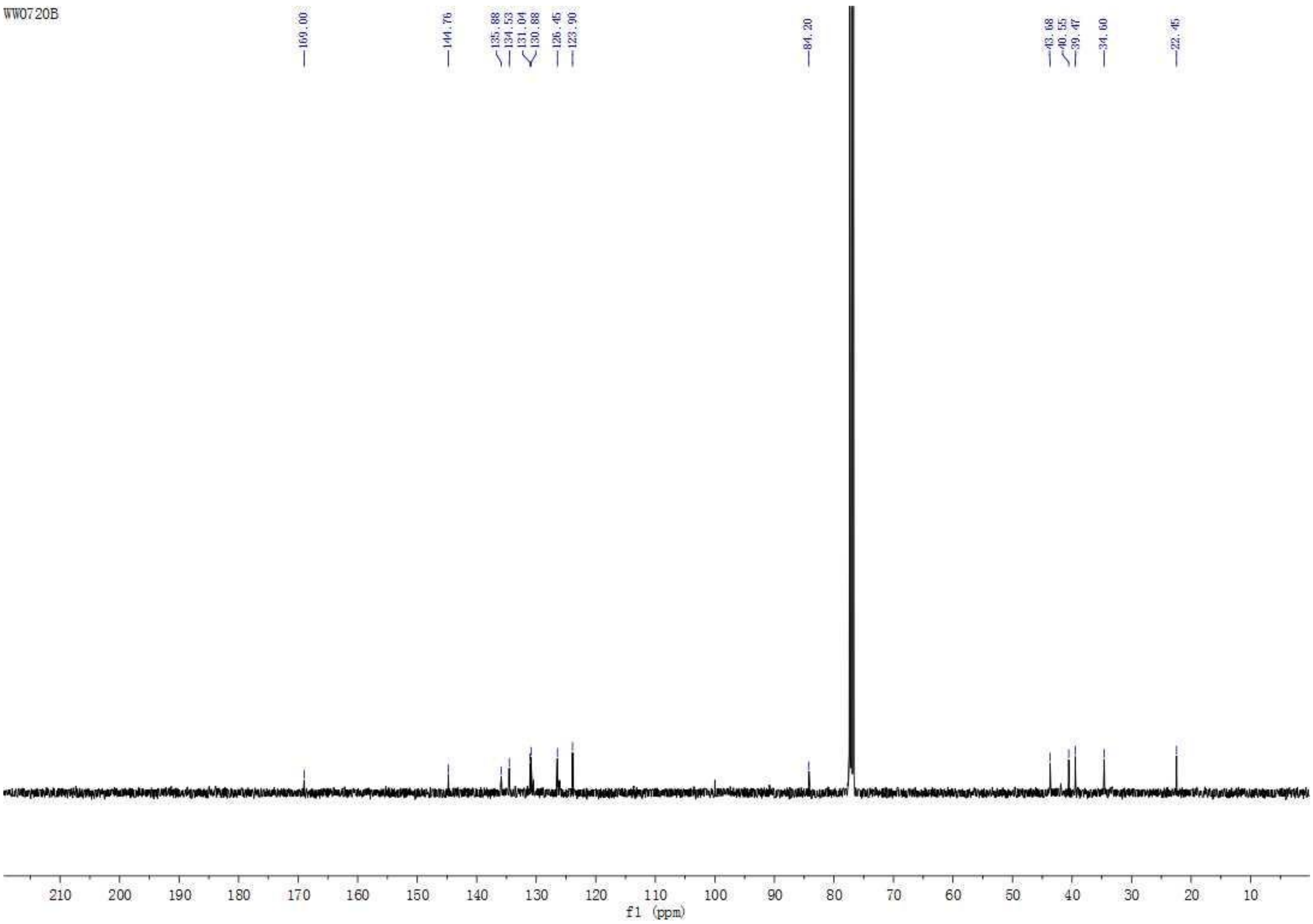
WW0727D
169.16
139.91
136.95
135.94
134.91
130.88
130.52
129.09
123.43
84.52
43.93
42.50
39.70
34.42
22.90
20.68
f1 (ppm)

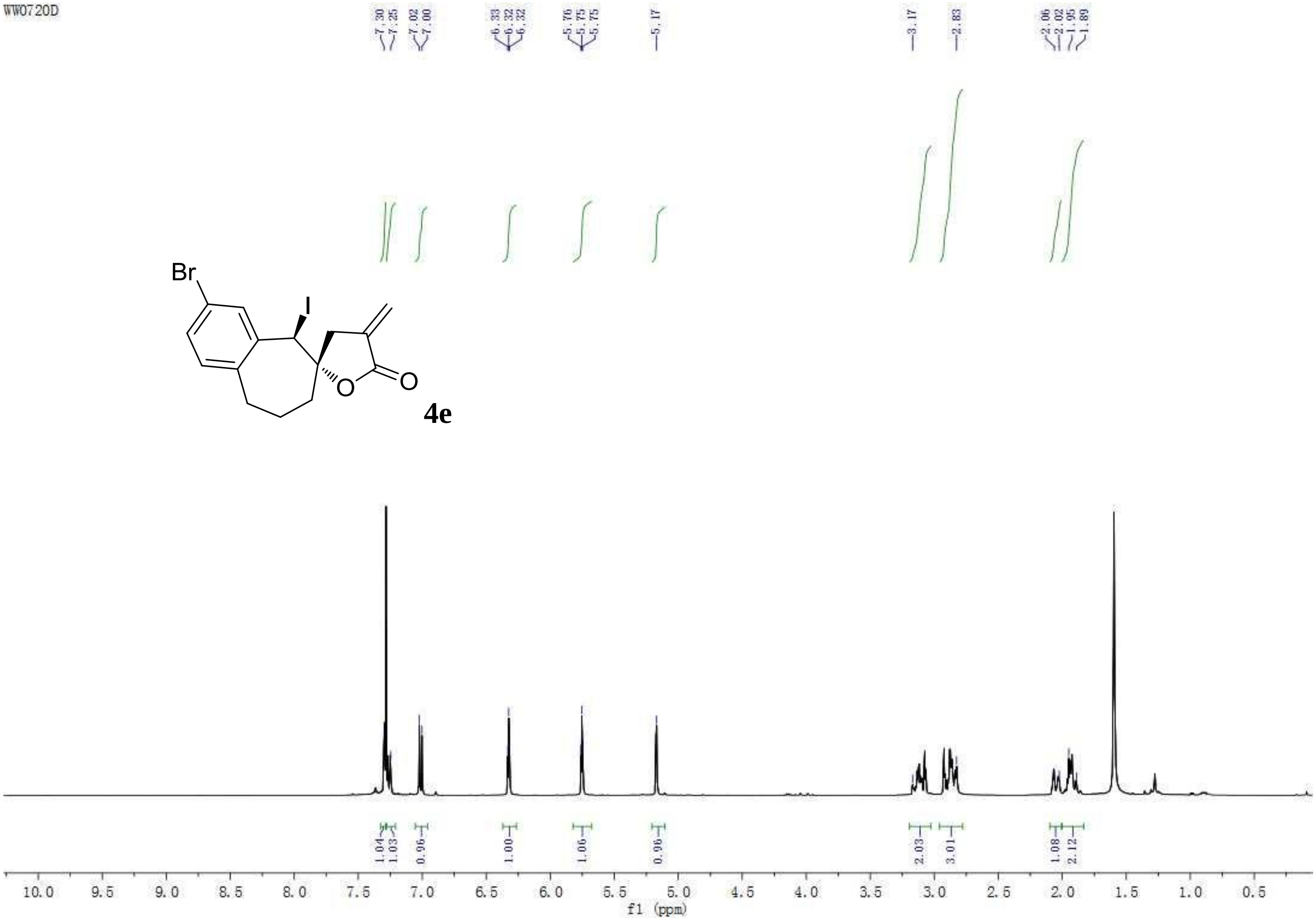

JXJ190528B
6.93
6.92
6.32
5.74
4.91
3.22
3.17
2.88
2.84
2.79
2.71
2.22
2.20
2.02
1.98
1.92
1.85
Me
Me
I
O
O
4c
2.20
1.00
1.09
1.00
2.11
1.13
2.30
6.11
1.35
2.46
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

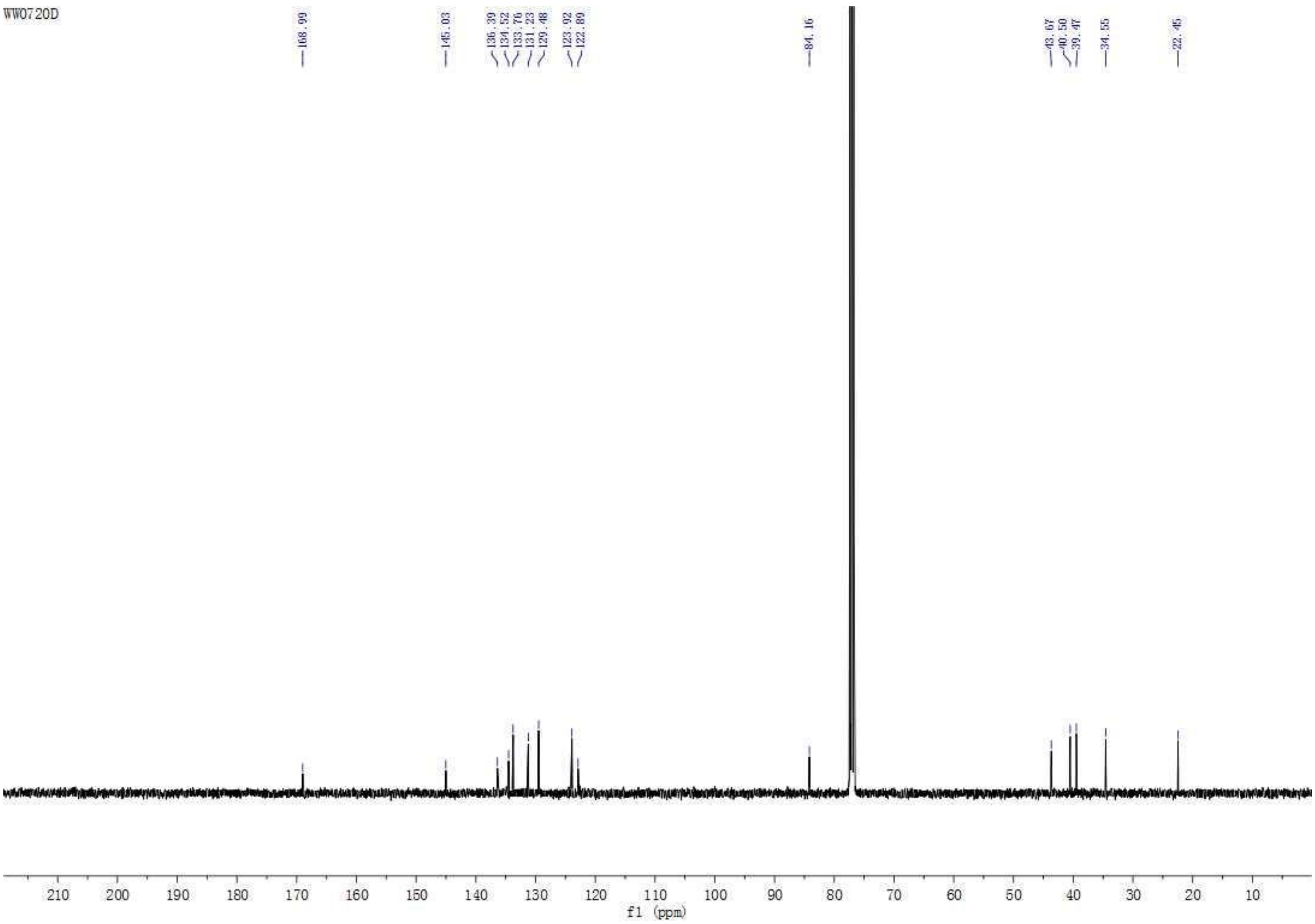

JXJ190528B
169.09
140.16
137.91
134.51
134.37
132.56
132.38
132.34
123.59
84.59
62.35
42.46
38.64
34.02
23.26
19.28
19.04
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

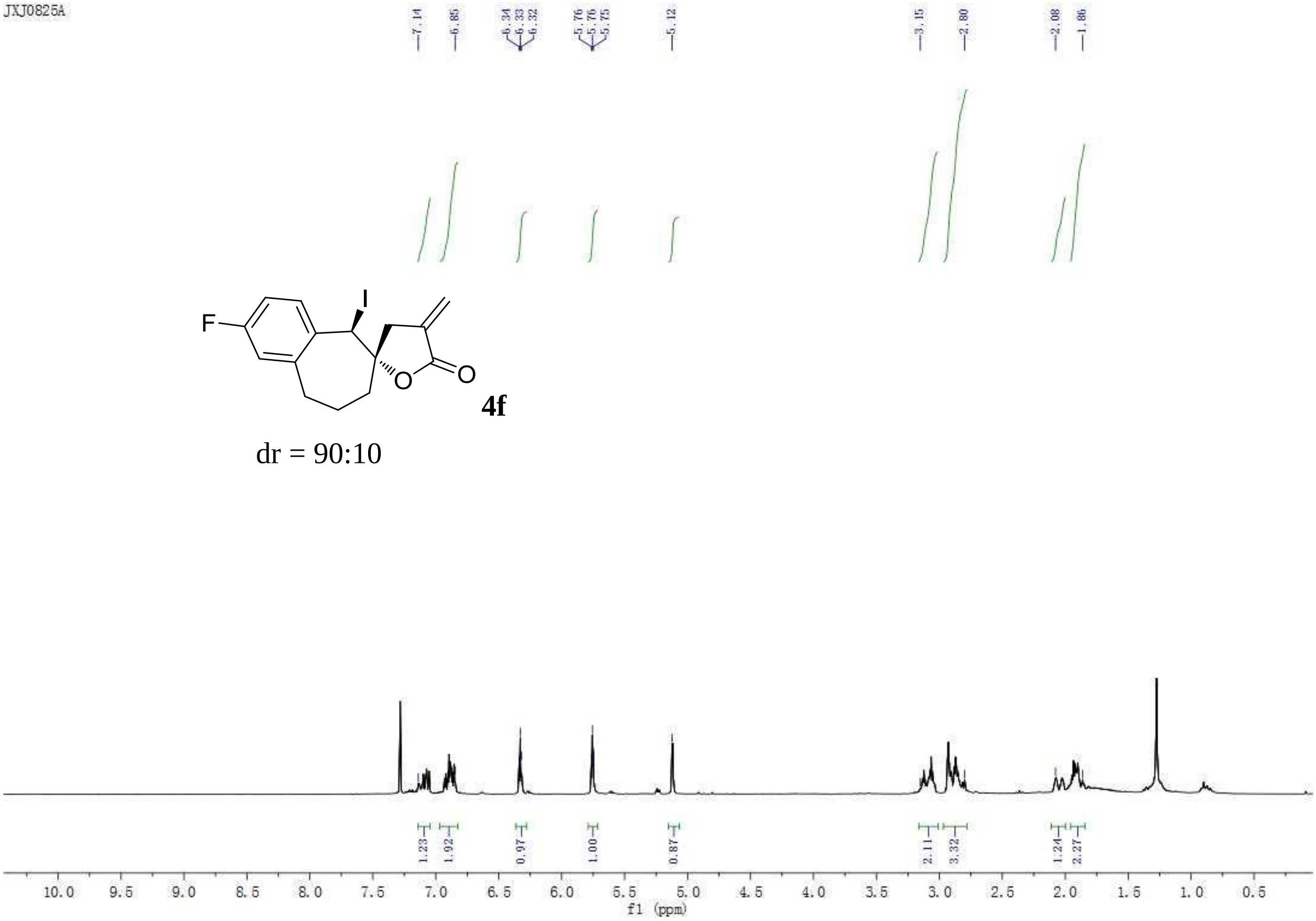

WW0720B
7.18
7.06
6.32
5.75
5.19
3.16
3.08
2.92
2.84
2.07
1.93
3.18
1.00
1.28
0.86
2.10
2.90
3.41
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

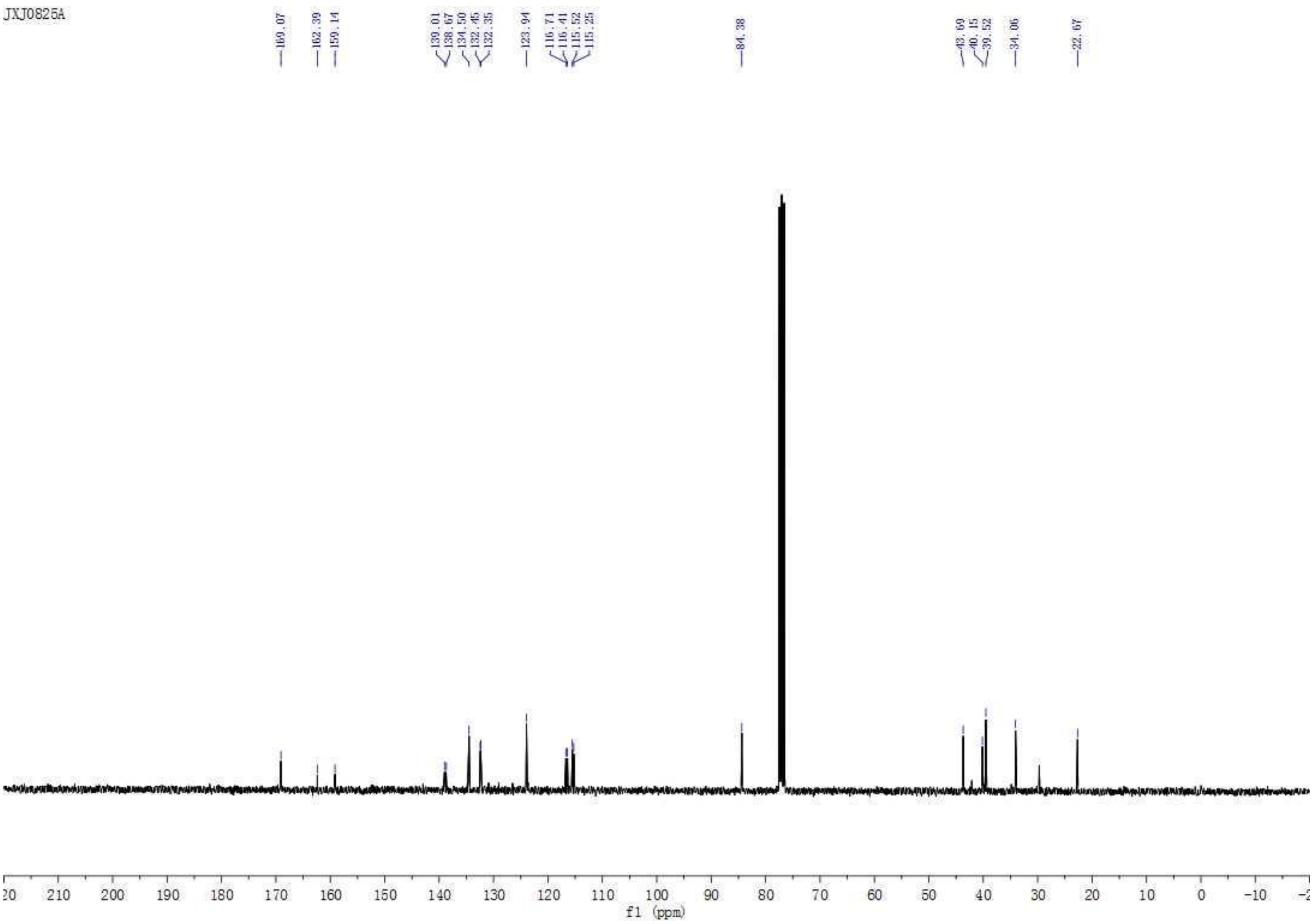
4d

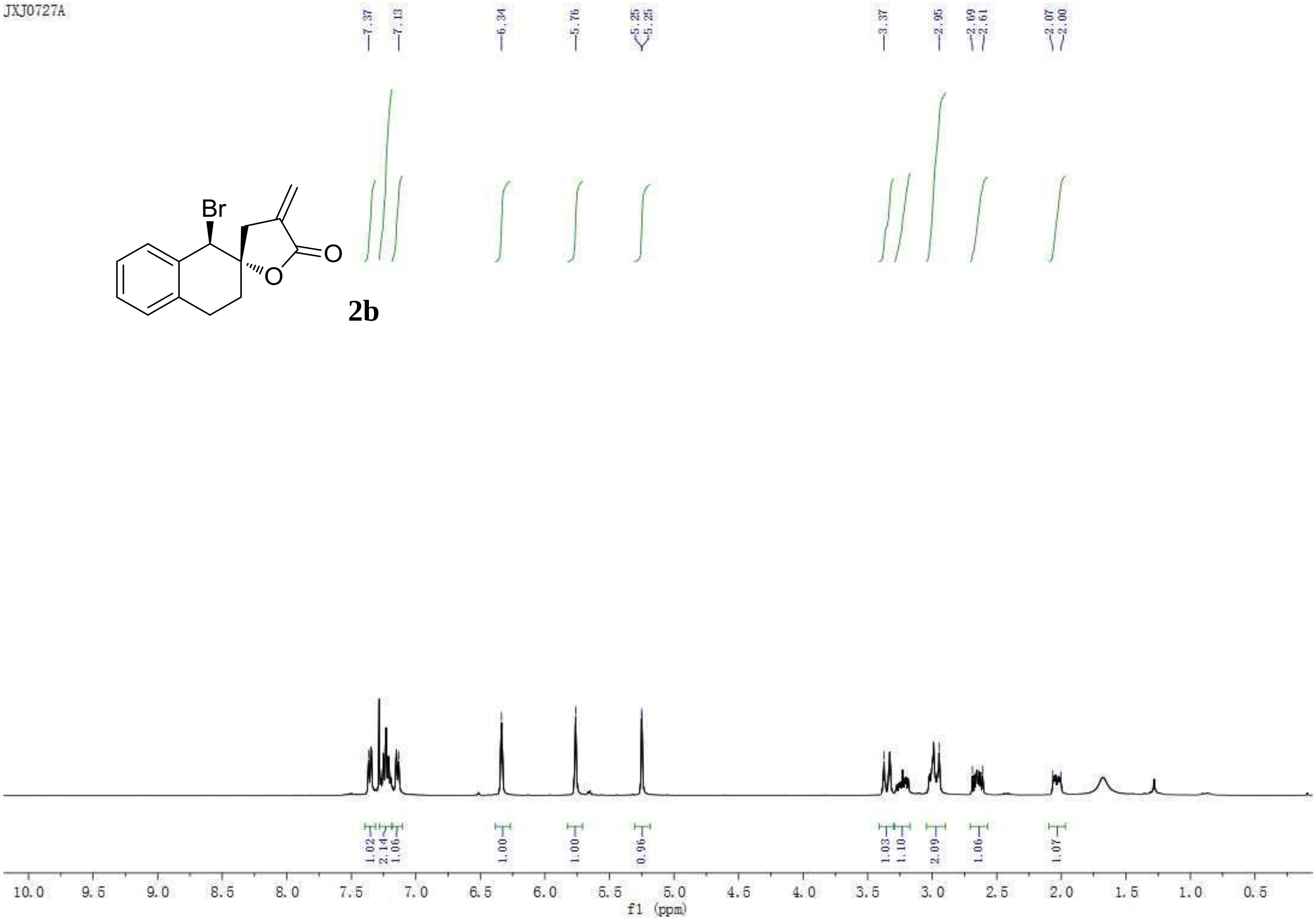

WW0720B
169.00
144.76
135.88
134.53
131.04
130.88
126.45
123.90
84.20
43.68
40.55
39.47
34.60
22.45
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

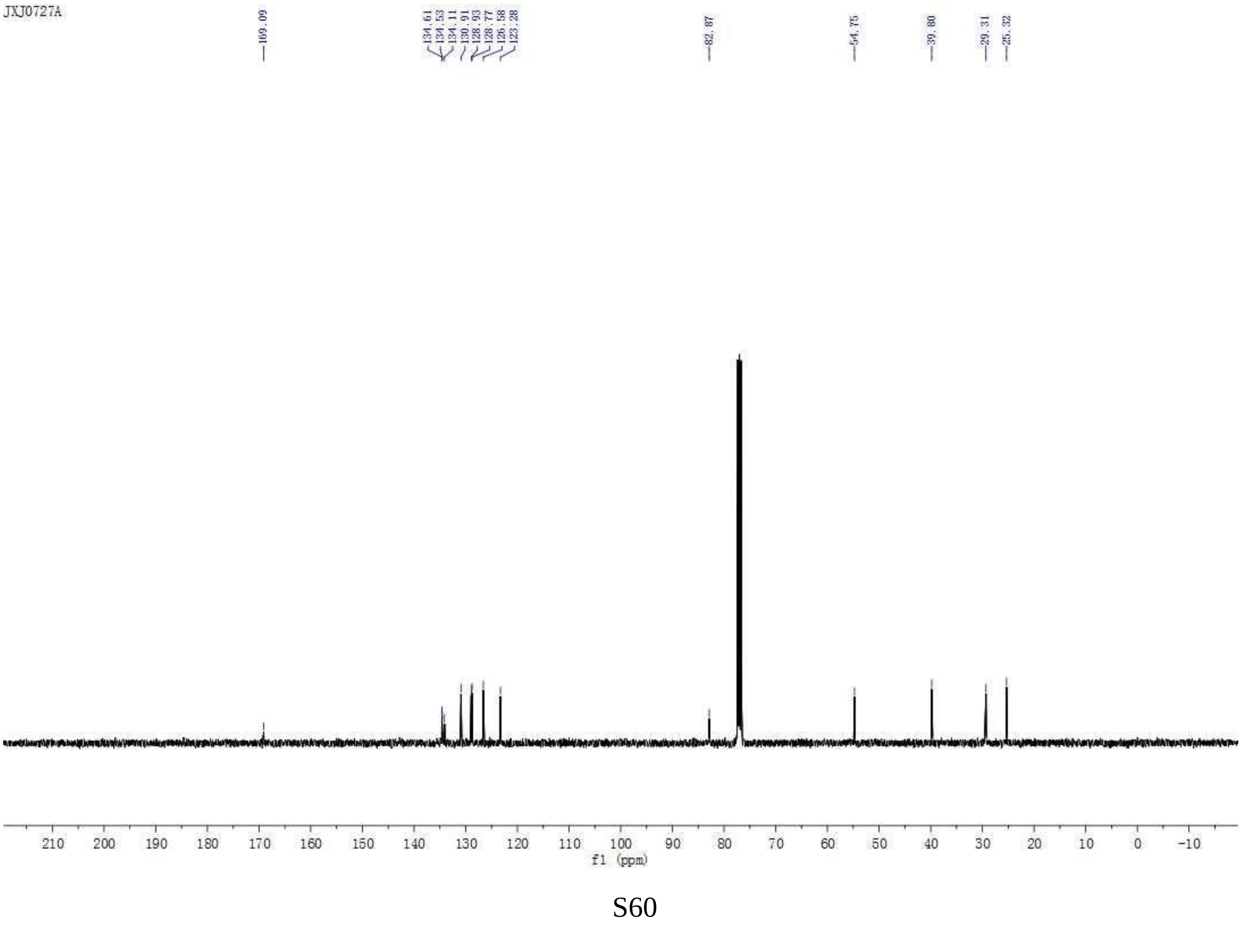

WW0720D
7.30
7.25
7.02
7.00
6.33
6.32
6.32
5.76
5.75
5.75
5.17
3.17
2.83
2.06
2.02
1.95
1.89
Br
I
O
O
4e
1.04
1.03
0.96
1.00
1.06
0.96
2.03
3.01
1.08
2.12
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

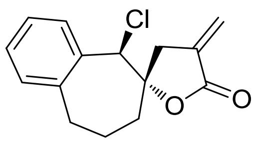

WW0720D
168.99
145.03
136.39
134.52
133.76
131.23
129.48
123.92
122.89
84.16
43.67
40.50
39.47
34.55
22.45
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)


JXJ0825A
F
I
O
O
4f
dr = 90:10
7.14
6.85
6.34
6.33
6.32
5.76
5.76
5.75
5.12
3.15
2.80
2.08
1.86
1.23
1.92
0.97
1.00
0.87
2.11
3.32
1.24
2.27
f1 (ppm)


JXJ0825A
169.07
162.39
159.14
139.01
138.67
134.50
132.45
132.35
123.94
116.71
116.41
115.52
115.25
84.38
43.69
40.15
39.52
34.06
22.67
f1 (ppm)

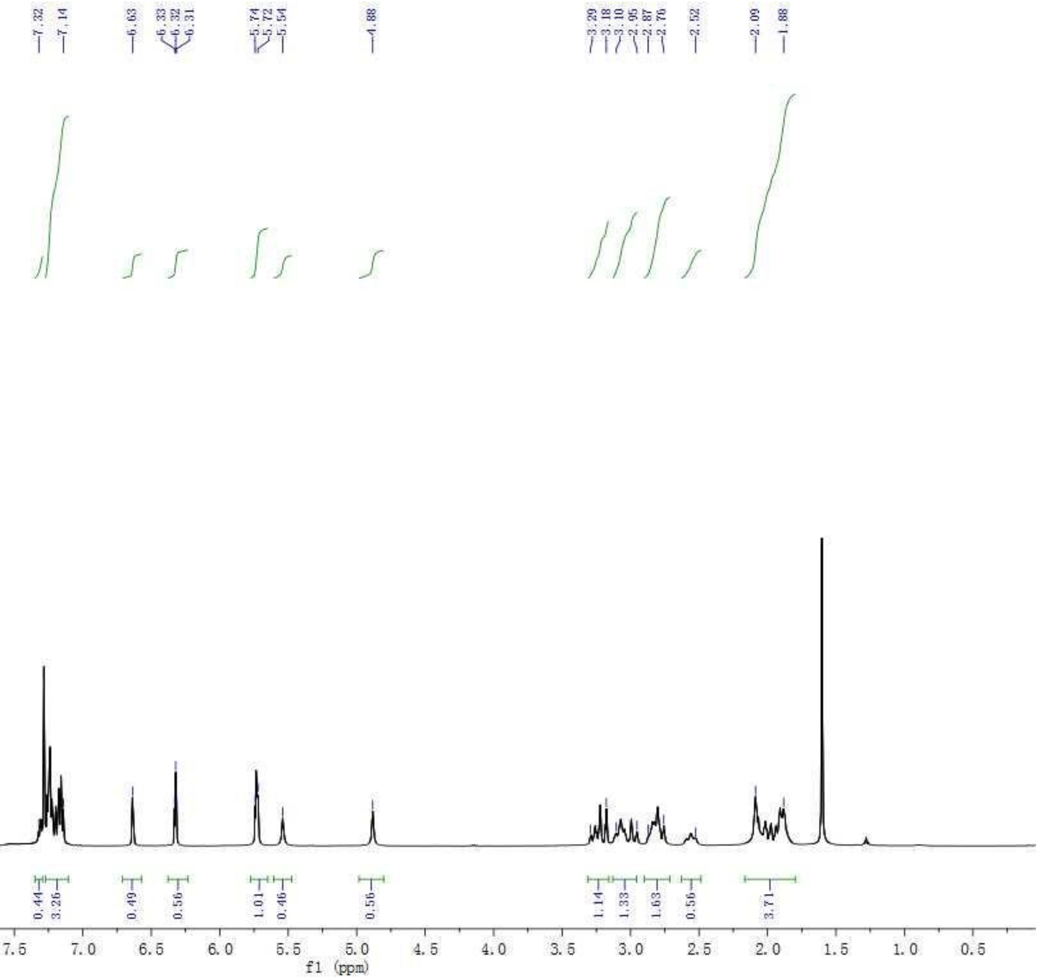

Br
O
O
2b
JXJ0727A
7.37
7.13
6.34
5.76
5.25
5.25
3.37
2.95
2.69
2.61
2.07
2.00
1.02
2.14
1.06
1.00
1.00
0.96
1.03
1.10
2.09
1.06
1.07
f1 (ppm)

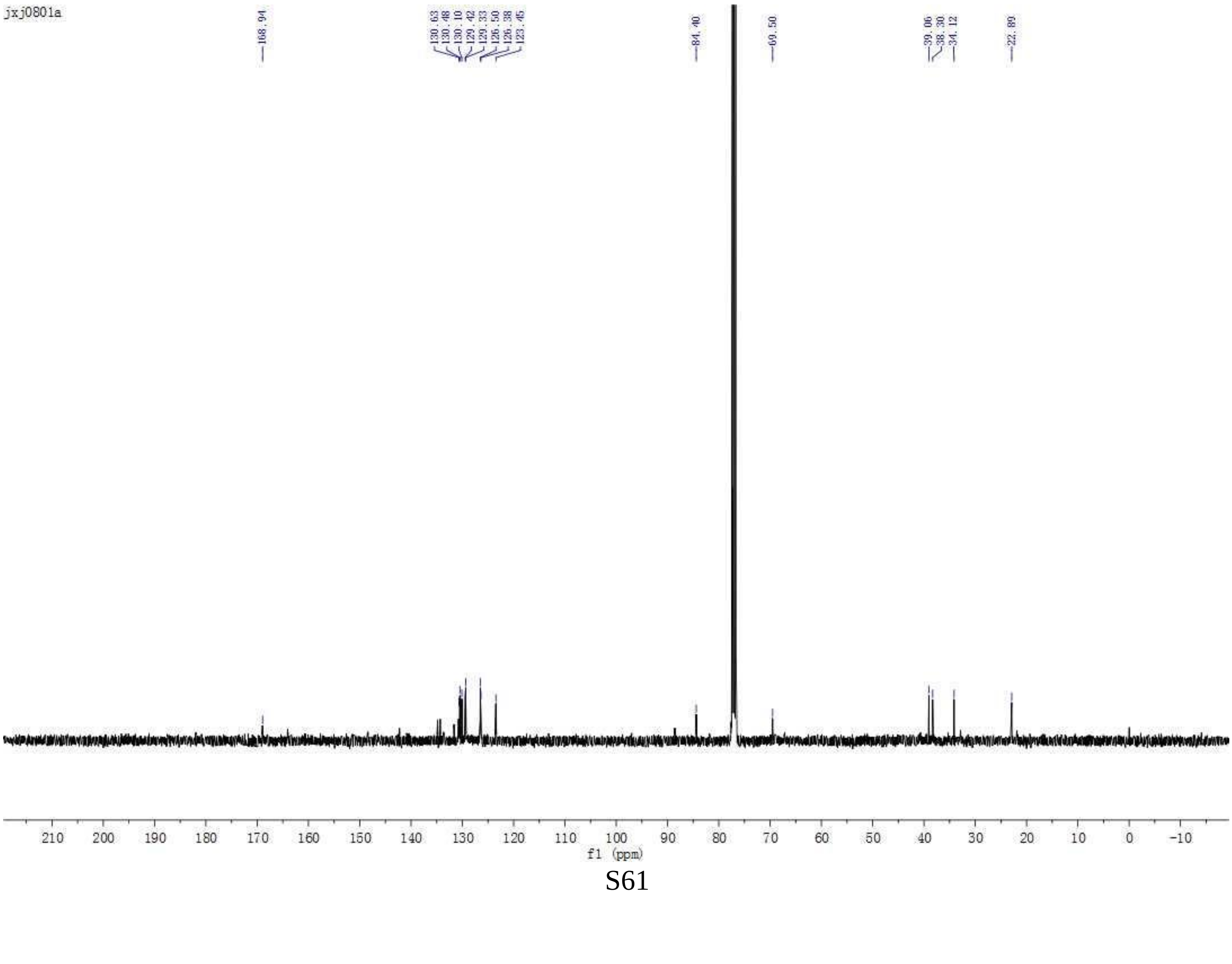

JXJ0727A
169.09
134.61
134.53
134.11
130.91
128.93
128.77
126.58
123.28
82.87
54.75
39.80
29.31
25.32
f1 (ppm)

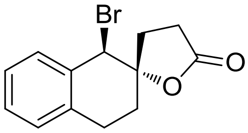

Cl
O
O

5

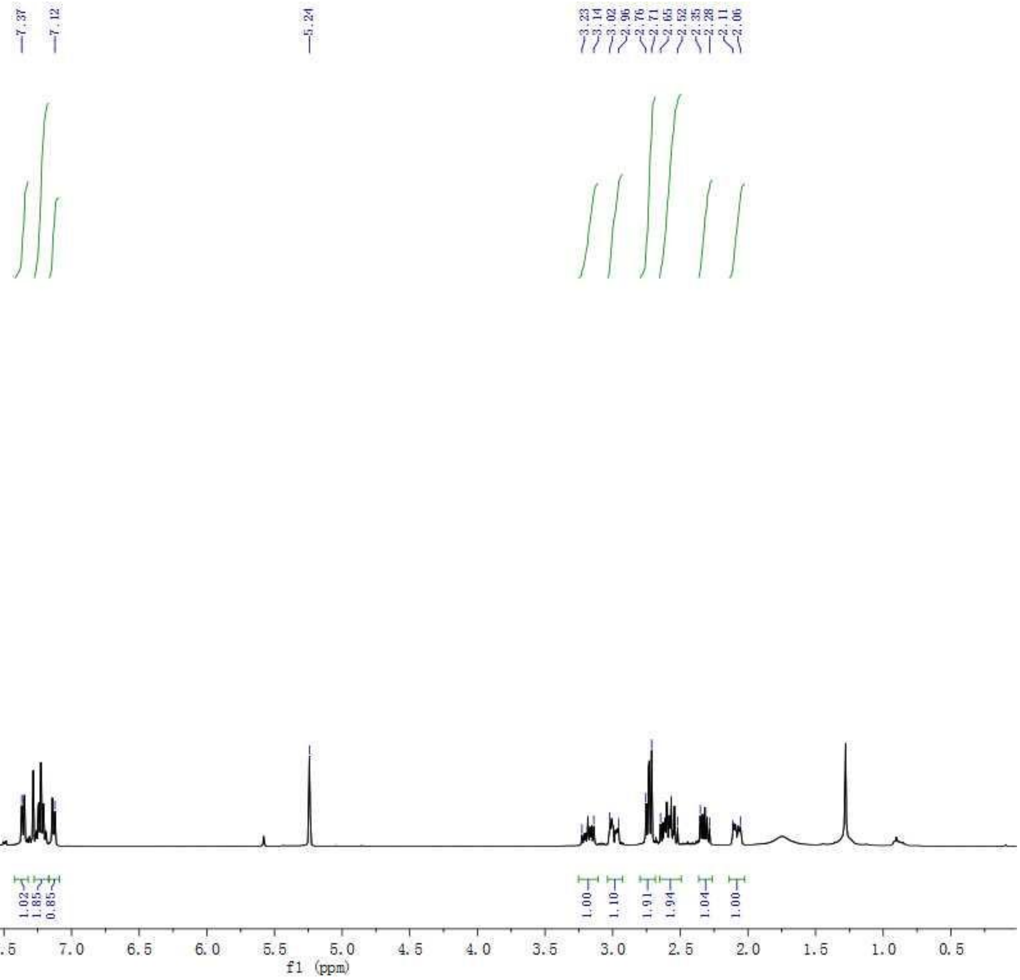
dr = 60:40

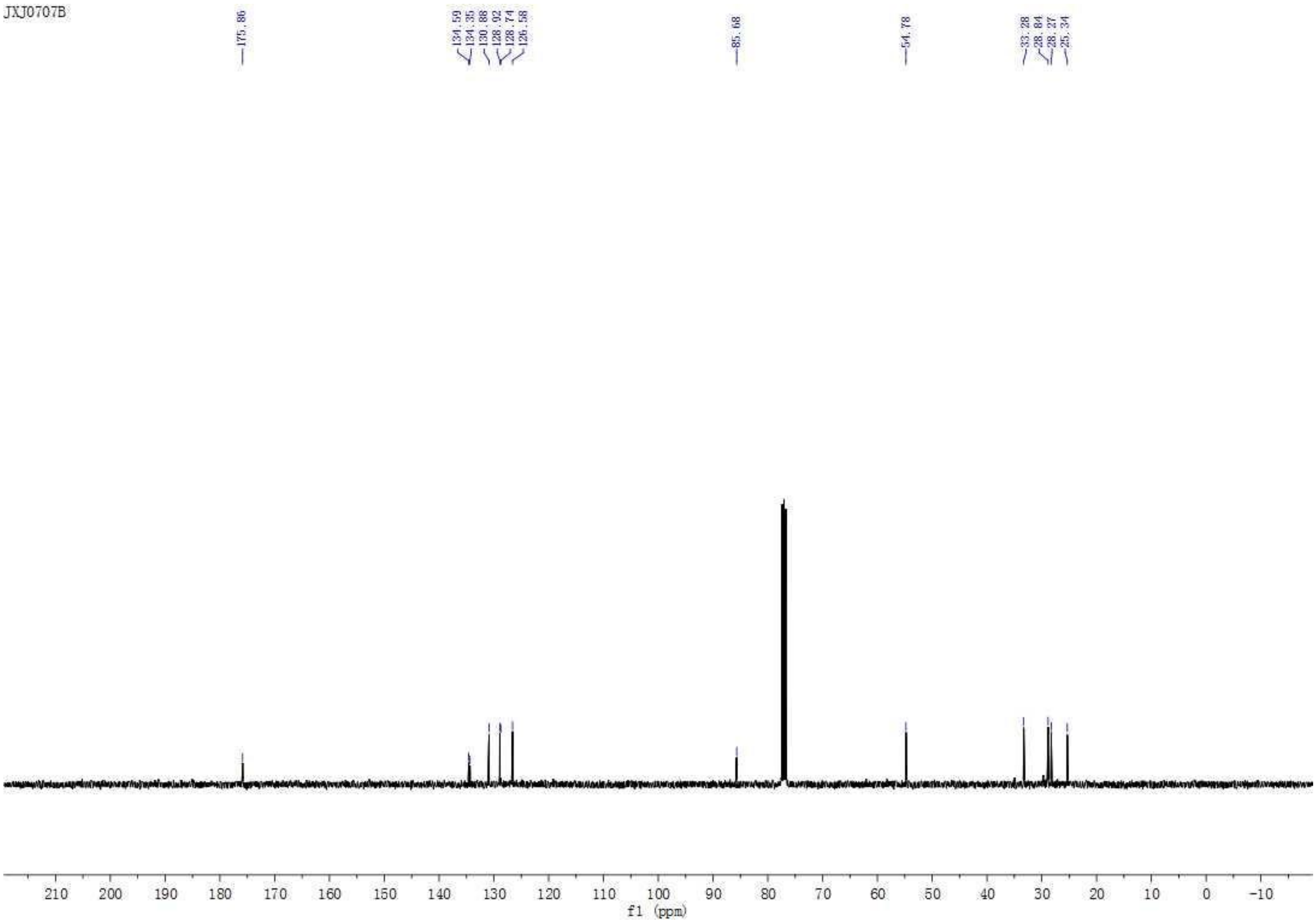

jxj0801a
7.32
7.14
6.63
6.33
6.32
6.31
5.74
5.72
5.54
4.88
3.29
3.18
3.10
2.95
2.87
2.76
2.52
2.09
1.88
0.44
3.26
0.49
0.56
1.01
0.46
0.56
1.14
1.33
1.63
0.56
3.71
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

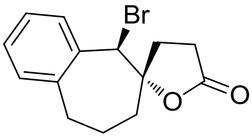

jxj0801a
168.94
130.63
130.48
130.10
129.42
129.33
126.50
126.38
123.45
84.40
69.50
39.06
38.30
34.12
22.89
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



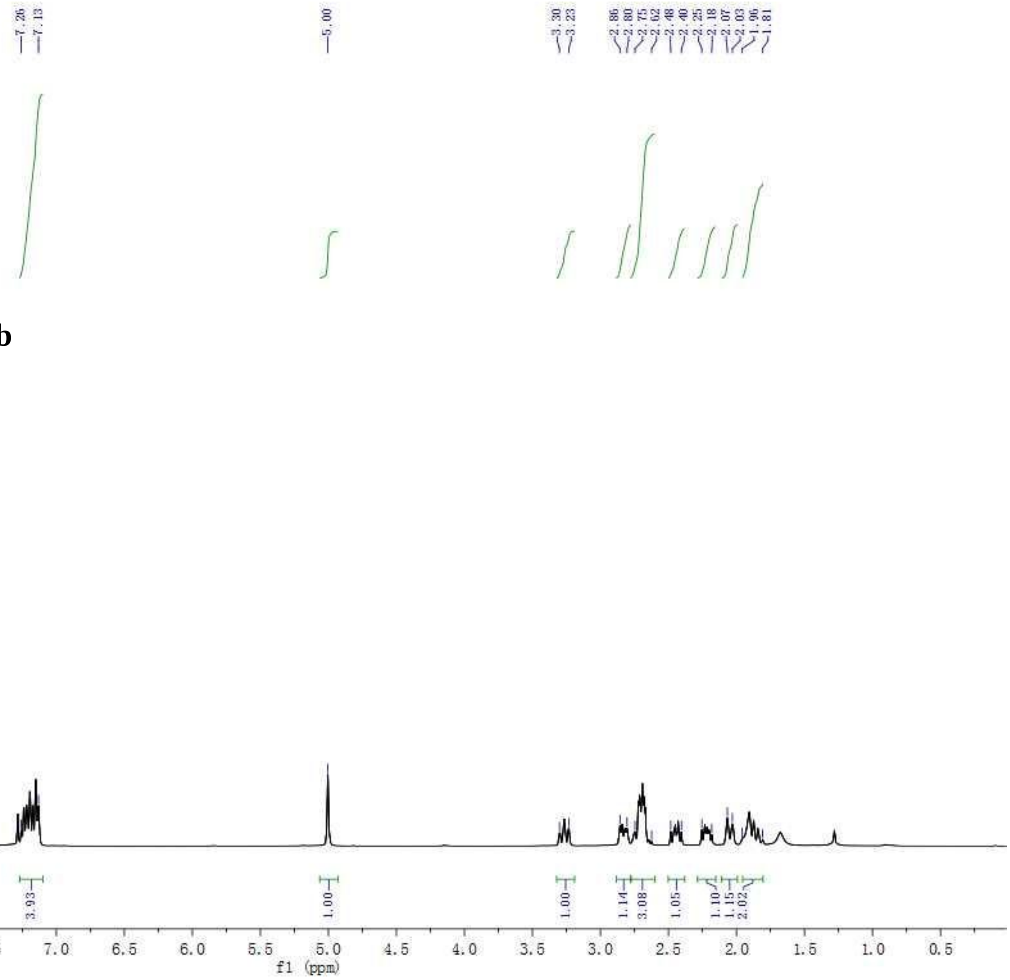
7a

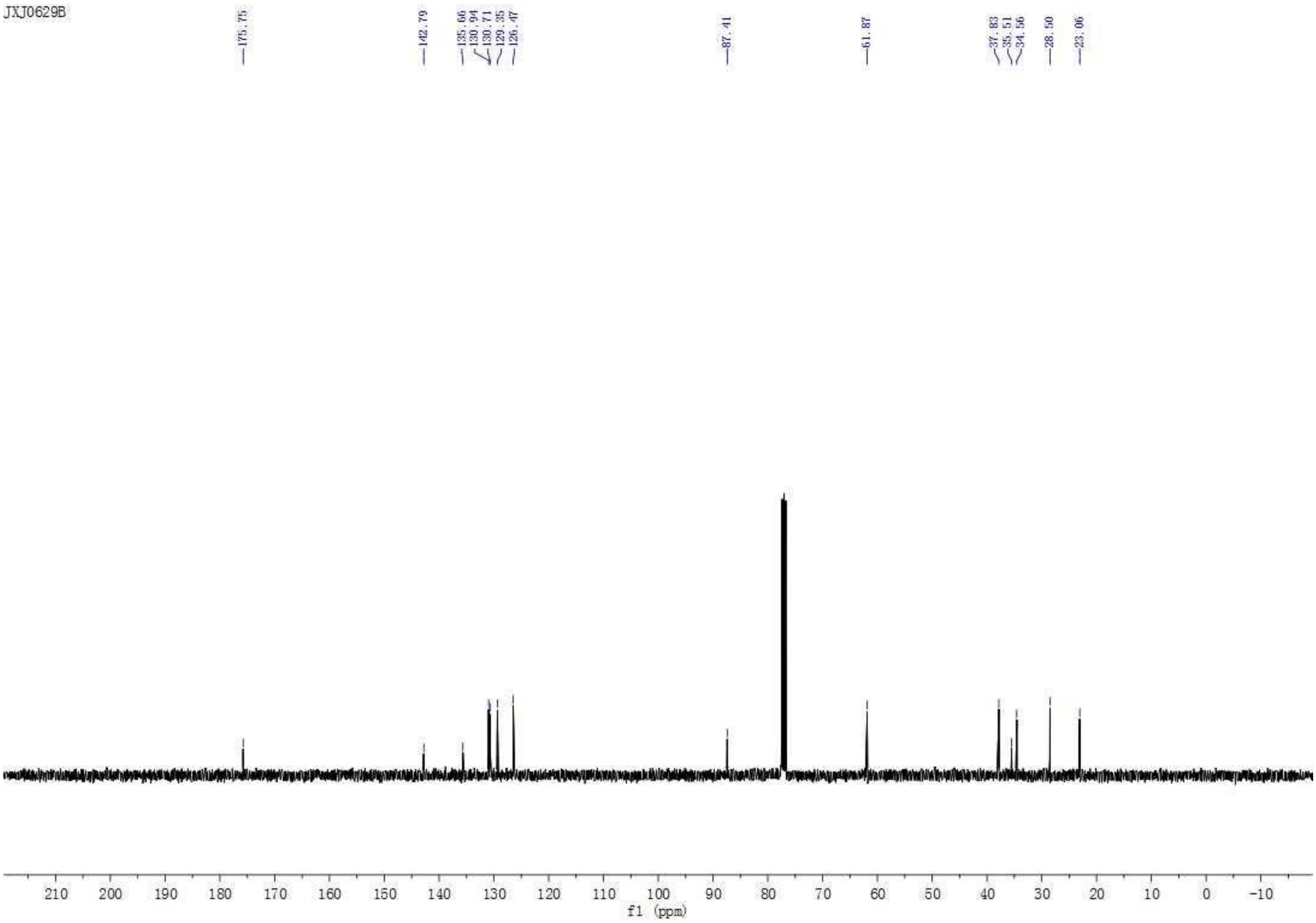

JXJ0707B
7.37
7.12
5.24
3.23
3.14
3.02
2.96
2.76
2.71
2.65
2.52
2.35
2.28
2.11
2.06
1.02
1.85
0.85
1.00
1.10
1.91
1.94
1.04
1.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)


JXJ0707B
175.86
134.59
134.35
130.88
128.92
128.74
126.58
85.68
54.78
33.28
28.84
28.27
25.34
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


Br
O
O

7b


JXJ0629B
7.26
7.13
5.00
3.30
3.23
2.86
2.80
2.75
2.62
2.48
2.40
2.25
2.18
2.07
2.03
1.96
1.81
3.93
1.00
1.00
1.14
3.08
1.05
1.10
1.15
2.02
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)


JXJ0629B
175.75
142.79
135.66
130.94
130.71
129.35
126.47
87.41
61.87
37.83
35.51
34.56
28.50
23.06
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)